TRANSIENT BROMOIODANE MEDIATED BROMOCYCLIZATION OF 2-ALKYNYLARYLOATE ESTERS

M. Sc. Thesis

By

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DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY INDORE

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A THESIS

Submitted in partial fulfillment of the requirements for the award of the degree
of
Master of Science

by

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CANDIDATE'S DECLARATION

I hereby certify that the work presented in this thesis entitled **TRANSIENT BROMOIODANE MEDIATED BROMOCYCLIZATION OF 2-ALKYNYLARYLOATE ESTERS** in the partial fulfillment of the requirements for the award of the degree of **MASTER OF SCIENCE** and submitted in the **DEPARTMENT OF CHEMISTRY, Indian Institute of Technology Indore**, is an authentic record of my work carried out during the time period from July 2022 to May 2023, under the supervision of Dr. Selvakumar Sermadurai, Assistant Professor, Department of Chemistry, IIT Indore.

Sodoor 15/05/2023
(Signature of the Student with the date)

Mohammad Sodoor

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

S. Selv 15/05/2023
(Signature of the Supervisor with the date)

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Mohammad Sodoor has successfully given his M.Sc. Oral Examination held on **May 16, 2023**.

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Date: 18-05-2023

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Date: 18/5/2023

Signature of PSPC Member
(Dr. Satya S. Bulusu)
Date: 18/5/23

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Mohammad Sodoor

Dedicated to My Family…

ABSTRACT

Isocoumarin is a class of *O*-containing heterocycles with a broad spectrum of applications in pharmacological, agrochemical, and material sciences. Introducing a halogen atom at the 4-position of isocoumarin provides a handle for further derivatization. We show an easy method to synthesize 4-bromoisocoumarin under very mild conditions, using a bench stable hypervalent iodine reagent and simply available alkali metal bromide. Our one-pot, one-step reaction follows a 6-*endo*-dig-cyclization strategy for making new bonds. The generality and mechanistic insight of the reaction are addressed here, followed by post-synthetic modifications. Also, a catalytic pathway has been uncovered side by side.

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I. LIST OF FIGURES

II. ABBREVIATIONS

°C	Degree Celsius
g	Gram
h	Hours
HIR	Hypervalent Iodine (III) reagent
mg	Milligram
mL	Milliliter
mmol	Millimole
min	Minutes
%	Percentage
rt	Room temperature

III. ACRONYMS

HTIB	Hydroxy(tosyloxy)iodobenzene
HTIB-1	1-[Hydroxy(tosyloxy)iodo]-4-chlorobenzene
HTIB-2	1-[Hydroxy(tosyloxy)iodo]-4-fluorobenzene
HTIB-3	1-[Hydroxy(tosyloxy)iodo]-4-methoxybenzene
HTIB-4	1-[Hydroxy(tosyloxy)iodo]-4-methylbenzene
NMR	Nuclear Magnetic Resonance
PIDA	Diacetoxyiodobenzene
PIFA	Bis(trifluoroacetoxy)iodobenzene

Chapter 1

INTRODUCTION

1.1. Oxygen-containing heterocycles

Heterocycles are prevalent fragments critical in many active pharmaceutical ingredients and excipients [1]. Many heterocyclic scaffolds show versatile binding properties. Five or six-membered ring compounds containing nitrogen, oxygen, or sulfur as a replacement of one or more carbon atoms can be seen frequently in biologically active compounds. Statistically, more than 80% of all biologically active compounds contain at least one heterocycle.

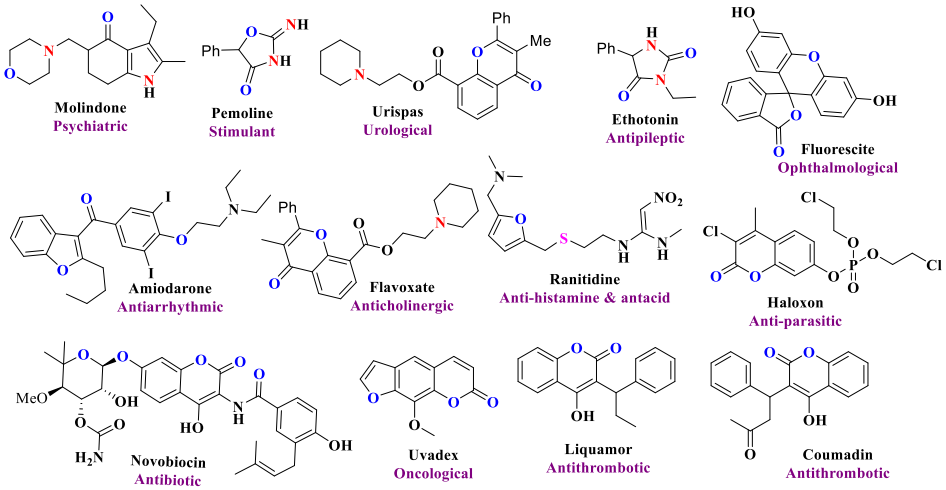


Figure 1: Some heterocycle-containing USFDA-approved drugs

Oxygen-containing heterocycles are abundant in nature with various biological roles. They constitute the second largest class of heterocycles after *N*-containing ones [2]. According to a report from 2014, nearly 59% of all USFDA-approved drugs had at least one *N*-containing heterocycle [3]. Some essential oxygen-containing heterocyclic cores commonly present in natural compounds are benzofuran, chromane, chromene, xanthene, 1,4-dibenzodioxins, coumarin, isocoumarin, etc. Among them, isocoumarin is an important compound class that occurs as natural (and synthetic) lactones.

1.2. Isocoumarin

Members of this class exhibit a wide range of biological activities. Besides, they also happen as synthetic intermediates while synthesizing many important heterocyclic and carbocyclic compounds [4]. An isocoumarin-based compound is efficient in nitrophenol sensing [5]. Figure 2 includes some selected examples of isocoumarin-containing compounds with activities such as antifungal, oncological, antibacterial, antiviral, etc. [6]. Isocoumarin-based compounds were also found to be effective in inhibiting the aldosterone synthase enzyme and serine protease enzyme. Aldosterone plays a role in blood pressure regulation, and the serine protease enzyme is related to blood coagulation after any injury or cut. This broad range of activities attracted scientists worldwide to develop methodologies for synthesizing such compounds. Mostly, 3-substituted and 3,4-disubstituted isocoumarin moieties are found in naturally occurring biologically active compounds.

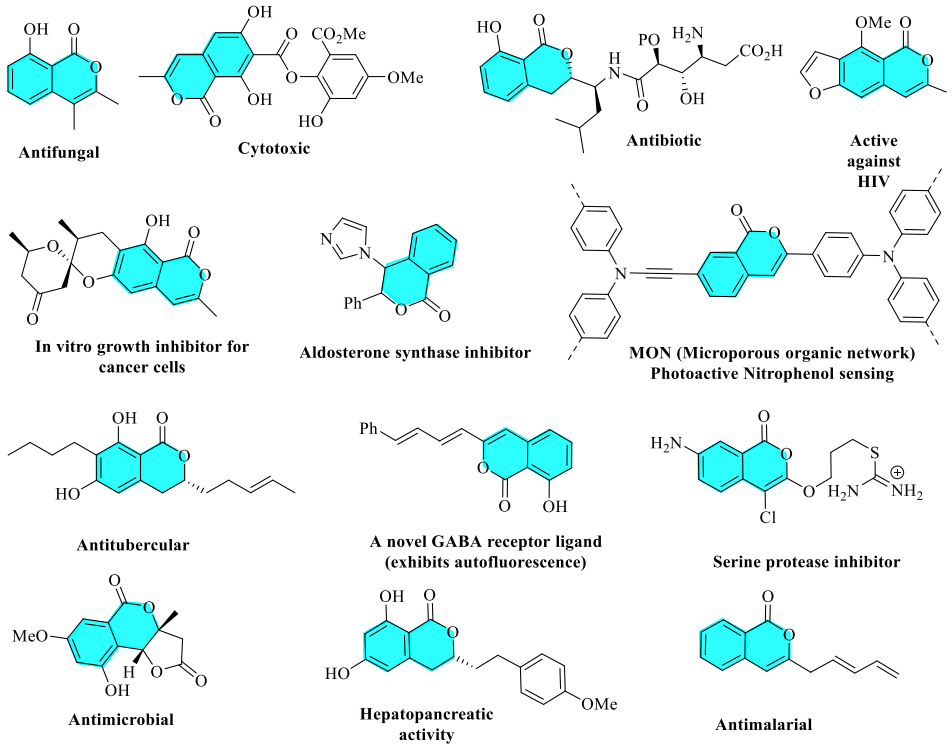


Figure 2: Some examples of isocoumarin-containing compounds

In this regard, a quest to synthesize 3-substituted and 3,4-disubstituted isocoumarin moieties was started long ago [16]. Scientists have developed multiple methods to make 3-substituted isocoumarin scaffolds using transition metal (Cu, Pd, Rh, Ir, Ru, Au, Ag, etc.) catalysts [7]. For making 3,4-disubstituted isocoumarin scaffolds, similar strategies were developed [8]. Recently, scientists have shifted their attention towards synthesizing 3-aryl-4-haloisocoumarin scaffolds, which can be converted into the 3-substituted or the 3,4-disubstituted isocoumarin-containing compounds. Following (Figure 3) is a retrosynthetic analysis of 3-substituted and 3,4-disubstituted isocoumarin-containing compounds. The hydrodehalogenation reactions can make the 3-substituted moieties, while the 3,4-disubstituted one can be made by using palladium-catalyzed cross-coupling reactions, using the 3-aryl-4-haloisocoumarin scaffolds as the common substrate. The 3-aryl-4-haloisocoumarin containing compounds are commonly synthesized from 2-alkynylaryloate esters by the alkyne activation followed by a 6-*endo*-dig selective cyclization strategy. Again, there is a list of methods to make 3-aryl-4-haloisocoumarin containing compounds from 2-alkynylaryloate esters. Some involve electrophile-mediated cyclization, and some follow a metal-catalyzed approach.

If we consider the reactivity of halogens towards the cross-coupling reactions, we can conclude that the 4-iodo and 4-bromo are more effective

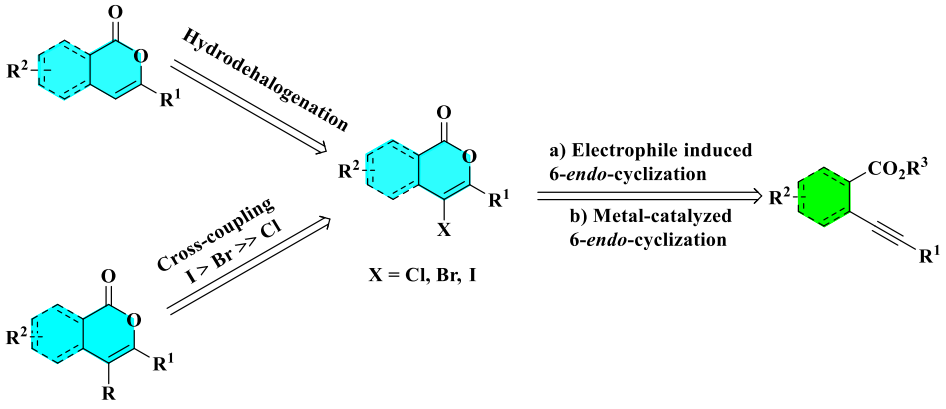


Figure 3: A retrosynthetic analysis of 3- and 3,4-di substituted isocoumarin-containing compounds

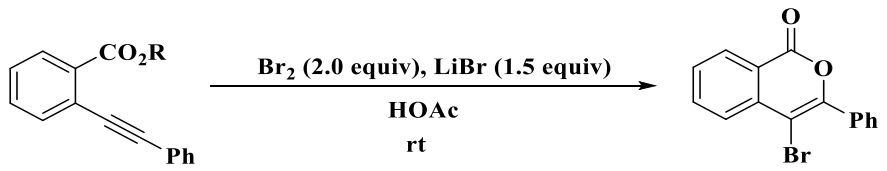
for such reactions than the 4-chloro ones. Isocoumarin-containing compounds substituted with iodo at the 4-position are well recorded in the literature, but we observed many limitations in the methods developed for making 4-bromoisocoumarin moieties.

1.3. 4-Bromoisocoumarin – Previous work

While doing the literature survey for synthesizing 4-bromoisocoumarins, we observed many methods but with limitations. Some used highly hazardous chemicals, while others required a very high temperature. The usage of transition metals was observed to be very common. We also noted in those methods that the substrate scope was too narrow. Substrate scope defines the generality of any reaction, and its narrowness can reduce the reliability of that reaction. So, we concluded that the synthesis of 4-bromoisocoumarin has not been explored much, and there is a window open for any novel, simple, and green synthetic route to make this critical core structure with bromine at the 4- position which will be of great value in synthetic and medicinal chemistry.

1.3.1.

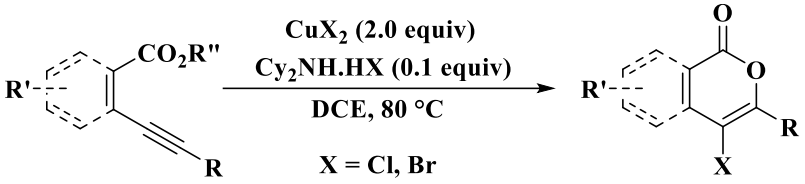
Michael A. Oliver and Richard D. Gandour, in 1983, while working on synthesizing some 1,2-dibromo-1,2-diphenylethene derivatives, observed that the bromination of methyl 2-(2-phenylethynyl) benzoate using liquid Br_2 in AcOH containing LiBr resulted into formation of a cyclized product which was later confirmed to be 4-bromo-3-phenyl isocoumarin [9]. They reported this method with **two examples** (78% yield) only.



Limitations: Handling bromine is the very first limitation of this method, followed by a very narrow substrate scope.

1.3.2.

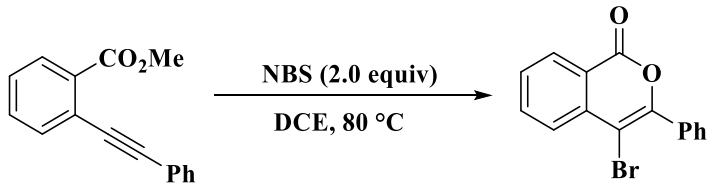
Li and co-workers, in 2006, reported another method to synthesize haloisocoumarins via a transition metal-catalyzed 6-*endo*-cyclization mechanism using dicyclohexylamine hydrohalide as an additive in DCE at 80 ºC [10]. They reported **18 examples** with **47-99% yield**.



Limitations: Metal halide had been used by them in their approach, which also required a high temperature.

1.3.3.

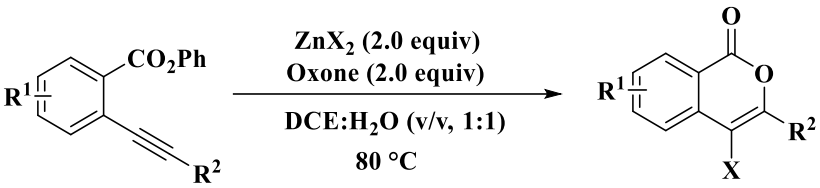
Yuan and co-workers, in 2017, discovered NBS-mediated 4-bromoisocoumarin synthesis while working on benzil-*o*-carboxylate synthesis from *o*-alkynylbenzoate and concluded the mechanism of benzil-*o*-carboxylate to follow a path *via* bromo-incorporated isocoumarin cation intermediate formation [11].



Limitations: They had reported this reaction with a **single example** (**65% yield**) and hadn't explored its scope, which is its primary limitation followed by high temperature.

1.3.4.

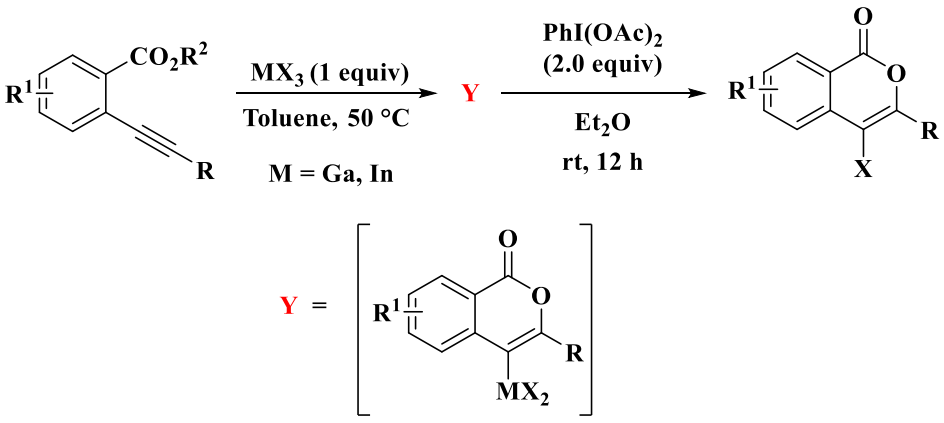
Yuan and co-workers, in the same year again, uncovered another methodology to prepare 4-haloisocoumarin (X = Cl, Br, I) by using transition metal halides from phenyl 2-alkynylaryloate ester [12].



Limitations: The use of the stoichiometric amount of transition metal halides, the requirement of high temperature, and the narrow substrate scope (**10 examples, 65-94% yield**) are some of the limitations in their method.

1.3.5.

Recently in 2018, Yuji Kita and co-workers revealed this method that involves carbon-metal (In or Ga) bond formation. In and Ga are very selective for the 6-*endo*-cyclization, unlike B, Al, Au, or Ag, which prefer 5-*endo* cyclization [13]. (X = Cl, I)

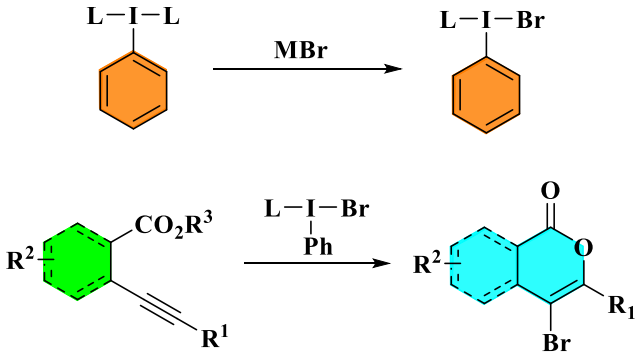


Limitations: Two-step reaction, use of metal halide, and high temperature are some of the primary drawbacks of this method. Additionally, a narrow substrate scope also increases this method's limitations. The authors included twelve examples, among which only **three** were reported for synthesizing 4-bromoisocoumarin with a **47-73% yield**.

1.4. Our hypothesis

Alkyne belongs to the family of the most versatile functional moieties and makes the *o*-alkynylaryloates very useful for synthesizing isocoumarins via the 6-*endo*-cyclization mechanism, where new bond formation occurs. The methods known to synthesize 4-bromoisocoumarin, summarized in section 1.3, involve either the electrophile-assisted 6-*endo* cyclization method or the transition metal-catalyzed 6-*endo* cyclization method. First, alkyne activation occurs, followed by the nucleophilic attack from the ester to complete the 6-membered cyclic structure. Previously known methods involve metallic conditions, and metal-free synthesis has not been explored perfectly yet.

To develop novel sustainable methods for synthesizing new bonds between carbon-carbon and carbon-heteroatom, we hypothesize 2-alkynylaryloates to convert into 4-bromoisocoumarin, forming new bonds, in good to excellent yield as a result of simultaneous alkyne activation and 6-*endo*-cyclization. Insitu, the generation of transient bromoiodane species using hypervalent (III) iodine reagent (HI-3) and alkali metal bromide is the critical approach in our hypothesis.



HIR reagents are highly stable, non-toxic, readily available, and easy to handle reagents. Their use is a step towards the practice of green chemistry because the waste can be treated as regular waste or even can be recycled if required. The chemistry shown by hypervalent iodine reagents is similar to the chemistry followed by transition metals [23]. The driving force of HIRs' reactions is the reduction of iodine to its most stable

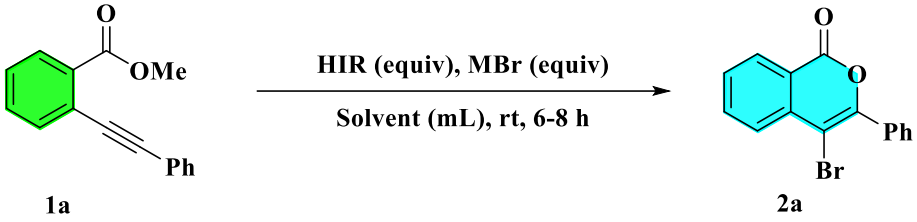
oxidation state [24]. Commonly used HIRs are *Dess-Martin*'s periodinane (DMP) and 2-iodoxybenzoic acid (IBX) which are iodine(V) reagents and widely used for oxidation reactions [25]. Compared to iodine(V) and iodine (VII), a large number of iodine(III) reagents are also being used and there are a higher number of transformations (arylation, dearomatization of phenols, cyclization, ethylenation, halogenation, etc.) supported by iodine(III) reagents compared to the other two [26].

To check the validity of our hypothesis, we synthesized methyl 2-(phenylethynyl)benzoate as our model substrate from a reported procedure [15] and started to imply various reaction conditions.

Chapter 2

RESULTS & DISCUSSION

2.1. Optimization of the best reaction conditions



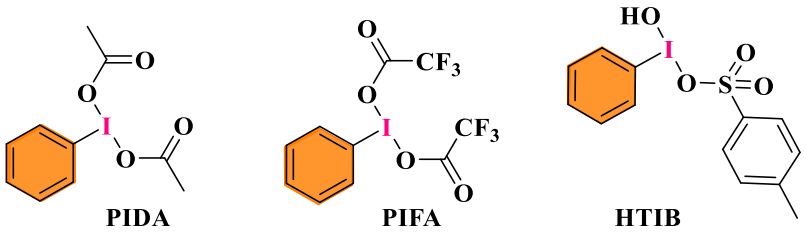
2.1.1. Screening of hypervalent iodine reagents (HIRs)

We started our optimization right from the screening of different hypervalent iodine reagents. All the reactions were performed at room temperature, and the recorded yields were isolated. In this regard, we did a reaction using PIDA (2.0 equiv) as the hypervalent iodine reagent, potassium bromide (2.0 equiv) as the source of bromide ion, and acetonitrile (1 mL) as the solvent for 0.1 mmol of the starting material **1a** (entry 01). We got no formation of the desired product **2a**. Instead, we observed a hydrolysis product.

Entry	HIR (equiv)	MBr (equiv)	Solvent (conc.)	Yield (%)
01	PIDA (2.0)	KBr (2.0)	CH_3CN (0.1 M)	-
02	PIFA (2.0)	KBr (2.0)	CH_3CN (0.1 M)	50
03	**HTIB (2.0)**	KBr (2.0)	CH_3CN (0.1 M)	60

After PIDA, we tried PIFA as the reagent, keeping other reaction parameters unchanged (entry 02). This time we got our desired product with a 50% yield. PIDA and PIFA are among the extreme hypervalent iodine reagents - PIDA is mildly reactive, while PIFA reacts aggressively. We wanted to try a reagent of in-between reactivity and reacted with Koser's reagent

(hydroxy tosyloxy iodo benzene or HTIB). With HTIB (2.0 equiv) and the rest things constant (entry 03), we got 60% of the desired product. After identifying the best reagent, we moved toward screening different solvents.



2.1.2. Solvent screening

Until here, we had entry 03 to be our best reaction condition. Now, we started to screen solvents other than acetonitrile, such as dichloromethane (entry 04), 1,1,1,3,3,3-hexafluoro-2-propanol (entry 05), dimethyl sulphoxide (entry 06), 1,2-dichloroethane (entry 07), trifluoromethyl benzene (entry 08), methanol (entry 09), and tetrahydrofuran (entry 10). Conditions other than the solvent were the same as entry 03, and we found that our desired product was not forming with HFIP and DMSO (entries 05 & 06), but with the other solvents (entries 04, 07 - 10). We found a 78% yield of our desired product when we used 1,2-DCE as the solvent (entry 07).

Entry	HIR (equiv)	MBr (equiv)	Solvent (conc.)	Yield (%)
03	HTIB (2.0)	KBr (2.0)	CH_3CN (0.1 M)	60
04	HTIB (2.0)	KBr (2.0)	DCM (0.1 M)	50
05	HTIB (2.0)	KBr (2.0)	HFIP (0.1 M)	-
06	HTIB (2.0)	KBr (2.0)	DMSO (0.1 M)	-
07	HTIB (2.0)	KBr (2.0)	**1,2-DCE (0.1 M)**	78
08	HTIB (2.0)	KBr (2.0)	$PhCF_3$ (0.1 M)	54
09	HTIB (2.0)	KBr (2.0)	MeOH (0.1 M)	53
10	HTIB (2.0)	KBr (2.0)	THF (0.1 M)	76

After the solvent screening, we selected 1,2-DCE as the best solvent for our reaction, and entry 07 became the best condition for our reaction. After getting the best HIR and the best solvent for our reaction, we moved towards studying the effect of different equivalents of reactants on our reaction. And we also screened the other alkali metal bromides too.

2.1.3. Equivalent adjustments and the screening of alkali metal bromide

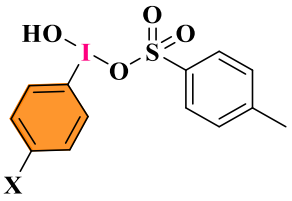
When we did reactions by taking HTIB (1.5 equiv), KBr (2.0 equiv) or by taking HTIB (2.0 equiv), KBr (1.5 equiv), both the time, we observed a decrement in the yield of the desired product (entries 11 & 12 respectively). We concluded that the 2.0 equiv of each HTIB and KBr is the best reaction condition. In addition to the effect of equivalent adjustments, we also performed a few reactions to study the effect of dilution on our reaction. We did reactions with different volumes of the solvent where we got 68%, 73%, and 68% yield for 0.5 mL, 1.5 mL, and 2.0 mL of 1,2-DCE, respectively (entries 13 - 15).

Entry	HIR (equiv)	MBr (equiv)	Solvent (mL)	Yield (%)
07	HTIB **(2.0)**	**KBr (2.0)**	1,2-DCE **(0.1 M)**	78
11	HTIB (1.5)	KBr (2.0)	1,2-DCE (0.1 M)	60
12	HTIB (2.0)	KBr (1.5)	1,2-DCE (0.1 M)	74
13	HTIB (2.0)	KBr (2.0)	1,2-DCE (0.2 M)	68
14	HTIB (2.0)	KBr (2.0)	1,2-DCE (0.07 M)	73
15	HTIB (2.0)	KBr (2.0)	1,2-DCE (0.05 M)	68
16	HTIB (2.0)	LiBr (2.0)	1,2-DCE (0.1 M)	57
17	HTIB (2.0)	NaBr (2.0)	1,2-DCE (0.1 M)	47

Later in this quest, we also optimized the different alkali metal bromides. With LiBr (2.0 equiv), we got 57% yield, while with NaBr (2.0 equiv), 47% only (entries 16 & 17, respectively).

2.1.4. Effect of substitution at the p-position of HTIB – Screening of HTIB derivatives

After optimizing all the reaction parameters, we studied the electronic effect of HTIB. For this, we tried different derivatives of HTIB; all were *para*-substituted derivatives substituted with electron-donating or electron-withdrawing substituents.



X = H; HTIB
X = Cl; HTIB-1
X = F; HTIB-2
X = Me; HTIB-3
X = OMe; HTIB-4

Entry	HIR (equiv)	MBr (equiv)	Solvent (mL)	Yield (%)
07	HTIB (2.0)	KBr (2.0)	1,2-DCE (0.1 M)	78
18	**HTIB-1** (2.0)	KBr (2.0)	1,2-DCE (0.1 M)	**91**
19	HTIB-2 (2.0)	KBr (2.0)	1,2-DCE (0.1 M)	79
20	HTIB-3 (2.0)	KBr (2.0)	1,2-DCE (0.1 M)	60
21	HTIB-4 (2.0)	KBr (2.0)	1,2-DCE (0.1 M)	5

We observed that our reaction was performing excellently with HTIB-1 (2.0 equiv), giving 91% yield (entry 18), and the yield was decreased again to 79% when we used fluoro (more electronegative than chloro) substituted reagent HTIB-2 (entry 19). With HTIB-3, we got 60% of the desired product (entry 20). While HTIB-4, with the substitution of an electron donating group (-OMe), was giving 5% of the desired product only. It happens because the HTIB-4 reagent is not stable at room temperature [21]. The effect of the substitutions at the *p*-position of HTIB on the reaction is also depicted through a line graph in figure 4.

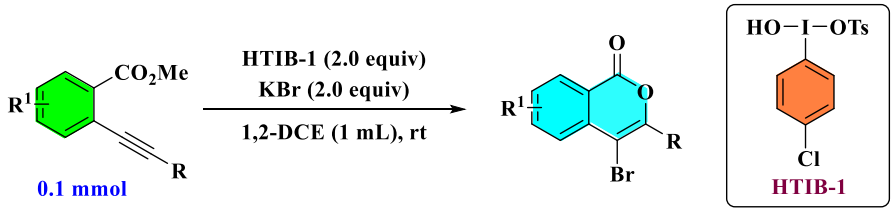
Figure 4: Effect of substitution at HTIB on the reaction

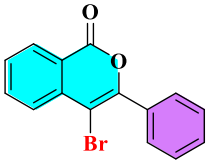
In this way, we got our best reaction conditions to be – HTIB-1 (2.0 equiv), KBr (2.0 equiv), 1,2-DCE (0.1 M) at room temperature, and after this, we moved towards checking the generality of our reaction.

2.2. Substrate scope

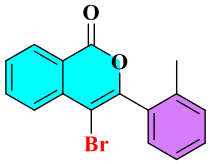
The generality of our best reaction conditions (entry 18) was studied with several substrates. We synthesized a library of starting materials by bringing various substitutions in the model substrate and employed them individually in our reaction conditions. First, we did reactions by varying the R-group attached to the alkyne. In this quest, we found substrates **1b**, **1c**, and **1d**, substituted with tolyl groups (electronically neutral) of different regioisomers in place of **R** on the alkyne, were working excellently in the optimized condition. The reaction of 2-tolyl, 3-tolyl, and 4-tolyl gave 80%, 78%, and 83% yield of the desired products **2b**, **2c**, and **2d,** respectively. Next, substrate **1e**, in this series, substituted with the methoxy group, was tested, and a significant amount (60%) of the desired product (**2e**) was observed. We did not find any electrophilic aromatic bromination on the ring (**R**). Our reaction was also working properly with halogen-substituted

substrates **1f-1h** in a good to excellent manner. The reaction of 3-F and 4-F containing

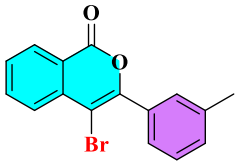




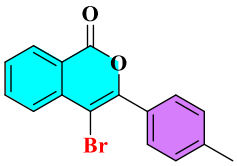
2a, 91%



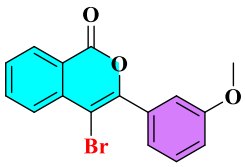
2b, 80%



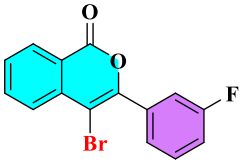
2c, 78%



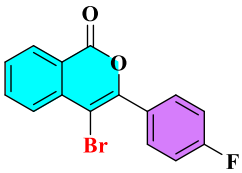
2d, 83%



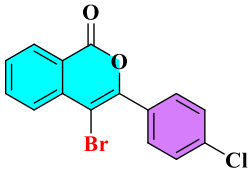
2e, 60%



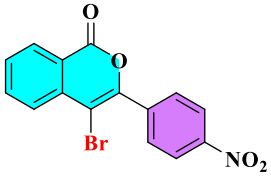
2f, 74%



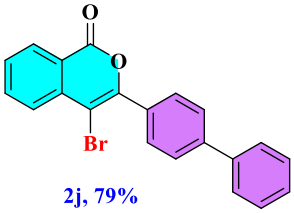
2g, 84%



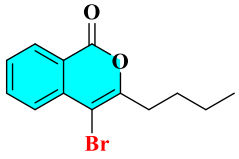
2h, 78%



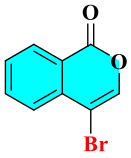
2i, 0%



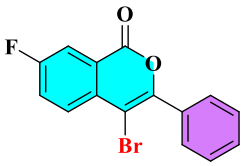
2j, 79%



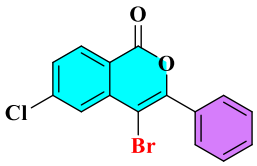
2k, 30%



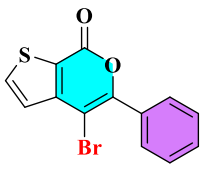
2l, 0%



2m, 78%

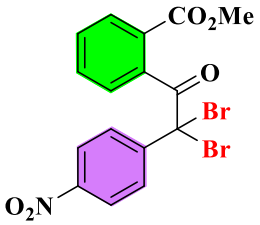


2n, 81%

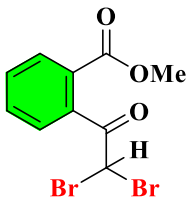


2o, 53%

substrates gave 74% and 84% yield of the desired products **2f** and **2g**, respectively. While the 4-Cl substituted substrate was also working efficiently, giving a 78% yield of the desired product **2h**. Another substrate in this series was tried with the nitro substitution at the 4- position of the phenyl attached to the alkyne (**1i**), but with this substrate, we did not observe the formation of our desired product (**2i**). Instead of the desired product, we got a different product **2i'** (63%). It was probably due to the carbocation's destabilization by the nitro group's electron-withdrawing nature. Further, a 4-phenyl substituted substrate (**1j**) was examined and found to work properly. It gave a 79% yield of the desired product (**2j**). In this series, we tried a ^{n}butyl substituted substrate **1k** and found a considerable amount (30%) of the desired product **2k**. After examining different substitutions on the alkyne, we also examined a substrate (**1l**) containing terminal alkyne. The reaction of **1l** did not give any desired product **2l**, but a by-product (**2l'**) was observed in a good amount (55%). After varying the R group, we moved towards changing the R^1 group. In this series, we tried substrates **1m** and **1n**. These two substrates were also giving good to excellent yields. On employing **1m** in our best reaction conditions, we got a 78% yield of **2m**,



2i', 63%



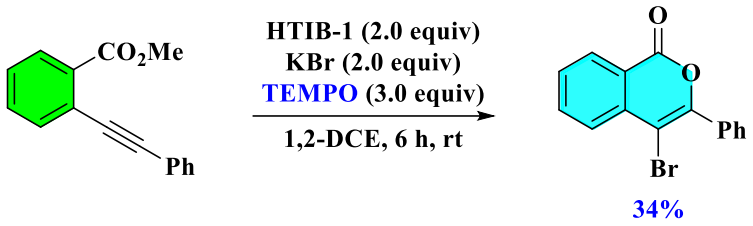
2l', 55%

and employing **1n** there gave an 81% yield of **2n**. We also found that a completely different substrate with thiophene instead of the usual phenyl ring was also working efficiently. With the substrate **1o**, we got a 53% yield of the desired product **2o**. After examining a range of substrates, we proposed a plausible mechanism for this reaction.

2.3. Mechanistic details

2.3.1. Control experiment

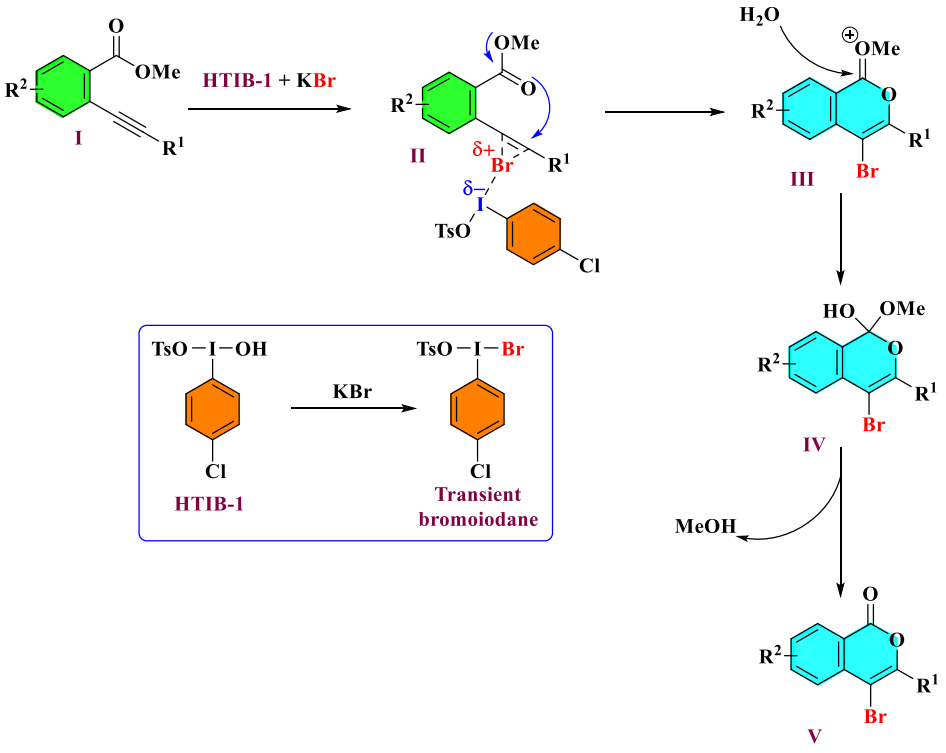
For insight into the reaction mechanism, we did a control experiment using TEMPO (3.0 equiv). In this experiment, we got a 34% yield of the desired product. This compelled us to believe that the reaction follows an ionic mechanism instead of a radical one.



The significant decrease in the yield was possibly due to the non-compatibility of TEMPO with the hypervalent iodine reagents.

2.3.2. Plausible mechanism for the desired product formation

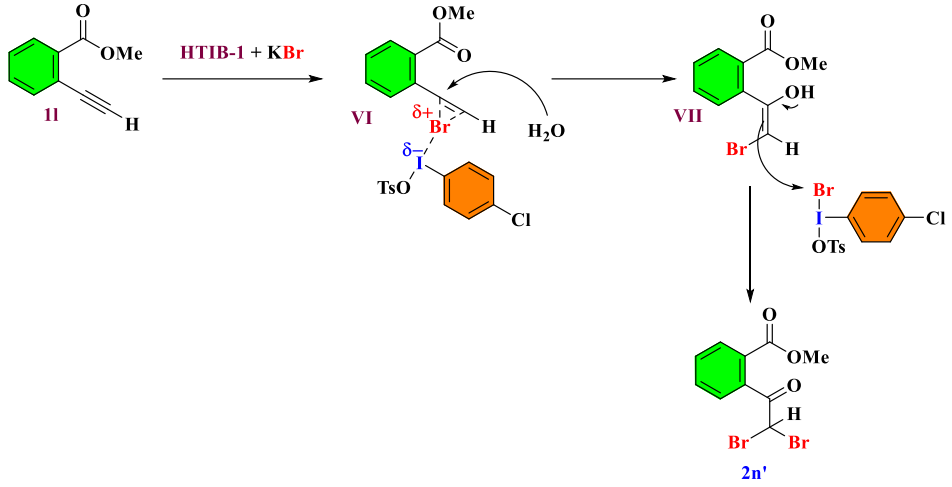
The mechanism starts with the reaction of HTIB-1 and KBr. They generate



a transient bromoiodane species, which activates the alkyne of substrate I to give an intermediate II. A nucleophilic attack from the ester group onto the activated alkyne (intermediate II) in a 6-*endo*-dig-selective manner completes the ring to give another intermediate III. Next, the water (moisture) comes into the picture and knocks off the methanol to give our desired product V *via* an intermediate IV.

2.3.3. Plausible mechanism for the by-product formation

With some substrates, the nucleophilic attack of the ester group onto the activated alkyne competes with the nucleophilic attack of the water (moisture) nucleophile. Because of this competition, we get a by-product **2l'**. This happens when the carbocation is not getting stabilized at the position of our interest. Because of this, instead of the nucleophilic attack from the ester, water attacks at the stabilized carbocation.

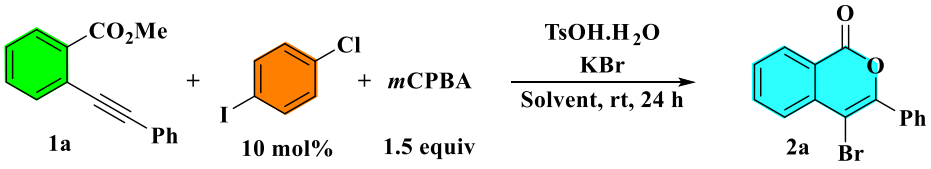


Chapter 3

CATALYTIC PATHWAY

3.1. Optimization of the catalytic reaction

In our reaction, the fate of HTIB-1 is the formation of 4-chloroiodobenzene. This led us to hypothesize this reaction catalytically. We were synthesizing HTIB-1 from 4-chloroiodobenzene and using that in the reaction in a stoichiometric amount. Later, we hypothesized to generate this reagent insitu itself. We again chose the previous model substrate **1a** and treated it with 4-chloroiodobenzene, *m*CPBA, *p*-toluenesulphonic acid, and KBr in 1,2-DCE for 24 h. In the first condition, we took 4-chloroiodobenzene 10 mol%, *m*CPBA (1.5 equiv), *p*-toluenesulphonic acid (1 equiv), and KBr (1 equiv) in 1,2-DCE (0.1 M), we got a 62% yield of **2a** (entry 1). Changing the solvent did not help much; we got a 65% of **2a** when we used THF instead of 1,2-DCE (entry 2).

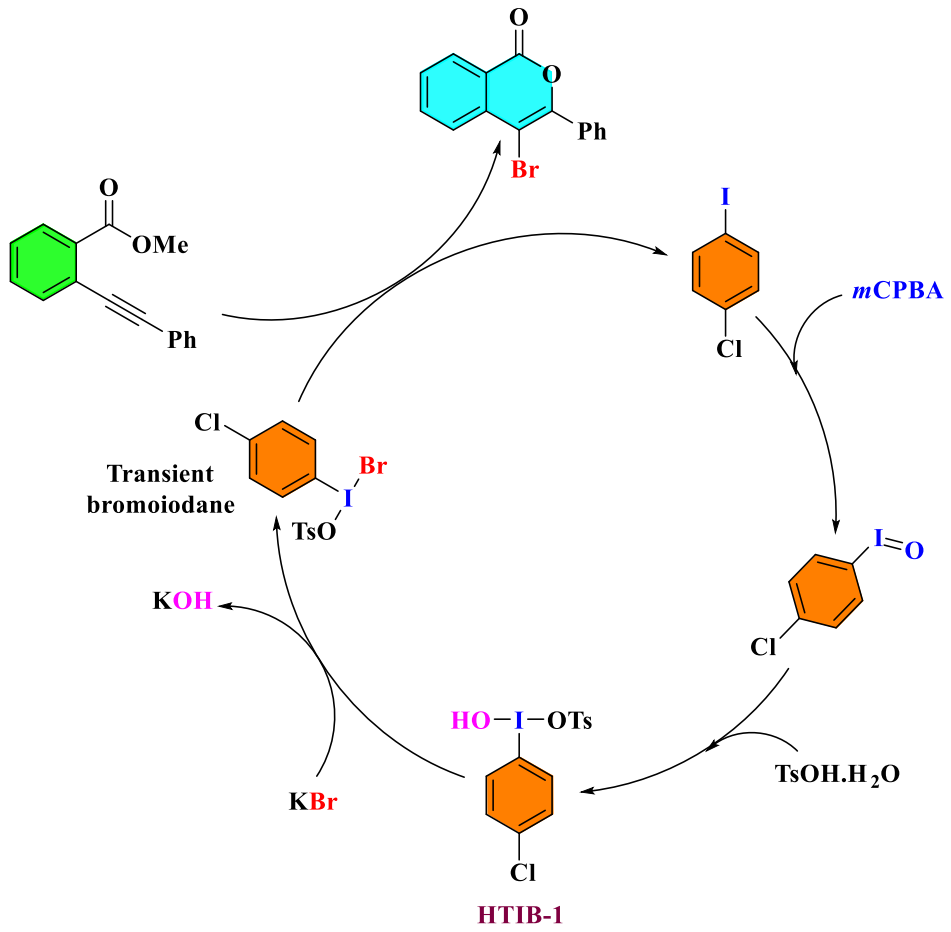


Entry	KBr (equiv)	TsOH.H$_2$O (equiv)	Solvent	Yield[a] (%)
1	1.0	1.0	1,2-DCE	62
2	1.0	1.0	THF	65
3	1.2	1.0	1,2-DCE	70
4	1.5	1.0	1,2-DCE	53
5[b]	1.2	1.0	1,2-DCE	52
6	1.2	-	1,2-DCE	0
7	1.2	0.2	1,2-DCE	20

Reaction condition: 0.1 mmol of 1a, 10 mol% of ArI, 0.15 mmol of *m*CPBA, 1 mL solvent. [a]Isolated yield. [b]using 15 mol% of ArI.

But increasing the amount of KBr helped significantly, and we got a 70% yield of **2a** (entry 3), while a further increase in that led to a decrease in the yield (entry 4). We repeated entry 3, but taking 15 mol% of 4-chloroiodobenzene instead of 10 mol%, a 52% yield of **2a** was recorded (entry 5). In a reaction (entry 6) without taking the *p*-toluenesulphonic acid, we tried and found no formation of the desired product, concluding that it is a necessary reactant of our catalytic cycle. We took $TsOH.H_2O$ in a catalytic amount (entry 7) but observed only a 20% yield. So, the best reaction conditions for our reaction in a catalytic manner are the entry 3 - 1.2 equiv KBr, 1.0 equiv of $TsOH.H_2O$, 10 mol% 4-chloroiodobenzene, and 1.5 equiv of *m*CPBA in 1 mL 1,2-DCE for 0.1 mmol of **1a**.

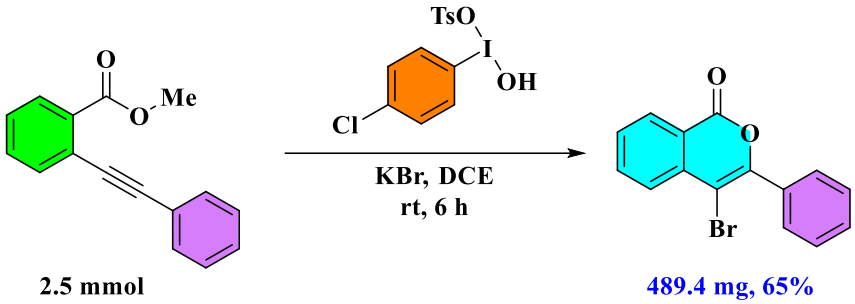
3.2. Plausible mechanism for the catalytic reaction



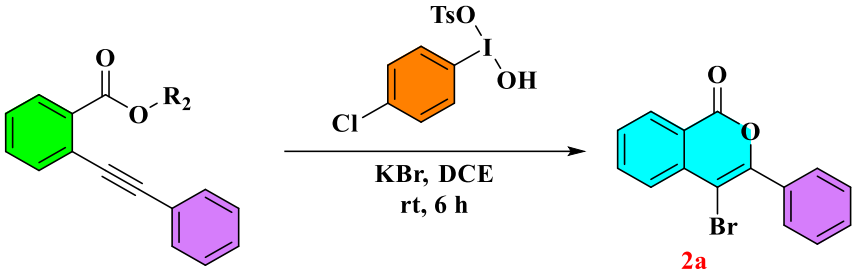
The hypervalent iodine reagent (HTIB-1) is generated in situ [14]. It reacts with KBr to give transient bromoiodane species, which activates the alkyne of the starting material, and after cyclization, we get our desired product. First, 4-chloroiodobenzene is oxidized by *m*CPBA to give 4-chloroiodosylbenzene, which reacts with $TsOH.H_2O$ to generate HTIB-1 in situ. The generated HTIB-1 reacts with KBr, and a ligand exchange occurs, providing a transient bromoiodane species. These transient bromoiodane species react to the substrate, similarly explained in section 2.3.3.

Chapter 4

LARGE-SCALE REACTION & SCOPE OF DIFFERENT ESTERS



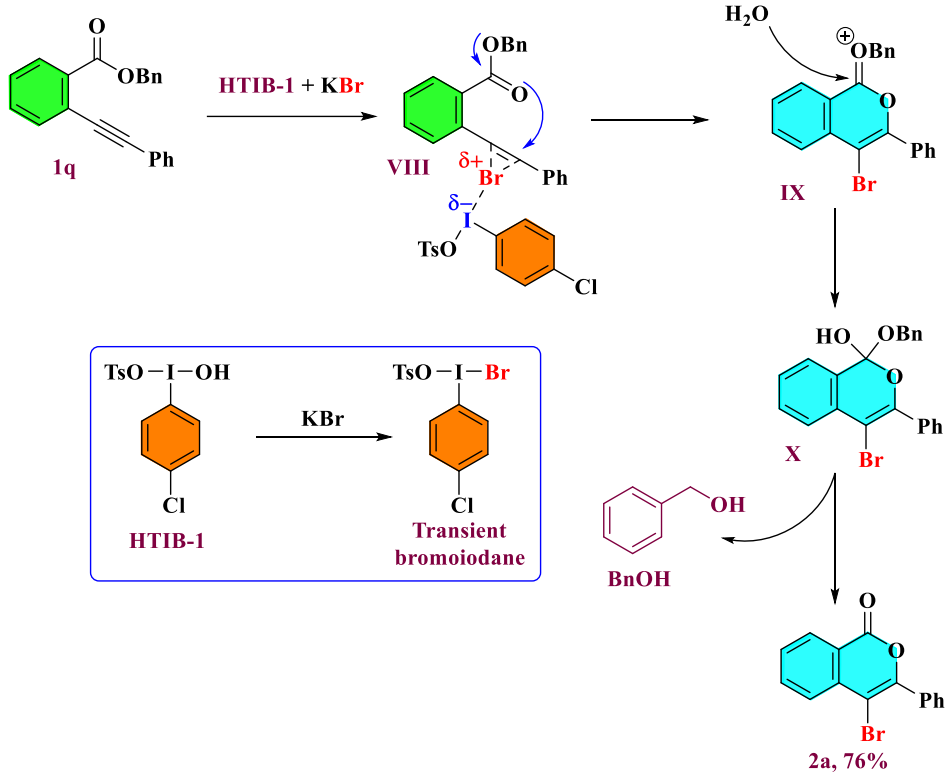
Our reaction was also found to be performing well in a large-scale reaction. With 2.5 mmol of **1a**, we got a 65% yield (489.4 mg, 1.63 mmol) of **2a**.



We tested some different esters instead of methyl ester for this reaction. In this series, we synthesized tert-butyl 2-(phenylethynyl)benzoate and benzyl 2-(phenylethynyl)benzoate following the reported procedures [19-20]. On employing them one by one in the optimized reaction conditions, we got 59% and 76% yields of **2a**, respectively.

R_2	2a
Methyl (1a)	**91 %**
tert-Butyl (1p)	**59%**
Benzyl (1q)	**76%**

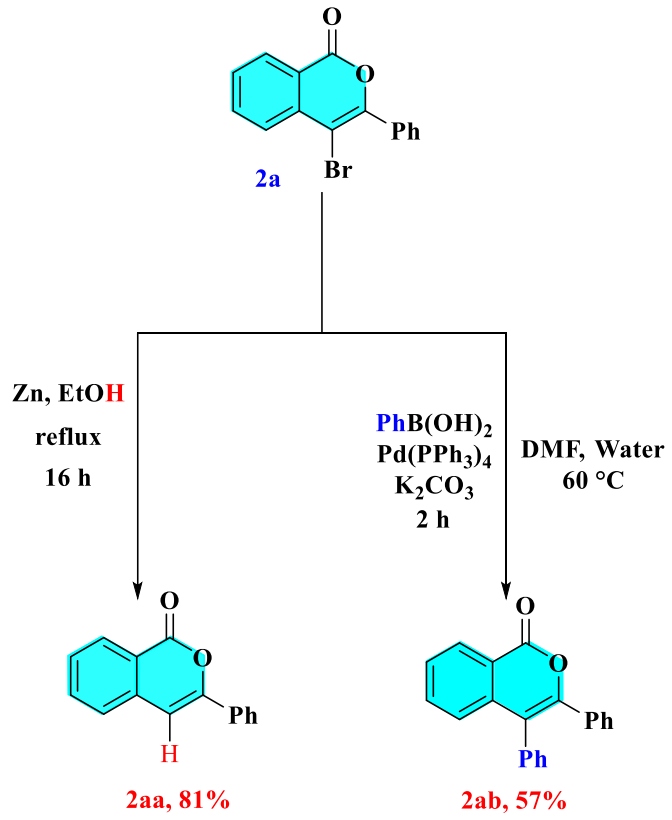
In the reaction using **1q** as the starting material, we observed an excellent amount of the desired product. Along with this, we also got a piece of useful information regarding the plausible mechanism - we observed the formation of benzyl alcohol which is in favour of our proposed mechanism.



Chapter 5.

POST-SYNTHETIC TRANSFORMATIONS

Bromine substituted at the 4-position of the isocoumarin scaffold provides a handle for further derivatization. A library of compounds can be prepared by various coupling reactions. Palladium-based coupling reactions such as Suzuki coupling, Sonogashira coupling, Heck coupling, etc. can be very useful in this regard. We also showed an example of Suzuki coupling using phenylboronic acid. This type of moiety finds applications in the pharmaceutical sectors as well as in the material sectors. By using above mentioned techniques, bigger molecule can also be prepared.



After getting a new method to synthesize 4-bromo-3-phenyl isocoumarin (**2a**), we did two more reactions where we showed how one could make a 3-substituted and 3,4-disubstituted isocoumarin moiety from **2a**. In the first reaction (hydrodehalogenation), we refluxed **2a** with zinc powder in ethanol

for 16 h, and we got **2aa** in a very good amount (81%). In another synthetic application, we did the Suzuki coupling treating the phenylboronic acid with **2a** at 60 ºC. We obtained **2ab** in a 57% yield in this palladium-catalyzed cross-coupling reaction.

Chapter 6

EXPERIMENTAL DETAILS

6.1. General information

All the reagents and solvents that we used during the synthesis of our substrates were purchased from local vendors, and the synthesis was done by the below-mentioned protocols. We used the purchased chemicals without purification. Hexane and ethyl acetate were distilled before using in the column chromatography. The reactions were performed in an inert atmosphere, and monitoring was done by a thin-layer chromatographic technique using Merck 60 F254 precoated silica gel plates. Products were observed by UV detection, and the purification was done by SiO_2 (100-200 mesh) column chromatography using hexane and ethyl acetate as the eluent.

6.2. Instrumentation

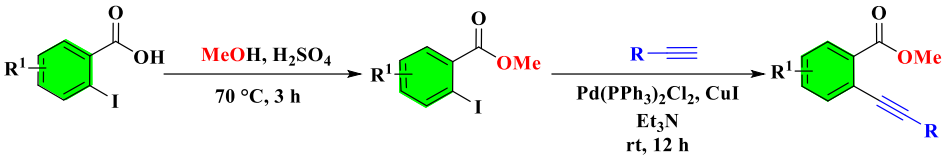
The authentication of the purified products was done by NMR spectroscopy (^1H) on an AVANCE NEO Ascend 500 Bruker BioSpin International AG (500 MHz) in $CDCl_3$, DMSO-d_6, or TMS as the reference. Chemical shift values (δ scale) mentioned here are only in parts per million (ppm). The residual solvent peaks of $CDCl_3$ and DMSO-d_6 were found at 7.26 and 2.50, respectively. The multiplicities of the desired peaks are denoted as:

Singlet	**s**
Doublet	d
Doublet of doublet	dd
Triplet	t
Triplet of doublet	td
Quartet	q
Multiplet	m

6.3. Synthesis of starting materials

6.3.1. General procedure for synthesizing the substrates 1a-1k, 1m, & 1n

[15]

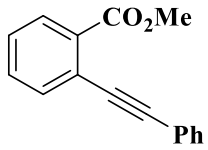


Synthesis of methyl 2-(alkynyl)benzoate was done in two steps: I) Methylation of 2-Iodobenzoic acid, II) Sonogashira coupling of Methyl-2-iodobenzoate with a terminal alkyne.

I) In a round bottom flask (50 mL), which was oven dried, we put a magnetic bead inside and charged it with *o*-iodobenzoic acid (1g, 4.0 mmol) followed by 10 mL 2.0M H_2SO_4 in methanol. The round bottom flask was clamped (dipped in an oil bath) over a magnetic stirrer and connected with a reflux condenser. The reaction mixture was stirred for 3h at 70 ºC. After 3h, we evaporated the solvent using a rotatory evaporator and extracted the crude product using $NaHCO_3$ and EtOAc (3×10 mL). The collected organic phases were washed (combinedly) with a brine solution. After washing, it was dried over anhydrous Na_2SO_4. After drying, filtration followed by concentration using a rotatory evaporator was done to get the crude product. Purification was done by column chromatography using SiO_2 as the stationary phase and a 5% EtOAc-hexane mixture as the mobile phase. The obtained pure product (900 mg, 3.4 mmol) was utilized in the second step.

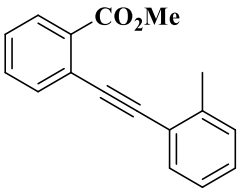
II) We charged Methyl-2-iodobenzoate (393 mg, 1.5 mmol, 1 equiv.) in a round bottom flask (oven dried, 25 mL) having a magnetic bead inside followed by Et_3N (4 mL), $Pd(PPh_3)_2Cl_2$ (5 mol%), and CuI (5 mol%) to get a solution (yellow) with solid suspension. A stream of nitrogen was passed through the solution for 15 min, followed by the addition of alkyne (1.25 equiv). As soon as we added alkyne to the solution, the color of the solution turned black. The stirring of the reaction mixture was done at rt for 18h.

After completion of the reaction (monitored by TLC, 10% EtOAc-hexane as the eluent), 9 mL saturated aq. NH_4Cl solution was added in the RB to dilute the reaction mixture, and extraction was performed using EtOAc (3×10 mL). The collected organic phases were washed (combinedly) with a brine solution. This was followed by drying over anhydrous Na_2SO_4. After drying, filtration concentration using a rotatory evaporator was done to get the crude. Purification was done by column chromatographic technique using SiO_2 as the stationary phase and a 2% EtOAc-hexane mixture as the mobile phase.



Methyl 2-(Phenylethynyl)benzoate (**1a**), 93% yield, yellow liquid.

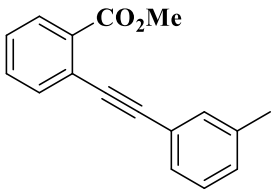
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.65 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.49 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40 – 7.32 (m, 4H), 3.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 134.1, 131.9, 131.8, 131.8, 130.6, 128.6, 128.4, 128.0, 123.8, 123.4, 94.4, 88.3, 52.3; IR (neat) 2949, 2217, 1727, 1493, 1291, 1248, 1126, 1077, 1598, 752, 689 cm^{-1}.



Methyl 2-(*o*-tolylethynyl)benzoate (**1b**), 95% yield, yellow liquid.

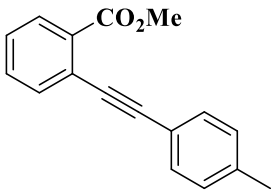
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.66 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H), 7.38

(td, J = 7.7, 1.3 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.20 – 7.16 (m, 1H), 3.96 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 140.6, 134.3, 132.4, 131.8, 131.8, 130.6, 129.6, 128.7, 128.0, 125.7, 124.0, 123.2, 93.6, 92.7, 52.4, 20.9; IR (neat) 2949, 2213, 1727, 1714, 1491, 1292, 1248, 1076, 752 cm^{-1}.



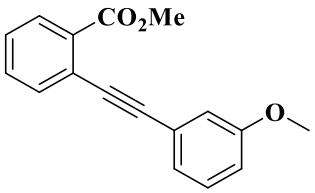
Methyl 2-(*m*-tolylethynyl)benzoate (**1c**), 99% yield, yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.9, 1.4 Hz, 1H), 7.64 (dd, J = 7.7, 1.4 Hz, 1H), 7.49 (td, J = 7.6, 1.4 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.27 – 7.23 (m, 1H), 7.17-7.15 (m, 1H), 3.97 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 138.2, 134.2, 132.4, 132.0, 131.8, 130.6, 129.6, 129.0, 128.4, 128.0, 124.0, 123.2, 94.7, 88.0, 52.3, 21.4.



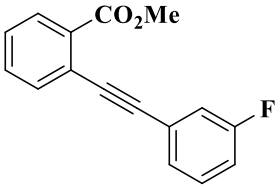
Methyl 2-(*p*-tolylethynyl)benzoate (**1d**), 99% yield, yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.9, 1.5 Hz, 1H), 7.64 (dd, J = 7.8, 1.3 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.37 (td, J = 7.7, 1.3 Hz, 1H), 7.19 – 7.15 (m, 2H), 3.97 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0, 138.9, 134.1, 132.0, 131.8, 130.6, 129.3, 127.8, 124.1, 120.4, 94.8, 87.8, 52.3, 21.7.



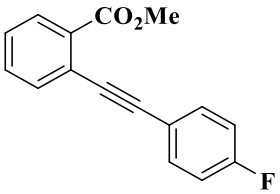
Methyl 2-(3-methoxyphenylethynyl)benzoate (**1e**), 99% yield, yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.65 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H), 7.39 (td, *J* = 7.7, 1.3 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.18 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.10 (dd, *J* = 2.6, 1.4 Hz, 1H), 6.91 (ddd, *J* = 8.4, 2.7, 1.0 Hz, 1H), 3.97 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 159.5, 134.2, 132.1, 131.8, 130.6, 129.6, 128.1, 124.5, 124.4, 123.8, 116.6, 115.3, 94.4, 88.2, 55.5, 52.4.



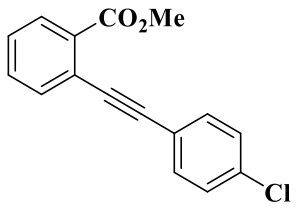
Methyl 2-(3-fluorophenylethynyl)benzoate (**1f**), 90% yield, yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.51 (td, *J* = 7.6, 1.4 Hz, 1H), 7.44 – 7.24 (m, 4H), 7.058-7.03 (m, 1H), 3.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 162.5 (d, *J* = 246.7 Hz), 134.2, 132.1, 131.9, 130.7, 130.1 (d, *J* = 8.6 Hz), 128.4, 127.8 (d, *J* = 3.1 Hz), 125.3 (d, *J* = 9.6 Hz), 123.4, 118.6 (d, *J* = 22.6 Hz), 116.0 (d, *J* = 21.4 Hz), 93.1 (d, *J* = 3.5 Hz), 89.2, 52.4.



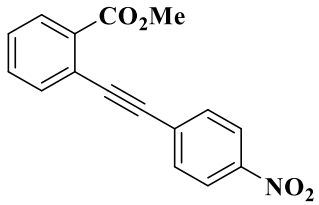
Methyl 2-(4-fluorophenylethynyl)benzoate (**1g**), 98% yield, yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H), 7.39 (td, *J* = 7.7, 1.3 Hz, 1H), 7.09 – 7.03 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 162.8 (d, *J* = 250.0 Hz), 134.1, 133.8 (d, *J* = 8.5 Hz), 131.9, 131.9, 130.6, 128.1, 123.8, 119.6 (d, *J* = 3.4 Hz), 115.8 (d, *J* = 22.1 Hz), 93.4, 88.1 (d, *J* = 2.1 Hz), 52.3.



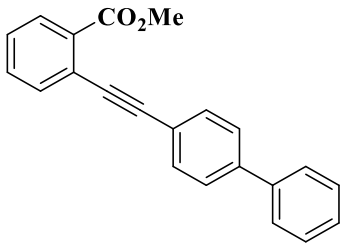
Methyl 2-(4-chlorophenylethynyl)benzoate (**1h**), 98% yield, yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.40 (td, *J* = 7.7, 1.3 Hz, 1H), 7.36 – 7.31 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 134.7, 134.1, 133.1, 132.0, 131.9, 130.7, 128.9, 128.3, 123.6, 122.0, 93.3, 89.3, 52.4.



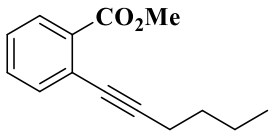
Methyl 2-(4-nitrophenylethynyl)benzoate (**1i**), 95% yield, yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 – 8.20 (m, 2H), 8.03 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.67 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.54 (td, *J* = 7.6, 1.4 Hz, 1H), 7.45 (td, *J* = 7.7, 1.4 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 147.3, 134.4, 132.6, 132.2, 132.1, 130.8, 130.4, 129.1, 123.8, 122.8, 93.5, 92.3, 52.5.



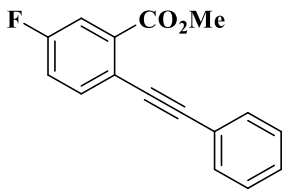
Methyl 2-([1,1'-biphenyl]-4-ylethynyl)benzoate (**1j**), 88% yield, yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.68 – 7.64 (m, 3H), 7.63 – 7.59 (m, 4H), 7.51 (td, *J* = 7.6, 1.4 Hz, 1H), 7.48 – 7.44 (m, 2H), 7.42 – 7.35 (m, 2H), 3.99 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 141.4, 140.5, 134.1, 132.3, 132.0, 131.8, 130.6, 129.0, 128.0, 127.8, 127.2, 124.0, 122.4, 94.4, 89.1, 52.4; HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{22}H_{16}O_2$ 335.1043; found 335.1043.



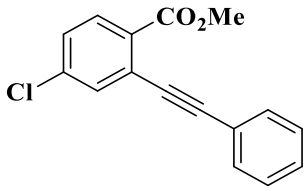
Methyl 2-(hex-1-ynyl)benzoate (**1k**), 94% yield, pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.41 (td, *J* = 7.6, 1.4 Hz, 1H), 7.30 (td, *J* = 7.7, 1.4 Hz, 1H), 3.91 (s, 3H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.66 – 1.60 (m, 2H), 1.56 – 1.45 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 134.4, 132.1, 131.6, 130.3, 127.2, 124.6, 96.1, 79.3, 52.2, 30.9, 22.2, 19.6, 13.8; IR (neat) 3066, 2955, 2932, 2863, 2230, 1731, 1716, 1484, 1432, 1292, 1275, 1247, 1082, 755, 701 cm^{-1}.



Methyl 2-(phenylethynyl) 5-fluorobenzoate (**1m**), 85% yield, yellow solid.

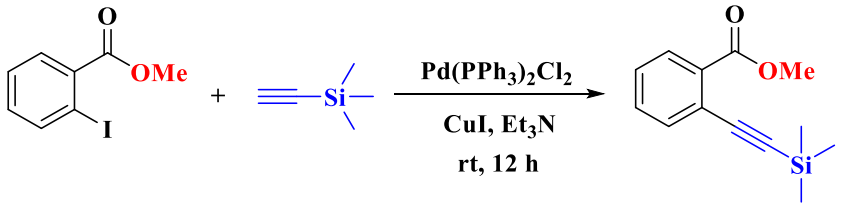
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.63 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.39 – 7.33 (m, 3H), 7.21 (ddd, *J* = 8.6, 7.7, 2.8 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7 (d, *J* = 2.7 Hz), 161.8 (d, *J* = 250.6 Hz), 136.0 (d, *J* = 8.0 Hz), 134.0 (d, *J* = 7.6 Hz), 131.8, 128.7, 128.5, 123.3, 120.1 (d, *J* = 3.7 Hz), 119.4 (d, *J* = 21.9 Hz), 117.7 (d, *J* = 23.9 Hz), 94.2, 87.3, 52.6.



Methyl 2-(phenyl*e*thynyl) 4-chlorobenzoate (**1n**), 97% yield, yellow liquid.

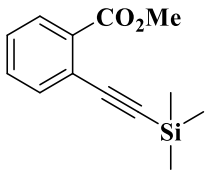
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 2.2 Hz, 1H), 7.59 – 7.55 (m, 2H), 7.39 – 7.33 (m, 4H), 3.96 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 138.2, 133.8, 132.0, 132.0, 130.2, 129.0, 128.6, 128.3, 125.7, 123.0, 95.8, 87.2, 52.5.

6.3.2. Synthetic procedure (2 steps) for the substrate 1l [15][17]



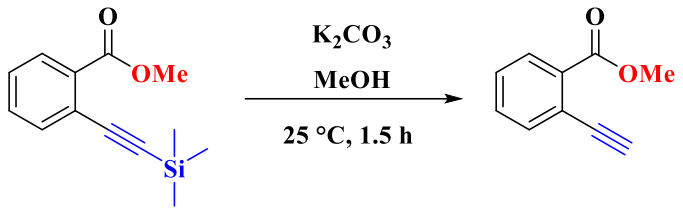
An oven-dried RB (25 mL) containing a magnetic stir bar inside, was charged with methyl 2-iodobenzoate (1 g, 3.82 mmol) followed by $Pd(PPh_3)Cl_2$ (5 mol%), CuI (5 mol%), and triethylamine (10 mL). The formed solution was degassed with a continuous stream of nitrogen for 10 min. Following this, trimethylsilylacetylene (470 mg, 4.78 mmol) was added, and the reaction mixture was allowed to stir for 12 h at rt. A saturated aq. NH_4Cl solution (20 mL) was added to the reaction mixture. The crude

product was extracted using EtOAc (3 x 10 mL). The organic phases were washed (combinedly) using a brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotatory evaporator. Pure methyl 2-(trimethylsilylethynyl)benzoate (**1L**) was obtained using SiO_2 column chromatography eluting with a 2% EtOAc-hexane mixture.

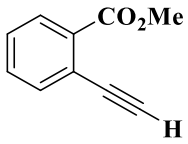


Methyl 2-(trimethylsilylethynyl)benzoate (**1l'**), 91%, yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.88 (m, 1H), 7.59 – 7.56 (m, 1H), 7.46 – 7.40 (m, 1H), 7.39 – 7.34 (m, 1H), 3.92 (s, 3H), 0.27 (s, 9H).



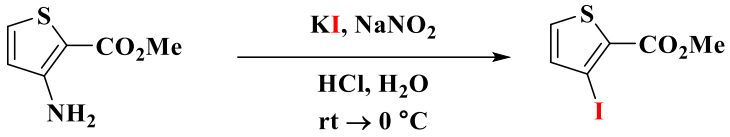
In an oven-dried RB (25 mL) equipped with a magnetic stir bar, we charged methyl 2-(trimethylsilylethynyl)benzoate (750 mg, 3.23 mmol) followed by K_2CO_3 (491 mg, 3.55 mmol) and MeOH (7 mL). The reaction mixture was stirred at 25 ºC for 1.5 h. The solvent was evaporated, and the crude mixture was diluted with water. The crude was extracted using DCM (3 x 10 mL). Combined organic phases were washed with a brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotatory evaporator. Purified methyl 2-ethynylbenzoate (**1l**) was obtained by SiO_2 column chromatography eluting with a 2% EtOAc-hexane mixture.



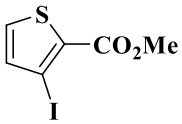
Methyl 2-ethynylbenzoate (**1l**), 64% yield, colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.48 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40 (td, *J* = 7.6, 1.4 Hz, 1H), 3.93 (s, 3H), 3.40 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.6, 135.1, 132.6, 131.9, 130.4, 128.6, 122.8, 82.4, 52.3.

6.3.3. Synthetic procedure (2 steps) for the substrate 1o [18][15]

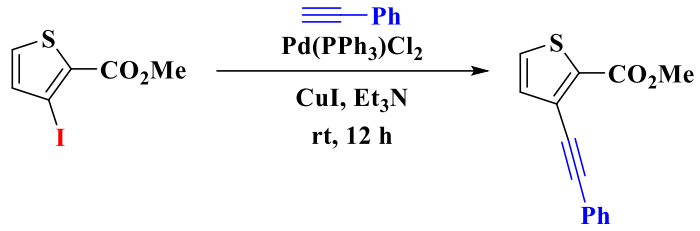


In an oven-dried RB equipped with a magnetic stir bar, we first charged HCl (1.5 mL 6 M) and dissolved methyl 3-aminothiophene-2-carboxylate (471.5 mg, 3 mmol) in it. After stirring for half an hour, we cooled the RB to 0 ºC, and added $NaNO_2$ (207 mg, 3 mmol) dissolved in water (0.5 mL) to that RB. Then stirred the reaction mixture for 1 h at 0 ºC, followed by the addition of KI (498.0 mg, 3 mmol) dissolved in conc. HCl (1.25 mL). After stirring for 1 h at 0 ºC, the RB was heated to 60 ºC. After half an hour, we cooled down the RB to room temperature. The crude was extracted using sat. aq. $Na_2S_2O_3$ solution and Et_2O (3 x 10 mL). The organic phases were washed (combinedly) with brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotatory evaporator. Purified methyl 3-iodothiophene-2-carboxylate (**1O**) was obtained by SiO_2 column chromatography eluting with a 2% EtOAc-hexane mixture.

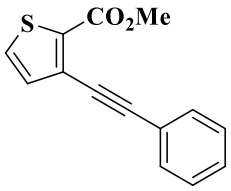


Methyl 3-iodothiphene-2-carboxylate (**1o'**), 30%, pale-yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 5.1 Hz, 1H), 7.23 (d, *J* = 5.1 Hz, 1H), 3.90 (s, 3H).



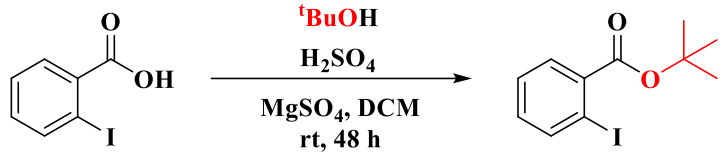
In the next step, methyl 3-iodothiophene-2-carboxylate (241 mg, 0.9 mmol) was charged in an oven-dried RB (10 mL) containing a magnetic stir bar inside. After this, we also added $Pd(PPh_3)Cl_2$ (5 mol%), CuI (5 mol%), and triethylamine (3 mL) to that RB. The formed solution was degassed by a continuous stream of nitrogen. After degassing, we added phenylacetylene (0.12 mL, 114.4 mg, 1.12 mmol), and allowed the reaction mixture to stir at rt for 12 h. A sat. aq. NH_4Cl (5 mL) solution was added, and the crude was extracted using EtOAc (3 x 5 mL). The organic phases were washed (combinedly) with a brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotatory evaporator. Pure methyl 3-(phenylethynyl)thiophene-2-carboxylate (**1o**) was obtained using SiO_2 column chromatography eluting with a 2% EtOAc-hexane mixture.



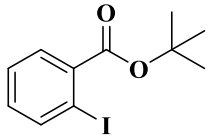
Methyl 3-(phenylethynyl) thiophene-2-carboxylate (**1o**), 93% yield, orange solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 2H), 7.47 (d, J = 5.1 Hz, 1H), 7.38 – 7.34 (m, 3H), 7.21 (d, J = 5.1 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 133.5, 132.2, 132.0, 130.6, 128.9, 128.5, 127.6, 123.0, 95.4, 84.0, 52.4.

6.3.4. Synthetic procedure (2 steps) for the substrate 1p

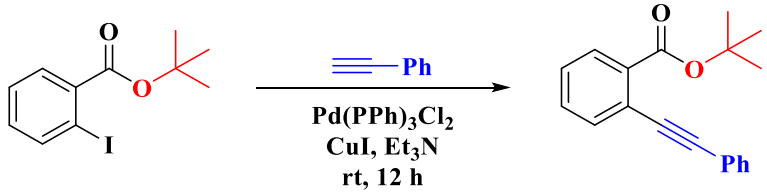


In an oven-dried RB (25 mL) containing a magnetic stir bar inside, a suspension of $MgSO_4$ (972.6 mg, 8.08 mmol) in DCM (10 mL) was made under a nitrogen atmosphere. To this stirred suspension, sulphuric acid (198.1 mg, 2.02 mL) was also added, and the mixture was allowed to stir for 15 min. Then, 2-iodobenzoic acid (500 mg, 2.02 mL) and tert-butanol (0.97 mL, 748.6 mg, 10.1 mmol) were also added. The reaction mixture was allowed to stir for 48 h at rt. Later, to obtain the crude product, a work-up was done using aq. $NaHCO_3$ solution and DCM (3 x 10 mL). The organic phases were washed (combinedly) with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotatory evaporator. Pure tert-butyl 2-iodobenzoate (**1p'**) was obtained after SiO_2 column chromatography using a 5% EtOAc-hexane mixture as the eluent. Further, this product was used in the next step to synthesize the substrate **1p**.

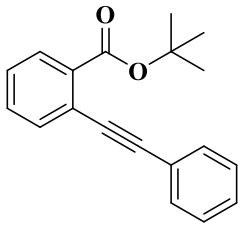


tert-butyl 2-iodobenzoate (**1p'**), 56% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, J = 7.9, 1.2 Hz, 1H), 7.68 (dd, J = 7.7, 1.7 Hz, 1H), 7.37 (td, J = 7.5, 1.1 Hz, 1H), 7.10 (td, J = 7.6, 1.7 Hz, 1H), 1.62 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 141.0, 137.6, 132.1, 130.6, 128.0, 93.5, 82.8, 28.3.



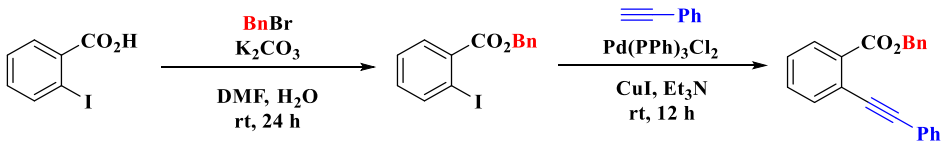
Tert-butyl 2-iodobenzoate (334.5 mg, 1.1 mmol) was charged in an oven-dried RB (25 mL) with a magnetic stir bar. Following this, $Pd(PPh_3)Cl_2$ (5 mol%), CuI (5 mol%), and triethylamine (3 mL) were also added. A clear solution with yellow suspension was observed. This solution was degassed using a continuous stream of nitrogen for 10 min. To this degassed solution, phenylacetylene (0.15 mL, 140.4 mg, 1.375 mmol) was added, as a result of this addition, color of the reaction mixture turned black instantaneously. We allowed the reaction mixture to stir for 12 h at rt. A saturated aq. NH_4Cl (7 mL) solution was added, and the extraction was performed using EtOAc (3 x 10 mL). The organic phases were washed (combinedly) with brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotatory evaporator. Pure tert-butyl 2-(phenylethynyl)benzoate was obtained using SiO_2 column chromatography using a 2% EtOAc-hexane mixture.



tert-butyl 2-(phenylethynyl)benzoate (**1p**), 92% yield, yellow liquid.

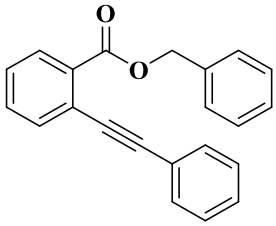
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, J = 7.8, 1.5 Hz, 1H), 7.62 (dd, J = 7.7, 1.4 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.45 (td, J = 7.6, 1.4 Hz, 1H), 7.39 – 7.32 (m, 4H), 1.61 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 134.3, 134.1, 131.7, 131.1, 130.1, 128.5, 128.0, 123.6, 123.1, 93.8, 88.6, 81.8, 28.4.

6.3.5. Synthetic procedure (2 steps) for the substrate 1q



In an over-dried RB (25 mL) containing a magnetic stir bar, firstly, we charged 2-iodobenzoic acid (744.1 mg, 3 mmol). Following this, benzyl bromide (0.71 mL, 1.026 g, 6 mmol), K_2CO_3 (829.3 mg, 6 mmol), and DMF (6 mL) were added to the RB. The reaction mixture was stirred for 24 h at rt. The reaction was quenched by diluting with water (10 mL), and the crude was extracted using EtOAc (3 x 10 mL). The organic phases were washed (combinedly) with water (3 x 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotatory evaporator. This crude product was used in the next step.

In an oven-dried RB (25 mL) containing a magnetic stir bar, we added the crude benzyl 2-iodobenzoate (3 mmol) followed by $Pd(PPh_3)Cl_2$ (5 mol%), CuI (5 mol%), and triethylamine (6 mL). The formed solution was degassed by a continuous stream of nitrogen for 10 min. Next, phenylacetylene (0.41 mL, 383 mg, 3.75 mmol) was added. The reaction mixture was allowed to stir for 12 h at rt. A saturated aq. NH_4Cl (15 mL) was added, and the extraction was performed using EtOAc (3 x 10 mL). The organic phases were washed (combinedly) with a brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotatory evaporator. Pure benzyl 2-(phenylethynyl)benzoate was obtained using SiO_2 column chromatography using a 2% EtOAc-hexane mixture.

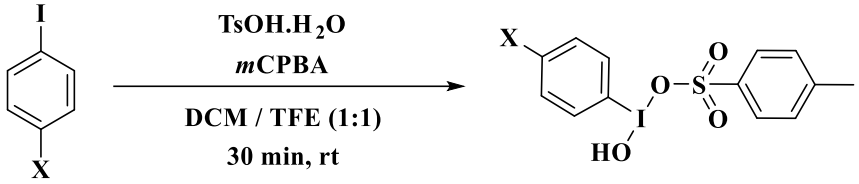


Benzyl 2-(phenylethynyl)benzoate (**1q**), 95% yield, brown liquid.

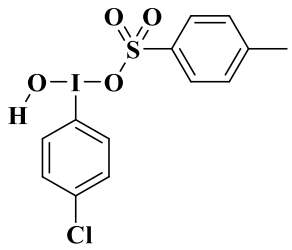
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.66 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.52 – 7.42 (m, 5H), 7.38 (td, *J* = 7.4, 1.3 Hz, 1H), 7.35 – 7.29 (m, 6H), 5.42 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 136.0,

134.3, 131.9, 131.9, 131.8, 130.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 124.0, 123.4, 94.6, 88.4, 67.2.

6.4. General procedure for synthesizing the hypervalent iodine reagent [21]



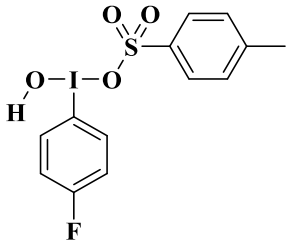
An oven-dried round bottom flask (100 mL) containing a magnetic bead of suitable size was charged with 4-X-iodobenzene (8.97 mmol, 1 equiv) followed by DCM / TFE (1:1) mixture (40 mL) to give a solution which was stirred for 10 min. After this, *p*-Toluene sulphonic acid - monohydrate (1.1 equiv) and 3-chloroperbenzoic acid (1.5 equiv) were added to that solution. The reaction mixture was stirred for half an hour at room temperature. The complete solvent was evaporated using a rotatory evaporator. Diethyl ether (20 mL) was added to the residue, filtered, washed with Et_2O and acetone, and dried in a desiccator.



1-[Hydroxy(tosyloxy)iodo]-4-chlorobenzene (**HTIB-1**), 82% yield, White solid.

^{1}H NMR (500 MHz, DMSO) δ 8.23 – 8.19 (m, 1H), 7.76 – 7.71 (m, 1H), 7.70 – 7.66 (m, 1H), 7.50 – 7.45 (m, 2H), 7.26 – 7.22 (m, 1H), 7.12 (d, *J* =

7.8 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.3, 139.0, 137.9, 133.1, 130.7, 128.2, 125.5, 92.7, 20.8.

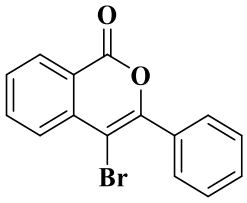


1-[Hydroxy(tosyloxy)iodo]-4-fluorobenzene (**HTIB-2**), 76% yield, White solid.

^{1}H NMR (500 MHz, DMSO) δ 8.30 – 8.24 (m, 1H), 7.76 – 7.71 (m, 1H), 7.52 – 7.47 (m, 2H), 7.47 – 7.42 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.10 – 7.01 (m, 1H), 2.29 (s, 3H).

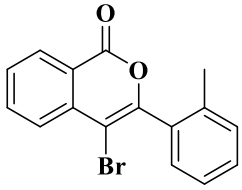
6.5. General procedure for synthesizing 4-bromoisocoumarin

In an oven-dried reaction tube with a magnetic bead inside, we charged the starting material (0.1 mmol, 1 equiv) followed by HTIB-1 (2 equiv), KBr (2 equiv), and DCE (1 mL). This reaction mixture was stirred at room temperature with monitoring by TLC analysis (5% EtOAc-hexane mixture). The stirring was turned off after the starting material was consumed completely (a color change was observed). The reaction mixture was concentrated using a rotatory evaporator. Purification was done by column chromatography using SiO_2 as the stationary phase and a 2% EtOAc-hexane mixture as the mobile phase.



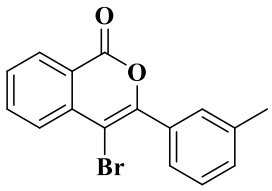
4-Bromo-3-phenyl-1*H*-isochromen-1-one (**2a**), 91% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.98 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.87 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.61 (td, *J* = 7.6, 1.1 Hz, 1H), 7.48 (h, *J* = 2.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 152.0, 136.8, 135.6, 133.0, 130.4, 130.0, 129.8, 129.4, 128.3, 126.8, 120.8, 101.5; IR (neat) 3056, 3026, 1733, 1618, 1599, 1472, 1444, 1314, 1230, 1085, 1073, 1052, 1018, 959, 750, 671, 641, 533 cm^{-1}.



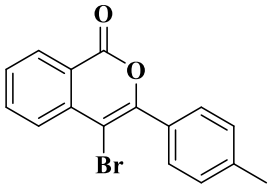
4-Bromo-3-(*o*-tolyl)-1*H*-isochromen-1-one (**2b**), 80% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.93 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.87 (ddd, *J* = 8.2, 7.2, 1.4 Hz, 1H), 7.63 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.39 (ddd, *J* = 7.3, 6.0, 1.7 Hz, 2H), 7.30 (dt, *J* = 8.4, 6.9 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 153.0, 137.3, 136.4, 135.7, 133.0, 130.5, 130.4, 130.1, 130.0, 129.4, 126.5, 125.9, 120.9, 103.3, 19.7; HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{16}H_{11}BrO_2$ 315.0015; found 315.0018.



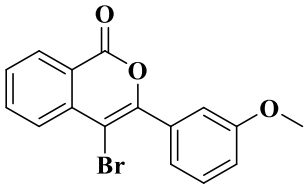
4-Bromo-3-(*m*-tolyl)-1*H*-isochromen-1-one (**2c**), 78% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.00 – 7.95 (m, 1H), 7.86 (ddd, *J* = 8.2, 7.3, 1.4 Hz, 1H), 7.65 – 7.57 (m, 3H), 7.37 (td, *J* = 7.6, 0.8 Hz, 1H), 7.29 (ddt, *J* = 7.6, 1.9, 0.9 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4, 152.2, 138.1, 136.8, 135.6, 132.8, 131.2, 130.3, 130.0, 129.3, 128., 127.1, 126.8, 120.7, 101.4, 21.6; HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{16}H_{11}BrO_2$ 315.0015; found 315.0017.



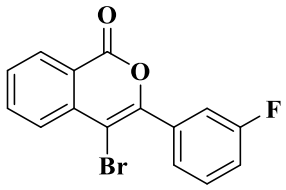
4-Bromo-3-(*p*-tolyl)-1*H*-isochromen-1-one (**2d**), 83% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.99 – 7.94 (m, 1H), 7.85 (ddd, *J* = 8.2, 7.3, 1.4 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.60 (ddd, *J* = 8.1, 7.3, 1.1 Hz, 1H), 7.31 – 7.27 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.4, 152.2, 140.7, 136.9, 135.6, 130.1, 129.9, 129.8, 129.2, 129.0, 126.8, 120.7, 101.2, 21.7; IR (neat) 3694, 2914, 2340, 1736, 1601, 1564, 1477, 1320, 1018, 956, 818, 756, 635 cm^{-1}.



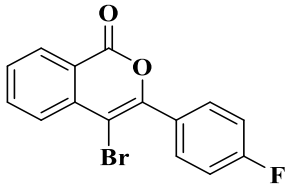
4-Bromo-3-(3-methoxyphenyl)-1*H*-isochromen-1-one (**2e**), 60% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.00 – 7.95 (m, 1H), 7.86 (ddd, *J* = 8.2, 7.3, 1.4 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.44 – 7.34 (m, 2H), 7.31 (dt, *J* = 2.3, 1.2 Hz, 1H), 7.03 (dt, *J* = 6.9, 2.6 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 159.3, 151.8, 136.8, 135.6, 134.1, 130.0, 129.4, 126.9, 122.3, 120.8, 116.4, 115.1, 101.6, 55.6; HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{16}H_{11}BrO_3$ 332.9946; found 332.9948.



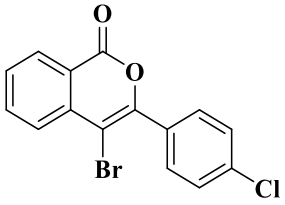
4-Bromo-3-(3-fluorophenyl)-1*H*-isochromen-1-one (**2f**), 74% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.98 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.88 (ddd, *J* = 8.4, 7.3, 1.4 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.53 (ddd, *J* = 9.6, 2.6, 1.7 Hz, 1H), 7.46 (td, *J* = 8.0, 5.7 Hz, 1H), 7.19 (tdd, *J* = 8.3, 2.6, 1.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, *J* = 247.1 Hz), 161.0, 150.5 (d, *J* = 2.4 Hz), 136.5, 135.8, 134.8 (d, *J* = 8.3 Hz), 130.1, 130.0 (d, *J* = 8.2 Hz), 129.7, 127.0, 125.67 (d, *J* = 3.2 Hz), 120.9, 117.4 (d, *J* = 21.1 Hz), 117.0 (d, *J* = 23.6 Hz), 102.1; IR (neat) 3083, 2922, 1737, 1607, 1581, 1485, 1177, 1064, 1022, 976, 918, 756, 682 cm^{-1}.



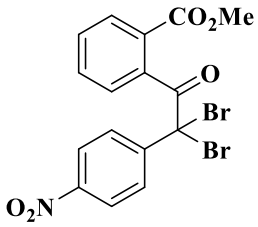
4-Bromo-3-(4-fluorophenyl)-1*H*-isochromen-1-one (**2g**), 84% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.97 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.87 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1H), 7.83 – 7.79 (m, 2H), 7.62 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 – 7.14 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.7 (d, *J* = 251.6 Hz), 161.1, 151.0, 136.7, 135.7, 132.1 (d, *J* = 8.7 Hz), 130.0, 129.4, 129.0 (d, *J* = 3.4 Hz), 126.8, 120.7, 115.5 (d, *J* = 21.9 Hz), 101.6; IR (neat) 2922, 2328, 1736, 1619, 1504, 1473, 1228, 1158, 1081, 1054, 1018, 961, 836, 758 cm^{-1}.



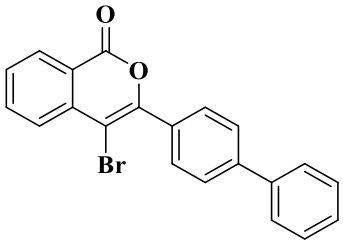
4-Bromo-3-(4-chlorophenyl)-1*H*-isochromen-1-one (**2h**), 78% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.97 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.87 (ddd, *J* = 8.2, 7.3, 1.4 Hz, 1H), 7.78 – 7.74 (m, 2H), 7.62 (td, *J* = 7.6, 1.1 Hz, 1H), 7.49 – 7.44 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.1, 150.8, 136.6, 136.5, 135.7, 131.3, 131.2, 130.0, 129.6, 128.6, 126.9, 120.8, 101.8; IR (neat) 2923, 2854, 1729, 1618, 1598, 1486, 1228, 1082, 1052, 1014, 961, 830, 758 cm^{-1}.



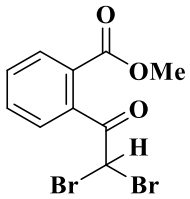
Methyl 2-(2,2-dibromo-2-(4-nitrophenyl)acetyl)benzoate (**2i'**), 63% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 – 8.20 (m, 4H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.5, 1.2 Hz, 1H), 7.57 (t, *J* = 7.5, 1.2 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.2, 166.4, 148.1, 145.7, 139.0, 132.8, 131.2, 130.4, 129.9, 129.3, 128.9, 123.0, 64.5, 53.1.



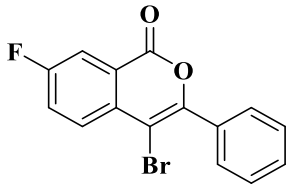
3-([1,1'-biphenyl]-4-yl)-4-bromo-1*H*-isochromen-1-one (**2j**), 79% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.02 – 7.98 (m, 1H), 7.93 – 7.85 (m, 3H), 7.73 – 7.70 (m, 2H), 7.69 – 7.60 (m, 3H), 7.48 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.42 – 7.37 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 151.7, 143.1, 140.2, 136.8, 135.6, 131.7, 130.3, 130.0, 129.3, 129.1, 128.1, 127.4, 126.9, 126.9, 120.8, 101.5; IR (neat) 3686, 2923, 2340, 1735, 1602, 1564, 1477, 1321, 1076, 1015, 956, 833, 755, 690 cm^{-1}; HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{21}H_{13}BrO_2$ 377.0172; found 377.0161.



Methyl 2-(2,2-dibromoacetyl)benzoate (**2l'**), 55% yield, colourless liquid.

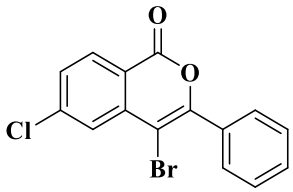
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8, 1.3 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.61 – 7.55 (m, 2H), 6.37 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.9, 166.3, 138.0, 133.2, 130.8, 130.5, 130.4, 127.6, 53.3, 44.3.



4-Bromo-7-fluoro-3-phenyl-1*H*-isochromen -1-one (**2m**), 78% yield, white solid.

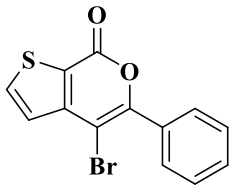
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.81 – 7.76 (m, 2H), 7.57 (ddd, *J* = 8.9, 7.9, 2.8 Hz, 1H), 7.49 (tt, *J* = 3.7, 2.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6 (d, *J* = 252.3 Hz), 160.4 (d, *J* = 3.3 Hz), 151.4 (d, *J* = 3.0 Hz), 133.4 (d, *J* = 2.9 Hz), 132.6, 130.5, 129.8, 129.6 (d, *J* = 7.8

Hz), 128.3, 123.7 (d, J = 23.0 Hz), 122.4 (d, J = 8.3 Hz), 115.5 (d, J = 23.5 Hz), 100.6; IR (neat) 3074, 2922, 1729, 1605, 1482, 1326, 1243, 1078, 965, 905, 831, 771, 727, 691, 645, 547 cm^{-1}.



4-Bromo-6-chloro-3-phenyl-1*H*-isochromen-1-one (**2n**), 81% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 7.81 – 7.78 (m, 2H), 7.56 (dd, J = 8.5, 2.0 Hz, 1H), 7.51 – 7.47 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 153.3, 142.7, 138.3, 132.6, 131.7, 130.6, 129.8, 129.8, 128.3, 126.7, 119.0, 100.1; IR (neat) 2922, 2854, 1740, 1599, 1522, 1469, 1310, 1228, 1073, 1041, 966, 691, 652 cm^{-1}; HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{15}H_8BrClO_2$ 358.9267; found 358.9267.

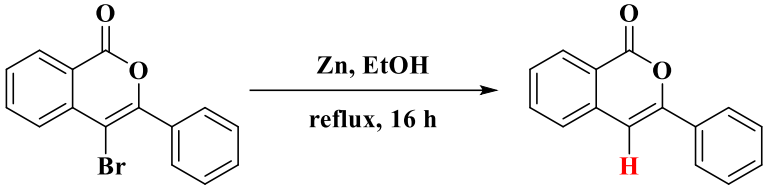


4-Bromo-5-phenyl-7*H*-thieno[2,3-*c*]pyran-7-one (**2o**), 53% yield, white solid.

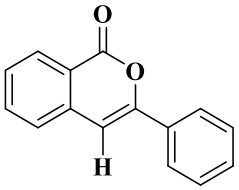
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 5.2 Hz, 1H), 7.83 – 7.81 (m, 2H), 7.50 – 7.47 (m, 3H), 7.44 (d, J = 5.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 153.8, 148.2, 136.8, 132.0, 130.5, 129.6, 128.4, 126.6, 122.8, 96.9; IR (neat) 3112, 3071, 2922, 1749, 1723, 1588, 1492, 1432, 1055, 997, 907, 753, 688 cm^{-1}.

6.6. Procedures for post-synthetic transformations

6.6.1. Procedure for synthesizing 2aa from 2a



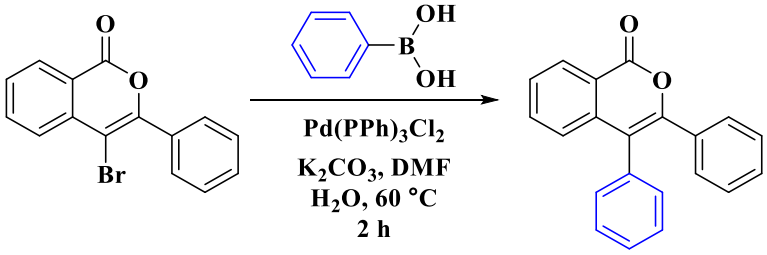
Compound **2a** (60.2 mg, 0.2 mmol) was charged in an oven-dried vial equipped with a magnetic stir bar, followed by Zn powder (130 mg, 2 mmol) and EtOH (3 mL). Then, we refluxed the reaction mixture for 16 h. After refluxing, the RB was cooled down to rt, and the mixture was filtered through a celite pad and washed with EtOAc. The filtrate was concentrated under reduced pressure using a rotatory evaporator, followed by purification through the SiO_2 column chromatography eluting with a 2% EtOAc-hexane mixture.



3-Phenyl-1*H*-isochromen-1-one (**2aa**), 81% yield, white solid.

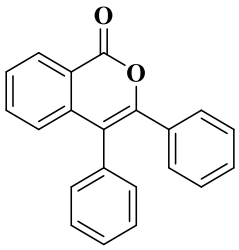
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 – 8.30 (m, 1H), 7.91 – 7.88 (m, 2H), 7.75 – 7.71 (m, 1H), 7.53 – 7.43 (m, 5H), 6.97 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5, 153.8, 137.7, 135.0, 132.1, 130.1, 129.8, 129.0, 128.3, 126.1, 125.4, 120.7, 102.0.

6.6.2. Procedure for synthesizing 2ab from 2a [22]



In an oven-dried vial containing a magnetic stir bar, we charged **2a** (60.2 mg, 0.2 mmol), phenylboronic acid (48.8 mg, 0.4 mmol), $Pd(PPh)_3Cl_2$ (5

mol%), and DMF (4 mL) were added. The mixture was stirred for half an hour, followed by adding K_2CO_3 (55.3 mg, 0.4 mmol) dissolved in water (1 mL). Then, we stirred he reaction mixture for 2 h at 60 ºC. The RB was cooled down to 0 ºC, and water (5 mL) was added to the mixture. Extraction was done by using DCM (3 x 5 mL). The organic phases were washed (combinedly) with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure using a rotatory evaporator. Purification through SiO_2 column chromatography eluting with 2% EtOAc-hexane mixture gave the product **2ab**.



3,4-Diphenyl-1*H*-isochromen-1-one (**2ab**), 53% yield, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.66 – 7.62 (m, 1H), 7.55 – 7.51 (m, 1H), 7.44 – 7.39 (m, 2H), 7.35 – 7.32 (m, 2H), 7.28 – 7.17 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 151.1, 139.0, 134.8, 134.5, 133.1, 131.4, 129.7, 129.4, 129.2, 129.1, 128.3, 128.2, 128.0, 125.5, 120.6, 117.0.

Chapter 7

CONCLUSION

Isocoumarins constitute a class of lactones – natural and synthetic both. They exhibit various biological activities such as anti-oncological, antiviral [16], antibacterial, antifungal, etc. Their applications are not just limited to biological activities; they also are very important scaffolds in material chemistry. Besides, they also happen as synthetic intermediates during the synthesis of many carbocyclic and heterocyclic compounds. Their wide application compelled chemists worldwide to develop methods for synthesizing such scaffolds. In this regard, 4-bromoisocoumarin is an important compound because it can be converted into a library of 3-substituted isocoumarins through hydrodehalogenation reactions and 3,4-disubstituted isocoumarins through cross-coupling reactions. We hypothesized and successfully developed a method to make this compound by using hypervalent iodine reagent and alkali metal bromide in a very mild condition from 2-alkynylaryloate esters. Our reaction was studied over various substrates and found effective in most. But the effect becomes odd when the alkyne is attached to any electron-withdrawing group. We have also optimized a catalytic pathway to make similar moieties, where the hypervalent iodine reagent is generated in situ. Plausible mechanisms are drawn for all the methods. Two post-synthetic reactions are also performed to show the formation of 3-substituted and 3,4-disubstituted isocoumarins.

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V. CHARACTERIZATION DATA

V.I. ^{1}H & ^{13}C NMR Spectra

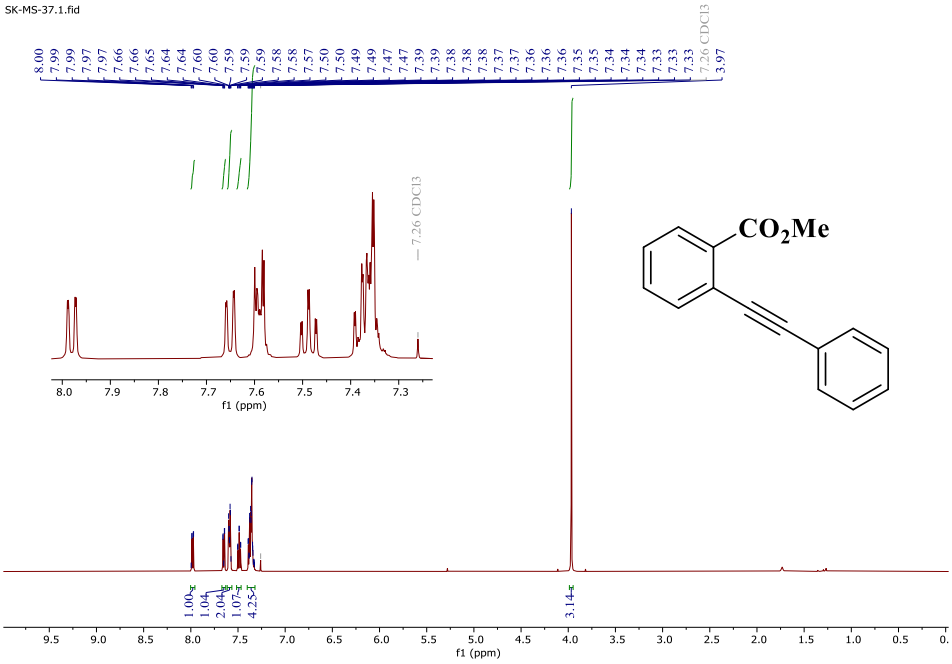

Figure 5: ^{1}H NMR spectrum of 1a

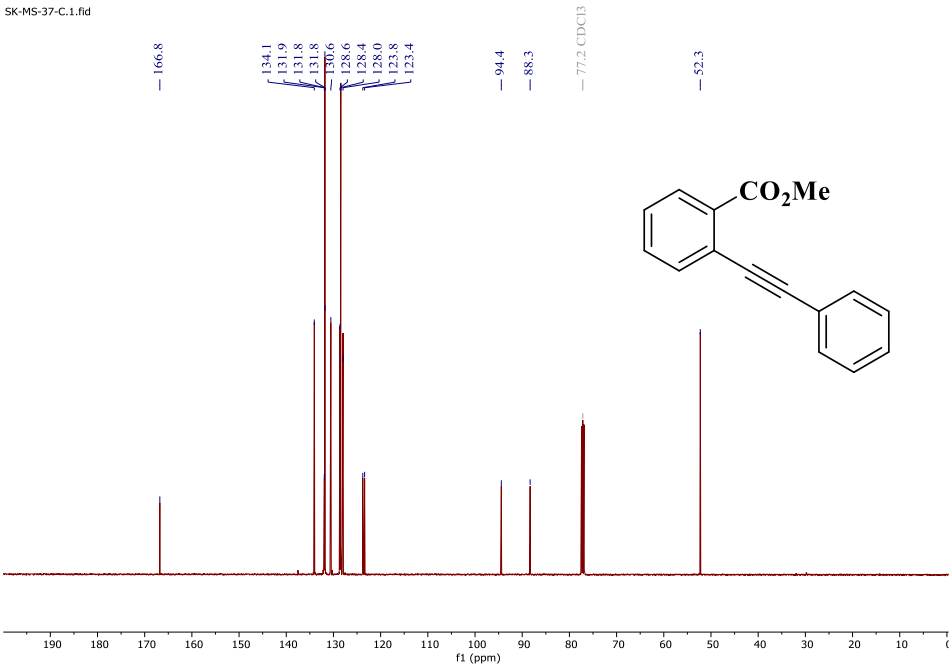

Figure 6: ^{13}C NMR spectrum of 1a

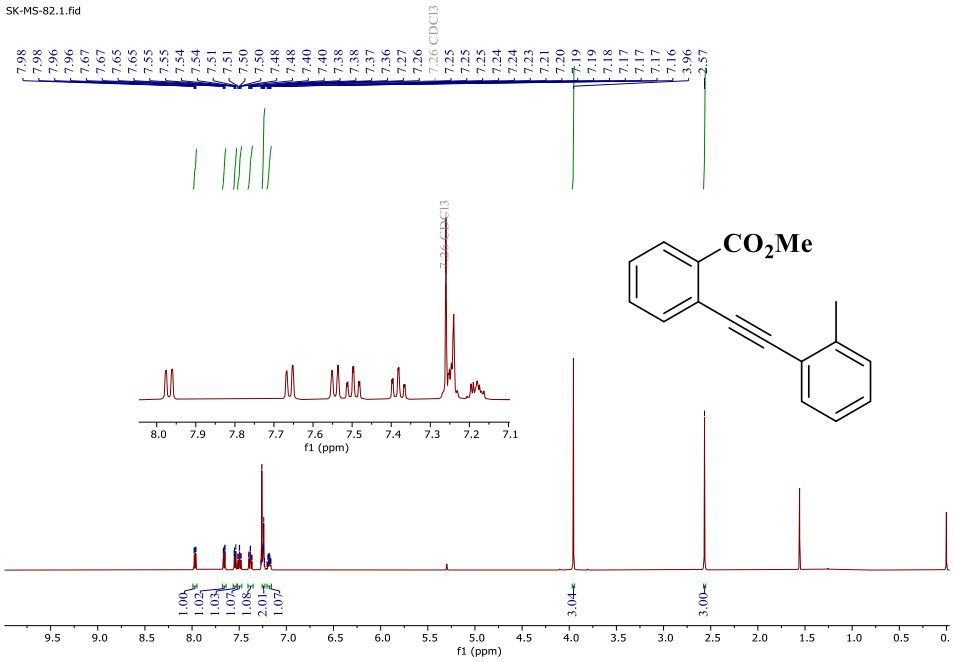

Figure 7: ^{1}H NMR spectrum of 1b

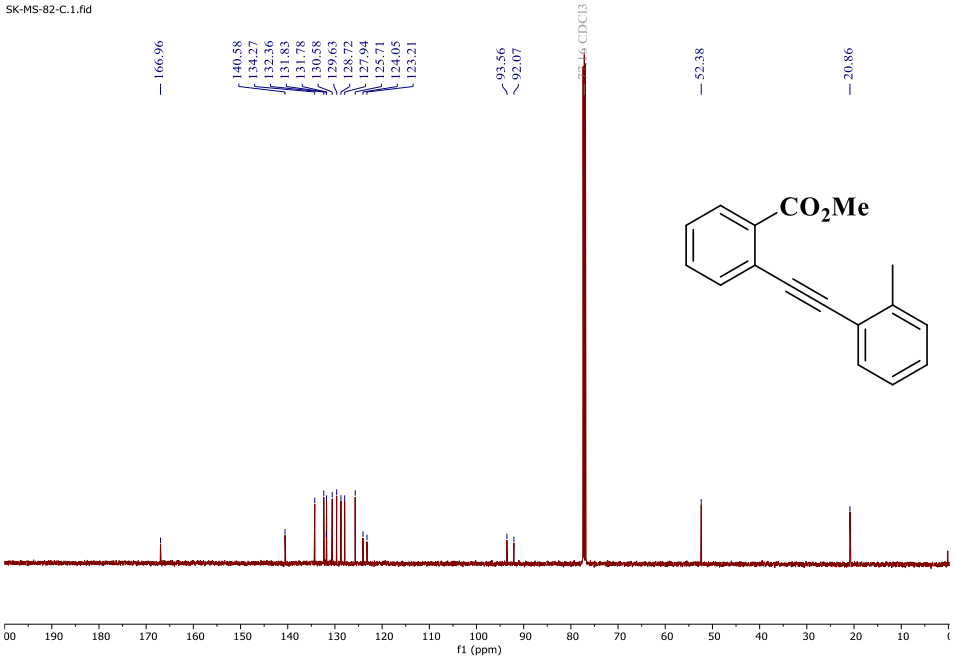

Figure 8: ^{13}C NMR spectrum of 1b

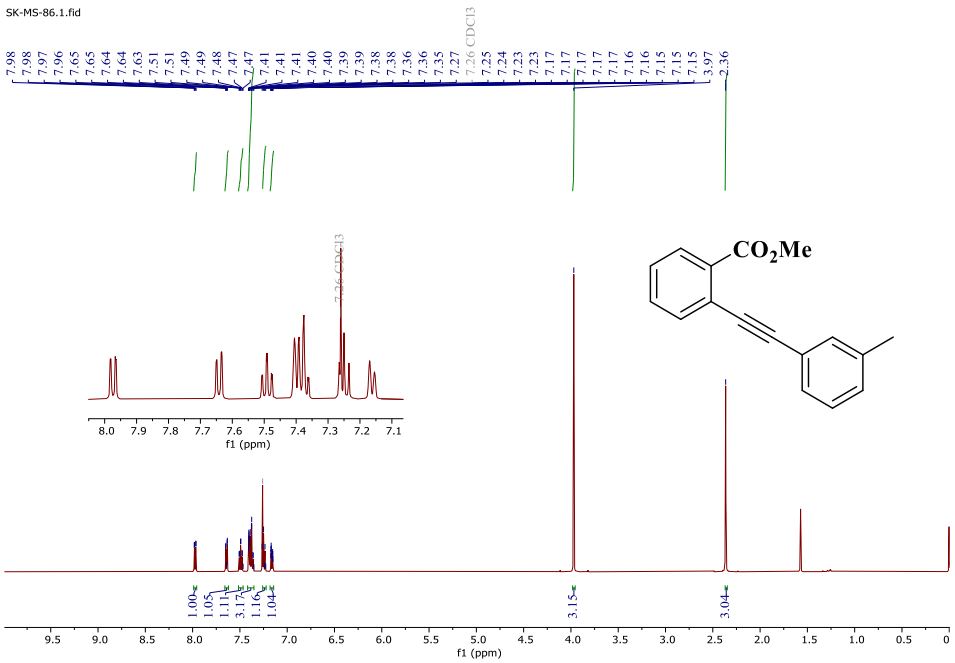

Figure 9: [1]H NMR spectrum of 1c

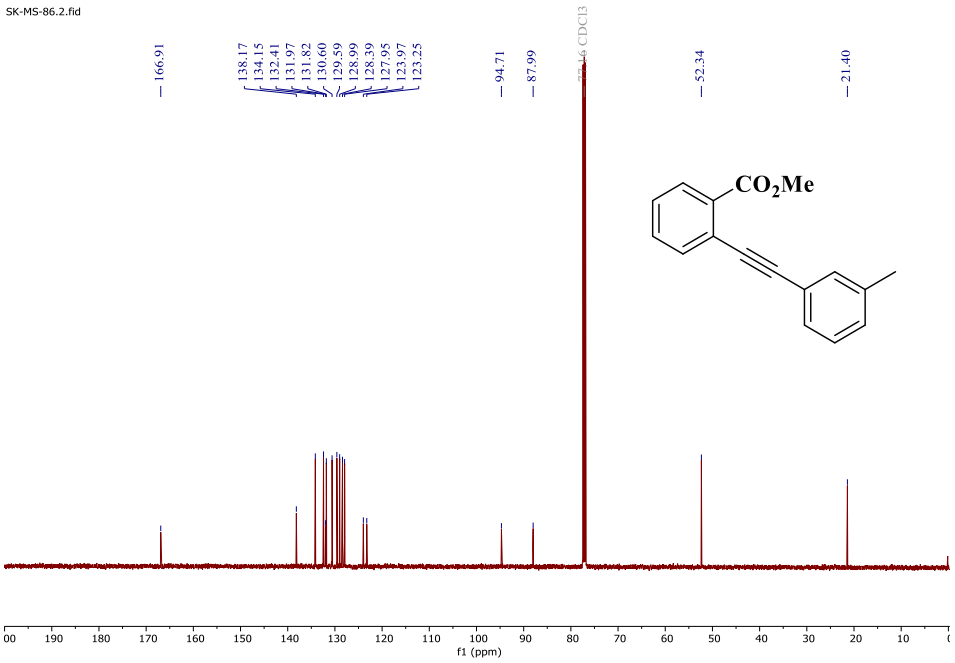

Figure 10: [13]C NMR spectrum of 1c

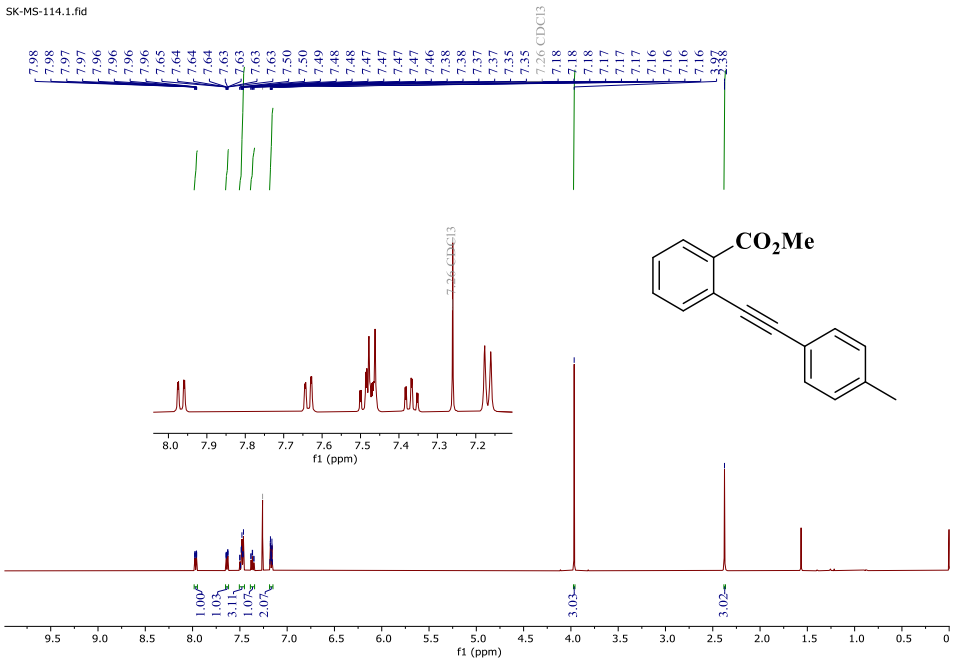

Figure 11: [1]H NMR spectrum of 1d

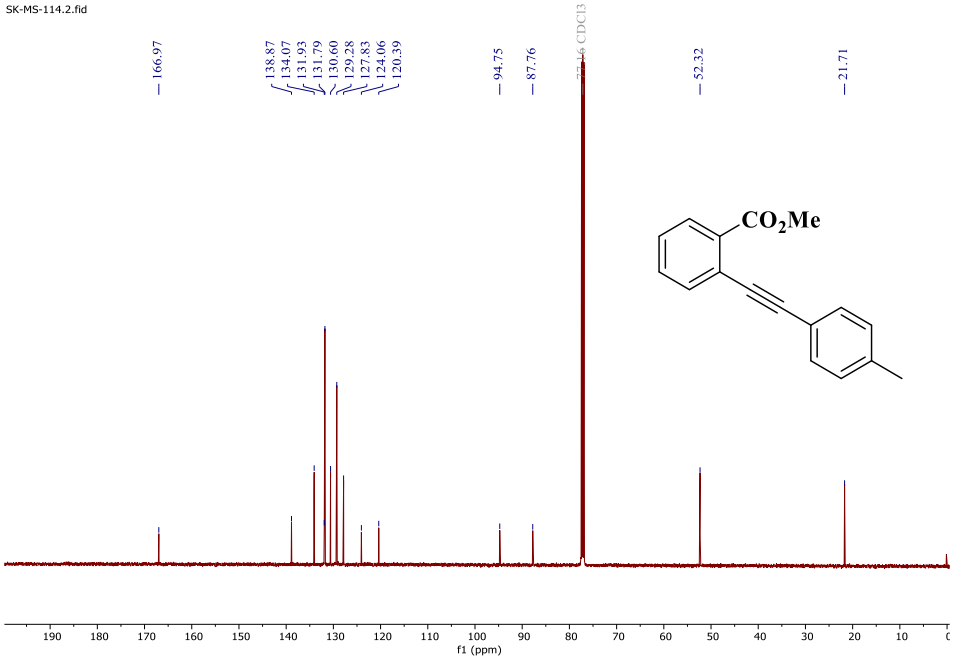

Figure 12: [13]C NMR spectrum of 1d

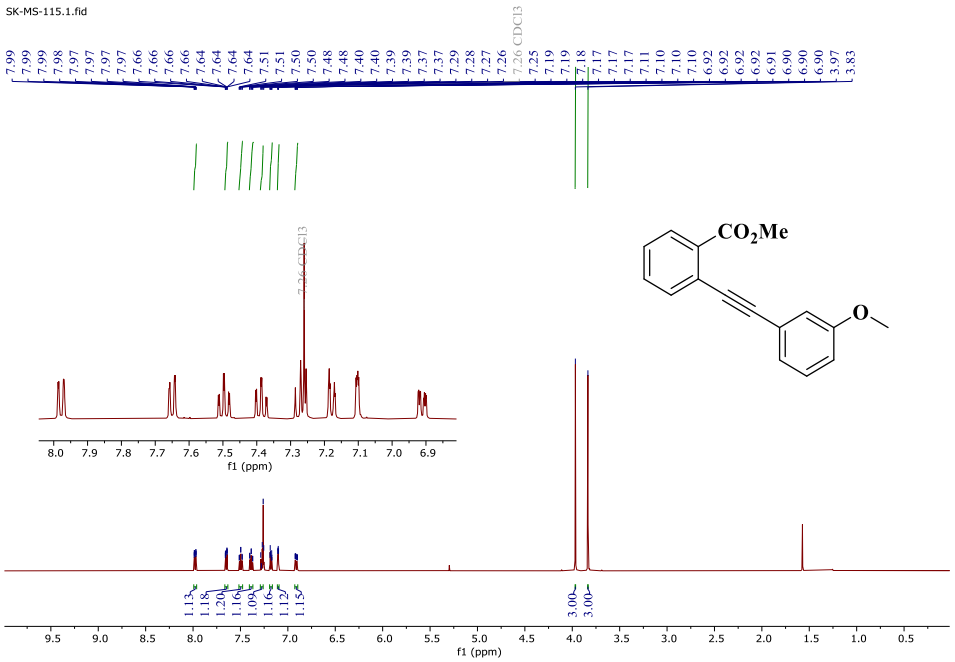

Figure 13: [1]H NMR spectrum of 1e

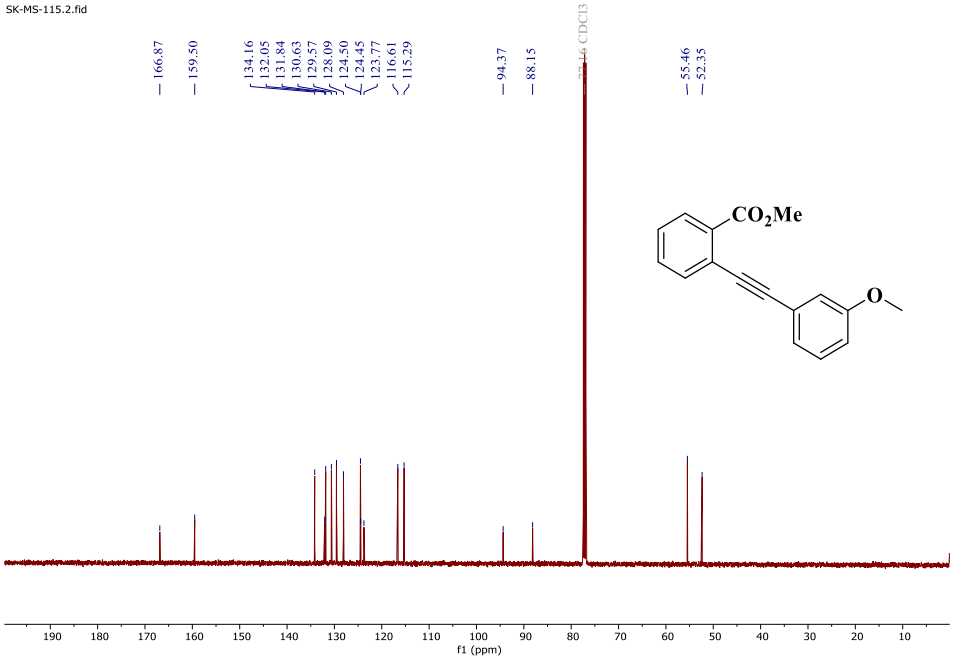

Figure 14: [13]C NMR spectrum of 1e

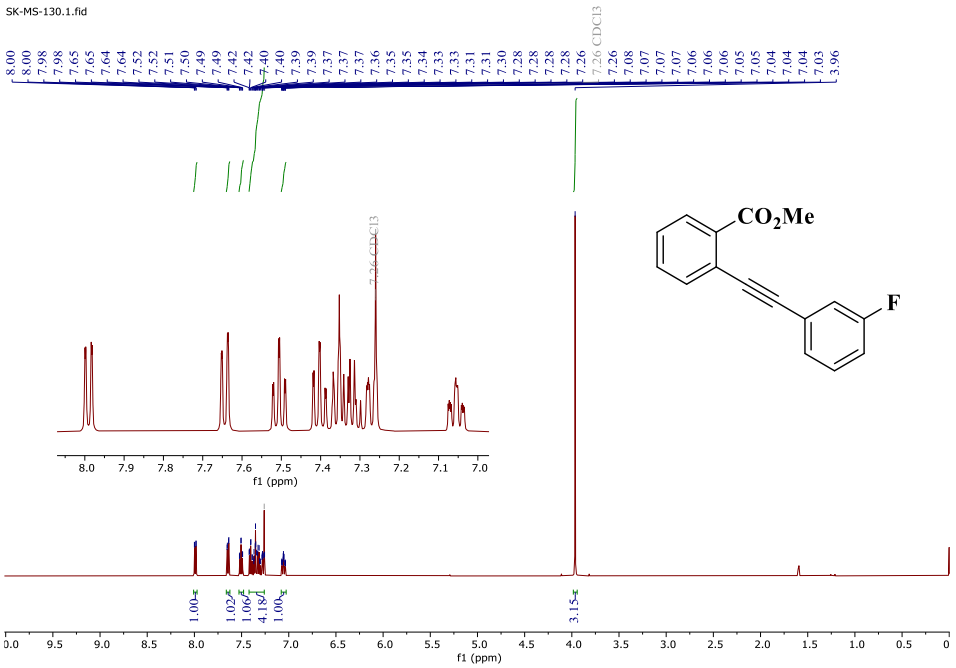

Figure 15: [1]H NMR spectrum of 1f

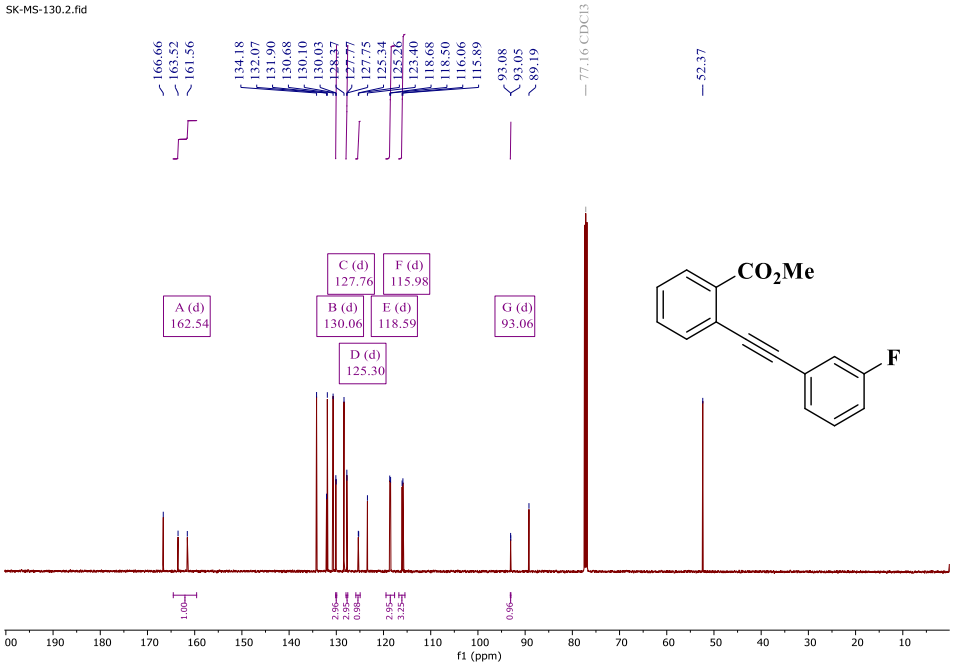

Figure 16: [13]C NMR spectrum of 1f

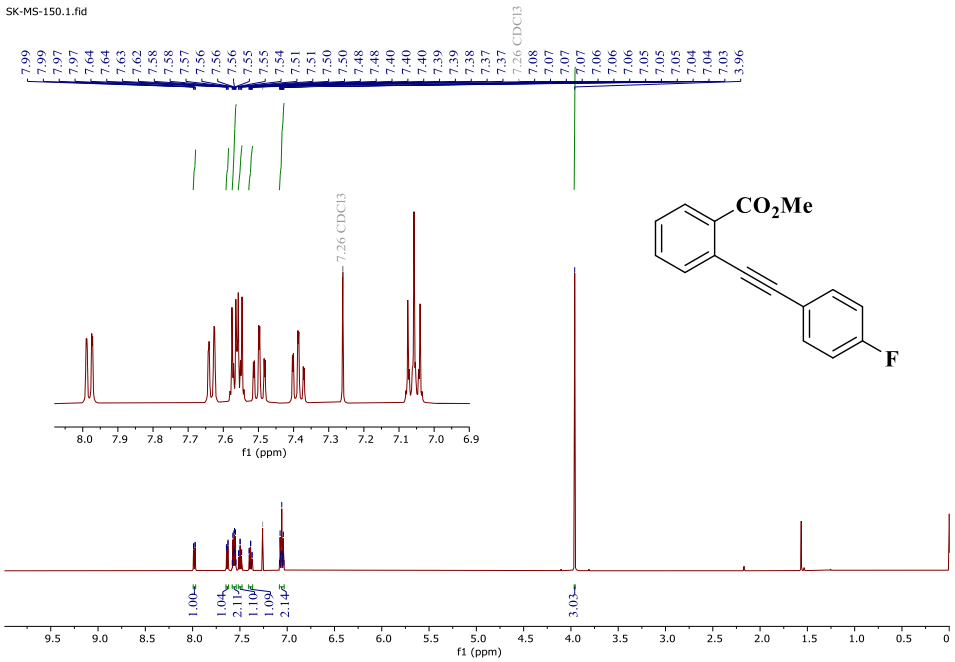

Figure 17: [1]H NMR spectrum of 1g

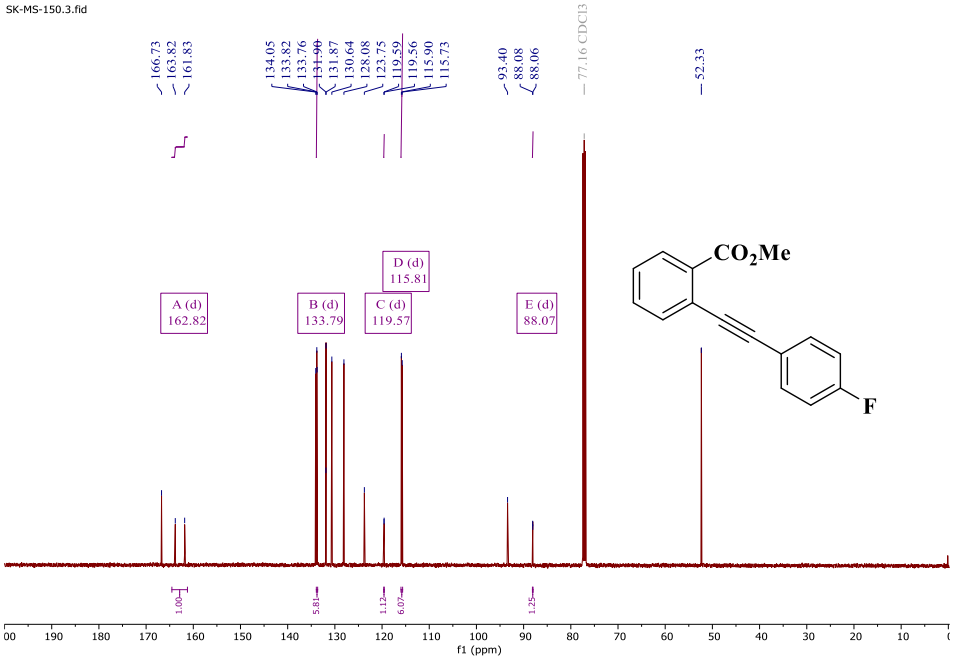

Figure 18: [13]C NMR spectrum of 1g

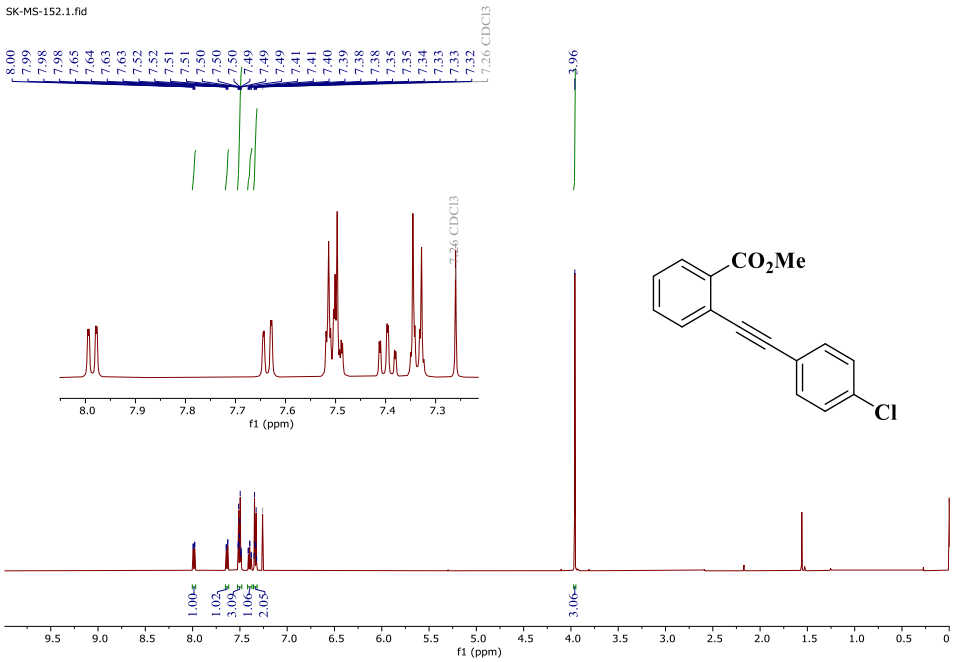

Figure 19: [1]H NMR spectrum of 1h

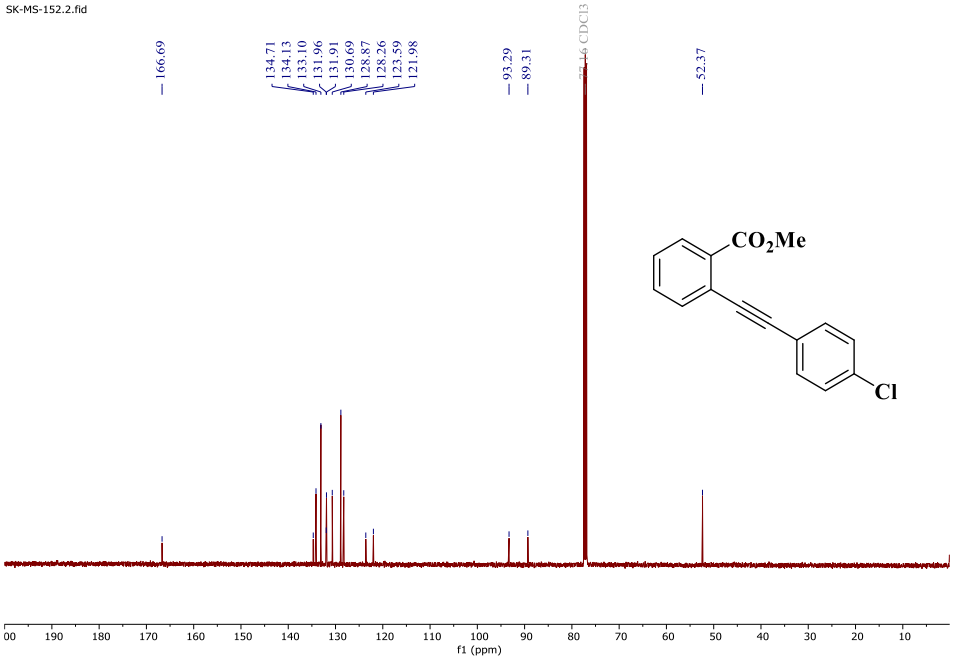

Figure 20: [13]C NMR spectrum of 1h

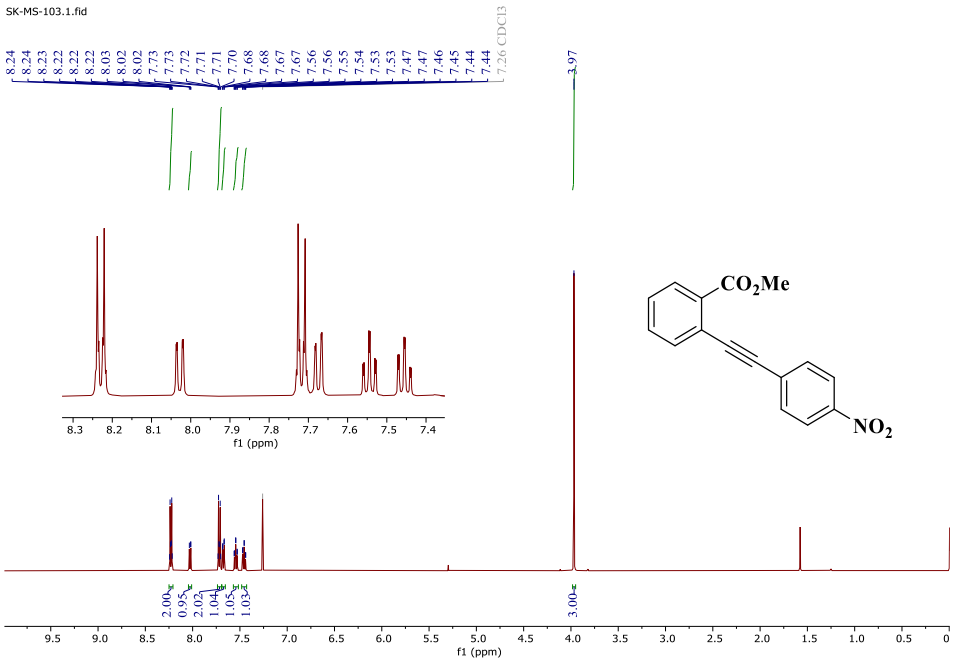

Figure 21: [1]H NMR spectrum of 1i

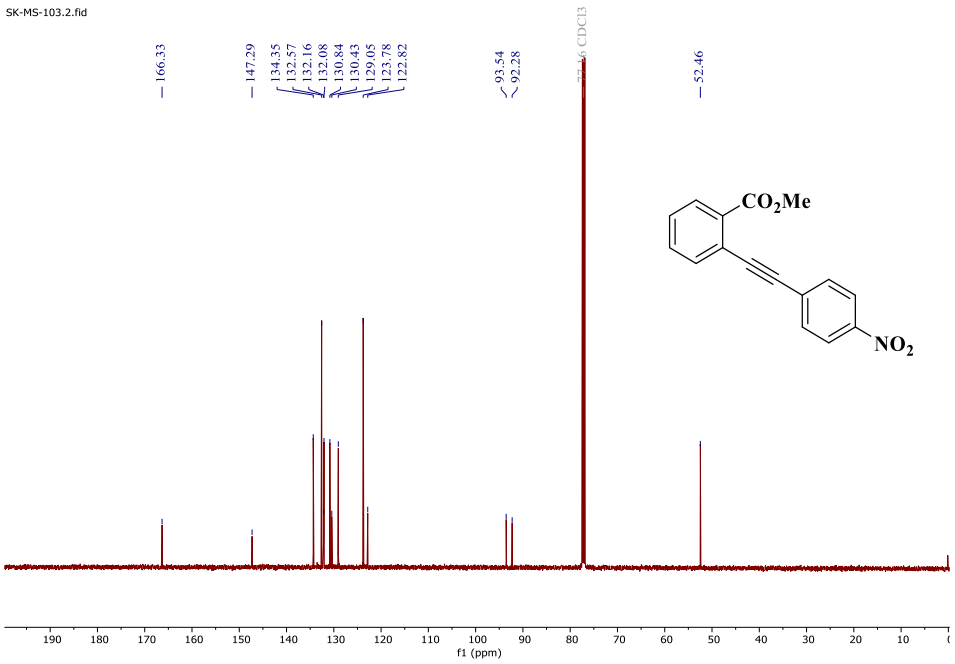

Figure 22: [13]C NMR spectrum of 1i

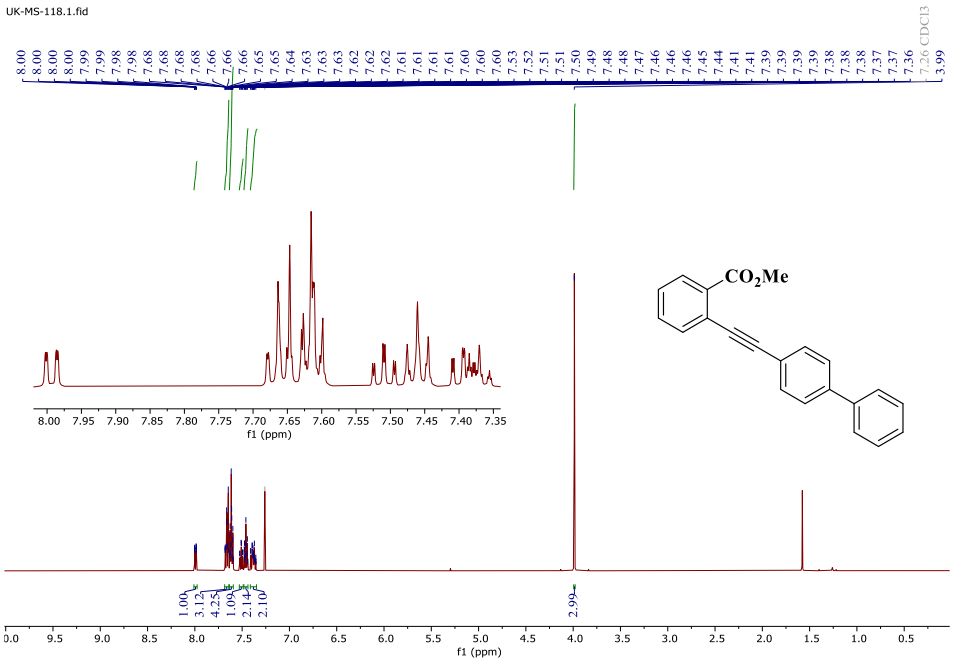

Figure 23: ^{1}H NMR spectrum of 1j

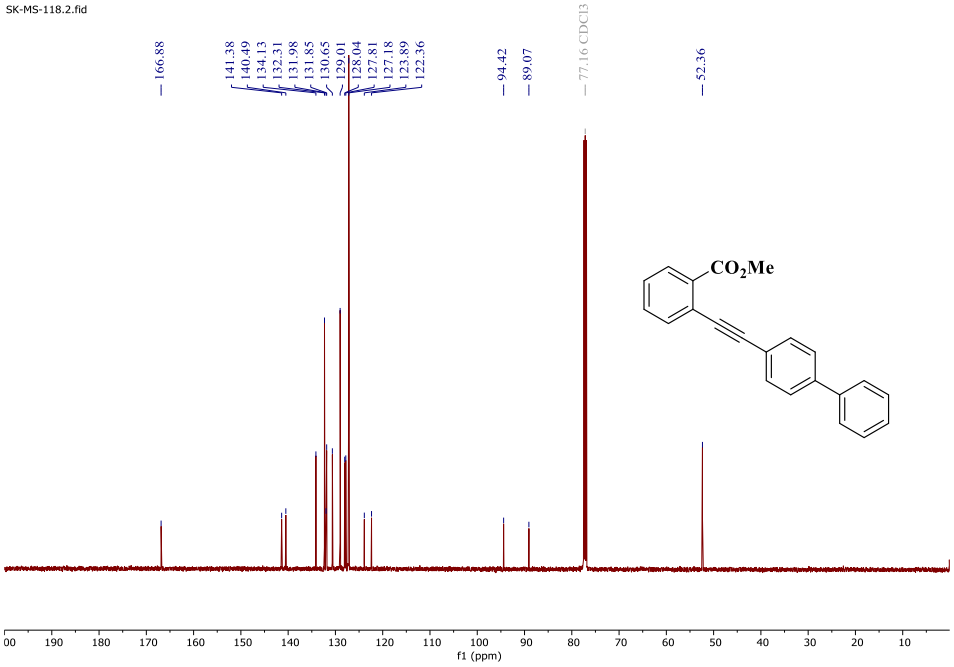

Figure 24: ^{13}C NMR spectrum of 1j

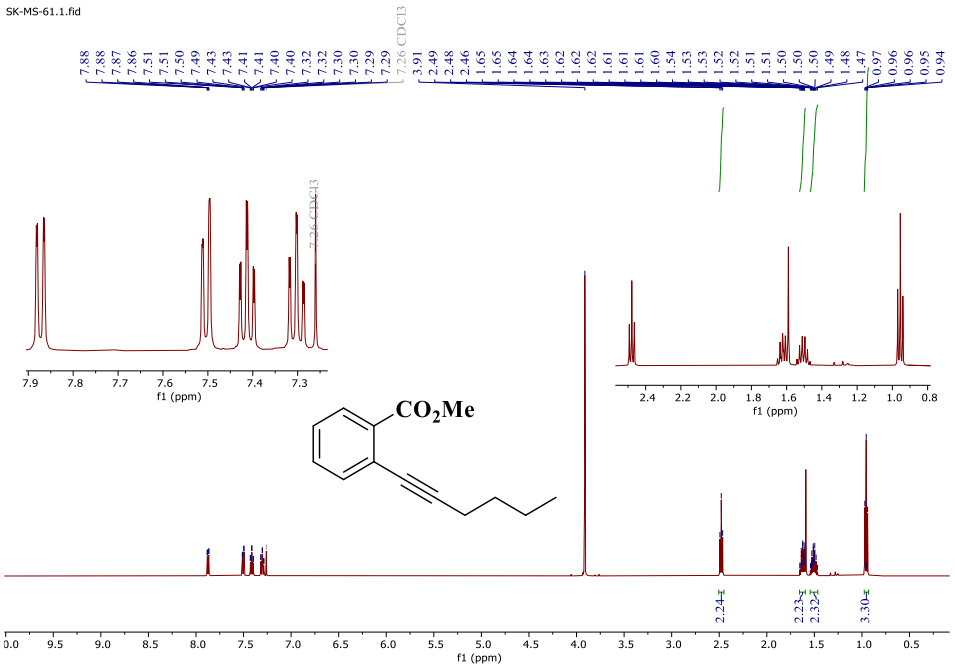

Figure 25: ^{1}H NMR spectrum of 1k

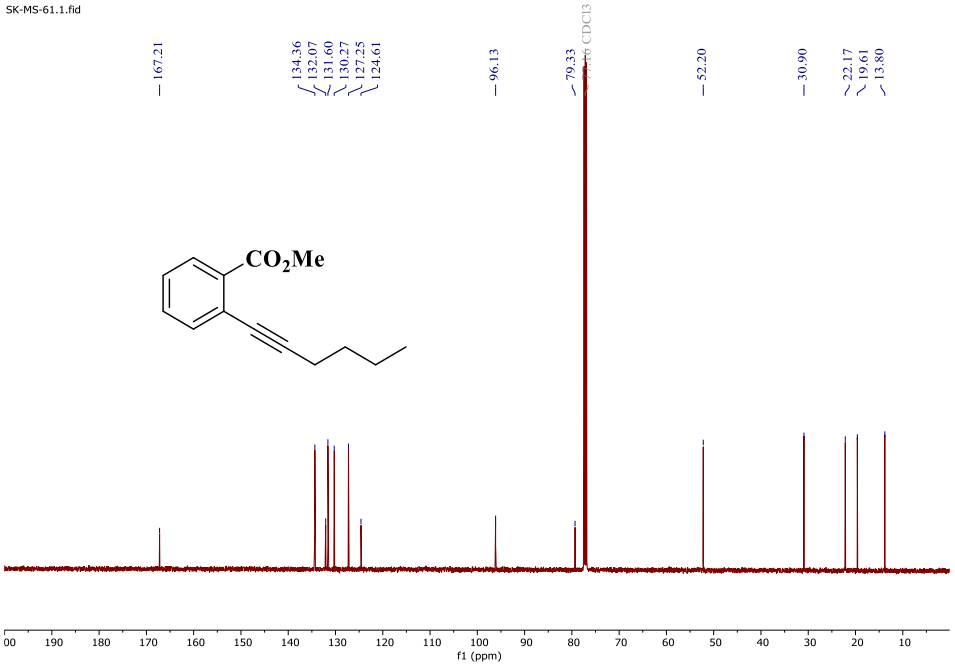

Figure 26: ^{13}C NMR spectrum of 1k

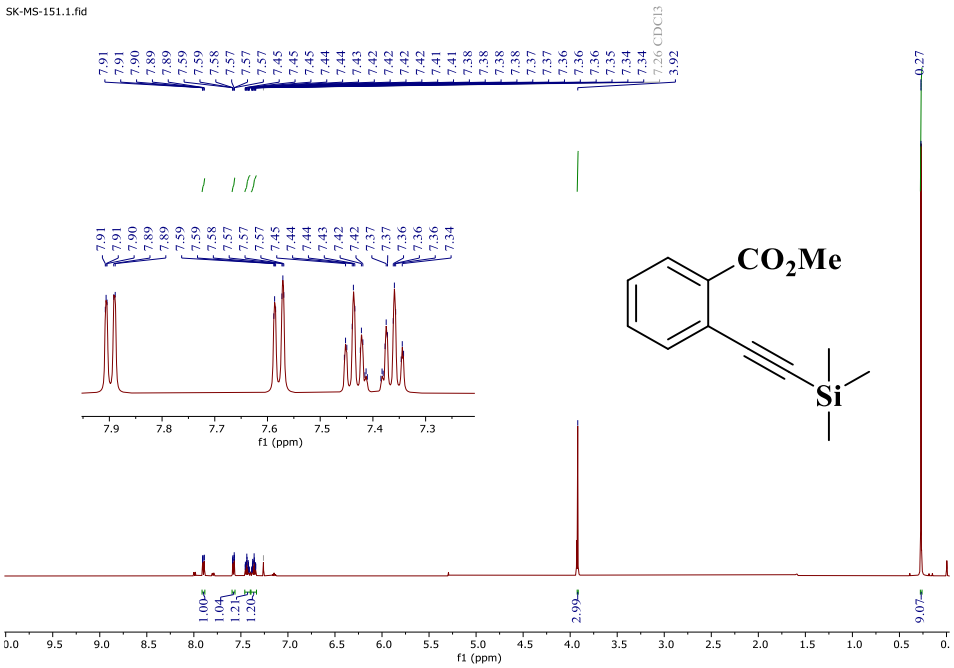

Figure 27: ^{1}H NMR spectra of 1l'

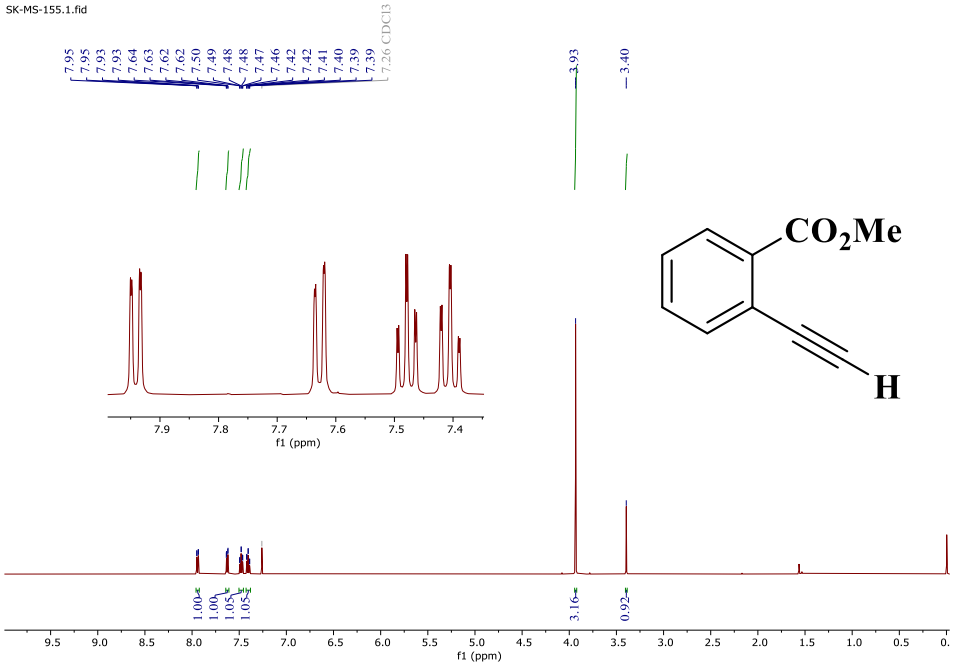

Figure 28: ^{1}H NMR spectrum of 1l

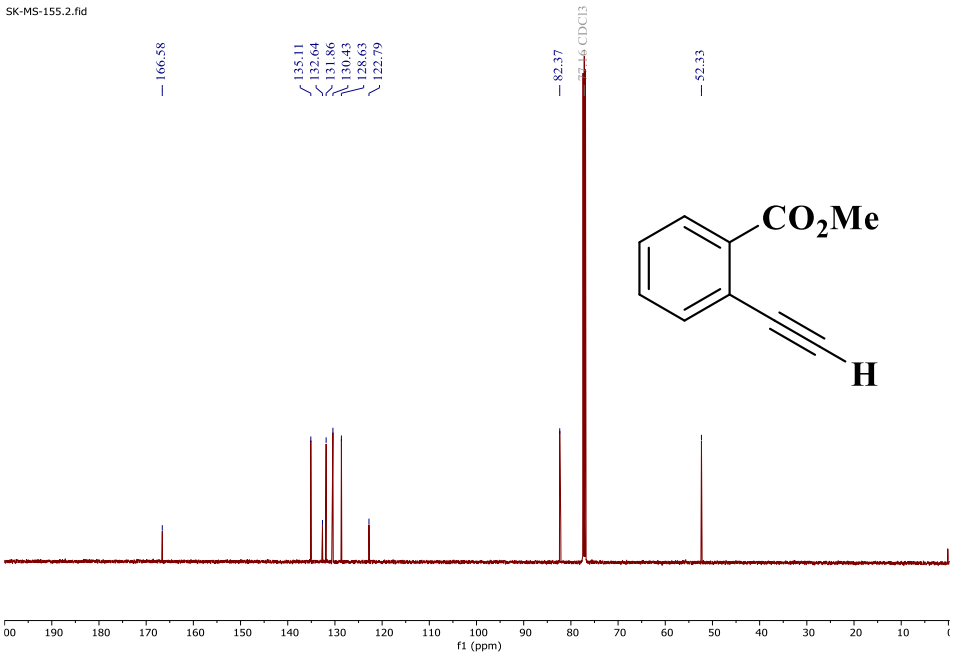

Figure 29: ^{13}C NMR spectrum of 1l

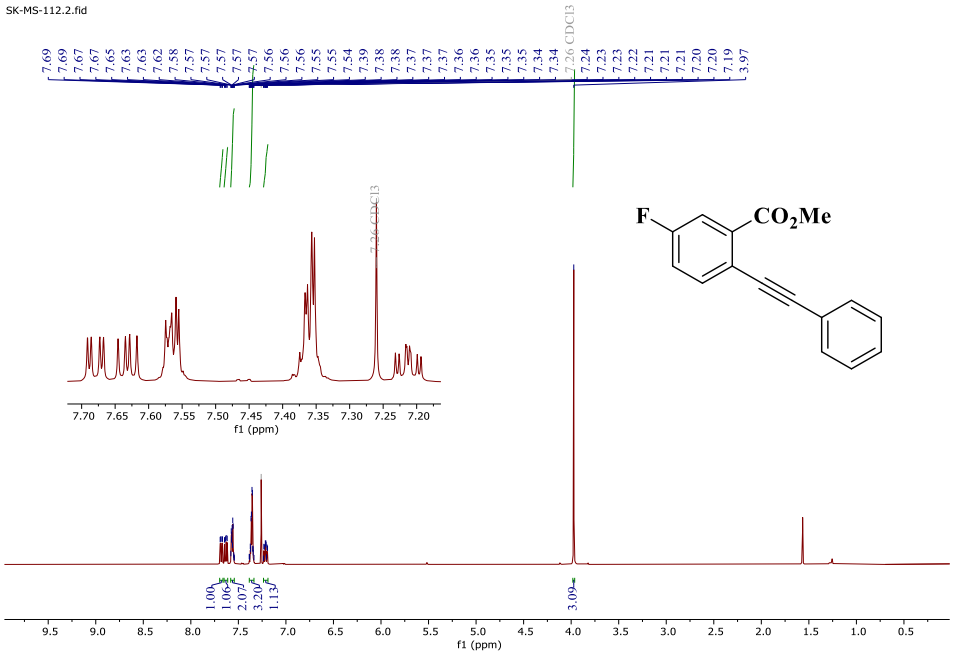

Figure 30: ^{1}H NMR spectrum of 1m

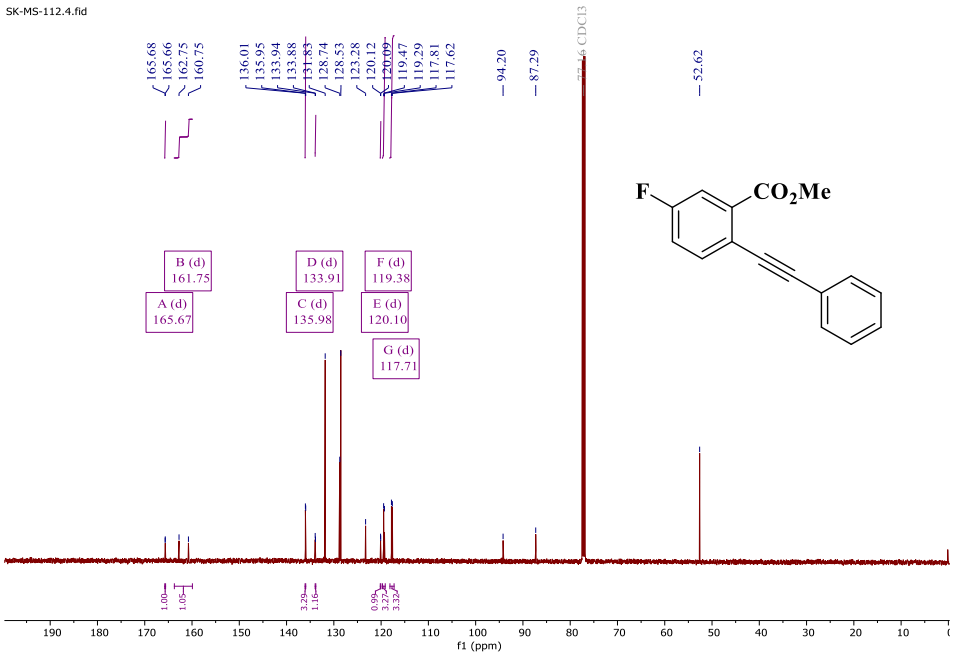

Figure 31: ^{13}C NMR spectrum of 1m

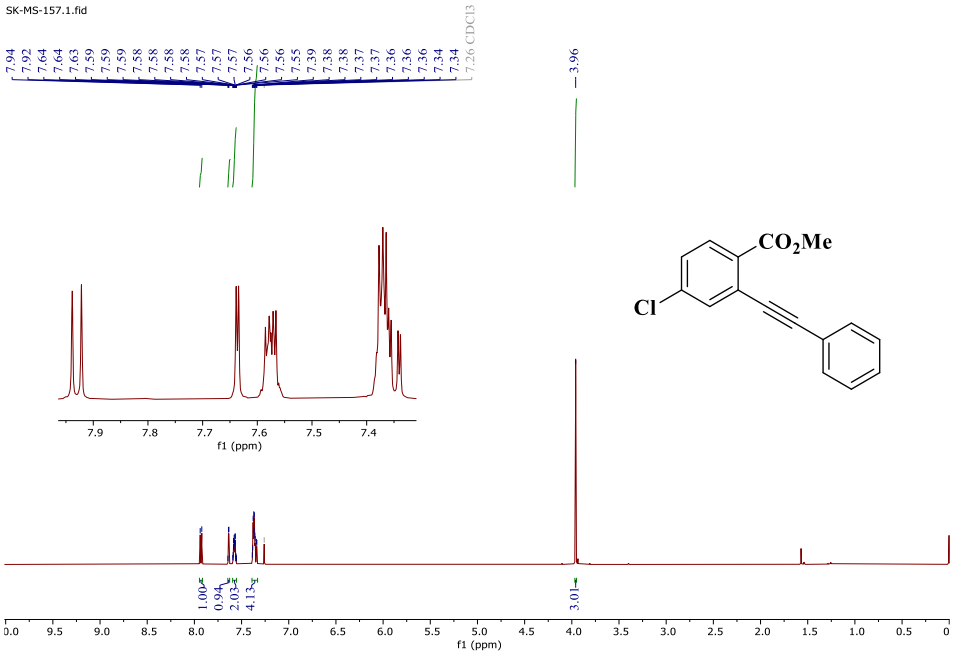

Figure 32: ^{1}H NMR spectrum of 1n

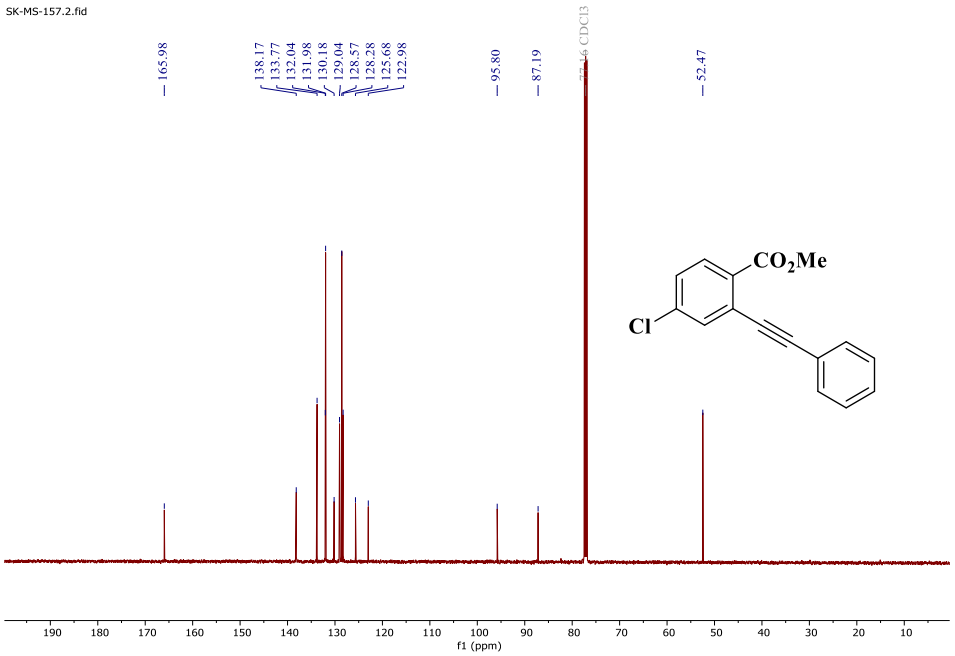

Figure 33: ^{13}C NMR spectrum of 1n

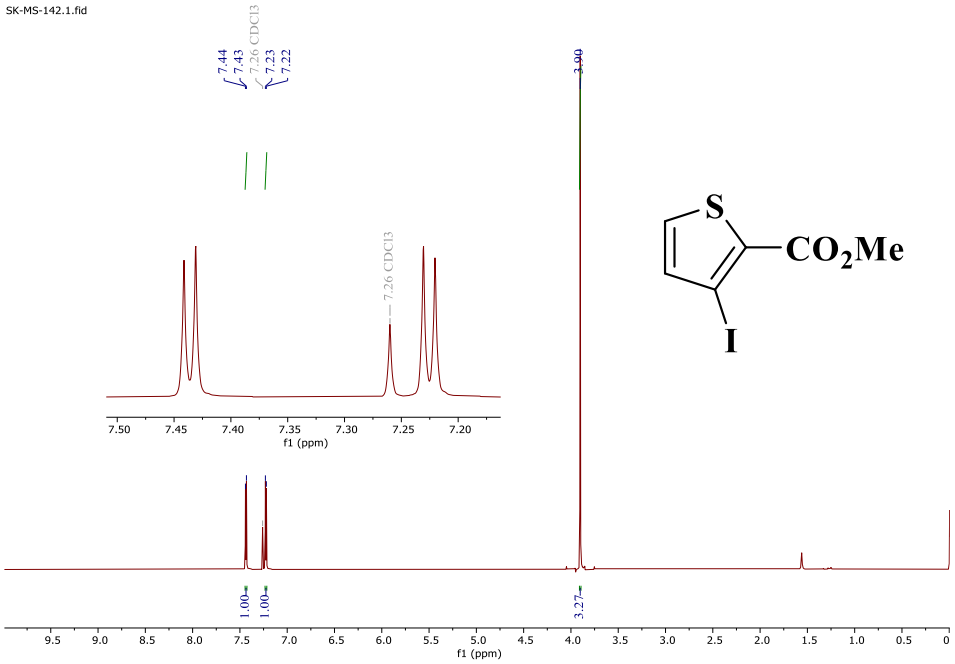

Figure 34: ^{1}H NMR spectrum of 1o'

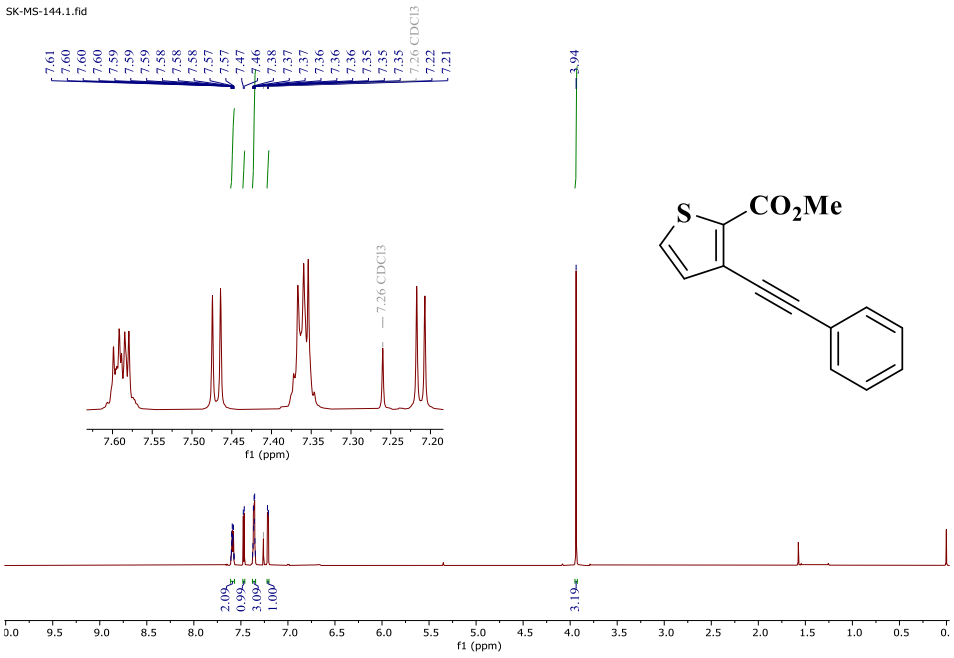

Figure 35: ^{1}H NMR spectrum of 1o

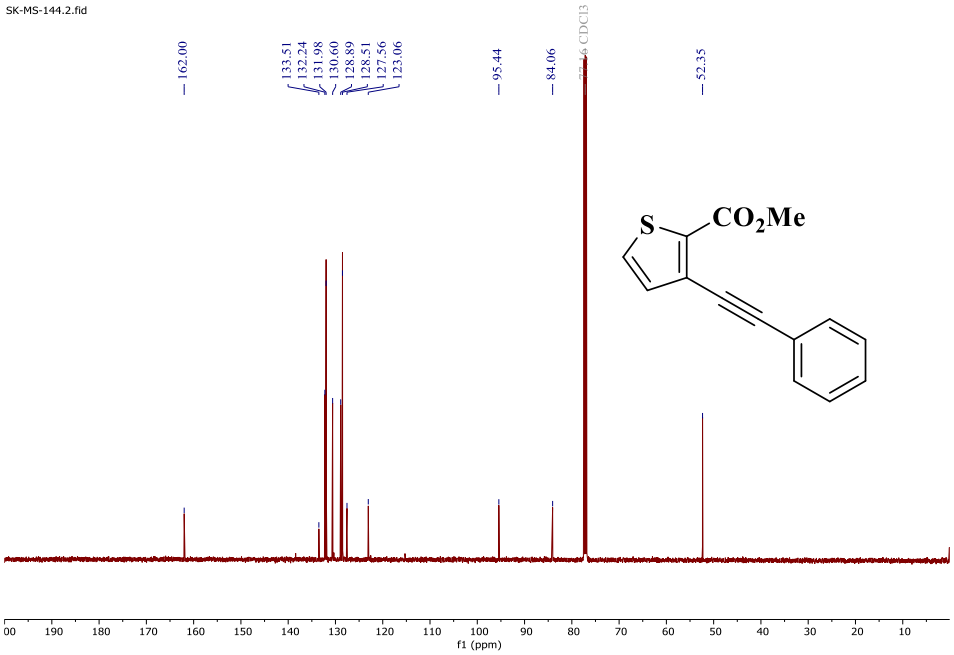

Figure 36: ^{13}C NMR spectrum of 1o

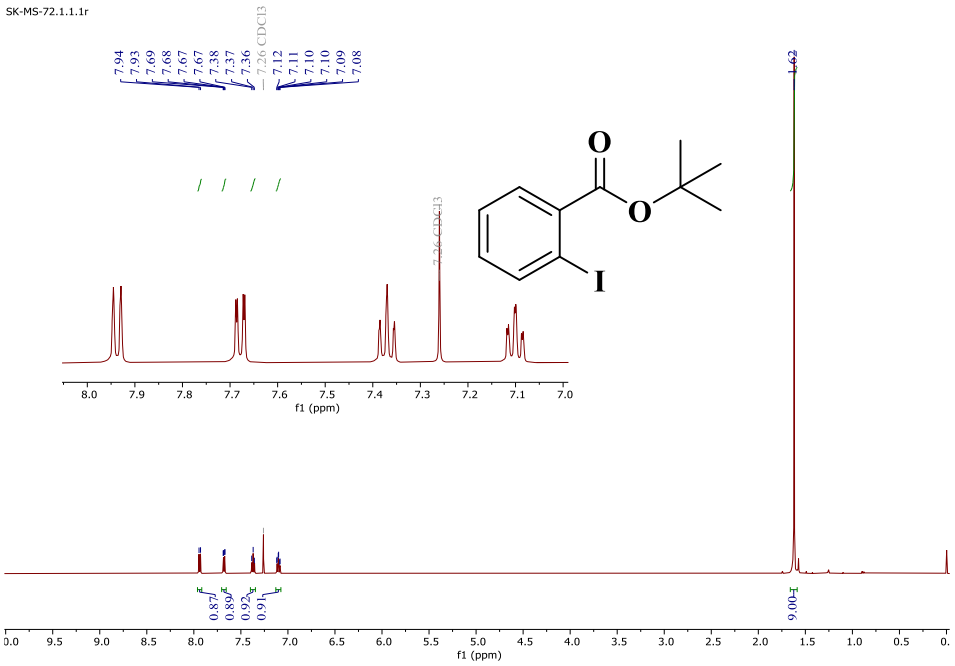

Figure 37: ^{1}H NMR spectrum of 1p'

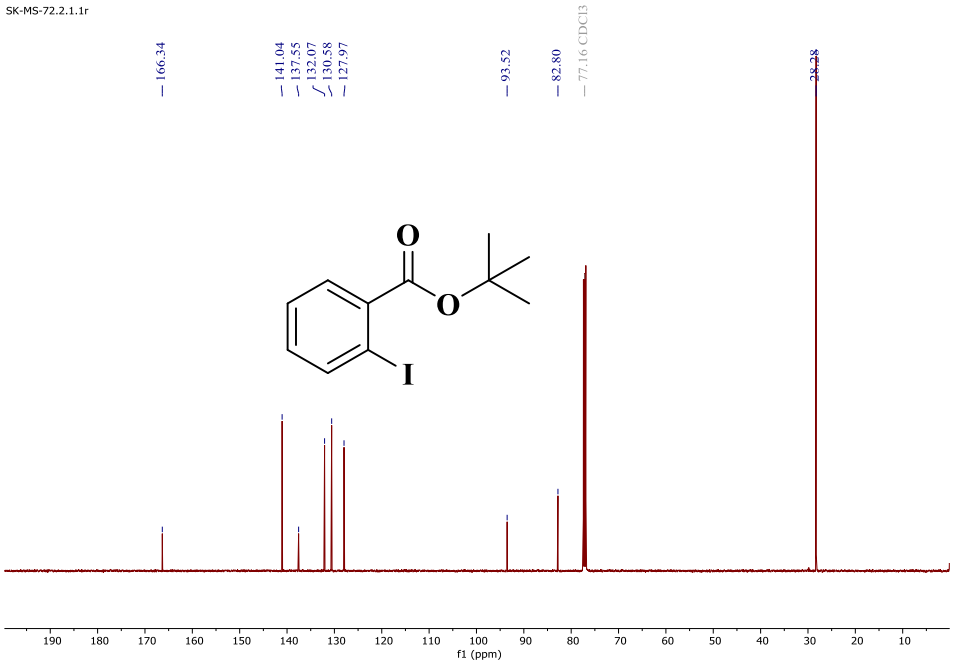

Figure 38: ^{13}C NMR spectrum of 1p'

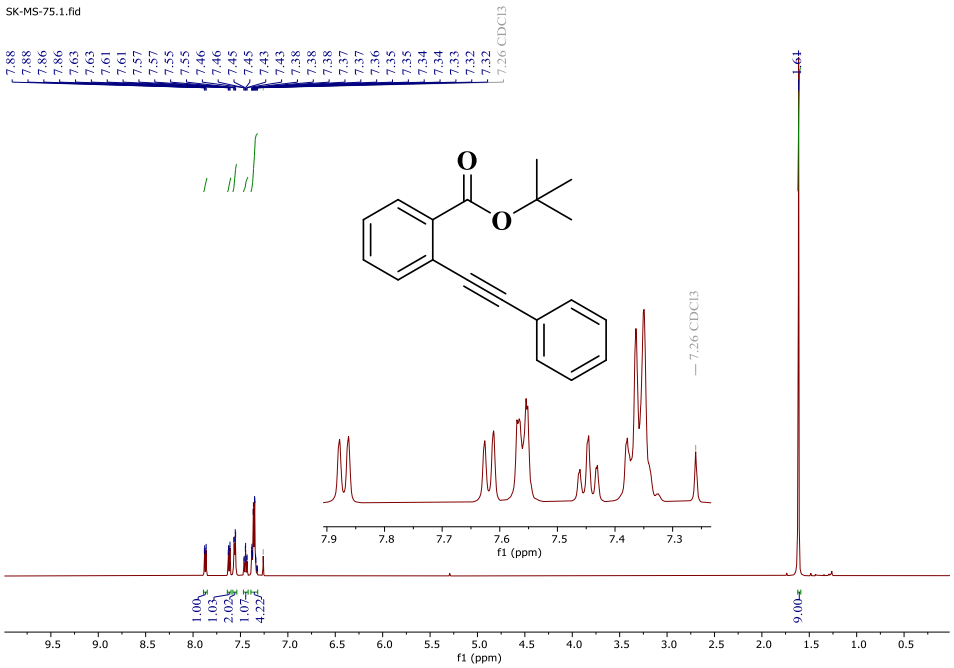

Figure 39: ^{1}H NMR spectrum of 1p

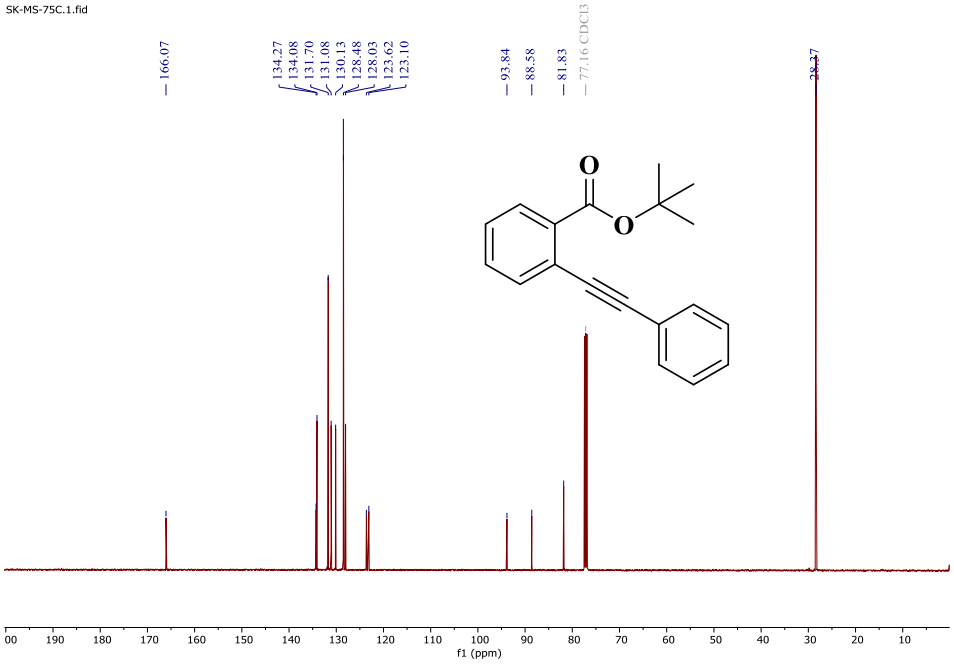

Figure 40: ^{13}C NMR spectrum of 1p

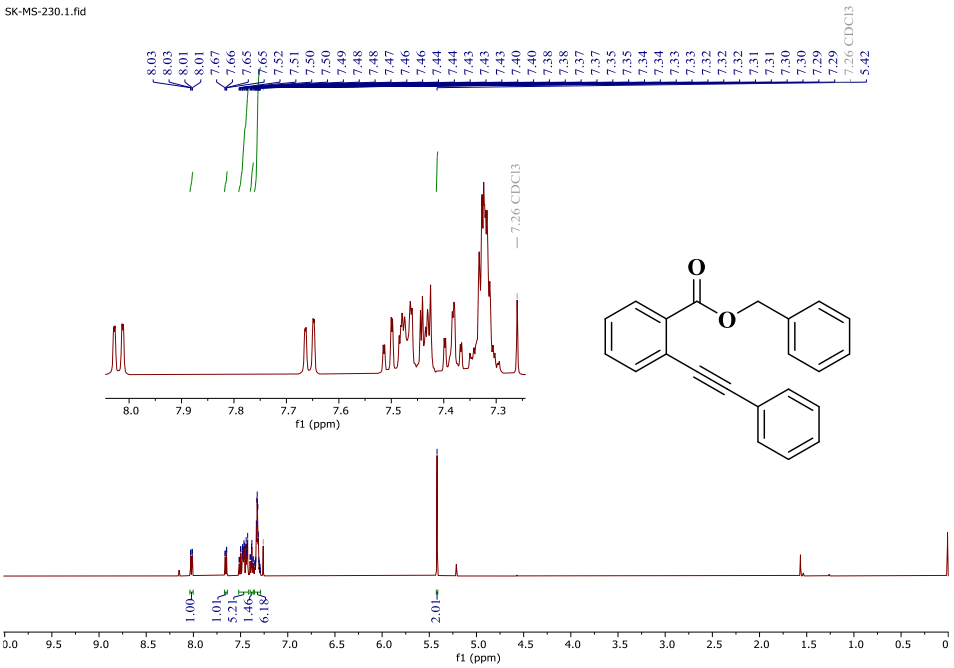

Figure 41: ^{1}H NMR spectrum of 1q

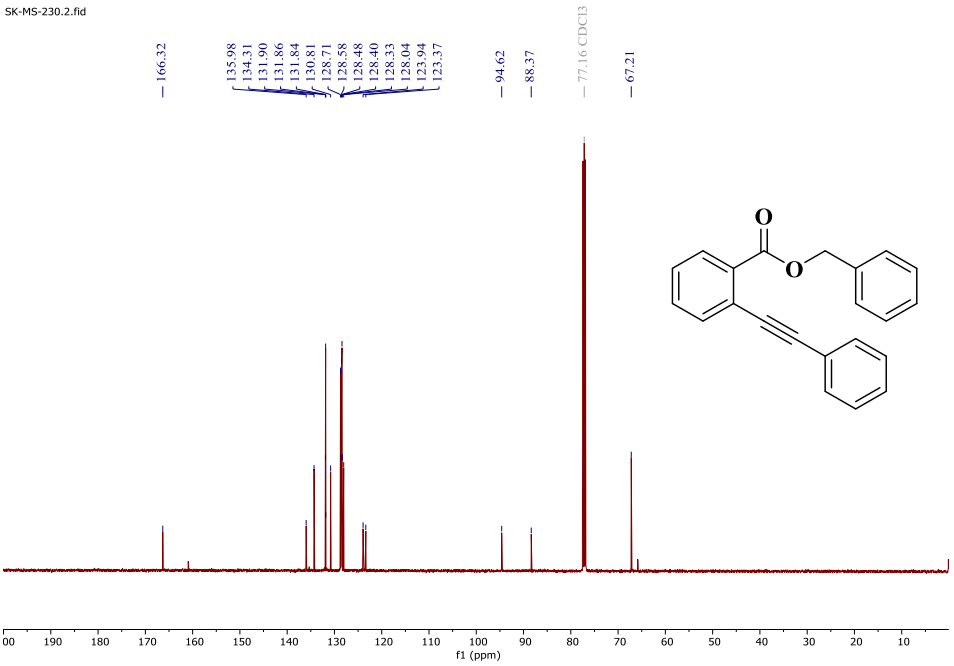

Figure 42: ^{13}C NMR spectrum of 1q

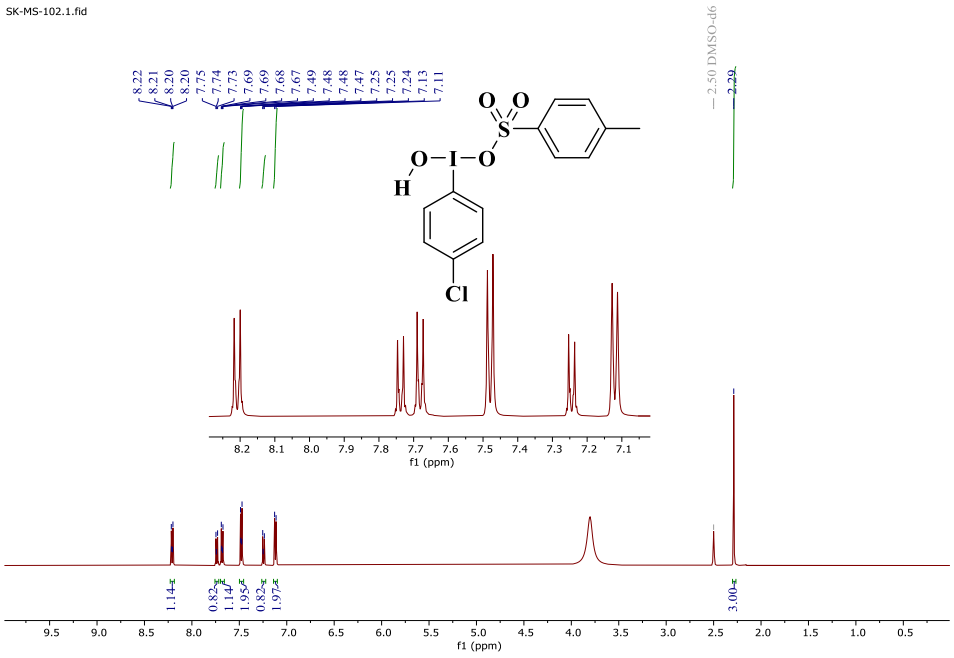

Figure 43: [1]H NMR spectrum of HTIB-1

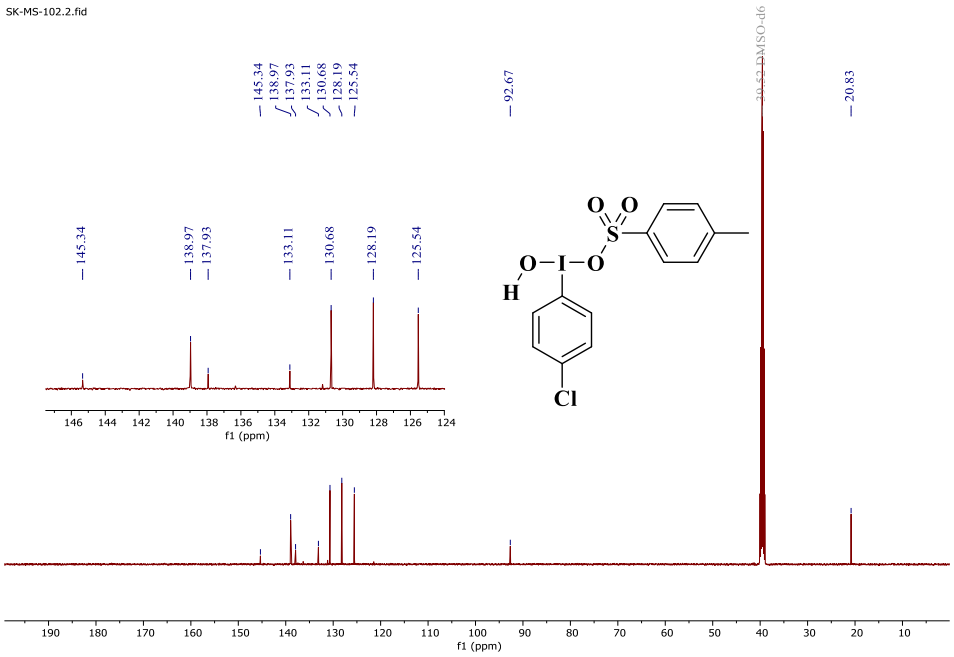

Figure 44: [13]C NMR spectrum of HTIB-1

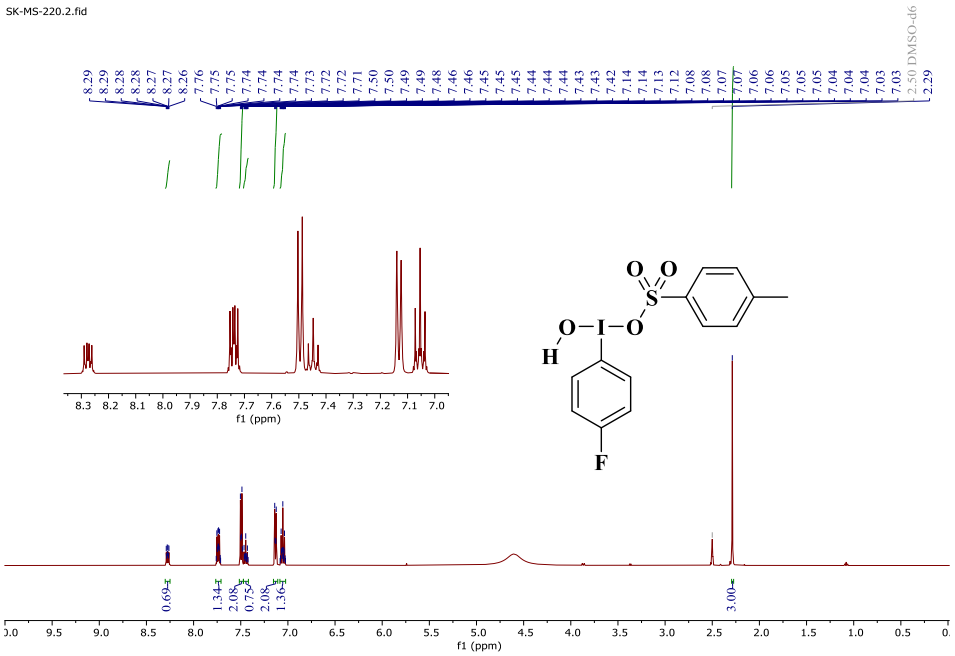

Figure 45: ^{1}H NMR spectrum of HTIB-2

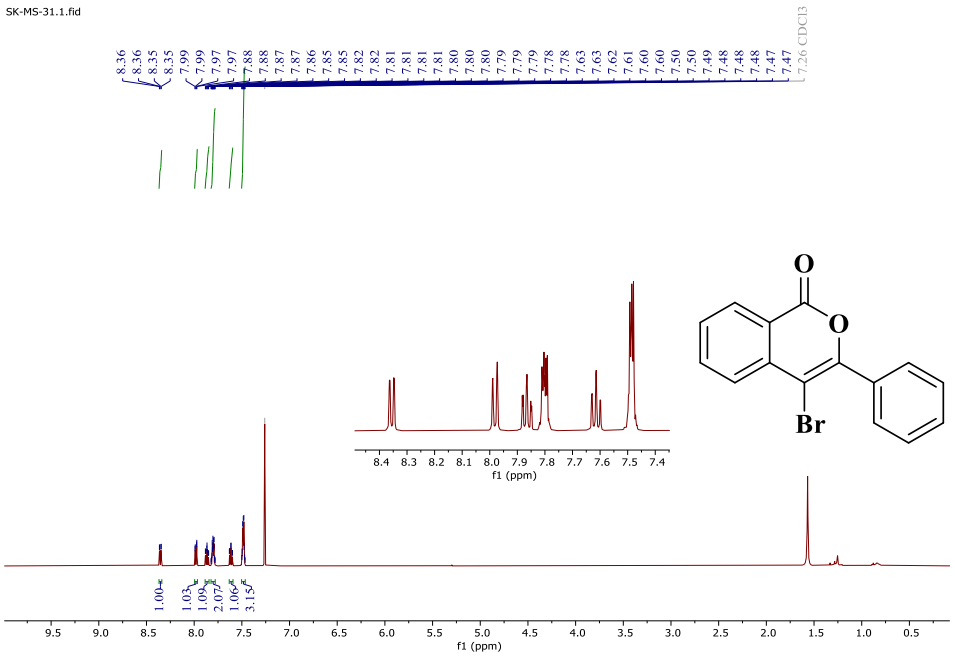

Figure 46: ^{1}H NMR spectrum of 2a

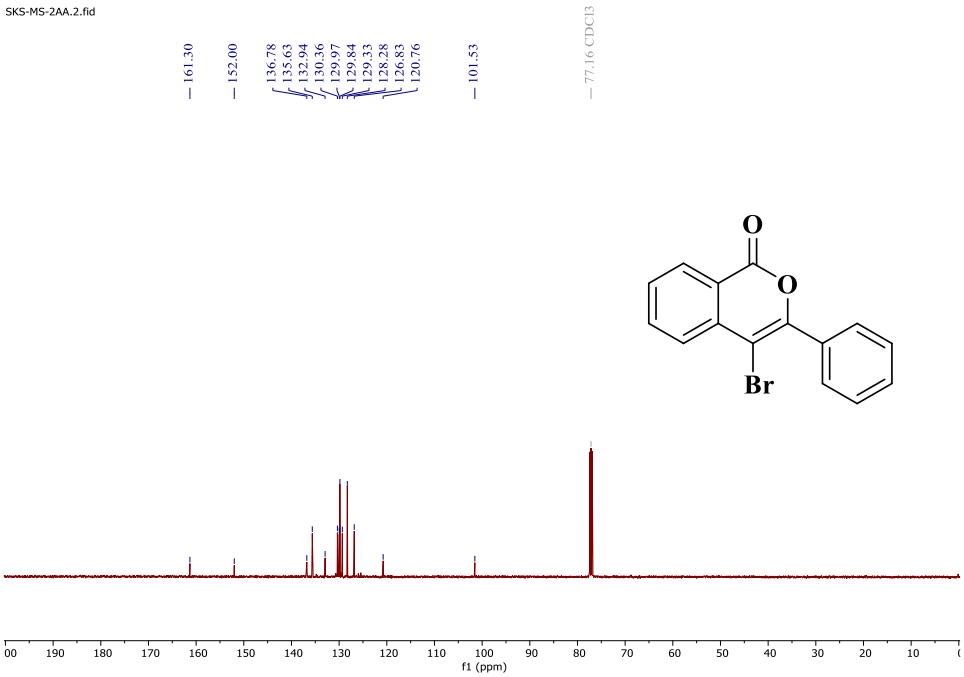

Figure 47: ^{13}C NMR spectrum of 2a

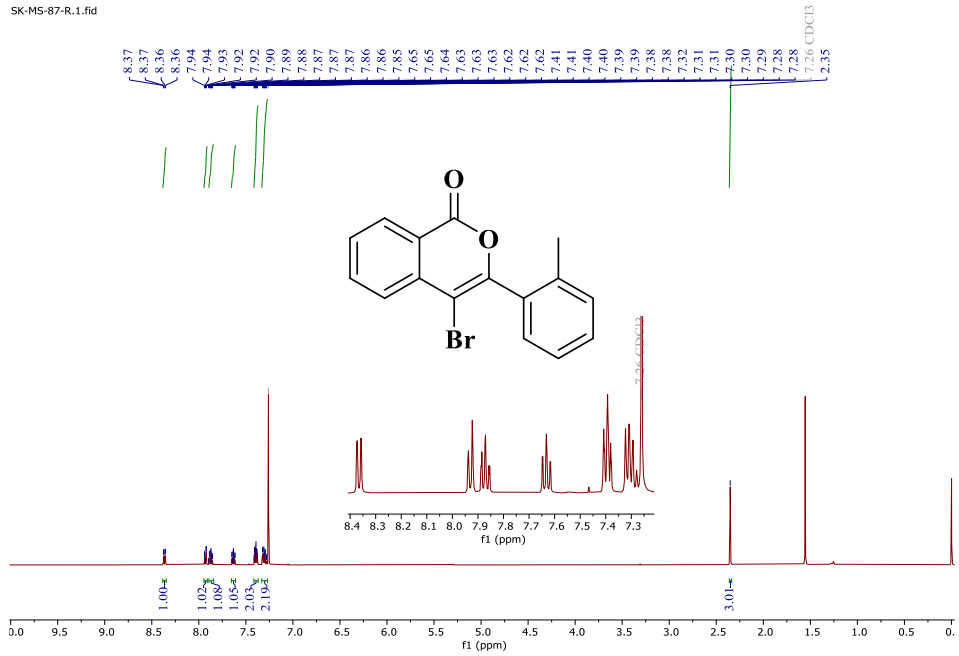

Figure 48: ^{1}H NMR spectrum of 2b

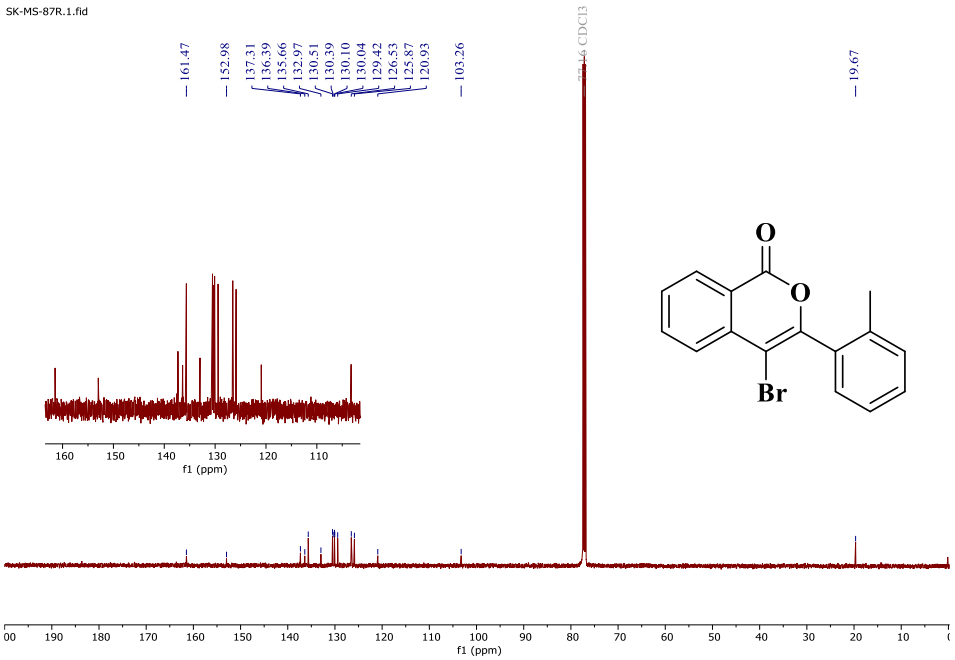

Figure 49: ^{13}C NMR spectrum of 2b

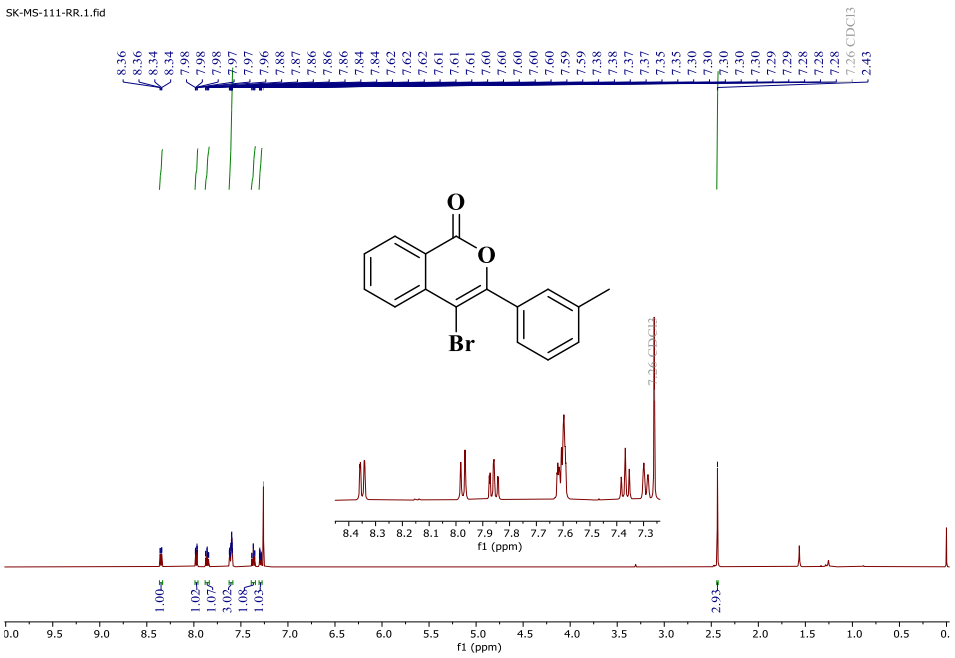

Figure 50: ^{1}H NMR spectrum of 2c

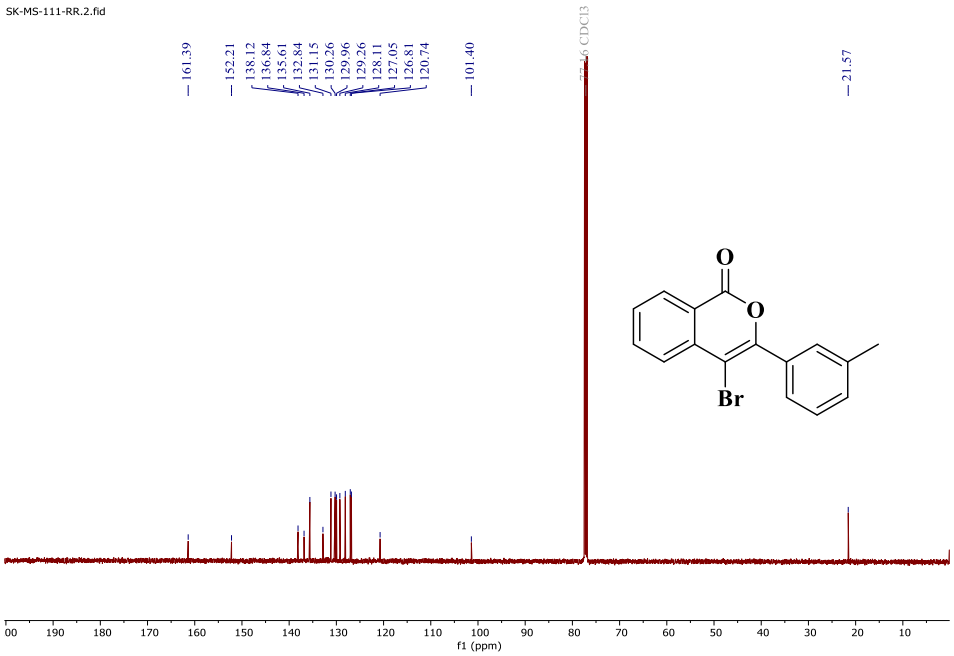

Figure 51: ^{13}C NMR spectrum of 2c

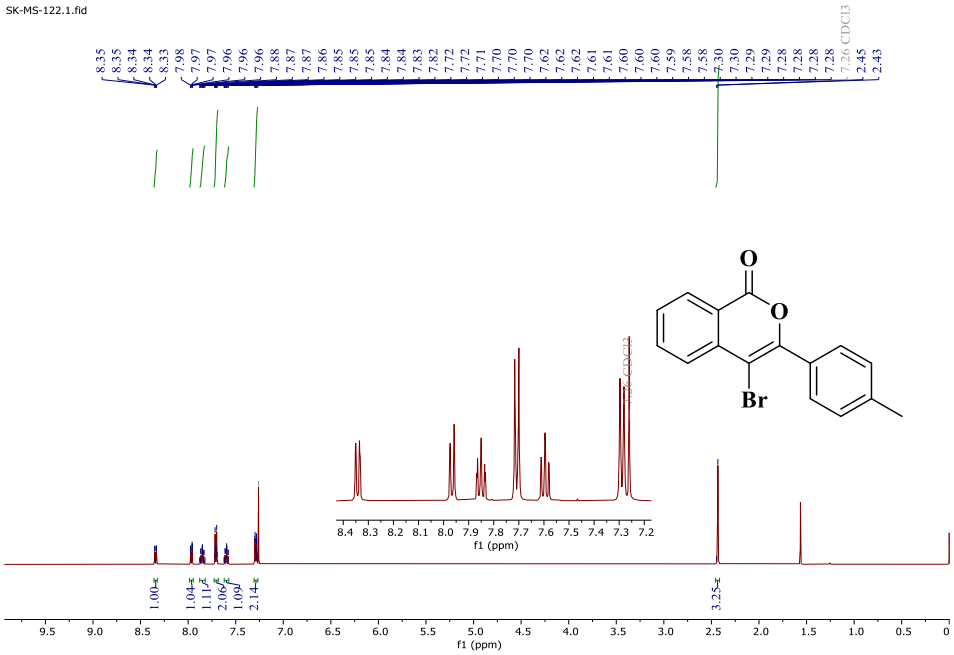

Figure 52: ^{1}H NMR spectrum of 2d

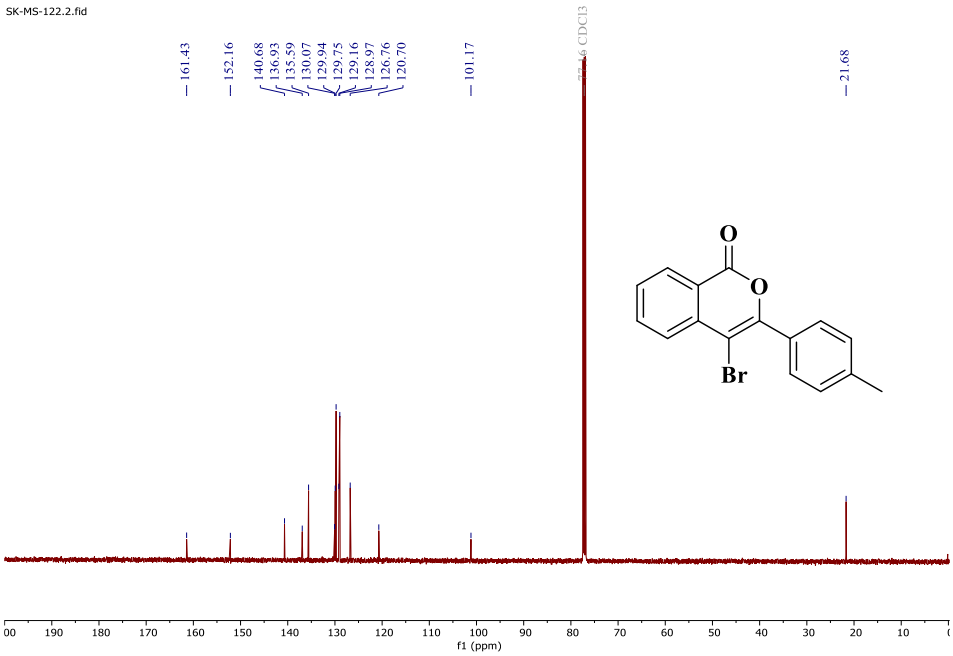

Figure 53: ^{13}C NMR spectrum of 2d

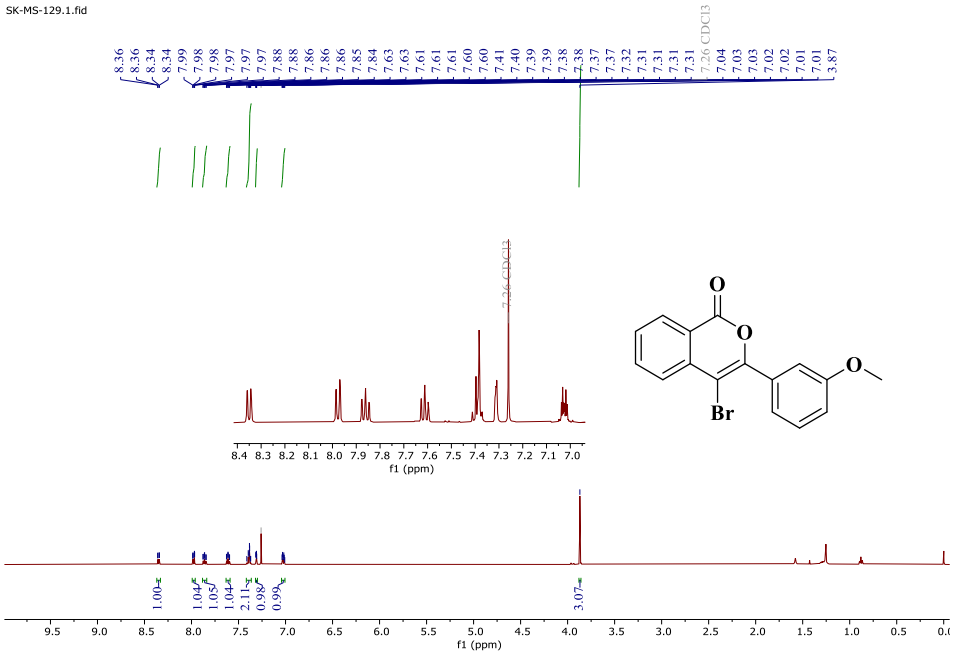

Figure 54: ^{1}H NMR spectrum of 2e

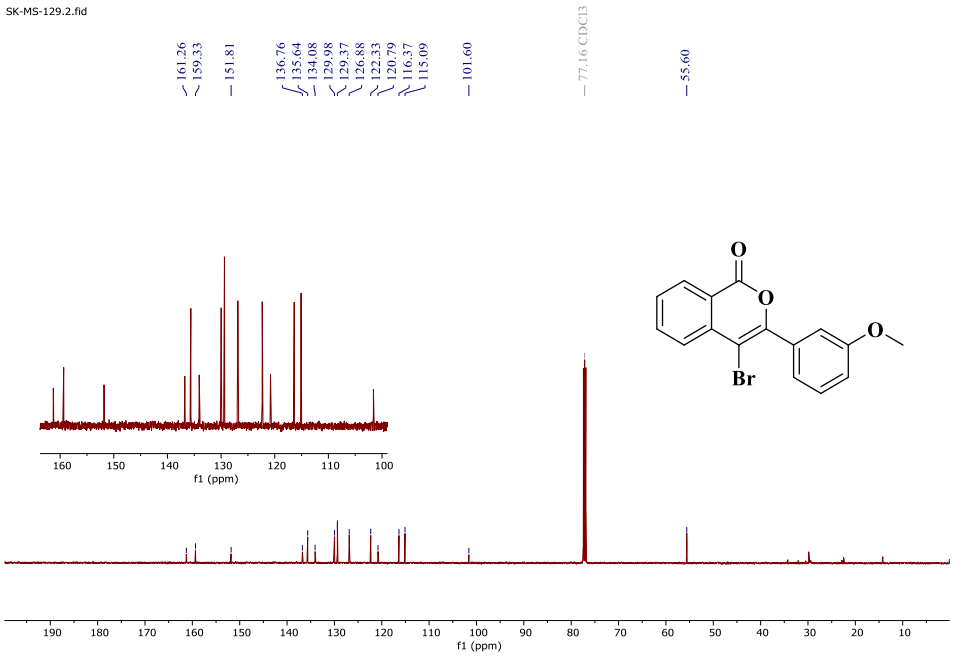

Figure 55: ^{13}C NMR spectrum of 2e

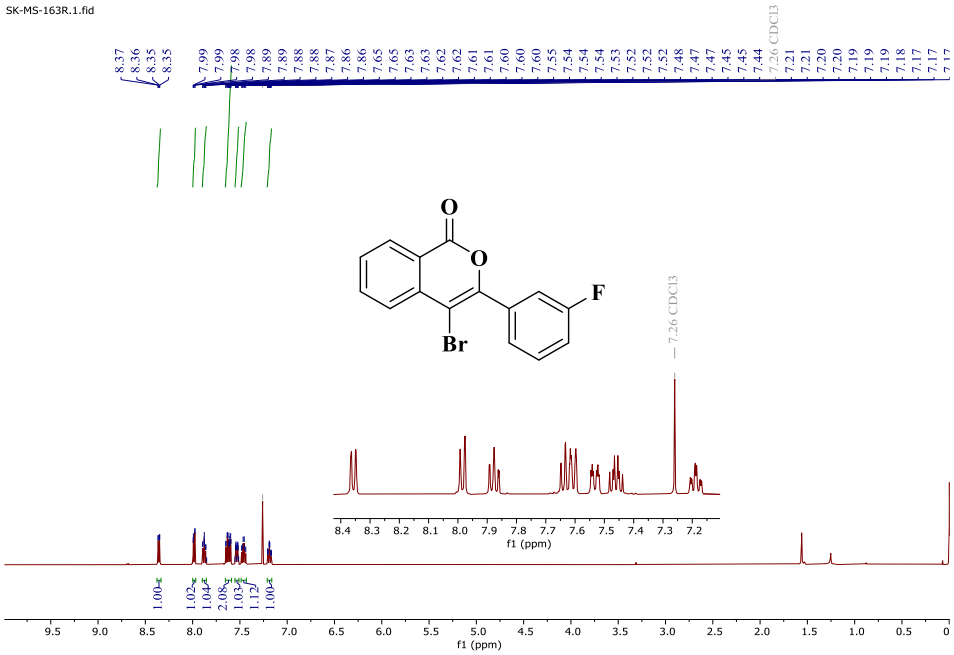

Figure 56: ^{1}H NMR spectrum of 2f

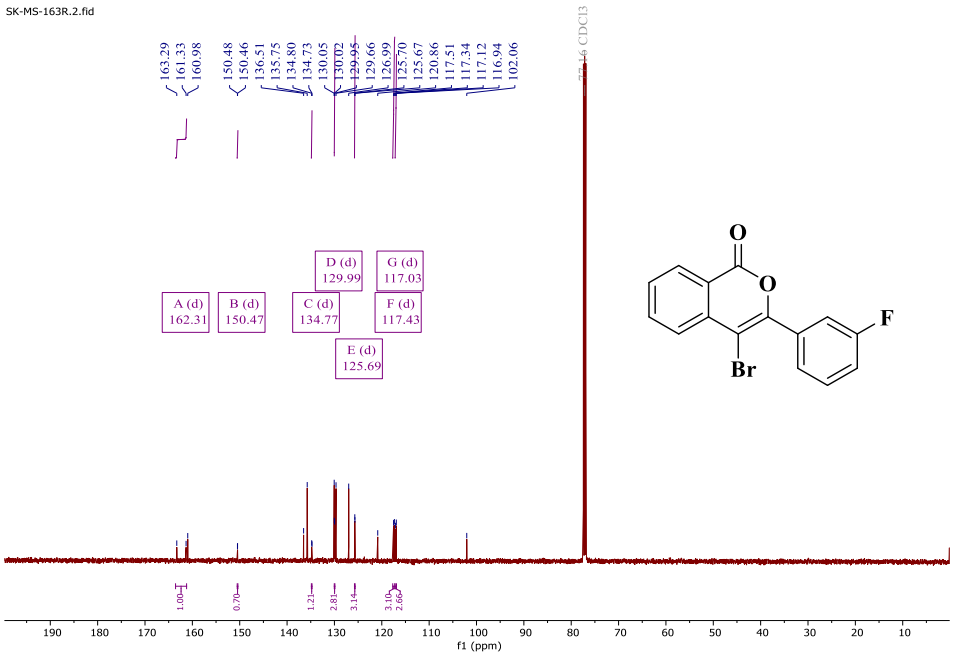

Figure 57: ^{13}C NMR spectrum of 2f

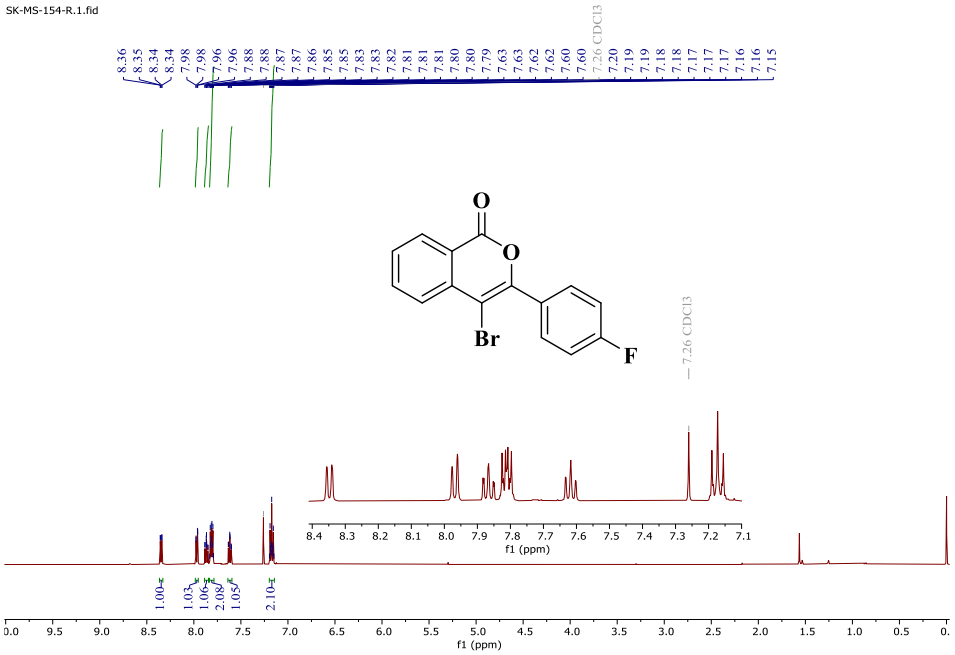

Figure 58: ^{1}H NMR spectrum of 2g

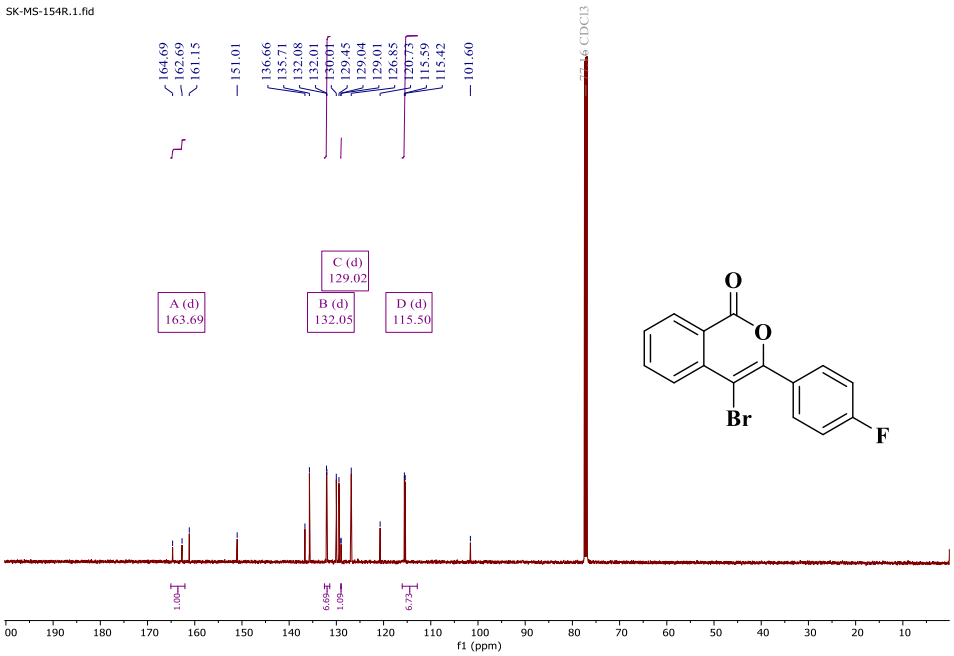

Figure 59: ^{13}C NMR spectrum of 2g

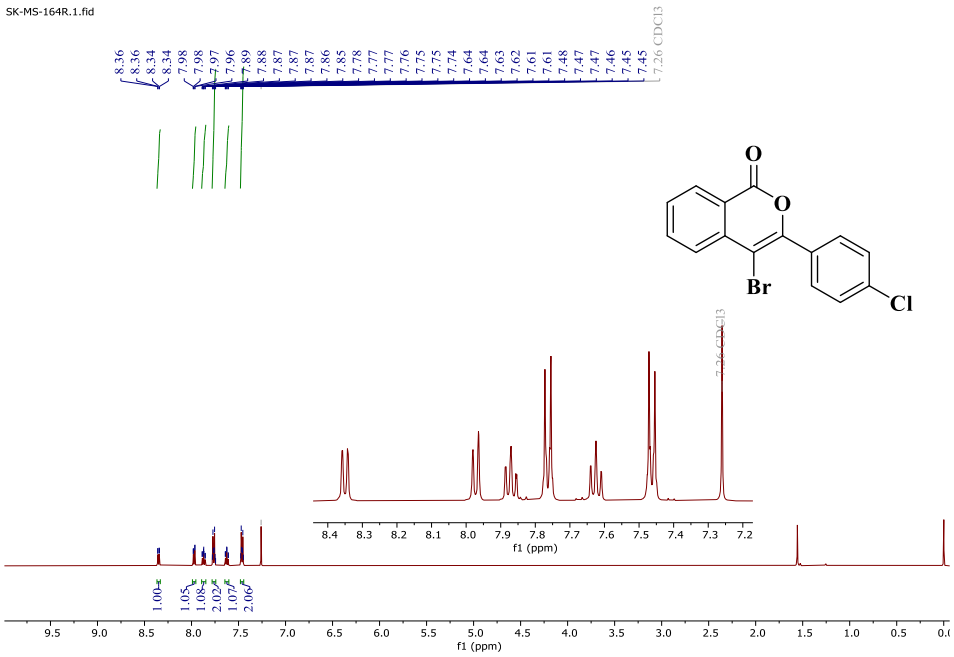

Figure 60: ^{1}H NMR spectrum of 2h

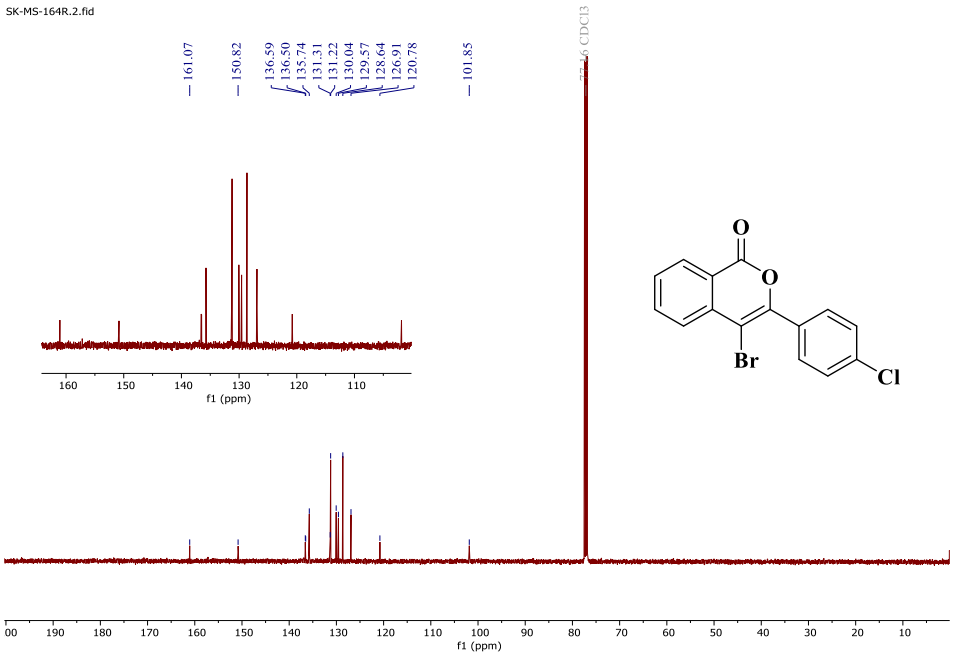

Figure 61: ^{13}C NMR spectrum of 2h

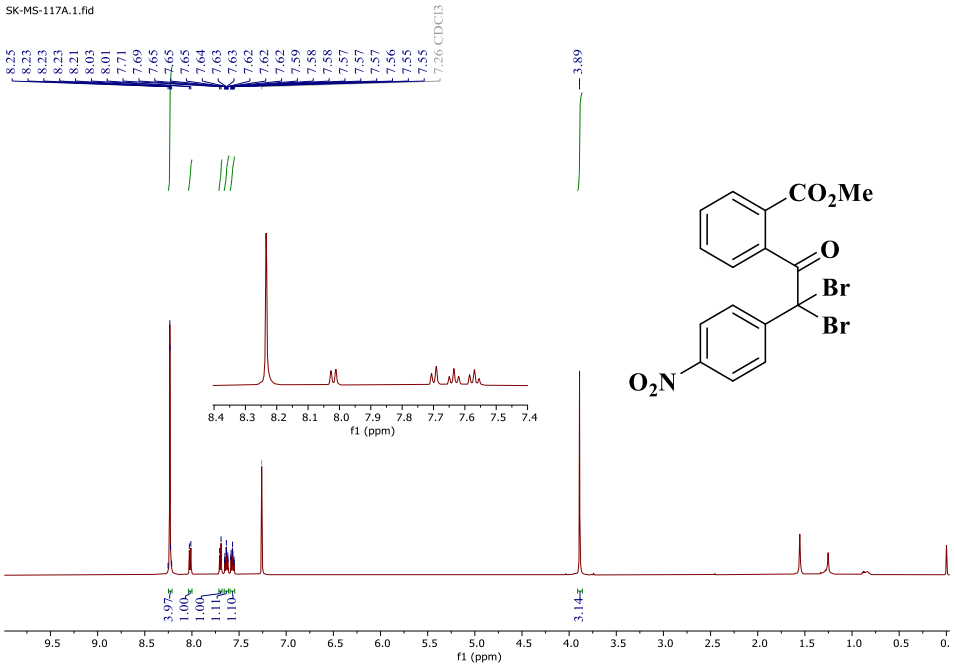

Figure 62: ^{1}H NMR spectrum of 2i'

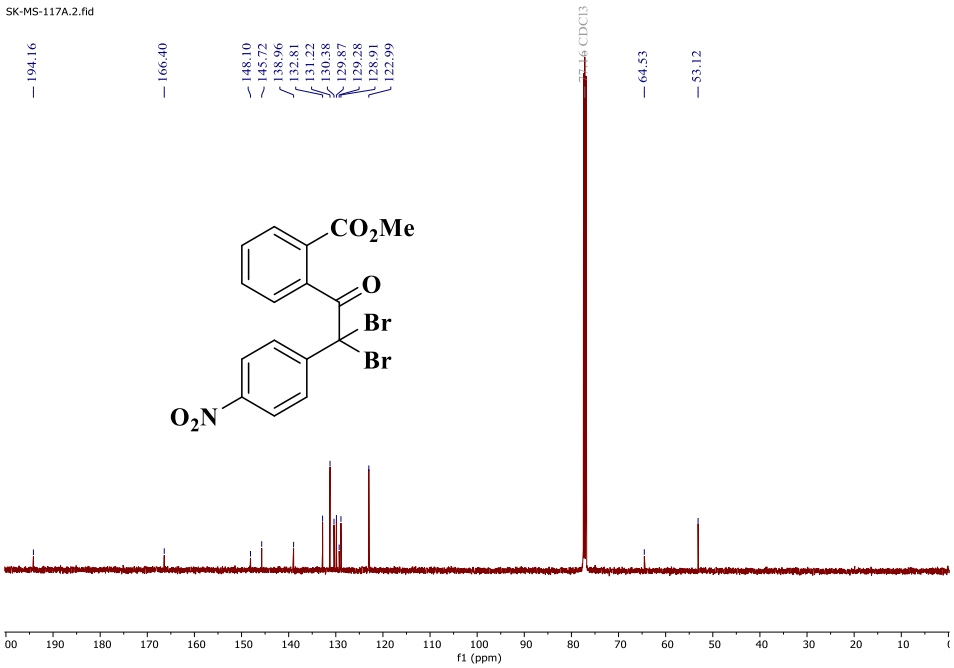

Figure 63: ^{13}C NMR spectrum of 2i'

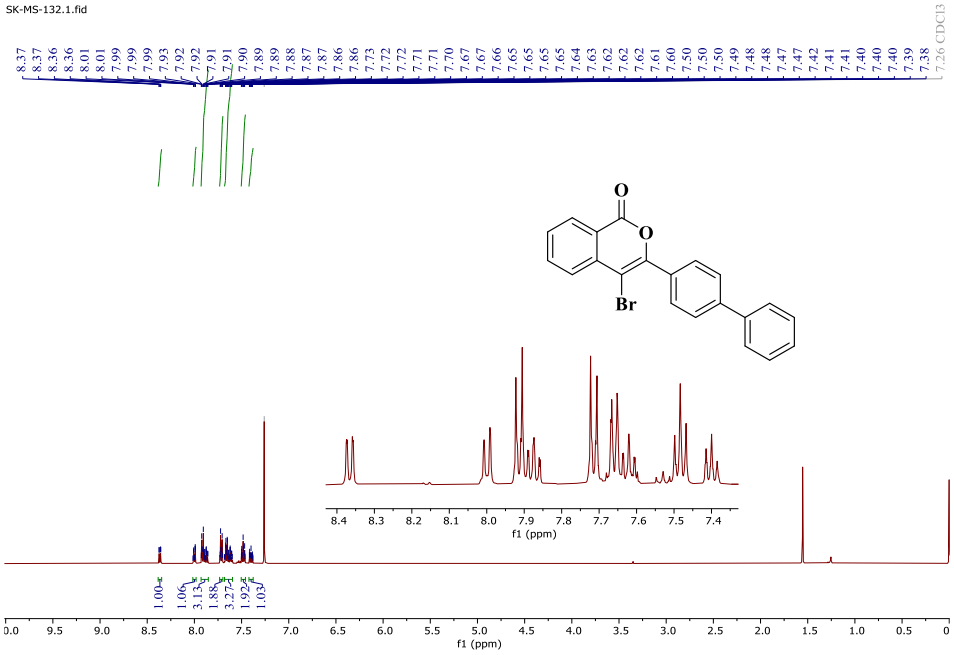

Figure 64: ^{1}H NMR spectrum of 2j

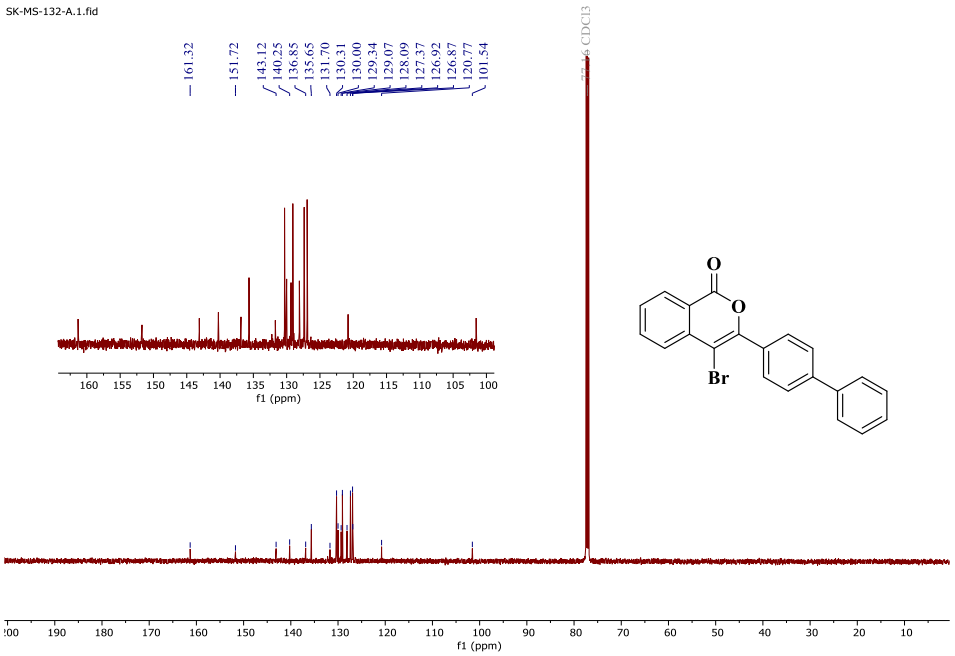

Figure 65: ^{13}C NMR spectrum of 2j

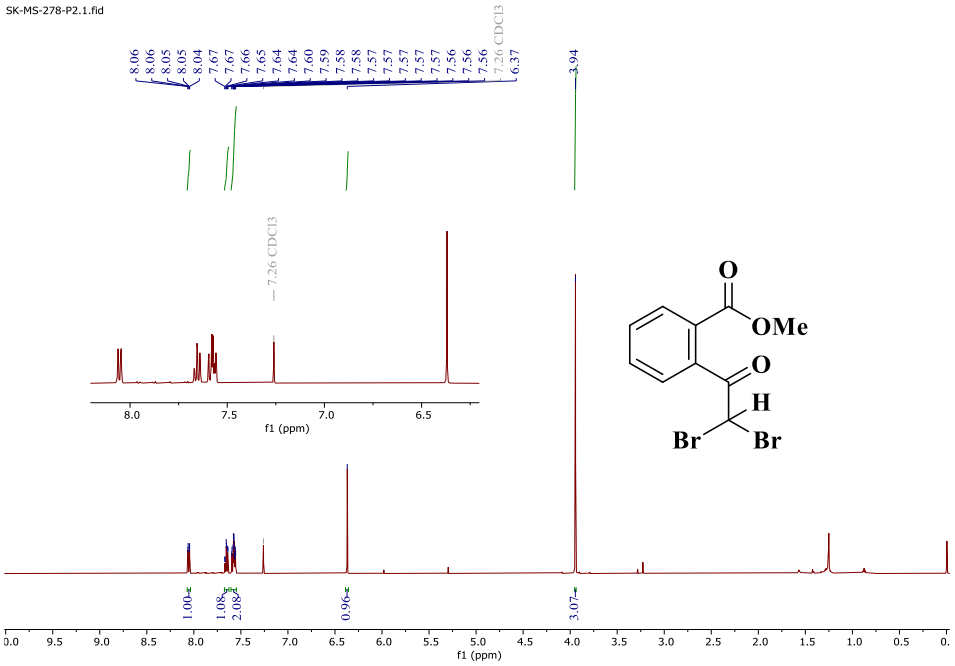

Figure 66: ^{1}H NMR spectrum of 2l'

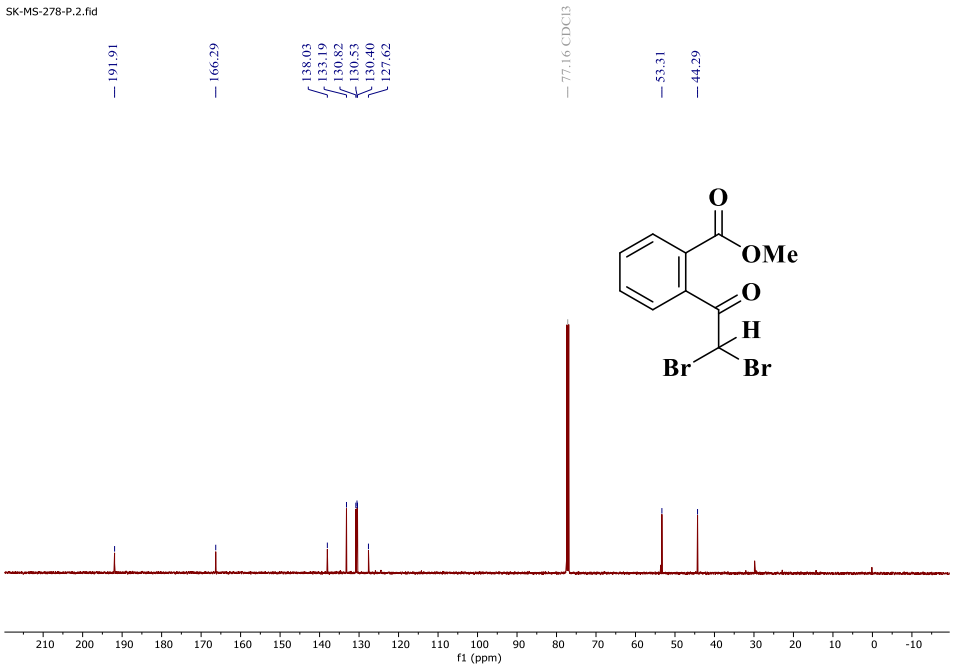

Figure 67: ^{13}C NMR spectrum of 2l'

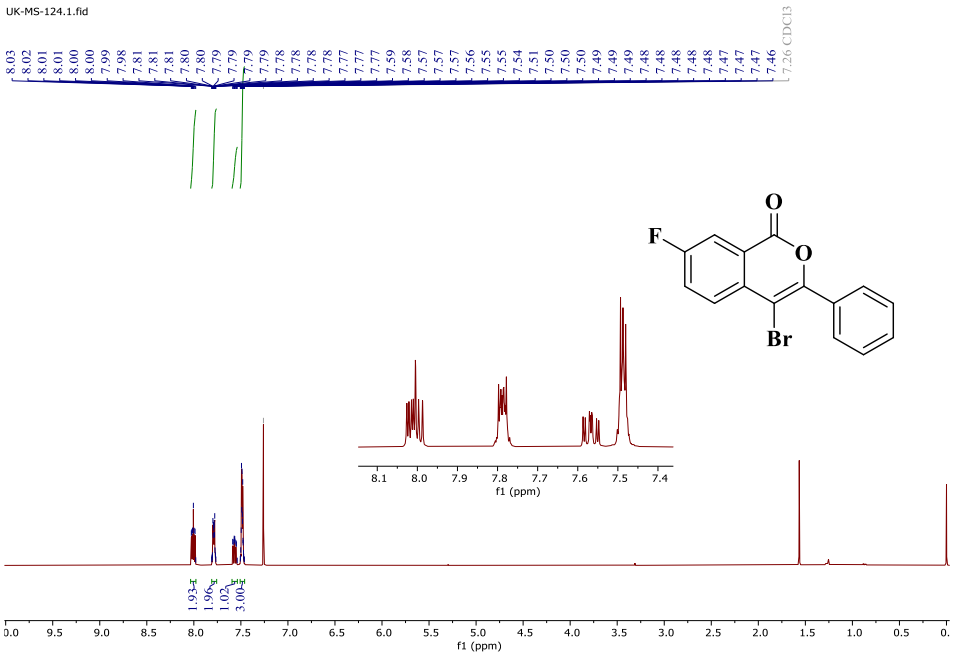

Figure 68: ^{1}H NMR spectrum of 2m

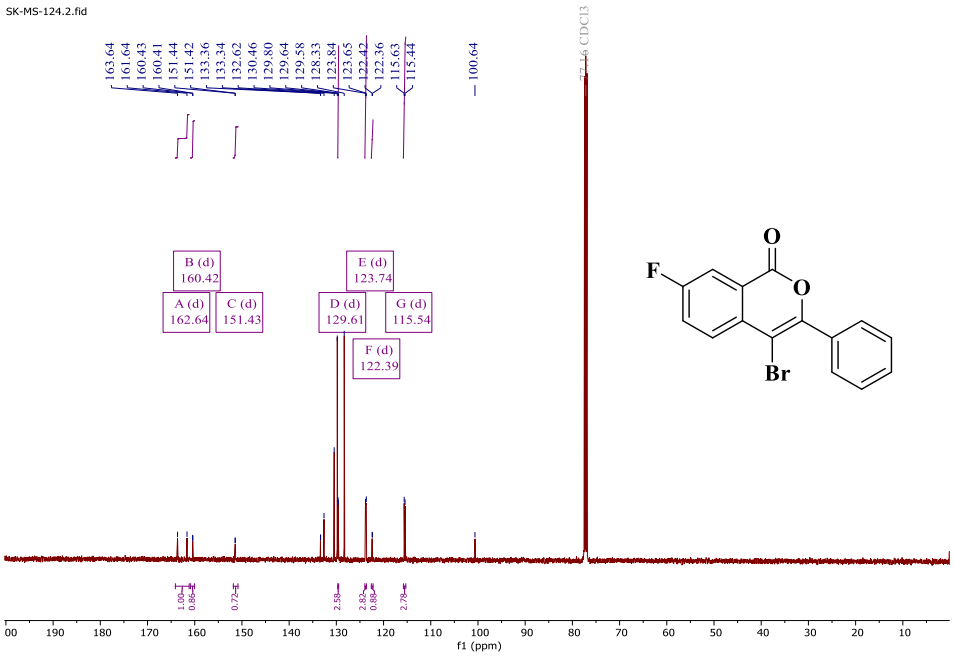

Figure 69: ^{13}C NMR spectrum of 2m

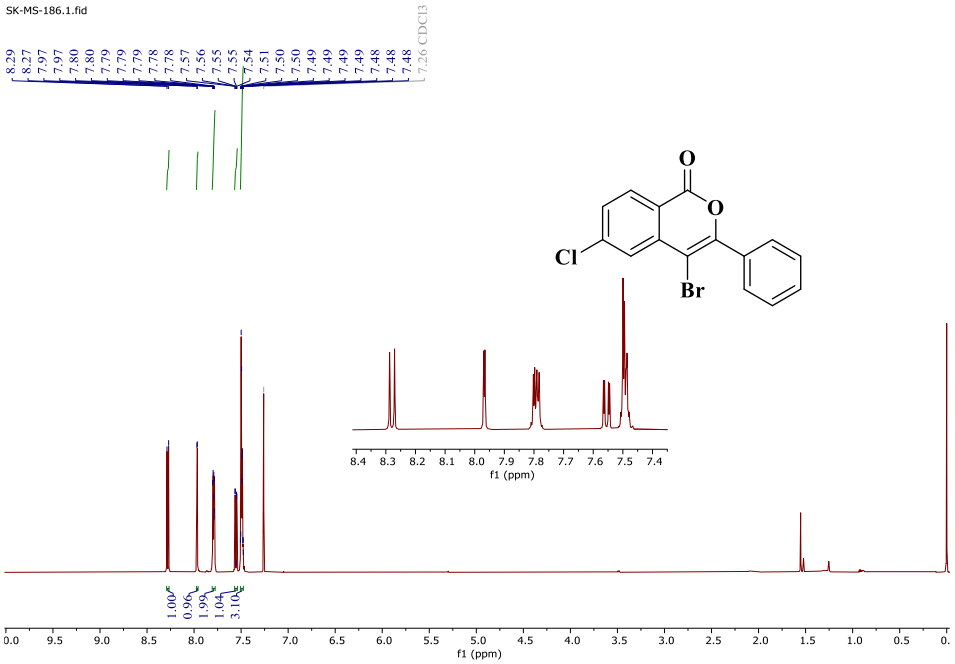

Figure 70: ^{1}H NMR spectrum of 2n

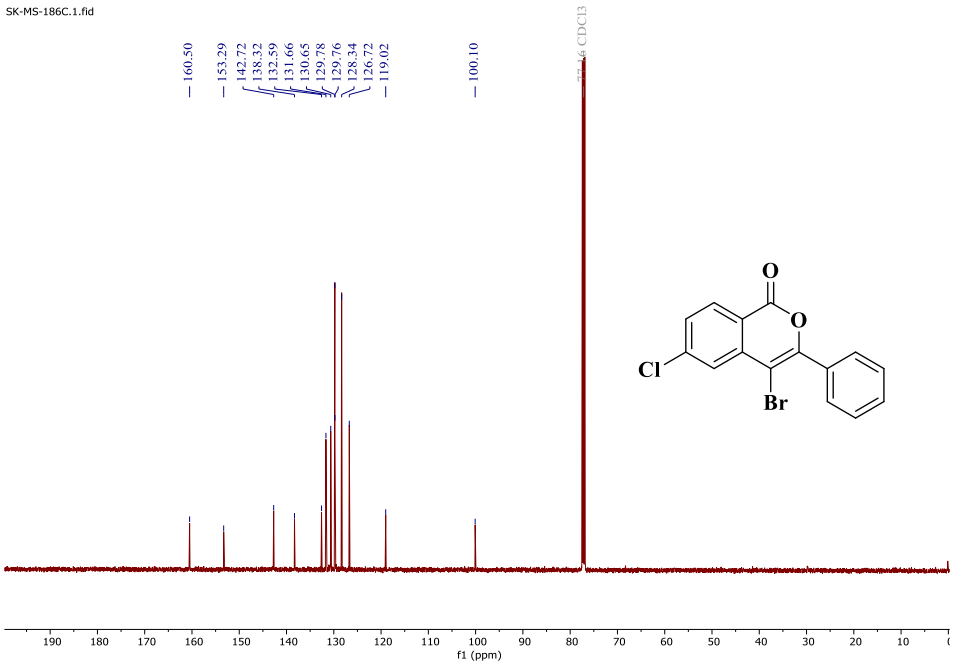

Figure 71: ^{13}C NMR spectrum of 2n

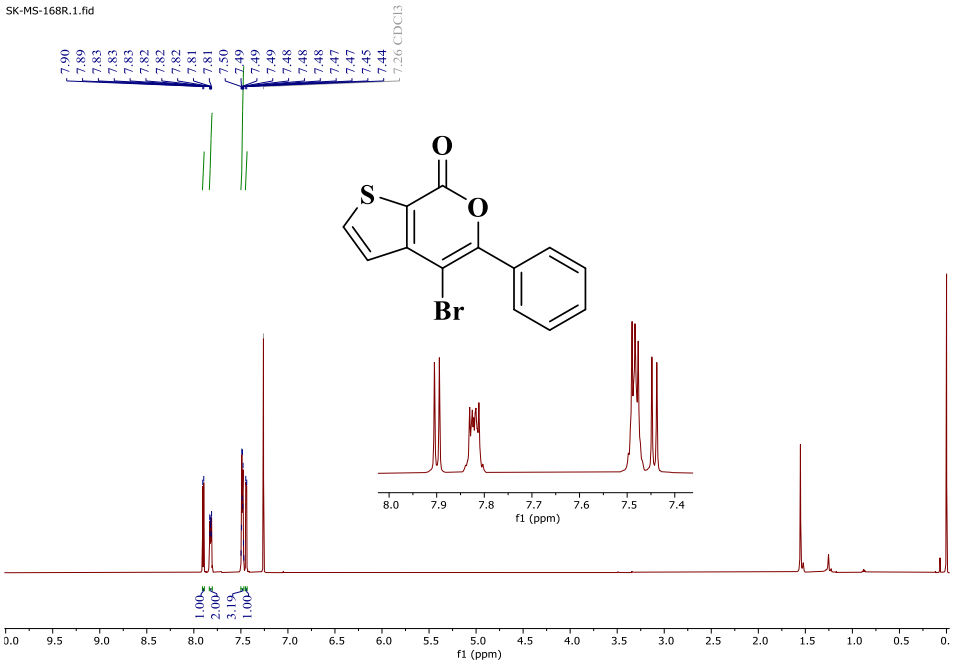

Figure 72: ^{1}H NMR spectrum of 2o

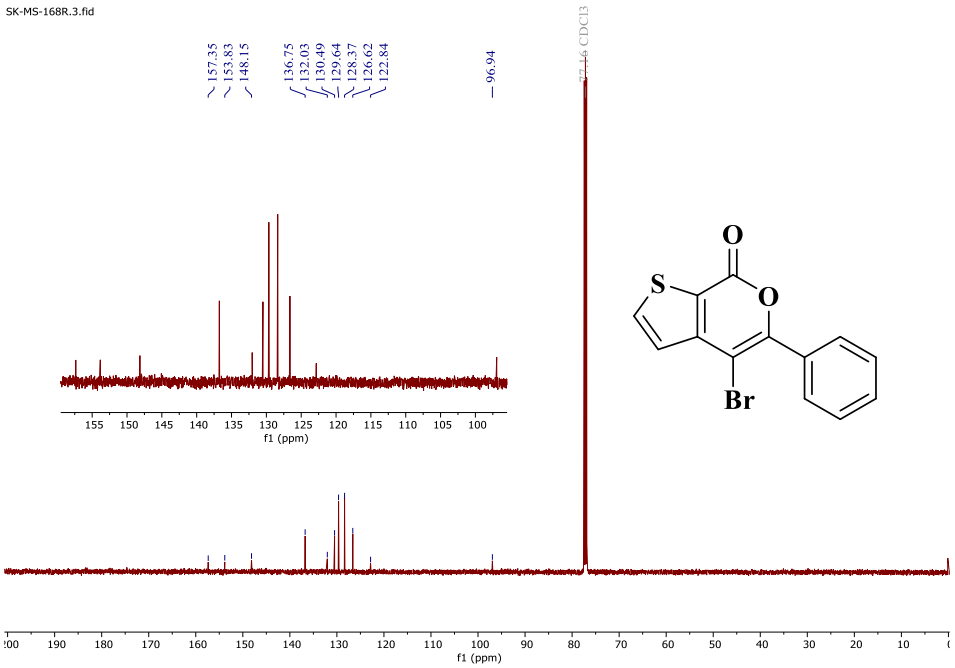

Figure 73: ^{13}C NMR spectrum of 2o

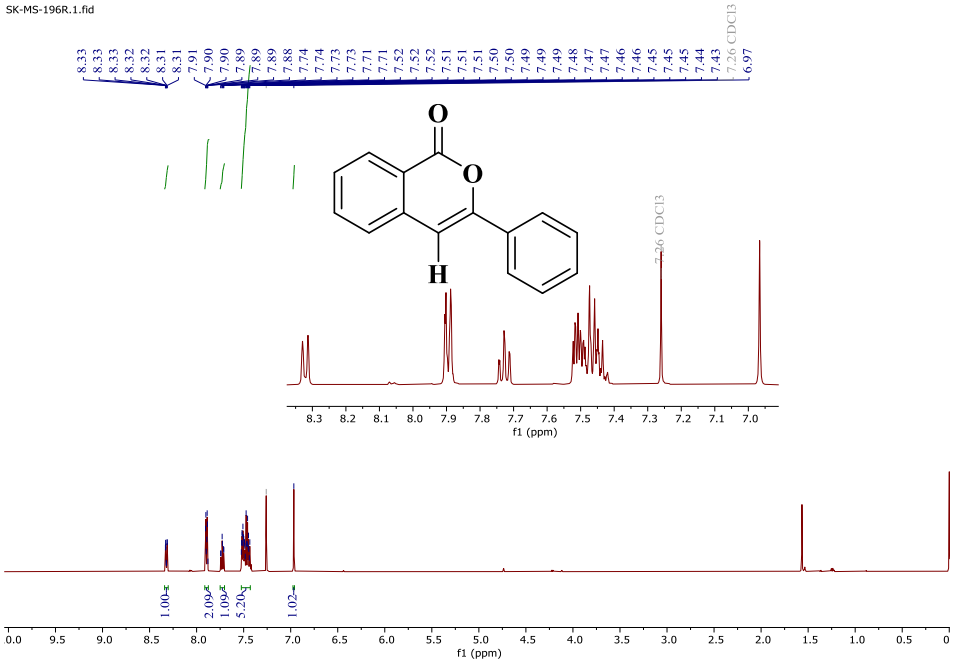

Figure 74: ^{1}H NMR spectrum of 2aa

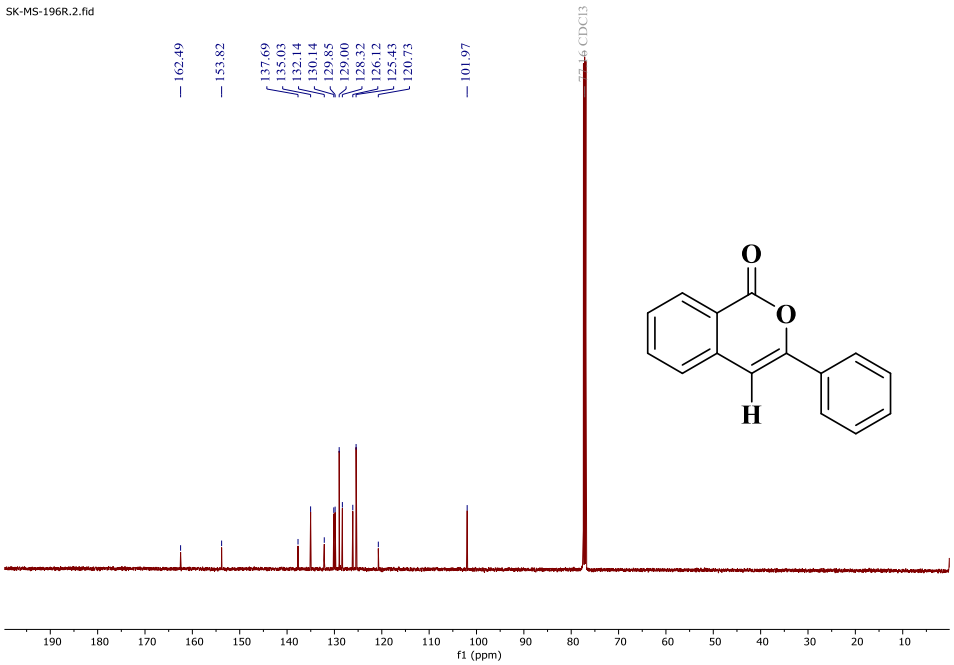

Figure 75: ^{13}C NMR spectrum of 2aa

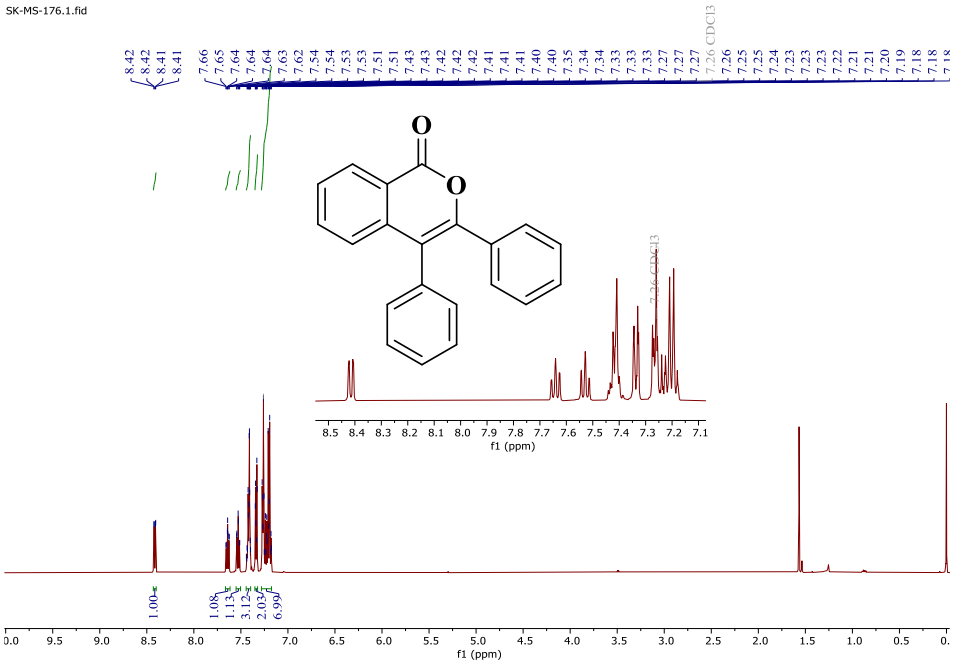

Figure 76: ^{1}H NMR spectrum of 2ab

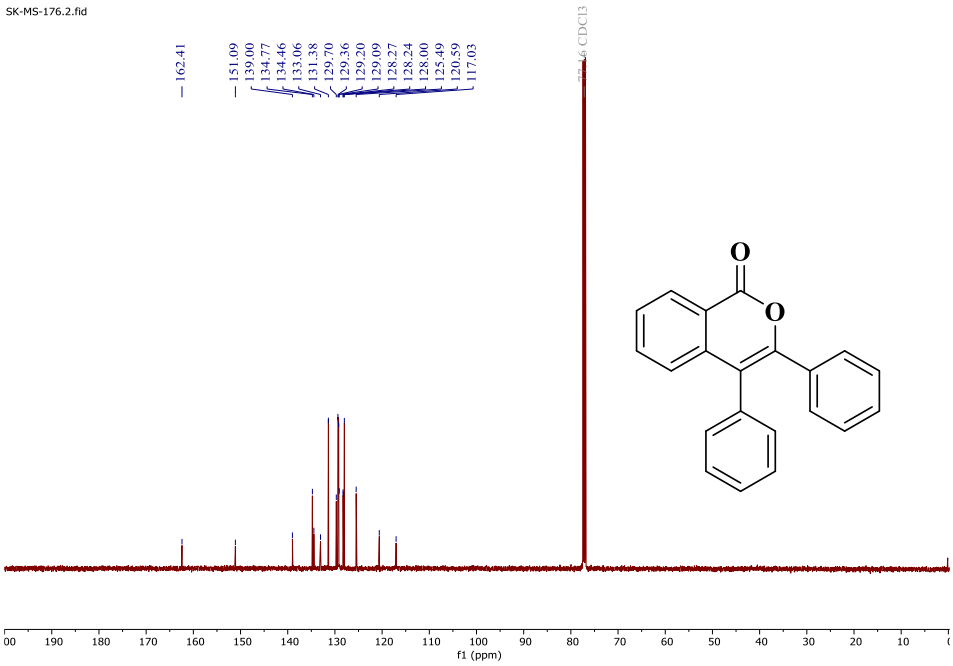

Figure 77: ^{13}C NMR spectrum of 2ab

V.II. HRMS Spectra

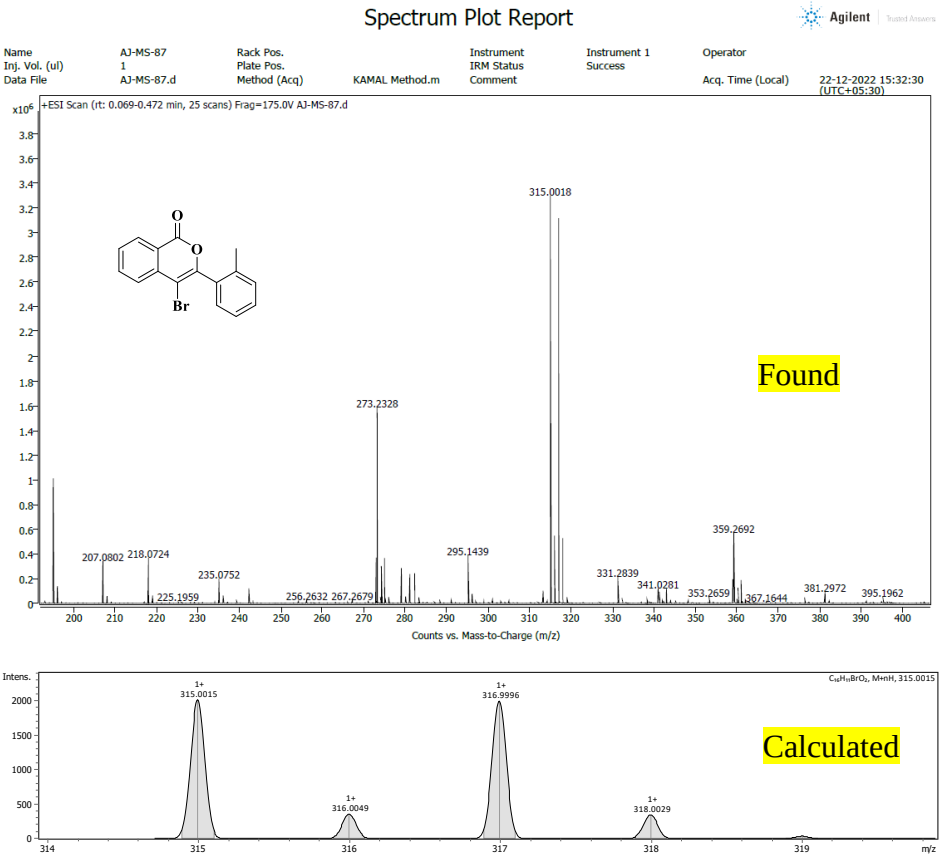

Figure 78: HRMS spectrum of 2b

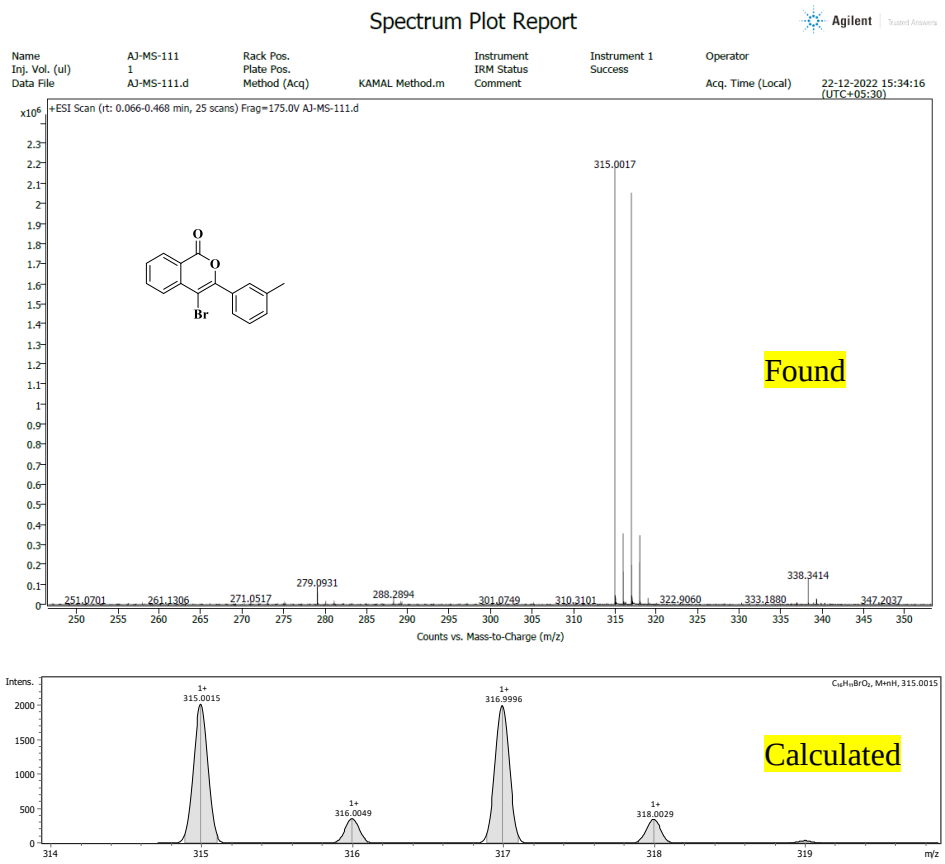

Figure 79: HRMS spectrum of 2c

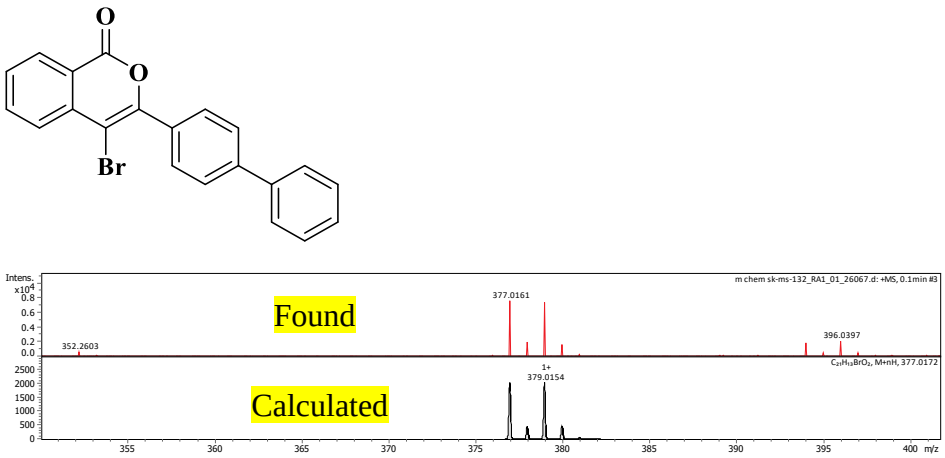

Figure 80: HRMS spectrum of 2j

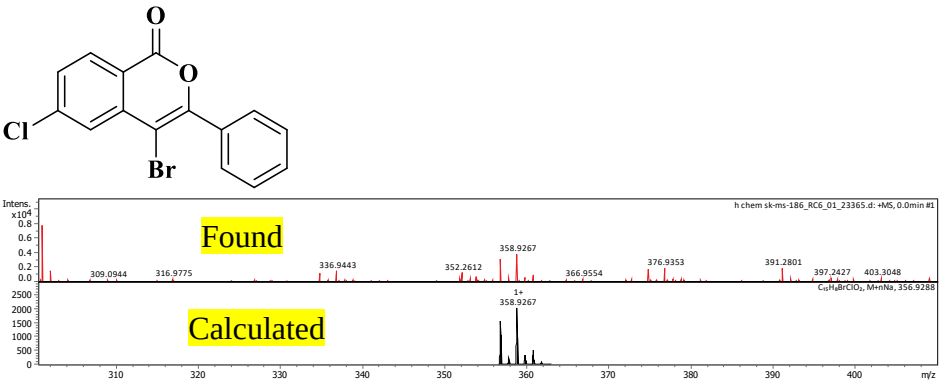

Figure 81: HRMS spectrum of 2n

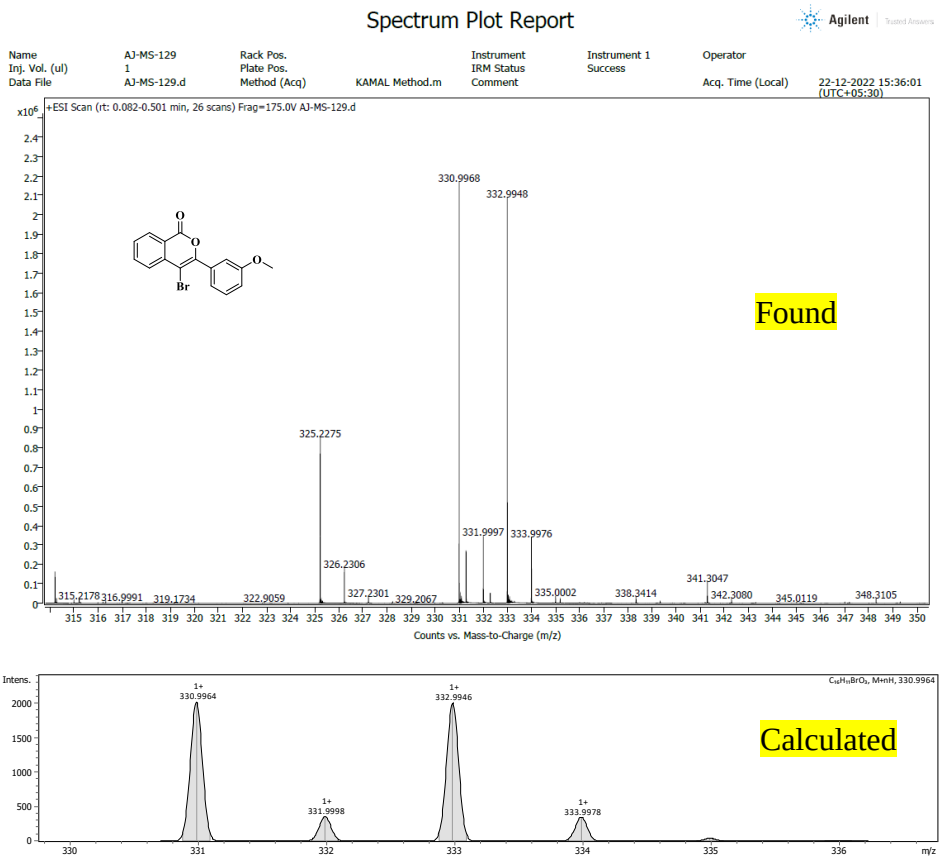

Figure 82: HRMS spectrum of 2e

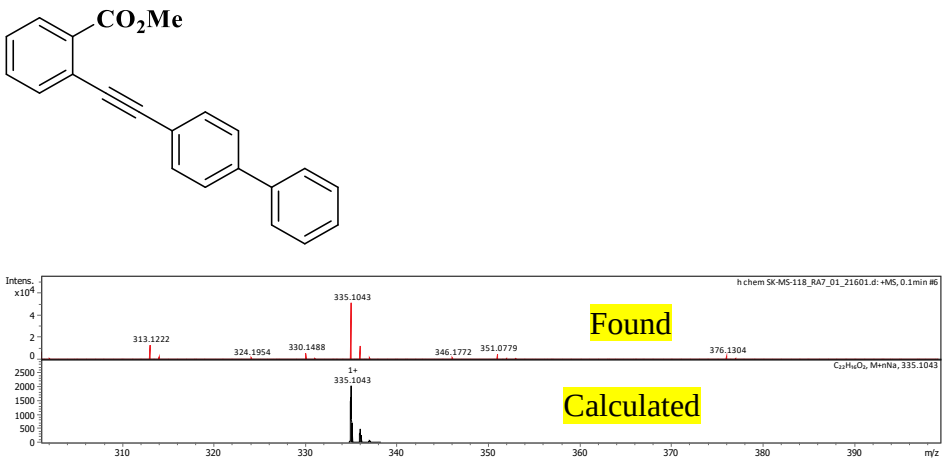

Figure 83: HRMS spectrum of 1j

-The End-