Development of methodologies for the synthesis of biologically important heterocyclic scaffolds

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Doctor of Philosophy (Science)

By

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CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled "**Development of methodologies for the synthesis of biologically important heterocyclic scaffolds**" Submitted by Sri **Subhendu Pramanik** who got his name registered on **04.09.2018 (Index No: 137/18/Chem./26)** for the award of Ph. D. (Science) degree of Jadavpur University, is absolutely based upon his own work under the supervision of **Dr Chinmay Chowdhury** and that neither this thesis nor any part of it has been submitted for either any degree / diploma or any other academic award anywhere before.

Chinmay Chowdhury
15/3/2022

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Declaration

I, **Subhendu Pramanik**, 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**, Senior Principal Scientist & Deputy Head, 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: 15.03.22 (Subhendu Pramanik)

Dedicated

To

My parents

Acknowledgments

This thesis is the outcome of a long journey in which I have been encouraged and supported by many people. It is indeed a pleasant moment to express my gratitude to them.

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

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The sweet tempered relationship with my Friends Ritesh Pal, Subhadip Palit, Anushree Achari, Dipendu Patra and many more from IICB and my roommate cum friend

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I pay my deep sense of reverence to my parents and my entire family for their silent blessing and encouragement enabling me to reach my goal. I specially express heartfelt gratitude to my sisters for their constant guidance, encouragement and inspiration right from the childhood.

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Date: 15.03.22

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Abbreviations

Ar	Aryl
Bn	Benzyl
Boc	di-*tert*-butyloxycarbonyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	*N*,*N*-dimethylformamide
EIMS	electron ionization mass spectroscopy
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
^{13}C NMR	carbon 13 nuclear magnetic resonance spectroscopy
ESI-MS	electron spray ionisation mass spectrometry
HRMS	high-resolution mass spectrometry
LAH	lithium aluminium hydride
Ns	4-nitro-benzenesulfonyl (nosyl) group
$PdCl_2(PPh_3)_2$	bis(triphenylphosphine)palladium(II) dichloride
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
$Pd(OAc)_2$	palladium(II) acetate
$PdCl_2$	palladium(II) chloride
PhSH	thiophenol
PPh_3	triphenylphosphine
TBAB	tetrabutylammonium bromide
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl (tosyl) group
D-CSA	D- camphor sulphonic acid

General remarks

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60-80 ^{o}C. DMF and DCM were dried over CaH_2, distilled, and stored over 3 Å 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 silica gel 60 F_{254} aluminium TLC sheets. Visualization of the developed Chromatogram was performed by UV absorbence or Iodine exposure. For the purification, column chromatography was performed using 60-120 or 100-200 or 230-400 mesh silica gel. All the reagents including $PdCl_2$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ were purchased from Aldrich, Merck, SRL, TCI etc. ^{1}H & ^{13}C NMR spectra were recorded using a Bruker 300, 400 or 600 MHz NMR using Tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) were given from TMS (δ = 0.0) 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 constant (*J*) were expressed in hertz (Hz), and spin multiplicities were given as s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplate) 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. Infrared spectra were obtained on JASCO FT/IR-4200 infrared spectrometer as neat or KBr plate. Crystallographic data were obtained using Bruker Kuppa Apex 2 instrument.

Preface

The research work embodied in this thesis describes efficient and elegant protocols for the synthesis of carbazoles, napthofurans, 5,6-Dihydrobenzo[*c*]phenanthridines and 6H-Dibenzo [*c, h*] chromenes through palladium catalyzed heteroannulation reactions. The work has been presented in three chapters.

Chapter-1 describes a direct and straightforward method for the synthesis of carbazoles having aryl and aryl ketone groups through Pd(II)-catalyzed cascade reactions between 1-(indol-2-yl) but-3-yn-1-ols and aldehydes**.**

Chapter-2 describes a palladium catalyzed cascade cyclization reaction for the synthesis of 5,6-Dihydrobenzo[*c*]phenanthridines and 6H-Dibenzo[*c,h*]chromenes.

Chapter-3 describes an efficient and facile method for the synthesis of Naphtho[1,2-*b*]furan through a palladium catalyzed *5-endo-dig* heteroannulation followed by a 1,2-nucleophilic addition on the aldehyde group and subsequent protonolysis, dehydration and isomerization.

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. 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 Chemistry, CSIR – Indian Institute of Chemical Biology, Kolkata (India), under the guidance of Dr Chinmay Chowdhury, Senior Principal Scientist and Deputy Head of the same Institute.

List of Author's Publications

1. Palladium-Catalyzed Benzannulations of 1-(Indol-2-yl)but-3-yn-1- ols: Easy Access to Functionalized Carbazoles; **Subhendu Pramanik**, Sarat Chatterjee, Rumjhum Banerjee, and Chinmay Chowdhury* Published on web as ASAP on 7 March, 2022. doi.org/10.1021/acs.orglett.2c00182.

2. 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*; **Subhendu Pramanik**,[+a] Moumita Jash,[+a] Debasmita Mondal,[a] and Chinmay Chowdhury[a],* *Adv. Synth. Catal.* **2019**, *361*, 5223– 5238.

3. Palladium(II)-Catalyzed Cascade Reactions of Ene−Ynes Tethered to Cyano/Aldehyde: Access to Naphtho[*1*,*2*-*b*]furans and Benzo[g]indoles; Moumita Jash, Sukanya De, **Subhendu Pramanik**, and Chinmay Chowdhury*, *J. Org. Chem.* **2019**, *84*, 8959−8975.

Reprints of Author's publications

OL Organic Letters

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Palladium-Catalyzed Benzannulations of 1-(Indol-2-yl)but-3-yn-1-ols: Easy Access to Functionalized Carbazoles

Subhendu Pramanik, Sarat Chatterjee, Rumjhum Banerjee, and Chinmay Chowdhury*

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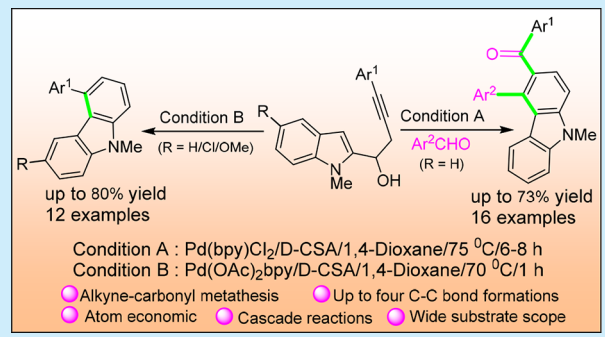
ABSTRACT: An atom-economical direct synthesis of carbazoles having aryl and aryl ketone groups has been achieved through Pd(II)-catalyzed cascade reactions between 1-(indol-2-yl)but-3-yn-1-ols and aldehydes. The reaction proceeds through alkyne−carbonyl metathesis, an uncommon pathway using palladium catalysts, and constitutes a fast intermolecular assembly through four carbon−carbon bond formations in one pot. Absence of the aldehyde substrate resulted in the formation of C4-aryl-substituted carbazoles. The reaction is amenable to the synthesis of biscarbazole derivatives.



Carbazoles are considered to be privileged scaffolds because they form the core structures of numerous bioactive alkaloids, serve as pharmacophores in medicinal chemistry, and constitute important building blocks in organic synthesis.[1] Besides, they are potential electroluminescent materials because of their photorefractive, photoconductive, and light-emitting properties.[2] A few important carbazole derivatives are shown in Figure S1. Attempts to synthesize them began in the late 19th century,[3] but the field continues to be an active area of research.

In the recent past, the synthesis of carbazoles has gained further momentum through the deployment of transition metal catalysts. Among the useful procedures, synthetic pathways for the formation of either a pyrrole ring[4] from diarylamine substrates or a benzene ring[5] from indole substrates are of particular interest. However, the latter strategy appears to be superior because of the easy accessibility of indoles and their notable reactivity at C1 and C2. The intermolecular version of the indole-to-carbazole strategy primarily relies on either Diels−Alder reactions or C−C bond formations through reactions of indoles with alkenes or alkynes.[5a−c] Intramolecular cycloisomerizations of indoles tethered with alkynes have also received substantial interest and provide rapid access to carbazoles in an atom-economical manner.[5d−f] More specifically, the metal-catalyzed cascade reactions of 1-(indol-3/2-yl)alk-3-yn-1-ols[6] proved to be an efficient strategy to deliver carbazoles in high yields. Typically, iodine-mediated[6a] and gold(I)-catalyzed[6b] cyclizations (5-*endo*-*dig*) of 1-(indol-3-yl)alk-3-yn-1-ols are reported to form carbazoles through a Wagner−Meerwein-type 1,2-alkyl shift. On the other hand, 1-(indol-2-yl)alk-3-yn-1-ols are used as potential substrates for benzannulations by the use of costly Au(I),[6c] Au(III),[6d] or Pt(IV)[6e,f] catalysts. Surprisingly, palladium-catalyzed reactions do not appear to have been explored for this purpose.

For some time,[7] we have been interested in palladium-catalyzed reactions of acetylenic substrates tethered with an aldehyde/cyano group for the synthesis of heterocycles of biological interest. We envisioned that palladium(II)-catalyzed intermolecular cascade reactions[8] between 1-(indol-2-yl)but-3-yn-1-ols **1** and aldehydes **2** might deliver carbazole derivatives **3** (Scheme 1a); surprisingly, the unexpected carbazole derivatives **4**, which are of interest in the areas of medicinal[9a,b] and materials sciences,[9c] were obtained instead. Notably, in addition to the classical reaction involving Friedel−Crafts acylation of carbazoles,[10a] a few metal-catalyzed syntheses of carbazoles having aryl ketone substitutions at C1 and C3 are known (Scheme 1b,c).[5b,10b] However, there is no report on the palladium-catalyzed synthesis of carbazoles **4**. Interestingly, the absence of aldehydes **2** in this reaction led to the formation of different carbazole derivatives **5** (Scheme 1a). We report herein the results obtained to date.

Initially, we carried out a model reaction (Table 1) between 1-(indol-2-yl)but-3-yn-1-ol (**1a**) (easily synthesized in two steps from indole-2-carbaldehyde;[11] see the Supporting Information) and 4-nitrobenzaldehyde (**2a**) in refluxing THF using the catalytic system $Pd(OAc)_2$bpy/D-(+)-camphorsulfonic acid (D-CSA) used in our previous study.[7b] However, this

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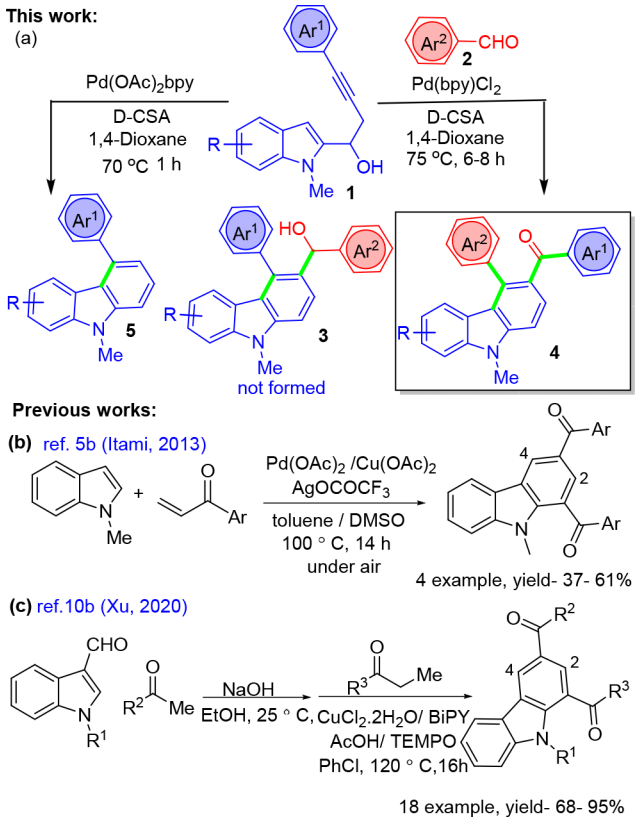
Scheme 1. Our Work and Previous Reports on Carbazole Synthesis

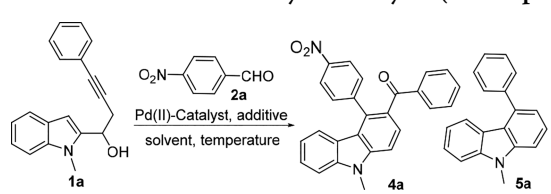


delivered **5a** (75%), a self-cyclized product of **1a**, without involving aldehyde **2a** (Table 1, entry 1). Gratifyingly, replacing the catalyst by $Pd(H_2O)_2bpy(OTf)_2$ and without using any additive allowed the participation of aldehyde **2a**, resulting in the formation of the new product **4a** in 45% yield instead of the expected one (i.e., **3a**, Ar^1 = Ph, Ar^2 = *p*-$NO_2C_6H_4$, R = H; see Scheme 1) together with **5a** in 35% yield (Table 1, entry 2). However, carrying out the same reaction at a higher temperature (i.e., 80 °C) diminished the yields of the products (Table 1, entry 3). Next, we carried out this reaction at 75 °C in 1,4-dioxane using $Pd(bpy)Cl_2$ and D-CSA as the catalyst and additive, respectively (Table 1, entry 4); to our satisfaction, exclusive formation of **4a** took place in 72% yield. Replacing D-CSA with another additive such as *p*-TsOH or AcOH (Table 1, entries 5 and 6) did not deliver **4a**; only **5a** was isolated in moderate yields (50−52%). We therefore persisted with D-CSA as the additive and switched to other solvent systems (Table 1, entries 7−9), including both high-polarity (DME/NMA) and low-polarity (THF) ones. Though THF delivered **4a** in good yield (62%), polar solvents failed to provide **4a**. We therefore concluded that the preferred conditions are those used in entry 4 of Table 1.

We then explored the substrate scope using various 1-(indol-2-yl)but-3-yn-1-ols **1a**−**e** and aryl aldehydes **2a**−**i** (Scheme 2). Initially, we checked the reactivity of **1a** (R^1 = Ph) with different aldehydes **2b**−**i** separately under the optimized reaction conditions. A strong electron-withdrawing group (EWG) (viz. R^2 = CF_3) at the *para* position of the phenyl ring of aldehyde **2b** facilitated the reaction with **1a**, resulting in the formation of **4b** within 6 h in 73% yield, comparable to that of **4a**. However, a moderate EWG (viz., R^2 = Br) as in substrate **2c** reduced the yield of the product **4c** considerably (53%). On the other hand, a strong electron-donating group (EDG) (viz., R^2 = OMe) at the *para* position as in **2d** afforded the product **4d** in a lower yield of 62% in 7 h, while the incorporation of two methoxy groups as in **2e** slightly enhanced the yield of the product **4e** compared with **4d** (64%). A moderate EDG like Me (at the *ortho* position of aldehyde **2f**) also gave the product **4f** in a lower yield (59%). Furthermore, reactions of **1a** with benzaldehyde (**2g**), naphthaldehyde (**2h**), and 2-formylthiophene (**2i**) furnished the products **4g**, **4h**, and **4i**, respectively, within 6−8 h in moderate yields (40−50%).

Next, we studied the reactivity of acetylene **1b** having an EDG (R^1 = OMe) on the phenyl ring attached to the acetylenic carbon with aldehydes **2a** (R^2 = NO_2) and **2b** (R^2 = CF_3) having an EWG at the *para* position. Gratifyingly, these reactions afforded products **4j** and **4k**, respectively, within 6−7

Table 1. Optimization of the Reaction Conditions for 3-Benzoyl-9-methyl-4-(4-nitrophenyl)-9*H*-carbazole (4a)[a]



					yield (%)[b]	
entry	catalyst	additive	solvent	temp. (°C)	**4a**	**5a**
1	$Pd(OAc)_2bpy$	D-CSA	THF	70	0	75
2	$Pd(H_2O)_2bpy(OTf)_2$	–	1,4-dioxane	70	45	35
3	$Pd(H_2O)_2bpy(OTf)_2$	–	1,4-dioxane	80	40	30
4	$Pd(bpy)Cl_2$	D-CSA	1,4-dioxane	75	72	0
5	$Pd(bpy)Cl_2$	*p*-TsOH	1,4-dioxane	70	0	52
6	$Pd(bpy)Cl_2$	AcOH	1,4-dioxane	75	0	50
7	$Pd(bpy)Cl_2$	D-CSA	DME	75	nr	–
8	$Pd(bpy)Cl_2$	D-CSA	NMA	75	nr	–
9	$Pd(bpy)Cl_2$	D-CSA	THF	70	62	0

[a]Reaction conditions: **1a** (0.18 mmol), **2a** (0.27 mmol, 1.5 equiv), Pd catalyst (10 mol %), and D-CSA (1.5 equiv) in the indicated solvent (3 mL) heated at the indicated temperature. [b]Isolated yields.

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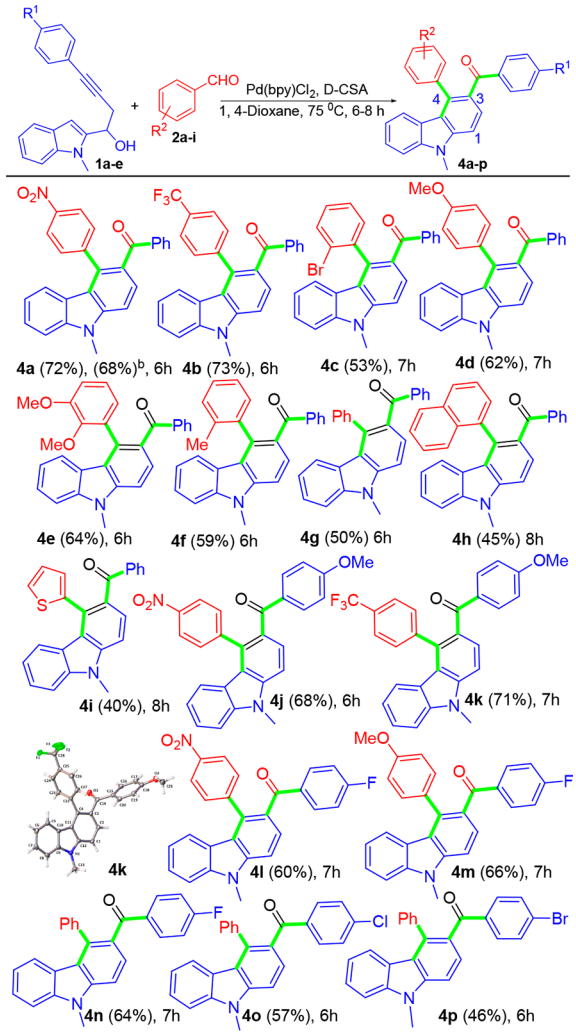
Scheme 2. Synthesis of 4-Aryl-3-(arylcarbonyl)carbazoles 4[a]



[a]Reaction conditions: **1** (0.18 mmol), **2** (0.27 mmol, 1.5 equiv), catalyst (10 mol %), and D-CSA (1.5 equiv) in 1,4-dioxane (3 mL) heated at 75 °C. Isolated yields are shown. [b]1.0 mmol-scale reaction (see p S22 in the Supporting Information).

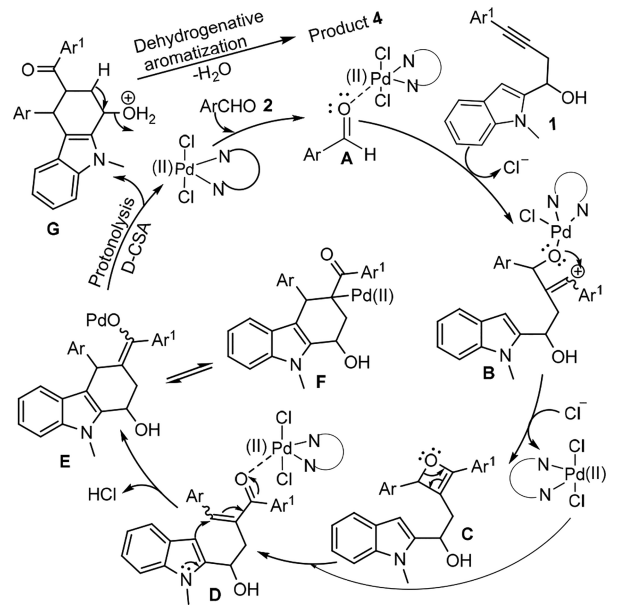
h in very good yields (68−71%). Substrate **1c** carrying an EWG (R^1 = F) also underwent reactions with *p*-nitrobenzaldehyde (**2a**), *p*-methoxybenzaldehyde (**2d**), and benzaldehyde (**2g**) to furnish the products **4l**, **4m**, and **4n**, respectively, within 7 h, albeit in somewhat lower yields (60−66%) compared with **4j** and **4k**.

Furthermore, replacing the fluoro group of acetylenic substrate **1c** by either chloro or bromo and allowing the resulting substrate (**1d** or **1e**) to undergo the reaction with benzaldehyde (**2g**) led to the generation of the desired product (**4o** or **4p**) within 6 h in moderate yield (46−57%).

Besides, we used an aliphatic aldehyde (EtCHO) instead of the aryl one (**2**) but obtained no such product **4.** In addition, the incorporation of an aliphatic group (i.e., Et) in place of the phenyl ring attached to the acetylenic carbon of substrate **1a** failed to deliver any of the desired product. Furthermore, the replacement of the *N*-methyl group of substrate **1a** by *N*-H also proved to be unsuccessful, showing the limitations of the reaction.

On the basis of the known palladium chemistry and alkyne−carbonyl metathesis reaction,[12] we propose a plausible reaction mechanism (Scheme 3). Initially, the carbonyl group of substrate **2** is activated by the palladium catalyst [$Pd(bpy)Cl_2$]

Scheme 3. Plausible Reaction Mechanism of Products 4



through a Lewis acid−base-type interaction[13] (species A) and undergoes nucleophilic attack by the alkyne moiety of **1**. This generates transient vinylic cation intermediate **B**, which is readily transformed into oxetene intermediate **C** with the liberation of the palladium(II) catalyst. Subsequently, formal (2 + 2) cycloreversion of the oxetene ring of **C** leads to the formation of vinylic ketone intermediate **D**, which undergoes an intramolecular Michael addition. The palladium catalyst[14,15] possibly activates the carbonyl group of species **D** for this purpose, resulting in the formation of intermediate **E** or **F**.[16] Thereafter protonolysis[7a] of the palladated intermediate **E** or **F** by D-CSA produces species **G** along with regeneration of the palladium(II) catalyst. Finally, dehydration and dehydrogenative aromatization of species **G** furnishes carbazole **4**.

Encouraged by the formation of carbazole **5a** (Table 1, entries 1−3) via self-cyclization of the acetylenic substrate **1a**, we tried to find out the optimized reaction conditions. Toward this objective, we set out to execute a model reaction on **1a** by changing the reaction parameters; some of the results are presented in Table S1. The best result was obtained when the reaction of **1a** was carried out at 70 °C for 1 h in 1,4-dioxane using $Pd(OAc)_2$bpy (5 mol %) and D-CSA (1.5 equiv), producing **5a** in 80% yield (Table S1, entry 6).

We next applied these conditions (Table S1, entry 6) on a variety of substrates **1a−l** (Scheme 4). This showed that incorporation of an EWG (viz., R = Cl) at C5 of the benzene ring in the indole moiety of the substrate as in **1f** reduced the product yield (64% for **5b**) compared with that obtained using an EDG (viz., R = OMe) as in **1g** (73% for **5c**). The lower yield of **5b** is ascribed to the electron-withdrawing effect of the chloro group, which induces delocalization of the electrons from the nitrogen atom of **1f** toward the benzene ring, thereby reducing the nucleophilicity of C3 of the indole ring to undergo cyclization.

We also studied the effects of different functional groups (R^1) at the *para* position of the phenyl ring of substrates **1**, as shown in Scheme 4. This showed that substrates (**1h**/**1i** or **1j**/

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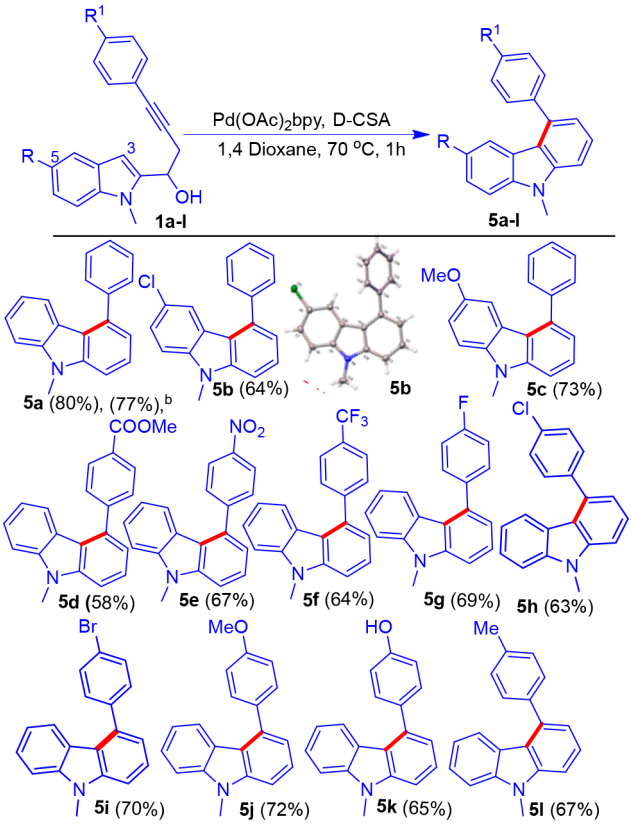
Scheme 4. Synthesis of 9-Methyl-4-aryl-9*H*-carbazoles 5a–l[a]



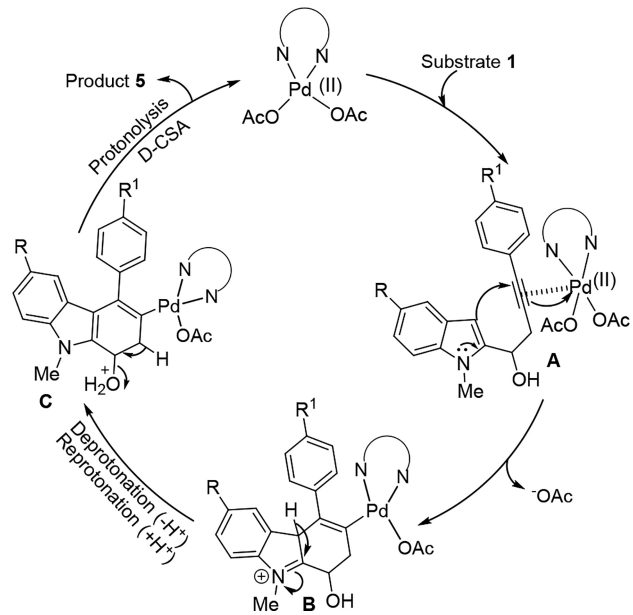
[a]Reaction conditions: **1** (0.18 mmol), Pd catalyst (5 mol %), and D-CSA (1.5 equiv) in 1,4-dioxane (2 mL) at 70 °C. Isolated yields are shown. [b]1.0 mmol-scale reaction (see p S29 in the Supporting Information).

1c/**1d**/**1e**) containing either a strong (R^1 = COOMe/NO_2) or moderate (R^1 = CF_3/F/Cl/Br) EWG hindered the reaction to some extent, delivering the products **5d–i** in good yields (58–70%). In addition, substrates (**1b**/**1k** or **1l**) containing either a strong (R^1 = OMe/OH) or moderate (R^1 = Me) EDG also facilitated the reaction, as is evident from the formation of products **5j**/**5k** or **5l** in 65–72% yield.

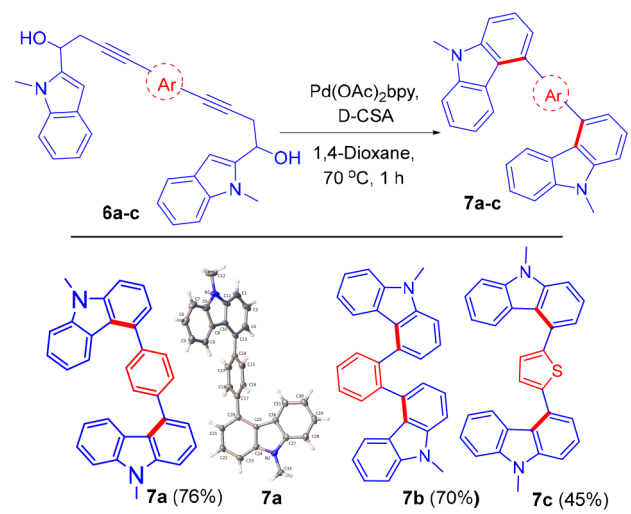
To explain the formation of products **5**, a plausible reaction mechanism is depicted in Scheme 5. Initially, $Pd(OAc)_2$bpy acting as a Lewis acid activates the triple bond[7c] of substrate **1** to generate species **A**. The triple bond of **A** may undergo intramolecular nucleophilic attack (*6-endo-dig*) by C3 of the indole ring to form palladated intermediate **B**. Subsequent deprotonation at C3 of the indole ring of **B** followed by reprotonation of the hydroxyl group could lead to transient intermediate **C**, dehydration and protonolysis[7b] of which forms carbazole **5** with regeneration of the palladium catalyst.

Biscarbazole derivatives serve as core structures of many bioactive alkaloids.[4a] For their one-pot synthesis, diacetylenic substrates **6a–c** (see the Supporting Information) were exposed to the optimized reaction conditions (Table S1, entry 6); gratifyingly, bis-benzoannulated products **7a–c** having two carbazole units[17] were found to be formed in 45–76% yield (Scheme 6). Thus, this method is also applicable for the one-pot synthesis of important molecules having polycarbazole units, which are of importance in optoelectronics.[18]

Scheme 5. Plausible Reaction Mechanism of Products 5



Scheme 6. Synthesis of Biscarbazole Derivatives 7[a]



[a]Reaction conditions: **6** (0.11 mmol), catalyst (10 mol %), and D-CSA (3 equiv) in 1,4-dioxane (2 mL) at 70 °C. Isolated yields are shown.

In conclusion, a Pd(II)-catalyzed cascade reaction of 1-(indol-2-yl)but-3-yn-1-ols **1** and aryl aldehydes **2** provides easy access to 3,4-disubstituted carbazoles **4**. This substitution pattern is difficult to obtain by classical routes such as the Fischer–Borsche synthesis and the Graebe–Ullmann synthesis. The method constitutes a fast intermolecular assembly involving the formation of four new C–C bonds in one pot. Although alkyne–carbonyl metathesis is usually carried out by coinage-metal catalysts,[12] this appears to be the first report of the same metathesis promoted by palladium catalysis. Omission of aldehyde **2** from the reaction led to the development of a general synthesis of carbazoles **5**. The reaction is also amenable to the synthesis of novel biscabazole derivatives.

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■ ASSOCIATED CONTENT

Supporting Information

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

Accession Codes

CCDC 2132274−2132278 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, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to the memory of Nitya G. Kundu, former professor and head, Department of Organic Chemistry, Indian Association for the Cultivation of Science, Kolkata, India.

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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

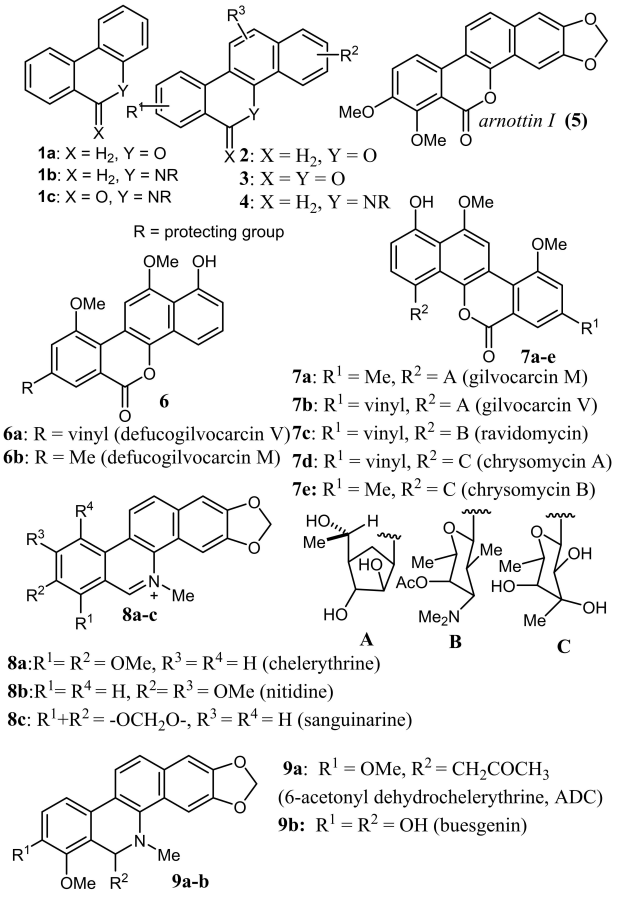


Figure 1. Biologically active dibenzo[*c,h*]chromen-6-ones 5–7, benzo[*c*]phenanthridines 8 and 5,6-dihydro- benzo[*c*]phenanthridines 9.

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

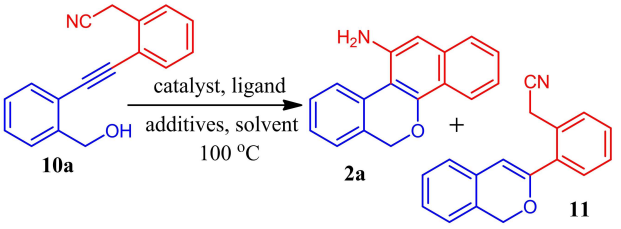
2.1. Synthesis of 6*H*-dibenzo[*c,h*]chromene derivatives 2/2′

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.

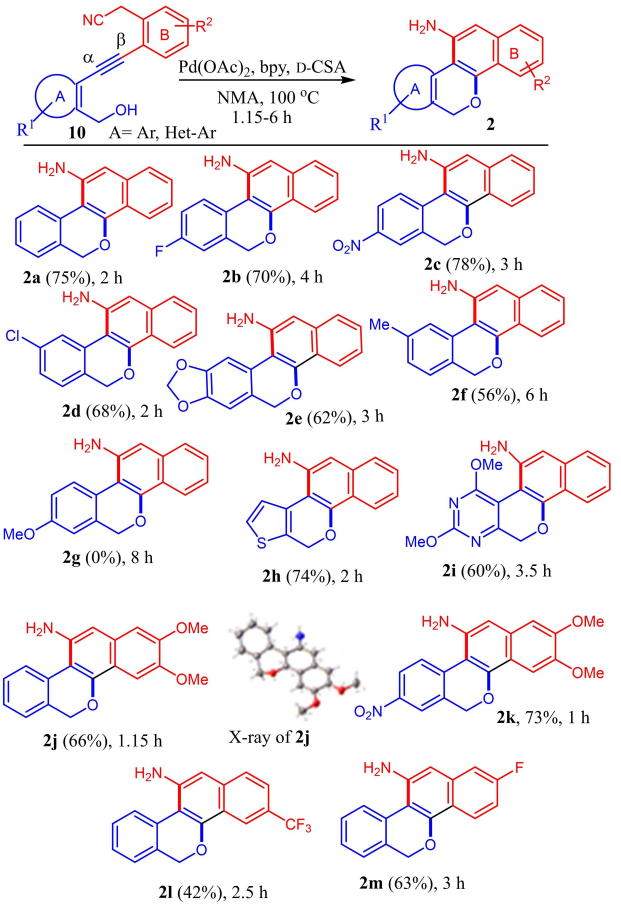
On the other hand, removal of D-CSA from the reaction did not produce **2a** at all, proving its necessity in this reaction (Table 1, entry 9), while carrying out this reaction using D-CSA alone was also unsuccessful (Table 1, entry 10). Thus reaction conditions of entry 5 of Table 1 appeared to be optimal.

Table 1. Optimization of the reaction conditions for 6*H*-dibenzo[*c*,*h*]chromen-11-amine **2 a**.[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: **10 a** (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 **10 a** 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.

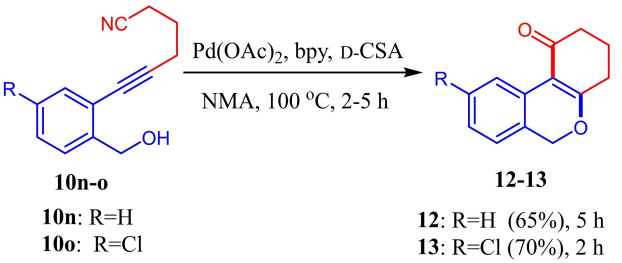
Scheme 1. Palladium-catalyzed synthesis of 11-amino-6*H*-dibenzo[*c*,*h*]chromenes **2**.[a,b]

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 **2 a–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 **2 b–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 (**2 f**), though the presence of two EDGs at *meta* and *para* positions (viz., R^1 = –OCH_2O–) delivered the product **2 e** within 3 h. Notably, placement of a strong electron donating group (viz., OMe) at *para* position did not furnish any desired product **2 g** 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., **2 h**/**2 i**) 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 **2 j** 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 **2 k** (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 (**2 l** or **2 m**) 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**.

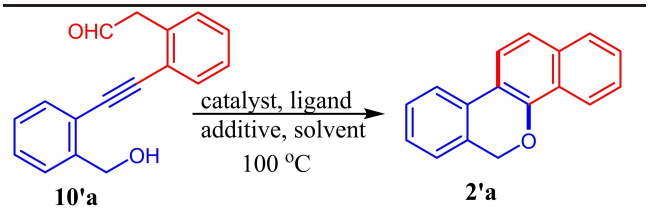
2.2. Synthesis of 6*H*-dibenzo[*c,h*]chromenes 2′

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]



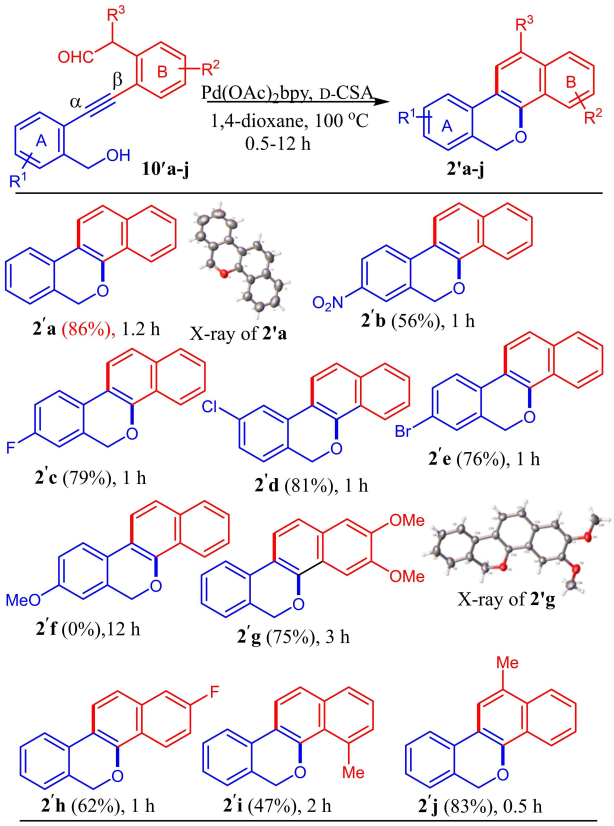
10'a **2'a**

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

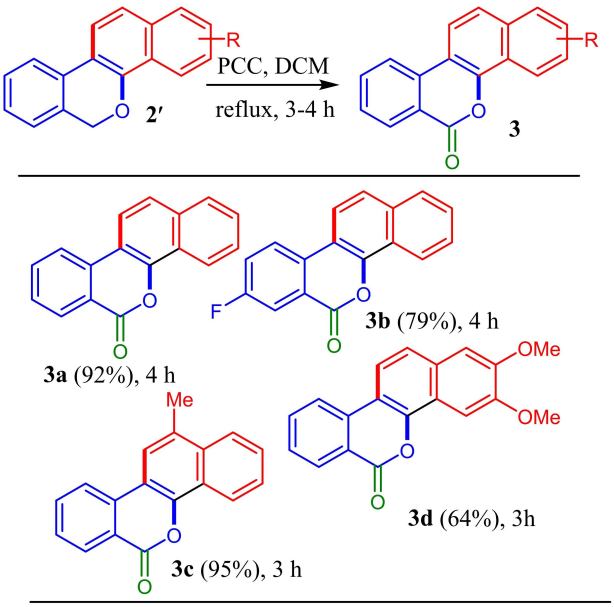


[a] Reaction conditions; **10′** (0.2 mmol), Pd(OAc)2bpy (5 mol %) and D-CSA (1.5 equiv. in 1,4-dioxane (2 mL) at 100 °C under argon atmosphere.
[b] Yield of the isolated pure products.

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).



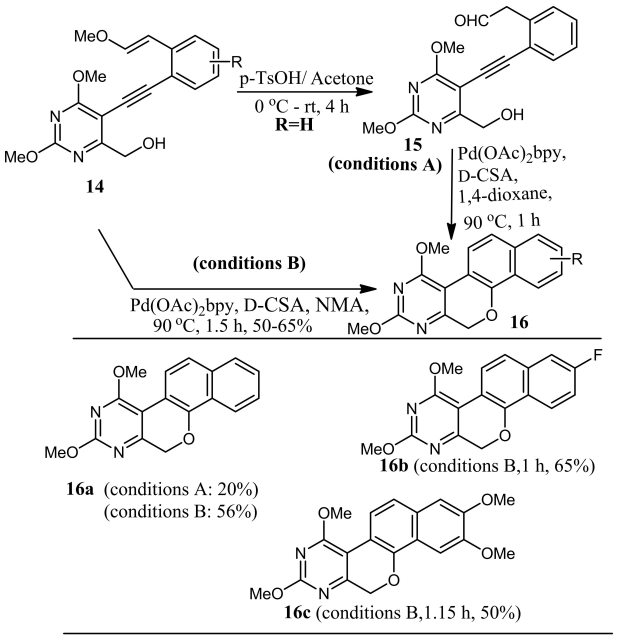
[a] Reaction conditons: A mixture of **2′** (0.086 mmol) and PCC (1.5 equiv.) in DCM (2 mL) was refluxed under argon atmosphere.
[b] Yield of the isolated pure product.

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

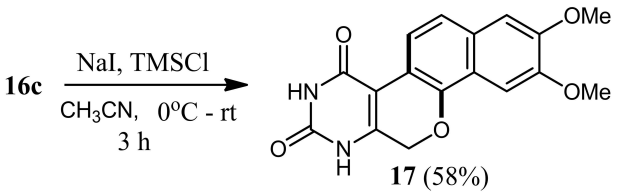
2.4. Synthesis of Pyrimidine (16) and Uracil (17) Derivatives

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**.



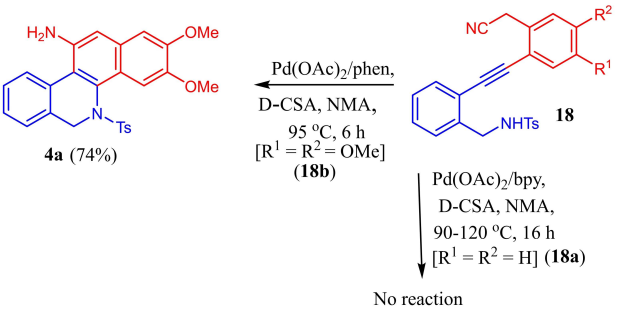
Scheme 6. Conversion of **16c** to uracil derivative **17**.

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.

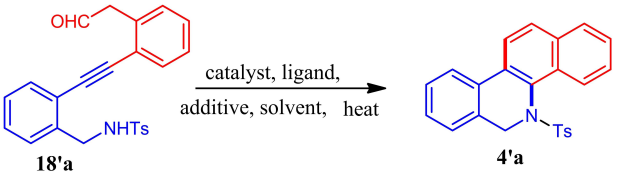
We then planned to modify the structure of substrate **18** by replacing its cyano group with a formyl one. Towards this, the substrate **18′a** prepared in few



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

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

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	$Pd(OAc)_2bpy$	-	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	**$Pd(OAc)_2bpy$**	-	**THF**	Reflux	**1.3**	**78**
5	$Pd(OAc)_2bpy$	-	NMA	100	2.5	41
6	$Pd(OAc)_2phen$	-	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.

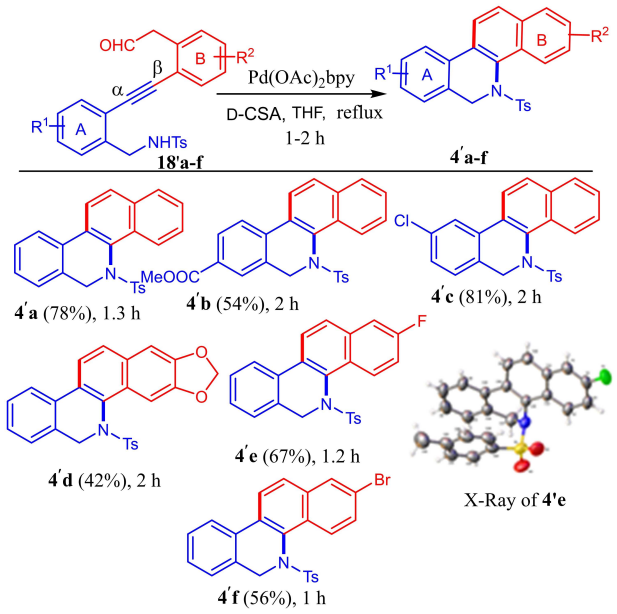
the use of catalyst and ligand separately instead of preformed $Pd(OAc)_2bpy$ was not helpful (Table 3, entry 2). But switching to a less polar solvent (i.e., THF) reduced the reaction time to 2 h and improved the yield to 62% (Table 3, entry 3). Use of the preformed catalyst $Pd(OAc)_2bpy$ improved 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

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.

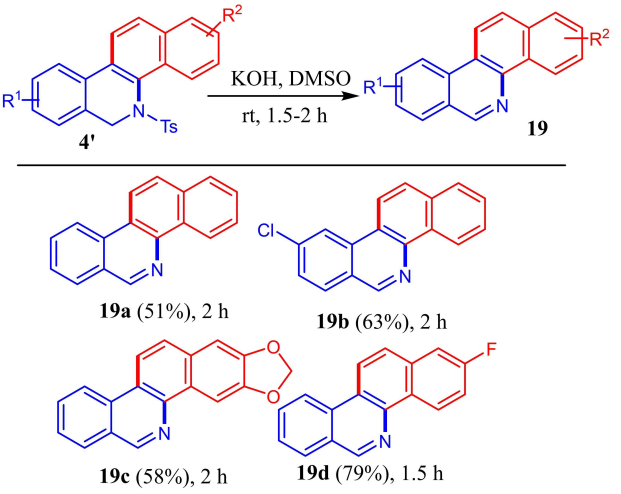


[a] Reactions conditons: **18′**(0.2 mmol), Pd(OAc)2bpy (5 mol %) and D-CSa (1.5 equiv.) in refluxing THF (2 mL) under argon atmosphere.
[b] Yield of the isolated pure products.

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–).

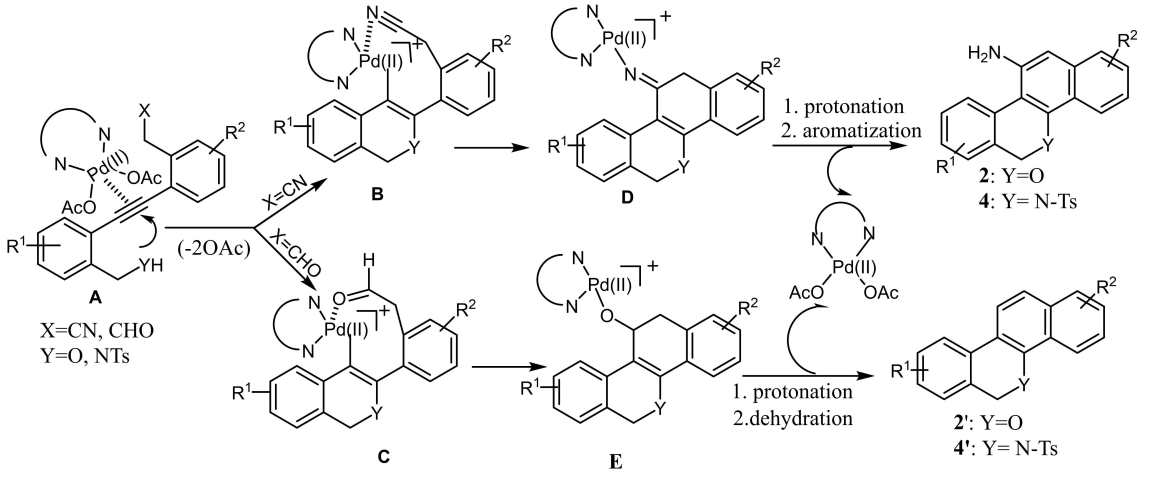


[a] Reaction condition: A mixture of **4′**(0.13 mmol) and KOH (5 equiv.) in DMSO was stirred at room temperature under argon atmosphere.
[b] Yield of the isolated product.

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

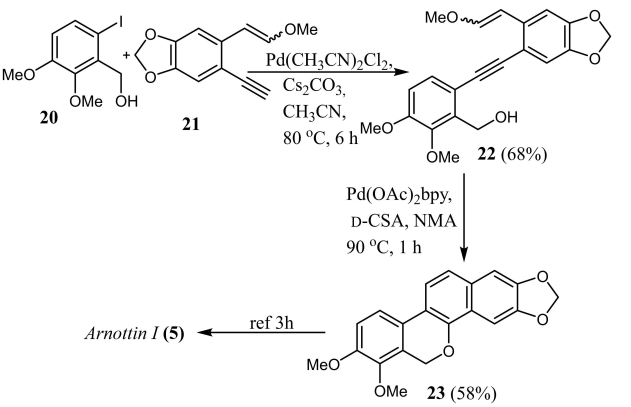


Scheme 10. Plausible mechanism for the formation of products **2/4** and **2′/4′**.

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 4a

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

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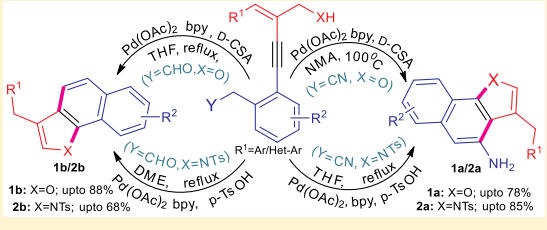
Supporting Information

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



INTRODUCTION

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

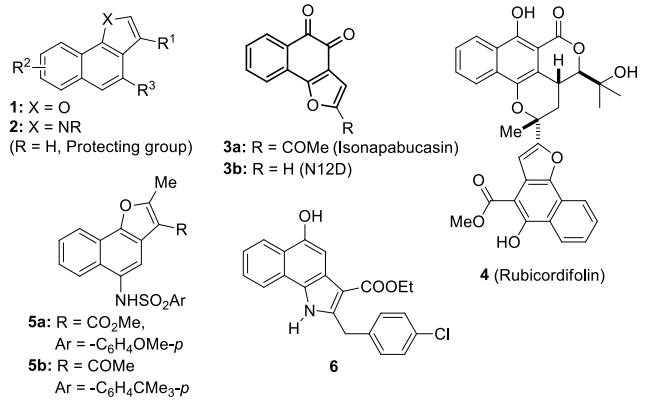


Figure 1. Few biologically active naphtho[1,2-*b*]furans and benzo[*g*]-indoles.

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

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

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

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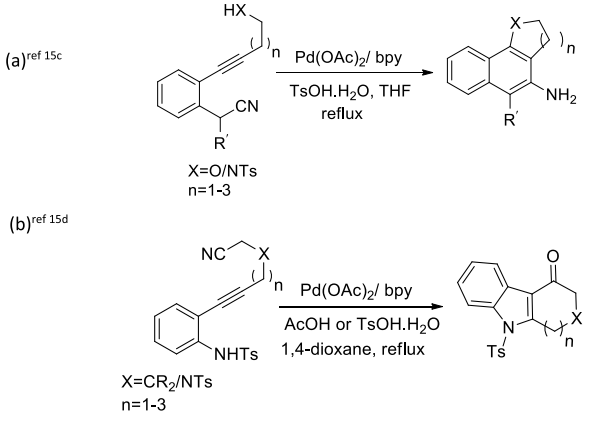
method using readily available and cheap substrates remains a challenge.

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

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

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



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

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

RESULTS AND DISCUSSION

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

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

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

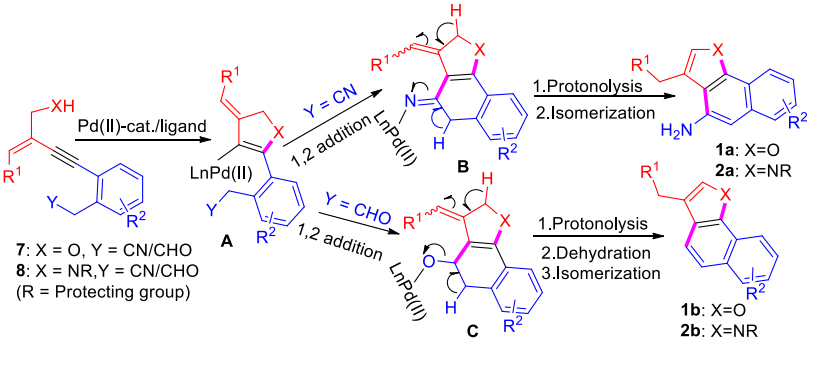


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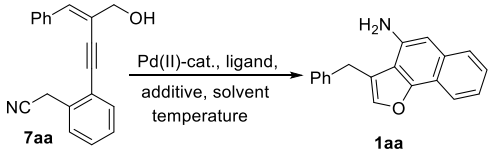
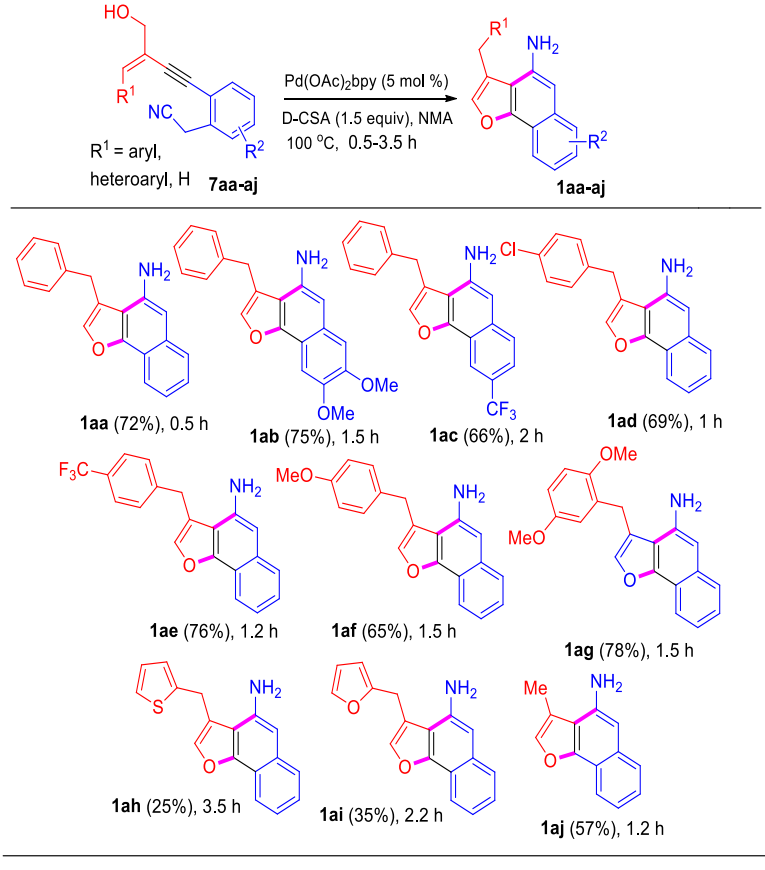
Table 1. Optimization of Reaction Conditions for the Synthesis of Naphtho[1,2-*b*]furan 1aa[a,b]



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

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

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



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

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

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

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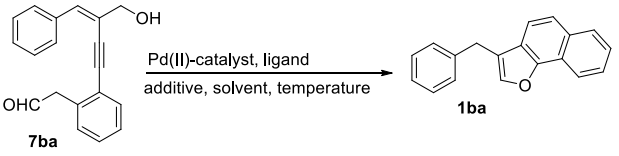
Table 2. Optimization of Reaction Conditions for the Synthesis of Naphtho[1,2-*b*]furan 1ba[a]



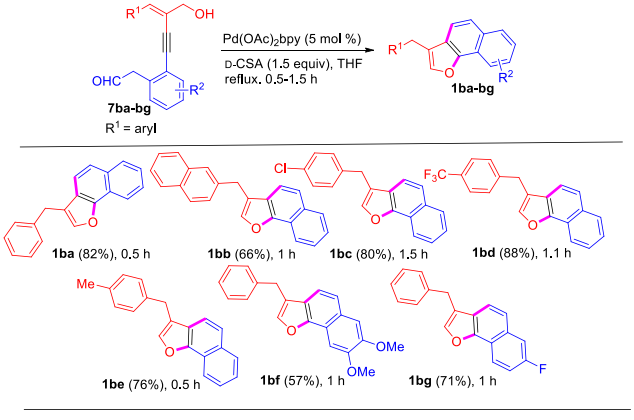
entry	catalyst	ligand	additive	solvent	temp (°C)	time (h)	yield (%)
1	$Pd(OAc)_2$bpy		D-CSA	NMA	100	3	42
2.	$Pd(OAc)_2$bpy		D-CSA	1,4-dioxane	100	1	80
3.	$Pd(OAc)_2$	bpy	D-CSA	1,4-dioxane	100	2	31
4.	$Pd(OAc)_2$bpy		D-CSA	THF	reflux	1	82
5.	$Pd(OAc)_2$	bpy	D-CSA	THF	reflux	4	42
6.	$Pd(OAc)_2$bpy		AcOH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

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

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

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

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



[a]Reaction conditions: **7ba** (0.18 mmol), $Pd(OAc)_2$bpy (5 mol %), and D-CSA (1.5 equiv) in refluxing THF (3 mL) under argon atmosphere.

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

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

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

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

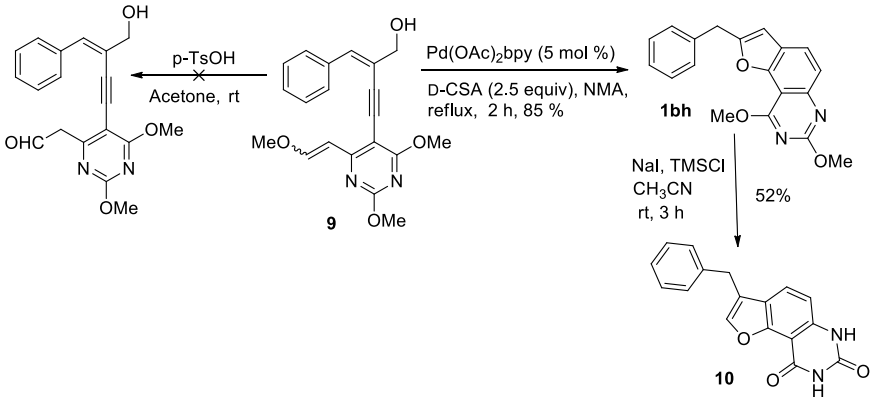
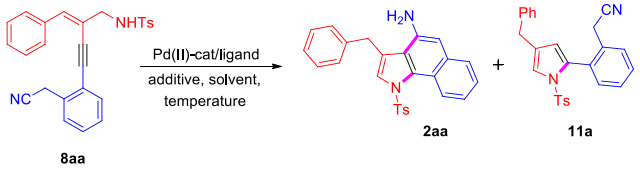


Table 3. Optimization of Reaction Conditions for the Synthesis of 4-Amino Benzo[*g*]indole 2aa[a]



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

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

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

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

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

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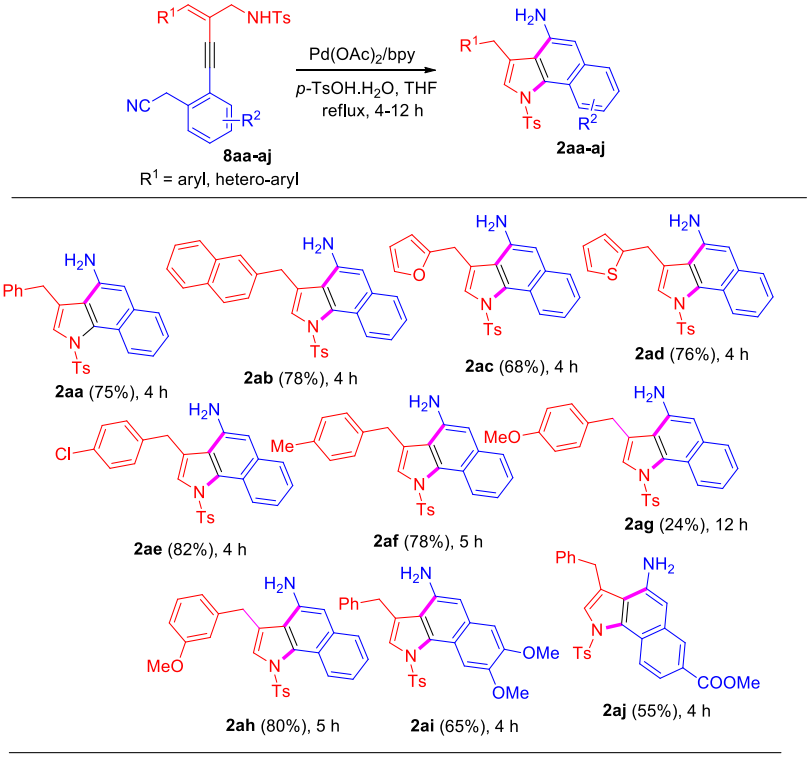
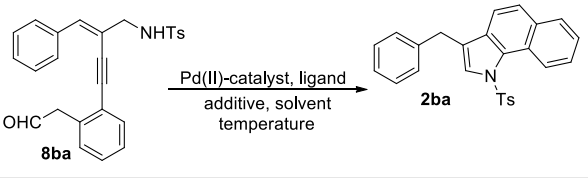
Scheme 6. Synthesis of 4-Amino Benzo[*g*]indole Derivatives 2aa–aj[a,b]



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

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



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

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

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

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

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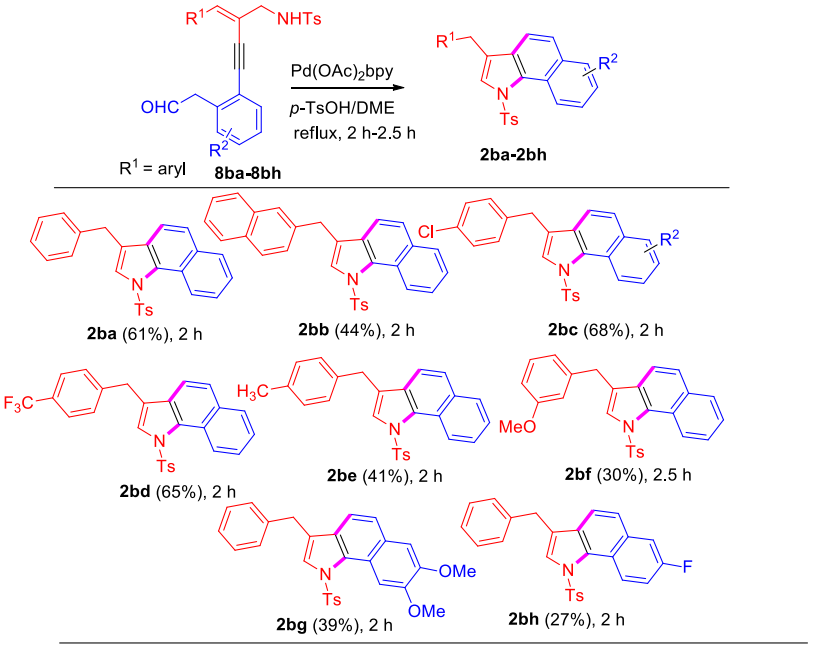
Scheme 7. Synthesis of Benzo[*g*]indole Derivatives 2ba–bh[a]

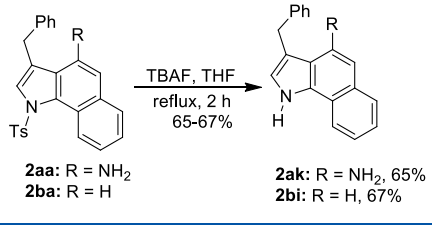


[a]Reaction conditions: **8a** (0.23 mmol), $Pd(OAc)_2$bpy (5 mol %), and *p*-TsOH·H_2O (1.5 equiv) were refluxed in DME (3 mL) under argon atmosphere.

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

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

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



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

EXPERIMENTAL SECTION

General. All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60–80 °C. Dichloromethane (DCM) was dried over phosphorous pentoxide, distilled, and stored over 3 Å molecular sieves in a sealed container. 1,4-Dioxane was distilled over sodium and benzophenone. Commercial grade dry dimethylformamide (DMF), dimethylacetamide (DMA), *N*-methylacetamide (NMA), and 1,2-dimethoxyethane (DME) were used as solvents. All reactions were carried out under argon atmosphere and anhydrous conditions unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} aluminum TLC sheets. Visualization of the developed chromatogram was performed by UV absorbance or iodine exposure. For purification, column chromatography was performed using 100–200 mesh silica gel. ^{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 singlet (s), doublet (d), double doublet (dd), triplet (t), triple doublet (td), quartet (q), multiplet (m), and broad (br), apparent (app). All ^{13}C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using electrospray ionization (ESI) time-of-flight or electron ionization (EI) mode.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

■ ASSOCIATED CONTENT

Supporting Information

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

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

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

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

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

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

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

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

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Contents

Summary

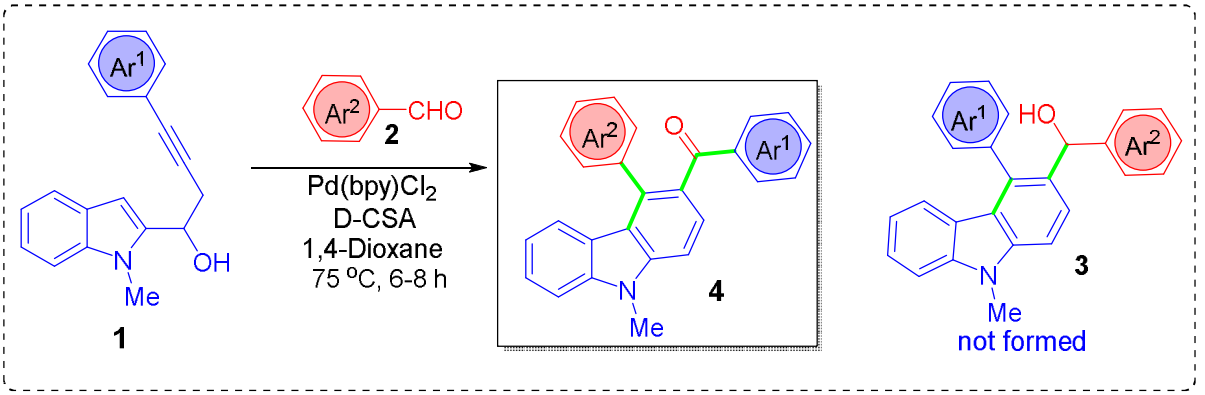
Development of methodologies for the synthesis of biologically important heterocyclic scaffolds.

The Thesis entitled "*Development of methodologies for the synthesis of biologically important heterocyclic scaffolds*" is divided into three chapters, each chapter consists of two parts (i.e., Part I & Part II). Part I of each chapter deals with a general survey of the importance and previous syntheses of compounds interest to us. Whereas Part II deals with the detailed methodology developed along with optimization study, experimental procedure and spectral data of the synthesized compounds. The following description summarizes the present work as detailed in part II of each chapter.

Chapter 1

Palladium-Catalyzed Benzannulations of 1-(Indol-2-yl)but-3-yn-1- ols: Easy Access to Functionalized Carbazoles

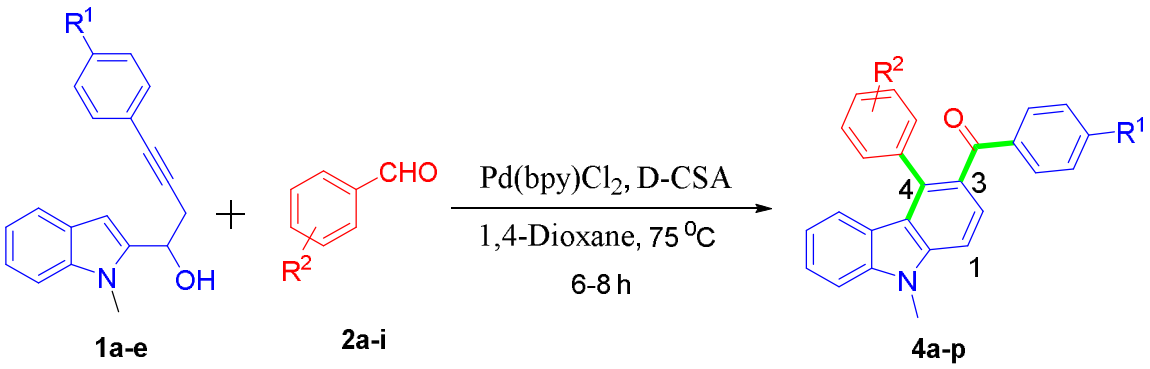
In the first chapter, an atom-economical direct synthesis of carbazoles having aryl and aryl ketone groups through Pd(II)-catalyzed cascade reactions between 1-(indol-2-yl)but-3-yn-1-ols **1** and aldehydes **2** has been discussed (Scheme 1).

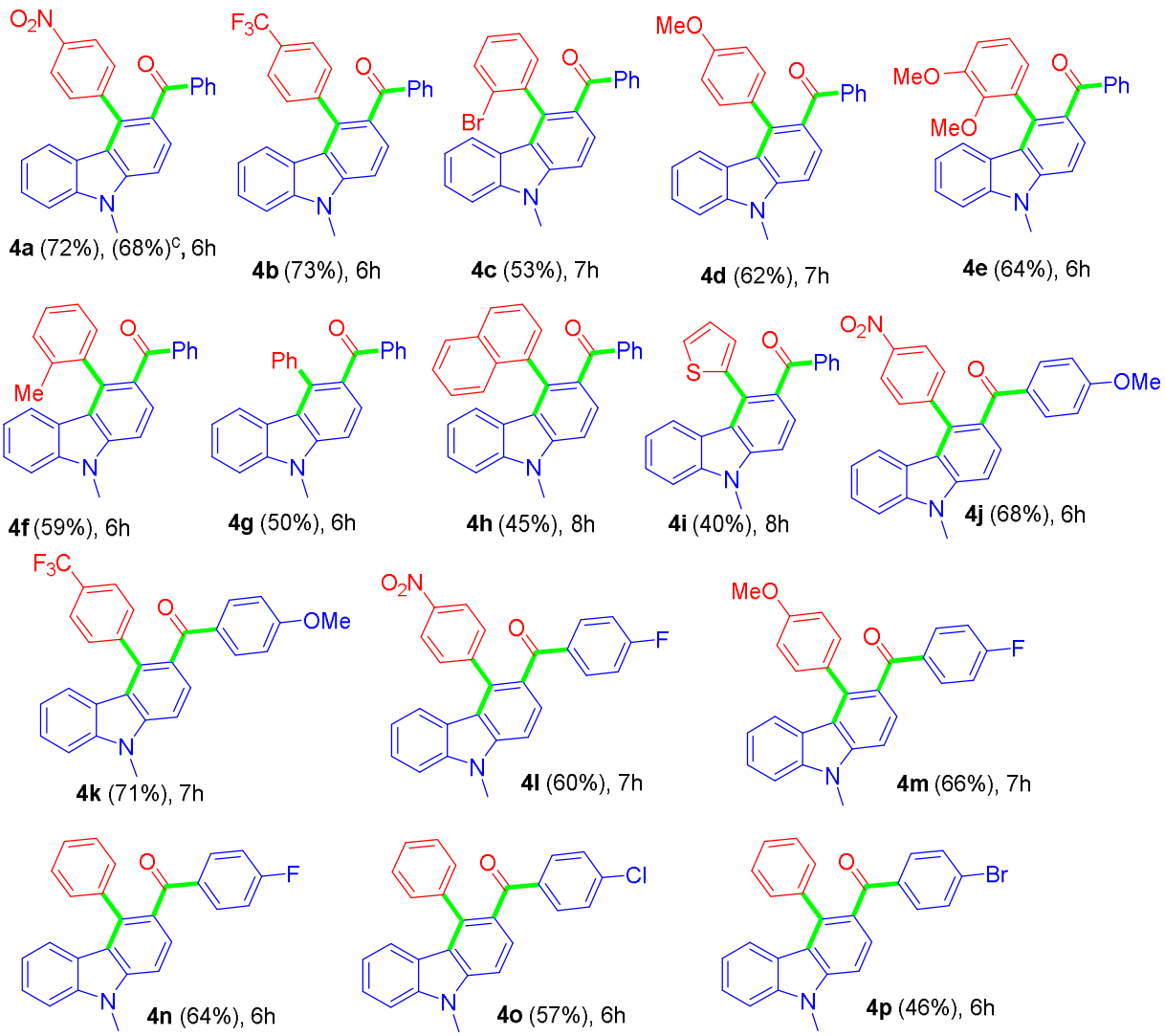


Scheme 1. Synthesis of carbazoles **4** having aryl and aryl ketone groups

Towards this objective, a series of reaction was carried out with variation of reaction parameter such as catalyst, solvent, additive, temperature for a model reaction between **1a** (Ar^1 = Ph) and aldehyde **2a** (Ar^2 = -$C_6H_4NO_2$-*p*). From this reaction product **4a** (Ar^1 = Ph, Ar^2 = -$C_6H_4NO_2$-*p*) was isolated instead of **3a** (Ar^1 = Ph, Ar^2 = -$C_6H_4NO_2$-*p*). However, the best result for the formation of **4a** was obtained when the reaction of **1a** was carried out with **2a** (Ar^2 = -$C_6H_4NO_2$-*p*) at 75 ^oC for 6 h in 1,4-dioxane using Pd(bpy)Cl_2 (10 mol %) and D-CSA (1.5 equiv.), producing **4a** in 72% yield. We next applied the optimized reaction conditions on a variety of substrates such as **1a-e** and **2a-i** to afford a range of products **4a-p** in moderate to very good yields (Scheme 2).

Scheme 2. Synthesis of 4-Aryl-3-arylcarbonyl-carbazoles **4**[a,b]





[a]Reaction Condition: **1**(0.18 mmol), **2** (0.27, 1.5 equiv), catalyst (10 mol %), and D-CSA (1.5 eqiv) in 3 mL solvent heated at temperature (as mentioned in table) under argon atmosphere.

[b]Yield of the isolated pure products. [c]1.0 mmol scale reaction.

The structure of the products were unambiguously deduced by spectral (^{1}H and^{13}C NMR, Mass and IR Spectra), analytical data and X-ray crystallography. In ^{1}H NMR, the protons for the methyl group attached to nitrogen atom of carbazole appears 3.44-3.95 ppm as singlet as expected, whereas remaining aromatic protons appears in the range 6.66-8.26 ppm. In ^{13}C NMR, carbonyl carbon appears in range 196.4-197.8 ppm and the carbon of the N-Me group appears in the range 29.64-29.71 ppm and other carbons appeared at appropriate positions. In addition, in IR spectra, carbonyl (C = O) stretching vibration band appears at 1661cm^{-1}.

Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of the compounds **4d**, **4e**, and **4k**.

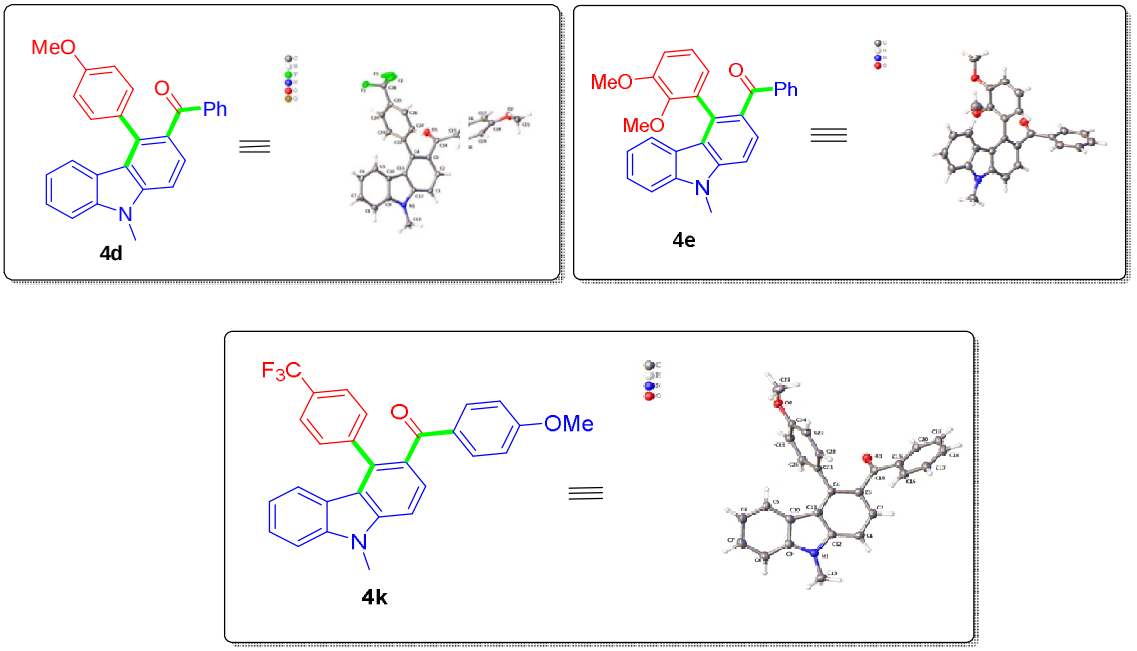
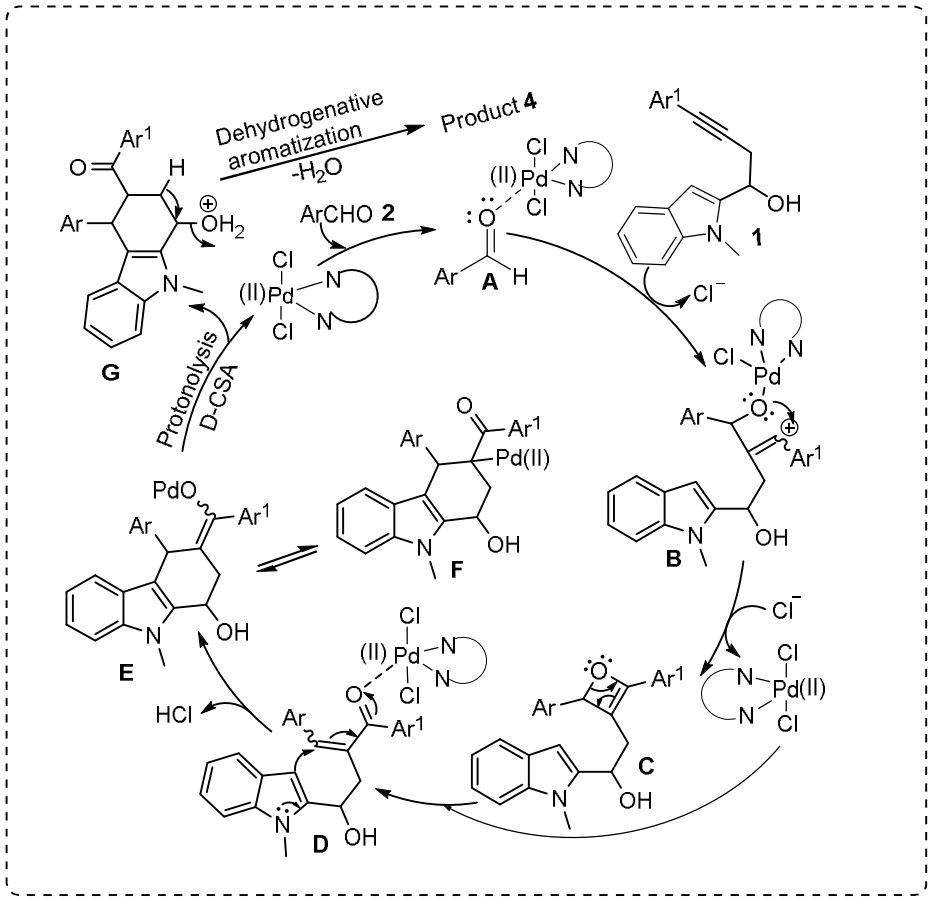


Figure 1. ORTEP Diagram (thermal ellipsoid plot) of Compounds **4d**, **4e** and **4k** (drawn at 50% probability level).

A plausible reaction mechanism outlined in Scheme 3 is proposed to explain the product formation. Initially, carbonyl group of substrate **2** is activated by the palladium catalyst [Pd(bpy)Cl_2] through Lewis acid-base type interaction (species **A**) to undergo a

nucleophilic attack by the alkyne moiety of **1**. This generates a transient vinylic cation intermediate **B** which readily transforms to an oxetene intermediate **C** with the liberation of the palladium(II) catalyst. Subsequently, a formal (2 + 2) cyclo-reversion of the oxetene ring of **C** leads to the formation of the vinylic ketone intermediate **D** which undergoes an intramolecular Michael addition. The palladium catalyst possibly activates the carbonyl group of species **D** for this purpose, resulting in the formation of intermediate **E** or **F**. Thereafter protonolysis of the palladated intermediate (**E** or **F**) by D-CSA produces species **G** along with regeneration of palladium(II) catalyst. Finally, dehydration and dehydrogenative aromatization of species **G** would furnish carbazole **4**.

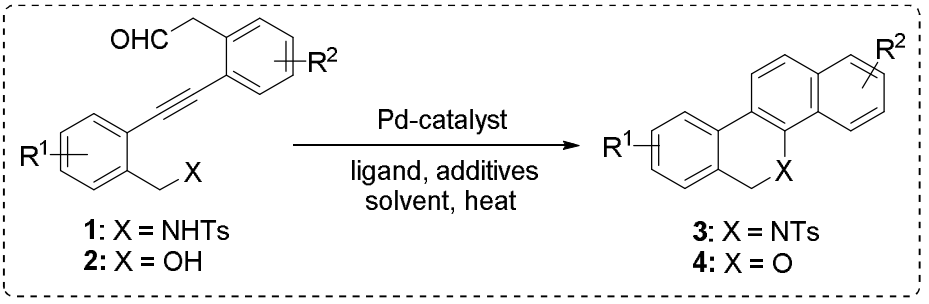


Scheme 3. A plausible reaction mechanism for the formations of products **4**

Chapter 2

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*

The second chapter deals with a study for the synthesis of 5,6-dihydro-benzo[*c*]phenanthridines **3** and 6*H*-dibenzo[*c,h*]chromenes **4** from the starting substrates 4-Methyl-N-(2-((2-(2-oxoethyl)phenyl)ethynyl)benzyl)benzenesulfonamide derivatives **1** (X = NHTs) and 2-(2-((2-(Hydroxymethyl)phenyl)ethynyl)phenyl)acetaldehyde derivatives **2** (X = OH), respectively (Scheme 1) via palladium catalyzed *6-endo-dig* cyclization followed by an intramolecular 1,2-nucleophilic addition onto the aldehyde group and subsequent dehydration.

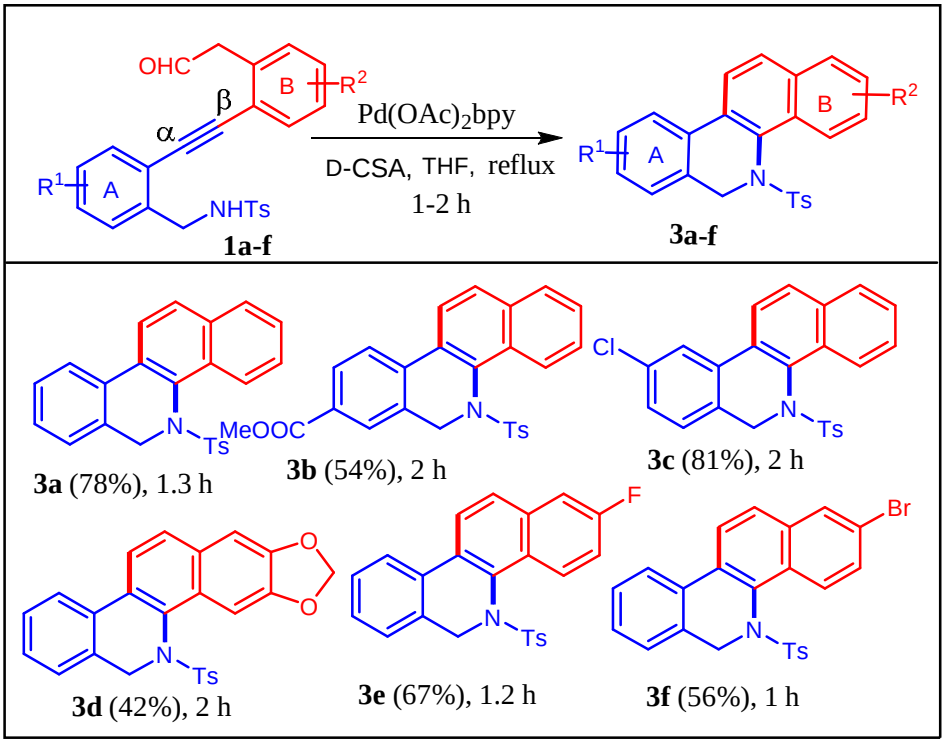


Scheme 1. Synthesis of 5,6-dihydro-benzo[*c*]phenanthridines **3** and 6*H*-dibenzo[*c,h*]chromenes **4**

For the synthesis of compound **3**, initially, the reaction was optimized using 4-Methyl-N-(2-((2-(2-oxoethyl)phenyl)ethynyl)benzyl)benzenesulfonamide **1a** ($R^1 = R^2 = H$, X = NHTs) as starting substrate with variation of reaction parameter such as catalyst, solvent, additive, temperature. It was however found that the corresponding desired product **3a** ($R^1 = R^2 = H$, X = NTs) can be achieved in highest yield (78%) when the starting material **1a** (0.2 mmol) was heated (1.3 h) in refluxing THF (2 mL) in the presence of $Pd(OAc)_2$bpy (5 mol %) and D-CSA (1.5 equiv). The optimized reaction conditions thus obtained was then applied

on a diversely substituted acetylenic substrates **1** to assess the scope and limitations of this reaction (Scheme 2).

Scheme 2. Palladium-catalyzed synthesis of N-tosyl-5,6-dihydrobenzo[*c*]phenanthridines **3**[a,b]



[a]Reaction conditions: **1** (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 product.

The structure of the products were unambiguously deduced by spectral (^1H and ^{13}C NMR, Mass and IR Spectra) and analytical data. In mass spectra (ESI and EI), the molecular ion peak in positive mode of all the compounds appeared as M^+ or protonated $[M + H]^+$ and /or sodiated $[M + Na]^+$ ion. In ^1H NMR, the protons for the methyl group of tosyl moiety appears in the range 2.17-2.19 ppm as singlet as expected, whereas aromatic protons appear in the range 6.64-8.72 ppm. Two methylene, protons appear as a doublet separately, one of them appears in the range 4.48-4.58 ppm, J = 16.2-16.8 Hz, while other one is found in the

range 5.27-5.35 ppm , J = 16.2-16.8 Hz. Thus, the spectral data (^{1}H,^{13}C, Mass Spectra, IR Spectra) provided the support in favour of the structure **3** (Scheme-2).

Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of the compound **3e**.

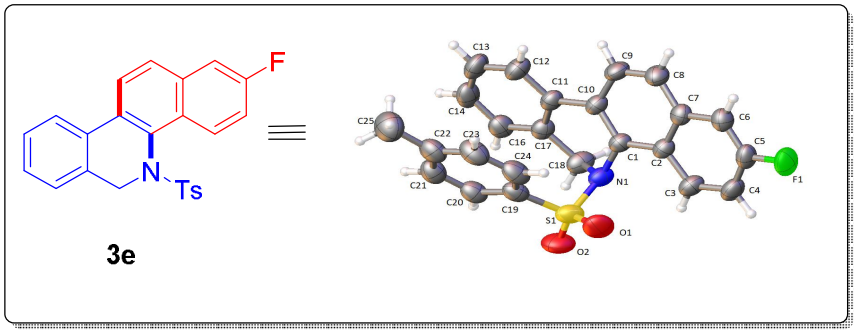
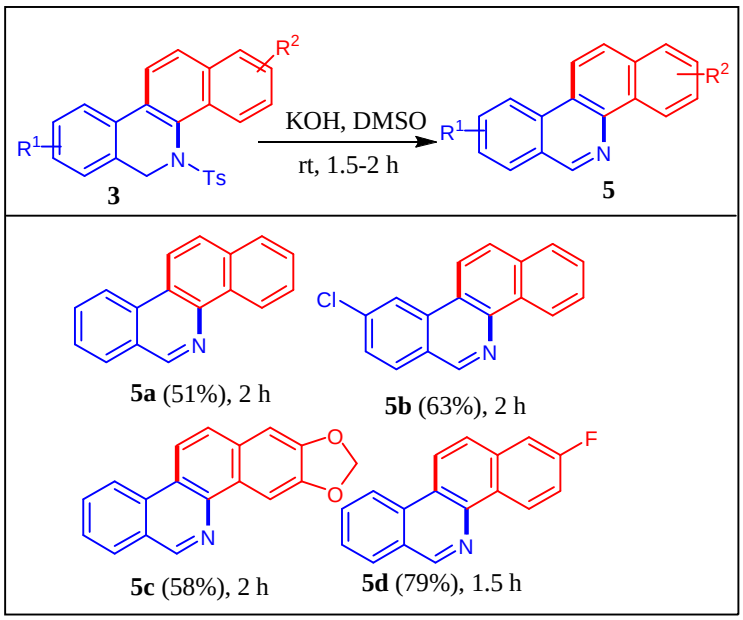


Figure 1. Ortep Diagram (drawn at 50% probability level) of compound **3e**.

Next we checked a base induced elimination reactions for the synthesis of benzo[*c*]phenanthridines **5** as shown Scheme 3. Transformation of **3** to **5** can easily be accomplished using potassium hydroxide as a base in DMSO.

Scheme 3. Base promoted synthesis benzo[*c*]phenanthridines **5**.[a,b]

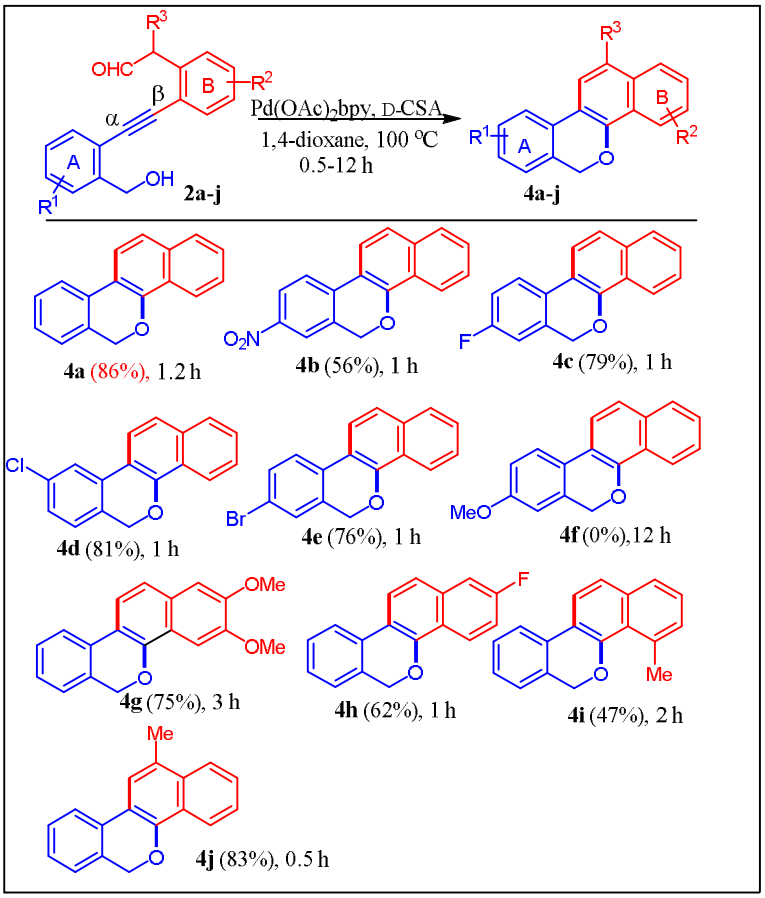


[a]Reaction condition: A mixture of **3** (0.13 mmol) and KOH (5 equiv) in DMSO was stirred at room temperature under argon atmosphere.

[b]Yield of the isolated product

To the syntheize 6H-dibenzo[*c,h*] chromenes **4,** the reaction was optimized using 4-Methyl-N-(2-((2-(2-oxoethyl)phenyl)ethynyl)benzyl)benzenesulfonamide **2a** (R^1 = R^2 = R^3 = H, X = OH) as starting substrate with variation of reaction parameter such as catalyst, solvent, additive, temperature. It was found that the exposer of the starting material **2a** (0.2 mmol) with $Pd(OAc)_2$bpy (5 mol %) and D-CSA (1.5 equiv) in 1,4-dioxane (2 mL) at 100 ^oC for 1.2 h under argon atmosphere afforded the desired product **4a (**R^1 = R^2 = R^3 = H) in highest yield (86%). The optimized reaction conditions in hand, the scope and limitations of this reaction was then assessed using diversely substituted acetylenic substrates **2** as shown under Scheme 4.

Scheme 4. Palladium-catalyzed synthesis of 6H-dibenzo[*c,h*] chromenes **4** [a,b]

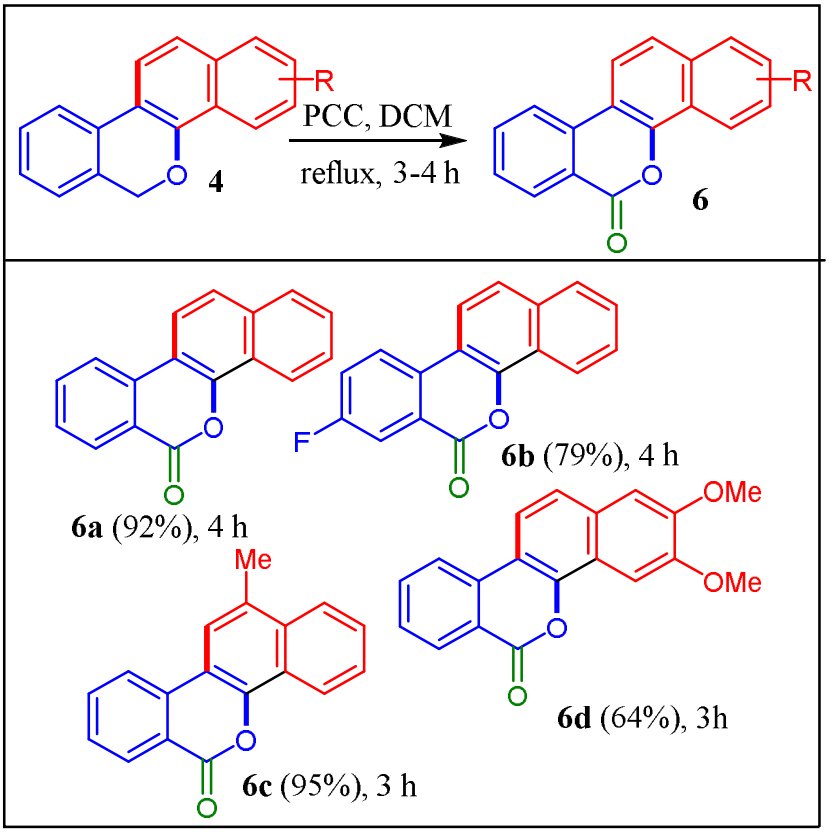


[a]Reaction conditions: **2**(0.2 mmol), $Pd(OAc)_2$bpy (5 mol %) and D-CSA (1.5 equiv) in 1,4-dioxane (2 mL) at 100 ^oC under argon atmosphere.

[b]Yield of the isolated pure products.

Next we attempted benzylic oxidation of products 6H-dibenzo[*c,h*] chromeness **4** which could provide easy access to dibenzo[*c,h*]chromen-6-ones **6** as shown Scheme 5. Transformation of **4** to **6** can easily be accomplished using PCC as an oxidizing agents in refluxing DCM. On the other hand, the same product **6a** could also derived directly from the substrate **7** having ortho-carboxylic acid group in place of benzylic alcohol (of **2a**) under our optimized reaction conditions as shown in Scheme 7.

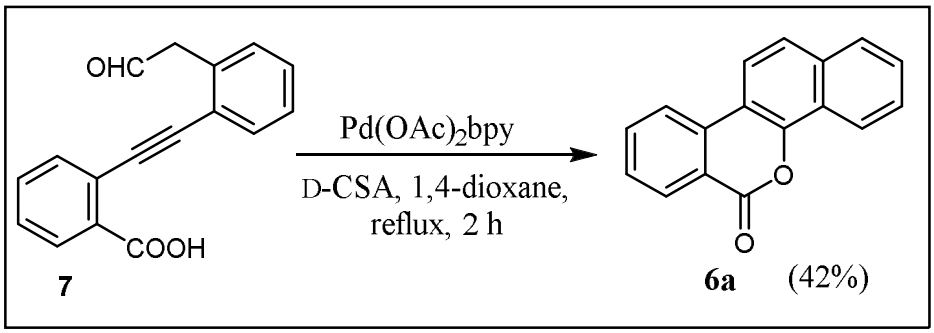
Scheme 6. Conversion of products 4 to 6H-dibenzo[*c,h*]chromen-6-ones **6.** [a,b]



[a]Reaction conditions: A mixture of **4** (0.086 mmol) and PCC (1.5 equiv) in DCM (2 mL) was refluxed under argon atmosphere.

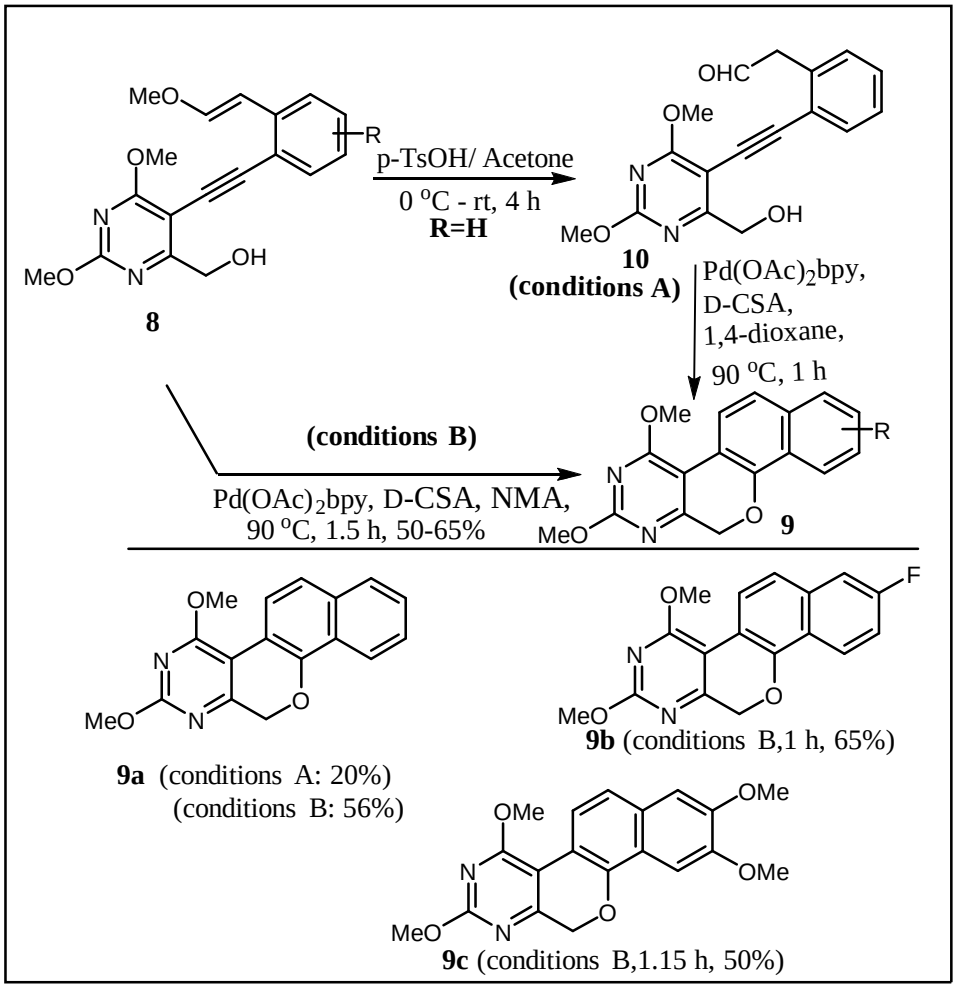
[b]Yield of the isolated pure product.

Scheme 7: One-pot Synthesis of 6*H*-dibenzo[*c*,*h*]chromen-6-one **6a** using 2-((2-(2-oxoethyl)phenyl)ethynyl)benzoic acid **(7)** as substrate



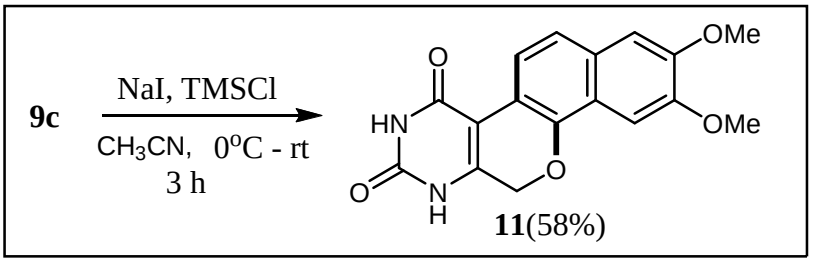
We also decided to apply the methodology for the synthesis of Pyrimidine molecules **9** from the acetylenic substrates **8** as shown in Scheme 8**.** But here masked aldehyde (Conditons B) responded better and furnished the desired product **9** with good yield.

Scheme 8. Synthesis of 2,4-dimethoxy-12H-benzo[7,8]chromeno[3,4-*d*]pyrimidines **9**



Next we tested demethylation reactions for transformation of compound **9** to uracil derivatives. Transformation of **9c** to **11** can easily be accomplished using TMSCl/NaI at room temperature as shown in Scheme 9.

Scheme 9. Conversion of **9c** to uracil derivative **11**



The structure of the aforesaid products **4**, **6**, **9**, **11** were unambiguously deduced by spectral (^{1}H and ^{13}C NMR, Mass and IR Spectra) and analytical data. In mass spectra (ESI and EI), 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 case of compound **4**, ^{1}H NMR of the two methylene appears in the range 5.23-5.40 ppm as singlet as expected, whereas aromatic protons appear in the range 6.94-8.29 ppm. Methylene carbon appears in the range 68.2-68.9 ppm. Thus, the spectral data (^{1}H,^{13}C, Mass Spectra, IR Spectra) provided the support in favour of the structure **4** (Scheme 4).

Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of the compounds **4a** and **4g**.

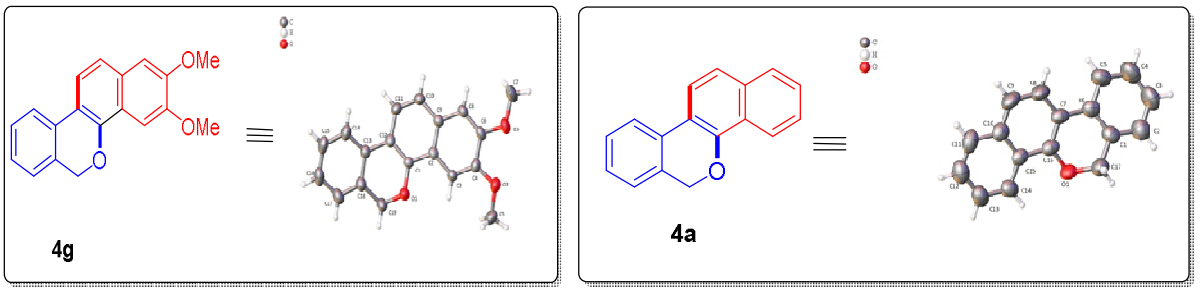
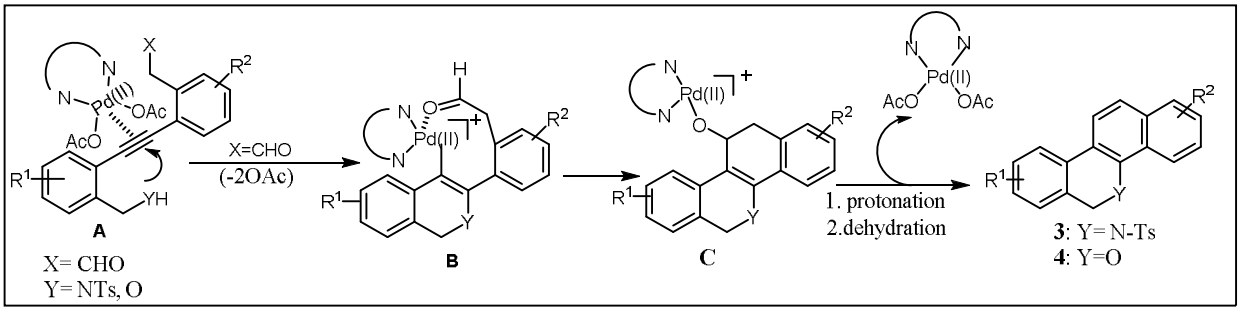


Figure 9. Ortep Diagram (drawn at 50% probability level) of compounds **4a** and **4g**.

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)

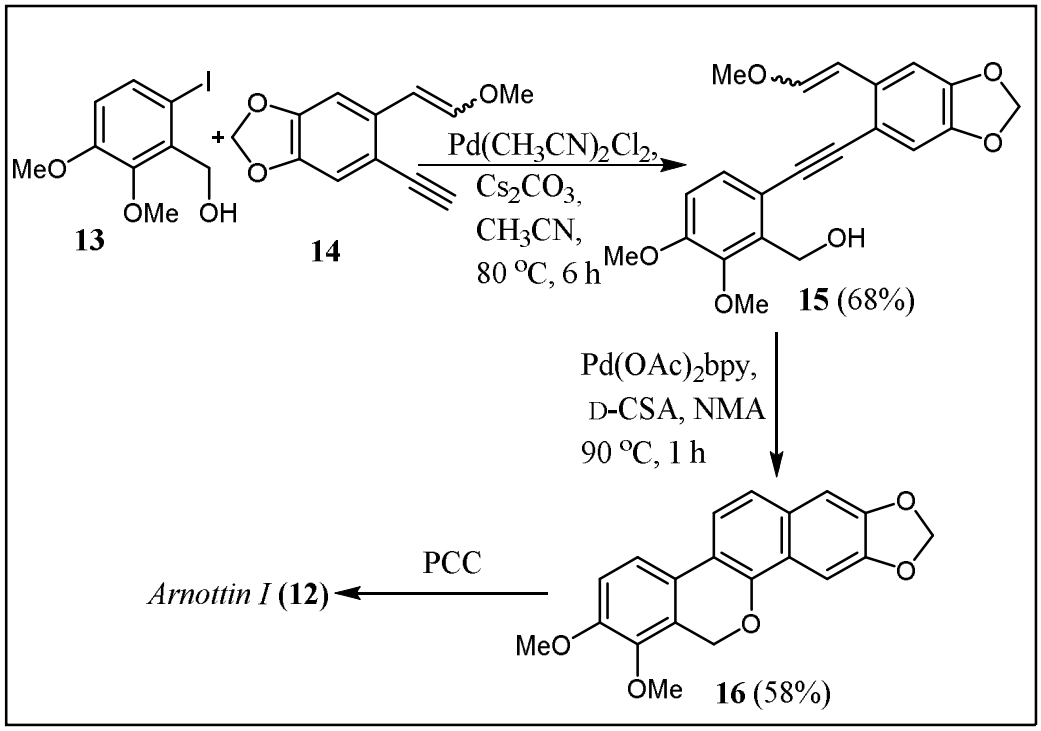
catalyst leads to the formation of species **A** which may trigger heteroannulation through *trans-oxo* palladation pathway resulting in the formation of the transient intermediate species **B**. Next, species **B** may undergo intramolecular Grignard type nucleophilic addition over a tethered aldehyde group to produce the corresponding palladated species **C**. While species **C** upon protonolysis using D-CSA followed by dehydration would afford the desired product **3**/**4**.



Scheme 10. Plausible mechanism for the formation of products **3** and **4**

In order to enlarge the scope of this heteroannulation reaction further, we undertook a formal total synthesis of *Arnottin I* in a concise manner as shown under Scheme 11.

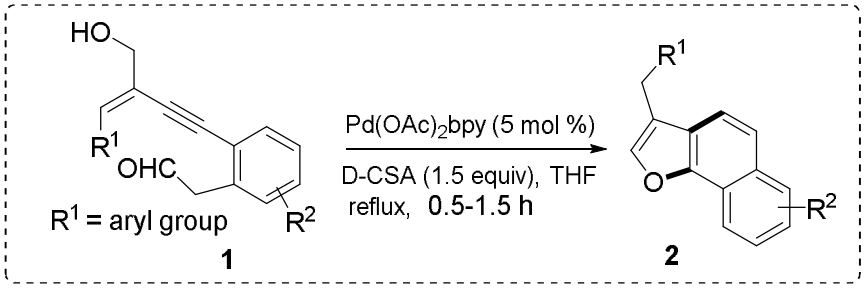
Scheme 11. Formal total synthesis of *Arnottin I* **(12)**



Chapter 3

Palladium(II)-Catalyzed Cascade Reactions of Ene−Ynes Tethered to Aldehyde: Access to Naphtho[1,2-*b*]furans.

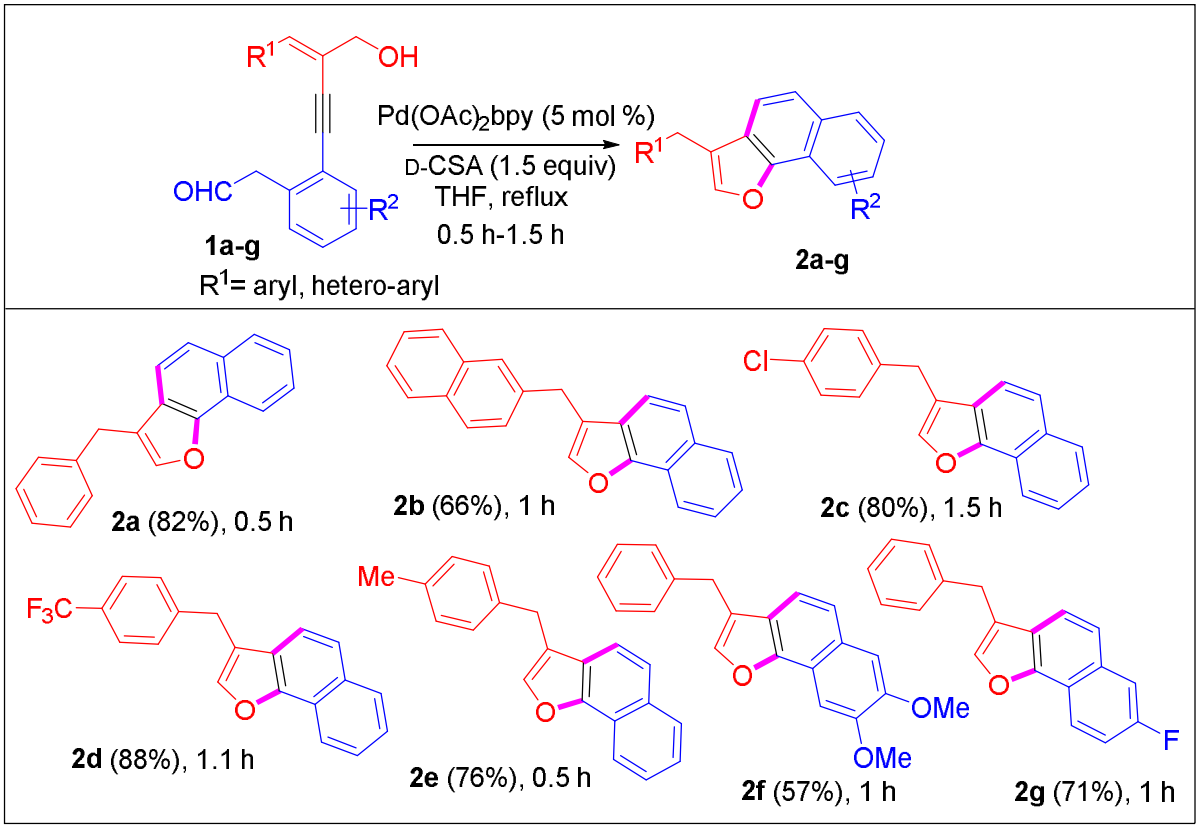
The third chapter deals with a study for the synthesis of Naphtho[1,2-*b*]furan **2** from starting substrate (*Z)-2-(2-(3-(Hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)phenyl)acetaldehyde* derivatives **1** through a palladium catalyzed cyclizations (*5-endo-dig)* followed by an intramolecular 1,2-nucleophilic addition onto the aldehyde group and, subsequent protonolysis, and dehydration (Scheme 1).



Scheme 1. Synthesis of naphtho[1,2-*b*]furan **2**

Towards this objective, a series of reaction was carried out with variation of reaction parameter such as catalyst, solvent, additive, temperature for a model conversion of (*Z)-2-(2-(3- (Hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)phenyl)acetaldehyde* (**1a**) (R^1 = Ph, R^2 = H) into *3-Benzylnaphtho[1,2-b]furan* (**2a**) (R^1 = Ph, R^2 = H). The best result for the formation of **2a** can be achieved when **1a** (0.18 mmol) was exposed to $Pd(OAc)_2$bpy (5 mol %), and D-CSA (1.5 equiv) in refluxing THF (3 mL) under argon atmosphere for 0.5 h. Under the said optimized reaction conditions, a diverse range of substrate **1** (i.e. **1a-g**) responded well to give the desired products **2a-g** in moderate to good yield (Scheme 2).

Scheme 2. Synthesis of the Naphtho[1,2-*b*]furan Derivatives **2a-g**[a]



[a] Reaction conditions: **1** (0.18 mmol), $Pd(OAc)_2bpy$ (5 mol %), and D-CSA (1.5 equiv) in refluxing THF (3 mL) under argon atmosphere.

All the structures were firmly established by spectral (^1H, ^{13}C, DEPT, Mass Spectra) and analytical data. In mass spectra (ESI and EI), the molecular ion peak in positive mode of all the compounds appeared as M^+ or protonated $[M+H]^+$ and/or sodiated $[M+Na]^+$ ion. In ^1H NMR the methylene protons of compounds **2** appears as singlet in the range of δ_H 4.07-4.29 ppm, while methylene carbon appears in the range of δ_C 29.5-30.2 ppm. On the other hand, the proton (at 2- position) of the furan ring was observed as singlet in the range δ_H 7.56-7.55 ppm in few cases but in most of the cases this found to be overlapped with other aromatic protons. Besides, in ^{13}C NMR and DEPT experiments the peaks were appeared at their appropriate positions providing further support in favour of the structure.

Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of compound **2a** (Fig. 1)**.**

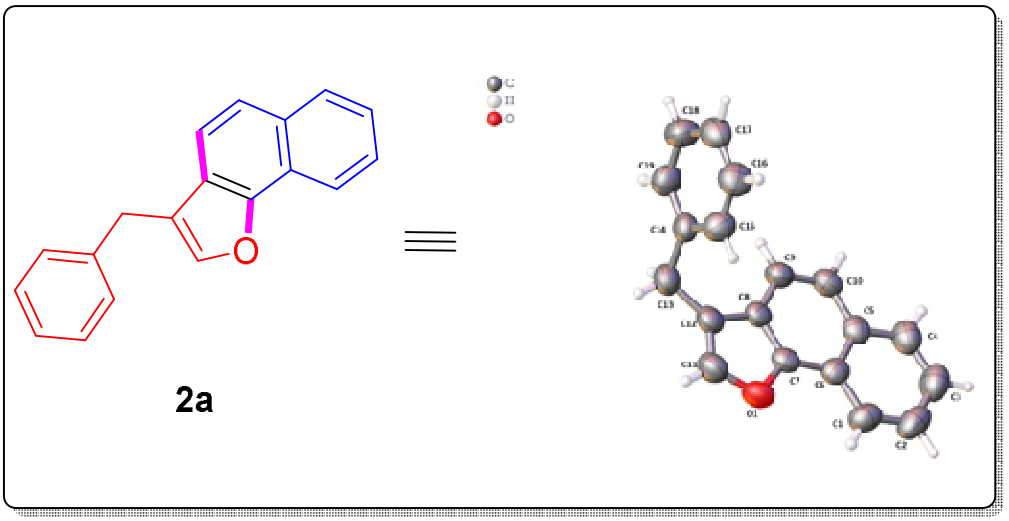
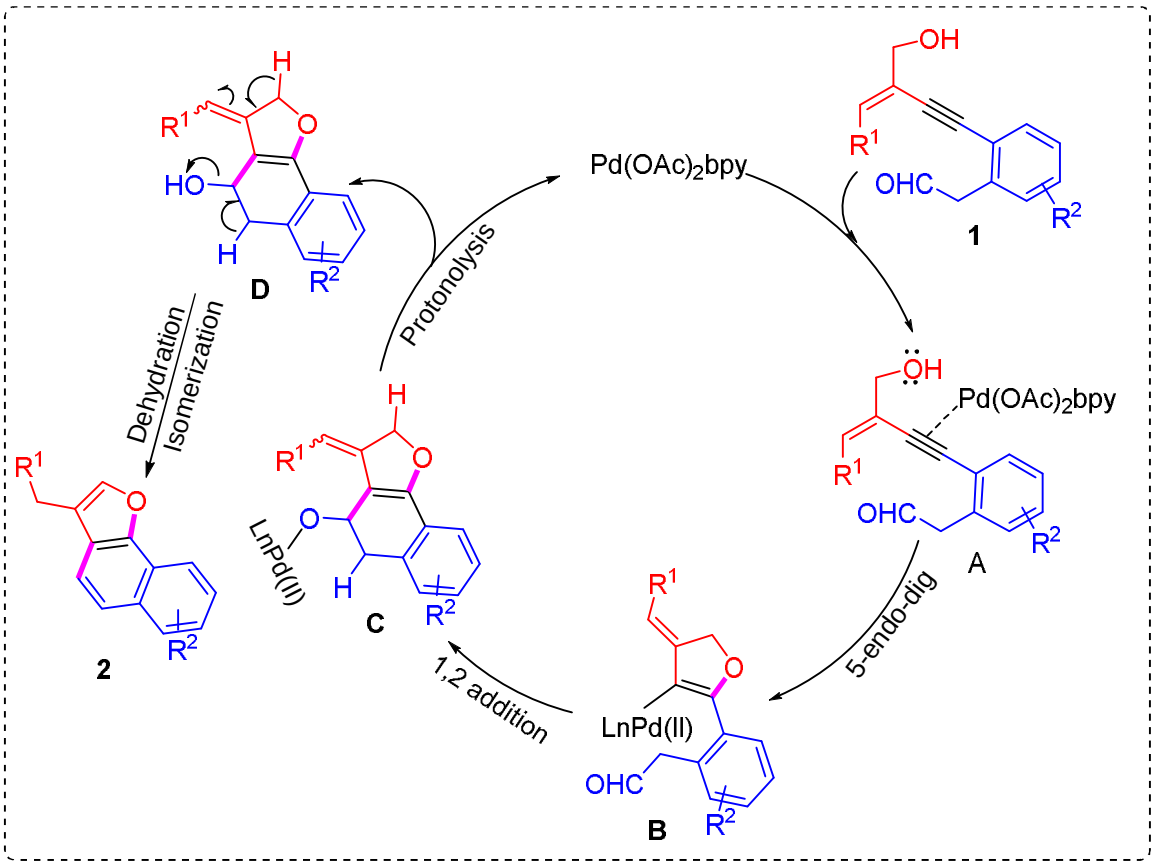


Fig. 1. Ortep Diagram of compound **2a** (drawn at 50% probability level).

A plausible reaction mechanism was depicted in Scheme 3. In the first step, activation of the triple bond of the substrates **1** by Pd(II) catalyst gives a complex **A** which then undergoes 5-*endo-dig* cyclization resulting in the formation of an intermediate **B.** Then, species **B** undergoes subsequent intramolecular 1,2-addition onto suitably placed carbon−heteroatom multiple bond (−CHO) resulting in the transient species **C**. Protonolysis of **C** gives the intermediate **D** and releases the palladium catalyst to participate into next catalytic cycle. Finally, Isomerization of the dihydrofuran ring of **D** and dehydration of the same intermediate could easily deliver the product **2**.

Scheme 3. Envisaged pathways for the formation of products **2**



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Chapter 1

Palladium-Catalyzed Benzannulations of 1-(Indol-2-yl)but-3-yn-1-ols: Easy Access to Functionalized Carbazoles

Part I

(A Short Review)

1. 1.1. INTRODUCTION

1.1.1.1. Importance of carbazole

The Carbazole scaffolds is the key structure motif of many biologically active compounds including natural and synthetic products.[1] Origin of Carbazole alkaloids mainly from higher plants of genera *Murraya*, *Glycosmis*, *Clausena*, and *Micromelum* all from the family of Rutaceae.[2] Bacteria (e.g. *Streptomyces*), algue (e.g., *Hyella Cacepitosa*), and fungi (e.g. *Aspergillus* species) are also origin of Carbazole alkaloids. However, the parent Carbazole i.e., 9H -Carbazole was isolated from coal tar in 1872 by Graebe and Glazer.[3] Thereafter, in the year 1965, a plant-based carbazole, namely *Murrayafoline A* **1**, was first isolated from the tree *Murraya koenigii* by Chakraborty[4] and co-workers. Importantly, *Murrayafoline A* has antibiotic and antitumor properties. Besides, *Murrayafoline A*[5] **1** showed potent anti-leukemic properties[6] (against HL-60 cell lines).

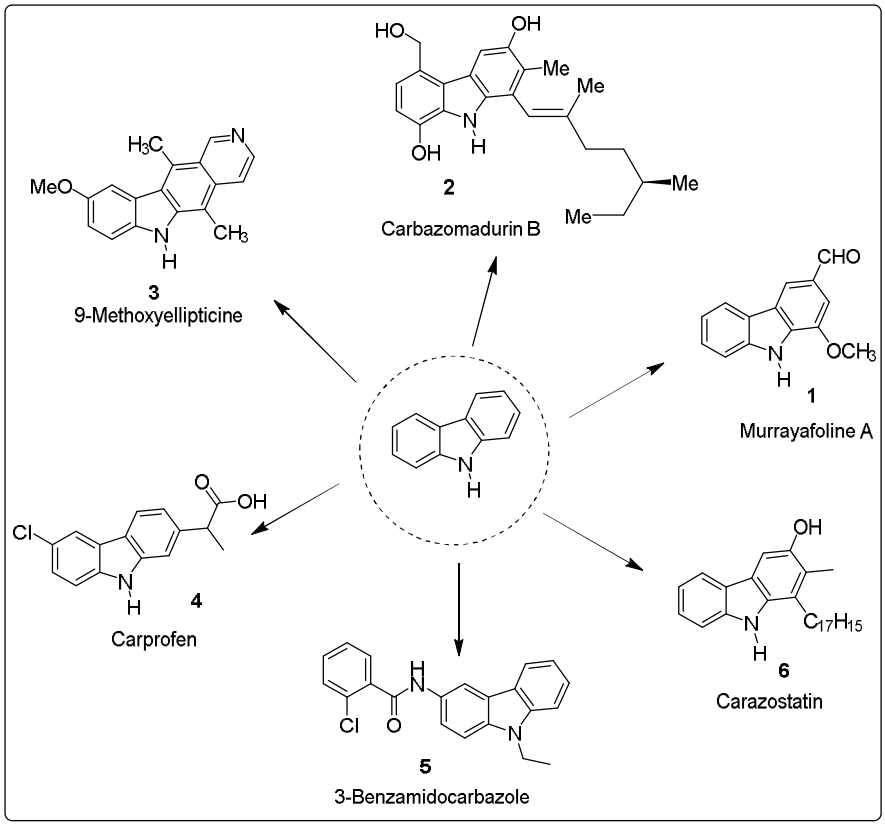


Fig. 1: Some naturally occurring biologically active carbazoles

Later on, many carbazole derivatives have been synthesized and are well known for their pharmacological activities such as anti-bacterial, anti-oxidant, anti-flammatory, anti-tumour, anti-convulsant, anti-phychotic and anti–diabetic[7] etc. Some naturally occurring biologically active compounds are represented in Fig. 1. For example, *Carbazomadurin B*[8] **2**, a protective agent against glutamate toxicity (in neuronal hybridoma N18-RE-105 cells), *9-Methoxyellipticine*[9] **3**, a potent antitumor agent, *Carprofen*[10] **4** used as anti-inflammatory drug (NSAID)[11], *3-Benzamidocarbazole*[10] **5**, an inhibitor of PGE2 Production,[12] *Carazostatin*[10] **6** having antioxidant activity,[13]. Furthermore, Carbazole derivatives also serve as important building block for the synthesis of functional materials such as organic emitting diodes (OLEDs).[14] Besides, carbazole based dyes are also reported.[15]

1.1.1.2 Bioactive carbazoles having electron-withdrawing group at C3 position:

Carbazoles having electron-withdrawing group at C3 position serve as core structure of many biologically active natural products (Fig. 2). For example, *Murrayafoline A* **1** possess antimicrobial properties[16] along with other activities as described previously. While *Clauszoline-I*[11] **7**, a potent anti-cancer agent[17] that displayed significant growth inhibitory activities against four cancer cell lines (cervical carcinoma, glioblastoma, nasopharyngeal carcinoma, hormone-independent breast cancer) and Carbazole **8** identified as novel anti-trypanosomal[18] lead compound.

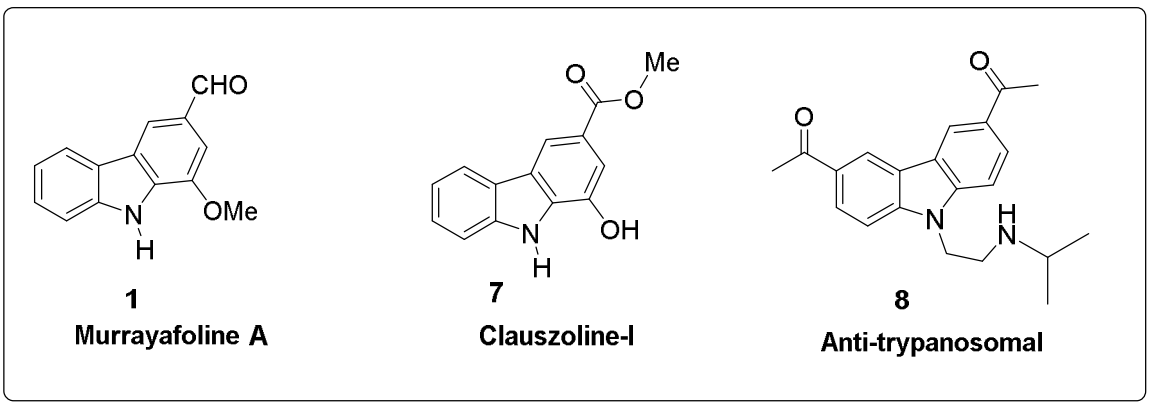


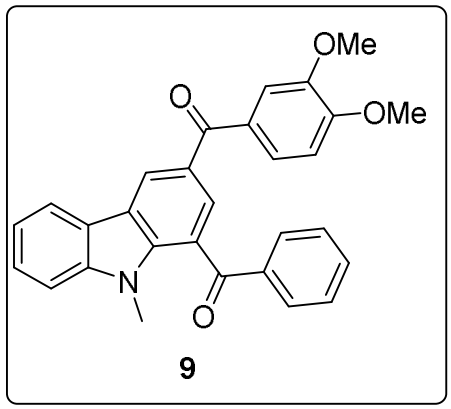
Fig. 2 Few naturally occurring carbazoles having electron-withdrawing group at C3 position.

Furthermore, such type of compounds also showed wide applications in material sciences and medicinal chemistry which is discussed briefly below.

1.1.1.3. Importance of Carbazole having keto-aryl group (at C3 position) in material science:

In particular, carbazole having keto-aryl group at C3 position have shown various applications in material sciences; some of them are discussed below.

1.1.1.3.1. Aggregation Induced emission (AIE): Guo *et al.*[19] repoted that carbazole compounds carrying keto-aryl group at C1 & C3 positions displayed unusual aggregation-induced emission (AIE)[20] properties in solid state, which were very different from the reported solvent fluorescence emission.[21] The emission maximum of carbazoles **9** (Fig. 3) ranges from 425 to 440 nm. Owing to the unique AIE property, products **9** showed for future applications in various fields such as fluorescence sensing and one and two photon bioimaging.[22]



9

Fig. 3 Carbazoles **9** as a representative example

1.1.1.3.2. Ultralong organic phosphorescence (UOP): Nidhankar *et al.*[23] reported that 3,6-phenylmethanone functionalized 9-hexylcarbazole **10**, (Fig. 4) exhibits a remarkable improvement in phosphorescence lifetime (>4.1 sec) and quantum yield (11 %) due to an

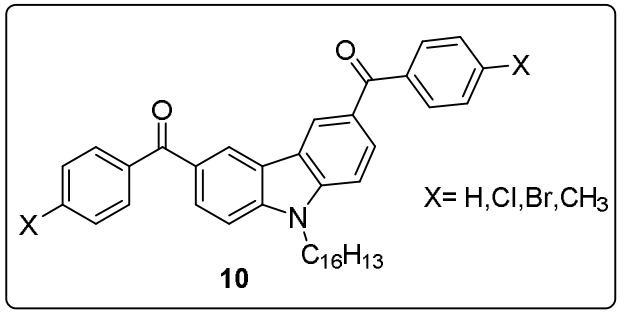


Fig. 4 3,6-Phenylmethanone functionalized 9-hexylcarbazole **10**

efficient molecular packing in the crystal state. The same group reported a series of compound of type **10** (X= H,Cl, Br,CH_3). A helical array by the peculiar molecular packing of 3,6-bis(phenylmethanone) substituted 9-hexylcarbazole in the crystal state enabled to mix up the singlet triplet states to create hybrid triplets to enhance the intersystem crossings. By optimizing the molecular structure and a strained crystal packing, a metal- and heavy atom-free carbazole derivative resulted in a significant improvement of phosphorescence lifetime and quantum yield.

1.1.1.3.3. Radical and Cationic polymerizations: Liu *et al.*[24] reported that bifunctional benzophenone-carbazole BPC (Fig. 5) was indentified as a photoinitiator. Interestingly, BPC could efficiently initiate the free radical photopolymerization (FRP) of acrylates without addition of any extra hydrogen donors demonstrating a monocomponent Type II behavior but also fast rates were obtained in the presence of an amine and/or an iodonium salt under LED@365 nm irradiation. Meanwhile, BPC can also interact with the iodonium salt to generate cationic species for the cationic photopolymerization (CP) of epoxides. BPC was

found as a versatile photoinitiator that can be used for both radical and cationic polymerizations.

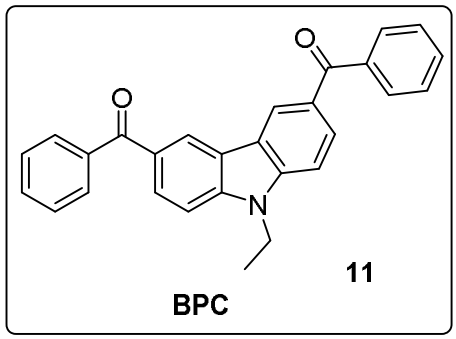


Fig. 5 Bifunctional benzophenone-carbazole (BPC) **11**

1.1.1.3.4. Luminescent materials ECPPTT and ECDPTT: Dong *et al.*[25] has demonstrated two luminescent materials ECPPTT (**13**) and ECDPTT (**14**) (Fig. 6) which were synthesized from the precursor molecule **13**. ECPPTT and ECDPTT possess obvious AIE and TADF capabilities, and showed good thermal stability in their thin film of 240 ^{0}C and 262 ^{0}C, respectively.

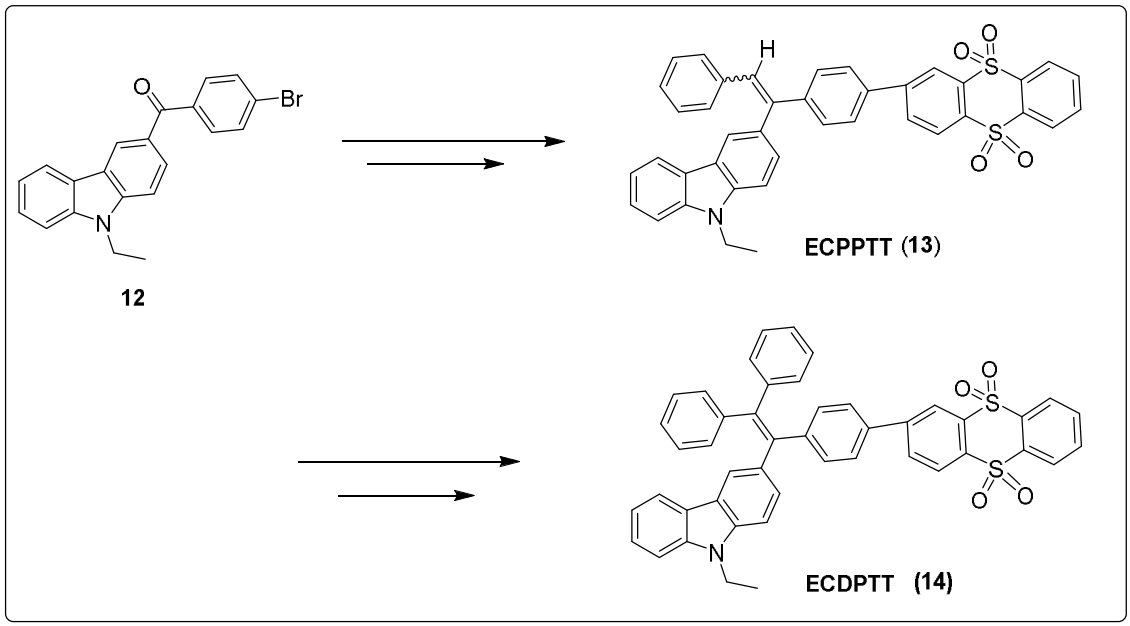


Fig. 6 Luminescent materials ECPPTT (**13**) and ECDPTT (**14**)

Non-doped organic light emitting diodes (OLED) using ECPPTT and ECDPTT as emission layer are prepared and exhibit blue-green and green emission color with peaks at 494, 517 nm, respectively. The non-doped OLED based on ECPPTT provided good peak EL efficiencies of 3.437 cdA^{-1} and 10090 cdm^{-2}; while non-doped OLED fabricated with ECDPTT afforded a maximum current efficiency and a maximum luminance of 2.478 cdA^{-1} and 7561 cdm^{-2}. These results demonstrated the feasibility of combing AIE and TADF units to design new molecules.

1.1.1.3.5 Carbazole-containing tetraphenylethene DCDPE: **Liu** *et al.*[26] has designed and synthesized DCDPE (**16**) from precursor molecule **15** (**Fig. 7**). They investigated its optical, thermal and optoelectronic properties.

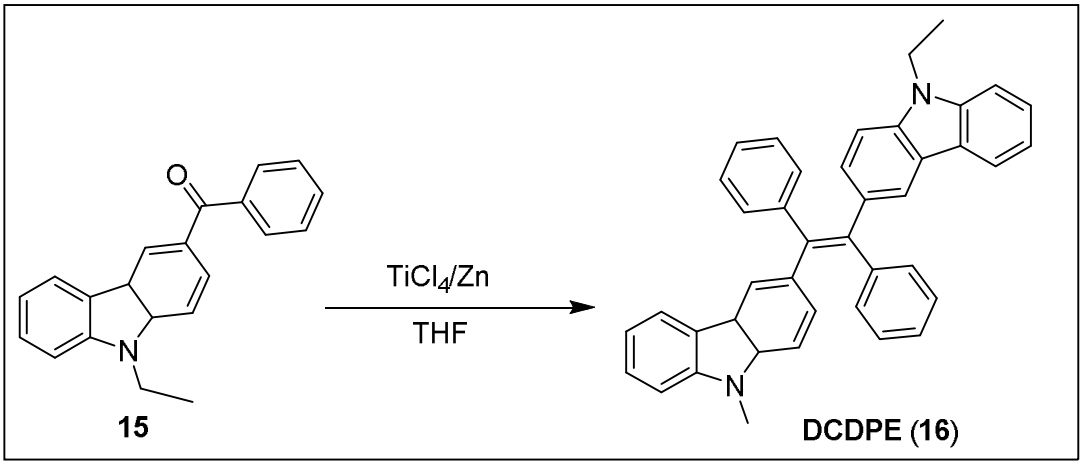


Fig. 7 Synthesis of DCDPE (**16**)

The dye exhibited typical aggregation-induced emission property and became non-luminescent when molecularly dissolved in solutions while intensely emissive in the aggregate form. Close inspection of the geometric structure and packing motifs of DCDPE in the crystalline state revealed a loose packing characteristic due to the severely twisted conformation and the absence of strong intermolecular π-π interaction. On the other hand, the multiple weak intermolecular C–H--π hydrogen bonds rigidifyed the molecular conformation

and lock the vibrational and rotational freedom of the four aromatic substituents, accounting for the extremely high solid state quantum yield.[27] The dye crystallized into strong blue emissive fibers showing an optical waveguide effect. The OLED devices using it as both light-emitting and hole-transporting material showed superior performances. In a word, both enhanced optical and electronic properties were achieved in DCDPE. The present results demonstrated the promise of the carbazole-containing AIE luminogen as an optoelectronic candidate especially for future laser applications.

1.1.1.4. Importance of carbazoles having keto-aryl group (at C3 position) in Medicinal Chemistry:

Carbazoles having keto aryl group at C3 position proved to be important in Medicinal chemistry as described below.

1.1.1.4.1. Curaxins have the potential to be developed into effective and safe anticancer drugs. **Gurava** *et al*.[28] have isolated and structurally optimized small molecules like curaxins, that simultaneously activate p53 and inhibit NF-κB without causing detectable genotoxicity. Curaxins demonstrated anticancer activity against all tested human tumor xenografts grown in mice. Several compounds were identified.[29] For example, the carbazole derivative CBLC000, **17** (**Fig. 8**), that was capable of simultaneously inhibiting NF-κB and activating p53. Curaxins were found to be more toxic to tumor than to normal cells. Another carbazole derivative, namely CBLC137, **19** (**Fig. 8**), displayed comparable or superior efficacy to current standard chemotherapeutic drugs, 5-fluorouacil, irinotecan, and oxaliplatin, and a new targeted therapy used in the clinic, sunitinib.

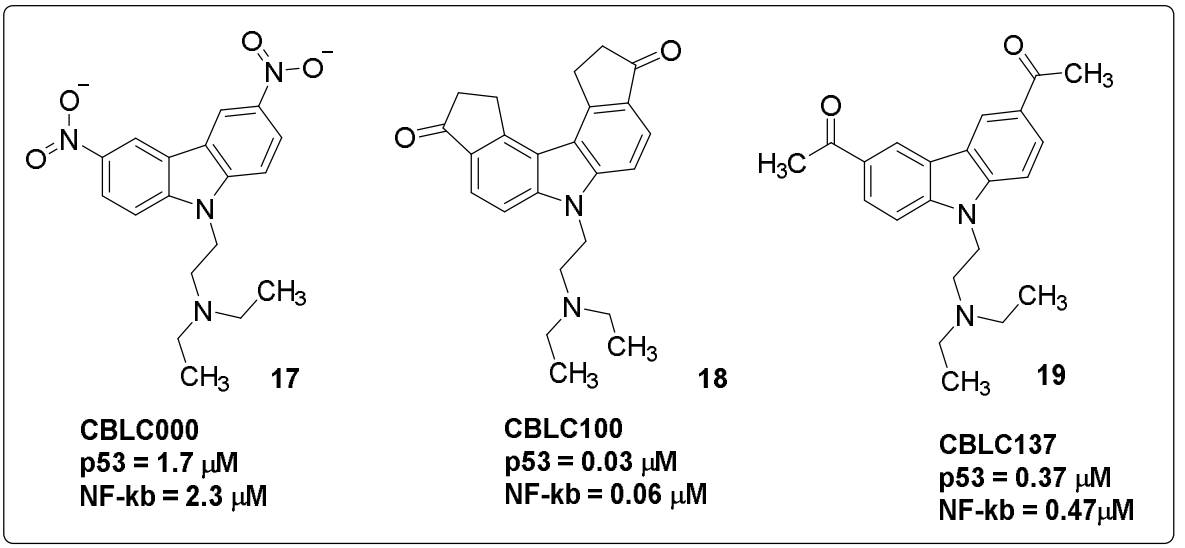


Fig. 8 Structural formulas of curaxins CBLC000 (**17**), CBLC100 (**18**), and CBLC137 (**19**)

1.1.1.4.2. Petrov *et al.*[30] reported that the carbazole **20** (**Fig. 9**) exhibited [^{35}S]GTP-γ-S inverse agonist activity and inhibited compound CP55,940 (**Fig. 9**) induced CB2 internalization.

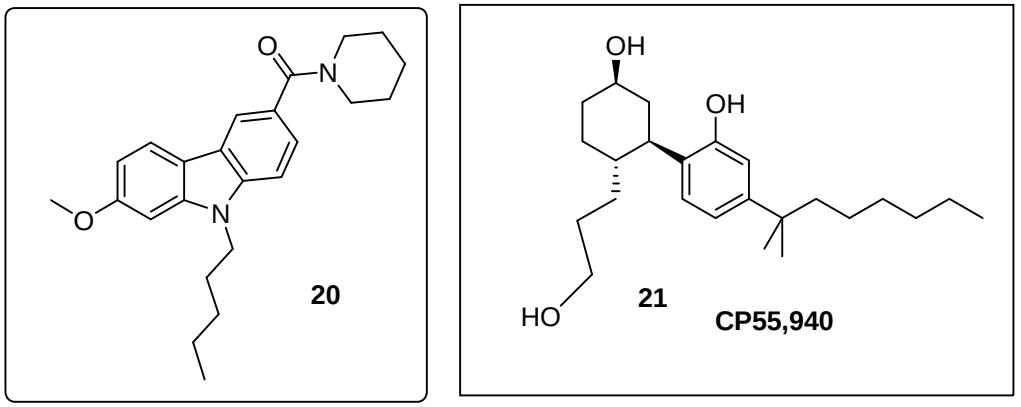


Fig. 9 Compounds **20** and CP55940 **21**

1.1.1.4.3. Diaz *et al.*[31] reported a series of carbazole-based compounds **22** as microtubule-targeting agents (MTAs) and studied their antitumor activity in both GBM cell lines and patient-derived GBM cells in culture. They also studied how the antitumor activity of carbazole analogues exhibited their ability to disrupt MT. They investigated antitumor

activity of eighteen carbazoles derivatives in T98G cells in culture and found that fourteen modified carbazoles that all have an ethyl moiety linked to the nitrogen of the carbazole and a carbonyl moiety linked to the C3 position of carbazole exhibited remarkably impressive EC50s. Moreover, replacement of the methylnaphthyl group present in the most potent compound **22A** (87 nM) by either toluyl as in **22B** (993 nM) or a non-substituted naphthyl moiety as in **22D** (1.7 µM) or a benzyl moiety as in **22C** (inactive) increased EC50s values by 11-fold, 20-fold and more than 115-fold, respectively as shown in Fig 5.

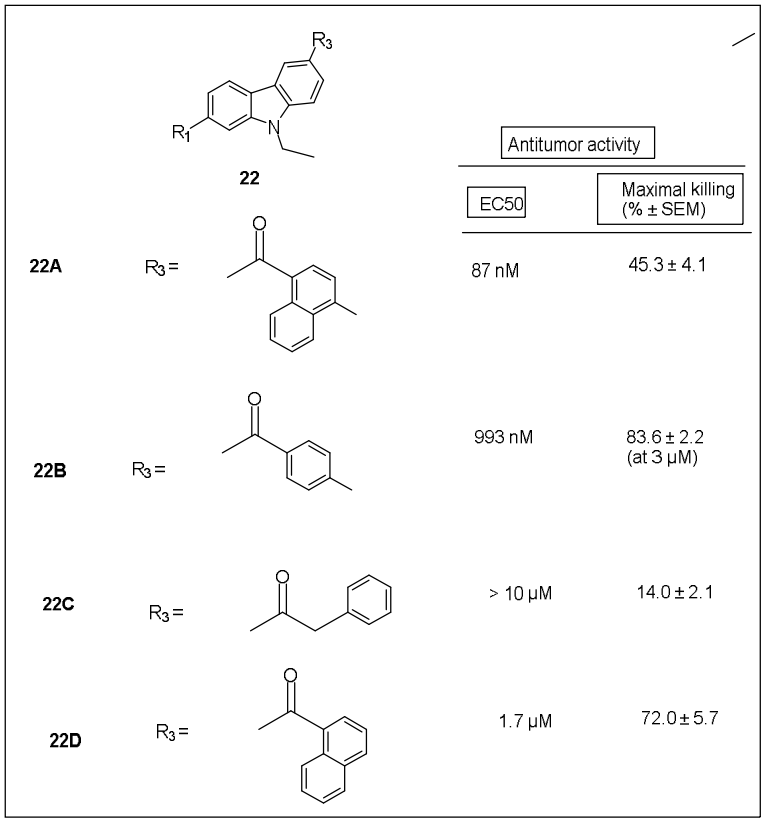


Fig. 10 Antitumor activity few carbazoles in T98G cells in culture.

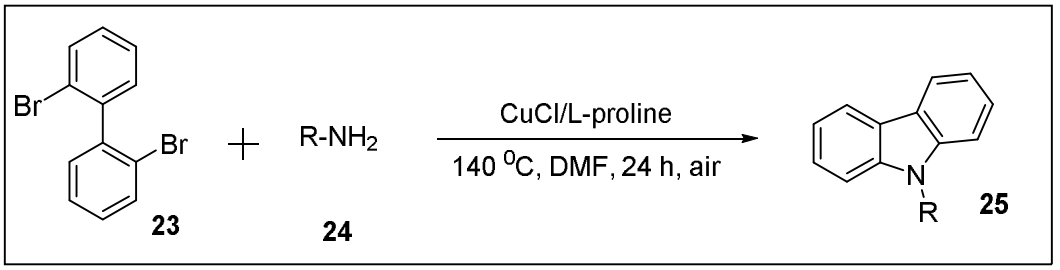
Finally, they also reported a novel series of modified carbazoles that destabilize MTs by binding to the colchicine site of tubulin in a similar mode to a-podophyllotoxin analogue and found to interact with a unique low interaction binding space. Several modified carbazoles triggered marked cell death in multiple GBM model systems but they showed considerably lower activity in the HepG2 liver cells, suggesting a promising therapeutic index.

1.1.2. Synthesis of Carbazoles:

In recent past, the synthesis of carbazoles has gained a great momentum by the deployment of transition metal catalyst resulting in the developments of many methods to get their access easily. Among many useful procedures to construct carbazoles, synthetic pathways of forming a pyrrole ring via in situ formation of diarylamine in the presence of palladium catalyst (using aryl halides and 2- haloanilines or 1,2-dihaloarenes as substrates) are of interests in recent times. Few of them are illustrated briefly below.

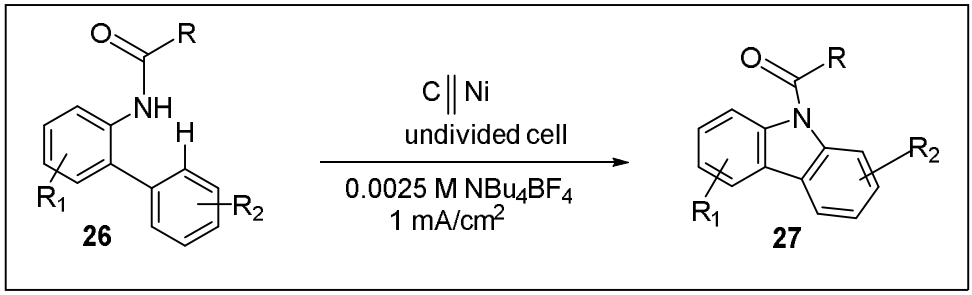
1.1.2.1. Synthetic pathways of forming a pyrrole ring:

1.1.2.1.1 Do *et al.*[32] reported an efficient Cu-catalyzed method for the synthesis of carbazole derivatives **25** via double C–N coupling reactions of 2,2′-dibromobiphenyl **23** and amines **24** in the presence of air (Scheme 1). The reactions were found to be high yielding. This method also tolerates a series of amines including neutral, electron-rich, electron-deficient aromatic amines and aliphatic amines.



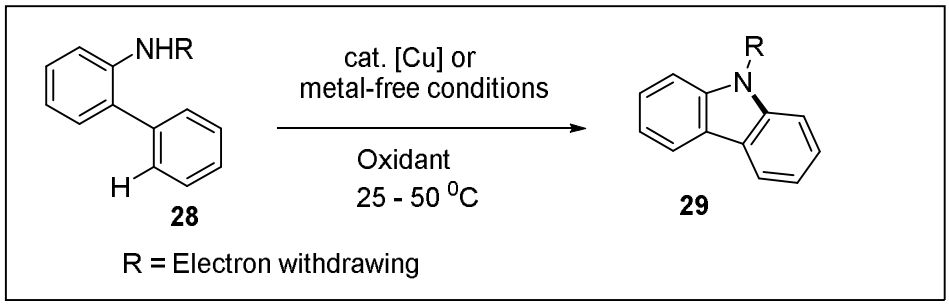
Scheme 1. Synthesis of carbazoles **25**.

1.1.2.1.2. Kehl *et al.*[33] reported a straight forward synthesis to gain access to N- protected carbazoles **27** through anodic N,C bond formation using directly generated amidyl radicals **26**. This reaction involves a constant current protocol, a remarkably low supporting electrolyte concentration, employing undivided cells, and inexpensive electrode materials (Scheme 2).



Scheme 2 Electrochemical Synthesis of Carbazoles **27**.

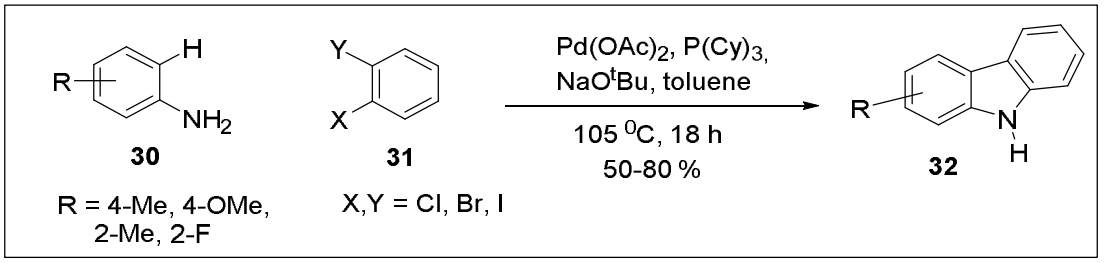
1.1.2.1.3. Cho *et al.*[34] developed a synthetic procedures for intramolecular oxidative C-N bond formations for the preparation of carbazoles **29** (Scheme 3) starting from N-substituted amido-biphenyls **28** under either Cu-catalyzed or metal-free conditions using hypervalent iodine(III) as an oxidant. Whereas iodobenzene diacetate or bis(trifluoroacetoxy)iodobenzene alone undergoes the reaction to provide carbazole products in moderate to low yields. However, combined use of copper(II) triflate and the iodine(III) species significantly improves the reaction efficiency, giving a more diverse range of products in good to excellent yields.



Scheme 3. Synthesis of carbazoles **29** via oxidative C-N bond formations under Cu-catalyzed or metal- free conditions.

1.1.2.1.4. Ackermann *et al.*[35] developed Pd(II)-catalyzed method for the synthesis of functionalized carbazoles which proceeds through annulation of aniline with dihaloarenes (Scheme 4) . The reaction sequence consists of an intermolecular amination followed by an

intramolecular direct arylation as key steps. As illustrated in Scheme 4, the Pd-catalyzed reactions of substituted anilines **30** and 1,2-dihalobenzenes (**31**) in the presence of PCy_3 ligand and NaO^tBu provided substituted carbazoles **32** in good yields .



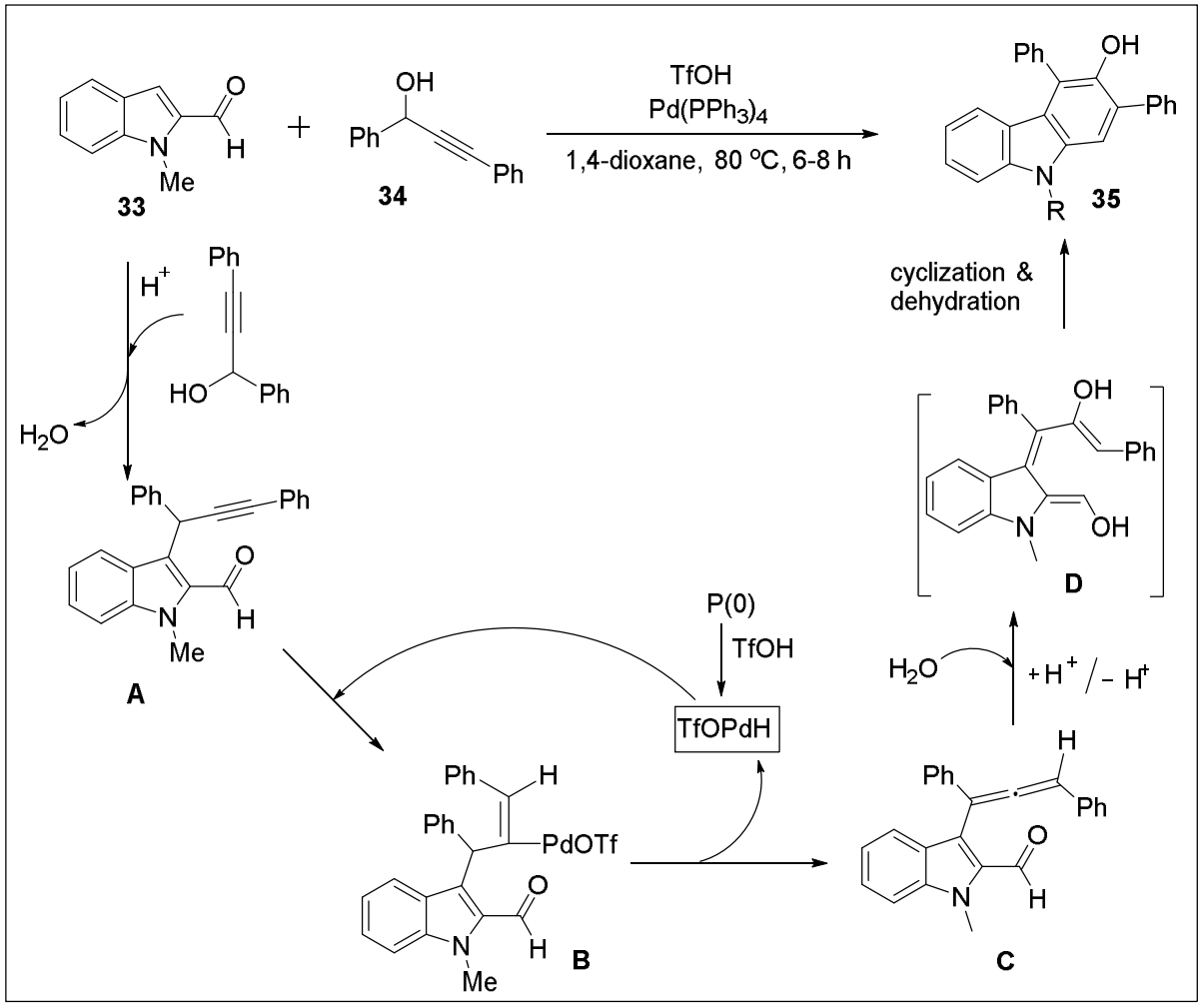
Scheme 4. Palladium(II)-catalyzed synthesis of carbazoles **32**

1.1.2.2. Synthesis of carbazoles from indoles

In additions to the aforesaid strategy of pyrrole ring formations, synthesis of carbazoles from indole substrates has also been accomplished by adopting the strategy of benzene ring[5] formations involving either inter- or intra-molecular reactions. Nevertheless, the intermolecular version of indole-to-carbazole strategy primarily relies on Diels−Alder reaction carried out under one pot or in multiple-steps where C−C bonds are formed through transition-metal-catalyzed reactions of indoles with alkenes or alkynes. Few of them are illustrated briefly below.

1.1.2.2.1 Intermolecular reactions between indoles and acetylenic substrates for the construction of carbazole rings via Diels−Alder reaction:

1.1.2.2.1.1. Reddy *et al.*[36] reported a method for the synthesis of 3-hydroxycarbazoles **35** which proceeds via propargylation followed by palladium-catalyzed hydroxylative benzannulation (Scheme 5). Mechanistically, reaction of N-methyl-indole-2-carbaldehyde **33** with propargylic alcohols **34** leads to

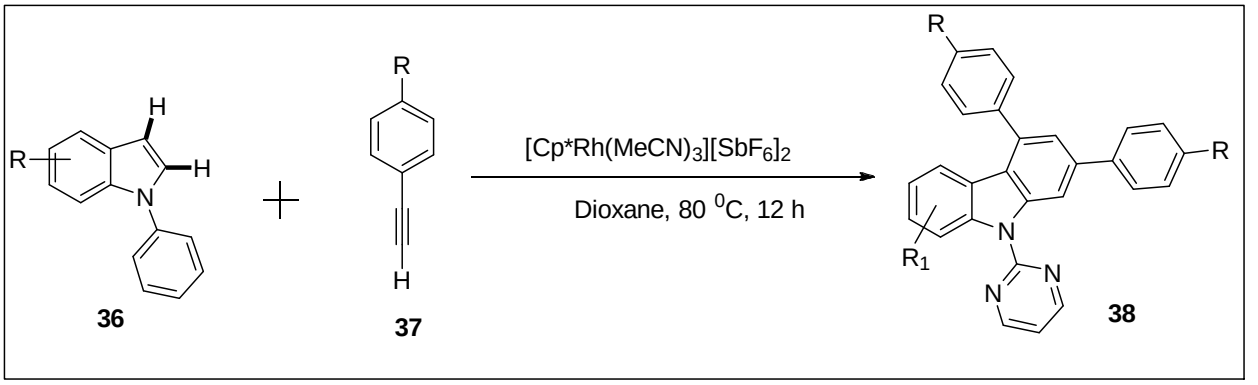


Scheme 5: Synthesis of 3-Hydroxycarbazoles **35** with a plausible reaction mechanism

intermediate species **A** which then undergoes hydropalladation to produce vinylpalladium complex **B**. Thereafter, β-elimination (-PdOTfH) from intermediate **B** leads to the formation of allene intermediate **C**. The hydration of **C** in the presence of acid provided the intermediate **D** which upon subsequent cyclization followed by dehydration leads to the desired carbazoles **35** in good yields.

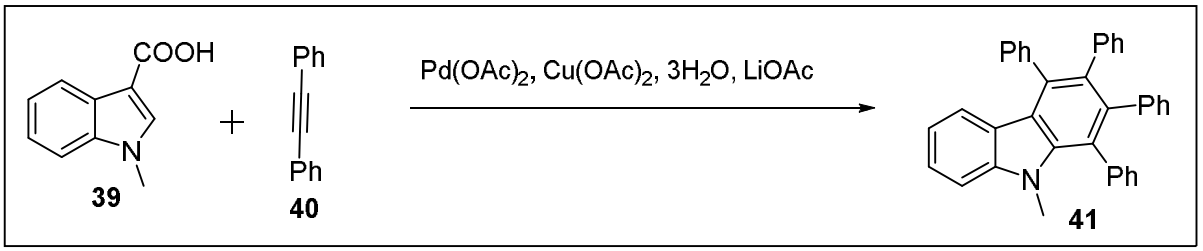
1.1.2.2.1.2. Jia *et al.*[37] reported a new, mild and efficient Rh(III)-catalyzed intermolecular annulation of indoles **36** with terminal alkynes **37** for the one-pot cascade synthesis of privileged carbazoles **38** (Scheme 6) by using the readily installable and removable pyrimidyl group as a DG (directing group).This transformation proceeds smoothly under air via C-H

activation possessing several advantageous features like good yields, exclusive regioselectivity, broad substrate scope and excellent functional group tolerance etc.



Scheme 6: Synthesis of carbazoles **38** through C-H activations

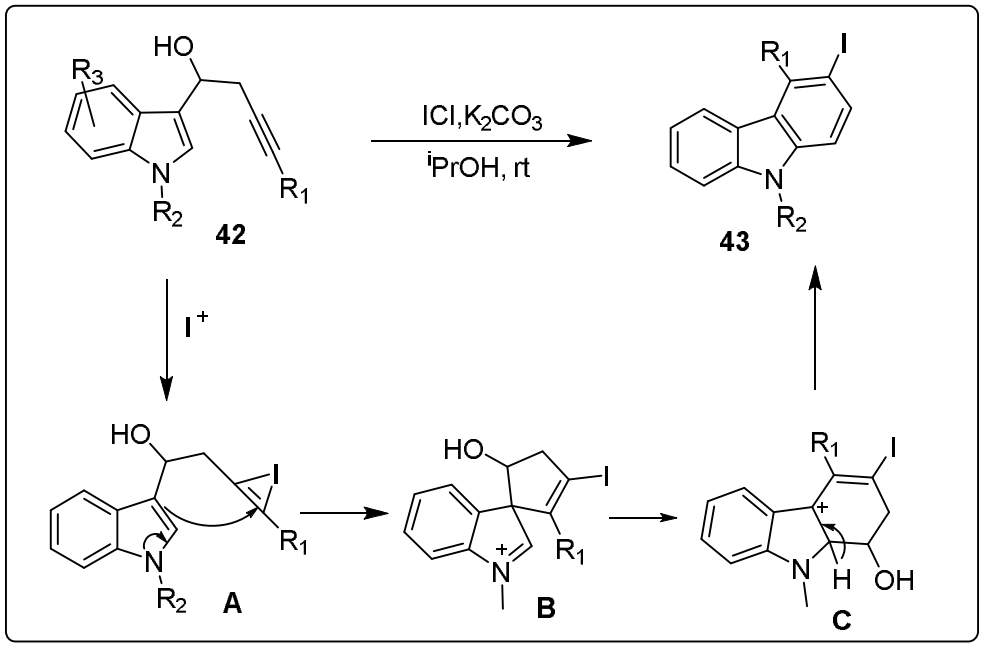
1.1.2.2.1.3. Yamashita *et al.*[38] described the selective synthesis of 1,2,3,4-tetrasubstituted carbazoles **41** through the palladium-catalyzed oxidative coupling reactions of N-substituted indoles or their carboxylic acid derivatives **39** with alkynes **40** in the presence of $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2 3H_2O$ as oxidant and LiOAc as additive (Scheme 7). For example, 1-methylindole-3-carboxylic acid smoothly underwent oxidative coupling followed by cycloaddition with diphenylacetylene to afford 1,2,3,4-tetraphenyl-9-methylcarbazolen **41**.



Scheme 7: Synthesis of carbazoles **41** via palladium-catalyzed oxidative coupling of indoles **39** with diphenylacetylene **40**.

1.1.2.2.2. Intramolecular cyclizations of indoles for the construction of carbazole rings:

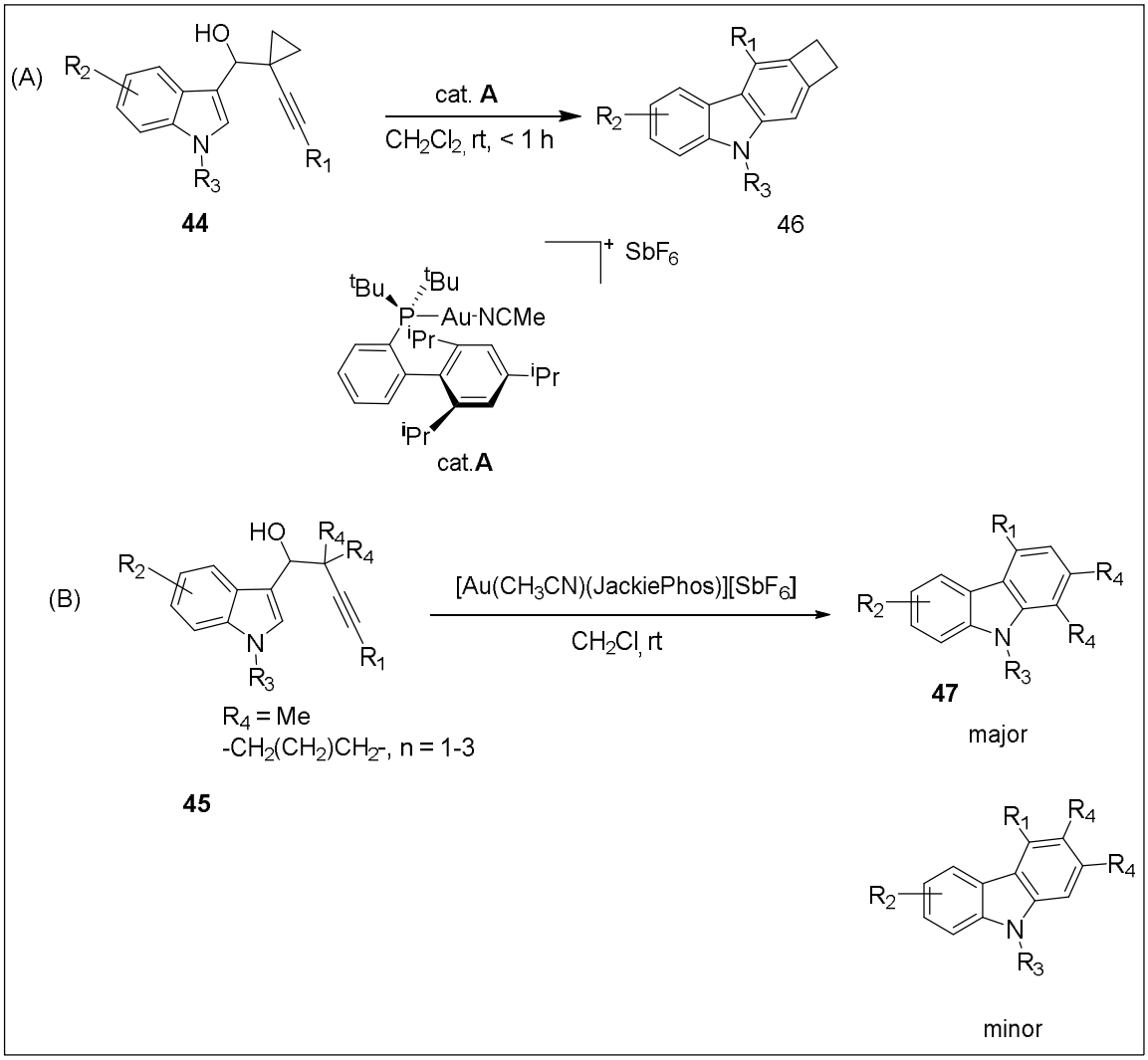
1.1.2.2.2.1. Wang *et al.*[39] reported a mild protocol for the synthesis of iodocarbazoles **43** from the indoles **42** tethered with an alkyne moiety (Scheme 8). Mechanistically, first alkyne moiety **42** activated by an iodide cation, produce the reactive species **A** which underwent nucleophilic attack by C3 position of the indole ring to afford spirocyclic cationic intermediate **B**. Subsequently, the 1,2-shift from the 3- to 2- position occurred to form the intermediate **C**. Then deprotonation followed by water elimination of water delivered the desired product **43** as depicted under Scheme 8.



Scheme 8 : Synthesis of Iodocarbazoles **43** with plausible reaction mechanism

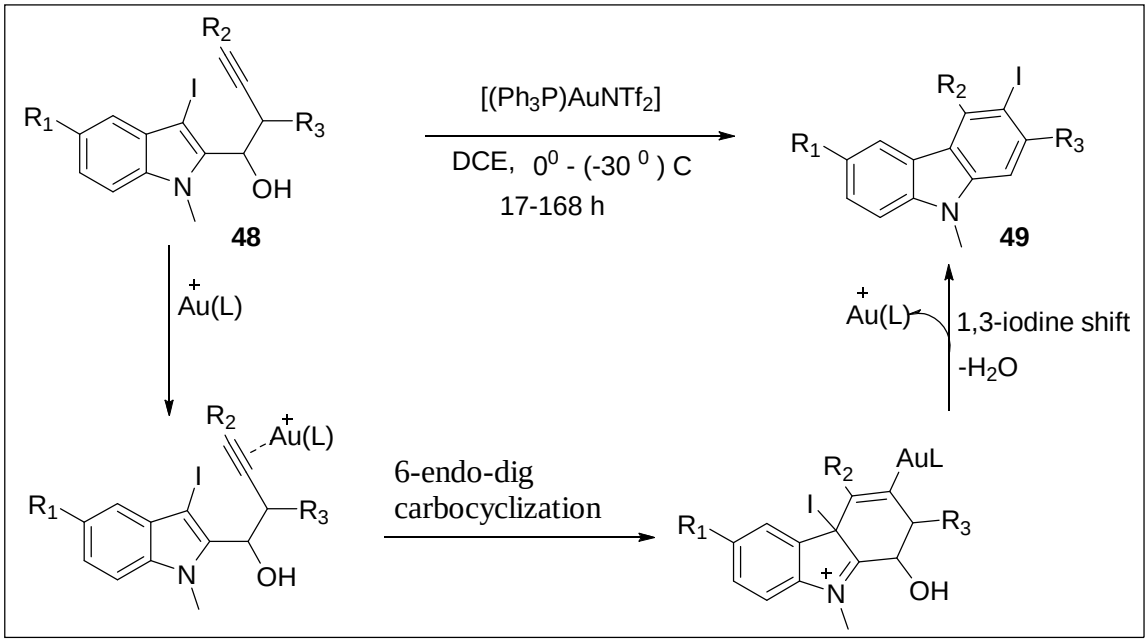
This sequential cascade process occurs at room temperature within a short time period. Importantly, the obtained carbazoles possessing iodo group (at C3) can be used as important intermediates to get access other valuable compounds by applying palladium-catalyzed coupling reactions.

1.1.2.2.2.2. Zhang *et al.*[40] reported a strategy for the efficient cyclization of 1- indol-3-yl)-3-alkyn-1-ols using cationic gold(I) complex, leading to annulated or specific substituted carbazoles as depicted in Scheme 9. They discovered divergent reaction pathway leading to the diversified carbazole structures depending on the reaction conditions and substitution pattern. Cycloalkyl-annulated [b]carbazoles **46** are obtained from 1-(indol-3-yl)-2-cyclopropyl-3-alkyn-1-ols **44** through 1,2-alkyl migration of the metal-carbene intermediates (Scheme 9A). Whereas cyclo alkyl-annulated[a]carbazoles **47** are obtained from 2,2-disubstited 1-(indol-3-yl)-3-alkyn-1-ols **45** through a Wagner–Meerwein type 1,2-alkyl shift (Scheme 9B).



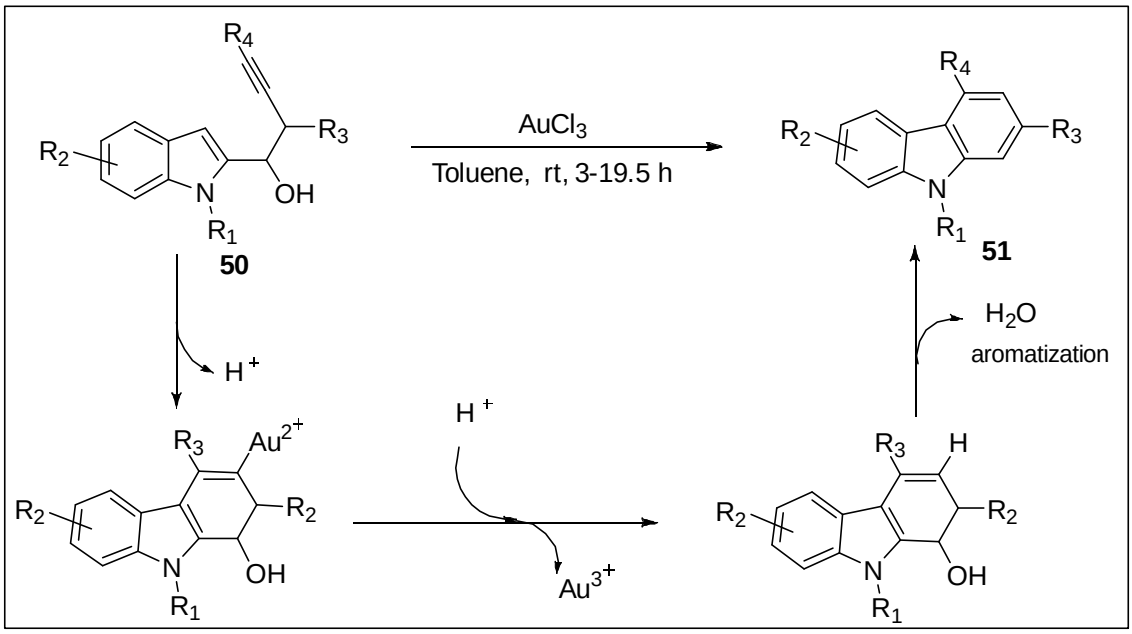
Scheme 9 : Gold-Catalyzed cyclizations of 1-(Indol-3-yl)-3-alkyn-1-ols.

1.1.2.2.2.3. Alcaide *et al.*[41] reported a gold-catalyzed benzannelation−iodine transfer method for the synthesis of 3-iodo-2,4,6-tri-substituted 9H-carbazoles **49** starting from 3-iodoindole tethered with an alkynol moiety **48** (Scheme 10). Reaction pathway has been investigated experimentally along with DFT study. The overall transformation can be rationalized through a *6-endo-dig* carbocyclizations where a chemo- and regio-specific nucleophilic attack of the C3 of the indole ring onto the alkyne moiety followed by 1,3-iodine shift and dehydration took place.



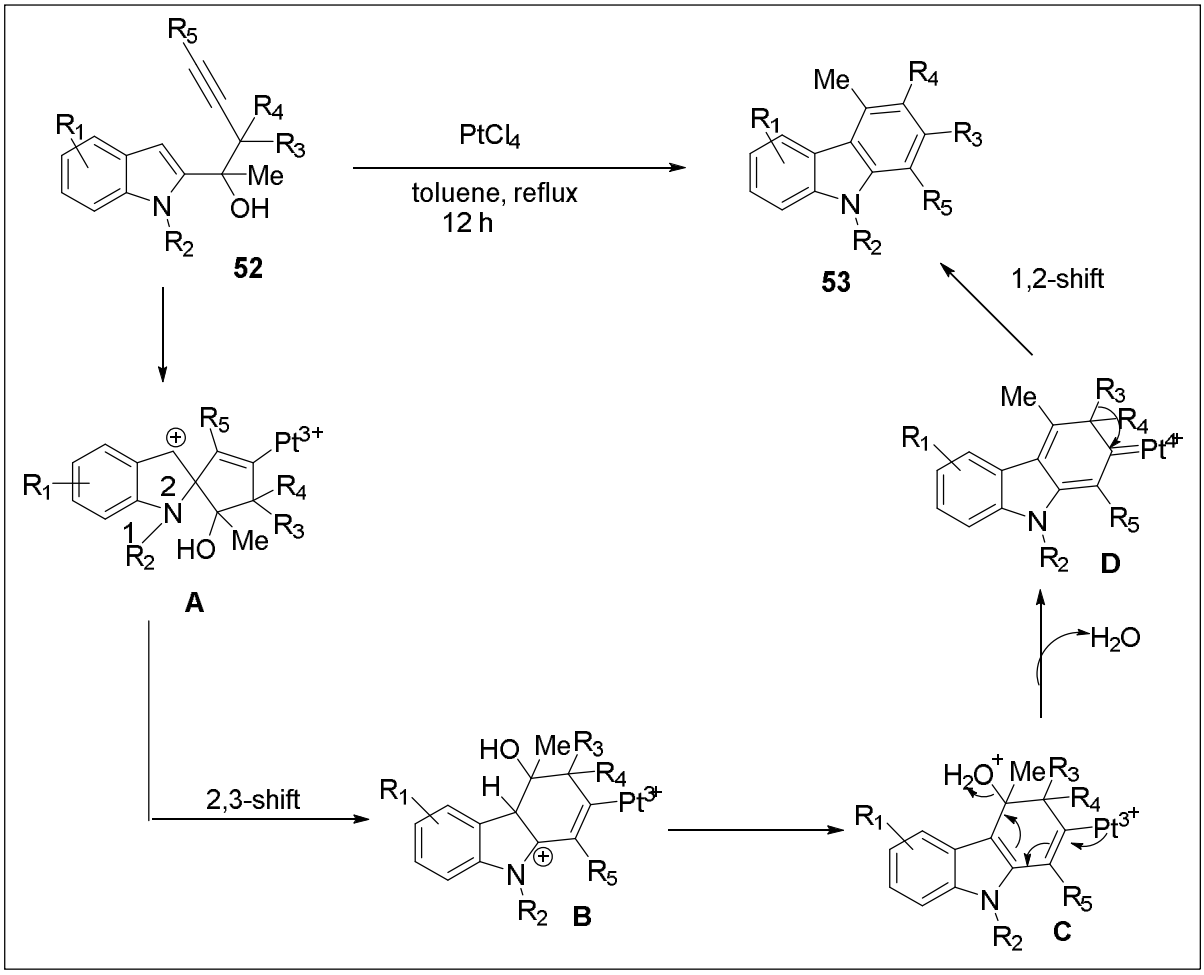
Scheme 10: Gold-catalyzed iodocarbocyclizations of (3-Iodoindol-2-yl)butynols with a plausible reaction mechanism

1.1.2.2.2.4. Qiu *et al.*[42] reported a method of $AuCl_3$-catalyzed reaction of 1-(indol-2-yl)-3-alkyn-1-ols **50** at room temperature to provide an efficient route to differently substituted carbazoles **51** in moderate to good yields (Scheme 11). Mechanistically, this reaction undergoes *6-endo-dig* cyclization triggered by gold(III)-catalyst which behaves as Lewis acid followed by dehydration.



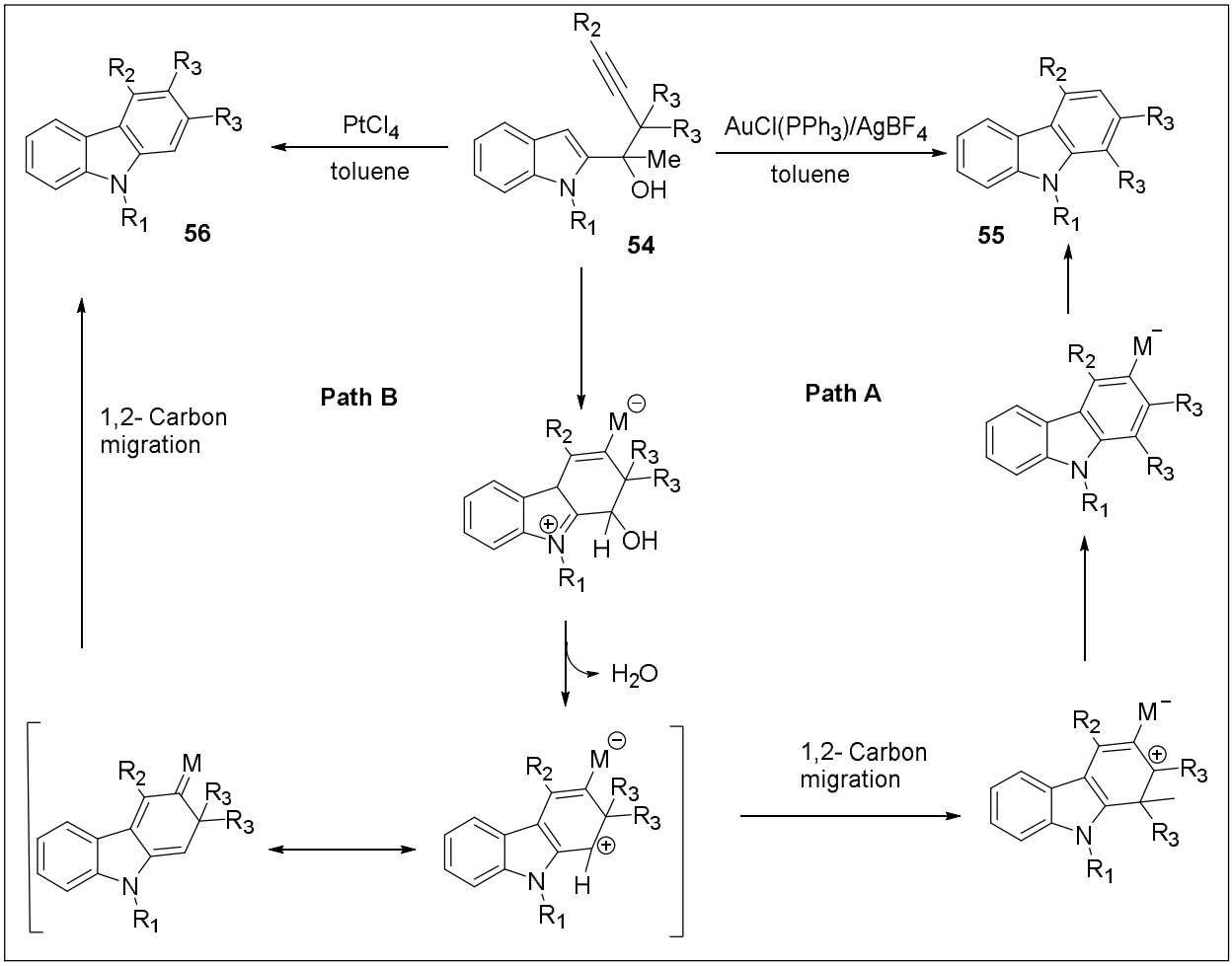
Scheme 11: $AuCl_3$-catalyzed cyclizations of 1-(Indol-2-yl)-3-alkyn-1-ols **50** with a plausible reaction mechanism.

1.1.2.2.2.5. Zhou *et al.*[43] reported a novel $PtCl_4$-catalyzed cyclizations of (indol-2-yl)-3-alkynols **52**, leading to the synthesis of poly-substituted carbazoles **53** which were found to be useful for different applications (Scheme 12) .The proposed reaction pathway involves the formation of a spiro-intermediate **A** via nucleophilic attack by the C-2 of indole ring onto the alkyne moiety. Next, intermediate **B** is formed by the ring expansion (via 2,3 shift of teriary alcohol) of **A**. Subsequent rearrangement followed by deprotonation restored the aromaticity of the indole ring. Finally, protonation of the hydroxyl group followed by dehydration of water led to the formation of the intermediate **C**. Thereafter, water elimination from **C** followed by 1,2-migration of the in situ generated vinylic platinum carbene intermediate **D** resulted in the formation carbazoles **53**.



Scheme 12: $PtCl_4$-catalyzed cyclization reaction of 2-(indol-2-yl)-4-alkyn-2- ols **52** with a plausible reaction mechanism.

1.1.2.2.2.6. Qiu *et al.*[44] reported (**Scheme 13**) a simple and efficient $AuCl(PPh_3)/AgBF_4$ or $PtCl_4$ catalyzed reaction of 1-(indol-2-yl)-2,2-dialkyl-substituted-3-alkyne-1-ols **54**, leading to the formations of differently substituted carbazoles in good isolated yields under very mild conditions. Different regioselective 1,2-alkyl migration pathways (A & B) have been established. In path A, carbazoles **55** could be obtained exclusively in the presence of $AuCl(PPh_3)/AgBF_4$ via a Wagner– Meerwein type 1,2-alkyl shift. While in some cases (path B), the use of $PtCl_4$ afforded inverted regioselectivity forming carbazoles **56** involving a platinum–carbene intermediate.



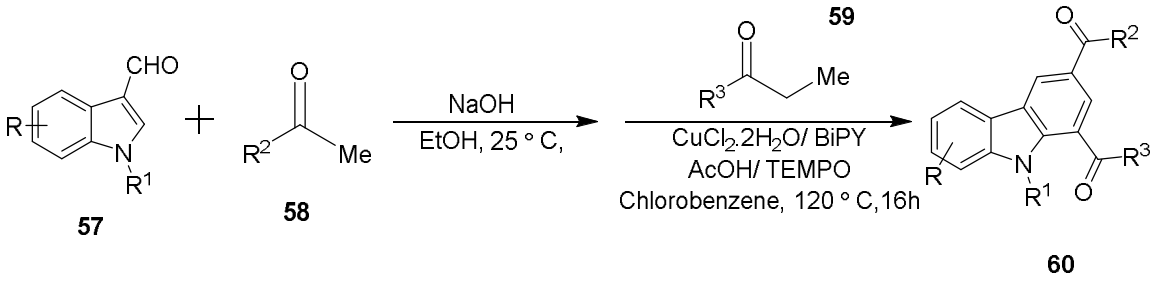
Scheme 13: Cyclizations of 1-(indol-2-yl)-3-alkyn-1-ols **54** with a plausible reaction mechanism.

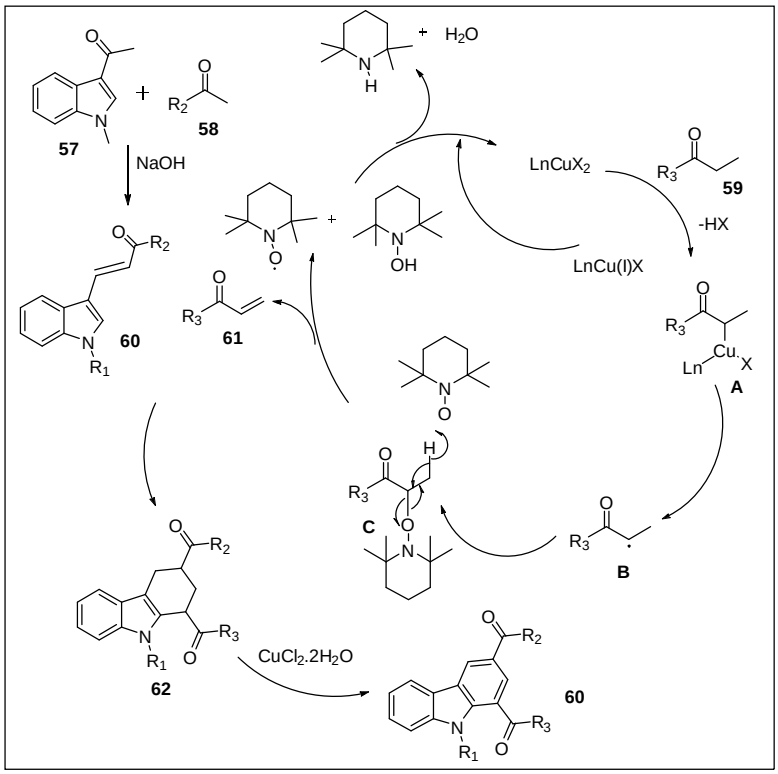
1.1.2.3. Synthesis of Carbazoles having keto-aryl group(at C3 position)

In recent past, carbazoles having keto-aryl group (at C1 and C3 positions) were found to be of substantial interests in biological and material sciences. Scrutiny of the literature, however, reveals that said keto-aryl group are installed on prefunctionlized carbazoles using *Friedel Crafts* acylation reaction. Recently, few modern methods have been disclosed wherein the construction of carbazole ring and functionalizations (at C1 & C3) of keto-aryl group are made simultaneously under one-pot using metal-catalyzed cascade reactions. These are illustrated briefly below.

Metal catalyzed reaction:

1.1.2.3.1. Guo *et al.*[19] reported a method for the synthesis of unsymmetrically substituted carbazoles **60** from Indole **57** by using saturated ketones as one-carbon **58** and two-carbon source **59**. This method however involves a copper-catalyzed, TEMPO-mediated three-component formal [3+1+2] benzannulation reactions. Reaction proceeds under one-pot through the sequence of two-steps comprising Aldol reaction followed by dehydrogenation/Diels-Alder cycloaddition/aromatization in next step as shown under Scheme-14. Such unsymmetrically substituted carbazoles regarded as promising solid fluorescence materials for optoelectronics.

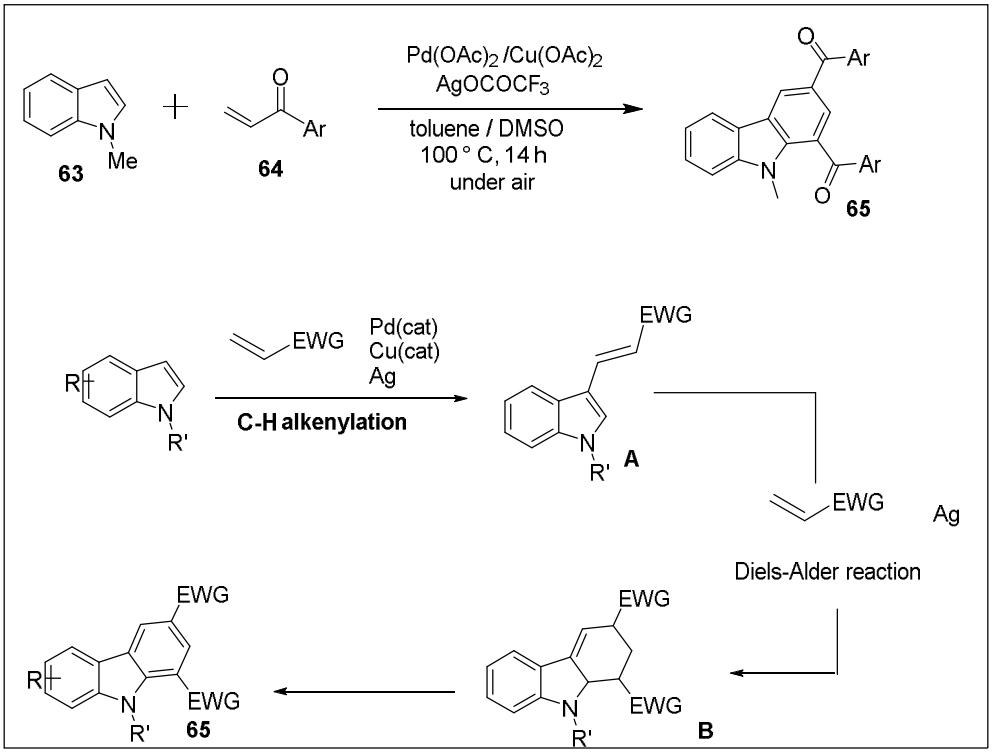




Scheme-14: Synthesis of carbazoles **60** under one pot with a plausible reaction mechanism.

Mechanistically, $CuCl_2 \cdot 2H_2O$ enolizes to saturated ketone **59** to give complex **A** which undergoes homolytic bond cleavage to generate Cu(I) species and intermediate **B** which upon reaction with TEMPO produced α-TEMPO-substituted ketone **C**. Next, another molecule of TEMPO then abstracts β-hydrogen of intermediate **C**, resulting in the elimination of TEMPOH and the desired enone **61**. Thereafter, Cu(I) species gets oxidized by TEMPO or TEMPOH to regenerate Cu(II) species. Besides, 3-alkenylated indoles **60** are generated through the aldol reactions of **57** with saturated ketones **58**. Finally, a Diels-Alder cycloaddition between enone **61** and **60** affords tetrahydrocarbazole **62**, which is subsequently oxidized to carbazoles **60** by the Cu(II), TEMPO and air.

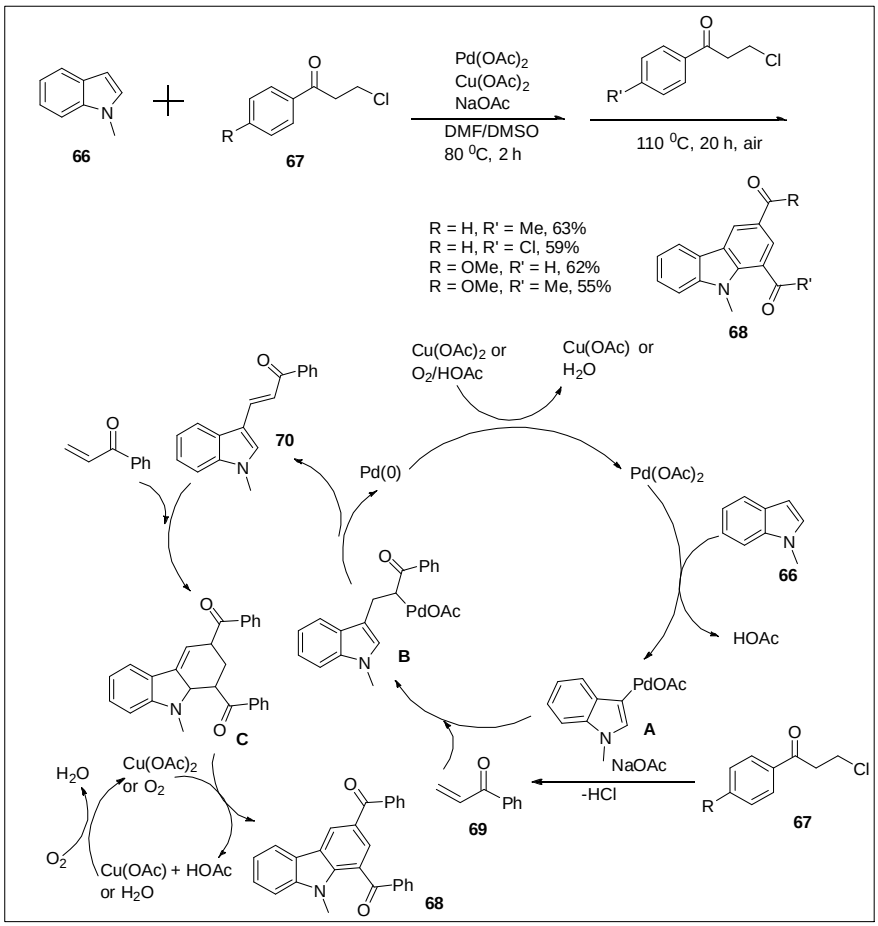
1.1.2.3.2. OZaki *et al.*[16] reported a Pd–Cu–Ag trimetallic catalyzed method for the synthsis of carbazoles **65** (Scheme-15) from indole **63** using electron-deficient alkenes as two-carbon units **64.**[1]Transformation of indole into carbazole is likely to proceed through the sequence of (i) Pd/catalyzed indole C–H alkenylation, (ii) Ag-promoted Diels–Alder reaction, and (iii) Ag-promoted dehydrogenative aromatization.



Scheme-15: Synthesis of carbazoles **65** with a plausible reaction mechanism.

Mechanistically, an indole derivative first reacts with Pd(II) to provide a 3-indolylpalladium(II) species by C–H palladation. Next, organopalladium species undergoes a *Mizoroki–Heck*-like reaction with an electrondeficient alkene to produce a C3-alkenylated indole intermediate **A**. In this C–H alkenylation process, it is assumed that copper salt and silver salt are acting as a Pd(0)/ Pd(II) oxidation catalyst and a terminal oxidant, respectively. Finally, a silver promoted Diels–Alder reaction of the 3-alkenylindole with an electron-deficient alkene delivers intermediate **B**, which upon subsequent dehydrogenative aromatization (oxidation) produces 1,3-disubstituted carbazole **65**.

1.1.2.3.3. Yu *et al.*[45] reported palladium(II)-catalyzed, copper(II)-mediated method for the synthsis of carbazoles **68** from N-protected indoles **66** with 3-chloropropiophenones **67** in the presence of a base. Reaction proceeds through the sequence a domino dehydrochlorination/alkenylation/cycloaddition–oxidation.



Scheme 16: Synthesis of carbazoles **68** with a plausible reaction mechanism.

The strategy employed in situ generated α,β-unsaturated carbonyls to avoid using a large excess of labile substrates and to minimize side reactions. This method provides an efficient route for synthesis of functionalized carbazoles **40**.

Mechanistically, indole substrate **66** initially undergoes palladation at its C3-position to form a palladated species **A** and HOAc. Species **A** reacts with **69** generated in situ (from **67)** to form an alkene insertion species **B**, which undergoes reductive elimination to produce 3-alkenylated indole **70** and Pd(0) Finally, Diels–Alder cycloaddition of **70** with en-one **69** forms tetrahydrocarbazole intermediate **C** which upon subsequent oxidation affords the desired product **68**. Besides, air facilitates regeneration of the Cu(II) oxidant and Pd(II) catalyst.

1.1.3. Concluding remarks:

A detailed review of the literature shows that carbazoles are considered as privileged scaffolds as these constitute the core structure of numerous bioactive alkaloids and serve as pharmacophore in medicinal chemistry and important building block in organic synthesis. For the synthesis of carbazoles, although many procedures adopting either classical reactions or using metal catalyzed reactions are known, most of these reactions, however, suffer from the need to synthesize complex starting materials or to use harsh reaction condition, or to employ multistep reactions with low overall yields. Recently, few metal-catalyzed methods wherein the construction of carbazoles having substitutions (at C1 & C3) with keto-aryl group are made under one-pot but there is no method for carbazoles having keto-aryl group at C3 position. Therefore, more convenient procedures involving one pot construction of carbazoles and particularly, substitution with keto aryl group at C3 position need to be developed. Detailed findings towards this objective have been discussed in part II of this chapter.

Part-II

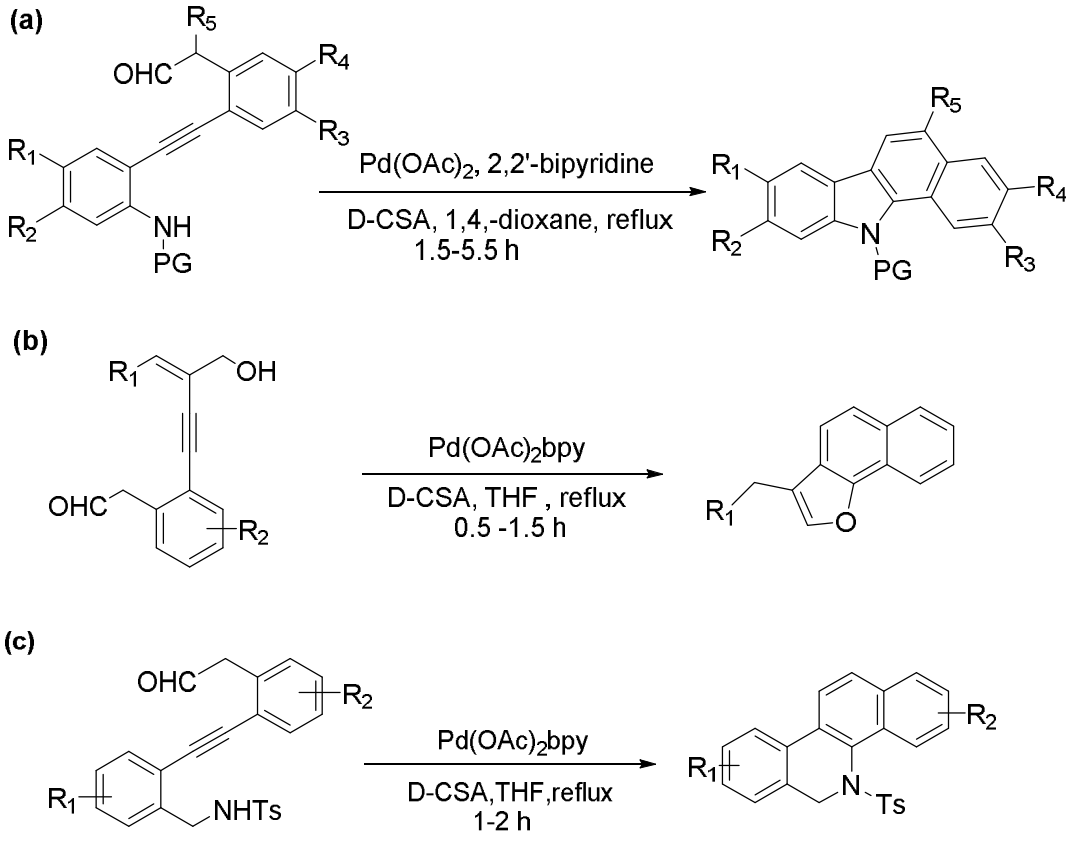
(Result & Discussion)

1.2.1. Introduction

In recent past, the synthesis of carbazoles has gained a great momentum by the deployment of transition metal catalyst resulting in developments of many methods to get their access easily. Among many useful procedures to construct carbazoles, (discussed previously in part-1) synthetic pathways of forming benzene ring starting from indole substrates are of particular interests. However, this strategy is considered to be superior because of the easy accessibility of the indoles and their notable reactivity at C1 and C2 positions, enabling them to participate easily in various carboannulations to deliver functionalized carbazoles instead of taking pre-functionalized substrates. Nevertheless, the intermolecular version of indole-to-carbazole strategy primarily relies on Diels−Alder reaction carried out under one pot or in multiple-step where C−C bonds are formed through transition-metal-catalyzed reactions of indoles with alkenes or alkynes. (Scheme 5-7 in part -1). While intramolecular cycloisomerisations of indoles tethered with alkene/alkynes have received substantial interests in recent past to provide rapid access to carbazoles in atom economical manner. More specifically, in recent years, metal catalyzed cascade reactions of 1-(indol-3/2-yl)alk-3-yn-1-ols proved to be a very efficient strategy to deliver carbazoles in high yields. Typically, iodine mediated and gold(I)-catalyzed cyclizations (5-*endo-dig*) of 1-(indol-3-yl)-3-alkyn-1-ols are reported to be formed carbazoles through a Wagner–Meerwein-type 1,2-alkyl shift (Scheme 8,9 in part-1). On the other hand, benzoanulations of 1-(indol-2-yl)-3-alkyn-1-ols are used as potential substrates by employing Au(I) & Au(III), and Pt(IV) catalyst (Scheme 10-13 in part -1). Surprisingly, to our best of knowledge, the palladium-catalyzed reactions of the aforesaid substrates has not been explored yet to gain access of the functionalized carbazoles.

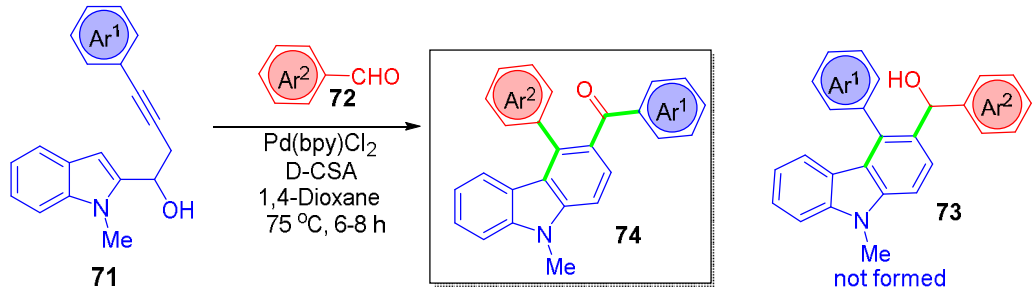
In continuation of our works[46] on palladium-catalyzed reactions of acetylenic substrates tethered with aldehyde group (Scheme:17a-c) for the synthesis of heterocycles of biological interests, we envisioned that palladium(II)-catalyzed intermolecular cascade reaction[47]

between 1-(indol-2-yl)but-3-yn-1-ols **71** with aldehydes **72** would lead to the formations of carbazole derivatives **73**; but we became surprise to find out an unexpected carbazole derivatives **74** of biological interests (discussed previously in part-1) instead of the expected product **73** (Scheme 18). Notably, metal-catalyzed synthesis of carbazoles having aryl substitutions at C3 with carbonyl linker has been limited (see, Schemes 14-16 of part 1 of this chapter) in few numbers where indole is used as starting substrate. But there is no report of pallaium-catalyzed synthesis of carbazoles **74** possessing the said keto-aryl moiety at C3 position. We therefore first report the synthesis of the aforesaid carbazoles **74** (Scheme 18) via Pd(II)-catalyzed alkyne-carbonyl metathesis reaction between 1-(indol-2-yl)but-3-yn-1-ols **71** and aryl aldehydes **72** where four new C-C bonds are formed under one pot. We discuss herein in details the results obtained so far.



Scheme 17. Previous works of our group on palladium-catalyzed reactions of acetylenic substrates tethered with aldehyde group..

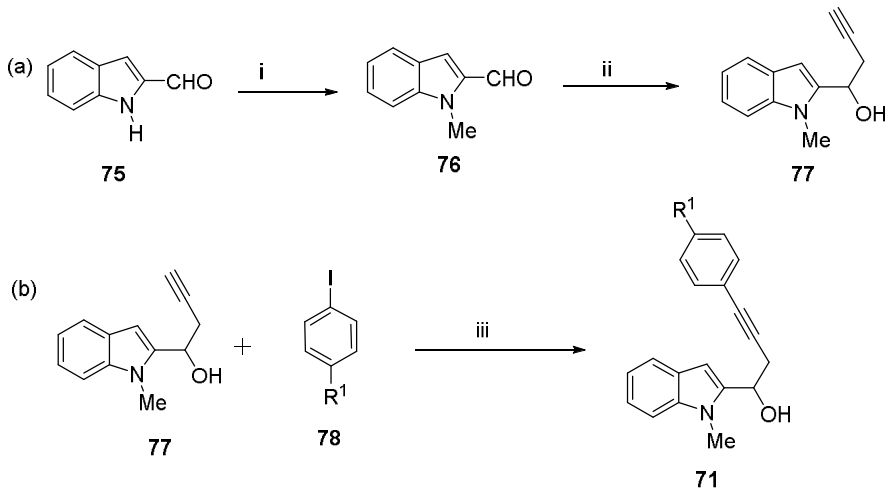
Present work:



Scheme 18. Palladium-catalyzed synthesis of carbazoles **74**

1.2.2. Synthesis of Starting Materials 71

With the objective of the synthesis of carbazoles 7**4**, initially, we focused our efforts for the preparation of the requisite starting materials **77** which can easily be synthesized in two steps starting from 1H-indole-2-carbaldehyde as shown in Scheme 19. Initially, methylation of indole-2-carbaldehyde **75** using methyl iodide and sodium hydride in DMF afforded N-methylated indole **76.**[48] Then, 1-(indol-2-yl)but-3-yn-1-ols **77** was synthesized from N-methylated indole-2-carbaldehyde **76** by using[49] Zn dust and propargyl bromide in THF/NH_4Cl (aq. sat) at 0 ^{0}C. Thereafter, product **77** underwent "*Sonogashira coupling reaction*" with commercially available *para*-iodo phenyl derivatives **78** to afford the requisite starting materials 7**1.**



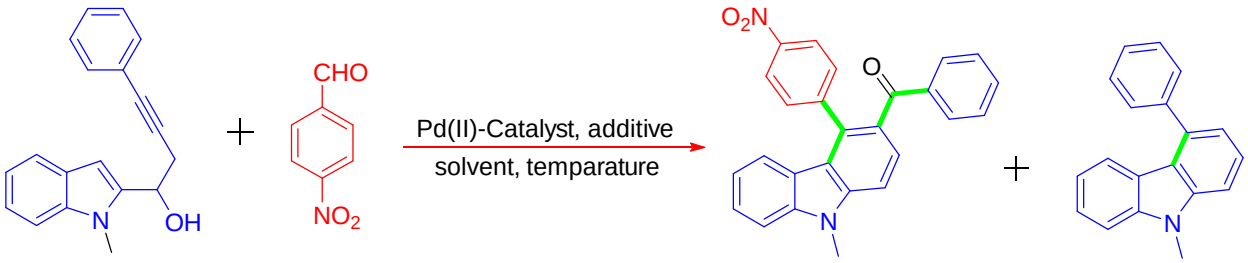
Scheme 19. (i) NaH, DMF, Me-I, rt, 1-2 h, 95 %; (ii) Zn dust, propagyl bromide, THF/NH_4Cl (aq. sat), 0 ^{0}C, 4-5 h 90%; (iii) $PdCl_2(PPh_3)_2$, CuI, Et_3N, rt, overnight, 76-85 %.

1.2.3. Synthesis of Carbazoles 74 having Aryl group at C4 & Keto-aryl group at C3 position:

1.2.3.1. Optimization of Reaction Condition for the Synthesis of (9-Methyl-4-(4-nitrophenyl)-9H-carbazol-3-yl)(phenyl)methanone 74a

Initially, with an objective to synthesize carbazole 7**4**, we initiated a model reaction (see, **Table 1**) between 1-(indol-2-yl)but-3-yn-1-ols **71a** (R^1 = H) synthesized easily in two steps starting from indole-2-carbaldehyde (as shown in Scheme 19) and 4-nitrobenzaldehyde **72a** in refluxing THF using the catalytic system [i.e., $Pd(OAc)_2$bpy/D-CSA] used in our previous study,[46c] this reaction however culminated in the formation of **79** (75%), a self-cyclised product of **71a,** making the aldehyde **72a** inert toward this reaction (Table 1, entry 1). To our surprise, replacing the catalyst with $Pd(H_2O)_2bpy(OTf)_2$ and not using any additive made the aldehyde **72a** reactive resulting in the formation of a new product **74a** (45%) instead of expected one (i.e., **73,** Ar^1 = Ph, Ar^2 = -$C_6H_4NO_2$-*p*; see Scheme 18) together with **79** (35%) (Table 1, entry 3). But carrying out the same reaction at higher temperature (i.e., 80 ^oC) diminished the yields of the products in some extent (Table 1, entry 3). In order to enhance the efficacy of the reaction for the formation of product 7**4a**, we carried out this reaction at 75 ^oC in 1,4-dioxane using $Pd(bpy)Cl_2$ and D-CSA as catalyst and additive, respectively (Table 1, entry 4); to our pleasure, an exclusive formation of **74a** took place in 72% yield with complete suppression of the side product **79**. Nevertheless, replacing D-CSA with other additive (i.e., TsOH/AcOH) in subsequent reactions (Table 1, entries 5-6) showed no sign (TLC) of the formation of **74a** except the side product **79** which was isolated in moderate yields (50-52%). We therefore persisted with the previous additive (D-CSA) but switched on

Table 1. Optimization of the Reaction Conditions for the Synthesis of (9-methyl-4-(4-nitrophenyl)-9H-carbazol-3-yl)(phenyl)methanone 74a[a]



71a **72a** **74a** **79**

Entry	Catalyst	Additive	Solvent	Temp (^{0}C)	Yield[b] (%) **74a**	**79**
1.	$Pd(OAc)_2bpy$	D-CSA	THF	70	00	75
2	$Pd(H_2O)_2bpy(OTf)_2$	——	1,4-Dioxane	70	45	35
3.	$Pd(H_2O)_2bpy(OTf)_2$	——	1,4-Dioxane	80	40	30
4	**$Pd(bpy)Cl_2$**	**D-CSA**	**1,4-Dioxane**	**75**	**72**	00
5.	$Pd(bpy)Cl_2$	*P*-TSA	1,4-Dioxane	70	00	52
6.	$Pd(bpy)Cl_2$	AcOH	1,4-Dioxane	75	00	50
7.	$Pd(bpy)Cl_2$	D-CSA	DME	75	nr	-
8.	$Pd(bpy)Cl_2$	D-CSA	NMA	75	nr	-
9.	$Pd(bpy)Cl_2$	D-CSA	THF	70	62	00

[a]Reaction Conditions: 7**1a** (0.18 mmol), **72a** (0.27mmol, 1.5 equiv), catalyst (10 mol %), and D-CSA (1.5 equiv) in 3 mL solvent heated at temperature (as mentioned in table) under argon atmosphere .

[b]Yields of the isolated pure products.

to the other solvent systems (Table 1, entries 7-9) including both high (DME/NMA) and low (THF) polar ones; though THF triggered the formation of **74a** in good yield (62%), polar

solvents (DME/NMA) did not facilitated this reaction at all thereby making hindrance to the formation of **74a**. From the aforesaid study we concluded that the conditions used in entry 4 of Table 1 as the preferred ones to explore the scope of this reaction (Scheme-20) as described below.

1.2.3.2. Scope of the reaction

We then explored the substrate scope using various 1-(indol-2-yl)but-3-yn-1-ols **71a−e** and aryl aldehydes **2a−i** (Scheme 20). Initially, we checked the reactivity of **71a** (R^1 = Ph) with different aldehydes **2b−i** separately under the optimized reaction conditions. A strong electron-withdrawing group (EWG) (viz. $R^2 = CF_3$) at the para position of the phenyl ring of aldehyde **72b** facilitated the reaction with **71a**, resulting in the formation of **74b** within 6 h in 73% yield, comparable to that of **74a**. However, a moderate EWG (viz., R^2 = Br) as in substrate **72c** reduced the yield of the product **74c** considerably (53%). On the other hand, a strong electron-donating group (EDG) (viz., R^2 = OMe) at the para position as in **72d** afforded the product **74d** in a lower yield of 62% in 7 h, while the incorporation of two methoxy groups as in **72e** slightly enhanced the yield of the product **74e** compared with **74d** (64%). A moderate EDG like Me (at the ortho position of aldehyde **72f**) also gave the product **74f** in a lower yield (59%). Furthermore, reactions of **71a** with benzaldehyde (**72g**), naphthaldehyde (**72h**), and 2-formylthiophene (**72i**) furnished the products **74g**, **74h**, and **74i**, respectively, within 6−8 h in moderate yields (40−50%).

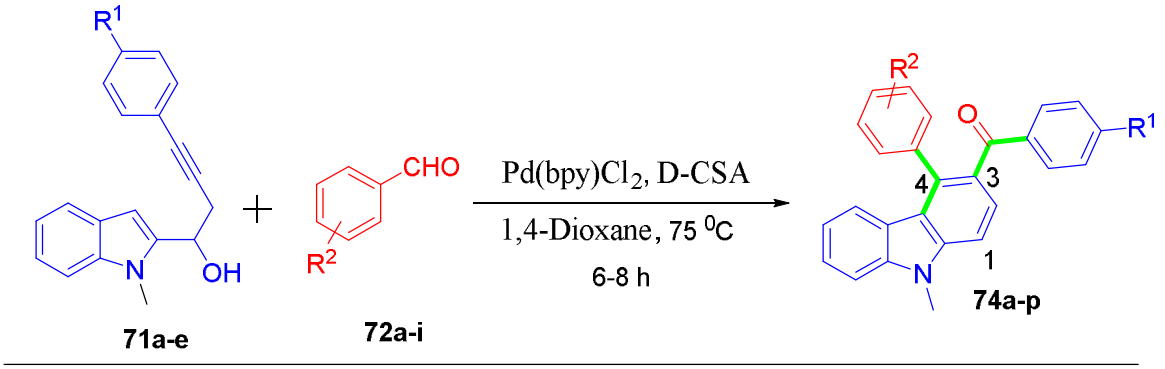
Next, we studied the reactivity of acetylene **71b** having an EDG (R^1 = OMe) on the phenyl ring attached to the acetylenic carbon with aldehydes **72a** ($R^2 = NO_2$) and **72b** ($R^2 = CF_3$) having an EWG at the para position. Gratifyingly, these reactions afforded products **74j** and **74k**, respectively, within 6−7h in very good yields (68−71%). Substrate **71c** carrying an

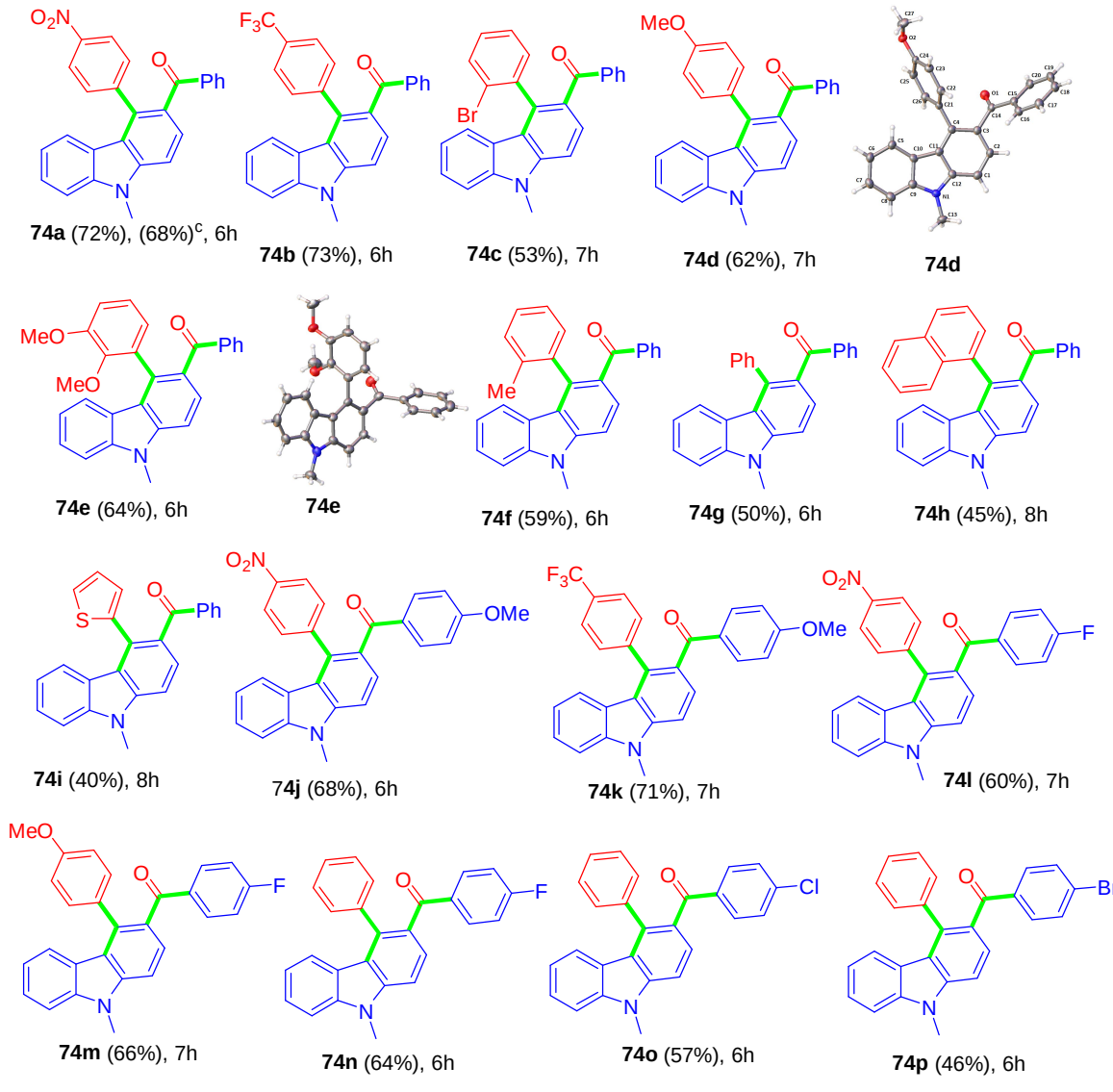
EWG (R^1 = F) also underwent reactions with *p*-nitrobenzaldehyde (**72a**), *p*-methoxybenzaldehyde (**72d**), and benzaldehyde (**72g**) to furnish the products **74l**, **74m**, and **74n**, respectively, within 7 h, albeit in somewhat lower yields (60−66%) compared with **74j** and **74k**.

Furthermore, replacing the fluoro group of acetylenic substrate **71c** by either chloro or bromo and allowing the resulting substrate (**71d** or **71e**) to undergo the reaction with benzaldehyde (**72g**) led to the generation of the desired product (**74o** or **74p**) within 6 h in moderate yield (46−57%).

Besides, we used an aliphatic aldehyde (EtCHO) instead of the aryl one (**72**) but obtained no such product **74**. In addition, the incorporation of an aliphatic group (i.e., Et) in place of the phenyl ring attached to the acetylenic carbon of substrate **71a** failed to deliver any of the desired product. Furthermore, the replacement of the N-methyl group of substrate **71a** by N-H also proved to be unsuccessful, showing the limitations of the reaction.

Scheme 20. Synthesis of 4-Aryl-3-arylcarbonyl-carbazoles **74a-p**[a,b]



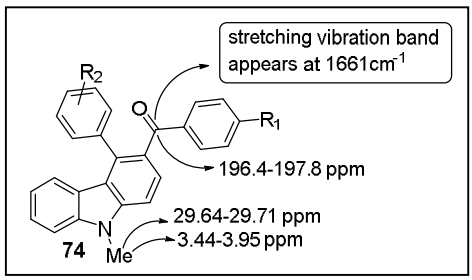


[a]Reaction Condition: **71** (0.18 mmol), **72** (0.27, 1.5 equiv), catalyst (10 mol %), and D-CSA (1.5 eqiv) in 3 mL solvent heated at temperature (as mentioned in table) under argon atmosphere.

[b]Yield of the isolated pure products. [c]1.0 mmol scale reaction.

1.2.4. Nature and Characterization of Products 74

All the synthesized products are moderately stable at room temperature but can be stored at



room temperature (4 ^{o}C) for the several months. The structure of the products were unambiguously deduced by spectral (^{1}H and^{13}C NMR, Mass and IR Spectra) and analytical data. In mass spectra (ESI and EI), the molecular ion peak in positive mode of all the compounds appeared as M^{+} or protonated [M + H]$^{+}$ and /or sodiated [M + Na]$^{+}$ ion. In ^{1}H NMR, the protons for the methyl group attached to nitrogen atom of carbazole appear 3.44-3.95 ppm as singlet as expected, whereas remaining aromatic protons appear in the range 6.66-8.26 ppm. In ^{13}C NMR, carbonyl carbon appears in range 196.4-197.8 ppm and the carbon of the N-Me group appears in the range 29.64-2971 ppm and other carbons appeared at appropriate positions. In addition, in IR spectra, carbonyl (C=O) stretching vibration band appears at 1661cm^{-1} . Thus, the spectral data (^{1}H,^{13}C, Mass Spectra, IR Spectra) provided support in favour of the structure **74** (Scheme-18).

Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of the compounds **74d**, 7**4e**, and **74k**. The single crystal was obtained by slow evaporation (at room temperature) of a solution of petroleum ether and dichloromethane. The ORTEP diagrams of the crystal structures are shown in Figures **11**, **12**, and **13,** respectively.

ORTEP diagram of 74d

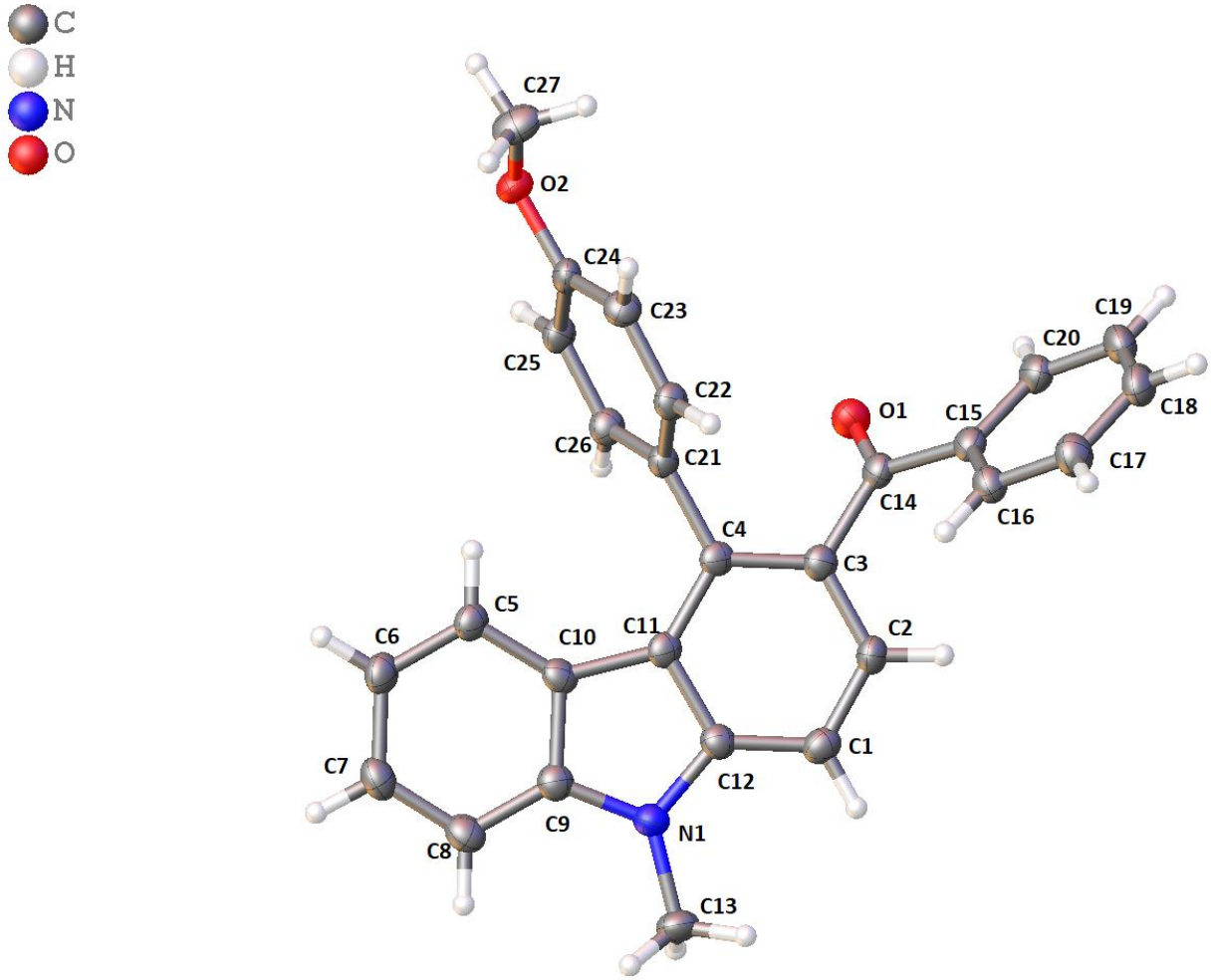


Figure 11. ORTEP Diagram (thermal ellipsoid plot) of 7**4d** (drawn at 50% probability level)

ORTEP diagram of 74e

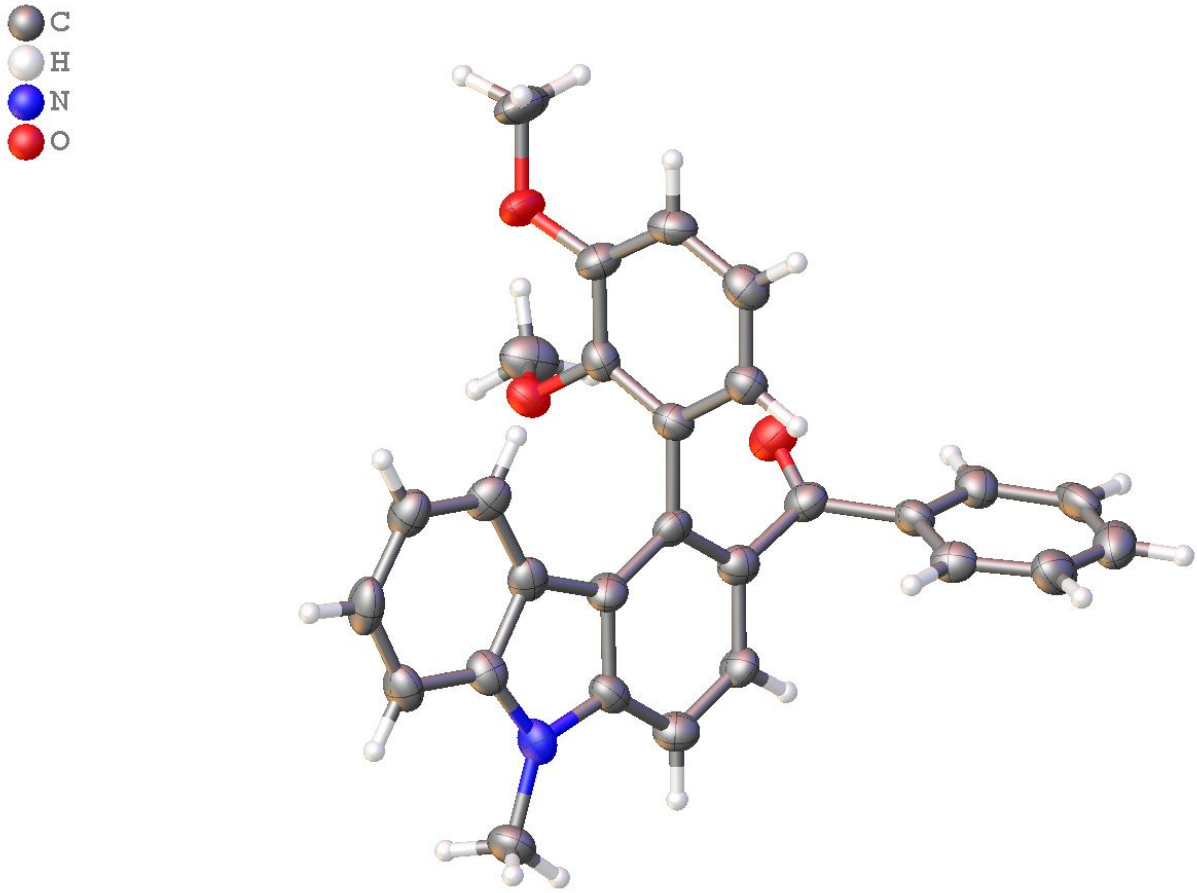


Figure 12. ORTEP Diagram (thermal ellipsoid plot) of 7**4e** (drawn at 50% probability level)

ORTEP diagram of 74k

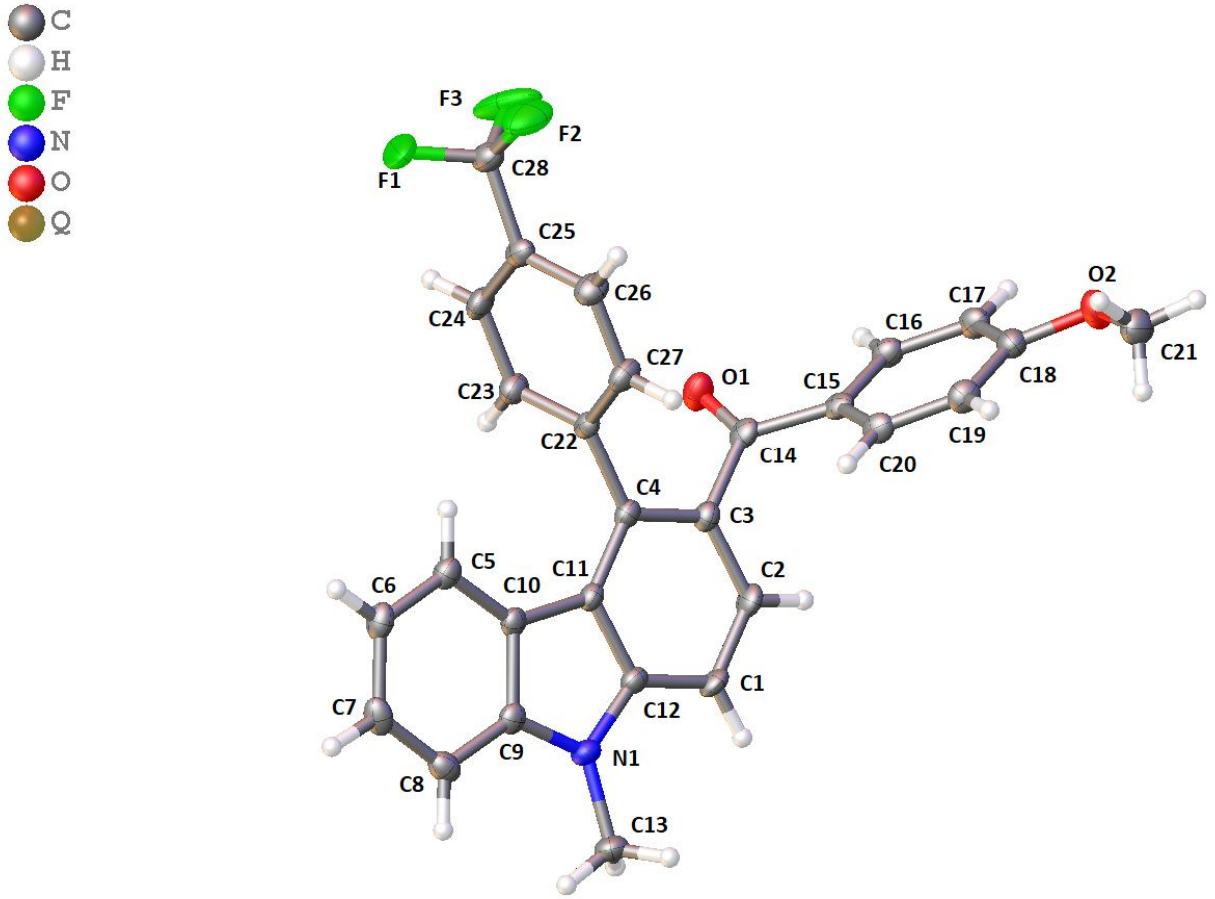


Figure 13. ORTEP Diagram (thermal ellipsoid plot) of 7**4k** (drawn at 50% probability level)

Table 2: Important crystal data of product **74d**

Empirical formula	$C_{27}H_{21}NO_2$
Formula weight	391.45
Temperature	100 K
Wavelength	1.54184
Crystal system	'Monoclinic'
Space group	'P 21/C'
Unit cell dimensions	a = 10.7450(13) Å α = 90
	b = 19.499(3) Å β = 96.687(11)
	c = 9.6209(14) Å γ = 90
Volume	2002.0(5) $Å^3$
Z	4
Density (calculated)	1.299 g/cm^3
Absorption coefficient (Mu)	0.644mm^{-1}
F(000)	824
Theta range for data collection	4.143^0 to 68.484^o
Index ranges	-12<=h<=12, -23<=k<=23, -11<=l<=11
Reflection collected	61859
Independent reflections	3663 [R(int) = 0.0946]
Completeness to theta	99.6 %
Absorption correction	multi-scan
Max. and min. transmission	0.713 and 0.879
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3663/0/ 274
Goodness-of-fit on F^2	1.179
Final R indices [I>2sigma(I)]	R1 = 0.0782, wR2 = 0.1832
R indices (all data)	R1 = 0.0803, wR2 = 0.1848
Largest diff. peak and hole	0.409 & -0.360 $e.A^{-3}$

The single crystal of compound **74d** 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 **74d** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2132274**.

Table 3: Important crystal data of product **74e**

Empirical formula	$C_{28}H_{23}NO_3$
Formula weight	421.47
Temperature	100 K
Wavelength	1.54184
Crystal system	'Monoclinic'
Space group	'P 21'
Unit cell dimensions	a = 7.5075(3) Å α = 90
	b = 8.6220(3) Å β = 90.360(1)
	c = 16.7.66(7) Å γ = 90
Volume	1081.39 (7) $Å^3$
Z	2
Density (calculated)	1.294 g/cm^3
Absorption coefficient (Mu)	0.669mm^{-1}
F(000)	444
Theta range for data collection	5.30^0 to 69.74^o
Index ranges	-9<=h<=9, -10<=k<=10, -20<=l<=20
Reflection collected	23321
Independent reflections	3972 [R(int) = 0.0490]
Completeness to theta	97 %
Absorption correction	multi-scan
Max. and min. transmission	0.713 and 0.83
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3972/1/ 294
Goodness-of-fit on F^2	1.211
Final R indices [I>2sigma(I)]	R1 = 0.0381, wR2 = 0.1023
R indices (all data)	R1 = 0.0416, wR2 = 0.1132
Largest diff. peak and hole	0.486 & -0.486 $e.A^{-3}$

The single crystal of compound **74e** 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 **74e** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2132275**.

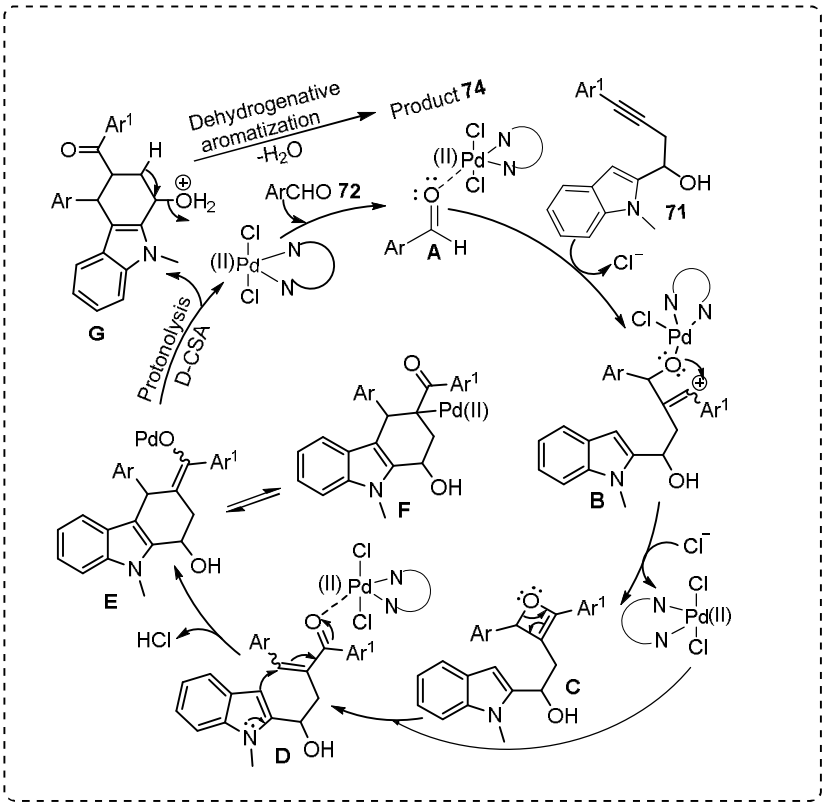
Table 4: Important crystal data of product 7**4k**

Empirical formula	$C_{28}H_{20}F_3NO_2$
Formula weight	459.45
Temperature	293 K
Wavelength	1.54184
Crystal system	'Monoclinic'
Space group	'P 21/C'
Unit cell dimensions	a = 15.076(9) Å α = 90
	b = 8.954(2) Å β = 111.34(4)
	c = 17.120(6) Å γ = 90
Volume	2152.6 (17) $Å^3$
Z	4
Density (calculated)	1.418 g/cm^3
Absorption coefficient (Mu)	0.893mm^{-1}
F(000)	952
Theta range for data collection	3.147^0 to 66.744^o
Index ranges	-17<=h<=17, -10<=k<=10, -18<=l<=20
Reflection collected	26178
Independent reflections	3764 [R(int) = 0.0775]
Completeness to theta	98.7%
Absorption correction	multi-scan
Max. and min. transmission	0.614 and 0.836
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3764/0/ 307
Goodness-of-fit on F^2	1.054
Final R indices [I>2sigma(I)]	R1 = 0.0586, wR2 = 0.1537
R indices (all data)	R1 = 0.0621, wR2 = 0.1570
Largest diff. peak and hole	0.436 & -0.383 e.A^{-3}

The single crystal of compound **74k** 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 **74k** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **2132276.**

1.2.5. Plausible Reaction Mechanism for the Formation of the Products 74

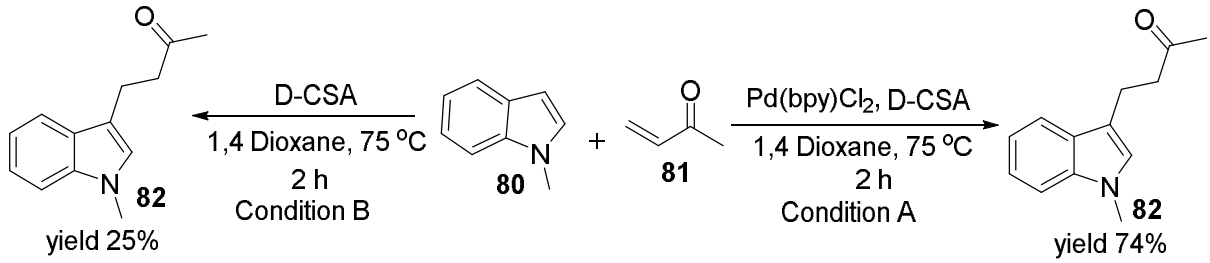
On the basis of the known palladium chemistry and alkyne-carbonyl metathesis reaction,[50] we propose a plausible reaction mechanism (Scheme 3). Initially, carbonyl group of substrate **72** is activated by the palladium catalyst [Pd(bpy)Cl_2] through Lewis acid-base type interaction[51] (species A) to undergo a nucleophilic attack by the alkyne moiety of **71**. This generates a transient vinylic cation intermediate **B** which readily transforms to an oxetene intermediate **C** with the liberation of the palladium(II) catalyst. Subsequently, a formal (2 + 2) cyclo-reversion of the oxetene ring of **C** leads to the formation of the vinylic ketone intermediate **D** which undergoes an intramolecular Michael addition. The palladium catalyst[52] possibly activates the carbonyl group of species **D** for this purpose, resulting in the formation of intermediate **E** or **F**.[53] Thereafter protonolysis[46b] of the palladated intermediate (**E** or **F**) by D-CSA produces species **G** along with regeneration of palladium(II) catalyst. Finally, dehydration and dehydrogenative aromatization of species **G** would furnish carbazole **74**.



Scheme 21. A plausible reaction mechanism for the formations of products **74**

1.2.5.1. Control Experiment:

In a control experiment, N-methyl indole **80** (1 mmol) was allowed to react with methyl vinyl ketone **81** (1.5 mmol) in 1,4-dioxane (3 mL) under our optimized reaction conditions [i.e., $Pd(bpy)Cl_2$ (10 mol%), D-CSA (1.5 equiv.), 75 ^oC] for 2h; pleasingly, the desired Michael addition product **82** (at C3 position of the indole) was found to be formed in 74% yield; whereas omitting the catalyst from this reaction dropped the yield of the same product to 25% suggesting the role of palladium in this reaction.



Scheme 22. Formation of Michael addition product **82**

1.2.6 Conclusion:

In conclusion, we have disclosed a novel Pd(II)-catalyzed cascade reactions of simple substrates such as 1-(indol-2-yl)but-3-yn-1-ol **71** and aryl aldehydes **72** resulting in a facile method for a general synthesis of carbazoles **74** having aryl and keto-aryl substitutions at C4 and C3, respectively. This substitution pattern is diffcult to obtain by classical routes such as *Fischer–Borsche* synthesis and the *Graebe–Ullmann* synthesis. The newly developed method constitute a fast intermolecular assembly involving a novel Pd(II)-catalyzed alkyne-carbonyl metathesis reaction where four new C-C bonds are formed under one pot. Although alkyne-carbonyl metathesis is usually carried out by coinage metal catalyst,[50] to the best of our knowledge, the same metathesis promoted by palladium catalysis is yet to be achieved. The reactions are operationally simple, compatible with a range of functional groups, atom

economic and environmental friendly as water is the only by-product. We believe that this novel method will be useful to the practitioners engaged in organic and medicinal chemistry.

1.2.7 Experimental Section:

General: 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), NMA (*N*-Methylacetamide) and DME (1,2-Dimethoxyethane) 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 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. Reactions that require heating, oil bath containing of silicon oil is use as a heat source.

General Procedure for the Preparation of the Starting Substrates 71

Procedure for the synthesis of 1-methyl-1H-indole-2-carbaldehyde (**76**) *(Part a, Scheme* 19):

A oven dried, 50 mL two necked round bottom flask was charged with NaH (60% dispersion in mineral oil, 4.14 mmol) and DMF (4 mL) under argon atmosphere. Next, 1H-indole-2-carbaldehyde **75** (2.07 mmol) in DMF (2 mL) was added drop wise at 0^o C and the stirring was continued for 30 minutes. To this stirred solution, methyl iodide (3.10 mmol) was added dropwise at 0^o C and the whole reaction mixture was allowed to warm to room temperature with stirring until the starting material disappeared (TLC). The resulting mixture was then quenched by dropwise addition (2-3 mL) of water at 0^o C, extracted with ethyl acetate (EtOAc) (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was then purified by column chromatography over silica gel (100-200 mesh) using 15% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired product N-protected indole aldehyde **76** (0.312 g) in 95% yield.

Procedure for the Synthesis[49] *of 1-(Indol-2-yl)-3-butyne-1-ol 77 (Part II,* **Scheme 19**)**:**

To a well-stirred mixture of activated zinc (0.55 g, 8.49 mmol) in THF (3 mL) was added propargyl bromide (0.3 mL, 3.54 mmol) and the mixture allowed to stir at 0 °C for 1 h. Next, 1-methyl-1H-indole-2-carbaldehyde **76** (0.23 g, 1.45 mmol) was added to the reaction mixture and stirred at the same temperature for another 2 h. Saturated aqueous NH_4Cl solution (10 mL) was then added at 0 °C, and the reaction mixture was stirred for another 30 min. After completion of the reaction (TLC), the reaction mixture was filtered, and the filtrate was then extracted with ethyl acetate (3 × 30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting liquid residue was

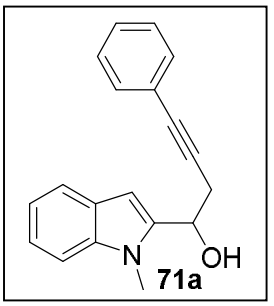
purified through silica gel (100−200 mess) column chromatography (ethyl acetate−petroleum ether) to afford the requisite intermediate 1-(indol-3-yl)-3-butyne-1-ol **77** (0.25 g) in 87% yield.

*General Procedure for the Synthesis of Substrate **71** (*Part II, Scheme 19)**:**

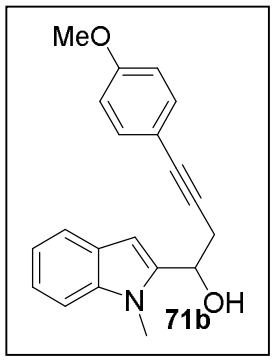
To a well-stirred solution of **77** (1.01 mmol, 1 equiv.) in Et_3N (3 mL) was added $PdCl_2(PPh_3)_2$ (1 mol %) and CuI (2 mol %) and the whole reaction mixture was stirred for 5 minutes under argon. A solution of aryl iodide **78** (2.02 mmol, 2 equiv.) in Et_3N (1 mL) was then added dropwise for 5 minutes. The resulting solution was then stirred at room temperature for overnight. When the reaction was found to be completed (TLC), the reaction mixture was then quenched by addition of water (2 mL), extracted with ethyl acetate (3 x 40 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was then purified through silica gel (100−200 mess) column chromatography (ethyl acetate−petroleum ether) to afford the requisite product **71** (0.21 g) in 76-85% yield.

Spectral data of compounds 71a-1e:

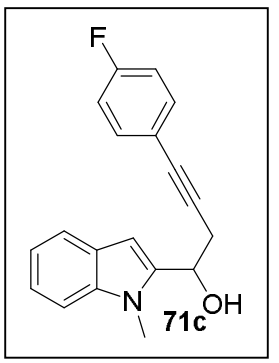
1-(1-methyl-1H-indol-2-yl)-4-phenylbut-3-yn-1-ol (71a) : Brown solid (226.8 mg, 82% yield) isolated using 15% ethyl acetate-petroleum ether (v/v); mp 88-92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (dt, *J* = 8, 0.8 Hz, 1H), 7.42-7.40 (m, 2H), 7.33-7.31 (m, 1H), 7.30-7.27 (m, 3H), 7.25-7.21 (m, 1H), 7.12-7.08 (m, 1H), 6.60 (s, 1H), 5.12 (q, *J* = 5.6 Hz, 1H), 3.84 (s, 3H), 3.21-3.10 (m, 2H), 2.36 (d, *J* = 5.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 140.0, 138.0, 131.8, 128.4,128.2,127.2,123.2, 122.1, 120.99, 119.7, 109.2, 100.0, 99.5, 85.5, 83.8, 65.6, 30.3, 27.7 ppm. HRMS (ESI^+) m/z calculated for $C_{19}H_{18}NO$ $[M+H]^+$ 276.1388, found 276.1390.



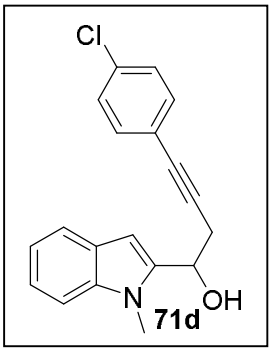
4-(4-methoxyphenyl)-1-(1-methyl-1H-indol-2-yl)but-3-yn-1-ol (71b): White brown solid (260.7 mg, 85% yield) isolated using 20% ethyl acetate-petroleum ether (v/v); mp 128-130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.36-7.31 (m, 3H), 7.24-7.20 (m, 1H), 7.11-7.07 (m, 1H), 6.81 (dt, *J* = 8.8, 2.8 Hz, 2H), 6.59 (s, 1H), 5.11 (q, *J* = 6 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.18-3.08 (m, 2H), 2.39 (d, *J* = 6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 159.5, 140.1, 138.0, 1332.2, 127.2, 122.1, 120.96, 119.7, 115.3, 113.9, 109.2, 99.5, 83.9, 83.7, 65.6, 55.4, 30.3, 27.8 ppm. HRMS (ESI+) m/z calculated for $C_{20}H_{20}NO_2$ $[M+H]^+$ 306.1494, found 306.1490.



4-(4-fluorophenyl)-1-(1-methyl-1H-indol-2-yl)but-3-yn-1-ol (71c) : White brown solid (232.8 mg, 79% yield) isolated using 16% ethyl acetate-petroleum ether (v/v); mp 102-103 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.41-7.35 (m, 2H), 7.33-7.31 (m, 1H), 7.26-7.22(m, 1H), 7.13-7.09 (m, 1H), 7.00-6.95 (m, 2H), 6.58 (s, 1H), 5.11 (q, *J* = 5.6 Hz, 1H), 3.83 (s, 3H), 3.18-3.08 (m, 2H), 2.36 (d, *J* = 5.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 162.46(d, *J* = 247.8 Hz), 139.99, 138.1, 133.64 (d, *J* = 9 Hz), 127.1, 122.2, 120.99, 119.8, 119.3, 119.25, 115.6 (d, *J* = 22 Hz), 109.3, 99.5, 85.3, 82.7, 65.6, 30.3, 27.6 ppm. ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -111.1 (s, 1F) ppm; HRMS (ESI+) m/z calculated for $C_{19}H_{17}FNO$ $[M+H]^+$ 294.1294, found 294.1296.

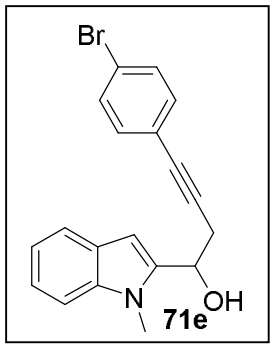


4-(4-chlorophenyl)-1-(1-methyl-1H-indol-2-yl)but-3-yn-1-ol (71d): Brown solid (252.1 mg, 81% yield) isolated using 16% ethyl acetate-petroleum ether (v/v); mp 98-100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.32 (dt, *J* =



8.8, 2.4 Hz, 3H), 7.26-7.21 (m, 3H), 7.12-7.08 (m, 1H), 6.58 (t, *J* = 0.8 Hz, 1H), 5.12 (s, 1H), 3.84 (s, 3H), 3.19-3.09 (m, 2H), 2.29 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.9, 138.1, 134.2, 133.0, 128.7, 127.1, 122.2, 121.7, 120.99, 119.8, 109.3, 99.5, 86.7, 82.7, 65.5, 30.3, 27.7 ppm. HRMS (ESI^+) m/z calculated for $C_{19}H_{17}ClNO$ $[M+H]^+$ 310.0999, found 310.1001.

4-(4-bromophenyl)-1-(1-methyl-1H-indol-2-yl)but-3-yn-1-ol (71e):



71e

Brown solid (284.7 mg, 80% yield) isolated using 16% ethyl acetate-petroleum ether (v/v); mp 112-114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.41 (dt, *J* = 8.8, 2.4 Hz, 2H), 7.32 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.26-7.21 (m, 3H), 7.12-7.08 (m, 1H), 6.58 (t, *J* = 0.8 Hz, 1H), 5.12 (t, *J* = 6 Hz, 1H), 3.84 (s, 3H), 3.19-3.08 (m, 2H), 2.31 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.9, 138.05, 133.2, 131.6, 127.1, 122.4, 122.2, 122.16, 120.99, 119.8, 109.2, 99.5, 86.9, 82.7, 65.5, 30.3, 27.7 ppm. HRMS (ESI^+) m/z calculated for $C_{19}H_{17}BrNO$ $[M+H]^+$ 354.0494, found 354.0496.

General Procedure for the Synthesis of the Carbazole Products 74:

A mixture of $Pd(bpy)Cl_2$ (6.05 mg, 0.02 mmol, 10 mol %), D-CSA (60.81 mg, 0.27 mmol, 1.5 equiv) and aldehyde **72** (41.21 mg, 0.27 mmol, 1.5 equiv) in dry 1,4-Dioxane (1.5 mL) was stirred at 75^{o}C for 20 min under argon atmosphere. Then the acetylenic substrate **71** (0.18 mmol, 1 equiv) dissolved in 1,4-dioxane (1.5 mL) was added drop wise to the reaction and the whole reaction mixture was allowed to stir with heating (at 75 ^{o}C) for few hours until completion of the reaction (TLC). Thereafter, the reaction mixture was neutralized (adjusting the pH to ~7) by 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

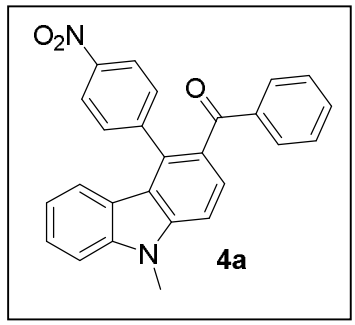
reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography using 10-20% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired product **74** in 40-73% yield.

10. Synthetic Method for the Synthesis of the Carbazole Products 74a at 1 mmol scale:

A mixture of $Pd(bpy)Cl_2$ (33.3 mg, 0.1 mmol, 10 mol %), D-CSA (334.5 mg, 1.5 mmol, 1.5 equiv) and 4-nitrobenzaldehyde **72a** (226.7 mg, 1.5 mmol, 1.5 equiv) in dry 1,4-Dioxane (4 mL) in two necked 50 mL round bottom flask was stirred at 75^{o}C for 20 min under argon atmosphere. Then the acetylenic substrate 1-(1-methyl-1H-indol-2-yl)-4-phenylbut-3-yn-1-ol **71a** (1 mmol, 1 equiv) dissolved in 1,4-dioxane (3 mL) was added drop wise to the reaction and the whole reaction mixture was allowed to stir with heating (at 75 ^{o}C) for 6 hours. Thereafter, the reaction mixture was neutralized (adjusting the pH to ~7) by drop wise addition of 20% aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 × 30 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% ethyl acetate-petroleum ether (v/v) as eluent to afford the desired product **74a** in 68% yield (276.1 mg).

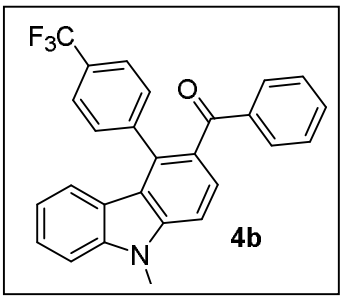
Spectral data of compounds 74a-74p:

(9-Methyl-4-(4-nitrophenyl)-9H-carbazol-3-yl)(phenyl)methanone (74a): Orange gummy liquid (53.1 mg, 72% yield) isolated using 15% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dt, *J* = 8.4, 2.4 Hz, 2H), 7.69-7.66 (m, 3H), 7.58 (dt, *J* = 8.8, 2.0 Hz, 2H), 7.51-7.45(m, 4H), 7.35 (t, *J* = 8 Hz, 2H),

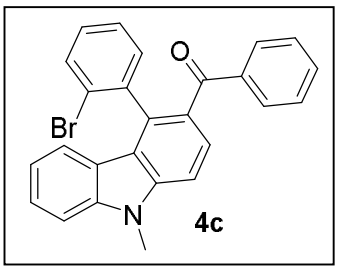


6.99-6.95 (m, 1H), 6.87 (d, *J* = 8 Hz, 1H), 3.95 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 197.7, 146.4, 142.3, 141.9, 138.9, 135.4, 132.7, 130.7,130.1, 129.7, 128.3, 127.7, 126.7, 123.6, 122.2, 122.19, 121.1, 119.9, 109.01, 107.5, 29.5 ppm. HRMS (ESI^+) m/z calculated for $C_{26}H_{19}N_2O_3$ $[M+H]^+$ 407.1396, found 407.1400.

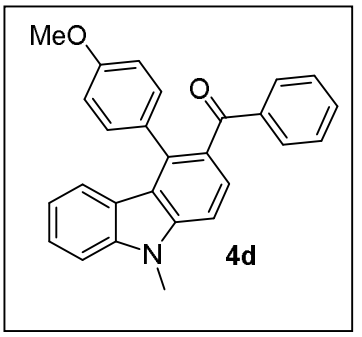
(9-Methyl-4-(4-(trifluoromethyl)phenyl)-9H-carbazol-3-yl)(phenyl)methanone (74b): Orange gummy liquid (56.9 mg, 73% yield) isolated using 14% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67-7.60 (m, 5H), 7.51-7.43(m, 6H), 7.32 (t, *J* = 8 Hz, 2H), 6.99-6.95 (m, 1H), 6.89 (dt, *J* = 8, 0.8 Hz, 1H), 3.94 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 198.3, 142.8 (q, *J* = 1.6 Hz), 142.2, 141.9, 139.3, 136.1, 132.5, 130.2, 130.1, 129.9, 129.8 (q, *J* = 32 Hz) 128.1, 127.4, 126.5, 125.3 (q, J = 3.9 Hz), 124.3 (q, *J* = 270.7 Hz) 122.4, 122.3, 121.2, 119.7, 108.8, 107.2, 29.4 ppm.^{19}F $\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ – 62.3 (s, 3F) ppm. HRMS (ESI^+) m/z calculated for $C_{27}H_{19}F_3NO$ $[M+H]^+$ 430.1419, found 430.1429.



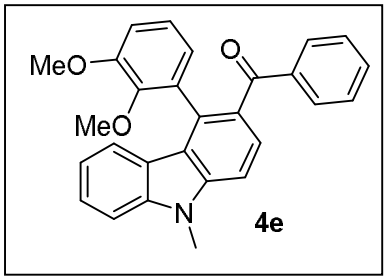
(4-(2-Bromophenyl)-9-methyl-9H-carbazol-3-yl)(phenyl)methanone (74c): Yellow gummy liquid (42.4 mg, 53% yield) isolated using 10% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76-7.73 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.64 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.50-7.46 (m, 2H), 7.44-7.40 (m, 3H), 7.39-7.34 (m, 3H), 7.29-7.25 (m, 1H), 6.99-6.95 (m, 1H), 6.74 (dt, *J* = 8, 1.2 Hz, 1H), 3.93 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 197.5, 142.3, 141.8, 139.8, 139.2, 136.6, 132.7, 132.2, 131.6, 130.3, 129.4, 129.3, 128.1, 127.99, 127.4, 126.4, 123.7, 122.7, 122.3, 121.7, 119.9, 108.7, 106.9, 29.4 ppm. HRMS (ESI^+) m/z calculated for $C_{26}H_{19}BrNO$ $[M+H]^+$ 440.0650, found 440.0657.



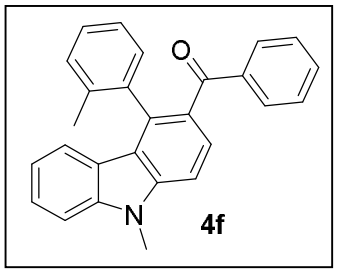
(4-(4-Methoxyphenyl)-9-methyl-9H-carbazol-3-yl)(phenyl)methanone (74d): Brown solid (44.1 mg, 62% yield) isolated using 17% ethyl acetate-petroleum ether (v/v); mp 174-176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64-7.60 (m, 3H),7.44-7.39 (m, 4H), 7.31-7.28 (m, 3H), 7.27-7.26 (m, 1H), 7.13 (dt, *J* = 8, 0.8 Hz, 1H), 6.98-6.94(m, 1H), 6.85 (dt, *J* = 8.8, 2.8 Hz, 2H), 3.92 (s, 3H),3.81 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 198.6, 158.6, 141.6, 141.3, 138.8, 136.6, 131.7, 130.4, 130.38, 129.5, 127.4, 126.5, 125.6, 122.4, 122.2, 121.1, 118.9, 113.2, 108.1, 106.1, 54.8, 28.8 ppm. HRMS (ESI^+) m/z calculated for $C_{27}H_{22}NO_2$ $[M+H]^+$ 392.1651, found 392.1652.



(4-(2,3-Dimethoxyphenyl)-9-methyl-9H-carbazol-3-yl)(phenyl)methanone (74e): Brown solid (48.9 mg, 64% yield) isolated using 20% ethyl acetate-petroleum ether (v/v); mp 80-82 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74-7.72 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.48-7.44 (m, 1H), 7.42-7.39 (m, 3H), 7.37-7.33 (m, 2H), 7.10-7.06 (m, 1H), 7.00-6.97 (m, 3H), 6.93 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.91 (s, 3H) 3.87 (s, 3H) 3.44 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 197.6, 152.8, 146.6, 142.4, 141.8, 139.3, 134.3, 133.2, 132.0, 130.3, 129.9, 127.93, 127.91, 126.1, 123.96, 123.1, 123.06, 122.7, 122.0, 119.6, 112.3, 108.5, 106.3, 60.5, 55.9, 29.3 ppm. HRMS (ESI^+) m/z calculated for $C_{28}H_{24}NO_3$ $[M+H]^+$ 422.1756, found 422.1762.

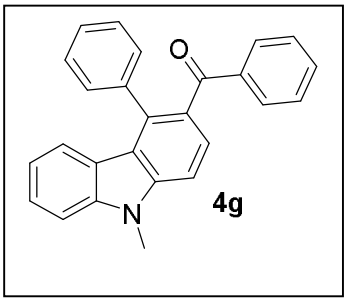


(9-Methyl-4-(o-tolyl)-9H-carbazol-3-yl)(phenyl)methanone (74f): Brown solid (40.2 mg, 59% yield) isolated using 10% ethyl acetate-petroleum ether (v/v); mp 168-170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.64 (m, 3H), 7.48-7.40 (m, 4H), 7.36-7.31(m, 2H),

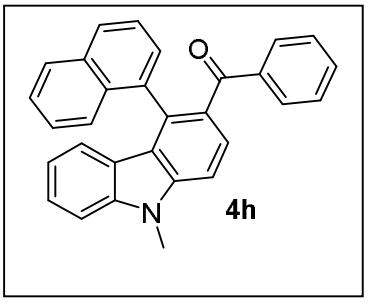


7.29-7.26 (m, 1H), 7.25-7.22 (m, 1H), 7.16-7.14 (m, 2H), 6.96-6.92 (m, 1H), 6.7 (dt, *J* = 8.0, 0.8 Hz, 1H), 3.93 (s, 3H) 2.03 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 198.1,142.1,141.7,139.4, 138.3, 137.3, 136.7, 132.2, 129.97, 129.90, 129.8, 129.2, 127.97, 127.9, 127.5, 126.2, 125.8, 123.0, 122.2, 121.6, 119.8, 108.5, 106.4, 100.0, 29.4, 19.96 ppm. HRMS (ESI^+) m/z calculated for $C_{27}H_{22}NO$ $[M+H]^+$ 376.1701, found 376.1688.

(9-Methyl-4-phenyl-9H-carbazol-3-yl)(phenyl)methanone (74g): Yellow gummy liquid (32.8 mg, 50% yield) isolated using 10% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65-7.62 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.43-7.39 (m, 3H), 7.38-7.34 (m, 2H), 7.33-7.26 (m, 5H), 7.01 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.96-6.92 (m, 1H), 3.93 (s, 3H); 13C{1H} NMR ($CDCl_3$, 100 MHz) δ 199.9, 142.2, 141.8, 139.4, 138.7, 137.4, 132.2, 130.6, 130.02, 129.8, 128.3, 127.9, 127.7, 127.00, 126.2, 122.8, 122.7, 121.4, 119.4, 108.6, 106.8, 100.0, 29.4 ppm. HRMS (ESI+) m/z calculated for $C_{26}H_{20}NO$ $[M+H]^+$ 362.1545, found 362.1551.

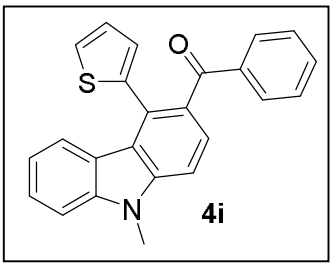


(9-methyl-4-(naphthalen-1-yl)-9H-carbazol-3-yl)(phenyl)methanone (74h): Brown solid (33.6 mg, 45% yield) isolated using 10% ethyl acetate-petroleum ether (v/v); mp 162-164 °C;^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84-7.88 (m, 3H), 7.73-7.71 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.61-7.58 (m, 2H), 7.53 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.49-7.39 (m, 5H), 7.37-7.31 (m, 1H), 7.23-7.19 (m, 2H), 6.96 (dt, *J* = 8.0, 0.8 Hz, 1H), 6.87-6.83 (m, 1H), 3.95 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ 198.3, 141.7, 141.3, 138.8, 136.8, 135.8, 132.8, 132.2, 131.6, 130.3, 129.4, 128.1, 127.7, 127.6, 127.35, 127.29, 127.27, 126.6, 125.7, 125.56, 125.54, 122.2, 120.9, 118.9, 108.1,

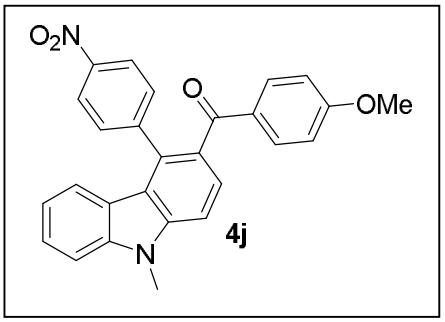


106.4, 28.9 ppm. HRMS (ESI$^+$) m/z calculated for $C_{30}H_{22}NO$ $[M+H]^+$ 412.1701, found 412.1703.

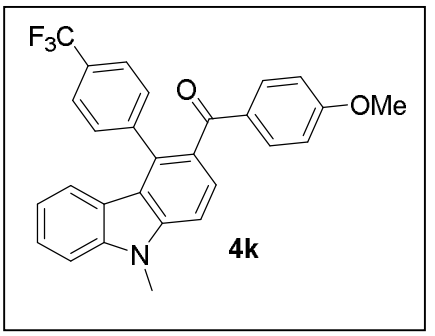
(9-Methyl-4-(thiophen-2-yl)-9H-carbazol-3-yl)(phenyl)methanone (74i): Yellow gummy liquid (26.7 mg, 40% yield) isolated using 10% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67-7.65 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.48-7.41 (m, 4H), 7.34-7.29 (m, 3H), 7.19 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.04-6.99 (m, 3H), 3.92 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 198.6, 141.9, 141.8, 139.0, 138.6, 132.4, 132.3, 130.0, 128.4, 127.98, 127.1, 126.6, 126.5, 126.4, 122.3, 119.6, 108.6, 107.8, 29.4 ppm. HRMS (ESI$^+$) m/z calculated for $C_{24}H_{18}NOS$ $[M+H]^+$ 368.1109, found 368.1101.



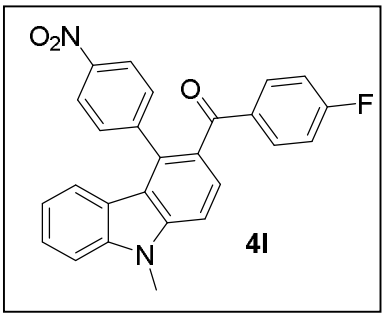
(4-Methoxyphenyl)(9-methyl-4-(4-nitrophenyl)-9H-carbazol-3-yl)methanone (74j) : Brown solid (48.6 mg, 68% yield) isolated using 10% ethyl acetate-petroleum ether (v/v); mp 146-148 °C;^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.25 (dt, *J* = 8.8, 2.4 Hz, 2H), 7.68 (dt, *J* = 8.8, 2.8 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 1H) 7.59 (dt, *J* = 8.8, 2.4 Hz, 2H) 7.49 (d, *J* = 8.4 Hz, 1H) 7.46-7.44 (m, 2H), 6.99-6.95 (m, 1H), 6.89 (dt, *J* = 8.0, 0.8 Hz, 1H), 6.84 (dt, *J* = 9.2, 2.8 Hz, 2H), 3.95 (s, 3H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 196.4, 163.4, 147.4, 146.4, 142.0, 141.9, 134.8, 132.6, 131.6, 130.7, 130.3, 127.0, 126.6, 123.6, 122.2, 120.9, 119.7, 113.5, 108.9, 107.5, 100.0, 55.6, 29.4 ppm. HRMS (ESI$^+$) m/z calculated for $C_{27}H_{21}N_2O_4$ $[M+H]^+$ 437.1501, found 437.1516.



4-Methoxyphenyl)(9-methyl-4-(4-(trifluoromethyl)phenyl)-9H-carbazol-3-yl)methanone (74k): Pale yellow solid (53.4 mg, 71% yield) isolated using 15% ethyl acetate-petroleum ether (v/v); mp 178-180 °C;^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66-7.61 (m, 5H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.45-7.43 (m, 2H), 6.99-6.95 (m, 1H), 6.89 (dt, *J* = 8.0, 0.8 Hz, 1H), 6.81 (dt, *J* = 8.8, 2.8 Hz, 2H), 3.94 (s, 3H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 196.9, 163.3, 142.8(q, *J* = 1.6 Hz), 141.9, 141.8, 135.6, 132.4, 131.9, 130.6, 130.2, 129.7 (q, *J* = 32.2 Hz), 126.8, 126.4, 125.3 (q, *J* = 3.9 Hz), 124.3 (q, *J* = 270.7 Hz), 122.4, 122.3, 121.1, 119.6, 113.4, 108.8, 107.2, 55.5, 29.4 ppm. ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ – 62.3 (s, 3F) ppm; HRMS (ESI^{+}) m/z calculated for $C_{28}H_{21}F_3NO_2$ $[M+H]^+$ 460.1524, found 460.1534.

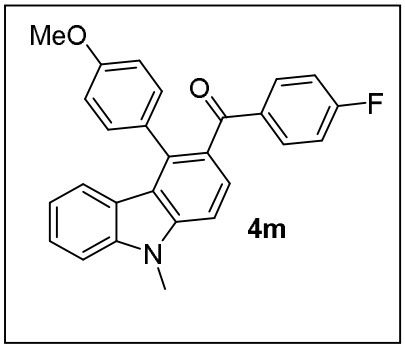


(4-Fluorophenyl)(9-methyl-4-(4-nitrophenyl)-9H-carbazol-3-yl)methanone (74l): Yellow gummy liquid (43.4 mg, 60% yield) isolated using 15% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.30 (d, *J* = 9.0 Hz, 2H), 7.75-7.73 (m, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.50-7.47 (m, 2H), 7.06 (t, *J* = 8.4 Hz, 2H), 7.01 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.98 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 195.6, 165.0 (d, J = 253.2 Hz), 146.9, 145.7, 141.7, 141.4, 134.8, 134.7 (d, J = 3 Hz), 132.2 (d, J = 9.1 Hz), 130.2, 128.8, 126.8, 126.3, 123.2, 121.7, 121.6, 120.6, 119.4, 114.9 (d, J = 21.75 Hz),108.5, 107.1, 28.9 ppm. ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ – 105.3 (s, 1F) ppm; HRMS (ESI+) m/z calculated for $C_{26}H_{18}FN_2O_3$ $[M+H]^+$ 425.1301, found 425.1312.

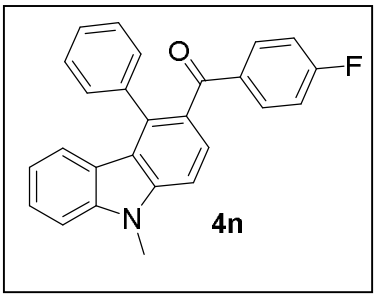


(4-Fluorophenyl)(4-(4-methoxyphenyl)-9-methyl-9H-carbazol-3-yl)methanone

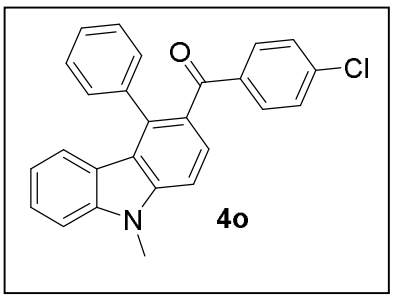
(74m): Brown solid (46.1 mg, 66% yield) isolated using 15% ethyl acetate-petroleum ether (v/v); mp 134-136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65-7.616 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.45-7.42 (m, 3H), 7.26 (dt, *J* = 8.8, 2.8 Hz, 2H), 7.14 (dt, *J* = 8.0, 0.8 Hz, 1H), 6.99-6.91 (m, 3H), 6.86 (dt, *J* = 8.8, 2.8 Hz, 2H), 3.92 (s, 3H), 3. 81 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 197.7, 165.2 (d, *J* = 252.2 Hz), 159.2, 142.2, 141.8, 136.9, 135.7 (d, *J* = 2.9 Hz), 132.5 (d, *J* = 9.1 Hz), 130.99, 130.73, 130.69, 126.6, 126.2, 122.8, 122.7, 121.5, 119.4, 115.0 (d, *J* = 21.7 Hz), 113.8, 108.6, 106.8, 55.3, 29.4 ppm. ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ – 106.6 (s, 1F) ppm; HRMS (ESI^+) m/z calculated for $C_{27}H_{21}FNO_2$ $[M+H]^+$ 410.1556, found 410.1546.



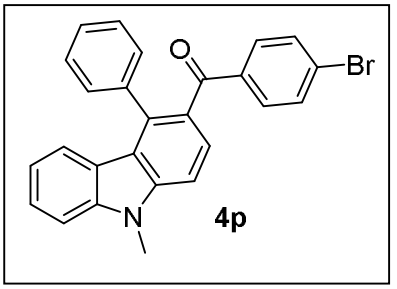
(4-Fluorophenyl)(9-methyl-4-phenyl-9H-carbazol-3-yl)methanone (74n): Yellow gummy liquid (41.4 mg, 64% yield) isolated using 10% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65-7.61 (m, 3H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.43-7.42 (m, 1H), 7.42 (d, *J* = 0.8 Hz, 1H), 7.36-7.31 (m, 5H), 7.03 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.96-6.91 (m, 3H), 3. 93 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 197.5, 165.2 (d, *J* = 252.3 Hz), 142.0, 141.8, 138.5, 137.2, 135.7 (d, *J* = 3.1 Hz), 132.5 (d, *J* = 9.3 Hz), 130.4, 129.8, 128.3, 127.8, 126.7, 126.2, 122.7, 122.6, 121.3, 119.5, 115.0 (d, *J* = 21.8 Hz), 108.6, 106.99, 29.4 ppm. ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ – 106.4 (s, 1F) ppm; HRMS (ESI^+) m/z calculated for $C_{26}H_{19}FNO$ $[M+H]^+$ 380.1451, found 380.1450.



(4-Chlorophenyl)(9-methyl-4-phenyl-9H-carbazol-3-yl)methanone(74o): Yellow gummy liquid (36.4 mg, 57% yield) isolated using 10% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, *J* = 8.8 Hz, 1H), 7.55 (dt, *J* = 8.4, 2.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.43-7.42 (m, 1H), 7.41 (d, *J* = 1.2 Hz, 1H), 7.35-7.31 (m, 5H), 7.25-7.24 (m, 1H), 7.22 (t, *J* = 2 Hz, 1H), 7.02 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.96-6.92 (m, 1H), 3. 93 (s, 3H) ; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 197.7, 142.3, 141.8, 138.5, 138.47, 137.7, 137.3, 131.3, 130.1, 129.8, 128.3, 128.2, 127.8, 126.8, 126.3, 122.7, 122.67, 121.3, 119.5, 108.6, 107.0, 29.4 ppm. HRMS (ESI$^+$) m/z calculated for $C_{26}H_{19}ClNO$ $[M+H]^+$ 396.1155, found 396.1142.



(4-Bromophenyl)(9-methyl-4-phenyl-9H-carbazol-3-yl)methanone (74p): Yellow gummy liquid (28.6 mg, 46% yield) isolated using 10% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, *J* = 8.4 Hz, 1H), 7.49-7.44 (m, 3H), 7.43-7.38 (m, 4H), 7.35-7.31 (m, 5H), 7.02 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.96-6.92 (m, 1H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 197.9, 142.3, 141.8, 138.5, 138.1, 137.4, 131.4, 131.2, 130.1, 129.8, 128.3, 127.8, 127.2, 126.8, 126.3, 122.7, 121.3, 119.5, 108.6, 106.99, 29.4 ppm. HRMS (ESI$^+$) m/z calculated for $C_{26}H_{19}BrNO$ $[M+H]^+$ 440.0650, found 440.0655



Procedure for the Synthesis of the Michael Addition Product 82

*Procedure for the Synthesis of the Michael Addition Product **82** (under conditions A)*:

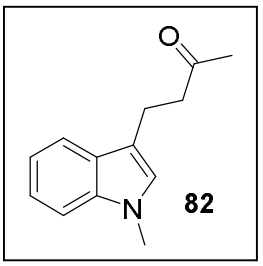
A mixture of Pd(bpy)Cl_2 (12.7 mg, 0.04 mmol, 10 mol %), D-CSA (127.6 mg, 0.57 mmol, 1.5 equiv.) and N-methyl indole **80** (0.38 mmol, 1 equiv.) in dry 1,4-dioxane (2.5 mL) was

stirred at 75^{o}C for 20 min under argon atmosphere. Then methyl vinyl ketone **81** (0.05 mL. 0.57 mmol, 1.5 equiv) dissolved in 1,4-dioxane (2.5 mL) was added drop wise to the reaction and the whole reaction mixture was allowed to stir with heating (at 75 ^{o}C) for 2h until completion of the reaction (TLC). Thereafter, the reaction mixture was neutralized (adjusting the pH to ~7) by 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 15% ethyl acetate-petroleum ether (v/v) as eluent to afford the product **82** in 74% yield.

*Procedure for the Synthesis of the Michael Addition Product **82** (under conditions B):*

A mixture of D-CSA (127.6 mg, 0.57 mmol, 1.5 equiv.) and N-methyl indole **80** (0.38 mmol, 1 equiv.) in dry 1,4-Dioxane (2.5 mL) was stirred at 75^{o}C for 20 min under argon atmosphere. Then methyl vinyl ketone **81** (0.05 mL, 0.57 mmol, 1.5 equiv) dissolved in 1,4-dioxane (2.5 mL) was added drop wise to the reaction and the whole reaction mixture was allowed to stir with heating (at 75 ^{o}C) for 2h until completion of the reaction (TLC). Thereafter, the reaction mixture was neutralized (adjusting the pH to ~7) by 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 15% ethyl acetate-petroleum ether (v/v) as eluent to afford the product **82** in 25% yield.

Spectral data of compound Michael addition product 82



4-(1-Methyl-1H-indol-3-yl)butan-2-one (82): Yellow gummy liquid (45.4 mg, 74% yield) isolated using 5% ethyl acetate-petroleum ether (v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.42-7.38 (m, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.97 (s, 1H), 3.85 (s, 3H), 3.16 (t, *J* = 7.5 Hz, 2H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ 208.4, 136.5, 127.1, 125.9, 121.1, 118.3, 113.2, 108.8, 43.9, 32.1, 29.6, 18.8 ppm. HRMS (EI^{+}) m/z calculated for $C_{13}H_{15}NO$ $[M]^{+}$ 201.1154, found 201.1142.

1.2.8. References:

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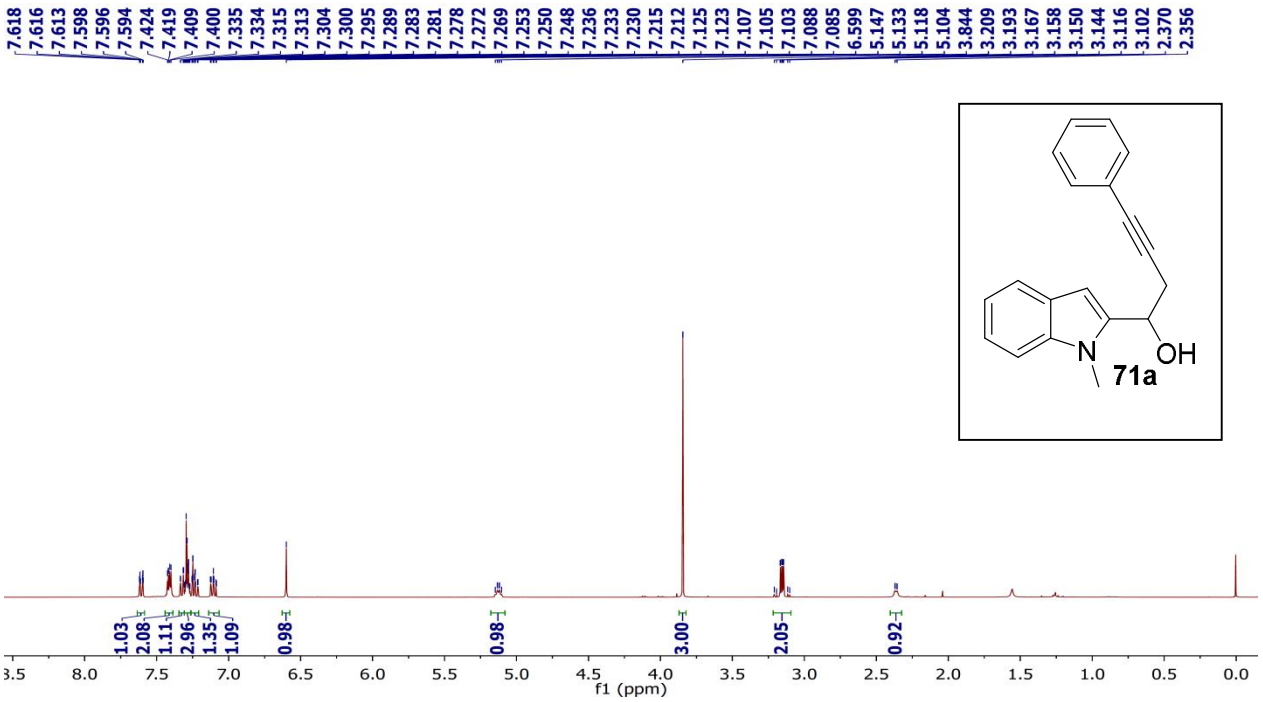
1.2.9. Copies of NMR Spectra

^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **71a**:



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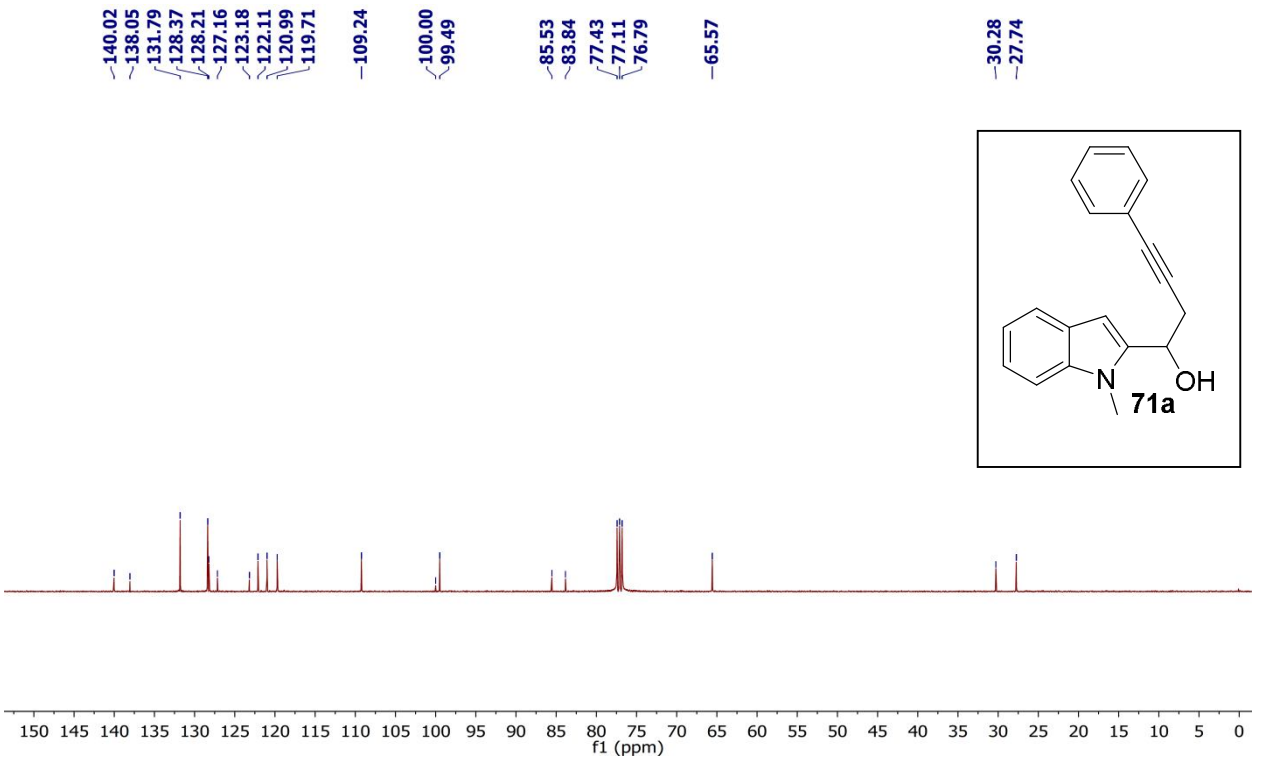
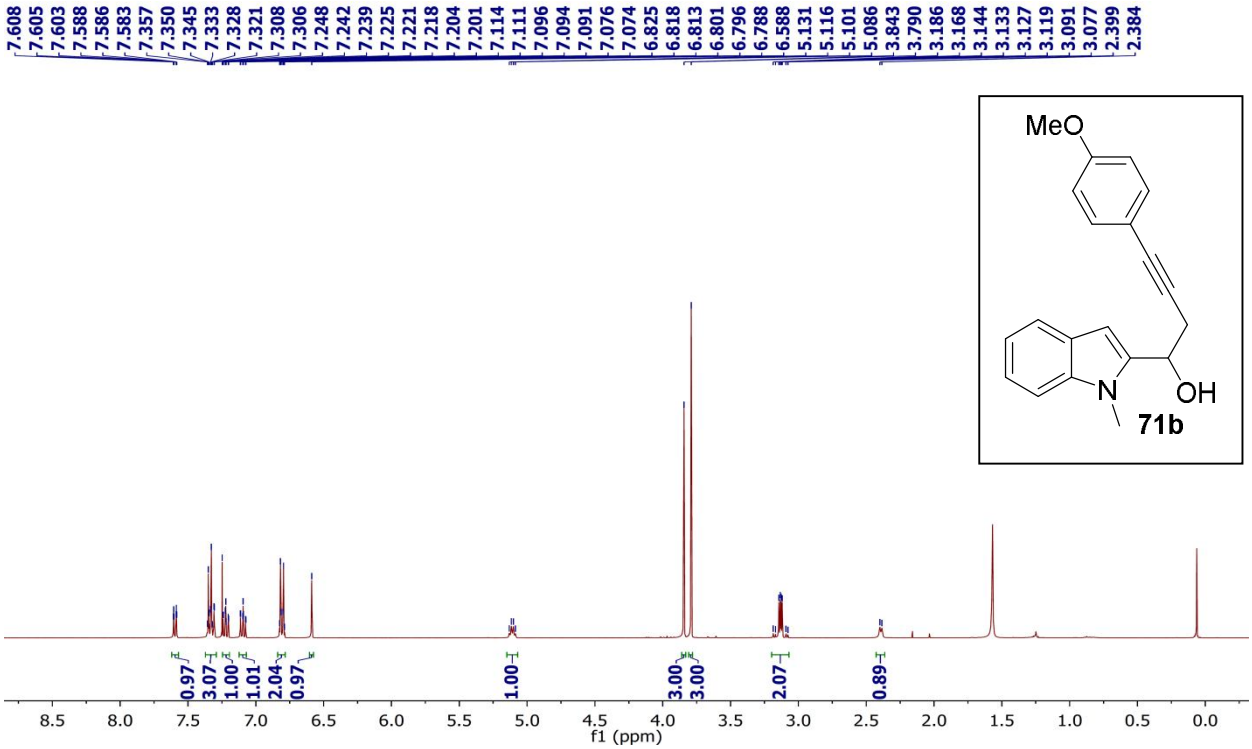


^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **71b**:



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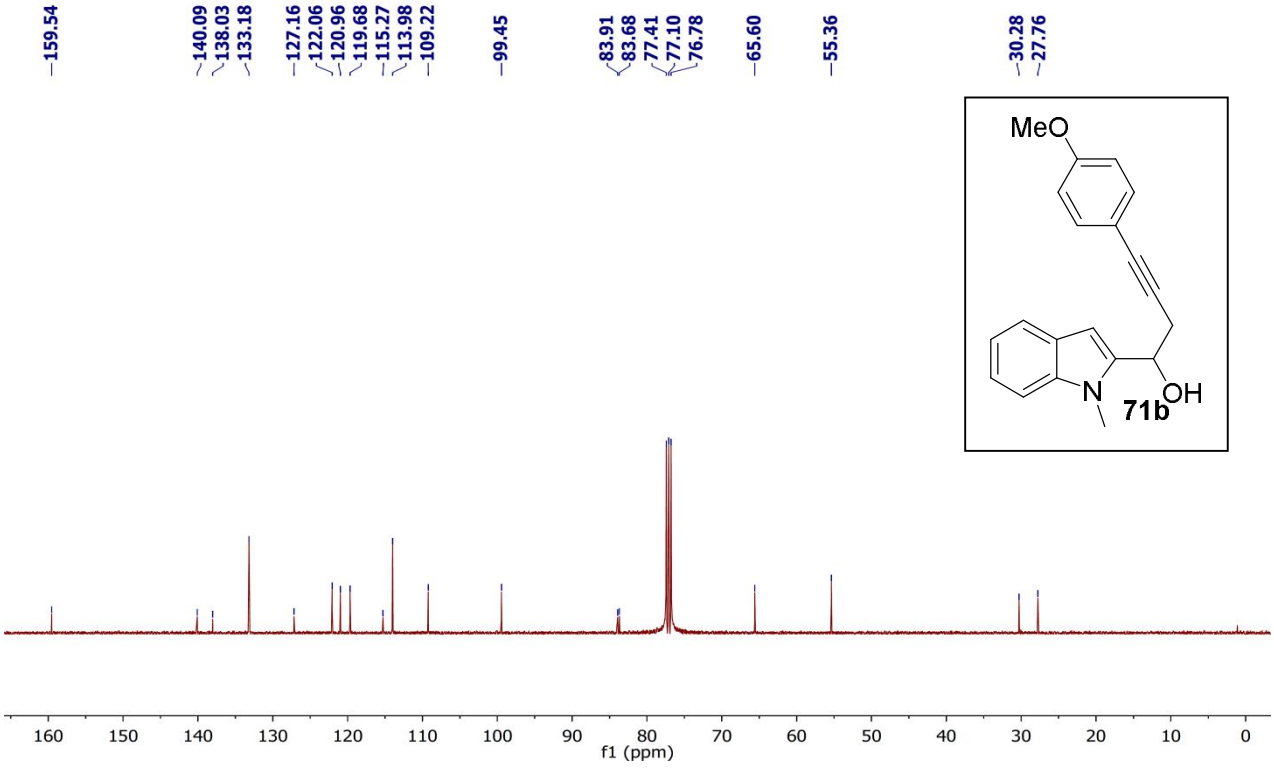
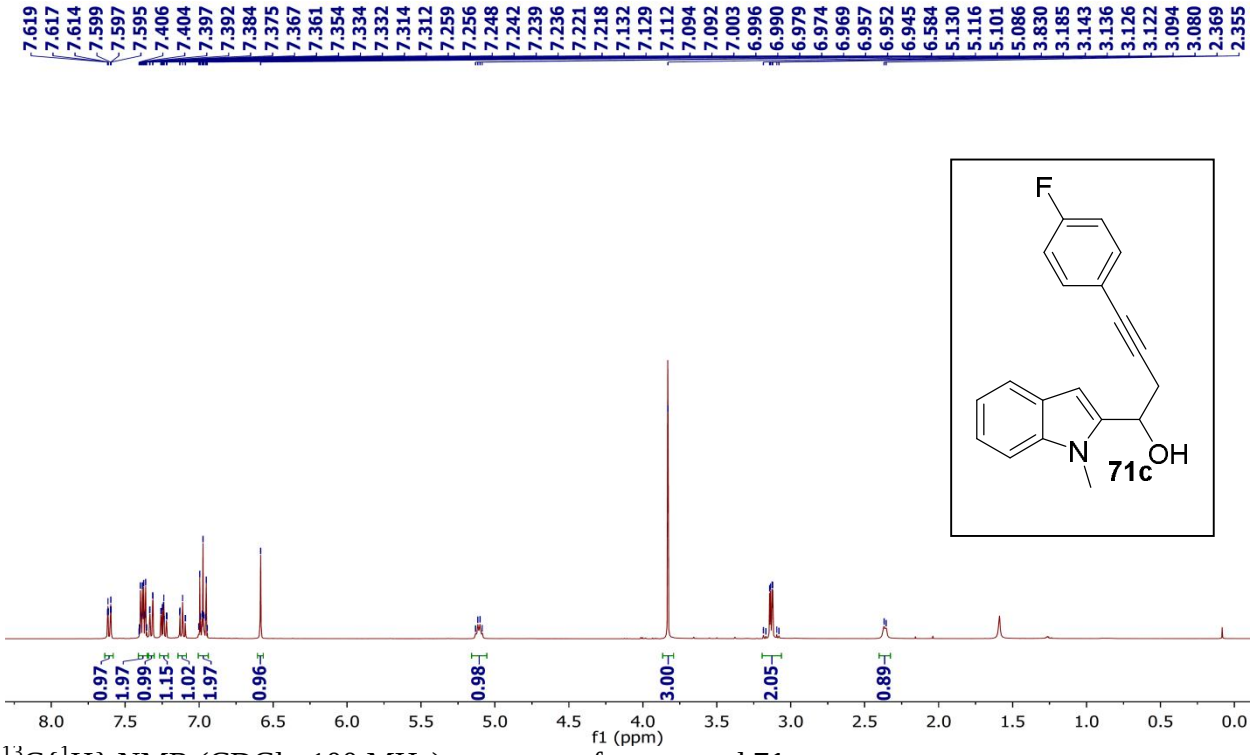


^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **71c**:



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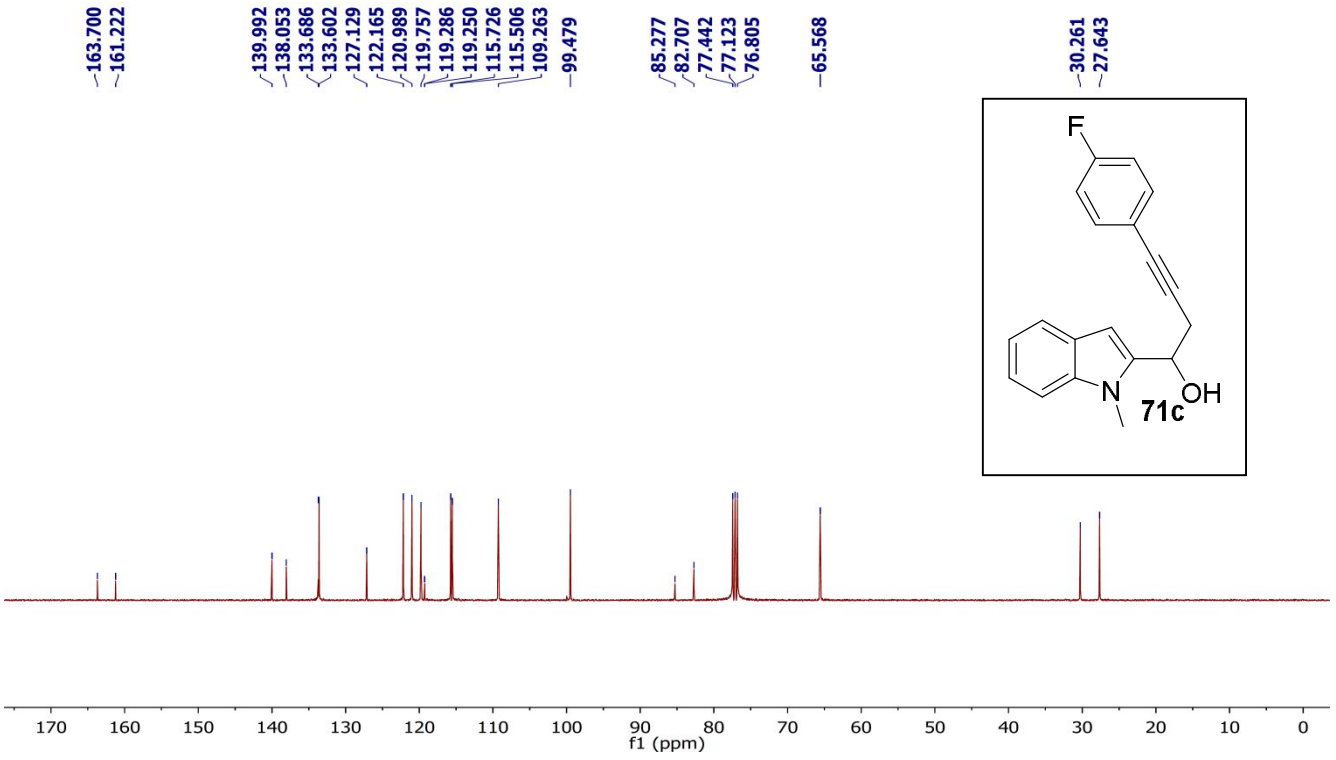
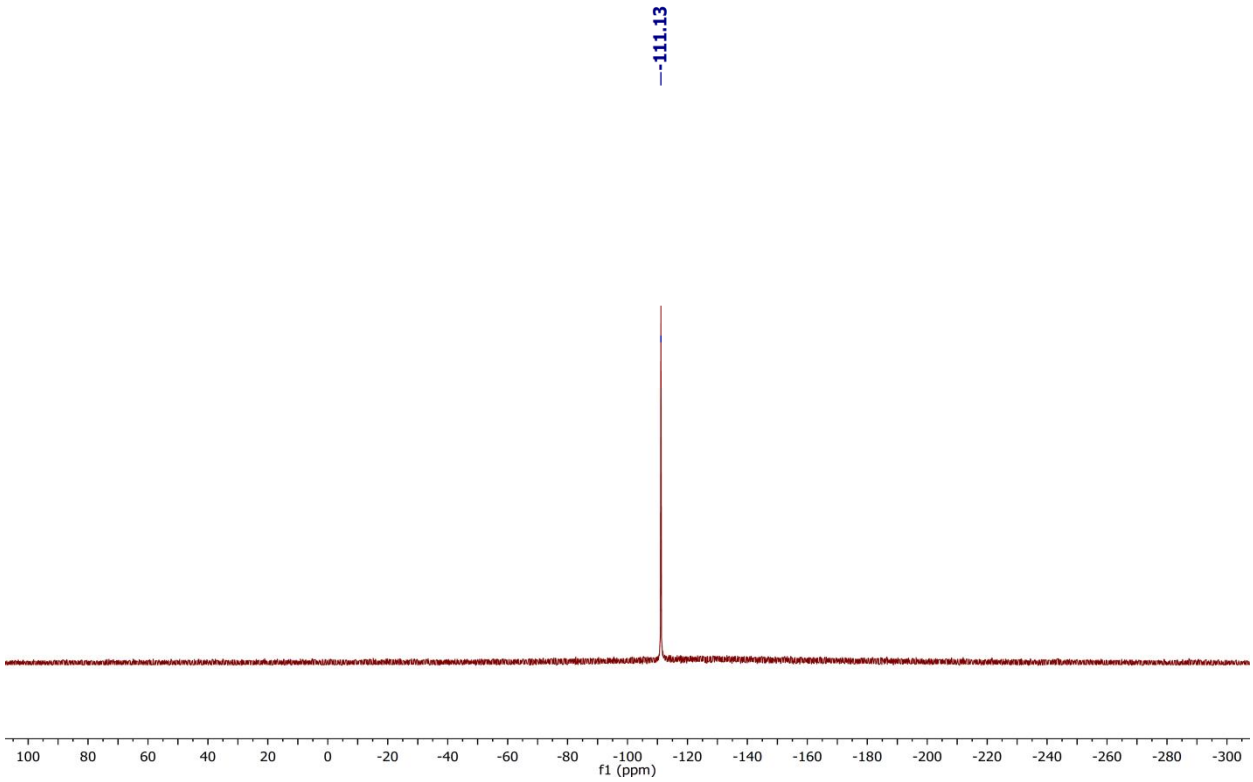


$^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 376 MHz) spectrum of compound **71c:**



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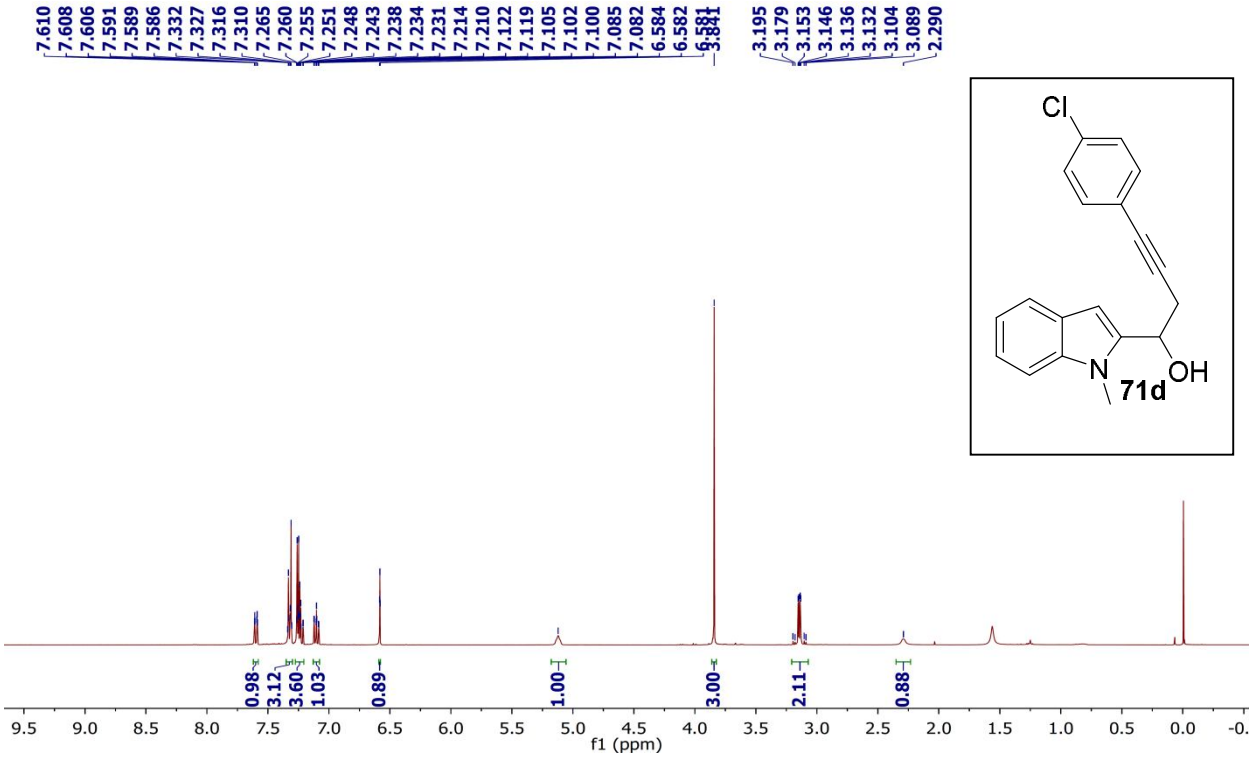

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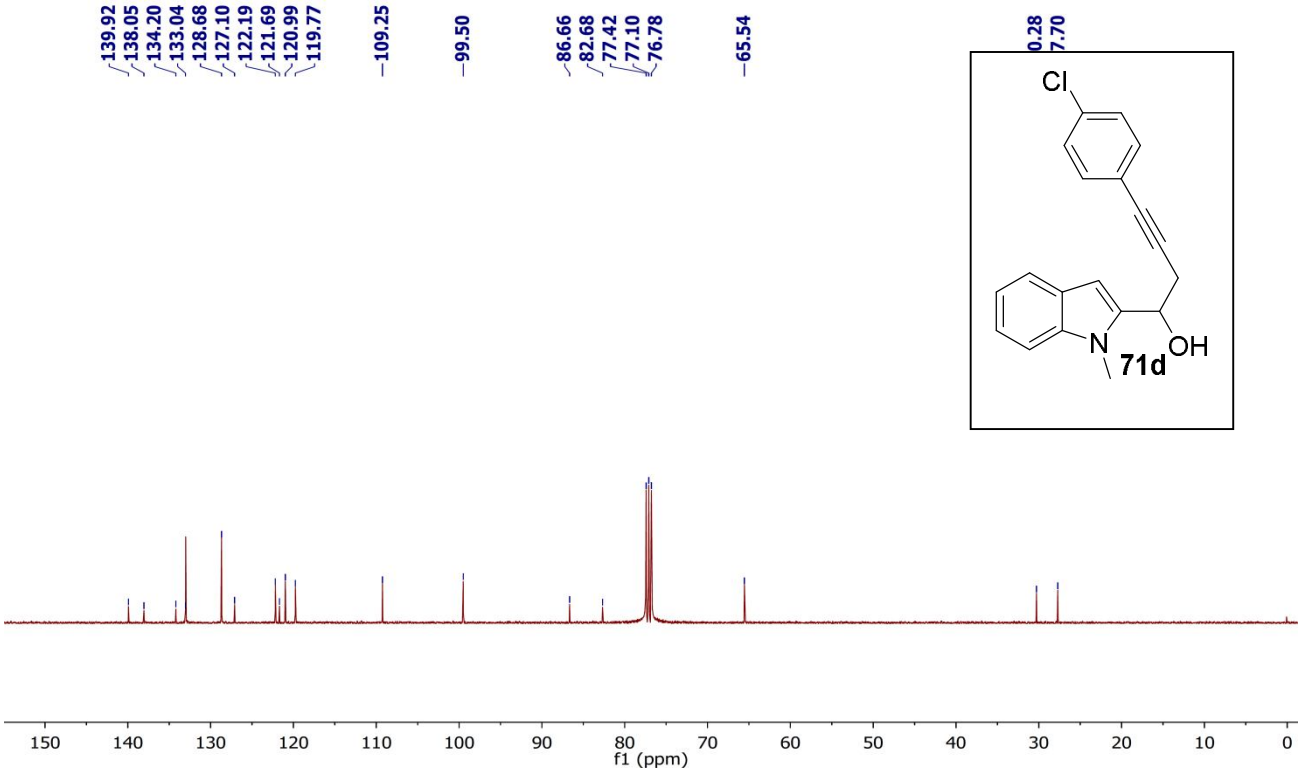

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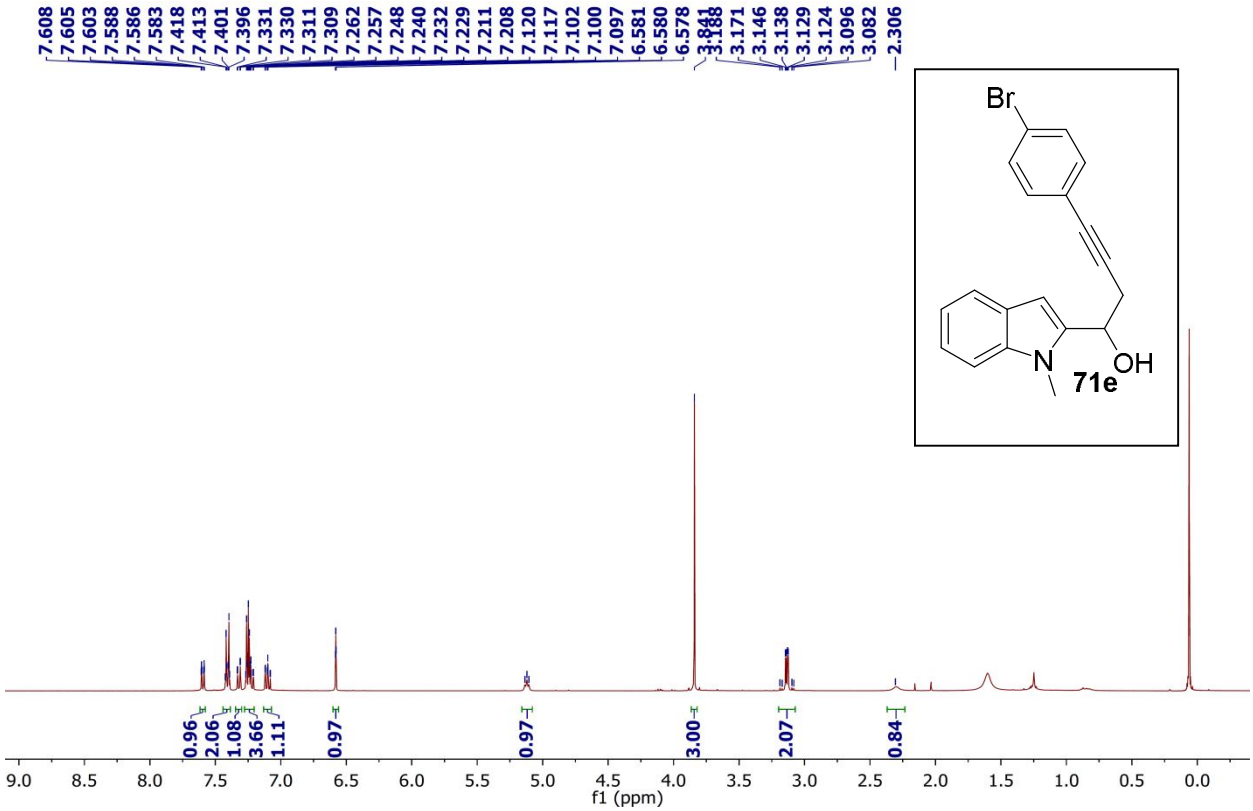

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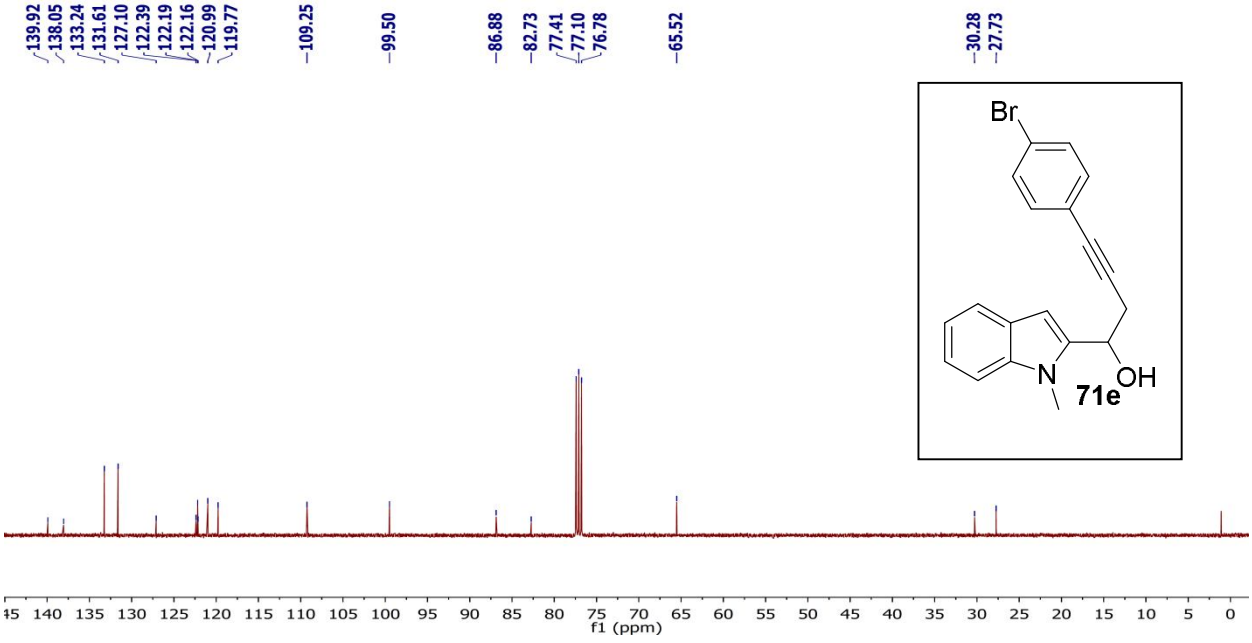
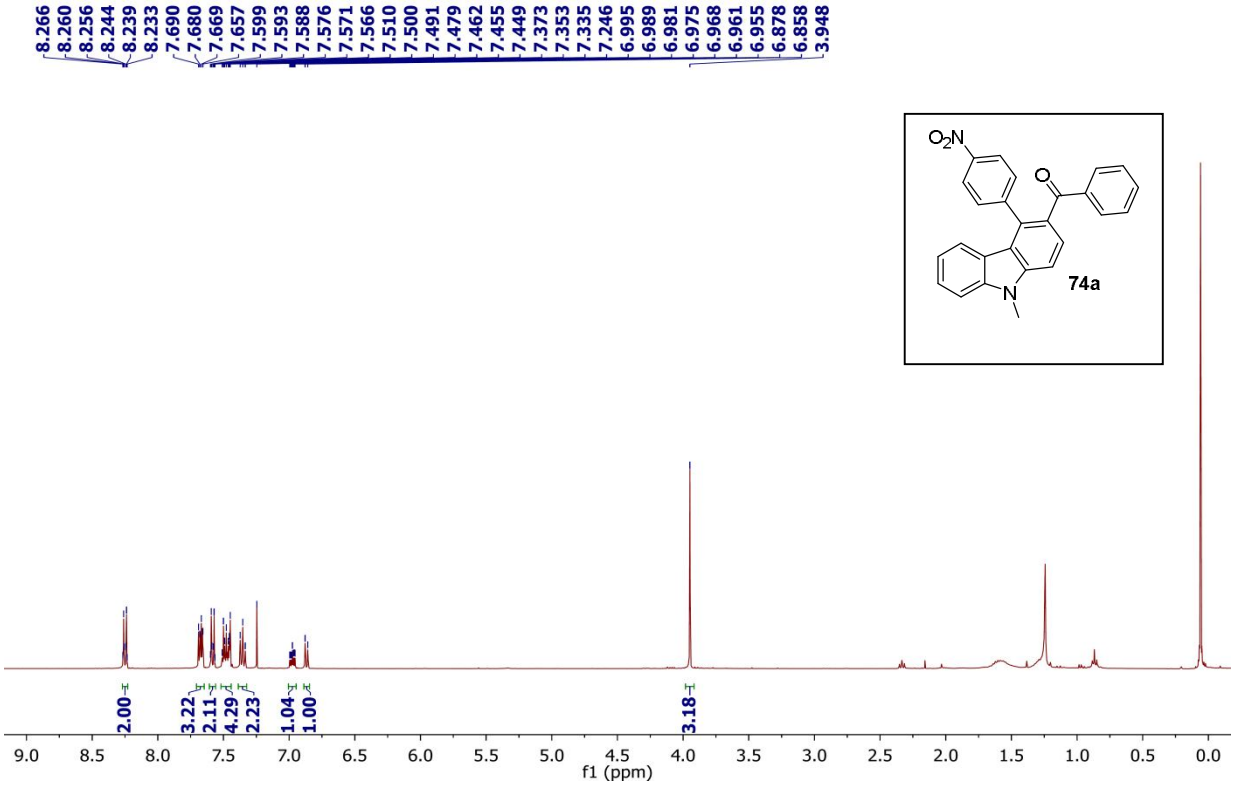


NMR spectra of compounds 74a-74p

^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74a**:



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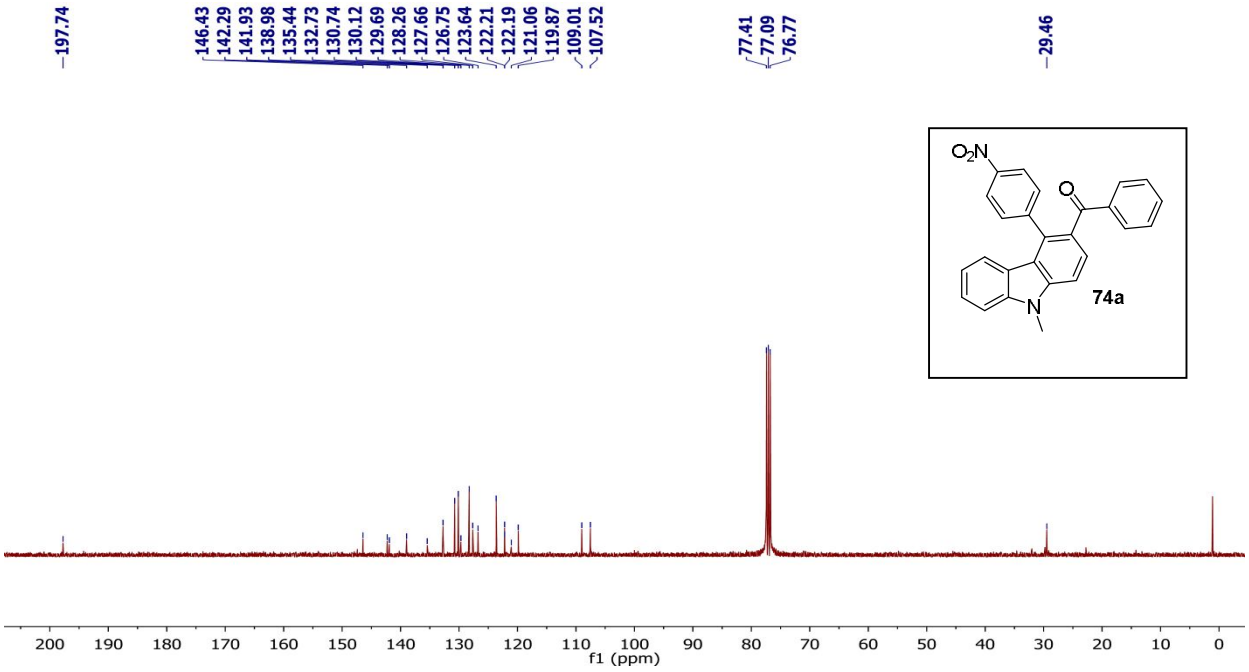
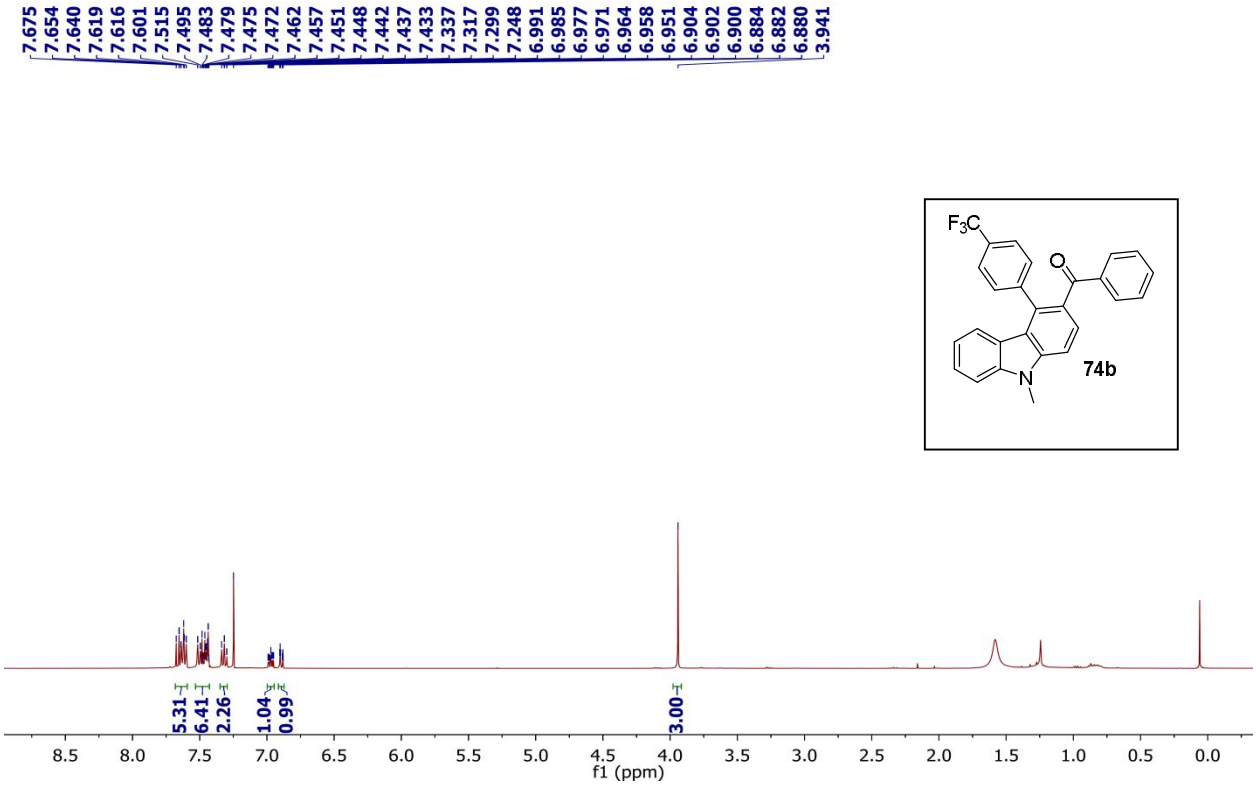


^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74b**:



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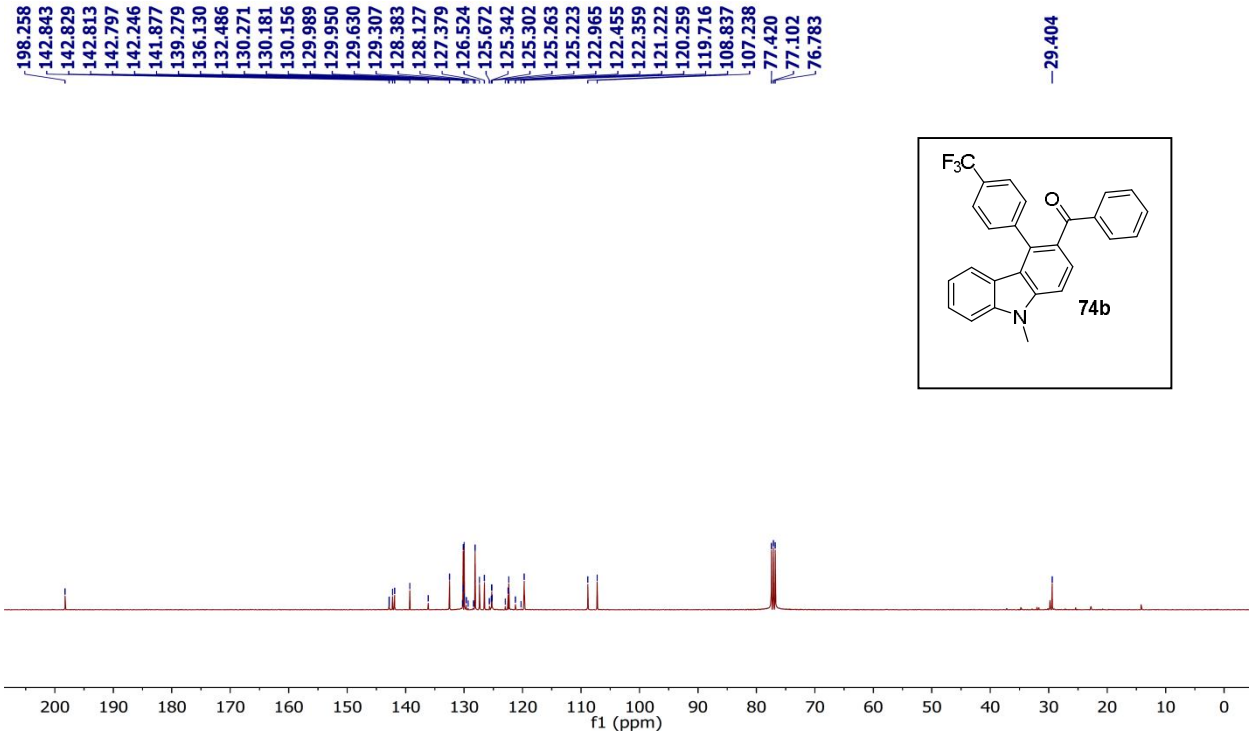
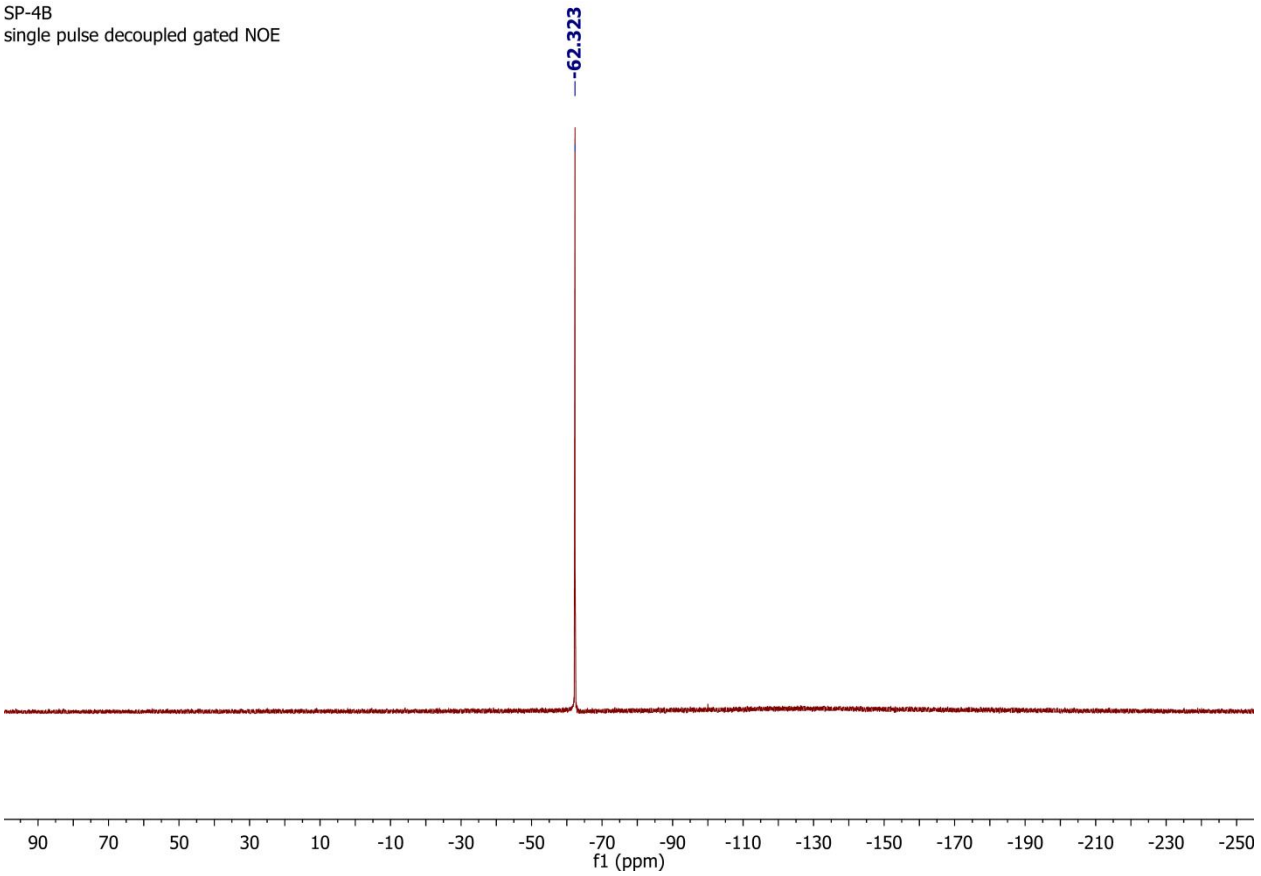
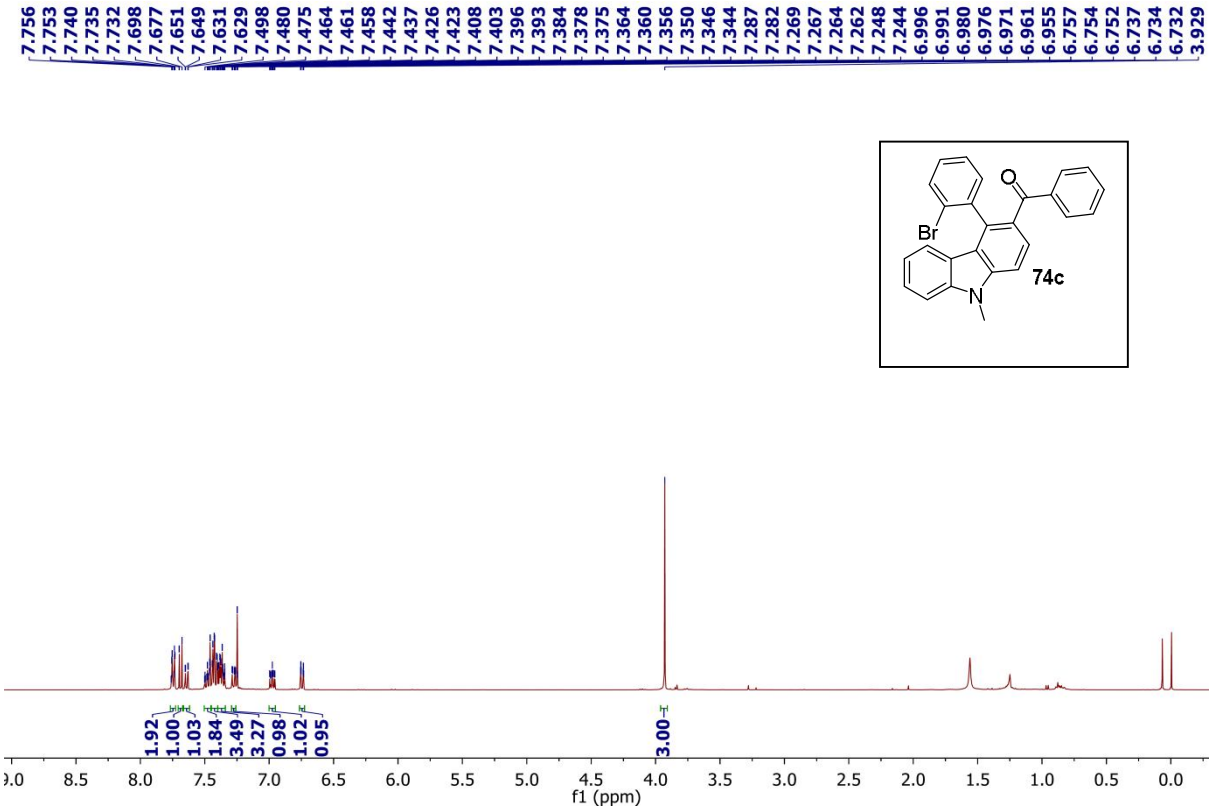


$^{19}F\{^{1}H\}$ NMR (376 MHz) of **74b**:



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74c**:



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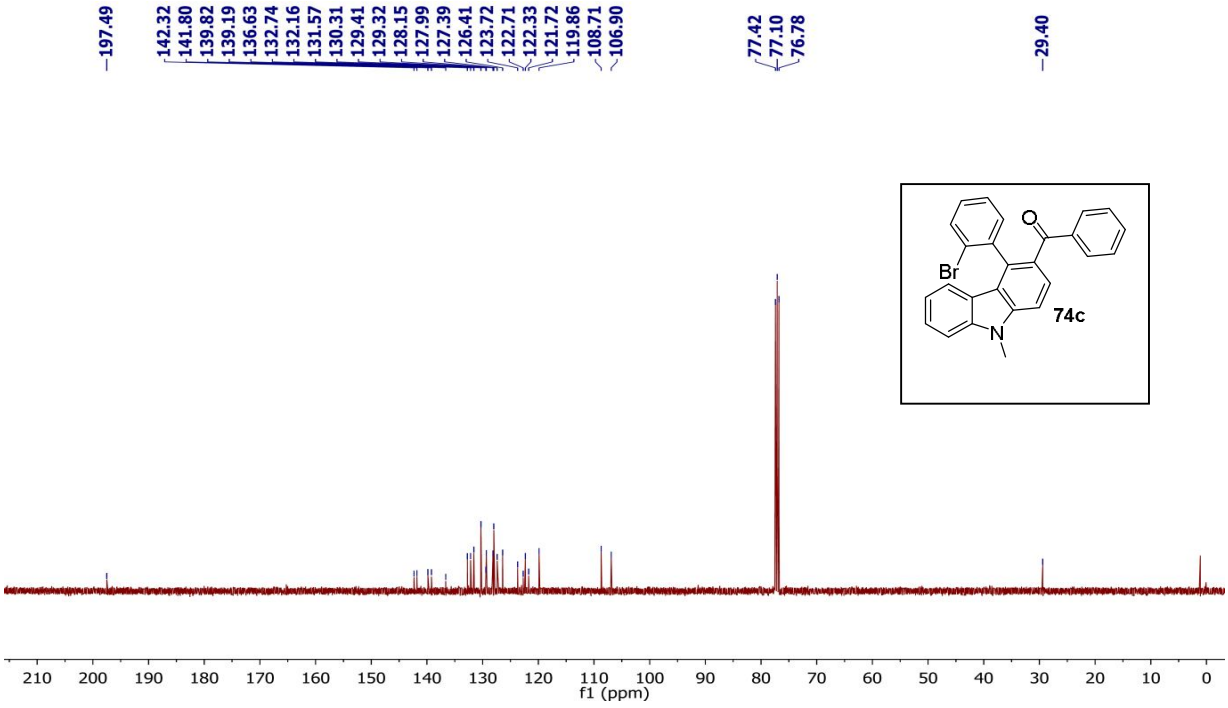
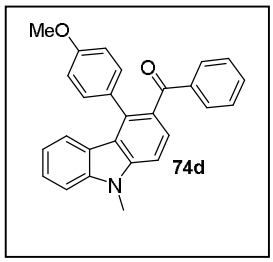
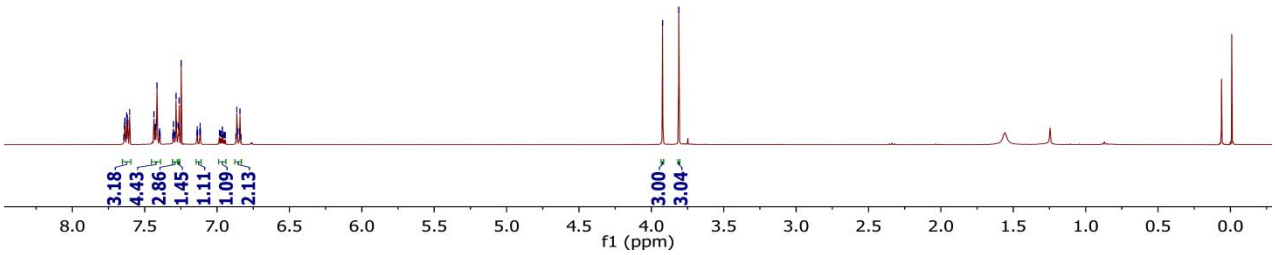


^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74d**:





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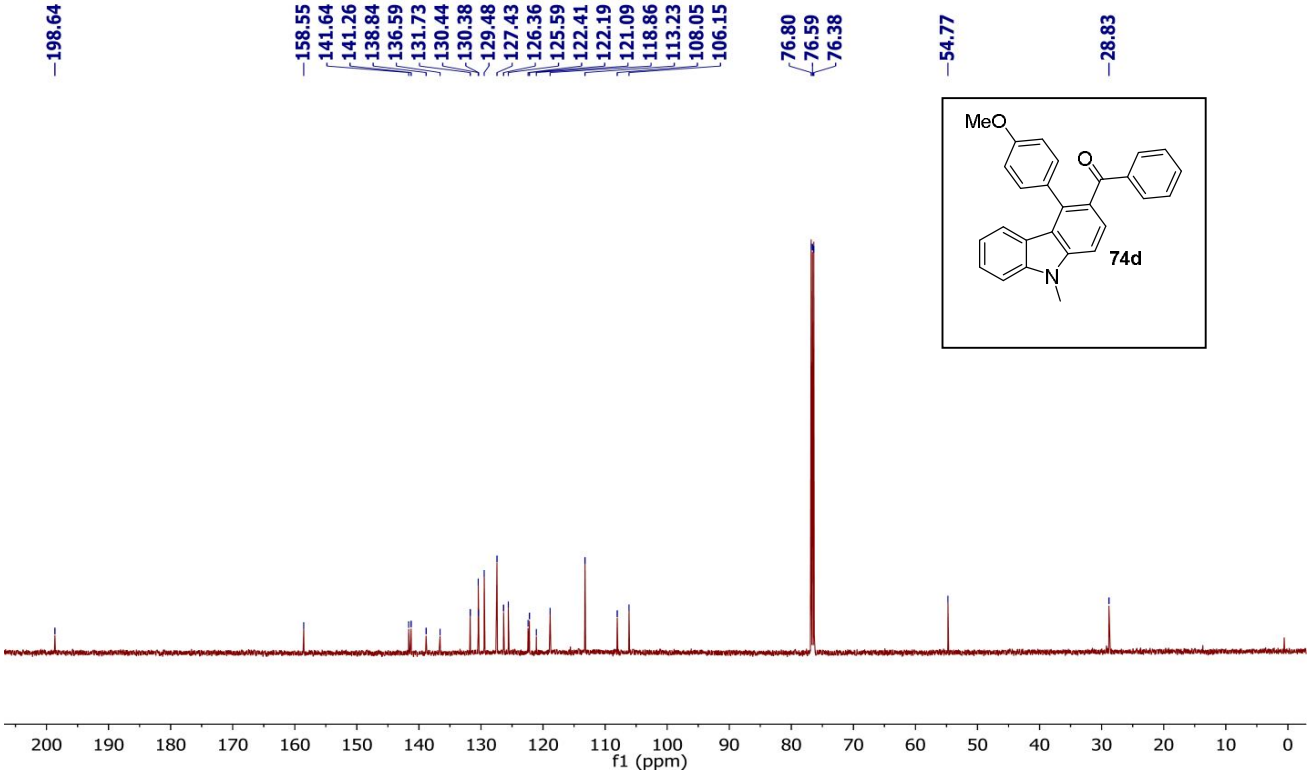
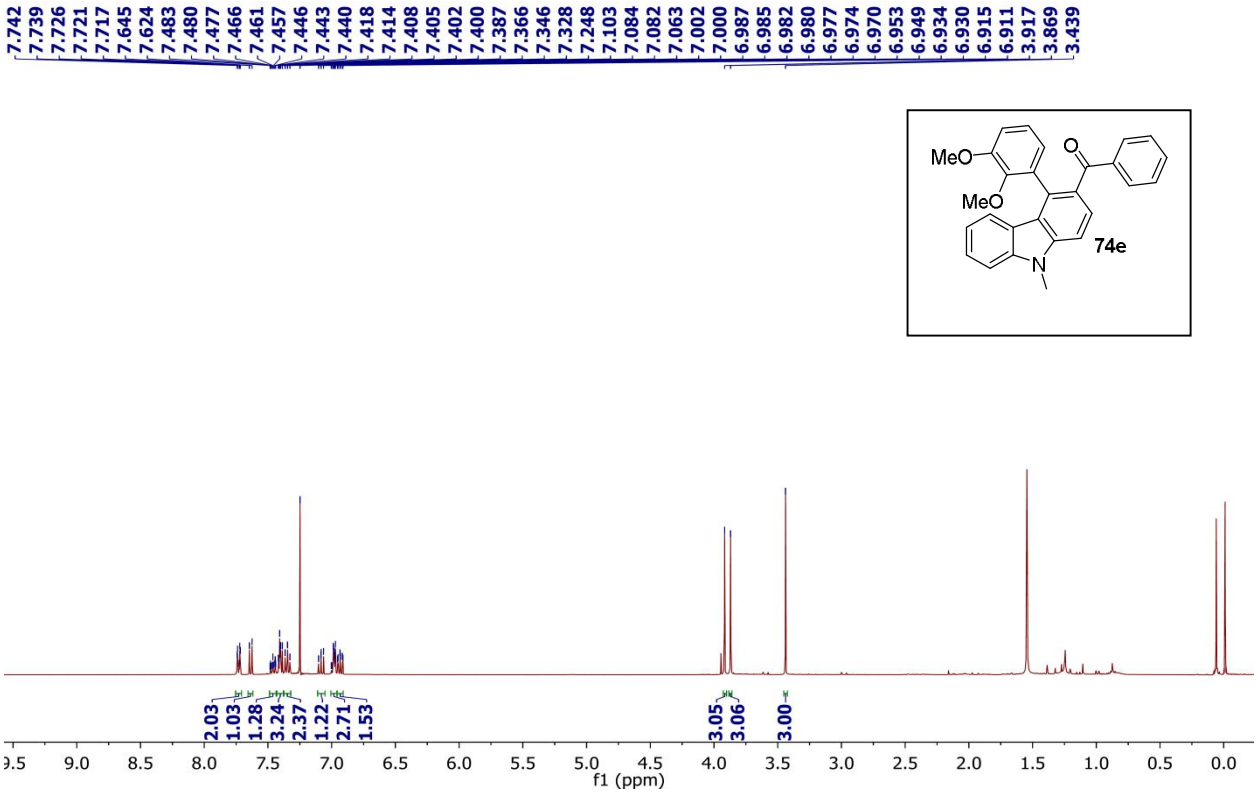
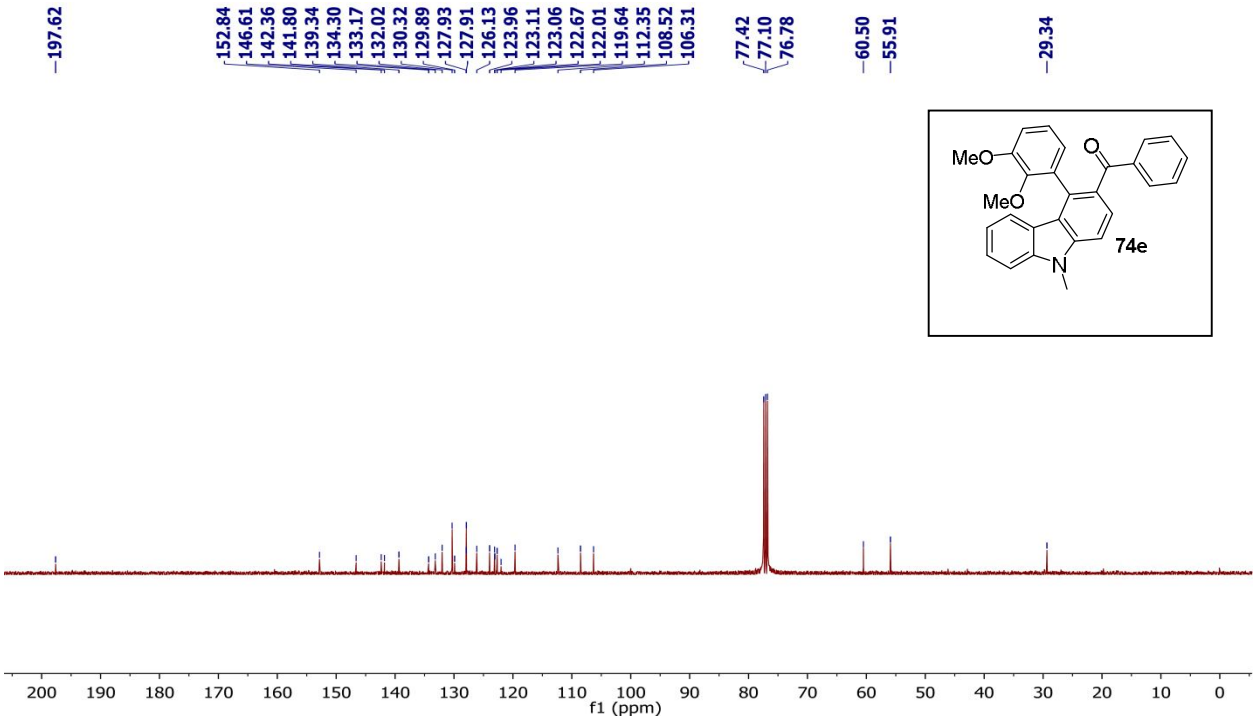


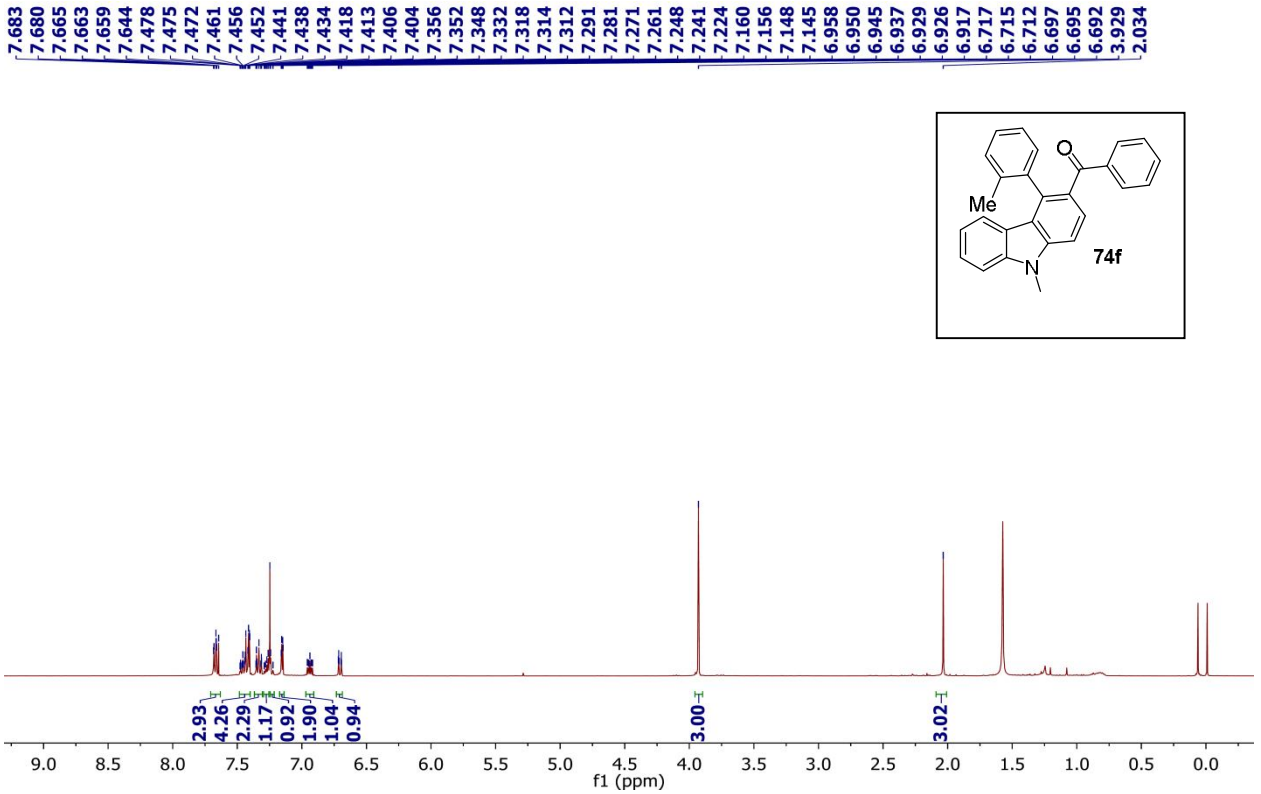
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74e**:



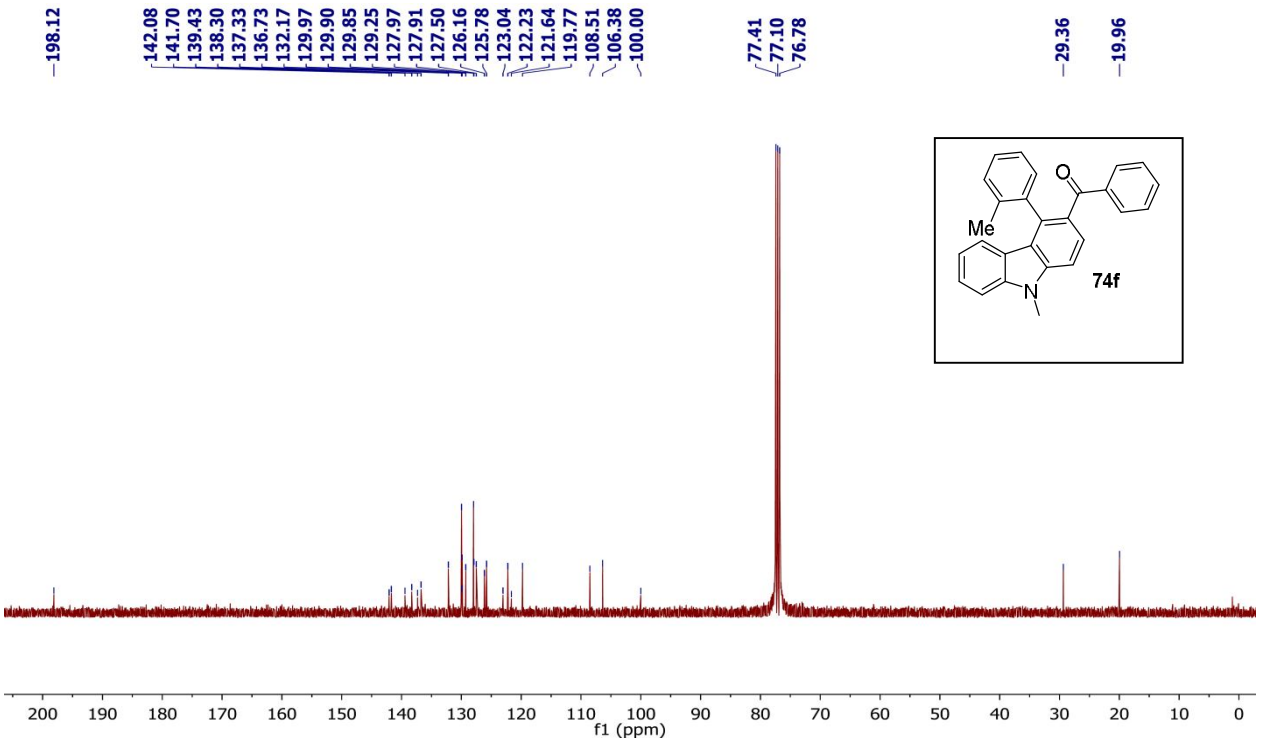
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74e:**



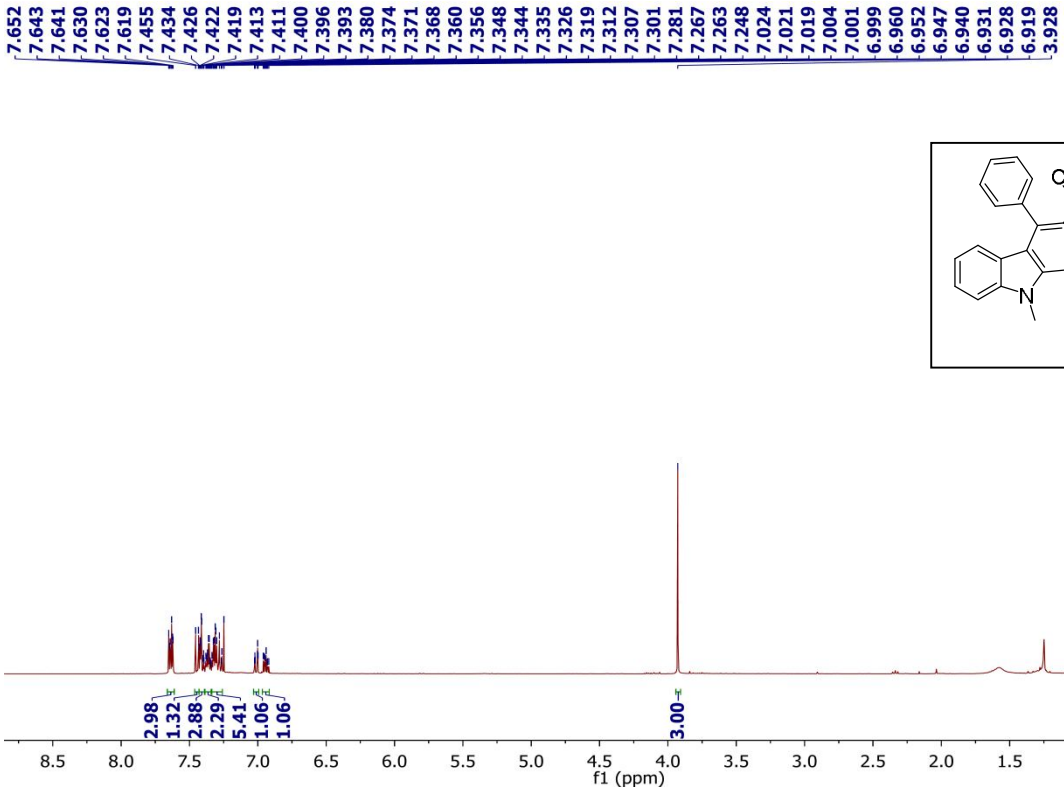
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74f**:



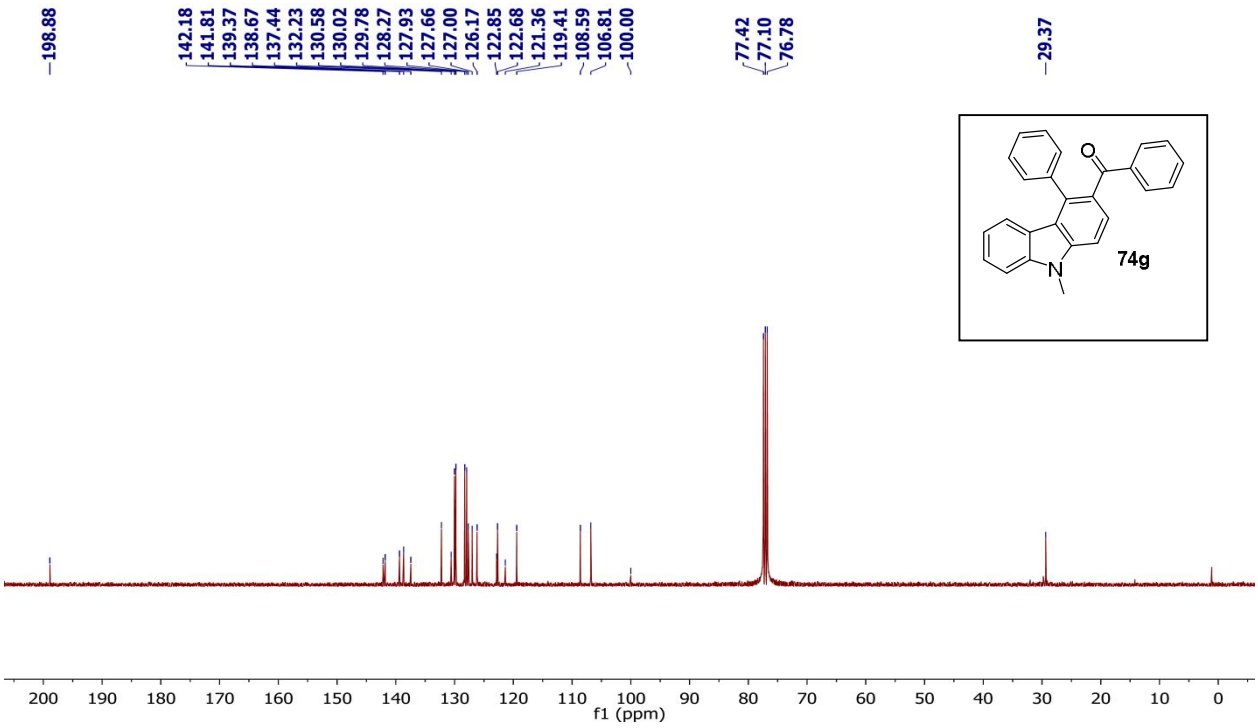
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74f:**



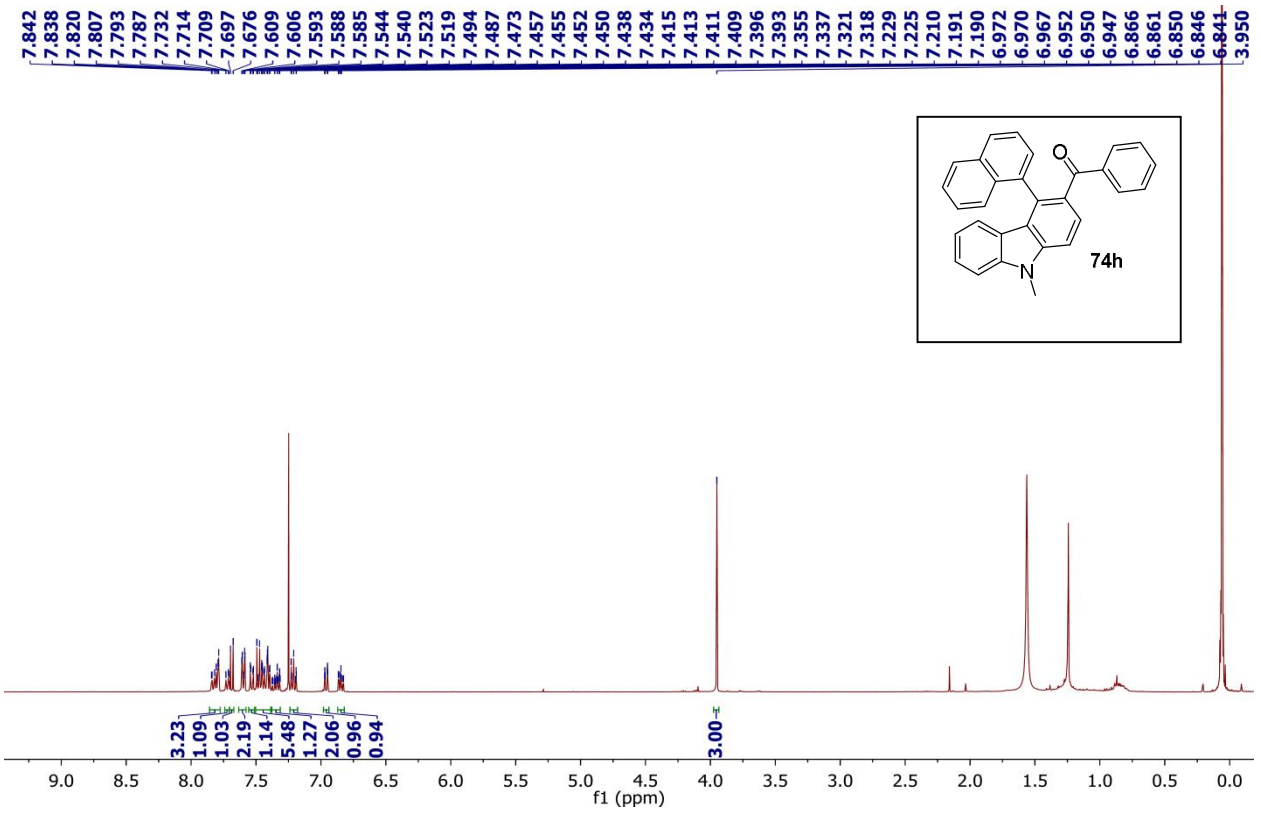
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74g**:



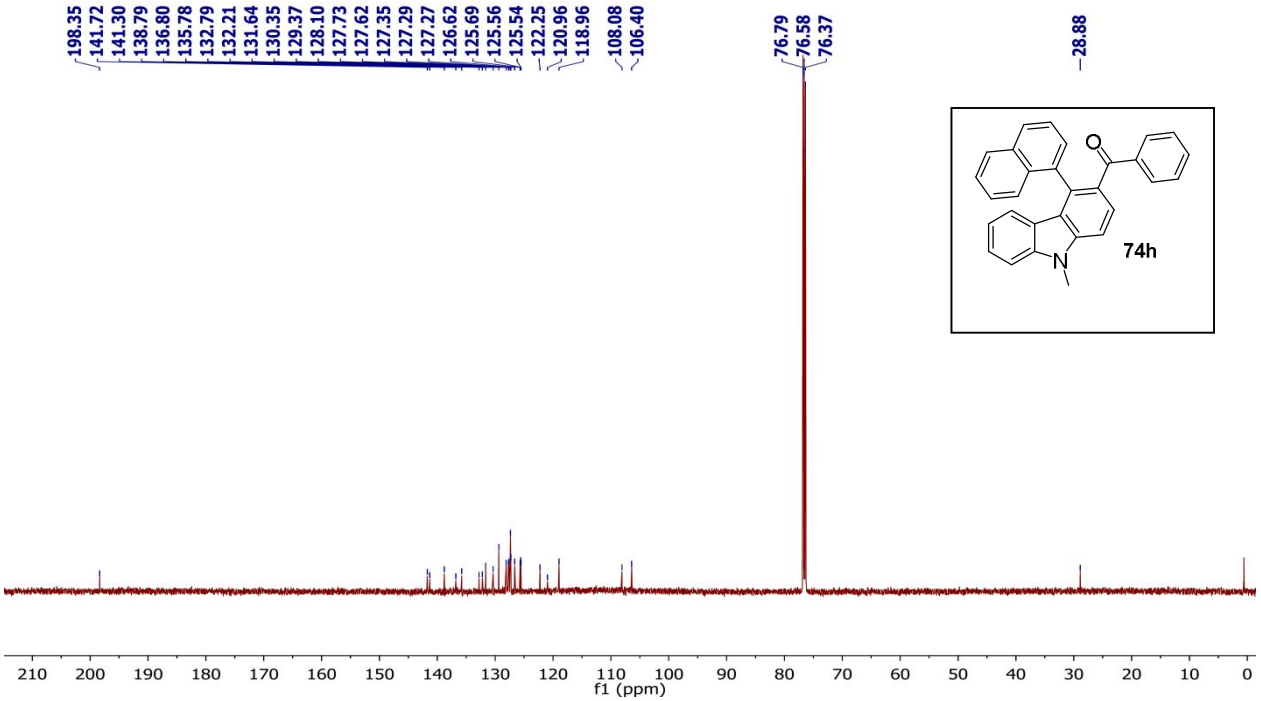
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74g:**



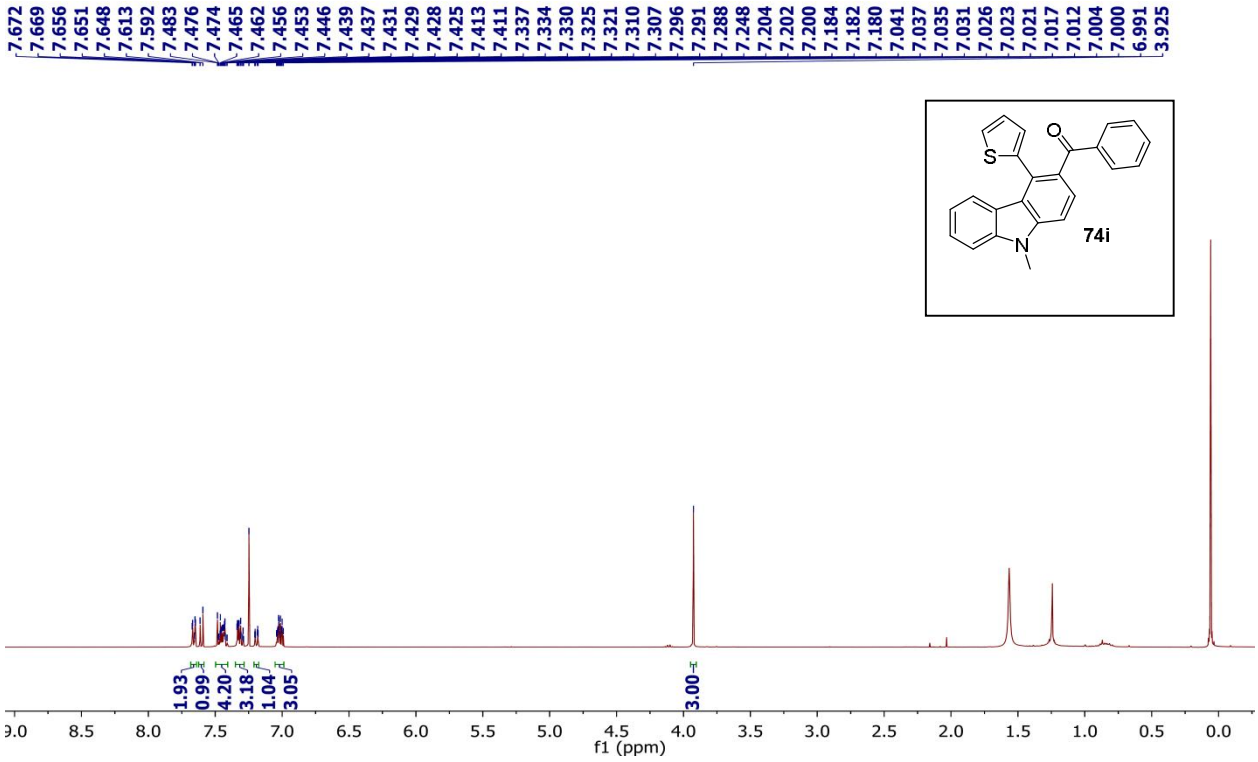
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74h**:



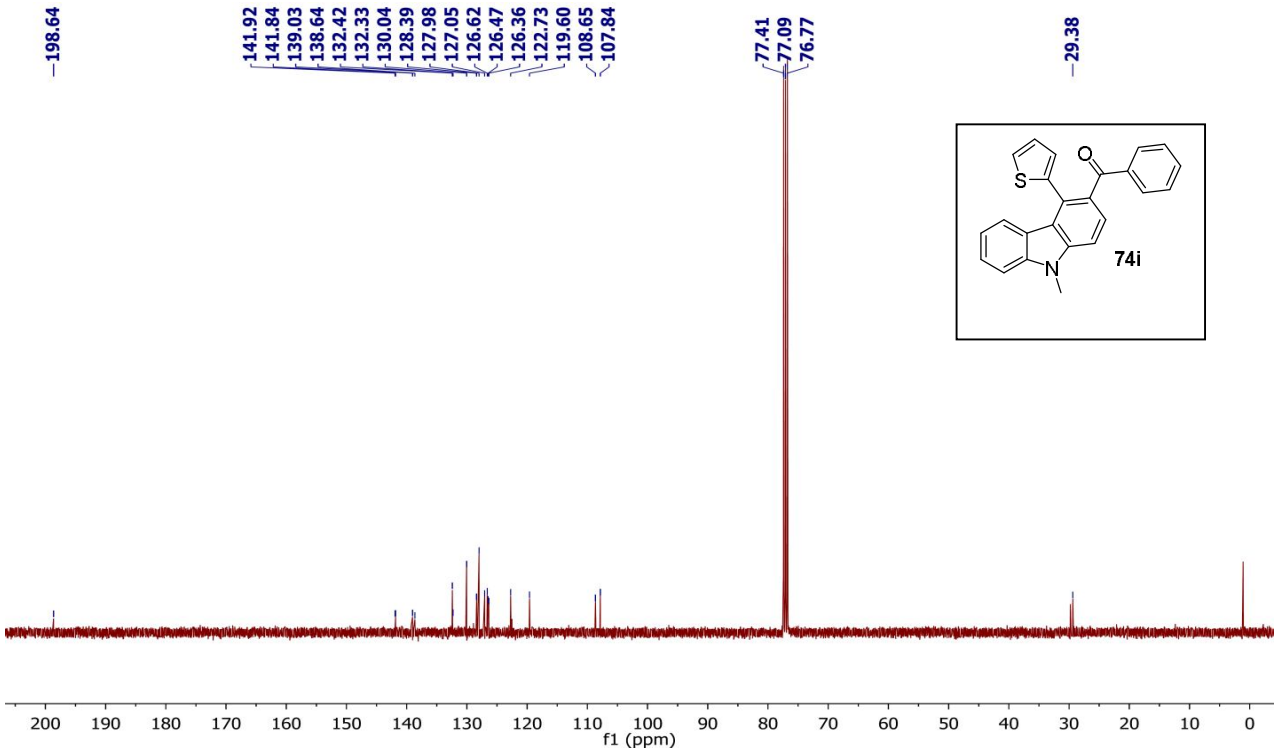
^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) spectrum of compound **74h:**



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74i**:



^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74i:**



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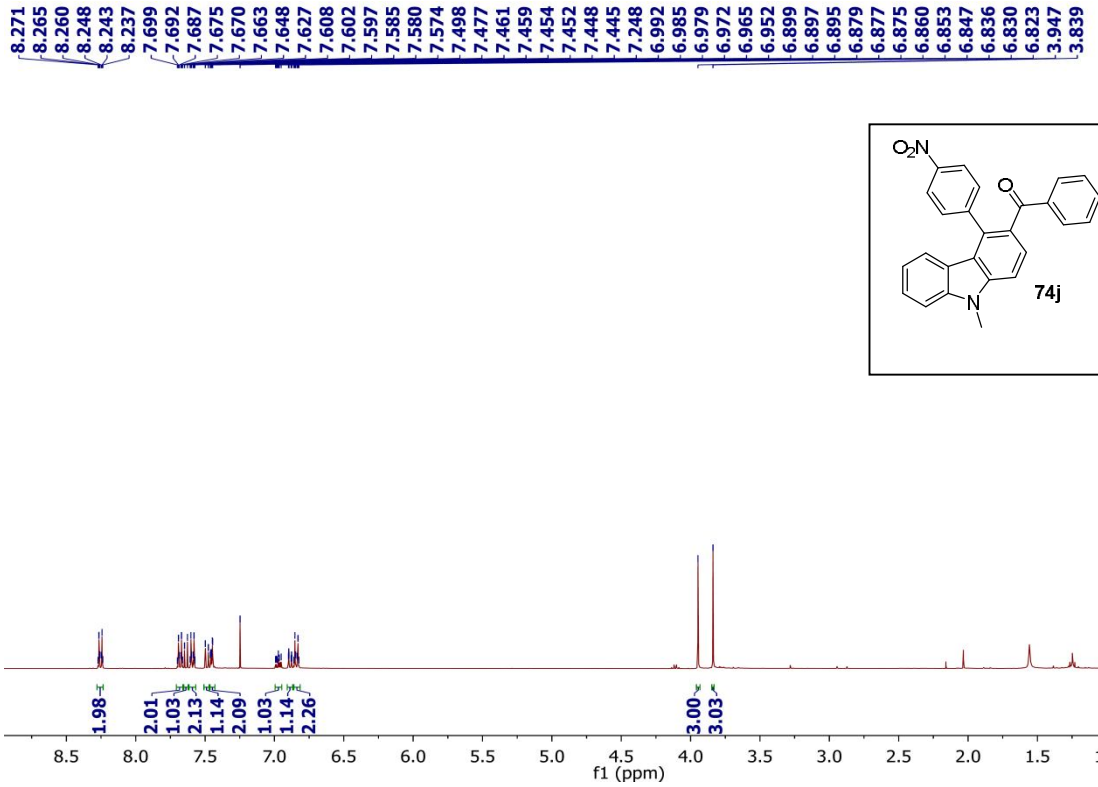

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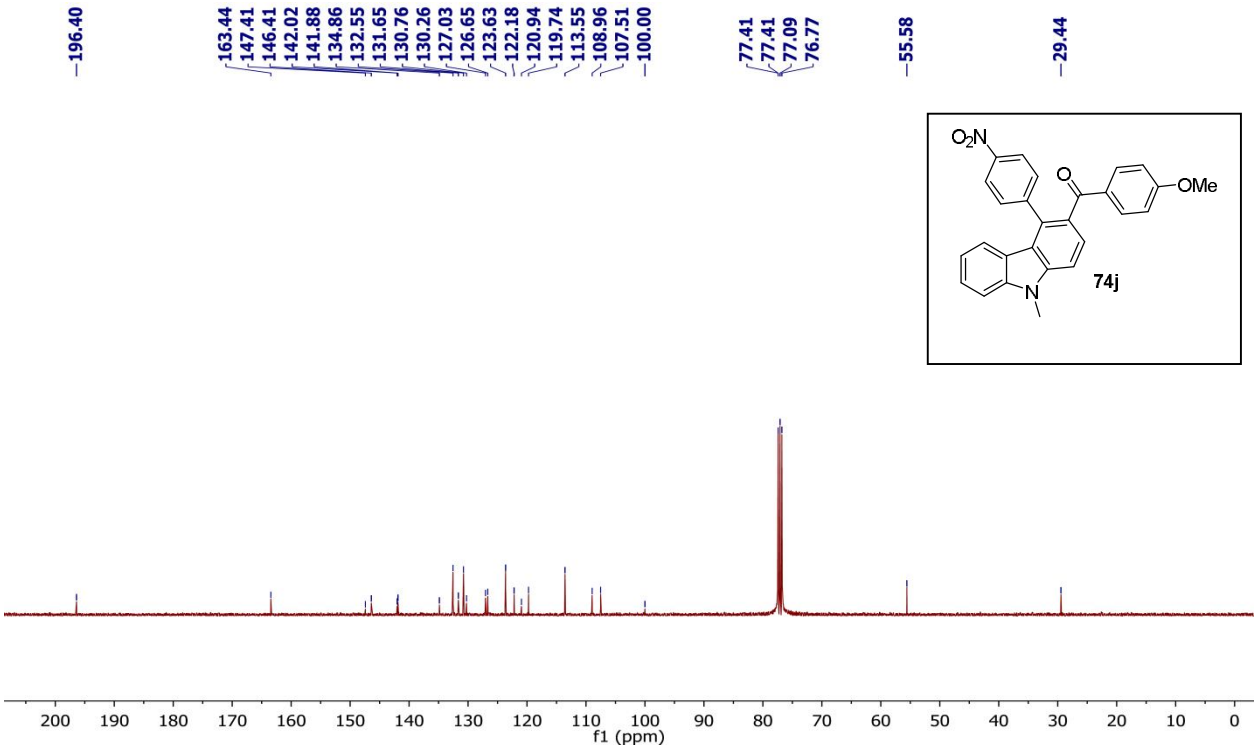
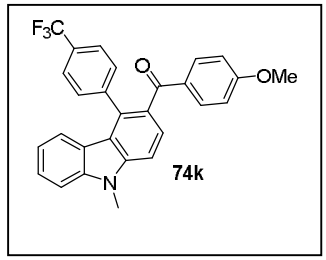
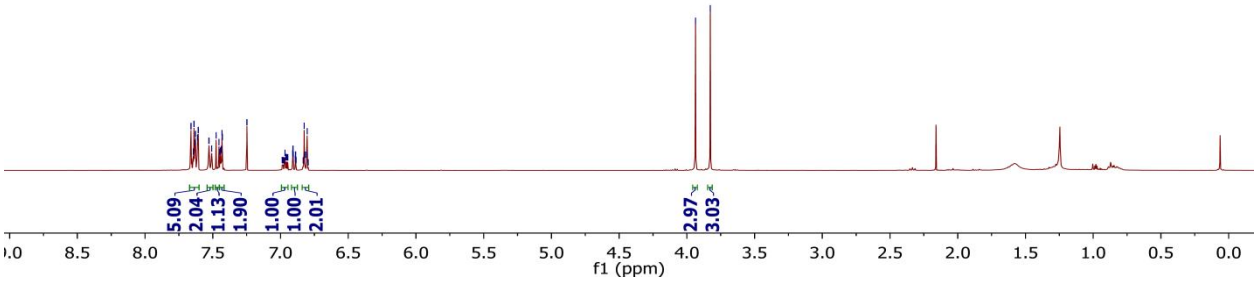
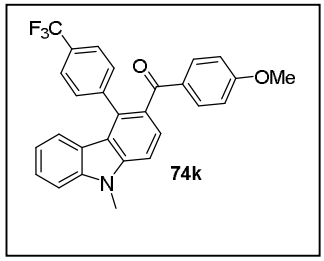


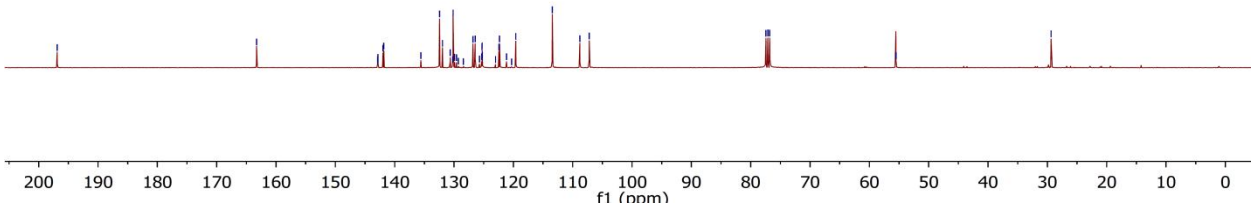
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74k**:



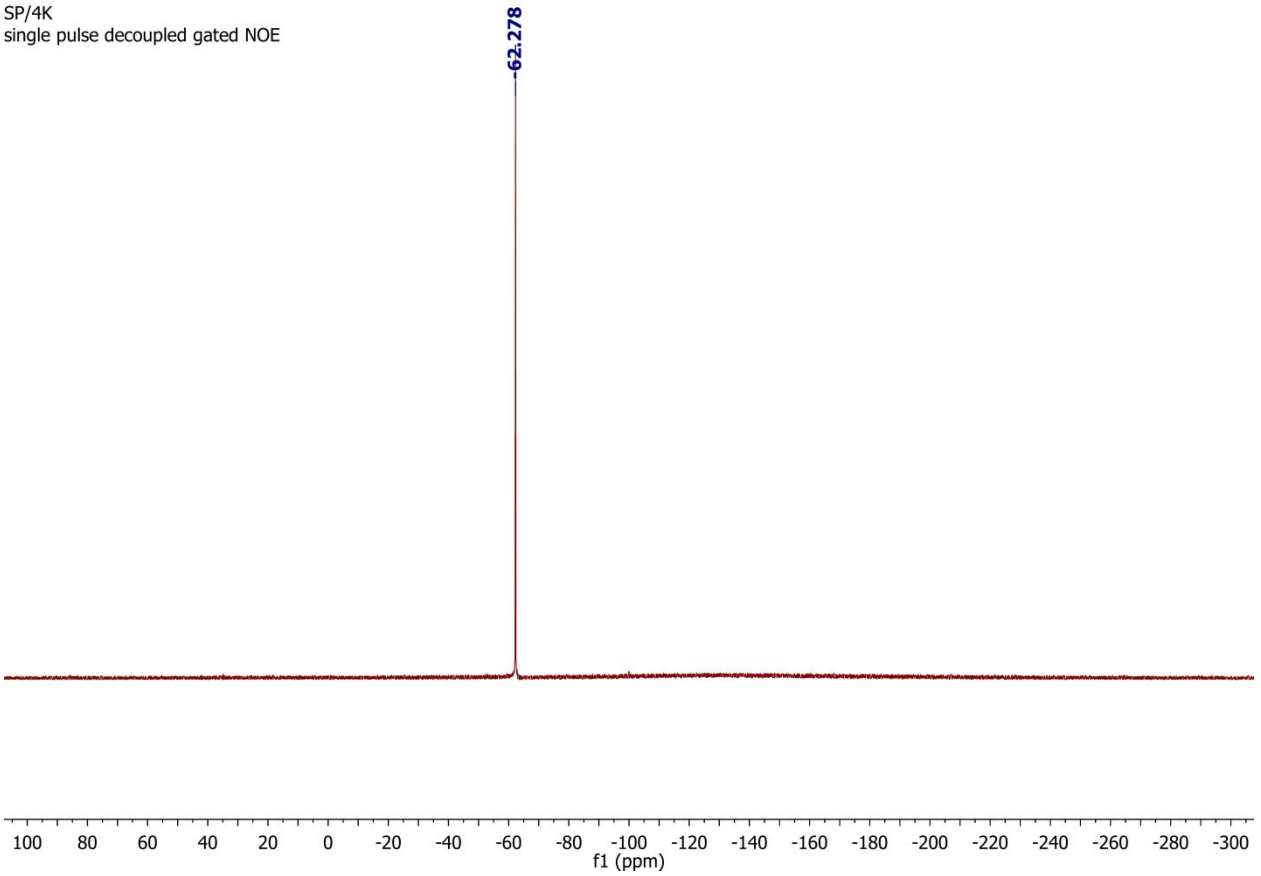


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74k:**

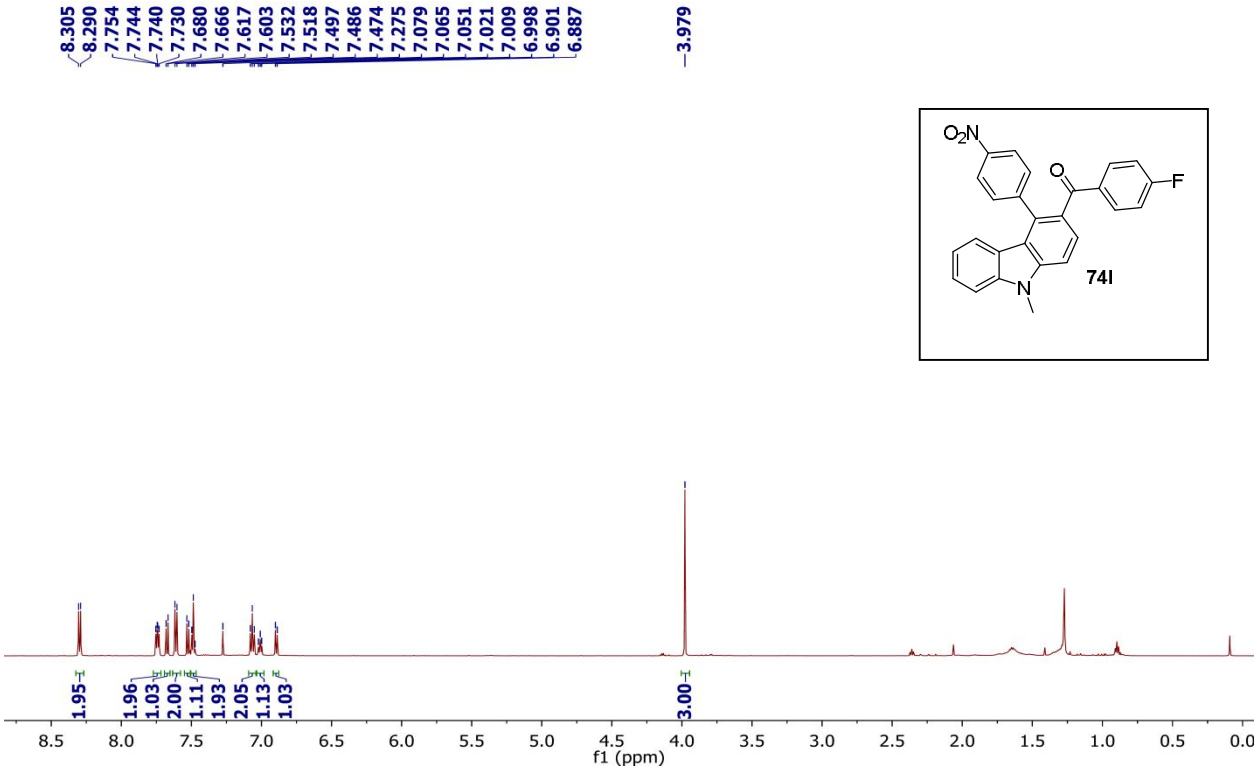




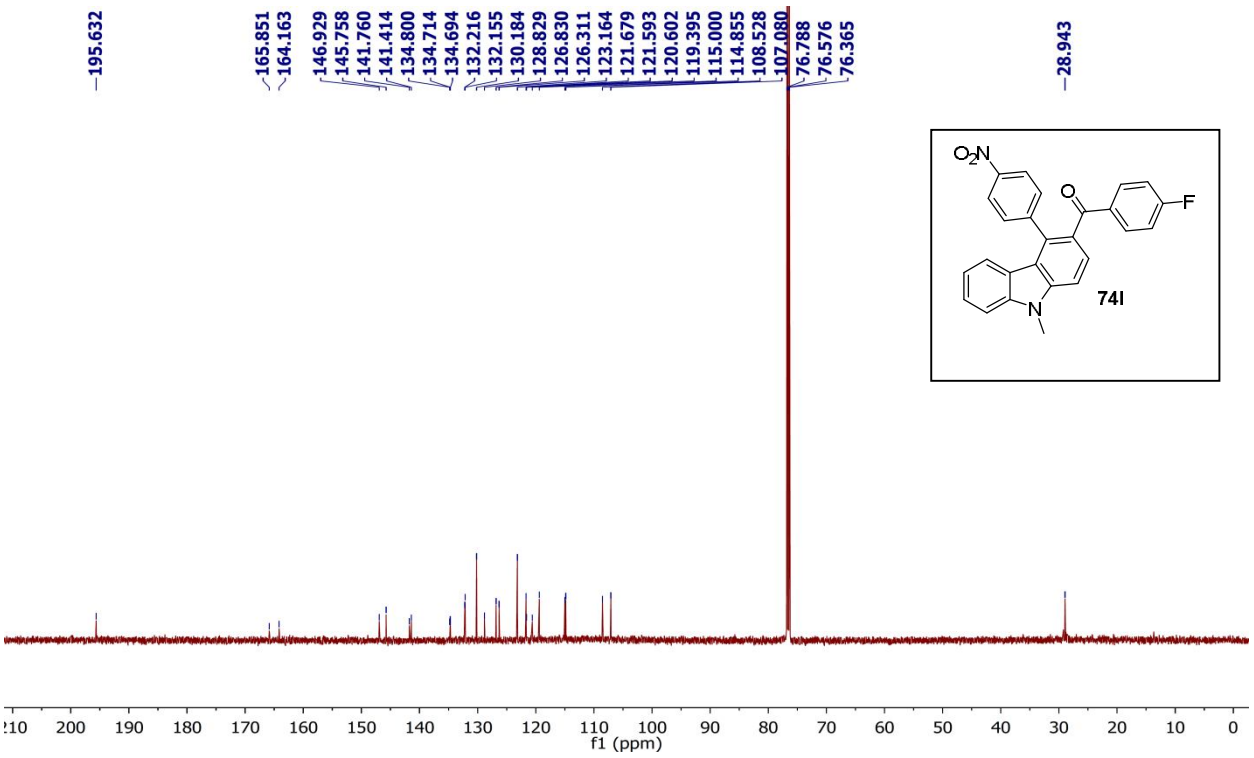
$^{19}F\{^{1}H\}$ NMR (376 MHz) of **74k**:



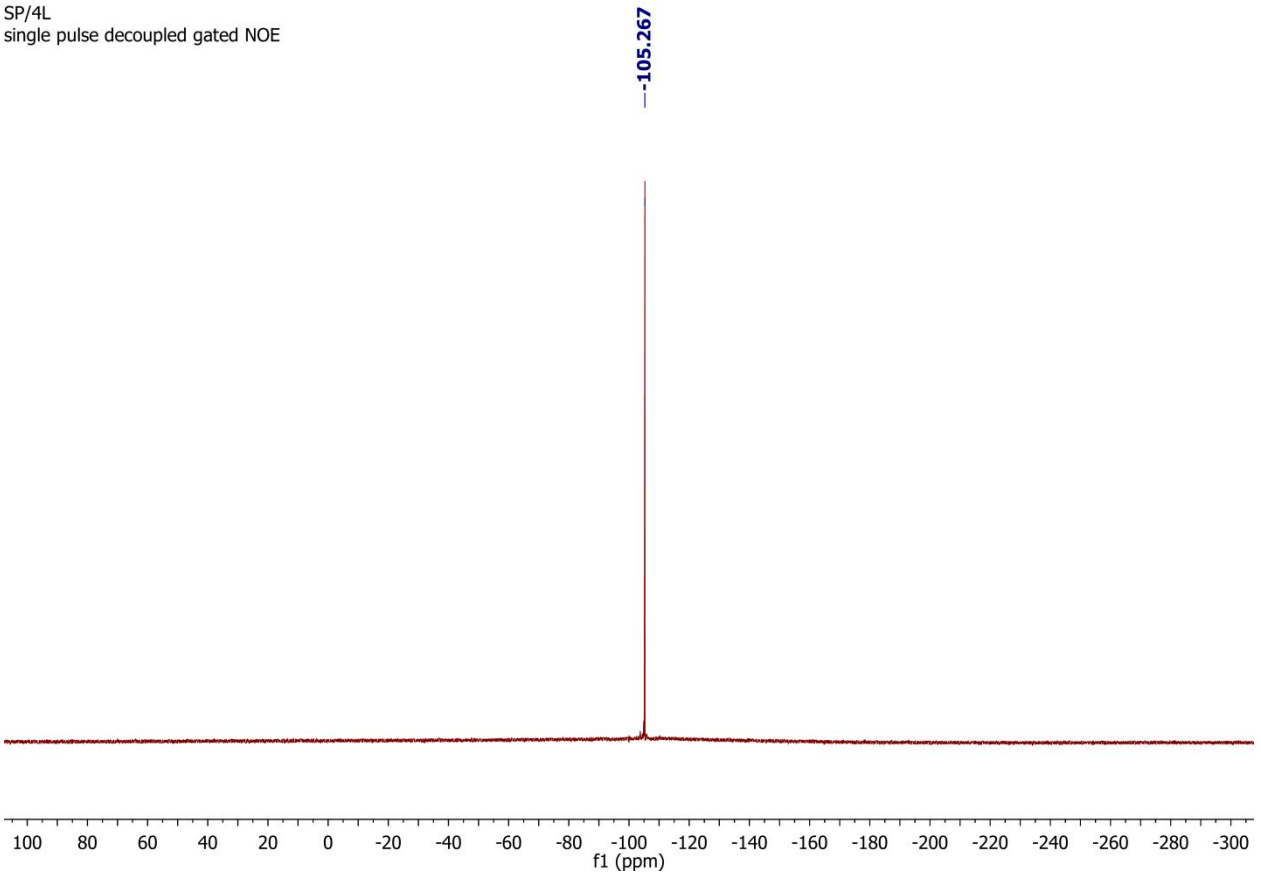
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **74l**:



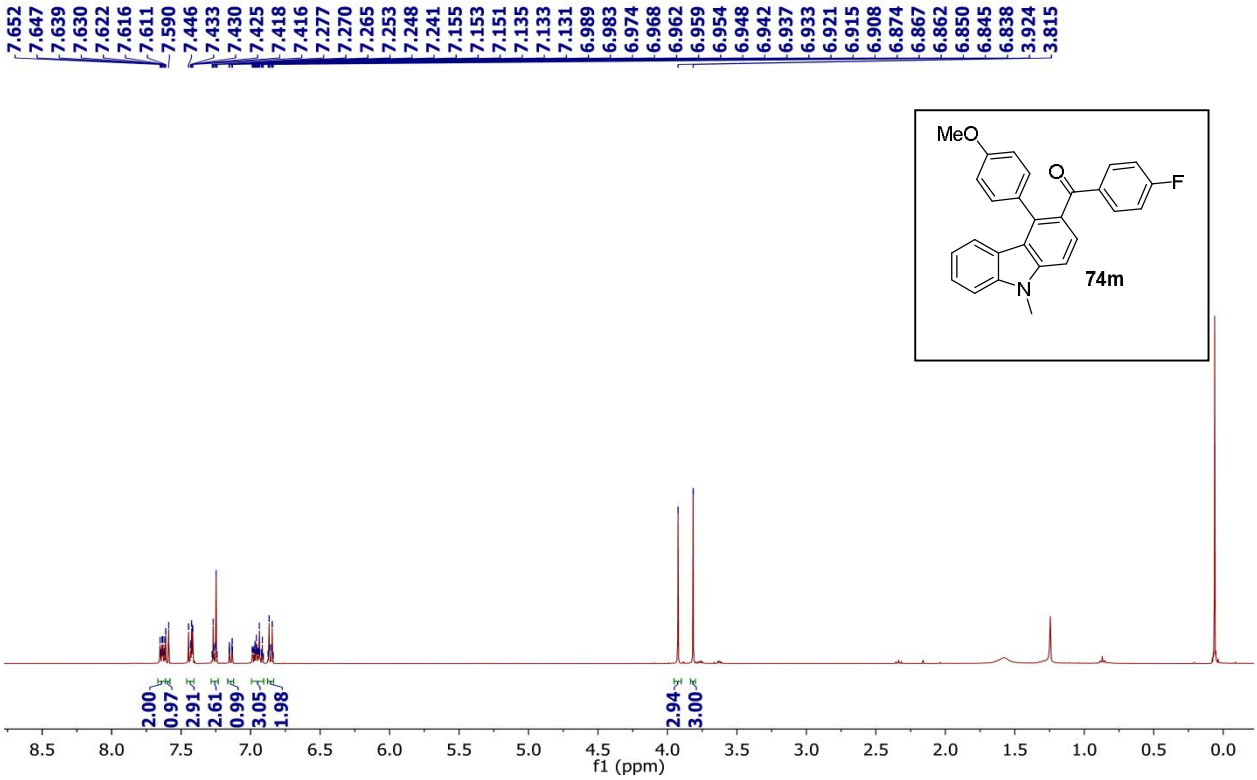
^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) spectrum of compound **74l:**



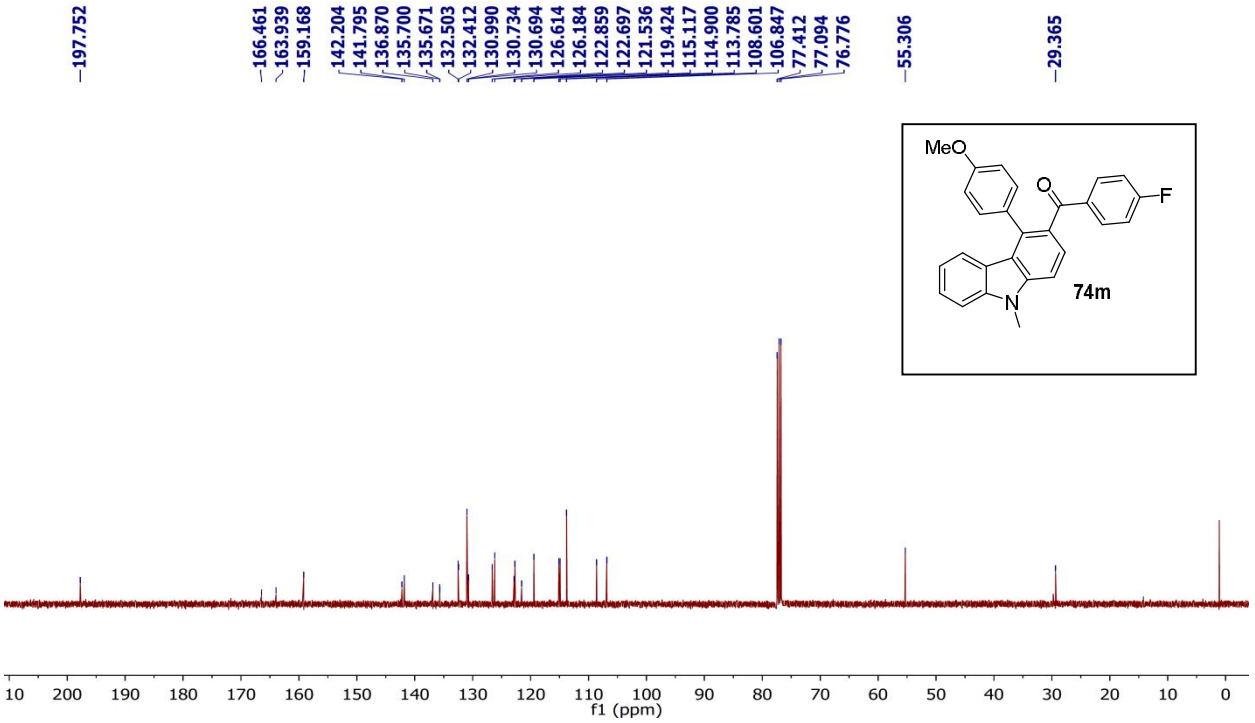
$^{19}F\{^{1}H\}$ NMR (376 MHz) of **74l**:



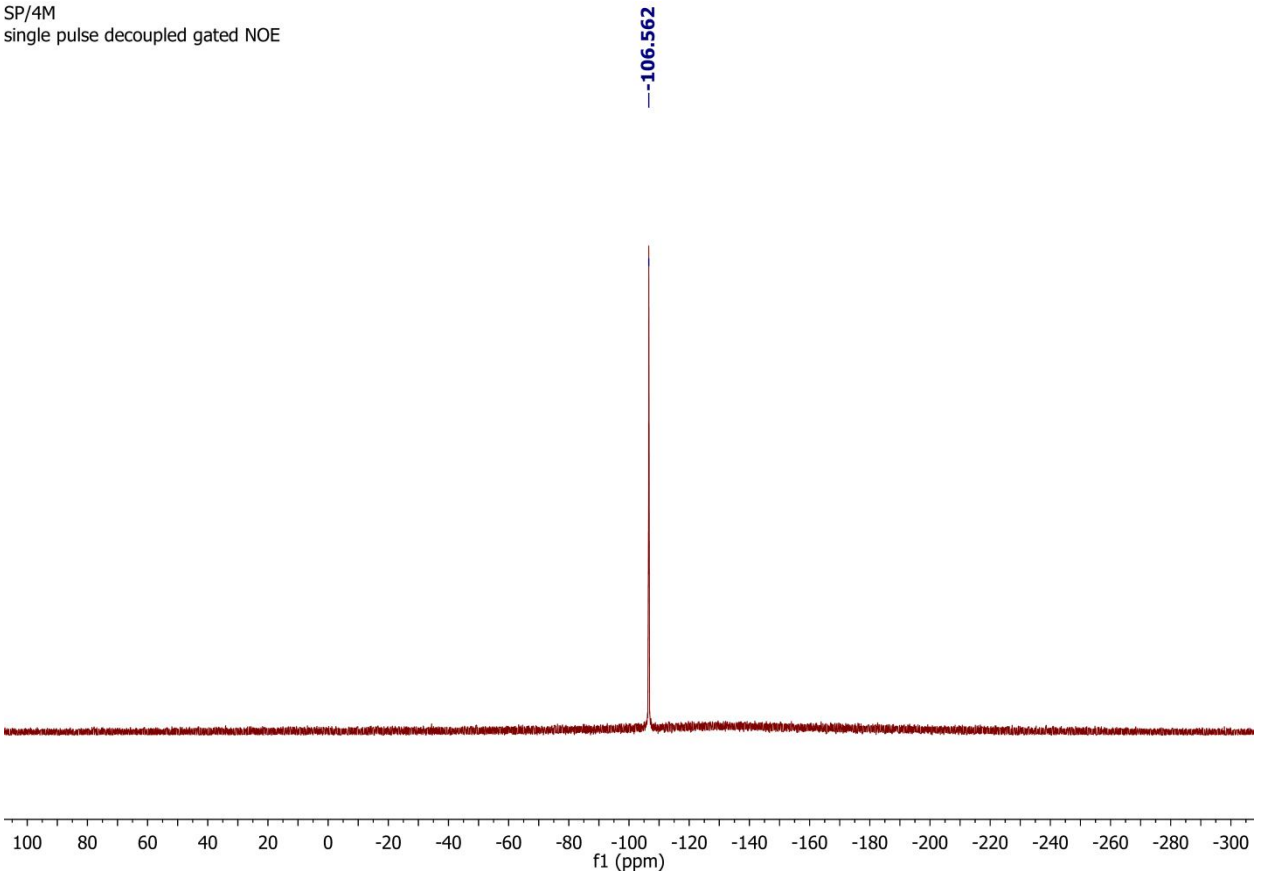
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74m**:



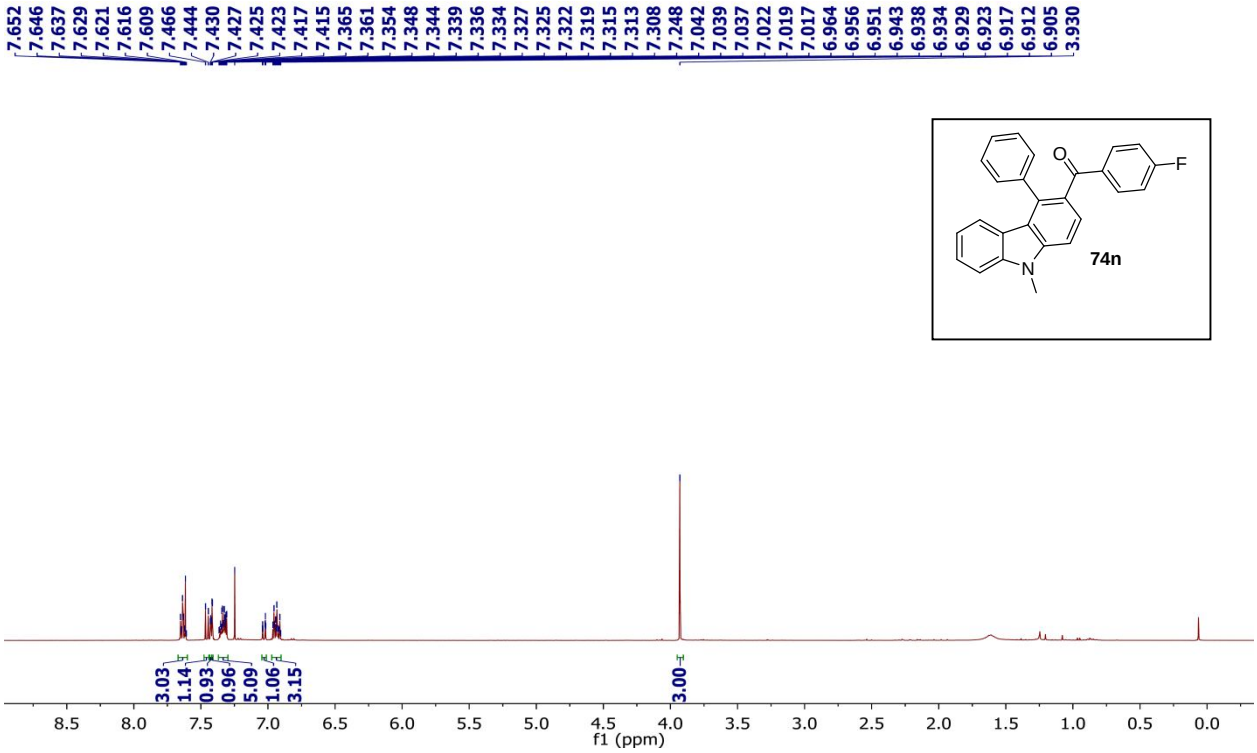
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74m:**



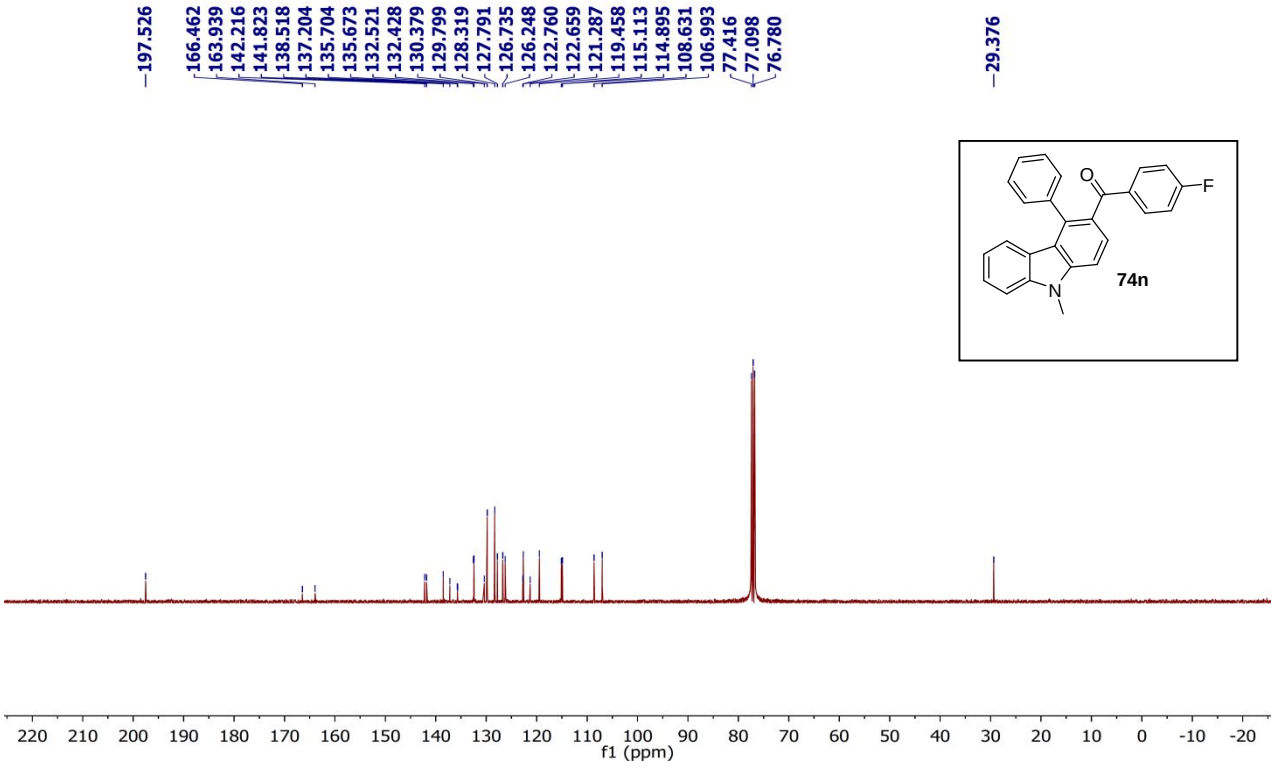
$^{19}F\{^{1}H\}$ NMR (376 MHz) of **74m**:



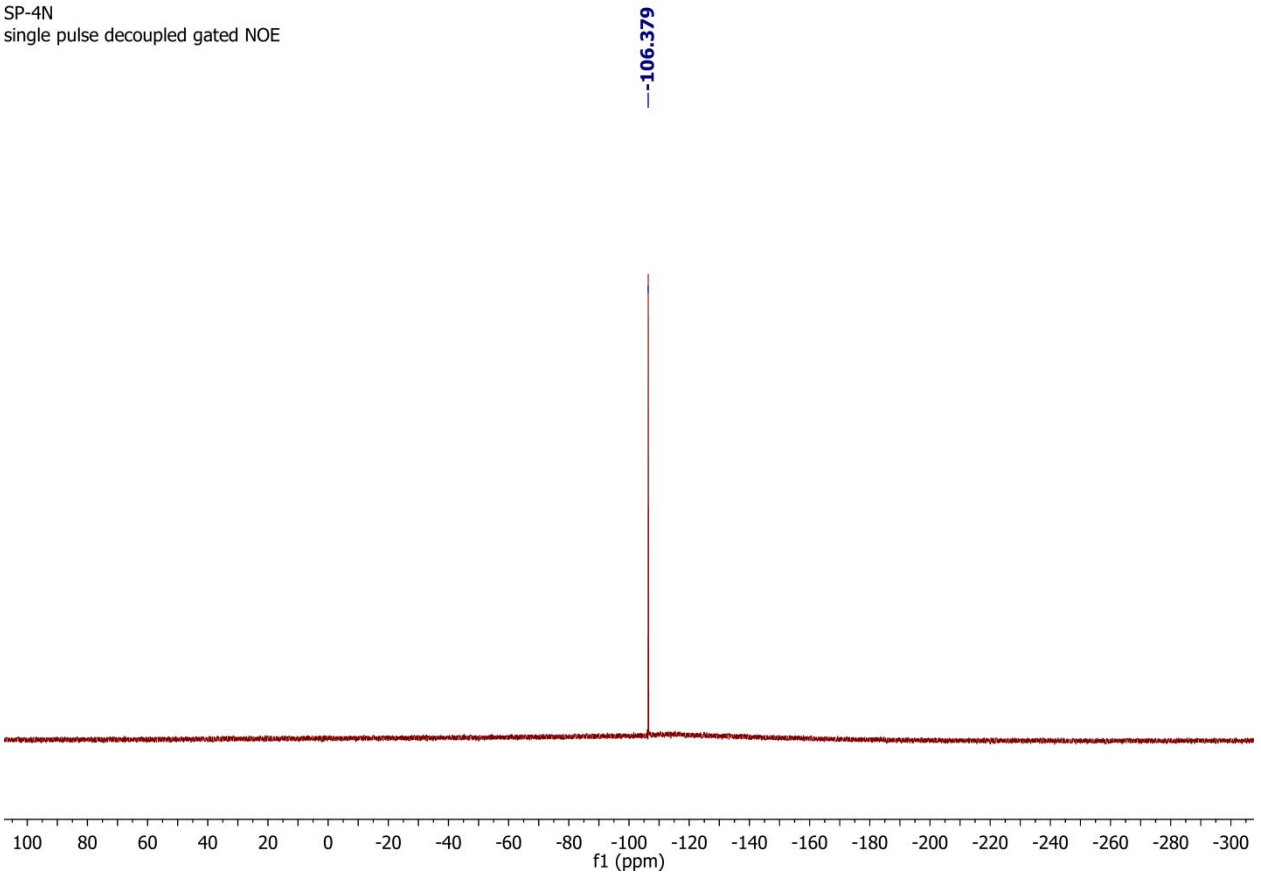
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74n**:



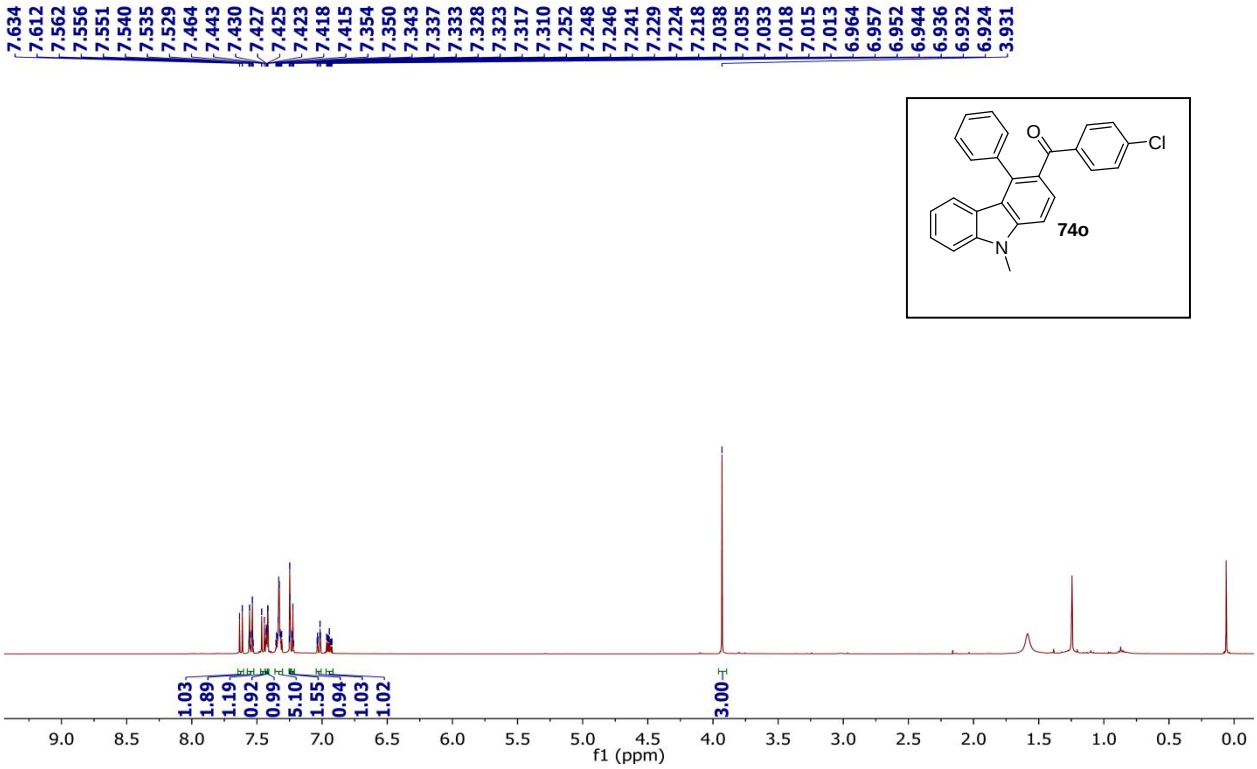
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74n:**



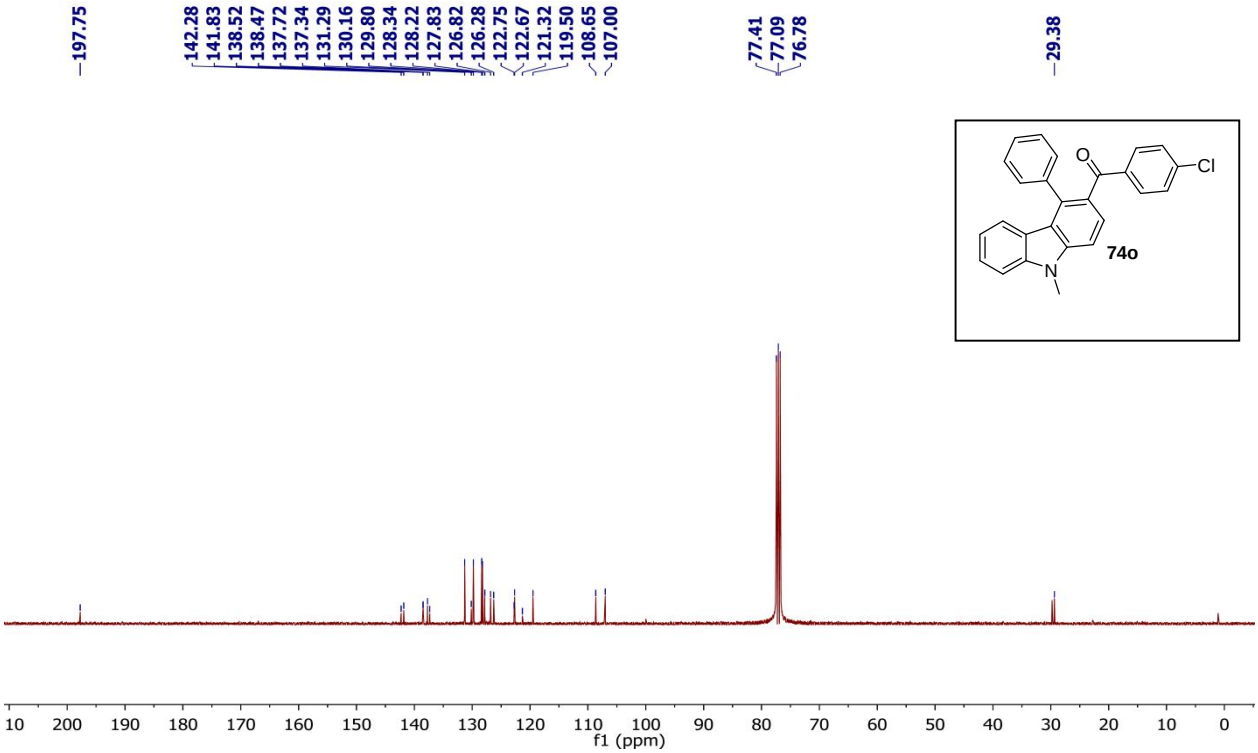
$^{19}F\{^{1}H\}$ NMR (376 MHz) of **74n**:



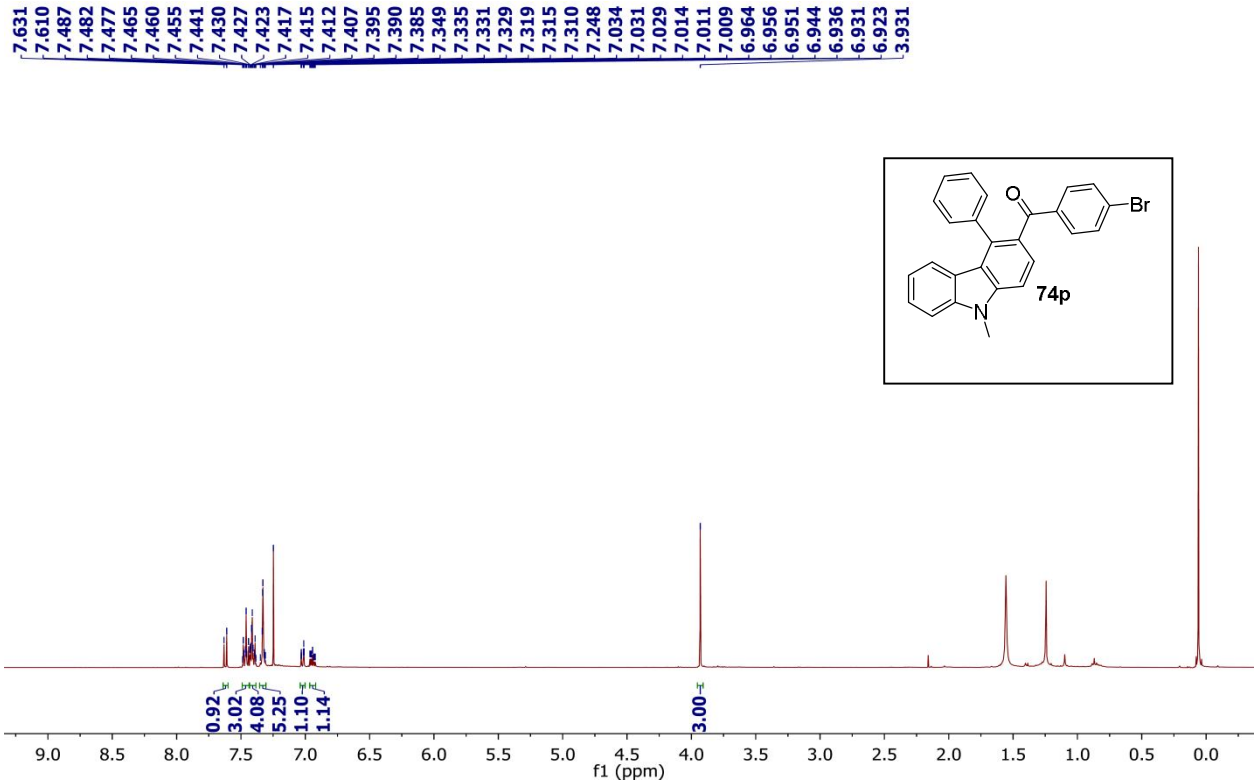
^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74o**:



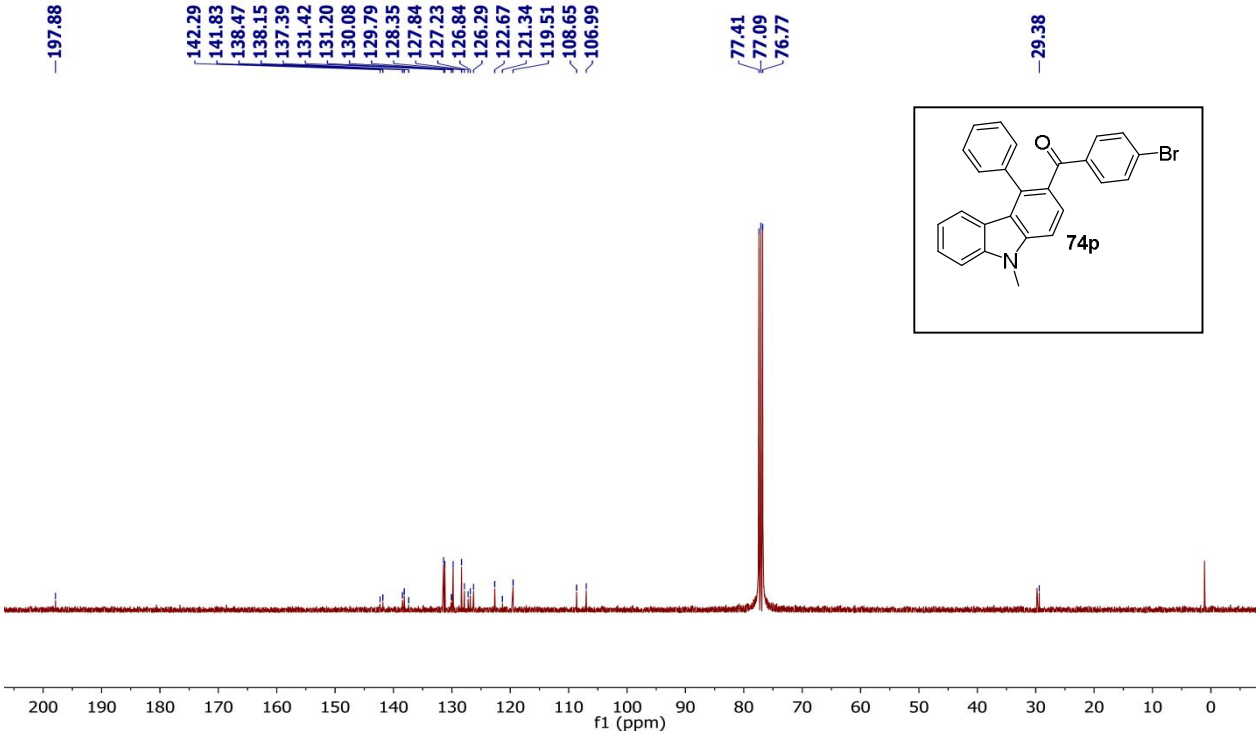
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74o:**



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **74p**:

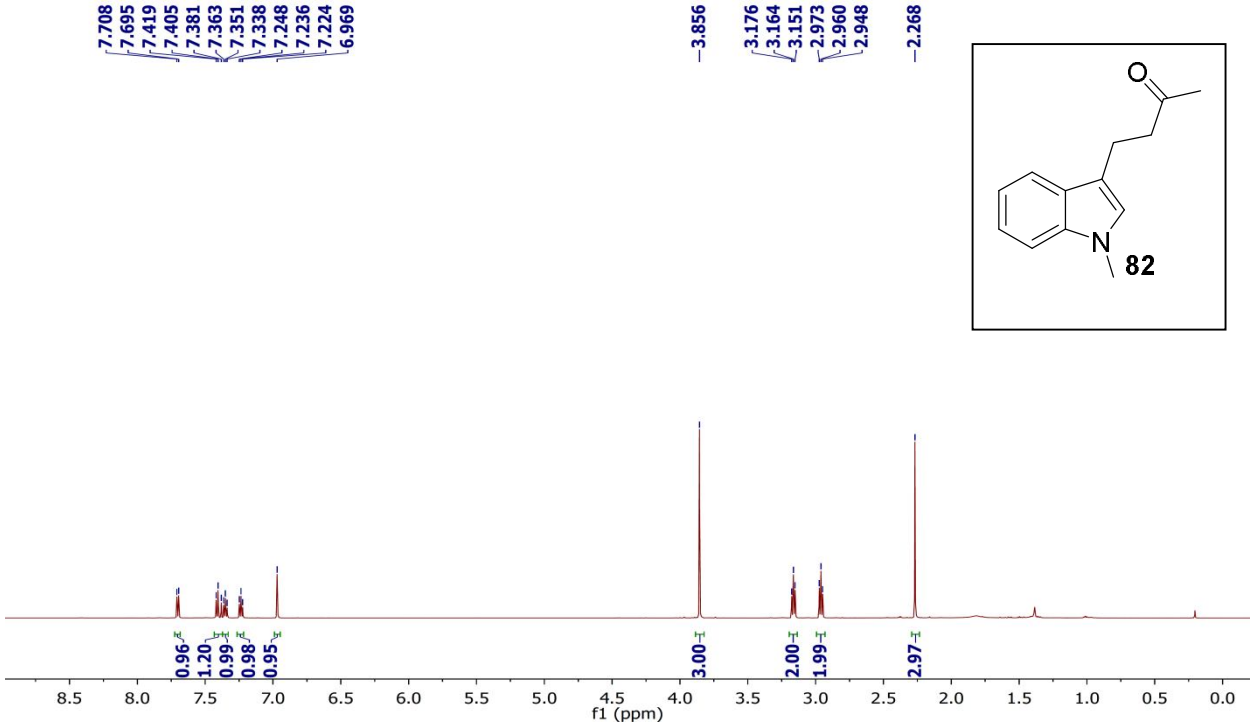


^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) spectrum of compound **74p:**

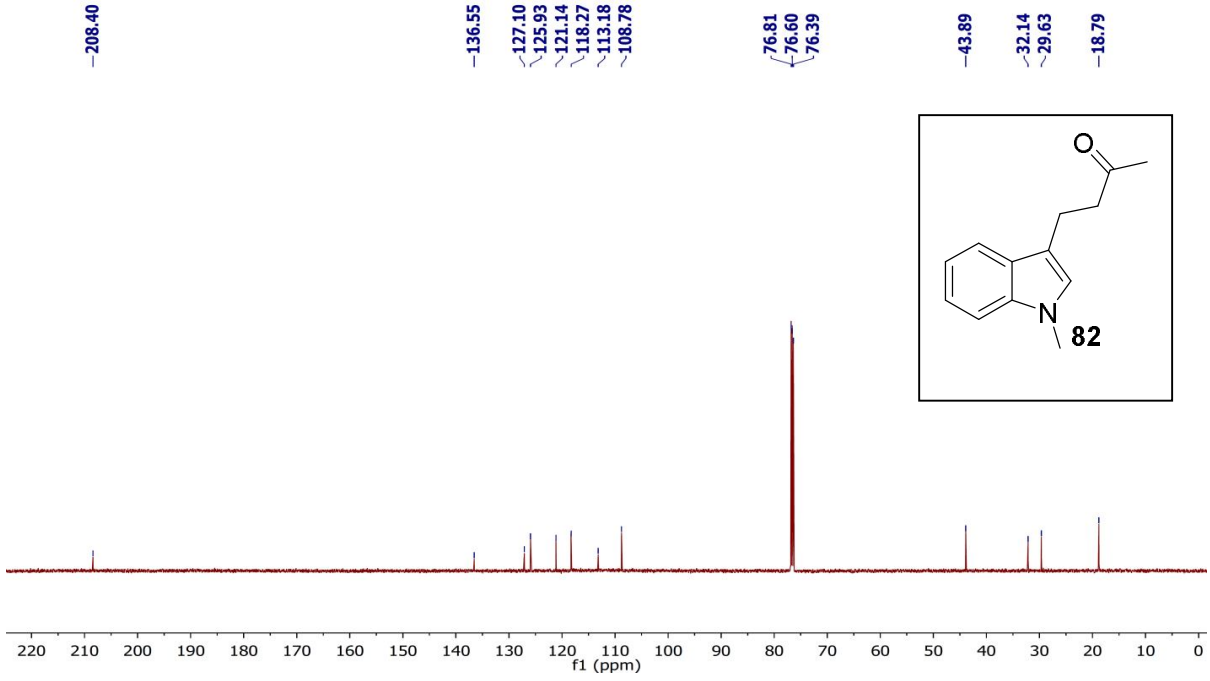


NMR spectra of compound 82

^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **82**:



^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) spectrum of compound **82:**



Chapter 2

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

Part I

(A Short Review)

2.1.1. Introduction:

Phenanthridines (I)

Phenanthridines (I) represent a core structure of a number of biologically active natural products and other compounds pharmacological interests such as antimalarial,[1]cytotoxic,[2] antibacterial,[3] anticancer,[4] antifungal [5] and SPECT tracers[6] etc. For example (Fig. 1), naturally occurring *Trisphaeridine* **1** exhibited anticancer activities[7], *Phenanthriplatin* **2**, a monofunctional platinum(II) compound, displayed significant antitumor properties,[8] *Bicolorine* **3** showed antiproliferative and antimigratory activity against metastatic human prostate cancer cell line PC-3 cells without cytotoxicity,[9]*Asiaticumines*[10] **4** had cytotoxic activities against different human tumor cell lines A549, LOVO, HL-60, and 6T-CEM etc.

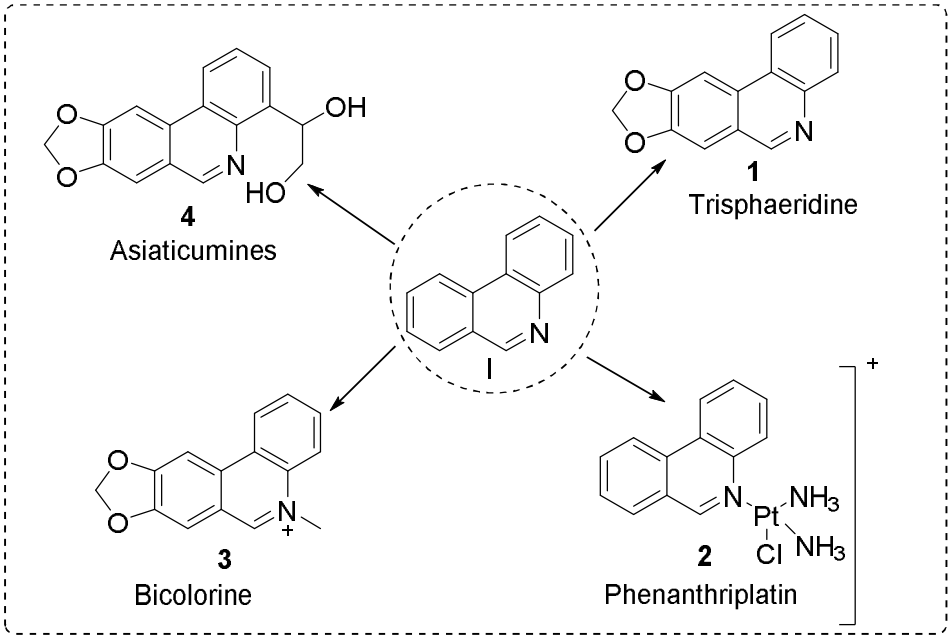


Fig. 1. Some examples of biologically active phenanthridine derivatives

Dihydrophenanthridines (II)

On the other hand, dihydrophenanthridine (**II**) though less abundant in nature exhibit biological activities compared to that of phenanthridine (**I**).[11] For example (Fig. 2),

Amaryllidaceae alkaloids 5,6-dihydrobicolorin **5** isolated from *Narcissus* species showed different pharmacological activities,[12] Several secolycorine derivatives **6** possessing a 5,6-dihydrophenanthridine skeleton shows potent inhibitory activity against acetylcholinesterase with the IC50 value at micromolar range[13], while compound **7** derived from natural alkaloid possess potent inhibitory activities against acetylcholine esterase,[14] compound **8** acts as bradykinin B1 antagonist[15] and compound **9** is known as potassium channel inhibitor and immune suppressant as well.[16]

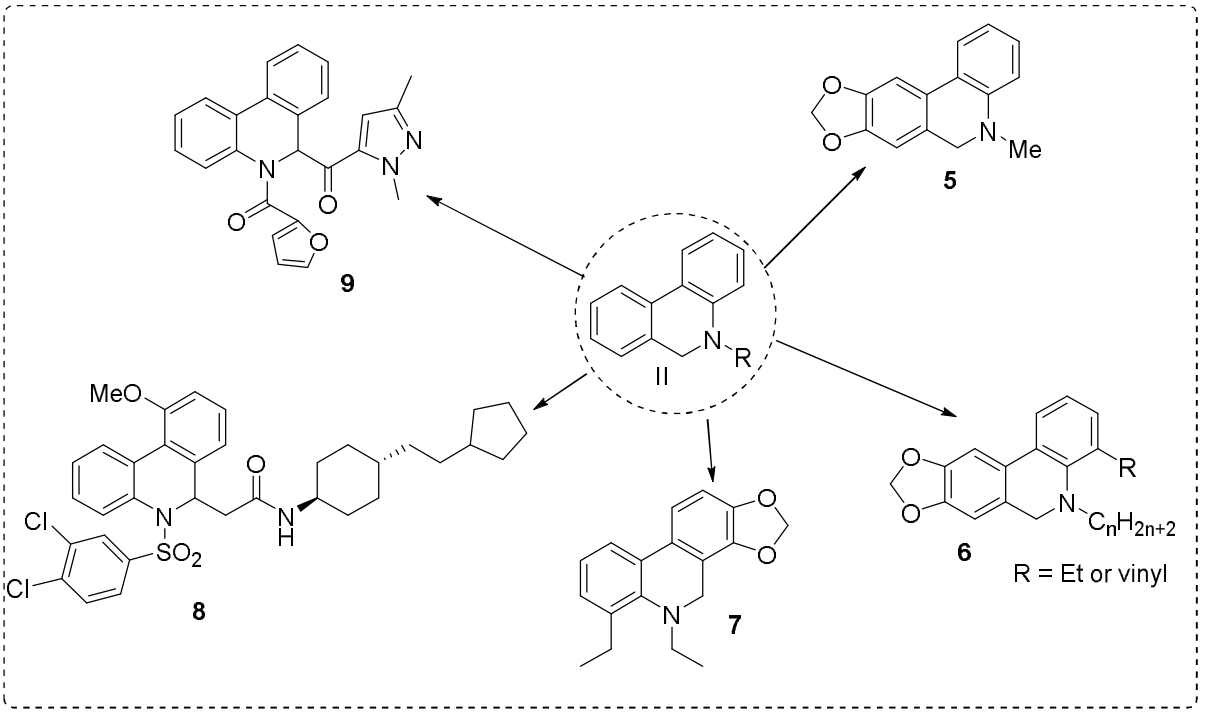


Fig. 2. Some examples of biologically active dihydrophenanthridine derivatives

2.1.2. Benzo[*c*]phenanthridines

More importantly, fusion of an additional benzene ring to phenanthridine (**I**) resulted in the formation of the structure benzo[*c*]phenanthridine (**III**) which is found as core structure in a number of compounds with remarkable therapeutic efficacies. For example (**Fig. 3**), *Chelerythrine* **10** acts as G-quadruplex DNA stabilizer,[17] *Nitidine* **11** is known as topisomerase I/II inhibitor[18] and *Sanguinarine* **12** is identified as lipoxygenase inhibitor[19] ,

Isofagaridine **13** is found to inhibit the topoisomerase-I mediated DNA relaxation[20] and to stabilize the covalent complex between the enzyme and DNA. (Fig.3).

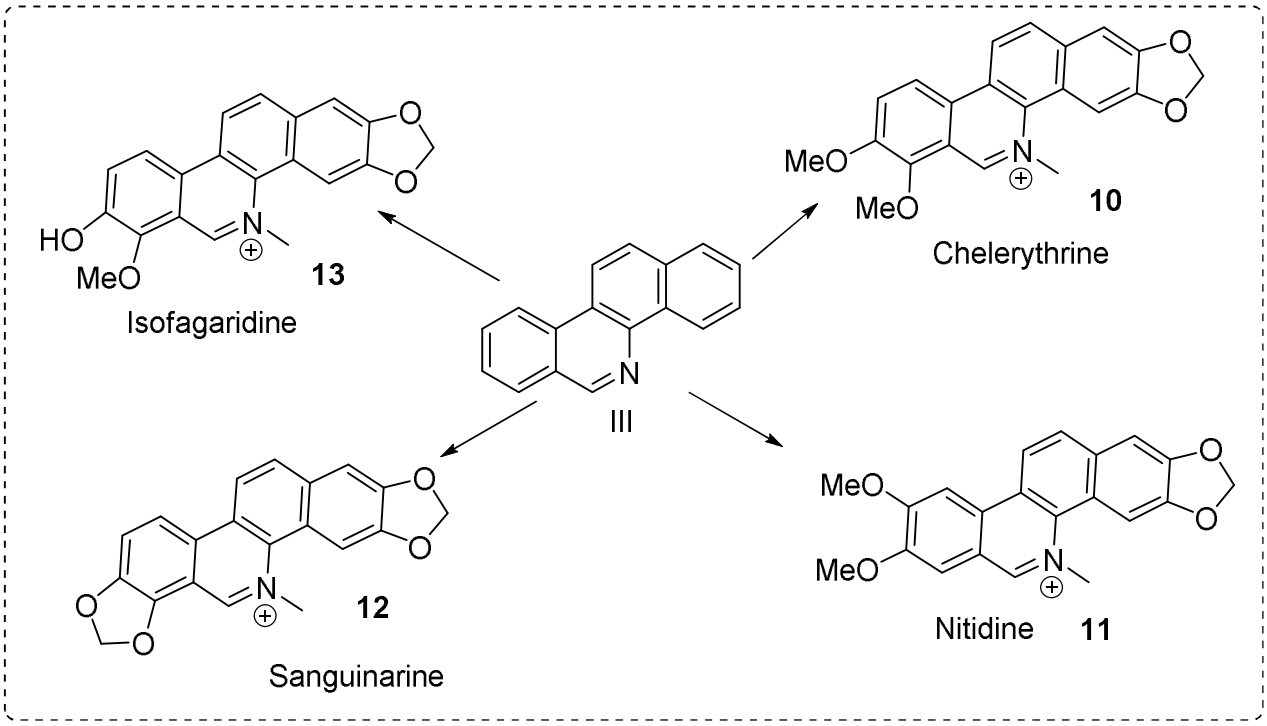
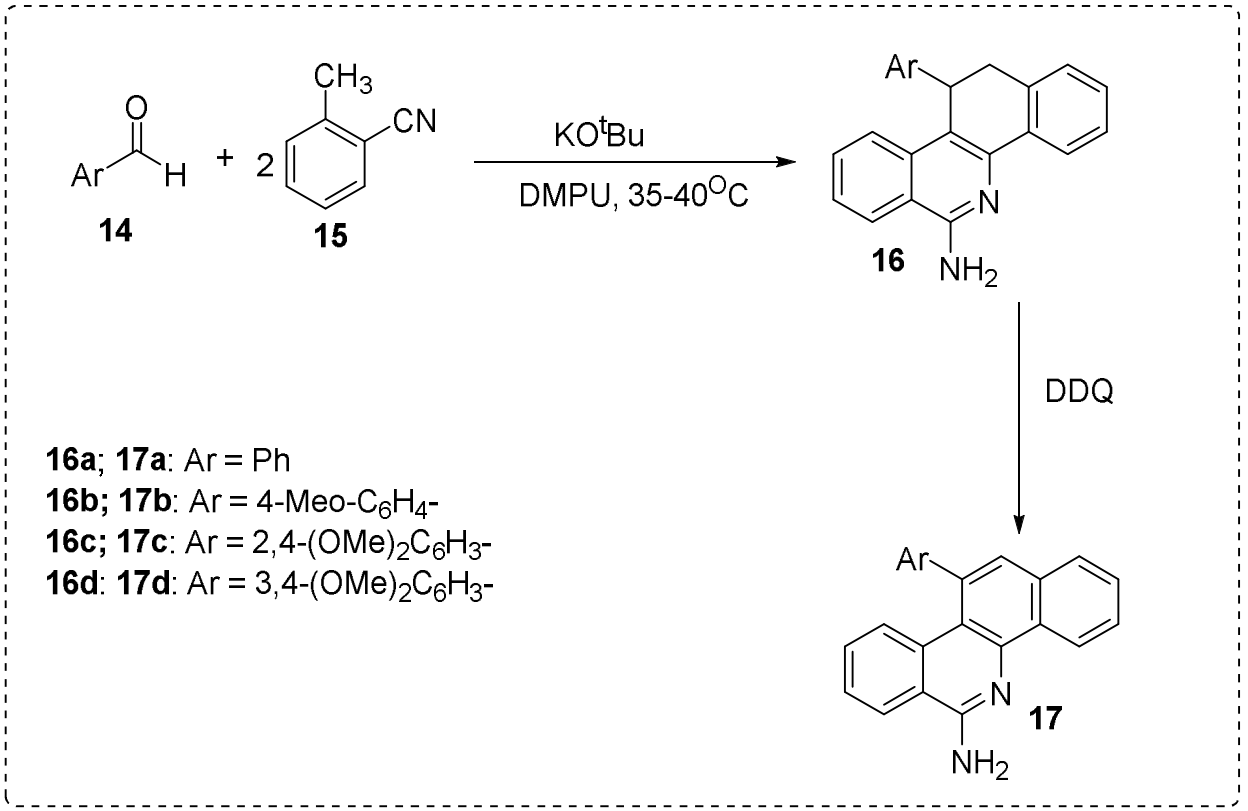


Fig.3. Some examples of biologically active benzo[*c*]phenanthridine derivatives

2.1.2.1. Synthesis of Benzo[*c*]phenanthridines

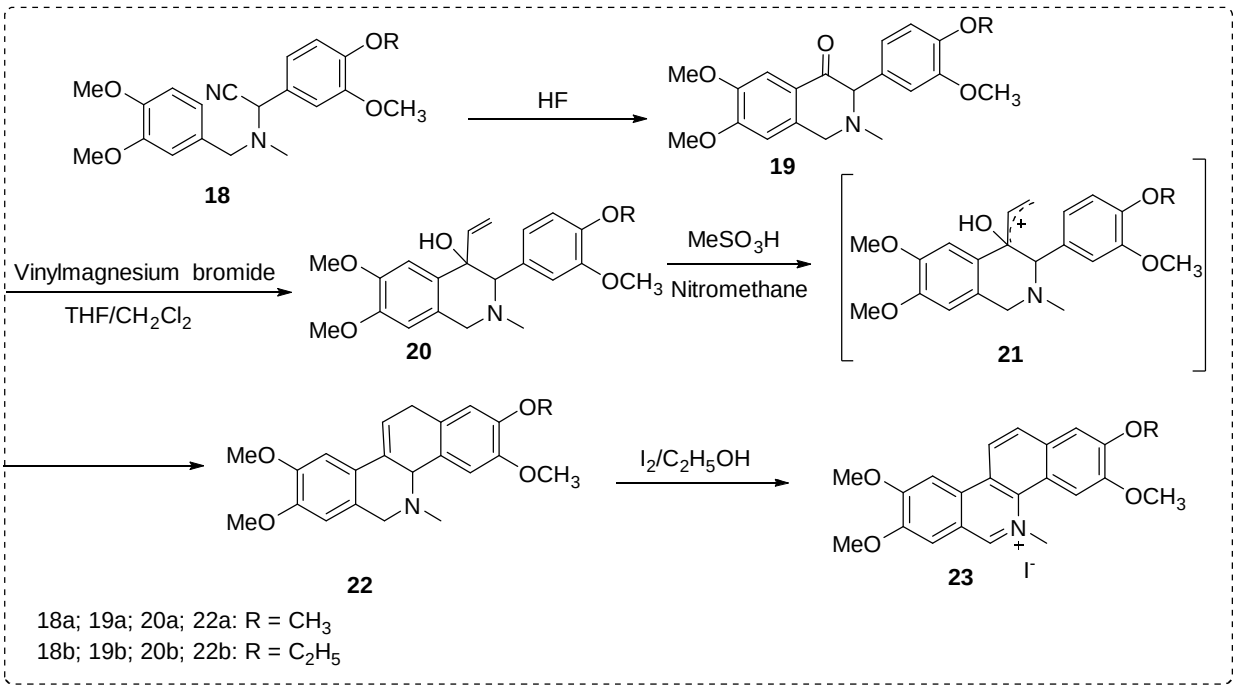
2.1.2.1.1. Classical methods for the synthesis of Benzo[*c*]phenanthridines

In recent past, **Clement** *et al.*[21] described a highly efficient and versatile synthesis of 11-substituted 6-amino-benzo[*c*]phenanthridines **17** starting from simple substrates (Scheme 1). The synthesis is based upon a condensation of 2 equivalents of 2-methylbenzonitrile (**15**) and various aromaticaldehydes **14**, and this condensation reaction is catalyzed by potassium *t*-butoxide in DMPU solvent (Scheme 1). In next step, product **16** is converted into 6-amino-benzo[*c*]phenanthridines **17**.



Scheme 1. Synthesis of 6-amino-benzo[*c*]phenanthridines **17**

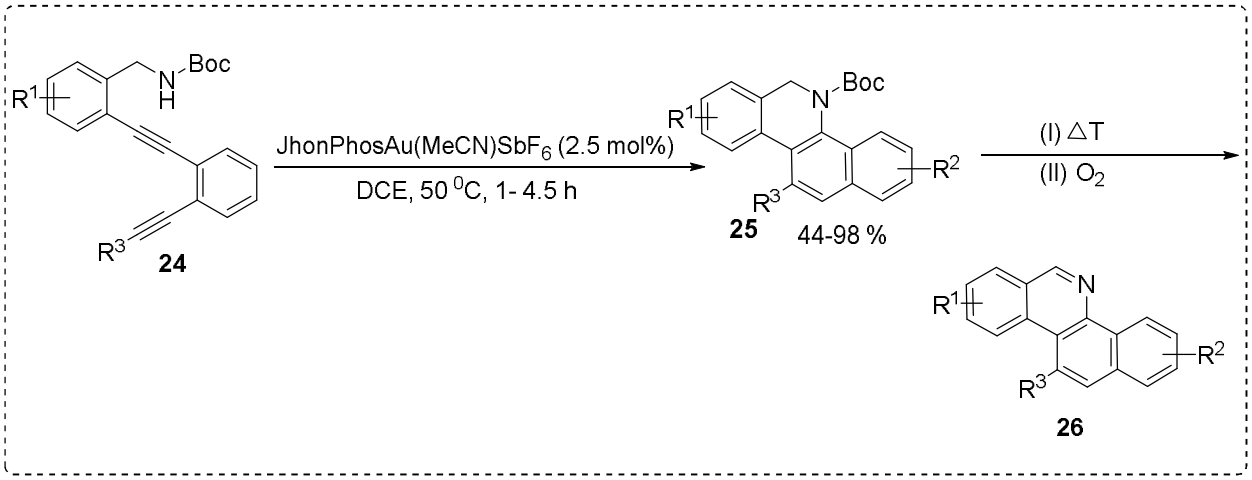
Duval *et al.*[22] described a five step synthesis of benzo[*c*]phenanthridines **23** as described under Scheme 2. Initially, an amino nitrile derivative **18** was cyclised into amino ketone **19** employing anhydrous hydrofluoric acid. In next step, the Grignard addition of vinylmagnesium bromide to the aminoketone **19** furnished the vinyl alcohol **20**. The alcohol **20** upon treatment with methanesulphonic acid in nitromethane afforded precursor intermediate **22** (of benzo[*c*]phenanthridine product **23**) via α-vinyl cationic intermediate **21**. Finally, product **22** was converted into aromatic derivative **23** by the treatment with iodine in ethanol.



Scheme 2. Synthetic route towards benzo[*c*]phenanthridines **23**

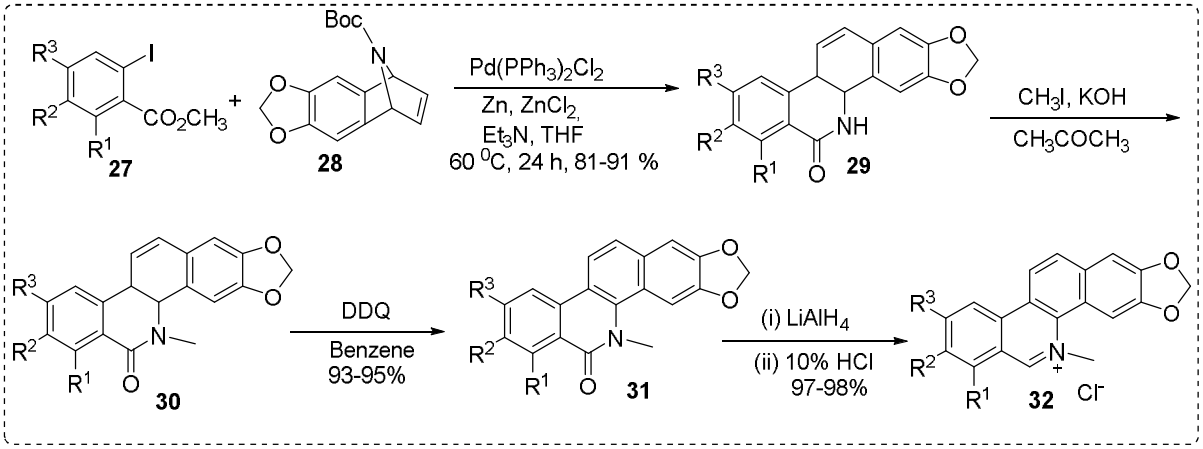
2.1.2.1.2. Metal catalyzed methods for the synthesis of Benzo[*c*]phenanthridines

Hashmi *et al.*[23]described a gold-catalyzed cascade cyclizations of Boc-protected benzylamines **24** bearing two tethered alkyne moieties in a domino reaction involving 6-*endo-dig* cyclization (Scheme 3). The reaction was initially screened intensively to find the optimized reaction conditions of product **25** and then the scope of this reaction was explored in details to synthesize various new Boc-protected dihydrobenzo[*c*]phenanthridines **25** with 44-98% yields. Furthermore, thermal cleavage of the Boc-group and subsequent oxidation gave substituted benzo[*c*]phenanthridines **26** in up to quantitative yields.



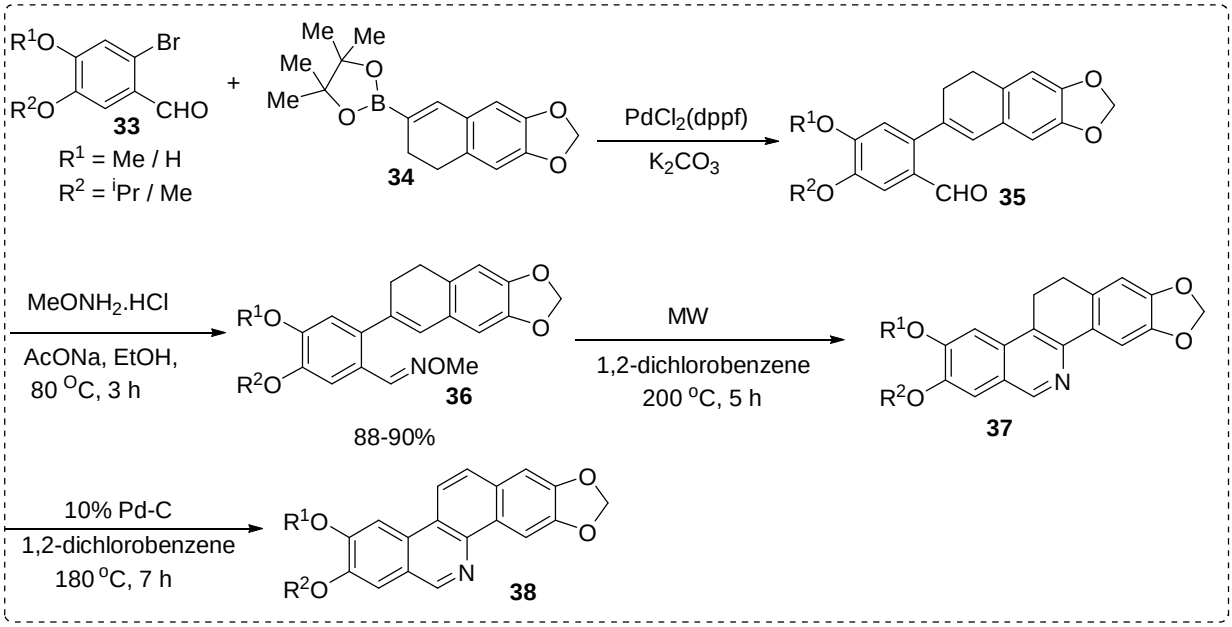
Scheme 3. Gold–catalyzed synthesis of Benzo[*c*]phenanthridines **26**

Xu *et al.*[24] reported a concise and efficient synthesis of benzo[*c*]phenanthridines **32** as shown in Scheme 4. In first step, a palladium-catalyzed tandem coupling–cyclization of functionalized *o*-iodobenzoates **27** with azabicycle **28** were carried out to achieve dihydrobenzo[*c*]phenanthridinones **29** in good yields. Thereafter, treatment of dihydrobenzo[*c*]phenanthridinones **29** with iodomethane and potassium hydroxide in acetone afforded the corresponding *N*-methylated products **30** in quantitative yields. Oxidation of **30** with DDQ was successfully carried out, giving intermediate **31** in excellent yields. Finally, reduction of benzo[*c*]phenanthridones **31** with $LiAlH_4$ followed by treatment with HCl afforded the desired quaternary benzo[*c*]phenanthridine chlorides **32** in high yields.



Scheme 4: Synthetic route for benzo[*c*]phenanthridines **32**

Hibino *et al.*[25] reported a concise route for benzo[*c*]phenanthridines as depicted under Scheme 5. Thus, Suzuki-Miyaura reaction of *O*-protected benzaldehyde **33** with 2-(6,7-methylenedioxy-3,4-dihydronephthyl)boronic acid pinacol ester **34** afforded 2-cycloalkenylbenzaldehyde **35** in good yields. Treatment of the obtained 2-cycloalkenylbenzaldehyde **35** with hydroxylamine methyl ether gave benzaldoxime **36** which was subjected to the microwave-assisted thermal aza-electrocylic reaction in 1,2-dichlorobenzene to yield the 11,12-dihydrobenzophenanthridine **37.** Finally, upon treatment of intermediate **37** with Pd/C at elevated temperature afforded the desired benzo[*c*]phenanthridines **38** in good yields.

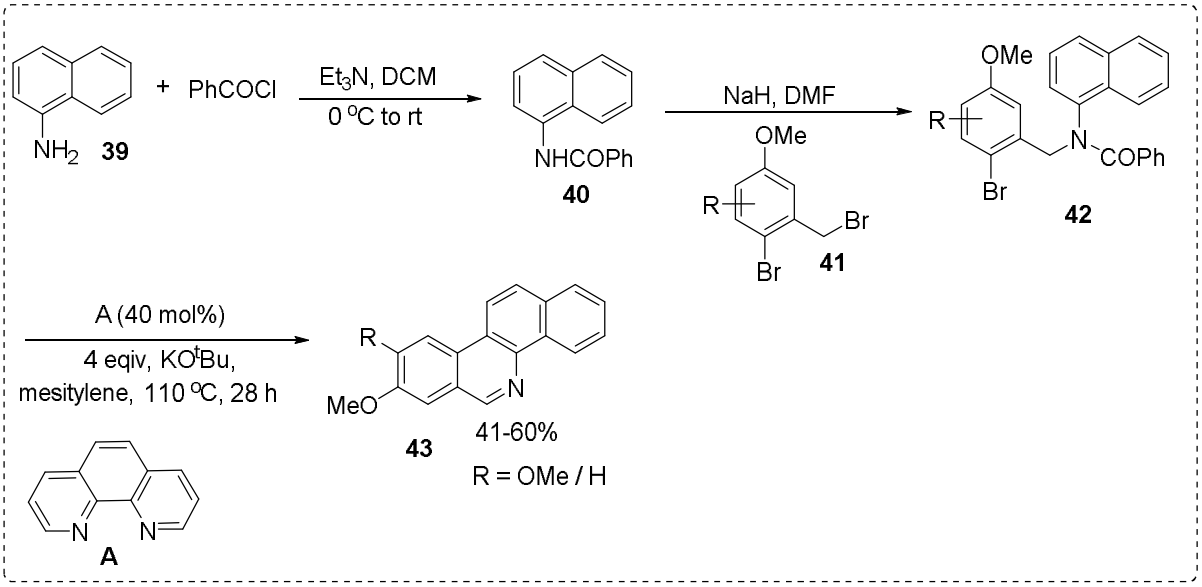


Scheme 5. Synthetic route for benzo[*c*]phenanthridines **38**

2.1.2.1.3. Metal free method for the synthesis of Benzo[*c*]phenanthridines.

Bisai *et al.*[26] reported a *"transition metal-free*' intramolecular biaryl-coupling strategy for the synthesis of benzo[*c*]phenanthridines as depicted under Scheme 6. Thus, a series of *N*-benzoyl-2-bromo-*N*-(α-naphthyl)benzylamines **42** were synthesized in two steps *following N-benzoylation* in the presence of Et_3N from α-naphthylamine **39** followed by *N*-benzylations

with 2-bromobenzyl bromides **41** in the presence of NaH in DMF. Thereafter, intramolecular coupling of **42** carried out under one-pot where biaryl-coupling, deprotection, and oxidation took place simultaneously resulting in the synthesis of benzo[*c*]phenanthridines **43** in good yields.



Scheme 6. A-metal-free approach for the synthesis of benzo[*c*]phenanthridine **43**

2.1.3. 5,6-Dihydro-benzo[*c*]phenanthridines and their importance

Fusion of an additional benzene ring to dihydrophenanthridines (**II**) as shown under Fig. 2 results in the formation of the structure 5,6-dihydro-benzo[*c*]phenanthridine (**IV**) which are less naturally abundant but often exhibit distinct biological profiles. For example, 6-acetonyl dihydrochelerythrine (ADC) **44** displays significant anti-HIV[27] and anti-apoptotic[28] effects, while buesgenin **45**[29] isolated from *Fagara tessmannii* exhibited high anti-bacterial activity while being non-toxic towards the normal cells, on the other hand, dihydrochelerythrine(DHCHL) **46** exhibits the G-quadruplex binding activity and anticancer activity,[30] dihydronitidine **47** manifested its characteristics in the tumor selective cytotoxicity, contrasting with the case of a known anticancer agent *camptothecin* (CPT)[31](Fig.4).

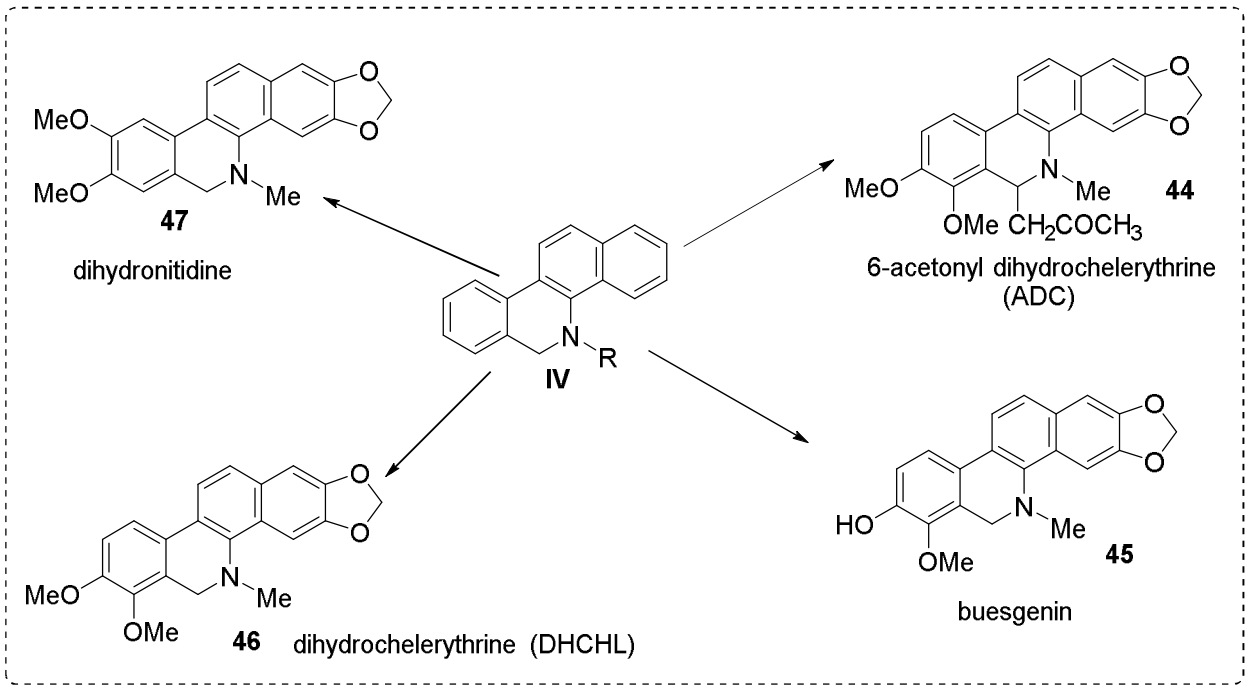
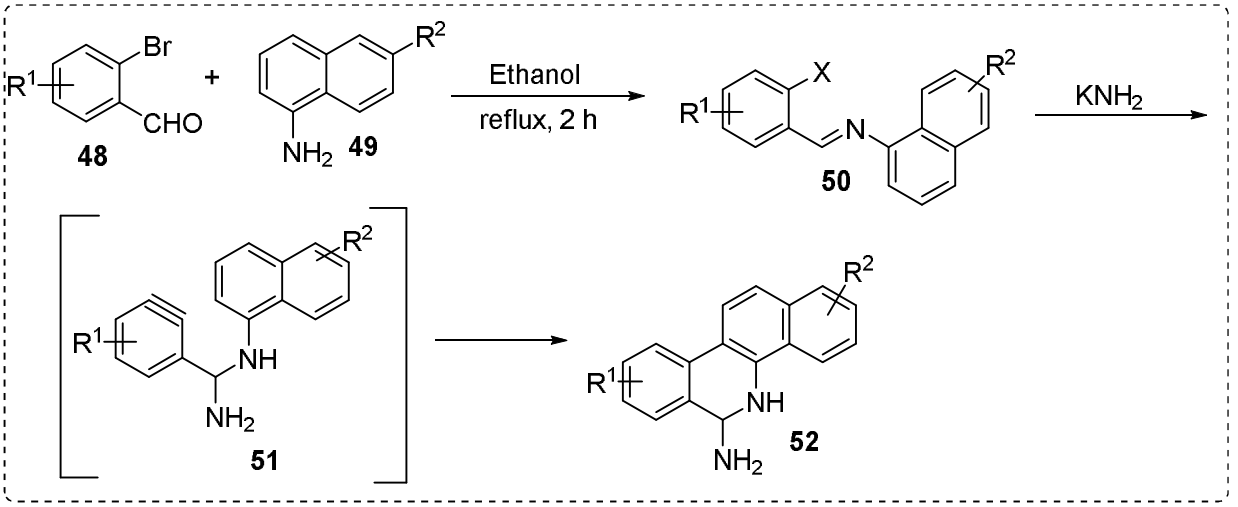


Fig.4. Some examples of biologically active 5,6-dihydro-benzo[*c*]phenanthridine derivatives

2.1.3.1. Synthesis of 5,6-dihydro-benzo[*c*]phenanthridine

2.1.3.1.1. Classical methods for the synthesis of 5,6-dihydro-benzo[*c*]phenanthridine

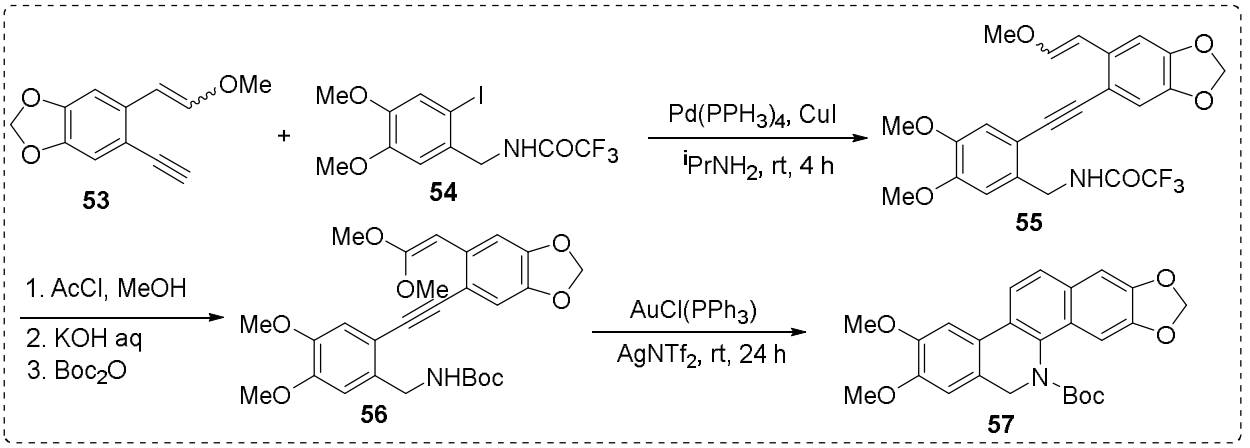
Kessar *et al*[32] described a benzyne-mediated cyclization method for the synthesis of 5,6-dihydro- benzo[*c*]phenanthridine **52** (Scheme-7). The method involves the reaction of equimolar quantities of the halo aldehyde **48** and the amine **49** in ethanol under refluxing condition leading to the formation of N-benzylidene-1-naphthylamine **50** which on treatment with KNH_2 affords the desired product **52** through the formation of benzyne inetermediate **51**.



Scheme 7. Synthetic route towards 5,6-dihydro-benzo[*c*]phenanthridines **52**

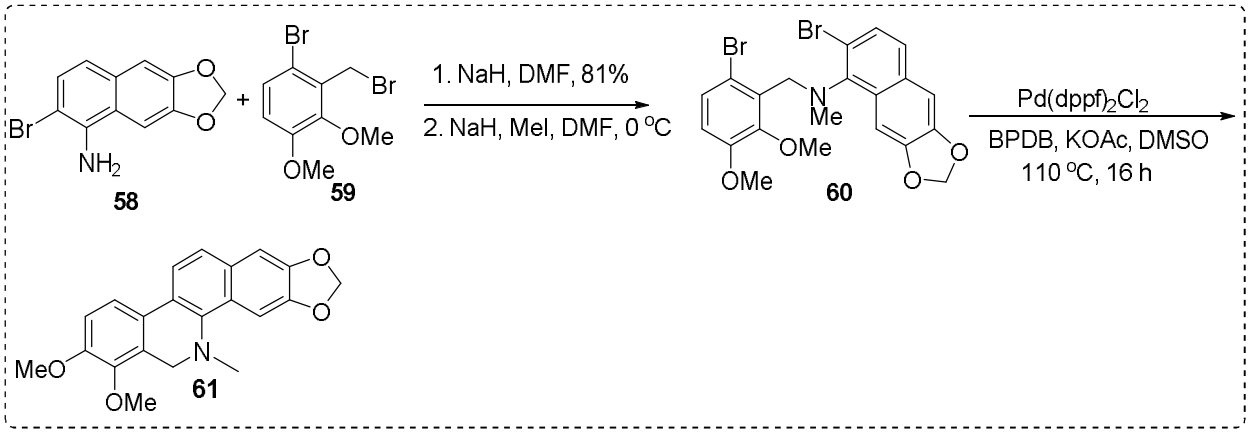
2.1.3.1.2. Metal catalyzed methods for the synthesis of 5,6-dihydro-benzo[*c*]phenanthridine

Takemoto *et al.*[33] reported a gold(I)-catalyzed tandem reactions for the synthesis of 5,6-dihydro- benzo[c]phenanthridine derivative **57** (Scheme-8)**.** Reaction pathway involves Pd-catalyzed Sonogashira reaction of **53** and **54** resulting in the formation of the product **55**. Thereafter, the requisite acetal intermediate **56** was synthesized by the acetalization, hydrolysis, and N-Boc protection of the acetamide. Finally, the compound **56** undergoes tandem cyclization reaction using gold catalyst to afford the desired product **57**.



Scheme 8. Synthesis of 5,6-dihydro- benzo[*c*]phenanthridine derivative **57.**

Hajra *et al.*[30] reported a method for the synthesis of dihydrochelerythrine (DHCHL) **61** as depicted under Scheme 9. Thus, N-benzylation of bromonaphthyl amine **58** with 6-bromo-2,3- dimethoxybenzyl bromide **59** in presence of NaH in DMF, followed by N-methylation gave desired intermediate **60.** Then dibromo-substrate **60** undergoes a Pd-catalyzed cyclization in the presence of bispinacolatodiborane (BPDB) to afford the desired product **61** (Scheme-9).



Scheme 9. Synthetic route for 5,6-dihydro-benzo[*c*]phenanthridine derivative **61**

2.1.4. 6H-Benzo[*c*]chromene

Introduction:

6H-Benzo[*c*]chromene **V**, a well-known privileged structural motif, is widely found in many natural products which showed widespread and diverse biological activities.[34] For example, *Pulchrol* **62** isolated from the plant *Bourreria pulchra* possess interesting antiprotozoal activities towards *Leishmania mexicana* and *Trypanosoma cruzi*.[35] *Cannabinol* **63** (*Cannabis sativa*) displayed potent antibacterial and antimitotic activities; [36,37] while synthetic benzo[c]chromenes such as compound **64** displayed the property of selective progesterone receptor modulators (SPRMs) and G-proteincoupled receptors (GPCRs).[38,39] Besides, another

compound, namely, *AL-438* **65** is known as selective and dissociated glucocorticoid receptor (GR) agonist [40] (Fig 5).

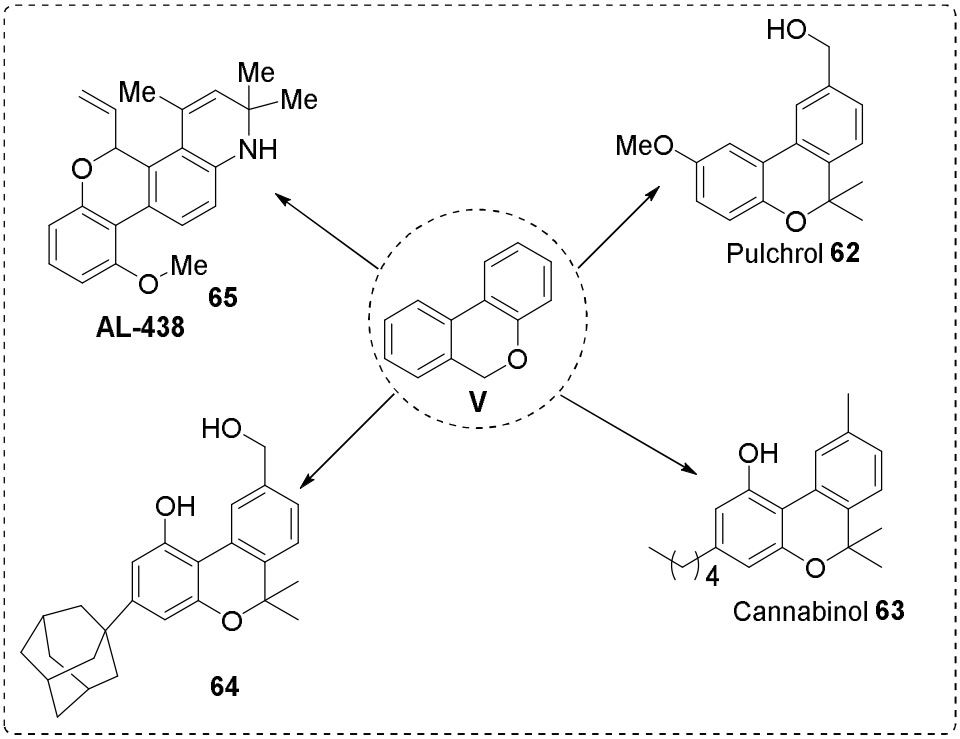


Fig 5. Few biologically active 6H-Benzo[*c*]chromene derivatives

2.1.4.1. Importance of 6H-Dibenzo[*c,h*]chromenes,Vi & Dibenzo[*c,h*]chromen-6-one, Vii:

Importantly, fusion of an additional benzene ring to 6H-Benzo[*c*]chromenes **V** results in the formation of 6H-dibenzo[*c,h*]chromene **VI** which is found as core structure of many natural and synthetic compounds possessing diverse biologically activities (Fig. 6).[41] Furthermore, oxidation of 6H-dibenzo[*c,h*]chromene will lead to the formation of 6H-dibenzo[*c,h*]chromen-6-one, **VII** [42] which constitute the core structures of a broad spectrum of natural products and others compounds possessing bactericidal and other biological effects.[43] For example, *Arnottin I* [44a-h] **66**, isolated in 1977 by Ishikawa and co-workers as a minor constituent from the bark of *Xanthoxylum arnottianum* exhibits anti-bacterial properties; it is also considered to be a potential intermediate in the biosynthetic pathway

for the formation of *Chelerythrine* alkaloid which has shown significant antileukemic properties. Besides, *Defucogilvocarcin V* **67** shows antimicrobial activity against *Staphylococcus aureus, Micrococcus lureus, Bacillus subtilis,* and membrane-permeable *Escherichia coli* (BIA) though it is inactive against wild type *E. coli* and *Candida albicans.*[45a-c] *Fucogilvocarcin M* **68** is well-known as an important member of gilvocarcin-class antibiotics.[45d] The names *Gilvocarcin M* and *Gilvocarcin V* are given based on their structure in which vinyl group and methyl group are borne respectively. In addition, the *Gilvocarcins*[46] (**69a-b**) are metabolites of certain Streptomyces species and constitute a novel class of aryl C-glycoside antibiotics. These compounds share a common tetracyclic aromatic nucleus, 6H-benzo[*d*]-naphtho[*1,2-b*]pyran-6-one, to which rare sugars are attached as a C-glycoside at the C(4) position. Fucose, in furanosyl form, is the sugar of the gilvocarcins, and there are two congeners which differ in the C(8) substituent, i.e., methyl, and vinyl. These are *Gilvocarcin M* (**69a**) and *V* (**69b**), respectively. Among these, the vinyl congener **69b** has attracted considerable attention with its remarkable antitumor activity and exceptionally low toxicity. The presence of the vinyl group is essential to the biological activities and is known to be responsible for enhancement of the biological activity under irradiation with low-energy UV or visible light. On the other hand, *ravidomycin* **69c**[47] is active against Gram-positive bacteria including mycobacteria. It shows only weak activity against Gram-negative organisms and no activity against fungi. Ravidomycin C exhibits potent antitumor activity against P388 lymphocytic leukemia, Colon 38 tumor and CD8F1 mammary tumor. Besides, *Chrysomycins* (**69d-e**)[48] consist of Chrysomycin A (major), and Chrysomycin B (minor) differeing only through the replacement of a vinyl group of Chrysomycin A by methyl in Chrysomycin B and these are well known aryl C-glycoside anti-biotics.[49]

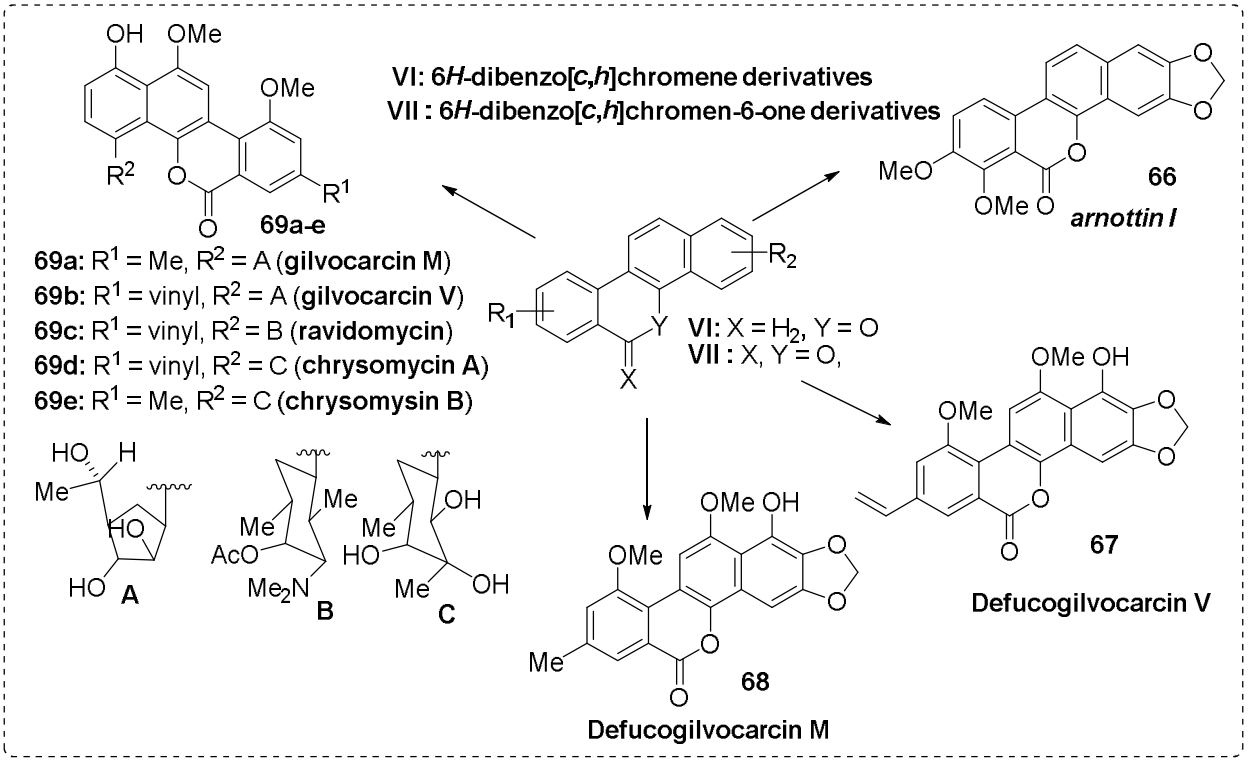
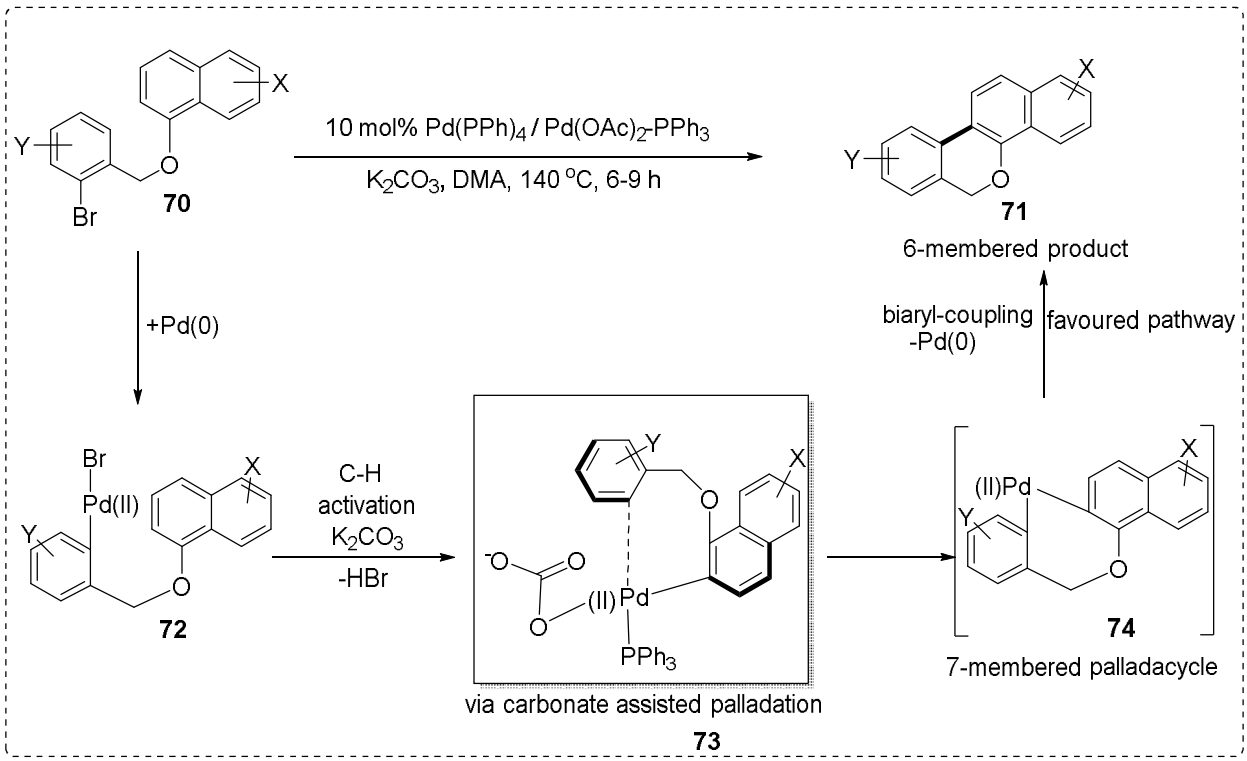


Fig 6. Some examples of biologically active 6H-Dibenzo[*c,h*]chromenes **VI** and Dibenzo[c,h]chromen-6-one **VII** derivatives

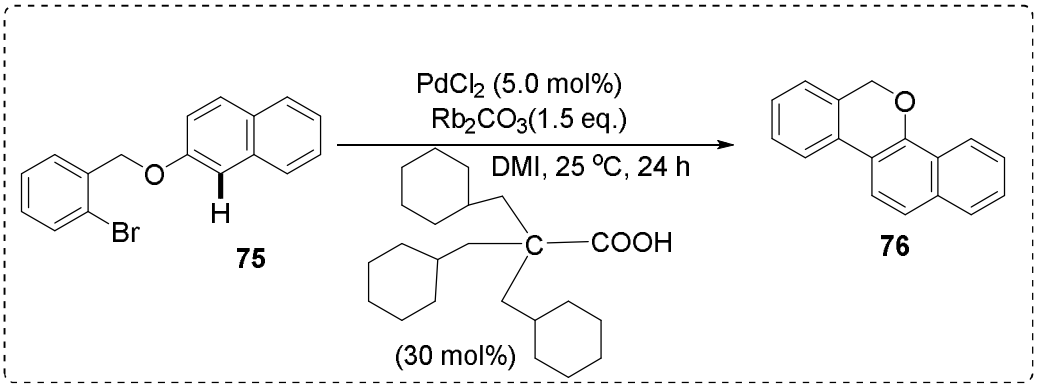
2.1.4.2. Synthesis of 6H-Dibenzo[*c,h*]chromenes VI

Bisai *et al.*[50] reported a method for the synthesis of 6H-dibenzo[*c,h*]chromenes **71** from 2-bromobenzyl-α-naphthyl ethers **70** via a Pd-catalyzed intramolecular direct-arylation using palladium-catalyst [$Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$] at elevated temperature (Scheme 10). A plausible mechanism involves via a carbonate-assisted palladation as outlined in Scheme 10. With the aid of Pd(0)-catalyst, the substrate, i.e., 2-bromobenzyl-a-naphthyl ether **70**, undergoes oxidative addition to provide intermediate **72.**Intermediate **72** then participates in C-H activation at C-2 position to form intermediate **74** (a 7-membered palladacycle) via carbonate-assisted palladation which in turn could afford expected 6H-dibenzo[*c,h*]chromenes **71** upon reductive elimination.



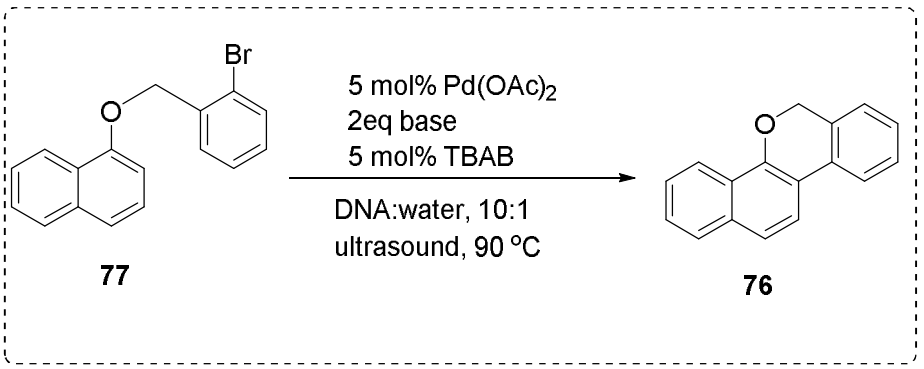
Scheme 10. Synthesis of 6H-dibenzo[*c,h*]chromenes 7**1** with a plausible mechanism.

Tsuji *et al.*[51] reported a method for the synthesis of 6H-dibenzo[*c,h*]chromenes **76** using Pd-catalyzed intramolecular C(sp^2)–H bond arylation reactions of 2-((2-bromobenzyl)oxy)naphthalene **75** (Scheme 11). Tri(cyclohexylmethyl)acetic acid act as an efficient ligand source in this reaction. The reactions proceed smoothly in 1,3-dimethyl-2-imidazolidinone (DMI) as solvent under mild reaction conditions, even at room temperature, taking advantage of the steric bulk of the carboxylate ligands, which accelerates the rate-determining C–H bond activation step in the catalytic cycle. The C(sp^2)–H bond arylation of naphthalene **75** leads to the desired product 6H-dibenzo[*c,h*]chromenes **76.** (Scheme-11).



Scheme 11. Synthesis of 6H-dibenzo[*c,h*]chromenes **76**

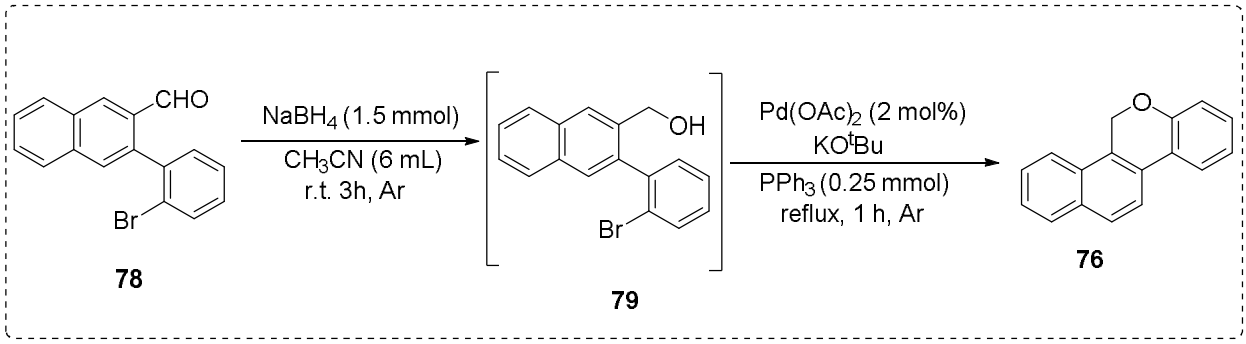
Li *et al.*[52] described a mild and efficient intramolecular direct arylation of aryl bromides in a continuous flow capillary micro-reactor with assistance of ultrasonic irradiation (Scheme 12). Applying this method, they synthesized 6H-dibenzo[*c,h*]chromenes **76** from aryl bromide **77.** The hall-marks of this intramolecular direct arylation process are high selectivity, ligand-free process, broad substrate scope and compatible to functional groups. Furthermore, ultrasound irradiation not only greatly improved the reaction conversion and selectivity, but also solved the clogging problem of micro-reactor for solid-forming reactions and made the reaction to run smoothly.



Scheme 12. Synthesis of 6H-dibenzo[*c,h*]chromenes **76**

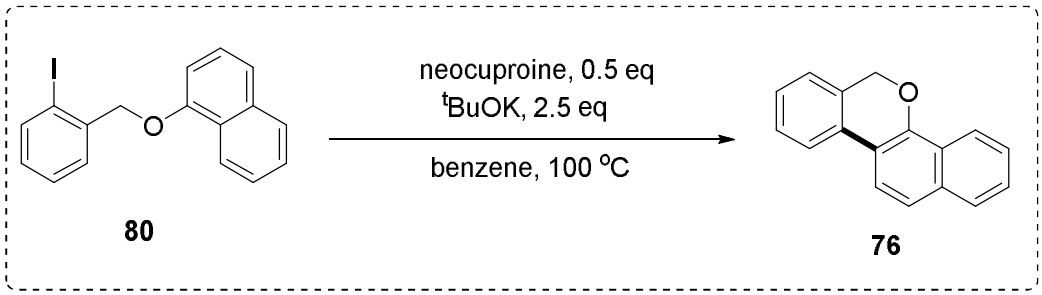
Ray *et al.*[53] reported an efficient one-pot synthetic method for the synthesis of 6H-dibenzo[c,lz]chromenes **76** from 2'-bromo-biaryl-2-carbaldehyde **78** via tandem reduction

followed by palladium-catalyzed and KO^{t}Bu-promoted C_{aryl}–$O_{alcoholic}$ coupling (Scheme 13). However, only three examples of products **76** were reported.



Scheme 13: Synthesis of 6H-dibenzo[*c,h*]chromenes **76**

Shi *et al.*[54] developed an intramolecular radical substitution to construct 6H-dibenzo[c,h]chromene **76** from (2-Iodobenzyl)(1-naphthyl)ether **80** via Neocuproine–KO^{t}Bu promoted intramolecular cross coupling between C-I and C-H bonds. This reaction provides a simple , efficient, transition-metal-free method for the synthesis of fused-heterocyclic structures by avoiding the use of transition metal catalysts.

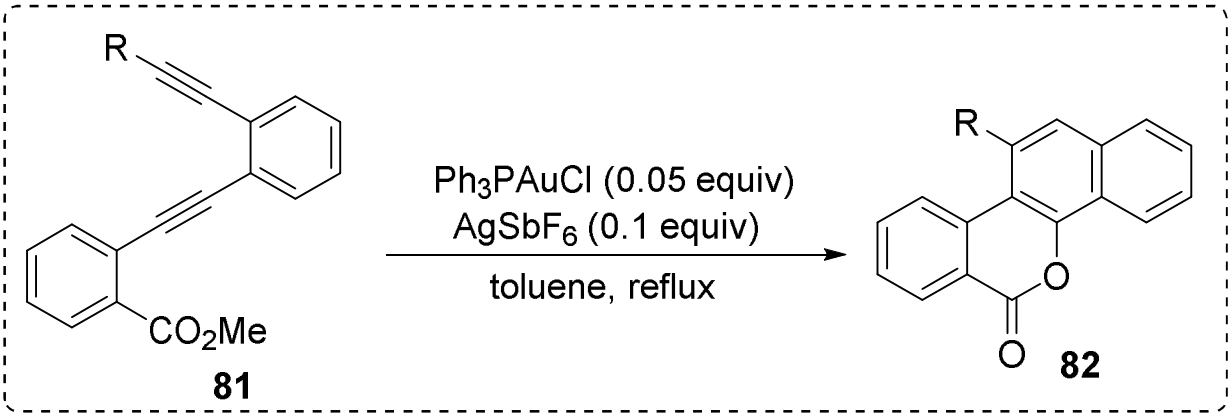


Scheme 14. Synthesis of 6H-dibenzo[*c,h*]chromenes **76**

2.1.4.3. Synthesis of Dibenzo[c,h]chromen-6-one, VI:

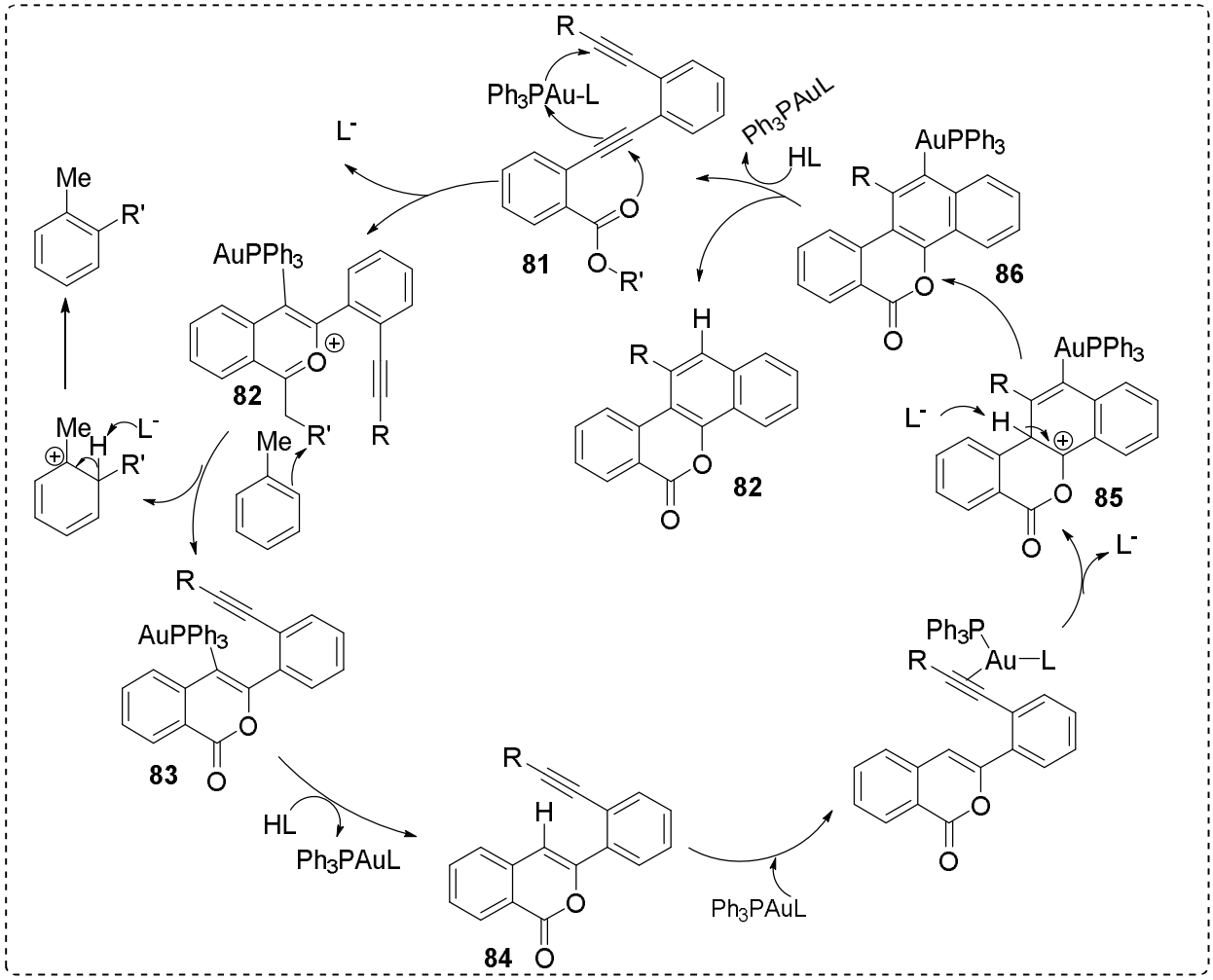
Wu *et al.*[55] reported a method that involves gold-catalyzed cyclizations of enediynes **81** to dibenzo[c,h]chromen-6-one derivatives **82**. Thus treatment of arenediynes **81** with 5 mol %

Ph_3PAuCl and 10 mol % of $AgSbF_6$ in refluxing toluene gave dibenzo[*c*,*h*]chromen-6-ones **82** in good yields (Scheme 15).



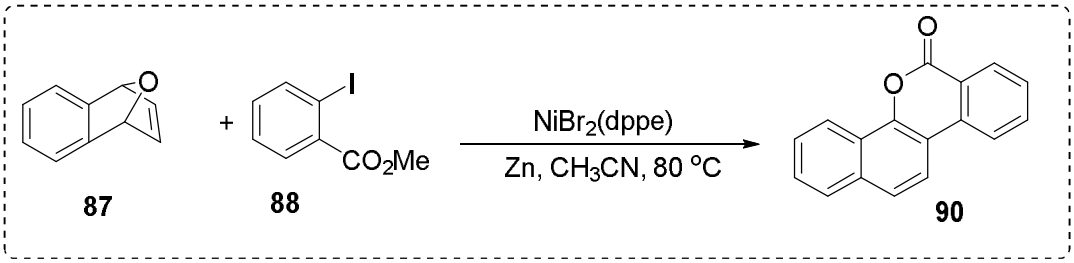
Scheme 15. Synthesis of dibenzo[*c*,*h*]chromen-6-one **82**

The reaction mechanism of this gold-catalyzed cyclization reaction is shown under Scheme 16. First of all, the gold catalyst would coordinate to one of the triple bonds of compound **81** to trigger the formation of cyclized intermediate **82**. The solvent toluene would facilitate the generation of intermediate **83** (via Frieldel-Crafts alkylation reaction) as shown under Scheme 16. Thereafter a proton-gold exchange reaction would convert **83** to **84**. The gold catalyst would then coordinate again with the triple bond of **84** to promote another cyclization reaction to furnish the intermediate **85**. Deprotonation of **85** would provide **86** which would undergo demetallation (via protonation) affording the final product **82**.



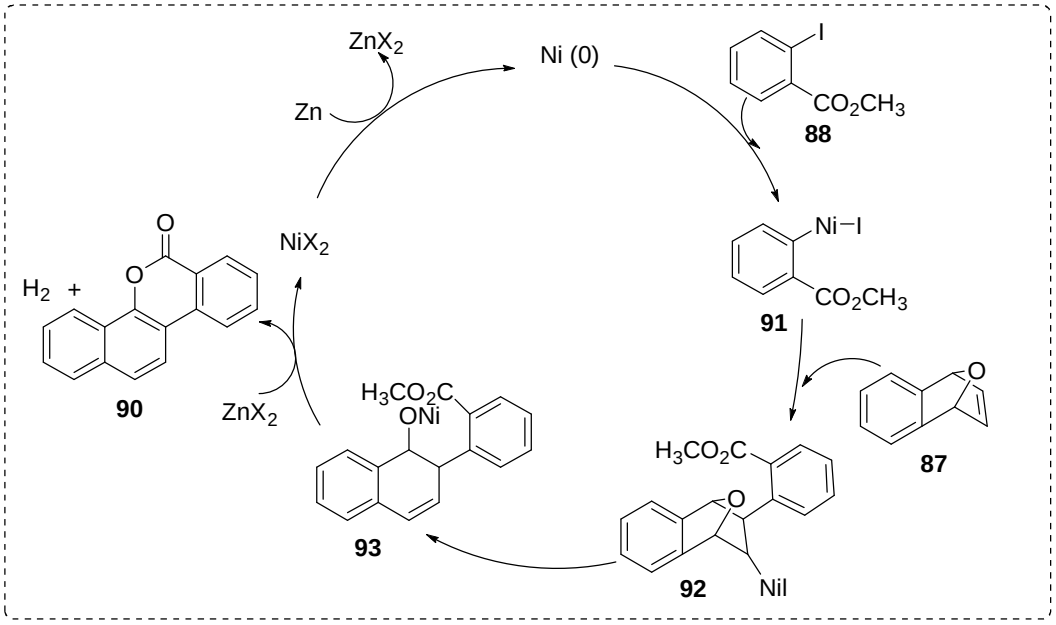
Scheme 16. Plausible reaction mechanism for the formation of product **82**

Cheng *et al.*[56] reported that oxa-bicyclic olefins **87** would undergo cyclization with o-iodobenzoate **88** in presence of Ni(dppe)Br_2 and Zn powder in acetonitrile at 80 °C to give dibenzo[*c*,*h*]chromen-6-one **90** in moderate to good yields (Scheme 17).



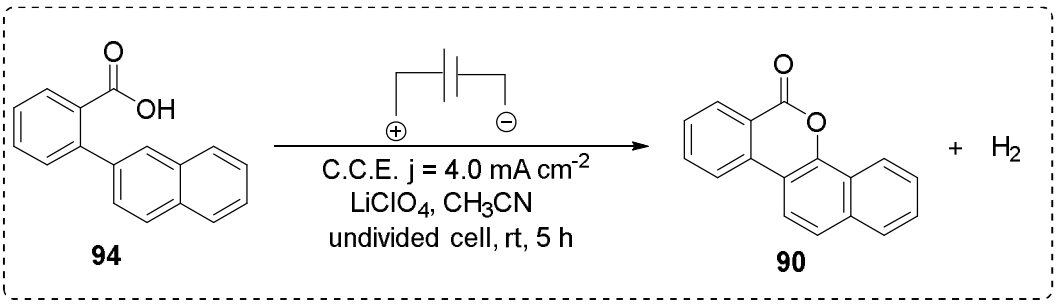
Scheme 17. Synthesis of dibenzo[*c*,*h*]chromen-6-one **90**

Reaction mechanism based on nikel chemistry, reduction of Ni(II) by zinc to Ni(0) likely initiates the catalytic cycle. Oxidative addition of **88** to nickel(0) yields nickel(II) intermediate **91**. Coordination of 7-oxabenzonorbornadine **87** and subsequent insertion leads to the formation of **92**. Then, β-oxyelimination of **92** occurs to give nickel alkoxide **93**, which undergoes transmetalation with ZnX_2, followed by lactonization and dehydrogenation to give the final product **90** and Ni(II) species. The latter is reduced by Zn to regenerate the Ni(0) catalyst for the catalytic cycle (Scheme 18).



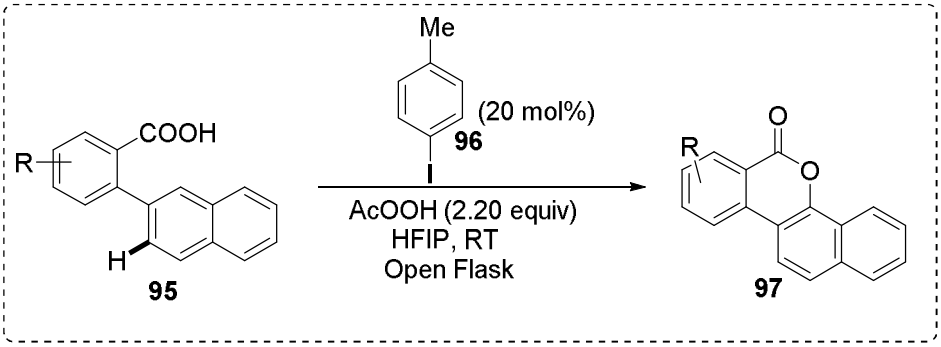
Scheme 18. Plausible reaction mechanism for the Synthesis of dibenzo[*c,h*]chromen-6-one **90**

Xu *et al.*[57] described an efficient and robust methodology based on electrochemical techniques for the direct synthesis of aromatic lactones via dehydrogenative C–O cyclization. This electrochemical reaction can tolerate a variety of functional groups, and is scalable upto 100 grams under mild conditions. Thus, C– O cyclization of 2-napthyl benzoic acid **94** using electrochemical reaction leads to the desired product **90** (Scheme 19).



Scheme 19. Synthesis of Dibenzo[*c,h*]chromen-6-one **90**

Martin *et al.*[58] developed a C(sp^2)-H functionalization/C-O bond-forming process catalyzed by I^{III} reagents generated in situ. Thus substrate **95** upon treatment with *p*-iodo-toluene **96** (20 mol %) in the presence of HFIP and AcOOH as oxidant underwent cyclization to produce the product **97** in good yield (Scheme 20).



Scheme 20. Synthesis of dibenzo[*c,h*]chromen-6-one **97**

2.1.5. Conclusion

From the literature survey, it concluded that benzo[*c*]phenanthridines, 5,6-dihydrobenzo[*c*]phenanthridines , 6H-Dibenzo[*c,h*]chromenes and dibenzo[*c,h*]chromen-6-ones have a considerable attention over the years in drug discovery and medicinal chemistry. However, despite its importance there is a single method for the general synthesis of the 6H-Dibenzo[*c,h*]chromenes and most of the procedure for synthesis of others compounds are multistep and require long reaction times. Thus development of a convenient method using readily available and cheap substrates remains challenge. Detailed finding towards the all compounds discussed in part II of this chapter.

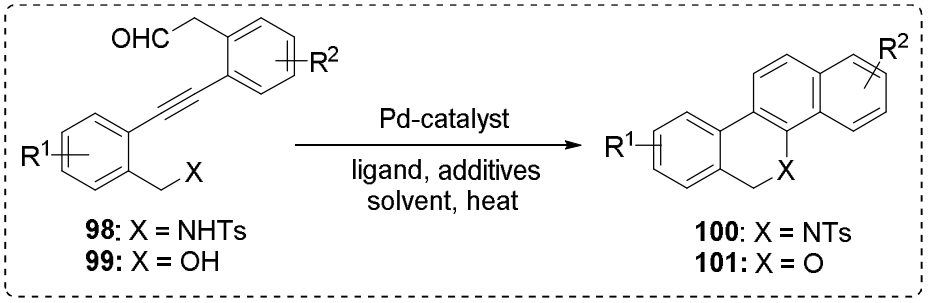
Part II

(Result & Discussion)

2.2.1. Introduction

In view of the immense importance of 5,6-dihydro-benzo[*c*]phenanthridines **IV** and 6H dibenzo[*c,h*]chromenes **VI** being the core structure of many natural product and medicinally active compounds, the development of facile method for these heterocyclic core structures appears to be an important objective. Scrutiny of the literature reveals that there is no the general method for the synthesis of **IV** to date though few specific examples (discussed previously Schemes 7-9) were reported during the synthesis of other heterocycles; whereas a single method (discussed previously Scheme 10) for a general synthesis of **VI** is known to date along with few other reports (discussed previously Schemes 11-14) of specific derivatives (of **VI**) during the course of related heterocycles. This clearly pointed out to the urgency of establishing a general and straight forward method for the synthesis of **IV** & **VI** starting from simple and easily accessible materials.

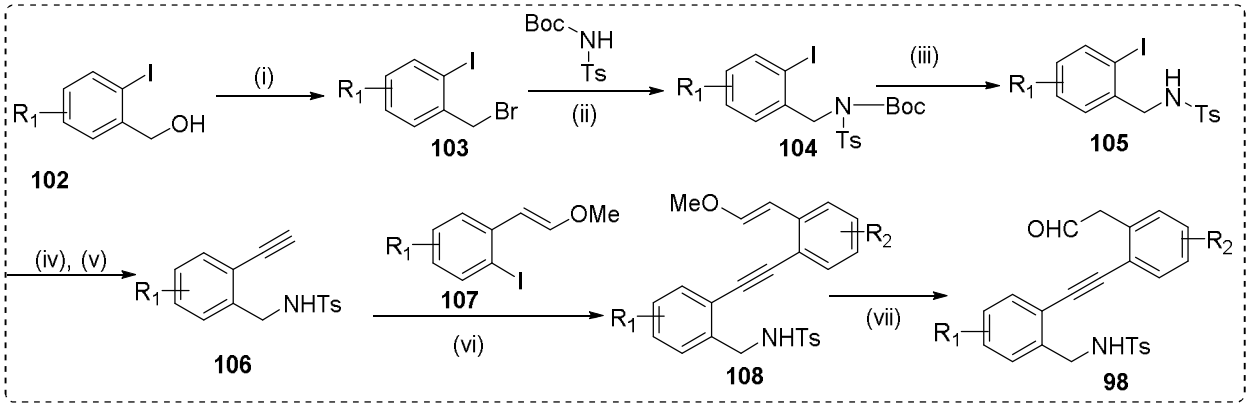
In recent times, domino reactions have emerged as efficient tools for the construction of complex molecules from the viewpoints of operational simplicity, atom economy and assemble efficiency.[59] In particular, reactions[60] involving 1,2-addition of a vinyl palladium species onto a carbon-heteroatom 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,[60a] Lu[60b] and Wang.[60c] In continuation of our work on palladium catalyzed reactions,[61] we therefore anticipated that a general synthesis of 5-tosyl-5,6-dihydrobenzo[*c*]phenanthridine **100** and 6H-dibenzo[*c,h*]chromene **101** (Scheme 21) 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.



Scheme 21. A general synthesis of 5,6-dihydro-benzo[*c*]phenanthridines **100** and 6*H*-dibenzo[*c,h*]chromenes **101**

2.2.2. Preparation of Starting Material 98

The requisite starting material **98** was prepared through a sequence of reactions starting from 2-iodobenzyl alcohol**.** First, bromination of 2-iodobenzyl alcohol **102** was carried out with phosphorus tribromide and pyridine in dry DCM as solvent at 0 ^{o}C to produce 2-iodobenzyl bromide **103**. The latter was then treated with *tert*-butyl tosylcarbamate (Ts-NH-Boc) in presence of potassium carbonate in acetonitrile under refluxing condition resulting in the formation of tosylated derivative **104**. In next step, boc-protected intermediate **104** was treated with trifluoroacetic acid in DCM at 0 ^{o}C to obtain boc-deprotected product **105**[62] reported previously. Coupling of this *N*-(2-iodobenzyl)-4-methylbenzenesulfonamide **105** with TMS-acetylene under "*Sonogashira reaction*'' conditions gave the silylated acetylene intermediate which is desilylated with potassium carbonate leading to the formation of acetylene substrate **106.**[63] Then, 1-Iodo-2-(2-methoxyvinyl)benzene[64] **107** prepared through the reported procedure was coupled with acetylenic compound **106** using "*Sonogashira reaction*" resulting in the formation of the intermediate **108**. Next, the masked aldehyde **108** was deprotected under acidic conditions to prepare desired starting compound **98**.



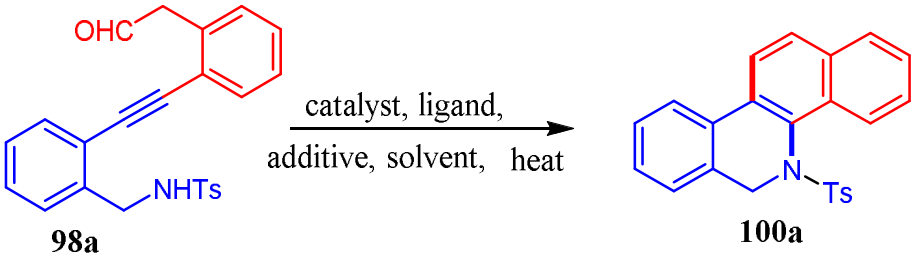
Scheme 22: Reaction Conditions: (i) PBr_3, pyridine, DCM, 0 ^oC, 0.5-1 h; (ii) K_2CO_3, CH_3CN, reflux, 2-6 h, 70-85%; (iii) TFA, DCM, 0 ^oC-rt, 2-3 h, 75-90%; (iv) TMS-acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N:DMF (3:1, v/v), rt, 75-85%; (v) K_2CO_3, MeOH, 0.5-1.5 h, 56-72%;**(vi)** $PdCl_2(PPh_3)_2$, CuI, Et_3N-DMF (3:1), rt, 60-70%; (vii) *p*-TsOH, acetone, 0 ^oC to rt, 49-95%.

2.2.3. Synthesis of N-tosyl5,6-dihydrobenzo[*c*]phenanthridine 100:

2.2.3.1. Optimization of the reaction conditions for the model synthesis of 100a

We commenced the investigation with a model study on substrate **98a (R_1 = R_2 = H)** (Scheme 22); selected results are presented in Table 1. First, we planned the substrate treated with ligated catalyst $Pd(OAc)_2$bpy in 1,4-dioxane at 100 ^oC furnished the desired product **100a** with only 53% yield (Table 1, entry 1). Even the use of catalyst and ligand separately instead of preformed $Pd(OAc)_2$ bpy was not helpful (Table 1, 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 1, entry 3). Use of the preformed catalyst $Pd(OAc)_2$bpy improved it further (Table 1, entry 4). But the reaction carried out in NMA required (Table 1, entries 5–6) longer time (2.5–3 h) and resulted in lower yields (38–41%), arguing against the use of polar solvent systems. Thus, the reaction conditions of entry 4 proved optimum.

Table 1. Optimization of the reaction conditions for *N*-tosyl 5,6-dihydrobenzo[c] phenanthridine **100a**[a,b]



98a **100a**

Entry	Catalyst	Ligand	Solvent	Temp (°C)	Time (h)	Yield (%)[c]
1	$Pd(OAc)_2bpy$	-	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	**$Pd(OAc)_2bpy$**	-	**THF**	Reflux	**1.3**	**78**
5	$Pd(OAc)_2bpy$	-	NMA	100	2.5	41
6	$Pd(OAc)_2phen$	-	NMA	100	3	38

[a] In all entries, D-CSA was used as an additive.

[b] Reaction conditions: A mixture of **98a** (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.

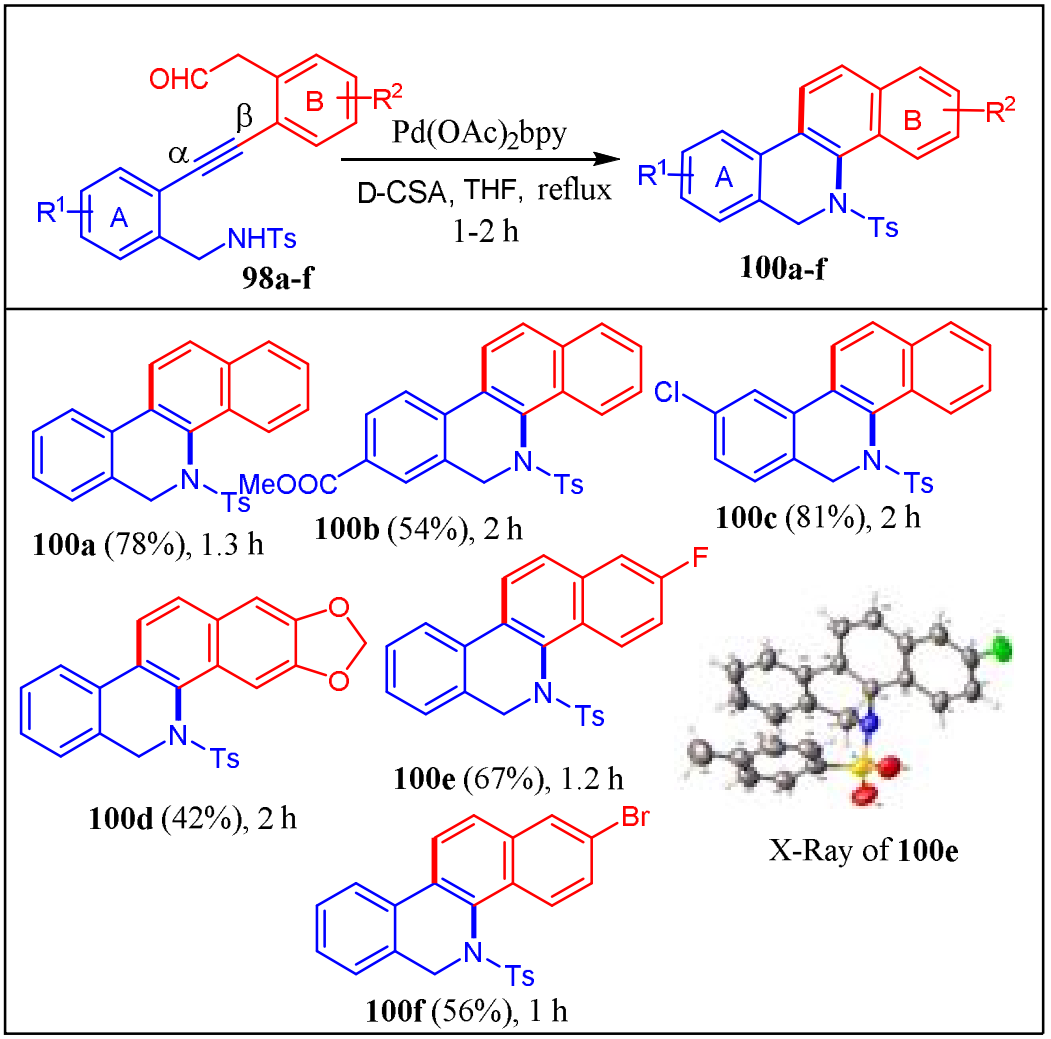
[c] Yield of the isolated pure products.

2.2.3.2. Scope of the reaction for the Synthesis of N-tosyl-5,6-dihydrobenzo[*c*]phenanthridine 100:

To establish the generality of the synthesis of **100**, we applied the optimized reaction conditions on substrates **98** having various substitutions (Scheme 23). Initially, we used a strong electron-withdrawing group (viz., $R^1 = CO_2Me$) in ring A *para* to the alkyne moiety of

substrate **98b**; indeed, it furnished the desired product **100b** in 2 h with 54% yield, while a moderately electron-withdrawing group (i. e., R^1 = Cl) at meta position afforded the desired product **100c** 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 **98b**) failed despite our sincere efforts.

Scheme 23. Palladium-catalyzed synthesis of N-tosyl-5,6-dihydrobenzo[*c*]phenanthridines **100**[a,b]



[a]Reaction conditions: **98** (0.2 mmol), $Pd(OAc)_2$bpy (5 mol %) and D-CSA (1.5 equiv) in refluxing THF (2 mL) under argon atmosphere.

[b]Yield of the isolated pure product.

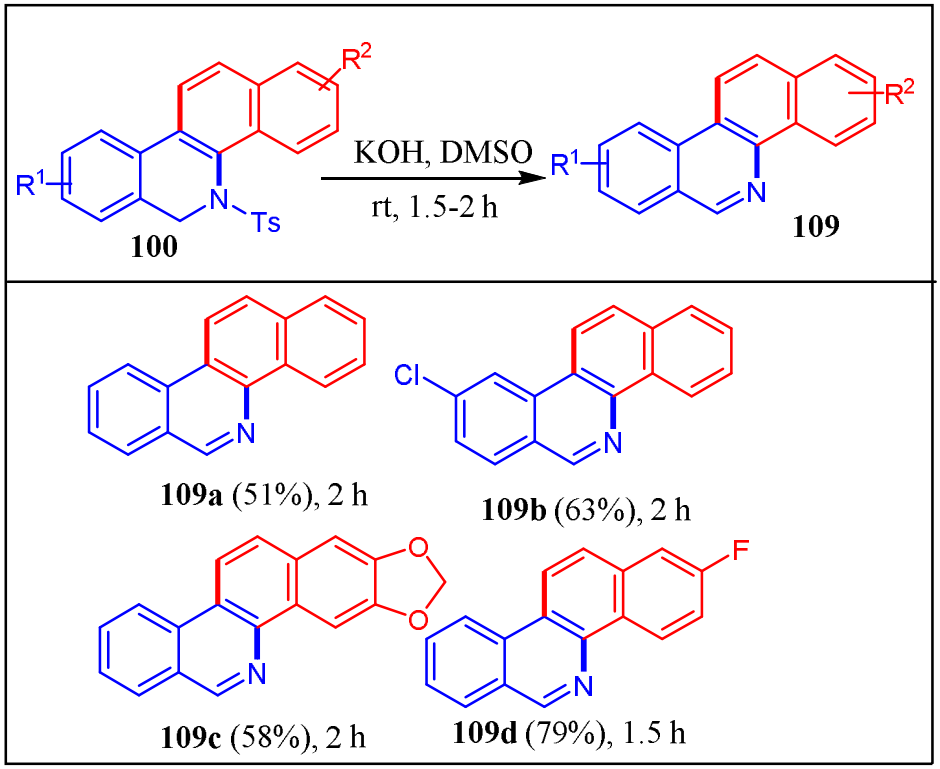
Regarding the effect of ring B substituents, an electron-donating methylenedioxy group as in substrate **98d** resulted in product **100d** within 2 h albeit in moderate yield (42%). While the electron-withdrawing fluoro group at para position (**98e**) afforded the product **100e** in 1.2 h with a good yield (67%), the less electron-withdrawing bromo group (in **98f**) lowered the reaction time (1 h) but also the yield (56%) simultaneously.

Additionally, in order to check the role of N-protecting group in substrate **98**, 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 1); 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.

2.2.3.3. Application of the methodology for the synthesis of benzo[*c*]phenanthridines 109:

Though some traditional and palladium-catalyzed methods[65] (few are discussed previously Scheme 1-6 in part-I) for the synthesis of benzo[*c*]phenanthridines **109** exist in the literature, we felt that synthesis could easily be attained from **100** 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 $–OCH_2O-$).

Scheme 24. Base promoted synthesis benzo[*c*]phenanthridines 109.[a,b]

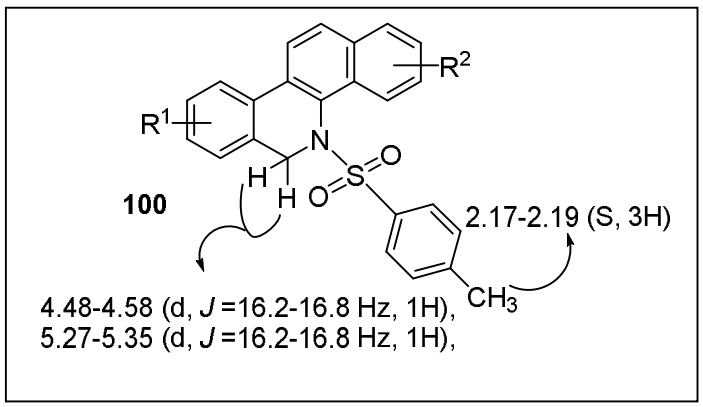


[a]Reaction condition: A mixture of **100** (0.13 mmol) and KOH (5 equiv) in DMSO was stirred at room temperature under argon atmosphere.

[b]Yield of the isolated product

2.2.4. Nature and Characterization of Products 100:

All the synthesized products are moderately stable at room temperature and can be stored at



room temperature (4 ^{o}C) for the several months. The structure of the products were unambiguously deduced by spectral (^{1}H and ^{13}C NMR, Mass and IR Spectra) and analytical data. In mass spectra (ESI and EI), the molecular ion peak in positive mode of all the compounds appeared as M^{+} or

protonated [M + H]$^+$ and /or sodiated [M + Na]$^+$ ion. In ^{1}H NMR, the protons for the methyl group of tosyl moiety appears in the range 2.17-2.19 ppm as singlet as expected, whereas aromatic protons appear in the range 6.64-8.72 ppm. Two methylene, protons appear as a doublet separately, one of them appears in the range 4.48-4.58 ppm, J = 16.2-16.8 Hz, while other one is found in the range 5.27-5.35 ppm, J = 16.2-16.8 Hz. Thus, the spectral data (^{1}H,^{13}C, Mass Spectra, IR Spectra) provided the support in favour of the structure **100** (Scheme-23).

Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of the compound **100e**. The single crystal was obtained by slow evaporation (at room temperature) of a solution of petroleum ether and dichloromethane. The ORTEP diagrams of the crystal structures are shown in Figures 7.

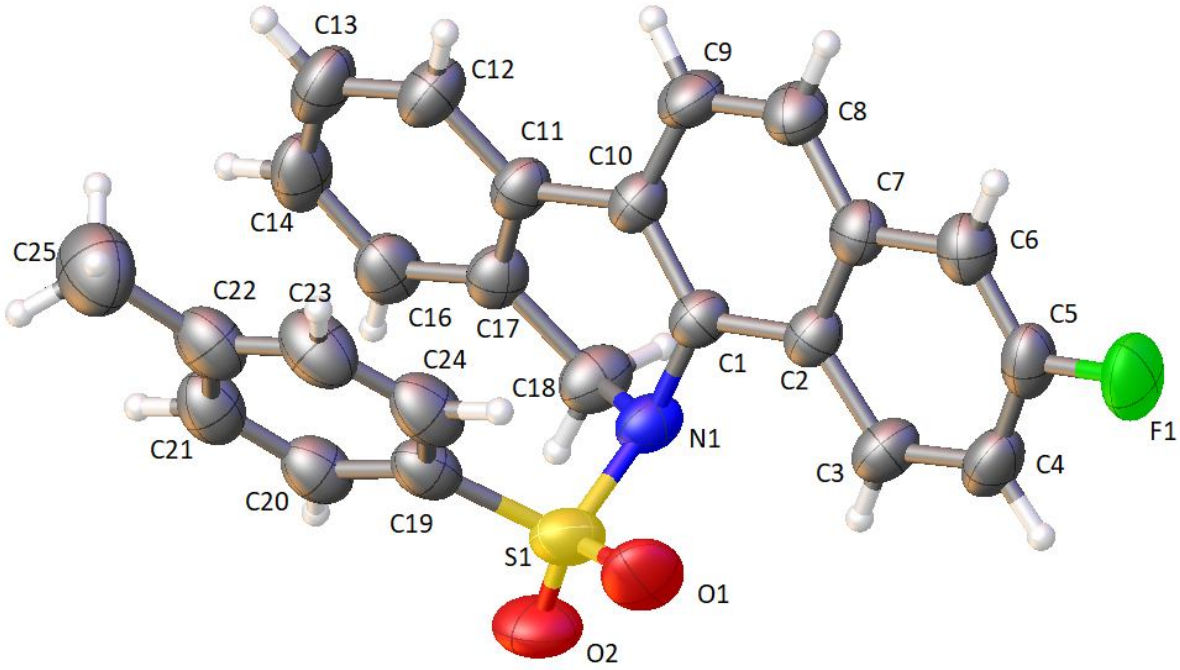


Figure 7. Ortep Diagram (drawn at 50% probability level) of compound **100e**.

Table 2: Important crystal data of product **100e**

Empirical formula	$C_{24}H_{18}FNO_2S$
Formula weight	403.45
Temperature	296 K
Wavelength	0.71073
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	a = 12.892(2)Å α = 62.537°(4)
	b = 13.215(2)Å β = 72.842 °(4)
	c = 13.439(3)Å γ = 78.228°(4)
Volume	1935.0(6)$Å^3$
Z	4
Density (calculated)	1.385 g/cm^3
Absorption coefficient (Mu)	0.197 mm^{-1}
F(000)	840.0
Theta range for data collection	2.307 to 27.548
Index ranges	-16<=h<=16, -17<=k<=17, -17<=l<=17
Reflection collected	5927
Independent reflections	8824 [R(int) = 0.0425]
Completeness to theta = 25.44°	98.8 %
Absorption correction	multi-scan
Max.and min. transmission	0.992 and 0.940
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8824 /0/525
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0440, wR2 = 0.1121
R indices (all data)	R1 = 0.0719, wR2 = 0.1121
Largest diff. peak and hole	0.220 &-0.339 $e.A^{-3}$

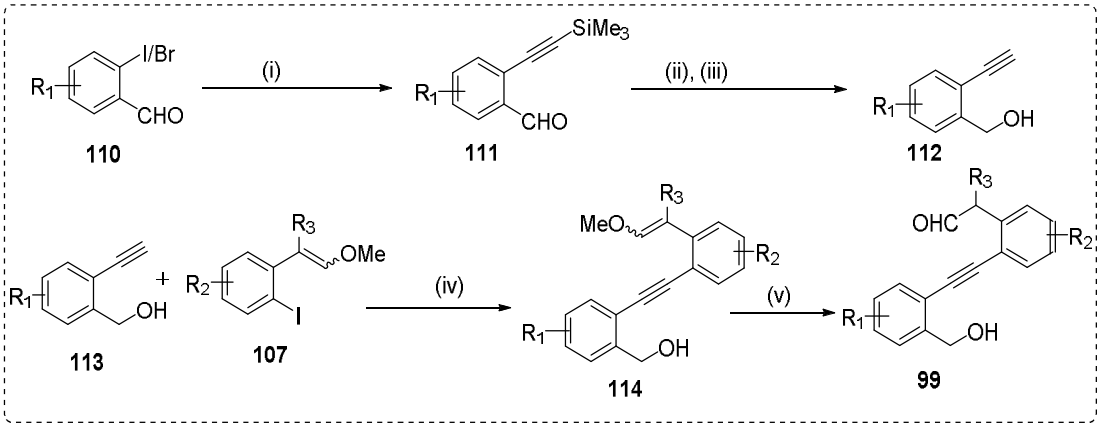
Single crystal of compound **100e** suitable for X-ray crystallographic determination was obtained by Recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **100e** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **1901867**.

2.2.5. Extension of the methodology for the synthesis of 6*H*-dibenzo[*c*,*h*]chromenes 101

Encouraged by the above results, we decided to check the viability of the methodology using alkyne substrate tethered with aldehyde **99** where necleophile is oxygen instead of nitrogen.

2.2.6. Synthesis of Starting material 99

The requisite starting materials **99** was prepared through a sequence of reactions starting from 2-iodo/bromo benzaldehyde. In the first step the (ortho-ethylphenyl)methanol derivatives **112** were prepared in two step starting from 2-iodo/bromo benzaldehyde derivatives **110** using known methods.[66] Coupling of this 2-iodo/bromobenzaldehyde **110** with TMS-acetylene under "*Sonogashira reaction*" conditions gave the silylated acetylene **111** which was reduced with sodium borohydride. The resulting silylated alcohol thus produced is desilylated with potassium carbonate in the same pot (without work up) leading to the desired product (ortho-ethynylphenyl)methanol derivatives **112**[66] reported previously. Then, 1-Iodo-2-(2-methoxyvinyl)benzene[64] **107** prepared through the reported procedure was coupled with acetylenic compound **113** using "*Sonogashira reaction*" resulting in the formation of the intermediate **114**. Next, the masked aldehyde **114** was deprotected under acidic conditions to prepare desired starting compound **99** (Scheme 25).



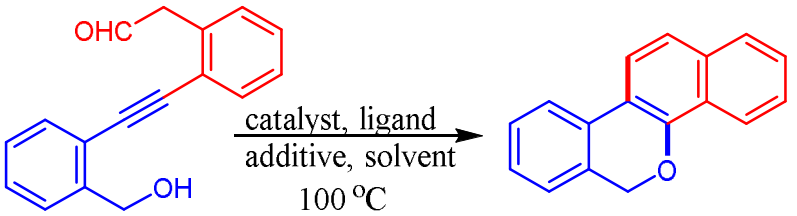
Scheme 25. Reagents and conditions: (i) TMS-acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, rt, 1-3 h, 56-90%; (ii) $NaBH_4$, MeOH, 0.5 h, 0 ^oC-rt; (iii) K_2CO_3, MeOH, rt, 0.5 h, 42-67%;(iv) $PdCl_2(PPh_3)_2$, CuI, dry Et_3N, rt, 1-5 h, 70-85%; (v) *p*-TsOH, dry acetone 0 ^oC-rt, 3-4 h, 42-61%.

2.2.7. Synthesis of 6H-dibenzo[*c,h*]chromenes 101:

2.2.7.1. Optimization of the reaction conditions for the model synthesis of 101a

We commenced the investigation with a model study on substrate **99a** (R_1 = R_2 = H) (Scheme 25); selected results are presented in Table 3. First, we planned the substrate treated with $Pd(OAc)_2$ as a catalyst and bpy as a ligand in NMA at 100 °C furnished the desired product **101a** with only 42% yield (Table 3, 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 3, entry 2).

Table 3. Optimization of the reaction conditions for 6Hdibenzo[*c,h*]chromene **101a.** [a]



99a **101a**

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: **99a** (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.

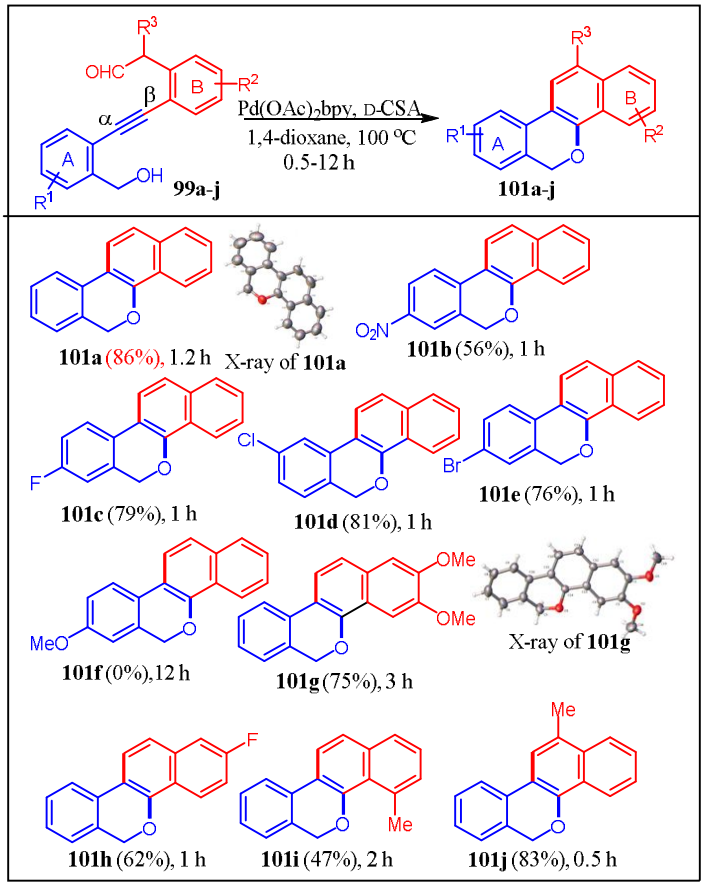
[c] Starting material was recovered. Abbreviations: n.r.: no reaction, bpy: bipyridine, phen: phenanthroline.

Though removal of the additive or changing the ligand to phenanthroline did not help (Table 3, 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 3, entry 5). Replacing D-CSA by p-TsOH or decreasing the polarity of the solvent further had detrimental effect on the yield (Table 3, entries 6–8). Thus the reaction conditions of entry 5 of Table 3 appeared best.

2.2.7.2. Scope of the reaction for the Synthesis of 6H-dibenzo[*c,h*]chromene 101

To establish the generality of this methodology, the optimized reaction condition was then applied to a range of substrates (Scheme 26). Various substituents (e.g. NO_2, OMe, Me, F, Cl, Br etc.) in the aryl moiety of substrate **99** were well tolerated. But a strongly electron-

Scheme 26. **Palladium-catalyzed synthesis of 6H-dibenzo[*c,h*] chromenes 101** [a,b]



[a]Reaction conditions: **99**(0.2 mmol), $Pd(OAc)_2$bpy (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.

withdrawing group ($R^1 = NO_2$) in ring A para to the alkyne moiety lowered the yield of the product (**101b**, 56%) considerably, while moderately active ones (R^1 = F/Cl/Br) either at para or meta position had little impact (**101c**/**101d**/**101e**). Of particular note, employment of an electro-donating group (viz., R^1 = OMe) at para position in the same ring (**99f**) yielded no product, leaving the starting material intact (TLC). The inertness of these substrates (**99g**/**99f**) 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 methyl group [see, species A (Y = O) under Scheme 33, vide infra]. In contrast, when the methoxy groups are placed at meta and para positions in ring B of the substrate (**99g**), the expected product **101g** 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.

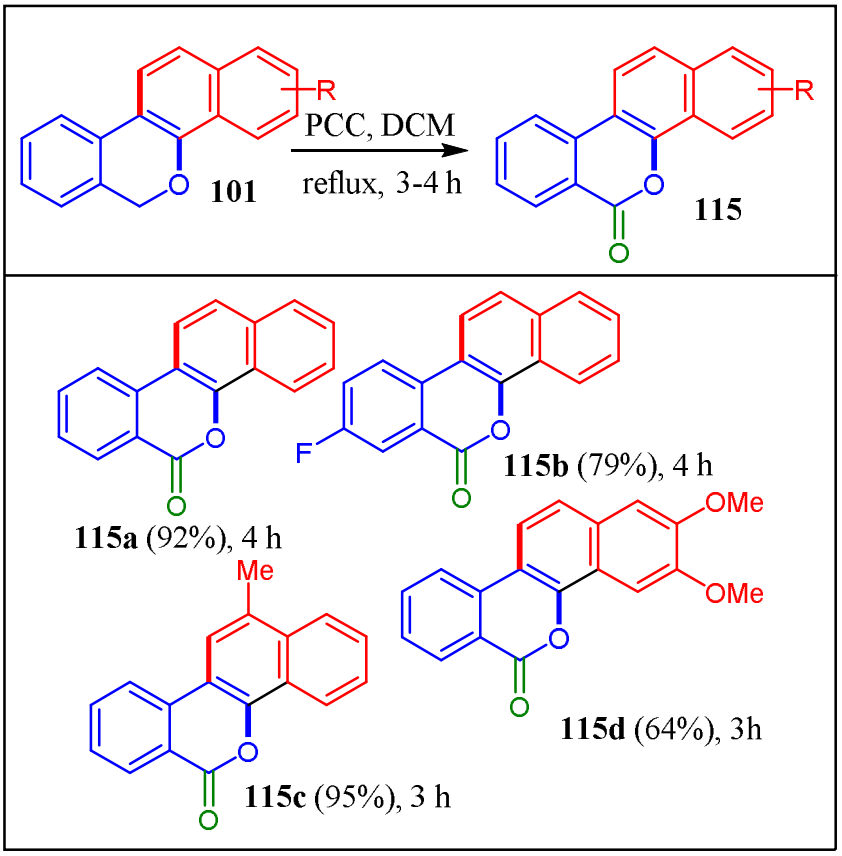
As anticipated, employing an electron-withdrawing substituent (viz., R^2 = F) at para position (substrate **99h**) indeed produced the product **101h**, though in reduced yield (62%) as compared to **101c.** On the other hand, the use of an electron donating methyl group at meta position (**99i**) led to the product **101i** with a moderate yield (47%). Even the substrate **99j** with an alpha substituted aldehyde group reacted equally well, showing no influence of the steric effect at this site.

2.2.8. Application of the Methodology: Synthesis of dibenzo[*c,h*]chromen-6-ones 115

After achieving a general synthesis of 6H-dibenzo[*c,h*] chromenes **101**, we became interested to test the applicability of this reaction through synthetic transformation of the products prepared. Initially we attempted benzylic oxidation of products **101** which could provide easy access to dibenzo[*c,h*]chromen-6-ones **115**. Of the various oxidizing agents tested, PCC appeared to be the best, furnishing the desired products **115a–d** within few hours with very

good to excellent yields (79–95%, Scheme 27). Thus synthesis of dibenzo[*c*,*h*]chromen-6-ones **115** could easily be achieved in two steps starting from acetylenic substrate **99** and overall yields were found to be between 48–81%.

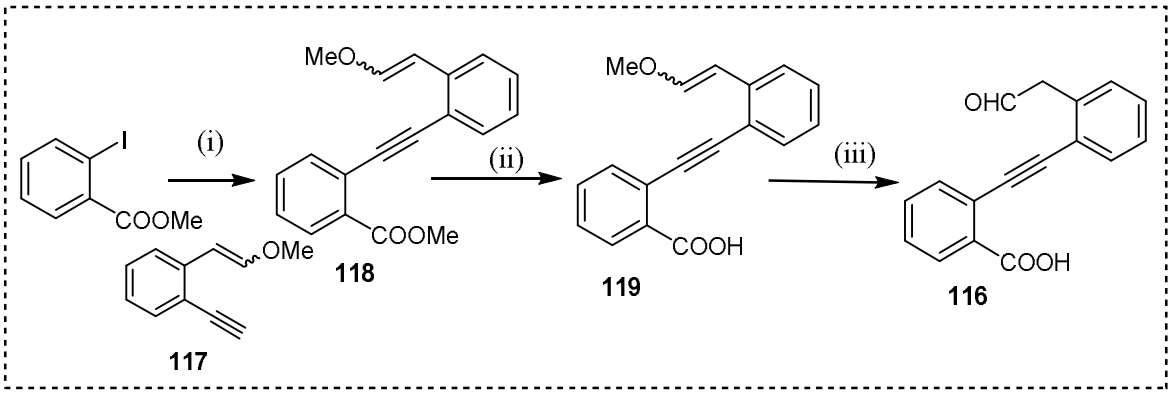
Scheme 27. Conversion of products 101 to 6H-dibenzo[*c*,*h*]chromen-6-ones 115. [a,b]



[a]Reaction conditions: A mixture of **101** (0.086 mmol) and PCC (1.5 equiv) in DCM (2 mL) was refluxed under argon atmosphere.
[b]Yield of the isolated pure product.

In view of the prospect of synthesizing the products **115** directly, we carried out a reaction on substrate **116** having ortho-carboxylic acid group in place of benzylic alcohol (of **99a**)(See, Scheme 28) under our optimized reaction conditions (entry 5 of Table 3); to our surprise, the desired product **115a** was still found to be formed within 2 h but only in moderate yield (42%) (See, Scheme 29)

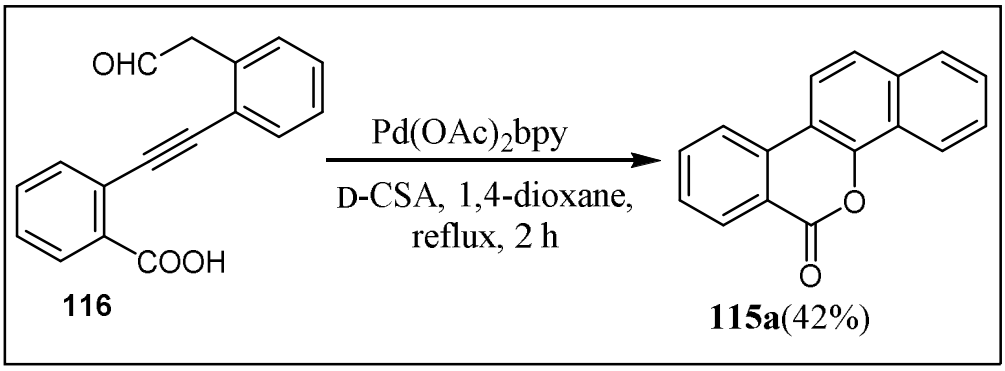
2.2.8.1. Schematic representation and procedure for the synthesis of substrate 116



Scheme 28. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, CuI, dry Et_3N, rt, 2 h, 74%; (ii) Saturated NaOH solution,MeOH, 1 h, 72%; (iii) *p*-TsOH, dry acetone 0 ^oC-rt, 4 h, 58%.

1-ethynyl-2-(2-methoxyvinyl)benzene[67] **117** prepared through the reported procedure was coupled with methyl-2-iodobenzoate[68] using "*Sonogashira reaction*" resulting in the formation of the intermediate **118**. Then, base hydrolysis of ester substrate using sodium hydroxide leds to the formation of acid products **119.** Finally, the masked aldehyde **119** was deprotected under acidic conditions to prepare desired starting compound **116** (Scheme 28).

2.2.8.2. One-pot Synthesis of 115a using 2-((2-(2-oxoethyl)phenyl)ethynyl)benzoic acid (116) as substrate:



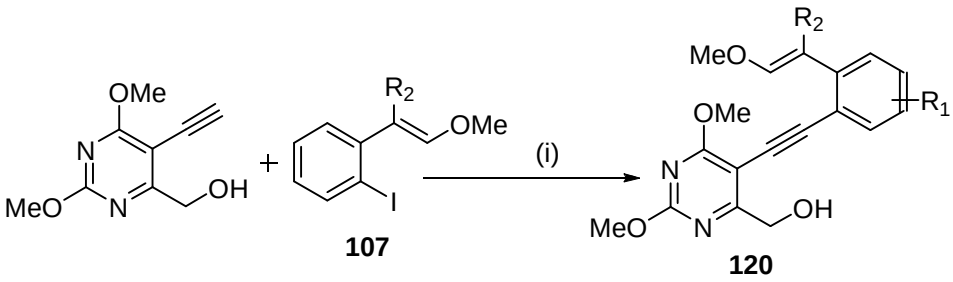
Scheme 29: One-pot Synthesis of 6*H*-dibenzo[*c,h*]chromen-6-one **115a** using 2-((2-(2-oxoethyl)phenyl)ethynyl)benzoic acid (**116**) as substrate.

2.2.9. Application of the Methodology: Synthesis of Pyrimidine (122) and Uracil (123) Derivatives

In view of the immense biological activity of uracil derivatives in cancer chemotherapy[69a–d] and our own interest in this field,[69e] we decided to apply the methodology for the synthesis of such molecules. The requisite starting material **121**, synthesized from precursor masked aldehyde **120a** (R_1= R_2 = H) (for synthesis see Scheme 30) by treating with p-TsOH, was exposed to conditions A as shown in Scheme 31; to our disappointment, the desired product **122a** (R = H) was obtained only in 20% yield. Gratifyingly, the masked aldehyde **120a**, used under conditions B (where NMA is used instead of 1,4-dioxane), responded better and furnished the desired product **122a** with 56% yield. Substrates **120b** and **120c** containing electron withdrawing (R = F) and donating (R = OMe) group, respectively, also proved to be effective, affording the expected products (**122b** and **122c**) with 50–65% yield (Scheme 31).

2.2.9.1. Synthesis of 2,4-dimethoxy-12H-benzo[7,8]chromeno[3,4-d]pyrimidines 122

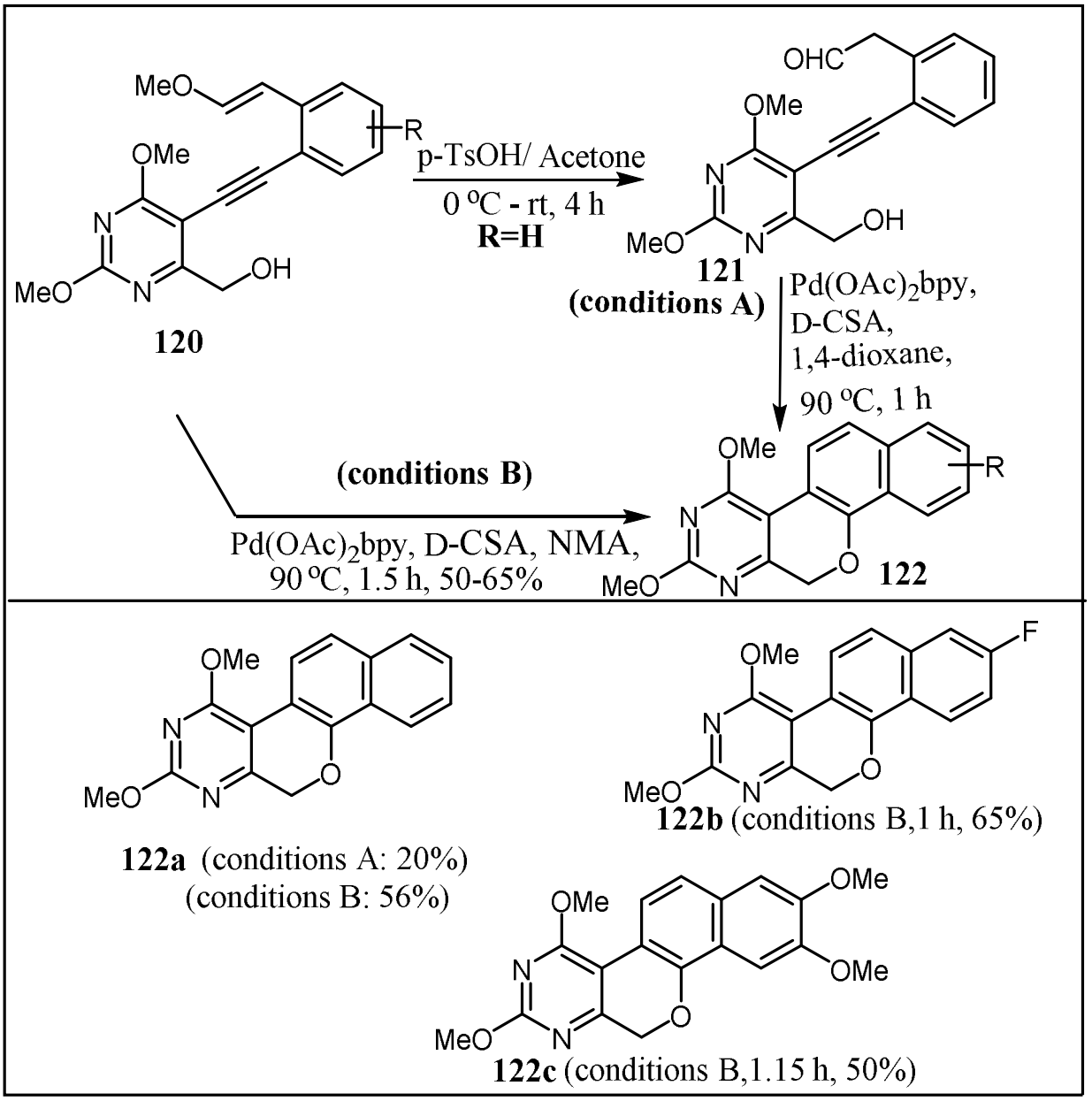
Schematic representation and procedure for the synthesis of the substrates 120



Scheme 30: (i)$PdCl_2(PPh_3)_2$, CuI, Et_3N : DMF (4:1) , rt, 2-3 h, 62-75%.

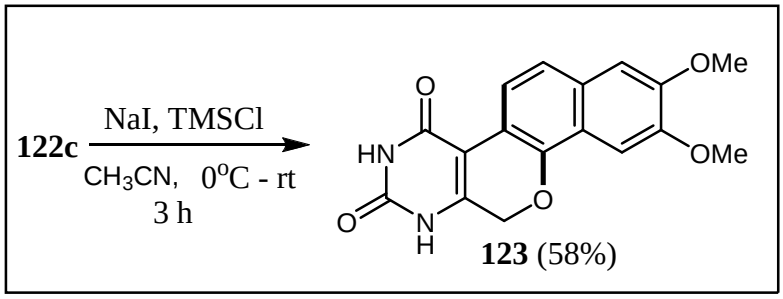
1-Iodo-2-(2-methoxyvinyl)benzene[64] **107** prepared through the reported procedure was coupled with (5-ethynyl-2,6-dimethoxypyrimidin-4-yl)methanol using "*Sonogashira reaction*" resulting in the formation of the starting material **120**.

Scheme 31. Synthesis of 2,4-dimethoxy-12H-benzo[7,8]chromeno[3,4-*d*]pyrimidines 122



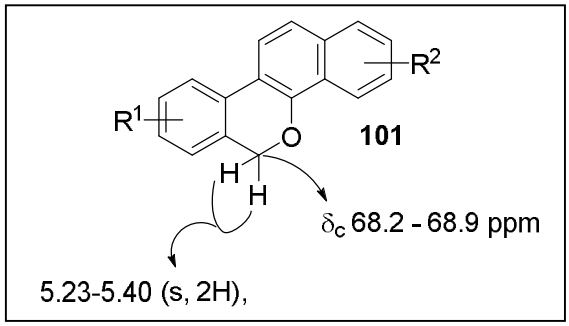
For transformation to uracil derivatives, one of the products was tested for chemoselective demethylation. When **122c** was treated with TMSCl/NaI at room temperature (Scheme 31), the desired product **123** was formed easily albeit in moderate yield (58%). Anti-cancer screening of **123** in various cell lines and preparation of other related uracil derivatives are currently underway.

Scheme 32. **Conversion of 122c to uracil derivative 123**



2.2.10. Nature and Characterization of Products 101

All the synthesized products are moderately stable at room temperature and can be stored at



room temperature (4 ^{o}C) for the several months. The structure of the products were unambiguously deduced by spectral (^{1}H and ^{13}C NMR, Mass and IR Spectra) and analytical data. In mass spectra (ESI and EI), the molecular ion peak in positive mode of all the compounds appeared as M^{+} or protonated $[M + H]^{+}$ and /or sodiated $[M + Na]^{+}$ ion. In ^{1}H NMR, the Two methylene appears in the range 5.23-5.40 ppm as singlet as expected, whereas aromatic protons appear in the range 6.94-8.29 ppm. Methylene carbon appears in the range 68.2-68.9 ppm. Thus, the spectral data (^{1}H,^{13}C, Mass Spectra, IR Spectra) provided the support in favour of the structure **101** (Scheme-26).

Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of the compounds **101a** and **101g**. The single crystal was obtained by slow evaporation (at room temperature) of a solution of petroleum ether and dichloromethane. The ORTEP diagrams of the crystal structures are shown in Figures 8 and 9.

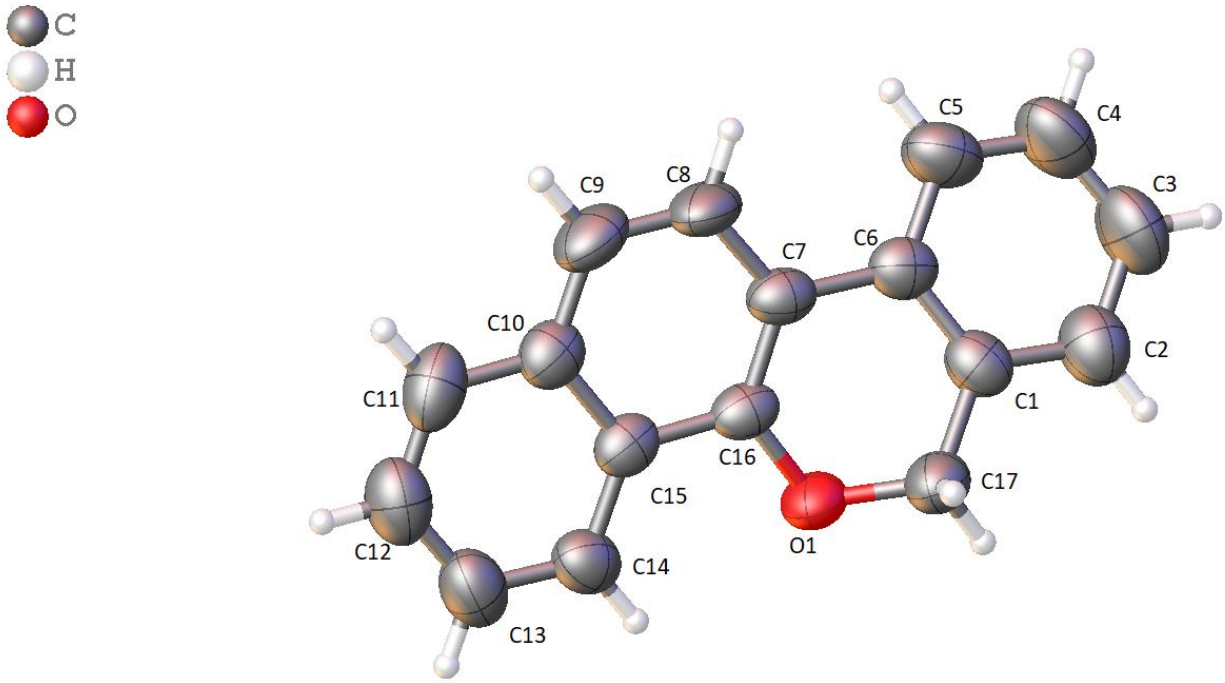


Figure 8. Ortep Diagram (drawn at 50% probability level) of compound **101a**.

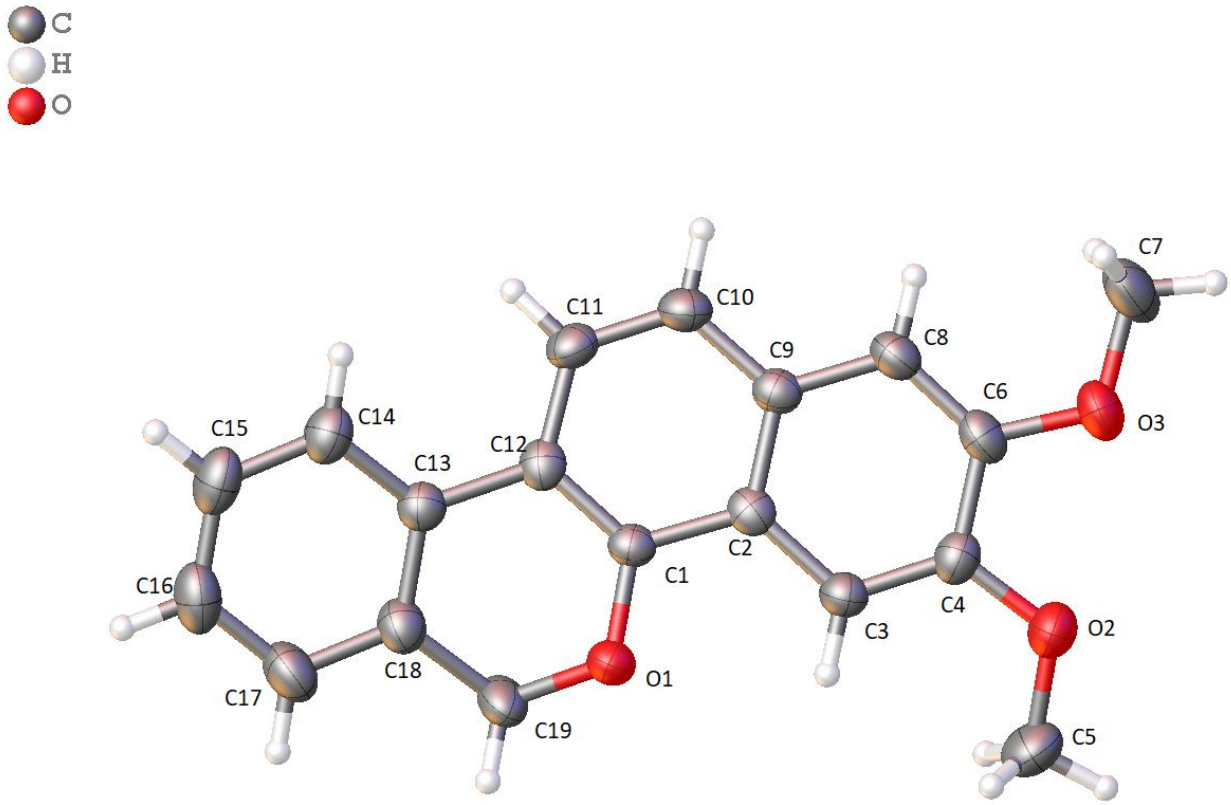


Figure 9. Ortep Diagram (drawn at 50% probability level) of compound **101g**.

Table 3: Important crystal data of product **101a**

Empirical formula	C_{17} H_{12} O
Formula weight	232.27
Temperature	296 K
Wavelength	0.71073
Crystal system	orthorhombic
Space group	P n a 21
Unit cell dimensions	a = 8.3541(7)Å α = 90.00°
	b = 12.9546(11)Å β = 90.00°
	c = 22.118(2)Å γ = 90.00°
Volume	2393.7(4)Å^3
Z	8
Density (calculated)	1.289 g/cm^3
Absorption coefficient (Mu)	0.079 mm^{-1}
F(000)	976.0
Theta range for data collection	2.901° to 27.498
Index ranges	-10<=h<=10, -16<=k<=16, -21<=l<=28
Reflection collected	16520
Independent reflections	4991 [R(int) = 0.0344]
Completeness to theta = 25.44°	99.4 %
Absorption correction	multi-scan
Max. and min. transmission	0.948 and 0.995
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4991/1/325
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0476, wR2 = 0.1174
R indices (all data)	R1 = 0.0772, wR2 = 0.1378
Largest diff. peak and hole	0.220 &-0.137 e.A^{-3}

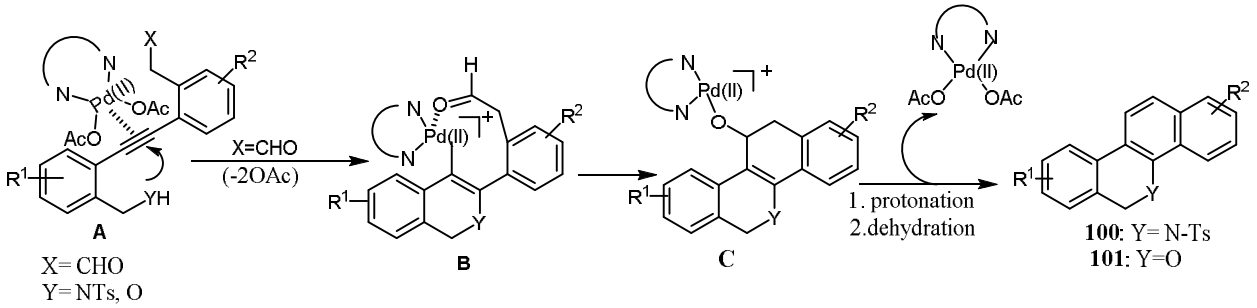
The single crystal of compound **101a** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleum ether and dichloromethane at room temperature. The crystal data of product **101a** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **1901864**.

Table 4: Important crystal data of product **101g**	
Empirical formula	$C_{19}\ H_{16}\ O_3$
Formula weight	292.32
Temperature	296 K
Wavelength	0.71073
Crystal system	orthorhombic
Space group	P c a 21
Unit cell dimensions	a = 17.432(5)Å $\alpha = 90.00^o$
	b = 13.354(4)Å $\beta = 97.587^o(3)$
	c = 6.2510(17)Å $\gamma = 90.00^o$
Volume	1455.2(7)$Å^3$
Z	4
Density (calculated)	1.334 g/cm^3
Absorption coefficient (Mu)	0.090 mm^{-1}
F(000)	616.0
Theta range for data collection	2.791 to 24.991
Index ranges	-20<=h<=9, -15<=k<=12, -2<=l<=6
Reflection collected	2407
Independent reflections	1442 [R(int) = 0.0403]
Completeness to theta = 25.44^o	100.2 %
Absorption correction	multi-scan
Max. and min. transmission	0.992 and 0.940
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1442 /1/202
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0384, wR2 = 0.0932
R indices (all data)	R1 = 0.0525, wR2 = 0.1004
Largest diff. peak and hole	0.150 &-0.168 $e.A^{-3}$

Single crystal of compound **101g** suitable for X-ray crystallographic determination was obtained by recrystallizing from a solution containing petroleumether and dichloromethane at room temperature. The crystal data of product **101g** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **1901866.**

2.2.11. Mechanism for the formation of Products 100 and 101:

On the basis of our experimental results and known palladium chemistry, a plausible reaction mechanism is depicted (Scheme 33) 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 pathway[61d, 70] resulting in the formation of the transient intermediate species **B**. Next, species **B** may undergo intramolecular Grignard type nucleophilic addition over a tethered aldehyde group to produce the corresponding palladated species **C**[71,60b], While species **C** upon protonolysis[72] using D-CSA followed by dehydration would afford the desired product **100**/**101**.



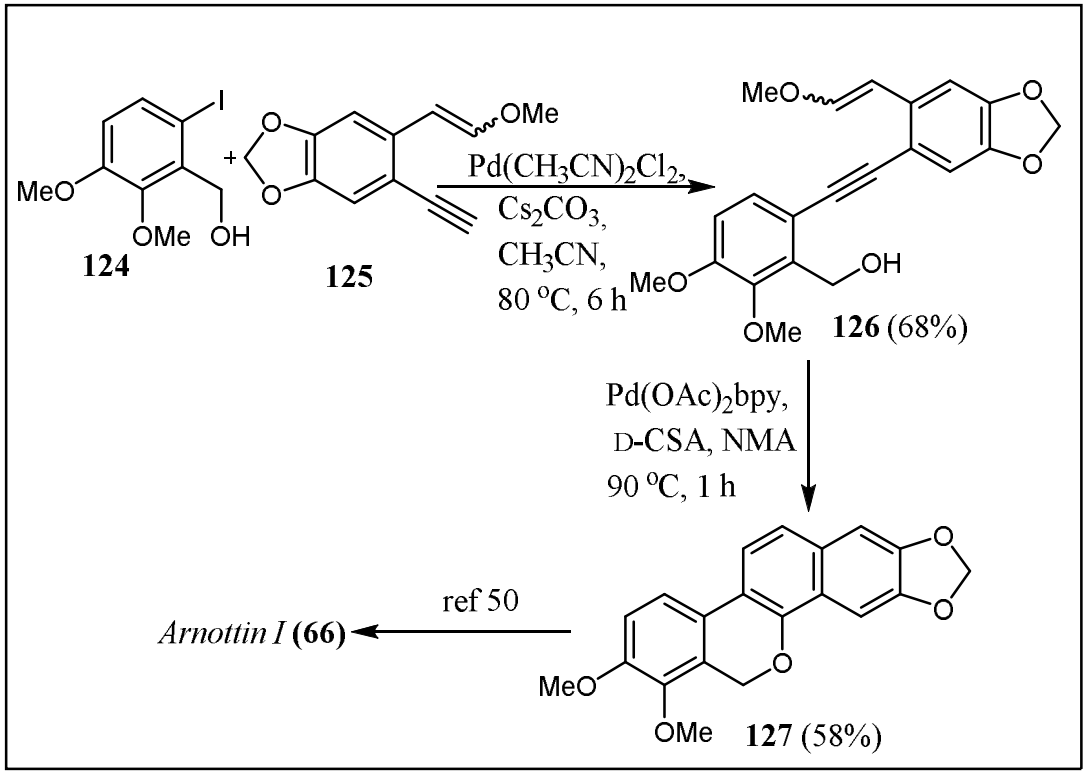
Scheme 33. Plausible mechanism for the formation of products **100** and **101**

2.2.12. Application to the Formal Total Synthesis of *Arnottin I* (66)

In order to enlarge the scope of this heteroannulation reaction further, we undertook a total synthesis of *Arnottin I* (**66,** see, Figure 6) in a concise manner as shown under Scheme 34. This natural product was isolated as a minor constituent from the bark of *Xanthoxylum arnottianum*,[11a–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,[73] while *chelerythrine* (**10**, see Figure 3) proved to be of

interest in cancer chemotherapy due to its ability to stabilize the c-MYC and c-KIT quadruplex DNAs[74a–b] (overexpression of which has been associated[74c] with numerous cancers) in addition to its role as G-quadruplex DNA stabilizer.[17a] These findings provided impetus to develop various strategies[11b–h] in order to get easy access to **66**. However, some of them use long synthetic routes using conventional reagents,[11b,11f–g] while others, employing either palladium[11c–d,11h] or nickel catalyst,[11e] required starting materials that were difficult to access.

Scheme 34. Formal total synthesis of *Arnottin I* (66)



We felt that an intramolecular heteroannulation of intermediate **126**, which in turn could be synthesized through a palladium-catalyzed coupling between **124**[75] and **125**[33] , may lead to **127** 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 **126** should be preferred as substrate. Indeed, the desired product **127** was thus isolated in 58% yield within 1 h as shown in Scheme 34.

2.2.13. Conclusion

In conclusion, we have described a palladium-catalyzed expeditious approach for the general synthesis of 5,6-dihydrobenzo[*c*]phenanthridines **100** and dibenzo[*c,h*]chromen-6-ones **101** through intramolecular domino reactions of acetylenic substrates involving trans-oxo palladation followed by nucleophilic addition to 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 onestep conversion of our products paved the way for easily accessing benzo[*c*]phenanthridines **109** and 6H-dibenzo[*c,h*]chromen-6-ones **115** 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.

2.2.14. Experimental Section

General Information

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 13C 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 13C NMR spectra were obtained with complete proton decoupling. Mass spectra were performed using ESI-TOF or EI mode.

General procedure for the synthesis of the substrate 98:

Procedure for the Synthesis of the Intermediate 106

To a well-stirred and ice-cooled solution of 2-iodophenyl alcohol derivative (4.27 mmol, 1 equiv) in dry DCM (3 mL) was added dry pyridine (0.34 mL, 4.27 mmol, 1 equiv) and PBr_3 (0.61 mL, 6.4 mmol, 1.5 equiv) successively and the whole reaction mixture was allowed to stir at the same temperature for 30 minutes until complete conversion of the starting material (TLC). The reaction was quenched by the addition of water (5 mL) and extracted with DCM (3x10 mL). The combined organic extracts were dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain the crude 2- iodobenzyl bromide **103** derivatives which was used immediately (without purification) in the next step as it is somewhat unstable in nature.

To a well-stirred solution of the product **103** (3.38 mmol) in dry acetonitrite (10 mL) were added K_2CO_3 (560 mg, 4.06 mmol, 1.2 equiv), tert-butyl tosylcarbamate (Ts-NH-Boc) (1832 mg, 6.76, 2 equiv) successively. The whole reaction mixture was heated at 70 ^{0}C for 2-6 hours until complete conversion of the staring material (TLC). The solvent was evaporated and diluted with water (8 mL). It was then extracted with ethyl acetate (3 x 30 mL); the combined organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain the crude product which was then purified by silica gel (100-200 mesh) column chromatography with 15-30% ethylacetate/petroleum ether (v/v) to furnish the pure product **104** in 70-85% yield.

In next step, boc-protected intermediate **104** (1.6 mmol, 1 equiv) dissolved in dry DCM (5 mL) was treated with trifluoroacetic acid (16 mmol, 10 equiv) at 0 ^{o}C and the recation mixture was then allowed to warm to room temperature for 2 h until complete consumption of the starting material (TLC). The reaction mixture is neutralised with saturated $NaHCO_3$ solution and extracted with DCM (3x10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified by silica gel (100-200 mesh) column chromatography with 10-20% ethyl-acetate pet ether (v/v) to furnish the pure product N-(2-iodobenzyl)-4-methylbenzenesulfonamide derivatives **105**[62] derivatives in 75-90% yield.

To a well stirred solution and ice-cooled solution of N-(2-iodobenzyl)-4-methylbenzenesulfonamide derivatives **105** (1.3 mmol, 1 equiv) in Et_3N: DMF (4:1, 3 mL) were added $Pd(PPh_3)_2Cl_2$ (26.6 mg, 0.04 mmol, 3 mol %), trimethylsilylacelene (0.3 ml, 1.42 mmol, 1.1 equiv) and CuI (14.6 mg, 0.08 mmol, 6 mol %) successively. The reaction mixture was then stirred at room temperature under argon atmosphere. After completion of the reaction (TLC), solvent was removed under reduced pressure. The resulting crude mixture was extracted with ethyl acetate (3 × 30 mL); the combined organic extracts were washed

with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography and eluted with 10-20% ethyl acetate-petroleum ether (v/v) to afford the desired silylated acetylenic products in 76-85% yield.

The said silylated acetylenic compound (1.26 mmol, 1 equiv) dissolved in dry methanol (5 mL) was treated with K_2CO_3 (17.4 mg, 0.1 equiv) and the reaction mixture was then allowed to stir at room temperature for 30 min to 1h until complete consumption of the starting material (TLC). The crude product was diluted with water (10 mL), extracted with ethyl acetate (3x30 mL). The combined organic extracts were dried over anhydrous sodium sulphate, evaporated under reduced pressure and purified by column chromatography using 15-25% ethyl acetate-petroleum ether (v/v) as eluent to afford pure desired product **106**[63] in 56-72% yield.

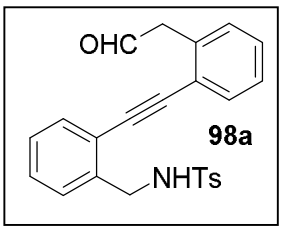
*Procedure for the synthesis of the starting substrate **98***

To an ice-cooled solution of 1-iodo-2-(2-methoxyvinyl)benzene[64] (0.77 mmol, 1equiv) in triethylamine (1.5 mL) were added $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol, 3 mol %), acetylene **106** (1.1 equiv) dissolved in dry DMF (0.5 mL) and CuI (7.6 mg, 0.04 mmol, 6 mol %) successively. The whole reaction mixture was then allowed to stir at room temperature until the complete conversion of starting material (TLC). The resulting crude mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography and eluted with 20-35% ethyl acetate-petroleum ether (v/v) to afford the desired product in **108** in 60-70% yield.

To an ice-cooled solution of compound **108** (0.48 mmol, 1 equiv) in dry acetone (2.5 mL) was added p-toluenesulphonic acid (146.3 mg, 0.77 mmol, 1.6 equiv) in portion wise. The whole reaction mixture was allowed to stir to room temperature for 3-4 hours until the completion of the reaction (TLC). The reaction mixture was neutralized with 10% aqueous sodium bicarbonate solution and extracted with DCM (3 x 10 mL); the combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel (100-200 mesh) column chromatography to yield the pure product **98** in 49-95% yields.

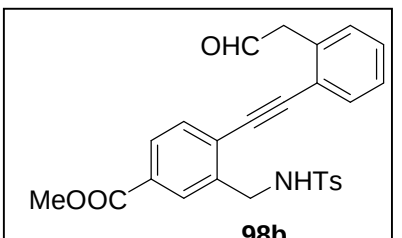
Spectral data of substrates 98a-f:

4-Methyl-N-(2-((2-(2-oxoethyl)phenyl)ethynyl)benzyl)benzenesulfonamide (98a): Brown solid (168.3 mg, 87% yield), mp 96-98 ^oC, R_f = 0.41 (30% ethyl acetate in petroleum ether, v/v); ^1H NMR ($CDCl_3$, 300 MHz) δ_H 9.69 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.50-7.48 (m, 1H), 7.46-7.41 (m, 2H), 7.38- 7.28 (m, 5H), 7.19 (d, *J* = 8.1 Hz, 2H), 5.22 (t, *J* = 6.15 Hz, 1H), 4.33 (d, *J* = 6.3 Hz, 2H), 3.84 (s, 2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 199.1, 143.3, 137.8, 136.9, 133.9, 132.6, 132.5, 130.4, 129.6, 129.3, 129.0, 128.9, 127.9, 127.7, 127.1, 123.3, 121.9, 92.1, 91.3, 49.5, 46.0, 21.5; HRMS (ESI^+) m/z calculated for $C_{24}H_{22}NO_3S$ $[M+H]^+$ 404.1320, found 404.1318.



98a

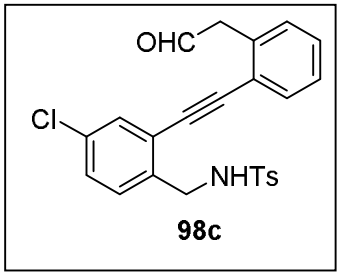
Methyl 3-(((4-methylphenyl)sulfonamido)methyl)-4-((2-(2-oxoethyl)phenyl)ethynyl)benzoate (98b): Yellow colored solid (170.4 mg, 77% yield), mp 126-128 ^oC, R_f = 0.23 (30% ethyl acetate in petroleum ether, v/v); ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.72 (t, *J* = 2.1 Hz, 1H) 7.89 (dd, *J* = 1.5, 8.1 Hz, 1H), 7.86 (d, *J* = 1.2 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.55 (dd, *J* = 0.9, 7.5 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.43 (td, *J* = 1.4,



98b

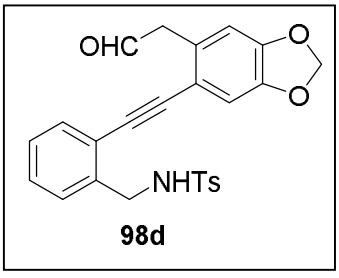
7.5 Hz, 1H), 7.36 (td, *J* = 1.2, 7.5 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 5.22 (t, *J* = 6.6 Hz, 1H), 4.39 (d, *J* = 6.6 Hz, 2H), 3.93 (s, 3H), 3.88 (d, *J* = 1.8 Hz,2H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 198.9, 166.0, 143.4, 137.9, 136.9, 134.1, 132.9, 132.6, 130.5, 130.1, 129.9, 129.8, 129.6, 128.9, 127.8, 127.2, 126.5, 122.8, 95.0, 90.6, 52.4, 49.6, 45.8, 21.5; HRMS (ESI+) m/z calculated for C26H24NO5S [M+H]+ 462.1375, found 462.1388.

N-(4-Chloro-2-((2-(2-oxoethyl)phenyl)ethynyl)benzyl)-4-methylbenzenesulfonamide (98c): Brown solid (199.3 mg, 95% yield), mp 104-106 ^{o}C, R_f = 0.41 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.69 (t, *J* = 2.1 Hz, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.45-7.44 (m, 1H), 7.39 (td, *J* = 7.6, 1 Hz, 1H), 7.34-7.32 (m, 1H),7.30-7.28(m, 2H),7.26-7.24 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 5.19 (t, *J* = 5.1 Hz, 1H), 4.34 (d, *J* = 6 Hz, 2H), 3.85(d, *J* = 2.4 Hz, 2H), 2.38 (s, 3H) ; ^{13}C NMR($CDCl_3$, 150 MHz) δ_C 199.2, 143.3, 137.8, 137.0, 134.0, 132.7, 132.5, 130.4, 129.6, 129.3, 129.1, 129.0, 127.9, 127.7, 127.1, 123.3, 121.9, 92.1, 91.4, ,49.5, 46.0, 21.5; HRMS (ESI^+) m/z calculated for $C_{24}H_{20}ClNNaO_3S$ $[M+Na]^+$ 460.0750 , found 460.0756.



98c

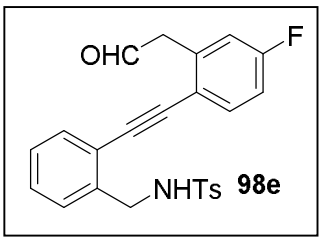
4-Methyl-N-(2-((6-(2-oxoethyl)benzo[d][1,3]dioxol-5-yl)ethynyl)benzyl)benzenesulfonamide (98d): Yellow gum (143.7 mg, 67% yield), R_f = 0.36 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.64 (t, *J* = 2.1 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.40-7.39 (m, 1H), 7.28- 7.27 (m, 1H), 7.22-7.21 (m, 4H), 6.86 (s, 1H), 6.71 (s, 1H), 6.01 (s, 2H), 5.31 (t, *J* = 6.3Hz, 1H),4.29 (d, *J* = 6.6 Hz, 2H), 3.75 (d, *J* = 1.8 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 199.2, 148.7, 147.0, 143.4, 137.6, 136.9, 132.3, 129.7, 128.9, 128.8, 127.9, 127.1,



98d

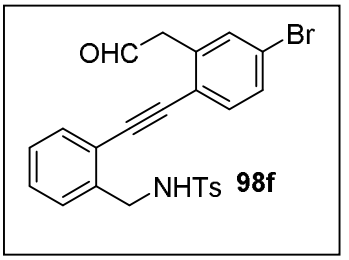
122.0, 116.3, 111.9, 110.5, 101.8, 92.3, 89.9, 49.2, 45.9, 21.5; HRMS (ESI^+) m/z calculated for $C_{25}H_{22}NO_5S$ $[M+H]^+$ 448.1219, found 448.1220.

N-(2-((4-Fluoro-2-(2-oxoethyl)phenyl)ethynyl)benzyl)-4-methylbenzenesulfonamide



(98e) : Yellow gum (135.4 mg, 67% yield), R_f = 0.42 (30% ethyl acetate in petroleum ether, v/v); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 9.54 (s, 1H), 7.56-7.54 (m, 2H), 7.34-7.27 (m, 2H), 7.10-7.03 (m, 5H), 6.87-6.83 (m, 2H), 5.12 (s, 1H), 4.16 (s, 2H), 3.69 (s, 2H), 2.22 (s, 3H); z), 134.4 (d, *J* = 9 Hz), 132.4, 129.5, 128.9 (d, *J* = 17 Hz), 127.8, 127.1, 121.8, 119.5, 117.5 (d, *J* = 23 Hz), 114.9 (d, *J* = 22 Hz), 91.2, 90.9, 49.2, 45.9, 21.4. HRMS (ESI^+) m/z calculated for $C_{24}H_{21}FNO_3S$ $[M+H]^+$ 422.1226, found 422.1215.

N-(2-((4-Bromo-2-(2-oxoethyl)phenyl)ethynyl)benzyl)-4-methylbenzenesulfonamide



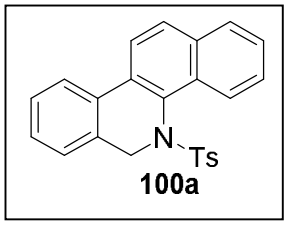
(98f) : Brown gum (113.1 mg, 49% yield), R_f = 0.44 (30% ethyl acetate in petroleum ether, v/v); ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.56 (s, 1H), 7.59-7.57 (m, 2H), 7.31 (s, 3H), 7.23-7.21 (m, 1H), 7.13-7.12 (m, 3H), 7.09-7.07 (m, 2H), 4.98 (s, 1H), 4.18 (d, *J* = 5.2 Hz, 2H), 3.69 (s, 2H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 198.0, 143.9, 143.4, 137.8, 136.9, 135.9, 133.8, 133.3, 132.5, 130.9, 129.6, 129.2, 128.9, 127.9, 127.1, 123.2, 122.3, 121.7, 92.3, 91.2, 49.0, 45.9, 21.5; HRMS (ESI^+) m/z calculated for $C_{24}H_{21}BrNO_3S$ $[M+H]^+$ 482.0426, found 482.0425.

General procedure of synthesis of 5-tosyl5,6-dihydrobenzo[*c*]phenanthridines 100

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 **98** (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

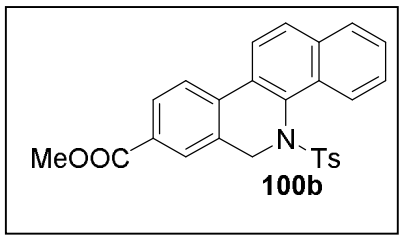
hours until the completion of the reaction (TLC). Thereafter the reaction mixture was neutralized by adjusting the pH (~7) through drop wise addition of 20% aqueous sodium bicarbonate solution and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with saturated brine (10 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 **100.**

5-Tosyl-5,6-dihydrobenzo[c]phenanthridine (100a): 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.



100a

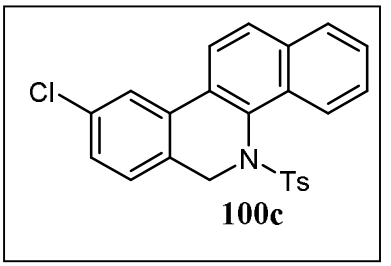
Methyl 5-tosyl-5,6-dihydrobenzo[c]phenanthridine-8-carboxylate(100b): Brown solid (47.8 mg, 54% yield), mp 106–108°C, R_f = 0.22 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.74 (d, *J* = 9.0 Hz, 1H), 7.90-7.86 (m, 2H), 7.77–7.75 (m, 2H), 7.68–7.65 (m, 2H), 7.60–7.58 (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,



100b

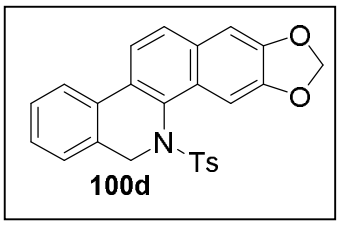
133.57, 132.2, 131.4, 129.2, 128.8, 128.7, 128.4, 128.1, 127.7, 127.5, 127.4, 127.3, 127.0, 126.8, 123.1, 121.3, 52.4, 50.8, 21.3; HRMS (ESI^+) m/z calculated for $C_{26}H_{22}NO_4S$ $[M+H]^+$ 444.1270, found 444.1270.

9-Chloro-5-tosyl-5,6-dihydrobenzo[c]phenanthri-dine (100c): Yellow solid (67.9 mg, 81% yield), mp 140–142 °C, R_f = 0.46 (5% ethyl acetate in petroleum ether, v/v); ^1H 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.



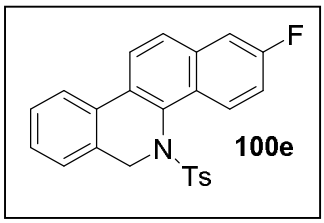
100c

12-Tosyl-12,13-dihydro-[1,3]dioxolo[4',5':4,5]ben-zo[1,2-c] phenanthridine (100d): Pale yellow solid (36.1 mg, 42% yield), mp 74–78°C, R_f = 0.55 (20% ethyl acetate in petroleum ether, v/v); ^1H 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.

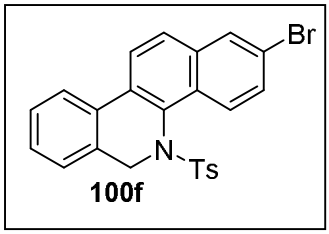


100d

2-Fluoro-5-tosyl-5,6-dihydrobenzo[c]phenanthri- dine (100e): 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 (100f): 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.

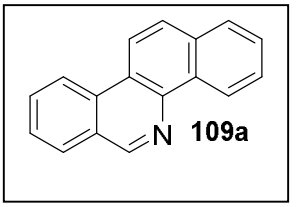


Procedure for the Synthesis of Benzo[*c*]phenanthridine 109

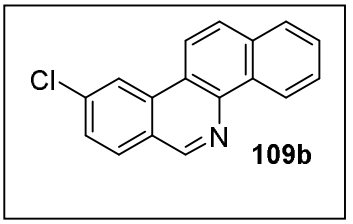
To a solution of compound **100** (0.13 mmol,1 equiv.)in dry DMSO (3 mL)was added finely ground KOH pellets (36.4 mg, 0.65 mmol, 5 equiv.) and the reaction was allowed to stir at room temperature for 1–2 h. After completion of the reaction (TLC), the reaction mixture was

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 **109** in 51–79% yield.

Benzo[c]phenanthridine (109a): 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.

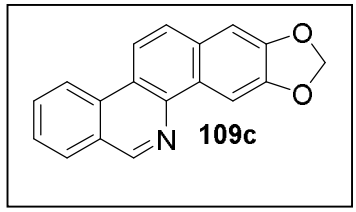


9-Chlorobenzo[c]phenanthridine (109b): White solid (21.5 mg, 63% yield), mp 102–104°C, R_f = 0.76 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.44 (s, 1H), 9.38 (d, *J* = 8.4 Hz, 1H), 8.64 (s, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 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.



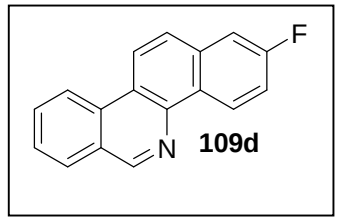
[1,3]Dioxolo[4',5':4,5]benzo[1,2-c]phenanthridine (109c): White solid (20.6 mg, 58% yield), mp 176–178°C, R_f = 0.41 (5% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.42 (s, 1H), 8.75 (s, 1H), 8.67 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 9.0 Hz, 1H),

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.



109c

2-Fluorobenzo[c]phenanthridine (109d): 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.



109d

Procedure for the synthesis of the starting material 99 :

*Synthesis of the Intermediate Alkyne **114**:*

To a well stirred solution of 1-iodo-2-(2-methoxyvinyl)benzene[64] derivatives (0.77 mmol, 1 equiv) in dry triethylamine (1.5 mL) was added $PdCl_2(PPh_3)_2$ (16.2 mg, 0.023 mmol, 0.03 equiv), (orthoethynylphenyl)methanol derivative **112** (0.84 mmol, 1.1 equiv) and CuI (8.8 mg, 0.046 mmol, 0.06 equiv) successively under ice cold conditions and the whole reaction mixture was allowed to stir at room temperature for 1-5 hours until TLC showed complete conversion of starting material. The solvent was evaporated under reduced pressure and extracted with ethyl acetate (3x20 mL); the combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced

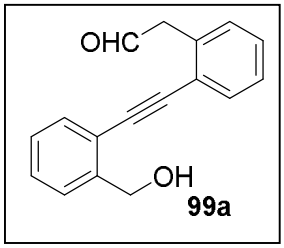
pressure. The resulting crude was purified by silica gel (100-200 mesh) column chromatography using 10-18% ethyl acetate-petroleum ether (v/v) as eluent to provide the pure product **114** in 70-85% yield.

Synthesis of the substrate 99

The intermediate product **114** (0.75 mmol, 1 equiv) dissolved in dry acetone (3 mL) was treated (portion wise) with *p*-toluenesulphonic acid (1.2 mmol, 1.6 equiv) under ice-cold conditions. Next the whole reaction mixture was allowed to stir to room temperature for 3-4 hours until complete conversion of the starting material as indicated by TLC. The reaction mixture was then neutralized with dilute sodium bicarbonate solution and extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The resulting crude product was purified by silica gel (100-200 mesh) column chromatography using 20-30% ethyl acetatepetroleum ether (v/v) to yield the desired starting material **99** in 42-61% yield.

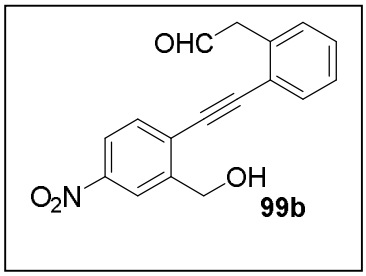
Spectral data of the substrates 99a-j:

2-(2-((2-(Hydroxymethyl)phenyl)ethynyl)phenyl)acetaldehyde (99a): Yellowish gummy liquid (105 mg, 56 % yield), R_f = 0.39 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.77 (t, *J* = 2.2 Hz, 1H), 7.60-7.58 (m, 1H), 7.52 (d, *J* = 6.8 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.38- 7.36 (m, 1H), 7.34-7.33 (m, 1H), 7.32-7.30 (m, 1H),7.28 (d, *J* = 1.6 Hz, 1H), 7.27-7.25 (m, 1H), 4.85 (d, *J* = 6 Hz, 2H), 3.94 (d, *J* = 2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 198.5, 142.3, 134.4, 134.3, 132.4, 129.2, 127.7, 127.69, 121.0, 117.6, 117.5, 115.2, 115.0, 91.4, 90.8, 63.8, 49.4; HRMS (ESI^+) m/z calculated for $C_{17}H_{15}O_2$ $[M+H]^+$ 251.1072, found 251.1069.

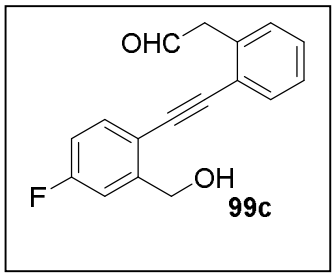


99a

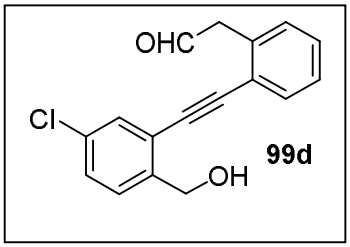
2-(2-((2-(Hydroxymethyl)-4-nitrophenyl)ethynyl)phenyl)acetaldehyde(99b): Yellowish gummy liquid (134.9 mg, 61% yield), R_f = 0.39 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.76 (t, *J* = 1.8 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 2.4 Hz,1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.41-7.38 (m, 1H), 7.36-7.3 (m, 2H),7.31-7.30 (m, 1H), 4.82 (s, 2H), 3.94 (d, *J* = 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 199.3, 140.8, 134.1, 133.2, 132.8, 131.9, 130.5, 129.5, 129.2, 129.0, 127.8, 123.2, 122.7, 92.8, 90.3, 63.1, 49.6; HRMS (EI^+) m/z calculated for : $C_{17}H_{14}NO_4$ $[M+H]^+$ 296.0923, found 296.0920.



2-(2-((4-Fluoro-2-(hydroxymethyl)phenyl)ethynyl)phenyl)acetaldehyde (99c): Yellowish gum (84.4 mg, 42% yield), R_f = 0.49 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.75 (s, 1H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.49-7.47 (m, 1H), 7.37-7.36 (m, 1H), 7.34-7.33 (m, 1H), 7.29-7.28 (m, 1H), 7.25-7.23 (m, 1H), 6.98-6.95 (m, 1H), 4.84 (s, 2H), 3.92 (s, 2H); ^{13}C NMR ($CDCl_3$, 600 MHz) δ_C 199.6, 162.99 (d, *J* = 249 Hz), 145.4 (d, *J* = 7.5 Hz),134.1 (d, *J* = 7.5 Hz), 133.9, 132.6, 130.4, 129.2, 127.8, 123.6, 114.6, 114.5 (d, *J* = 7.5 Hz), 114.4, 91.6, 90.7, 63.1, 49.6; HRMS (EI^+) m/z calculated for $C_{17}H_{14}FO_2$ $[M+H]^+$ 269.0978, found 269.0973.

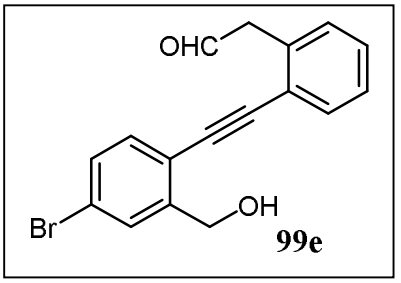


2-(2-((5-Chloro-2-(hydroxymethyl)phenyl)ethynyl)phenyl)acetaldehyde (99d): Yellowish gum (110.7 mg, 52% yield), R_f = 0.24 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.78 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H),7.39- 7.36 (m, 2H), 7.30-7.29 (m, 2H), 4.87 (s,

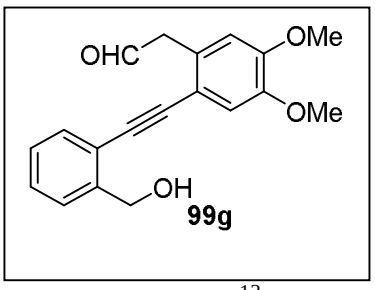


2H), 3.95 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 199.5, 142.4, 134.0, 132.6, 132.4, 130.4, 129.2, 129.1, 127.7, 127.6, 123.7, 121.2, 91.8, 91.7, 63.9, 49.6; HRMS (EI+) m/z calculated for $C_{17}H_{13}ClNaO_2$ $[M+Na]^+$ 307.0502, found 307.0503.

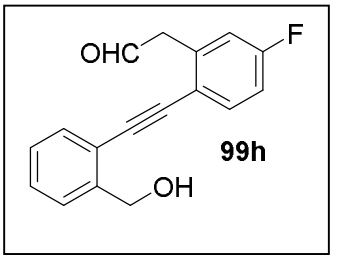
2-(2-((4-Bromo-2-(hydroxymethyl)phenyl)ethynyl)phenyl)acetaldehyde (99e) : Yellowish gum (113.2 mg, 46% yield), R_f = 0.54 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.74 (s, 1H), 7.66 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.41-7.39 (m, 1H), 7.37-7.36 (m, 1H), 7.35-7.31 (m, 2H), 7.29-7.28 (m, 1H), 4.82 (s, 2H), 3.92 (s, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ_C 199.5, 144.3, 133.9, 133.5, 132.6, 130.6, 130.5, 130.4, 129.4, 127.8, 123.4, 123.3, 119.7, 92.9, 90.7, 63.1, 49.6; HRMS(EI^+) m/z calculated for : $C_{17}H_{14}BrO_2[M+H]^+$ 329.0177, found 329.0175.



2-(2-((2-(Hydroxymethyl)phenyl)ethynyl)-4,5-dimethoxyphenyl)acetaldehyde (99g): Yellowish gum (130.2 mg, 56% yield), R_f = 0.26 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 9.74 (s, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 8.2 Hz, 1H),7.28 (d, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 6.76 (s, 1H), 4.85 (s, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.88 (s, 2H), 3.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 199.5, 150.0, 148.3, 142.2, 132.3, 128.9, 127.8, 127.7, 127.3, 121.5, 115.7, 114.8, 113.1, 92.1, 90.3, 64.0, 56.2, 56.1, 49.3; HRMS(EI^+) m/z calculated for : $C_{19}H_{19}O_4[M+H]^+$ 311.1283, found 311.1274.

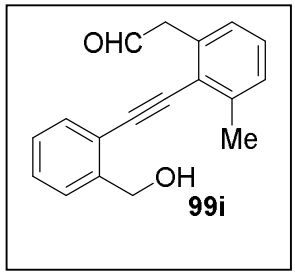


2-(5-Fluoro-2-((2-(hydroxymethyl)phenyl)ethynyl)phenyl)acetaldehyde (99h): Yellowish gum (84.4 mg, 42 % yield), R_f = 0.43 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.78 (s, 1H), 7.67-7.56 (m, 1H), 7.50 (t, *J* = 8.7 Hz, 2H), 7.38 (t, *J* = 7.2



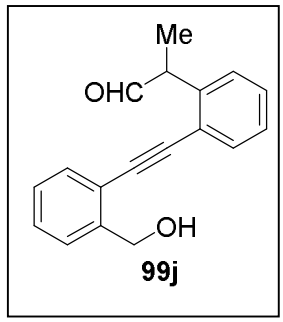
Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H, 1H), 7.02 (d, *J* = 9 Hz, 2H), 4.85 (d, *J* = 5.1 Hz, 2H), 3.95 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 198.5, 162.6 (d, *J* = 250.5 Hz), 142.3,136.6, 136.57, 134.4 (d, *J* = 7.5 Hz), 132.4, 129.1, 127.7, 127.69, 121.0, 117.6 (d, *J* = 22.5 Hz), 115.1 (d, *J* = 21 Hz), 91.4, 90.8, 63.8, 49.4; HRMS(EI$^+$) m/z calculated for : $C_{17}H_{14}FO_2$ $[M+H]^+$ 269.0978, found 269.0979.

2-(2-((2-(Hydroxymethyl)phenyl)ethynyl)-3-methylphenyl)acetaldehyde (99i): Yellowish gummy liquid (102.9 mg, 52% yield), R_f = 0.43 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.77 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.25-7.23 (m, 2H), 7.13 (d, *J* = 7.2 Hz, 1H), 4.89 (s, 2H), 3.94 (d, *J* = 1.8 Hz, 2H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 199.9, 142.1, 141.2, 134.2, 132.4, 129.0, 128.9, 128.6, 127.71, 127.70, 127.67, 123.6, 121.4, 96.2, 90.7, 63.9, 49.9, 21.3; HRMS (ESI+) m/z calculated for C18H17O2 [M+H]+ 265.1229, found 265.1228.



99i

2-(2-((2-(Hydroxymethyl)phenyl)ethynyl)phenyl)propanal (99j): Yellowish gummy liquid (89.1 mg, 45% yield), R_f = 0.55 (30% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.77 (s, 1H), 7.62 (d, *J* = 7.8, Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.41-7.37 (m, 2H), 7.34-7.29 (m, 2H), 7.21 (d, *J* = 7.8 Hz, 1H), 4.88 (s, 2H), 4.23-4.19 (q, 1H),1.52 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 201.4, 142.4, 139.7, 133.0, 132.3, 129.3, 129.1, 127.9, 127.6, 127.5, 123.3, 121.1, 91.7, 63.8, 51.3, 14.2; HRMS(EI$^+$) m/z calculated for : $C_{18}H_{17}O_2$ $[M+H]^+$ 265.1229, found 265.1232.

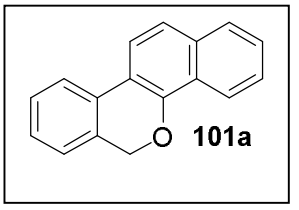


99j

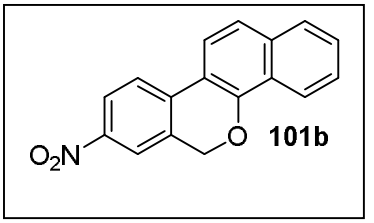
General Procedure for the Synthesis of 6H-dibenzo [*c,h*]chromenes 101

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 **99** (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 **101** in 47–86% yield.

6H-Dibenzo[*c,h*]chromene (101a): 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.

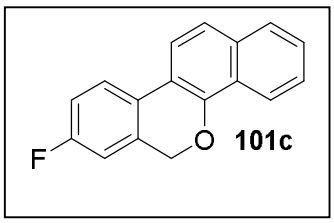


8-Nitro-6H-dibenzo[*c,h*]chromene (101b): Yellow solid (30.0 mg, 56% yield); mp 158–160°C; R_f = 0.63 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.29-8.27 (m, 2H), 8.12 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz,1H), 7.84–7.82 (m, 2H),

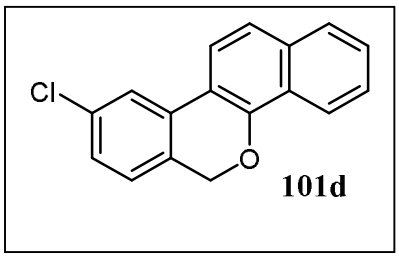


7.58(d, *J* = 8.4 Hz, 1H), 7.57- 7.53 (m, 2H), 5.40 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 151.9, 146.6, 137.3, 135.4 131.3, 127.9, 127.8, 126.4, 125.1, 124.1, 122.6, 122.5, 122.4, 120.8, 120.2, 115.3, 68.3; HRMS (ESI^+) m/z calculated for $C_{17}H_{12}NO_3$ $[M+H]^+$ 278.0817, found 278.0814.

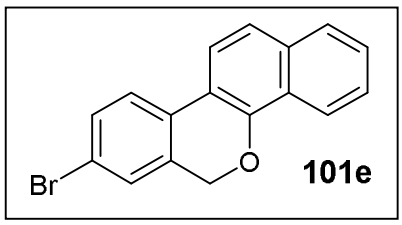
8-Fluoro-6H-dibenzo[*c,h*]chromene (101c): White solid (39.5 mg, 79% yield), mp 158–160 °C, R_f = 0.54 (petroleum ether); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.27–8.26 (m, 1H), 7.82-7.81 (m, 1H), 7.78(d, *J* = 8.4 Hz, 1H), 7.70-7.68 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.52-7.49(m, 2H), 7.11(td, *J* = 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 (101d): 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.

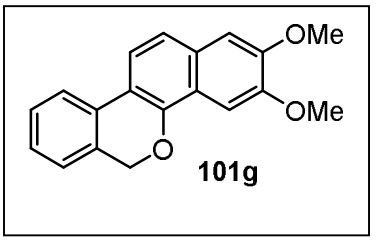


8-Bromo-6H-dibenzo[*c,h*]chromene (101e): White solid (47.1 mg, 76% yield), mp 140–142 °C, R_f = 0.54 (petroleum ether); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.26-8.24 (m, 1H), 7.81– 7.79 (m, 1H), 7.78 (d, *J*

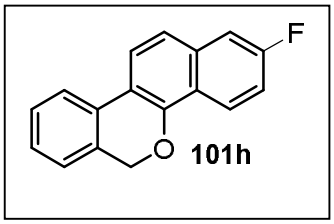


= 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.55–7.52 (m, 2H), 7.51–7.49 (m, 2H), 7.37 (s, 1H), 5.27 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 150.3, 134.5, 132.6, 131.6, 129.8, 127.7, 126.9, 126.0, 125.3, 123.6, 122.3, 121.8, 121.0, 120.6, 116.3, 68.2; HRMS (ESI^+) m/z calculated for $C_{17}H_{12}BrO$ $[M+H]^+$ 311.0072, found 311.0066.

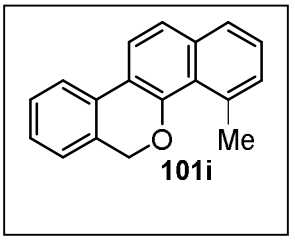
2,3-Dimethoxy-6H-dibenzo[*c*,*h*]chromene (101g): Yellow solid (43.8 mg, 75% yield), mp 140–144 °C, R_f = 0.55 (20% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.73–7.71 (m, 2H), 7.54 (s, 1H), 7.42–7.39 (m, 2H), 7.28 (td, *J* = 1.0, 7.35 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 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 (101h): 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.

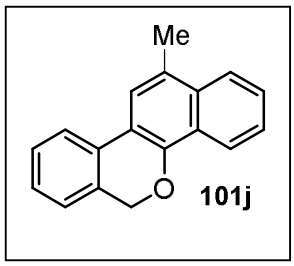


4-Methyl-6H-dibenzo[*c*,*h*]chromene (101i): Yellow solid (23.1 mg, 47% yield), mp 70–72 °C, R_f = 0.56 (petroleum ether); ^{1}H NMR ($CDCl_3$, 600 MHz) δH 7.82 (d, J=8.4 Hz, 1H), 7.74 (d, J=7.8 Hz, 1H), 7.63 (d, J=8.4 Hz,



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 (101j): 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 C18H15O $[M+H]^+$ 247.1123, found 247.1125.

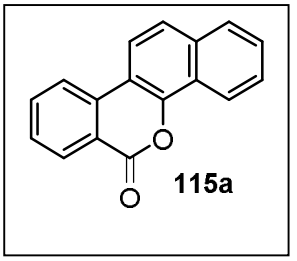


Synthesis of 6H-dibenzo[*c,h*]chromen-6-ones (115) from 6H-dibenzo[*c,h*]chromenes 101 by benzylic oxidation:

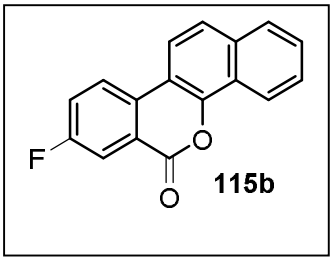
General procedure for the synthesis of 6H-dibenzo[*c,h*]chromen-6-ones (115)

To a solution of **101**(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 **115** in 64–95% yield.

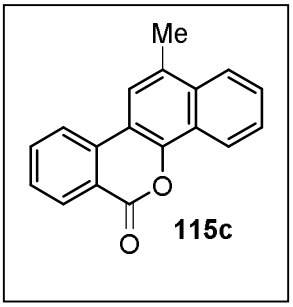
6H-Dibenzo[*c,h*]chromen-6-one (115a): White solid (19.4 mg, 92% yield), mp 188–190°C, R_f = 0.53 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.59 (d, *J* = 7.5 Hz, 1H), 8.47 (d, *J* = 7.8 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.06(d, *J* = 9.0 Hz, 1H), 7.89–7.85 (m, 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.



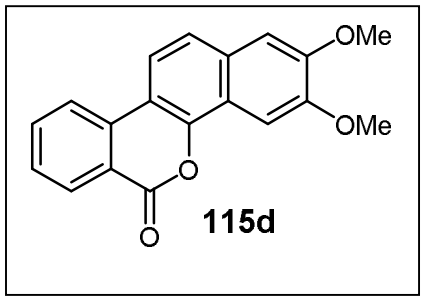
8-Fluoro-6H-dibenzo[*c,h*]chromen-6-one (115b): White solid (17.9 mg, 79% yield), mp 219–221°C, R_f = 0.55 (10% ethyl acetate in petroleum ether, v/v); 1 H NMR ($CDCl_3$, 600 MHz) δ_H 8.55 (d, *J* = 8.4 Hz, 1H), 8.19.–8.17 (m, 1H), 8.10 (dd, *J* = 3, 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *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 (115c): 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 (115d): 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.



One-pot Synthesis of 115a using 2-((2-(2-oxoethyl)phenyl)ethynyl)benzoic acid (116) as substrate:

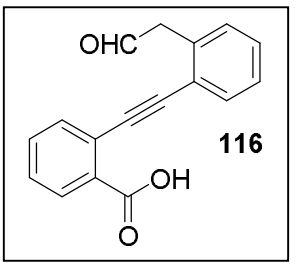
Procedure for the synthesis of substrate 116:

To a well stirred and ice-cooled solution of methyl-2-iodobenzoate[68] (500 mg, 1.91 mmol, 1 equiv) in dry Et_3N (3 mL) were added $Pd(PPh_3)_2Cl_2$ (40.1 mg, 0.06 mmol, 3 mol %), 1-ethynyl-2-(2- methoxyvinyl)benzene[67] **117** (331.6 mg, 2.09 mmol, 1.1 equiv), CuI (21.7 mg, 0.11 mmol, 6 mol %), successively. The whole the reaction mixture was then allowed to stir at room temperature under argon atmosphere. After completion of the reaction (TLC), solvent was removed under reduced pressure. The resulting crude mixture was extracted with ethyl acetate (3 × 20 mL); the combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography and eluted with 20% ethyl acetate-petroleum ether (v/v) to afford the desired substrate **118** in (416 mg, 74%) yield.

To a well stirred solution of **118** (400 mg, 1.36 mmol) was added saturated solution of NaOH in water and stirred for one hour until the completion (TLC). The reaction mixture was then neutralised with 3N HCl and extracted with EtOAc (3x 20 mL). The combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh) column chromatography and eluted with 45 % ethyl acetate-petroleum ether (v/v) to afford the desired substrate **119** in (272 mg, 72%) yield. The intermediate product **119** (200 mg, 0.72mmol, 1 equiv) dissolved in dry acetone (3 mL) was treated (portion wise) with p-toluenesulphonic acid (198 mg, 1.2 mmol, 1.6 equiv) under ice-cold conditions. Next, the whole reaction mixture was then allowed to reach at room temperature; the whole reaction mixture was then stirred at rt for another 4 hours until complete consumption of the starting material (TLC). The reaction mixture was then neutralized with 10% sodium bicarbonate solution and extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The resulting crude product was purified by silica gel (100-200 mesh) column chromatography using 70% ethyl acetate-petroleum ether (v/v) as eluent to yield the desired starting material **116** in (110 mg, 58 %) yield.

Spectral data of the substrate 116

2-((2-(2-oxoethyl)phenyl)ethynyl)benzoic acid (116): Yellowish gummy liquid (110 mg, 58% yield), R_f = 0.32 (70% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.81 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.66-7.63 (m, 2H), 7.56-7.55 (m, 1H), 7.42-7.41 (m, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.29 (t, *J* =7.2 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 4.03 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 200.1, 134.4, 132.8, 132.4, 132.3, 132.1, 131.3, 130.2, 129.1, 128.6, 128.5, 128.2, 127.5, 123.8, 93.1, 92.5, 49.0.



Procedure for the synthesis of 115a from substrate 116

A mixture of $Pd(OAc)_2$bpy (2.1 mg, 0.009 mmol, 5 mol %), and D-CSA (65.9 mg, 0.28 mmol, 1.5 equiv) in dry 1,4-dioxane (2 mL) was stirred at 90 ^oC for 5 min under argon atmosphere. Next the starting material **116** (0.19 mmol) dissolved in 1,4-dioxane (2 mL) was added to the reaction mixture at the same temperature and the whole mixture was allowed to stir at heating conditions (100 ^oC) 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 10% 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 20% ethyl acetate-petroleum ether (v/v) as eluent to afford desired product **115a** in (19.6 mg, 42 %) yield.

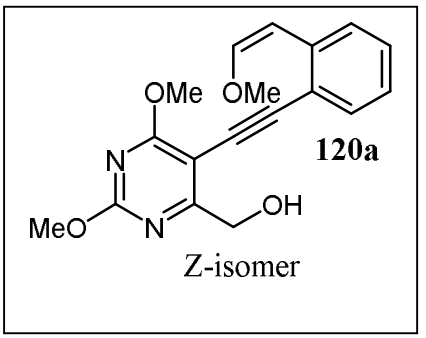
General procedure for the synthesis of substrates 120

To a well stirred and ice-cooled solution of 1-iodo-2-(2-methoxyvinyl)benzene derivatives **107** (0.77 mmol, 1 equiv) in Et_3N: DMF (4:1, 2 mL) were added $Pd(PPh_3)_2Cl_2$ (16.2 mg, 0.023 mmol, 3 mol %), (5-ethynyl-2,6-dimethoxypyrimidin-4-yl)methanol (164.9 mg, 0.85 mmol, 1.1 equiv), CuI (8.8 mg, 0.046 mmol, 6 mol %), successively. The whole the reaction mixture was then allowed to stir at room temperature under argon atmosphere. After completion of the reaction (TLC), solvent was removed under reduced pressure. The resulting crude mixture was extracted with ethyl acetate (3 × 30 mL); the combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100-200 mesh)

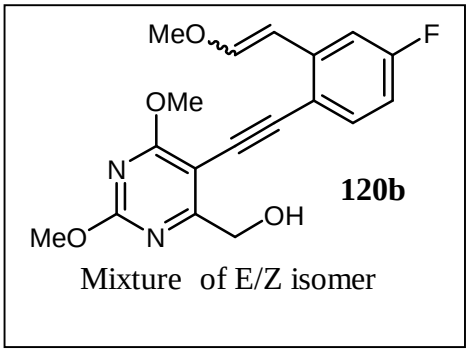
column chromatography and eluted with 10-40% ethyl acetate-petroleum ether (v/v) to afford the desired substrate **120** (62-75%).

Spectral data of the substrates 120a-c

(Z)-(2,6-dimethoxy-5-((2-(2-methoxyvinyl)phenyl)ethynyl)pyrimidin-4-yl)methanol (120a): (one isomer): yellow solid (170.7 mg, 68%), mp 97-99 ^{o}C; R_f = 0.67 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.08 (d, *J* = 8 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.28 (td, *J* = 7.8, 1.2 Hz, 1H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 6.27 (d, *J* = 7.2 Hz, 1H), 5.81 (d, *J* = 7.2 Hz, 1H), 4.85 (s, 2H), 4.08 (s, 3H), 4.06 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 170.74, 170.67, 163.1, 149.3, 137.2, 131.9, 128.75, 128.72, 125.5, 120.4, 103.1, 99.7, 95.9, 82.5, 62.4, 60.9, 55.3, 54.9. HRMS (ESI^+) m/z calculated for $C_{18}H_{19}N_2O_4$ $[M+H]^+$ 327.1345, found 327.1347.

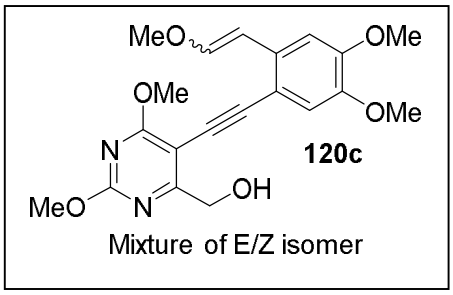


(5-((4-fluoro-2-(2-methoxyvinyl)phenyl)ethynyl)-2,6-dimethoxypyrimidin-4-yl)methanol (120b): (an inseparable mixture of E/Z isomers in the ratio 1:1): Yellow Solid (198.7 mg, 75% yield), mp 118- 120 ^{o}C; R_f = 0.63 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.85 (dd, *J* = 2.4, 11.4 Hz), 7.45-7.42 (m), 7.20 (d, *J* = 12.6 Hz), 7.05 (dd, *J* = 2.4, 10.2 Hz), 6.83 (t, *J* = 8.4 Hz), 6.32 (d, *J* = 7.2 Hz), 6.27 (d, *J* = 13.2 Hz), 5.80 (d, *J* = 7.2 Hz), 4.86-4.84 (m), 4.08 (s), 4.07 (s), 3.84 (s), 3.76 (s) ; ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 170.6 (d, *J* = 13.5 Hz), 163.0 (d, *J* = 6 Hz), 162.0, 151.4, 150.3, 140.5 (d, *J* = 9 Hz), 139.3 (d, *J* = 9 Hz), 134.1 (*J* = 10.5 Hz), 133.4 (d, *J* = 9 Hz), 116.3 (d, *J* = 3 Hz), 116.1 (d, *J* = 1.5 Hz), 115.4, 115.3, 112.9, 112.7, 110.2, 110.1, 102.7 (d, *J* = 3 Hz), 102.3 (d, *J* = 3 Hz),



98.6, 98.4, 95.7, 95.6, 82.25, 82.01, 62.2, 61.1, 56.5, 55.3, 55.24, 54.9, 54.8. HRMS (ESI^+) m/z calculated for $C_{18}H_{18}FN_2O_4$ $[M+H]^+$ 345.1251, found 345.1255.

(5-((4,5-dimethoxy-2-(2-methoxyvinyl)phenyl)ethynyl)-2,6-dimethoxypyrimidin-4-yl)methanol (120c): (an inseparable mixture of E/Z isomers in the ratio 7:3): Yellow Solid (184.5 mg, 62% yield) mp 101-103 oC; R_f = 0.39 (40% ethyl acetate in petroleum ether, v/v); ^1H NMR ($CDCl_3$, 600 MHz) δ_H 7.71 (s), 7.12 (d, *J* = 12.6 Hz), 6.93 (s), 6.92 (s), 6.82 (s), 6.25 (d, *J* = 13.2 Hz), 6.21 (d, *J* = 7.2 Hz), 5.77 (d, *J* = 7.2 Hz), 4.87 (s), 4.09 (s), 4.07 (s), 3.91 (s), 3.89(s), 3.81 (s), 3.74 (s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 170.5, 170.2, 162.8, 149.9, 149.4, 147.1, 131.9, 114.2, 111.9, 106.4, 103.2, 99.5, 95.9, 81.3, 62.3, 56.4, 56.0, 55.8, 55.2, 54.8. HRMS (ESI^+) m/z calculated for $C_{20}H_{23}N_2O_6$ $[M+H]^+$ 387.1556, found 387.1558.

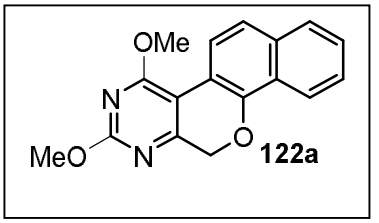


General procedure for the synthesis of 2,4-dimethoxy-12H-benzo[7,8]chromeno[3,4-d] pyrimidine 122

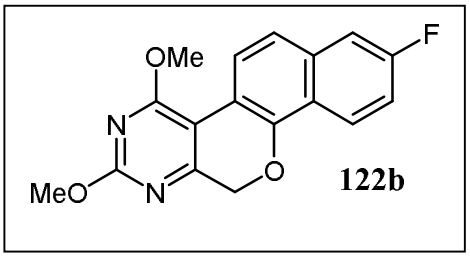
A mixture of $Pd(OAc)_2$bpy (5.7 mg, 0.015 mmol, 5 mol%), DCSA (139.2 mg, 0.6 mmol, 2 equiv.) in dry NMA (2 mL) was stirred at 90 °C for 5 min under argon atmosphere. The substrate **120** (0.3 mmol, 1 equiv.) dissolved in NMA (1.0 mL) was then added dropwise and the whole mixture was allowed to stir 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 **122** in 50–65% yield.

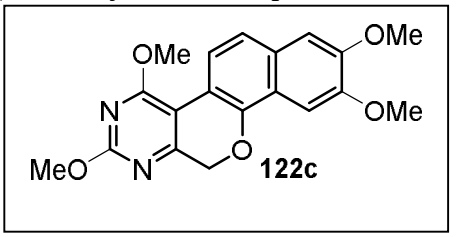
2,4-Dimethoxy-12H-benzo[7,8]chromeno[3,4-d]pyrimidine (122a): Pale yellow solid (49.4 mg, 56% yield), mp 119–121°C, R_f = 0.43 (20% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.84 (d, *J* = 1.2 Hz, 1H), 7.57-7.55(m,2H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.27–7.24 (m, 1H), 7.19 (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 (122b): 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 (122c): 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,

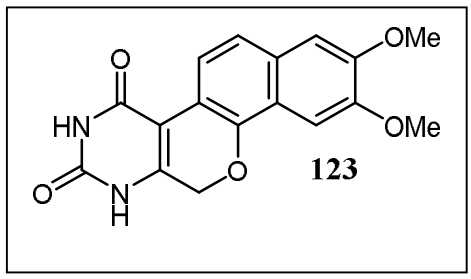


3H), 4.01(s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C 166.6, 163.5, 161.4, 150.1, 149.4, 148.1, 129.8, 122.5, 119.9, 119.8, 111.9, 106.1, 105.8, 100.8, 69.2, 56.0, 55.9, 54.9, 54.3; HRMS (ESI^+) m/z calculated for $C_{19}H_{19}N_2O_5$ $[M+H]^+$ 355.1294, found 355.1299.

General procedure for the synthesis of 8,9-dimethoxy-1H-benzo[7,8]chromeno[3,4-d]pyrimi-dine-2,4(3H,12H)-dione (123)

To a well stirred and ice-cooled solution of **122c** (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 **123.**

8,9-Dimethoxy-1H-benzo[7,8]chromeno[3,4-d]pyri-midine-2,4(3H,12H)-dione (123): Pale yellow solid (16.4 mg, 58% yield), mp >260 °C; ^{1}H NMR (DMSO-d6, 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.



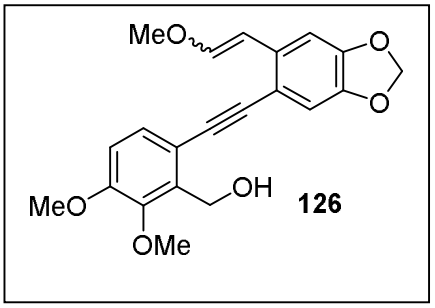
123

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 **124**[75] (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 **125**[33] (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 **126** in 68% yield.

(2,3-Dimethoxy-6-((6-(2-methoxyvinyl)benzo [d][1,3]dioxol-5-yl)ethynyl) phenyl) methanol (126) (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.

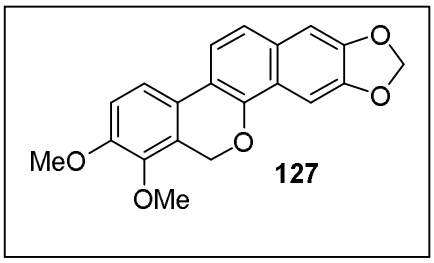


126

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 **126** (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 **127**.

1,2-Dimethoxy-13H-[1,3]dioxolo[4',5':4,5]benzo [1,2-h]benzo[*c*]chromene (127): 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.



127

2.2.15. References:

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72. β-Hydride elimination from intermediate species E might be ruled out as it would not lead to the desired product **100/101**

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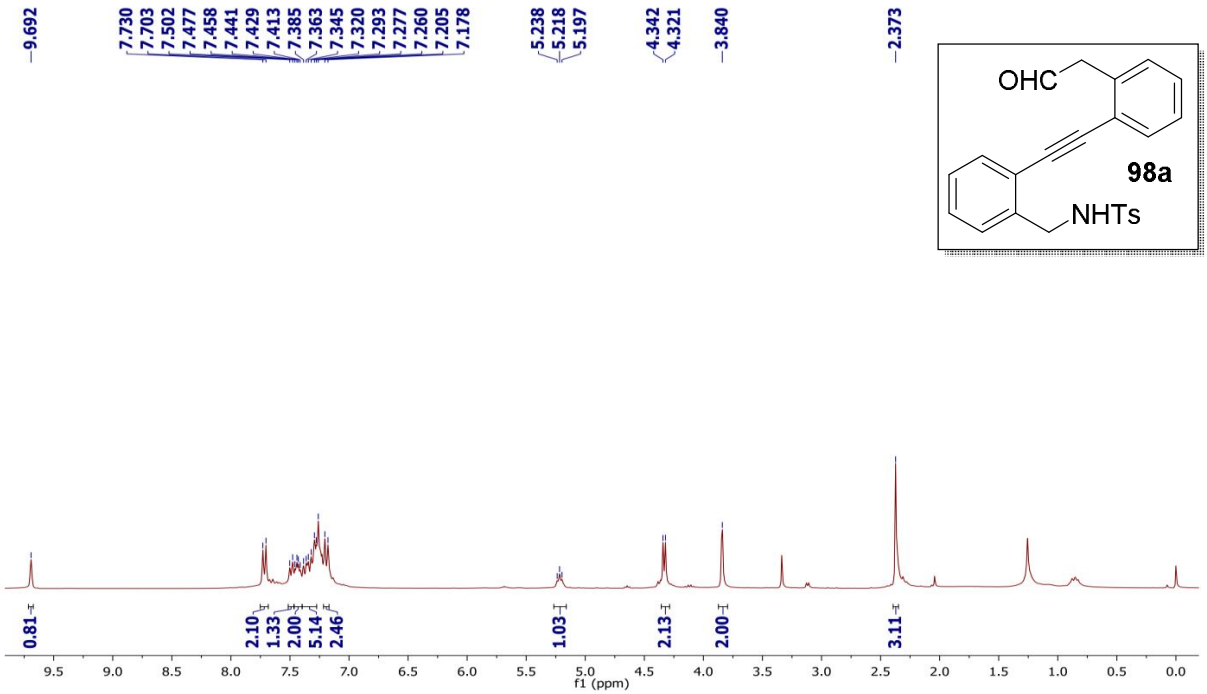
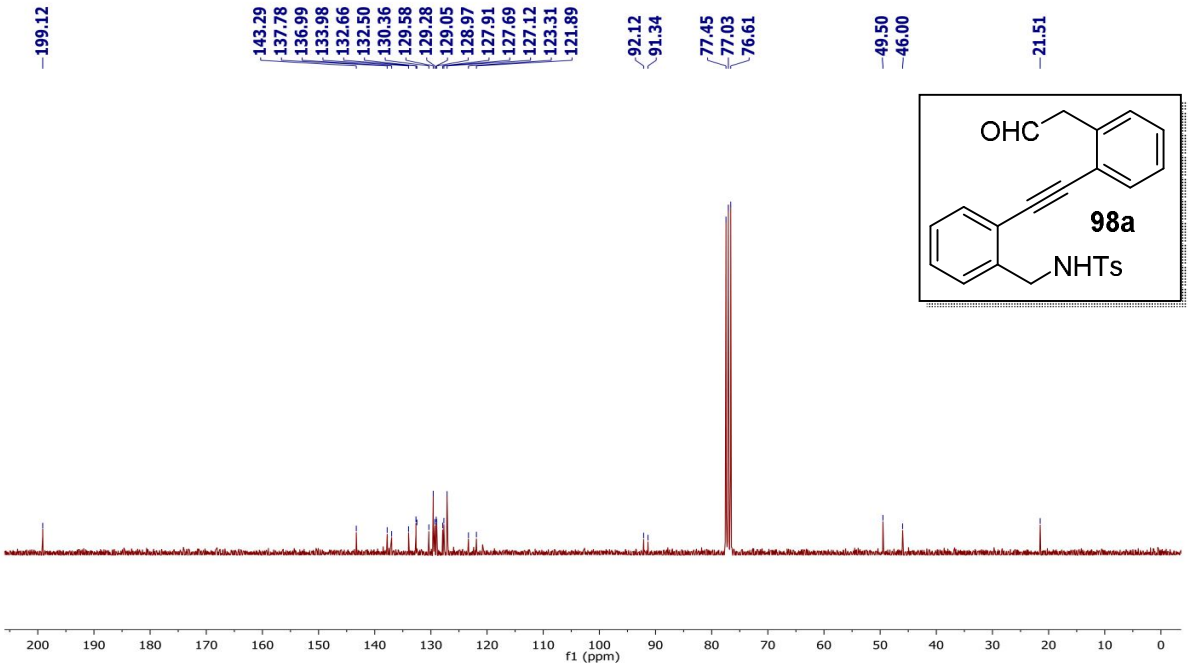
2.2.16. Copies of NMR spectra

NMR Spectra of Compounds 98a –f:

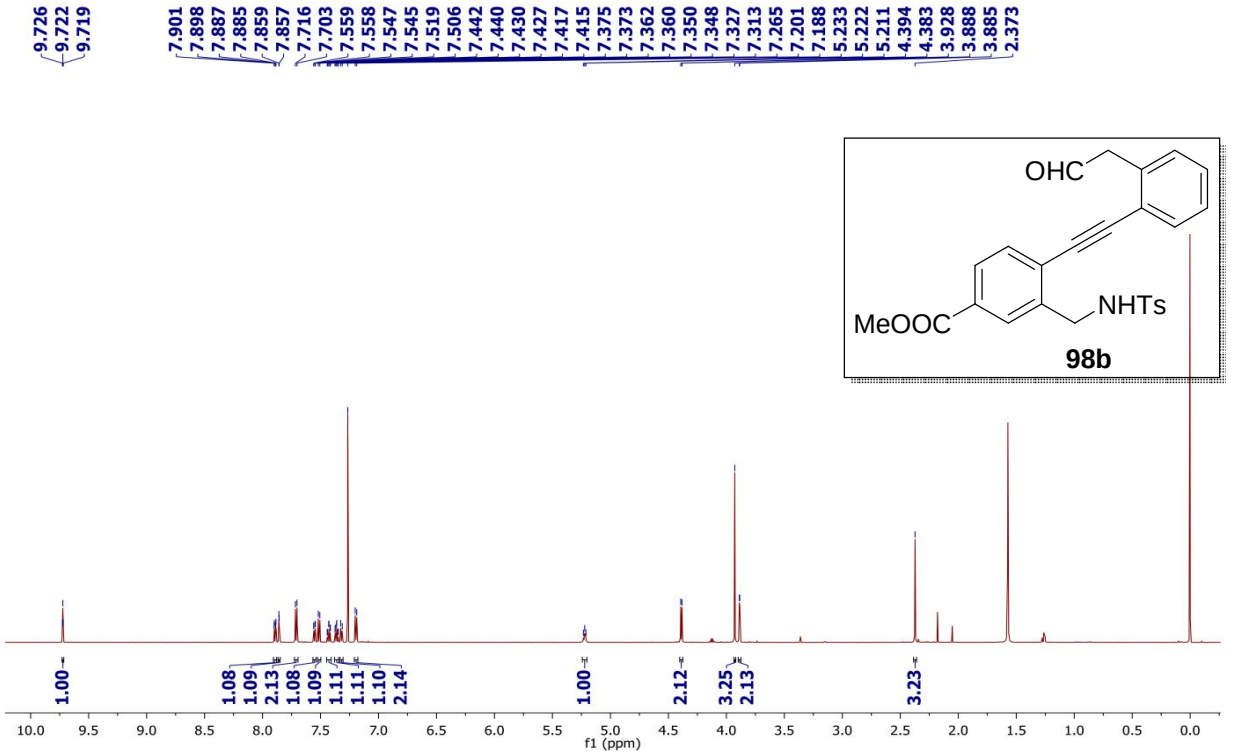
^{1}H NMR (300 MHz) of **98a:**



^{13}C NMR (75 MHz) of **98a:**



^{1}H NMR (150 MHz) of **98b:**



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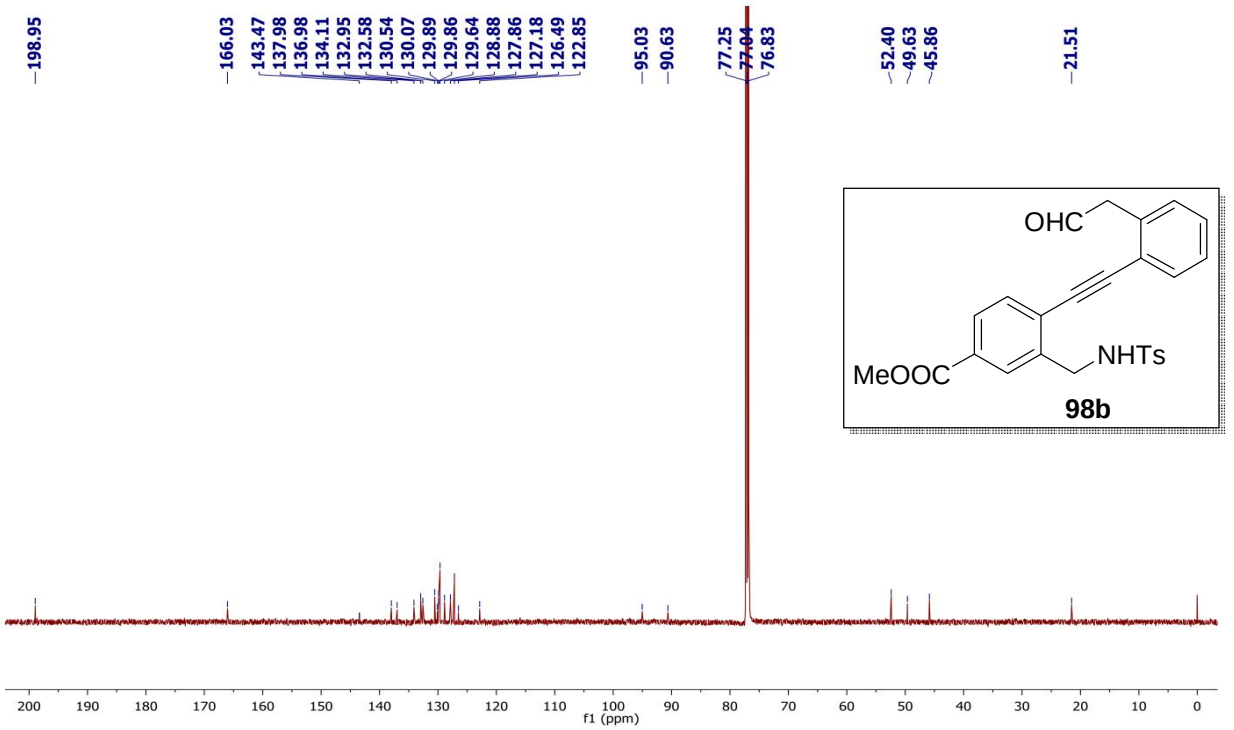
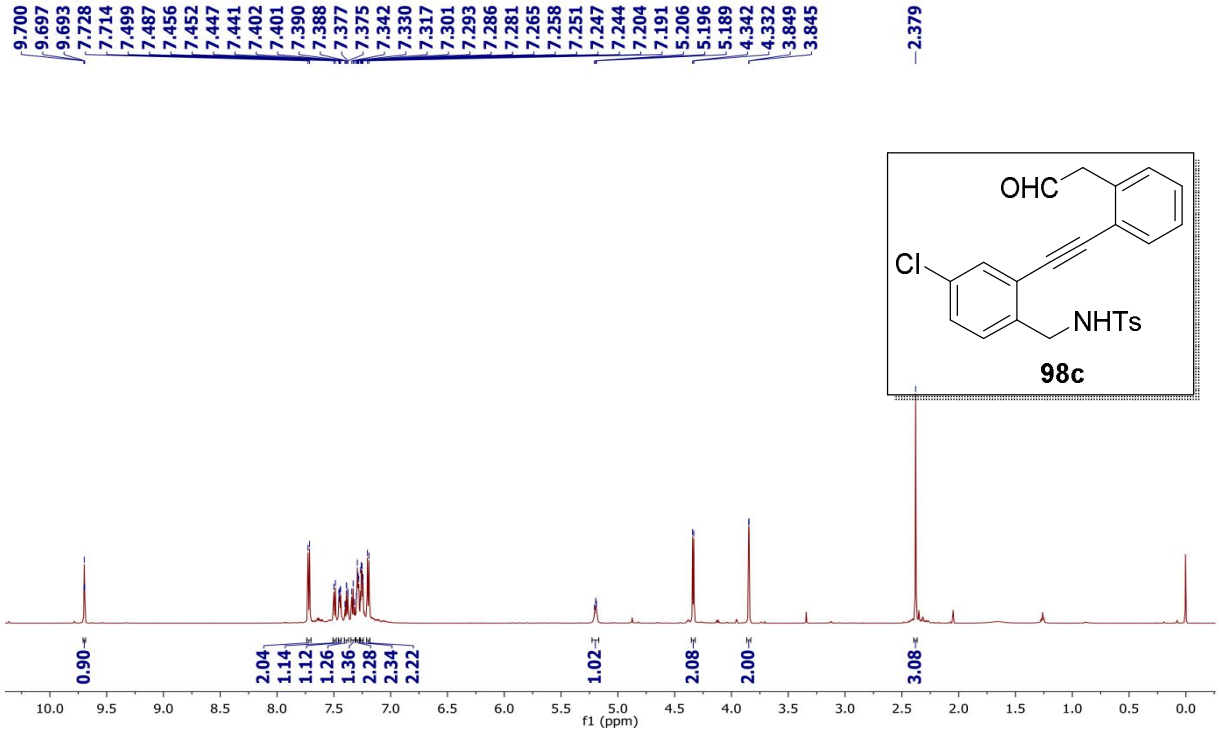
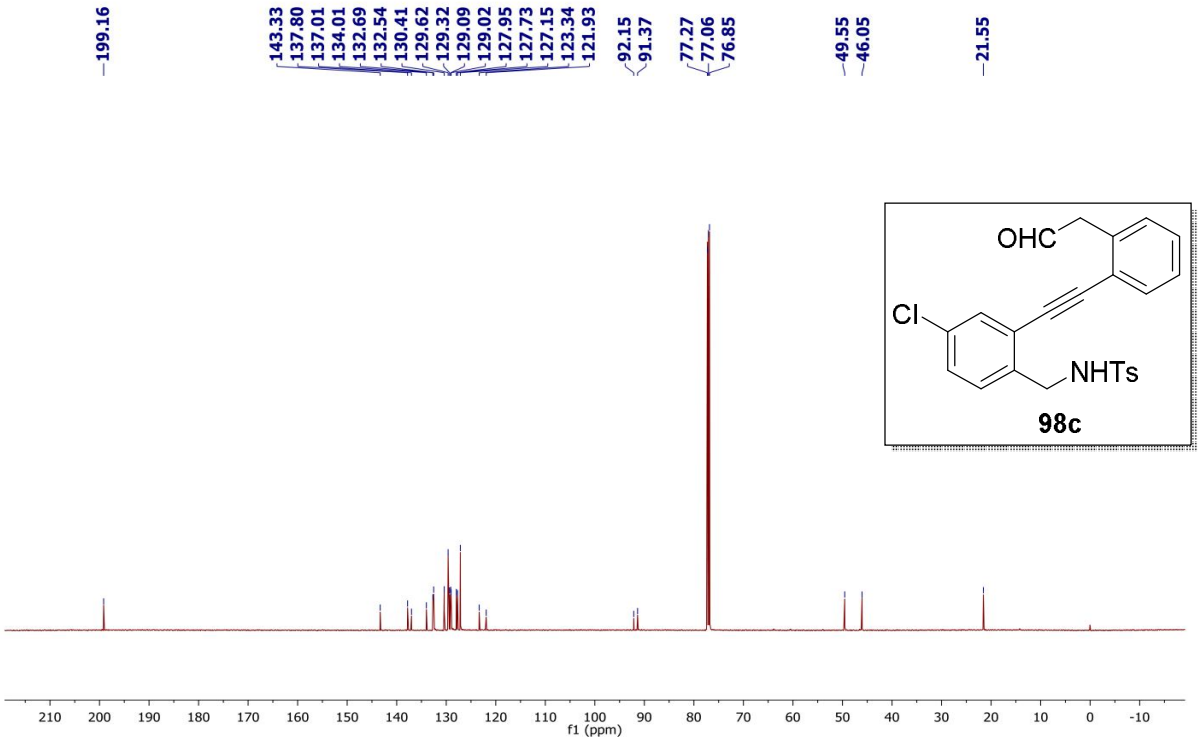


^{1}H NMR (600 MHz) of **98c:**



^{13}C NMR (150 MHz) of **98c:**



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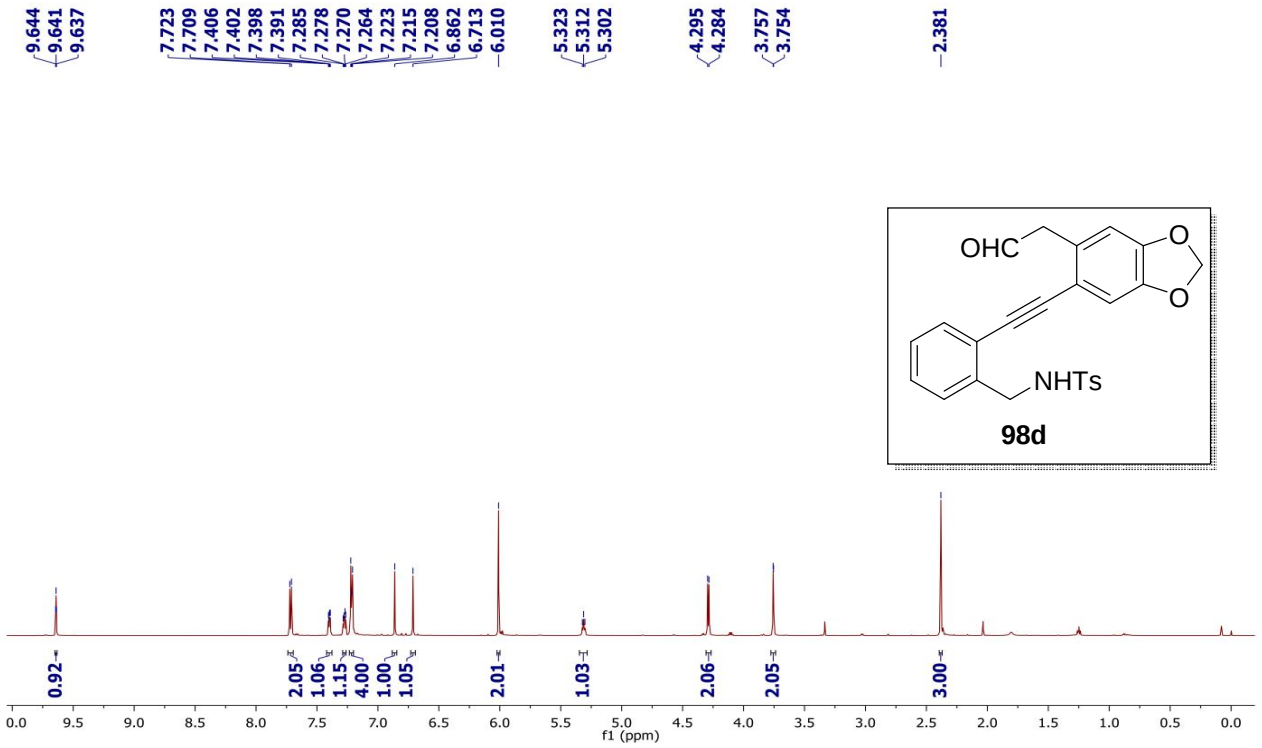
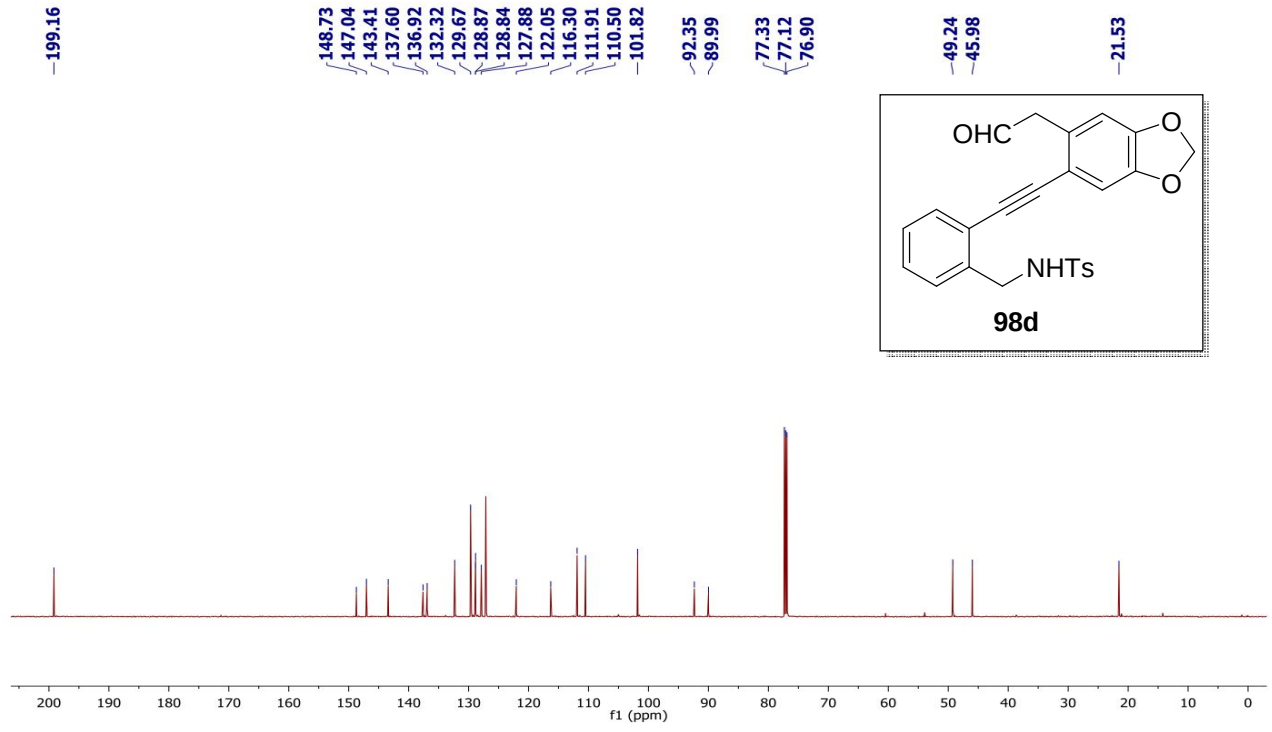
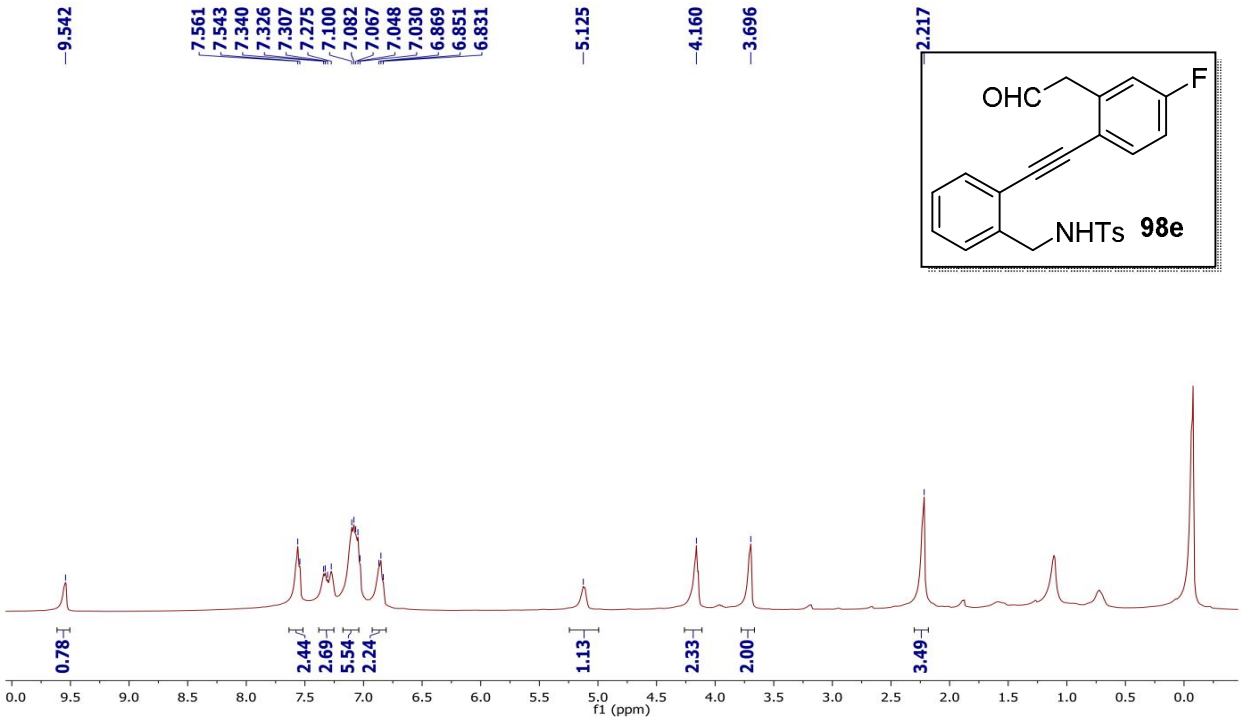


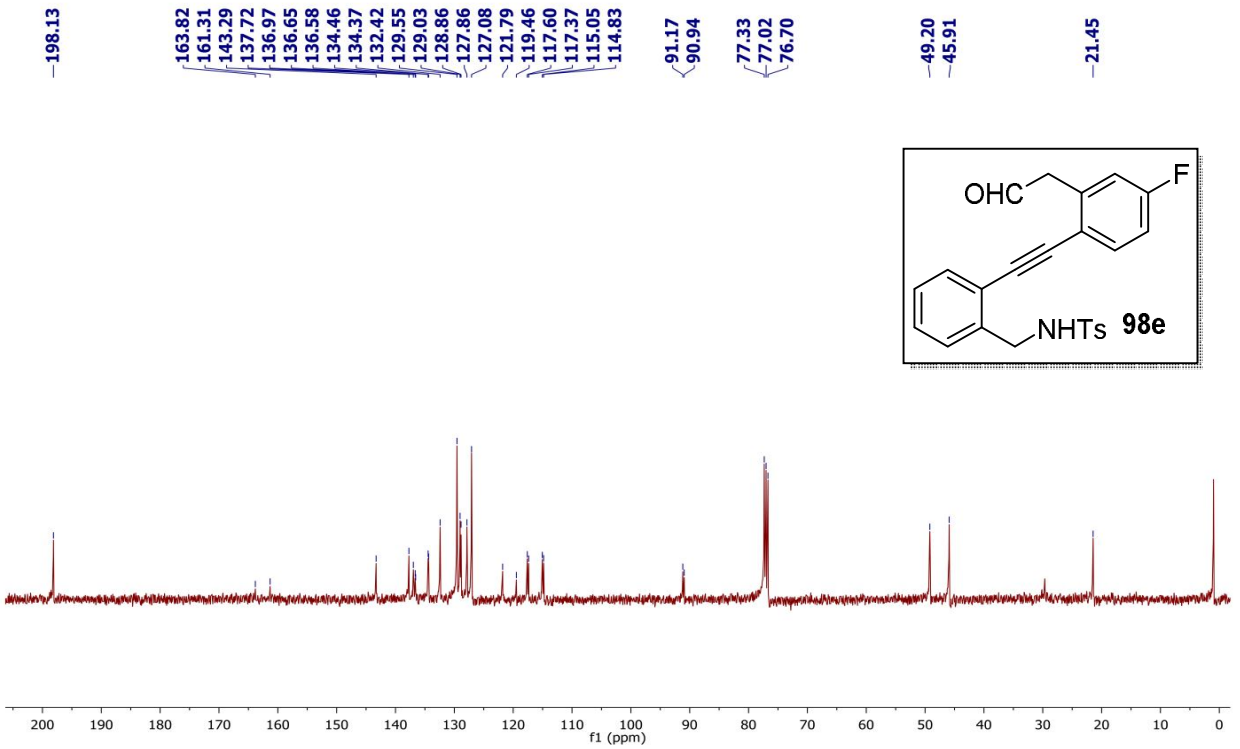
^{13}C NMR (150 MHz) of **98d:**



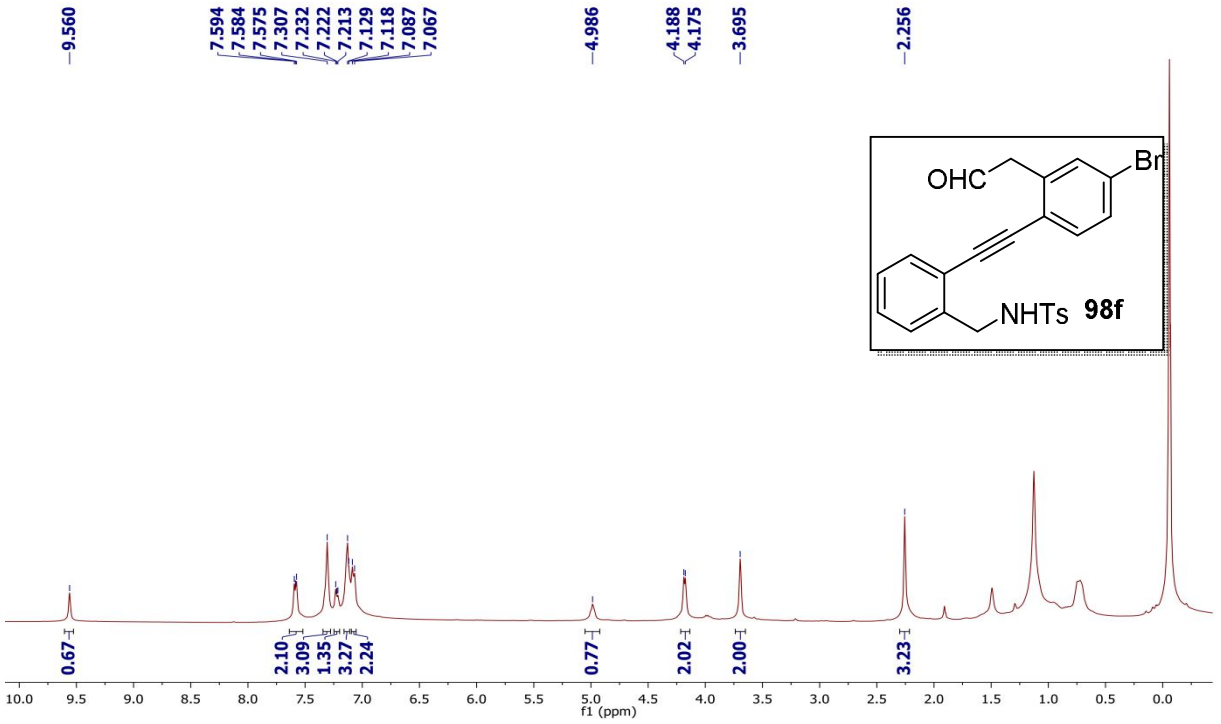
^{1}H NMR (400 MHz) of **98e:**



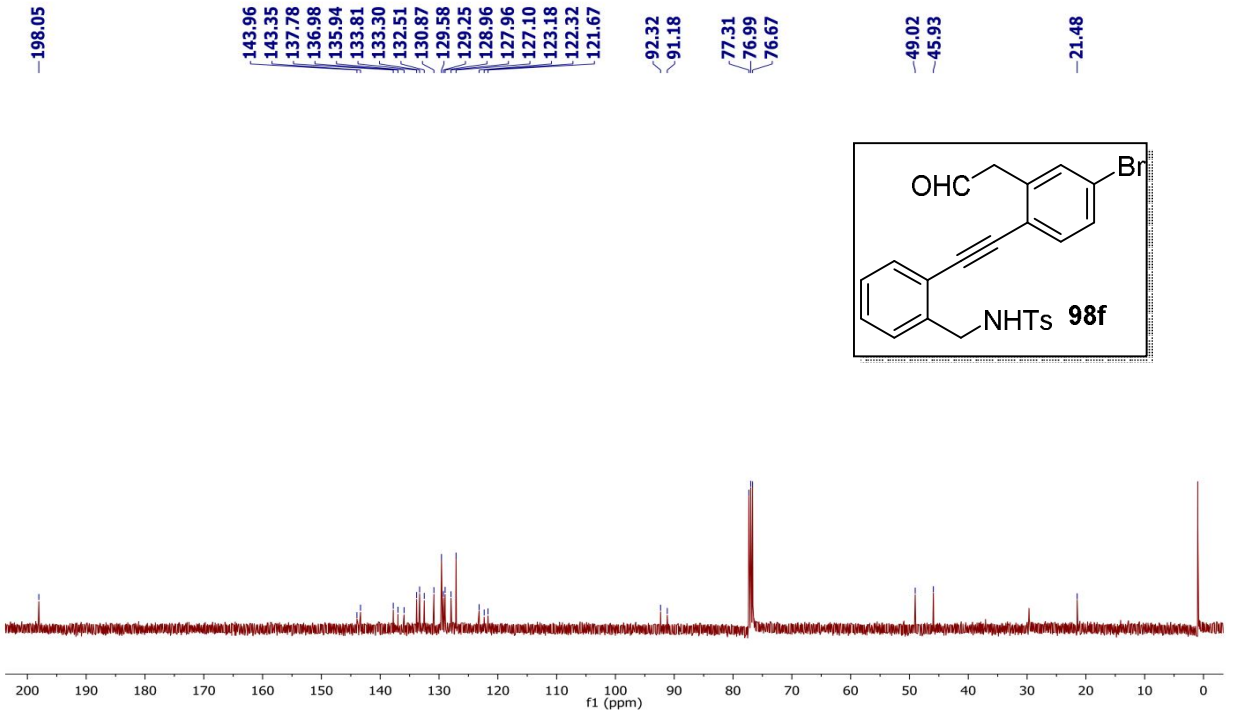
^{13}C NMR (100 MHz) of **98e:**



^{1}H NMR (400 MHz) of **98f:**

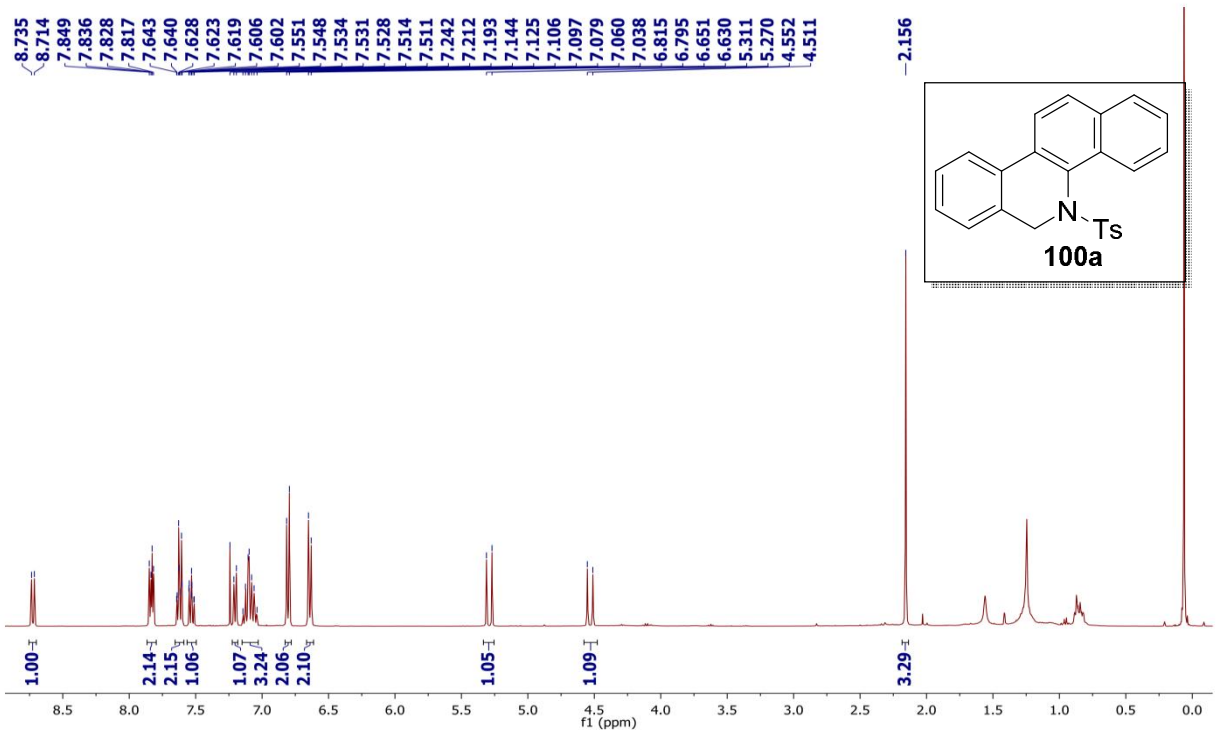


^{13}C NMR (100 MHz) of **98f:**

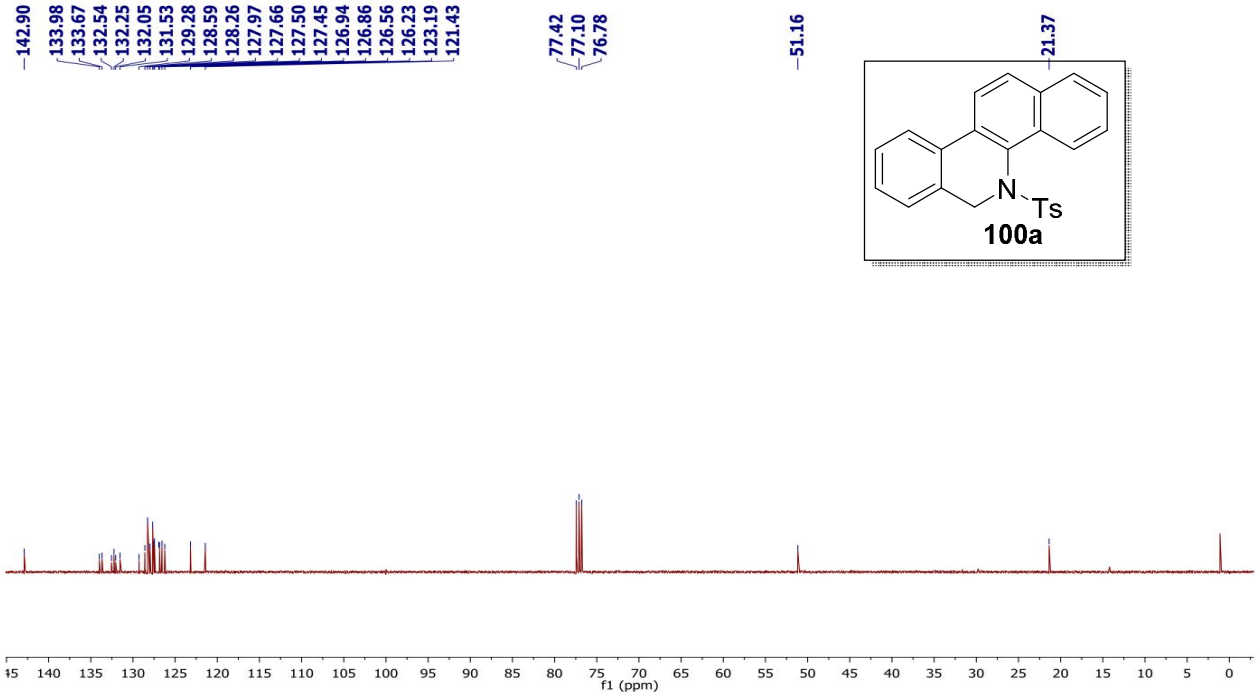


NMRS pectra of Compounds 100a–f :

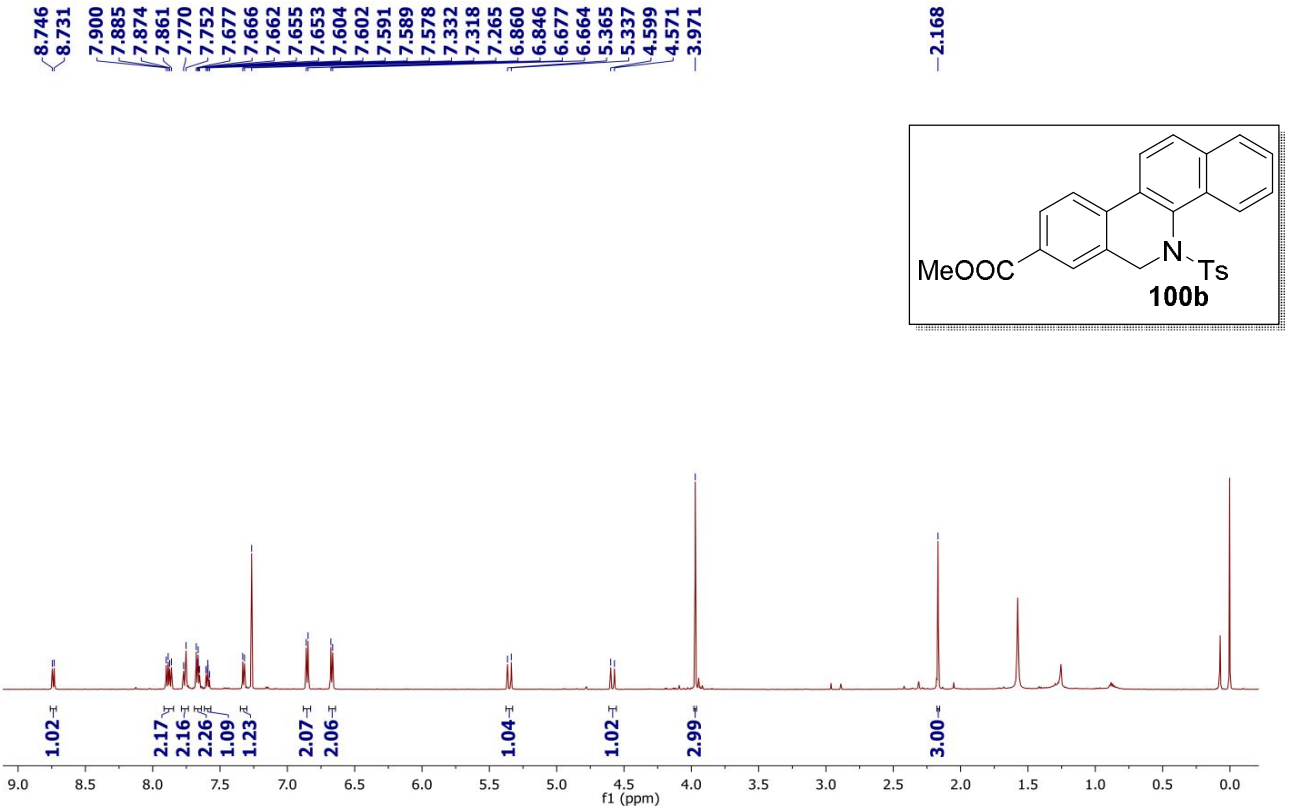
^{1}H NMR (400 MHz) of **100a:**



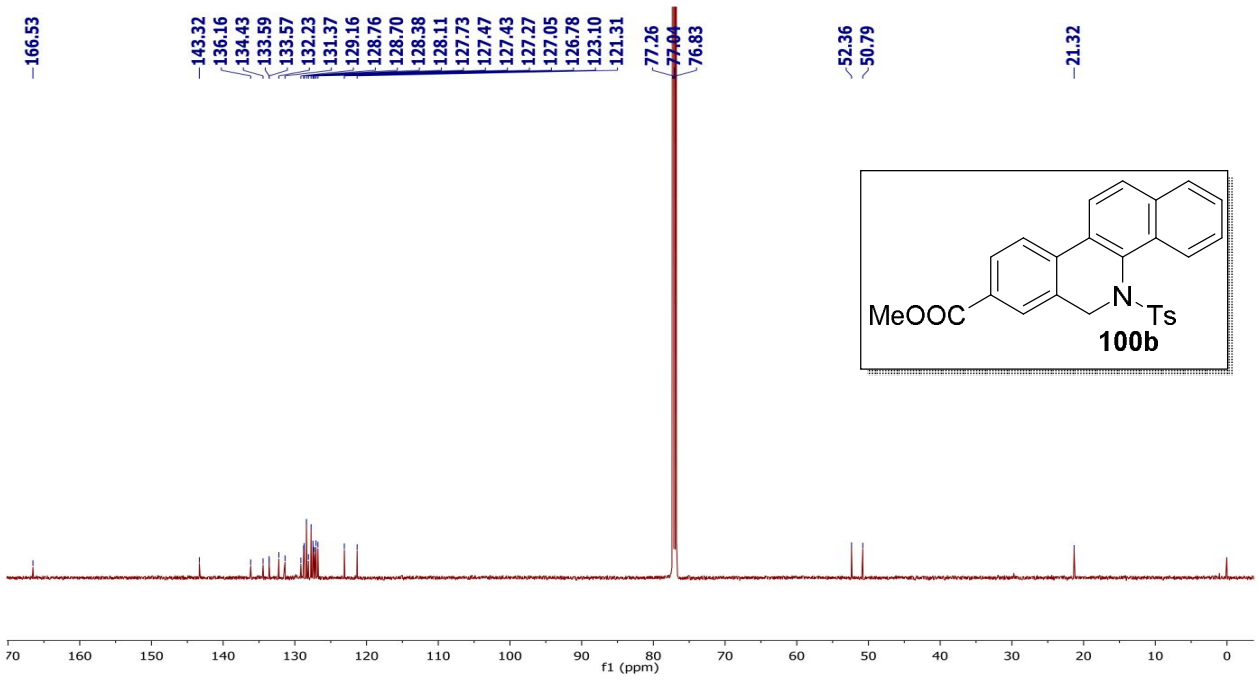
^{13}C NMR (100 MHz) of **100a:**



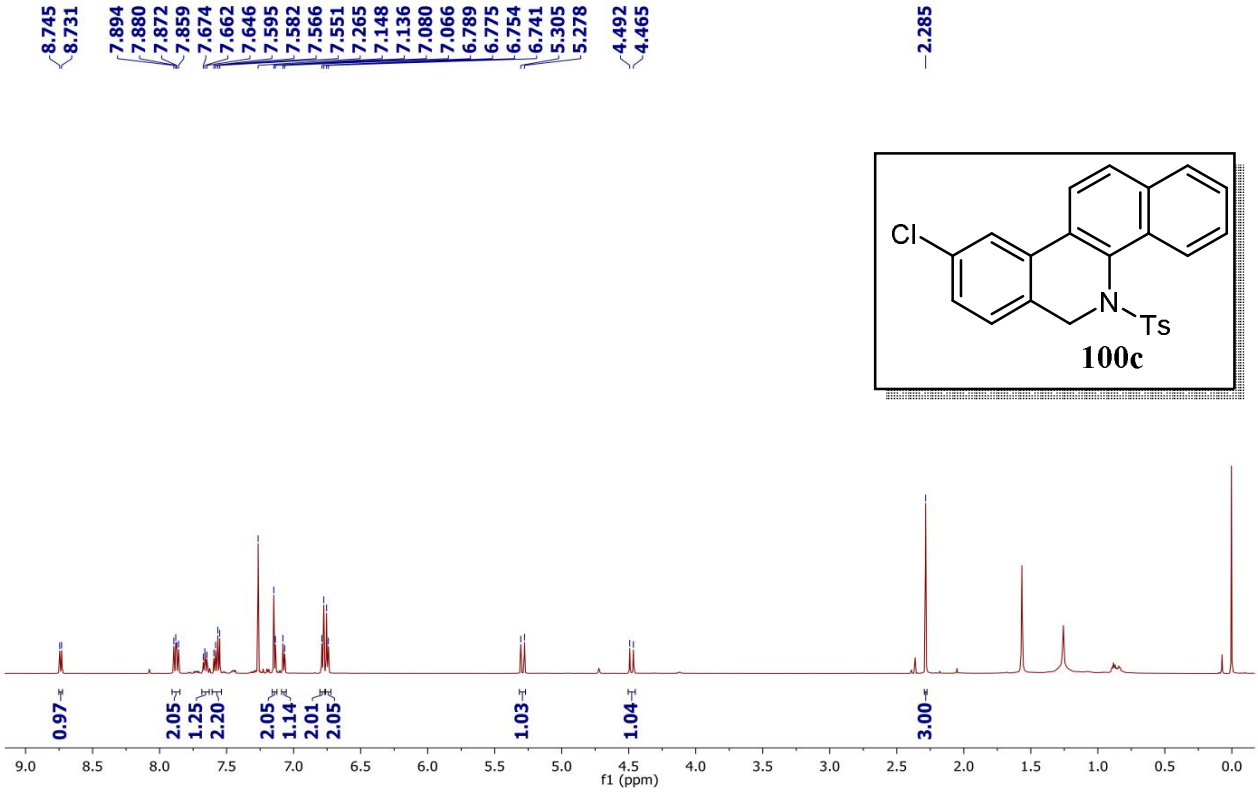
^{1}H NMR (600 MHz) of **100b:**



^{13}C NMR (150 MHz) of **100b:**



^{1}H NMR (600 MHz) of **100c:**



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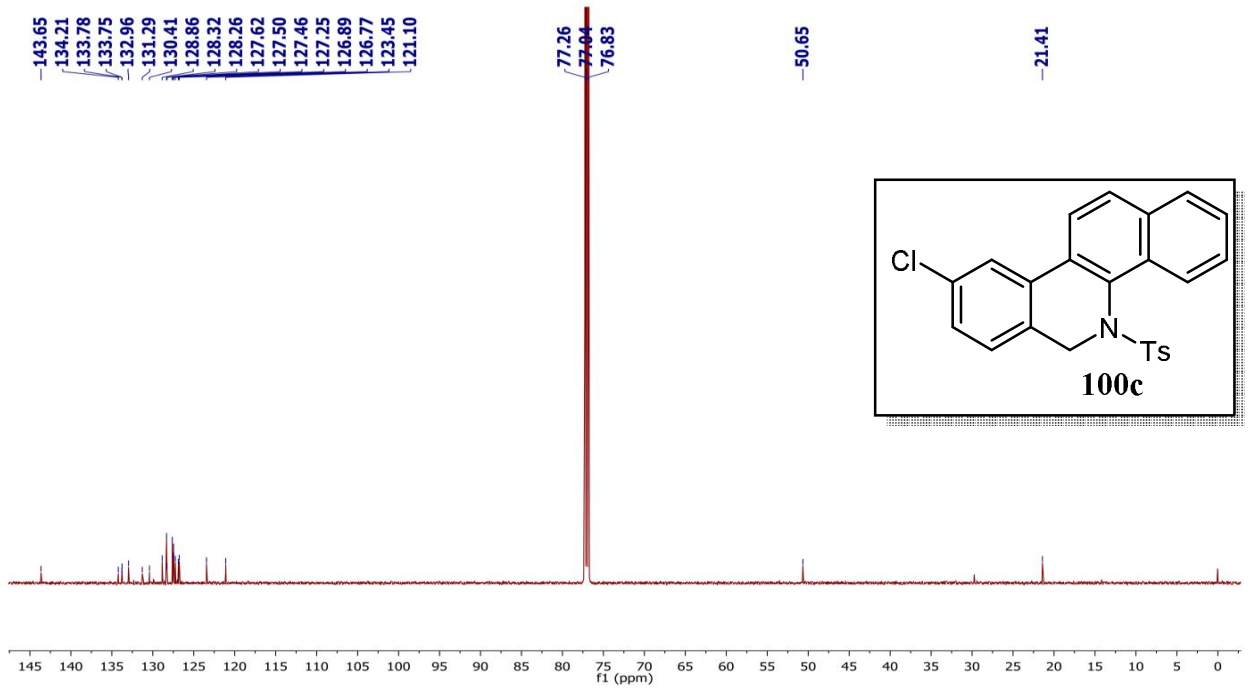
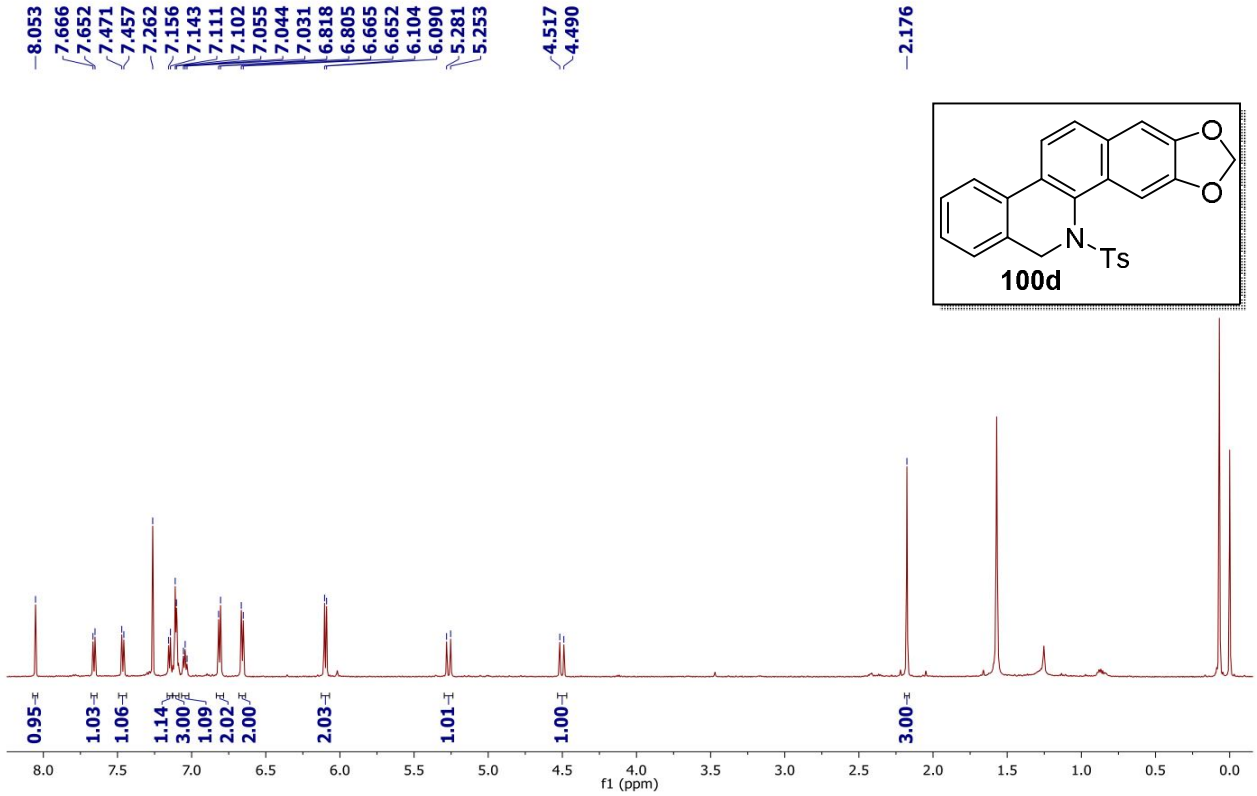


^{1}H NMR (600 MHz) of **100d:**



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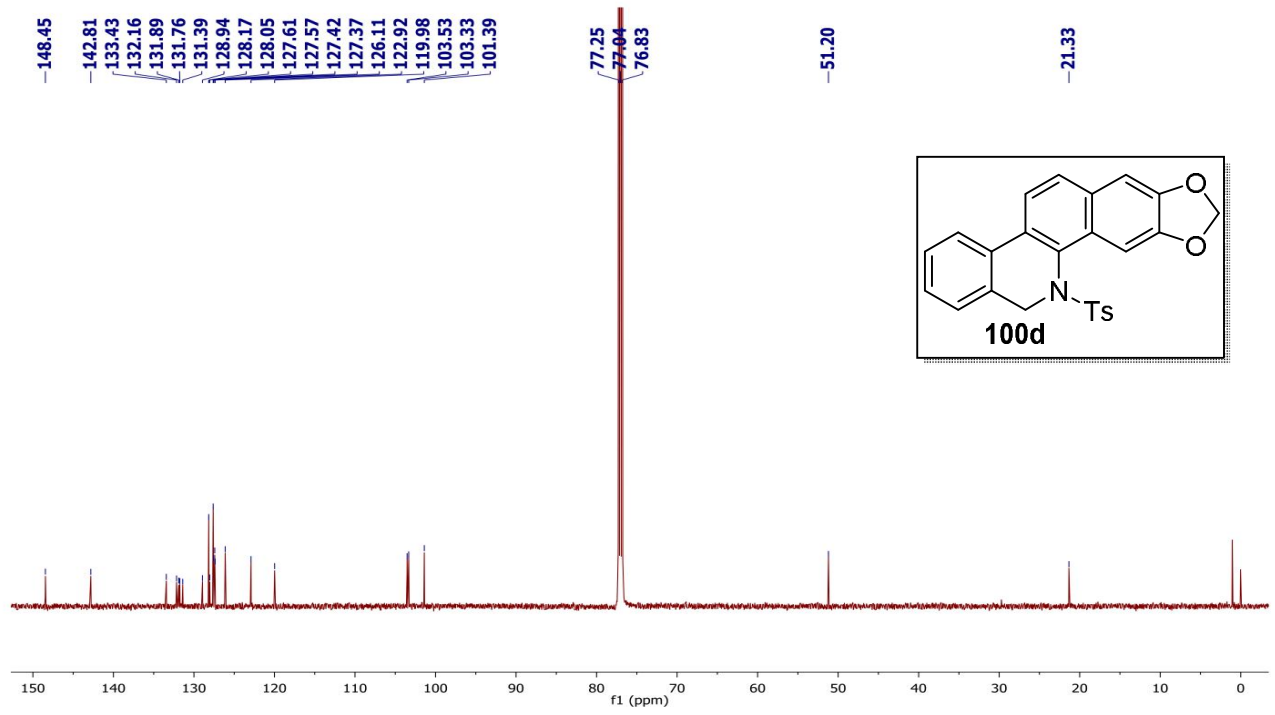
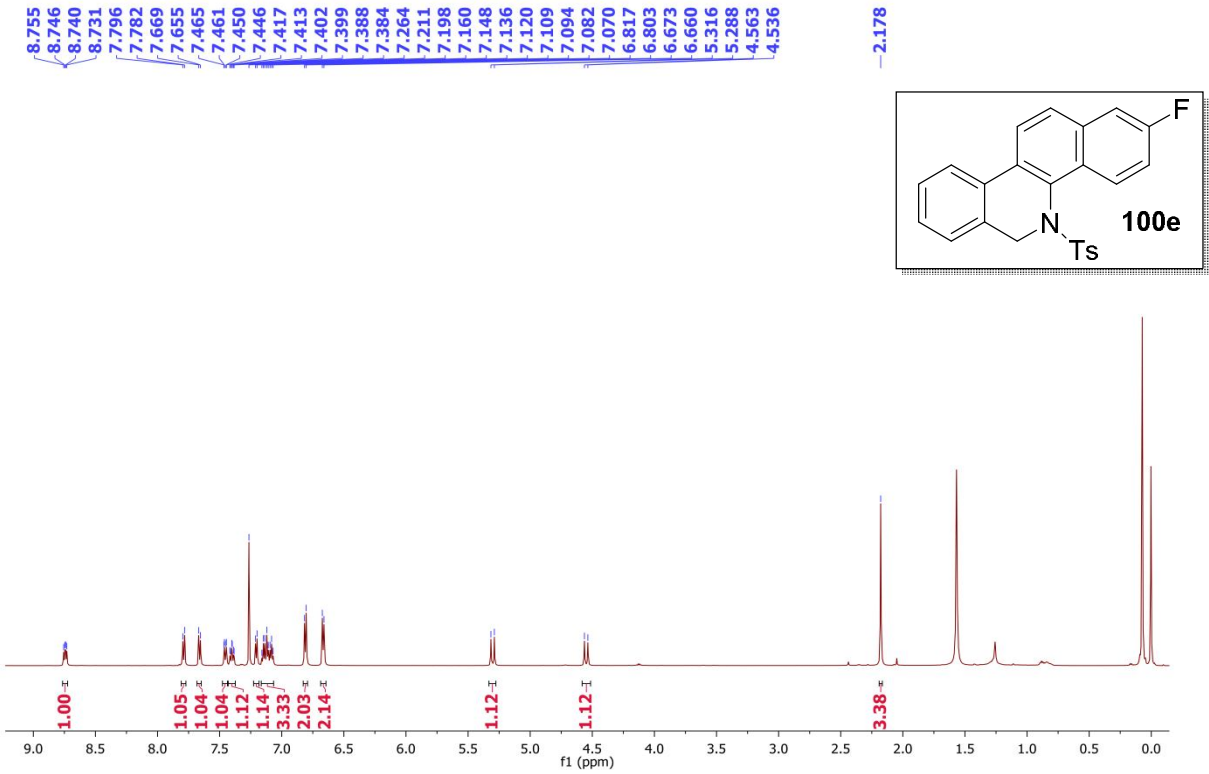
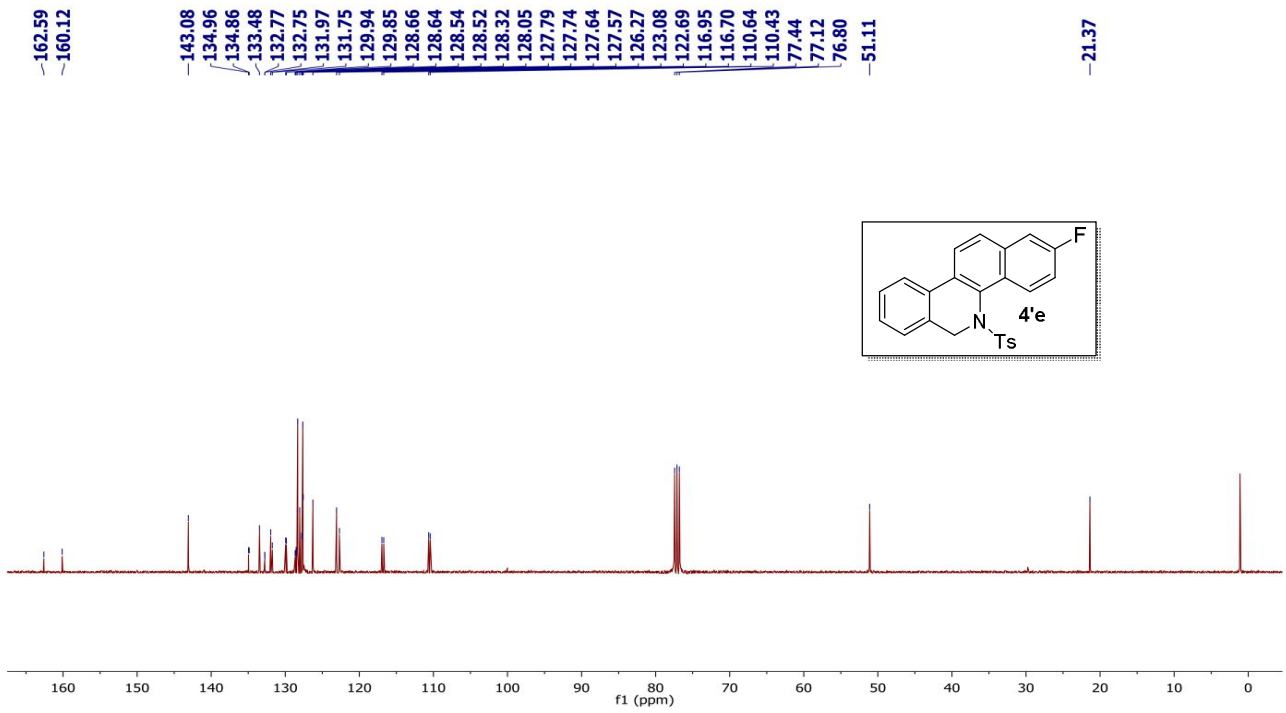


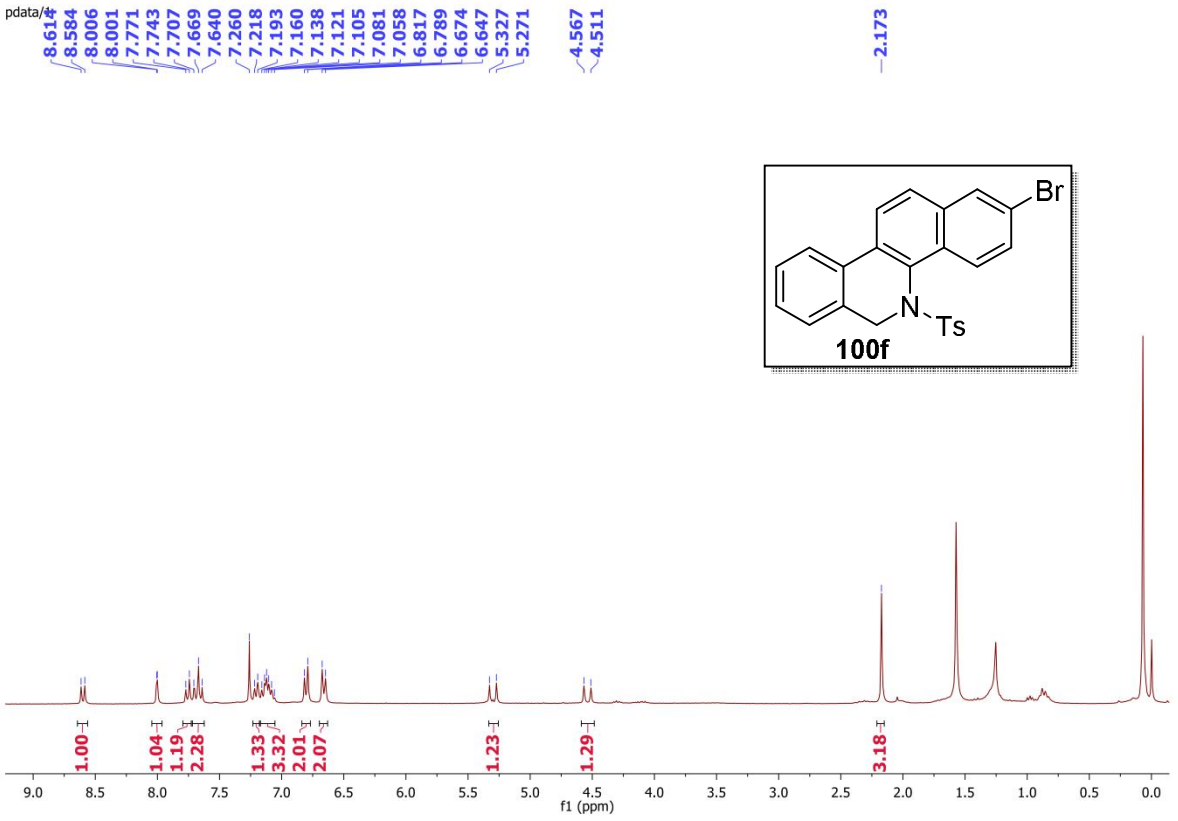
^{1}H NMR (600 MHz) of **100e:**



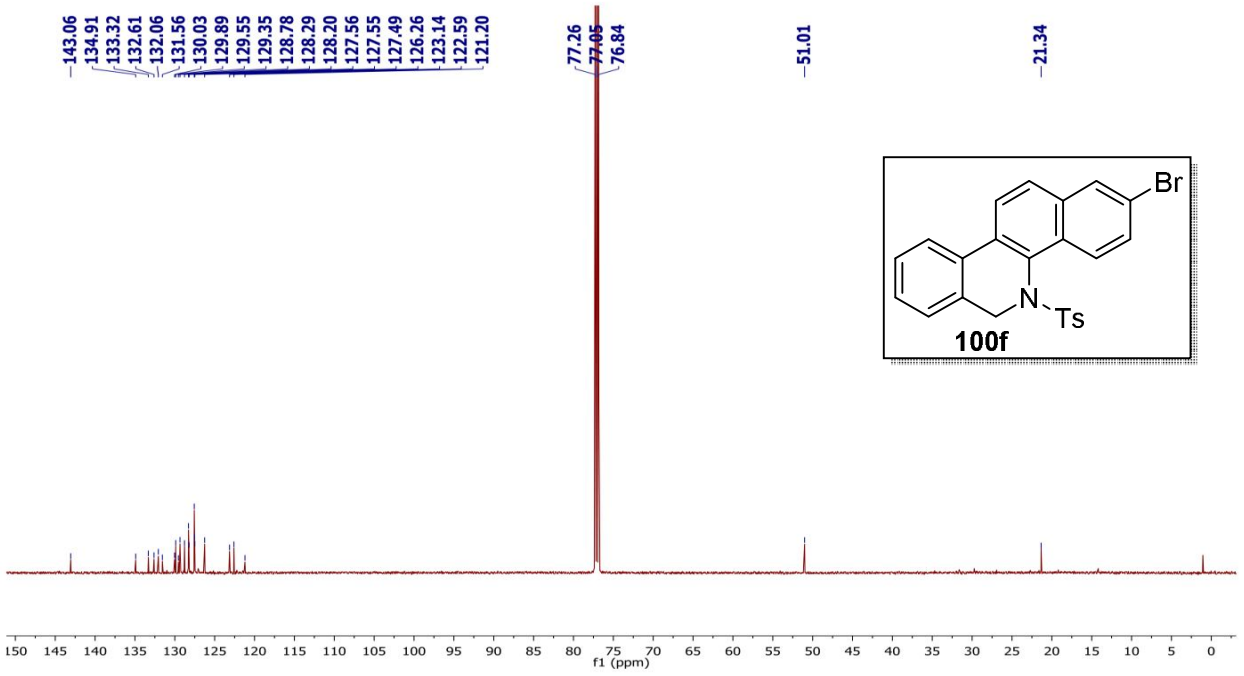
^{13}C NMR (100 MHz) of **100e:**



^{1}H NMR (300 MHz) of **100f:**

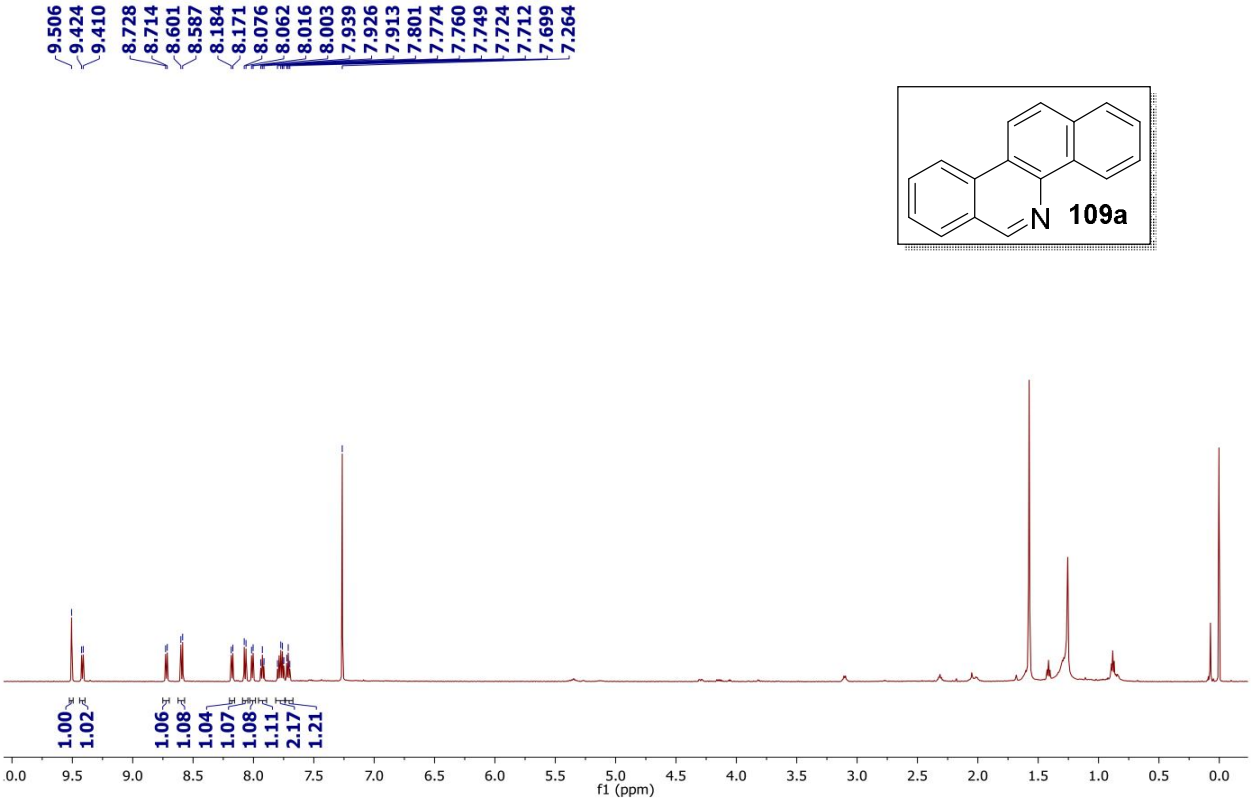


^{13}C NMR (150 MHz) of **100f:**

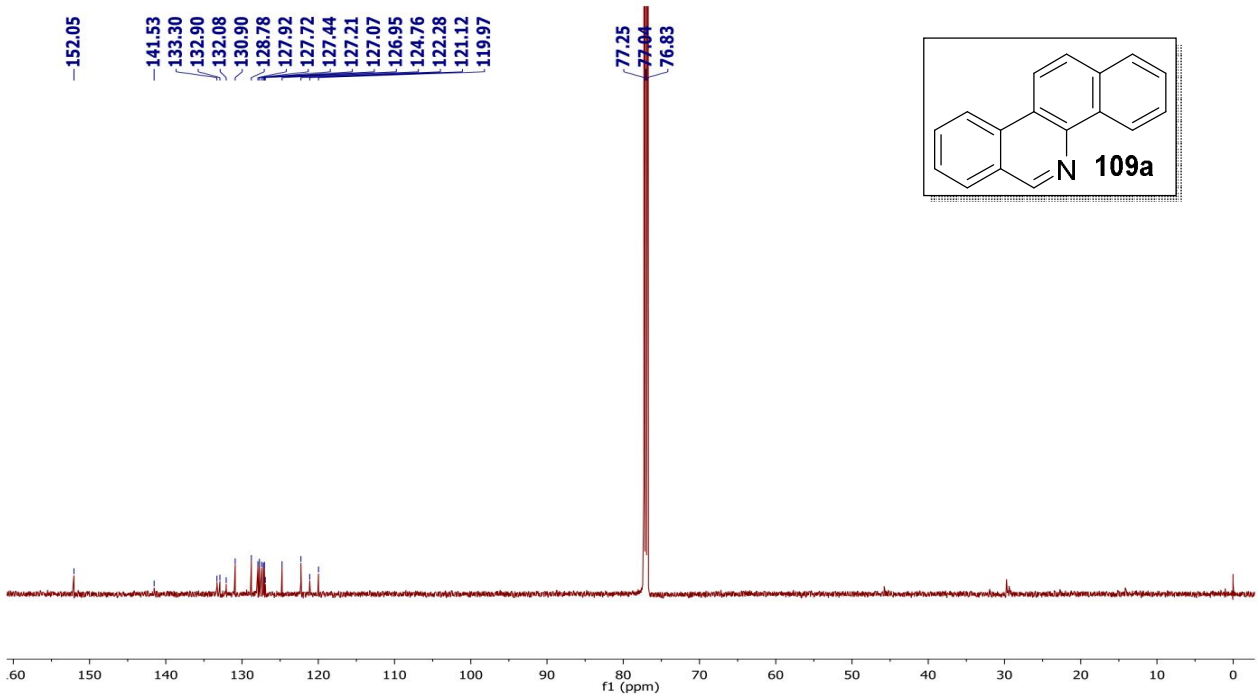


NMR Spectra of Compounds 109a–d:

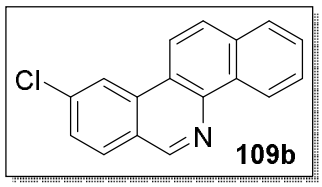
^{1}HNMR (600 MHz) of **109a:**

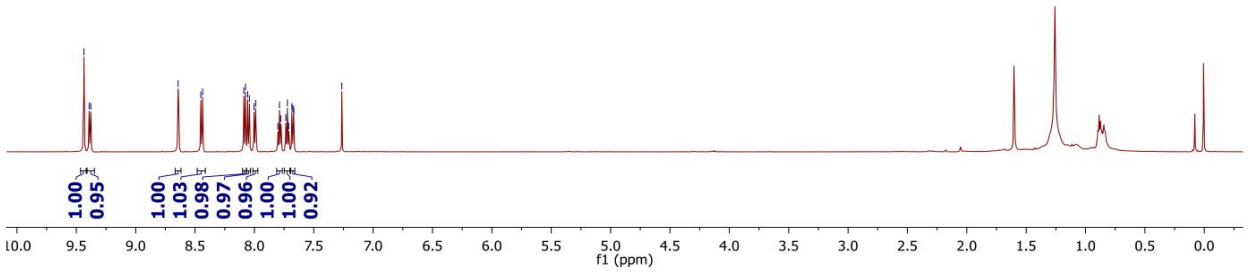


^{13}C NMR (150 MHz) of **109a:**

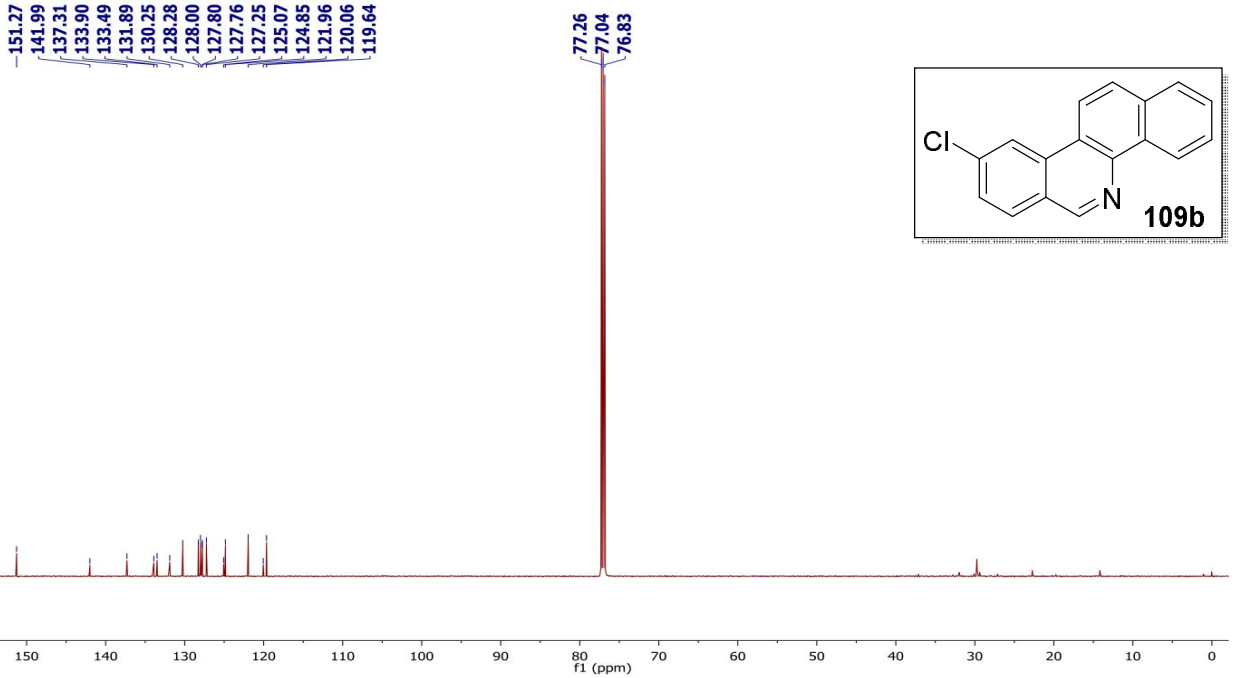


^{1}HNMR (600 MHz) of **109b:**

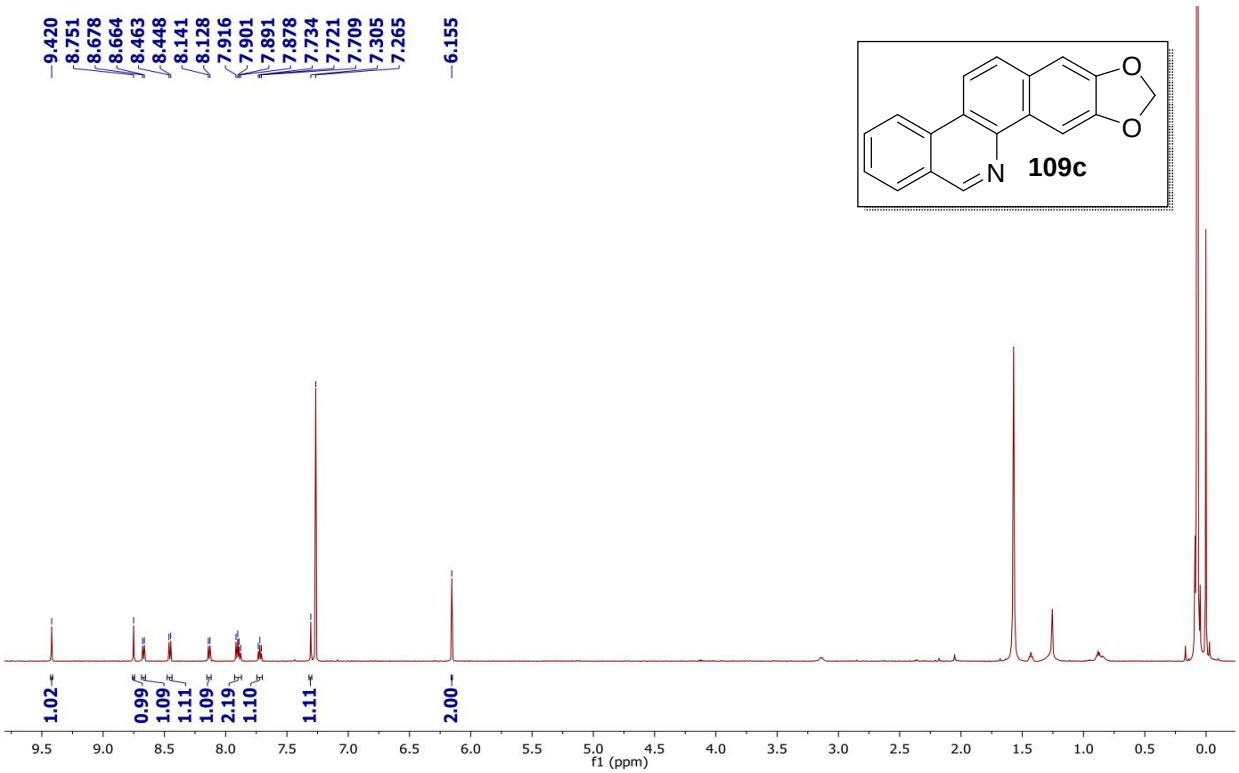




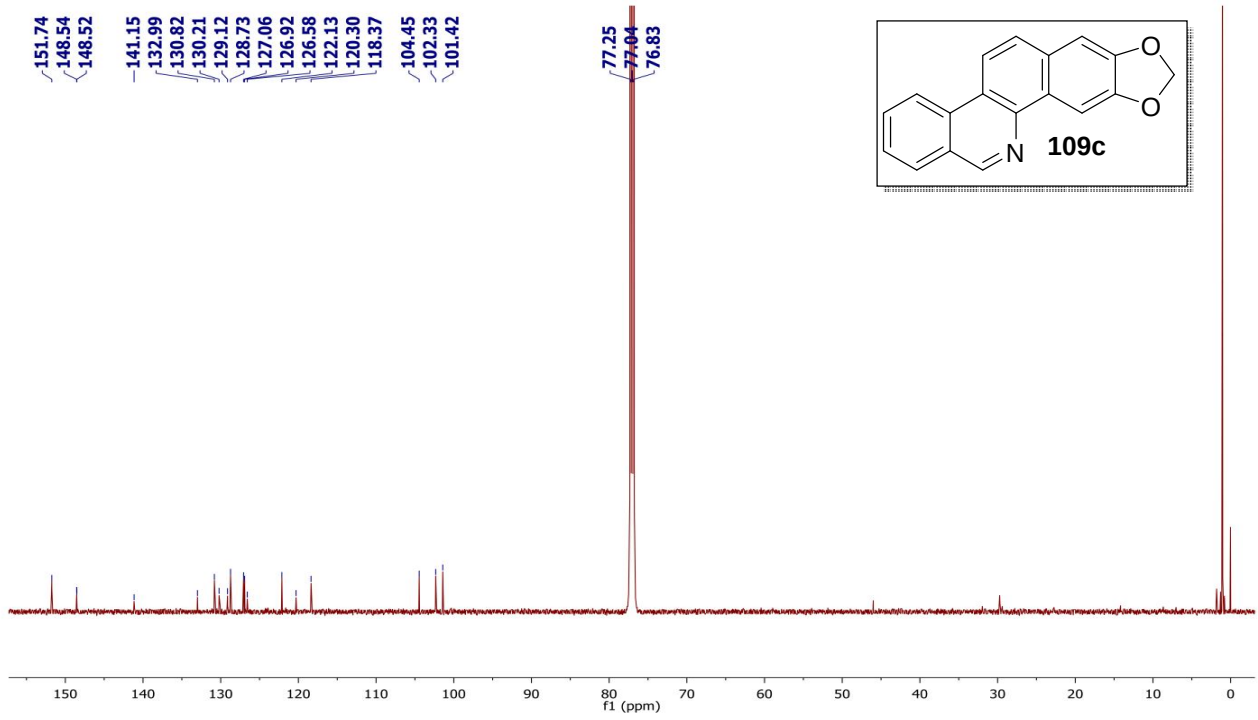
^{13}C NMR (150 MHz) of **109b:**



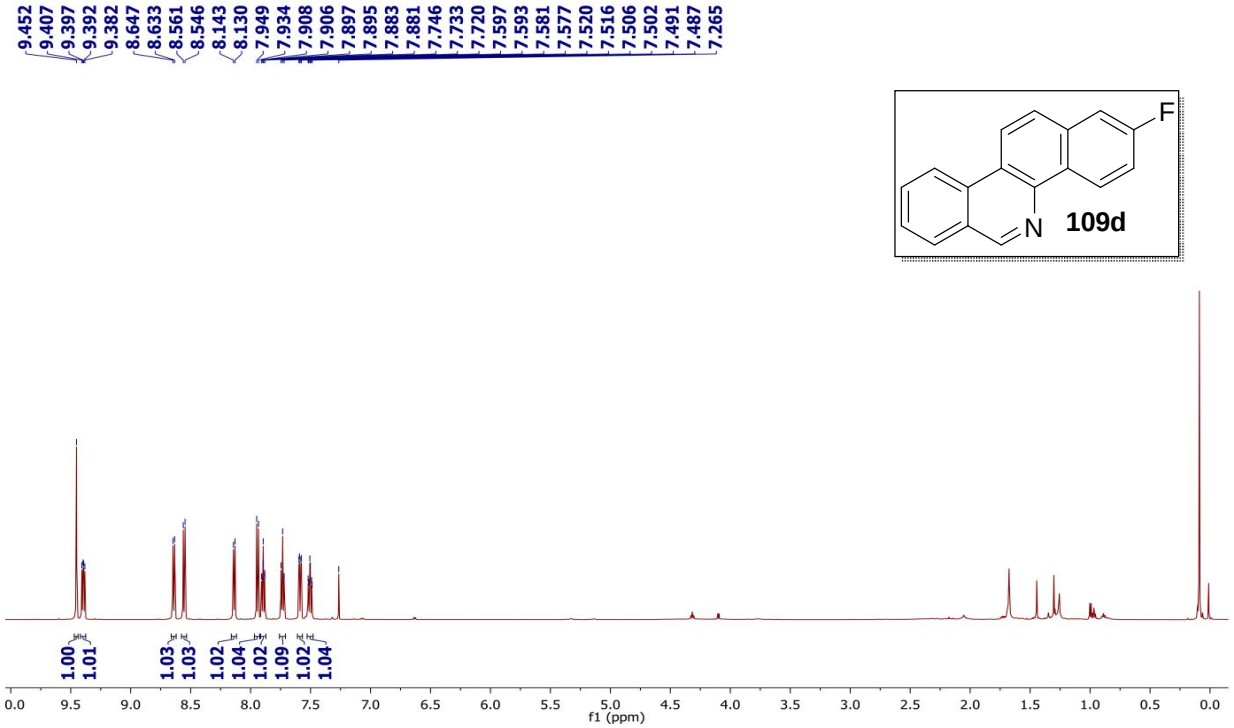
^{1}H NMR (600 MHz) of **109c:**



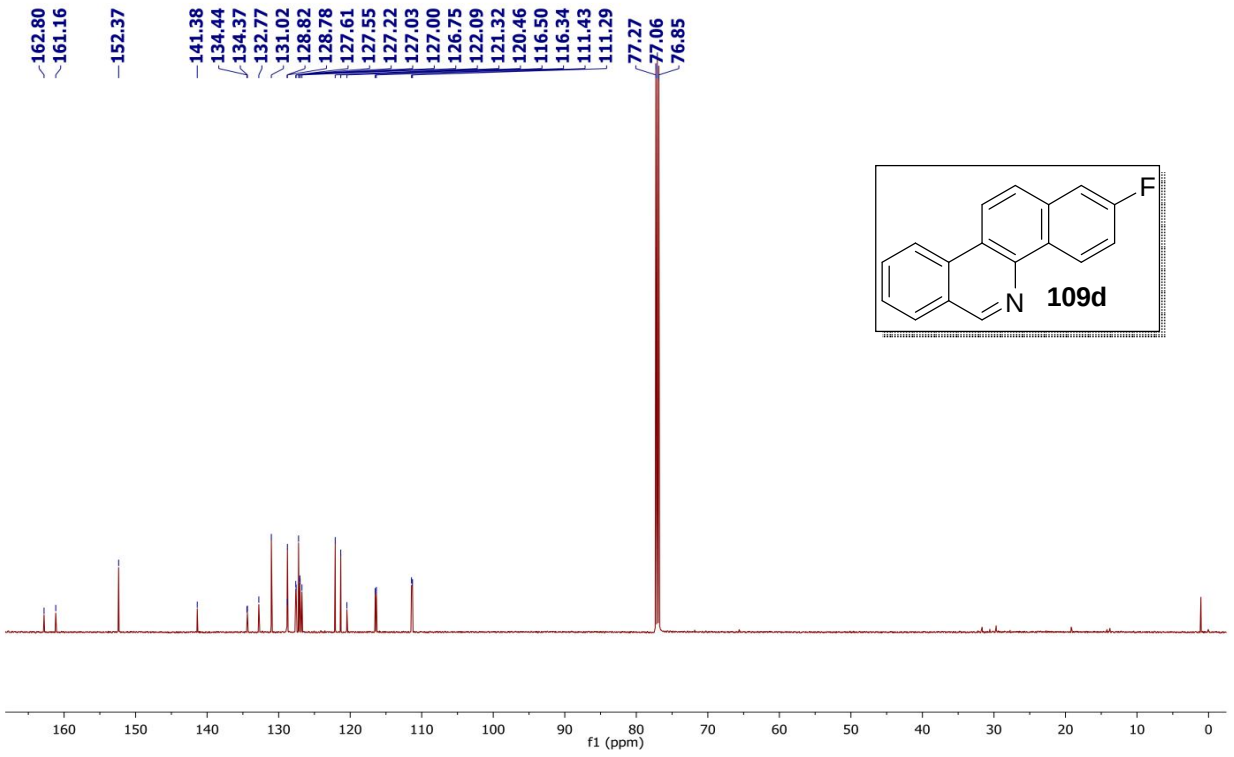
^{13}C NMR (150 MHz) of **109c:**



^{1}H NMR (600 MHz) of **109d:**

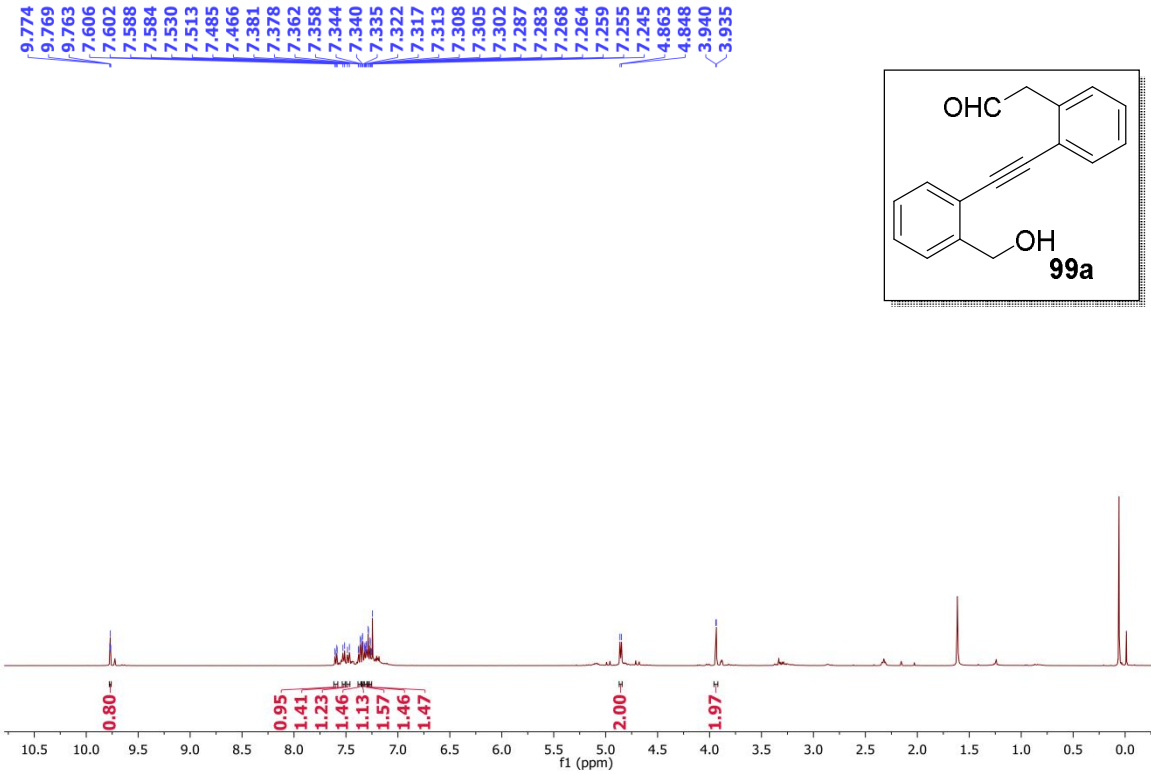


^{13}C NMR (150 MHz) of **109d:**

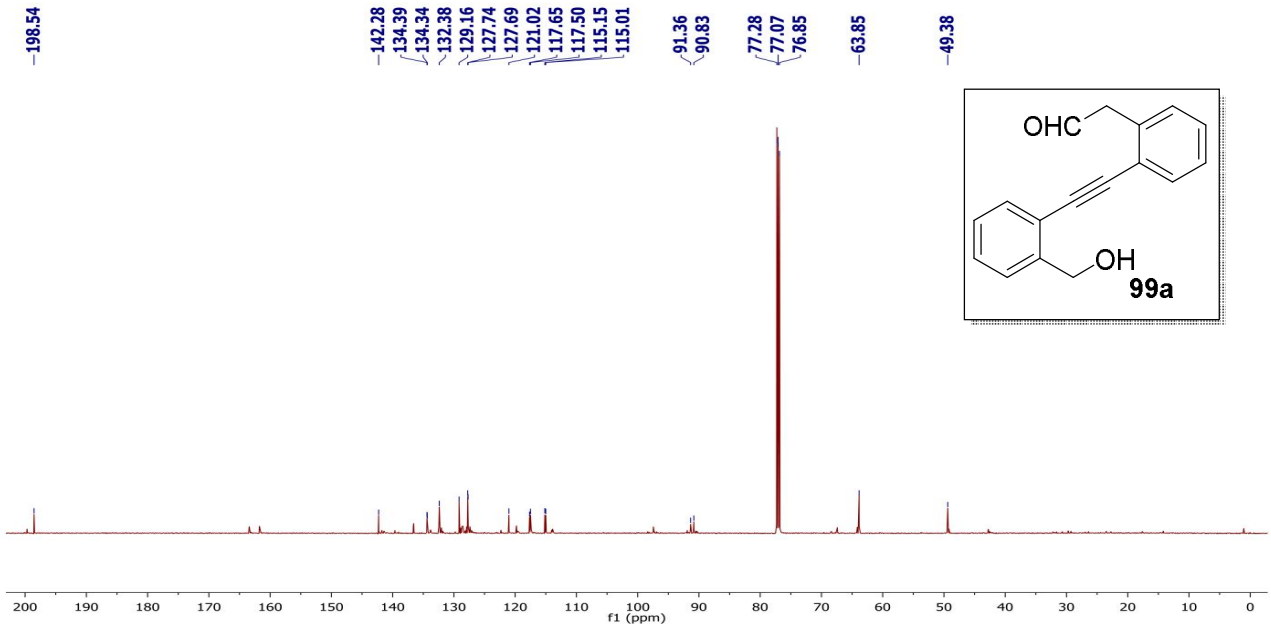


NMR Spectra of Compounds 99a–j:

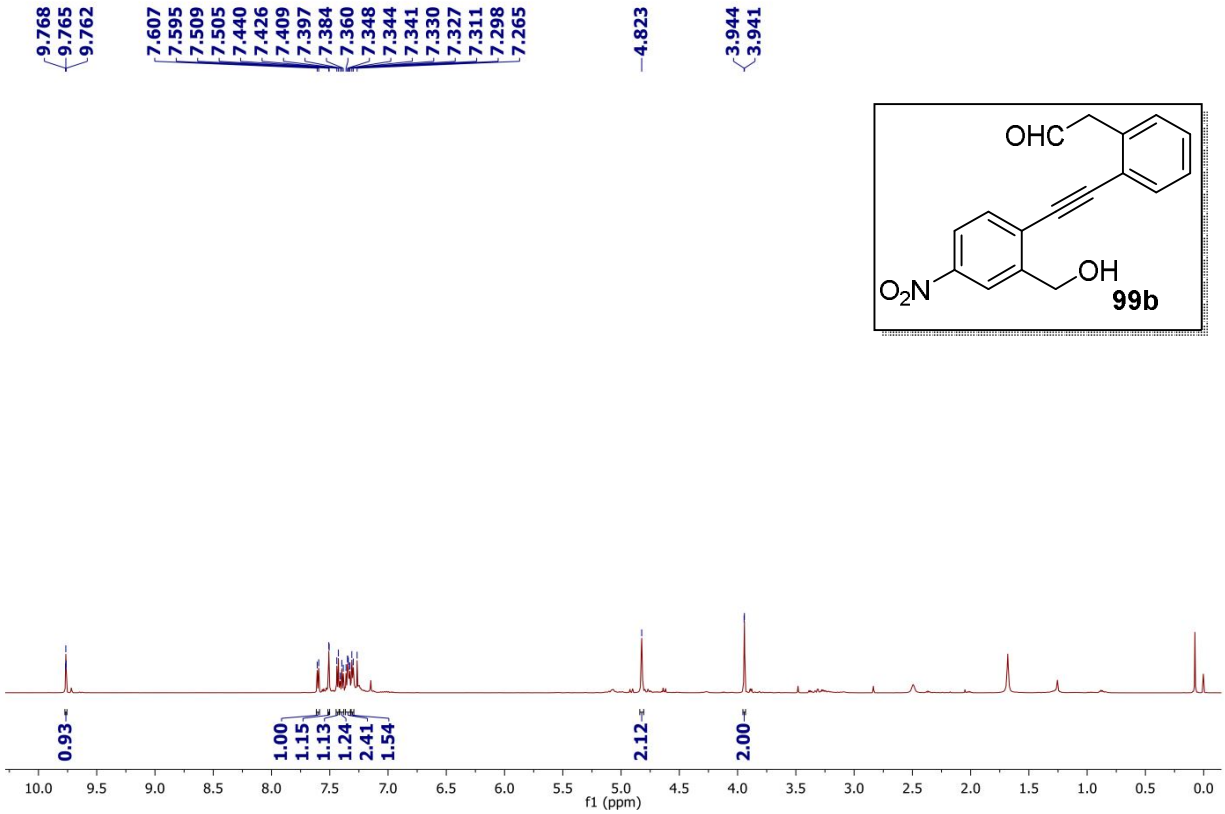
^{1}H NMR (400 MHz) of **99a:**



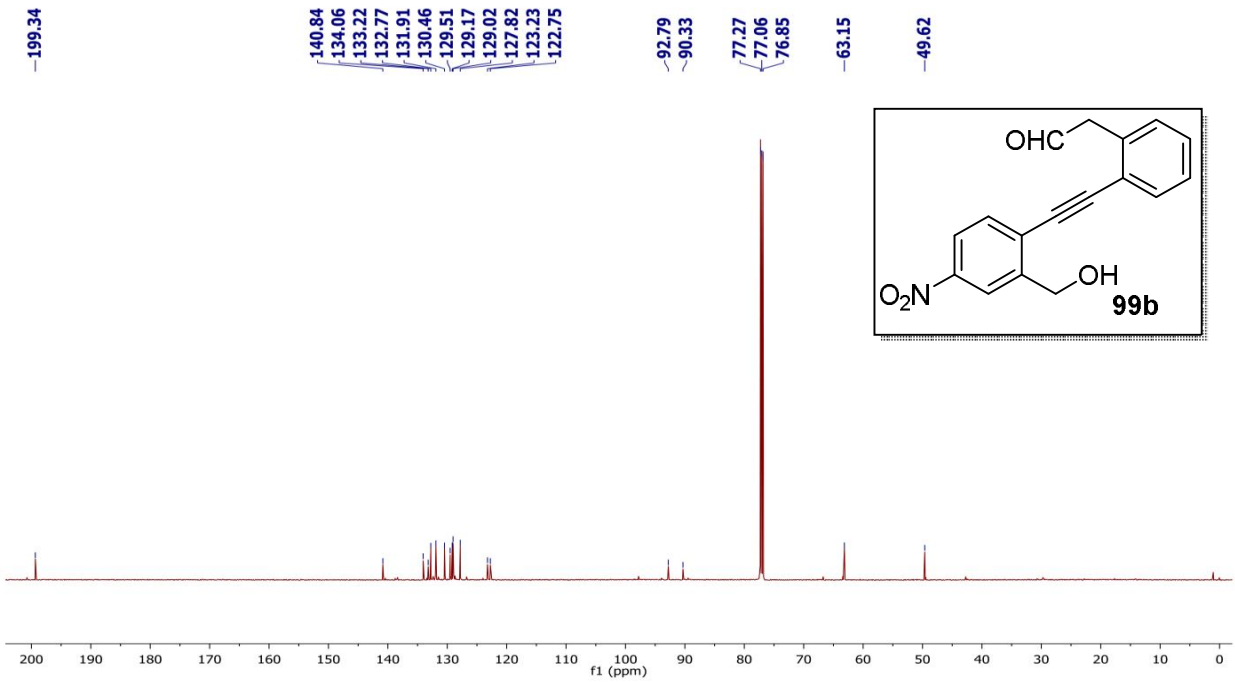
^{13}C NMR (150 MHz) of **99a:**



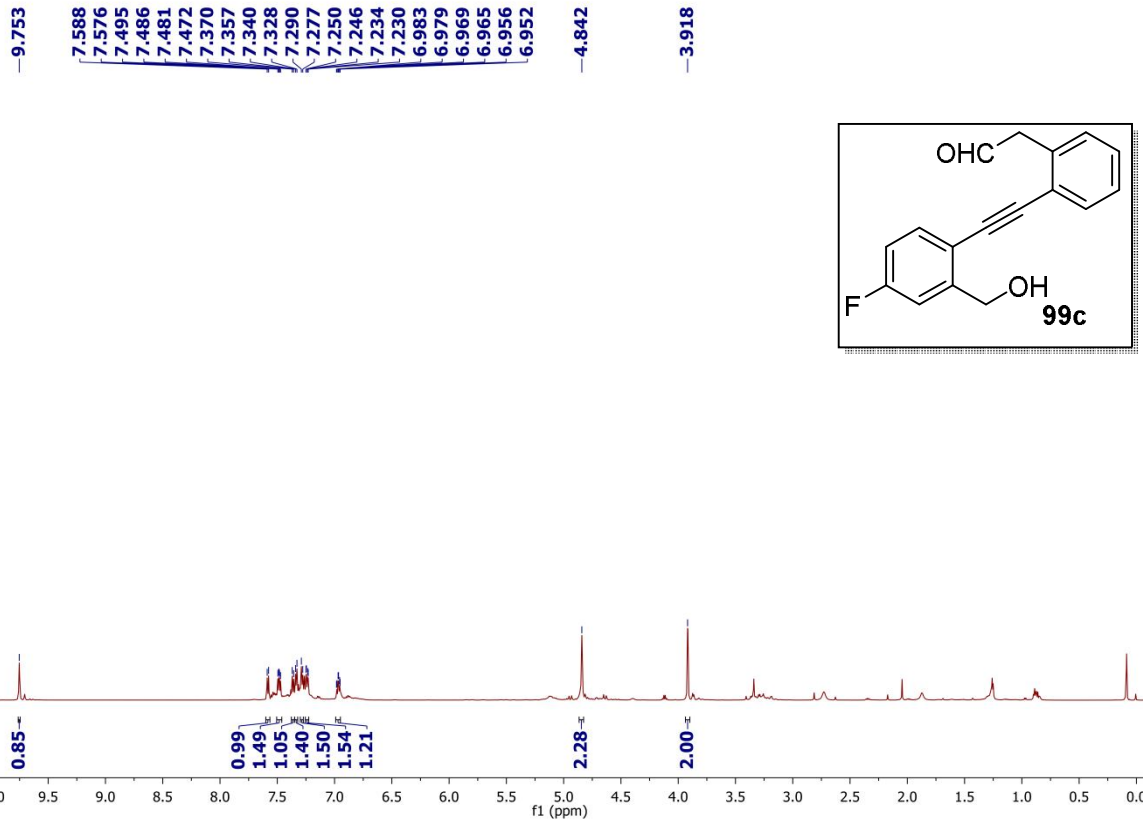
^{1}HNMR (600 MHz) of **99b:**



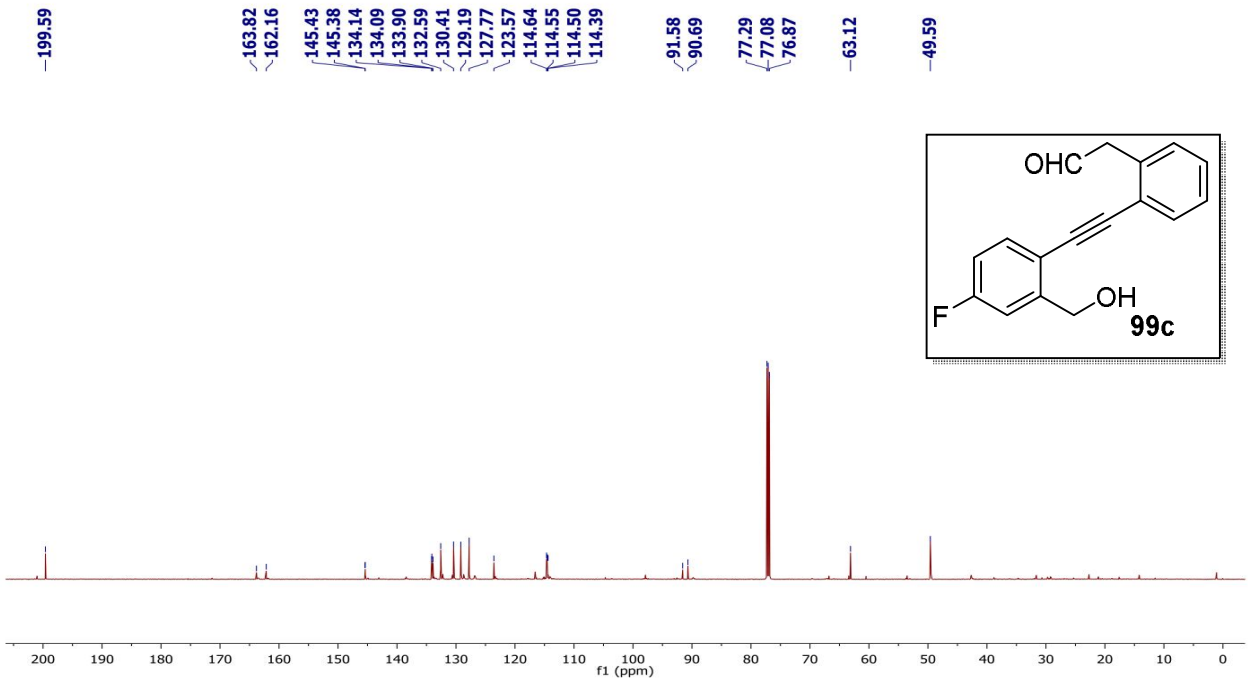
^{13}CNMR (150 MHz) of **99b**:



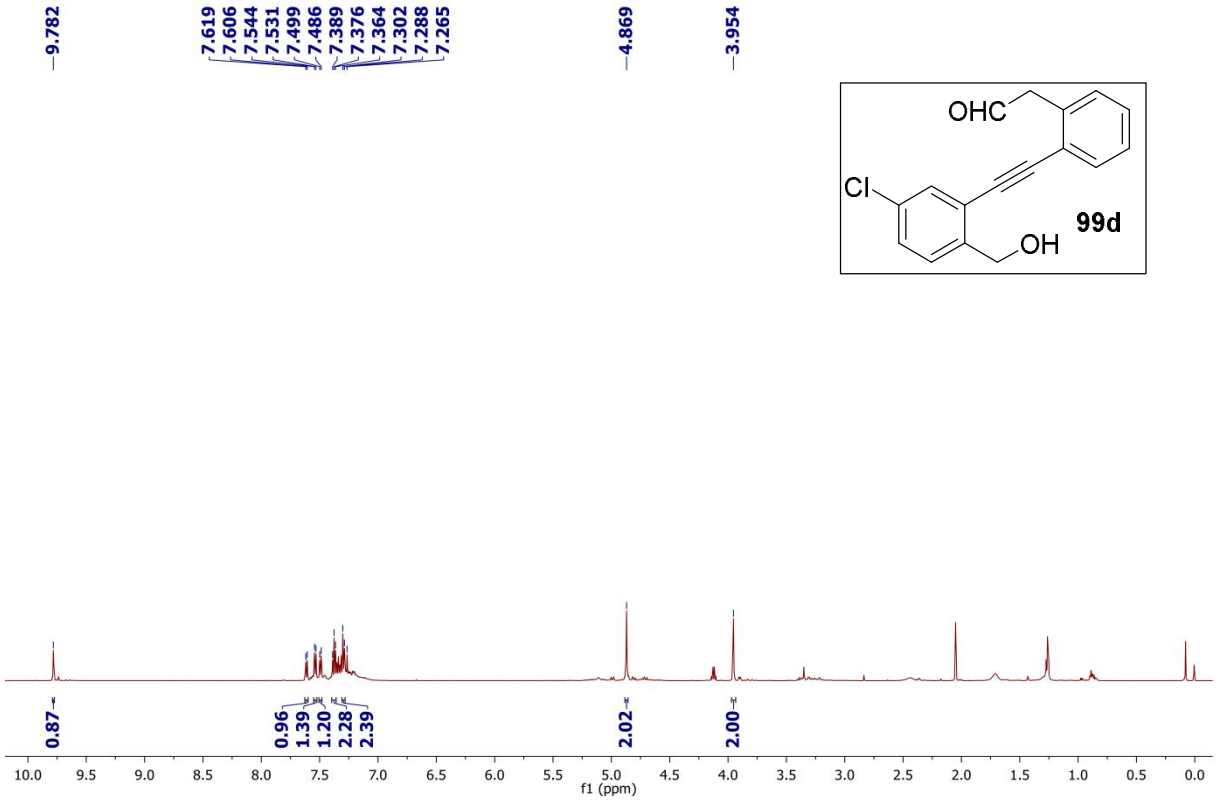
^{1}H NMR (600 MHz) of **99c:**



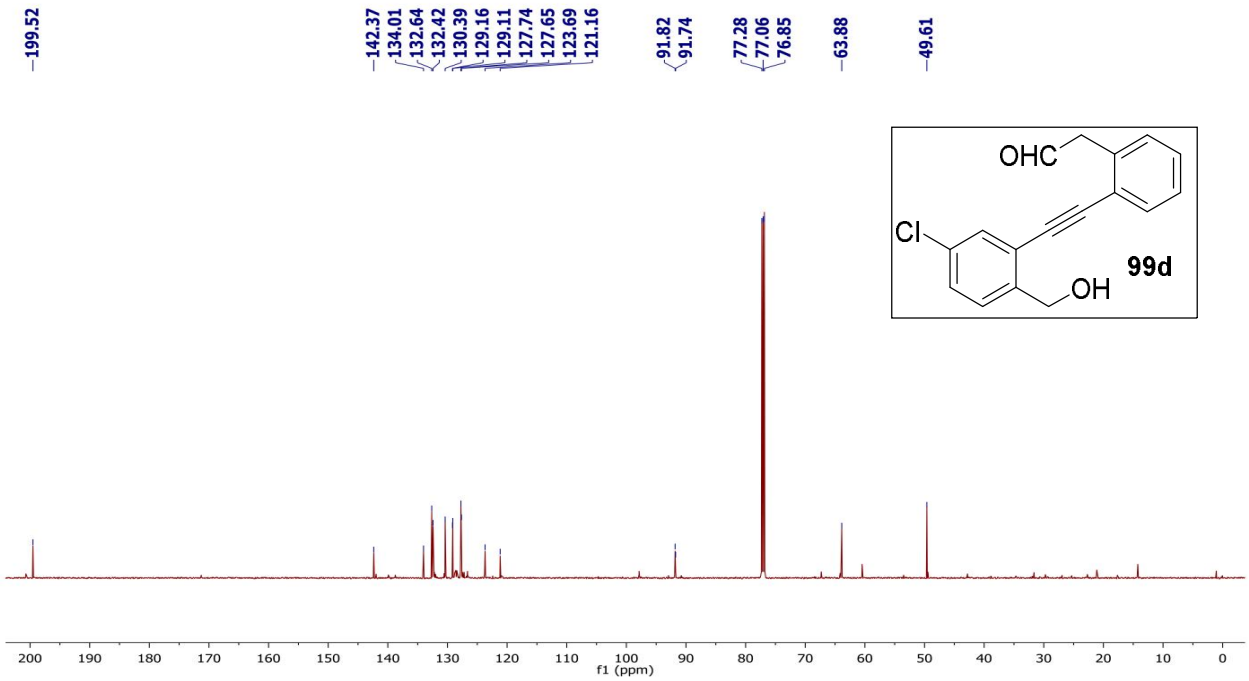
^{13}C NMR (150 MHz) of **99c**:



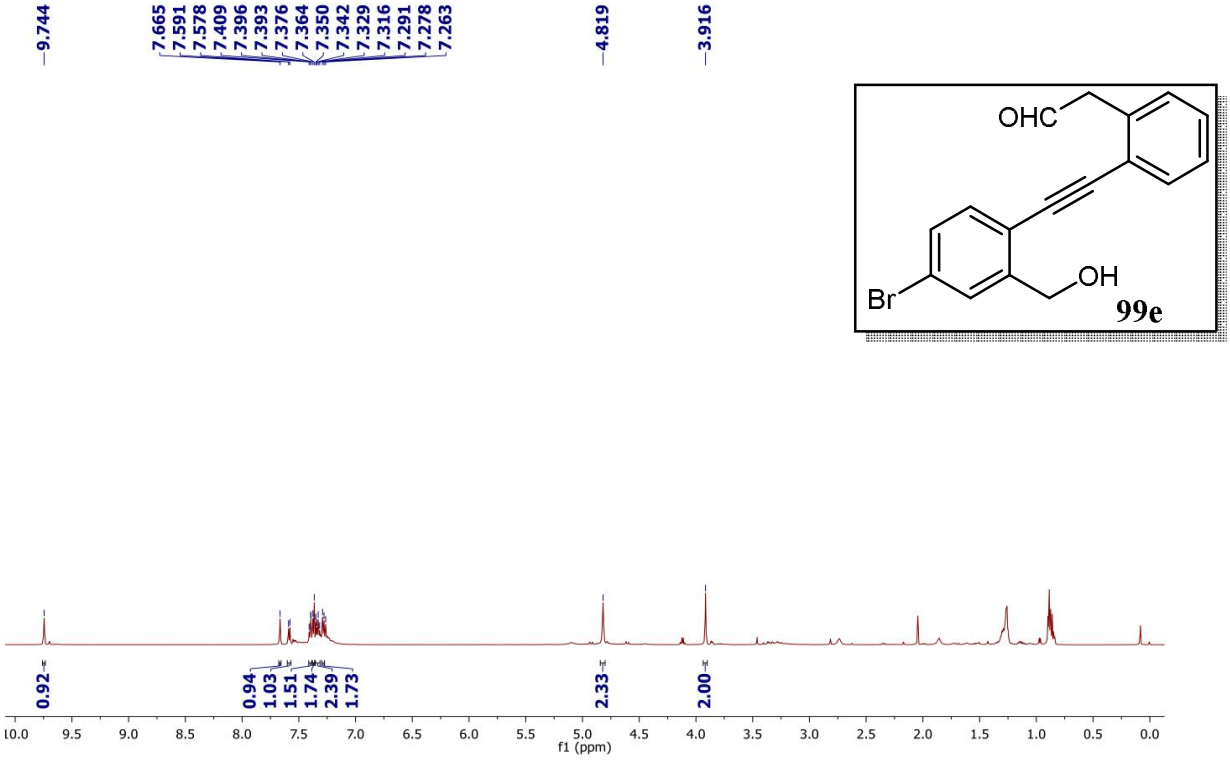
^{1}H NMR (600 MHz) of **99d:**



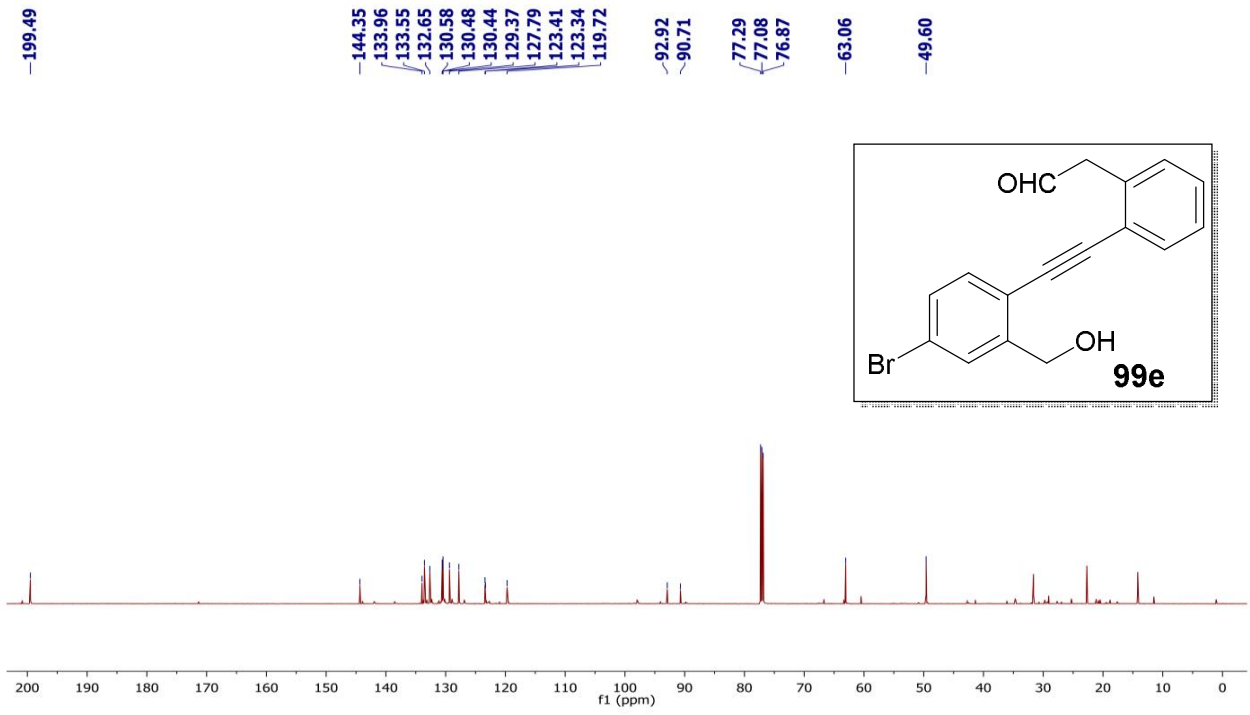
^{13}C NMR (150 MHz) of **99d:**



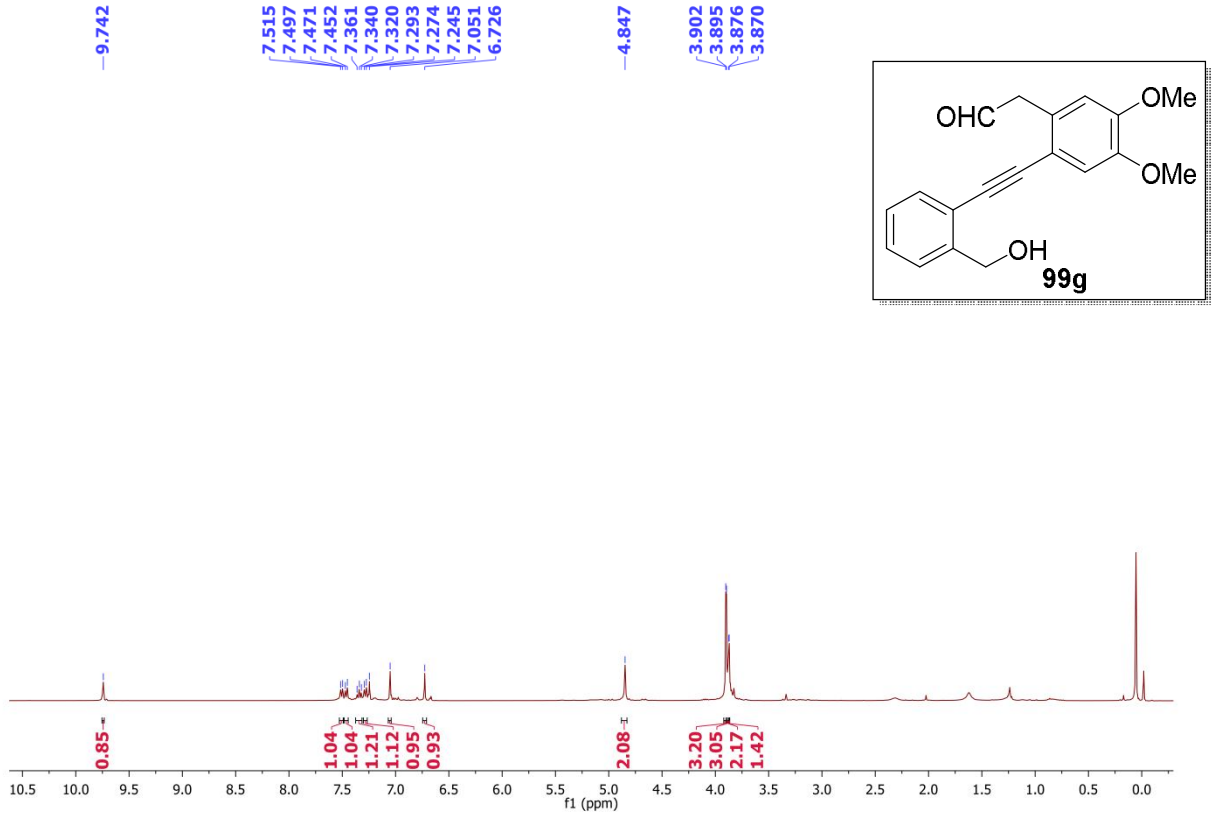
^{1}H NMR(600 MHz) of **99e:**



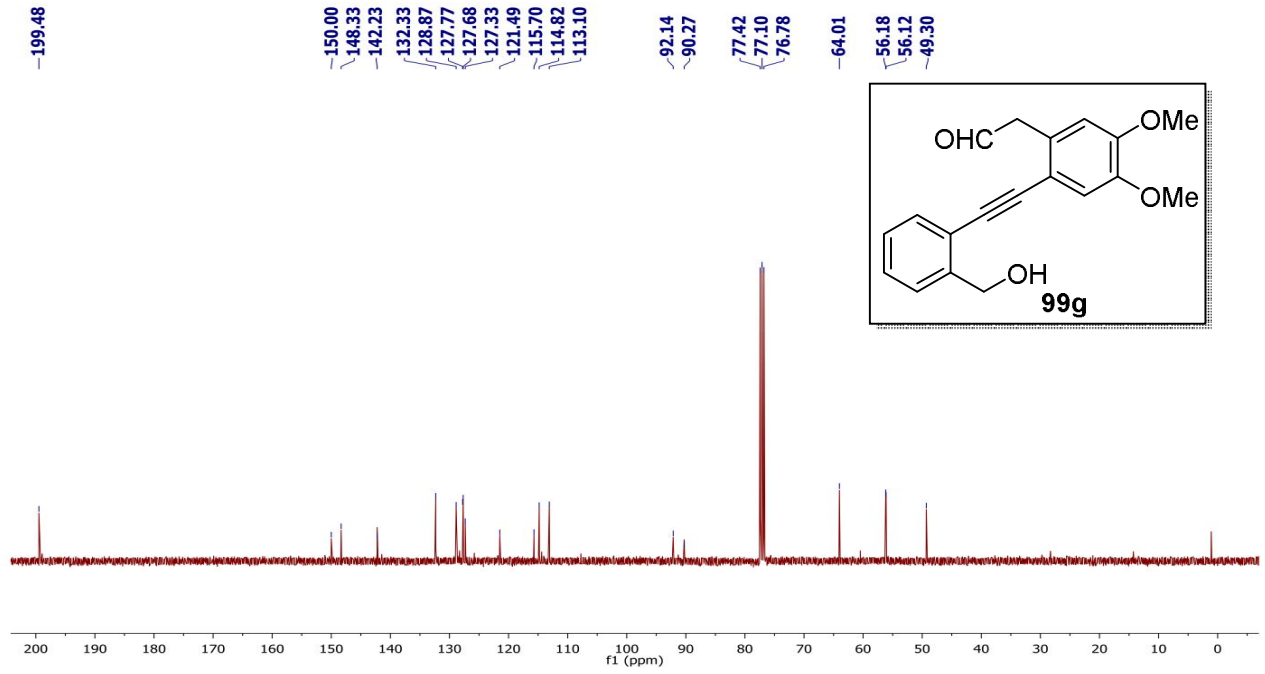
^{13}C NMR (150 MHz) of **99e:**



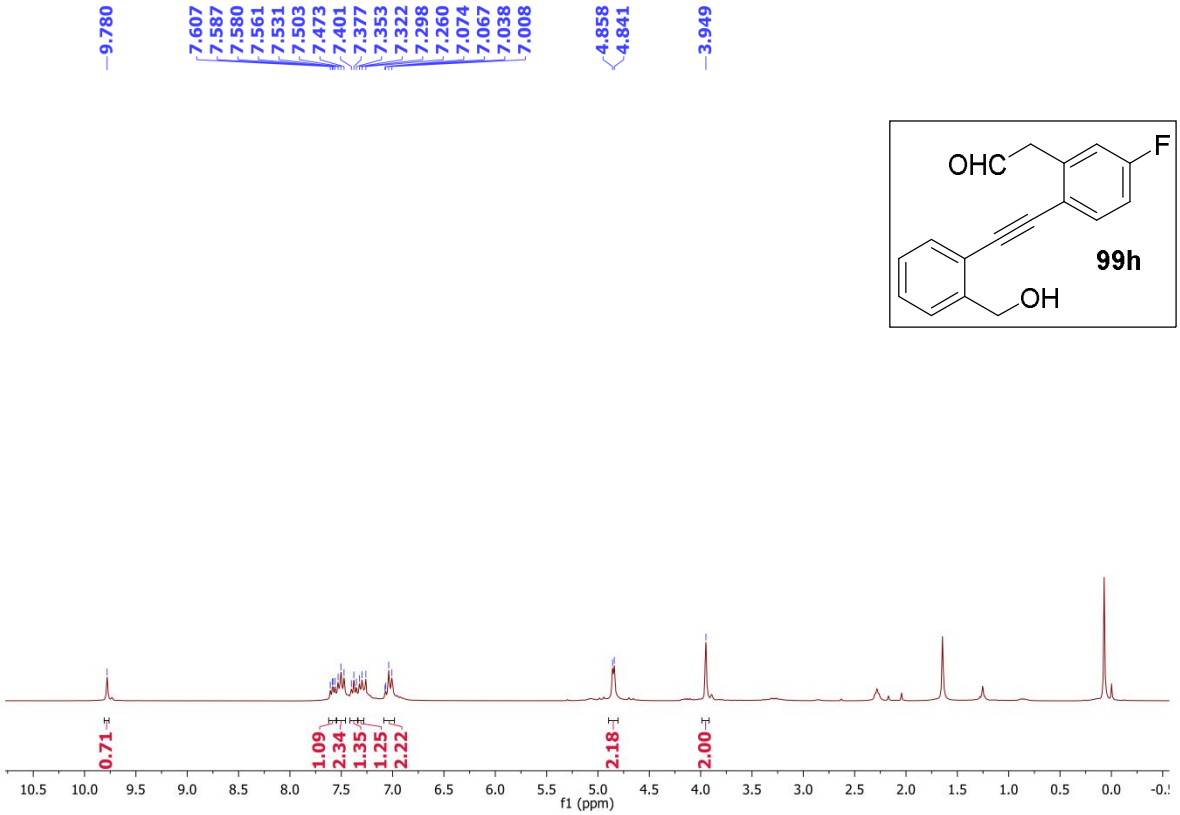
^{1}HNMR (400 MHz) of **99g:**



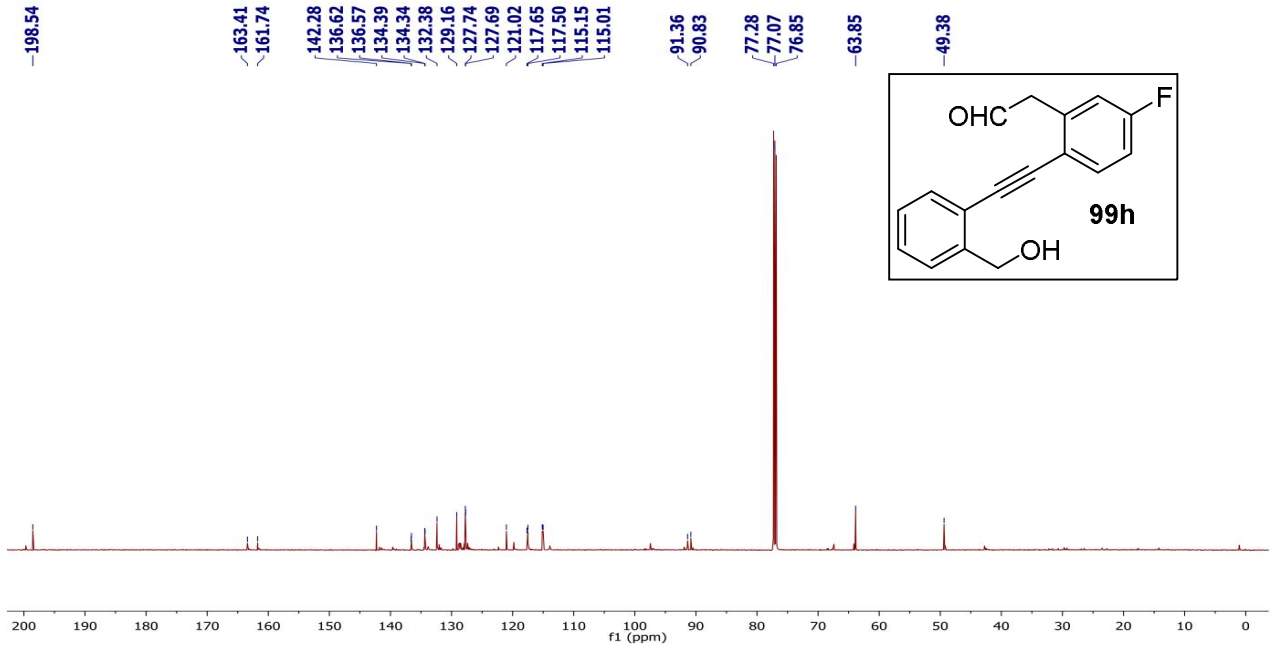
^{13}CNMR (100 MHz) of **99g:**



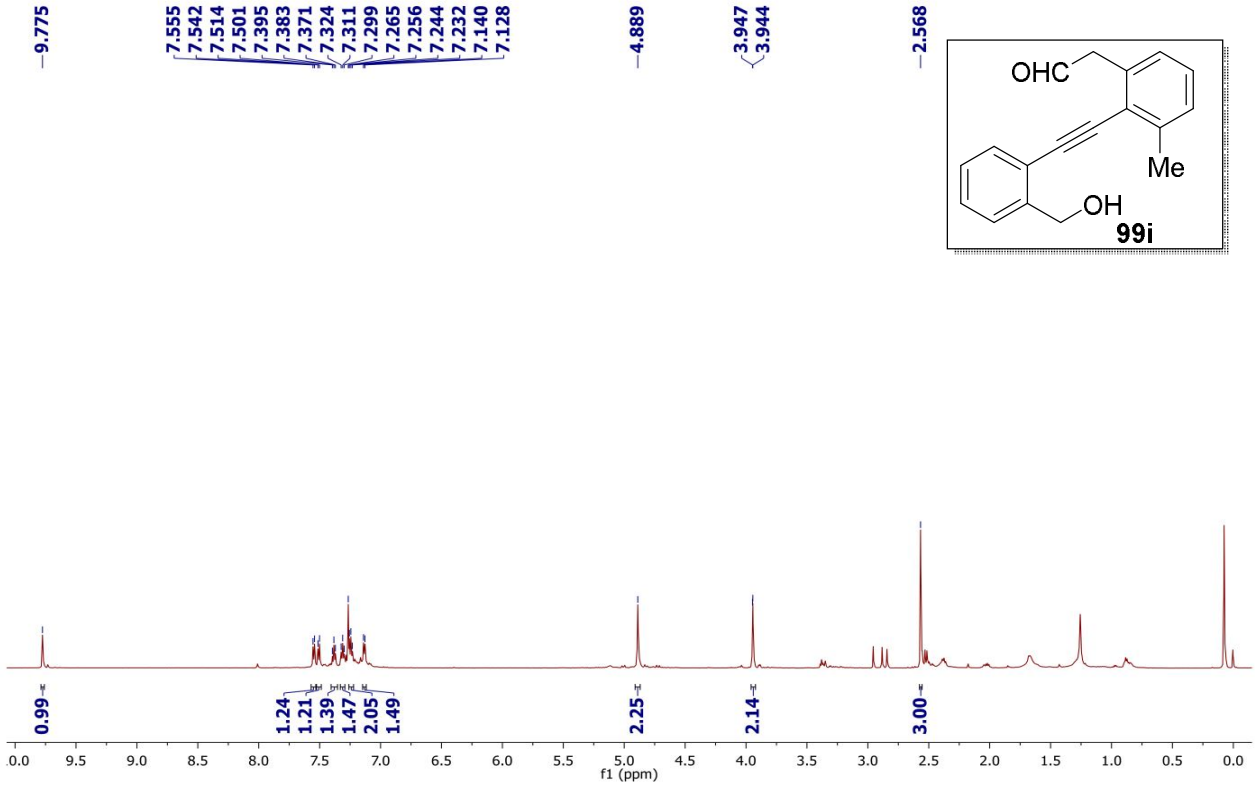
[1]HNMR (600 MHz) of **99h:**



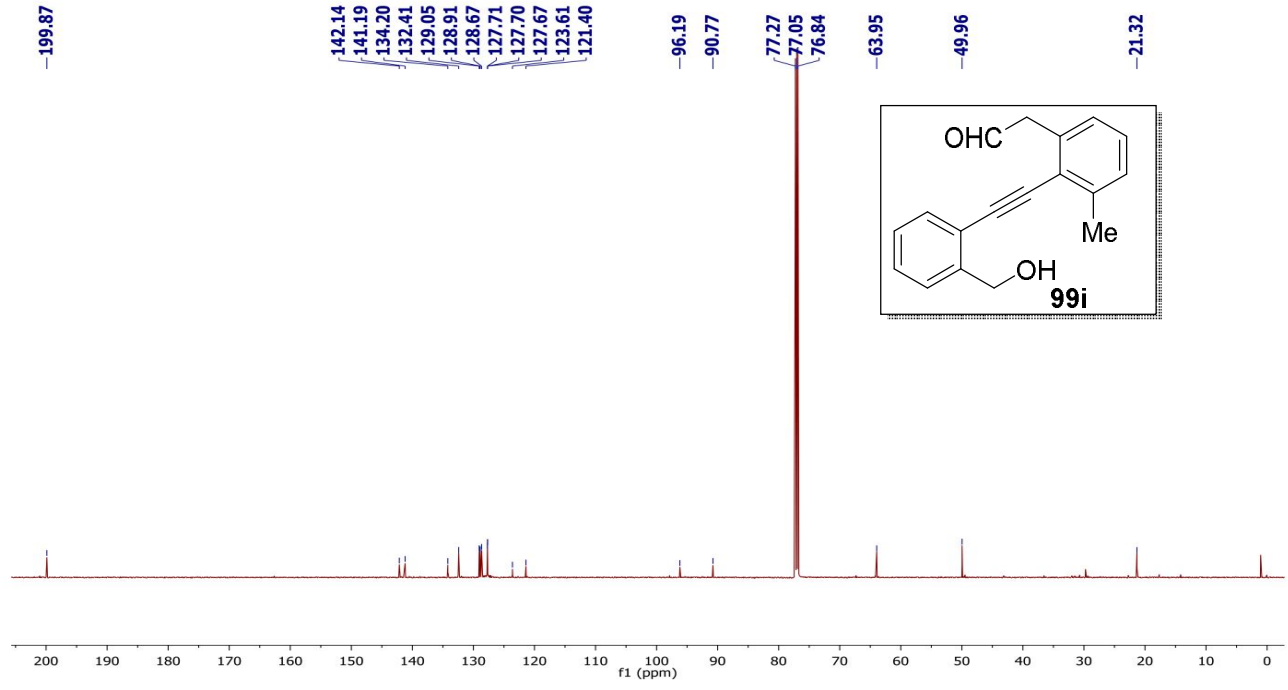
[13]CNMR (150 MHz) of **99h:**



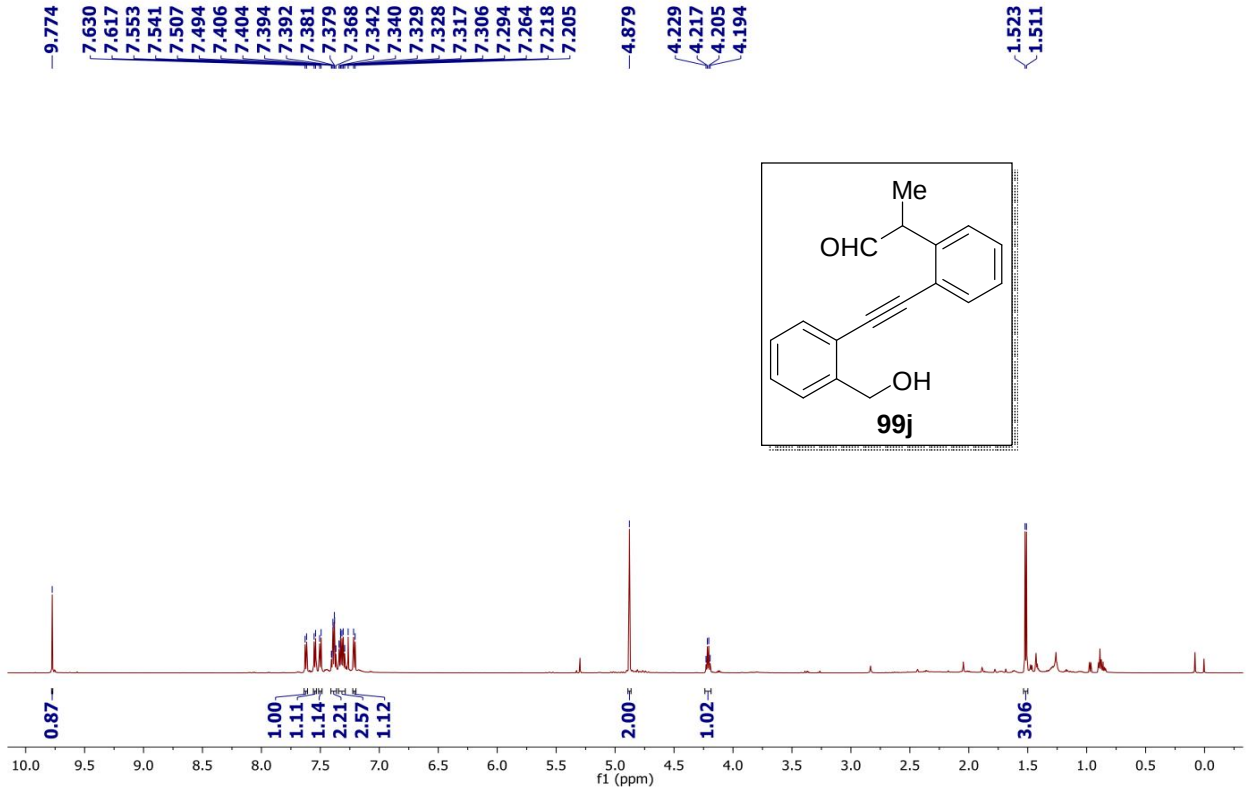
^{1}HNMR (600 MHz) of **99i:**



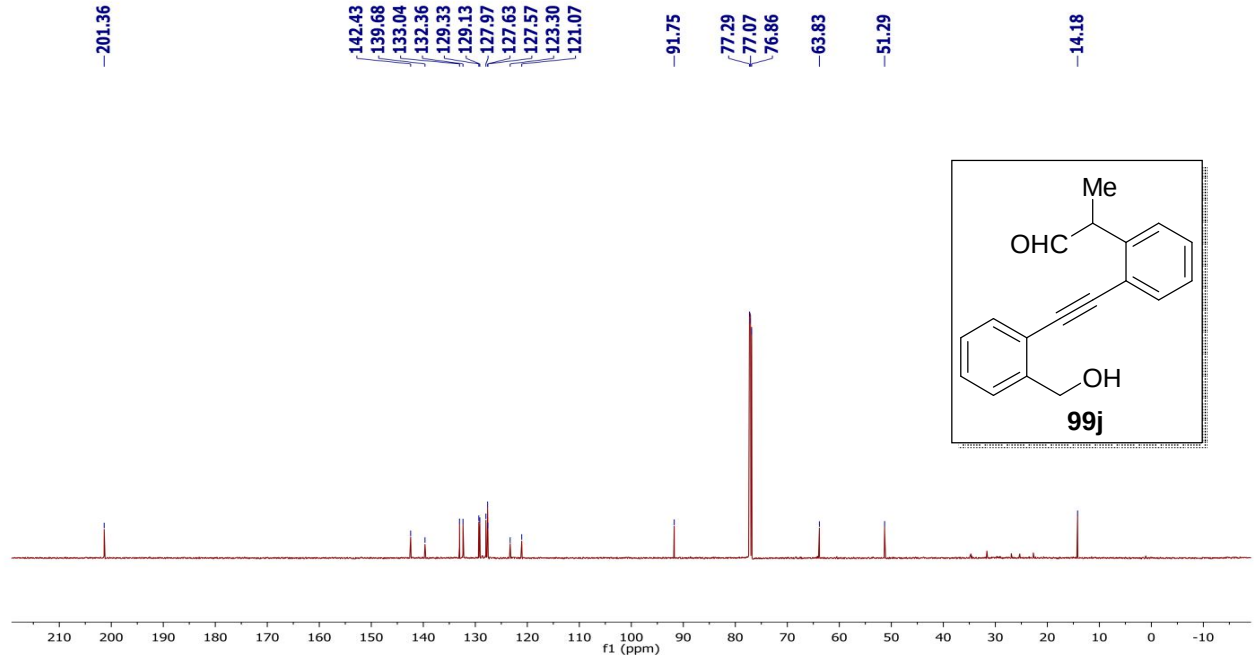
^{13}CNMR (150 MHz) of **99i:**



^{1}HNMR (600 MHz) of **99j:**

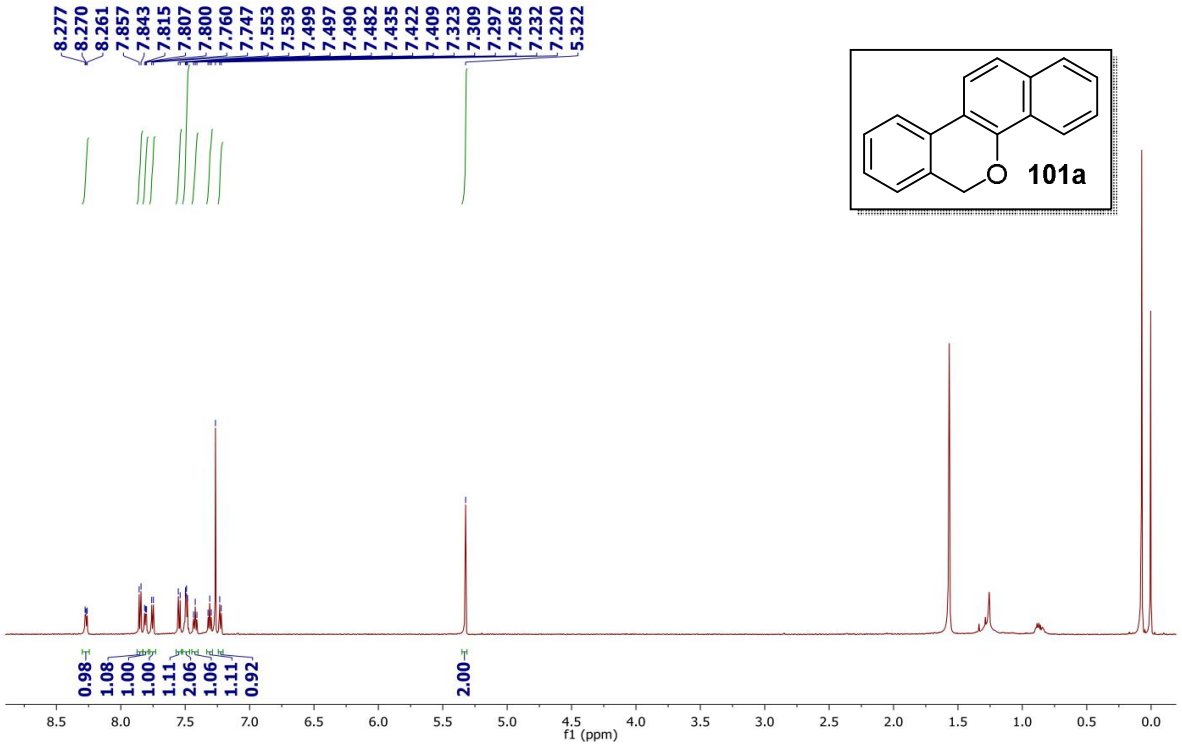


^{13}CNMR (150 MHz) of **99j:**

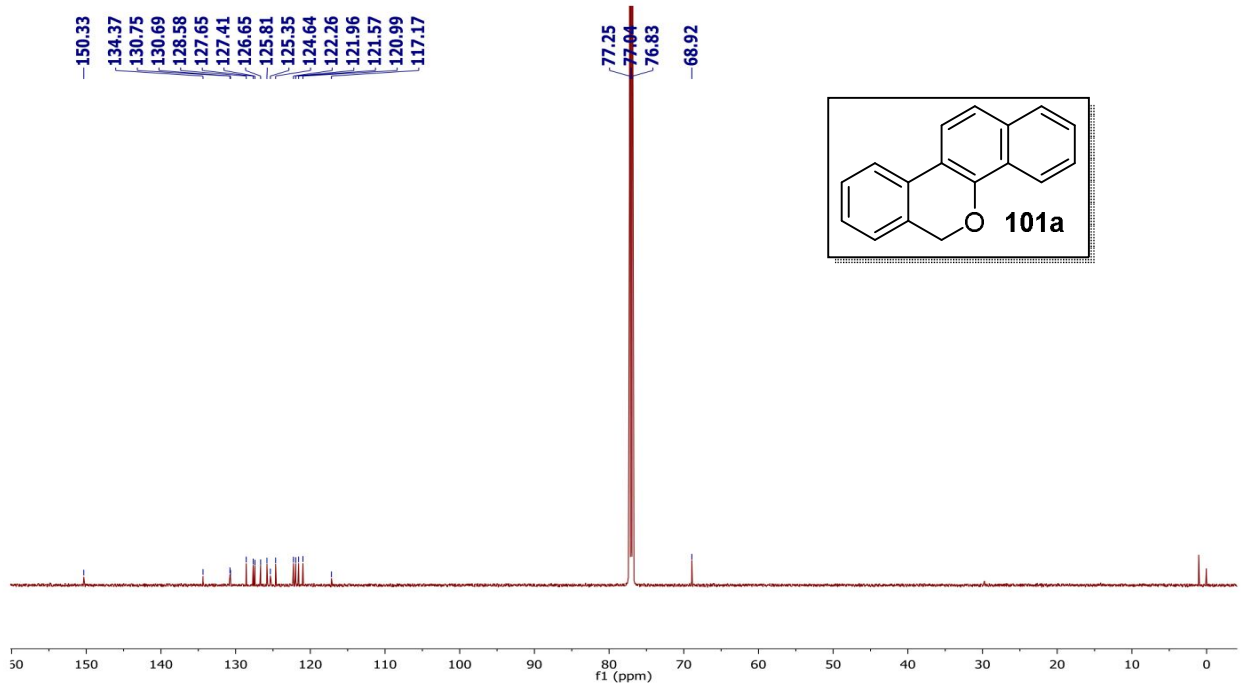


NMR Spectra of Compounds 101a -j:

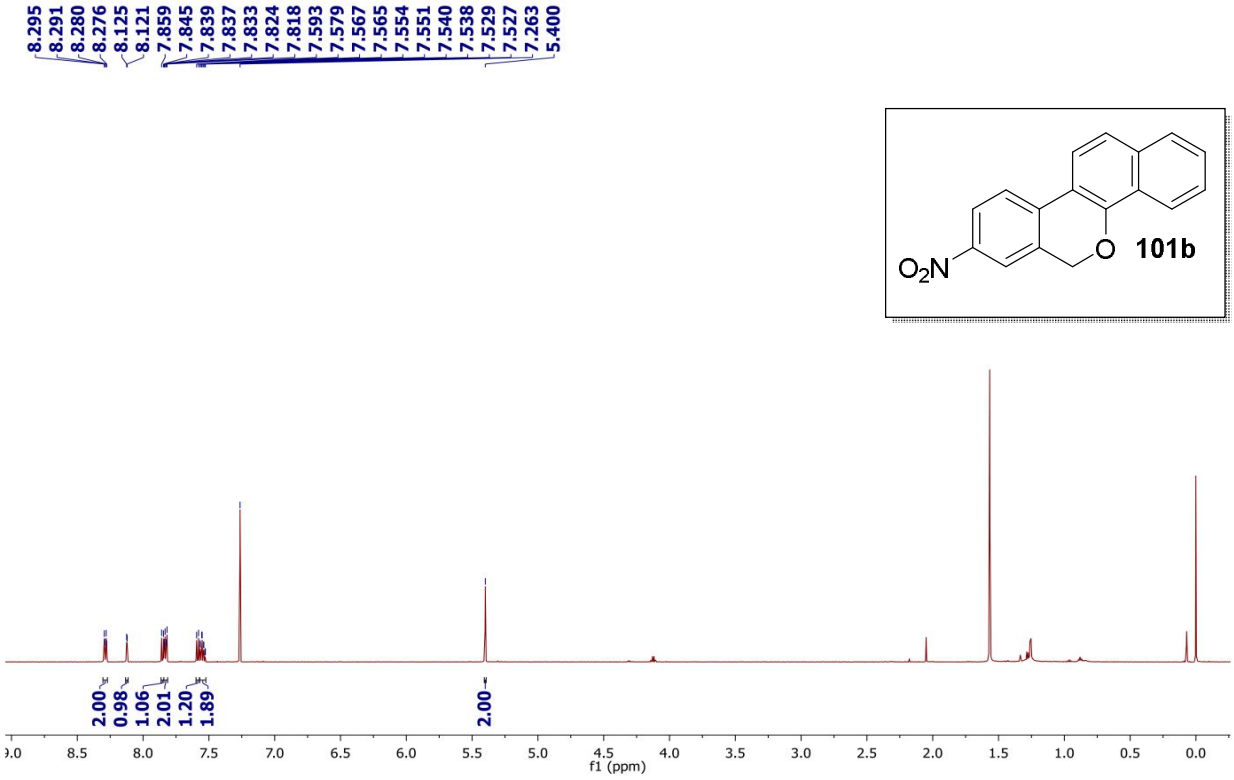
^{1}HNMR (600 MHz) of **101a**



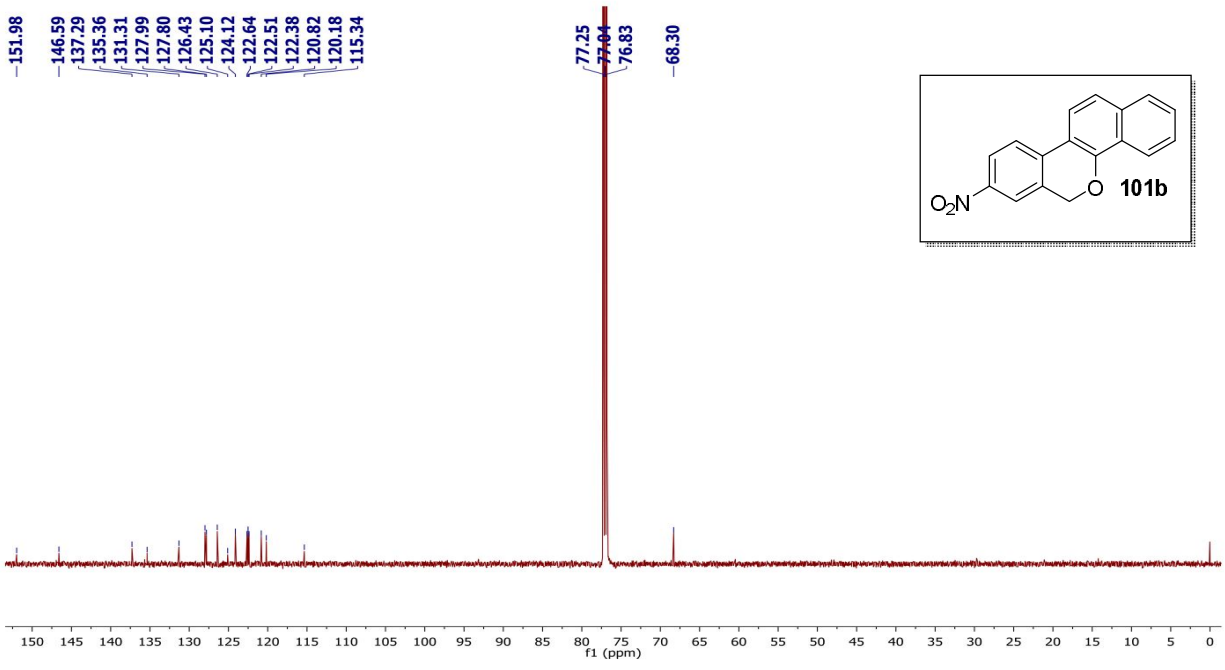
^{13}CNMR (150 MHz) of **101a**



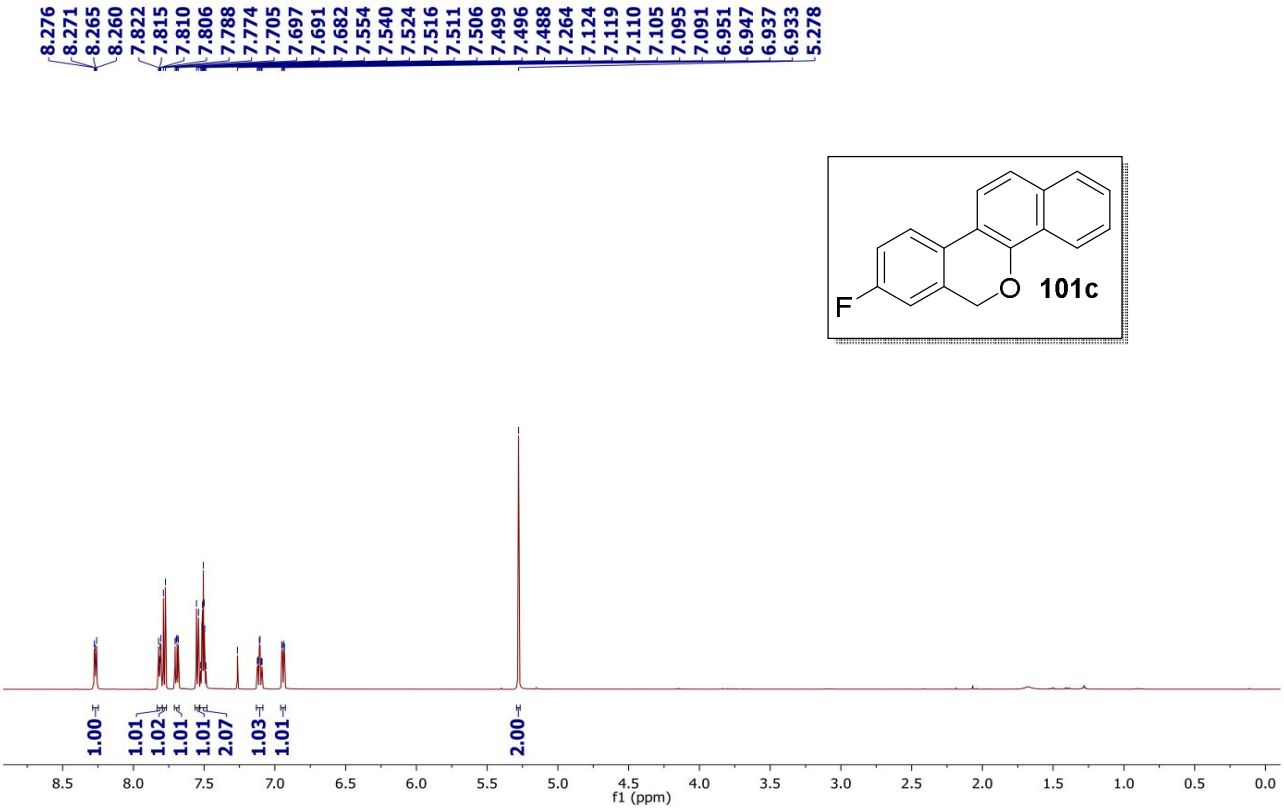
^{1}HNMR (600 MHz) of **101b**



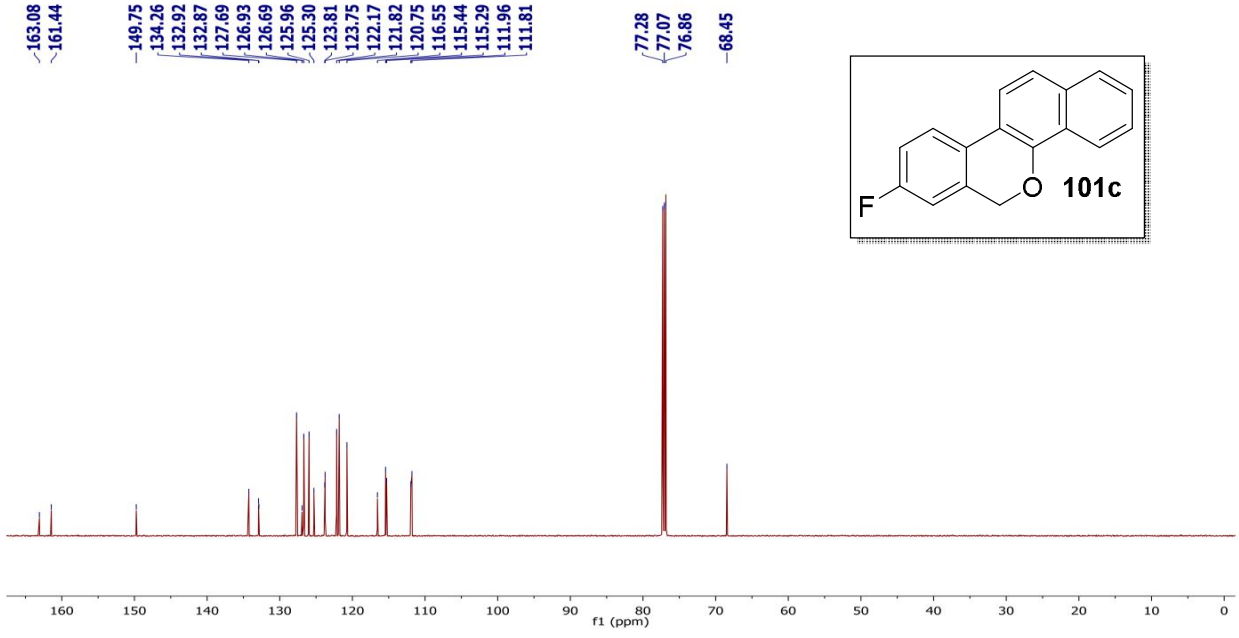
^{13}CNMR (150 MHz) of **101b**



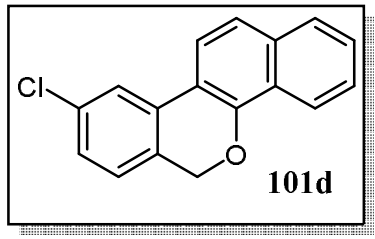
^{1}HNMR(600 MHz) of **101c**

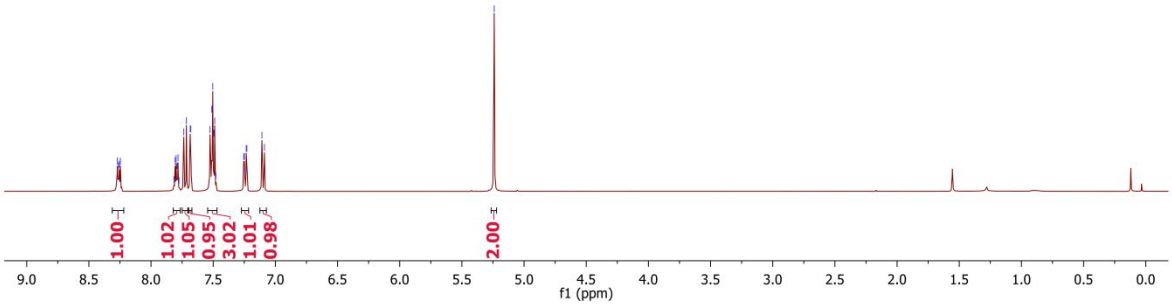


^{13}CNMR (150 MHz) of **101c**

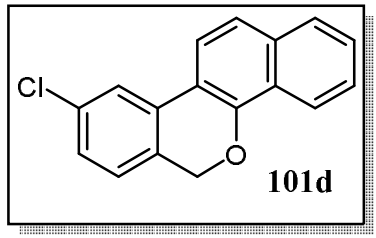


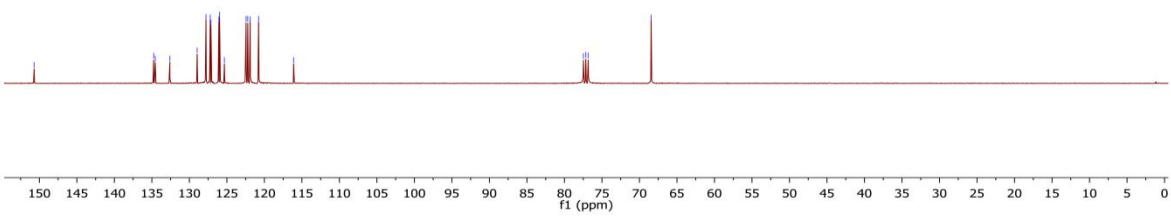
^{1}HNMR (400 MHz) of **101d:**



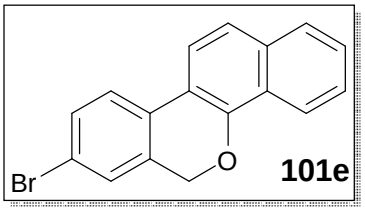


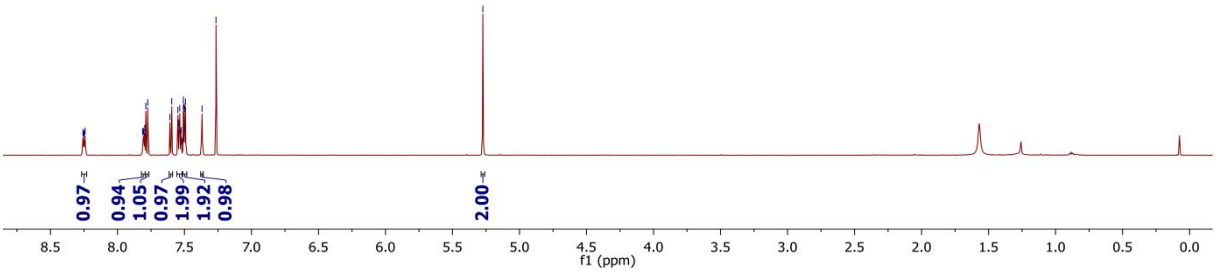
^{13}CNMR (100 MHz) of **101d:**



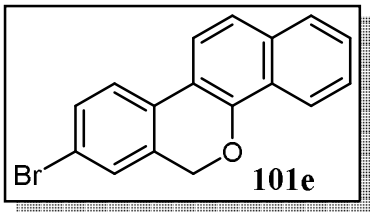


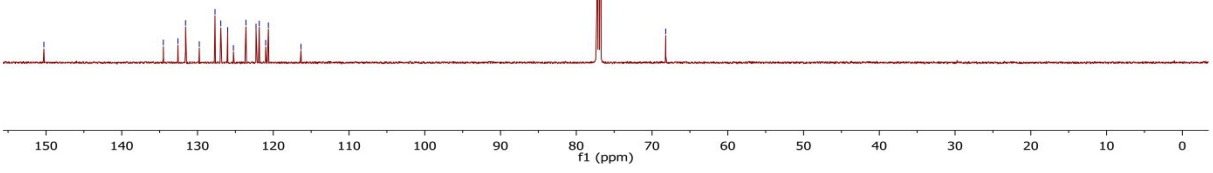
^{1}HNMR (600 MHz) of **101e:**



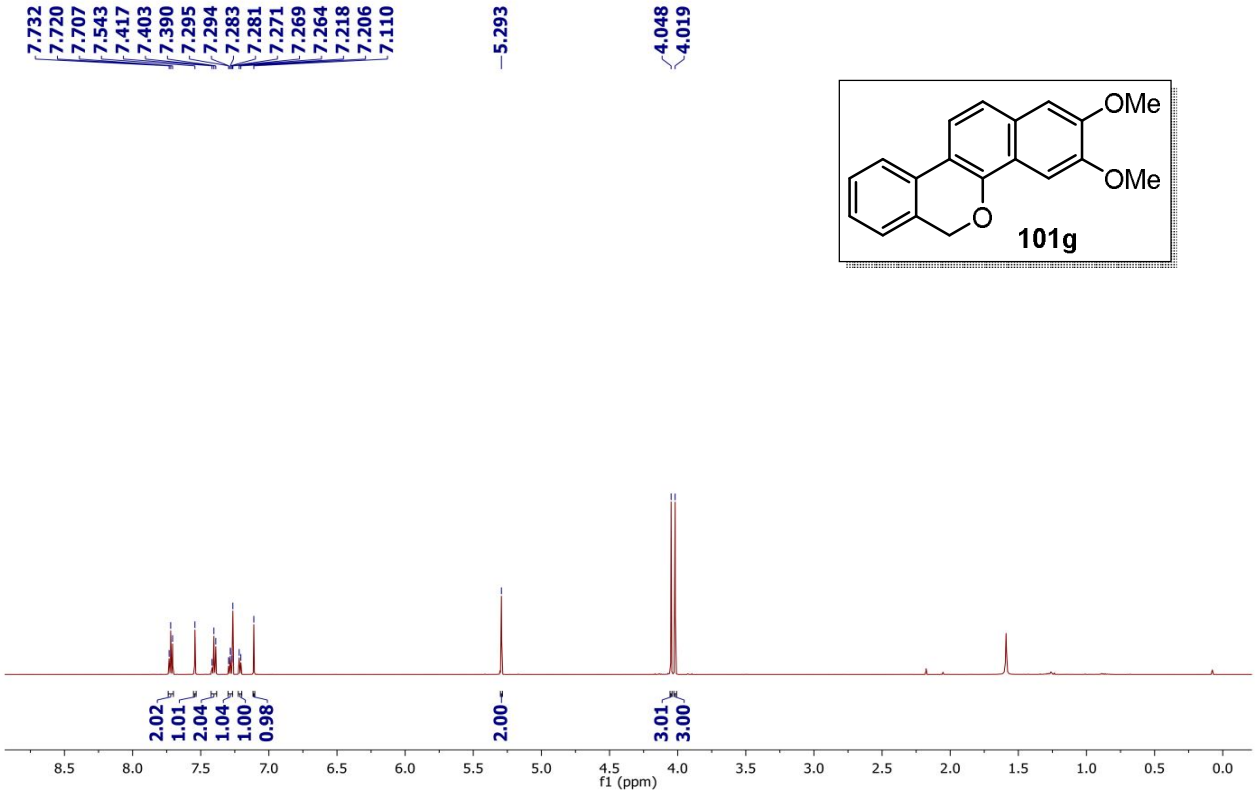


^{13}CNMR (150 MHz) of **101e:**

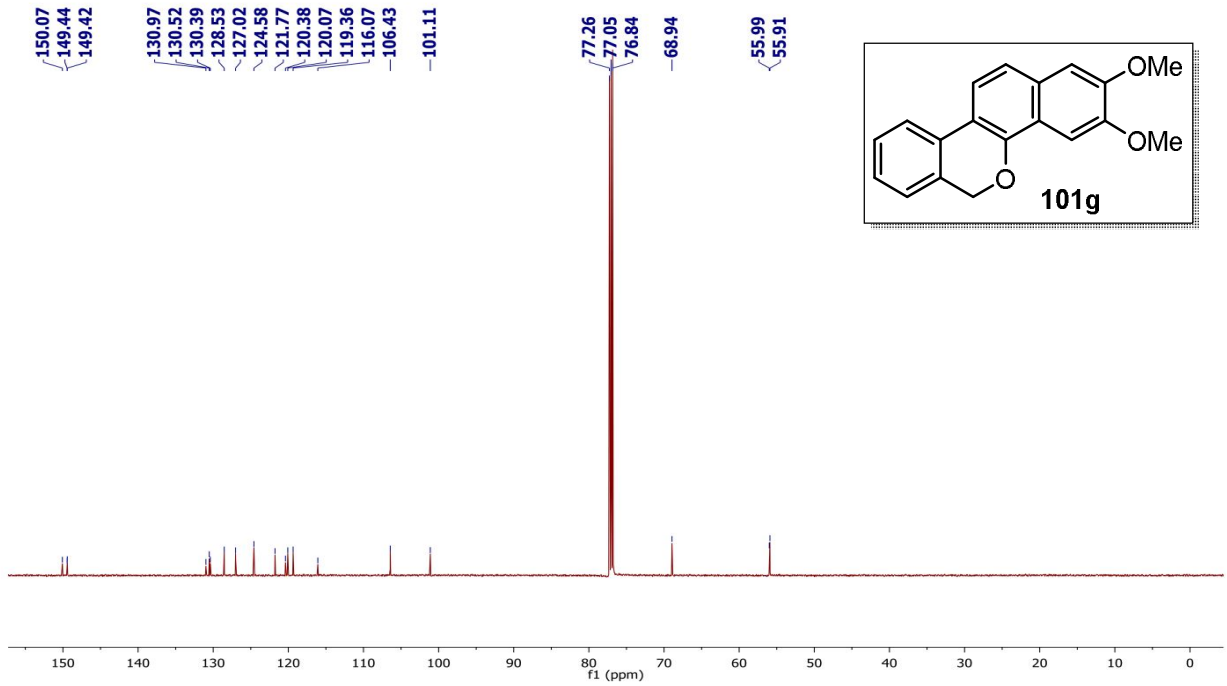




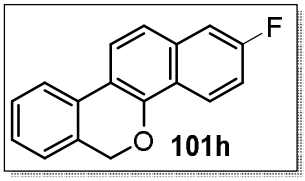
[1]HNMR (600 MHz) of **101g:**

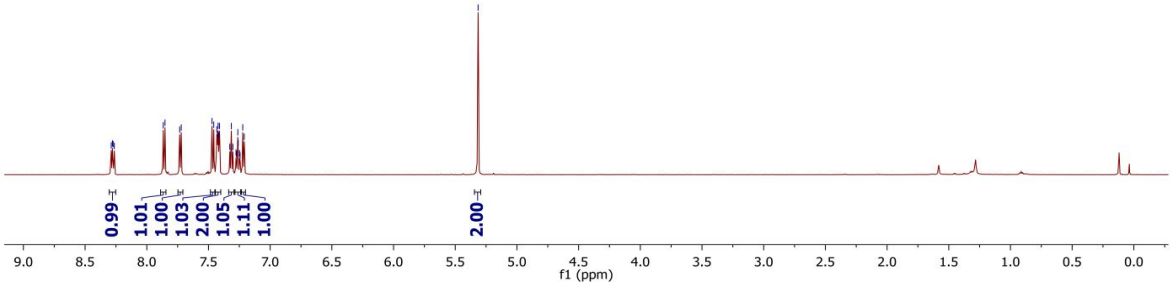


[13]CNMR (150 MHz) of **101g:**

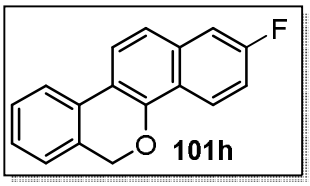


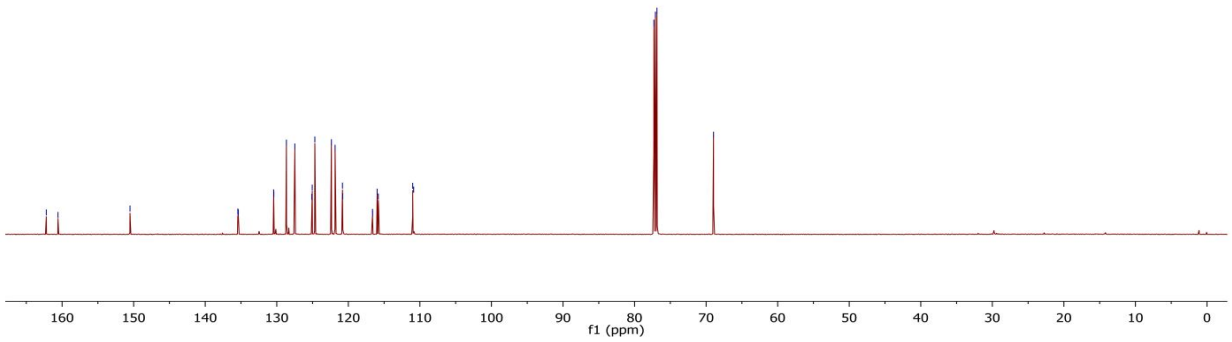
^{1}HNMR (600 MHz) of **101h:**



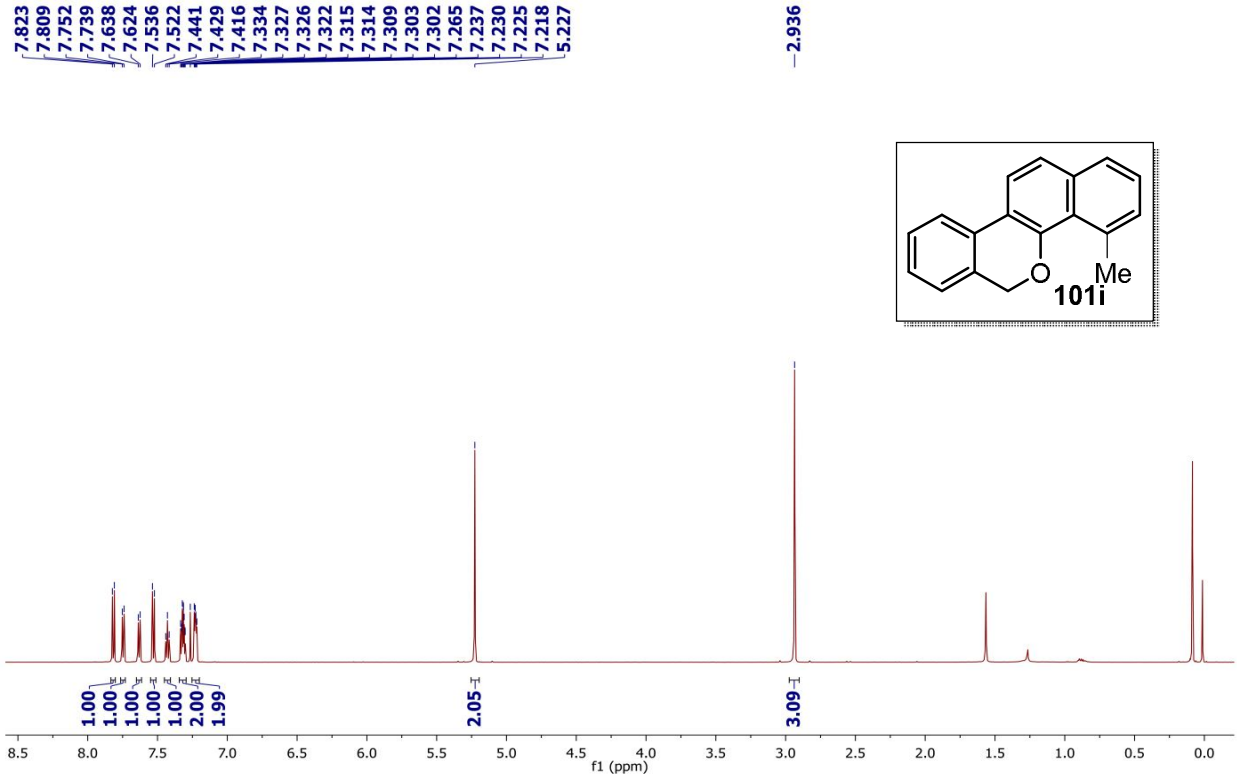


^{13}CNMR (150 MHz) of **101h:**

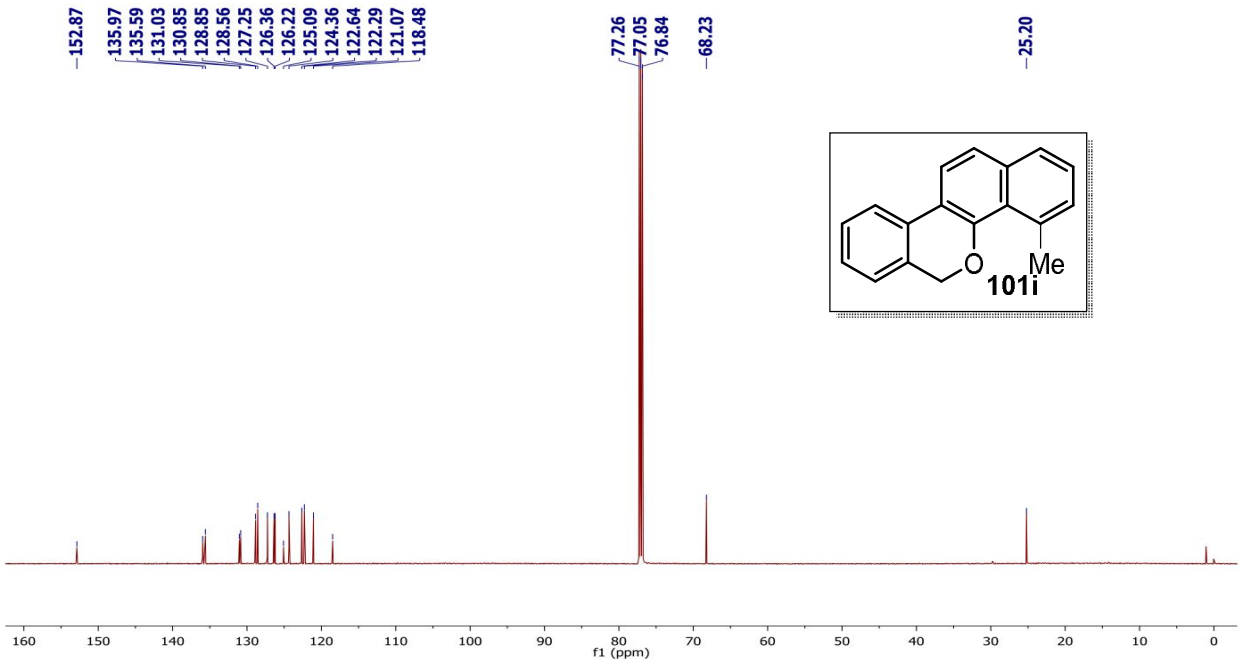




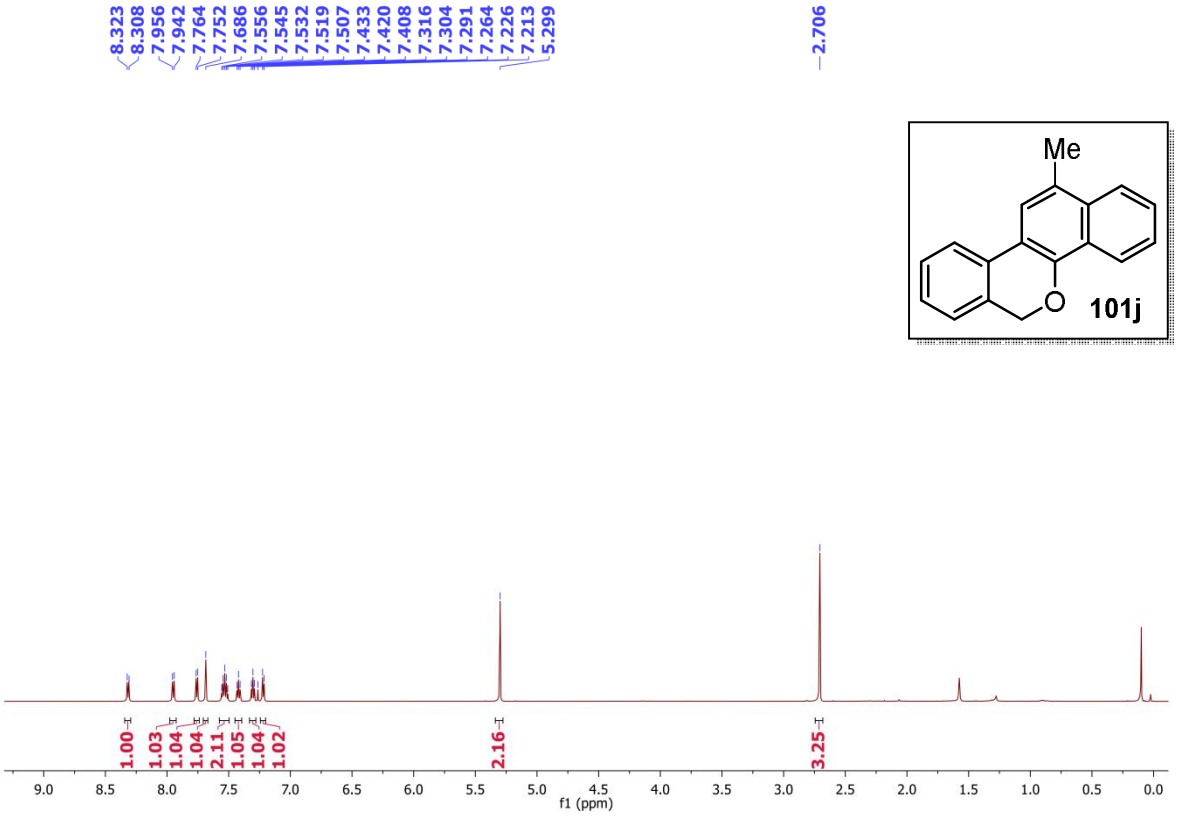
^{1}HNMR (600 MHz) of **101i:**



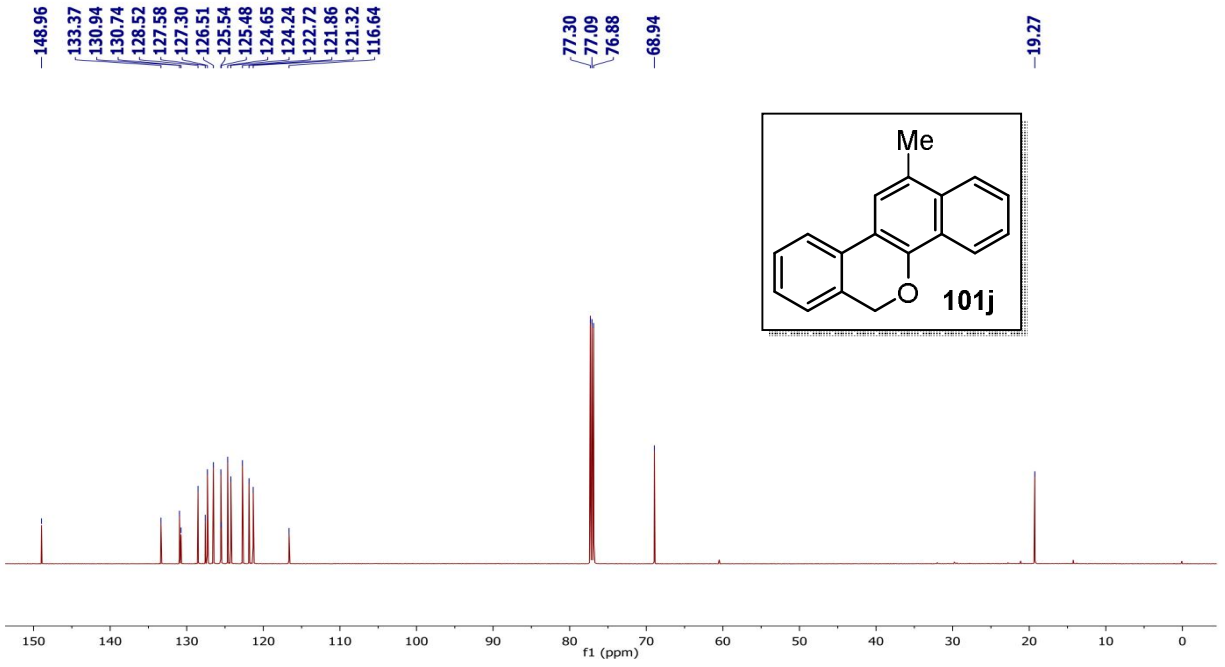
^{13}C NMR (150 MHz) of **101i:**



[1]HNMR (600 MHz) of **101j:**

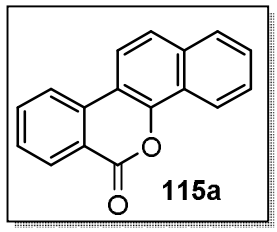


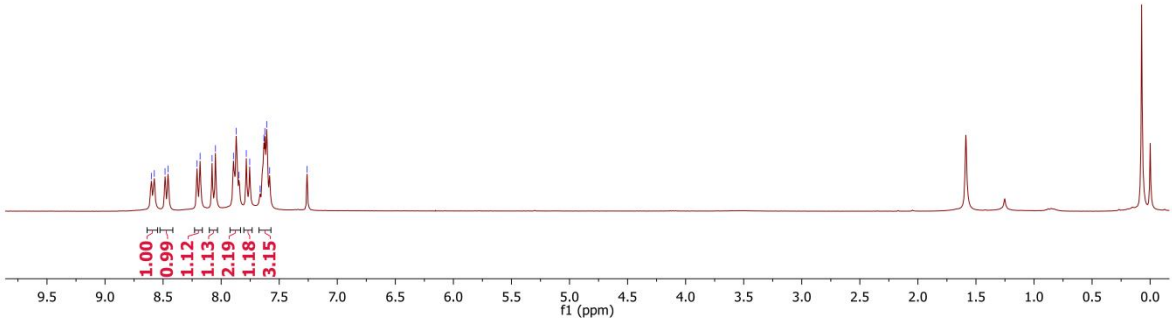
[13]CNMR (150 MHz) of **101j:**



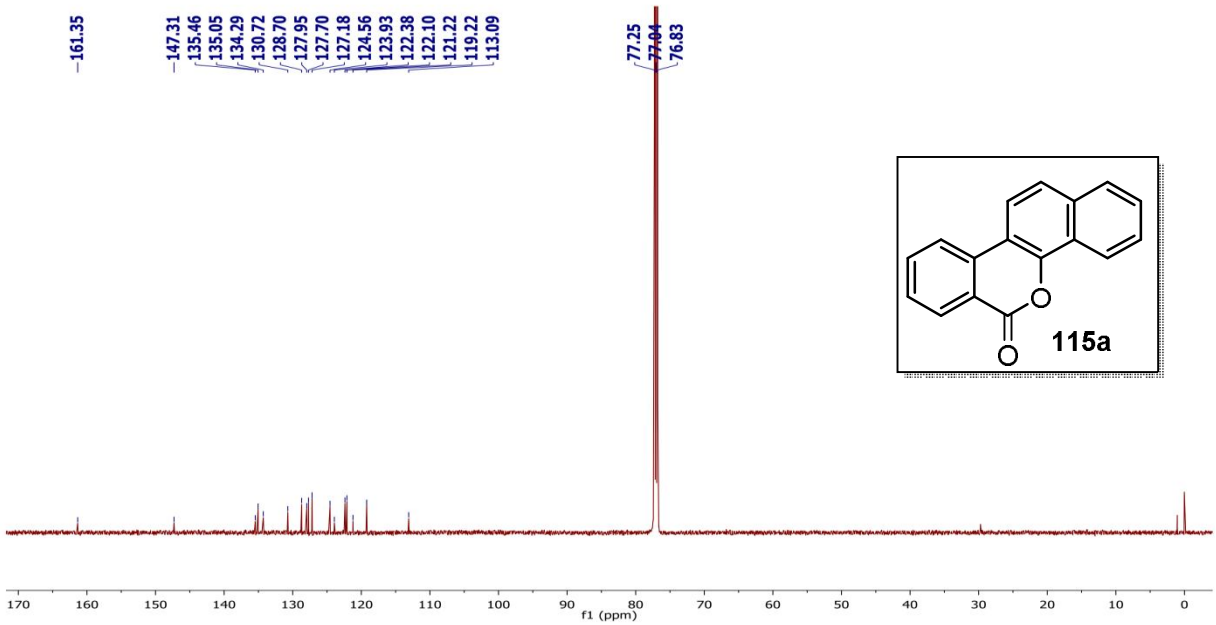
NMR Spectra of Compounds 115a–d:

^{1}H NMR (300 MHz) of **115a:**

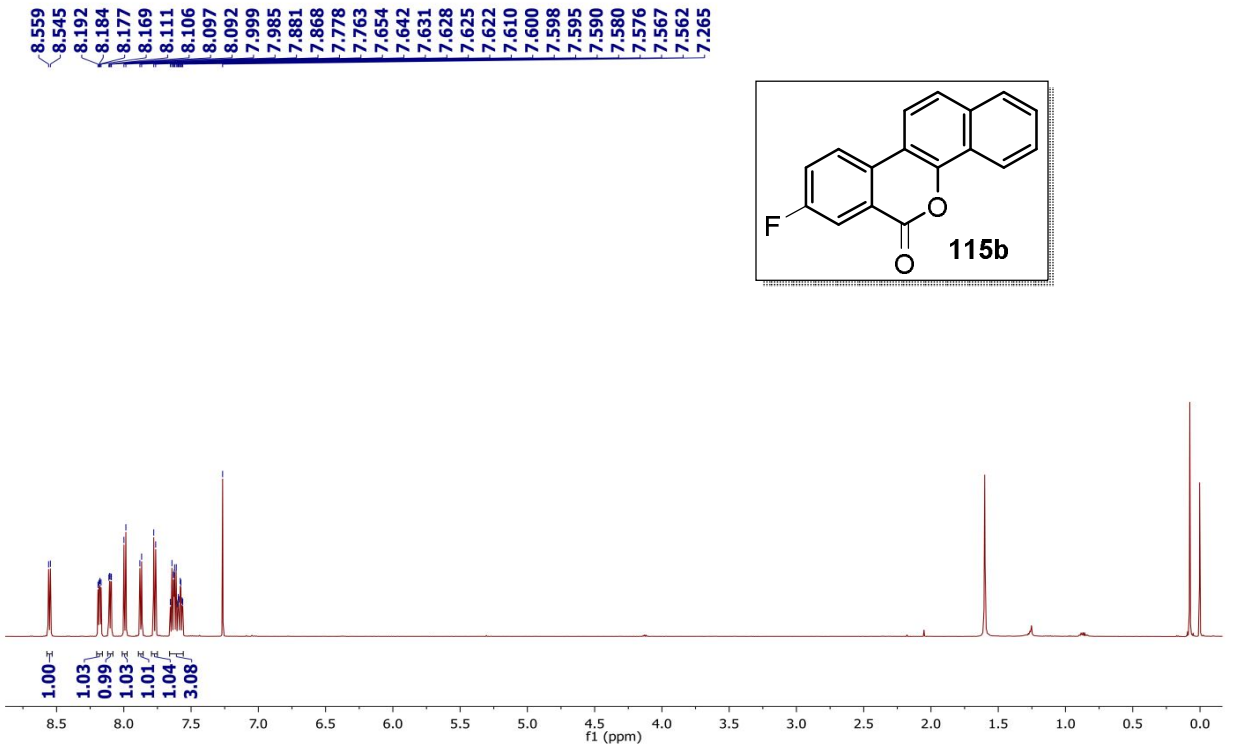




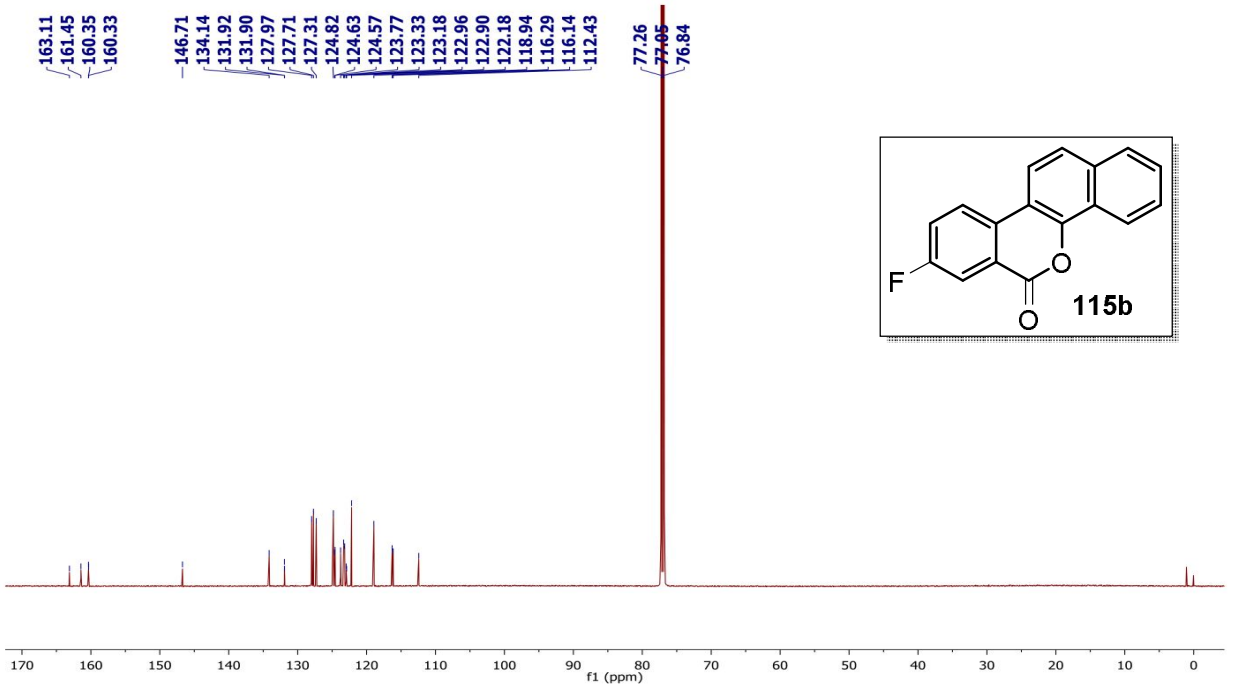
^{13}C NMR (150 MHz) of **115a:**



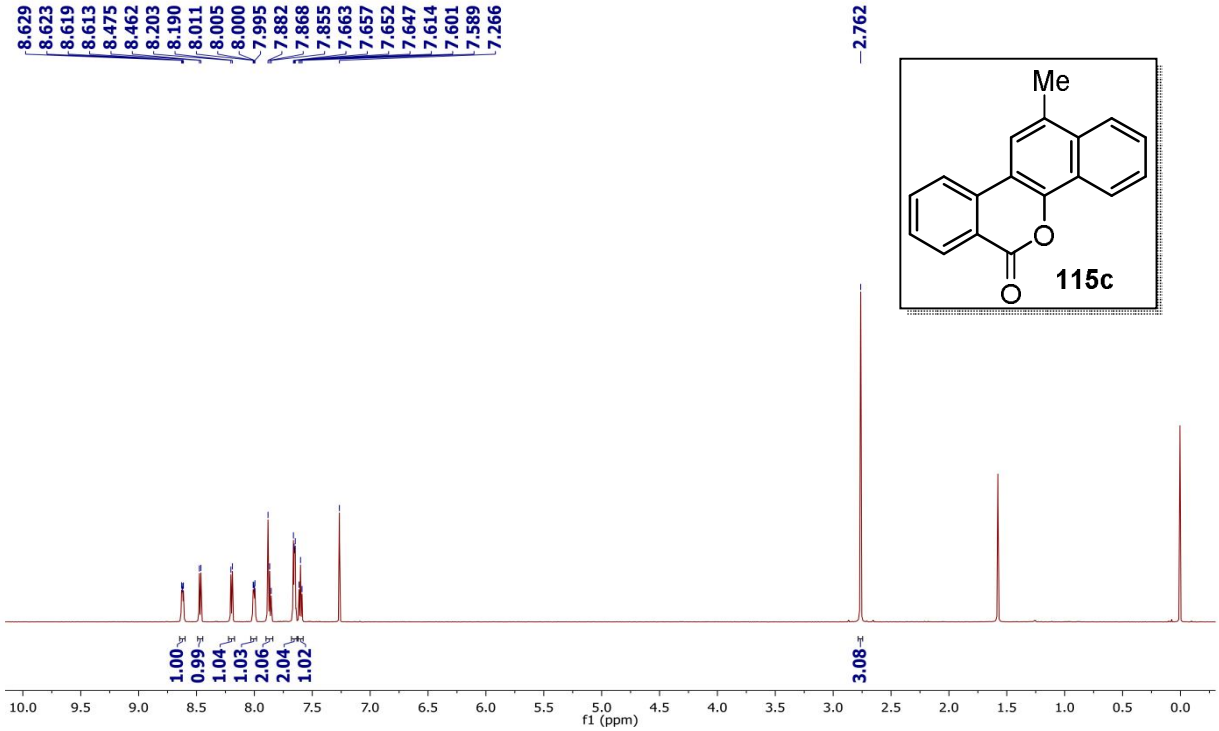
^{1}H NMR(600 MHz) of **115b:**



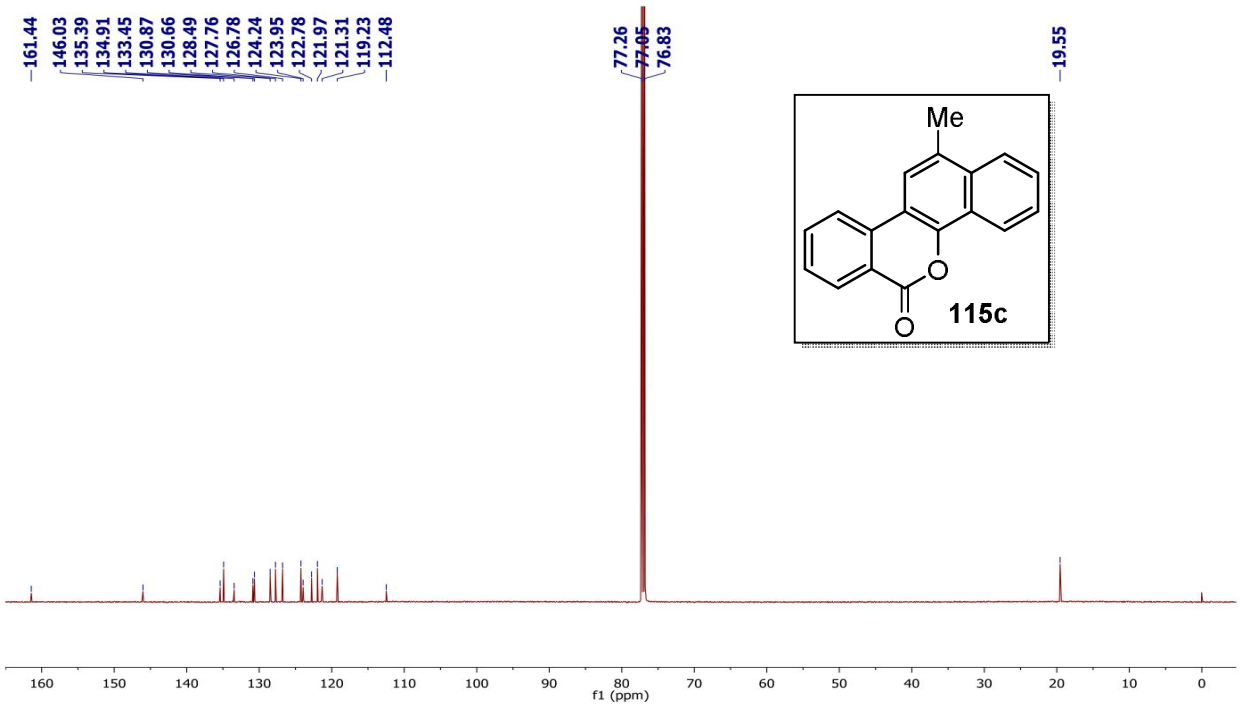
^{13}C NMR (150 MHz) of **115b:**



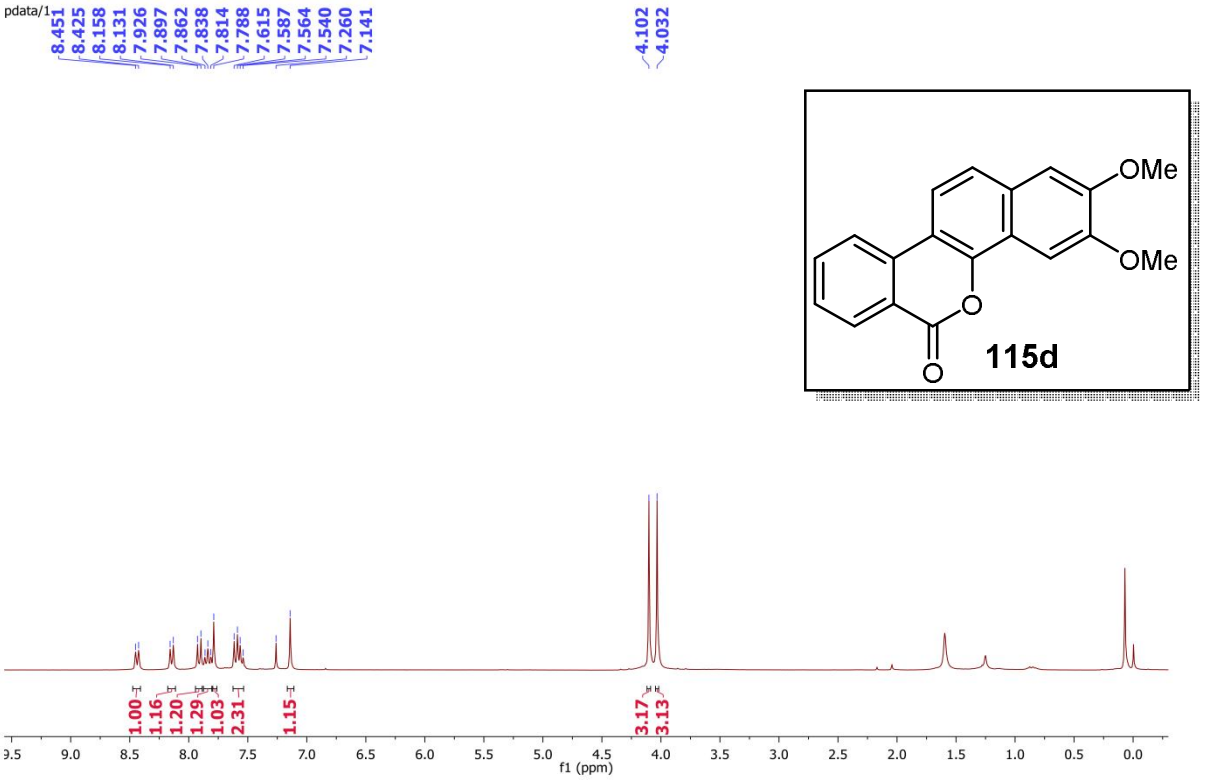
^{1}H NMR (600 MHz) of **115c:**



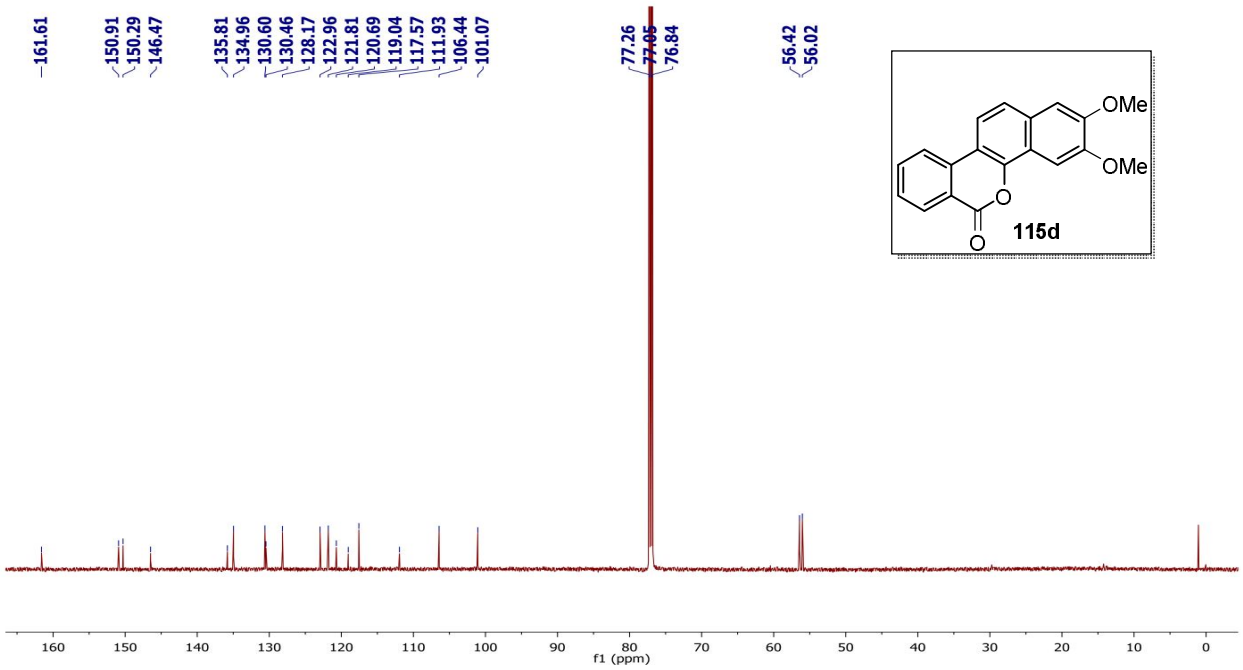
^{13}C NMR (150 MHz) of **115c:**



^{1}H NMR (300 MHz) of **115d:**

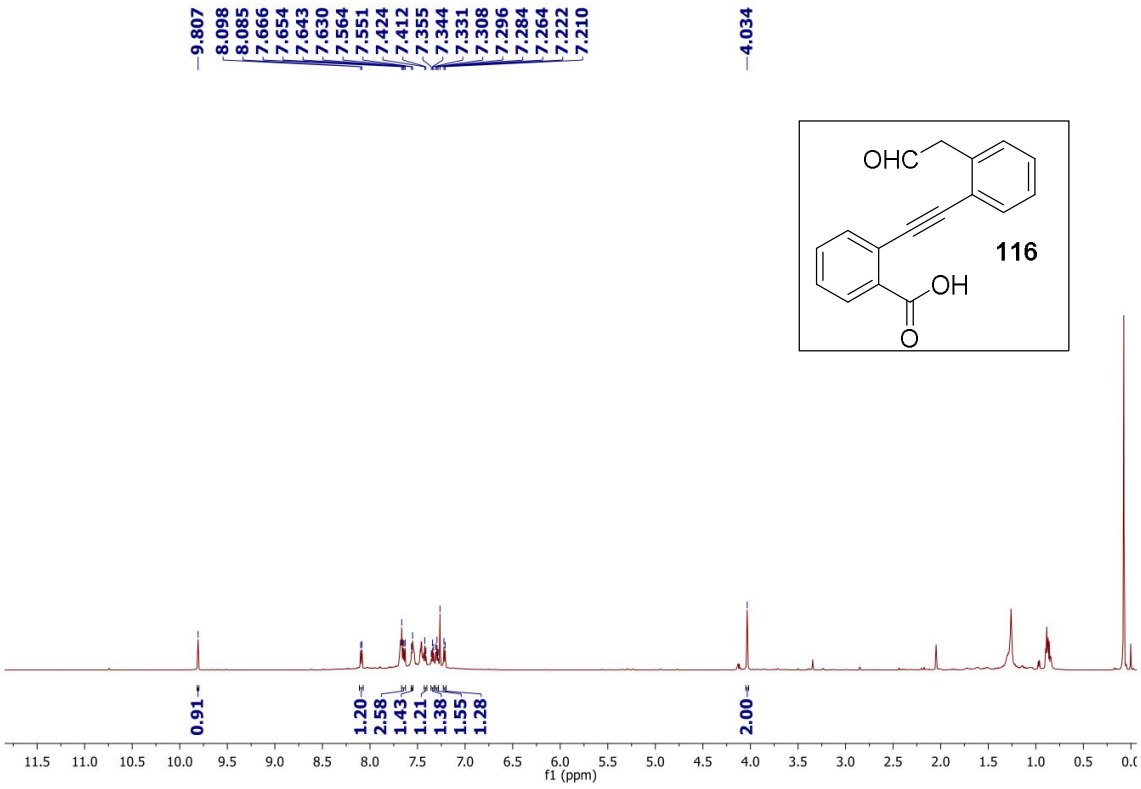


^{13}C NMR (150 MHz) of **115d:**

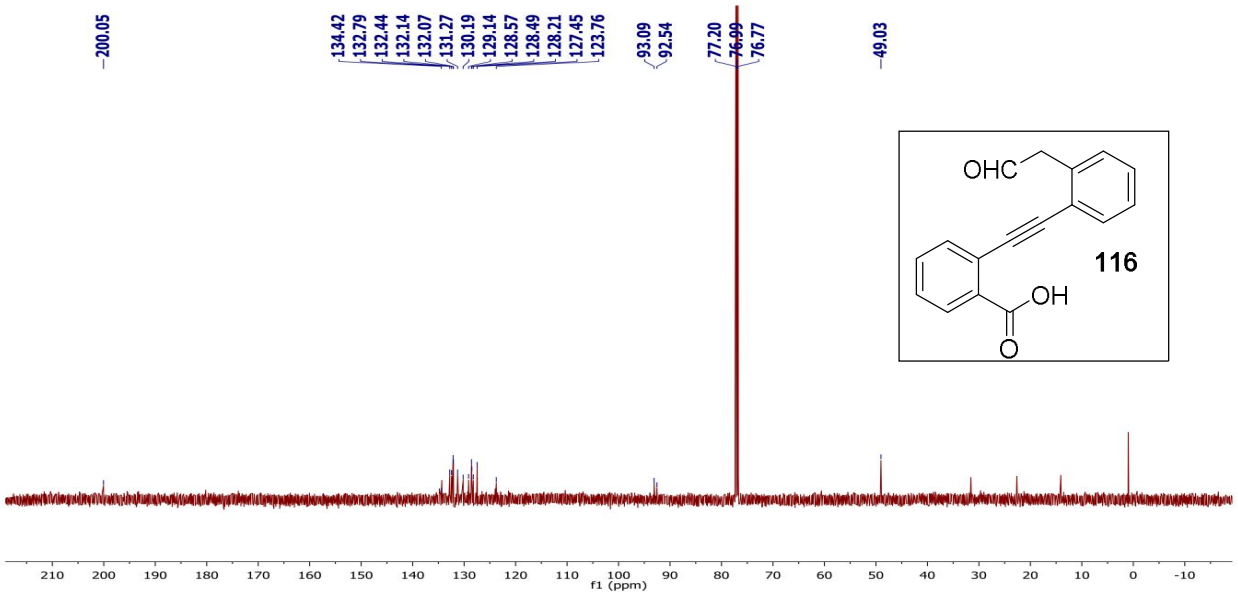


NMR Spectra of Compound 116:

^{1}HNMR (600 MHz) of **116:**

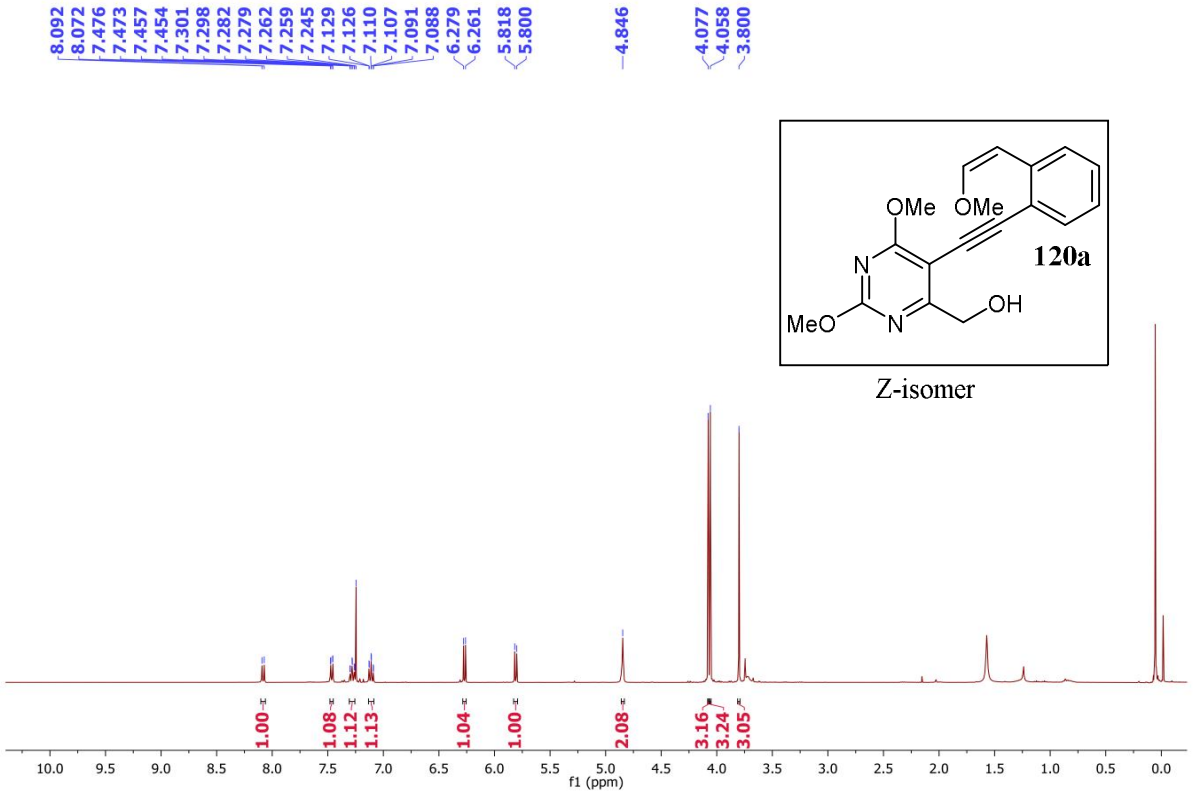


^{13}C NMR (150 MHz) of **116:**



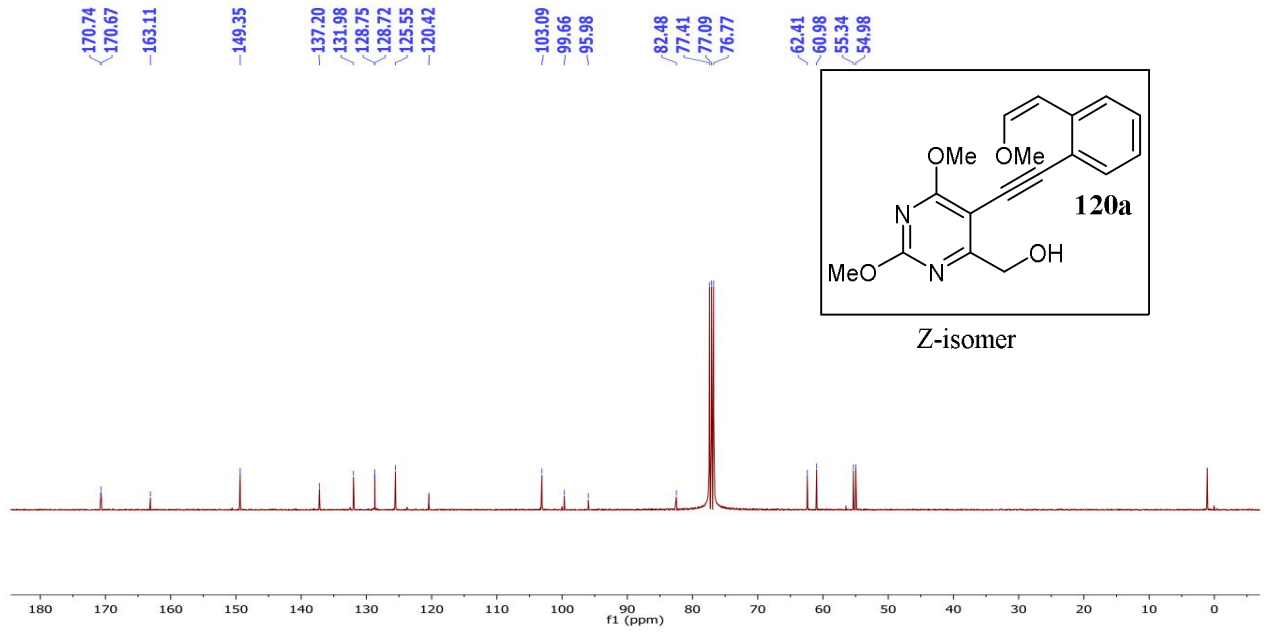
NMR Spectra of Compounds 120a-c

^{1}H NMR 120a (600 MHz)



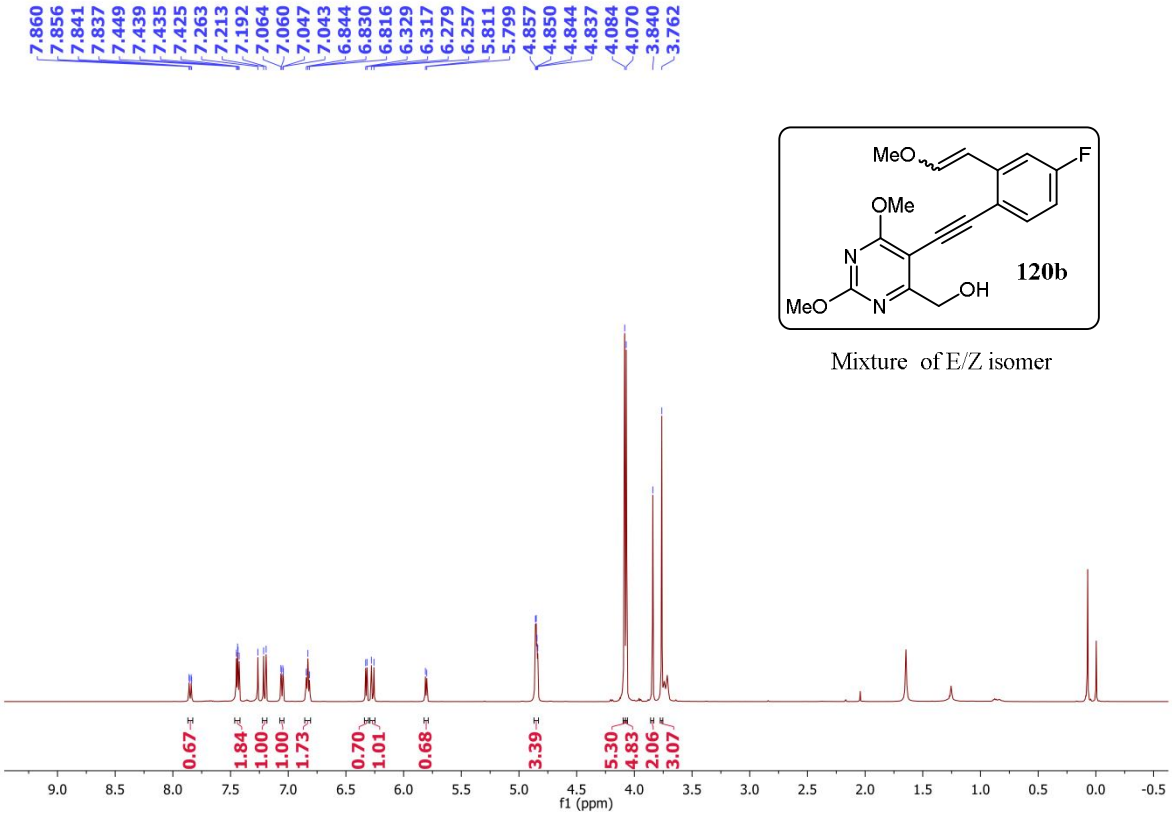
Z-isomer

^{13}C NMR 120a (100 MHz)

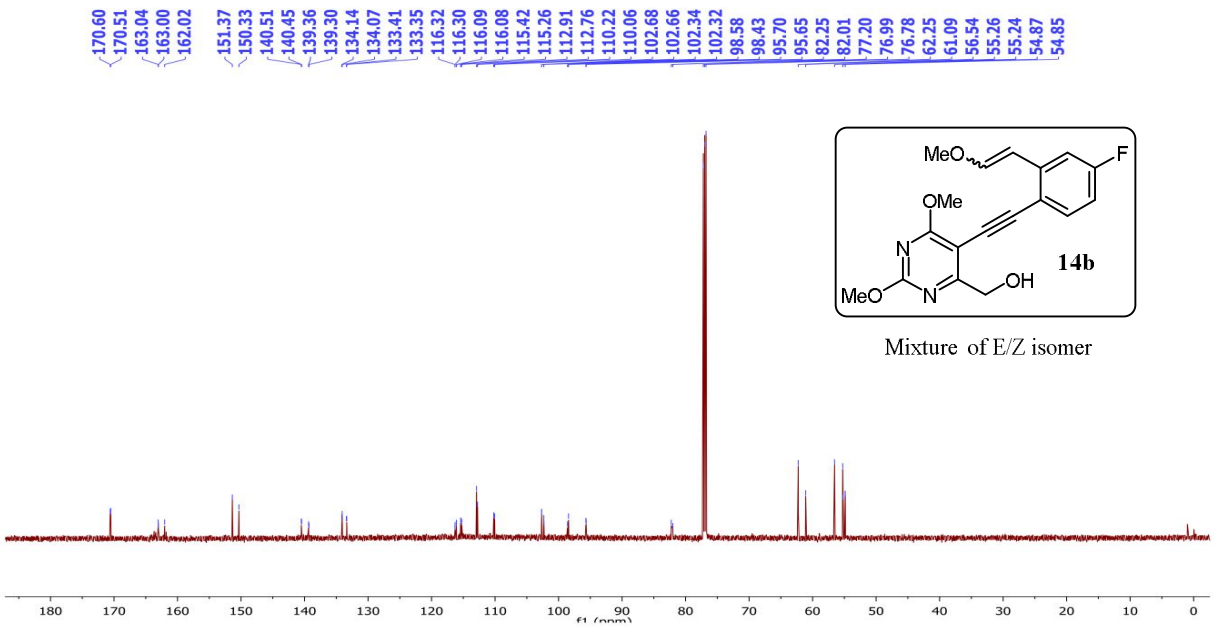


Z-isomer

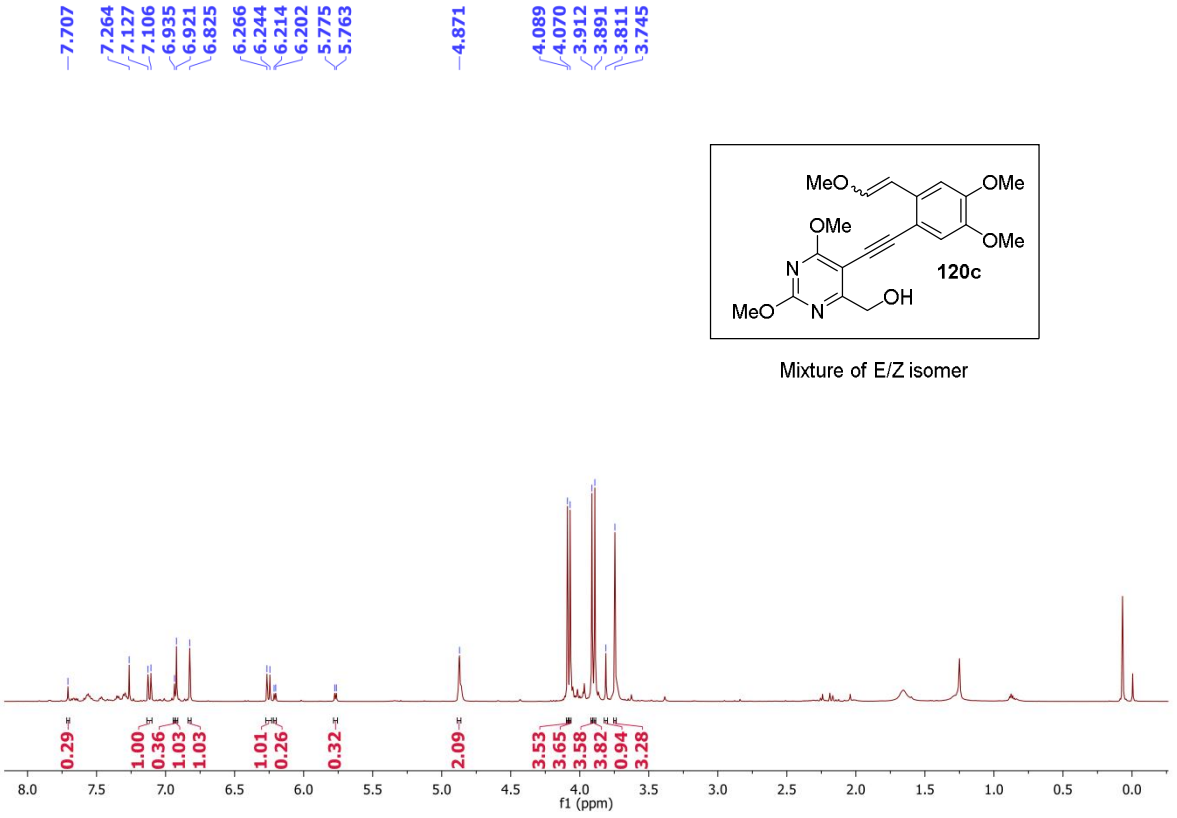
\[1]H NMR 120b (600 MHz)



[13] C NMR 120b (150 MHz)

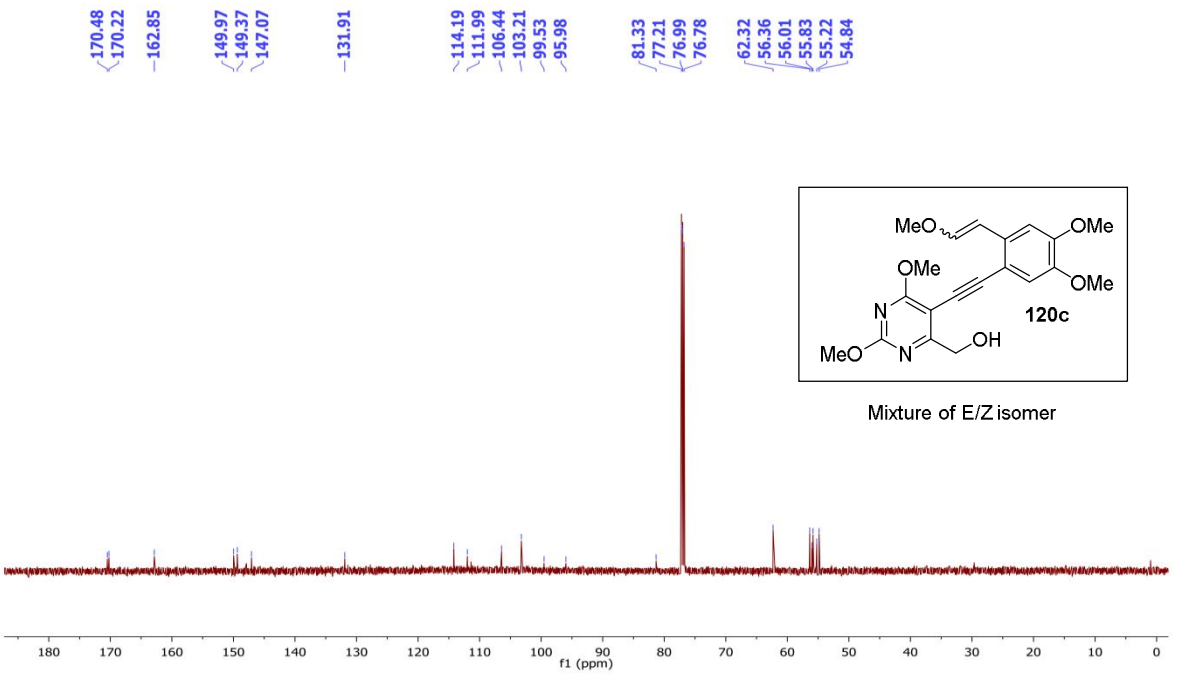


^{1}H NMR 120c (600 MHz)



Mixture of E/Z isomer

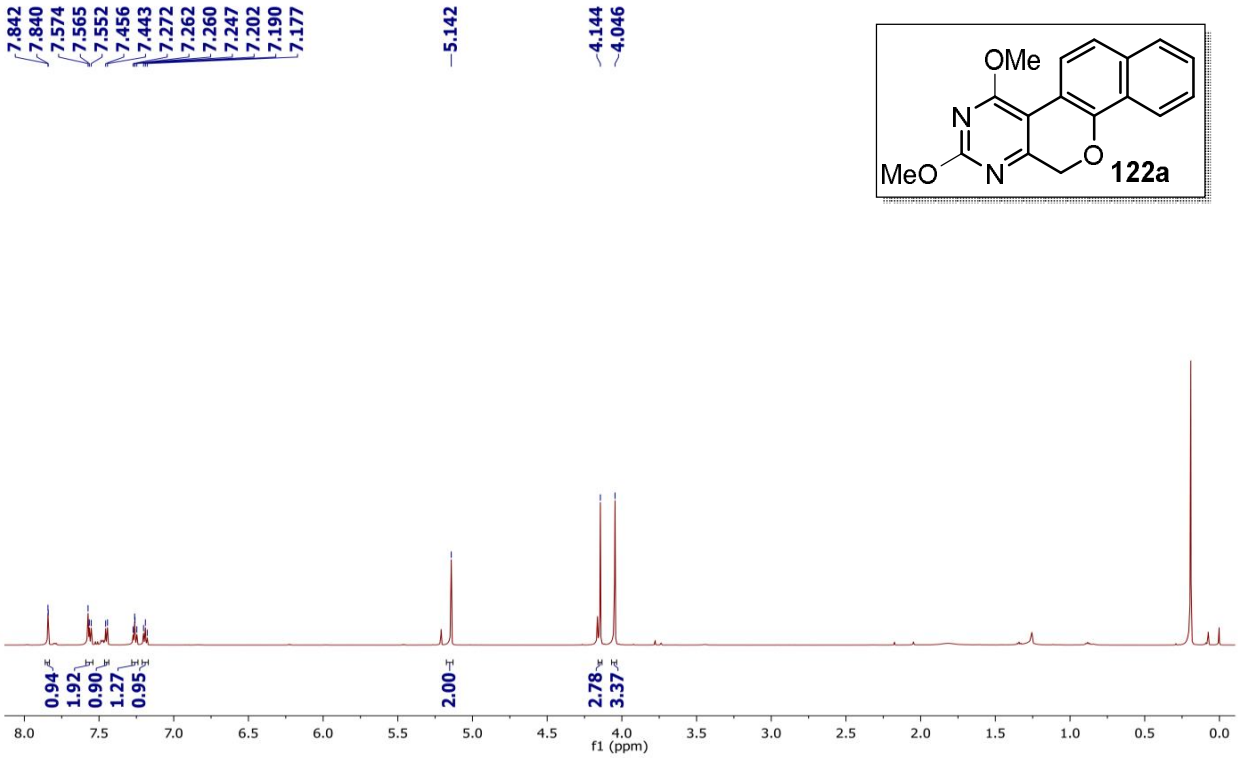
^{13}C NMR 120c (150 MHz)



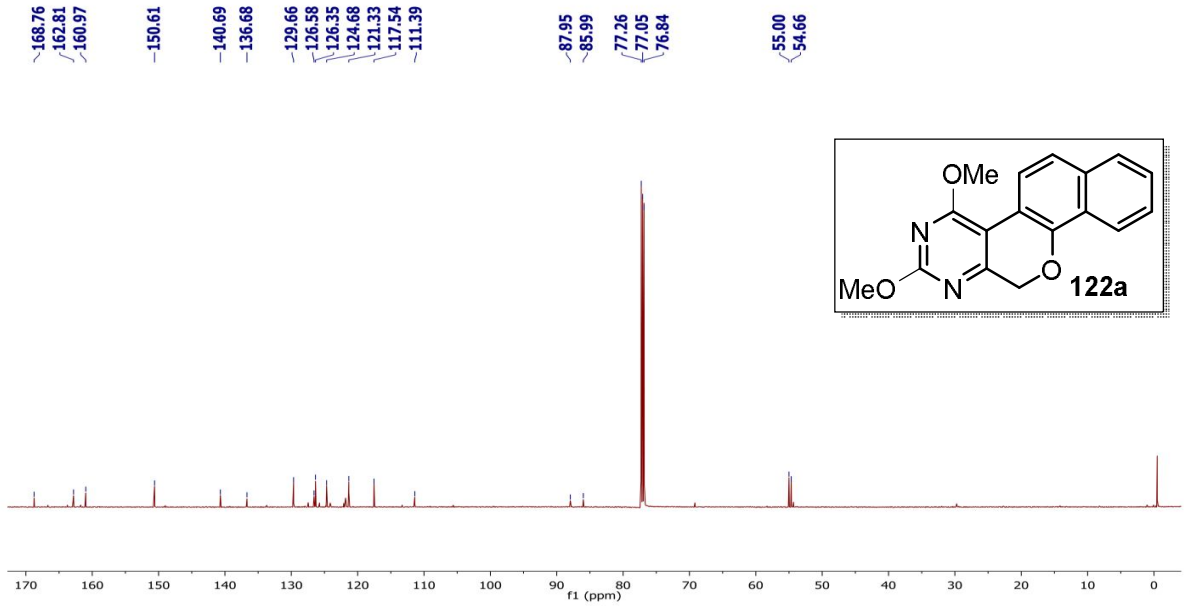
Mixture of E/Z isomer

NMR Spectra of Compounds 122a–c:

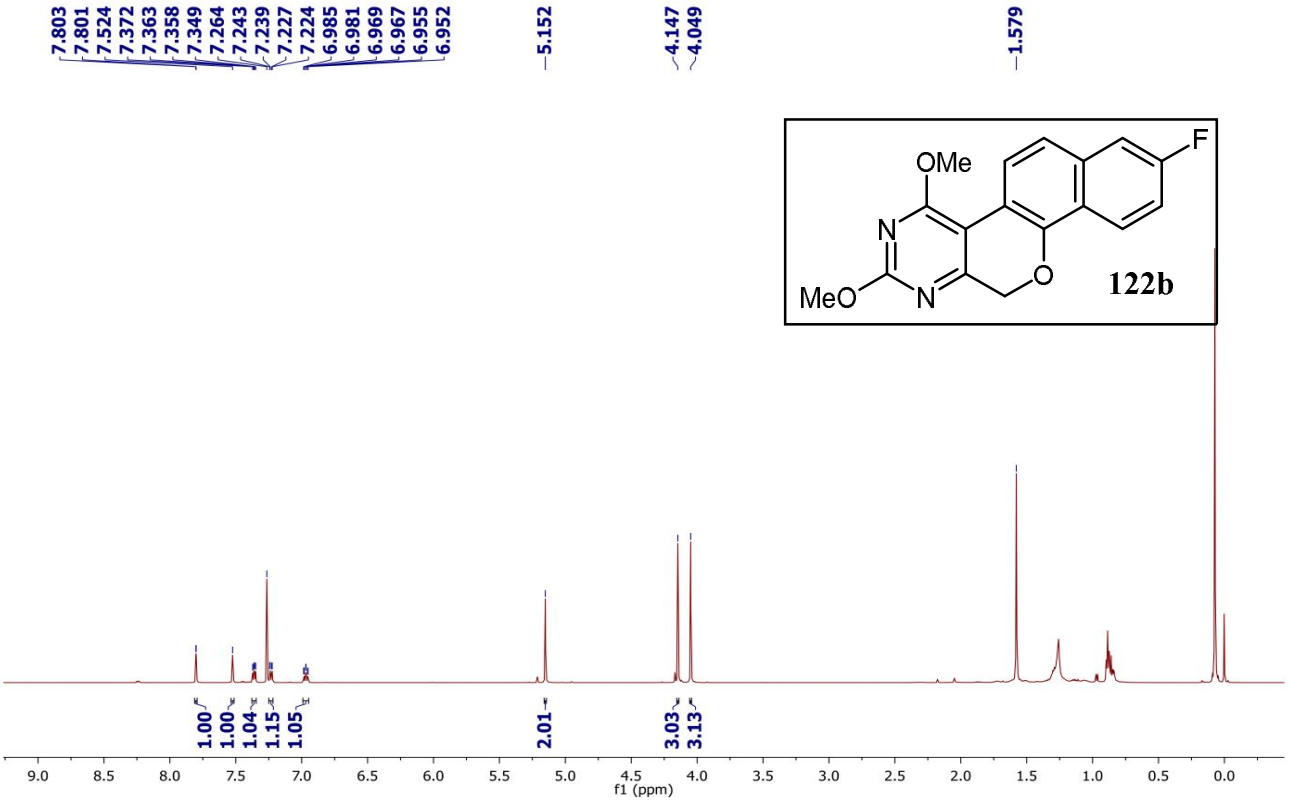
^{1}H NMR (600 MHz) of **122a:**



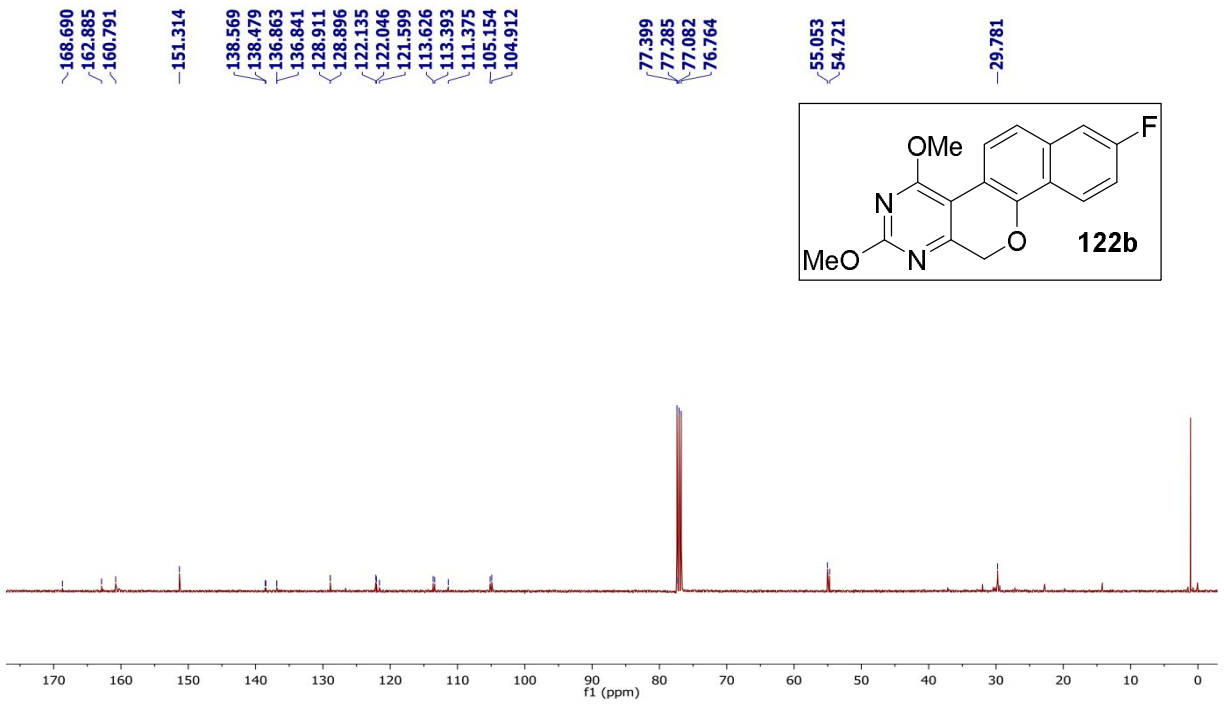
^{13}C NMR (150 MHz) of **122a:**



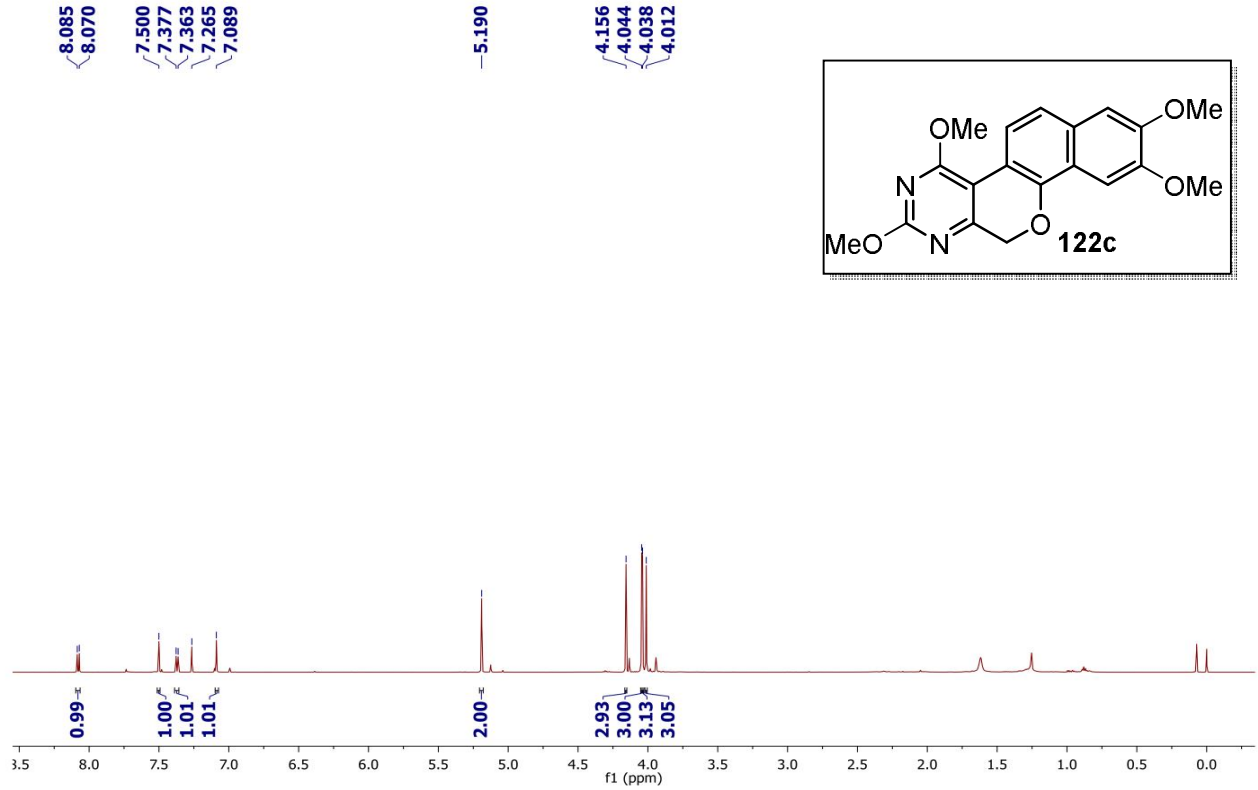
^{1}H NMR (600 MHz) of **122b:**



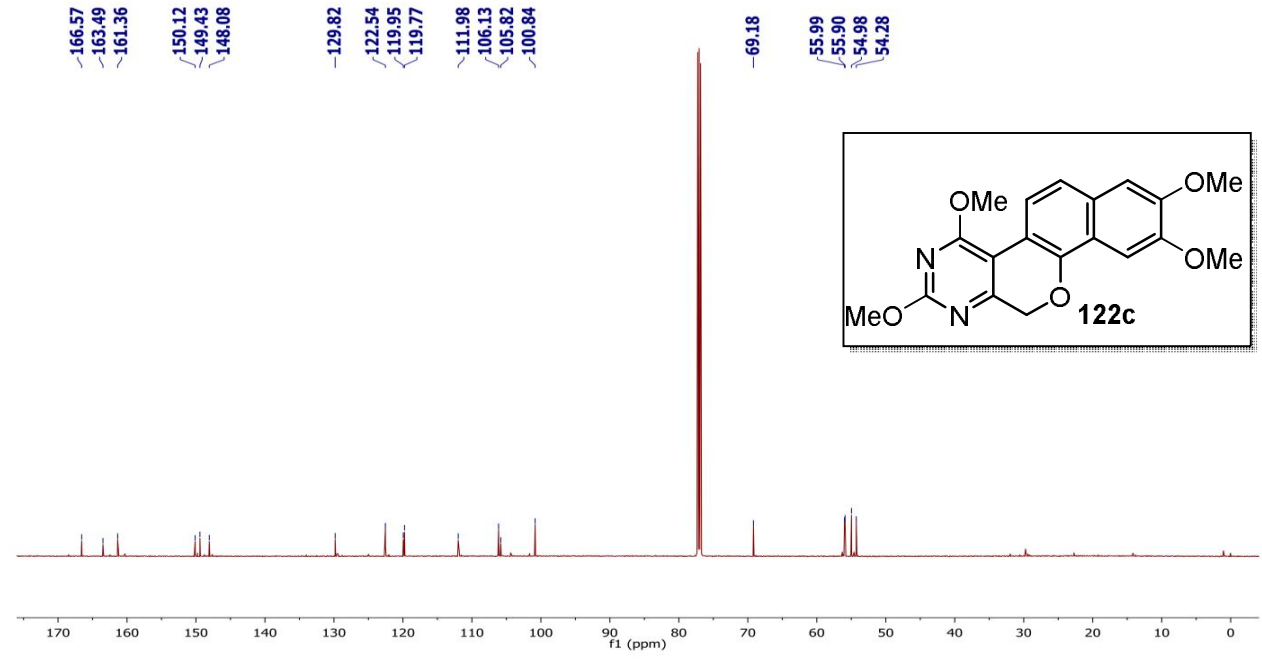
^{13}C NMR (100 MHz) of **122b:**



^{1}H NMR (600 MHz) of **122c:**

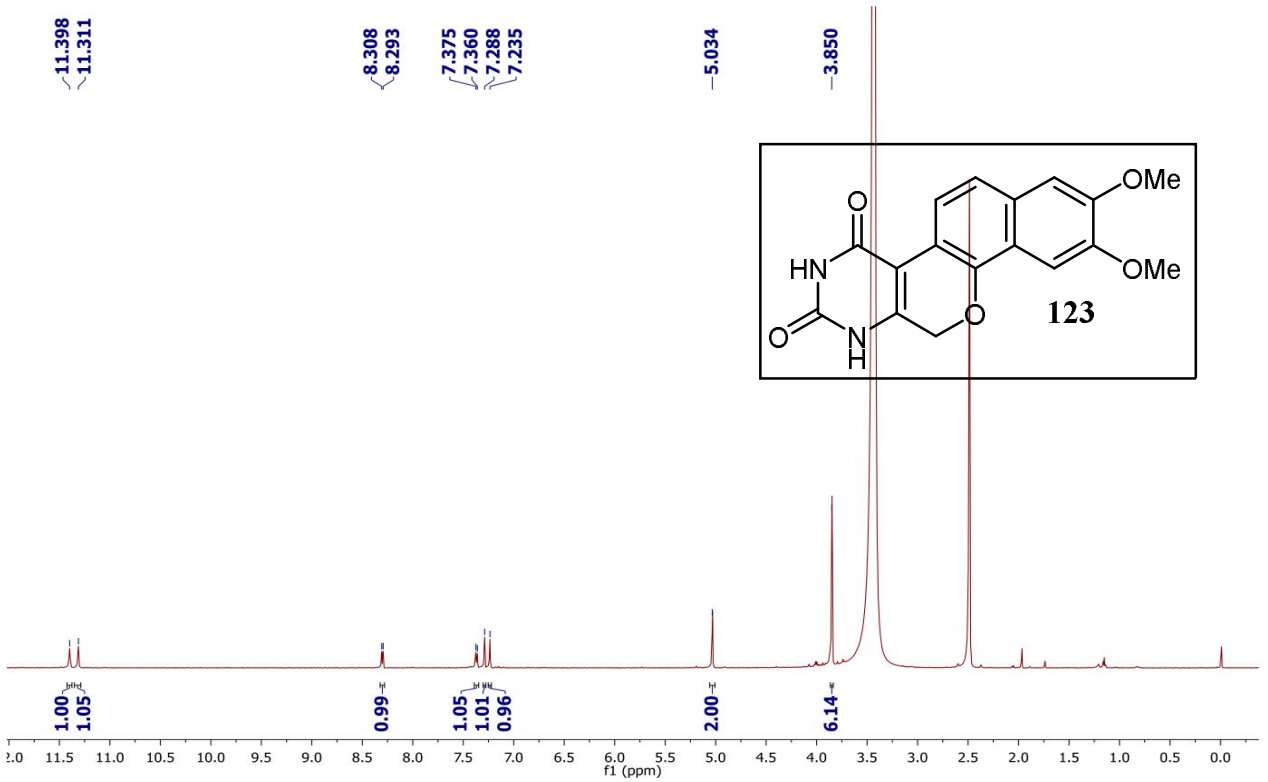


^{13}C NMR (150 MHz) of **122c:**

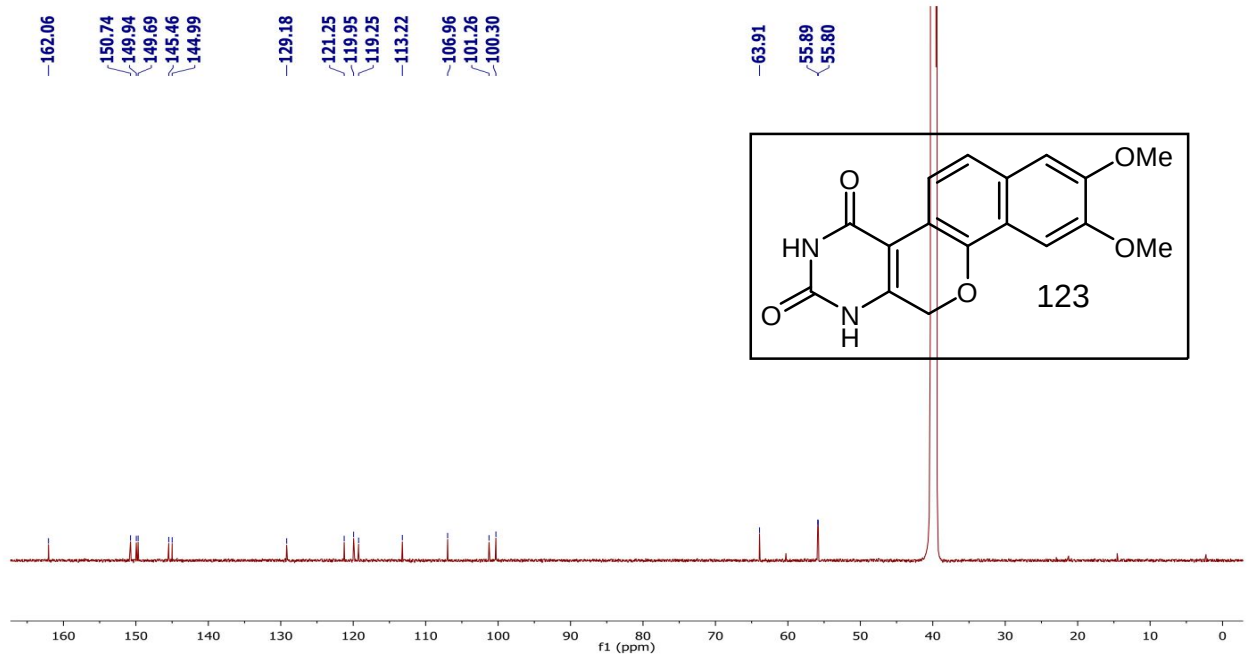


NMR Spectra of Compounds 123:

^{1}H NMR (600 MHz) of **123:**

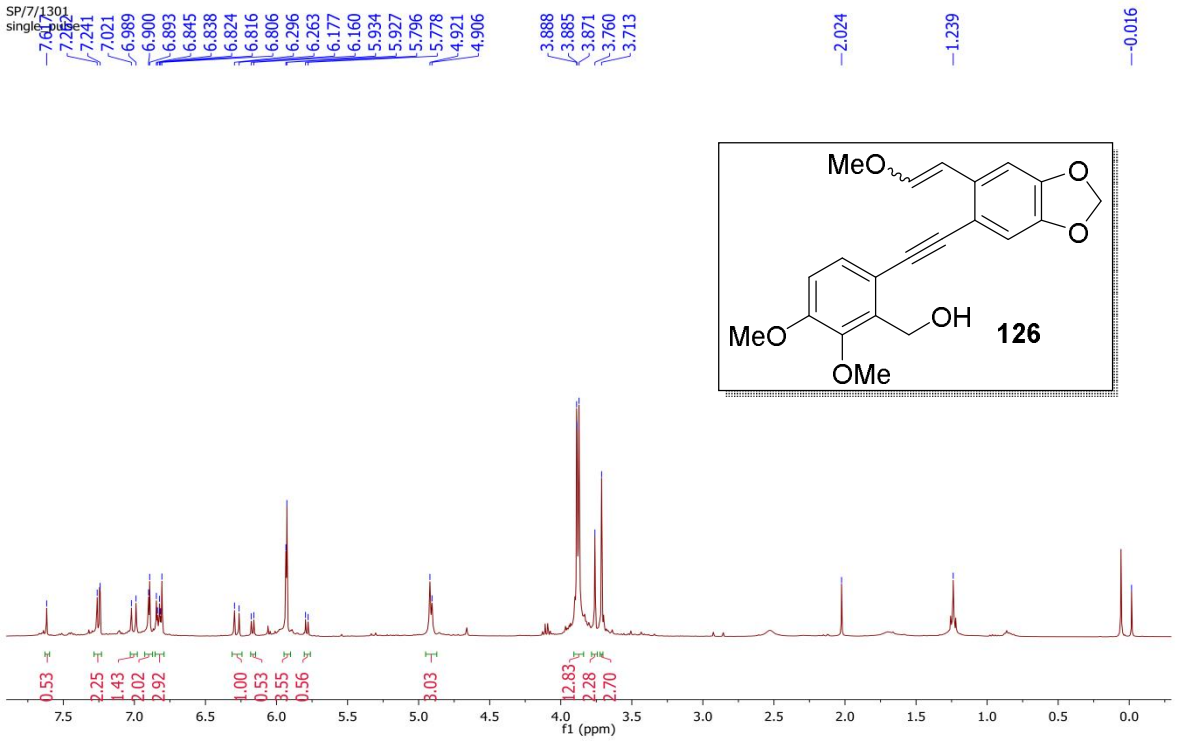


^{13}C NMR (150 MHz) of **123**:

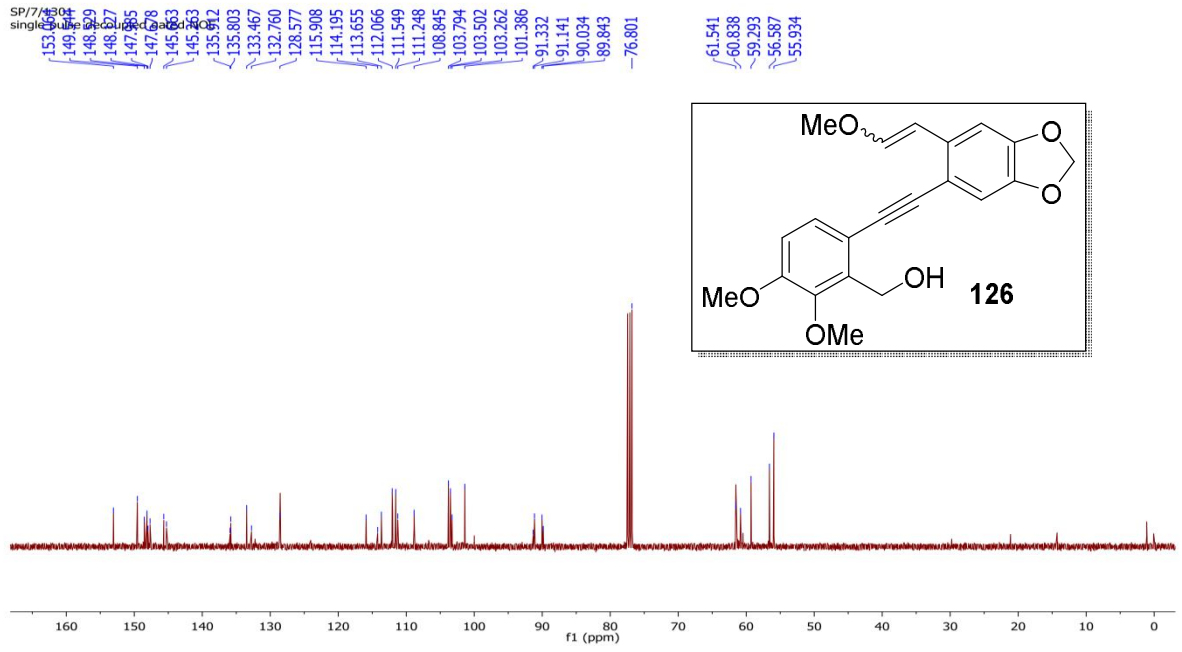


NMR Spectra of Compounds 126:

^{1}H NMR (400 MHz) of **126:**

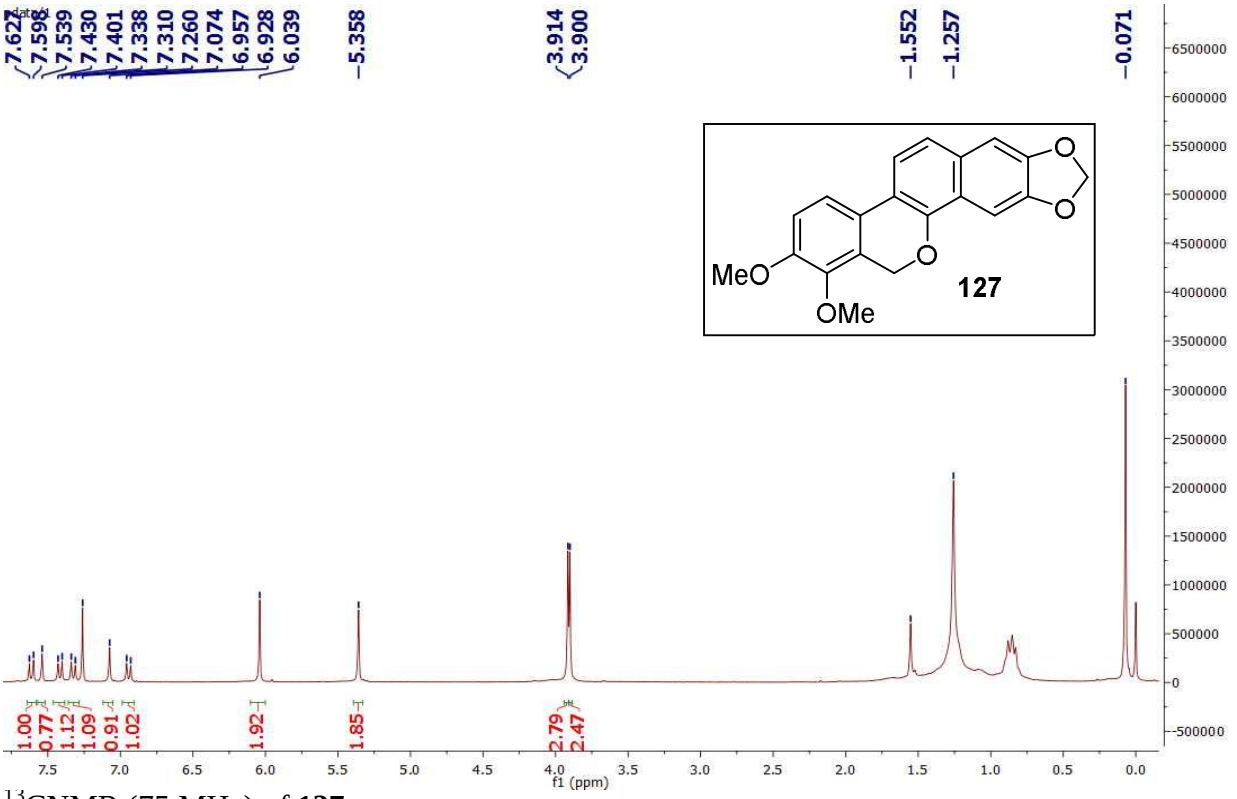


^{13}C NMR (100 MHz) of **126:**

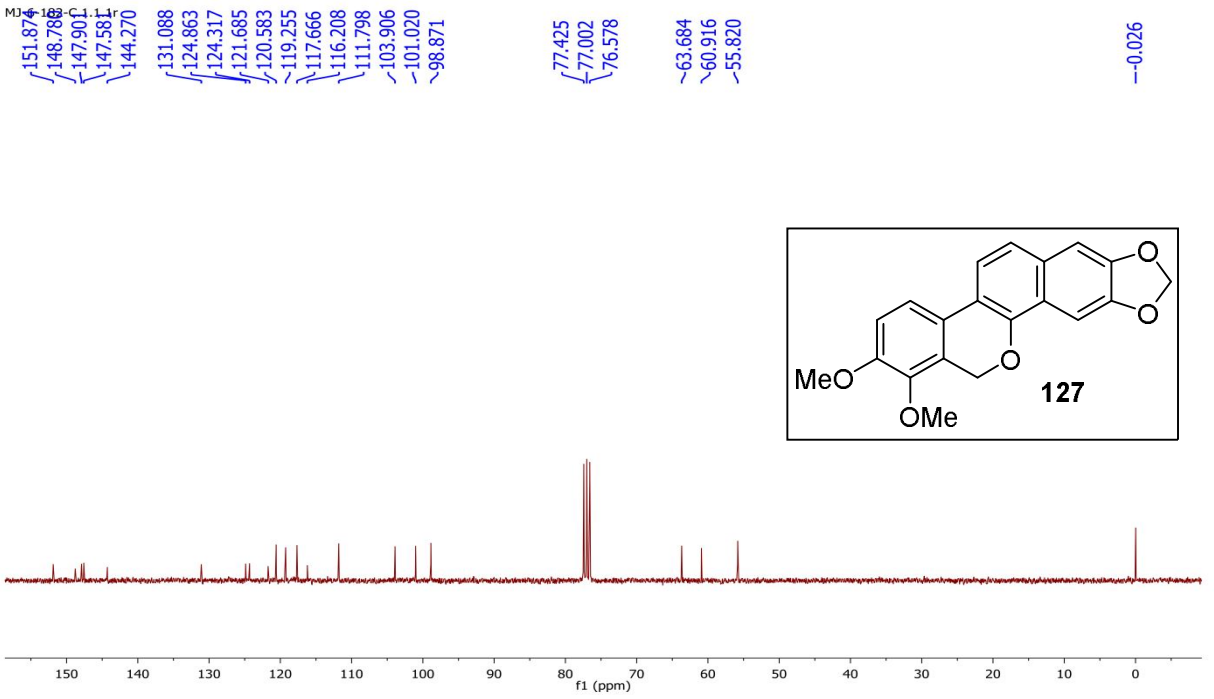


NMR Spectra of Compounds 127:

^{1}HNMR (300 MHz) of **127:**



^{13}CNMR (75 MHz) of **127:**



Chapter 3

Palladium(II)-Catalyzed Cascade Reactions of Ene−Ynes Tethered to Aldehyde: Access to Naphtho[1,2-b]furans

Part I

(A Short Review)

3.1.1. Introduction

Naphtho[*b*]furans are structural components of a large number of natural and synthetic compounds (Figure 1).[1] Some naturally occurring substances in this family exhibit a variety of interesting pharmacological properties.[2] Structurally, there are two types of naphtho[*b*]furans, namely, (a) naphtho[1,2-*b*]furans **A** and (b) naphtho[2,1-*b*]furans **B** as shown in Fig. 1. Due to wide applications in medicinal chemistry as well as in material sciences, herein, we have been interested in the synthesis of naphth[1,2-*b*]furans **A.**

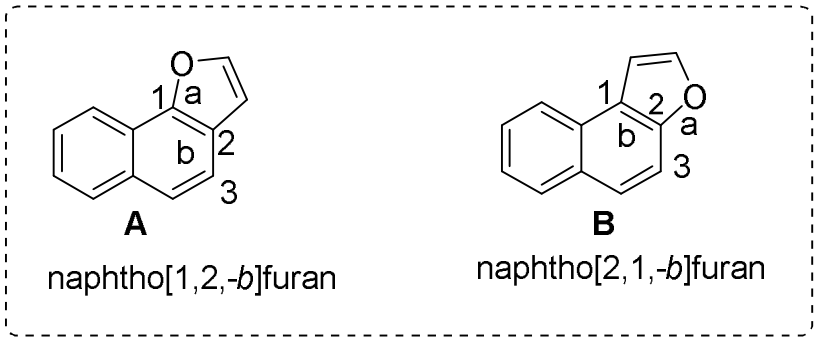


Fig .1. Structures of naphtho[1,2-*b*]furan **A** and naphtho[2,1-*b*]furan **B**

3.1.1.1. Importance of Naphtho[1,2-*b*]furans in Medicinal Chemistry

Naphtho[1,2-*b*]furans[3] **I** is the core structure of a large number of biologically active natural and synthetic compounds. For example, *isonapabucasin* **1a**[4] (Figure 2), which strongly inhibited the growth of human breast cancer cells (MDA-MB-231) and is twice as potent against STAT 3 as *napabucasin*, a recently approved drug for the treatment of pancreatic cancer. While naphtho[1,2-*b*]furan-4,5-dione or N12D **1b** isolated from mangrove plants, which exhibited significant biological activity against hepatoma, squamous cell carcinoma and breast cancer,[5] and methicillin-resistant *Staphylococcus aureus*. Besides, compound **2** is an efficient material for altering the lifespan of eukaryotic organisms.[6] Compound **3** acts as a potential drug to treat cancer.[7] *Furomollugin* **4** isolated from several members of the

Rubiaceae family including *Rubia cordifolia* [8] exhibits cytotoxic activity against human colon carcinoma cells (HT-29) through suppression of HBsAg secretion of human hepatoma Hep3B cells[9], and exhibits inhibitory activity against DNA topoisomerases I and II. [10] *Radermachol* **5** isolated from *Radermachera xylocarpa* K. Schum in India [11,12] and it has been used as nervine, calmative, antispasmodic, emetic, anthelmintic, abortifacient, as well as a substitute for ipecacuanha [11,12]. *Balsaminone A* **6** shows antipruritic activities.[13] *Rubicordifolin* **7**, a constituent of Rubiacordifolia, displayed significant efficacy by inhibiting the growth of sarcoma ascites in mice at low concentrations.[14] While arylsulfonamide naphtho[1,2-*b*]furan derivative **8a** is a selective inhibitor of triple-negative breast cancer,[15a] and **8b** displayed significant activity in lung and colon cancer cells.[15b] (Fig. 2).

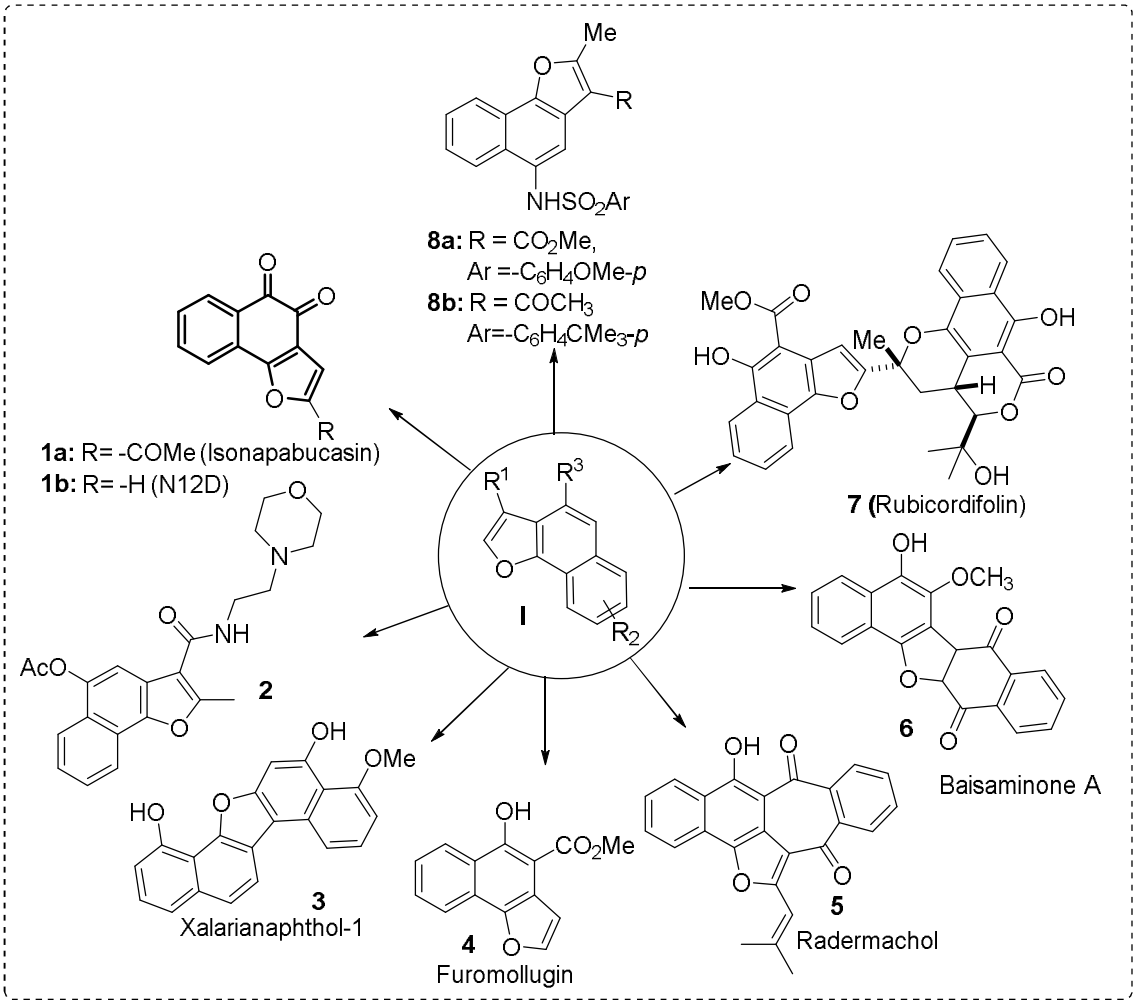


Fig.2. Some biologically active naphtho[1,2-*b*]furans derivatives

3.1.1.2. Applications of Naphtho[1,2-*b*]furans in Material Sciences

Leo *et al*[16] synthesized the compound NF-BDP **9** (Fig. 3) that act as a dye. Emission peaks can be tuned in wide range from 777 to 707 nm for NF-BDP with decreasing concentration in solution. Excellent photostability and thermal stability are demonstrated in this dye with negligible photobleaching and high decomposition temperature. It's absorption and emission spectra were found to be red-shifted into NIR region peaking over 700 nm in vacuum-deposited film. Ogilby et al.[17] synthesized naphtho[1,2-*b*]furan derivatives **10** (Fig. 3) as sensitizer. The data indicate that the two-photon absorption cross sections of those compounds are comparatively large and depend significantly on the functional groups attached to the chromophore. Singlet molecular oxygen ($a^1\Delta_g$) produced and optically detected upon two-photon nonlinear excitation of a sensitizer with a focused laser beam. Two-photon absorption cross sections of those compounds are comparatively large and depend significantly on the functional groups attached to the chromophore. *Fulgides* **11** (Fig. 3) based on naphtho[1,2-*b*]furans were prepared and their photochromic properties were studied.[18] *Fulgides* shows promising photochromic properties which found potential applications in three-dimensional optical data storage devices and optical molecular switches due to high stability of their initial and photo induced forms. Interestingly, *Fulgides* **11** showed fluorescence and high thermal stability of photo generated cyclic form. Besides, these compounds also showed repeated photocoloration—photobleaching properties which was accompanied by reversible photo induced *E*—*Z* isomerization.

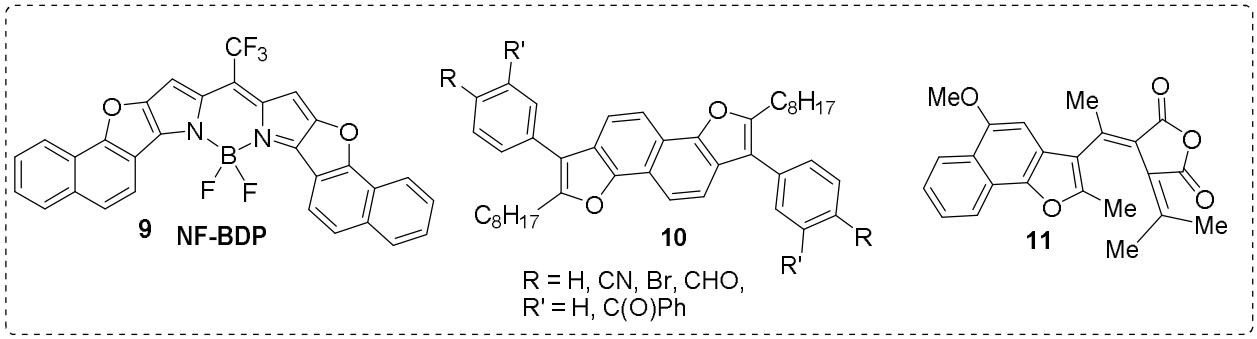
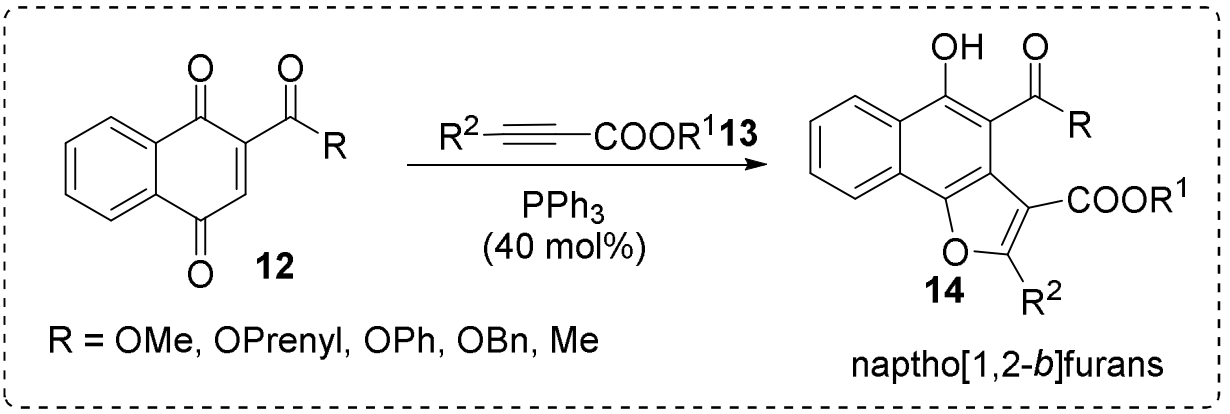


Fig. 3. Few naphtho[1,2-*b*]furans derivatives having applications in material sciences.

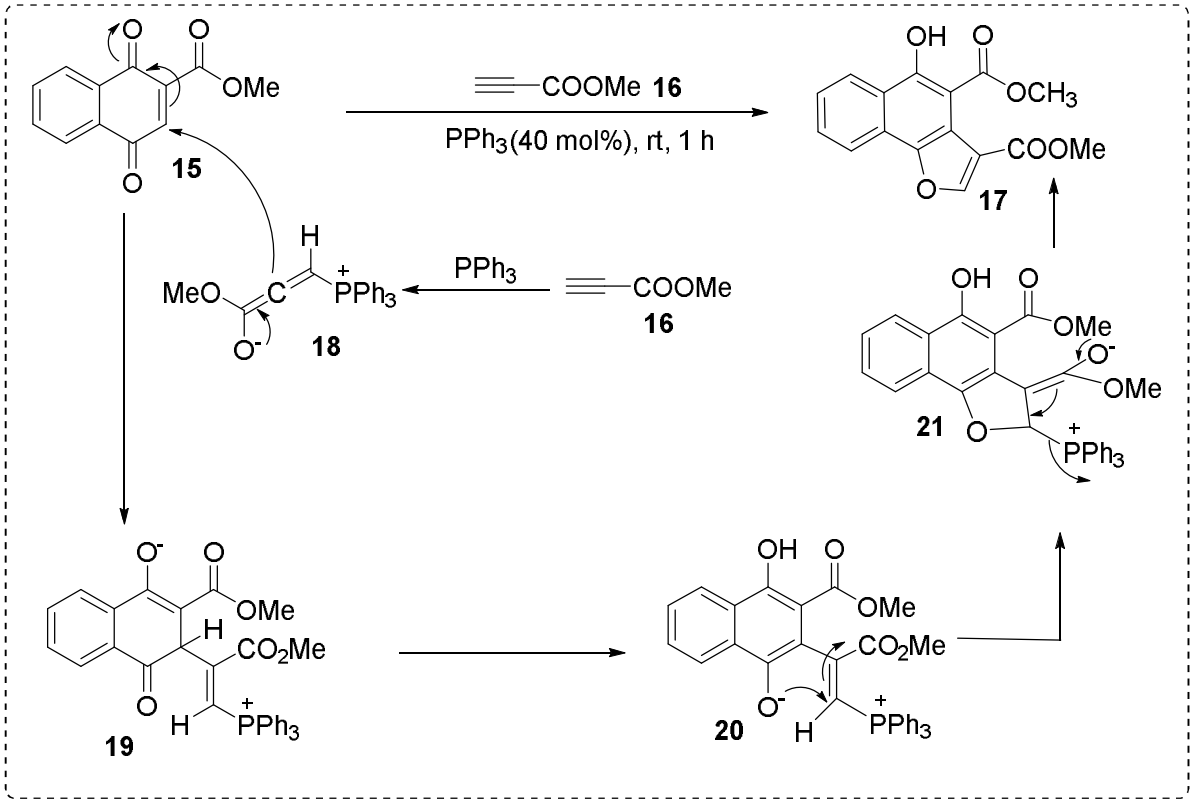
3.1.2. Synthesis of Naphtho[1,2-*b*]furans

3.1.2.1 General methods for the synthesis of naphtho[1,2-*b*]furans using conventional reactions

Lee *et al.*[19] reported phosphine-catalyzed [3+2] annulation reactions of activated 1,4-naphthoquinones **12** and acetylenecarboxylates **13** to produce a variety of biologically interesting naphtho[1,2-*b]*furan derivatives **14** (Scheme 1). For example, 1,4-naphthoquinones **15** treated with methyl propiolate **16** in MeCN in presence of triphenylphosphine (TPP, 40 mol%) at room temperature leads to naphtho[1,2-*b*]furan product **17** (Scheme 2). Reaction pathway involves the following step: methyl propiolate **16** in the presence of PPh_3 gives zwitterion **18**, which then reacts with **15** to furnish intermediate **19**. Aromatization of **19** followed by proton transfer to furnish the intermediate **20**. Finally, intermediate **20** undergoes [3+2] annulation to trigger the formation of product **17** via intramolecular 1,4-addition of **20** and subsequent elimination of PPh_3.

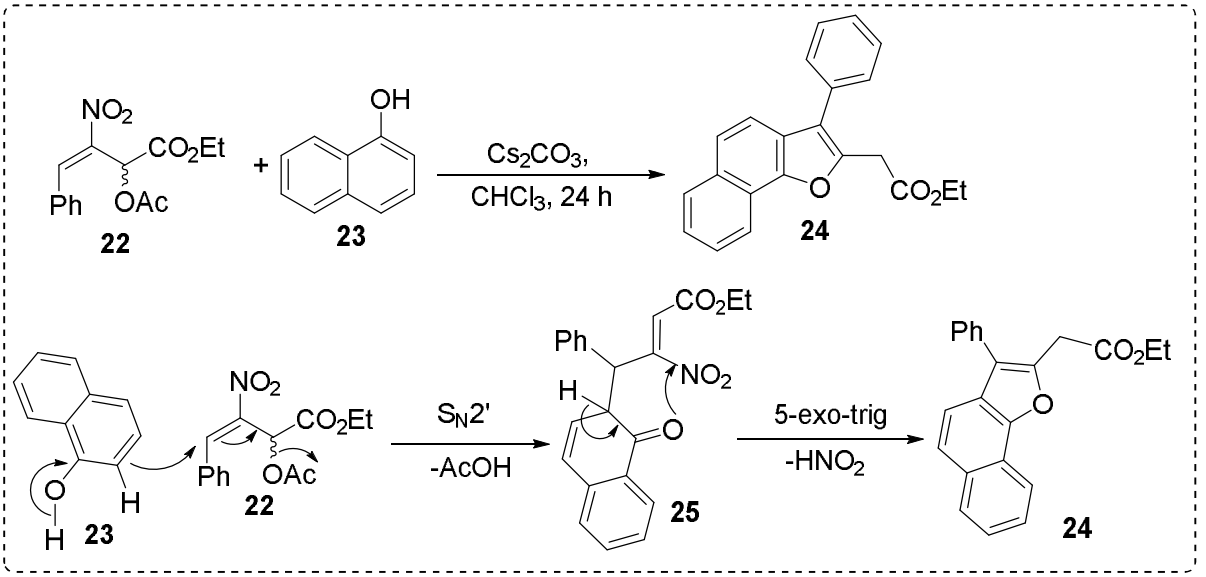


Scheme 1. Synthetic strategy for naphtho[1, 2-*b*]furans derivatives **14**



Scheme 2. Synthesis of naphtho[1, 2-*b*]furans derivatives **17** with a plausible mechanism**.**

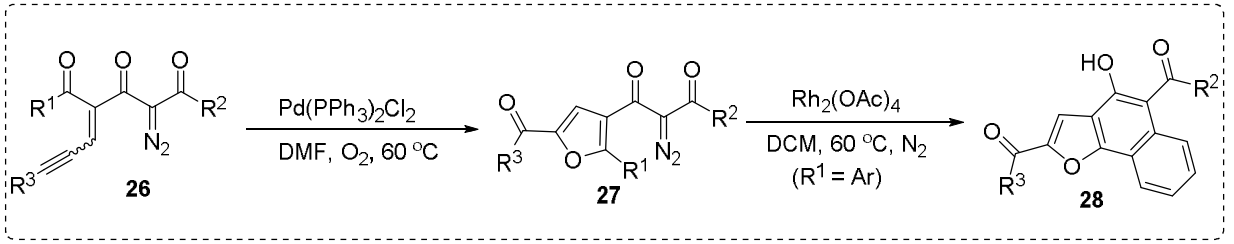
Chen *et.al.*[20] reported a method for the synthesis of naphtho[1,2-*b*]furan derivatives **24** by treatment of naphthols with nitroallylic acetates through a substitution–elimination process promoted by cesium carbonate. Mechanistically, naphthol **23** undergoes a Friedel–Crafts-type reaction with nitroallylic acetate **22** followed by intramolecular Oxa-Michael cyclization resulting into functionalized naphthofurans **24** as shown under Scheme 3.



Scheme 3. Synthesis of naphtho[1, 2-*b*]furans derivatives **24** with a plausible mechanism**.**

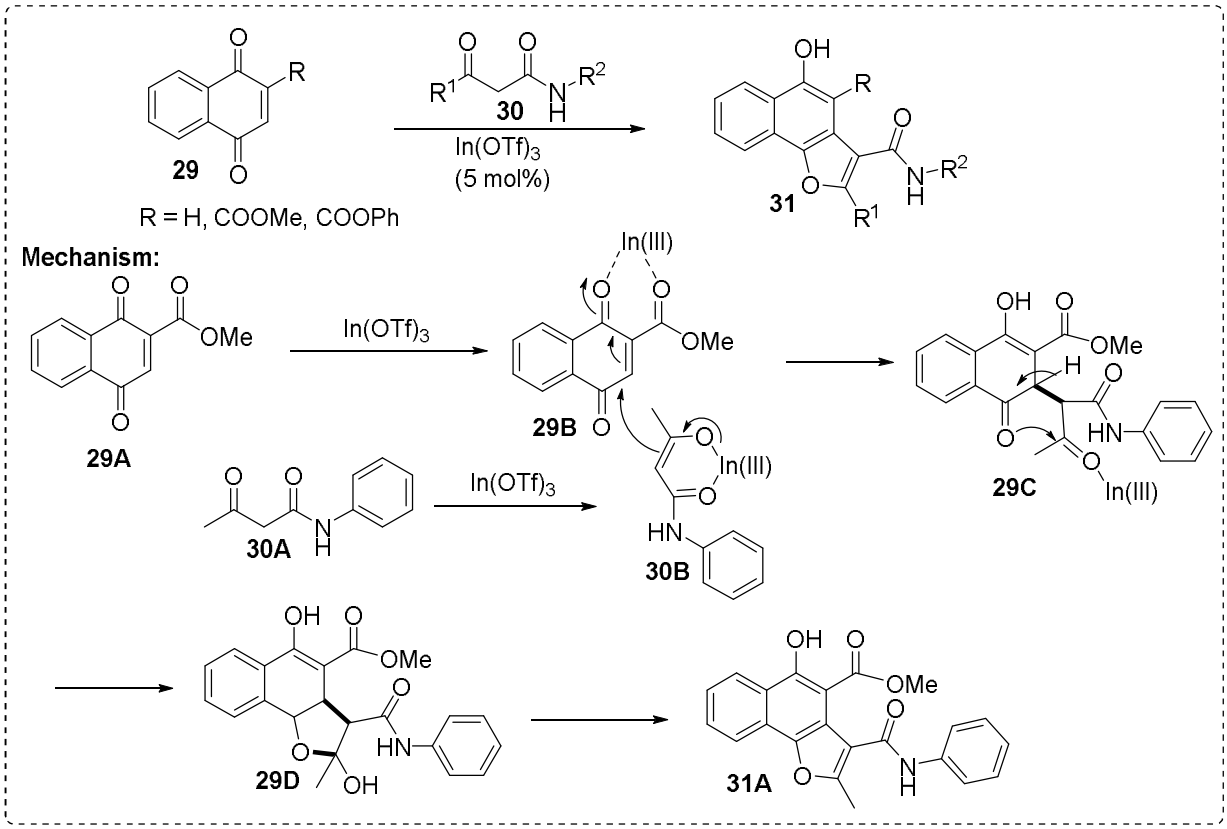
3.1.2.2 General methods for the synthesis of naphtho[1,2-*b*]furans through metal-catalyzed reactions

Deng *et al.*[21] reported a method for the synthesis of naphtho[1,2-*b*]furan derivatives **28** starting from diazo ene-yne-ketones **26** based on Pd-catalyzed heteroannulation and subsequent Rh-catalyzed benzannulation. More specifically, $Pd(PPh_3)_2Cl_2$-catalyzed selective tandem cyclization/oxidation of conjugated diazo ene-yne-ketones **26** under O_2 atmosphere led to the formation of diazo trisubstituted furans **27**. Next, $Rh_2(OAc)_4$-mediated selective $C(sp^2)$- H insertion at the ortho-position of 2-aryl group (R^1) of the furan moiety under N_2 atmosphere occurred to construct naphthalene moiety, affording trifunctionalizd naphtho[1,2-*b*]-furans **28** (Scheme 4).



Scheme 4. Synthesis of naphtho[1, 2-*b*]furans derivatives **28.**

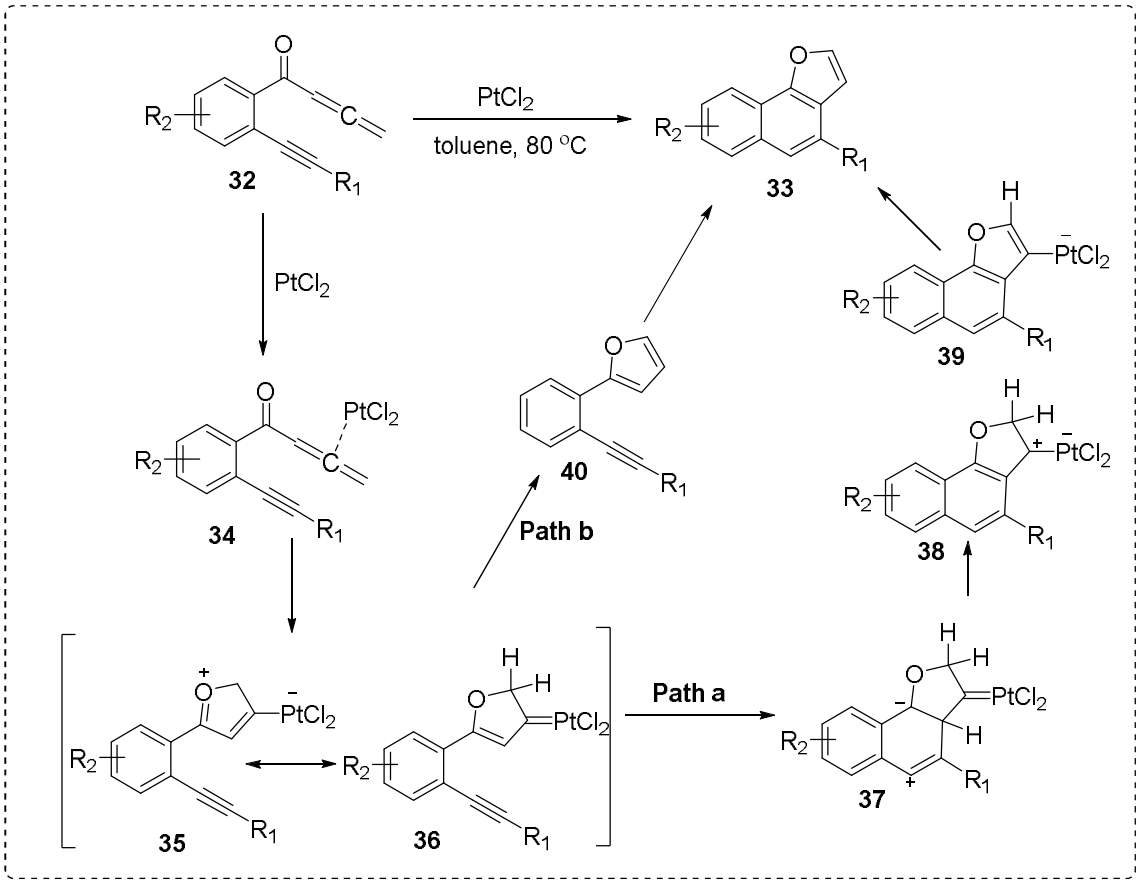
Lee *et al.*[22] developed a method for the synthesis of naphtho[1,2-*b*]furan-3-carboxamides **31 (**Scheme 5). This method involves $In(OTf)_3$-catalyzed cascade formal [3 + 2] cycloaddition of 1,4-naphthoquinones **29** with b-ketoamides **30**. For example, naphtho[1,2-*b*]furan-3-carboxamides **31A is** synthesized from 1,4-naphthoquinones **29A** following the mechanism as shown under Scheme 5. Mechanistically, methyl-1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate **29A** produces complex **29B** in the presence of $In(OTf)_3$ catalyst. On the other side, $In(OTf)_3$ catalyzes the enolization of the b-ketoamide **30a** to produce a reactive nucleophile **30B**, which undergoes nucleophilic attack with complex **29B** to generate the intermediate **29C**. The aromatization of **29C** followed by intramolecular cyclization gives hemiacetal **29D**, which undergoes dehydration to give the final product **31A**.



Scheme 5. Synthesis of naphtho[1, 2-*b*]furans derivatives **31** with a plausible reaction mechanism for the formation of naphtho[1, 2-*b*]furans **31A.**

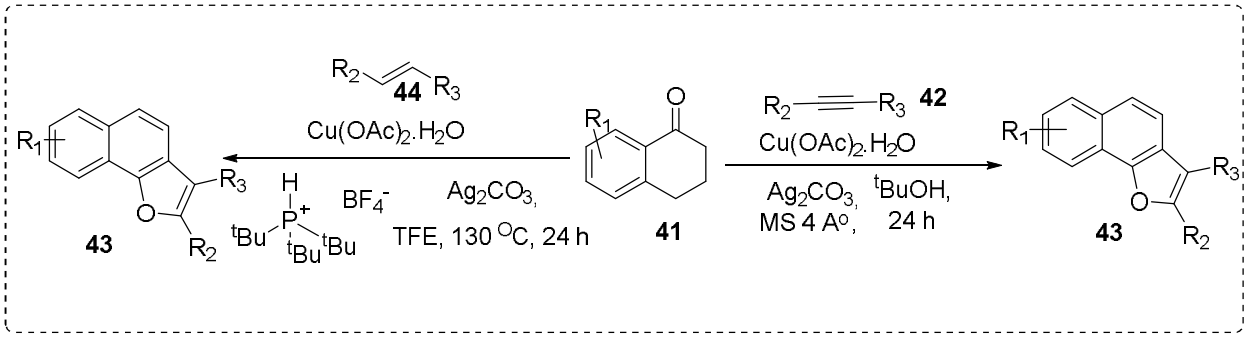
Xu *et al.*[23] developed an efficient method for constructing various substituted naphtho[1,2-*b*]furan **33** via Pt catalyzed tandem cycloisomerization and 6π-electrocycliztion type reaction (Scheme 6). They proposed two mechanistic pathways for this reaction shown in Scheme 6. The intermediate **34**, generated from compound **32** with $PtCl_2$, is converted into α,β-unsaturated carbene complex **36** through intramolecular nucleophilic attack (by the oxygen atom) onto the allenic double bond which undergoes complexation with $PtCl_2$. In path a, platinum carbene **36** (or **35**) converts into **37** through a 6π-electrocyclization-type reaction. Intermediate **37** then undergoes a 1,3-hydrogen shift followed by the loss of a proton to furnish the intermediate **39**. Finally, demetalation of the intermediate **39** will ultimately lead to the product **33**.

Alternatively, (path b), platinum carbene **36** undergoes a 1,2-hydrogen shift to produce the intermediate **40**. Thereafter, a 6-endocyclization of **40** leads to product **33**.



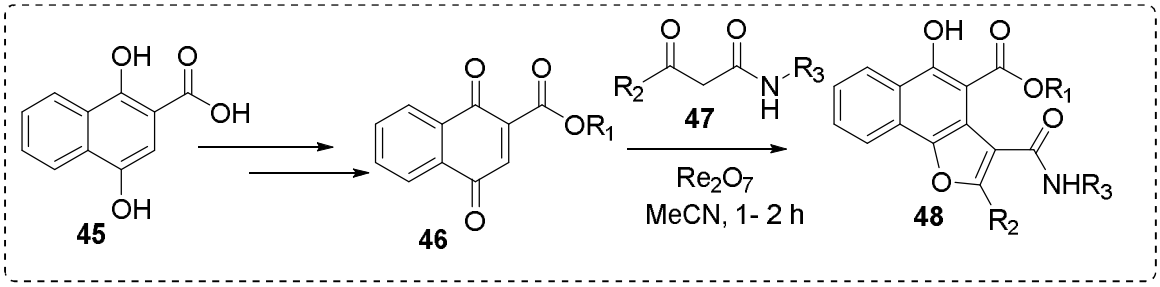
Scheme 6. Synthesis of naphtho[1, 2-*b*]furans derivatives **33** with a plausible mechanism .

Maiti *et al*[24]. reported a novel [3+2] cycloaddition reaction for the synthesis of naphtho[1,2-*b*]furans derivatives **43** between a variety of cyclic ketones **41** and diverse olefins **44** or alkynes **42** (Scheme 7). When olefins **44** are used, the reactions were promoted by copper in combination with the *tri-tert*-butylphosphine [P(^{t}Bu)$_3$] ligand. But *tri-tert*-butylphosphine [P(^{t}Bu)$_3$] ligand was not required when the same cycloaddition was carried out with alkyne **42**. This protocol however provides excellent selectivity and represents an extremely simple and atom-economic way to construct substituted naphthofurans from readily available starting materials under mild reaction conditions.

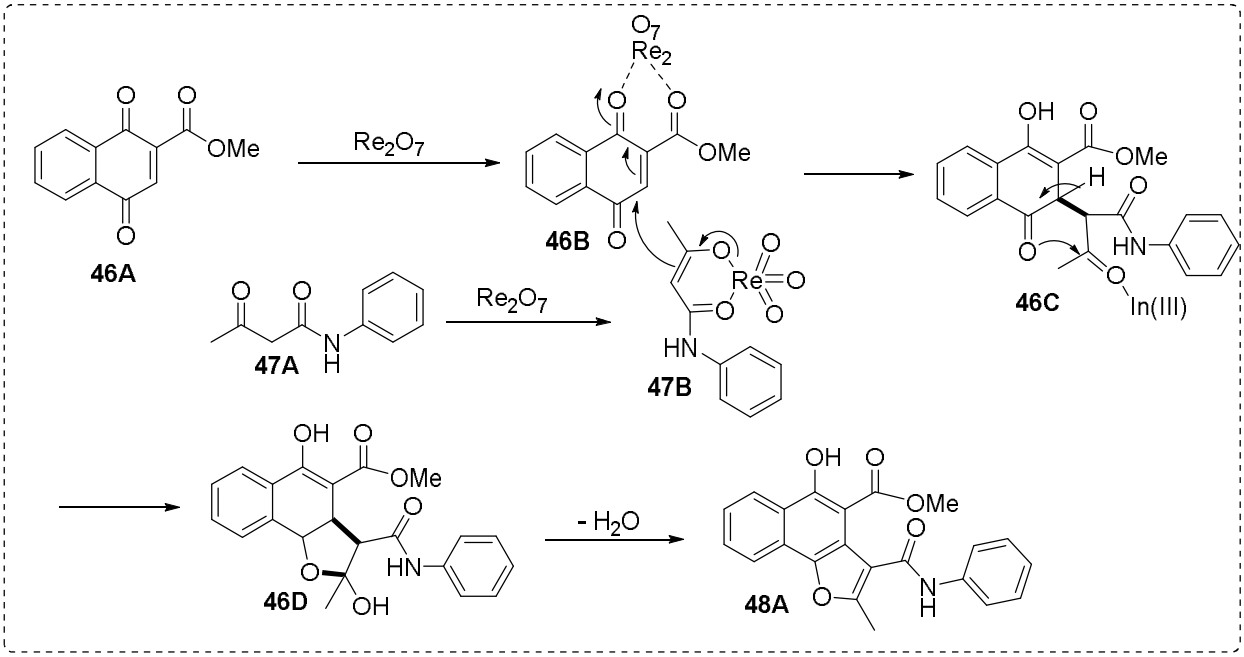


Scheme 7. Synthesis of naphtho[1, 2-*b*]furans derivatives **43**

Lee *et al.*[25] repoted a mehod for the synthesis of naphtho[1,2-*b*]furan-3-carboxamide derivatives **48** in high yield via a novel Re_2O_7-catalyzed formal [3+2] cycloaddition of 1,4-naphthoquinones **46** with β-ketoamides **47** as the key step (Scheme 8). The formation of products **48** is explained by the mechanism as proposed using an example of product **48A** (Scheme 9). Accordingly, methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate **46a** produces Re(VII)- complex **46B** in the presence of Re_2O_7 catalyst. On the other hand, Re_2O_7 catalyzes the enolization of β-ketoamide **47A** to produce a reactive nucleophile **47B**, which then attacks complex **46B** to produce intermediate **46C**. Next, the aromatization of **46C** followed by intramolecular cyclization gives hemiacetal **46D**, which undergoes dehydration to afford the final product **48A** .

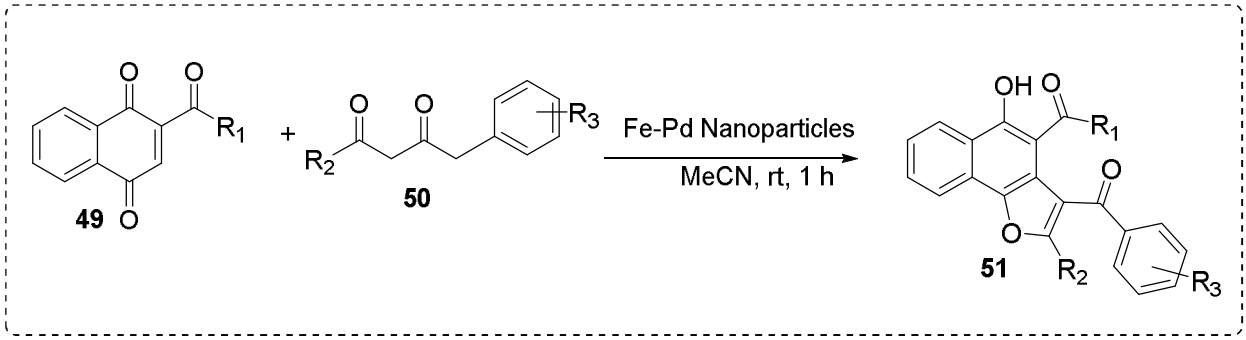


Scheme 8. Synthesis of [1,2-*b*]furan-3-carboxamide derivatives **48**



Scheme 9. A Plausible Mechanism for the formation of product **48A**

Lee *et al.*[26] reported a green and facile approach for the synthesis of Fe, Pd and Fe–Pd bimetallic nanoparticles using an aqueous bark extract of *Ulmus davidiana* and their application as magnetically recoverable catalysts for the [3 + 2] cycloaddition of 1,4-naphthoquinones **49** with β-ketoamides **50** (Scheme 10). The bimetallic nanoparticles exhibited strong catalytic activity in high yield for the synthesis of naphtha[1,2-*b*]furan-3-carboxamides **51** compared to their respective monometallic nanoparticles. The nanocatalyst was recovered easily using an external magnetic field and recycled five times without significant loss in activity.



Scheme 10. Synthesis of naphtho[1,2-*b*]furan-3-carboxamides derivatives **51**

3.1.3. Concluding Remarks

From the literature survey, it concluded that naphtho[1,2-*b*]furan have a considerable attention over the years in synthetic and medicinal chemistry. However, most of the procedure for its synthesis are multistep and require long reaction times. Thus development of a convenient method using readily available and cheap substrates remains challenge. Detailed finding towards the naptho[1,2-*b*]furans discussed in part II of this chapter.

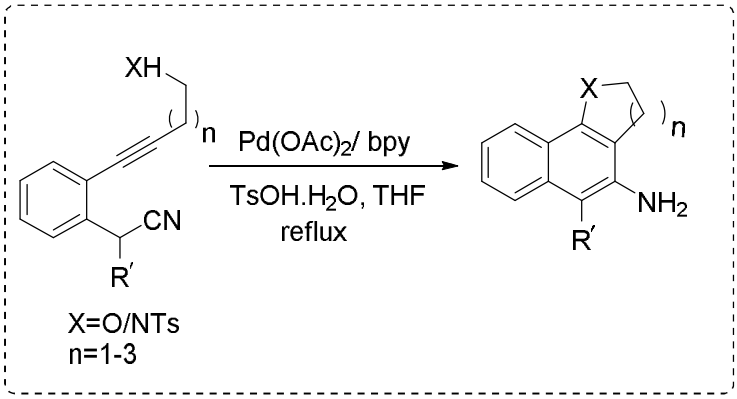
Part-II

(Result & Discussion)

3.2.1. Introduction

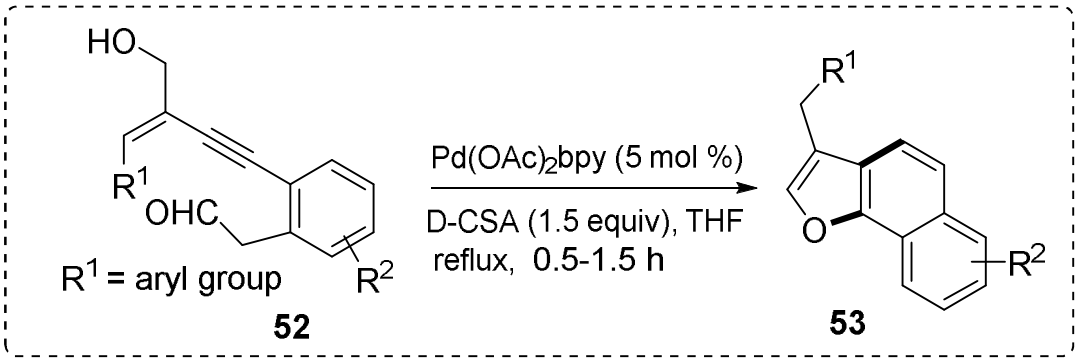
In view of the immense importance of naphtho[1,2-*b*]furans, various synthetic efforts have been devoted to their constructions. Although there are several examples on their preparation as part of the synthesis of different oxygen heterocycles, there are only few reports on their general synthesis (discussed previously Schemes 1-10). However, development of a convenient, scalable, and practical method using readily available and cheap substrates remains a challenge.

In recent years, cascade reactions have gained immense interest because of several advantages and many pioneering works in this regard have been well-documented in the literature.[27] Among them, palladium(II)-catalyzed synthesis of 2,3-dihydro derivatives of naphtho[1,2-b]furans (Scheme 11) reported by Lu et al. deserves particular mention.



Scheme 11. Reported work

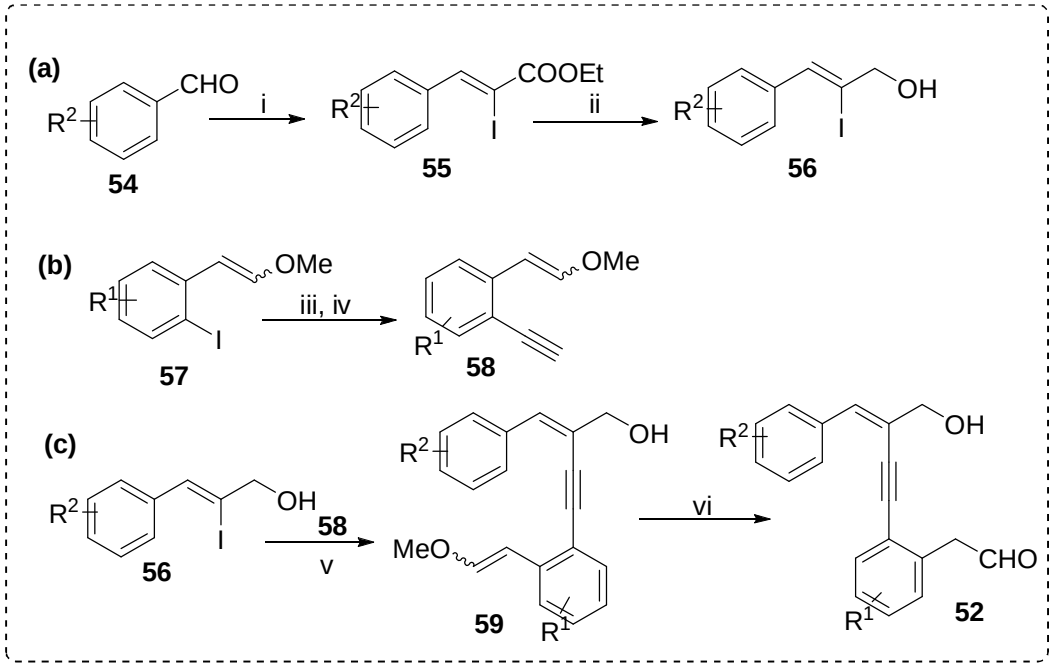
In continuation of our work[28] on palladium-catalyzed reactions, we envisioned that compounds **53** could be built up by exploring the palladium-catalyzed cascade reactions of ene−ynes **52** containing aldehyde group, as depicted in Scheme 12. The concept appeared to be viable upon choosing appropriate palladium catalyst, additive and solvent as shown under Scheme 12.



Scheme 12. Present work

3.2.2. Synthesis of Starting Material

The requisite starting material **52** was synthesized in few steps starting from commercially available substituted benzaldehyde derivatives **54** which were converted into their corresponding *α,β*- unsaturated ester **55** employing a halo-Wittig reaction, and the resulting product was then reduced to the corresponding *α,β*-unsaturated alcohol **56** using DIBAL-H.[29] Thereafter, the acetylenic compound **58** was prepared from iodo compound **57** via ‘’*Sonogashira reaction*’’ followed by desilylation as shown in Scheme 13b. Next, intermediate **58** underwent the coupling reaction with **56** employing the aforesaid ‘’*Sonogashira reaction*’’ to furnish the product **59**. Finally, the exposure of **59** to acidic conditions led to the formation of the desired substrate **52**.



Scheme 13. Reagents and Conditions: (i) (a) $Ph_3P^+CH_2CO_2Et.Br^-$, I_2, K_2CO_3, CH_3OH, 0- 5 °C, 1.5 h; (b) Tetrabutylammonium bromide, K_2CO_3, 40 °C, 2-8 h, 60-75%; (ii) DIBAL-H, CH_2Cl_2, -5 ^oC-rt, 2-6 h, 42-76%; (iii) $PdCl_2(PPh_3)_2$,TMS-acetylene, CuI,Et_3N, 1-1.5 h, 90-95%; (iv) K_2CO_3, MeOH, 0.5-1 h, 56-60%; (v) $PdCl_2(PPh_3)_2$, CuI, Et_3N, rt, 1-2h, 78-90%; (vi) *p*-TsOH , acetone, 0 ^oC- rt, 3-4h, 42-76%.

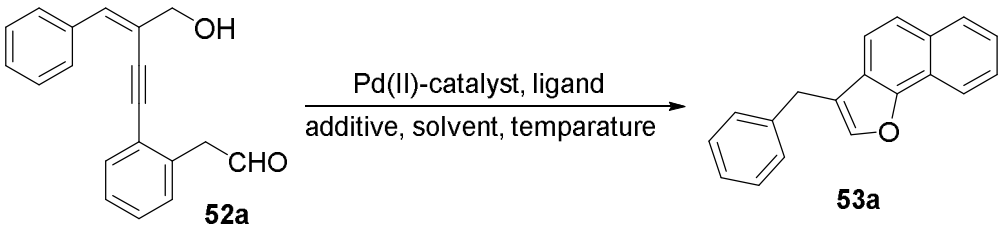
3.2.3. Synthesis of Naphtho[1,2-*b*]furan

3.2.3.1. Optimization of the reaction condition for the model synthesis of 53a

Initially we set out with a model study for the synthesis of **53a** using substrate **52a** (R^1, R^2 = H,) to find out the optimized reaction condition through variation of reaction parameters such as catalyst, ligand, solvent, additive etc.; few selected results are represented in Table 1. Initially, carrying out this reaction in N-methylacetamide (NMA) employing $Pd(OAc)_2$(bpy) and using D-(+)-camphorsulfonic acid (D-CSA)as an additive led to the desired naphtho[1,2-*b*]furan **53a** with only moderate yield (42%)(Table 1, entry 1). Then, Changing the solvent from NMA to the less polar 1,4-dioxane increased the yield (80%) and reduced the reaction

time (1 h) remarkably (Table 1, entry 2). But the yield of **53a** dropped to 31% (Table 1 entry 3) when $Pd(OAc)_2$ and bpy were separately used instead of $Pd(OAc)_2$bpy in 1,4-dioxane, underlining the necessity of using $Pd(OAc)_2$bpy in the reaction. Interestingly, executing the reaction in a less polar solvent like THF successfully increased the yield to 82% (Table 1, entry 4). However, using the catalyst and the ligand separately in THF decreased the yield to 42% (Table 1, entry 5). When the additive was changed to acetic acid instead of D-CSA, product formation did not take place at all proving D-CSA to be a better additive (Table 1, entry 6). Thus, the reaction conditions of entry 4 were found to be optimal. So, we pursued this reaction in THF for further exploration as discussed below.

Table 1. Optimization of reaction conditions for the synthesis of naphtho[1,2-*b*]furan 53a[a]



52a **53a**

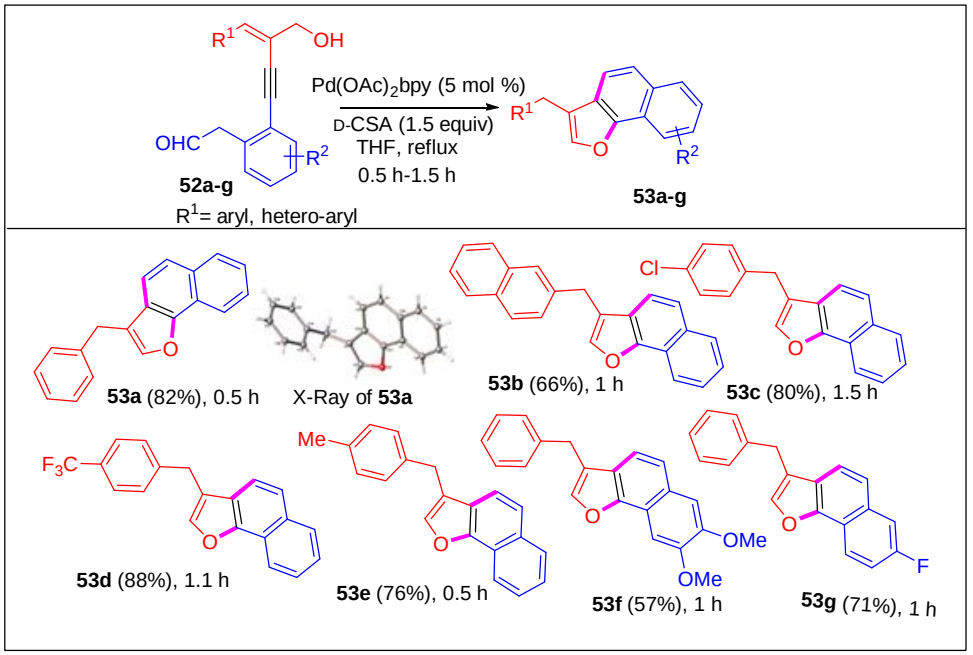
Entry	Catalyst	additive	Ligand	Solvent	Temp(^oC)	Time (h)	Yield[b] (%)
1	$Pd(OAc)_2$bpy	D-CSA	-	NMA	100	3	42
2.	$Pd(OAc)_2$bpy	D-CSA	-	1,4 dioxane	100	1	80
3.	$Pd(OAc)_2$	D-CSA	bpy	1,4 dioxane	100	2	31
4.	**$Pd(OAc)_2$bpy**	D-CSA	-	**THF**	**Reflux**	**1**	**82**
5.	$Pd(OAc)_2$	D-CSA	bpy	THF	Reflux	4	42
6.	$Pd(OAc)_2$bpy	AcOH		THF	Reflux	2	nr

[a] Reaction conditions: **52a** (0.18 mmol), catalyst (5 mol %), ligand (6 mol %), and additive (1.5 equiv) in 3 mL of solvent heated at specified temperature under argon atmosphere.

3.2.3.2. Scope of the reaction

Accordingly, a number of diversely substituted ene−yne substrates **52** were investigated (Scheme 14). Different functional groups (viz., F, Cl, CF_3, Me, OMe, etc.) were found to be compatible for this reaction. Nevertheless, replacing phenyl group attached to the double bond in substrate by a bulky naphthyl group (R^1 = 2-naphthyl) required slightly longer reaction time (1 h) and reduced the yield (of **53b**) to 66%. In contrast, employment of electron-withdrawing group at the para position of the phenyl ring in substrates (R^1 = *p*-ClC_6H_4−/*p*-$CF_3C_6H_4$−) afforded the products (**53c**/**53d**) within 1.1−1.5 h with excellent yields (80−88%), while introduction of an electron-donating methyl group at the same position (R^1 = *p* MeC_6H_4−) furnished the product **53e** within 0.5 h, but with a slightly reduced yield (76%). On the other hand, the electron-donating methoxy group (R^2 = OMe) placed at meta and para positions (substrate **52f**) produced the expected product **53f** within 1 h with a moderate yield of 57%, whereas an electron-withdrawing group (i.e., F) at para position enhanced the yield (of **53g**) to 71%.

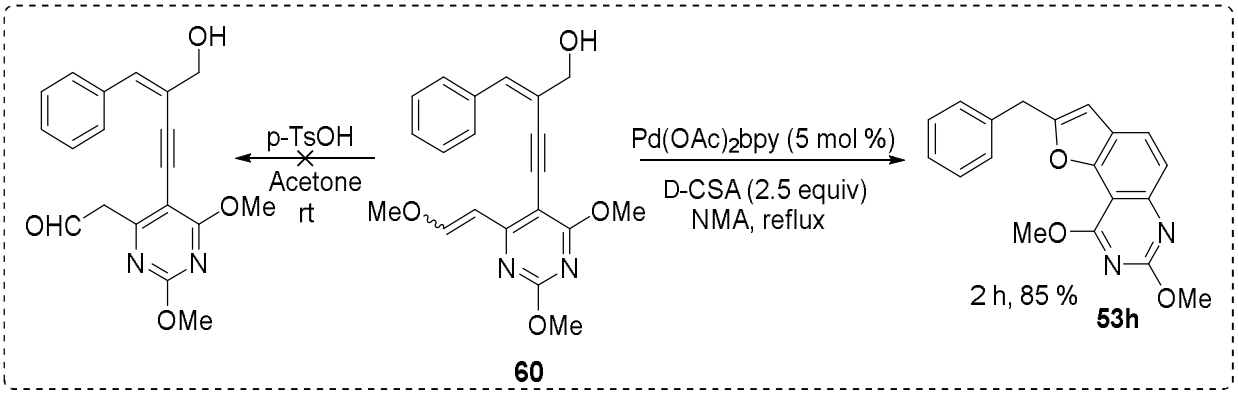
Scheme 14. Synthesis of the Naphtho[1,2-*b*]furan Derivatives 53a-53g[a]



[a] Reaction conditions: **52** (0.18 mmol), $Pd(OAc)_2$bpy (5 mol %), and D-CSA (1.5 equiv) in refluxing THF (3 mL) under argon atmosphere.

Furthermore, replacement of the aryl moiety in substrates by a heteroaryl one (R^1 = het-aryl) did not work well since only a trace amount of the desired product was observed in few cases. But employment of the heterocyclic moiety (viz., 2,4-dimethoxy pyrimidine) at the other end of the substrate (i.e., **60**) proved to be effective (Scheme 15) although NMA had to be used in place of THF and the masked aldehyde was deployed as potential substrate as the free aldehyde could not be generated despite repeated efforts. The desired product **53h** was thus produced within 2 h with 85% yield.

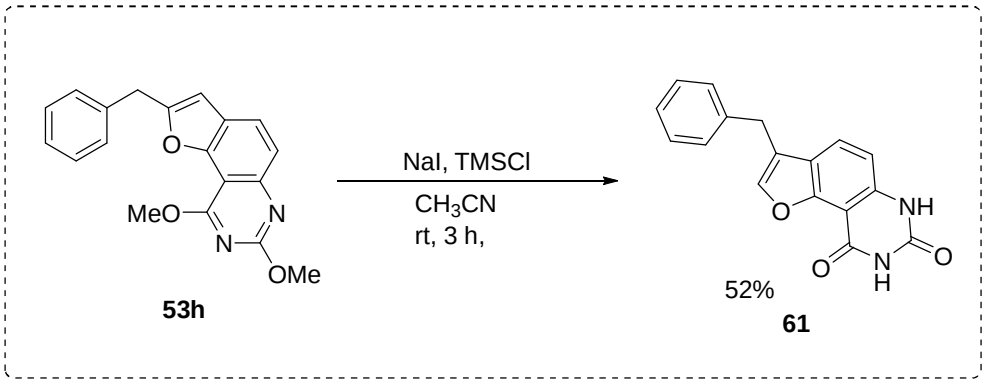
Scheme 15. Synthesis of naphtho[1,2-*b*]furan 53h



3.2.4. Application of our method: Synthesis of the uracil derivatives

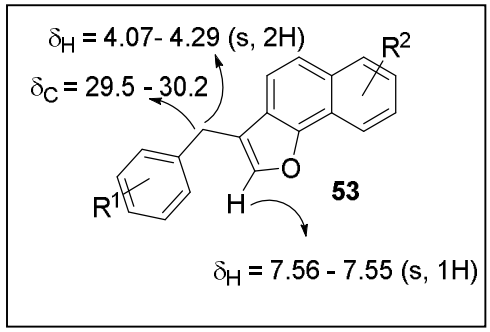
In view of the immense importance of the uracil derivatives in cancer chemotherapy[30a,b] and our own interest,[30c] we planned to convert our product **53h** to the uracil derivative **61** (Scheme 16). Pleasingly, treatment of **53h** with sodium iodide and trimethylsilyl chloride in dry acetonitrile at room temperature (rt) was found to be successful for the formation of **61** albeit in moderate yield (52%). The synthesis of more uracil derivatives and testing the anticancer activity (in vitro) of product **61** in different cancer cell lines are under study.

Scheme 16. Synthesis of uracil derivative 61



3.2.5. Nature and Characterisation of Products 53

All the synthesized products were sufficiently stable at room temperature but are preferred to to be stored at refrigerator (4 ^{o}C). All the structures were firmly established by spectral (^{1}H, ^{13}C, DEPT, Mass Spectra) and analytical data. In mass spectra (ESI and EI), the molecular ion peak in positive mode of all the compounds appeared as M^{+} or protonated $[M+H]^{+}$ and/or sodiated $[M+Na]^{+}$ ion. In ^{1}H NMR the methylene protons of compounds **53** appear as singlet in the range of δ_H 4.07-4.29 ppm, while methylene carbon appears in the range of δ_C 29.5-30.2 ppm. On the other hand, the proton (at 2- position) of the furan ring was observed as singlet in the range δ_H 7.56-7.55 ppm in few cases but in most of the cases this found to be overlapped with other aromatic protons. Besides, in ^{13}C NMR and DEPT experiments the peaks were appeared at their appropriate positions providing further support in favour of the structure.



Finally, the structural conclusion was further supported by single crystal X-ray diffraction analysis of compound **53a.** The single crystal was obtained by slow evaporation (at room temperature) of a solution of **53a** in a mixture of petroleum ether and dichloromethane. The ORTEP diagram of the crystal structure are shown in the Fig. 4. In this context some important crystal data are summarized in the following Table 2.

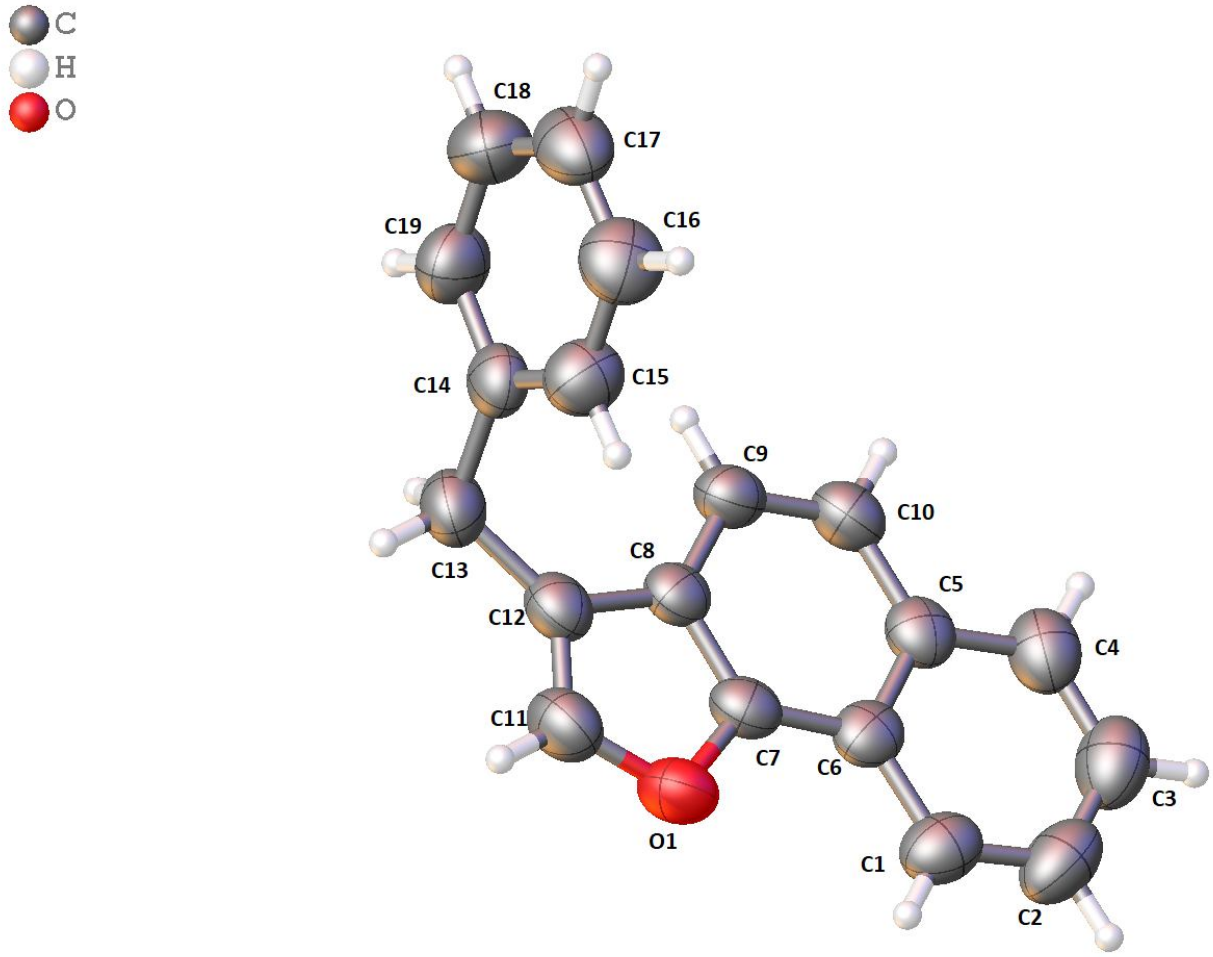


Fig. 4. Ortep Diagram of compound **53a** (drawn at 50% probability level).

Table 2: Important crystal data of product **53a**

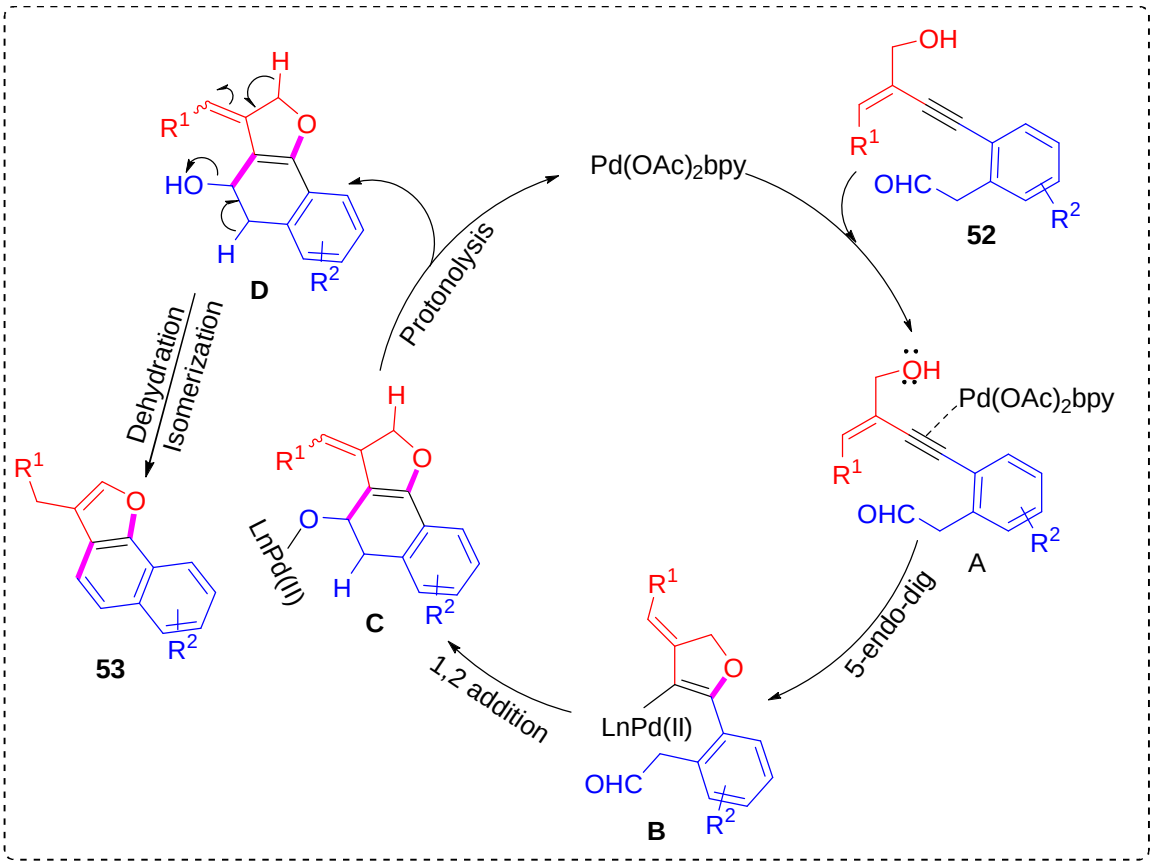
Empirical formula	$C_{19}H_{14}O$
Formula weight	258.30
Temperature	296 K
Wavelength	0.71073
Crystal system	Monoclinic
Space group	P 1 21/n 1
Unit cell dimensions	a = 6.1367(17)Å α = 90°
	b = 10.652(3)Å β = 90°
	c = 20.542(6)Å γ = 90°
Volume	1342.7(6)Å^3
Z	4
Density (calculated)	1.277 g/cm^3
Absorption coefficient (Mu)	0.077mm^{-1}
F(000)	544.0
Theta range for data collection	2.75° to 25.55°
Index ranges	-7<=h<=7, -12<=k<=12, -26<=l<=26
Reflection collected	16449
Independent reflections	2566 [R(int) = 0.0391]
Completeness to theta= 25.44°	97.0 %
Absorption correction	multi-scan
Max. and min. transmission	0.85 and 0.7
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2566 /0/181
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0381, wR2 = 0.1003
R indices (all data)	R1 = 0.0463, wR2 = 0.1090
Largest diff. peak and hole	0.160 &-0.120 e.A^{-3}

The crystal data of product **53a** has already been deposited at Cambridge Crystallographic Data Centre. The CCDC reference number is **1897156**

3.2.6. Plausible mechanism for the formation of the product 53

A plausible reaction mechanism was depicted in Scheme 17. In the first step, activation of the triple bond of the substrates **52** by Pd(II) catalyst gives a complex **A** which then undergoes 5-*endo-dig* cyclization resulting in the formation of an intermediate **B.** Then, species **B** undergoes subsequent intramolecular 1,2-addition onto suitably placed carbon−heteroatom multiple bond (−CHO) resulting in the transient species **C**. Protonolysis of **C** gives the intermediate **D** and releases the palladium catalyst to participate into next catalytic cycle. Finally, Isomerization followed by dehydration of **D** could easily deliver the product **53**.

Scheme 17. Envisaged pathways for the formation of products 53



3.2.7. Conclusion

In conclusion, we have developed a Pd(II)-catalyzed cascade reaction for a facile and general synthesis of naphtho[1,2-*b*]furans **53** using simple and readily available substrates. The newly

developed method constitutes a fast intramolecular assembly involving *trans*-oxo palladation of alkyne, followed by nucleophilic 1,2-addition to aldehyde group. The reactions are operationally simple, compatible with a range of functional groups, and atomeconomical. We believe that this novel method will find significant applications in organic, medicinal, and material chemistry as well.

3.2.8. EXPERIMENTAL SECTION

General.

All solvents were distilled prior to use. Petroleum ether refers to fraction boiling in the range 60−80 °C. Dichloromethane (DCM) was dried over phosphorous pentoxide, distilled, and stored over 3 Å molecular sieves in a sealed container. 1,4-Dioxane was distilled over sodium and benzophenone. Commercial grade dry dimethylformamide (DMF), dimethylacetamide (DMA), N-methylacetamide (NMA), and 1,2-dimethoxyethane (DME) were used as solvents. All reactions were carried out under argon atmosphere and anhydrous conditions unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 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 singlet (s), doublet (d), double doublet (dd), triplet (t), triple doublet (td), quartet (q), multiplet (m), and broad (br), apparent (app). All 13C NMR spectra were obtained with complete proton

decoupling. Mass spectra were performed using electrospray ionization (ESI) time-of-flight or electron ionization (EI) mode.

General Synthesis of α,β-Unsaturated Esters **55** *via Halo-Wittig Reaction (Scheme 13a)*

To a well-stirred and cooled (−5 °C) solution of (ethoxycarbonylmethyl) triphenyl-phosphonium bromide (500 mg, 1.17 mmol) dissolved in dry MeOH (10 mL) were added molecular iodine (572 mg, 2.26 mmol) and freshly activated K_2CO_3 (160 mg, 1.17 mmol) successively. The temperature of the reaction mixture was strictly maintained between −5 and 5 °C over a period of 1.5 h, resulting in the formation of a brown-colored suspension. To this, the aldehyde derivatives **54** (0.98 mmol), tetrabutylammonium bromide (16.1 mg, 0.05 mmol), and K_2CO_3 (22.3 mg, 0.16 mmol) were added successively and stirred for few minutes. The reaction pot was then removed from the low-temperature bath (using ice−salt mixture) and heated at 40 °C for another 2−8 h. During this time period, additional amount of K_2CO_3 (2 × 0.05 mmol) was added in two portions at 2 h intervals. Upon completion of reaction (TLC), MeOH was evaporated under vacuum and the crude residue was treated with 2 M sodium thiosulfate solution to remove the excess iodine. It was then extracted with ethyl acetate (2 × 20 mL); the combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh) column chromatography eluting with 10−40% ethyl acetate−petroleum ether to obtain α,βunsaturated esters **55** in 60−75% yield.

General Synthesis of α,β-Unsaturated Alcohols **56** *(Scheme 13a)*

To a well-stirred and cooled (using ice−salt mixture) solution of unsaturated ester **55** (0.69 mmol, 1.0 equiv) dissolved in dry DCM (5 mL) was added DIBAL hydride (1.2 M in toluene,

1.74 mL, 2.08 mmol, 3 equiv) solution dropwise under argon atmosphere and stirring was continued for another 2−3 h at the same temperature. Upon completion of the reaction (TLC), the reaction mixture was quenched with 15% sodium hydroxide solution (15 mL) and diluted with DCM (20 mL). The resulting thick reaction mixture was filtered through a bed of celite to obtain a clear layer separation. The organic layer was taken out and washed successively with water (8 mL) and brine solution (8 mL). The combined organic extracts were dried over Na2SO4, concentrated, and purified by silica gel (100−200 mesh) column chromatography using 15−25% ethyl acetate in pet−ether (v/v) as eluent. The pure α,βunsaturated alcohols **56** were obtained in 42−76% yields.

Preparation of Acetylenic Compounds **58** *(Scheme 13b)*

To a well-stirred and ice-cooled solution of **57**[31] (1.92 mmol, 1 equiv) in Et_3N (5 mL) were added $PdCl_2(PPh_3)_2$ (40.4 mg, 0.057 mmol, 3 mol %), CuI (21.9 mg, 0.115 mmol, 6 mol %), and trimethylsilylacetylene (1.1 equiv) sequentially. The reaction mixture was allowed to reach rt and stirring was continued for 1−1.5 h until completion of the reaction (TLC). Thereafter, the solvent was removed under reduced pressure, diluted with water (10 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude mass was purified through column chromatography using silica gel (100−200 mesh) to afford pure silylated acetylenic compound (90−95% yield), which was then desilylated. Thus, silylated compound (1.82 mmol, 1 equiv) dissolved in methanol was stirred at rt for 0.5−1 h in the presence of K_2CO_3 (0.1 equiv). Upon completion of reaction, the reaction mixture was diluted with water (10 mL), extracted with ethyl acetate (2 × 15 mL), and concentrated under reduced pressure. The

crude product obtained was purified by silica gel (100−200 mesh) column chromatography to obtain the acetylenic compounds **58** in 56−60% yield.

Preparation of the Intermediates **59** *(Scheme 13c)*

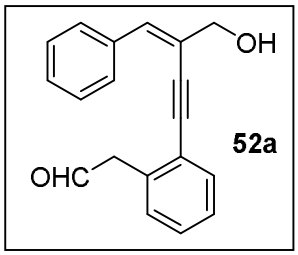
To a well-stirred and ice-cooled solution of **56** (0.77 mmol, 1 equiv) in Et_3N (2 mL) were added $Pd(PPh_3)_2Cl_2$ (16.2 mg, 0.023 mmol, 3 mol %), acetylenic intermediate **58** (0.846 mmol, 1.1 equiv), and CuI (8.8 mg, 0.046 mmol, 6 mol %) successively. The reaction mixture was then stirred at rt under argon atmosphere for 1−2 h until the completion of the reaction (TLC). Thereafter, the solvent was removed under reduced pressure and the resulting crude mixture was extracted with ethyl acetate (3 × 30 mL); the combined organic extracts were washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified through silica gel (100−200 mesh) column chromatography eluting with 10−40% ethyl acetate− petroleum ether (v/v) to afford the desired compounds **59** in 78− 90% yield.

Preparation of the Ene−Yne Substrates **52** *(Scheme 13c)*

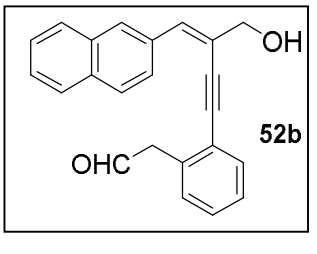
To a well-stirred and ice-cooled solution of **59** (0.69 mmol, 1 equiv) in dry acetone, p-TsOH (210.9 mg, 1.11 mmol, 1.6 equiv) was added in portions over a period of 20 min and the reaction mixture was stirred at rt for another 3−4 h until completion of reaction (TLC). Next, the reaction mixture was neutralized with dilute sodium bicarbonate solution and extracted with DCM (2 × 10 mL). The combined organic extracts were evaporated under reduced pressure; the resulting crude product was purified by silica gel (100−200 mesh) column chromatography to afford the desired starting materials **52** in 42−76% yield.

Spectral Data for Starting Materials 52a−g

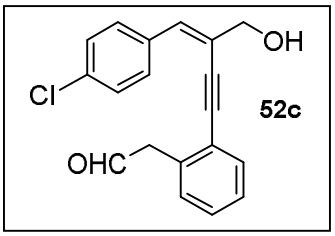
(*Z*)-2-(2-(3- (Hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)phenyl)acetaldehyde (**52a**). Yellow gum (144.7 mg, 76%), R_f = 0.36 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.69 (t, *J* = 2.1 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 3H), 7.33−7.31 (m, 3H), 6.85 (s, 1H), 4.39 (s, 2H), 3.89 (d, *J* = 1.8 Hz, 2H), 3.32 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 135.8, 135.2, 132.5, 131.6, 129.3, 128.7, 128.4, 128.2, 122.6, 121.1, 117.6, 93.5, 92.9, 67.1, 22.8; HRMS (ESI) m/z calcd for $C_{19}H_{17}O_2$ $[M + H]^+$ 277.1229, found, 277.1228.



(Z)-2-(2-(3-(Hydroxymethyl)-4-(naphthalen-2-yl)but-3-en-1-yn-1-yl)phenyl)acetaldehyde (**52b**). Yellow gum (150.7 mg, 67%), R_f = 0.31 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.69 (t, *J* = 2.1 Hz, 1H), 8.26 (s, 1H), 7.84−7.82 (m, 5H), 7.50−7.48 (m, 5H), 7.01 (s, 1H), 4.45 (s, 2H), 3.91 (d, *J* = 1.8 Hz, 2H), 2.84 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ_C 199.4, 134.8, 133.8, 133.5, 133.2, 132.4, 130.5, 129.2, 128.5, 128.3, 127.9, 127.8, 127.6, 126.5, 126.3, 126.1, 123.8, 121.7, 67.5, 49.6; HRMS (ESI) m/z calcd for $C_{23}H_{19}O_2$ $[M + H]^+$ 327.1385, found 327.1375.

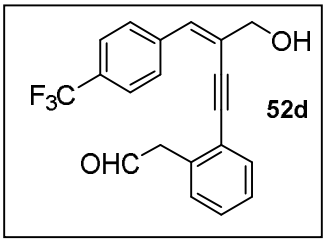


(Z)-2-(2-(4-(4-Chlorophenyl)-3-(hydroxymethyl)but-3-en-1-yn-1-yl)phenyl)acetaldehyde (**52c**). Yellow gum (98.4 mg, 46%), R_f = 0.31 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.68 (t, *J* = 2.1 Hz, 1H), 7.76 (d, *J* = 9 Hz, 2H), 7.34−7.32 (m, 4H), 7.29−7.28 (m, 2H), 6.78 (s, 1H), 4.37 (d, *J* = 4.2 Hz, 2H), 3.87 (d,

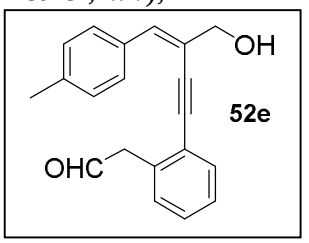


J = 1.8 Hz, 2H), 3.32 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 199.3, 134.4, 134.0, 133.8, 133.2, 132.5, 130.5, 129.9, 129.3, 128.5, 127.8, 123.6, 122.0, 95.1, 91.9, 67.2, 49.7; HRMS (ESI) m/z calcd for $C_{19}H_{15}ClNaO_2$ $[M + Na]^+$ 333.0658, found 333.0662.

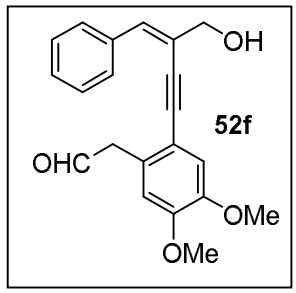
(Z)-2-(2-(3-(Hydroxymethyl)-4-(4-(trifluoromethyl)phenyl)but-3-en-1-yn-1-yl)phenyl)acetaldehyde (**52d**). Yellow liquid (163.8 mg, 69%), R_f = 0.28 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.69 (t, *J* = 2.1 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.41 (td, *J* = 7.5, 1.2 Hz, 1H), 7.35 (td, *J* = 7.65, 1.4 Hz 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 6.88 (s, 1H), 4.42 (d, *J* = 6.6Hz, 2H), 3.88 (d, *J* = 2.4 Hz, 2H), 2.57 (t, *J* = 6.9 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 199.3, 139.3, 133.9, 132.5, 130.3,129.9 (q, JC−F = 32.4 Hz), 129.5, 128.7, 127.8, 125.2 (q, JC−F = 3.7 Hz), 124.1, 124.0 (q, JC−F = 270.3 Hz), 123.4, 95.5, 91.6, 66.9, 49.7; HRMS (ESI) m/z calcd for $C_{20}H_{15}F_3NaO_2$ $[M + Na]^+$ 367.0922, found 367.0922.



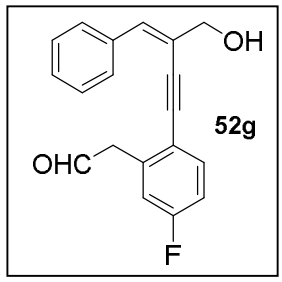
(Z)-2-(2-(3-(Hydroxymethyl)-4-(p-tolyl)but-3-en-1-yn-1-yl)- phenyl)acetaldehyde (**52e**). Yellow gum (84.0 mg, 42%), Rf = 0.37 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.71 (t, *J* = 2.25 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.58−7.55 (m, 1H), 7.37−7.29 (m, 3H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.81 (s, 1H), 4.38 (s, 2H), 3.90 (d, *J* = 2.1 Hz, 2H), 2.37 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz) δ_C 199.5, 138.6, 134.8, 133.8, 133.2, 132.5, 130.4, 129.0, 128.7, 127.7, 123.9, 120.3, 94.4, 92.7, 67.4, 49.6, 21.4; HRMS (ESI) m/z calcd for $C_{20}H_{18}NaO_2$ $[M + Na]^+$ 313.1204, found 313.1202.



(Z)-2-(2-(3-(Hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)-4,5-dimethoxyphenyl)acetaldehyde (**52f**). Yellow gum (115.9 mg, 50%), R_f = 0.21 (10% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.66 (t, *J* = 1.8 Hz, 1H), 7.79 (d, *J* = 6.8 Hz, 2H), 7.32−7.31 (m, 2H), 7.28−7.26 (m, 1H), 6.98 (s, 1H), 6.80 (s, 1H), 6.68 (s, 1H), 4.35 (s, 2H), 3.87 (s, 1H), 3.86 (s, 3H), 3.858 (s, 3H), 3.78 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 199.4, 149.9, 148.1, 136.1, 133.7, 128.6, 128.2, 127.2, 121.7, 115.7, 114.7, 112.9, 94.7, 90.7, 67.1, 56.0, 55.9, 49.0; HRMS (ESI) m/z calcd for $C_{21}H_{21}O_4$ $[M + H]^+$ 337.1440, found 337.1437.



(Z)-2-(4-Fluoro-2-(3-(hydroxymethyl)-4-phenylbut-3-en-1-yn-1-yl)phenyl)acetaldehyde (**52g**). Yellow gum (97.4 mg, 48%), R_f = 0.35 (40% ethyl acetate in petroleum ether, v/v); ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 9.67 (t, *J* = 1.8 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 2H), 7.53−7.51 (m, 1H), 7.37 (t, *J* = 7.8 Hz, 3H), 7.02 (td, *J* = 8.4, 2.4 Hz, 1H), 6.99 (dd, *J* = 9, 2.4 Hz, 1H), 6.85 (s, 1H), 4.37 (s, 2H), 3.87 (d, *J* = 1.8 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 198.4, 162.5 (d, *J* = 249 Hz), 136.5 (d, *J* = 7.5 Hz), 135.9, 134.8, 134.2 (d, *J* = 9 Hz), 128.6, 128.5, 128.3, 121.2, 119.8, 117.6 (d, *J* = 22.5 Hz), 115.1 (d, *J* = 21.0 Hz), 93.4, 91.9, 67.2, 49.3; HRMS (ESI) m/z calcd for $C_{19}H_{15}FKO_2$ $[M + K]^+$ 333.0693, found 333.0689.



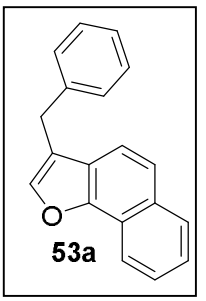
General Procedure for the Synthesis of Products 53.

A mixture of $Pd(OAc)_2$bpy (3.4 mg, 0.009 mmol, 5 mol %) and D-CSA (62.6 mg, 0.27 mmol, 1.5 equiv) in dry THF (2 mL) was stirred at 60 °C under argon atmosphere. Then, **52** (0.18 mmol) dissolved in dry THF (1.0 mL) was added at the same temperature (i.e., 60 °C) and the mixture was refluxed for 1−2 h until the completion of the reaction (TLC). The mixture was neutralized by adjusting the pH (~7) through dropwise addition of 20% aqueous

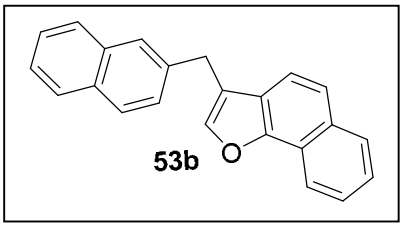
sodium bicarbonate solution and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with saturated brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100−200 mesh) column chromatography using 1−8% ethyl acetate−petroleum ether (v/v) as eluent to afford desired product **53a−g** in 57−88% yield.

Spectral Data for Products 53a−g.

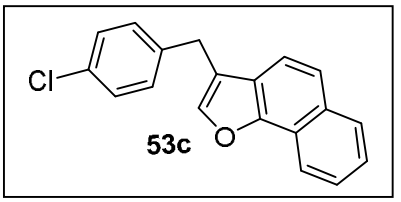
3-Benzylnaphtho[1,2-b]furan (**53a**). Brown solid (38.1 mg, 82%), R_f = 0.71 (5% ethyl acetate in petroleum ether, v/v), mp 80−82 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.31 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.62−7.58 (m, 2H), 7.56 (s, 1H), 7.51−7.47 (m, 2H), 7.33 (s, 2H), 7.32 (d, *J* = 1.8 Hz, 2H), 7.26−7.23 (m, 1H), 4.13 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 151.1, 141.4, 139.4, 131.4, 128.6, 128.5, 128.3, 126.4, 126.2, 125.1, 123.4, 123.0, 121.5, 120.7, 119.9, 118.4, 30.0; HRMS (ESI) m/z calcd for $C_{19}H_{14}NaO$ $[M + Na]^+$ 281.0942, found 281.0945.



3-(Naphthalen-2-ylmethyl)naphtho[1,2-b]furan (**53b**). White solid (36.6 mg, 66%), R_f = 0.62 (5% ethyl acetate in petroleum ether, v/v), mp 108−110 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.34 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.79−7.77 (m, 2H), 7.62−7.59 (m, 3H), 7.51−7.45 (m, 5H), 4.29 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 151.2, 141.6, 136.9, 133.6, 132.2, 131.4, 128.3, 128.2, 127.65, 127.57, 127.2, 126.8, 126.3, 126.0, 125.4, 125.1, 123.5, 123.1, 121.5, 120.6, 120.0, 118.5, 30.2; HRMS (ESI) m/z calcd for $C_{23}H_{16}NaO$ $[M + Na]^+$ 331.1099, found 331.1098.

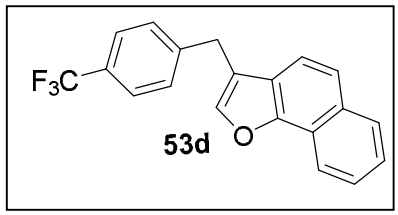


3-(4-Chlorobenzyl)naphtho[1,2-b]furan (**53c**). Yellow gum (42.1 mg, 80%), R_f = 0.71 (5% ethyl acetate in petroleum ether, v/v), ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 8.29 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H),

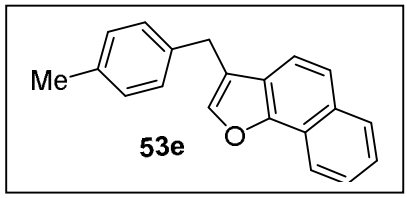


7.61−7.56 (m, 2H), 7.54 (t, *J* = 1 Hz, 1H), 7.50−7.46 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.28−7.21 (m, 4H), 4.07 (s, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ_C 151.3, 141.5, 137.9, 132.3, 131.5, 130.0, 128.7, 128.4, 126.5, 125.3, 123.3, 121.6, 120.3, 120.1, 118.3, 29.5; HRMS (ESI) m/z calcd for $C_{19}H_{14}ClO$ $[M + H]^+$ 293.0733, found 293.0733.

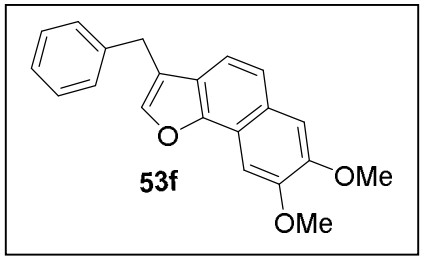
3-(4-(Trifluoromethyl)benzyl)naphtho[1,2-b]furan (**53d**). Yellow solid (51.6 mg, 88%), R_f = 0.60 (5% ethyl acetate in petroleum ether, v/ v), mp 60−62 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.32 (d, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.63−7.59 (m, 2H), 7.58−7.56 (m, 3H), 7.52−7.50 (m, 1H), 7.43−7.42 (m, 3H), 4.18 (s, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 151.2, 143.5, 141.5, 131.5, 128.8, 128.7, 128.3, 126.4, 125.5 (q, JC−F = 3.8 Hz), 125.3, 124.2 (app q, JC−F = 270.1 Hz), 123.2, 123.1, 121.5, 119.9, 119.7, 118.1, 29.9; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ = −162.2 (s, 3F); HRMS (ESI) m/z calcd for $C_{20}H_{14}F_3O$ $[M + H]^+$ 327.0997, found 327.0993.



3-(4-Methylbenzyl)naphtho[1,2-b]furan (**53e**). Brown solid (37.2 mg, 76%), R_f = 0.73 (5% ethyl acetate in petroleum ether, v/v); mp 44− 46 °C ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.31 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.62−7.57 (m, 2H), 7.55 (s, 1H), 7.50−7.47 (m, 2H), 7.21 (d, J = 7.8 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.09 (s, 2H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 151.1, 141.4, 136.3, 135.8, 131.4, 129.2, 128.5, 128.3, 126.2, 125.0, 123.5, 122.9, 121.5, 120.9, 119.9, 118.5, 29.7, 21.0; HRMS (ESI) m/z calcd for $C_{20}H_{16}NaO$ $[M + Na]^+$ 295.1099, found 295.1100.

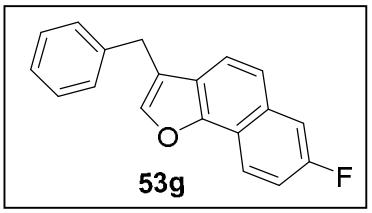


3-Benzyl-7,8-dimethoxynaphtho[1,2-b]furan (**53f**). White solid (32.6 mg, 57%), R_f = 0.17 (5% ethyl acetate in petroleum ether, v/v), mp 120−122 °C; 1 H NMR ($CDCl_3$, 600 MHz) δ_H 7.59 (s, 1H), 7.49−



7.47 (m, 2H), 7.35−7.32 (m, 5H), 7.26−7.23 (m, 2H), 4.10 (s, 2H), 4.08 (s, 3H), 4.01 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 150.8, 149.7, 148.7, 140.7, 139.5, 128.6, 128.5, 126.9, 126.3, 122.4, 121.6, 120.8, 116.6, 116.5, 107.4, 99.3, 56.0, 55.8, 30.1; HRMS (ESI) m/z calcd for $C_{21}H_{18}NaO_3$ $[M + Na]^+$ 341.1154, found 341.1150.

3-Benzyl-7-fluoronaphtho[1,2-b]furan (**53g**). Brown solid (35.3 mg, 71%), R_f = 0.69 (5% ethyl acetate in petroleum ether, v/v), mp 48− 50 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 8.31−8.828 (m, 1H), 7.56− 7.53 (m, 3H), 7.51−7.49 (m, 1H), 7.36 (td, *J* = 8.7, 2.4 Hz, 1H), 7.34− 7.33 (m, 4H), 7.27−7.25 (m, 1H), 4.12 (s, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 150 MHz) δ_C 160.2 (d, *J* = 243.0 Hz), 151.2, 141.3, 139.3, 132.3 (d, *J* = 9.0 Hz), 128.6, 128.5, 126.4, 122.9, 122.4 (d, *J* = 9.0 Hz), 122.3 (d, *J* = 4.5 Hz), 120.8, 119.8, 118.5, 116.3, 116.1, 111.8, 111.7, 30.1; ^{19}F NMR$\{^{1}H\}$ (376 MHz, $CDCl_3$) δ = −115.6 (s, 1F); HRMS (ESI) m/z calcd for $C_{19}H_{13}OFK$ $[M + K]^+$ 315.0588, found 315.0585.

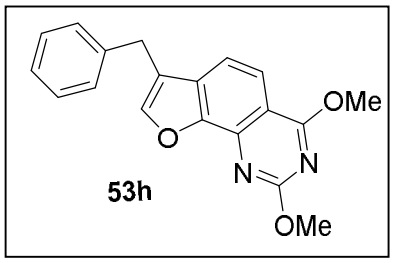


53g

Procedure for the Synthesis of 7-Benzyl-2,4-dimethoxyfuro[3,2-h]quinazoline (53h).

A mixture of $Pd(OAc)_2$bpy (2.7 mg, 0.007 mmol, 5 mol %) and D-CSA (82.4 mg, 0.355 mmol, 1.5 equiv) in dry THF (2 mL) was stirred at 60 °C under argon atmosphere. The substrate **60** (50 mg, 0.14 mmol) dissolved in NMA (1.0 mL) was then added to the reaction mixture, which was heated at 70 °C until the completion of the reaction (TLC). The reaction mixture was neutralized by adjusting the pH (∼7) through dropwise addition of 20% aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100− 200 mesh) column chromatography using 10% ethyl acetate− petroleum ether (v/v) as eluent to afford desired product **53h** in 85% yield.

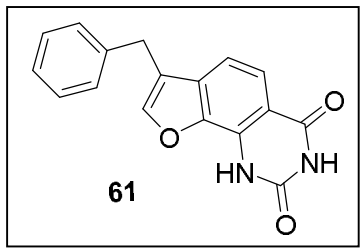
7-Benzyl-2,4-dimethoxyfuro[3,2-h]quinazoline (**53h**). Brown solid (38.6 mg, 85%), R_f = 0.39 (20% ethyl acetate in petroleum ether, v/v), mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 7.72 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.32−7.27 (m, 4H), 7.25−7.22 (m, 1H), 4.29 (s, 3H), 4.11 (s, 3H), 4.10 (s, 2H); ^{13}C{1H} NMR ($CDCl_3$, 100 MHz) δ_C 167.8, 161.6, 151.9, 149.8, 142.5, 139.0, 128.7, 128.6, 126.6, 126.2, 123.9, 121.3, 120.5, 101.8, 54.9, 54.8, 29.8; HRMS (ESI) m/z calcd for$C_{19}H_{17}N_2O_3$ $[M + H]^+$ 321.1239, found 321.1244.



Procedure for the Synthesis of Uracil Derivative 61.

To a wellstirred solution of **53h** (30 mg, 0.085 mol, 1 equiv) in dry acetonitirile was added NaI (380 mg, 2.55 mmol, 3.0 equiv); this was followed by dropwise addition of trimethylsilyl chloride (0.3 mL, 2.55 mmol, 3.0 equiv), and the reaction was stirred at rt for 3 h until TLC showed complete conversion. The solvent was removed under vacuum and the crude mass was filtered, washed with ethyl acetate followed by water, and dried to obtain the pure product **61** in 52% yield.

*7-Benzylfuro[3,2-h]quinazoline-2,4(1H,3H)-dione (***61**). Yellow solid (11.2 mg, 52%), mp > 250 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 11.28 (s, 1H), 11.26 (s, 1H), 7.89 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.30−7.27 (m, 4H), 7.19−7.17 (m, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 4.01 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz) δ_C 161.0, 152.5, 150.6, 143.1, 139.84, 139.83, 128.9, 127.0, 126.7, 123.3, 119.9, 111.2, 101.6, 29.0; HRMS (ESI) m/z calcd for $C_{17}H_{13}N_2O_3$ $[M+H]^+$ 293.0926, found 293.0923.



3.2.9. References:

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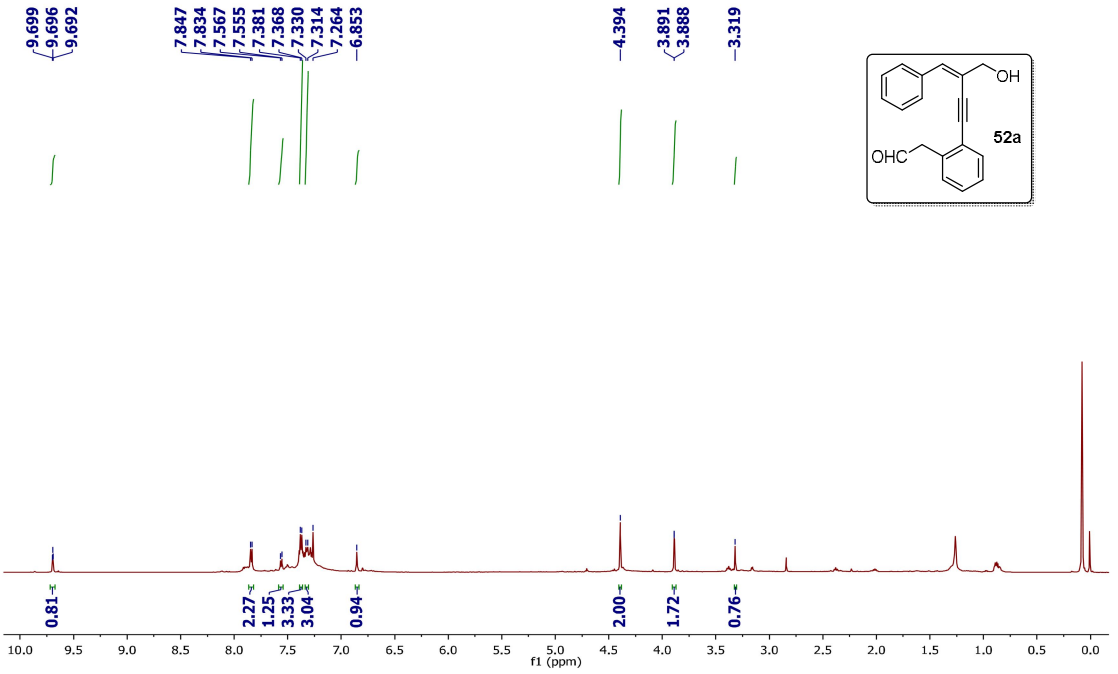
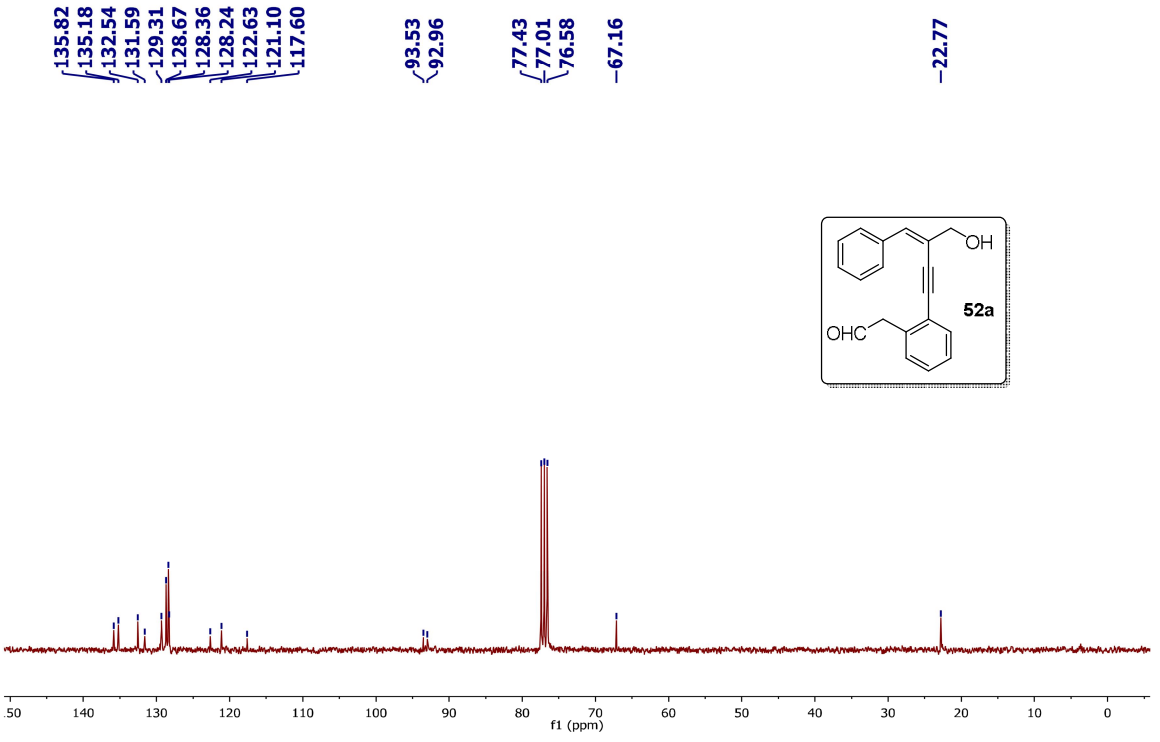
3.2.10. Copies of NMR Spectra:

NMR Spectra of Compounds 52a-52g :

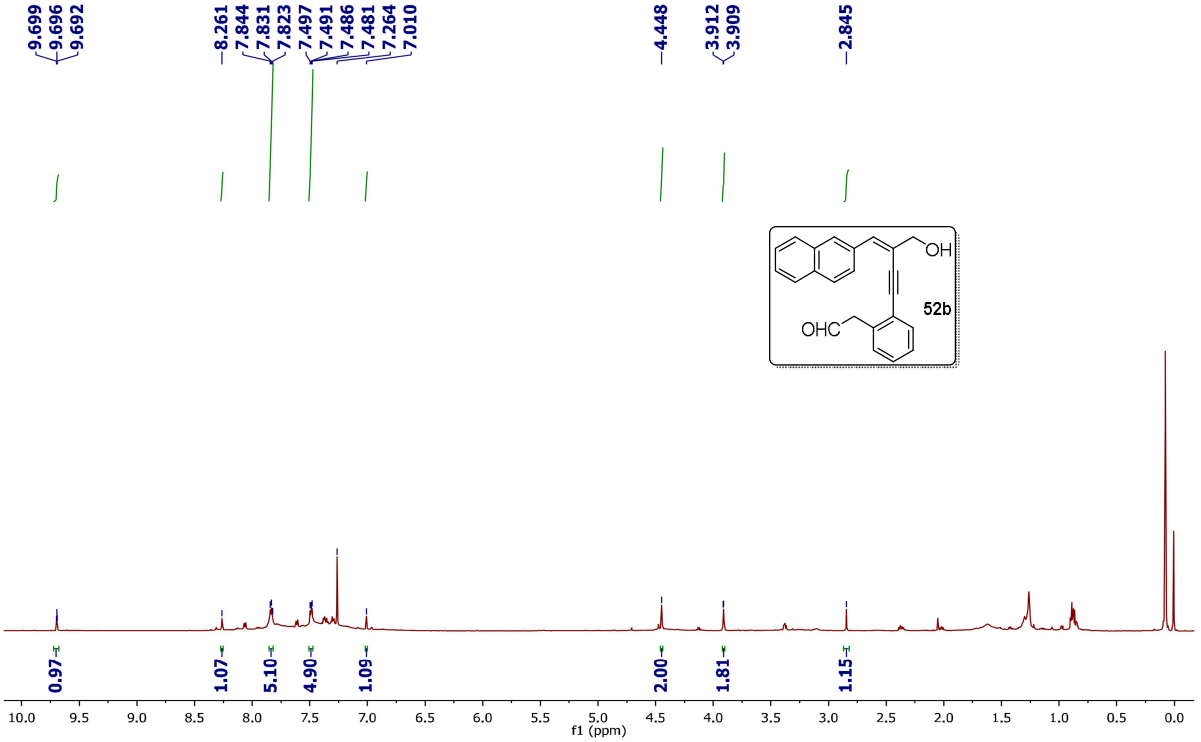
^{1}H NMR (600 MHz) of **52a:**



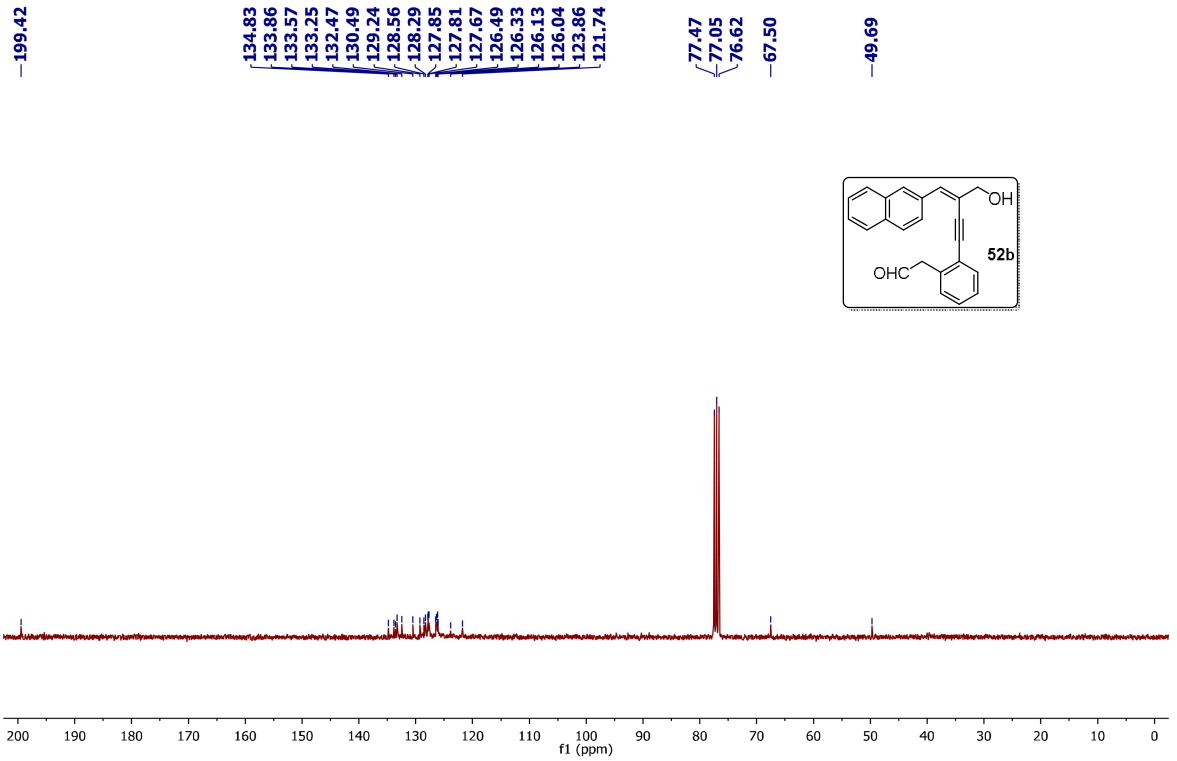
^{13}C NMR (75 MHz) of **52a:**



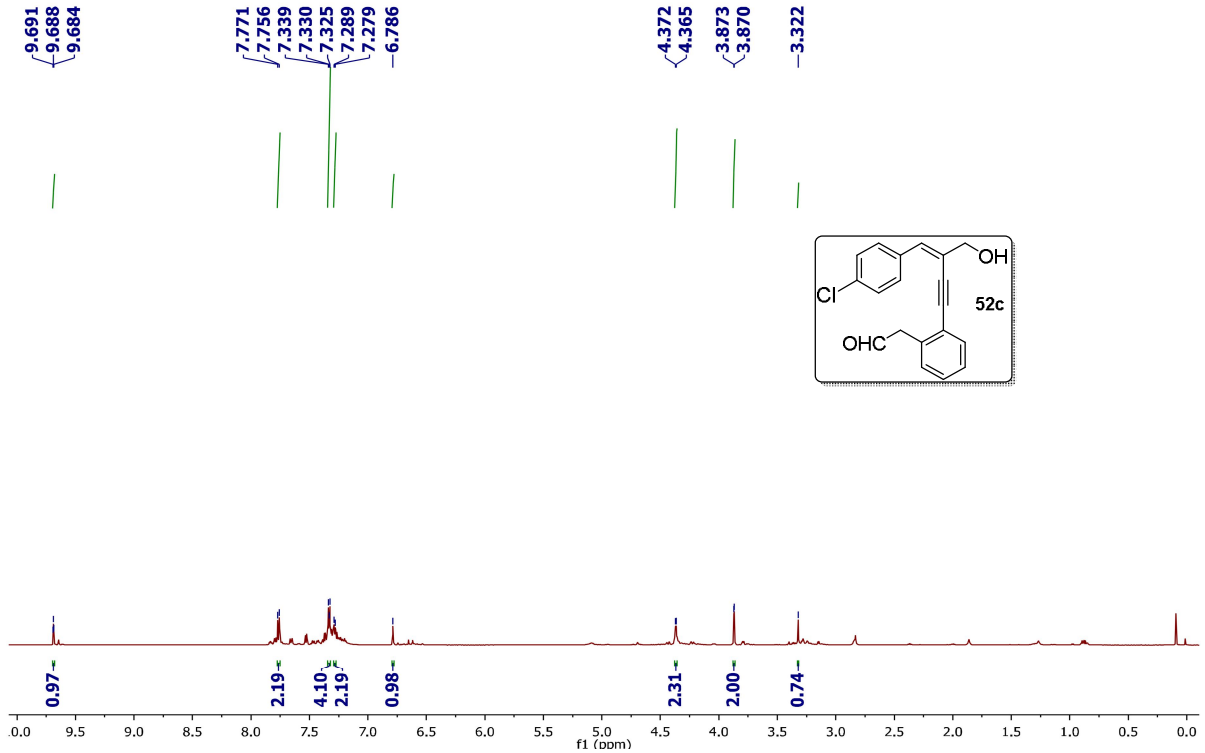
^{1}H NMR (600 MHz) of **52b**



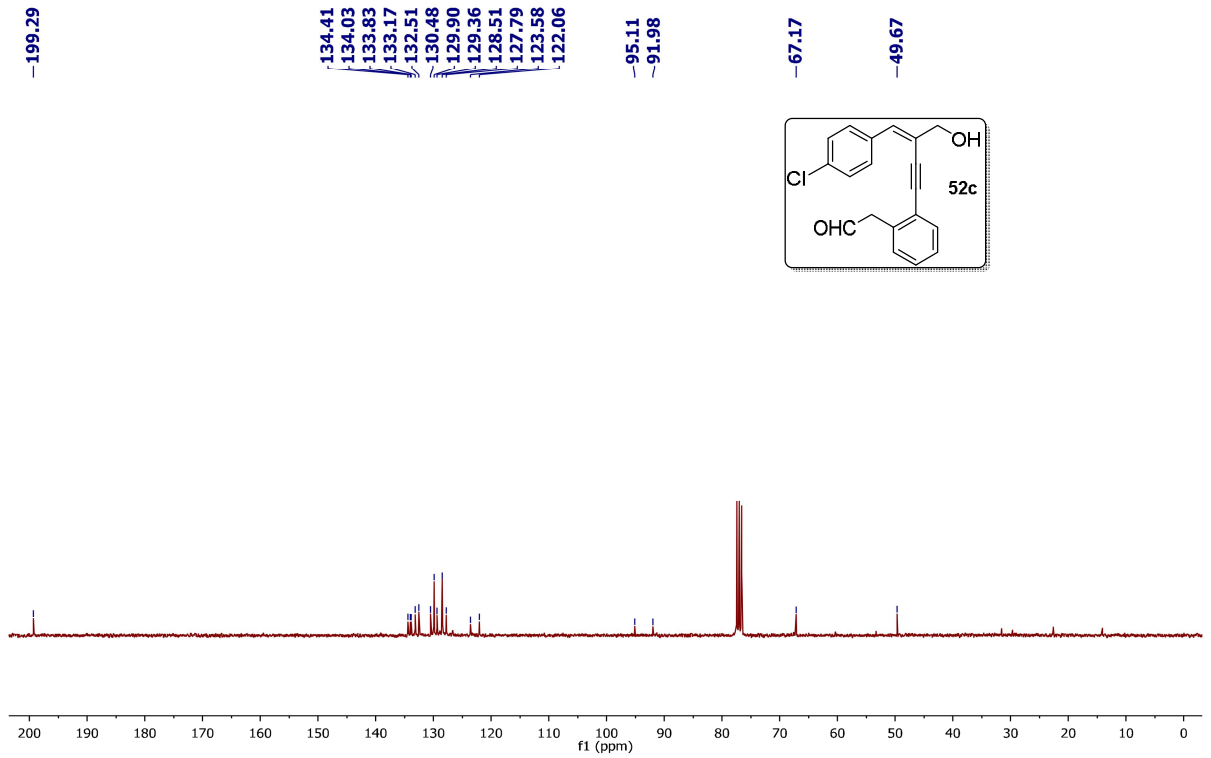
^{13}C NMR (75 MHz) of **52b:**



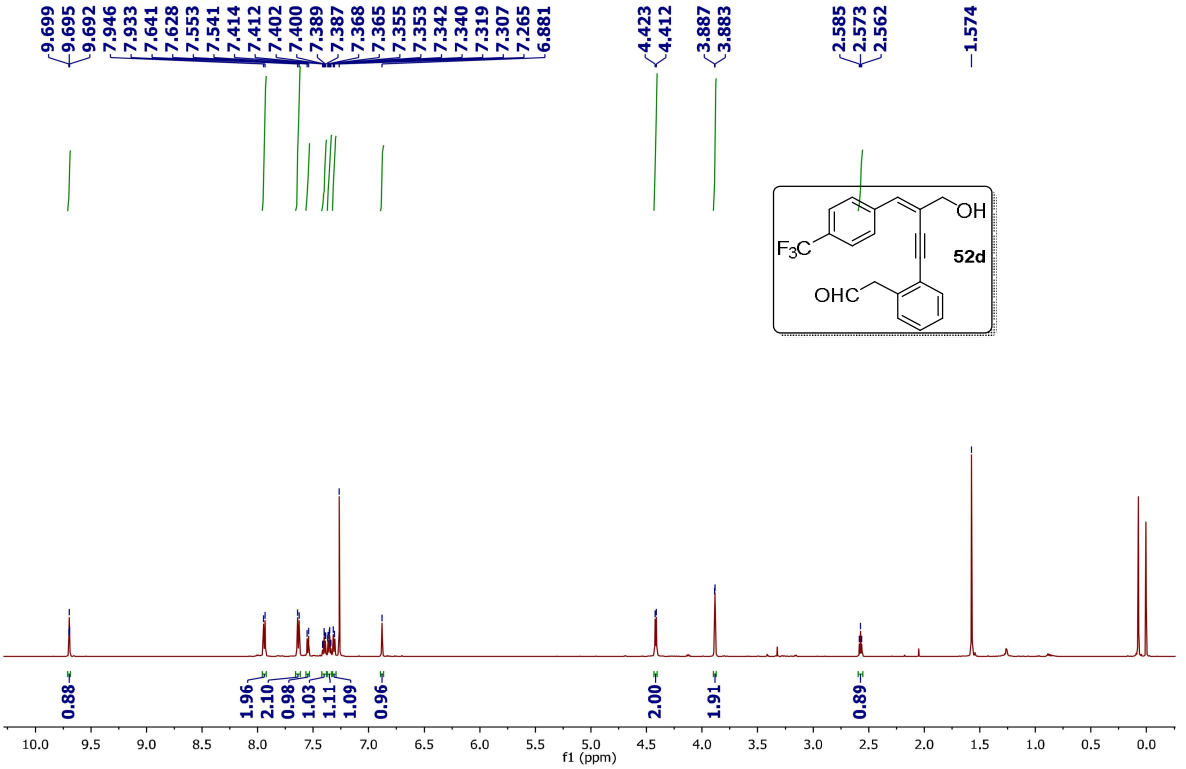
^{1}H NMR (600 MHz) of **52c**



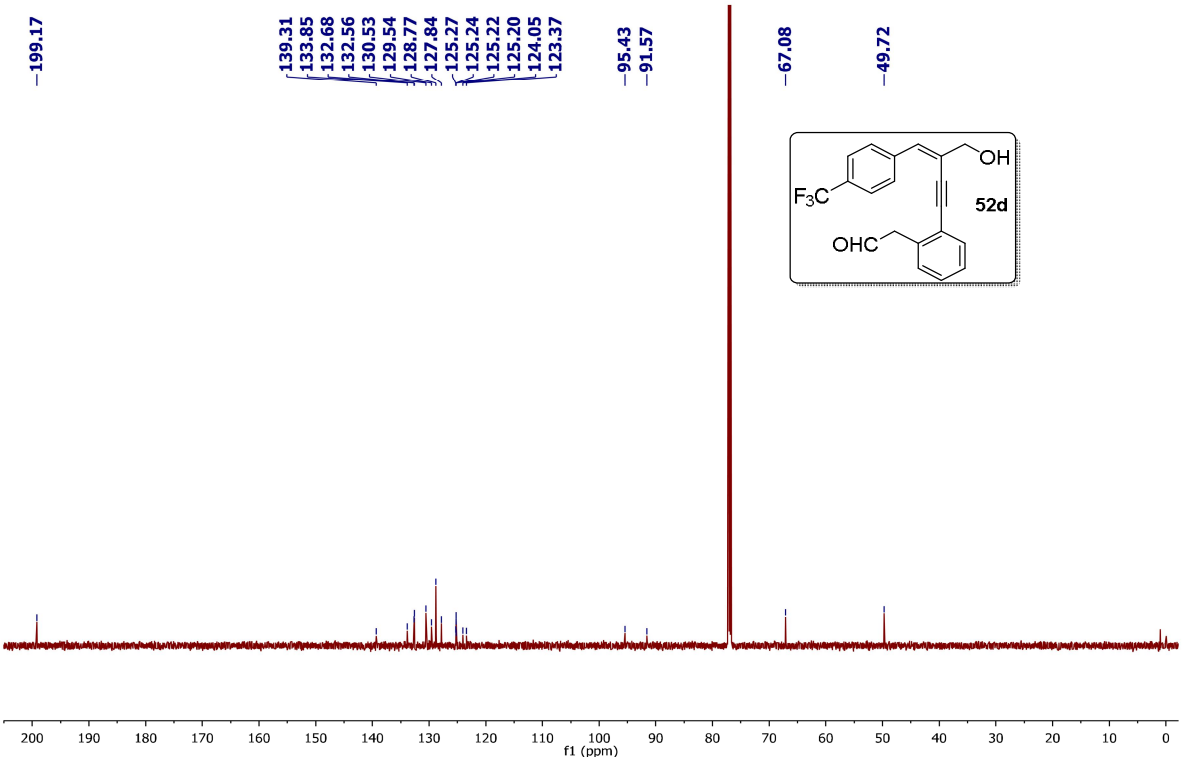
^{13}C NMR (75 MHz) of **52c:**



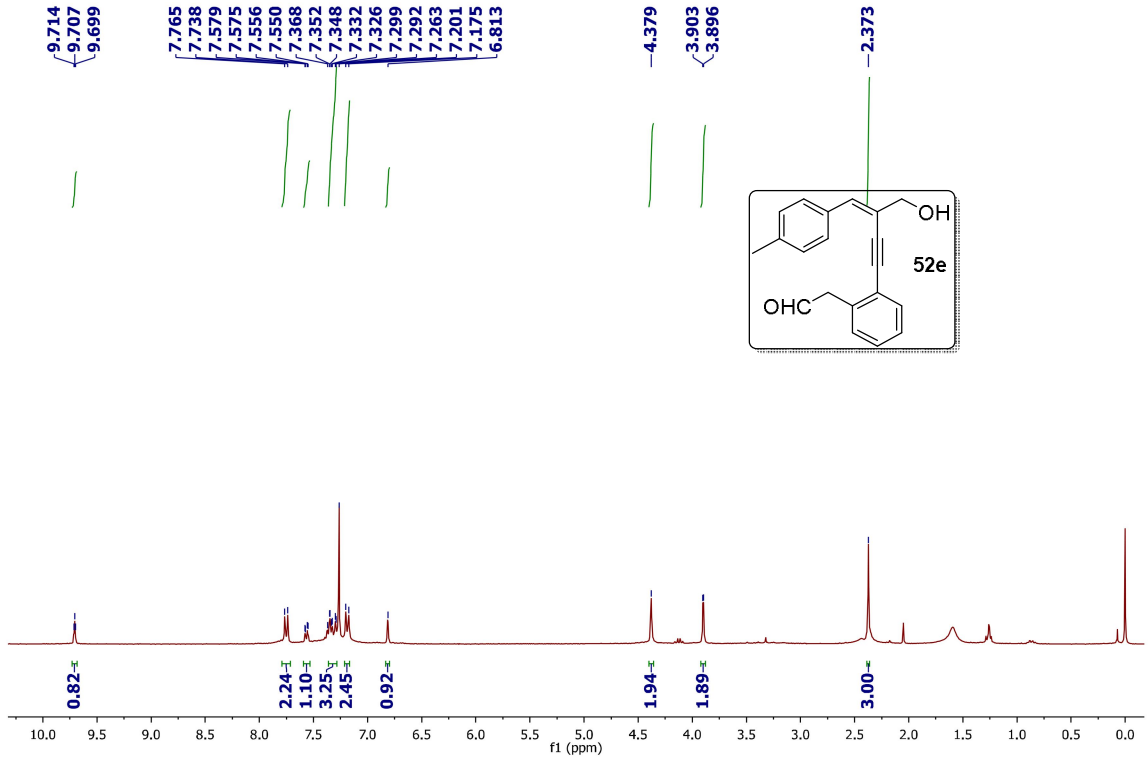
^{1}H NMR (600 MHz) of **52d:**



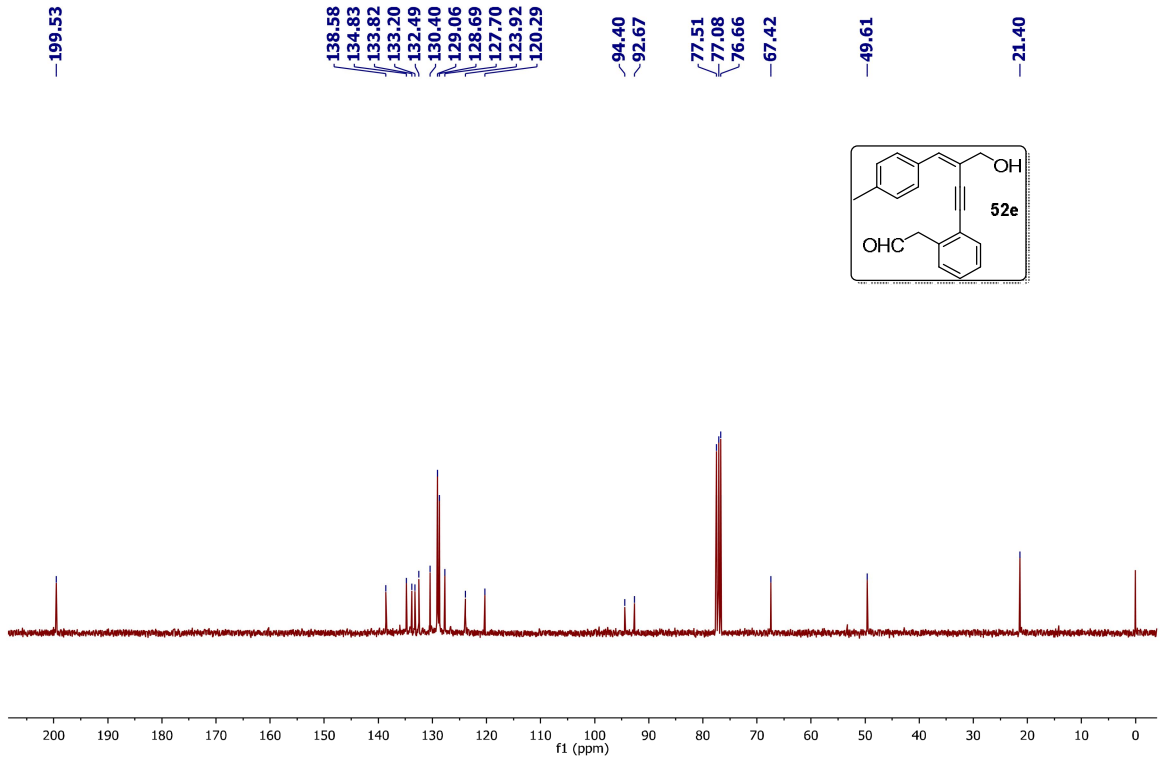
^{13}C NMR (150 MHz) of **52d:**



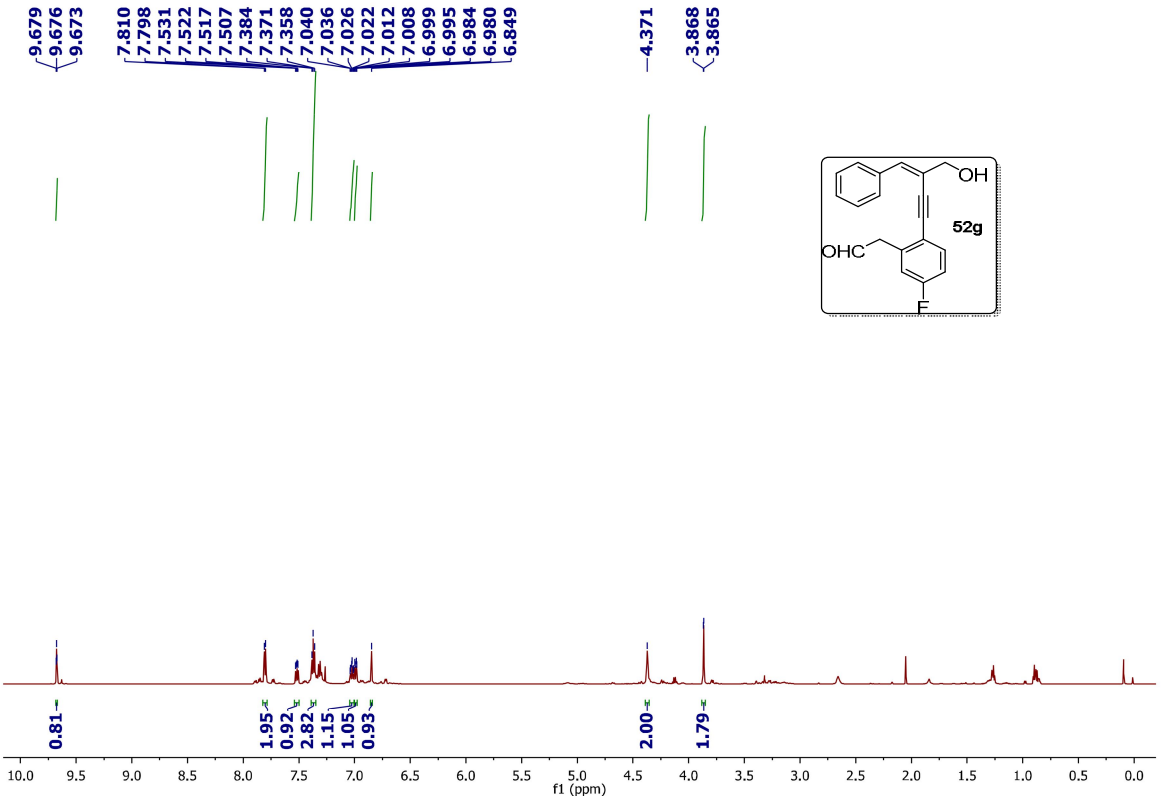
^{1}H NMR (300 MHz) of **52e:**



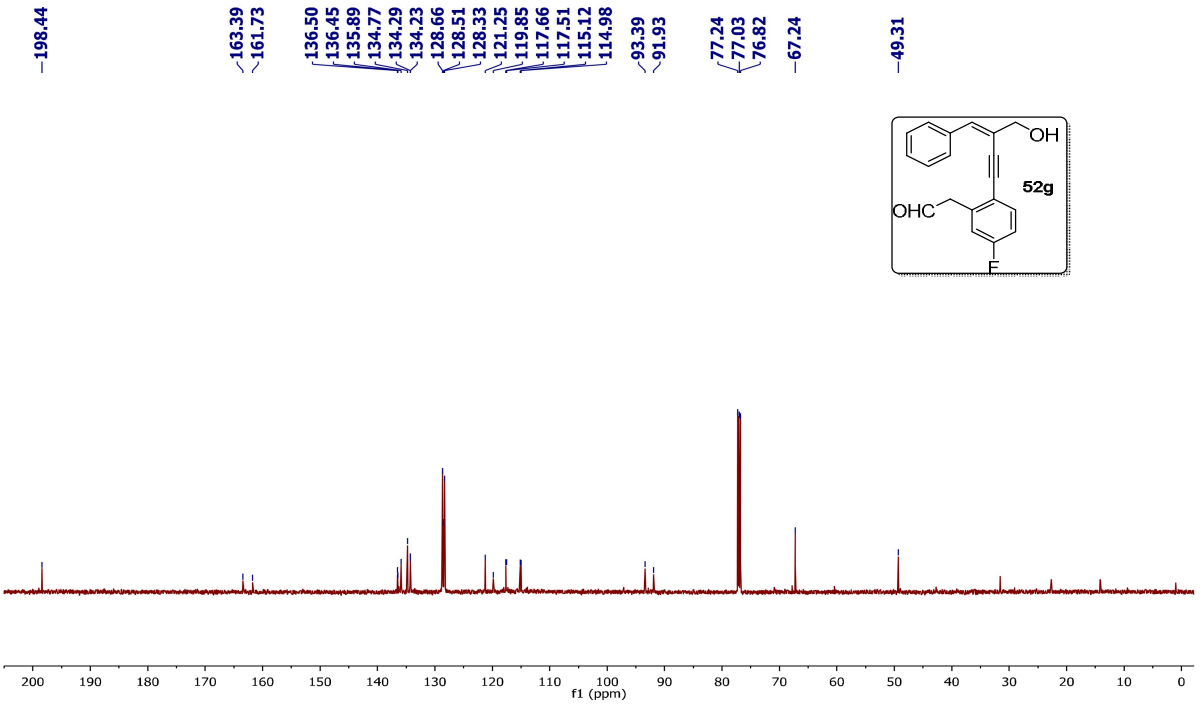
^{13}C NMR (75 MHz) of **52e:**



^{1}H NMR (600 MHz) of **52g:**

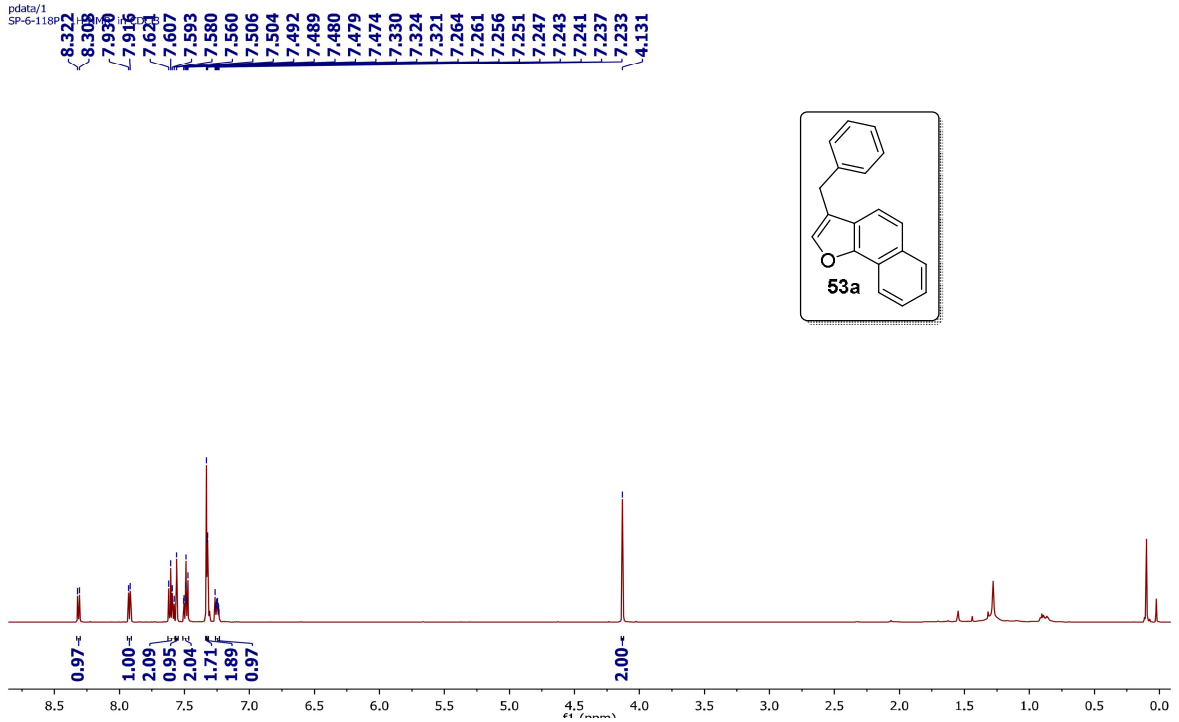


^{13}C NMR (150 MHz) of **52g:**

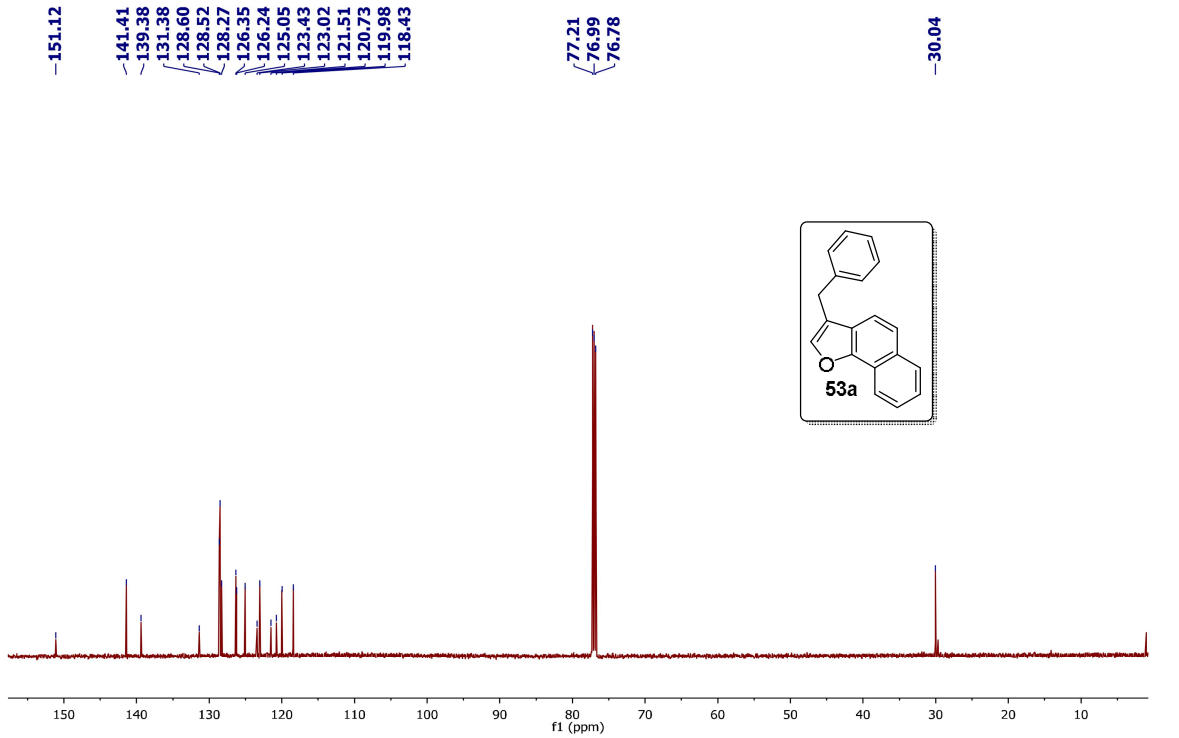


NMR Spectra of Compounds 53a-53g :

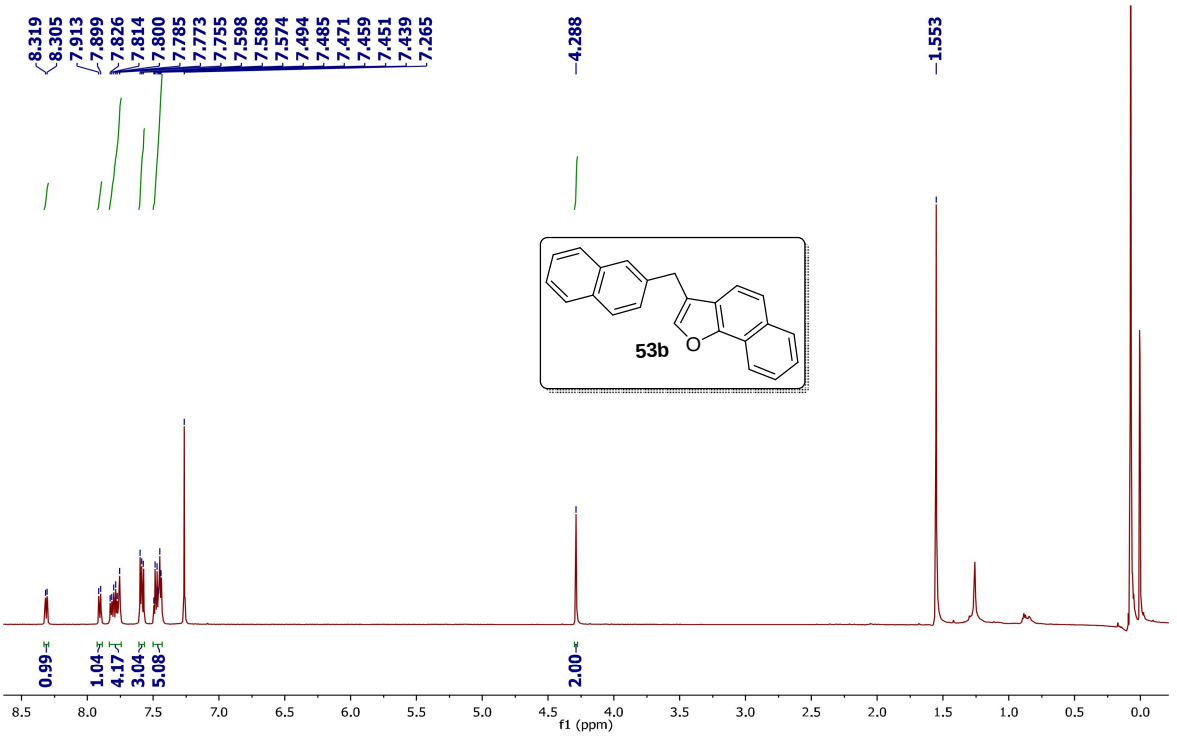
^{1}H NMR (600 MHz) of **53a:**



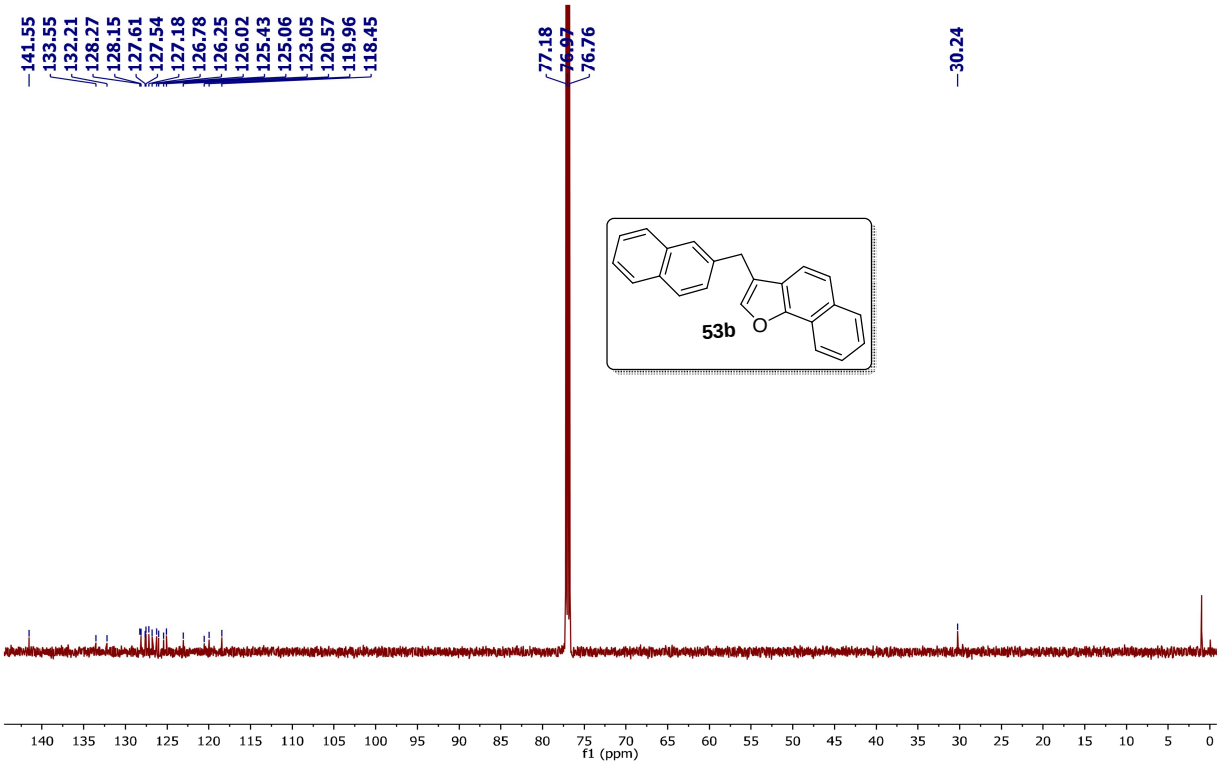
^{13}C NMR (150 MHz) of **53a:**



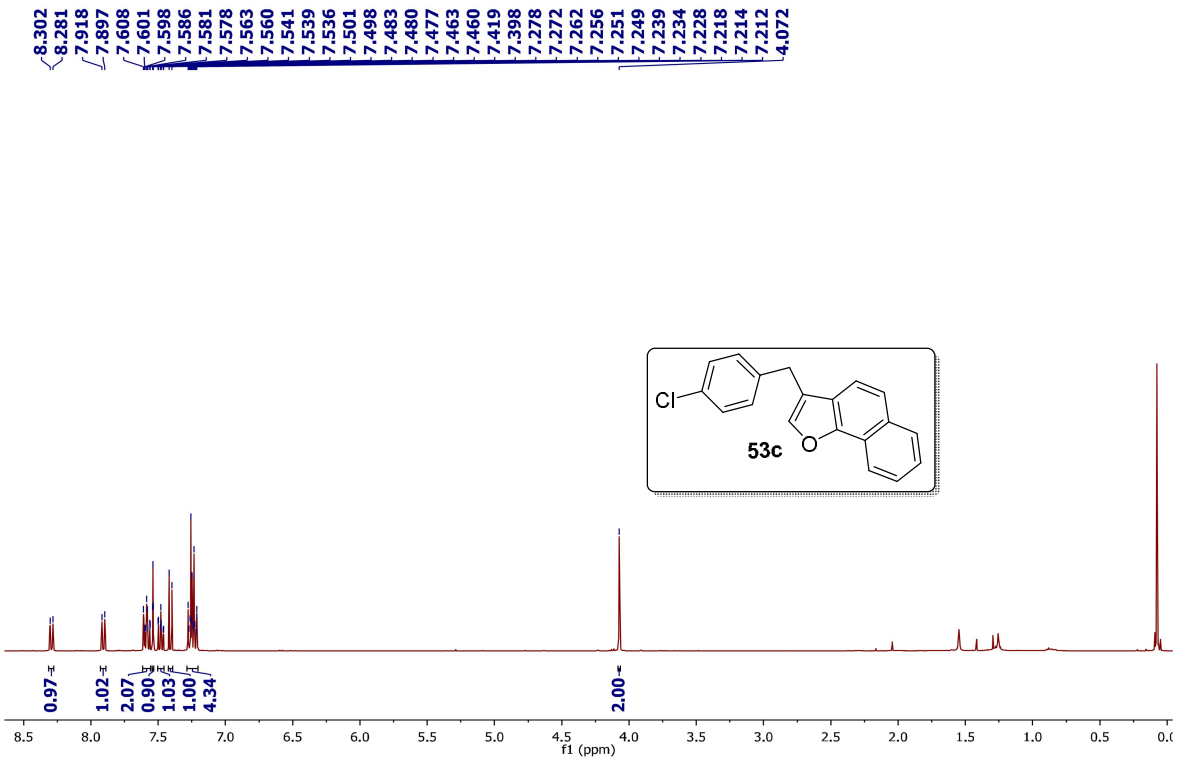
^{1}H NMR(600 MHz) of **53b:**



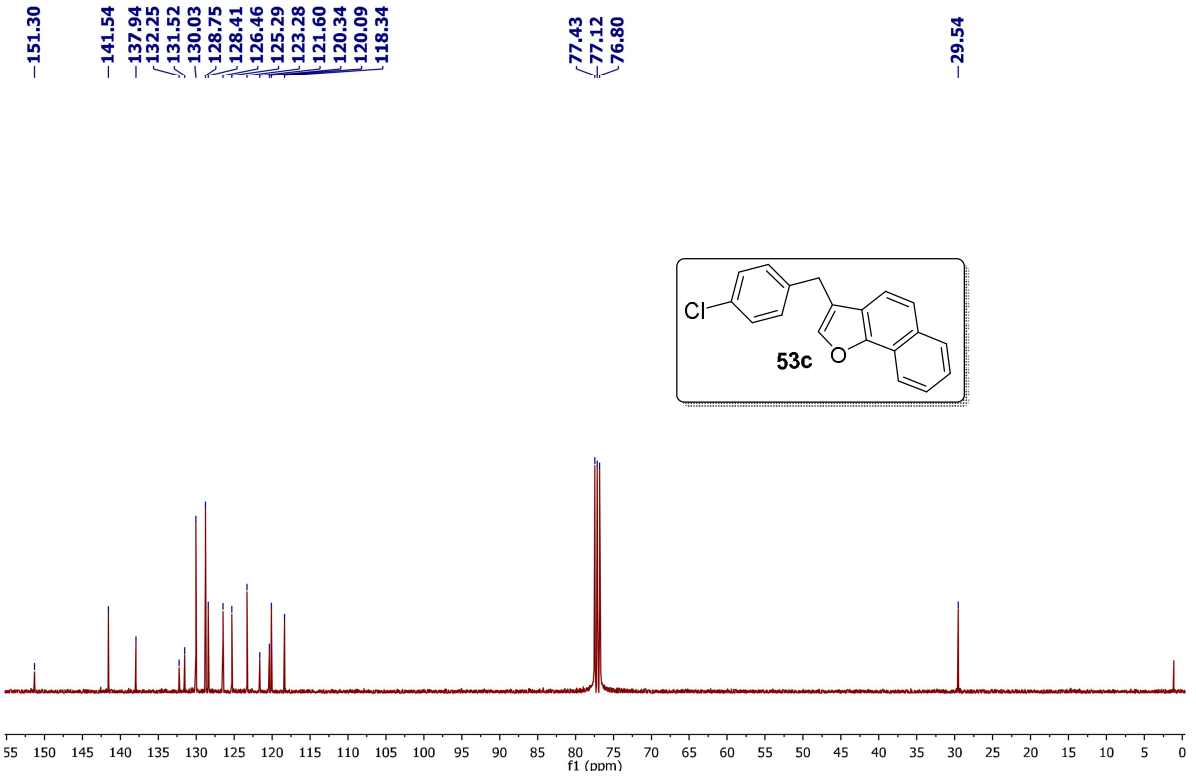
^{13}C NMR (150 MHz) of **53b:**



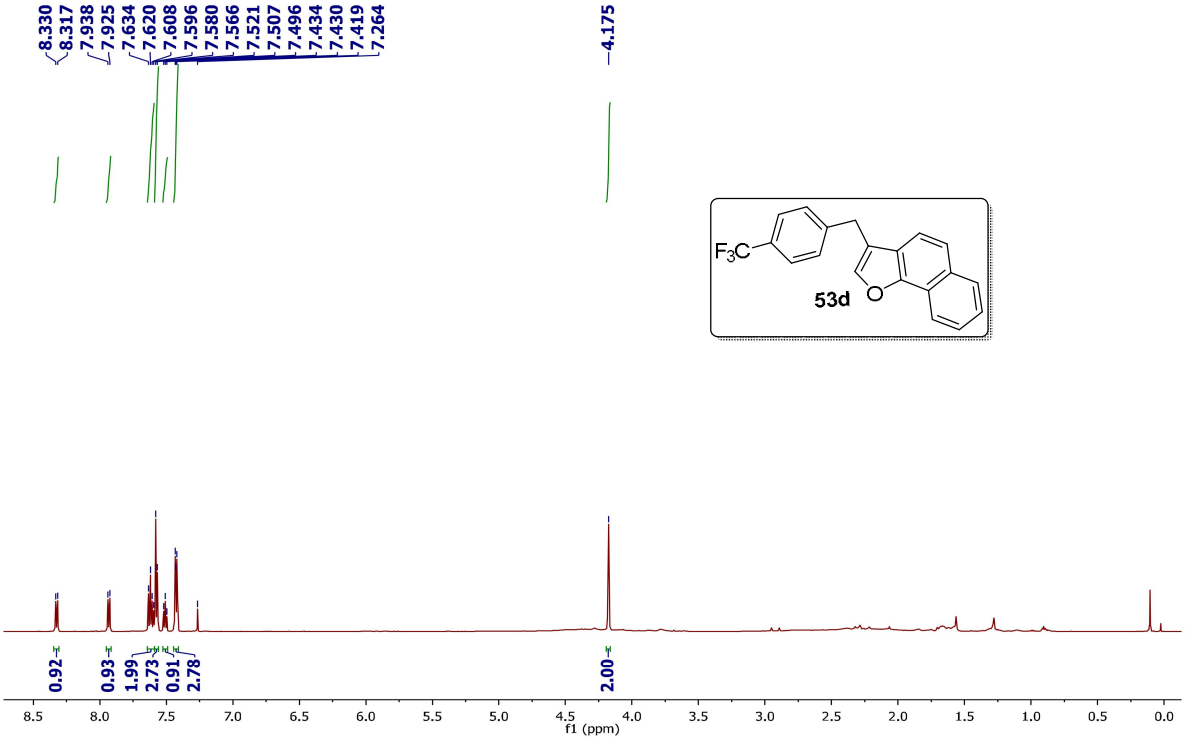
^{1}H NMR (400 MHz) of **53c:**



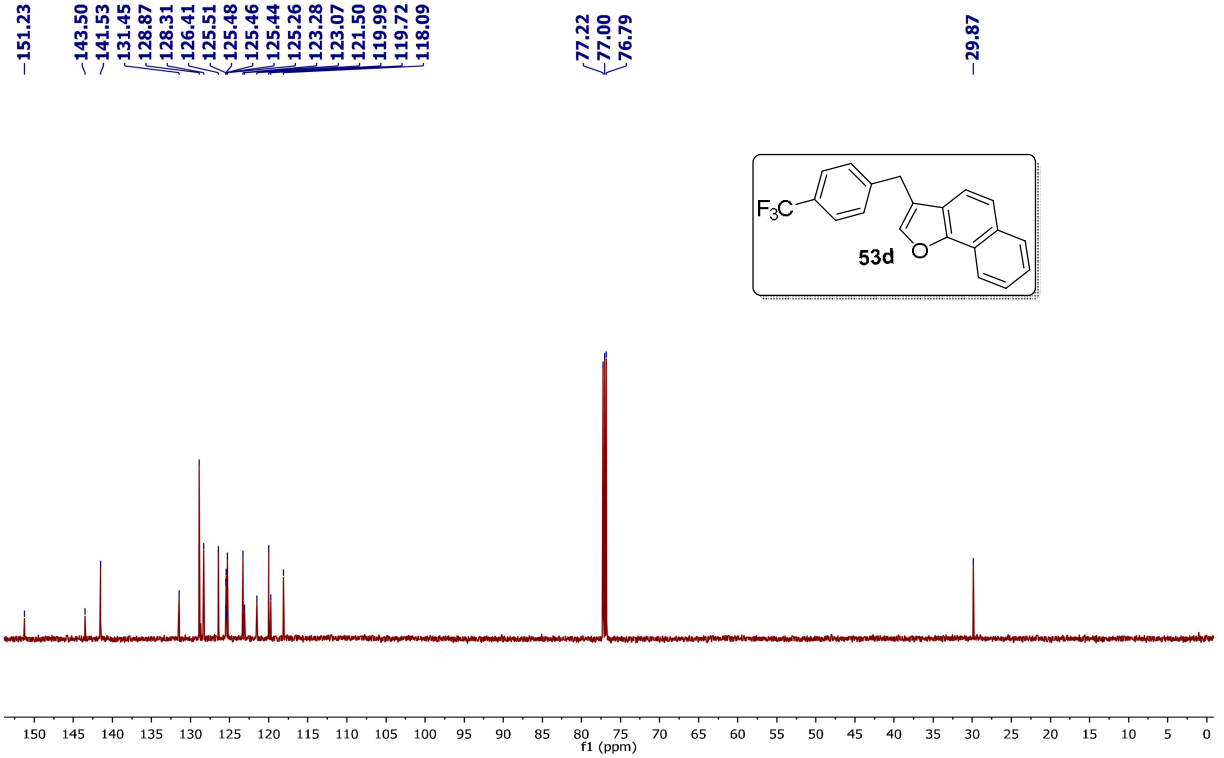
^{13}C NMR (100 MHz) of **53c:**



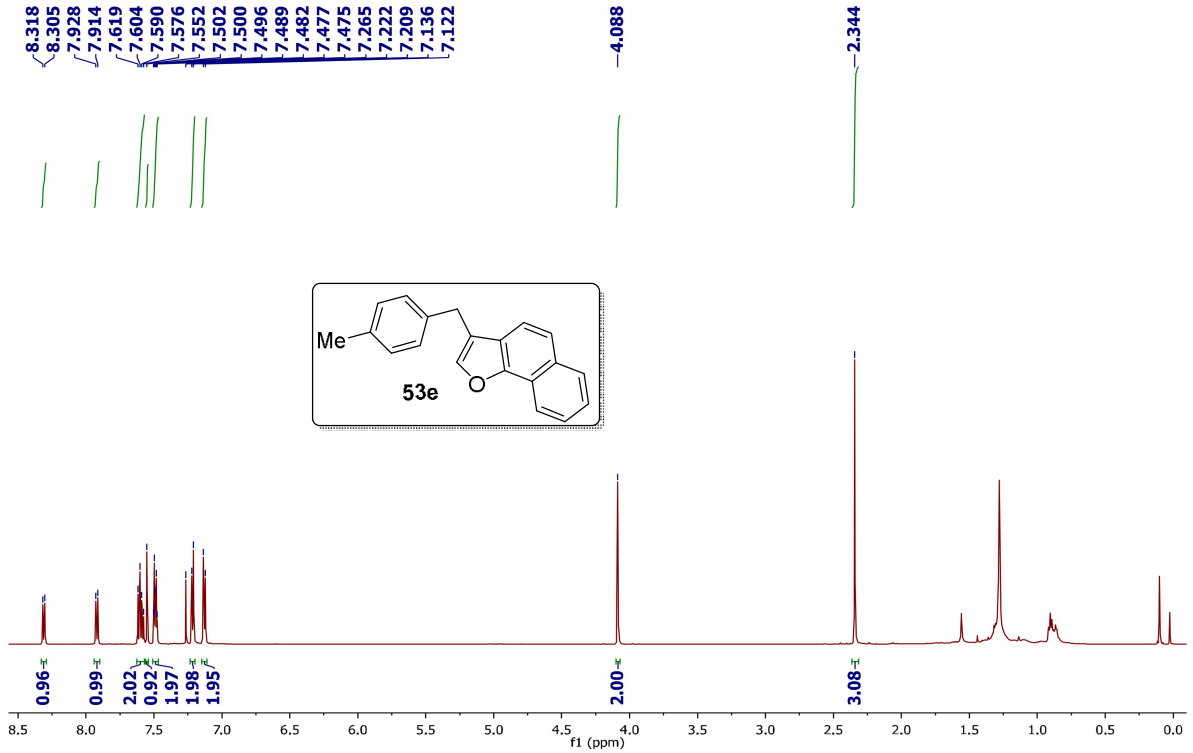
^{1}H NMR (600 MHz) of **53d:**



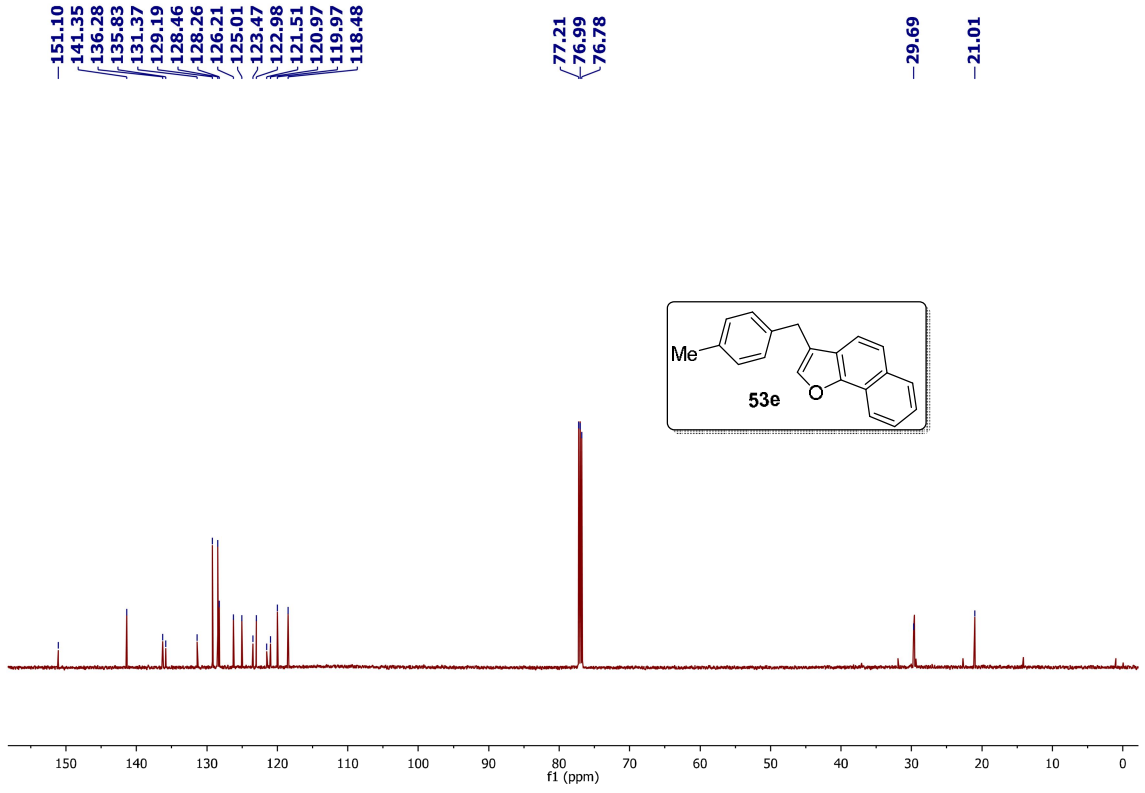
^{13}C NMR (150 MHz) of **53d:**



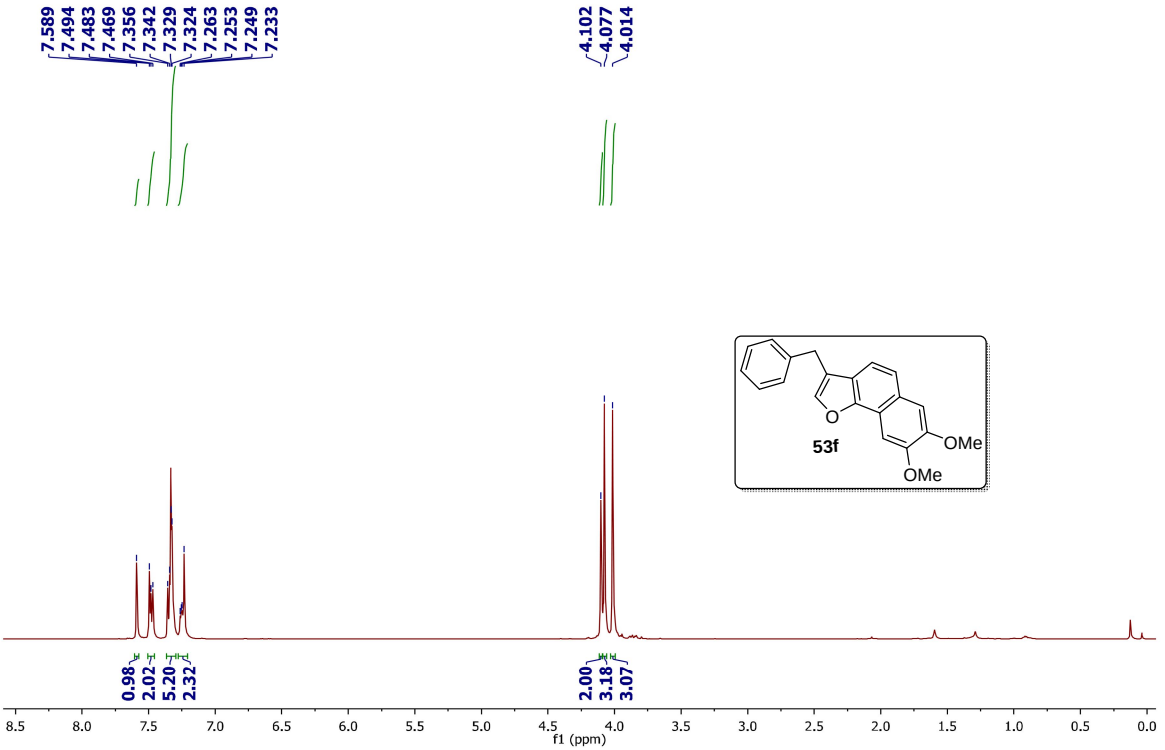
^{1}H NMR (600 MHz) of **53e:**



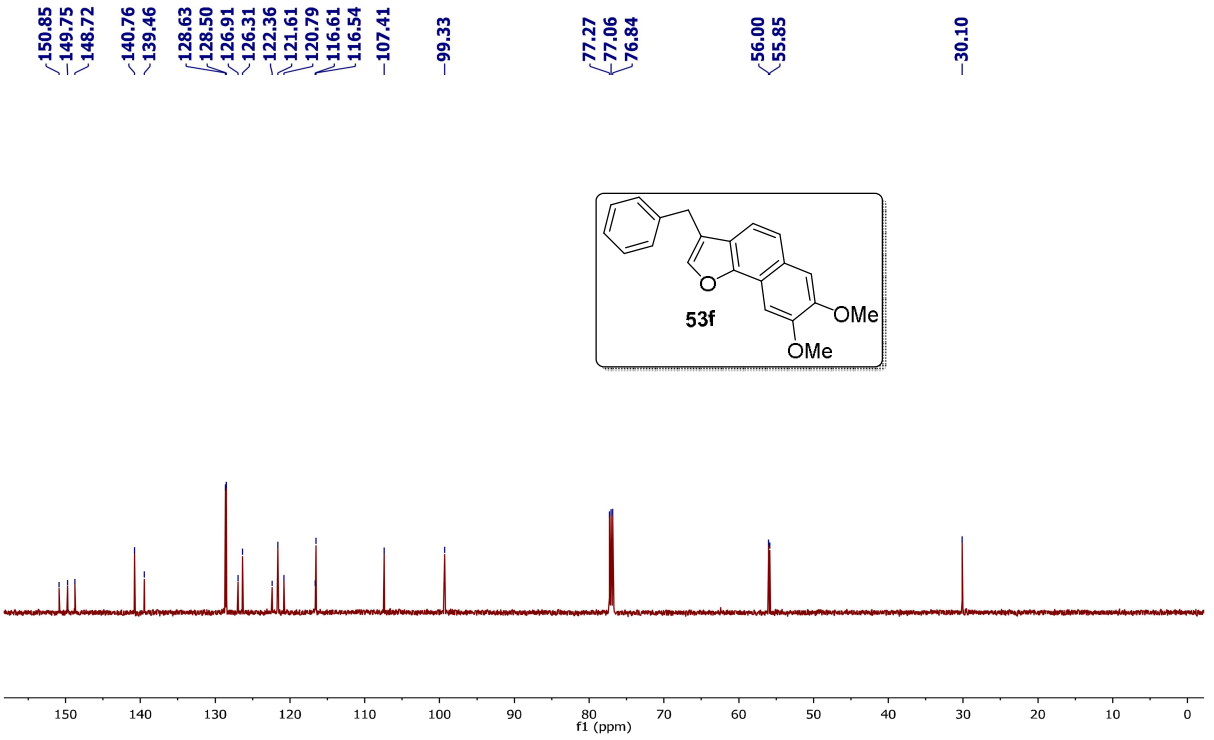
^{13}C NMR (150 MHz) of **53e:**



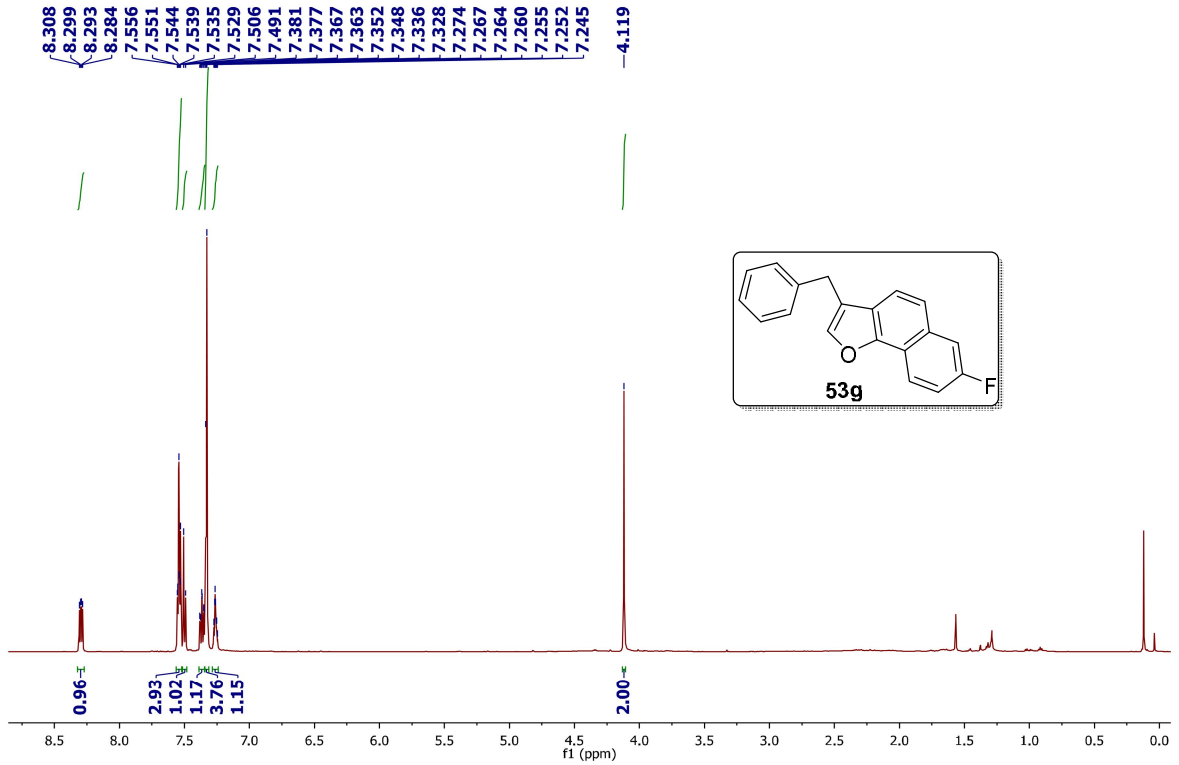
^{1}H NMR (600 MHz) of **53f :**



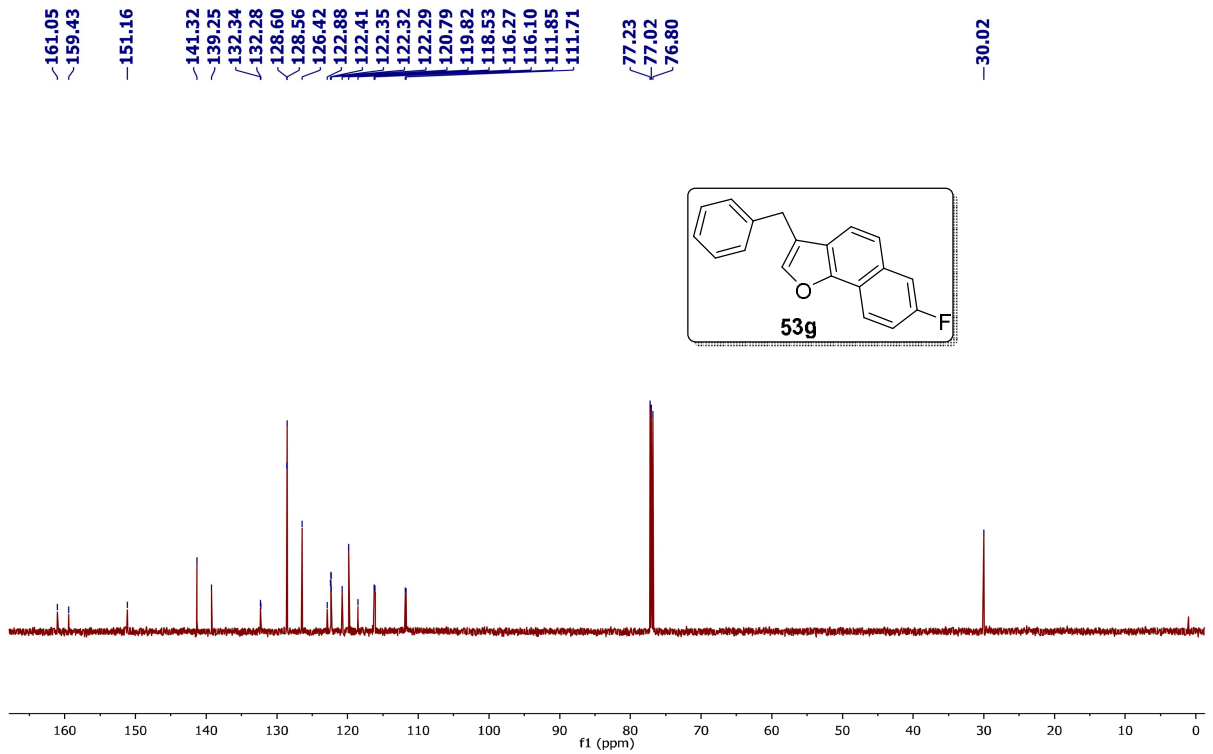
^{13}C NMR (150 MHz) of **53f:**



^{1}H NMR (600 MHz) of **53g:**

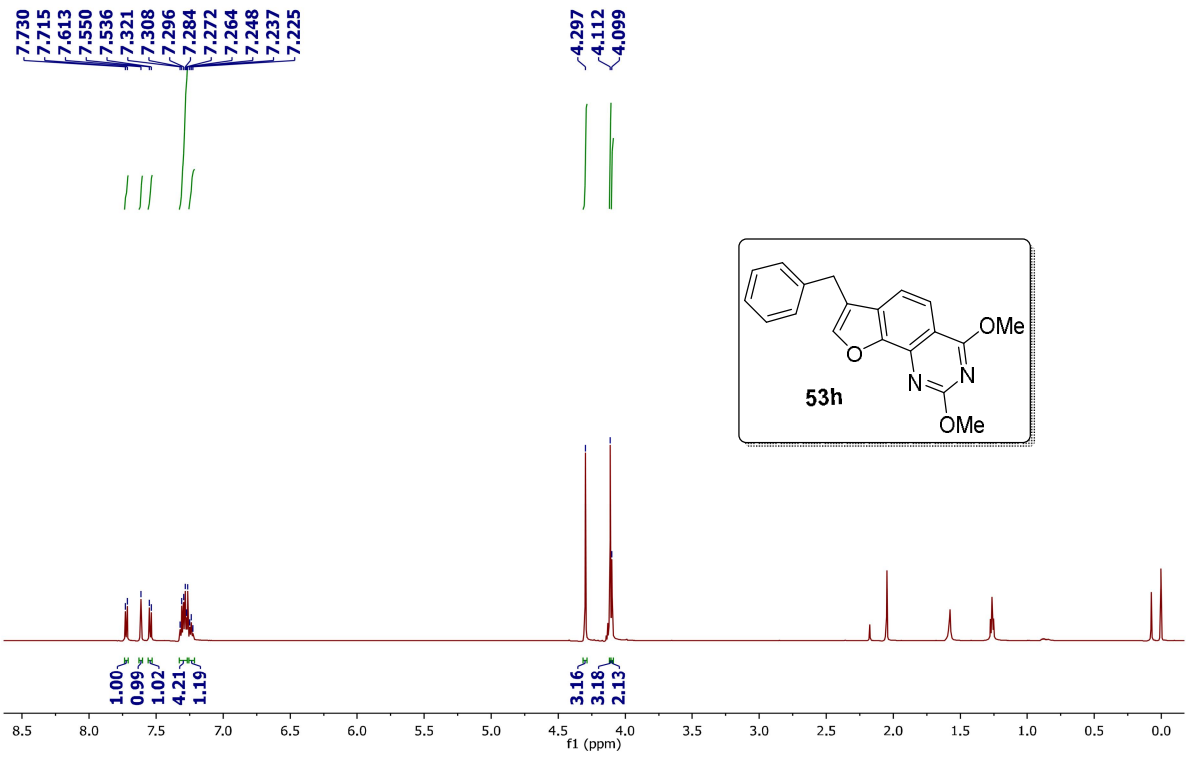


^{13}C NMR (150 MHz) of **53g:**

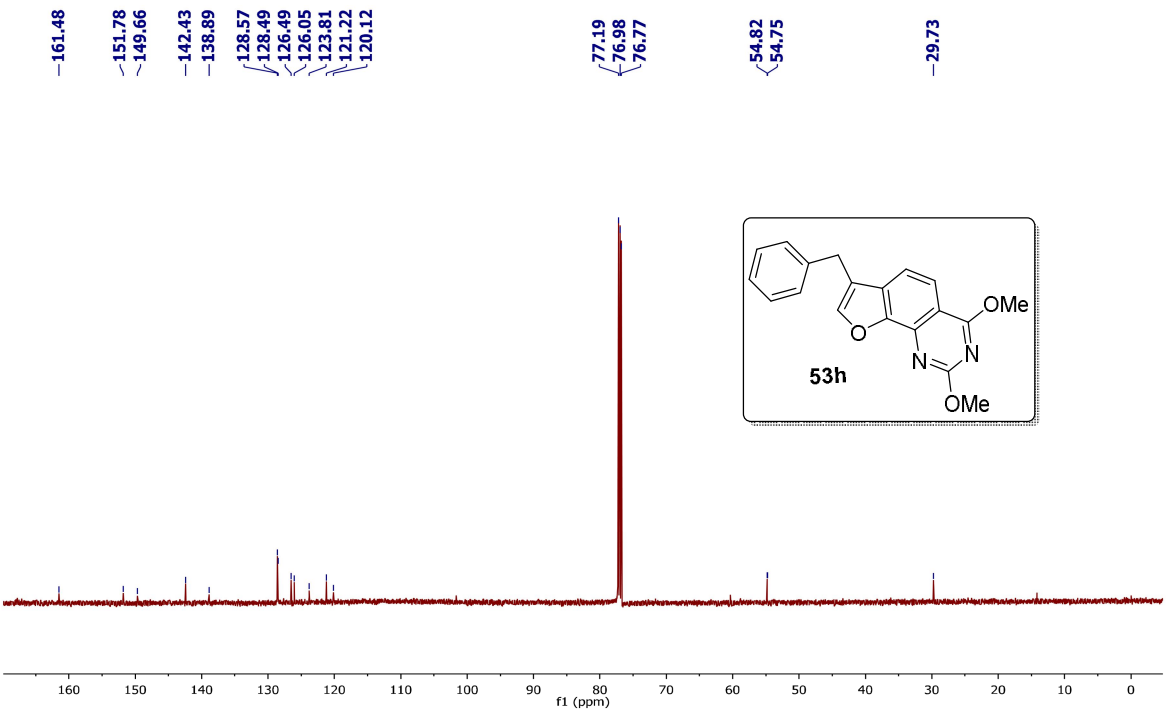


NMR Spectra of Compounds 53h and 61:

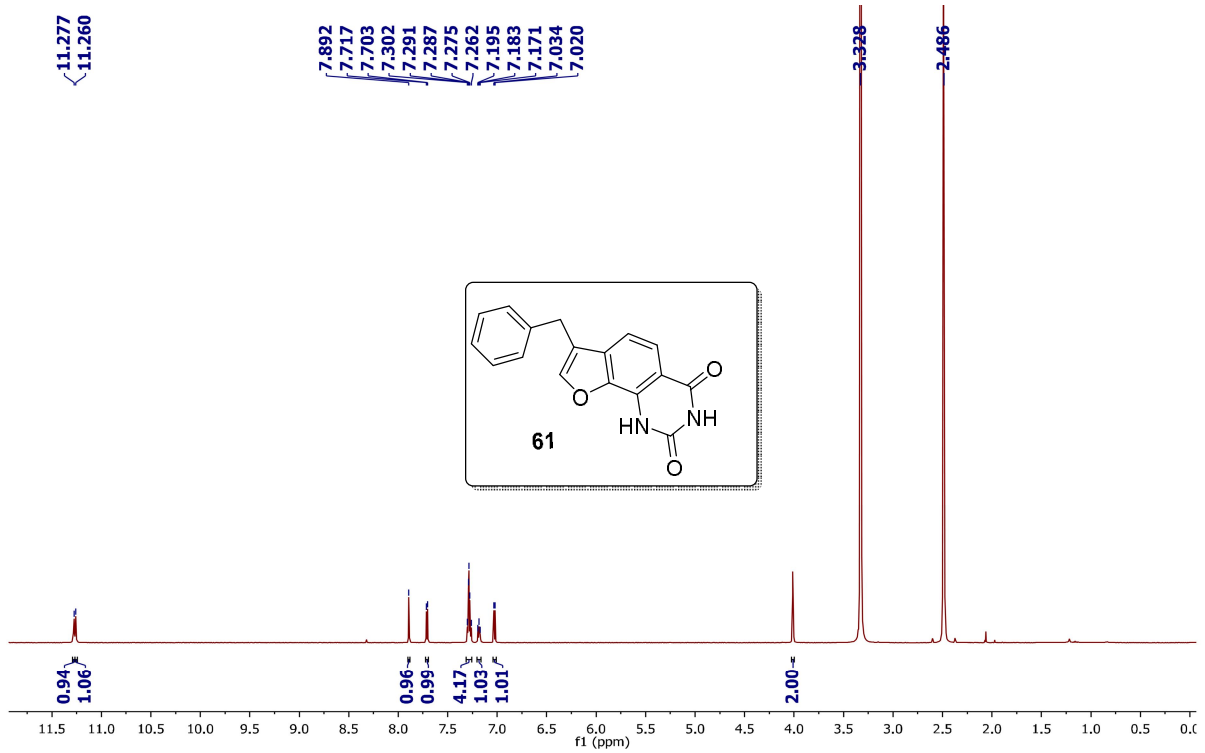
^{1}HNMR (600 Mz) of 53h:



^{13}CNMR(150) of 53h



^{1}H NMR (600 MHz) of compound 61



^{13}C NMR (150 MHz)of compound 61