Hypervalent Iodine Reagent Mediated Halocyclization of *N*-Arylpropynamides

M.Sc. Thesis

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DEPARTMENT OF CHEMISTRY

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Hypervalent Iodine Reagent Mediated Halocyclization of *N*-Arylpropynamides

A

THESIS

Submitted in partial fulfilment of the

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of

Master of Science

By

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INDIAN INSTITUTE OF TECHNOLOGY INDORE

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CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled **Hypervalent Iodine Reagent Mediated Halocyclization of *N*-Arylpropynamides**the partial fulfilment 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 own work carried out during the time period from August 2021 of joining the M.Sc. program to May 2022 of M.Sc. Thesis submission under the supervision of Dr. Selvakumar Sermadurai, IIT Indore. The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other institute.

P.Jangir 25/05/22

Pankaj Jangir

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

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DEDICATION

Every challenging work needs self-endeavour and the blessings of elders.

My modest effort I dedicate to my concern and supporting

FAMILY

Whose motivation, love, and encouragement

make me able to complete my work efficiently.

Along with all inspiring and respected

TEACHERS

ABSTRACT

Researchers are currently interested in the synthesis of Heterocyclic spiro compound, because of this biological activity. The main aim of thesis is to develop hypervalent iodine reagent mediated oxidative hallocyclization of 4-para unsubstituted n-aryl propynamides. Our method is more effective than other method because all product reaction is setup on room temperature without using Heat or light. This method is applicable both substituted and unsubstituted n-aryl propynamides. All the synthesized molecules are characterized by using different analytical technique such as ^{1}H, ^{13}C NMR and Sc-XRD.

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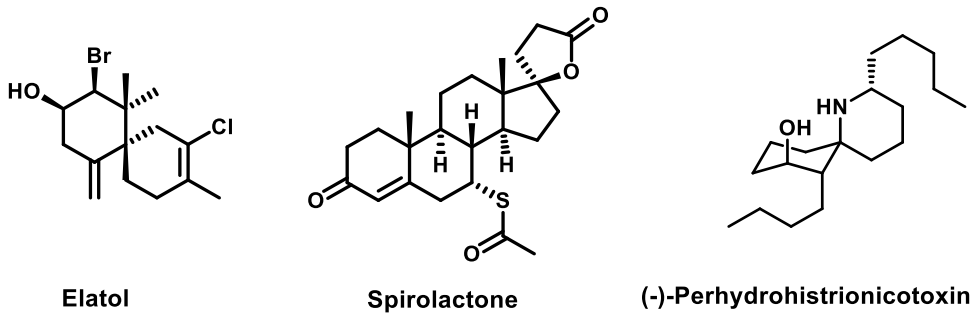
2. ACRONYMS

Ar	Aryl
OAc	Acetate
DCC	*N*, *N*-dicyclohexylcarbodiimide
DCE	Dichloroethane
DMAP	4-Dimethylaminopyridine
Equiv	Equivalent
ppm	parts per million
NBS	*N*-Bromosuccinimide
PIDA	Phenyliodine(III)diacetate
PIFA	Phenyliodinebis(trifluoroacetate)
TBAB	Tetra-*N*-butylammonium bromide
TLC	Thin-layer chromatography
UV	Ultraviolet

3. INTRODUCTION

Heterocyclic compounds with three, four, five, or six-membered ring containing nitrogen (*N*), oxygen (*O*), or sulphur (*S*) atoms as heteroatoms in their structure are ubiquitous in several natural products. Among them five-or six-membered heterocycles are more prevalent in pharmaceuticals. Many biological active compounds like nucleic acids, amino acids and proteins are containing heterocyclic compounds in their structure. Other naturally occurring heterocyclic compounds are pigments, antibiotics, alkaloids and vitamins. Spiro compounds are the organic compound that has twisted structure of two or more rings, in which two or three rings are linked *via* one common atom. In 1900, Von Baeyer synthesized the first Spiro compound designated as a bicyclic hydrocarbon connected *via* a single carbon. Because of the tetrahedral nature of spiro carbon, the ring planes are approximately perpendicular.Spiro molecules are of current interest in organic synthesis due to their fascinating conformational features and their structural inferences on biological systems.[1] The retention of neurotoxic properties of perhydrohistrionicotoxin, a correspondent of a natural product is a clear indication of the role of spiro carbon in navigation of biological activity.



Elatol Spirolactone (-)-Perhydrohistrionicotoxin

Figure 1: Examples of spirocyclic compounds.

Spiro compound are of two types carbocyclic and heterocyclic, carbocyclic spiro compounds arebicyclic ring structures that have two fully carbocyclic rings linked through just one carbon atom and heterocyclic spiro compound are those which have spiro atom or any other should be a heteroatom. Some poly spiro compounds are also present in nature which have two or more spiroatoms making up three or more rings.

N-spiro heterocyclic compounds are spiro compound containing *N* as heteroatom in their structure. *N*-spiro heterocyclic compounds are present in many natural products and contained several biological activities.[2] Theconformational features of central spiro carbon of *N*-spiro heterocycles place crucial role in their biological activities. Primary *N*-containing spirocyclic compounds are present in several biologically active molecules, such as

strychnos, amaryllidaceae, erythrina and aspidosperma families which have biological activities like CNS activity, neuromuscular blocking, sedative and hypnotic etc. (Figure 2). Because of wide biological activities of *N*-spiro heterocyclic, the synthesis of *N*-spiro heterocyclic compound and their derivatives have attractedsynthetic chemists to construct them efficiently. So, we are interested in the synthesis of *N*-Spiro heterocycles via Spirocyclization of *N*-Arylpropynamides.

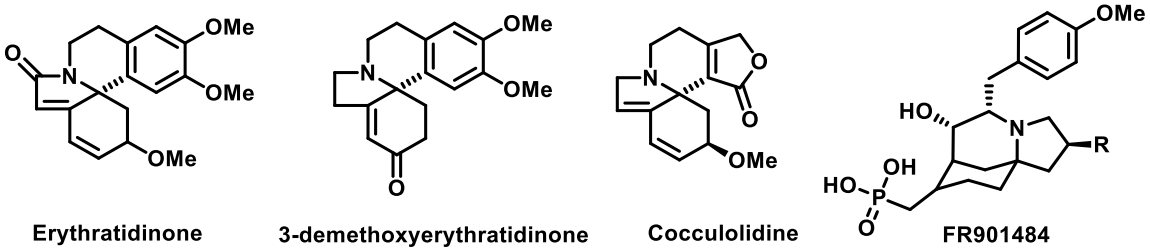
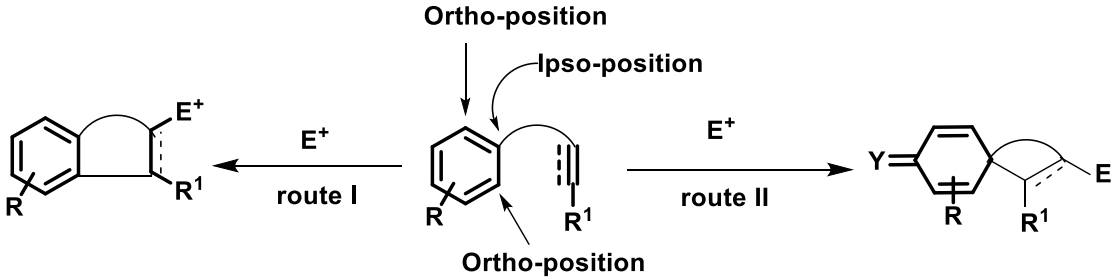


Figure 2: Biologically active *N*- spiro heterocycles.

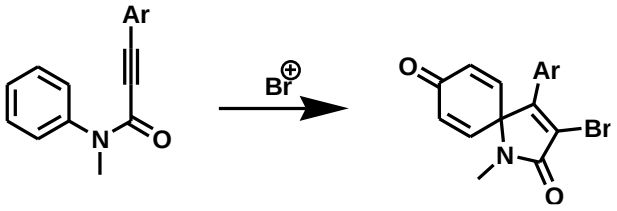
Synthesis of *N* spiro-heterocycles:

Several protocols have been reported for the preparation of spiro heterocycles namely *via* alkylation, rearrangement, transition- metal based intramolecular cyclization and cycloaddition reactions. Among them intramolecular cyclization reactions stand out as a best approach for the construction of spiro heterocycles either *via* radical or ionic condition. Very recently, electrophilic cyclization approach[3,4]got more attention towards the synthesis of important carbo- and heterocycles through formation of a carbon – carbon and a carbon-heteroatom bond in a single reaction.



Scheme 1: Proposed synthesis of *N*-spiro-heterocycles *via* electrophilic intramolecular cyclization approach.

Among above two routes (Scheme 1), in route I substitution takes place at ortho position of the aromatic ring, whereas in route II substitution takes place at *ipso* position of the aromatic ring.Inspired by the above strategy, we proposed to develop a mild and effective method for the construction *N*-spiro heterocyclic scaffold through halocyclization of N-Arylpropynamides (Scheme 2).

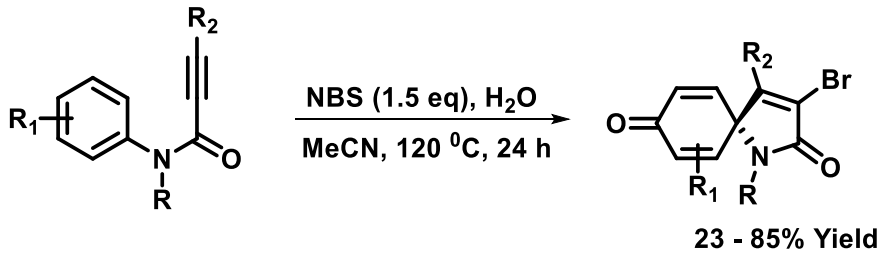


Scheme 2: Synthesis of spirocyclic compound via brominium cation.

4. LITERATURE REVIEW

Halocyclization of *N*-Arylpropynamides

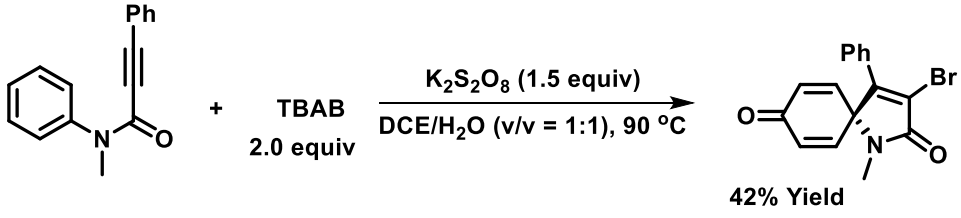
Tang and coworker[5] reported intramolecular *ipso*-bromocyclization of 4-(*p*-unsubstituted-aryl)-1-alkynes using NBS as bromide cation (electrophile) source for the preparation of spiro [4,5]trienones (Scheme 3). This reaction was proposed to proceed *via*electrophilic pathway for the product formation under thermal condition.



Scheme 3: synthesis of *N*-spiro-heterocycles using NBS as electrophile.

Although this reaction was compatible for range of substituents, one of the main drawbacks is that this reaction requires high temperature. To overcome this drawback several other groups developed different protocol for the halocyclization of *N*-Arylpropynamides.

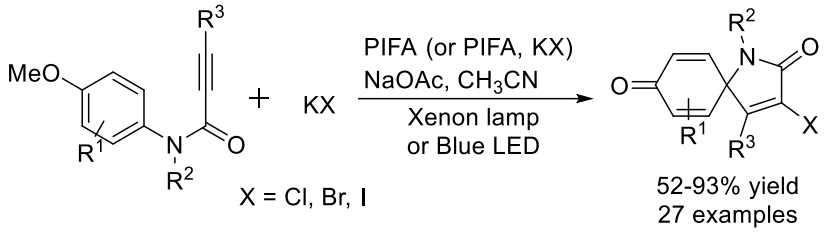
Guanyinsheng and coworkers[6] reported that TBAB can be used as a source of bromine cation while using potassium peroxydisulfate based oxidant for the preparation of Spiro[4,5]trienones. Although the temperature has been reduced to 90 C, but the desired products formed in poor yield (Scheme 4).



Scheme 4: Synthesis of *N*-spiro-heterocycles using TBAB as electrophile.

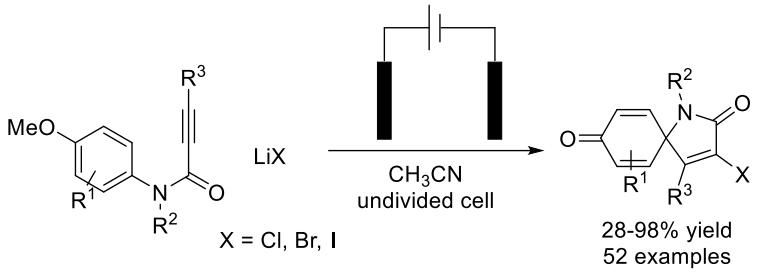
Duan and coworkers[7] reported light mediated oxidative spirocyclization of *N*-(*p*-methoxyaryl)propiolamides using (PIFA)phenyliodine bis(trifluoroacetate) as an oxidant.

Alkali halide such as LiCl, LiBr and LiCl has been used as halogen source under photo catalyst free irradiation. Although this reaction afforded moderate to good yield of halogenated product, this method is limited to 4-methoxy aniline derived substrate (Scheme 5).



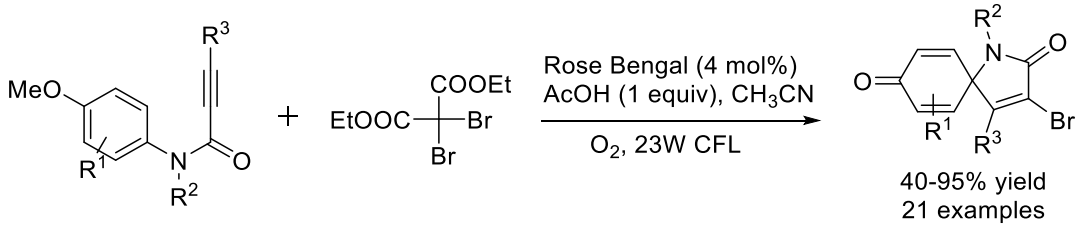
Scheme 5: Hypervalent iodine reagent mediated oxidative halocyclization of *N*-arylalkynamides.

Chen and coworkers[8] recently reported electrochemical oxidative halocyclization of *N*-arylalkynamides using LiCl, LiBr and LiCl as halogen source under metal and oxidant free condition. Though this reaction afforded moderate to good yield of halogenated product at room temperature, this method is limited to 4-methoxy aniline derived substrate (Scheme 6).



Scheme 6: Electrochemical oxidative halocyclization of *N*-arylalkynamides.

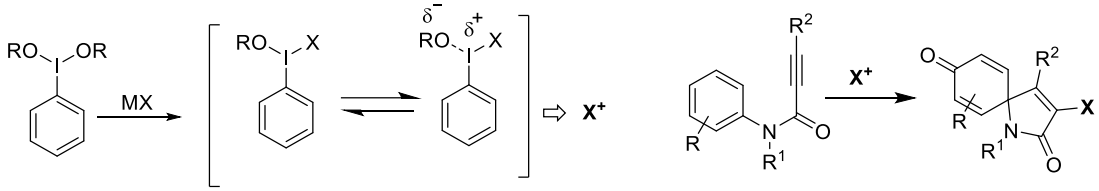
Soon later, He and coworkers[9] reported visible light mediated photocatalytic oxidative bromocyclization of *N*-phenylpropynamides using diethyl 2,2-dibromomalonate as bromide source. Based on control experiments, the reaction was proposed to go *via* a cascade radical addition followed by ipso-cyclization and oxidation process (Scheme 7).



Scheme 7: Photocatalytic halocyclization of *N*-arylalkynamides.

5. OBJECTIVE

It was observed from the above work that 4-methoxy substituent was crucial to obtain 3-bromo-1-azaspiro-[4.5] trienones under mild condition. As we know hypervalent iodine (III) reagents are green and economical reagent, used as oxidizing agent and a suitable substitute for heavy metal based toxic reagents. So, we hypothesized the use of hypervalent iodine as an oxidant to generate halo cation from alkali halides for the oxidative spiro-bromocyclization of propiolamide. Hypervalent iodine (III) reagent are known for its wealth of ionic reactivity. Hypervalent iodine (III) oxidizes the potassium halide to halo cation (Scheme 8). In this reaction potassium halide react with hypervalent iodine (III) reagent and form interhalogen bond which is partially ionic and forms a halo-cation. The formed halo cation can react with *N*-methyl-*N*-Phenylpropiolamide.



Scheme 8: Proposed halocyclization of propiolamide using Hypervalent iodine(III) reagent.

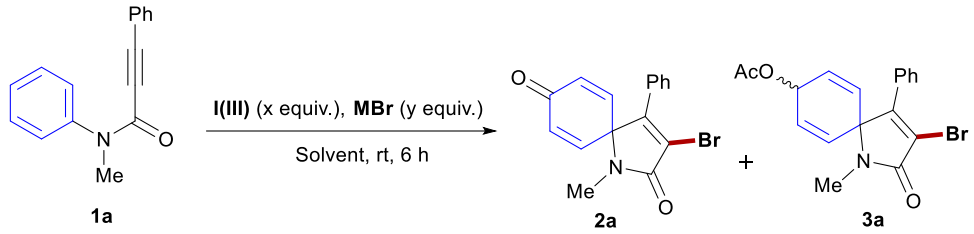
Objective of this project is to develop hypervalent iodine reagent mediated oxidative spiro-halocyclization of propiolamide without methoxy substituent on the aryl ring.

6. RESULTS AND DISCUSSION

At the outset, we began our investigation with *N*-methyl-*N*,3-diphenylpropiolamide **1a** as alkynyl partner to evaluate the ideal conditions for the bromination reaction (Table 1). We were delighted to find that by using water as solvent with 2 equivalents phenyliodine diacetate (PIDA) and KBr afforded the desired product **2a** in 74% yield along with the formation of by product spiro[4,5]trienyl acetates **3a** in 21% yield (Table 1, entry 1). In order to make the reaction mixture homogeneous, acetonitrile was used in different ratio with water to identify the ideal condition. Yield of the desired spiro[4.5]trienones **2a** found to improve significantly to 89% on using mixture of water and acetonitrile in 10:1 (Table 1, entry 3). In the case of acetonitrile as solvent, both the mixture of spiro trienones **2a** and trienyl acetate **3a** was obtained in 41% and 55% respectively (Table 1, entry 6). Further investigation of different halides such as sodium bromide (NaBr), lithium bromide (LiBr) and tetrabutylammonium bromide (TBAB) found to be less efficient than potassium bromide (KBr) (Table 1, entries 7-9). Replacement of PIDA with more reactive hypervalent iodine reagent phenyliodine bistrifluoroacetate (PIFA) displayed a lower yield (Table 1, entry 10).

Further increase in equivalent of PIDA shows a dramatic enhancement in the formation of desired spiro trienones **2a** to 98% yield (Table 1, entries 11 and 12).

Table 1: Reaction optimization



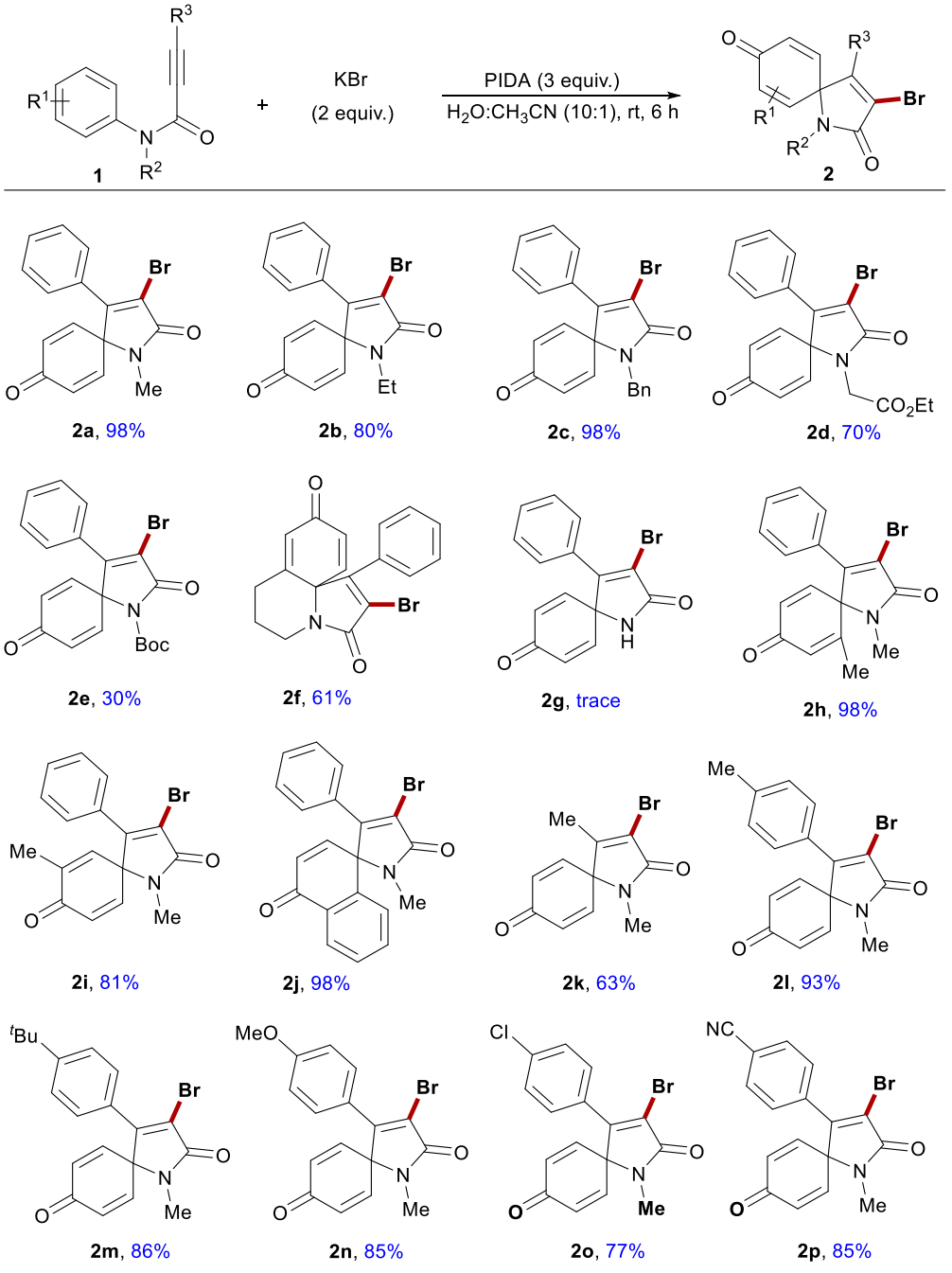
Entry	I(III) (x equiv)	MBr (y equiv)	solvent	Yield (%)[b] 2a	3a
1	PIDA (2)	KBr (2)	H_2O	74	21
2	PIDA (2)	KBr (2)	H_2O:CH_3CN (20:1)	85	10
3	PIDA (2)	KBr (2)	H_2O:CH_3CN (10:1)	89	06
4	PIDA (2)	KBr (2)	H_2O:CH_3CN (5:1)	88	06
5	PIDA (2)	KBr (2)	H_2O:CH_3CN (1:1)	75	06
6	PIDA (2)	KBr (2)	CH_3CN	41	55
7	PIDA (2)	NaBr (2)	H_2O:CH_3CN (10:1)	83	13
8	PIDA (2)	LiBr (2)	H_2O:CH_3CN (10:1)	77	19
9	PIDA (2)	TBAB (2)	H_2O:CH_3CN (10:1)	69	19
10	PIFA (2)	KBr (2)	H_2O:CH_3CN (10:1)	58	none
11	PIDA (2.5)	KBr (2)	H_2O:CH_3CN (10:1)	91	05
12	**PIDA (3)**	**KBr (2)**	**H_2O:CH_3CN (10:1)**	**98**	**none**
13	PIDA (2)	KBr (1)	H_2O:CH_3CN (10:1)	62	05
14	PIDA (2.5)	KBr (1.5)	H_2O:CH_3CN (10:1)	82	16
15[c]	PIDA (3)	KBr (2)	H_2O:CH_3CN (10:1)	93	trace
16	PIDA (3)	KBr (2)	H_2O	83	12
17[d]	PIDA (3)	KBr (2)	CH_3CN	25	72

[a]Reaction conditions: **1a** (0.2 mmol), **I(III)** (0.2x mmol), MBr (0.2y mmol) in solvent (1 ml) stirred at rt for 6 h. [b]Isolated yield.
[c]Reaction performed in dark. [d]*cis: trans* ratio = 1.0:1.1

Similarly, variation in equivalents of potassium bromide reveals that 2 equivalent of KBr is required for this reaction (Table 1, entries 13 and 14). Notably, the reaction proceeds with same efficacy even it was performed in the dark condition (Table 1, entry 15). On subjecting the optimized reaction condition using water as only solvent afforded the corresponding trienones **2a** in 83% yield (Table 1, entry 16). This result clearly indicates the practicality of the reaction. Finally, the yield of by-product spiro[4,5]trienyl acetates **3a** has been improved to 72% under optimized condition using acetonitrile as only solvent (Table 1, entry 17). In the end, the optimized reaction condition for the formation of brominated spiro[4.5]trienones

2a were found to be 0.2 mmol of **1a**, 2 equiv. of KBr, 3 equiv. of PIDA using mixture of H_2O and CH_3CN in 10:1 ratio as solvent at rt for 6 h.

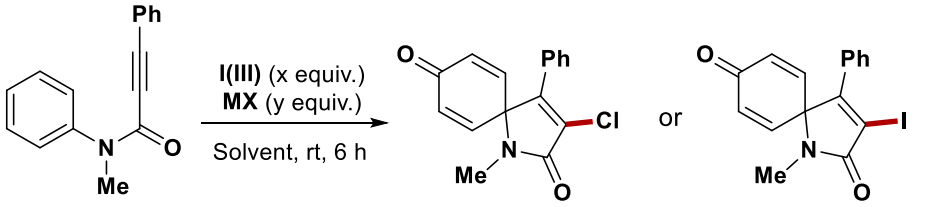
Figure 3. Substrate scope for the bromocyclization of *N*-arylpropynamides[a,b]



With the optimized reaction conditions in hand, we next examined the substrate scope for the bromo spiro[4.5]trienones (Scheme 9). Firstly, variation in alkyl substituents on nitrogen such as methyl, ethyl, benzyl and methyl carboxylates afforded the corresponding brominated product ranging from 70% to 98% (**2a-2d**). Electron withdrawing substituent such as *tert*-butoxycarbonyl (Boc) also provided the desired product (**2e**) albeit in lower yield. Importantly, a brominated tricyclic framework (**2f**) can be constructed in moderate yield

using this strategy with tetrahydroquinoline derived propiolamide as substrate. In addition, the substrate with free N-H desired product was found only in trace amount of (**2g**). When R^1 was 2-methyl, reaction afforded the desired product (**2h**) in 98% which clearly indicates that there is no steric effect from the *N*-aryl substituents on the reaction. Similarly, with 3-methyl aniline and naphthyl amine derived propiolamide provided the corresponding products in excellent yields of 81% and 98% respectively (**2i**and **2j**). To our surprise, desired product (**2k**) was obtained in moderate yield even with alkyne bearing methyl group. On varying substituents at the phenyl ring of alkyne revealed that both electron-releasing (**2l**-**n**) and electron-withdrawing group (**2o**-**p**) at the *para*-position of the aryl ring afforded corresponding product in excellent yields.

Table 2: Reaction optimization for Chlorination and Iodination



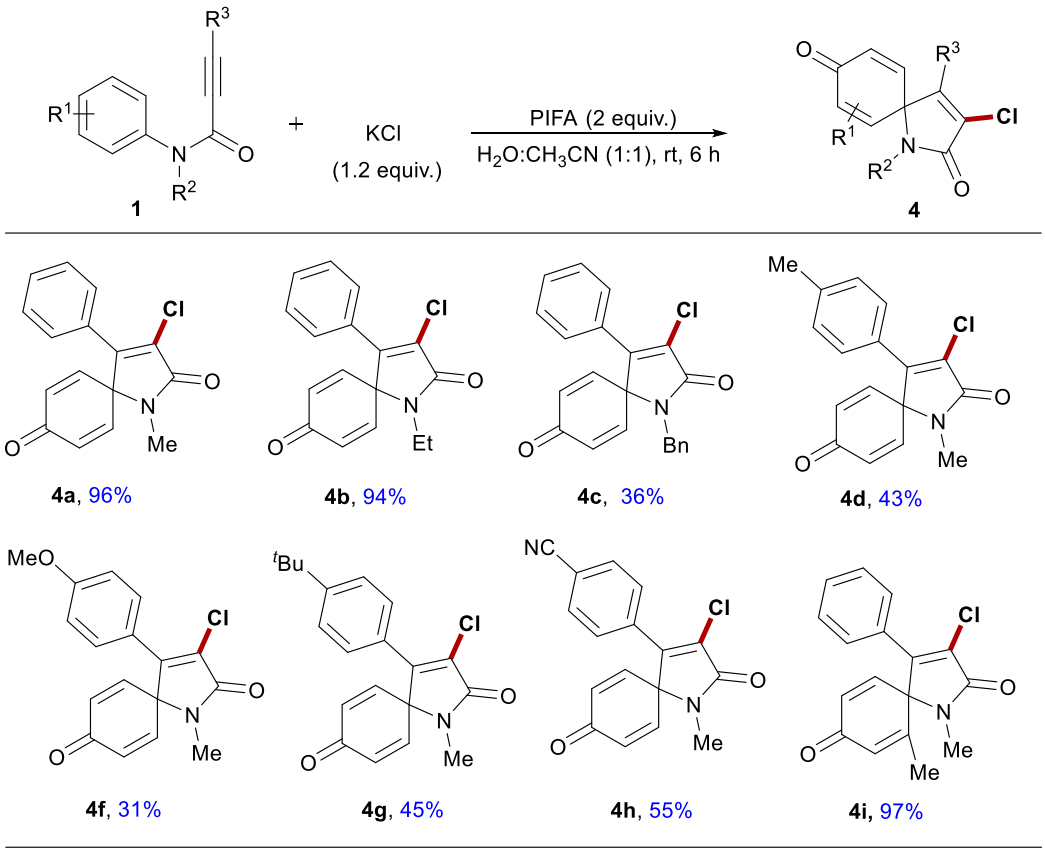
Entry	I(III) (x equiv)	MX (y equiv)	solvent	Yield (%)[b] 4a	5a
1	PIDA (3)	KCl (2)	H_2O:CH_3CN (10:1)	45	NA
2	PIDA (3)	KI (2)	H_2O:CH_3CN (10:1)	NA	52
3	PIFA (2)	KCl (2)	H_2O:CH_3CN (1:1)	63	NA
4	**PIFA (2)**	**KI (2)**	**H_2O:CH_3CN (1:1)**	**NA**	**90**
5[c]	PIFA (2)	KBr (2)	H_2O:CH_3CN (1:1)	NA	NA (65% of **3a**)
6	PIFA (2)	KCl (1.5)	H_2O:CH_3CN (1:1)	75	NA
7	**PIFA (2)**	**KCl (1.2)**	**H_2O:CH_3CN (1:1)**	**96**	**NA**
8[d]	PIFA (2)	KI (2)	H_2O:CH_3CN (1:1)	NA	58
9[d]	PIFA (2)	KCl (1.2)	H_2O:CH_3CN (1:1)	75	NA
10	PIFA (2)	none	H_2O:CH_3CN (1:1)	NA	none

[a]Reaction conditions: **1a** (0.2 mmol), **I(III)** (0.2x mmol), MBr (0.2y mmol) in solvent (1 ml) stired at rt for 6 h. [b]Isolated yield. [c]65% of **3a** was obtained. [d]Reaction performed under dark.

Encouraged by the results of bromo spirocyclization, we turned our attention towards the preparation of chlorinated and iodinated spiro[4.5]trienones from *N*-methyl-*N*,3 diphenylpropiolamide **1a**. On adopting the optimized condition used for bromination provided the desired chlorinated (**4a**) and iodinated (**5a**) spiro[4.5]trienones in only 45% and 52% respectively (Table 2). Subsequently, by varying the amount of KCl, switching hypervalent iodine reagent from PIDA to PIFA and by changing solvent ratio, an optimized condition for chloro spirocyclization were achieved. Gratifyingly, treatment of *N*-methyl-*N*,3 diphenylpropiolamide **1a** with 2 equiv. of PIFA and 1.2 equiv. of KCl in H_2O:CH_3CN (1:1)

mixture afforded desired chlorinated spiro[4.5]trienones (**4a**) in 96% yield at room temperature. With the optimized condition in hand, scope of the chlorination reaction was examined as shown in scheme 10.

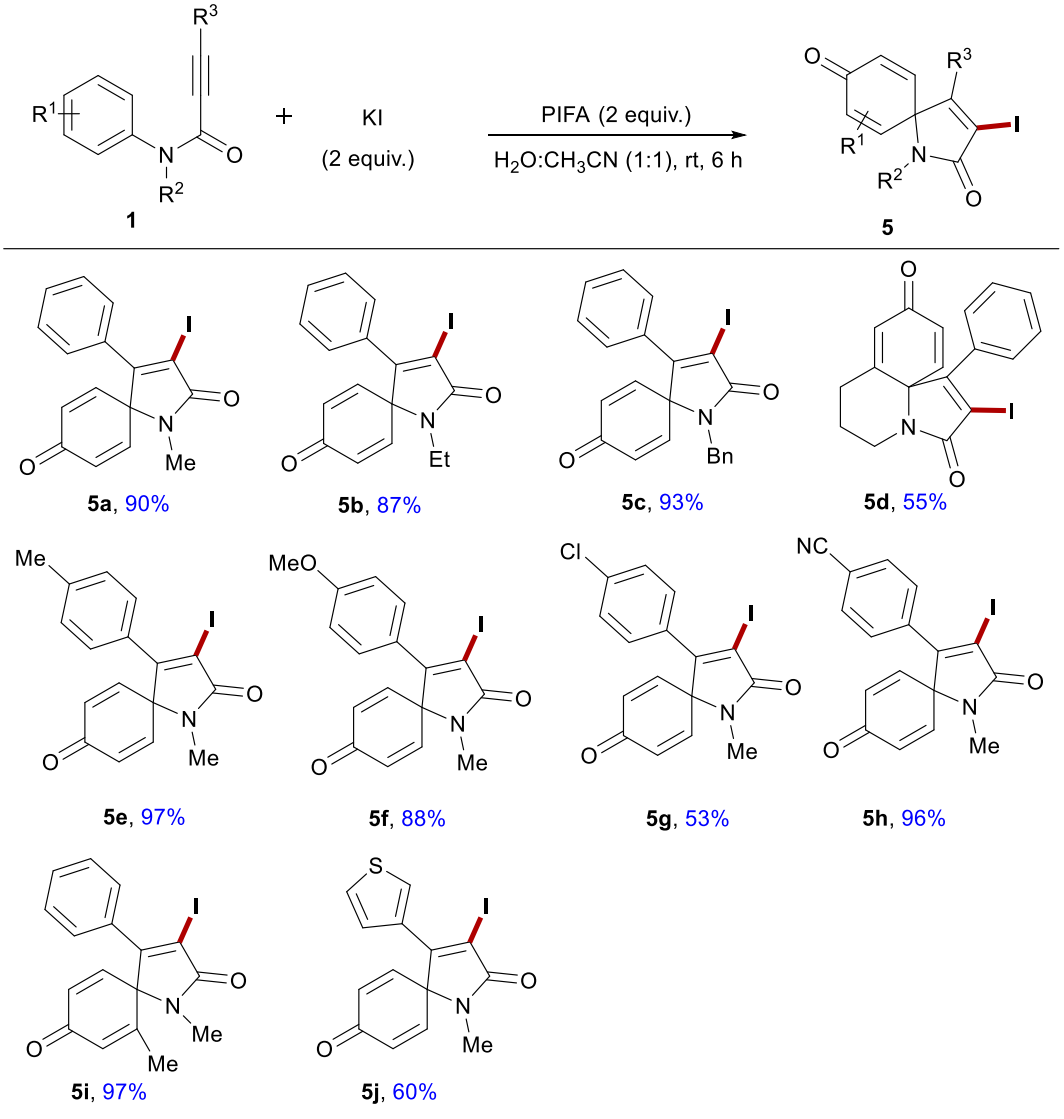
Figure 4. Substrate scope for the chlorocyclization of *N*-arylpropynamides[a,b]



Like *N*-methyl substituent, *N*-ethyl substituted propiolamide also underwent spirocyclization with same efficiency to give desired product (**4b**) in excellent yield. On varying substituents at the phenyl ring of alkyne revealed that both electron-donating (**4d-g**) and electron-withdrawing group (**4h**) at the *para*-position of the aryl ring afforded corresponding product in moderate yields. In the case 2-methyl aniline derived propiolamide, desired cyclized product (**4i**) was obtained in excellent yield. In the same way, iodination of *N*-methyl-*N*,3 diphenylpropiolamide **1a** was optimized(Table 2) and found that with the mixture of 2 equiv. of PIFA and 2 equiv. of KI in H_2O:CH_3CN (1:1) solvent mixture afforded desired iodinated spiro[4.5]trienones (**5a**) in 90% yield at room temperature. With the above optimized condition, scope of the iodination reaction was investigated as shown in scheme 11. It shows uniform reactivity with different *N*-alkyl substituents to give provide iodinated spiro[4.5]trienones (**5a-5c**) in excellent yields. In analogues to bromination reaction, iodinated tricyclic framework (**5d**) can be constructed in 55% yield using this strategy with tetrahydroquinoline derived propiolamide as substrate. Variation in substitutions at the *para*-

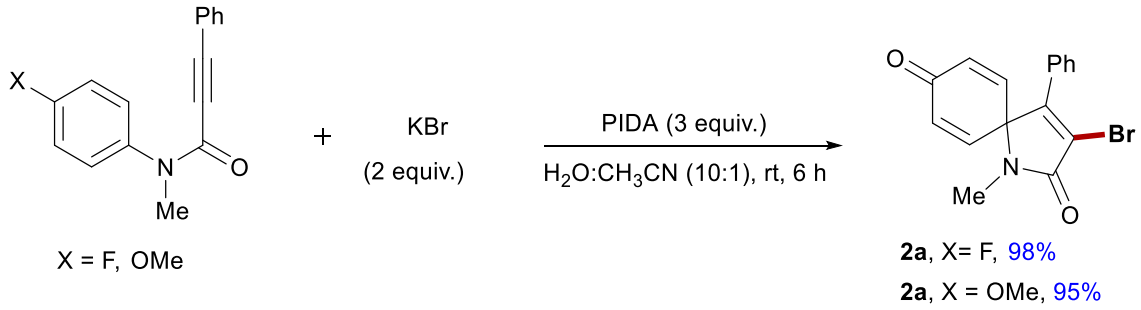
position of aryl ring attached to the alkyne shows good tolerance with both electron-releasing and electron-deficient groups to give the corresponding product (**5e**-**5h**) in good to excellent yields. Furthermore, steric effect has no influence on the iodo spirocyclization process as well, the spirocyclization (**5i**) takes place smoothly with *ortho*-methyl substitution on phenyl attached with alkyne. Interestingly, with 3-thienyl ring attached to the alkyne substrate reaction proceeded smoothly to give desired product (**5j**) in 60% yield.

Figure 5. Scope for the iodocyclization of *N*-arylpropynamides[a,b]



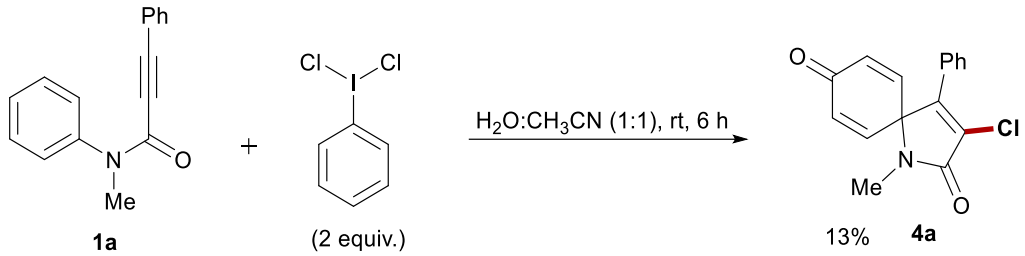
In the case of substrate bearing a fluoro or methoxy substituent at the 4-position of the aniline ring, the bromination reaction continued smoothly to provide the bromo spiro[4.5]trienones (**2a**) in 98% and 95% yield respectively (Scheme 12). This result clearly indicates that both *para*-substituted and *para*-unsubstituted propiolamides shares a similar mechanistic pathway that give rise to the formation of bromo spiro[4.5]trienones (**2a**).

Scheme 9. Reaction of *N*-(*p*-substituted phenyl)-*N*-methyl-3-phenylpriolamide



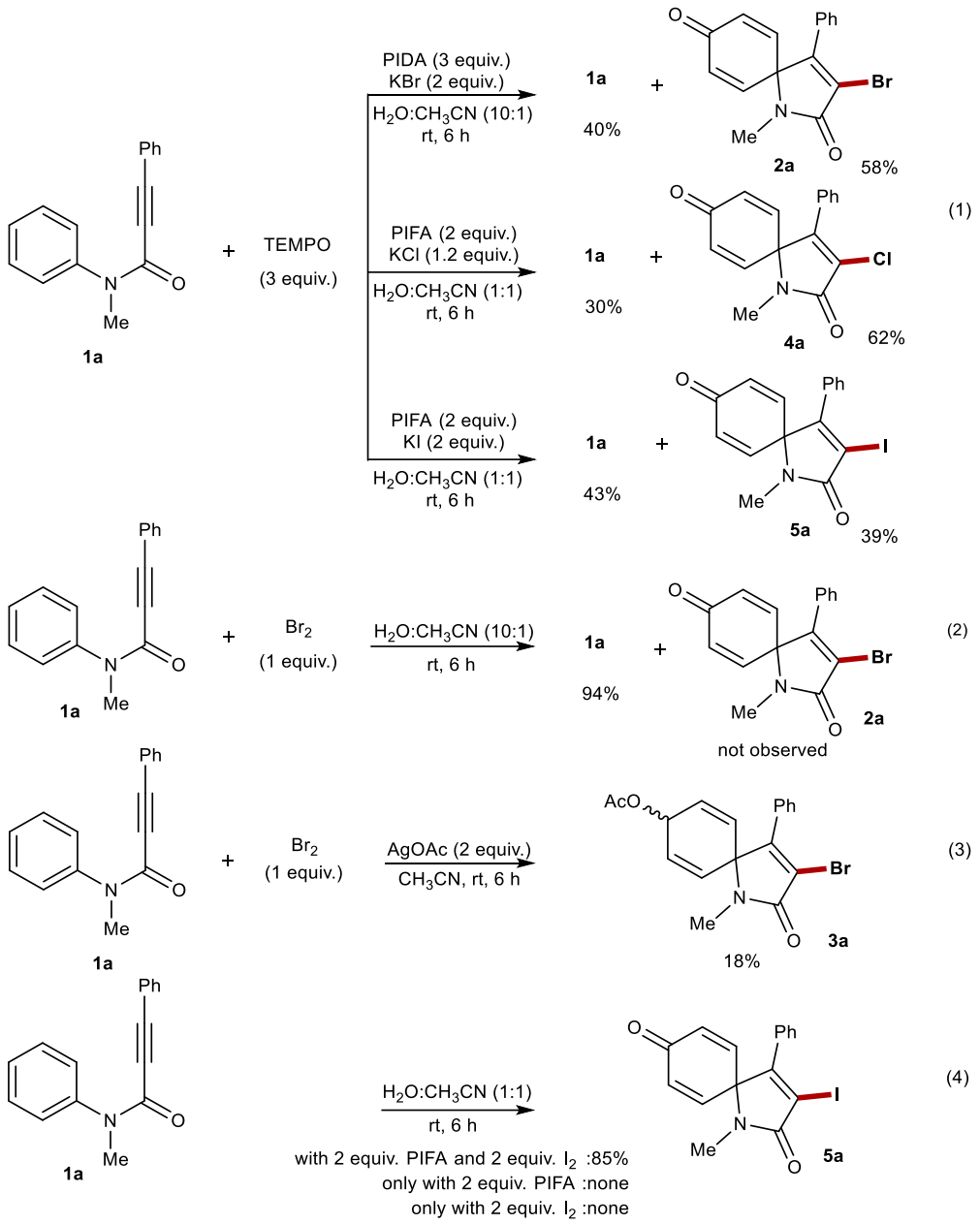
In order to identify the chlorinating species responsible for the chlorination of propiolamides, *N*-methyl-*N*,3-dipehnylpropiolamide was treated with 2 equiv. of $PhICl_2$in H_2O:CH_3CN (1:1) mixture at rt for 6 h. It was found that the reaction was not clean and the desired chloro spiro[4.5]trienones (**4a**) was obtained only in 13% yield. This result suggest that the lower efficiency of the chlorination process might have caused by the parallel reaction facilitated by the $PhICl_2$, that was competitively formed from the reaction between PIFA and KCl (Scheme 13).

Scheme 10. $PhICl_2$ mediated chlorocyclization of *N*-arylpropynamides



To shed light on plausible reaction mechanism, a series of control experiments were carried out (Scheme 14). Initially, radical trapping experiments were performed. When 3 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were added to the optimized reaction system for halogenation, it shows a slight decrease in the formation of desired product **2a**/**4a**/**5a** in 58%, 62% and 49% yield respectively (Scheme 14, eqn (1)), indicating that the halogenation reaction predominantly proceeds through ionic pathway. In addition, the reduction of PIFA to iodobenzene by TEMPO also contributed to the reduction in the conversion of this reaction. Reaction failed to give any brominated product **2a** on treatment of bromine (Br_2) with **1a** rules out the involvement of insitu generated molecular bromine as halogen source (Scheme 14, eqn (2)).

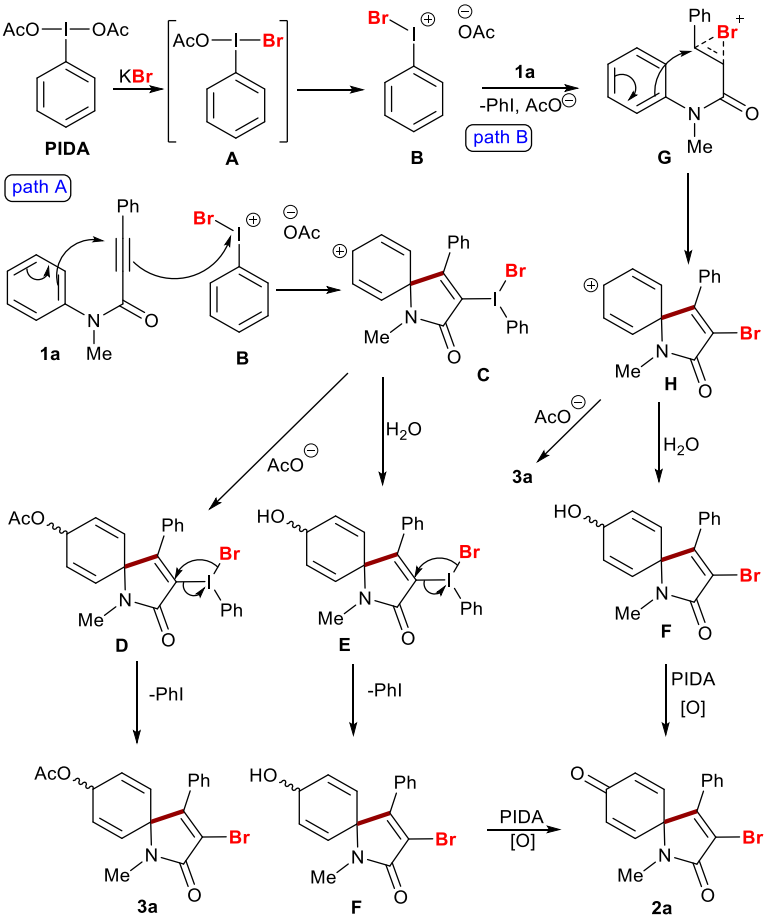
Scheme 11. Control experiments



In order to check the involvement of acetyl hypobromite (CH_3COOBr) as a potential halogen source, it was generated insitu on treating silver acetate with bromine and then subjected it to react with **1a** in CH_3CN at rt for 6 h. It was found that the reaction is slow and affords brominated spiro[4,5]trienyl acetates **3a**as only product in 18% yield (Scheme 14, eqn (3)). This result indicates that acetyl hypobromite generated from the reaction of PIDA and KBr could be competitively one of the possible reactive species that give rise to the formation of **3a**. In the case of iodination reaction, reaction failed to give any product in the absence of KI, suggesting that iodine atom present in the PIFA is not an iodine source as in the case of previously reported hypervalent iodine based spirocyclization process. Similarly, reaction

didn't afford the desired product on treating with molecular iodine. However, subjecting the reaction with mixture of 2 equiv. of PIFA and 2 equiv. of I_2 provided the desired product **5a** in 85% yield This result supports the involvement of trifluoroacetyl hypoiodite (CF_3COOI)[24] derived from the reaction of PIFA with either KI or I_2 as a potential electrophilic iodine source in this reaction (Scheme 14, eqn (4)).

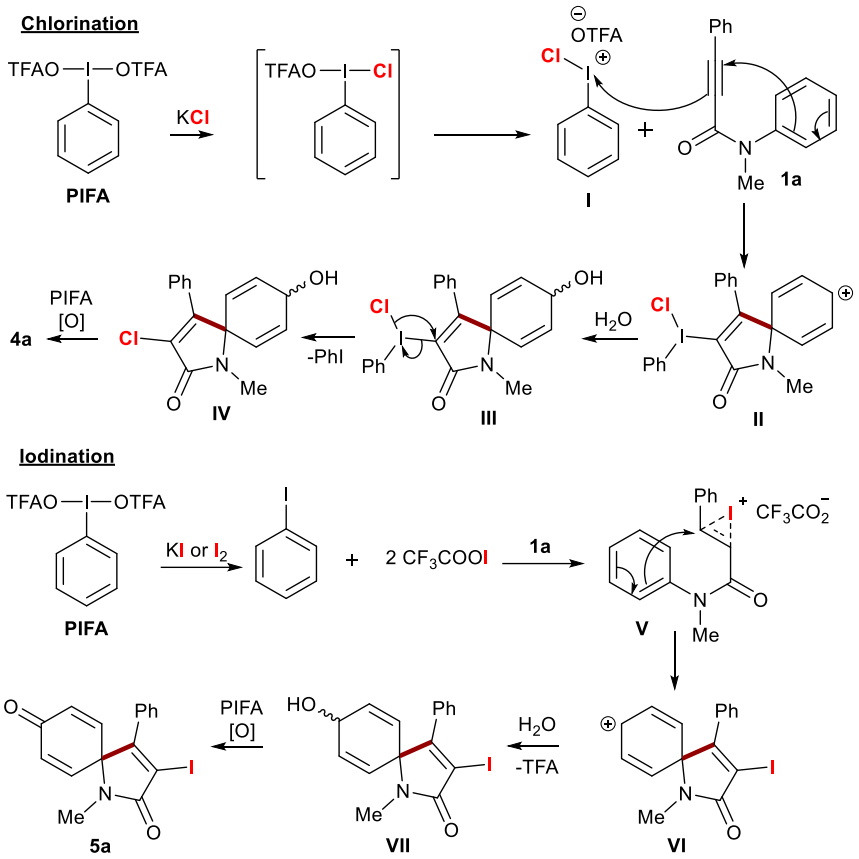
Scheme 12. Proposed reaction mechanism for bromo-spirocyclization



Based on the results of control experiments and literature reports, a plausible reaction mechanism has been proposed for the bromo-spirocyclization reaction as outlined in Scheme 15. Two possible pathways have been postulated, in path A PIDA on ligand exchange with KBr give rise to transient iodane species **B**. Followed by the addition of alkyne triple bond with electrophilic species **B** via spirocyclization and dearomatization to give spiro diallyl cation **C**. Subsequent trapping of cation with acetate anion or water molecule leads to spiro acetate **D** or hydroxyl intermediate **E** respectively. The spiro acetate intermediate **D** on reductive elimination of PhI delivers brominated spiro[4,5]trienyl acetates **3a**. Similarly, the hydroxyl intermediate **E**on reductive elimination of PhI followed by the oxidation with PIDA leads to desired brominated spiro[4,5]trienones**2a**. Whereas in path B, electrophilic spirocyclization of **1a** with insitu generated acetyl hypobromite would lead to spiro diallyl

cation **H**. Subsequent trapping of cation **H** with acetate anion or water molecule leads to brominated spiro[4.5]trienyl acetate **3a** or hydroxyl intermediate **F** respectively. The hydroxyl intermediate **E**on gets oxidized by PIDA leads to desired brominated spiro[4,5]trienones**2a**.

Scheme 13. Proposed reaction mechanism for chloro and Iodo-spirocyclization



The possible mechanism for chlorinated and iodinated spirocyclization reaction are described in Scheme 16. In the case of chlorination, PIFA on ligand exchange with KCl give rise to transient iodane species **I**. Subsequent addition of alkyne triple bond with electrophilic species **I** via spirocyclization and dearomatization to give spiro diallyl cation **II**. Finally, the trapping of cation **II** by water molecule gave a hydroxyl intermediate **III**, which on reductive elimination of PhI and subsequent oxidation with PIDA leads to desired chlorinated spiro[4,5]trienones**4a**. For iodination reaction, since the reaction proceeds in equal ease on using PIFA with KI or I_2, involvement of trifluoroacetyl hypoiodite (CF_3COOI)as electrophilic iodo source has been invoked. Addition of alkyne triple bond with insitu generated electrophilic trifluoroacetyl hypoiodite via spirocyclization and dearomatization leads to spiro diallyl cation **VI**. Finally, the trapping of cation **VI** by water molecule gave a hydroxyl intermediate **VII**, which on reductive elimination of PhI and subsequent oxidation with PIDA leads to desired iodinated spiro[4,5]trienones**5a**.

Conclusions

We have established a mild and environmentally benign method for the construction of halogenated spiro[4.5]trienones from *N*-phenylpropynamides using hypervalent iodine reagents PIDA/PIFA and KX (X= Cl, Br, I) through spirocyclization-dearomatization under aqueous condition at room temperature. An important feature of the approach is that unlike the existing methods it doesn't require *para*-methoxy or *para*-fluoro substituents on the *N*-aryl ring of *N*-phenylpropynamides. Further examination of the reaction mechanism and utilization of this protocol on synthesis of other halogenated molecules is currently being carried out in our laboratory.

7. EXPERIMENTAL SECTION

7.1. General method:

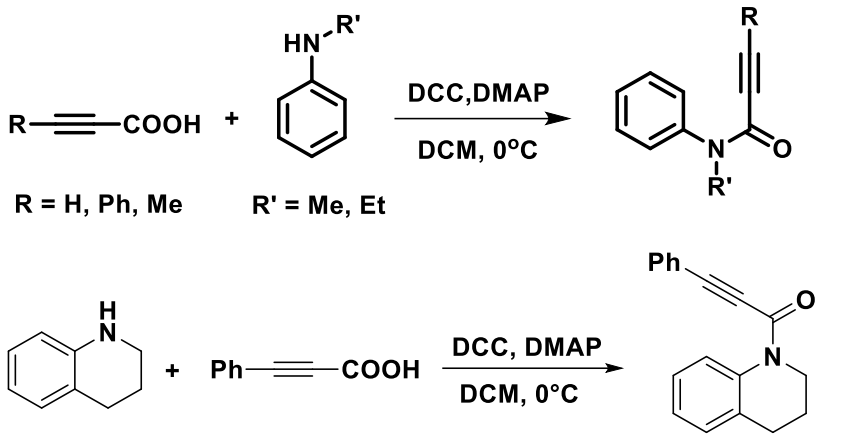
All the reagents and solvents were purchased from local vendors. The substrates were synthesized as enlisted in the conventional protocol mentioned below. The reagents and solvents were used without any purification. Ethyl acetate and hexane were distilled before use. All of the reactions were performed in inert medium and supervised by thin-layer chromatography (TLC) using Merck 60 F254 precoated silica gel plates, and the products were observed by UV detection. Purification of the synthesized products was executed by Column Chromatography filled with silica gel (100-200 mesh).

7.2. Instrumentation:

(The purified products were authenticated through NMR Spectra recorded on a Bruker Advance 400 and 500 Spectrometer (400 MHz& 500MHz) (^{1}H) in $CDCl_3$ and DMSO-d_6 using tetramethylsilane as an internal standard. All chemical shift values are mentioned in δ scale in parts per million (ppm). The residual solvent peaks of $CDCl_3$ and DMSO-d_6 were recorded at 7.26 and 2.50 ppm respectively. The crystal data recorded on dual core agilent technologies Oxford Diffraction Super Nova CCD System and solved on CryAlispro Software and Olex2-1.5.

8. General procedure for starting material :-

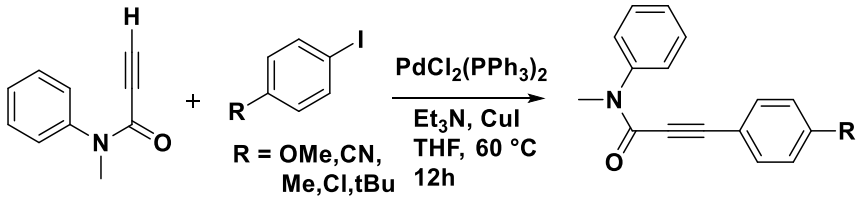
8.1 Preparation of *N*-methyl-*N*, 3-diphenylpropiolamide:



Scheme 14. Preparation of derivative of *N*-alkyl-*N*, 3-diphenylpropiolamide.

N-substituted anilinewas taken in a clean round bottom flask and then DCM (0.25M) was added to it. Respective propiolic acid (1.1eq.) was added into the solution and kept the solution in ice bath (0°C). A mixture of DCC (1.5eq.) and DMAP (0.1eq.) was prepared in a separate beaker and added to the above solution. The reaction was allowed to stir overnight. After the completion of reaction as indicated by TLC (Using 20% EtOAc-Hexane) then the workup was done by adding 1N HCl and extracted by using DCM. Anhydrous Na_2SO_4 was used to remove water droplets. Then the solvent was evaporated in vacuum, and the residue was purified by flash chromatography on silica gel (100-200 mesh using 20% EtOAc and hexane mixture as eluent to obtain target compound as white solid.

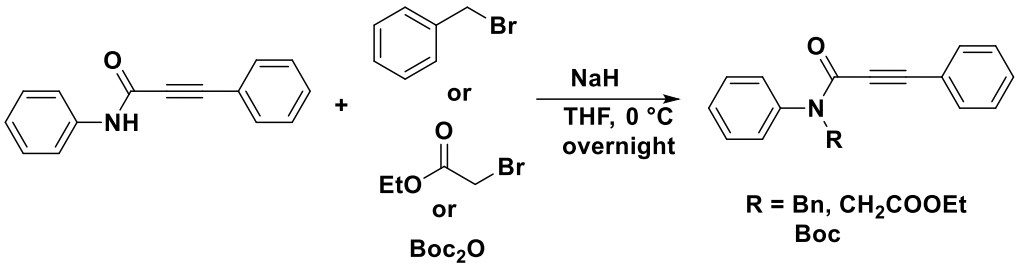
8.2 Synthesis of *N*-methyl-*N*, 3-diphenylpropiolamide derivative:



Scheme 15. Synthesis of *N*-methyl-*N*, 3-diphenylpropiolamide derivative.

In an oven dried round bottom flask charged with magnetic stir bead,*N*-Methyl-*N*-phenyl-propiolamide (10 mmol)added in dry THF (60 mL) then substituted iodobenzene(10 mmol), Et_3N (50 mL), $PdCl_2(PPh_3)_2$(0.05 eq) and CuI (0.1 eq) added to the above reaction mixture and parched with N_2 Gas. The reaction mixture heated to 60 °C for 12h. After 12h cool-down the reaction mixture and filter the mixture. Remove the solvent under reduced pressure byvacuum. Mixture extracted with EtOAc (100 mL × 3) and dry over anhydrous Na_2SO_4. Evaporate the solvent under vacuum and purify the residue by silica gel column chromatography (20% EA/Hexane).

8.3 Synthesis of *N*, 3-diphenylpropiolamide derivative:



Scheme 16. Synthesis of *N*, 3-diphenylpropiolamide derivative.

N, 3-diphenylpropiolamide (5 mmol) taken in a flame dried RB-flask with stir bar and dry THF (30 mL) added. Addition of NaH (1.5 eq.) at 0 °C by cool-down the mixture on ice-bath and stir the reaction mixture for 30 min. After that corresponding Bromo-Compound or Boc-anhydride (2.5 eq) added to the reaction mixture. Stir the reaction at rt for overnight. Extract the reaction mixture with DCM (50 mL × 3) and washed with brine and dried over sodium sulphate. Evaporate the solvent under vacuum and purify the residue by column chromatography on silica gel (EA/Petroleum ether 1:5).

9. General procedure for product synthesis:-

9.1 General procedure for hypervalent iodine mediated Spiro cyclization for Bromination :

N-methyl-*N*, 3-diphenyl propiolamide**1a** (1 equiv., 0.2 mmol) was taken in glass vial then solvent was added. After that $PhI(OAc)_2$ (3 equiv., 0.6 mmol) and potassium bromide (2 equiv., 0.4 mmol) was added to the above solution. Then the reaction mixture was stirred at rt for 6 h. After the completion of reaction as indicated by TLC (using 30% EtOAc-Hexane), reaction mixture was extracted by adding EtOAc. The solvent was evaporated by using rotavapor. Then the residue was purified by flash chromatography on silica gel using EA/hexane mixture as eluent to obtain pure sample of **2a** and **3a** as white solid.

9.2 General procedure for hypervalent iodine mediated Spiro cyclization for Chlorination :

N-methyl-*N*, 3-diphenyl propiolamide**1a** (1 equiv., 0.2 mmol) was taken in glass vial then solvent was added. After that PIFA (2 eq., 0.4 mmol) and potassium chloride (1.2 eq., 0.24 mmol) was added to the above solution. Reaction mixture was stirred at rt for 6 h. After the completion of reaction as indicated by TLC (using 30% EtOAc-Hexane), reaction mixture was extracted by adding EtOAc. The solvent was evaporated by using rotavapor. Then the

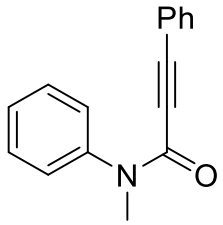
residue was purified by flash chromatography on silica gel using ethyl acetate and hexane mixtures as eluent to obtain pure product **4a**.

9.3 General procedure for hypervalent iodine mediated Spiro cyclization for Iodination:

N-methyl-*N*, 3-diphenyl propiolamide**1a** (1 equiv., 0.2 mmol) was taken in glass vial then solvent was added. After that PIFA (2 eq., 0.4 mmol) and potassium iodide (2 eq., 0.4 mmol) was added to the above solution. Reaction mixture was stirred at rt for 6 h. After the completion of reaction as indicated by TLC (using 30% EtOAc-Hexane), reaction mixture was extracted by adding EtOAc. The solvent was removed by using rotavapor. Then the residue was purified by flash chromatography on silica gel using EA/hexane mixture as eluent to obtain pure product **5a**.

10. Characterization

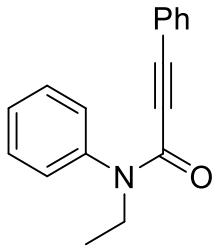
***N*-methyl-*N*, 3-diphenylpropiolamide (1a)**



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.42 - 7.47 (m, 2 H), 7.39 (d, 1 H), 7.34 - 7.38 (m, 2 H), 7.29 - 7.34 (m, 1 H), 7.23 (m, 2 H), 7.14 (m, 2 H), 3.39 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 154.48, 143.41, 132.58, 130.06, 129.30, 128.45, 128.07, 127.57, 120.58, 90.98, 82.71, 36.51.

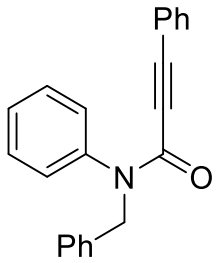
***N*-ethyl-*N*,3-diphenylpropiolamide (1b)**



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.49 - 7.37 (m, 3 H), 7.35 - 7.27 (m, 3 H), 7.24 - 7.19 (m, 2 H), 7.12 - 7.06 (m, 2 H), 3.88 (q, *J* = 7.2 Hz, 2 H), 1.19 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 154.1, 141.8, 132.5, 130.0, 129.3, 128.8, 128.4, 128.2, 120.6, 90.8, 82.9, 43.6, 13.1.

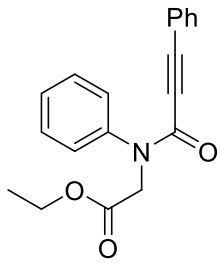
_N_-benzyl-_N_,3-diphenylpropiolamide (1c)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.38 - 7.08 (m, 15 H), 5.01 (s, 2 H).

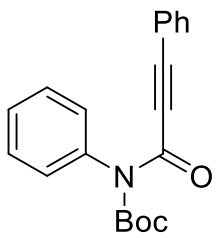
^{13}C NMR (126MHz, $CDCl_3$) δ = 154.6, 141.9, 136.8, 132.6, 130.1, 129.2, 128.9, 128.8, 128.6, 128.4, 128.3, 127.7, 120.5, 91.6, 82.7, 52.4.

Ethyl _N_-phenyl-_N_-(3-phenylpropioloyl)glycinate (1d)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.50 - 7.37 (m, 5 H), 7.34 - 7.29 (m, 1 H), 7.22 (t, *J* = 7.7 Hz, 2 H), 7.14 - 7.09 (m, 2 H), 4.49 (s, 2 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H).
^{13}C NMR (126MHz, $CDCl_3$) δ = 168.4, 154.6, 142.1, 132.5, 130.2, 129.2, 128.5, 128.4, 128.4, 120.2, 91.8, 82.1, 61.5, 50.5, 14.2.

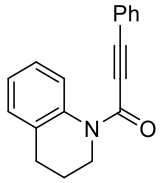
tert-butyl phenyl(3-phenylpropioloyl)carbamate (1e)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.47 - 7.23 (m, 10 H), 1.46 (s, 9 H).

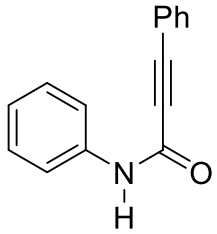
^{13}C NMR (126MHz, $CDCl_3$) δ = 153.8, 151.4, 138.1, 133.0, 130.6, 129.2, 128.8, 128.6, 128.6, 120.3, 94.0, 84.2, 83.3, 28.0.

1-(3,4-dihydroquinolin-1(2H)-yl)-3-phenylprop-2-yn-1-one (1f)



^{1}H NMR (500MHz, $CDCl_3$) δ = 8.16 - 7.48 (m, 2 H), 7.47 - 7.25 (m, 4 H), 7.24 - 7.02 (m, 3 H), 4.18 - 3.72 (m, 2 H), 2.90 - 2.69 (m, 2 H), 2.11 - 1.90 (m, 2 H).

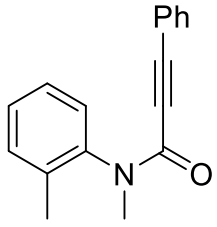
***N*,3-diphenylpropiolamide (1g)**



^{1}H NMR (500MHz, $CDCl_3$) δ = 8.07 - 7.90 (br, s 1 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 7.56 - 7.52 (m, 2 H), 7.44 - 7.39 (m, 1 H), 7.36 - 7.31 (m, 4 H), 7.16 - 7.11 (m, 1 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 151.2, 137.5, 132.7, 130.4, 129.2, 128.7, 125.0, 120.1, 120.1, 85.9, 83.6.

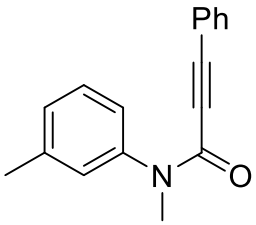
***N*-methyl-3-phenyl-*N*-(o-tolyl)propiolamide (1h)**



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.34 - 7.32 (m, 2 H), 7.31 - 7.25 (m, 3 H), 7.23 - 7.19 (m, *J* = 7.7 Hz, 2 H), 7.07 – 7.03 (m, 2 H), 3.31 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 154.8, 142.1, 136.5, 132.7, 131.2, 130.0, 128.8, 128.8, 128.4, 127.2, 120.5, 90.1, 82.4, 35.4, 17.6.

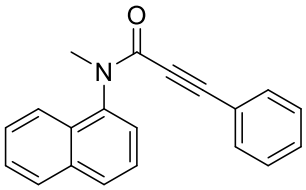
_N_-methyl-3-phenyl-_N_-(m-tolyl)propiolamide (1i)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.34 - 7.31 (m, 2 H), 7.26 – 7.22 (m, *J* = 9.0 Hz, 2 H), 7.21 – 7.19 (m, 1 H), 7.17 – 7.14 (d, *J* = 2.9 Hz, 4 H), 3.38 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 154.4, 143.3, 139.3, 132.5, 130.0, 129.0, 128.7, 128.4, 128.0, 124.5, 120.7, 90.8, 82.8, 36.5, 21.4.

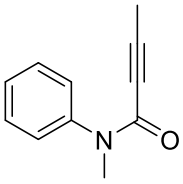
_N_-methyl-_N_-(naphthalen-1-yl)-3-phenylpropiolamide (1j)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.96 (br. s., 2 H), 7.89 (d, *J* = 8.1 Hz, 1 H), 7.63 - 7.49 (m, 4 H), 7.25 - 7.19 (m, 1 H), 7.13 - 7.07 (m, 2 H), 3.50 (s, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 155.2, 139.5, 134.4, 132.2, 130.5, 129.6, 128.9, 128.3, 128.0, 127.2, 126.5, 126.1, 125.4, 122.5, 120.1, 90.4, 82.4, 36.4.

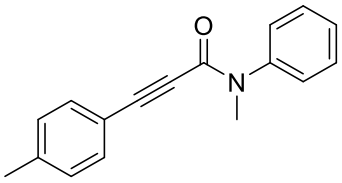
_N_-methyl-_N_-phenylbut-2-ynamide (1k)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.42 - 7.25 (m, 6 H), 3.30 (s, 3 H), 1.71 (s, 3 H).

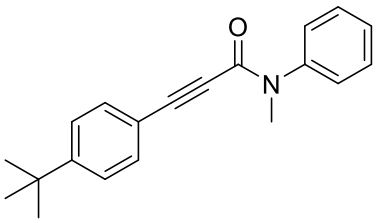
^{13}C NMR (126MHz, $CDCl_3$)δ = 153.9, 142.8, 128.7, 127.3, 126.7, 125.1, 89.4, 73.7, 35.9.

_N_-methyl-_N_-phenyl-3-(p-tolyl) propiolamide (1l)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.46 - 7.42 (m, 2 H), 7.40 - 7.34 (m, 3 H), 7.07 - 7.00 (m, 4 H), 3.39 (s, 3 H), 2.31 (s, 3 H).

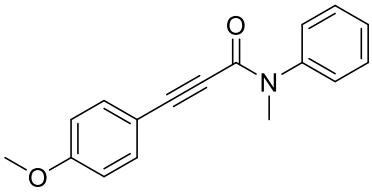
3-(4-(tert-butyl)phenyl)-_N_-methyl-_N_-phenyl propiolamide (1m)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.48 - 7.35 (m, 6 H), 7.27 (m, 1 H), 7.09 (m, 2 H), 3.40 (s, 3 H), 1.27 (s, 9 H).

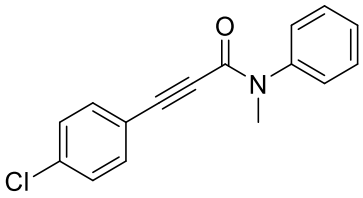
^{13}C NMR (126MHz, $CDCl_3$) δ = 154.5, 153.5, 143.4, 132.3, 129.1, 127.8, 127.4, 125.3, 117.4, 91.3, 82.2, 36.3, 34.9, 31.0.

3-(4-methoxyphenyl)-_N_-methyl-_N_-phenylpropiolamide (1n)



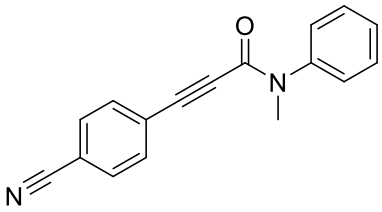
^{1}H NMR (500MHz, $CDCl_3$) δ = 7.47 - 7.42 (m, 2 H), 7.38 (s, 3 H), 7.07 (d, *J* = 8.7 Hz, 2 H), 6.75 (d, *J* = 8.7 Hz, 2 H), 3.77 (s, 3 H), 3.39 (s, 3 H).

3-(4-chlorophenyl)-_N_-methyl-_N_-phenylpropiolamide (1o)



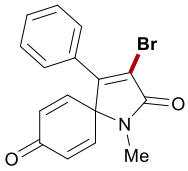
^{1}H NMR (500MHz, $CDCl_3$) □ = 7.46 - 7.42 (m, 2 H), 7.41 (s, 1 H), 7.36 (s, 2 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 7.05 (d, *J* = 8.5 Hz, 2 H), 3.39 (s, 3 H).

3-(4-cyanophenyl)-*N*-methyl-*N*-phenylpropiolamide (1p)



^{1}H NMR (500MHz ,$CDCl_3$) δ = 7.56 - 7.50 (m, 2 H), 7.48 - 7.43 (m, 2 H), 7.43 - 7.39 (m, 1 H), 7.37 - 7.33 (m, 2 H), 7.24 - 7.19 (m, 2 H), 3.40 (s, 3 H)

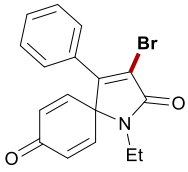
3-bromo-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2a)



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.35 - 7.44 (m, 5 H), 6.47 - 6.56 (m, 4 H), 2.94 (s, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 183.7, 165.8, 151.3, 144.1, 133.5, 130.3, 130.2, 128.8, 127.8, 119.9, 68.3, 26.6.

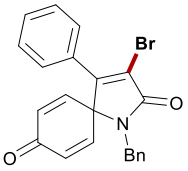
3-bromo-1-ethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2b)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.43 - 7.33 (m, 5 H), 6.57 (s, 2 H), 6.47 (s, 2 H), 3.42 - 3.37 (m, 2 H), 1.23 (t, *J* = 7.2 Hz, 3 H)

^{13}C NMR (126MHz, $CDCl_3$) δ = 183.9, 165.7, 151.2, 144.4, 132.9, 130.2, 130.1, 128.7, 127.8, 120.3, 68.7, 36.7, 15.1

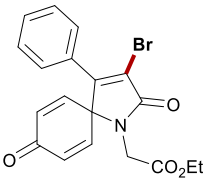
1-benzyl-3-bromo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2c)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.40 - 7.37 (m, 1 H), 7.34 (m, 2 H), 7.28 (m, 4 H), 7.26 - 7.21 (m, 3 H), 6.37 - 6.32 (m, 2 H), 6.30 - 6.24 (m, 2 H), 4.59 (s, 2 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 183.8, 166.0, 151.8, 144.2, 137.0, 132.6, 130.2, 130.17, 130.0, 128.9, 128.6, 128.6, 128.0, 127.8, 119.9, 68.78, 45.4.

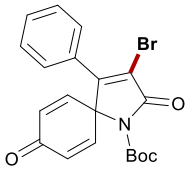
3-bromo-1-(2-oxobutyl)-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2d)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.46 - 7.35 (m, 5 H), 6.69 - 6.63 (m, 2 H), 6.46 - 6.39 (m, 2 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.02 (s, 2 H), 1.28 (t, *J* = 7.2 Hz, 3 H).

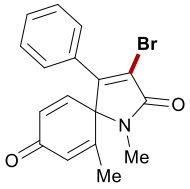
^{13}C NMR (126MHz, $CDCl_3$) δ = 183.7, 168.1, 165.8, 152.6, 143.6, 133.1, 130.4, 130.1, 128.8, 127.8, 119.4, 68.3, 61.9, 41.9, 14.1.

tert-butyl-3-bromo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-1-carboxylate (2e)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.44 - 7.34 (m, 3 H), 7.22 - 7.15 (m, 2 H), 6.68 - 6.60 (m, 2 H), 6.41 - 6.35 (m, 2 H), 1.46 (s, 8 H), 1.53 - 1.37 (m, 9 H).

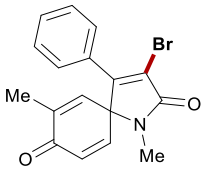
3-bromo-1,6-dimethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2h)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.46 - 7.35 (m, 5 H), 6.53 - 6.46 (m, 2 H), 6.37 (br. s., 1 H), 2.85 (s, 3 H), 1.75 (s, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 184.4, 166.3, 152.6, 151.2, 144.4, 132.9, 132.2, 130.4, 130.0, 128.9, 127.5, 119.7, 70.4, 26.2, 17.7.

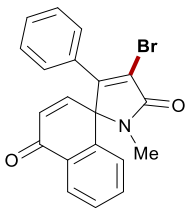
3-bromo-1,7-dimethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2i)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.42 - 7.34 (m, 5 H), 6.47 (s, 2 H), 6.28 (d, *J* = 1.2 Hz, 1 H), 2.92 (s, 3 H), 1.94 (d, *J* = 1.5 Hz, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 184.5, 165.8, 151.7, 144.0, 140.7, 138.8, 133.2, 130.4, 130.1, 128.7, 127.7, 119.4, 68.8, 26.6, 15.9.

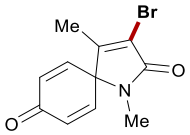
4'-bromo-1'-methyl-3'-phenyl-4*H*-spiro[naphthalene-1,2'-pyrrole]-4,5'(1'*H*)-dione (2j)



^{1}H NMR (500MHz,$CDCl_3$) δ = 8.17 (dd, *J* = 1.1, 7.8 Hz, 1 H), 7.70 - 7.62 (m, 1 H), 7.59 - 7.52 (m, 1 H), 7.31 - 7.27 (m, 1 H), 7.23 (m, 1 H), 7.22 - 7.17 (m, 2 H), 6.94 - 6.86 (m, 2 H), 6.65 - 6.51 (m, 2 H), 2.78 (s, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 182.9, 166.3, 154.5, 144.4, 136.5, 134.0, 133.2, 132.5, 130.1, 130.0, 129.7, 128.5, 127.7, 127.6, 126.0, 118.8, 69.4, 26.4.

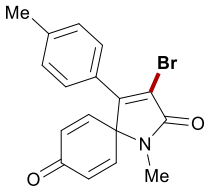
3-bromo-1,4-dimethyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2k)



^{1}H NMR (500MHz, $CDCl_3$) δ = 6.57 (d, *J* = 10.1 Hz, 2 H), 6.40 - 6.31 (m, 2 H), 2.92 (s, 3 H), 1.86 (s, 3 H).

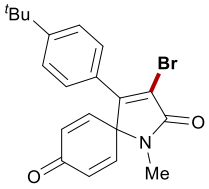
^{13}C NMR (126MHz, $CDCl_3$) δ = 183.7, 165.9, 149.7, 144.6, 133.6, 119.1, 68.5, 27.0, 12.4.

3-bromo-1-methyl-4-(p-tolyl)-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2l)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.32 (d, *J* = 8.2 Hz, 2 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 6.50 (s, 4 H), 2.93 (s, 3 H), 2.36 (s, 3 H).

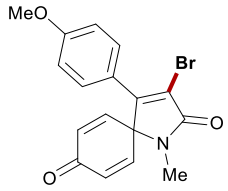
3-bromo-4-(4-(*tert*-butyl)phenyl)-1-methyl-1-azaspiro[4.5]deca-3,6,9 triene 2,8-dione (2m)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.45 - 7.36 (m, 4 H), 6.52 (s, 4 H), 2.93 (s, 3 H), 1.31 (s, 9 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 183.9, 166.0, 153.7, 150.9, 144.5, 133.3, 127.4, 127.2, 125.7, 119.1, 68.1, 34.9, 31.1, 26.5.

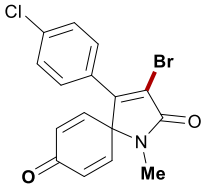
3-bromo-4-(4-methoxyphenyl)-1-methyl-1-azaspiro [4.5] deca-3,6,9-triene-2,8-dione (2n)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.48 - 7.42 (m, 2 H), 6.91 - 6.85 (m, 2 H), 6.51 (s, 4 H), 3.81 (s, 3 H), 2.92 (s, 3 H).

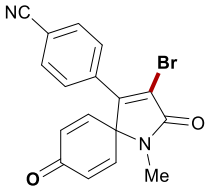
^{13}C NMR (126MHz, $CDCl_3$) δ = 183.8, 166.0, 161.0, 150.6, 144.6, 133.2, 129.3, 122.3, 118.3, 114.2, 68.1, 55.3, 26.5.

3-bromo-4-(4-chlorophenyl)-1-methyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2o)



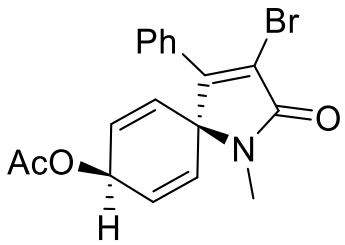
^{1}H NMR (500MHz, $CDCl_3$) δ = 7.36 (s, 4 H), 6.54 - 6.47 (m, 4 H), 2.94 (s, 3 H).

4-(3-bromo-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-3,6,9-trien-4-yl)benzonitrile (2p)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.74 - 7.69 (m, 2 H), 7.58 - 7.52 (m, 2 H), 6.59 - 6.50 (m, 4 H), 2.98 (s, 3 H).

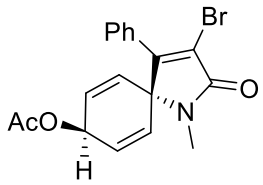
(5s,8s)-3-bromo-1-methyl-2-oxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-8-yl acetate (3a)



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.35 - 7.43 (m, 5 H), 6.19 (dd, *J*=10.1, 3.1 Hz, 2 H), 5.60 (dd, *J*=10.1, 3.1 Hz, 2 H), 5.41 (m, 1 H), 2.92 (s, 3 H), 2.10 (s, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 170.4, 165.7, 154.9, 131.3, 130.5, 129.7, 128.5, 127.9, 127.9, 118.3, 67.1, 63.3, 26.2, 21.0.

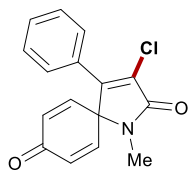
(5r,8r)-3-bromo-1-methyl-2-oxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-8-yl acetate (3b)



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.60 (dd, *J*=7.7, 1.7 Hz, 2 H), 7.36 - 7.41 (m, 3 H), 6.27 (dd, *J*=10.0, 3.5 Hz, 2 H), 5.70 (m, 1 H), 5.65 (dd, *J*=10.0, 3.5 Hz, 2 H), 2.82 (s, 3 H), 2.03 (s, 3 H).

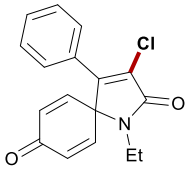
^{13}C NMR (126MHz, $CDCl_3$) δ = 170.4, 165.7, 154.9, 131.3, 130.5, 129.7, 128.5, 127.9, 127.9, 118.4, 67.1, 63.3, 26.2, 21.0.

3-chloro-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (4a)



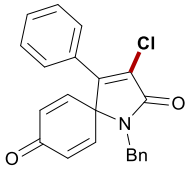
^{1}H NMR (500MHz, $CDCl_3$) δ = 7.50 - 7.35 (m, 5 H), 6.52 (s, 4 H), 2.93 (s, 3 H).

3-chloro-1-ethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (4b)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.47 - 7.33 (m, 5 H), 6.69 - 6.36 (m, 4 H), 3.38 (q, *J* = 7.2 Hz, 2 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

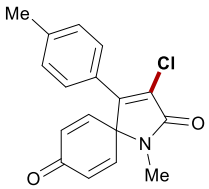
1-benzyl-3-chloro-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (4c)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.40 - 7.33 (m, 5 H), 7.30 - 7.26 (m, 3 H), 7.25 - 7.22 (m, 2 H), 6.37 - 6.33 (m, 2 H), 6.31 - 6.27 (m, 2 H), 4.58 (s, 2 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 183.8, 165.4, 147.9, 144.5, 136.9, 132.7, 130.3, 129.1, 128.9, 128.7, 128.6, 128.5, 128.0, 127.9, 67.1, 45.2.

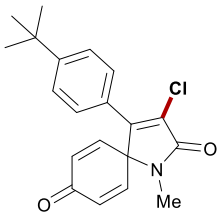
3-chloro-1-methyl-4-(*p*-tolyl)-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (4d)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.2 Hz 2 H), 6.52 (m, 4 H), 2.91 (s, 3 H), 2.36 (s, 3 H)

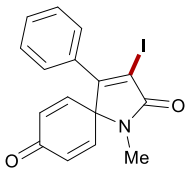
^{13}C NMR (126MHz, $CDCl_3$) δ = 183.8, 147.2, 144.7, 140.8, 133.4, 132.7, 129.5, 127.7, 126.4, 126.3, 66.5, 26.3, 21.4

4-(4-(*tert*-butyl)phenyl)-3-chloro-1-methyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (4g)



^{1}H NMR (500MHz,$CDCl_3$) δ = 7.51 - 7.47 (m, 2 H), 7.40 - 7.37 (m, 2 H), 6.59 - 6.47 (m, 4 H), 2.91 (s, 3 H), 1.31 (s, 9 H).

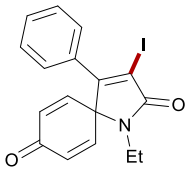
3-iodo-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (5a)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.44 - 7.34 (m, 3 H), 7.30 (m, 2 H), 6.54 - 6.44 (m, 4 H), 2.96 (s, 3 H).

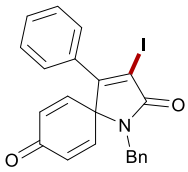
^{13}C NMR (126MHz, $CDCl_3$) δ = 183.7, 167.4, 157.9, 144.1, 133.3, 131.9, 130.1, 128.7, 127.7, 98.2, 70.4, 27.0.

1-ethyl-3-iodo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (5b)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.44 - 7.33 (m, 3 H), 7.27 - 7.24 (m, 2 H), 6.61 - 6.37 (m, 4 H), 3.41 (q, *J* = 7.2 Hz, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

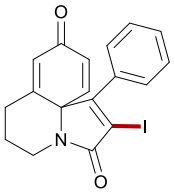
1-benzyl-3-iodo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (5c)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.41 - 7.32 (m, 3 H), 7.27 - 7.24 (m, 5 H), 7.21 - 7.17 (m, 2 H), 6.41 - 6.16 (m, 4 H), 4.60 (s, 2 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 183.9, 167.6, 158.4, 144.2, 137.1, 132.4, 131.8, 130.0, 129.0, 128.6, 128.0, 127.8, 98.2, 70.8, 45.8.

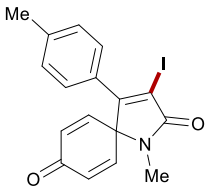
2-iodo-1-phenyl-6,7-dihydro-3*H*-pyrrolo[2,1-*j*]quinoline-3,9(5*H*)-dione (5d)



^{1}H NMR (500MHz,$CDCl_3$) δ = 7.42 - 7.31 (m, 3 H), 7.09 - 7.03 (m, 2 H), 6.53 (d, *J* = 9.8 Hz, 1 H), 6.35 (t, *J* = 1.5 Hz, 1 H), 6.19 (dd, *J* = 1.7, 9.8 Hz, 1 H), 4.29 - 4.20 (m, 1 H), 2.85 (ddd, *J* = 7.6, 10.5, 14.1 Hz, 1 H), 2.58 - 2.44 (m, 2 H), 2.12 - 2.02 (m, 1 H), 1.92 - 1.81 (m, 1 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 184.3, 171.3, 159.7, 157.3, 145.5, 132.0, 131.5, 130.0, 129.3, 128.5, 127.9, 98.2, 74.1, 37.6, 26.9, 26.1

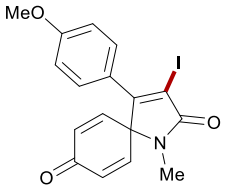
3-iodo-1-methyl-4-(p-tolyl)-1- azaspiro [4.5]deca-3,6,9-triene-2,8-dione (5e)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.24 - 7.14 (m, 4 H), 6.53 - 6.43 (m, 4 H), 2.95 (s, 3 H), 2.36 (s, 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 183.8, 167.5, 157.9, 144.3, 140.4, 133.2, 129.4, 128.9, 127.5, 70.3, 27.0, 21.4.

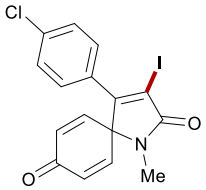
3-iodo-4-(4-methoxyphenyl)-1-methyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (5f)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.38 - 7.31 (m, 2 H), 6.92 - 6.84 (m, 2 H), 6.54 - 6.43 (m, 4 H), 3.82 (s, 3 H), 2.94 (s, 3 H).

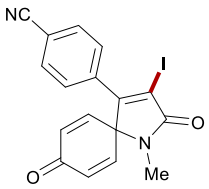
^{13}C NMR (126MHz, $CDCl_3$) δ = 183.8, 167.6, 160.9, 157.2, 144.5, 133.1, 129.2, 123.9, 114.1, 96.8, 70.2, 55.3, 26.9.

4-(4-chlorophenyl)-3-iodo-1-methyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (5g)



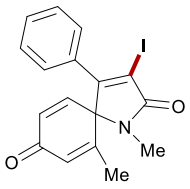
^{1}H NMR (500MHz, $CDCl_3$) δ = 7.40 - 7.33 (m, 2 H), 7.26 (s, 1 H), 7.26 - 7.24 (m, 1 H), 6.48 (s, 4 H), 2.96 (s, 3 H).

4-(3-iodo-1-methyl-2,8-dioxo-1-azaspiro[4.5]deca-3,6,9-trien-4-yl)benzonitrile (5h)



^{1}H NMR (500MHz, $CDCl_3$) δ = 7.69 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 6.54 - 6.45 (m, 4 H), 2.97 (s, 3 H).

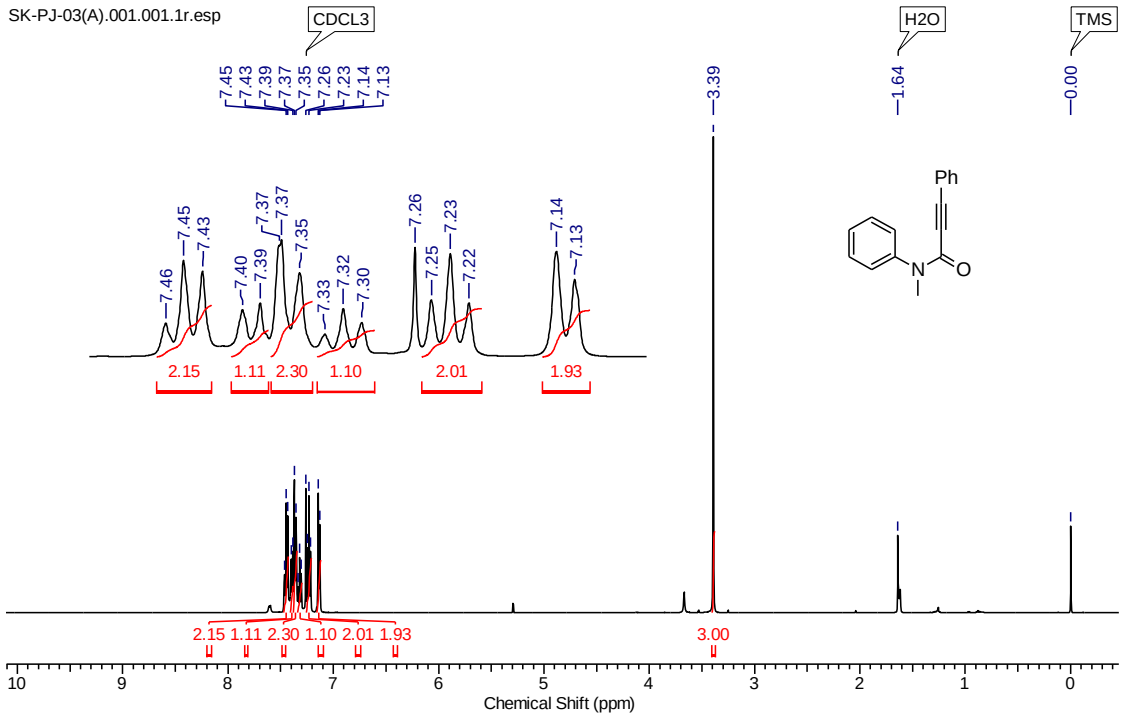
3-iodo-1,6-dimethyl-4-phenyl-1-azaspiro [4.5]deca-3,6,9-triene-2,8-dione (5i)



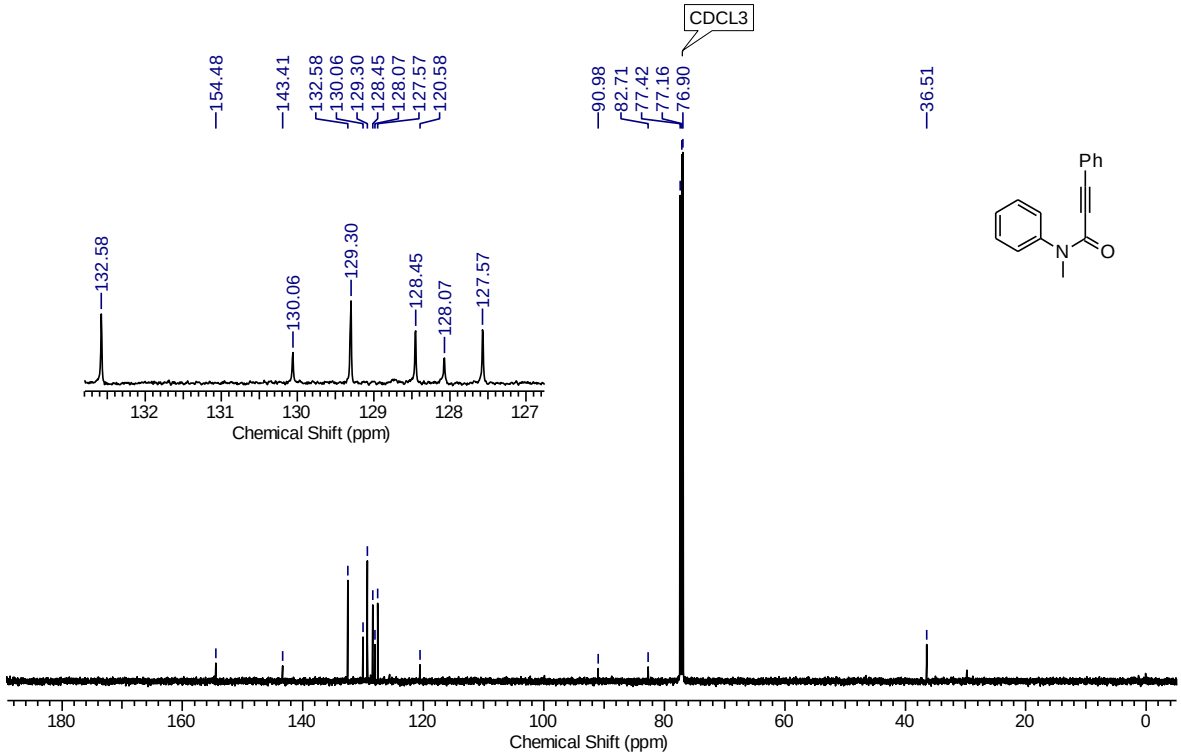
^{1}H NMR (500MHz, $CDCl_3$) δ = 7.47 - 7.28 (m, 5 H), 6.47 (s, 2 H), 6.33 (d, *J* = 1.4 Hz, 1 H), 2.87 (s, 3 H), 1.76 (br. s., 3 H).

^{13}C NMR (126MHz, $CDCl_3$) δ = 184.4, 167.9, 157.9, 152.4, 144.2, 132.8, 132.1, 131.6, 130.3, 128.8, 127.4, 97.9, 72.6, 26.5, 17.7.

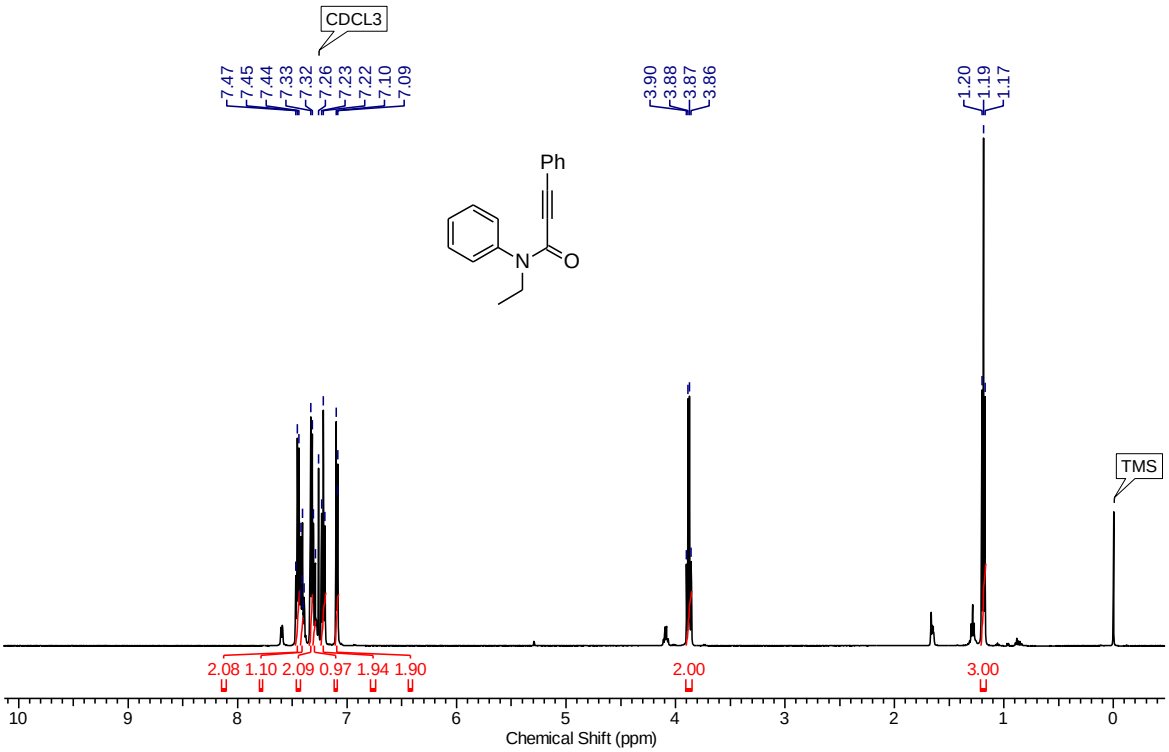
^{1}H NMR spectrum of **1a** in $CDCl_3$



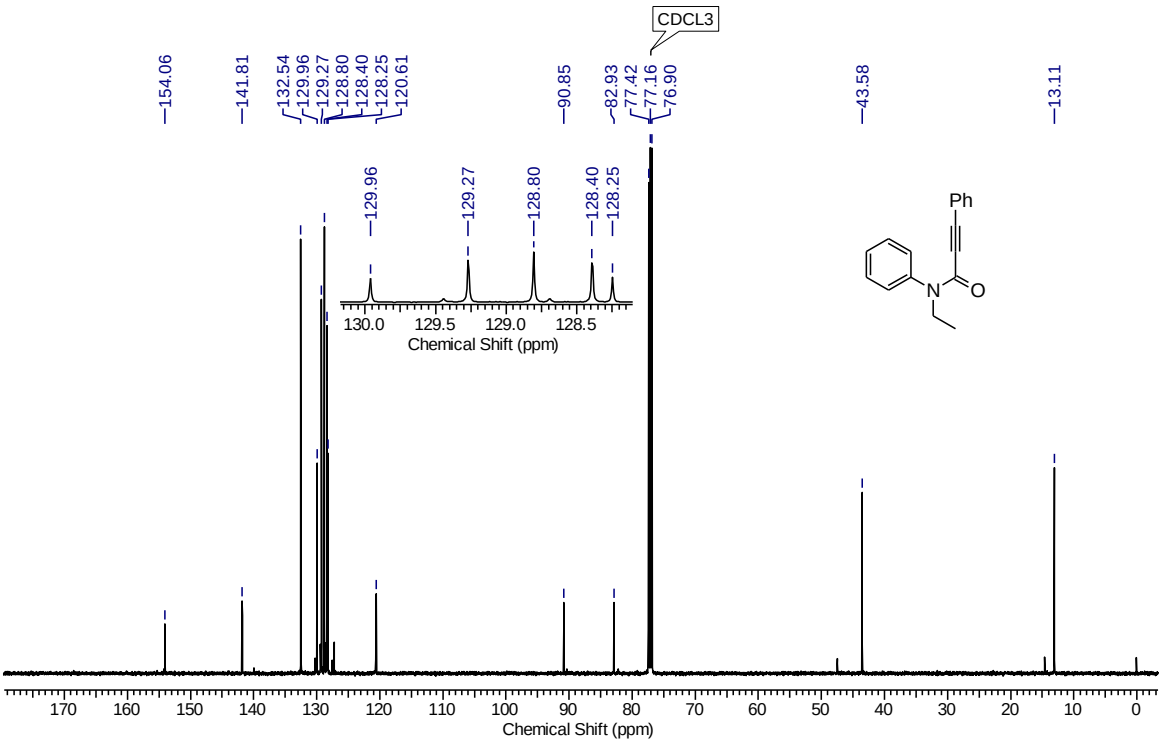
^{13}C NMR spectrum of **1a** in $CDCl_3$



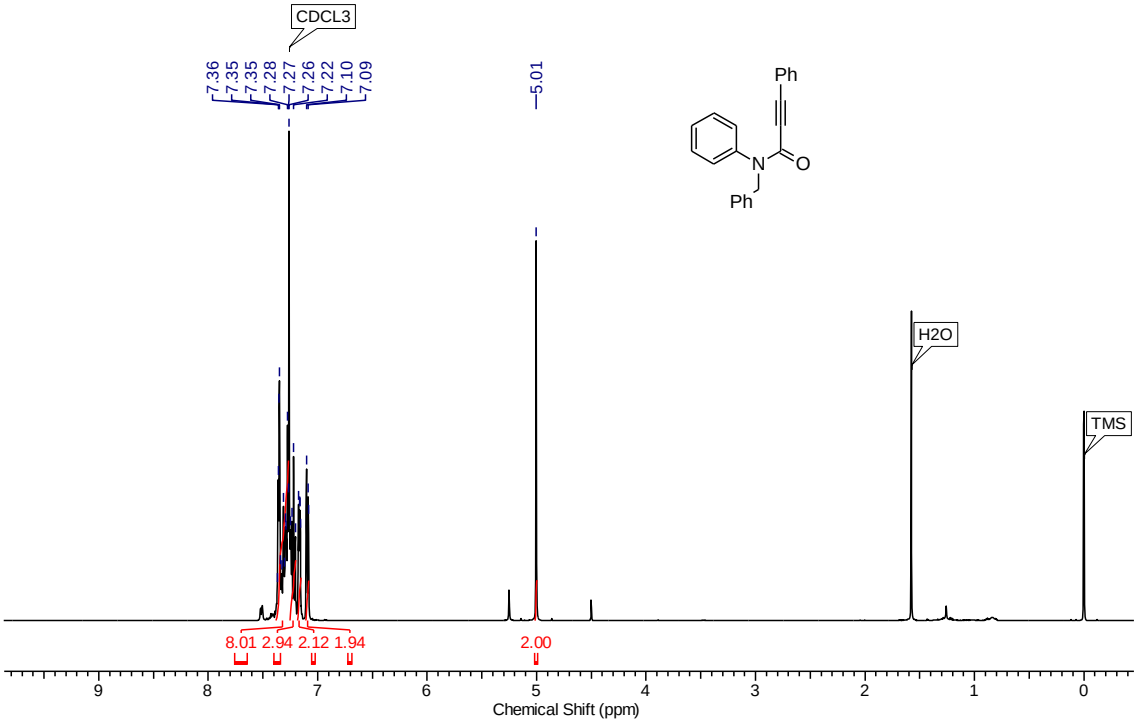
^{1}H NMR spectrum of **1b** in $CDCl_3$



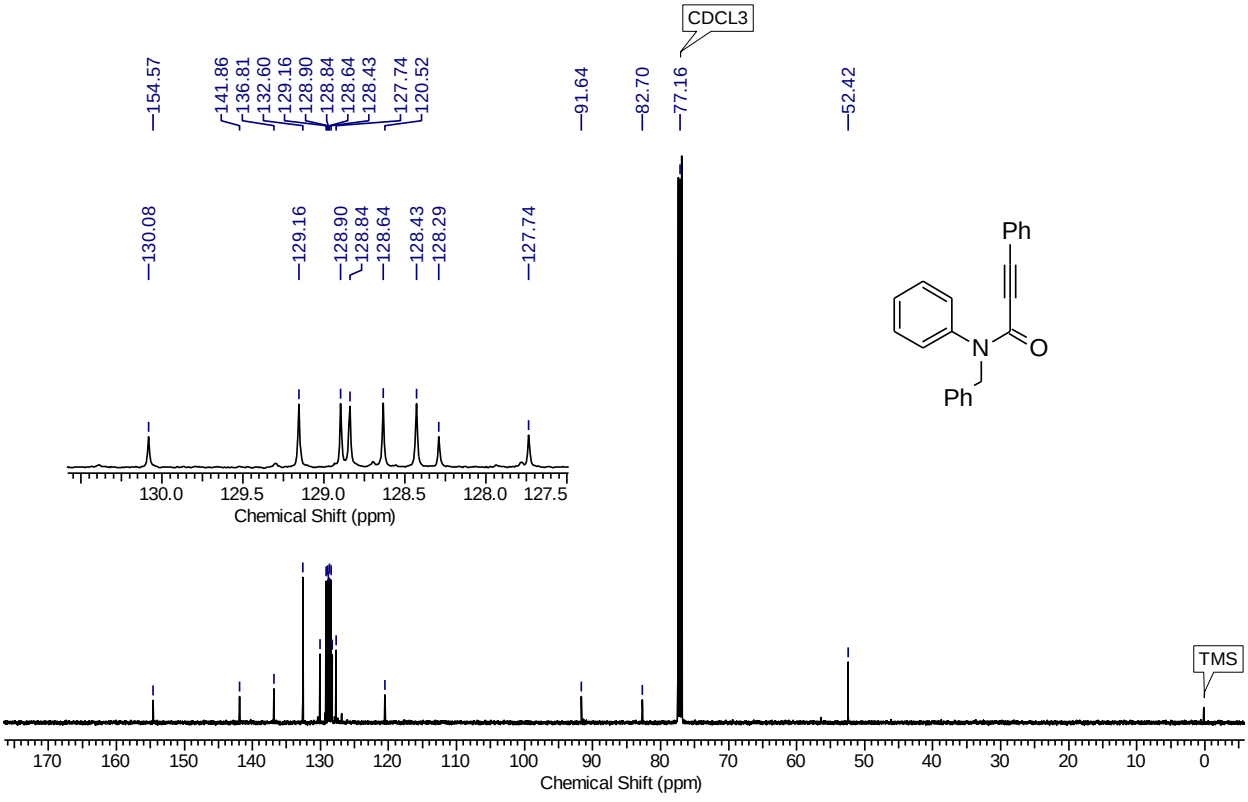
^{13}C NMR spectrum of **1b** in $CDCl_3$



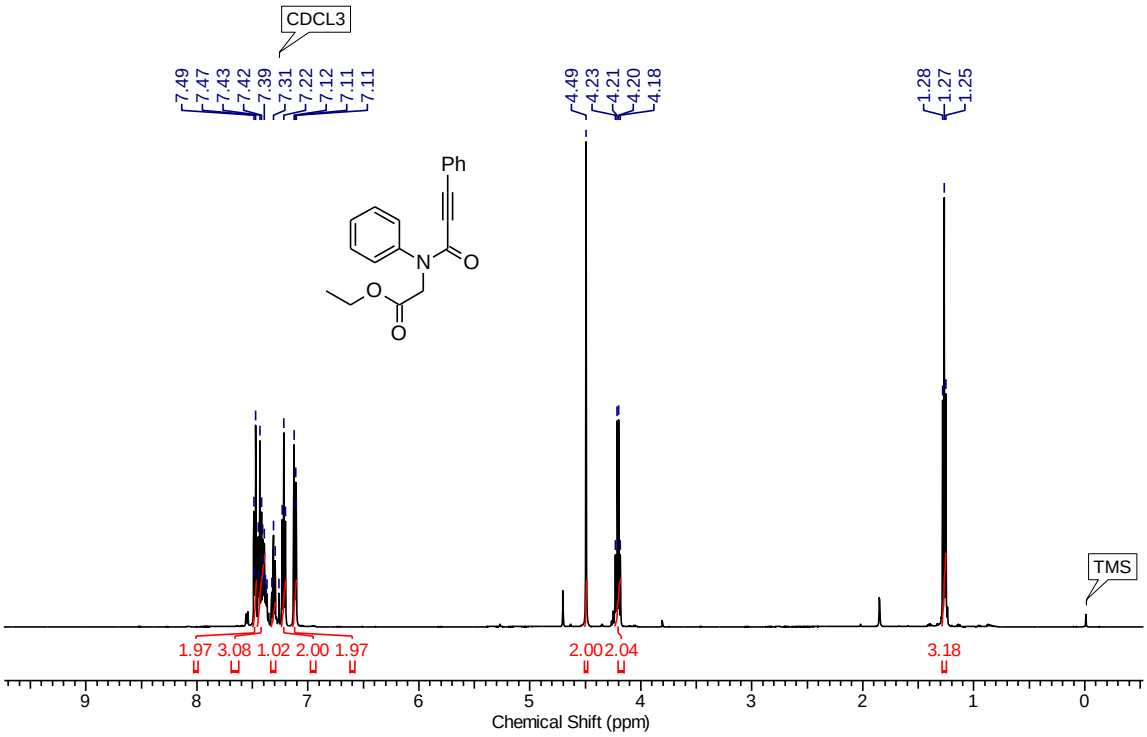
^{1}H NMR spectrum of **1c** in $CDCl_3$



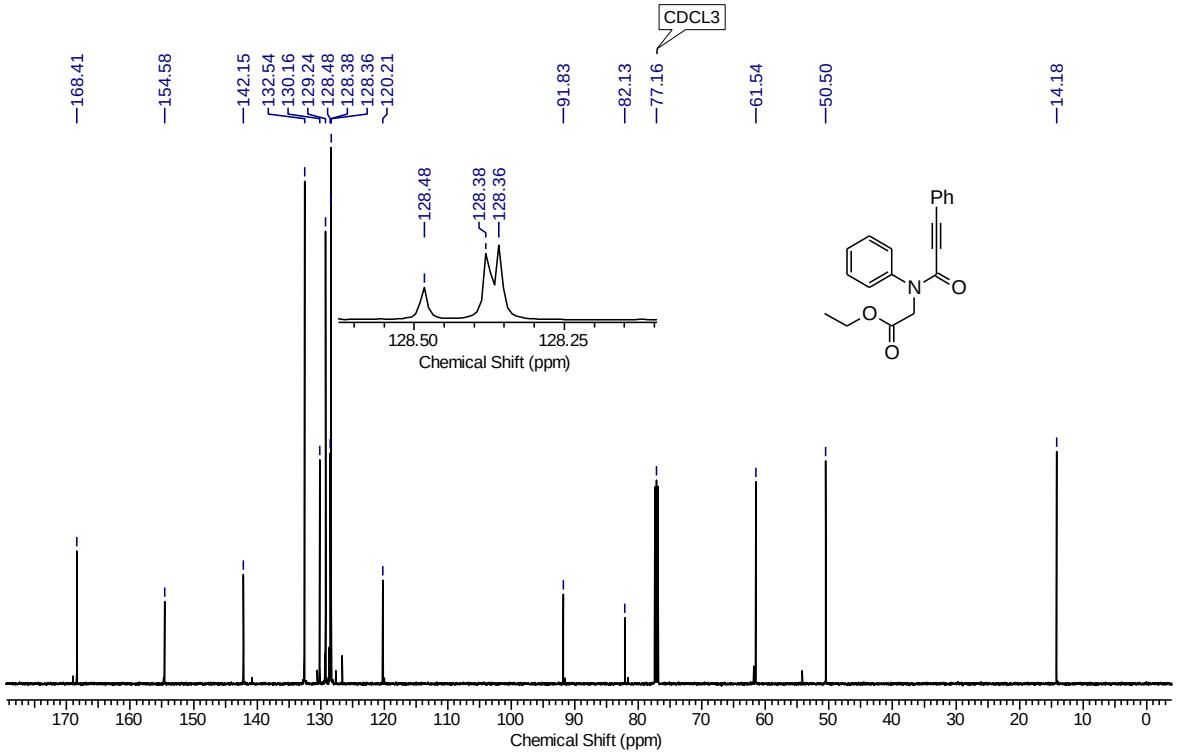
^{13}C NMR spectrum of **1c** in $CDCl_3$



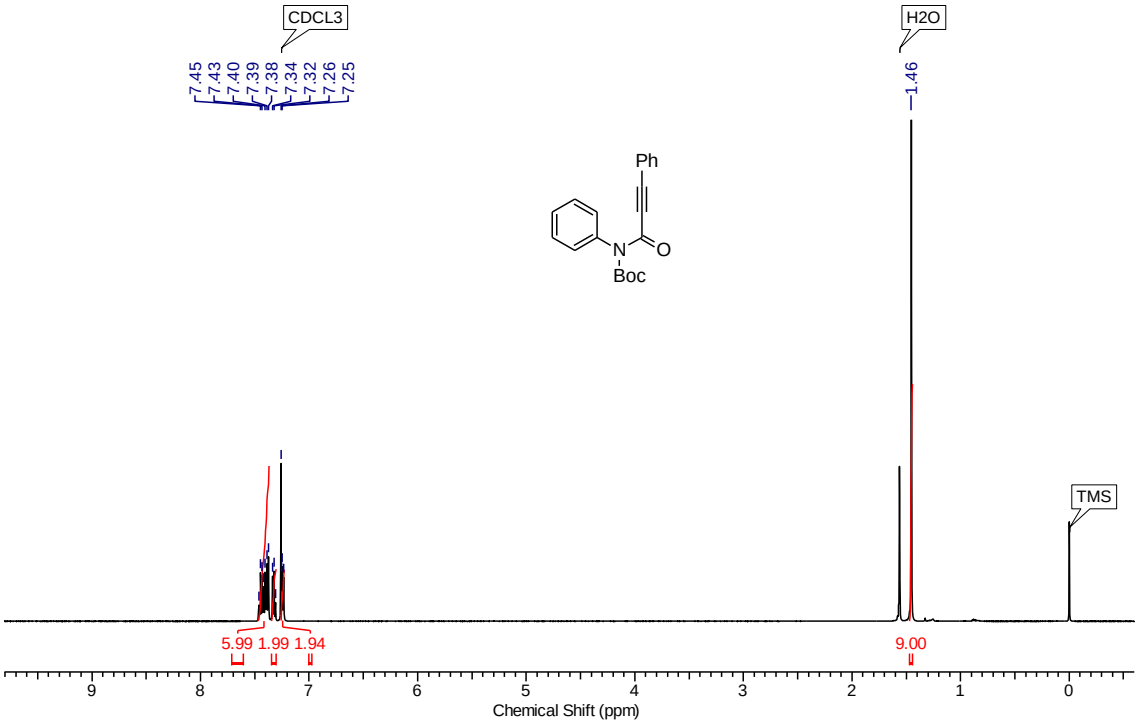
^{1}H NMR spectrum of **1d** in $CDCl_3$



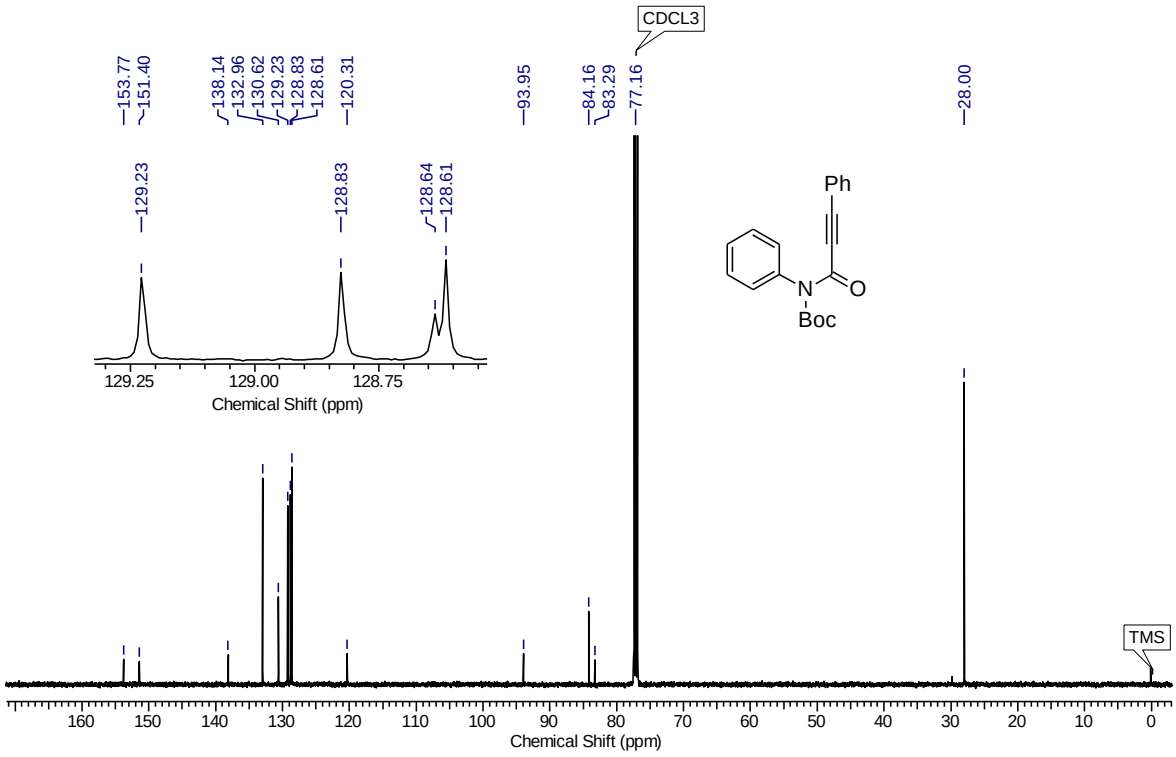
^{13}C NMR spectrum of **1d** in $CDCl_3$



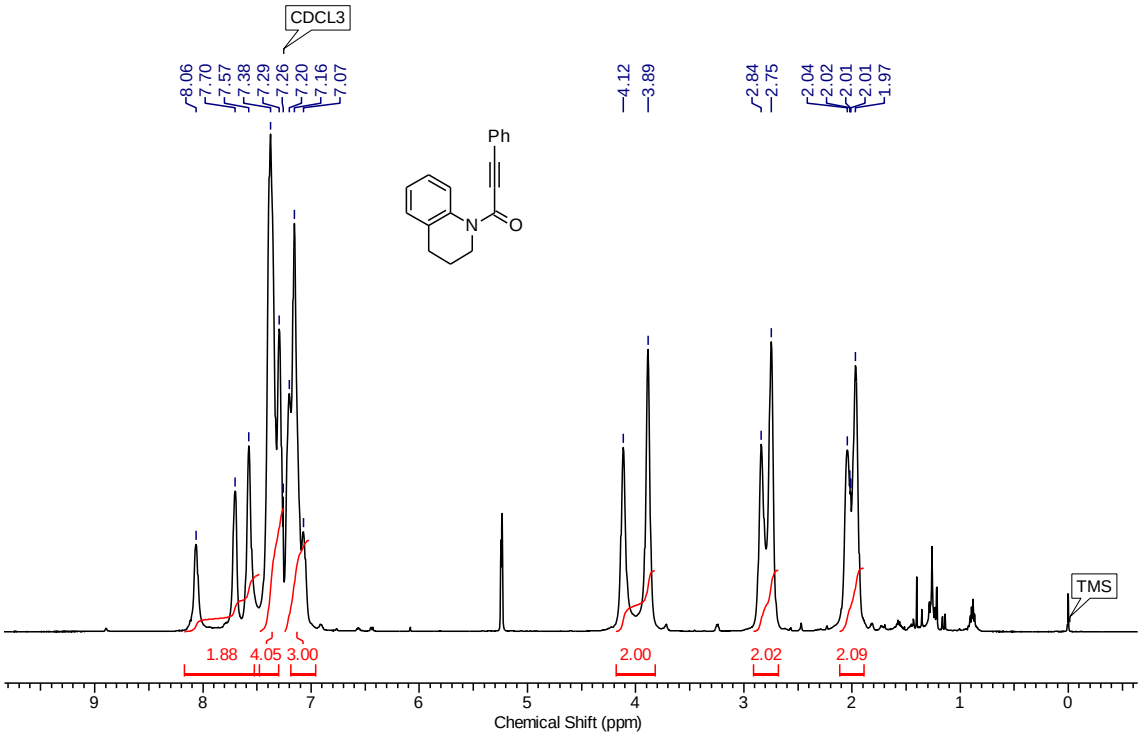
^{1}H NMR spectrum of **1e** in $CDCl_3$



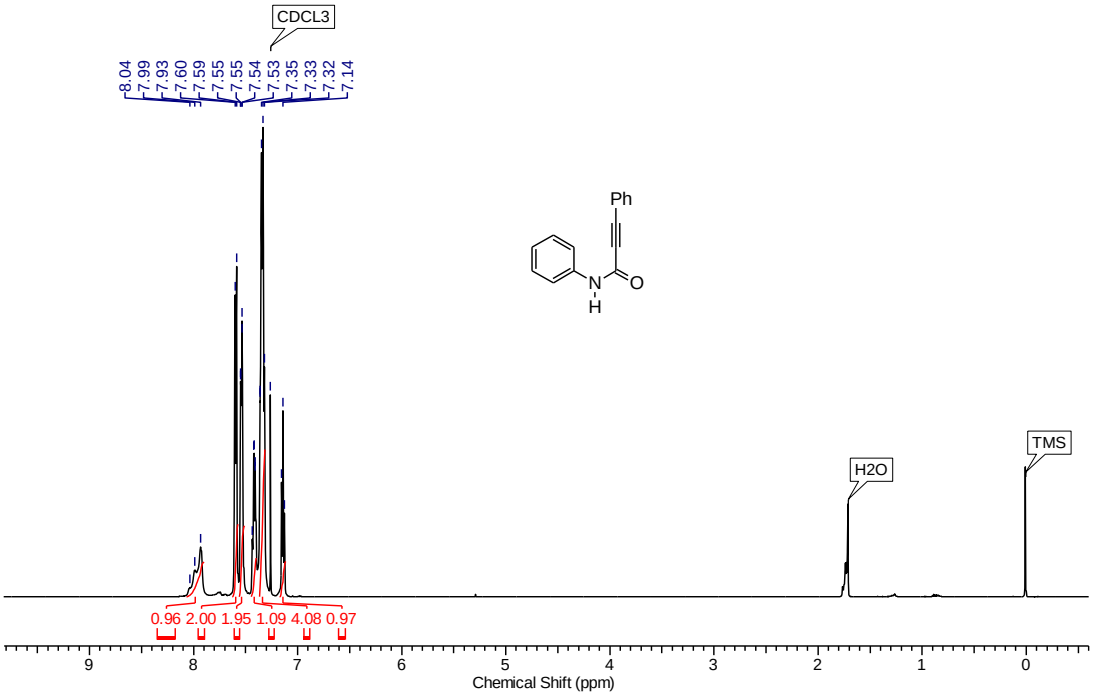
^{13}C NMR spectrum of **1e** in $CDCl_3$



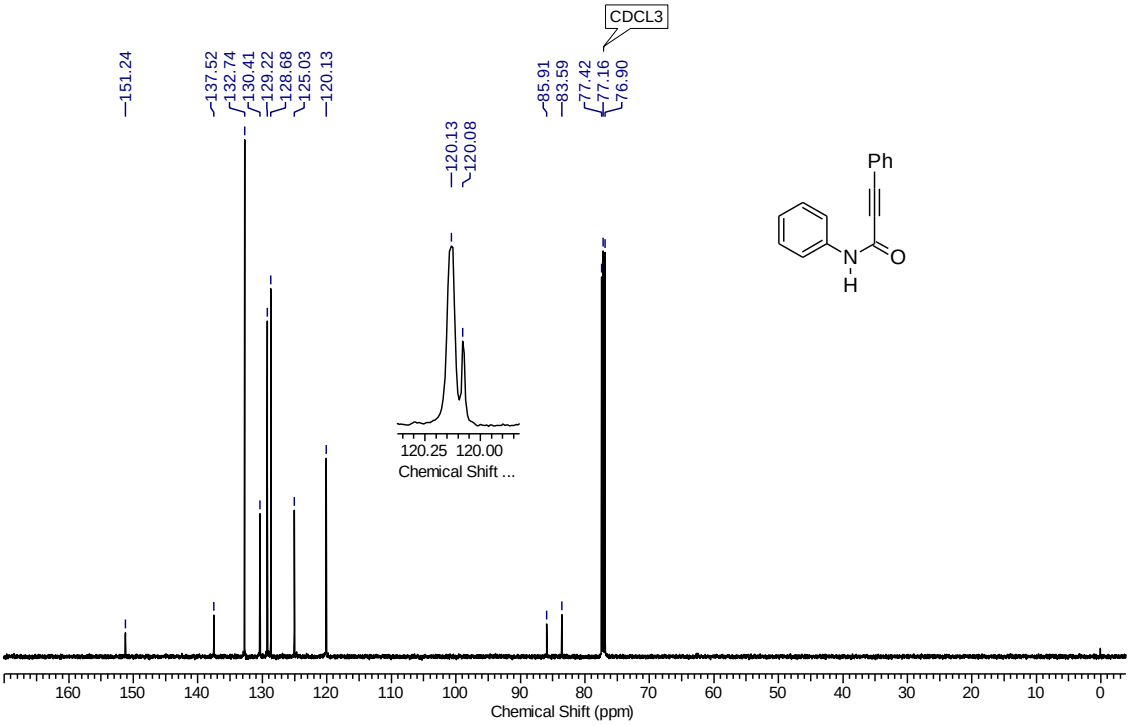
^{1}H NMR spectrum of **1f** in $CDCl_3$



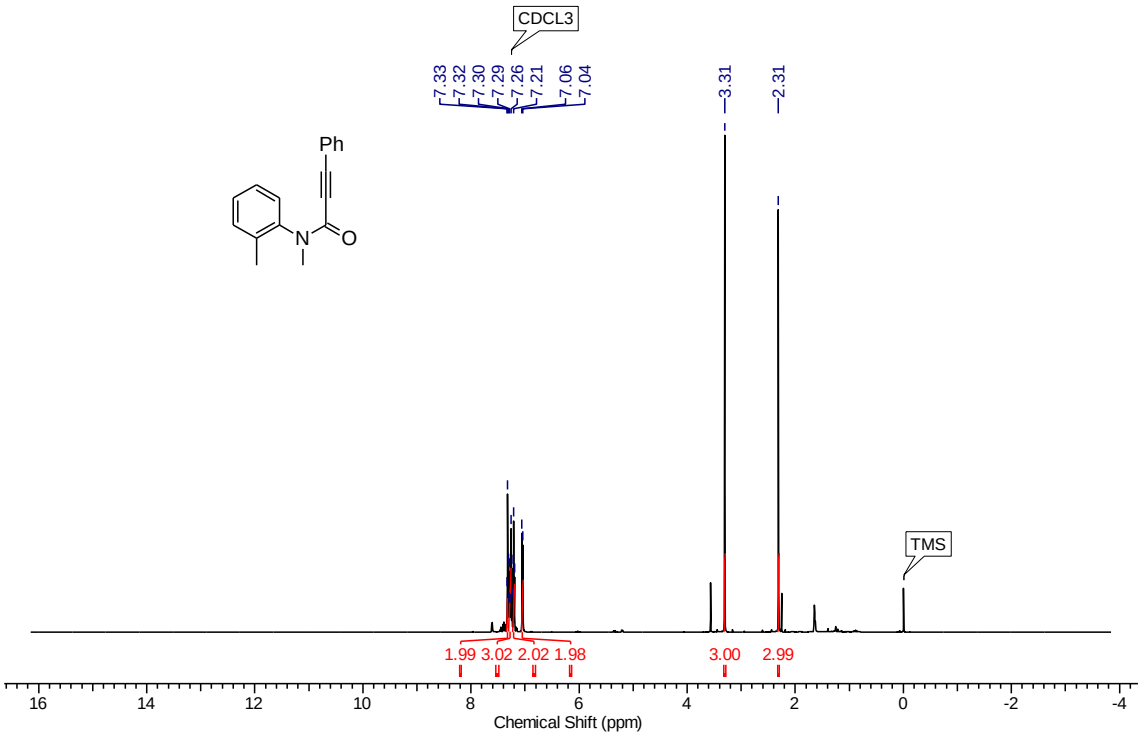
^{1}H NMR spectrum of **1g** in $CDCl_3$



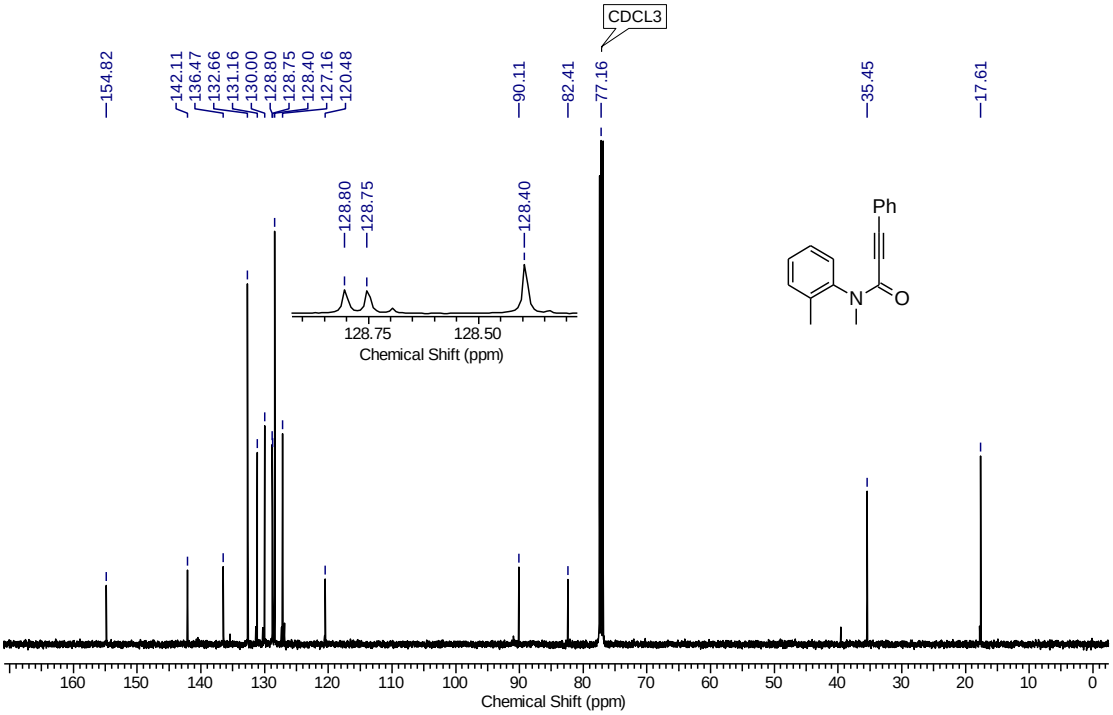
^{13}C NMR spectrum of **1g** in $CDCl_3$



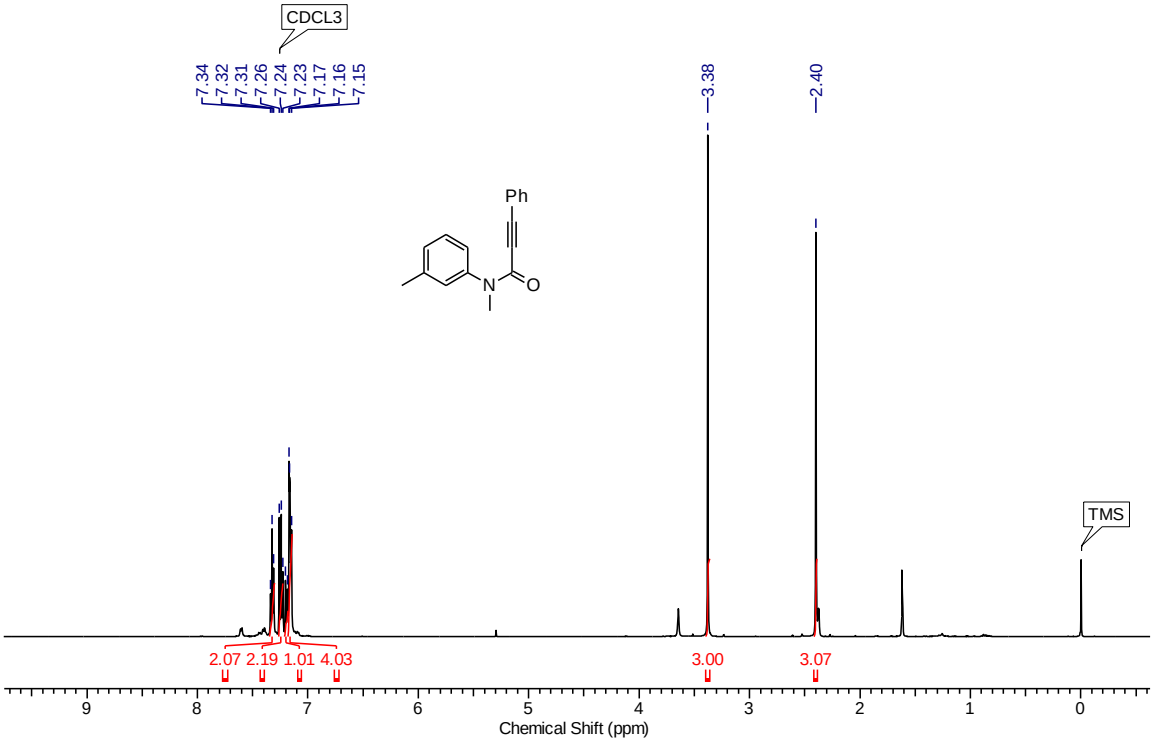
^{1}H NMR spectrum of **1h** in $CDCl_3$



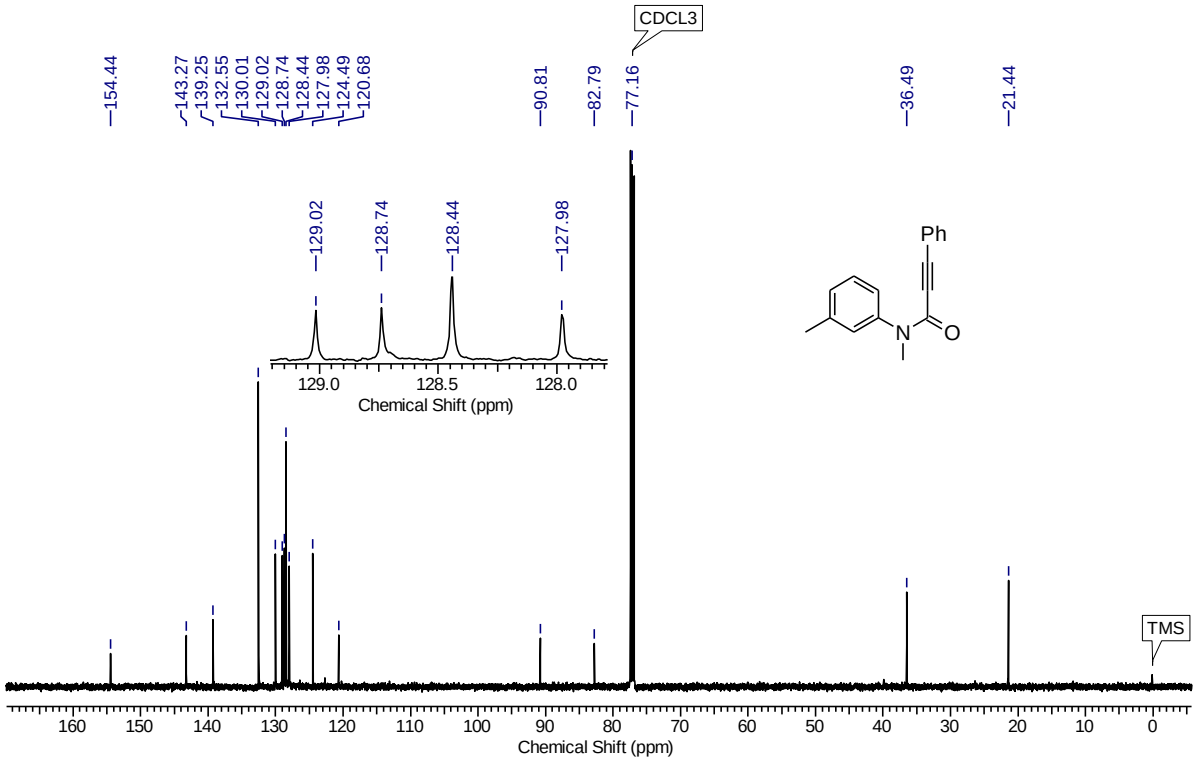
^{1}H NMR spectrum of **1h** in $CDCl_3$



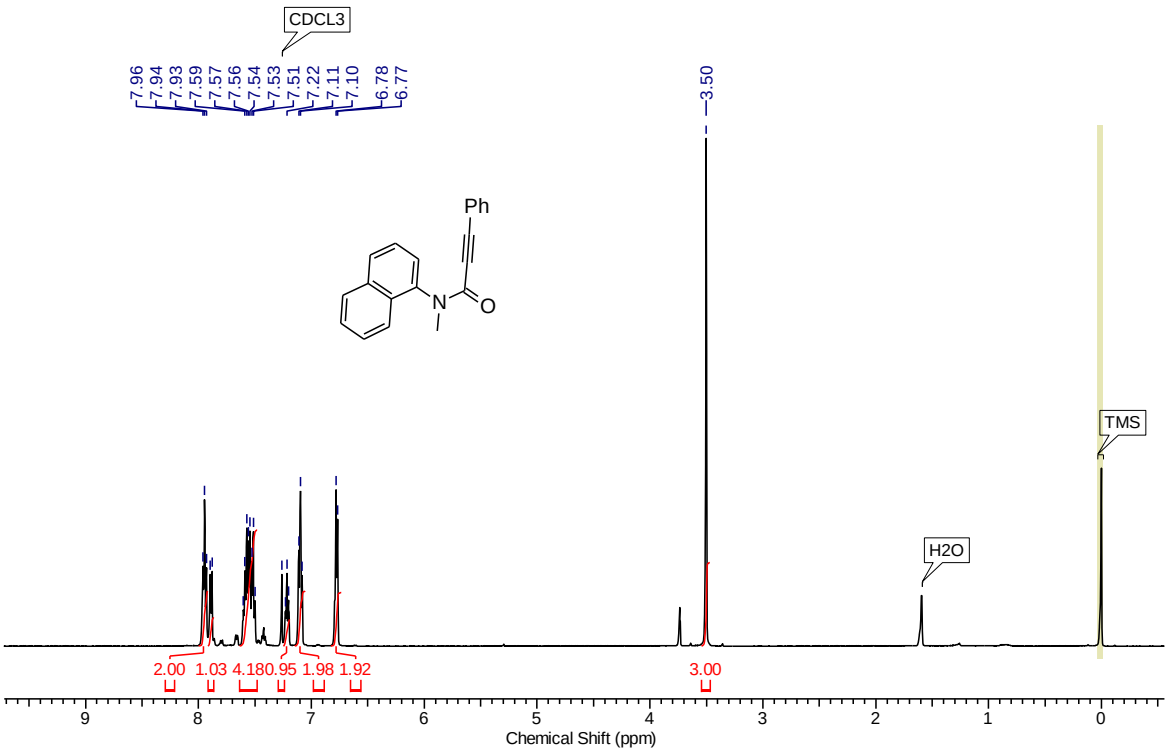
^{1}H NMR spectrum of **1i** in $CDCl_3$



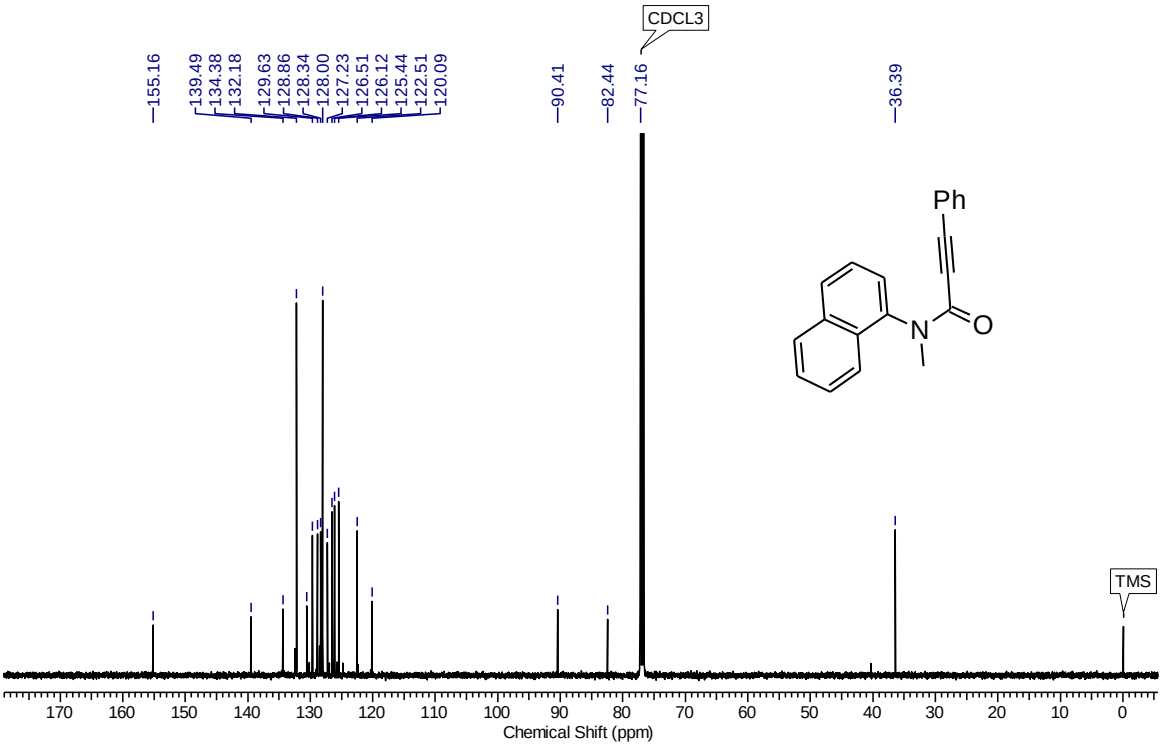
^{13}C NMR spectrum of **1i** in $CDCl_3$



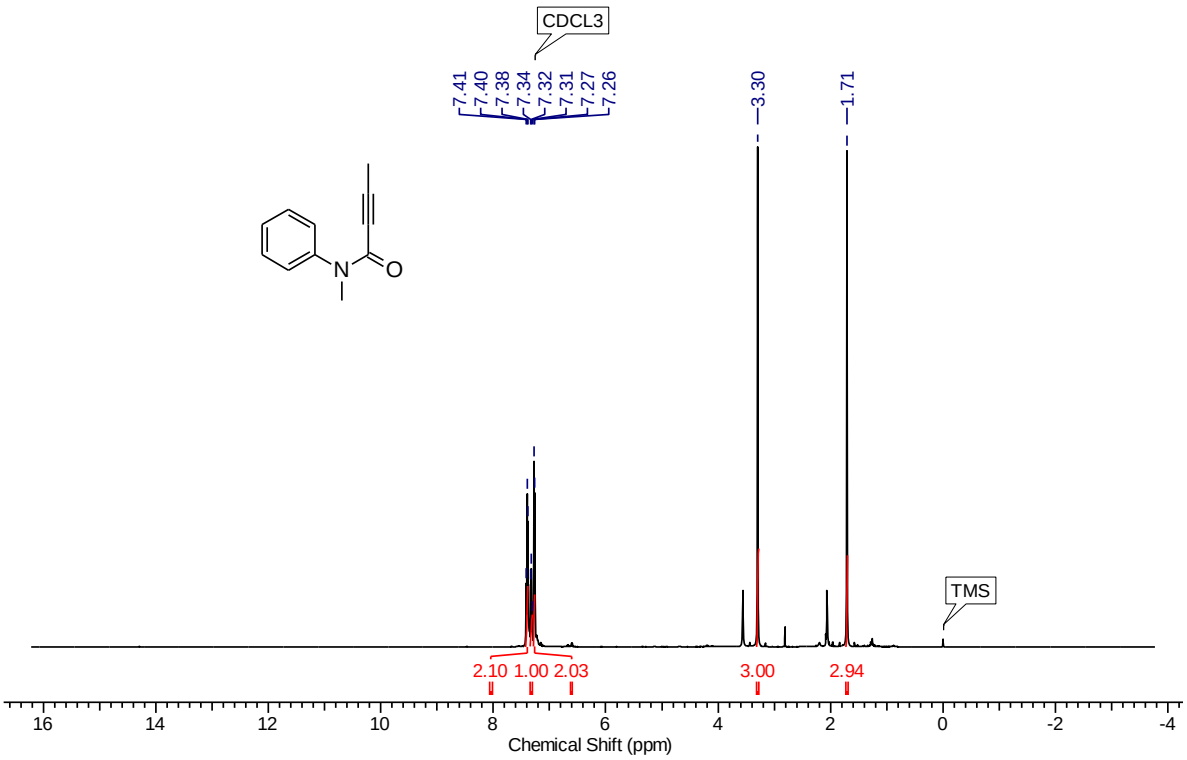
^{1}H NMR spectrum of **1j** in $CDCl_3$



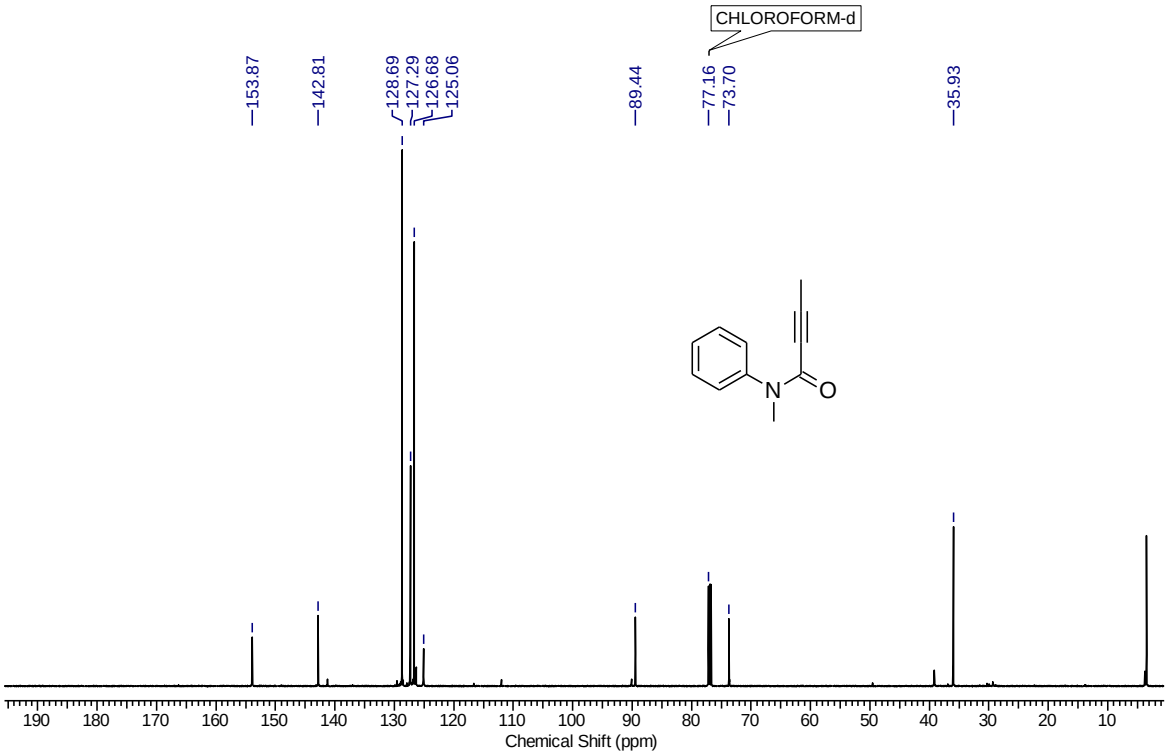
^{13}C NMR spectrum of **1j** in $CDCl_3$



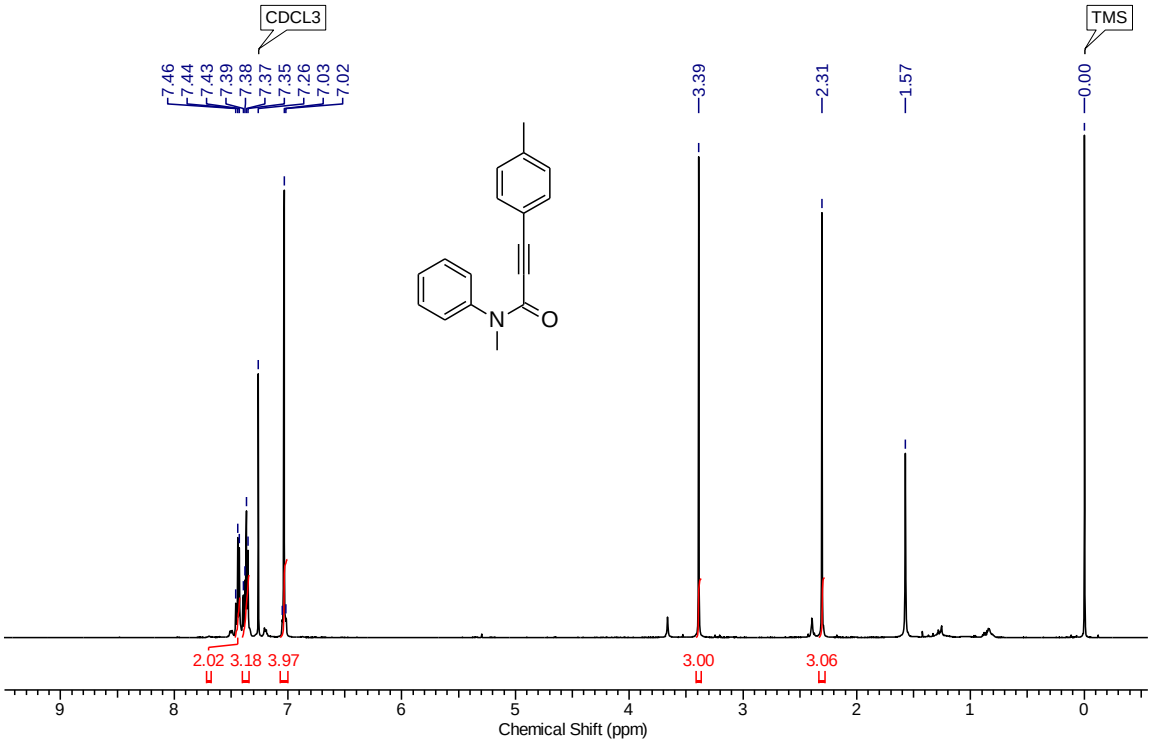
^{1}H NMR spectrum of **1k** in $CDCl_3$



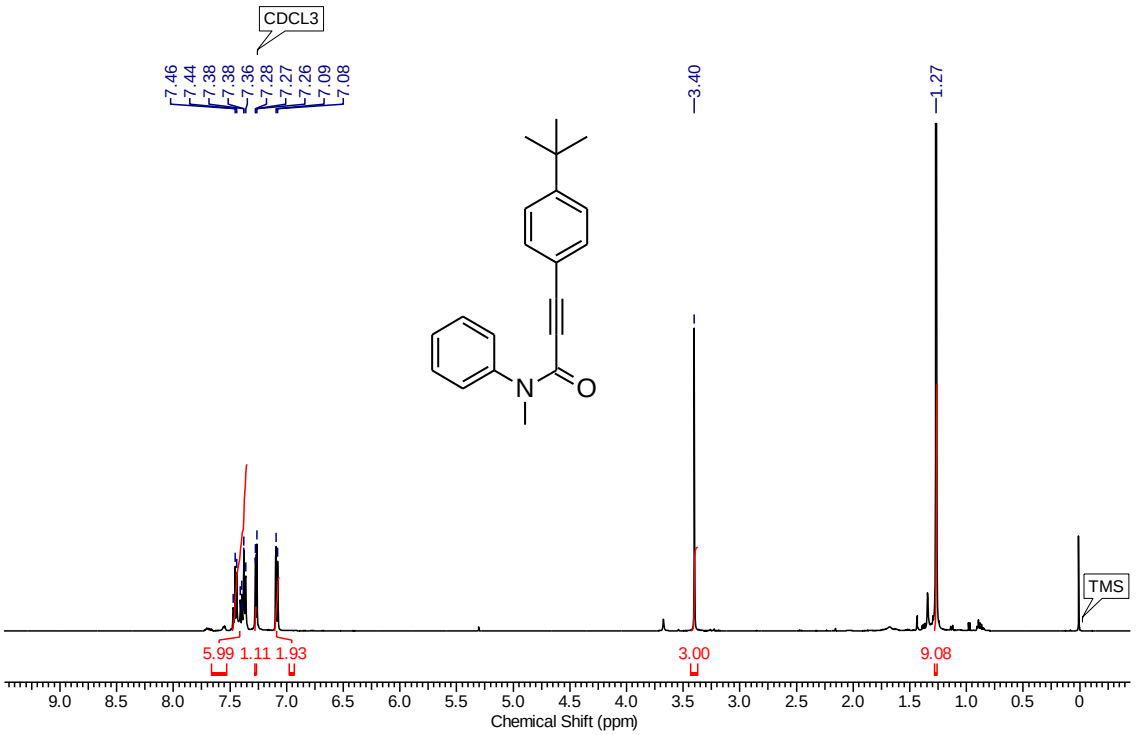
^{13}C NMR spectrum of **1k** in $CDCl_3$



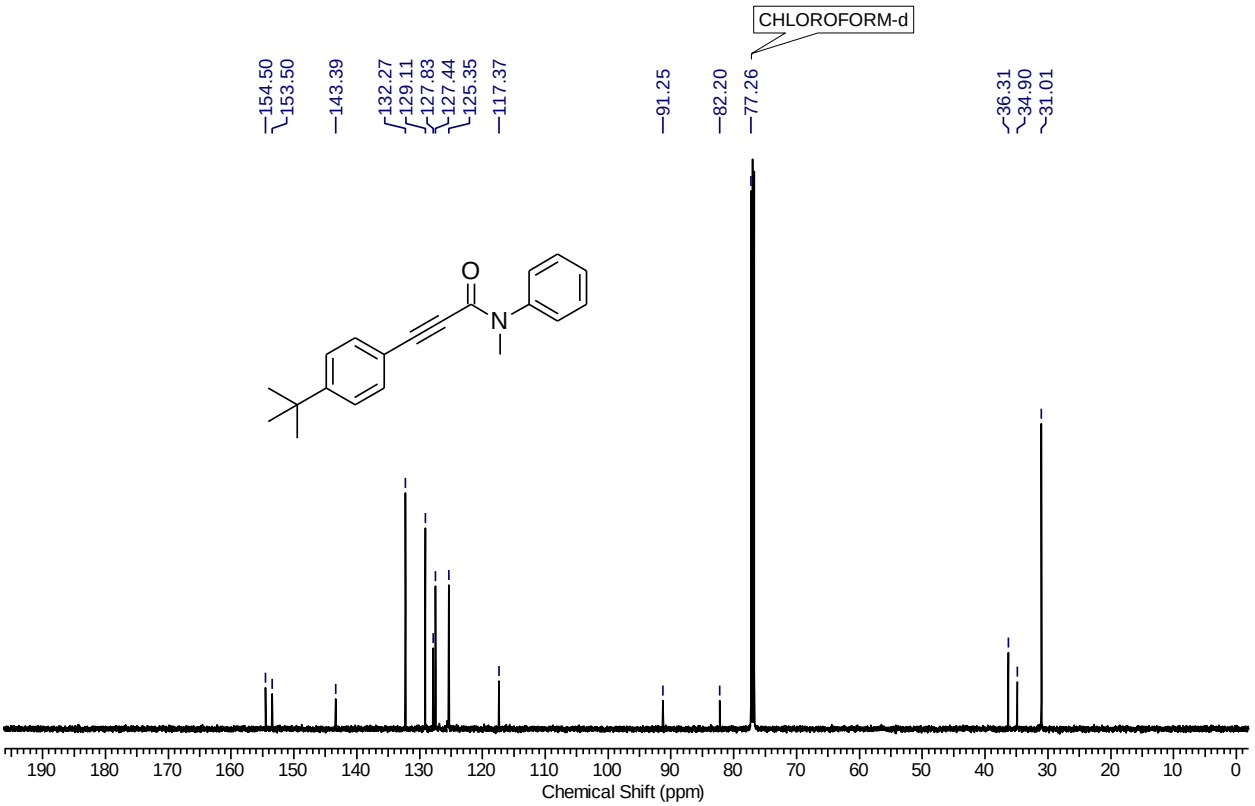
^{1}H NMR spectrum of **1l** in $CDCl_3$



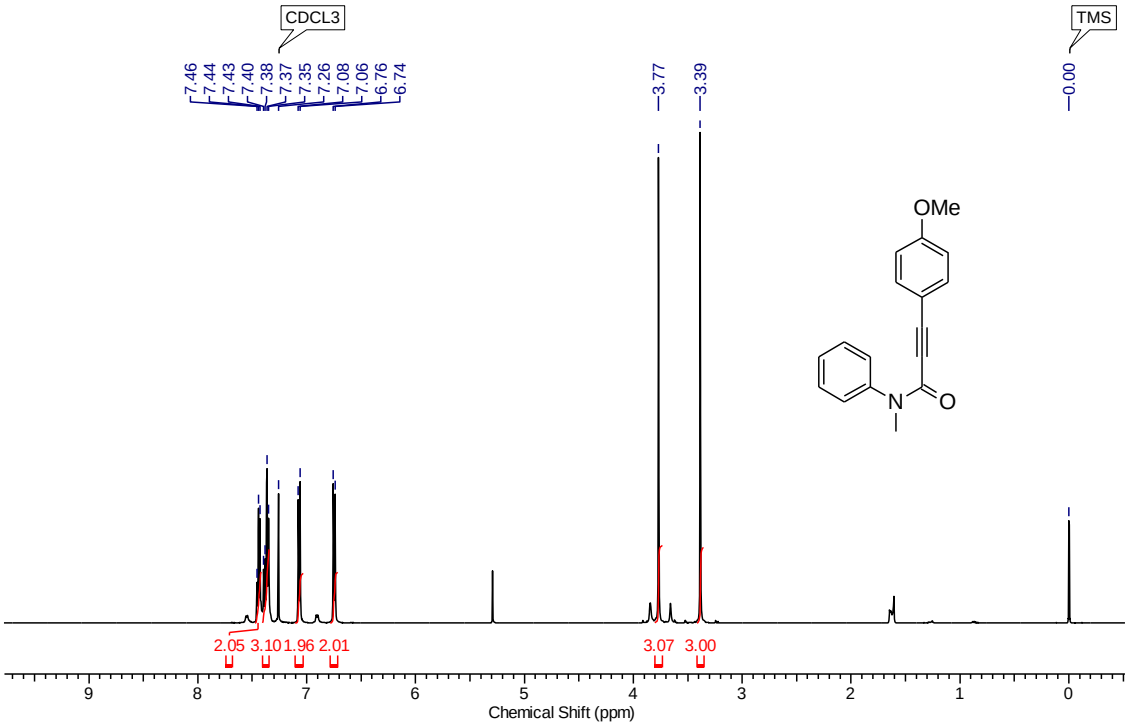
^{1}H NMR spectrum of **1m** in $CDCl_3$



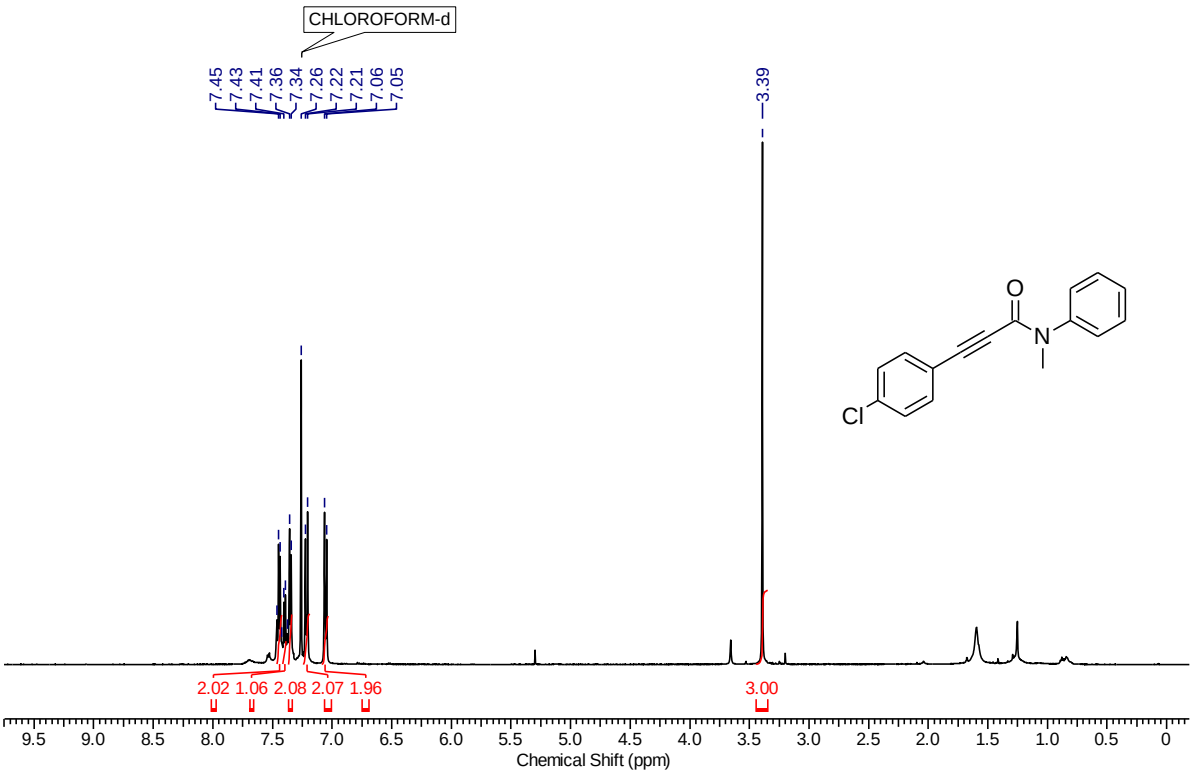
^{13}C NMR spectrum of **1m** in $CDCl_3$



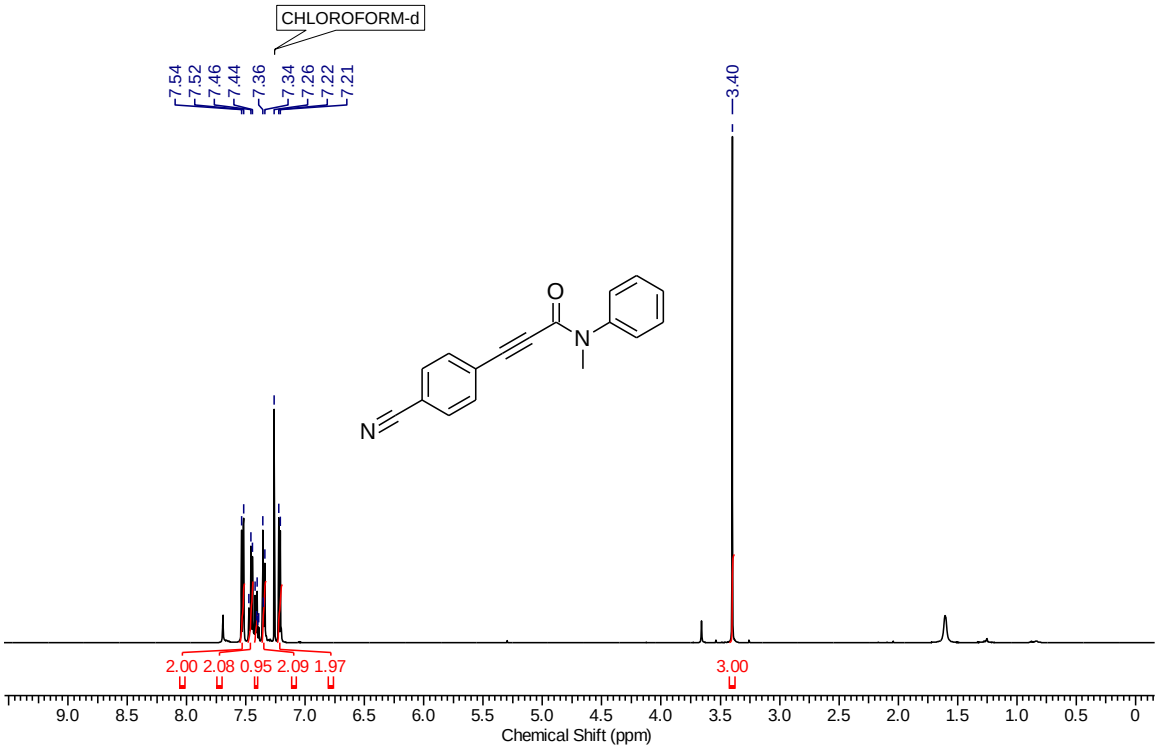
^{1}H NMR spectrum of **1n** in $CDCl_3$



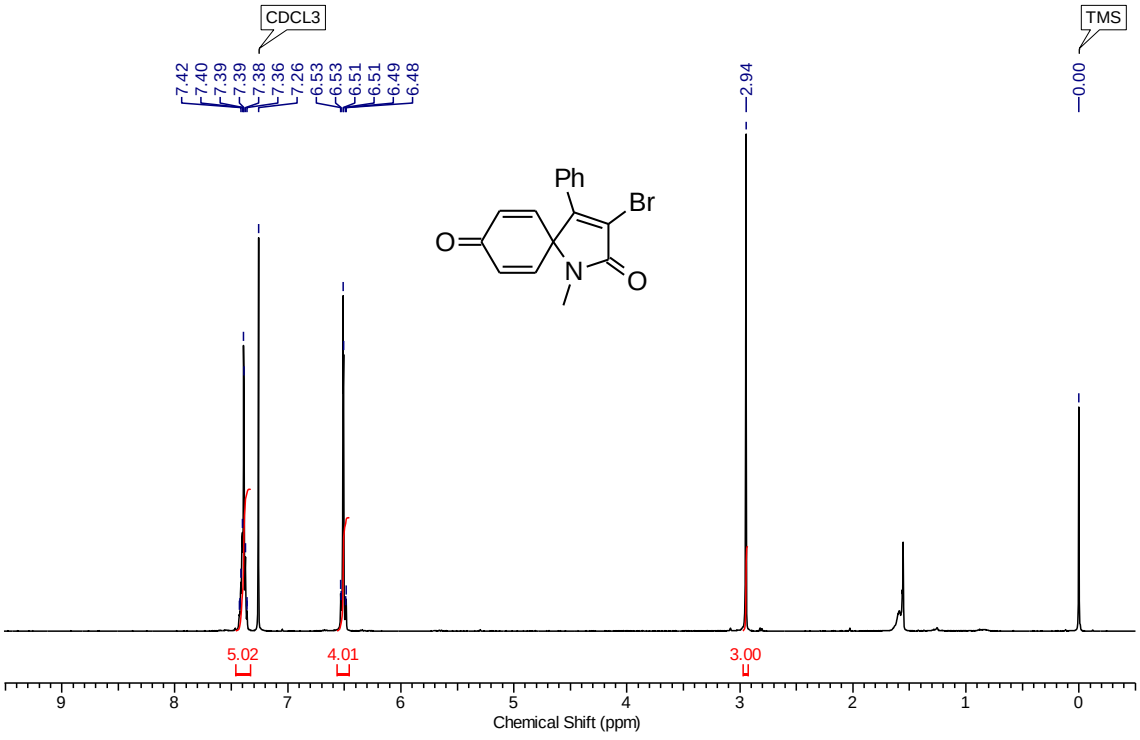
^{1}H NMR spectrum of **1o** in $CDCl_3$



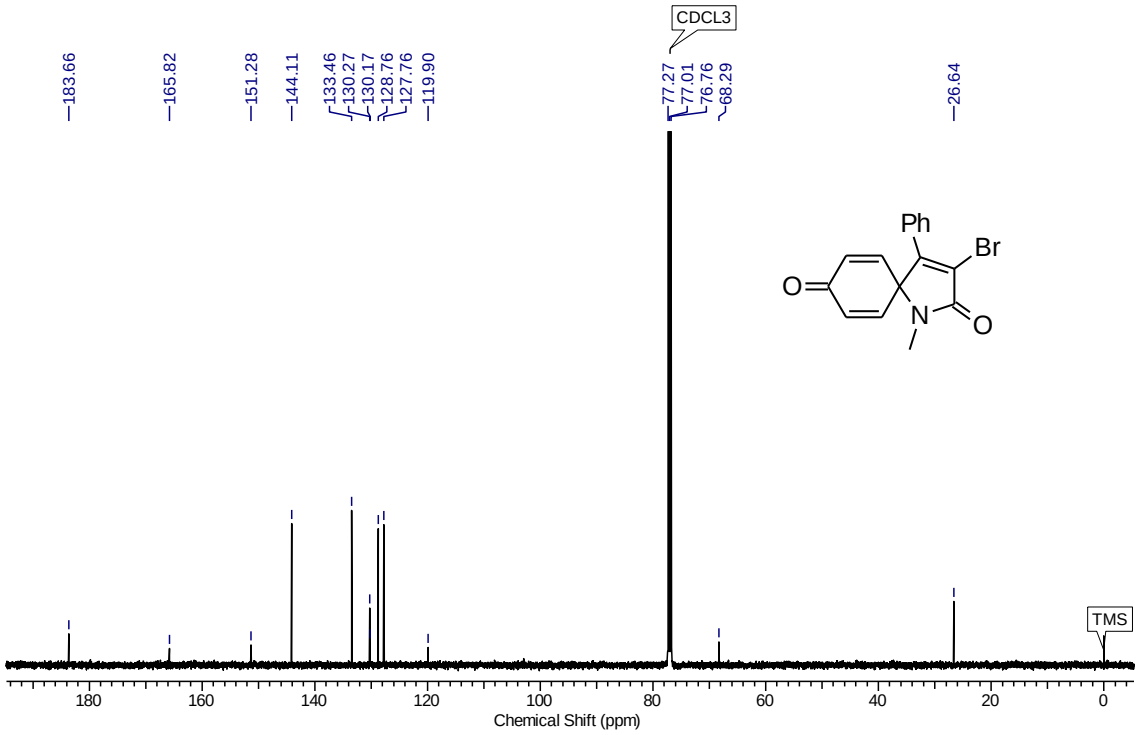
^{1}H NMR spectrum of **1p** in $CDCl_3$



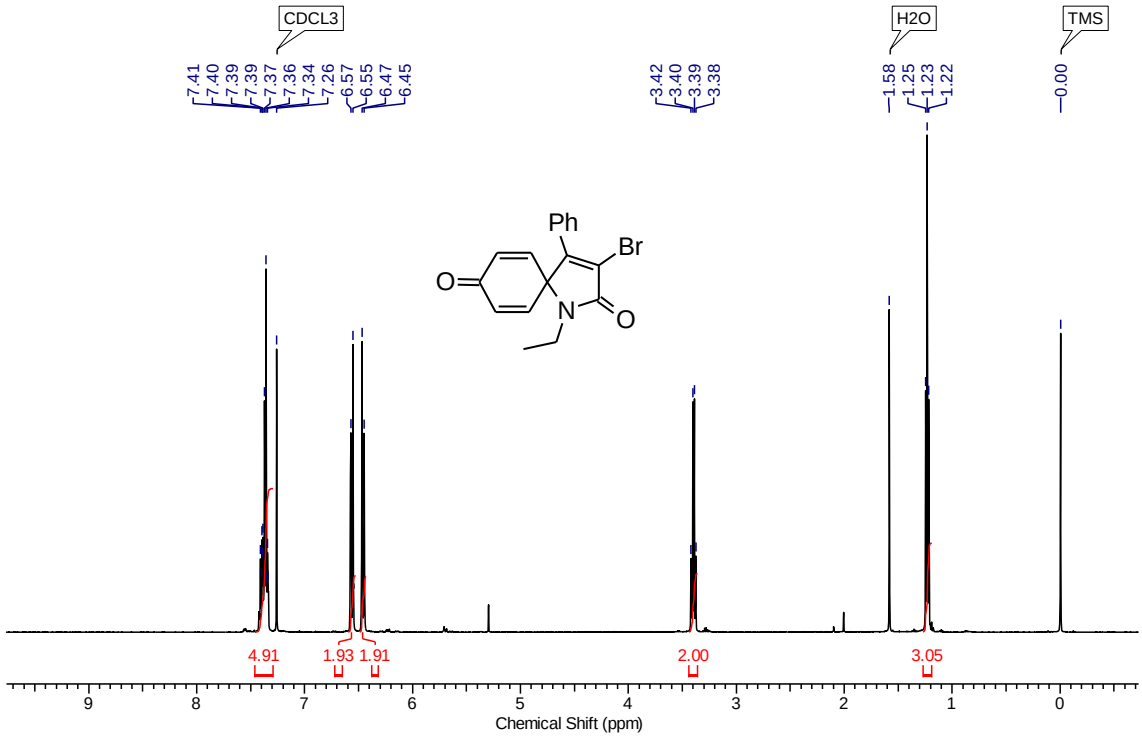
^{1}H NMR spectrum of **2a** in $CDCl_3$



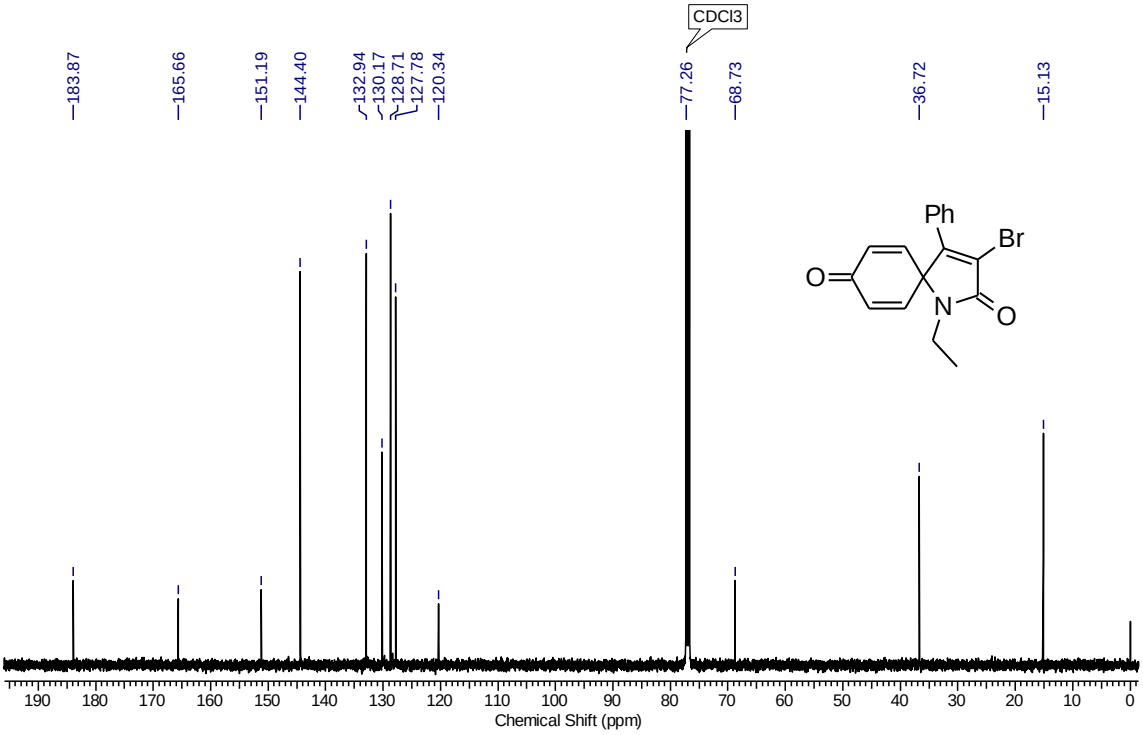
^{13}C NMR spectrum of **2a** in $CDCl_3$



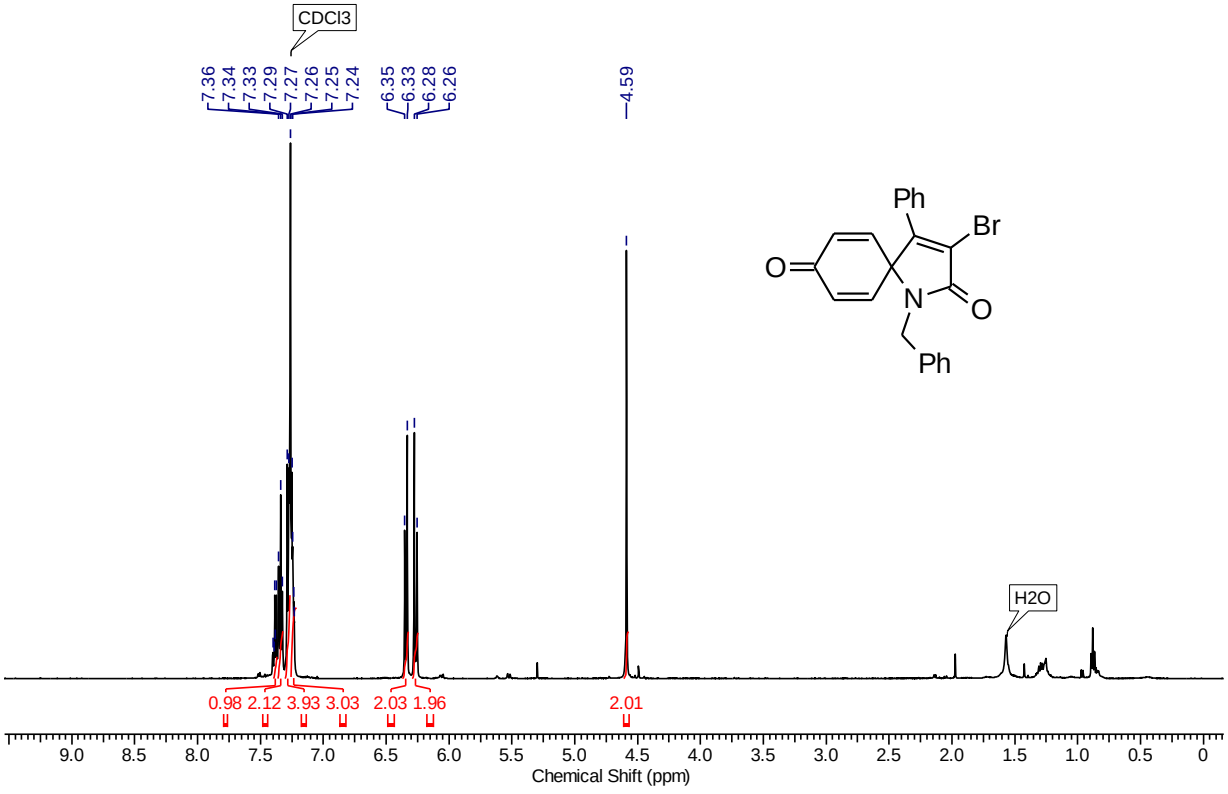
^{1}H NMR spectrum of **2b** in $CDCl_3$



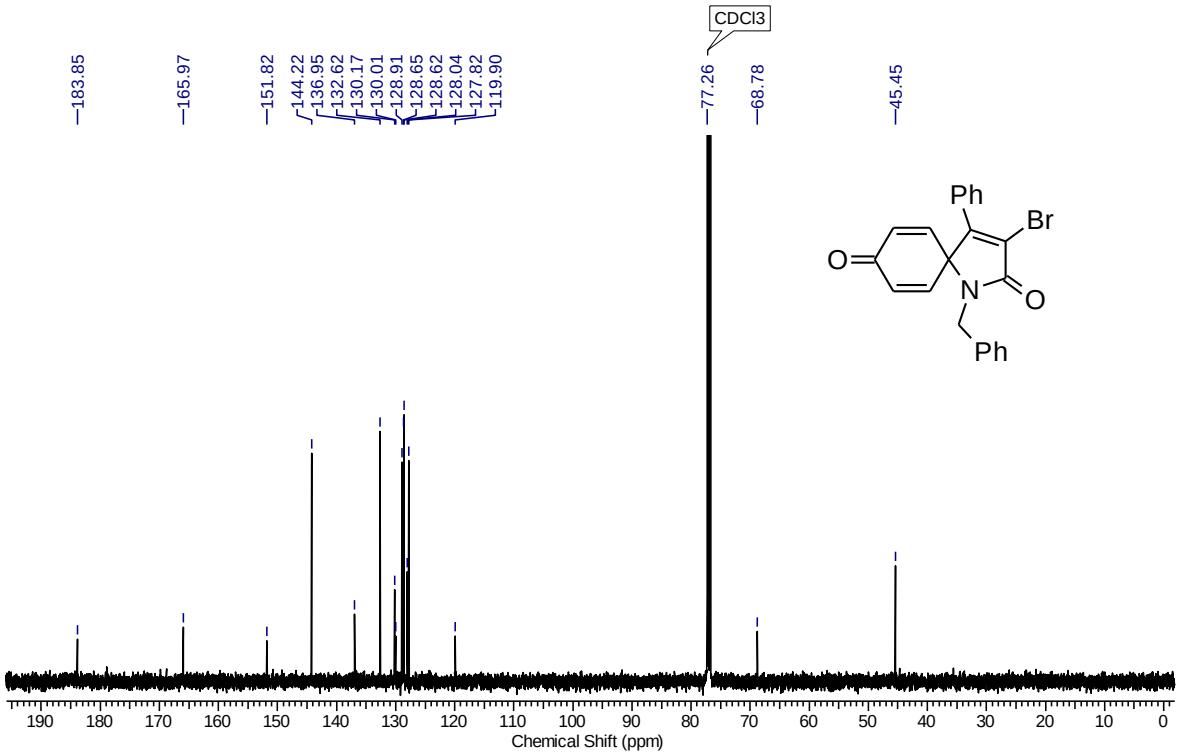
^{13}C NMR spectrum of **2b** in $CDCl_3$



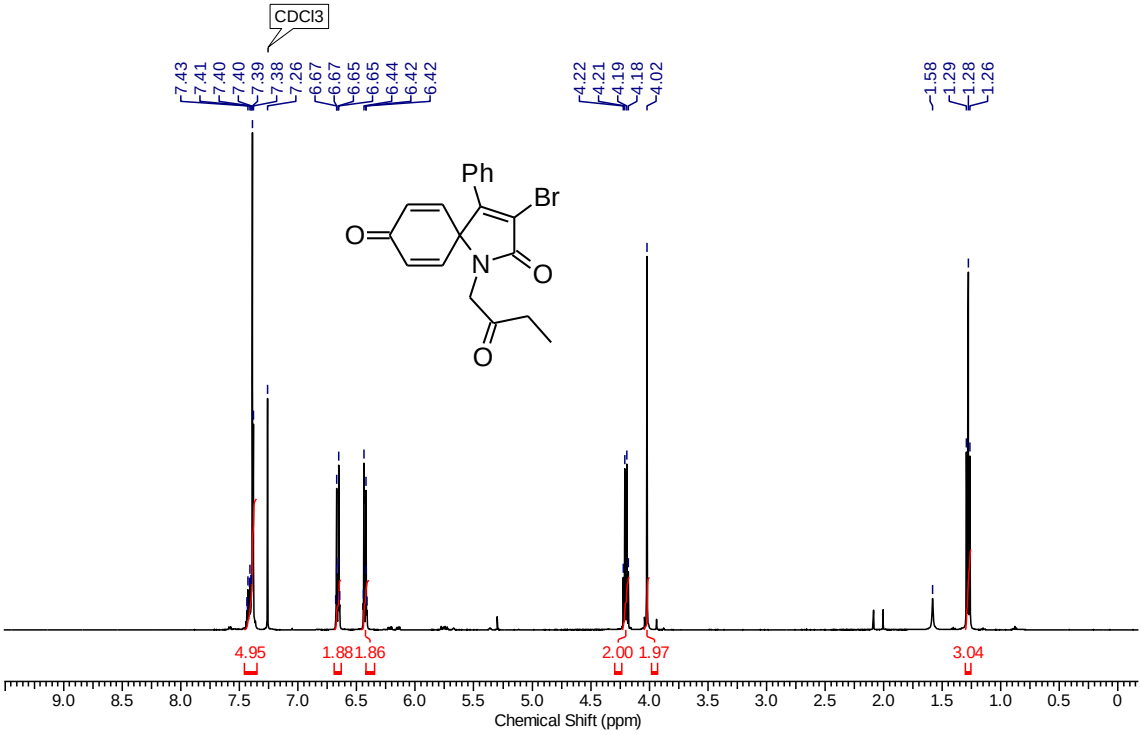
^{1}H NMR spectrum of **2c** in $CDCl_3$



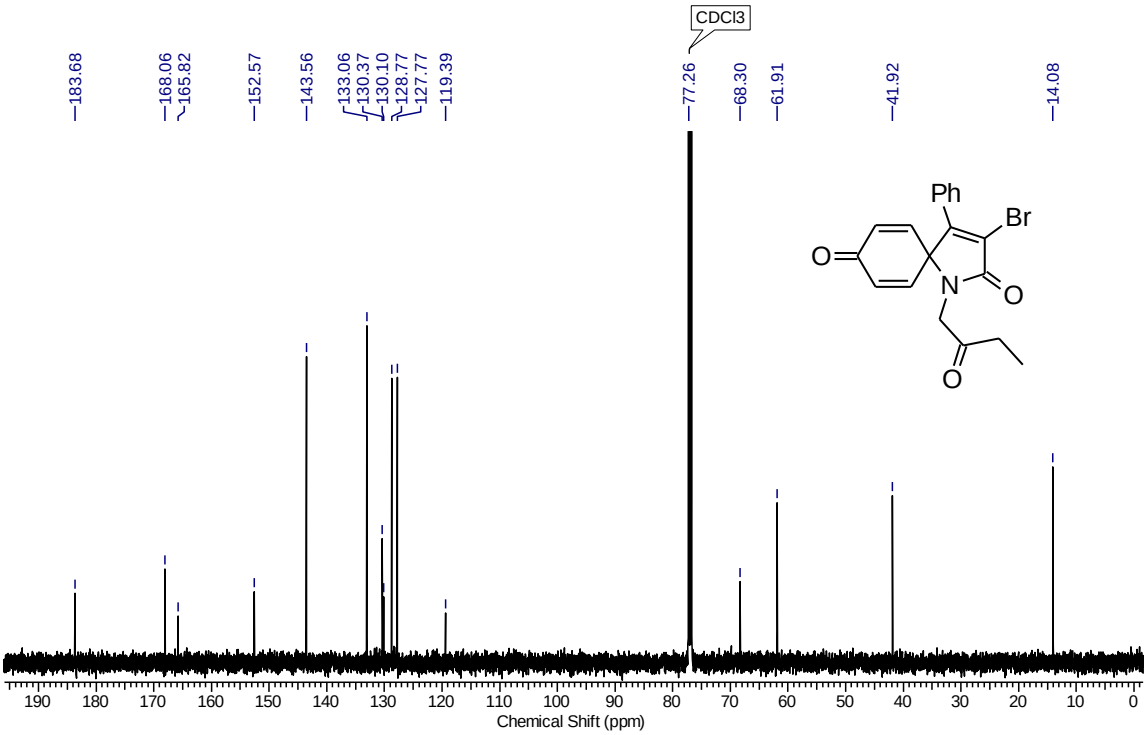
^{13}C NMR spectrum of **2c** in $CDCl_3$



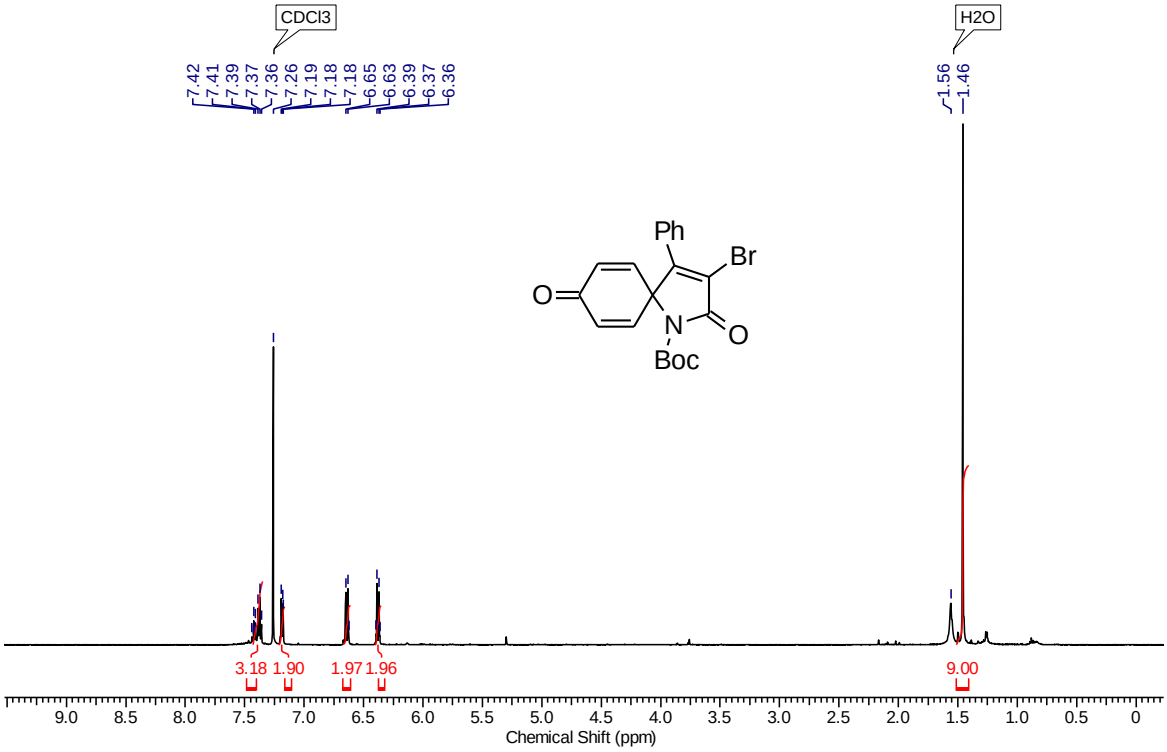
^{1}H NMR spectrum of **2d** in $CDCl_3$



^{13}C NMR spectrum of **2d** in $CDCl_3$



^{1}H NMR spectrum of **2e** in $CDCl_3$



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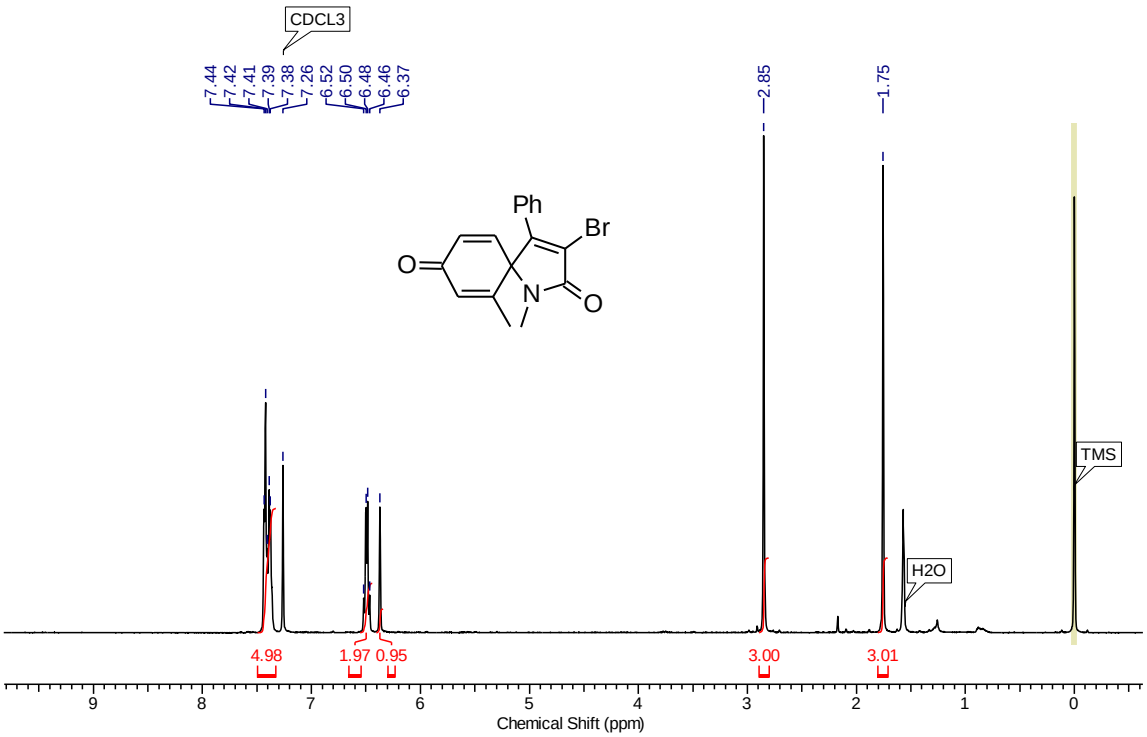
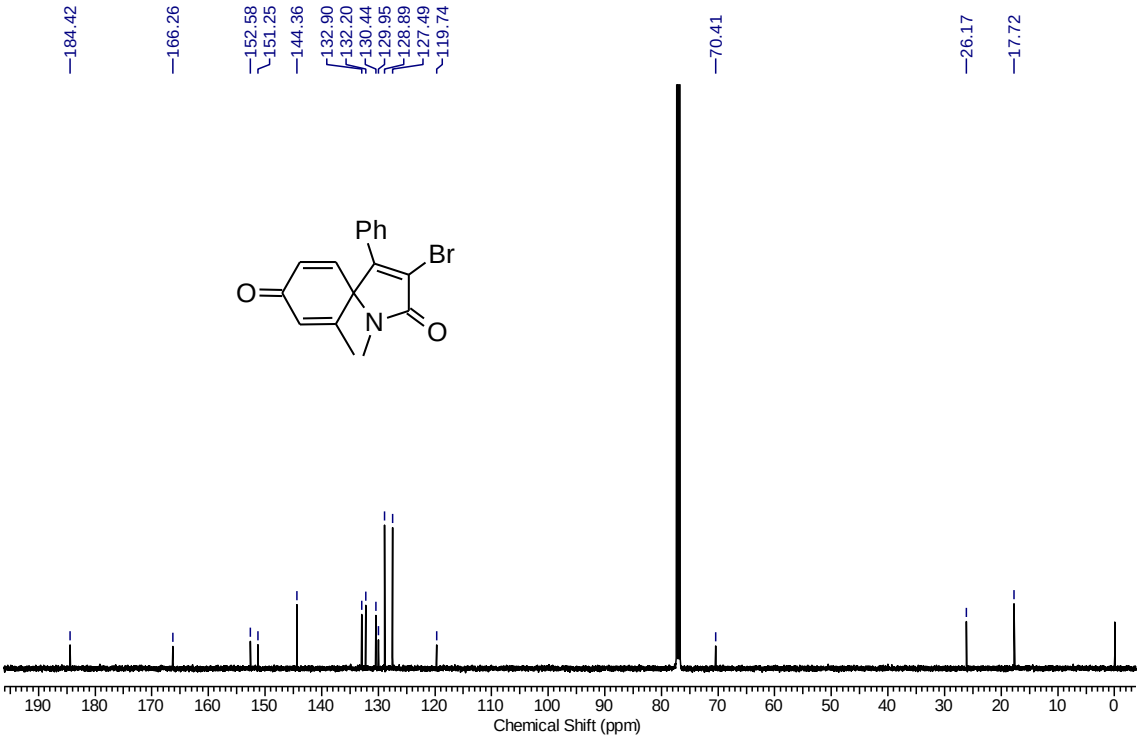
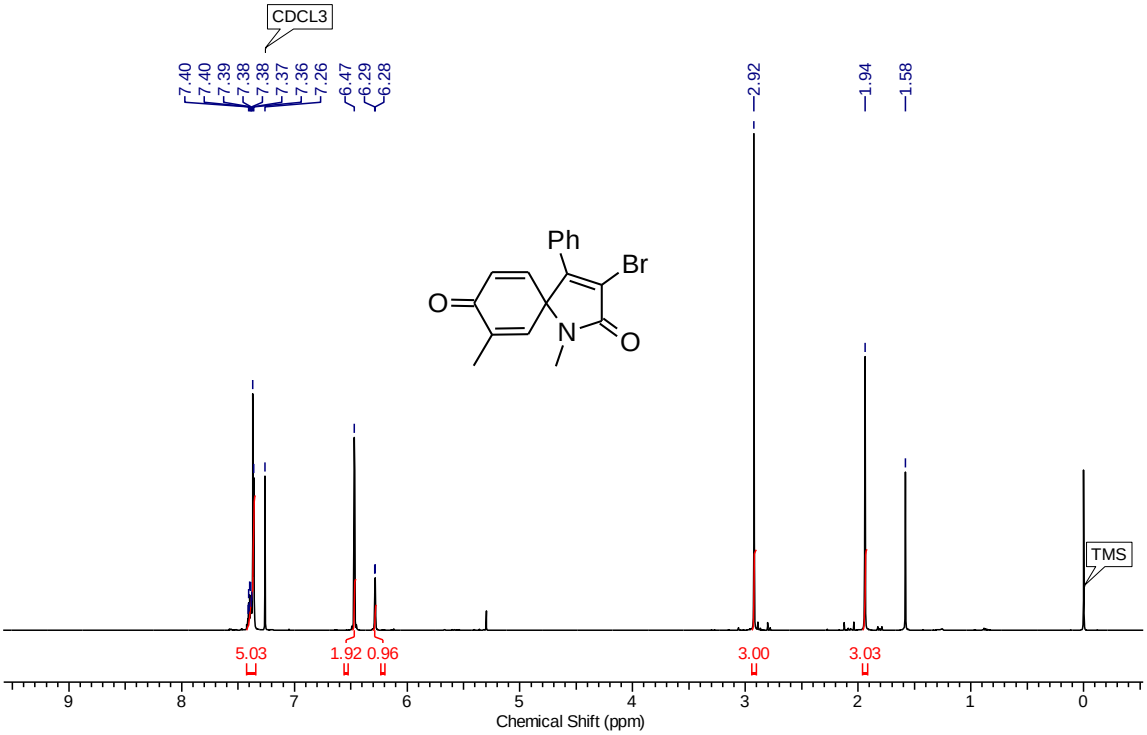


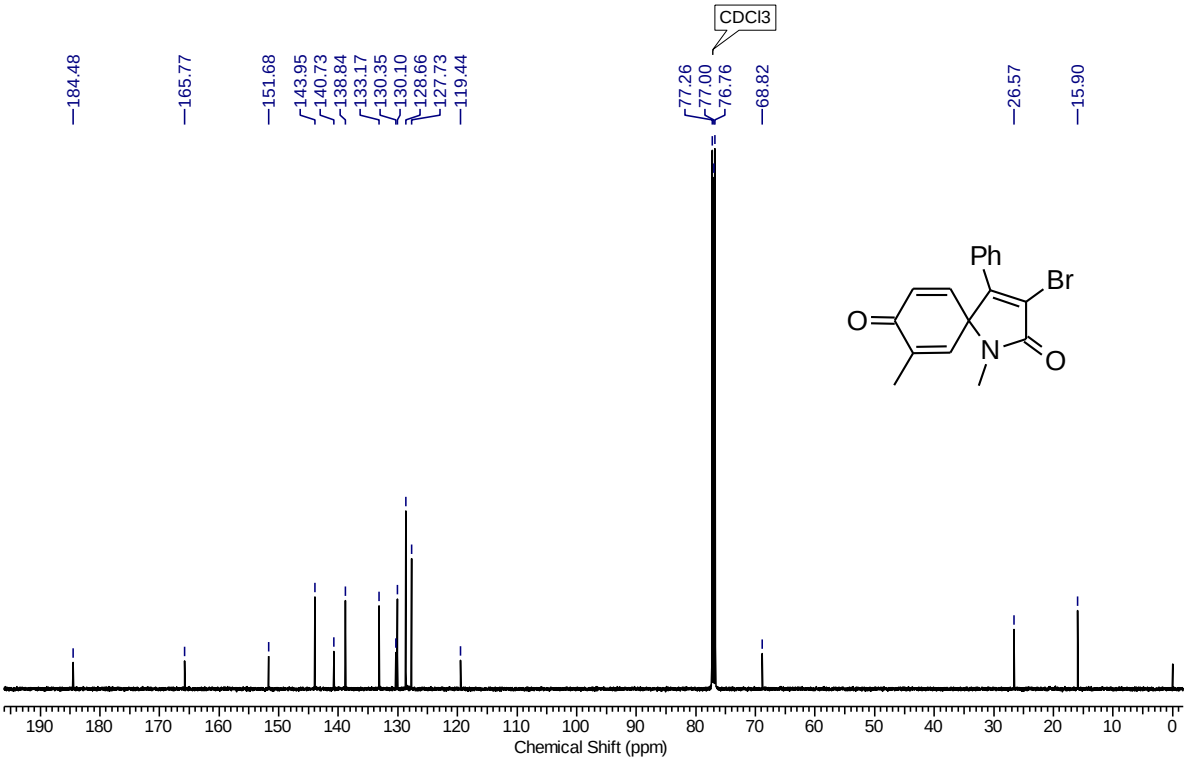
^{13}C NMR spectrum of **2h** in $CDCl_3$



^{1}H NMR spectrum of **2i** in $CDCl_3$



^{1}H NMR spectrum of **2i** in $CDCl_3$



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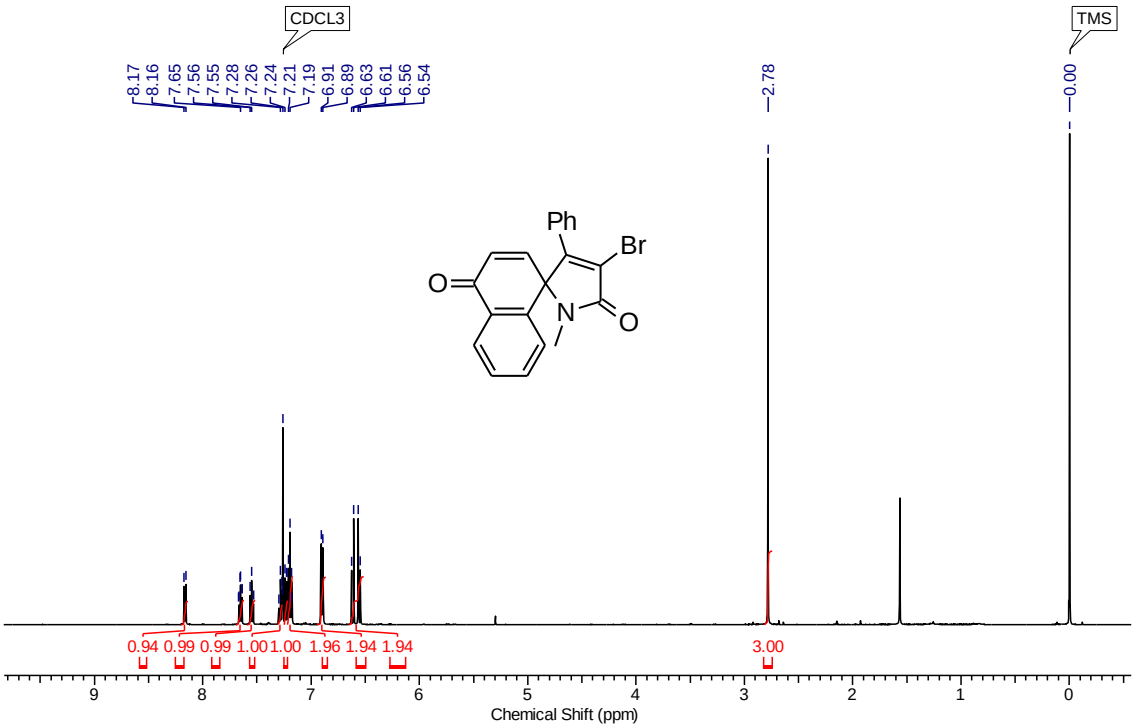

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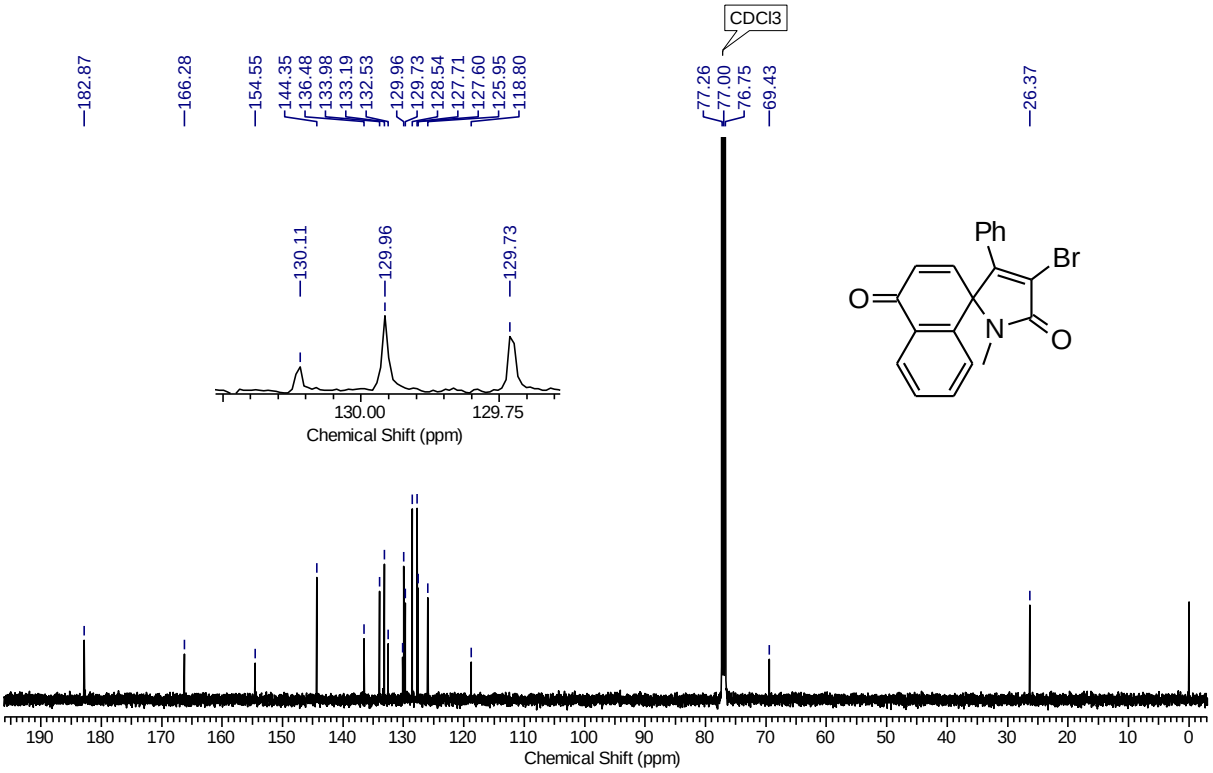

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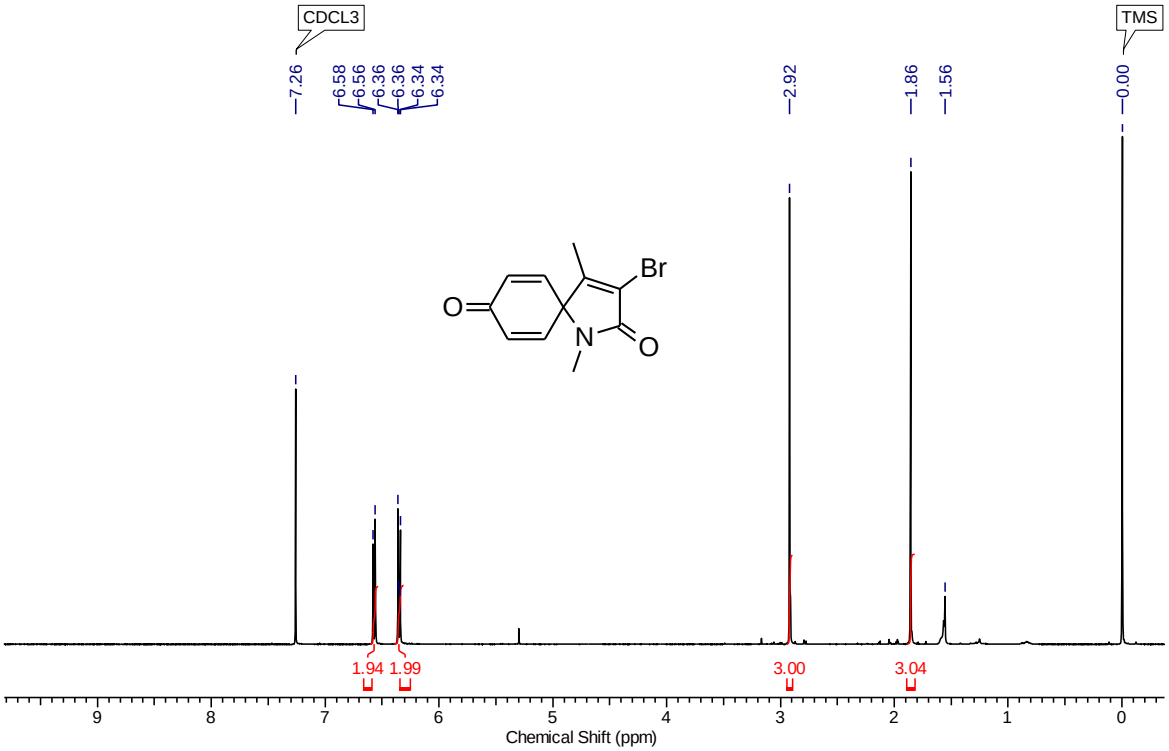

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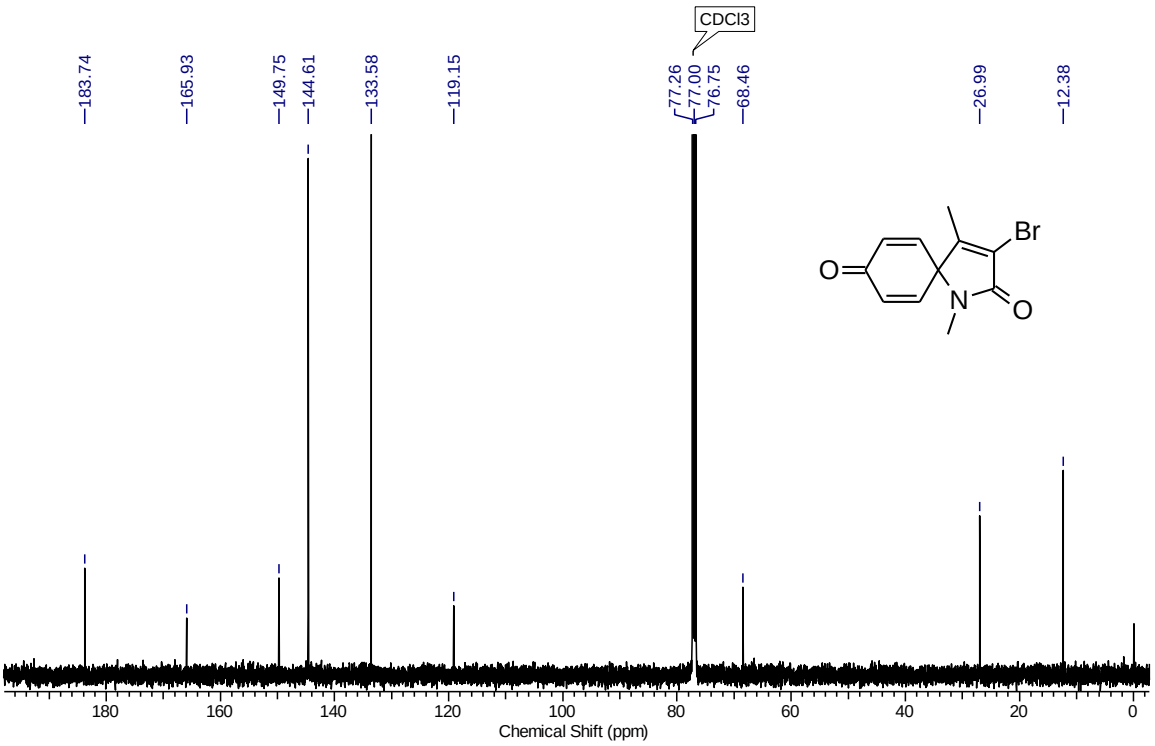
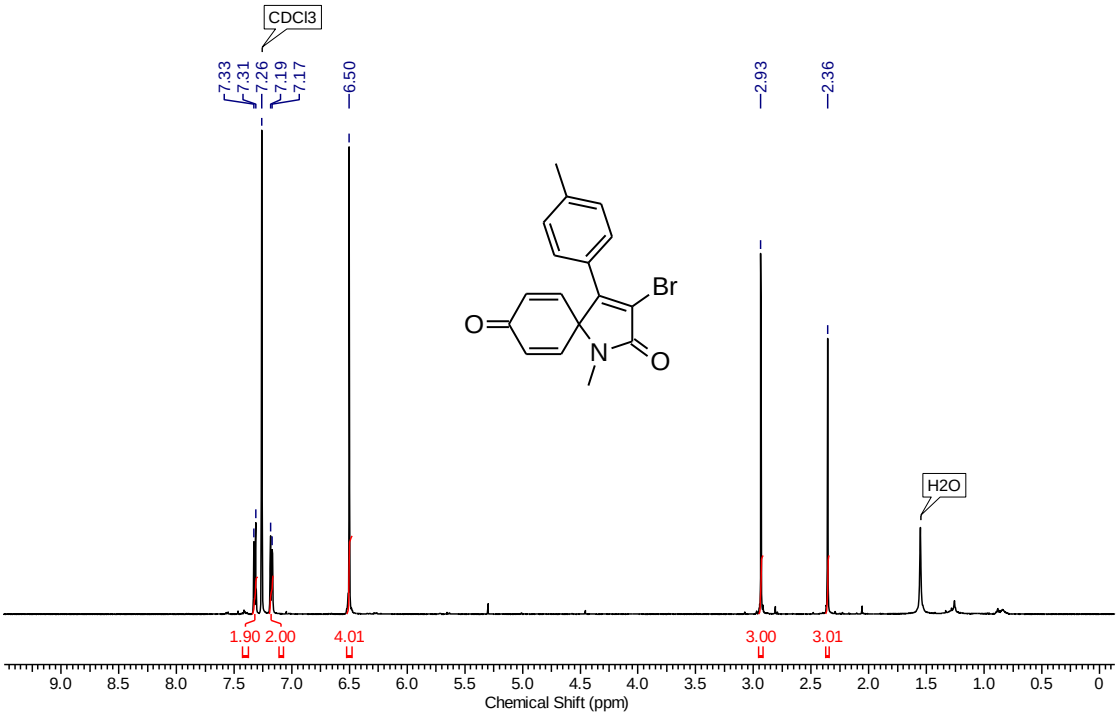
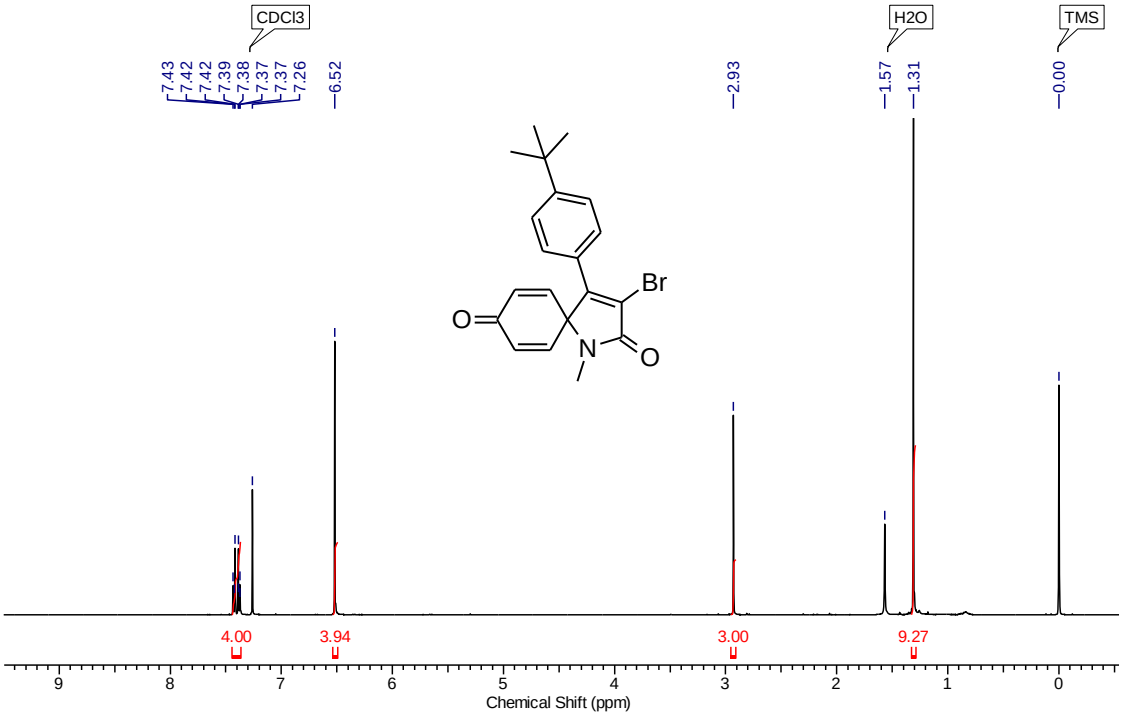


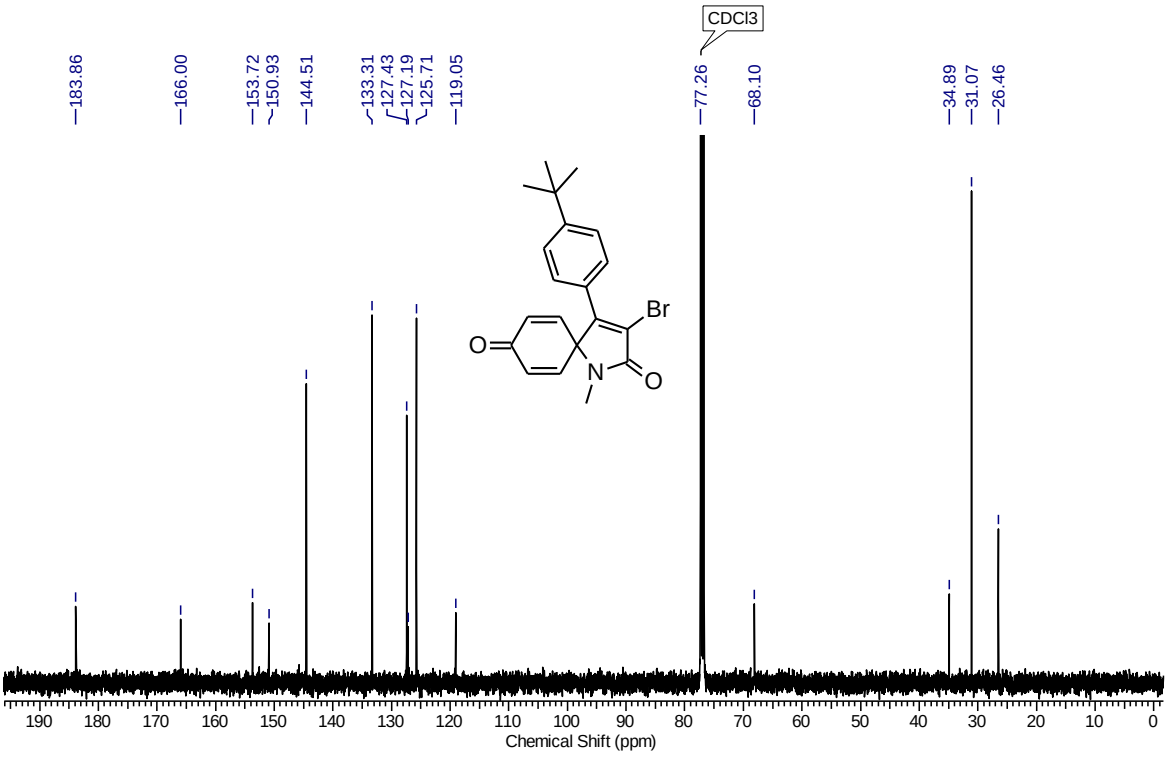
^{1}H NMR spectrum of **2l** in $CDCl_3$



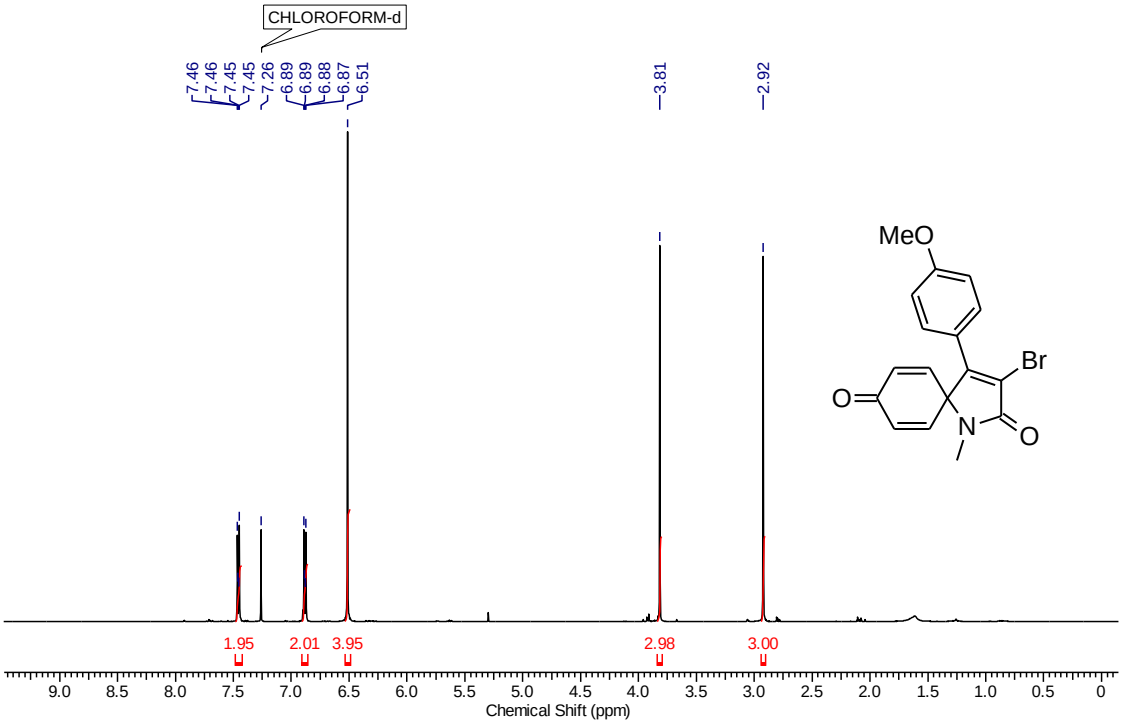
^{1}H NMR spectrum of **2m** in $CDCl_3$



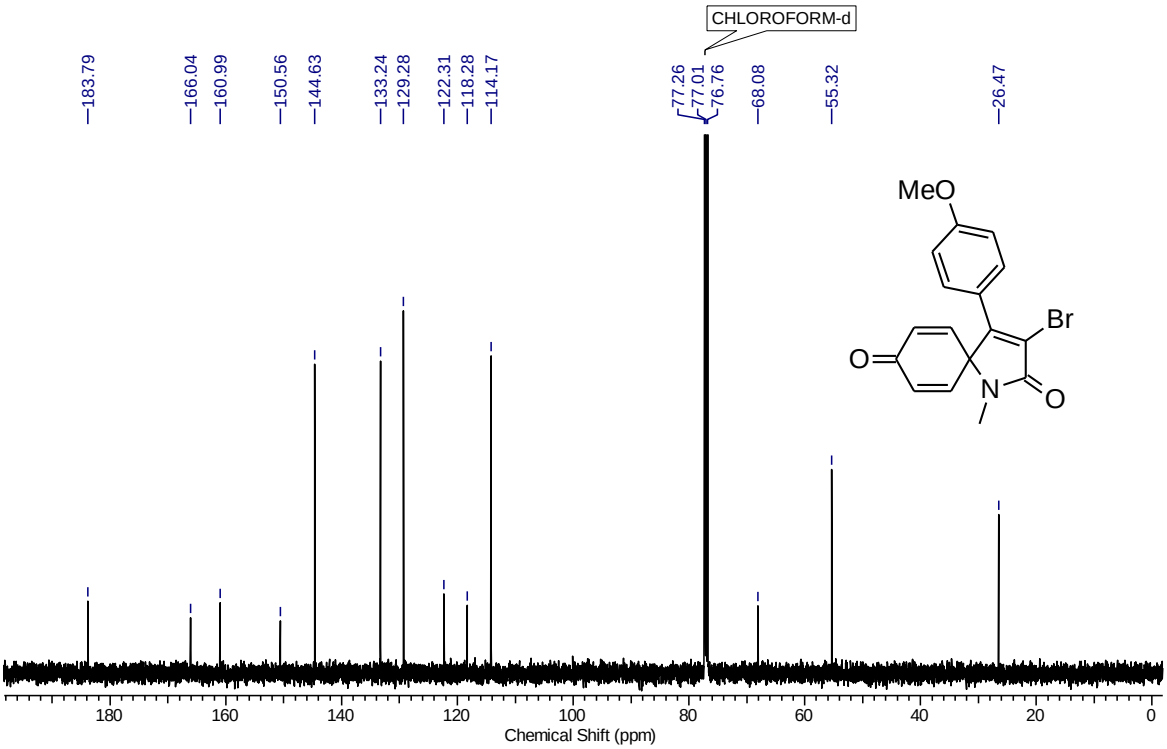
^{13}C NMR spectrum of **2m** in $CDCl_3$



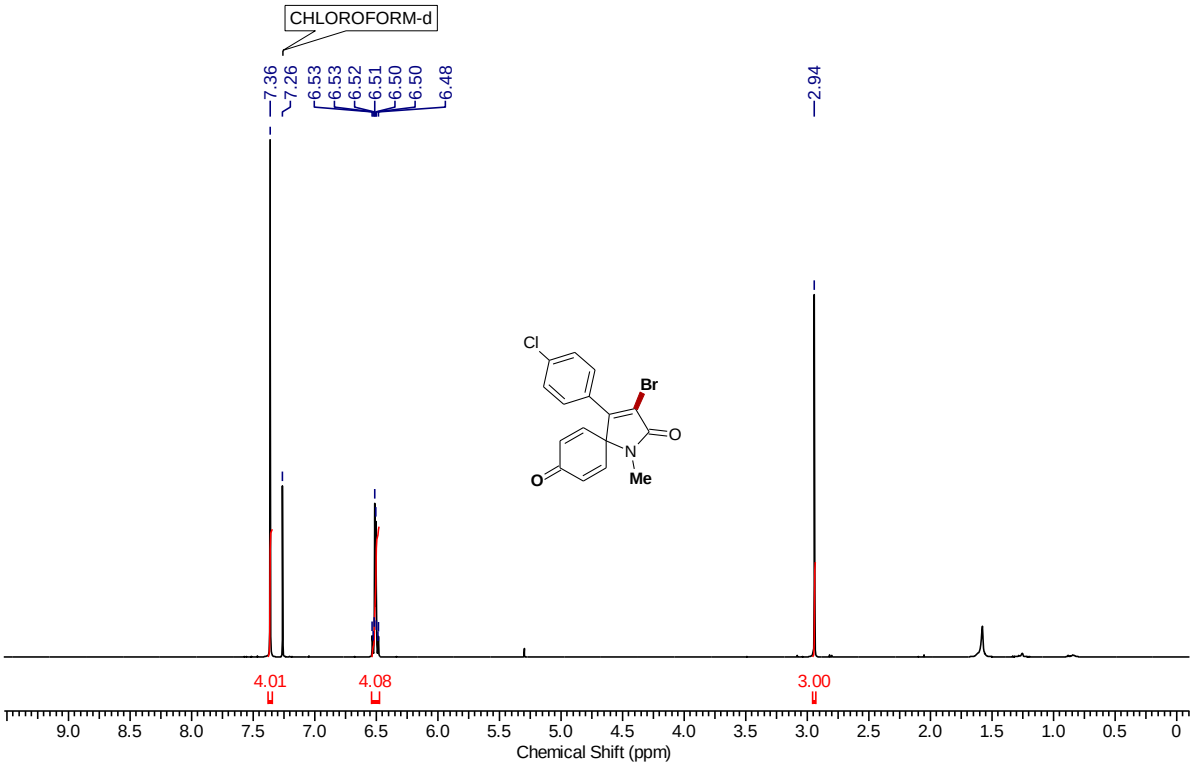
^{1}H NMR spectrum of **2n** in $CDCl_3$



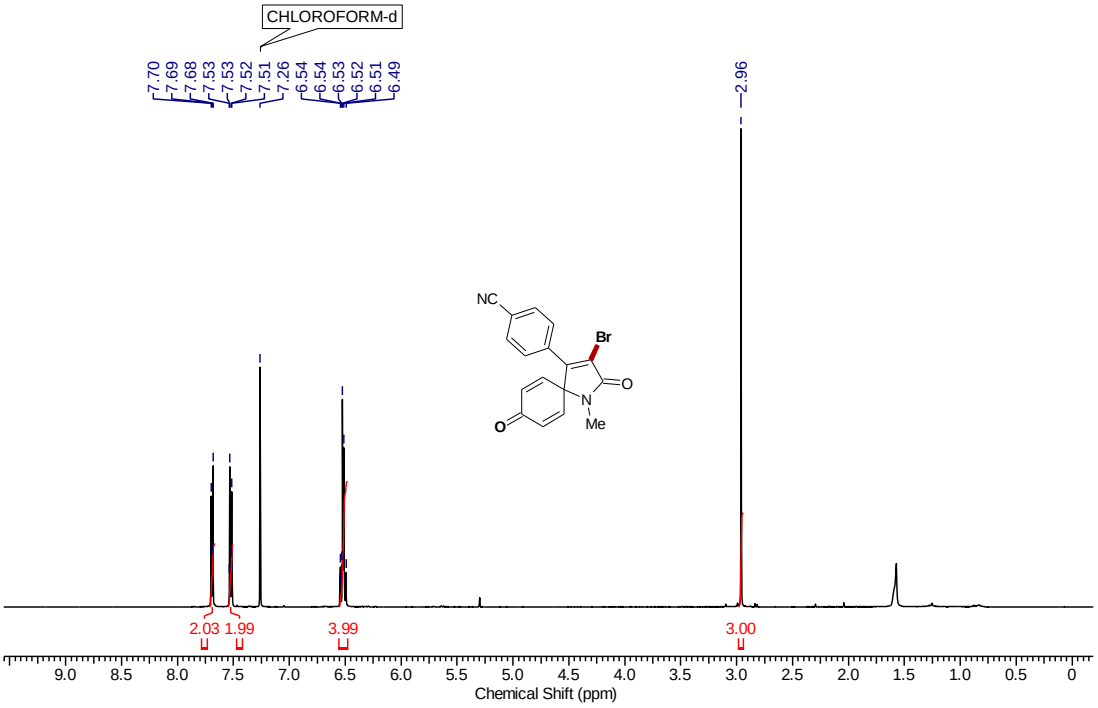
^{13}C NMR spectrum of **2n** in $CDCl_3$



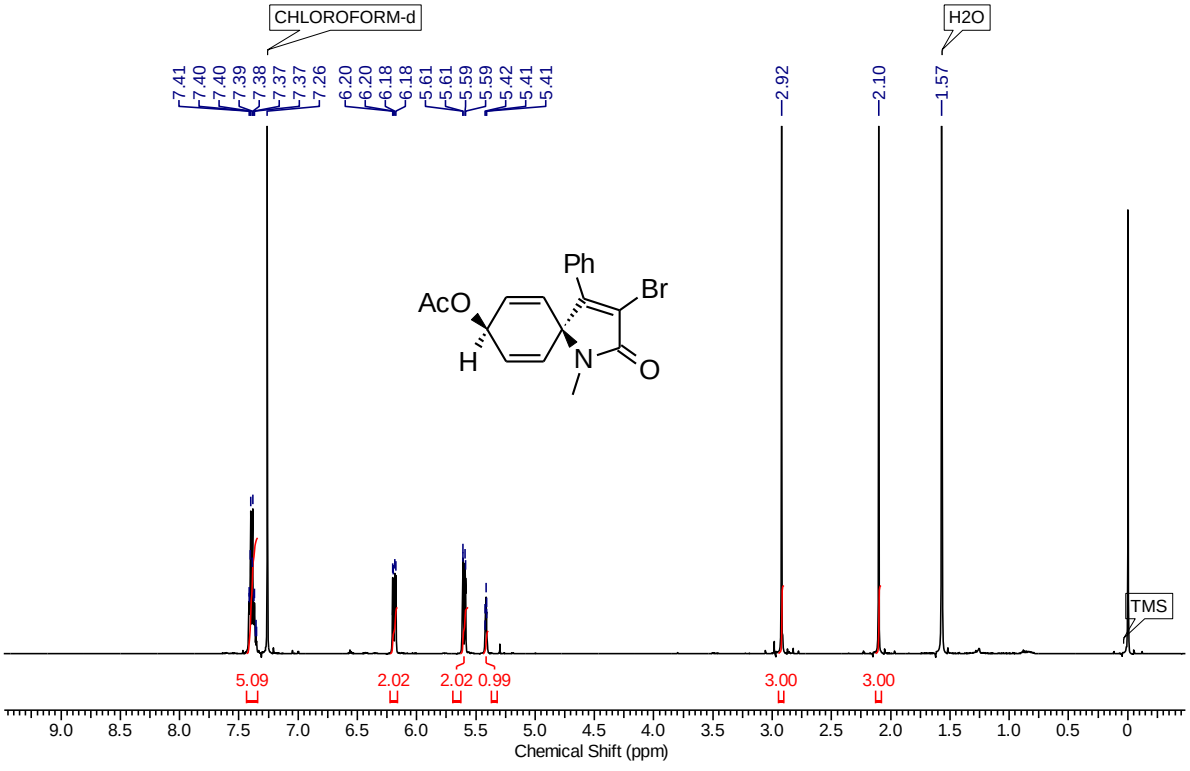
^{1}H NMR spectrum of **2o** in $CDCl_3$



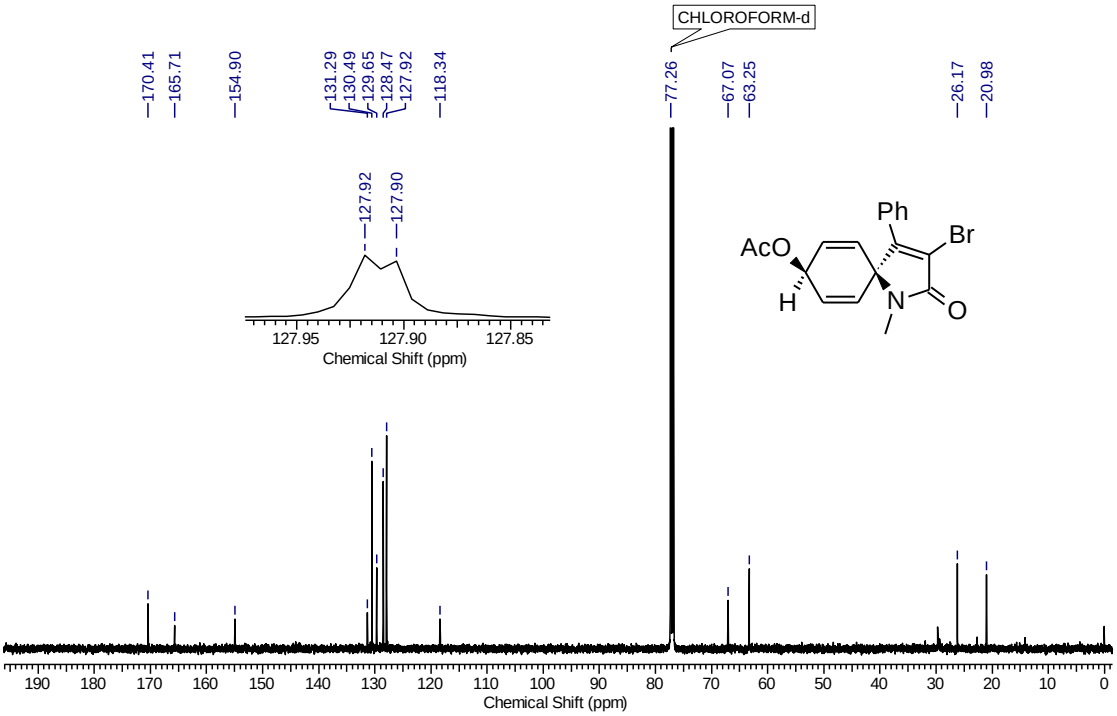
^{1}H NMR spectrum of **2p** in $CDCl_3$



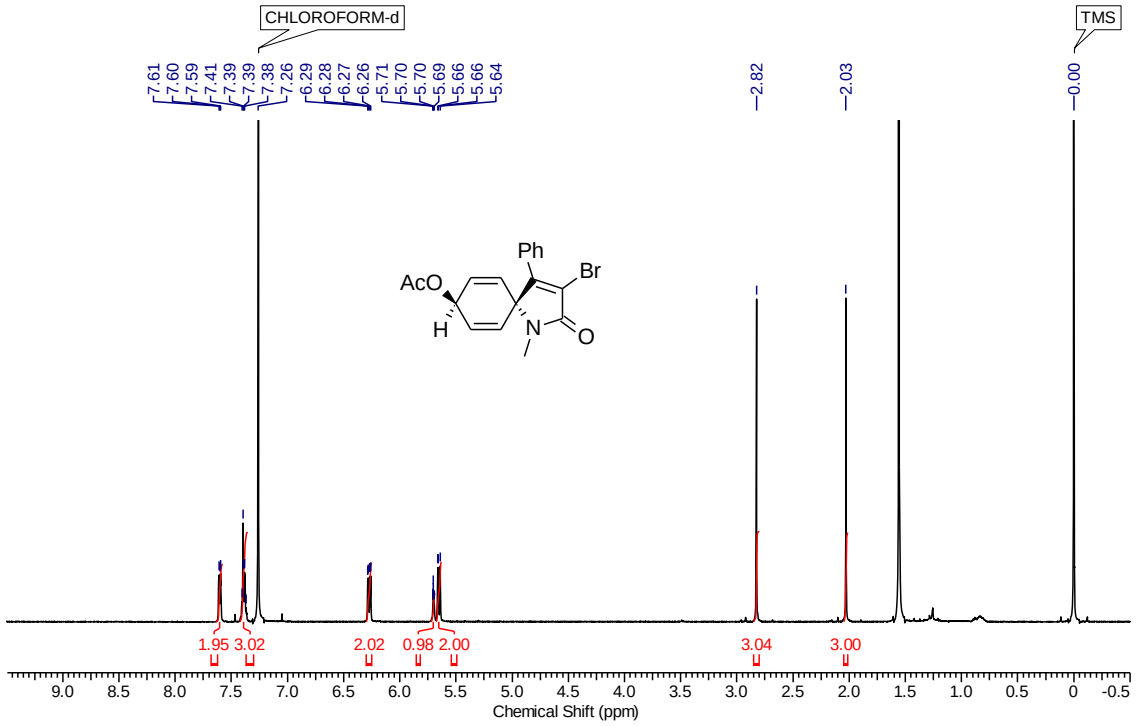
^{1}H NMR spectrum of **3a** in $CDCl_3$



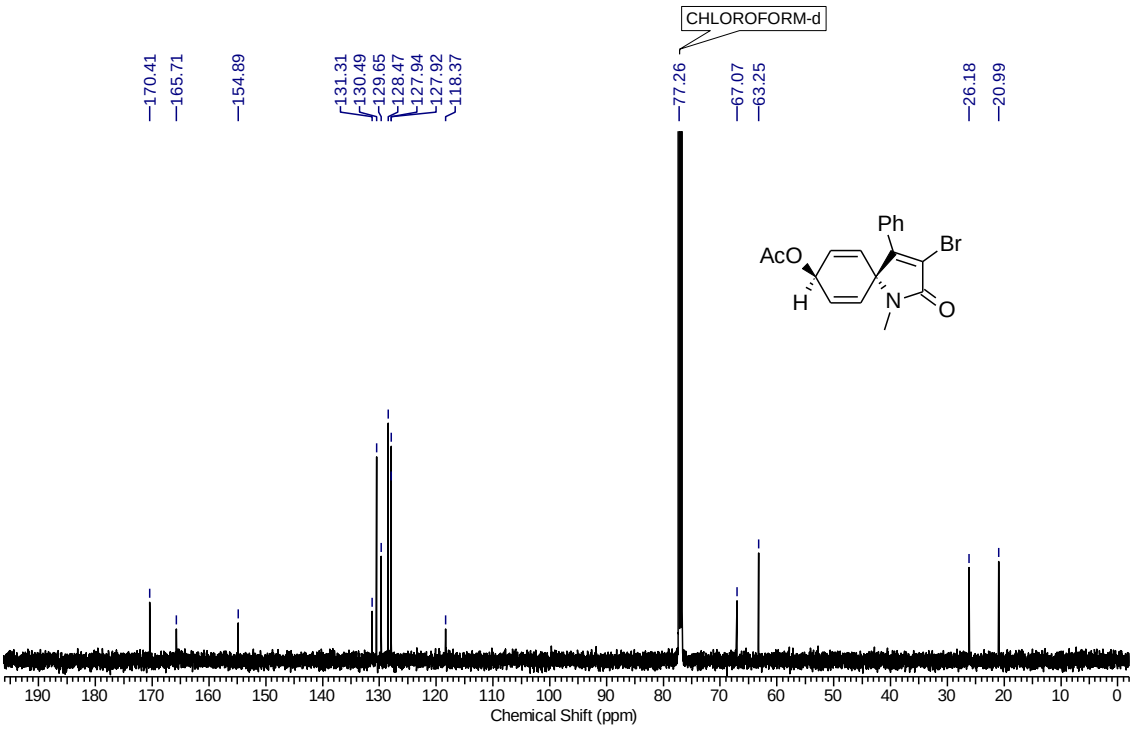
^{13}C NMR spectrum of **3a** in $CDCl_3$



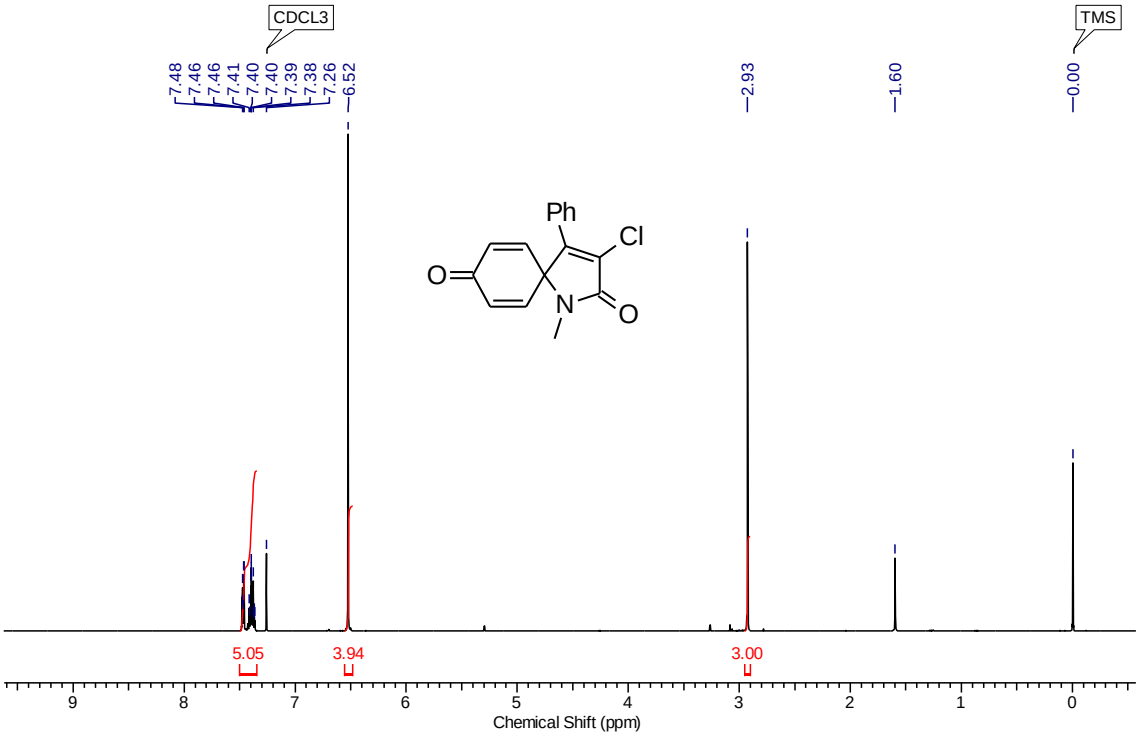
^{1}H NMR spectrum of **3b** in $CDCl_3$



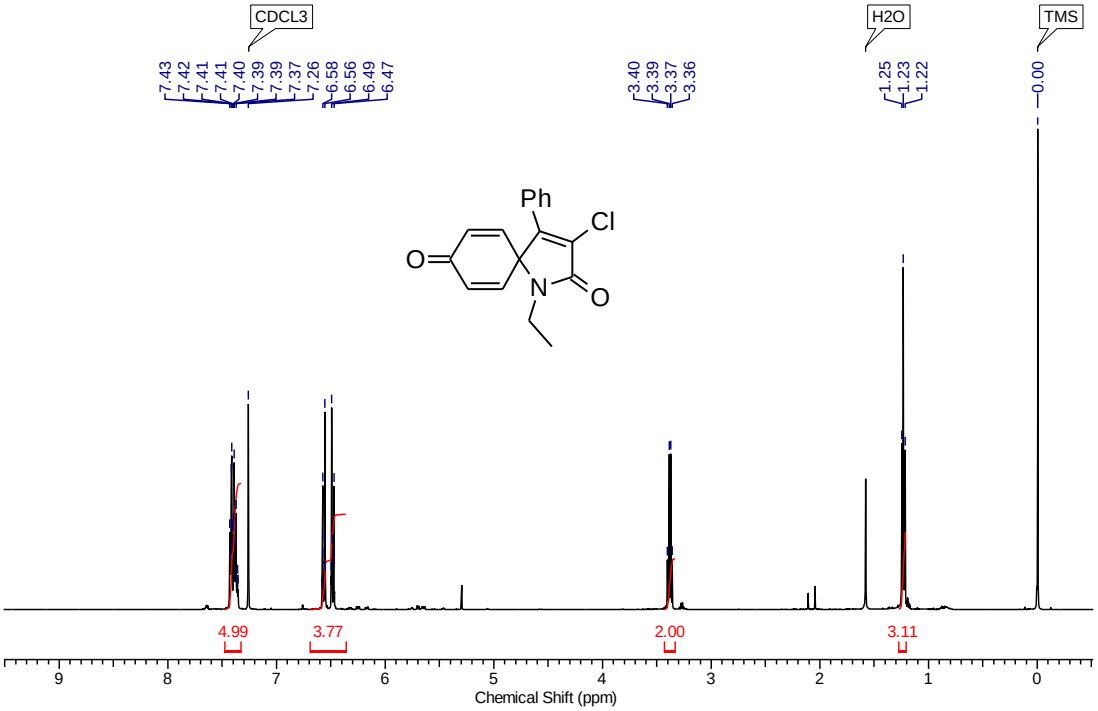
^{13}C NMR spectrum of **3b** in $CDCl_3$



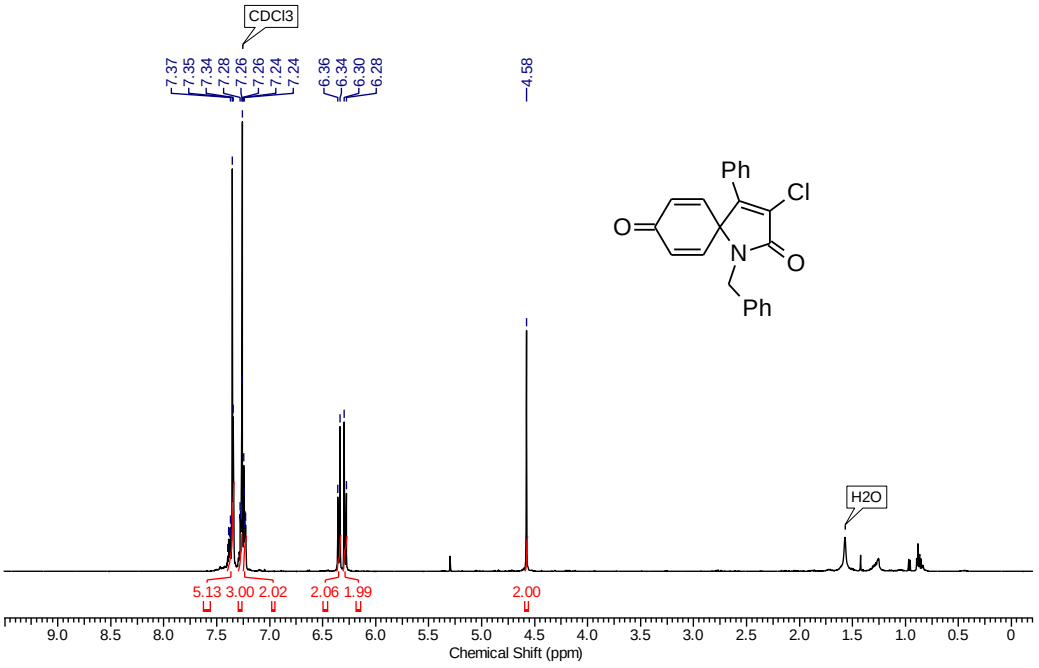
^{1}H NMR spectrum of **4a** in $CDCl_3$



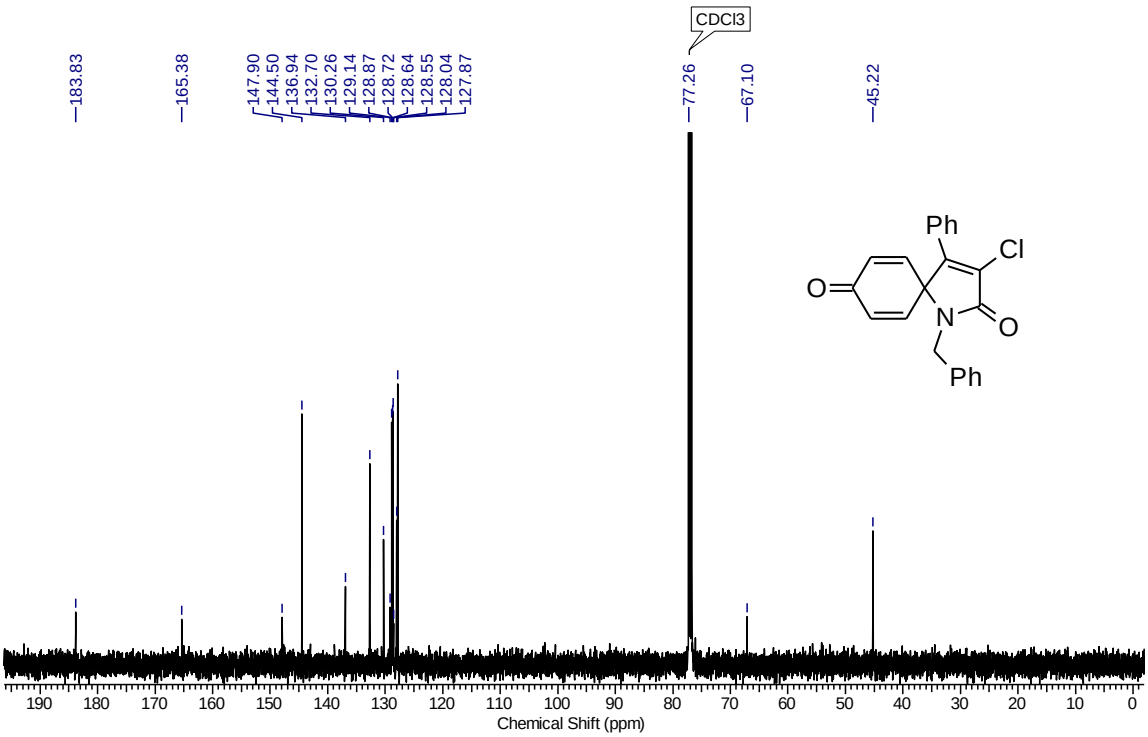
^{1}H NMR spectrum of **4b** in $CDCl_3$



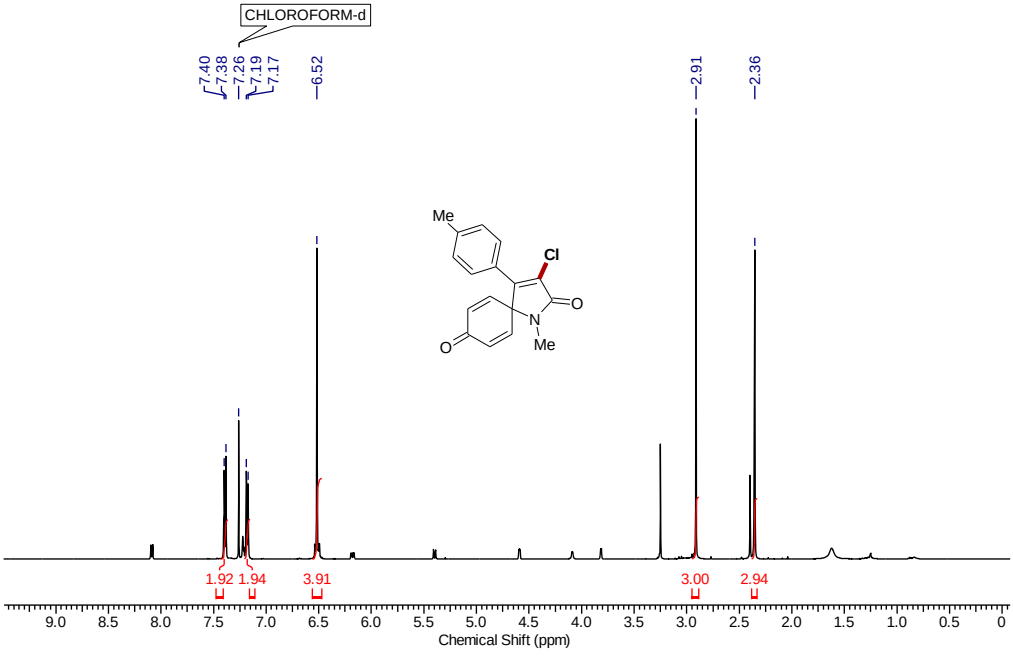
^{1}H NMR spectrum of **4c** in $CDCl_3$



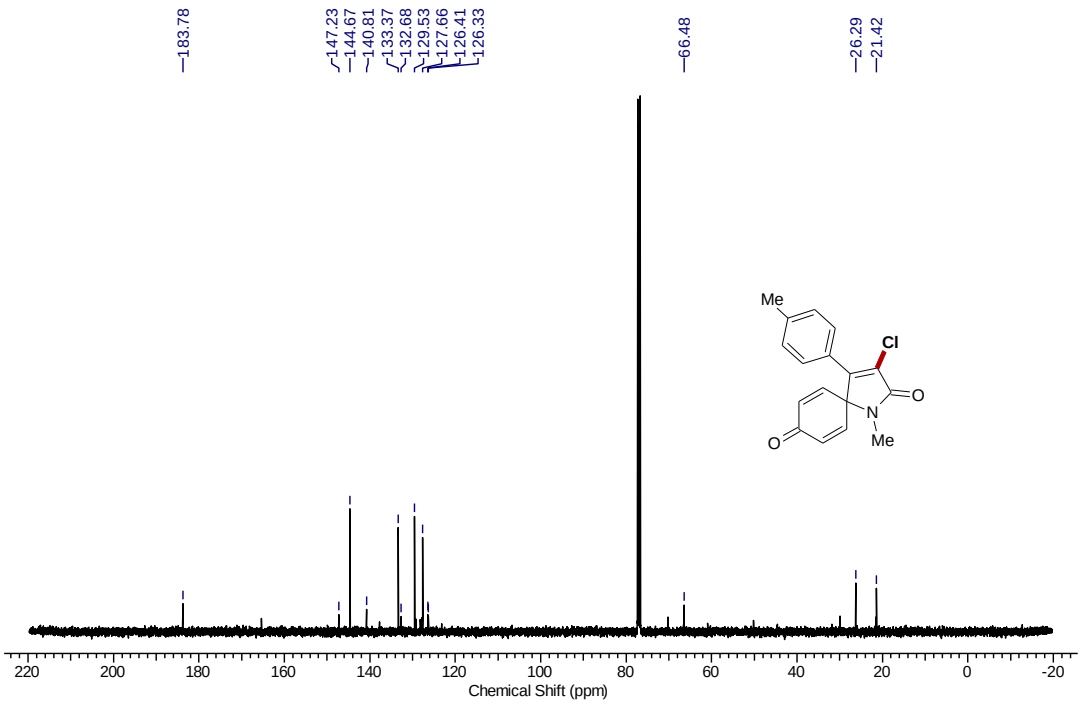
^{13}C NMR spectrum of **4c** in $CDCl_3$



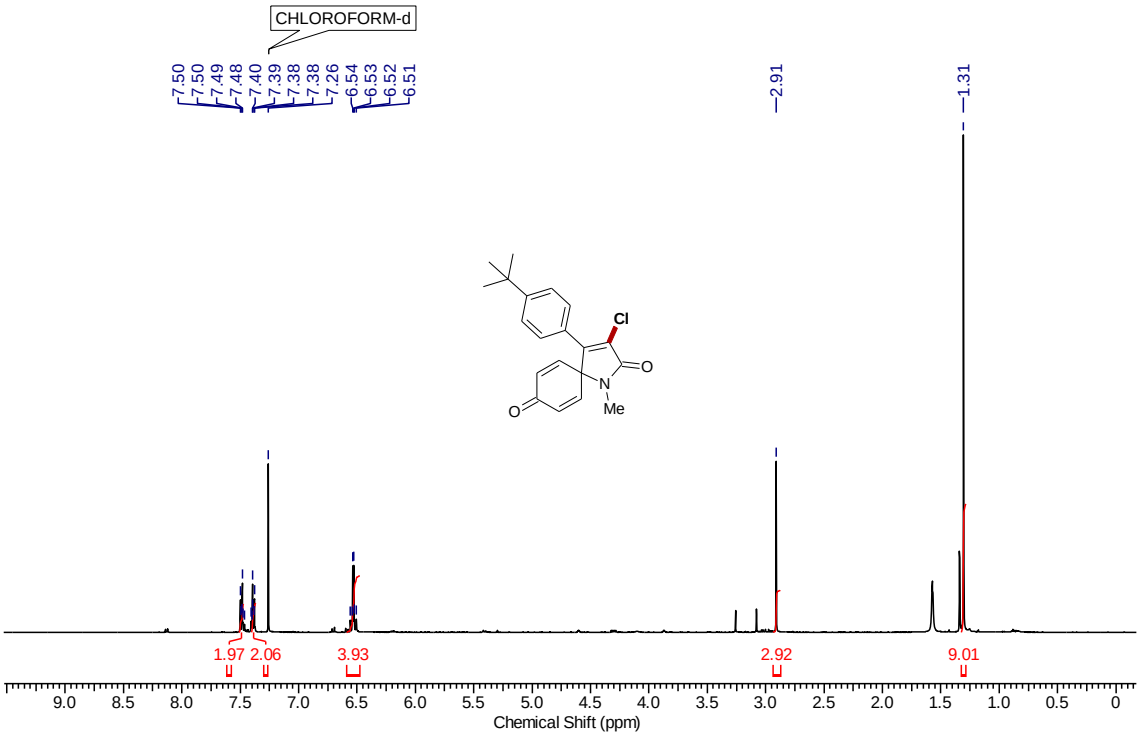
^{1}H NMR spectrum of **4d** in $CDCl_3$



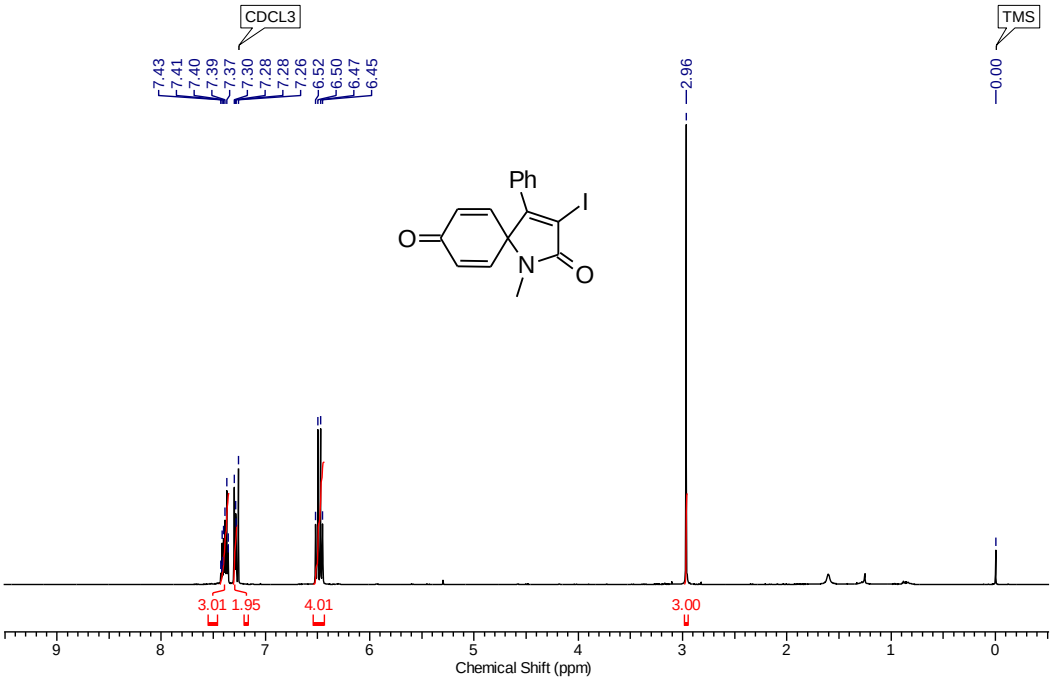
^{13}C NMR spectrum of **4d** in $CDCl_3$



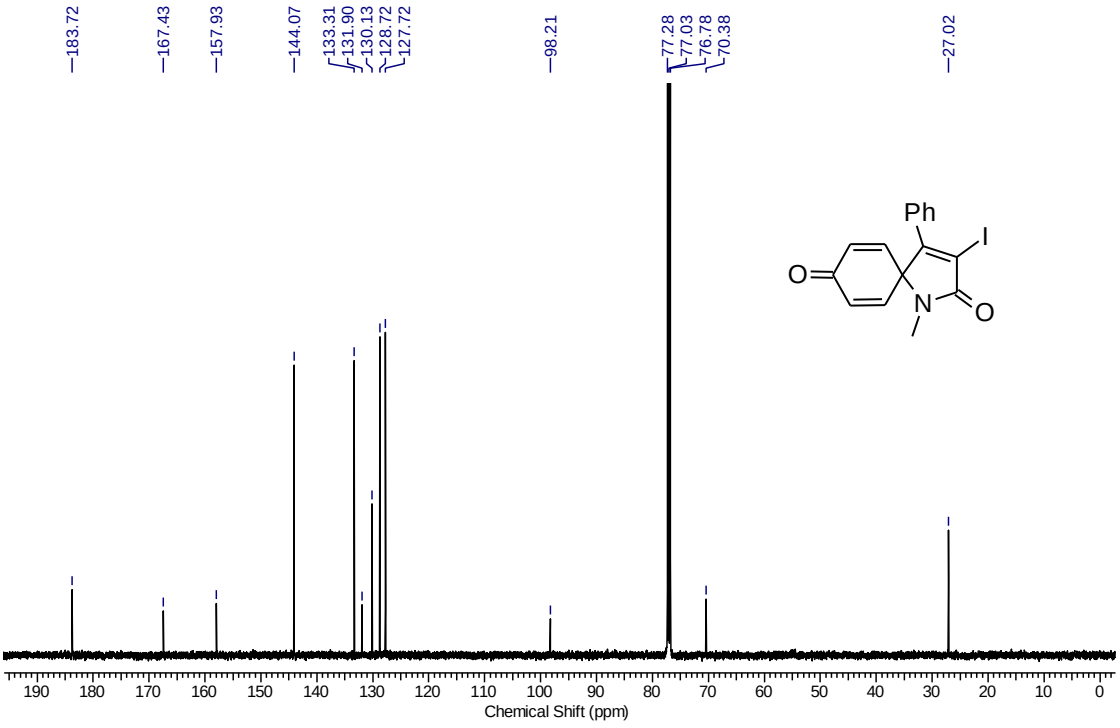
^{1}H NMR spectrum of **4g** in $CDCl_3$



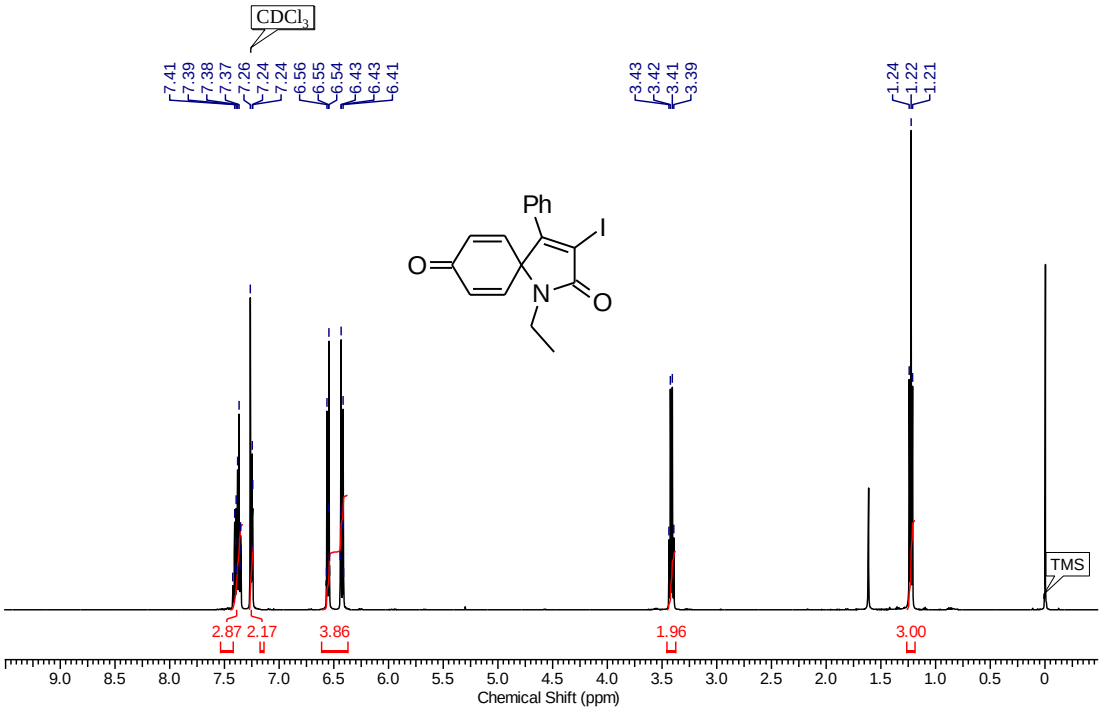
^{1}H NMR spectrum of **5a** in $CDCl_3$



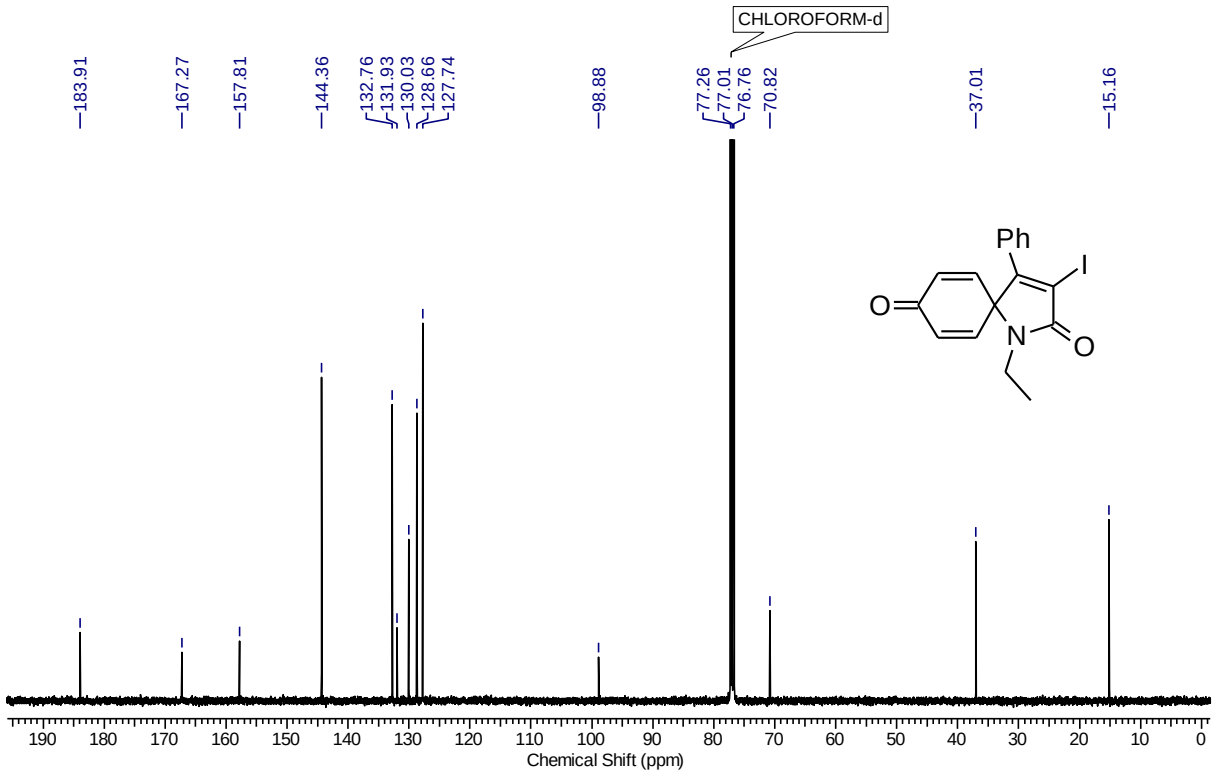
^{13}C NMR spectrum of **5a** in $CDCl_3$



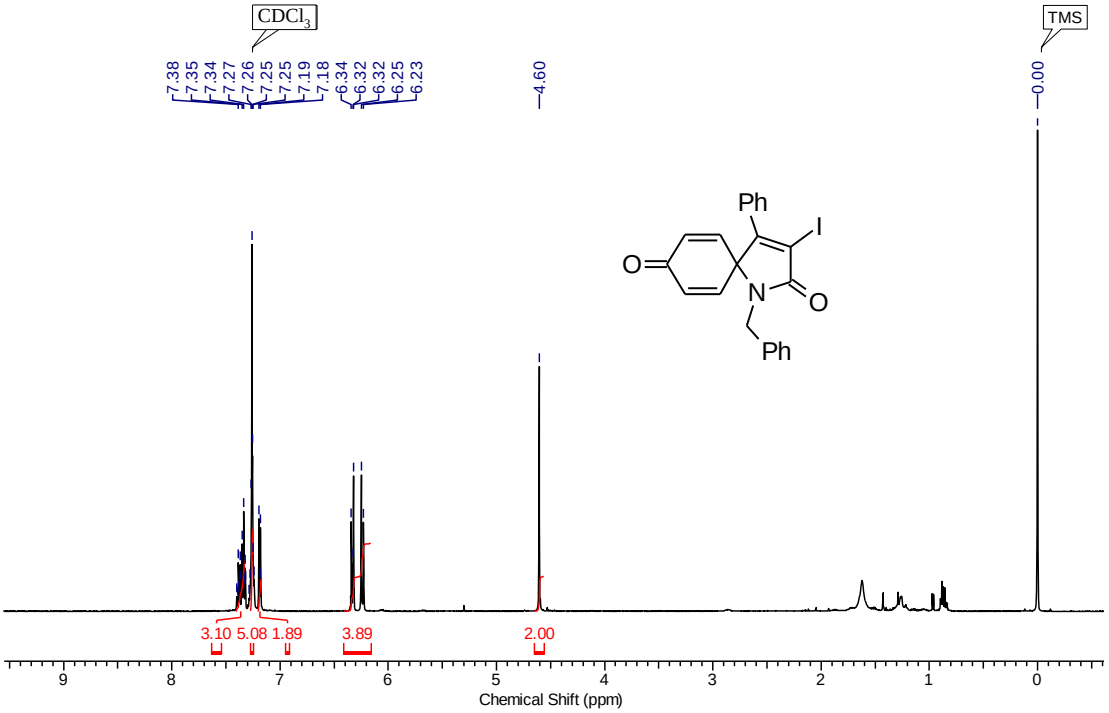
^{1}H NMR spectrum of **5b** in $CDCl_3$



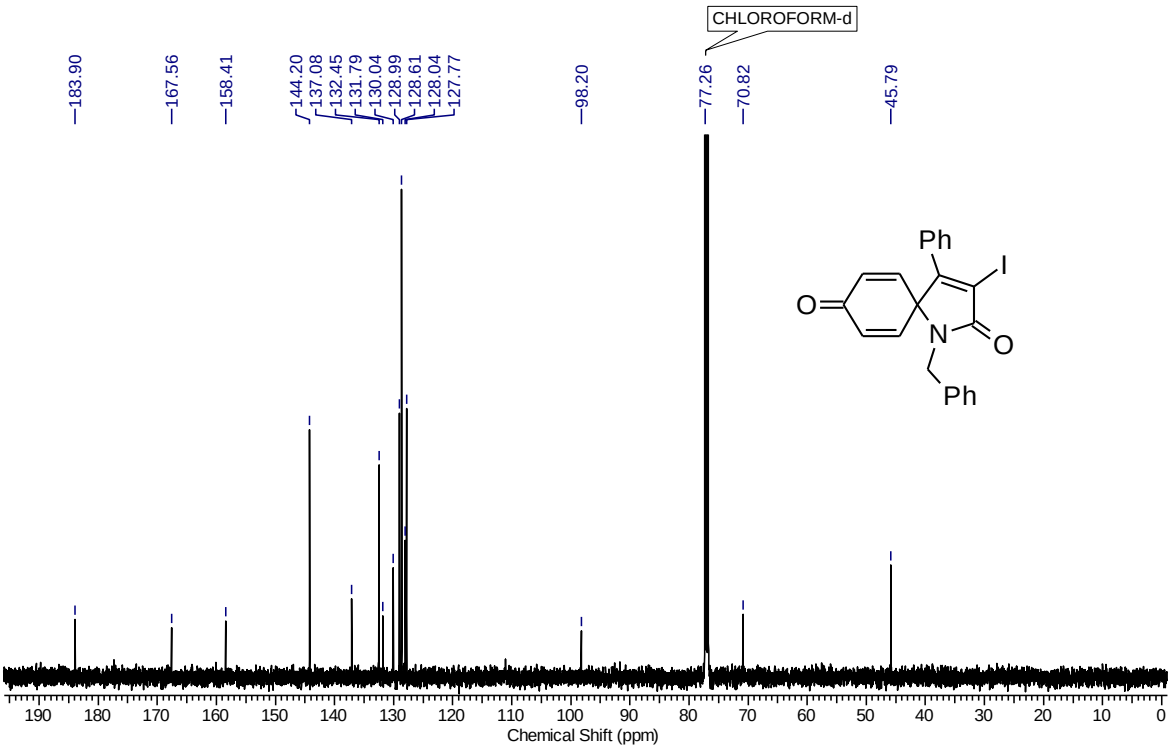
^{13}C NMR spectrum of **5b** in $CDCl_3$



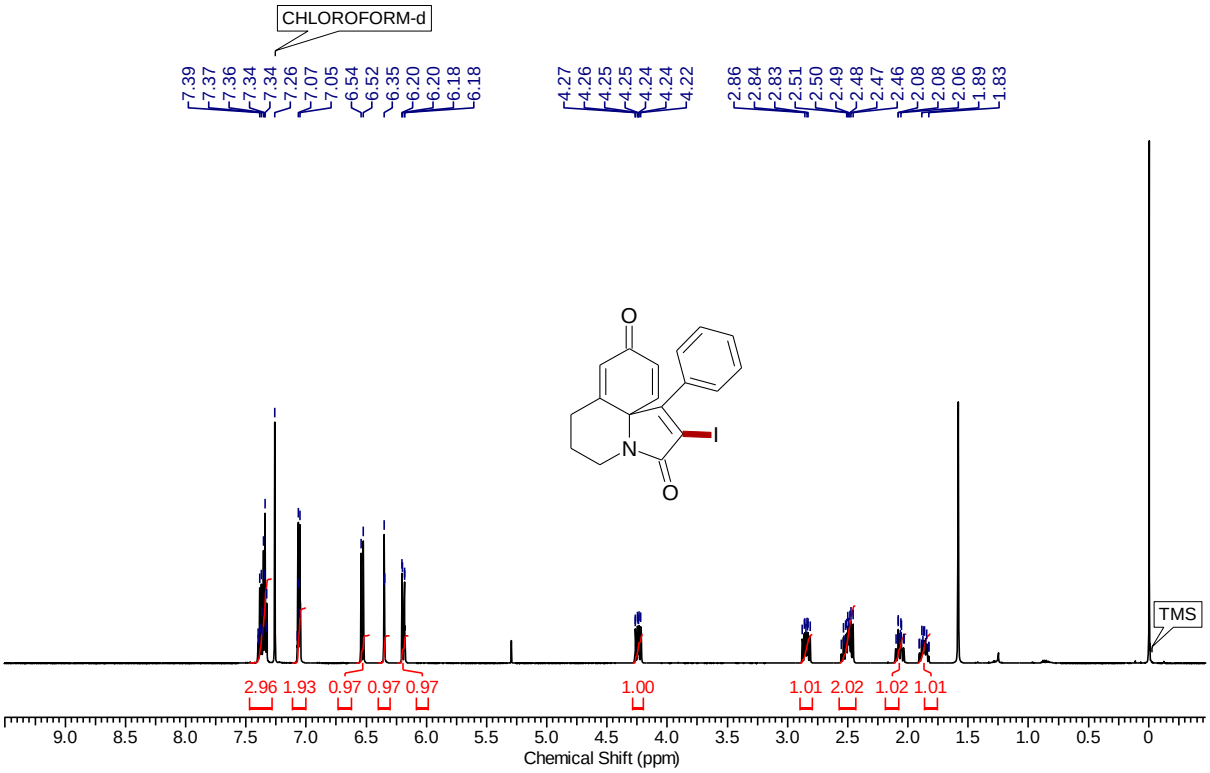
^{1}H NMR spectrum of **5c** in $CDCl_3$



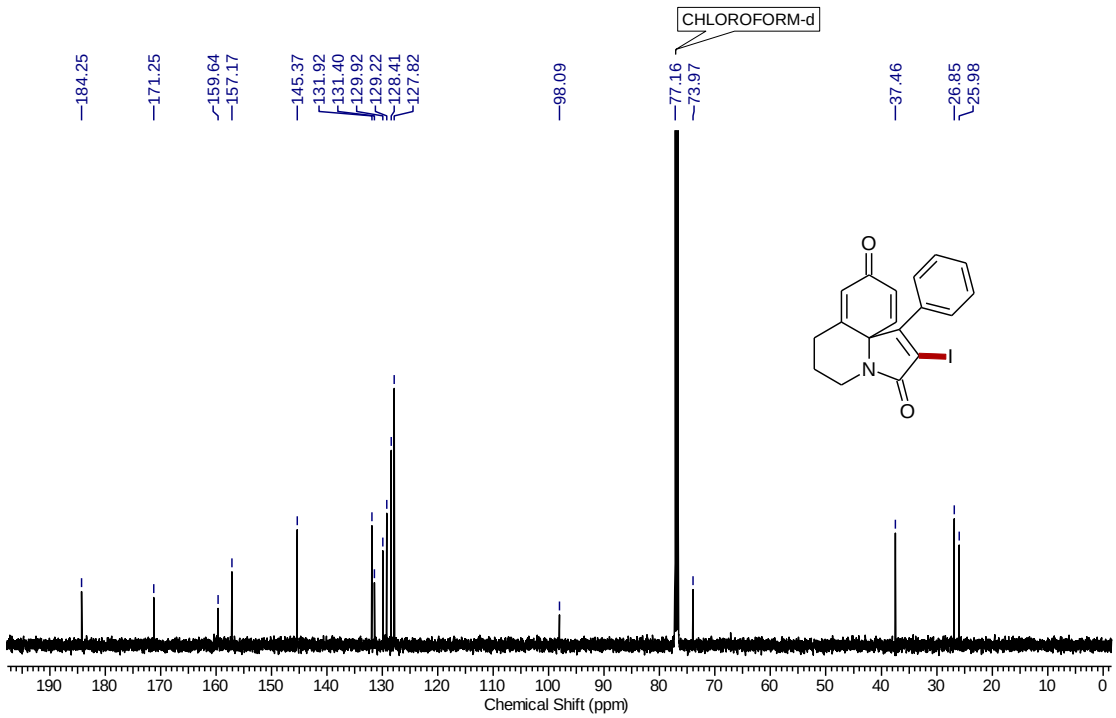
^{13}C NMR spectrum of **5c** in $CDCl_3$



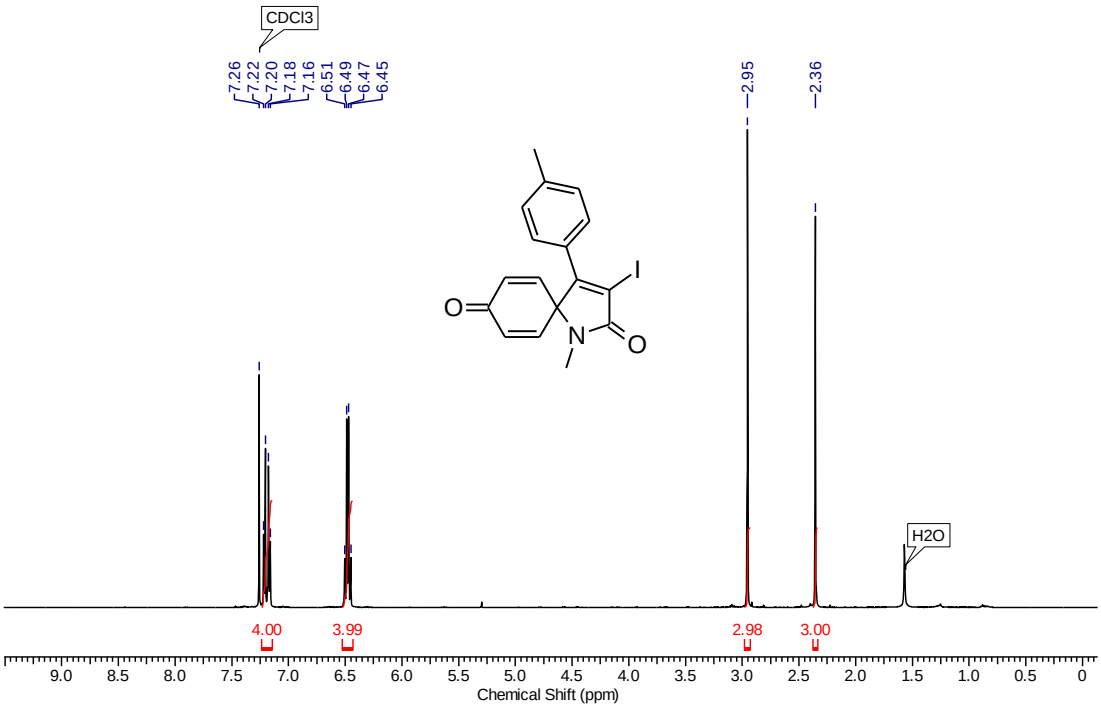
^{1}H NMR spectrum of **5d** in $CDCl_3$



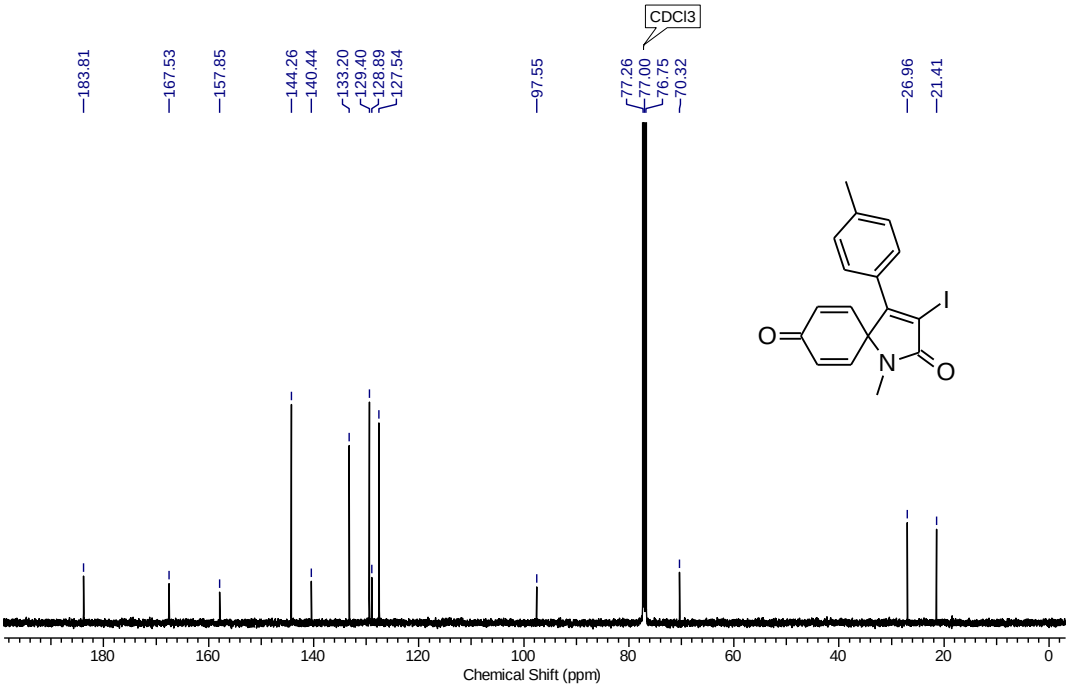
^{13}C NMR spectrum of **5d** in $CDCl_3$



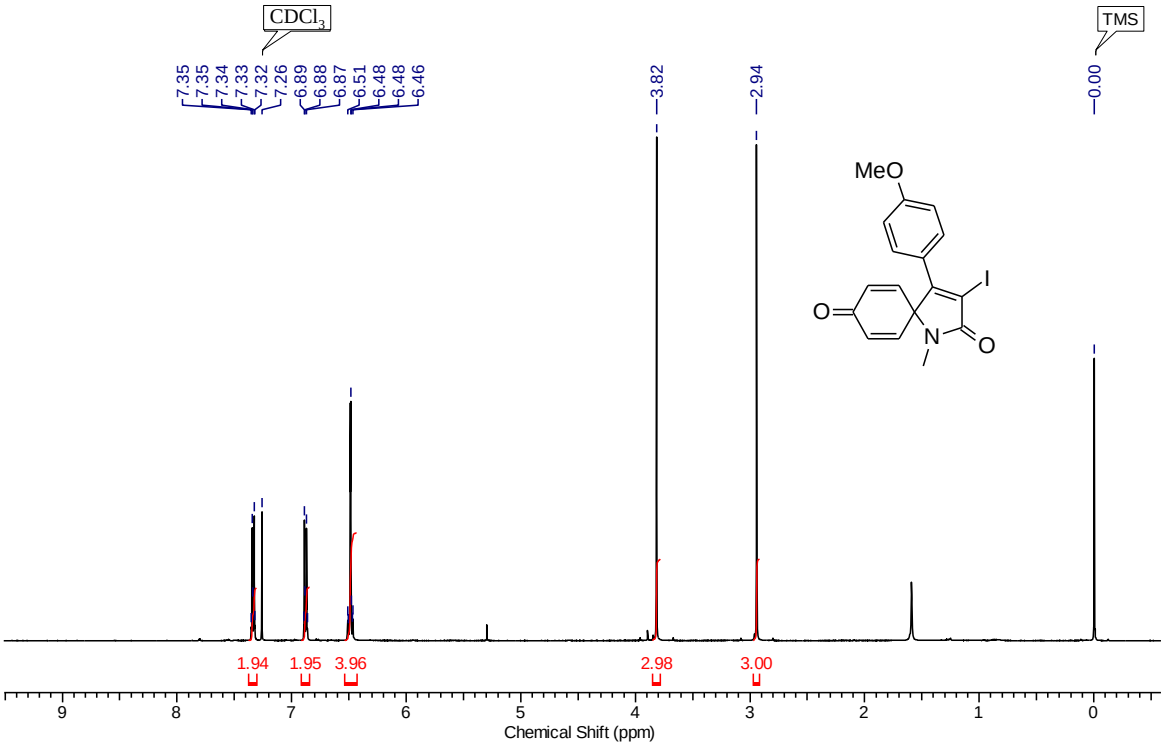
^{1}H NMR spectrum of **5e** in $CDCl_3$



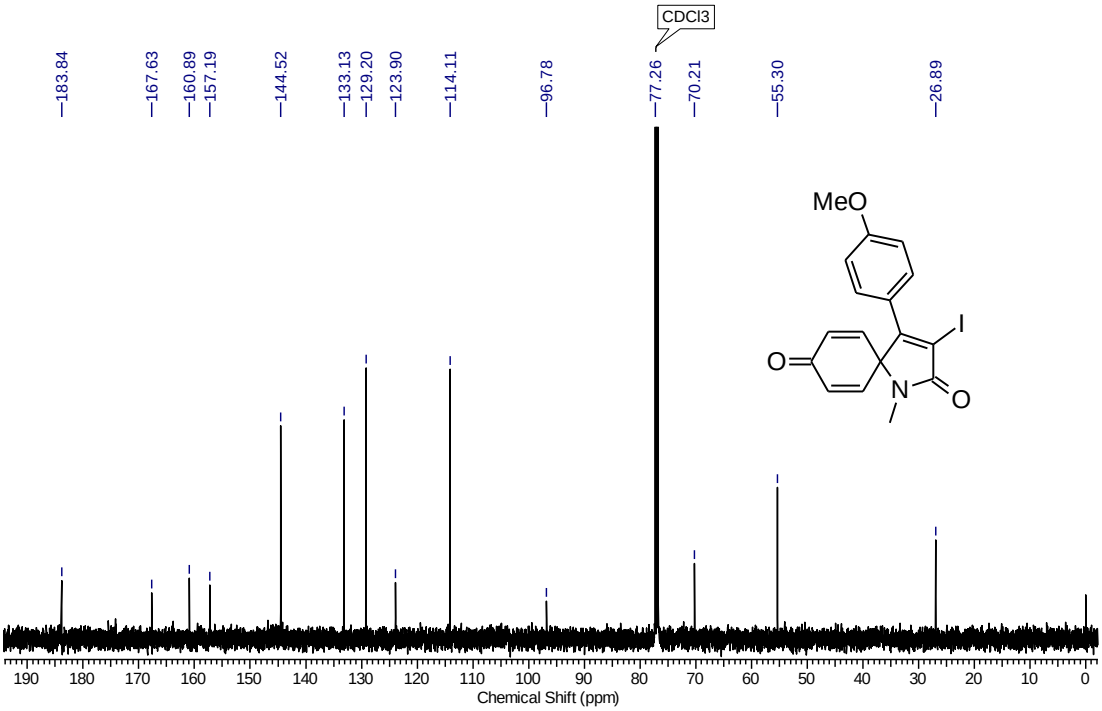
^{13}C NMR spectrum of **5e** in $CDCl_3$



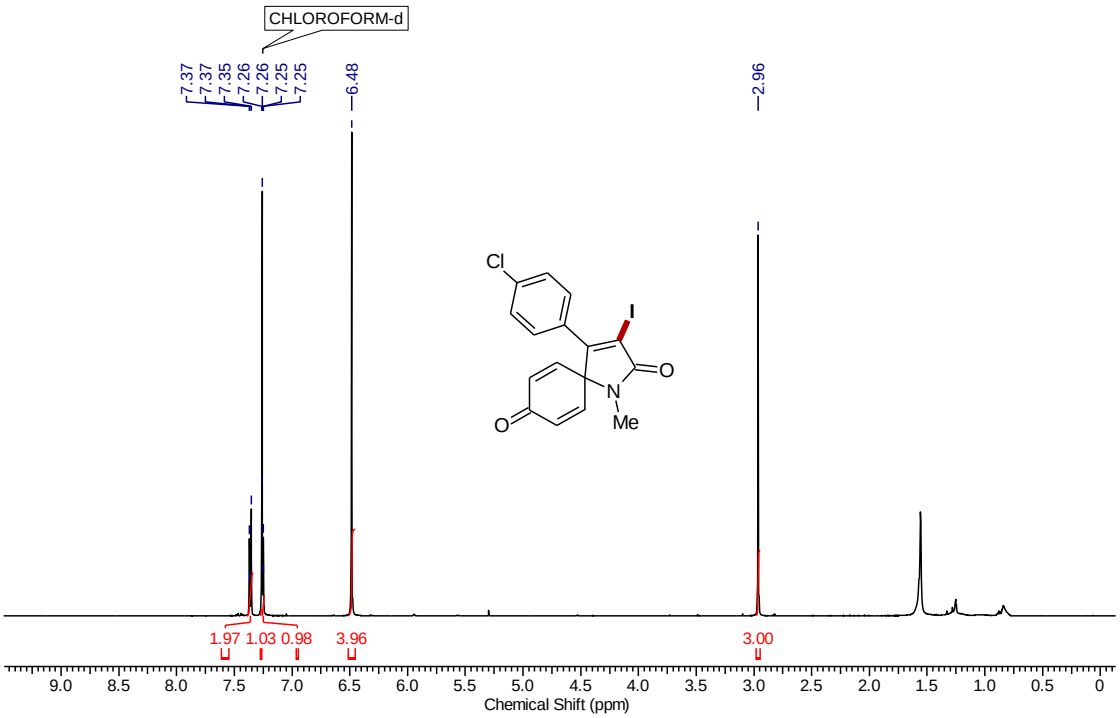
^{1}H NMR spectrum of **5f** in $CDCl_3$



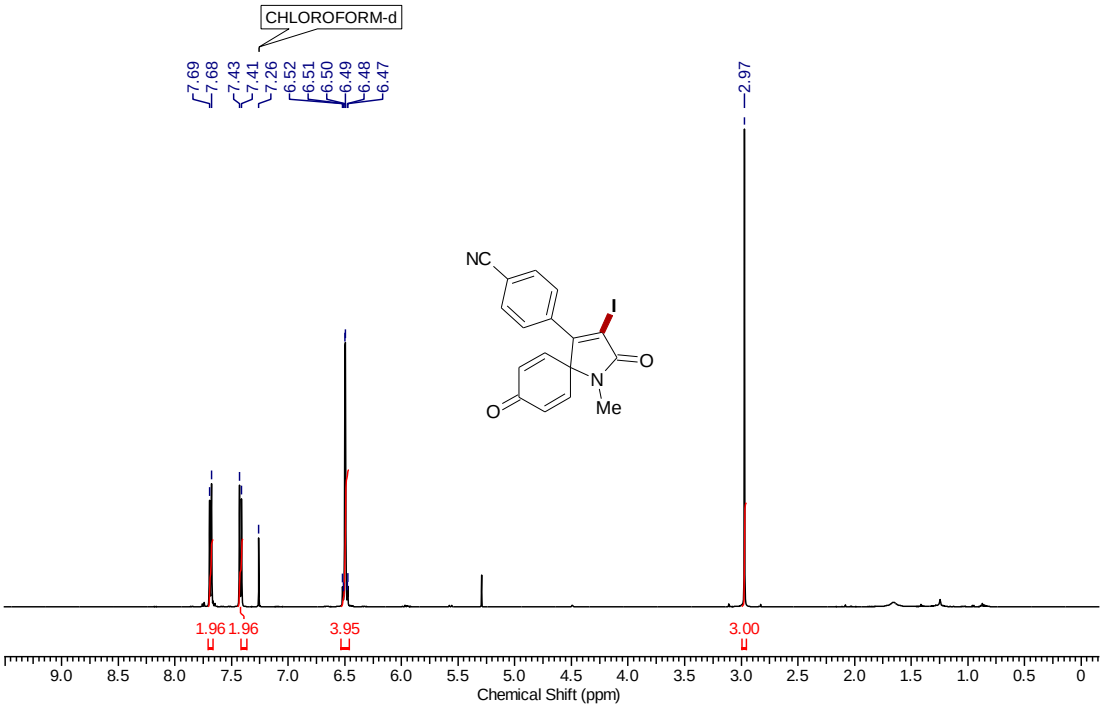
^{13}C NMR spectrum of **5f** in $CDCl_3$



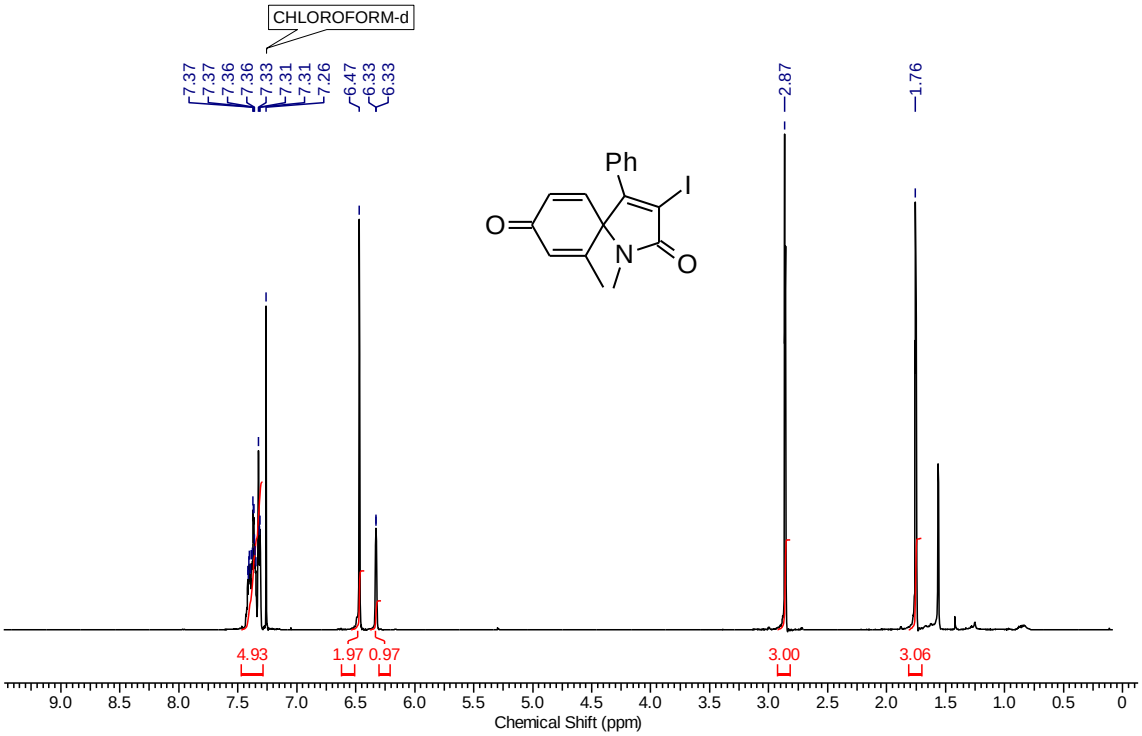
^{1}H NMR spectrum of **5g** in $CDCl_3$



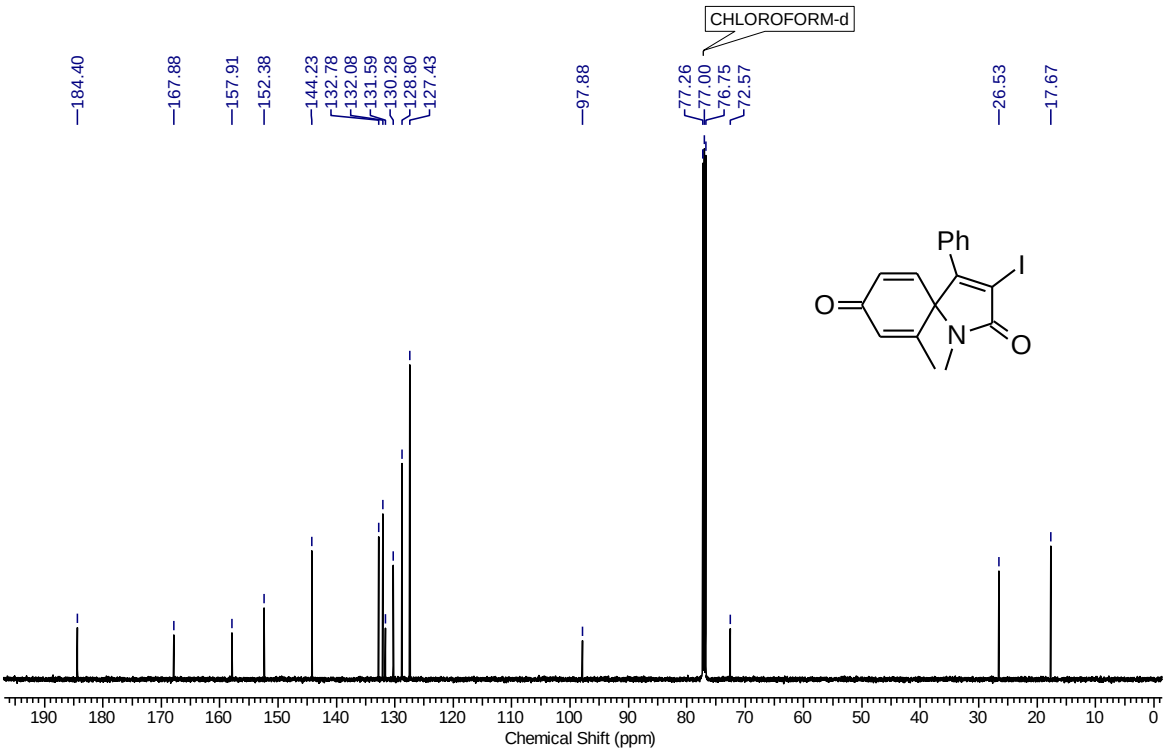
^{1}H NMR spectrum of **5h** in $CDCl_3$



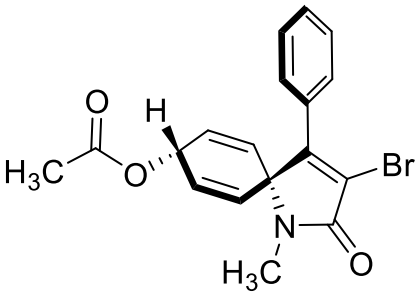
^{1}H NMR spectrum of **5i** in $CDCl_3$

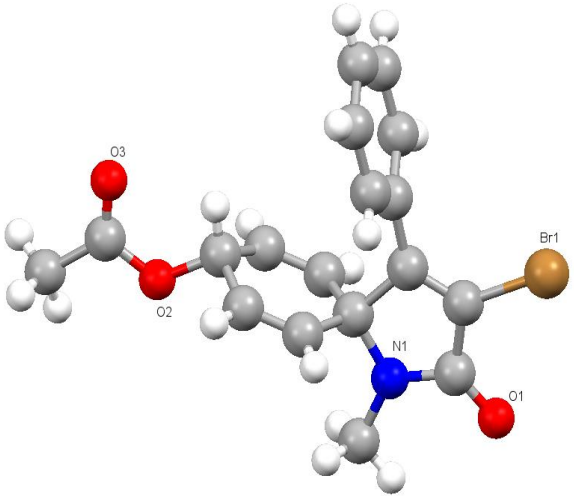


^{13}C NMR spectrum of **5i** in $CDCl_3$



11. Sc-XRD Structure of 3a:-





Identification code	red3
Empirical formula	$C_{18}H_{16}BrNO_3$
Formula weight	374.23
Temperature/K	293(2)
Crystal system	triclinic
Space group	P-1
a/Å	7.8783(5)
b/Å	15.2352(8)
c/Å	16.3952(11)
α/°	117.537(6)
β/°	100.635(6)
γ/°	92.597(5)
Volume/ $Å^3$	1695.6(2)
Z	4
P_{calc} gm/cm3	1.466
μ/mm^{-1}	2.438
F(000)	760.0
Crystal size/mm^3	0.5 × 0.4 × 0.4
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/^{o}	6.1 to 59.77
Index ranges	$-10 \leq h \leq 10$, $-20 \leq k \leq 19$, $-22 \leq 1 \leq 20$
Reflections collected	22412
Independent reflections	8202 [R_{int} = 0.0667, R_{sigma} = 0.1086
Data/restraints/parameters	8202/0/419
Goodness-of-fit on F^2	1.008
Final R index [1>=2σ(1)]	R_1 = 0.0569, wR_2 = 0.1074
Final R index [all data] Largest diff. peak/hole / $eÅ^{-3}$ 0.32/-0.41	R_1 = 0.1504, wR_2 = 0.1401

12. REFERENCES

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