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The Discovery and Development of Metal-Free Arylation Reactions with Unsymmetrical Diaryliodonium Salts

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The Discovery and Development of Metal-Free Arylation Reactions with Unsymmetrical Diaryliodonium Salts

by

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Dissertation Committee:
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Abstract

Functionalizing arenes and heteroarenes has been an active area of research since the 19th century, due to the presence of these molecular structures in many industrially important sectors. A tremendous amount of research has been published in achieving these chemical transformations using stoichiometric reagents and transition metal-catalyzed reactions. However, challenges still remain. An alternative and comparable methodology to metal-catalyzed reactions to overcome the drawbacks will advance this particular area of research is desirable.

Hypervalent iodine compounds offer a promising approach to metal-free arylation reactions. These mild, air and moisture stable compounds have showed significant success as non-toxic and metal-free reagents for the arylation reactions. In particular, unsymmetrical diaryliodonium salts offer functionalization of complex arene structure in an efficient and sustainable pathway.

A base-mediated coupling reaction for the metal-free synthesis of alkyl-aryl ethers by using unsymmetrical diaryliodonium salts and aliphatic alcohols is described. This method shows broad substrate scope with respect to both of the coupling partners to produce industrially useful alkyl-aryl ethers in moderate to excellent yields. The reaction is operationally simple, proceeds at mild temperature, and is atom-economical. Sustainability and synthetic utility of this reaction is demonstrated by the use of unsymmetrical

aryl(mesityl)iodonium salts as the arylating agents. A limitation of poor reactivity of electron rich unsymmetrical diaryliodonium salts was overcome by designing 2nd generation conditions and using trimethoxy benzene (TMP) as the auxiliary group.

Additionally discovery and development of an efficient method to access highly functionalized arynes from unsymmetrical aryl(mesityl)iodonium tosylate salts is presented. The aryne intermediates are generated by ortho C-H deprotonation of aryl(mesityl)iodonium salt with an amide base and subsequently trapped in a cycloaddition reaction with furan in moderate to good yields. Selective iodonium moiety elimination is discussed and the effect of auxiliary and temperature to reduce the regioisomeric ratio is demonstrated. Finally, additional coupling partner including benzyl azide and aliphatic amines are presented to show further utility of this methodology. Also, mechanistic investigations leading to the moderate reactivity of some electron rich unsymmetrical diaryliodonium salts is discussed.

Dedicated to my little brother

Vinod Sundalam (1992 - 2012)

We wish you were still among us

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Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

Ar – Aryl

BF_4 – Tetrafluroborate

Br – Bromide

Cl – Chloride

DBU - 1,8-Diazabicyclo(5.4.0)undec-7-ene

DEAD - Diethyl azodicarboxylate

DPE - 1,1-diphenylethyl- ene

Et – Ethyl

EDG – Electron donating group

EWG – Electron withdrawing group

GC-MS – Gas Chromatography Mass Spectrometry

KBr – Potassium bromide

LG – Leaving group

Me – Methyl

Mes – 1,3,5 –Trimethylphenyl

NMR - Nuclear Magnetic Resonance spectroscopy

Nu – Nucleophile

OTs – Tosylate

OTf – Triflate

Ph – Phenyl

PF_6 – Hexaflurophosphate

TFA – Trifluroacetate

THC – Tetrahydrocannabinol

TMS - Tetramethylsilane

TMB – 1,3,5-Trimethoxybenzene

TMP – 2,4,6 -Trimethoxyphenyl

TBAF – Tetrabutylammonium fluoride

TMAF – Tetramethylammonium fluoride

Th – Thienyl

Chapter 1

Importance of Arylation and its Real World Applications

1.1 Introduction and Background

1.1.1 Aromatic rings are important structural motifs for synthetic studies

Arenes and heteroarenes are ubiquitous groups in active pharmaceutical ingredients (API),[1] agrochemicals,[2] natural products,[3] liquid crystal displays,[4] and conducting polymers[5] (Figure 1.1, red). Of the top 200 pharmaceuticals prescribed in the United States in 2012, 157 possessed one or more aromatic rings.[6] Hence, functionalizing aromatic compounds

[1] For reviews, see: (a) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11905–12042; (b) Bagley, M. C.; Dale, J. W.; Meritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685–714; (c) Riego, E.; Hernandez, D.; Alberico, F.; Alvarez, M. *Synthesis* **2005**, 1907–1922; (d) Hughes, R. A.; Moody, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7930–7954.

[2] (a) Leroux, P.; Lanen, C.; Fritz, R. *Pestic. Sci*. **2006**, *36*, 255–261; (b) The Agrochemical Handbook; Hartley, D., Kidd, H., Eds.; *Royal Society of Chemistry*, University of Nottingham: England, 1991; (c) Baker, D.R.; Basarab, G.S.; Fenyes, J.G. Eds., *Synthesis and Chemistry of Agrochemicals* IV, Oxford University Press; ACS Symposium Series No 584, Washington, D.C., **1995**; (d) Modern Crop Protection Compounds; Kra¨mer, W., Schirmer, U., Eds.; Wiley-VCH: Weinheim, **2007**.

[3] For representative recent examples, see: (a) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843–868; (b) Mason, J. J.; Bergman, J.; Janosik, T. J. *Nat. Prod.* **2008**, *71*, 1447–1450; (c) Chen, Y.; Wei, X.; Xie, H.; Deng, H. *J. Nat. Prod*. **2008**, *71*, 929–932; (d) Fehe´ r, D.; Barlow, R. S.; Lorenzo, P. S.; Hemscheidt, T. K. *J. Nat. Prod*. **2008**, 71, 1970–1972; (e) Wang, Y.; Shang, X.-Y.; Wang, S.-J.; Mo, S.-Y.; Li, S.; Yang, Y.-C.; Ye, F.; Shi, J.-G.; He, L. J. *Nat. Prod*. **2007**, 70, 296–299

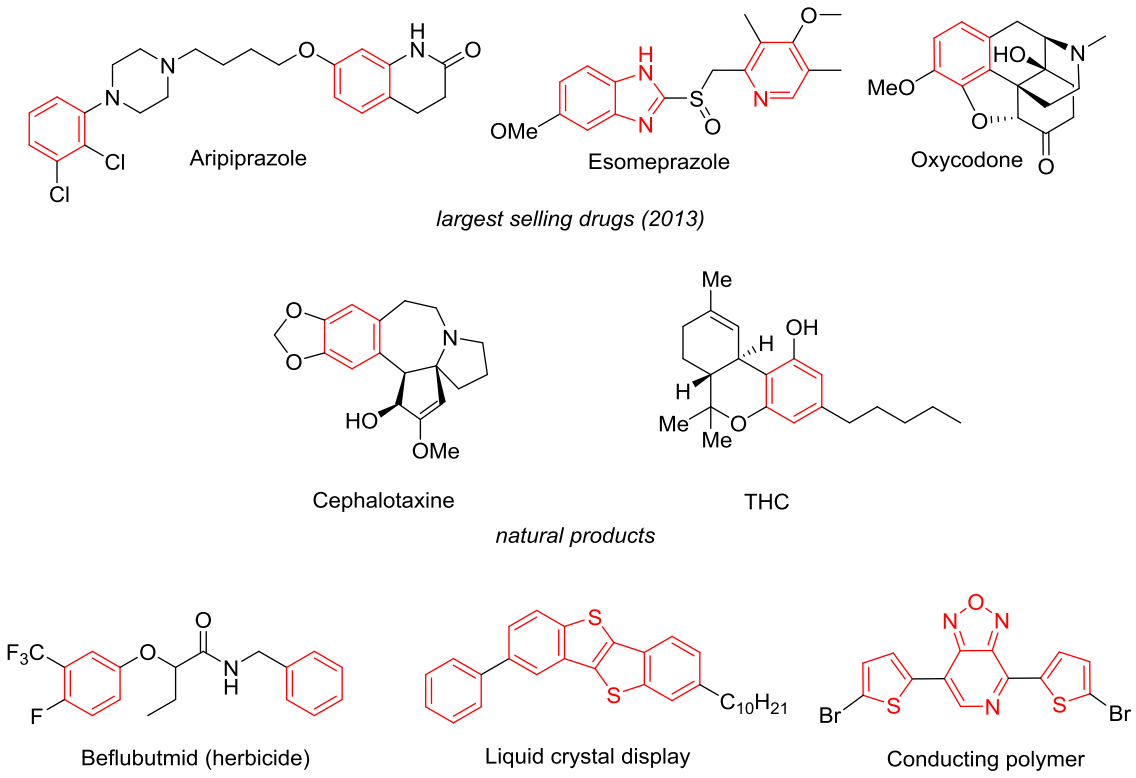
[4] Hiroaki Iino, Takayuki Usui & Jun-ichi Hanna, *Nature Communications, 6,* **2015**, 6828

[5] For representative recent examples, see: (a) Zhong, C.; He, A.; Guo, R.; Huang, H. *Synth. Met*. **2008**, *158*, 33–37; (b) Atwani, O.; Baristiran, C.; Erden, A.; Sonmez, G. *Synth. Met*. **2008**, *158*, 83–89; (c) Ha, Y.; Seo, J.-H.; Kim, Y. K. *Synth. Met*. **2008**, *158*, 548–552; (d) Blouin, N.; Michaud, A.; Gendron, D.; Wakim, S.; Blair, E.; Neagu-Plesu, R.; Bellete ̂te, M.; Durocher, G.; Tao, Y.; Leclerc, M. *J. Am. Chem. Soc.* **2008**, *130*, 732–742; (e) Xin, H.; Lim, F. S.; Jenekhe, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 5424–5425

[6] http://www.pharmacytimes.com/publications/issue/2013/july2013/top-200-drugs-of-2012

forming new carbon-carbon and carbon-heteroatom bonds constitute a significant portion of organic synthesis.[7] For over a century, the synthesis and functionalization of aromatic compounds have been an active area of research.

Figure 1.1 Industrially important molecules containing aromatic rings.



[7] Steven V. Ley and Andrew W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400 – 5449; b) F. Bellina, R. Rossi / *Tetrahedron 65* **2009**, 10269–10310.

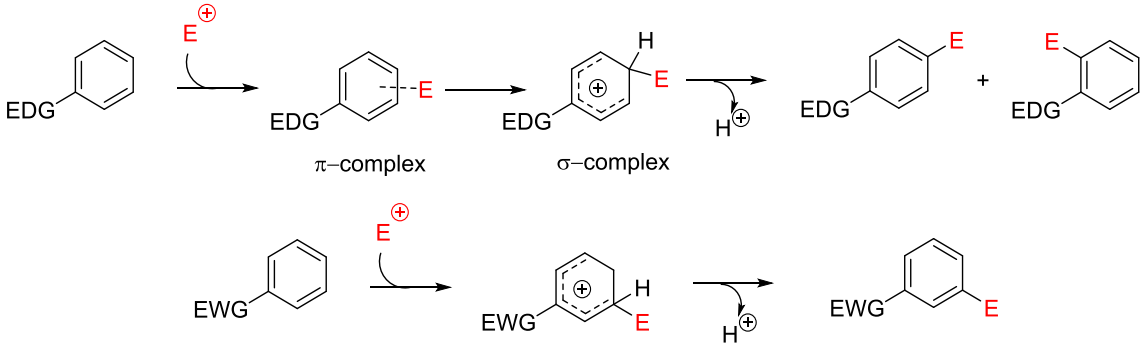
1.2 Strategies to Functionalize Arenes

1.2.1 Non-metal catalyzed reactions

A) Electrophilic Aromatic Substitution; S_EAr Reaction (EAS)

Electrophilic aromatic substitution reactions are one of the most extensively studied reactions in organic synthesis. Since its discovery in the 19th century, the utilization of this chemistry at an industrial level has been ongoing. The two stages of reactions involving π and σ complexes are very well-studied[8] and contribute to a significant portion of arylation reactions (Scheme 1.1). In this reaction, an incoming group is added to the arene ring as the electrophile. Depending on the type of group present on the arene ring, the incoming electrophile is directed onto different positions of the arene ring. Electron donating groups (R, OR, $N(H_2)/(R_2)$, NHR, OH, etc.) and weak electron withdrawing groups (halogens) direct the incoming electrophiles to *ortho* and *para* positions; whereas, strong electron

Scheme 1.1: Electrophilic aromatic substitution reaction



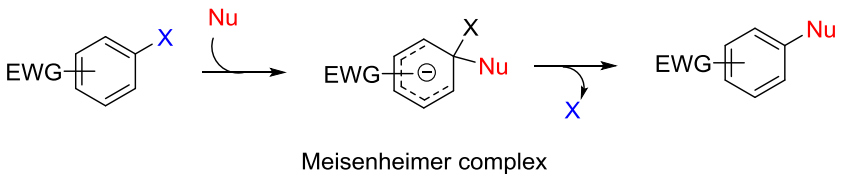
[8] a)Arene Chemistry: *Reaction Mechanisms and Methods for Aromatic Compounds*; Mortier, J., Ed.; Wiley: Hoboken, NJ, **2016**. b) Ingold, C. K.*Structure and Mechanism in Organic Chemistry*; Cornell University Press: Ithaca, NY, **1969**; Chapter 6. c) Carey, F. A.; Sundberg, R. J.*Advanced Organic Chemistry, Part A: Structure and Mechanisms, 5th ed.; Springer*: New York,**2007**; Chapter 9. d) Olah, G. A.Mechanism of Electrophilic Aromatic Substitutions*Acc. Chem. Res.* **1971**, *4*, 240–248 e) Taylor, R.*Electrophilic Aromatic Substitution;* Wiley: New York, **1990**.

withdrawing groups (-C=O, NO_2, CN, NR_3^+, etc.) direct to *meta* positions. Several classic reactions including nitration, halogenation, sulfonation, and Friedel-Crafts alkylation and acylation reactions follow the S_EAr mechanism.[1]

B) Nucleophilic Aromatic Substitution: S_NAr Reaction (NAS)

A complementary approach to EAS towards the arylation of aromatic compounds is the S_NAr reaction — a well-established and versatile method both for industrial and academic processes.[9] In this process, an incoming nucleophile replaces a halide from an aromatic ring which undergoes through a resonance-stabilized Meisenheimer complex (Scheme 1.2). Strong electron withdrawing groups (NO_2, CN, etc.) are required to stabilize this complex, which limits the reactivity only to aromatic moieties containing these groups. Additionally, electron withdrawing groups must be located on either *ortho* or *para* position for this reaction to proceed.

Scheme 1.2: Nucleophlilic aromatic substitution reaction



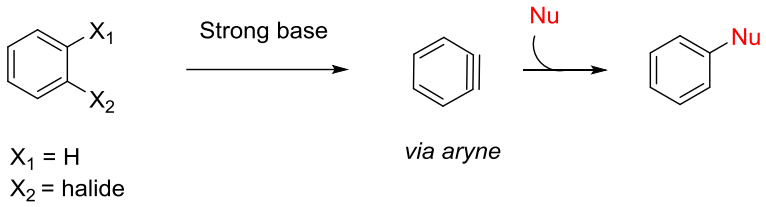
C) Aryne Reaction

Contrary to the above mentioned strategies, functionalizing arenes is also accomplished by

[9] 1. Schlosser, M.; Ruzziconi, R.Synthesis 2010, **2010**, 2111–2123 B) Miller, J. Aromatic Nucleophilic Substitution; Elsevier: Amsterdam, **1968**. C) March, J.; Smith, M. B.March's Advanced Organic Chemistry, Reactions, Mechanism and Structure, 6th ed.; John Wiley & Sons: New York, **2007**. D) Mąkosza, M. *Chem. Soc. Rev.* **2010**, 39, 2855–2868 e) Terrier, F.Modern Nucleophilic Aromatic Substitution; *Wiley-VCH*: Weinheim, Germany, **2013**

the generation of aryne intermediates using strong base on a mono or dihalogenated/pseudo-halogenated arenes (Scheme 1.3). Thus, the highly reactive aryne intermediates generated are used in several different transformations to functionalize arenes (Chapter 3).

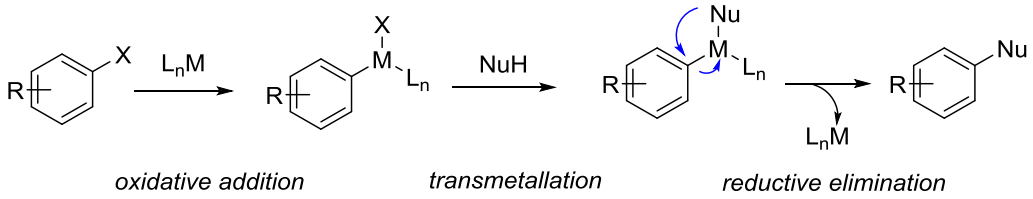
Scheme 1.3: aryne reaction



1.2.2 Metal catalyzed reactions

Transition metal catalyzed reactions are currently state-of-the-art in the formation of aromatic carbon-carbon or carbon-heteroatom bonds.[10] These reactions have received enormous attention as they have significantly increased the breadth of the scope of substrates that participate in arylation reactions.[11] This is due to the new mode of reactivity

Scheme 1.4: Catalytic pathway using transition metals



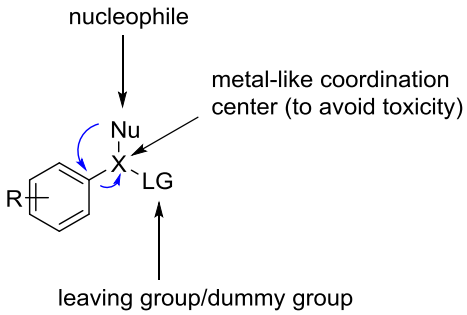
[10] D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; b) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev*. **2007**, 36, 1173–1193; c) T. Satoh, M. Miura, *Chem. Lett*. **2007**, *36*, 200–205; d) R. G. Bergman, *Nature* **2007**, *446*, 391–393;

[11] Kumada, M. *Pure Appl. Chem***. 1980**, *52*, 669–679 b) Stille, J. K. *Angew. Chem. Int. Ed*. **1986**, *25*, 508–523. C) Negishi, E., Baba, S. J. *Chem. Soc., Chem. Commun*. **1976**, 596–597; d) Baba, S., Negishi, E. *J. Am. Chem. Soc*. **1976**, *98*, 6729–6731. E) Sonogashira, K., Tohda, Y., Hagihara, N. *Tetrahedron Lett*. **1975**, 4467–4470. F) Miyaura, N., Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457–2483. G) Suzuki, A. *Pure Appl. Chem*. **1991**, *63*, 419–422.

of transition metals, which follow a completely different mechanism compared to previously described methods (Scheme 1.4). As the reductive elimination step completely avoids the formation and stabilization of charged intermediates, such as the Meisenheimer complex, limitations to substrate scope are greatly reduced.[12] These reactions allowed the researcher to attain transformations which were not possible with classic reaction pathways and have greatly advanced the field of organic synthesis.

1.3 Alternatives for Metal-catalyzed Reactions are Needed

Figure 1.2: Metal-like alternative



Although transition metal-catalyzed reactions are synthetically useful, challenges still remain. For example, residual metal removal from the end product is difficult and cumbersome, and the cost of transition metals (especially Pd, Pt) and some additional reactions require expensive or proprietary designer ligands. Metal-free arylation methods are emerging to address these issues.[13] Medicinal and process chemists are primarily

[12] For reviews, see: (a) Hartwig, J. F. in Handbook of Organopalladium Chemistry for Organic Synthesis, b) Negishi, E., Ed., *Wiley-Interscience*, New York, **2002**, 1051–1096; (c) Muci, A. R., Buchwald, S. L. *Top. Curr. Chem*. **2002**, 219, 131–209.
[13] Anup Bhunia , Santhivardhana Reddy Yetra and Akkattu T. Biju *Chem. Soc. Rev.*, **2012**, *41*, 3140-3152 b) Lutz Ackermann, Monica Dell'Acqua, Sabine Fenner, Rubén Vicente, and René Sandmann *Org. Lett.*, **2011**, *13*, 2358–2360 c) Jalalian, N., Petersen, T. B. and Olofsson, B., *Chem. Eur. J*., **2012,** *18*, 14140–14149.

interested in mild and economically feasible synthetic methods that ensure functionalization of aromatic rings that will tolerate a wide range of functional groups. New reaction modules, which enable a metal-free reaction scheme which address these challenges and advance organic synthesis, are cost-effective, do not need further purification of the end product, and are atomically economical (Figure 1.2).

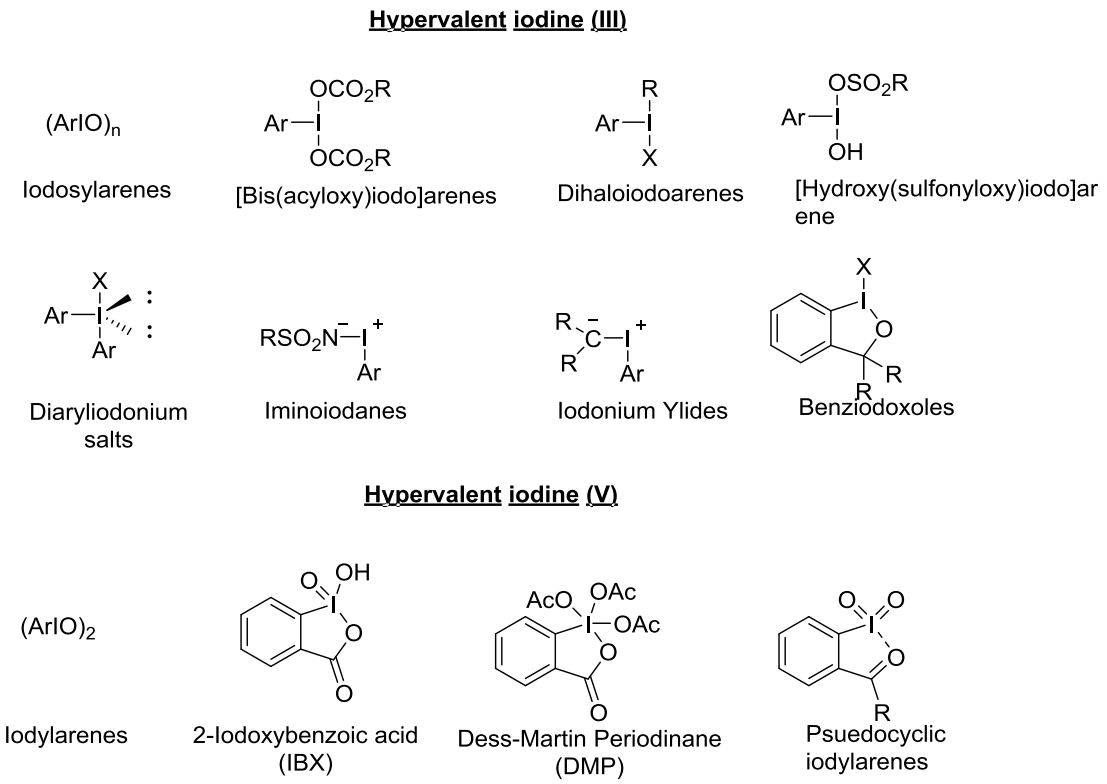
1.4 Hypervalent Iodine Compounds

1.4.1 Hypervalent iodine offers a promising metal-free approach

Hypervalent iodine compounds (Figure 1.3) have recently attracted significant attention as non-toxic, mild, and selective reagents in organic synthesis and as oxidants and electrophilic reagents.[14] Trivalent hypervalent iodine (III) compounds are named λ^3-iodanes according to IUPAC nomenclature.[15] These salts with an aryl group are more stable than the other types of hypervalent iodine compounds and are mostly used in chemical transformations; however, pentavalent iodine (V) reagents, specifically Dess-Martin periodinane (DMP) and 2-iodoxybenzoic acid (IBX), are often used as oxidizing reagents.[16]

[14] a) T. Wirth, *Angew. Chem*. **2005**, *117*, 3722; *Angew. Chem*. Int.Ed. **2005**, *44*, 3656; b) R. D. Richardson, T. Wirth, *Angew. Chem.* **2006**, *118*, 4510; *Angew. Chem*. Int. Ed. **2006**, *45*, 4402.
[15] Wirth, T., Ed. Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis. Top. Curr. Chem. **2003**, *224*, 1−248.
[16] Zhdankin, V. V. Organoiodine(V) Reagents in Organic Synthesis. *J. Org. Chem.* **2011**, *76*, 1185−1197.

Figure 1.3: Types of hypervalent iodine compounds



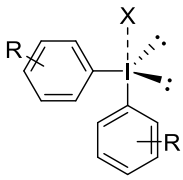
1.4.2 Diaryliodonium salts: significance and structure[15]

Diaryliodonium salts were discovered in 1894 by Hartmann and Meyer and have received significant attention in comparison to other hypervalent iodine compounds.[17] Despite the discovery of these reagents over a century ago, their use as metal-free reagents for various reaction platforms continues to evolve. Diaryliodonium salts are air and moisture stable, offer mild reaction conditions, and are synthetically accessible. Analogous to transition

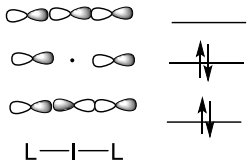
[17] a)Zhdankin, V. V.; Stang, P. *J. Chem. Rev*. **2008**, *108*, 5299−5358. b) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052−9070. c) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOK*, **2011**, 370−409. Ochiai, M. Wirth, T., Ed.; *Springer-Verlag*: Berlin, 2003; Vol. 224, pp 5−68. d) Zhdankin, V. V., *John Wiley & Sons*: West Sussex, **2014**, 145−336. e) Hartmann, C.; Meyer, V. *Chem. Ber*. **1894**, 27, 426.

metals, hypervalent iodine compounds oxidatively facilitate the formation of aryl-nucleophile bonds due to their high oxidation state.

Figure 1.4: Structure of diaryliodonium salt



X = OTs, OTf, BF_4, Br, Cl, PF_6



molecular orbitals in hypervalent iodine

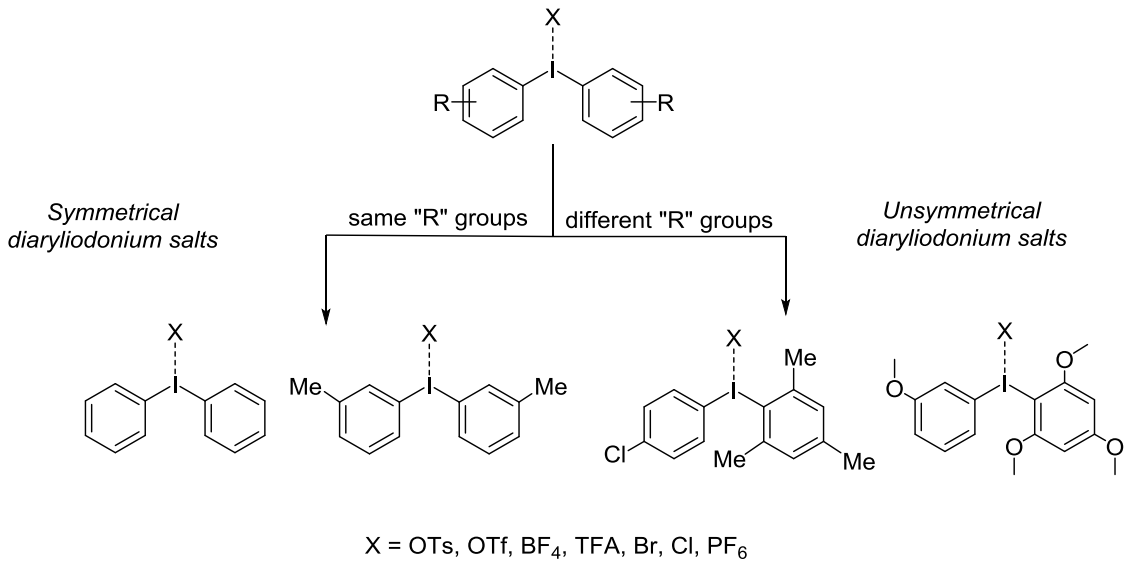
Diaryliodonium salts consist of hypervalent iodine (III) bonded to two aryl groups (ligands) occupying the equatorial position and a counter-anion X located in axial positions, giving the molecules pseudo-trigonal bipyramidal, or T-shape, geometry (Figure 1.4, left). The high electrophilic reactivity of hypervalent iodine compounds arises due to the bonding orbitals in λ^3- iodanes. These bonding orbitals are engaged by two electrons from the non-hybridized 5p orbital of iodine and one electron of each ligand L resulting in long, weak, and highly polarized hypervalent bond (Figure 1.4, right).[12] The counter-anion X plays a crucial role in the solubility and reactivity of these salts. The common counter-anions employed are OTf, OTs, BF_4, Br, Cl, PF_6, etc., Salts containing halides as the counter-anions are usually less soluble in organic solvents compared to other counter-anions. However, the effect of counter-anions on the reactivity of these salts is not well-understood.

1.4.3 Types of diaryliodonium salts

Diaryliodonium salts can be categorized into two types, based on the different aryl groups present. If the two aryl groups are the same (Ar = Ar), they are referred as symmetrical diaryliodonium salts (Figure 1.5, left). If they are different (Ar ≠ Ar), they are called unsymmetrical diaryliodonium salts (Figure 1.5, right). Symmetrical salts compared to unsymmetrical salts avoid chemo-selectivity issues that may arise due to sterics and electronics;[18] however, symmetrical diaryliodonium salts present challenges in the synthesis of elaborated/complex symmetrical salts, thus, limiting their utility to only simple diaryliodonium salts. Unsymmetrical salts, on the contrary, can offer advantage over symmetrical salts where one of the aryl groups (auxiliary) is electronically rich and acts as the spectator group. There are several different auxiliary groups synthesized, including mesityl (Mes), trimethoxyphenyl (TMP), thienyl etc. These unsymmetrical diaryliodonium salts overall transfer the most electron-deficient aryl groups to the nucleophile.

[18] N. R. Deprez, M. S. Sanford, *Inorg. Chem.* **2007**, *46*, 1924-1935; b) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330-7331; c) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593-1597. d) Lancer, K.M. , Wiegand, G.H, *J. Org. Chem.* **1976**, *41*, 3360.

Figure 1.5: Types of diaryliodonium salts



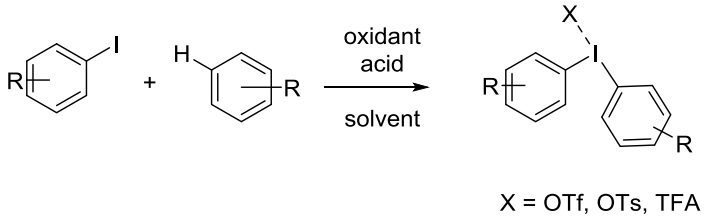
1.4.4 Synthetic methodologies to access diaryliodonium salts

Diaryliodonium salts can be conveniently prepared via one pot synthetic route each typically with an initial oxidation of aryl iodide and ligand exchange with an arene to yield the salts. Other methods starting from aryl boronic acids and molecular iodine are also well developed.

A) From Aryl iodides[19]

The most common route to synthesize diaryliodonium salts is by initial oxidation of aryl iodide to an iodine (III) species followed by subsequent ligand exchange with simple arenes or organometallic reagents in acidic or neutral conditions; and the anion is usually generated from acid used (Scheme 1.5). The commonly employed acids are trifluoromethane sulfonic acid (TfOH) and p-toluenesulfonic acid (TsOH). Many inorganic acids are also employed, but the use of organic acids is advantageous due to their solubility in organic solvents and their easy isolation as triflate or tosylate salts without an anion exchange step. Both symmetrical and unsymmetrical diaryliodonium salts can prepared conveniently with this route.

Scheme 1.5: Preparation of diaryliodonium salts from aryl iodides



B) From Arylboronic acids

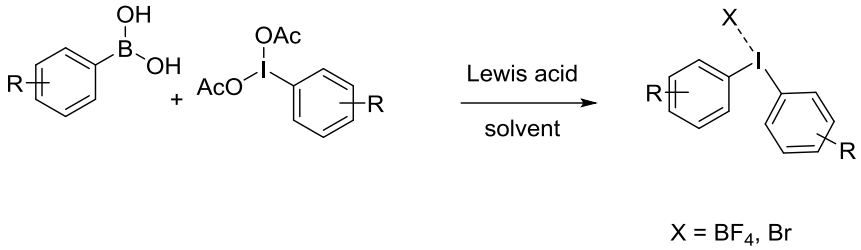
This method was first developed by Ochiai et al.[20] In this method, high yielding diaryliodonium salts were synthesized using hypervalent diacetoxyiodoarenes and alkali metal tetraarylborates. Later, the use of arylboronic acids was developed in the presence of

[19] a) Kryska, A.; Skulski, L. *Molecules* **2001**, *6*, 875−880. b) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, 2521−2523. c) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610−2618. d) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, *2008*, 592−596. e) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602−4607. Dohi, T.; Yamaoka, N.; Itani, I.; Kita, Y. Aust. *J. Chem.* **2013**, *64*, 529−535. f) Qin, L.; Hu, B.; Neumann, K. D.; Linstad, E. J.; McCauley, K.; Veness, J.; Kempinger, J. J.; DiMagno, S. G. Eur. *J. Org. Chem.* **2015**, *2015*, 5919−5924.

[20] M. Ochiai, M. Toyonari, T. Sueda, Y. Kitagawa, *Tetrahedron Lett.* **1996**, *37*, 8421.

a Lewis acid e.g., boron trifluoride (Scheme 1.6).[21] The tetrafluoroborate salts are easily isolated after the anion exchange step. Our group has isolated bromide salts using saturated KBr in the anion exchange reaction instead of tetrafluroborates, which were more bench stable diaryliodonium salts.[22]

Scheme 1.6: preparation of diaryliodonium salts from arylboronic acids



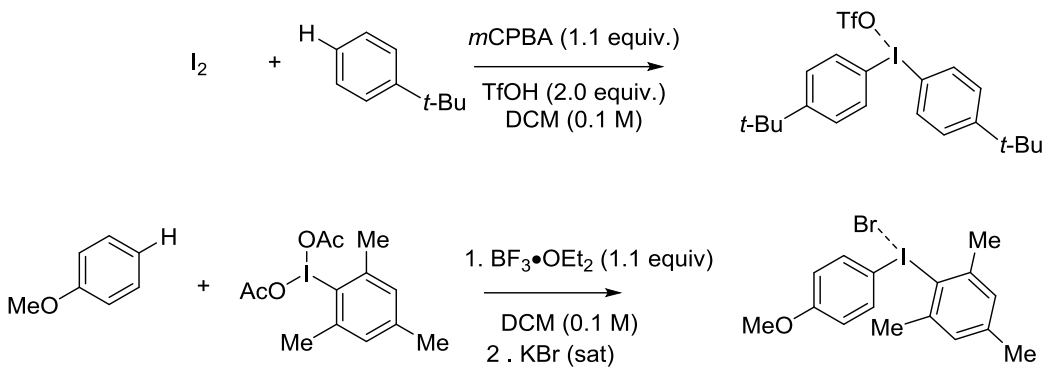
C) From Simple Arenes

Synthesis of diaryliodonium salts can also be accomplished using only simple arenes and molecular iodine or hypervalent diacetoxyiodoarenes. Using molecular iodine follows a similar oxidation approach as used in method A but instead, utilized simple arene and I_2; however, this method can only be applied to make symmetrical salts and is limited to a few groups, such as benzene, *tert*-butylbenzene and halobenzene (Scheme 1.7).[23]

Another method, which involves the modification of Ochiai's, is the use of diacetoxyiodoarene with simple arene instead of a boronic acid, and subsequent addition of saturated KBr to yield unsymmetrical diaryliodonium bromide salts.[23]

[21] M. Ochiai, M. Toyonari, T. Nagaoka, D.-W. Chen, M. Kida, *Tetrahedron Lett*. **1997**, *38*, 6709.
[22] Sundalam, S. K.; Stuart, D. R. *J. Org. Chem*. **2015**, *80*, 6456−6466.
[23] M. D. Hossain,Y. Ikegami, T. Kitamura, J. Org. Chem. 2006, 71, 9903.b) M. D. Hossain, T. Kitamura, Bull. *Chem. Soc. Jpn*. **2007**, 80, 2213.

Scheme 1.7: preparation of diaryliodonium salts from simple arenes



1.4.5 General reactions of diaryliodonium salts

Diaryliodonium salts have shown several applications in organic synthesis.[12] In 1953, Beringer established the reactivity of diaryliodonium salts primarily with diphenyliodonium bromide.[24] This reagent has been employed in arylation of carbon nucleophiles such as enolates,[25] alkyl Grignard reagents[26] and a wide range of heteroatom nucleophiles such as nitrogen,[27] oxygen,[28] and fluorine,[29] under metal-free conditions. However, these reactions are mostly explored using symmetrical diaryliodonium salts; additionally to diphenyliodonium salts, show poor atom economy. Hence, unsymmetrical diaryliodonium salts can be more efficient in accessing complex aryl groups and also avoid

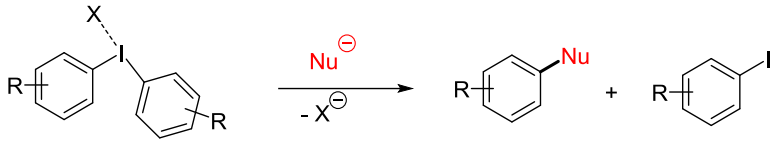
[24] Beringer, F. M.; Brierley, A.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2708−2712.
[25] J. H. Ryan, P. J. Stang, *Tetrahedron* Lett. **1997**, *38*, 5061.
[26] C. H. Oh, J. S. Kim, H. H. Jung, *J. Org. Chem*. **1999**, *64*, 1338.
[27] M. A. Carroll, R. A. Wood, *Tetrahedron* **2007**, *63*, 11349.
[28] J. R. Crowder, E. E. Glover, M. F. Grundon, H. X. Kaempfen, *J. Chem. Soc*. **1963**, 4578. b) Lindstedt, E.; Ghosh, R.; Olofsson, B. *Org. Lett.* **2013**, *15*, 6070−6073. c) Ghosh, R.; Lindstedt, E.; Jalalian, N.; Olofsson, B. *ChemistryOpen*, **2014**, *3*, 54−57.
[29] a) M. A. Carroll, J. Nairne, J. L.Woodcraft, *J. Labelled Compd.Radiopharm*. **2007**, *50*, 452; b) S. Martin-Santamaria, M. A.Carroll, C. M. Carroll, C. D. Carter, H. S. Rzepa, D. A. Widdowson, V.W. Pike, *Chem. Commun*. **2000**, 649; c) M. A.Carroll, J. Nairne, G. Smith, D. A. Widdowson, *J. Fluorine Chem*. **2007**, 128, 127.

waste of aryl iodide byproduct as they bear a cheap (reusable) auxiliary group.

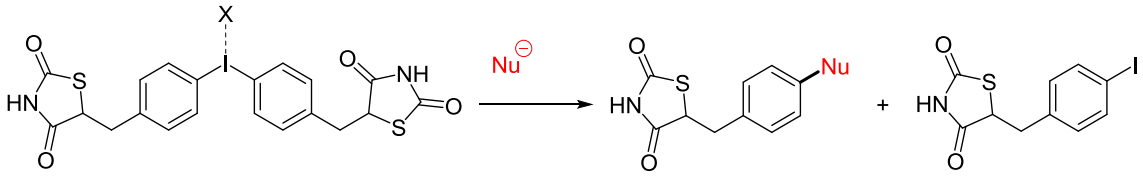
1.4.6 Unsymmetrical salts are advantageous over symmetrical salts

General reactions of diaryliodonium salts with a nucleophile provide the desired coupling product and aryl iodide side product (Scheme 1.8). In symmetrical diaryliodonium salts, an equal ratio of aryl iodide side product is generated along with the desired ligand coupling product. In simple symmetrical diaryliodonium salts, this may not be an issue, but in complex symmetrical diaryliodonium salts, a significant portion of the starting material is wasted (Scheme 1.8.1). Unsymmetrical diaryliodonium salts contain an auxiliary (or spectator group) as the other aryl group. The stoichiometric quantity of this generated auxiliary iodide is inexpensive and can be reused to synthesize diaryliodonium salts (Scheme 1.8.2). [21] These salts are more atom economical compared to symmetrical diaryliodonium salts. A current challenge is identifying competent auxiliary groups and controlling aryl transfer selectivity.

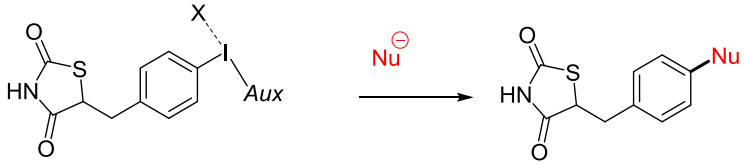
Scheme 1.8: General reaction an diaryliodonium salt



Scheme 1.8.1: Using symmetrical diaryliodonium salts



Scheme 1.8.2: Using unsymmetrical diaryliodonium salts



by product
less wasteful
recoverable and reusable

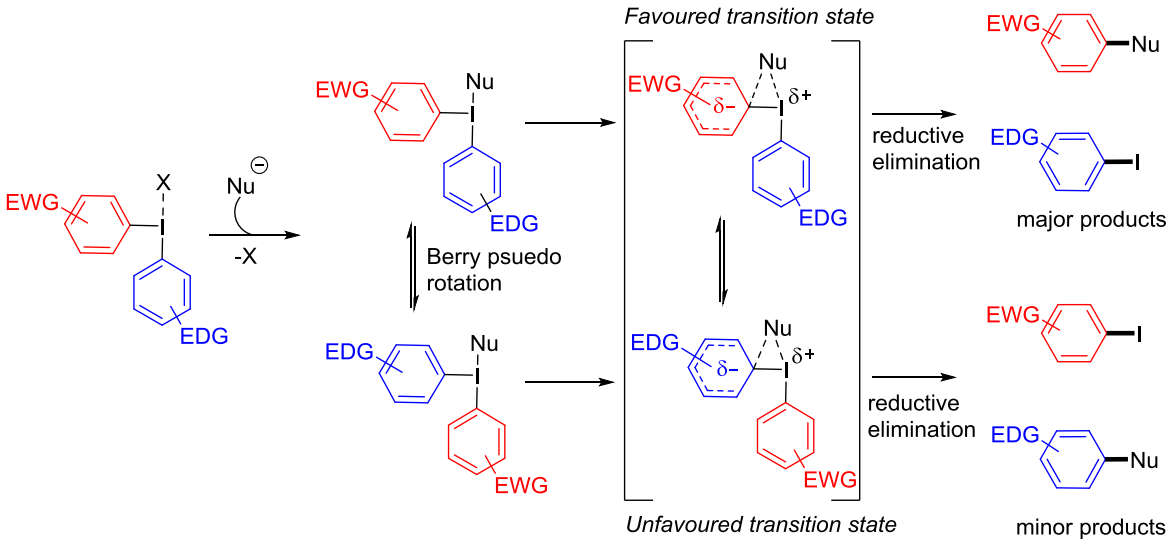
Aux = Mes,TMP, Thienyl..

We have focused our attention on using unsymmetrical diaryliodonium salts as they are a critical area of future study in metal-free arene functionalization reactions. These salts offer more atom economic strategies to arylation compared to symmetrical salts, which is important for the transfer of more elaborate "real-world" aryl groups. Additionally, the synthesis of complex and highly functionalized symmetrical diaryliodonium salts can be very challenging as opposed to the synthesis of unsymmetrical diaryliodonium salts. Even if one succeeds to make elaborate symmetrical diaryliodonium salts, the loss of an equivalent group as an iodide is not very practical compared to losing an inexpensive dummy/auxiliary group (such as Mes, TMP etc.) in the case of unsymmetrical diaryliodonium salts.

1.4.7 Reactivity of diaryliodonium salts via nucleophilic addition

The general mechanism of the nucleophilic addition reaction of unsymmetrical diaryliodonium salts is shown in Scheme 1.9. In this, upon the addition of the nucleophile, the electrophilic hypervalent iodine center is attacked by the nucleophile replacing the counter-anion X, and forming a 3-centered complex. This complex is in equilibrium with its geometric isomer formed via Berry pseudorotation-like process, the top structure being the major lower energy species. This is due to the presence of the electron withdrawing group present on the aryl group, which is axial to the nucleophile making the aryl group more electron deficient. The interaction of the nucleophile with the ipso-carbon of the electron withdrawing aryl group causes the formation of the transition state which will ultimately undergo ligand coupling to yield the desired nucleophile coupling product and reductive elimination of aryl iodide.

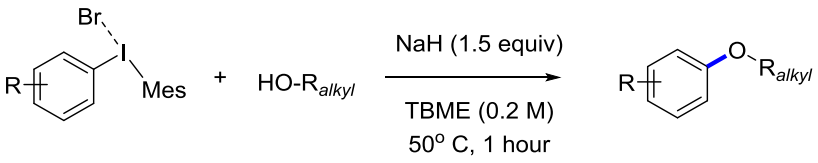
Scheme 1.9 : Proposed mechanism of nucleophilic addition on diaryliodonium salts



Chapter 2: Part I

Base Mediated Synthesis of Alkyl-Aryl Ethers from the Reaction of Aliphatic Alcohols and Unsymmetric Diaryliodonium Salts[30]

Scheme 2.1: Base mediated synthesis of alkyl-aryl ethers



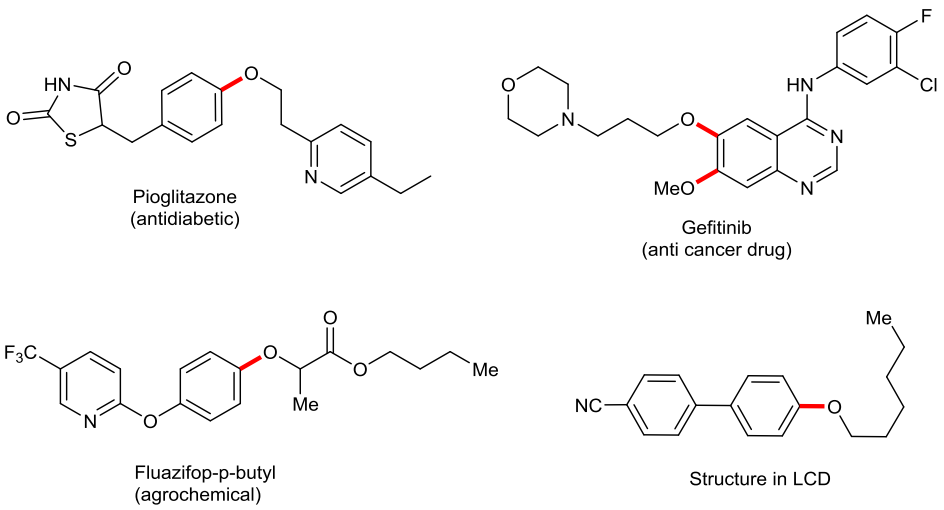
This work demonstrates metal-free synthesis of alkyl-aryl ethers by using unsymmetrical diaryliodonium salts and aliphatic alcohols through a base-mediated coupling reaction (Scheme 2.1). This method shows broad substrate scope with respect to both of the coupling partners to produce industrially useful alkyl-aryl ethers in moderate to excellent yields. The reaction is operationally simple, proceeds at low temperature, and is atom-economical. Sustainability and synthetic utility of this reaction is demonstrated by the use of unsymmetrical aryl(mesityl)iodonium salts as the arylating agents.

[30] S. K. Sundalam, D. R. Stuart, *J. Org. Chem*. **2015**, *80*, 6456 – 6466.

2.1 Significance of Alky-Aryl Ethers

Alkyl-aryl ethers are important building blocks in pharmaceuticals, agrochemicals, and high-tech devices such as liquid crystal displays (Figure 2.1).[31] Three of the five top-selling drugs in 2012 contained alkyl-aryl ether linkages in their structures.[32] Among all of the heteroatoms, nitrogen constitutes the most abundant heteroatom, present in more than half of the drugs known so far. Oxygen, although not as abundant as nitrogen, is the next most abundant heteroatom in industrially important molecules.[33] Aside from pharmaceuticals, a myriad of naturally occurring compounds contain alkyl-aryl ether linkages, for example, alkaloids and lignins.[31] Many of these natural compounds have a vital role in biological processes.

Figure 2.1: Industrially important compounds with alkyl-aryl ether linkages



[31] a) J. J. Li, D. S. Johnson, D. R. Sliskovic, B. D. Roth, Contemporary Drug Synthesis, *Wiley*, **2004**; (b) J. J. Li and D. S. Johnson, Modern Drug Synthesis, Wiley, **2010**; (c) H.-G. Elias, An Introduction to Polymer Science, *Wiley-VCH*, 1997; (d) F.Muller, Agrochemicals, Wiley-VCH, **1999.** e) Puterova, Zita et al, *Tetrahedron*, **2012,** *68*, 8172-8180

[32] http://www.pharmacytimes.com/publications/issue/2013/July2013/Top-200-Drugs-of-2012

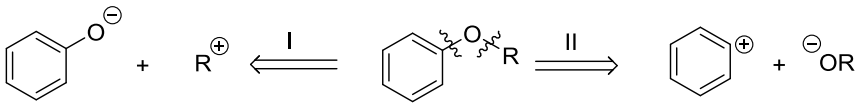
[33] Carey, J.S., Laffan, D., Thomson, C., Williams, M.T. *Org. Biomol. Chem*. **2006**, *4*, 2337 – 2347.

Given the abundance of the alkyl-aryl ether motif in man-made and naturally occurring molecules, the development of synthetic methods to form these bonds is of crucial importance. Despite their prevalence, the direct synthesis of these linkages by C_{aryl}-O bond formation remains relatively underdeveloped. Although, various methodologies have recently emerged, novel synthetic protocols are still of interest for this particular transformation.

2.2 Literature Precedent for the Synthesis of Alkyl-Aryl Ethers

The retro synthesis shown in Scheme 2.2 describes two conceptual paths that may be taken towards the formation of the alkyl-aryl ether linkage. The two paths differ by the nature of the nucleophiles and electrophiles used in the forward synthesis. I have specifically focused on the development of the type II pathway in this work.

Scheme 2.2: Retro synthetic disconnections towards alkyl-aryl ether synthesis



2.2.1 Type I: Formation of C_{alkyl}-O_{aryl} ether bond

In this type of bond formation reaction, phenolic nucleophiles and alkyl electrophiles react to form alkyl-aryl ether bonds. Traditional syntheses of alkyl-aryl ethers using this approach are the classic Williamson ether synthesis,[34] the Mitsunobu reaction,[35] and the

[34] Juršić, B. *Tetrahedron* **1988**, *44*, 6677−6680.
[35] Gentles, R. G.; Wodka, D.; Park, D. C.; Vasudevan, A. J. *Comb. Chem*. **2002**, *4*, 442−456.

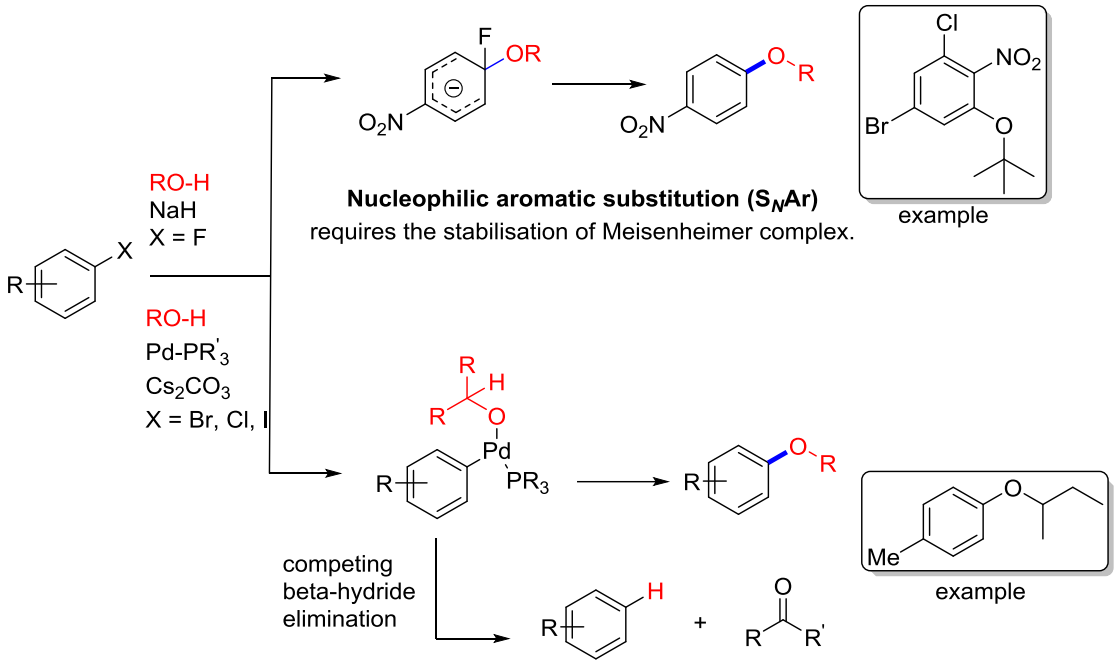
condensation of phenols and alcohols using Bronsted or Lewis acids.[36] In the case of the Williamson ether synthesis, an example of phenol alkylation proceeds by the formation of a phenolic nucleophile in the presence of base, followed by SN_2 attack on the electrophilic alkylating agents, such as alkyl halides. This reaction suffers from the drawbacks of using toxic alkylating agents and the substrate scope is limited. The other reaction of this type is the Mitsunobu reaction, which replaces the use of toxic alkylation agents by alcohols. In this reaction, a phenolic nucleophile is formed, followed by nucleophilic substitution on the alcohol. However, this reaction suffers from the drawbacks of using toxic phosphine reagents and explosive reagents such as DEAD. The substrate scope of these reactions is limited due to all the aforementioned drawbacks.

2.2.2 Type II: Formation of C_{aryl}-O_{alkyl} ether bond

In the second scenario, the aromatic group is the electrophile and is attacked by an alkoxide nucleophile. A good example of this type of reaction is the traditional nucleophilic aromatic substitution (S_NAr) of aryl halide with metal alkoxide,[37] (Scheme 2.3, top) which is a direct method for the formation of alkyl-aryl ethers. However, the aryl substrate scope is limited due to the formation of an anionic intermediate Meisenheimer complex, which is only stabilized by strong electron withdrawing substituents (NO_2, CN, etc.).

[36] Simons, J. H.; Passino, H. J. *J. Am. Chem. Soc.* **1940**, *62*, 1624
[37] March, J. Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 4th ed.; John Wiley & Sons: *New York*, **1992**; 501−569, 641−676.

Scheme 2.3: Protocols towards the synthesis of C_{aryl}-O_{alkyl} ethers



Another method to form this type of alkyl-aryl ether bond is via transition metal-catalysis (Scheme 2.3, bottom). Transition metal-catalyzed coupling chemistry is currently the "state-of-the-art" and a very powerful protocol for the carbon-carbon and carbon-heteroatom bond formation. Despite the success that has been achieved with this type of reaction, there is still further improvement needed considering sustainability and environmental issues. One of the drawbacks of the metal-catalyzed reaction is the use of expensive and designer catalyst-ligand combinations and heavy metal toxicity. The common aryl substrates used for this chemistry are aryl halides or pseudo-halides, which are replaced by an oxygen nucleophile during the reaction. Palladium, copper, and nickel are the most commonly used metals in these metal-catalyzed coupling reactions. A

common challenge for metal-catalyzed reactions is the competing β-hydride elimination from the palladium alkoxide intermediate and reductive elimination of the C-H bond, which results in an oxidized alcohol and a reduced arene, ultimately lowering the yield of the desired product.

Consequently, there is a need for a new approach that is operationally simple and avoids the limitations of the traditional approaches and eliminates the use of transition metals to avoid further purification of the end product. A method which will provide a broad substrate scope both with reference to the aryl group and alcohols group would advance this particular field of forming alkyl-aryl ether bonds.

2.3 Literature Precedent from Diaryliodonium Salts

Using unsymmetrical diaryliodonium salts for the synthesis of alkyl-aryl ethers was first discovered by Beringer in 1953 by refluxing diaryliodonium salt and sodium methoxide in methanol (Scheme 2.4, 1st reaction). In this work, two diaryliodonium salts were presented, and it was demonstrated that the nucleophile favored the attack on the electron deficient aryl group when unsymmetrical diaryliodonium salts were used.[38] After 20 years, McEwen and co-workers applied this approach to ethoxide and 2-propoxide, which were generated from their respective alcohols. They also identified a radical pathway that formed alcohol oxidation products, which they mitigated by adding a radical trap (DPE) and using non

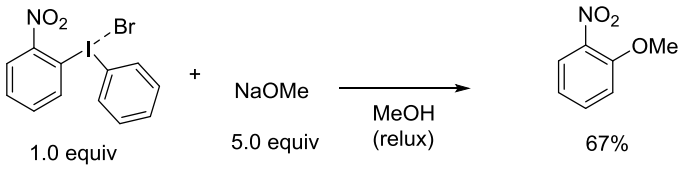
[38] Beringer, F. M.; Brierley, A.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2708−2712.

polar solvents (Scheme 2.4, second reaction).[39] In 2006, Fujita and Okuyama demonstrated that solvolysis of diaryliodonium salts takes place in alcohols at higher temperatures (130^{o}C) even in the absence of a base to generate alkyl-aryl ethers (Scheme 2.4, third reaction).[40] Olofsson's group, in 2013, provided a milder and synthetically useful reaction to form alkyl-aryl ethers. Alcohols, including allylic, benzylic, and also phenolic groups were coupled to diaryliodonium salts in aqueous medium using hydroxide base.[41] In 2014, a modified method was developed from the same group with aliphatic alcohol coupling partners as they were not tolerated in the previous work (Scheme 2.4, fourth reaction).[42] In the latter work, sodium *t*-butoxide was used to deprotonate the aliphatic alcohol to form an alkoxide in presence of toluene as the solvent. At last in 2016 (Scheme 2.4, 5th reaction), after our work was published, Oloffsson's group showed a similar reaction using tertiary alcohols on sterically hindered diaryliodonium salts where the *ortho* positions were blocked or replaced by other groups instead of hydrogens. In all cases, addition of the nucleophile to the most electron-deficient aryl group is observed, which is consistent with other reactions of unsymmetrical diaryliodonium salts.

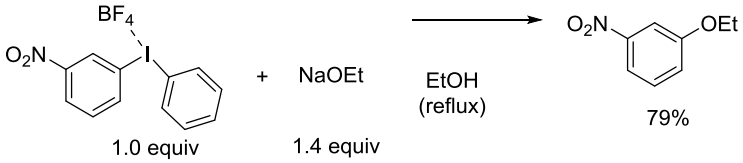
[39] McEwen, W. E.; Lubinkowski, J. J.; Knapczyk, J. W. *Tetrahedron Lett.* **1972**, *32*, 3301−3304. b) Lubinkowski, J. J.; Knapczyk, J. W.; Calderon, J. L.; Petit, L. R.; McEwen, W. E. *J. Org. Chem*. **1975**, *40*, 3010−3015.
[40] Fujita, M.; Mishima, E.; Okuyama, T. *J. Phys. Org. Chem.* **2007**, *20*, 241−244.
[41] Lindstedt, E.; Ghosh, R.; Olofsson, B. *Org. Lett.* **2013**, *15*, 6070−6073.
[42] Ghosh, R.; Lindstedt, E.; Jalalian, N.; Olofsson, B *ChemistryOpen*, **2014**, *3*, 54−57.

Scheme 2.4: Literature precedent for the syntheis alkyl-aryl ethers from diaryliodonium salts

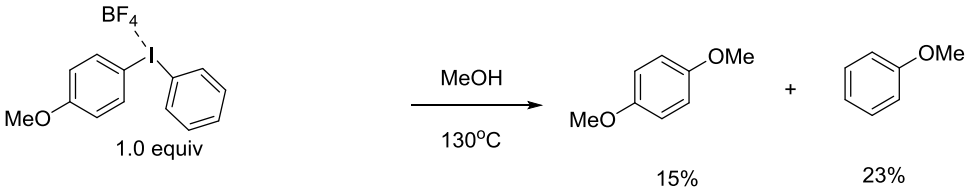
Beringer 1953



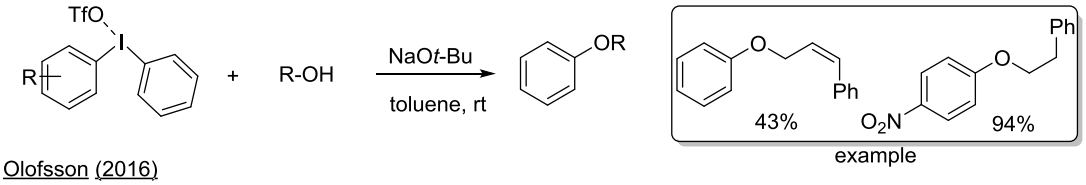
McEwen (1975, 1980)



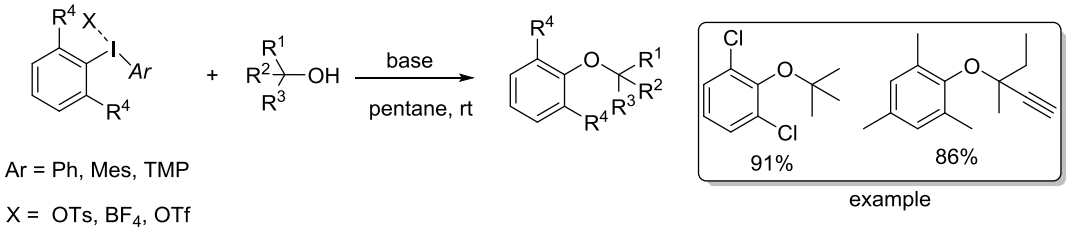
Fujita and Okuyama (2006)



Olofsson (2014)



Olofsson (2016)



Ar = Ph, Mes, TMP

X = OTs, BF_4, OTf

2.4 Reaction Discovery

The initial discovery of alkyl-aryl ether bond formation in our lab was observed when an unsymmetrical diaryliodonium salt was reacted with $CF_3B(OMe)_3$ in an attempt to arylate the trifluoromethyl group in the presence of copper iodide and bipyridyl ligand. To our surprise, instead of a C_{aryl}-CF_3 bond, we witnessed the formation of a C_{aryl}-O ether bond. Although it was not the product we desired to form, we were intrigued by this transformation. We sought to develop this transformation because of the prevalence of alkyl-aryl ether linkages mentioned in the introduction section of this chapter.

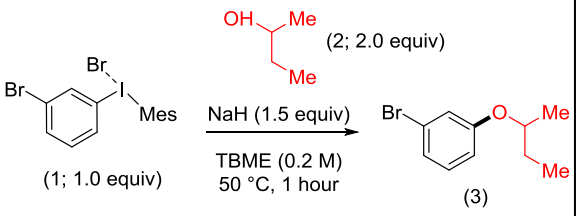
With a few modifications to the reaction conditions, the preliminary results were determined to be profitable using with both symmetrical and unsymmetrical diaryliodonium salts to form alkyl-aryl ethers; in these conditionsan alkoxide which was generated *insitu* using a strong base. On the basis of these promising preliminary results, we sought to further develop the base-mediated O-arylation chemistry to be extensible towards a range of aryl electrophiles and also to enable a broad scope with respect to the choice of alcohols.

2.5 Reaction Development

To optimize the reaction, 3-bromophenyl derived iodonium salt was selected since the 3-bromo group is only mildly electron withdrawing. 2-butanol was chosen as the alcohol group, since the secondary alcohol is challenging in the metal-catalyzed reactions due to

the formation of alcohol oxidation product. This combination successfully established an overall advance in this transformation. After running a series of reactions, optimized conditions provided a yield of 81% and complete consumption of starting material was observed in the crude ^{1}H NMR spectrum vs 1,3,5-trimethoxybenze as internal standard (Table 2.1, entry 1). While optimizing the reaction parameters, interesting observations were made that merit discussion. First, to eliminate the possibility of S$_N$Ar reaction, the precursor iodide, 3-bromoiodobenze, was used instead of diaryliodonium salt (Table 2.1, entry 2). Unsurprisingly, there was no reaction, suggesting that the reaction is not going through S$_N$Ar. A series of auxiliary groups were tested including phenyl (1-Ph), 2-thienyl (1-Th), trimethoxybenzene (1-TMB), and mesityl (Mes) auxiliary, which provided the highest yield (see entry 3-5).

Table 2.1: Optimization



Entry	Deviation from "Standard Conditions"[a]	Yield of 3[b]
1	none	81%
	Structure of 1	
2	3-bromoiodobenzene instead of 1	-[c]
3	1-Ph instead of 1	27%
4	1-Th instead of 1	51%
5	1-TMP instead of 1	68%
6	BF_4 instead of Br on iodane	76%
7	OTf instead of Br on iodane	81%
	Other Bases	
8	Na_2CO_3 instead of NaH	-[c]
9	NaO*t*-Bu instead of NaH	70%
10	NaHMDS instead of NaH	22%
	Stoichiometry of 2 and base	
11	1 equiv of OH instead of 2	71%
12	1 equiv instead of 1.5 equiv of NaH	64%
	Reaction solvent	
13	Toluene instead of TBME	72%
14	DCE instead of TBME	29%
15	DMF instead of TBME	-[c]
	Reaction temperature	
16	30 °C instead of 50 °C	76%
17	70 °C instead of 50 °C	70%

[a] Conditions: 1 (0.1 mmol, 0.2 M, 1 equiv), 2 (0.2 mmol, 2 equiv.), NaH (1.5 mmol, 1.5 equiv.), TBME (0.5 mL), 50 °C, 1 hour (unless otherwise stated above). [b] ^{1}H NMR yield vs 1,3,5-trimethoxybenzene as internal standard. [c] No detectable product in crude ^{1}HNMR spectrum.

This auxiliary not only gave the highest yields but also enabled easy separation of the product by column chromatography.

Additionally, installing mesityl auxiliary presented an advantage over the other auxiliary groups due to its commercial availability as simple arene mesitylene, iodomesitylene, and iodomesitylene diacetate. This mes auxiliary group enabled the corresponding unsymmetrical diaryliodonium salts synthesis with the use of simple aryl iodides, simple arenes, and arylboronic acids (Section 1.4). Counter-anions tetrafluroborate (BF_4) and triflate (OTf) had little to no effect on the yield (Table 2.1, entries 6 and 7). Therefore, bromide (Br) was chosen as the counter ion because it is relatively cheaper than the other two and are easy to triturate, and we observed that they are more bench stable compared to OTf and BF_4. Other inorganic bases were tested but sodium hydride provided the highest yields (Table 2.1, see entries 8-10). Interestingly, amine bases showed little to no reactivity. Two equivalents of alcohol and 1.5 equivalents of sodium hydride, with respect to iodonium salt, provided the best yield (see entry 1 vs 11 and 12 respecively). The solvent had a significant effect on the yield of the reaction. Toluene was the next best solvent (72%) to TBME, 1,2-dichloroethane gave low yield (29%), and a polar protic solvent (DMF) provided no detectible product in the crude ^{1}H NMR spectrum (Table 2.1, see entries 13-15). Lower and higher temperatures yielded less product vs 50 ^{o}C (Table 2.1, see entries 16 and 17). Finally, the concentration of the reaction was tested, and 0.2 M using tert-butyl methyl ether (TBME) solvent gave the best yield; the reaction was complete in one hour.

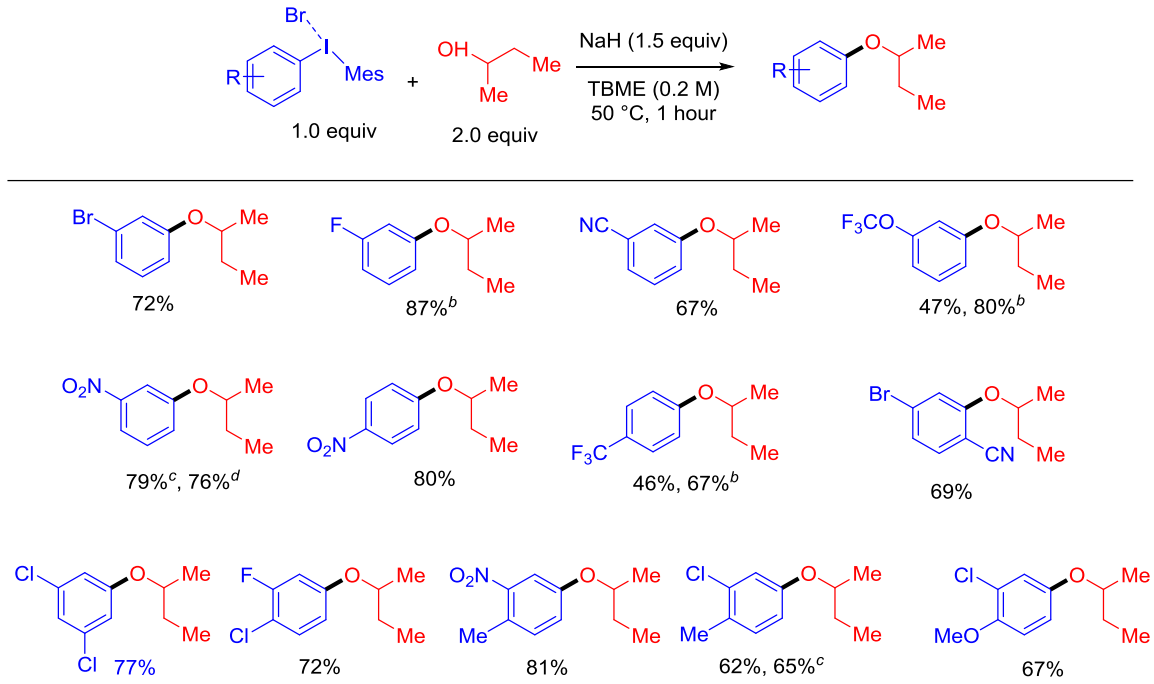
2.6 Scope of the Reaction

To demonstrate the breadth of scope of this transformation, several different unsymmetrical diaryliodonium salts and various alcohols were employed, which showed varying impacts of steric and electronics in this reaction.

2.6.1 Aryl group substrate scope

The reaction scope with respect to the selection of aryl group showed that all possible substitutions *(i.e., ortho, meta, and para)* are tolerated. A broad range of functional groups are acceptable, such as halides, nitrile, carbonyl, trifluoromethoxy, nitro, trifluoromethyl, methoxy, and methyl on the aryl electrophile. In S_NAr chemistry, only *ortho* and *para* substituted aryl groups that are highly electron deficient are tolerated, which distinguishes our work since various more substitution patterns are tolerated as are less electron deficient aryl groups showed reactivity. To the best of our knowledge, no prior diaryliodonium salt chemistry had shown that poly-substituted aryl groups react with aliphatic alcohol to provide good yields. These multi-substituted aryl groups will facilitate further functionalization of the product. Electron rich diaryliodonium salts suffered in this reaction. However, in these cases, where electron rich groups were involved, the presence of an additional electron deficient functional group on the ring was shown to overcome the challenge to produce good reactivity. In total, 13 different aryl groups were shown to be reactive to provide moderate to excellent yields (Table 2.2).

Table 2.2: Aryl scope for the synthesis of alkyl-aryl ethers



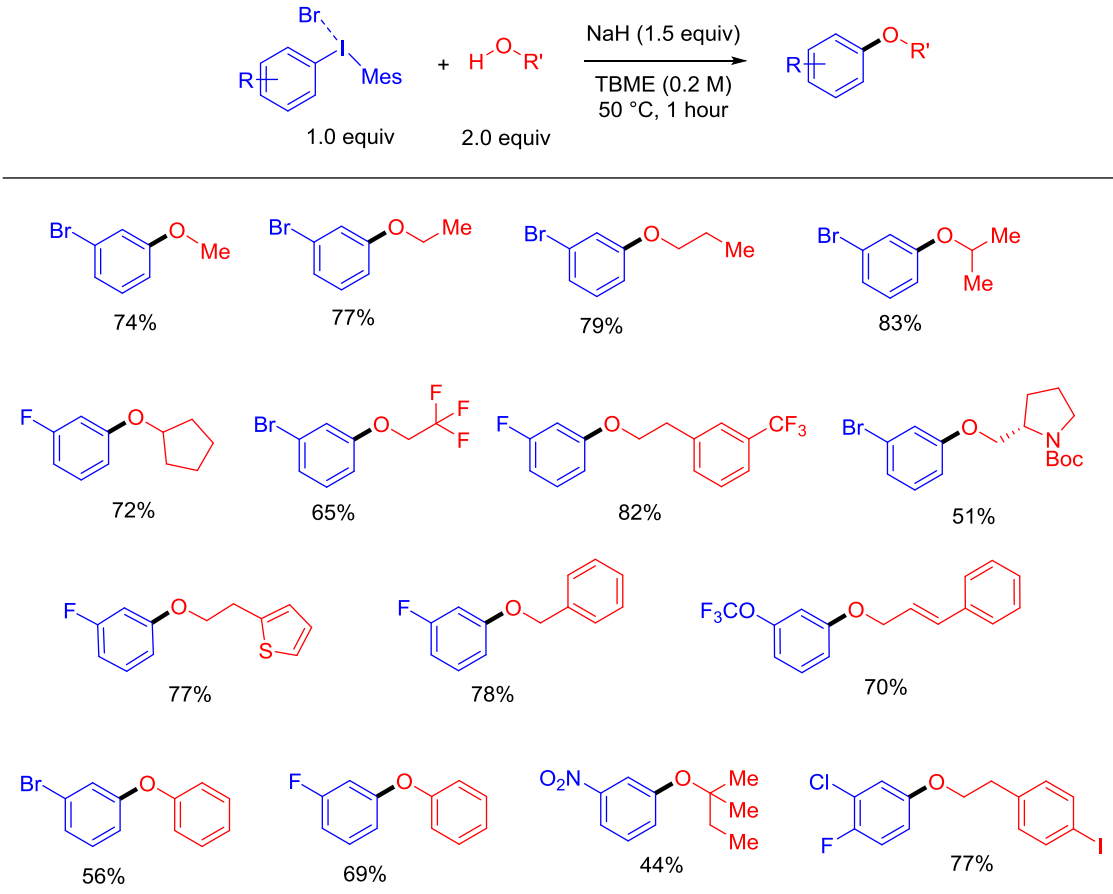
[a]Conditions: 1 (0.5 mmol, 0.2 M, 1 equiv), 2 (1 mmol, 2 equiv), NaH (0.75 mmol, 1.5 equiv), TBME (2.5 mL), 50 °C, 1 hour. [b]Yield determined from the crude ^{1}H NMR spectrum against 1,3,5-trimethoxybenzene as an internal standard (0.1 mmol scale reaction). [c]Reaction scale: 1 mmol of 1. [d]Reaction scale: 5 mmol of 1.

2.6.2 Alcohol group substrate scope

Primary, secondary, and tertiary aliphatic alcohols were reacted with unsymmetrical diaryliodonium salts to form alkyl-aryl ethers in moderate to good yields (Table 2.3). In addition, benzylic, allylic, and phenolic alcohols were well tolerated in the reaction. In the case of the benzyl alcohol derived product, only 3% oxidation product (benzaldehyde) was observed in the crude ^{1}H NMR spectrum. In comparison to the metal-catalyzed and other reactions, oxidation product formation is significantly suppressed representing an advantage of this reaction. Thus, a variety of complex aromatic groups bearing alcohols

proceeded in this reaction with ease. This scope also shows the compatibility of various fluorinated reagents which are desirable in pharmaceuticals and agrochemicals. Fluoride is usually a leaving group in S_NAr reaction. Heteroatom containing alcohols such as thiophene and pyridine were reactive as well.

Table 2.3: Alcohol scope for the synthesis of alkyl-aryl ethers

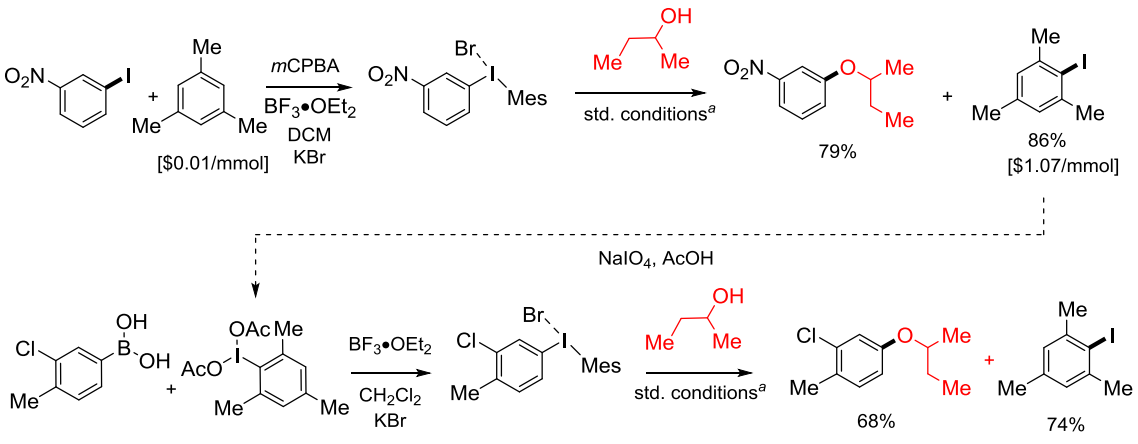


[a]Conditions: 1 (0.5 mmol, 0.2 M, 1 equiv), 2 (1 mmol, 2 equiv), NaH (0.75 mmol, 1.5 equiv), TBME (2.5 mL), 50 °C, 1 hour (yields are reported for isolated materials after chromatography as an average of two experiments).

2.7 Sustainability of the Reaction

To demonstrate the sustainability of this reaction using unsymmetrical diaryliodonium salts, 3-nitrophenyl(mesityl)bromide was prepared by a one-pot method using 3-iodonitrobenzene and mesitylene (Scheme 2.5, top). Further reaction of the unsymmetrical diaryliodonium salt under our standard conditions yielded alkyl-aryl ether product and mesityl iodide as the byproduct in high yield. The formed mesityl iodide gains a 100 fold increase in value ($1.07/mmol) vs. its precursor, mesitylene ($0.01/mmol). Mesityl iodide can be readily converted to hypervalent diacetoxymesityliodide, which can be used as the starting material in a complementary synthesis to form unsymmetrical diaryliodonium salt using arylboronic acids. (Scheme 2.5, bottom). Recovery and reuse of the mesityl group highlights that the reaction is not only metal-free but also shows that the byproduct can be used for further transformations in a sustainable manner.

Scheme 2.5: Sustainability of the reaction; recovery and reuse of the auxiliary group

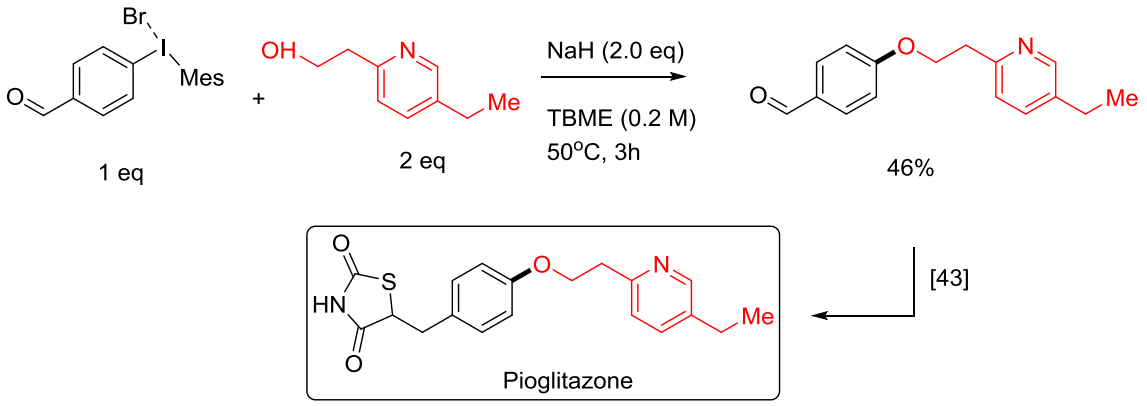


Conditions: 1 (0.5 mmol, 0.2 M, 1 equiv), 2 (1 mmol, 2 equiv), NaH (0.75 mmol, 1.5 equiv), TBME (2.5 mL), 50 °C, 1 hour.

2.8 Formal synthesis of Pioglitazone

To further emphasize the efficacy of this protocol, the active pharmaceutical ingredient (API) of the antidiabetic drug Actos was synthesized. The formal synthesis of pioglitazone was achieved in two steps from commercial materials (Scheme 2.6). Step one was the synthesis of diaryliodonium salt from the 4-iodobenzaldehyde and followed by the coupling reaction with the alcohol. Further, the isolated aldehyde product is converted to Actos in two steps.[43] This synthesis demonstrates that an aldehyde and pyridine functional groups are tolerated in our conditions.

Scheme 2.6: Formal synthesis of Pioglitazone



[43] Bhanja, C.; Jena, S. J. *Chem. Pharm.* Res. **2012**, *9*, 4323−4333.

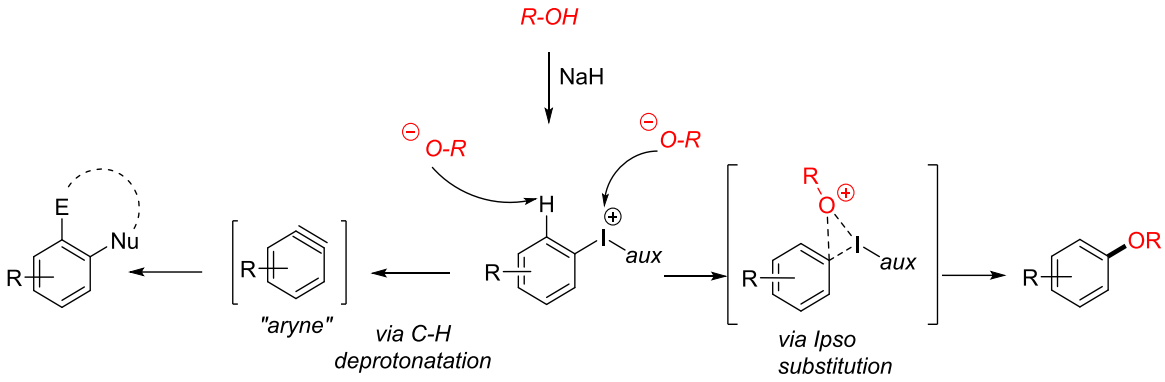
Chapter 2: **Part II**

Base-Mediated O-Arylation of Electron Rich Unsymmetrical Diaryliodonium Salts with Aliphatic Alcohols

A limitation of the previous work was that it does not proceed with unsymmetrical diaryliodonium salts containing electron rich aryl groups, leading to poor yields. We have observed decomposition of the electron rich diaryliodonium salts under these conditions. After discovering that the unsymmetrical diaryliodonium salts could potentially proceeds through the aryne pathway in the presence of strong bases, we suspected that the poor reactivity could be due to the competing C-H deprotonation of the salts. Overcoming this limitation would result in a method that works with all types of unsymmetrical diaryliodonium salts and alcohols and will represent an advancement in the overall utility of this transformation.

2.9 Proposed Reaction Mechanisms Occurring in Presence of a Strong Base with Unsymmetrical Diaryliodonium Salts

Scheme 2.7: Alkoxide nucleophiles trigger two different pathways with diaryliodonium salts



2.10 Reaction Development

Preliminary experiments to suppress the formation of arynes and to favor the *ipso* substitution was very challenging using electron rich unsymmetrical diaryliodonium salts. We have witnessed that in electron poor unsymmetrical diaryliodonium salts ipso substitution overrides C-H deprotonation. So we suspected that this inherent reactivity could be related to the electronics of the aryl group which could be indirectly affecting the acidity of the *ortho* proton and thus resulting in competing pathways for electron rich salts. In our aryne methodology, we have demonstrated that using sterically bulky bases selective C-H deprotonation can be achieved even with electron rich unsymmetrical diaryliodonium salts (Chapter 3). After a series of preliminary experiments with the electron rich unsymmetrical salt 4-tolyl(TMP)bromide and *n*-butanol, it was determined that the auxiliary group has the most significant effect in determining the mechanism of the reaction.

2.11 Auxiliary Screen

The mesityl group which was the best auxiliary group in both of the previous projects was selected to learn about this reaction. An electron rich unsymmetrical diaryliodonium salt 4-biphenyl(mesityl)iodonium salt was chosen as the optimal substrate and *n*-butanol as the alcohol. First, to assess and quantify the generation of aryne, furan was added to the reaction an aryne trap after the deprotonation step. The reaction resulted in a low yield of 23% ipso substituted product (25% without adding aryne trap) and 5% of aryne cyclo adduct (Table 2.4, entry 1). It was unclear if the reaction was undergoing decomposition or if there is a selectivity issue due to the similarity in the electronics of both the aryl groups of the salt.

So, more electron rich auxiliaries, such as anisole and thienyl, were synthesized and subjected to the reaction conditions. The thienyl group resulted in 33% yield, whereas the anisole auxiliary resulted in 52% yield (Table 2.4, entries 2 and 3). It was indicated at this point that increasing the electronics of the auxiliary has a positive effect on the percent yield. Therefore, a much more electronically rich trimethoxyphenyl group (TMP) was installed as the auxiliary group and was tested in the reaction. There was a significant increase in the percent yield of the ipso substituted product (~80%). After a little further optimization, we attained a yield of 92% (82% isolated) (Table 2.4).

Our groups have published an efficient one-pot method to synthesize aryl(TMP)iodonium salts using aryl iodides[44] which were cumbersome to prepare using previously developed methods.

2.12 Parameters Affecting the Reaction Yield

This reaction is very robust. Synthetically useful yields were obtained after varying multiple parameters. There was no parameters except the auxiliary that resulting in complete decomposition or low yield of the product.

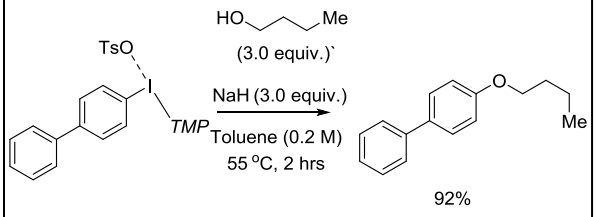
To start off, counter-anions Br, OTf, BF_4 and TFA in place of OTs had little to no effect on the percent yield (Table 2.4, entries 4-7). OTs was the best yielding counter-anion, thus the synthesis route developed by our group yields iodonium tosylate and does not require further steps to convert the counter anions. TFA was the next best counter-anion (88%). It is important to note that some electron rich diaryliodonium salts were made by a modified method where TFA was used as the acid instead of TsOH.[45]

Bulky bases such as NaO*t*-Bu and LiHMDS (Table 2.4, entries 8-9) provided synthetically useful yields. However it was interesting to see that weak inorganic base Cs_2CO_3 performed exceptionally well in this setup to furnish a yield of 82% (Table 2.4, entry 10). Solvent screening revealed that several types of solvents could be employed in this reaction and achieve synthetically useful yields; however, toluene gave the best yield (Table 2.4, entries

[44] T. L. Seidl, S. K. Sundalam, B. McCullough, D. R. Stuart, *J. Org. Chem*. **2016**, *81*, 1998 – 2009
[45] V. Carreras, A. H. Sandtorv, and D. R. Stuart *J. Org. Chem.*, **2017**, *82* 1279–1284

11-14). Temperature (Table 2.4, entries 15-16) had an insignificant effect towards the reaction, room temperature furnished a lower yield than the optimal and high temperature was very close to the standard yield. Lastly, furan was added as an aryne trap to infer how much aryne was forming in the reaction. Surprisingly, the yield of the reaction was substantially lower compared to without addition of aryne trap and there was only 4% of the aryne adduct formed. This could be due to the competition of two pathways occurring at the same time leading to a lower yield of the products. With optimal conditions at our disposal, we continued to the next step of the project: scope.

Table 2.4: Reaction development



92%

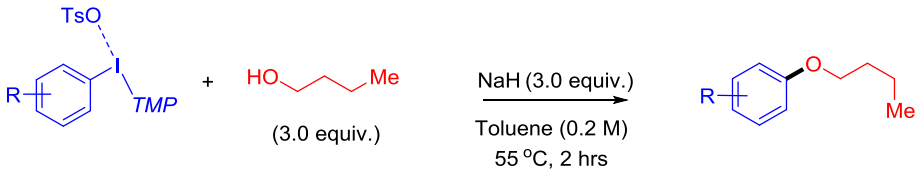
Entry	deviation from std conditions	%Yield of product[a]
	"auxiliary"	
1.	Mes instead of TMB	25
2.	Anisole instead of TMB	52
3.	Thiophene instead of TMB	33
	"Counter anion"	
4.	Br instead of OTs	88
5.	OTf instead of OTs	81
6.	TFA instead of OTs	85
7.	BF_4 instead of OTs	84
	"Bases"	
8.	NaO*t*-Bu instead of NaH	60
9.	LiHMDS instead of NaH	75
10.	Cs_2CO_3 instead of NaH	82
	"Solvents"	
11.	TBME instead of Toluene	70
12.	1,4-dioxane instead of Toluene	74
13.	DCE instead of Toluene	61
14.	THF instead of Toluene	69
	"Temperature"	
15.	Room temp instead of 55° C	78
16.	85 °C instead of 55° C	85
17.	Furan added (5.5 equiv)	73, 4[b]

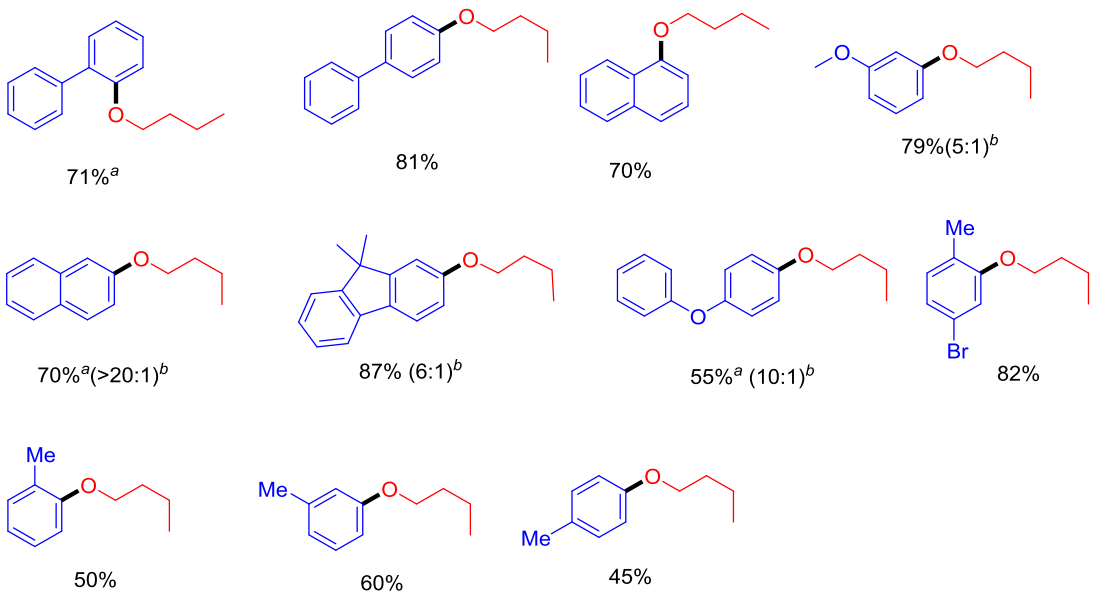
[a] ^{1}H NMR yield based on the crude spectrum vs 2,4-dichlorobenzaldehyde as the internal std.
[b] Cyclo adduct product formed with furan.

2.14 Scope of Electron Rich Unsymmetrical Diaryliodonium Salts

Several different electron rich unsymmetrical diaryliodonium salts were tested and have been successfully shown to be reactive in the coupling reaction with *n*-butanol to give alkyl-aryl ethers in moderate to good yields (Table 2.5). 4-biphenyl as well as 2-biphenyl(TMP) iodonium salts furnished good yields of 81% and 71%, respectively. 2-napthyl and 3-napthyl groups both gave 70% yields; however, very minute amounts of regioisomers were observed in the latter (20:1:1). Bulky electron rich substrates, such as 9,9-dimethyl-9H-fluoren-2-yl and diphenyl ether, provided synthetically useful yields of 85% and 55% respectively. In both cases, regioisomer mixtures of 6:1 and 10:1 were observed. Other electron rich aryl groups including *ortho, meta and, para* tolyl and *meta* anisyl iodonium salts were shown to be reactive with moderate to good yields alkyl-aryl ethers ranging from 45% to 87%.

Table 2.5: Aryl scope for the synthesis of alkyl-aryl ethers using electron rich unsymmetrical diaryliodonium salts





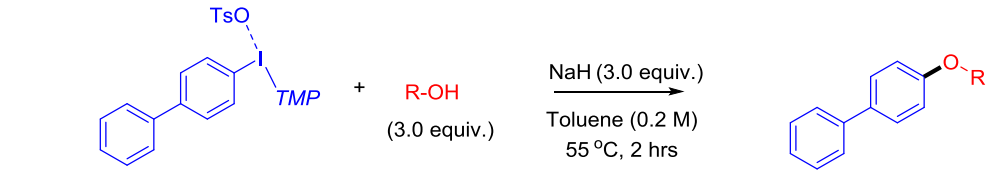
[a] TFA is used as the counter anion. [b] mixture of regioisomers

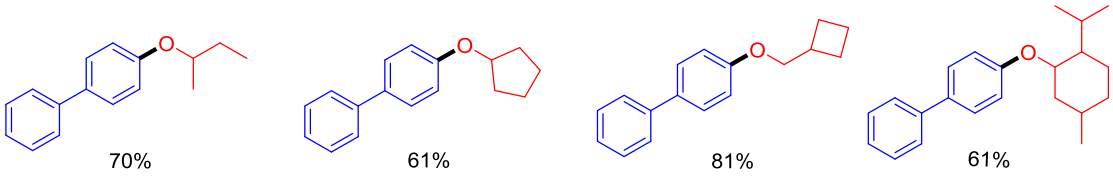
2.15 Scope of Alcohols

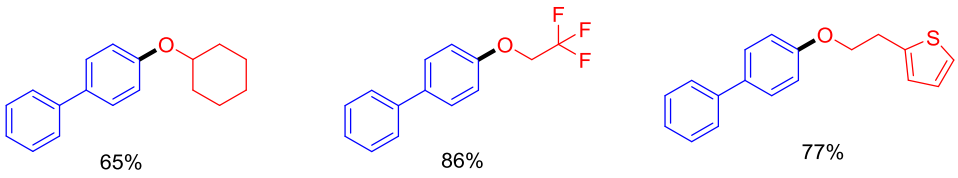
Alcohol scope was investigated, using the unsymmetrical diaryliodonium 4-biphenyl(TMP)iodonium tosylate, to show compatibility with a wide variety of alcohols (Table 2.6). Primary and secondary aliphatic alcohols were well-tolerated producing good yields ranging 61% to 89%. Interestingly, sterically hindered menthol produced similar yield (61%) compared to non-hindered cyclohexanol (61%). The fluorinated alcohol, 2,2,2-trifluroethanol also furnished excellent yield (86%). Additionally, alcohols bearing

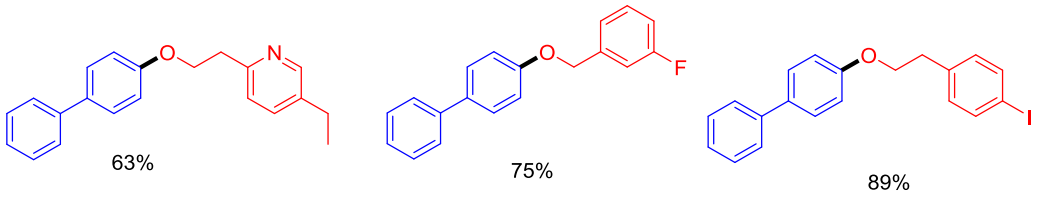
aromatic groups, such as thiophene and pyridine, were well-received. Finally halogenated aromatic alcohols, which allowed further functionalization of the product, gave excellent yields.

Table 2.6: Alcohol scope for the synthesis of alkyl-aryl ethers using electron rich unsymmetrical diaryliodonium salts









2.16 Conclusion

In conclusion, a mild and convenient method to synthesize industrially crucial molecules containing alkyl-aryl ether bonds was developed. A broad range of unsymmetrical diaryliodonium salts were coupled with a range of aliphatic alcohols including primary, secondary, and tertiary; moderate to excellent yields were achieved in all cases. Additionally, allylic, phenolic, and aromatic alcohols were also shown to provide good yields under this protocol. To highlight this method, sustainability of the reaction was demonstrated using unsymmetrical aryl(mesityl)iodonium salt by recovery and reuse of the auxiliary group. Finally, formal synthesis of Pioglitazone (API of Actos) was shown, which demonstrates that this chemistry can be applied to pharmaceuticals industries with ease. A limitation of poor reactivity of electron rich unsymmetrical diaryliodonium salts was overcome by modifying the reaction and using 2,4,6-trimethoxyphenyl (TMP) as the auxiliary group.

Chapter 3

Discovery and Development of Arylation Reactions Through "Arynes" Generated from Unsymmetrical Aryl(mesityl)iodonium Salts[46]

3.1 Importance of Arynes as the Intermediates in Organic Synthesis.

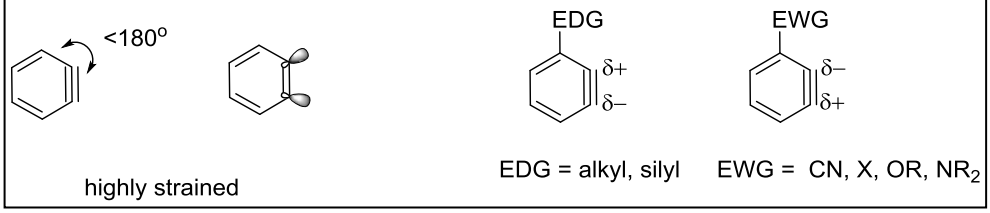
Arynes are highly reactive intermediates, which offer rapid functionalization of aromatic rings by forming multiple carbon-carbon and carbon-heteroatom bonds. The high reactivity of arynes is due to the presence of a strained triple bond within a 6-membered ring system, resulting in distorted bond angles of the alkyne. Classically, arynes are generated by *ortho* deprotonation of an aromatic ring with a halide leaving group. In the early stages after the discovery of arynes, their synthetic utility was limited due to the harsh conditions required to generate these intermediates. However, milder reaction conditions have been developed over time and have led to their use in diverse reaction schemes, including natural product total synthesis.

[46] Sundalam, S. K.; Nilova, A.; Seidl, T. L.; Stuart, D. R. *Angew. Chem. Int. Ed*. 2016, 55, 8431 - 8434

3.2 Structure and Regio-selectivity of Arynes.

The triple bond is highly strained within the ring system and therefore there is a substantial deviation from the preferred alkyne bond angle of 180° (Figure 3.1, left). This deviation results in a low energy LUMO and leads to rapid reactions with nucleophiles. This highly strained intermediate is polarized by electron donating and withdrawing effects from the neighboring groups. For example, the *ortho* group next to the triple bond exercises more influence than one situated on the *meta* position.

Figure 3.1: Structure and regio-selectivity in arynes



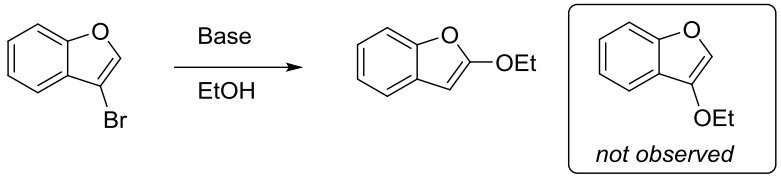
It is noteworthy that the reactive π-orbitals are situated in the plane of the ring and not in the π-orbitals of the aromatic system, which makes them insusceptible to the resonance effects of the substituents on the ring. However, the polarization occurs due to inductive effects via σ-bonds. Hence heteroatoms bearing lone pairs such as oxygen and nitrogen behave as electron withdrawing groups due to inductive effects based on electronegativity rather than resonance effects (Figure 3.1, right). Interestingly, the experiments done by Biehl and coworkers in 1969 revealed that the inductively donating and withdrawing groups make benzyne more reactive than the unsubstituted molecule.[47]

[47] Biehl, E. R.; Nieh, E.; Hsu, K. C. J. Org. Chem. **1969**, *34*, 3595–3599.

3.3 Initial Discovery of Arynes

In 1902, Stoermer and Kahlert[48] observed the formation of 2-ethoxybenzofuran as product of the reaction of 3-bromobenzofuran with KOH in the presence of ethanol (Scheme 3.1). They were not able to explain the reason for this type of reactivity at the time, however an aryne intermediate mechanism was proposed later to explain the uncommon regiochemistry of this reaction.[49]

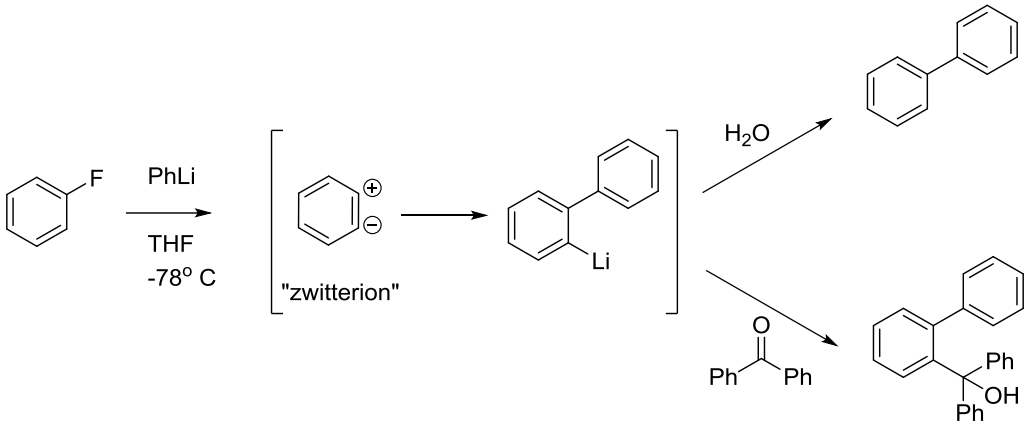
Scheme 3.1: Reaction developed by Stoermer and Kahlert in 1902.



The benzyne hypothesis was made by Wittig in 1940 and 1942[50] based on the reaction of pheyllithium and flourobenzene and work up with water or benzophenone. In the former, biphenyl was isolated; in the latter, 2-biphenyldiphenylcarbinol was observed (Scheme 3.2). This led to the assumption that nucleophilic attack on the electrophile in the final step (water or benzophenone) via lithiated biphenyl yielded the observed products. Although Wittig didn't propose the shape of the cyclic alkyne, due to the overpowering ring strain, he proposed that regio-specific reactions can occur through a zwitterionic species. Later on, his studies were proven incorrect, but his contributions significantly broadened the knowledge of the subject and led to the discovery of benzyne.

[48] R. Stoermer, B. Khalert, Ber. Dtsch. Chem. Ges **1902**, *35*.
[49] W. E. Bachmann, H. T. Clarke, J. Am. Chem. Soc. **1927**, *49*, 2089.
[50] Wittig, G.; Pieper, G.; Fuhrmann, G. *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 1193–1197. (b) Wittig, G.; Fuhrmann, G. *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 1197–1218. (c) Wittig, G. *Naturwiss.* **1942**, *30*, 696–703.

Scheme 3.2: Reaction scheme proposed by Georg Wittig and coworkers in 1940-42



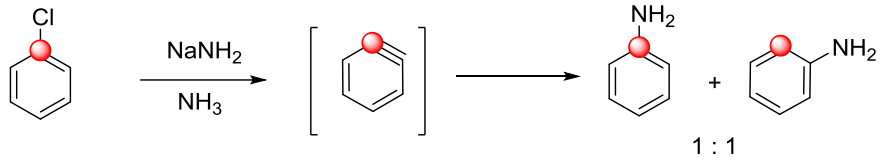
Several mechanistic proposals were made in the mid 1940's majorly concentrated on the amination of aryl halides to form anilines.[51] S_NAr displacement was the commonly accepted pathway at the time,[52] however, it could not explain the rearrangements that were taking place nor the regioisomers being formed.

Roberts and co-workers in 1953 published an alternative mechanism to describe this unusual rearrangements observed (Scheme 3.3).[53] The authors proposed an elimination-addition mechanism involving an electronically neutral species they labeled "*benzyne"* based on several observations made, such as; a) the amination reactions are very fast, b) the amine group is always attached only one carbon away from the leaving halide, c) starting materials and products are not isomerized under the reaction conditions, and d)

[51] (a) Gilman, H.; Avakian, S. *J. Am.Chem. Soc.* **1945**, *67*, 349–351. (b) Gilman, H.; Nobis, J. F. *J. Am. Chem. Soc.*
1945, *67*, 1479–1480. (c) Gilman, H.; Crounse, N. N.; Massie, S. P., Jr.; Benkeser, R. A.; Spatz, S. M. *J. Am. Chem. Soc.* **1945**, *67*, 2106–2108. (d) Urner, R. S.; Bergstrom, F. W. *J. Am. Chem. Soc.* **1945**, *67*, 2108–2109. (e) Gilman, H.; Kyle, R. H.; Benkeser, R. A. *J. Am. Chem. Soc.* **1946**, *68*, 143–144.
[52] For a review of nucleophilic aromatic substitution reactions, see: Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273–412.
[53] Roberts, J. D.; Simmons, H. E., Jr.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291.

no reaction was observed when there was no C-H group *ortho* to the halide (e.g. bromomesitylene).

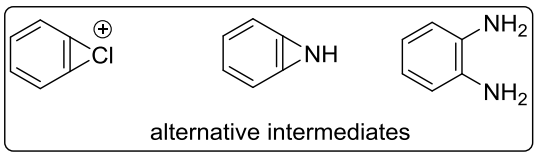
Scheme 3.3: Reaction scheme proposed by John D. Roberts in 1953



They have tested this hypothesis by performing amination reactions using isotopically labelled aryl halide, chlorobenzene-1-^{14}C (Scheme 3.3, red color carbon).[54] According to the proposed scheme 3.3, if the proposed intermediate "*benzyne"* is indeed the electrophile, then amination should yield a product with a mixture of aniline-1-^{14}C and aniline-2-^{14}C. After performing the reaction, the desired aniline-1-^{14}C was isolated in 43% yield and the rearranged product aniline-2-^{14}C was formed in 52% yield. This is in line with the formation of a symmetrical intermediate, benzyne. However, at the time the authors did not rule out the formation of other potential intermediates (Figure 3.2).

Subsequently, they performed several experiments to determine the rates of the reaction and to eliminate the other possible intermediates before finally concluding that benzyne

Figure 3.2: Alternative aryne intermediates proposed by J. Roberts

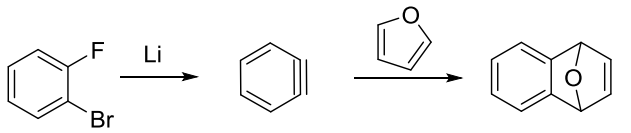


[54] Roberts, J. D.; Semenow, D. A.; Simmons, H. E., Jr.; Carlsmith, L. A. *J. Am. Chem. Soc.* **1956**, *78*, 601–611.

is the key intermediate in these reactions.[55]

Later on, other labs published results in the support of the aryne intermediate. In 1955, Witting and Pohmer trapped the aryne intermediate using furan to form naphthalene-1,4-epoxide likely via a Diels-Alder cycloaddition reaction, when bromoflourobenzene was treated with lithium metal (Scheme 3.4).[56]

Scheme 3.4: Reaction pathway proposed by Witting and Pohmer in 1955



cycloadduct
76%

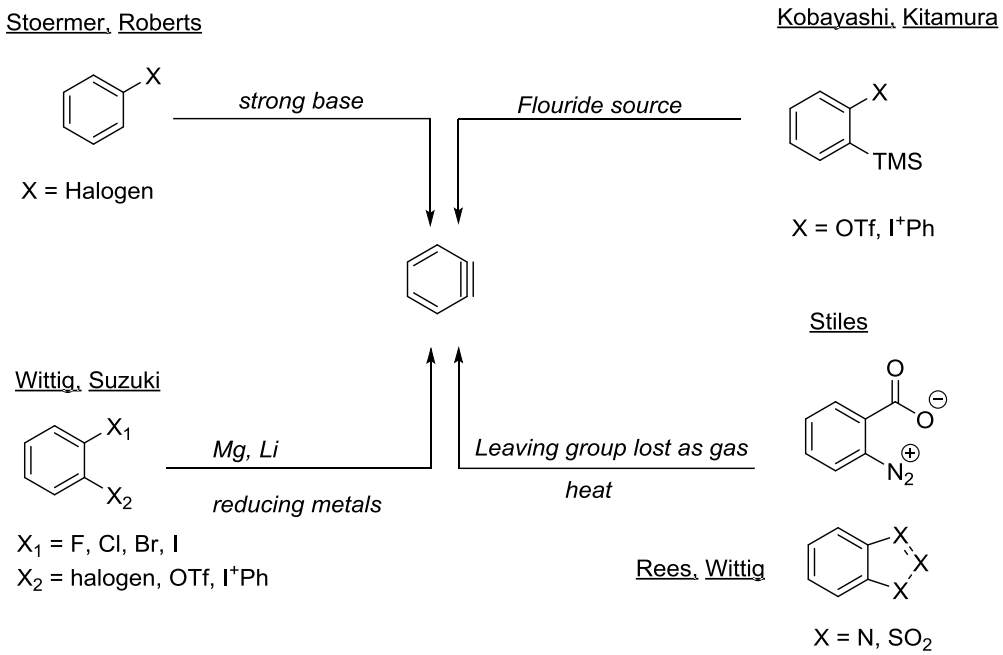
After this support for the benzyne intermediate was offered, several researchers discovered different ways to generate benzyne to overcome the harshness of the reaction and to enable further studies.

3.4 Types of Methods to Generate Arynes

Generation of benzynes can occur in two ways: 1) β-elimination from an aryl anion that was generated from a 1,2-subsititued aryl precursor and 2) retro-cycloaddition of benzo-fused heterocycles (Figure 3.3).

[55] Hall, G. E.; Piccolini, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1955**, *77*, 4540–4543.
Panar, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1960**, *82*, 3629–3632.
[56] (a) Wittig, G.; Pohmer, L. Angew. Chem. 1955, 67, 348. (b) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334–1351.

Figure 3.3: Types of methods to generate "arynes"



In the early stages, benzyne was mostly generated by using a strong base on a mono halide aryl group (Figure 3.3, left top) until Witting and Pohmer (1955)[57] showed a method using 2-bromoflourobenzene – a dihalogenated benzene – instead of mono halogenated benzene which effectively promoted the formation of benzyne when treated with lithium or magnesium metal (Figure 3.3. left bottom). This method of generating arynes was employed in several transformations involving enamines, sulfides, phosphorous and dienes compounds.[58]

[57] (a) Wittig, G.; Pohmer, L. *Angew. Chem.* **1955**, *67*, 348. (b) Wittig, G.; Pohmer, L. *Chem. Ber*. **1956**, *89*, 1334–1351.

[58] Kuehne, M. E. *J. Am. Chem. Soc.* **1962**, *84*, 837–847.
(a) Wittig, G.; Härle, H. *Justus Liebigs Ann. Chem.* **1959**, *623*, 17–34. (b) Huisgen, R.; Knorr, R. *Tetrahedron Lett.* **1963**, *4*, 1017–1021. c) Hellmann, H.; Eberle, D. *Justus Liebigs Ann. Chem.* **1963**, *662*, 188–201. d) Seyferth, D.; Burlitch, J. M. *J. Org. Chem.* **1963**, *28*, 2463–2464. (e) Griffin, C.; Castellucci, N. *J. Org. Chem.* **1961**, *26*, 629–630.

Between 1960 and 1964, a different way to generate benzyne was invented using the concept of retro-cycloaddition of benzo fused rings, ultimately evolving a gas to yield benzyne. Stiles and Miller applied this type of pathway using an anthranilic acid derivative, phenyldiazonium-2-carboxylate which, upon heating, released two different gases (CO_2 and N_2) to produce benzyne.[59] Then Wittig used benzo-1,2,3-thiadiazole-1,1-dioxide which decomposes at room temperature to yield benzyne, whereas Huang used (2-carboxyphenyl)phenyliodonium salts which require high temperatures and a longer reaction period to fully furnish benzyne (Figure 3.3, right bottom). Regardless of the drawbacks of these compounds, including careful handling and low temperature storage to avoid the evolution of gases, this technique was used over several years as it avoids the use of strong base and organometallic reagents.[60] Campbell and Rees, using a similar principle, applied the methodology to 1-aminobenzotriazole under mild conditions at room temperature to form benzyne in the presence of lead(IV) tetraacetate.[61] Although this reaction is instantaneous, the use of a stoichiometric amount of toxic metal led to the limitation of this method in large scale synthesis.

For the next 30 years after the discovery of benzyne, it was extensively used as a key intermediate to undergo several reaction transformations and as a facile route to natural

[59] Stiles, M.; Miller, R. G. *J. Am. Chem. Soc.* **1960**, *82*, 3802.
[60] For examples of aryne precursors employed in synthesis using retro-cycloaddtion of benzofused rings, see: (a)
Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, 4014–4021. (b) Nair, V.; Kim, K. H. *J. Org. Chem.* **1975**, *40*, 3784–3786. (c) Saá, C.; Guitián, E.; Castedo, L.; Suau, R.; Saá, J. M. *J. Org. Chem.* **1986**, *51*, 2781–2784. (d) Atanes, N.; Castedo, L.; Guitián, E.; Saá, C.; Saá, J. M.; Suau, R. *J. Org. Chem.* **1991**, *56*, 2984–2988. (e) Matsumoto, K.; Katsura, H.; Uchida, T.; Aoyama, K.; Machiguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2599–2602. (f) Yamabe, S.; Minato, T.; Ishiwata, A.; Irinimihira, O.; Machiguchi, T. *J. Org. Chem.* **2007**, *72*, 2832–2841.
[61] (a) Campbell, C. D.; Rees, C. W. *Proc. Chem. Soc.* **1962**, 296. (b) Campbell, C.D.; Rees, C. W. *J. Chem. Soc. C* **1969**, 742–747.

product synthesis. However, the methods available by that time to make benzyne still demanded either strong bases, metallic reagents, high temperatures, and/or extreme caution during their synthesis. This changed in 1983, when Kobayashi developed a mild and convenient method for the generation of arynes by the fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates (Figure 3.3 right top).[62] The mild conditions applied in this procedure are tolerant of a wide variety of reagents, substrates, functional groups, and even transition metal catalysts. The authors showed that a wide range of fluoride sources (TBAF, TMAF, CsF, KF) could be used in this reaction with several solvents (MeCN, THF, DME). Because of these attributes, this protocol has been the most widely used and effective method for the generation of arynes. Recent examples of aryne generation have been developed by Suzuki and Kitamura and are similar in concept, but using (phenyl)[o-(trimethylsilyl) phenyl] iodonium triflate.[63]

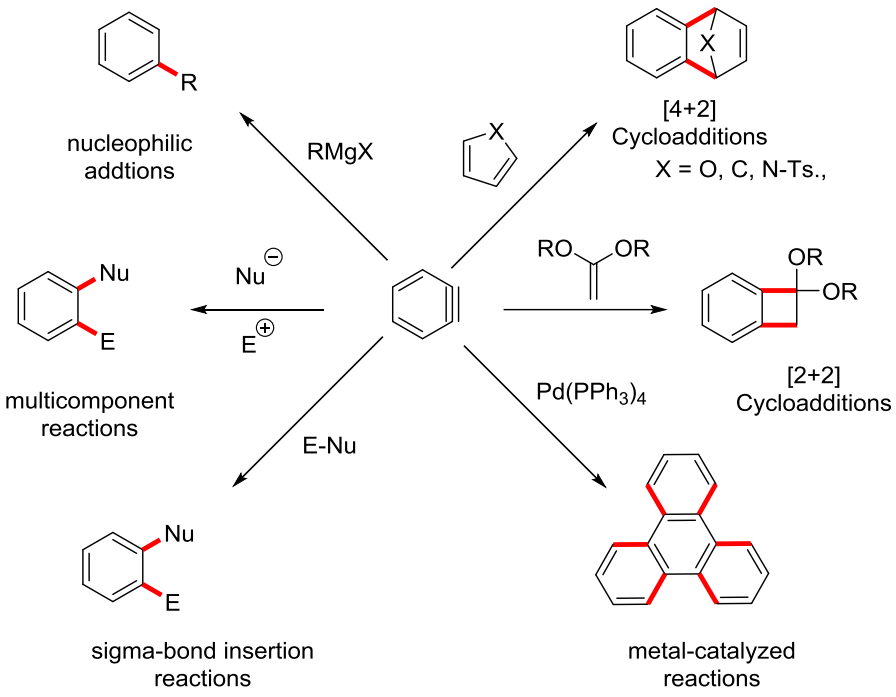
Henceforth, utilizing the method developed by Kobayashi and also with other previously developed methods, a significant amount of research has been published utilizing "benzyne" as the strategic intermediate in order to access benzenoid compounds.

[62] Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211–1214.
[63] A) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735–6736. b) Kitamura, T.; Yamane, M. *J. Chem. Soc., Chem. Commun.* **1995**, 983–984.

3.5 Representative Reactions of Arynes

Due to the distorted structure and poor orbital overlap, arynes are highly electrophilic; they react with nucleophiles in a wide variety of reaction classes such as pericyclic reactions, transition metal-catalyzed reactions, σ-bond insertion reactions, nucleophilic addition reactions, and multi-component coupling reactions (Figure 3.4, bonds in red are formed by the reaction of arynes with various nucleophiles).

Figure 3.4: Representative reaction of "arynes"



3.5.1 Pericyclic Reactions

Due to their highly strained nature, arynes act as excellent dienophiles in pericyclic reactions. Specifically, they are compatible in [2+2], [3+2], and [4+2] cycloaddition reactions to form diverse polycyclic products. The earliest cyclo addition reaction dates back to 1955 when Wittig and Pohmer trapped benzyne with furan to form a cycloadduct in a Diels-Alder type reaction representing a classic [4+2] cycloaddition. Several reactions have been shown to utilize [4+2] cycloaddition and thus the use of aryne became popular, especially in natural product synthesis.[64] In addition to [4+2] cycloadditions, arynes have been shown to undergo [3+2] cycloaddition reactions with a range of 1,3-dipolar compounds, such as organic azides to form benzotriazoles.[65] Nitrones, nitrile oxides, α-diazoketones, and azomethine ylides, etc., showed [3+2] cycloadditions with aryne.[66] Finally, [2+2] cycloaddition reactions also have been reported over the years.[67]

[64] For selected total syntheses featuring aryne annulation via [4 + 2] cycloaddition, see: (a) Best, W. M.; Wege, D. *Aust. J. Chem.* **1986**, *39*, 647–666. (b) Rigby, J. H.; Holsworth, D. D. *Tetrahedron Lett.* **1991**, *32*, 5757–5760. (c) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568–3570. (d) Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 5911–5917. (e) Hosoya, T.; *Chapter 2 – Orthogonal Synthesis of Indolines and Isoquinolines via Aryne Annulation* 100 Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004–1015. (f) González, C.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1995**, *60*, 6318–6326. (g) Venkatram, A.; Colley, T.; DeRuiter, J.; Smith, F. *J. Heterocycl. Chem.* **2005**, *42*, 297–301.

[65] Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, 4014–4021,

[66] (a) Minisci, F.; Quilico, A. *Chimica e Industria* **1964**, *46*, 428. (b) Kitamura, T.; Mansei, Y.; Fujiwara, Y. *J. Organomet. Chem.* **2002**, *646*, 196–199. C) Huisgen, R.; Knorr, R. *Naturwiss.* **1961**, *48*, 716. (d) Matsumoto, T.; Sohma, T.; Hatazaki, S.; Suzuki, K. *Synlett* **1993**, 843–846. e) Matsumoto, K.; Uchida, T.; Sugi, T.; Yagi, Y. *Chem. Lett.* **1982**, 869–870. f) Yamazaki, T.; Shechter, H. *Tetrahedron Lett.* **1972**, *13*, 4533–4536

[67] For a review of methods for the synthesis of benzocyclobutenes, including [2 + 2] cycloadditions between arynes and olefins, see: Klundt, I. L. *Chem. Rev.* **1970**, *70*, 471–487.

3.5.2 σ-bond Insertion Reactions

This new technique of using arynes to insert into a σ-bond of the nucleophiles emerged just over a decade ago. In 2002, Shirakawa and Hiyama were the first to report insertion of arynes into a C-N bond of cyclic urea to yield benzannulated diazocines in good yields.[68] The Stoltz group in 2005 presented an aryne insertion into a C-C bond of cyclic β-ketoesters to form benzannulated and dibenzannulated carbocycles.[69] Similar contributions to the subject were made by Kunai, Li, and Huang using cyclic malonates, β-ketophosphonates, and β-ketosulfones, respectively, to form a variety of benzannulated rings.[70]

3.5.3 Transition Metal-catalyzed Annulations

Arynes have also been reported to show reactivity in the presence of transition-metal complexes to undergo various annulation or insertion type reactions. Transition metal complexes along with aryne intermediates have shown an interesting [2+2+2] cyclotrimerzation annulation with diynes and benzyne. One such approach was investigated by Pérez and co-workers in 2003 in an effort to develop kinamycin antibiotics and formed substituted benzo[b]fluorenones.[71] Analogous to σ-bond insertion, Kunai et al.

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[68] Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247–3249.
[69] Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341.
[70] a)Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292–3294. b) Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 5691–5694. c) Zhang, T.; Huang, X.; Xue, J.; Sun, S. *Tetrahedron Lett.* **2009**, *50*, 1290–1294, d) Ebner, D. C.; Tambar, U. K.; Stoltz, B. M. *Org. Synth.* **2009**, *86*,161.
[71] Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2659–2661. (b) Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Org. Lett.* **1999**, *1*, 1555–1557. (c) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E.; Castedo, L. *Org. Lett.* **2000**, *2*, 1629–1632. (d) Peña, D.; Cobas, A.; Pérez, D.;

developed a Pd-catalyzed reactions to insert aryne in Si-Si bonds of 5-membered disilanes to form benzannulated disilacarbocycles.[72] Subsequently in 2007, Zhang synthesized indolo[1,2-*f*]phenanthridines from *N*-aryl indoles and arynes[73] and in 2008 Larock et al. prepared fluoren-9-ones from *ortho*-halobenzaldehydes and arynes.[74]

3.5.4 Nucleophilic addition reactions

Due to the highly strained ring system and their highly electrophilic nature, arynes undergo nucleophilic addition even with neutral nucleophiles. Neutral amine nucleophiles such as morpholine and N-methyl anilines have added to arynes.[75]

3.5.5 Multicomponent Reactions (MCRs)

A unique feature of arynes is their ability to participate in multi-component reactions, which have received attention recently. These reactions usually are initiated by nucleophilic addition followed by electrophile addition to trap the generated partial negative charge. This method of using two different reagents as nucleophile and electrophile enables the formation of complex molecules. The use of isocyanides and

Guitián, E.; Castedo, L. *Org. Lett.* **2003**, *5*, 1863–1866. Peña, D.; Pérez, D.; Guitián, E.; Castedo, L. *Eur. J. Org. Chem.* **2003**, 1238–1243.
[72] Yoshida, H.; Ikadai, J.; Shudo, M.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2003**, *125*, 6638–6639.
[73] Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem.* **2007**, *72*, 5431–5434.
[74] Waldo, J. P.; Zhang, X.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 6679–6685.
[75] Adam E. Goetz and Neil K. Garg. *Nat. Chem.* **2013**, *5*, 54–60.

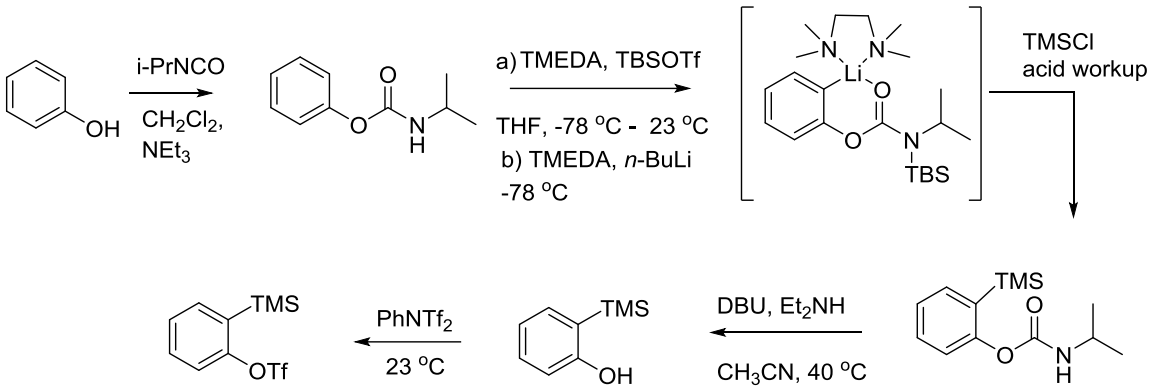
aldehydes leading to the formation of benzannulated iminofurans on reaction with aryne was demonstrated by Kunai et al.[76]

3.6 Limitations to Kobayashi's Method need to be addressed

In many recent strategies, generation of arynes was achieved using Kobayashi's method via fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflate. However, a major limitation of the approach is the synthesis of the starting material 2-(trimethylsilyl)aryl triflate. Typically, 3-5 steps are required to install the TMS and OTf groups *ortho* to each other on the aryl ring (Scheme 3.5). In addition, it requires the usage of harsh reagents such as *n*-butyl lithium, LDA and triflic anhydride. All these harsh reagents significantly reduce the functional group tolerance, which ultimately results in poor access to complex aryl groups. Furthermore, the method shown in scheme 3.5 requires the isolation of product using column chromatography to furnish the 2-(trimethylsilyl)aryl triflate; precursor of the aryne.[78,77]

[76] H. Yoshida, H. Fukushima, J. Ohshita and A. Kunai, *Angew. Chem., Int. Ed*., **2004**, *116*, 4025–4028.
[77] S. M. Bronner, N. K. Garg, *J. Org. Chem.* **2009**, *74*, 8842 – 8843.

Scheme 3.5: Most recent efficient method to synthesize 2-(trimethylsilyl)aryl triflate



Consequently, it is mostly used to generate 2-(trimethylsilyl)phenyl triflate, the simplest aryne possible. However, relatively few examples with additional substitutions have been reported and fluoride sensitive functional groups such as silanes and sulfonates are not tolerated. Although this method is the most widely used as aryne precursor, an alternative method that allows the scientific community to access complex and multi-substituted functional groups containing aryl rings that are easy to prepare would advance the current field of arynes. This would ultimately allow for late-stage benzyne reactions.

3.7 Diaryliodonium Salts as Aryne Precursors

Using diaryliodonium salts offers advantages over Kobayashi's method, especially with reference to accessing complex arynes and their ease of synthesis. Diaryliodonium salts can be generated through a convenient one-pot method using aryl iodides or arylboronic acids (Scheme 1.4.4). Many different functional groups have been installed on these

diaryliodonium salts, which offers further functionalization opportunity. Substitution patterns that were not accessed through Kobayashi's method could be achieved.

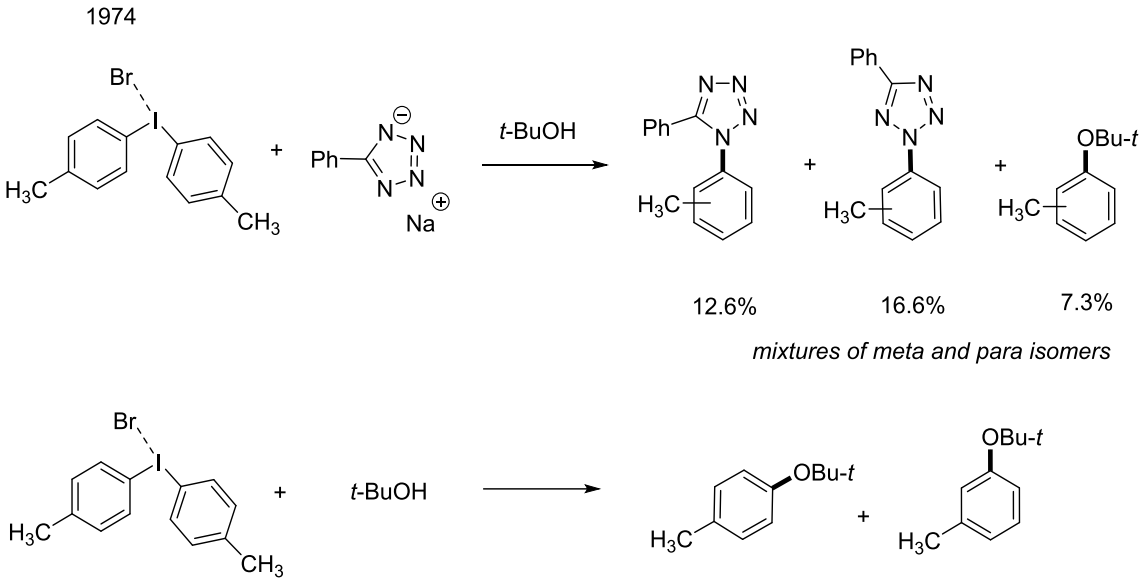
3.8 Literature Precedent for the Generation of Arynes via C-H Deprotonation of Aryl Halides

The generation of benzyne via C-H deprotonation from diaryliodonium salt was first observed in 1974.[78] In the seminal reports of reactions of diaryliodonium salts by Beringer and Forgione, which proposed the mechanisms of radical-pair and nucleophilic substitution, aryne pathway was also suggested but without sufficient compelling evidence.[79] Hence the authors from Kyoto University pursued a mechanistic investigation to demonstrate a plausible pathway taking place with diaryliodonium salts.

They treated ditolyliodonium bromide with tetrazole in the presence of tert-butanol in reflux conditions and observed benzyne reactivity yielding a mixture of products. (Scheme 3.6, top reaction). To further confirm that the reaction products were indeed formed by a benzyne pathway, they conducted another experiment wherein ditolyliodonium bromide was treated with sodium tert-butoxide in *tert*-butanol. In this experiment, a 1:1 ratio of both *meta* and *para* isomers of *tert*-butyltolyether in a total of 27% yield was observed. (Scheme 3.6, bottom reaction).

[78] Akiyama, T.; Imasaki, Y.; Kawmisi, M. *Chem. Lett.* **1974**, *3*, 229–230.
[79] F. M. Beringer and P. S. Forgione, *Tetrahedron*, 19, 739 (**1963**). b) Y. Yamada and M. Okawara, Bull. *Chem. Soc. Japan*, **1972**, *45*, 1860.

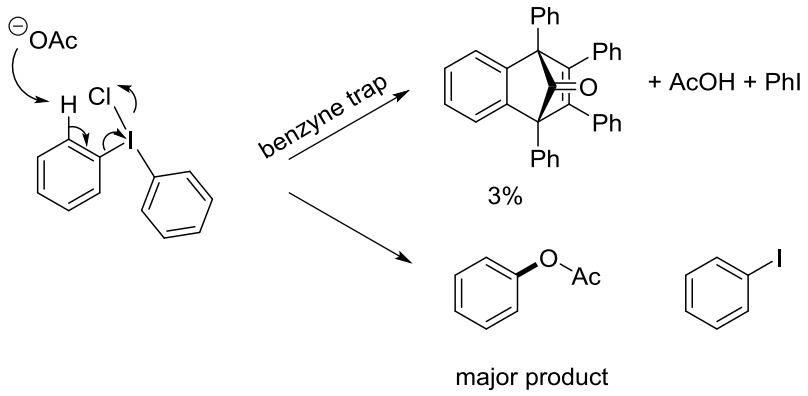
Scheme 3.6: Literature precedent for the generation of arynes via C-H deprotonation of aryl halides



Later, another work was published that further confirmed this type C-H deprotonation of diaryliodonium salts. In this work, diphenyliodonium chloride was reacted with sodium acetate and a benzyne trap, 1,2,3,4-tetraphenylcyclopentadienone, was added in the reaction mixture. The authors isolated a mixture of compounds and also the benzyne adduct 1,2,3,4-tetraphenylnaphthalene in 3% yield.[80] (Scheme 3.7)

[80] Sharp, J. T. ; Sledzinski, B; Wilson, N.; Cadogan, J.I.*G J.C.S, Perkin Transactions 1*, **1975**, *11*, 1072-1074.

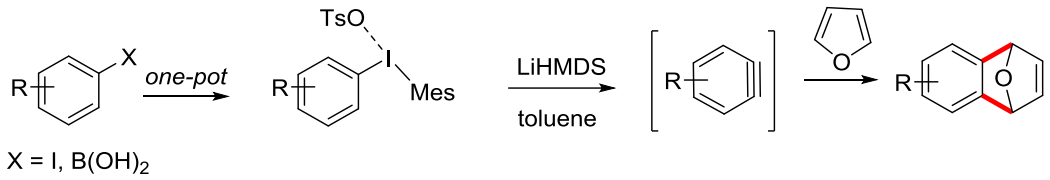
Scheme 3.7: Trapping of benzyne formed from sodium acetate and diphenyliodonium chloride



Both of these reactions shed some light on a new type of reactivity of diaryliodonium salts. However, they were very low yielding and suffered from selectivity problems. While other examples of aryne pathway as a side reaction have been observed in the reaction of diaryliodonium salts, the synthetic utility of this approach remained undeveloped until recently.

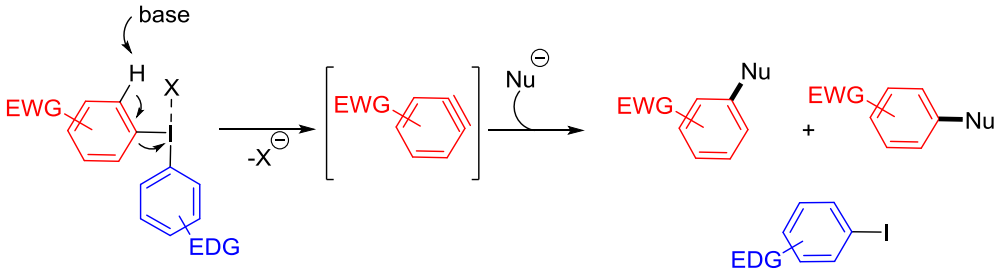
3.9 Generation of Arynes using Unsymmetrical Aryl(mesityl)iodonium salts via C-H Deprotonation

Scheme 3.8: Our work



Herein, we describe an efficient method to access highly functionalized arynes using aryl(mesityl)iodonium salts, which are conveniently prepared by a one-pot method either from aryl iodides or arylboronic acids. The generated aryne was trapped with furan in moderate to high yields (Scheme 3.8). Other nucleophiles, such as alicyclic amines, and 1,3-dipoles such as benzyl azide, were also shown to work with this method. The mechanism is believed to proceed via C-H deprotonation on the *ortho* position to the iodonium moiety by a strong base and further elimination of the iodonium group generating an aryne.

Scheme 3.9: Proposed reaction mechanism of C-H deprotonation on unsymmetrical diaryliodonium salts



3.10 Reaction Discovery

3.10.1 Preliminary experiments showing benzyne type reactivity

Soon after our success with the development of a C_{aryl}-O_{alkyl} bond forming arylation reaction (Chapter 2), we further envisioned the application of this direct and metal-free reaction to other heteroatom nucleophiles. Nitrogen nucleophiles were chosen as the molecules of interest due to their prevalence in many industrially important compounds.

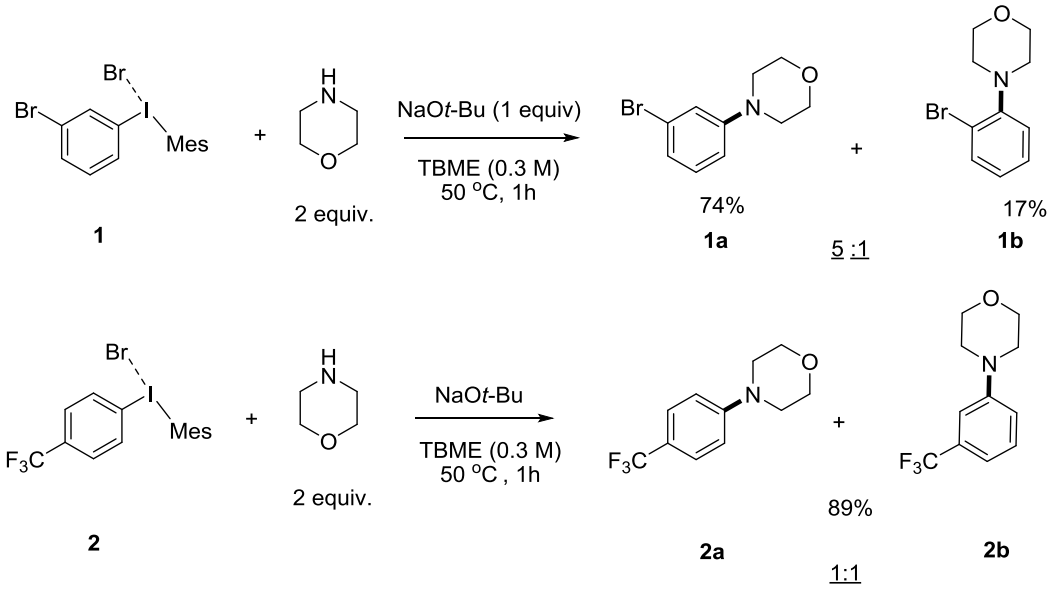
The secondary alkyl anime morpholine was selected as the model molecule for this chemistry due to its inclusion in biologically active compounds. The diaryliodonium salt 3-bromophenyl(mesityl) bromide (**1**) was chosen as this aryl ring stands in the region between electron donating and electron withdrawing aryl groups. After initial experiments applying similar conditions as in the previously developed etherification standard conditions, we have witnessed the formation of C_{aryl}-N_{alkyl} bond between the unsymmetrical diaryliodonium salt and the alicyclic amine morpholine to form the product **1a** in 48% yield.[81] Upon optimization of the reaction's conditions with various bases and counter anions, we arrived at a 74% yield of the product **1a** using NaO*t*-Bu as the base and the triflate counter anion (Scheme 3.10, top reaction). Intriguingly, up on the careful analysis of the crude ^{1}H NMR spectrum, we found morpholine peaks corresponding to another regioisomer, which we initially thought was unreacted morpholine; it had been added in 2 equivalents to that of the diaryliodonium salt. After isolation of the products, we were surprised to see that there were indeed two regioisomers formed in this reaction.

[81] Yield determined from ^{1}H NMR spectrum of the crude reaction mixture versus 1,3,5-trimethoxybenzene as an internal standard

One was the expected *ipso*-substitution product **1a** and the other was an unexpected *cine*-substitution product **1b** in the ratio 5:1. The overall yield of the reactions was 91% calculated using crude ^{1}H NMR (Scheme 3.10, top reaction).

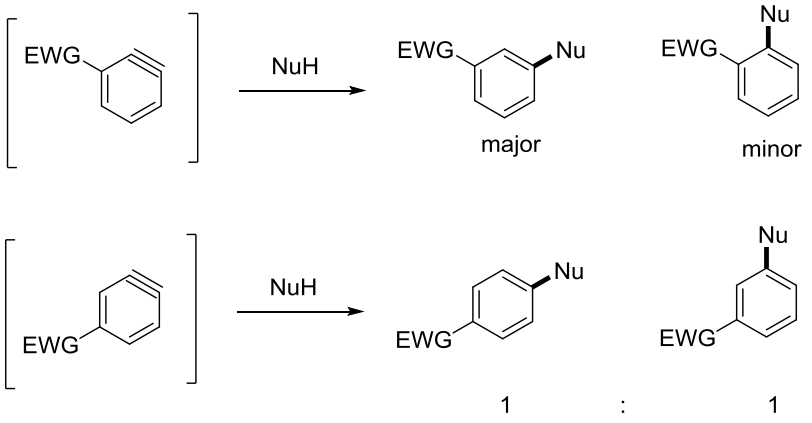
Despite the formation of the other regioisomer, the desired product was formed in synthetically useful yield. We also examined into other aryl groups, and the pattern of the regioisomer formation remained the same when the substituent was on the *meta*-position of the iodonium salt. However, when the unsymmetrical para-substituted diaryliodonium salt (**2**) was used, the regioisomers were formed in a 1:1 ratio with an overall yield of 89% (Scheme 3.10, bottom reaction). On the contrary, we have not observed regioisomers in the previously developed etherification chemistry, which led us to suspect that this chemistry may not be following the same mechanism as the etherification.

Scheme 3.10: Preliminary reactions towards the discovery of arynes generated via C-H deprotonation of unsymmetrical diaryliodonium salts



This unusual reactivity of diaryliodonium salts resembles the type of reactivity observed by Roberts in 1953 when he first discovered arynes.[82] The ratio of isomers formed by 4-substituted and 3-subsitituted benzynes are in line with the ratios formed by this reaction of unsymmetrical diaryliodonium salts (Scheme 3.11).[83]

Scheme 3.11: Product distribution of previously reported aryne mechanism



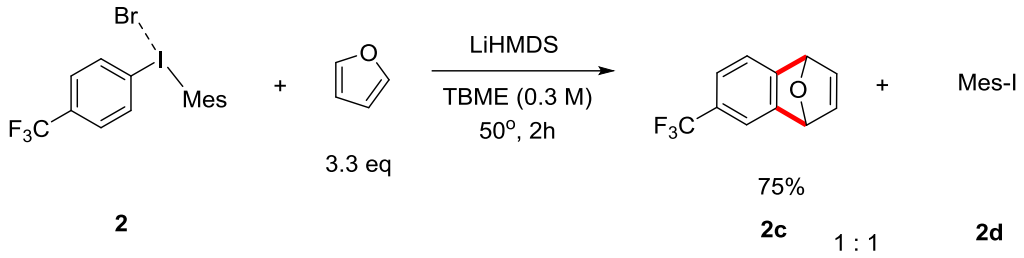
3.10.2 Trapping experiments of aryne with furan

To determine whether the formation of regioisomers is the result of generation arynes, furan, a classic aryne trap, was added to the unsymmetrical diaryliodonium salt **2** instead of morpholine. In this experiment, the aryne was successfully trapped by furan to form the cycloadduct 6-(trifluoromethyl)-1,4-dihydro-1,4-epoxynaphthalene **2c** in high yield (Scheme 3.12). The reaction was highly selective in forming only one aryne product in

[82] J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith, C. W. Vaughan, *J. Am. Chem. Soc.*, **1953**, *75*, 3290 – 3291.
[83] Adam E. Goetz and Neil K. Garg. *Nat. Chem.* **2013**, *5*, 54–60.

addition to the by-product mesityl iodide **2d** in 1:1 ratio. To the best of our knowledge, this is the highest yield reported for the C-H deprotonation product of diaryliodonium salts since the first seminal reports in 1974-75 discussed in the above literature precedent section (Scheme 3.6). We envisioned this opportunity to address the challenges of the current aryne generating methods which limit highly functionalized arynes or poly substituted aryl groups. Hence, using unsymmetrical diaryliodonium salts as aryne precursors may offer a significant advantage, as there are many methods to synthesize elaborate unsymmetrical diaryliodonium salts.

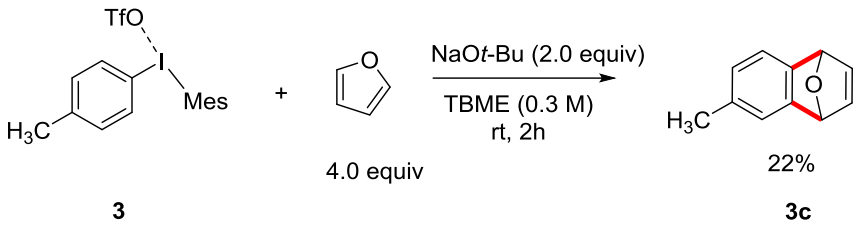
Scheme 3.12: Trapping of aryne formation with furan.



3.11 Reaction Development

The electron rich 4-phenyl(mesityl)iodonium triflate salt **3** was chosen to optimize this reaction as electron rich diaryliodonium salts are challenging substrates in the coupling reactions of hypervalent iodine chemistry. Success with these substrates would indicate that the reaction should work using electron neutral and electron poor salts as well. Furan was chosen as it is widely used as an aryne trap.

Scheme 3.13: Model reactions using electron rich unsymmetrical diaryliodonium salt

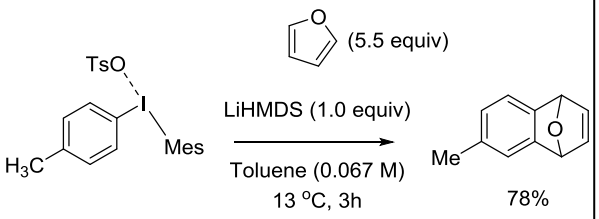


3 **3c**

With an initial yield of 22% (Scheme 3.13), we imagined that there is a lot of room for improvement. This reaction landscape had several parameters such as auxiliary groups, counter anions, type of base, solvents, temperature, and concentration that can be optimized to increase the % yield (Table 3.1). For example, when the base was switched to an amide base (e.g., NaHMDS) and the counter anion to tosylate, a significant increase in the yield from 22% to 39% was observed vs NaO*t*-Bu (entries 7 and 8). Among the amide bases, LiHMDS provided about a 10% increase in the yield. The solvent had also been switched to toluene as the amide bases were solutions in toluene. A slight increase in the yield to 52% was observed when the temperature was lowered to 13 ^{o}C from room temperature. After this point, it became immensely challenging to increase the % yield of the reaction. Other counter anions OTf, Br, and, BF_4 had little effect and OTs provided the highest yield (entries 1-3). Other auxiliary groups such as phenyl (entry 4, 20% and trimethoxyphenyl (TMP) (entry 5, 67%) furnished lower product than mesitylene (Mes).

Finally, we learned that the equivalents of base and furan had the highest impact on the % yield. Lower equivalents of furan (1.0 equiv) and higher equivalents of base (3.0 equiv) were detrimental to the reaction and only produced a 14% yield (entry 11). Higher equivalents of furan (4.0 equiv) and lower equivalents of base (1.0 equiv) furnished 62% of the cycloadduct, which was further increased to 78% upon increasing the equivalents of the furan to 5.5. Further increments didn't increase the yield, but we with all parameter optimized, the yield increased from 22% to a synthetically useful yield of 78%. We have isolated the cycloadduct using these reaction conditions and obtained the product in 70% yield.

Table 3.1: Optimization of aryne chemistry



Entry	Deviation from "Standard Conditions"	Yield[b]
	Counter anion	
1.	OTf instead of OTs	62%
2.	Br instead of OTs	59%
3.	BF_4 instead of OTs	59%
	Auxiliary group	
4.	Phenyl instead of Mes	30%
5.	TMP instead of Mes	67%
	Nature of Base (in TBME)	
6.	$NaNH_2$	20%
7.	Na/KHMDS	36%
8.	LiHMDS	39%
9.	NaO*t*-Bu in TBME	22%
	Amount of Base and Furan	
10.	2 equiv. of base and 4.0 equiv of Furan	67%
11.	3 equiv. of base and 1.0 equiv of Furan	14%

[b] Yield determined from 1H NMR spectrum of the crude reaction mixture versus 1,3,5-trimethoxybenzene as an internal standard.

3.12 Scope of the Reaction

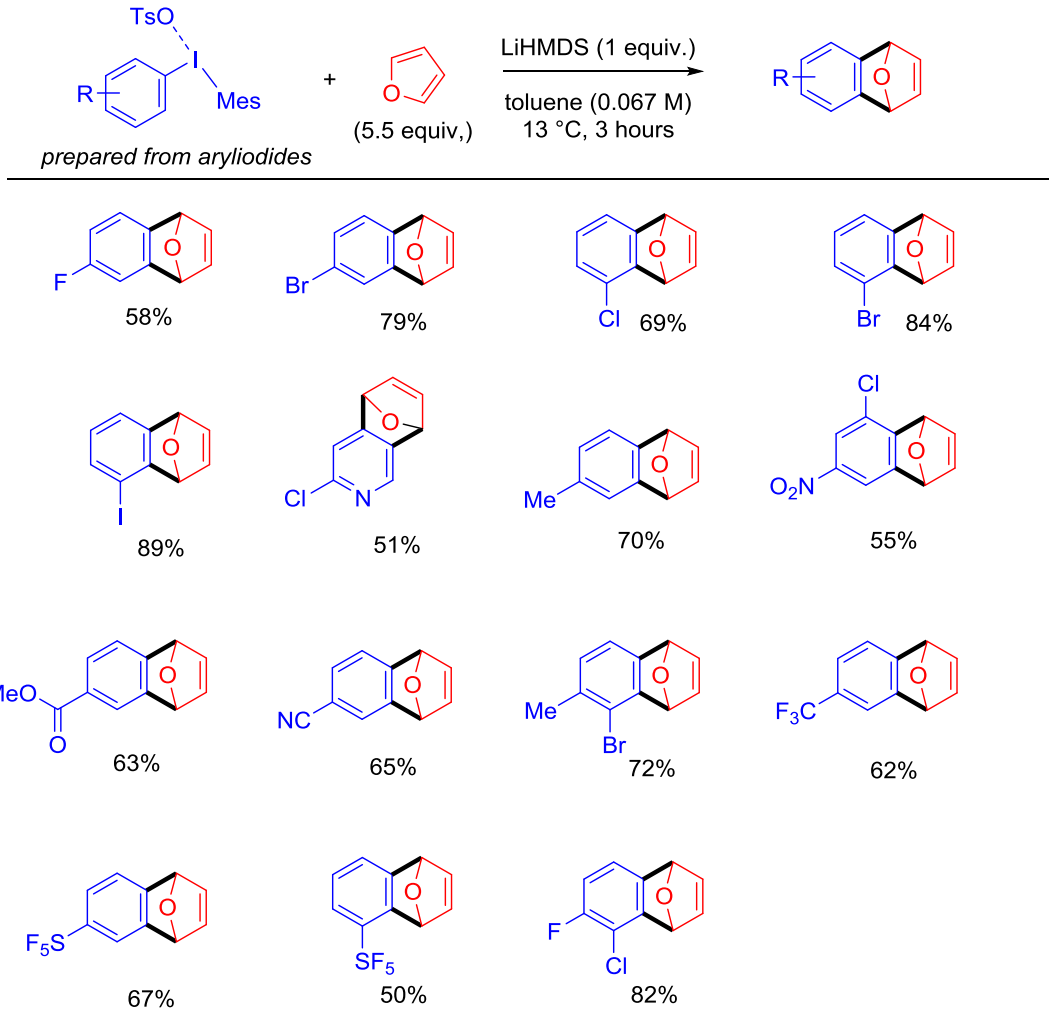
With optimized conditions at hand, we explored the scope of this reaction. As this method highlights an efficient aryne reaction pathway and offers opportunity for a broader substrate scope with reference to the aryl group, more focus was emphasized on the diaryliodonium salt substrates. The scope of this reaction is categorized in to two; depending on the preparation of unsymmetrical diaryliodonium salts: either from commercially available aryl iodides or from arylboronic acids in a one-pot method (see section 1.4.4 for synthesis). This simple and practical method provides these salts in good yield (70% average) by easy trituration and filtration and completely avoids the use of column chromatography or further purification.

3.12.1 From aryl iodides

This scope represents the cycloaddition products trapped by furan, that are formed by the *ortho* C-H deprotonation of the unsymmetrical diaryliodonium salts, which were synthesized using aryl iodides is shown in table 3.2. The scope table demonstrates that all the different halogens are well tolerated resulting in moderate to excellent yields. Poly-substituted functional groups have also shown good reactivity and highlight opportunity for further elaboration of these formed substrates. All the positions, *ortho*, *meta,* and *para* have been shown to work in this cycloaddition reaction. Pentafluorosulfanyl (SF_5) group,

which is recognized as an important moiety in biomedical and materials chemistry,[84] was easily introduced via its aryl iodide and shown to react in C-H deprotonation chemistry to form its cycloadduct. Both *meta* and *para* substituted SF_5 products were obtained in decent yield. Heteroaromatic substrate 2-chloropyridyl demonstrates that this chemistry could be applied to heteroaromatic compounds, which are vital in pharmaceutical industries. It is

Table 3.2: Scope of aryl groups generated from aryliodides and trapped with furan



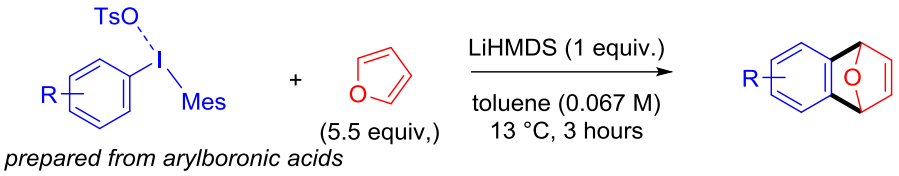
[84] For a review, see: S. Altomonte , M. Zanda , *J. Fluorine Chem.*, **2012** , *143* , 57 –93 .

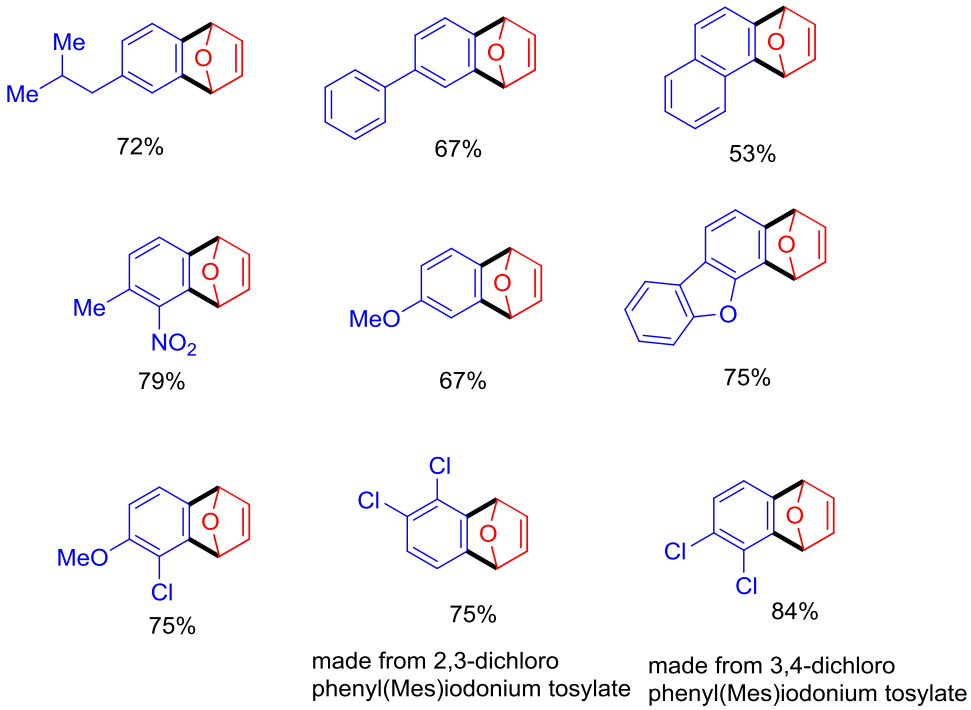
worth mentioning that the presence of two or more electron withdrawing groups, such as ester functional groups, on the aryl group resulted in poor yield (~30%).

3.12.2 From arylboronic acids

This scope represents the cycloaddition products trapped by furan which are formed by the *ortho* C-H deprotonation of the unsymmetrical diaryliodonium salts that were synthesized using arylboronic acids is shown in table 3.3. These scope entries highlight the aryl groups which have electron donating groups on the arynes and seamlessly undergo cycloaddition reaction with furan to produce moderate to good yields. The dibenzofuran substrate shows that this reaction can be used at a late stage synthesis to form structures with complex substitutions (e.g., 2,3-dichlorophenyl and 3,4-dichlorophenyl substrate, both of which form the same cycloadduct products). This example demonstrates that the iodonium group is the only preferred leaving group, which undergoes reductive elimination to form aryne.

Table 3.3: Scope of aryl groups generated from arylboronic acids and trapped with furan



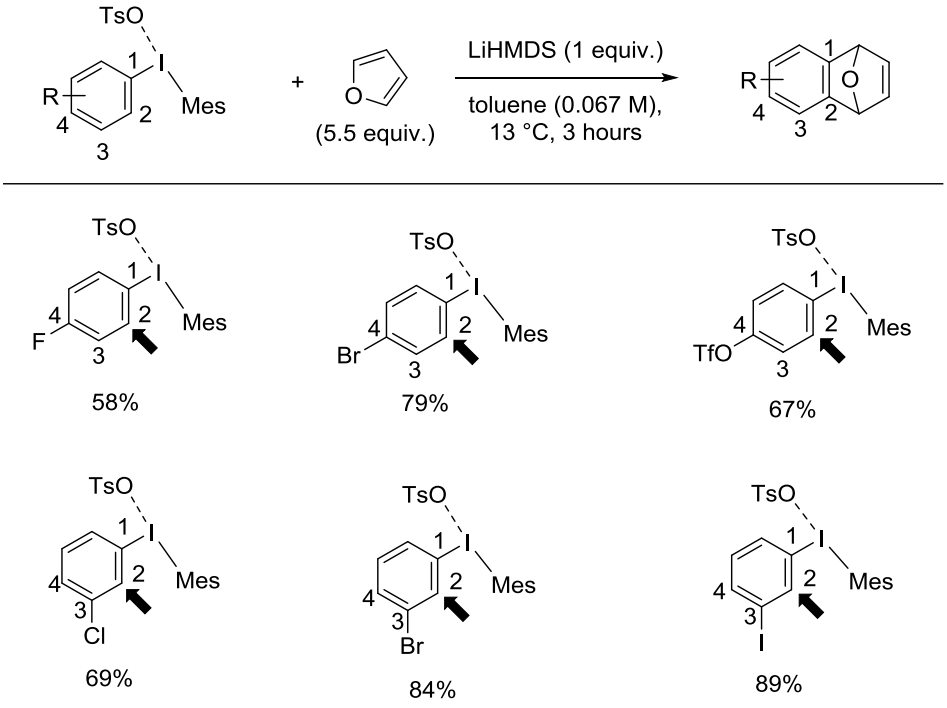


3.13 Aryne Formation with Selective Iodonium Elimination

This study represented in table 3.4 demonstrates that the iodonium group is selectively eliminated even in the presence of halide or pseudo halide after the *ortho* C-H deprotonation step to form the aryne. In the top row of table 3.4, it is shown that 4-substituted diaryliodonium salts are only deprotonated selectively on the 2-position (indicated with arrows), as evidenced by the observation that only one cyclo adduct product is observed in the crude ^{1}H NMR spectrum. This is the result of deprotonation at the 2-

postion to eliminate the iodonium group to form the arynes which leaves the halide or pseudo halide group on the 4th position intact. However, in the bottom row of the table 3.4, where the halide is situated on the 3-position, selective elimination of iodonium group takes place even though elimination of halide is possible.[85]

Table 3.4: Trapped aryne product froma a variety of iodonium salts formation with selective iodonium elimination



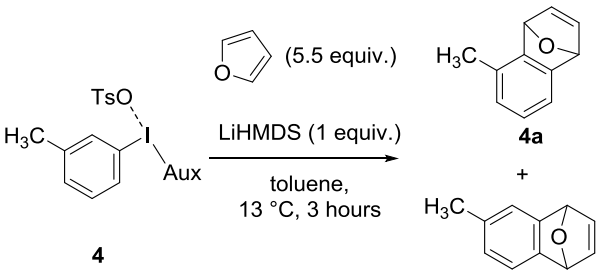
the yields represent the the aryne cycloadduct product formed after trapping with furan calculated using the standard 1,3,5-trimethoxybenzene

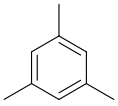
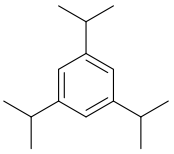
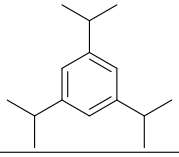
[85] Joseph F. Bunnett, Francis J. Kearley Jr, *J. Org. Chem.*, **1971**, *36*, 184–186.

3.14 Auxiliary and Temperature Controlled Selectivity of C-H Deprotonation

Formation of two regioisomers **4a** and **4b** was observed when an electron donating and sterically bulky salt, 3-methlyphenyl(aux)iodonium tosylate **4**, was employed in the trapping reaction with furan. This is in contrast to the result observed with electron withdrawing group in the 3-postion. In the case of electron withdrawing groups, a single regioisomer is observed and we hypothesize that this is due to proximity induced acidity.[86] Deprotonation at 2-postion and the 6-postion led to the formation of two products in 4.2:1 ratio when Mes was used as the auxiliary. A study of auxiliaries revealed that the ratio of the desired isomer increased to 5.3:1 if 2,4,6-triisopropylphenyl auxiliary was used (Table 3.5, entry 2). Lowering the temperature to -10 ^{o}C further improved to the selectivity to 6.7:1 (Table 3.5, entry 3). This was probably due to restricting the access to 6-position proton because of its sterically hindering groups.

Table 3.5: Auxiliary and temperature controlled selectivity of C-H deprotonation.



Entry	"*Aux*"	ratio of a : b
1.		4.2 : 1
2.		5.3 : 1
3.		6.7:1 (-10 ^{o}C)

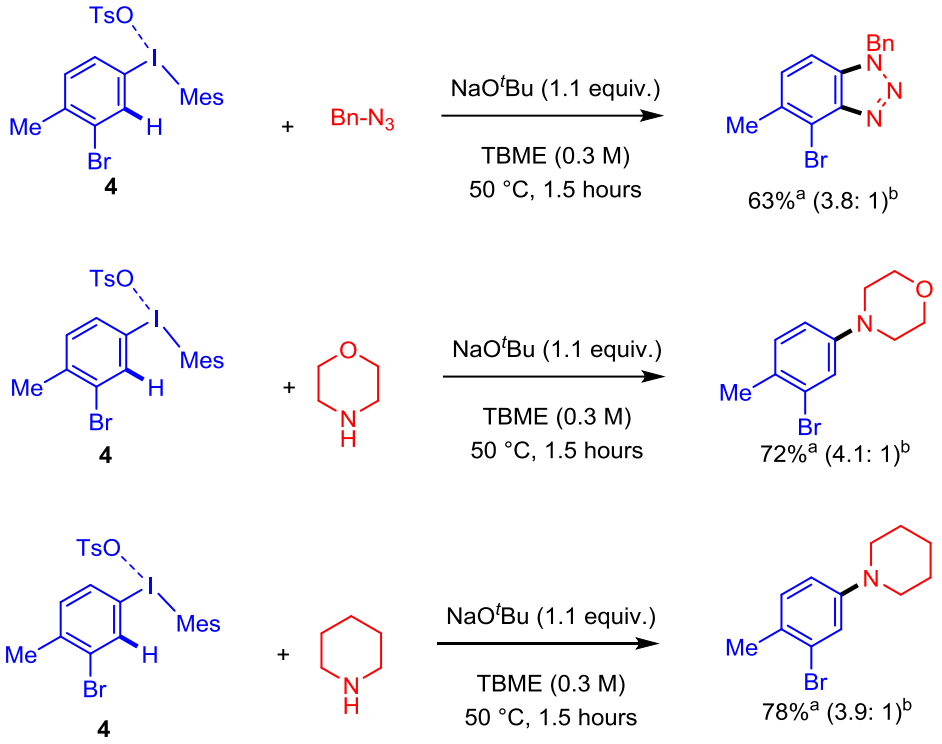
[86] K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, *Tetrahedron*, **2007**, *63*, 1568 – 1576.

3.15 Representative Examples of Cycloaddition and Nucleophilic Addition Reactions

To further demonstrate the synthetic utility of this method, other reaction classes have been shown under slightly modified conditions. The reaction of unsymmetrical diaryliodonium salt **4** with benzyl azide in a cycloaddition reaction produced a mixture of benzotriazole in 3.8:1 regioisomeric ratio with a total yield of 63%. Other nitrogen nucleophiles were added in a nucleophilic addition type pathway to form the respective product in an expected regioisomeric ratio.[87] Addition of morpholine to trap the aryne resulted the major isomer in 58% yield (72% combined yield) and piperidine gave a 62% yield of major isomer (78% combined yield) respectively.

[87] J. M. Medina, J. L. Mackey, N. K. Garg, K. N. Houk, J. Am. Chem. Soc. 2014, 136, 15798 – 15805, b) E. Picazo, K. N. Houk, N. K. Garg, Tetrahedron 2015, 56, 3511 – 3514, and references therein.

Scheme 3.14: Representative examples of cycloaddition and nucleophilic addition reactions



[a]Combined yield of regioisomers

[b] Ratio of regioisomers; major regioisomer:minor regioisomer

3.16 Conclusion

A novel and efficient method to access highly functionalized arynes is demonstrated, which avoids the usage of transition metals or multistage syntheses. The aryne intermediates were trapped by furan, benzyl azide, and secondary amine nucleophiles to show the synthetic utility of this protocol. The utilization of hypervalent iodine compounds in this new and unique way highlights their use as emerging transition metal-free compounds to undergo various arylation reactions.

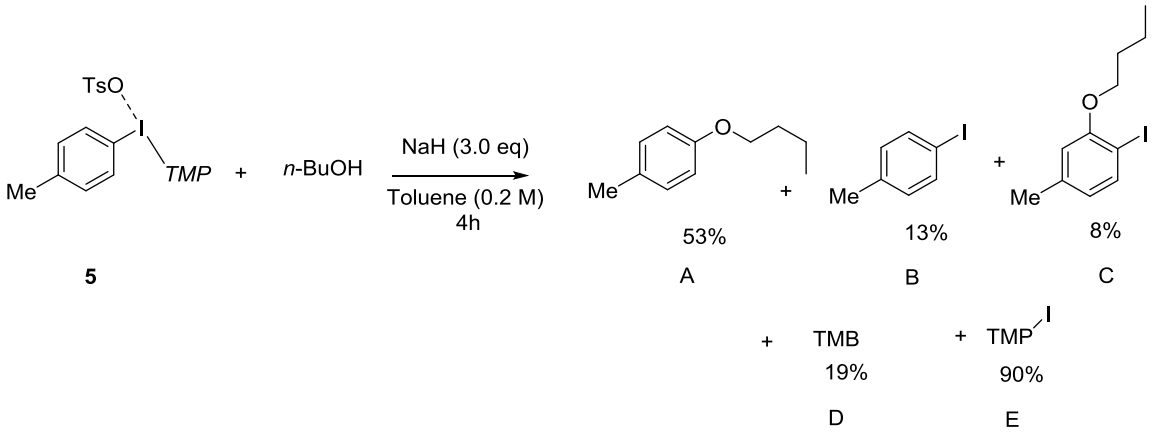
Chapter 4

Mechanistic Investigations of Different Modes of Reactivity of Unsymmetrical Diaryl iodonium Salts

4.1 Investigation of Product Distribution for Some Electron Rich Unsymmetrical Diaryliodonium salts

We wanted to further explore the cause of moderate yielding unsymmetrical diaryliodonium salts in the etherification reactions. 4-Toyl(TMP)iodonium tosylate **5** was chosen as the substrate to study in this case as it provided 53% yield (lowest yield) in the coupling reaction with *n*-butanol (Scheme 4.1). Upon careful investigation of the crude ^{1}H NMR spectrum we identified several side products that shed light on reactions that compete with formation of the desired coupling product (A, 53%) and co-product TMP-I, (E, 90%). The formation of tolyl iodide (B, 13%) and TMB (D, 19%) were also observed. An unusual side product (C, 8%) was additionally observed and has been tentatively assigned by ^{1}H NMR and GC-MS as 2-butoxy-1-iodo-4-methylbenzene.

Scheme 4.1: Analysis of product and side product distribution for an electron rich unsymmetrical diaryliodonium salt in a C-O coupling reaction

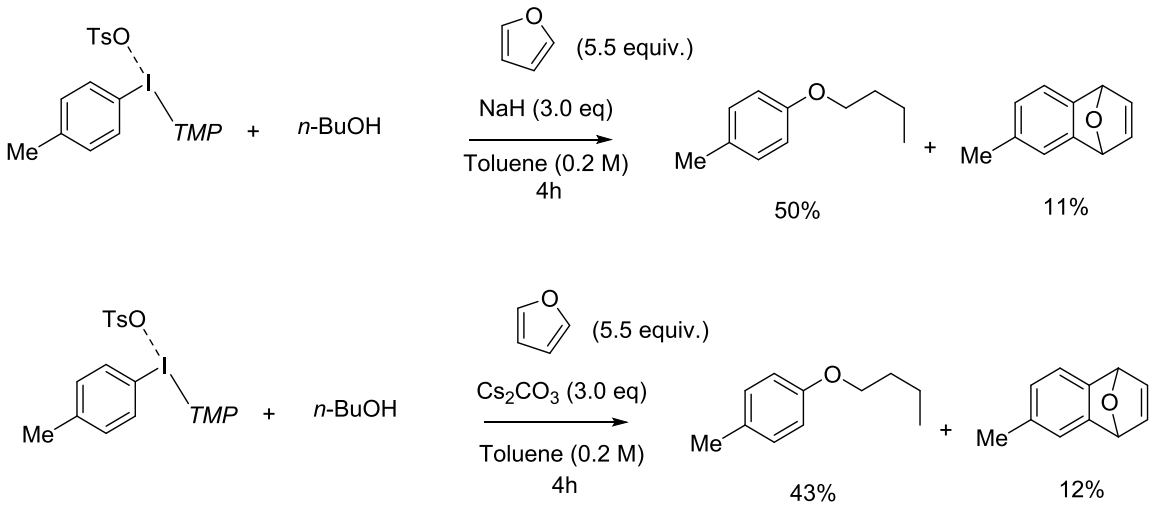


4.2 Addition of Aryne Trap

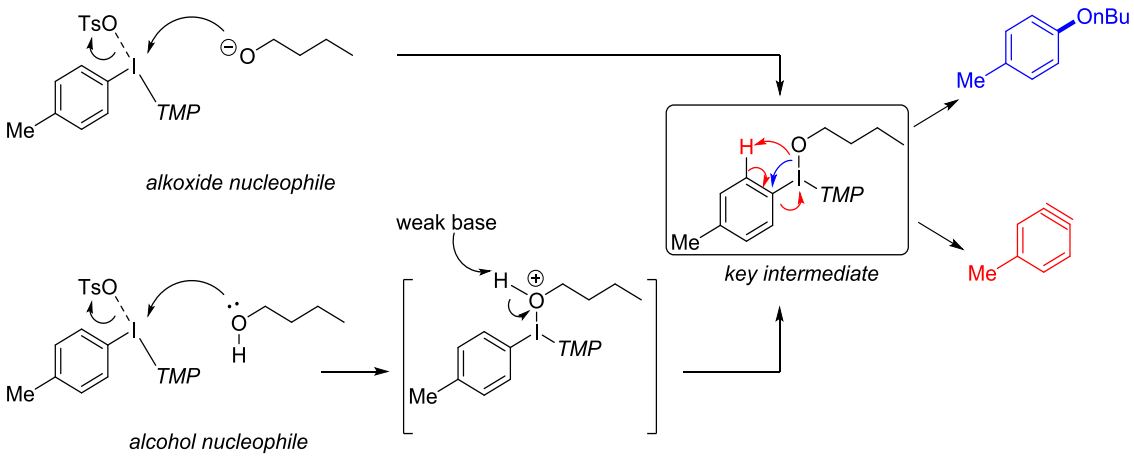
In our work shown in scheme 4.1, the 4-tolyl moiety is not fully accounted for in the mass balance. Moreover, with the previous knowledge that alkoxide nucleophiles generate arynes, we sought to quantify the amount of aryne produced in this reaction, which may account for the lower yield of *ipso* product compared to other salts. Interestingly when furan was added as an aryne trap, 11% of the cycloadduct was observed in the crude ^{1}H NMR spectrum along with a similar yield (50%) of the desired product relative to without addition of furan (Scheme 4.2, top reaction). We hypothesized that the presence of stoichiometric alkoxide leads to C-H deprotonation and aryne formation. However, when milder bases, such as Cs_2CO_3, were employed in the reaction similar product distribution was observed (Scheme 4.2, bottom reaction). Despite the fact that carbonate base is not basic enough to stoichiometrically deprotonate an alcohol. The product distribution is consistent with a common intermediate (described in Scheme 4.3). This key intermediate containing the butoxide on the λ^3-iodane can undergo two different pathway to furnish the

ipso-substituted product via the attack of butoxide on the *ipso* carbon and cycloaddition product via C-H deprotonation respectively.

Scheme 4.2: Addtion of aryne trap to the moderate yielding iodonium salt with NaH (top) and Cs_2CO_3 (bottom)



Scheme 4.3: Plausible mechanism when milder base is employed



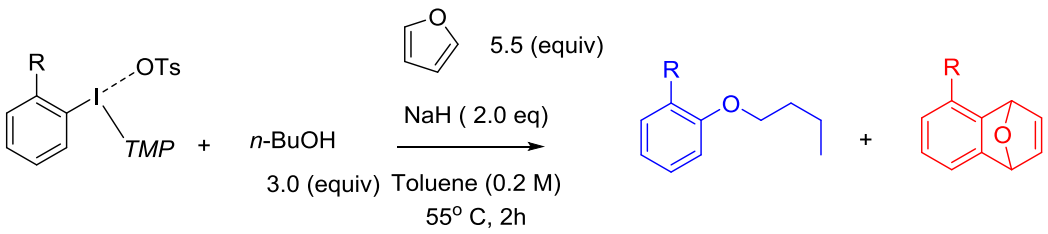
4.3 Influence of the "Position and Electronics" of the Functional Group on the Iodonium salt

We were interested to see if the competition between the two pathways shown in scheme 4.3 is affected by the position and electronic effect of ring substituents. Three different functional groups Me, Cl, and NO_2 were chosen as their electronic effects differ significantly. Intriguing observations were made when these different substrates were subjected to coupling reaction with *n*-butanol and furan.

4.3.1 Effect arising due to ortho groups

Ortho substituted iodonium salts exclusively formed only the *ipso* substitution product. No cycloadduct was observed in the crude ^{1}H NMR spectrum of any of the three functional groups. The yield of *ortho* NO_2 was lower than that of Me and Cl, which is unusual because NO_2 substituted iodonium salts typically furnish better yields compared to the other

Scheme 4.4: Product distribution when ortho substituted salts are employed



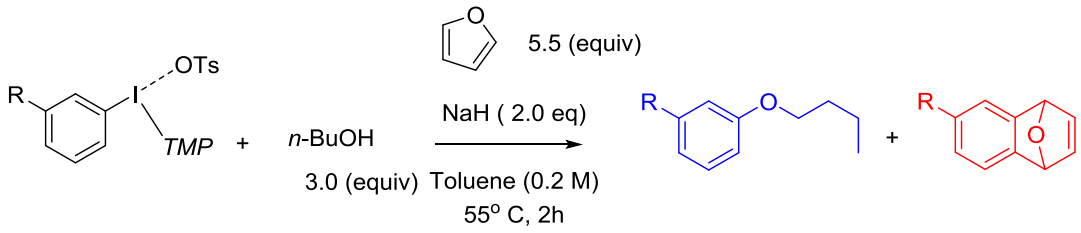
R = Me	66%	0%
Cl	60%	0%
NO_2	46%	0%

functional groups. This disparity might be arising due to the o*rtho* effect [88](interaction of *ortho* groups with the iodonium group favoring reductive elimination).

4.3.2 Effect arising due to meta groups

When the functional groups were situated on the *meta* position, the selectivity of the reaction changed dramatically, especially with Cl and NO_2 groups. Methyl substituted iodonium salt majorly generated *ipso* product (50%) and only 2% and 6% of the cycloadduct isomers. However, in the case of iodonium salts which contain Cl and NO_2 functional groups, cycloaddition products are formed in a significantly higher quantity 43% and 65% respectively than the *ipso* products 23% and 21%.

Scheme 4.5: Product distribution when meta substituted salts are employed



R = Me	50%	2%/6%
Cl	23%	43%
NO_2	21%	65%

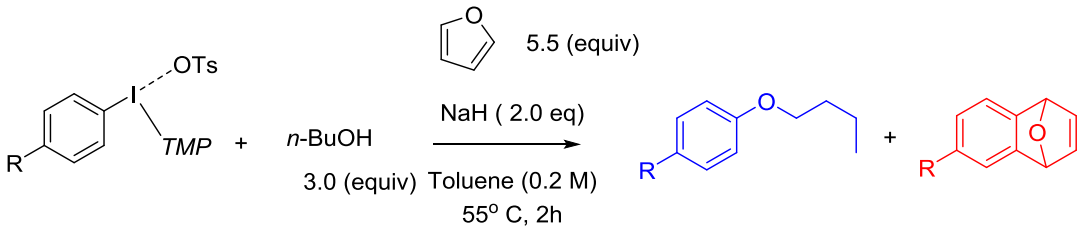
4.3.3 Effect arising due to para groups

Finally, *para* substituted iodonium salts were tested in the reaction, and competition between the two mechanistic pathways was observed for the Me and Cl substituted salts.

[88] Joel Malmgren, Stefano Santoro, Nazli Jalalian, Fahmi Himo* and Olofsson, B., *Chem. Eur. J.*, **2013,** *19*, 10334–10342.

The electronic effects of the NO_2 group may have overridden the formation of aryne in this case yielding only *ipso* substituted product.

Scheme 4.6: Product distribution when para substituted salts are employed



R = Me	50%	11%
Cl	51%	29%
NO_2	66%	0%

Both Me and Cl substituted salts furnished similar yields with respect to *ipso* product however, higher percentage of aryne cycloadduct was observed in the later (29%, compared to 11%).

4.4 Computational Studies are needed (future outlook)

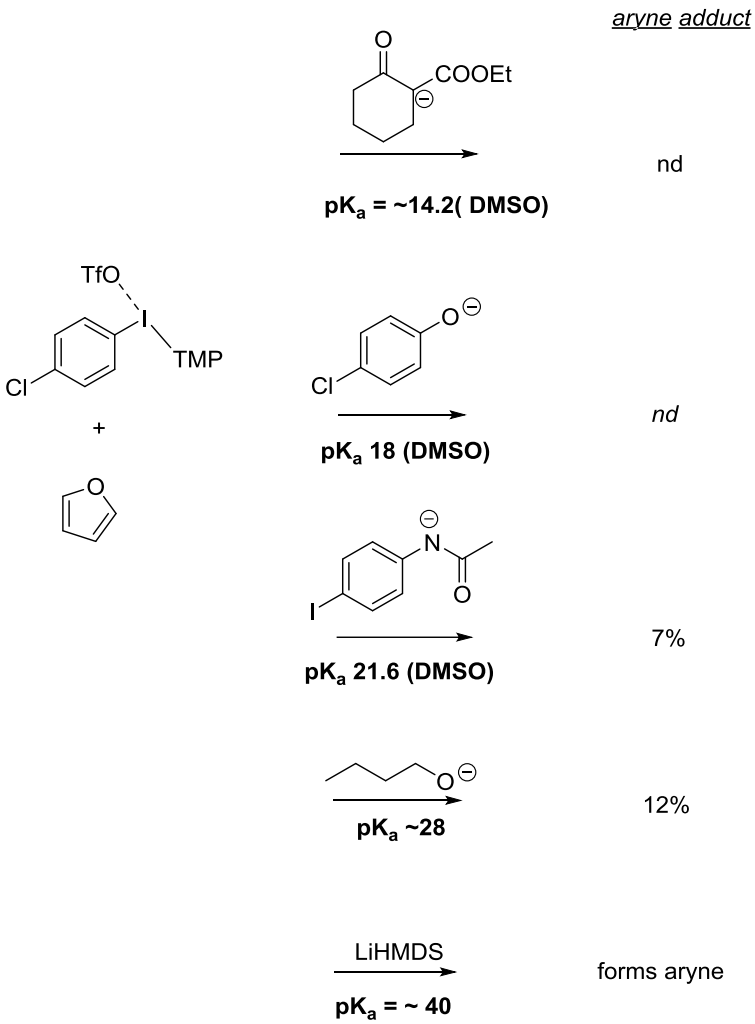
We believe that the selectivity of these reactions can be better explained with the help of computational studies in determining the effect of electronic and steric parameters. They could be playing a huge roll in lowering or raising the energy barriers for the formation of *ipso* or aryne pathways leading to the respective products. With the knowledge gained from these computations we believe that we can design reaction conditions to dictate where the salt should undergo *ipso* or aryne pathway.

4.5 Nature of the Nucleophile and its pK_a effects on the Aryne formation

We have performed a study to understand what nucleophiles actually trigger aryne pathway and also to see if the pK_a of these nucleophiles could be the reason for the C-H deprotonation of iodonium salt. So, we have selected a few reactions reported in the literature of diaryliodonium salts with different types of nucleophiles and added furan as the aryne trap (Scheme 4.7). Interesting observations were made in this study. 4-chlorophenyl(TMP) triflate was chosen as the common iodonium salt in all the cases. Aryne formation was not observed when carbon nucleophiles and phenolic nucleophiles were employed. Amide nucleophiles resulted in the formation of aryne in 7% yield. Alkoxide nucleophiles, as we have observed from our previous study, also gave aryne in 12% yield. Finally, strong base LiHMDS furnished arynes as well. It was interesting to learn that when pK_a values reached around 21, the formation of aryne pathway was triggered and it continued to do so when the pK_a was increased. This study definitely needs more experimental data and different nucleophiles to make conclusive results.

The knowledge gained from this study can be very beneficial to the iodonium salt community to inform the researchers that nature and pK_a of the nucleophiles could be a key parameter to avoid or trigger aryne pathway.

Scheme 4.7: Nature and pK_a of nucleophiles triggering aryne pathway



Chapter 5

Experimental Section

5.1 General Considerations

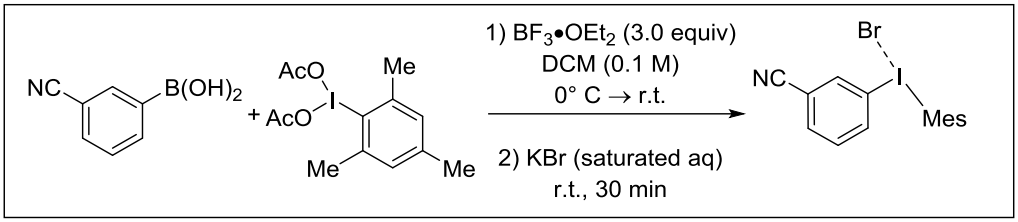
Materials: Commercially available reagents and solvents were used without further purification unless otherwise stated. *tert*-Butyl methyl ether (TBME), dimethylformamide (DMF) and dichloromethane (DCM) were purchased from Acros Organics. Tetrahydrofuran was purchased from Omnisolv. Anhydrous DCM was obtained from Sigma-Aldrich which was dried through an MBRAUN solvent purification system. Arylboronic acids were purchased from either Sigma-Aldrich or Frontier Scientific. Iodobenzene diacetate and iodomesitylene diacetate were purchased from TCI America and stored at 5 °C. BF_3•OEt_2 was purchased from Acros Organics and stored at 5 °C under a nitrogen atmosphere. Alcohols were purchased from Sigma-Aldrich or TCI America. Potassium bromide (KBr) was purchased from Fisher Scientific, sodium triflate (NaOTf) was purchased from TCI America, sodium tetrafluoroborate ($NaBF_4$) was purchased from Sigma-Aldrich. *m*-Chloroperoxybenzoic acid (~ 70% oxidant), sodium hydride and magnesium sulfate were purchased from Sigma-Aldrich. All other materials were prepared by known literature procedures or are described in detail below.

Methods: Reactions performed above ambient room temperature were done so in an oil bath or aluminum block heated externally by a Heidolph MR Hei-Standard heating/stirring mantel equipped with a Heidolph EKT HeiCON temperature control. Crude reaction mixtures were analyzed by ^{1}H NMR or ^{19}F NMR spectroscopy and thin-layer chromatography (TLC) on Selecto Scientific Flexible TLC plates (silica gel 60 Å F-254) and visualized by UV. Crude material was purified by flash column chromatography on Silicycle silica gel SiliaFlash P60, unless otherwise stated. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (with tetramethylsilane as an internal standard) on a Bruker Avance II 400 MHz spectrometer; the following notation is used: br – broad, s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet, dd – doublet of doublets. FTIR spectra were recorded on Thermo Scientific Nicolet iS5 Infra-red spectrometer. High resolution mass spectrometry (HRMS (ESI+)) data were recorded on Thermo Scientific LTQ Orbitrap Mass Spectrometer by electrospray ionization (ESI) and JEOL MSRoute by Positive Electron impact detector (EI^+). Melting points were recorded on Mel-Temp (Thermo scientific) and are reported as uncorrected.

5.2 Synthesis of aryl(mesityl)iodonium bromide salts

5.2.1: Representative procedure A:[1]

Scheme 5.1: Representative procedure A

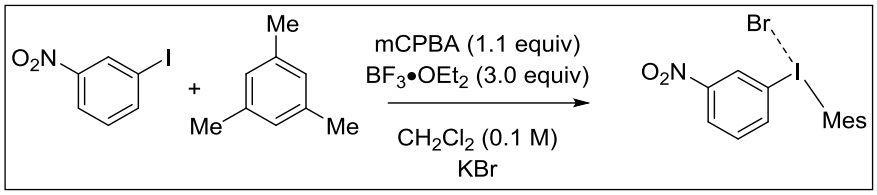


3-Cyanophenylboronic acid (0.8810 g, 6.0 mmol, 1.0 equiv.) was weighed and transferred to a pear-shaped flask equipped with a magnetic stir bar and rubber septa. The flask was flushed with nitrogen and left under a static nitrogen atmosphere. DCM (60 mL) is added via syringe to the arylboronic acid and the solution is cooled to ~ 0° C in an ice-water bath with stirring. BF_3•OEt_2 (0.81 mL, 6.6 mmol, 3.0 equiv.) is added via syringe to the arylboronic acid solution and the reaction mixture was stirred for 10 minutes at 0° C. Iodomesitylene diacetate (2.4035 g, 6.6 mmol, 1.1 equiv.) was weighed and transferred to a separate pear-shaped flask equipped with rubber septa. The flask was flushed with nitrogen and left under a static nitrogen atmosphere. DCM (20 mL) was added to the iodomesitylene diacetate. The iodomesitylene diacetate solution was added to the arylboronic acid/BF_3•OEt_2 solution drop-wise via syringe at ~ 0° C. The reaction mixture was allowed to warm to ambient room temperature and stirred overnight. The septa was removed and an aqueous saturated solution of KBr (100 mL) was added with vigorous stirring for ~ 30 minutes. The biphasic mixture was added to a separatory funnel and the DCM/water layers separated. The water layer was extracted with DCM (3 × 30 mL). The combined DCM layers were dried over $MgSO_4$, filtered, and the DCM removed on a

rotovap. The crude residue was triturated with diethyl ether to yield analytically pure bromo-3-cyanophenyl(mesityl)-λ^3-iodane. See below for yield and characterization data.

5.2.2 Representative procedure B: [90]

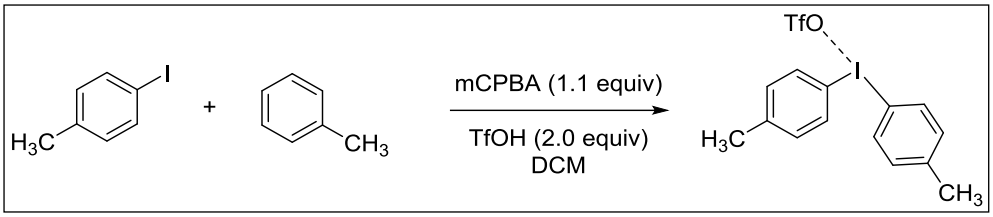
Scheme 5.2: Representative procedure B



Step 1: To a stirred solution of 1-iodo-3-nitrobenzene (2.5055 g, 10.0 mmol, 1.0 equiv.) in DCM (100 mL) was added *m*-CPBA (2.720 g, 11.0 mmol, 1.1 equiv.). The resulting solution was cooled to 0°C. BF_3•OEt_2 (3.7 mL, 30.0 mmol, 3.0 equiv.) is added slowly via syringe to the above solution and the reaction mixture was stirred for 2 hours at 0° C. Mesitylene (1.5 mL, 11.0 mmol, 1.1 equiv.) was added and the reaction mixture was allowed to warm to ambient room temperature and stirred overnight. The septa was removed and an aqueous saturated solution of KBr (200 mL) was added with vigorous stirring for ~ 30 minutes. The biphasic mixture was added to a separatory funnel and the DCM/water layers separated. The water layer was extracted with DCM (3 × 50 mL). The combined DCM layers were dried over $MgSO_4$, filtered, and the DCM removed on a rotovap. The crude residue was triturated with diethyl ether to yield analytically pure bromo-3-nitrophenyl(mesityl)-λ^3-iodane. See below for yield and characterization data.

5.2.3: Representative procedure C:[91]

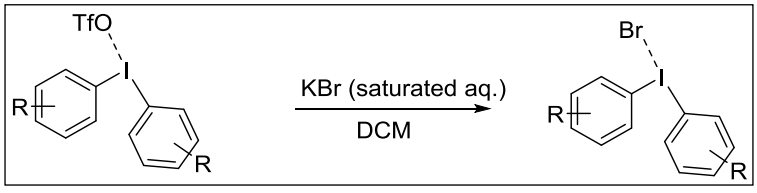
Scheme 5.3: Representative procedure C



To a solution of the 4-iodotoluene (4.3700 g, 20.0 mmol, 1.0 equiv.) and dried *m*-CPBA (3.7900 g, 22.0 mmol, 1.1 equiv.) in DCM (85 mL) at 0 °C was added trifluoromethanesulfonic acid (3.5 mL, 40 mmol, 2.0 equiv.) dropwise over 2 minutes. The ice bath was removed and the reaction stirred for 2 hours at room temperature. It was then cooled to 0 °C and toluene (2.3 mL, 22.0 mmol, 1.1 equiv.) was added dropwise over 2 minutes. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed in vacuo and diethyl ether added. The resulting solid was filtered and washed with diethyl ether to give the iodonium triflate as a solid that was dried under vacuum for 1 hour. See below for yield and characterization data.

5.2.4: Representative procedure D

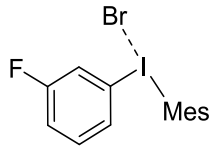
Scheme 5.4: Representative procedure D



To a stirred solution of crude diaryl iodonium triflate in DCM (0.1 M) a saturated solution of KBr was added and stirred for 30 minutes at room temperature. The organic layer was

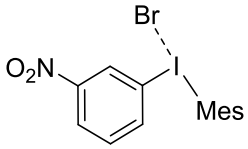
separated and the aqueous layer was extracted with DCM. The combined organic layer is dried over $MgSO_4$ and evaporated on the rotovap. The resulting solid was triturated with diethyl ether and isolated by filtration to give diaryl iodonium bromide. See below for yield and characterization data.

Compound 1.1



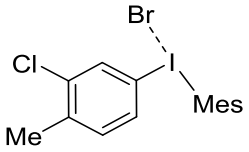
Prepared according to representative procedure A on 10.0 mmol-scale and obtained in 49% isolated yield (2.1000 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 7.86-7.83 (m, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.50-7.38 (m, 2H), 7.16 (s, 2H), 2.58 (s, 6H), 2.27 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 161.9 (d, $J_{C\text{-}F}$ = 252.9 Hz), 142.3, 140.8, 132.9 (d, $J_{C\text{-}F}$ = 7.9 Hz), 129.5 (d, $J_{C\text{-}F}$ = 3.0 Hz), 129.4, 125.8 120.7 (d, $J_{C\text{-}F}$ = 24.8 Hz), 118.9 (d, $J_{C\text{-}F}$ = 7.2 Hz), 118.1 (d, $J_{C\text{-}F}$ = 21.1 Hz), 26.1, 20.4.
^{19}F NMR (377 MHz, DMSO-*d*$_6$): δ (ppm) -108.38
FTIR: 3061**,** 1585, 1468, 1213 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{15}H_{15}FI^+$ $[M - Br]^+$: 341.0197; observed: 341.0214
MP (DCM/Et$_2$O): 126.6 – 128.8 °C

Compound 1.2



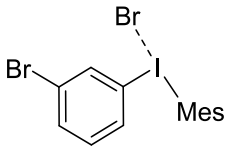
Prepared according to representative procedure B 10.0 mmol-scale and obtained in 72% isolated yield (3.2400g)
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 8.70 (t, *J* = 1.8 Hz, 1H) 8.35-8.33 (m, 1H), 8.10-8.08 (m, 1H), 7.68 (t, *J* = 8.8 Hz, 1H), 7.20 (s, 2H), 2.60 (s, 6H) 2.29 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 148.3, 142.6, 140.9, 138.9, 132.3, 129.5, 128.0, 125.7, 125.5, 119.2, 26.2, 20.4.
FTIR: 3106, 2223, 1524, 1346, 1293 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{15}H_{15}INO_2^+$ $[M - Br]^+$: 368.0142; observed: 368.0157
MP (DCM/Et$_2$O): 140.5 – 142.2 °C

Compound 1.3



Prepared according to representative procedure A on 5.0 mmol-scale and obtained in 87% isolated yield (1.9659 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): 8.01 (d, *J* = 1.93 Hz, 1H), 7.65-7.63 (dd, *J* = 6.5 Hz, 1.6 Hz, 1H), 7.39 (d, *J* = 8.34 Hz, 1H), 7.16 (s, 2H) 2.58 (s, 6H), 2.31 (s, 3H), 2.27 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 142.3, 140.8, 139.1, 134.9, 133.5, 133.2, 132.1, 129.4, 125.4, 115.3, 26.1, 20.4, 19.3
FTIR: 2950, 2920, 1465, 1055 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{16}H_{17}ClI^+$ [M – Br] $^+$: 371.0058; observed: 371.0075
MP (DCM/Et$_2$O): 151.3 – 153.9 °C

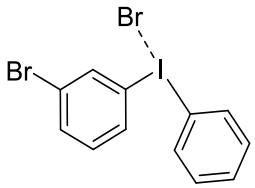
Compound 1.4 - Mes



Prepared according to representative procedure A on 10.0 mmol-scale and obtained in 71% isolated yield (3.4260 g). The ^{1}H NMR spectra of the corresponding triflate and tetrafluoroborate counter ions are consistent with that of the bromide salt.
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 8.15 (t, *J* = 1.6 Hz, 1H), 7.74 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.17 (s, 2H), 2.60 (s, 6H), 2.29 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 142.4, 140.9, 135.4, 133.8, 133.1, 132.2, 129.5, 125.4, 123.1, 119.3, 26.1, 20.4
FTIR : 2976, 2936, 1587, 1474 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{15}H_{15}BrI^+$ [M – Br] $^+$: 400.9396; observed: 400.9418
MP (DCM/Et$_2$O): 145.4 – 146.8 °C

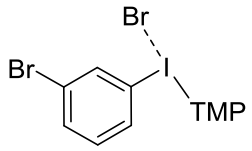
The corresponding compounds with triflate and tetrafluoroborate counter ions had identical ^{1}H NMR and ^{13}C NMR spectra.
^{19}F NMR (377 MHz, DMSO-*d*$_6$) of the OTf: δ (ppm) -77.75
^{19}F NMR (377 MHz, DMSO-*d*$_6$) of the BF$_4$: δ (ppm) -148.26

Compound 1.4 – Ph



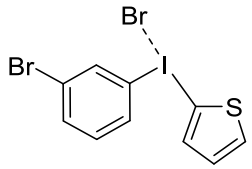
Prepared according to representative procedure A using benzene diacetate on 1.0 mmole scale and obtained in 83% isolated yield (0.03806g).
^{1}H NMR (400 MHz, DMSO) δ 8.59 (t, *J* = 1.6 Hz, 1H), 8.28 (t, *J* = 8.5 Hz, 3H), 7.87 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.49 (dd, J = 14.9, 6.9 Hz, 1H)
^{13}C NMR (100 MHz, DMSO) δ 136.8, 135.1, 134.9, 133.9, 133.3, 132.1, 131.7, 123.1, 116.9, 116.7
FTIR: 1238, 11673, 1026, 769 cm^{-1}
HRMS (ESI^{+}): Calculated for [M – Br] $^{+}$: 358.8926; observed: 358.8935
MP (DCM/Et$_2$O): 166^{o}C -169 ^{o}C

Compound 1.4 - TMP



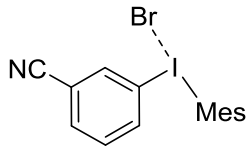
Prepared according to representative procedure F and converted to bromide salt using representative procedure D on 2 mmol scale and obtained in 17% isolated yield (0.1516g)
^{1}H NMR (400 MHz, DMSO) δ 8.11 (t, *J* = 1.8 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.76 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 6.44 (s, 2H)
^{13}C NMR (101 MHz, DMSO) δ 165.7, 159.1, 135.7, 133.7, 132.9, 132.6, 122.6, 119.0, 91.9, 90.4, 57.1, 55.9
FTIR: 2948, 2839, 1581, 1453, 1221, 1122, 769 cm^{-1}
HRMS (ESI^{+}): Calculated for [M – Br] $^{+}$: 448.9243; observed: 448.9234
MP (DCM/Et$_2$O): 175^{o}C -179 ^{o}C

Compound 1.4 - Th



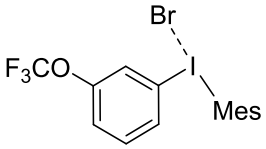
Prepared according to representative procedure F and converted to bromide salt using representative procedure D on 2 mmol scale and obtained in 53% isolated yield (0.5611g)
^{1}H NMR (400 MHz, DMSO) δ 8.50 (t, *J* = 1.8 Hz, 1H), 8.26 – 8.17 (m, 1H), 8.03 – 7.93 (m, 1H), 7.89 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.48 – 7.38 (m, 1H), 7.18 – 7.08 (m, 1H)
^{13}C NMR (100 MHz, DMSO) δ 139.1, 136.2, 136.0, 134.1, 133.2, 132.9, 129.1, 122.6, 122.6, 106.3
FTIR: 1224, 777 cm^{-1}
HRMS (ESI^{+}): Calculated for [M – Br] $^{+}$: 364.8491; observed: 364.8495
MP (DCM/Et$_2$O): 149^{o}C -159 ^{o}C

Compound 1.5



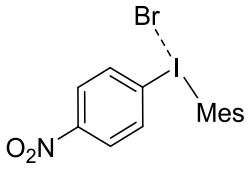
Prepared according to representative procedure A on 6.0 mmol-scale and obtained in 20% isolated yield (0.5100 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 8.49 (s, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 7.62 (t, *J* = 8.3 Hz, 1H), 7.19 (s, 2H), 2.58 (s, 6H), 2.28 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 142.4, 140.9, 138.1, 137.01, 134.6, 131.9, 129.5, 125.6, 119.1, 117.0, 113.5, 26.2, 20.4.
FTIR: 3020, 2226, 1457 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{16}H_{15}IN^+$ [M – Br] $^+$: 348.0244; observed: 348.0259
MP (DCM/Et$_2$O): 138.8 – 140.0 °C

Compound 1.6



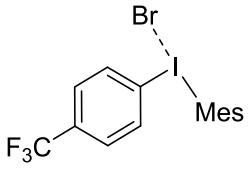
Prepared according to representative procedure A on 4.8 mmol-scale and obtained in 51% isolated yield (1.200 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 8.00 (s, 1H), 7.77-7.74 (m, 1H), 7.59 (m, 2H), 7.18 (s, 2H), 2.59 (s, 6H), 2.28 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 148.6, 142.4, 140.8, 132.9, 132.2, 129.5, 126.2, 125.76, 123.5, 119.8 (q, $J_{C\text{-}F}$ = 254.7 Hz), 119.2, 26.1, 20.4.
^{19}F NMR (377 MHz, DMSO-*d*$_6$): δ (ppm) -57.02
FTIR: 2924, 1579, 1468, 1257, 1218, 1202, 1163 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{16}H_{15}F_3IO^+$ [M – Br] $^+$: 407.0114; observed: 407.0130
MP (DCM/Et$_2$O): 155.5 – 158.0 °C

Compound 1.7



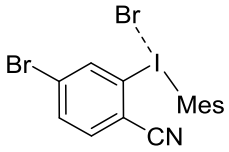
Prepared according to representative procedure C using mesitylene instead of toluene and converted to bromide salt using representative D on 4.1 mmol-scale and obtained in 79% isolated yield (1.4480 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 8.21 (d, *J* = 9.2 Hz, 2H), 8.10 (d, *J* = 9.1 Hz, 2H), 7.20 (s, 2H), 2.59 (s, 6H), 2.30 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 148.7, 142.6, 140.9, 134.8, 129.6, 125.7, 125.4, 125.1, 26.1, 20.4.
FTIR: 3084, 3047, 1532, 1354 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{15}H_{15}INO_2^+$ [M – Br] $^+$: 368.0142; observed Mass: 368.0157
MP (DCM/Et$_2$O): 144.0 – 145.0 °C

Compound 1.8



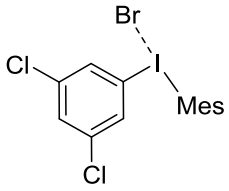
Prepared according to representative procedure A on 3.7 mmol-scale and obtained in 81% isolated yield (1.4157 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 8.07 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.20 (s, 2H), 2.59 (s, 6H), 2.29 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 142.5, 140.9, 134.4, 130.8 (q, $J_{C\text{-}F}$ = 31.7 Hz), 129.5, 127.8 (q, $J_{C\text{-}F}$ = 3.7 Hz), 125.5, 123.6 (q, $J_{C\text{-}F}$ = 270.5 Hz), 123.1, 26.1, 20.4.
^{19}F NMR (377 MHz, DMSO-*d*$_6$): δ (ppm) -61.61
FTIR: 2920, 1593, 1329, 1127, 1066, 1002 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{16}H_{15}F_3I^+$ [M – Br] $^+$ 391.0165; observed: 391.0183
MP (DCM/Et$_2$O): 162.0 – 162.5 °C

Compound 1.9



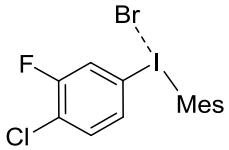
Prepared according to general procedure A on 5.0 mmol-scale and obtained in 82% isolated yield (1.9326 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 8.36 (dd, *J* = 23.3, 1.2 Hz, 1H), 8.05 – 7.95 (m, 2H), 7.17 (s, 2H), 3.32 (s, 1H), 2.67 (s, 6H), 2.28 (s, 3H).
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 142.5, 141.1, 138.4, 136.4, 134.9, 129.7, 128.6, 126.2, 125.3, 117.6, 115.1, 26.2, 20.3,
FTIR: 2976, 2947, 2288, 1444 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{16}H_{17}ClIO^+$ [M – Br] $^+$: 425.9348; observed: 425.9347
MP (DCM/Et$_2$O): 161.0 – 164.0 °C

Compound 1.10



Prepared according to representative procedure A on 3.2 mmol-scale and obtained in 40% isolated yield (0.6036 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 7.86 (d, *J* = 1.8 Hz, 2H), 7.8 (t, *J* = 1.2 Hz, 1H), 7.18 (s, 2H), 2.60 (s, 6H), 2.29 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 142.5, 140.9, 135.5, 131.4, 130.8, 129.5, 125.8, 120.7, 26.2, 20.4
FTIR: 3042 1577, 1574, 1404 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{15}H_{14}Cl_2I^+$ [M – Br] $^+$: 390.9512; observed: 390.9533
MP (DCM/Et$_2$O): 143.0 – 147.0 °C

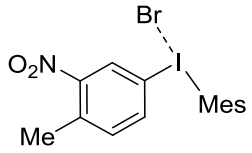
Compound 1.11



Prepared according to representative procedure A on 3.9 mmol-scale and obtained in 79% isolated yield (1.4395 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 8.22-8.20 (dd, *J* = 4.7 Hz, 2.3 Hz, 1H), 7.78-7.75 (m, 1H), 7.47 (t, *J* = 9.0 Hz, 1H), 7.16 (s, 2H), 2.59 (s, 6H), 2.28 (s, 3H)

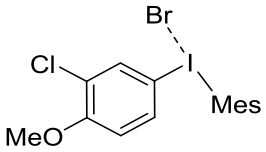
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 158.5 (d, J = 251.1 Hz), 142.4, 140.8, 135.5, 134.5 (d, $J_{C\text{-}F}$ = 8.11 Hz), 129.4, 125.9, 121.8 (d, $J_{C\text{-}F}$ = 18.54 Hz), 119.6 (d, $J_{C\text{-}F}$ = 22.0 Hz), 113.7, 26.1, 20.4
^{19}F NMR (377 MHz, DMSO-*d*$_6$): δ (ppm) -111.31
FTIR: 3011, 1474, 1263, 1063 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{15}H_{14}ClFI^+$ [M – Br] $^+$: 374.9807; observed: 374.9826
MP (DCM/Et$_2$O): 142.5 – 146.8 °C

Compound 1.12



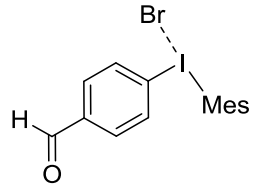
Prepared according to representative procedure A on 5.0 mmol-scale and obtained in 46% isolated yield (1.0523 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 8.5 (d, *J* = 1.9 Hz, 1H), 7.97-7.94 (dd, *J* = 6.4 Hz, 2.0 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.18 (s, 2H), 2.60 (s, 6H), 2.48 (s, 3H), 2.29 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 149.5, 142.4, 140.9, 137.4, 135.7, 135.2, 129.5, 129.1, 125.6, 115.6, 26.18, 20.4, 19.1
FTIR: 3028, 2365, 1524, 1340 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{16}H_{17}INO_2^+$ [M – Br] $^+$: 382.0299; observed: 382.0316
MP (DCM/Et$_2$O): 135.8 – 138.8 °C

Compound 1.13



Prepared according to general procedure A on 5.0 mmol-scale and obtained in 82% isolated yield (1.9326 g).
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ (ppm) 8.00 (t, *J* = 2.0 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.19-7.15 (m, 3H), 3.87 (s, 3H), 2.59 (s, 6H), 2.27 (s, 3H)
^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ (ppm) 156.6, 142.3, 140.8, 134.6, 134.4, 129.4, 125.28, 122.9, 115.31, 106.4, 56.4, 26.1, 20.3
FTIR: 3014, 1568, 1304, 1279, 1063 cm^{-1}
HRMS (ESI$^+$): Calculated for $C_{16}H_{17}ClIO^+$ [M – Br] $^+$: 387.0007; observed: 387.0025
MP (DCM/Et$_2$O): 151.0 – 156.0 °C

Compound 1.14

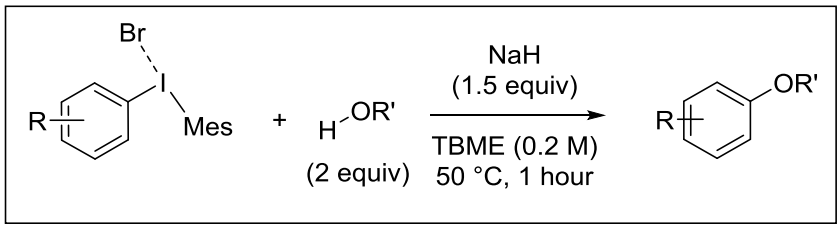


Prepared from the corresponding aryl boronic acid on a 5.0 mmol-scale and obtained in 81% isolated yield as a white powder (1.7 g).
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.08 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.18 (s, 2H), 2.59 (s, 6H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d_6): δ 192.4, 142.1, 140.7, 137.0, 134.2, 131.4, 129.4, 126.3, 125.8, 26.1, 20.4.
FTIR: 3102, 1699, 1264, 728 cm−1.
HRMS (ESI) : [M − Br]+ calculated for $C_{16}H_{16}IO^{+}$ 351.0240; observed 351.0255.
Melting point (DCM/Et_2O): 173−177 °C.

5.3: Synthesis of alkyl-aryl ethers

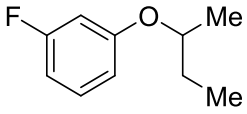
5.3.1: General procedure for the synthesis of alkyl-aryl ethers E:

Scheme 5.5: General procedure for the synthesis of alkyl-aryl ethers E



Sodium hydride (0.75 mmol, 1.5 equiv. based on 60 wt % dispersion in mineral oil) was weighed out to air and transferred to an oven-dried vial equipped with a magnetic stir bar. The vial was sealed with a cap and Teflon-lined septum and purged with nitrogen. A solution of the alcohol (1 mmol, 2 equiv) in TBME (2.5 mL) was added dropwise to the sodium hydride and the cloudy white mixture stirred at ambient room temperature for at least 15 min. Compound 1 (0.5 mmol, 1 equiv) was powdered into the reaction vial. The vial was sealed with a solid cap and placed into a preheated (50 °C) aluminum block for 1 h. The reaction was then removed from the heat and quenched with 5 mL of a saturated solution of ammonium chloride. The biphasic mixture was transferred to a separatory funnel and the aqueous layer extracted with DCM (3 × 10 mL). The combined DCM layers were dried over MgSO4, filtered, and the DCM removed on a rotary evaporator. The crude residue was purified by flash column chromatography on silica gel (see below for specific eluent composition). In cases where duplicate experiments were performed on the same mmol-scale, the range of yields and average yield are reported; the average yield is reported.

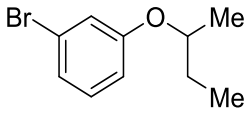
Compound 1.15



Reaction conducted according to general procedure E on 0.1 mmol-scale. Due to the volatility of this compound, the yield was obtained from the crude ^{1}H NMR spectra versus 1,3,5-trimethoxybenzene as an internal standard in 88% and 86% yield (87% average of two runs). This compound is commercially available, CAS: 1340125-14-5.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23-7.67 (m, 1H), 6.68-6.53 (m, 3H), 4.31-4.23 (m, 1H), 1.80-1.57 (m, 2H), 1.29 (d, *J* = 6.0 Hz, 3H), 0.98 (t, *J* = 8.5 Hz, 3H)

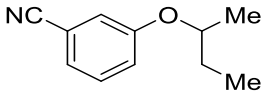
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.8 (d, J_{C-F} = 243.2 Hz) 160.7 (d, J_{C-F} = 11.4 Hz), 130.0 (d, J_{C-F} = 9.2 Hz) 110.4 (d, J_{C-F} = 2.9 Hz), 107.2 (d, J_{C-F} = 21.2 Hz), 102.1 (d, J_{C-F} = 24.9 Hz), 72.3, 34.5, 24.8, 18.5
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.99
R_f : 0.64 in 100% hexane

Compound 1.16



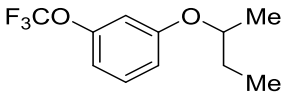
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 78% (0.0899g) and 67% (0.0765g) isolated yields (72% average of two runs). This compound is commercially available, CAS: 1042560-11-1.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.13 (t, *J* = 8.1 Hz, 1H), 7.05-7.03 (m, 2H), 6.83-6.80 (m, 1H), 4.30-4.23 (m, 1H), 1.79-1.56 (m, 2H), 1.28 (d, *J* = 6.3 Hz, 3H), 0.97 (t, *J* = 8.1 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.1, 130.5, 123.4, 122.7, 119.0, 114.7, 75.4, 29.1, 19.1, 9.7
R_f : 0.42 in 100% hexane

Compound 1.17



Prepared according to general procedure E on 0.5 mmol-scale and obtained in 70% (0.0614 g) and 65% (0.057g) isolated yields (67% average of two runs). This compound is commercially available, CAS: 902093-86-1
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (t, *J* = 8.1 Hz, 1H), 7.20-7.18 (m, 1H), 7.12-7.08 (m, 2H), 4.34-4.26 (m, 1H), 1.80-1.58 (m, 2H), 1.30 (d, *J* = 6.1 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.1, 130.5, 123.4, 122.7, 119.0, 114.7, 75.4, 29.1, 19.1, 9.7 (one signal missing due to overlapping peaks)
R_f : 0.25 in 5% diethyl ether/hexane

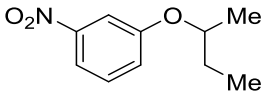
Compound 1.18



Prepared according to general procedure E on 0.5 mmol-scale and obtained in 47% (0.0528g) isolated yield. Due to the volatility of this compound, the yield was obtained

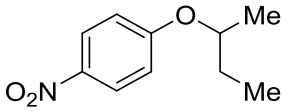
from the crude ^{1}H NMR spectra versus 1,3,5-trimethoxybenzene as an internal standard in 82% and 79% (80% average of two runs).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24 (t, *J* = 16.5 Hz, 1H), 6.81-6.73 (m, 3H), 4.31-4.24 (m, 1H), 1.79-1.57 (m, 2H) 1.29 (d, *J* = 6.2 Hz, 3H) 0.97 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.3, 150.2, 130.1, 120.1 (q, $J_{C\text{-}F}$ = 260.8 Hz) 114.0, 112.5, 108.8, 75.4, 29.0, 19.0, 9.7
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -57.75
FTIR: 2976, 2936, 1589, 1260, 1008 cm^{-1}
HRMS (EI^+): Calculated; 234.08677; observed: 234.08763
R_f : 0.42 in 100% hexane

Compound 1.19



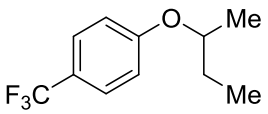
Prepared according to general procedure E on 1.0 mmol-scale and obtained in 79% (0.1537g) and on 5.0 mmole and obtained in 76% (0.7820g) isolated yields (77% average of two runs).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.78-7.75 (m, 1H), 7.70 (t, *J* = 2.3Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.20-7.17 (m, 1H), 4.42-4.34 (m, 1H), 1.82-1.60 (m, 2H), 1.32 (d, *J* = 6.2 Hz, 3H), 0.98 (t, *J* =5.5 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 158.8, 149.2, 129.9, 122.6, 115.3, 109.9, 75.9, 29.0, 18.9, 9.6
FTIR: 2976, 2936, 1529, 1349, 1150 cm^{-1}
HRMS (EI^+): Calculated: 195.0895; observed: 195.0903
R_f : 0.41 in 50% diethyl ether/hexane

Compound 1.20



Prepared according to general procedure E on 0.5 mmol-scale and obtained in 77% (0.0754g) and 83% (0.0833g) isolated yields (80% average of two runs). Spectroscopic data was consistent with that previously reported.[92]
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17 (d, *J* = 9.3 Hz, 2H), 6.91 (d, *J* = 9.3 Hz, 2H), 4.45-4.37 (m, 1H), 1.83-1.61 (m, 2H), 1.33 (d, *J* = 6.2 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.4, 135.3, 120.6, 114.6, 75.8, 29.0, 19.0, 9.6
R_f : 0.46 in 5% Ether/Hexane

Compound 1.21



Prepared according to general procedure E on 0.5 mmol-scale and obtained 39% (0.0422g) isolated yield. Due to the volatility of this compound the yield was obtained from the crude ^{1}H NMR spectra versus 1,3,5-trimethoxybenzene as an internal standard in 67% and 68% (67% average of two runs). Spectroscopic data was consistent with that previously reported.[93]

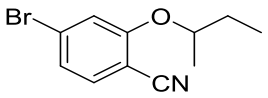
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.40-4.32 (m, 1H), 1.82-1.59 (m, 2H), 1.31 (d, *J* = 6.0 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H),

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.8, 129.4, 126.8 (q, $J_{C\text{-}F}$ = 3.8 Hz), 122.3 (q, $J_{C\text{-}F}$ = 32.3 Hz), 115.4, 75.2, 29.0, 19.0, 9.7

^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -61.45

R_f : 0.44 in 100% hexane

Compound 1.22



Prepared according to general procedure E on 0.4 mmol-scale and obtained in 69% (0.0751 g) and 0.5 mmole scale and obtained 70% (0.0882g) isolated yields (69% average of two runs).

^{1}H NMR (400 MHz, CDCl3) δ 7.43 – 7.36 (m, 1H), 7.14 – 7.12 (m, 1H), 7.12 – 7.08 (m, 1H), 4.40 (m, 1H), 1.92 – 1.63 (m, 2H), 1.36 (d, J = 6.1 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H).

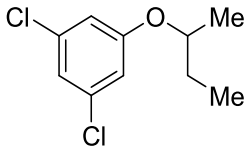
13C NMR (101 MHz, CDCl3) δ 160.5, 134.5, 128.5, 123.8, 117.1, 115.9, 101.9, 76.7, 28.9, 18.9, 9.5,

FTIR: 2976, 2936, 2278, 1444, 1220 1070 cm^{-1}

HRMS (EI^+): Calculated: 253.0102; observed: 253.0102

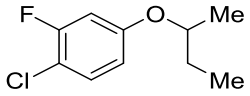
R_f : 0.40 in 5% diethyl ether/hexane

Compound 1.23



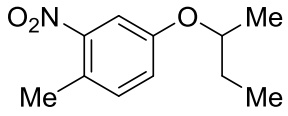
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 72% (0.0787 g) and 82% (0.0903g) isolated yields (77% average of two runs).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.06 (t, *J* = 1.2 Hz, 1H), 6.98 (d, *J* = 1.9 Hz, 2H), 4.50-4.43 (m, 1H), 1.67-1.49 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.4, 135.3, 120.6, 114.6, 75.5, 29.0, 19.0, 9.6
FTIR: 2976 2936 1588 1444 1230 1090 cm^{-1}
HRMS (EI^+): Calculated: 218.0265; observed: 218.0207
R_f : 0.48 in 100% hexane

Compound 1.24



Prepared according to general procedure E on 0.5 mmol-scale and obtained in 68% (0.0700g) and 77% (0.078g) isolated yields (72% average of two runs). This compound is commercially available, CAS: 1548170-27-9
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.01 (t, *J* = 3.7 Hz, 1H), 6.92-6.90 (m, 1H), 6.75-6.71 (m, 1H), 4.22-4.15 (m, 1H), 1.73-1.55 (m, 2H), 1.27 (d, *J* = 6.0 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.4 (d, $J_{C\text{-}F}$ = 2.1 Hz), 152.5 (d, $J_{C\text{-}F}$ = 241.1 Hz), 121.0 (d, $J_{C\text{-}F}$ = 20.4 Hz), 117.7, 116.7 (d, $J_{C\text{-}F}$ = 22.1 Hz), 115.6 (d, $J_{C\text{-}F}$ = 6.7 Hz), 76.3, 29.0, 19.0, 9.7
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.31
R_f : 0.26 in 100% hexane

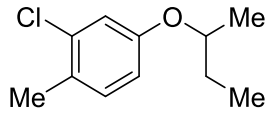
Compound 1.25



Prepared according to general procedure E on 0.5 mmol-scale and obtained 79% (0.0835g) and 84% (0.0874g) isolated yields (81% average of two runs).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (d, *J* = 2.8 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.20-7.18 (dd, *J* = 7.4 Hz, 2.3 Hz, 1H), 4.48-4.10 (m, 1H), 2.39 (s, 3H), 1.70-1.51 (m, 2H),1.21 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H)

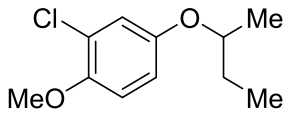
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.7, 149.4, 133.4, 125.1, 121.4, 111.1, 75.8, 29.0, 19.7, 19.0, 9.6
FTIR: 2970, 2934, 1710, 1626, 1527, 1243, 1024 cm^{-1}
HRMS (EI^+): Calculated: 209.1051; observed: 209.1053
R_f : 0.29 in 2.5% diethyl ether/hexane

Compound 1.26



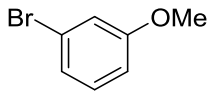
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 70% (0.0702g) and 1.0 mmole and obtained in 65% (0.1321g) isolated yields (67% average of two runs).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.09 (d, *J* = 8.6 Hz, 1H), 6.91 (d, *J* = 2.6 Hz, 1H), 6.72-6.69 (dd, *J* = 5.6 Hz, 2.0 Hz, 1H), 4.25-4.21 (m, 1H), 2.29 (s, 3H), 1.76-1.56 (m, 2H), 1.26 (d, *J* = 6.0 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 156.9, 134.5, 131.1, 127.6, 116.5, 114.6, 75.5, 29.1, 19.1, 19.0, 9.74
FTIR: 2975, 2935, 1609, 1493, 1240 1040 cm^{-1}
HRMS (EI^+): Calculated: 198.0811; observed: 198.0810

Compound 1.27



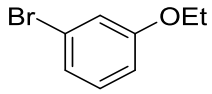
Prepared according to general procedure F on 0.35 mmol-scale and obtained in 67% (0.0508g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.02 (d, *J* = 9.1 Hz 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 6.87-6.84 (dd, *J* = 6.0 Hz, 2.1 Hz, 1H), 4.30-4.23 (m, 1H), 3.77 (s, 3H), 1.65-1.46 (m, 2H), 1.17 (d, *J* = 6.0 Hz, 3H), 0.89 (t, *J* = 7.8 Hz, 3H)
^{13}C NMR (100 MHz, DMSO): δ (ppm) 156.6, 135.5, 131.5, 126.7, 115.9, 114.6, 74.5, 28.4, 18.3, 18.5, 9.3
FTIR: 2973, 2936, 2838, 1497, 1272, 1211, 1059
HRMS (EI^+): Calculated: 214.0760; observed: 214.0762
R_f : 0.45 in 10% Ether/ Hexane

Compound 1.28



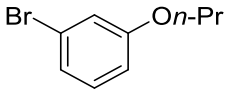
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 77% (0.073g) and 71% (0.0666g) isolated yields (74% average of two runs). Spectroscopic data was consistent with that previously reported.[94]
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.13 (t, *J* = 5.2 Hz, 1H), 7.08-7.04 (m, 2H) 6.83-6.80 (m, 1H) 3.70 (s, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.3, 130.5, 123.7, 122.8, 117.1, 113.0, 55.4
R_f : 0.24 in 100% hexane

Compound 1.29



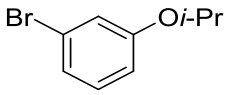
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 78% (0.0837g) and 77% (0.0774g) isolated yields (77% average of two runs). Spectroscopic data was consistent with that previously reported.[95]
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.11 (t, *J* = 16.1 Hz, 1H), 7.06-7.03 (m, 2H), 6.82-6.79 (m, 1H) 4.01-3.96 (q, *J* = 7.0 Hz, 2H) 1.39 (t, *J* = 7.0 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.7, 130.4, 123.5, 122.7, 117.6, 113.5, 63.6, 14.7
R_f : 0.38 in 100% hexane

Compound 1.30



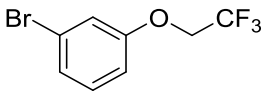
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 77% (0.084g) and 81% (0.0881g) isolated yields (79% average of two runs). This compound is commercially available, CAS: 149557-17-5.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.10 (t, *J* = 8.3 Hz, 1H), 7.05-7.03 (m, 2H), 6.82-6.80 (m, 1H) 3.87 (t, *J* = 6.6 Hz, 2H) 1.89-1.73 (m, 2H) 1.01 (t, *J* = 7.4 Hz, 3H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.9, 130.4, 123.5, 122.7, 117.7, 113.5, 69.7, 22.4, 10.4
R_f : 0.39 in 100% hexane

Compound 1.31



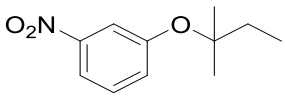
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 81% (0.087g) and 86% (0.0933g) isolated yields (83% average of two runs). Spectroscopic data was consistent with that previously reported[96]
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.10 (t, *J* = 8.3 Hz, 1H), 7.05-7.02 (m, 2H) 6.81-6.78 (m, 1H) 4.54-4.45 (septet, *J* = 6.23 Hz, 1H) 1.31 (d, *J* = 6.24 Hz, 6H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 158.7, 130.5, 123.5, 122.7, 119.0, 114.7, 70.2, 21.9
R_f : 0.48 in 100% Hexane

Compound 1.32



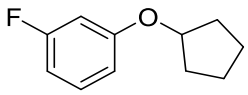
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 65% (0.0832g) and 65% (0.0832g) isolated yields (65% average of two runs). This compound is commercially available, CAS: 888327-41-1.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.21-7.18 (m, 2H), 7.12-7.11 (m, 1H) 6.91-6.86 (m, 1H), 4.36-4.30 (m, 2H)
^{13}C NMR (100 MHz, $CDCl_3$): 157.9**,** 130.8, 127.9, 125.7, 123.0, 123.8 (q, J = 277.8 Hz), 118.4, 65.9 (q, *J* = 35.6 Hz),
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -73.94
R_f : 0.34 in 100% hexane

Compound 1.33



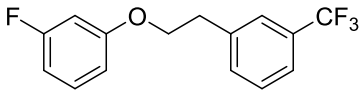
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 44% (0.0463g) and 45% (0.0474g) isolated yields (44% average of two runs).
^{1}H NMR (400 MHz, CDCl3) δ 7.92 (dd, J = 8.2, 2.2 Hz, 1H), 7.82 (t, J = 2.2 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 7.33 – 7.27 (m, 1H), 1.79 – 1.65 (m, 2H), 1.33 (s, 6H), 1.02 (t, J = 7.5 Hz, 3H).
^{13}C NMR (101 MHz, CDCl3): δ 156.5, 148.7, 129.7, 129.4, 118.0, 117.7, 82.6, 34.5, 26.0, 8.5.
FTIR: 2970, 2934, 1710, 1243, 1026 m^{-1}
HRMS (EI+): Calculated : 209.1051; observed: 209.1048
R_f : 0.32 in 10% Ether/ Hexane

Compound 1.34



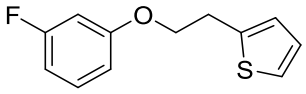
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 69% (0.0625g) and 74% (0.0670g) isolated yields (72% average of two runs). This compound is commercially available, CAS: 1344108-50-4.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.20-7.14 (m, 1H), 6.64-6.55 (m, 3H), 4.73-4.68 (m, 1H), 1.93-1.73 (m, 6H) 1.66-1.55 (m, 2H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.6 (d, J_{C-F}=245.2 Hz), 159.5 (d, J_{C-F}= 10.8 Hz), 130.0 (d, J_{C-F}=10.3 Hz), 111.3 (d, J_{C-F}=2.8 Hz), 106.9 (d, J_{C-F}=21.9), 103.0 (d, J_{C-F}=24.2 Hz), 79.7, 32.7, 24.0
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.98
R_f : 0.32 in 100% hexane

Compound 1.35



Prepared according to general procedure E on 0.5 mmol-scale and obtained 78% (0.1136g) and 86% (0.1227g) isolated yields (82% average of two runs).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57-7.42 (m, 4H), 7.25-7.19 (m, 1H), 6.70-6.60 (m, 3H) 4.18 (t, J = 6.8 Hz, 2H) 13.16 (t, J = 6.7 Hz, 2H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.6 (d, J_{C-F} = 245.6 Hz), 159.5 (d, J_{C-F} = 10.3 Hz), 139.1, 132.4 (d, J_{C-F} = 1.4 Hz), 130.8 (q, J = 31.8 Hz), 130.2 (d, J_{C-F} = 9.5 Hz), 128.9, 125.7 (q, J_{C-F} = 3.7 Hz), 124.3 (q, J_{C-F} = 274.3 H), 123.4 (q, J_{C-F} = 3.6 Hz), 110.3 (d, J_{C-F} = 3.1 Hz), 107.6 (d, J_{C-F} = 21.2 Hz), 102.3 (d, J_{C-F} = 24.7 Hz), 68.3, 35.4
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.59, -62.60
FTIR: 3086, 2961, 2936, 2867, 1607, 1488, 1124, 1066 cm^{-1}
HRMS (EI^+): Calculated: 284.0824; observed: 284.0822
R_f : 0.28 in 100% hexane

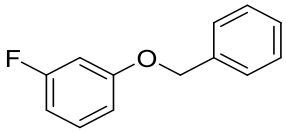
Compound 1.36



Prepared according to general procedure E on 0.5 mmol-scale and obtained in 76% (0.086g) and 78% (0.090g) isolated yields (77% average of two runs). This compound is commercially available, CAS: 1477672-83-5.
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.22-7.14 (m, 2H), 6.95-6.89 (m, 2H), 6.69-6.59 (m, 3H), 4.15 (t, J = 6.6 Hz, 2H), 3.29 (t, J = 6.7 Hz, 2H)

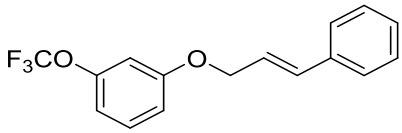
^{13}C NMR (100 MHz, $CDCl_3$): 163.7 (d, J_{C-F} = 252.8 Hz), 159.9 (d, J_{C-F} = 11.4 Hz), 140.0 130.2 (d, J_{C-F} =10.3 Hz), 126.8, 125.5, 124.0, 110.3 (d, J_{C-F} = 2.4 Hz), 107.6 (d, J_{C-F} = 21.5 Hz), 102.3 (d, J_{C-F} = 25.0 Hz), 68.6, 29.8
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.63
R_f : 0.18 in 100% hexane

Compound 1.37

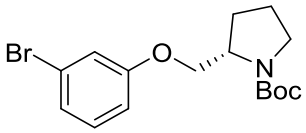


Prepared according to general procedure E on 0.5 mmol-scale and obtained in 77% (0.0804g) and 79% (0.080g) isolated yields (78% average of two runs). Spectroscopic data was consistent with that previously reported.[97]
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41-7.28 (m, 5H), 7.22-7.16 (m, 1H), 6.75-6.62 (m, 3H), 5.00 (s, 2H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 163.7 (d, J_{C-F} = 246.4 Hz), 160.1 (d, J_{C-F} = 10.5 Hz), 136.4, 130.2 (d, 1C, J_{C-F} = 10.3 Hz), 128.6, 128.1, 127.4, 110.6 (d, J_{C-F} = 2.8 Hz), 107.7 (d, J_{C-F} = 22.4 Hz), 102.6 (d, J_{C-F} = 24.7 Hz), 70.2.
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -111.50
R_f : 0.22 in 100% hexane

Compound 1.38

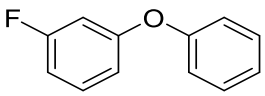


Prepared according to general procedure E on 0.5 mmol-scale and obtained in 73% (0.112g) and 67% (0.0996g) isolated yields (70% average of two runs).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41-7.38 (m, 2H), 7.34-7.23 (m, 4H), 6.89-6.86 (dd, J = 6.4 Hz, 2.1 Hz, 1H) 6.83-6.81(m, 2H), 6.73 (d, J = 15.9 Hz, 1H), 6.41-6.34 (m, 1H), 4.68-4.67 (dd, J = 7.6 Hz, 3.2Hz, 2H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.6, 150.1 (d, J_{C-F} =1.4 Hz), 136.2, 133.5, 130.2, 128.6, 128.0, 126.6, 123.6, 123.7, 120.5 (q, J = 258.2 Hz), 113.1 (d, J_{C-F}= 7.02 Hz), 107.9, 68.9
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) – 57.71
FTIR: 3028, 2936, 1610 1490 1259 1142 cm^{-1}
HRMS (EI^+): Calculated: 294.0867; observed: 294.0862
MP (DCM/Et_2O): 38.6 – 39.8 °C
R_f : 0.27 in 100% hexane
Compound 1.39



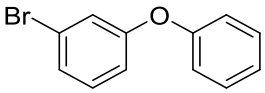
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 50% (0.087g) and 53% (0.0955g) isolated yields (51% average of two runs).
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.12-7.06 (m, 3H), 6.85 (br, 1H), 4.13- 4.08 (b, 2H), 3.83 (b, 1H), 3.37 (br, 2H), 1.99-1.82 (m, 4H), 1.469 (s, 1H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.6, 154.5, 130.5, 123.8, 122.7, 118.0, 113.3, 79.6, 68.3, 55.8, 46.7, 28.5, 28.4, 23.4
FTIR: 2970, 2937, 1691, 1590, 1476, 1392, 1167, 1034 cm^{-1}
HRMS (ESI^+): Calculated for $C_{16}H_{22}BrNNaO_3^+$ $[M+Na]^+$: 378.0675; observed: 378.0675
R_f : 0.6 in 50% diethyl ether/hexane

Compound 1.40



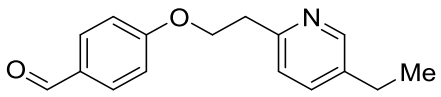
Prepared according to general procedure E on 0.5 mmol-scale and obtained in 68% (0.0618g) and 71% (0.0665g) isolated yields (69% average of two runs). Spectroscopic data was consistent with that previously reported. [98]
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (t, J = 8.0 Hz, 2H), 7.24-7.20 (m, 1H), 7.12 (t, J = 7.4 Hz, 1H), 7.02-7.00 (dd, J = 8.7, 1.2 Hz, 2H), 6.78-6.73 (m, 2H), 6.69-6.65 (m, 1H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)) 163.4 (d, $J_{C\text{-}F}$ = 246.2 Hz), 158.9 (d, $J_{C\text{-}F}$ = 10.4 Hz), 156.2, 130.4 (d, $J_{C\text{-}F}$ = 9.6 Hz), 129.9, 124.0, 119.5, 113.9 (d, $J_{C\text{-}F}$ = 3.9 Hz), 109.9 (d, $J_{C\text{-}F}$ = 21.0), 105.9 (d, $J_{C\text{-}F}$ = 24.8 Hz).
^{19}F NMR (377 MHz, $CDCl_3$): δ (ppm) -110.99
R_f : 0.38 in 100% Hexane

Compound 1.41



Prepared according to general procedure E on 0.5 mmol-scale and obtained in 56% (0.071g) and 57% (0.0722g) isolated yields (56% average of two runs). Spectroscopic data was consistent with that previously reported.[99]
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (t, J = 8.0 Hz, 2H), 7.24-7.14 (m, 4H), 7.05-7.02 (dd, J = 8.5, 0.9 Hz, 2H), 6.96-6.93 (m, 1H)
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 158.3, 156.2, 130.7, 129.9, 126.0, 123.9, 122.8, 121.6, 119.3, 117.1
R_f : 0.42 in 100% Hexane

Compound 1.42



Prepared according to the general procedure above on a 0.51 mmol scale and obtained in 45% (0.059 g) isolated yield as a colorless oil. Spectroscopic data were consistent with those previously reported.[100]

^{1}H NMR (400 MHz, CDCl3) δ 9.87 (s, 1H), 8.41 (d, *J* = 1.9 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.47 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.27 (s, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.0 (d, *J* = 8.2 Hz, 2H), 4.44 (t, *J* = 6.5 Hz, 2H), 3.27 (t, *J* = 6.7 Hz, 2H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 9.4, 3H).

^{13}C NMR (101 MHz, CDCl3): δ (ppm) 190.8, 163.9, 155.0, 149.0, 137.3, 136.0, 131.9, 129.9, 123.4, 114.8, 67.6, 37.2, 25.7, 15.3.

R_f: 0.25 in 60% ethyl acetate/hexane.

5.4: Synthesis and Characterization of aryl(TMP)iodonium salts

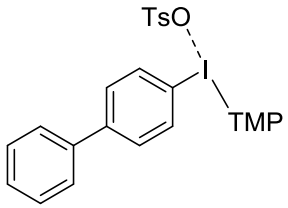
5.4.1: General procedure to synthesize diaryliodonium tosylates A[101]

Literature procedure cited was followed to make the diaryliodonium tosylate salts with a slight modification. Oxidation was performed at room temperature instead of 78 ºC and the temperature was slowly increased to 55 ºC until the reaction turned clear.

5.4.2: General procedure to synthesize diaryliodonium trifluoroacetates B[102]

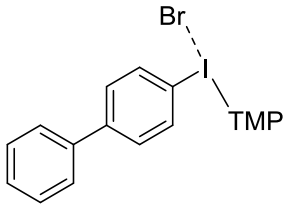
Literature procedure cited was followed to make the diaryliodonium trifluoroacetate salts. See below for the specific scale of reactions and characterization data of individual compounds.

Compound 1.43



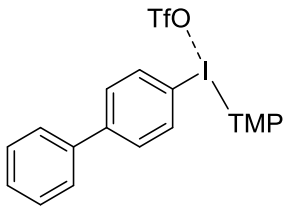
Prepared according to the general procedure A on 5.0 mmol scale and obtained in 65% yield (2.04 g).[101]

Compound 1.43 - Br



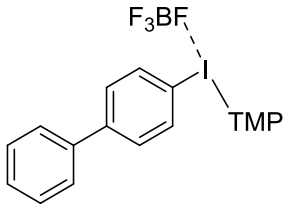
Prepared according to the ion exchange method described in the literature[101] on 2.5 mmol and obtained in 96% yield (1.28 g).

Compound 1.43- OTf



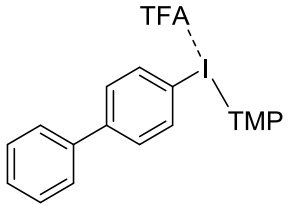
Prepared according to the ion exchange method described in the literature[101] on 1.0 mmol and obtained in 85% yield (0.511 g).

Compound 1.43 – BF_4



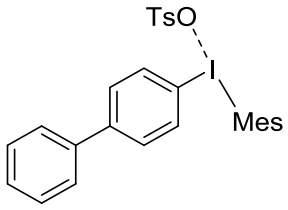
Prepared according to the ion exchange method described in the literature[101] on 1.0 mmol and obtained in 72% yield (0.388 g).

Compound 1.43 - TFA



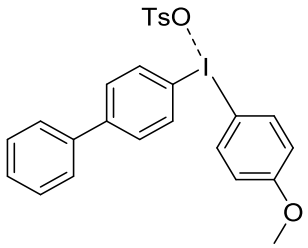
Prepared according to the ion exchange method described in the literature[101] on 1.0 mmol and obtained in 86% yield (0.481 g).

Compound 1.43 - Mes



Prepared according to the general procedure A on 3.0 mmol scale using mesitylene instead of TMB and obtained in 78% isolated yield (1.72 g).
Spectral data were consistent with previously reported compound[48]

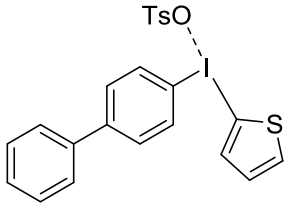
Compound 1.43 - anisole



Prepared according to the general procedure A on 2.0 mmol scale using anisole instead of TMB and obtained in 54% yield (0.602 g).
Melting point (Ethyl acetate/Et_2O): 143.2 – 144.6 °C

^{1}H NMR (400 MHz, DMSO) δ 8.25 (dd, *J* = 22.3, 8.7 Hz, 4H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 7.4 Hz, 2H), 7.55 – 7.37 (m, 5H), 7.10 (dd, *J* = 12.5, 8.5 Hz, 4H), 3.80 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ = 162.4, 146.1, 143.9, 138.6, 138.1, 137.8, 135.9, 130.1, 129.6, 129.1, 128.5, 127.5, 126.0, 117.9, 116.0, 106.1, 56.2, 21.3.
FTIR: 3091, 3051, 3040, 2962, 2901, 2859, 2840, 1395, 1254, 1181, 815 cm^{-1}
HRMS (ESI$^+$) m/z: $[M - OTs]^+$: Calculated: 387.0240 Observed: 387.0248

Compound 1.43 - thienyl

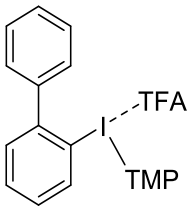


Prepared according to the general procedure A on 2.0 mmol scale using thiophene instead of TMB and obtained in 79% yield (0.842 g).
Melting point (Ethyl acetate/Et_2O): 152.2 – 153.1 °C

^{1}H NMR (400 MHz, DMSO) δ 8.33 (d, *J* = 8.5 Hz, 2H), 8.12 (d, *J* = 3.1 Hz, 1H), 7.99 (d, *J* = 4.8 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.55 – 7.39 (m, 5H), 7.20 (dd, *J* = 5.1, 4.0 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 2H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ = 146.1, 144.1, 140.9, 138.5, 138.1, 137.8, 135.7, 130.2, 130.1, 129.6, 129.1, 128.5, 127.6, 126.0, 118.3, 101.4, 21.3.
FTIR: 3092, 3060, 2962, 2922, 2867, 1652, 1392, 1214, 1190, 1022, 811 cm^{-1}
HRMS (ESI$^+$) m/z: $[M - OTs]^+$: Calculated: 362.9699; Observed: 362.9695

Compound 1.44



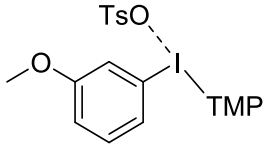
Prepared according to the general procedure 2 on 3.03 mmol scale and obtained 84% yield (1.427 g).[2]

Melting point (Ethyl acetate/Et_2O): 159.0 – 160.8 °C

^{1}H NMR (400 MHz, DMSO) δ 8.33 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.60 – 7.39 (m, 7H), 6.29 (s, 2H), 3.82 (s, 3H), 3.66 (s, 6H).

^{13}C NMR (101 MHz, DMSO) δ = 166.3, 159.7, 145.1, 141.5, 138.6, 132.8, 131.7, 130.4, 129.7, 128.9, 128.8, 119.9, 119.3, 116.3, 92.0, 57.3, 56.5.
^{19}F NMR (376 MHz, DMSO) δ = -73.4.
FTIR: 3065, 2937, 2836, 1683, 1423, 1344, 1242, 1198, 1122, 828, 799, 719 cm^{-1}
HRMS (ESI$^+$) m/z: $[M - TFA]^+$: Calculated: 447.0452 ; observed: 447.0448

Compound 1.45



Prepared according to the general procedure B on 1.0 mmol scale and converted to TFA salt using ion exchange method and obtained in 87% yield (0.500 g)

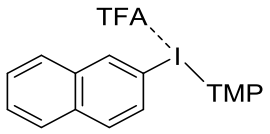
Melting point ($MeCN/Et_2O$): 150.9 – 152.5 °C

^{1}H NMR (400 MHz, DMSO) δ 7.49 (d, *J* = 7.7 Hz, 3H), 7.40 (dt, *J* = 16.0, 7.9 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.48 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H), 3.78 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ = 166.7, 160.7, 159.9, 138.1, 132.7, 128.5, 126.4, 125.9, 120.0, 117.6, 116.5, 92.5, 57.8, 56.6, 56.2, 21.2.
FTIR: 3082, 3020, 2938, 2901, 1630, 1567, 1331, 1220, 1177, 1032, cm^{-1}

HRMS (ESI$^+$) m/z: $[M - OTs]^+$: Calculated: 401.0244; observed: 401.0249

Compound 1.46

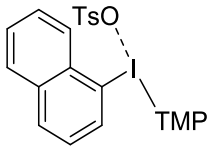


Prepared according to the general procedure B on 3.0 mmol scale and obtained in 80% yield (1.295 g).

Melting point (Ethyl acetate/Et_2O): 159.8 – 162.6 °C

^{1}H NMR (400 MHz, DMSO) δ 8.21 (d, *J* = 1.8 Hz, 1H), 7.71 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.53 – 7.41 (m, 3H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.45 (s, 2H), 3.95 (s, 6H), 3.85 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ = 166.5, 159.7, 146.1, 140.3, 138.9, 138.1, 135.4, 133.1, 128.5, 125.9, 122.3, 120.0, 107.5, 92.6, 57.7, 56.6.
^{19}F NMR (376 MHz, DMSO) δ = -73.4.
FTIR: 3048, 3014, 2959, 2839, 1679, 1583, 1341, 11570, 1124, 826, 718 cm^{-1}
HRMS (ESI$^+$) m/z: $[M - TFA]^+$: Calculated: 421.0295; observed: 421.0292

Compound 1.47

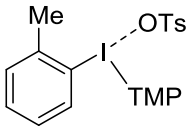


Prepared according to the general procedure B on 1.0 mmol scale and converted to OTs salt with ion exchange method obtained in 62% yield (0.3748)

Melting point (Ethyl acetate/Et_2O): 159.0 – 160.8 ^oC

^{1}H NMR (400 MHz, DMSO) δ 8.49 (d, *J* = 7.1 Hz, 1H), 8.23 (m, 2H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.85 (t, *J* = 7.3 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 7.3 Hz, 2H), 6.39 (s, 2H), 3.96 (s, 6H), 3.80 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ = 166.4, 159.8, 156.4, 154.0, 142.2, 137.1, 134.2, 130.4, 129.4, 127.9, 123.5, 123.4, 121.6, 114.8, 92.5, 88.0, 57.7, 56.6, 47.7, 26.8.
FTIR: 3087, 3058,2962, 2871, 1642, 1586, 1468, 1332, 1209, 1033, 816, 765 cm^{-1}
HRMS (ESI$^+$) m/z: $[M - OTs]^+$: Calculated: 421.0295 ; observed: 421.0297

Compound 1.47

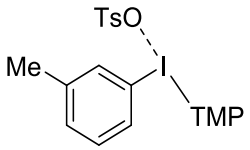


Prepared according to the general procedure A on 10.0 mmol scale and obtained in 90% yield (5.041 g)

Melting point (Ethyl acetate/Et_2O): 177.2 – 179.1 °C

^{1}H NMR (400 MHz, DMSO) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.40 (m, 4H), 7.22 (td, *J* = 7.1, 5.9, 3.2 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.44 (s, 2H), 3.95 (s, 6H), 3.85 (s, 3H), 2.60 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ = 166.4, 159.8, 146.3, 140.9, 138.0, 137.6, 132.8, 131.5, 129.3, 128.5, 125.9, 121.8, 92.5, 87.1, 57.7, 56.6, 25.3, 21.2.
FTIR: 3023, 1642, 1585, 1458, 1414, 1207, 1185, 1035, 816 cm^{-1}
HRMS (ESI$^+$) m/z: $[M - OTs]^+$: Calculated: 385.0295(1) ; observed: 385.0295(4)

Compound 1.49



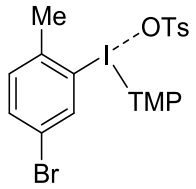
Prepared according to the general procedure A on 5.0 mmol scale and obtained in 94% yield (2.649 g)

Melting point (Ethyl acetate/Et_2O): 172.6 – 173.8 °C

^{1}H NMR (400 MHz, DMSO) δ 7.78 (s, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.47 (s, 2H), 3.96 (s, 5H), 3.87 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ = 166.6, 159.9, 146.2, 141.9, 138.1, 134.9, 132.7, 131.9, 131.7, 128.5, 126.0, 116.4, 92.5, 87.4, 57.8, 56.6, 21.2, 21.2.
FTIR: 3028, 1645, 1584, 1459, 1415, 1206, 1189, 1035, 817 cm^{-1}

HRMS (ESI$^+$) m/z: $[M - OTs]^+$: Calculated: 385.0295 ; observed: 385.0298

Compound 1.50

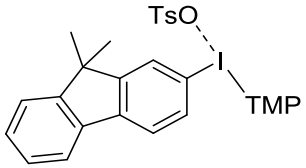


Prepared according to the general procedure A on 4.0 mmol scale and obtained in 76% yield (1.94 g)

Melting point (Ethyl acetate/Et_2O) 182.5 – 183.4 °C

^{1}H NMR (400 MHz, DMSO) δ 8.22 (d, *J* = 1.9 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 3H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.46 (s, 2H), 3.96 (s, 6H), 3.86 (s, 3H), 2.55 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ = 166.6, 159.8, 146.1, 140.3, 138.9, 138.1, 135.4, 133.1, 128.5, 125.9, 122.3, 120.0, 92.6, 87.3, 57.7, 56.6, 24.7, 21.3.
FTIR: 3026, 1641, 1589, 1457, 1413, 1210, 1189, 1037, 815 cm^{-1}
HRMS (ESI$^+$) m/z: $[M - OTs]^+$: Calculated: 462.94003 ; observed: 462.9400(7)

Compound 1.51

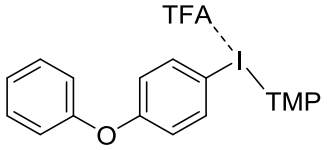


Prepared according to the general procedure B on 1.0 mmol scale and converted to OTs salt with ion exchange method and obtained in 71% yield (0.454 g)

Melting point (MeCN/Et_2O): 177.2 – 177.9 ºC

^{1}H NMR (400 MHz, DMSO) δ 8.47 (d, *J* = 7.4 Hz, 1H), 8.22 (dd, *J* = 13.4, 8.4 Hz, 2H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.39 (s, 2H), 3.95 (s, 6H), 3.80 (s, 3H), 3.33 (s, 6H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, DMSO) δ = 166.5, 159.8, 156.4, 154.0, 146.3, 142.2, 138.0, 137.1, 134.3, 130.4, 129.5, 128.5, 127.9, 126.0, 123.6, 123.4, 121.7, 114.7, 92.5, 57.7, 56.6, 47.7, 26.8, 21.2.
FTIR: 3023, 1642, 1585, 1458, 1414, 1207, 1185, 1035, 816 cm^{-1}
HRMS (ESI$^+$) m/z: $[M - OTs]^+$: Calculated: 487.0764 ; observed: 487.0767

Compound 1.52



Prepared according to the general procedure B on 3.0 mmol scale and obtained in 78% yield (1.261 g)

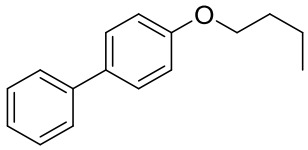
^{1}H NMR (400 MHz, DMSO) δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.47 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H).

^{13}C NMR (101 MHz, DMSO) δ = 166.5, 160.3, 158.3, (q, J_{C-F} = 30.9 Hz), 159.8, 155.1, 137.2, 130.9, 125.5, 120.6, 120.5, 117.9 (q, J_{C-F} = 301.0 Hz), 108.3, 92.5, 88.2, 57.7, 56.6.
^{19}F NMR (376 MHz, DMSO) δ = -73.4.
FTIR: 3066, 2947, 2846, 1680, 1583, 1479, 1413, 1345, 1243, 1198, 1124, 826, 797, 718 cm^{-1}
HRMS (ESI$^+$) m/z: $[M - OTs]^+$: Calculated: 463.0400 ; observed: 463.0401
Melting point (Ethyl acetate/Et_2O): 165.6 – 166.5 ºC

5.4.3: General procedure C; Synthesis of alkyl-aryl ethers

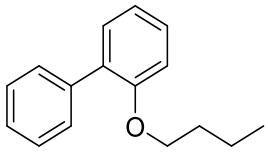
Sodium hydride (60 wt% dispersion in mineral oil) (0.060g, 1.5 mmol, 3.0 equiv.) was weighed out to air and transferred to an oven-dried vial equipped with a magnetic stir bar. The vial was sealed with a cap and Teflon-lined septa and purged with nitrogen. Toluene (2.5 mL) was added to the vial followed by the addition of alcohol (3.0 equiv.). The reaction was stirred for 30 mins at room temperature. Diaryliodonium salts (0.5 mmol, 1 equiv.) was transferred at once into the reaction vial after 30 mins. The vial was sealed with a solid cap and placed into a pre-heated (55 °C) aluminum block for 2 hours. The reaction was then removed from the heat and quenched with 2.5 mL of a saturated solution of ammonium chloride. The biphasic mixture was extracted with DCM (3 x 5 mL). This combined DCM extracts were dried using $MgSO_4$ and the solvent removed on a rotary evaporator. The crude residue was purified by flash column chromatography on silica gel (see below for specific eluent composition).

Compound 1.53



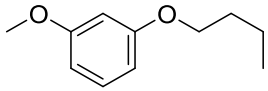
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 81% (0.0918 g) isolated yield.
Spectral data matches to the previously reported compound[102]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.48 (m, 4H), 7.41 - 7.37 (m, 2H), 7.29 – 7.25 (m, 1H), 6.96 – 6.94 (m, 2H), 3.97 (t, *J* = 6.5 Hz, 2H), 1.84 – 1.69 (m, 2H), 1.50 (h, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.8, 140.9, 133.4, 128.7, 128.1, 126.7, 126.5, 116.1, 75.1, 29.2, 19.3, 9.8.

Compound 1.54



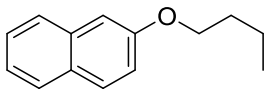
Prepared according to General procedure C on 0.49 mmol-scale and obtained in 71% (0.0818 g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.23 (m, 3H), 7.02 - 6.95 (m, 2H), 3.94 (t, *J* = 6.4 Hz, 2H), 1.74 – 1.61 (m, 2H), 1.46 – 1.33 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 138.6, 130.9, 130.8, 129.6, 128.5, 127.8, 126.7, 120.7, 112.5, 68.1, 31.2, 19.3, 13.8.
FTIR: 3060, 2958, 2933, 2871, 1596, 1483, 1433, 1261, 1235, 1125, 1070, 752, 731 cm^{-1}
HRMS (ESI^+): Calculated: 227.1430; observed: 227.1434
R_f : 0.42 in 2% Ether/ Hexane

Compound 1.55



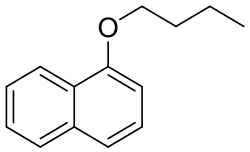
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 79% (0.0717 g) isolated yield. Regioisomers are observed in 5:1 ratio.
Spectral data matches to the previously reported compound. [103]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 8.1 Hz, 1H), 6.55 – 6.40 (m, 3H), 3.94 (t, *J* = 6.5 Hz, 2H), 3.79 (s, 3H), 1.81 – 1.69 (m, 2H), 1.54 – 1.42 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.8, 160.4, 129.8, 106.7, 106.1, 100.9, 67.7, 55.2, 31.3, 19.3, 13.9.

Compound 1.56



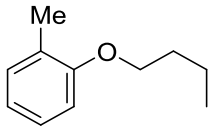
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 70% (0.0707 g) isolated yield.
Regioisomers are observed in 20:1:1 ratio.
Spectral data matches to the previously reported compound.[104]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.66 (m, 3H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.15 – 7.11 (m, 2H), 4.05 (t, *J* = 6.5 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.55 – 1.50 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.1, 134.6, 129.3, 128.9, 127.6, 126.7, 126.2, 123.4, 119.0, 106.5, 67.7, 31.3, 19.3, 13.9.

Compound 1.57



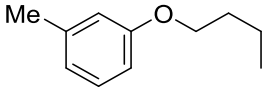
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 70% (0.0706 g) isolated yield.
Spectral data matches to the previously reported compound. [106]
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 – 8.22 (m, 1H), 7.82 – 7.71 (m, 1H), 7.51 – 7.27 (m, 4H), 6.77 (d, *J* = 7.4 Hz, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 1.94 – 1.83 (m, 2H), 1.63 - 1.53 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, CDCl$_3$) δ = 154.9, 134.5, 127.4, 126.3, 125.9, 125.8, 125.0, 122.1, 119.9, 104.5, 67.8, 31.4, 19.5, 13.9.

Compound 1.58



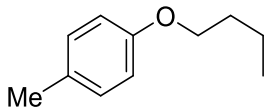
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 50% (0.042 g) isolated yield.
Spectral data matches to the previously reported compound.[107]
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.15 - 7.11 (m, 2H), 6.87 – 6.77 (m, 2H), 3.96 (t, *J* = 6.4 Hz, 2H), 2.22 (s, 3H), 1.83 – 1.71 (m, 2H), 1.58 – 1.42 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, CDCl$_3$) δ = 157.2, 130.5, 126.8, 126.7, 120.0, 110.9, 67.6, 31.5, 19.4, 16.2, 13.9.

Compound 1.59



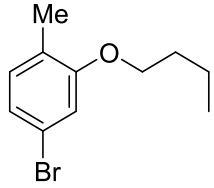
Prepared according to General procedure C on 0.46 mmol-scale and obtained in 60% (0.046 g) isolated yield.
Spectral data matches to the previously reported compound.[108]
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.15 (t, *J* = 7.7 Hz, 1H), 6.77 – 6.67 (m, 3H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.32 (s, 3H), 1.81 – 1.71 (m, 2H), 1.53 - 1.44 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, CDCl$_3$) δ = 159.2, 139.4, 129.1, 121.3, 115.4, 111.3, 67.5, 31.4, 21.5 19.3, 13.9.

Compound 1.60



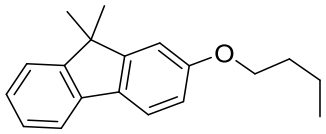
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 45% (0.036 g) isolated yield.
Spectral data matches to the previously reported compound.[108]

Compound 1.61



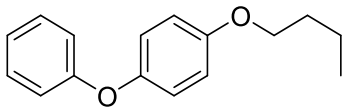
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 82% (0.1005 g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 – 6.91 (m, 3H), 3.92 (t, *J* = 6.4 Hz, 2H), 2.15 (s, 3H), 1.83 – 1.70 (m, 2H), 1.55 – 1.45 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.9, 131.5, 125.8, 122.8, 119.4, 114.3, 67.9, 31.3, 19.3, 15.9, 13.9.
FTIR: 2957, 2929, 2871, 1591, 1491, 1471, 1304, 1241, 1190, 836, 799 cm^{-1}
HRMS (ESI^+): Calculated: 243.0379 ; observed: 243.0378
R_f: 0.52 in 5% Ether/ Hexane

Compound 1.62



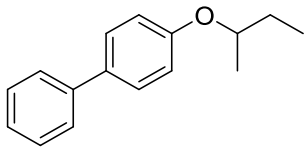
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 87% (0.101 g) isolated yield.
Regioisomers are observed in 6:1 ratio.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (t, *J* = 7.3 Hz, 2H), 7.38 (d, *J* = 7.3 Hz, 1H), 7.33 – 7.18 (m, 2H), 6.97 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 8.3, 2.3 Hz, 1H), 4.07 – 3.94 (m, 2H), 1.89 – 1.73 (m, 2H), 1.58 – 1.48 (m, 2H), 1.46 (s, 6H), 0.99 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.2, 155.4, 153.1, 139.2, 131.9, 126.9, 126.0, 122.4, 120.7, 119.1, 112.9, 109.2, 67.9, 46.8, 31.5, 27.3, 23.8, 19.3, 13.9.
FTIR: 2958, 2930, 2870, 1609, 1581, 1491, 1459, 1428, 1286, 1270, 1191, 1074, 757, 734 cm^{-1}
HRMS (ESI^+): Calculated: 267.1743 ; observed: 267.1742
R_f: 0.18 in 5% Ether/ Hexane

Compound 1.63



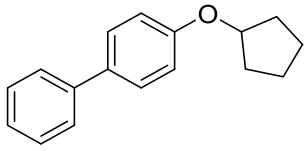
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 55% (0.0674 g) isolated yield.
Regioisomers are observed 10: 1 ratio
Spectral data matches to the previously reported compound.[109]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 6.99 – 6.83 (m, 7H), 3.94 (t, *J* = 6.5 Hz, 2H), 1.82 – 1.69 (m, 2H), 1.57 – 1.44 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.6, 155.5, 149.9, 129.6, 122.3, 120.8, 117.5, 115.5, 68.1, 31.4, 19.3, 13.9.

Compound 1.64



Prepared according to General procedure C on 0.5 mmol-scale and obtained in 70% (0.0802 g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 4H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 4.35 – 4.28 (m, 1H), 1.77 – 1.59 (m, 2H), 1.31 (d, *J* = 6.1 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.8, 140.9, 133.4, 128.7, 128.1, 126.7, 126.5, 116.1, 75.1, 29.2, 19.3, 9.8.
FTIR: 3030, 2971, 2933, 2876, 1607, 1517, 1485, 1433, 1267, 1244, 761, 697 cm^{-1}
HRMS (ESI^+): Calculated: 227.1430; observed: 227.1431
R_f: 0.41 in 2% Ether/ Hexane

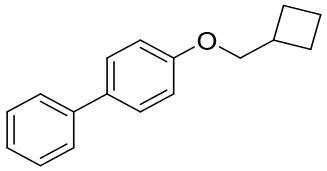
Compound 1.65



Prepared according to General procedure C on 0.5 mmol-scale and obtained in 61% (0.073 g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 18.7, 8.1 Hz, 4H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 4.84 – 4.73 (m, 1H), 2.00 – 1.74 (m, 6H), 1.70 – 1.57 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.7, 140.9, 133.2, 128.7, 128.0, 126.7, 126.5, 115.8, 79.2, 32.9, 24.0.
FTIR: 3030, 2963, 2871, 1604, 1581, 1487, 1269, 1247, 1169, 984, 831, 759, 689 cm^{-1}
HRMS (ESI^+): Calculated: 239.1430; observed: 239.1424

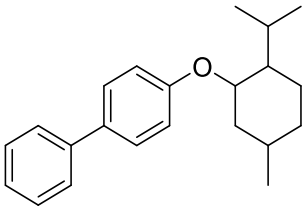
R_f: 0.42 in 2% Ether/ Hexane
Melting point ($CDCl_3$): 77.5 – 80.9 °C

Compound 1.66



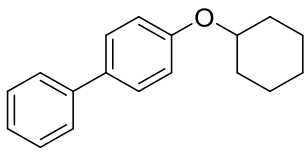
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 81% (0.0967 g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.47 (m, 4H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 3.93 (d, *J* = 6.7 Hz, 2H), 2.80 – 2.73 (m, 1H), 2.22 – 2.07 (m, 2H), 1.99 – 1.8 (m, 4H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.8, 140.8, 133.5, 128.7, 128.0, 126.7, 126.6, 114.8, 72.1, 34.6, 24.9, 18.6.
FTIR: 3031, 2972, 2935, 2864, 1605, 1522, 1488, 1253, 1024, 816, 762, 689 cm^{-1}
HRMS (ESI^+): Calculated: 239.1430 ; observed: 239.1423
R_f: 0.42 in 2% Ether/ Hexane
Melting point ($CDCl_3$): 77.6 – 78.8 °C

Compound 1.67



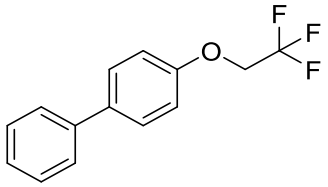
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 61% (0.094 g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 4H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 4.09 – 4.03 (m, 1H), 2.30 – 2.14 (m, 2H), 1.81 – 1.65 (m, 2H), 1.59 – 1.40 (m, 2H), 1.17 – 0.98 (m, 2H), 0.93 (t, *J* = 6.5 Hz, 7H), 0.79 (d, *J* = 7.0 Hz, 3H). Overlapping signals
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.9, 140.9, 133.4, 128.7, 128.2, 126.7, 126.5, 116.0, 77.5, 48.1, 40.3, 34.5, 31.4, 26.1, 23.7, 22.1, 20.8, 16.6.
FTIR: 2957, 2920, 2865, 1604, 1582, 1468, 1265, 1245, 835, 762, 713 cm^{-1}
HRMS (ESI^+): Calculated: 309.2213 ; observed: 309.2216
R_f: 0.38 in 2% Ether/ Hexane
Melting point ($CDCl_3$): 126.8 – 127.2 °C

Compound 1.68



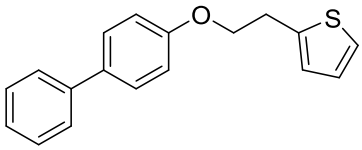
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 63% (0.089 g) isolated yield.
Spectral data matches to the previously reported compound[109]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 4H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 4.30 – 4.24 (m, 1H), 2.08 – 1.91 (m, 2H), 1.87 – 1.72 (m, 2H), 1.62 – 1.47 (m, 3H), 1.45 – 1.23 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.3, 140.9, 133.5, 128.7, 128.1, 126.7, 126.5, 116.2, 75.4, 31.8, 25.6, 23.8.

Compound 1.69



Prepared according to General procedure C on 0.5 mmol-scale and obtained in 86% (0.1091 g) isolated yield.
Spectral data matches to the previously reported compound [110]
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 4H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 4.35 (q, $J_{C\text{-}F}$ = 8.1 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.9, 140.3, 135.7, 128.8, 128.4, 127.1, 126.8, 123.6 (q, J_{C-F} = 278 Hz), 115.2, 65.9 (q, J_{C-F} = 35 Hz)

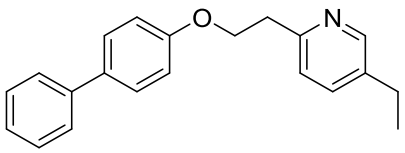
Compound 1.70



Prepared according to General procedure C on 0.5 mmol-scale and obtained in 77% (0.109 g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.47 (m, 4H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 5.1 Hz, 1H), 6.99 – 6.86 (m, 4H), 4.17 (t, *J* = 6.7 Hz, 2H), 3.28 (t, *J* = 6.7 Hz, 2H).

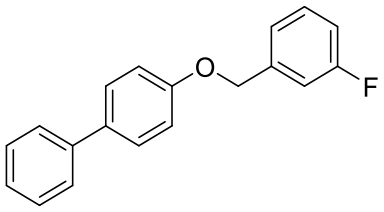
^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.3, 140.9, 140.5, 134.1, 128.9, 128.3, 127.0, 126.8(4), 126.8(1), 125.7, 124.1, 115.0, 68.6, 30.1.
FTIR: **3060,** 2952, 2871, 1606, 1489, 1270, 1251, 1197, 1043, 832, 763, 693 cm^{-1}
HRMS (ESI^+): Calculated: 281.0995 ; observed: 281.0997
R_f: 0.46 in 5% Ether/ Hexane
Melting point ($CDCl_3$): 61.6 – 63.6 ºC

Compound 1.71



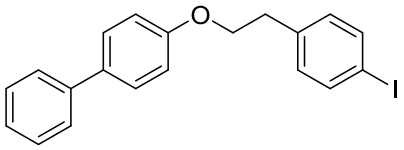
Prepared according to General procedure C on 0.5 mmol-scale and obtained in 63% (0.0952 g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 1.6 Hz, 1H), 7.56 – 7.35 (m, 7H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 4.38 (t, *J* = 6.7 Hz, 2H), 3.25 (t, *J* = 6.7 Hz, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.4, 155.6, 149.0, 140.8, 137.0, 135.8, 133.7, 128.7, 128.1, 126.7, 126.6, 123.3, 114.9, 67.4, 37.6, 25.7, 15.3.
FTIR: 3033, 2965, 2930, 2872, 1602, 1520, 1487, 1285, 1268, 1248, 1030, 835, 763 cm^{-1}
HRMS (ESI^+): Calculated: 304.1696 ; observed: 304.1701
R_f: 0.19 in 30% Ethyl acetate/ Hexane
Melting point ($CDCl_3$): 88.8 – 89.8 ºC

Compound 1.72



Prepared according to General procedure C on 0.5 mmol-scale and obtained in 75% (0.105 g) isolated yield.
Small amount of trimethoxy benzene is present.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 4H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.35 – 7.25 (m, 3H), 7.19 – 7.14 (m, 2H), 7.00 (d, *J* = 8.7 Hz, 2H), 5.05 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 161.7, 140.6, 139.5 (d, J_{C-F} = 7.3 Hz), 134.2, 130.1 (d, J_{C-F} = 8.2 Hz), 128.7, 128.1, 126.7, 126.7, 122.6 (d, J_{C-F} = 2.9 Hz), 115.0, 114.7 (d, J_{C-F} = 21.1 Hz), 114.1 (d, J_{C-F} =22.0 Hz), 69.1.
^{19}F NMR (376 MHz, $CDCl_3$) δ = -112.6.
FTIR: 3035, 2907, 2869, 1591, 1490, 1450, 1258, 1146, 1024, 825, 757, 711 cm^{-1}
HRMS (ESI^+): Calculated: 279.1180; observed: 279.1196
R_f : 0.5 in 5% Ether/ Hexane
Melting point ($CDCl_3$): 112.5 – 113.8 ºC

Compound 1.73



Prepared according to General procedure C on 0.5 mmol-scale and obtained in 89% (0.180 g) isolated yield.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.53 – 7.47 (m, 4H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.14 (t, *J* = 6.8 Hz, 2H), 3.02 (t, *J* = 6.8 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.1, 140.7, 137.9, 137.5, 133.9, 131.0, 128.8, 128.7, 128.1, 126.8, 126.6, 114.8, 68.2, 35.2.
FTIR: 3021, 2943, 2921, 2868, 1680, 1583, 1483, 1249, 1201, 1030, 831, 760 cm^{-1}
HRMS (ESI^+): Calculated: 401.0397 ; observed: 401.0398
R_f : 0.52 5% Ether/ Hexane
Melting point ($CDCl_3$): 122.3 – 124.5 ^oC

5.5: Synthesis and Characterization of aryl(mesityl)iodonium tosylate salts.

5.5.1: General procedure from aryl iodides[101]

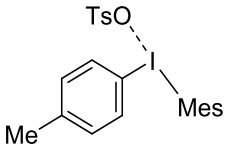
Aryl iodide (3.0 mmol, 1.0 equiv.) and acetonitrile (3 mL) were added to a 12 mL oven dried vial, equipped with a magnetic stir bar. p-toluenesulfonic acid (3.3 mmol, 1.1 equiv.) was added in one portion, followed by one portion of *m*-CPBA (3.3 mmol, 1.1 equiv.) and sealed with a closed cap. The reaction was transferred to a pre heated aluminum block set to 77 °C and stirred vigorously. After 30 min, added 1,3,5-trimethylbenzene (3.3 mmol, 1.1 equiv.) in one portion and stirring was continued at 77 °C for 3h. The reaction was removed from heat and concentrated under reduced pressure. The resulting crude residue was triturated with diethyl ether and isolated by filtration to give analytically pure aryl(mesityl) iodonium tosylate. See below for the specific scale of reactions and characterization data of individual compounds.

5.5.2: General procedure from arylboronic acids[111]

Arylboronic acid (3.0 mmol, 1.0 equiv.) was weighed and transferred to a pear-shaped flask equipped with a magnetic stir bar and rubber septum. The flask was flushed with nitrogen and left under a static nitrogen atmosphere. DCM (30 mL) was added via syringe to the aryl boronic acid and the solution was cooled to ~0 °C in an ice−water bath with stirring. BF_3•OEt_2 (1.1 mL, 9.0 mmol, 3.0 equiv.) is added via syringe to the aryl boronic acid solution and the reaction mixture was stirred for 10 min at 0 °C. Mesitylene iododiacetate (1.20 g, 3.3 mmol, 1.1 equiv) was weighed and transferred to a separate pear-shaped flask equipped with rubber septum. The flask was flushed with nitrogen and left under a static nitrogen atmosphere. DCM (9 mL) was added to the mesitylene iododiacetate. The

mesitylene iododiacetate solution was added to the aryl boronic acid/BF_3•OEt_2 solution dropwise via syringe at ~0 °C. The reaction mixture was allowed to warm to ambient room temperature and stirred overnight. The septum was removed, and an aqueous solution of NaOTs (60 mmol, 20 equiv. in 30 mL of water) was added with vigorous stirring for ~30 min. The biphasic mixture was added to a separatory funnel, and the DCM/water layers separated. The water layer was extracted with DCM (3 × 30 mL). The combined DCM layers were dried over $MgSO_4$, filtered, and the DCM removed on a rotovap. The crude residue was triturated with diethyl ether to yield analytically pure aryl(mesityl)iodonium tosylate. See below for the specific scale of reactions and characterization data of individual compounds.

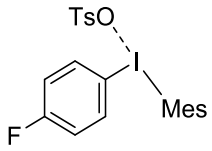
Compound 2.1



Prepared according to the general procedure A on 5.0 mmol and obtained an isolated yield of 71% (1.8143 g) as a a white powder.

Melting point (MeCN/Et_2O): 152.3 – 154.6 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 7.85 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.19 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.59 (s, 6H), 2.32 (s, 3H), 2.28 (s, 6H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 145.7, 142.9, 142.1, 141.4, 137.5, 134.4, 132.4, 129.6, 128.0, 125.4, 122.7, 110.9, 26.2, 20.7, 20.7, 20.5.
FTIR: 3023, 2921, 1455, 1173, 1120, 1032, 1008 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{18}I^+$: 337.0448; found: 337.0459

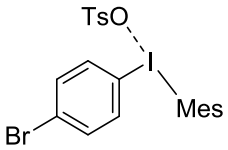
Compound 2.2



Prepared according to the general procedure A on 3.0 mmol and obtained an isolated yield of 82% (2.460 g) as a white powder.

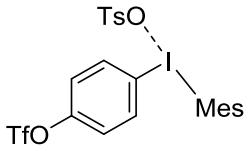
Melting point (MeCN/Et_2O): 172.4 – 174.4 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.12 – 7.96 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.37 (t, *J* = 8.9 Hz, 2H), 7.21 (s, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 2.59 (s, 6H), 2.30 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 163.6 (d, J_{C-F} = 251.0 Hz), 145.3 , 143.0 , 141.3 , 137.6 , 137.1 (d, J_{C-F} = 9.0 Hz), 129.6 , 127.9 , 125.3 , 122.8 , 119.1 (d, J_{C-F} = 22.8 Hz), 108.5 (d, J_{C-F} = 3.1 Hz), 26.1 , 20.6 , 20.4.
^{19}F NMR (377 MHz, $CDCl_3$) δ = -107.8
FTIR: 3005, 2921, 1739, 1366, 1275, 1261, 750 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{15}H_{15}FI^+$: 341.0197; found: 341.0224

Compound 2.3



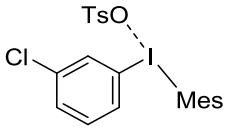
Prepared according to the general procedure A on 3.0 mmol and obtained an isolated yield of 83% (1.440 g) as a white powder.
Melting point (MeCN/Et_2O): 150.0 – 153.7 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 7.88 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.21 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.58 (s, 6H), 2.30 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 145.5, 143.0, 141.4, 137.5, 136.2, 134.5, 129.7, 127.9, 125.6, 125.4, 122.7, 113.0, 26.2, 20.7, 20.4.
FTIR: 3010, 2921, 1469, 1380, 1168, 1031, 1008 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{15}H_{15}BrI^+$: 400.9396; found: 400.9419

Compound 2.4



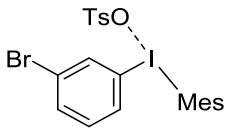
Prepared according to the general procedure A on 4.18 mmol and obtained an isolated yield of 60% (1.629 g) as a white powder.
Melting point (MeCN/Et_2O): 162.6 – 170.7 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.14 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.24 (s, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 2.59 (s, 6H), 2.31 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 150.7, 145.4, 143.2, 141.6, 137.6, 136.9, 129.8, 128.0, 125.4, 124.9, 122.9, 118.1 (q, $J_{C\text{-}F}$ = 323 Hz), 114.0, 26.2, 20.7, 20.5,
^{19}F NMR (377 MHz, [D_6] DMSO) δ = -73.1
FTIR: 2987, 1423, 1275, 1269, 1208, 1139, 749 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{15}F_3IO_3S^+$: 470.9733; found: 470.9754

Compound 2.5



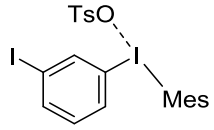
Prepared according to the general procedure B on 3.0 mmol and obtained an isolated yield of 84% (1.346 g) as a white powder.
Melting point (MeCN/Et_2O): 153.2 – 153.9 °C.
^{1}H NMR (400 MHz, [D_6] DMSO): δ = 8.14 (t, *J* = 1.7 Hz , 1H), 7.85 (d, *J*=8.1 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.22 (s, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 2.59 (s, 6H), 2.30 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 141.5, 133.4, 133.1, 132.7, 131.7, 129.7, 127.9, 125.3, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 38.7, 26.2, 20.4.
FTIR: 3058, 2982, 2921, 1569, 1457, 1169, 1031, 1007 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{15}H_{15}ClI^+$: 356.9901; found: 356.9914

Compound 2.6



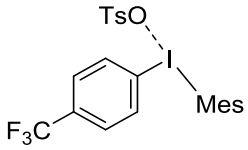
Prepared according to the general procedure B on 5.0 mmol and obtained an isolated yield of 67% (1.919 g) as a white powder.
Melting point (MeCN/Et_2O): 151.2 – 153.9 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.26 (t, *J* = 1.8 Hz, 1H), 7.91 – 7.77 (m, 2H), 7.49 – 7.39 (m, 3H), 7.22 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.59 (s, 6H), 2.30 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 145.4, 143.1, 141.6, 137.5, 136.0, 134.6, 133.4, 133.0, 129.7, 127.9, 125.3, 123.3, 122.6, 114.9, 26.2, 20.7, 20.4.
FTIR: 2986, 2970, 1555, 1453, 1180, 1050, 750 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{15}H_{15}BrI^+$: 400.9396; found: 400.9407

Compound 2.7



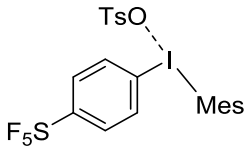
Prepared according to the general procedure B on 3.0 mmol and obtained an isolated yield of 90% (1.677 g) as a white powder.
Melting point (MeCN/Et_2O): 163.1 – 166.5 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.38 (t, *J* = 1.6 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 10.5 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.22 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.60 (s, 6H), 2.30 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 141.6, 141.3, 133.5, 133.1, 129.7, 127.9, 125.3, 40.0, 39.8, 39.6, 39.4, 39.2, 39.0, 38.8, 26.2, 20.7, 20.4.
FTIR: 2987, 1736, 1451, 1275, 1189, 750 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{15}H_{15}I_2^+$: 448.9258; found: 448.9262

Compound 2.8



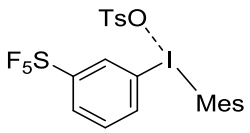
Prepared according to the general procedure A on 3.0 mmol and obtained an isolated yield of 76% (1.279 g) as a white powder.
Melting point ($MeCN/Et_2O$): 181.0 – 182.5 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.15 (d, *J* = 8.3 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.23 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.59 (s, 6H), 2.31 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 145.4, 143.3, 141.6, 137.6, 135.0, 131.5 (q, J_{C-F} = 32.6 Hz), 129.8, 128.2 (q, J_{C-F} = 4.0 Hz), 128.0, 125.4, 123.3 (q, J_{C-F} = 273.0 Hz), 122.7, 118.8, 26.2, 20.7, 20.5.
^{19}F NMR (376 MHz, [D_6] DMSO) δ = -61.7.
FTIR: 3000, 2970, 1738, 1367, 1323, 1199, 1132, 750 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{15}F_3I^+$: 391.0165; found: 391.0173

Compound 2.9



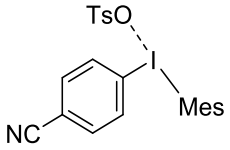
Prepared according to the general procedure A on 3.03 mmol and obtained an isolated yield of 73% (1.3773 g) as a white powder. (~94% pure bases on ^{1}H NMR integration).
Melting point ($MeCN/Et_2O$): 180.4 – 182.1 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.12 (d, *J* = 8.9 Hz, 2H), 8.02 (d, *J* = 9.2 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.25 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.59 (s, 6H), 2.31 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 154.4, 145.4, 143.4, 141.7, 137.6, 135.0, 129.8, 128.8, 128.0, 125.4, 122.6, 118.3, 26.2, 20.7, 20.5.
^{19}F NMR (377 MHz, [D_6] DMSO) δ = 84.80 (p, J_{F-F} = 151.9 Hz), 63.72 (d, J_{F-F} = 151.2 Hz).
FTIR: 3010, 2970, 1738, 1456, 1215, 1168, 842 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{15}H_{15}F_5IS^+$: 448.9854; found: 448.9863

Compound 2.10



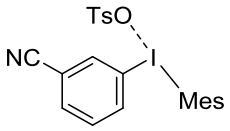
Prepared according to the general procedure A on 2.99 mmol and obtained an isolated yield of 66% (1.233 g) as a white powder.
Melting point (MeCN/Et_2O): 182.4 – 183.9 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.67 (t, *J* = 1.8 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.70 (t, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.24 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.60 (s, 6H), 2.31 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 153.3, 145.5, 143.4, 141.7, 137.5, 133.0, 131.3, 129.8, 128.8, 127.9, 125.4, 122.8, 114.4, 26.2, 20.7, 20.4. One carbon signal is missing due to overlapping signals.
^{19}F NMR (377 MHz, [D_6] DMSO) δ = 84.74 (p, J_{F-F} = 152.0, 150.6 Hz), 64.09 (d, J_{F-F} = 151.6 Hz).
FTIR: 3006, 1734, 1275, 1261, 750 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{15}H_{15}F_5IS^+$: 448.9854; found: 448.9864

Compound 2.11



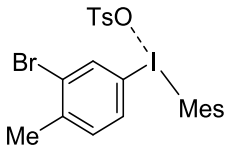
Prepared according to the general procedure A on 3.0 mmol and obtained an isolated yield of 72% (1.130 g) as a white powder.
Melting point (MeCN/Et_2O): 172.3 – 174.9 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.11 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.23 (s, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 2.57 (s, 6H), 2.30 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 145.2, 143.3, 141.6, 137.7, 134.9, 129.8, 128.0, 125.4, 122.7, 119.4, 117.4, 114.2, 26.2, 20.7, 20.4. One carbon signal is missing due to overlapping signals.
FTIR: 3010, 2231, 1651, 1474, 1215, 1189 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{15}IN^+$: 348.0244; found: 348.0258

Compound 2.12



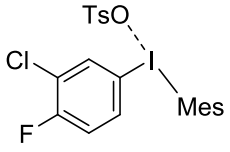
Prepared according to the general procedure A on 5.0 mmol and obtained an isolated yield of 71% (1.867 g) as a white powder.
Melting point (MeCN/Et_2O): 171.3 – 172.7 °C.
^{1}H NMR (600 MHz, [D_6] DMSO) δ = 8.55 (t, *J* = 1.5 Hz, 1H), 8.25 – 8.19 (m, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.21 (s, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 2.59 (s, 6H), 2.29 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (151 MHz, [D_6] DMSO) δ = 145.8, 143.8, 142.2, 139.4, 138.3, 138.2, 135.9, 132.9, 130.3, 128.6, 125.9, 123.4, 117.4, 115.1, 114.5, 26.8, 21.3, 21.0.
FTIR: 3009, 2233, 1661, 1464, 1211, 1190 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{15}IN^+$: 348.0244; found: 348.0251

Compound 2.13



Prepared according to the general procedure A on 5.0 mmol and obtained an isolated yield of 83% (2.446 g) as a white powder.
Melting point (MeCN/Et_2O): 180.8 – 183.6 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.25 (d, *J* = 1.8 Hz, 1H), 7.79 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.47-7.43 (m, 3H), 7.21 (s, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 2.59 (s, 6H), 2.35 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 145.4, 143.0, 141.8, 141.5, 137.7, 136.7, 133.8, 133.3, 129.7, 127.9, 125.8, 125.4, 122.7, 111.3, 26.2, 22.2, 20.7, 20.4.
FTIR: 3011, 2922, 1461, 1214, 1188, 1032 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{17}BrI^+$: 414.9553; found: 414.9568

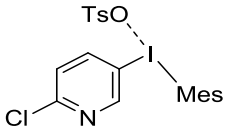
Compound 2.14



Prepared according to the general procedure A on 5.0 mmol and obtained an isolated yield of 78% (2.127 g) as a white powder.
Melting point (MeCN/Et_2O): 163.8 – 164.1 °C.

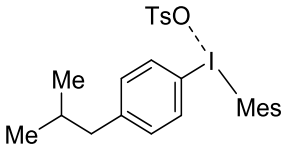
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.35 (dd, *J* = 6.8, 2.2 Hz, 1H), 7.94-7.90 (m, 1H), 7.55 (t, *J* = 9.0 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.21 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.60 (s, 6H), 2.30 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 159.07 (d, J_{C-F} = 253.1 Hz), 145.3, 143.2, 141.5, 137.6, 136.3, 135.5 (d, J_{C-F} = 8.2 Hz), 129.7, 127.9, 125.3, 122.9, 122.2 (d, J_{C-F} = 18.7 Hz), 120.1 (d, J_{C-F} = 22.2 Hz), 108.6 (d, J_{C-F} = 3.9 Hz), 26.2, 20.6, 20.4.
^{19}F NMR (376 MHz, [D_6] DMSO) δ = -110.8.
FTIR: 3080, 2921, 1476, 1171, 1120, 1031, 1008, 815 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{15}H_{14}ClFI^+$: 374.9807; found: 374.9822

Compound 2.15



Prepared according to the general procedure A on 5.0 mmol and obtained an isolated yield of 50% (1.3264 g) as a light brown powder.
Melting point (MeCN/Et_2O): 160.2 – 162.7 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.91 (d, *J* = 2.0 Hz, 1H), 8.41 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H)), 7.46 (d, *J* = 8.1 Hz, 2H), 7.21 (s, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 2.60 (s, 6H), 2.30 (s, 3H), 2.29 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 153.5, 152.9, 145.3, 145.0, 143.2, 141.5, 137.6, 129.7, 128.0, 127.5, 125.3, 122.9, 112.2, 26.2, 20.7, 20.4.
FTIR: 3044, 2981, 1554, 1445, 1216, 1169, 1008, 749 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{14}H_{14}ClIN^+$: 357.9854; found: 357.9866

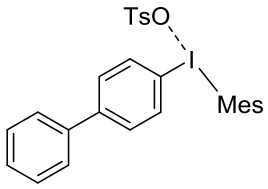
Compound 2.16



Prepared according to the general procedure B on 3.0 mmol and obtained an isolated yield of 81% (1.347 g) as a white powder.
Melting point (MeCN/Et_2O): 166.9 – 168.9 °C.

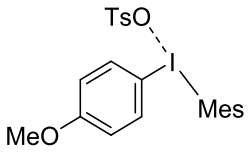
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 7.88 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.20 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.59 (s, 6H), 2.47 (d, *J* = 7.2 Hz, 2H), 2.29 (s, 3H), 2.28 (s, 3H), 1.80 (sept, 1H), 0.82 (d, *J* = 6.6 Hz, 6H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 145.7, 145.5, 142.9, 141.5, 137.5, 134.4, 132.4, 129.7, 128.0, 125.4, 122.6, 111.2, 43.8, 29.4, 26.2, 21.9, 20.7, 20.5.
FTIR: 2955, 2923, 1458, 1172, 1120, 1032, 1008 680 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{19}H_{24}I^+$: 379.0917; found: 379.0932

Compound 2.17



Prepared according to the general procedure B on 5.09 mmol and obtained an isolated yield of 71% (2.065 g) as a white powder.
Melting point (MeCN/Et_2O): 183.5 – 186.4 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.04 (d, *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 7.1 Hz, 2H), 7.54 – 7.38 (m, 5H), 7.23 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 2.63 (s, 6H), 2.30 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 145.7, 143.3, 143.0, 141.5, 138.0, 137.5, 134.9, 129.8, 129.7, 129.1, 128.6, 128.0, 127.0, 125.4, 122.6, 113.0, 26.3, 20.7, 20.5.
FTIR: 2978, 2966, 1474, 1176, 1009, 680 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{21}H_{20}I^+$: 399.0604; found: 399.0615

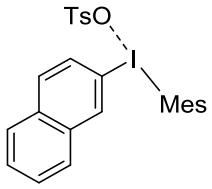
Compound 2.18



Prepared according to the general procedure B on 3.05 mmol and obtained an isolated yield of 50% (0.804 g) as grey powder.
Melting point (MeCN/Et_2O): 164.9 – 168.9 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 7.91 (d, *J* = 9.1 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.18 (s, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 9.1 Hz, 2H), 3.77 (s, 3H), 2.59 (s, 6H), 2.28 (s, 6H, overlapping methyl signals).

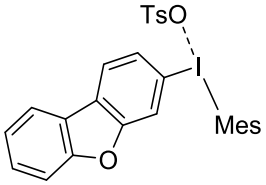
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 161.6, 145.6, 142.8, 141.3, 137.6, 136.5, 129.6, 128.0, 125.4, 123.1, 117.4, 103.4, 55.6, 26.2, 20.7, 20.4.
FTIR: 2919, 1573, 1487, 1298, 1255, 1174, 1031, 1009, 817 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{18}IO^+$: 353.0397 ; found: 353.0409

Compound 2.19



Prepared according to the general procedure B on 3.0 mmol and obtained an isolated yield of 56% (0.925 g) as light orange powder.
Melting point (MeCN/Et_2O): 163.5- 165.2 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.76 (d, *J* = 1.8 Hz, 1H), 8.09 – 7.99 (m, 3H), 7.96 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.19 (s, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 2.67 (s, 6H), 2.28 (s, 6H, overlapping methyl signals). Two carbon signals are missing due to overlapping signals.
^{13}C NMR (101 MHz, DMSO) δ = 145.4, 142.9, 141.5, 137.6, 135.3, 133.9, 133.2, 131.3, 129.6, 128.7, 128.0, 127.9, 127.7, 125.4, 122.7, 111.5, 26.3, 20.7, 20.4.
FTIR: 3053, 2998, 1576, 1455, 1173, 1120, 1031, 1008, 814 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{19}H_{18}I^+$: 373.0448; found: 373.0460

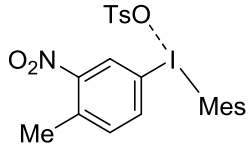
Compound 2.20



Prepared according to the general procedure B on 3.0 mmol and obtained an isolated yield of 36% (0.788 g) as a light orange powder.
Melting point (MeCN/Et_2O): 169.5 – 171.8 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.45 (d, *J* = 7.6 Hz, 1H), 8.33 (d, *J* = 7.9 Hz, 1H), 8.23 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.69 – 7.60 (m, 1H), 7.54 – 7.49 (m, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.14 (s, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 2.76 (s, 6H), 2.28 (s, 3H), 2.22 (s, 3H).

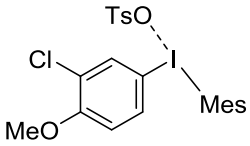
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 154.8, 153.3, 145.5, 142.7, 141.5, 137.5, 134.0, 129.5, 129.0, 127.9, 125.5, 125.5, 125.4, 125.3, 124.3, 123.4, 123.1, 122.1, 111.8, 96.1, 26.2, 20.7, 20.3.
FTIR: 3008, 2989, 1576, 1455, 1173, 1120, 1031, 1008, 814 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{21}H_{18}IO^+$: 413.0397; found: 413.0408

Compound 2.21



Prepared according to the general procedure B on 3.22 mmol and obtained an isolated yield of 68% (1.120 g) as a white powder.
Melting point (MeCN/Et_2O): 181.4 – 183.7 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.11 (d, *J* = 1.9 Hz, 1H), 7.56 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 2H), 6.73 (s, 2H), 6.60 (d, *J* = 7.8 Hz, 2H), 2.10 (s, 6H), 2.02 (s, 3H), 1.81 (s, 3H), 1.79 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 149.6, 145.5, 143.2, 141.6, 138.0, 137.5, 136.6, 135.6, 129.9, 129.7, 127.9, 125.3, 122.8, 110.9, 26.2, 20.7, 20.4, 19.1.
FTIR: 2988, 1524, 1345, 1174, 1120, 1007, 680 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{17}INO_2^+$: 382.0298; found: 382.0313

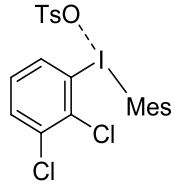
Compound 2.22



Prepared according to the general procedure B on 2.99 mmol and obtained an isolated yield of 84% (1.410 g) as a white powder.
Melting point (MeCN/Et_2O): 185.2 – 187.5 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.15 (d, *J* = 2.3 Hz, 1H), 7.89 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.20 (s, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 3.89 (s, 3H), 2.60 (s, 6H), 2.29 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 157.1, 145.6, 142.9, 141.4, 137.5, 135.2, 135.2, 129.6, 127.9, 125.4, 123.1, 123.1, 115.6, 102.8, 56.6, 26.2, 20.7, 20.4.
FTIR: 3018, 2918, 1736, 1457, 1373, 1216, 1008 cm^{-1}

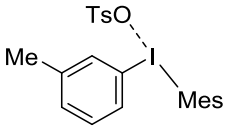
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{17}ClIO^+$: 387.0007; found: 387.0016

Compound 2.23



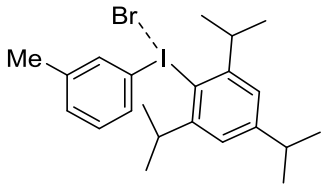
Prepared according to the general procedure B on 3.02 mmol and obtained an isolated yield of 85% (1.4485 g) as a white powder.
Melting point ($MECN/Et_2O$): 161.5 – 163.2 °C.
^{1}H NMR (400 MHz, $[D_6]$ DMSO) δ = 8.18 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.92 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.21 (s, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 2.61 (s, 6H), 2.29 (s, 6H, overlapping methyl signals).
^{13}C NMR (101 MHz, $[D_6]$ DMSO) δ = 145.3, 143.1, 141.8, 137.6, 137.4, 134.3, 133.8, 132.3, 131.2, 129.9, 127.9, 125.3, 123.1, 117.9, 26.1, 20.7, 20.4.
FTIR: 3012, 2990, 1456, 1403, 1168, 1119, 1030, 1007 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{15}H_{14}Cl_2I^+$: 390.9512; found: 390.9523

Compound 2.24



Prepared according to the general procedure A on 3.0 mmol and obtained an isolated yield of 81% (1.236 g) as a white powder.
Melting point ($MeCN/Et_2O$): 167.2 – 169.1 °C.
^{1}H NMR (400 MHz, $[D_6]$ DMSO) δ = 7.84 (s, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.45 (m, 3H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.19 (s, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 2.60 (s, 6H), 2.31 (s, 3H), 2.28 (s, 6H, overlapping methyl signals).
^{13}C NMR (101 MHz, $[D_6]$ DMSO) δ = 145.5, 142.8, 141.8, 141.4, 137.5, 134.5, 132.3, 131.5, 131.4, 129.6, 127.9, 125.4, 122.4, 114.2, 26.2, 20.7, 20.6, 20.4.
FTIR: 3017, 2921, 1595, 1452, 1172, 1120, 1032, 1008 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{16}H_{18}I^+$: 337.0448; found: 337.0457

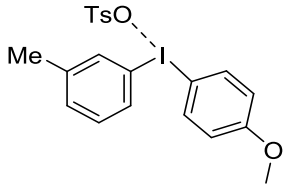
Compound 2.25



Prepared according to the general procedure A on 3.0 mmol and tri-isopropyl benzene (0.79 mL, 3.3mmol, 1.1 equiv.) was used instead of mesitylene. After the reaction, MeCN was evaporated and KBr (sat) was added (10 mL) and extracted the organic layer with DCM (3 X 5 mL). The organic layer was evaporated and triturated with diethyl ether and obtained an isolated yield of 50% (0.755 g) as a white powder.

Melting point (MeCN/Et_2O): 163.5 – 165.2 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 7.77 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.30 (m, 2H), 7.26 (s, 2H), 3.52 – 3.32 (m, 2H), 2.96 (m, 1H), 2.29 (s, 3H), 1.24 (d, *J* = 6.7 Hz, 12H), 1.21 (d, *J* = 6.9 Hz, 6H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 153.3, 150.5, 141.2, 133.7, 131.6, 131.2, 130.3, 125.8, 124.2, 118.1, 38.5, 33.2, 23.8, 23.4, 20.7.
FTIR: 3019, 2998, 1277, 1189, 1008 cm^{-1}
HRMS (ESI) m/z: $[M - Br]^+$ calculated for $C_{22}H_{30}I^+$: 421.1387; found: 421.1372

Compound 2.26

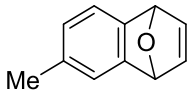


Prepared according to the general procedure A on 3.0 mmol and anisole (0.36 mL, 3.3 mmol, 1.1 equiv.) was used instead of mesitylene and obtained an isolated yield of 84% (1.2612 g) as a white powder.
Melting point (MeCN/Et_2O): 122.3 – 123.1 °C.
^{1}H NMR (400 MHz, [D_6] DMSO) δ = 8.16 (d, *J* = 9.0 Hz, 2H), 8.08 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 9.1 Hz, 2H), 3.78 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H).
^{13}C NMR (101 MHz, [D_6] DMSO) δ = 161.8, 145.5, 141.4, 137.5, 137.1, 134.9, 132.3, 131.8, 131.1, 127.9, 125.4, 117.3, 116.7, 105.3, 55.6, 20.7, 20.6.
FTIR: 3058, 2922, 1574, 1488, 1256, 1177, 1120, 1031, 1009 cm^{-1}
HRMS (ESI) m/z: $[M - OTs]^+$ calculated for $C_{14}H_{14}IO^+$: 325.0084; found: 325.0078

5.6: General procedure for the coupling reaction with furan

The iodonium salt (0.5 mmol, 1 equiv.) is weighed out in air and placed in an oven-dried vial containing a magnetic stir bar and is sealed with a Teflon-lined septum cap. The vial is purged with nitrogen gas for approximately 10 minutes. Toluene (7 mL) and furan (200 µL, 2.75 mmol, 5.5 equiv.) are added sequentially via syringe through the septum. The vial is placed in an ice-cooled water bath maintained at 13 °C. LiHMDS (0.5 mL (1 M in toluene), 0.5 mmol, 1 equiv.) is added via syringe through the septum and the reaction is stirred for 3 hours. The vial is removed from the ice-bath and the reaction is quenched with an aqueous solution of ammonium chloride (5 mL). The biphasic mixture is placed in a separatory funnel and washed with DCM (3 × 5 mL). The combined organic phases are dried with $MgSO_4$, the drying agent removed by suction filtration, and the solvent removed on the rotary evaporator. The crude residue is purified by flash column chromatography on silica gel with ether/hexane mixture as the eluent.

Compound 2.27

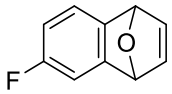


Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 70% (0.0563 g) as a yellow liquid. Spectral data is consistent with that of previously reported.[112]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (d, *J* = 7.2 Hz, 1H), 7.08 (s, 1H), 7.04 – 6.95 (m, 2H), 6.76 (dd, *J* = 7.2, 0.7 Hz, 1H), 5.66 (m, 2H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.3, 146.0, 143.2, 142.7, 134.7, 125.0, 121.6, 119.9, 82.3, 82.2, 21.3.

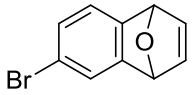
Compound 2.28



Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 58% (0.047 g) as yellow liquid. Spectral data is consistent with that of previously reported.[113]

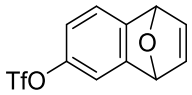
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.17 – 7.11 (m, 1H), 7.08 – 6.95 (m, 3H), 6.63 (m, 1H), 5.69 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.5 (d, $J_{C\text{-}F}$ = 244.8 Hz), 151.9 (d, $J_{C\text{-}F}$ = 8.5 Hz), 144.2 (d, $J_{C\text{-}F}$ = 2.5 Hz), 143.5, 142.5, 120.6 (d, $J_{C\text{-}F}$ = 8.8 Hz), 110.3 (d, J = 22.6 Hz), 109.6 (d, $J_{C\text{-}F}$ = 25.3 Hz), 82.3 (d, $J_{C\text{-}F}$ = 2.6 Hz), 82.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ = -117.6.

Compound 2.29



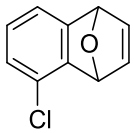
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 79% (0.085 g) as yellow liquid. Spectral data is consistent with that of previously reported.[114]
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 (s, 1H), 7.12-7.08 (m, 2H), 7.05 – 6.95 (m, 2H), 5.67 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.7, 148.2, 143.1, 142.6, 127.6, 123.9, 121.4, 118.7, 82.0. One carbon signal is missing due to overlapping signals.

Compound 2.30



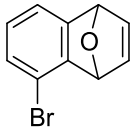
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 67% (0.0984 g) as yellow liquid.
R_f = 0.21 in 20% diethyl ether in hexanes
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.25 (d, J = 7.6 Hz, 1H), 7.16 (s, 1H), 7.05 (s, 2H), 6.88 (d, J = 7.8 Hz, 1H), 5.73 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.4, 149.4, 146.8, 143.1, 142.8, 120.9, 118.7 (q, $J_{C\text{-}F}$ = 321.0 Hz), 117.6, 114.5, 82.2, 82.0.
^{19}F NMR (376 MHz, $CDCl_3$) δ = -72.8.
FTIR: 3019, 1419, 1209, 1139, 845 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{11}H_8F_3O_4S^+$: 293.0090; found: 293.0084

Compound 2.31



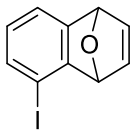
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 69% (0.062 g) as yellow liquid.
R_f = 0.36 in 20% diethyl ether in hexanes
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.13 – 7.09 (m, 1H), 7.09 – 7.02 (m, 2H), 6.91 (m, 2H), 5.87 (br, 1H), 5.74 (br, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.6, 149.8, 143.4, 142.5, 128.4, 127.1, 119.0, 114.6, 83.2, 82.8.
FTIR: 3071, 3017, 1588, 1450, 1279, 1115, 854 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{10}H_8ClO^+$: 179.0258; found: 179.0257

Compound 2.32



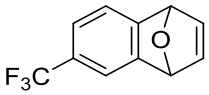
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 84% (0.0945 g) as pale yellow liquid. Spectral data is consistent with that of previously reported.[115]
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.14 (d, *J* = 7.0 Hz, 1H), 7.09 – 7.00 (m, 3H), 6.83 (dd, *J* = 8.2, 7.0 Hz, 1H), 5.80 – 5.78 (m, 1H), 5.78 – 5.75 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.6, 149.8, 143.4, 142.5, 128.4, 127.1, 119.0, 114.6, 83.2, 82.8.

Compound 2.33



Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 89% (0.1207 g) as yellow liquid.
R_f = 0.41 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 1H), 7.10 – 7.03 (m, 2H), 6.74 – 6.65 (m, 1H), 5.83 (m, 1H), 5.63 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.6, 151.1, 143.4, 142.4, 133.8, 127.1, 119.7, 86.3, 85.6, 83.5.
FTIR: 3009, 2948, 1574, 1447, 1278, 1098, 1053 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{10}H_8IO^+$: 270.9614; found: 270.9606

Compound 2.34



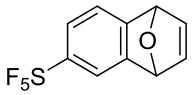
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 65% (0.063 g) as yellow liquid. Spectral data is consistent with that of previously reported.[116]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (s, 1H), 7.35 – 7.25 (m, 2H), 7.08 – 6.99 (m, 2H), 5.75 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.2, 150.3, 143.1, 142.7, 127.5 (q, J_{C-F} = 33.0 Hz), 124.3 (q, J_{C-F} = 272.0 Hz), 123.0 (q, J_{C-F} = 4.0 Hz), 120.0, 116.9 (q, J_{C-F} = 4.0 Hz), 82.1. One carbon signal is missing due to overlapping signals.

^{19}F NMR (376 MHz, $CDCl_3$) δ = -61.9.

Compound 2.35



Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 67% (0.0906 g) as colorless liquid.

R_f = 0.31 in 20% diethyl ether in hexanes

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, J = 1.8 Hz, 1H), 7.43 (dd, J = 7.8, 1.9 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.09 – 7.01 (m, 2H), 5.78 – 5.72 (m, 2H).

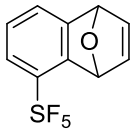
^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.8, 151.0 (p, J = 17.0 Hz), 150.3, 143.2, 142.5, 123.6 (p, J = 5.0 Hz), 118.0 (p, J = 4.7 Hz), 82.2, 81.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ = 86.02 – 82.09 (p, J_{F-F} = 151.0 Hz), 64.63 (d, J_{F-F} = 149.7 Hz).

FTIR: 3099, 3019, 2919, 1455, 1415, 1281, 1063, 994, 832 cm^{-1}

HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{10}H_8F_5OS^+$: 271.0211 ; found: 271.0200

Compound 2.36

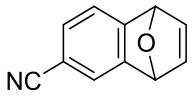


Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 50% (0.0684 g) as colorless liquid.

R_f = 0.29 in 20% Diethyl ether in hexanes

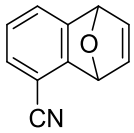
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 7.0 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.10 – 7.00 (m, 3H), 6.16 – 6.03 (m, 1H), 5.86 – 5.75 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.8, 147.2 (p, $J_{C\text{-}F}$ = 18.2 Hz), 146.6 (p, $J_{C\text{-}F}$ = 3.5 Hz), 144.1, 142.1, 126.2, 122.7, 122.2 (p, $J_{C\text{-}F}$ = 4.2 Hz), 83.4 (p, $J_{C\text{-}F}$ = 3.2 Hz), 82.4.
^{19}F NMR (377 MHz, $CDCl_3$) δ = 85.56 – 83.09 (p, $J_{F\text{-}F}$ = 150.0 Hz), 64.63 (d, $J_{F\text{-}F}$ = 149.7 Hz).
FTIR: 3021, 2919, 1457, 1418, 1282, 1011, 831 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{10}H_8F_5OS^+$: 271.0211 ; found: 271.0202

Compound 2.37



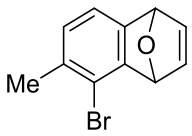
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 65% (0.056 g) as yellow liquid. Spectral data is consistent with that of previously reported.[117]
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 – 7.42 (m, 1H), 7.38 – 7.29 (m, 2H), 7.04 (m, 2H), 5.76 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.6, 150.5, 143.1, 142.5, 130.9, 122.8, 120.7, 119.1, 108.7, 82.1, 81.8.

Compound 2.38



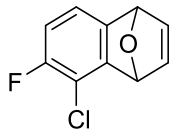
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 40% (0.0345 g) as yellow liquid.
R_f = 0.27 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 7.1 Hz, 1H), 7.19 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.14 – 7.04 (m, 3H), 5.94 (m, 1H), 5.79 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.6, 150.7, 143.7, 142.2, 127.1, 126.1, 123.8, 116.8, 105.1, 82.4, 81.5.
FTIR: 3009, 2971, 2231, 1456, 1278, 1054, 1036cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{11}H_8NO^+$: 170.0600; found: 170.0602

Compound 2.39



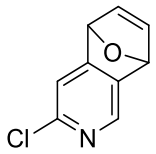
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 72% (0.0872 g) as yellow liquid.
R_f = 0.45 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 – 7.00 (m, 3H), 6.83 (dd, *J* = 7.1, 0.8 Hz, 1H), 5.79 (m, 1H), 5.75 (m, 1H), 2.32 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.5, 148.8, 143.7, 142.2, 134.6, 127.2, 118.7, 117.5, 83.3, 83.2, 22.1.
FTIR: 3009, 2971, 1453, 1278, 1102, 1054, 1032, 861 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{11}H_{10}BrO^+$: 236.9910; found: 236.9908

Compound 2.40



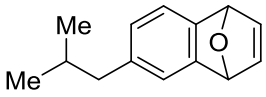
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 82% (0.0818 g) as yellow liquid.
R_f = 0.30 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.12 – 6.97 (m, 3H), 6.72 (dd, *J* = 9.5, 7.7 Hz, 1H), 5.87 (m, 1H), 5.73 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8 (d, J_{C-F} = 248.1 Hz), 150.2, 146.0 (d, J_{C-F} = 2.8 Hz), 143.9, 142.0, 118.6 (d, J_{C-F} = 7.8 Hz), 115.2 (d, J_{C-F} = 21.7 Hz), 112.0 (d, J_{C-F} = 22.7 Hz), 82.7, 81.4 (d, J_{C-F} = 2.8 Hz).
^{19}F NMR (376 MHz, $CDCl_3$) δ = -121.9.
FTIR: 3084, 3019, 1598, 1456, 1248, 1125, 867 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{10}H_7ClFO^+$: 197.0164; found: 197.0163

Compound 2.41



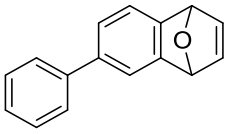
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 51% (0.0461 g) as yellow liquid
R_f = 0.06 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 (s, 1H), 7.23 (s, 1H), 7.07 (dd, *J* = 5.6, 1.9 Hz, 1H), 6.98 (dd, *J* = 5.6, 1.9 Hz, 1H), 5.83 – 5.77 (m, 1H), 5.74 – 5.68 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.6, 148.5, 143.5, 143.5, 141.4, 138.8, 117.3, 81.5, 80.2.
FTIR: 3021, 2920, 1605, 1579, 1453, 1342, 1298, 1132, 847 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_9H_7ClNO^+$: 180.0211; found: 180.0208

Compound 2.42



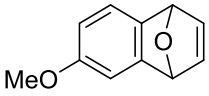
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 72% (0.0730 g) as yellow liquid.
R_f = 0.36 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.13 (d, *J* = 7.2 Hz, 1H), 7.05 (s, 1H), 7.03 – 6.97 (m, 2H), 6.75 – 6.69 (m, 1H), 5.67 (m, 2H), 2.41 (d, *J* = 7.2 Hz, 2H), 1.81 (m, 1H), 0.88 (m, 6H, overlapping methyl signals).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.0, 146.2, 143.1, 142.8, 138.6, 125.3, 121.5, 119.7, 82.3, 82.2, 45.3, 30.2, 22.4, 22.3.
FTIR: 3008, 2954, 1599, 1465, 1281, 1226, 1090, 950 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{14}H_{17}O^+$: 201.1274; found: 201.1274 (it is same)

Compound 2.43



Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 67% (0.0738 g) as yellow liquid.
R_f = 0.16 in 15% Diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 – 7.49 (m, 2H), 7.48 – 7.44 (m, 1H), 7.44 – 7.35 (m, 2H), 7.34 – 7.24 (m, 2H), 7.17 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.02 (s, 2H), 5.89 – 5.48 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.9, 148.0, 142.9, 142.9, 141.2, 138.5, 128.7, 127.2, 127.1, 124.0, 120.3, 119.6, 82.4, 82.2.
FTIR: 2948, 2835, 1652, 1455, 1413, 1138, 1031 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{13}O^+$: 221.0961; found: 221.0971

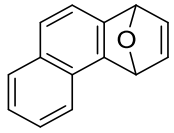
Compound 2.44



Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 67% (0.0596 g) as yellow liquid. Spectral data is consistent with that of previously reported.[118]
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (d, *J* = 7.8 Hz, 1H), 7.05 – 6.94 (m, 2H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.41 (dd, *J* = 7.8, 2.3 Hz, 1H), 5.69 – 5.62 (m, 2H), 3.76 (s, 3H).

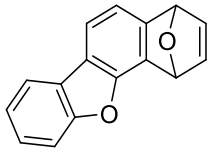
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.4, 151.0, 143.5, 142.2, 140.4, 120.3, 109.7, 107.2, 82.4, 82.0, 55.5.

Compound 2.45

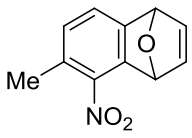


Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 53% (0.0525 g) as yellow liquid.
R_f = 0.40 in 20% Diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 – 7.73 (m, 2H), 7.59 – 7.48 (m, 2H), 7.45-7.41 (m, 1H), 7.37-7.33 (m, 1H), 7.17 (m, 2H), 6.24 (m, 1H), 5.90 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.3, 147.8, 144.8, 143.4, 131.7, 128.7, 127.6, 126.2, 125.3, 125.1, 122.6, 119.3, 83.4, 81.2.
FTIR: 3006, 1517, 1276, 1038, 1003, 823 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{14}H_{11}O^+$: 195.0804; found: 195.0801

Compound 2.46



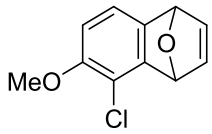
Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 75% (0.0879 g) as yellow liquid.
R_f = 0.34 in 20% Diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 – 7.84 (m, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.41 (td, *J* = 8.3, 7.8, 1.3 Hz, 1H), 7.29 (td, *J* = 7.3, 1.3 Hz, 2H), 7.13-7.09 (m, 2H), 6.22 (m, 1H), 5.86 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.6, 150.0, 149.0, 143.9, 142.7, 131.1, 127.3, 124.2, 123.5, 122.8, 120.7, 117.3, 115.4, 111.5, 82.9, 80.1.
FTIR: 3011, 1650, 1459, 1414, 1278, 1182 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{16}H_{11}O_2^+$: 235.0754; found: 235.0750
Compound 2.47



Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 79% (0.0809 g) as brown solid.
R_f = 0.22 in 20% diethyl ether in hexanes
Melting point = 87.2 – 88.0 ^{o}C

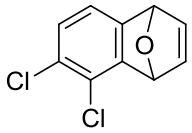
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (d, *J* = 7.2 Hz, 1H), 7.12 (m, 2H), 6.99 – 6.89 (m, 1H), 6.12 – 6.07 (m, 1H), 5.77 (s, 1H), 2.49 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.0, 147.3, 144.2, 143.7, 142.1, 129.4, 129.1, 123.4, 82.7, 82.1, 19.7.
FTIR: 3029, 2990, 1537, 1350, 1278, 1108 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{11}H_{10}NO_3^+$: 204.0655; found: 204.0650

Compound 2.48



Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 83% (0.083 g) and 90% (0.090 g) as brown oil.
R_f = 0.26 in 15% Diethyl ether in hexanes
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.05-7.02 (m, 3H), 6.43 (d, *J* = 7.7 Hz, 1H), 5.86 (m, 1H), 5.70 (m, 1H), 3.84 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.9, 149.2, 144.1, 143.9, 142.0, 141.7, 118.4, 107.1, 82.7, 81.6, 56.5.
FTIR: 3013, 2941, 2836, 1589, 1467, 1432, 1345, 1265, 1082, 1057,863 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{11}H_{10}ClO_2^+$: 209.0363(8); found: 209.0364(0)

Compound 2.49

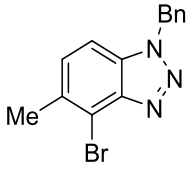


Prepared according to the general procedure C on 0.5 mmol scale and obtained an isolated yield of 75% (0.0806 g) as yellow liquid.
R_f = 0.41 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.12 – 7.00 (m, 4H), 5.86 (m, 1H), 5.73 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.9, 149.8, 143.7, 142.1, 129.3, 127.1, 125.4, 119.0, 82.9, 81.9.
FTIR: 2949, 2837, 1649, 1420, 1031, 861 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{10}H_7Cl_2O^+$: 212.9868; found: 212.9864

5.7: General procedure for coupling of arynes with nitrogen arynophiles

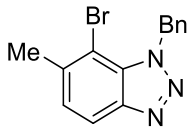
The iodonium salt (0.5 mmol, 1 equiv.) is weighed out in air and placed in an oven-dried vial containing a magnetic stir bar and is sealed with a Teflon-lined septum cap. The vial is purged with nitrogen gas for approximately 10 minutes. TBME (1.6 mL) and arynophile (1.0 mmol, 2.0 equiv.) are added sequentially via syringe through the septum. NaO^{t}-Bu (0.55 mmol, 1.1 equiv.) was added and the reaction is stirred at 50 ^{o}C for 90 mins. The vial is removed from the oil-bath and the reaction is quenched with an aqueous solution of ammonium chloride (5 mL). The biphasic mixture is placed in a separatory funnel and washed with DCM (3 × 5 mL). The combined organic phases are dried with $MgSO_4$, the drying agent removed by suction filtration, and the solvent removed on the rotary evaporator. The crude residue is purified by flash column chromatography on silica gel with ether/hexane mixture as the eluent.

Compound 2.50



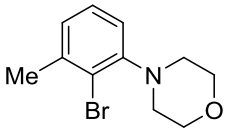
Prepared according to the general procedure D on 0.5 mmol scale and obtained an isolated yield of 50% (0.0703 g) as brown solid.
R_f = 0.18 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 6H), 7.15 (d, *J* = 8.4 Hz, 1H), 5.80 (s, 2H), 2.51 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.1, 134.4, 133.7, 132.1, 130.4, 129.0, 128.5, 127.5, 114.1, 108.4, 52.6, 30.9.
FTIR: 3031, 2922, 1649, 1495, 1252, 1088 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{14}H_{13}BrN_3^+$: 302.0287; found: 302.0280

Compound 2.51



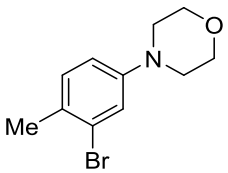
Prepared according to the general procedure D on 0.5 mmol scale and obtained an isolated yield of 13% (0.0184 g) as brown solid. The isomers were identified using NOESY and also from previously reported data.[119]
R_f = 0.20 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.23 (m, 4H), 7.21 – 7.15 (m, 2H), 6.22 (s, 2H), 2.52 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.1, 138.3, 136.6, 132.0, 128.7, 127.9, 127.5, 126.9, 118.6, 103.9, 52.5, 22.8.
FTIR: 3032, 2921, 1648, 1488, 1212 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{14}H_{13}BrN_3^+$: 302.0287 ; found: 302.0283

Compound 2.52



Prepared according to the general procedure D on 0.5 mmol scale and obtained an isolated yield of 14% (0.019 g) as yellow oil.
R_f = 0.5 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 (t, *J* = 7.7 Hz, 1H), 7.02 – 6.94 (m, 1H), 6.94 – 6.87 (m, 1H), 3.94 – 3.80 (m, 4H), 3.06 – 2.95 (m, 4H), 2.43 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.7, 139.8, 127.5, 125.9, 122.8, 118.3, 67.3, 52.4, 24.1.
FTIR: 2948, 2935, 1650, 1453, 1373, 1229, 1031 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{11}H_{15}BrNO^+$: 256.0332; found: 256.0327

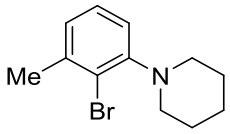
Compound 2.53



Prepared according to the general procedure D on 0.5 mmol scale and obtained an isolated yield 58% (0.0760 g) as yellow oil.
R_f = 0.32 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (d, *J* = 8.4 Hz, 1H), 7.08 (d, *J* = 2.6 Hz, 1H), 6.77 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.90 – 3.79 (m, 4H), 3.16 – 3.04 (m, 4H), 2.31 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.5, 130.9, 128.9, 125.4, 119.4, 114.9, 66.8, 49.4, 21.8.

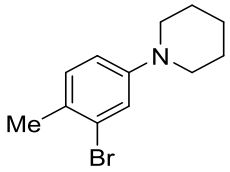
FTIR: 2961, 2853, 1606, 1497, 1449, 1379, 1230, 1121, 1025, 941 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{11}H_{15}BrNO^+$: 256.0332; found: 256.0327

Compound 2.54



Prepared according to the general procedure D on 0.5 mmol scale and obtained an isolated yield of 16% (0.0206 g) as yellow liquid.
R_f = 0.9 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.14 (t, *J* = 7.7 Hz, 1H), 6.95 – 6.86 (m, 2H), 2.92 (m, 4H), 2.42 (s, 3H), 1.80 – 1.69 (m, 4H), 1.58 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.4, 139.5, 127.2, 125.1, 123.1, 118.4, 53.7, 26.3, 24.3, 24.2.
FTIR: 2919, 2850, 1456, 1241, 1116, 1027 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_{17}BrN^+$: 254.0539 ; found: 254.0537

Compound 2.55



Prepared according to the general procedure D on 0.5 mmol scale and obtained an isolated yield of 62% (0.078 g) as yellow liquid.
R_f = 0.83 in 20% diethyl ether in hexanes
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.09 (d, *J* = 2.6 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.15 – 3.02 (m, 4H), 2.29 (s, 3H), 1.73 – 1.64 (m, 4H), 1.60 – 1.51 (m, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.4, 130.7, 127.9, 125.3, 120.1, 115.8, 50.7, 25.7, 24.2, 21.7.
FTIR: 2920, 2850, 1605, 1495, 1232, 1026 cm^{-1}
HRMS (ESI) m/z: $[M + H]^+$ calculated for $C_{12}H_{17}BrN^+$: 254.0539; found: 254.0533

5.8: ^{1}H, ^{13}C, ^{19}F NMR spectra of new compounds

Figure 5.1: ^{1}H NMR of 1.1 at 400 MHz in DMSO-d_6 at 298K

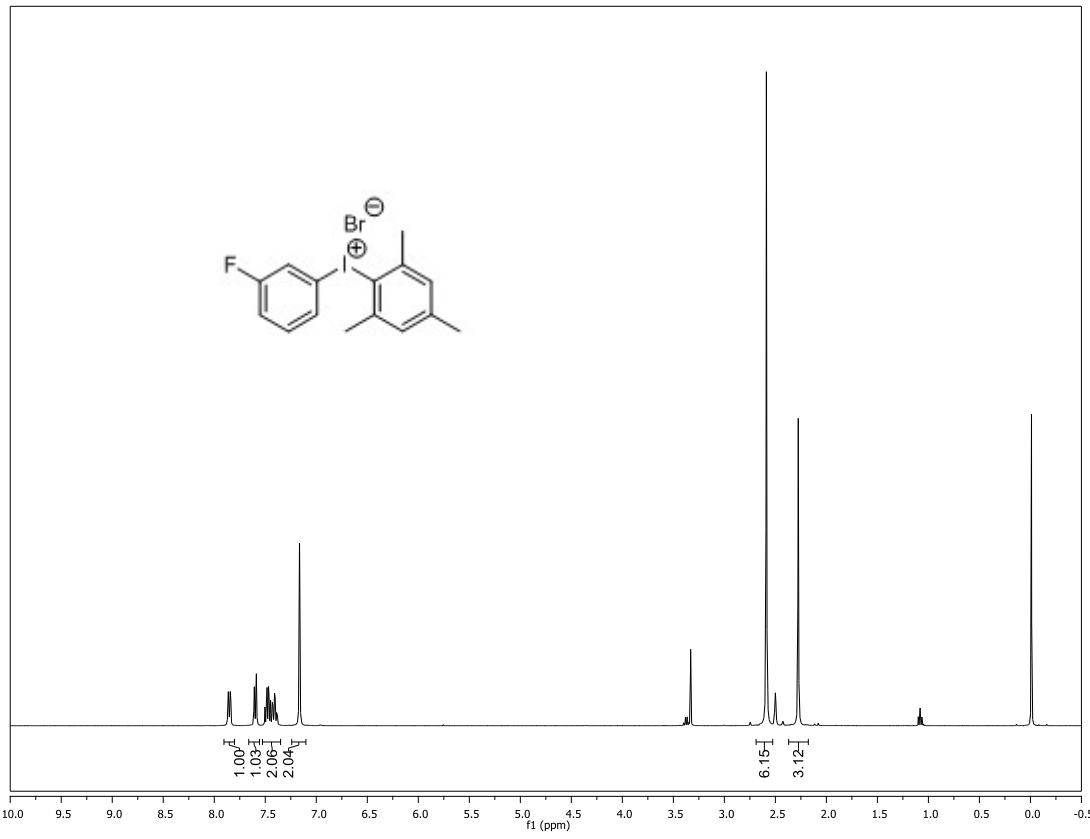


Figure 5.2: ^{13}C NMR of 1.1 at 100 MHz in DMSO-d_6 at 298K

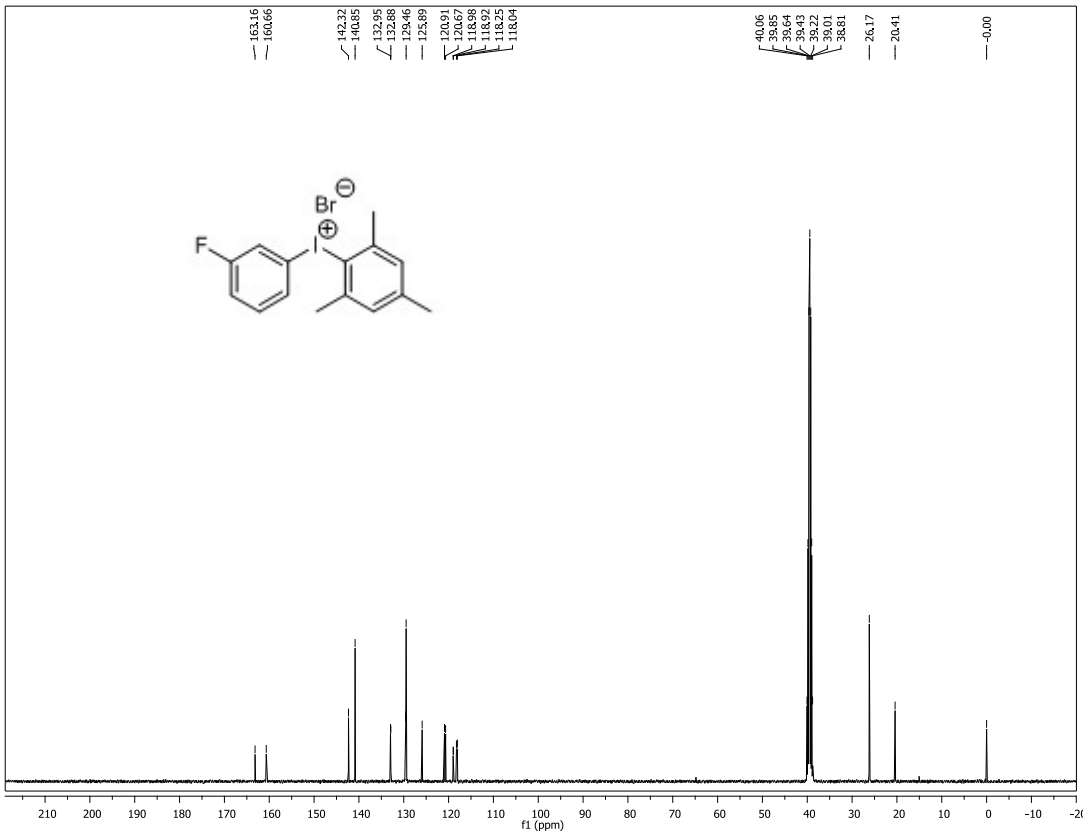


Figure 5.3: ^{19}F NMR of 1.1 at 377 MHz in DMSO-d_6 at 298K

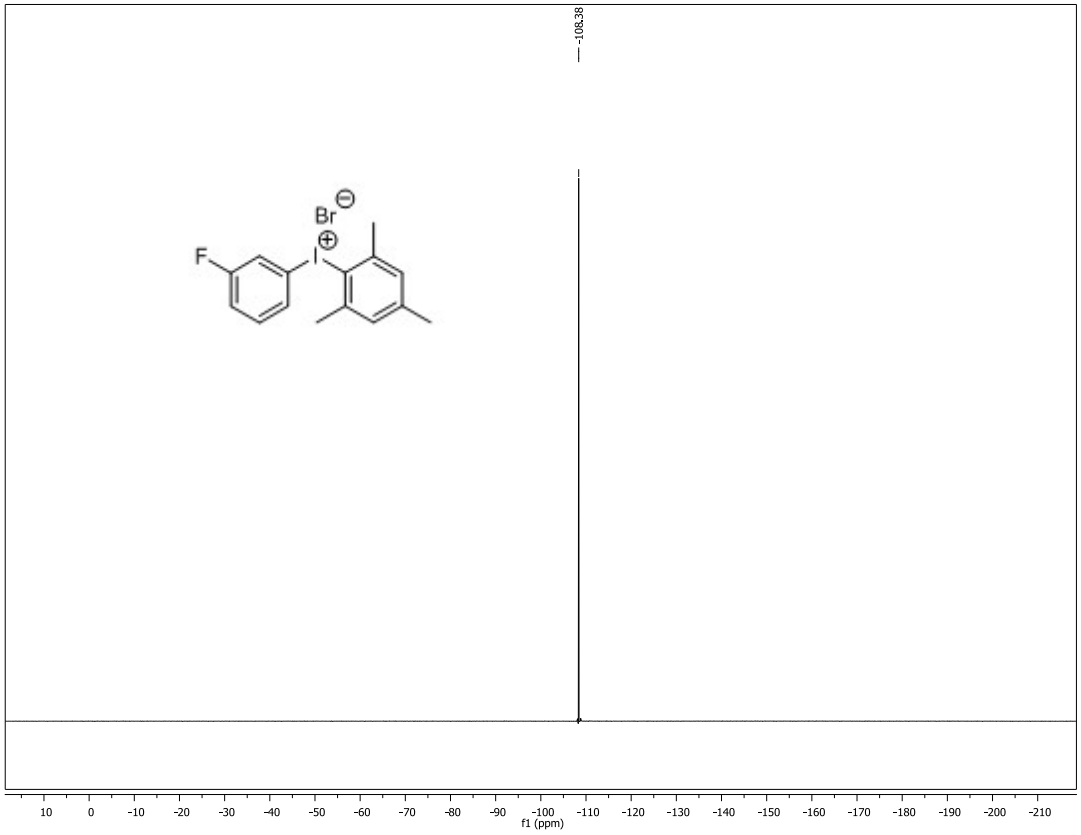


Figure 5.4: ^{1}H NMR of 1.2 at 400 MHz in DMSO-d_6 at 298K

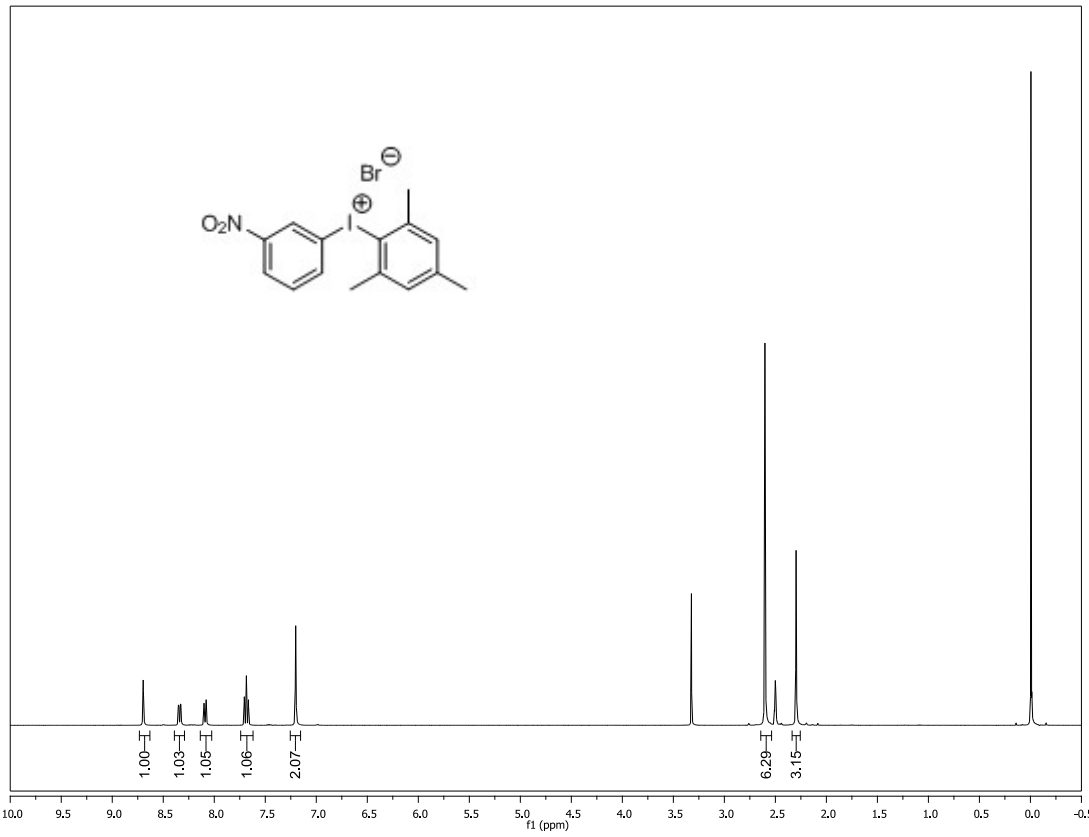


Figure 5.5: ^{13}C NMR of 1.2 at 100 MHz in DMSO-d_6 at 298K

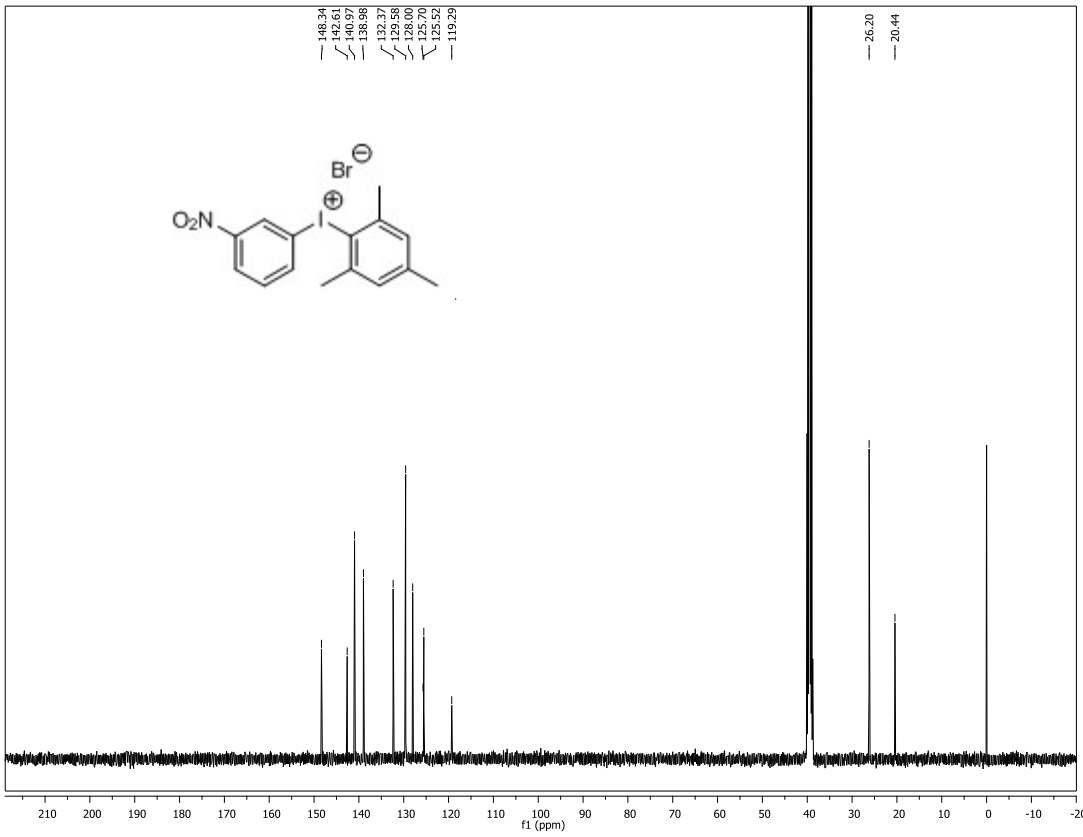


Figure 5.6: ^{1}H NMR of 1.3 at 400 MHz in DMSO-d_6 at 298K

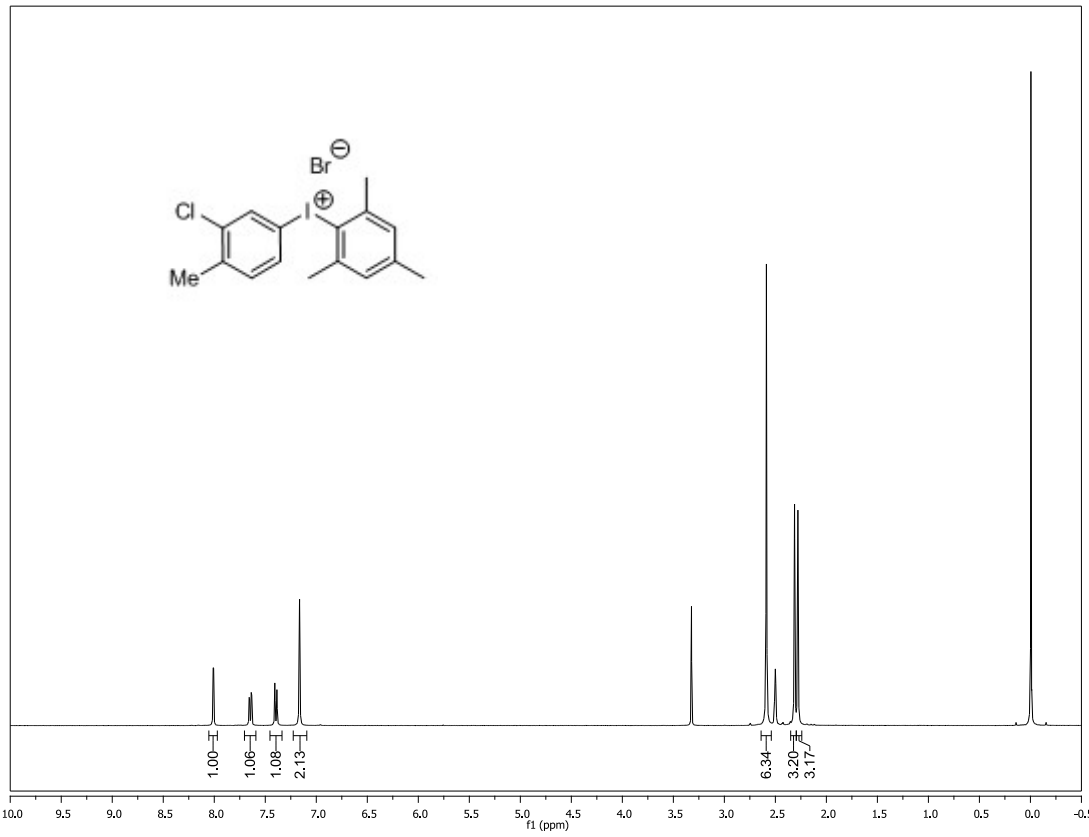


Figure 5.7: ^{13}C NMR of 1.3 at 100 MHz in DMSO-d_6 at 298K

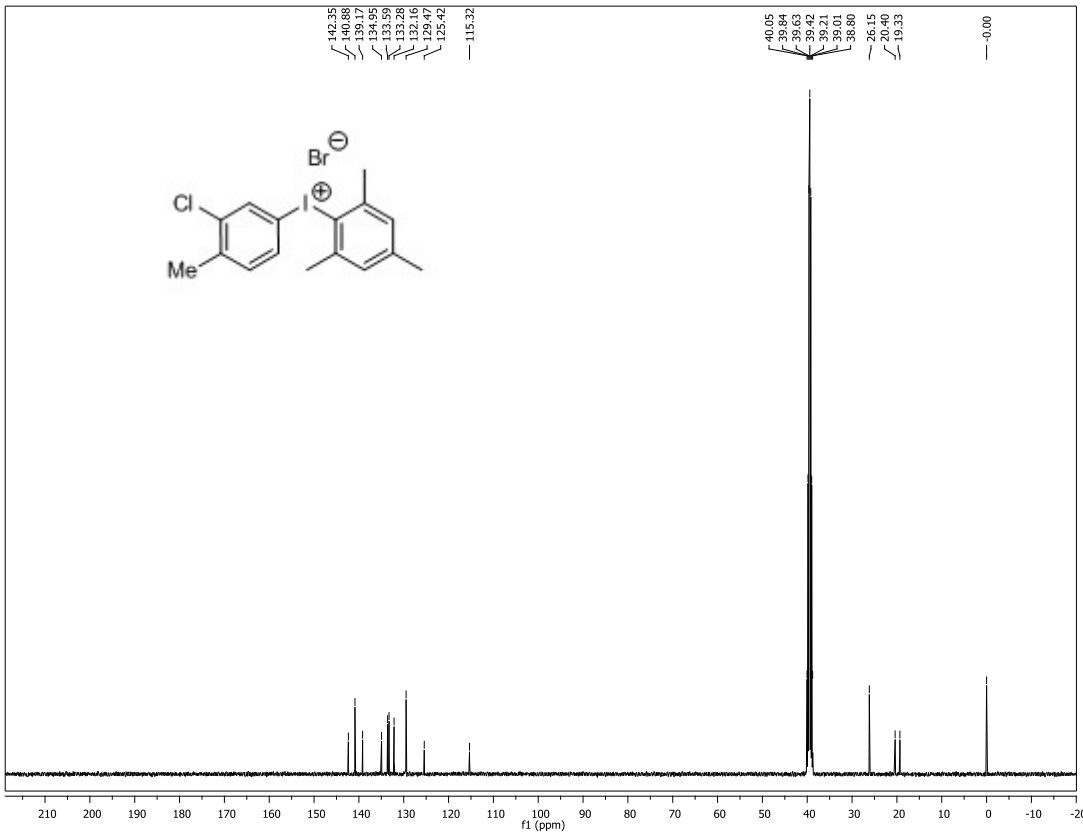


Figure 5.8: ^{1}H NMR of 1.4 - Mes at 400 MHz in DMSO-d_6 at 298K

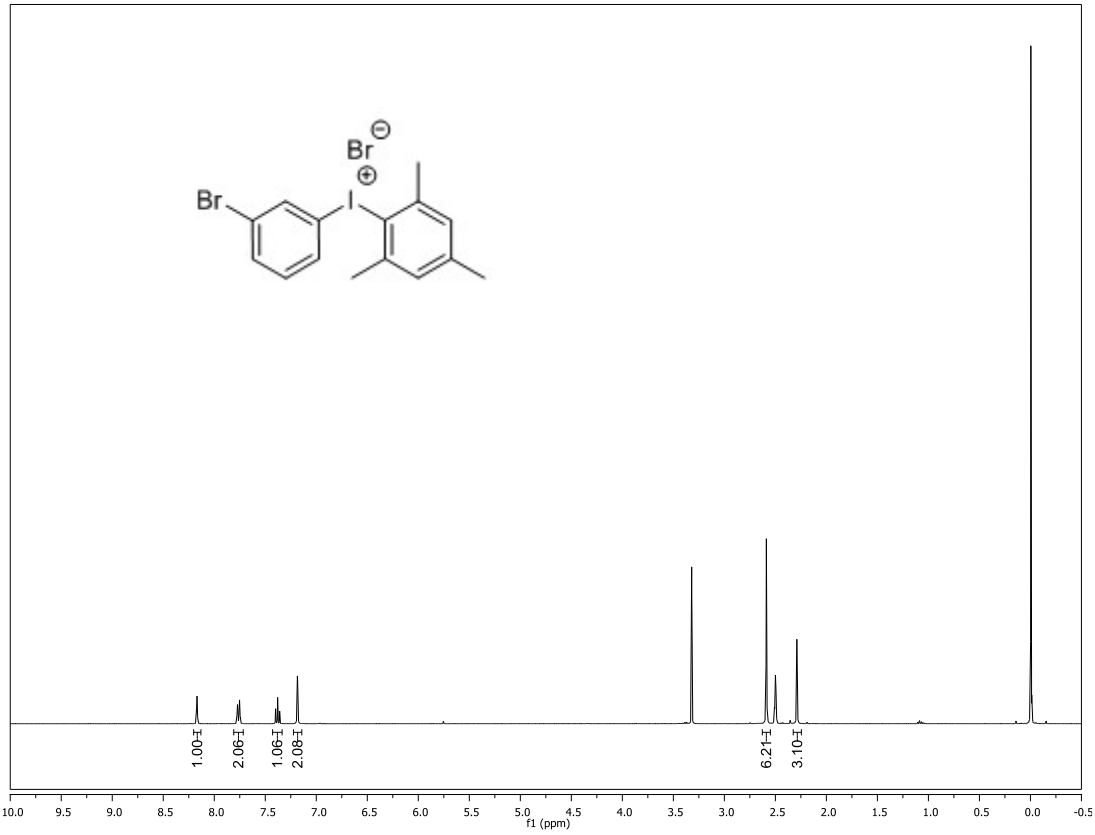


Figure 5.9: ^{13}C NMR of 1.4 - Mes at 100 MHz in DMSO-d_6 at 298K

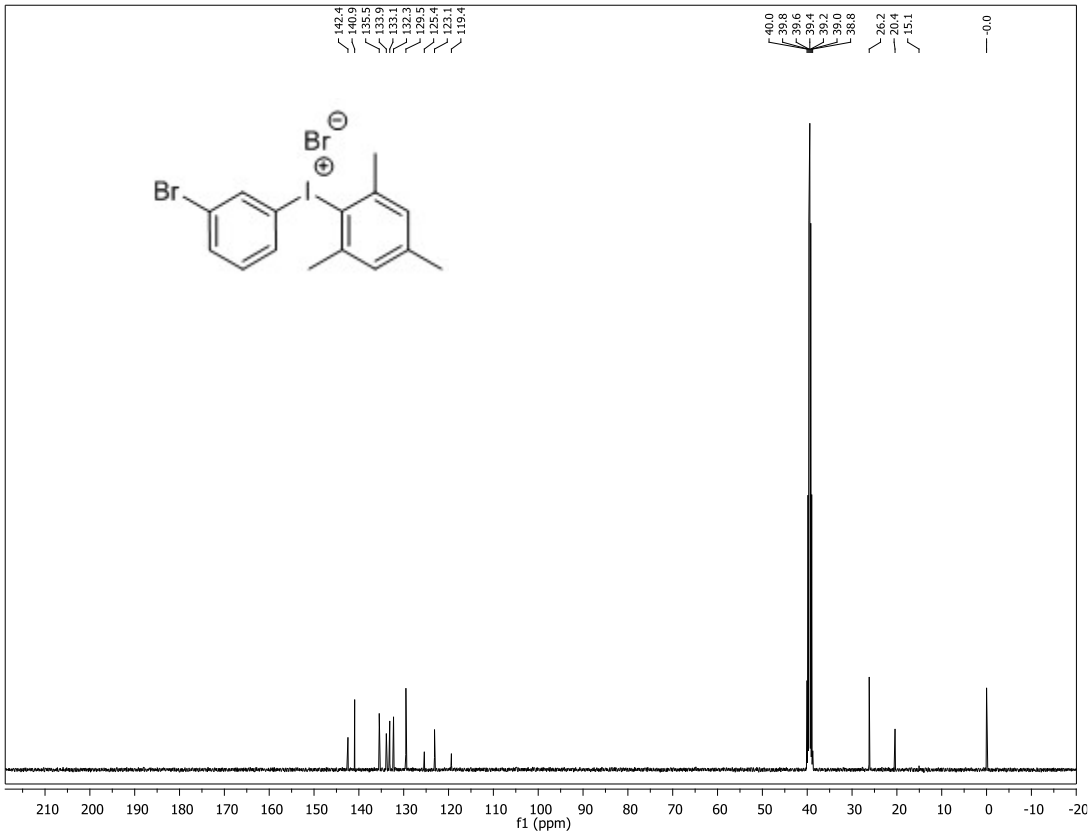


Figure 5.10: ^{1}H NMR of 1.4 - Ph at 400 MHz in DMSO-d_6 at 298K

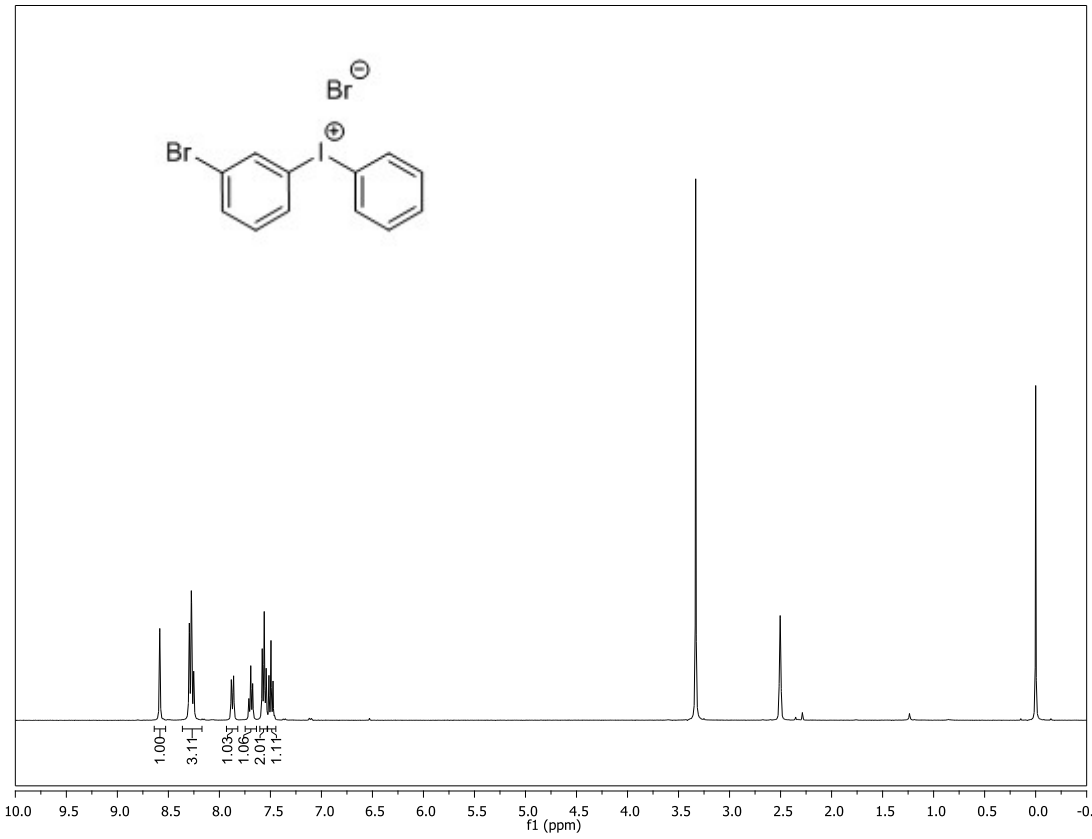


Figure 5.11: ^{13}C NMR of 1.4 - Ph at 100 MHz in DMSO-d_6 at 298K

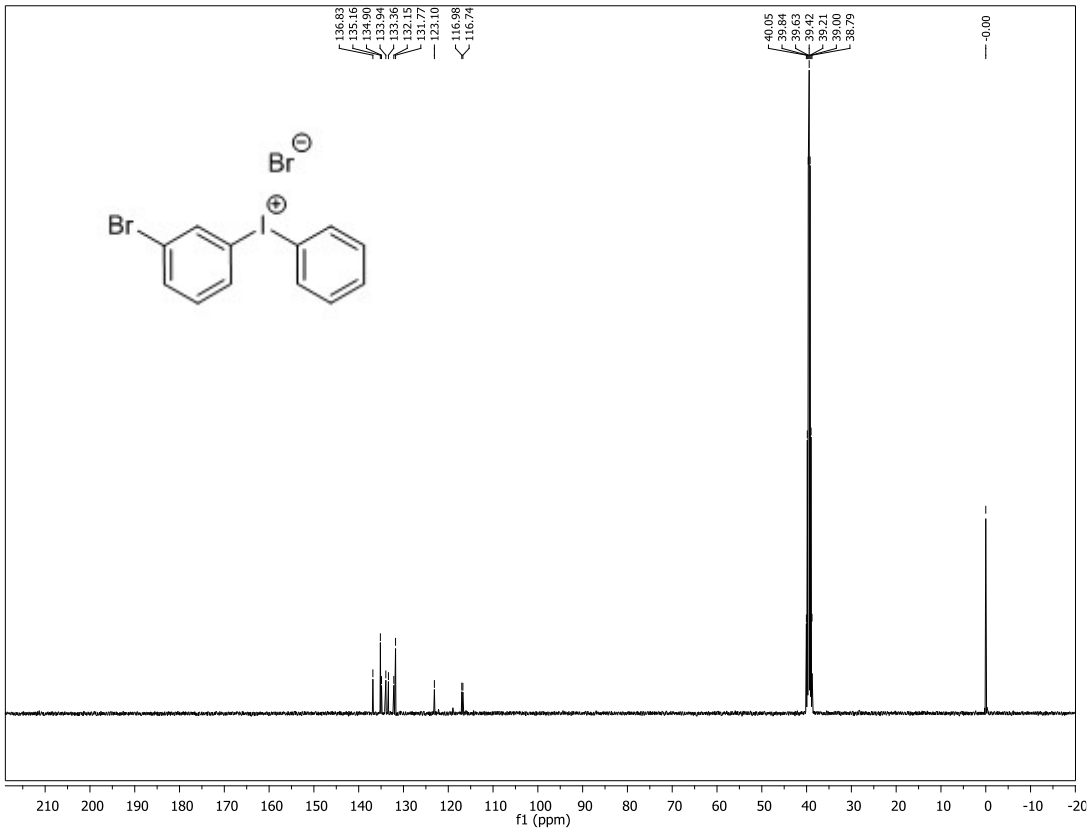


Figure 5.12: ^{1}H NMR of 1.4 -TMB at 400 MHz in DMSO-d_6 at 298K

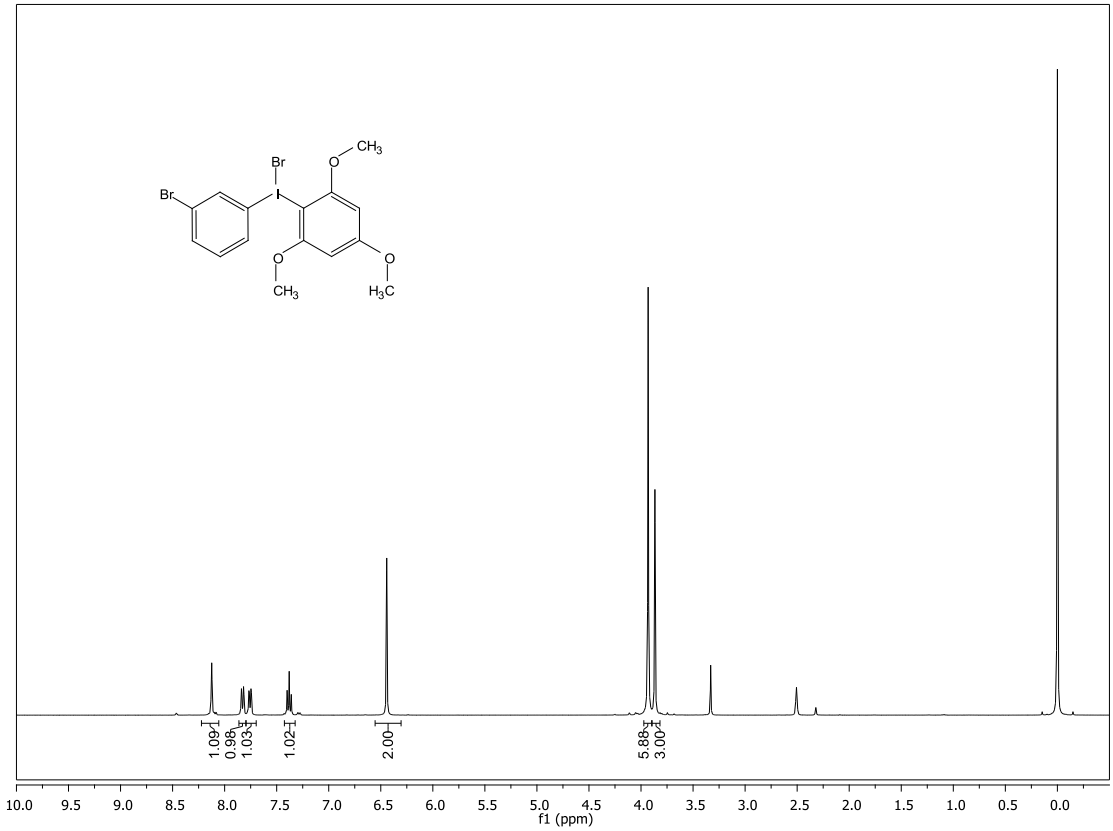


Figure 5.13: ^{13}C NMR of 1.4 -TMB at 400 MHz in DMSO-d_6 at 298K

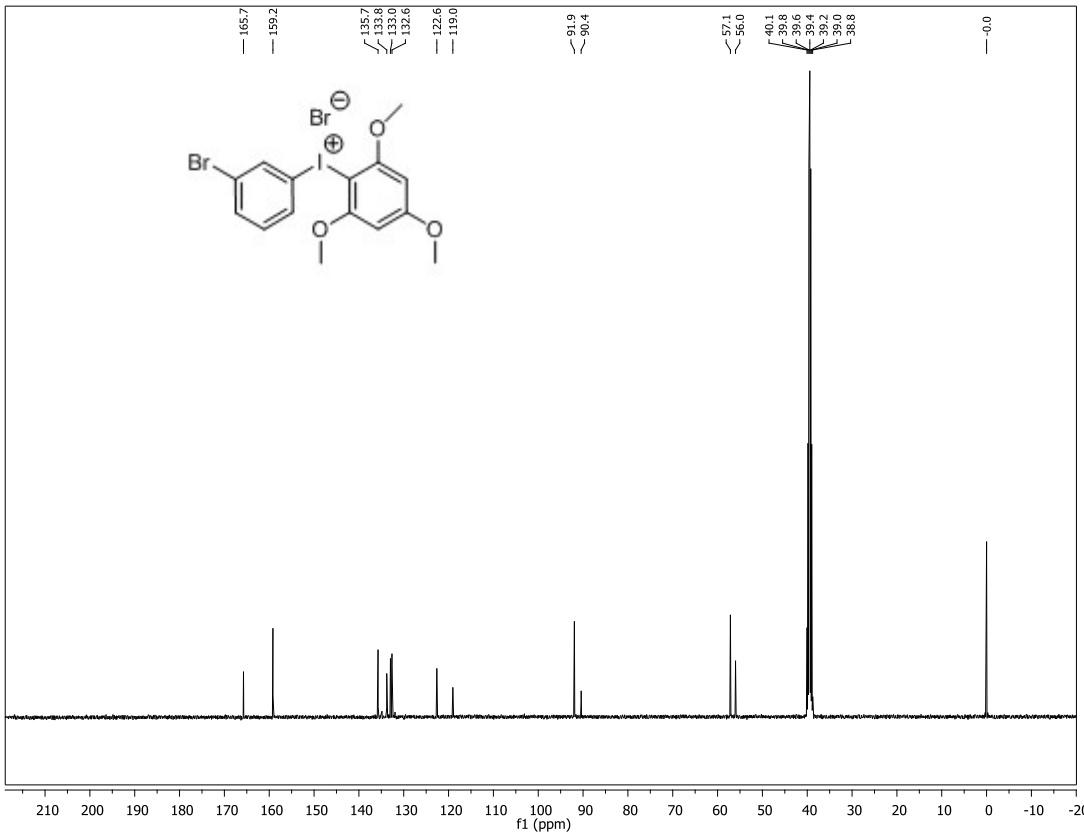


Figure 5.14: ^{1}H NMR of 1.4 -Th at 400 MHz in DMSO-d_6 at 298K

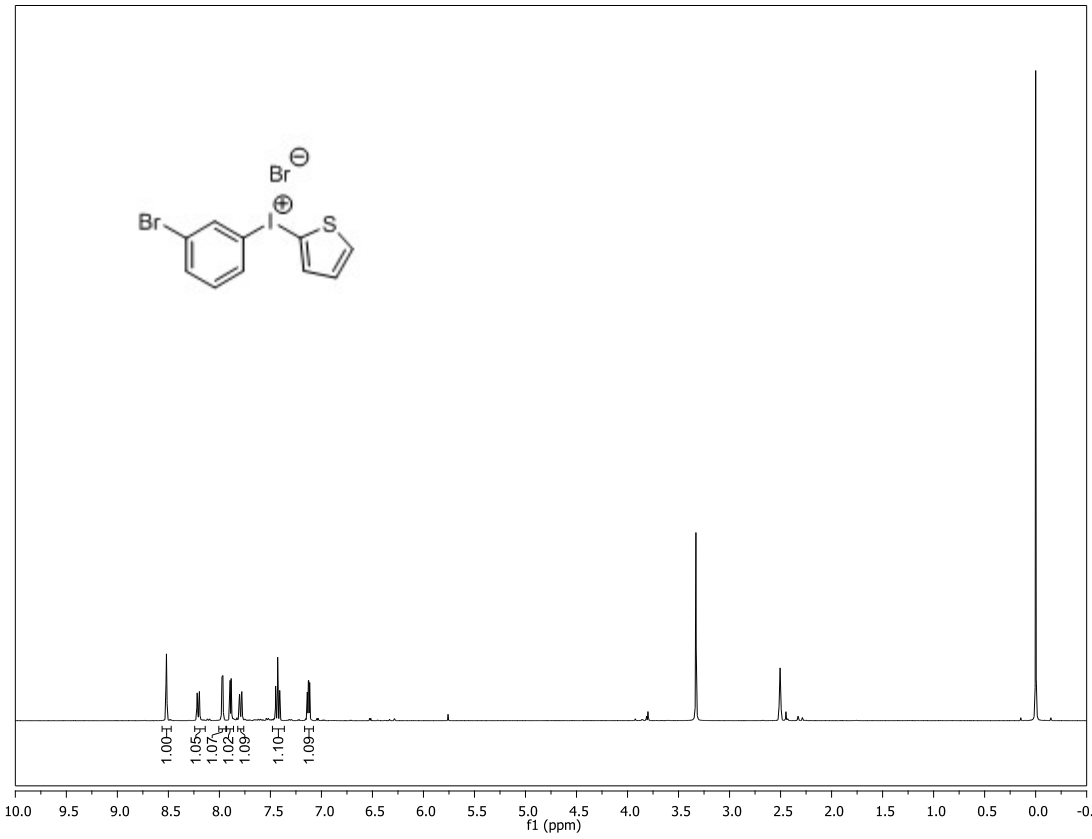


Figure 5.15: ^{13}C NMR of 1.4 -Th at 100 MHz in DMSO-d_6 at 298K

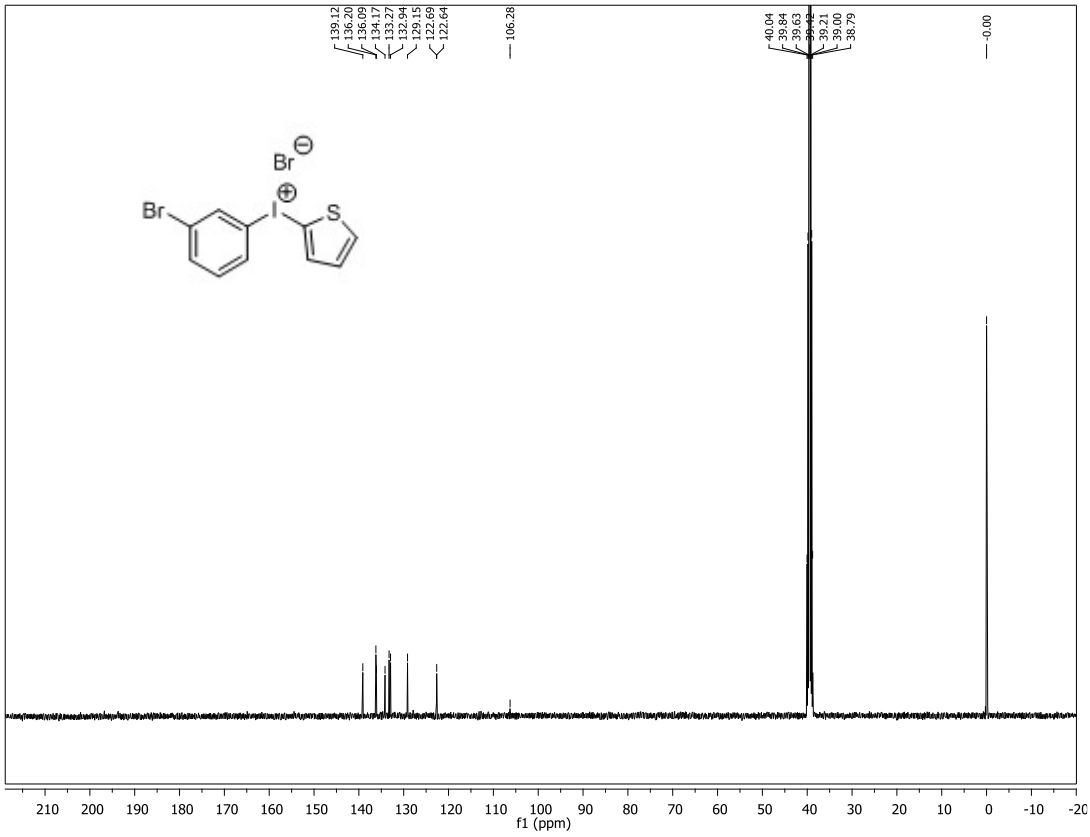


Figure 5.16: ^{1}H NMR of 1.5 at 400 MHz in DMSO-d_6 at 298K

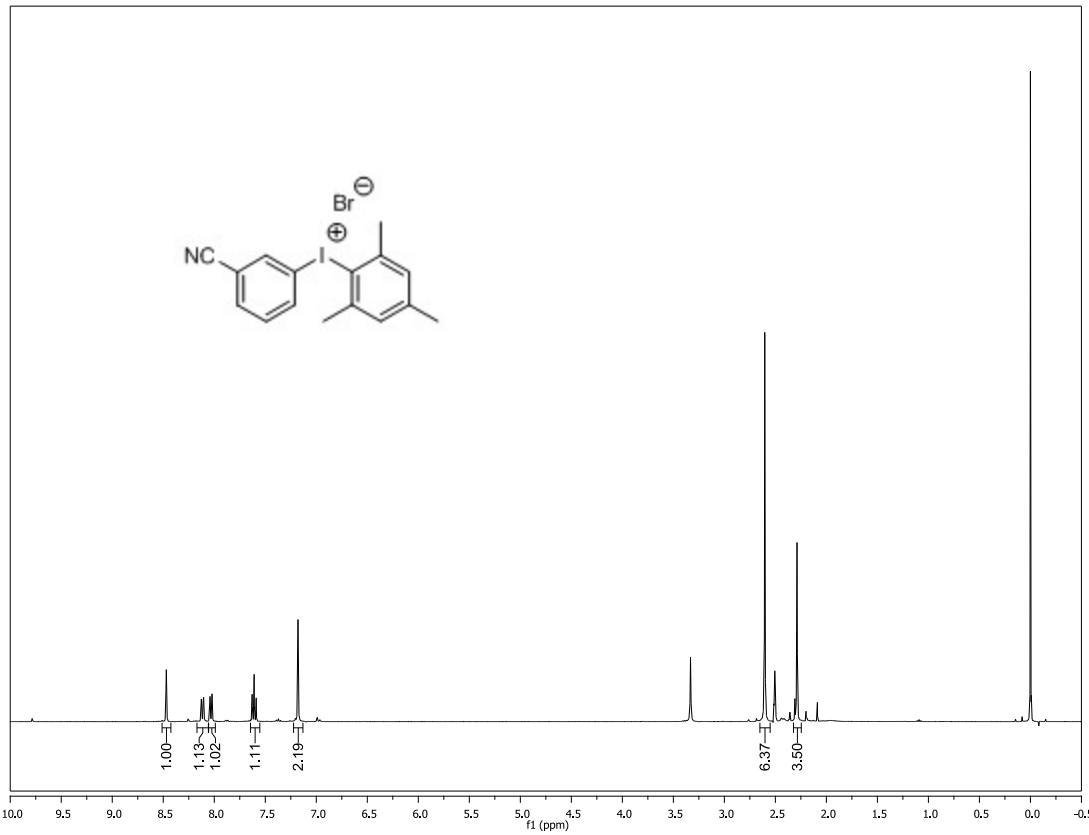


Figure 5.17: ^{13}C NMR of 1.5 at 100 MHz in DMSO-d_6 at 298K

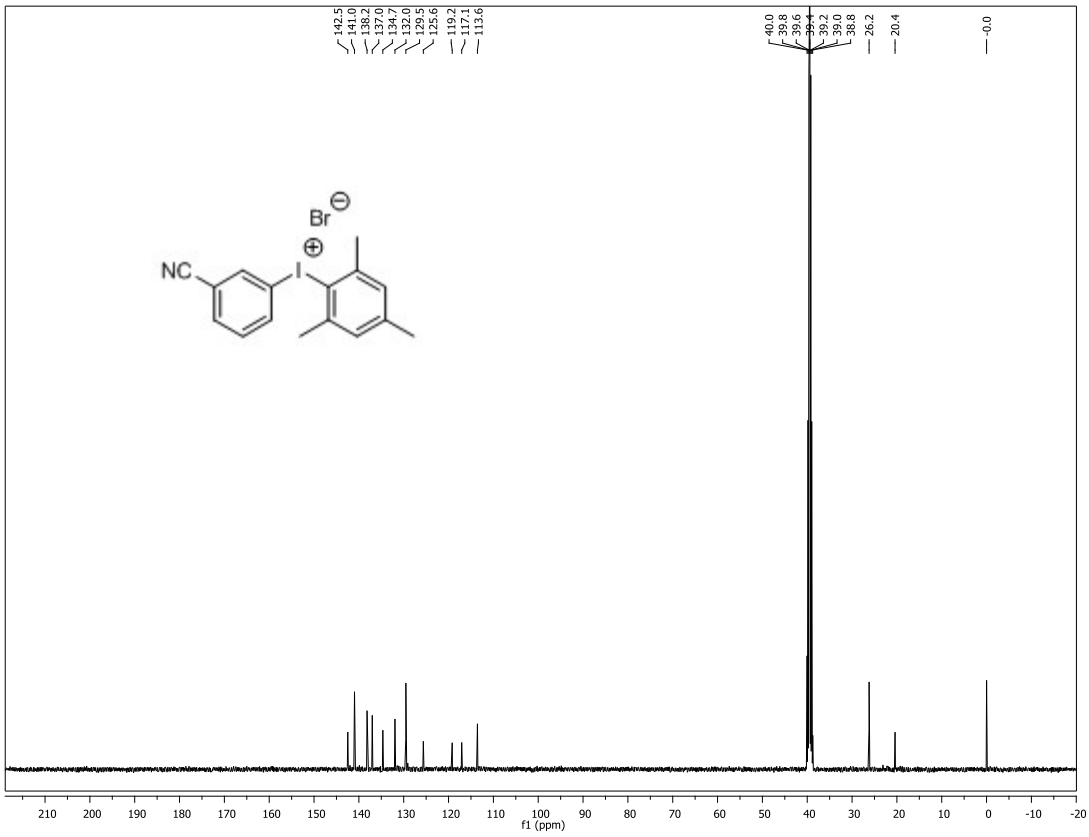


Figure 5.18: ^{1}H NMR of 1.6 at 400 MHz in DMSO-d_6 at 298K

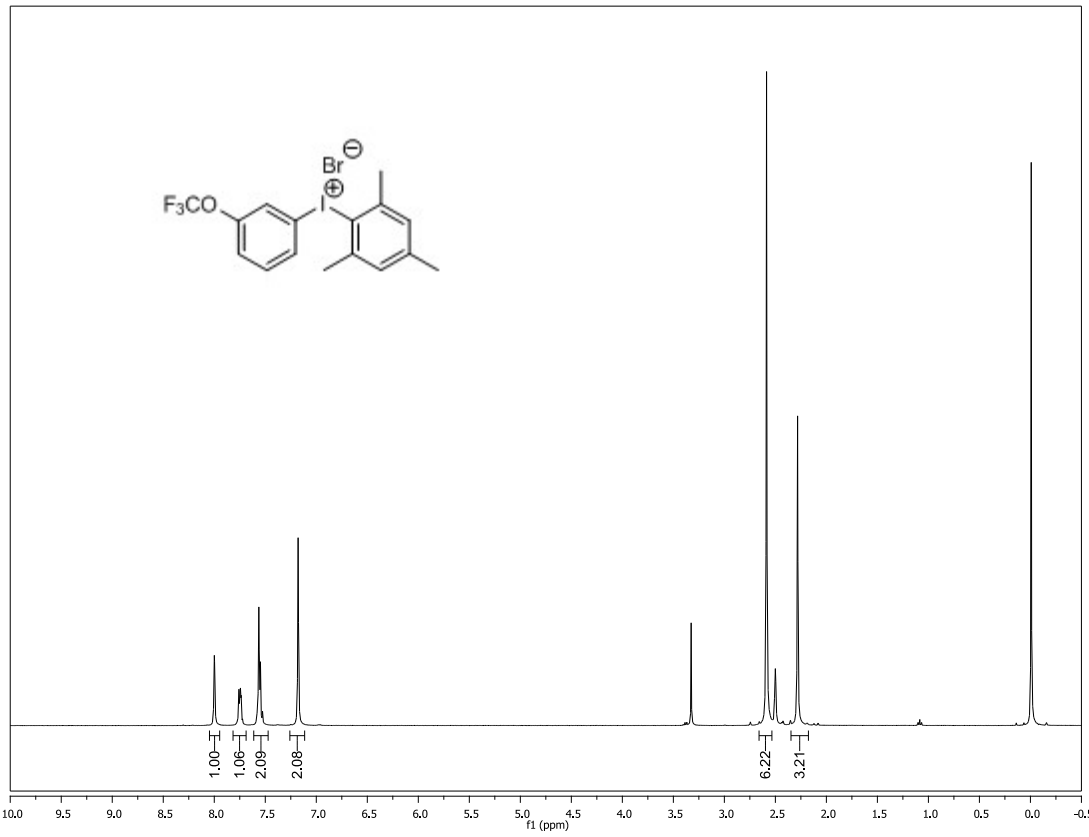


Figure 5.19: ^{13}C NMR of 1.6 at 100 MHz in DMSO-d_6 at 298K

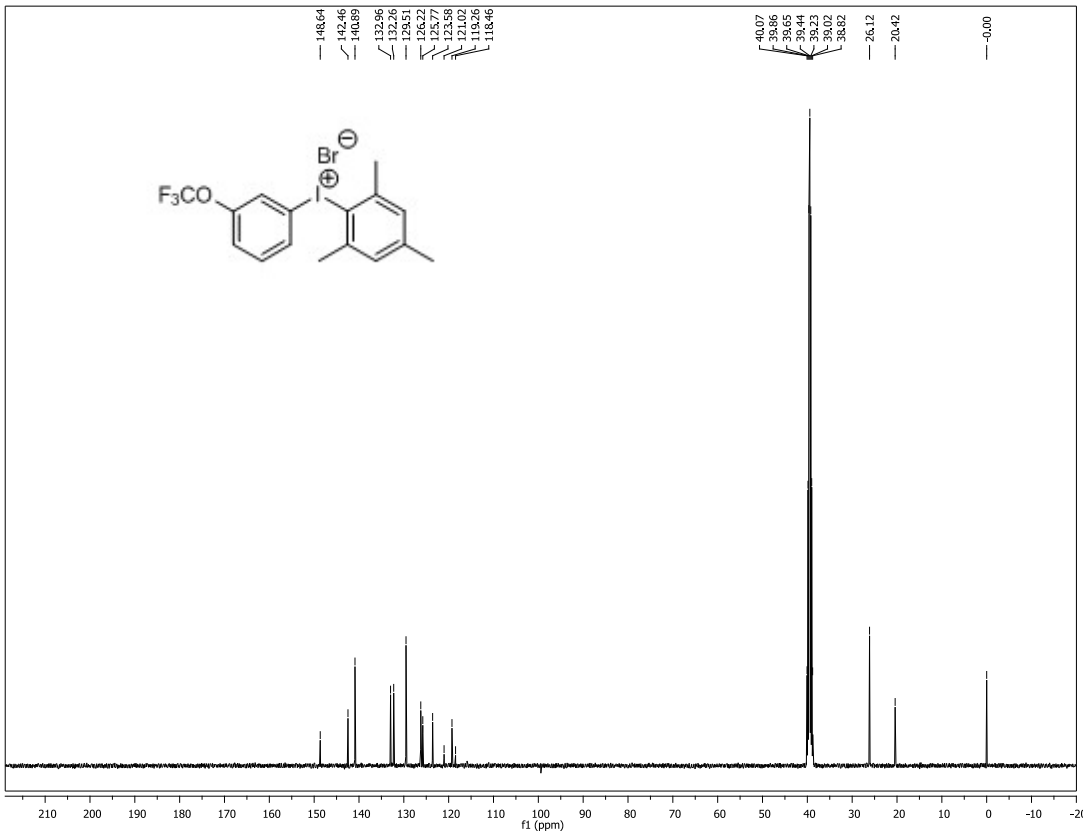


Figure 5.20: ^{19}F NMR of 1.6 at 377 MHz in DMSO-d_6 at 298K

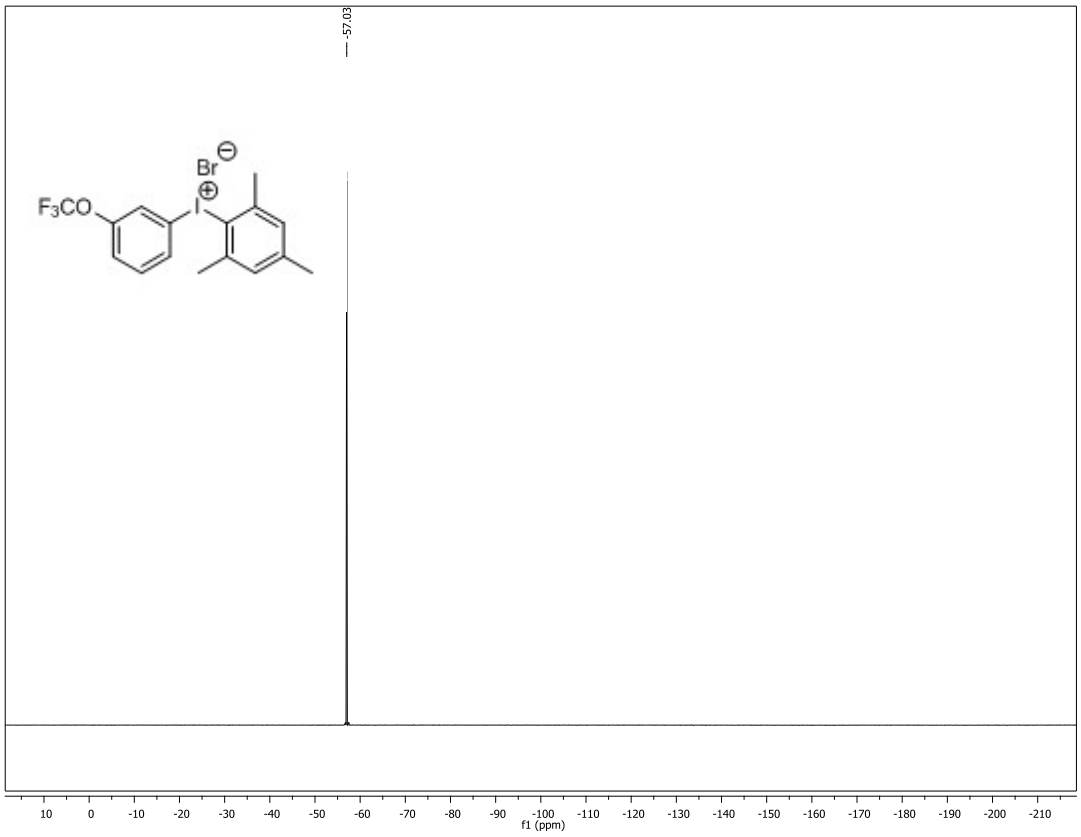


Figure 5.21: ^{1}H NMR of 1.7 at 400 MHz in DMSO-d_6 at 298K

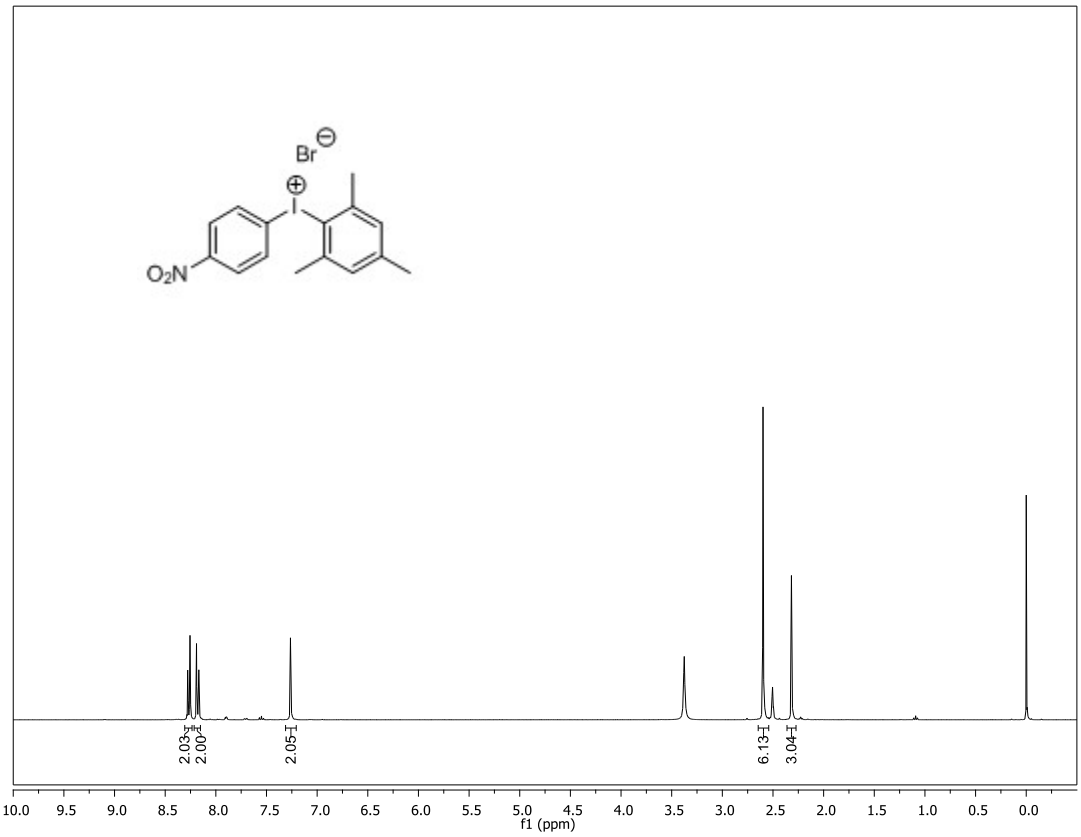


Figure 5.22: ^{13}C NMR of 1.7 at 100 MHz in DMSO-d_6 at 298K

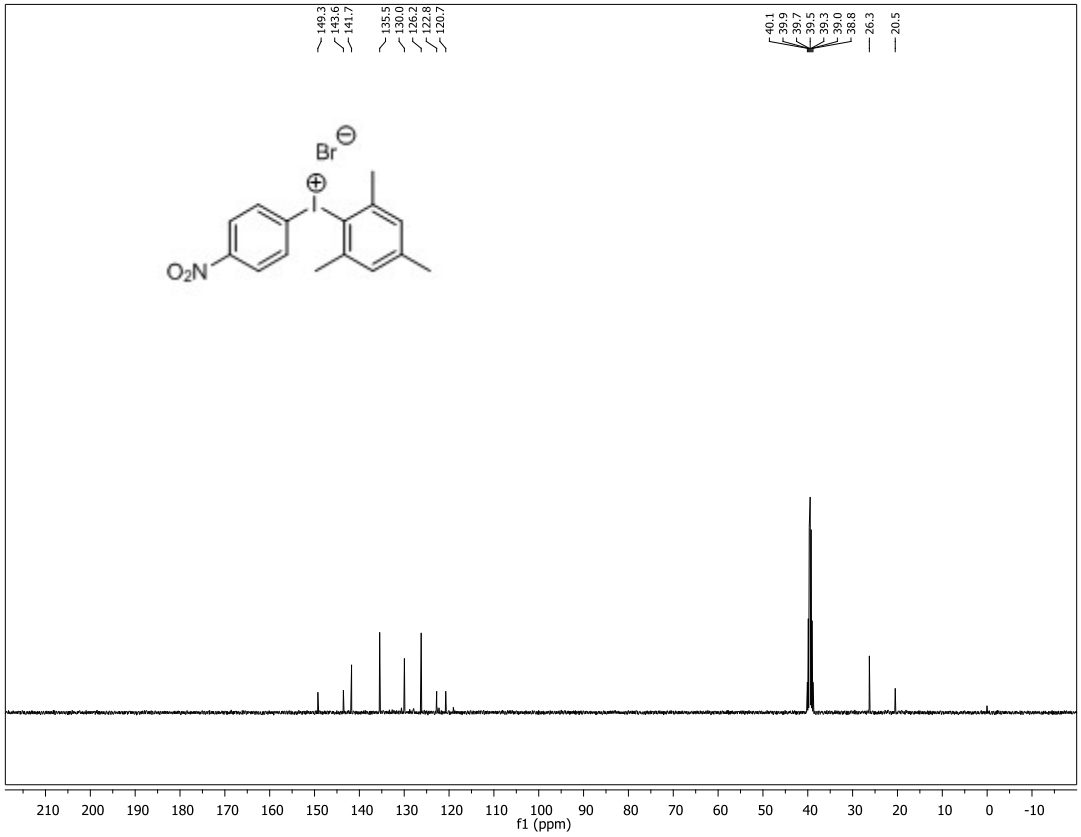


Figure 5.23: ^{1}H NMR of 1.8 at 400 MHz in DMSO-d_6 at 298K

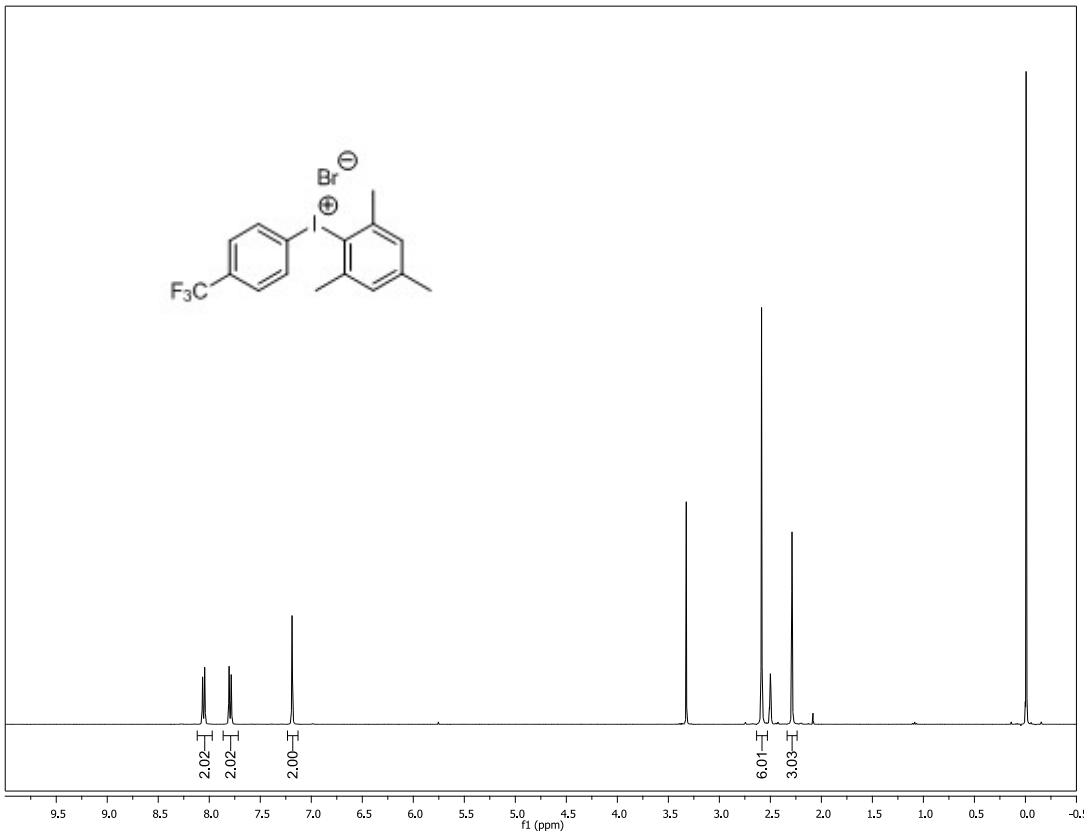


Figure 5.24: ^{13}C NMR of 1.8 at 100 MHz in DMSO-d_6 at 298K

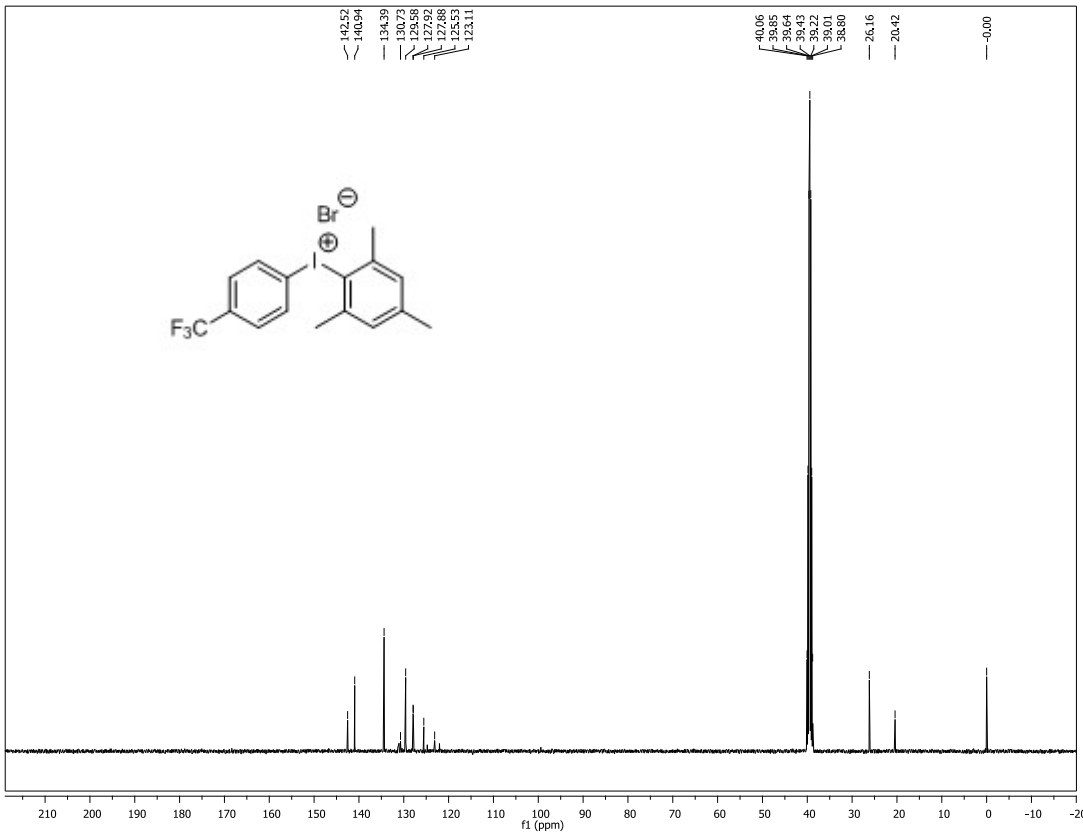


Figure 5.25: ^{19}F NMR of 1.8 at 377 MHz in DMSO-d_6 at 298K

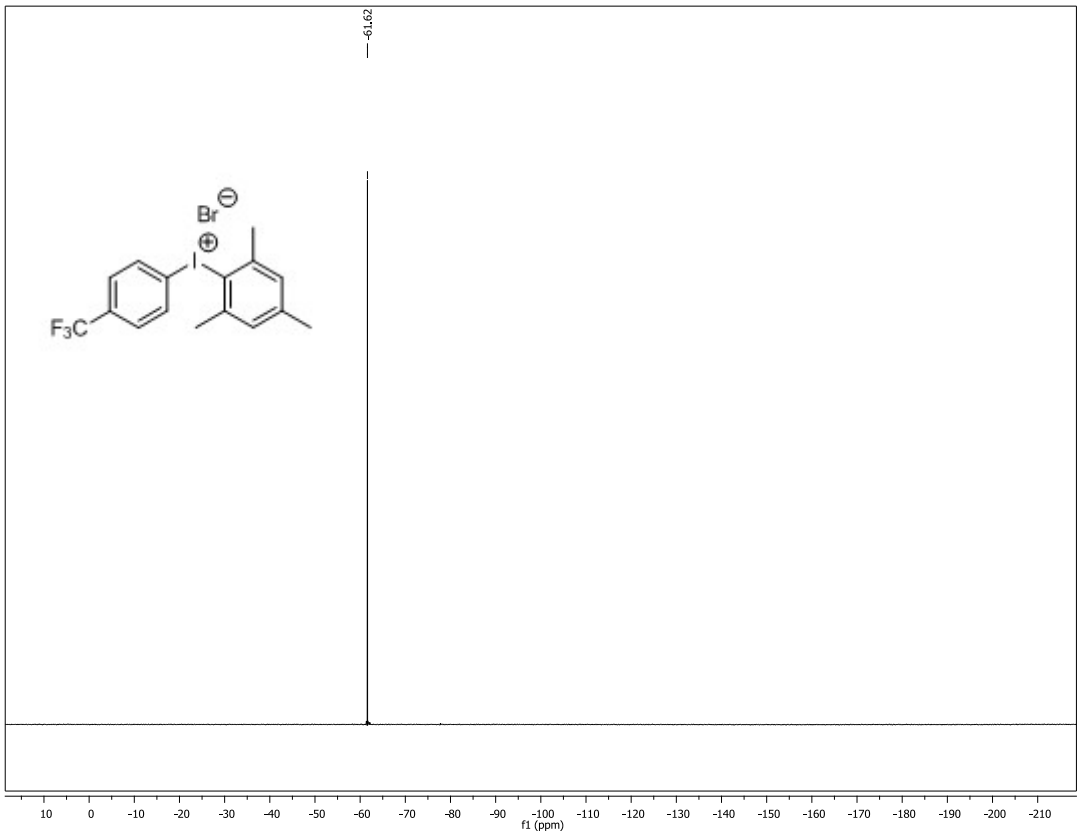


Figure 5.26: ^{1}H NMR of 1.9 at 400 MHz in DMSO-d_6 at 298K

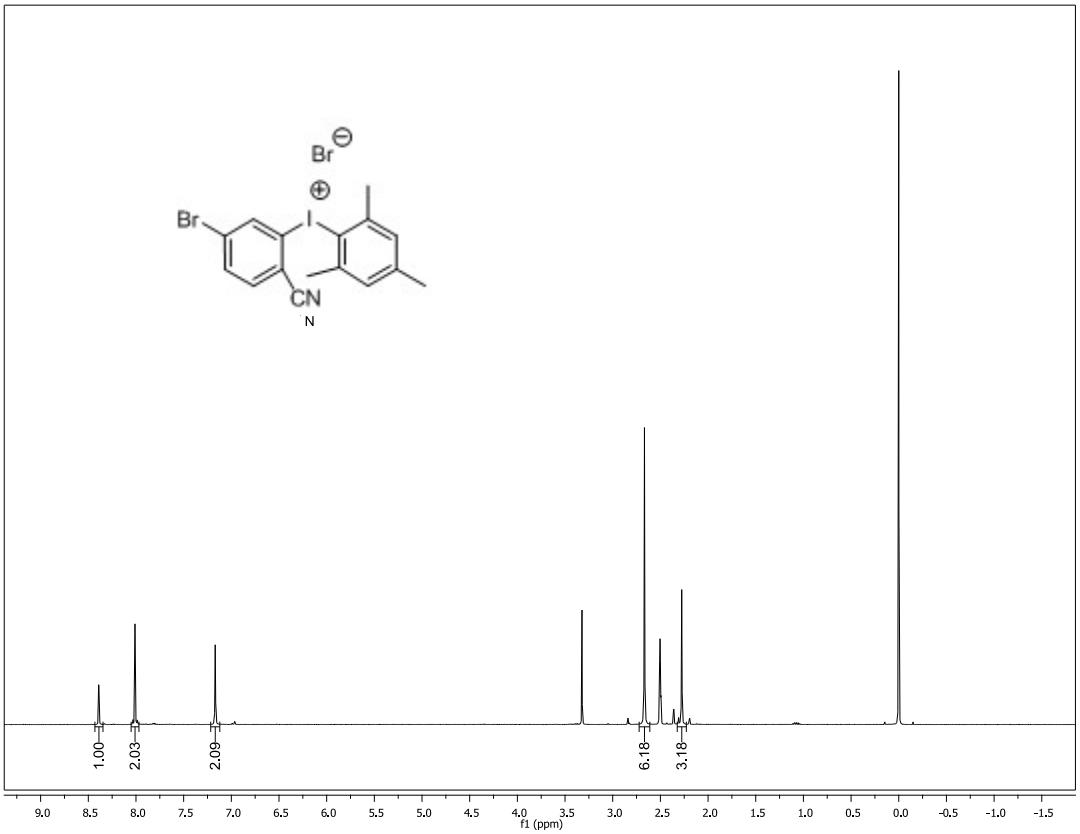


Figure 5.27: ^{13}C NMR of 1.9 at 100 MHz in DMSO-d_6 at 298K

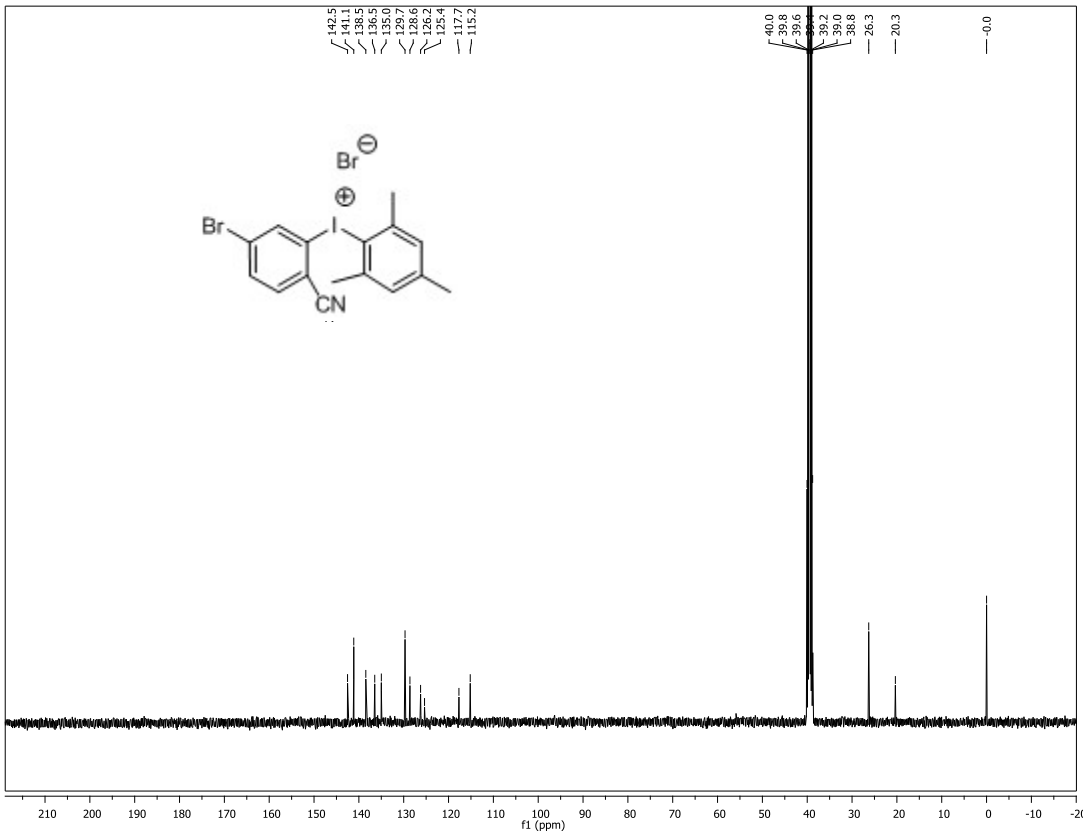


Figure 5.28: ^{1}H NMR of 1.10 at 400 MHz in DMSO-d_6 at 298K

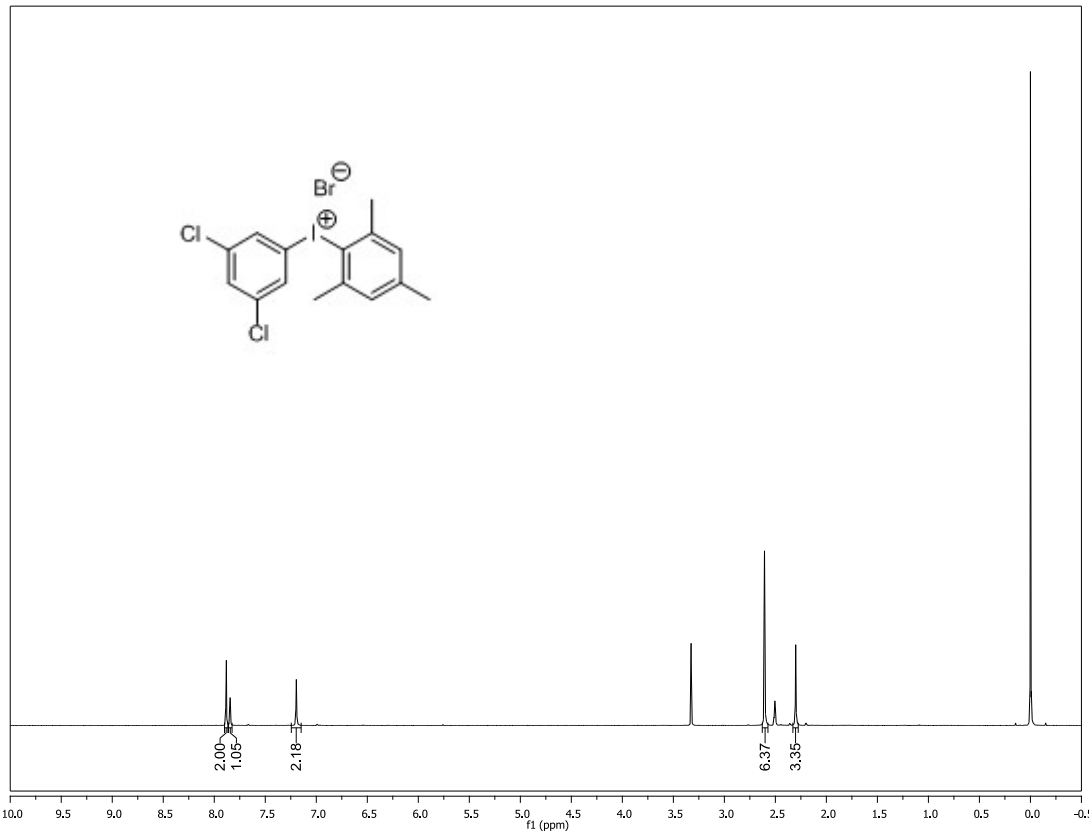


Figure 5.29: ^{13}C NMR of 1.10 at 100 MHz in DMSO-d_6 at 298K

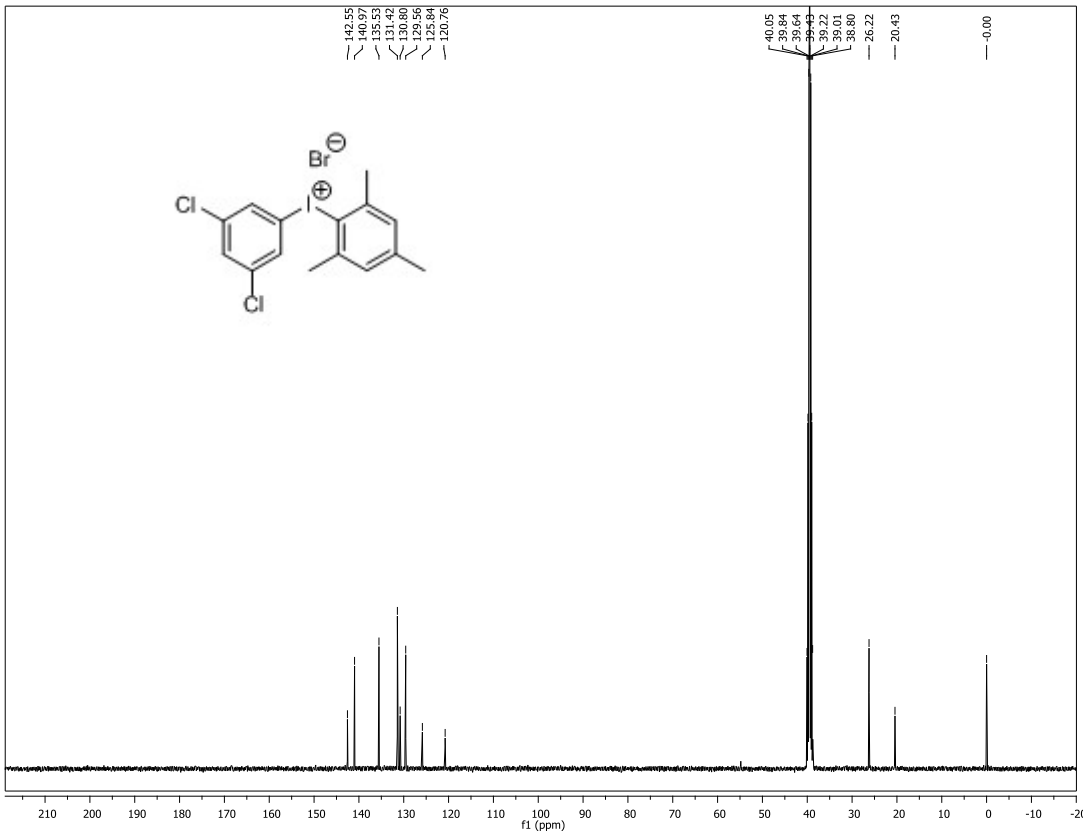


Figure 5.30: ^{1}H NMR of 1.11 at 400 MHz in DMSO-d_6 at 298K

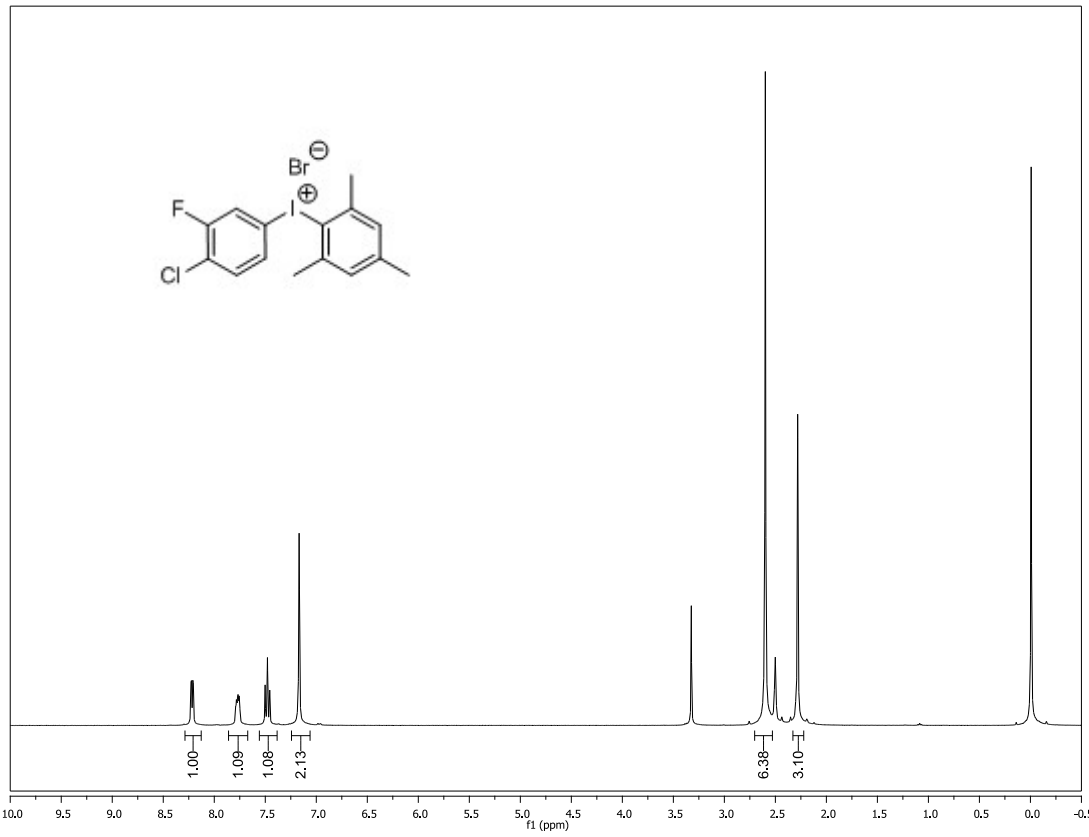


Figure 5.31: ^{13}C NMR of 1.11 at 100 MHz in DMSO-d_6 at 298K

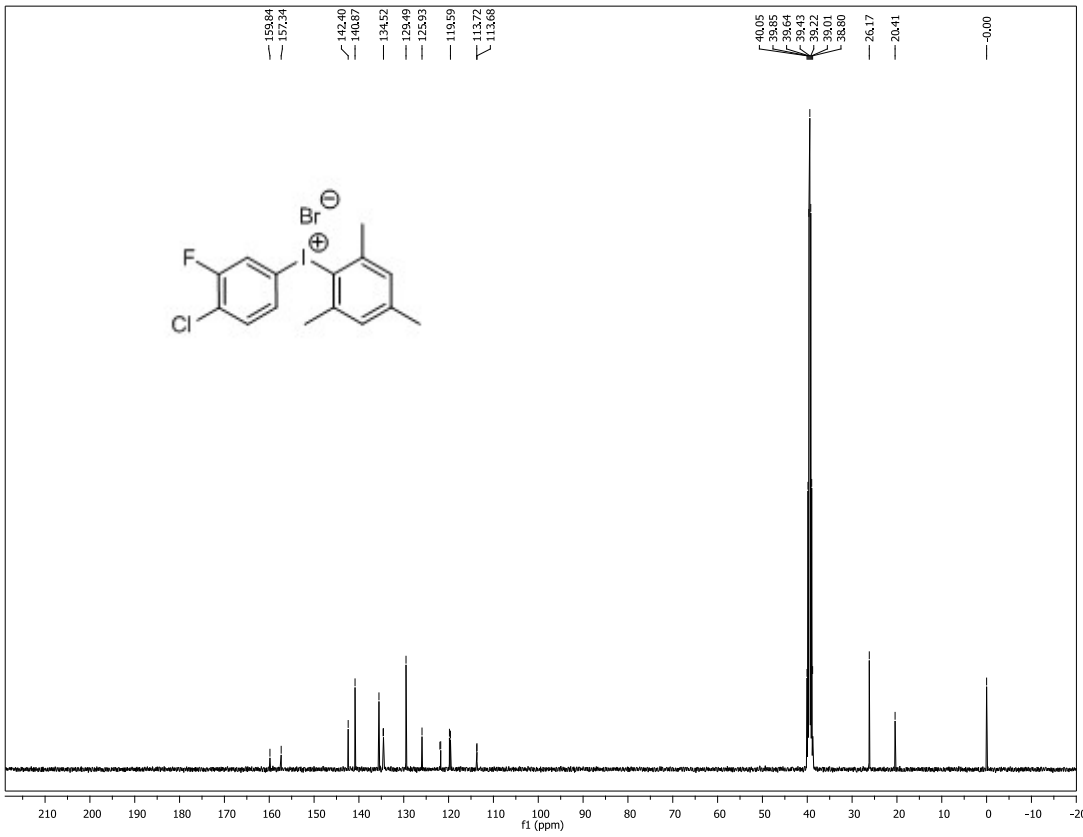


Figure 5.32: ^{19}F NMR of 1.11 at 377 MHz in DMSO-d_6 at 298K

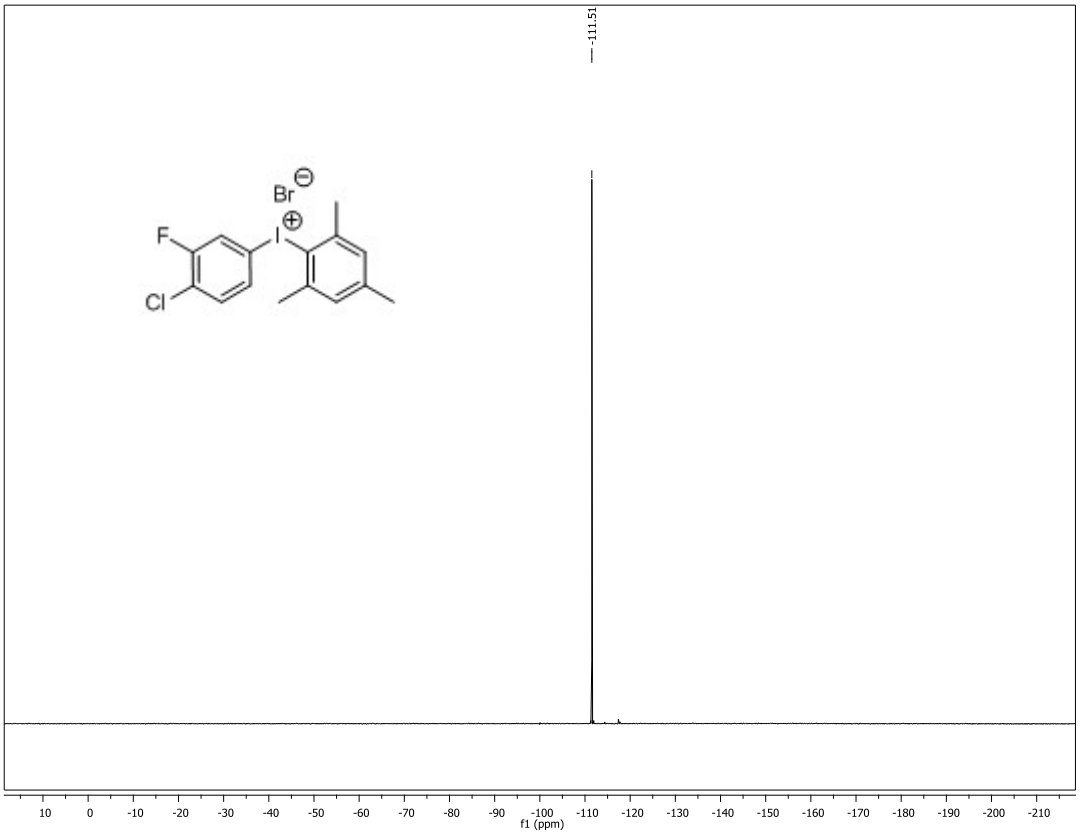


Figure 5.33: ^{1}H NMR of 1.12 at 400 MHz in DMSO-d_6 at 298K

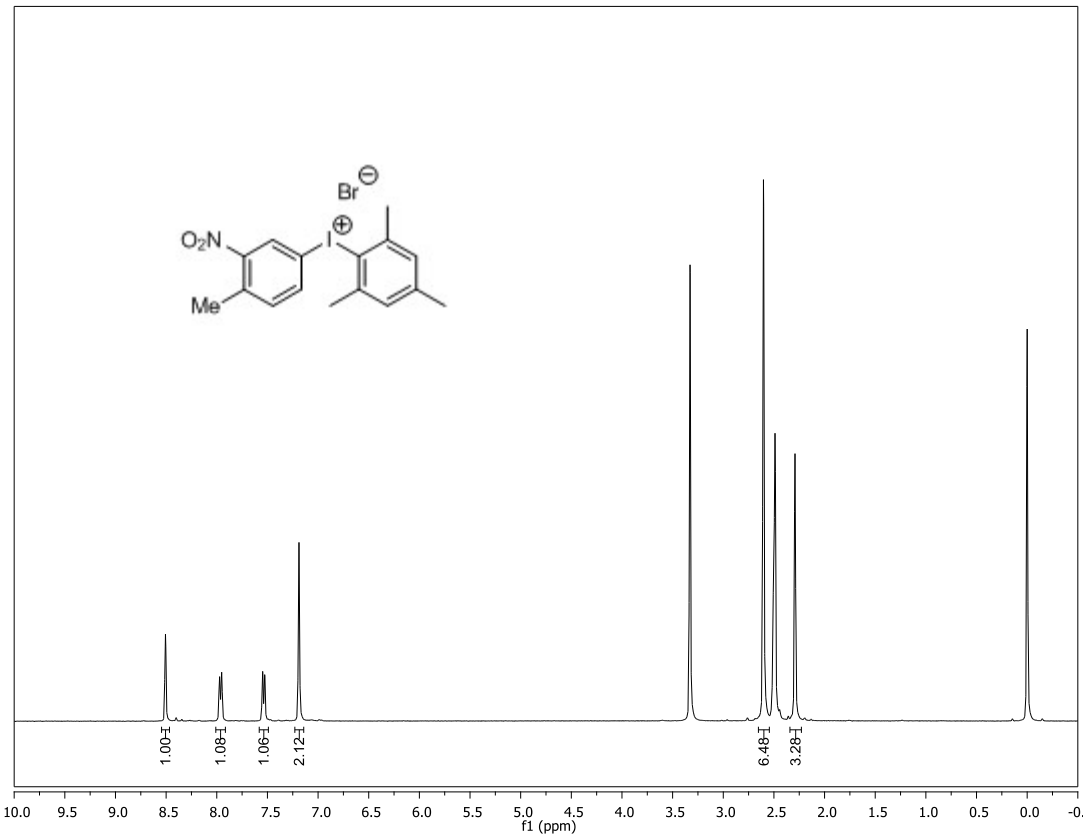


Figure 5.34: ^{13}C NMR of 1.12 at 100 MHz in DMSO-d_6 at 298K

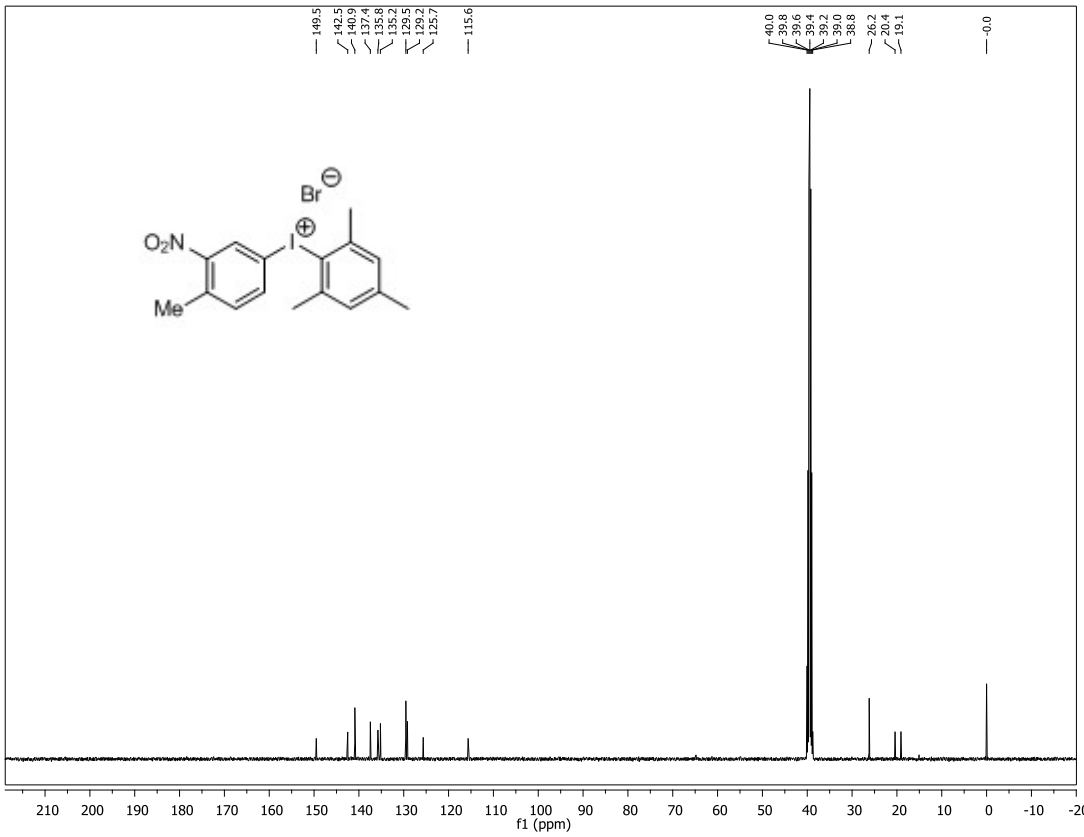


Figure 5.35: ^{1}H NMR of 1.13 at 400 MHz in DMSO-d_6 at 298K

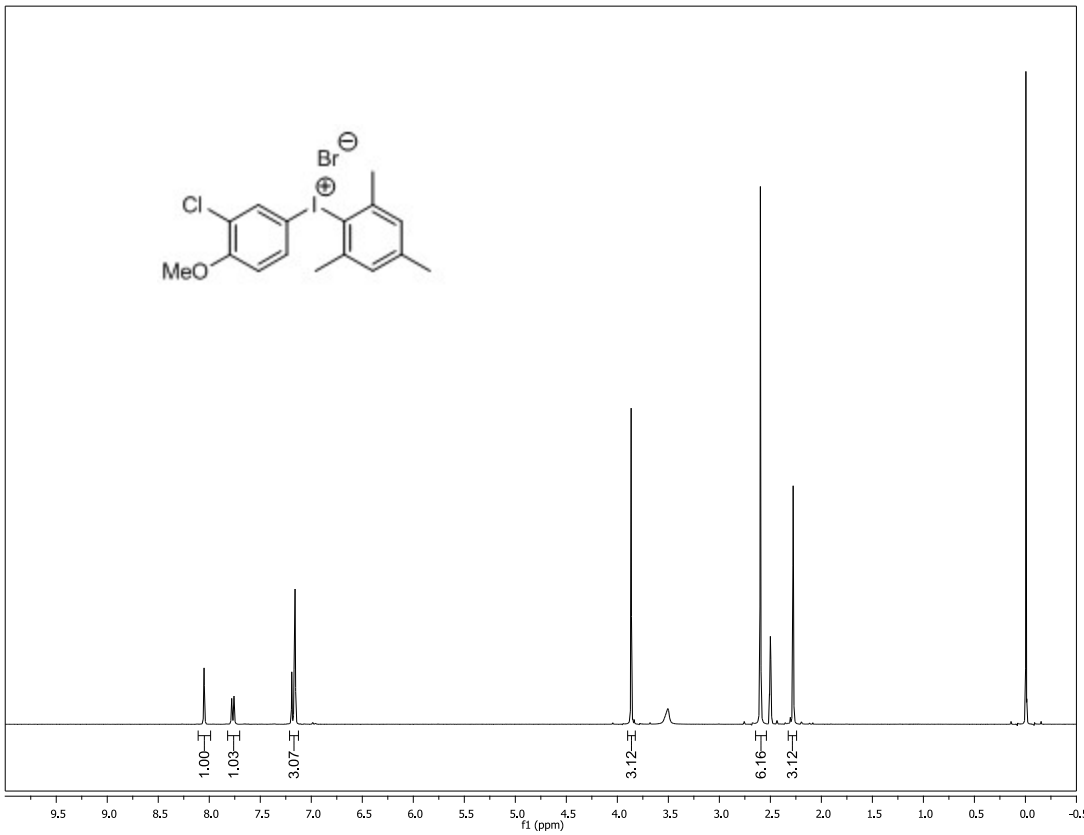


Figure 5.36: ^{13}C NMR of 1.13 at 100 MHz in DMSO-d_6 at 298K

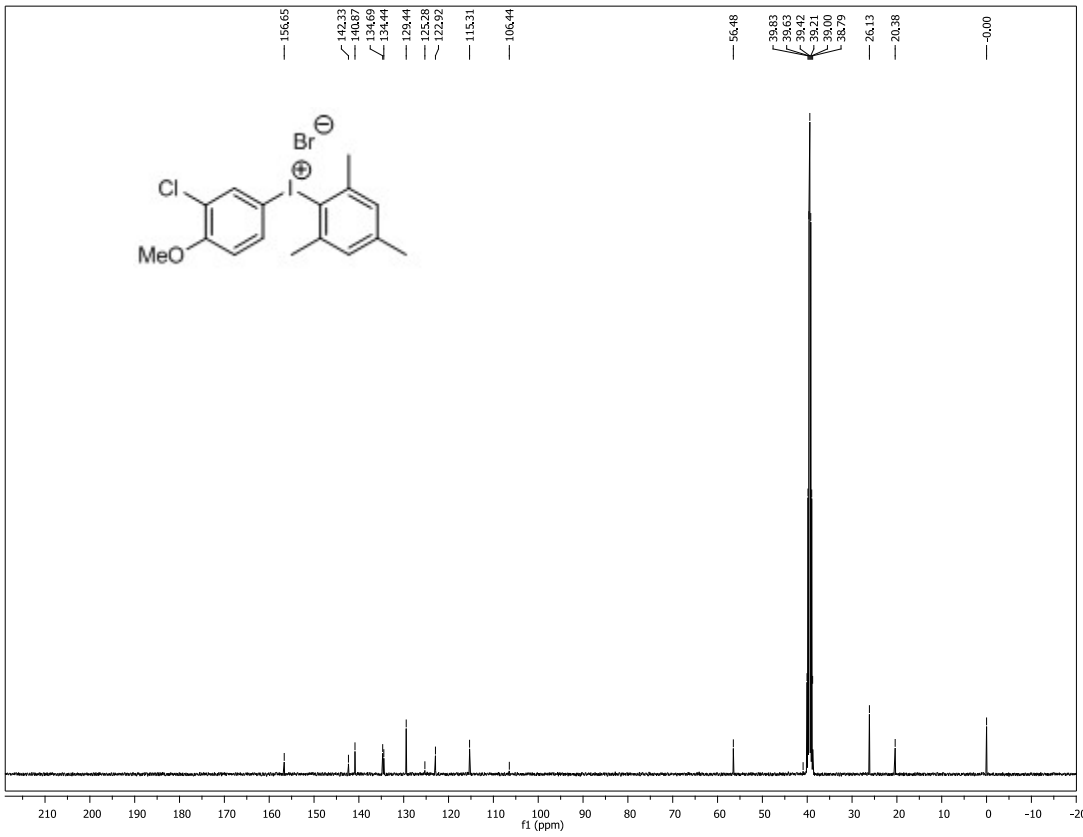


Figure 5.37: ^{1}H NMR of 1.14 at 400 MHz in DMSO-d_6 at 298K

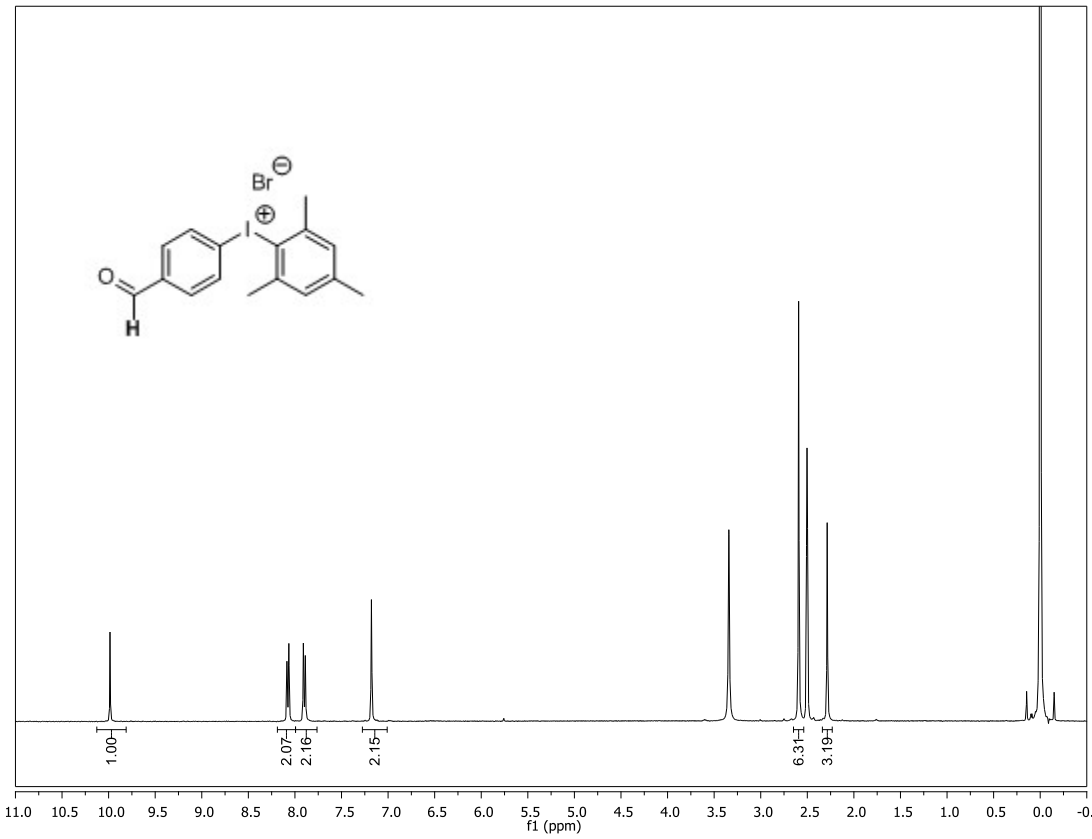


Figure 5.38: ^{13}C NMR of 1.15 at 100 MHz in DMSO-d_6 at 298K

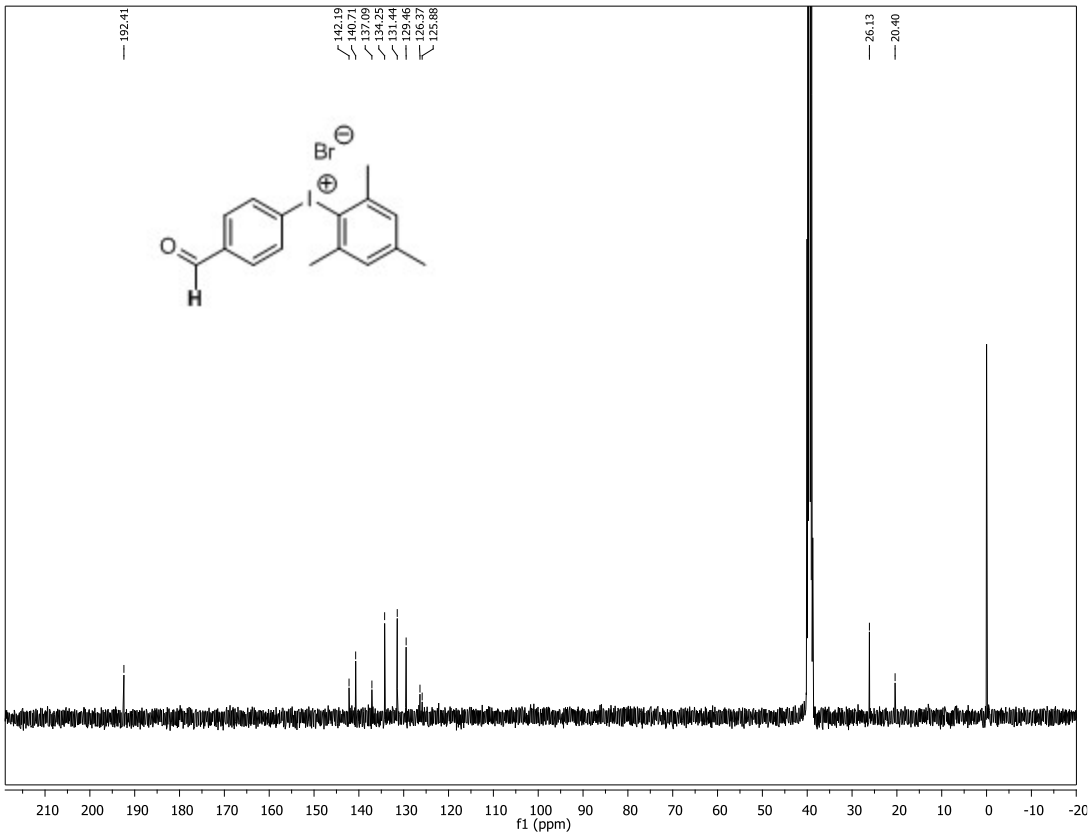


Figure 5.39: ^{1}H NMR of 1.16 at 400 MHz in CDl_3 at 298K

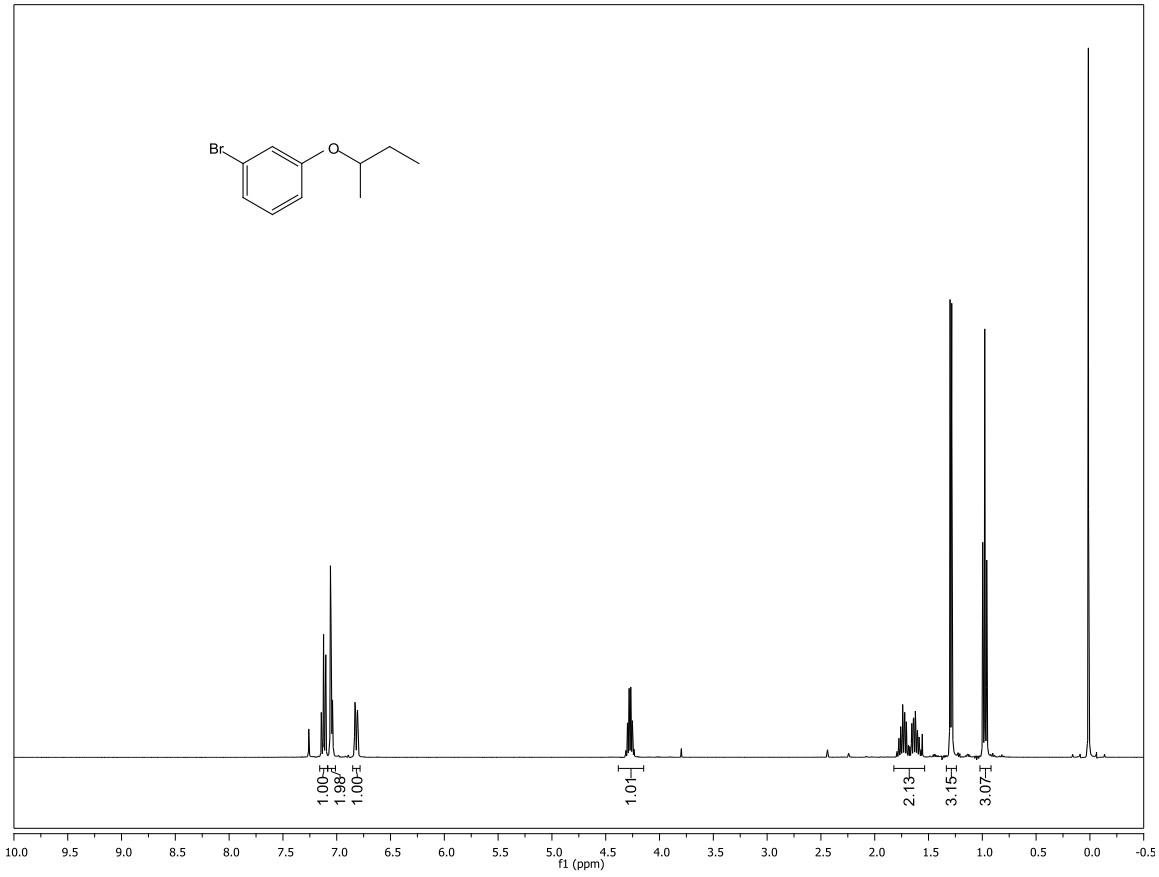


Figure 5.40: ^{13}C NMR of 1.16 at 100 MHz in CDl_3 at 298K

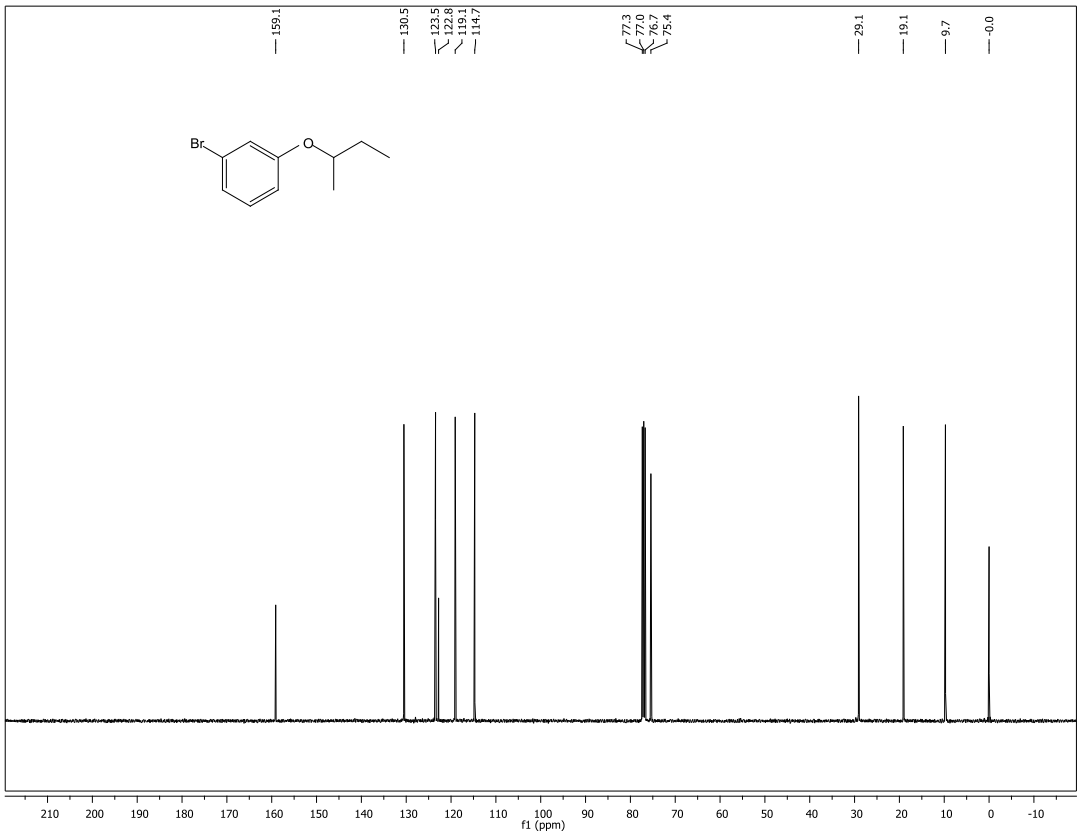


Figure 5.41: ^{1}H NMR of 1.17 at 400 MHz in CDl_3 at 298K

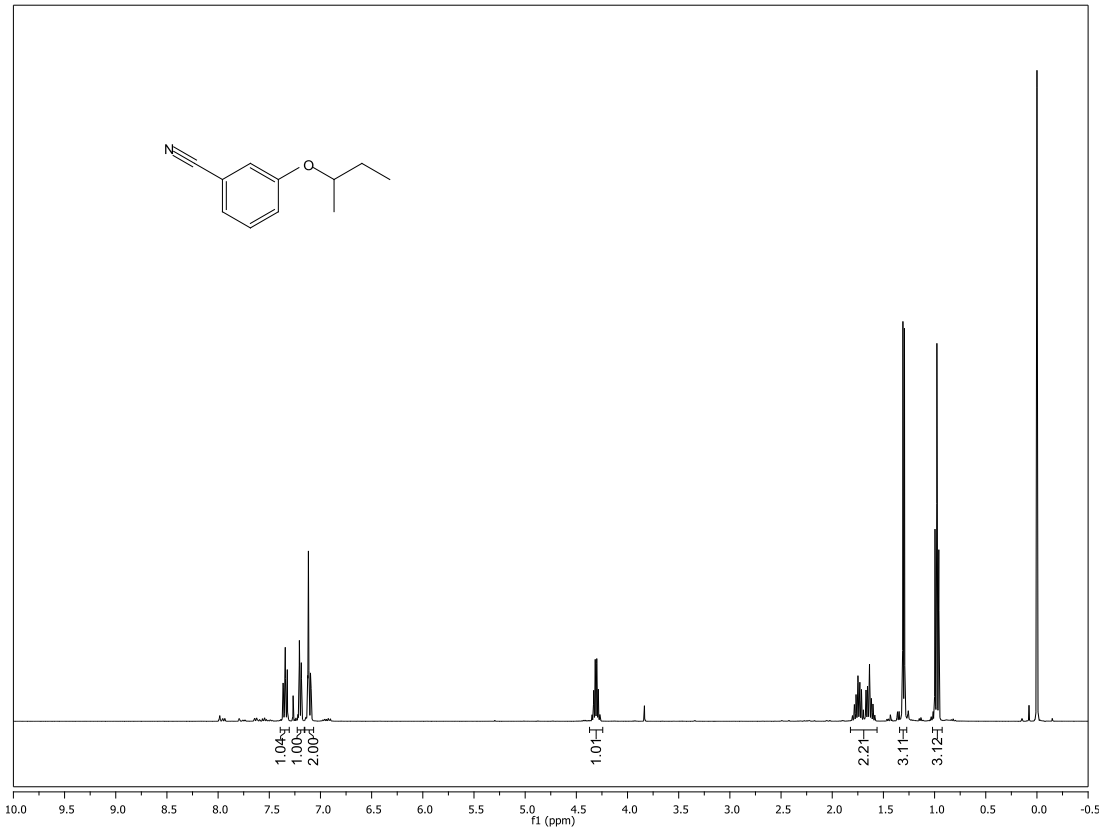


Figure 5.42: ^{13}C NMR of 1.17 at 100 MHz in CDl_3 at 298K

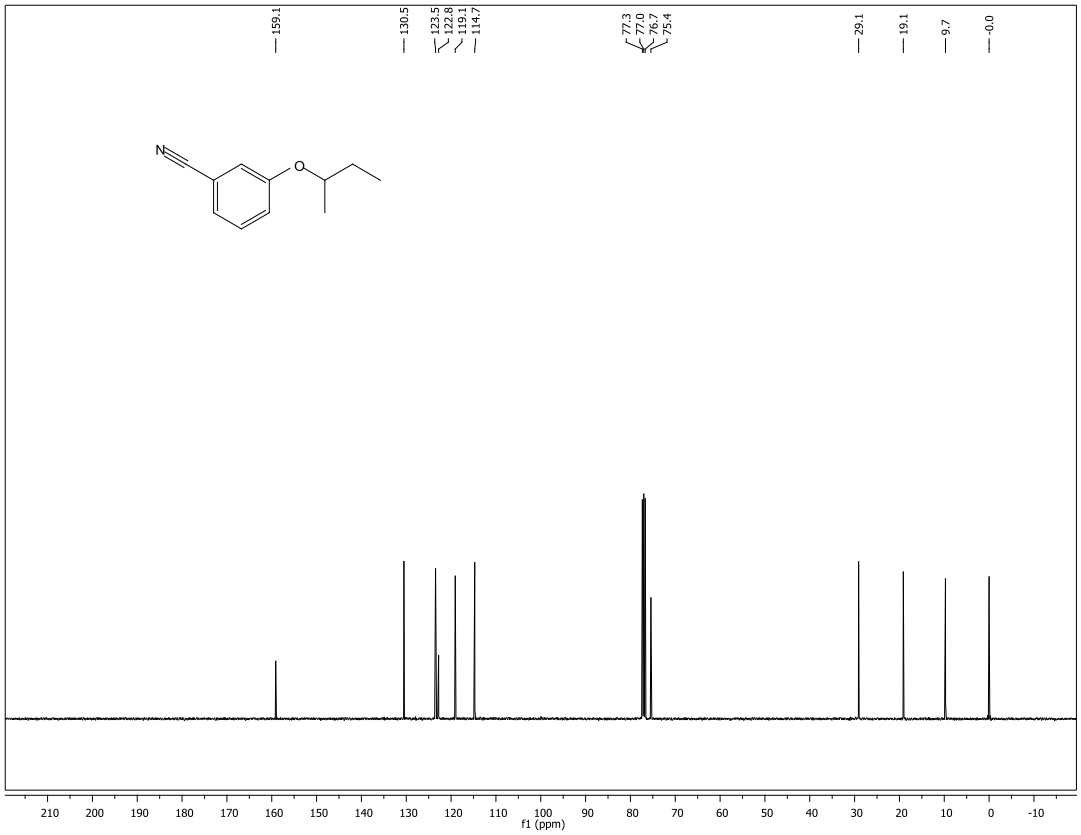


Figure 5.43: ^{1}H NMR of 1.18 at 400 MHz in CDl_3 at 298K

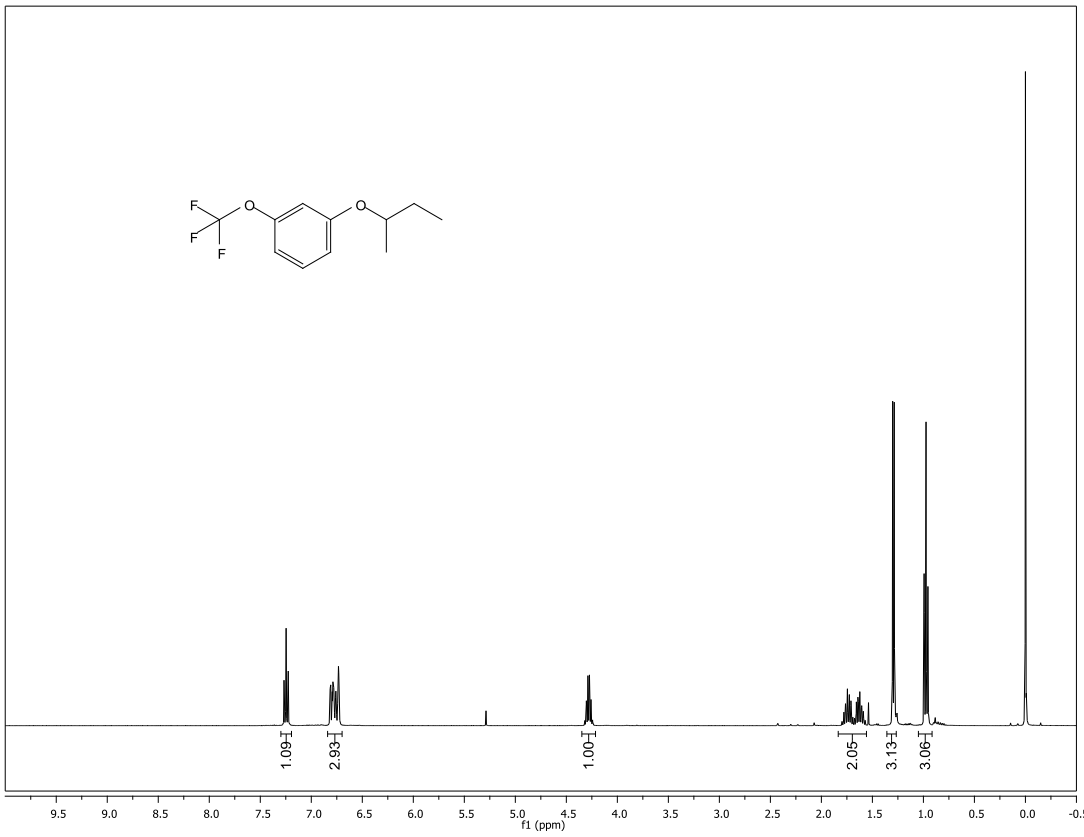


Figure 5.44: ^{13}C NMR of 1.18 at 100 MHz in CDl_3 at 298K

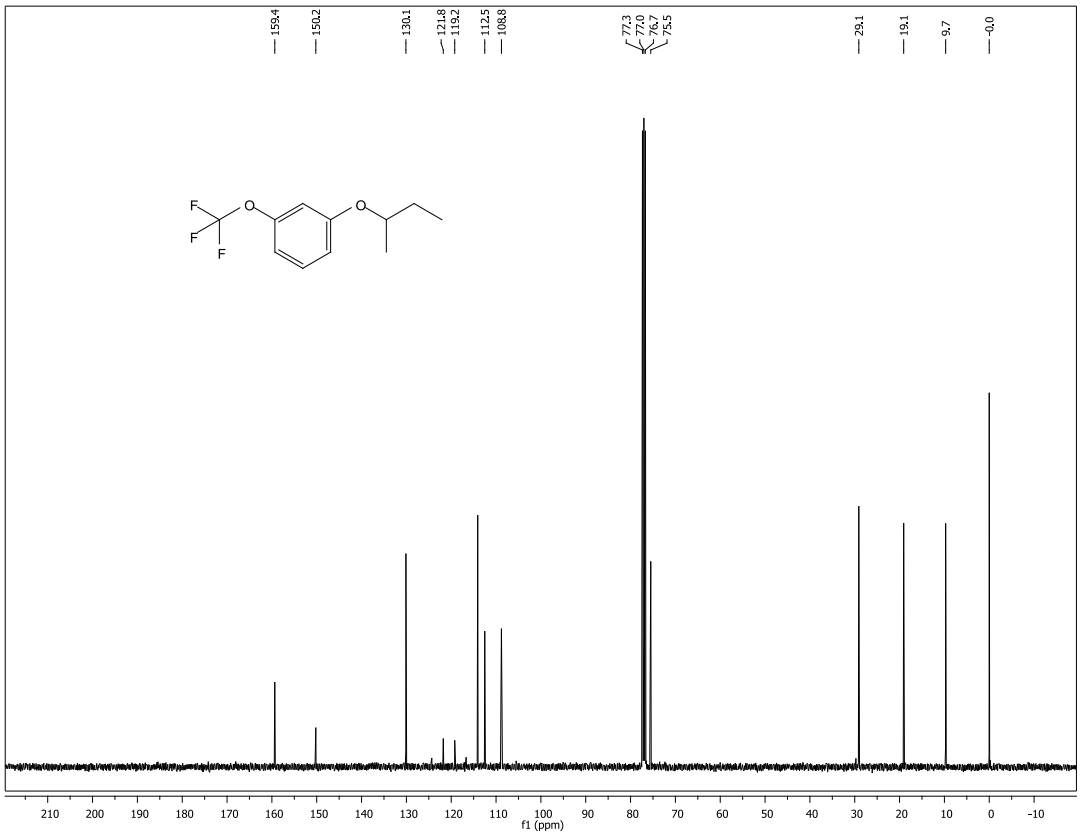


Figure 5.45: ^{19}F NMR of 1.18 at 377 MHz in CDl_3 at 298K

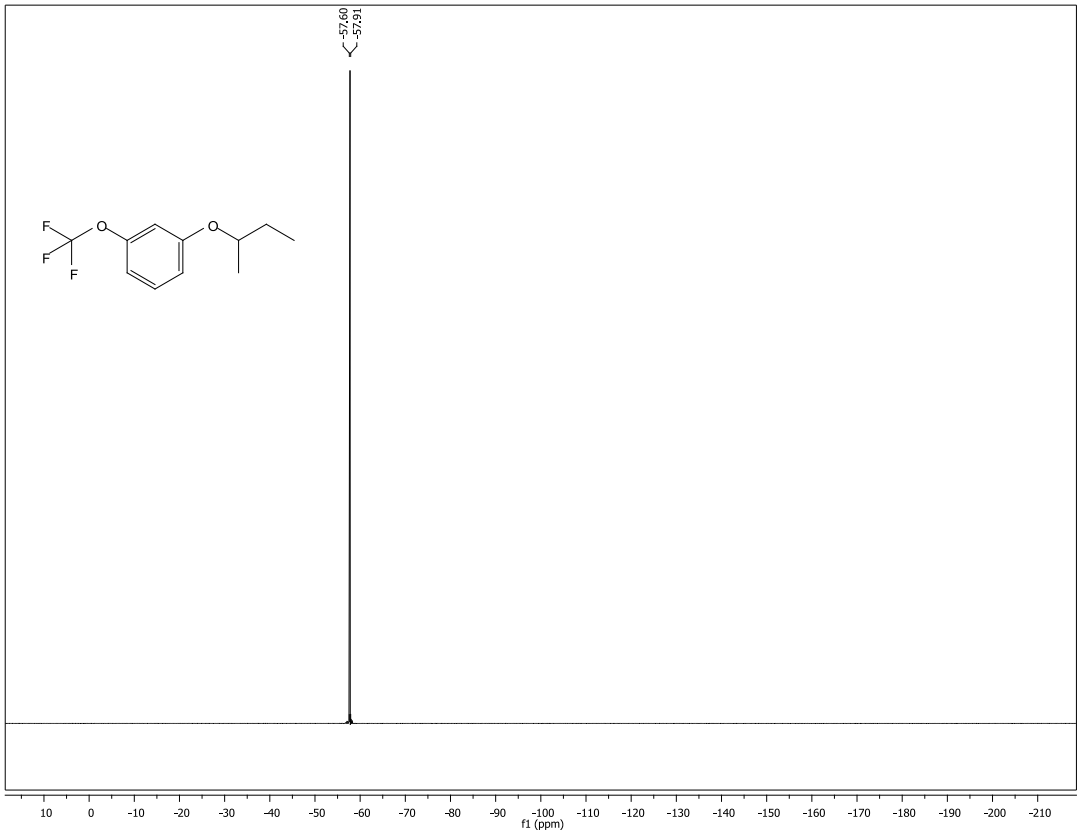


Figure 5.46: ^{1}H NMR of 1.19 at 400 MHz in CDl_3 at 298K

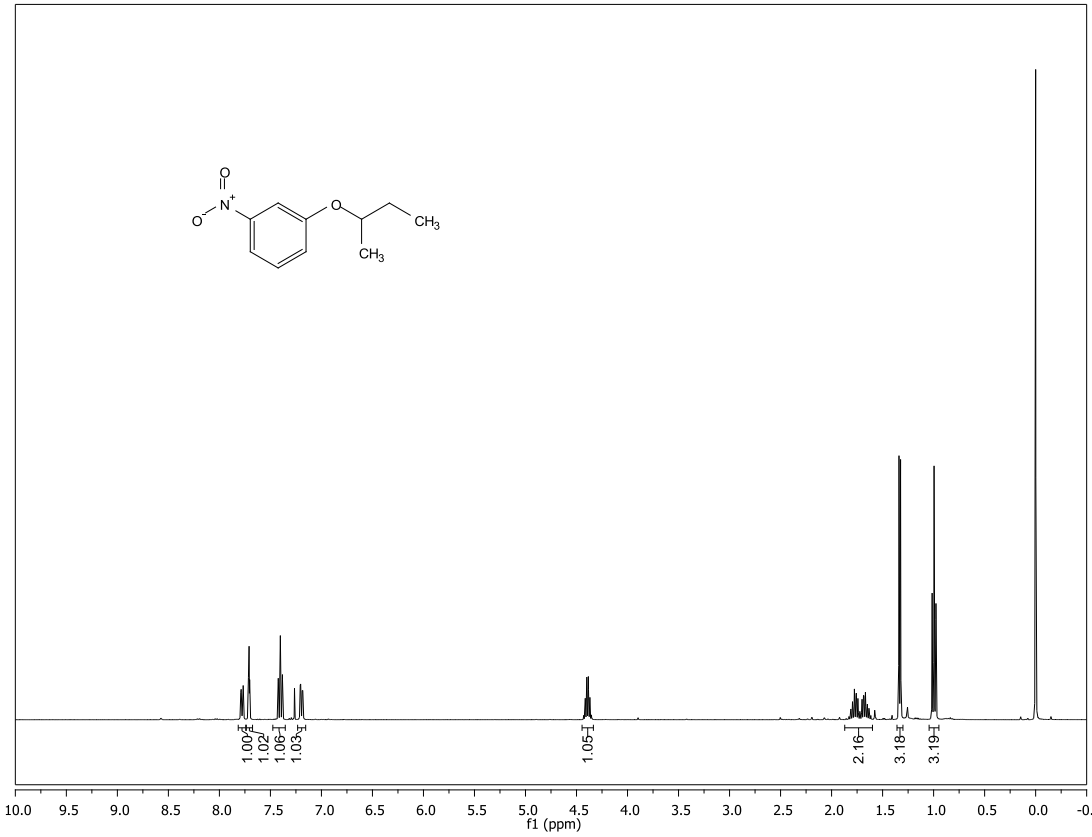


Figure 5.47: ^{13}C NMR of 1.19 at 100 MHz in CDl_3 at 298K

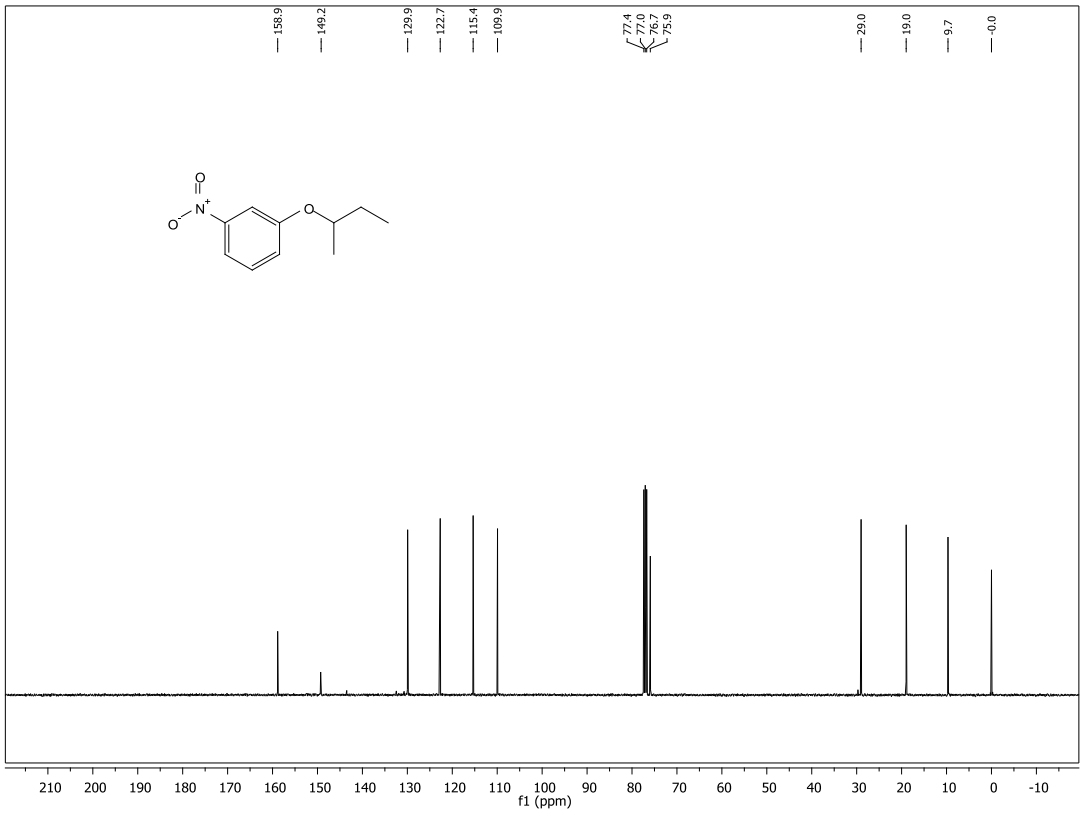


Figure 5.48: ^{1}H NMR of 1.20 at 400 MHz in CDl_3 at 298K

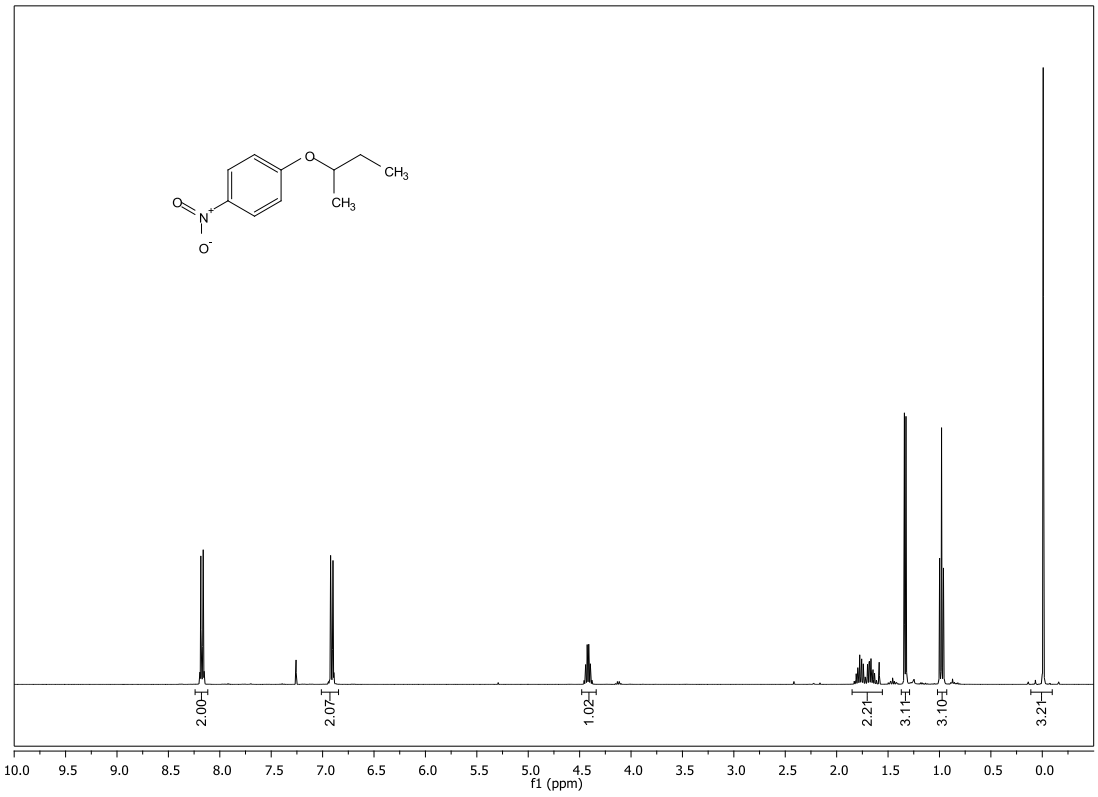


Figure 5.49: ^{1}H NMR of 1.21 at 400 MHz in CDl_3 at 298K

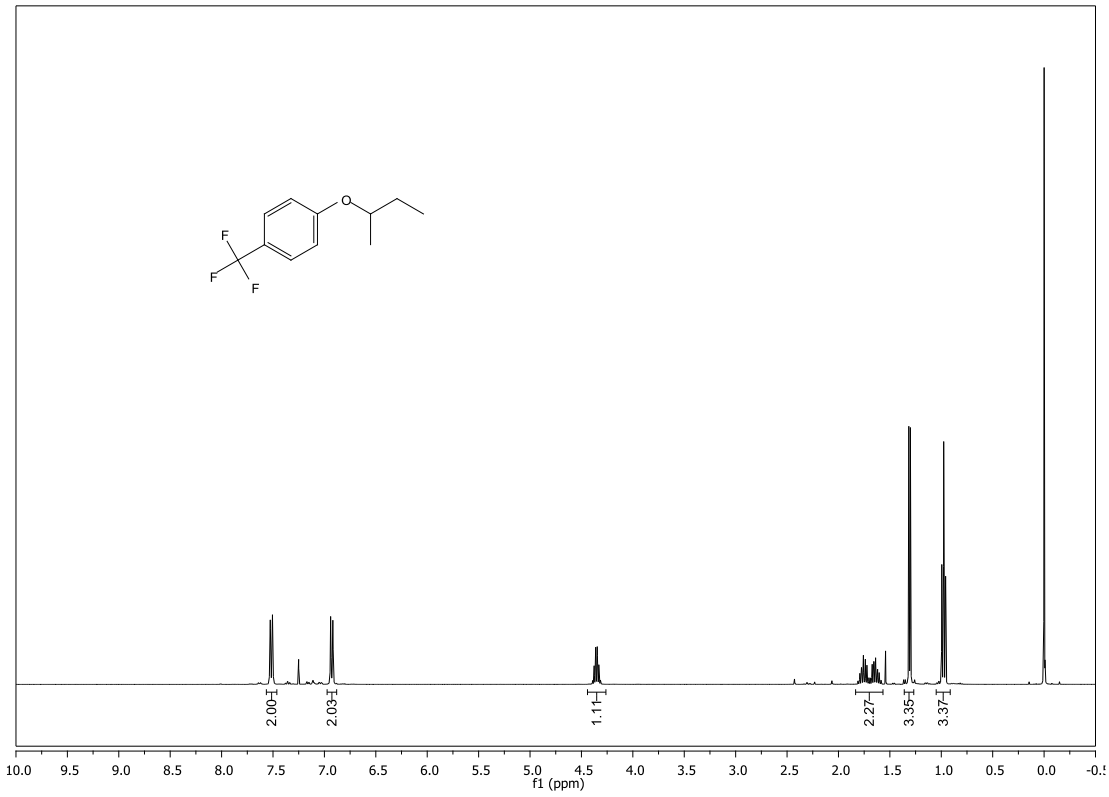


Figure 5.50: ^{1}H NMR of 1.22 at 400 MHz in CDl_3 at 298K

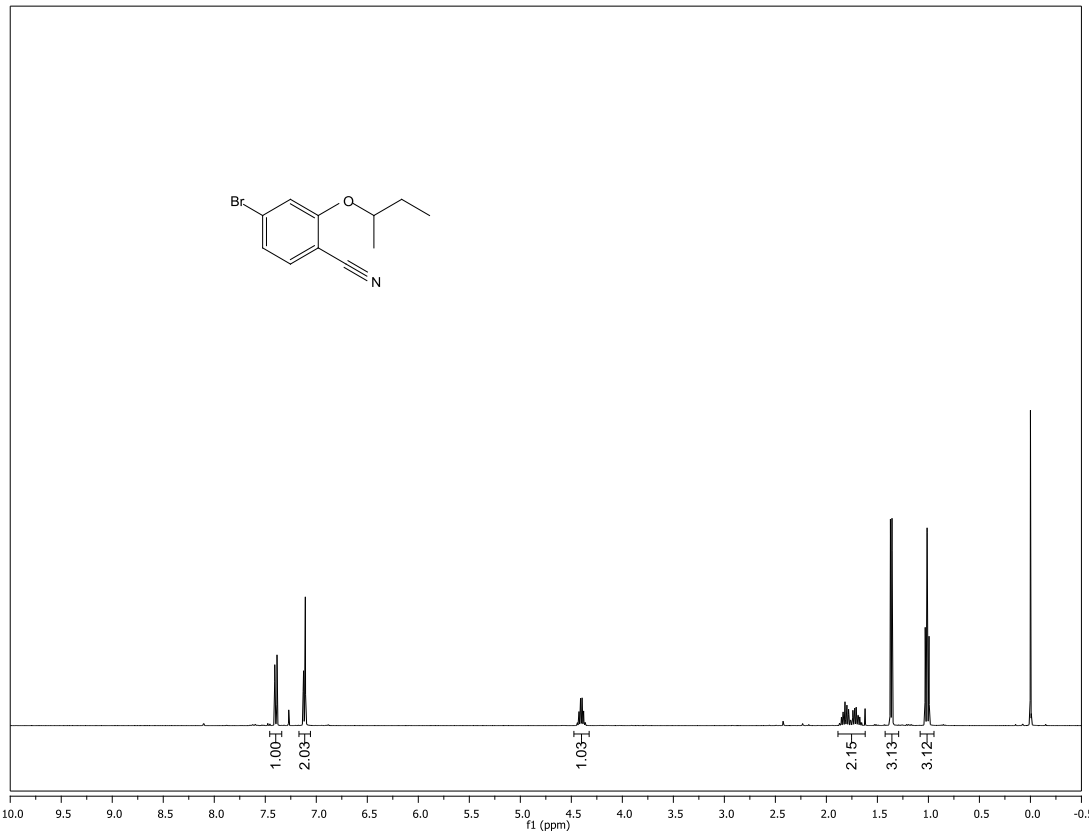


Figure 5.51: ^{13}C NMR of 1.22 at 100 MHz in CDl_3 at 298K

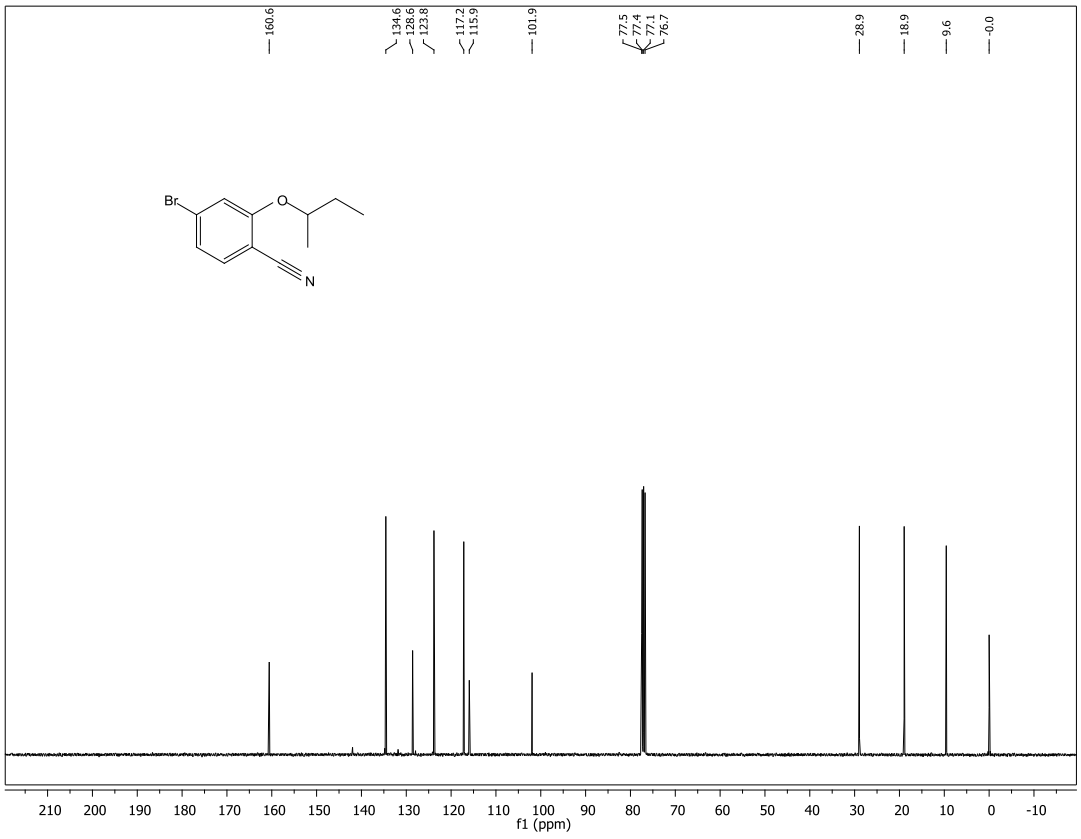


Figure 5.52: ^{1}H NMR of 1.23 at 400 MHz in CDl_3 at 298K

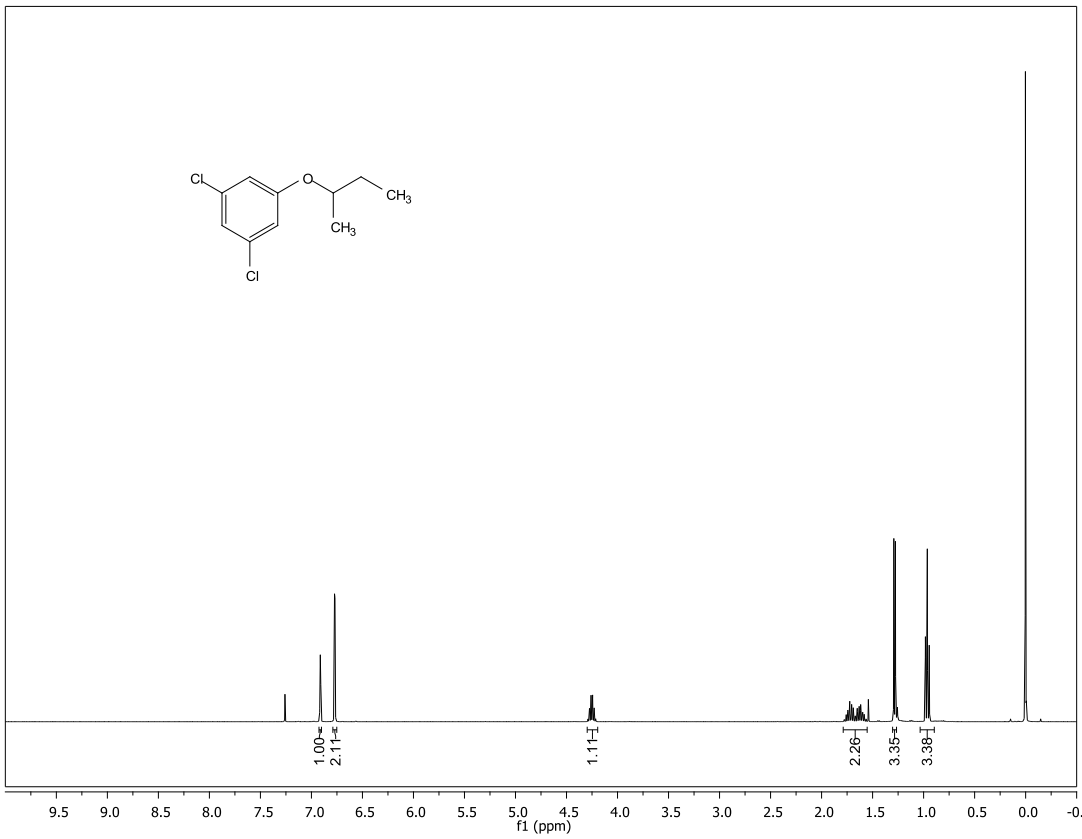


Figure 5.53: ^{13}C NMR of 1.23 at 100 MHz in CDl_3 at 298K

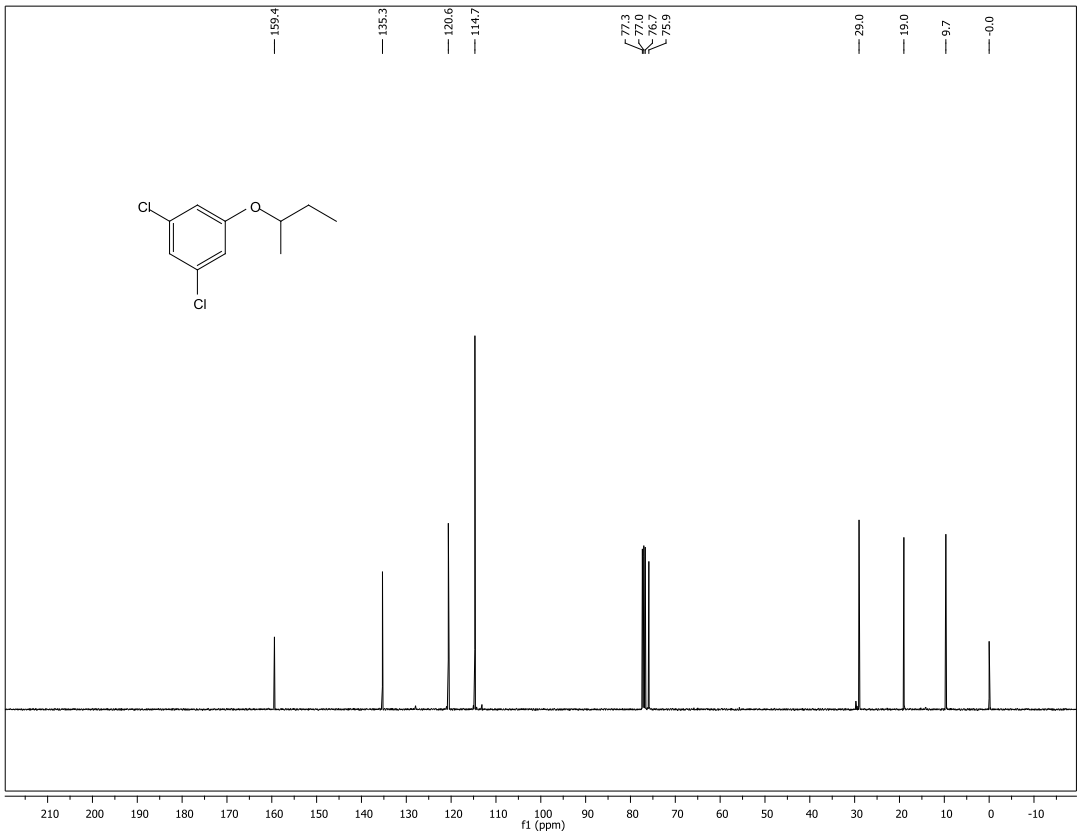


Figure 5.54: ^{1}H NMR of 1.24 at 400 MHz in CDl_3 at 298K

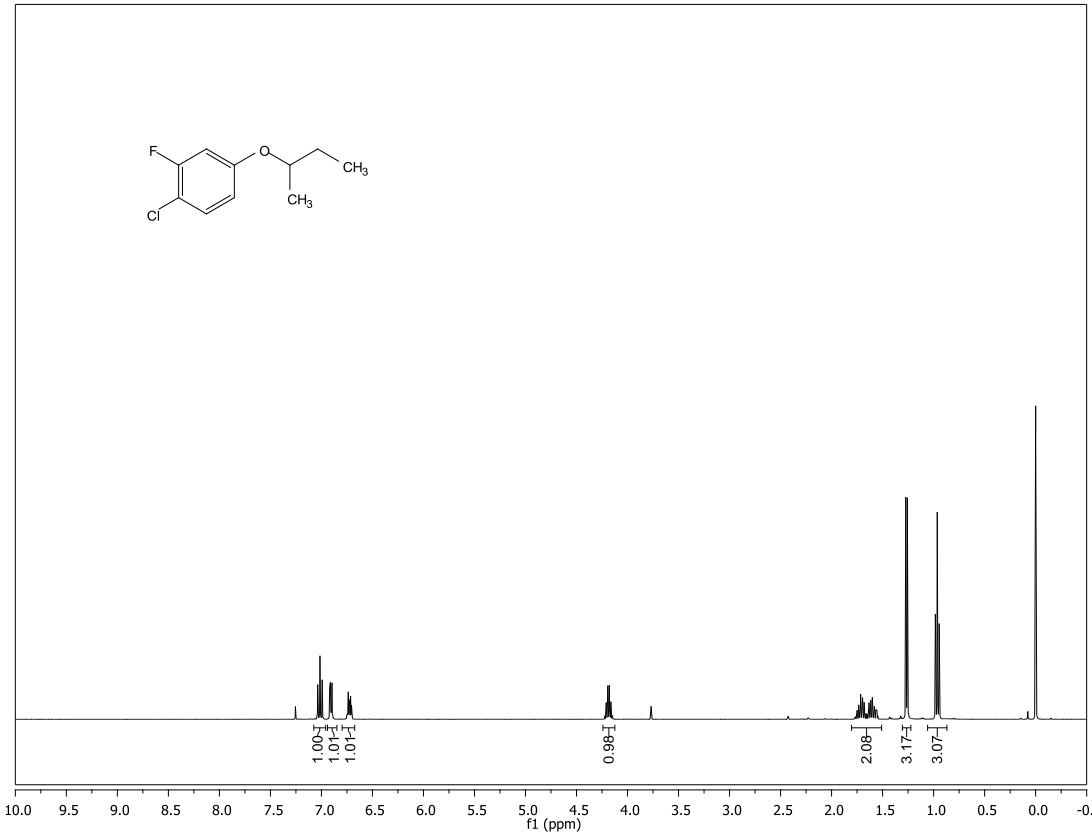


Figure 5.55: ^{13}C NMR of 1.24 at 100 MHz in CDl_3 at 298K

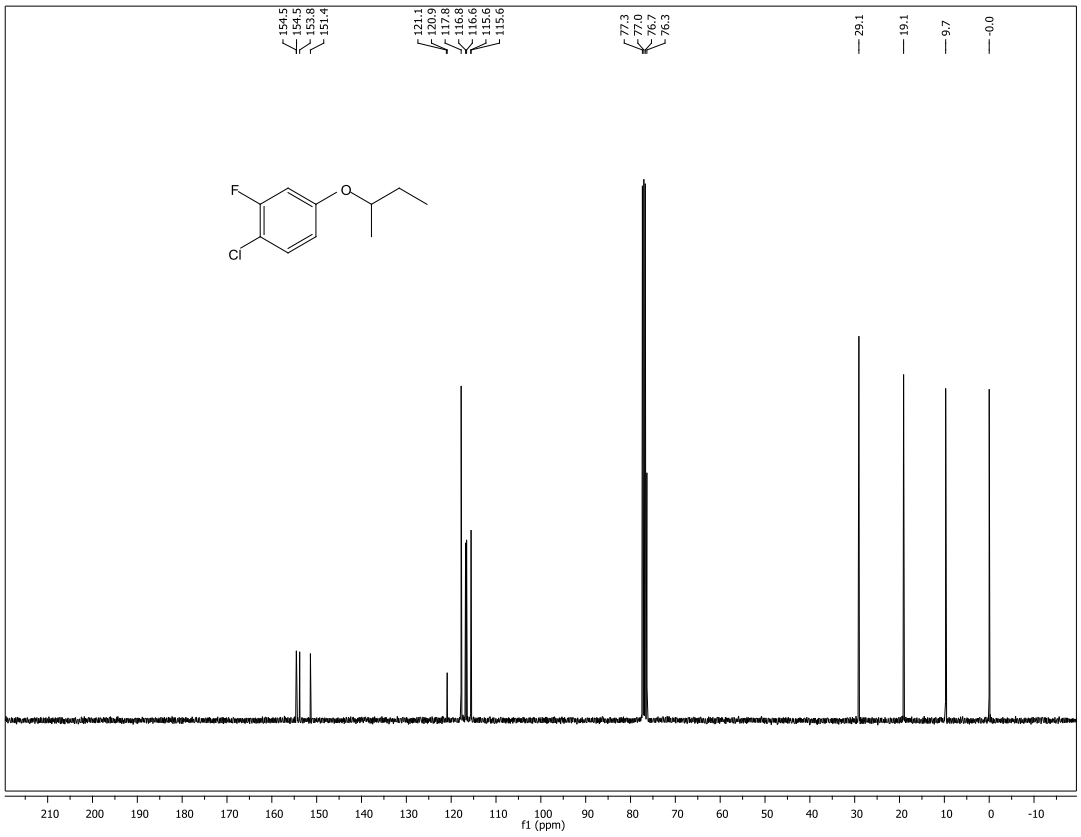


Figure 5.56: ^{19}F NMR of 1.24 at 377 MHz in CDl_3 at 298K

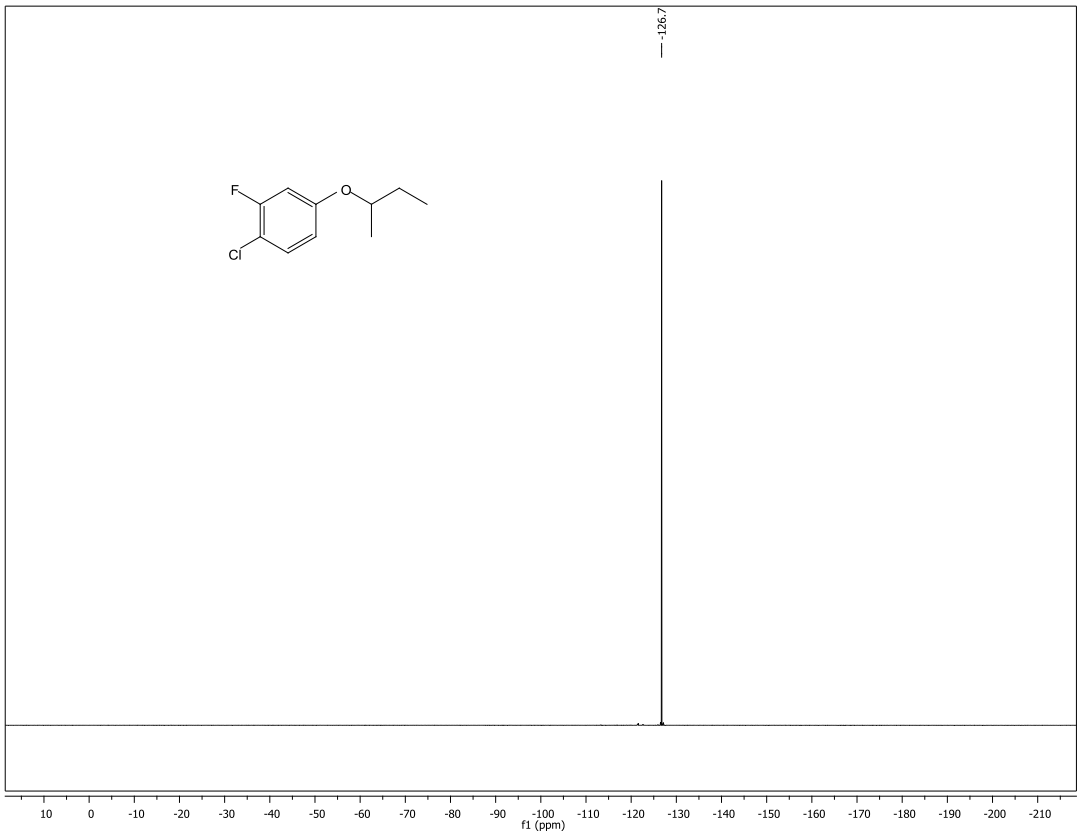


Figure 5.57: ^{1}H NMR of 1.25 at 400 MHz in CDl_3 at 298K

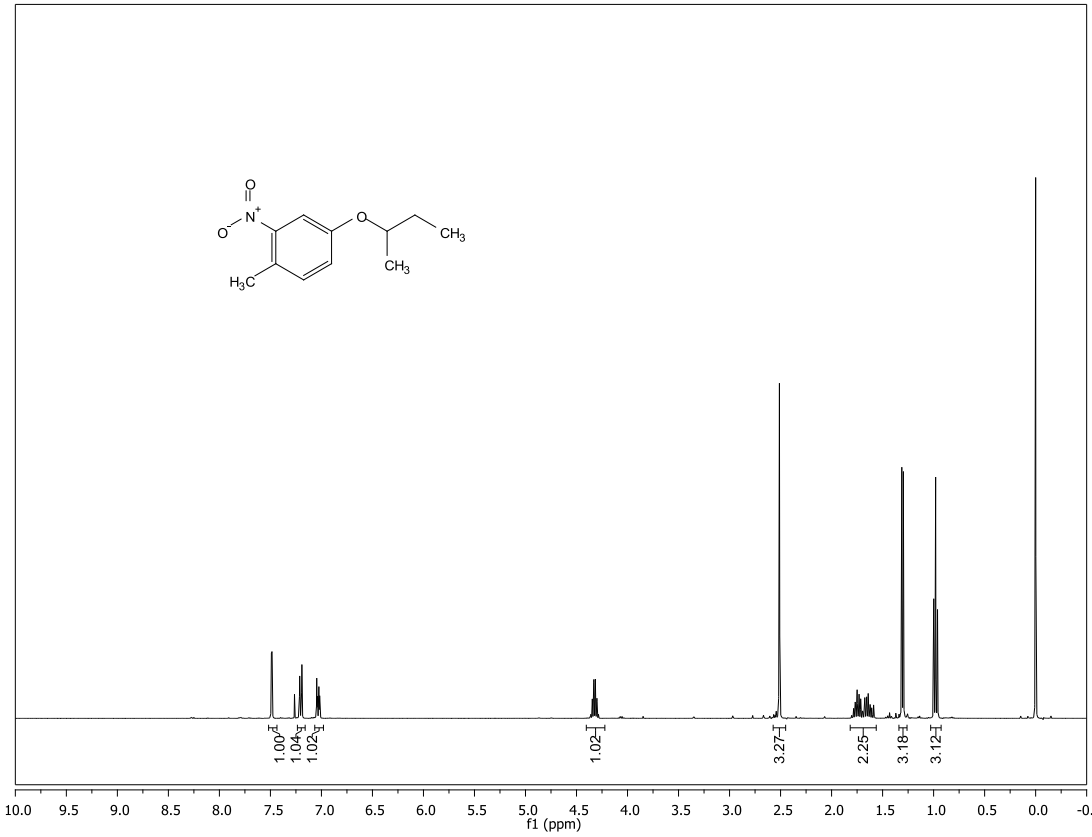


Figure 5.58: ^{13}C NMR of 1.25 at 100 MHz in CDl_3 at 298K

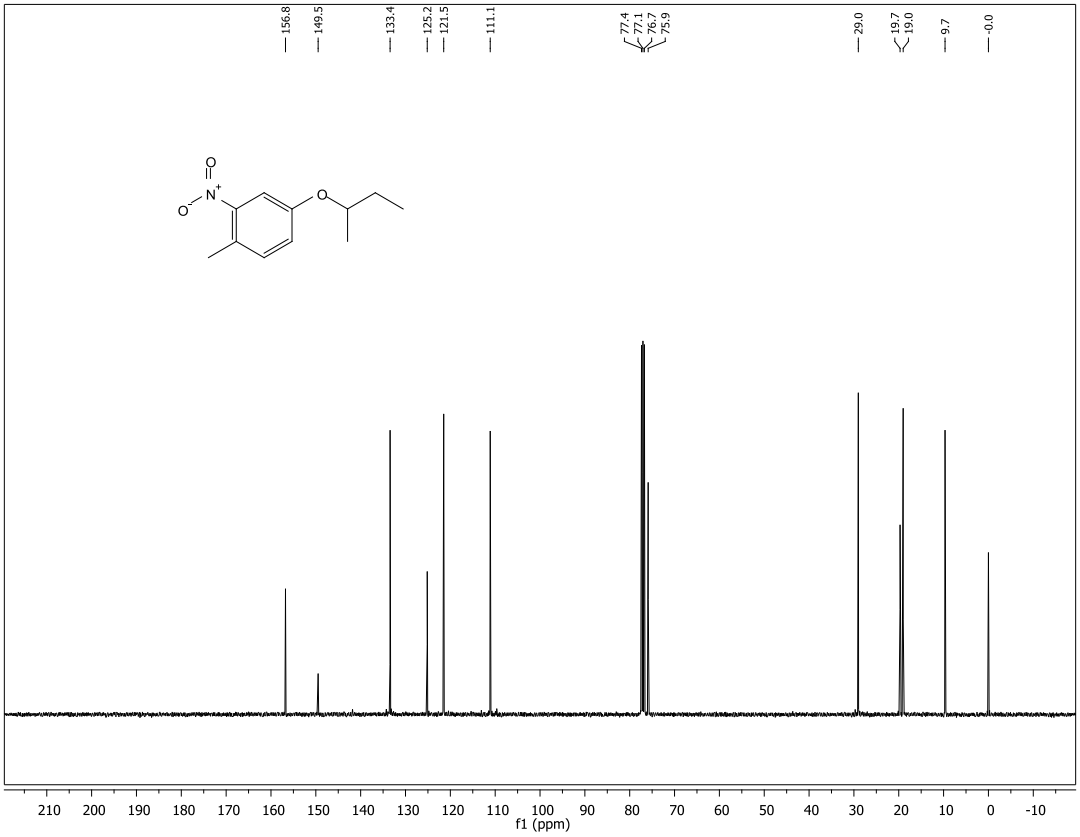


Figure 5.59: ^{1}H NMR of 1.26 at 400 MHz in CDl_3 at 298K

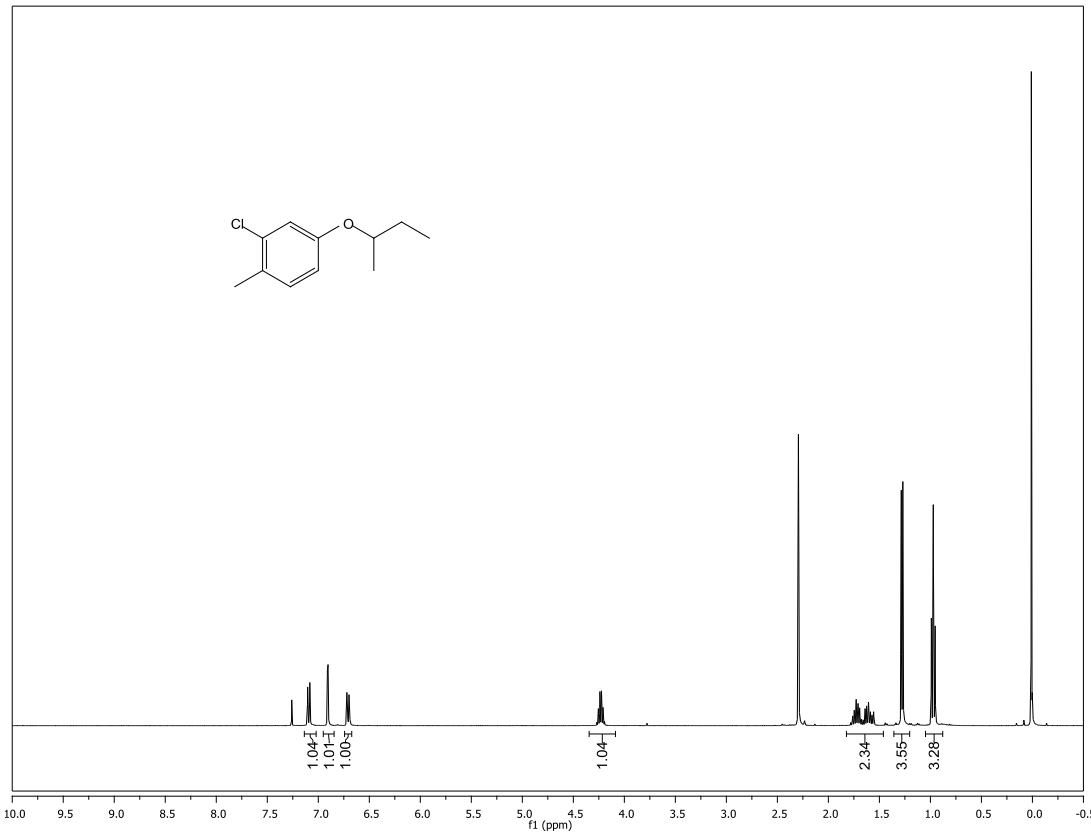


Figure 5.60: ^{13}C NMR of 1.26 at 100 MHz in CDl_3 at 298K

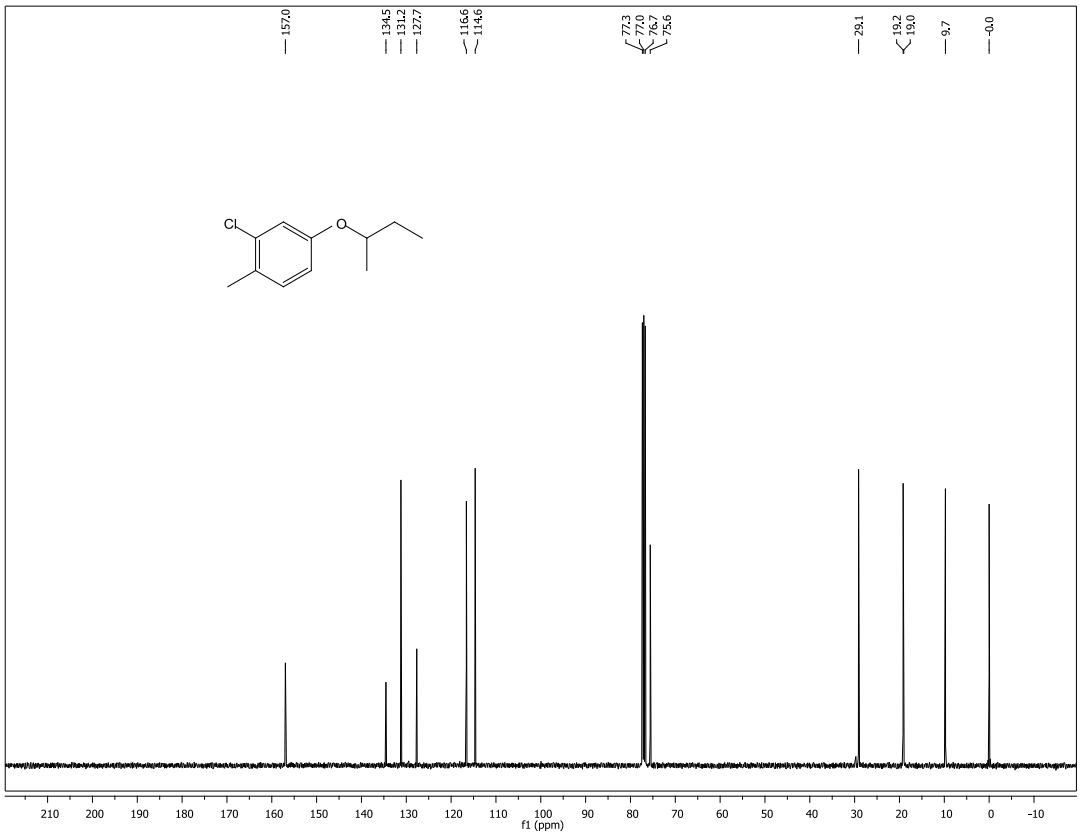


Figure 5.61: ^{1}H NMR of 1.27 at 400 MHz in CDl_3 at 298K

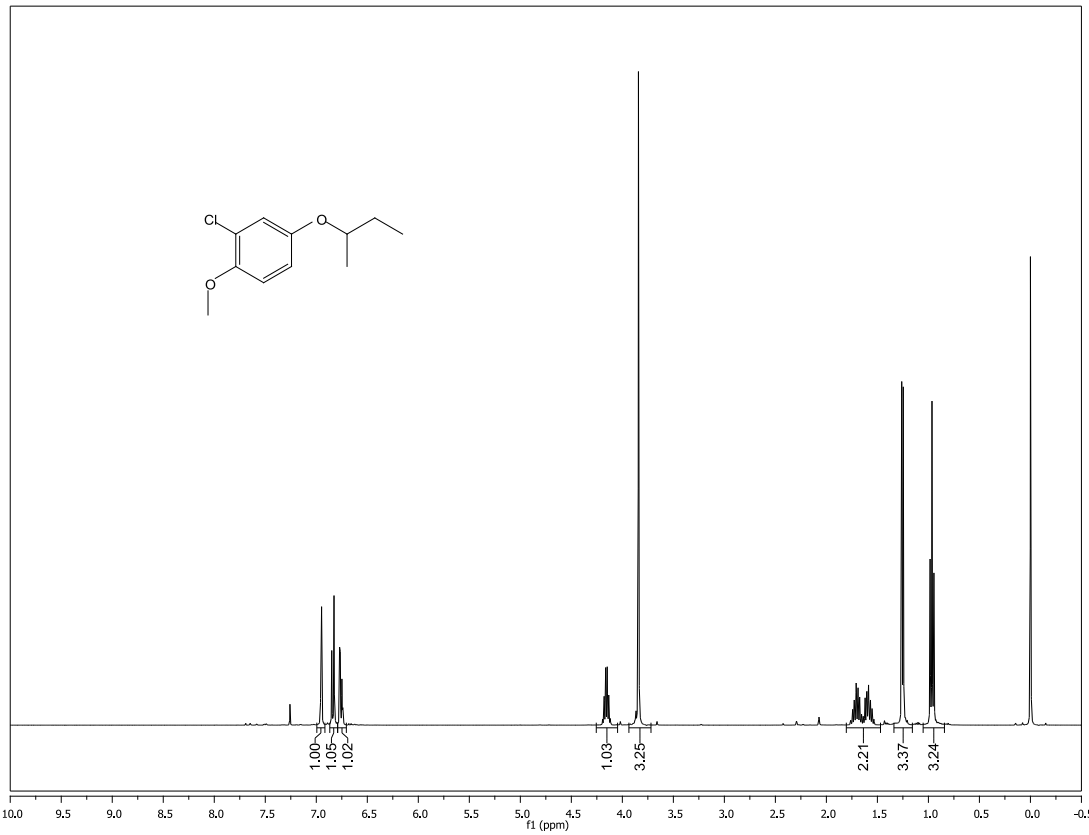


Figure 5.62: ^{13}C NMR of 1.27 at 100 MHz in CDl_3 at 298K

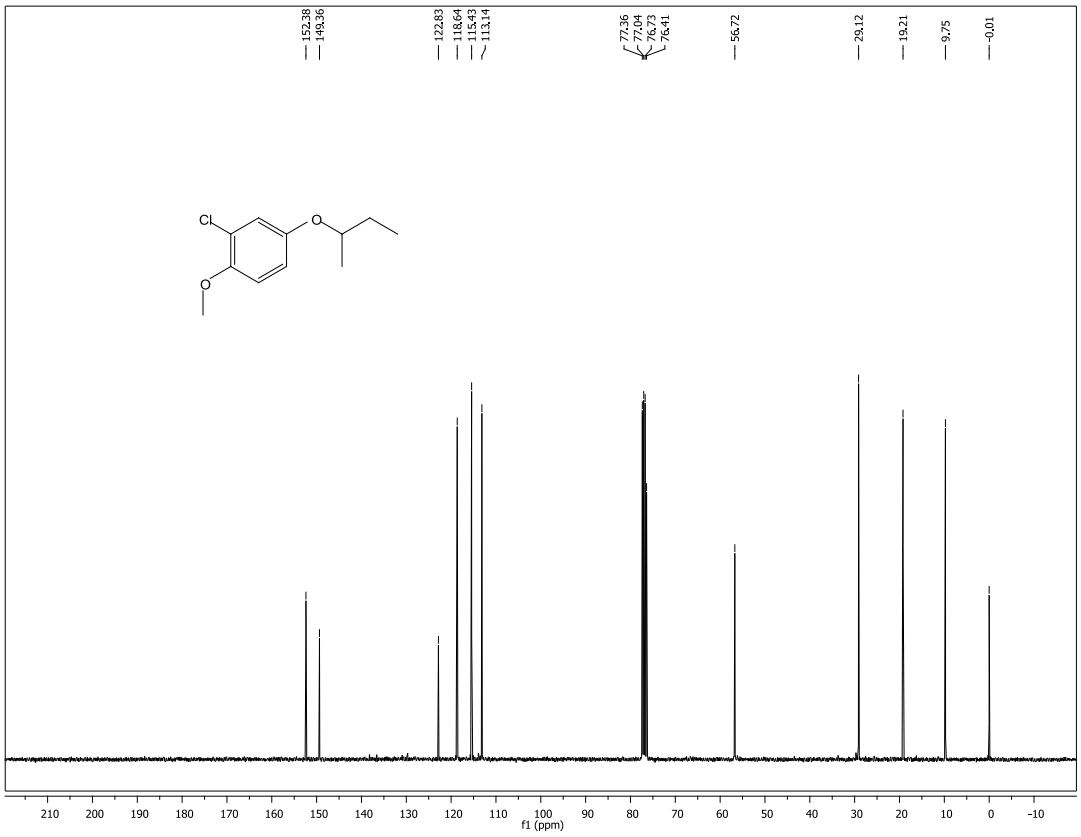


Figure 5.63: ^{1}H NMR of 1.28 at 400 MHz in CDl_3 at 298K

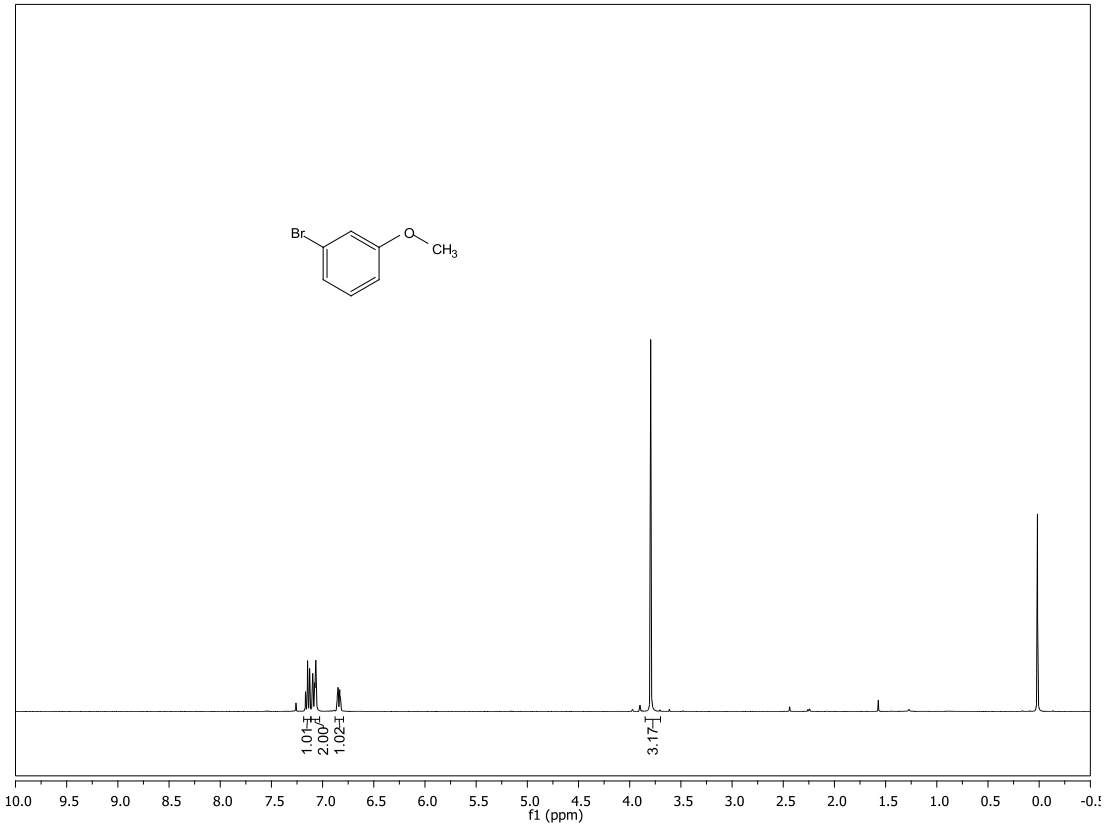


Figure 5.64: ^{1}H NMR of 1.29 at 400 MHz in CDl_3 at 298K

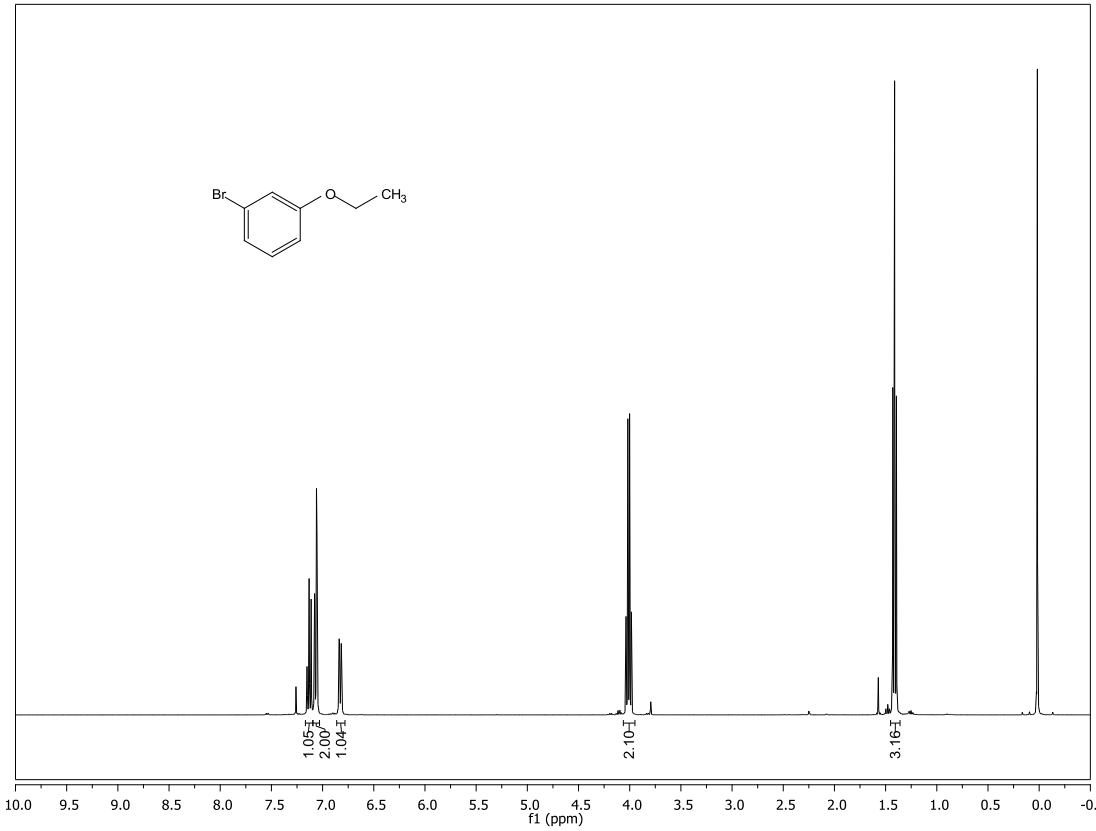


Figure 5.65: ^{1}H NMR of 1.30 at 400MHz in CDl_3 at 298K

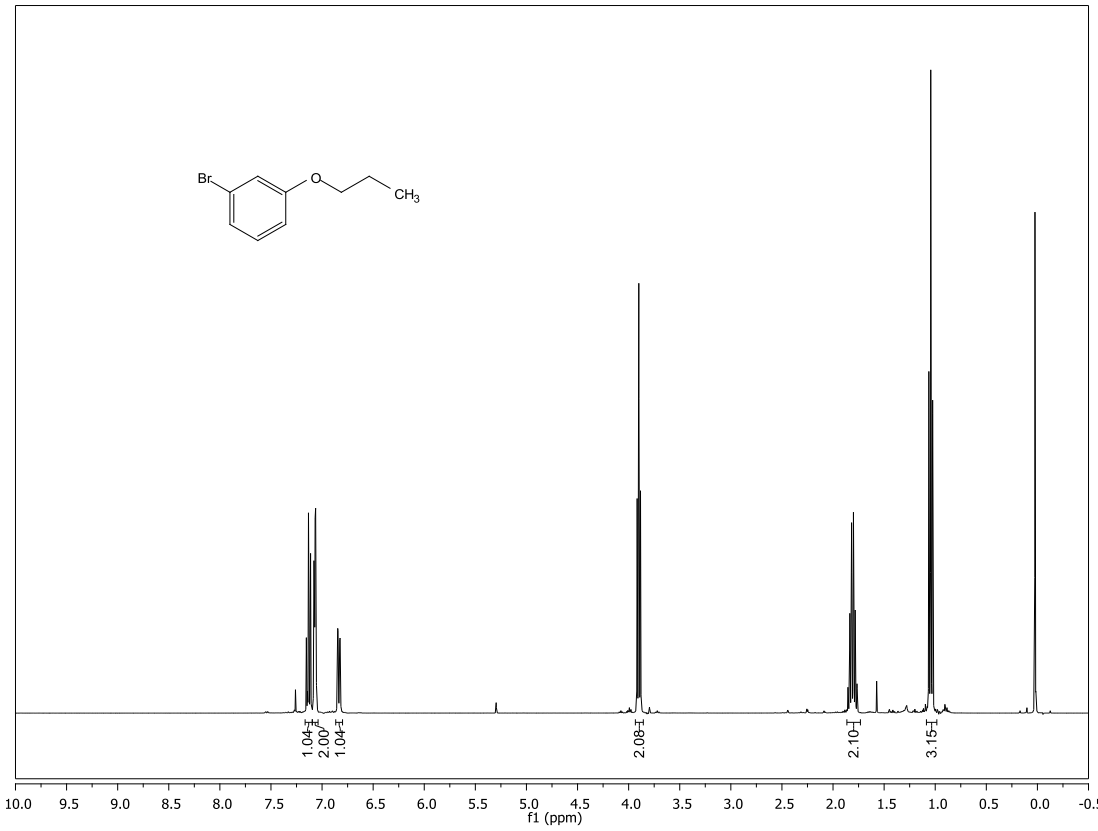


Figure 5.66: ^{13}C NMR of 1.30 at 100 MHz in CDl_3 at 298K

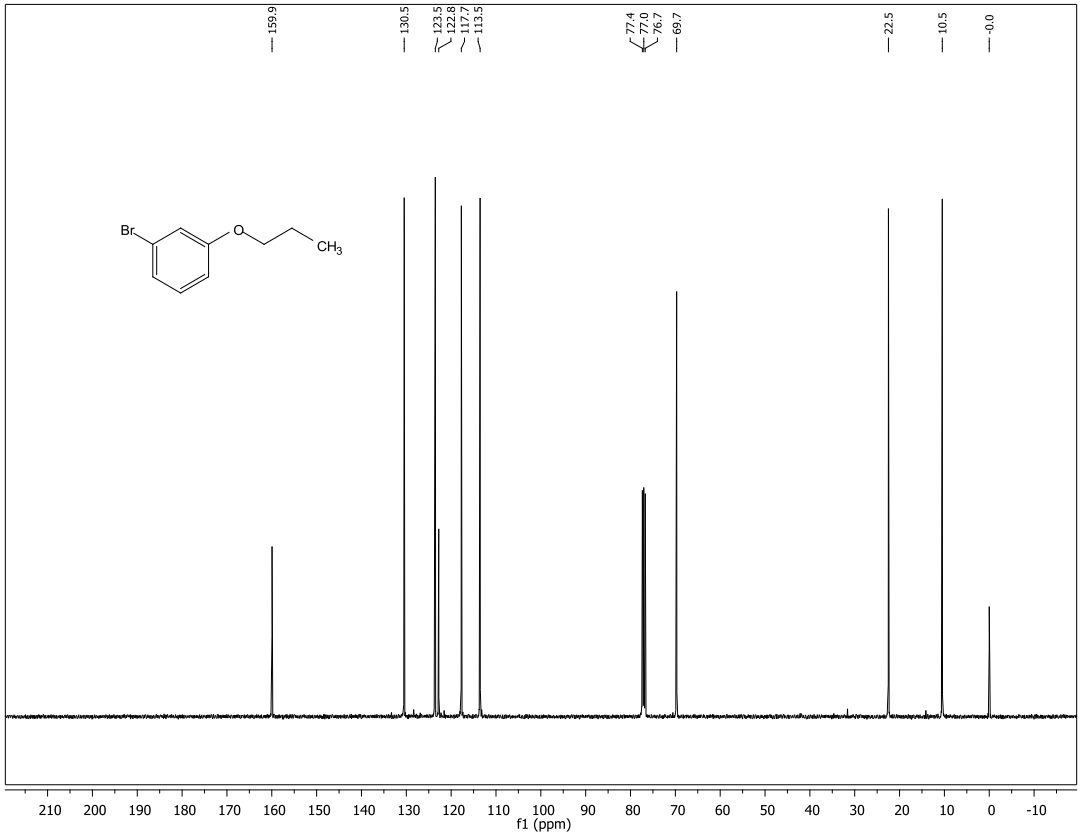


Figure 5.67: ^{1}H NMR of 1.31 at 400 MHz in CDl_3 at 298K

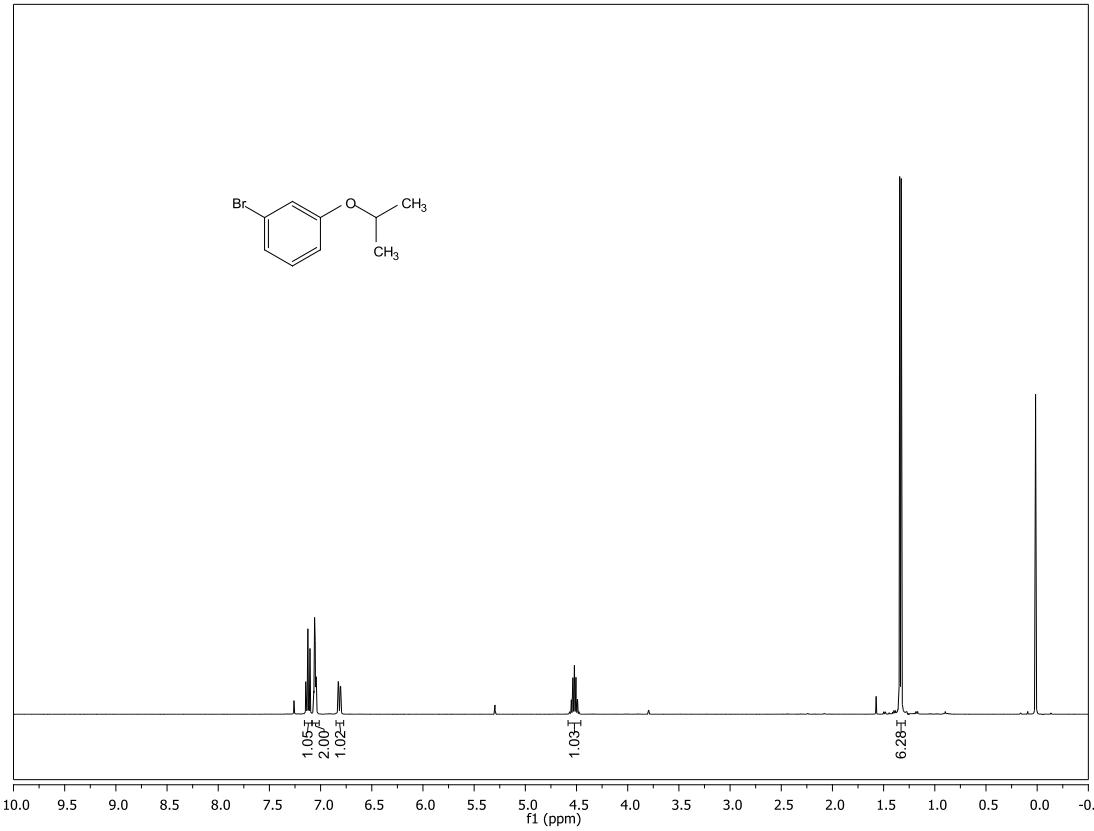


Figure 5.68: ^{1}H NMR of 1.32 at 400 MHz in CDl_3 at 298K

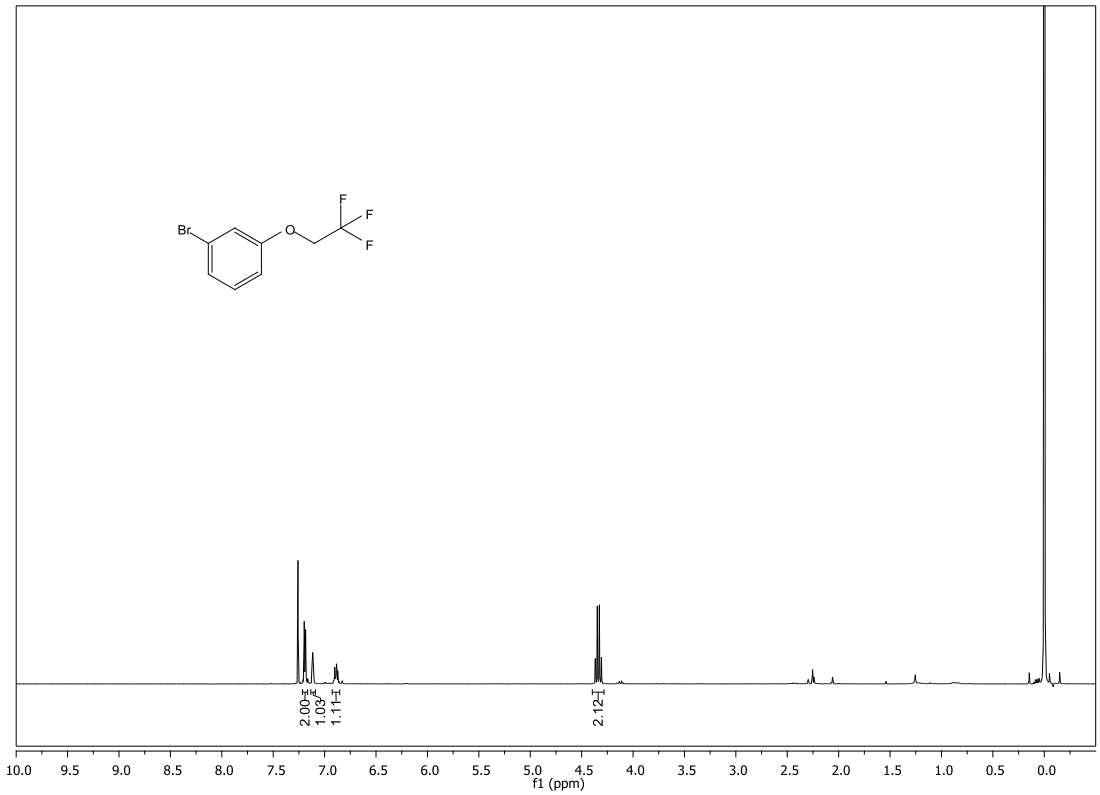


Figure 5.69: ^{13}C NMR of 1.32 at 100 MHz in CDl_3 at 298K

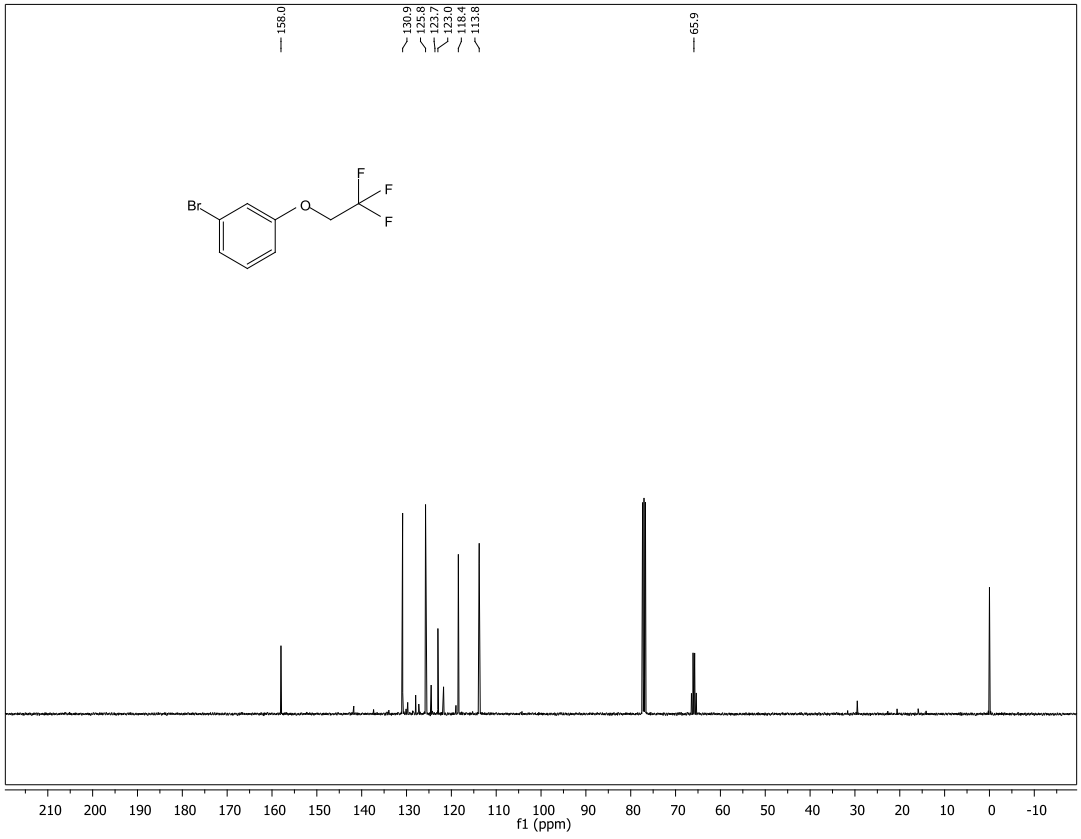


Figure 5.70: ^{19}F NMR of 1.32 at 377 MHz in CDl_3 at 298K

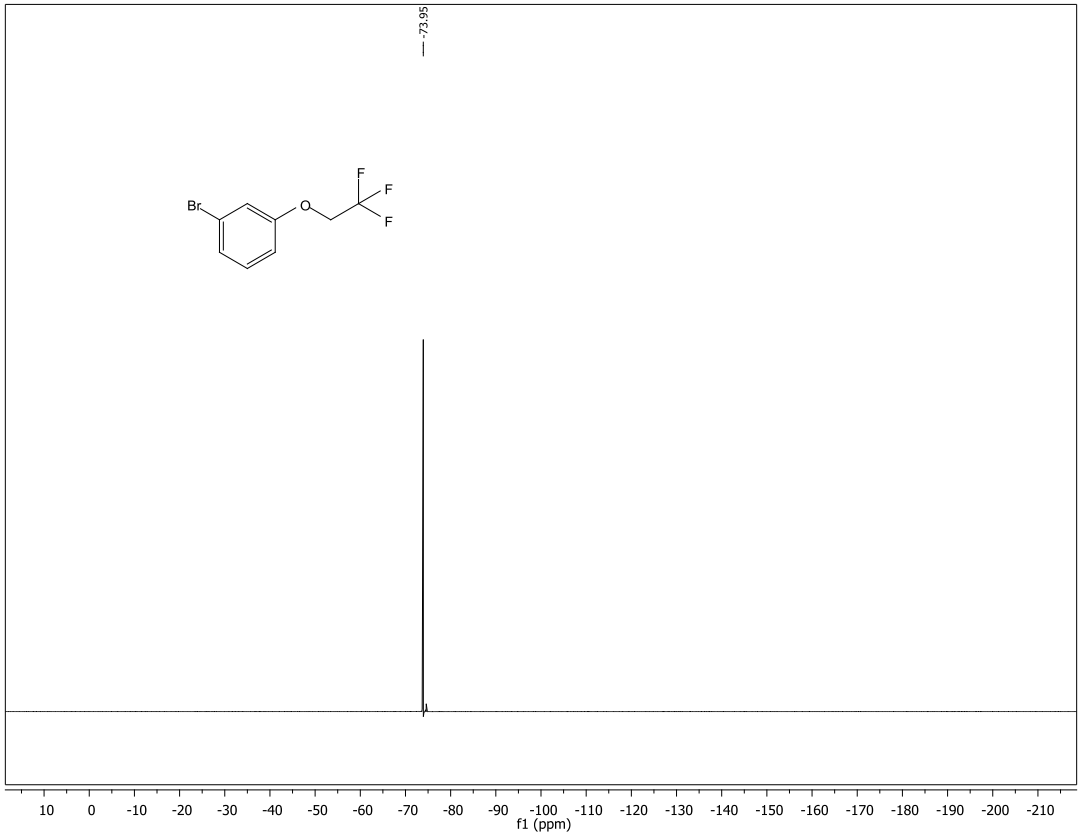


Figure 5.71: ^{1}H NMR of 1.33 at 400 MHz in CDl_3 at 298K

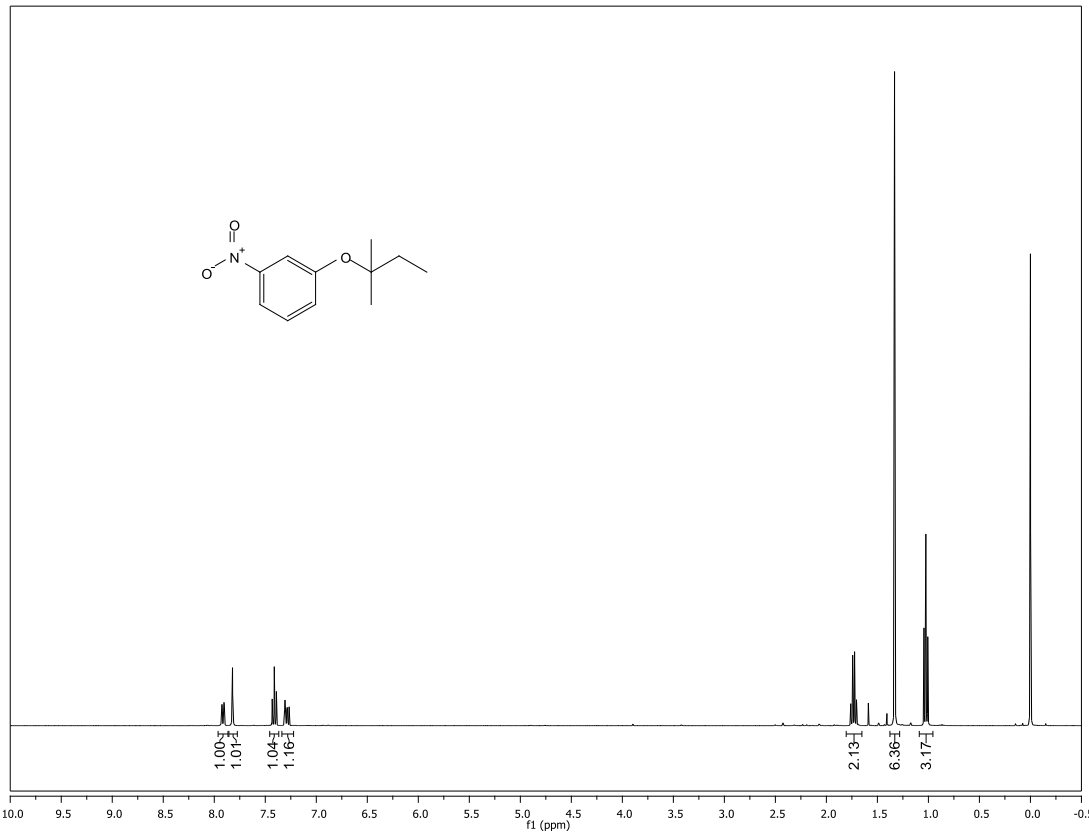


Figure 5.72: ^{13}C NMR of 1.33 at 100 MHz in CDl_3 at 298K

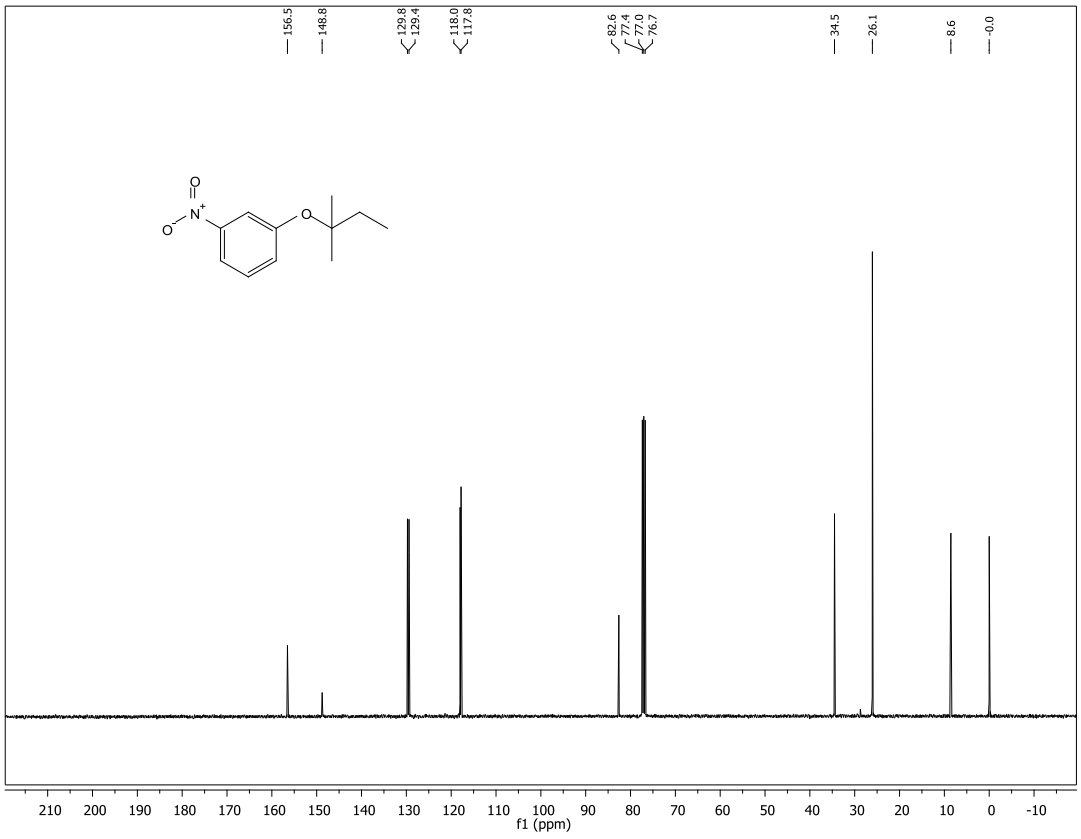


Figure 5.73: ^{1}H NMR of 1.34 at 400 MHz in CDl_3 at 298K

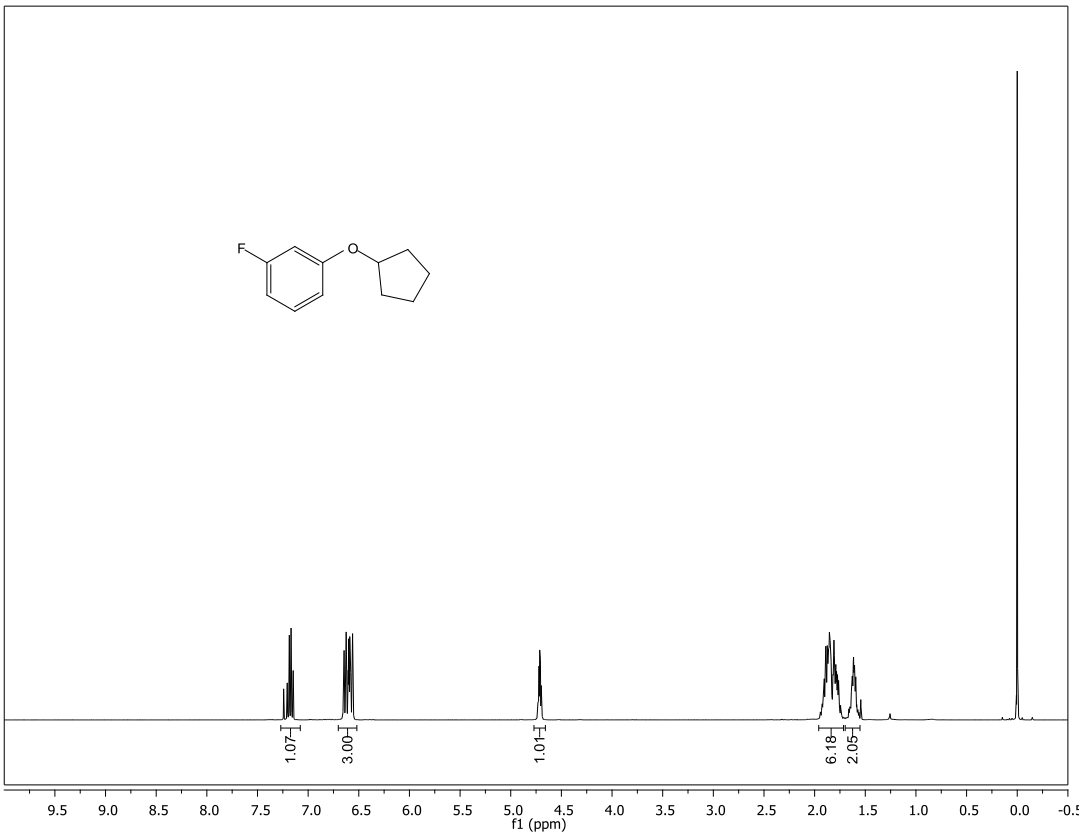


Figure 5.74: ^{13}C NMR of 1.34 at 100 MHz in CDl_3 at 298K

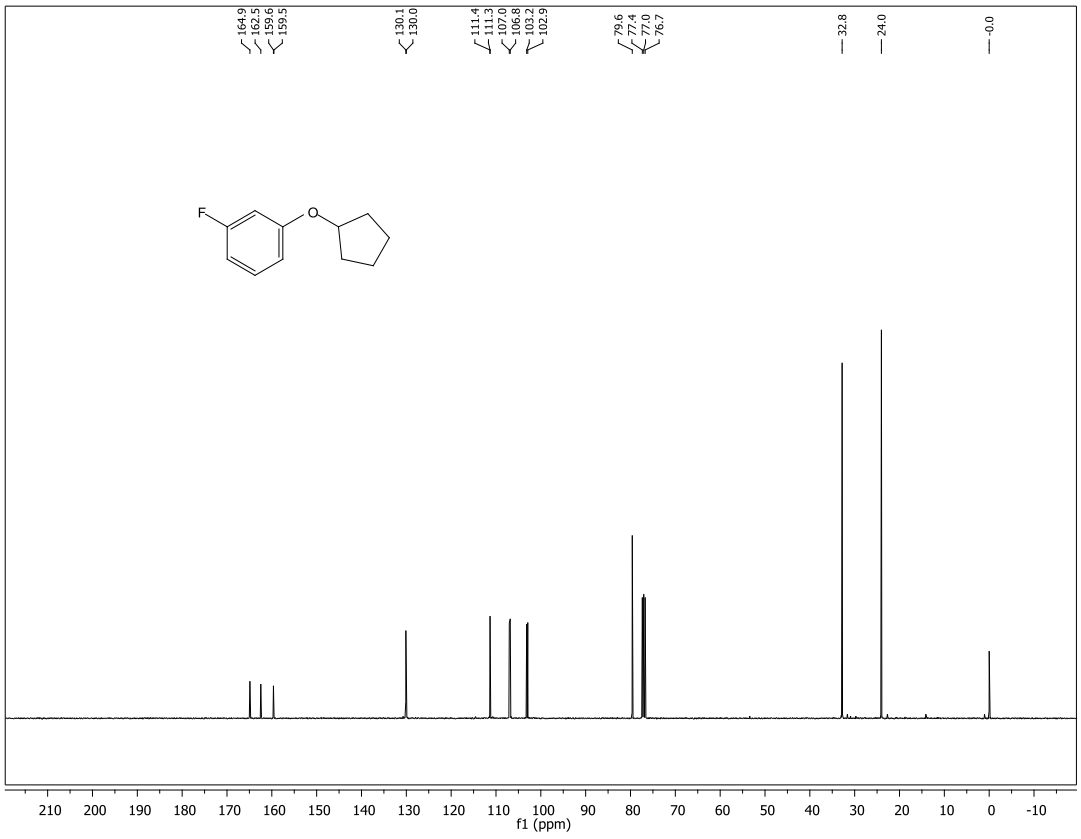


Figure 5.75: ^{19}F NMR of 1.34 at 377 MHz in CDl_3 at 298K

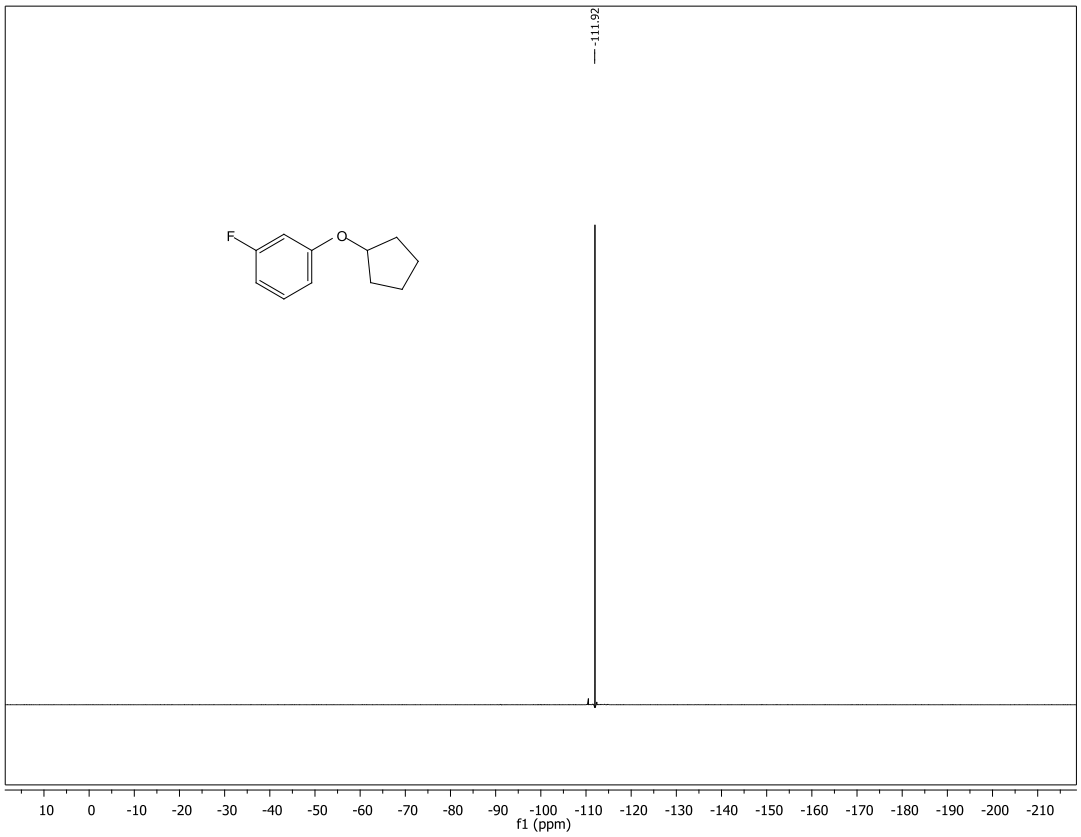


Figure 5.76: ^{1}H NMR of 1.35 at 400 MHz in CDl_3 at 298K

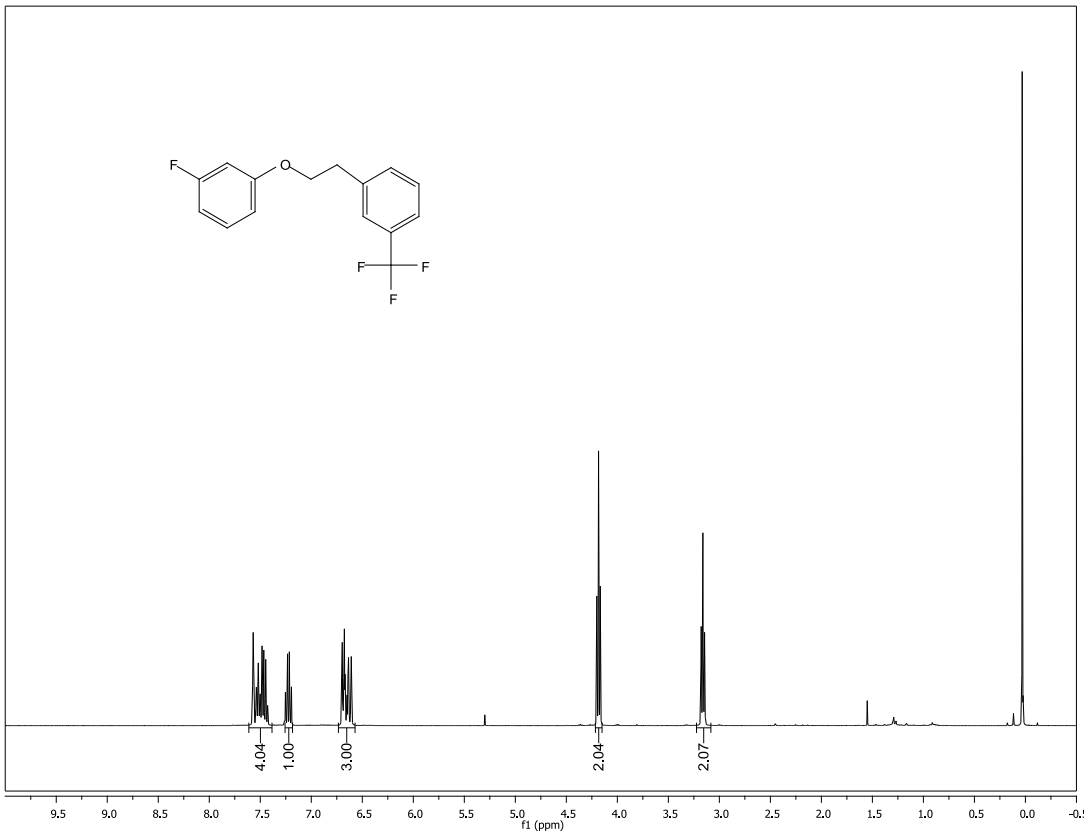


Figure 5.77: ^{13}C NMR of 1.35 at 100 MHz in CDl_3 at 298K

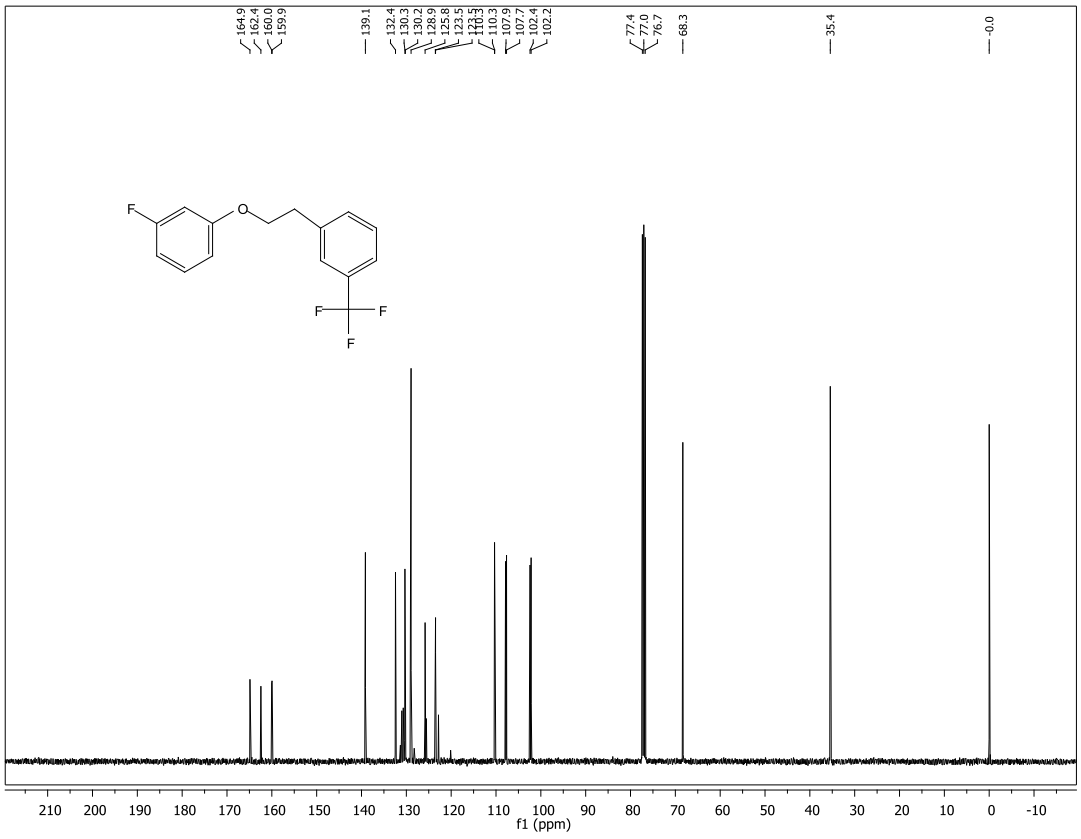


Figure 5.78: ^{19}F NMR of 1.35 at 377 MHz in CDl_3 at 298K

Figure 5.79: ^{1}H NMR 1.36 at 400 MHz in CDl_3 at 298K

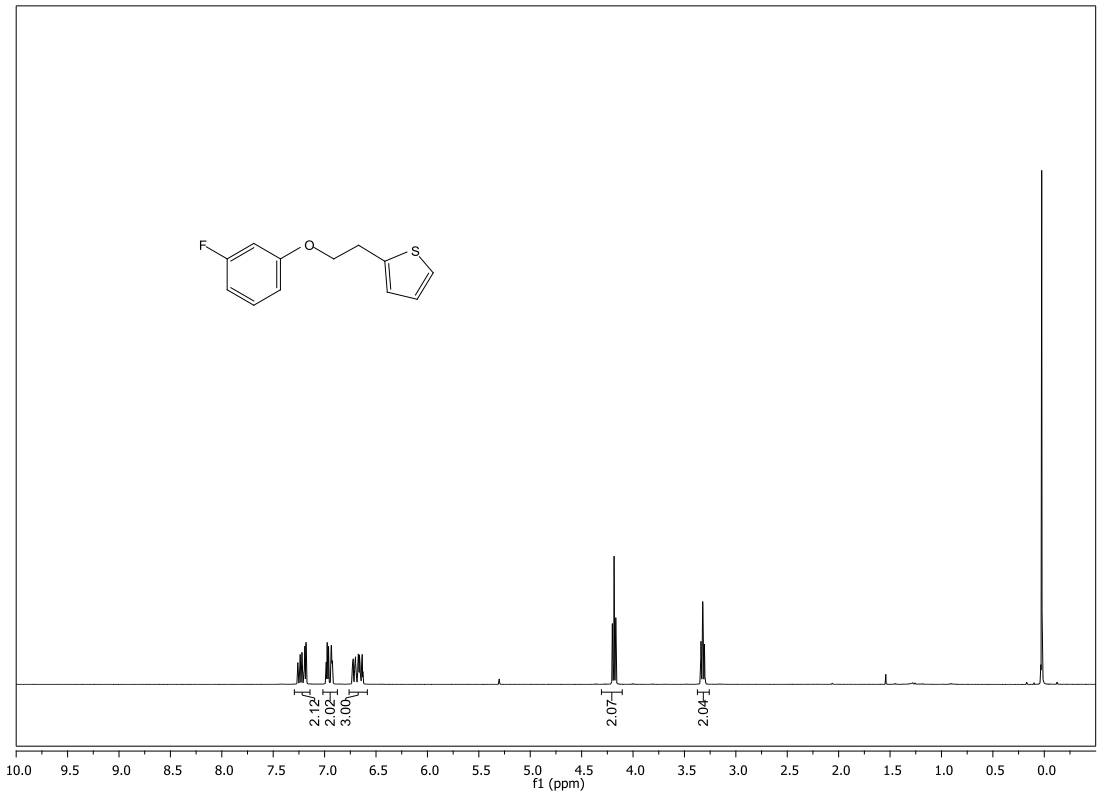


Figure 5.80: ^{13}C NMR of 1.36 at 100 MHz in CDl_3 at 298K

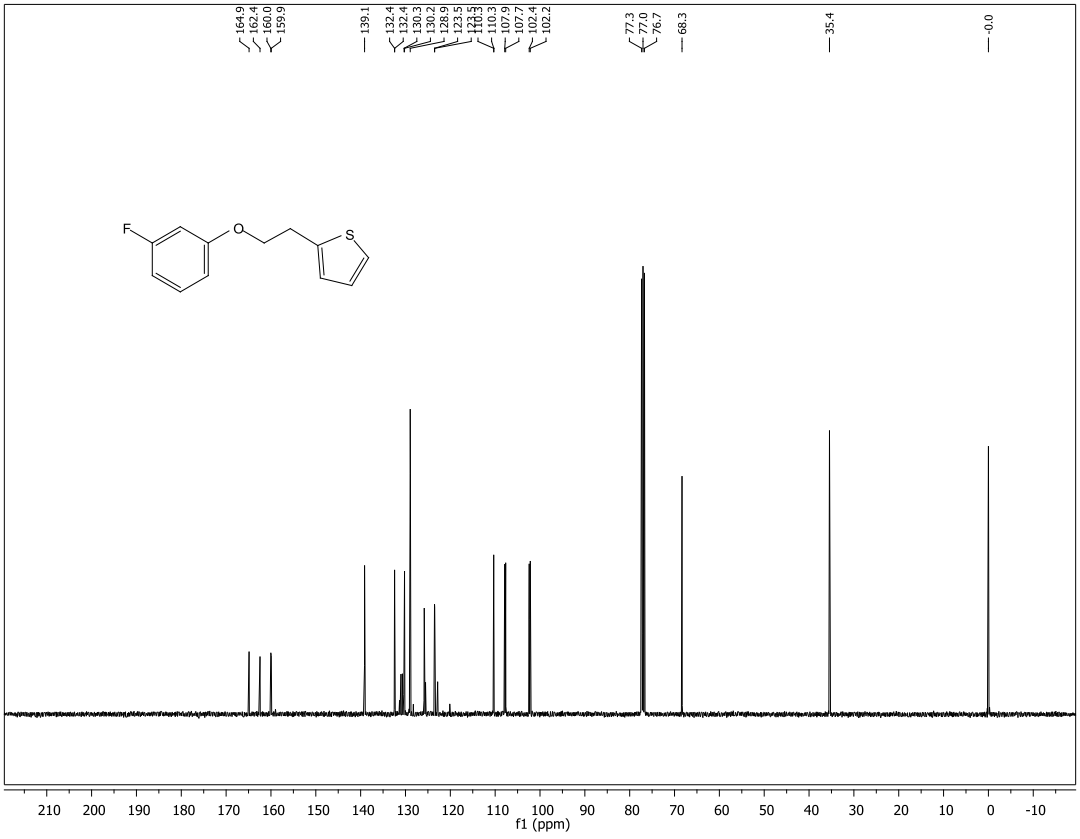


Figure 5.81: ^{19}F NMR of 1.36 at 377 MHz in CDl_3 298K

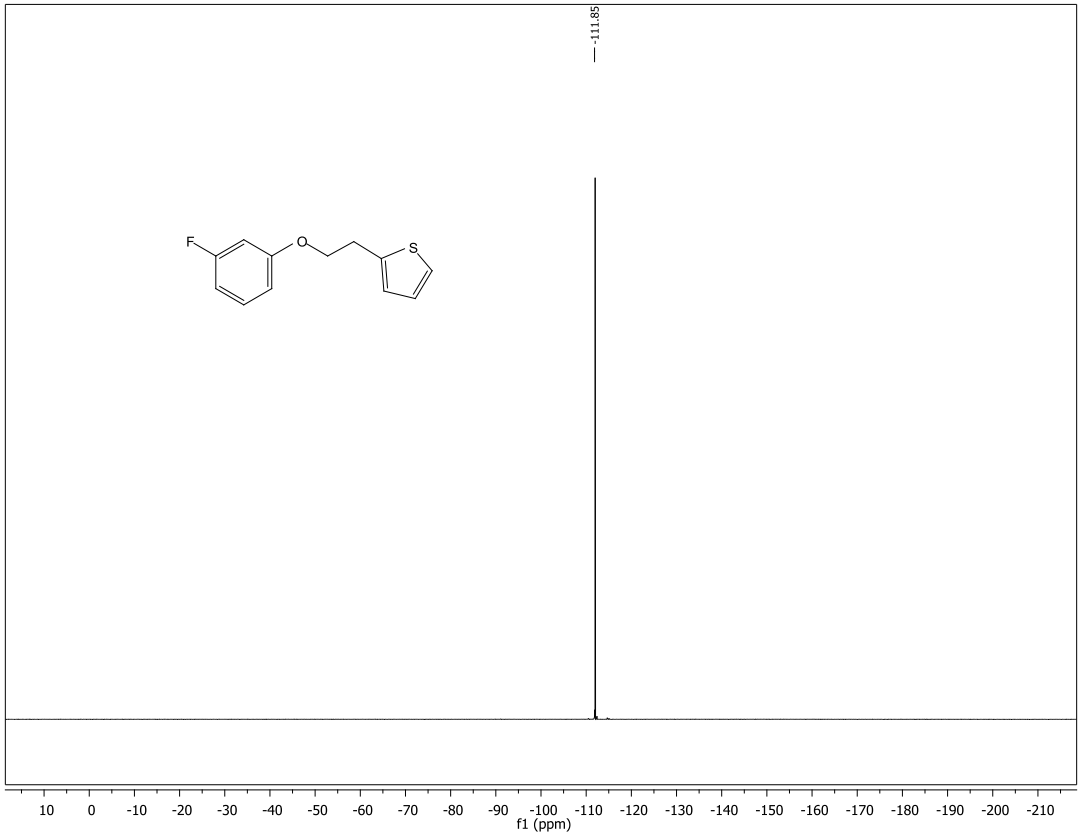


Figure 5.82: ^{1}H NMR of 1.37 at 400 MHz in CDl_3 at 298K

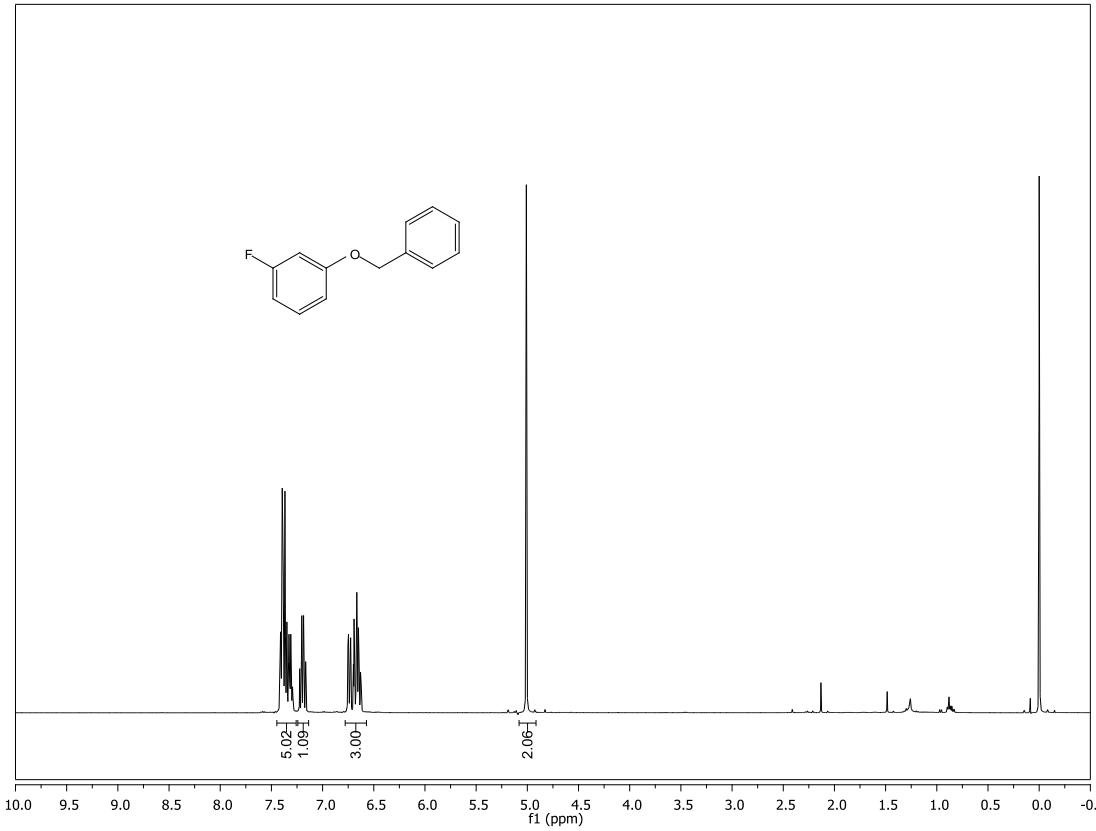


Figure 5.83: ^{1}H NMR of 1.38 at 400 MHz in CDl_3 at 298K

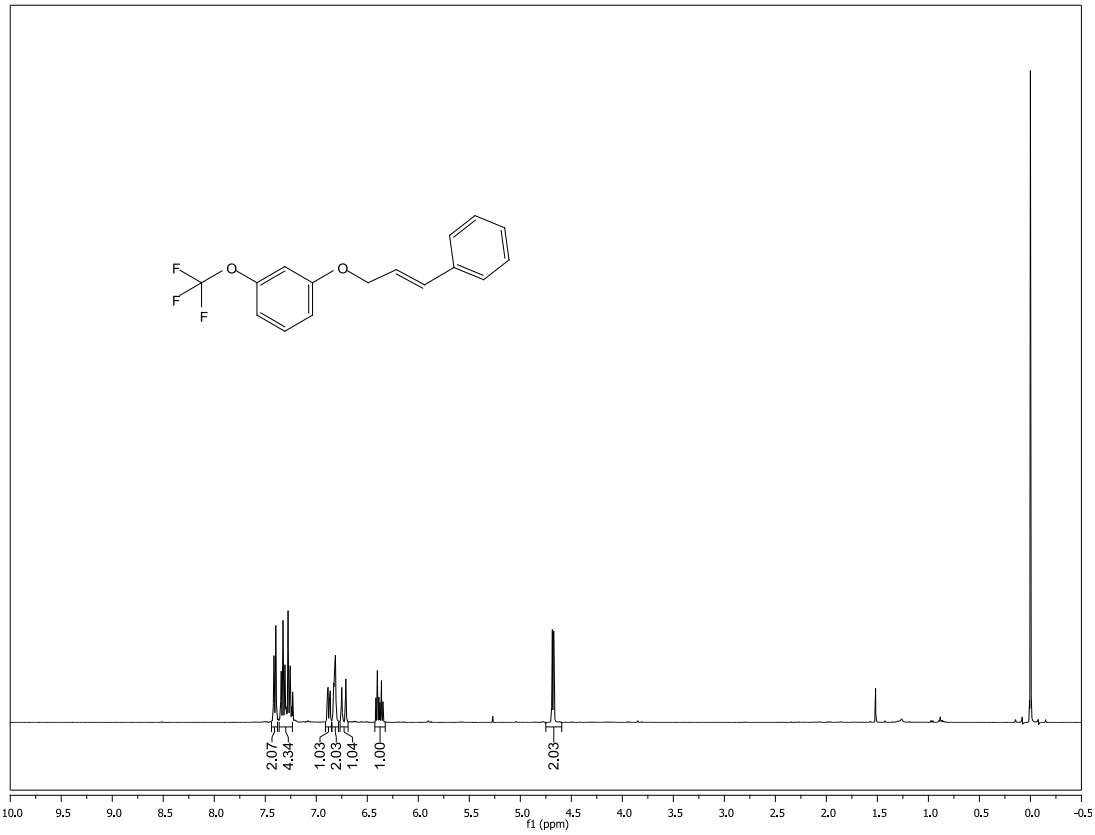


Figure 5.84: ^{13}C NMR of 1.38 at 100 MHz in CDl_3 at 298K

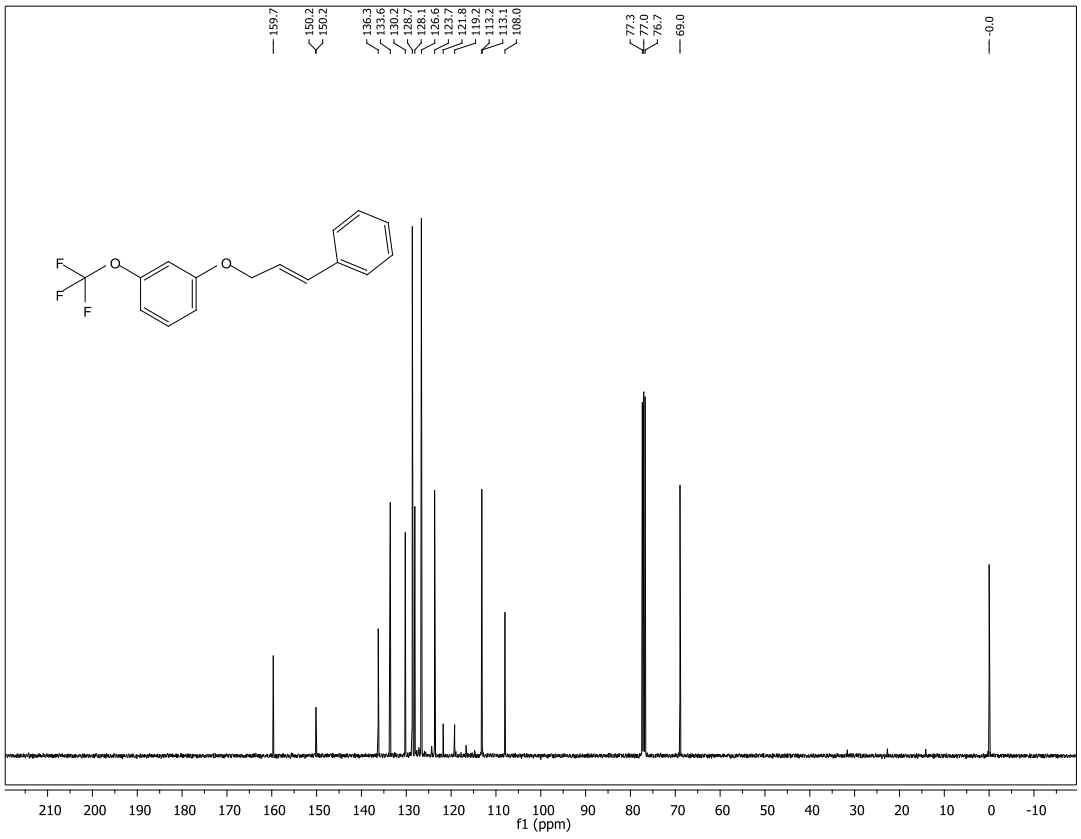


Figure 5.85: ^{19}F NMR of 1.38 at 377 MHz in CDl_3 at 298K

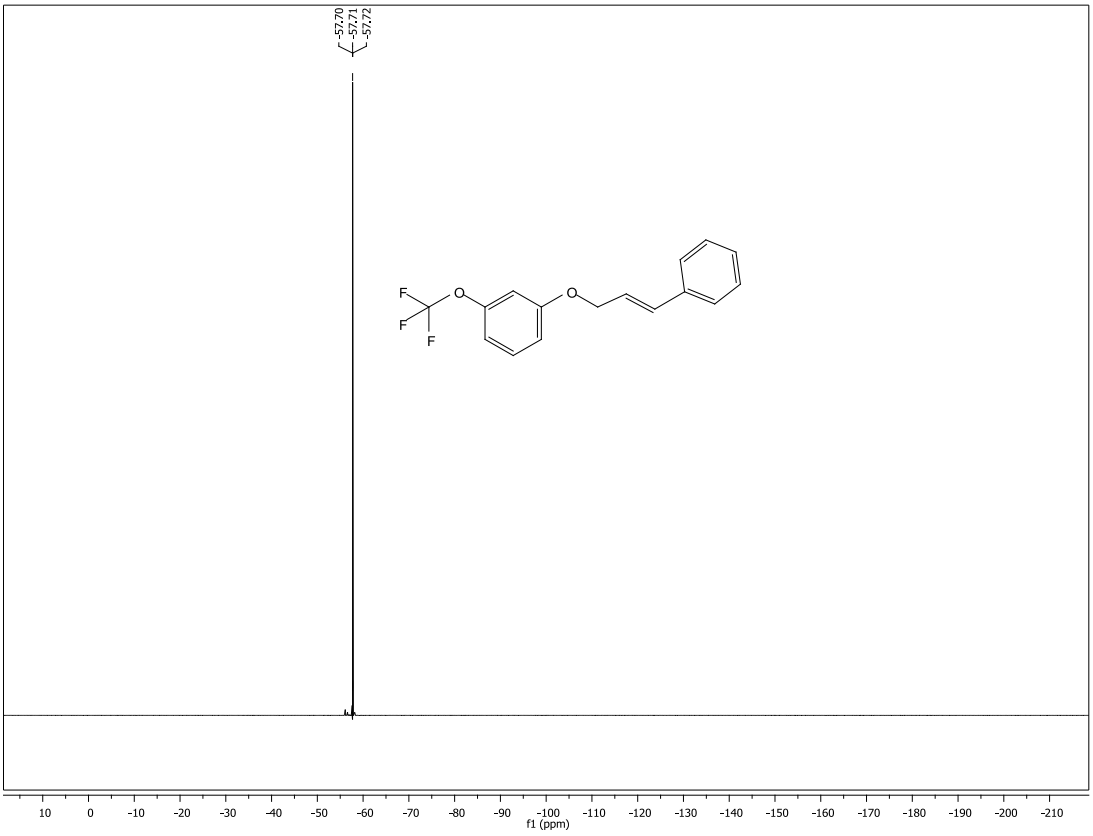


Figure 5.86: ^{1}H NMR 1.39 at 400 MHz in DMSO-d_6 at 298K

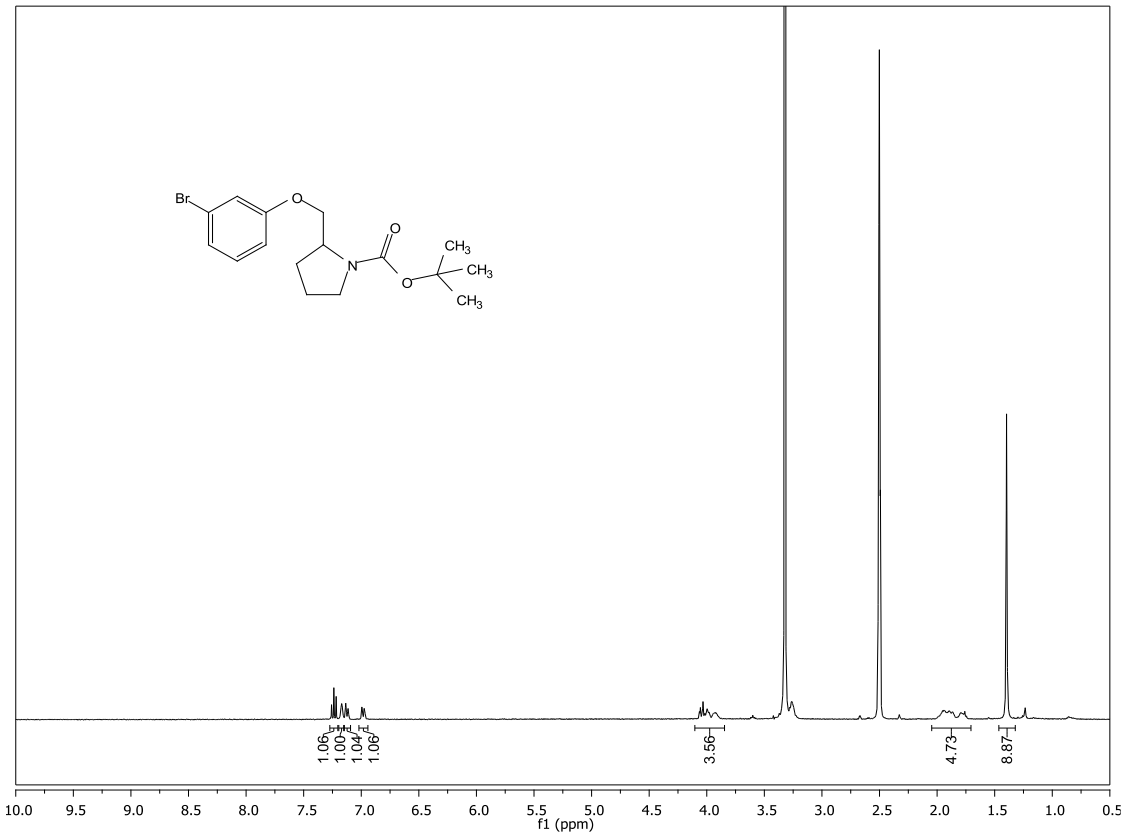


Figure 5.87: ^{1}H NMR 1.39 at 400 MHz in DMSO-d_6 at 373K

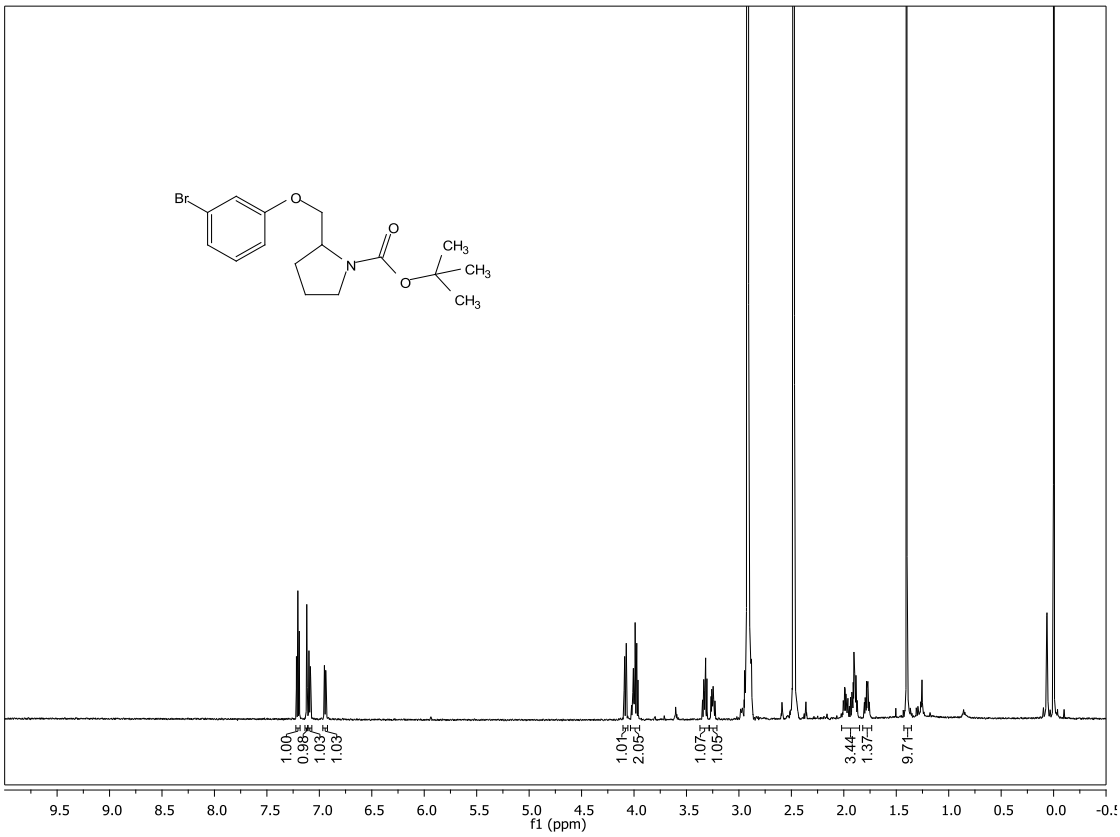


Figure 5.88: ^{1}H NMR of 1.39 at 400 MHz in CDl_3 at 298K

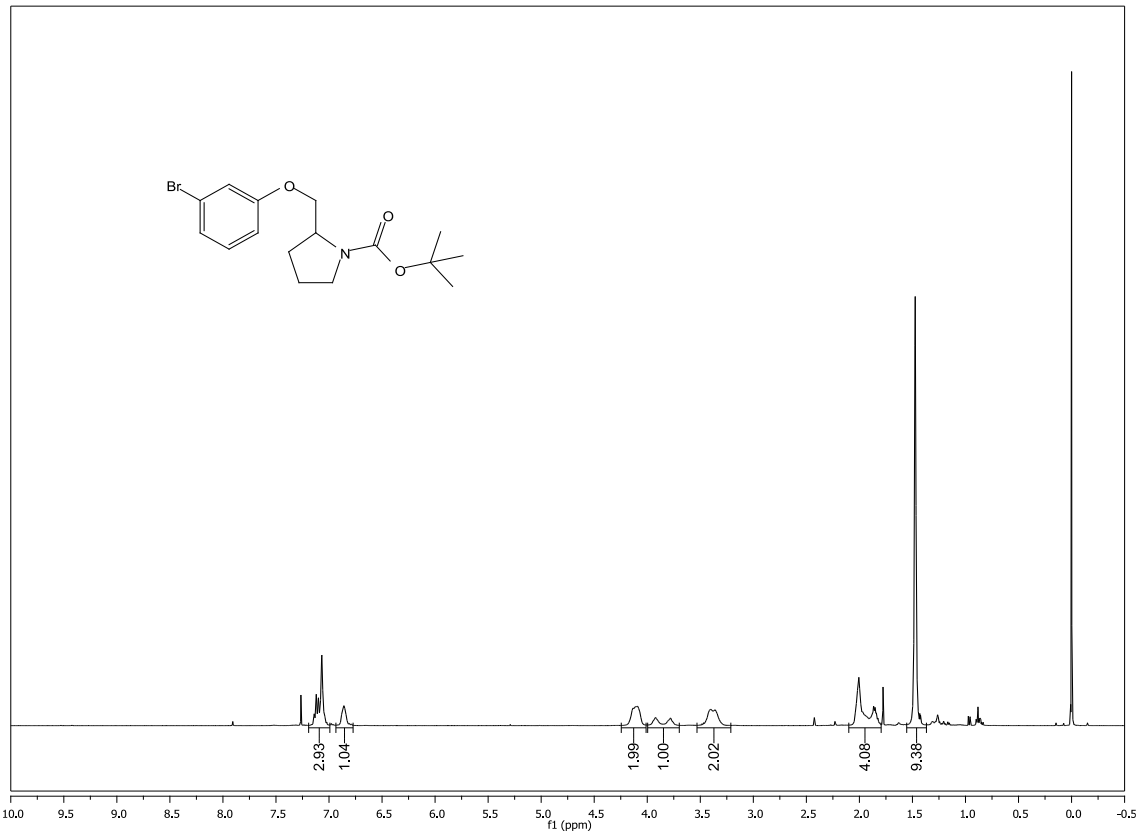


Figure 5.89: ^{13}C NMR of 1.39 at 100 MHz in CDl_3 at 298K

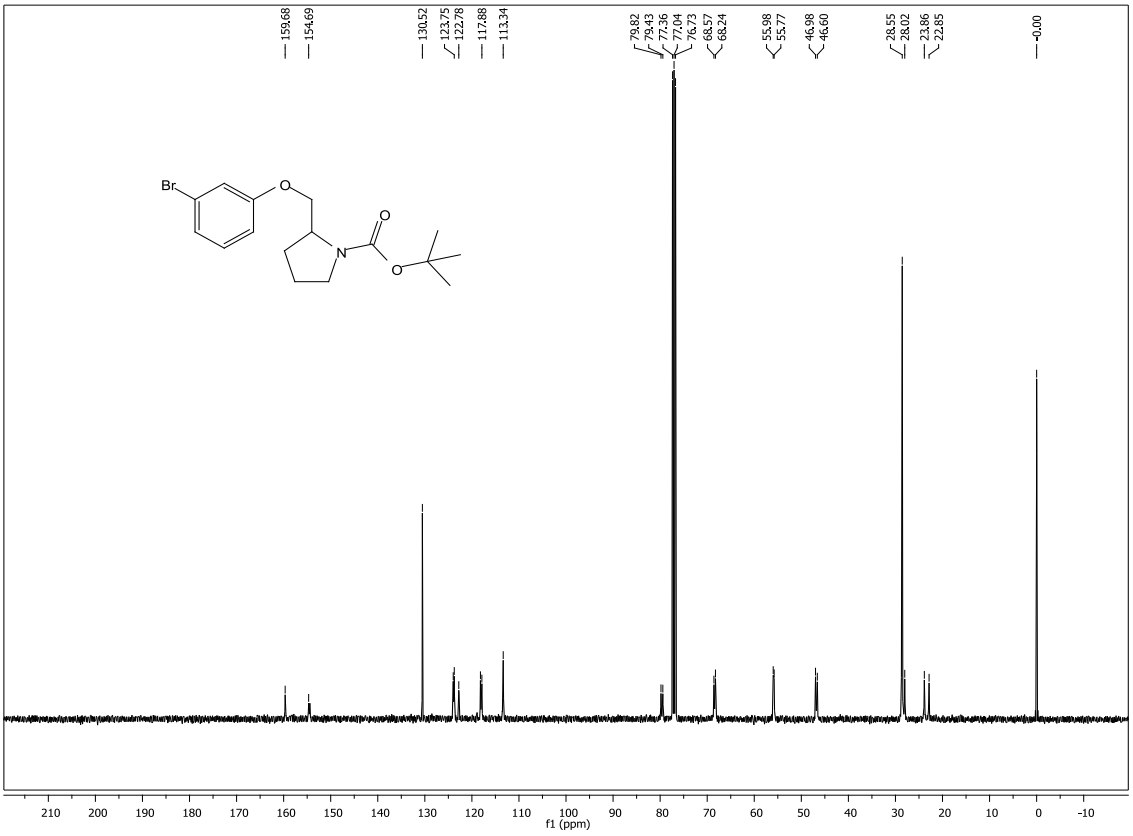


Figure 5.90: ^{1}H NMR of 1.40 at 400 MHz in CDl_3 at 298K

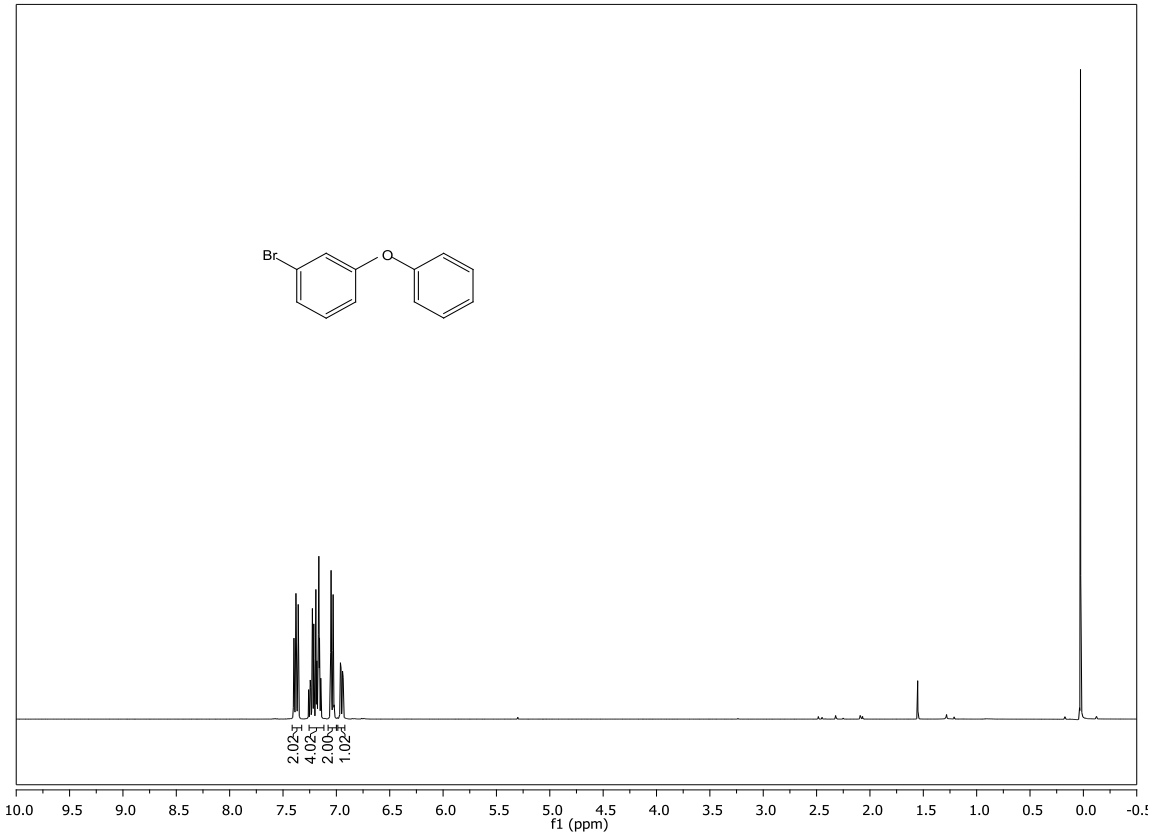


Figure 5.91: ^{1}H NMR of 1.41 at 400 MHz in CDl_3 at 298K

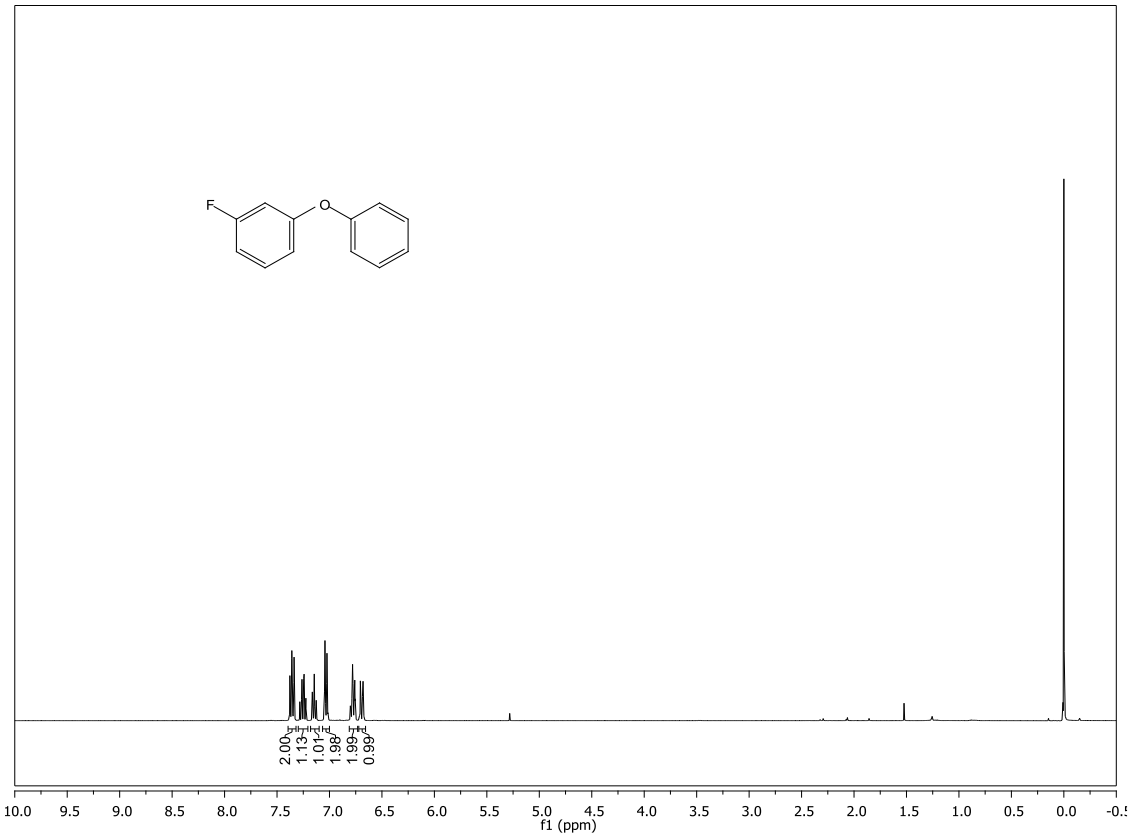


Figure 5.92: ^{13}C NMR of 1.41 at 100 MHz in CDl_3 at 298K

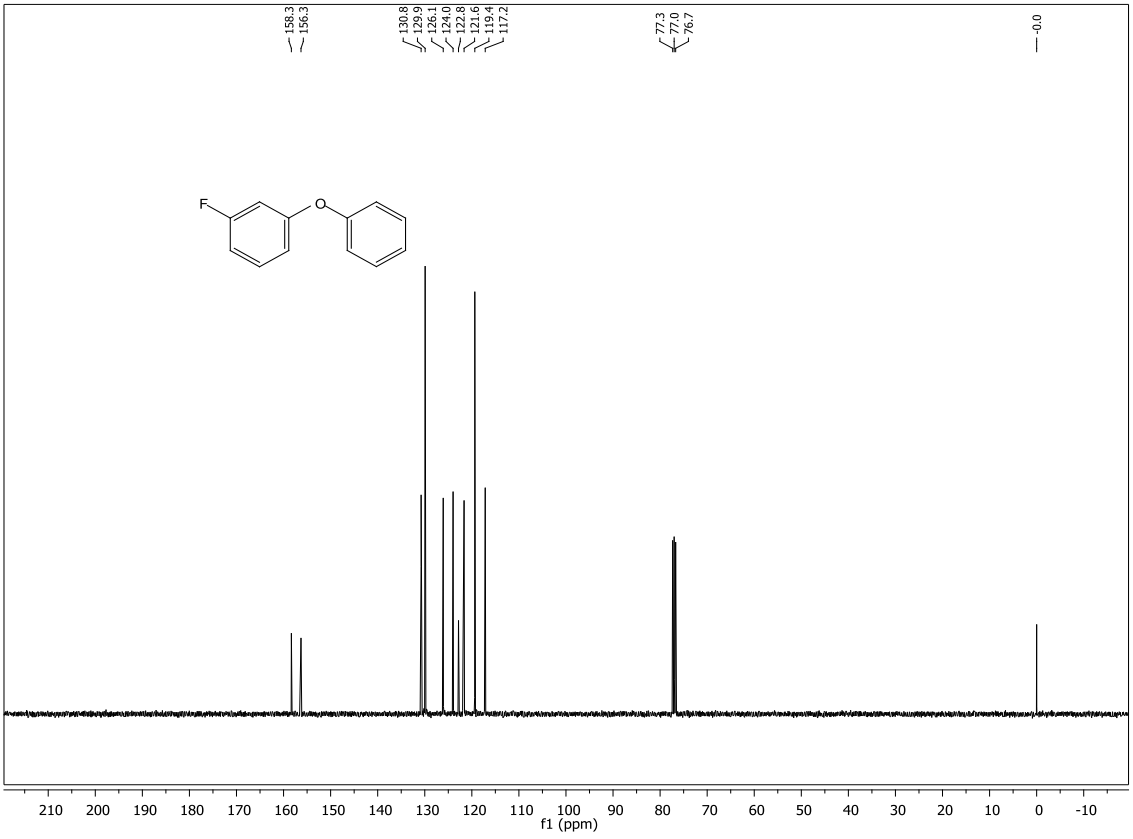


Figure 5.93: ^{19}F NMR of 1.41 at 377 MHz in CDl_3 at 298K

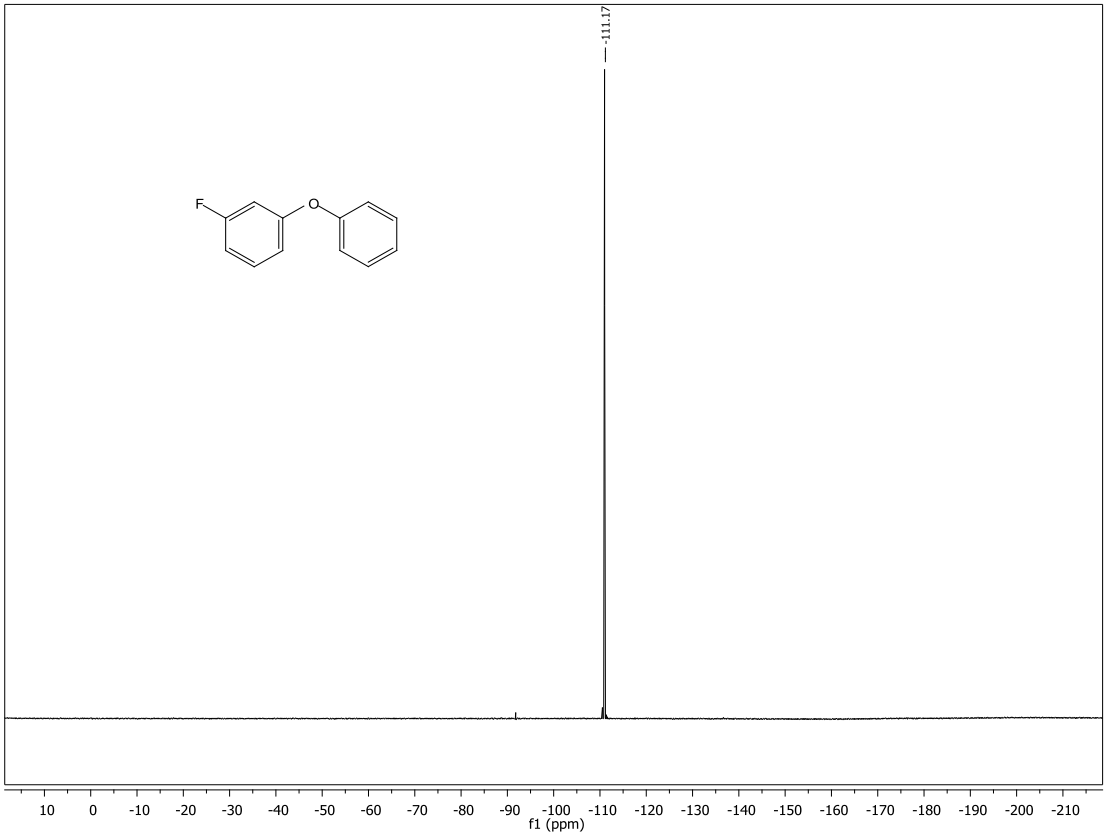


Figure 5.94: ^{1}H NMR of 1.42 at 400 MHz in CDl_3 at 298K

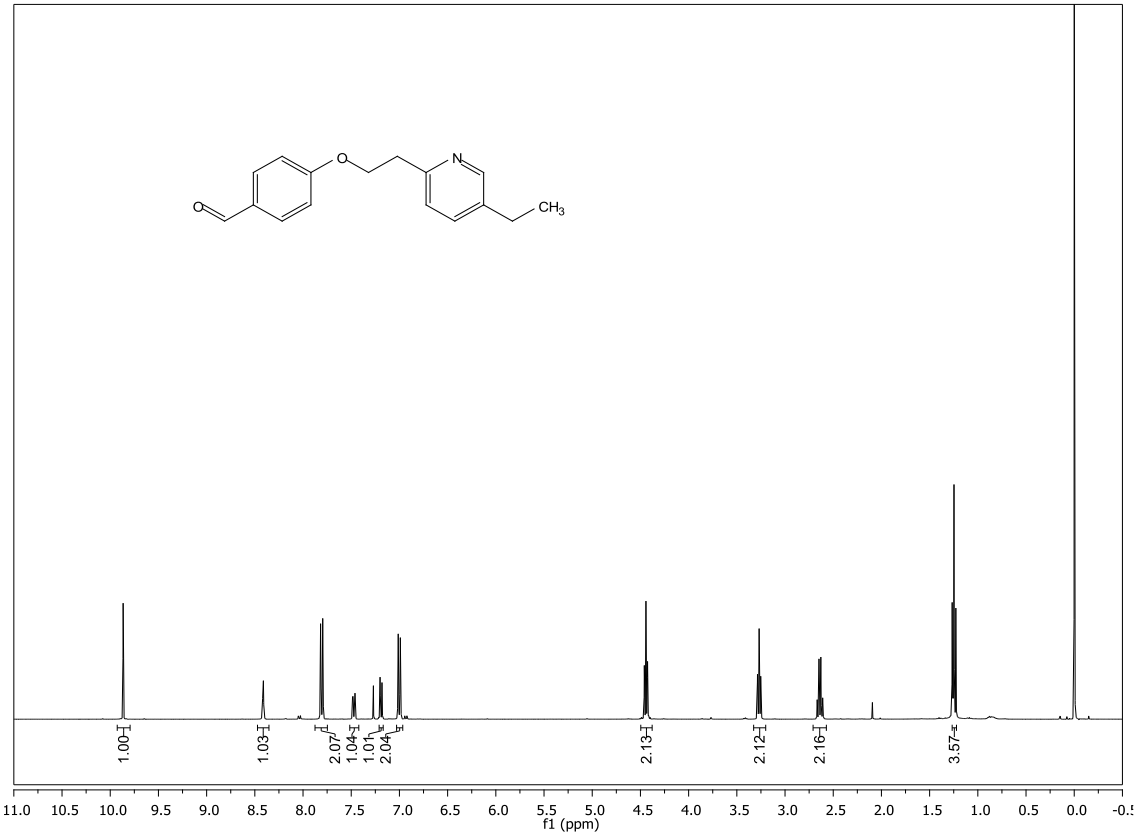


Figure 5.95: ^{13}C NMR of 1.42 at 100 MHz in CDl_3 at 298K

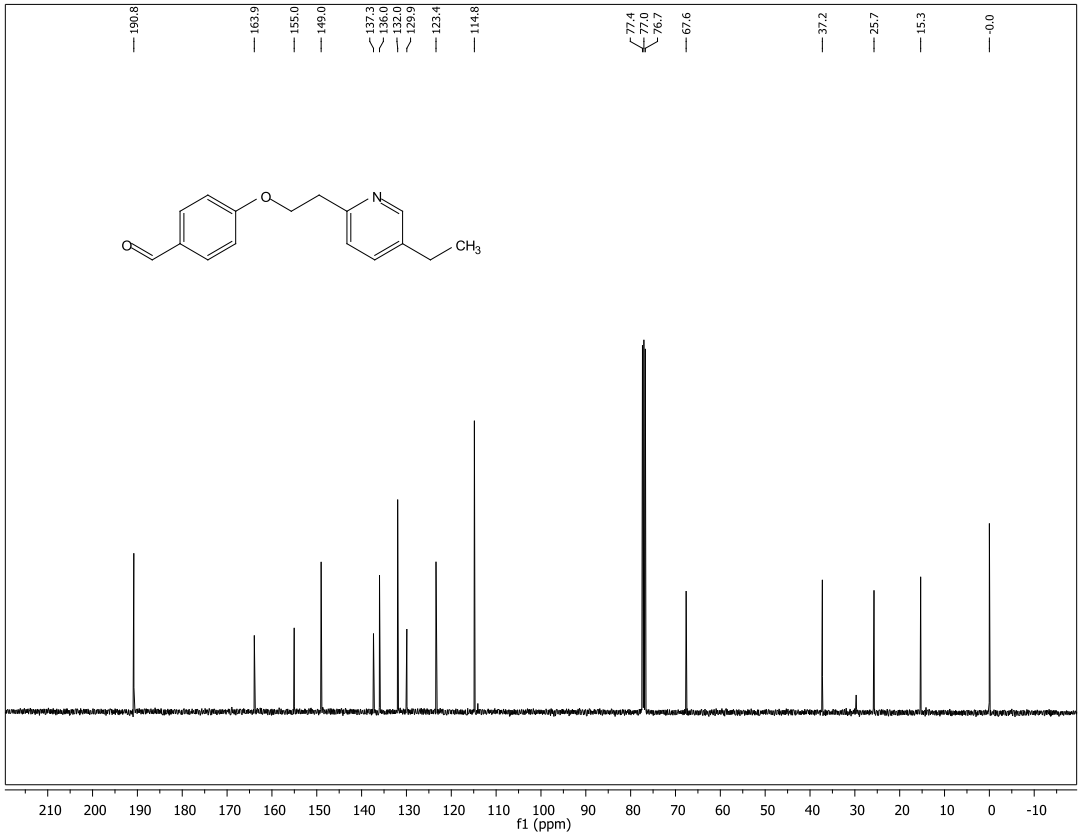


Figure 5.96: ^{1}H NMR of 1.43-anisole at 400 MHz in DMSO-d_6 at 298K

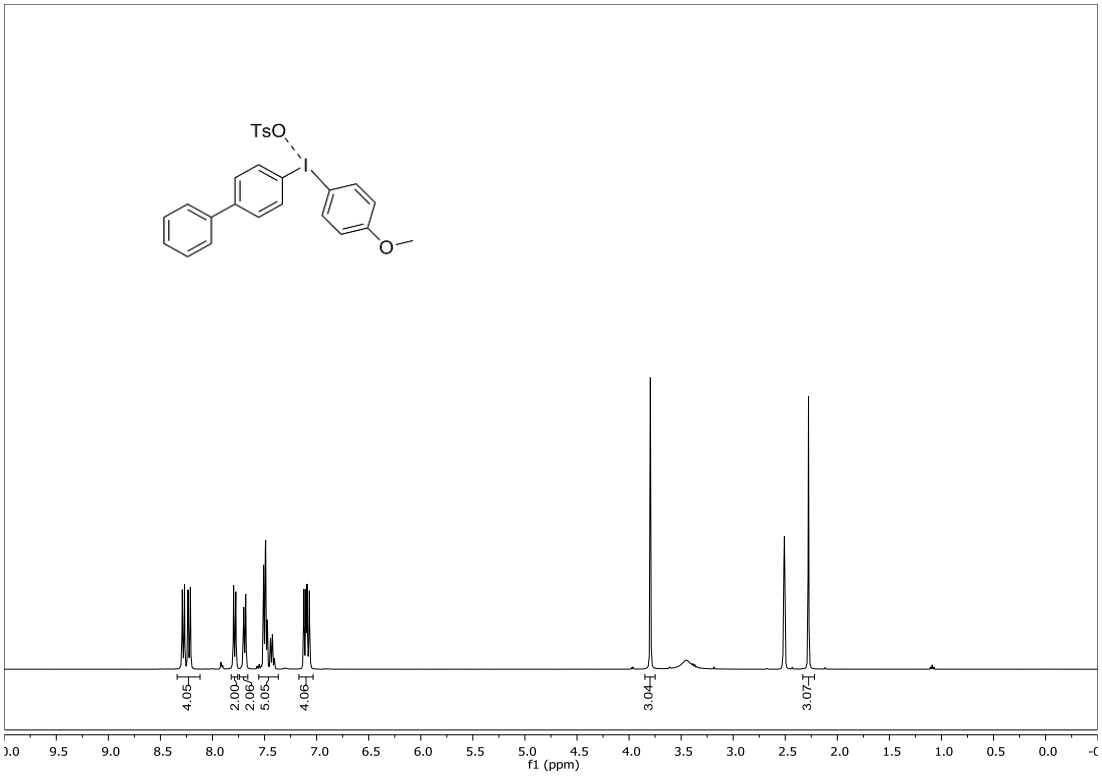


Figure 5.97: ^{13}C NMR of 1.43-anisole at 100 MHz in DMSO-d_6 at 298K

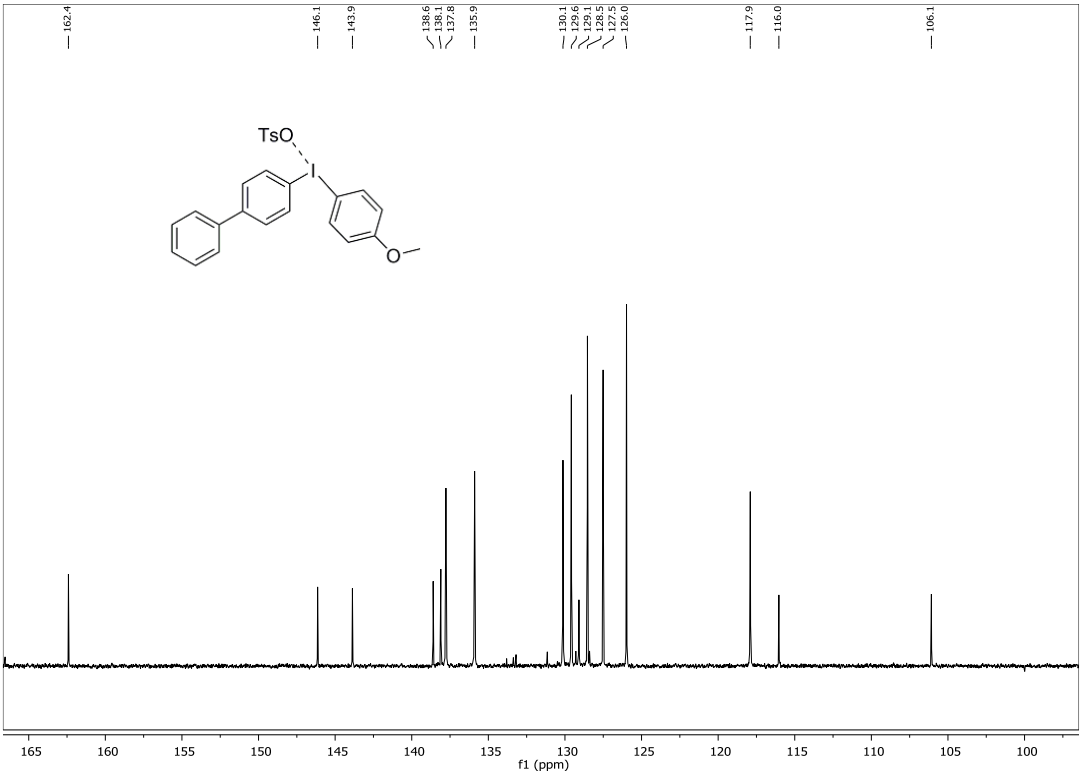


Figure 5.98: ^{1}H NMR of 1.43-thienyl at 400 MHz in DMSO-d_6 at 298K

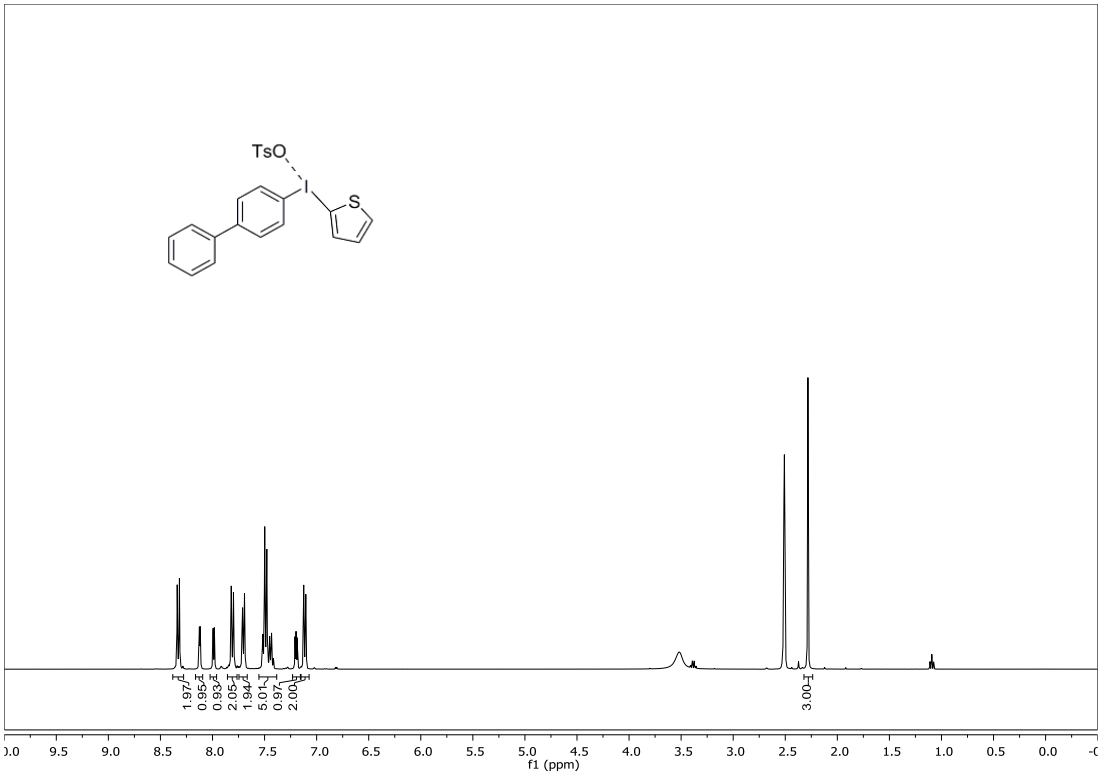


Figure 5.99: ^{13}C NMR of 1.43-thienyl at 100 MHz in DMSO-d_6 at 298K

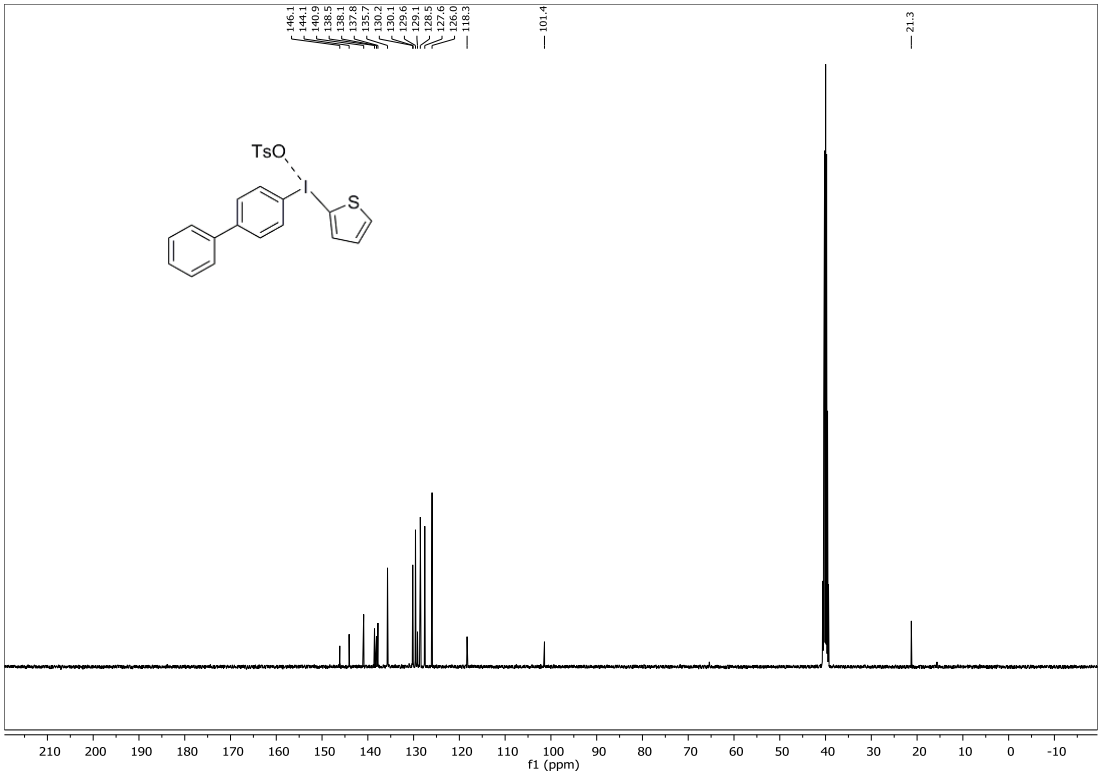


Figure 5.100: ^{1}H NMR of 1.44 at 400 MHz in DMSO-d_6 at 298K

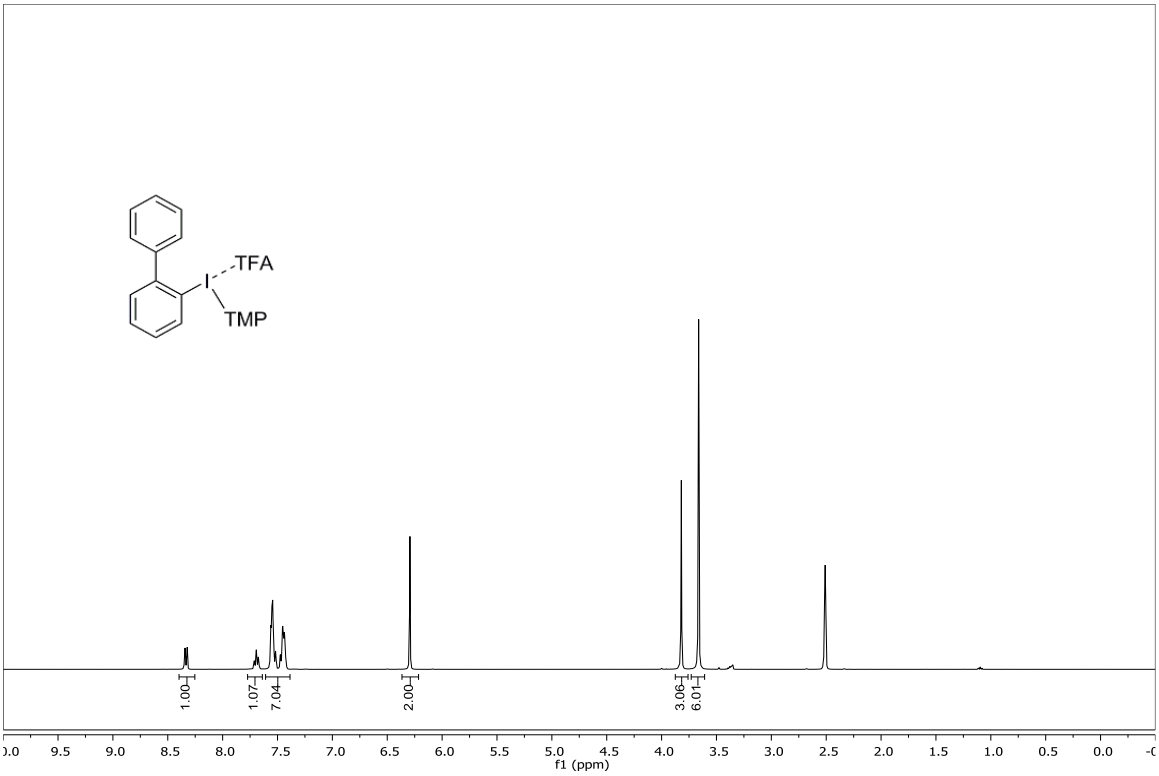


Figure 5.101: ^{13}C NMR of 1.44 at 100 MHz in DMSO-d_6 at 298K

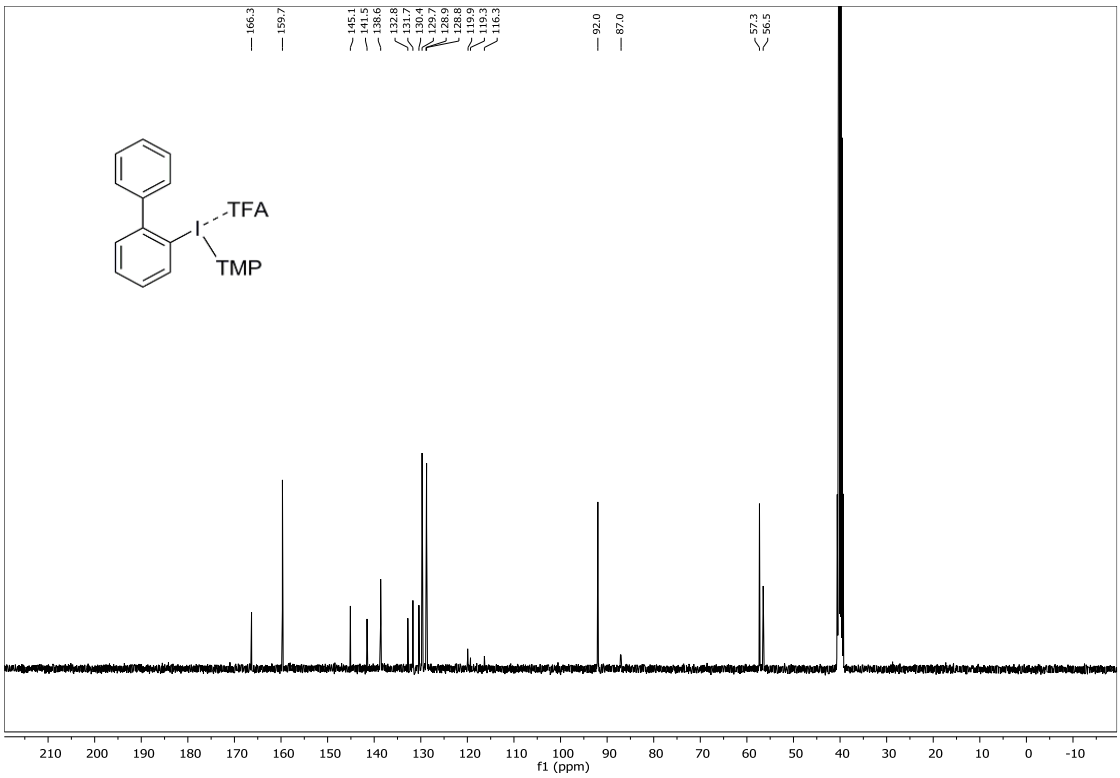


Figure 5.102: ^{19}F NMR of 1.44 at 377 MHz in DMSO-d_6 at 298K

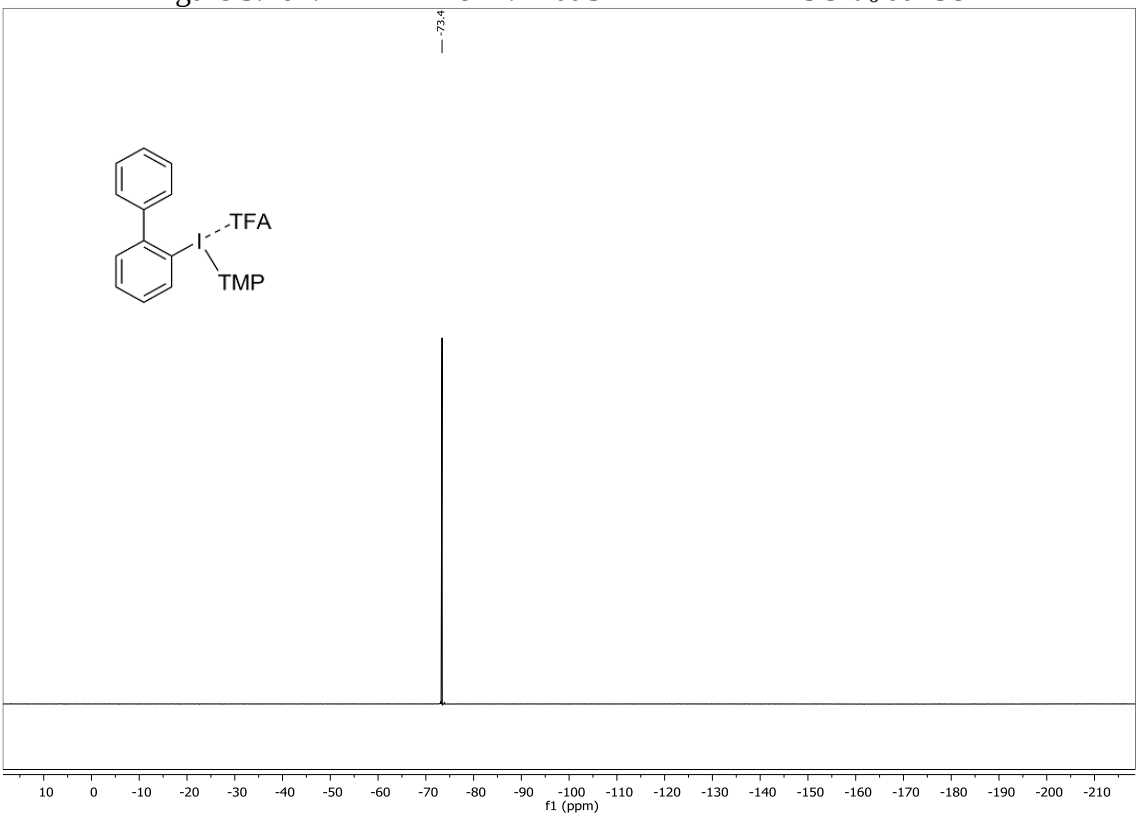


Figure 5.103: ^{1}H NMR of 1.45 at 400 MHz in DMSO-d_6 at 298K

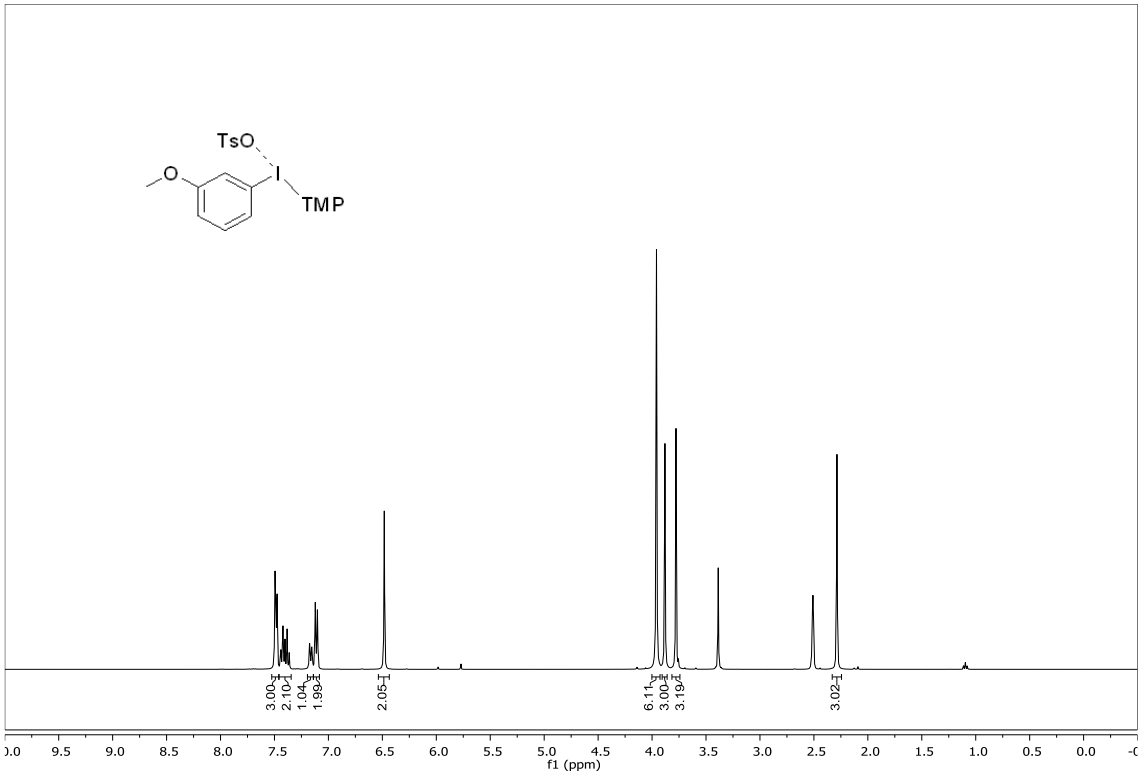


Figure 5.104: ^{13}C NMR of 1.45 at 100 MHz in DMSO-d_6 at 298K

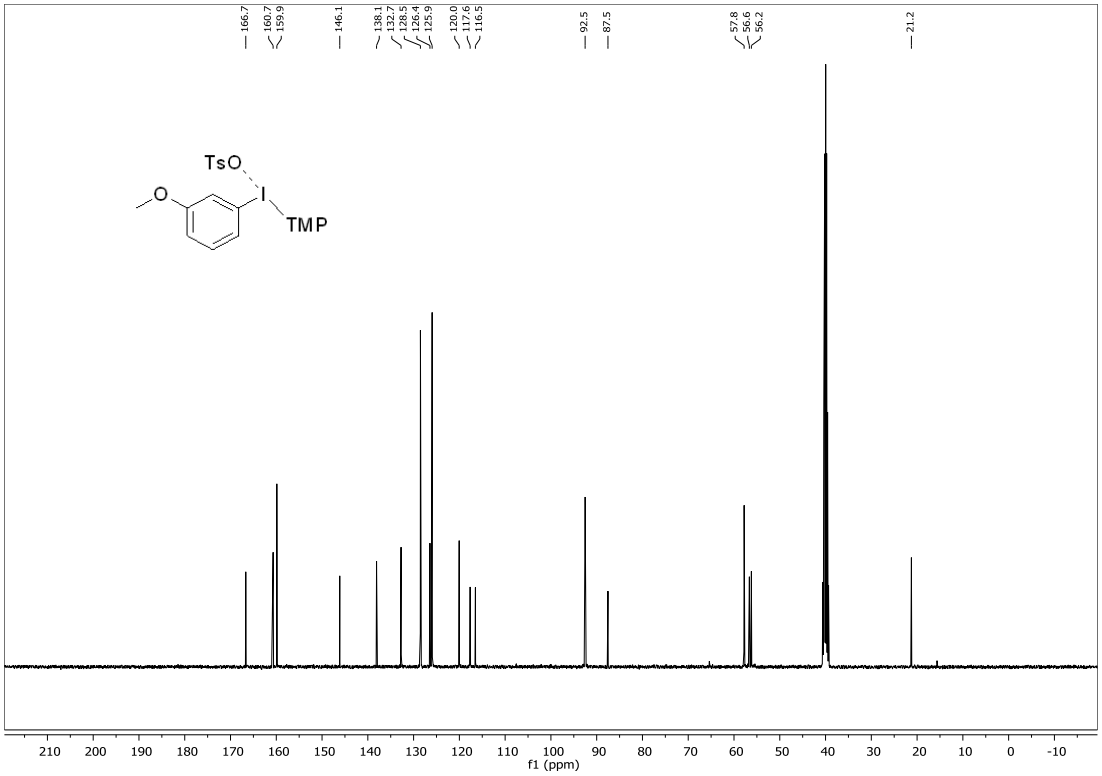


Figure 5.105: ^{1}H NMR of 1.46 at 400 MHz in DMSO-d_6 at 298K

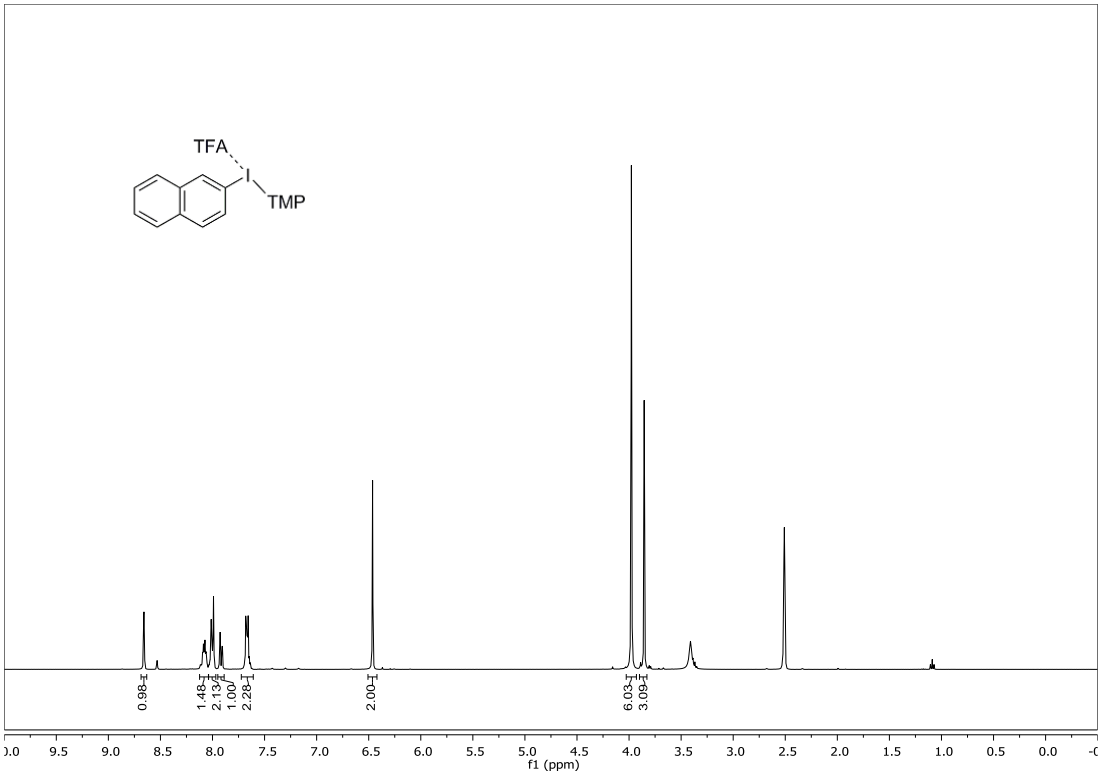


Figure 5.106: ^{13}C NMR of 1.46 at 100 MHz in DMSO-d_6 at 298K

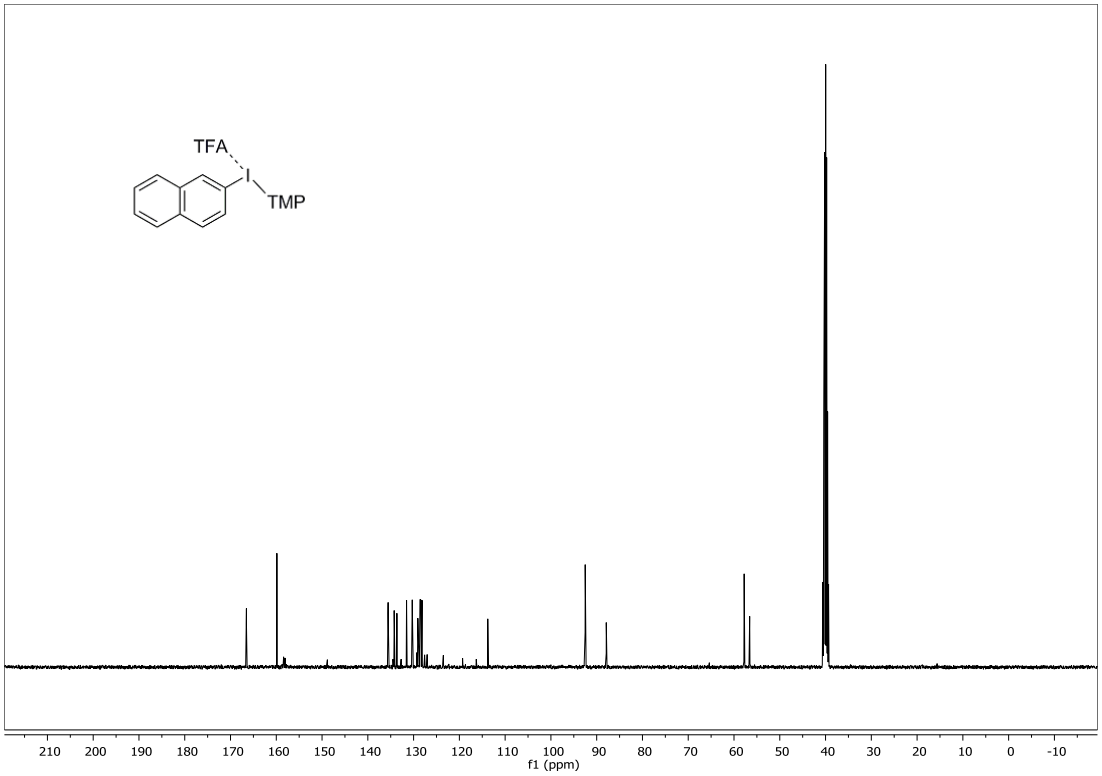


Figure 5.107: ^{1}H NMR of 1.47 at 400 MHz in DMSO-d_6 at 298K

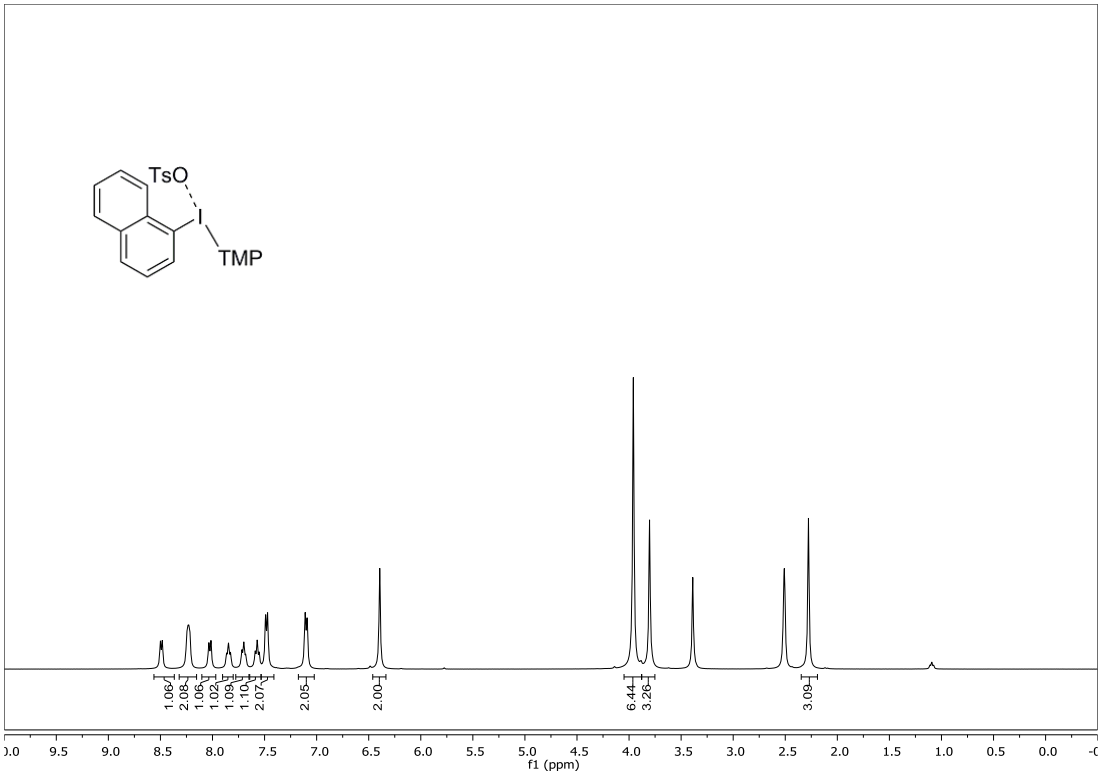


Figure 5.108: ^{13}C NMR of 1.47 at 100 MHz in DMSO-d_6 at 298K

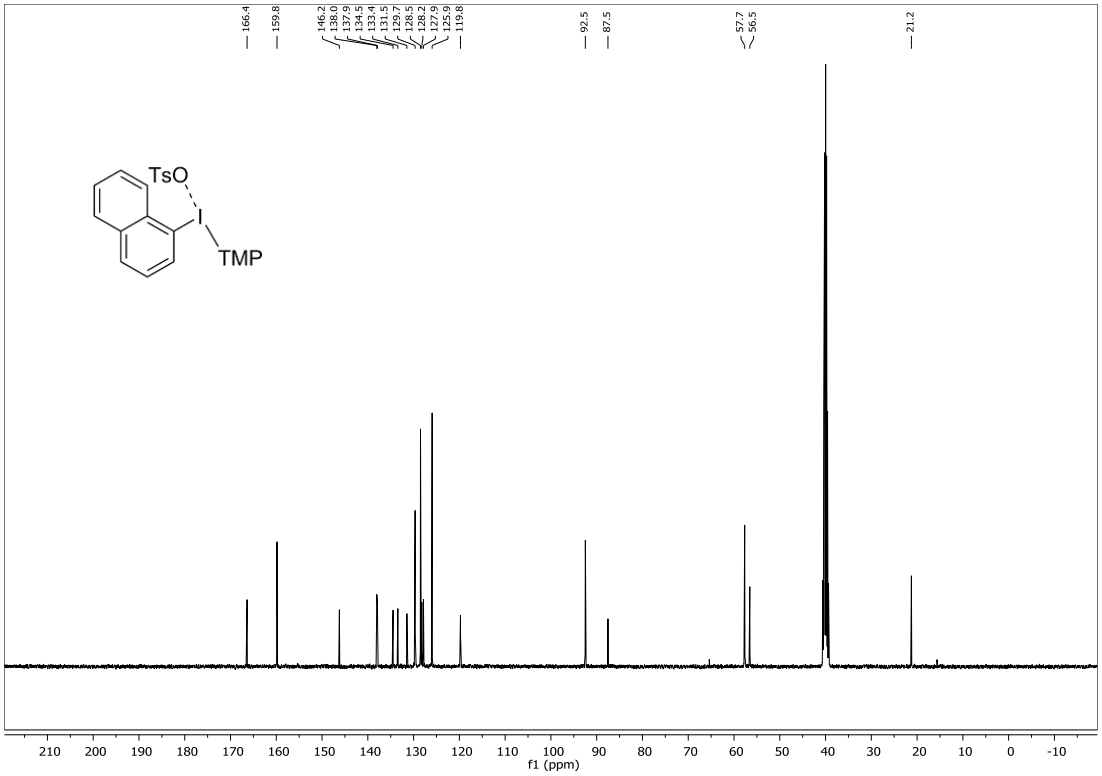


Figure 5.109: ^{1}H NMR of 1.48 at 400 MHz in DMSO-d_6 at 298K

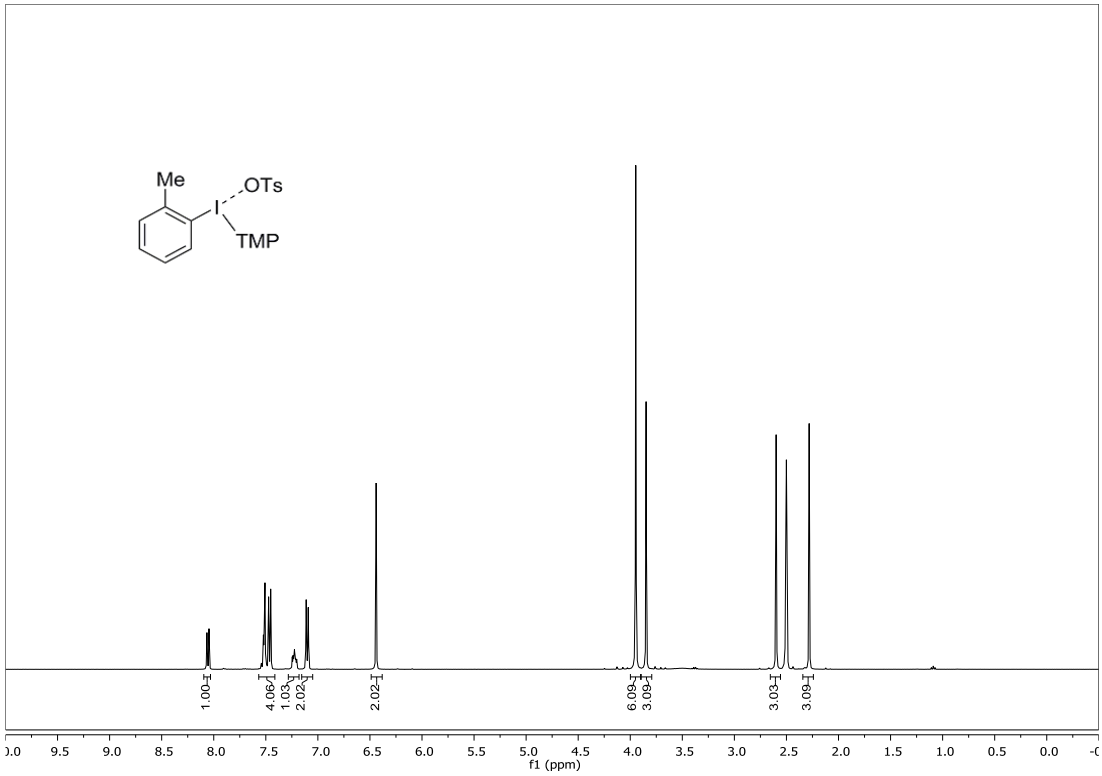


Figure 5.110: ^{13}C NMR of 1.48 at 100 MHz in DMSO-d_6 at 298K

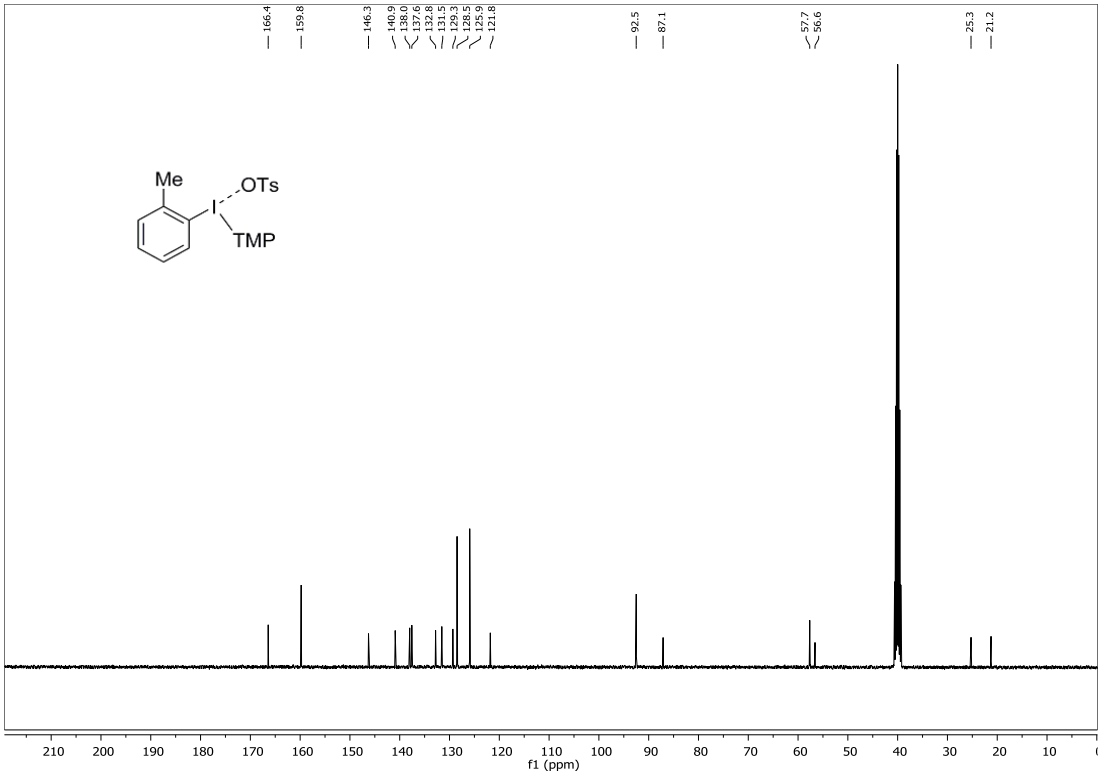


Figure 5.111: ^{1}H NMR of 1.49 at 400 MHz in DMSO-d_6 at 298K

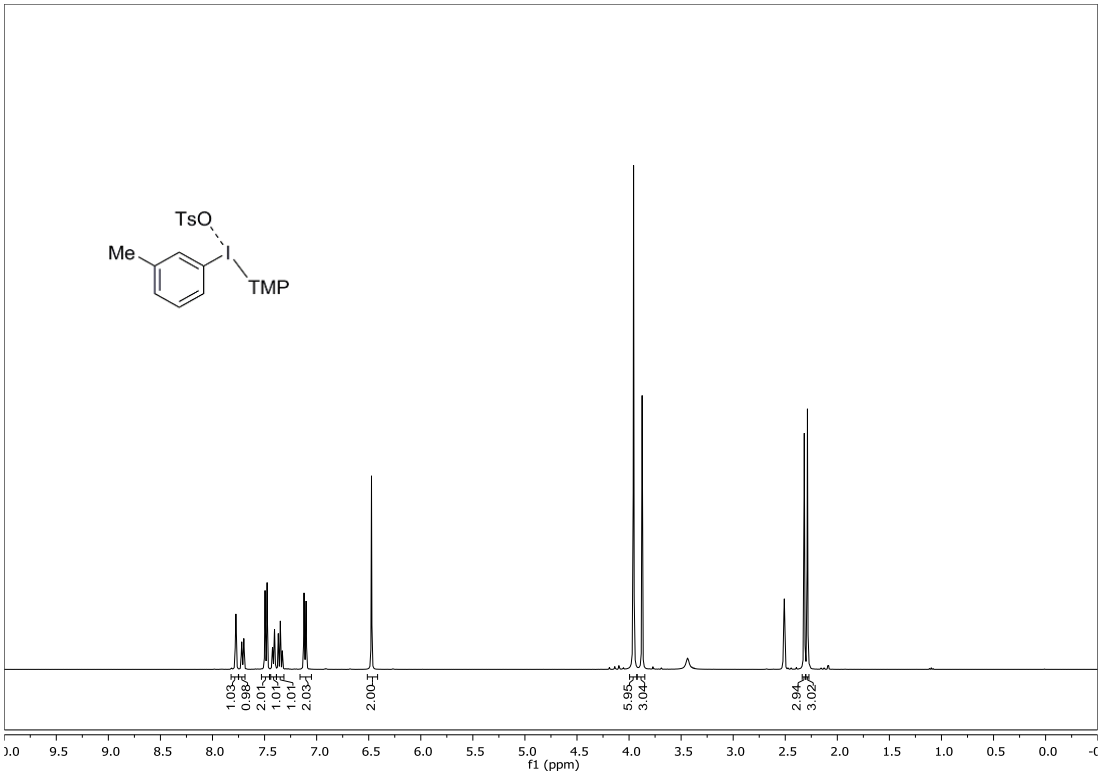


Figure 5.112: ^{13}C NMR of 1.49 at 100 MHz in DMSO-d_6 at 298K

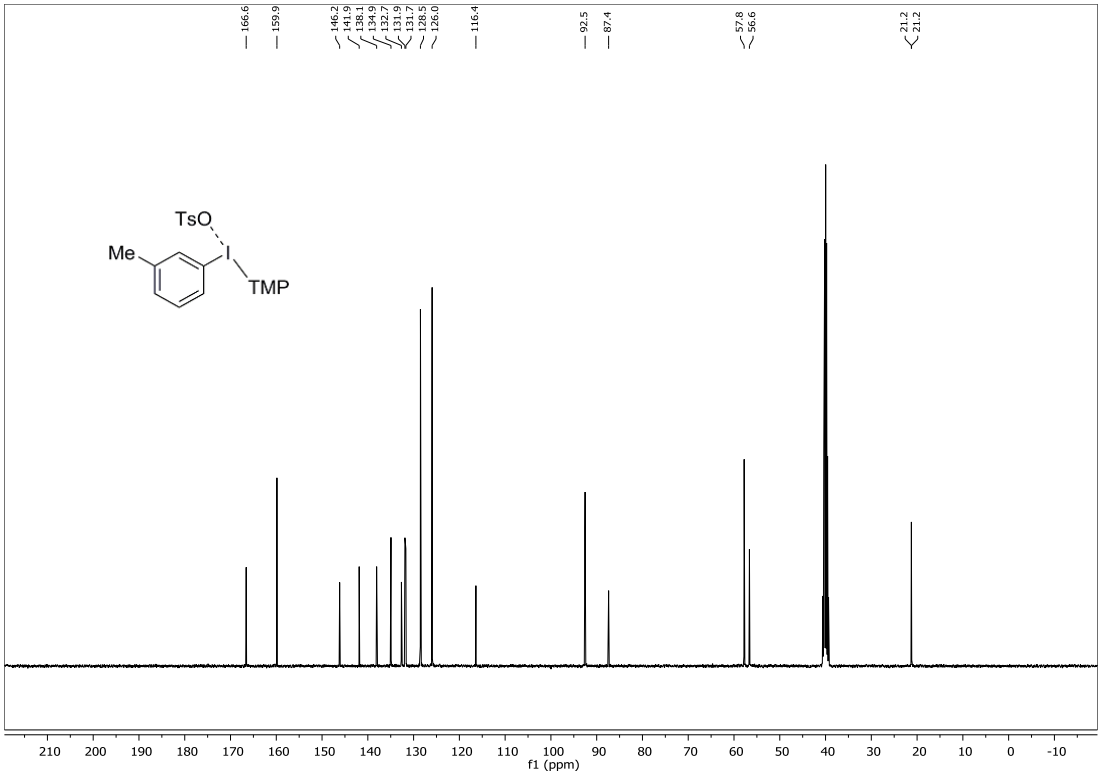


Figure 5.113: ^{1}H NMR of 1.50 at 400 MHz in DMSO-d_6 at 298K

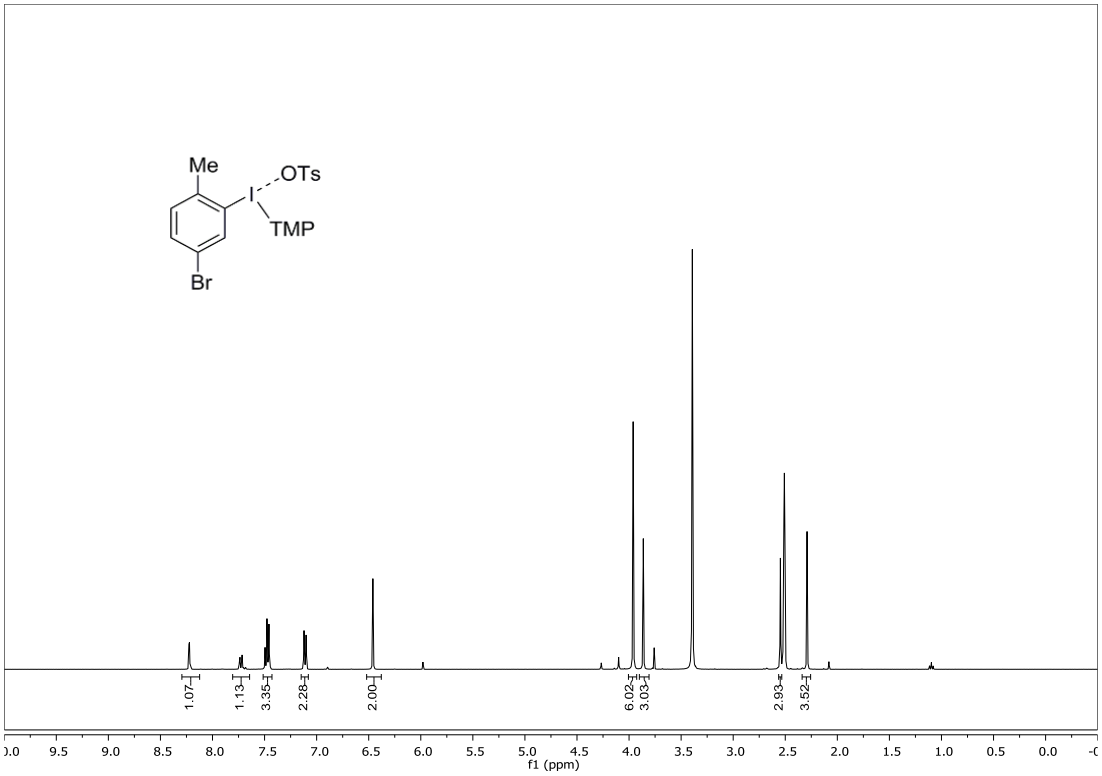


Figure 5.114: ^{13}C NMR of 1.50 at 100 MHz in DMSO-d_6 at 298K

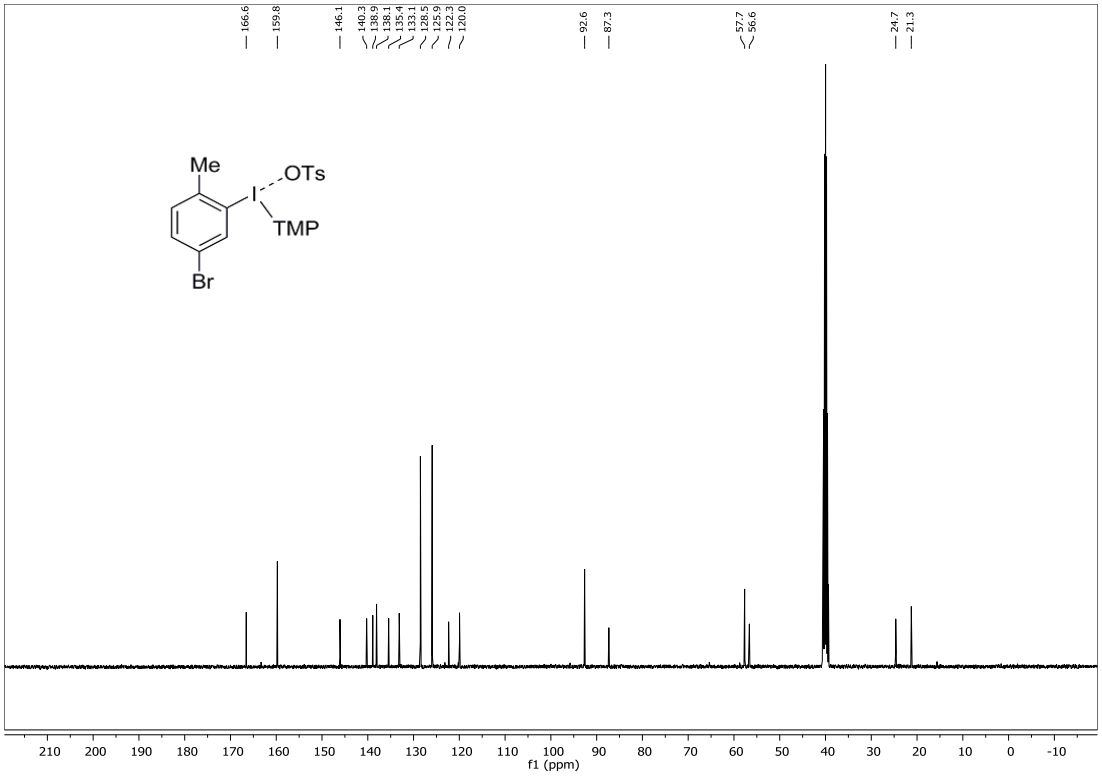


Figure 5.115: ^{1}H NMR of 1.51 at 400 MHz in DMSO-d_6 at 298K

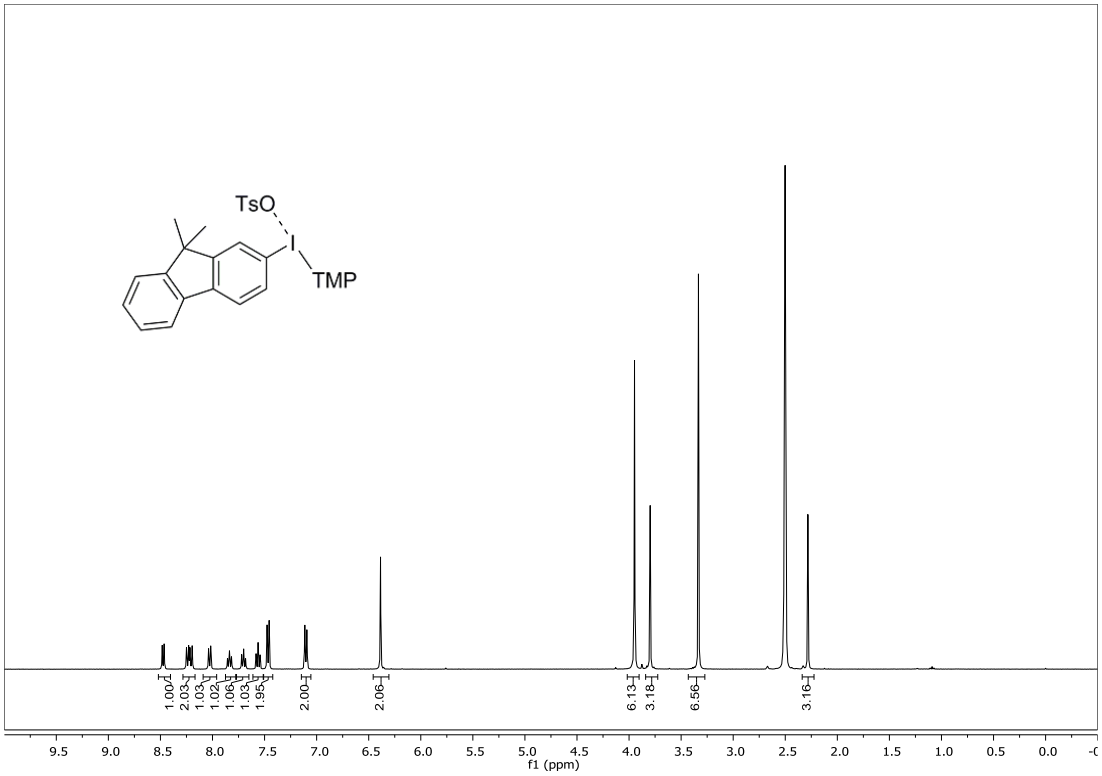


Figure 5.116: ^{13}C NMR of 1.51 at 100 MHz in DMSO-d_6 at 298K

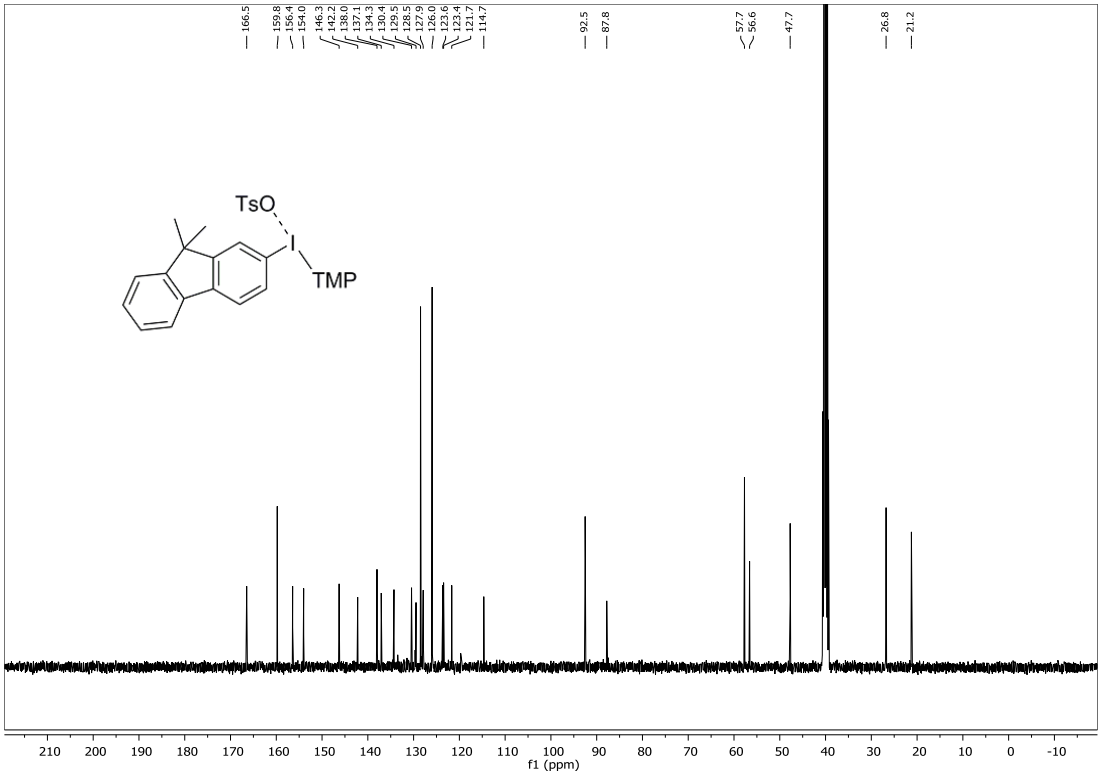


Figure 5.117: ^{1}H NMR of 1.52 at 400 MHz in DMSO-d_6 at 298K

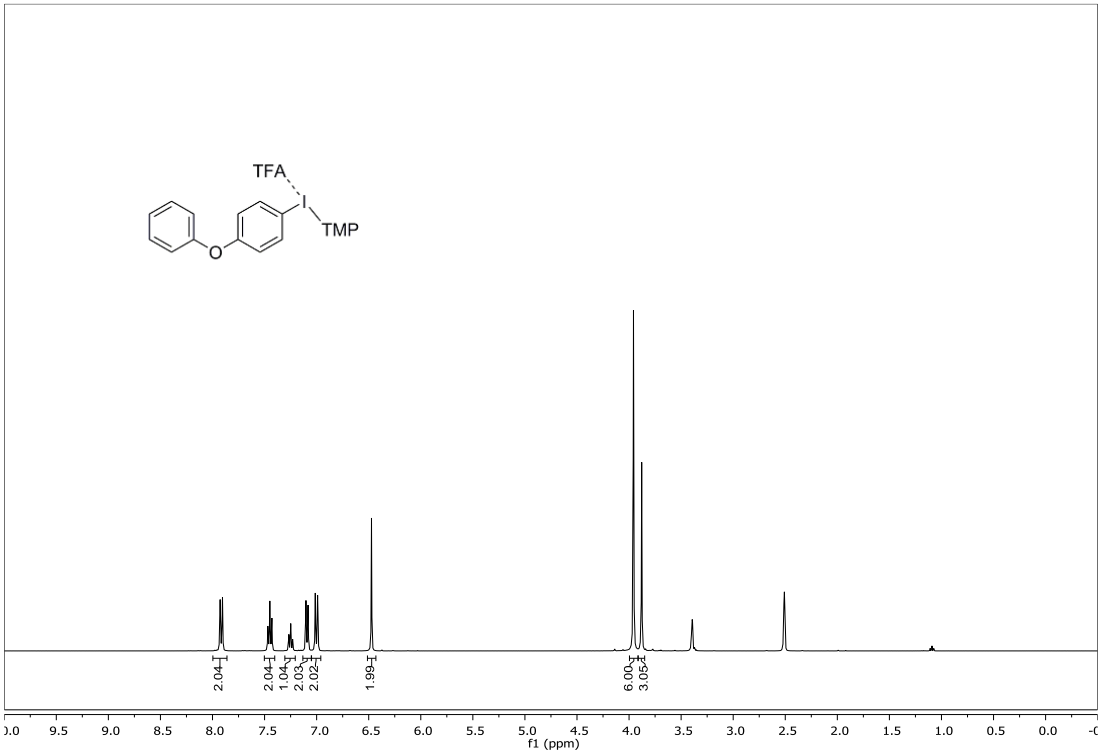


Figure 5.118: ^{13}C NMR of 1.52 at 100 MHz in DMSO-d_6 at 298K

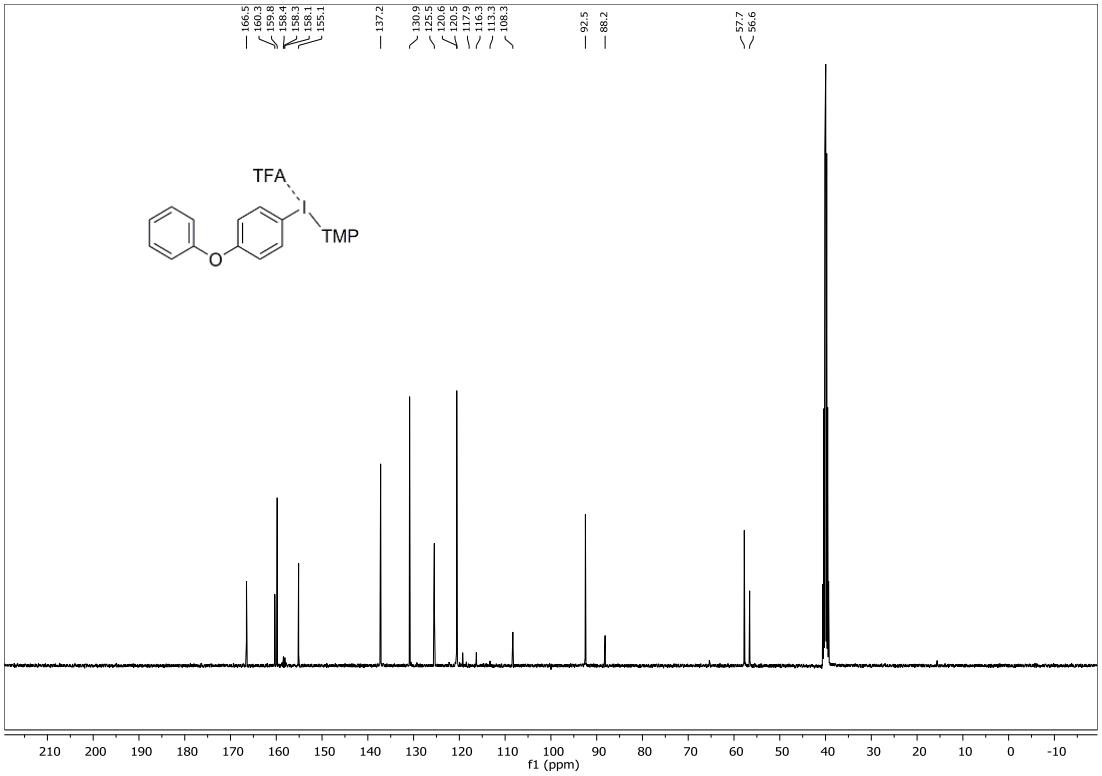


Figure 5.119: ^{19}F NMR of 1.52 at 377 MHz in DMSO-d_6 at 298K

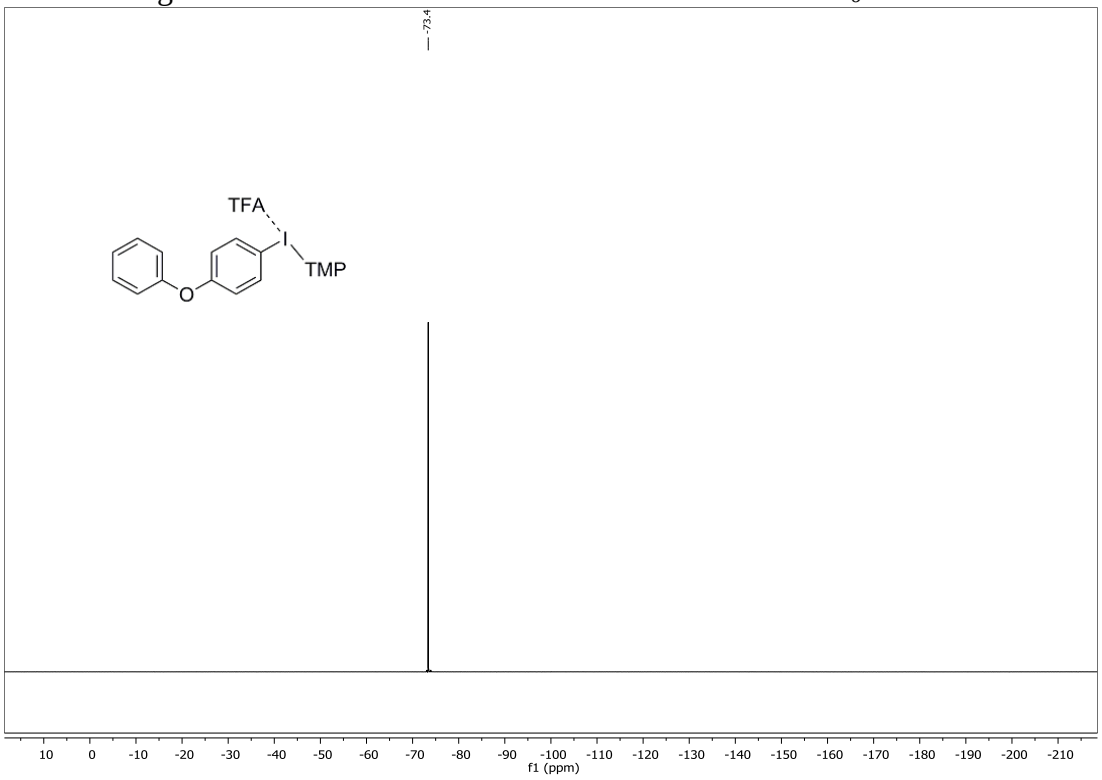


Figure 5.120: ^{1}H NMR of 1.53 at 400 MHz in $CDCl_3$ at 298K

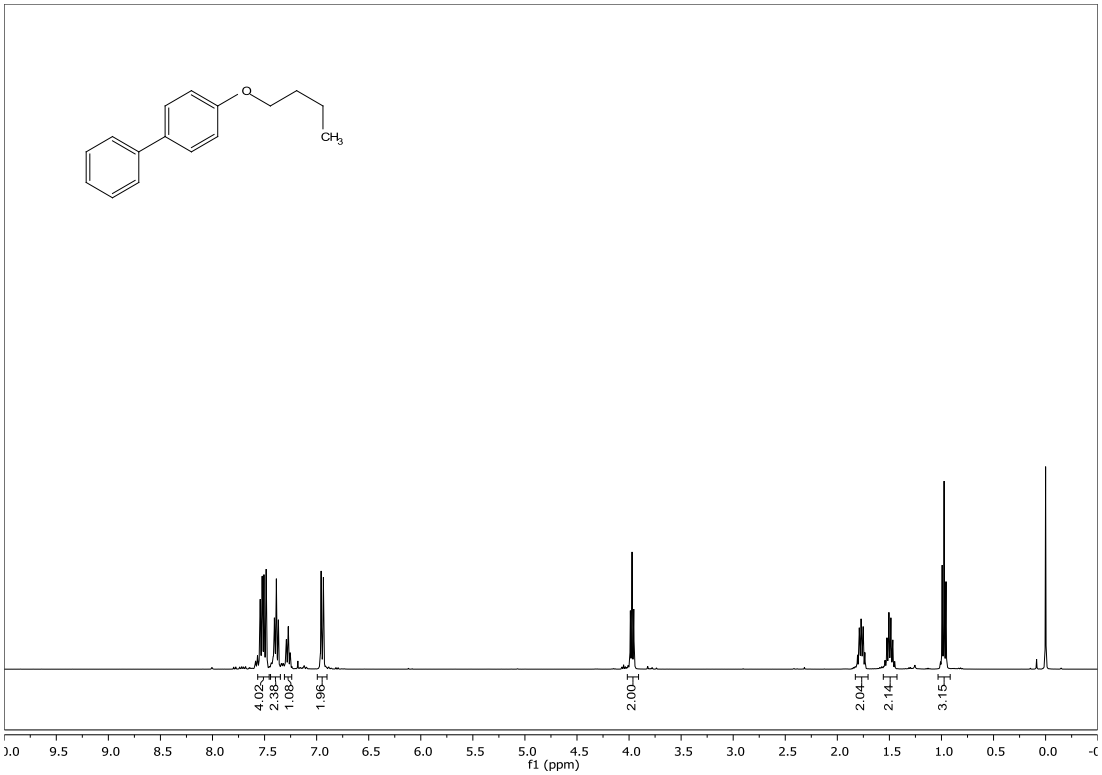


Figure 5.121: ^{13}C NMR of 1.53 at 100 MHz in DMSO-d_6 at 298K

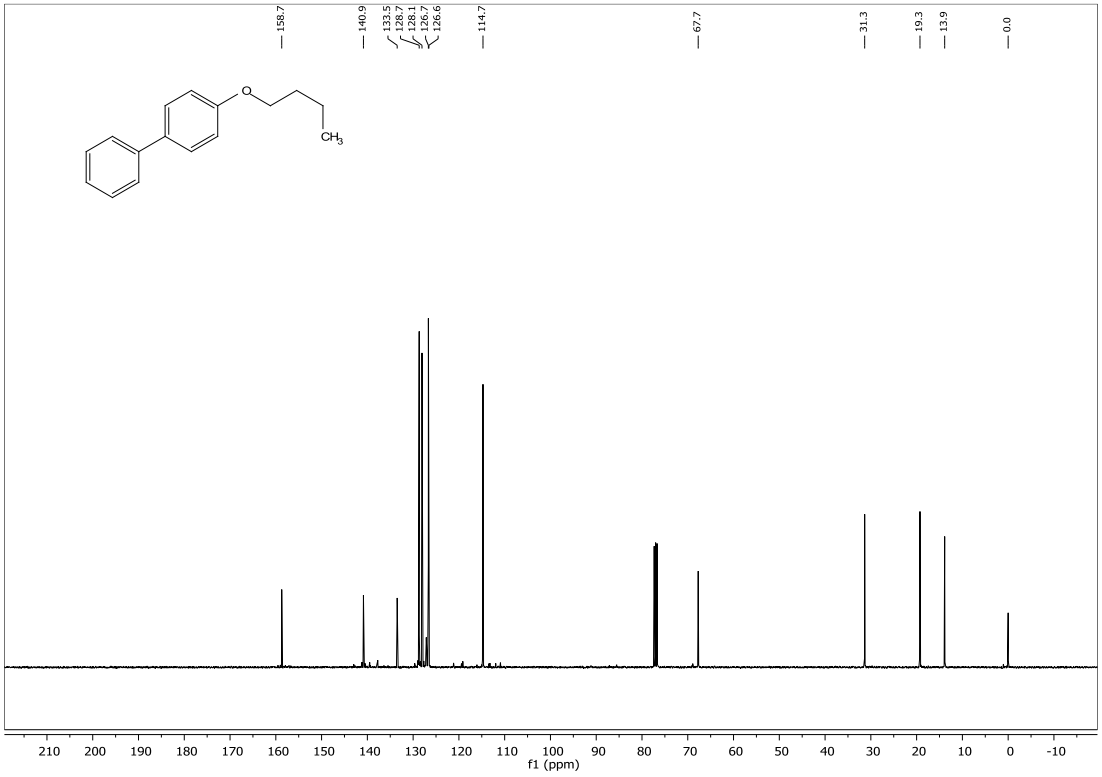


Figure 5.122: ^{1}H NMR of 1.54 at 400 MHz in $CDCl_3$ at 298K

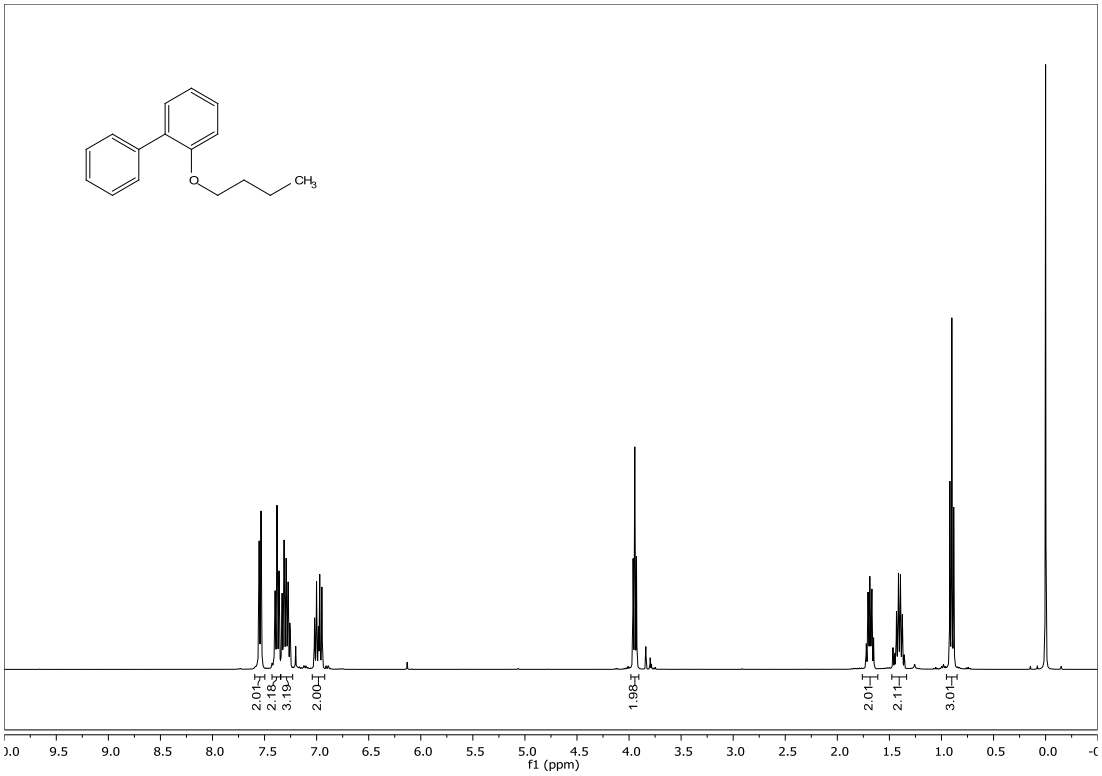


Figure 5.123: ^{13}C NMR of 1.54 at 100 MHz in DMSO-d_6 at 298K

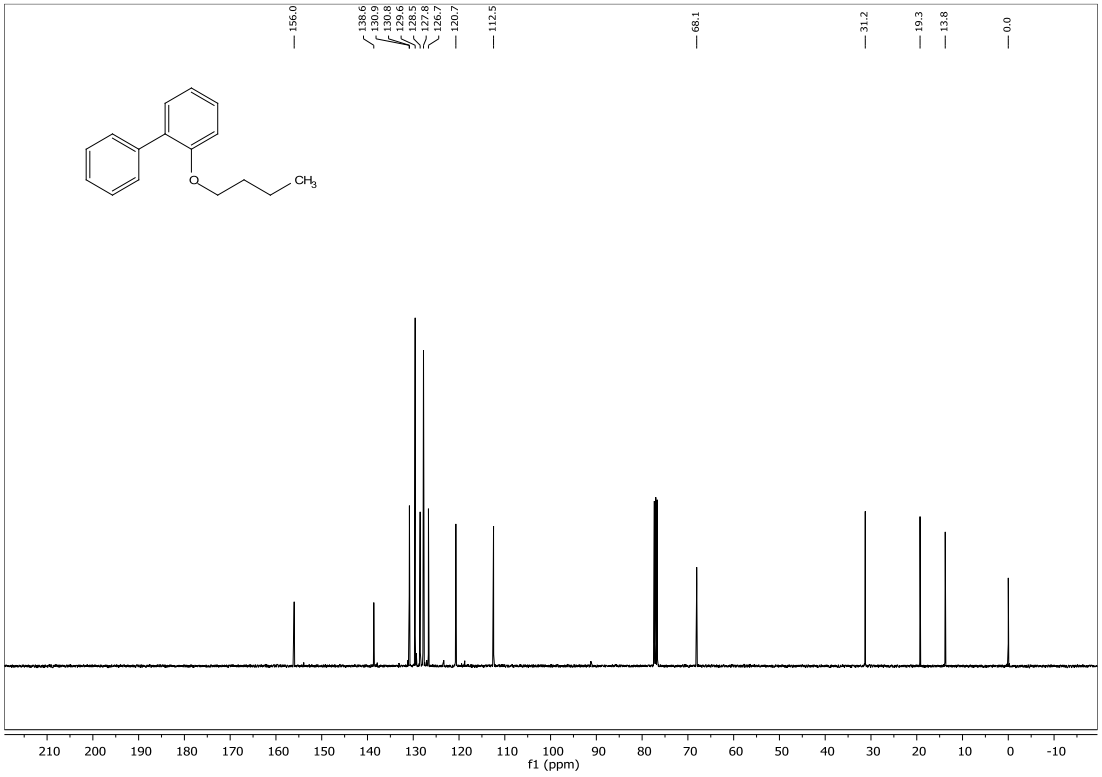


Figure 5.124: ^{1}H NMR of 1.55 at 400 MHz in $CDCl_3$ at 298K

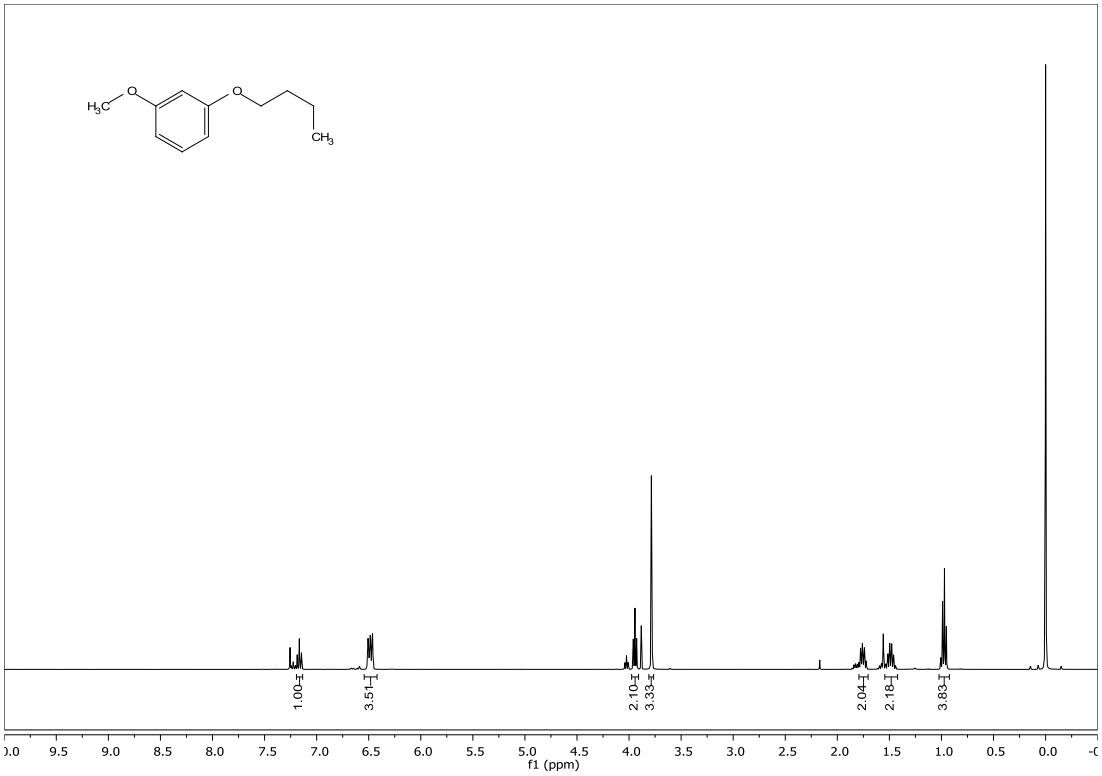


Figure 5.125: ^{13}C NMR of 1.55 at 100 MHz in DMSO-d_6 at 298K

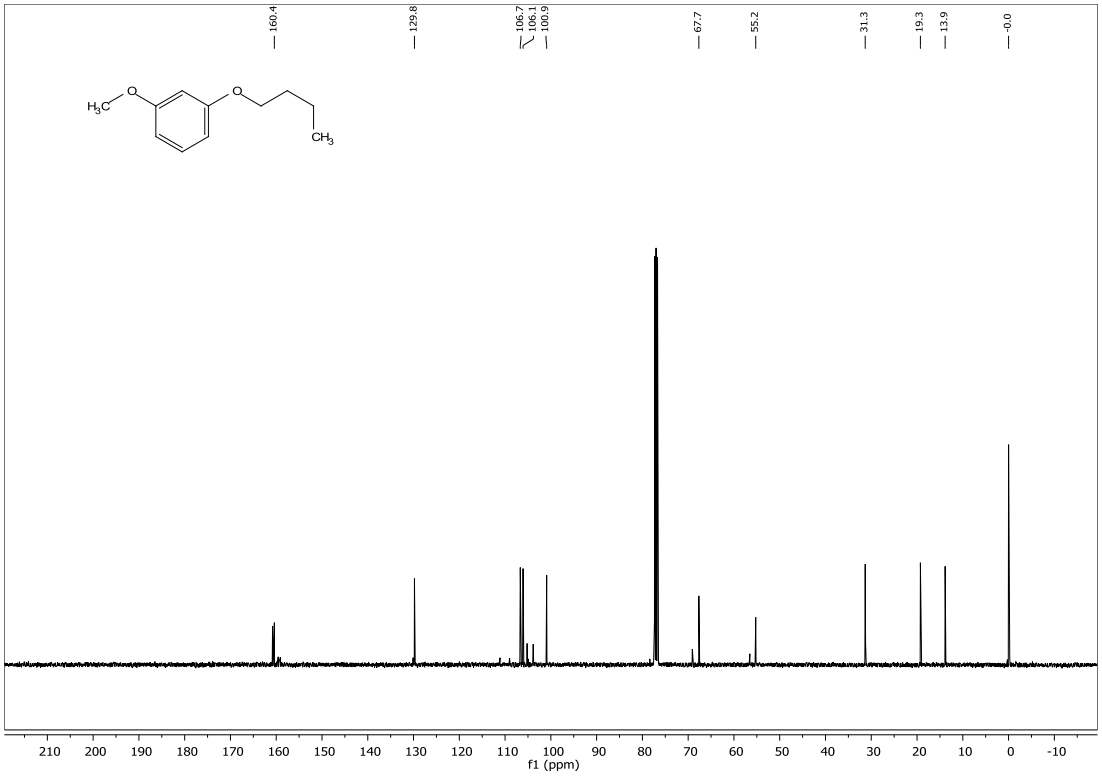


Figure 5.126: ^{1}H NMR of 1.56 at 400 MHz in $CDCl_3$ at 298K

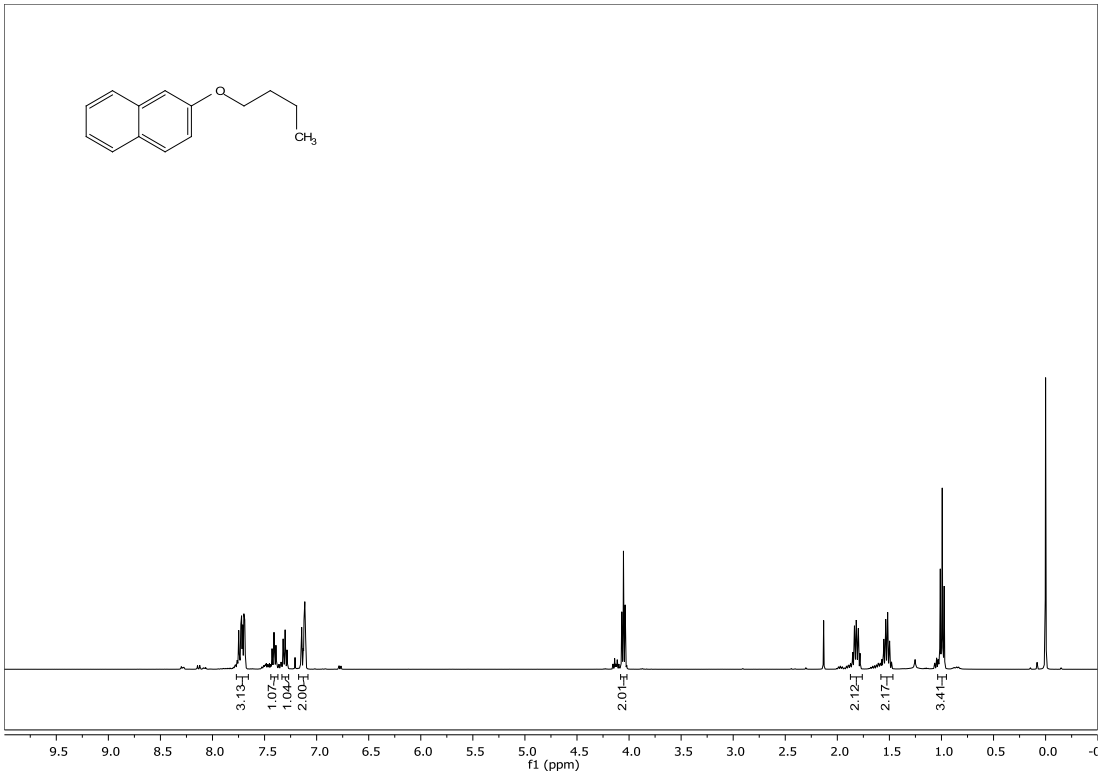


Figure 5.127: ^{13}C NMR of 1.56 at 100 MHz in DMSO-d_6 at 298K

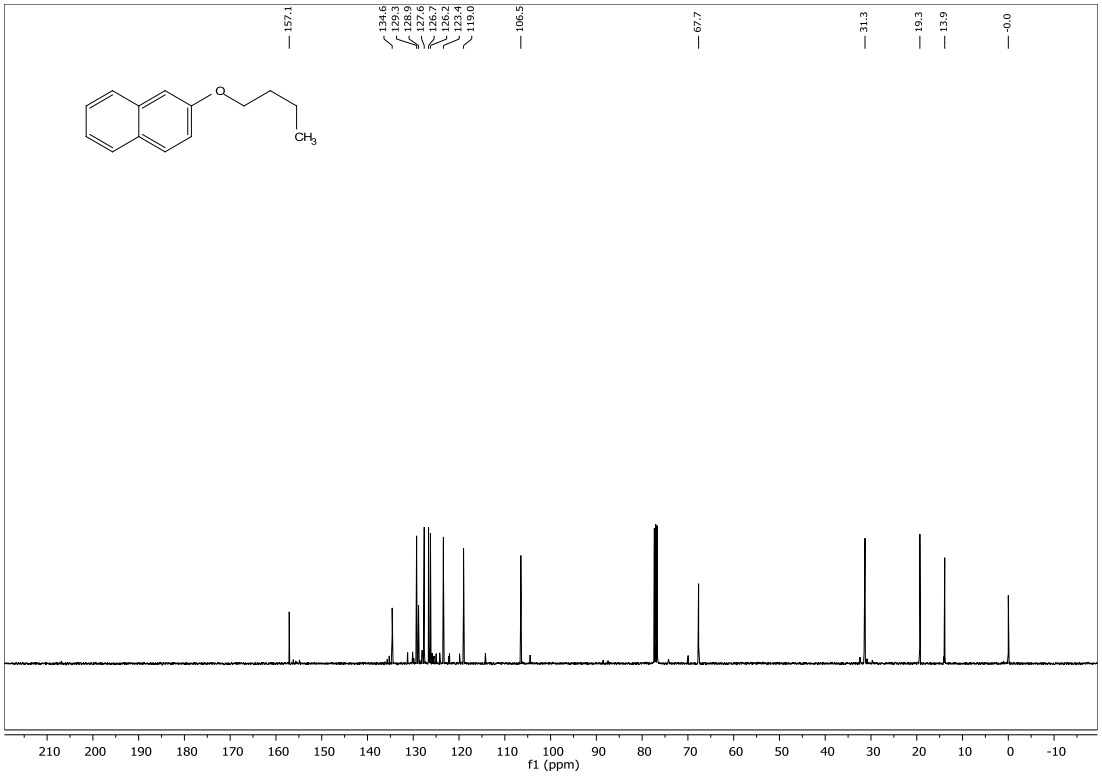


Figure 5.128: ^{1}H NMR of 1.57 at 400 MHz in $CDCl_3$ at 298K

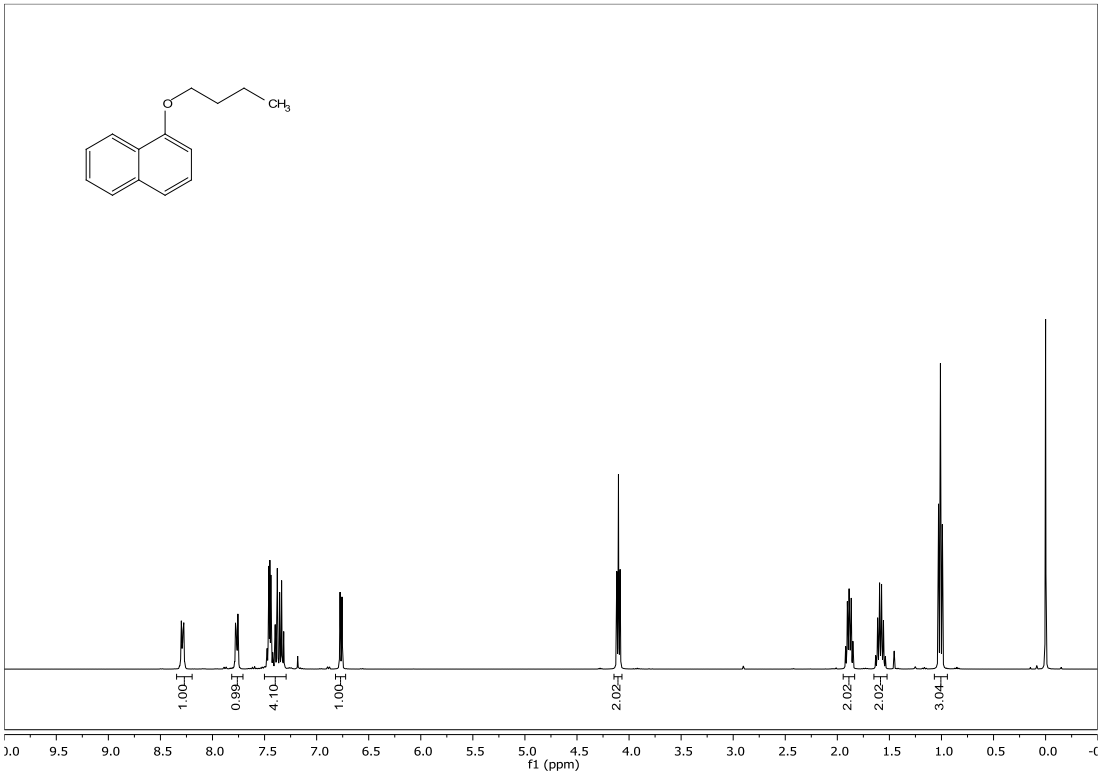


Figure 5.129: ^{13}C NMR of 1.57 at 100 MHz in DMSO-d_6 at 298K

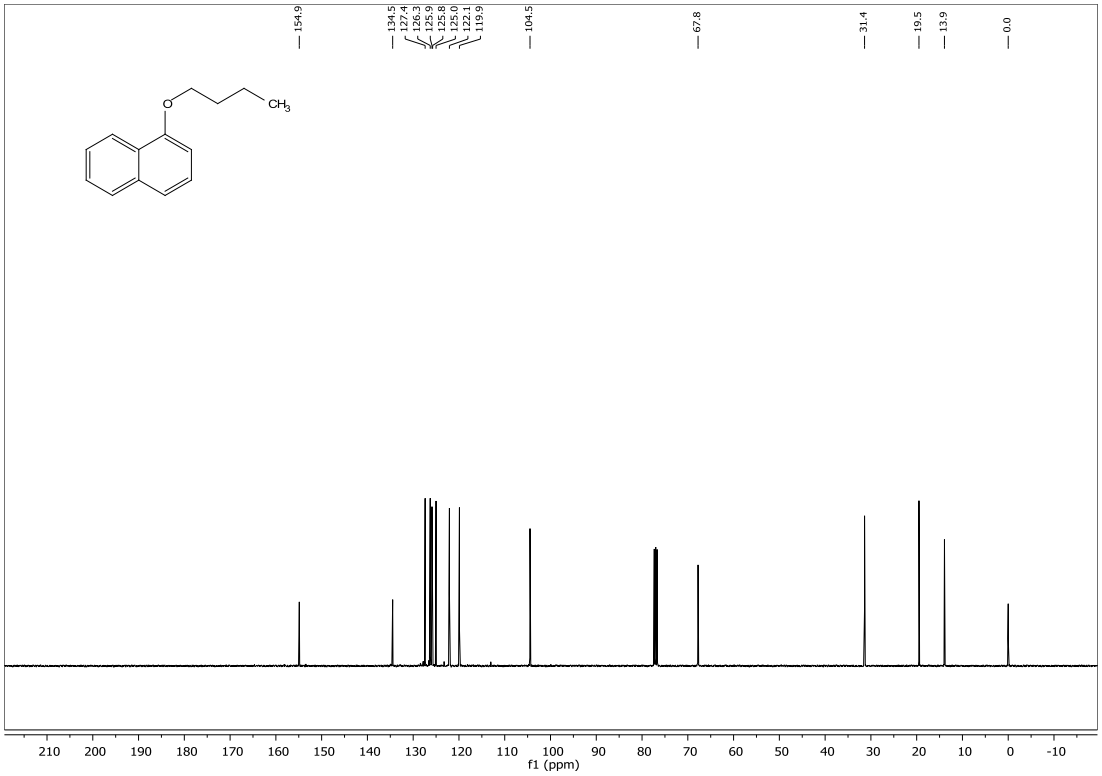


Figure 5.130: ^{1}H NMR of 1.58 at 400 MHz in $CDCl_3$ at 298K

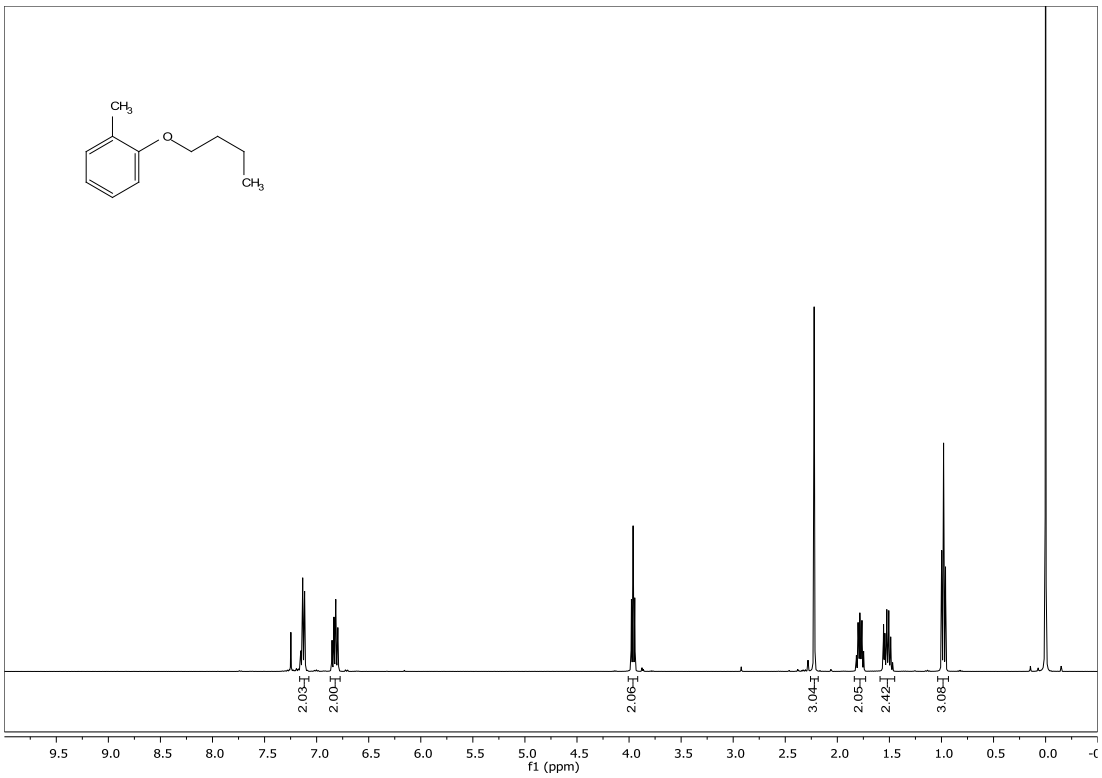


Figure 5.131: ^{13}C NMR of 1.58 at 100 MHz in DMSO-d_6 at 298K

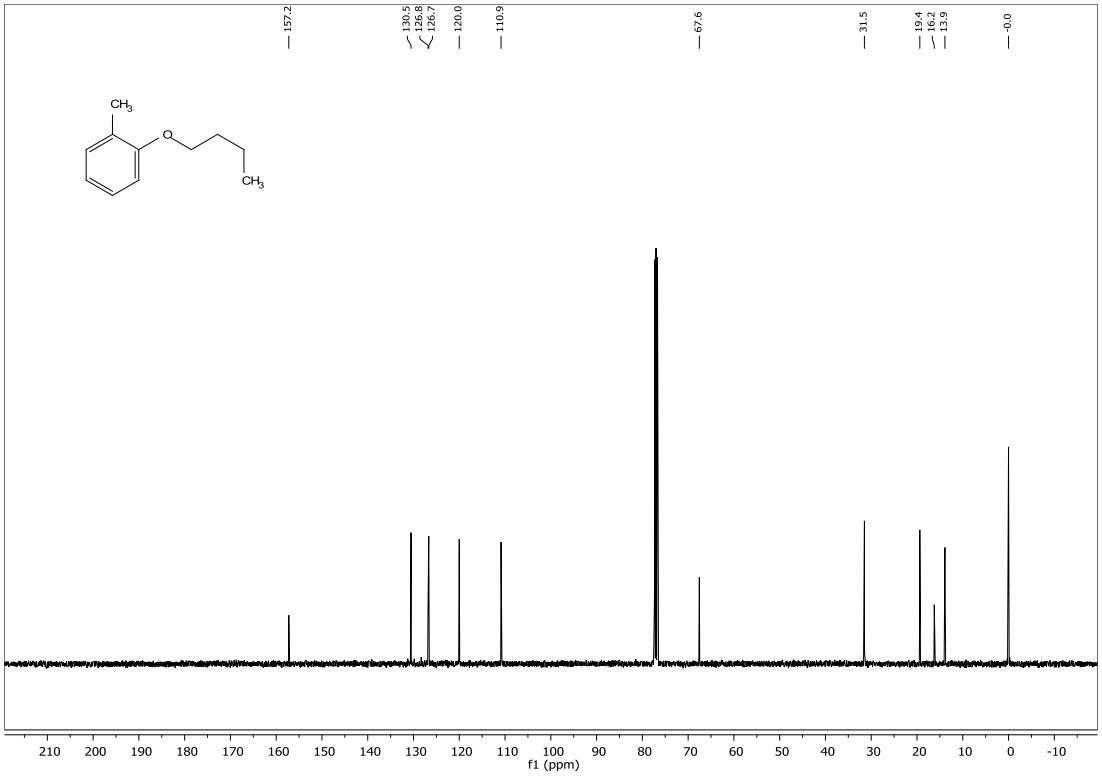


Figure 5.132: ^{1}H NMR of 1.59 at 400 MHz in $CDCl_3$ at 298K

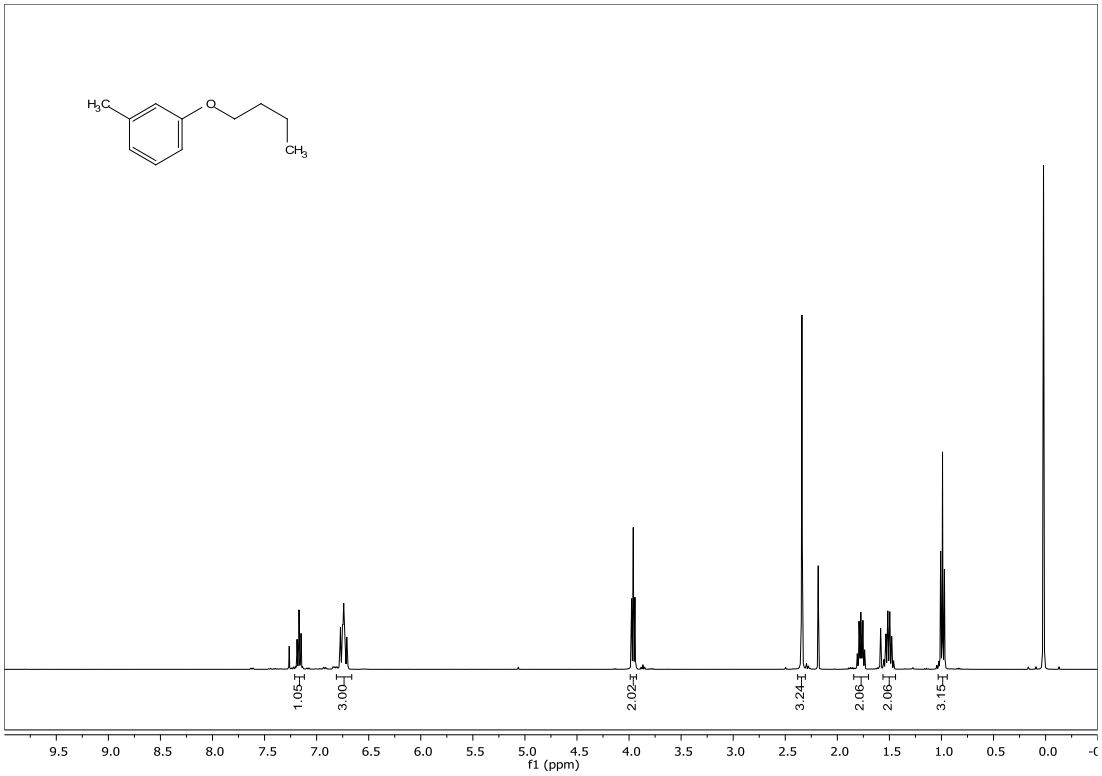


Figure 5.133: ^{13}C NMR of 1.59 at 100 MHz in DMSO-d_6 at 298K

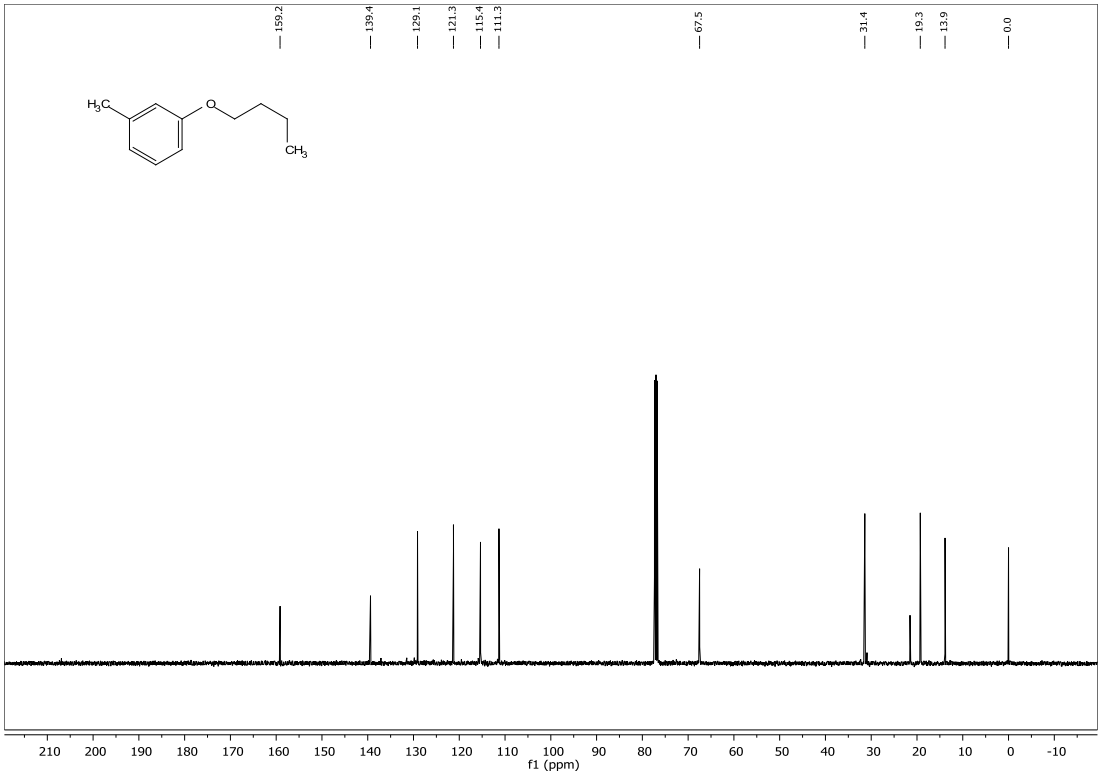


Figure 5.134: ^{1}H NMR of 1.61 at 400 MHz in $CDCl_3$ at 298K

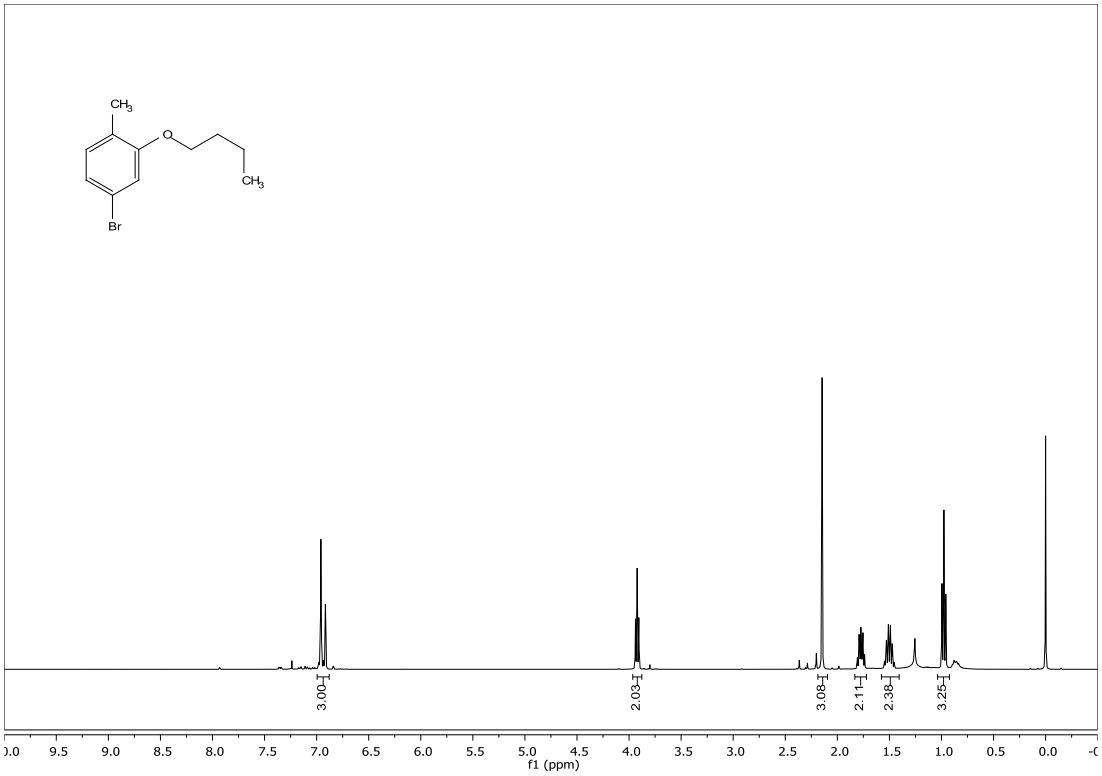


Figure 5.135: ^{13}C NMR of 1.61 at 100 MHz in DMSO-d_6 at 298K

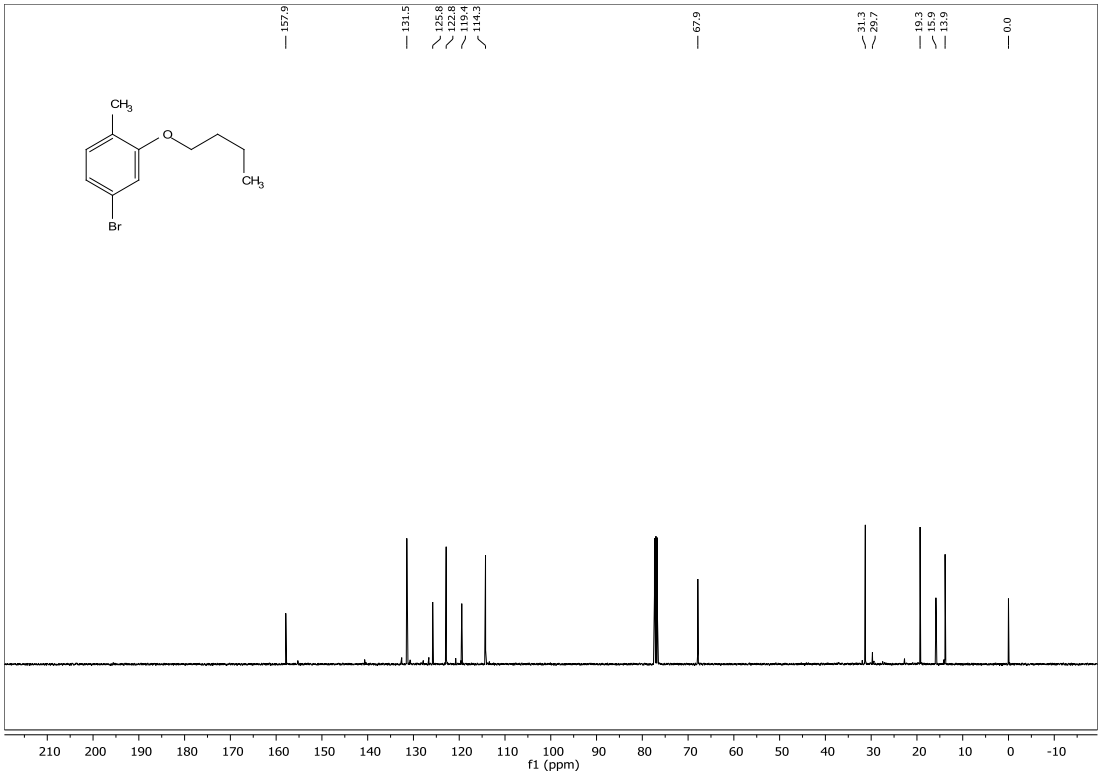


Figure 5.136: ^{1}H NMR of 1.62 at 400 MHz in $CDCl_3$ at 298K

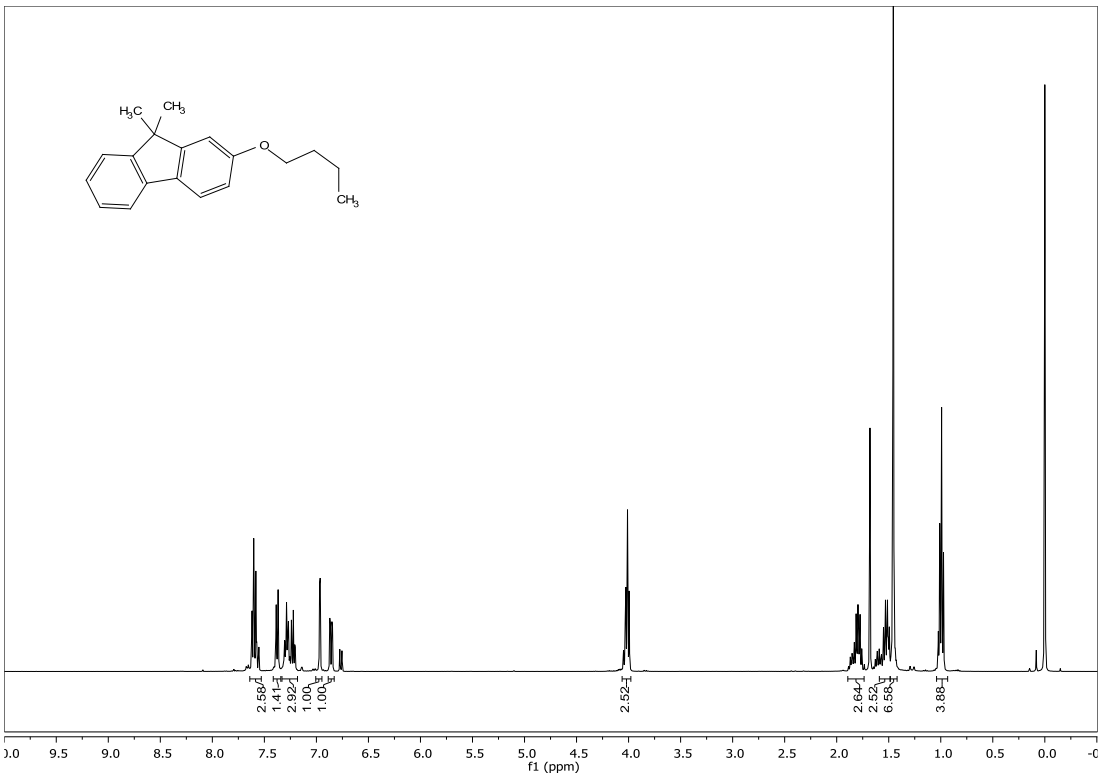


Figure 5.137: ^{13}C NMR of 1.62 at 100 MHz in DMSO-d_6 at 298K

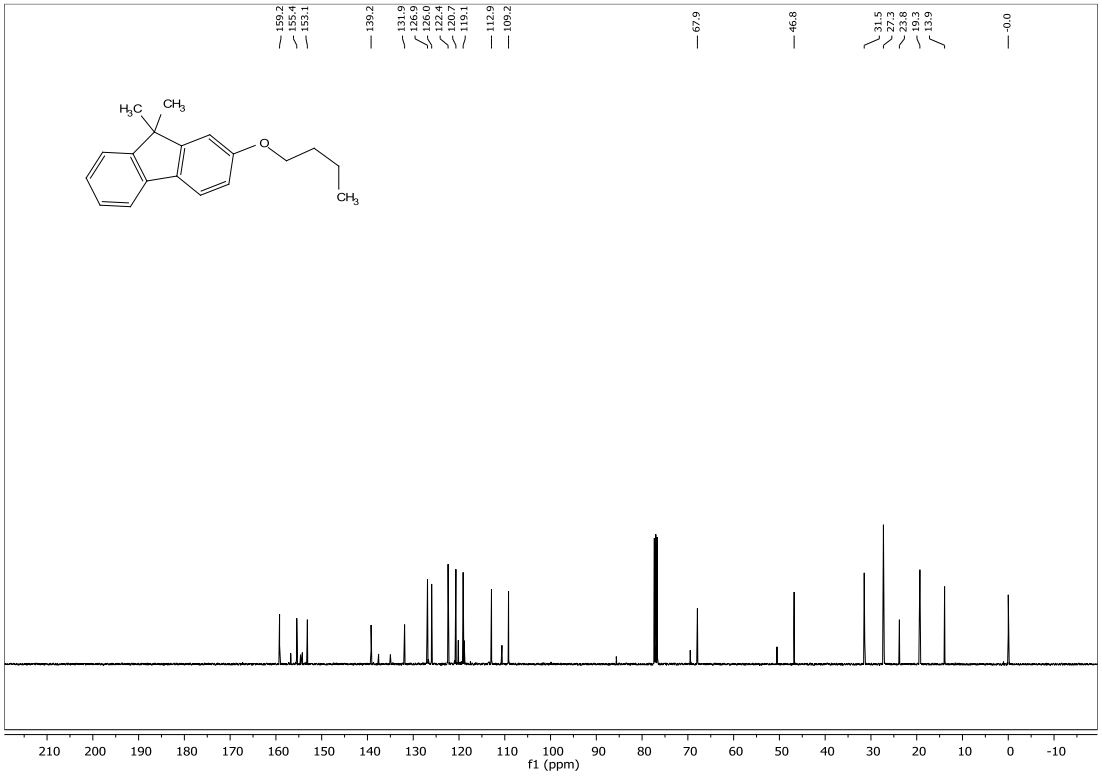


Figure 5.138: ^{1}H NMR of 1.63 at 400 MHz in $CDCl_3$ at 298K

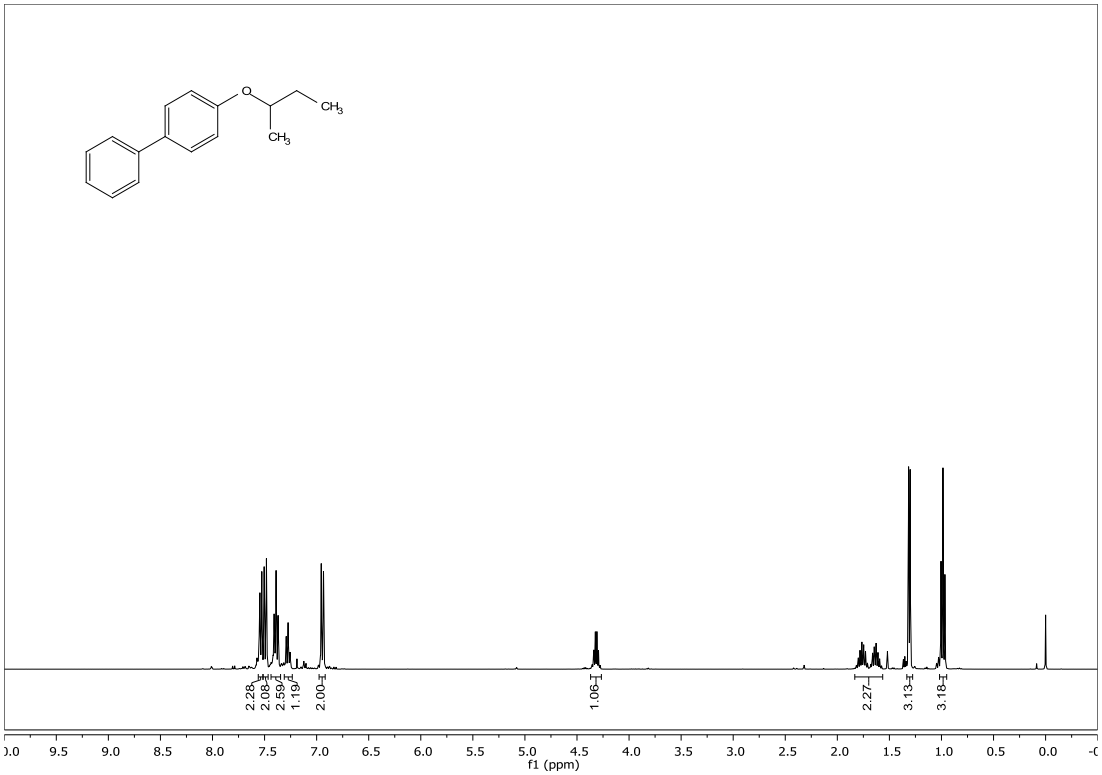


Figure 5.139: ^{13}C NMR of 1.63 at 100 MHz in DMSO-d_6 at 298K

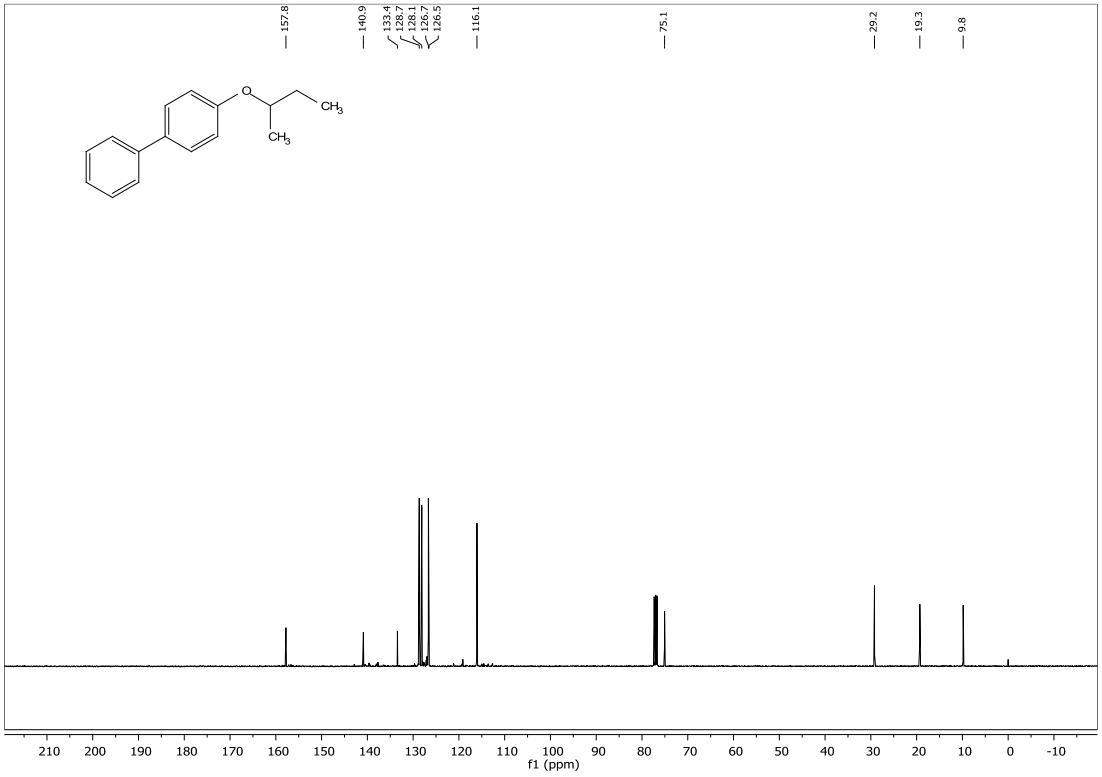


Figure 5.140: ^{1}H NMR of 1.64 at 400 MHz in $CDCl_3$ at 298K

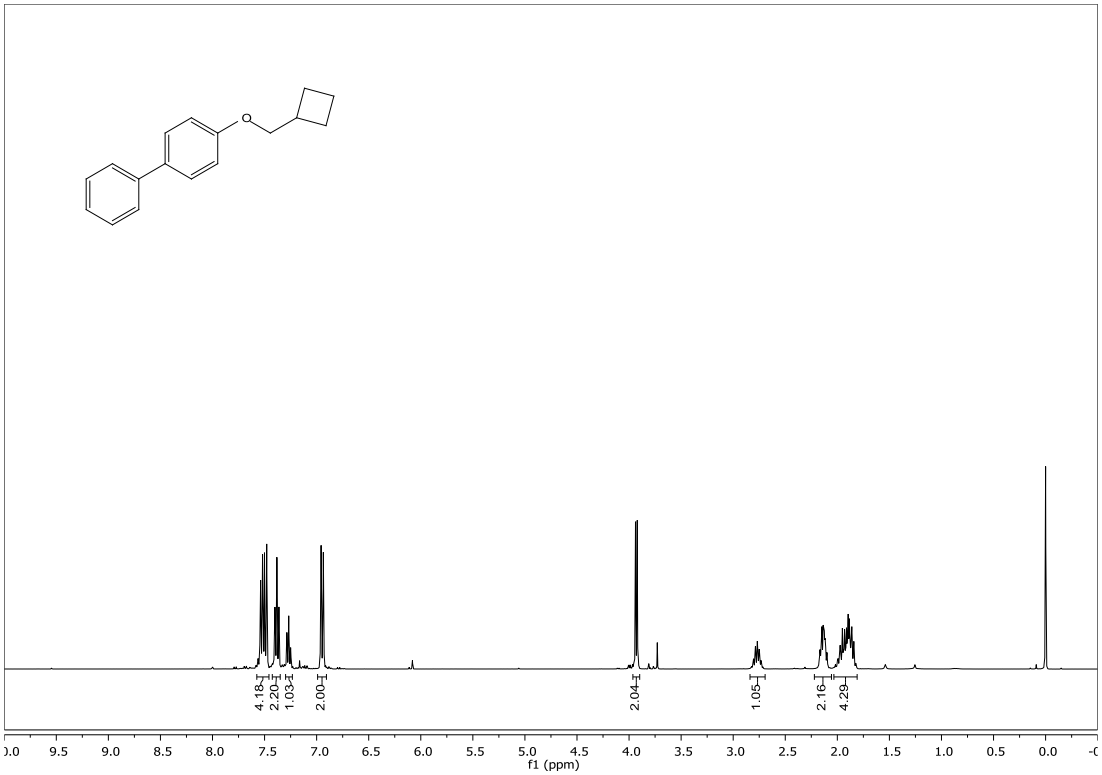


Figure 5.141: ^{13}C NMR of 1.64 at 100 MHz in DMSO-d_6 at 298K

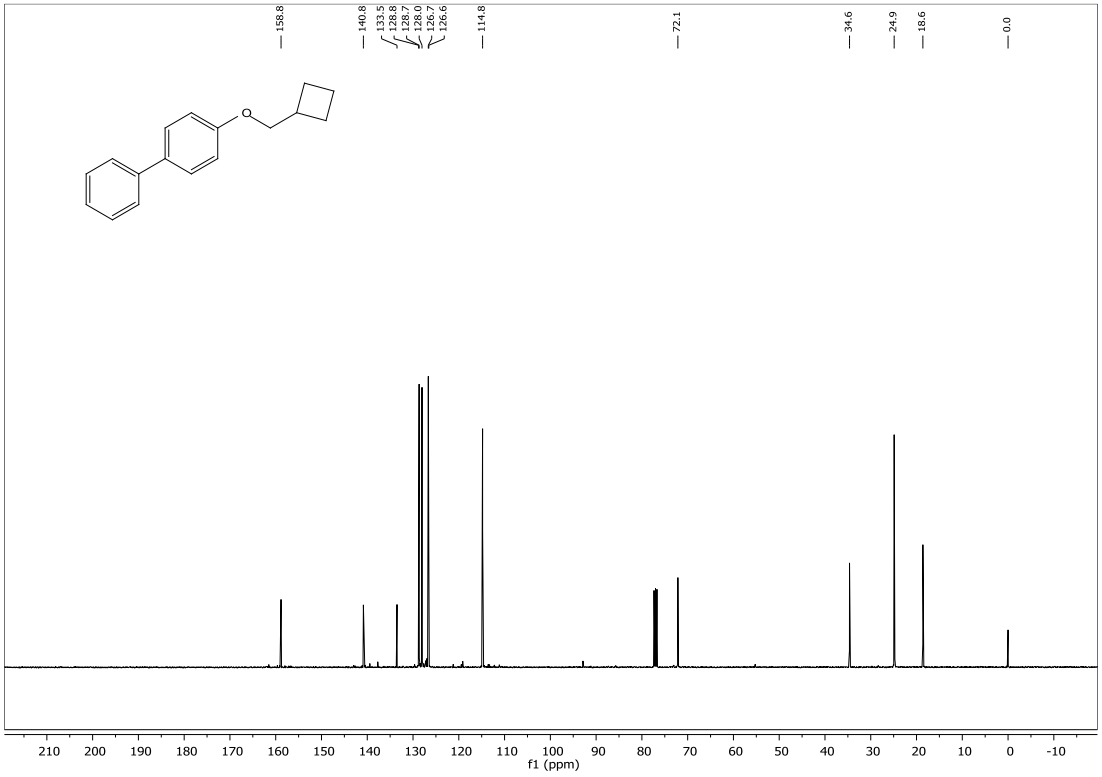


Figure 5.142: ^{1}H NMR of 1.65 at 400 MHz in $CDCl_3$ at 298K

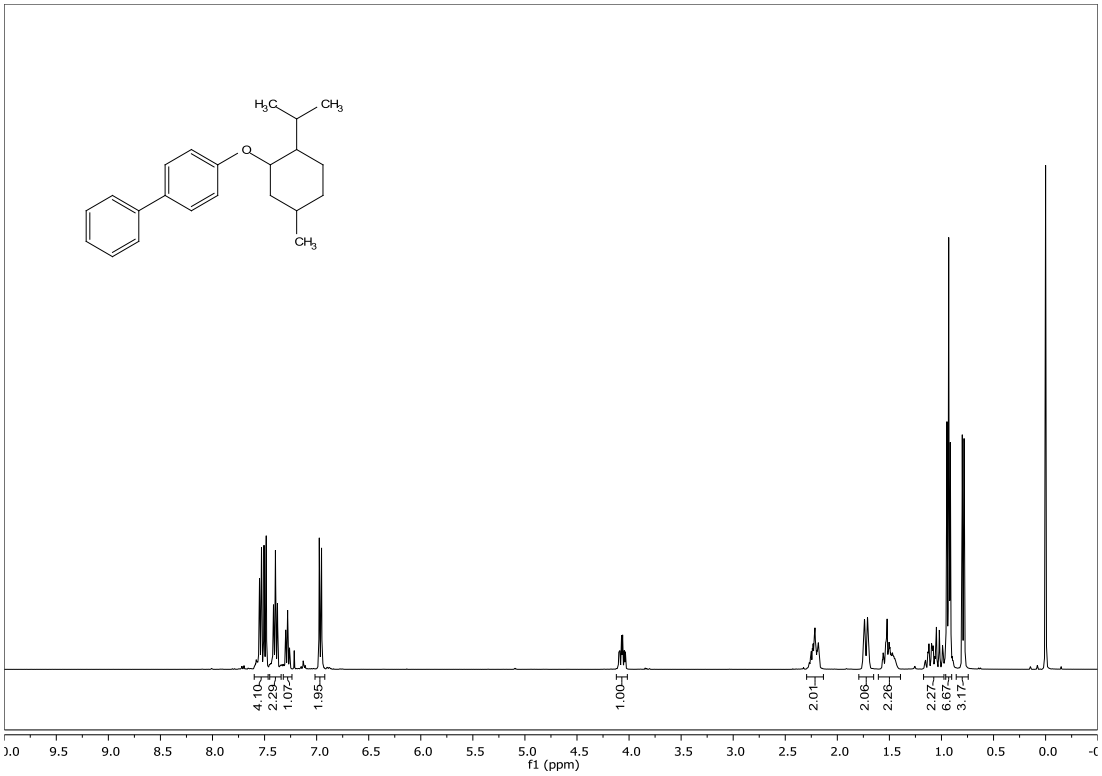


Figure 5.143: ^{13}C NMR of 1.65 at 100 MHz in DMSO-d_6 at 298K

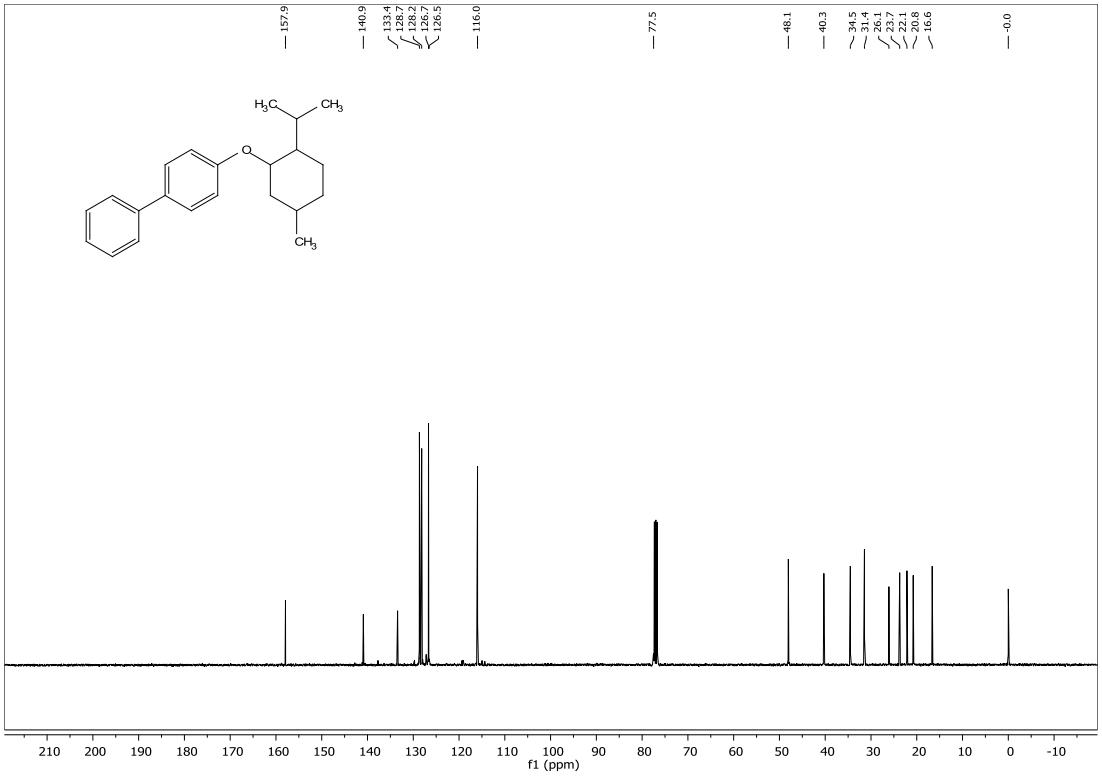


Figure 5.144: ^{1}H NMR of 1.66 at 400 MHz in $CDCl_3$ at 298K

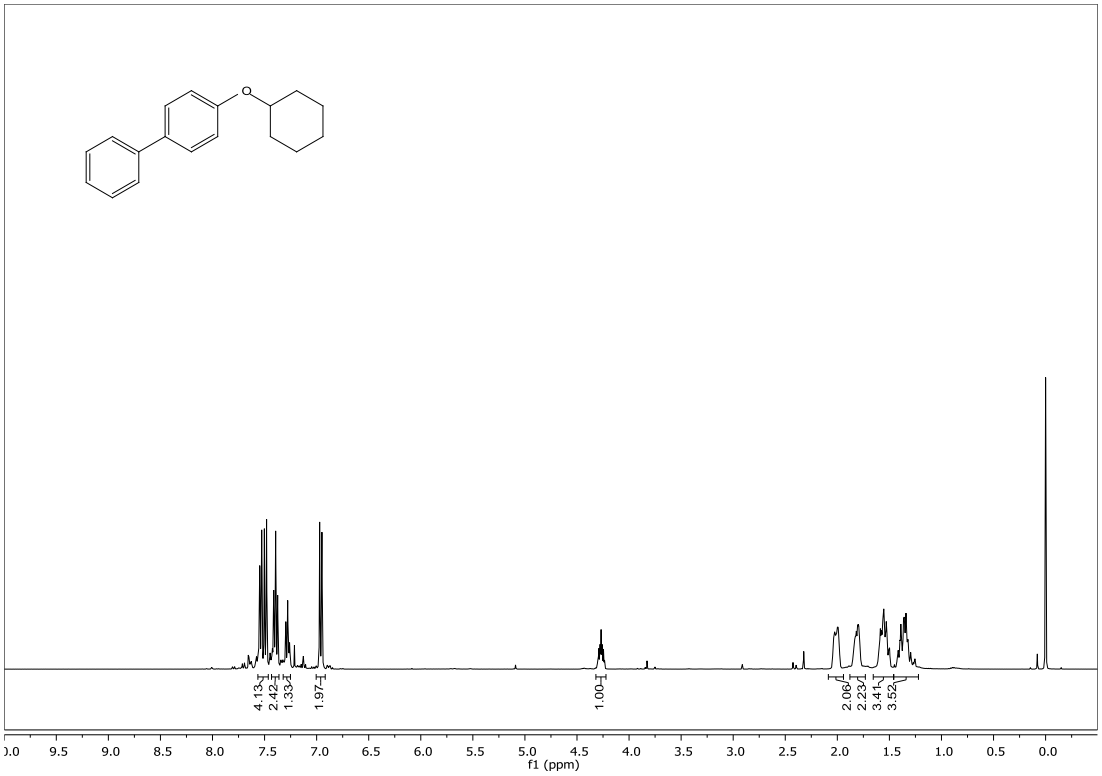


Figure 5.145: ^{13}C NMR of 1.66 at 100 MHz in DMSO-d_6 at 298K

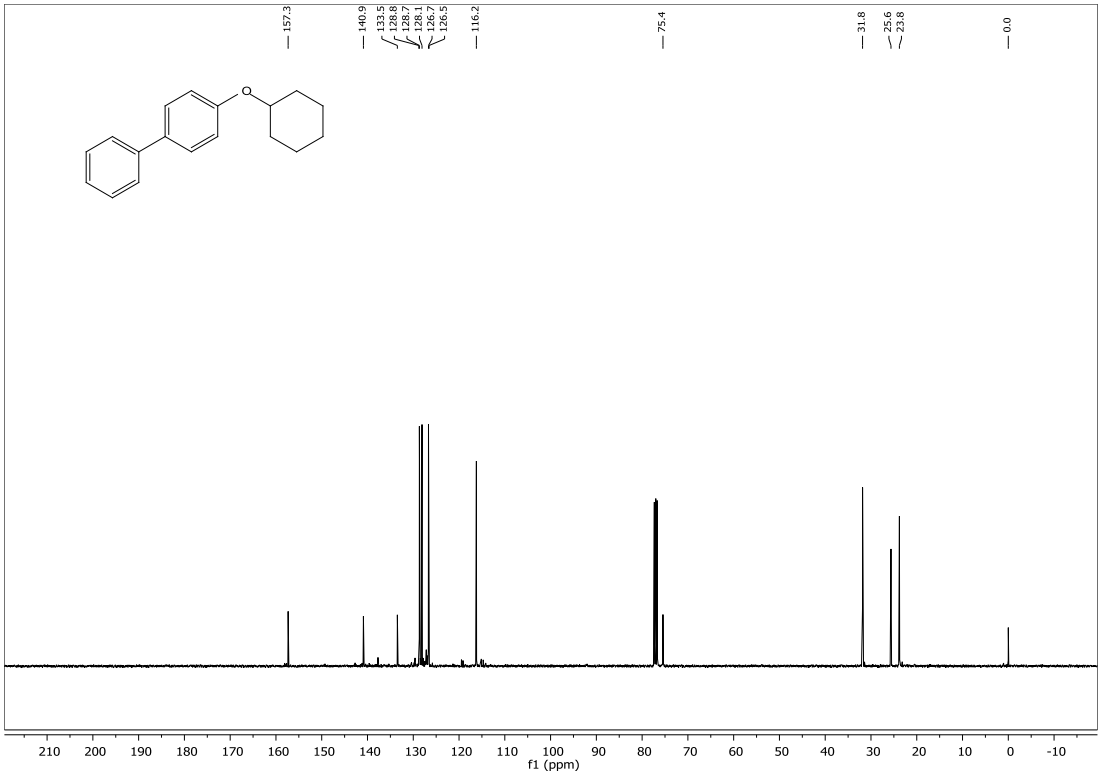


Figure 5.146: ^{1}H NMR of 1.67 at 400 MHz in $CDCl_3$ at 298K

Figure 5.147: ^{13}C NMR of 1.67 at 100 MHz in DMSO-d_6 at 298K

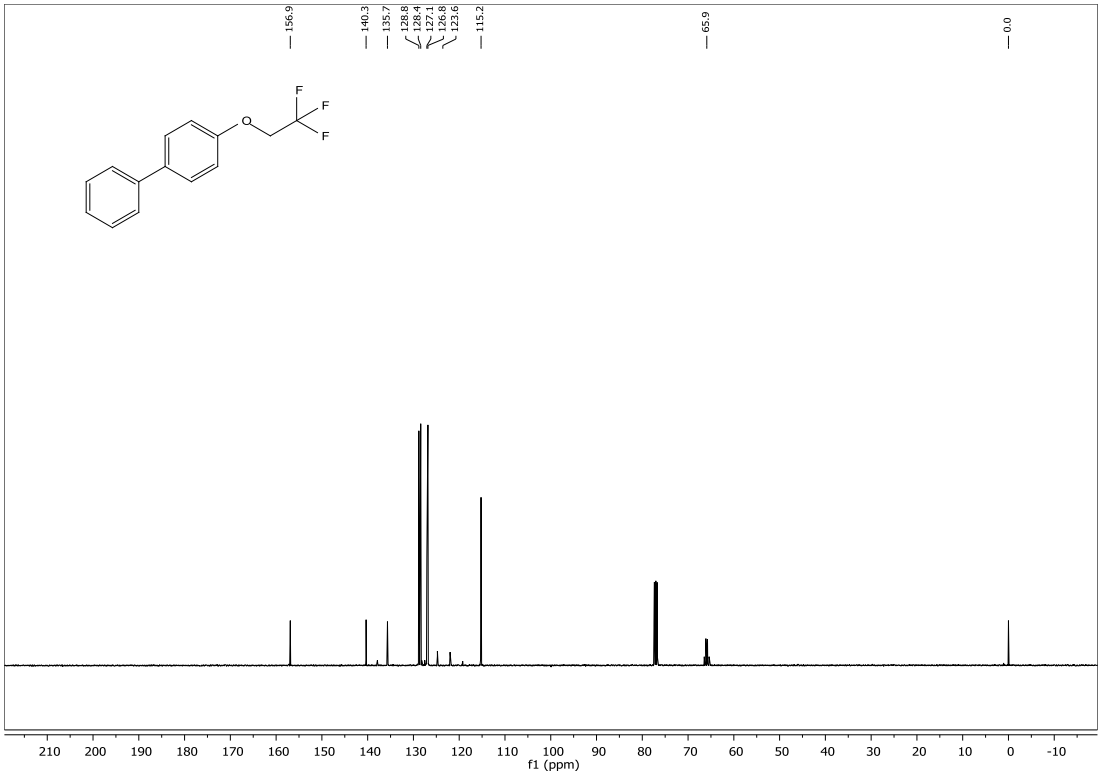


Figure 5.148: ^{1}H NMR of 1.68 at 400 MHz in $CDCl_3$ at 298K

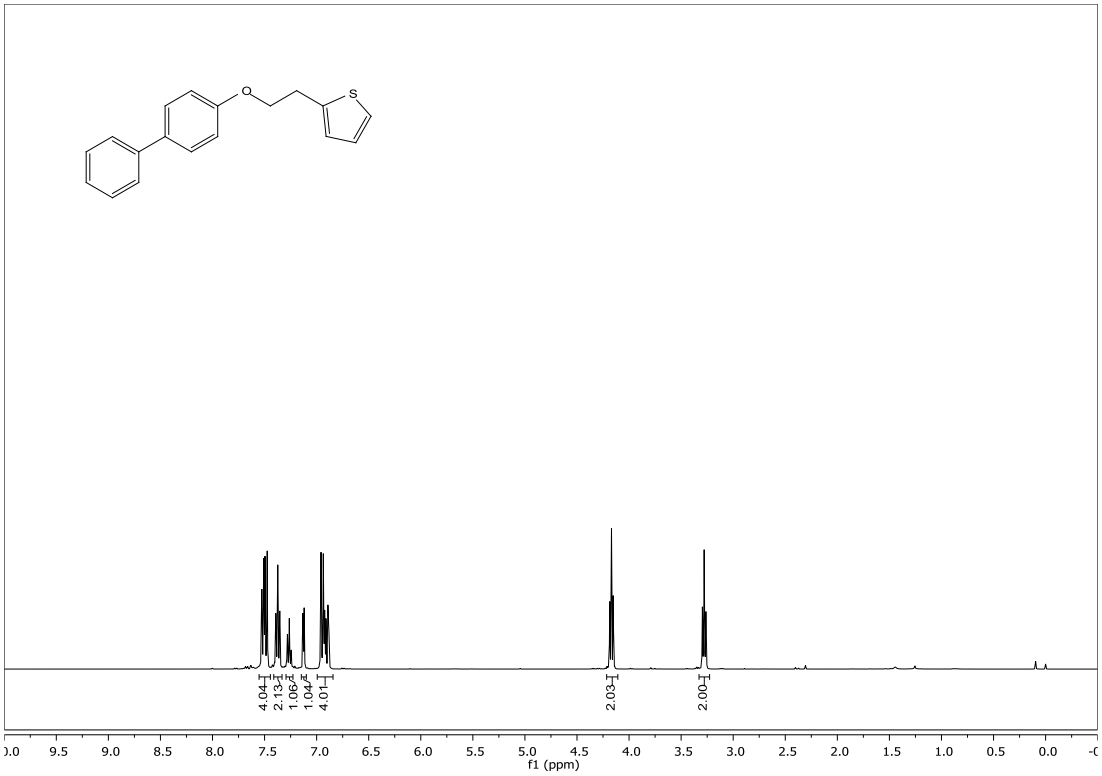


Figure 5.149: ^{13}C NMR of 1.68 at 100 MHz in DMSO-d_6 at 298K

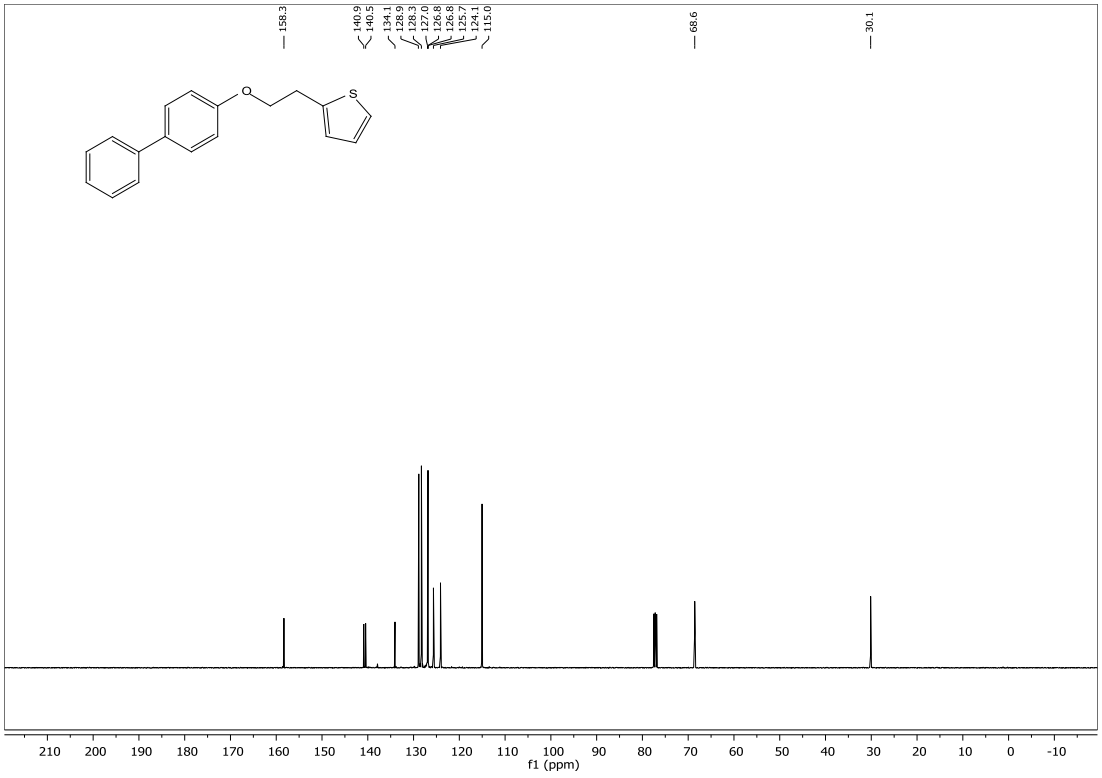


Figure 5.150: ^{1}H NMR of 1.69 at 400 MHz in $CDCl_3$ at 298K

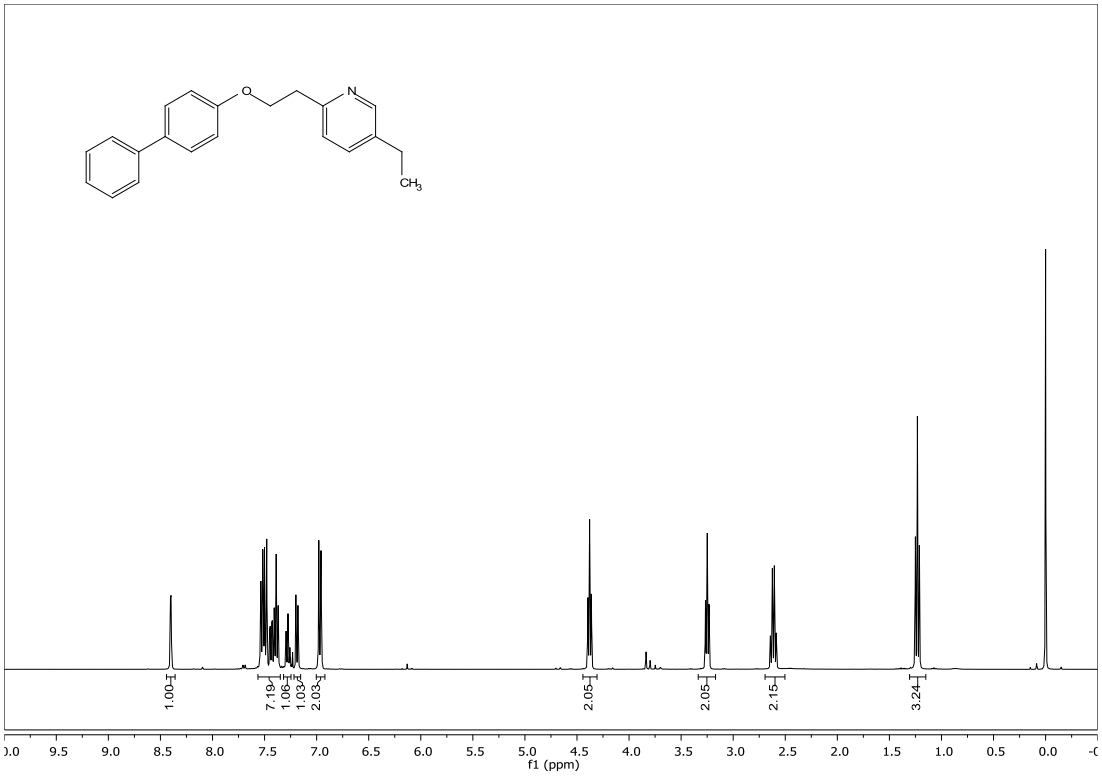


Figure 5.151: ^{13}C NMR of 1.69 at 100 MHz in DMSO-d_6 at 298K

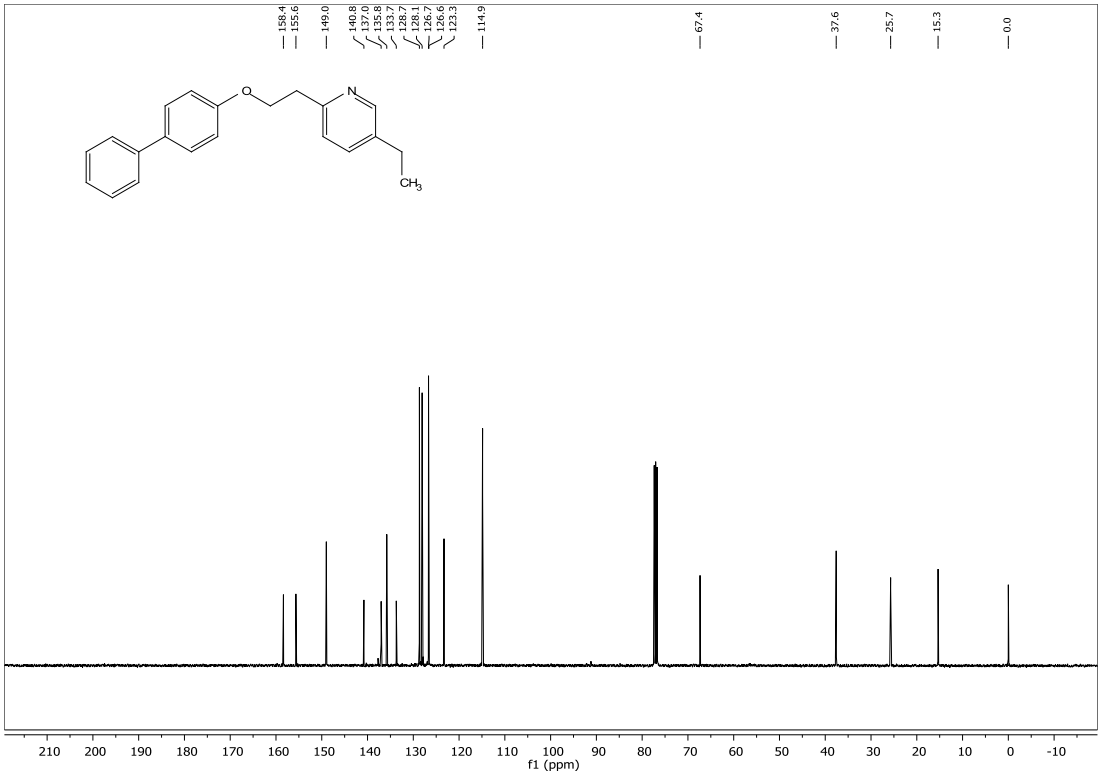


Figure 5.152: ^{1}H NMR of 1.70 at 400 MHz in $CDCl_3$ at 298K

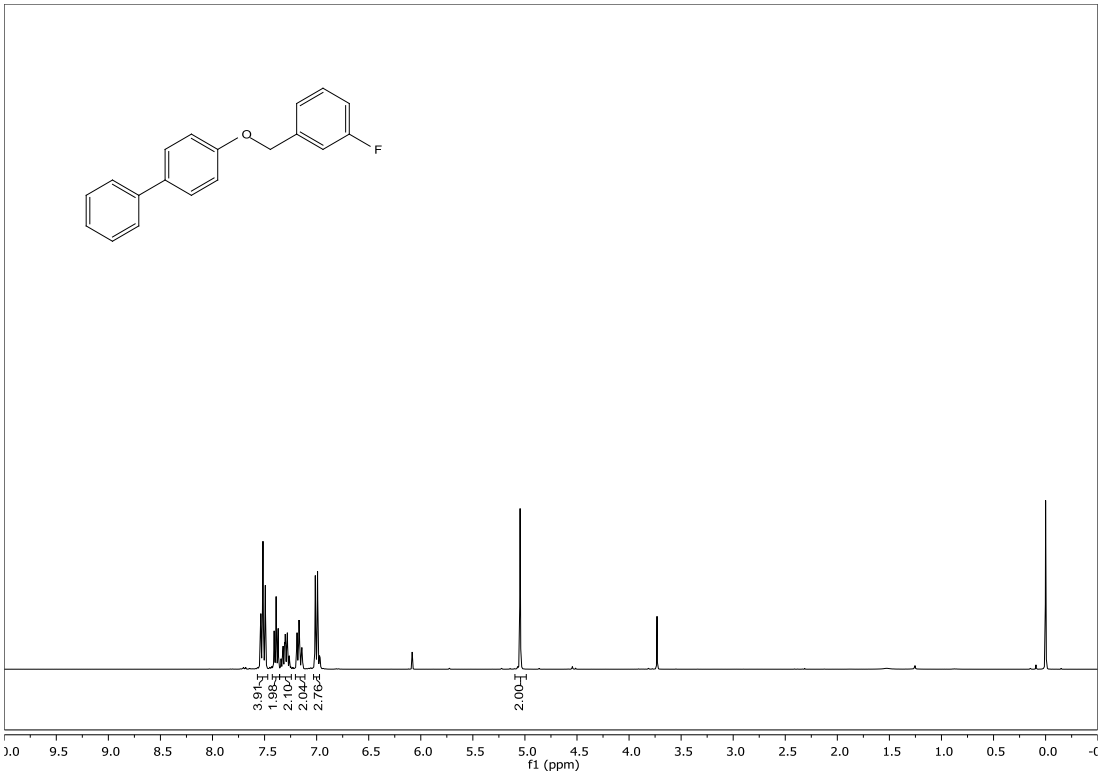


Figure 5.153: ^{13}C NMR of 1.70 at 100 MHz in DMSO-d_6 at 298K

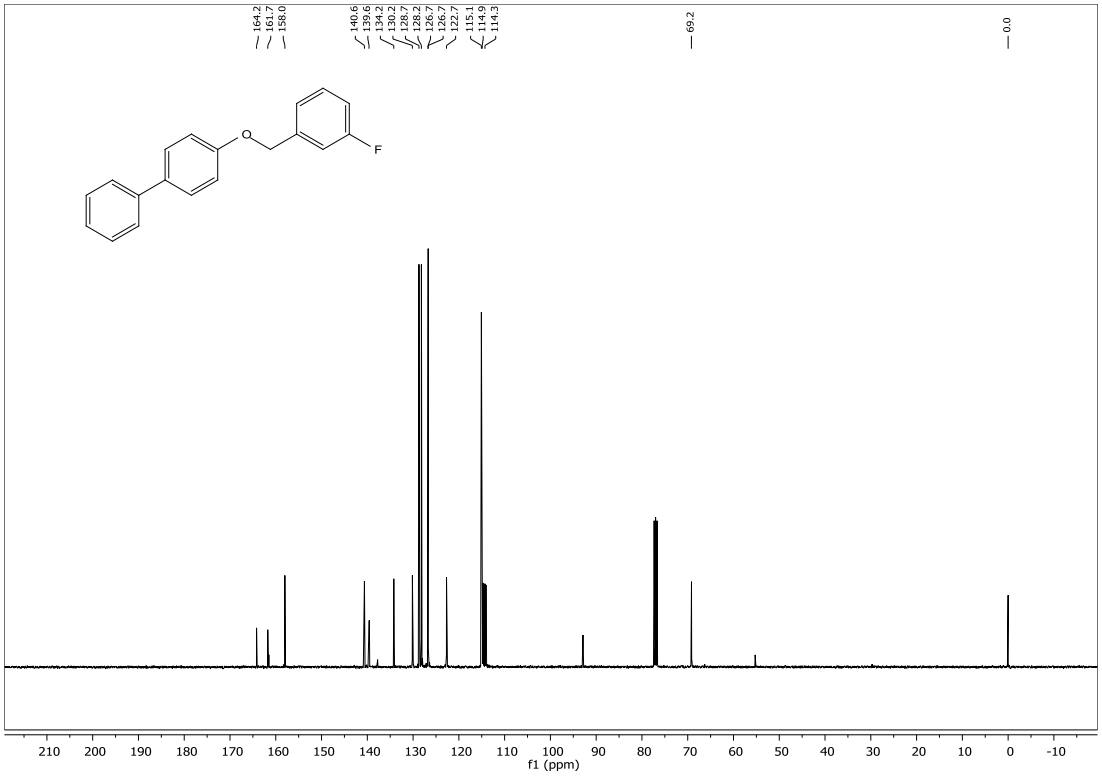


Figure 5.154: ^{19}F NMR of 1.70 at 377 MHz in CDl_3 at 298K

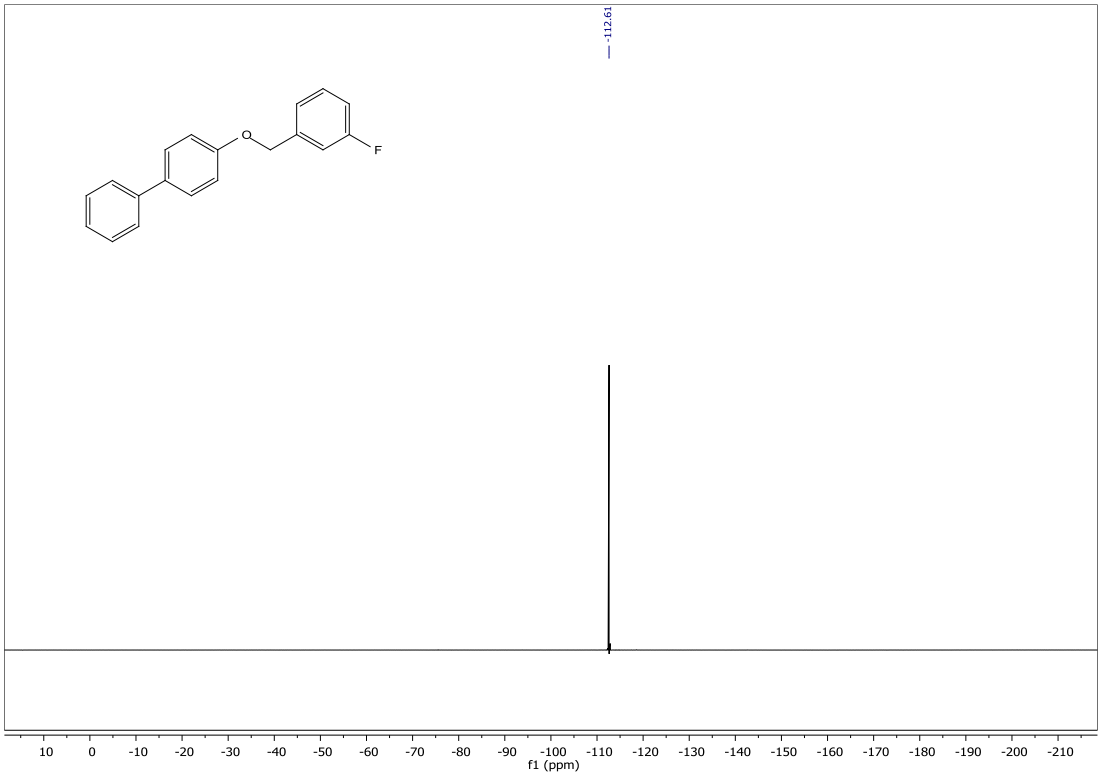


Figure 5.155: ^{1}H NMR of 1.71 at 400 MHz in $CDCl_3$ at 298K

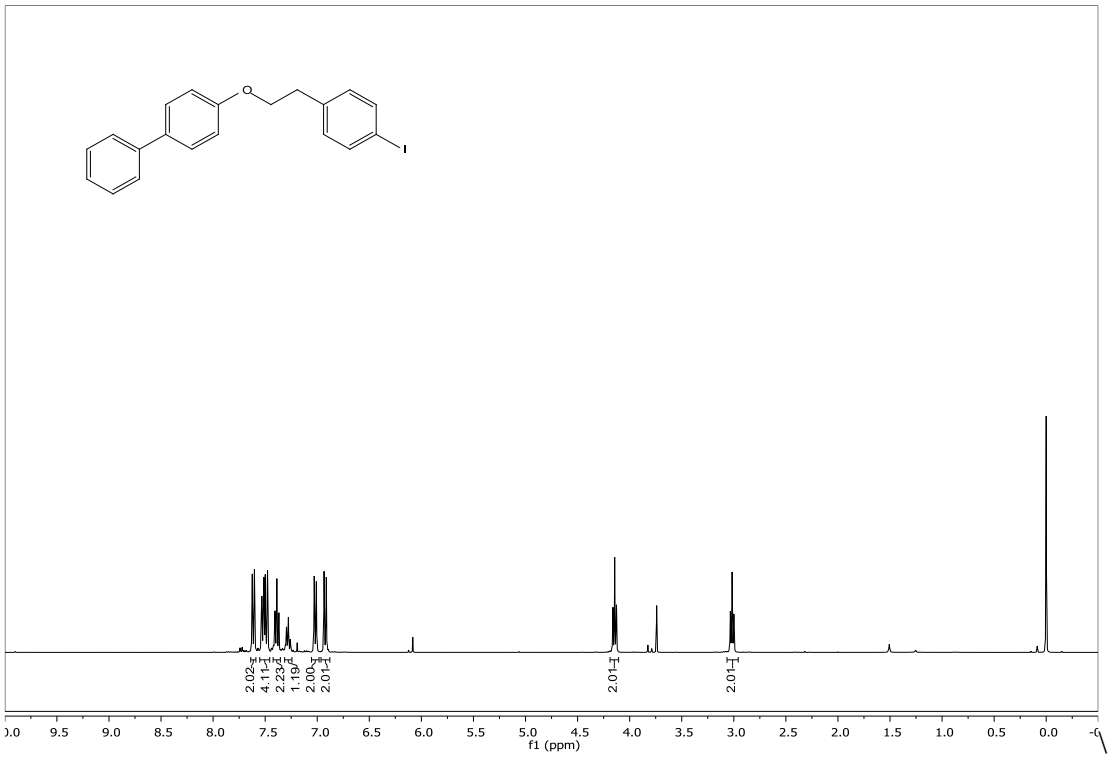


Figure 5.156: ^{13}C NMR of 1.71 at 100 MHz in DMSO-d_6 at 298K

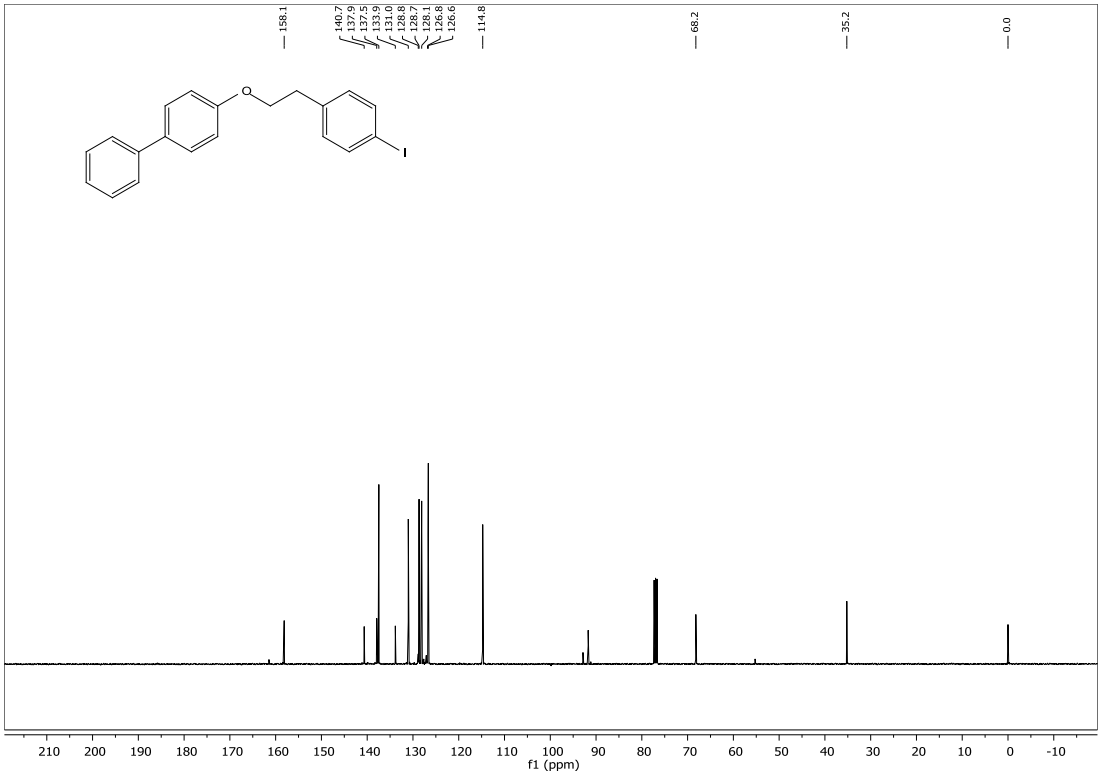


Figure 5.157: ^{1}H NMR of 2.1 at 400 MHz in DMSO-d_6 at 298K

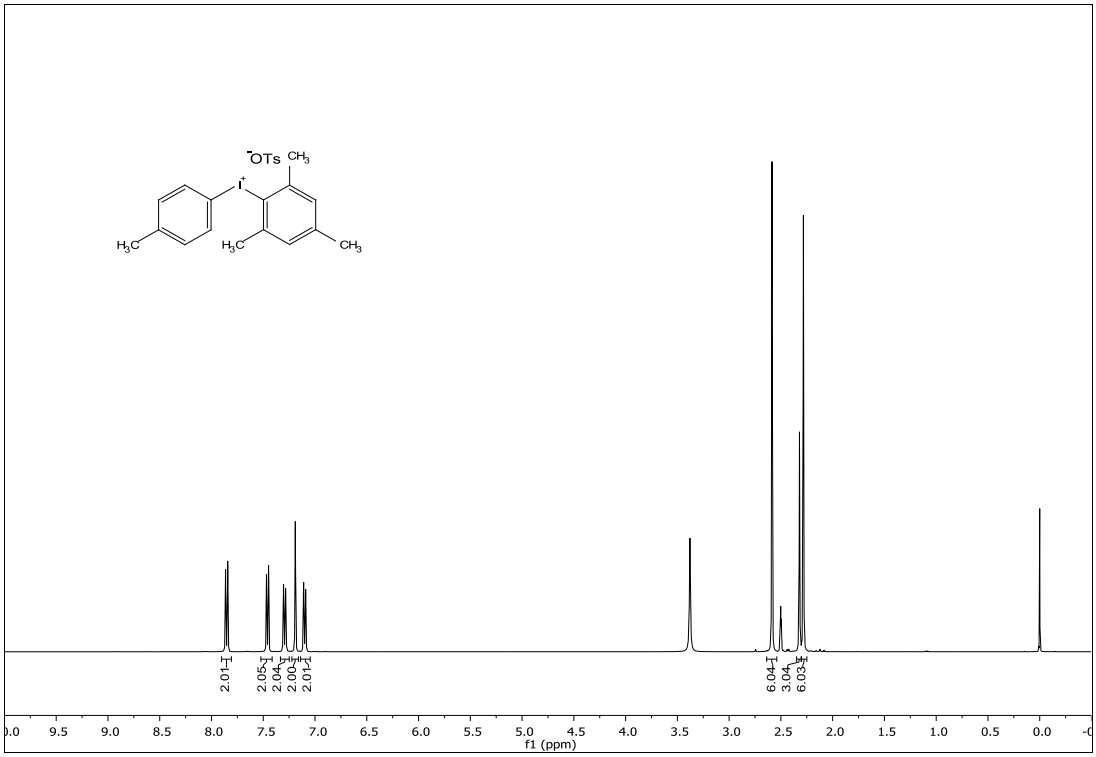


Figure 5.158: ^{13}C NMR of 2.1 at 101 MHz in DMSO-d_6 at 298K

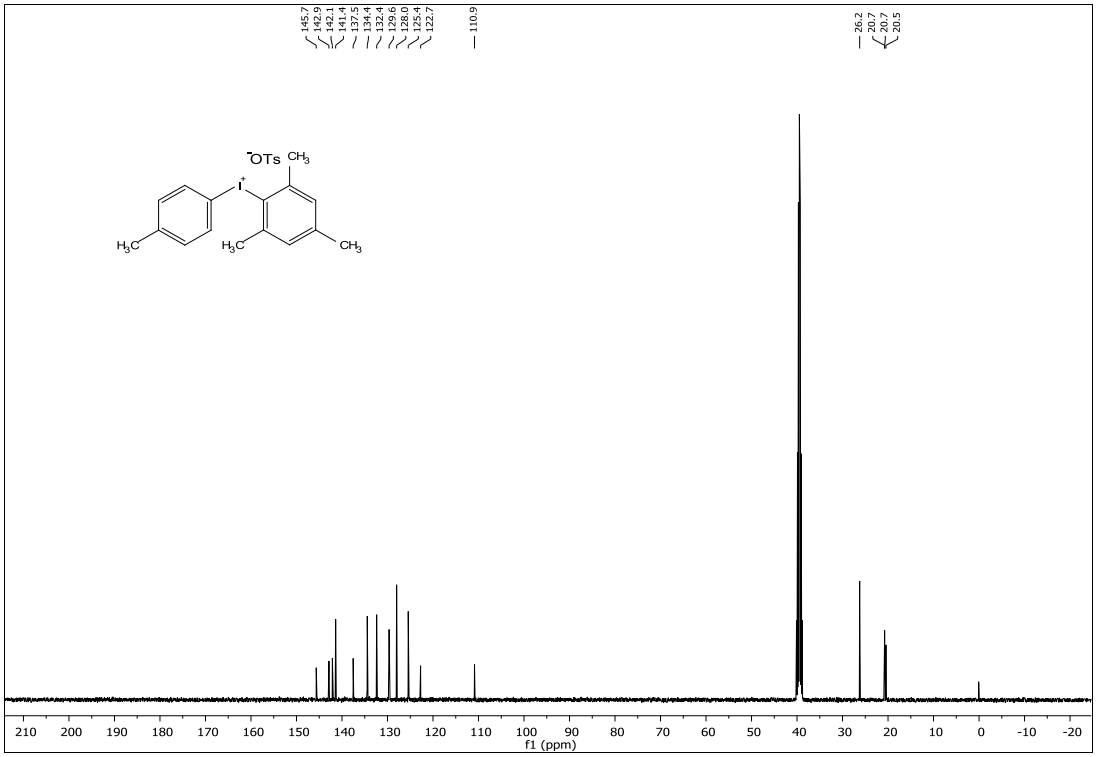


Figure 5.159: ^{1}H NMR of 2.2 at 400 MHz in DMSO-d_6 at 298K

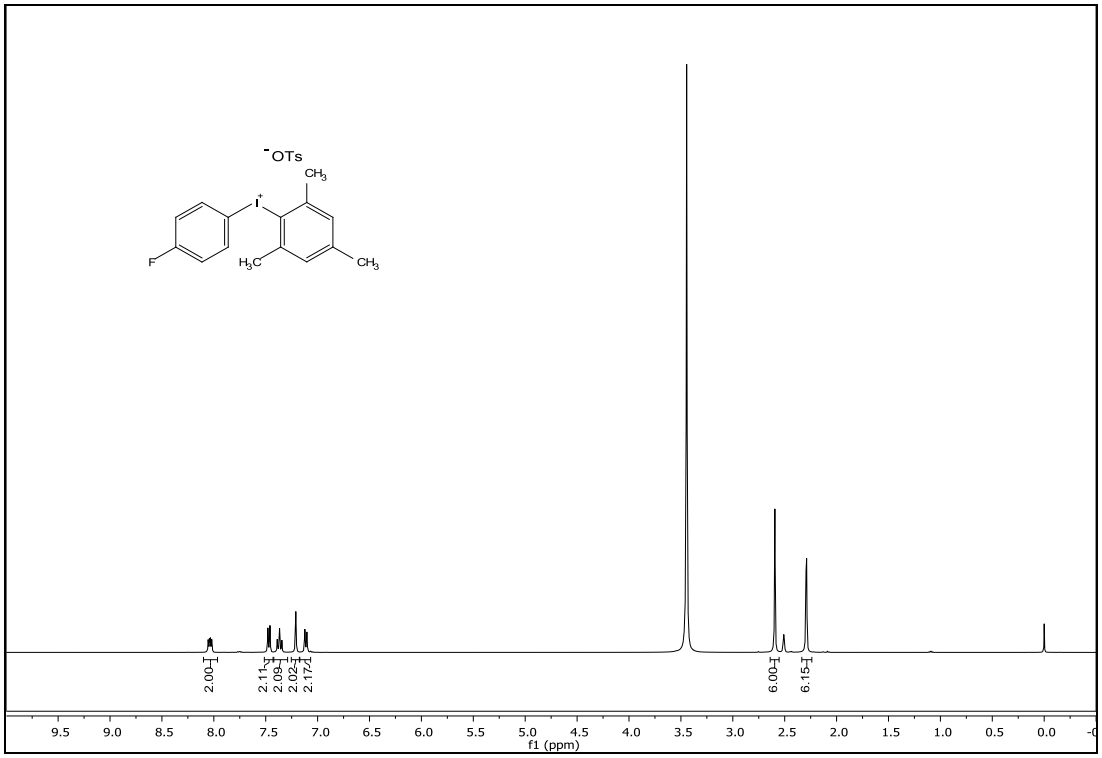


Figure 5.160: ^{13}C NMR of 2.2 at 101 MHz in DMSO-d_6 at 298K

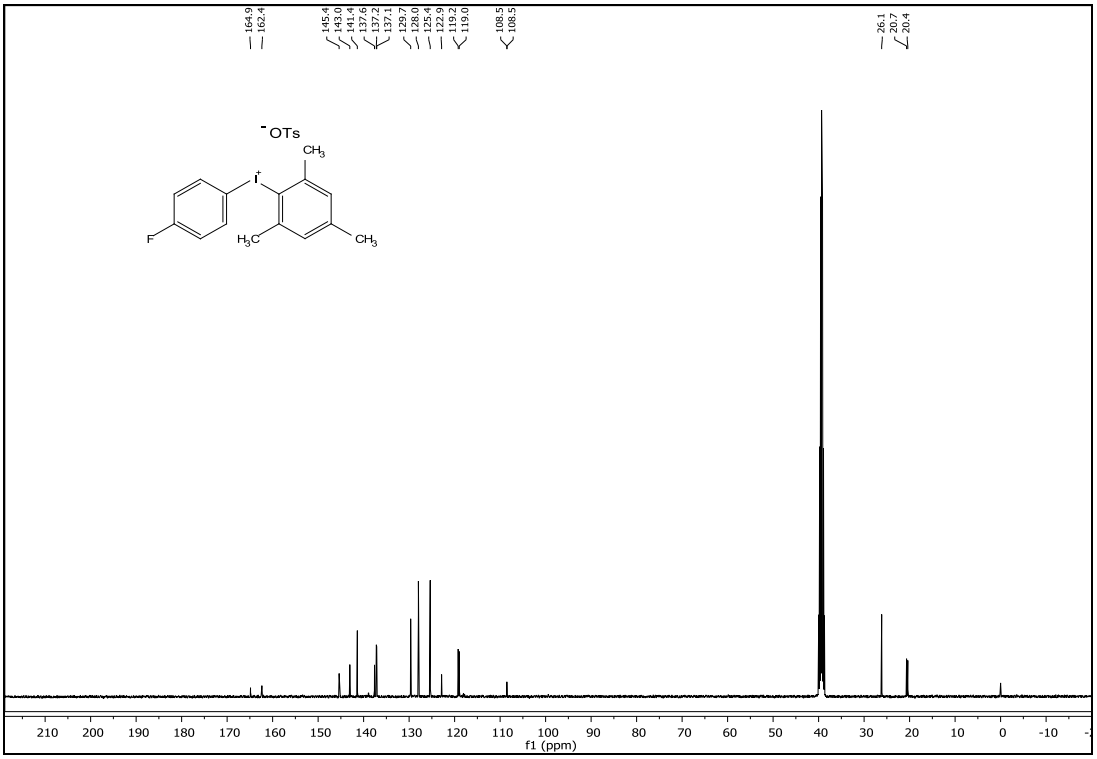


Figure 5.161: ^{19}F NMR of 2.2 at 377 MHz in DMSO-d_6 at 298K

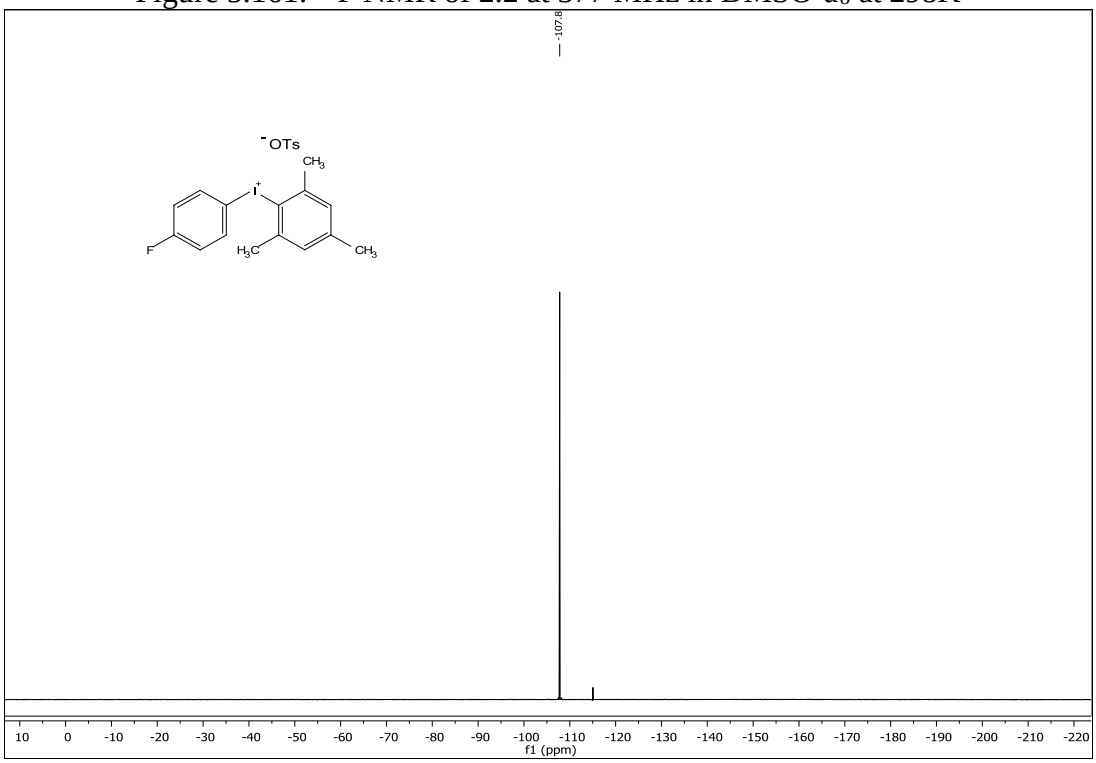


Figure 5.162: ^{1}H NMR of 2.3 at 400 MHz in DMSO-d_6 at 298K

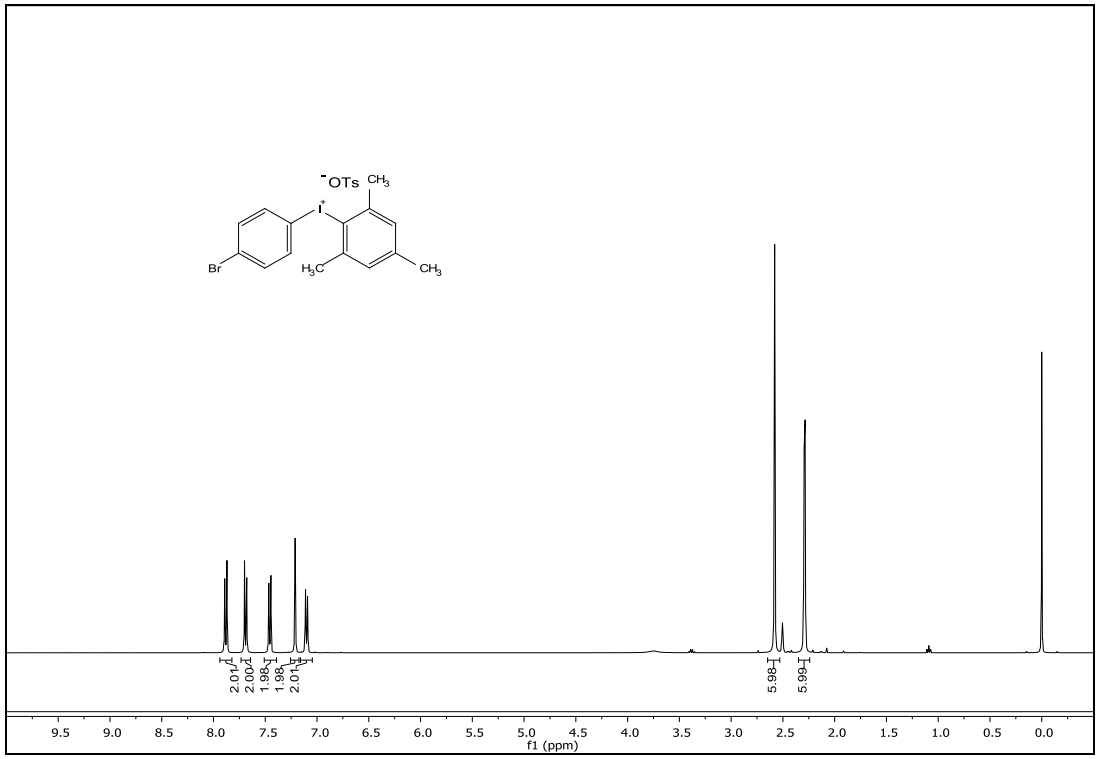


Figure 5.163: ^{13}C NMR of 2.3 at 101 MHz in DMSO-d_6 at 298K

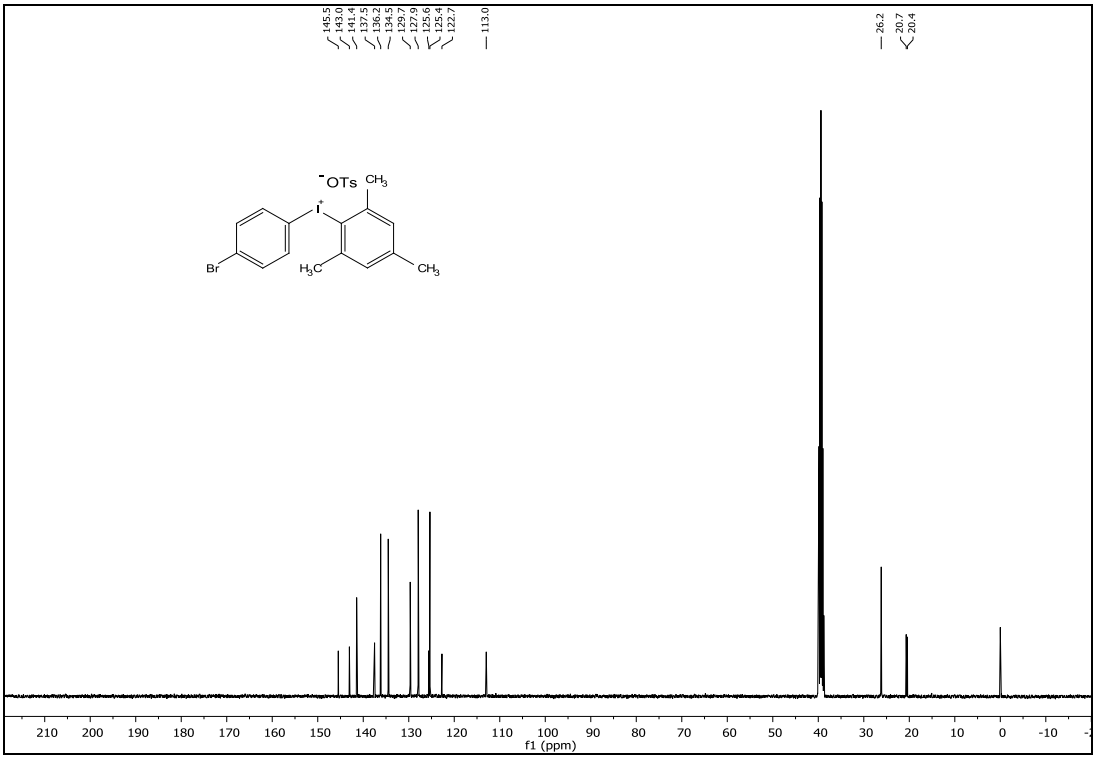


Figure 5.164: ^{1}H NMR of 2.4 at 400 MHz in DMSO-d_6 at 298K

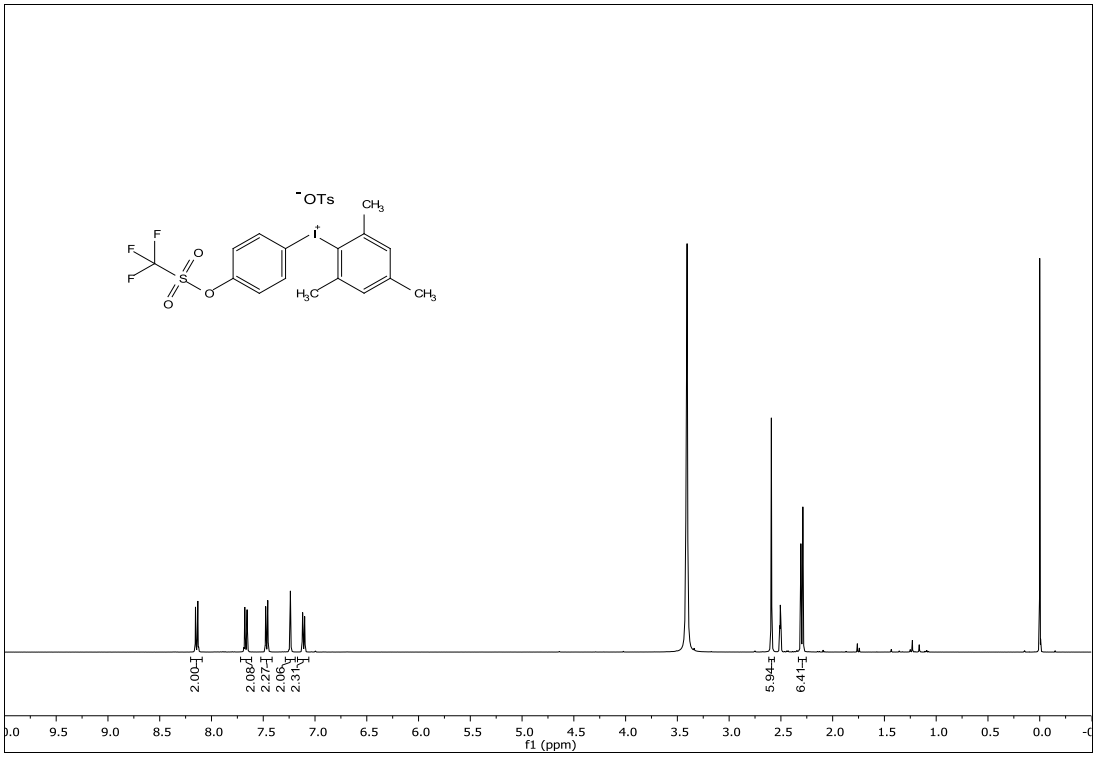


Figure 5.165: ^{13}C NMR of 2.4 at 101 MHz in DMSO-d_6 at 298K

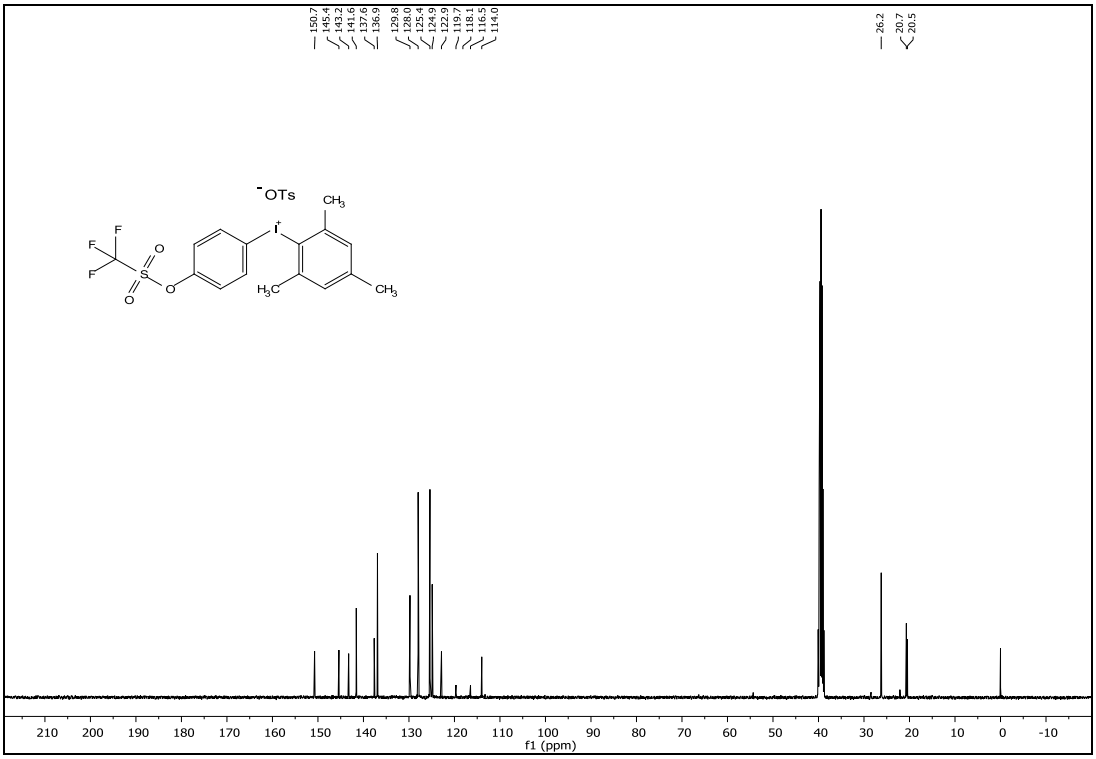


Figure 5.166: ^{19}F NMR of 2.4 at 377 MHz in DMSO-d_6 at 298K

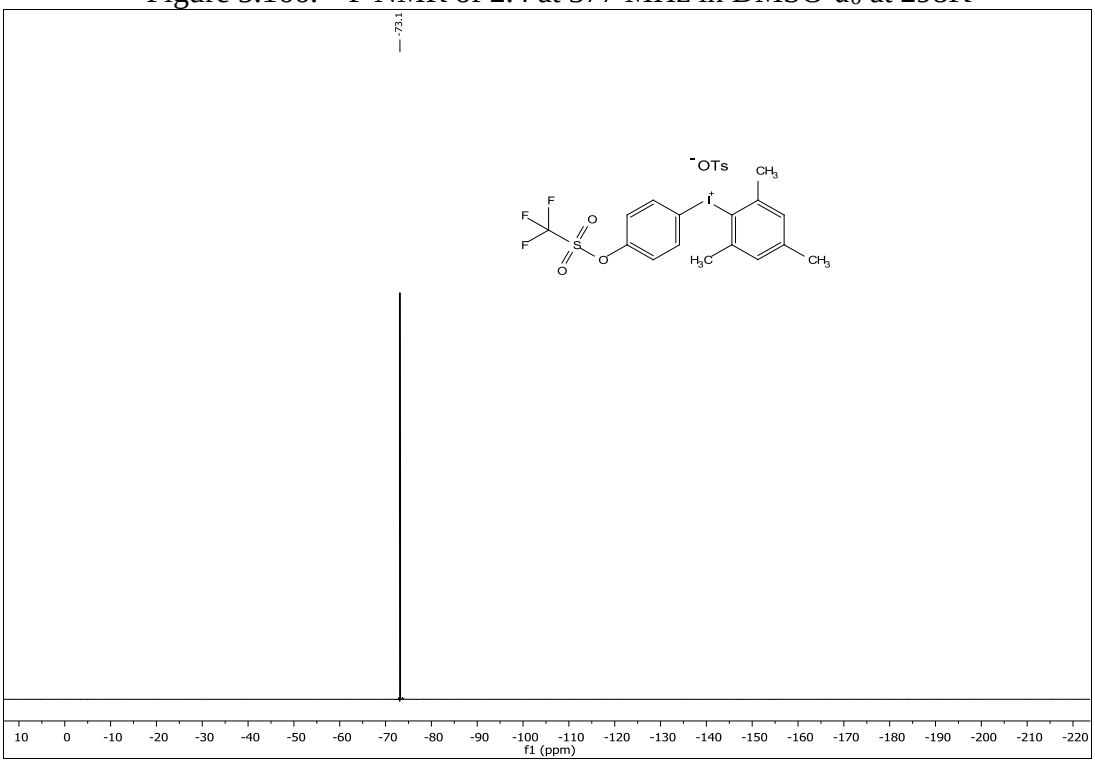


Figure 5.167: ^{1}H NMR of 2.5 at 400 MHz in DMSO-d_6 at 298K

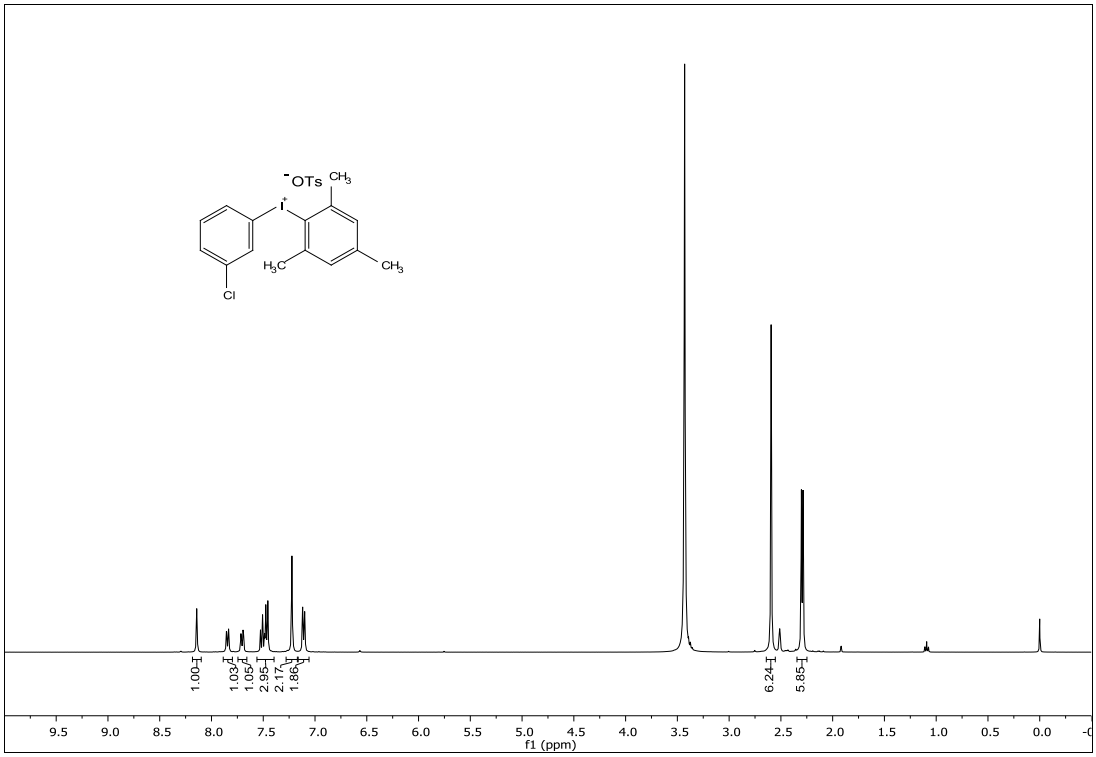


Figure 5.168: ^{13}C NMR of 2.5 at 101 MHz in DMSO-d_6 at 298K

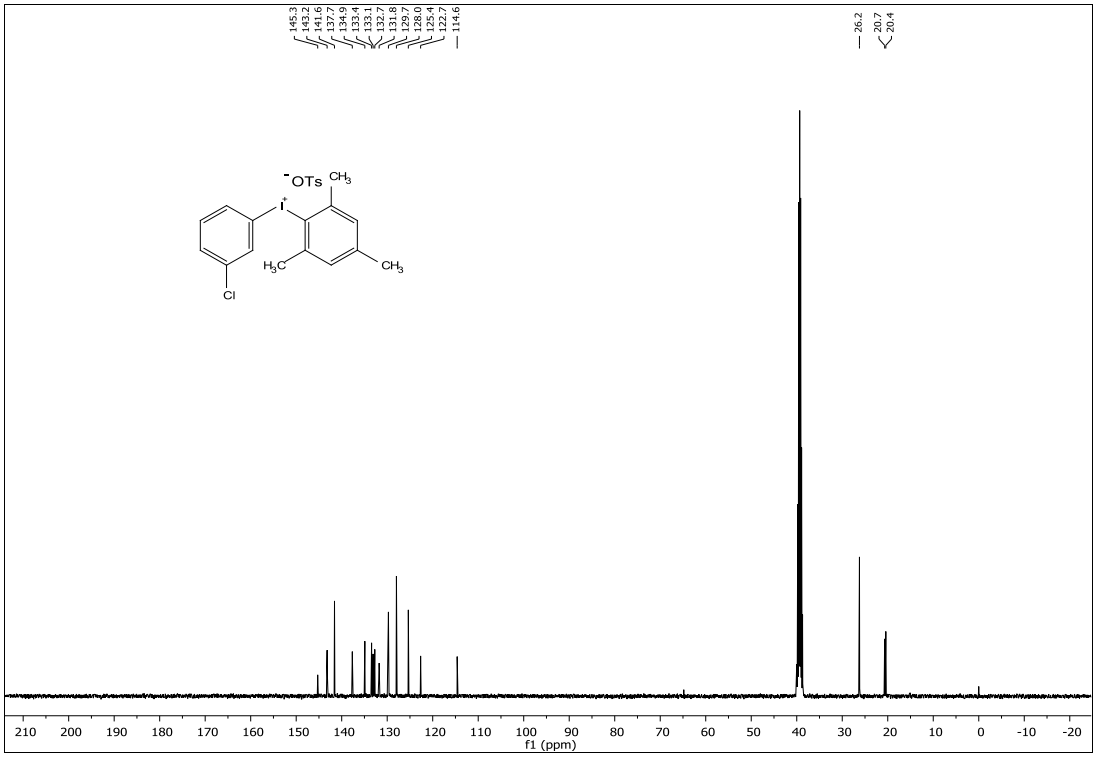


Figure 5.169: ^{1}H NMR of 2.6 at 400 MHz in DMSO-d_6 at 298K

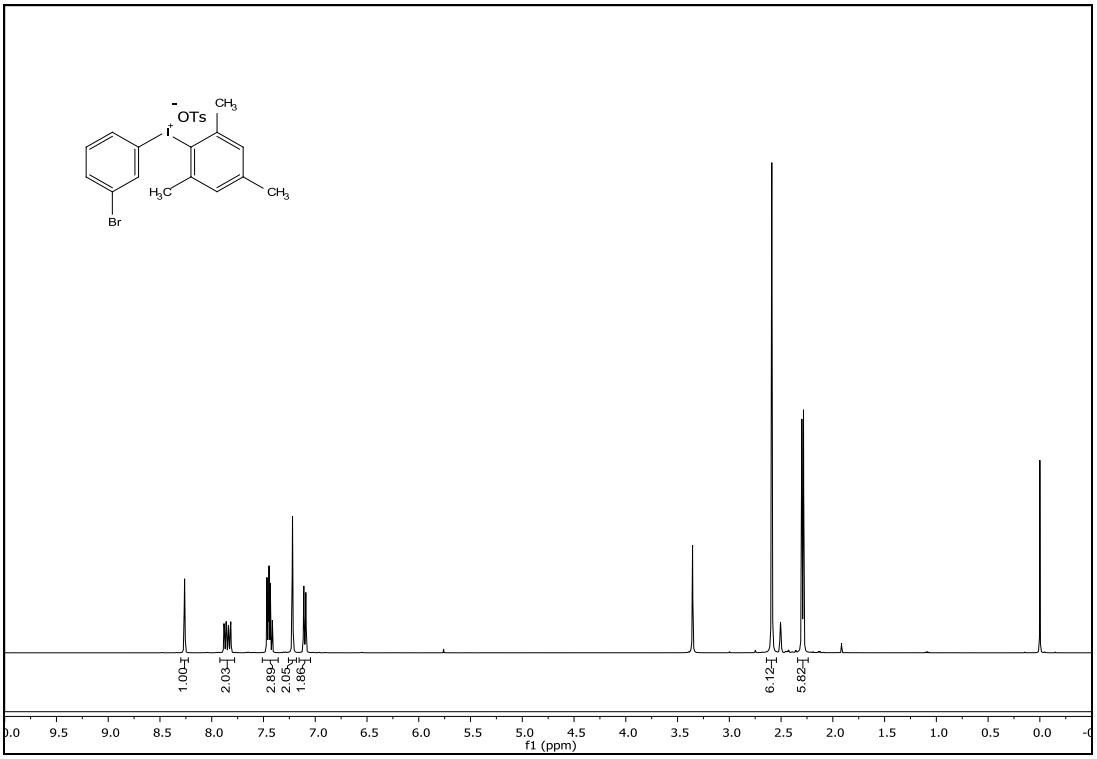


Figure 5.170: ^{13}C NMR of 2.6 at 101 MHz in DMSO-d_6 at 298K

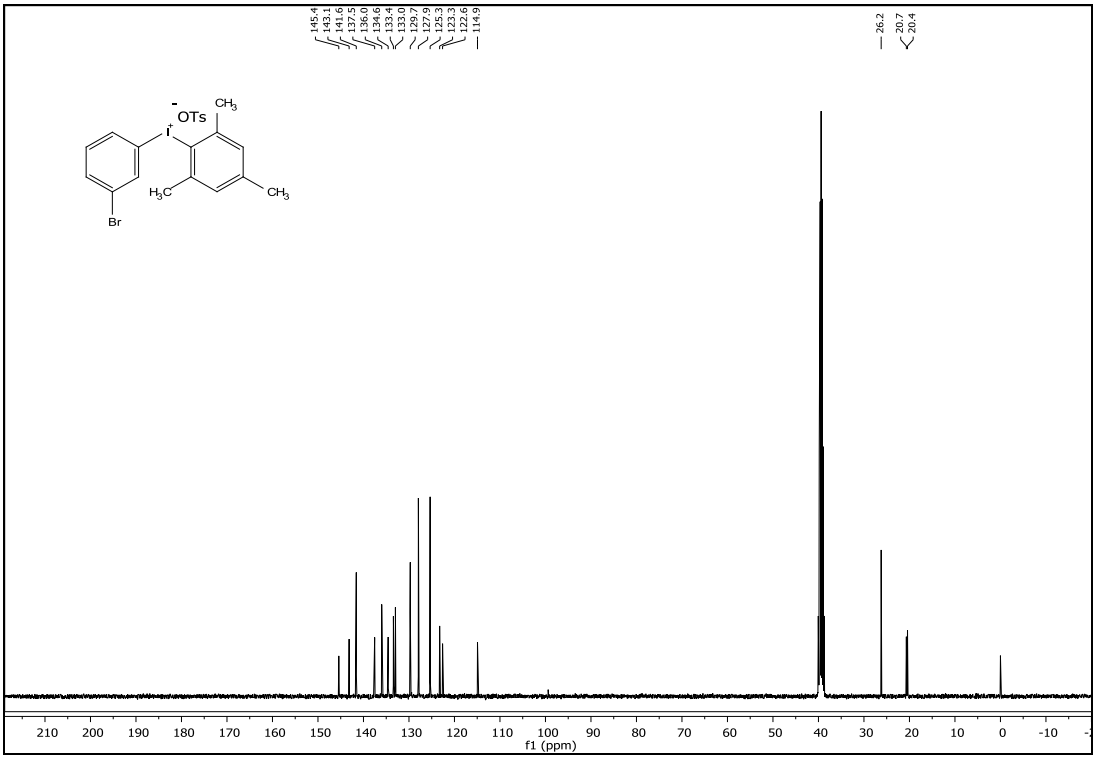


Figure 5.171: ^{1}H NMR of 2.7 at 400 MHz in DMSO-d_6 at 298K

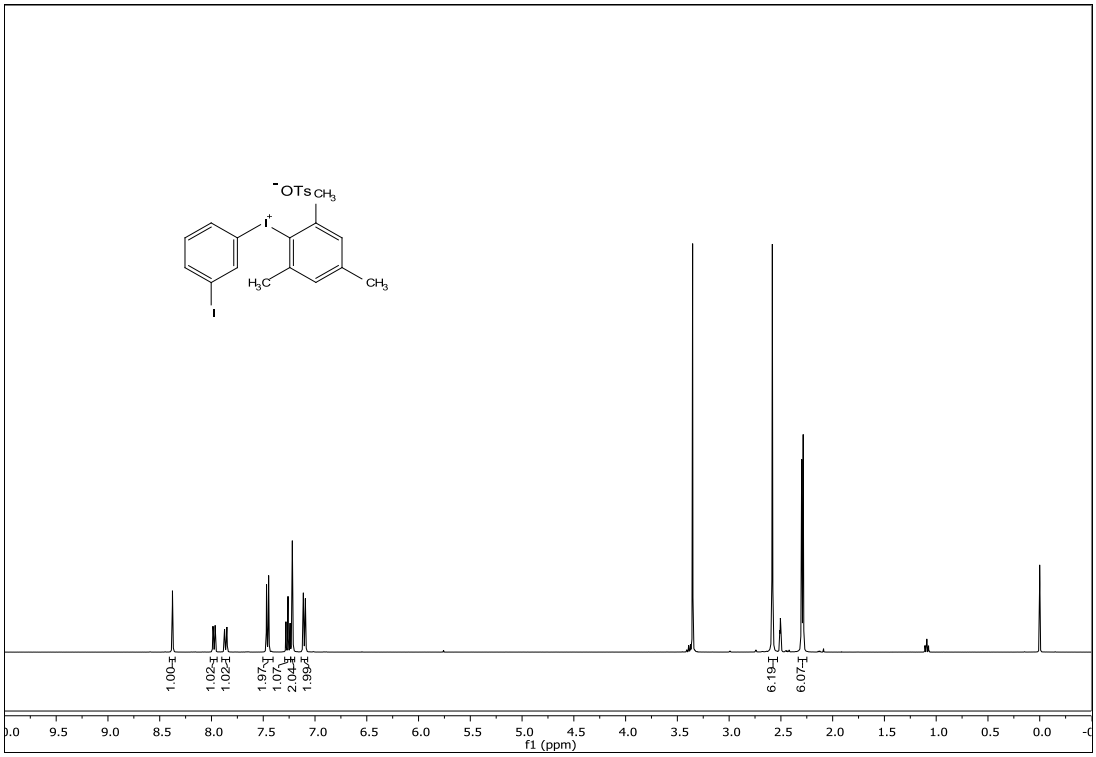


Figure 5.172: ^{13}C NMR of 2.7 at 101 MHz in DMSO-d_6 at 298K

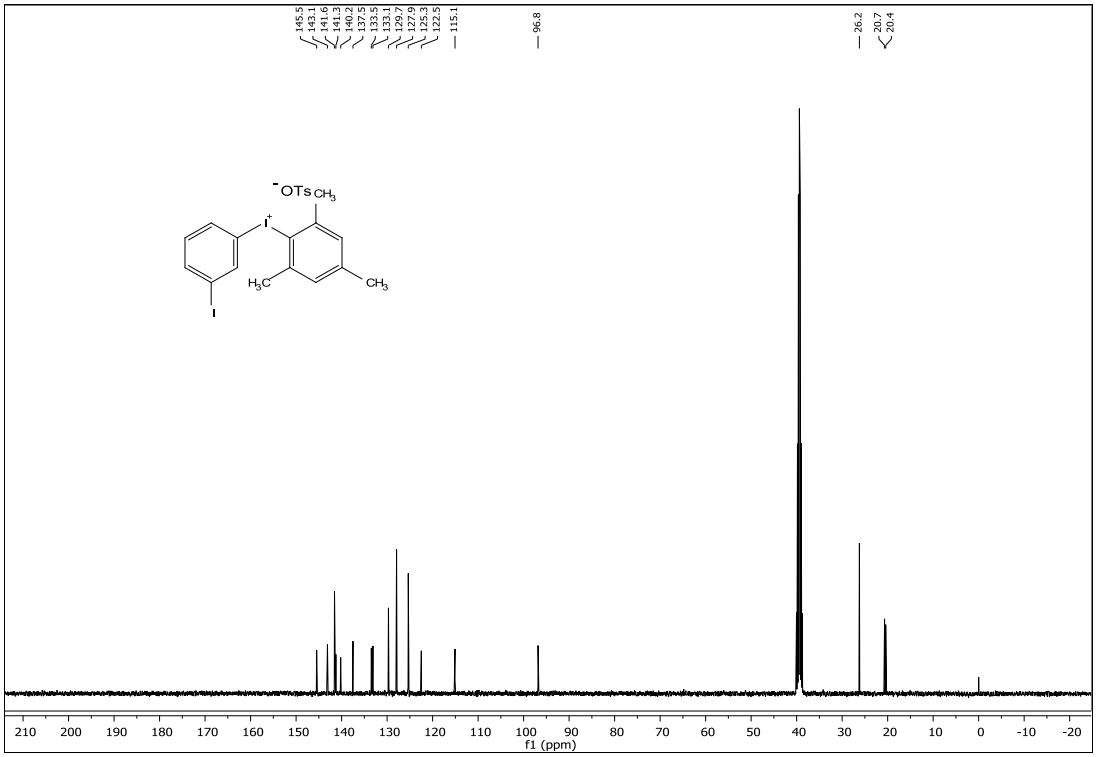


Figure 5.173: ^{1}H NMR of 2.8 at 400 MHz in DMSO-d_6 at 298K

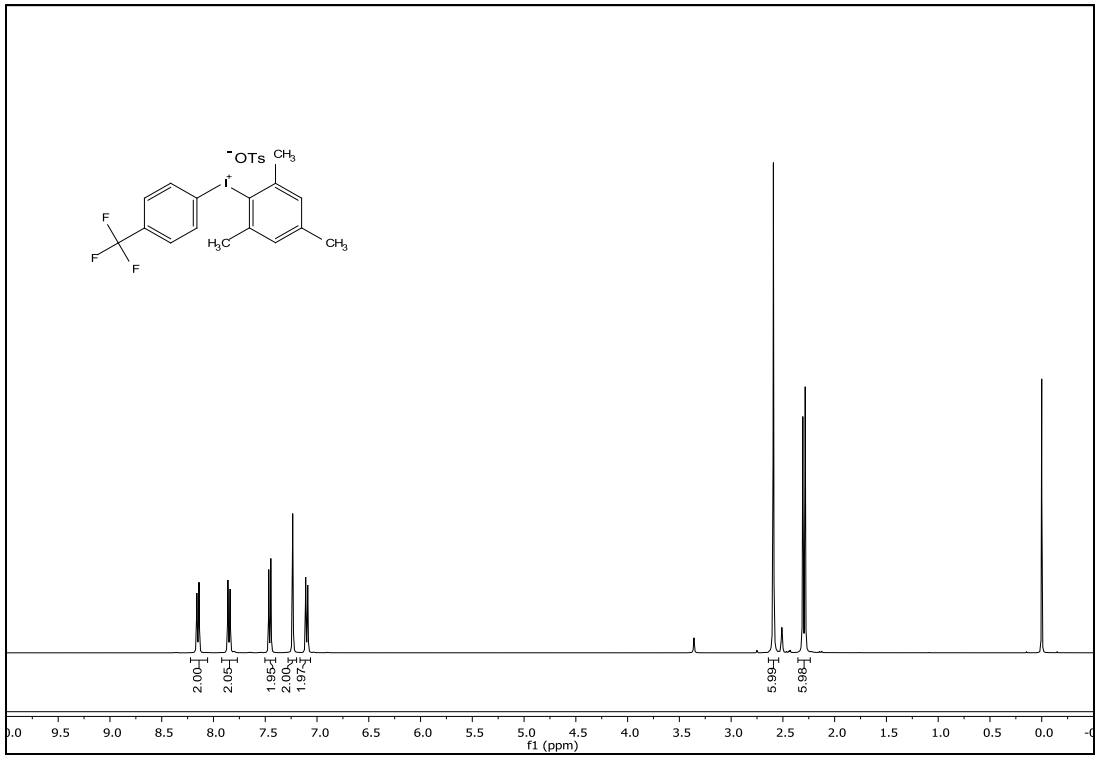


Figure 5.174: ^{13}C NMR of 2.8 at 101 MHz in DMSO-d_6 at 298K

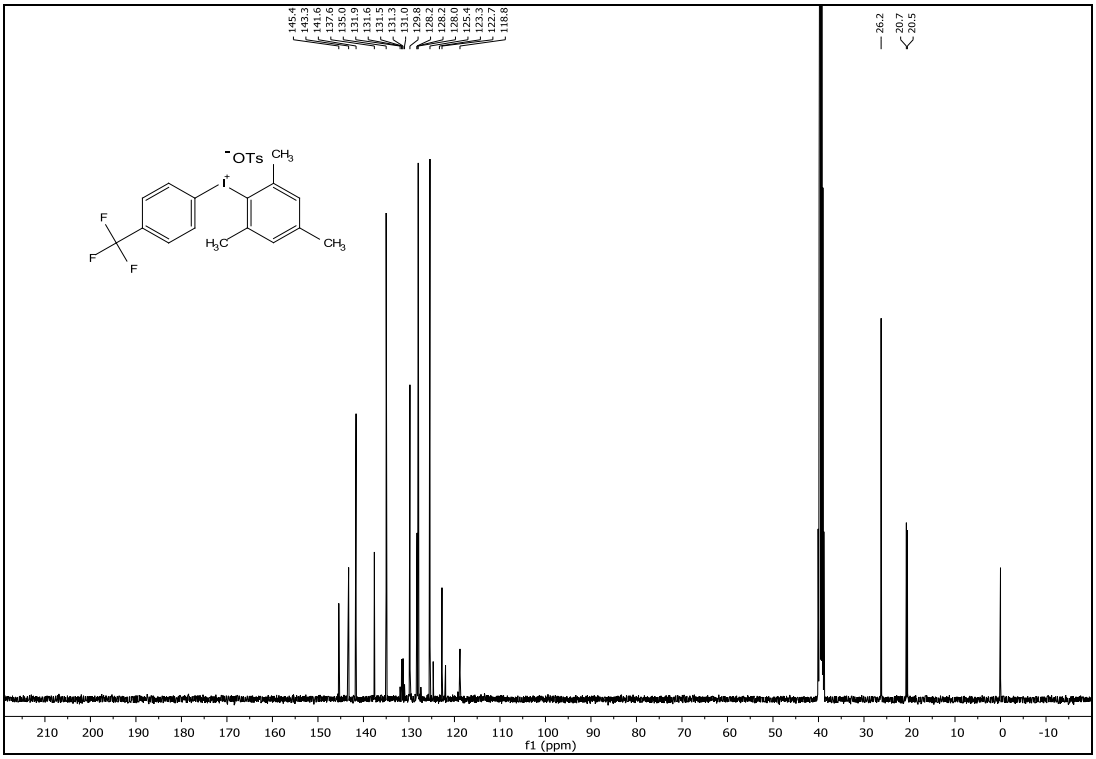


Figure 5.175: ^{19}F NMR of 2.8 at 377 MHz in DMSO-d_6 at 298K

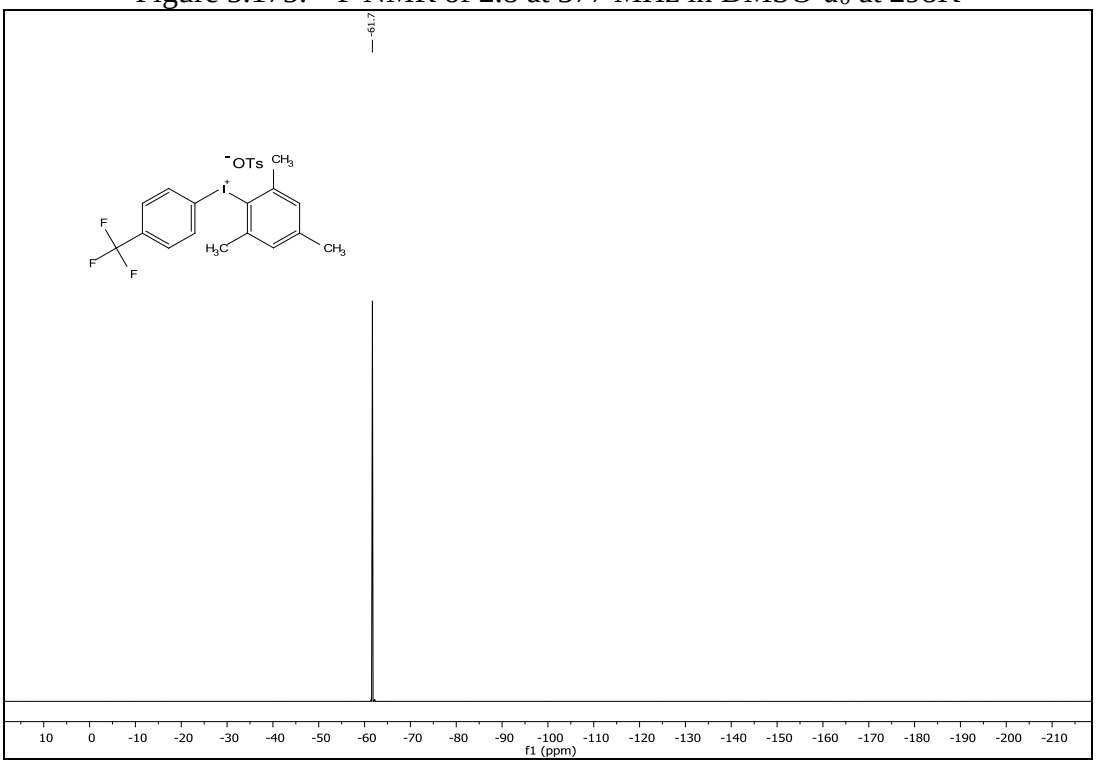


Figure 5.176: ^{1}H NMR of 2.9 at 400 MHz in DMSO-d_6 at 298K

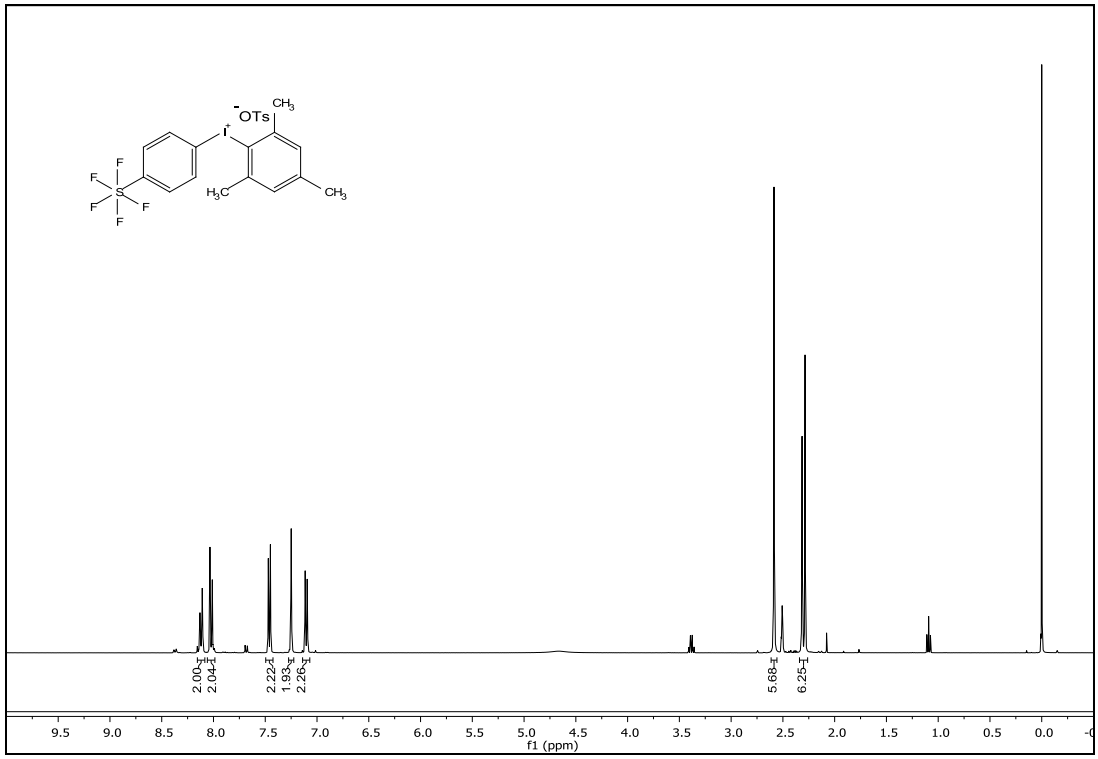


Figure 5.177: ^{13}C NMR of 2.9 at 101 MHz in DMSO-d_6 at 298K

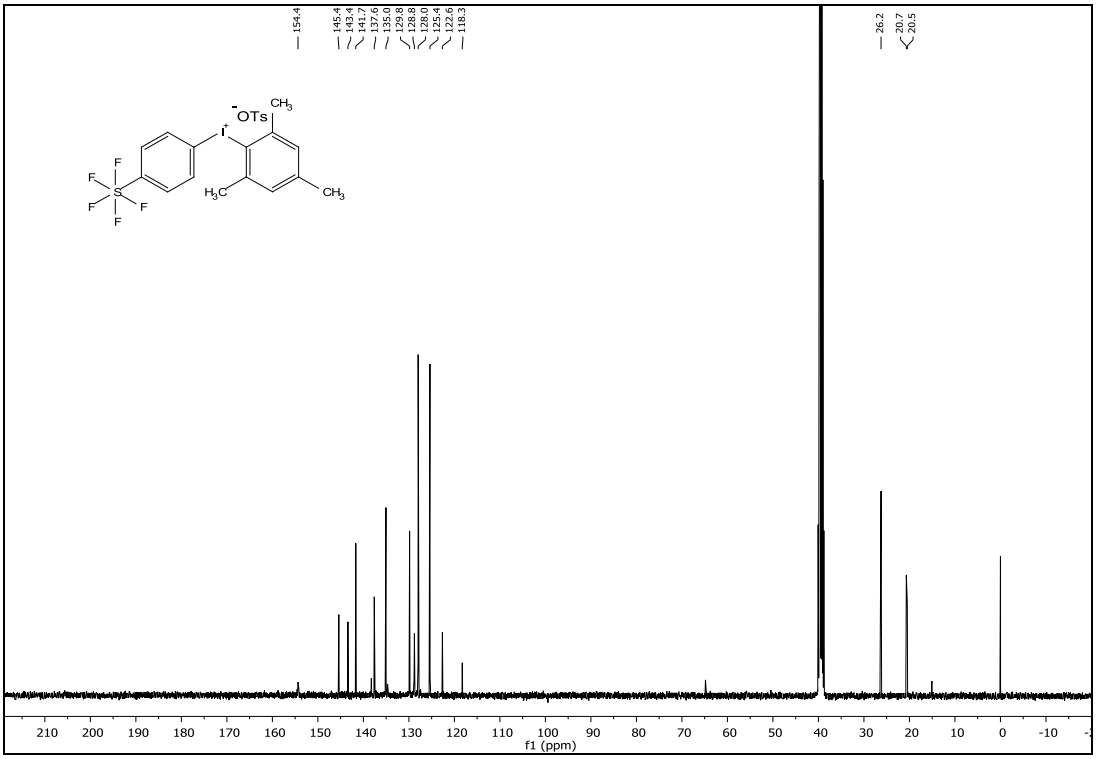


Figure 5.178: ^{19}F NMR of 2.9 at 377 MHz in DMSO-d_6 at 298K

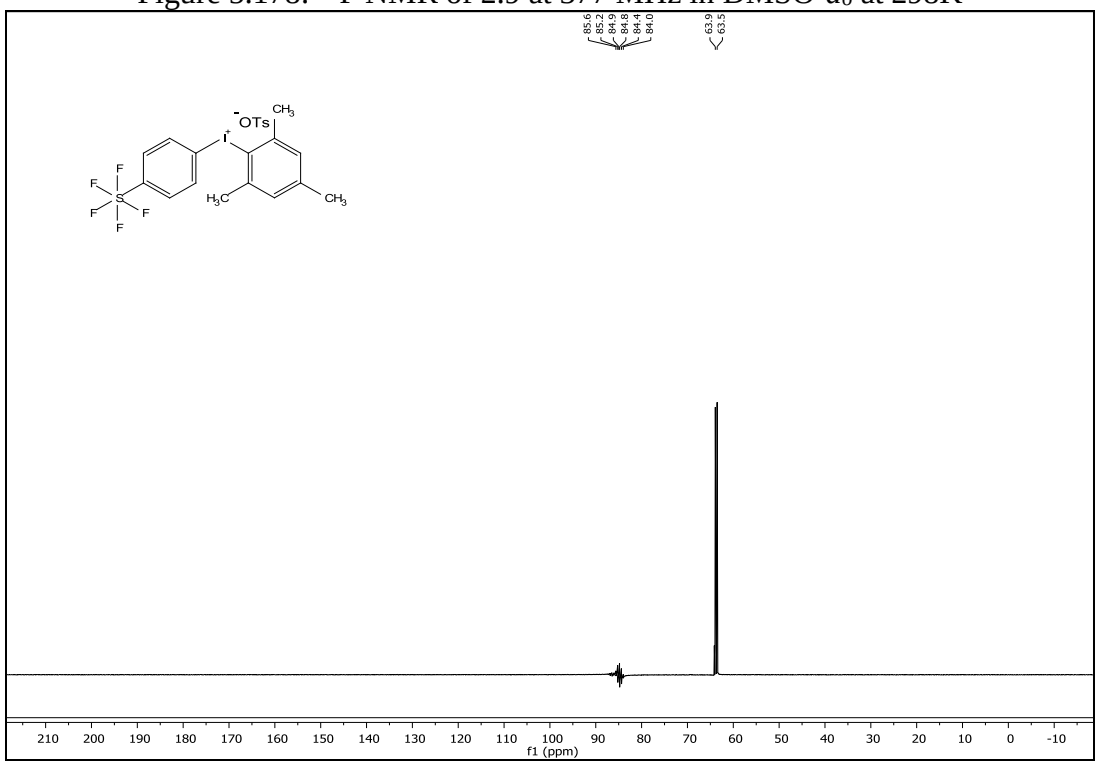


Figure 5.179: ^{1}H NMR of 2.10 at 400 MHz in DMSO-d_6 at 298K

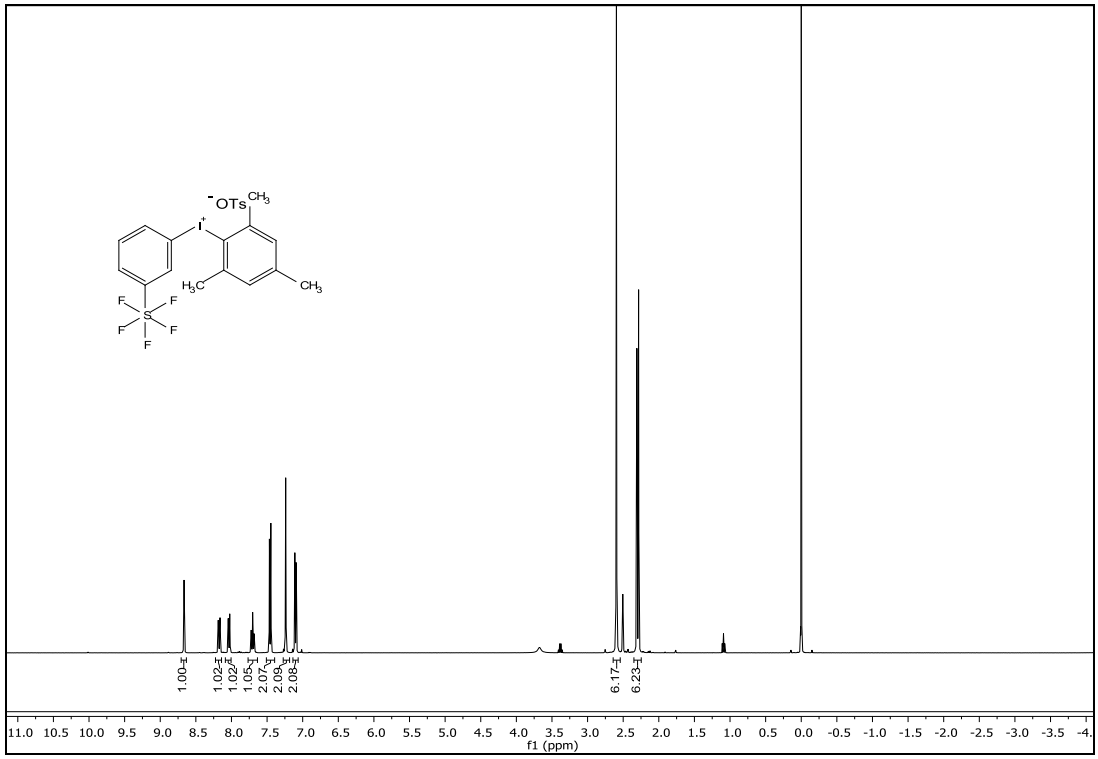


Figure 5.180: ^{13}C NMR of 2.10 at 101 MHz in DMSO-d_6 at 298K

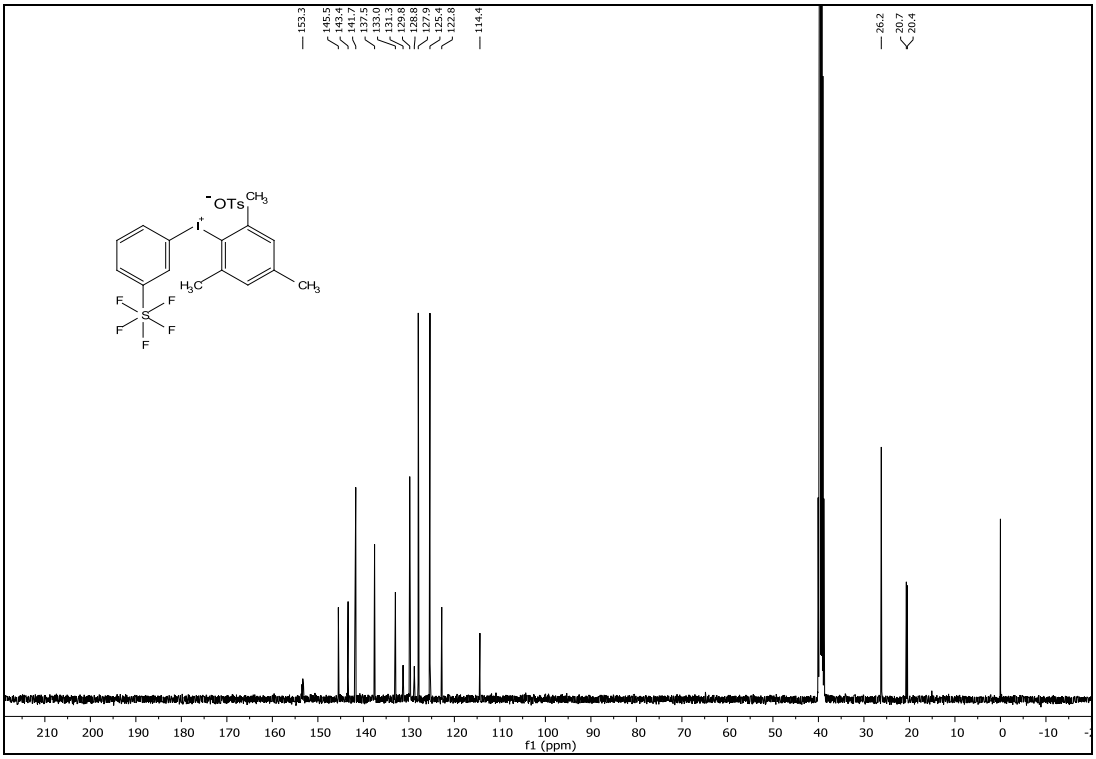


Figure 5.181: ^{19}F NMR of 2.10 at 377 MHz in DMSO-d_6 at 298K

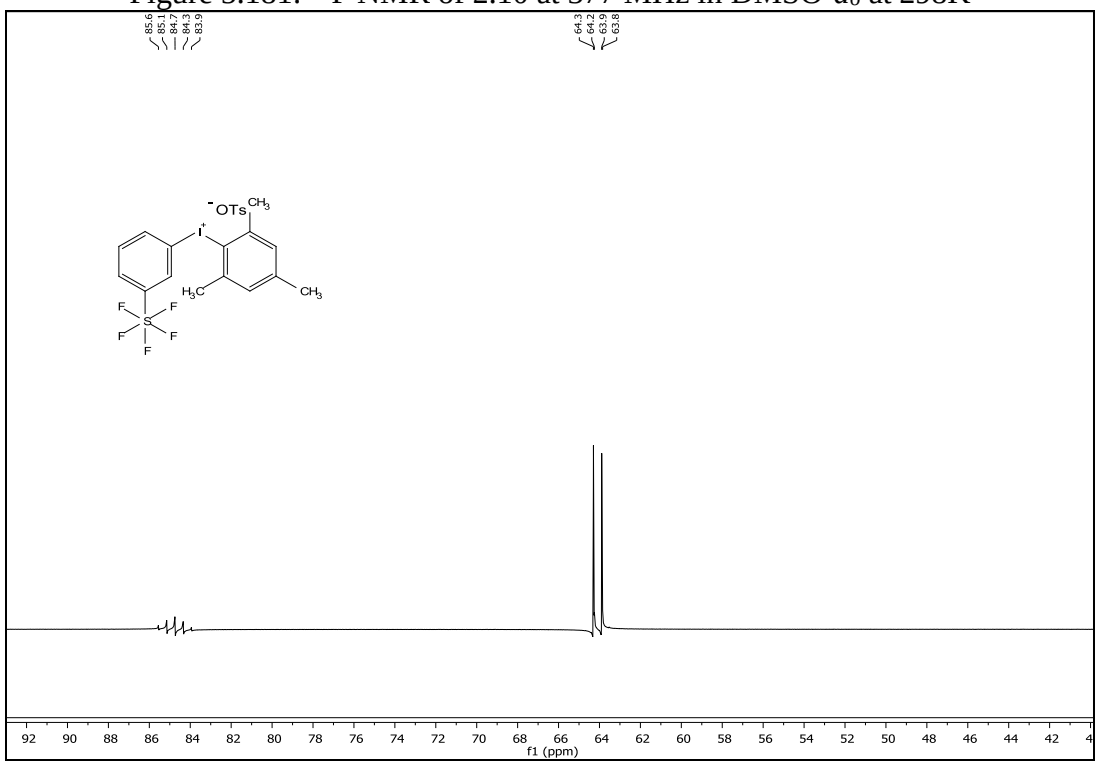


Figure 5.182: ^{1}H NMR of 2.11 at 400 MHz in DMSO-d_6 at 298K

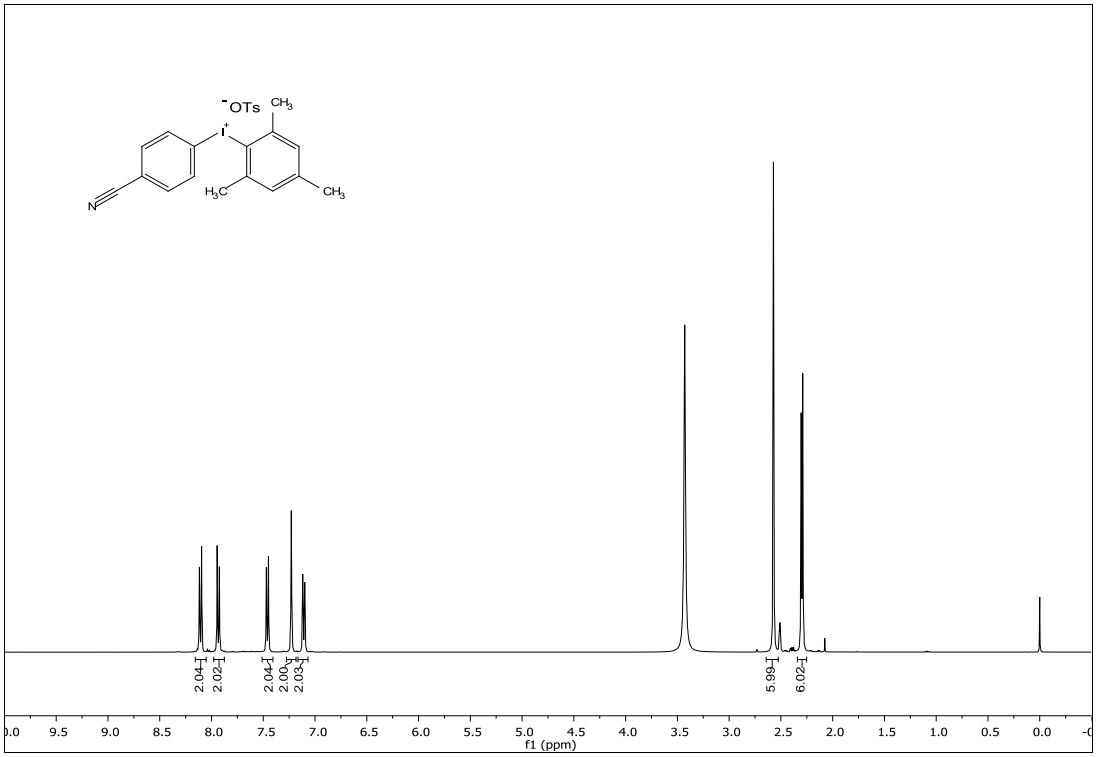


Figure 5.183: ^{13}C NMR of 2.11 at 101 MHz in DMSO-d_6 at 298K

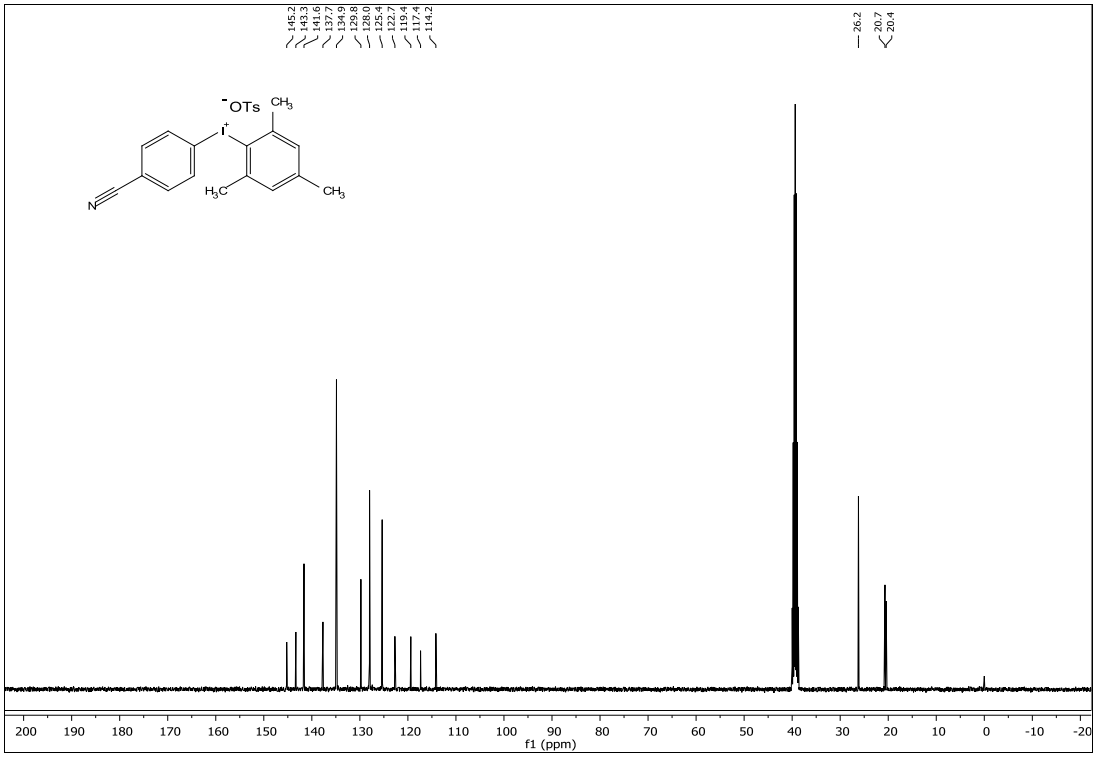


Figure 5.184: ^{1}H NMR of 2.12 at 400 MHz in DMSO-d_6 at 298K

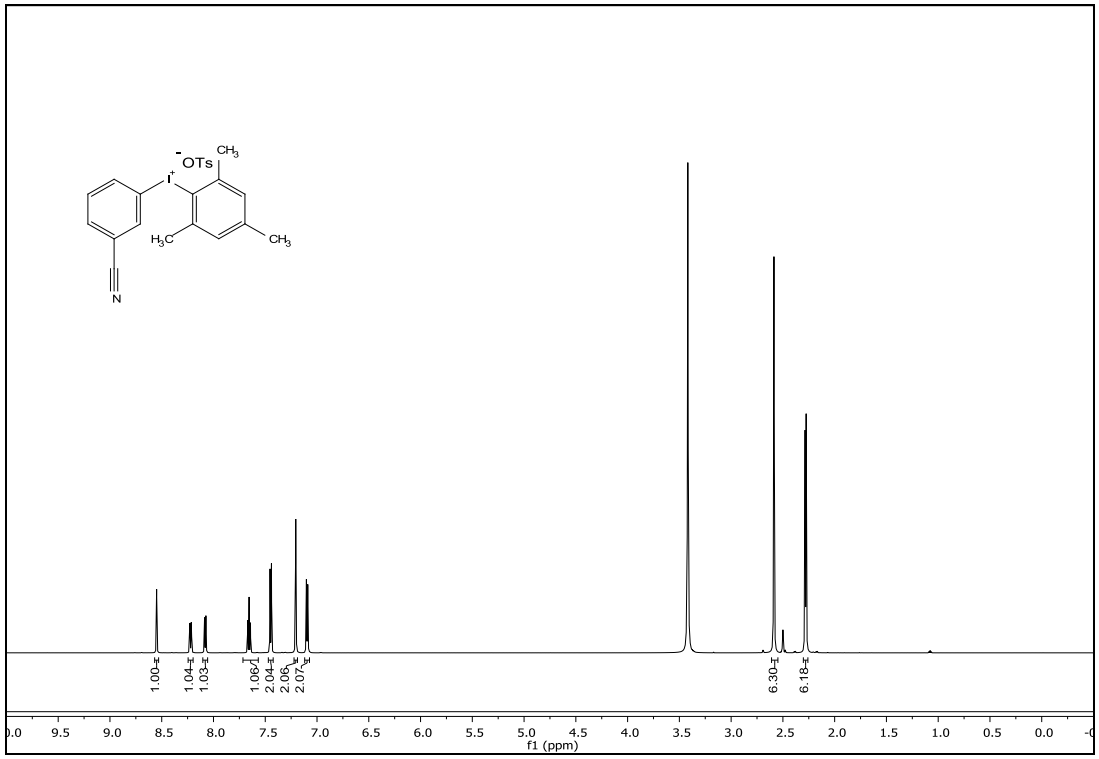


Figure 5.185: ^{13}C NMR of 2.12 at 101 MHz in DMSO-d_6 at 298K

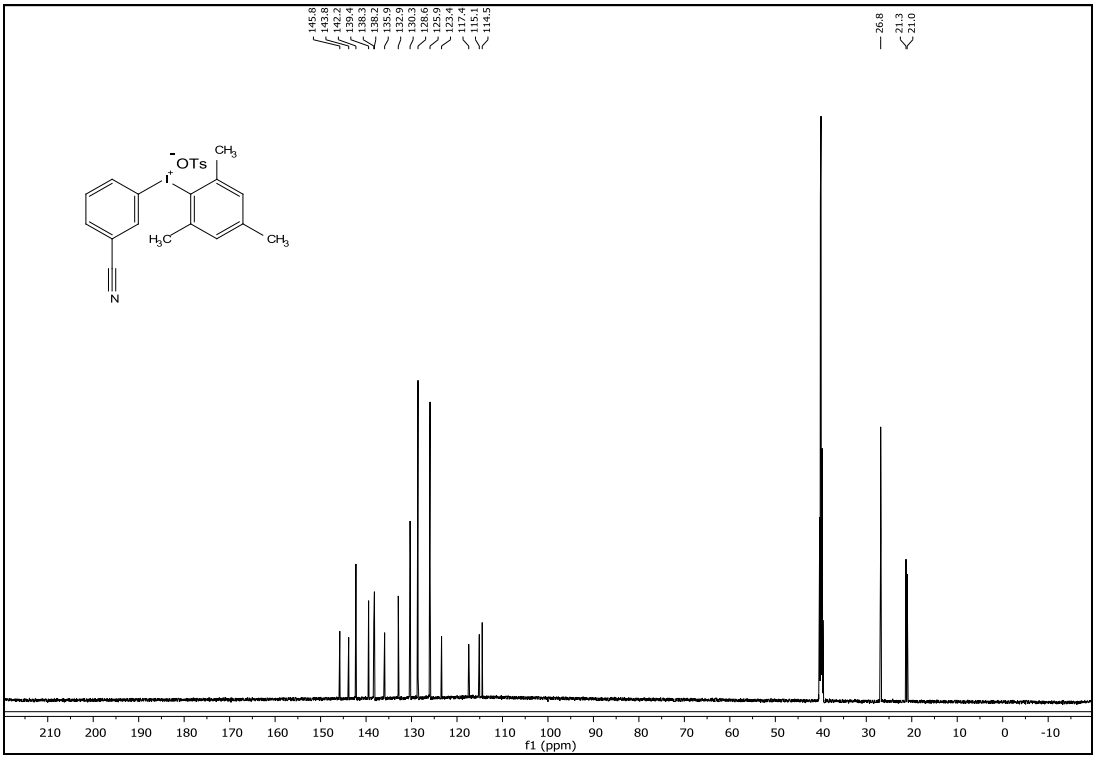


Figure 5.186: ^{1}H NMR of 2.13 at 400 MHz in DMSO-d_6 at 298K

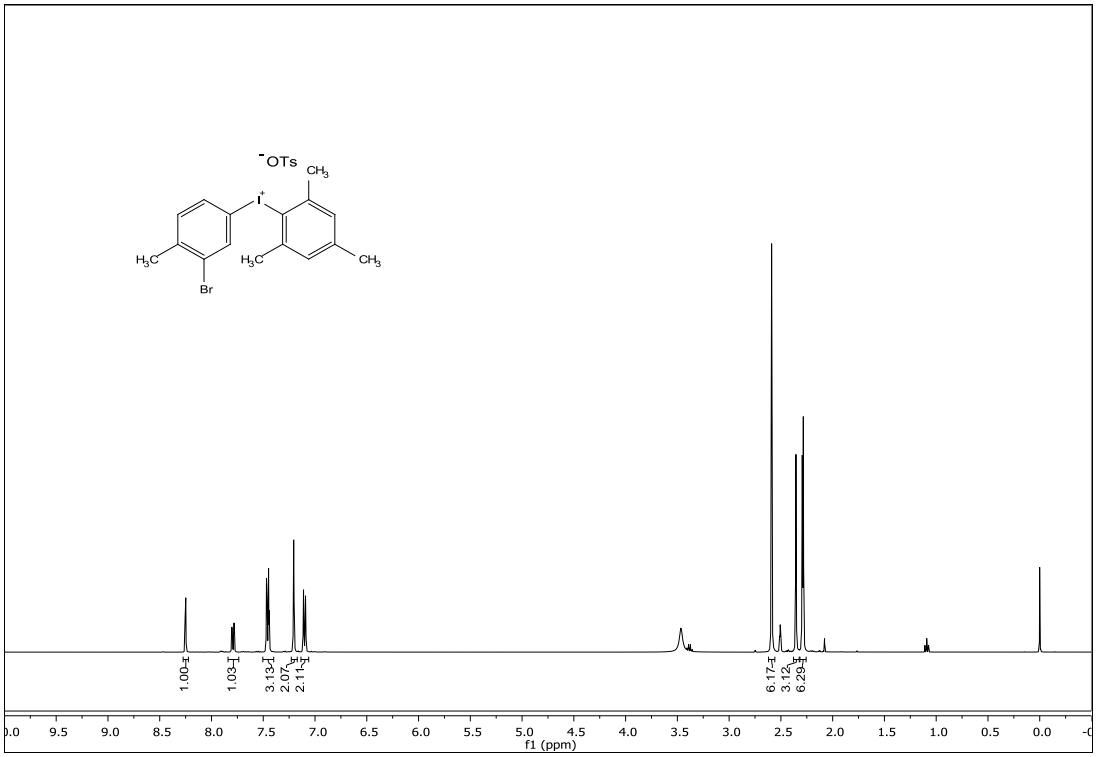


Figure 5.187: ^{13}C NMR of 2.13 at 101 MHz in DMSO-d_6 at 298K

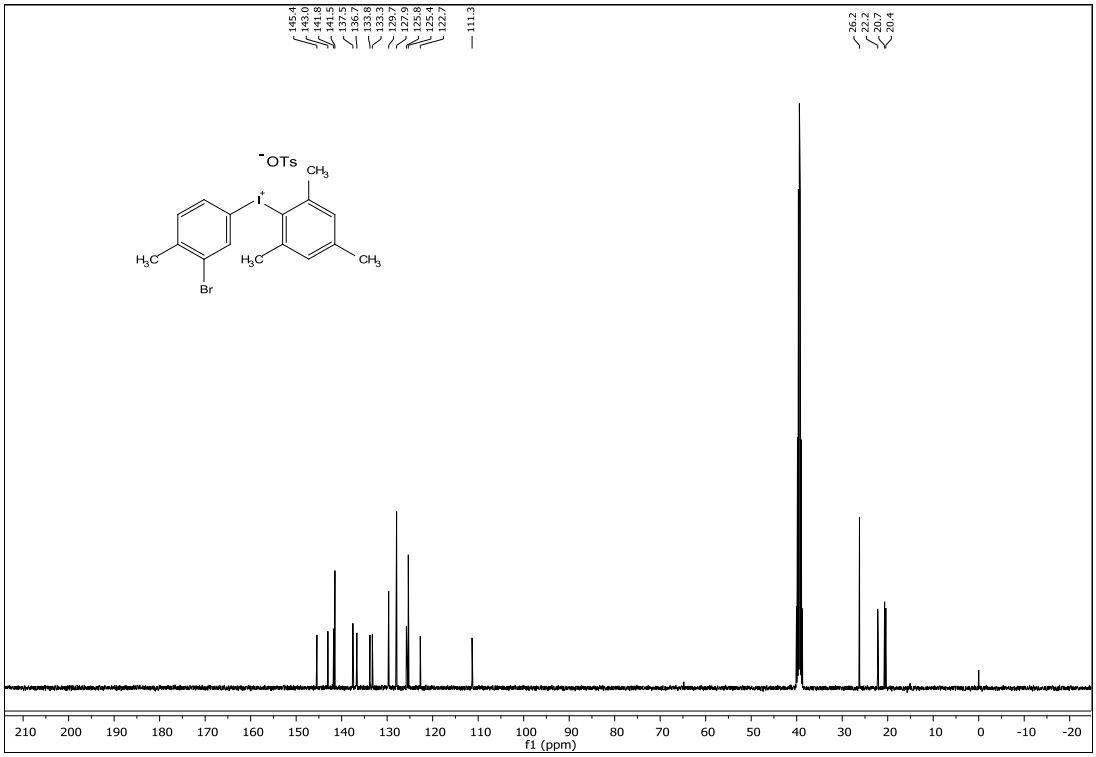


Figure 5.188: ^{1}H NMR of 2.14 at 400 MHz in DMSO-d_6 at 298K

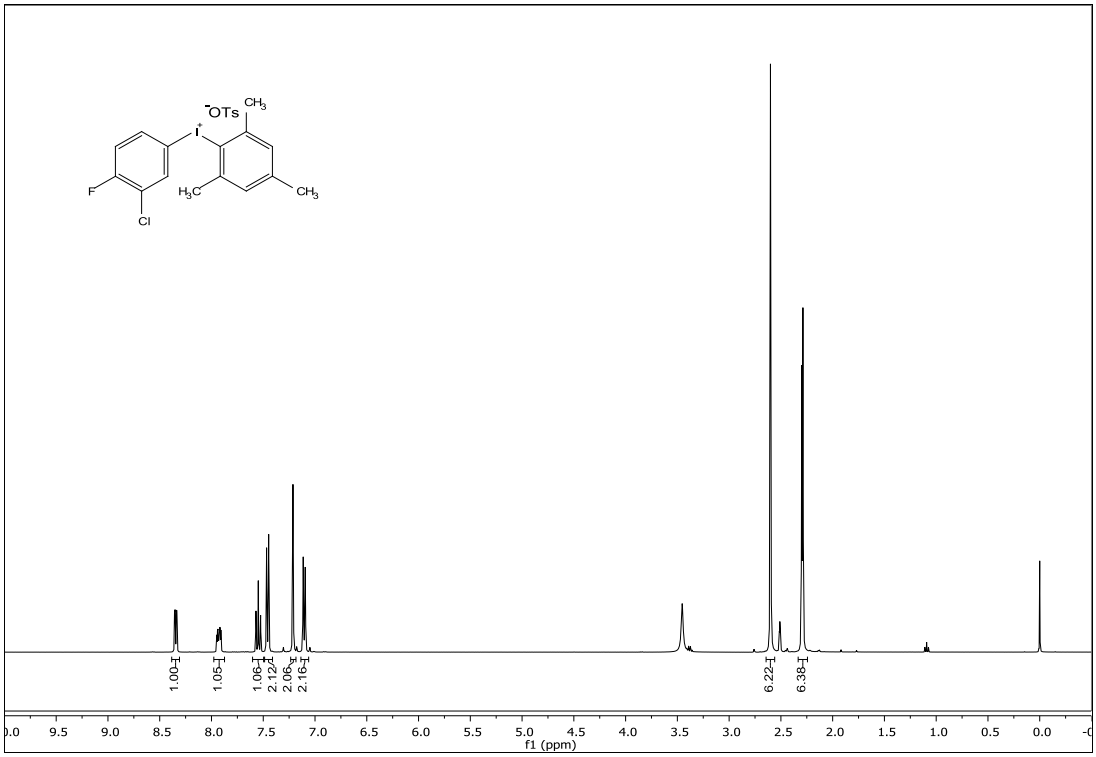


Figure 5.189: ^{13}C NMR of 2.14 at 101 MHz in DMSO-d_6 at 298K

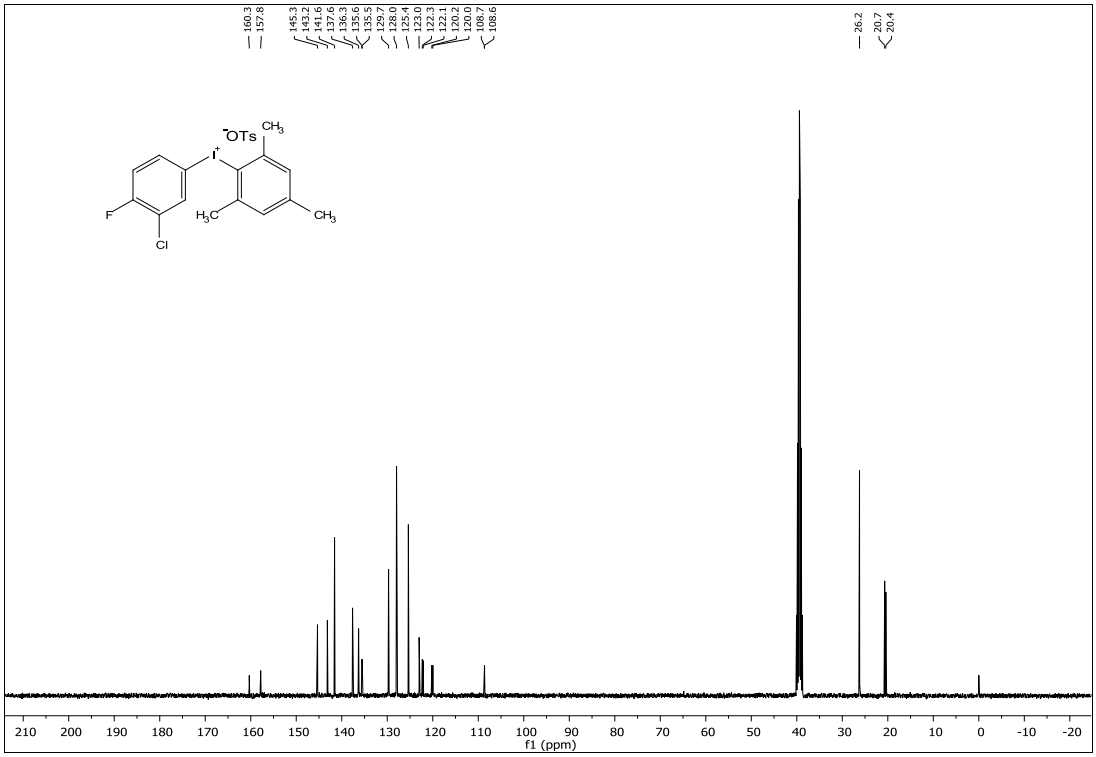


Figure 5.190: ^{19}F NMR of 2.14 at 377 MHz in DMSO-d_6 at 298K

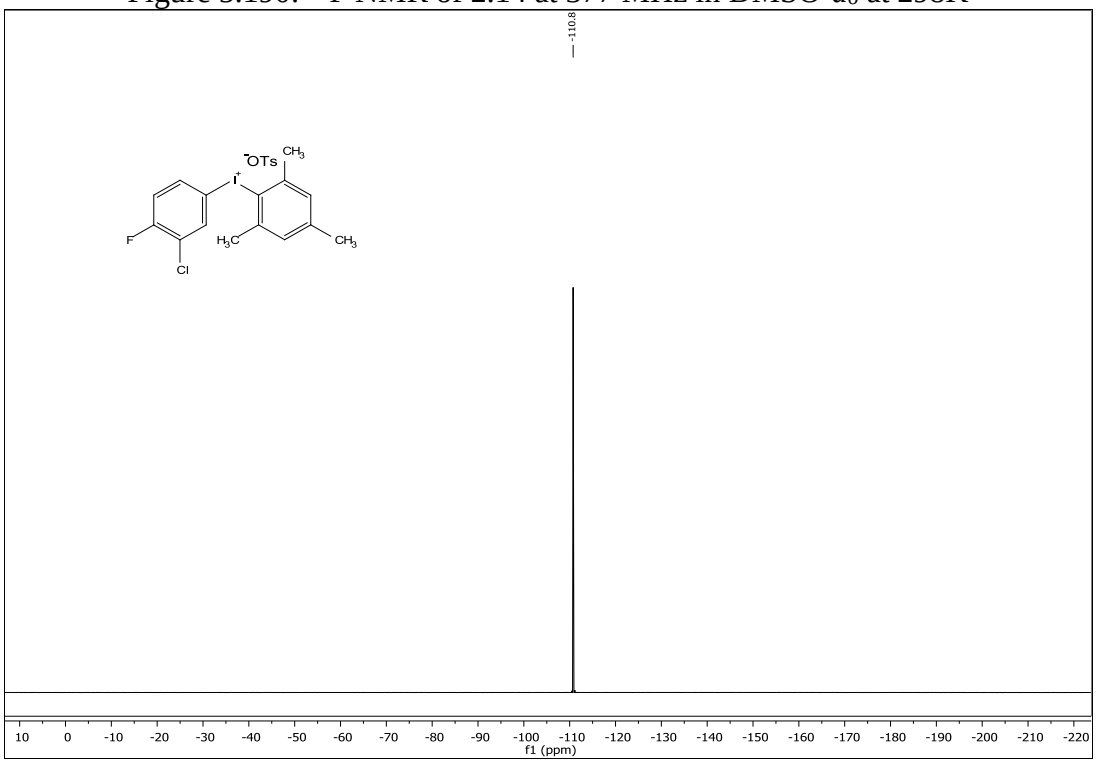


Figure 5.191: ^{1}H NMR of 2.15 at 400 MHz in DMSO-d_6 at 298K

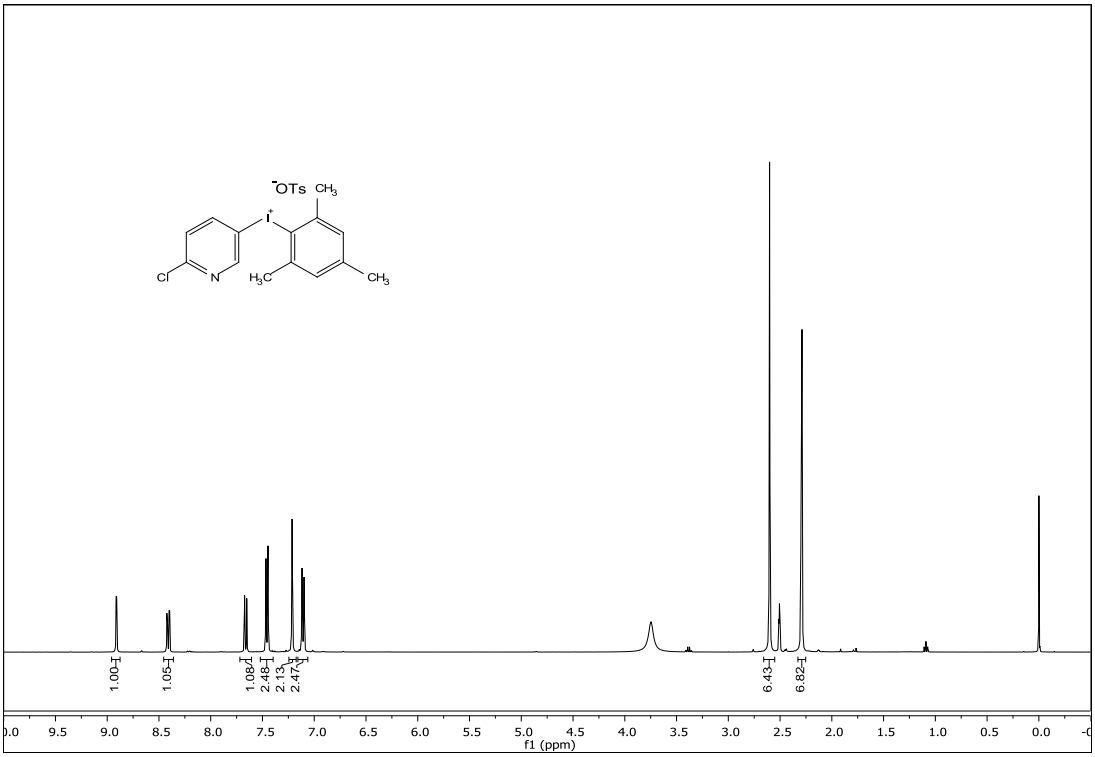


Figure 5.192: ^{13}C NMR of 2.15 at 101 MHz in DMSO-d_6 at 298K

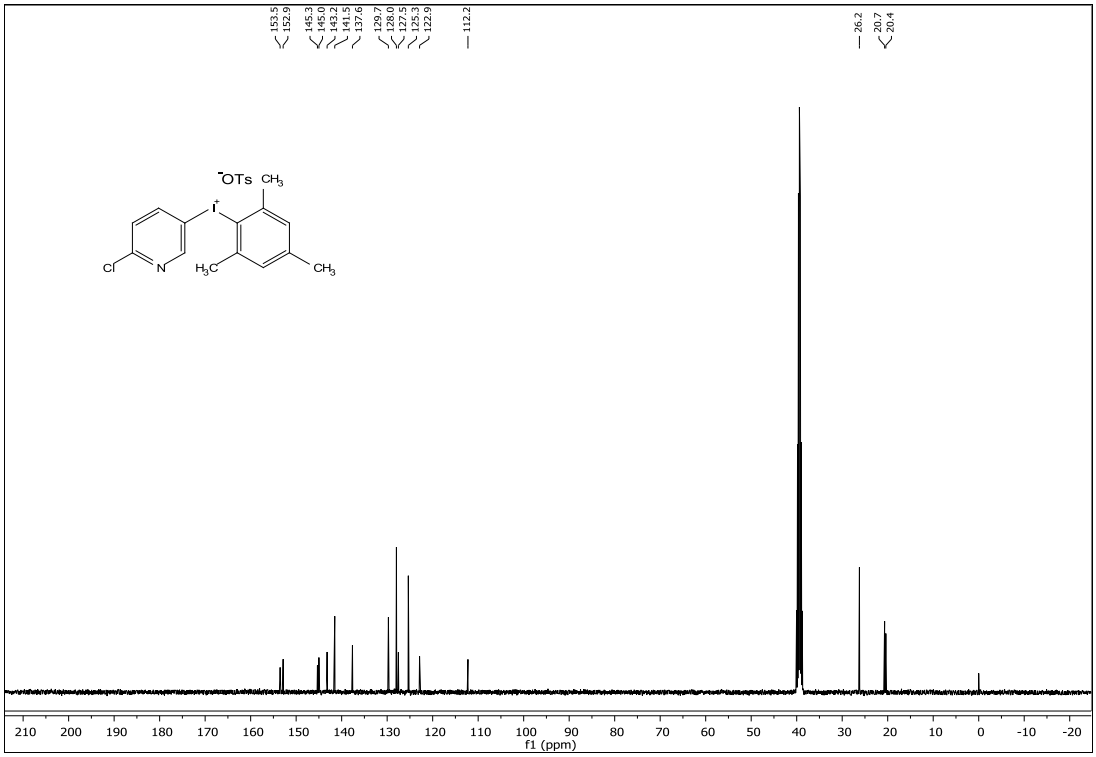


Figure 5.193: ^{1}H NMR of 2.16 at 400 MHz in DMSO-d_6 at 298K

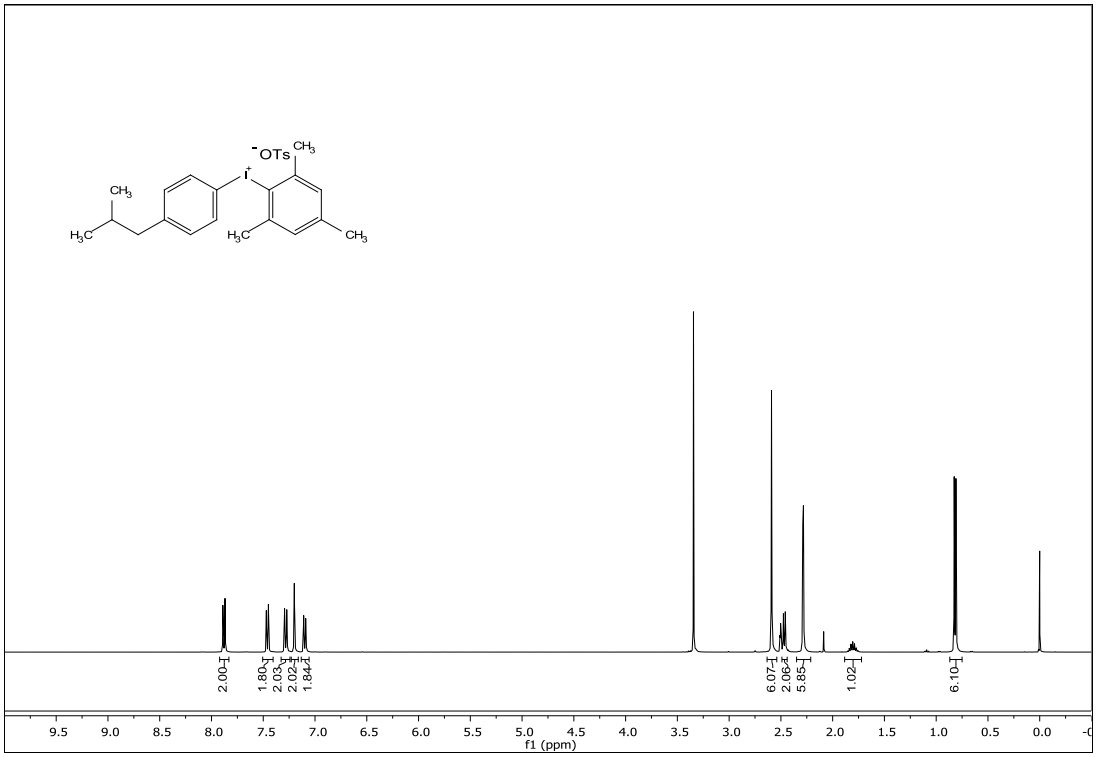


Figure 5.194: ^{13}C NMR of 2.16 at 101 MHz in DMSO-d_6 at 298K

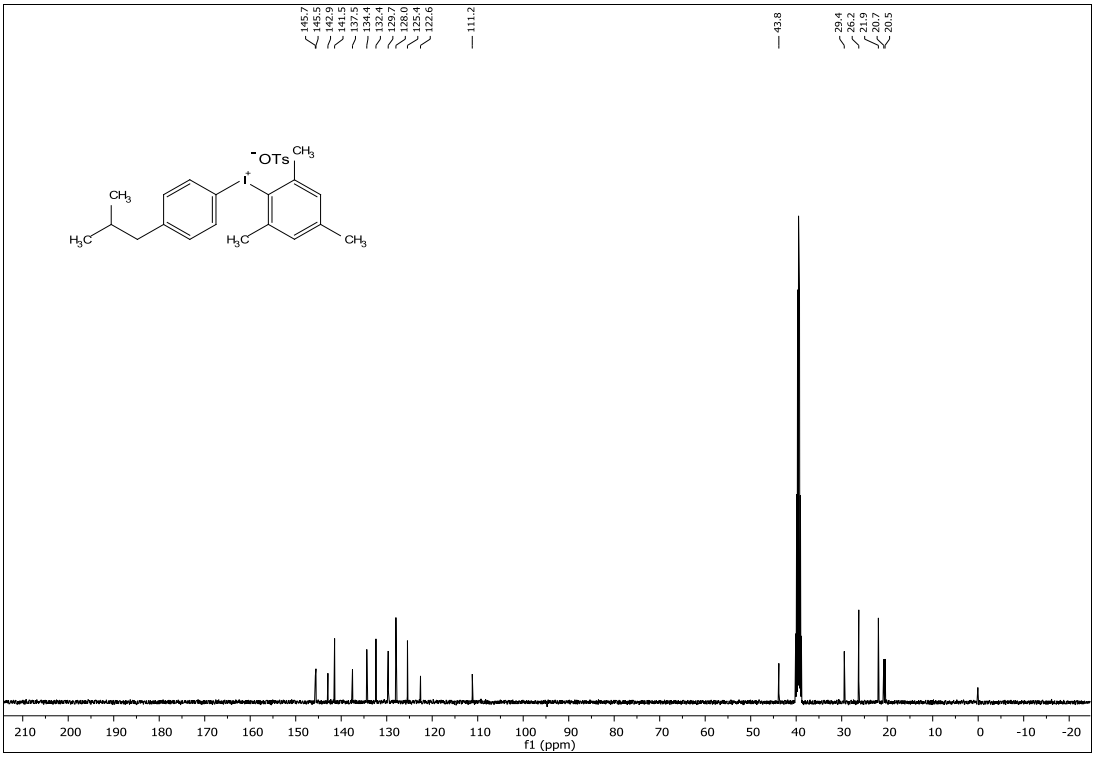


Figure 5.195: ^{1}H NMR of 2.17 at 400 MHz in DMSO-d_6 at 298K

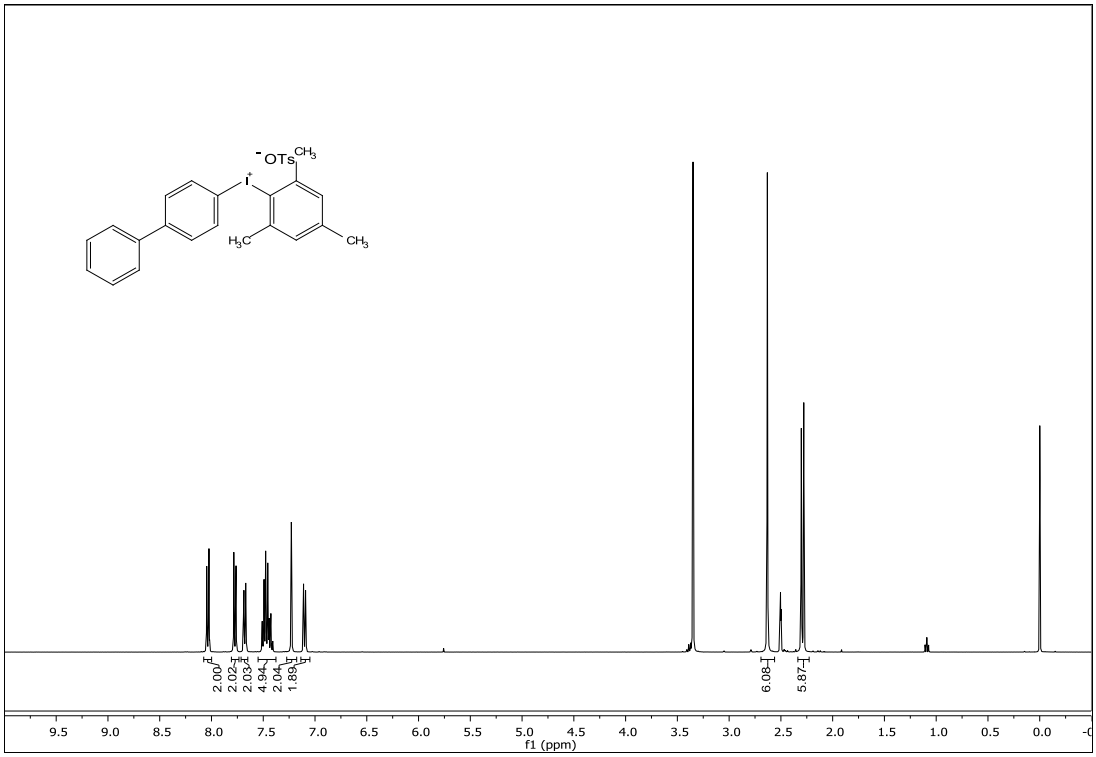


Figure 5.196: ^{13}C NMR of 2.17 at 101 MHz in DMSO-d_6 at 298K

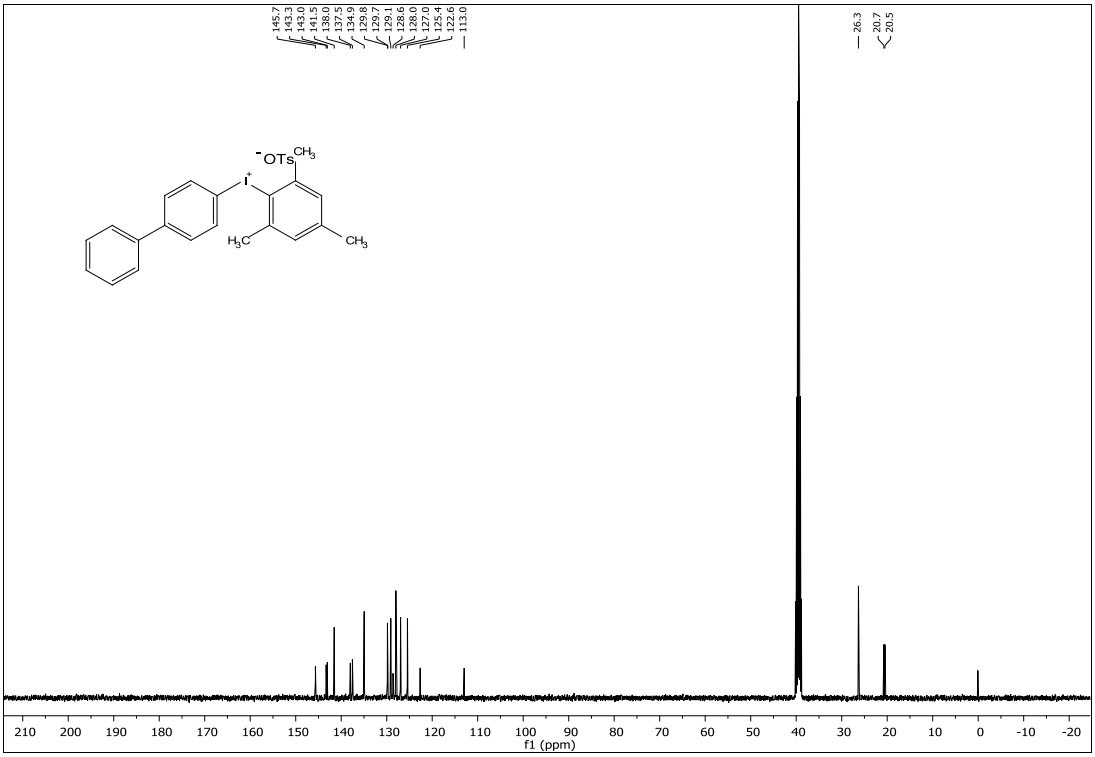


Figure 5.197: ^{1}H NMR of 2.18 at 400 MHz in DMSO-d_6 at 298K

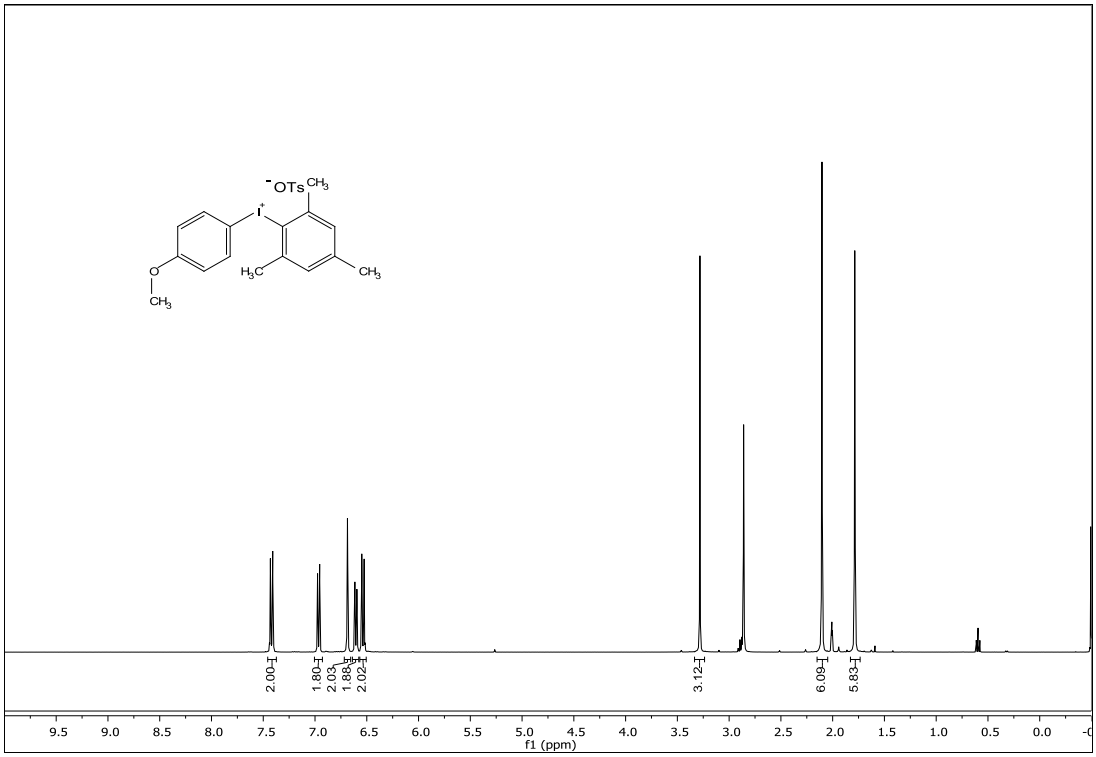


Figure 5.198: ^{13}C NMR of 2.18 at 101 MHz in DMSO-d_6 at 298K

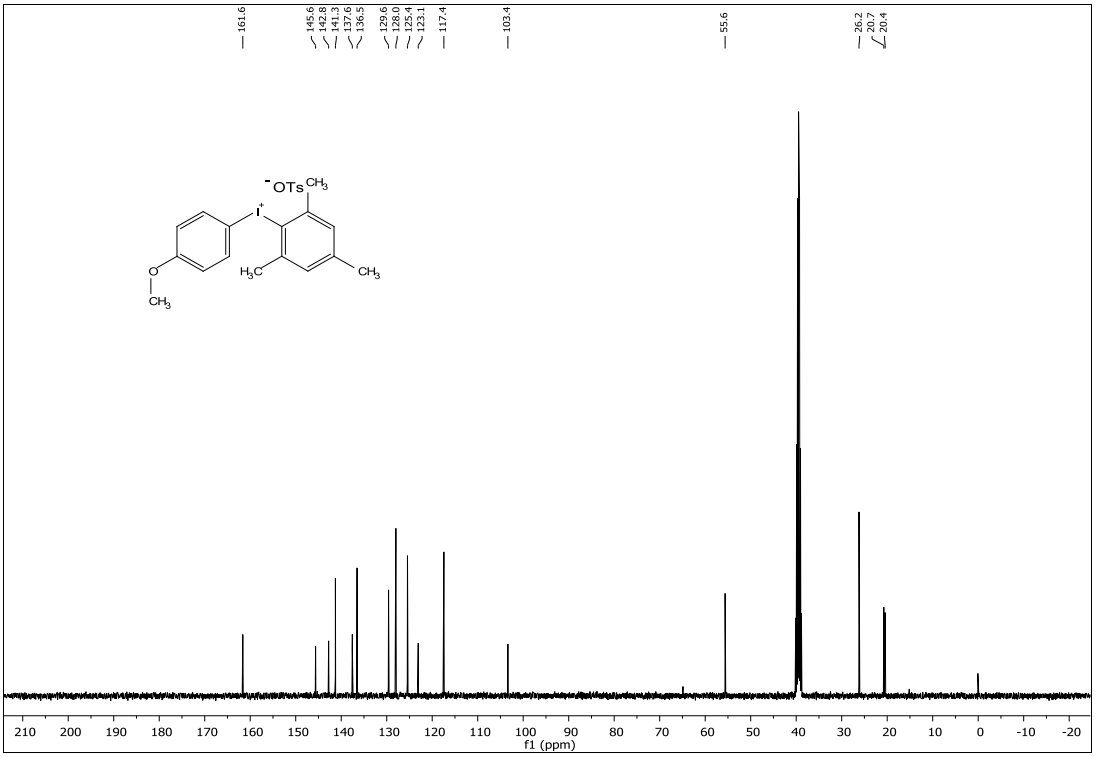


Figure 5.199: ^{1}H NMR of 2.19 at 400 MHz in DMSO-d_6 at 298K

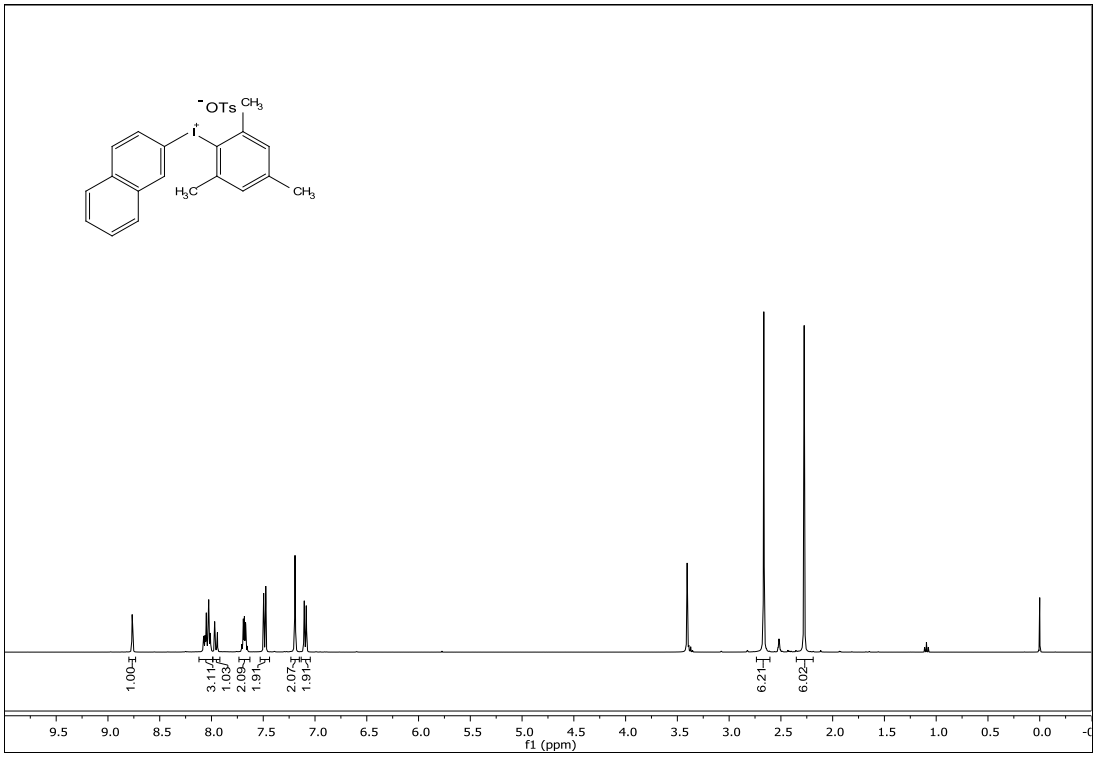


Figure 5.201: ^{13}C NMR of 2.19 at 101 MHz in DMSO-d_6 at 298K

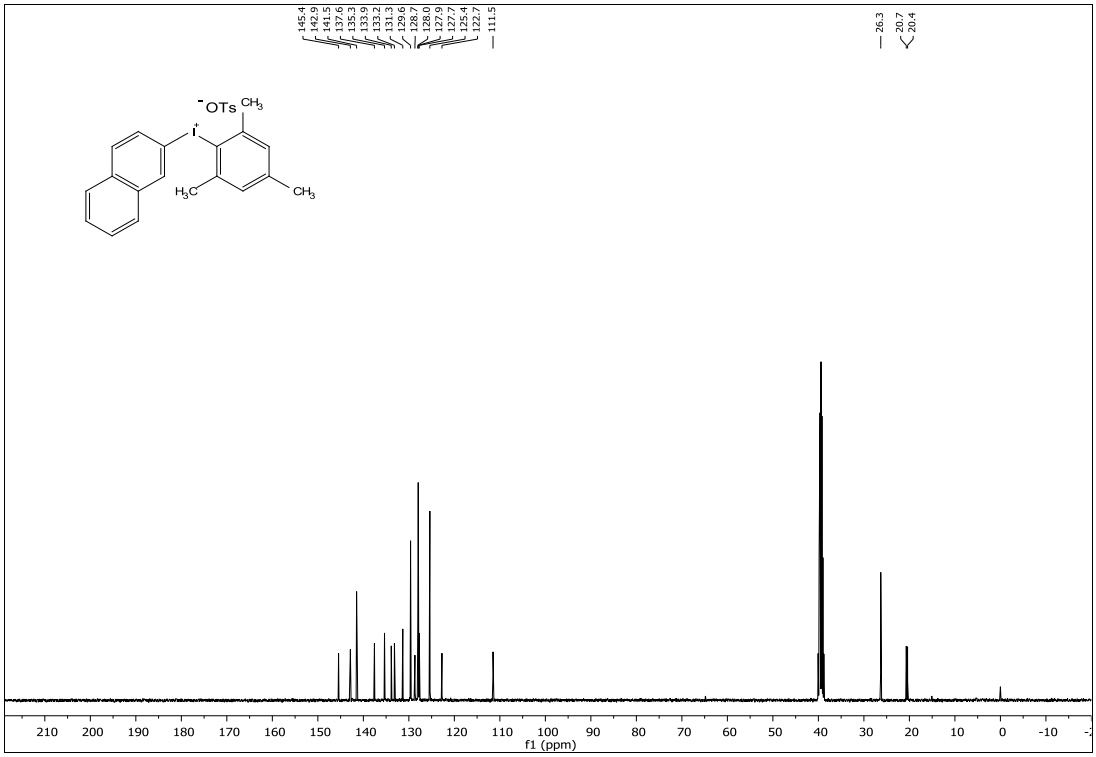


Figure 5.201: ^{1}H NMR of 2.20 at 400 MHz in DMSO-d_6 at 298K

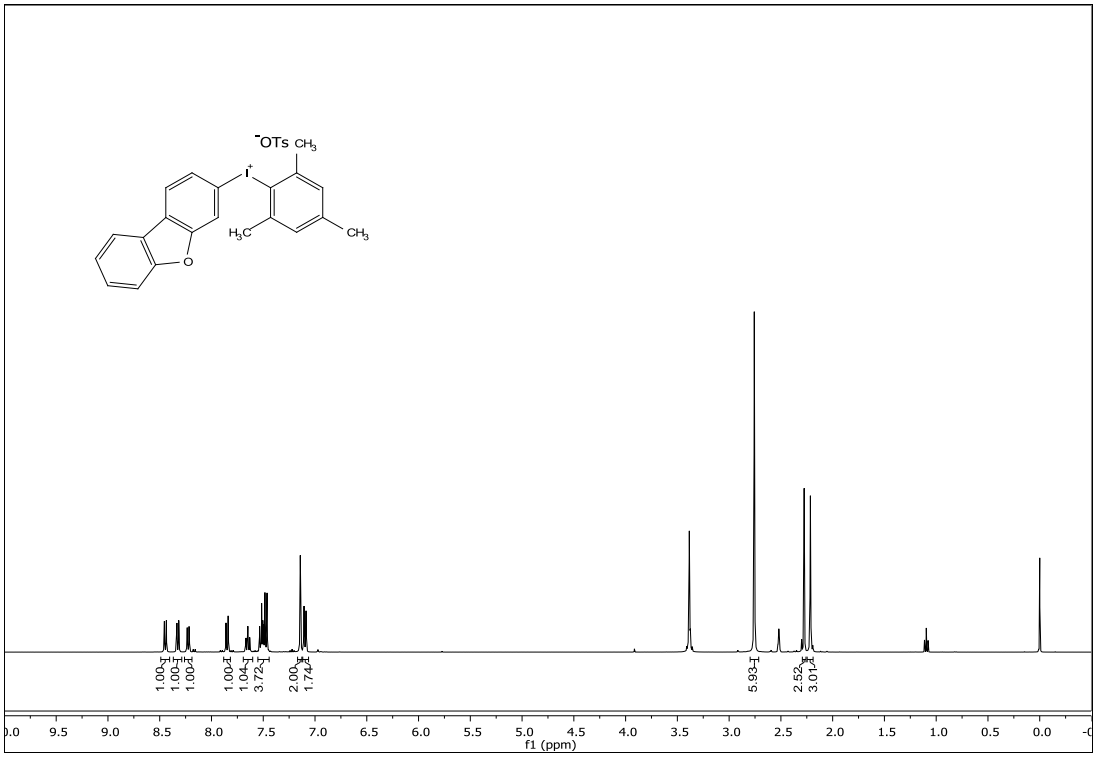


Figure 5.202: ^{13}C NMR of 2.20 at 101 MHz in DMSO-d_6 at 298K

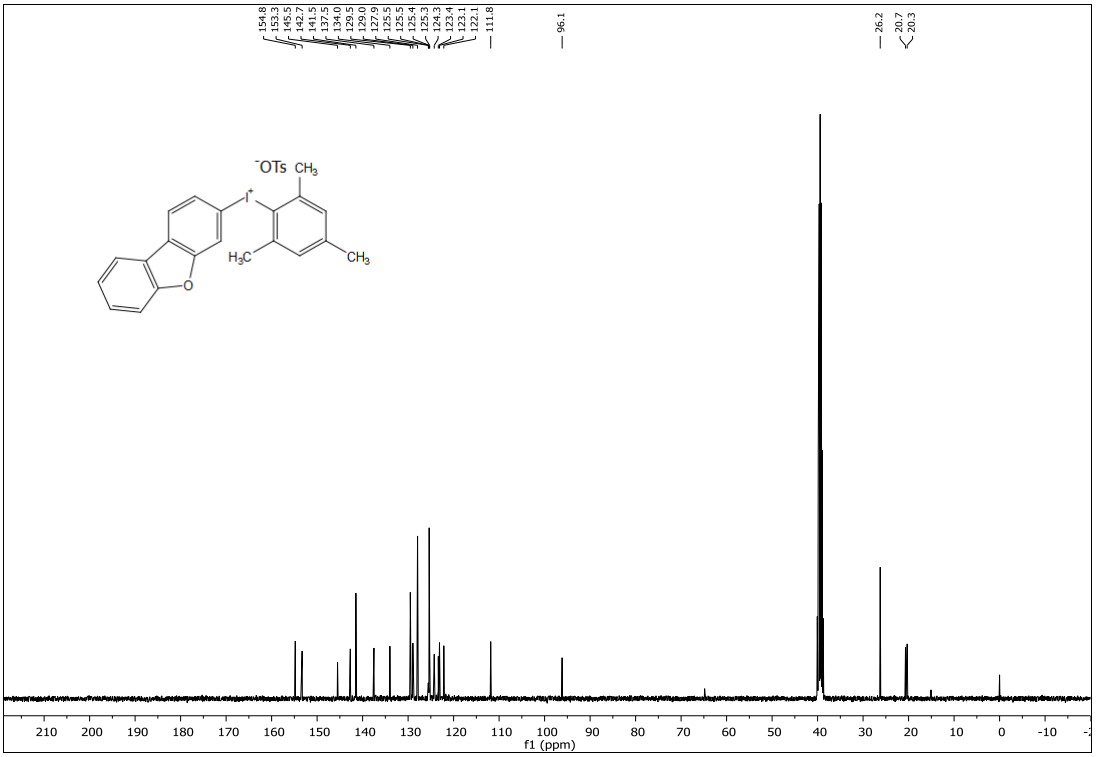


Figure 5.203: ^{1}H NMR of 2.21 at 400 MHz in DMSO-d_6 at 298K

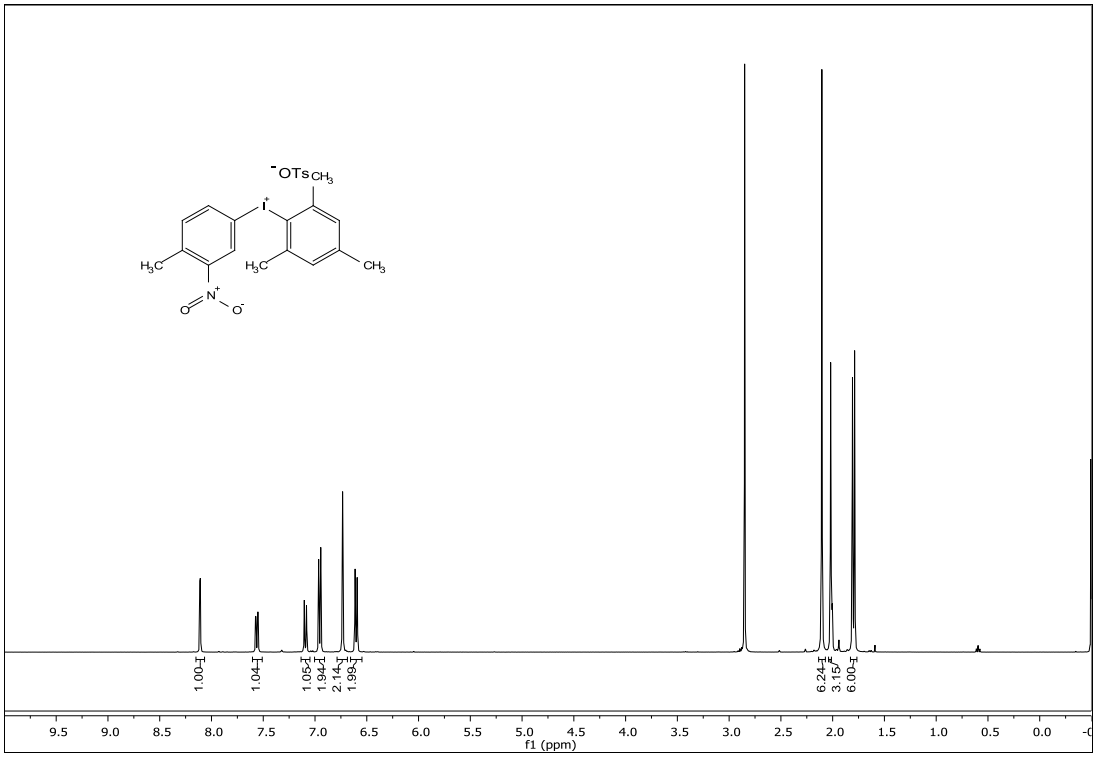


Figure 5.204: ^{13}C NMR of 2.21 at 101 MHz in DMSO-d_6 at 298K

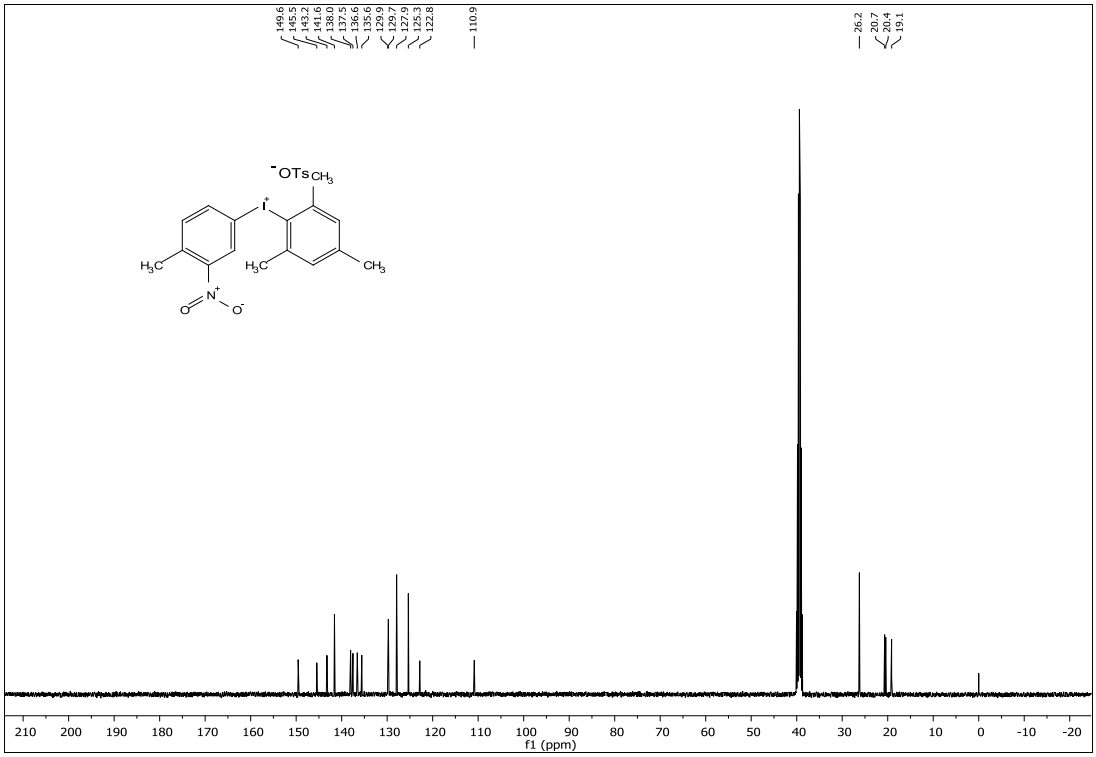


Figure 5.205: ^{1}H NMR of 2.22 at 400 MHz in DMSO-d_6 at 298K

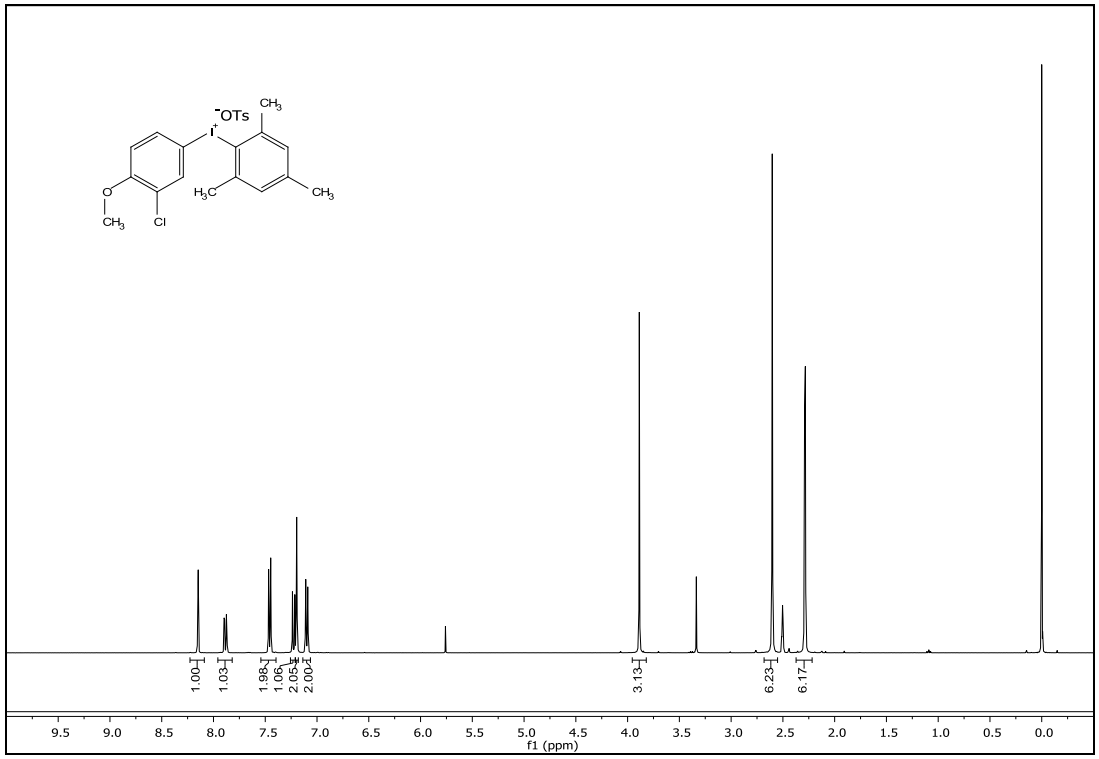


Figure 5.206: ^{13}C NMR of 2.22 at 101 MHz in DMSO-d_6 at 298K

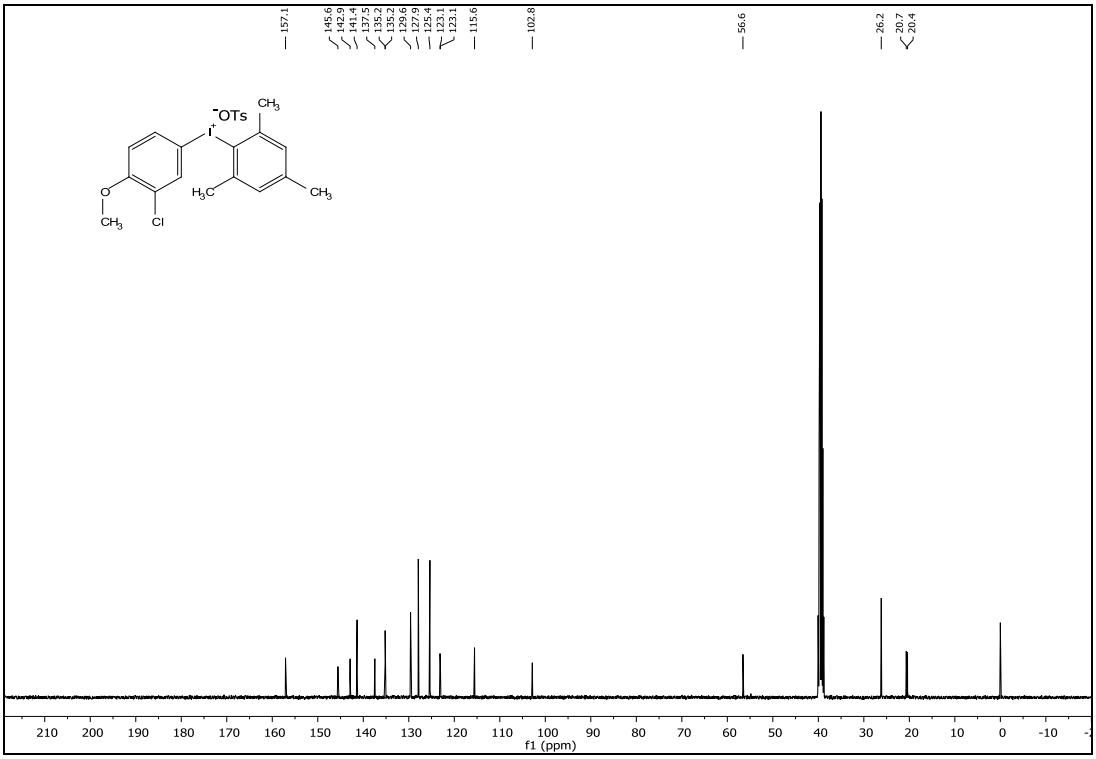


Figure 5.207: ^{1}H NMR of 2.23 at 400 MHz in DMSO-d_6 at 298K

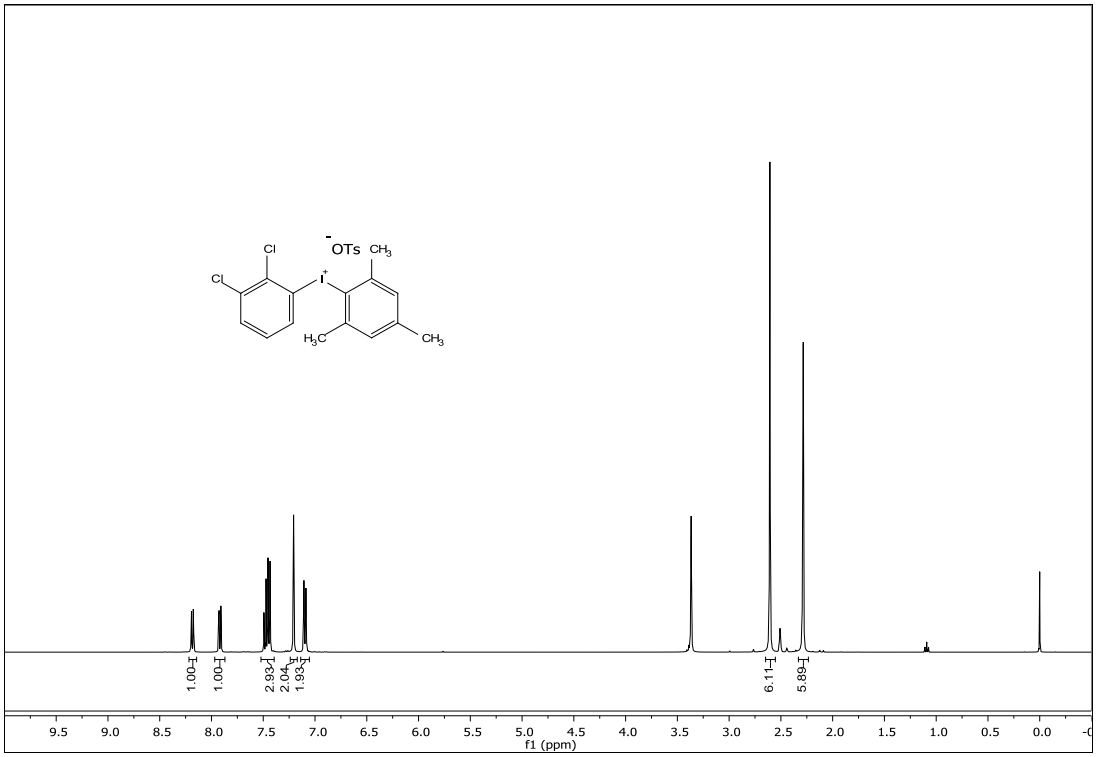


Figure 5.208: ^{13}C NMR of 2.23 at 101 MHz in DMSO-d_6 at 298K

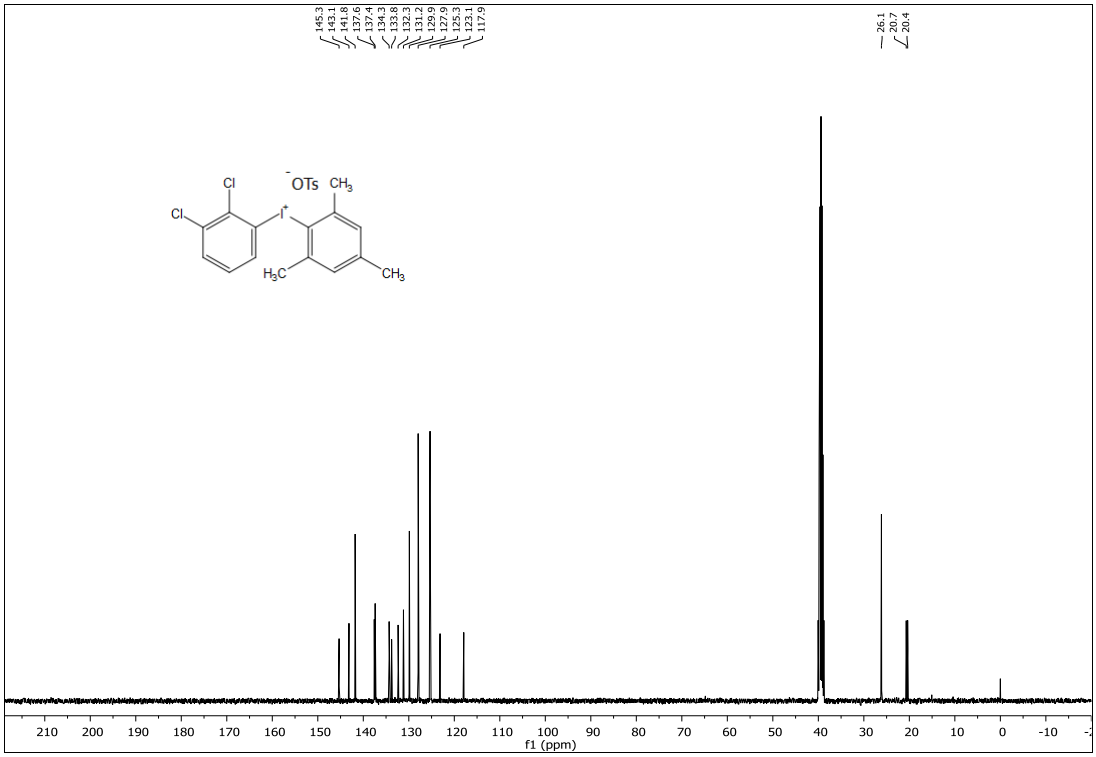


Figure 5.209: ^{1}H NMR of 2.24 at 400 MHz in DMSO-d_6 at 298K

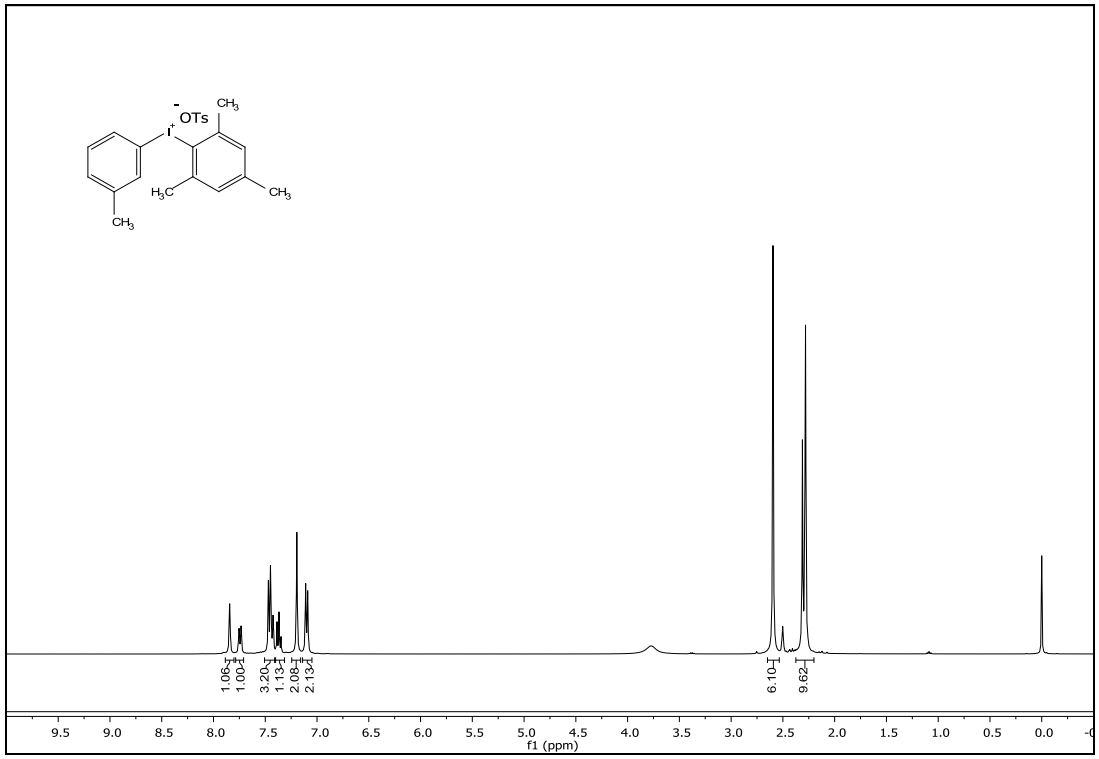


Figure 5.210: ^{13}C NMR of 2.24 at 101 MHz in DMSO-d_6 at 298K

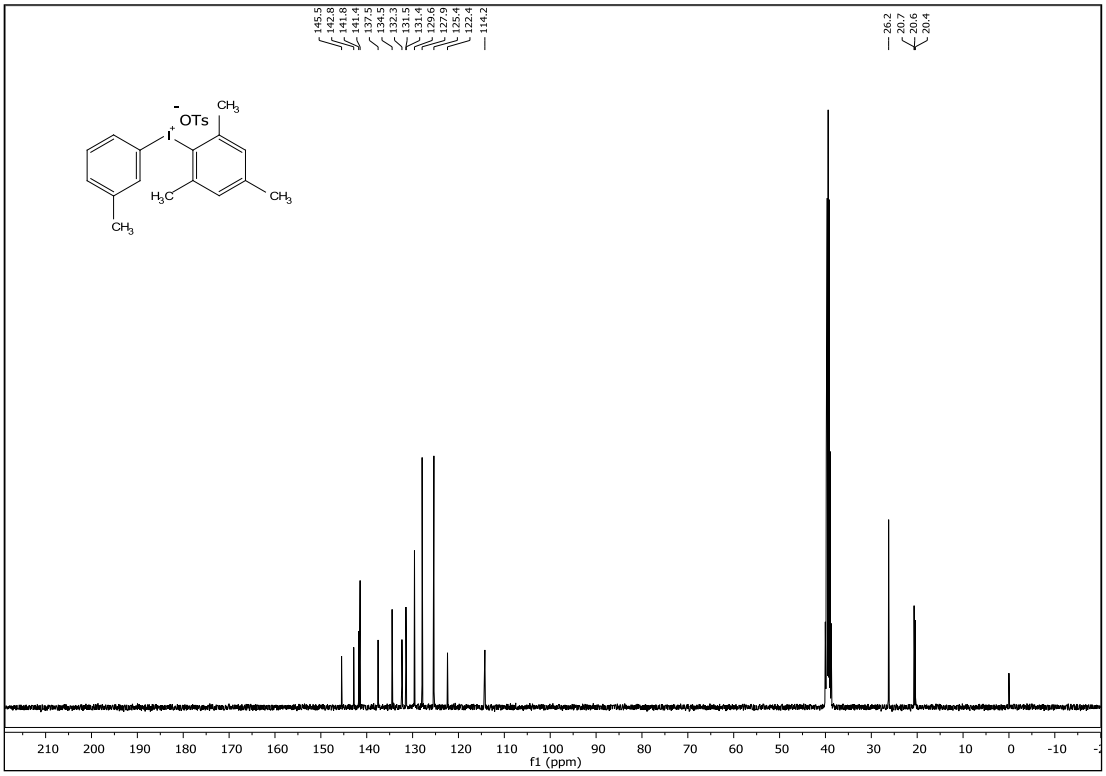


Figure 5.211: ^{1}H NMR of 2.25 at 400 MHz in DMSO-d_6 at 298K

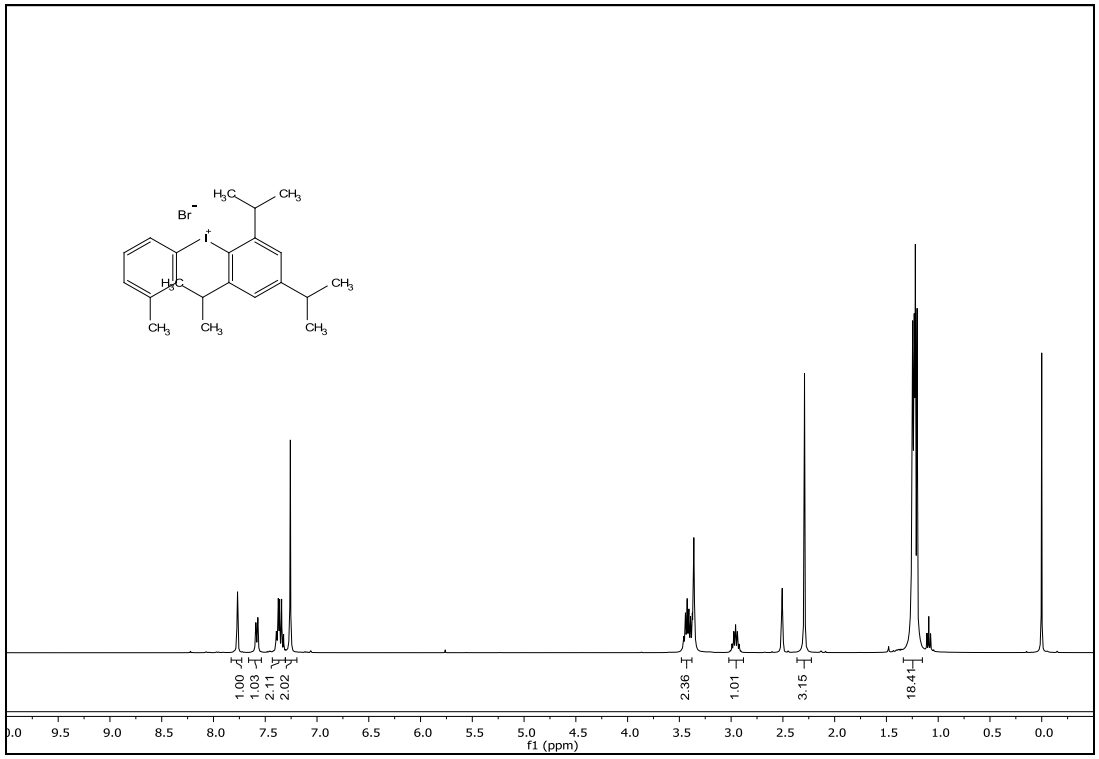


Figure 5.212: ^{13}C NMR of 2.25 at 101 MHz in DMSO-d_6 at 298K

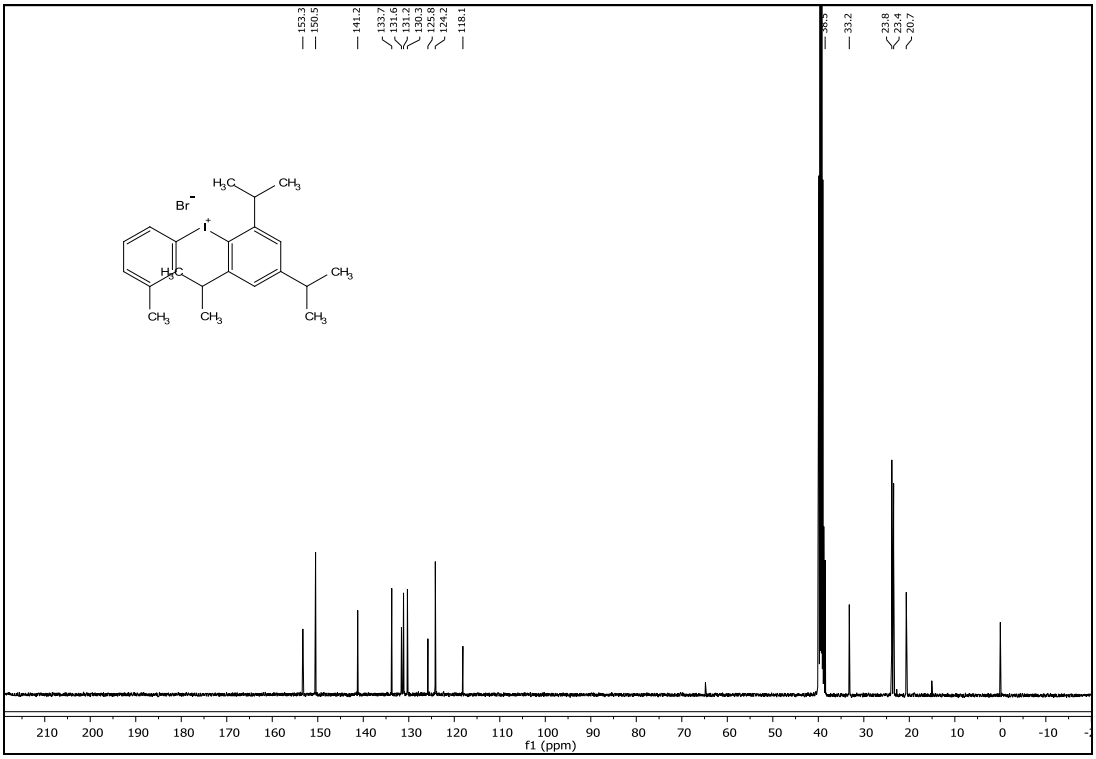


Figure 5.213: ^{1}H NMR of 2.26 at 400 MHz in DMSO-d_6 at 298K

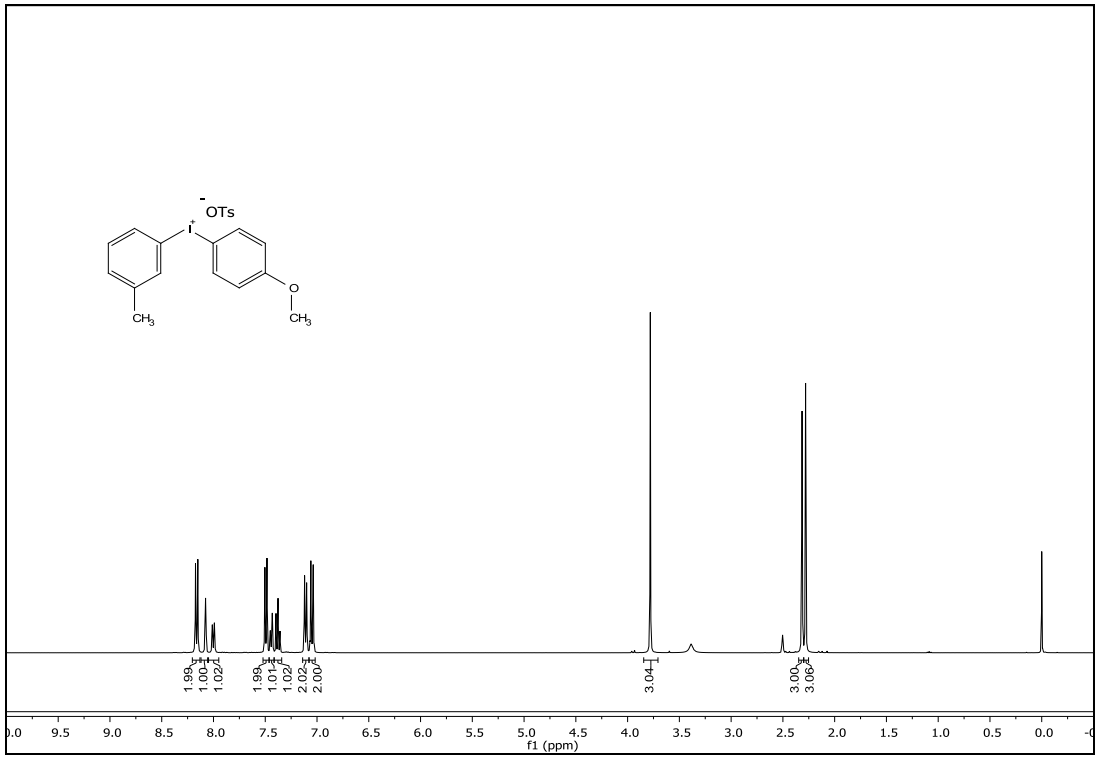


Figure 5.214: ^{13}C NMR of 2.26 at 101 MHz in DMSO-d_6 at 298K

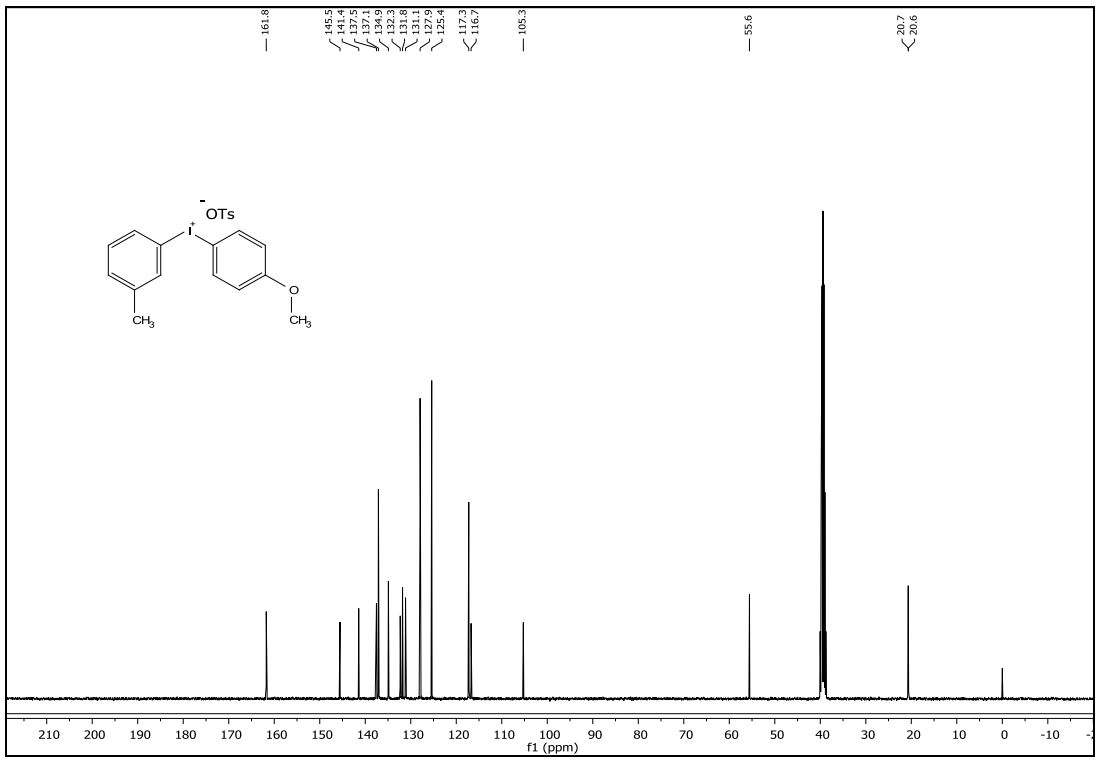


Figure 5.215: ^{1}H NMR of 2.27 at 400 MHz in $CDCl_3$ at 298K

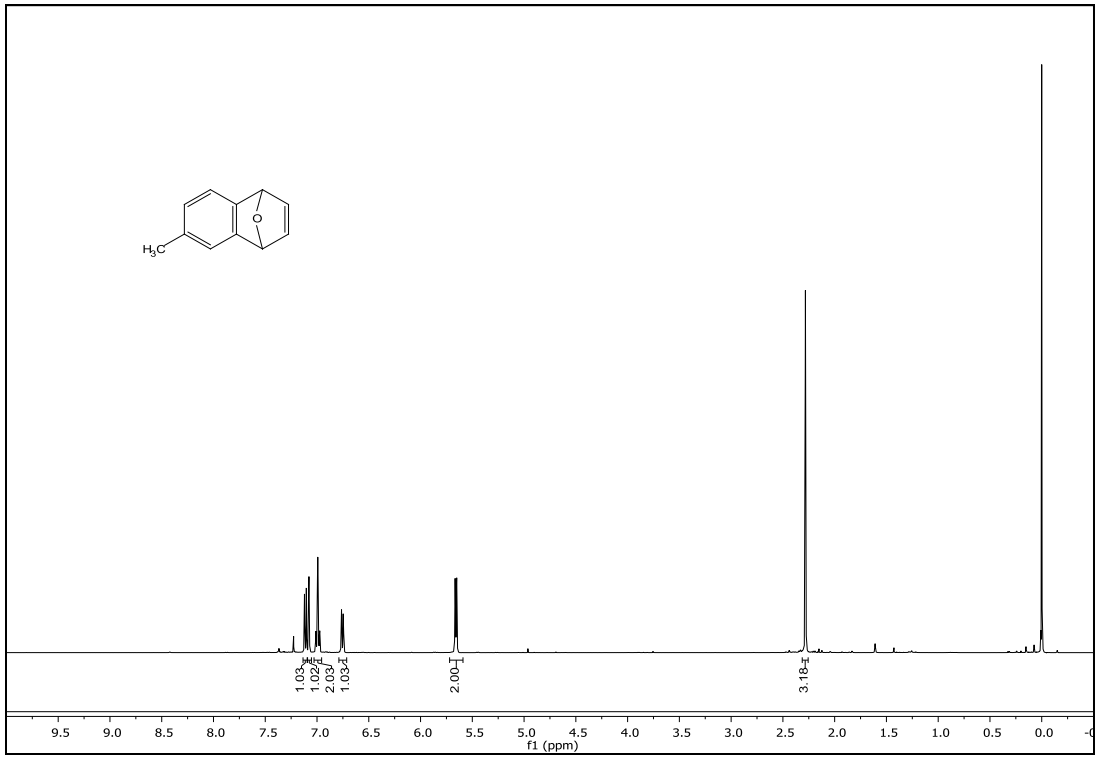


Figure 5.216: ^{13}C NMR of 2.27 at 101 MHz in $CDCl_3$ at 298K

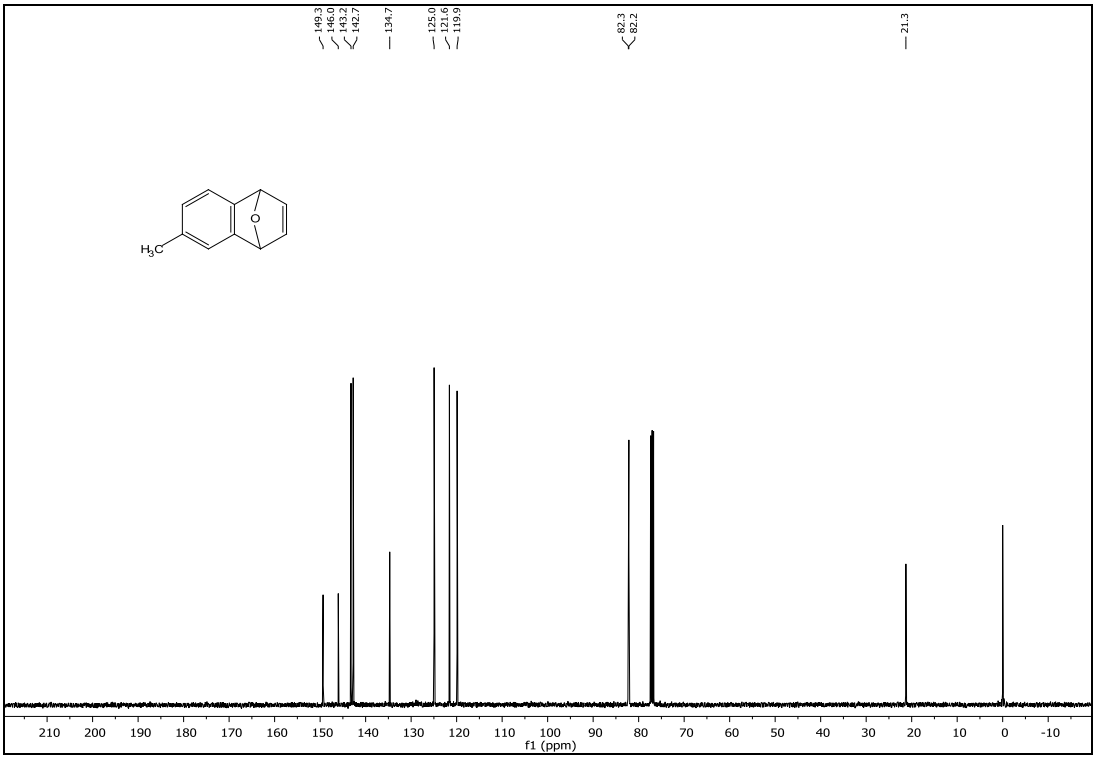


Figure 5.217: ^{1}H NMR of 2.28 at 400 MHz in $CDCl_3$ at 298K

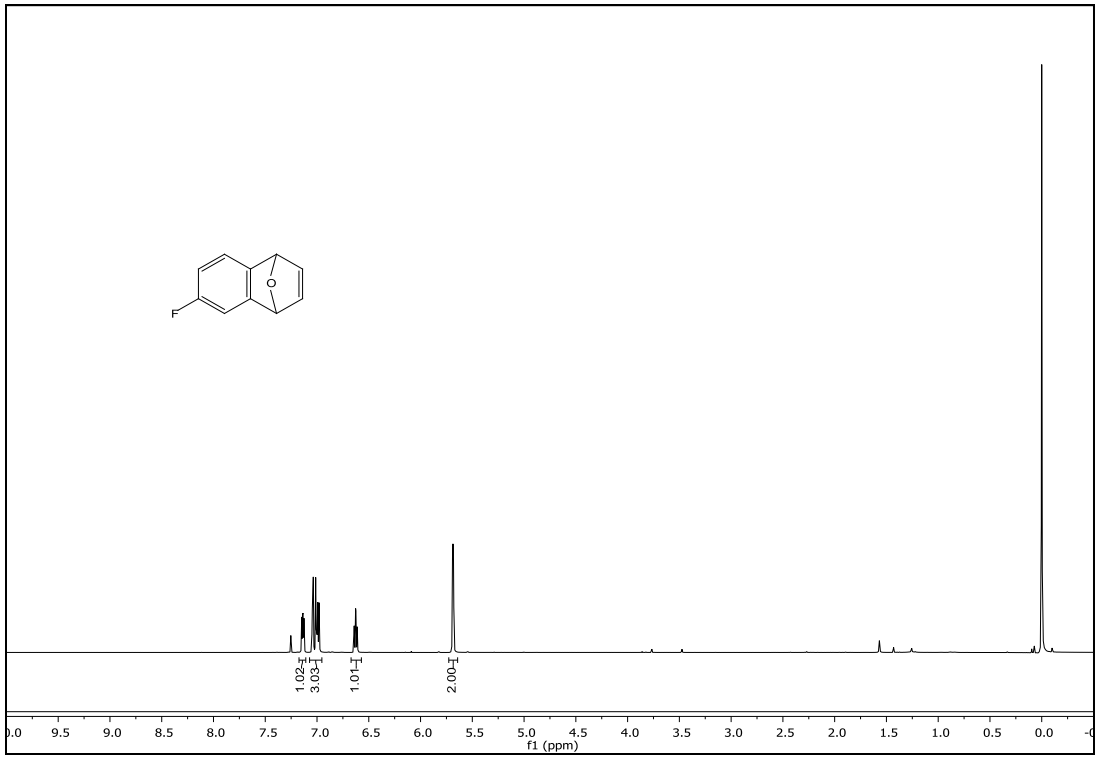


Figure 5.218: ^{13}C NMR of 2.28 at 101 MHz in $CDCl_3$ at 298K

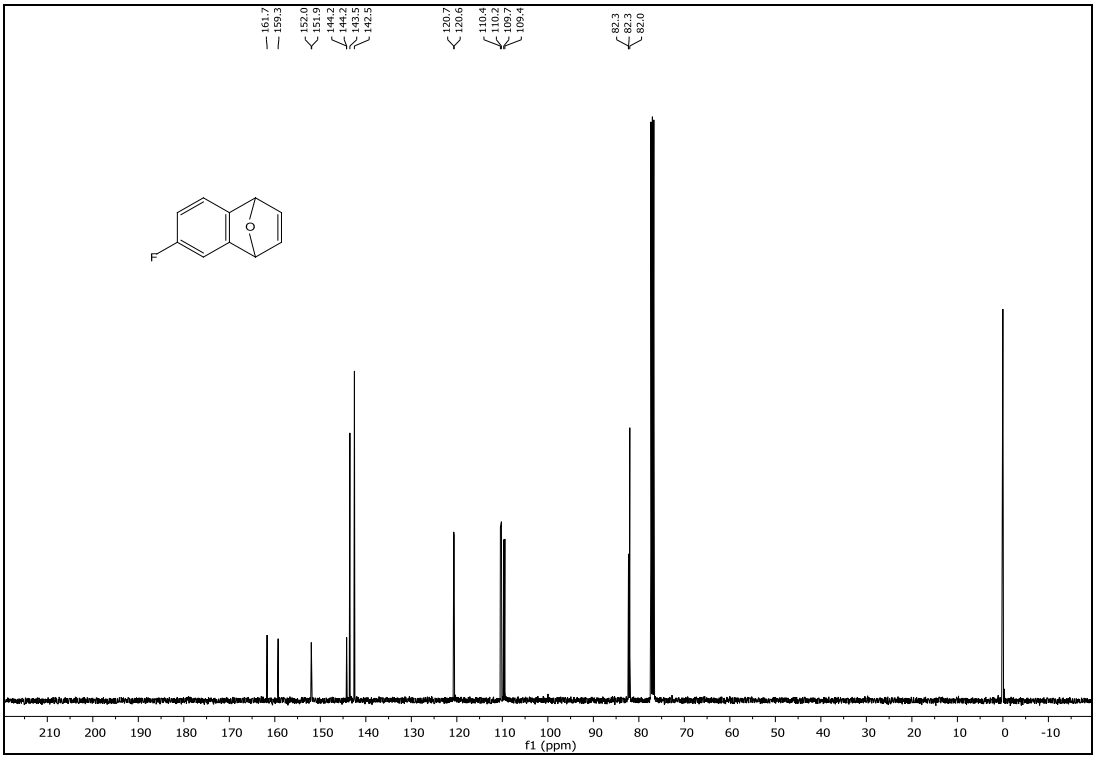


Figure 5.219: ^{19}F NMR of 2.28 at 377 MHz in $CDCl_3$ at 298k

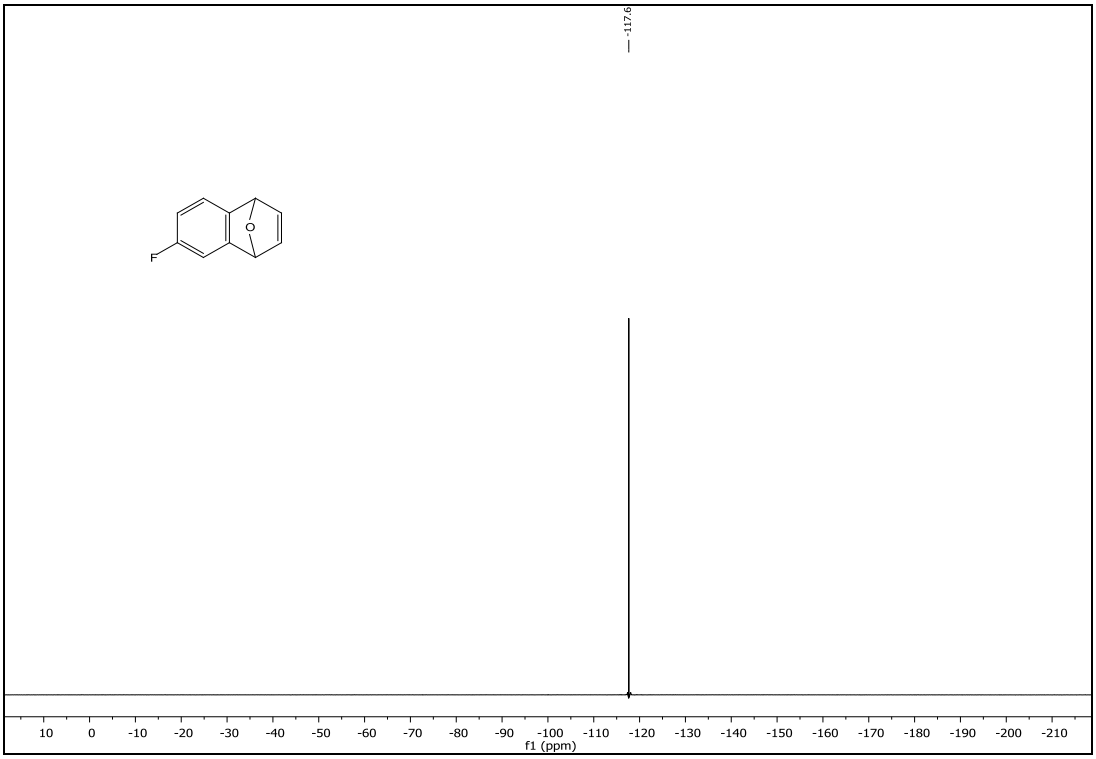


Figure 5.220: ^{1}H NMR of 2.29 at 400 MHz in $CDCl_3$ at 298K

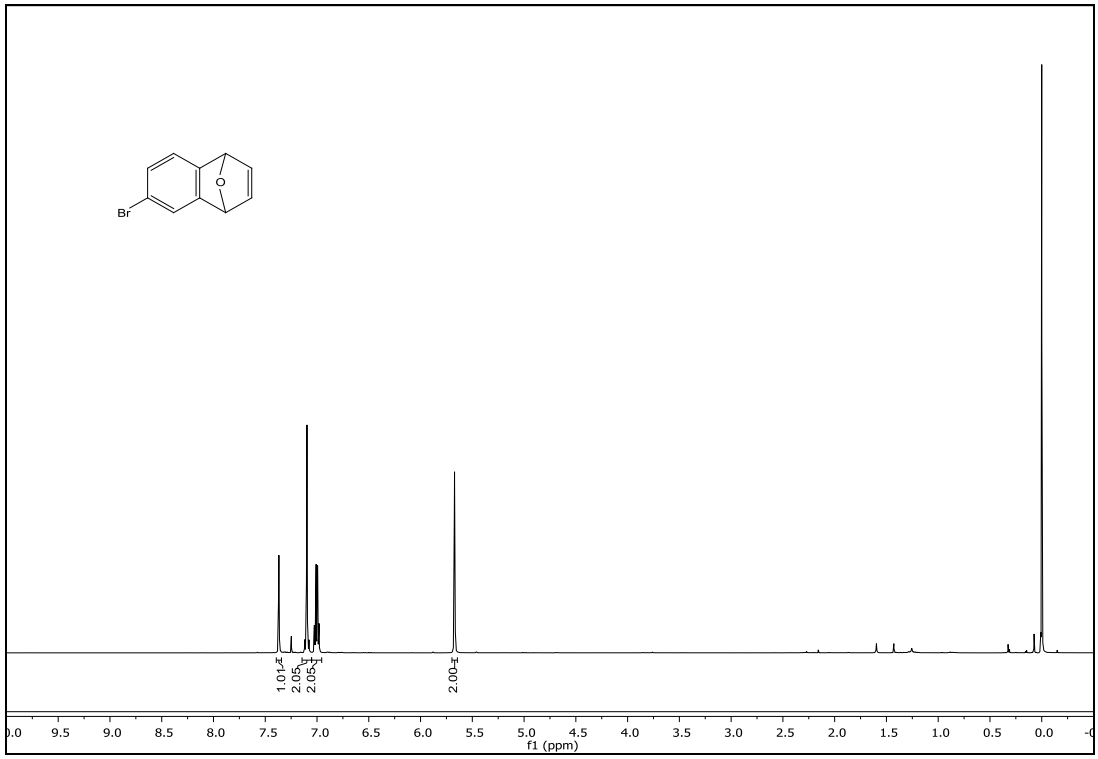


Figure 5.221: ^{13}C NMR of 2.29 at 101 MHz in $CDCl_3$ at 298K

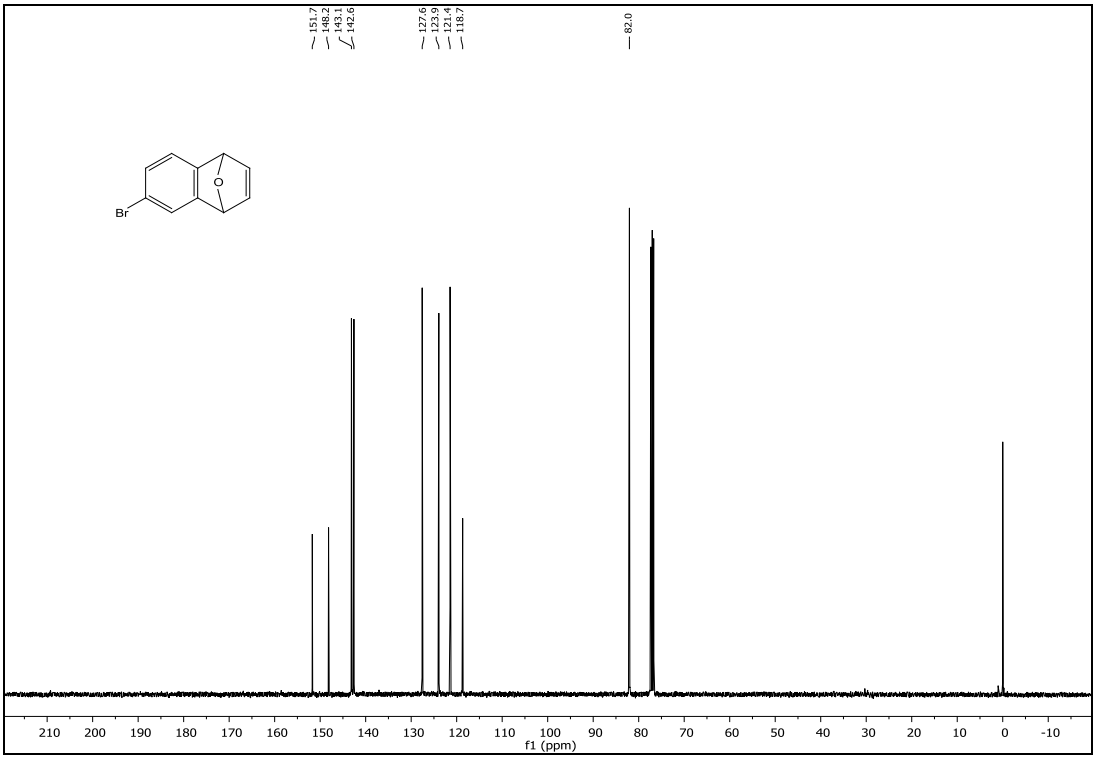


Figure 5.222: ^{1}H NMR of 2.30 at 400 MHz in $CDCl_3$ at 298K

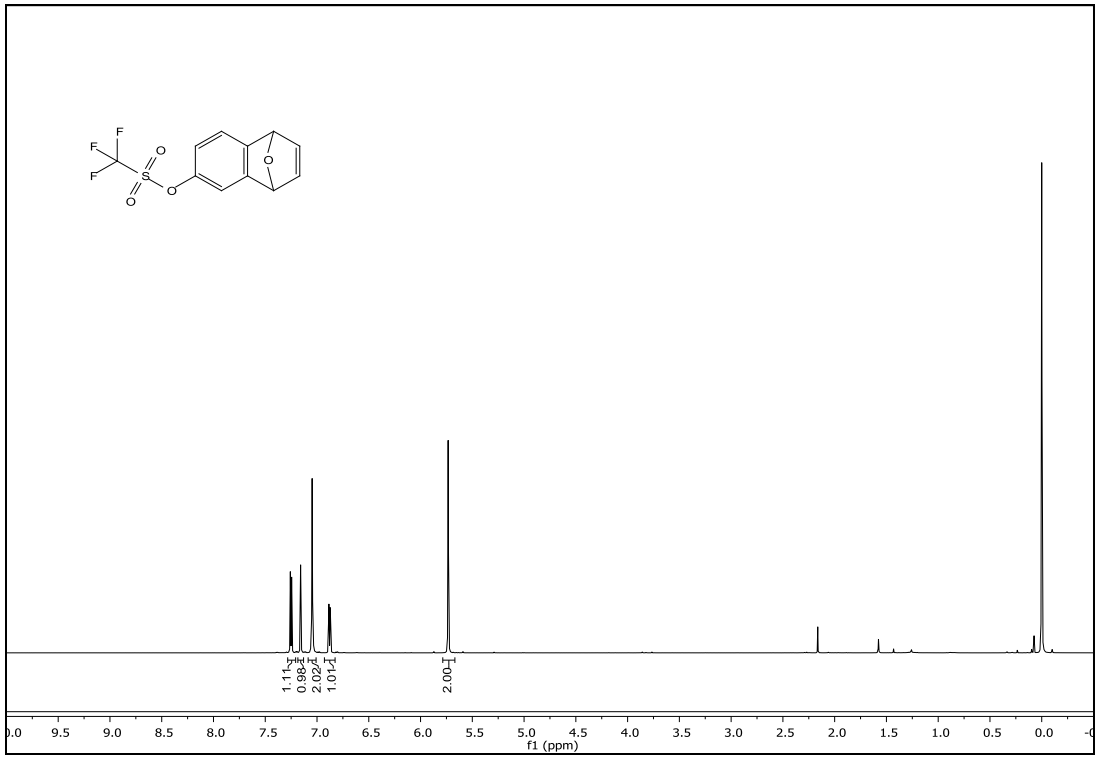


Figure 5.223: ^{13}C NMR of 2.30 at 101 MHz in $CDCl_3$ at 298K

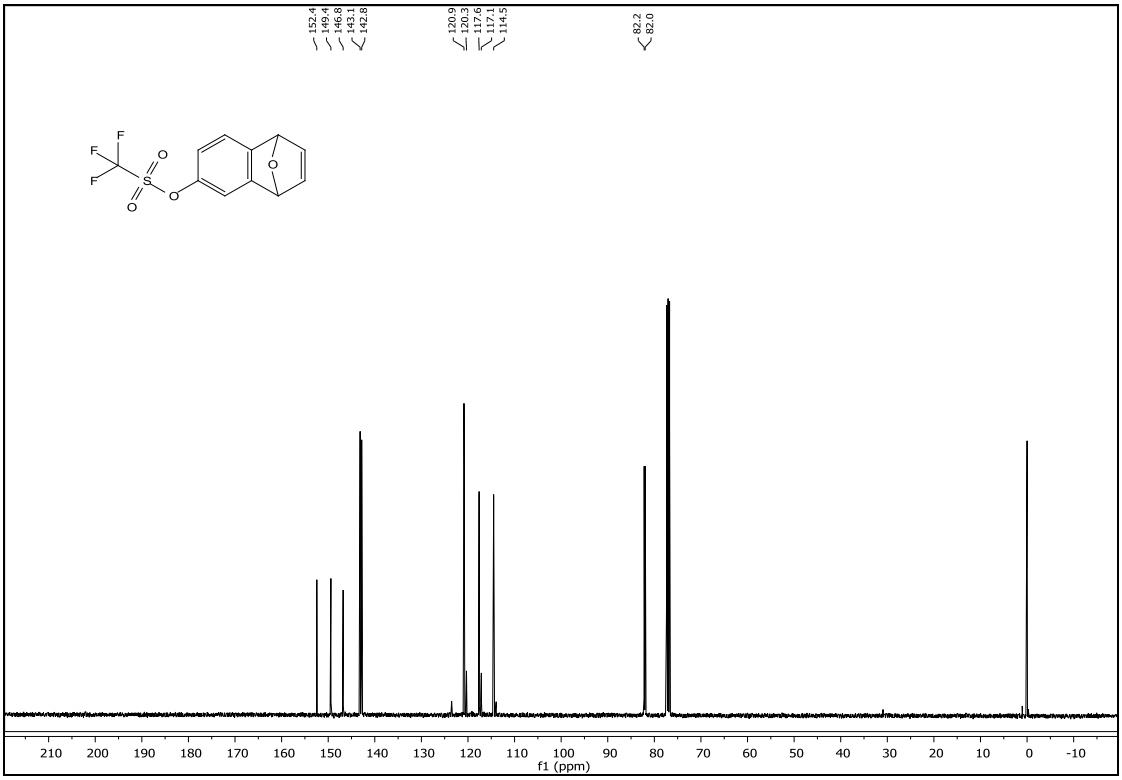


Figure 5.224: ^{19}F NMR of 2.30 at 377 MHz in $CDCl_3$ at 298K

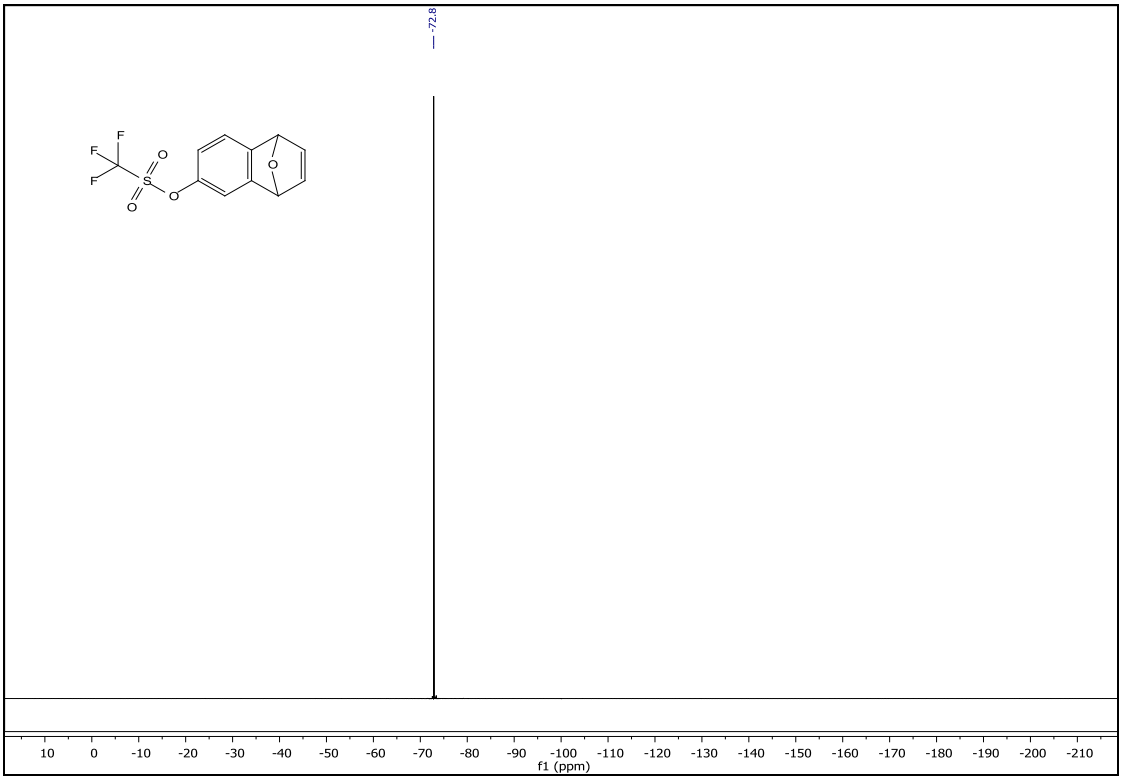


Figure 5.225: ^{1}H NMR of 2.31 at 400 MHz in $CDCl_3$ at 298K

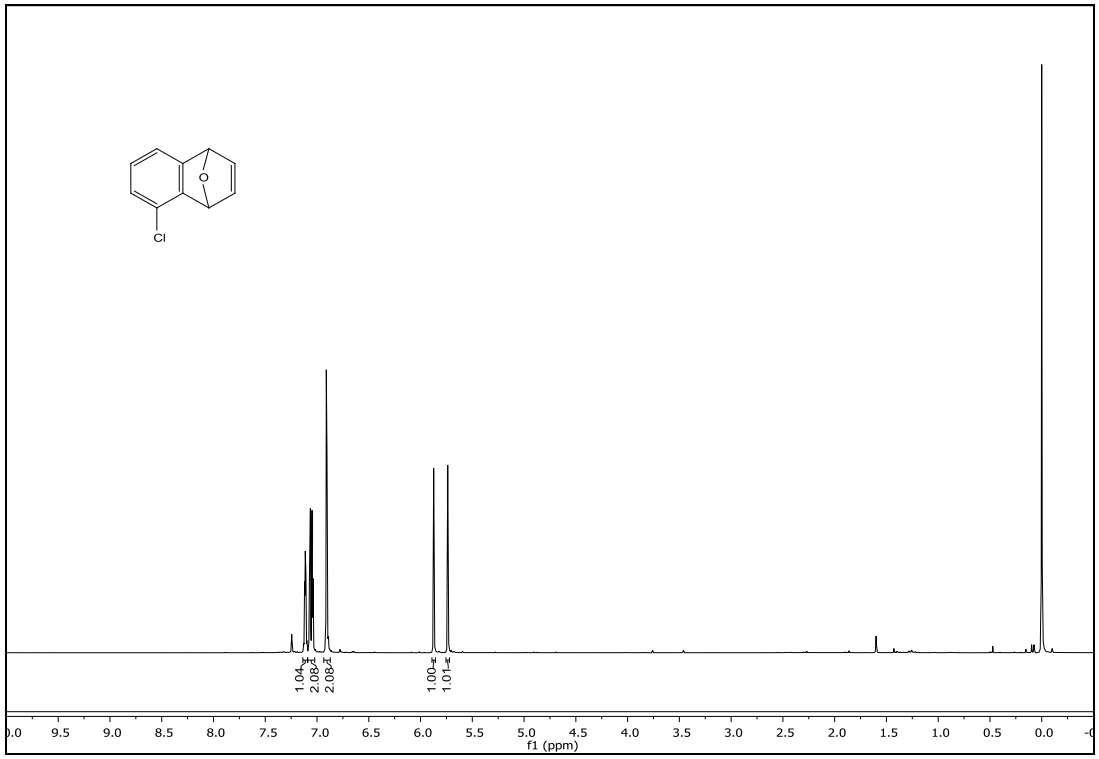


Figure 5.226: ^{13}C NMR of 2.31 at 101 MHz in $CDCl_3$ at 298K

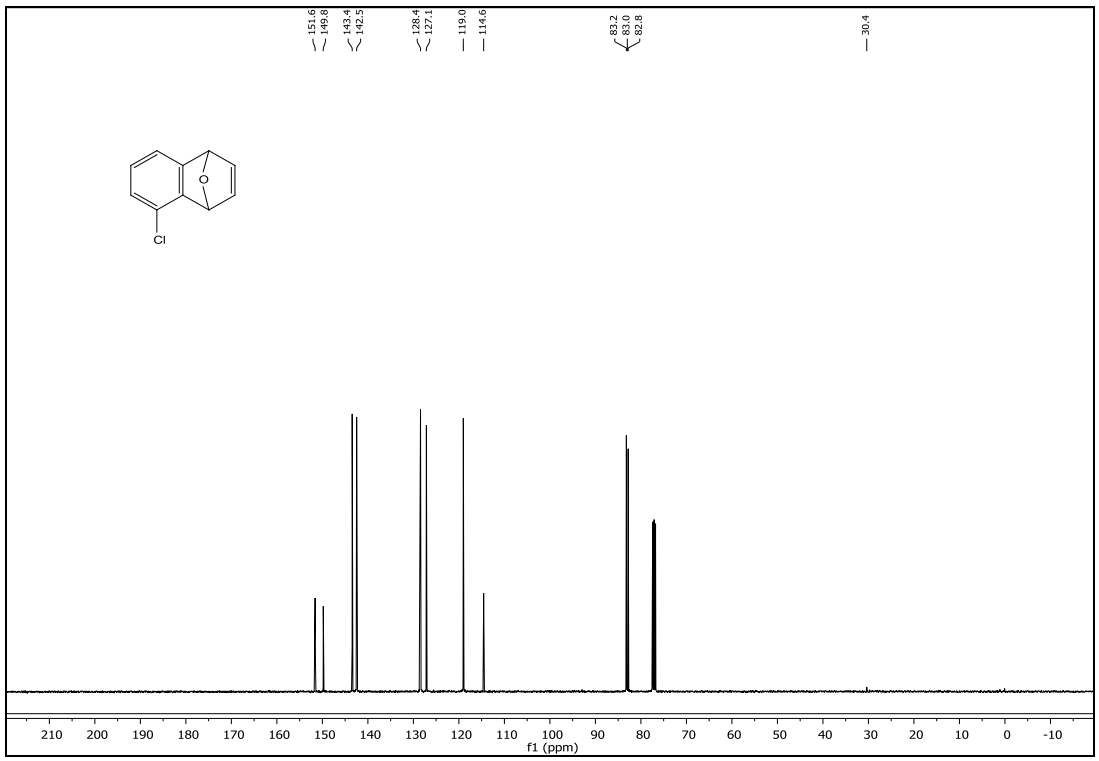


Figure 5.227: ^{1}H NMR of 2.32 at 400 MHz in $CDCl_3$ at 298K

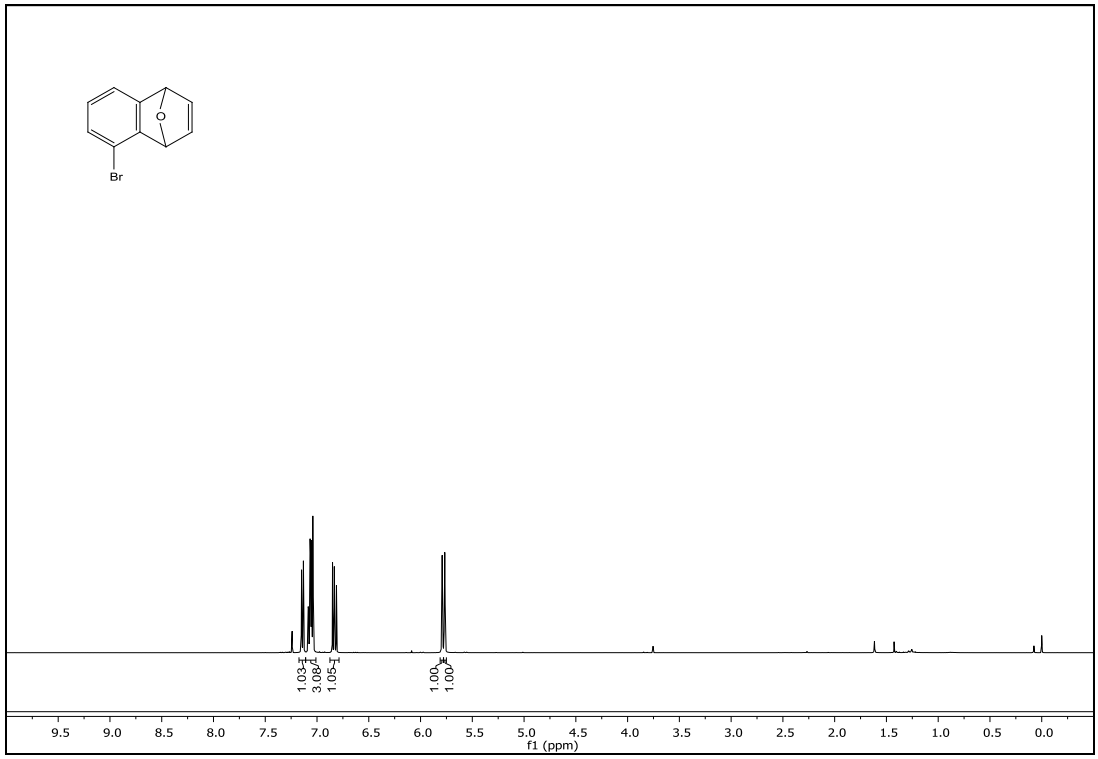


Figure 5.228: ^{13}C NMR of 2.32 at 101 MHz in $CDCl_3$ at 298K

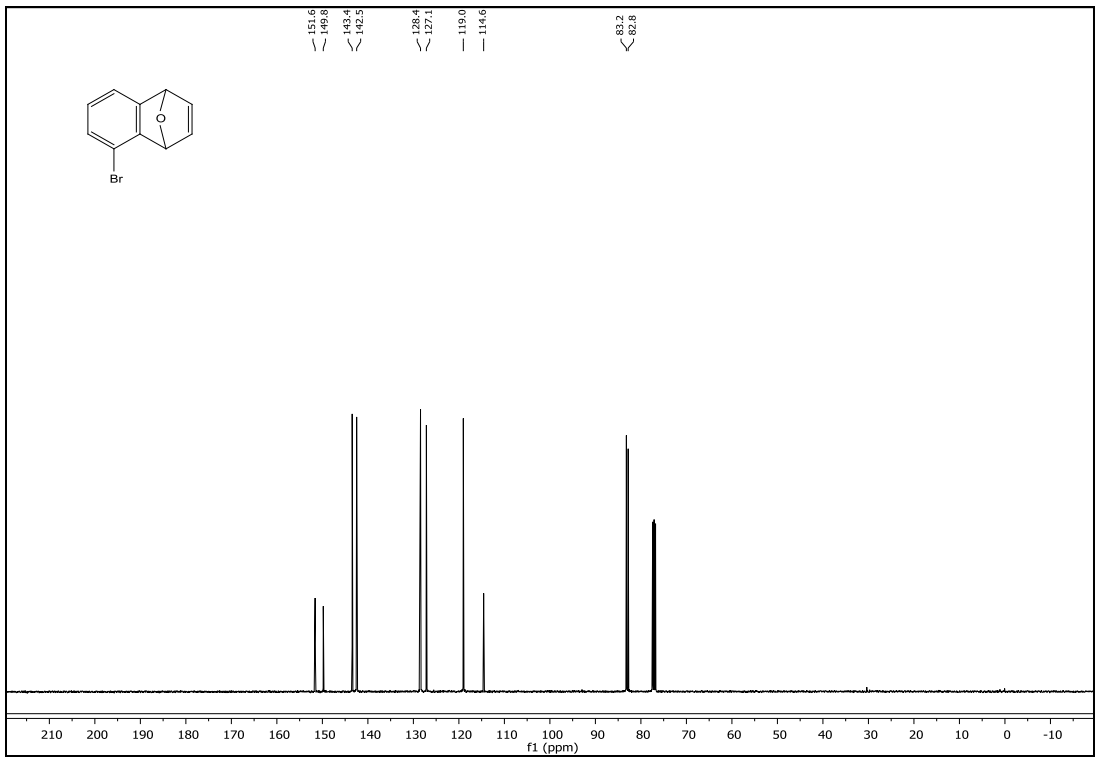


Figure 5.229: ^{1}H NMR of 2.33 at 400 MHz in $CDCl_3$ at 298K

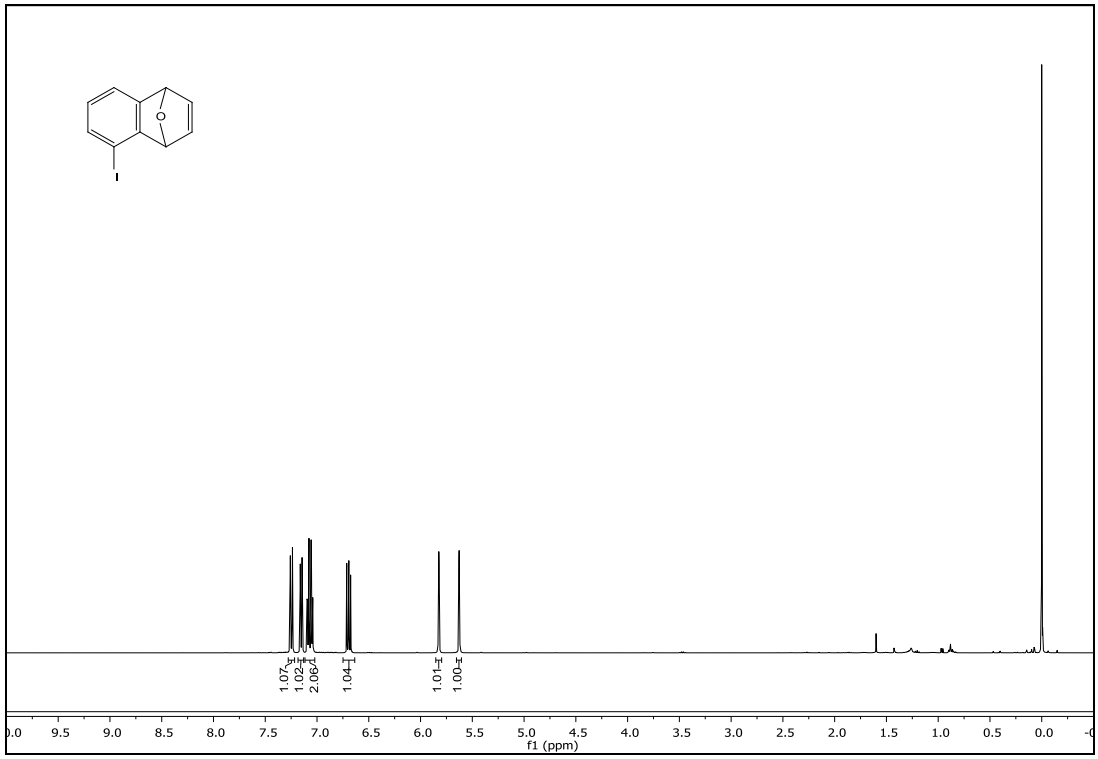


Figure 5.230: ^{13}C NMR of 2.33 at 101 MHz in $CDCl_3$ at 298K

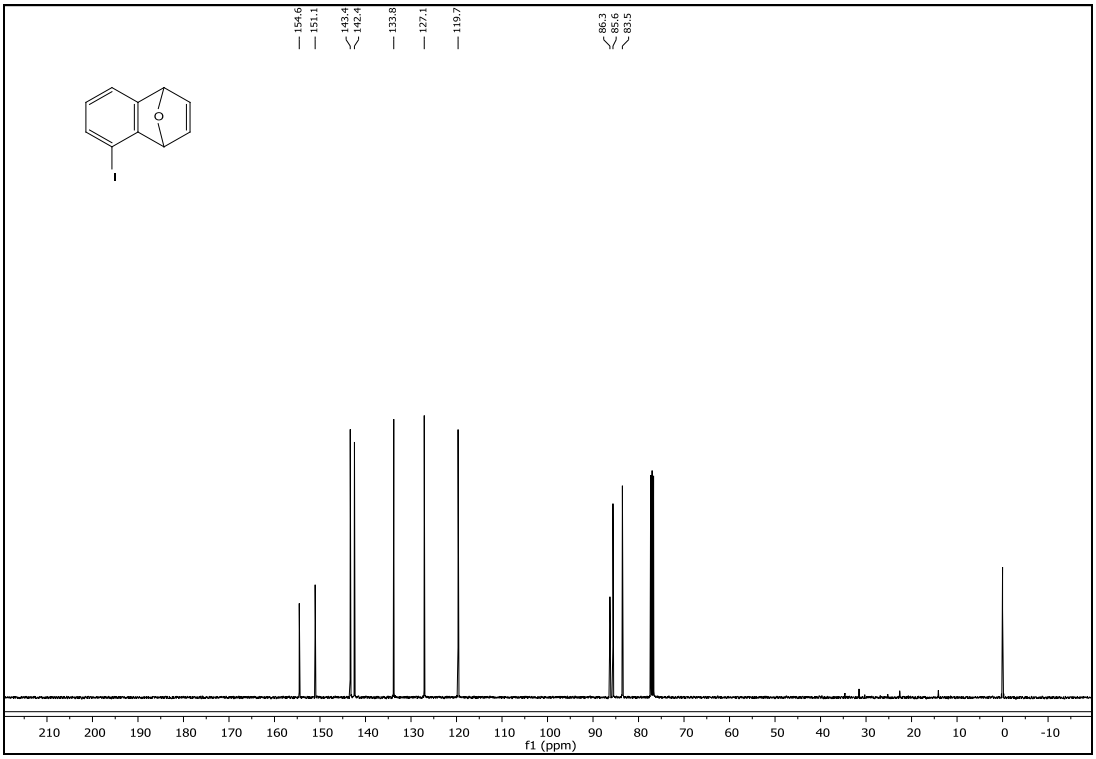


Figure 5.231: ^{1}H NMR of 2.34at 400 MHz in $CDCl_3$ at 298K

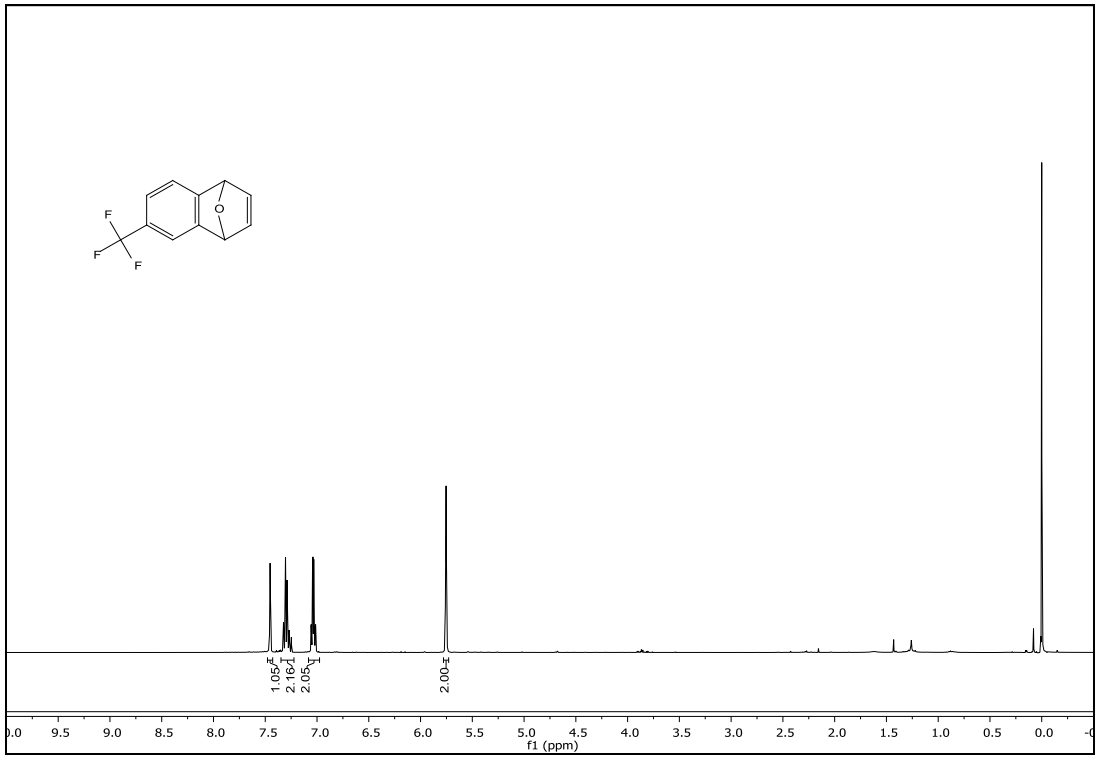


Figure 5.232: ^{13}C NMR of 2.34 at 101 MHz in $CDCl_3$ at 298K

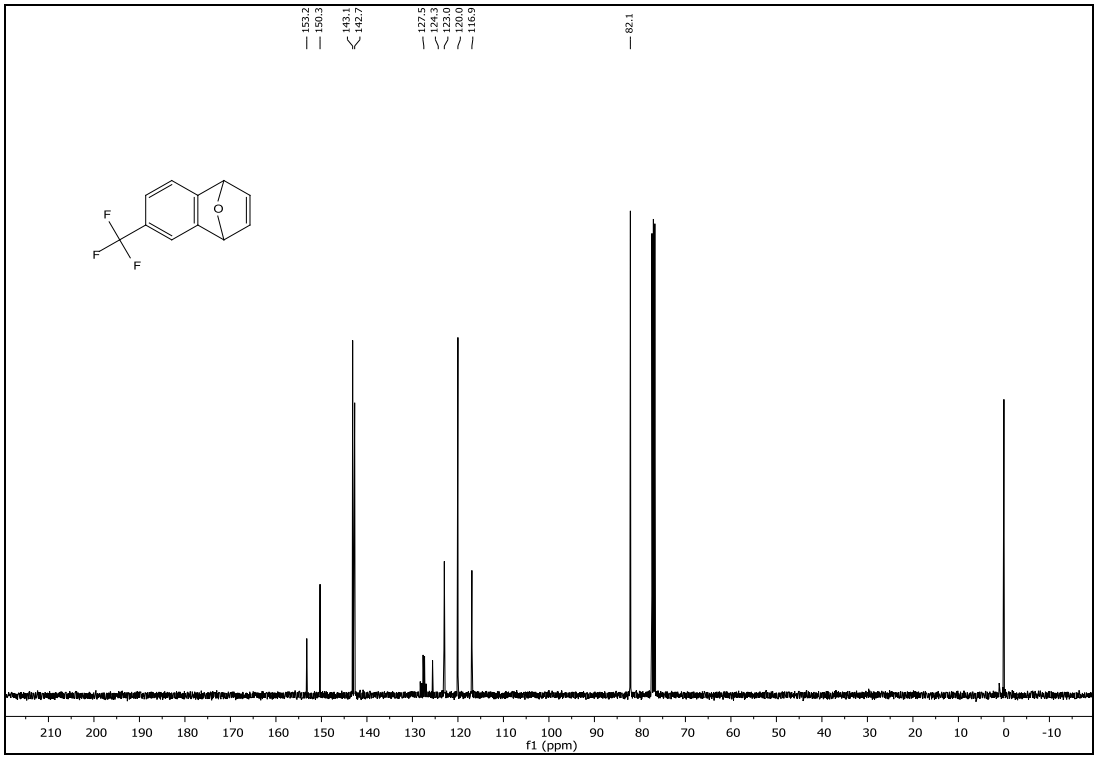


Figure 5.233: ^{19}F NMR of 2.34 at 377 MHz in $CDCl_3$ at 298K

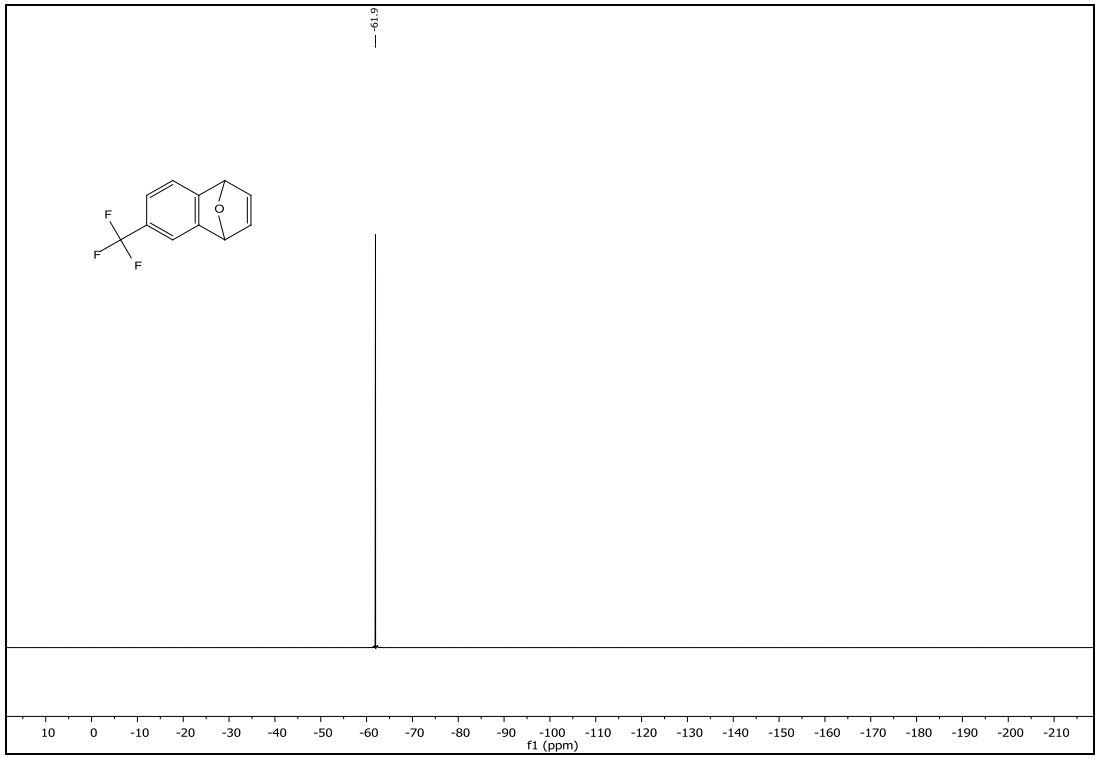


Figure 5.234: ^{1}H NMR of 2.35 at 400 MHz in $CDCl_3$ at 298K

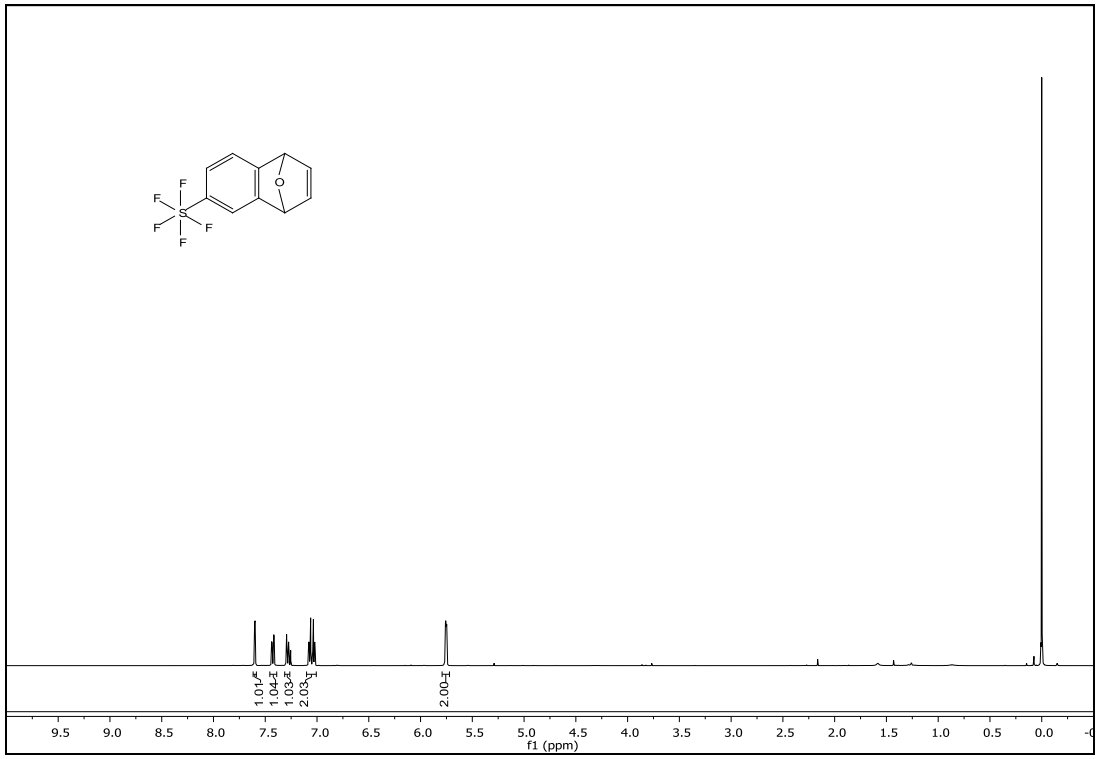


Figure 5.235: ^{13}C NMR of 2.35 at 101 MHz in $CDCl_3$ at 298K

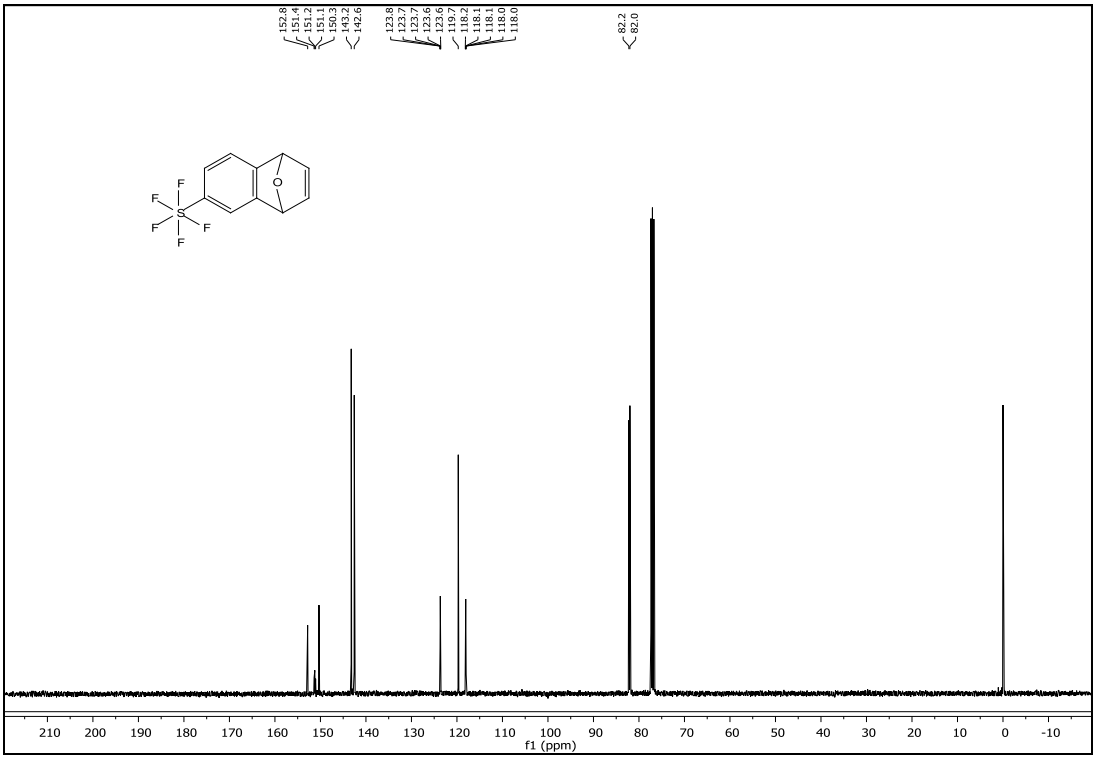


Figure 5.236: ^{19}F NMR of 2.35 at 377 MHz in $CDCl_3$ at 298K

Figure 5.237: ^{1}H NMR of 2.36 at 400 MHz in $CDCl_3$ at 298K

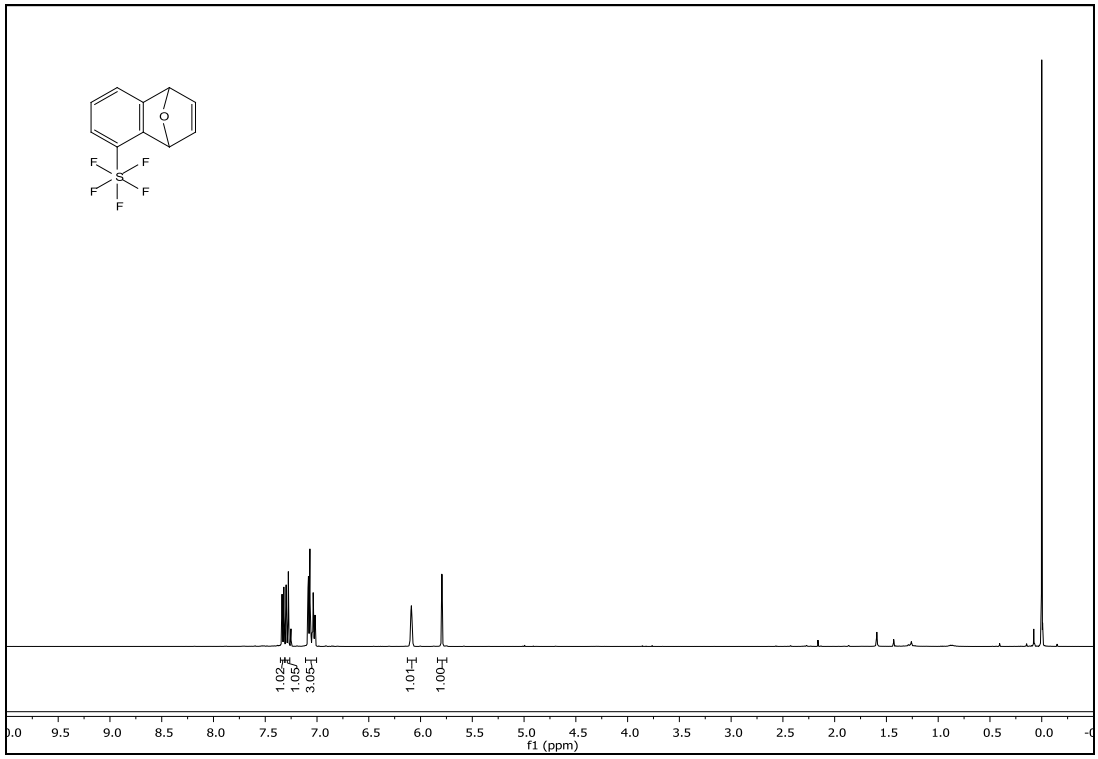


Figure 5.238: ^{13}C NMR of 2.36 at 101 MHz in $CDCl_3$ at 298K

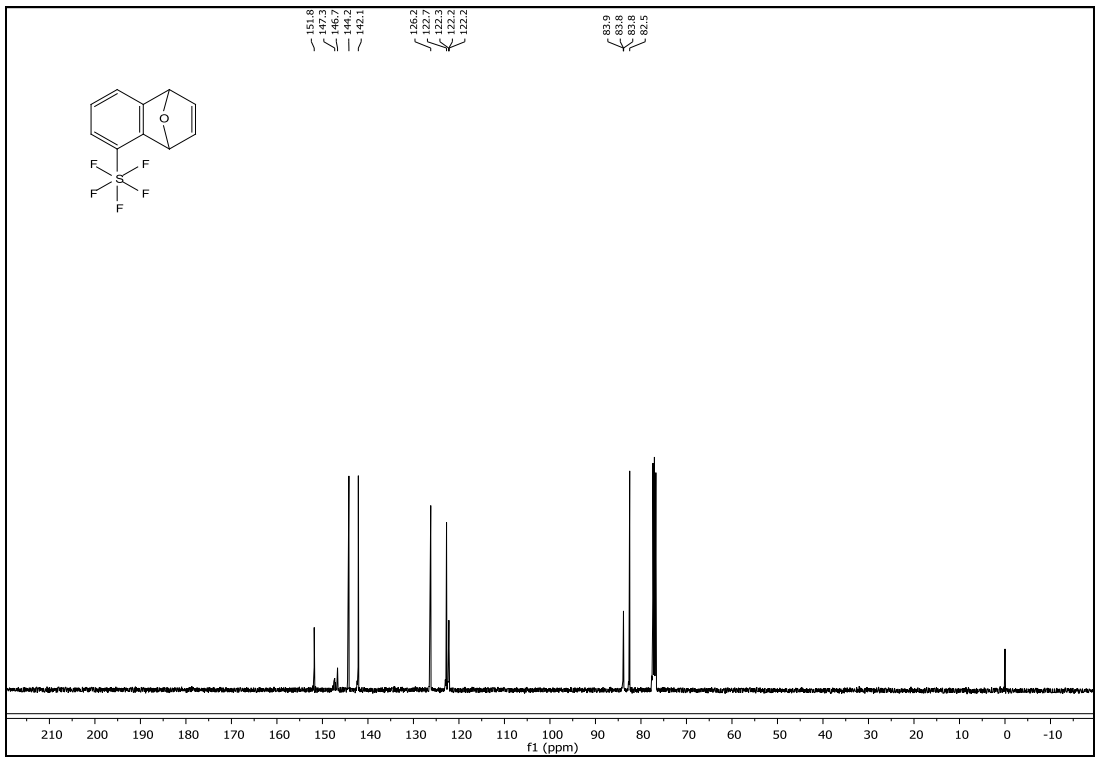


Figure 5.239: ^{19}F NMR of 2.36 at 377 MHz in $CDCl_3$ at 298K

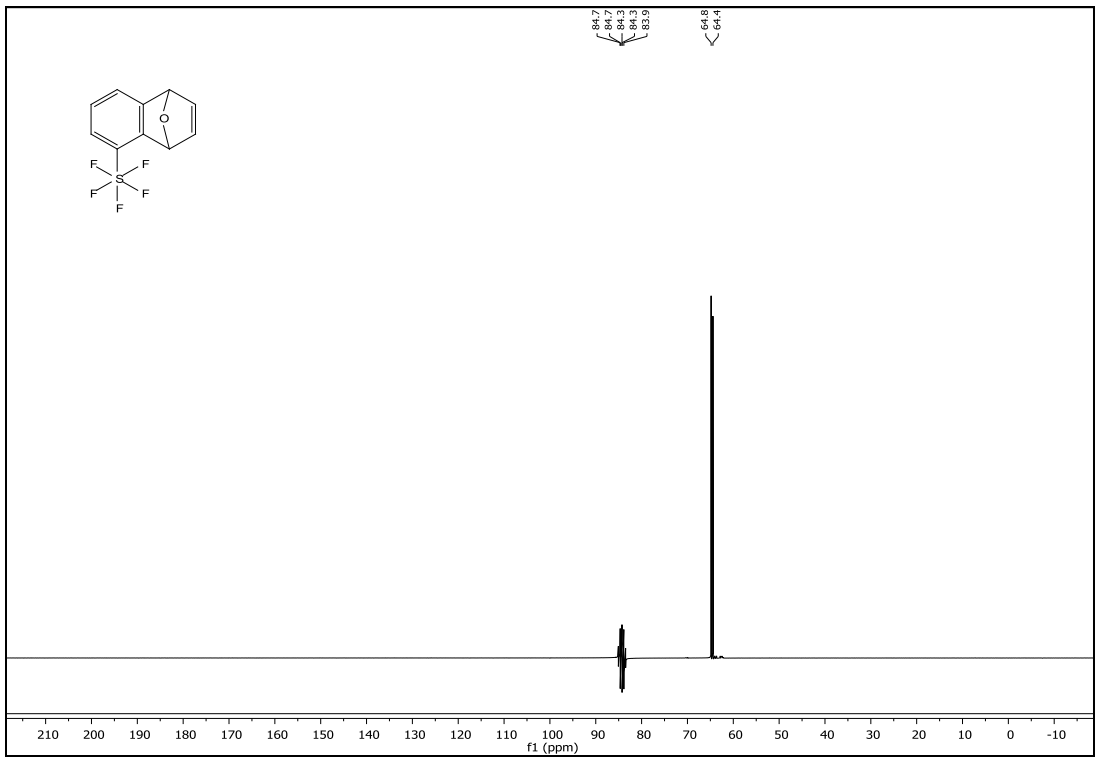


Figure 5.240: ^{1}H NMR of 2.37 at 400 MHz in $CDCl_3$ at 298K

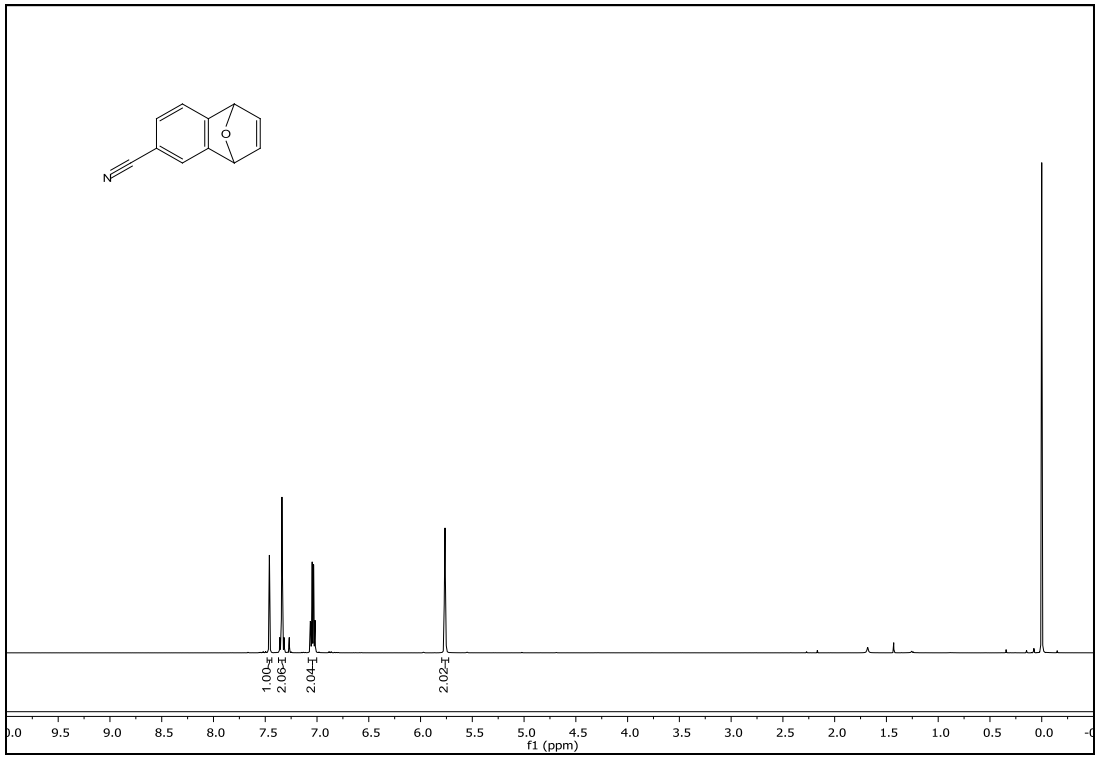


Figure 5.241: ^{13}C NMR of 2.37 at 101 MHz in $CDCl_3$ at 298K

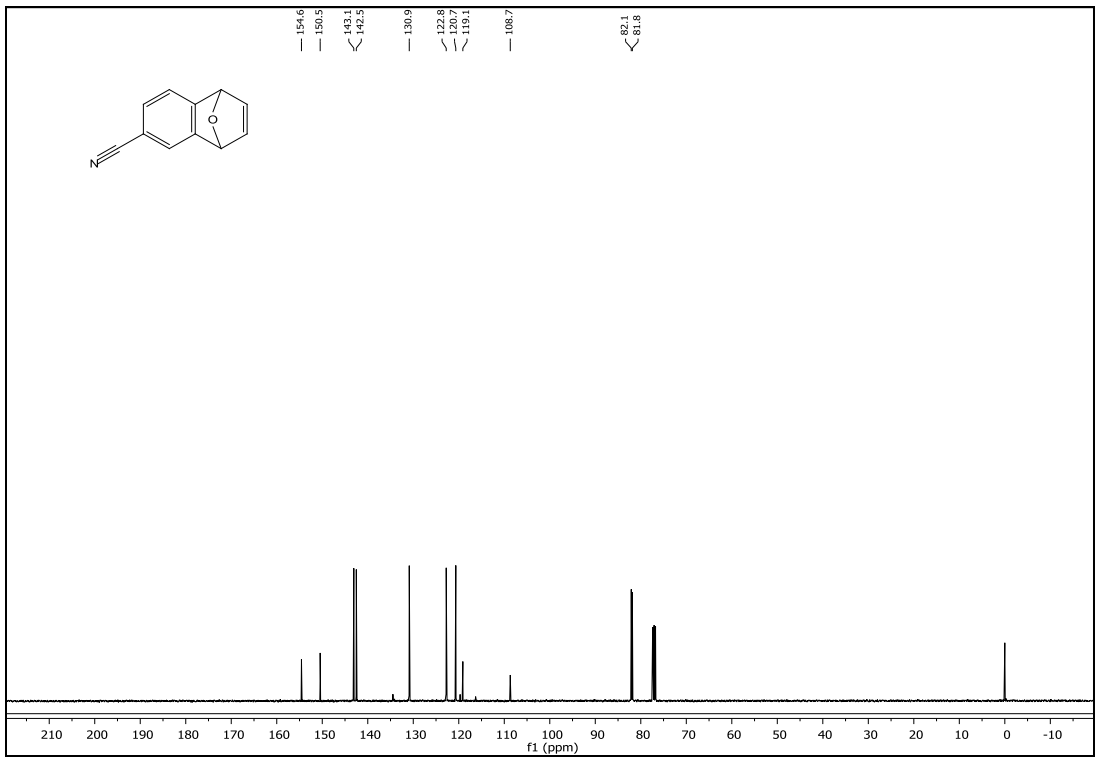


Figure 5.242: ^{1}H NMR of 2.38 at 400 MHz in $CDCl_3$ at 298K

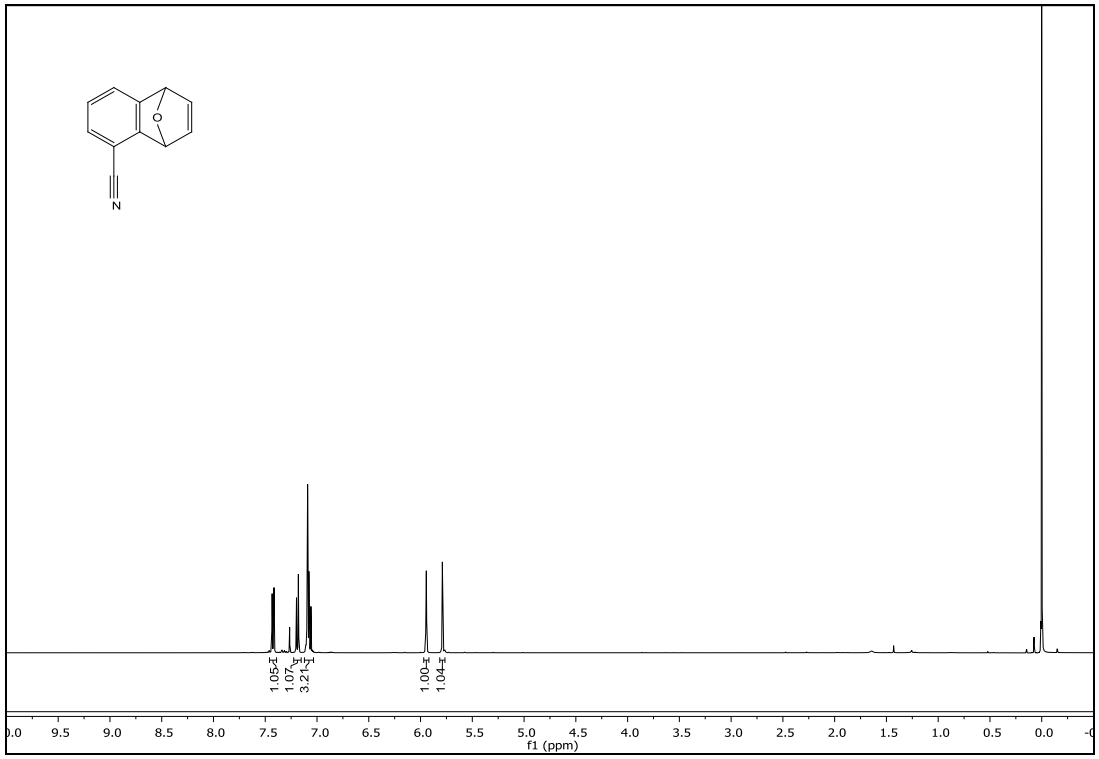


Figure 5.243: ^{13}C NMR of 2.38 at 101 MHz in $CDCl_3$ at 298K

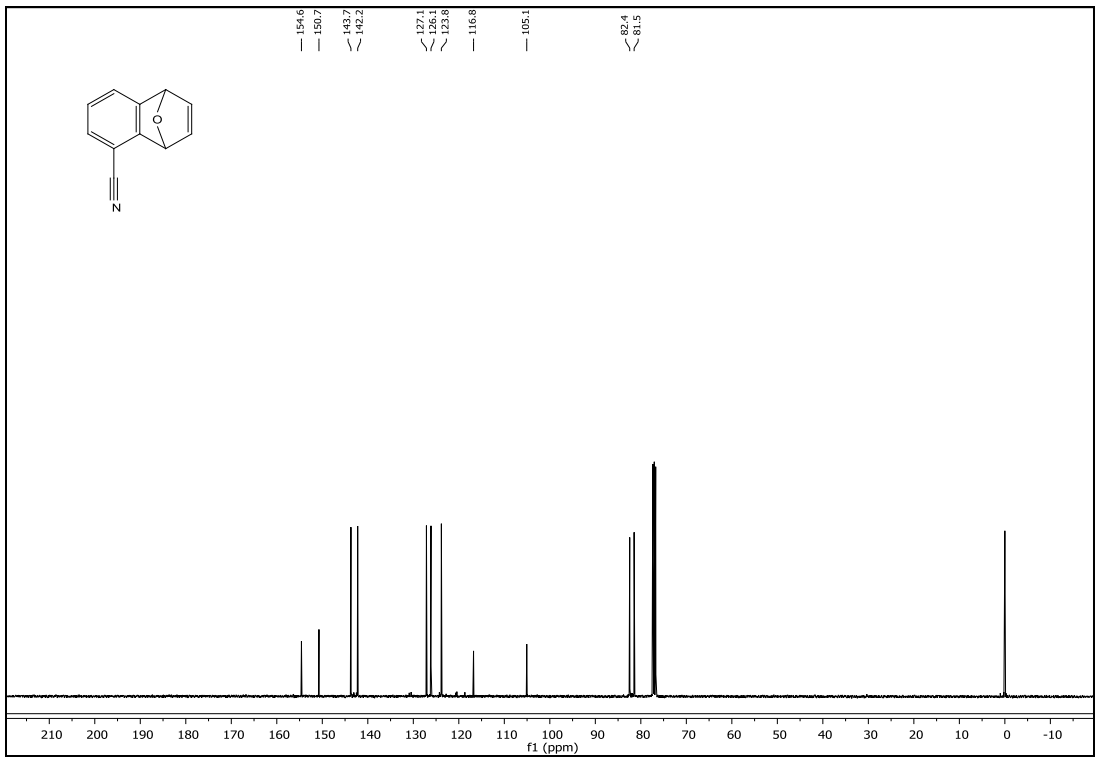


Figure 5.244: ^{1}H NMR of 2.39 at 400 MHz in $CDCl_3$ at 298K

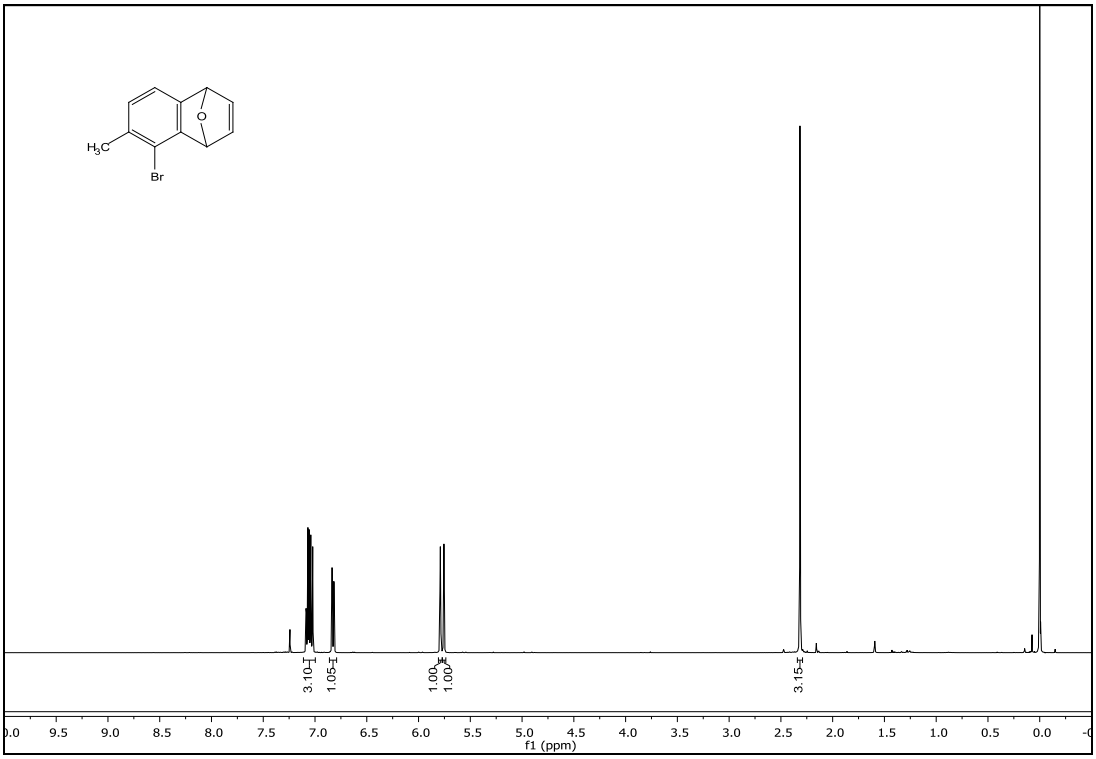


Figure 5.245: ^{13}C NMR of 2.39 at 101 MHz in $CDCl_3$ at 298K

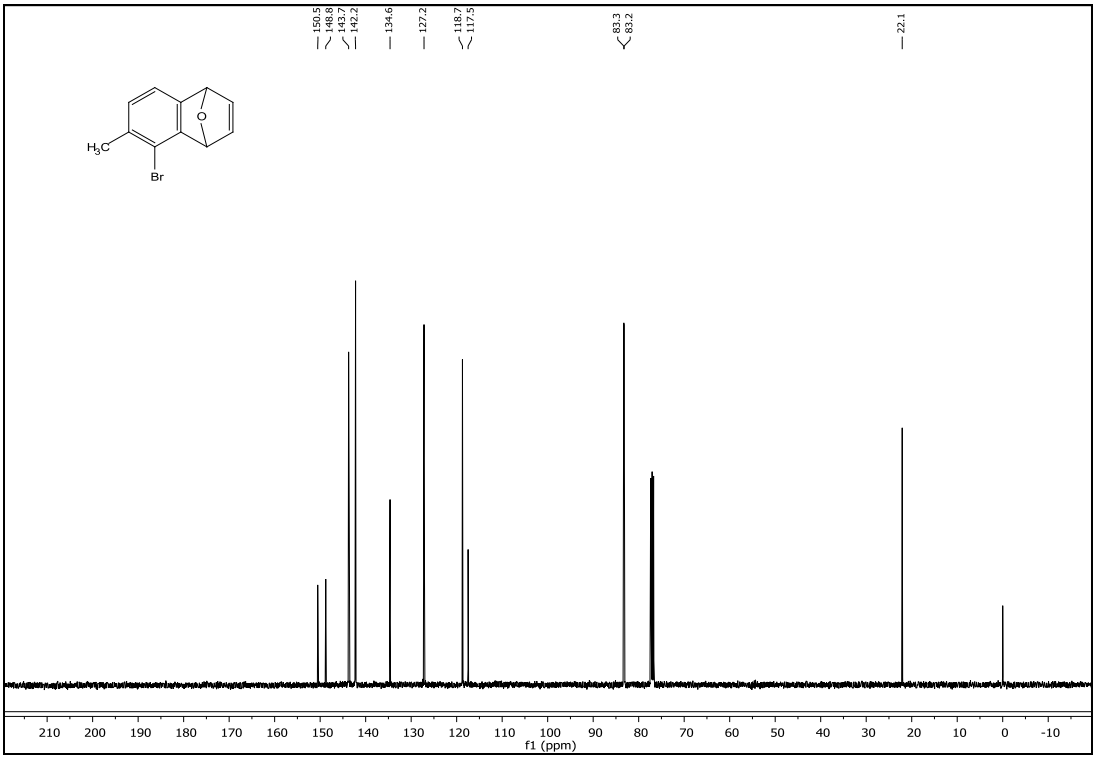


Figure 5.246: ^{1}H NMR of 2.40 at 400 MHz in $CDCl_3$ at 298K

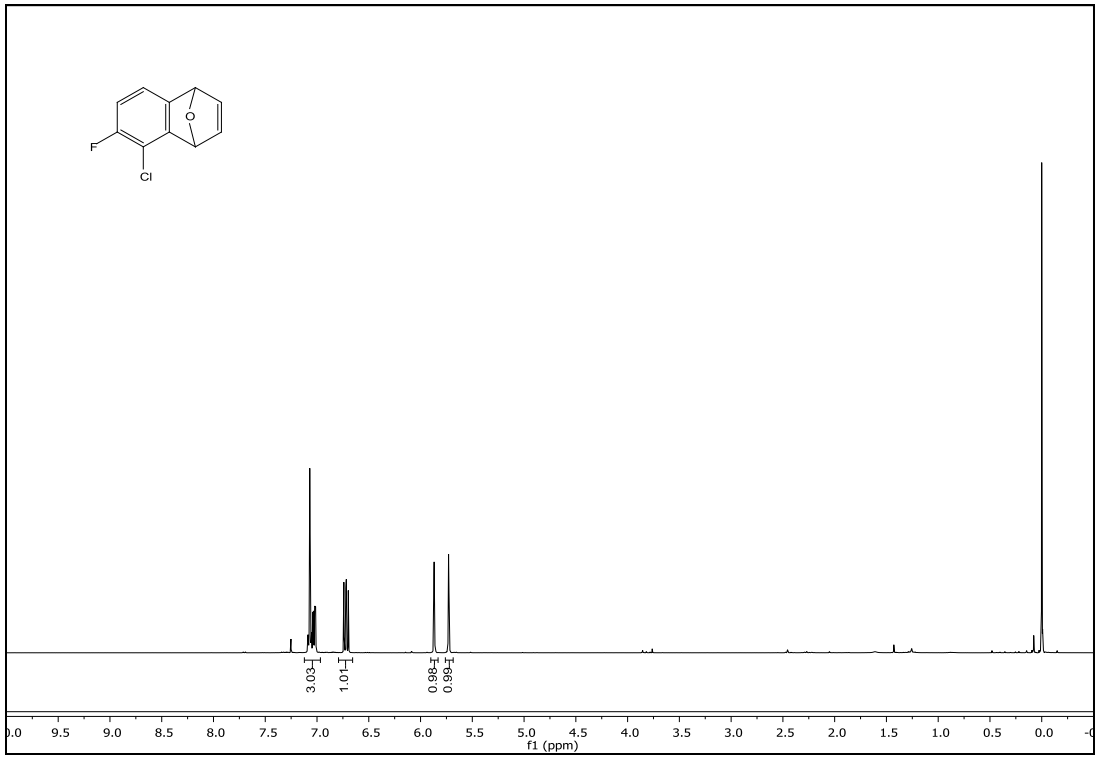


Figure 5.247: ^{13}C NMR of 2.40 at 101 MHz in $CDCl_3$ at 298K

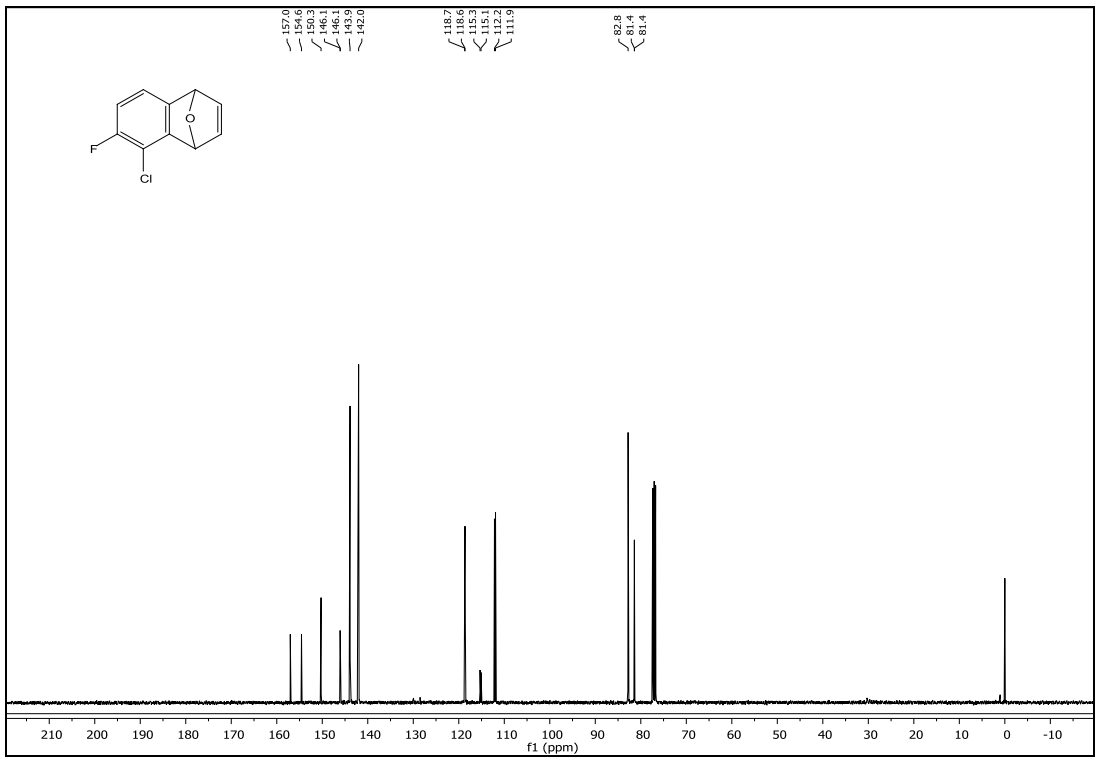


Figure 5.248: ^{19}F NMR of 2.40 at 377 MHz in $CDCl_3$ at 298K

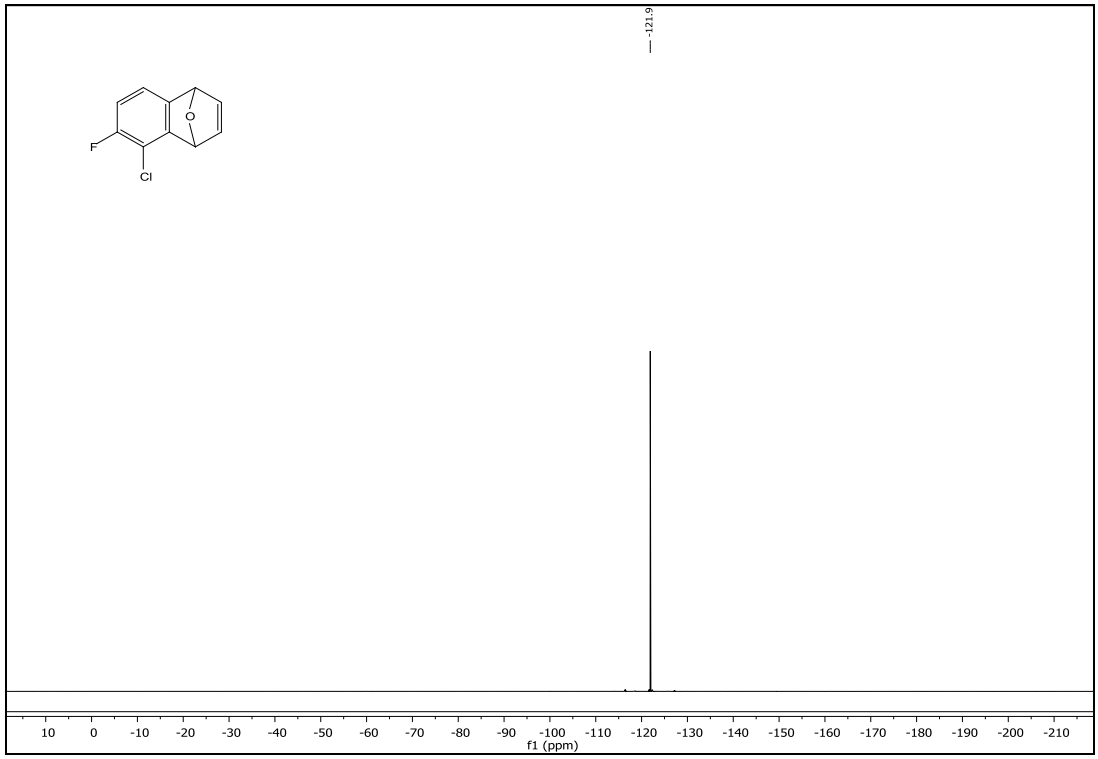


Figure 5.249: ^{1}H NMR of 2.41 at 400 MHz in $CDCl_3$ at 298K

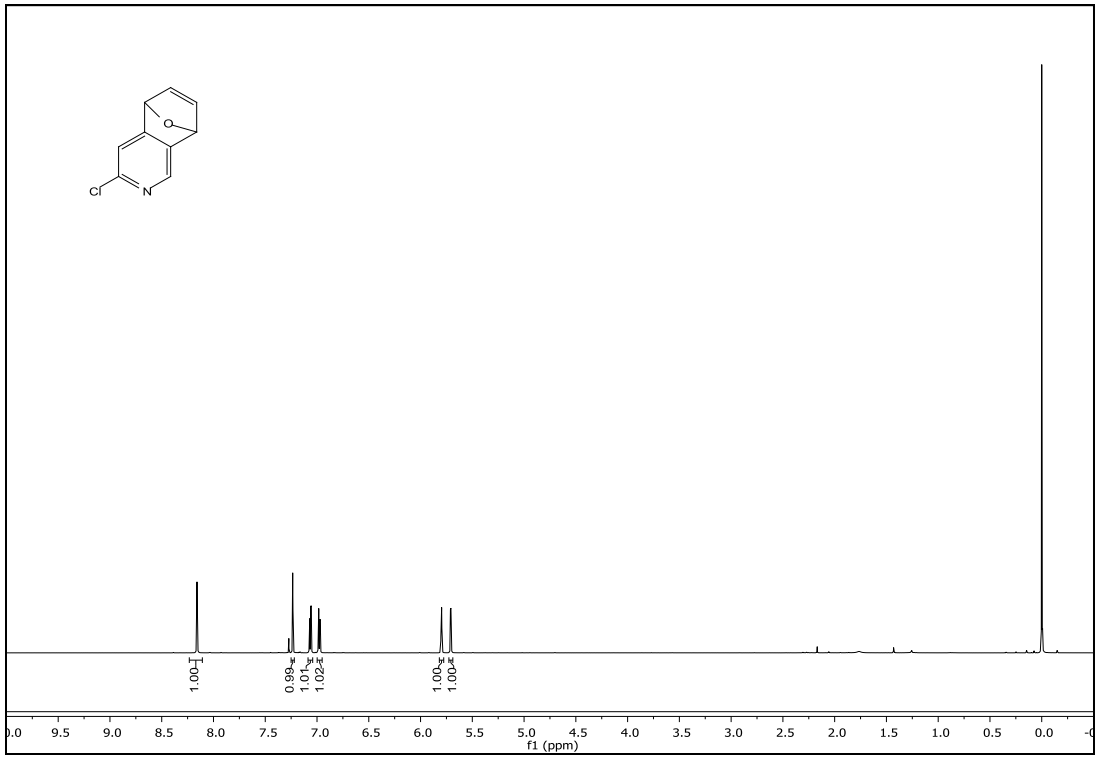


Figure 5.250: ^{13}C NMR of 2.41 at 101 MHz in $CDCl_3$ at 298K

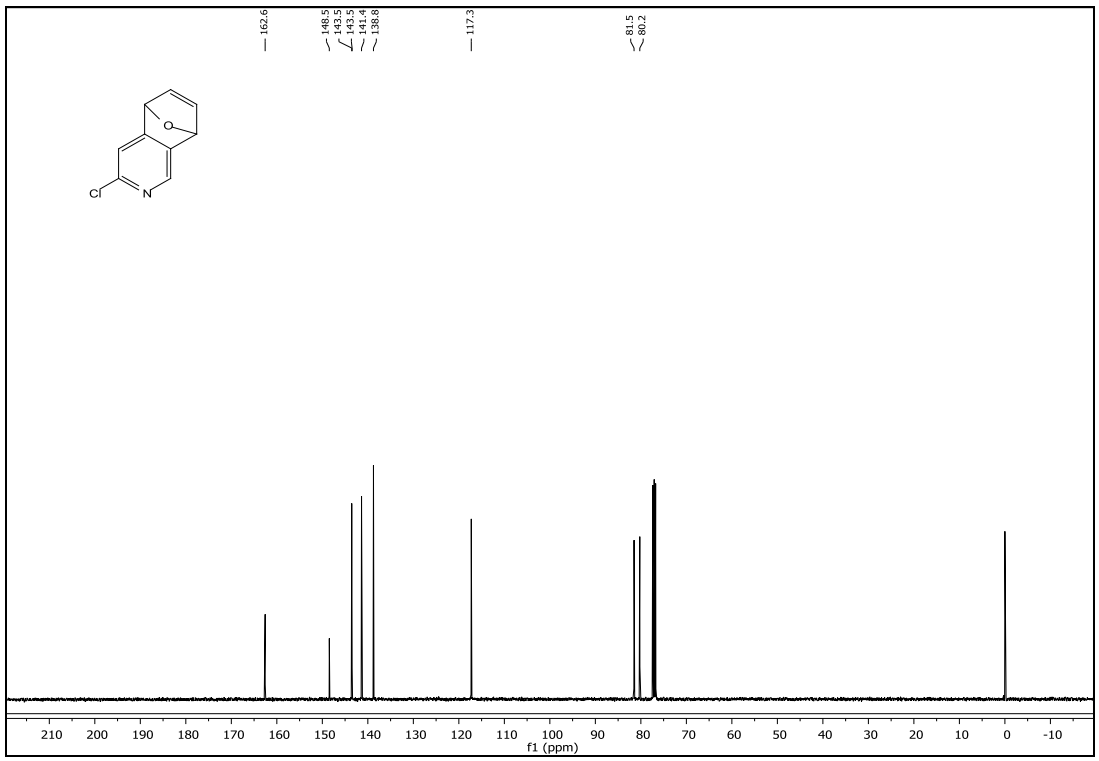


Figure 5.251: ^{1}H NMR of 2.42 at 400 MHz in $CDCl_3$ at 298K

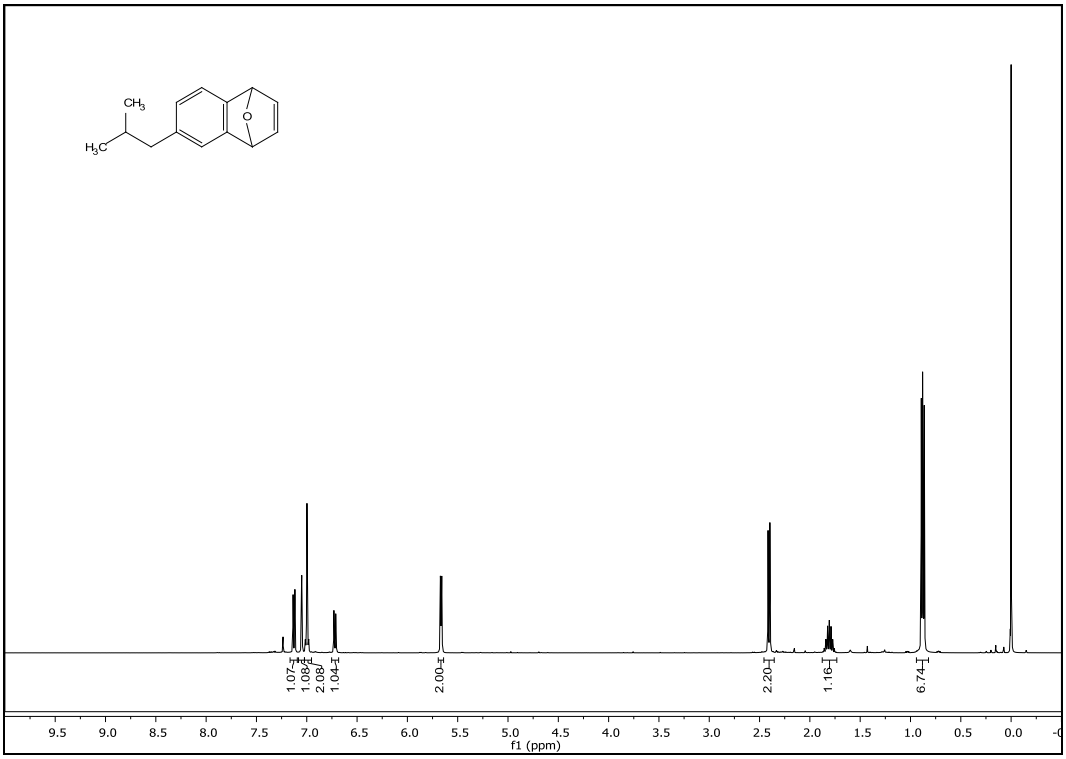


Figure 5.252: ^{13}C NMR of 2.42 at 101 MHz in $CDCl_3$ at 298K

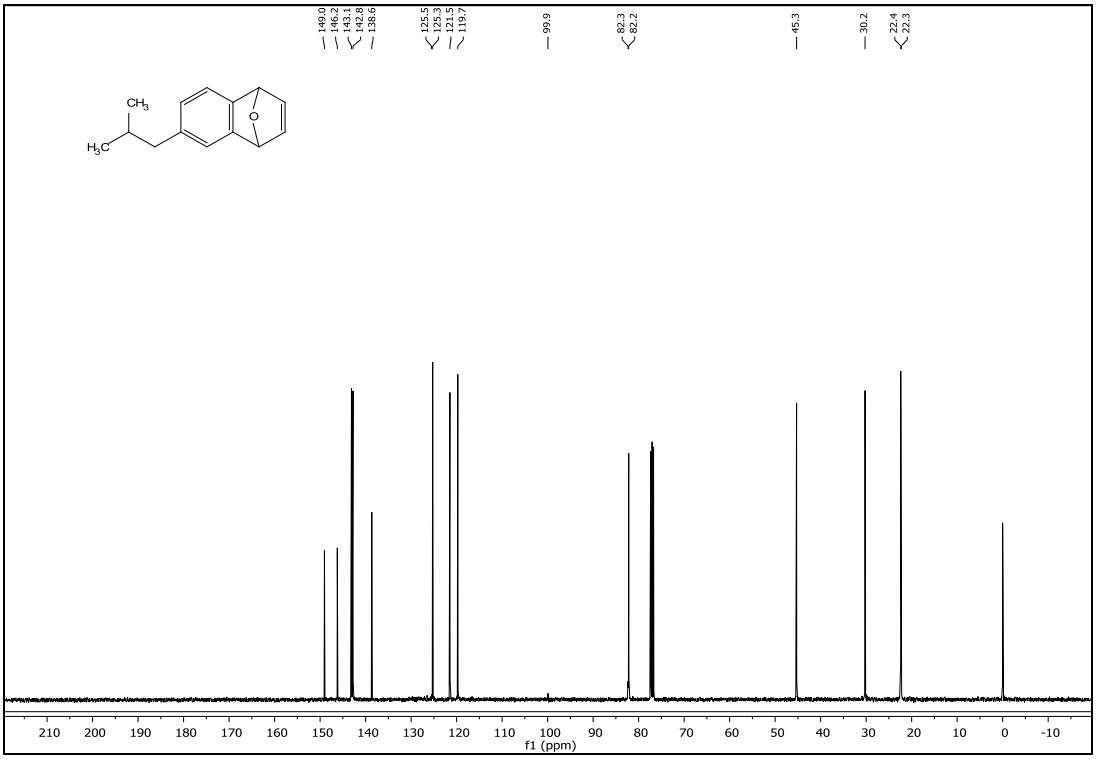


Figure 5.253: ^{1}H NMR of 2.43 at 400 MHz in $CDCl_3$ at 298K

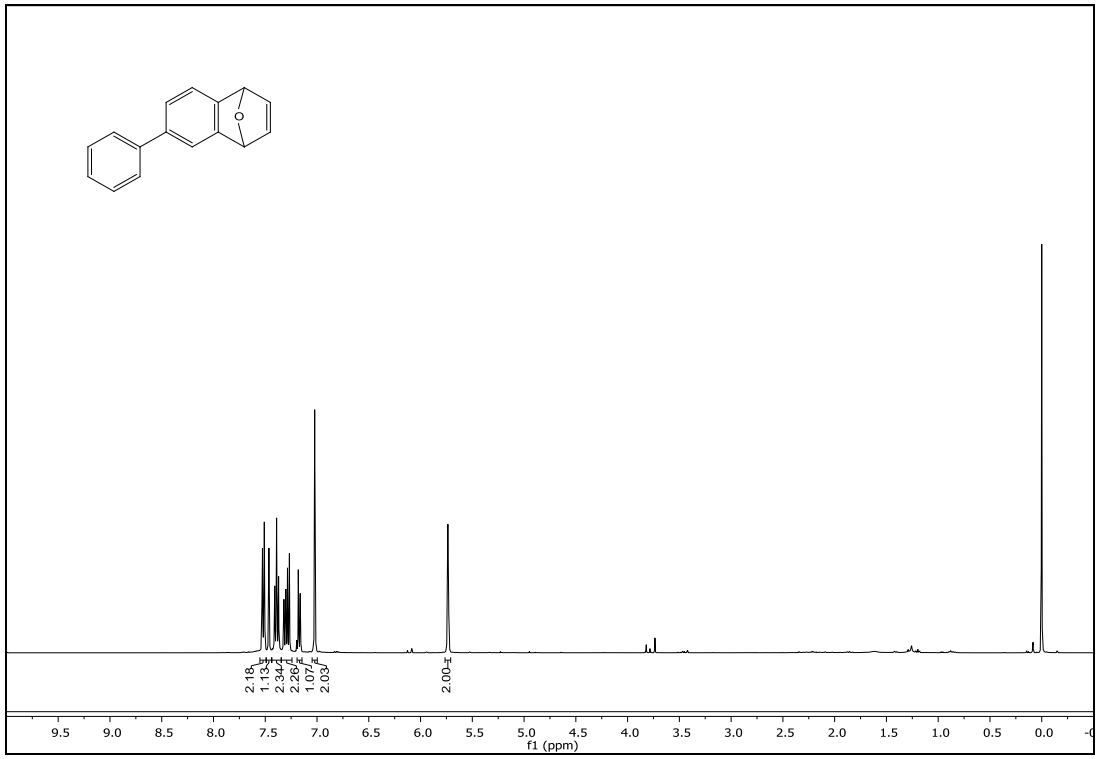


Figure 5.254: ^{13}C NMR of 2.43 at 101 MHz in $CDCl_3$ at 298K

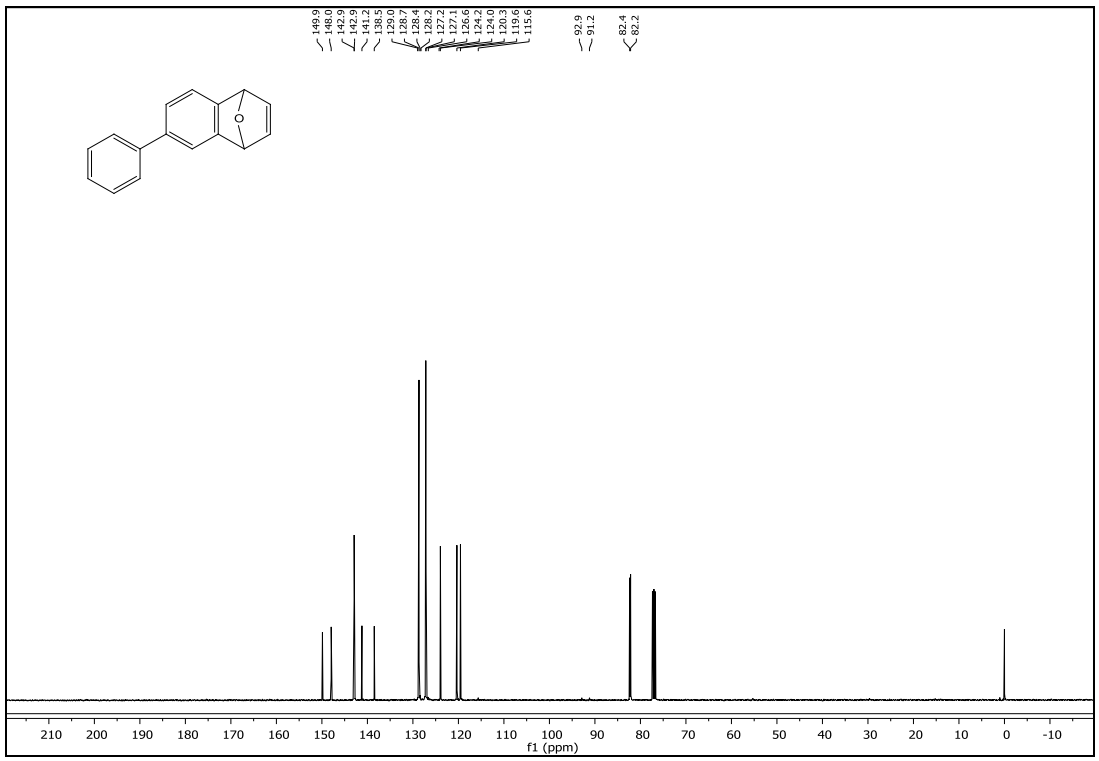


Figure 5.255: ^{1}H NMR of 2.44 at 400 MHz in $CDCl_3$ at 298K

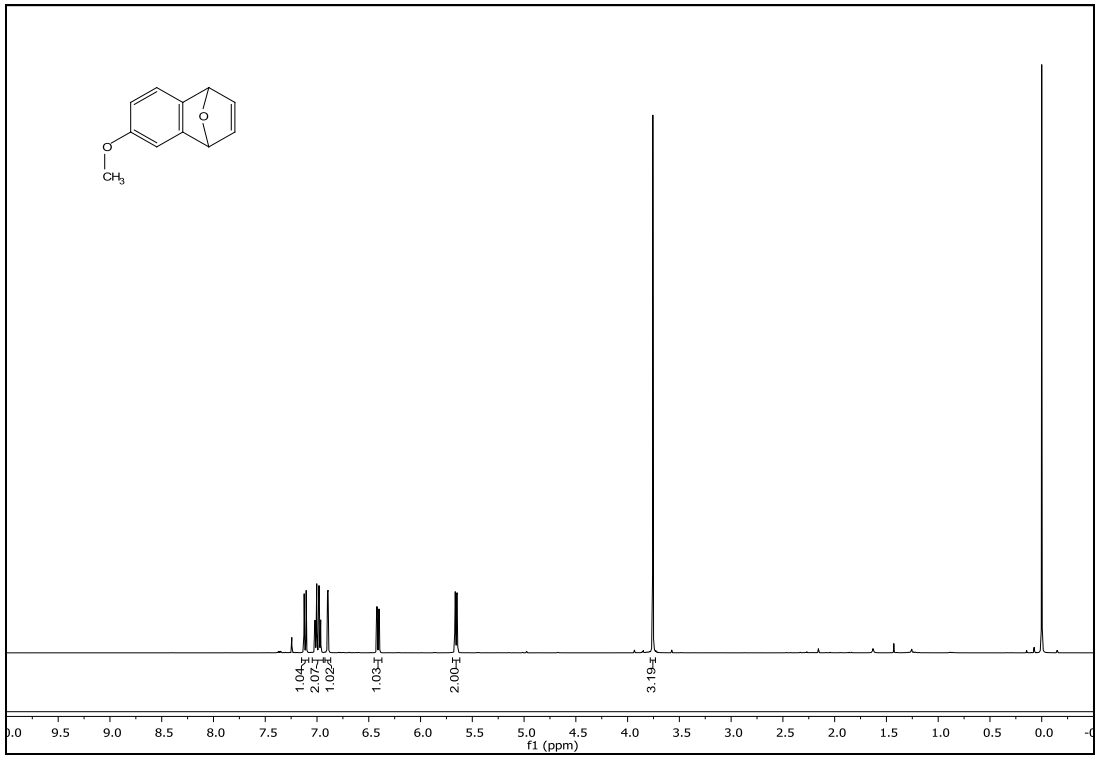


Figure 5.256: ^{13}C NMR of 2.44 at 101 MHz in $CDCl_3$ at 298K

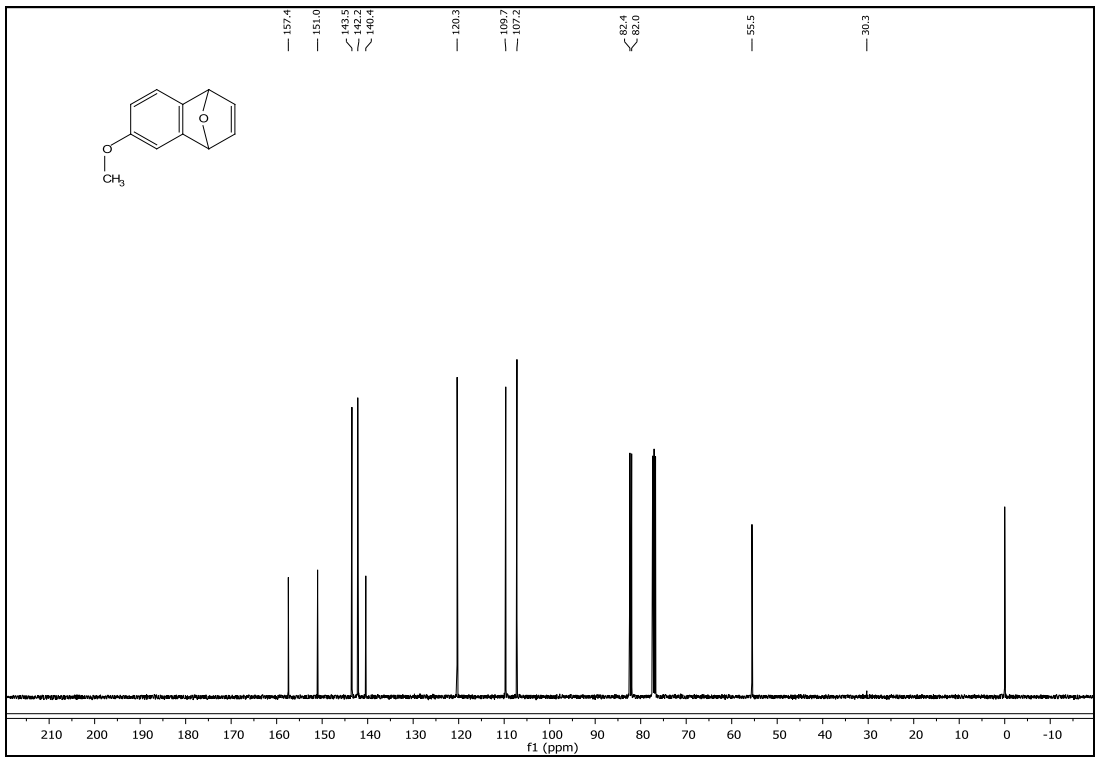


Figure 5.257: ^{1}H NMR of 2.45 at 400 MHz in $CDCl_3$ at 298K

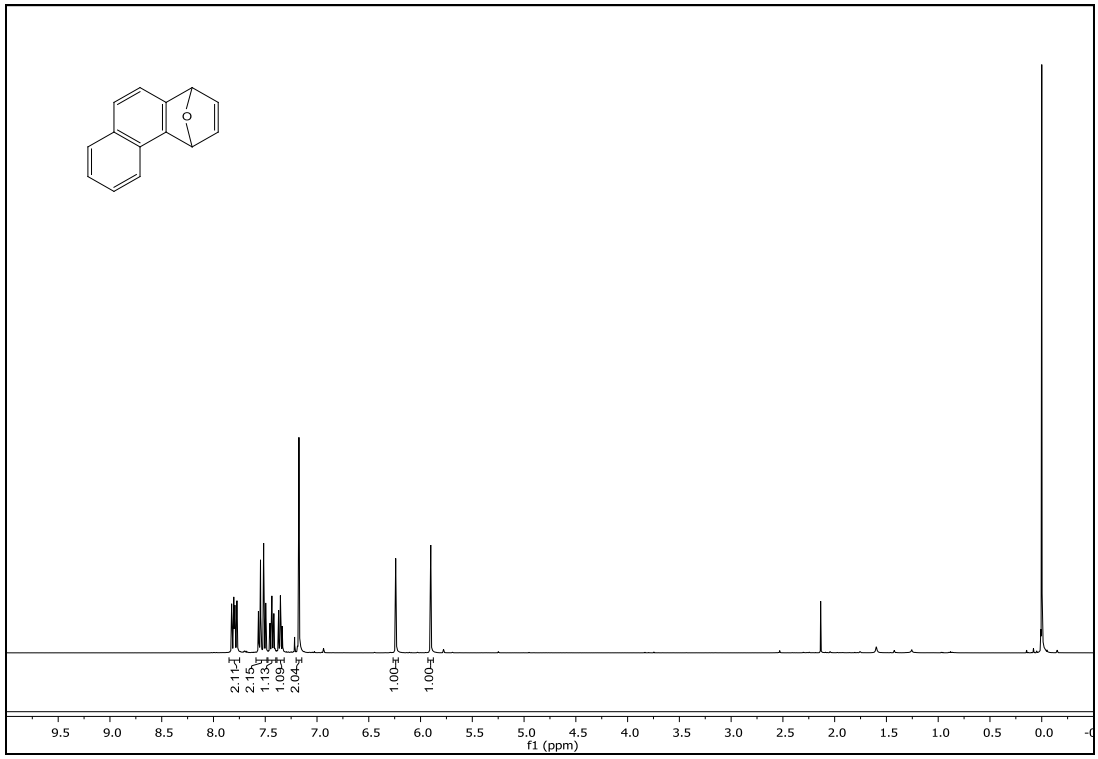


Figure 5.258: ^{13}C NMR of 2.45 101 MHz in $CDCl_3$ at 298K

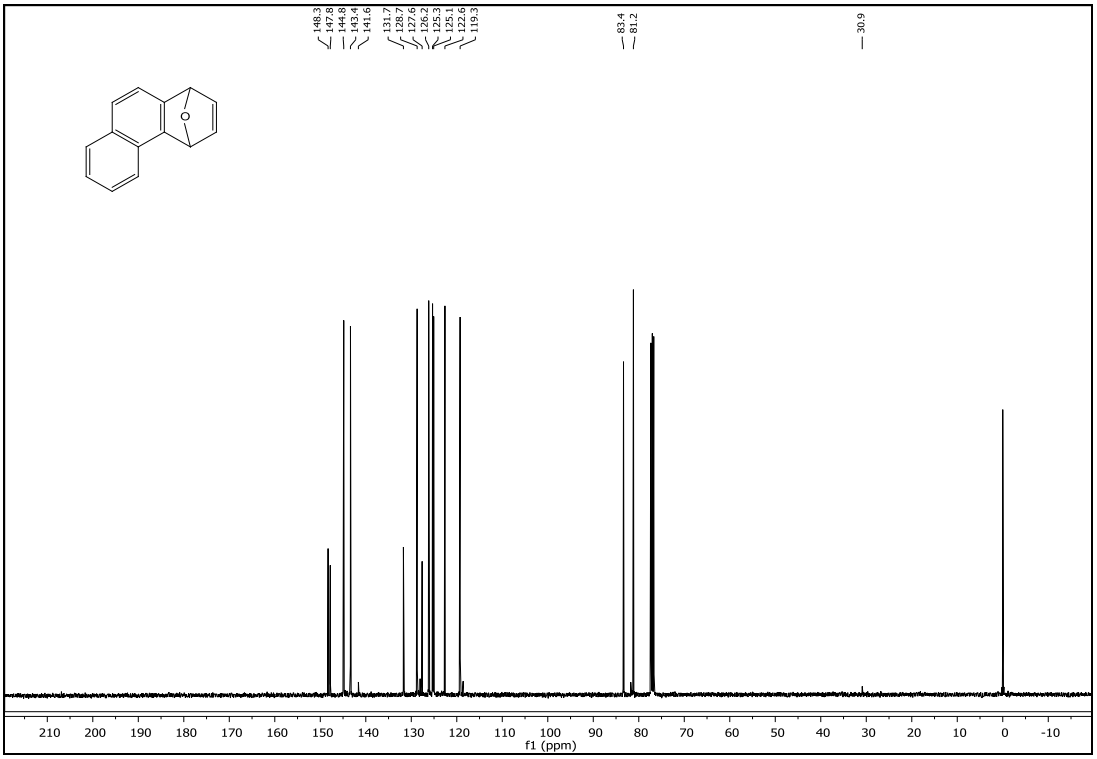


Figure 5.259: ^{1}H NMR of 2.46 at 400 MHz in $CDCl_3$ at 298K

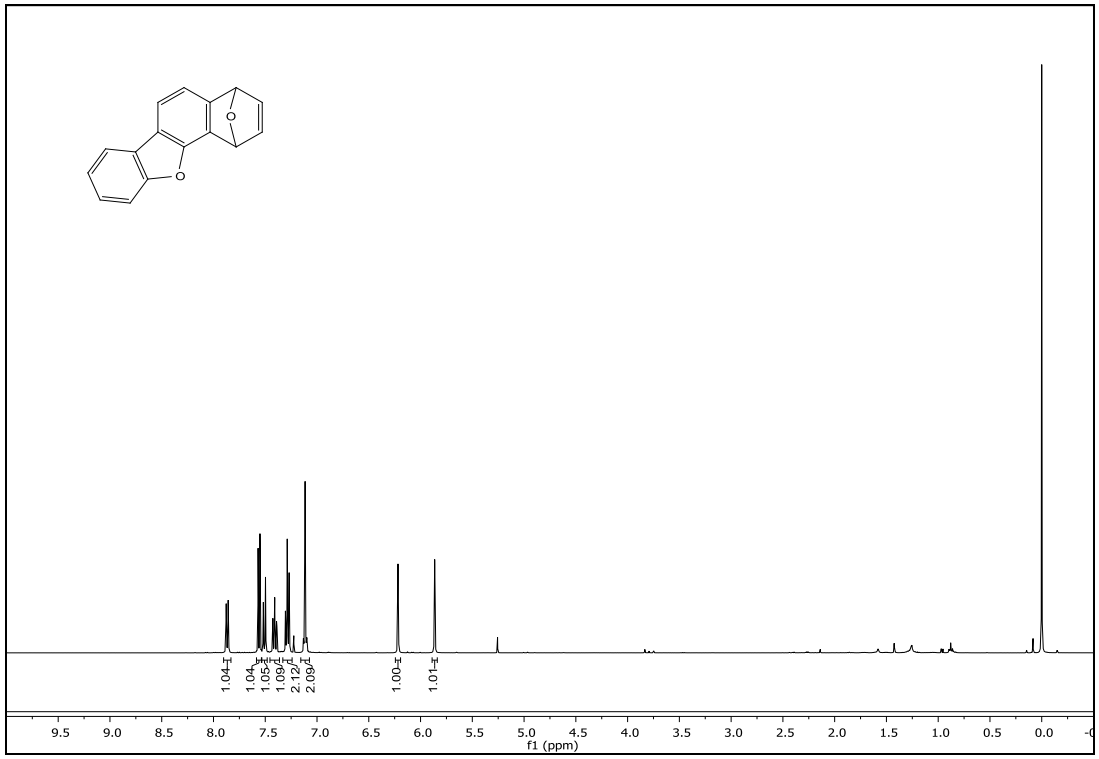


Figure 5.260: ^{13}C NMR of 2.46 101 MHz in $CDCl_3$ at 298K

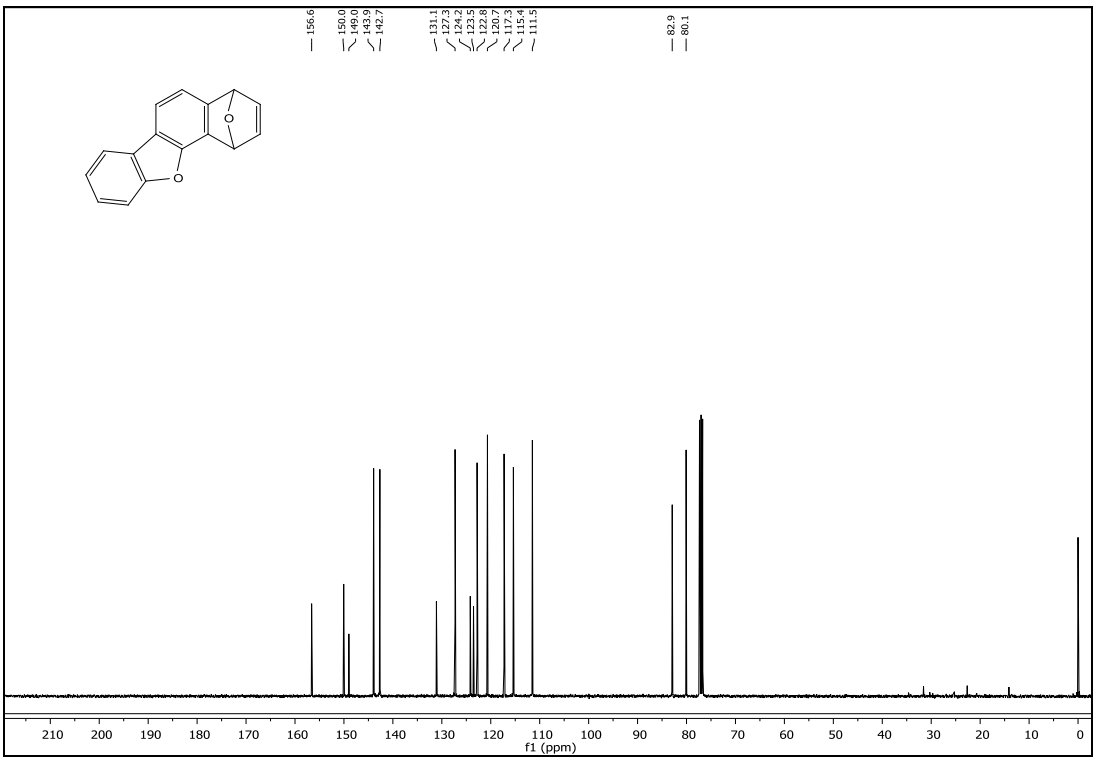


Figure 5.261: ^{1}H NMR of 2.47 at 400 MHz in $CDCl_3$ at 298K

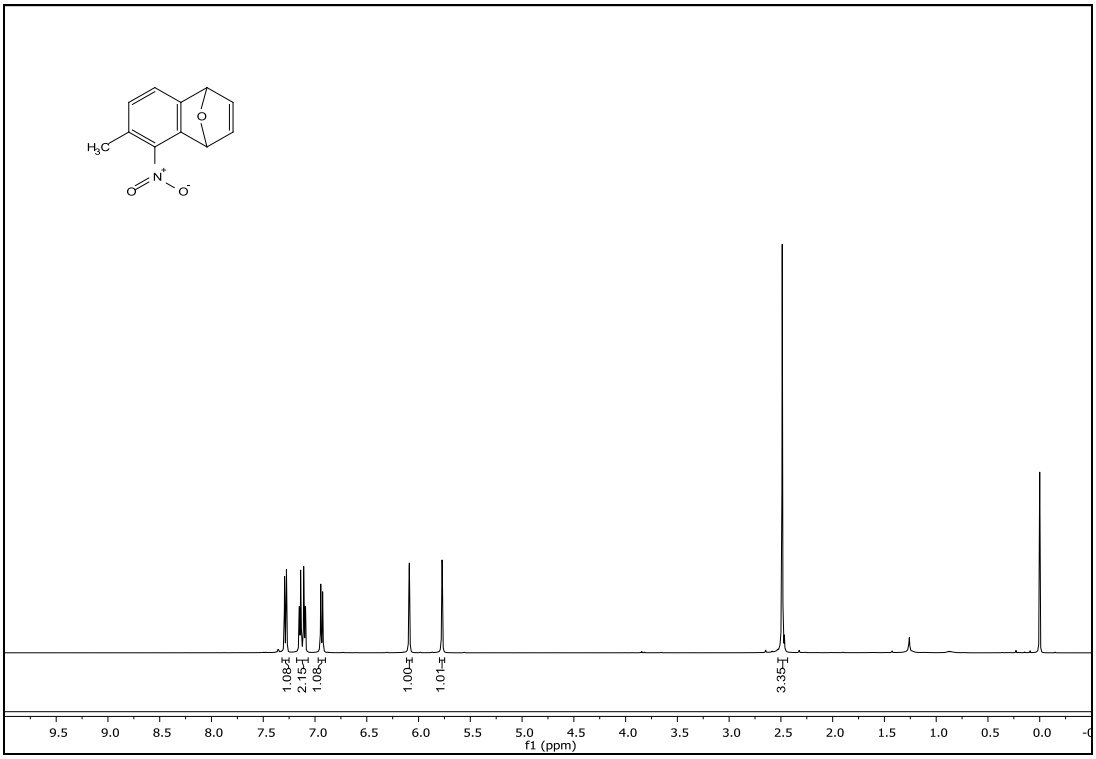


Figure 5.262: ^{13}C NMR of 2.47 101 MHz in $CDCl_3$ at 298K

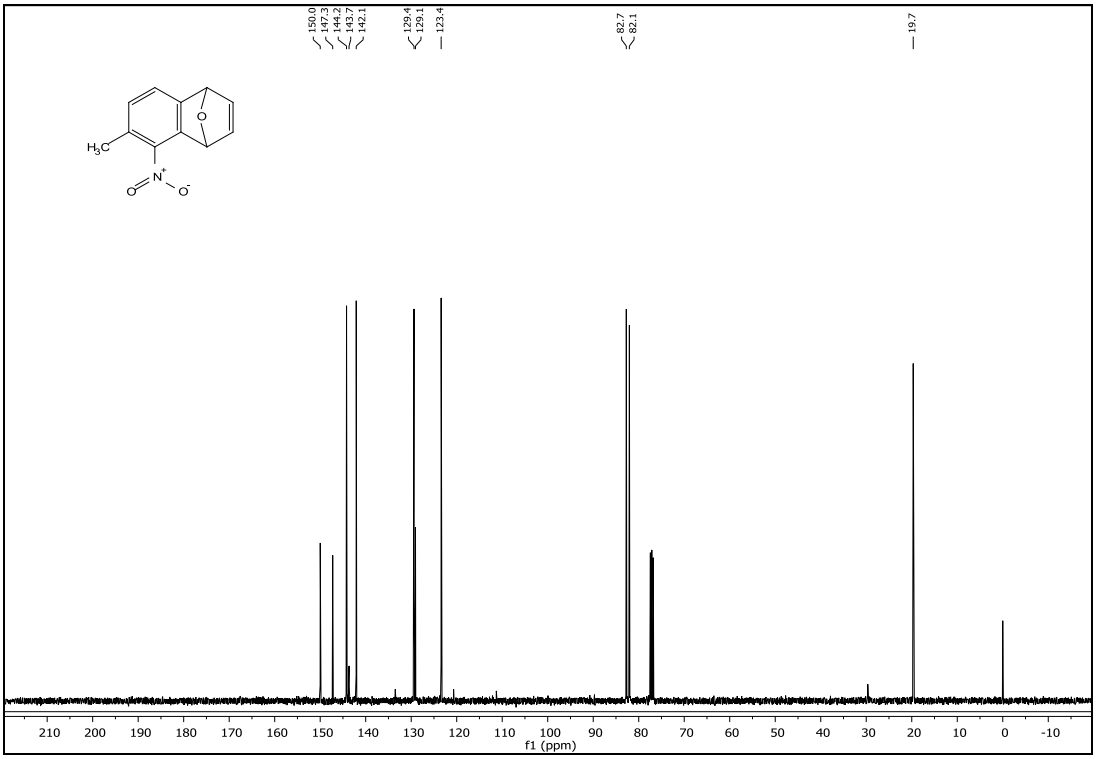


Figure 5.263: ^{1}H NMR of 2.48 at 400 MHz in $CDCl_3$ at 298K

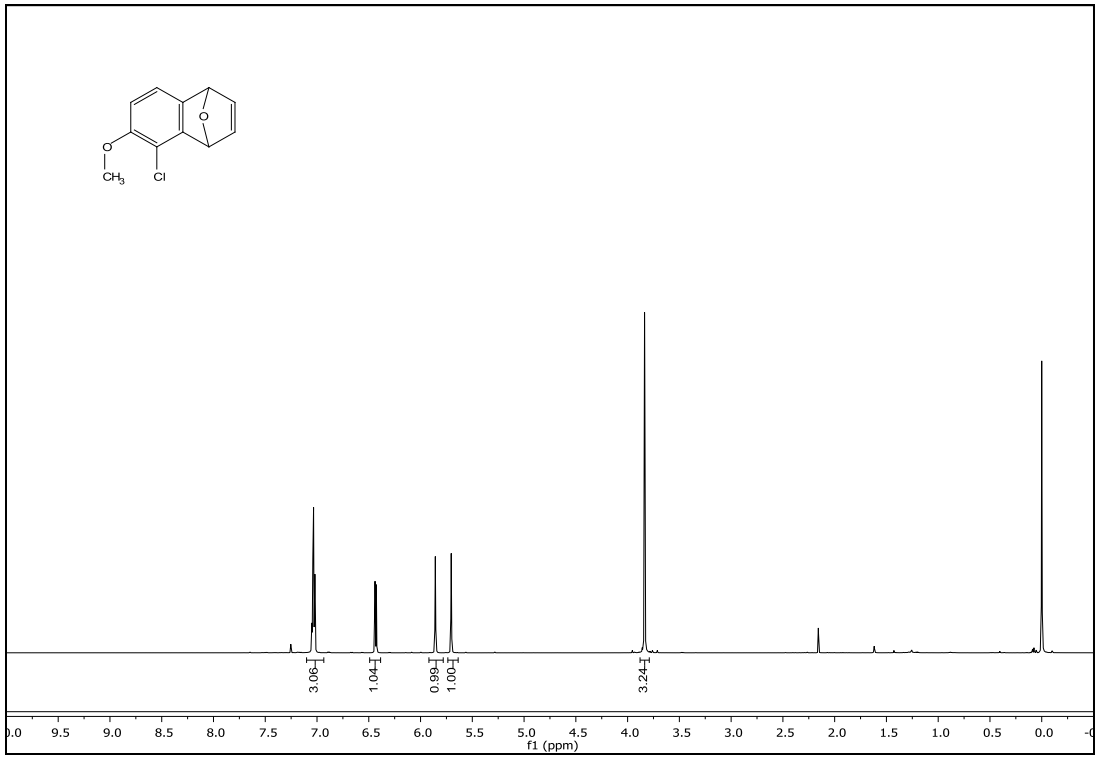


Figure 5.264: ^{13}C NMR of 2.48 101 MHz in $CDCl_3$ at 298K

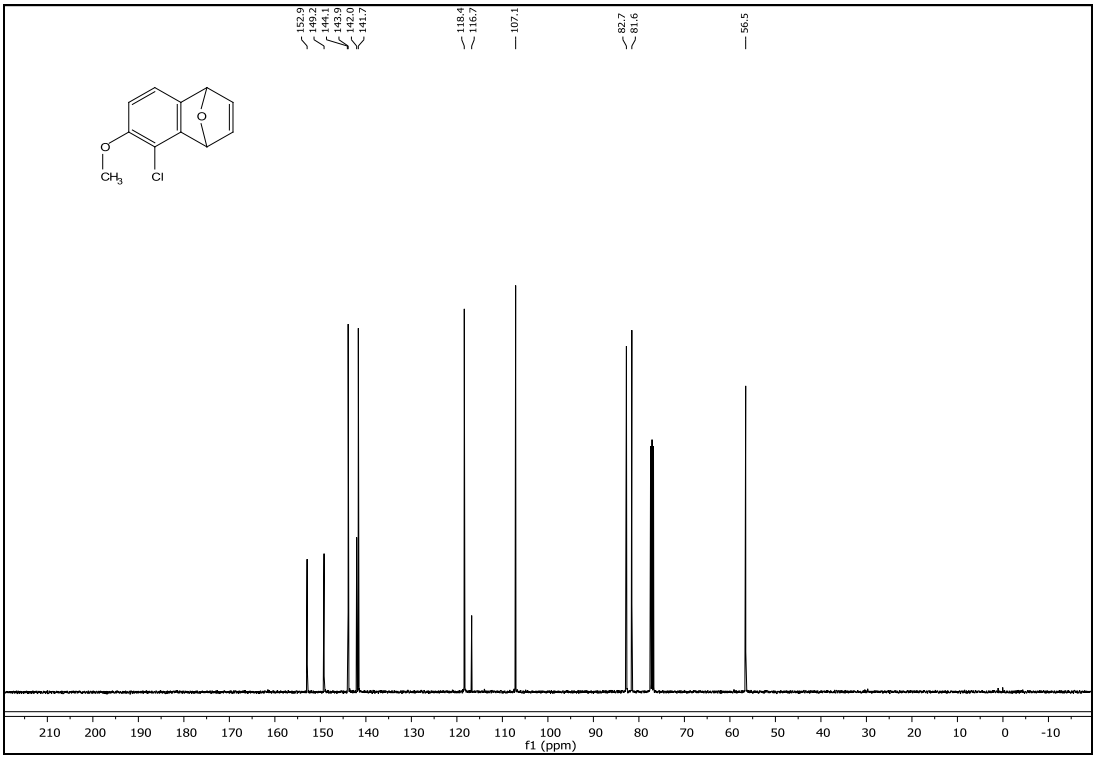


Figure 5.265: ^{1}H NMR of 2.49 at 400 MHz in $CDCl_3$ at 298K

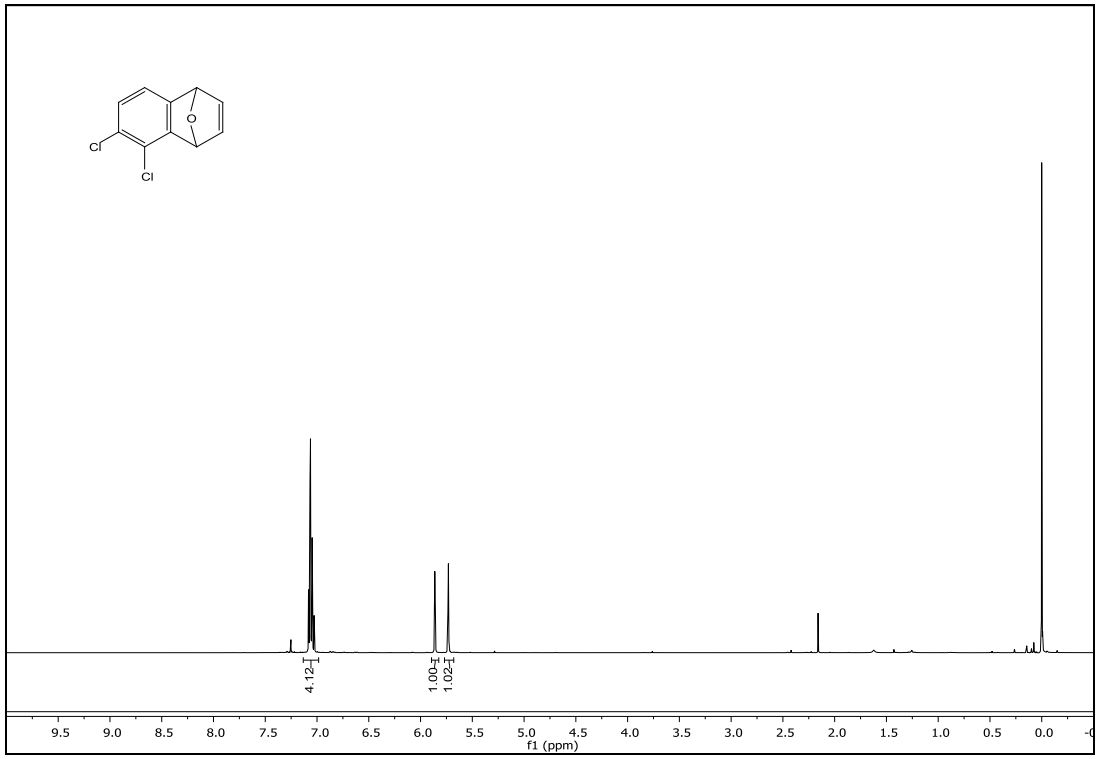


Figure 5.266: ^{13}C NMR of 2.49 101 MHz in $CDCl_3$ at 298K

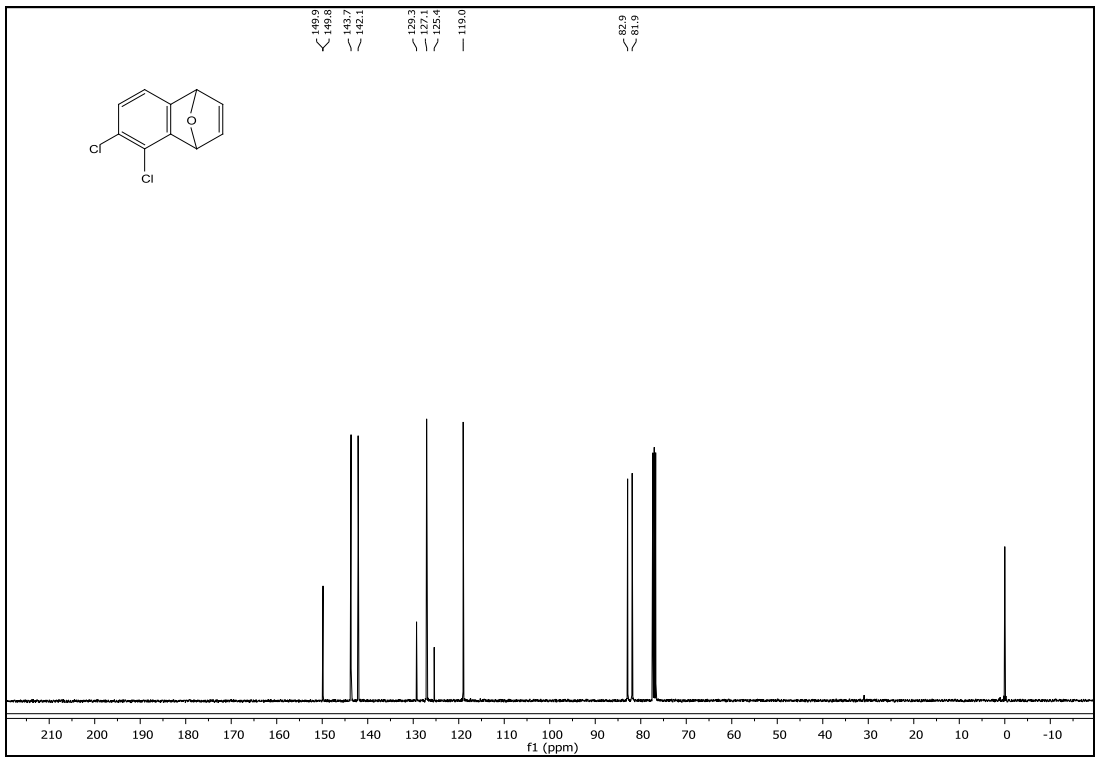


Figure 5.267: ^{1}H NMR of 2.50 at 400 MHz in $CDCl_3$ at 298K

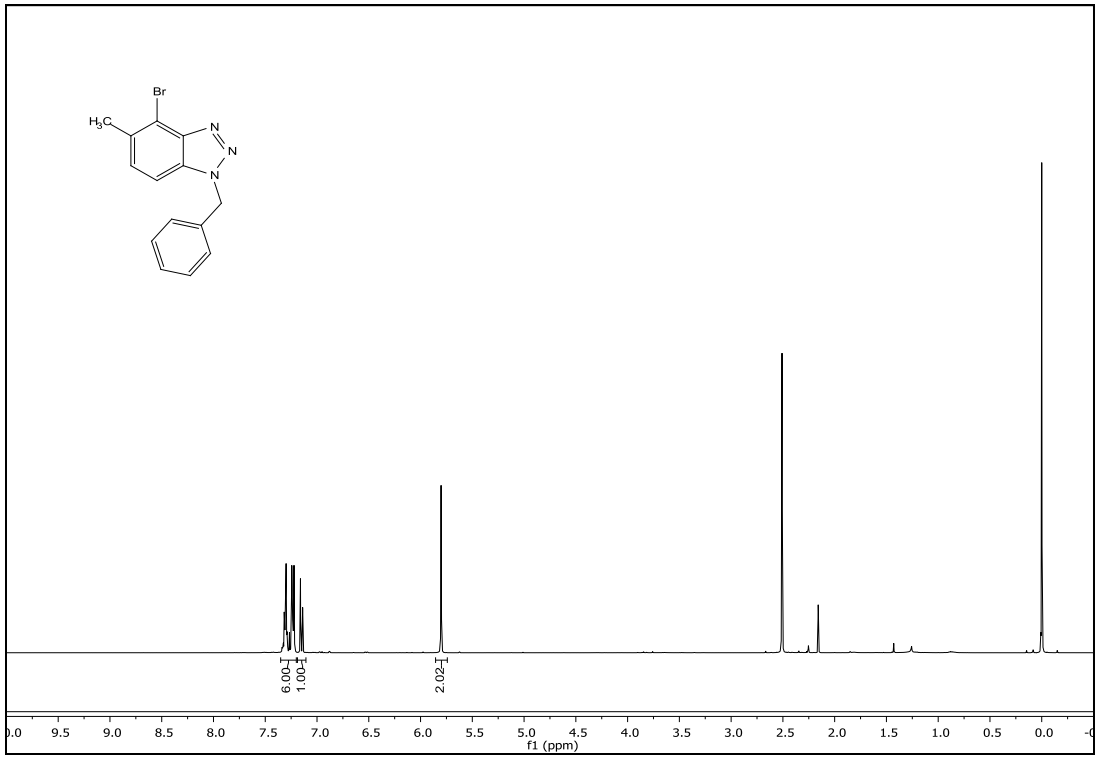


Figure 5.268: ^{13}C NMR of 2.50 101 MHz in $CDCl_3$ at 298K

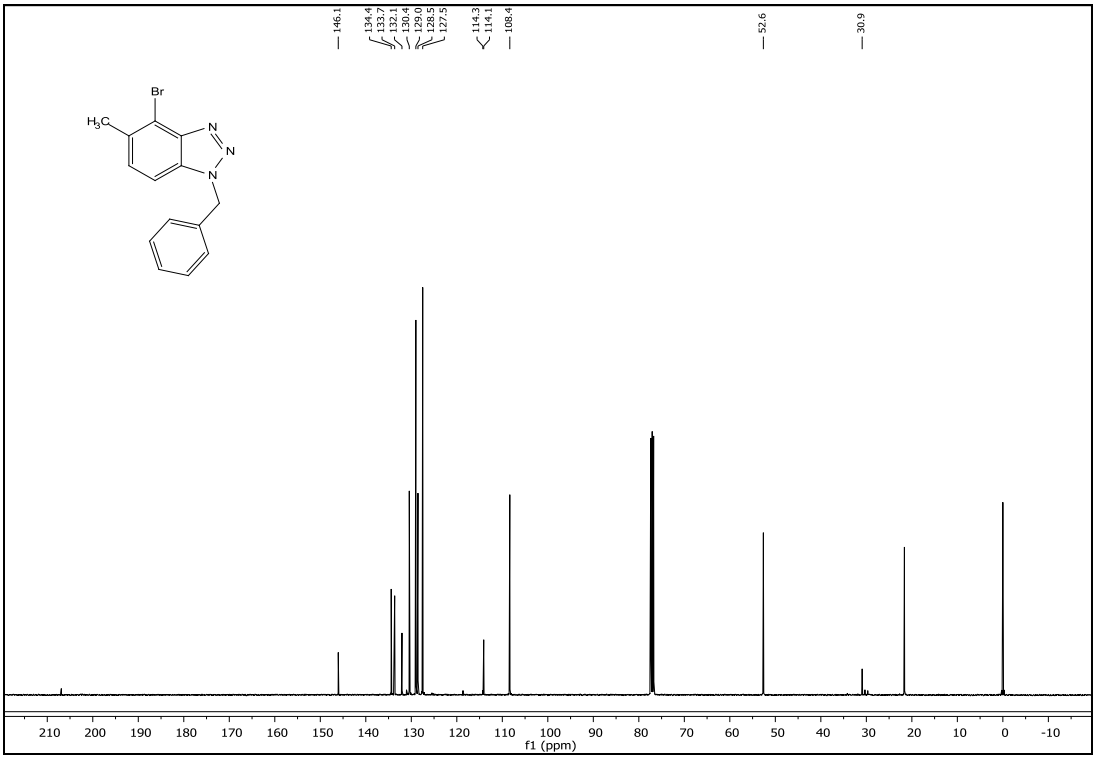


Figure 5.269: ^{1}H NMR of 2.51 at 400 MHz in $CDCl_3$ at 298K

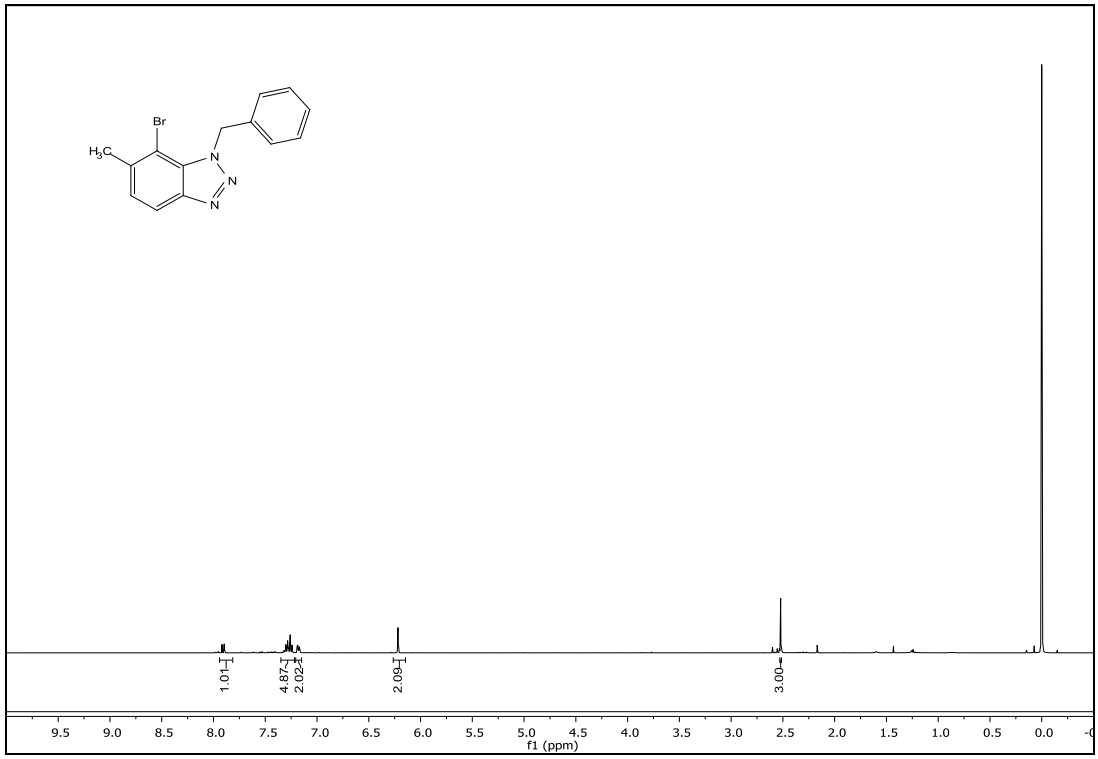


Figure 5.270: ^{13}C NMR of 2.51 101 MHz in $CDCl_3$ at 298K

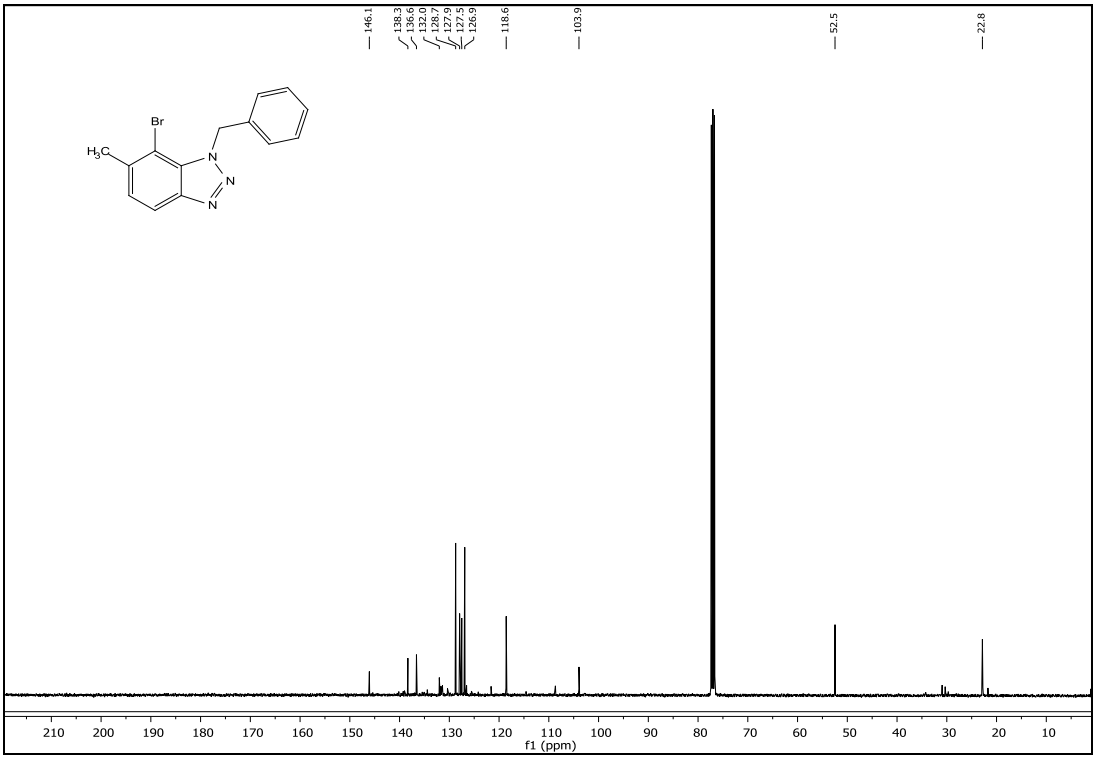


Figure 5.271: ^{1}H NMR of 2.52 at 400 MHz in $CDCl_3$ at 298K

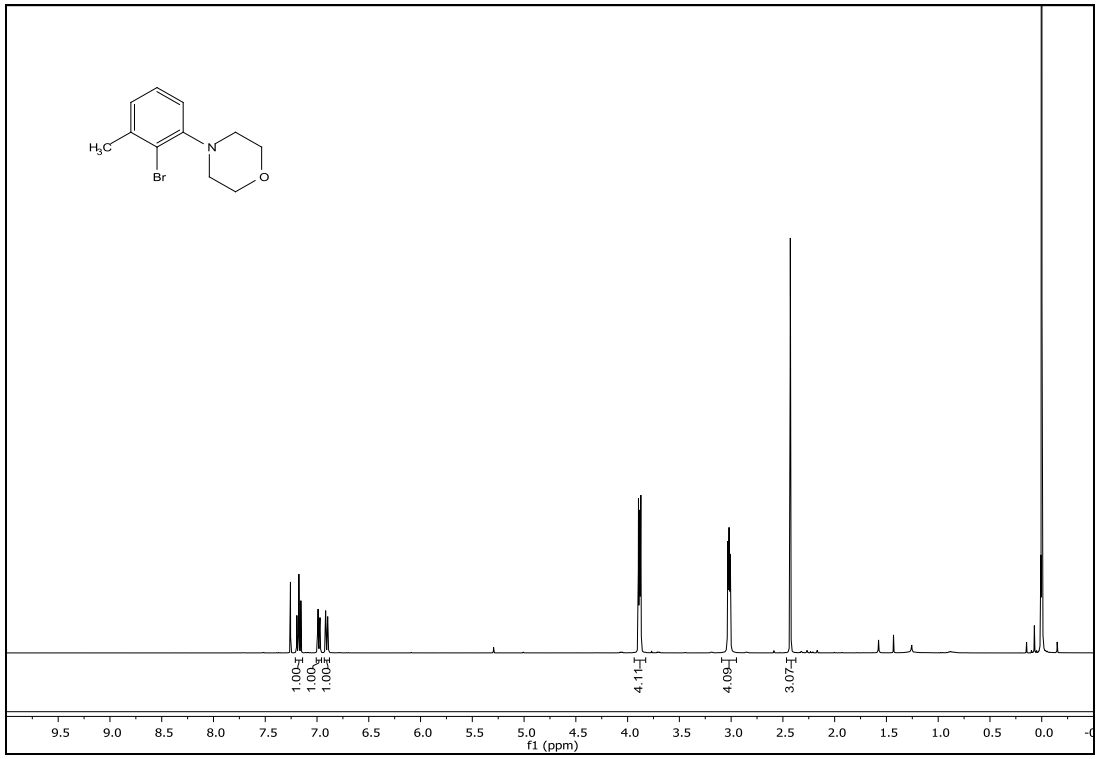


Figure 5.272: ^{13}C NMR of 2.52 101 MHz in $CDCl_3$ at 298K

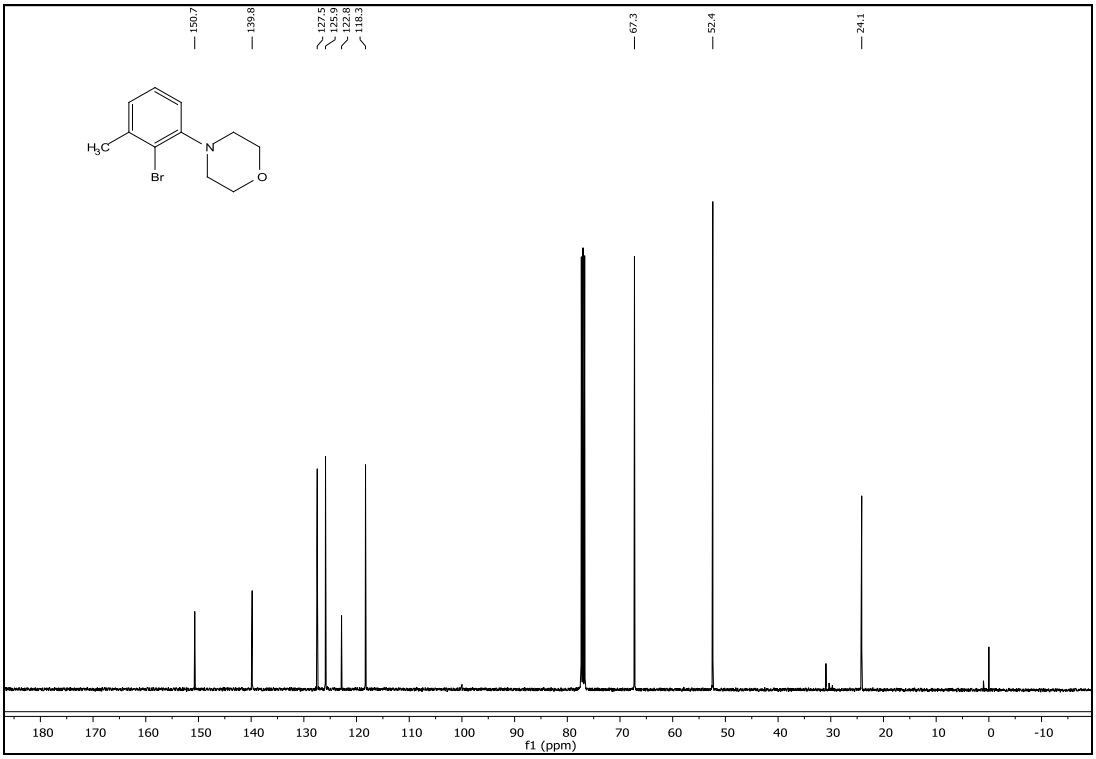


Figure 5.273: ^{1}H NMR of 2.53 at 400 MHz in $CDCl_3$ at 298K

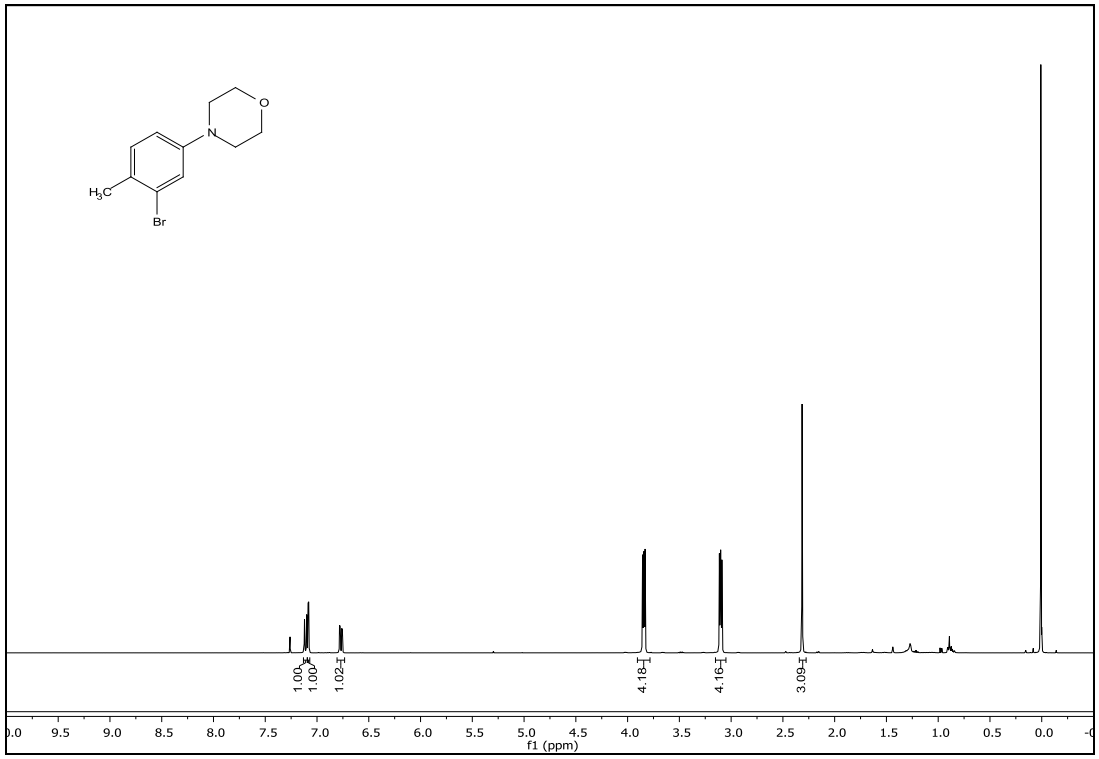


Figure 5.274: ^{13}C NMR of 2.53 at 101 MHz in $CDCl_3$ at 298K

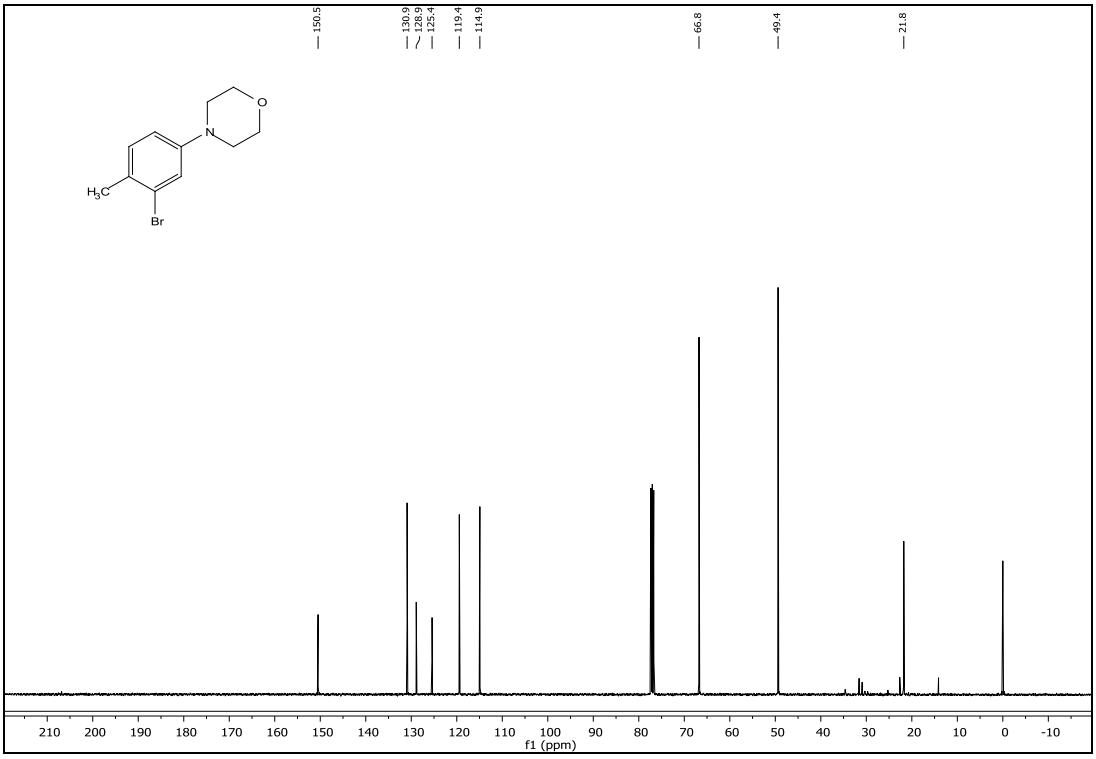


Figure 5.275: ^{1}H NMR of 2.54 at 400 MHz in $CDCl_3$ at 298K

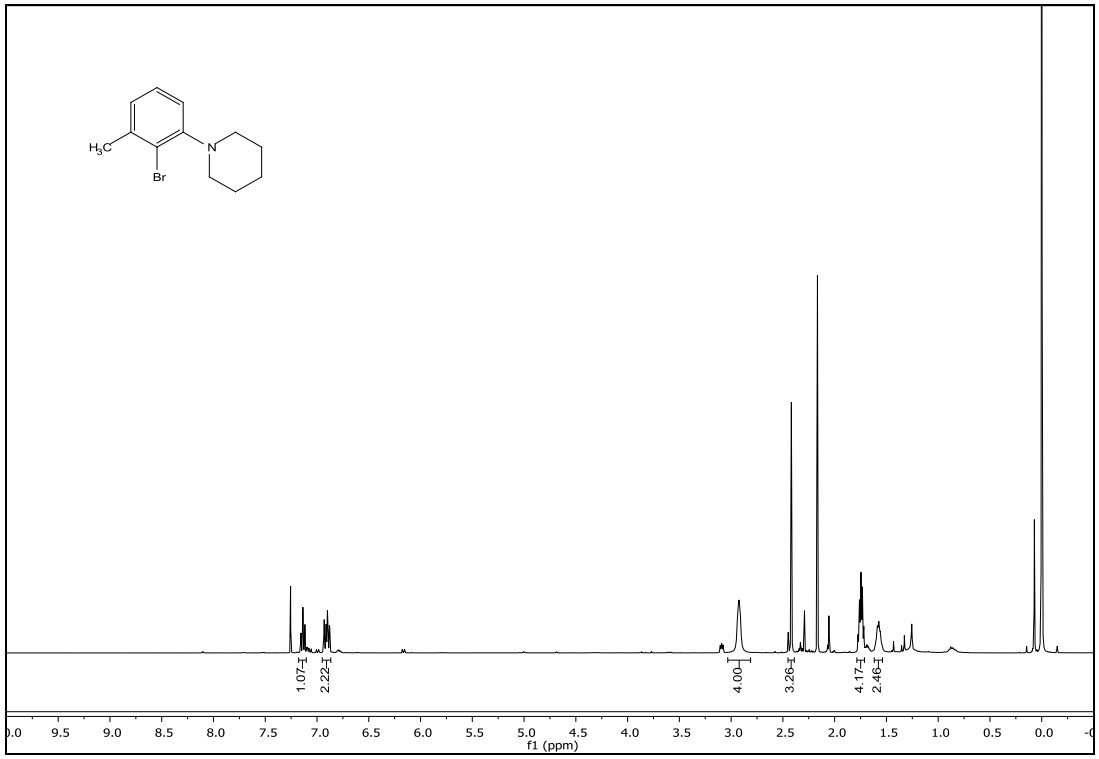


Figure 5.276: ^{13}C NMR of 2.54 at 101 MHz in $CDCl_3$ at 298K

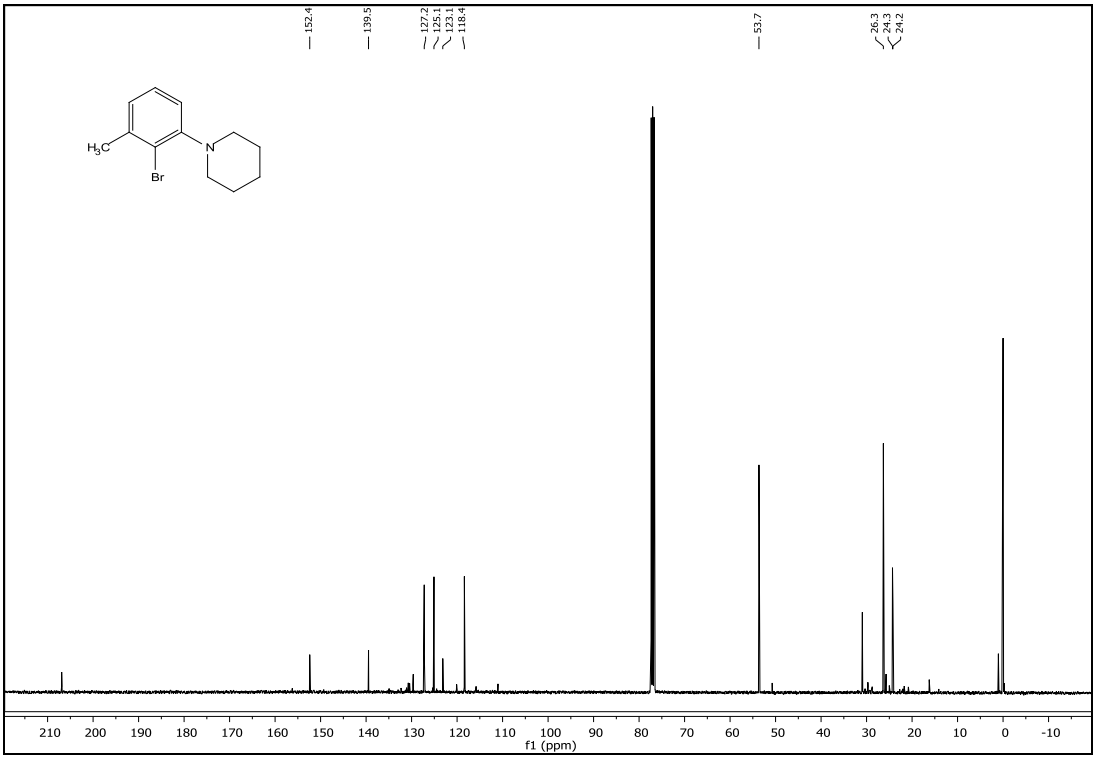


Figure 5.277: ^{1}H NMR of 2.55 at 400 MHz in $CDCl_3$ at 298K

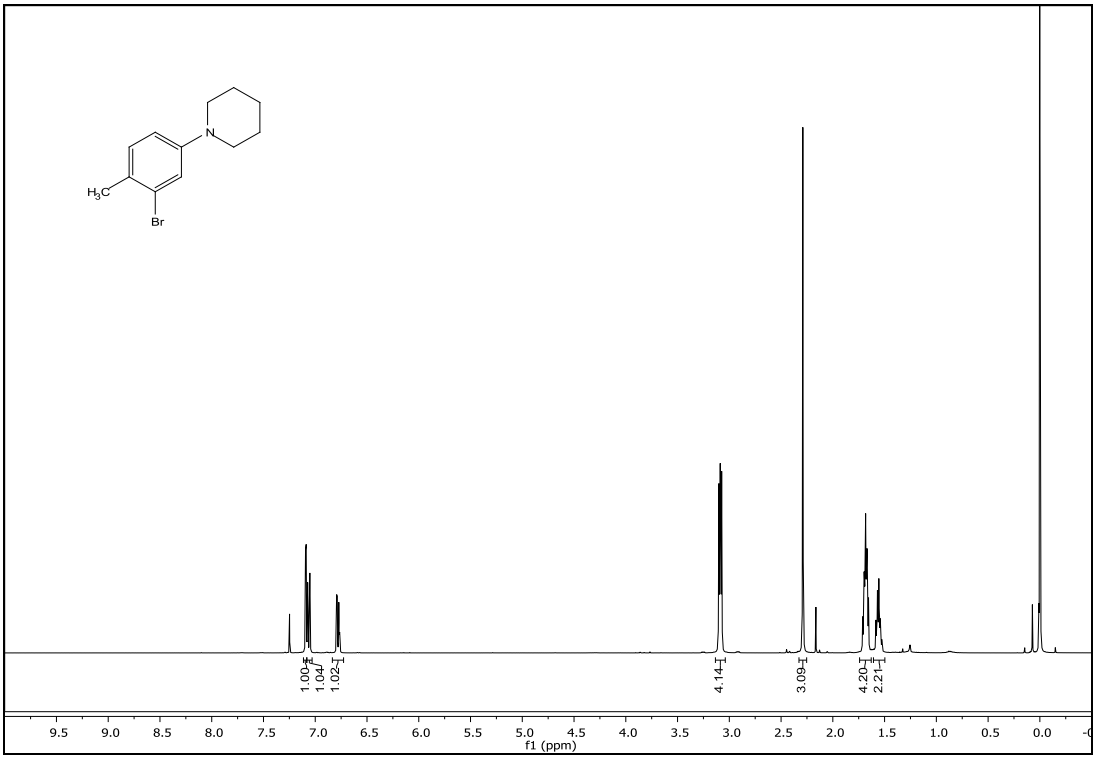
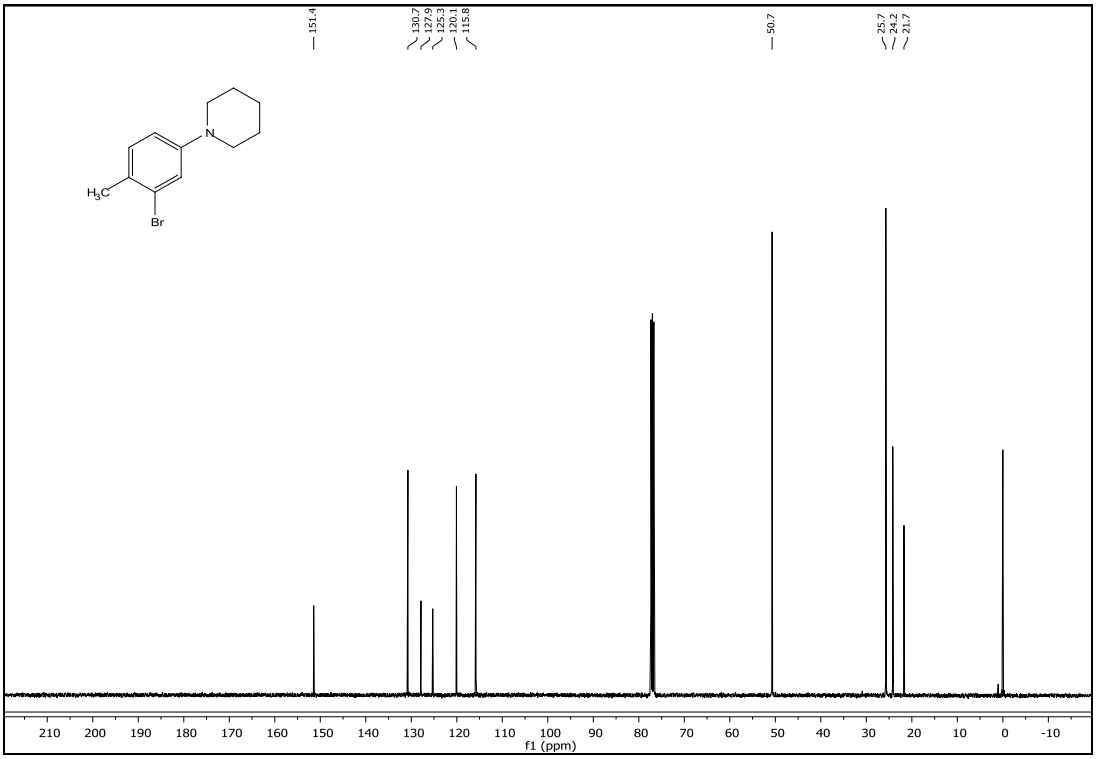


Figure 5.278: ^{13}C NMR of 2.55 101 MHz in $CDCl_3$ at 298k



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