DISSERTATION

FUNCTIONALIZATION OF PYRIDINES AND PYRIMIDINES VIA RING-OPENED INTERMEDIATES

Submitted by

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ABSTRACT

FUNCTIONALIZATION OF PYRIDINES AND PYRIMIDINES VIA RING-OPENED INTERMEDIATES

Pyridines and pyrimidines are prevalent in pharmaceuticals and agrochemicals, yet site-selective functionalization methods of these valuable structures are often limited. In this dissertation, we describe the development of pyridine and pyrimidine functionalization methods that will enable organic chemists to access functionalized heterocyclic materials more easily.

Chapter One describes the importance of pyridines and pyrimidines in industry, along with current methods and limitations in functionalizing these azines. Chapter Two introduces a 3-selective chlorination of pyridines using ring-opened Zincke imine intermediates. The method differs from a method our group reported in 2022 by ring-opening pyridine with aniline instead of dibenzylamine. Ring-opening azines with aniline produces imines and N-Ph azine salts with interesting properties, and enables the transformations described in every chapter of this dissertation. Chapter Three describes a 3-selective fluorination of pyridines using Zincke imine intermediates.

Chapter Four provides an overview of Structure-Activity-Relationship (SAR) studies, *de novo* heterocycle synthesis, and skeletal editing strategies, then describes a deconstruction-reconstruction approach for pyrimidine diversification. Chapter Five discusses stable isotopes in medicinal chemistry, then expands on the deconstruction-reconstruction strategy for stable isotope incorporation into pyrimidines.

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TABLE OF CONTENTS

ABSTRACT ii
ACKNOWLEDGEMENTS iii
CHAPTER 1. Importance of Pyridines and Pyrimidines 1
1.1 Importance of Nitrogen-containing Heterocyclic Compounds in Pharmaceuticals and Agrochemicals 1
1.2 Challenges in Azine Functionalization 2
1.3 Existing Methods for Pyridine and Pyrimidine Functionalization 3
1.4 Conclusions 4
REFERENCES 5
CHAPTER 2. 3-Selective Chlorination of Pyridines via Zincke Imine Intermediates 9
2.1 Chapter Overview 9
2.2 Introduction to Halogenated Arenes 9
2.2.1 Methods for Arene Halogenation 11
2.2.2 Methods to Halogenate Pyridines 12
2.3 Halogenation via Zincke Intermediates 16
2.3.1 Background on the Zincke Reaction 16
2.3.2 N-Tf Zincke Imine Discovery and Applications 17
2.3.3. Halogenation of Pyridines via N-Tf Zincke Imine Intermediates 19
2.4 Development of a 3-Selective Chlorination of Pyridines via Aniline-Based Zincke Imines 20
2.4.1 Introduction to Pyridine Ring-Opening with Aniline 20
2.4.2 Chlorination of N-Phenyl Zincke Imines 22
2.4.3 Mechanistic Studies of 3-Selective Chlorination 24
2.5 Selectivity Switching Iodination of Aniline-Derived Zincke Imines 25
2.6 Conclusion 27
REFERENCES 28
CHAPTER 3. 3-Selective Pyridine Fluorination via Zincke Imine Intermediates 34
3.1 Chapter Overview 34
3.2 Importance of Fluoropyridines in Pharmaceuticals and Agrochemicals 34
3.3 Existing Methods to Fluorinate Pyridines 35

3.4 Development of a 3-Selective Fluorination of Pyridines 37
3.5 Scope of 3-Selective Pyridine Fluorination 39
3.5 Conclusions 42
REFERENCES 44
CHAPTER 4. A Deconstruction-Reconstruction Strategy for Pyrimidine Diversification 48
4.1 Chapter Overview 48
4.2 Structure-Activity-Relationship Studies in Medicinal Chemistry 48
4.2.1 Introduction to Structure-Activity-Relationship Studies 48
4.2.1 De Novo Heterocycle Synthesis 50
4.2.2 Skeletal Editing as a Tool for Drug Discovery 52
4.3 Introduction to Pyrimidine Deconstruction-Reconstruction 54
4.4 Scope of Pyrimidine Deconstruction-Reconstruction 58
4.5 Formal N–C Replacement Converting Pyrimidines to Pyridines 63
4.6 Mechanistic Studies of Pyrimidinium Salt Formation 66
4.7 Functional Group Metathesis via Deconstruction-Reconstruction 68
REFERENCES 71
CHAPTER 5. Stable Isotope Labeling of Pyrimidines Using a Deconstruction-Reconstruction Strategy 76
5.1 Chapter Overview 76
5.2 Introduction to Stable Isotopes in Medicinal Chemistry 76
5.3 Existing Methods to Isotopically Label Pyrimidines 78
5.4 Development of a Pyrimidine Isotope Exchange Method by Deconstruction-Reconstruction 79
5.5 Scope of Pyrimidine Isotopic Enrichment Procedure 81
5.6 Deuteration of Vinamidinium Salts and Access to Diverse Isotopologs 83
5.7 Conclusions 84
REFERENCES 86
APPENDIX ONE: HALOGENATION OF PYRIDINES VIA ZINCKE IMINES: EXPERIMENTAL 88
APPENDIX TWO: PYRIMIDINE DIVERSIFICATION VIA DECONSTRUCTION-RECONSTRUCTION: EXPERIMENTAL 261
APPENDIX THREE: PYRIMIDINE STABLE ISOTOPE INCORPORATION: EXPERIMENTAL 518

CHAPTER 1. IMPORTANCE OF PYRIDINES AND PYRIMIDINES

1.1 Importance of Nitrogen-containing Heterocyclic Compounds in Pharmaceuticals and Agrochemicals

Pharmaceuticals play a critical role in modern medicine and disease treatment. Small molecules (MW < 900 Daltons) make up nearly 90% of FDA-approved drugs, [1] and a 2014 survey by Njardarson found that 59% of all small molecule FDA-approved drugs contain a nitrogen heterocycle (*N*-heterocycle).[2] Of those *N*-heterocycles, pyridine was the second most prevalent among FDA-approved drugs, and pyrimidines were the 10th most-prevalent. Furthermore, the Njardarson group studied drugs approved between 2013-2023 and found that *N*-heterocycles increased in prevalence to 82%.[3] They also found pyridine to be the most prevalent, with pyrimidines as the fifth most-prevalent, indicating an increased presence of these heterocycles in recently-developed drugs. Figure 1.1 shows six pyridine- and pyrimidine-containing pharmaceuticals, with varying levels of structural complexity and biological applications.

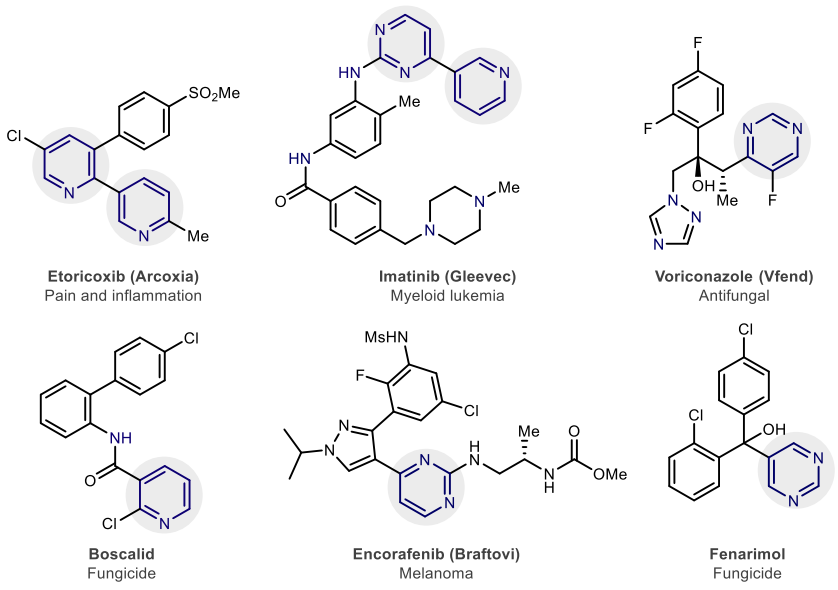


Figure 1.1. Examples of pyridine and pyrimidine-containing drugs and agrochemicals.

Six-membered aromatic *N*-heterocycles, also known as azines, are prevalent in pharmaceuticals for a number of reasons. Replacing a benzene ring with a pyridine ring can improve the bioavailability and pharmacokinetics of a drug, with some examples improving efficacy >500-fold.[4] This is due, in large part, to the lone pair on the pyridine and pyrimidine nitrogen, which can improve drug-protein interactions, improve solubility of drug molecules in aqueous environments, and improve cell permeability. Replacing a benzene ring with an azine can also improve metabolic stability, as azines are more electron-deficient than benzene, making them more stable to oxidative metabolism by Cytochrome P-450 enzymes.[6]

1.2 Challenges in Azine Functionalization

Pyridine is structurally similar to benzene where one carbon is replaced with an sp^2–hybridized nitrogen. Nitrogen is more electronegative than carbon, resulting in a net dipole in the ring. The nitrogen lone pair is positioned in the plane of the aromatic ring and unable to donate electron density into the π-system of the ring. Though azines resemble benzene in structure, they react very differently. Aromatic carbocycles are often better π-nucleophiles and engage in electrophilic aromatic substitution (EAS) reactions much more readily, whereas azine heterocycles are more electrophilic. Pyridines react better with nucleophiles but require forcing conditions to undergo EAS.[7] The pyridine nitrogen lone pair can serve as a Brønsted or Lewis acid, coordinating to protons, transition metals, and electrophiles, disrupting transition metal-catalyzed reactions and rendering pyridine less reactive towards electrophilic substitution. This can be exploited to form N-H or N-R pyridiniums, promoting nucleophilic reactions on *N*-heteroaromatic rings.

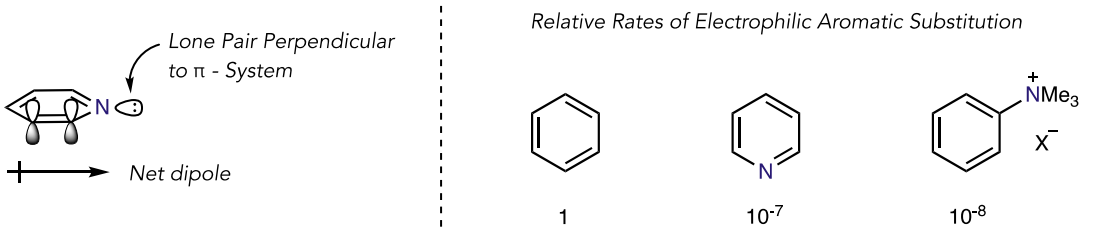


Figure 1.2 Properties of electron-deficient azaarenes.

Similarly, pyrimidines are diazines with two sp^2 nitrogens in the ring with a one-carbon spacer between the nitrogens. Due to the additional electronegative nitrogen, pyrimidines have significantly increased π-deficiency, are even less reactive to EAS, and exhibit decreased basicity.[8]

Despite the prevalence of *N*-heterocycles in biologically-relevant molecules, modern approaches to their synthesis still have significant limitations, and methods to selectively functionalize them are in high demand. Methods to functionalize azines often require pre-installed directing groups or functional handles and suffer from poor positional selectivity.

1.3 Existing Methods for Pyridine and Pyrimidine Functionalization

Despite the challenges associated with azine reactivity, organic chemists have developed numerous strategies to functionalize and diversify *N*-heterocycles. Several strategies exist for functionalizing pyridine, including the Chichibabin amination and the Minisci reaction (Fig. 1.3). In 1914, Chichibabin demonstrated that pyridines can undergo amination with sodium amide ($NaNH_2$), yielding 2-aminopyridine derivatives.[9] However, the method requires high temperatures and uses a strongly basic reagent, which restricts its broader applicability. Later, in 1971, Minisci reported that alkyl radicals could be introduced to pyridine rings, typically resulting in a mixture of 2- and 4-substituted products, demonstrating a lack of selectivity.[10] Both of these approaches function on pyrimidines with similar limitations.[11] Another common strategy for azine functionalization involves metalating pyridine and pyrimidine with reagents like organolithiums, generating reactive organometallic intermediates.[12] The lithiated intermediates can be subsequently reacted with electrophiles, often requiring directing groups often that determine reaction selectivity. Classical approaches to the functionalization of *N*-heterocycles often use harsh reagents leading to poor functional group tolerance and selectivity issues.

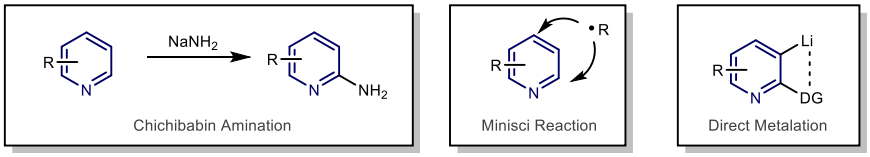


Figure 1.3 Classical pyridine functionalization reactions.

In recent years, more moderate and versatile methods for azine functionalization have emerged, demonstrating compatibility with structurally complex, drug-like compounds (Figure 1.4). To improve upon the limitations of the Chichibabin reaction, researchers at Merck, along with Fier, introduced a bifunctional chloropyrazine reagent that enables the installation of an NH_2Boc group at the 2-position of pyridines via an addition–elimination mechanism.[13] Additionally, the Hartwig group has developed a fluorination technique targeting the 2-position of Ag-pyridinium intermediates, yielding products well-suited for subsequent S_NAr chemistry.[14] Their work also includes selective incorporation of pinacol boronic esters at the 3-position, producing intermediates that participate readily in further transformations.[15] While these advancements have significantly expanded the available tools for modifying azines and enabled access to valuable derivatives previously out of reach, continued innovation is necessary to functionalize other positions on N-heterocycles and to address existing methodological constraints.

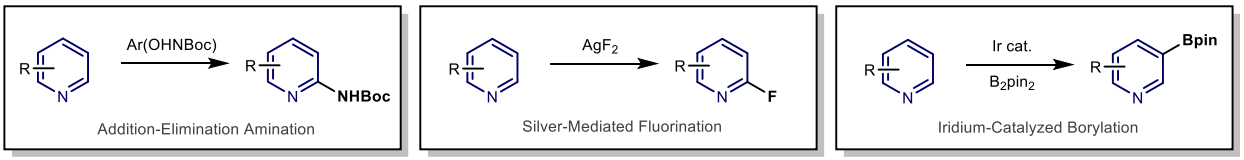


Figure 1.4 Modern approaches for pyridine functionalization.

1.4 Conclusions

This chapter establishes the critical importance of nitrogen-containing heterocycles, particularly pyridines and pyrimidines, in the pharmaceutical and agrochemical industries. These six-membered aromatic azines are highly prevalent in FDA-approved small molecule drugs due to their ability to enhance bioavailability, solubility, and metabolic stability. Despite their utility,

pyridines and pyrimidines present significant synthetic challenges due to their electron-deficient nature, poor reactivity toward electrophilic aromatic substitution, and interference in transition metal-catalyzed reactions. Traditional methods such as the Chichibabin amination and Minisci reaction have enabled limited functionalization but suffer from harsh conditions and low selectivity. Recent innovations, including milder and more selective methods, have improved functional group compatibility and positional selectivity, yet challenges remain in accessing underexplored substitution patterns. This chapter underscores the ongoing need for new strategies to selectively modify these privileged scaffolds for drug development and beyond.

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CHAPTER 2. 3-SELECTIVE CHLORINATION OF PYRIDINES VIA ZINCKE IMINE INTERMEDIATES

2.1 Chapter Overview

This chapter describes a novel strategy to chlorinate the 3-position of pyridines by extending an approach developed by the McNally group in 2022. The importance of halogenated arenes and halopyridines will be discussed, in addition to an overview of classical and modern approaches for arene and pyridine halogenation. A historical background of pyridine ring-opening reactions will be presented, followed by a description of our initial discovery of *N*-Tf Zincke imine derivates and their reactions with electrophilic halogenation reagents. Building upon this initial report, an alternative approach using aniline as a ring-opening nucleophile will be presented, along with a 3-selective chlorination of aniline Zincke imines.

2.2 Introduction to Halogenated Arenes

Halogenated small molecules are valuable in organic and medicinal chemistry due to their functional versatility and influence on drug properties (Fig. 2.1). They are common in pharmaceuticals, with nearly 150 fluorinated and 200 chlorinated FDA-approved drugs.[1] With the exception of fluorine, halogens can engage in halogen bonding, enhancing drug–target binding.[2] Halogens also increase lipophilicity, aiding cell permeability, and often serve as bioisosteric replacements for groups like –H, –CH_3, or –CN to improve solubility, reduce toxicity, and enhance metabolic stability.[3]

Beyond their function in bioactive molecules, halogenated arenes are useful as synthetic intermediates in the drug-discovery process. They are foundational in many chemical transformations, as aryl halides react with nucleophiles (via nucleophilic aromatic substitution),

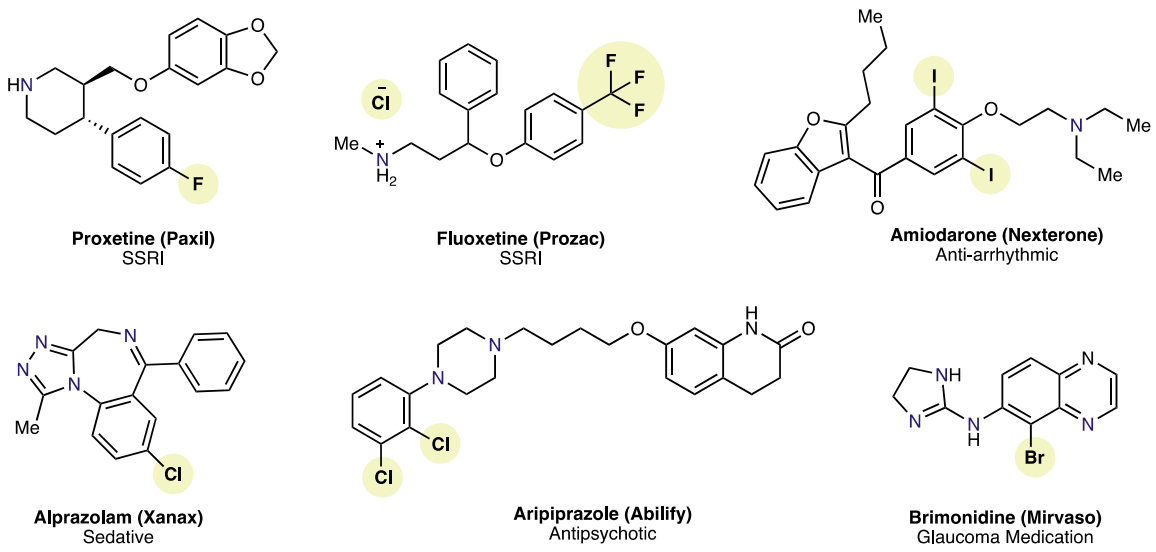


Figure 2.1 Examples of halogen-containing pharmaceuticals

electrophiles (via lithium-halogen exchange), and radicals (Fig. 2.2).[4–7] Critically, various metals undergo oxidative addition into carbon-halogen bonds, allowing for metal-catalyzed cross-coupling reactions such as the Suzuki-Miyuara, Sonogashira, and Buchwald-Hartwig couplings (Fig. 4, D). [8–10] In fact, halogenated arenes are components of at least 5 of the 20 most-used reaction types in medicinal chemistry publications.[11]

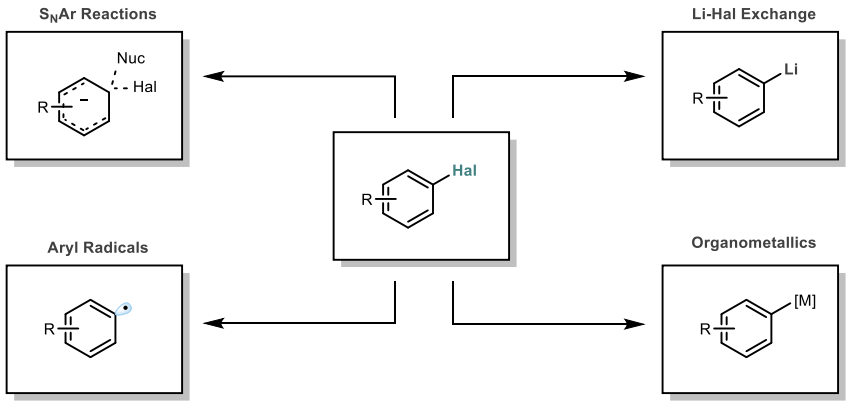


Figure 2.2 Aryl halides as functional handles.

A diverse range of halogenated building-block materials are commercially available, but the reactivity of halogenated molecules often precludes advancing them through multiple steps of

a synthesis. Due to the significance of halogenated pharmaceuticals, organic chemists are naturally interested in reactions that install halogens directly from C-H precursors on complex targets. Ideally, these reactions should tolerate a range of functional groups, react selectively at one position, and use inexpensive and readily available reagents. Many existing methods do not meet all of these criteria, and the inability to synthesize a halogenated molecule limits the ability of chemists to explore various substitution patterns in structure-activity-relationship (SAR) studies.

2.2.1 Methods for Arene Halogenation

Common classical methods for arene halogenation include electrophilic aromatic substitution (EAS) and directed metalation followed by trapping of an electrophilic halogen source. Electron-rich and π-nucleophilic aromatic compounds can be chlorinated or brominated by EAS using an electrophilic halogen source, such as Cl_2 or Br_2, a Lewis or Brønsted acid, and heat (Fig. 2.3).[12–14] This method suffers from over-halogenation, poor regioselectivity, poor functional tolerance on complex molecules, and is challenging on electron-deficient arenes. When applied to activated electron-rich arenes, halogenation occurs at the *ortho* or *para* positions.[15] Directed metalation uses a strong organometallic base to deprotonate an arene and trap the resulting aryl-metal intermediate with an electrophilic halogen source.[16,17] Regioselectivity is controlled by directing groups, such as carbamates, amines, sulfonamides, esters, ethers, and halogens, which direct metalation to the *ortho* position.[18] The scope of this strategy is limited because organometallic bases are highly reactive and incompatible with many sensitive functional groups. Transition-metal catalyzed halogenations similarly employ directing groups to activate an *ortho* C-H bond and use much milder reagents than organolithiums.[19,20] However, the directing groups required are much more restrictive. An alternative strategy is indirect halogenation, where an intermediate functional group is first introduced and later replaced with a halogen.[21] One example

is a two-step sequence developed by Hartwig, which involves iridium-catalyzed borylation followed by conversion of the resulting boronate ester to an aryl halide.[22] The regioselectivity of borylation is primarily governed by steric effects, enabling halogenation at the *meta* position in 1,3-disubstituted arenes.

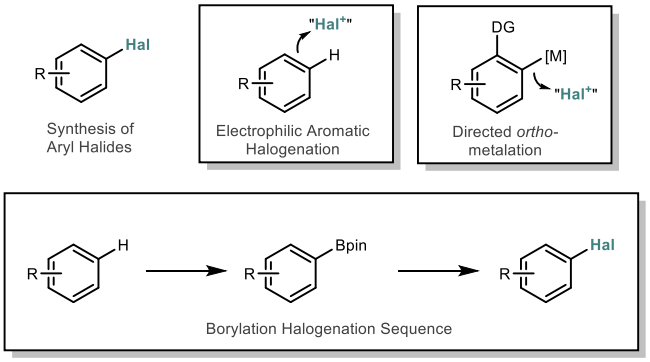


Figure 2.3 Strategies for arene halogenation.

2.2.2 Methods to Halogenate Pyridines

Due to the widespread use of both pyridines and halogenated aromatics in chemical synthesis, the ability to transform pyridines into halopyridines is essential. Halogenated azines are featured in numerous pharmaceutical and agrochemical compounds (Figure 2.4).[23,24] Although the previously mentioned halogenation methods can be applied to pyridines, achieving site-selective halogenation—especially on structurally complex molecules—continues to pose significant challenges for synthetic chemists.

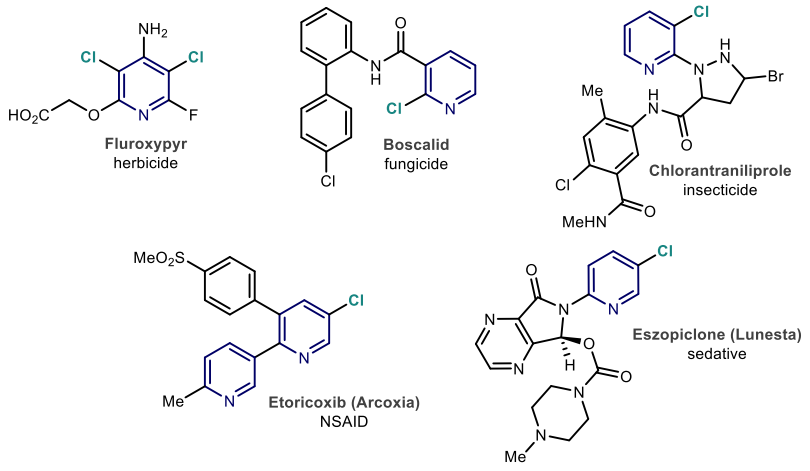


Figure 2.4 Prevalence of chlorinated pyridines in pharmaceuticals and agrochemicals.

Much like the halogenation of arenes, azines can be halogenated via electrophilic aromatic substitution, directed lithiation, and various two-step halogenations. However, halogenation of pyridines and other electron-deficient *N*-heteroaromatic rings via EAS is challenging due to poor π-nucleophilicity. For example, the bromination of unactivated pyridines requires heating at high temperatures (>150 ºC) in the presence of excess fuming sulfuric acid and elemental bromine (Fig. 2.4).[25,26] This method preferentially brominates at the 3- or 5-position of pyridine. The use of strong acid, heat, and elemental bromine reduces the functional group tolerance of this halogenation, often leading to over-bromination. Even fairly unreactive groups, such as benzene rings, will react preferentially with bromine, resulting in poor selectivity on functionalized pyridines. Directed lithiation and quenching with an electrophilic halogen source remains a viable option for pyridine. The halogenation can be tuned with directing groups and ligands to access a variety of substitution patterns. A directing group at the 2- or 4-position directs lithiation at the 3-position, while a directing group at the 3-position directs lithiation at the 4-position.[27] The pyridine nitrogen can also serve as a directing group when combined with reagents like dimethylamino ethanol (DMAE), directing lithiation to the 2-position.[28]

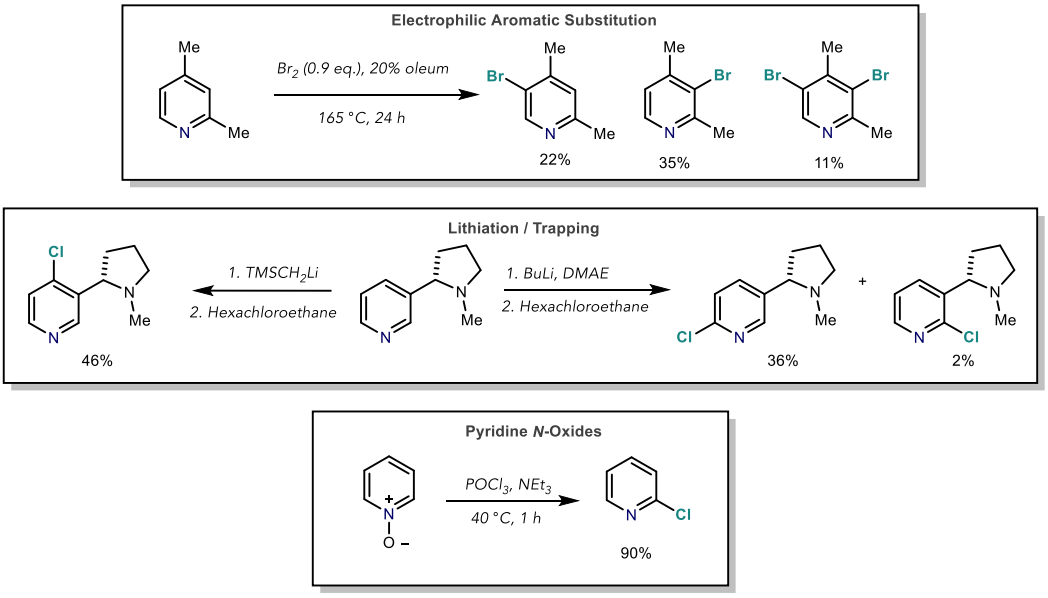


Figure 2.4 Strategies for pyridine halogenation.

Pyridine can also be activated via oxidation of the nitrogen atom to form pyridine *N*-oxides, enhancing both nucleophilicity and electrophilicity.[29,30] Pyridine *N*-oxides react with PCl_5 or $POCl_3$ to form 2-chlorinated pyridines. Though these methods are more selective, they require the use of heat and strong acids, as well as the oxidizing conditions needed to make the pyridine *N*-oxide, severely limiting the practicality and functional tolerance of these methods.

Iridium-catalyzed borylation and subsequent halogenation is also applicable to pyridines (Fig. 2.5).[22] The borylation step often gives mixtures of 3- and 4-borylated products, and the pyridine scope is limited. In 2020, the McNally group published a two-step 4-selective halogenation of pyridines and diazines using phosphonium salt intermediates.[31] The procedure uses lithium halide salts as nucleophilic halogen sources, applies to iodination, bromination, and chlorination, and supports a broad substrate scope.

At the outset of this study, 3-selective chlorination of pyridines had not been accomplished from C–H precursors. Concurrent with our development of a 3-selective pyridine chlorination described in Chapter 2.4.2, the Studer group published a similar transformation using dearomatized

oxazinopyridine intermediates.[32] The process supports a broad scope of pyridines, is 3-selective for chlorination and 5-selective for bromination and iodination. In 2025, the Studer group published a 3-selective fluorination using the same oxazinopyridine approach, which will be discussed in Chapter 3.3.[33]

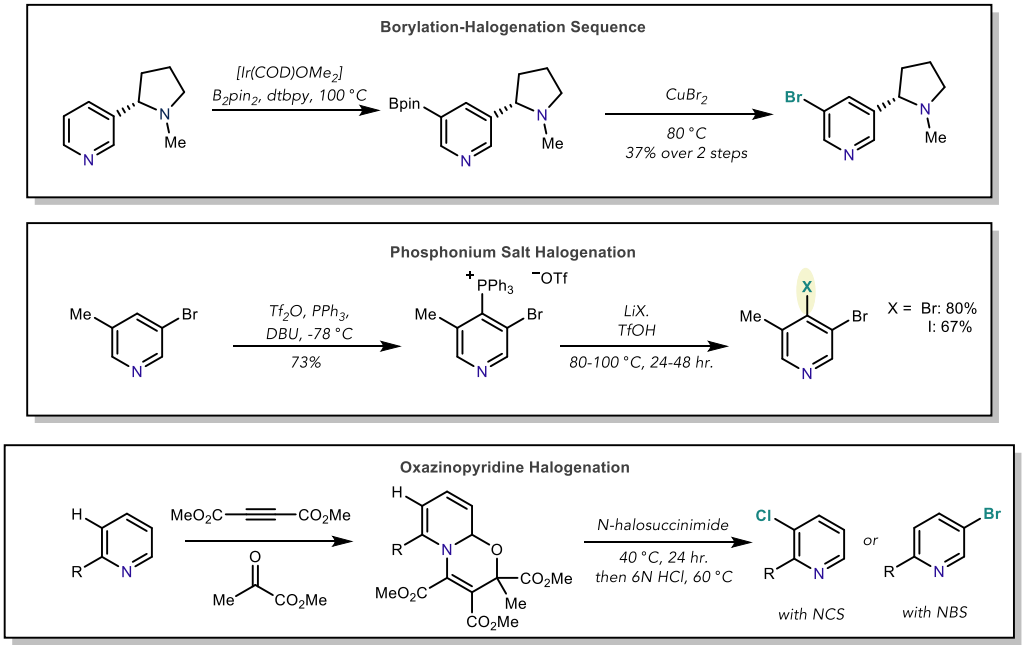


Figure 2.5 Modern advancements in pyridine halogenation.

Despite the existence of methods for pyridine halogenation, developing a general yet efficient protocol remains a challenge. Many procedures require preexisting or installed functional groups, harsh conditions, and multistep procedures which necessitate intermediate isolations. Strategies to selectively halogenate the 3- or 5-position of pyridine are rare and often suffer from regioselectivity or over-halogenation issues. Additionally, while existing methods work on simple building block pyridines, few of them are applicable for use on complex molecules typically encountered in medicinal chemistry.

2.3 Halogenation via Zincke Intermediates

2.3.1 Background on the Zincke Reaction

Discovered in 1904, the Zincke reaction uses 2,4-dinitrochlorobenzene to activate pyridine via an S_NAr reaction to form a Zincke pyridinium salt (Figure 2.6).[34] Subsequently, in the presence of aqueous base, nucleophilic addition of an amine to the 2-position of the Zincke salt forms a ring-opened conjugated imine product. When a primary amine is used, the ring-opened imine undergoes ring-closing to form an *N*-aryl or *N*-alkyl pyridinium. When a secondary amine is used, this ring-closure does not occur, and aqueous base converts the resulting imine into a "Zincke aldehyde." Zincke aldehydes have been studied in natural product synthesis and as dienes in the Diels-Alder reaction.[35] The Zincke reaction requires high temperatures and activation with 2,4-dinitrochlorobenzene does not occur on 2-substituted pyridines, limiting the use of the Zincke reaction as a general tool for pyridine functionalization.

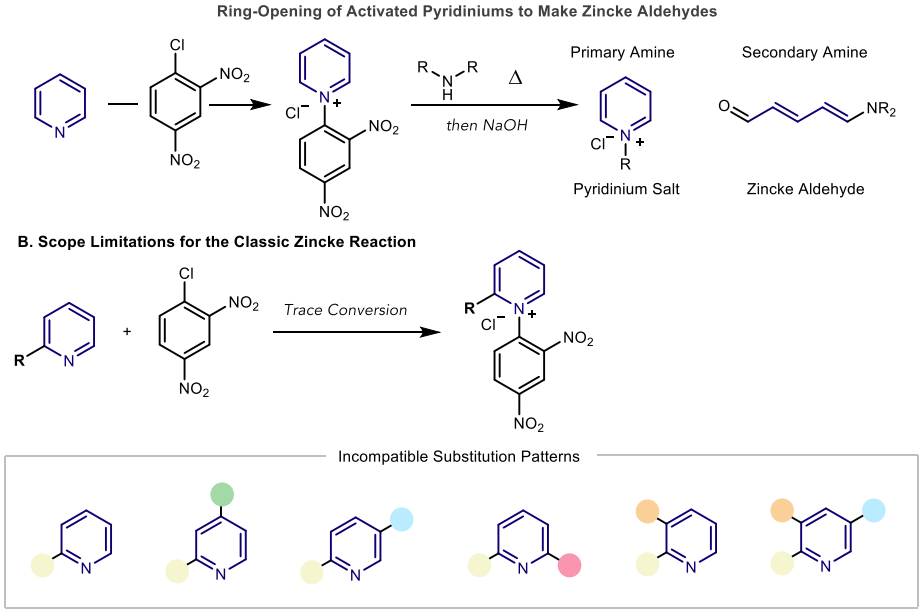


Figure 2.6 Conditions and limitations of the Zincke reaction.

2.3.2 *N*-Tf Zincke Imine Discovery and Applications

The McNally group in 2022 published a pyridine halogenation reaction using a ring-opening, functionalization, ring-closing approach from Zincke imine intermediates.[36] Our group has a longstanding interest in the reactivity of *N*-Tf pyridinium salts and have demonstrated a wide array of reactions using triflic anhydride (Tf_2O) activation of pyridines.[37] Toscano *et al.* initially reported a ring-opening of *N*-Tf pyridiniums with diethylamine, but did not demonstrate a broad pyridine scope of the ring-opening or additional applications of the *N*-Tf Zincke imine they reported.[38] My coworkers Ben Boyle and Jeff Levy developed an improved ring-opening of pyridines by first activation with Tf_2O, followed by addition of piperidine resulting in novel Zincke imine **2.1** and Zincke iminium **2.2** (Fig. 2.7). Optimization of the ring-opening found that using dibenzylamine as the amine nucleophile and adding collidine as a base resulted in Zincke imine **2.3** in high yield without unwanted iminium impurity.

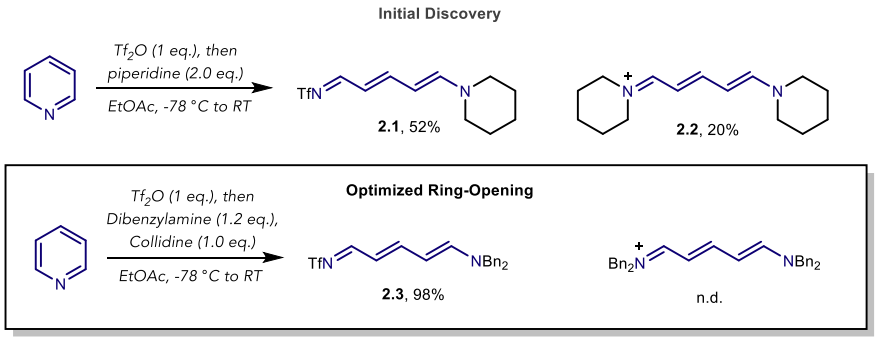


Figure 2.7 Development and optimized *N*-Tf Zincke imine ring-opening.

Unlike the parent pyridine, the *N*-Tf Zincke imine behaves both as an electron donor and acceptor because the lone pair on the amine nitrogen can donate into the conjugated π -system. Due to its enamine resonance structures, the 3- and 5-positions of the imine are nucleophilic and the 2-, 4-, and 6-positions are electrophilic (Figure 2.8). These Zincke imines are easily formed

and isolated using pyridines with various substitution patterns, including 2-substituted pyridines, with broad functional group tolerance.

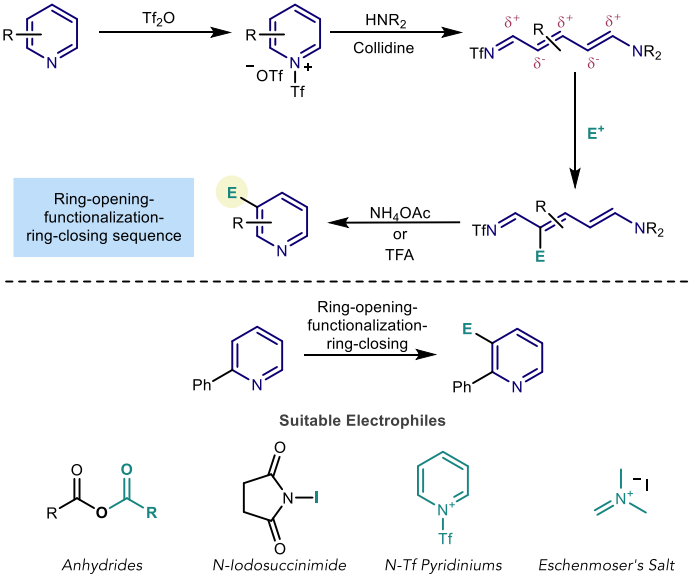
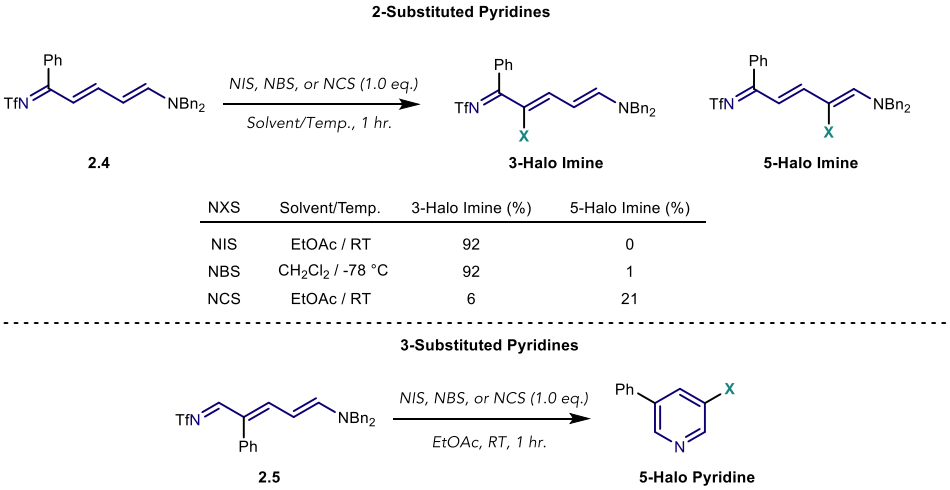


Figure 2.8 A ring-opening-functionalization-ring-closing sequence to functionalize pyridines.

Using the 2-phenylpyridine Zincke imine as a test substrate, my coworkers found that the Zincke imines reacted with electrophiles like *N*-halosuccinimides, anhydrides, and Eschenmoser's Salt. The products from these reactions can be ring-closed using NH_4OAc or trifluoroacetic acid (TFA) and heat to form functionalized pyridines through a ring-opening-functionalization-ring-closing process. Notably, the ring-opening of pyridine into a Zincke imine desymmetrizes the ring, enabling different reactivity at the 3- or 5-position. Some of the reactions, such as iodination and bromination with *N*-halosuccinimides, have >20:1 selectivity for the 3-position. This platform is distinct from traditional pyridine functionalizations because it transforms the electron-deficient pyridine into a nucleophile, and site-selectivity is determined by properties inherent to the conjugated azatriene and not from prefunctionalized directing groups or steric interactions.

2.3.3. Halogenation of Pyridines via *N*-Tf Zincke Imine Intermediates

The pyridine ring-opening, functionalization, ring-closing procedure described in the previous section was first described with *N*-halosuccinimides to achieve a pyridine halogenation procedure. During the development of the halogenation procedure, the 2-phenyl pyridine Zincke imine (**2.**4) was selected as a model substrate. My coworkers found that **2.4** reacts with *N*-iodosuccinimide (NIS) or *N*-bromosuccinimide (NBS) with >20:1 selectivity for the 3-position (Fig. 2.9). Unfortunately, when *N*-chlorosuccinimide (NCS) was used, low yields and poor selectivity was observed. In the case of 3-phenyl pyridine Zincke imine (**2.5**) and other pyridines with 3-substituents, iodination, bromination, and chlorination occurs at the 5-position with the addition of acids like TFA or HCl, followed by *in-situ* ring-closure to form 5-halopyridines.



NXS	Solvent/Temp.	3-Halo Imine (%)	5-Halo Imine (%)
NIS	EtOAc / RT	92	0
NBS	CH_2Cl_2 / -78 °C	92	1
NCS	EtOAc / RT	6	21

NXS	Acid (Eq.)	5-Halo Pyridine (%)
NIS	TFA (2.0)	90
NBS	TFA (2.0)	76
NCS	HCl (4.0)	76

Figure 2.9 Halogenation of 2-phenyl and 3-phenyl NBn_2 Zincke imines.

The halogenation reaction was then combined with ring-opening and ring-closing to develop a one-pot halogenation of pyridines (Fig. 2.10). The procedure first activates pyridine with triflic anhydride (Tf_2O) and ring-opens to a Zincke imine upon addition of dibenzylamine and

collidine. The Zincke adduct can then be halogenated using *N*-halosuccinimides. The halogenated imine is then recyclized using NH_4OAc and heat. No isolation of intermediates is necessary, and complex pyridines are amenable to this one-pot procedure. This reaction represents a significant achievement for site-selective halogenation of pyridines, albeit with limitations.

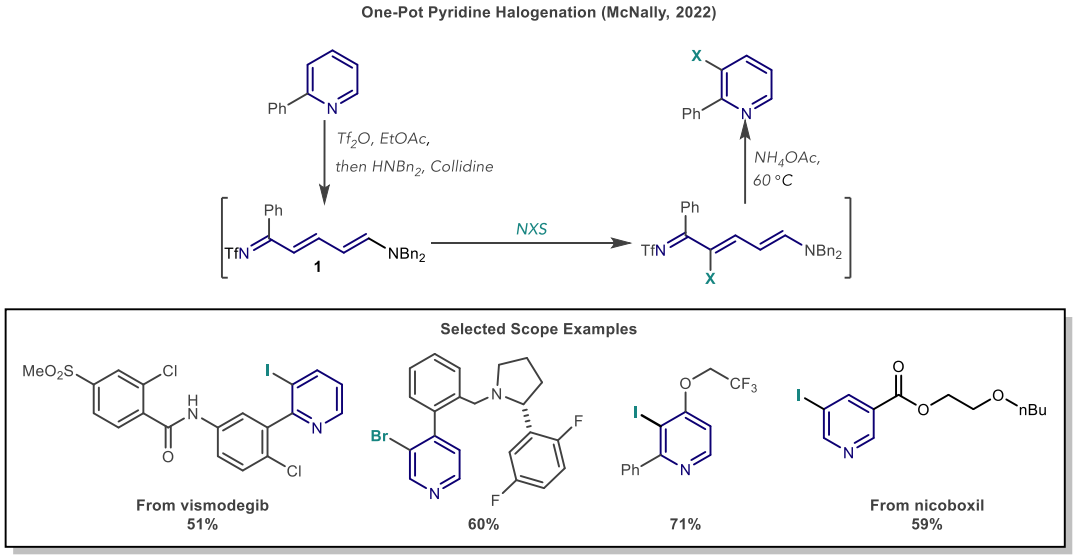


Figure 2.10 Reported one-pot pyridine halogenation using Zincke imine intermediates.

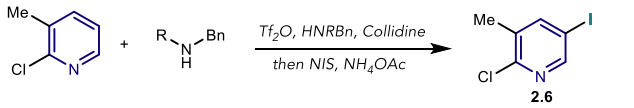
As shown in Figure 2.9, selective chlorination using this method is limited to 3-substituted pyridines, and results in low yields and site-selectivity in the absence of 3-substituents. A host of chlorinating reagents, solvents, and other condition variables were tested with no significant improvement. As described in **Chapter 2.2.2** and shown in Figure 2.4, chloropyridines are prevalent in drugs and agrochemicals, so methods to selectively chlorinate a diverse array of pyridine starting materials are highly desirable.

2.4 Development of a 3-Selective Chlorination of Pyridines via Aniline-Based Zincke Imines

2.4.1 Introduction to Pyridine Ring-Opening with Aniline

During the study of pyridine halogenation via *N*-Tf Zincke imine intermediates, other secondary amines were demonstrated to ring-open *N*-Tf pyridiniums in moderate-to-high yields to

form Zincke imines with different electronic properties. For example, iodination of 2-chloro-3-methylpyridine using the ring-opening, iodination, ring-closing sequence was unsuccessful due to poor ring-opening using dibenzylamine (Fig. 2.11). Instead, *N*-benzylaniline was used with good ring-opening yield to form the desired iodinated product (**2.6**).



R =	Product (%)
Bn	0
Ph	44

Figure 2.11 Different ring-opening nucleophile for improved halogenation.

The classic Zincke reaction has been demonstrated with primary amines, but instead of observing ring-opened Zincke imines, *N*-alkyl or *N*-aryl pyridiniums form under the reaction conditions. To our surprise, when we reacted *N*-Tf pyridinium **2.7** with aniline in the presence of collidine, we observed *N*-phenyl Zincke imine **2.8** as the major product, with no N-Ph pyridinium detected (Fig. 2.12).

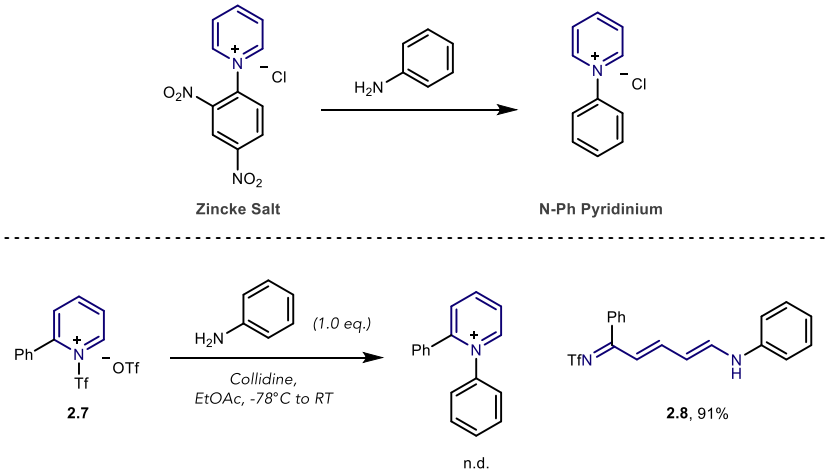
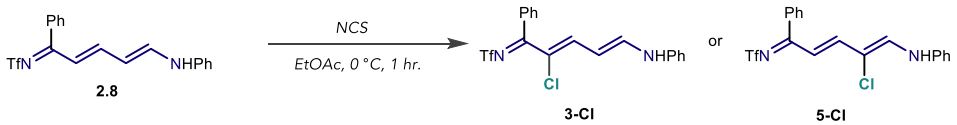


Figure 2.12 Discovery of N-Ph Zincke imines.

2.4.2 Chlorination of N-Phenyl Zincke Imines

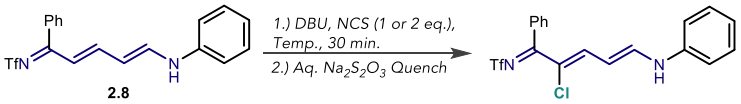
We wondered if selective chlorination would be possible using this new class of Zincke imine. As discussed in Chapter 2.2.3, dibenzylamine Zincke imine **2.4** reacted with NCS to form a mixture of halogenated products, with an overall yield of 27% and 3:1 selectivity for the 5-chloro product. Interestingly, when imine **2.8** was subjected to NCS, 5:1 selectivity for the 3-position is observed with an overall 57% yield (Fig. 2.13). An interesting feature of the *N*-phenyl Zincke imines is that the N–H proton can be deprotonated to further modify the nucleophilicity of the imine. We hypothesized that **2.8** would become significantly more reactive under basic conditions, so we repeated the halogenation reaction in the presence of the organic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). We were pleased to see an improvement in yield to 86% with >20:1 selectivity for the 3-position. This was the first time we had observed selective, high-yielding chlorination using a Zincke imine on a sterically unbiased system, so we pursued this deprotonation-chlorination strategy.



Additive	Yield	3-Cl : 5-Cl Selectivity
None	57%	5:1
DBU (1.0 equiv.)	86%	> 20:1

Figure 2.13 Observation of a 3-selective chlorination of N-Ph Zincke imines.

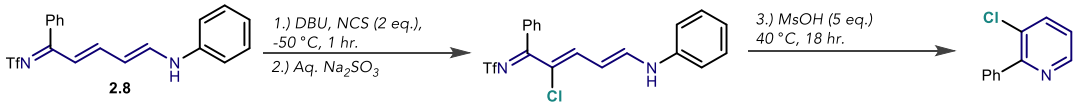
Motivated by the high yield and selectivity of the newly discovered deprotonation-chlorination, we developed a one-pot procedure using 2-phenylpyridine as a model substrate. We found that the reaction is sensitive to excess NCS at 0 °C, with 2 equivalents decreasing the yield by 52% (Fig. 2.14). Fortunately, by cooling the reaction to -50 °C and quenching any unreacted NCS with aqueous sodium thiosulfate before warming to room temperature, high chlorination



Eq. NCS	Temp. (°C)	Yield (%)
1	0	84
2	0	32
1	-50	89
2	-50	89

Figure 2.14 Temperature dependence for reaction sensitivity to excess NCS.

yields are observed regardless of ring-opening yields. Removing the aqueous layer and heating with methanesulfonic acid gives the 3-chlorinated pyridines in reasonable yield (Figure 2.15).



Quench Procedure	Step 2 Yield (%)	Step 3 Yield (%)
Aq. Na_2SO_3	85	0
Aq. Na_2SO_3 *(removed before Step 3)*	81	77

Figure 2.15 Procedure for sequencing chlorination and recyclization steps.

Next, we explored the pyridine scope of the one-pot chlorination procedure (Fig. 2.16). Notably, we did not test 3-substituted pyridines for this process, because we established an efficient chlorination of 3-substituted pyridines in our previous report. Our model substrate, 2-phenylpyridine, was chlorinated in a one-pot fashion in 64% yield (**2.9**). We tested a series of 2-alkyl pyridines, which were all chlorinated in reasonable yields (**2.10-2.13**). We found that 2,5-disubstituted pyridines function well in the reaction when *o*-toluidine is used as a ring-opening nucleophile instead of aniline (**2.14-2.18**). We also found that 2-arylpyridines with a variety of electron-donating and electron-withdrawing groups (**2.19-2.22**), in addition to 2-heterocyclic pyridines (**2.23**), are chlorinated in good yields. Finally, we found that the procedure tolerates complex drug-like pyridines, and even pharmaceuticals like bisacodyl and vismodegib are chlorinated using this procedure (**2.24-2.28**).

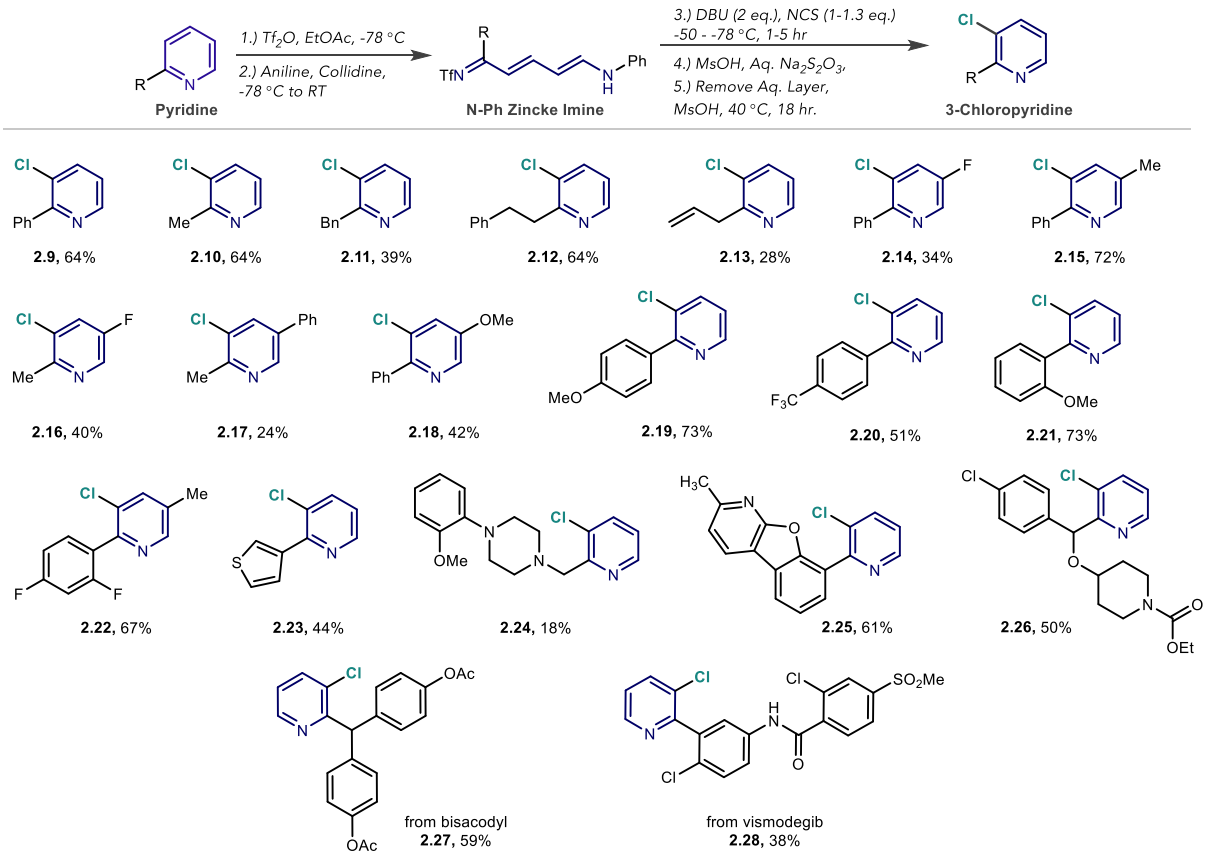


Figure 2.16 Scope of the one-pot pyridine chlorination procedure.

2.4.3 Mechanistic Studies of 3-Selective Chlorination

We were interested in studying the mechanism and understanding the origin of 3-selectivity in the base-mediated chlorination of N-Ph Zincke imines. Due to the strong base-dependence on improved yields and selectivity, our proposed mechanism starts with partial or full deprotonation of the N–H bond present in **2.29** (Figure 2.17). This is supported by studies which found that strong organometallic bases like *n*-BuLi and NaH result in the same selectivity and similar high yields of chlorination, but weak bases like Et_3N resulted in similar yields and selectivity as reactions without base additives. Following partial or complete deprotonation of the imine N–H bond, the anion resonates through the conjugated system to react with NCS, resulting in adduct **2.30**. Finally, acid additives reconjugate the Zincke imine to give the observed 3-chloro product (not shown).

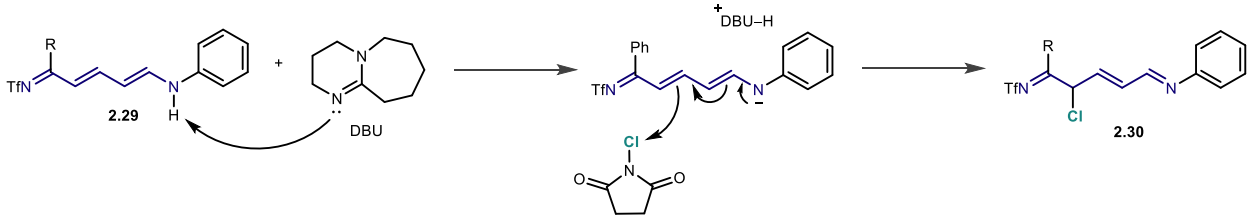


Figure 2.17 Proposed mechanism of 3-selective chlorination.

The proposed mechanism does not explain selectivity for the 3-position over the equally activated 5-position. In order to better understand the origin of selectivity, we relied on computations by Louis de Lescure, who was co-advised by Professor Rob Paton. We hypothesized that the 3-position might be inherently more reactive than the 5-position by holding more electron density. Natural Bond Orbital (NBO) calculations, which are used to determine localized charge distributions, found that the two positions were relatively similar, with the 3-position favored by only 0.020 charge occupancy character (Fig. 2.18).

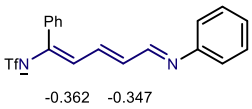


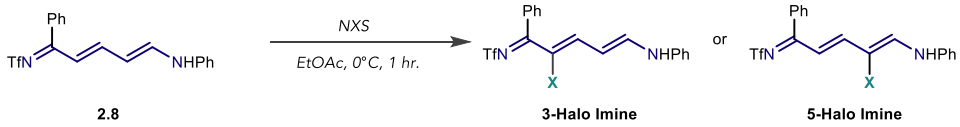
Figure 2.18 Charge density calculations using NBO calculations.

The difference in electron density was not large enough to explain the high degree of selectivity observed in all chlorination cases. We hypothesized that the mechanism of chlorination may be more complex than we expected, and a Cl–DBU^+ species may be involved as the active chlorination species, but that still does not explain the high degree of 3-selectivity observed when strong bases like NaH were used in the reaction. At this time, the origin of selectivity is still unclear.

2.5 Selectivity Switching Iodination of Aniline-Derived Zincke Imines

When we observed that the reactivity of N-Ph Zincke imines with NCS was different than with NBn_2 Zincke imines, we wondered how the reactivity might differ with other halosuccinimide reagents. We again found very different reactivity using N-Ph Zincke imines, especially when we probed base additives in the reaction mixture (Fig. 2.19). In the case of NBS, we observed a 71%

combined yield of brominated imines, with 16:1 selectivity for the 3-bromo imine. The yield and selectivity were not better than what was observed using NBn_2 Zincke imines and was not pursued as a bromination strategy. In the presence of DBU, the yield decreased to 51% and the selectivity decreased to 2:1 selectivity for the 3-position. When we tried NIS, a significant amount of decomposition was observed, and only 4% of the 3-iodo imine and 1% of the 5-iodo imine was observed. Interestingly, when DBU was added to the reaction mixture, a high yield of the 5-iodo imine product was observed with no 3-iodo imine detected.



2.8 **3-Halo Imine** **5-Halo Imine**

No DBU Additive

Halogen Source	Yield	3-Hal : 5-Hal Selectivity
NIS	5%	4:1
NBS	71%	16:1

With DBU Additive

Halogen Source	Yield	3-Hal : 5-Hal Selectivity
NIS	89%	>1:99
NBS	51%	2:1

Figure 2.19 Yields and selectivity of iodination and bromination of N-Ph Zincke imines.

We were surprised to observe such a stark change in iodination selectivity, especially because the NBn_2 Zincke imines iodinate at the 3-position in >1:99 selectivity for most substrates. This result demonstrates that the same pyridine ring-opened with different amine nucleophiles can be iodinated at the 3- or the 5-position, which could be useful for chemists hoping to make libraries of pyridine derivatives.[39] A more practical 5-selective iodination was developed by our lab by using Zincke iminium intermediates (not published), so this procedure has not been studied further or applied to a broad scope of pyridines.

The use of N-Ph Zincke imines was also crucial in developing a 3-selective fluorination of pyridines, which will be discussed in detail in Chapter 3.

2.6 Conclusion

This chapter shows that pyridines can be selectively chlorinated at the 3-position using N-Ph Zincke imines and strongly basic additives. The reaction has been extended to a one-pot chlorination process that functions on a broad scope of pyridines, including pyridine-containing drugs. N-Ph Zincke imines have also been demonstrated in 5-selective iodination and 3-selective fluorination of pyridines.

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CHAPTER 3. 3-SELECTIVE PYRIDINE FLUORINATION VIA ZINCKE IMINE INTERMEDIATES

3.1 Chapter Overview

This chapter describes a novel strategy to fluorinate the 3- and 5-position of pyridines.[1] The importance of fluoropyridines in pharmaceuticals and agrochemicals will be discussed, followed by a description of classical and modern approaches to pyridine fluorination. A novel pyridine fluorination method using Zincke imine intermediates will be presented, with a discussion of reaction development and scope. My coworker Jeff Levy made the initial discovery that pyridines can be fluorinated via Zincke imine intermediates, and my coworker Marie Hart optimized the reaction and contributed significantly to the scope.

3.2 Importance of Fluoropyridines in Pharmaceuticals and Agrochemicals

Similarly to chloroarenes discussed in Chapter 2, fluorinated small molecules are valuable in pharmaceuticals and agrochemicals due to their many influences on drug properties. Fluorine-containing drugs are a rapidly growing class of organic molecules due to a variety of factors.[2] To begin with, the fluorine atom (F), which has a van der Waals radius of 1.47 Å, is only slightly larger than hydrogen (H, with a radius of 1.20 Å).[3] As a result, substituting H with F in drug molecules typically does not lead to major structural changes. Additionally, the C–F bond is among the strongest bonds carbon can form, often enhancing the metabolic resilience of fluorinated pharmaceuticals.[4] Fluorine's high electronegativity (3.98) induces bond polarization, influencing the compound's balance between lipophilicity and hydrophilicity. Moreover, fluorine can act as a moderate hydrogen bond acceptor, drawing a parallel to the behavior of carbonyl groups, as the

dipole moments of C–F and C–O bonds can be quite similar.[5] C–F bonds also act as bioisosteres, primarily for C–H bonds, while attenuating lipophilicity and metabolism.

Given the many ways in which fluorinated molecules are valuable in drug discovery, it is unsurprising that fluorinated pyridines are also common in FDA-approved drugs and agrochemicals (Fig. 3.1). Fluorine atoms attenuate the basicity of the pyridine nitrogen, altering its binding affinity with targets and other pharmacokinetic properties.[6]

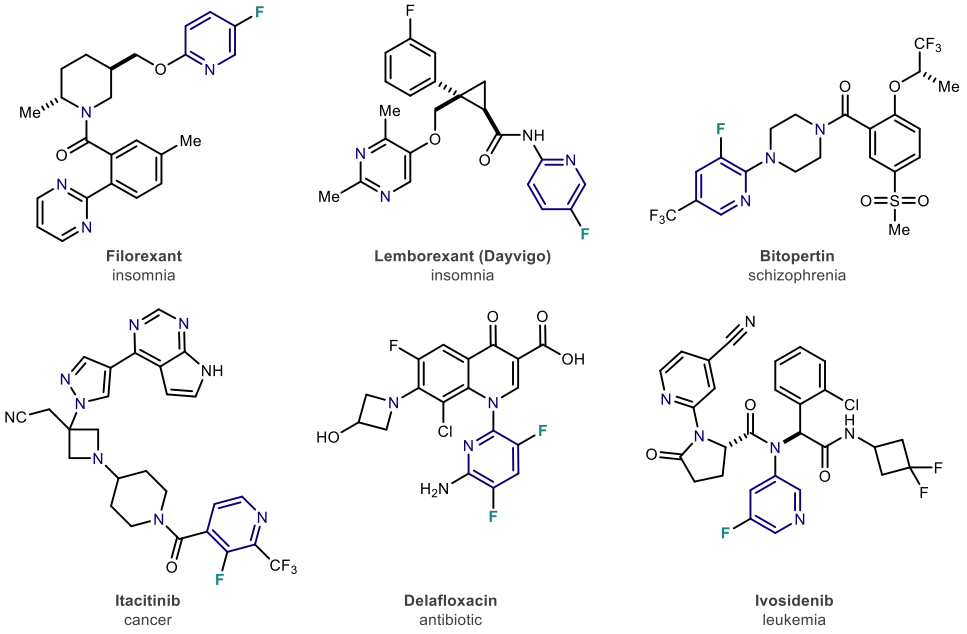


Figure 3.1 Examples of fluoropyridine pharmaceuticals.

3.3 Existing Methods to Fluorinate Pyridines

There are two general strategies for synthesizing fluoropyridines. First are strategies which transform existing functional groups into fluorine, second being C–H bond functionalization reactions. Processes that transform existing functional groups include the Balz-Schiemann reaction and a variety of methods that convert other halopyridines to fluoropyridines in transition metal-catalyzed halogen exchanges (Fig. 3.2).[7] The Balz-Schiemann reaction first oxidizes an aniline nitrogen to a diazonium salt, which decomposes in the presence of heat or light to an aryl cation

species which can abstract fluoride from a tetrafluoroborate anion.[8,9] The formation of explosive diazonium salts makes the reaction quite dangerous, but a recent improvement on the method from Ritter has demonstrated the reaction in one-pot without the accumulation of explosive diazonium salts.[10,11] Halogen exchange reactions can be used to replace halides or pseudohalides with fluorine, but require access to prefunctionalized precursors. Sanford demonstrated access to 3-fluoropyridines from 3-chloropyridines, Buchwald reported conversion of aryl triflates to aryl fluorides, and Hartwig demonstrated a similar transformation from aryl iodides.[12–14]

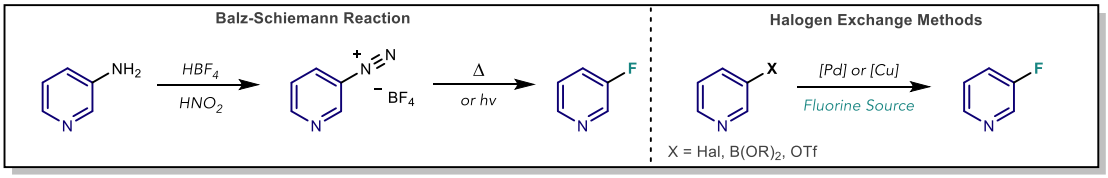


Figure 3.2 Fluoropyridine synthesis from functionalized intermediates.

Pyridine fluorination methods from C–H precursors are rarer and are helpful to categorize by their positional selectivity (Fig. 3.3). As discussed in Chapter 1, Hartwig reported a 2-selective fluorination using AgF_2 as a reagent, and a report from Wu and Cai demonstrated 2-fluorination via a radical-based process.[15,16] A 4-selective fluorination of quinolines was reported by Ritter using electron-transfer processes, and Jiao and Song showed that 4-position fluorination was possible from pyridine N-oxides.[17,18] Pyridine fluorination has also been demonstrated using XeF_2, but the method is hazardous.[19] Reactions which fluorinate the 3- and 5-positions of pyridines are much less common. Gryaznova reported an electrochemical approach, albeit with only two examples; pyridine and 4-ethylpyridine.[20] Concurrent with our development of a C–H fluorination via Zincke imine intermediates, two reports of C3-selective fluorination were published. Studer reported an approach using dearomatized oxazinopyridine intermediates, which functions on pyridines, isoquinolines, and a modest scope of bioactive compounds.[21] Also in this period, Li showed a 5-position fluorination of a limited number of C3-substituted pyridines using the

classical Zincke reaction.[22] They did not show C3- or C5-selectivity in unbiased pyridines, and did not include examples of complex or bioactive pyridines. Broad, regioselective methods for pyridine C–H fluorination are still in demand, so we aimed to offer a complementary strategy to the Studer approach that could selectively fluorinate a broad range of pyridines and pyridine-containing drugs.

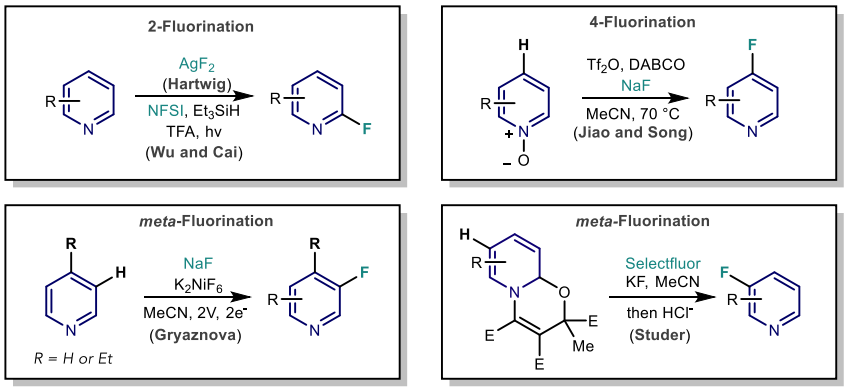
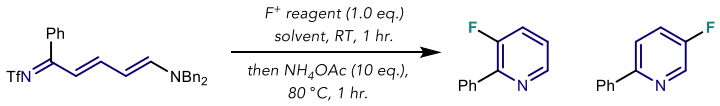


Figure 3.3 Pyridine fluorination from C–H precursors.

3.4 Development of a 3-Selective Fluorination of Pyridines

Due to its previous applicability in 3-selective halogenation reactions, we began our study using *N*-Tf Zincke imine **3.1**, derived from 2-phenylpyridine, dibenzylamine, and Tf_2O.[23] Unlike other halogens, which have a diverse range of electrophilic halogenating reactions, commercial electrophilic fluorinating reagents are limited and include N-fluoropyridinium salts, Selectfluor, and NFSI.[24] We explored a range of fluorinating reagents and reaction conditions before ring

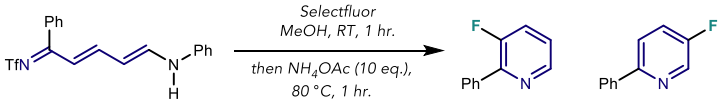


3.1 **3.2** **3.3**

entry	F^+ reagent	solvent	% **3.2**	% **3.3**
1	*N*-F-pyr•BF_4	MeCN	10	16
2	NFSI	IPAc	1	30
3	Selectfluor	MeOH	20	6

Table 3.2 Fluorination of *N*-Phenyl Zincke imine.

closure using NH_4OAc (Table 3.1). Entries 1−3 show that fluorination is viable and that the C3- vs C5-selectivity (**3.2** vs **3.3**) varies depending on the fluorinating reagent. However, the combined yields of fluorinated products were poor, and further changes to the reaction conditions failed to improve this outcome. As discussed in Chapter 2, Zincke imine reactivity can be significantly altered by exchanging the ring-opening nucleophile. We modified the Zincke imine to adduct **3.4** (discussed in Chapter 2) by using aniline as a nucleophile and tested fluorination conditions (Table 3.2). Using Selectfluor in methanol resulted in a C3-selective outcome but again in a poor yield (entry 1). As discussed in Chapter 2, imine **3.4** has a mildly acidic N−H bond which can be used to tune the imine reactivity by adjusting the basicity of the reaction. Yields improved and the reaction became exclusively C3-selective when we added bases, with Na_2CO_3 being the most promising (entries 2 and 3). Increasing the equivalents of Na_2CO_3 and diluting the reaction mixture substantially increased the yield (entries 4−6). The optimized conditions employ 1.3 eq. of Selectfluor and 0 °C as the reaction temperature (entry 7).



3.4 **3.2** **3.3**

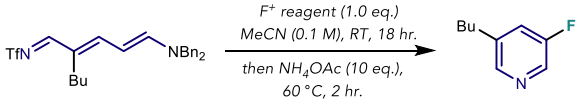
entry	MeOH (M)	Base (eq.)	% **3.2**	% **3.3**
1	0.1	None	18	2
2	0.1	DBU (1.1)	25	0
3	0.1	Na_2CO_3 (1)	31	0
4	0.1	Na_2CO_3 (2)	41	0
5	0.05	Na_2CO_3 (2)	51	0
6	0.02	Na_2CO_3 (2)	62	0
7	0.02	Na_2CO_3 (2)	68[a]	0

[a]Using 1.3 eq. of Selectfluor and run for 2 h at 0 °C.

Table 3.2 Fluorination of N-phenyl Zincke imine.

We then turned our attention to pyridines with 3-substiuents. We avoided aniline as a ring-opening nucleophile because 3- and 4-substituted pyridines tend to form N-phenyl pyridiniums instead of Zincke imines under the ring-opening conditions with primary amines.[25] We studied the

fluorination reaction using Zincke imine **3.5**, derived from 3-butylpyridne and dibenzylamine. We tested the same set of electrophilic halogenation reagents and recyclizing with NH_4OAc, finding NFSI gave the highest fluorination yield, confirming a tendency for NFSI to react with the 5-position observed in Table 3.1. After extensive testing of solvents, temperatures, and additives by

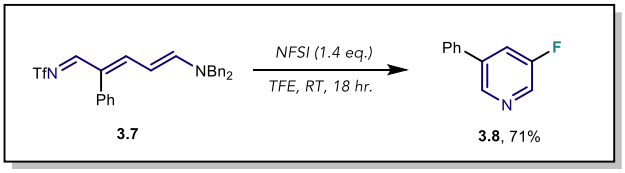


3.5 **3.6**

entry	F^+ reagent	% **3.2**
1	*N*-F-pyr•BF_4	16
2	NFSI	32
3	Selectfluor	11

Table 3.3 Fluorination of 3-substituted Zincke imines.

my coworker Marie Hart, we found optimized conditions using TFE as a solvent and 1.4 equiv. of NFSI (Fig. 3.4). Notably, the fluorinated Zincke imine recyclizes *in situ* in slightly acidic TFE, obviating the need for an additional recyclization step. Using these optimized conditions, imine **3.7**, derived from 3-phenylpyridine, was transformed to fluoropyridine **3.8** in 71% yield.



3.7 **3.8**, 71%

Figure 3.4 Optimized fluorination of 3-substituted pyridines.

3.5 Scope of 3-Selective Pyridine Fluorination

We next explored the pyridine scope of the fluorination procedure using the two sets of optimized conditions (Fig. 3.5). We began by testing a series of pyridines without 3-substituents, first by isolating the N-Ph Zincke imines and then applying the fluorination and cyclization conditions. As demonstrated by **3.9-3.13**, a variety of electron-rich and electron-poor arenes, as well as heteroarenes, are tolerated at the 2-position. Existing methods to selectively fluorinate the

3-position of pyridines do not tolerate 2-alkylpyridines.[21] We were pleased to see that a series of alkyl pyridines (**3.14-3.18**), including a piperidine derivative (**3.19**) are fluorinated in reasonable yields. Finally, 2,5-disubstituted pyridines are fluorinated at the 3-position, and can be used to form 3,5-dihalopyridines (**3.20-3.22**).

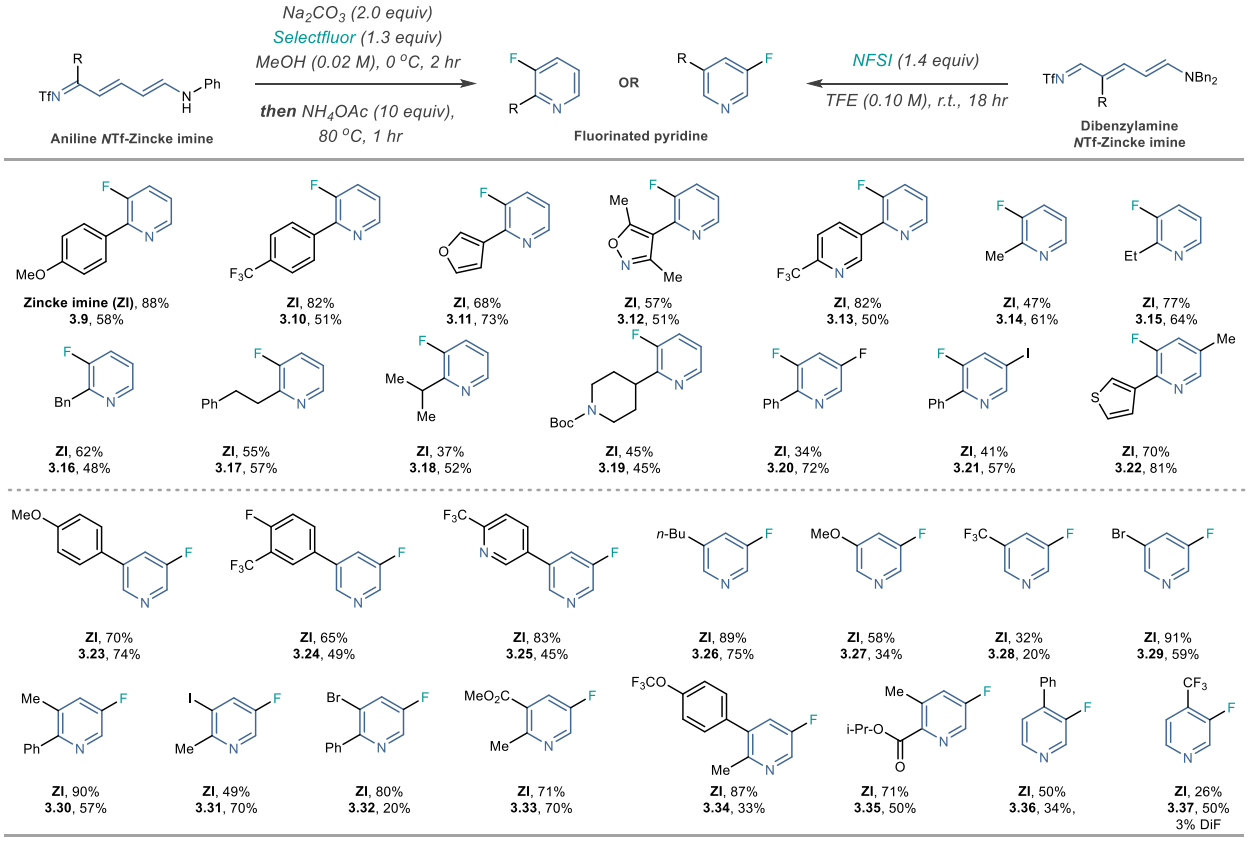


Figure 3.5 Scope of pyridine fluorination reaction. "ZI" Yields refer to isolated yields of Zincke imines.

Reverting to the conditions we optimized for 3-substituted pyridines, we again found that the fluorination is effective on 3-aryl, 3-heteroaryl, and 3-alkylpyridines (**3.23-3.26**). The reaction tolerates heteroatoms at the 3-position, as demonstrated by 3-methoxypyridine **3.27** and 3-bromopyridine **3.29**. We also demonstrated that 2,3-disubstituted pyridines are selectively fluorinated using this method (**3.30-3.35**). Finally, 4-substituted pyridines were fluorinated. In the

case of 4-phenylpyridine, we used a Zincke iminium intermediate (**3.36**), and 4-CF_3-pyridine, where a minor amount of difluorination was observed (**3.37**).

We also wanted to demonstrate that fluorination is possible in a one-pot fashion, with no intermediate isolation of Zincke imine intermediates (Figure 3.6). Performing the reaction in a single pot has significant advantages, such as expediting access to fluorinated products for Structure-Activity-Relationship (SAR) studies. On the other hand, separation of fluoropyridines from their C–H precursors can be very challenging, and complete separation of Zincke imines from starting materials can be quite advantageous. We found that the reaction is amenable to one-pot conditions by combining the ring-opening, fluorination, and ring-closing steps in a single pot, with an intermediate solvent-exchange following ring-opening. The one-pot yields are often similar to the combined yields of ring-opening and subsequent fluorination-ring-closing yields reported in the two-pot scope table (**3.38-3.42**).

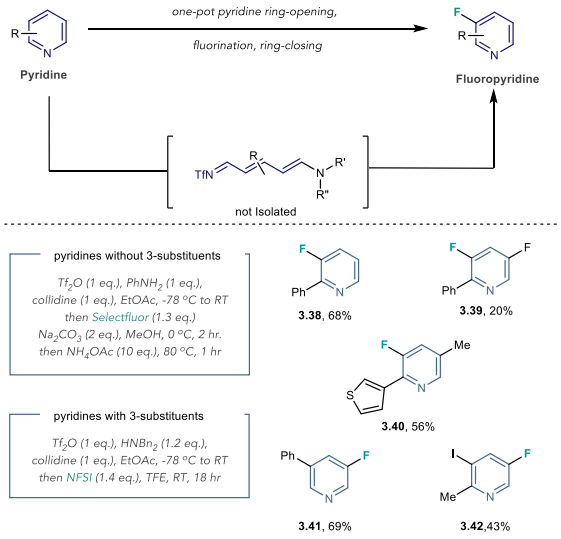


Figure 3.6 One-pot fluorination of pyridines.

We also demonstrated the fluorination reaction on a series of complex pyridines and pharmaceuticals (Fig. 3.7). These pyridines contain multiple reactive functional groups and

demonstrating C−H fluorination in a late-stage fashion shows that our method could be used in a medicinal chemistry setting to test fluoropyridine efficacy in active pharmaceutical ingredients. We isolated low to moderate yields of fluorinated products when we tested a series of drug-like intermediates with 2-aryl and 3-aryl substituents (**3.43-3.46**). We then fluorinated an analogue of the antihistamine bepotastine (**3.47**) and a protected version of pioglitazone (**3.48**), a treatment for diabetes. We also demonstrated fluorination of the leukemia drug vismodegib (**3.49**), and the antihistamine loratadine (**3.5**), albeit in low yields.

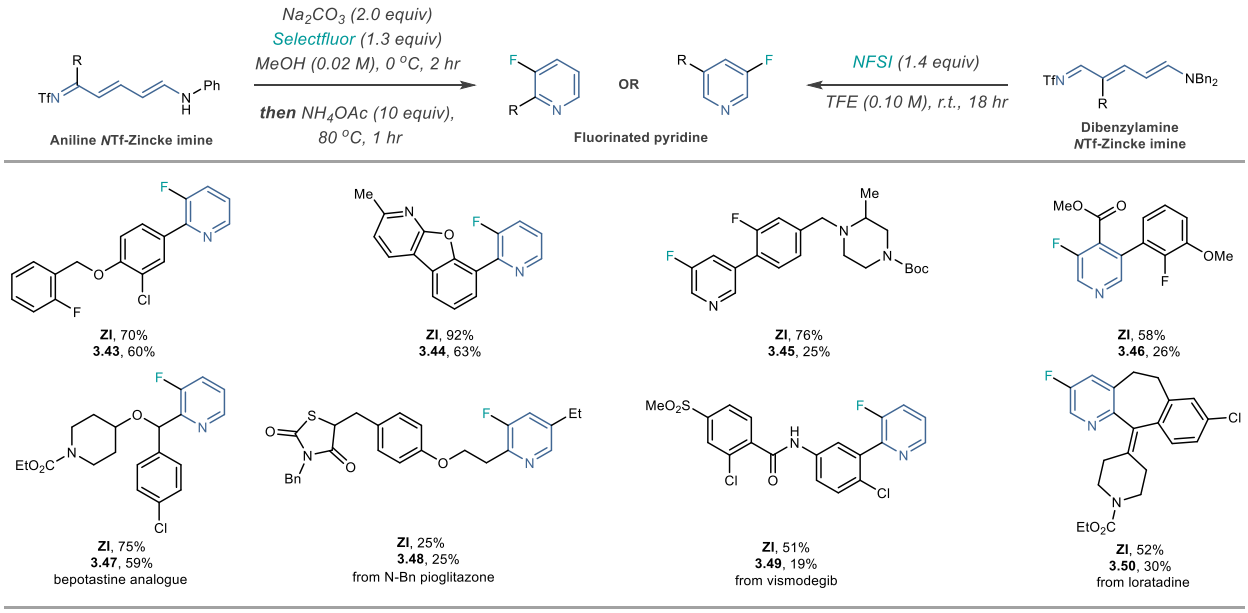


Figure 3.7 Fluorination of complex drug-like pyridines and pharmaceuticals. "ZI" refers to Zincke imine yield.

3.5 Conclusions

In this chapter we showed that pyridines can be selectively fluorinated at the 3-position using Zincke imine intermediates. 2-Substituted pyridines are most efficiently fluorinated with Selectfluor via N-Ph Zincke imines in the presence of Na_2CO_3 base, which mimics the deprotonation-chlorination discussed in Chapter 2. Pyridines without 2-substituents are fluorinated with NFSI via NBn_2 Zincke imines. The procedure functions on a broad range of simple pyridines with varying substitution patterns and excellent functional group tolerance. The fluorination was

demonstrated in a one-pot fashion and was effective on a series of drug-like pyridines and pharmaceuticals.

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CHAPTER 4. A DECONSTRUCTION-RECONSTRUCTION STRATEGY FOR PYRIMDINE DIVERSIFICATION

4.1 Chapter Overview

This chapter describes a novel strategy to diversify pyrimidines by first deconstructing them into versatile iminoenamine intermediates then employing traditional condensation chemistry to transform pyrimidines into C2-functionalized pyrimidines, pyrazoles, isoxazoles, and pyridines.[1] Structure-Activity-Relationship (SAR) studies and *de novo* heterocycle synthesis will be introduced, along with an introduction of "skeletal editing" reactions and their role in drug discovery. The prevalence of pyrazoles and 1,2-oxazoles in pharmaceuticals will also be described. Finally, the development of a pyrimidine deconstruction-reconstruction will be discussed, along with a demonstration of reaction scope and future directions. This project was accomplished in collaboration with my coworkers Celena Josephitis and Louis de Lescure. Celena developed the formal N to C (pyrimidine to pyridine) transformation and contributed to scope exploration. Louis performed all computational mechanistic calculations for this study.

4.2 Structure-Activity-Relationship Studies in Medicinal Chemistry

4.2.1 Introduction to Structure-Activity-Relationship Studies

Structure–activity relationship (SAR) analysis plays a vital role in the drug discovery process by helping researchers refine the physicochemical characteristics of potential therapeutic compounds. Through this approach, medicinal chemists apply targeted synthetic modifications to a molecule's structure and evaluate how these changes influence its biological activity.[2] By identifying specific structural features essential for target interaction, SAR studies guide the intentional design of new variants aimed at improving a drug candidate's potency and

bioavailability. This iterative optimization continues until the compound exhibits the desired pharmacological profile.

In modern drug discovery and design, candidates are often assessed using high-throughput studies with large sets of active pharmaceutical ingredients (APIs).[3] Bringing new pharmaceuticals to market in a timely and cost-effective manner relies on expedited access to new chemical analogs. Thus, methods that enable rapid access to a multitude of minor modifications to drug structures are increasingly valuable in drug discovery. These methods often rely on pre-installed functional handles or C–H functionalization to rapidly build libraries of target compounds.[4]

To illustrate how SAR modifications impact the discovery of real FDA-approved drugs, an anticancer drug, Dabrafenib, is shown in Figure 4.1. In 2013, medicinal chemists at GlaxoSmithKline (GSK) were studying a candidate for B-Raf kinase inhibition, which showed

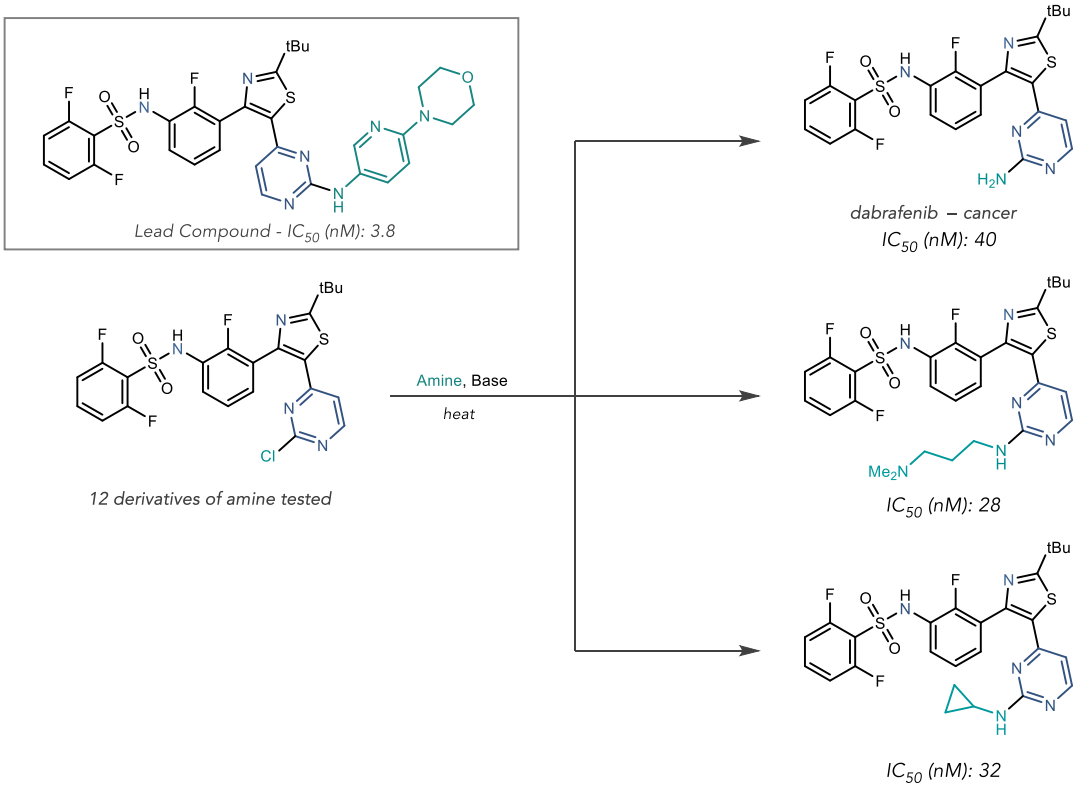


Figure 4.1 SAR Study in the development of Dabrafenib.

promising results for slowing cancerous tumor growth.[5] A lead compound demonstrated *in vitro* kinase inhibition of B-Raf^{V600E}, however, the amine motif at the pyrimidine C2-position showed poor metabolic stability, making it inadequate for human consumption. Therefore, SAR studies focused on altering the identity of the 2-amino group and testing how these modifications impacted the drug's pharmacokinetic and pharmacodynamic (PKPD) properties. Using a 2-chloropyrimidine as a starting material, the team at GSK used S_NAr reactions with nucleophilic amines to generate twelve 2-aminopyrimidine derivatives of their lead compound. They found that a free amine at the C2-position had the optimal PKPD profile and potency. After minor modifications to the rest of the drug scaffold, this variant became the anti-cancer drug dabrafenib.

The SAR study of dabrafenib illustrates the importance of medicinal chemist's ability to selectively alter the substituents of drug scaffolds on complex molecules. Fortunately for this synthesis, a reactive chloride functional handle was installed late in the synthesis to enable late-stage diversification. Due to the many challenges associated with late-stage functionalization of *N*-heterocycles discussed in Chapter 1, altering substituents on heterocyclic structures within drug candidates must often be done early in the construction of drug molecules. Furthermore, when current methods fail to enable the target transformation selectively, medicinal chemists often turn to *de novo* synthesis to form heterocyclic portions of the molecule.

4.2.1 *De Novo* Heterocycle Synthesis

Due to the general lack of methods to functionalize *N*-heterocycles like pyridine and pyrimidine, synthetic chemists often use *de novo* synthesis of these structures.[6] *De novo* heterocycle synthesis refers to the construction of heterocyclic compounds from simple, non-cyclic starting materials rather than modifying existing rings.[7] These reactions offer a tailored approach which allows organic chemists to form heterocycles with the exact substitution pattern they desire,

they are more practical in early stages of drug discovery and are far less suitable for SAR studies on more complex candidate structures. This is due to the reactivity of heterocyclic precursors, which are typically too reactive to preserve through several synthetic steps. *De novo* heterocycle synthesis has been studied for well over a century, and there are many methods to synthesize building-block heterocycles.[6] Many of these reactions are limited to a single class of heterocycle, but some heterocyclic precursors have many methods to transform them into a host of different ring-structures.

Condensation reactions are a foundational tool for constructing a wide variety of heterocycles efficiently from dicarbonyl starting materials (Fig. 4.2).[8] A particularly diverse class of heterocyclic precursor are 1,3-dicarbonyls, which have been demonstrated to undergo condensation with a variety of reagents to form five-membered and six-membered heterocycles. For example, Knorr reported in 1883 that 1,3-dicarbonyls react with hydrazines to form pyrazoles, and Claisen reported in 1888 that they react with hydroxylamine to generate isoxazoles.[9,10] Similarly, the Pinner pyrimidine synthesis reacts 1,3-dicarbonyls with amidines to form pyrimidines.[11]

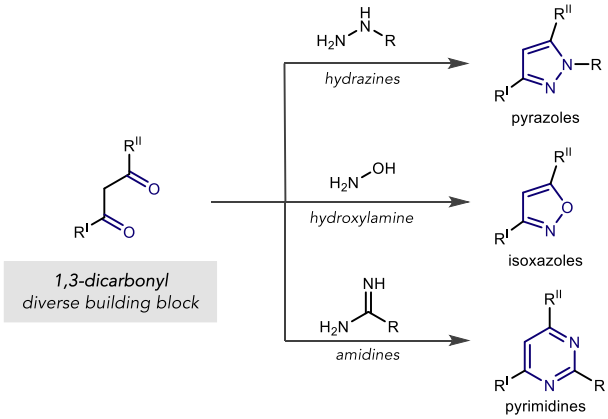


Figure 4.2 De novo synthesis of 5- and 6-membered heterocycles from 1,3-dicarbonyls.

4.2.2 Skeletal Editing as a Tool for Drug Discovery

As discussed in previous chapters, methods to diversify pharmaceutical candidates typical fall within three general categories: C–H functionalization, functional group interconversion, and *de novo* synthesis. In the past five years, an alternative approach known as "skeletal editing" has gained popularity in synthetic methods discovery.[12] These reactions take many forms, but the most practical versions typically fall into these three categories: (1) single-atom insertion, (2) single-atom deletion, and (3) single-atom exchange. Each of these categories have seen considerable attention in recent years.

Single-atom insertion in the context of heterocycles refers to expanding the ring-size by one, typically by introducing a carbon or nitrogen atom between two atoms in the ring (Figure 4.3). The 1881 Ciamician-Dennstedt reaction generates a reactive carbene species from $CHCl_3$ and strong base which unselectively adds to pyrroles to make pyridines.[13] Building on this reactivity, two reports by Levin in 2021 and 2022 exemplify this transformation. They generate a carbene from practical chlorodiazarene precursors, which add adjacent to small substituents on pyrroles and indoles, ring-expanding them (single-carbon insertion) to form pyridines and quinolines.[14] Their subsequent report transforms pyrazoles and indoles into pyrimidines and quinazolines by

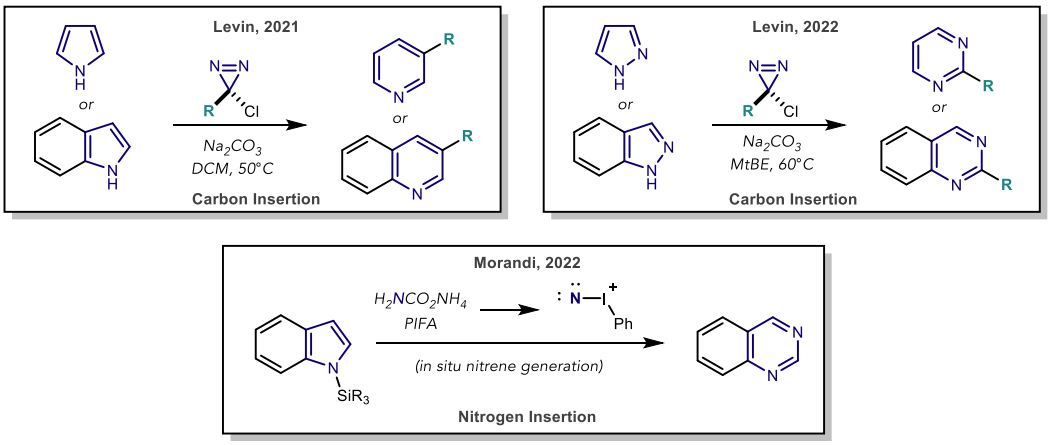


Figure 4.3 Examples of single-atom insertion reactions.

single-carbon insertion between the N–N bond.[15] Beyond insertions of carbon, the Morandi group published a 2022 report of single-nitrogen insertion using nitrenes to convert indoles to quinazolines.[16]

Single-atom deletion reactions have also been reported (Fig. 4.4). A nitrogen deletion of saturated heterocycles was reported by Levin in 2021, and a carbon deletion of pyrimidines to form pyrazoles was reported by Sarpong in 2023.[17,18]

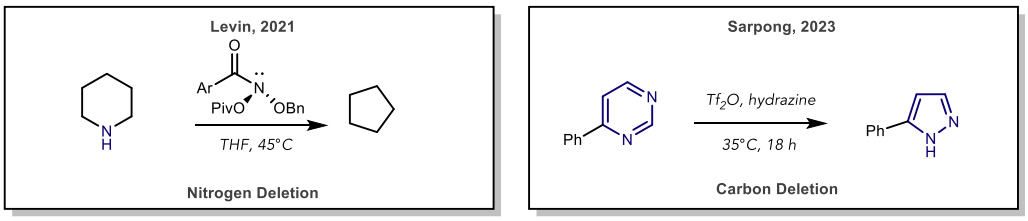


Figure 4.4 Examples of single-atom deletion skeletal editing reactions.

Numerous examples of single-atom exchange have been reported as well (Fig. 4.5). Pyridine to benzene (C–N exchange) reactions have been reported by Studer and Greaney, and an impressive report from Levin in 2023 showed the opposite reaction by demonstrating benzene to pyridine by N–C exchange.[19–21]

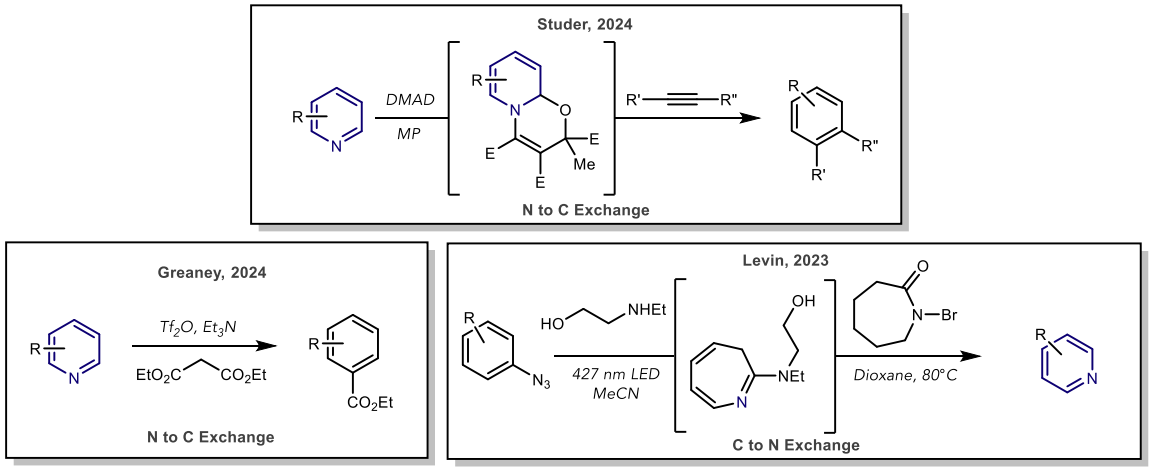


Figure 4.5 Examples of single-atom exchange skeletal editing reactions.

This popular field of synthetic development has only been a focus of organic chemists in recent years, and it is too early to know if these methods will find widespread use in drug discovery. However, skeletal editing reactions may be powerful tools in medicinal chemistry because they enable direct modifications to the core framework of a molecule, rather than just altering side chains. This allows medicinal chemists to explore entirely new chemical space while preserving key functional groups, potentially improving properties like potency, selectivity, or metabolic stability. By enabling the transformation of one scaffold into another, skeletal editing can rapidly generate diverse analogs, streamline hit-to-lead optimization, and uncover novel bioactive chemotypes that may be missed through traditional approaches. Chemists developing these types of reactions point to examples from drug discovery campaigns where modifying a heterocycle for another within the drug scaffold led to tremendous changes in potency.[22] Figure 4.6 shows an example from drug discovery where exchanging a benzene ring to a pyridine ring resulted in >500-fold potency for the desired target. This transformation could be accomplished via C–N exchange, demonstrating how skeletal editing can expedite the drug discovery process.

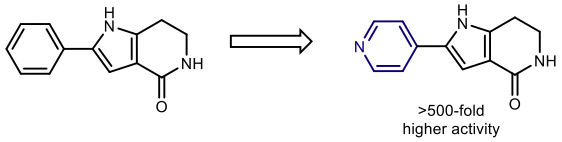


Figure 4.6 Example of increased drug potency through a formal C–N exchange.

4.3 Introduction to Pyrimidine Deconstruction-Reconstruction

Despite the growing number of reported molecular editing strategies, approaches that enable access to a wide array of products from a single precursor remain limited. Such methods would be highly beneficial for structure–activity relationship (SAR) studies by facilitating the rapid generation of compound libraries from a common lead structure. As outlined in Section 4.2.2, existing molecular editing techniques often involve modifying a single atom and typically yield

only one type of heterocycle. In contrast, we explored an alternative approach that involves breaking down a heterocyclic starting material late in the synthesis to produce a flexible intermediate, such as a 1,3-dicarbonyl surrogate. This intermediate can then participate in condensation reactions, similar to those used in de novo heterocycle synthesis, to form a range of new heterocyclic structures. Figure 4.7 demonstrates an ideal case of the transformation we developed. We expect that medicinal chemists undergoing an SAR campaign on a pyrimidine-containing drug candidate will deconstruct the pyrimidine to a 1,3-dicarbonyl surrogate and employ traditional condensation chemistry to generate libraries of analogs.

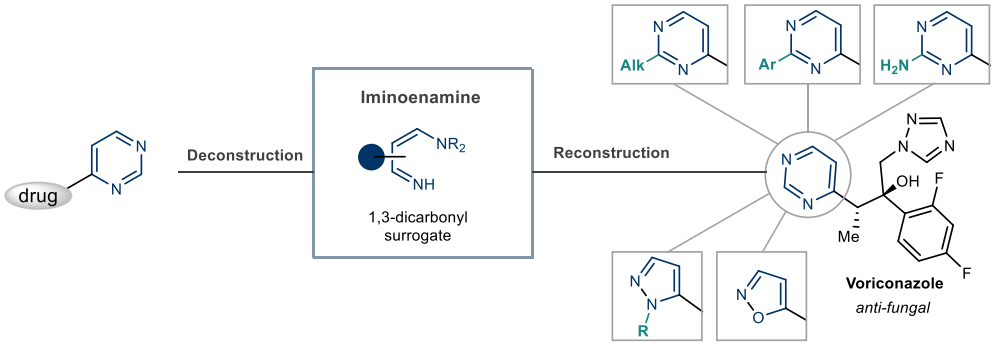


Figure 4.7 Heterocycle diversification via a deconstruction-reconstruction strategy.

The discovery of this reaction platform began with a serendipitous discovery while exploring the ring-opening scope of pyridines and diazines with aniline (discussed in Chapter 2.4.1). We found that *N*-Tf pyrimidines react with $HNBn_2$ similarly to pyridines, albeit in lower yields, forming aza-Zincke imines with loss of mass balance due to decomposition (Fig. 4.8).[23] When we used aniline as a ring-opening nucleophile, we observed the unexpected formation of an N-Ph pyrimidinium salt instead of a ring-opened aza-Zincke imine. In the case of 4-phenylpyrimidine, the conversion to pyrimidinium salt (**4.1**) is nearly quantitative.

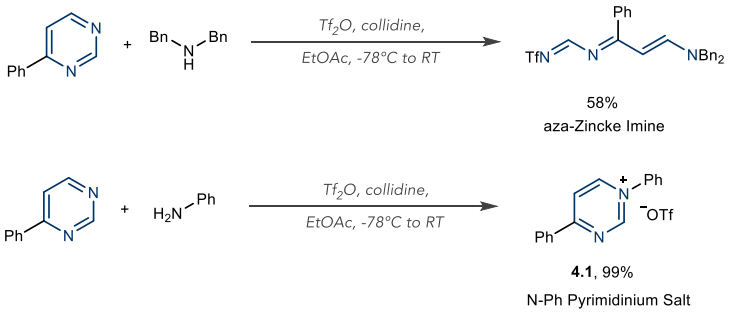


Figure 4.8 Unexpected reaction between pyrimidines, triflic anhydride, and aniline.

We hypothesized that the highly activated pyrimidinium salt would be susceptible to C2-cleavage to form a 3-carbon unit resembling a 1,3-dicarbonyl. Indeed, when we added piperidine to ethanolic solutions of **4.1**, we observed nearly quantitative excision of the C2 carbon atom, obtaining an 85% yield of iminoenamine **4.2** with minor amounts (13%) of vinamidinium salt **4.3** by crude ^{1}H-NMR (Fig. 4.9). Iminoenamines are surrogates of 1,3-dicarbonyl compounds, so we hypothesized that we could recombine the cleaved intermediates with hydrazine or amidines to form pyrazoles or pyrimidine products.

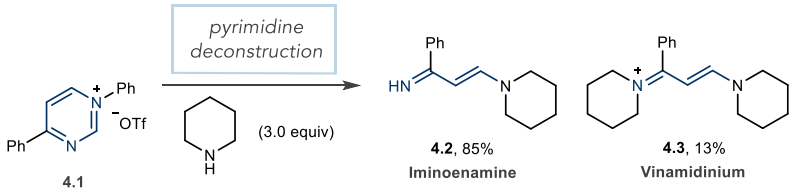
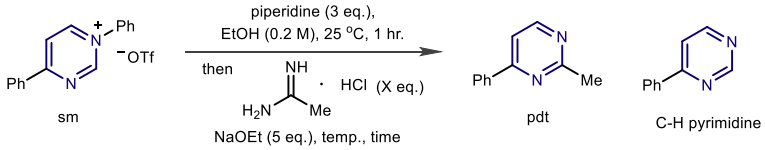


Figure 4.9 C2 carbon atom cleavage of pyrimidinium salts.

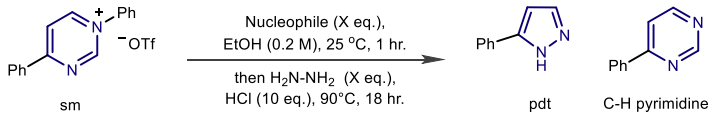
Table 4.1 shows the optimization study for C2-functionalization of pyrimidines using acetamidine hydrochloride to effect C2-methylation as a model system. We began with the conditions shown in Fig. 4.9 to deconstruct pyrimidines into iminoenamines and varied amidine equivalents, reaction time and temperature, in the presence of 5.0 equiv. of NaOEt as a base additive. We found that 3.0 equiv. of acetamidine, 90°C, and 18 hours resulted in the highest yield of 2-methyl-4-phenylpyrimidine.



entry	amidine equiv	temperature (°C)	time (hr.)	C-H pyrimidine	pdt
1	1.5	90	18	03	32
2	3	90	18	06	72
3	5	90	18	16	65
4	3	50	18	05	38
5	3	70	18	05	54
6	3	90	1	04	38
7	3	90	5	04	51

Table 4.1 Optimization of C2-functionalization of pyrimidines via deconstruction-reconstruction.

Table 4.2 shows the optimization study for ring-conversion pyrimidines to pyrazoles with hydrazine. Our initial discovery of the ring-conversion used NaOH as a ring-cleavage nucleophile, resulting in an 83% yield of 3-phenylpyrazole product. We found that we could use 3.0 equiv. of piperidine for the cleavage step, 3.0 equiv. of hydrazine, and 10.0 equiv. of HCl at 90°C for 18 hours to form 3-phenylpyrazole in 92% yield.



entry	nucleophile ID	nucleophile equiv	hydrazine equiv	C-H pyrimidine	pdt
1	NaOH	3	3	n.d.	83
2	NaOH	5	3	n.d.	88
3	NaOH	3	5	n.d.	92
4	NaOH	5	5	n.d.	87
5	piperidine	3	3	01	92
6	piperidine	3	5	01	88

Table 4.2 Optimization of pyrimidine to pyrazole ring-conversion.

Figure 4.10 shows that recyclization of the crude reaction mixture using guanidine and NaOEt forms 2-aminopyrimidine **4.4** in high yield. Similarly, adding hydroxylamine and HCl to the crude mixture forms high yields of 3-phenylisoxazole **4.5** in a 2:1 regiomeric ratio. These initial

results gave credence to our hypothesis that pyrimidines could act as starting materials for many transformations, including substituting the 2-position of the starting pyrimidine, and conversion to other heterocycles, such as pyrazoles.

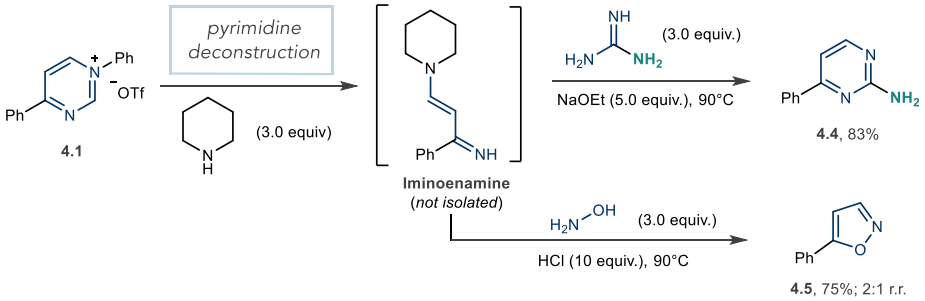


Figure 4.10 Deconstruction-reconstruction to form 2-aminopyrimidines and pyrazoles.

4.4 Scope of Pyrimidine Deconstruction-Reconstruction

With our promising initial result with 4-phenylpyrimidine, we turned our attention to examining the scope of the ring-opening-ring-closing process to form N-Ph pyrimidinium salts (Fig. 4.11). We found that the scope of this process was quite general, and functions on a wide range of 4-(hetero)arylpyrimidines (**4.6-4.10**), tolerates electron donating (**4.11, 4.12**) and electron-withdrawing (**4.13**) groups, and a host of disubstituted and fused pyrimidines (**4.14-4.21**).

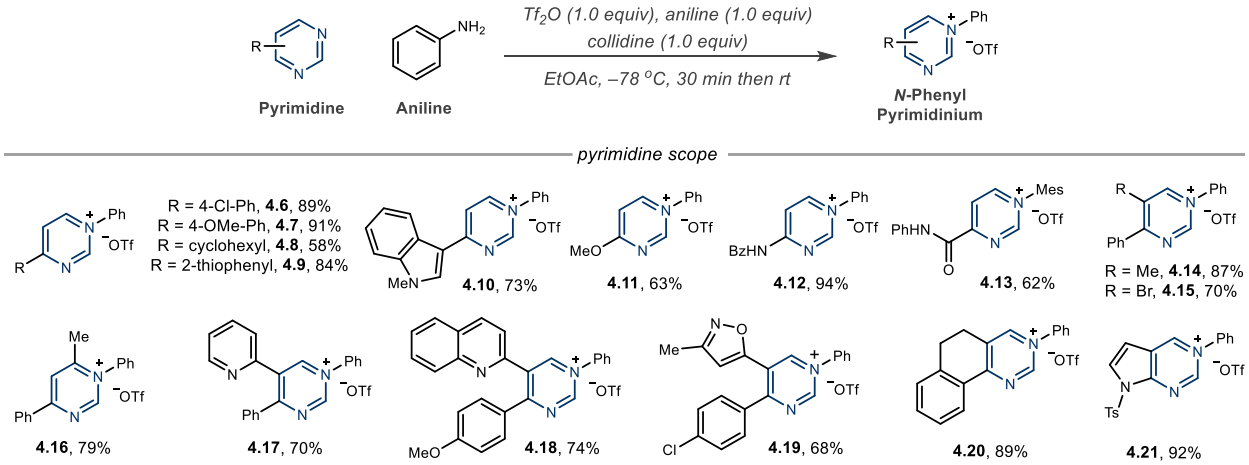


Figure 4.11 Selected scope of pyrimidine ring-opening-ring-closing process.

We next examined 5-monosubstituted pyrimidines in this process and found that instead of cleanly converting to N-Ph pyrimidinium salts in the first step, the form mixtures of pyrimidinium salts, aza-Zincke imines and aniline-derived iminoenamines. We found that the mixture of products could be carried forward into the reconstruction step without intermediate isolation to form desired products in a one-pot fashion. Figure 4.12 shows this modified procedure with 5-phenylpyrimidine, forming 2-amino-5-phenylpyrimidine **4.22** in reasonable yields.

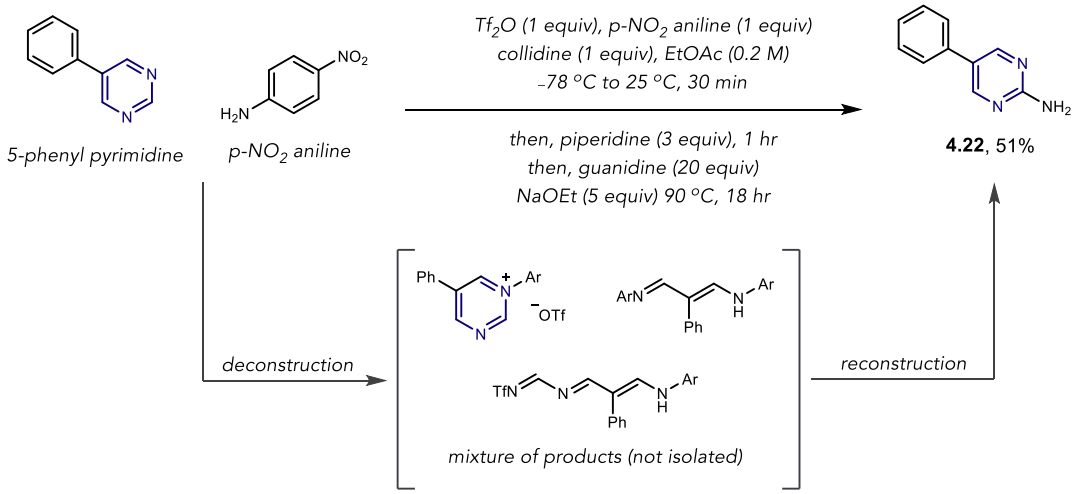


Figure 4.12 One-pot deconstruction-reconstruction procedure for 5-monosubstituted pyrimidines.

Using the robust strategy for pyrimidinium salt formation, we next examined the scope of the deconstruction-reconstruction process (Fig. 4.13). Condensation with urea and thiourea resulted in pyrimidone **4.23** and thiopyrimidine **4.24**, respectively. 2-Alkyl groups, such as methyl, cyclopropyl, and trifluoromethyl, are installed efficiently by using the corresponding amidines in the cyclization step (**4.25-4.27**). Impressively, this process can also be used to form biheteroaryls in moderate to good yields (**4.28-4.32**) from C–H precursors.

C–H functionalization reactions that function on pyrimidines and especially complex pyrimidines are quite limited. A 2-selective C–H amination reaction has been reported from pyrimidine N-oxides, and Minisci-type can alkylate the 2-position of pyrimidines, but they tend to

give unselective mixtures of products.[24,25] Forming the C–heteroatom and C–C bonds in **4.23-4.37** would typically require a (pseudo)halide precursor and employ S_NAr or metal-catalyzed cross-coupling. These reactions are often challenging on complex azines and can be unselective on complex molecules with multiple reactive sites.[26–28]

We continued to test this deconstruction–reconstruction approach to effect net C–H functionalization reactions. We demonstrated the reaction on a pyrimidine-containing analogue of pregnenolone, effecting a 2-cyclopropylation product (**4.33**). We next examined a series of complex drug-like 5-monosubstituted pyrimidines in this process (**4.35-4.37**) using the modified one-pot procedure shown in Fig. 4.12.

We also extended the process shown in Fig. 4.10 to convert pyrimidines into azoles. We formed 1,2-oxazole **4.38** from an amido-substituted pyrimidinium salt. Polypyrimidines also undergo controlled ring contraction. Using 4,5-bipyrimidine, we performed a round of pyrimidinium salt formation, cleavage to the iminoenamine and recyclization with N-phenylhydrazine to install a pyrazole. Then, a second round culminating instead with hydroxylamine resulted in pyrazole-1,2-oxazole heteroaryl **4.40**. We demonstrated the pyrimidine to azole ring-conversion on a series of disubstituted pyrimidines, which all convert cleanly to the desired isoxazole or pyrazole products (**4.41-4.43**).

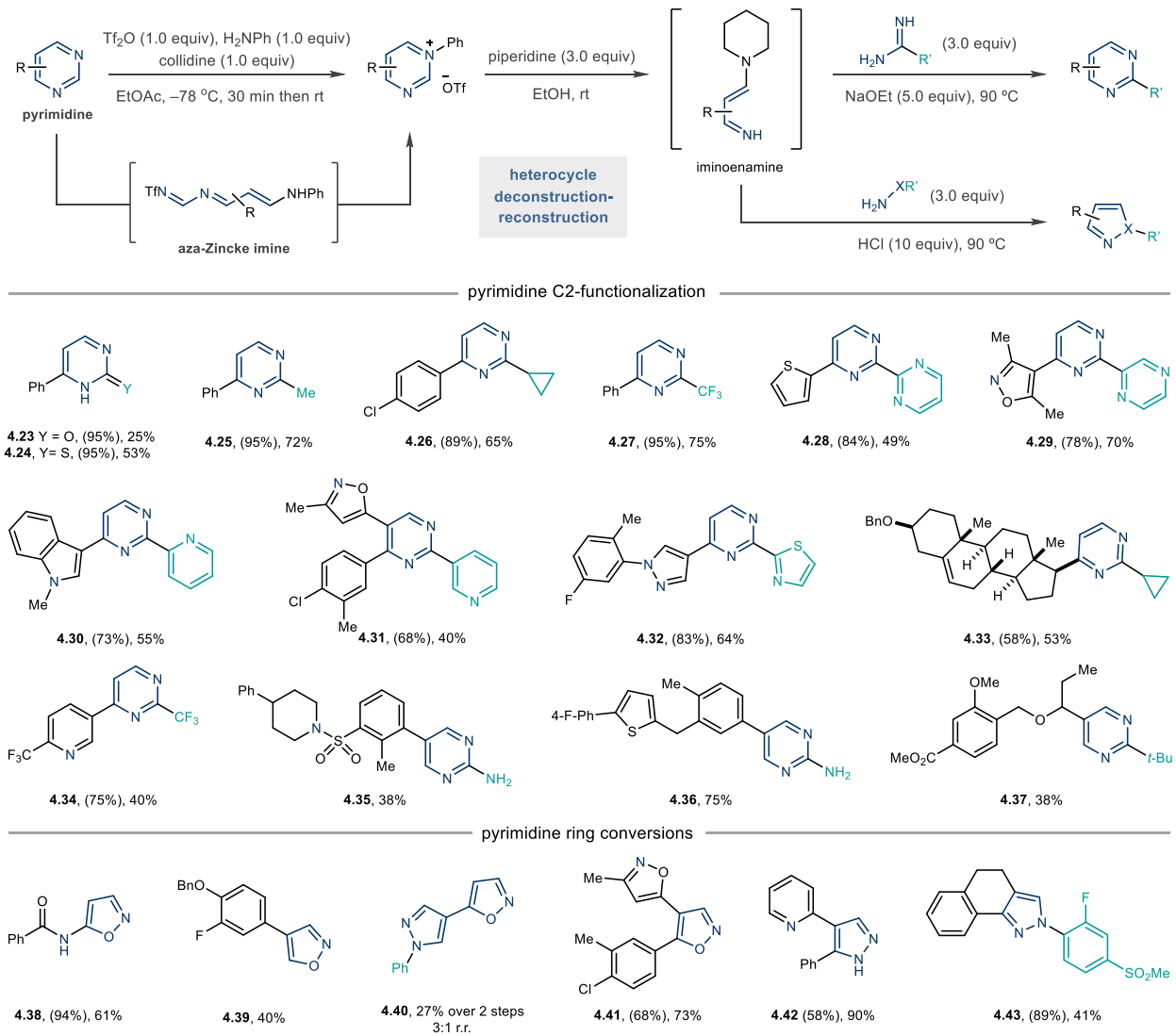


Figure 4.13 Selected scope of the deconstruction-reconstruction process. Yields in parenthesis are of pyrimidinium salts.

At this point, we applied our deconstruction–reconstruction strategy to transform bioactive compounds into structurally diverse analogues, aligning with approaches commonly employed in pharmaceutical and agrochemical research (Fig. 4.14). As a proof of concept, we modified the fungicide fenarimol (**4.44**), generating amino, cyclopropyl, and phenyl analogues (**4.45-4.47**) through efficient one-pot syntheses. To further challenge this methodology, we selected dabrafenib—a clinically approved melanoma therapy containing a pyrimidine core—as a more complex target. The intermediate **4.48**, a precursor to dabrafenib, features a pyrimidine ring with

a C–H bond at the 2-position. In a sequential one-pot protocol, the N-arylpyrimidinium salt was formed in situ, followed by treatment with piperidine in ethanol to yield the iminoenamine intermediate **4.49**. Subsequent reaction with guanidine under basic conditions led to C2-amination and formation of dabrafenib (**4.50**). Using similar reaction conditions, cyclopropylated and trifluoromethylated variants (**4.51** and **4.52**) were synthesized by introducing amidines during the ring-forming step. We also demonstrated that the core scaffold could be exchanged for different heterocycles. For instance, isolating the N-arylpyrimidinium intermediate from **4.48** and treating it with hydrazines yielded pyrazoles **4.53** and **4.54**. Likewise, reacting iminoenamine **4.49** with hydroxylamine generated the 1,2-oxazole **4.55** with a regioisomeric ratio of 16:1. These six derivatives underscore the versatility of the three-carbon iminoenamine intermediate **4.49** as a central scaffold for constructing a broad range of pyrimidine-based structures.

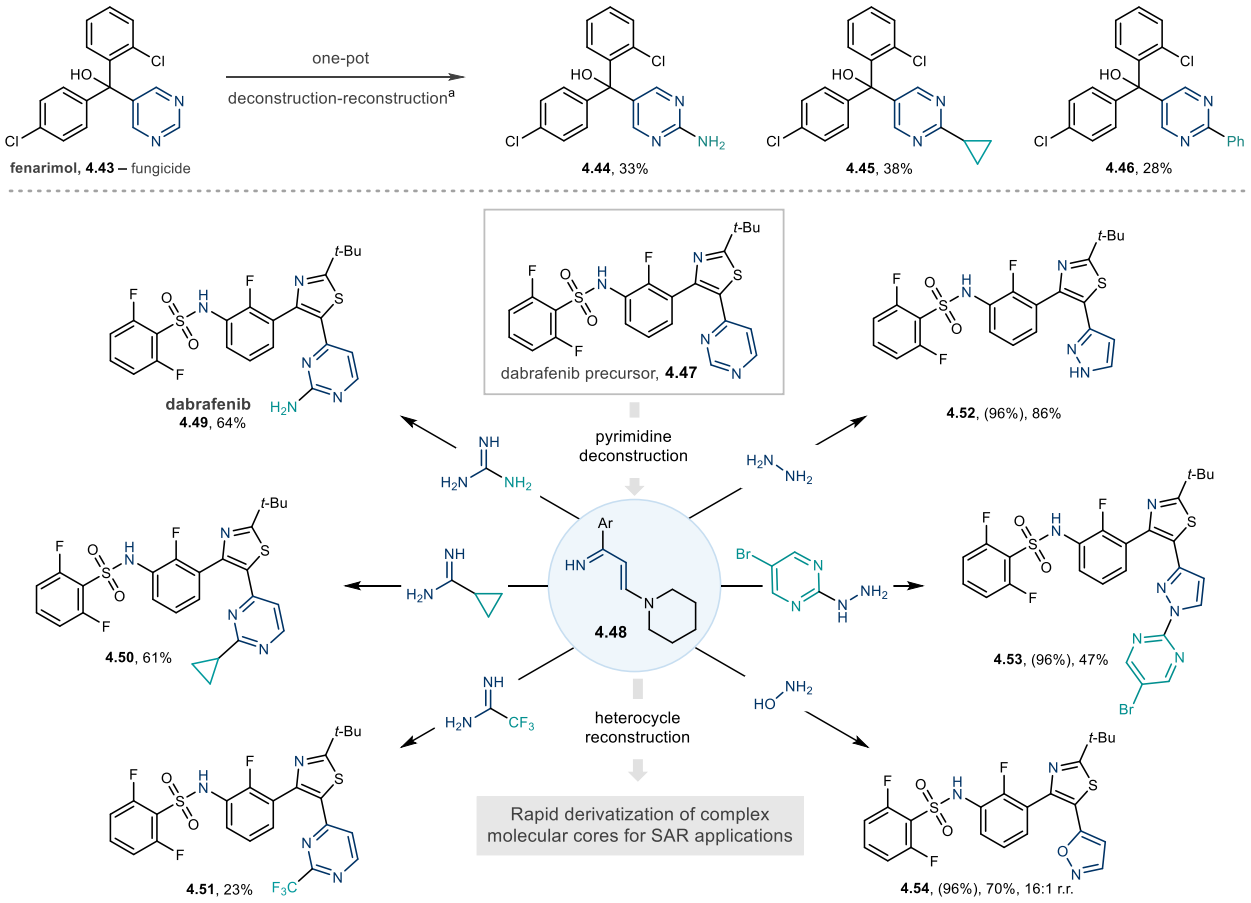


Figure 4.14 Complex pyrimidine derivatization via deconstruction-reconstruction.

Chapters 2 and 3 focus on functionalizing ring-opened heterocycles. We wondered if iminoenamine intermediates could react with N-halosuccinimides to functionalize the 5-position of pyrimidines, then reconstruct with functionalized amidines to form 2,5-difunctionalized pyrimidines. Figure 4.15 shows an example of pyrimidine difunctionalization via deconstruction-reconstruction. We began by cleaving pyrimidinium salt **4.55** using our established protocol, then directly introduced N-chlorosuccinimide and trifluoroacetic acid into the reaction mixture to generate the chloroiminoenamine intermediate **4.56**. Subsequent application of the pyrimidine reconstruction sequence using cyclopropaneamidine afforded the 2,5-disubstituted product **4.57**. The resulting C–Cl bond is particularly useful in medicinal chemistry, both as a bioactive moiety and as a synthetic handle for further modification at a distinct site on the heterocycle.[29] Notably, this transformation represents a net C–H difunctionalization, differing from traditional methods that typically modify only a single site. By introducing two substituents in a single sequence, this strategy opens new avenues for diversifying pyrimidine scaffolds in SAR studies.

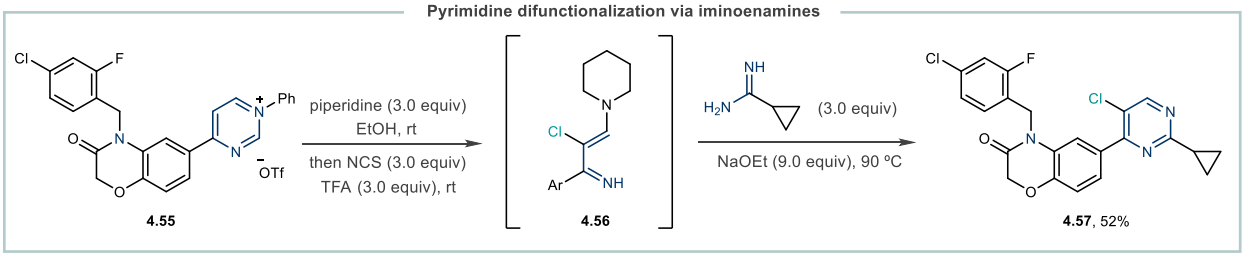


Figure 4.15 Pyrimidine difunctionalization via deconstruction-reconstruction.

4.5 Formal N–C Replacement Converting Pyrimidines to Pyridines

We next applied our deconstruction–reconstruction strategy to convert pyrimidines into pyridines by leveraging the formation of vinamidinium salts. As discussed in Section 4.3, when piperidine is used for ring-opening, both iminoenamine and vinamidinium intermediates are generated. However, using an excess (six equivalents) of pyrrolidine shifts the outcome strongly toward vinamidinium salt formation, yielding 97% in the case of 4-phenyl pyridine. Prior studies

have demonstrated that vinamidinium salts can react with enolates derived from ketones to form 1,5-dicarbonyl surrogates *in situ*. These intermediates can then undergo tautomerization and subsequent cyclization with ammonium salts to give pyridine products.[30] Building on this, we proposed that enolates derived from acyl silanes might show similar reactivity and, following desilylation, could enable a formal nitrogen-to-carbon (N–C) atom exchange (Fig. 4.16). If successful, this would offer a new method for transforming pyrimidines into pyridines via single-atom editing—a potentially powerful strategy for generating novel analogs during SAR studies.

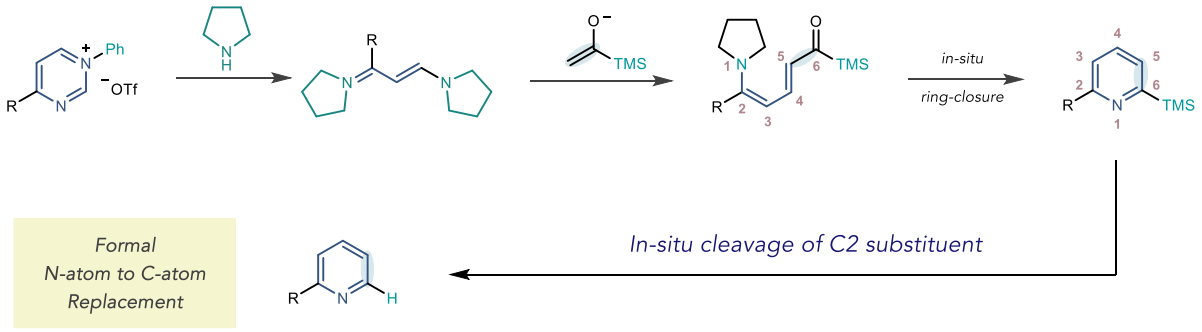


Figure 4.16 Design of pyrimidine to pyridine conversion.

By modifying a method originally reported by Marcoux, we were able to accomplish a single-atom transformation of pyrimidines into pyridines. This was achieved by treating the vinamidinium salt with three equivalents of the lithium enolate derived from commercially available acetyltrimethylsilane, followed by heating with a mixture of ammonium acetate and acetic acid at 95 °C (Fig. 4.17). We demonstrated this procedure on four complex pyrimidines reminiscent of those found in drug-discovery campaigns. The pyrimidine to pyridine conversion is tolerant of a wide array of functional groups, such as electron-rich aromatics like pyrazoles, amides, aryl halides, and saturated heterocycles (**4.58-5.61**). We hypothesize the silyl group is cleaved after heterocycle formation under the reaction conditions.

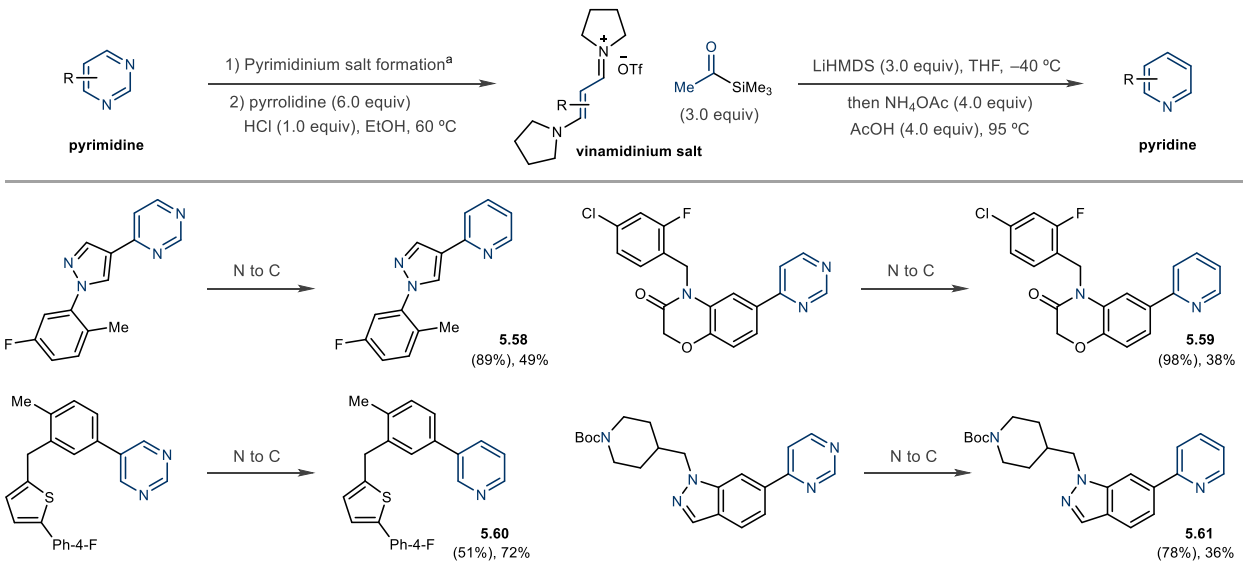


Figure 4.17 Scope of complex pyrimidine to pyridine conversions. Yields in parenthesis are of vinamidinium salts.

Beyond the formal nitrogen-to-carbon atom substitution, we also demonstrated that the pyridine ring could be selectively functionalized at either the C2 or C5 position using enolates derived from ketones or hydrazones, rather than those from acylsilanes (Fig. 4.18). For example, compounds **5.62** and **5.63** illustrate that depending on whether acylsilanes or hydrazone-based

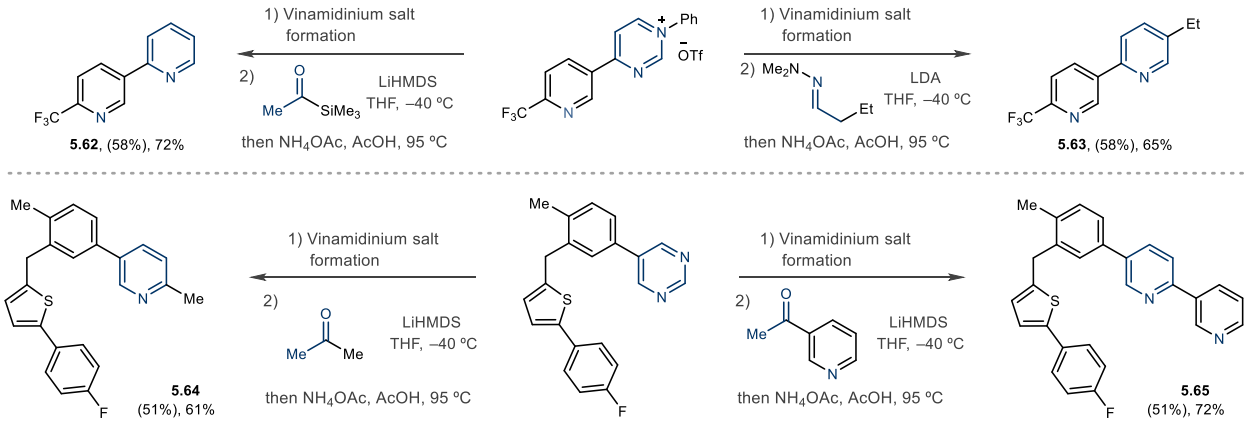


Figure 4.18 Diverse pyridines resulting from single pyrimidine starting materials. Yields in parenthesis are of vinamidinium salts.

enolates are used, the resulting products differ, yielding either unsubstituted pyridines or C5-ethylated analogs. This selectivity provides a powerful tool for controlling product outcomes based on enolate choice, enabling rapid diversification. To showcase this potential, we generated four

distinct pyridine analogues from a common precursor by simply varying the ketone component, successfully installing methyl or pyridyl groups at the C2 position (**5.64** and **5.65**).

4.6 Mechanistic Studies of Pyrimidinium Salt Formation

In the final part of this study, we studied the mechanism of pyridine ring-opening/ringclosing in collaboration with the Paton group at Colorado State University. Mechanistic studies were conducted computationally by performing quantum chemical calculations at the ωB97XD/def2-TZVP// Q13 ωB97X-D/6-31+G(d,p) level in ethyl acetate (Fig. 4.19). In the first step of the reaction mechanism, 4-phenyl pyrimidine undergoes an exergonic trifylation process with triflic anhydride forming **Int-Act**. From this intermediate, attack of the nucleophilic aniline occurs at either the C2 or the C6 position. We found attack at the C6-position (ΔG ‡=15.1 kcal mol^{-1}) is kinetically favored over the C2-position (ΔG ‡=15.9 kcal mol^{-1}) at −78°C. Subsequent deprotonation by collidine yields **Int-I** as a dihydropyrimidine. Although attack of the aniline nucleophile is an endergonic process, deprotonation of collidine is energetically barrierless driving the formation of **Int-I** forward.

Next, **Int-I** undergoes ring-opening to the aza-triene intermediate (aza-Zincke imine) through an endergonic process. Then, the aza-Zincke imine tautomerizes to **Int-II** before ringclosing via a polar mechanism to dihydropyrimidine, **Int IV**. Ring-closure represents the highest barrier across the reaction profile making this step rate-limiting. Finally, extrusion of the triflimide counterion and counterion exchange with the collidine triflate salt completes the reaction mechanism yielding the pyrimidinium product. We also found the steric and electronic properties of substituents at the C4-position of the pyrimidine substituents have an impact on the energy barriers for pyrimidinium formation. In the ring-closure step, substituents at the C4-position experience destabilizing allylic strain ($A^{1,3}$) with its neighboring allylic hydrogens in **TS-IV**.

Increasing the allylic strain with sterically encumbering substituents also increases ground state destabilization; thus, the energetic barriers for ring-closure decrease. This is exemplified by comparing the energetic barriers of ring-closure among various substituents. Phenyl groups and methyl groups (ΔG ‡=18.1 and 18.0 kcal mol^{-1}, respectively) at the C4 position have lower barriers for ring-closure compared to hydrogen groups (ΔG ‡=22.7 kcal mol^{-1}).

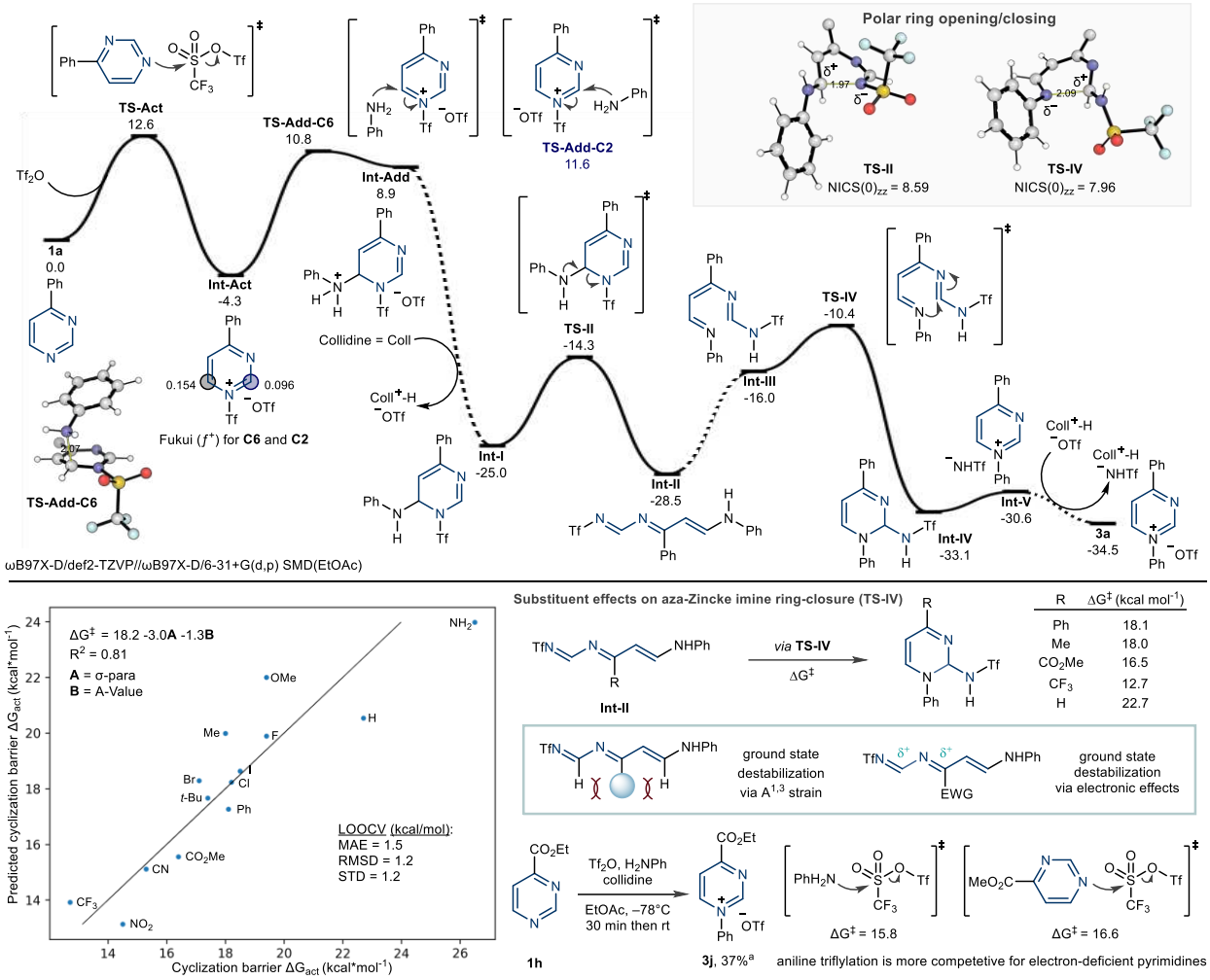


Figure 4.17 Computational studies of pyrimidinium salt formation.

Electron-withdrawing groups at C4 also destabilize **Int-II** and lower the cyclization barrier by affecting the electronic properties of aza-Zincke imine. Although the barrier for cyclization is much lower than sterically encumbering groups, the yield of N-aryl pyrimidinium formation is much lower. We hypothesize electronic-deficient pyrimidines do not effectively react with triflic

anhydride. Thus, competitive trifylation with the aniline nucleophile hinders product formation. However, employing sterically encumbered aniline nucleophiles, such as 2,4,6-trimethylaniline, to prevent competitive trifylation increases the yield of the pyrimidinium product.

4.7 Functional Group Metathesis via Deconstruction-Reconstruction

Given the success of functionalizing C2-unsubstituted pyrimidines via a deconstruction-reconstruction approach, we wondered if it would be possible to deconstruct C2-functionalized pyrimidines into iminoenamine intermediates. This would be an incredibly powerful maneuver during SAR studies, because it would enable practitioners to transform the substituent at the 2-position by eliminating the original substituent from the drug (deconstruction) and replacing it with the substituent of choice (reconstruction).[31] Another motivation for this transformation is the high prevalence of pyrimidine-containing drugs with 2-substituents, especially 2-aminopyrimidines.[32] My coworkers Celena Josephitis, David Thomas, and Enrique Hernandez Salcido spearheaded a new method to ring-open and cleave 2-substituted pyrimidine to enable an exciting functional group metathesis platform.

Under the conditions developed for C2-unsubstituted pyrimidines, we found that most pyrimidines with C2-position substituents did not form N-Ph pyrimidinium salts under the reaction conditions. A number of 2-substituted pyrimidines were tested, finding that 2-alkyl-4-arylpyrimdines form desired pyrimidinium salts, but 2-aryl, amino, or alkoxypyrimidines yield unreacted starting material or decomposition. Fortunately, my coworkers observed that by using a thiol as a ring-opening nucleophile instead of an amine, and changing solvent and temperature, high yields of ring-opened thiol aza-Zincke imines are observed. We found that *in situ* deconstruction-reconstruction is then trivial by adding guanidines or amidines to the new ring-opened species to form substituent metathesized products.

Investigations into this alternative approach are ongoing, but transformations of most 2-substituents have been shown (Fig. 4.19). Once ring-opened, a wide array of transformations are possible depending on the amidine or guanidine selected for reconstruction. The transformation is demonstrated by changing the ring-size of 2-piperidine-4-phenylpyrimidine **4.66** (Fig. 4.18). The pyrimidine is ring-opened with *tert*-butylthiol and isolated (**4.67**), then using different ring-size saturated heterocycles on guanidine, transformed into various analogs of the starting pyrimidine (**4.68-4.71**).

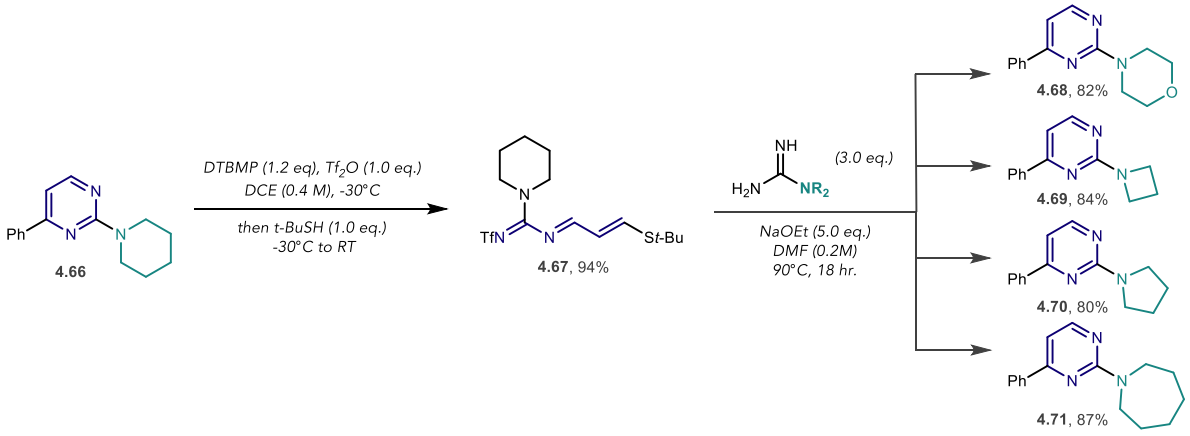


Figure 4.18 Preliminary examples of C2-substituent metathesis of pyrimidines.

We have demonstrated similar transformations on various C2-functionalized pyrimidines, such as 2-alkyl, 2-aryl, and 2-alkoxy group metathesis (Fig. 4.19). Investigations are ongoing into developing a one-pot metathesis reaction and expanding the reaction to complex pyrimidines and pharmaceuticals.

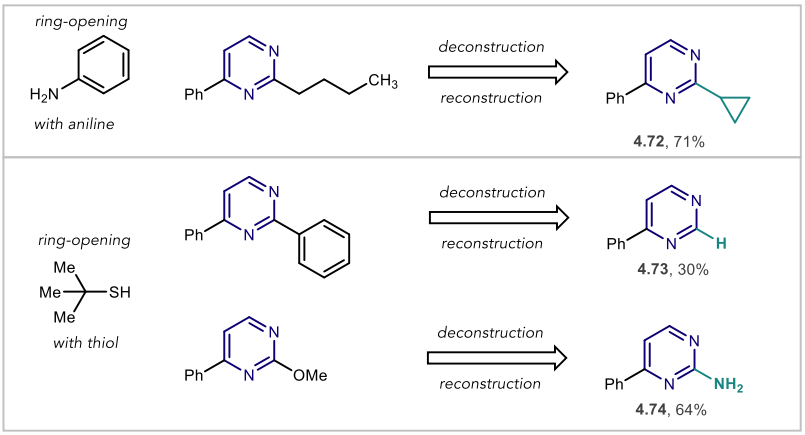


Figure 4.19 C2-substituent metathesis of alkyl, aryl, and alkoxy groups.

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CHAPTER 5. STABLE ISOTOPE LABELING OF PYRIMIDINES USING A DECONSTRUCTION-RECONSTRUCTION STRATEGY

5.1 Chapter Overview

This chapter describes a novel strategy to incorporate stable isotopes into pyrimidines by first deconstructing them into vinamidinium salts, then reconstructing them with isotopically-labeled amidines and guanidines. Stable-isotope chemistry will be introduced, along with the use of higher-mass isotopes in adsorption, distribution, metabolism, and excretion (ADME) studies. The development of a deconstruction-reconstruction strategy to incorporate higher-mass stable isotopes into pyrimidines will be discussed, along with a demonstration of reaction scope. Finally, a 5-selective deuteration of pyrimidines will be introduced, and implications to M+1 to M+5 pyrimidine synthesis will be shown.

5.2 Introduction to Stable Isotopes in Medicinal Chemistry

Stable isotopes have emerged as powerful tools in medicinal chemistry, offering unique advantages in the design, development, and evaluation of pharmaceutical agents. By substituting isotopes, such as deuterium (^{2}H), ^{13}C, or ^{15}N, into drug molecules, researchers can gain insights into metabolic pathways, improve pharmacokinetic and pharmacodynamic profiles, and enhance drug stability without altering biological activity.[1]

Stable isotopically labeled compounds play a critical role in ADME (Absorption, Distribution, Metabolism, and Excretion) studies by enabling precise tracking of drug molecules within biological systems.[2] This is accomplished by using isotopologs: molecules with identical structural identity to their non-labeled counterparts except for the substitution of atoms with non-radioactive isotopes. Their distinct mass signatures make them ideal for use in mass spectrometry,

where they facilitate clear differentiation from endogenous compounds or co-administered drugs.[3] For example, voriconazole is a pyrimidine-containing antifungal medication. After consumption, only 2% of a voriconazole dose is excreted unchanged in urine, meaning the drug is metabolized in the body prior to excretion.[4] A challenge for medicinal chemists is tracking a drug molecule in the body and detecting all metabolites and drug molecules in excretions. A common approach to these studies is to co-administer a drug with its higher-mass isotopolog. High-resolution mass spectrometry (HRMS) detects these as distinct twin peaks, separated by the number of incorporated isotopes (Fig. 5.1).[5] During ADME studies, both the parent drug and its metabolites exhibit this "twin-peak" signature, enabling straightforward tracking throughout the body and in excretions.

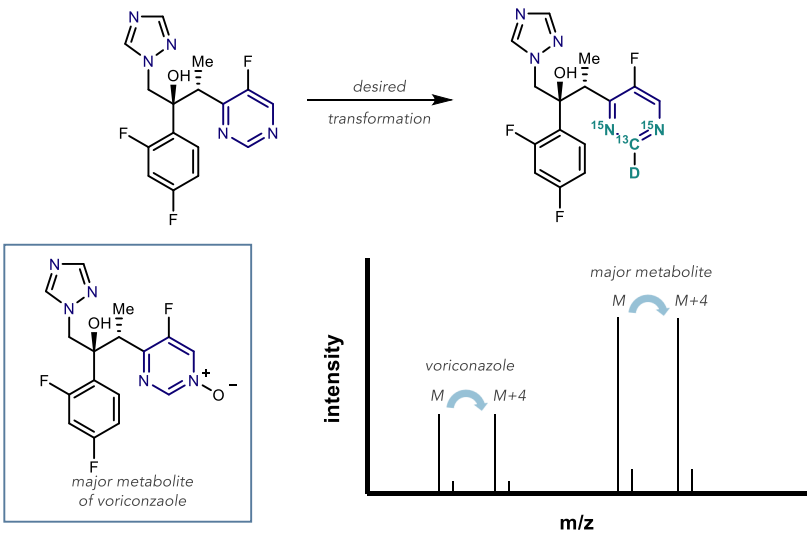


Figure 5.1 Higher mass stable isotopologs in ADME studies, with theoretical mass spectrometry trace of voriconazole metabolite.

In addition to mass spectrometry, stable isotopes are also analyzed via nuclear magnetic resonance (NMR). Naturally occurring isotopes like ^{12}C and ^{14}N are NMR-inactive.[6] Replacing these with NMR-active nuclei, such as ^{13}C or ^{15}N provides sharper, more interpretable signals. The ability to detect isotopically-labeled molecules by NMR enables medicinal chemists to elucidate the structure of metabolites, monitor binding with proteins and nucleic acids, and

determine absolute concentration of a drug or metabolites in complex mixtures.[7] Additionally, emerging SABRE-SHEATH techniques are used to amplify ^{15}N nuclei in NMR, with potential bioimaging applications.[8,9]

5.3 Existing Methods to Isotopically Label Pyrimidines

Due to the prevalence of pyrimidines in pharmaceuticals and agrochemicals, methods have been developed to synthesize isotopically-labeled pyrimidines. Isotopic labelling is typically performed using *de novo* synthesis with isotopically-labeled amidines or guanidines.[10] Recently, two approaches were reported for ^{15}N-isotope-exchange methods on pyrimidines (Fig. 5.2). A method developed by Sarpong uses Tf_2O to activate pyrimidines, then ^{15}N-aspartate mediates a ^{14}N-to-^{15}N exchange reaction, forming singly ^{15}N-labeled pyrimidines.[11] The reaction functions fairly well on 4-arylpyrimidines, with mono-^{15}N-incorporation generally > 90%. Unfortunately, the reaction only replaces one of the pyrimidine nitrogens and functions poorly on complex substrates and 5-substituted pyrimidines. The Audisio group reported a method to incorporate ^{15}N-atoms into pyridines using the *N*-Tf ring-opening method developed by our lab.[12,13] In their report, they demonstrated the same reaction conditions on 4-phenylpyrimidine and 5-phenylpyrimidine with low amounts of mono- and di-^{15}N-incorporation, averaging 43% isotopic enrichment (IE).

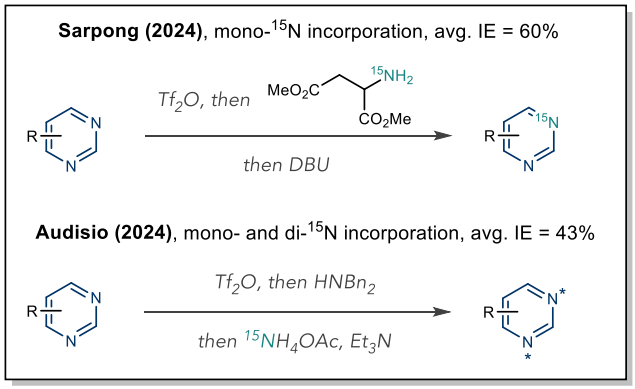


Figure 5.2 Existing pyrimidine ^{15}N-isotope exchange methods

5.4 Development of a Pyrimidine Isotope Exchange Method by Deconstruction-Reconstruction

After demonstrating several pyrimidine transformations are enabled using the deconstruction-reconstruction strategy described in Chapter 4, we hypothesized that we could use the same technique for isotope exchange.[14] The deconstruction step cleaves the C2-carbon atom along with both nitrogen atoms from the pyrimidine starting material, and reconstruction with amidines replaces the C2-carbon and both nitrogen atoms. We hypothesized that by performing the reconstruction step using isotopically enriched amidines, we would synthesize higher-mass isotopes of pyrimidines. For example, reconstructing with commercially available formamidine-^{13}C-1-d-$^{15}N_2$ acetate would generate a mass plus four (M+4) version of the parent pyrimidine (Fig. 5.3). Furthermore, deuterating the 3-position of the iminoenamine or vinamidinium salt intermediate enables variation in isotopic incorporation and access to isotopologs as high as M+5.

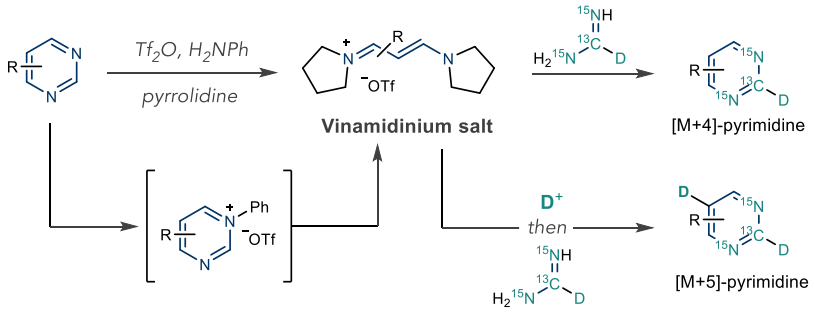


Figure 5.3 Proposed isotope exchange platform for pyrimidines.

To test the isotopic labeling platform, we selected 4-phenylpyrimidine as a model system, preparing pyrimidinium salt **5.1**. We then subjected it to cleavage conditions with piperidine, generating iminoenamine **5.2** in near quantitative yield. Finally we subjected the reaction mixture to formamidine-$^{15}N_2$ acetate, a reagent we synthesized from relatively inexpensive $^{15}NH_4Cl$, with a base to form isotopically-enriched **5.3** (Fig. 5.4). We assessed the ^{15}N incorporation by HRMS

and found that the major product was [$^{15}N_1$]-**5.3** with minor amounts of [$^{15}N_2$]-**5.3**, resulting in an overall isotopic enrichment of 53%. The low ^{15}N incorporation of the N3-nitrogen atom suggests that the imine nitrogen in **5.2** is retained during the reconstruction phase of the reaction. Our previous report disclosed a method for deconstructing pyrimidines into vinamidinium salts by ring-opening and cleaving **5.1** with pyrrolidine. We hypothesized that isolating vinamidinium salts prior to the reconstruction step would minimize unlabeled pyrimidine starting material impurities and, in turn, improve isotopic enrichment. Utilizing conditions to form vinamidinium salts, we tested the reconstruction without intermediate isolation, pleasingly observing a good yield of **5.3** with 92% IE, confirming our hypothesis that using vinamidinium salt intermediates improves enrichment of ^{15}N. When we isolate vinamidinium salt **5.4** by column chromatography prior to reconstruction with formamidine-$^{15}N_2$ acetate, we observed a 70% yield of **5.3** with > 99% IE. We then developed a more convenient precipitation process to isolate **5.4** in 84% yield and remove any unlabeled **5.1** from the crude reaction mixture to provide high yield and IE of **5.3**.

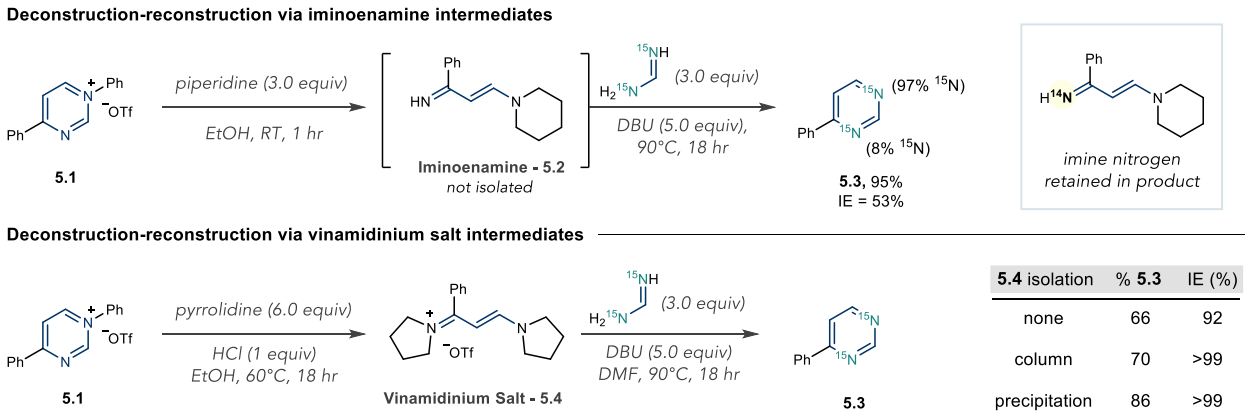


Figure 5.4 Optimization of the pyrimidine isotope-exchange method.

5.5 Scope of Pyrimidine Isotopic Enrichment Procedure

With optimized conditions in hand, we investigated the scope of pyrimidines in the isotopic enrichment process (Fig. 5.5). Most examples demonstrated excellent ^{15}N-incorporation, with many achieving >99% IE. In addition to 4-phenylpyrimidine, this process tolerates 4-

alkylpyrimidines, as demonstrated by 4-cyclopropylpyrimidine **5.5** and piperidine **5.6**. Examples **5.7-5.9** demonstrate that the procedure functions with 5-arylpyrimidines in moderate yields, tolerating halogens and ethers at various positions on the aryl substituent. Notably, 5-substituted pyrimidines did not suffer from the low isotopic enrichment observed in prior pyrimidine isotope exchange reports. Heterocycles at the pyrimidine 4-position are well-tolerated, with indole **5.10**, pyridine **5.11**, and thiophene **5.12** demonstrating excellent chemoselectivity for the pyrimidine. The method also tolerates carbonyls, as demonstrated by 4-amido-pyrimidine **5.13**. Example **5.14** demonstrates disubstituted pyrimidines are amenable to this procedure. We also examined a series of complex drug-like pyrimidines in the ^{15}N isotope-exchange procedure. These structures contain multiple Lewis basic atoms, (hetero)arenes, and reactive sites which could interfere with the pyrimidine deconstruction steps. Historically, synthesis of isotope-labeled versions of these complex pyrimidines required *de novo* synthesis of the pyrimidine core followed by lengthy multi-step synthesis of the drug candidate, potentially limiting their application in ADME studies. Examples **5.15** and **5.16**, 4-heteroarylpyrimidine derivatives which resemble drug fragments, were efficiently formed from the parent unlabeled pyrimidines. Similarly, complex 5-aryl **5.17** and

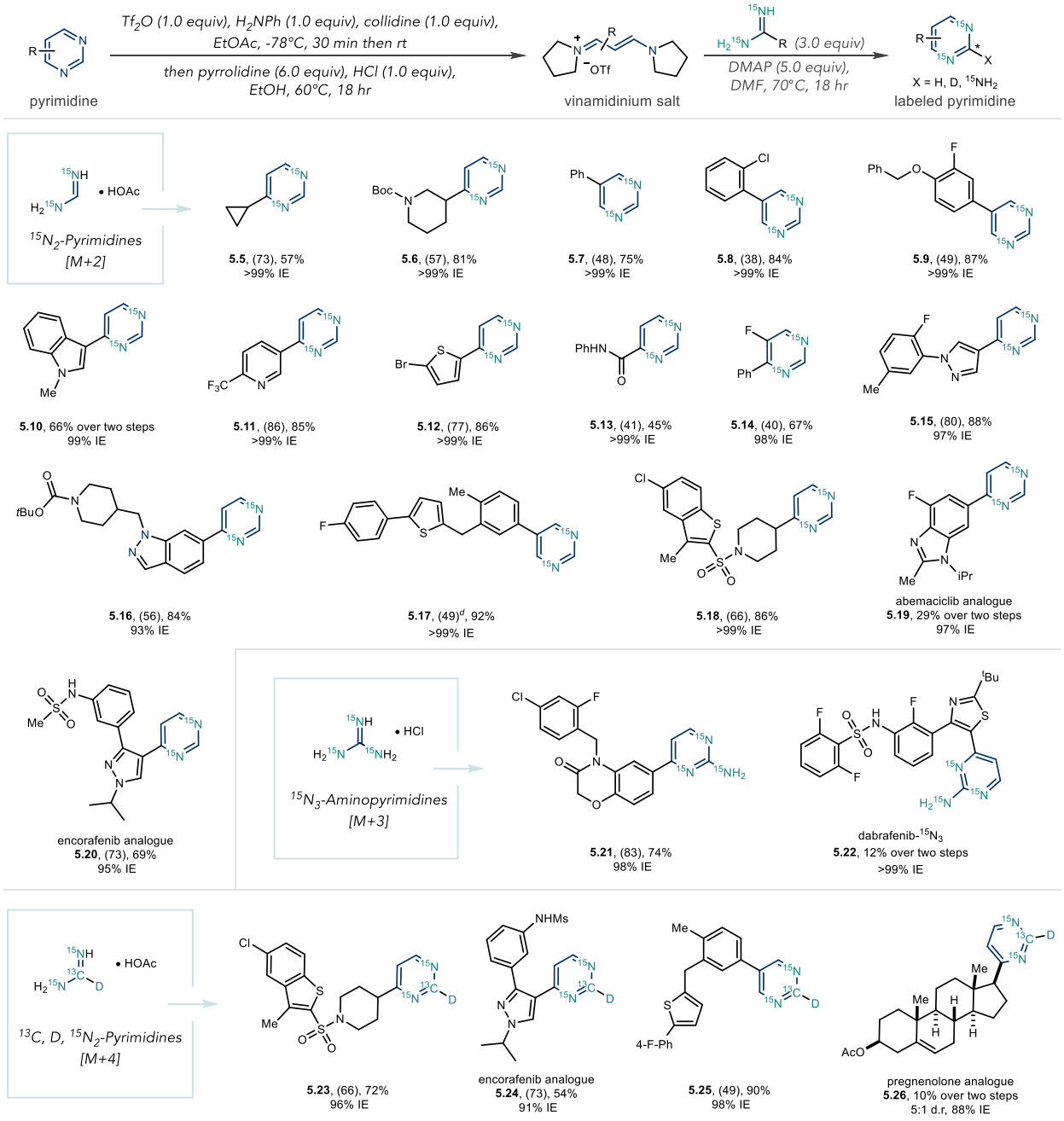


Figure 5.5 Scope of pyrimidine isotope labeling strategy. Yields in parenthesis are of isolated vinamidinium salts.

piperidine-containing **5.18** were formed with excellent isotopic enrichment. We extended the isotope exchange procedure to drug analogues, including a derivative of the metastatic breast cancer treatment abemaciclib (**5.19**). Similarly, we generated a $^{15}N_2$-enriched version of an

analogue of the melanoma and colorectal cancer drug, encorafenib (**5.20**). In our previous report, we demonstrated that deconstructed pyrimidines react with guanidine to form 2-aminopyrimidines. We employed guanidine-$^{15}N_3$ for the pyrimidine isotope labeling strategy, and generated **5.21**, an aminopyrimidine with three ^{15}N-atoms. The same procedure was applied to a precursor of dabrafenib, a B-Raf inhibitor for the treatment of melanoma and other cancers, to generate dabrafenib-$^{15}N_3$ (**5.22**) with >99% ^{15}N-incorporation. We selected four complex pyrimidine examples to demonstrate the formation of M+4 pyrimidine isotopologs using this procedure (**5.23-5.26**). In general, excellent isotopic enrichment was observed. We observed lower IE with **5.26**, a pyrimidine derived from pregnenolone, likely due to sluggish conversion of iminoenamine to vinamidinium salt due to steric bulk at the pyrimidine 4-position. Imperfect isolation of the vinamidinium salt resulted in undesired M+3 pyrimidine product.

5.6 Deuteration of Vinamidinium Salts and Access to Diverse Isotopologs

We demonstrated in a prior report that the 5-position of pyrimidines can be functionalized by reacting iminoenamine intermediates with *N*-chlorosuccinimide prior to recyclization.[14] Based on these observations, we hypothesized that vinamidinium intermediates could be selectively deuterated with deuterium acids, then reconstructed with formamidines to generate 5-deuteropyrimidines. We found that generating catalytic amounts of deuterium chloride (DCl) in deuterated ethanol (EtOD-*d1*) selectively deuterated the central position of the vinamidinium salt (Fig. 5.6). Condensation of the deuterated vinamidinium salt with formamidine generated **5.27** with 95% deuterium incorporation at the 5-position. Combining this deuteration procedure with the already established ^{15}N and ^{13}C incorporation procedure could be a useful maneuver to generate a variety of higher mass pyrimidine isotopologs. To demonstrate this application, we selected 4-aryl pyrimidine **5.28** and generated the vinamidinium salt (**5.29**). We first applied the

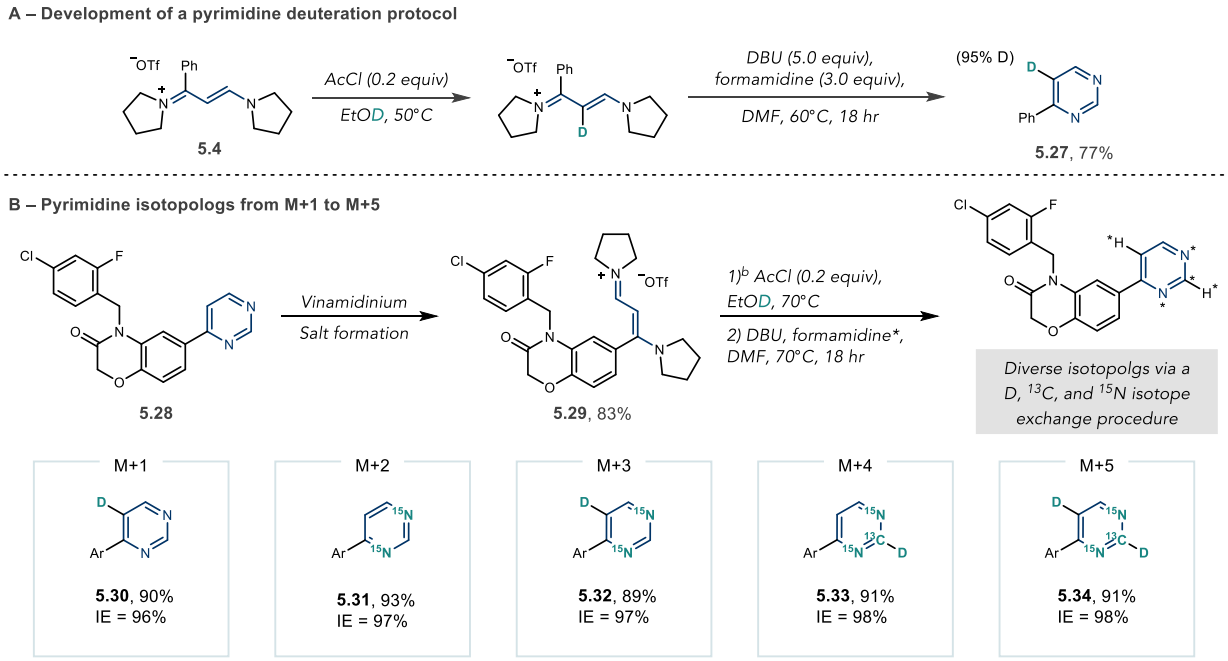


Figure 5.6 Deuteration of vinamidinium salts and access to diverse pyrimidine isotopologs. The deuteration procedure resulted in some off-target deuteration of the α-amido protons, which were corrected in the IE calculations.

deuteration procedure and then cyclized with formamidine under basic conditions to form 5-deuteropyrimidine **5.30** (M+1) with high deuterium incorporation. By cyclizing the vinamidinium salt with formamidine-$^{15}N_2$, we instead generate pyrimidine **5.31** (M+2) with 98% ^{15}N-incorporation. If we instead deuterate the vinamidinium salt prior to cyclization with isotopically enriched formamidine, we generate **5.32** (M+3), and when we cyclize the vinamidinium salt with formamidine-^{13}C-*d*-$^{15}N_2$, we form **5.33** (M+4). Finally, we form **5.34** (M+5) by first deuterating the vinamidinium salt, then cyclizing with M+4 formamidine. All of the isotopologs were formed with >95% IE.

5.7 Conclusions

In summary, we have developed a method to deconstruct pyrimidines into vinamidinium salts and recyclize with isotopically enriched amidines to form isotopically-labeled pyrimidines. The procedure functions on pyrimidines with a variety of substitution patterns and functional

groups and is viable on complex drug-like pyrimidine-containing molecules. When the protocol is extended to C5-deuterium labeling, the method can generate diverse pyrimidine isotopologs ranging from M+1 to M+5. The pyrimidines are labeled with excellent isotopic enrichment, making these higher mass isotopologs viable for ADMET studies coupled with LC-MS, ^{13}C, and ^{15}N NMR. We expect that commercially available formamidine-^{14}C acetate could be used to generate radiotracable pyrimidine-containing drugs via this method.

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APPENDIX ONE

HALOGENATION OF PYRIDINES VIA ZINCKE IMINES: EXPERIMENTAL

A 1.1 General Information

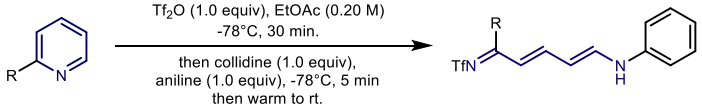
Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Bruker AV-111 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm), $(CD_3)_2CO$ (2.05 ppm), CD_3CN (1.94 ppm), D_2O (4.79 ppm), or $(CD_3)_2SO$ (2.50 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Bruker AV-111 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.01 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16 ppm), CD_3OD (49.00 ppm), $(CD_3)_2CO$ (29.84 ppm), CD_3CN (1.32 ppm), D_2O, or $(CD_3)_2SO$ (39.52 ppm).

Formimidamide-^{13}C-1-d-$^{15}N_2$ acetate (98% ^{15}N, 99% ^{13}C, 98% D) was purchased from Sigma-Aldrich (Isotec) and used without further purification. Tetrahydrofuran (THF), toluene, hexane, diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were dried and distilled using standard

methods, chloroform ($CHCl_3$), ethanol (EtOH), dimethylformamide (DMF), ethyl acetate (EtOAc), and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality and used without further purification. All reactions were monitored by TLC, ^1H NMR spectra taken from reaction samples. High-resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF LC/MS ("Q-TOF") interfaced to an Agilent 1200 HPLC with multi-mode (combined ESI and APCI) and Direct Analysis in Real Time (DART) sources. Infrared (IR) spectra were recorded on a Nicolet IS-50 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in $CHCl_3$, with absorptions reported in wavenumbers (cm^{-1}). Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass-backed silica gel plates (Silicagel 60 F254). Manual flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 mm (230-400 mesh) under a positive pressure of air unless otherwise stated. Automated flash column chromatography was undertaken using a Teledyne Isco CombiFlash NextGen 300+ using 12 g RediSep Gold Normal-Phase Silica cartridges. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with a chamber of I_2 in SiO_2, ceric ammonium molybdate, or basic potassium permanganate solutions as appropriate. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

A 1.2 Preparation of *N*-Tf Zincke Imines

General Procedure A (Aniline-Derived *N*Tf-Zincke Imine Formation)

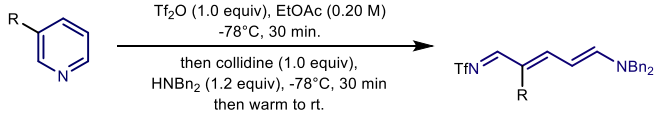


An oven dried round bottom flask equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.20 M) was added, the reaction vessel cooled to –78 ºC, and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction stirred for 30 minutes before the addition of collidine (1.0 equiv) followed by aniline (1.0 equiv). The reaction stirred for an additional 5 minutes at –78 ºC before the cooling bath was removed, and the reaction warmed to room temperature while stirring. The reaction was diluted with EtOAc, washed with H_2O (3x) and brine (1x). The organic extract was dried over $MgSO_4$ and filtered over a frit. After filtration, the organic extract was concentrated *in vacuo* at room temperature or with a stream of air, then redissolved in a minimal amount of acetone before precipitating dropwise from an excess of hexanes (approx. 100 mL per 1.00 mmol). After the solid settled, the hexanes were decanted over a frit, and the residual solid was washed with hexanes then collected. Any residue left was dissolved in acetone and concentrated *in vacuo* at room temperature to provide the aniline-derived *N*Tf-Zincke imine product.

Reaction Notes:

- Aniline imines are sensitive to heat and prone to form pyridinium byproducts if concentrated *in vacuo* so it is recommended to concentrate by blowing a stream of air without heat
- Adding aniline before collidine gives comparable yields in most cases
- Tf_2O addition works comparably in most cases in 0.10 M vs 0.20 M EtOAc

General Procedure B (Dibenzylamine-Derived *N*Tf-Zincke Imine Formation)

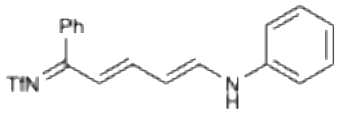


An oven dried round bottom flask equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.20 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction stirred for 30 minutes before the addition of collidine (1.0 equiv) w followed by the slow addition of dibenzylamine (1.2 equiv, as a 1.0 M solution in EtOAc). The reaction stirred for an additional 30 minutes at –78 ºC before the cooling bath was removed and the reaction warmed to room temperature while stirring. The reaction was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ (2x), brine (1x), aqueous Cu_2SO_4 (10% by weight, 2x), and brine (1x). The organic extract was dried over $MgSO_4$ and filtered over a frit. After filtration, the organic extract was concentrated *in vacuo* and redissolved in a minimal amount of CH_2Cl_2 before precipitating dropwise from an excess of hexanes (approx. 100 mL per 1.00 mmol). The resulting oil or solid was allowed to settle overnight in a –20 ºC fridge. After the oil or precipitate settled, the hexanes were decanted over a frit, and the residual material was washed with hexanes, then dissolved in CH_2Cl_2 and concentrated *in vacuo* to provide the dibenzylamine-derived *N*Tf-Zincke imine product.

Reaction Notes:

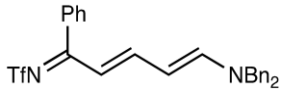
- The majority of substrates achieve higher yields when collidine is added before Bn_2NH
- Stirring is critical to achieve consistent yields during the reaction; recommended stirring 500-750 rpm
- Tf_2O addition works comparably in most cases in 0.10 M vs 0.20 M EtOAc

1,1,1-Trifluoro-*N*-((2*E*,4*E*)-1-phenyl-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide



Prepared according to general procedure A using 2-phenylpyridine (7.18 mL, 50.0 mmol), EtOAc (250 mL, 0.20 M), Tf_2O (8.40 mL, 50.0 mmol), collidine (6.60 mL, 50.0 mmol), and aniline (4.55 mL, 50.0 mmol). Isolated by precipitating in 2.00 L hexanes afforded the title compound (16.7 g, 44.0 mmol, 88% yield) as a red solid. mp: 155-158 ºC; IR ν_{max}/cm^{-1} (film): 3301, 3060, 1698, 1640, 1569, 1458, 1319, 1169; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 10.10 (s, 1H), 8.25 (d, *J* = 12.0 Hz, 1H), 7.69 – 7.45 (m, 6H), 7.43 – 7.32 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 13.8 Hz, 1H), 6.25 (d, *J* = 12.1 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 178.03, 160.37, 151.33, 139.63, 137.98, 131.18, 129.78, 129.57, 128.35, 124.44, 119.68 (q, *J* = 319.5 Hz), 116.59, 114.78, 107.35; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ: -80.56 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 381.1, $C_{18}H_{16}F_3N_2O_2S^+$ requires 381.1.

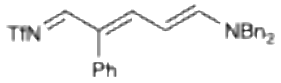
_N_-((1_Z_,2_E_,4_E_)-5-(Dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure B using 2-phenylpyridine (1.78 mL, 12.5 mmol), Tf_2O (2.10 mL, 12.5 mmol), dibenzylamine (2.90 mL, 15.0 mmol, 1.0 M in EtOAc), collidine (1.70 mL, 12.5 mmol), EtOAc (125 mL, 0.10 M). The crude material was purified by precipitation in hexanes (1.2 L) to afford the title compound as a red-brown solid (5.20 g, 10.8 mmol, 86% yield); ^1H NMR (400 MHz, $CDCl_3$) δ:7.64 – 7.56 (m, 2H), 7.55 – 7.31 (m, 10H), 7.31 – 7.27 (m, 1H), 7.21 – 7.09 (m, 4H), 6.71 (d, *J* = 13.7 Hz, 1H), 5.83 (t, *J* = 12.2 Hz, 1H), 4.46 – 4.39 (m, 4H) ; *m/z* LRMS (ESI

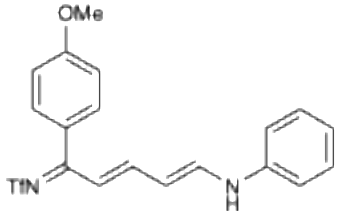
+ APCI) found $[M + H]^+$ 485.2, $C_{26}H_{24}F_2N_2O_2S^+$ requires 485.15.236. The data are consistent with those previously reported in the literature.

_N_-((1_E_,2_E_,4_E_)-5-(dibenzylamino)-2-phenylpenta-2,4-dien-1-ylidene)-1,1,1-Trifluoromethanesulfonamide



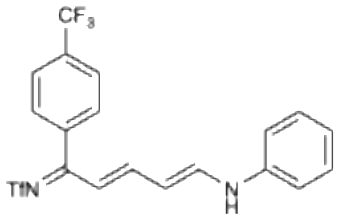
Prepared according to general procedure B using 3-phenylpyridine (2.87 mL, 20.0 mmol), Tf_2O (3.36 mL, 20.0 mmol), dibenzylamine (3.84 mL, 20.0 mmol, 1.0 M in EtOAc), collidine (2.64 mL, 20.0 mmol), EtOAc (200 mL, 0.10 M). Isolated by precipitating in 2.0 L hexanes to afford the title compound as a yellow solid (7.54 g, 15.6 mmol, 78% yield). ^{1}H NMR (400 MHz, CD_3CN) δ 8.22 (s, 1H), 7.95 (d, J = 11.9 Hz, 1H), 7.71 (d, J = 13.0 Hz, 1H), 7.49 – 7.39 (m, 3H), 7.39 – 7.27 (m, 8H), 7.13 – 7.03 (m, 4H), 5.76 (t, J = 12.5 Hz, 1H), 4.75 (s, 2H), 4.46 (s, 2H); ^{19}F NMR (375 MHz, CD_3CN) δ -79.26 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 485.2, $C_{26}H_{24}F_3N_2O_2S^+$ requires 485.1. The analytical data are consistent with those previously reported.

1,1,1-Trifluoro-_N_-((2_E_,4_E_)-1-(4-methoxyphenyl)-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide



Prepared according to general procedure A using 2-(p-OMe-phenyl)pyridine (926 mg, 5.00 mmol), EtOAc (25.0 mL, 0.20 M), Tf_2O (840 µL, 5.00 mmol), collidine (660 µL, 5.00 mmol), and aniline (455 µL, 5.00 mmol). Isolated by precipitating in 500 mL hexanes afforded the title compound (1.80 g, 4.40 mmol, 88% yield) as a red solid. mp: 154-156 ºC; IR ν_{max}/cm^{-1} (film): 3303, 1699, 1640, 1567, 1507, 1455, 1318, 1165; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.97 (s, 1H), 8.23 (d, *J* = 12.0 Hz, 1H), 7.71 – 7.57 (m, 3H), 7.43 – 7.34 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.69 (d, *J* = 13.9 Hz, 1H), 6.25 (t, *J* = 12.2 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 177.39, 162.94, 159.36, 150.23, 139.88, 131.93, 130.11, 129.76, 124.09, 119.75 (q, *J* = 319.7 Hz), 116.40, 114.86, 113.78, 106.99, 55.09; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.53 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 411.2, $C_{19}H_{18}F_3N_2O_3S^+$ requires 411.1.

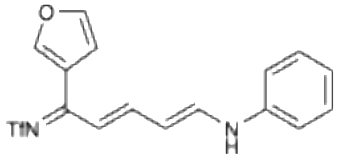
1,1,1-Trifluoro-*N*-((2*E*,4*E*)-5-(phenylamino)-1-(4-(trifluoromethyl)phenyl)penta-2,4-dien-1-ylidene)methanesulfonamide



Prepared according to general procedure A using 2-(p-CF_3-phenyl)pyridine (558 mg, 2.50 mmol), EtOAc (12.5 mL, 0.20 M), Tf_2O (420 µL, 2.50 mmol), collidine (330 µL, 2.50 mmol), and aniline (228 µL, 2.50 mmol). Isolated by precipitating in 250 mL hexanes afforded the title compound (922 mg, 2.10 mmol, 82% yield) as an orange solid. mp: 169-171 ºC; IR ν_{max}/cm^{-1} (film): 3199, 3064, 1699, 1388, 1325, 1195, 1171, 1128; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 10.39 (s, 1H), 8.36 (d, *J* = 11.3 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.71 – 7.60 (m, 1H), 7.49

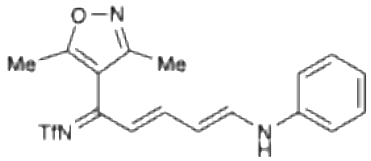
– 7.38 (m, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 6.72 (d, J = 13.8 Hz, 1H), 6.35 (t, J = 12.1 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 175.65, 160.94, 152.92, 141.98, 139.31, 131.61 (q, J = 32.4 Hz), 130.04, 129.83, 125.26 (q, J = 3.8 Hz), 125.00, 124.17 (q, J = 271.8 Hz), 119.67 (q, J = 319.5 Hz), 116.84, 114.30, 108.19; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -63.25 (s, 3F), -80.46 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 449.1, $C_{19}H_{15}F_6N_2O_2S^+$ requires 449.1.

1,1,1-Trifluoro-*N*-((2*E*,4*E*)-1-(furan-3-yl)-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide



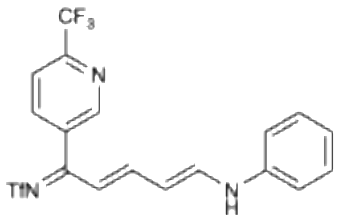
Prepared according to general procedure A using 2-(furan-3-yl)pyridine (479.0 mg, 3.30 mmol), EtOAc (16.5 mL, 0.20 M), Tf_2O (554 µL, 3.30 mmol), collidine (436 µL, 3.30 mmol), and aniline (300 µL, 3.30 mmol). Isolated by precipitating in 300 mL hexanes afforded the title compound (812 mg, 2.20 mmol, 66% yield) as a maroon solid. mp: 150-153 ºC; IR ν_{max}/cm^{-1} (film): 3299, 3059, 1698, 1556, 1512, 1454, 1320, 1179; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 10.07 (s, 1H), 8.34 (d, J = 12.1 Hz, 1H), 8.20 (s, 1H), 8.12 – 7.95 (m, 1H), 7.74 (s, 1H), 7.51 – 7.38 (m, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 6.81 (d, J = 2.1 Hz, 1H), 6.66 (d, J = 13.9 Hz, 1H), 6.25 (t, J = 12.3 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 169.03, 158.08, 151.12, 147.05, 144.18, 139.77, 129.79, 125.21, 124.35, 119.71 (q, J = 319.2 Hz), 116.56, 114.73, 110.82, 107.20; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.62 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 371.1, $C_{16}H_{14}F_3N_2O_3S^+$ requires 371.1.

_N_-((2_E_,4_E_)-1-(3,5-dimethylisoxazol-4-yl)-5-(phenylamino)penta-2,4-dien-1-ylidene)-1,1,1-Trifluoromethanesulfonamide



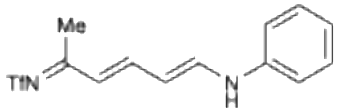
Prepared according to general procedure A using 3,5-dimethyl-4-(pyridin-2-yl)isoxazole (348 mg, 2.00 mmol), EtOAc (10.0 mL, 0.20 M), Tf_2O (336 µL, 2.00 mmol), collidine (264 µL, 2.00 mmol), and aniline (182 µL, 2.00 mmol). Isolated by precipitating in 200 mL hexanes afforded the title compound (453 mg, 1.14 mmol, 57% yield) as an orange solid. mp: 178-181 ºC; IR ν_{max}/cm^{-1} (film): 3300, 3062, 1568, 1513, 1458, 1417, 1317, 1170; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 10.39 (s, 1H), 8.45 (d, *J* = 11.4 Hz, 1H), 7.57 (t, *J* = 13.0 Hz, 1H), 7.50 – 7.37 (m, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.61 (s, 1H), 6.34 (t, *J* = 12.2 Hz, 1H), 2.42 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 169.32, 165.04, 161.70, 159.05, 157.38, 139.21, 130.27, 126.21, 120.00 (q, *J* = 322.0 Hz), 117.96, 114.73, 114.35, 110.18, 12.51, 10.67; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.48 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 400.2 , $C_{17}H_{17}F_3N_3O_3S^+$ requires 400.1.

1,1,1-Trifluoro-_N_-((2_E_,4_E_)-5-(phenylamino)-1-(6-(trifluoromethyl)pyridin-3-yl)penta-2,4-dien-1-ylidene)methanesulfonamide



Prepared according to general procedure A using 6'-(trifluoromethyl)-2,3'-bipyridine (1.12 g, 5.00 mmol), EtOAc (25.0 mL, 0.20 M), Tf_2O (840 µL, 5.00 mmol), collidine (660 µL, 5.00 mmol), and aniline (455 µL, 5.00 mmol). Isolated by precipitating in 500 mL hexanes afforded the title compound (1.84 g, 4.10 mmol, 82% yield) as a red solid. mp: 140-143 ºC; IR ν_{max}/cm^{-1} (film): 3214, 3067, 1700, 1385, 1338, 1236, 1189, 1142; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 10.63 (s, 1H), 8.89 (s, 1H), 8.48 (d, *J* = 11.5 Hz, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.73 (t, *J* = 13.1 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 13.6 Hz, 1H), 6.42 (t, *J* = 12.1 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 168.75, 159.99 (d, *J* = 276.5 Hz), 149.80, 147.60 (q, *J* = 34.2 Hz), 138.88, 138.07, 130.26, 126.86, 126.05, 123.33, 120.96, 120.60, 120.27 (q, *J* = 322.6 Hz), 118.44, 114.32, 112.16; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -68.41 (s, 3F), -80.25 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 450.1, $C_{18}H_{14}F_6N_3O_2S^+$ requires 450.1.

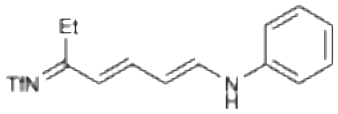
1,1,1-Trifluoro-*N*-((3*E*,5*E*)-6-(phenylamino)hexa-3,5-dien-2-ylidene)methanesulfonamide



Prepared according to general procedure A using 2-methylpyridine (247 µL, 2.50 mmol), EtOAc (12.5 mL, 0.20 M), Tf_2O (420 µL, 2.50 mmol), collidine (330 µL, 2.50 mmol), and aniline (228 µL, 2.50 mmol). Isolated by precipitating in 250 mL hexanes afforded the title compound (374 mg, 1.18 mmol, 47% yield) as a purple solid. mp: 128-130 ºC; IR ν_{max}/cm^{-1} (film): 3338, 3071, 1595, 1491, 1382, 1280, 1233, 1193; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.70 (s, 1H), 8.07 (d, *J* = 12.4 Hz, 1H), 7.85 (t, *J* = 12.8 Hz, 1H), 7.34 – 7.20 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.08 (d, *J* = 14.1 Hz, 1H), 5.98 (t, *J* = 11.6 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 180.56, 155.97, 149.58, 140.02, 129.77, 123.88, 119.45 (q, *J* = 319.1 Hz),

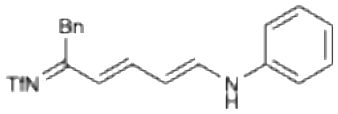
117.00, 116.24, 106.02, 22.03; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.75 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 319.1, $C_{13}H_{14}F_3N_2O_2S^+$ requires 319.1.

1,1,1-Trifluoro-*N*-((4*E*,6*E*)-7-(phenylamino)hepta-4,6-dien-3-ylidene)methanesulfonamide



Prepared according to general procedure A using 2-ethylpyridine (572 μL, 5.00 mmol), EtOAc (25.0 mL, 0.20 M), Tf_2O (840 μL, 5.00 mmol), collidine (660 μL, 5.00 mmol), and aniline (455 μL, 5.00 mmol). Isolated by precipitating in 500 mL hexanes afforded the title compound (1.28 g, 3.90 mmol, 77% yield) as a red-orange solid. mp: 131-133 ºC; IR ν_{max}/cm^{-1} (film): 3200, 3067, 2983, 1700, 1499, 1381, 1234, 1190; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.82 (s, 1H), 8.21 (d, *J* = 12.1 Hz, 1H), 8.00 (dd, *J* = 14.1, 12.0 Hz, 1H), 7.44 – 7.35 (m, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.31 (d, *J* = 14.1 Hz, 1H), 6.14 (t, *J* = 12.1 Hz, 1H), 2.79 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 183.22, 158.05, 153.67, 139.83, 130.21, 124.95, 119.74 (q, *J* = 320.8 Hz), 117.13, 113.66, 107.68, 29.19, 13.58; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ 80.76 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 333.1, $C_{14}H_{16}F_3N_2O_2S^+$ requires 333.1.

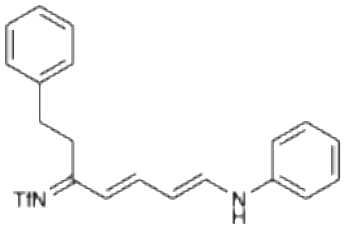
1,1,1-Trifluoro-*N*-((3*E*,5*E*)-1-phenyl-6-(phenylamino)hexa-3,5-dien-2-ylidene)methanesulfonamide (1j)



Prepared according to general procedure A using 2-benzylpyridine (1.61 mL, 10.0 mmol), EtOAc (50.0 mL, 0.20 M), Tf_2O (1.68 mL, 10.0 mmol), collidine (1.32 mL, 10.0 mmol), and aniline (910

μL, 10.0 mmol). Isolated by precipitating in 1.0 L hexanes afforded the title compound (2.44 g, 6.20 mmol, 62% yield) as a red solid. mp: 109-111 ºC; IR ν_{max}/cm^{-1} (film): 3221, 3062, 1699, 1570, 1497, 1455, 1389, 1190; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 10.08 (s, 1H), 8.29 (t, *J* = 9.8 Hz, 1H), 8.16 (dd, *J* = 13.9, 12.1 Hz, 1H), 7.45 – 7.20 (m, 9H), 7.15 (t, *J* = 7.3 Hz, 1H), 6.34 (d, *J* = 13.9 Hz, 1H), 6.16 (t, *J* = 12.1 Hz, 1H), 4.08 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 180.32, 157.09, 150.88, 139.60, 137.19, 129.80, 128.89, 128.52, 126.75, 124.37, 119.58 (q, *J* = 319.5 Hz), 116.51, 114.98, 106.76, 41.42j; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.62 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 395.1, $C_{19}H_{18}F_3N_2O_2S^+$ requires 395.1.

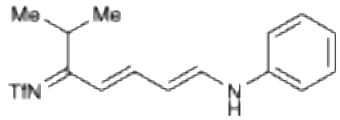
1,1,1-Trifluoro-*N*-((4*E*,6*E*)-1-phenyl-7-(phenylamino)hepta-4,6-dien-3-ylidene)methanesulfonamide



Prepared according to general procedure A using 2-phenethylpyridine (916.8 mg, 5.00 mmol), EtOAc (25.0 mL, 0.20 M), Tf_2O (840 μL, 5.00 mmol), collidine (660 μL, 5.00 mmol), and aniline (455 μL, 5.00 mmol). Isolated by precipitating in 500 mL hexanes afforded the title compound (1.115 g, 2.8 mmol, 55% yield) as an orange solid. mp: 100-103 ºC; IR ν_{max}/cm^{-1} (film): 3339, 3062, 2931, 1697, 1601, 1495, 1383, 1193; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.80 (s, 1H), 8.20 (d, *J* = 12.0 Hz, 1H), 7.96 (dd, *J* = 14.0, 12.1 Hz, 1H), 7.40 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.34 – 7.24 (m, 6H), 7.22 (h, *J* = 4.0 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.33 (d, *J* = 14.0 Hz, 1H), 6.13 (t, *J* = 12.1 Hz, 1H), 3.12 – 3.02 (m, 2H), 3.03 – 2.94 (m, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 182.08, 156.13, 150.24, 140.86, 139.85, 129.79, 128.48, 128.42, 126.18, 124.13, 119.57 (q, *J* = 319.3 Hz),

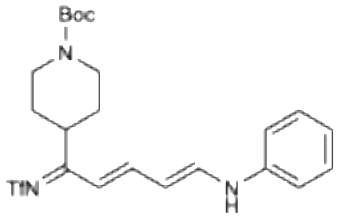
116.40, 115.41, 106.44, 37.59, 34.14; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.59 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 409.2, $C_{20}H_{20}F_3N_2O_2S^+$ requires 409.1.

1,1,1-Trifluoro-*N*-((4*E*,6*E*)-2-methyl-7-(phenylamino)hepta-4,6-dien-3-ylidene)methanesulfonamide



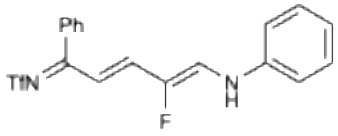
Prepared according to general procedure A using 2-isopropylpyridine (417.9 μL, 5.00 mmol), EtOAc (25.0 mL, 0.20 M), Tf_2O (840 μL, 5.00 mmol), collidine (660 μL, 5.00 mmol), and aniline (455 μL, 5.00 mmol). Isolated by precipitating in 500 mL hexanes afforded the title compound (634 mg, 1.90 mmol, 37% yield) as an orange solid. mp: 119-123 ºC; IR ν_{max}/cm^{-1} (film): 3307, 2971, 1568, 1454, 1248, 1151, 1085, 854; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.87 (s, 1H), 8.23 (d, *J* = 12.3 Hz, 1H), 8.05 (t, *J* = 13.1 Hz, 1H), 7.40 (td, *J* = 7.3, 2.1 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.42 (d, *J* = 14.1 Hz, 1H), 6.16 (t, *J* = 12.1 Hz, 1H), 3.46 (h, *J* = 6.6 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 187.79, 155.25, 149.89, 139.92, 129.77, 123.98, 119.48 (q, *J* = 319.0 Hz), 116.29, 113.50, 106.27, 32.61, 20.87; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.78 (d, *J* = 3.1 Hz, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 347.1, $C_{15}H_{18}F_3N_2O_2S^+$ requires 347.1.

***tert*-Butyl 4-((2*E*,4*E*)-5-(phenylamino)-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-1-yl)piperidine-1-carboxylate**



Prepared according to general procedure A using *tert*-butyl 4-(pyridin-2-yl)piperidine-1-carboxylate (1.30 g, 5.00 mmol), EtOAc (25.0 mL, 0.20 M), Tf_2O (840 µL, 5.00 mmol), collidine (660 µL, 5.00 mmol), and aniline (455 µL, 5.00 mmol). Isolated by precipitating in 500 mL hexanes afforded the title compound (1.08 g, 2.30 mmol, 45% yield) as a red-orange solid. mp: 168-170 ºC; IR ν_{max}/cm^{-1} (film): 3303, 2977, 1640, 1569, 1457, 1428, 1150, 1102; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.97 (s, 1H), 8.20 (d, *J* = 12.1 Hz, 1H), 8.13 (dd, *J* = 14.2, 11.9 Hz, 1H), 7.41 (dd, *J* = 9.7, 6.3 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.43 (d, *J* = 14.1 Hz, 1H), 6.18 (t, *J* = 12.0 Hz, 1H), 4.18 (d, *J* = 13.5 Hz, 2H), 3.37 (tt, *J* = 11.4, 3.8 Hz, 1H), 2.83 (s, 2H), 1.74 (d, *J* = 11.3 Hz, 2H), 1.63 (qd, *J* = 12.4, 4.3 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 184.79, 155.45, 154.13, 150.25, 139.86, 129.81, 124.15, 119.43 (q, *J* = 319.0 Hz), 116.39, 113.58, 106.48, 78.64, 43.32, 40.93, 30.59, 27.66; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.75 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 488.3 , $C_{22}H_{29}F_3N_3O_4S^+$ requires 488.2.

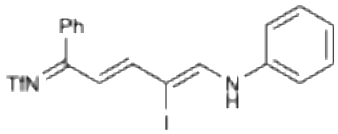
1,1,1-Trifluoro-*N*-((2*E*,4*Z*)-4-fluoro-1-phenyl-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide



Prepared according to general procedure A using 5-fluoro-2-phenylpyridine (348 mg, 2.00 mmol), EtOAc (10.0 mL, 0.20 M), Tf_2O (336 µL, 2.00 mmol), collidine (264 µL, 2.00 mmol), and aniline (182 µL, 2.00 mmol). Isolated by precipitating in 200 mL hexanes afforded the title compound

(267 mg, 0.68 mmol, 34% yield) as a purple solid. mp: 140-143 ºC; IR ν_{max}/cm^{-1} (film): 3195, 3064, 1699, 1587, 1451, 1295, 1166, 1126; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 9.80 (s, 1H), 7.96 (d, *J* = 24.4 Hz, 1H), 7.70 – 7.61 (m, 3H), 7.60 – 7.52 (m, 2H), 7.44 – 7.33 (m, 4H), 7.23 (q, *J* = 14.5 Hz, 1H), 7.15 (tt, *J* = 6.8, 2.0 Hz, 1H), 6.84 (d, *J* = 14.3 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 176.50, 143.91, 142.98 (q, *J* = 237.2 Hz), 139.57, 137.80 (d, *J* = 8.0 Hz), 137.65, 131.93, 130.11, 129.81, 129.09, 125.60, 119.75 (d, *J* = 321.2 Hz), 117.84, 107.93 (d, *J* = 3.6 Hz); ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.55 (d, *J* = 5.4 Hz, 3F), -146.47 (s, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 399.1, $C_{18}H_{15}F_4N_2O_2S^+$ requires 399.1.

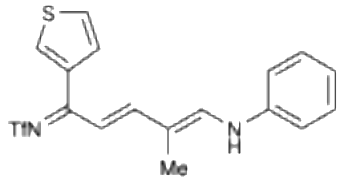
1,1,1-Trifluoro-*N*-((2*E*,4*Z*)-4-iodo-1-phenyl-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide



Prepared according to general procedure A using 5-iodo-2-phenylpyridine (379 mg, 0.75 mmol), EtOAc (3.75 mL, 0.20 M), Tf_2O (126 µL, 0.75 mmol), collidine (99.0 µL, 0.75 mmol), aniline (69.0 µL, 0.75 mmol). Isolation by precipitating in hexanes afforded the title compound (157 mg, 0.31 mmol, 41% yield) as a dark red solid and was used in the fluorination procedure without additional purification. mp: 145-148 ºC; IR ν_{max}/cm^{-1} (film): 3288, 1560, 1488, 1459, 1306, 1181; ^{1}H NMR (400 MHz, CD_3CN) δ 8.30 (s, 1H), 7.85 (s, 1H), 7.67 – 7.57 (m, 3H), 7.53 (dd, *J* = 8.3, 7.0 Hz, 2H), 7.44 – 7.33 (m, 3H), 7.30 – 7.23 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 13.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 181.30, 160.21, 152.78, 139.86, 138.51, 132.85, 130.66, 130.61, 129.53, 126.28, 120.37 (q, *J* = 317.0), 120.34, 119.11, 118.79; ^{19}F NMR (375 MHz,

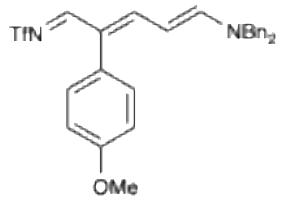
CD_3CN) δ -80.52 (s, 3F); LRMS (ESI+APCI) found $[M + H]^+$ 507.1, $C_{18}H_{15}F_3IN_2O_2S^+$ requires 507.0.

1,1,1-Trifluoro-*N*-((2*E*,4*E*)-4-methyl-5-(phenylamino)-1-(thiophen-3-yl)penta-2,4-dien-1-ylidene)methanesulfonamide



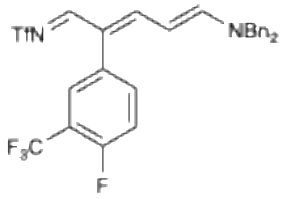
Prepared according to general procedure A using 5-methyl-2-(thiophen-3-yl)pyridine (351 mg, 2.00 mmol), EtOAc (10.0 mL, 0.20 M), Tf_2O (336 µL, 2.00 mmol), collidine (264 µL, 2.00 mmol), and aniline (182 µL, 2.00 mmol). Isolated by precipitating in 200 mL hexanes afforded the title compound (558 mg, 1.40 mmol, 70% yield) as a purple solid. mp: 148-152 ºC; IR ν_{max}/cm^{-1} (film): 3319, 1699, 1558, 1503, 1455, 1314, 1252, 1182; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.33 (s, 1H), 8.10 (s, 1H), 8.08 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.90 (d, *J* = 14.0 Hz, 1H), 7.62 (dd, *J* = 5.1, 2.9 Hz, 1H), 7.46 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.39 (d, *J* = 4.1 Hz, 4H), 7.14 (hept, *J* = 4.4 Hz, 1H), 6.77 (d, *J* = 14.0 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ170.96, 160.11, 149.54, 140.09, 139.89, 131.78, 129.67, 128.68, 126.48, 124.32, 119.82 (q, *J* = 319.6 Hz), 116.95, 113.18, 112.27, 9.38; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -80.43 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 401.1, $C_{17}H_{16}F_3N_2O_2S_2^+$ requires 401.1.

***N*-((1*E*,2*E*,4*E*)-5-(dibenzylamino)-2-(4-methoxyphenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



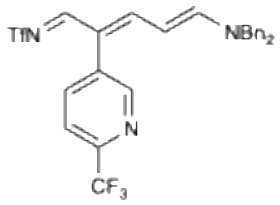
Prepared according to General Procedure B from 3-(4-methoxyphenyl)pyridine. ^{1}H NMR (400 MHz, CD_3CN) δ 8.29 (s, 1H), 7.50 (d, *J* = 12.1 Hz, 1H), 7.39 – 7.21 (m, 8H), 7.11 (qd, *J* = 6.6, 2.6 Hz, 2H), 7.01 – 6.94 (m, 2H), 6.71 (d, *J* = 7.2 Hz, 2H), 6.65 (dt, *J* = 7.6, 1.3 Hz, 1H), 5.78 (t, *J* = 12.4 Hz, 1H), 4.45 (s, 2H), 4.23 (s, 2H), 3.62 (s, 3H); ^{19}F NMR (375 MHz, CD_3CN) δ -77.78 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 515.2, $C_{27}H_{25}F_3N_2O_3S^+$ requires 515.2. The analytical data are consistent with those previously reported.

_N_-((1_E_,2_E_,4_E_)-5-(dibenzylamino)-2-(4-fluoro-3-(trifluoromethyl)phenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



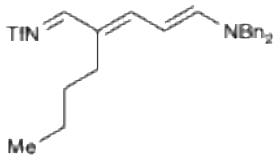
Prepared according to General Procedure B from 3-(4-fluoro-3-(trifluoromethyl)phenyl)pyridine. ^{1}H NMR (400 MHz, CD_3CN) δ 8.25 (s, 1H), 7.98 (d, *J* = 11.8 Hz, 1H), 7.75 (d, *J* = 13.3 Hz, 1H), 7.50 (d, *J* = 7.1 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 3H), 7.40 – 7.25 (m, 7H), 7.12 – 7.05 (m, 2H), 5.77 (s, 1H), 4.74 (s, 2H), 4.50 (s, 2H); ^{19}F NMR (375 MHz, CD_3CN) δ -61.85 (d, *J* = 13.0 Hz, 3F), -79.33 (s, 3F), -118.76 (dd, *J* = 15.7, 8.4 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 571.2 , $C_{27}H_{22}F_7N_2O_2S^+$ requires 571.1. The analytical data are consistent with those previously reported.

_N_-((1_E_,2_E_,4_E_)-5-(dibenzylamino)-2-(6-(trifluoromethyl)pyridin-3-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



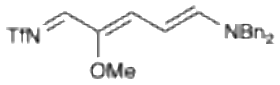
Prepared according to General Procedure B from 6-(trifluoromethyl)-3,3'-bipyridine. Used as a mixture of 14:1 title compound to *N*-benzyl-*N*-((2*E*,4*E*)-5-(dibenzylamino)-2-(6-(trifluoromethyl)pyridin-3-yl)penta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate (Zincke iminium). ^{1}H NMR (400 MHz, CD_3CN) δ 8.53 (s, 1H), 8.31 (s, 1H), 8.02 (d, *J* = 11.5 Hz, 1H), 7.86 – 7.64 (m, 3H), 7.49 – 7.40 (m, 3H), 7.34 (d, *J* = 6.5 Hz, 5H), 7.08 (dd, *J* = 6.2, 3.1 Hz, 2H), 5.79 (t, *J* = 12.5 Hz, 1H), 4.75 (s, 2H), 4.52 (s, 2H); ^{19}F NMR (375 MHz, CD_3CN) δ -68.31 (s, 3F), -79.23 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 554.2, $C_{26}H_{22}F_6N_3O_2S^+$ requires 554.1. The analytical data are consistent with those previously reported.

_N_-((1*E*,2*E*)-2-((*E*)-3-(dibenzylamino)allylidene)hexylidene)-1,1,1-trifluoromethanesulfonamide



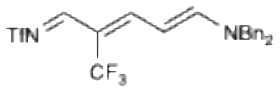
Prepared according to General Procedure B from 3-butylpyridine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.55 (d, *J* = 12.1 Hz, 1H), 7.50 – 7.31 (m, 6H), 7.29 – 7.16 (m, 5H), 5.81 (t, *J* = 12.3 Hz, 1H), 4.60 (s, 2H), 4.52 (s, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.39 – 1.16 (m, 4H), 0.84 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -77.92 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 465.3, $C_{24}H_{28}F_3N_2O_2S^+$ requires 465.2. The analytical data are consistent with those previously reported.

***N*-((1*E*,2*Z*,4*E*)-5-(dibenzylamino)-2-methoxypenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



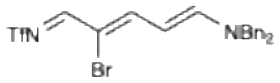
Prepared according to general procedure B using 3-methoxypyridine (1.51 mL, 15.0 mmol), EtOAc (150 mL, 0.10 M), Tf_2O (1.51 mL, 15.0 mmol), collidine (1.98 mL, 15.0 mmol), and dibenzylamine (2.88 mL, 15.0 mmol). Isolated by precipitating in 1.5 L hexanes afforded the title compound (3.83 g, 8.70 mmol, 58% yield) as a yellow solid. mp: 115-120 ºC; IR ν_{max}/cm^{-1} (film): 3031, 2937, 1491, 1442, 1328, 1156, 1099, 841; ^1H NMR (400 MHz, CD_3CN) δ 7.94 (d, J = 12.1 Hz, 1H), 7.72 (s, 1H), 7.49 – 7.30 (m, 8H), 7.34 – 7.22 (m, 3H), 6.16 (t, J = 12.4 Hz, 1H), 4.71 (s, 2H), 4.67 (s, 2H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 162.29, 160.99, 158.39, 144.11, 134.81 (d, J = 27.1 Hz), 129.63, 129.52, 129.29, 129.08, 128.70, 127.98, 120.89 (q, J = 323.3 Hz), 117.88, 102.02, 61.08, 59.13, 52.73; ^{19}F NMR (375 MHz, CD_3CN) δ -79.23 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 439.2, $C_{21}H_{22}F_3N_2O_3S^+$ requires 439.1.

***N*-((1*Z*,2*Z*,4*E*)-5-(dibenzylamino)-2-(trifluoromethyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



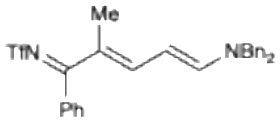
Prepared according to General Procedure B from 3-(trifluoromethyl)pyridine. ^1H NMR (400 MHz, CD_3CN) δ 8.35 (d, J = 11.2 Hz, 1H), 8.20 (s, 1H), 8.04 (d, J = 11.5 Hz, 1H), 7.48 – 7.37 (m, 9H), 7.30 – 7.23 (m, 2H), 4.85 (s, 2), 4.76 (s, 2H); ^{19}F NMR (375 MHz, CD_3CN) δ -60.97 (s, 3F), 79.40 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 477.2, $C_{21}H_{19}F_6N_2O_2S^+$ requires 477.1. The analytical data are consistent with those previously reported.

***N*-((1*E*,2*Z*,4*E*)-2-bromo-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



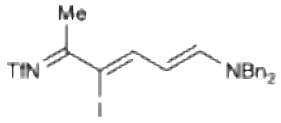
Prepared according to General Procedure A from 3-bromopyridine.[3] Used as a mixture of 4:1 title compound to *N*-benzyl-*N*-((2*Z*,4*E*)-2-bromo-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate (Zincke iminium). ^{1}H NMR (400 MHz, CD_3CN) δ 8.25 (s, 1H), 8.09 (d, *J* = 11.8 Hz, 1H), 7.85 (d, *J* = 12.4 Hz, 1H), 7.48 – 7.33 (m, 8H), 7.26 (d, *J* = 6.3 Hz, 2H), 6.27 (t, *J* = 12.1 Hz, 1H), 4.78 (s, 2H), 4.73 (s, 2H); ^{19}F NMR (375 MHz, CD_3CN) δ -79.26 (s, 3F). The analytical data are consistent with those previously reported.

***N*-((2*E*,4*E*)-5-(dibenzylamino)-2-methyl-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



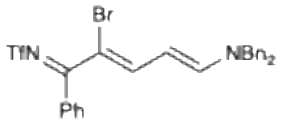
Prepared according to general procedure B using 3-methyl-2-phenylpyridine (2.20 g, 13.0 mmol), EtOAc (65.0 mL, 0.20 M), Tf_2O (2.18 mL, 13.0 mmol), collidine (1.72 mL, 13.0 mmol), and dibenzylamine (3.00 mL, 15.6 mmol, 1.0 M in EtOAc). Isolated by precipitating in 1.0 L hexanes afforded the title compound (5.80 g, 11.6 mmol, 90% yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3CN) δ 7.58 – 7.44 (m, 4H), 7.44 – 7.32 (m, 8H), 7.29 – 7.19 (m, 4H), 7.16 (d, *J* = 12.6 Hz, 1H), 5.90 (t, *J* = 12.3 Hz, 1H), 4.55 (d, *J* = 10.4 Hz, 4H), 1.93 (s, 3H);^{19}F NMR (375 MHz, CD_3CN) δ -80.90 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 499.3, $C_{27}H_{26}F_3N_2O_2S^+$ requires 499.2. The analytical data are consistent with those previously reported.

***N*-((2*E*,3*Z*,5*E*)-6-(dibenzylamino)-3-iodohexa-3,5-dien-2-ylidene)-1,1,1-trifluoromethanesulfonamide**



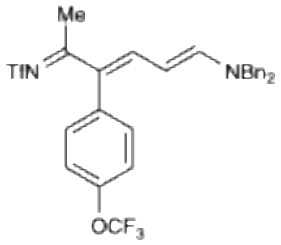
Prepared according to General Procedure B from 3-iodo-2-methylpyridine.[3] ^{1}H NMR (400 MHz, CD_3CN) δ 7.67 (d, *J* = 1.4 Hz, 1H), 7.64 (d, *J* = 2.3 Hz, 1H), 7.49 – 7.34 (m, 6H), 7.27 – 7.19 (m, 4H), 6.11 (t, *J* = 11.8 Hz, 1H), 4.54 (d, *J* = 13.1 Hz, 4H), 2.80 (s, 3H); ^{19}F NMR (375 MHz, CD_3CN) δ -79.23 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 549.1, $C_{21}H_{21}F_3IN_2O_2S^+$ requires 549.0. The analytical data are consistent with those previously reported.

***N*-((2*Z*,4*E*)-2-bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



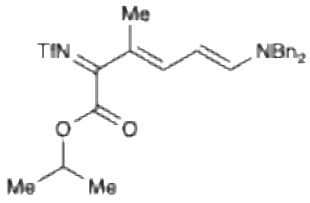
Prepared according to our group's previously reported procedure from 3-bromo-2-phenylpyridine.[2] ^{1}H NMR (400 MHz, CD_3CN) δ 7.78 (d, *J* = 11.9 Hz, 1H), 7.61 – 7.28 (m, 12H), 7.27 – 7.22 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.12 (t, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 4.4 Hz, 4H); ^{19}F NMR (375 MHz, CD_3CN) δ -80.69 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 563.1, $C_{26}H_{23}BrF_3N_2O_2S^+$ requires 563.1. The analytical data are consistent with those previously reported.

Ethyl (2*Z*,4*E*)-5-(dibenzylamino)-2-(1-(((trifluoromethyl)sulfonyl)imino)ethyl)penta-2,4-dienoate



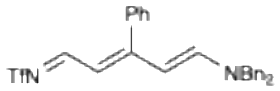
Prepared according to general procedure B using 2-methyl-3-(4-(trifluoromethoxy)phenyl)pyridine (633 mg, 2.50 mmol), EtOAc (12.5 mL, 0.20 M), Tf_2O (420 µL, 2.50 mmol), collidine (330 µL, 2.50 mmol), and dibenzylamine (228 µL, 2.50 mmol). Isolated by precipitation in 250 mL hexanes afforded the title compound (1.264 g, 2.20 mmol, 87% yield) as an orange solid. mp: 50-55 ºC; IR ν_{max}/cm^{-1} (film): 3067, 2939, 1612, 1468, 1417, 1260, 1176, 1113; ^{1}H NMR (400 MHz, CD_3CN) δ 8.12 (d, *J* = 12.4 Hz, 1H), 7.84 (d, *J* = 12.3 Hz, 1H), 7.48 – 7.38 (m, 3H), 7.38 – 7.27 (m, 5H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.02 – 6.94 (m, 2H), 5.23 (t, *J* = 12.4 Hz, 1H), 4.70 (s, 2H), 4.35 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 177.70, 160.43, 155.83, 148.24, 137.16, 135.63 (d, *J* = 34.2), 132.89, 129.59, 129.32, 129.11, 128.91, 128.36, 127.72, 125.97, 121.33, 121.15 (q, *J* = 255.2 Hz), 120.10 (q, *J* = 319.0 Hz), 117.87, 103.44, 61.56, 52.84, 21.60; ^{19}F NMR (375 MHz, CD_3CN) δ -58.57 (s, 3F), -80.69 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 583.2, $C_{28}H_{25}F_6N_2O_3S^+$ requires 583.1.

Isopropyl (3*E*,5*E*)-6-(dibenzylamino)-3-methyl-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-dienoate



Prepared according to our group's previously reported procedure from isopropyl 3-methylpicolinate. ^{1}H NMR (400 MHz, CD_3CN) δ 8.05 (d, *J* = 11.6 Hz, 1H), 7.53 (d, *J* = 12.9 Hz, 1H), 7.47 – 7.37 (m, 6H), 7.33 (dd, *J* = 7.4, 2.1 Hz, 2H), 7.28 – 7.24 (m, 2H), 6.19 (dd, *J* = 12.9, 11.6 Hz, 1H), 5.22 (h, *J* = 6.4 Hz, 1H), 4.71 (s, 4H), 1.83 (s, 3H), 1.37 (d, *J* = 6.3 Hz, 6H); ^{19}F NMR (375 MHz, CD_3CN) δ -79.89 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 509.3, $C_{25}H_{28}F_3N_2O_4S^+$ requires 509.2. The analytical data are consistent with those previously reported.

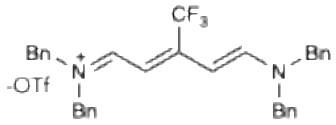
_N_-((1_E_,2_Z_,4_E_)-5-(dibenzylamino)-3-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure B using 4-phenylpyridine (1.55 g, 10.0 mmol), EtOAc (50.0 mL, 0.20 M), Tf_2O (1.68 mL, 10.0 mmol), collidine (1.32 mL, 10.0 mmol), and dibenzylamine (1.93 mL, 10.0 mmol). Isolated by precipitation in 1.00 L hexanes afforded the title compound in an 8:1 mixture with *N*-benzyl-*N*-((2*Z*,4*E*)-5-(dibenzylamino)-3-phenylpenta-2,4-dien-1-ylidene)-1-phenylmethanaminium trifluoromethanesulfonate (Zincke iminium). Silica plug in EtOAc to afford the title compound (2.40 g, 5.00 mmol, 50% yield) as a yellow solid. mp: 128-130 ºC; IR ν_{max}/cm^{-1} (film): 3036, 1552, 1517, 1357, 1242, 1177, 1160, 1117; ^{1}H NMR (400 MHz, CD_3CN) δ 7.65 (d, *J* = 11.6 Hz, 1H), 7.57 – 7.40 (m, 6H), 7.38 (dd, *J* = 6.6, 2.4 Hz, 4H), 7.30 (d, *J* = 7.1 Hz, 4H), 7.16 (s, 2H), 6.27 (d, *J* = 14.6 Hz, 2H), 4.69 (s, 2H), 4.52 (s, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 176.64, 170.28, 160.36, 149.88, 135.42, 134.63 (d, *J* = 5.7 Hz), 130.17 (d, *J* = 13.9 Hz), 129.59, 129.55, 129.24, 129.14, 128.95, 128.73, 128.03, 120.79 (q; *J* = 323.2 Hz), 117.85, 116.51, 107.53, 60.69 (d, *J* = 4.1 Hz), 53.00 (d, *J* = 8.9 Hz); ^{19}F NMR (375 MHz,

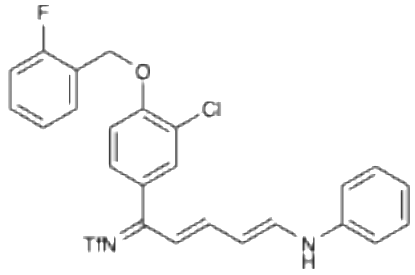
CD_3CN) δ -79.30 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 485.2, $C_{26}H_{24}F_3N_2O_2S^+$ requires 485.2.

((trifluoromethyl)sulfonyl)-λ1-oxidane, *N*-benzyl-*N*-((2*Z*,4*E*)-5-(dibenzylamino)-3-(trifluoromethyl)penta-2,4-dien-1-ylidene)-1-phenylmethanaminium salt



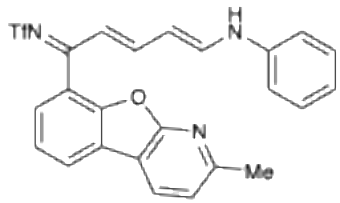
Prepared according to general procedure B (**except** using 2.0 equiv of dibenzylamine) using 4-trifluoromethylpyridine (580 µL, 5.00 mmol), EtOAc (50 mL, 0.1 M), Tf_2O (840 µL, 5.00 mmol), collidine (1.11 mL, 10.0 mmol), and dibenzylamine (1.92 mL, 10.0 mmol, added as a 2.0 M solution in EtOAc). Washed with 10% $CuSO_4$ (3x), then added 1.0 M NaOTf in MeOH (3x) with brine washings (1x) in between each NaOTf addition. Then washed sat. $NaHCO_3$ (3x), brine (1x), 10% $CuSO_4$ (3x), brine (3x). Isolated by precipitating in 500 mL hexanes afforded the title compound (950 mg, 1.40 mmol, 28% yield) as a yellow solid. mp: 104-106 ºC; IR ν_{max}/cm^{-1} (film): 3063, 1562, 1537, 1422, 1222, 1178, 1133, 1028; ^1H NMR (400 MHz, CD_3CN) δ 8.01 (s, 2H), 7.50 – 7.37 (m, 12H), 7.35 (d, *J* = 7.9 Hz, 4H), 7.26 (d, *J* = 8.3 Hz, 4H), 6.10 (s, 2H), 4.79 (s, 8H); ^{13}C NMR (100 MHz, CD_3CN) δ 159.16, 153.88 (q, *J* = 29.5 Hz), 134.35, 134.08, 129.72, 129.64, 129.56, 129.40, 128.97, 128.25, 124.06 (q, *J* = 146.6 Hz), 122.03, 120.14, 117.92, 98.63, 61.48, 53.69; ^{19}F NMR (375 MHz, CD_3CN) δ -79.19 (s, 3F), -80.54 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M – OTf]^+$ 525.3 $C_{34}H_{32}F_3N_2^+$ requires 525.3.

***N*-((2*E*,4*E*)-1-(3-chloro-4-((2-fluorobenzyl)oxy)phenyl)-5-(phenylamino)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide**



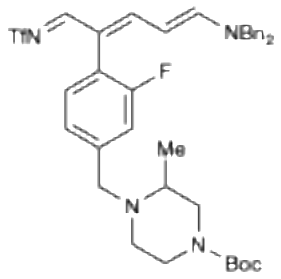
Prepared according to general procedure A using 2-(3-chloro-4-((2-fluorobenzyl)oxy)phenyl)pyridine (235 mg, 0.75 mmol), EtOAc (3.75 mL, 0.20 M), Tf_2O (126 µL, 0.75 mmol), aniline (69.0 µL, 0.75 mmol), collidine (99.0 µL, 0.75 mmol). Isolation by precipitation in 75.0 mL hexanes afforded the title compound along with a minor ^{19}F impurity (282 mg, 0.52 mmol, 70% yield) as a dark purple solid and used in the fluorination procedure without additional purification. mp: 154-158 ºC; IR ν_{max}/cm^{-1} (film): 3295, 1558, 1450, 1150, 1090, 752; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 8.30 (d, *J* = 12.0 Hz, 1H), 7.76 – 7.65 (m, 3H), 7.62 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.46 (tdd, J = 7.7, 5.4, 1.9 Hz, 1H), 7.43 – 7.35 (m, 3H), 7.30 (d, *J* = 8.3 Hz, 3H), 7.23 (dd, *J* = 10.4, 8.3 Hz, 1H), 7.14 (t, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 13.8 Hz, 1H), 6.29 (t, *J* = 12.1 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 176.28, 162.92, 161.06, 160.47, 157.51, 152.51, 140.50, 132.53, 132.23, 131.48 (d, *J* = 8.3 Hz), 131.28 (d, *J* = 3.8 Hz), 131.13, 130.72, 125.51 (d, *J* = 3.7 Hz), 124.26 (d, *J* = 14.4 Hz), 123.27, 120.66 (q, *J* = 319.5 Hz), 117.56, 116.27 (d, *J* = 21.1 Hz), 115.26, 114.18, 108.53, 65.82 (d, *J* = 4.4 Hz); ^{19}F NMR (375 MHz, CD_3CN) δ -80.30 (s, 3F), -119.73 (dt, *J* = 12.2, 6.0 Hz, 1F); LRMS (ESI+APCI) found $[M + H]^+$ 539.2, $C_{25}H_{20}ClF_4N_2O_3S^+$ requires 539.1.

1,1,1-Trifluoro-*N*-((2*E*,4*E*)-1-(2-methylbenzofuro[2,3-*b*]pyridin-8-yl)-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide



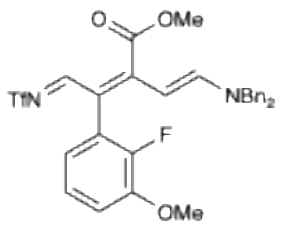
Prepared according to general procedure A using 2-methyl-8-(pyridin-2-yl)benzofuro[2,3-b]pyridine (1.30 g, 5.00 mmol), EtOAc (25.0 mL, 0.20 M), Tf_2O (841 µL, 5.00 mmol), aniline (457 µL, 5.00 mmol), collidine (661 µL, 5.00 mmol). Isolation by precipitation in 500 mL hexanes afforded the title compound and a minor ^{19}F impurity as a dark red solid (2.23 g, 4.60 mmol, 92% yield) and used in the fluorination procedure without additional purification. mp: 176-180 ºC; IR υ_{max}/cm^{-1} (film): 3301, 1566, 1449, 1150, 1093, 899, 625; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 8.54 (d, *J* = 7.8 Hz, 2H), 8.39 – 8.13 (m, 1H), 7.57 – 7.49 (m, 3H), 7.38 (dd, *J* = 17.8, 7.7 Hz, 3H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 13.2 Hz, 1H), 6.33 (t, *J* = 12.1 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $(CH_3)_2SO$) δ 162.41, 156.57, 150.50, 146.26, 138.61, 131.11, 129.72, 128.09, 125.70, 125.01, 123.41, 123.16, 122.88, 121.25, 119.49, 117.49, 114.39, 112.99, 110.21, 24.05; ^{19}F NMR (375 MHz, $CDCl_3$) $(CD_3)_2SO$) δ -78.38; LRMS (ESI+APCI) found $[M + H]^+$ 486.2, $C_{24}H_{19}F_3N_3O_3S^+$ requires 486.1.

***tert*-Butyl 4-(4-((1*E*,2*E*,4*E*)-5-(dibenzylamino)-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-2-yl)-3-fluorobenzyl)-3-methylpiperazine-1-carboxylate**



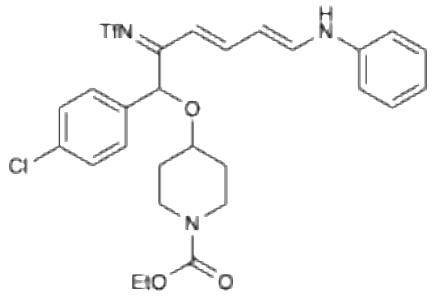
Prepared according to general procedure B using tert-butyl 4-(3-fluoro-4-(pyridin-3-yl)benzyl)-3-methyl piperazine-1-carboxylate (386 mg, 1.00 mmol), EtOAc (5.00 mL, 0.20 M), Tf_2O (168 µL, 1.00 mmol), dibenzylamine (192 µL, 1.00 mmol, as a 1.0 M solution in EtOAc), and collidine (132 µL, 1.00 mmol). Isolation by precipitation in 100 mL hexanes afforded the title compound (540 mg, 0.76 mmol, 76% yield) as a red flaky solid. mp: 92-100 ºC; IR υ_{max}/cm^{-1} (film): 2974, 1686, 1487, 1166, 1104, 852; ^1H NMR (400 MHz, CD_3CN) δ 8.26 (d, *J* = 1.1 Hz, 1H), 7.95 (d, *J* = 11.9 Hz, 1H), 7.78 (d, *J* = 13.0 Hz, 1H), 7.47 – 7.39 (m, 3H), 7.38 – 7.27 (m, 5H), 7.13 (s, 1H), 7.11 (s, 1H), 7.07 – 7.01 (m, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 5.56 (ddd, *J* = 13.0, 11.8, 1.3 Hz, 1H), 4.76 (s, 2H), 4.45 (s, 2H), 3.99 (d, *J* = 14.0 Hz, 1H), 3.68 (d, *J* = 13.1 Hz, 1H), 3.59 (d, *J* = 13.0 Hz, 1H), 3.26 (d, *J* = 14.0 Hz, 1H), 3.10 (ddd, *J* = 12.7, 9.3, 3.2 Hz, 1H), 2.90 (s, 1H), 2.66 (ddd, J = 11.7, 4.8, 3.2 Hz, 1H), 2.53 – 2.37 (m, 1H), 2.12 (ddd, *J* = 12.2, 9.4, 3.4 Hz, 1H), 1.43 (s, 9H), 1.11 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 171.71, 166.95, 163.46, 161.89, 159.45, 155.36, 135.30 (d, *J* = 13.5 Hz), 132.69 (d, *J* = 4.4 Hz), 129.93 (d, *J* = 20.9 Hz), 129.71, 129.50, 128.98, 128.21, 125.40, 121.34 (d, *J* = 17.1 Hz), 121.12 (q, *J* = 320.9 Hz), 120.46, 116.53 (d, *J* = 22.5 Hz), 105.11, 79.82, 62.24, 57.81, 55.70, 53.52, 28.53; ^{19}F NMR (375 MHz, CD_3CN) δ -79.26 (s, 3F), -114.87 (dd, *J* = 10.7, 7.3 Hz, 1F); LRMS (ESI+APCI) found $[M + H]^+$ 715.4, $C_{37}H_{43}F_4N_4O_4S^+$ requires 715.3.

Methyl (2*Z*,4*Z*)-2-((*E*)-2-(dibenzylamino)vinyl)-3-(2-fluoro-3-methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)imino)but-2-enoate



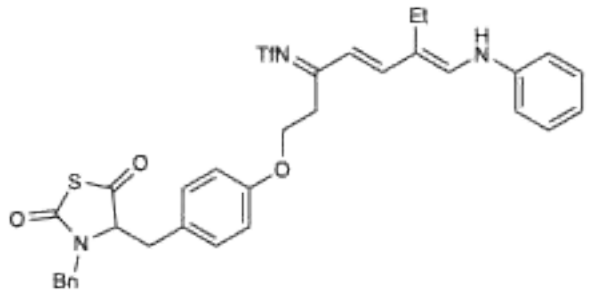
Prepared according to general procedure B using methyl 3-(2-fluoro-3-methoxyphenyl)isonicotinate (340 mg, 1.30 mmol), EtOAc (6.50 mL, 0.20 M), Tf_2O (219 µL, 1.30 mmol), dibenzylamine (250 µL, 1.30 mmol, as a 1.0 M solution in EtOAc), collidine (172 µL, 1.30 mmol). After the aqueous workup, the product was precipitated in 130 mL hexanes. The resulting crude product was then purified by column chromatography (silica gel, 40% EtOAc in hexanes). The product was dissolved in acetone and precipitated a second time in 100 mL hexanes to afford the title compound along with a significant unidentified alkyl impurity (443 mg, 0.75 mmol, 58% yield) as a red solid. The material was used in the fluorination procedure without additional purification. mp: 65-72 ºC; IR υ_{max}/cm^{-1} (film): 2952, 1729, 1613, 1476, 1168, 1104, 866; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 8.17 (s, 1H), 7.85 (d, *J* = 12.7 Hz, 1H), 7.41 – 7.25 (m, 5H), 7.20 (dd, *J* = 5.0, 1.9 Hz, 4H), 7.01 – 6.88 (m, 4H), 6.45 (d, *J* = 8.1 Hz, 1H), 4.44 (s, 3H), 3.80 (s, 4H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 169.59, 167.97, 158.49, 152.03, 149.58, 149.31 (d, *J* = 11.1 Hz), 135.44, 135.17, 130.16, 129.83 (d, *J* = 21.5 Hz), 129.82, 129.06, 128.38, 125.17 (d, *J* = 4.7 Hz), 123.81, 120.99 (q, *J* = 322.7 Hz), 114.17 (d, *J* = 2.1 Hz), 62.52, 56.52, 53.77 (d, *J* = 28.8 Hz); ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -79.10 (s, 3F), -136.06 (s, 1F); LRMS (ESI+APCI) found $[M + H]^+$ 591.3, $C_{29}H_{27}F_4N_2O_5S^+$ requires 591.2.

Ethyl 4-(((3*E*,5*E*)-1-(4-chlorophenyl)-6-(phenylamino)-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-dien-1-yl)oxy)piperidine-1-carboxylate



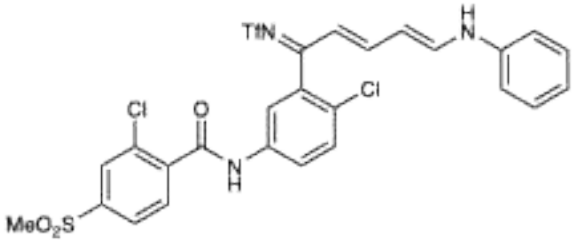
Prepared according to general procedure A using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (380 mg, 1.00 mmol), EtOAc (5.00 mL, 0.20 M), Tf_2O (168 µL, 1.00 mmol), aniline (91.0 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol). After aqueous workup, the product was isolated by repeated precipitations (2x) in 100 mL hexanes to afford the title compound and minor ^{19}F impurities as a dark red solid and used in the fluorination procedure without additional purification (447 mg, 0.75 mmol, 75% yield) as a dark red solid. mp: decomposes above 155 ºC; IR υ_{max}/cm^{-1} (film): 2931, 1568, 1426, 1151, 1074, 752; ^1H NMR (400 MHz, CD_3CN) δ 8.19 (t, *J* = 13.1 Hz, 1H), 8.07 (d, *J* = 11.7 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.34 (m, 4H), 7.29 – 7.14 (m, 3H), 6.43 (d, *J* = 13.6 Hz, 1H), 6.17 (t, *J* = 12.2 Hz, 1H), 5.71 (s, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.70 (ddt, *J* = 11.7, 7.9, 3.9 Hz, 2H), 3.15 (td, *J* = 9.2, 4.4 Hz, 1H), 1.86 (tdd, *J* = 6.2, 4.5, 2.4 Hz, 2H), 1.66 – 1.45 (m, 2H), 1.31 – 1.25 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 179.50, 159.08, 156.15, 154.80, 139.81, 139.46, 134.32, 130.82, 129.39, 126.45, 123.54, 121.06, 120.66 (q, *J* = 318.0 Hz), 112.71, 109.49, 79.85, 74.90, 61.85, 41.88 (d, *J* = 5.1 Hz), 32.21, 31.34, 23.32, 14.97; ^{19}F NMR (375 MHz, CD_3CN) δ -80.30 (s, 3F); LRMS (ESI+APCI) found $[M + H]^+$ 600.2, $C_{27}H_{30}ClF_3N_3O_5S^+$ requires 600.2.

_N_-((4_E_,6_E_)-1-(4-((3-benzyl-2,5-dioxothiazolidin-4-yl)methyl)phenoxy)-6-((phenylamino)methylene)oct-4-en-3-ylidene)-1,1,1-trifluoromethanesulfonamide



Prepared according to general procedure A using 3-benzyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl) thiazolidine-2,4-dione (447 mg, 1.00 mmol), EtOAc (5.00 mL, 0.20 M), Tf_2O (168 µL, 1.00 mmol), aniline (91.0 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol). After aqueous workup and precipitation in 100 mL hexanes, the product was purified by column chromatography (silica gel: 2:30:68 EtOAc:hexanes:CH_2Cl_2) to afford the title compound as a bright-red solid (172 mg, 0.25 mmol, 25% yield). The crude product contains minor aromatic and ^{19}F impurities and was used in the fluorination procedure without additional purification. mp: 66-71 ºC; IR υ_{max}/cm^{-1} (film): 3311, 2927, 1676, 1454, 1249, 1101, 1076; ^1H NMR (400 MHz, CD_3CN) δ 7.82 (d, *J* = 14.1 Hz, 1H), 7.76 (s, 1H), 7.40 (dd, *J* = 8.7, 7.3 Hz, 2H), 7.33 – 7.20 (m, 5H), 7.21 – 7.12 (m, 1H), 7.14 – 7.01 (m, 4H), 6.82 – 6.72 (m, 2H), 6.49 (d, *J* = 14.1 Hz, 1H), 4.68 – 4.58 (m, 3H), 4.26 (t, *J* = 6.4 Hz, 2H), 3.23 – 3.16 (m, 4H), 2.44 (q, *J* = 7.5 Hz, 2H), 1.08 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 174.90 (d, *J* = 3.1 Hz), 172.24, 158.77, 157.14, 141.30, 136.54, 131.81, 130.67, 130.17, 129.49, 129.02, 128.69, 128.64, 128.58, 127.93, 125.64, 120.54, 116.10, 115.35, 113.16, 66.71, 52.38, 52.19, 45.60, 37.23, 18.32, 12.81; ^{19}F NMR (375 MHz, CD_3CN) δ -80.37 (s, 3F); LRMS (ESI+APCI) found $[M + H]^+$ 672.3, $C_{33}H_{33}F_3N_3O_5S_2^+$ requires 672.2.

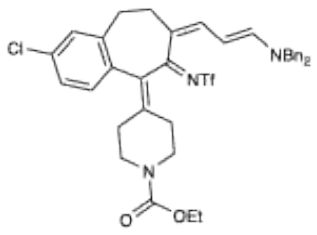
2-Chloro-*N*-(4-chloro-3-((2*E*,4*E*)-5-(phenylamino)-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-1-yl)phenyl)-4-(methylsulfonyl)benzamide



Prepared according to general procedure A using 2-chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (843 mg, 2.00 mmol), EtOAc (10.0 mL, 0.20 M), Tf_2O (336 µL, 2.00

mmol), aniline (183 μL, 2.00 mmol), collidine (264 μL, 2.00 mmol). Prior to the addition of Tf_2O, the suspension of starting material in EtOAc was heated to 60 ºC for 20 minutes until fully dissolved. Following aqueous workup and precipitation in 200 mL hexanes, the material was isolated by automated column chromatography to remove unreacted starting material (silica gel: 2-3% MeOH in 1:99 Et_3N:CH_2Cl_2). An additional precipitation in 200 mL hexanes afforded the title compound along with unidentified impurities (653 mg, 1.00 mmol, 51% yield) as a bright-orange solid. The material was used in the fluorination procedure without additional purification. mp: decomposes above 166 °C; IR υ_{max}/cm^{-1} (film): 3027, 1568, 1451, 1308, 1151, 1095, 821; ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.96 (s, 1H), 8.26 – 8.14 (m, 1H), 8.03 – 7.93 (m, 2H), 7.91 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 2.6 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.65 – 6.48 (m, 1H), 6.27 (t, *J* = 12.2 Hz, 1H), 3.20 (s, 4H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 164.57, 144.41, 141.56, 138.09, 132.33, 130.77, 130.70, 130.31, 129.51, 129.43, 129.27, 129.21, 127.21, 126.81, 125.69, 122.12, 121.67, 120.6 (q, *J* = 320.0 Hz), 119.98, 118.08, 115.53, 43.82; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -77.24 (s, 3F); LRMS (ESI+APCI) found $[M + H]^+$ 646.1, $C_{26}H_{21}Cl_2F_3N_3O_5S_2^+$ requires 646.0.

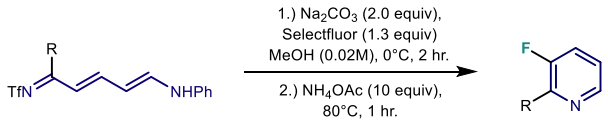
Ethyl 4-((6*Z*,7*Z*)-2-chloro-7-((*E*)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl)sulfonyl)imino)-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate



Prepared according to general procedure B using ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta [1,2- b]pyridin-11-ylidene)piperidine-1-carboxylate (1.914 g, 5.00 mmol), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), collidine (659 µL, 5.00 mmol), and EtOAc (50.0 mL). Precipitation in 500 mL hexanes afforded the title compound as a bright orange solid (1.85 g, 2.60 mmol, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 12.7 Hz, 1H), 7.55 (d, *J* = 12.0 Hz, 1H), 7.49 – 7.33 (m, 6H), 7.24 – 6.97 (m, 7H), 5.77 (t, *J* = 12.4 Hz, 1H), 4.50 (m, 4H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.89 – 3.64 (m, 2H), 3.29 (dddd, *J* = 16.6, 12.7, 8.4, 4.1 Hz, 2H), 3.12 (dt, *J* = 16.8, 3.8 Hz, 1H), 2.90 – 2.63 (m, 2H), 2.58 (dq, *J* = 13.7, 4.2 Hz, 2H), 2.45 – 2.05 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR (375 MHz, $CDCl_3$) δ –79.03 (s, 3F). The analytical data are consistent with those previously reported.

A 1.3 Preparation of 3-Fluoropyridines from Zincke Imine Intermediates

General Procedure C (3-Position Fluorination from Aniline-Derived NTf-Zincke Imines)



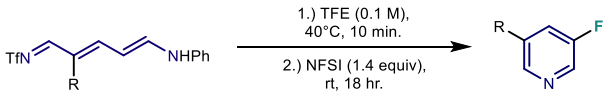
An oven dried 50 mL round bottom flask equipped with a stir bar was charged with an aniline-derived NTf-Zincke imine (1.0 equiv) and placed under a nitrogen atmosphere. Then Na_2CO_3 (2.0 equiv) and Selectfluor (1.3 equiv) were added followed by MeOH (0.02 M), and the reaction vessel was cooled to 0 ºC while stirring for two hours. The cooling bath was removed and NH_4OAc (10.0 equiv) was added. The reaction vessel was heated at 80 ºC with a reflux condenser for 1 hour while stirring. The reaction was then cooled to room temperature and concentrated via a stream of air to remove MeOH. The residue was diluted in minimal EtOAc, then washed with H_2O (2x) followed by brine (1x). The organic extract was dried with $MgSO_4$,

filtered, concentrated via a stream of air, and then the crude material was purified with automated flash column chromatography.

Reaction Notes:

- Due to volatility of products, all solvent was removed by blowing a stream of air at ambient temperature instead of concentrating in vacuo
- Na_3PO_4 gives comparable results to Na_2CO_3 in most cases
- Recyclization at 60ºC for 2 hours gives comparable results in most cases

General Procedure D (5-Position Fluorination from Dibenzylamine-Derived NTf-Zincke Imines)



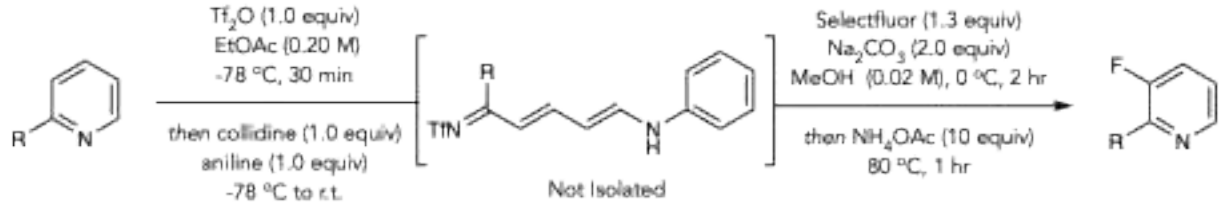
An oven dried 8 mL vial equipped with a stir bar was charged with the dibenzylamine-derived NTf-Zincke imine (1.0 equiv) and placed under a nitrogen atmosphere. TFE (0.10 M) was added, and the reaction vessel was heated to 40 ºC to fully dissolve imine for less than 10 minutes. The reaction vessel was cooled to room temperature, then NFSI (1.4 equiv) was added and the reaction stirred at room temperature for 18 hours. The reaction mixture was diluted with H2O and extracted with CH2Cl2 (3x). The organic extract was dried with MgSO4, filtered, concentrated via a stream of air to remove solvent, and then residue was purified with automated flash column chromatography.

Reaction Notes:

- Due to volatility of products, solvent was removed by blowing a stream of air at ambient temperature instead of concentrating in vacuo

- The reaction is sensitive to an excess of NFSI and is prone to increased decomposition when more than 1.5 equivalents are used
- Fully dissolving the Zincke imine in TFE gives more consistent results, if a Zincke imine is soluble at room temp it does not need to be heated to 40 ºC. If a Zincke imine still does not dissolve, the reaction can be run as is or CH_2Cl_2 (0.50 M) can be added with similar results
- Some reactions are finished after 3 hours but all fluorinated products are stable in the reaction mixture for the full 18 hours.

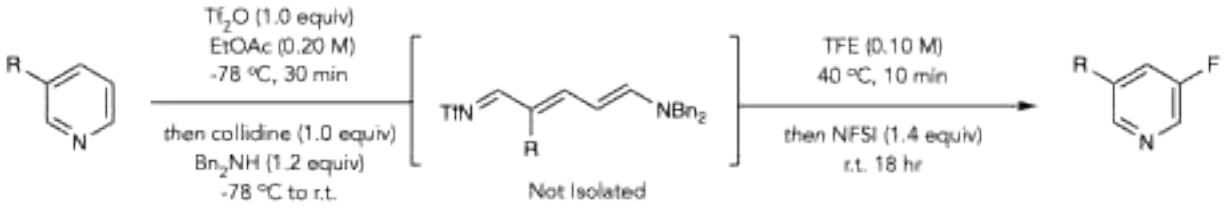
General Procedure E (One-Pot C3-Selective Fluorination of pyridines)



An oven dried 8 mL vial equipped with a stir bar was charged with heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.20 M) was added, the reaction vessel cooled to –78 ºC, and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction stirred for 30 minutes before the addition of collidine (1.0 equiv) followed by aniline (1.0 equiv). The reaction was stirred for a further 5 minutes at –78 ºC before the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring. The reaction was transferred to an oven dried 50 mL round bottom flask with a stir bar with MeOH (0.02 M) under a nitrogen atmosphere. Na_2CO_3 (2.0 equiv) and Selectfluor (1.3 equiv) were added and the reaction vessel cooled to 0 ºC. After stirring for two hours, the ice bath was removed and NH_4OAc (10.0 equiv) was added. The reaction vessel was heated at 80 ºC with a reflux condenser for 1 hour while stirring. The reaction was cooled to room temperature and concentrated by a stream of air to remove MeOH. The reaction was diluted in minimal EtOAc, then washed with H_2O (2x) and brine (1x). The organic extract was dried with

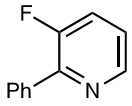
$MgSO_4$, filtered, and concentrated by a stream of air, then the residue was purified via automated flash column chromatography.

General Procedure F (One-Pot C5 Fluorination of 3-Substituted Pyridines)



An oven dried 16 mL vial equipped with a stir bar was charged with heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.20 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before collidine (1.0 equiv) was added followed by the dropwise addition of dibenzylamine (1.2 equiv). The reaction was stirred for an additional 30 minutes at –78 ºC before the cooling bath was removed and the reaction warmed to room temperature while stirring. TFE (0.10 M) was added followed by NFSI (1.4 equiv), and the reaction vessel stirred at room temperature for 18 hours. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (3x). The organic extract was dried with $MgSO_4$, filtered, and concentrated by a stream of air, then the residue was purified via automated flash column chromatography.

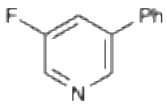
3-Fluoro-2-phenylpyridine



Prepared according to general procedure C using 1,1,1-trifluoro-N-((2E,4E)-1-phenyl-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide (190 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were

taken to determine the yield. Crude ^{1}H NMR showed 68% of the title compound compared to the internal standard mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 20% Et_2O in hexanes) to afford the title compound as a yellow solid (53.8 mg, 0.31 mmol, 62% yield). mp: 36-38 °C; IR ν_{max}/cm^{-1} (film): 3060, 1595, 1444, 1431, 1249, 1188; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dt, *J* = 4.6, 1.6 Hz, 1H), 7.90 (dt, *J* = 8.2, 1.6 Hz, 2H), 7.47 – 7.32 (m, 4H), 7.23 – 7.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.55 (d, *J* = 260.5 Hz), 146.27 (d, *J* = 10.6 Hz), 145.41 (d, *J* = 5.3 Hz), 135.36 (d, *J* = 5.4 Hz), 129.23, 128.80 (d, *J* = 5.7 Hz), 128.47, 124.10 (d, *J* = 20.7 Hz), 123.45 (d, *J* = 3.9 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -122.98 (ddt, *J* = 10.1, 3.6, 1.8 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 174.1, $C_{11}H_9FN^+$ requires 174.1. The analytical data are consistent with those previously reported.

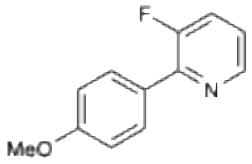
3-Fluoro-5-phenylpyridine



Prepared according to general procedure D using N-((1E,2E,4E)-5-(dibenzylamino)-2-phenylpenta-2,4-dien-1-ylidene)-1,1,1-Trifluoromethanesulfonamide (242 mg, 0.50 mmol), TFE (5.00 mL, 0.10 M), NFSI (221 mg, 0.70 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^{1}H NMR showed 71% of the title compound compared to the internal standard mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 20% EtOAc in hexanes) to afford the title compound as a yellow oil (60.2 mg, 0.35 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 3062, 1597, 1571, 1447, 1412, 1294, 1224, 1188; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.48 (d, *J* = 2.8 Hz, 1H), 7.66 – 7.56 (m, 3H), 7.52 (t, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.3

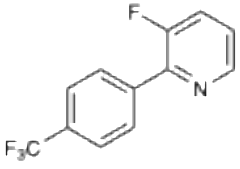
Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.75 (d, *J* = 256.9 Hz), 144.08 (d, *J* = 3.8 Hz), 138.33 (d, *J* = 3.7 Hz), 136.61 (d, *J* = 23.3 Hz), 136.39 (d, *J* = 1.6 Hz), 129.24, 128.74, 127.24, 121.06 (d, *J* = 18.5 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -127.10 (d, *J* = 9.7 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 174.1, $C_{11}H_9FN^+$ requires 174.1. The analytical data are consistent with those previously reported.

3-Fluoro-2-(4-methoxyphenyl)pyridine



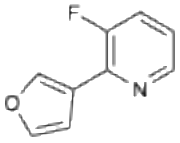
Prepared according to general procedure C using 1,1,1-trifluoro-N-((2E,4E)-1-(4-methoxyphenyl)-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide (205 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 0% to 20% Et_2O in hexanes) to afford the title compound as a yellow solid (59.3 mg, 0.29 mmol, 58% yield). mp: 30-32 ºC; IR ν_{max}/cm^{-1} (film): 3005, 2838, 1611, 1514, 1445, 1439, 1252, 1178; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dt, *J* = 4.6, 1.7 Hz, 1H), 7.89 (dd, *J* = 9.0, 1.6 Hz, 2H), 7.38 (ddd, *J* = 11.3, 8.3, 1.4 Hz, 1H), 7.13 (dt, *J* = 8.3, 4.1 Hz, 1H), 6.98 – 6.83 (m, 2H), 3.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.45, 157.32 (d, *J* = 259.6 Hz), 145.92 (d, *J* = 10.4 Hz), 145.22 (d, *J* = 5.2 Hz), 130.18 (d, *J* = 6.2 Hz), 127.92 (d, *J* = 5.7 Hz), 123.96 (d, *J* = 20.8 Hz), 122.70 (d, *J* = 3.9 Hz), 113.89, 55.34; ^{19}F NMR (375 MHz, $CDCl_3$) δ -123.11 – -123.19 (m, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 204.1, $C_{12}H_{11}FNO^+$ requires 204.1. The analytical data are consistent with those previously reported.

3-Fluoro-2-(4-(trifluoromethyl)phenyl)pyridine



Prepared according to general procedure C using 1,1,1-trifluoro-N-((2E,4E)-5-(phenylamino)-1-(4-(trifluoromethyl)phenyl)penta-2,4-dien-1-ylidene)methanesulfonamide (224 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 0% to 10% Et_2O in hexanes) to afford the title compound as a yellow solid (61.6 mg, 0.26 mmol, 51% yield). mp: 27-30 ºC; IR ν_{max}/cm^{-1} (film): 3070, 1447, 1406, 1327, 1168, 1253, 1128, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (dt, *J* = 4.6, 1.7 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.45 (ddd, *J* = 11.1, 8.3, 1.4 Hz, 1H), 7.25 (dt, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.78 (d, *J* = 261.5 Hz), 145.65 (d, *J* = 5.3 Hz), 144.55 (d, *J* = 10.3 Hz), 138.71 (dd, *J* = 5.8, 1.4 Hz), 130.99 (q, *J* = 32.6 Hz), 129.12 (d, *J* = 6.1 Hz), 125.36 (q, *J* = 3.8 Hz), 124.41 (d, *J* = 20.6 Hz), 124.39 (d, *J* = 4.2 Hz), 124.11 (q, *J* = 272.2 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -62.73 (s, 3F), -122.50 (ddd, *J* = 11.1, 3.3, 1.3 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 242.1, $C_{12}H_8F_4N^+$ requires 242.1. The analytical data are consistent with those previously reported.

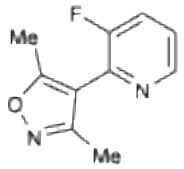
3-Fluoro-2-(furan-3-yl)pyridine



Prepared according to general procedure C using 1,1,1-trifluoro-N-((2E,4E)-1-(furan-3-yl)-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide (185 mg, 0.50 mmol), Na_2CO_3 (106

mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^1H NMR showed 73% of the title compound compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 20% Et_2O in hexanes) to afford the title compound as a yellow oil (32.8 mg, 0.20 mmol, 40% yield). IR ν_{max}/cm^{-1} (film): 3070, 1749, 1604, 1512, 1447, 1200, 1160, 907; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (dq, *J* = 4.6, 1.5 Hz, 1H), 8.07 – 8.01 (m, 1H), 7.44 (t, *J* = 1.8 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.09 (dtt, *J* = 6.6, 4.6, 2.5 Hz, 1H), 7.04 (dt, *J* = 1.9, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.80 (d, *J* = 259.4 Hz), 145.18 (d, *J* = 4.9 Hz), 143.33 (d, *J* = 14.5 Hz), 143.23, 140.57 (d, *J* = 13.4 Hz), 123.19 (d, *J* = 19.5 Hz), 122.36 (d, *J* = 4.0 Hz), 122.01 (d, *J* = 6.3 Hz), 109.22 (d, *J* = 2.7 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -120.59 (d, *J* = 10.9 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 164.1, $C_9H_7FNO^+$ requires 164.1.

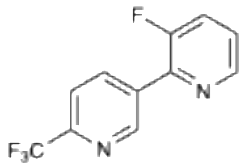
4-(3-fluoropyridin-2-yl)-3,5-Dimethylisoxazole



Prepared according to general procedure C using N-((2E,4E)-1-(3,5-dimethylisoxazol-4-yl)-5-(phenylamino)penta-2,4-dien-1-ylidene)-1,1,1-Trifluoromethanesulfonamide (200 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^1H NMR showed 51% of the title compound compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv). The

crude material was purified by automated flash chromatography (silica gel: 50% to 100% CH_2Cl_2 in hexanes) to afford the title compound as an orange solid (46.1 mg, 0.24 mmol, 48% yield). mp: 80-84 ºC; IR ν_{max}/cm^{-1} (film): 2932, 1634, 1470, 1446, 1414,1260, 1190, 907; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.53 (t, *J* = 9.0 Hz, 1H), 7.34 (dt, *J* = 8.6, 4.4 Hz, 1H), 2.46 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ168.25, 159.31, 157.09 (d, *J* = 258.4 Hz), 145.71 (d, *J* = 5.1 Hz), 139.25 (d, *J* = 14.5 Hz), 123.87 (d, *J* = 4.0 Hz), 123.73 (d, *J* = 19.9 Hz), 111.41 (d, *J* = 4.3 Hz), 12.13 (d, *J* = 4.0 Hz), 10.82 (d, *J* = 3.0 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -120.57 (d, *J* = 8.5 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 193.1, $C_{10}H_{10}FN_2O^+$ requires 193.1.

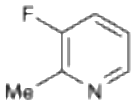
3-Fluoro-6'-(trifluoromethyl)-2,3'-bipyridine



Prepared according to general procedure C (except the fluorination ran at -20 ºC overnight instead of 0 ºC for 2 hrs) using 1,1,1-trifluoro-N-((2E,4E)-5-(phenylamino)-1-(6-(trifluoromethyl)pyridin-3-yl)penta-2,4-dien-1-ylidene)methanesulfonamide (225 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 0% to 80% CH_2Cl_2 in hexanes) to afford the title compound as a cream solid (60.3 mg, 0.25 mmol, 50% yield). mp: 35-38 ºC; IR ν_{max}/cm^{-1} (film): 2929, 1447, 1336, 1190, 1180, 1147, 1090, 906; ^1H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.62 (dt, *J* = 4.6, 1.6 Hz, 1H), 8.54 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.61 (ddd, *J* = 11.0, 8.4, 1.4 Hz, 1H), 7.42 (dt, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ158.05 (d, *J* = 262.3 Hz), 150.00 (d, *J* = 8.5 Hz), 148.06 (q, *J* = 35.0 Hz), 146.08 (d, *J* = 5.1 Hz), 141.75 (d, *J* = 10.6 Hz), 137.33 (d, *J* = 5.9 Hz), 133.88 (d, *J* = 5.9 Hz), 125.21 (d,

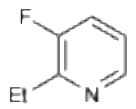
J = 4.2 Hz), 124.64 (d, J = 20.3 Hz), 121.53 (q, J = 274.2 Hz), 120.16 (q, J = 2.7 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -67.96 (s, 3F), -122.06 (dd, J = 11.0, 3.8 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 243.1, $C_{11}H_7F_4N_2^+$ requires 243.1.

3-Fluoro-2-methylpyridine



Prepared according to general procedure C (except the recyclization ran at 60 ºC for 2 hours instead of 80 ºC for 1 hour) using 1,1,1-trifluoro-N-((3E,5E)-6-(phenylamino)hexa-3,5-dien-2-ylidene)methanesulfonamide (31.8 mg, 0.10 mmol), Na_2CO_3 (21.2 mg, 0.20 mmol), Selectfluor (46.0 mg, 0.13 mmol), MeOH (5.00 mL, 0.02 M), NH_4OAc (77.1 mg, 1.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^{1}H NMR showed 60% of the title compound compared to the internal standard mesitylene (14.0 μL, 0.10 mmol, 1.0 equiv). ^{1}H NMR (400 MHz, CD_3CN) δ 8.28 (d, J = 4.8 Hz, 1H), 7.47 (t, J = 9.1 Hz, 1H), 7.26 (dt, J = 8.8, 4.5 Hz, 1H), 2.49 (d, J = 3.0 Hz, 3H); ^{19}F NMR (375 MHz, CD_3CN) δ -152.43 (s, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 112.1, $C_6H_7FN_2^+$ requires 112.1. Spectra matched an authentic sample purchased from Combi-Blocks.

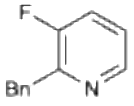
2-Ethyl-3-fluoropyridine



Prepared according to general procedure C (except the recyclization ran at 60 ºC for 2 hours instead of 80 ºC for 1 hour) using 1,1,1-trifluoro-N-((4E,6E)-7-(phenylamino)hepta-4,6-dien-3-ylidene)methanesulfonamide (33.2 mg, 0.10 mmol), Na_2CO_3 (21.2 mg, 0.20 mmol), Selectfluor

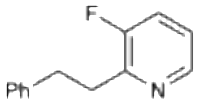
(46.0 mg, 0.13 mmol), MeOH (5.00 mL, 0.02 M), NH_4OAc (77.1 mg, 1.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^1H NMR showed 64% of the title compound compared to the internal standard mesitylene (14.0 μL, 0.10 mmol, 1.0 equiv). ^{19}F NMR (375 MHz, CD_3CN) δ -152.5 (s, 3F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 126.1, $C_7H_9FN^+$ requires 126.1.

2-Benzyl-3-fluoropyridine



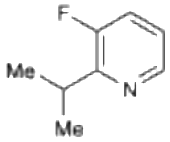
Prepared according to general procedure C using 1,1,1-trifluoro-N-((3E,5E)-1-phenyl-6-(phenylamino)hexa-3,5-dien-2-ylidene)methanesulfonamide (194 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Due to product volatility, an aliquot was taken to determine the yield. Crude ^1H NMR showed 48% of the title compound compared to the internal standard mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 40% CH_2Cl_2 in hexanes) to afford the title compound as a yellow oil (33.0 mg, 0.18 mmol, 35% yield). IR ν_{max}/cm^{-1} (film): 3030, 2927, 1599, 1494, 1446, 1246, 1094, 904; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (dt, *J* = 4.7, 1.5 Hz, 1H), 7.41 – 7.27 (m, 5H), 7.26 – 7.22 (m, 1H), 7.18 (dt, *J* = 8.5, 4.5 Hz, 1H), 4.24 (d, *J* = 2.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.68 (d, *J* = 256.7 Hz), 149.14 (d, *J* = 15.2 Hz), 145.10 (d, *J* = 5.5 Hz), 138.43, 128.93, 128.53, 126.46, 122.92 (d, *J* = 19.3 Hz), 122.91 (d, *J* = 3.7 Hz), 38.24 (d, *J* = 2.2 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -124.36 (d, *J* = 10.2 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 188.1, $C_{12}H_{11}FN^+$ requires 188.1.

3-Fluoro-2-phenethylpyridine



Prepared according to general procedure C using 1,1,1-trifluoro-N-((4E,6E)-1-phenyl-7-(phenylamino)hepta-4,6-dien-3-ylidene)methanesulfonamide (204 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^1H NMR showed 57% of the title compound compared to the internal standard mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 50% CH_2Cl_2 in hexanes) to afford the title compound as a yellow oil (43.3 mg, 0.22 mmol, 43% yield). IR ν_{max}/cm^{-1} (film): 3029, 2929, 1602, 1450, 1243, 1175, 1098, 906; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.7 Hz, 1H), 7.41 – 7.14 (m, 7H), 3.20 (tt, *J* = 7.5, 2.0 Hz, 2H), 3.08 (dd, *J* = 10.1, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.76 (d, *J* = 255.9 Hz), 149.63 (d, *J* = 15.4 Hz), 144.88 (d, *J* = 5.4 Hz), 141.38, 128.44 (d, *J* = 6.3 Hz), 126.06, 122.59 (d, *J* = 3.7 Hz), 122.56 (d, *J* = 19.4 Hz), 34.55 (d, *J* = 1.4 Hz), 33.44 (d, *J* = 2.5 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -125.45 (s, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 202.1, $C_{13}H_{13}FN^+$ requires 202.1.

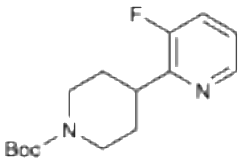
3-Fluoro-2-isopropylpyridine



Prepared according to general procedure C (except the fluorination ran at -20 ºC overnight and recyclized at 60 ºC for 2 hours instead of 80 ºC for 1 hour) using 1,1,1-trifluoro-N-((4E,6E)-2-methyl-7-(phenylamino)hepta-4,6-dien-3-ylidene)methanesulfonamide (34.6 mg, 0.10 mmol),

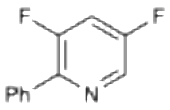
Na_2CO_3 (21.2 mg, 0.20 mmol), Selectfluor (46.0 mg, 0.13 mmol), MeOH (5.00 mL, 0.02 M), NH_4OAc (77.1 mg, 1.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^1H NMR showed 52% of the title compound compared to the internal standard mesitylene (14.0 µL, 0.10 mmol, 1.0 equiv). ^{19}F NMR (375 MHz, CD_3CN) δ -152.49 (d, *J* = 3.8 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 140.2, $C_8H_{11}FN^+$ requires 140.1.

***tert*-Butyl 4-(3-fluoropyridin-2-yl)piperidine-1-carboxylate**



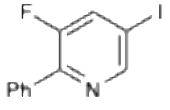
Prepared according to general procedure C using tert-butyl 4-((2E,4E)-5-(phenylamino)-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-1-yl)piperidine-1-carboxylate (244 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 0% to 20% EtOAc in hexanes) to afford the title compound as an orange oil (62.2 mg, 0.23 mmol, 45% yield). IR ν_{max}/cm^{-1} (film): 2980, 2858, 1682, 1452, 1428, 1367, 1243, 1169; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (dt, *J* = 4.7, 1.5 Hz, 1H), 7.35 (ddd, *J* = 9.9, 8.3, 1.4 Hz, 1H), 7.17 (dt, *J* = 8.5, 4.4 Hz, 1H), 4.28 (s, 2H), 3.21 (tq, *J* = 9.9, 3.1 Hz, 1H), 2.88 (s, 2H), 1.96 – 1.74 (m, 4H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.19 (d, *J* = 256.2 Hz), 154.72, 152.23 (d, *J* = 13.9 Hz), 144.91 (d, *J* = 5.4 Hz), 122.63 (d, *J* = 23.3 Hz), 122.55, 79.35, 43.97 (d, *J* = 56.6 Hz), 37.60 (d, *J* = 2.2 Hz), 30.11, 28.48; ^{19}F NMR (375 MHz, $CDCl_3$) δ -126.73 (d, *J* = 10.1 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 281.2, $C_{15}H_{22}FN_2O_2^+$ requires 281.2.

3,5-Difluoro-2-phenylpyridine



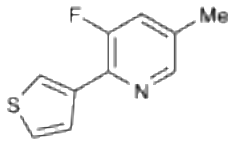
Prepared according to general procedure C using 1,1,1-trifluoro-N-((2E,4Z)-4-fluoro-1-phenyl-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide (199 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^1H NMR showed 72% of the title compound compared to the internal standard mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 40% CH_2Cl_2 in hexanes) to afford the title compound as a white solid (63.7 mg, 0.34 mmol, 68% yield). mp: 29-32 ºC; IR ν_{max}/cm^{-1} (film): 3093, 1321, 1191, 1157, 1101, 1037, 915, 733; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 2.3 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.56 – 7.42 (m, 3H), 7.33 (ddd, J = 10.4, 8.0, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.14 (dd, J = 261.9, 5.1 Hz), 156.72 (dd, J = 266.1, 5.6 Hz), 142.71 (dd, J = 10.6, 4.0 Hz), 134.65 (d, J = 5.8 Hz), 133.73 (dd, J = 22.4, 4.7 Hz), 128.92 (d, J = 65.2 Hz), 128.54, 112.21 (d, J = 44.8 Hz), 112.21 (d, J = 2.4 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -118.85 (dd, J = 10.6, 6.2 Hz, 1F), -125.67 (t, J = 7.1 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 192.1, $C_{11}H_8FN^+$ requires 192.1.

3-Fluoro-5-iodo-2-phenylpyridine



Prepared according to general procedure C using 1,1,1-Trifluoro-N-((2E,4Z)-4-iodo-1-phenyl-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide (253 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). The crude material was purified by automated flash chromatography (1st column: silica gel, 0% to 20% Et_2O in hexanes; 2nd column: silica gel, 50 to 100% CH_2Cl_2 in hexanes) to afford the title compound as a yellow solid (85.8 mg, 0.29 mmol, 57% yield). mp: 47-50 ºC; IR ν_{max}/cm^{-1} (film): 3062, 1574, 1546, 1439, 1390, 1246, 1164, 1017; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (t, *J* = 1.6 Hz, 1H), 7.97 (dt, *J* = 7.8, 1.7 Hz, 2H), 7.87 (dd, *J* = 10.1, 1.7 Hz, 1H), 7.56 – 7.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.67 (d, *J* = 267.5 Hz), 151.42 (d, *J* = 5.1 Hz), 145.21 (d, *J* = 10.3 Hz), 134.49 (d, *J* = 5.6 Hz), 132.45 (d, *J* = 22.5 Hz), 129.67, 128.68, 128.61 (d, *J* = 1.5 Hz), 90.17; ^{19}F NMR (375 MHz, $CDCl_3$) δ -119.37 (t, *J* = 9.0 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 300.0, $C_{11}H_{18}FIN^+$ requires 300.0.

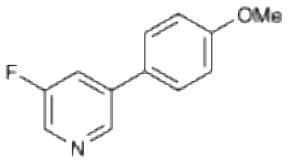
3-Fluoro-5-methyl-2-(thiophen-3-yl)pyridine



Prepared according to general procedure C using 1,1,1-trifluoro-N-((2E,4E)-4-methyl-5-(phenylamino)-1-(thiophen-3-yl)penta-2,4-dien-1-ylidene)methanesulfonamide (200 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^1H NMR showed 81% of the title compound compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 100% CH_2Cl_2

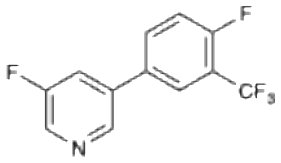
in hexanes) to afford the title compound as a yellow oil (65.4 mg, 0.34 mmol, 68% yield). IR ν_{max}/cm^{-1} (film): 3119, 2926, 1571, 1468, 1417, 1268, 1216, 1143; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.00 (dt, *J* = 2.9, 1.4 Hz, 1H), 7.82 (dt, *J* = 5.0, 1.3 Hz, 1H), 7.39 (dd, *J* = 5.1, 2.9 Hz, 1H), 7.32 – 7.25 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.58 (d, *J* = 260.3 Hz), 145.56 (d, *J* = 4.3 Hz), 139.31 (d, *J* = 11.4 Hz), 137.03 (d, *J* = 6.2 Hz), 133.43 (d, *J* = 4.0 Hz), 127.53 (d, *J* = 4.5 Hz), 125.40 (d, *J* = 10.6 Hz), 125.25 (d, *J* = 1.0 Hz), 124.20 (d, *J* = 19.8 Hz), 17.82; ^{19}F NMR (375 MHz, $CDCl_3$) δ -123.41 (d, *J* = 12.2 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 194.1 , $C_{10}H_9FNS^+$ requires 194.0.

3-Fluoro-5-(4-methoxyphenyl)pyridine



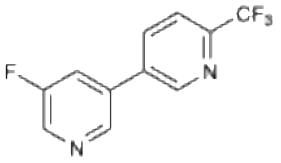
Prepared according to general procedure D using N-((1E,2E,4E)-5-(dibenzylamino)-2-(4-methoxyphenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (257.3 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). The crude material was purified by automated flash chromatography (silica gel: 0% to 100% CH_2Cl_2 in hexanes) to afford the title compound as an orange solid (75.5 mg, 0.37 mmol, 74% yield). mp: 62-65 ºC; IR ν_{max}/cm^{-1} (film): 2936, 2839, 1609, 1517, 1435, 1288, 1250, 1180; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.43 (s, 1H), 7.63 – 7.45 (m, 3H), 7.04 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.22, 159.79 (d, *J* = 255.4 Hz), 143.72, 137.98, 135.94 (d, *J* = 23.3 Hz), 128.75 (d, *J* = 1.6 Hz), 128.36, 120.46 (d, *J* = 18.4 Hz), 114.70, 55.41; ^{19}F NMR (375 MHz, $CDCl_3$) δ -127.27 (d, *J* = 9.2 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 204.1, $C_{12}H_{11}FNO^+$ requires 204.1.

3-Fluoro-5-(4-fluoro-3-(trifluoromethyl)phenyl)pyridine



Prepared according to general procedure D using N-((1E,2E,4E)-5-(dibenzylamino)-2-(4-fluoro-3-(trifluoromethyl)phenyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (228 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). The crude material was purified by automated flash chromatography (1st column: silica gel, 0% to 20% EtOAc in hexanes; 2nd column: silica gel, 100% CH_2Cl_2) to afford the title compound as a yellow oil (52.6 mg, 0.26 mmol, 51% yield). IR ν_{max}/cm^{-1} (film): 3057, 1510, 1435, 1337, 1247, 1144, 1130, 1058; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.54 (d, *J* = 2.8 Hz, 1H), 7.82 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.77 (ddd, *J* = 8.6, 4.6, 2.4 Hz, 1H), 7.60 (dt, *J* = 9.1, 2.3 Hz, 1H), 7.37 (t, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.03 (dd, *J* = 259.1, 2.0 Hz), 159.62 (d, *J* = 257.9 Hz), 143.87 (d, *J* = 3.9 Hz), 137.61 (d, *J* = 23.1 Hz), 135.99, 132.96 (dd, *J* = 4.0, 1.4 Hz), 132.67 (d, *J* = 8.7 Hz), 126.10 (qd, *J* = 4.6, 1.8 Hz), 122.27 (q, *J* = 272.7 Hz), 121.12 (d, *J* = 18.9 Hz), 119.41 (qd, *J* = 33.3, 13.0 Hz), 118.01 (d, *J* = 21.1 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -61.53 (d, *J* = 12.5 Hz, 3F), -114.21 – -114.41 (m, 1F), -126.12 (d, *J* = 9.3 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 260.1, $C_{12}H_7F_5N^+$ requires 260.0.

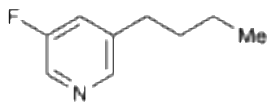
5-Fluoro-6'-(trifluoromethyl)-3,3'-bipyridine



Prepared according to general procedure D using N-((1E,2E,4E)-5-(dibenzylamino)-2-(6-(trifluoromethyl)pyridin-3-yl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (277

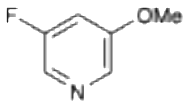
mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). The crude material was purified by automated flash chromatography (1st column: silica gel, 0% to 100% CH_2Cl_2 in hexanes; 2nd column: silica gel, 20% EtOAc in hexanes) to afford the title compound as a white solid (55.0 mg, 0.23 mmol, 45% yield). mp: 153-156 ºC; IR ν_{max}/cm^{-1} (film): 3055, 1586, 1440, 1360, 1140, 907, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.2 Hz, 1H), 8.73 (s, 1H), 8.63 (s, 1H), 8.09 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.67 (dt, *J* = 8.9, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.62 (d, *J* = 257.5 Hz), 148.40, 148.27 (q, *J* = 35.1 Hz), 144.05 (d, *J* = 4.1 Hz), 138.65 (d, *J* = 23.1 Hz), 135.95, 135.03, 133.65, 121.39 (d, *J* = 18.9 Hz), 121.38 (q, *J* = 274.3 Hz), 120.79 (q, *J* = 2.5 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -67.92(s, 3F), -125.30 (d, *J* = 8.9 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 243.2, $C_{11}H_7F_4N_2^+$ requires 243.1.

3-Butyl-5-fluoropyridine



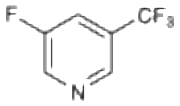
Prepared according to general procedure D using N-((1E,2E)-2-((E)-3-(dibenzylamino)allylidene)hexylidene)-1,1,1-trifluoromethanesulfonamide (232 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^{1}H NMR showed 75% of the title compound compared to the internal standard mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv). ^{19}F NMR (375 MHz, $CDCl_3$) δ -126.63 (d, *J* = 9.3 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 154.2, $C_9H_{13}FN^+$ requires 154.1.

3-Fluoro-5-methoxypyridine



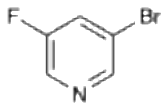
Prepared according to general procedure D using N-((1E,2Z,4E)-5-(dibenzylamino)-2-methoxypenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (176 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^{1}H NMR showed 34% of the title compound compared to the internal standard mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.5 Hz, 1H), 8.08 (d, *J* = 2.4 Hz, 1H), 7.01 (dt, *J* = 10.2, 2.4 Hz, 1H), 3.90 (s, 3H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -125.40 (d, *J* = 10.3 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 128.1, $C_6H_7FNO^+$ requires 128.1. Spectra matched an authentic sample from Enamine.

3-Fluoro-5-(trifluoromethyl)pyridine



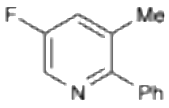
Prepared according to general procedure D using N-((1Z,2Z,4E)-5-(dibenzylamino)-2-(trifluoromethyl)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (238 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^{1}H NMR showed 38% of the title compound compared to the internal standard mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv). ^{19}F NMR (375 MHz, $CDCl_3$) δ -62.39 (s, 3F), -123.74 (s, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 166.1, $C_6H_4F_4N^+$ requires 166.0. Spectra matched an authentic sample purchased from Matrix.

3-Bromo-5-fluoropyridine (2x)



Prepared according to general procedure D (except the fluorination ran at 40 ºC instead of r.t.) using N-((1E,2Z,4E)-2-bromo-5-(dibenzylamino)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (195 mg, 0.40 mmol), NFSI (176 mg, 0.56 mmol), TFE (4.0 mL, 0.10 M). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^{1}H NMR showed 59% of the title compound compared to the internal standard mesitylene (56.0 µL, 0.40 mmol, 1.0 equiv). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.42 (d, J = 2.5 Hz, 1H), 7.68 (dt, J = 7.8, 2.2 Hz, 1H); ^{19}F NMR (375 MHz, $CDCl_3$) δ -122.89 (d, J = 7.8 Hz, 1F) ; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 176.0, $C_5H_4BrFN^+$ requires 176.0. Spectra matched an authentic sample purchased from Ambeed.

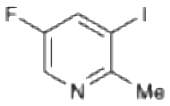
5-Fluoro-3-methyl-2-phenylpyridine



Prepared according to general procedure D using N-((2E,4E)-5-(dibenzylamino)-2-methyl-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (250 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). Due to product volatility, an aliquot was taken to determine the yield. Crude ^{1}H NMR showed 57% of the title compound compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (1st column: silica gel, 0% to 10% EtOAc in hexanes; 2nd column: silica gel, 0% to 100% CH_2Cl_2 in hexanes) to afford the title compound as a yellow oil (38.3 mg,

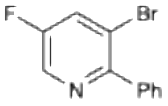
0.21 mmol, 41% yield). IR ν_{max}/cm^{-1} (film): 3059, 2982, 1597, 1463, 1447, 1430, 1269, 1192; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.8 Hz, 1H), 7.54 – 7.38 (m, 5H), 7.35 (ddd, *J* = 9.0, 2.8, 0.6 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.49 (d, *J* = 256.2 Hz), 155.02 (d, *J* = 3.8 Hz), 139.74, 134.91 (d, *J* = 22.7 Hz), 132.68 (d, *J* = 3.7 Hz), 128.95, 128.24, 128.05, 124.88 (d, *J* = 17.7 Hz), 20.14; ^{19}F NMR (375 MHz, $CDCl_3$) δ -130.65 (d, *J* = 9.0 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 188.1, $C_{12}H_{11}FN^+$ requires 188.1.

5-Fluoro-3-iodo-2-methylpyridine



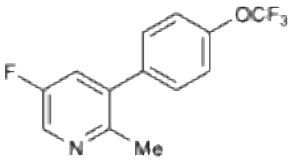
Prepared according to general procedure D using N-((2E,3Z,5E)-6-(dibenzylamino)-3-iodohexa-3,5-dien-2-ylidene)-1,1,1-trifluoromethanesulfonamide (274 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). Due to product volatility, an aliquot was taken to determine the yield. Crude ^{1}H NMR showed 70% of the title compound compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 10% EtOAc in hexanes) to afford the title compound as a yellow oil (37.0 mg, 0.35 mmol, 31% yield). IR ν_{max}/cm^{-1} (film): 2926, 2854, 1583, 1449, 1375, 1250, 1214, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 3.4 Hz, 1H), 7.84 (dt, *J* = 7.5, 2.0 Hz, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ156.40 (d, *J* = 260.5 Hz), 156.26 (d, *J* = 4.0 Hz), 136.22 (d, *J* = 22.1 Hz), 133.12 (d, *J* = 19.7 Hz), 94.51 (d, *J* = 1.8 Hz), 27.87 (d, *J* = 1.1 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -129.31 (d, *J* = 7.5 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 238.0, $C_6H_6FIN^+$ requires 238.0.

3-Bromo-5-fluoro-2-phenylpyridine



Prepared according to general procedure D (except imine was prestirred at r.t. instead of 40 ºC, and the fluorination ran at 40 ºC instead of r.t.) using N-((2Z,4E)-2-bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (282 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). The crude material was purified by automated flash chromatography (1st column: silica gel, 0% to 10% EtOAc in hexanes; 2nd column: silica gel, 0% to 100% CH_2Cl_2 in hexanes) to afford the title compound as a clear oil (60.2 mg, 0.35 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 2926, 2854, 1582, 1443, 1379, 1244, 1175, 905; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.81 (dd, *J* = 7.6, 2.5 Hz, 1H), 7.68 – 7.64 (m, 2H), 7.52 – 7.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.41 (d, *J* = 262.9 Hz), 154.62 (d, *J* = 4.0 Hz), 138.68, 136.35 (d, *J* = 22.2 Hz), 129.30, 128.86, 128.19 (d, *J* = 20.3 Hz), 128.06, 118.98; ^{19}F NMR (375 MHz, $CDCl_3$) δ -127.08 (d, *J* = 7.5 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 252.0, $C_{11}H_8BrFN^+$ requires 252.0.

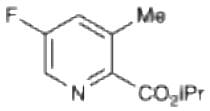
5-Fluoro-2-methyl-3-(4-(trifluoromethoxy)phenyl)pyridine



Prepared according to general procedure D (except imine was prestirred at r.t. instead of 40 ºC) using ethyl (2Z,4E)-5-(dibenzylamino)-2-(1-(((trifluoromethyl)sulfonyl)imino)ethyl)penta-2,4-dienoate (291 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). The crude material was purified by automated flash chromatography (1st column: silica gel, 0% to 10% EtOAc in hexanes; 2nd column: silica gel, 50% to 100% CH_2Cl_2 in hexanes) to afford the title

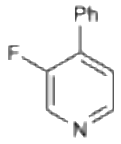
compound as a yellow oil (44.8 mg, 0.17 mmol, 33% yield). IR ν_{max}/cm^{-1} (film): 2929, 1512, 1451, 1258, 1215, 1171, 906, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.35 (q, *J* = 8.9 Hz, 4H), 7.28 (d, *J* = 7.4 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.97 (d, *J* = 256.9 Hz), 151.76, 149.00, 137.33, 136.51 (d, *J* = 53.8 Hz), 130.37, 124.01, 123.83, 121.06, 120.47 (q, *J* = 257.8 Hz), 22.68; ^{19}F NMR (375 MHz, $CDCl_3$) δ -57.82 (s, 3F), -131.79 (s, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 272.1, $C_{13}H_{10}F_4NO^+$ requires 272.1.

Isopropyl 5-fluoro-3-methylpicolinate



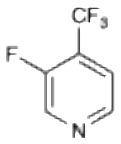
Prepared according to general procedure D (except the fluorination ran at 40 ºC instead of r.t.) using isopropyl (3E,5E)-6-(dibenzylamino)-3-methyl-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-dienoate (102 mg, 0.20 mmol), NFSI (88.2 mg, 0.28 mmol), TFE (2.00 mL, 0.10 M). Due to product volatility, an aliquot was taken to determine the yield. Crude ^{1}H NMR showed 50% of the title compound compared to the internal standard mesitylene (28.0 µL, 0.20 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 20% EtOAc in hexanes) to afford the title compound as a clear oil (10.1 mg, 0.10 mmol, 25% yield). IR ν_{max}/cm^{-1} (film): 2984, 2935, 1720, 1466, 1304, 1232, 1153, 1094; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.33 (dd, *J* = 8.9, 2.0 Hz, 1H), 5.33 (hept, *J* = 6.3 Hz, 1H), 2.61 (s, 3H), 1.44 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ165.07, 159.98 (d, *J* = 262.3 Hz), 144.47 (d, *J* = 3.8 Hz), 137.66 (d, *J* = 4.8 Hz), 135.41 (d, *J* = 23.7 Hz), 125.83 (d, *J* = 17.7 Hz), 69.46, 21.84, 20.14; ^{19}F NMR (375 MHz, $CDCl_3$) δ -127.08 (d, *J* = 7.5 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 198.1, $C_{10}H_{13}FNO_2^+$ requires 198.1.

3-Fluoro-4-phenylpyridine



Prepared according to general procedure D (except imine was prestirred at r.t. instead of 40 ºC) using N-((1E,2Z,4E)-5-(dibenzylamino)-3-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (242 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^{1}H NMR showed 34% of the title compound compared to the internal standard mesitylene (70.0 μL, 0.50 mmol, 1.0 equiv). The crude material was purified by automated flash chromatography (silica gel: 0% to 50% EtOAc in hexanes) to afford the title compound as a yellow oil (21.6 mg, 0.13 mmol, 25% yield). IR ν_{max}/cm^{-1} (film): 3069, 2929, 1609, 1478, 1416, 1268, 1208, 906; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.42 (s, 1H), 7.55 (dt, *J* = 8.0, 1.6 Hz, 2H), 7.46 – 7.39 (m, 3H), 7.39 – 7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.74 (d, *J* = 265.6 Hz), 145.90 (d, *J* = 5.2 Hz), 138.96 (d, *J* = 25.8 Hz), 136.16 (d, *J* = 10.0 Hz), 132.91 (d, *J* = 1.0 Hz), 129.30, 128.85, 128.82, 124.3; ^{19}F NMR (375 MHz, $CDCl_3$) δ -132.44 (s, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 174.1, $C_{11}H_9FN^+$ requires 174.1. The analytical data are consistent with those previously reported.

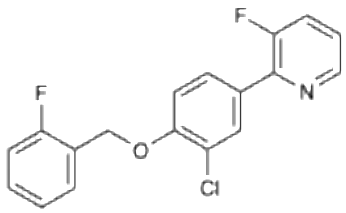
3-Fluoro-4-(trifluoromethyl)pyridine



Prepared according to general procedure D (except the fluorination ran at r.t. for 1 hour instead of 3 hours, then recyclized using NH_4OAc at 60 ºC for 2 hours) using ((trifluoromethyl)sulfonyl)-λ1-oxidane, N-Benzyl-N-((2Z,4E)-5-(dibenzylamino)-3-(trifluoromethyl)penta-2,4-dien-1-ylidene)-1-phenylmethanaminium salt (135 mg, 0.20 mmol), NFSI (110 mg, 0.28 mmol), TFE (2.0 mL, 0.10 M) NH_4OAc (154.2 mg, 2.00 mmol). Due to product volatility, the reaction was run in duplicate, and direct aliquots were taken to determine the yield. Crude ^1H NMR showed 50% of the title compound compared to the internal standard mesitylene (28.0 μL, 0.10 mmol, 1.0 equiv). ^{19}F NMR (375 MHz, $CDCl_3$) δ -62.99 (d, J = 12.5 Hz, 3F), -127.65 – -127.85 (m, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 166.1, $C_6H_4F_4N^+$ requires 166.0. Spectra matched an authentic sample purchased from Oakwood.

- 3% 3,5-difluoro-4-(trifluoromethyl)pyridine was present by crude ^1H NMR compared to mesitylene. Increasing reaction time will increase the amount of difluorination that occurs.

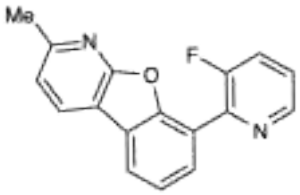
2-(3-Chloro-4-((2-fluorobenzyl)oxy)phenyl)-3-fluoropyridine



Prepared according to general procedure C using N-((2E,4E)-1-(3-chloro-4-((2-fluorobenzyl)oxy)phenyl)-5-(phenylamino)penta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (216 mg, 0.40 mmol), Na_2CO_3 (84.8 mg, 0.80 mmol), Selectfluor (184 mg, 0.52 mmol), MeOH (20.0 mL, 0.02 M), NH_4OAc (309 mg, 4.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 0% to 60% CH_2Cl_2 in hexanes) to afford the title compound as a cream solid (78.9 mg, 0.24 mmol, 60% yield). mp: 100-

103 ºC; IR ν_{max}/cm^{-1} (film): 3069, 2927, 1602, 1502, 1443, 1297, 1266, 1235; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dt, *J* = 4.6, 1.6 Hz, 1H), 8.14 (dd, *J* = 2.3, 1.1 Hz, 1H), 7.92 (dt, *J* = 8.6, 1.9 Hz, 1H), 7.64 (td, *J* = 7.5, 1.9 Hz, 1H), 7.50 (ddd, *J* = 11.3, 8.3, 1.4 Hz, 1H), 7.35 (tdd, *J* = 7.3, 5.3, 1.9 Hz, 1H), 7.30 – 7.25 (m, 1H), 7.22 (td, *J* = 7.6, 1.3 Hz, 1H), 7.16 – 7.08 (m, 2H), 5.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.19 (d, *J* = 246.6 Hz), 157.39 (d, *J* = 260.7 Hz), 154.64, 145.36 (d, *J* = 5.3 Hz), 144.38 (d, *J* = 10.2 Hz), 130.74 (d, *J* = 6.2 Hz), 129.74 (d, *J* = 8.1 Hz), 129.28 (d, *J* = 3.8 Hz), 129.24 (d, *J* = 5.8 Hz), 128.31 (d, *J* = 7.1 Hz), 124.45 (d, *J* = 3.6 Hz), 124.19 (d, *J* = 20.7), 123.53 (d, *J* = 14.0 Hz), 123.42, 123.37 (d, *J* = 4.0 Hz), 115.27 (d, *J* = 20.9 Hz), 113.40, 64.50 (d, *J* = 4.8 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -118.70 – -118.94 (m, 1F), -122.69 (d, *J* = 11.8 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 332.1, $C_{18}H_{13}ClF_2NO^+$ requires 332.1.

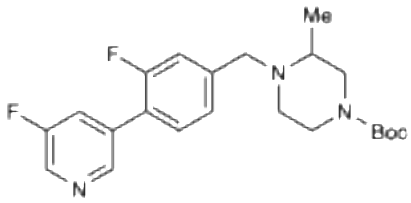
8-(3-fluoropyridin-2-yl)-2-Methylbenzofuro[2,3-*b*]pyridine



Prepared according to general procedure C using 1,1,1-trifluoro-N-((2E,4E)-1-(2-methylbenzofuro[2,3-b]pyridin-8-yl)-5-(phenylamino)penta-2,4-dien-1-ylidene)methanesulfonamide (243 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 0% to 20% EtOAc in hexanes) to afford the title compound as a yellow solid (86.7 mg, 0.32 mmol, 63% yield). mp: 162-165 ºC; IR ν_{max}/cm^{-1} (film): 3065, 2925, 1595, 1444, 1418, 1391, 1193, 1181; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.62 (dt, *J* = 4.6, 1.5 Hz, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 8.02 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.83 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.60 (ddd, *J* = 9.6, 8.4, 1.3 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.42 (dt, *J* = 8.5, 4.3 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.04, 157.58 (d, *J* = 261.2 Hz), 156.66, 151.85, 145.57 (d, *J* = 5.1 Hz), 143.21 (d, *J* = 15.2 Hz), 129.94, 128.69 (d, *J* = 1.6 Hz), 124.32 (d, *J* = 4.0 Hz), 123.85 (d, *J* = 19.8 Hz), 123.44, 123.19, 121.79, 120.72 (d, *J* = 4.2 Hz), 118.88, 113.59, 24.48; ^{19}F NMR (375 MHz, $CDCl_3$) δ -118.71 (dd, *J* = 9.6, 3.9 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 279.1 $C_{17}H_{12}FN_2O^+$ requires 279.1.

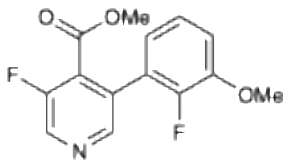
***tert*-Butyl 4-(3-fluoro-4-(5-fluoropyridin-3-yl)benzyl)piperazine-1-carboxylate**



Prepared according to general procedure D (except the fluorination ran at 40 ºC) using tert-butyl 4-(4-((1E,2E,4E)-5-(dibenzylamino)-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-2-yl)-3-fluorobenzyl)-3-methylpiperazine-1-carboxylate (357 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). The crude material was purified by automated flash chromatography (silica gel: 0% to 40% EtOAc in hexanes) to afford the title compound as a yellow oil (50.4 mg, 0.13 mmol, 25% yield). IR ν_{max}/cm^{-1} (film): 2980, 2935, 1685, 1456, 1432, 1406, 1271, 1170; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.40 (d, *J* = 2.8 Hz, 1H), 7.55 (ddt, *J* = 9.6, 3.0, 1.6 Hz, 1H), 7.35 – 7.23 (m, 1H), 7.18 – 7.12 (m, 2H), 3.93 (d, *J* = 14.0 Hz, 1H), 3.75 (s, 1H), 3.60 (dt, *J* = 13.0, 3.3 Hz, 1H), 3.18 (d, *J* = 13.9 Hz, 1H), 3.07 (t, *J* = 11.2 Hz, 1H), 2.85 (s, 1H), 2.60 (dt, *J* = 11.7, 3.9 Hz, 1H), 2.42 (dqd, *J* = 9.3, 6.2, 3.2 Hz, 1H), 2.07 (t, *J* = 10.9 Hz, 1H), 1.39 (s, 9H), 1.05 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.84 (d, *J* = 249.2 Hz),

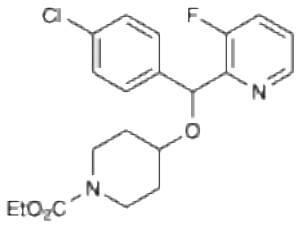
159.28 (d, *J* = 256.5 Hz), 154.74, 145.33 (t, *J* = 3.6 Hz), 142.91 (d, *J* = 7.5 Hz), 138.63, 136.85 (d, *J* = 23.2 Hz), 133.00 (d, *J* = 3.0 Hz), 130.06 (d, *J* = 3.2 Hz), 128.51 (d, *J* = 3.1 Hz), 127.35, 125.01 (d, *J* = 3.2 Hz), 123.06 (dd, *J* = 18.9, 4.0 Hz), 122.64 (dd, *J* = 13.5, 1.2 Hz), 116.51 (d, *J* = 22.6 Hz), 79.64, 57.26, 54.94, 52.32, 28.43; ^{19}F NMR (375 MHz, $CDCl_3$) δ -117.92 (dd, *J* = 11.8, 7.9 Hz, 1F), -127.08 (d, *J* = 9.6 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 404.3, $C_{22}H_{28}F_2N_3O_2^+$ requires 404.2.

Methyl 3-fluoro-5-(2-fluoro-3-methoxyphenyl)isonicotinate



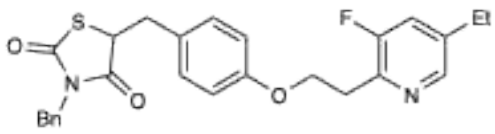
Prepared according to general procedure D (except imine prestirred at r.t. and the fluorination ran at 40 ºC) using methyl (2Z,4Z)-2-((E)-2-(dibenzylamino)vinyl)-3-(2-fluoro-3-methoxyphenyl)-4-(((trifluoromethyl)sulfonyl)imino)but-2-enoate (236 mg, 0.40 mmol), NFSI (176 mg, 0.56 mmol), TFE (4.00 mL, 0.10 M). The crude material was purified by automated flash chromatography (silica gel: 0% to 100% CH_2Cl_2 in hexanes to 10% acetone in CH_2Cl_2) to afford the title compound as a yellow oil (29.2 mg, 0.13 mmol, 26% yield). IR ν_{max}/cm^{-1} (film): 3009, 2955, 1742, 1580, 1485, 1409, 1290, 1274; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.44 (s, 1H), 7.09 (td, *J* = 8.0, 1.5 Hz, 1H), 6.98 (td, *J* = 8.1, 1.6 Hz, 1H), 6.81 (ddd, *J* = 7.8, 6.3, 1.6 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.51, 155.75 (d, *J* = 264.1 Hz), 149.50 (d, *J* = 247.8 Hz), 147.96 (d, *J* = 10.8 Hz), 147.09 (dd, *J* = 4.9, 1.5 Hz), 138.42 (d, *J* = 24.3 Hz), 130.66, 128.08 (d, *J* = 13.7 Hz), 124.34 (d, *J* = 4.8 Hz), 123.69 (dd, *J* = 12.8, 1.3 Hz), 121.85 (d, *J* = 1.4 Hz), 114.06 (d, *J* = 2.0 Hz), 56.35, 52.97; ^{19}F NMR (375 MHz, $CDCl_3$) δ -128.88 (s, 1F), -138.64 (t, *J* = 7.1 Hz, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 280.1, $C_{14}H_{12}F_2NO_3^+$ requires 280.1.

Ethyl 4-((4-chlorophenyl)(3-fluoropyridin-2-yl)methoxy)piperidine-1-carboxylate



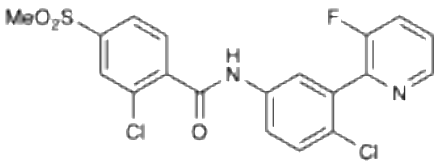
Prepared according to general procedure C using ethyl 4-(((3E,5E)-1-(4-chlorophenyl)-6-(phenylamino)-2-(((trifluoromethyl)sulfonyl)imino)hexa-3,5-dien-1-yl)oxy)piperidine-1-carboxylate (300 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). The crude material was purified by automated flash chromatography (silica gel: 0% to 40% EtOAc in hexanes) to afford the title compound as a yellow oil (116 mg, 0.30 mmol, 59% yield). IR ν_{max}/cm^{-1} (film): 2931, 2869, 1680, 1443, 1274, 1233, 1088, 904; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (dt, *J* = 4.7, 1.5 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.30 (ddd, *J* = 9.8, 8.3, 1.4 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.17 (dt, *J* = 8.5, 4.4 Hz, 1H), 5.84 (s, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 2H), 3.55 (tt, *J* = 7.8, 3.6 Hz, 1H), 3.13 – 3.01 (m, 2H), 1.80 – 1.71 (m, 2H), 1.58 (dddq, *J* = 16.9, 12.7, 8.4, 4.0 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ157.29 (d, *J* = 259.5 Hz), 155.51, 148.53 (d, *J* = 12.4 Hz), 145.35 (d, *J* = 5.2 Hz), 138.56, 133.49, 128.50, 128.22, 124.27 (d, *J* = 3.9 Hz), 123.69 (d, *J* = 19.1 Hz), 76.06, 73.37, 61.25, 41.13 (d, *J* = 3.5 Hz), 31.06, 14.69; ^{19}F NMR (375 MHz, $CDCl_3$) δ -124.89 (s, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 393.2, $C_{20}H_{23}ClFN_2O_3^+$ requires 393.1.

3-Benzyl-5-(4-(2-(5-ethyl-3-fluoropyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione



Prepared according to general procedure C using N-((4E,6E)-1-(4-((3-benzyl-2,5-dioxothiazolidin-4-yl)methyl)phenoxy)-6-((phenylamino)methylene)oct-4-en-3-ylidene)-1,1,1-trifluoromethanesulfonamide (269 mg, 0.40 mmol), Na_2CO_3 (84.8 mg, 0.80 mmol), Selectfluor (184 mg, 0.52 mmol), MeOH (20.0 mL, 0.02 M), NH_4OAc (308 mg, 4.00 mmol). The crude material was purified by automated flash chromatography (1st column: silica gel, 0% to 20% EtOAc in hexanes; 2nd column: silica gel, 0% to 1% MeOH in CH_2Cl_2) to afford the title compound as a yellow solid (58.1 mg, 0.13 mmol, 25% yield). mp: 93-96 ºC; IR ν_{max}/cm^{-1} (film): 2979, 2921, 1694, 1461, 1443, 1223, 1116, 997; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, *J* = 1.8 Hz, 1H), 7.21 – 7.12 (m, 6H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 4.68 – 4.52 (m, 2H), 4.35 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.25 (t, *J* = 6.9 Hz, 2H), 3.31 (dd, *J* = 14.2, 3.9 Hz, 1H), 3.22 (td, *J* = 6.9, 2.2 Hz, 2H), 3.00 (dd, *J* = 14.2, 8.8 Hz, 1H), 2.59 (q, *J* = 7.6 Hz, 2H), 1.18 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.71, 170.96, 158.17 (d, *J* = 256.6 Hz), 158.17, 144.20, 143.50 (d, *J* = 16.4 Hz), 139.97, 135.01, 130.39, 128.65, 128.62, 128.10, 127.43, 122.69 – 122.14 (m), 114.78, 66.10 (d, *J* = 1.1 Hz), 51.65, 45.15, 37.57, 30.88, 25.42, 15.00; ^{19}F NMR (375 MHz, $CDCl_3$) δ -126.64 (s, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 465.2, $C_{26}H_{26}FN_2O_3S^+$requires 465.2.

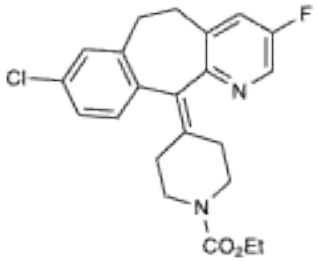
2-Chloro-*N*-(4-chloro-3-(3-fluoropyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide



Prepared according to general procedure C using 2-Chloro-N-(4-chloro-3-((2E,4E)-5-(phenylamino)-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-1-yl)phenyl)-4-(methylsulfonyl)benzamide (323 mg, 0.50 mmol), Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). The crude material

was purified by automated flash chromatography (silica gel: 0% to 20% Et_2O in hexanes) to afford the title compound as a red oil (41.0 mg, 0.10 mmol, 19% yield). IR ν_{max}/cm^{-1} (film): 3313, 2926, 1684, 1587, 1539, 1454, 1317, 1165; ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.25 (d, *J* = 4.7 Hz, 1H), 7.79 (s, 1H), 7.70 – 7.57 (m, 4H), 7.44 (t, *J* = 8.7 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.27 (dt, *J* = 8.5, 4.3 Hz, 1H), 2.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.56, 157.11 (d, *J* = 259.6 Hz), 145.21 (d, *J* = 15.9 Hz), 144.88 (d, *J* = 5.1 Hz), 142.70, 140.56, 136.45, 134.81 (d, *J* = 4.1 Hz), 132.36, 130.35 (d, *J* = 12.9 Hz), 129.09, 128.94, 125.82, 125.00 (d, *J* = 4.0 Hz), 124.10, 123.91, 122.80, 122.11, 44.38; ^{19}F NMR (375 MHz, $CDCl_3$) δ -118.90 (dd, *J* = 9.0, 4.1 Hz); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 439.1, $C_{19}H_{14}Cl_2FN_2O_3S^+$ requires 439.0.

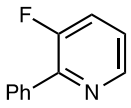
Ethyl 4-(8-chloro-3-fluoro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate



Prepared according to general procedure D (except the fluorination ran at 40 ºC) using Ethyl 4-((6Z,7Z)-2-chloro-7-((E)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl)sulfonyl)imino)-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate (356 mg, 0.50 mmol), NFSI (221 mg, 0.70 mmol), TFE (5.00 mL, 0.10 M). The crude material was purified by automated flash chromatography (silica gel: 0% to 100% CH_2Cl_2 in hexanes to 10% MeOH in CH_2Cl_2) to afford the title compound as a yellow oil (60.1 mg, 0.15 mmol, 30% yield). IR ν_{max}/cm^{-1} (film): 3035, 2927, 1680, 1511, 1418, 1381, 1329, 1247; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 2.9 Hz, 1H), 7.22 – 7.07 (m, 4H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.77 (m, 2H), 3.37 (dddt, *J* = 15.4, 10.6,

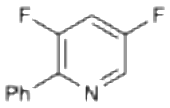
7.9, 3.9 Hz, 2H), 3.16 (ddd, *J* = 13.1, 9.2, 4.1 Hz, 2H), 2.93 – 2.74 (m, 2H), 2.54 – 2.19 (m, 4H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.41 (d, *J* = 256.6 Hz), 155.50, 153.09 (d, *J* = 3.7 Hz), 139.25, 138.19, 137.66, 135.14 (d, *J* = 3.3 Hz), 134.63 (d, *J* = 22.7 Hz), 133.20, 133.09, 130.47, 128.96, 126.36, 124.14 (d, *J* = 17.7 Hz), 61.38, 44.76 (d, *J* = 5.8 Hz), 31.67, 31.30, 30.66 (d, *J* = 25.7 Hz), 14.69; ^{19}F NMR (375 MHz, $CDCl_3$) δ -129.64 (s, 1F); *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 401.2 , $C_{22}H_{23}ClFN_2O_2^+$ requires 401.1.

3-Fluoro-2-phenylpyridine



Prepared according to general procedure E using 2-phenylpyridine (72 µL, 0.50 mmol), EtOAc (2.5 mL, 0.20 M), Tf_2O (84 µL, 0.50 mmol), collidine (66.0 µL, 0.50 mmol), and aniline (46.0 µL, 0.50 mmol). Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Crude ^{1}H NMR showed 68% of the title compound compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv). The analytical data match the product synthesized by a two-pot process.

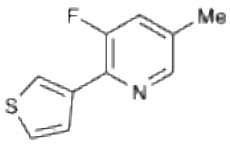
3,5-Difluoro-2-phenylpyridine



Prepared according to general procedure E using 5-fluoro-2-phenylpyridine (87.0 mg, 0.50 mmol), EtOAc (2.50 mL, 0.20 M), Tf_2O (84.0 µL, 0.50 mmol), collidine (66.0 µL, 0.50 mmol), and aniline (46.0 µL, 0.50 mmol); Na_2CO_3 (106 mg, 1.00 mmol). Crude ^{1}H NMR showed 53% of the product compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv). Reaction mixture

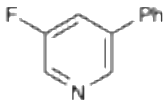
was used directly in the fluorination without purification. Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Crude ^1H NMR showed 20% of the title compound compared to the internal standard mesitylene. The analytical data match the product synthesized by a two-pot process.

3-Fluoro-5-methyl-2-(thiophen-3-yl)pyridine



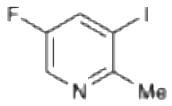
Prepared according to general procedure E using 5-methyl-2-(thiophen-3-yl)pyridine (88.0 mg, 0.50 mmol), EtOAc (2.50 mL, 0.20 M), Tf_2O (84.0 µL, 0.50 mmol), collidine (66.0 µL, 0.50 mmol), and aniline (46.0 µL, 0.50 mmol); Na_2CO_3 (106 mg, 1.00 mmol), Crude ^1H NMR showed 78% of **1p** compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv) after ring opening. Reaction mixture was used directly in the fluorination without purification. Na_2CO_3 (106 mg, 1.00 mmol), Selectfluor (230 mg, 0.65 mmol), MeOH (25.0 mL, 0.02 M), NH_4OAc (386 mg, 5.00 mmol). Crude ^1H NMR showed 56% of the title compound compared to the internal standard mesitylene. The crude material was purified by automated flash chromatography. (silica gel: 0% to 20%CH_2Cl_2 in hexanes) to afford the title compound as a yellow oil (34.0 mg, 0.18 mmol, 35% yield). The analytical data match the product synthesized by a two-pot process.

3-Fluoro-5-phenylpyridine



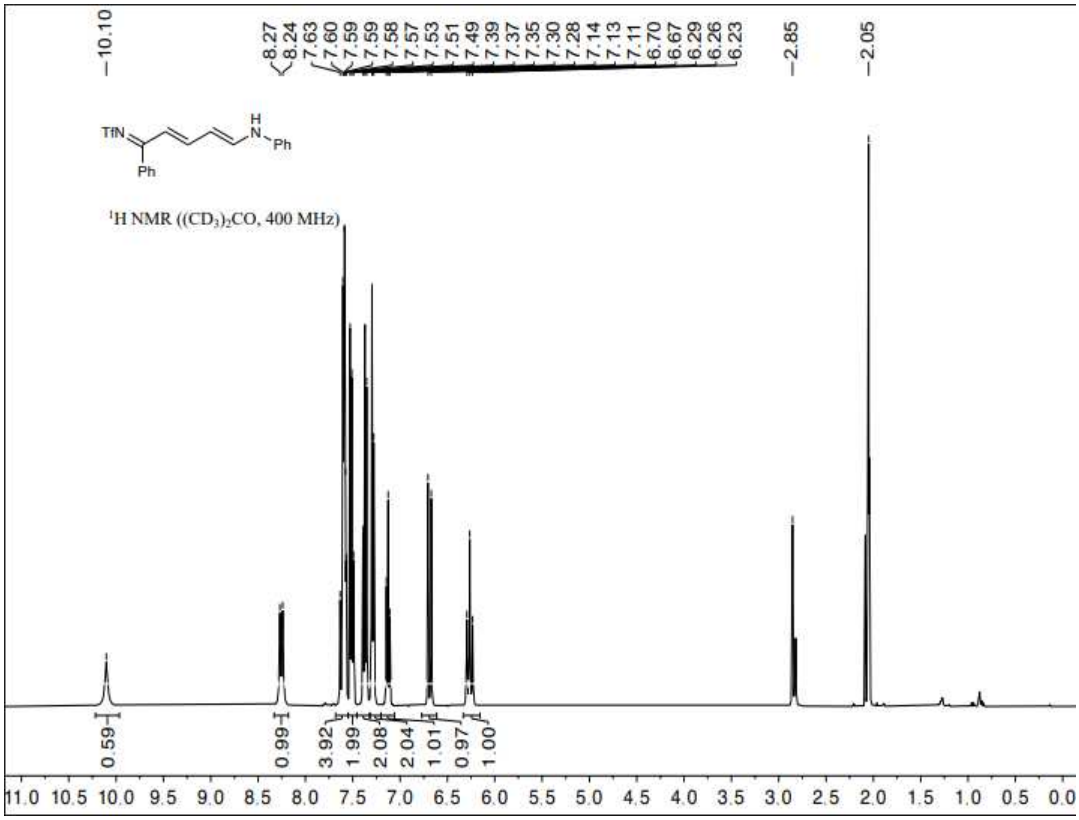
Prepared according to general procedure E using 3-phenylpyridine (72.0 µL, 0.50 mmol), EtOAc (2.50 mL, 0.20 M), Tf_2O (84.0 µL, 0.50 mmol), collidine (66.0 µL, 0.50 mmol), and dibenzylamine (116 µL, 0.60 mmol). Crude ^1H NMR showed 92% of the product compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv). Reaction mixture was used directly in the fluorination without purification. TFE (5.00 mL, 0.10 M), NFSI (221 mg, 0.70 mmol). Crude ^1H NMR showed 69% of the title compound compared to the internal standard mesitylene. The crude material was purified by automated flash chromatography (silica gel: 0% to 10% EtOAc in hexanes) to afford the title compound as a yellow oil (34.4 mg, 0.20 mmol, 40% yield). The analytical data match the product synthesized by a two-pot process.

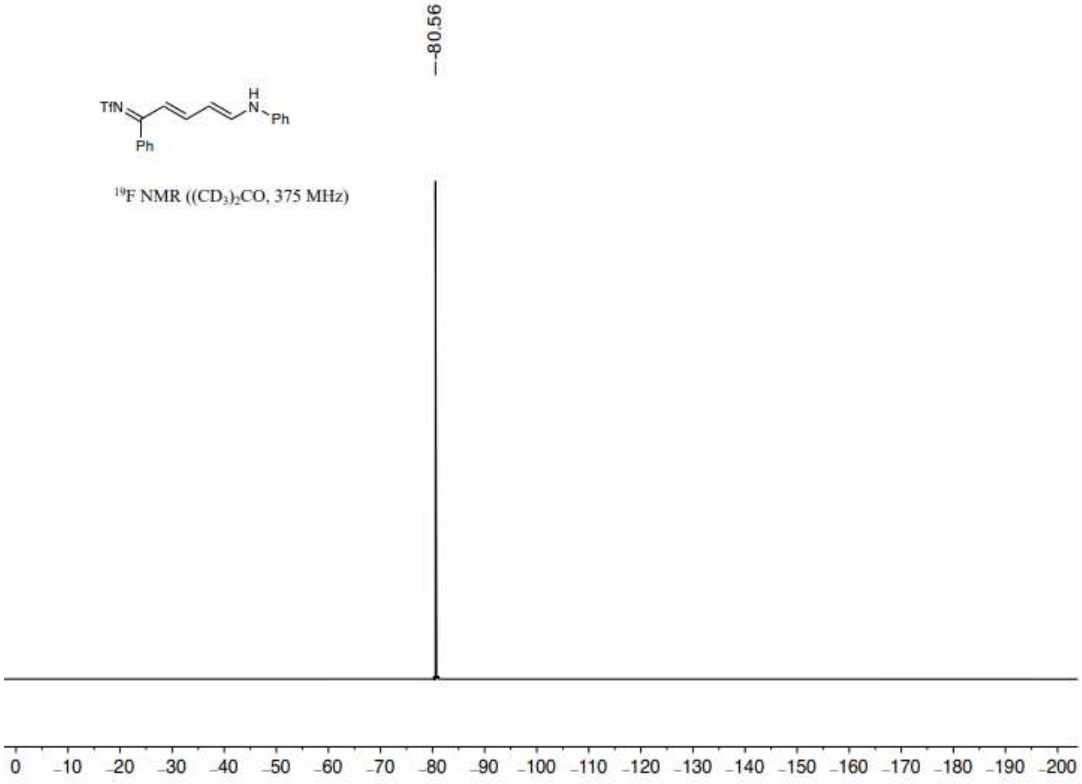
5-Fluoro-3-iodo-2-methylpyridine

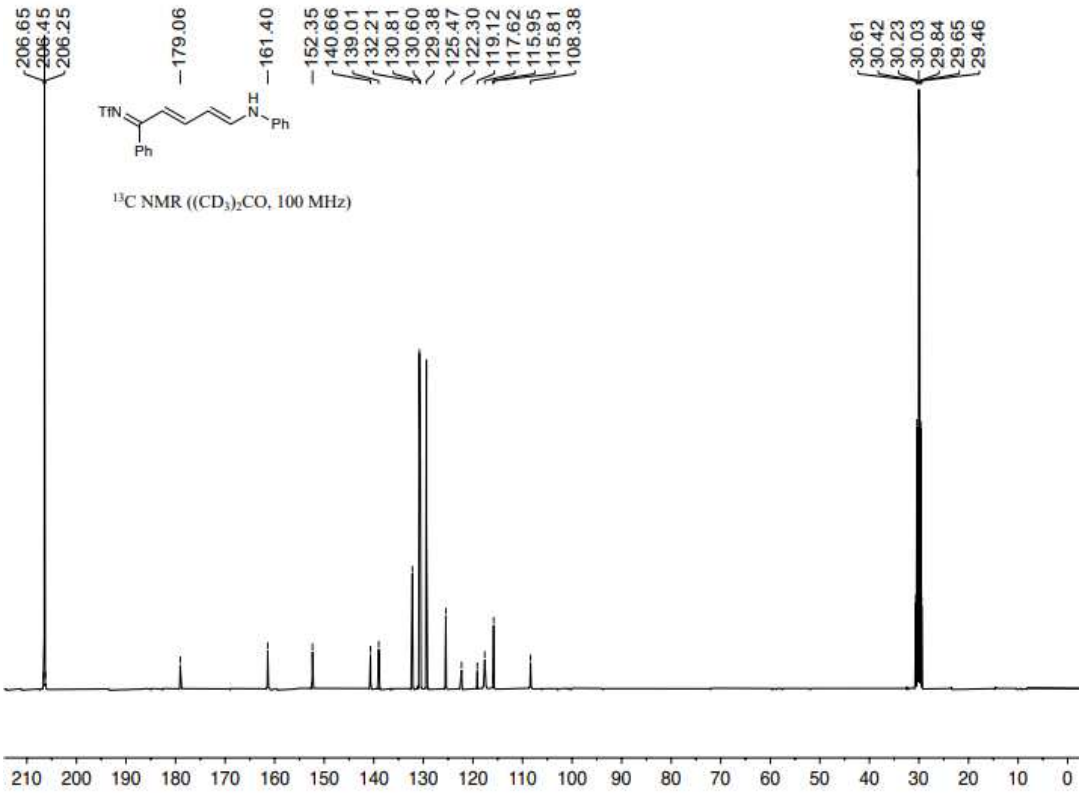


Prepared according to general procedure E using 3-iodo-2-methylpyridine (110 mg, 0.50 mmol), EtOAc (2.50 mL, 0.20 M), Tf_2O (84.0 µL, 0.50 mmol), collidine (66.0 µL, 0.50 mmol), and dibenzylamine (116 µL, 0.60 mmol). Crude ^1H NMR showed 76% of the product compared to the internal standard mesitylene (70.0 µL, 0.50 mmol, 1.0 equiv). Reaction mixture was used directly in the fluorination without purification. TFE (5.00 mL, 0.10 M), NFSI (221 mg, 0.70 mmol). Crude ^1H NMR showed 43% of the title compound compared to the internal standard mesitylene. The analytical data match the product synthesized by a two-pot process.

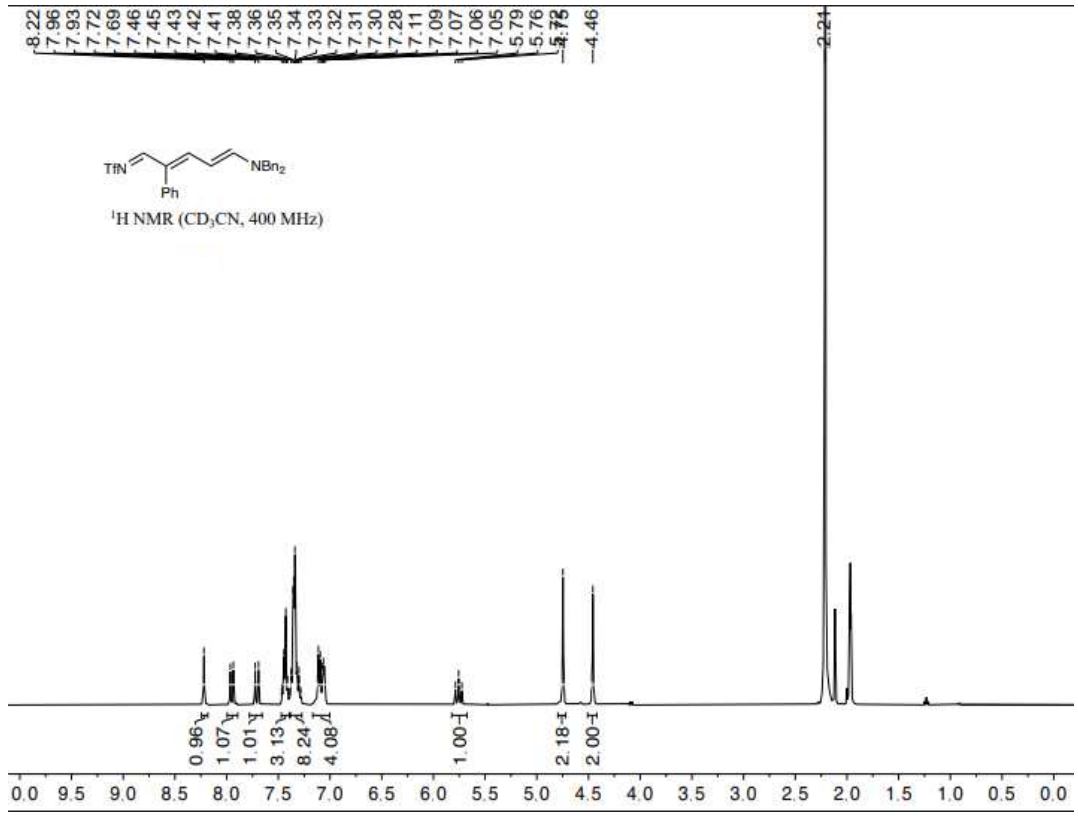
A 1.4 NMR Spectra


10.10
8.27
8.24
7.63
7.60
7.59
7.59
7.58
7.57
7.53
7.51
7.49
7.39
7.37
7.35
7.30
7.28
7.14
7.13
7.11
6.70
6.67
6.29
6.26
6.23
2.85
2.05
TfN
H
N
Ph
Ph
^{1}H NMR ((CD$_3$)$_2$CO, 400 MHz)
0.59
0.99
3.92
1.99
2.08
2.04
1.01
0.97
1.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

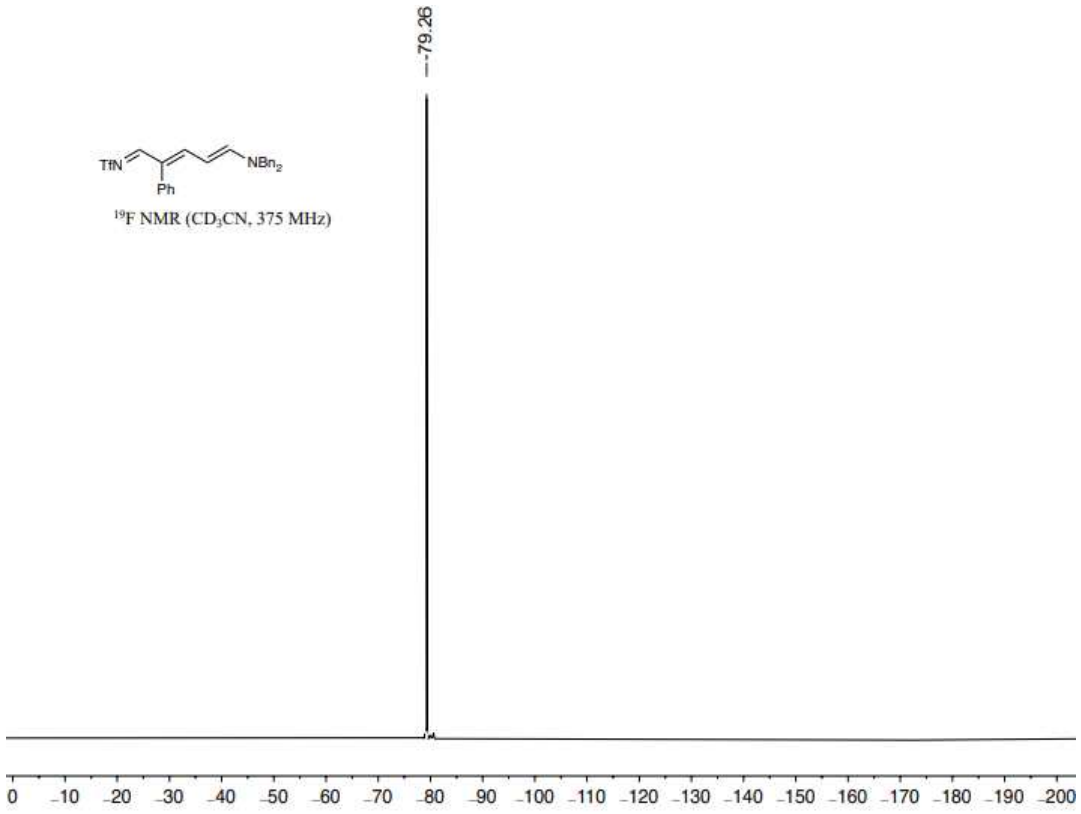

80.56
TfN
H
N
Ph
Ph
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200



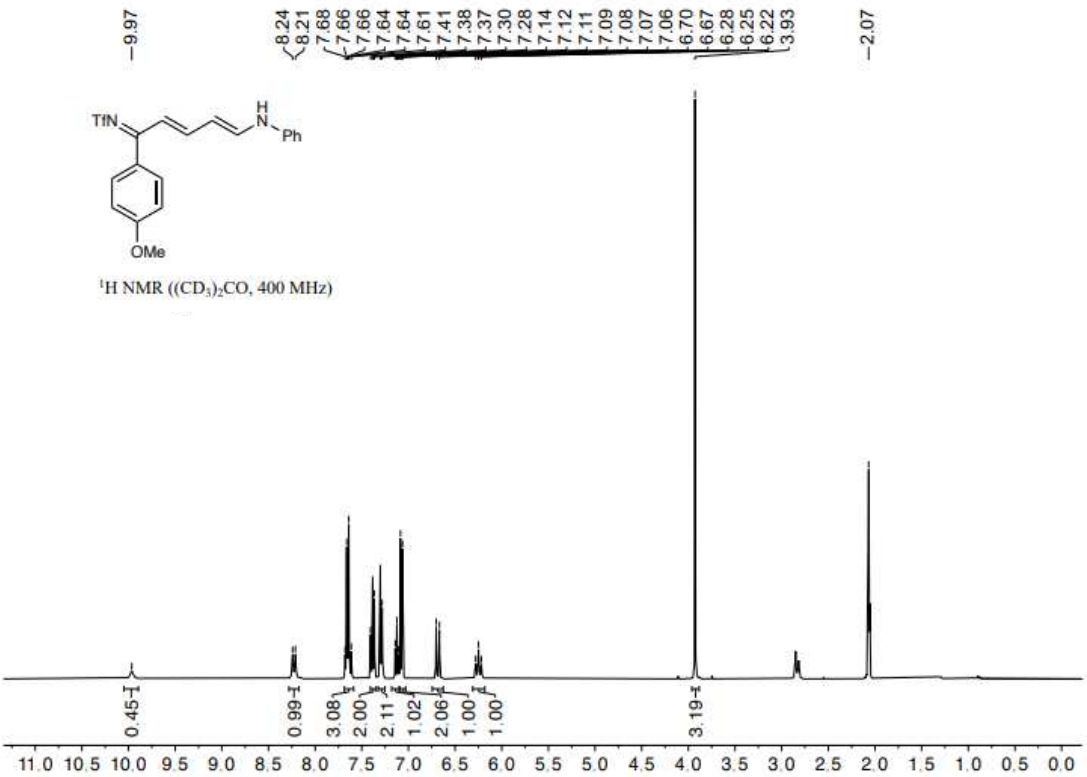
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)



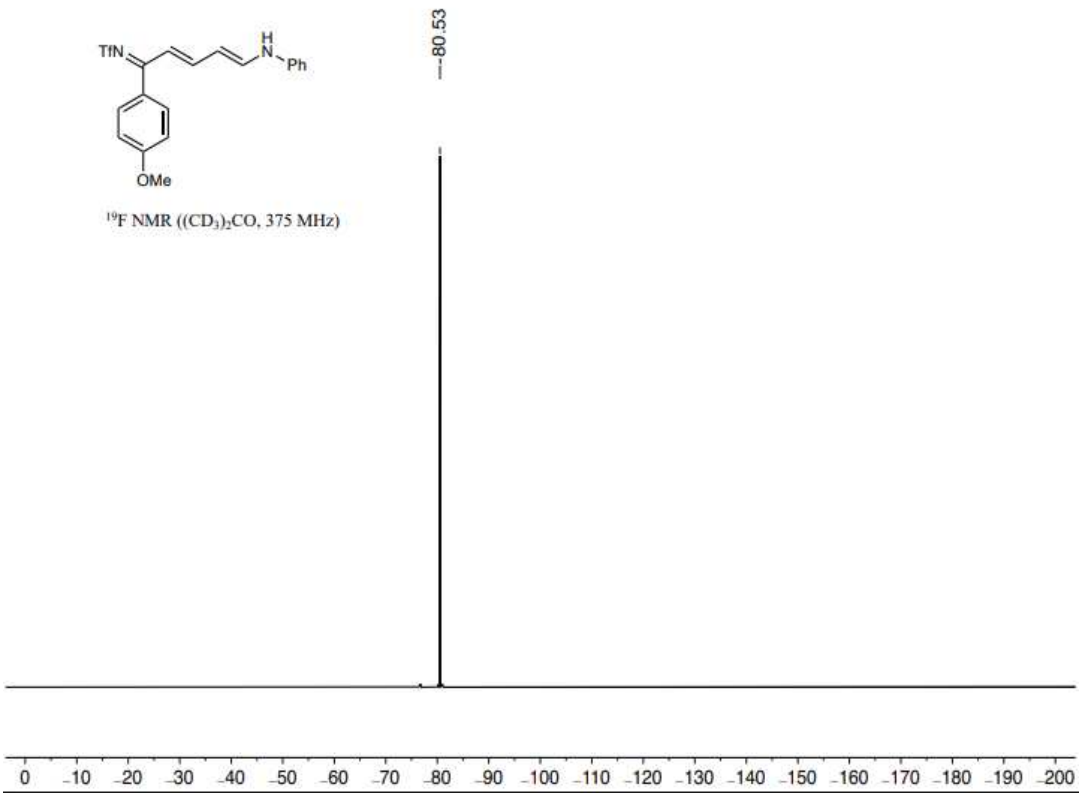
^{1}H NMR (CD$_3$CN, 400 MHz)



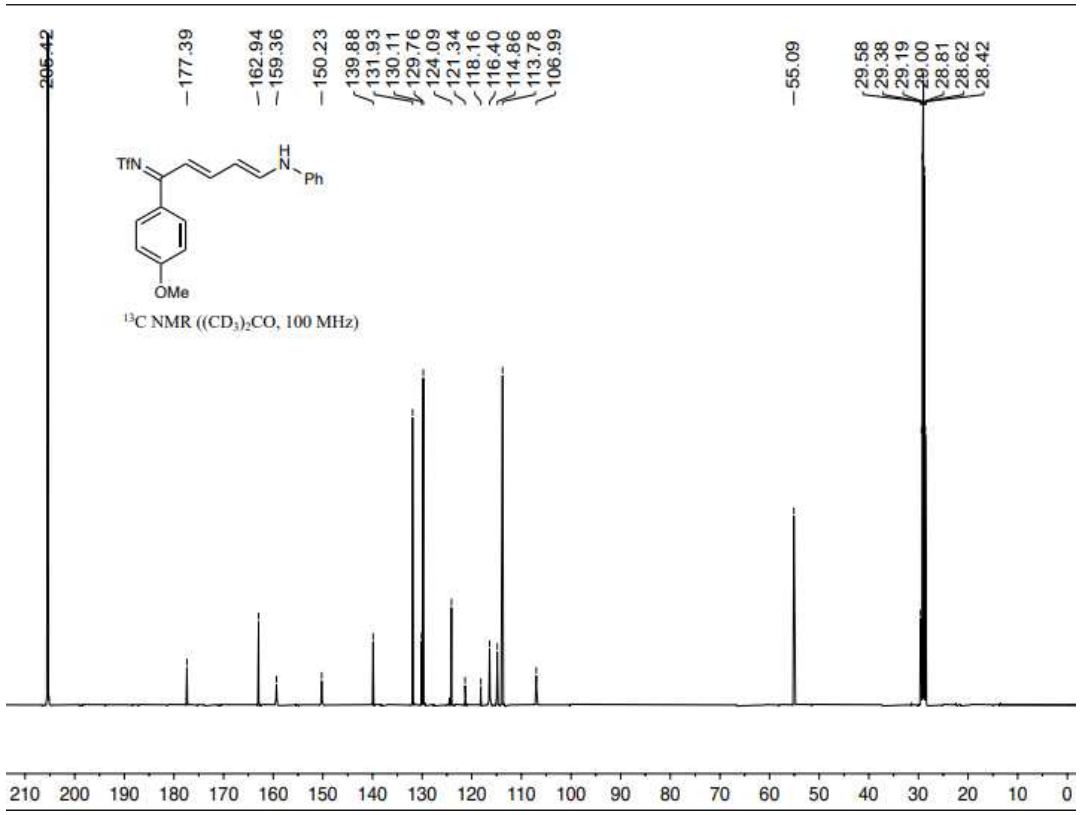
^{19}F NMR (CD_3CN, 375 MHz)



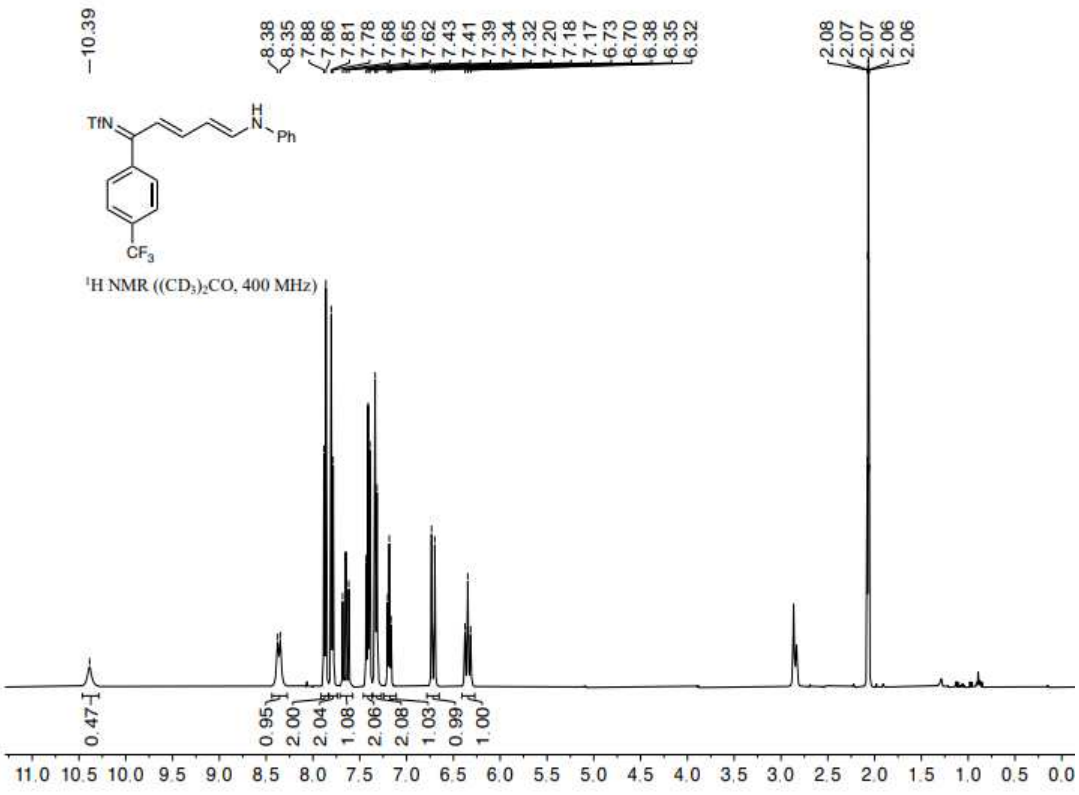
^{1}H NMR ($(CD_3)_2CO$, 400 MHz)

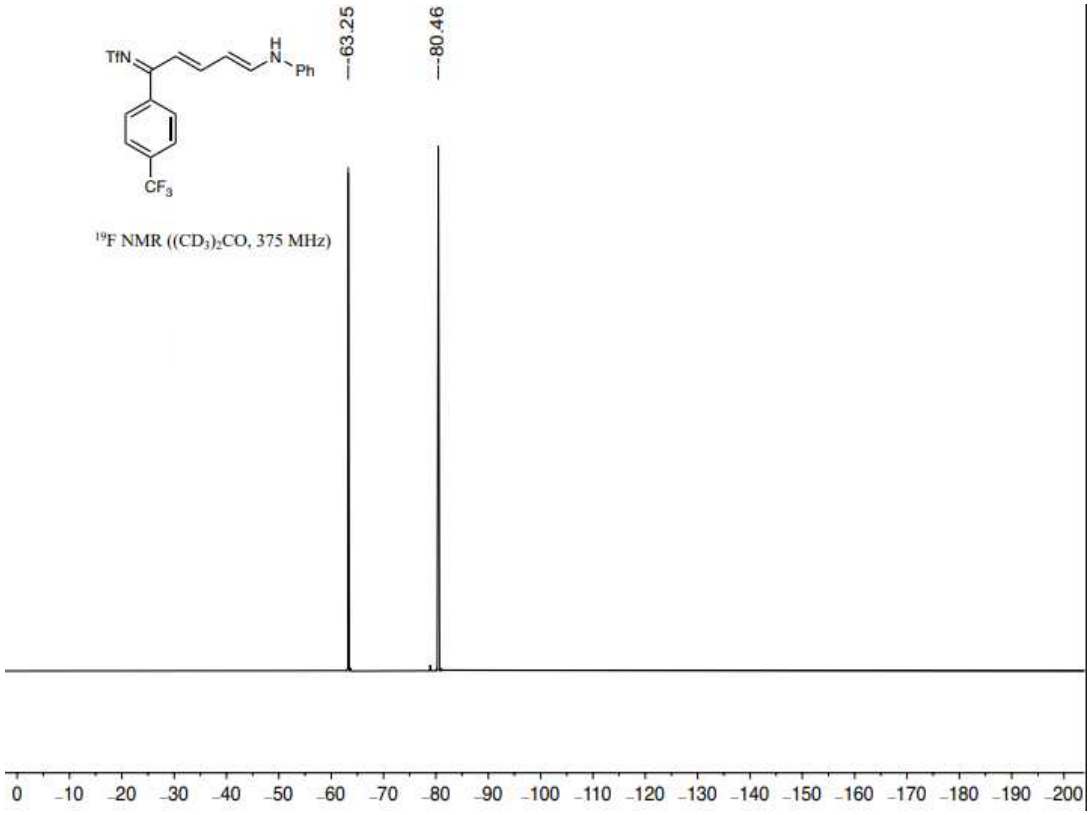


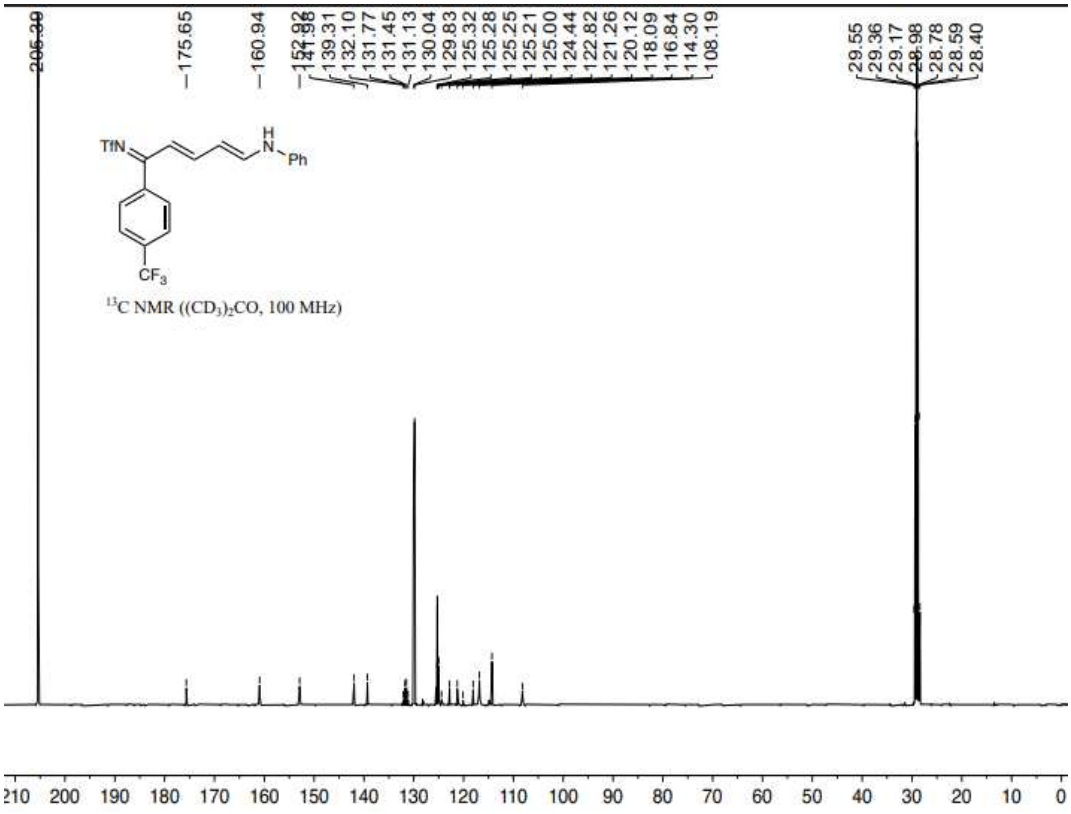
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)

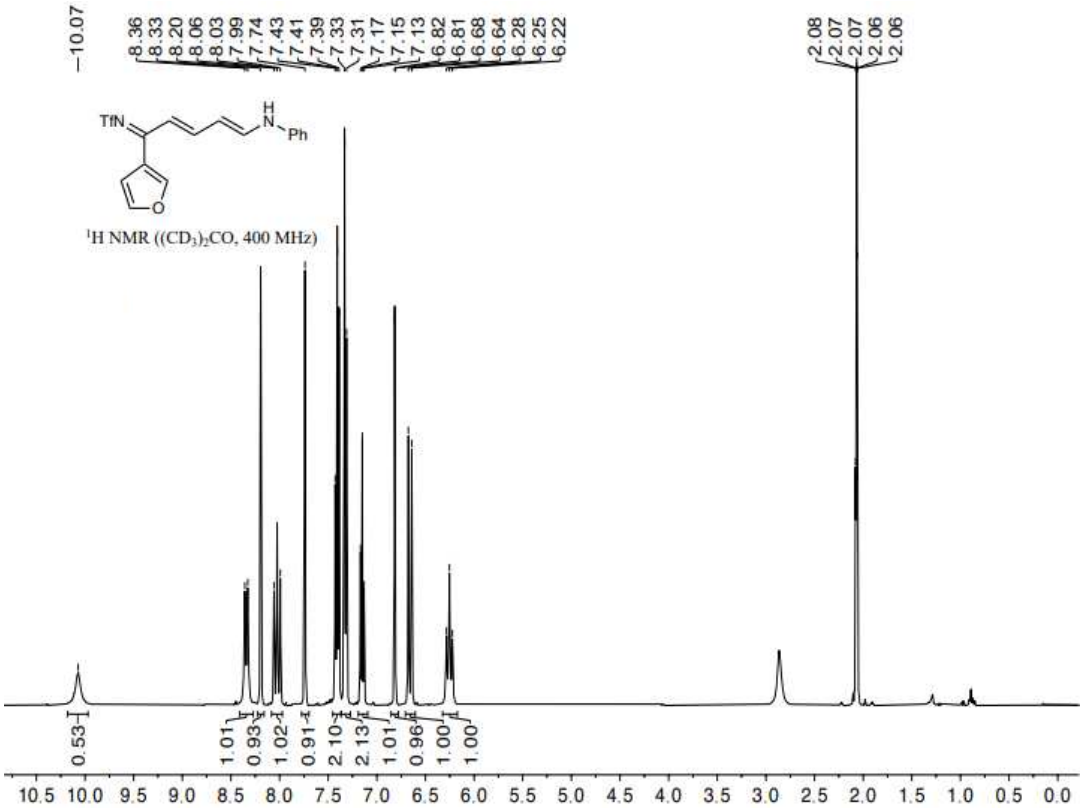


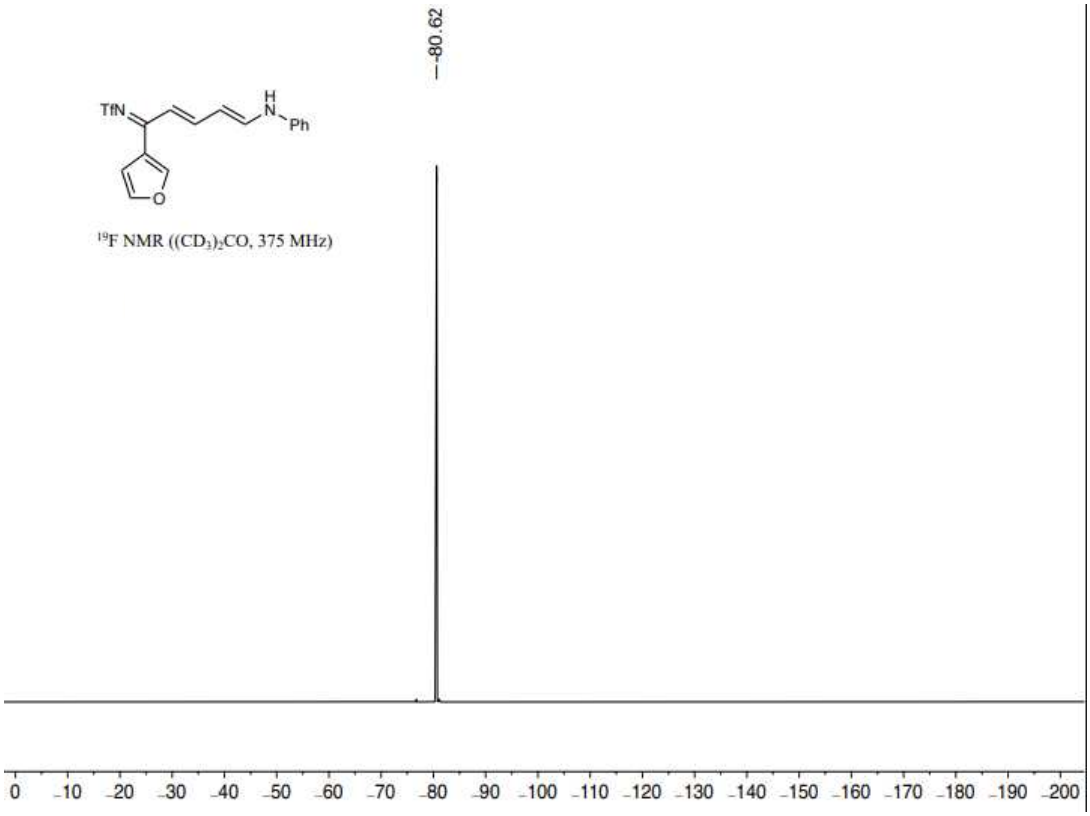
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)


10.39
8.38
8.35
7.88
7.86
7.81
7.78
7.68
7.65
7.62
7.43
7.41
7.39
7.34
7.32
7.20
7.18
7.17
6.73
6.70
6.38
6.35
6.32
2.08
2.07
2.07
2.06
2.06
TfN
Ph
CF3
1H NMR ((CD3)2CO, 400 MHz)
0.47
0.95
2.00
2.04
1.08
2.06
2.08
1.03
0.99
1.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

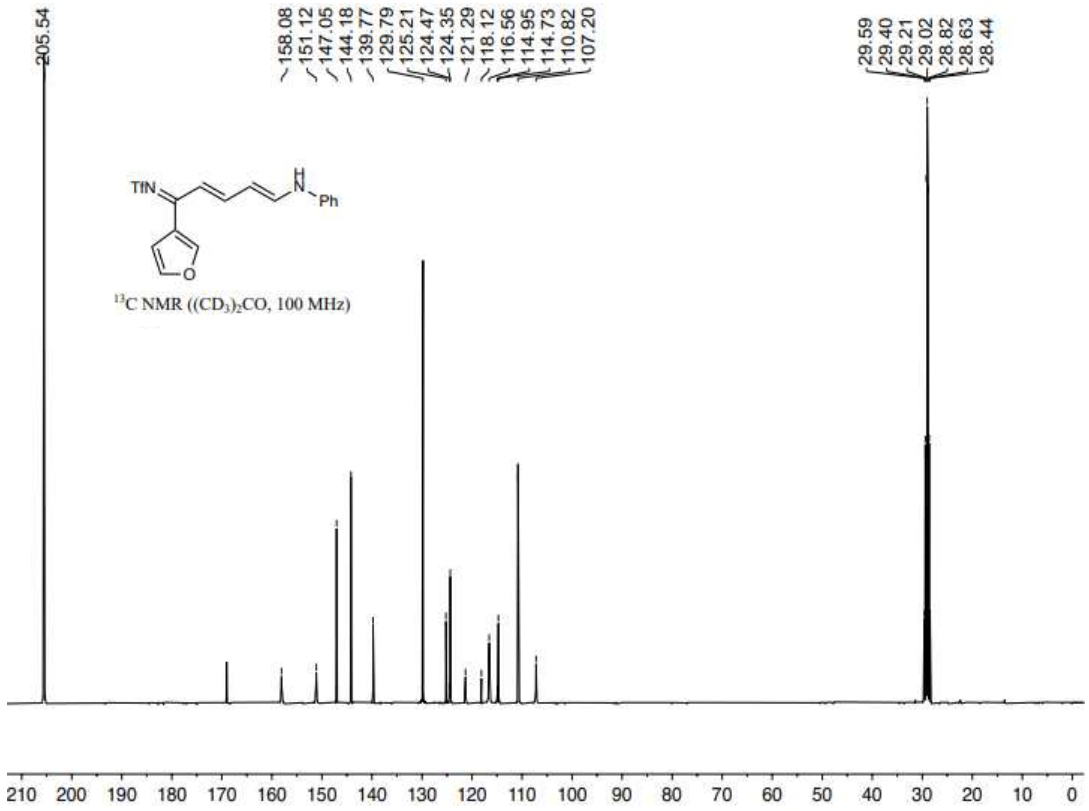

TfN
Ph
CF3
63.25
80.46
19F NMR ((CD3)2CO, 375 MHz)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200


206.30
175.65
160.94
152.92
141.98
139.31
132.10
131.77
131.45
131.13
130.04
129.83
125.32
125.28
125.25
125.21
125.00
124.44
122.82
121.26
120.12
118.09
116.84
114.30
108.19
29.55
29.36
29.17
28.98
28.78
28.59
28.40
TfN
H
N
Ph
CF3
13C NMR ((CD3)2CO, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

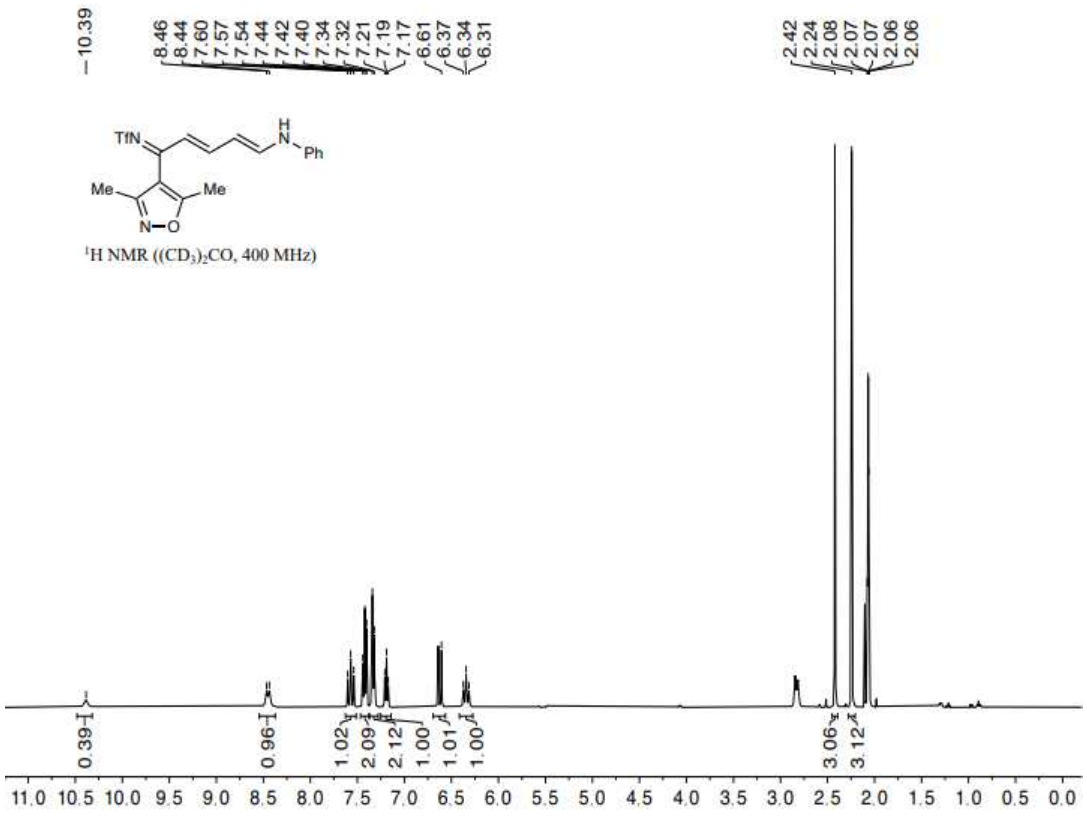

10.07
8.36
8.33
8.20
8.06
8.03
7.99
7.74
7.43
7.41
7.39
7.33
7.31
7.17
7.15
7.13
6.82
6.81
6.68
6.64
6.28
6.25
6.22
2.08
2.07
2.07
2.06
2.06
TfN
H
N
Ph
O
1H NMR ((CD3)2CO, 400 MHz)
0.53
1.01
0.93
1.02
0.91
2.10
2.13
1.01
0.96
1.00
1.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0



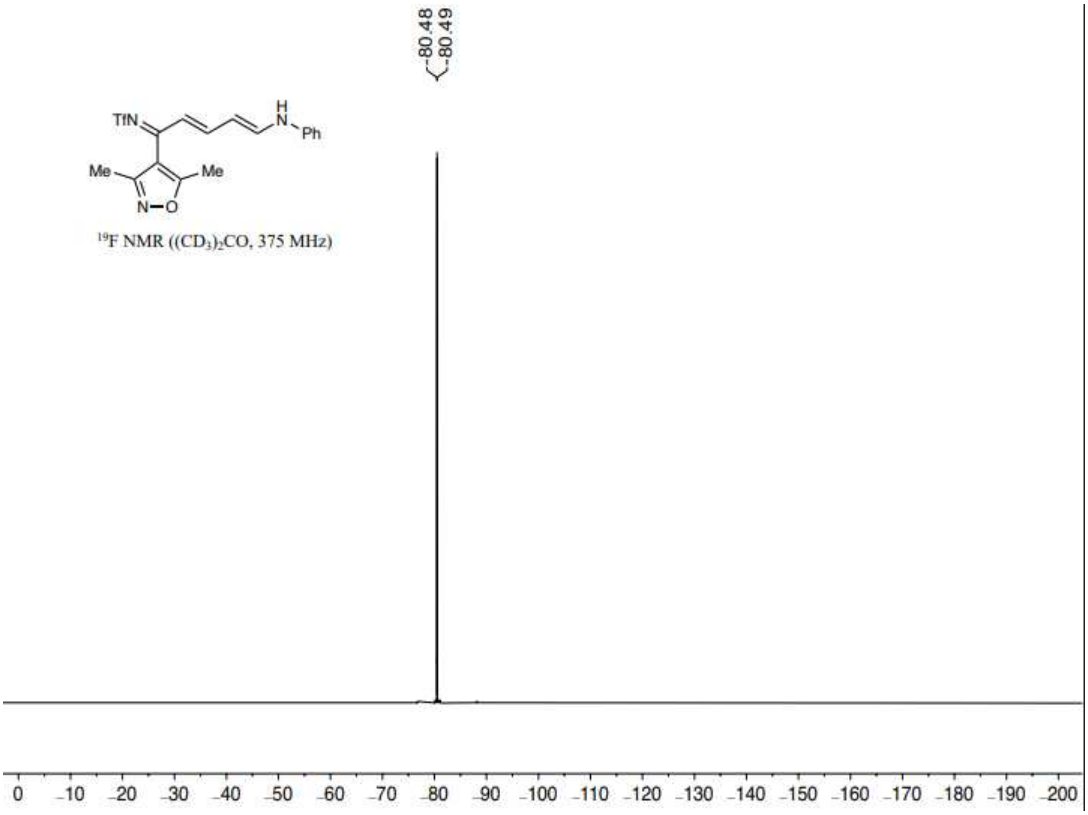
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)



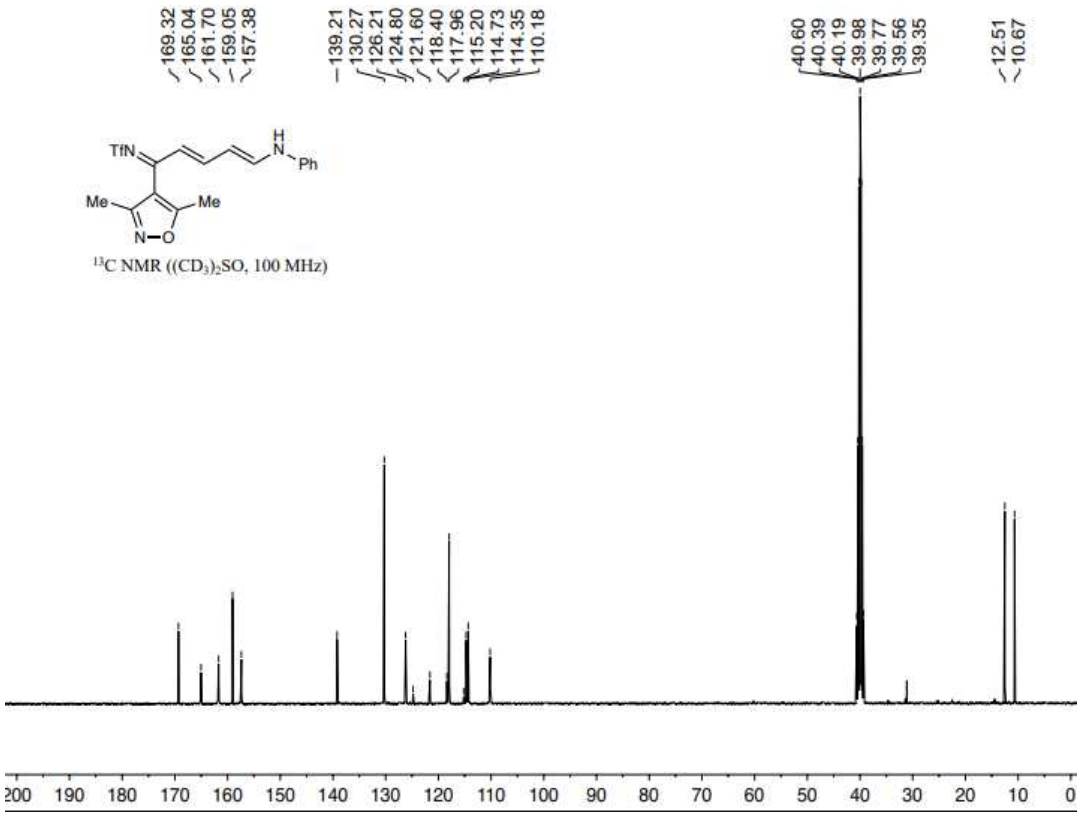
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)



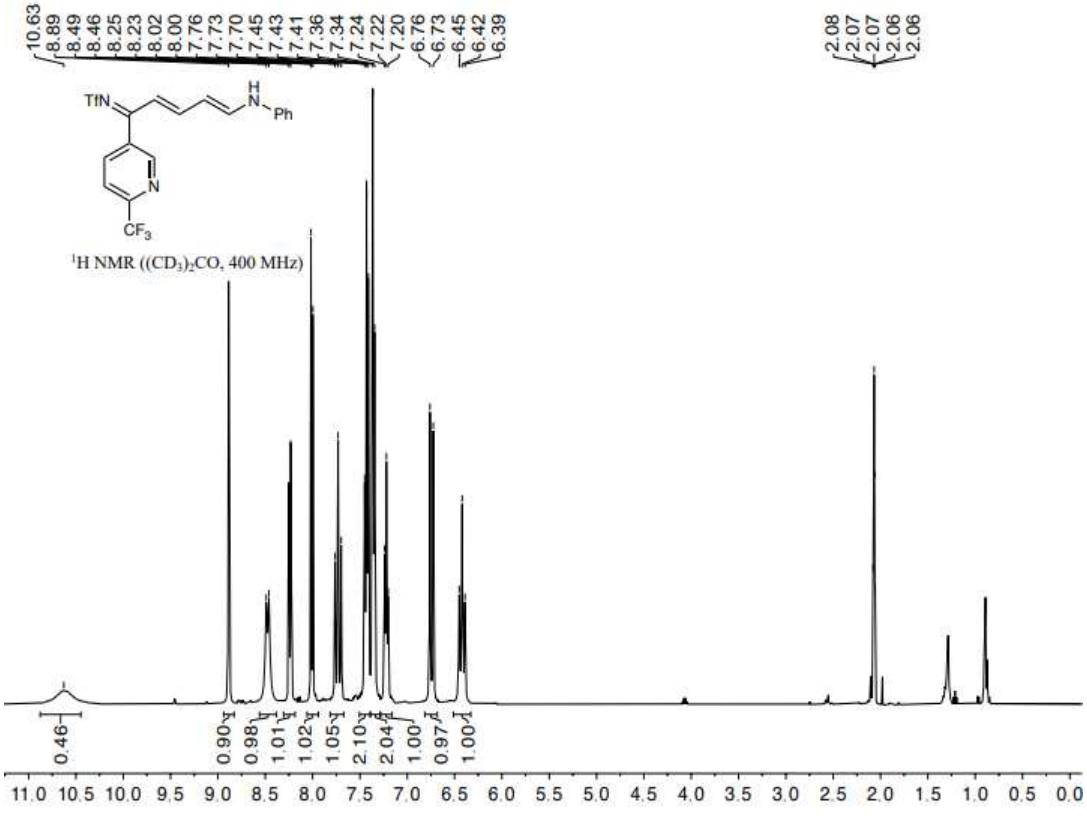
^{1}H NMR ((CD$_3$)$_2$CO, 400 MHz)



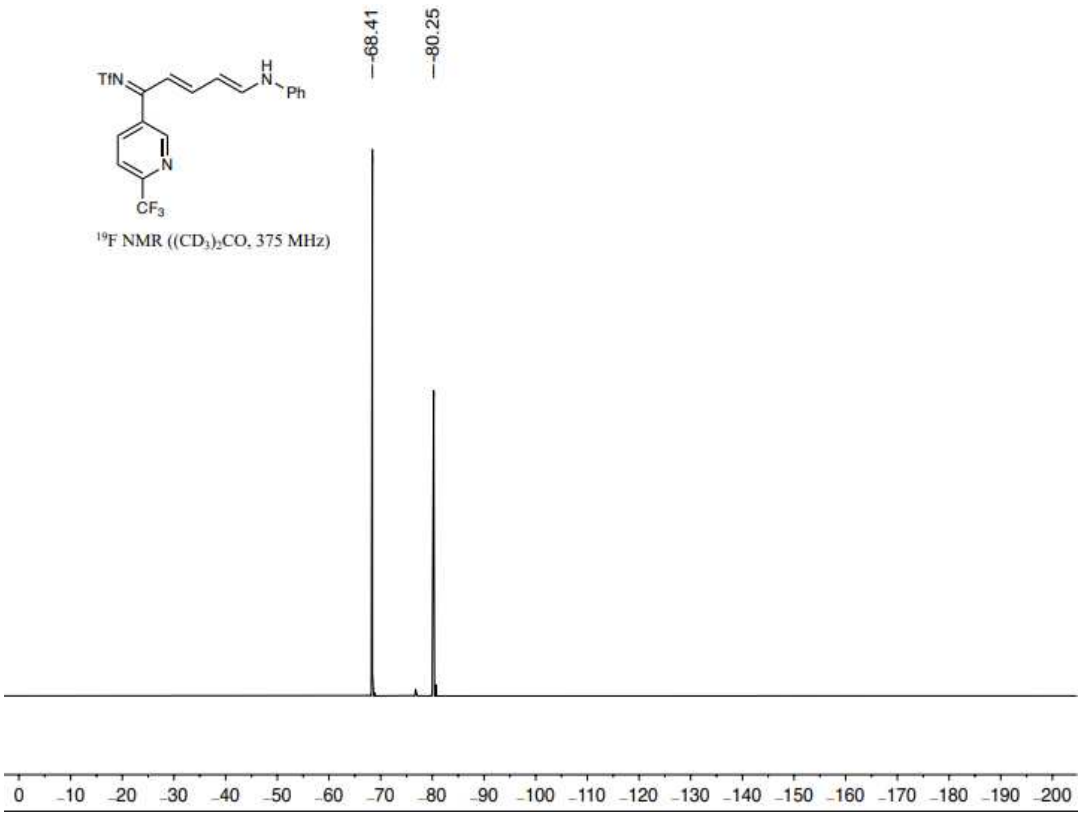
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)



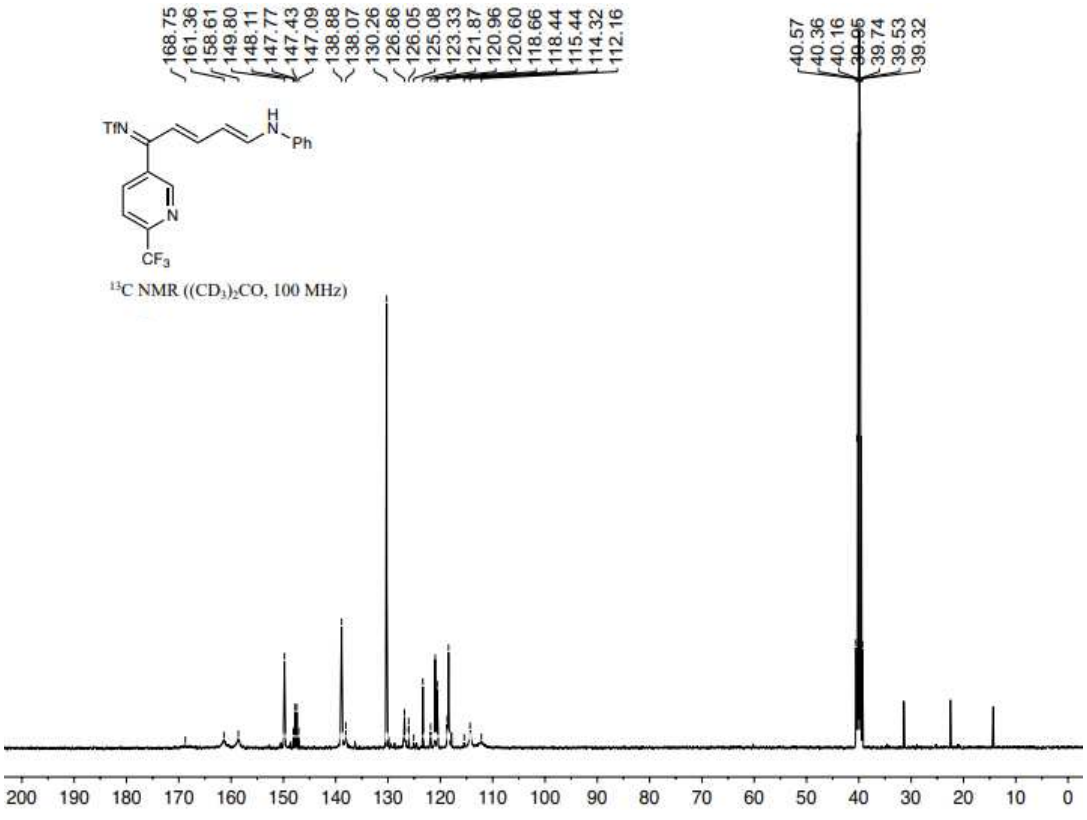
^{13}C NMR ((CD$_3$)$_2$SO, 100 MHz)



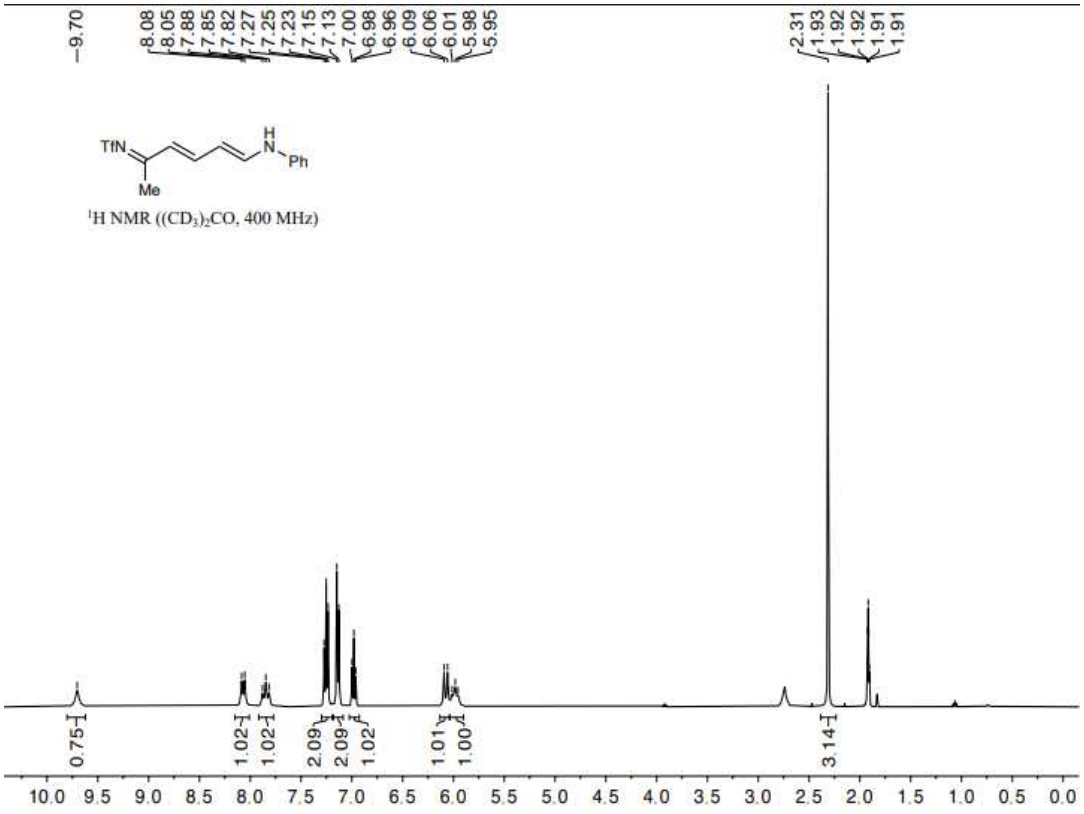
^{1}H NMR ((CD$_3$)$_2$CO, 400 MHz)



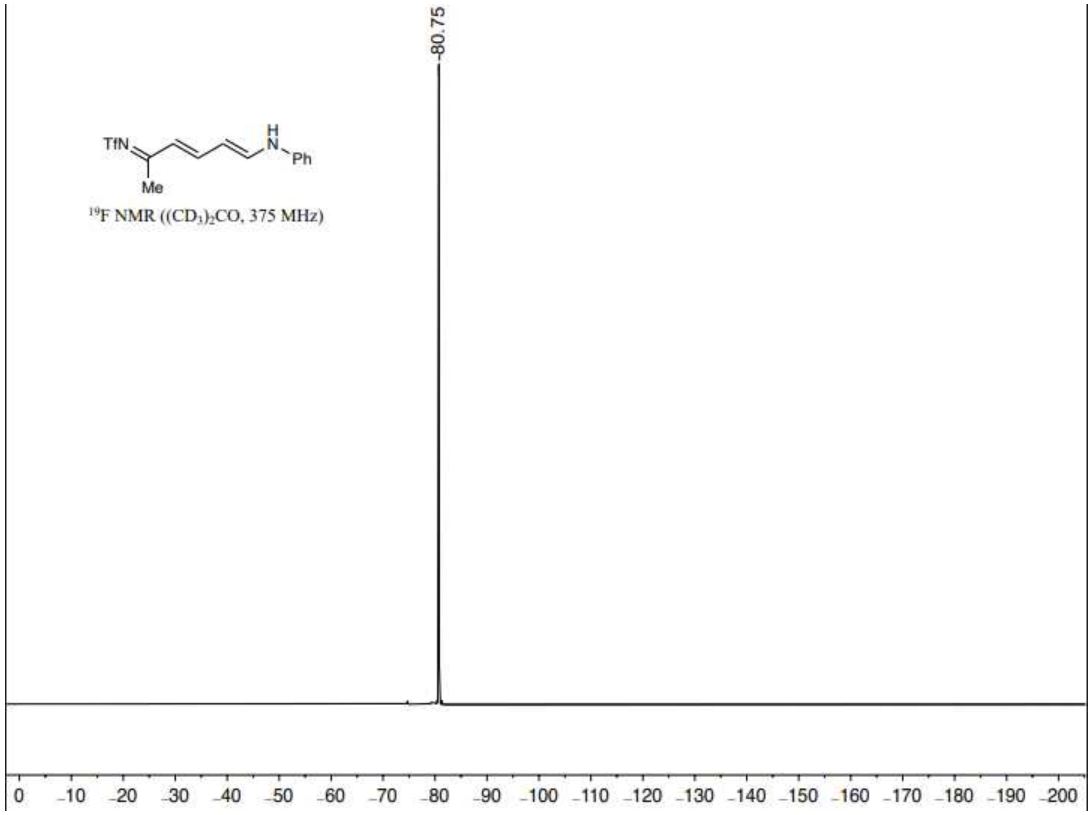
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)



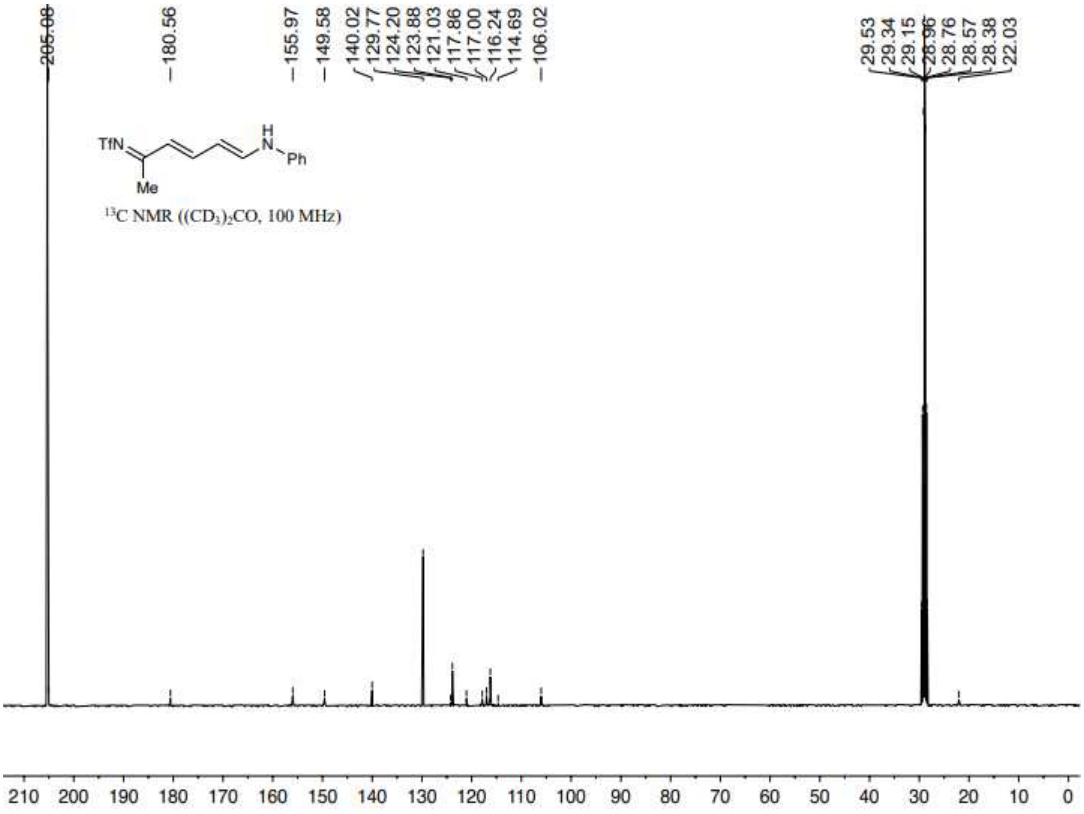
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)



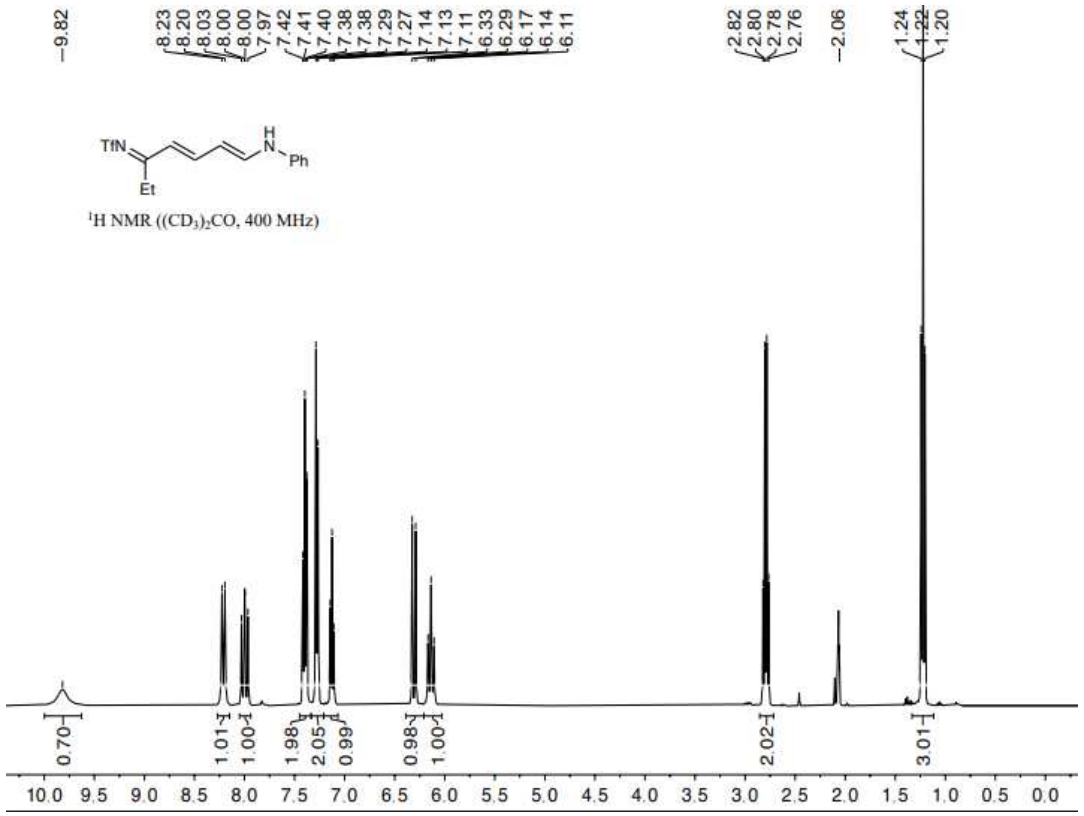
^{1}H NMR ((CD$_3$)$_2$CO, 400 MHz)



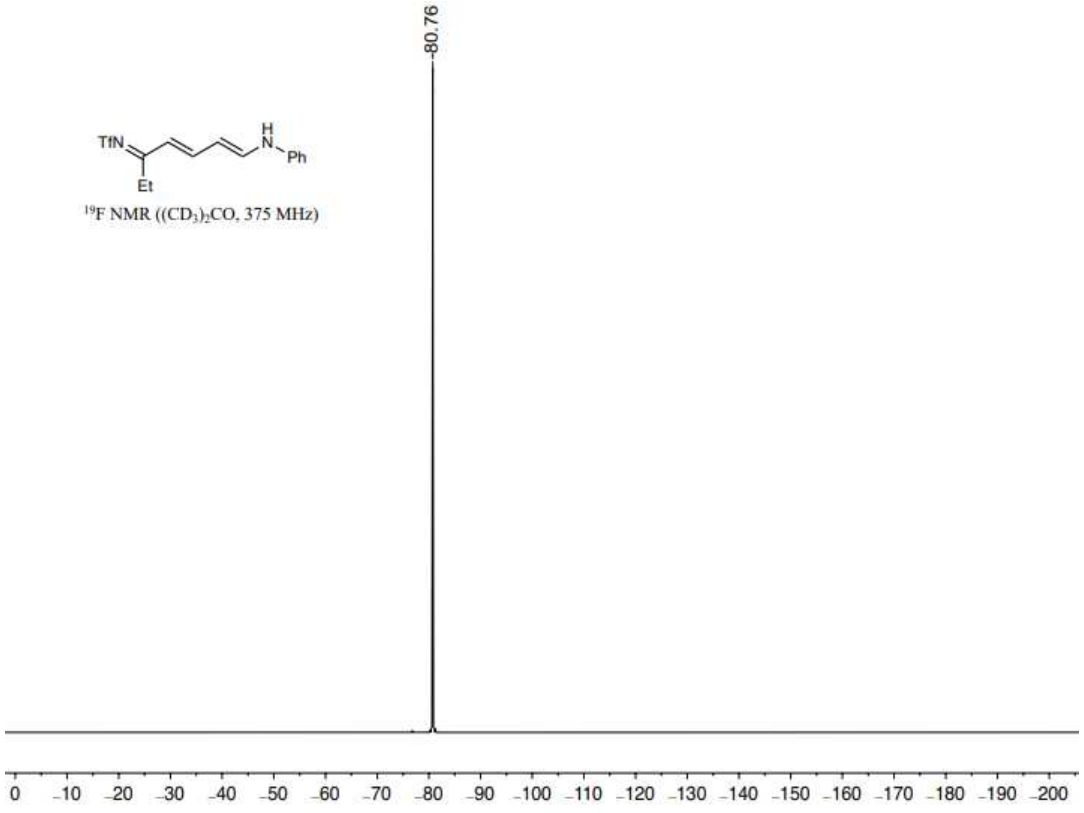
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)



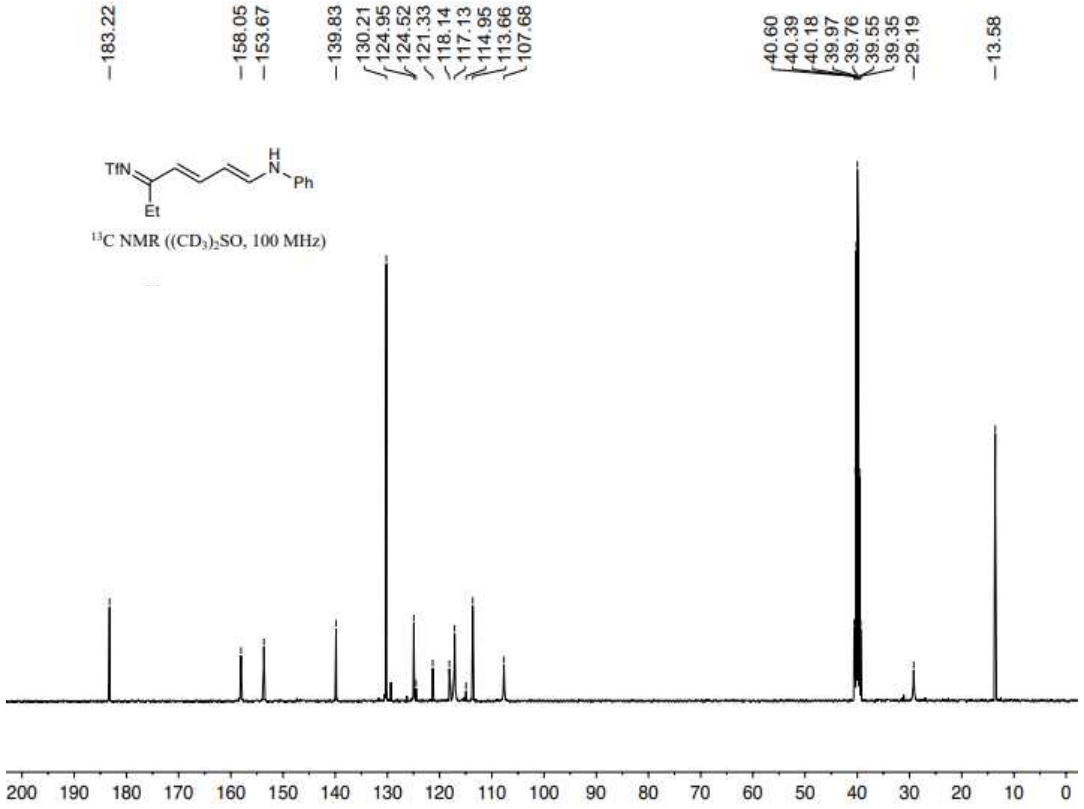
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)



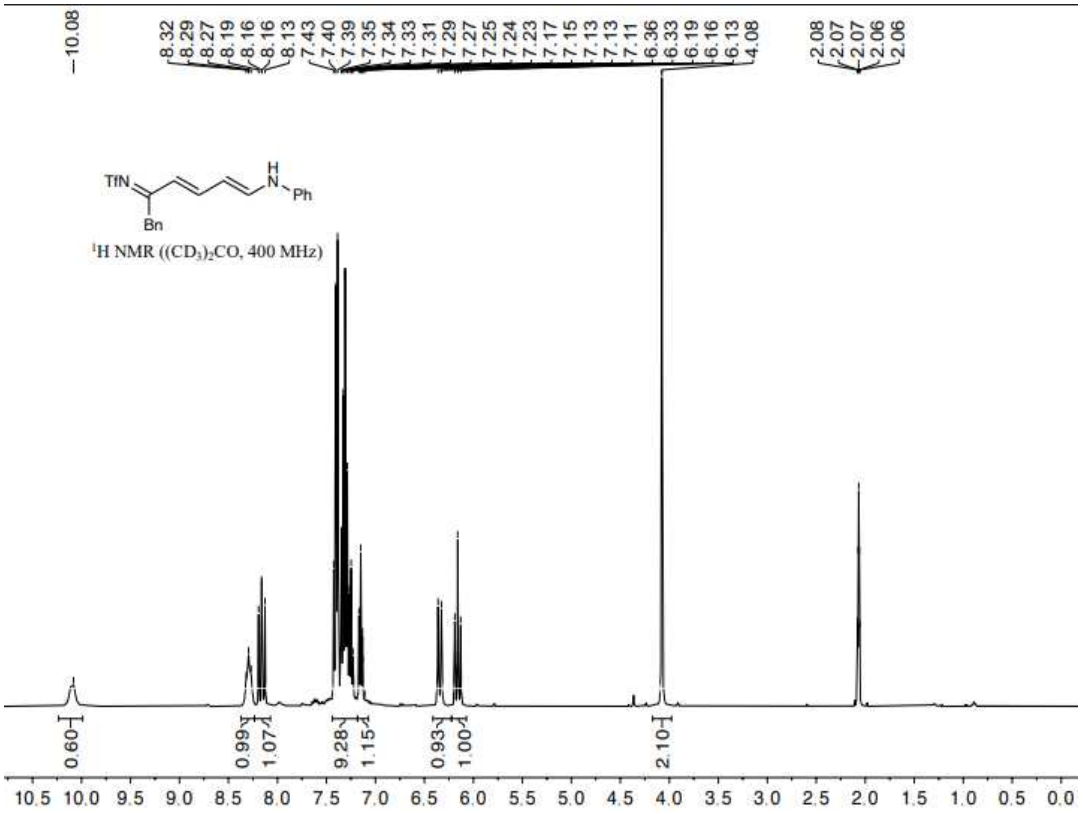
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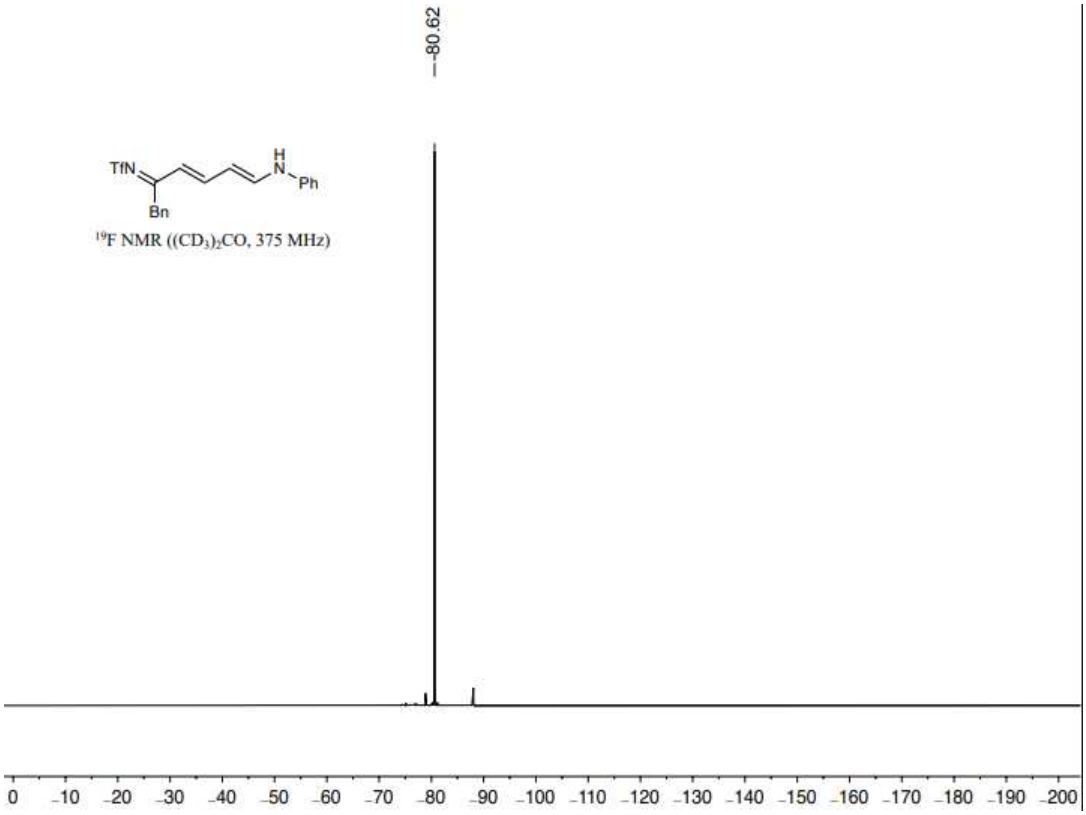
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)



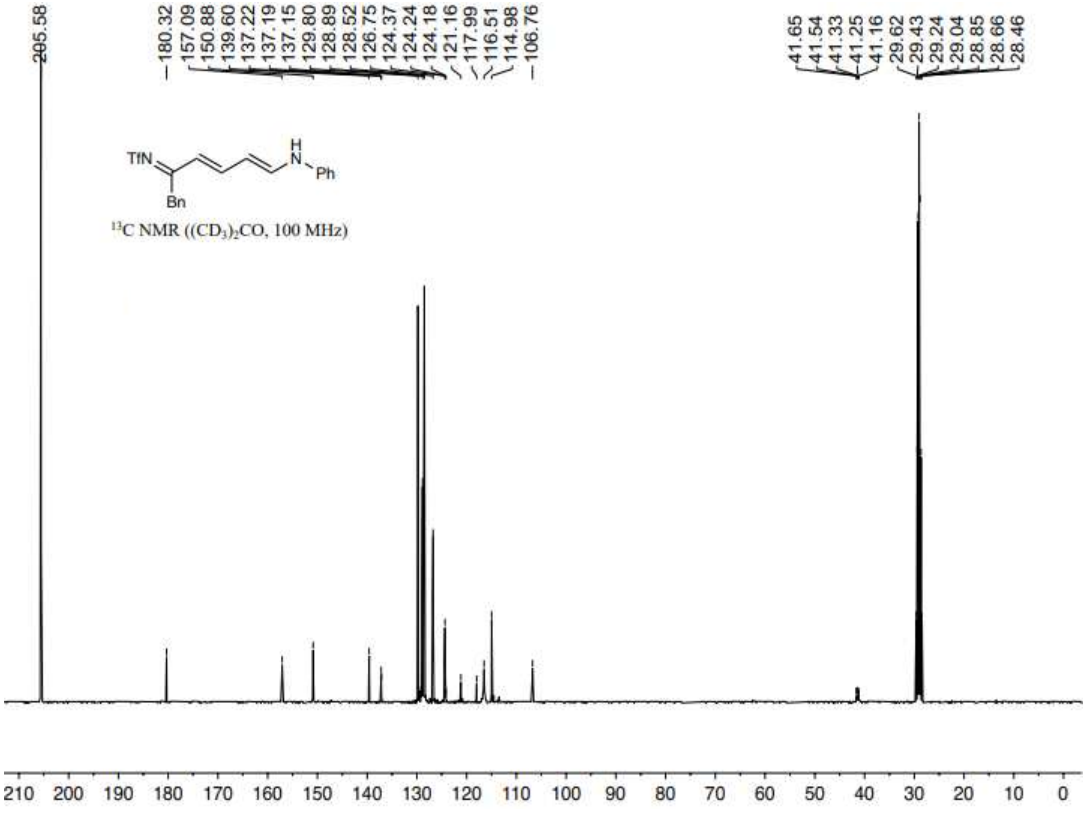
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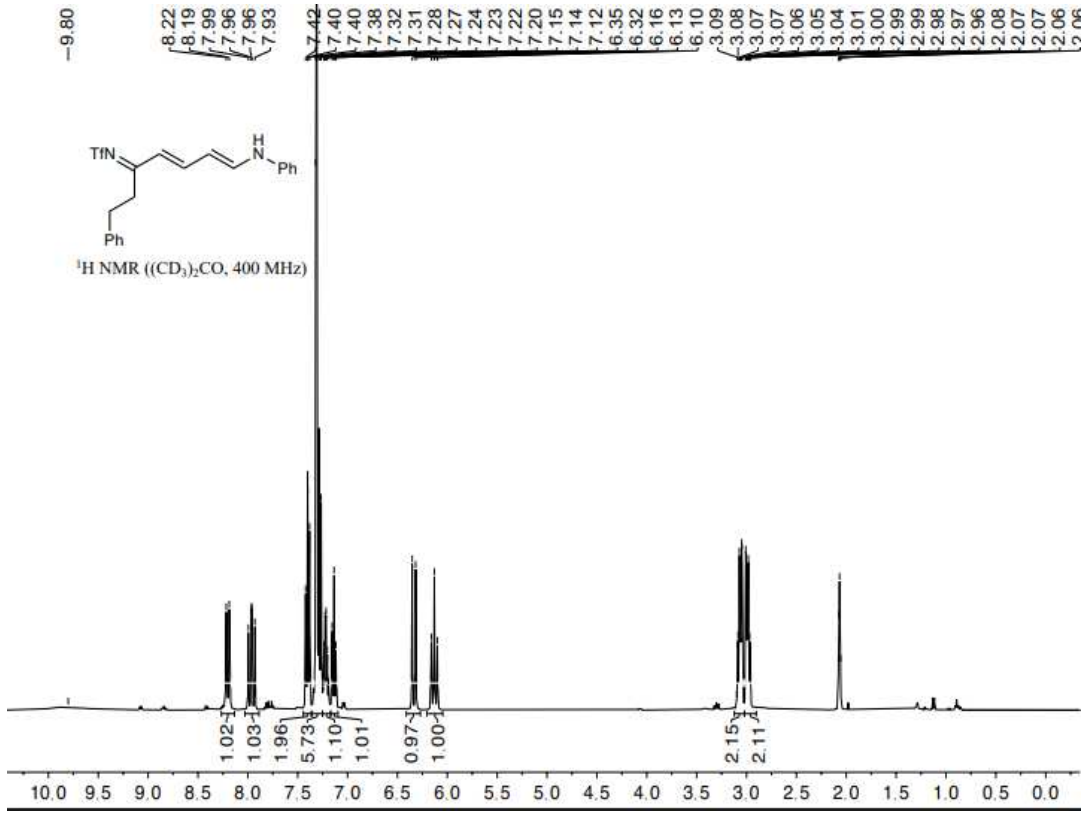
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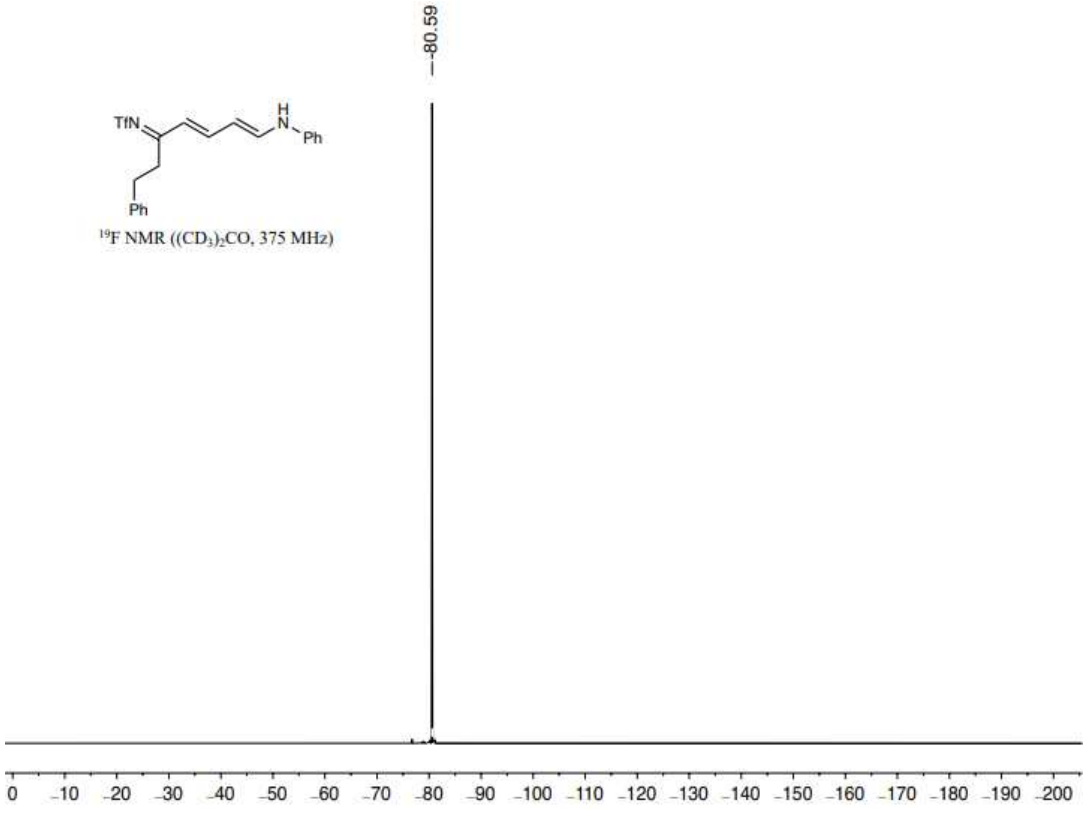
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)



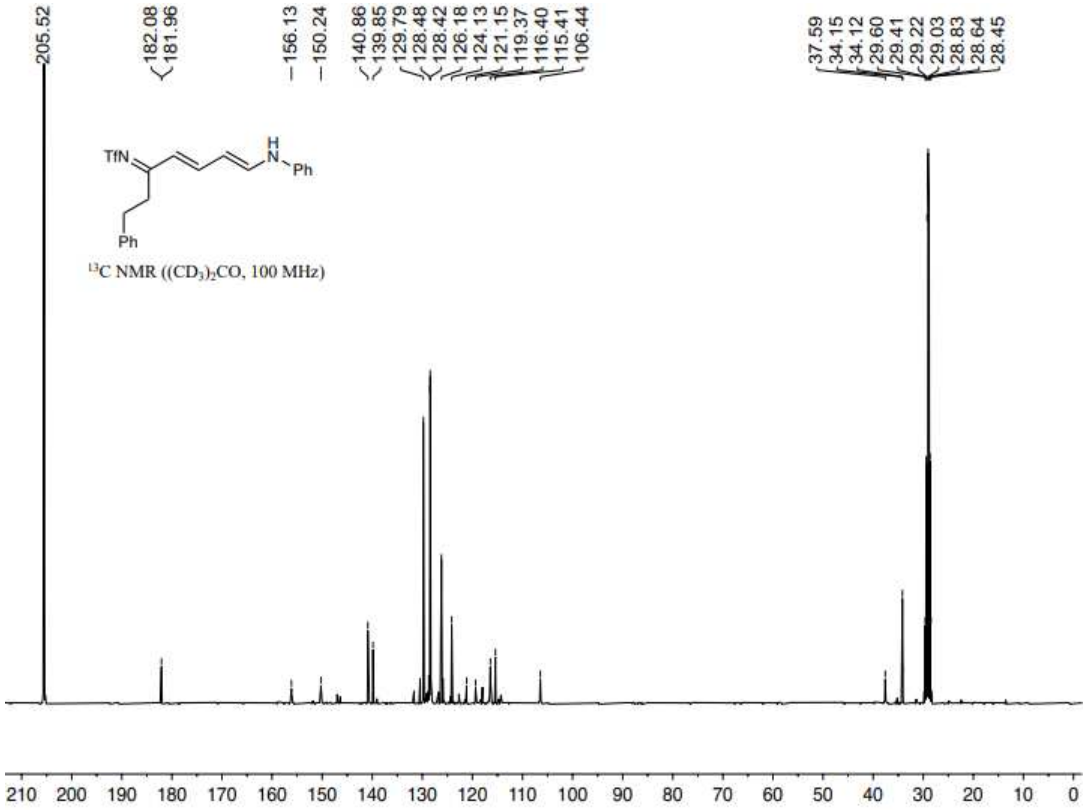
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)



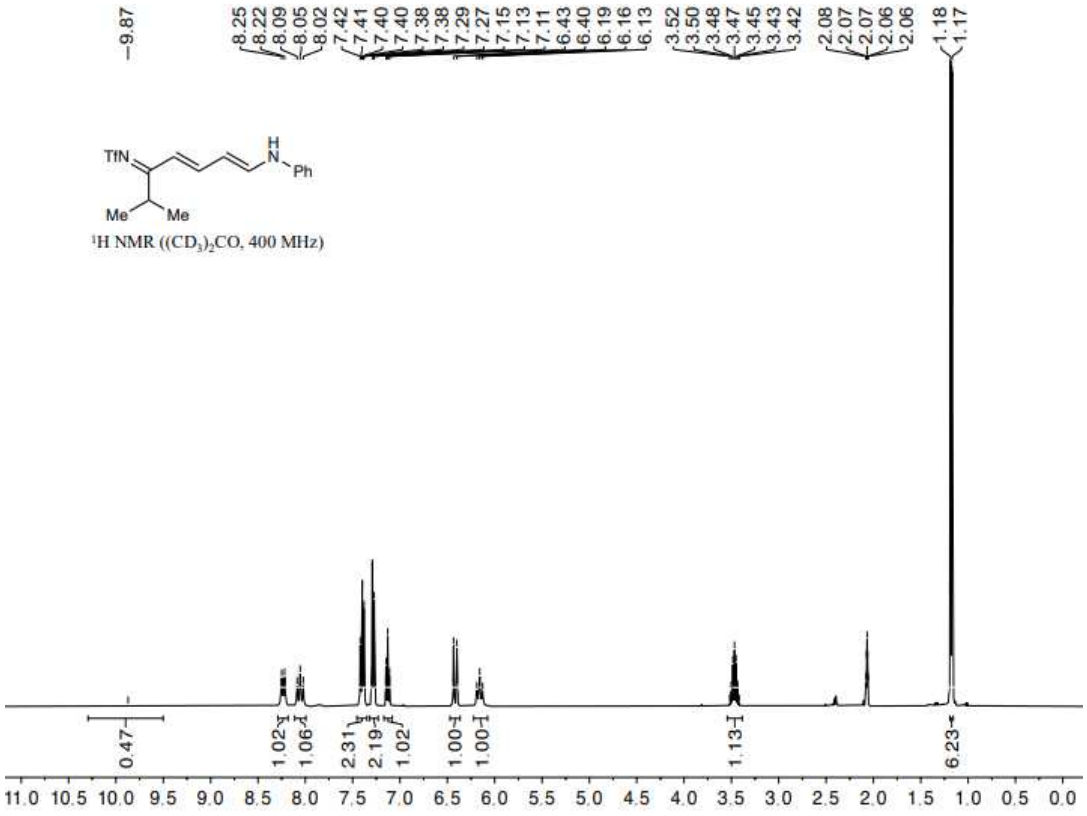
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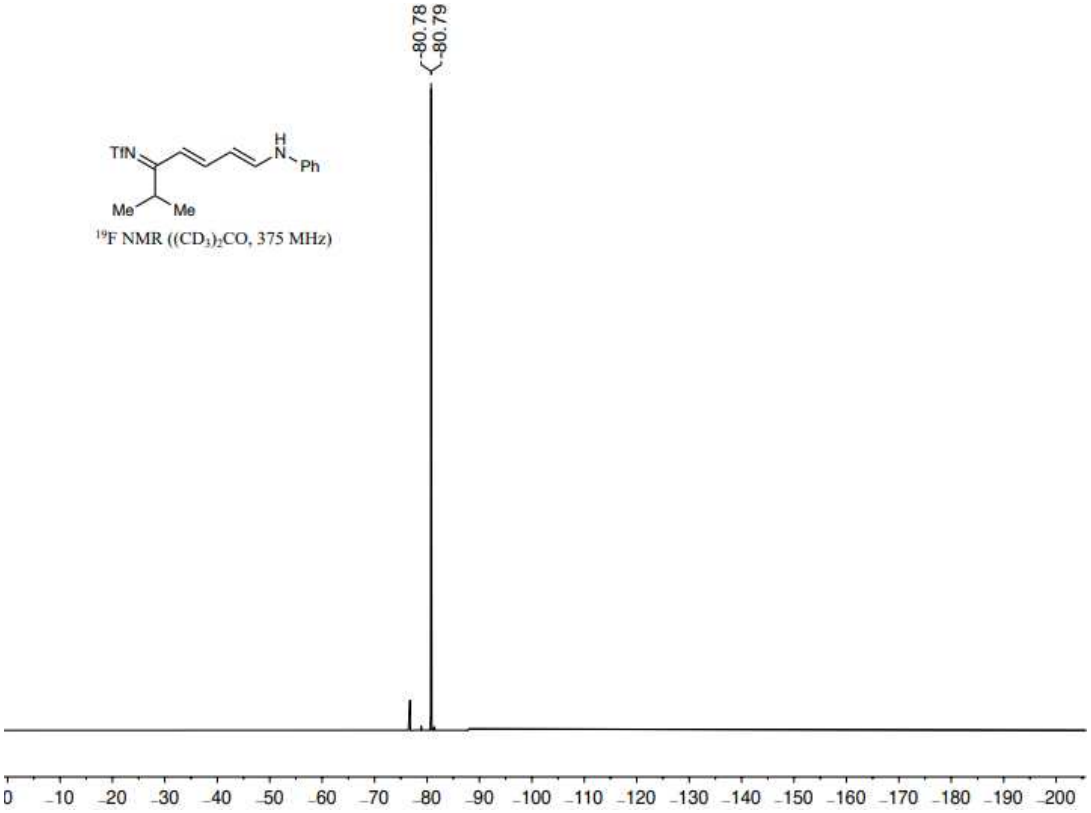
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)



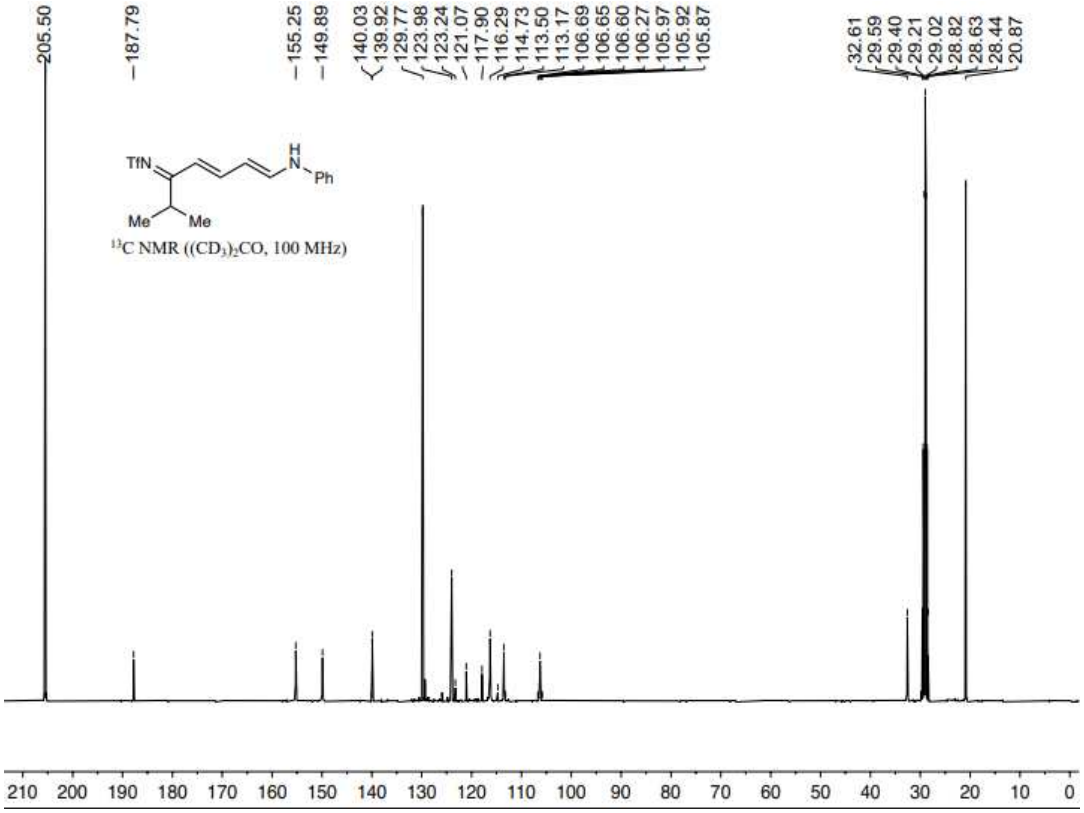
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)



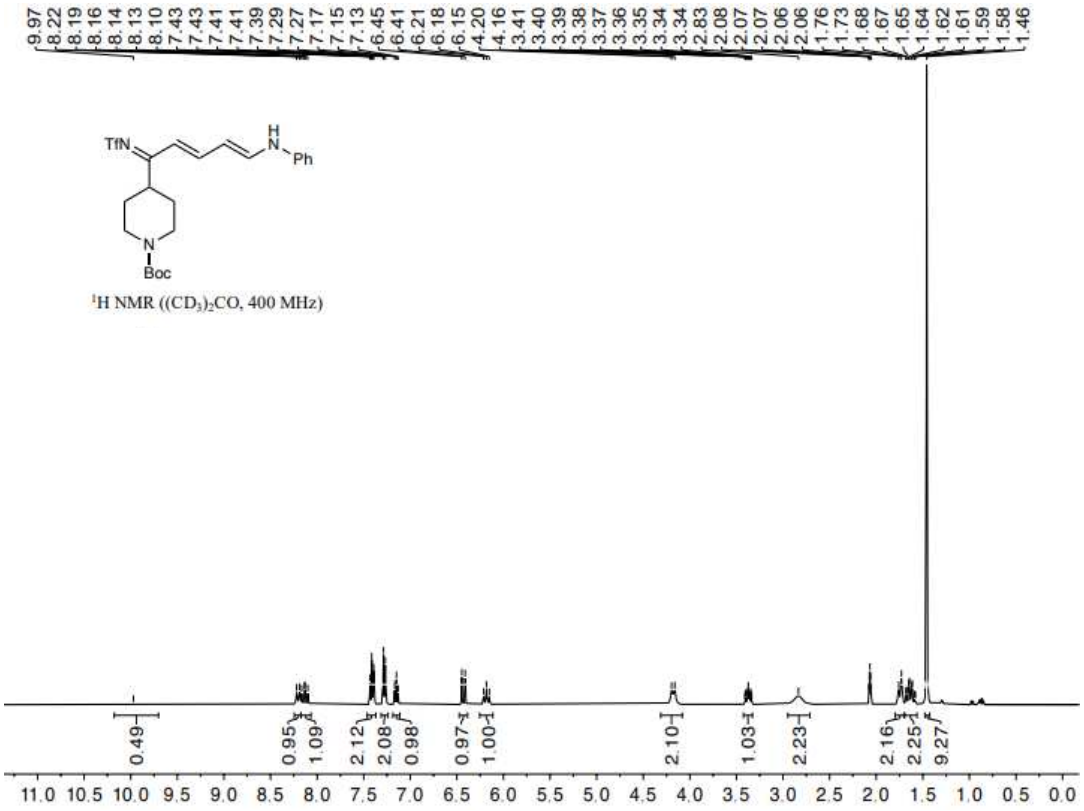
^{1}H NMR ((CD$_3$)$_2$CO, 400 MHz)



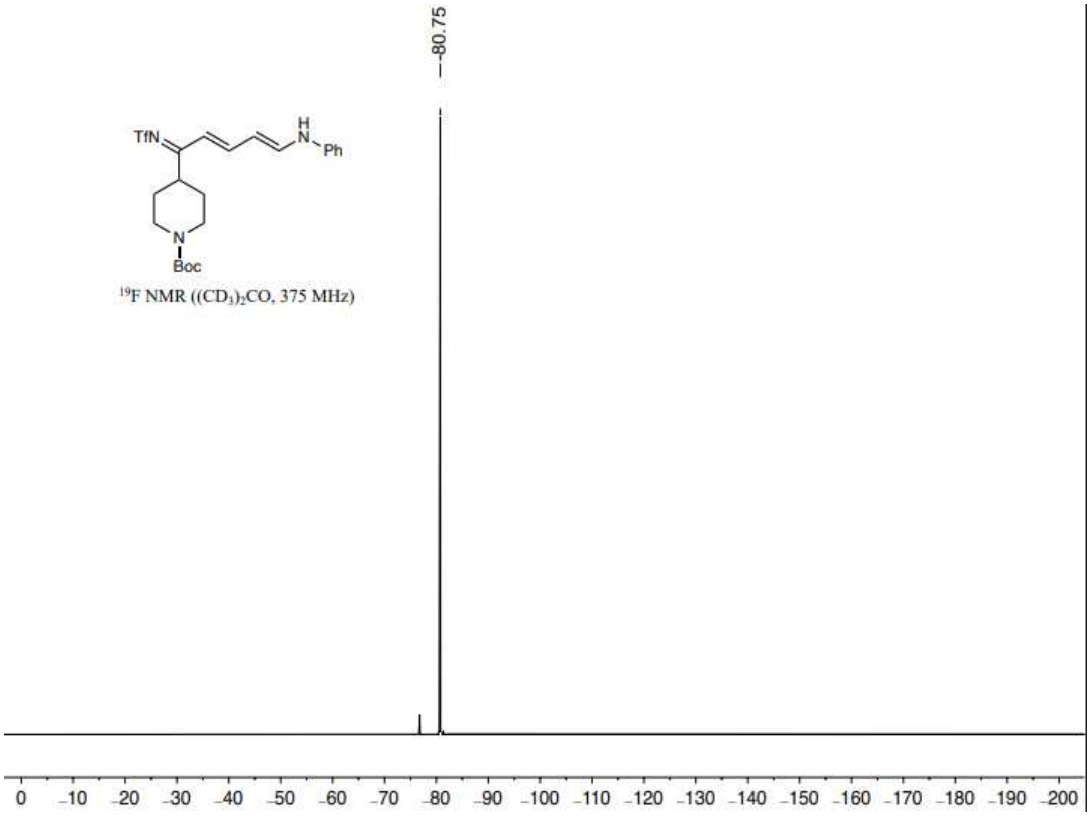
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)



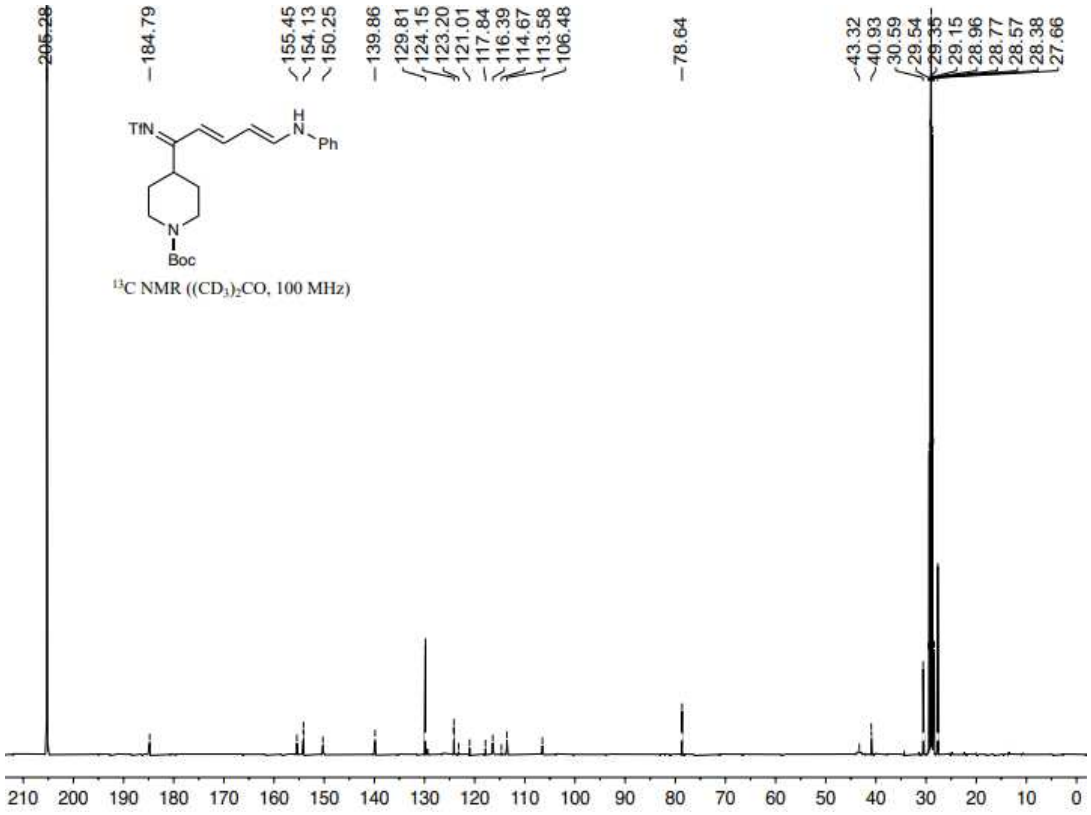
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)



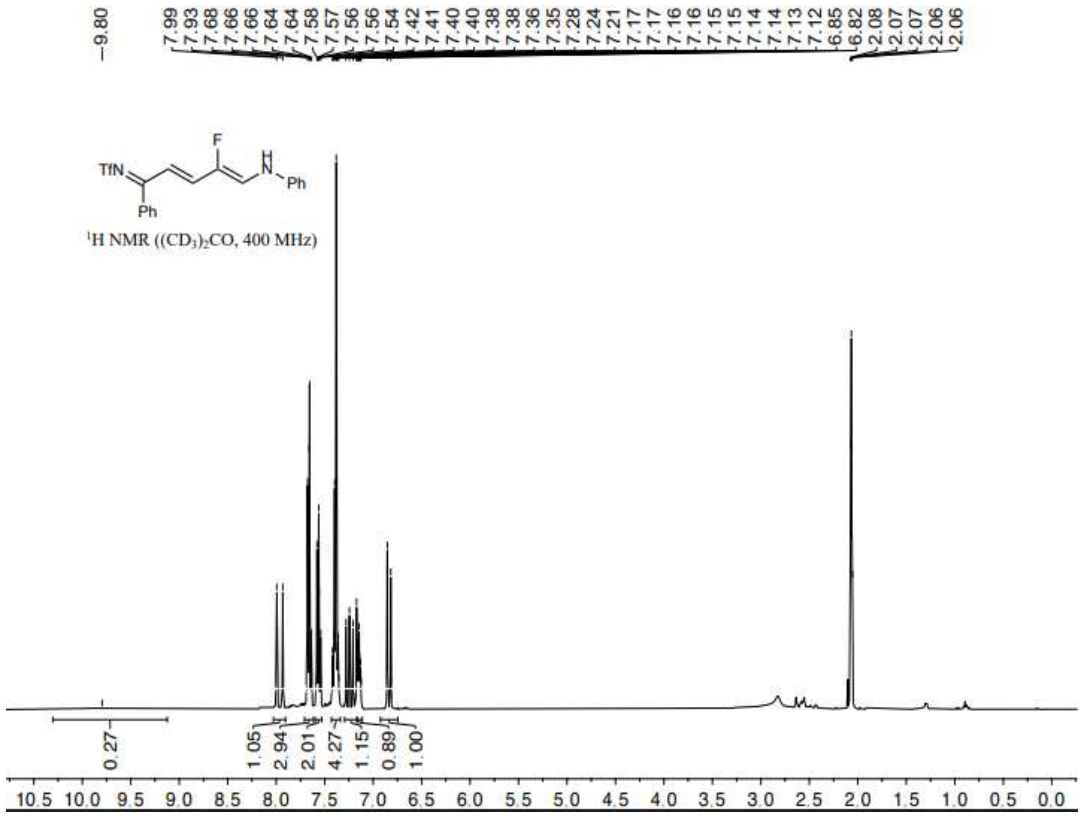
^{1}H NMR ((CD$_3$)$_2$CO, 400 MHz)



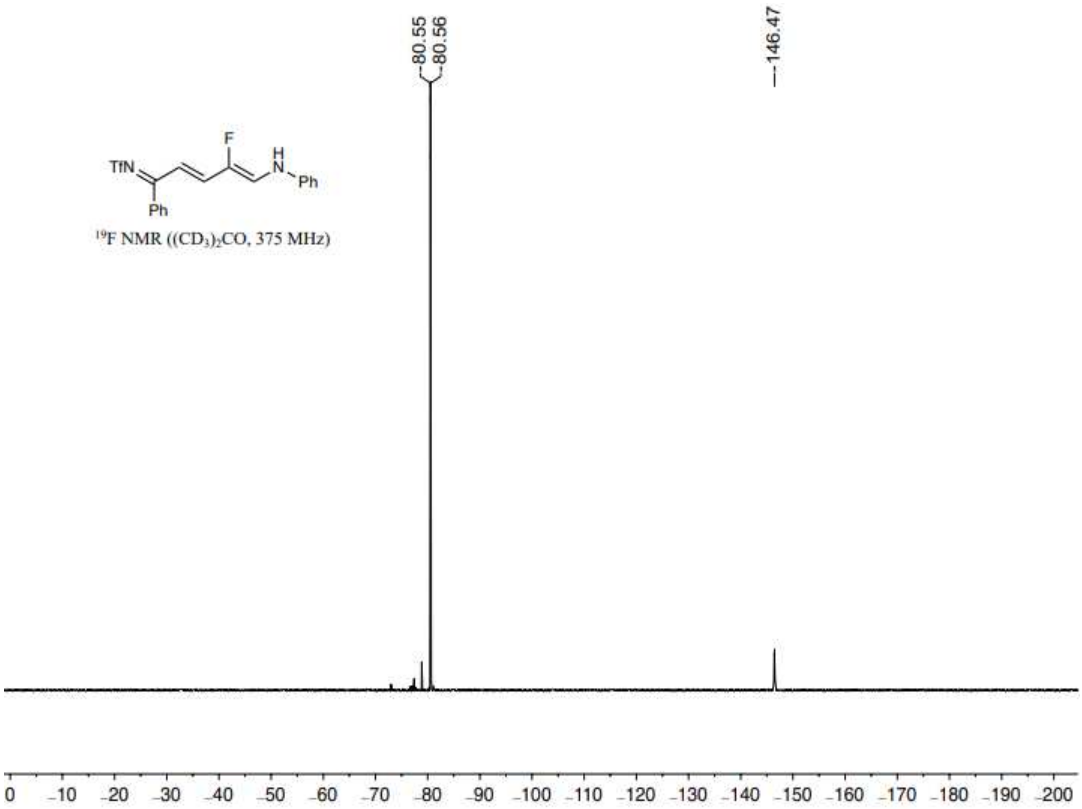
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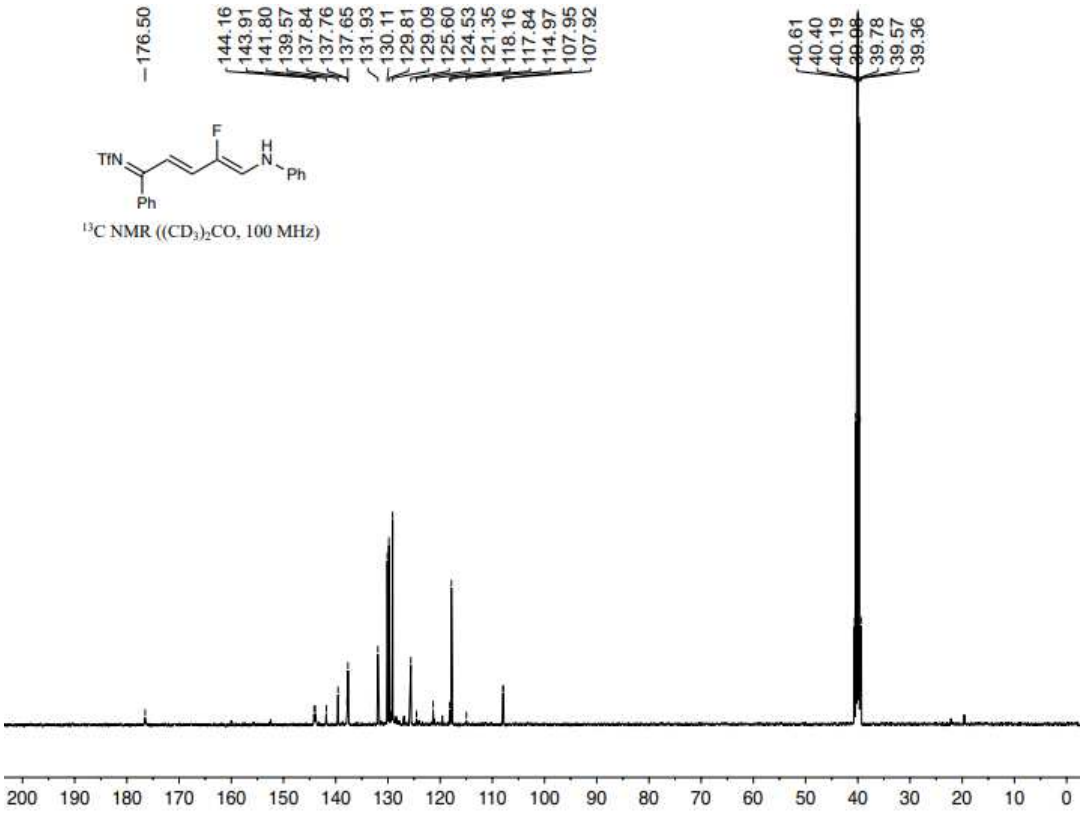
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)



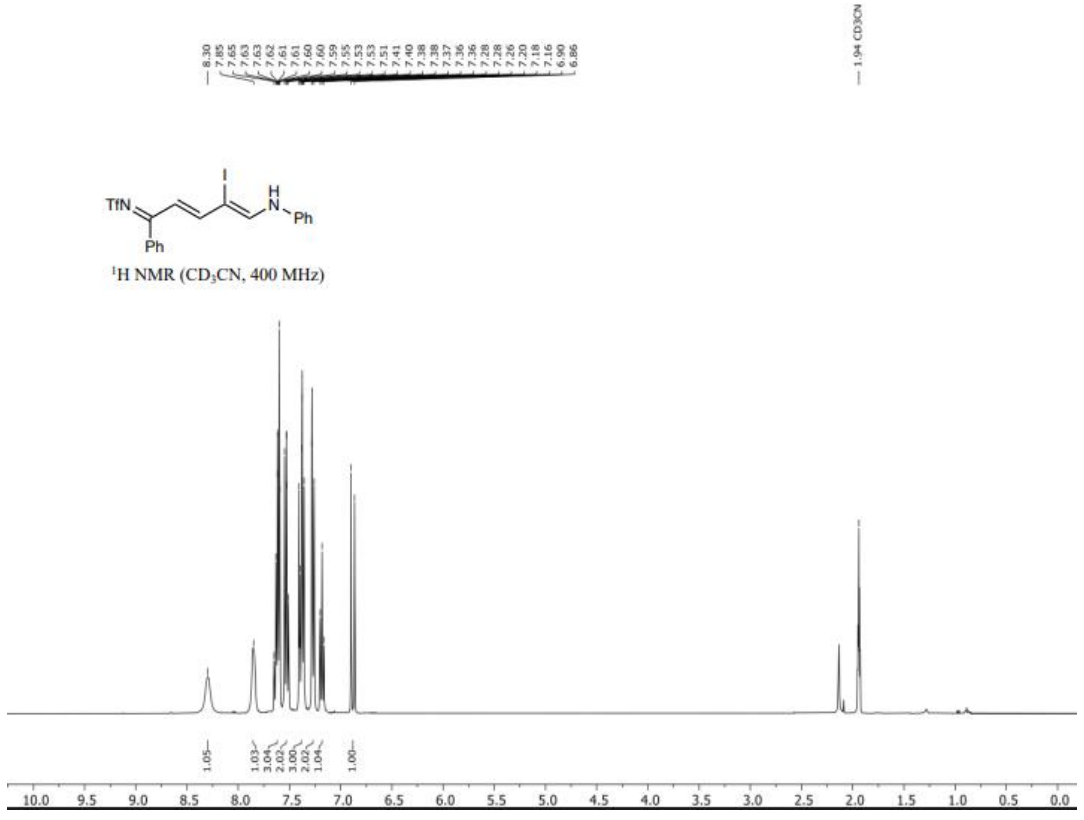
^{1}H NMR ((CD$_3$)$_2$CO, 400 MHz)



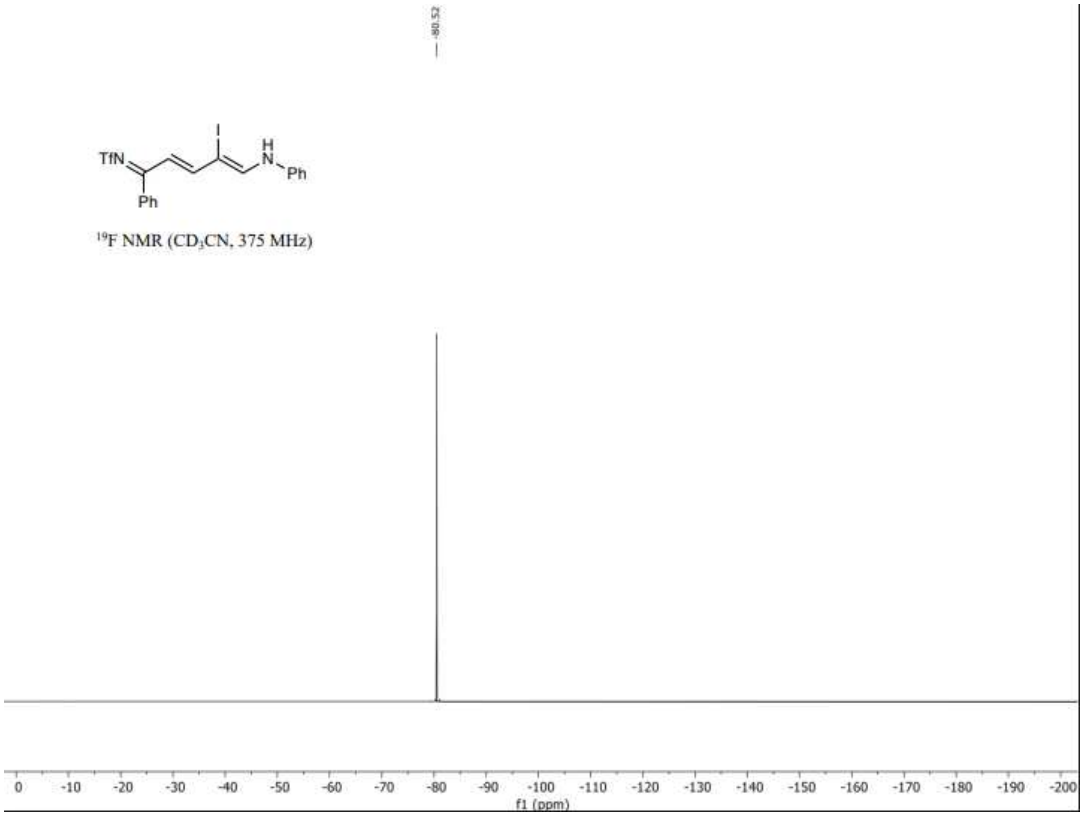
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)



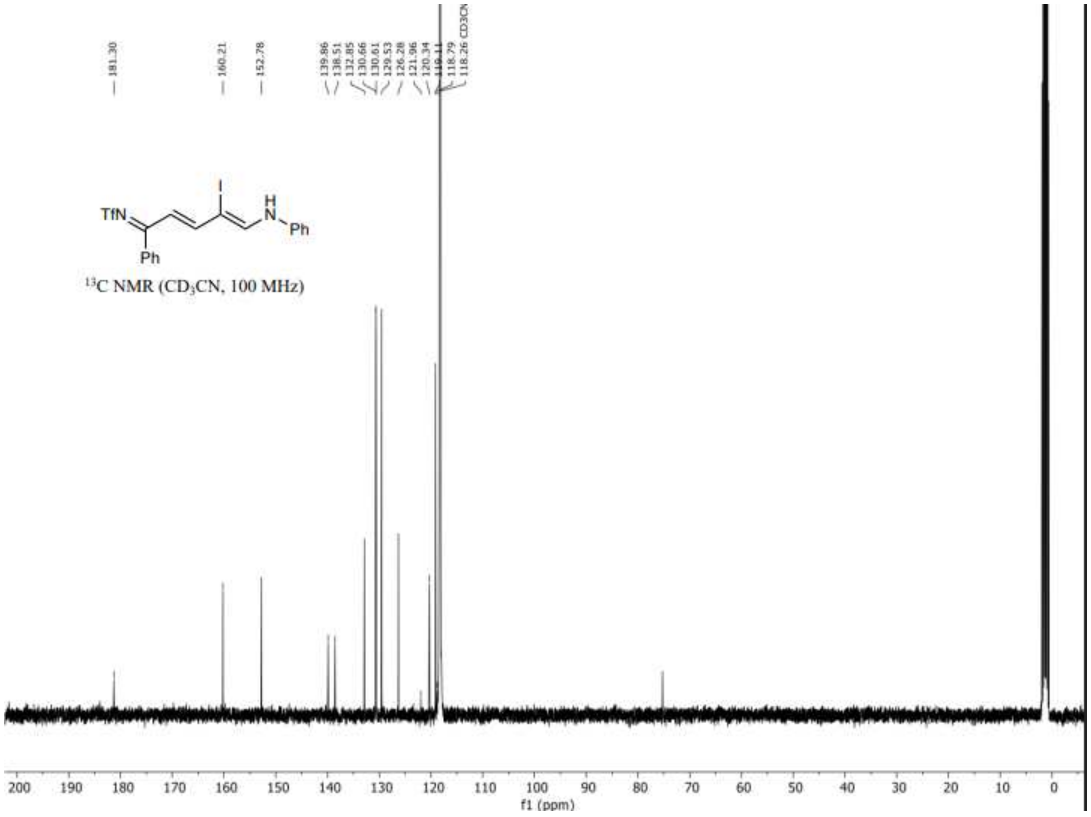
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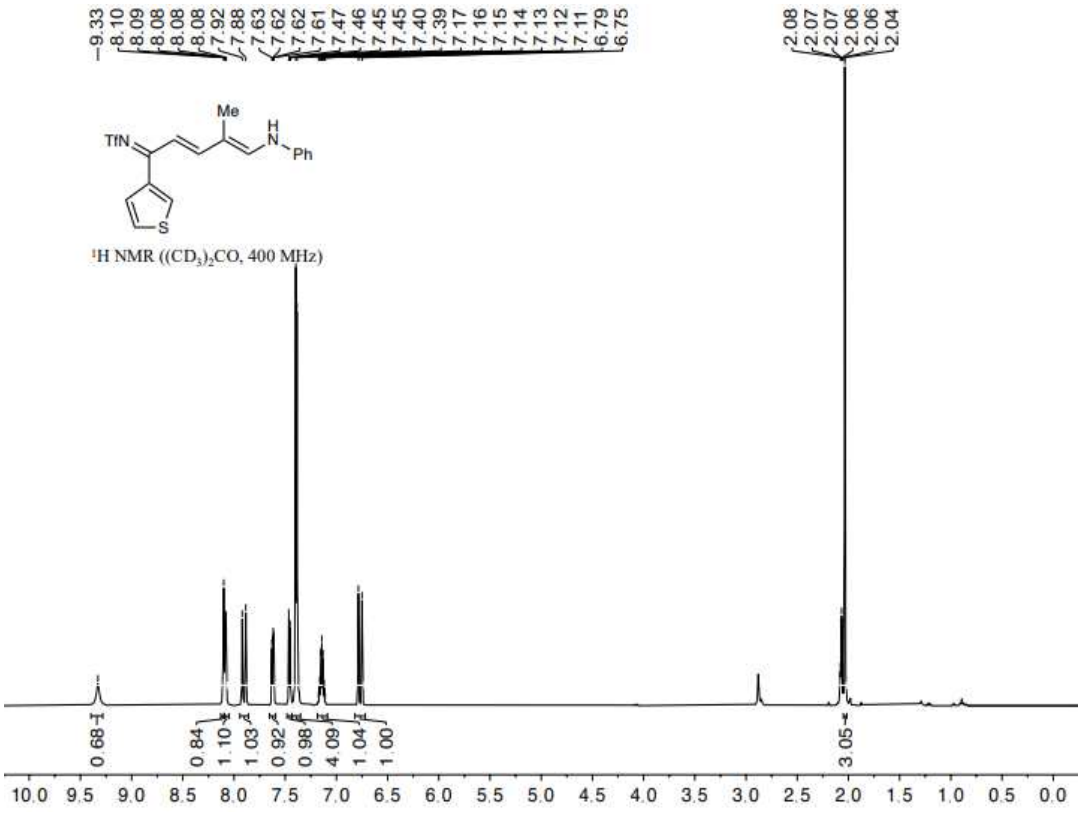
^{1}H NMR (CD_3CN, 400 MHz)



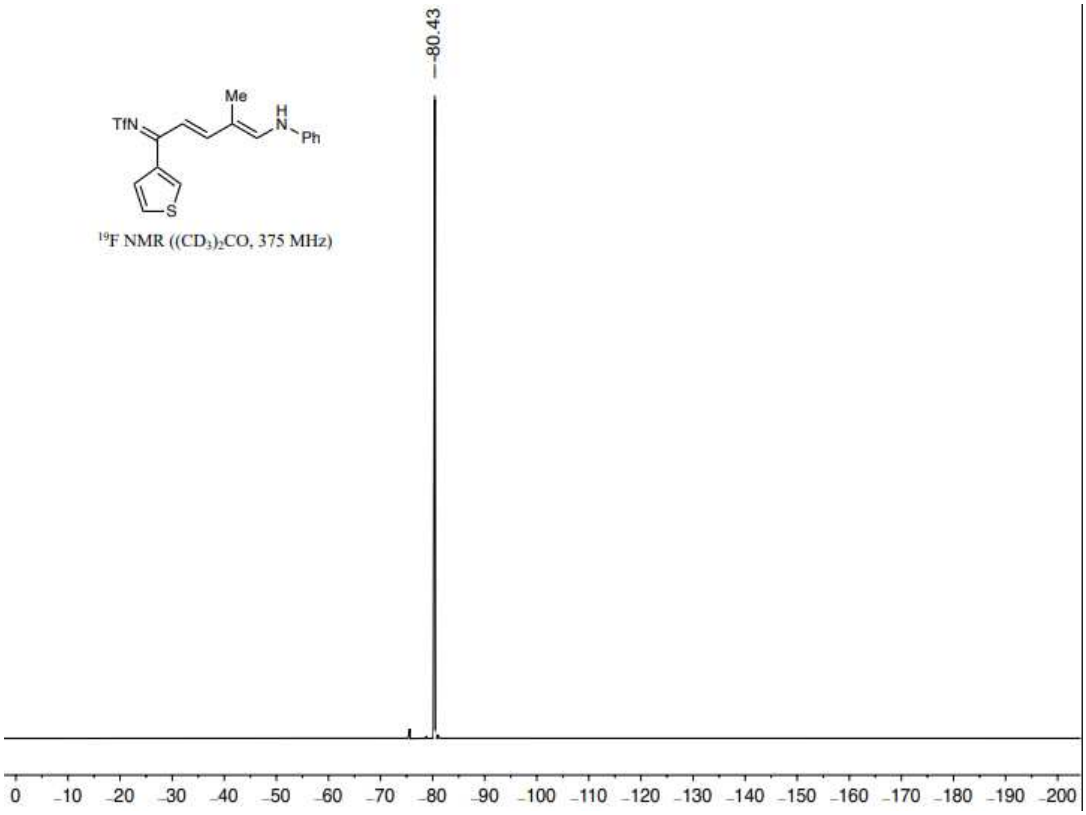
^{19}F NMR (CD_3CN, 375 MHz)



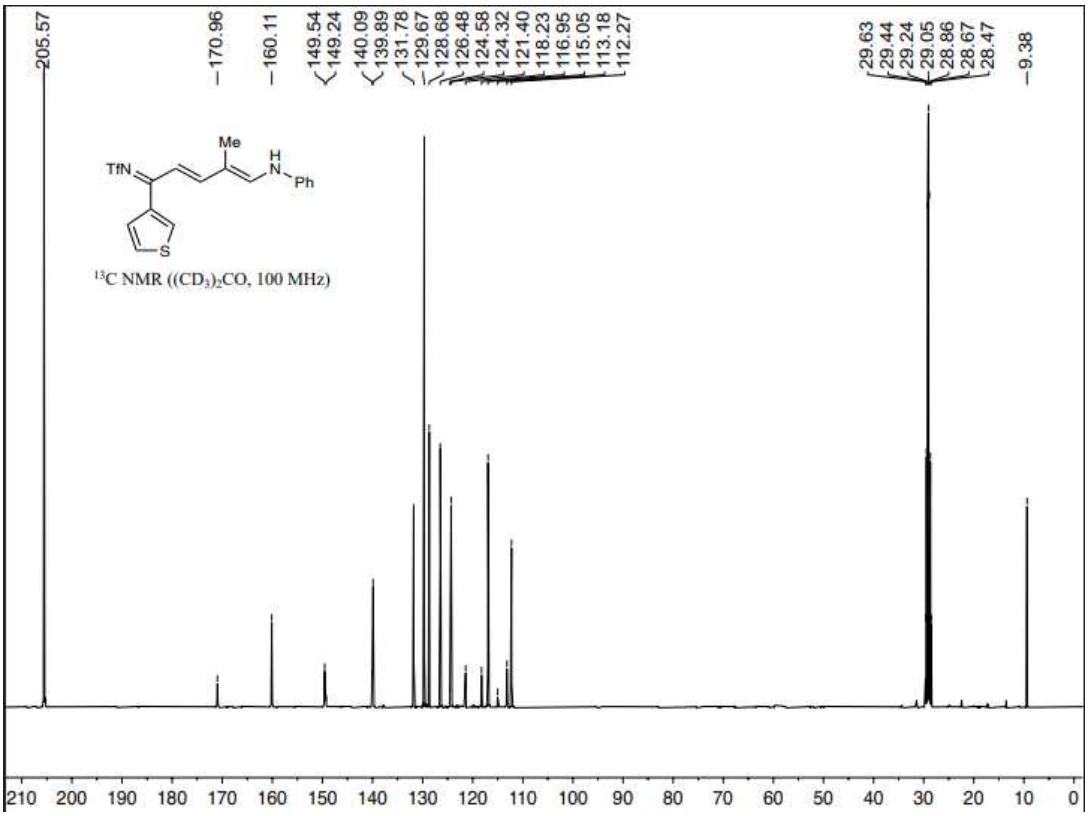
^{13}C NMR (CD_3CN, 100 MHz)

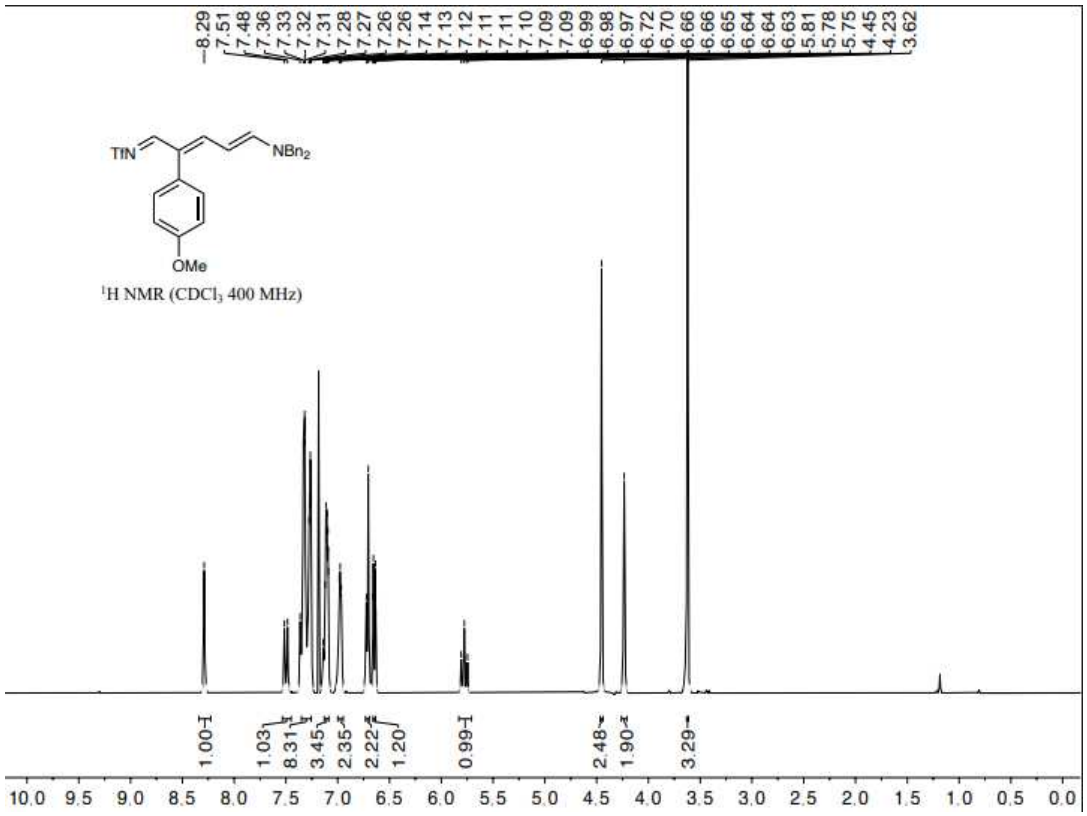


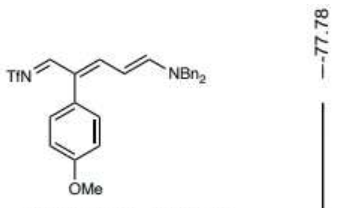
^{1}H NMR ((CD$_3$)$_2$CO, 400 MHz)



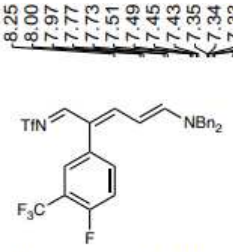
^{19}F NMR ((CD$_3$)$_2$CO, 375 MHz)


205.57
170.96
160.11
149.54
149.24
140.09
139.89
131.78
129.67
128.68
126.48
124.58
124.32
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113.18
112.27
29.63
29.44
29.24
29.05
28.86
28.67
28.47
9.38
Me
TfN
H
N
Ph
S
^{13}C NMR ((CD$_3$)$_2$CO, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

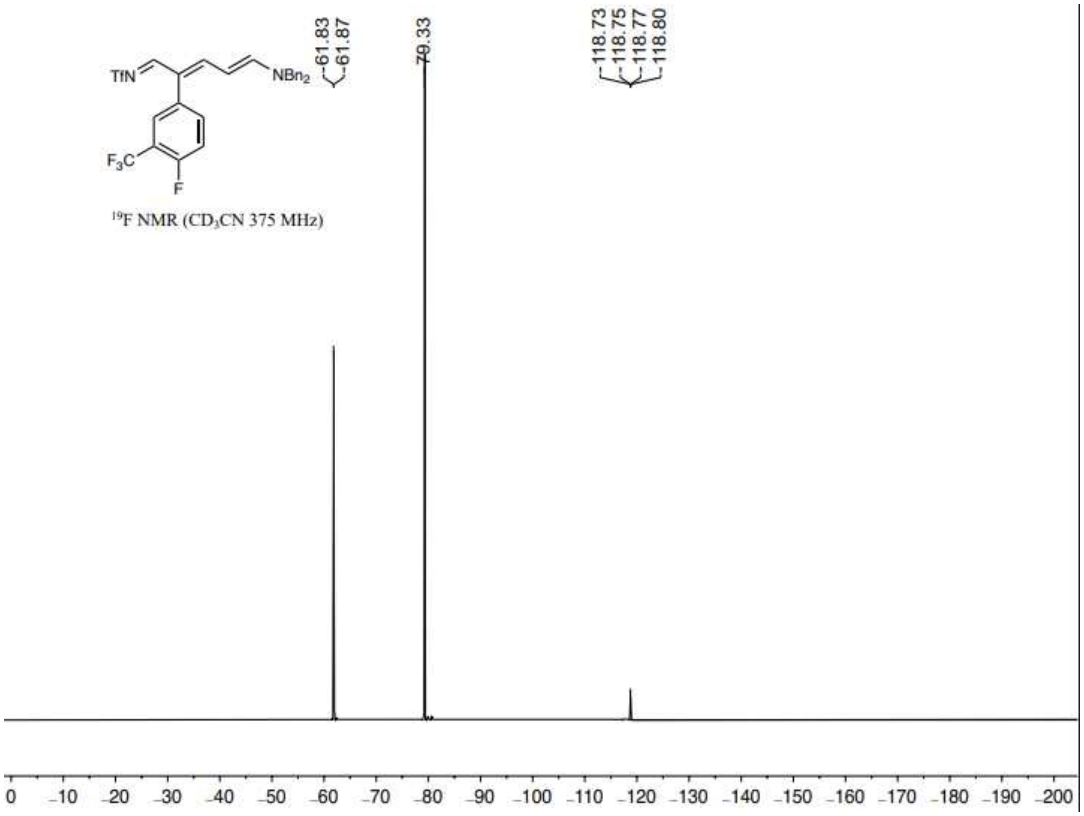

8.29
7.51
7.48
7.36
7.33
7.32
7.31
7.28
7.27
7.26
7.26
7.14
7.13
7.12
7.11
7.11
7.10
7.09
7.09
6.99
6.98
6.97
6.72
6.70
6.66
6.66
6.65
6.64
6.64
6.63
5.81
5.78
5.75
4.45
4.23
3.62
TfN
NBn$_2$
OMe
^{1}H NMR (CDCl$_3$ 400 MHz)
1.00
1.03
8.31
3.45
2.35
2.22
1.20
0.99
2.48
1.90
3.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

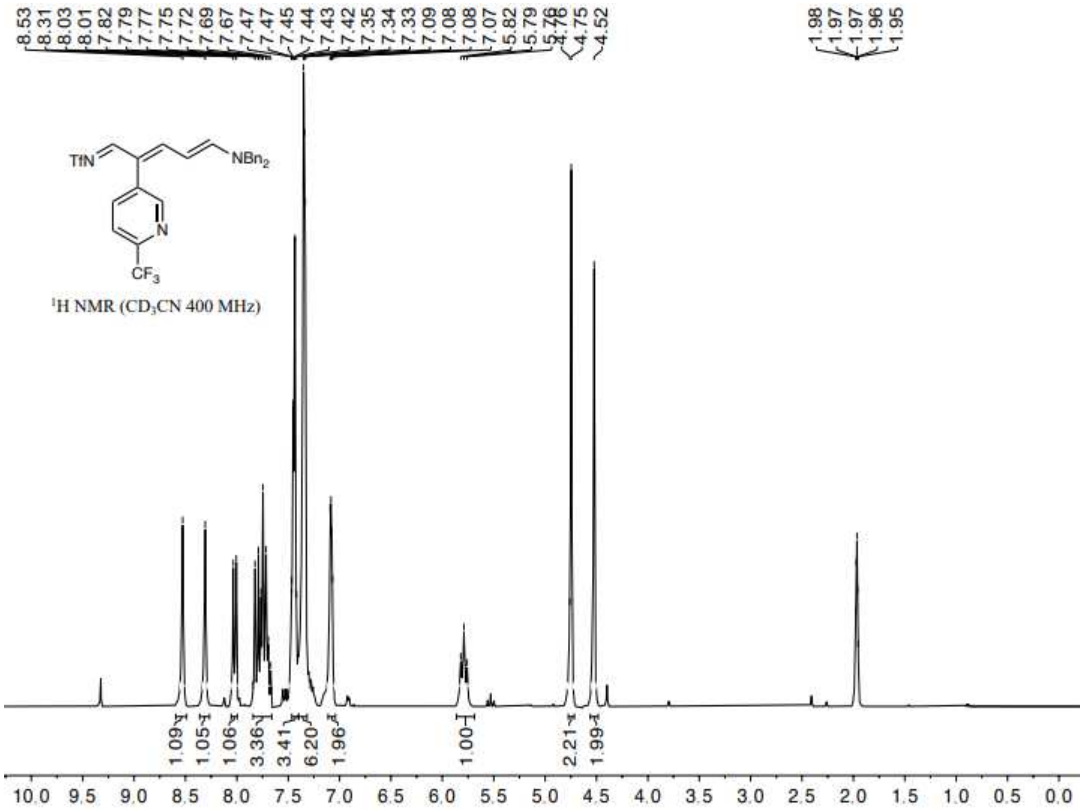


^{19}F NMR ($CDCl_3$ 375 MHz)



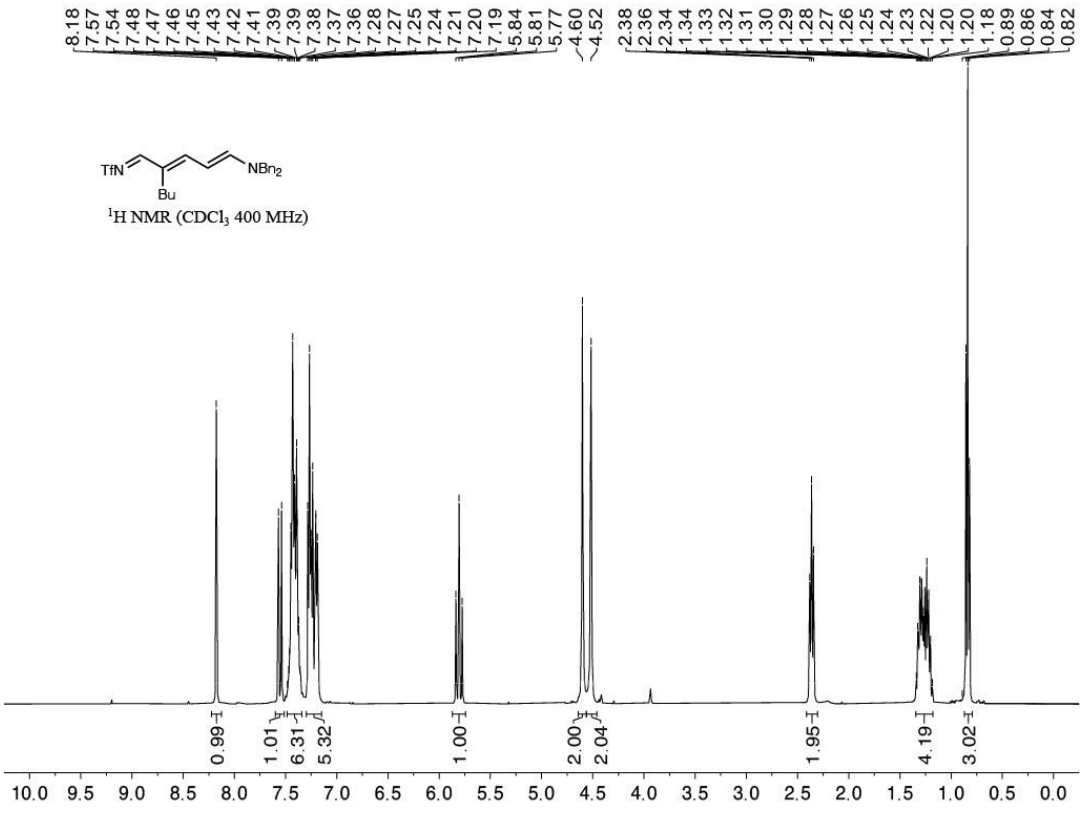
^{1}H NMR (CD_3CN 400 MHz)


TfN
NBn2
F3C
F
61.83
61.87
79.33
118.73
118.75
118.77
118.80
19F NMR (CD3CN 375 MHz)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

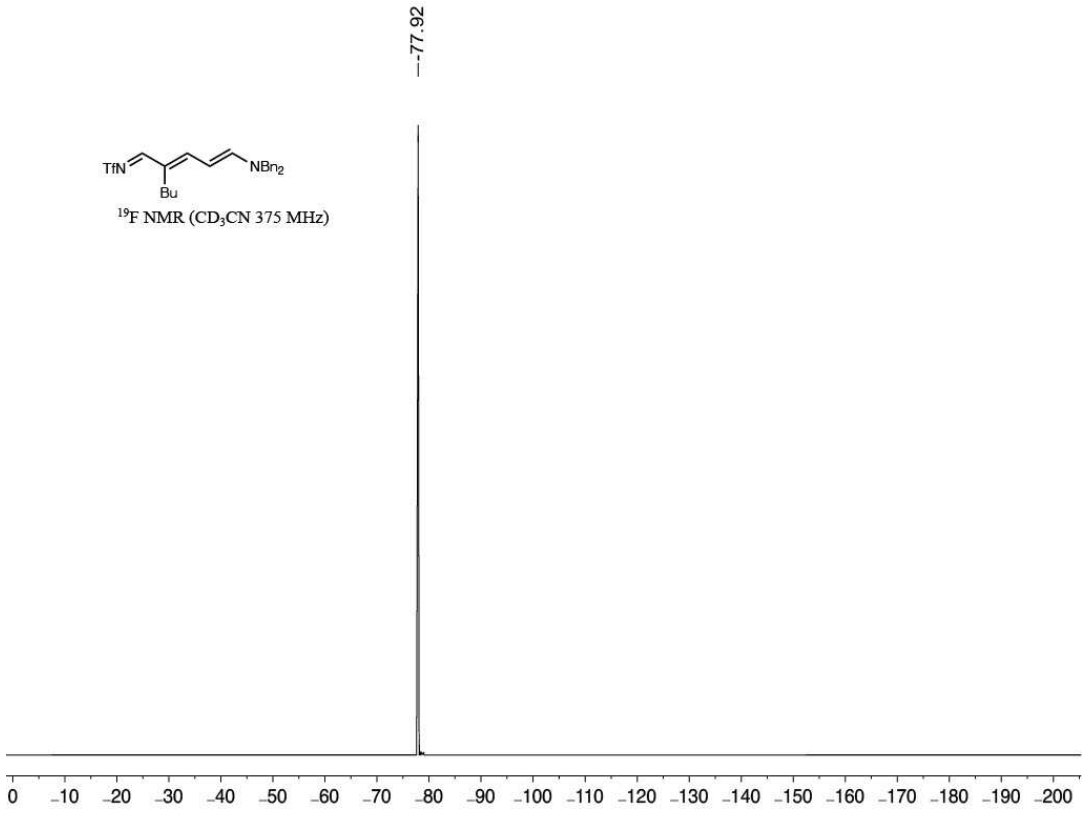

8.53
8.31
8.03
8.01
7.82
7.79
7.77
7.75
7.72
7.69
7.67
7.47
7.45
7.44
7.43
7.42
7.35
7.34
7.33
7.09
7.08
7.08
7.07
5.82
5.79
4.75
4.52
1.98
1.97
1.97
1.96
1.95
TfN
NBn2
N
CF3
1H NMR (CD3CN 400 MHz)
1.09
1.05
1.06
3.36
3.41
6.20
1.96
1.00
2.21
1.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0



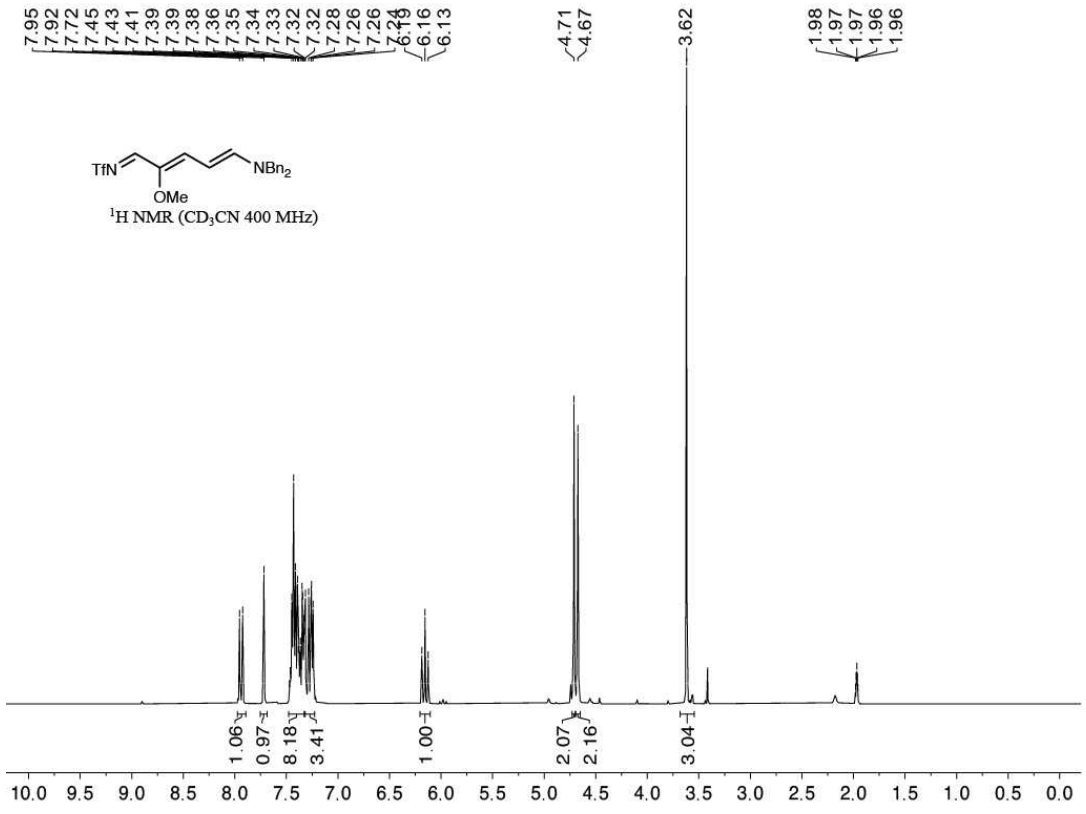
^{19}F NMR (CD_3CN 375 MHz)



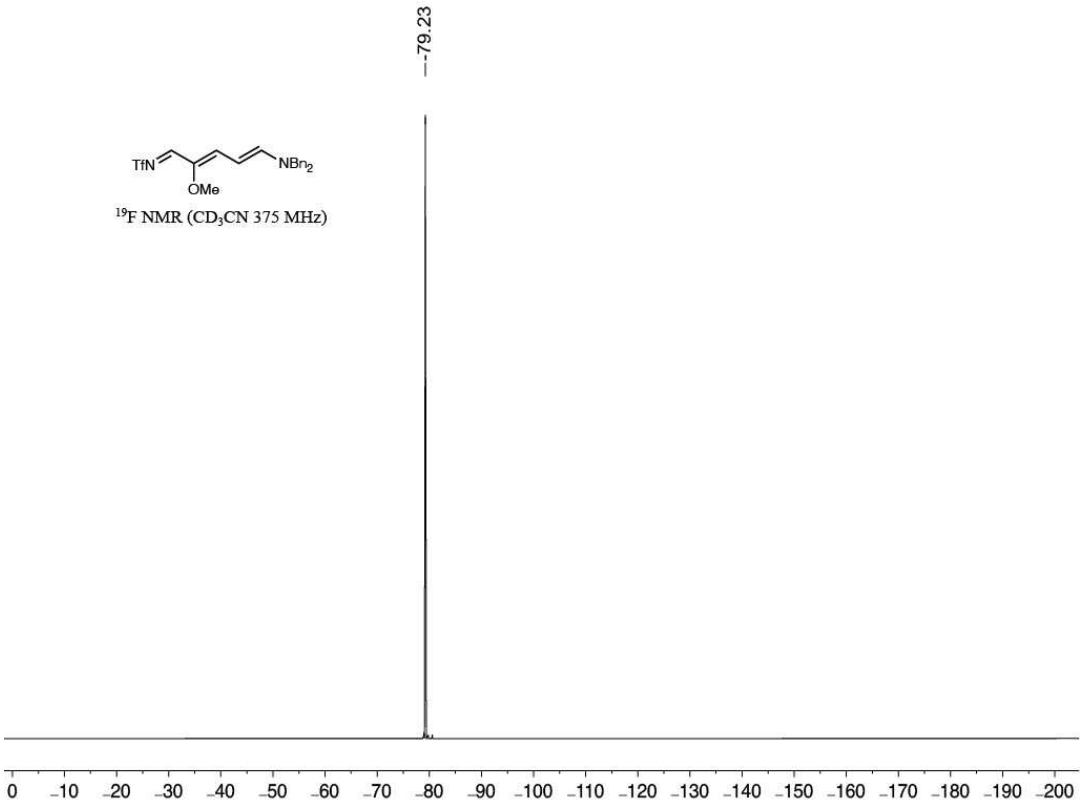
^{1}H NMR ($CDCl_3$ 400 MHz)

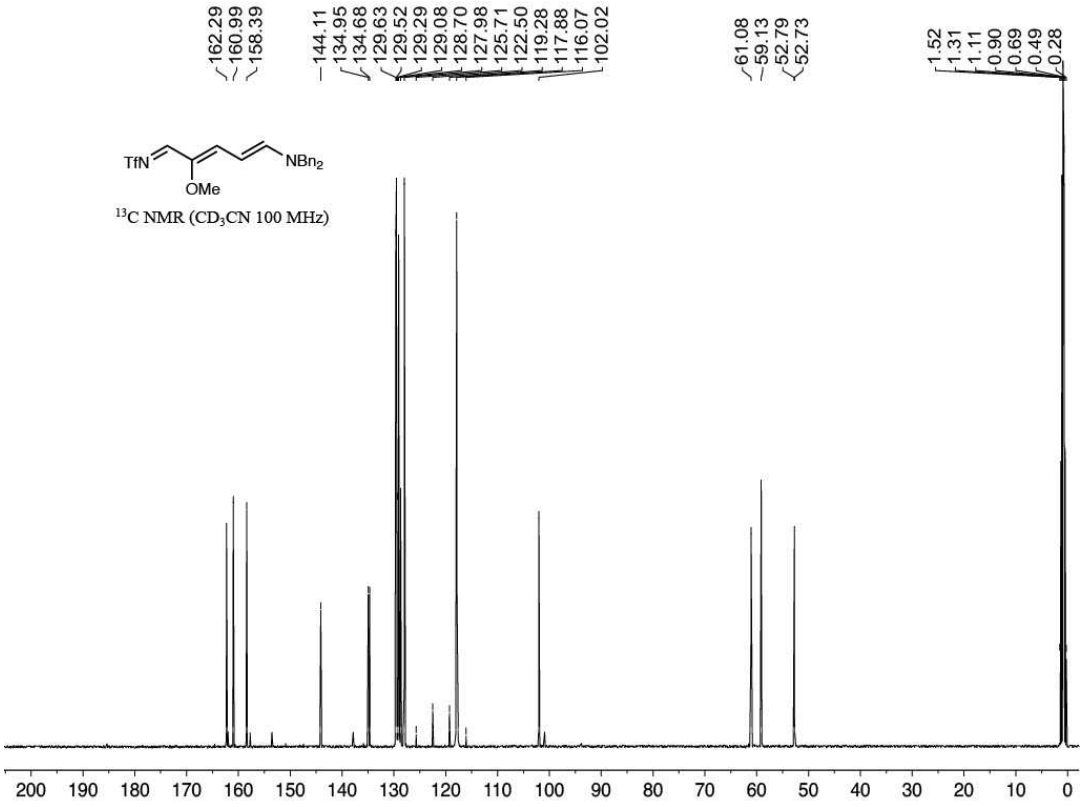


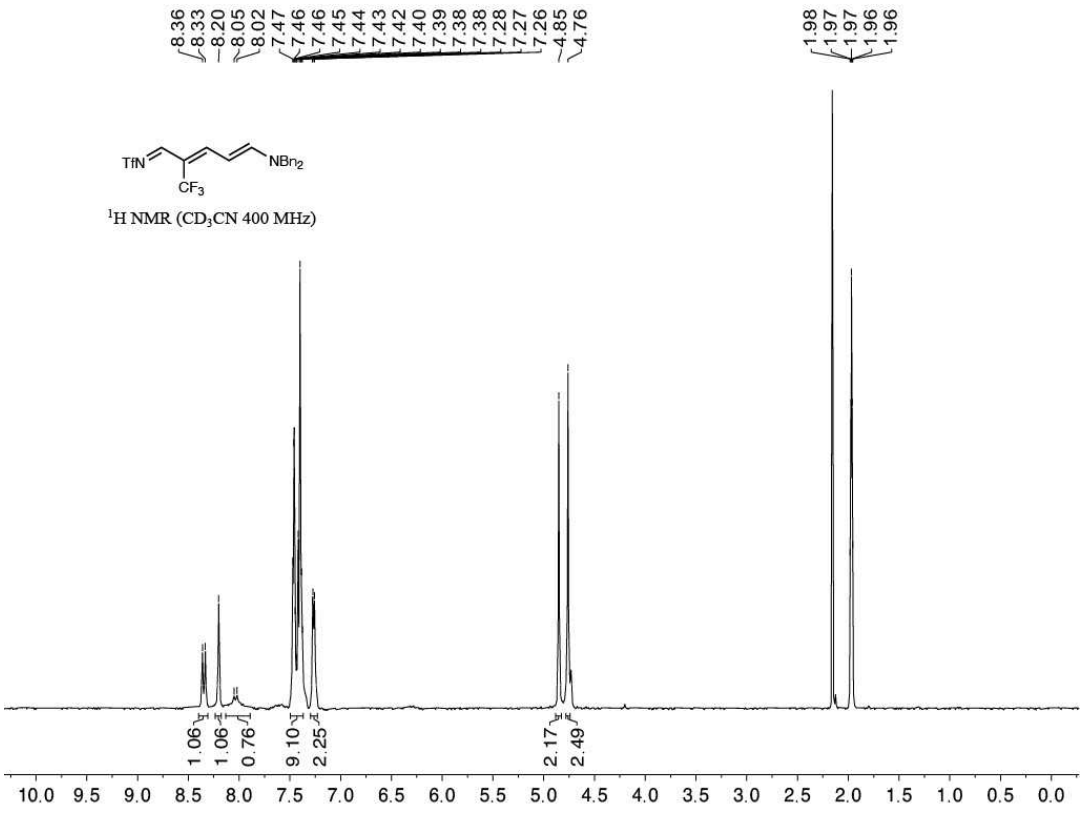
^{19}F NMR (CD_3CN 375 MHz)



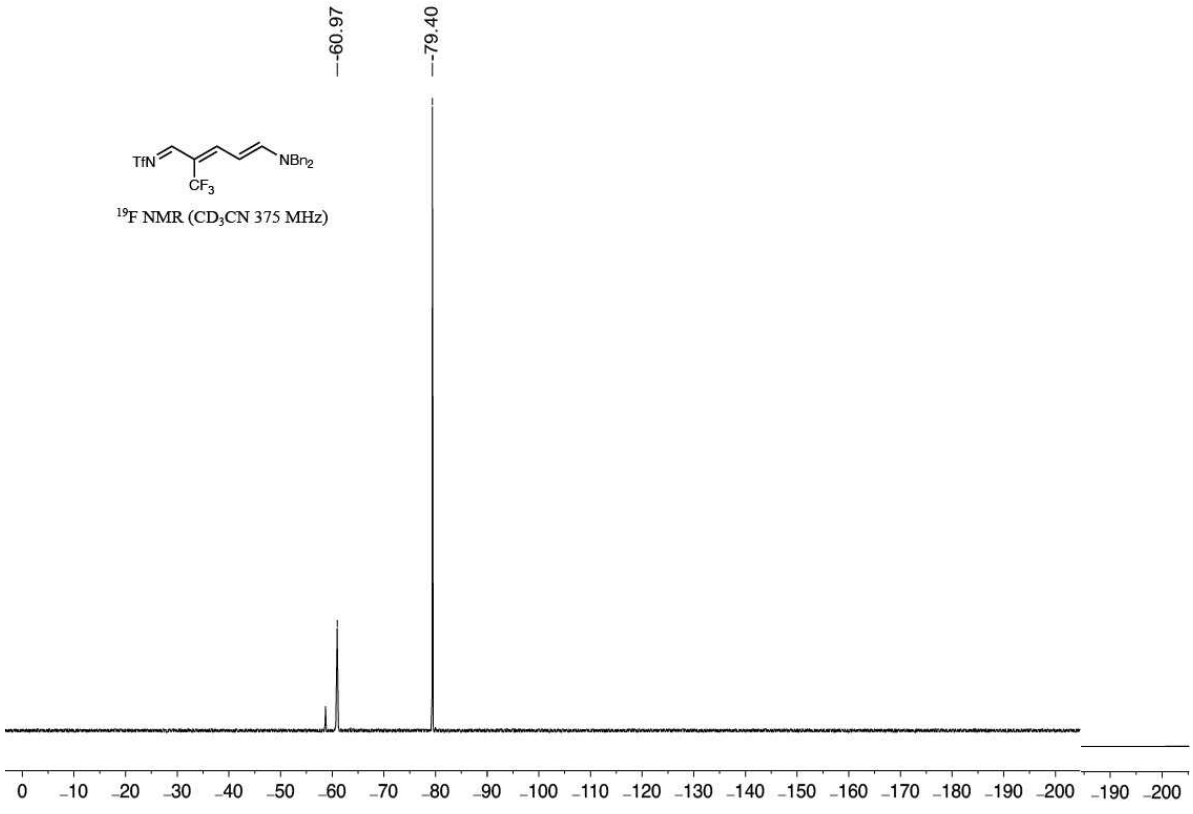
^{1}H NMR (CD_3CN 400 MHz)


-79.23
TfN
NBn2
OMe
19F NMR (CD3CN 375 MHz)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

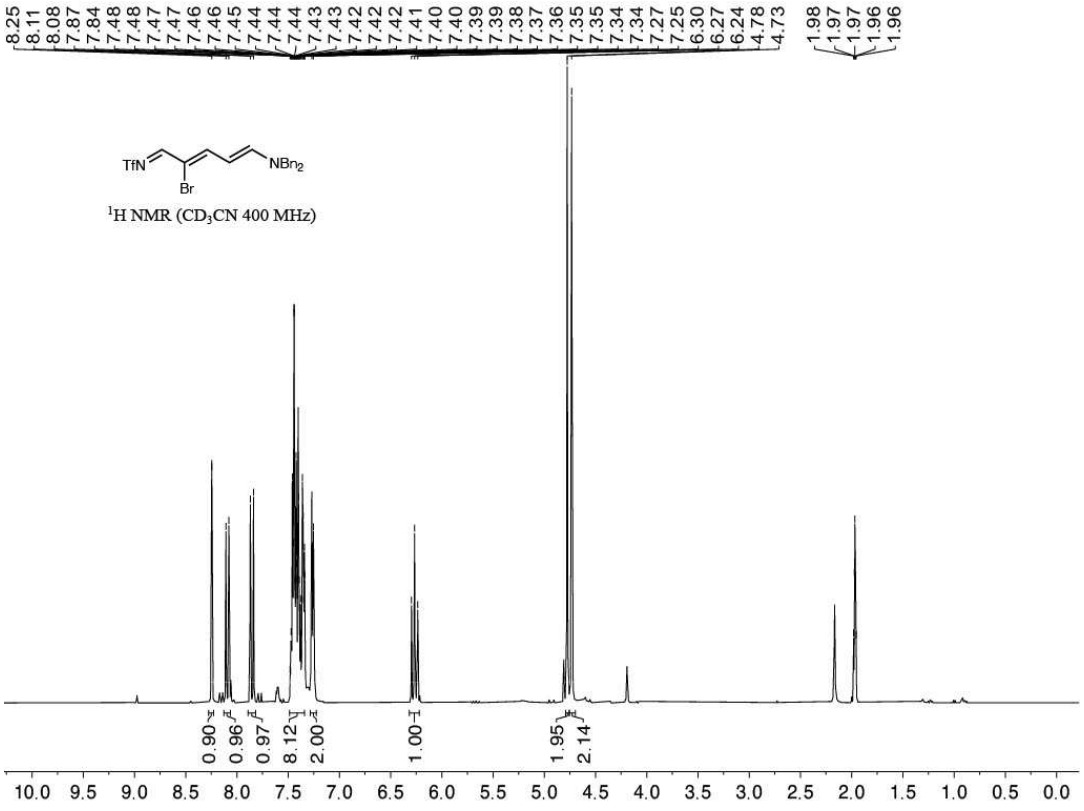

162.29
160.99
158.39
144.11
134.95
134.68
129.63
129.52
129.29
129.08
128.70
127.98
125.71
122.50
119.28
117.88
116.07
102.02
61.08
59.13
52.79
52.73
1.52
1.31
1.11
0.90
0.69
0.49
0.28
TfN
NBn2
OMe
13C NMR (CD3CN 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



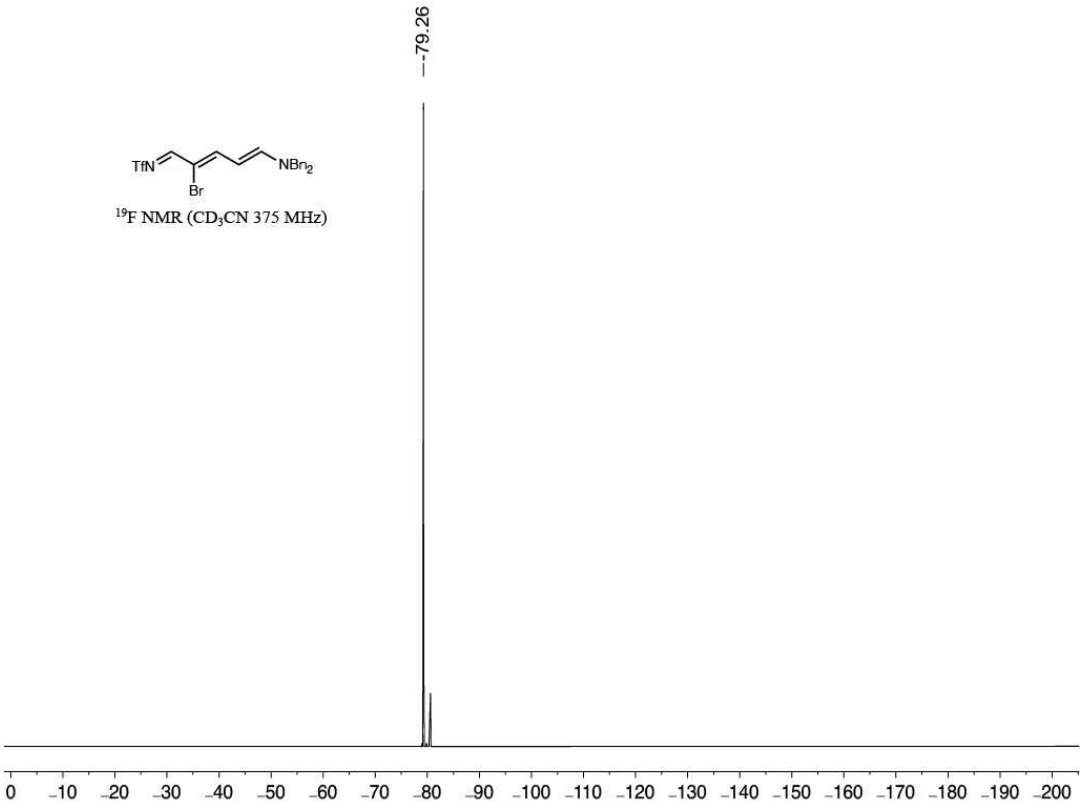
^{1}H NMR (CD_3CN 400 MHz)



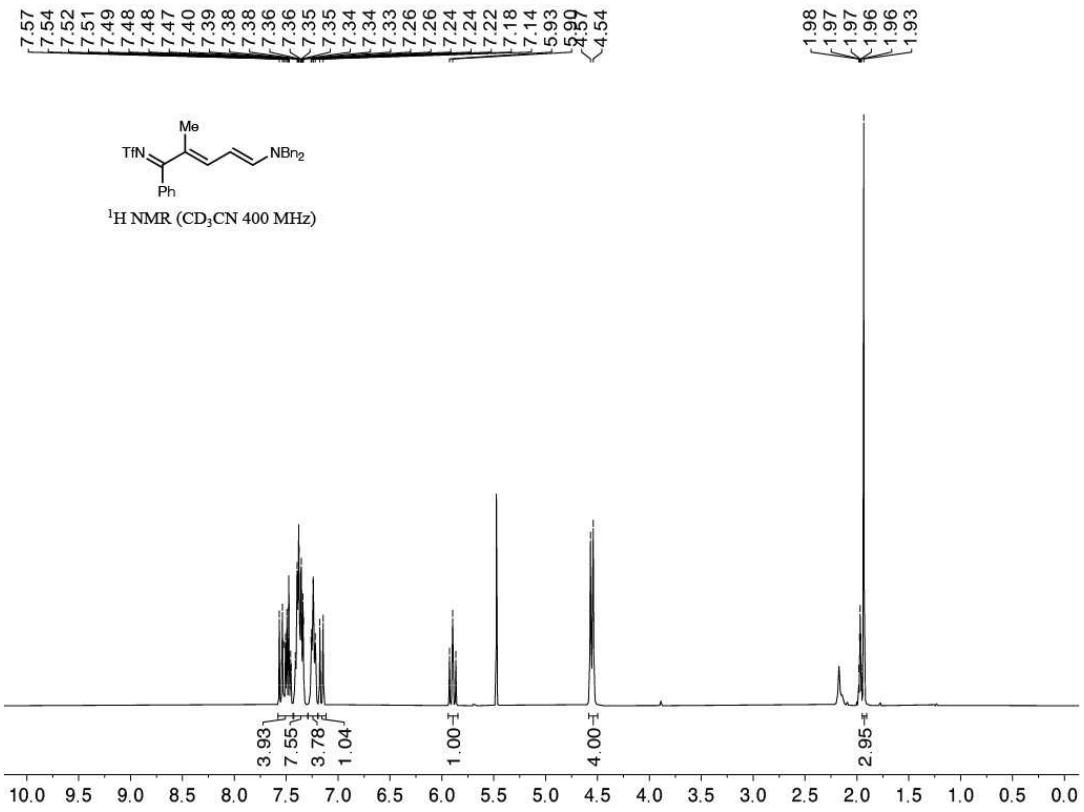
^{19}F NMR (CD_3CN 375 MHz)



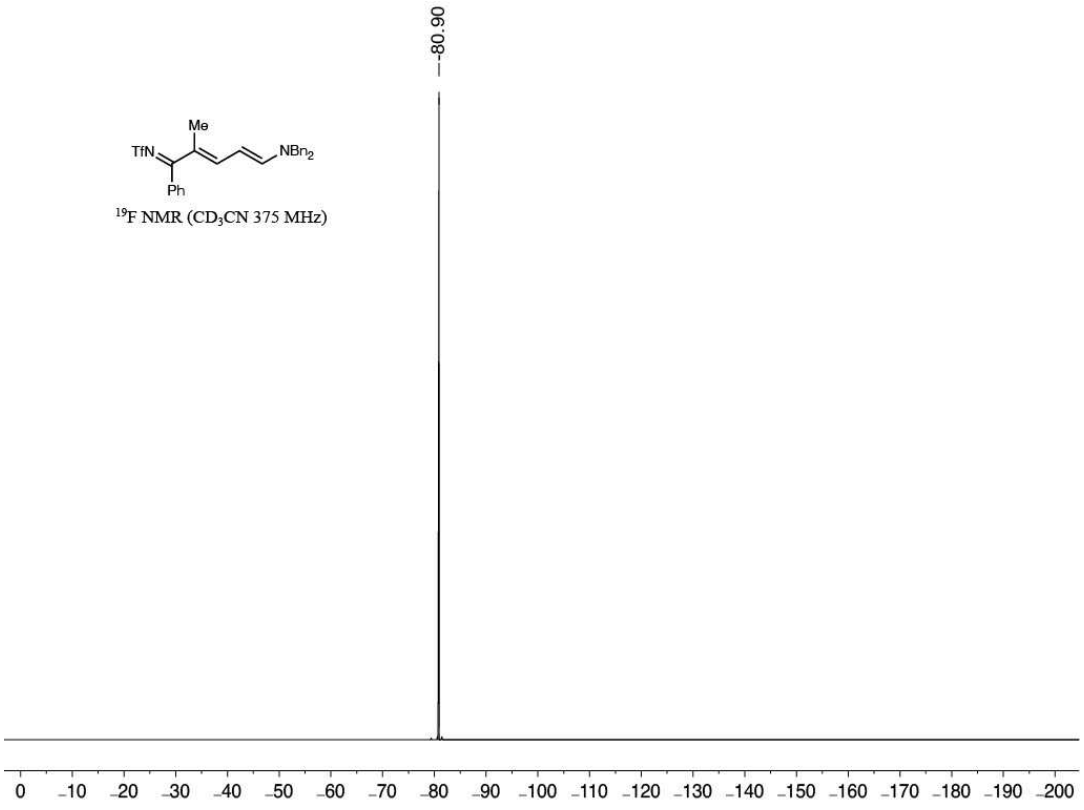
^{1}H NMR (CD_3CN 400 MHz)



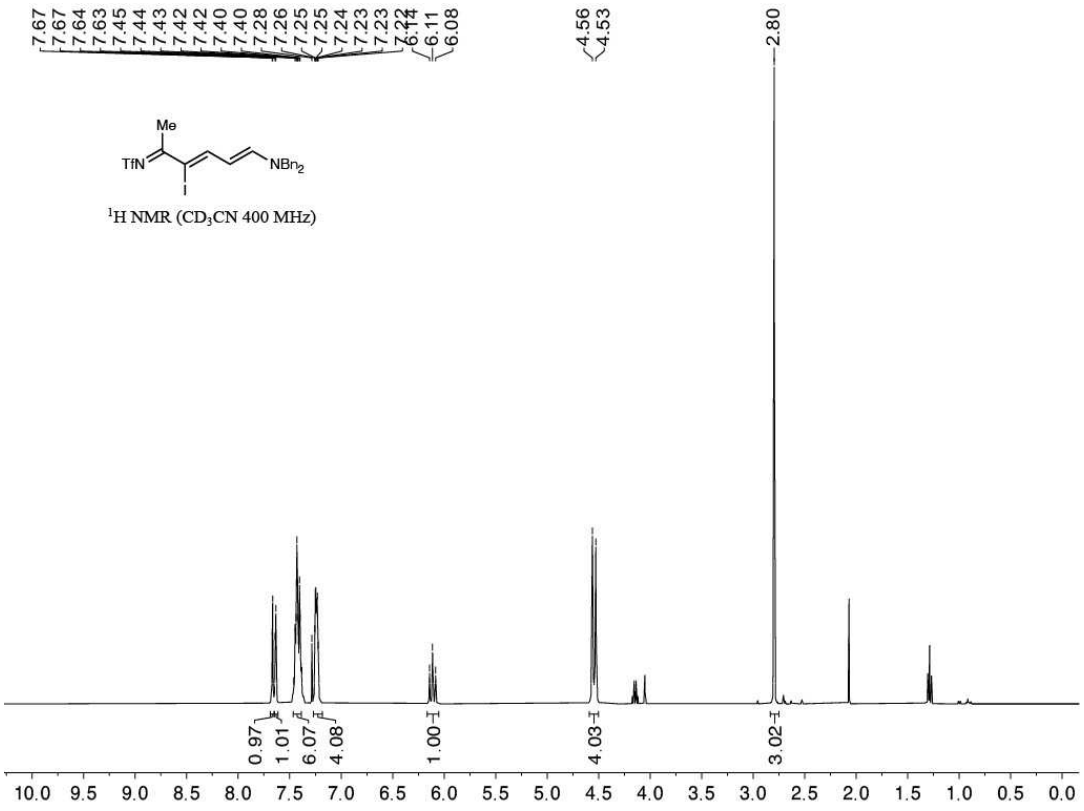
^{19}F NMR (CD_3CN 375 MHz)



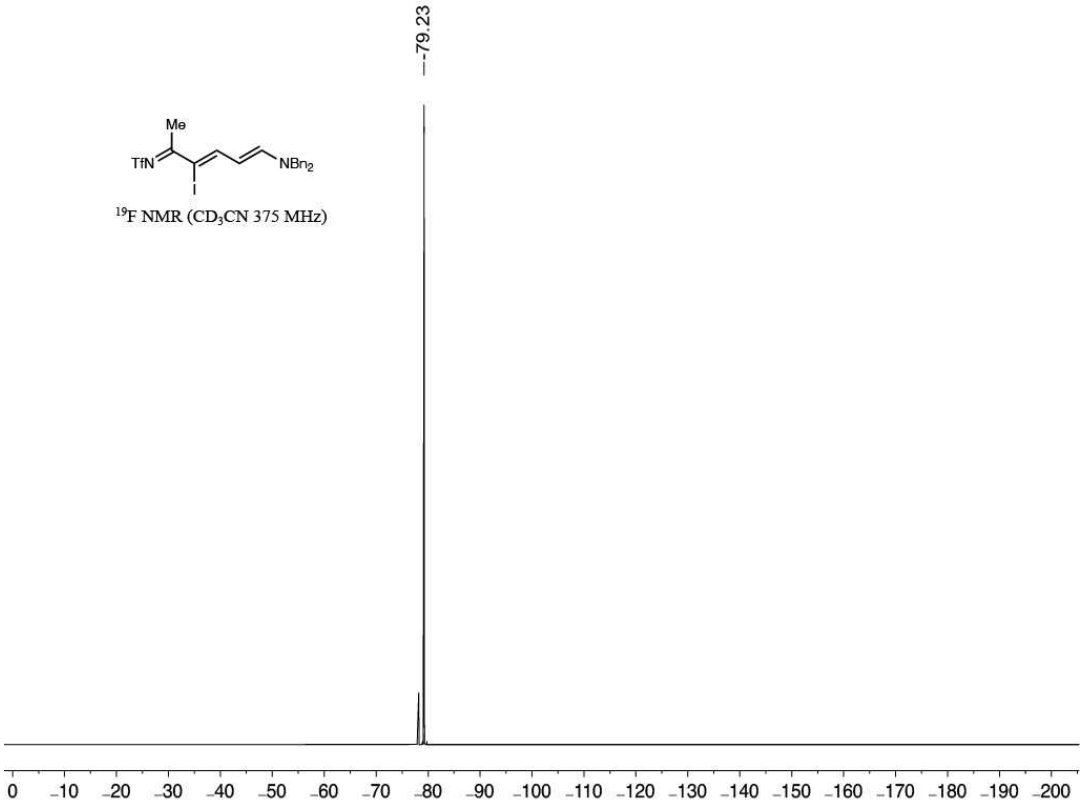
^{1}H NMR (CD_3CN 400 MHz)



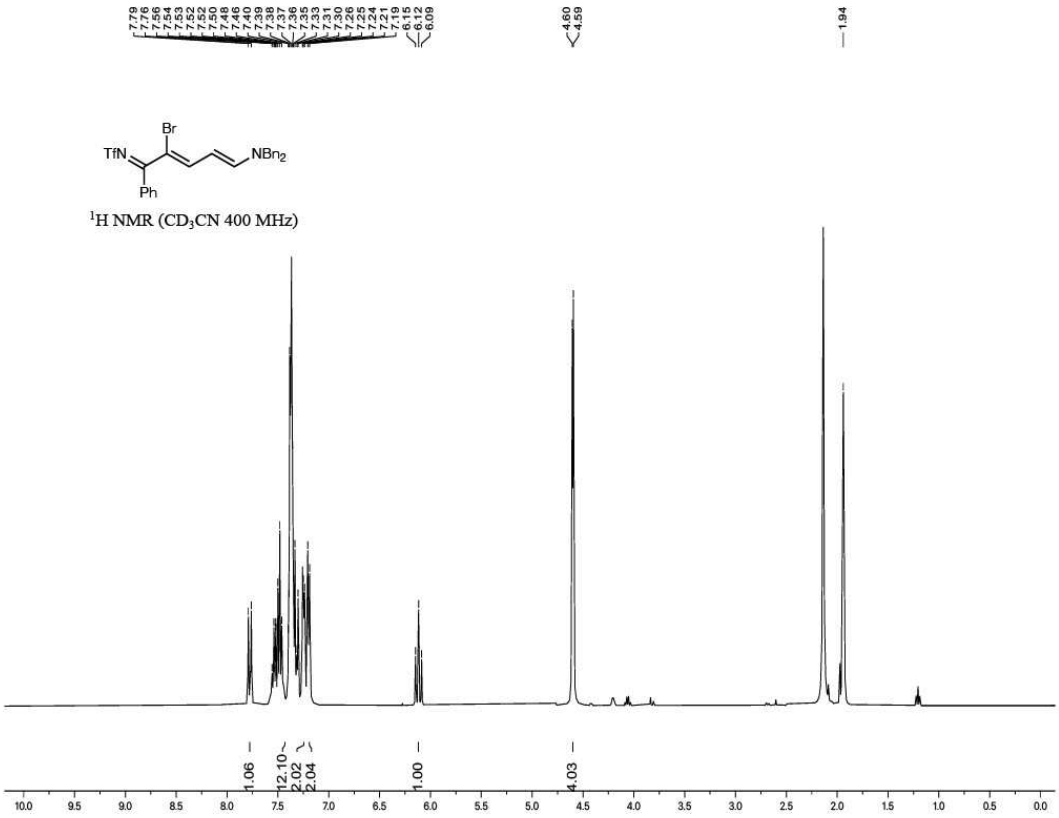
^{19}F NMR (CD_3CN 375 MHz)

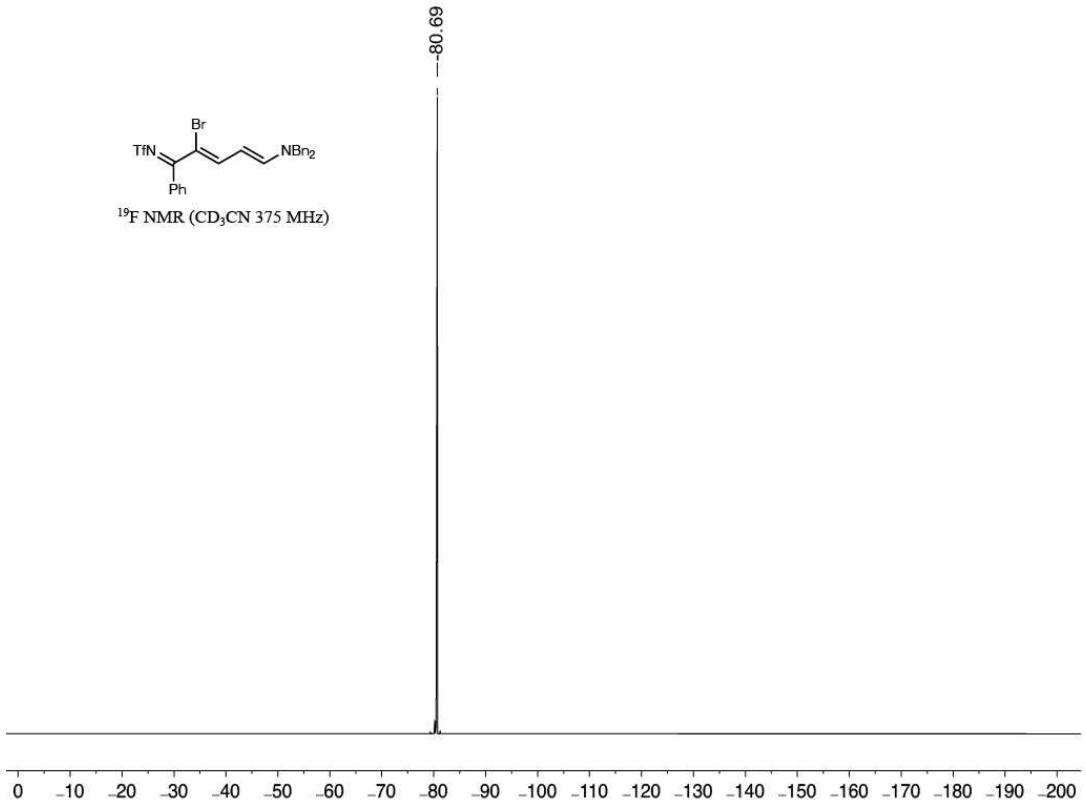


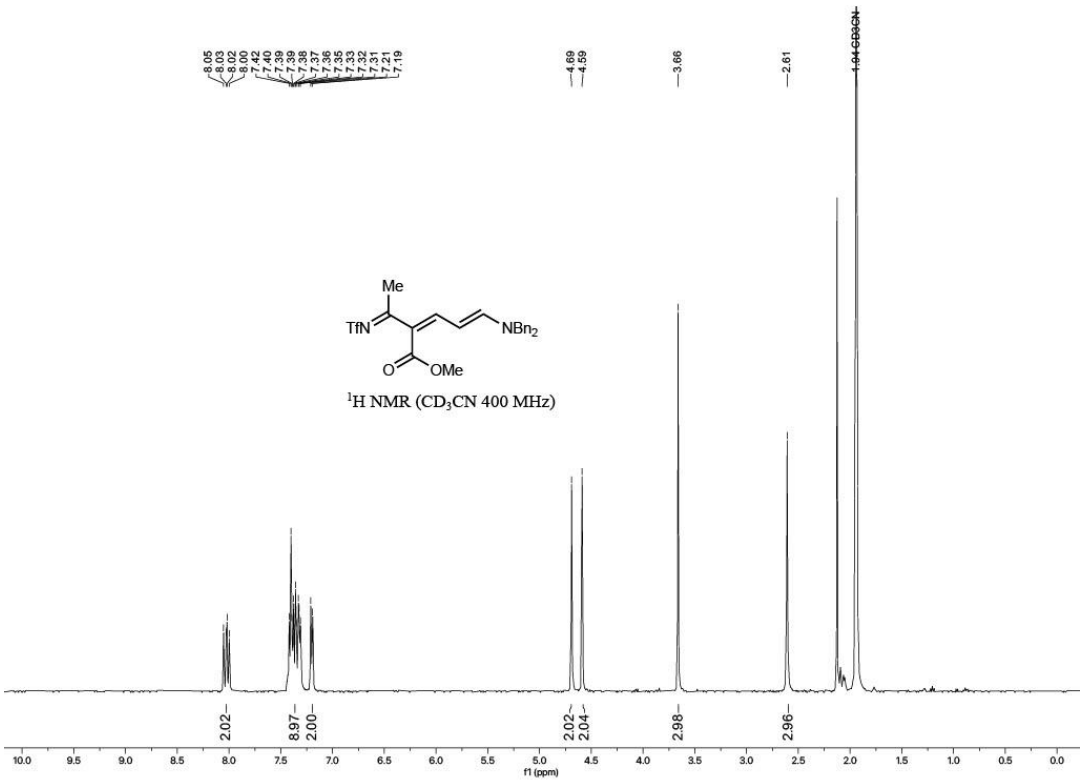
^{1}H NMR (CD_3CN 400 MHz)



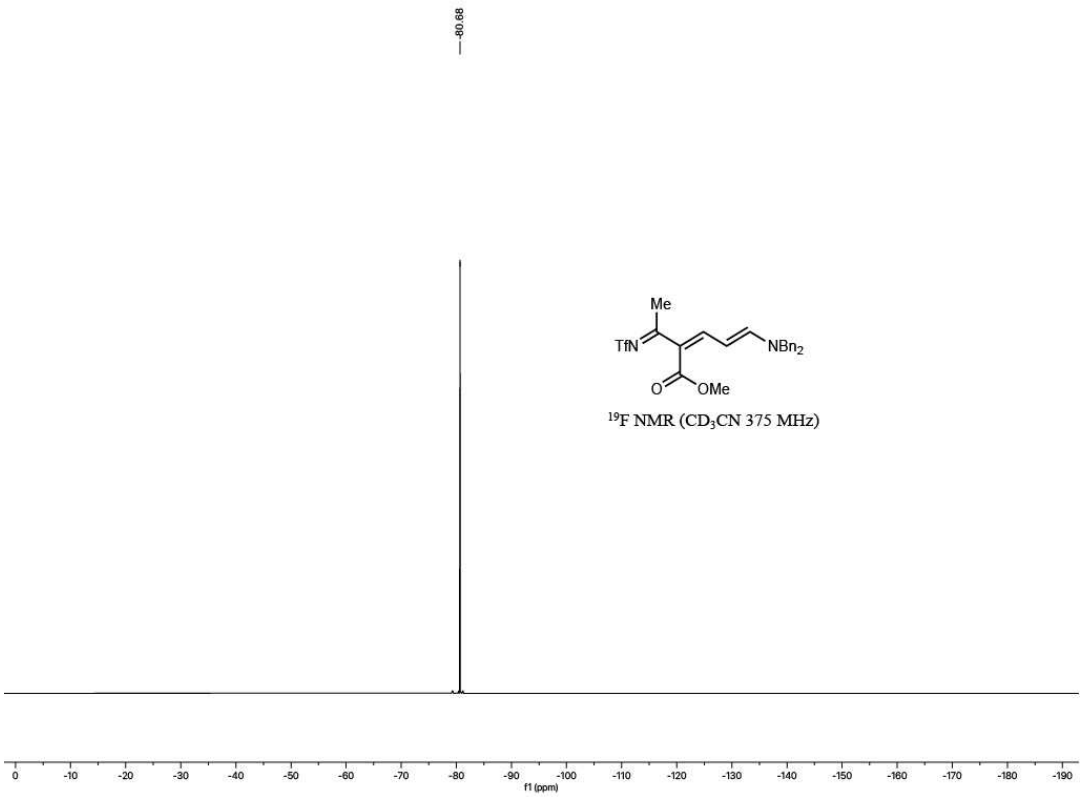
^{19}F NMR (CD_3CN 375 MHz)


7.79
7.76
7.56
7.54
7.53
7.52
7.50
7.48
7.46
7.40
7.39
7.38
7.37
7.36
7.35
7.33
7.31
7.30
7.26
7.25
7.24
7.21
6.19
6.15
6.12
6.09
4.60
4.59
1.94
Br
TfN
NBn2
Ph
1H NMR (CD3CN 400 MHz)
1.06
12.10
2.02
2.04
1.00
4.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

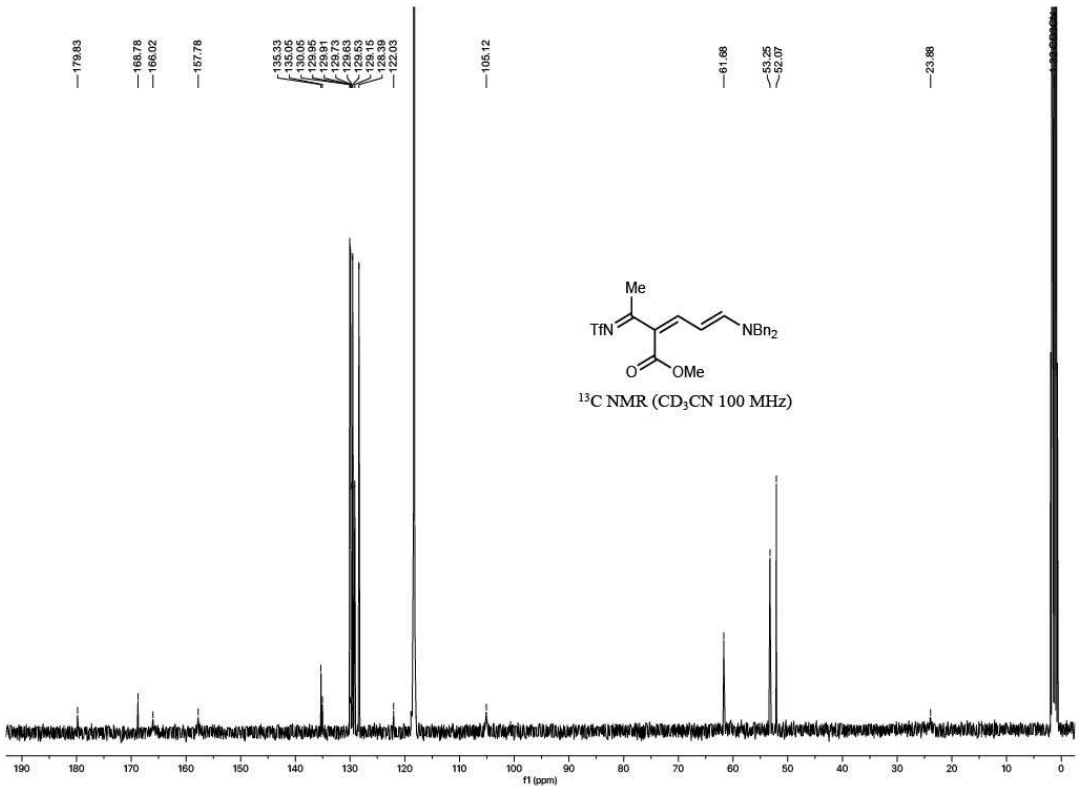

-80.69
Br
TfN
NBn2
Ph
19F NMR (CD3CN 375 MHz)
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200



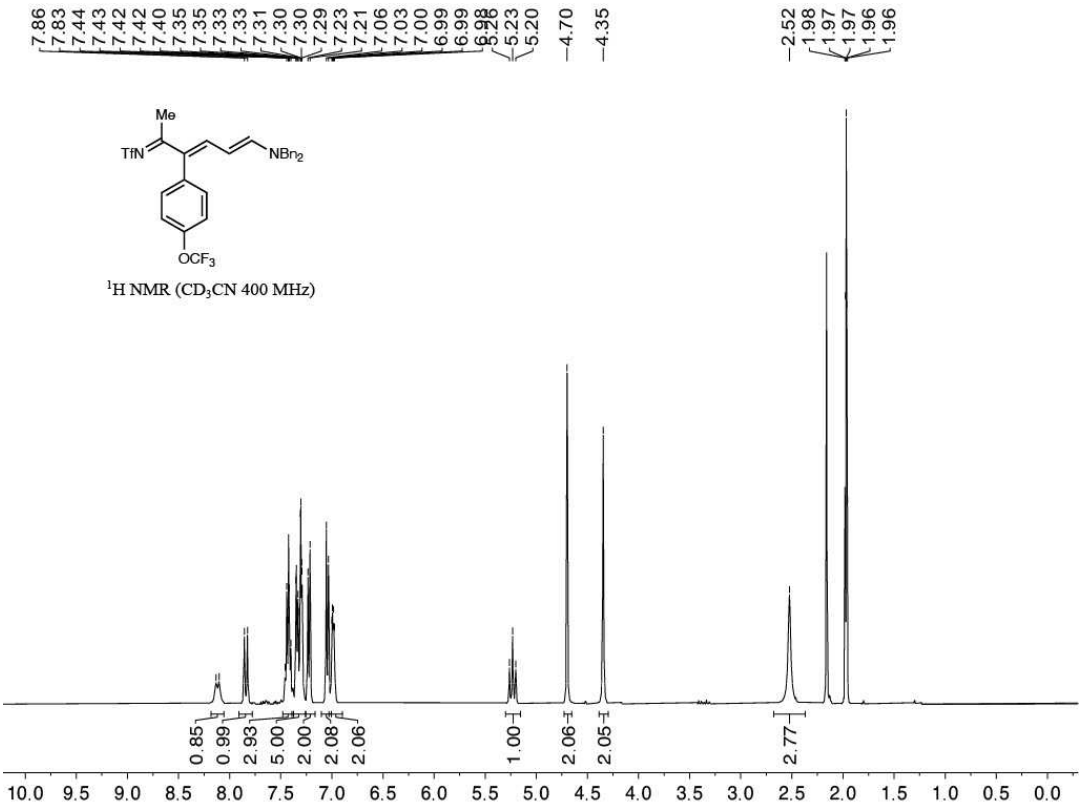
^{1}H NMR (CD_3CN 400 MHz)



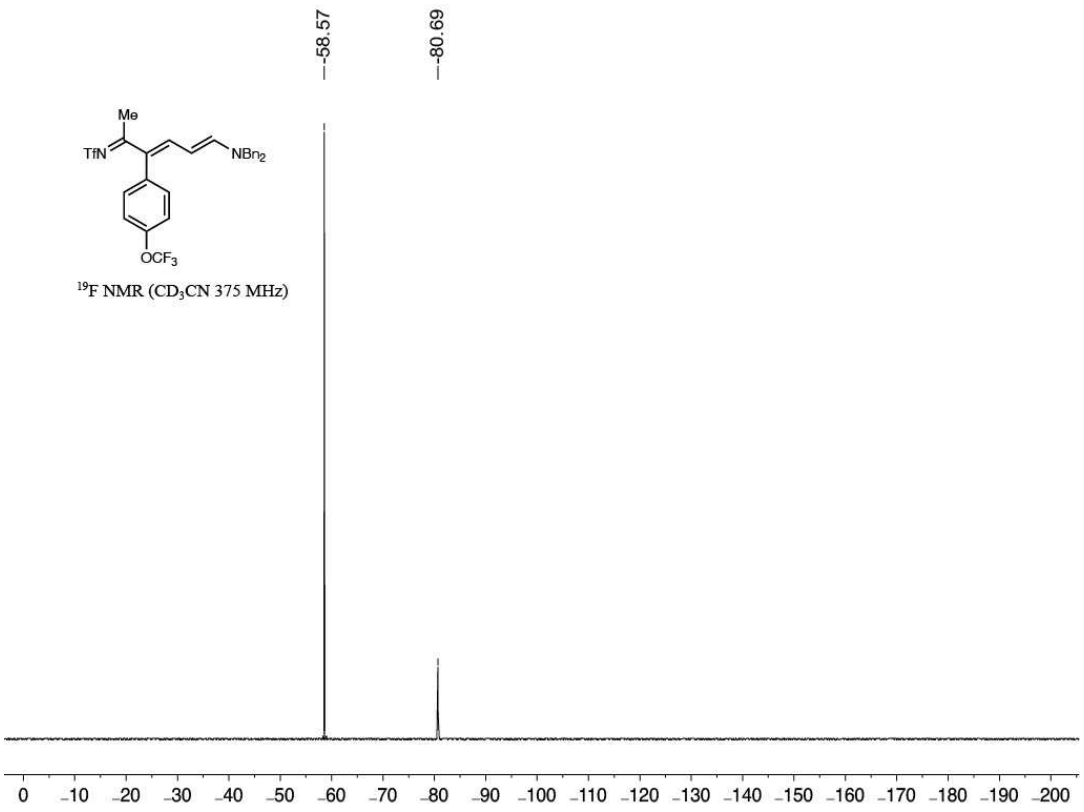
^{19}F NMR (CD_3CN 375 MHz)



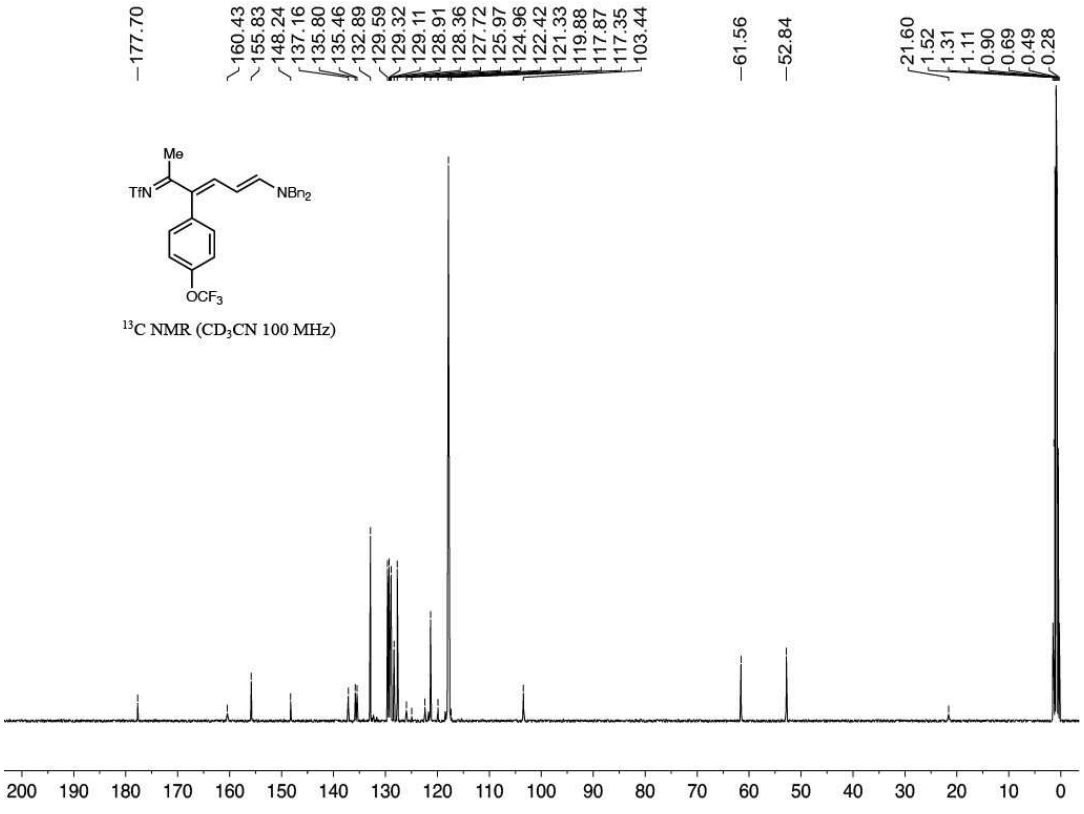
^{13}C NMR (CD_3CN 100 MHz)



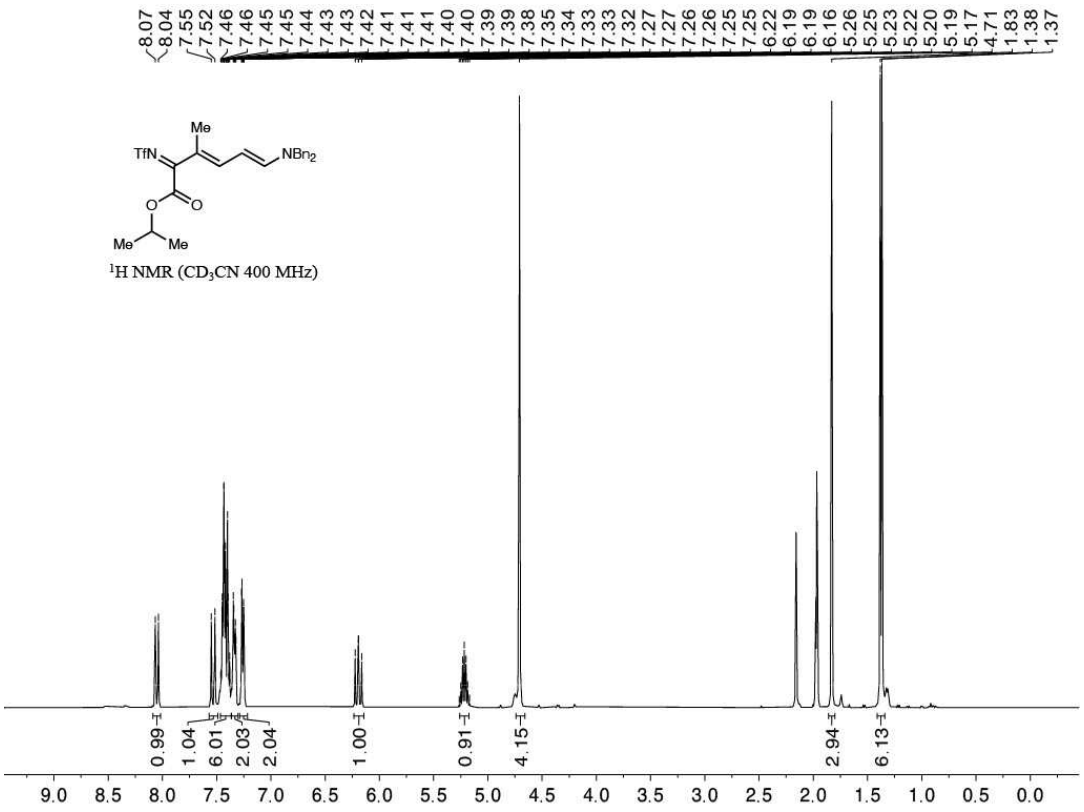
^{1}H NMR (CD_3CN 400 MHz)



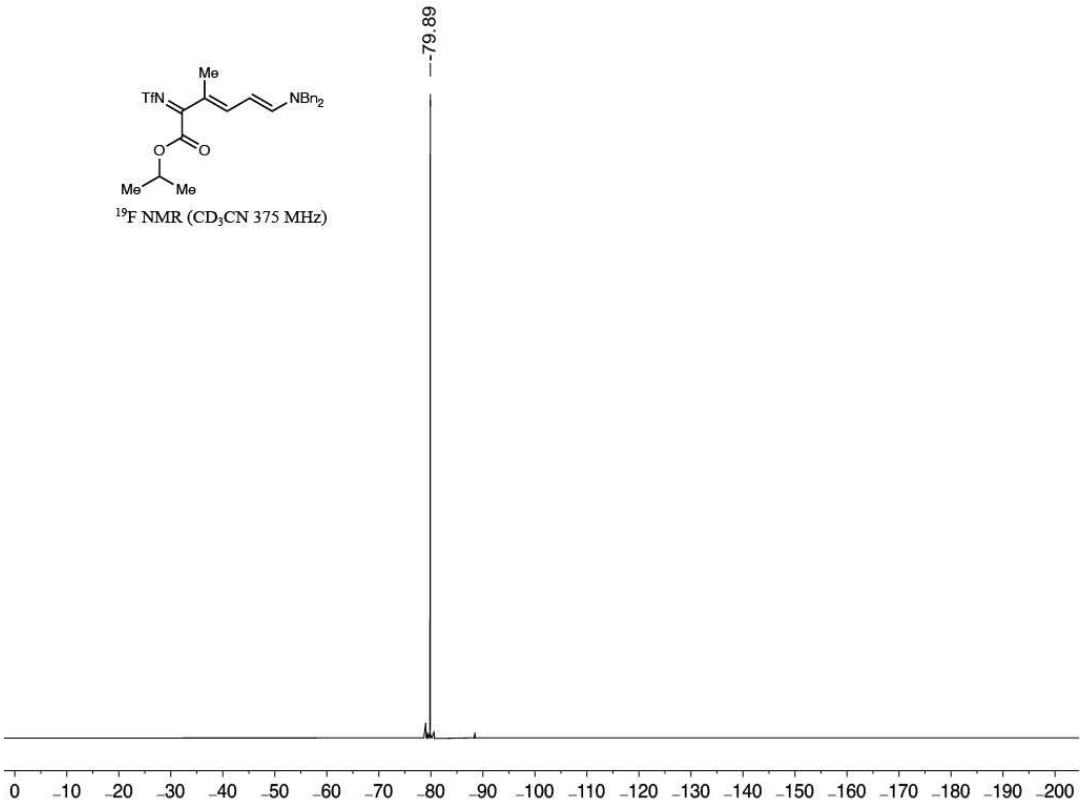
^{19}F NMR (CD_3CN 375 MHz)



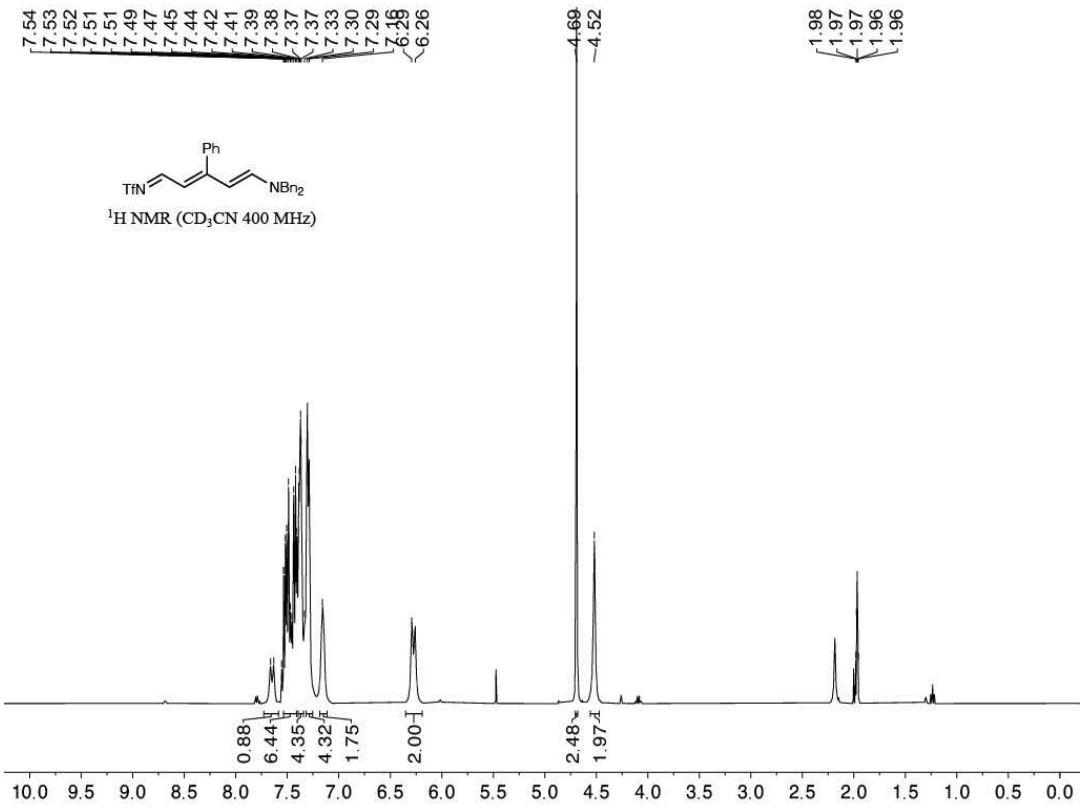
^{13}C NMR (CD_3CN 100 MHz)



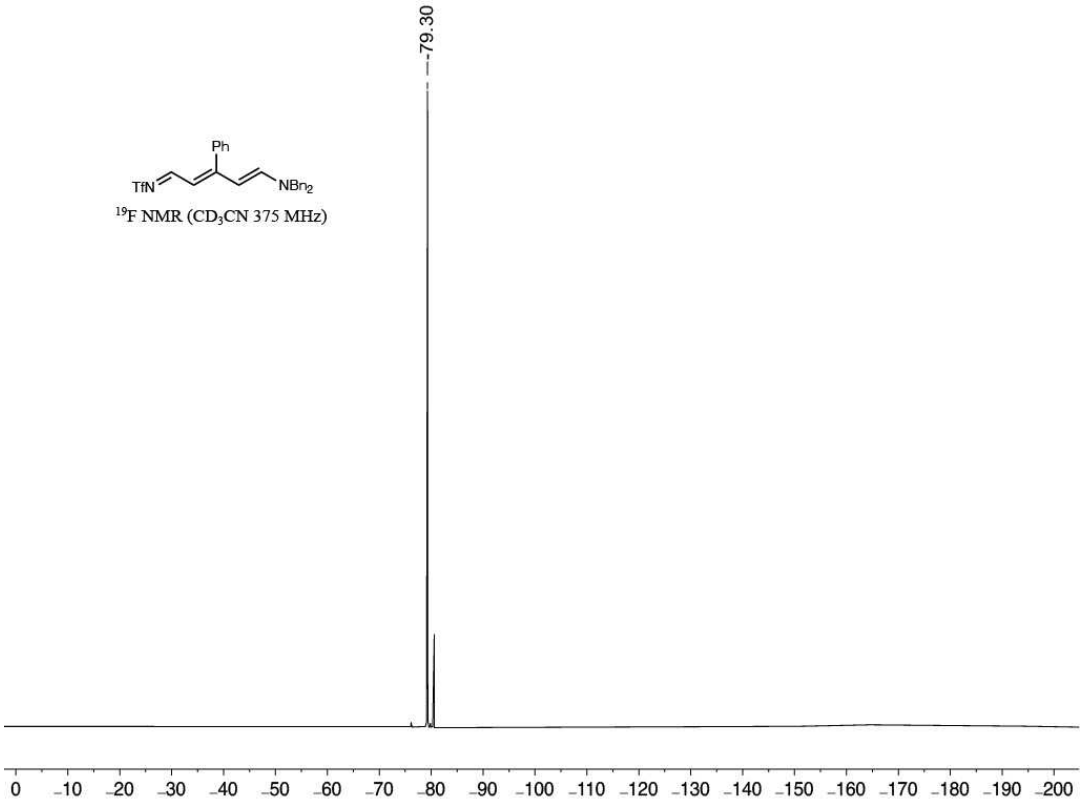
^{1}H NMR (CD_3CN 400 MHz)



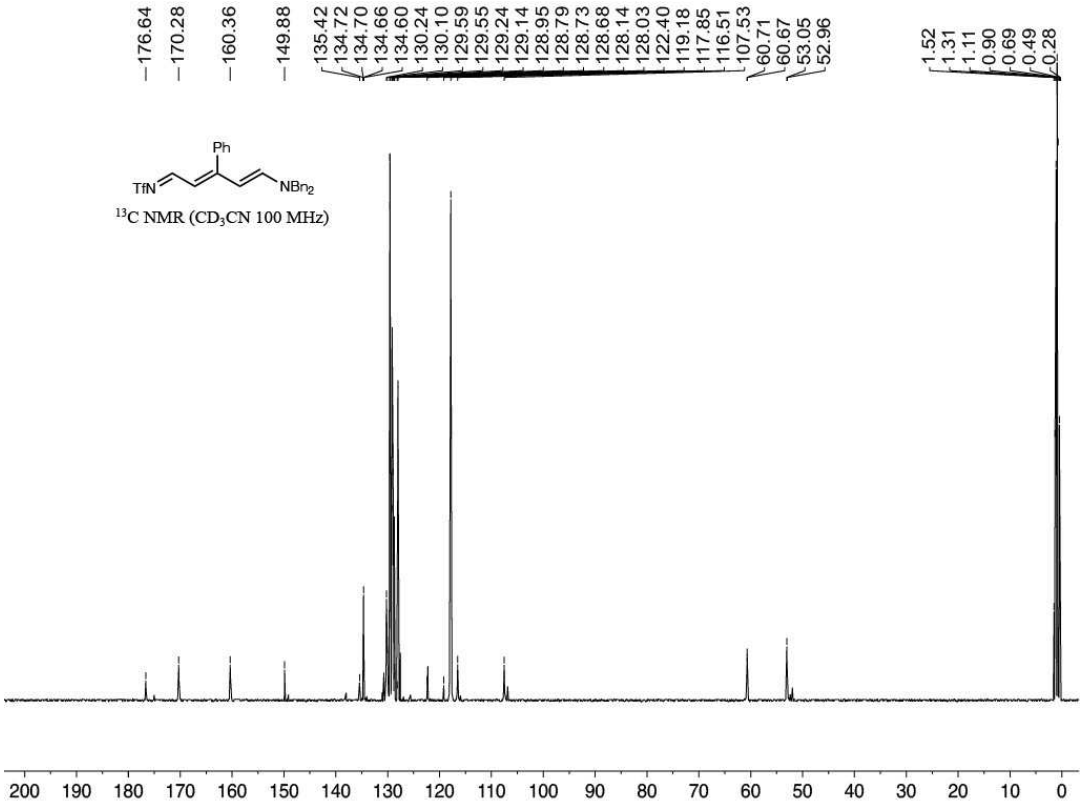
^{19}F NMR (CD_3CN 375 MHz)

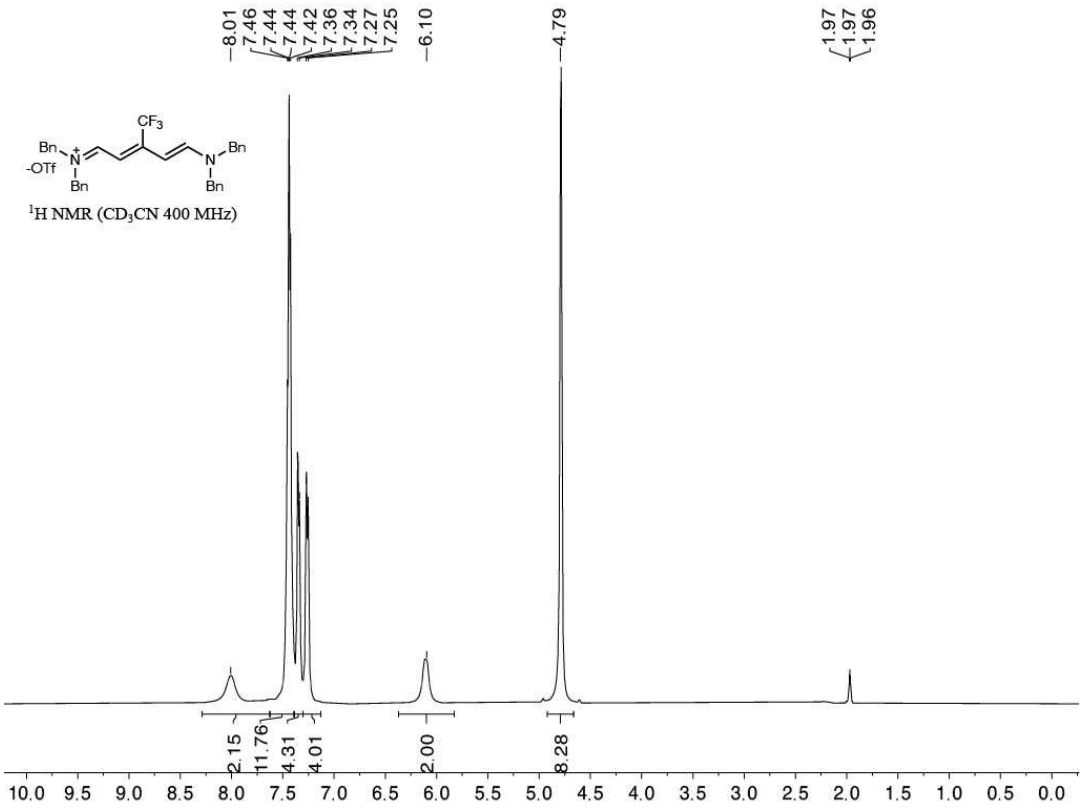


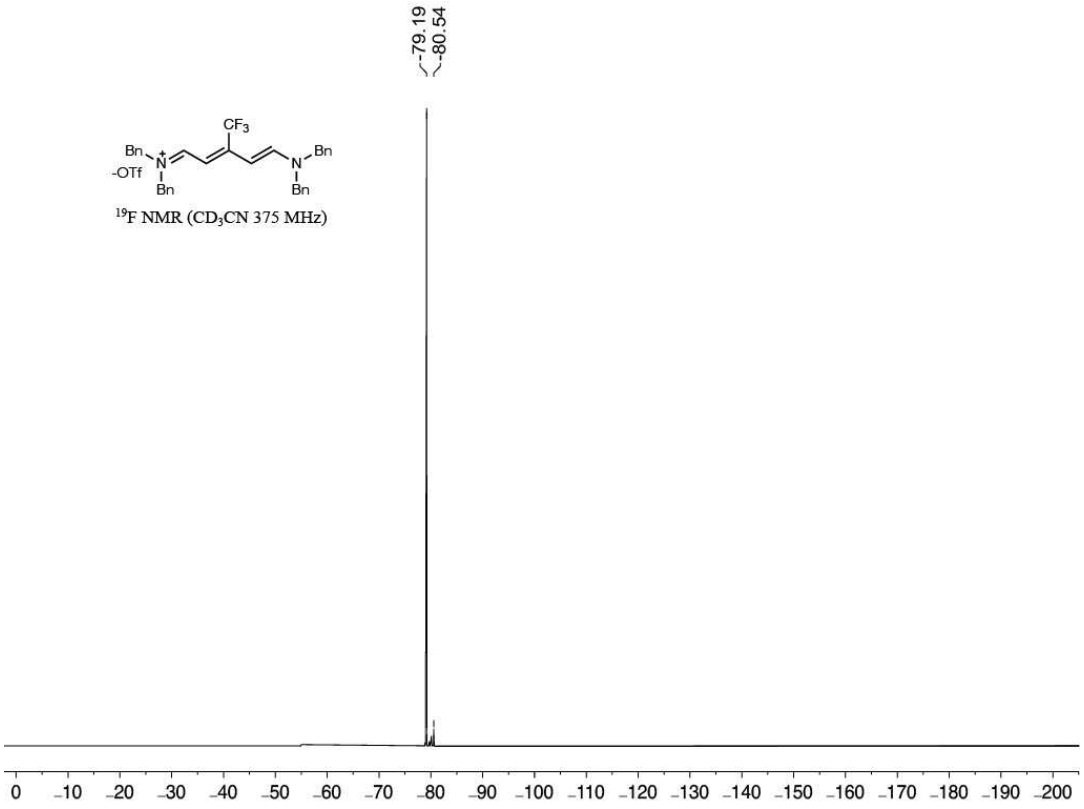
^{1}H NMR (CD_3CN 400 MHz)

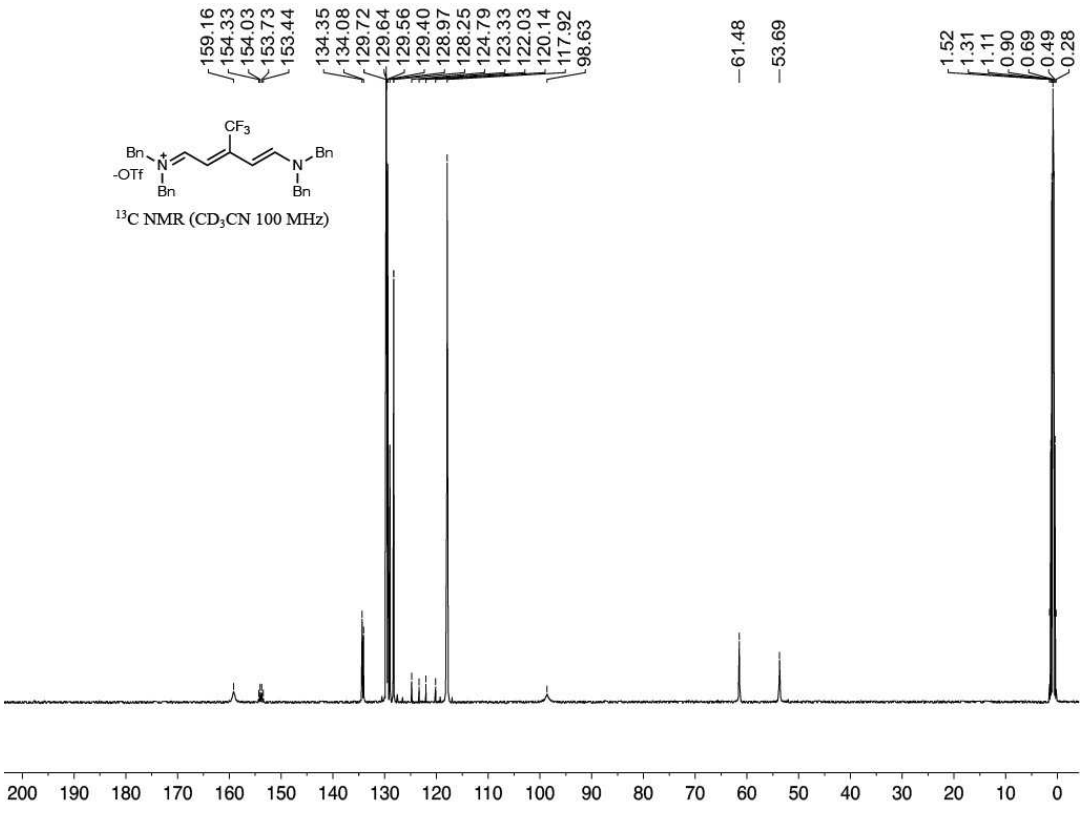


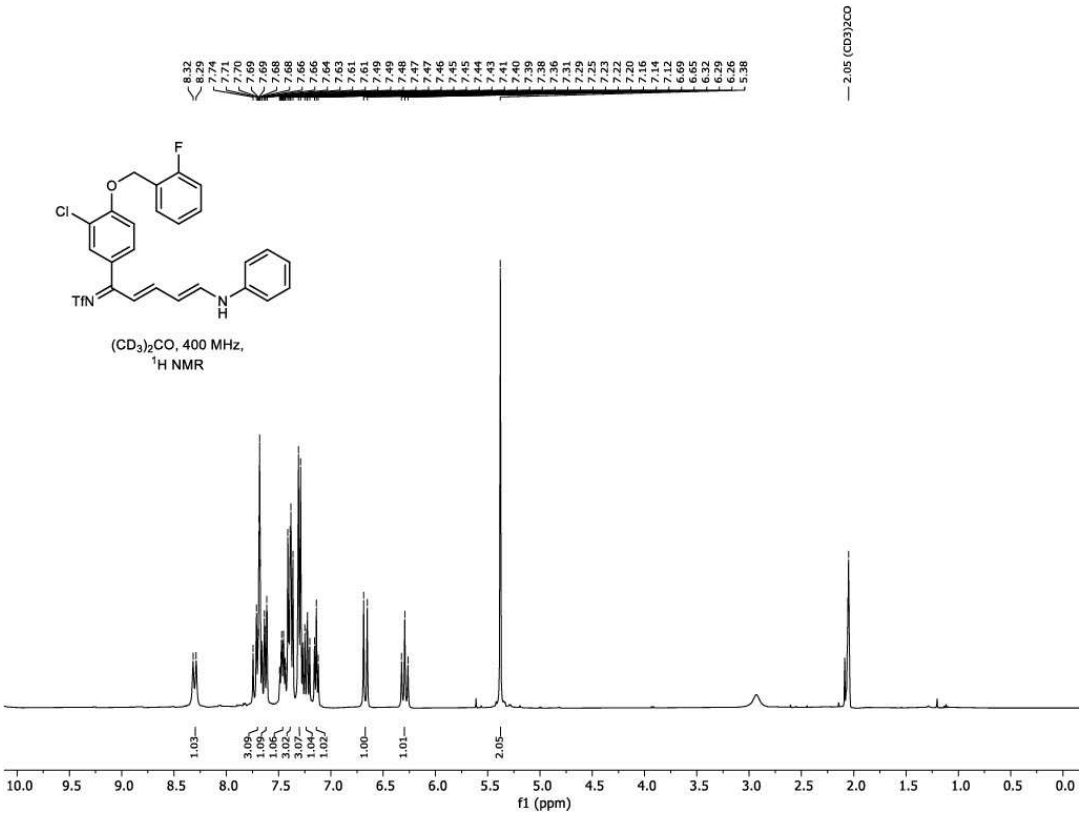
^{19}F NMR (CD_3CN 375 MHz)

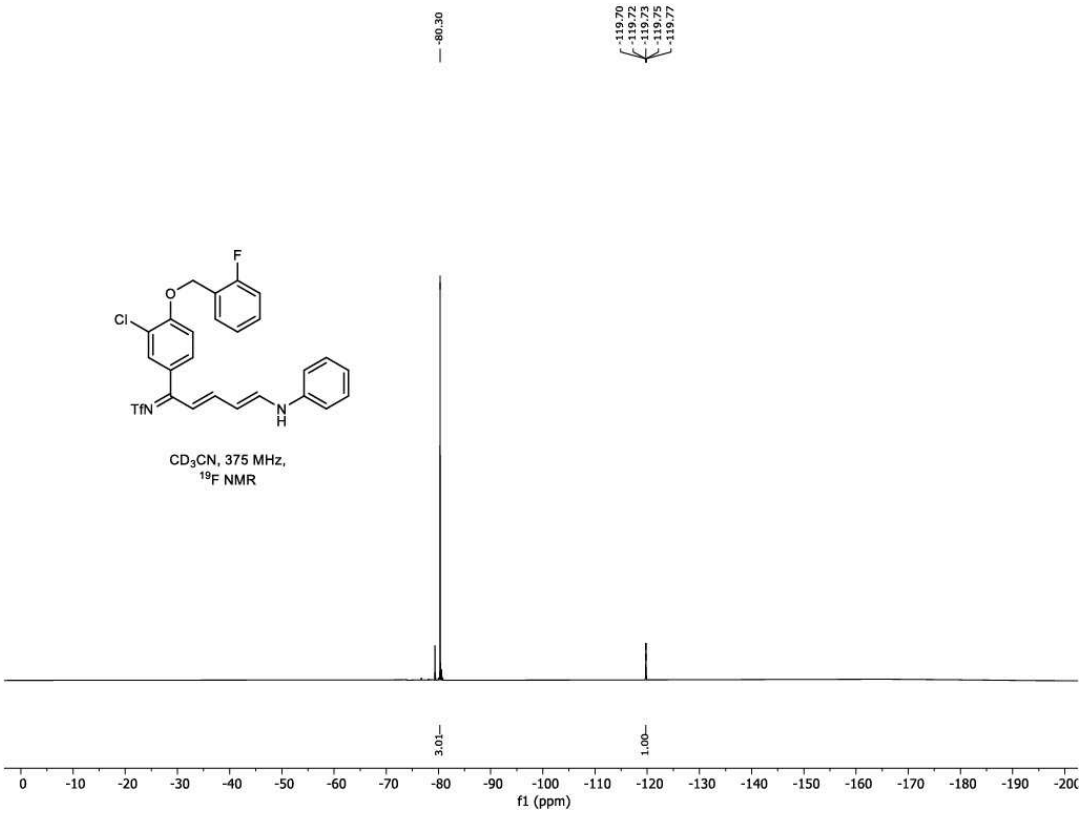

176.64
170.28
160.36
149.88
135.42
134.72
134.70
134.66
134.60
130.24
130.10
129.59
129.55
129.24
129.14
128.95
128.79
128.73
128.68
128.14
128.03
122.40
119.18
117.85
116.51
107.53
60.71
60.67
53.05
52.96
1.52
1.31
1.11
0.90
0.69
0.49
0.28
Ph
TfN
NBn2
13C NMR (CD3CN 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

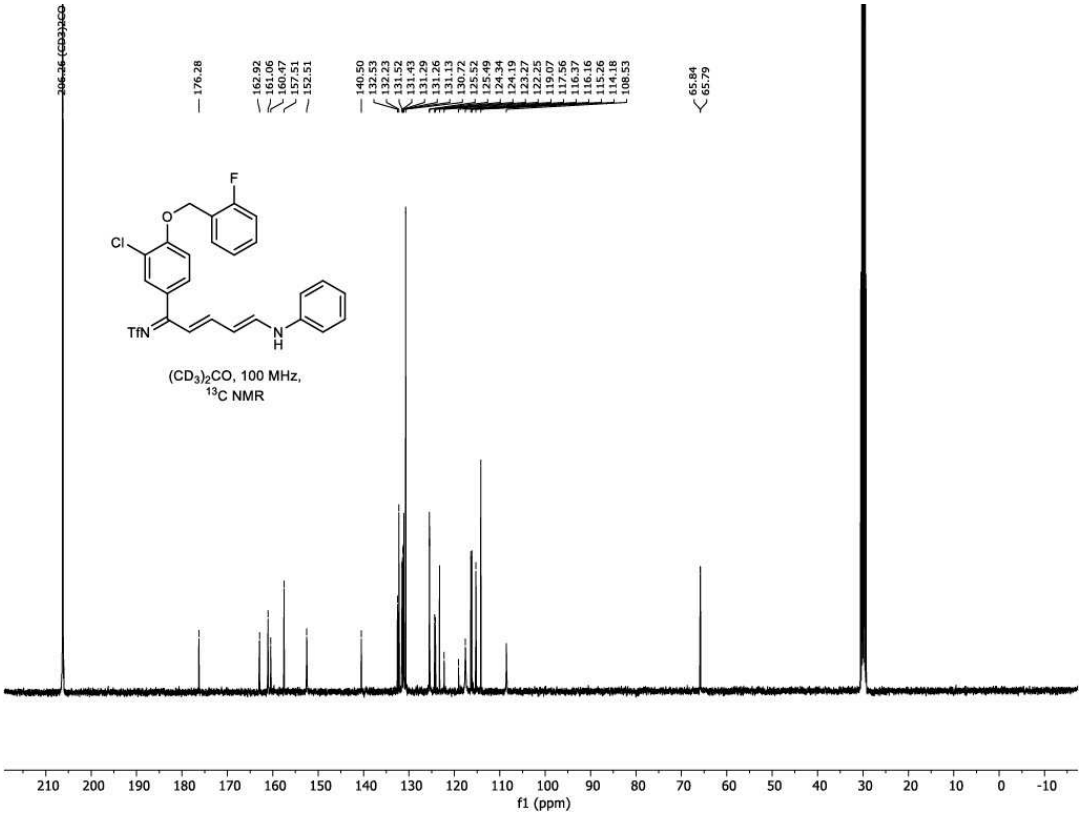

8.01
7.46
7.44
7.44
7.42
7.36
7.34
7.27
7.25
6.10
4.79
1.97
1.97
1.96
CF3
Bn
-OTf
N
Bn
Bn
N
Bn
1H NMR (CD3CN 400 MHz)
2.15
11.76
4.31
4.01
2.00
8.28
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

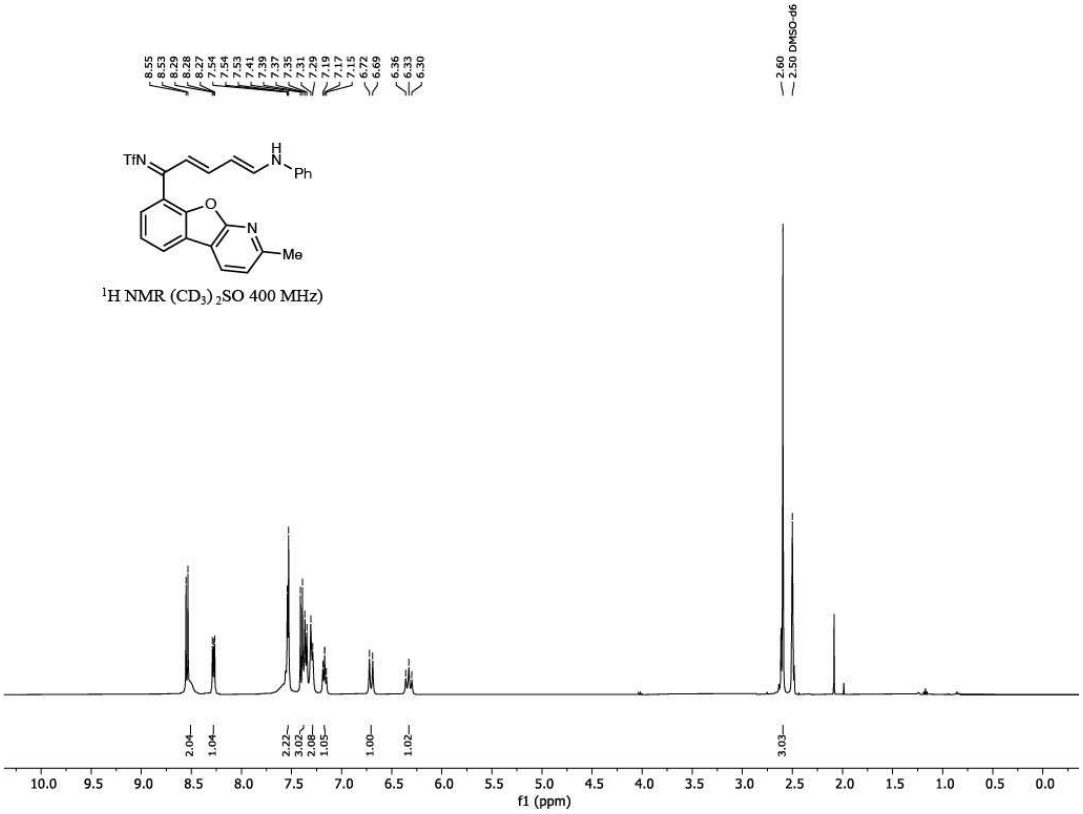

-79.19
-80.54
CF3
Bn
-OTf
N
Bn
Bn
N
Bn
Bn
19F NMR (CD3CN 375 MHz)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

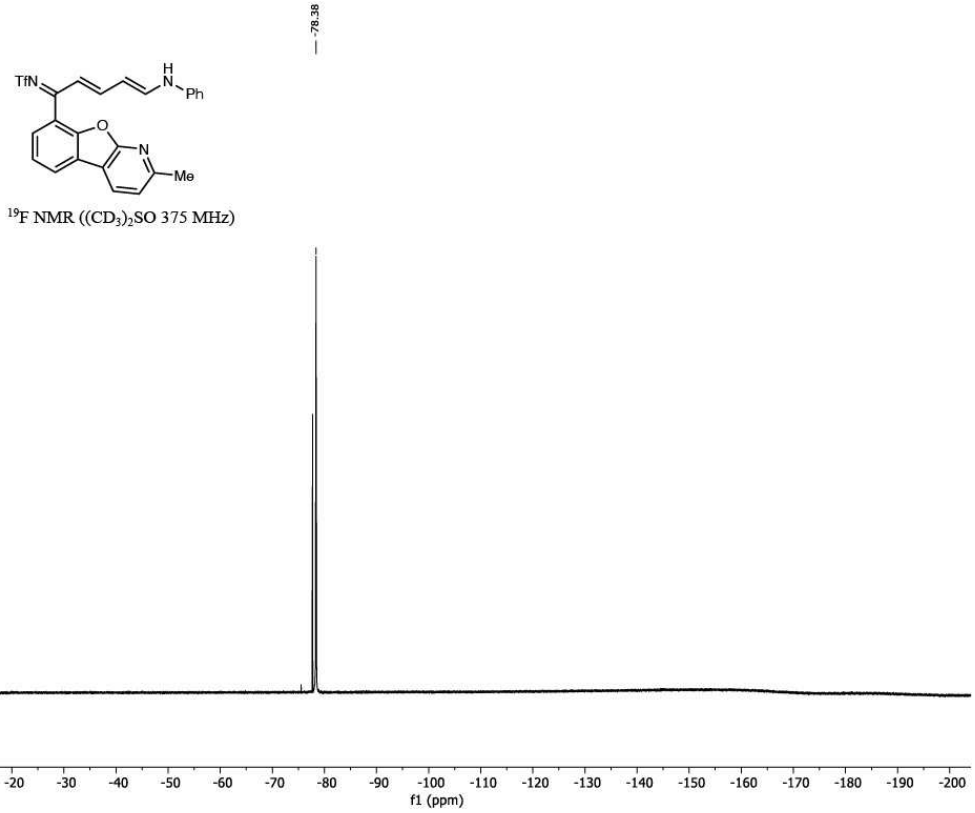

159.16
154.33
154.03
153.73
153.44
134.35
134.08
129.72
129.64
129.56
129.40
128.97
128.25
124.79
123.33
122.03
120.14
117.92
98.63
61.48
53.69
1.52
1.31
1.11
0.90
0.69
0.49
0.28
CF3
Bn
-OTf
N
Bn
Bn
N
Bn
Bn
13C NMR (CD3CN 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


F
O
Cl
TfN
N
H
(CD3)2CO, 400 MHz,
1H NMR
f1 (ppm)

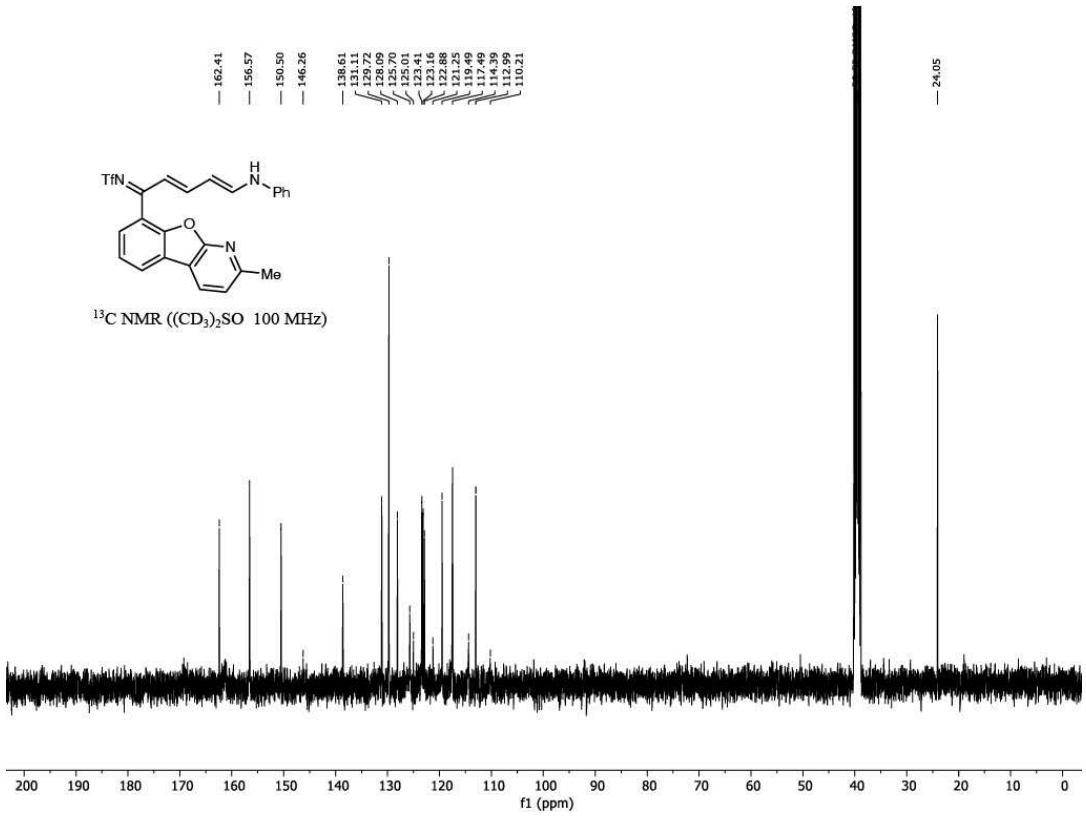

F
O
Cl
TfN
N
H
CD3CN, 375 MHz,
19F NMR
f1 (ppm)


206.26 ((CD3)2CO
176.28
162.92
161.06
160.47
157.51
152.51
140.50
132.53
132.23
131.52
131.43
131.29
131.26
131.13
130.72
125.52
125.49
124.34
124.19
123.27
122.25
119.07
117.56
116.37
116.16
115.26
114.18
108.53
65.84
65.79
F
O
Cl
TfN
N
H
(CD3)2CO, 100 MHz,
13C NMR
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

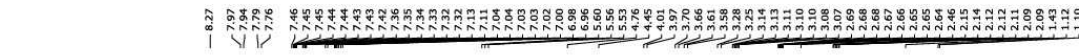

8.55
8.53
8.29
8.28
8.27
7.54
7.53
7.41
7.39
7.37
7.35
7.31
7.29
7.19
7.17
7.15
6.72
6.69
6.36
6.33
6.30
2.60
2.50 DMSO-d6
TfN
H
N
Ph
O
N
Me
1H NMR (CD3) 2SO 400 MHz)
2.04
1.04
2.22
3.02
2.08
1.05
1.00
1.02
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

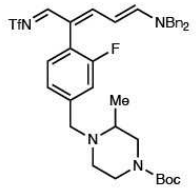


^{19}F NMR ($(CD_3)_2SO$ 375 MHz)

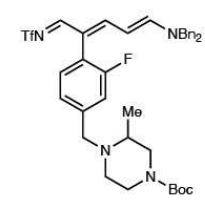


^{13}C NMR ($(CD_3)_2SO$ 100 MHz)

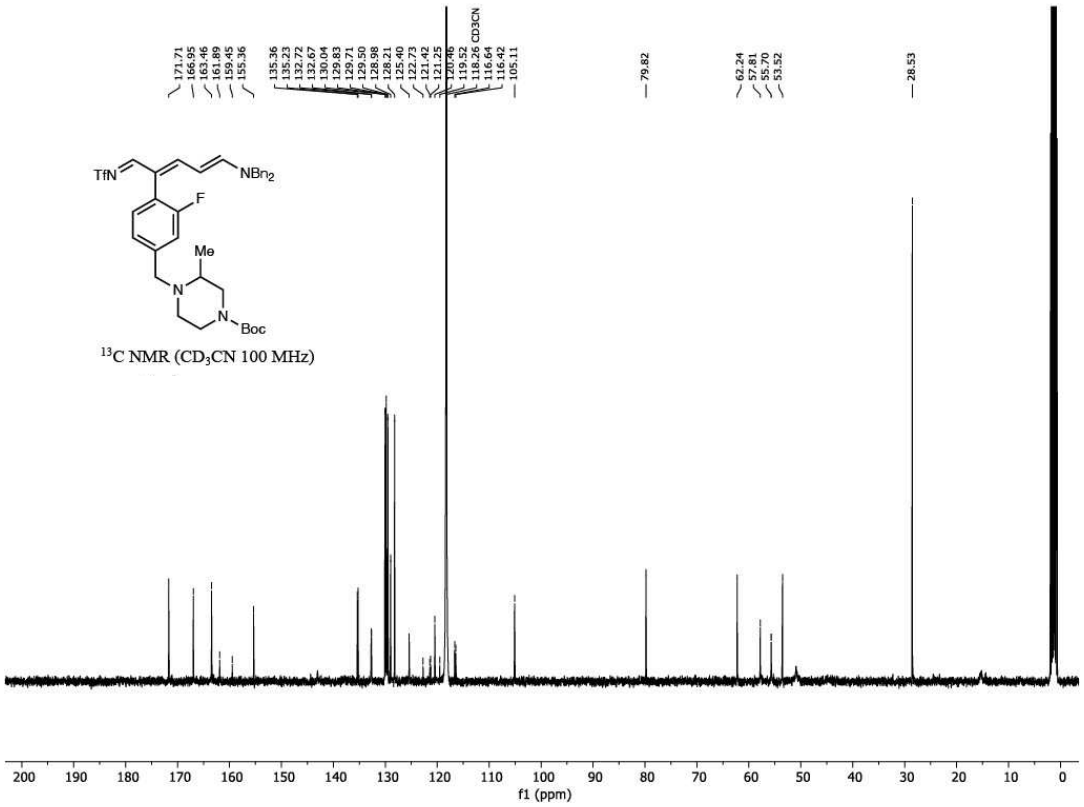




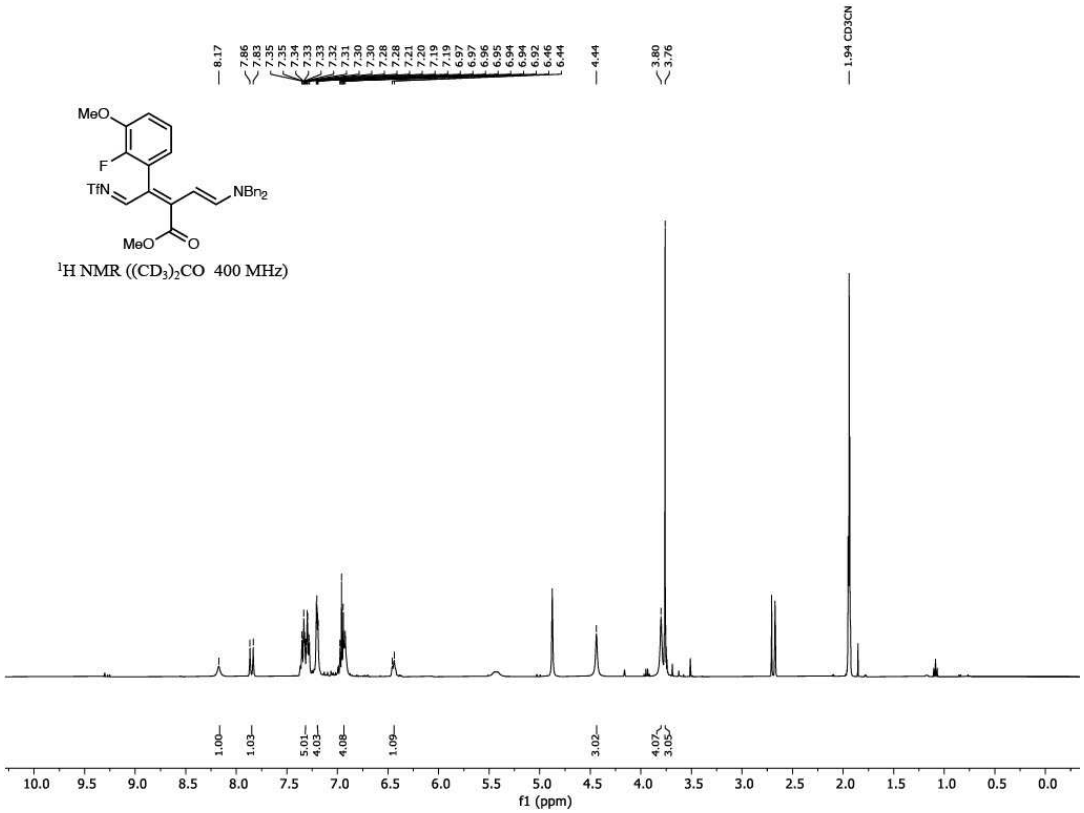
^{1}H NMR (CD_3CN 400 MHz)



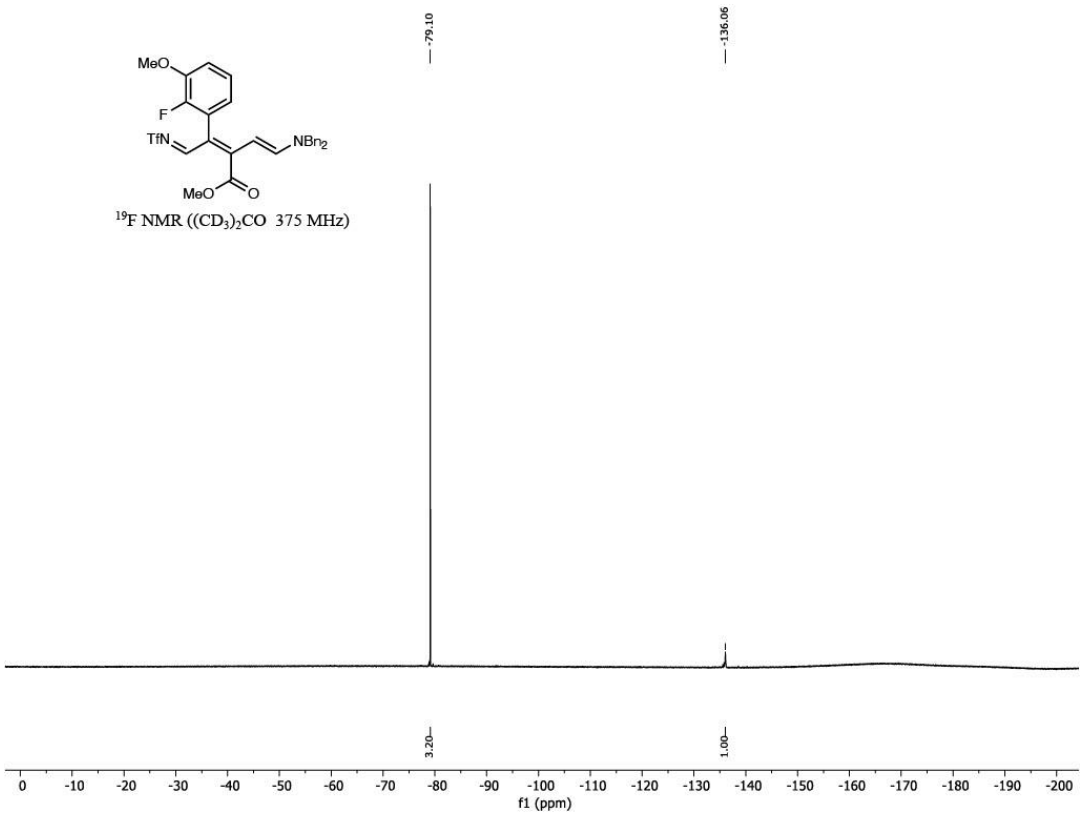
^{19}F NMR (CD_3CN 375 MHz)



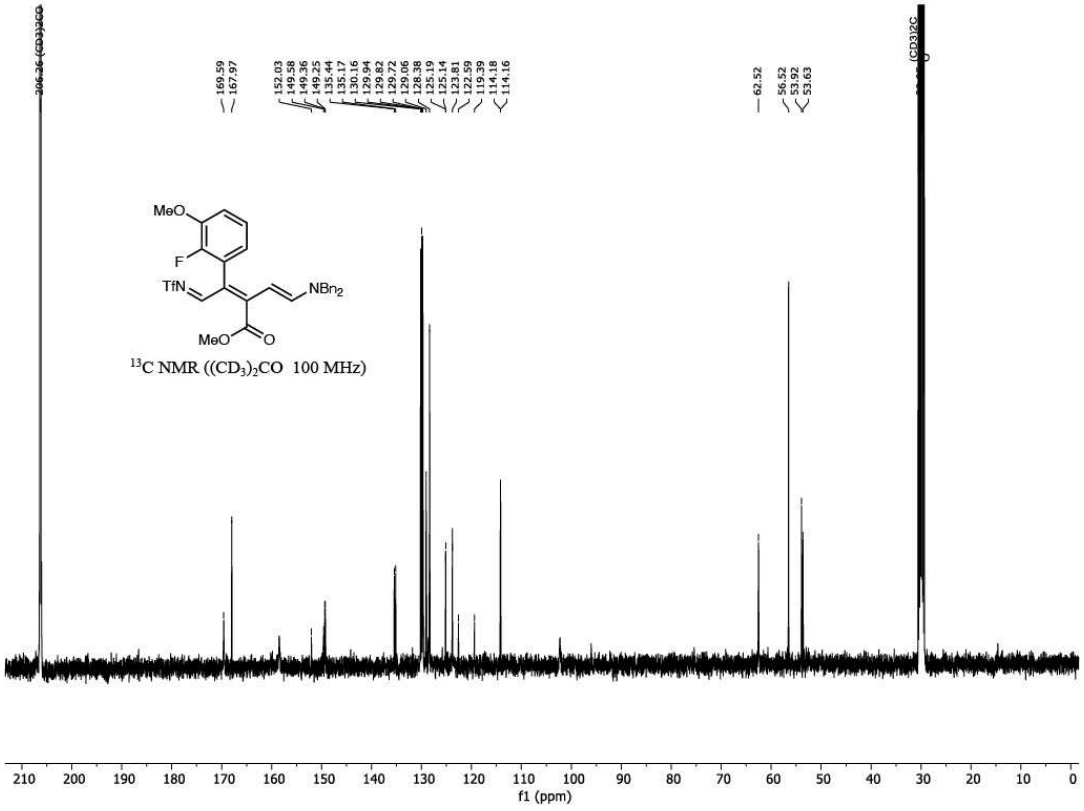
^{13}C NMR (CD_3CN 100 MHz)



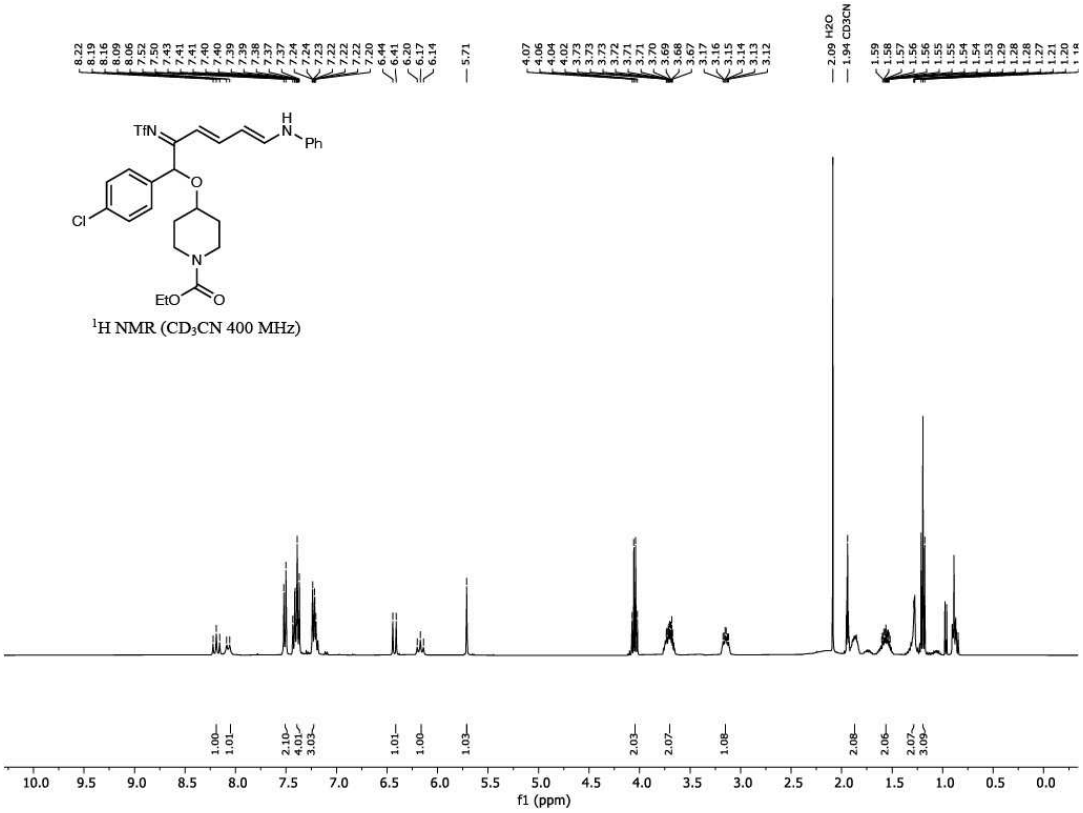
^{1}H NMR ($(CD_3)_2CO$ 400 MHz)



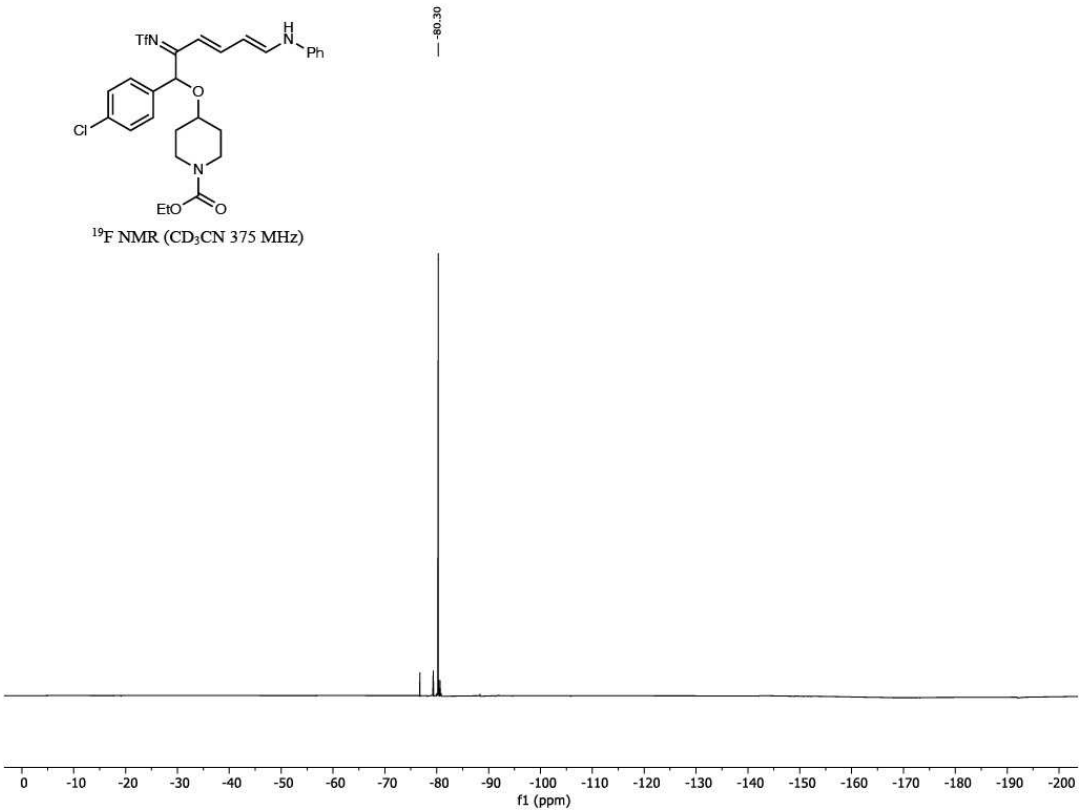
^{19}F NMR ((CD$_3$)$_2$CO 375 MHz)



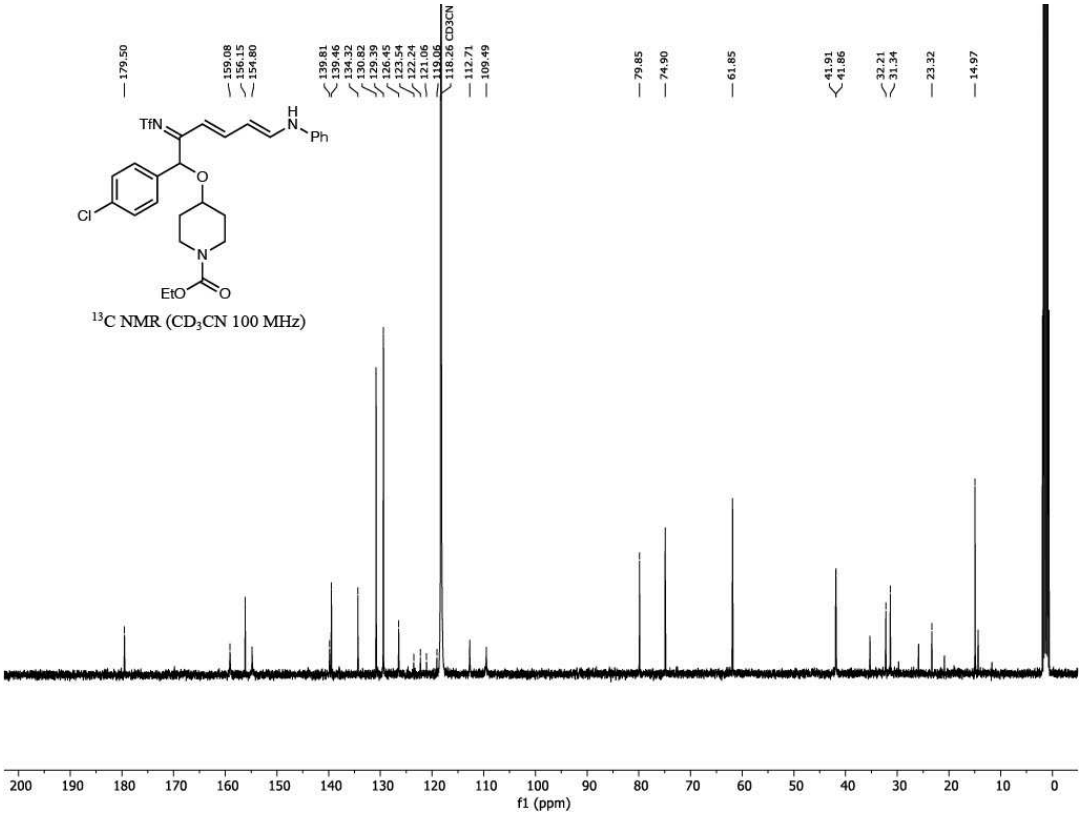
^{13}C NMR ((CD$_3$)$_2$CO 100 MHz)

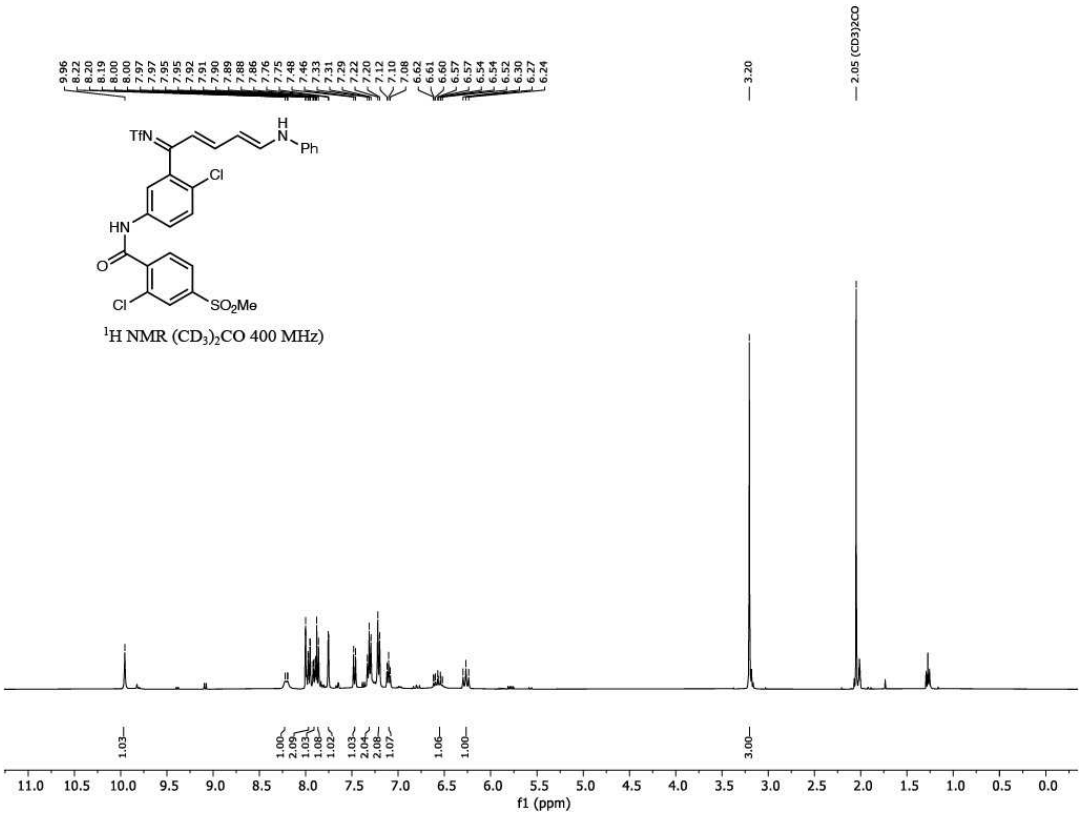


^{1}H NMR (CD_3CN 400 MHz)

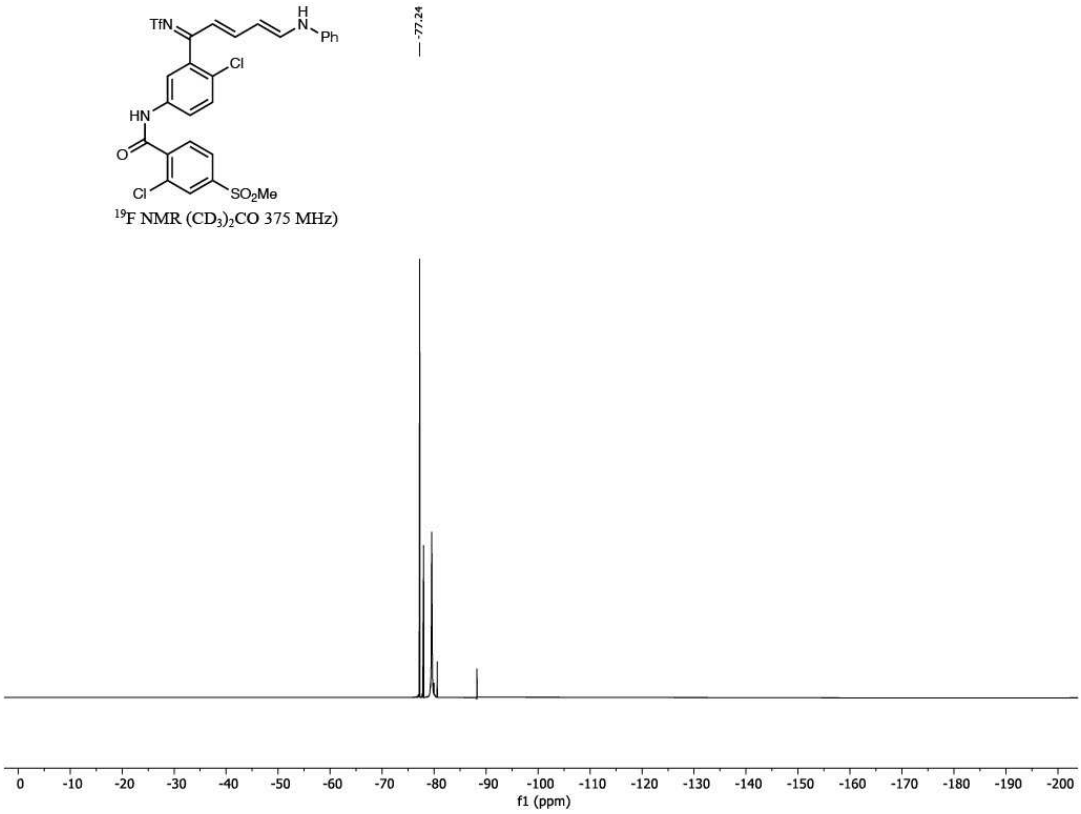


^{19}F NMR (CD_3CN 375 MHz)

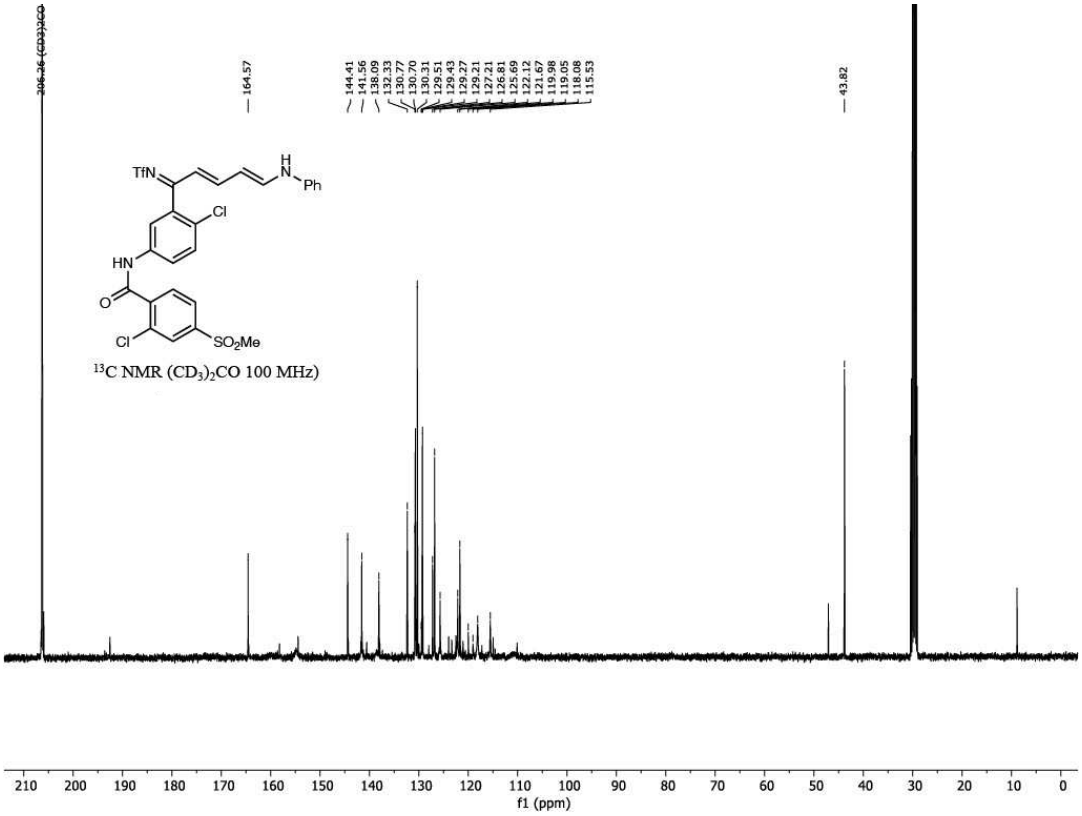

179.50
159.08
156.15
154.80
139.81
139.46
134.32
130.82
129.39
126.45
123.54
122.24
121.06
119.06
118.26 CD3CN
112.71
109.49
79.85
74.90
61.85
41.91
41.86
32.21
31.34
23.32
14.97
TfN
H
N
Ph
O
Cl
N
EtO
O
13C NMR (CD3CN 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

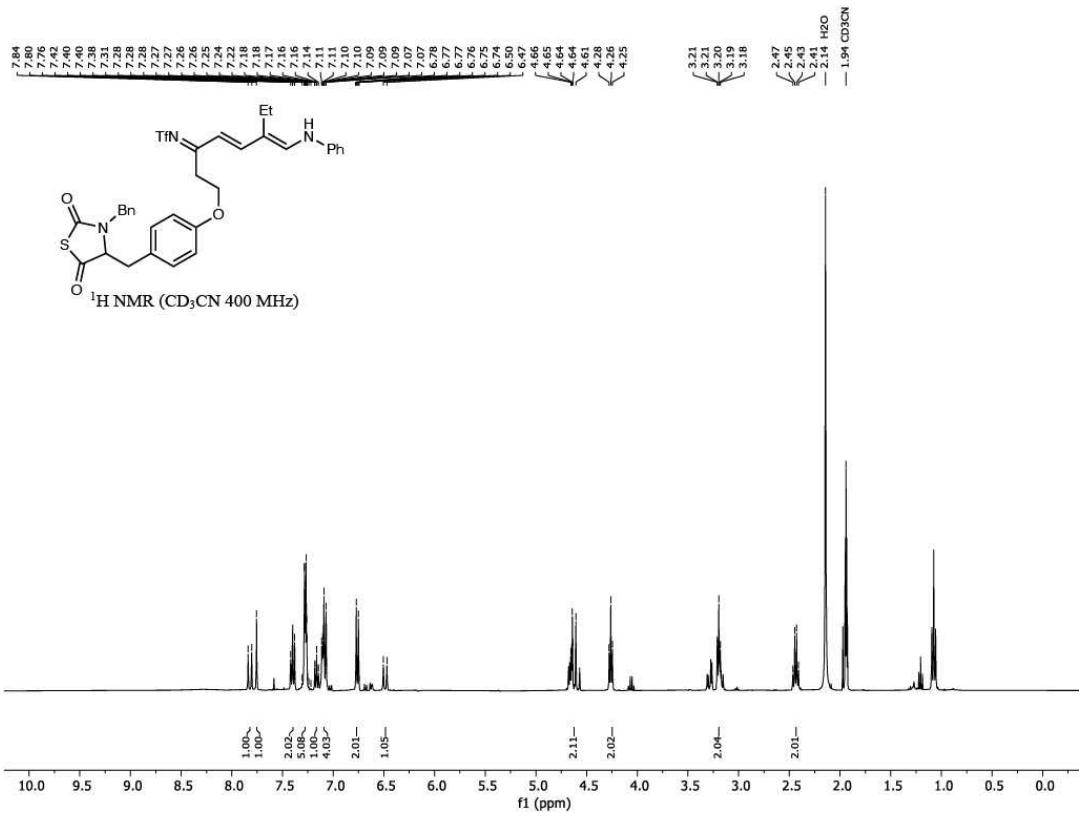


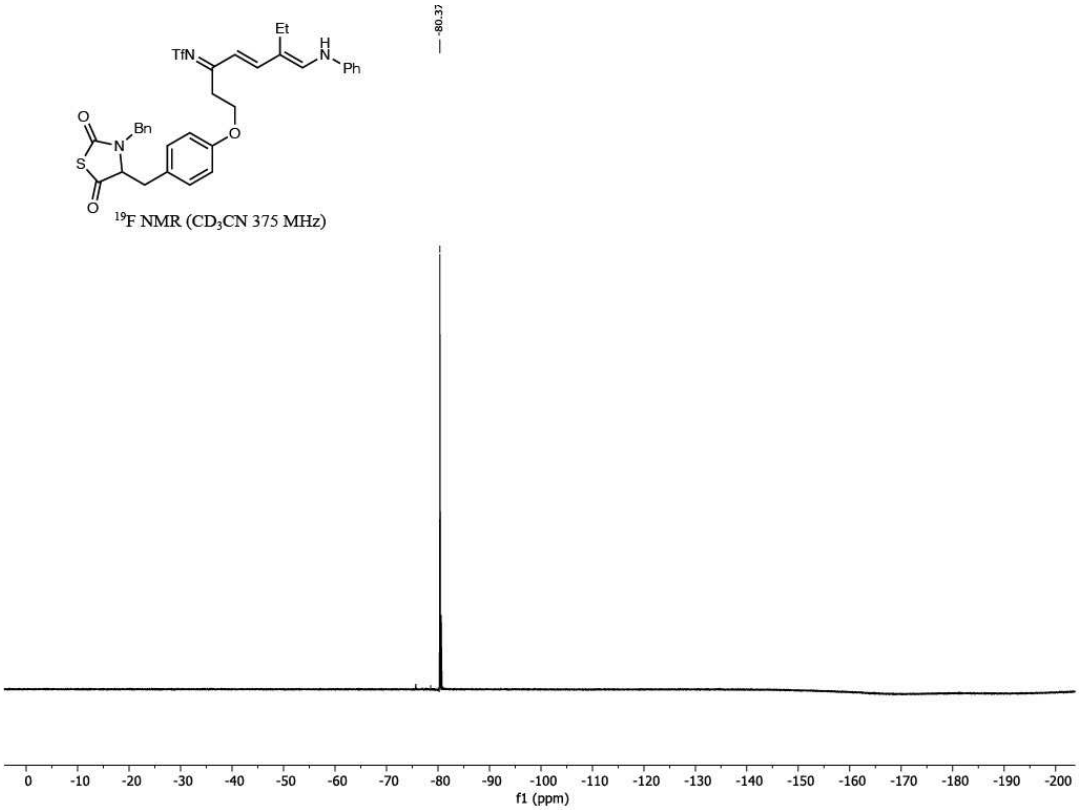
^{1}H NMR $(CD_3)_2CO$ 400 MHz)

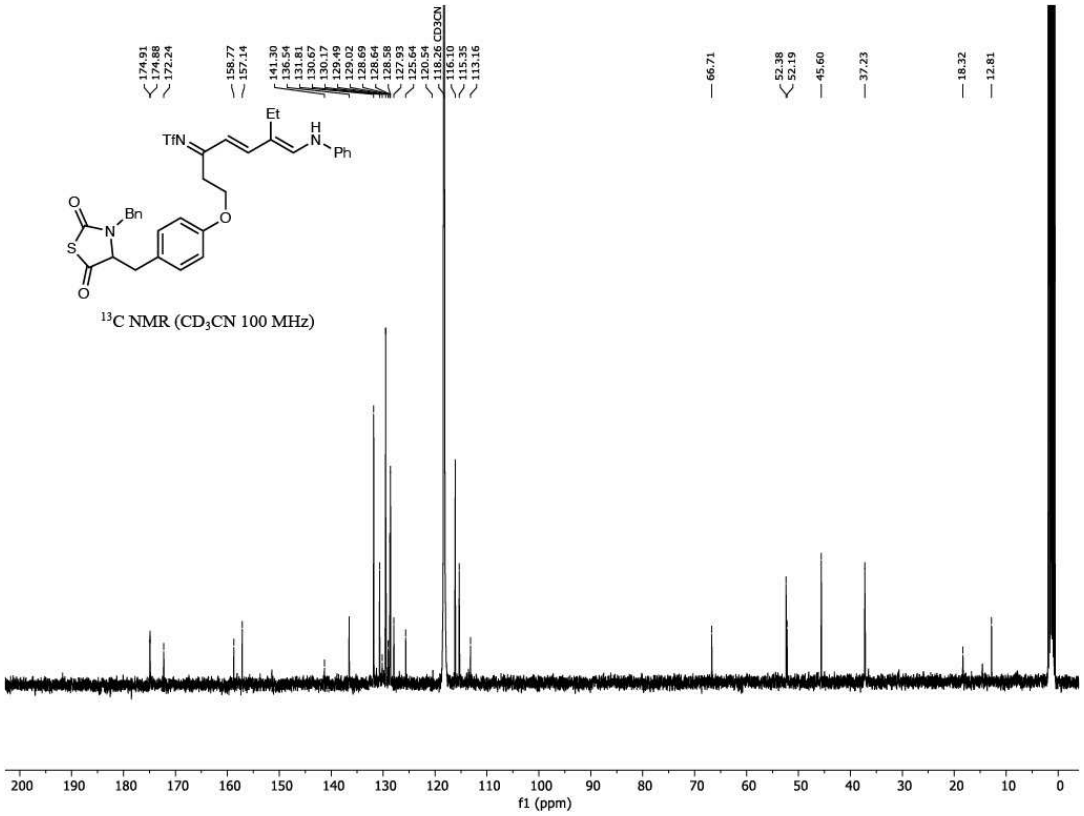


^{19}F NMR $(CD_3)_2CO$ 375 MHz)

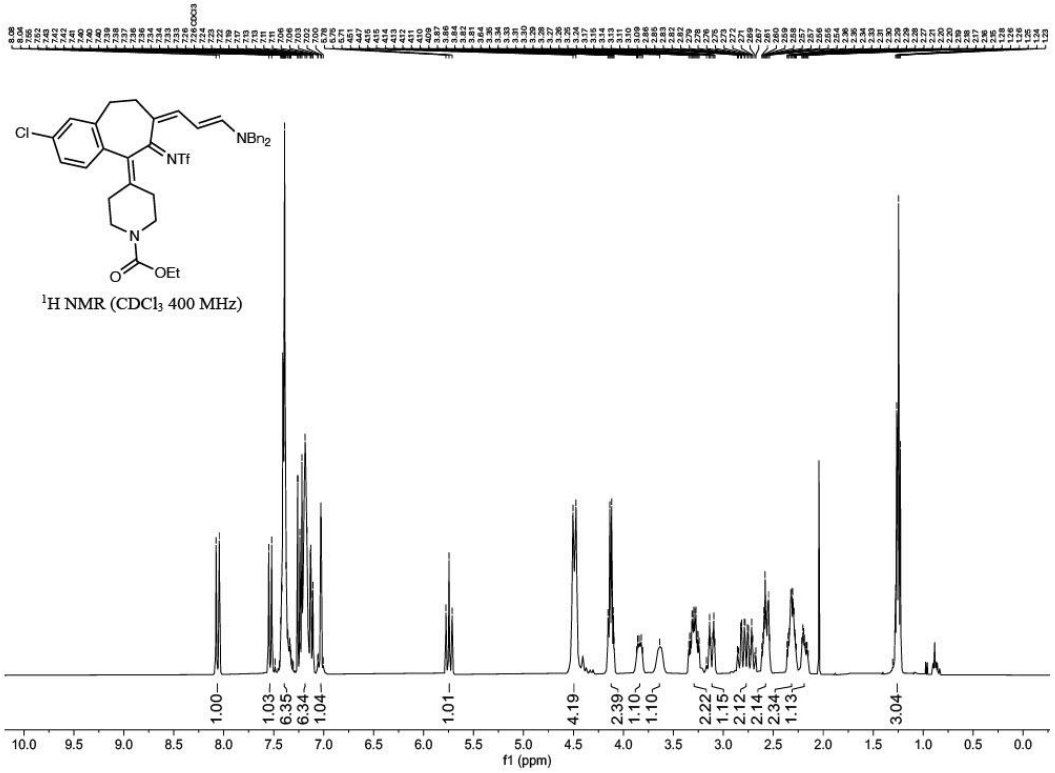

206.26 (CD3)2CO
164.57
144.41
141.56
138.09
132.33
130.77
130.70
130.31
129.51
129.43
129.27
129.21
127.21
126.81
125.69
122.12
121.67
119.98
119.05
118.08
115.53
43.82
TfN
H
N
Ph
Cl
HN
O
Cl
SO2Me
13C NMR (CD3)2CO 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Et
TfN
H
N
Ph
O
N
Bn
S
O
O
O
1H NMR (CD3CN 400 MHz)
f1 (ppm)

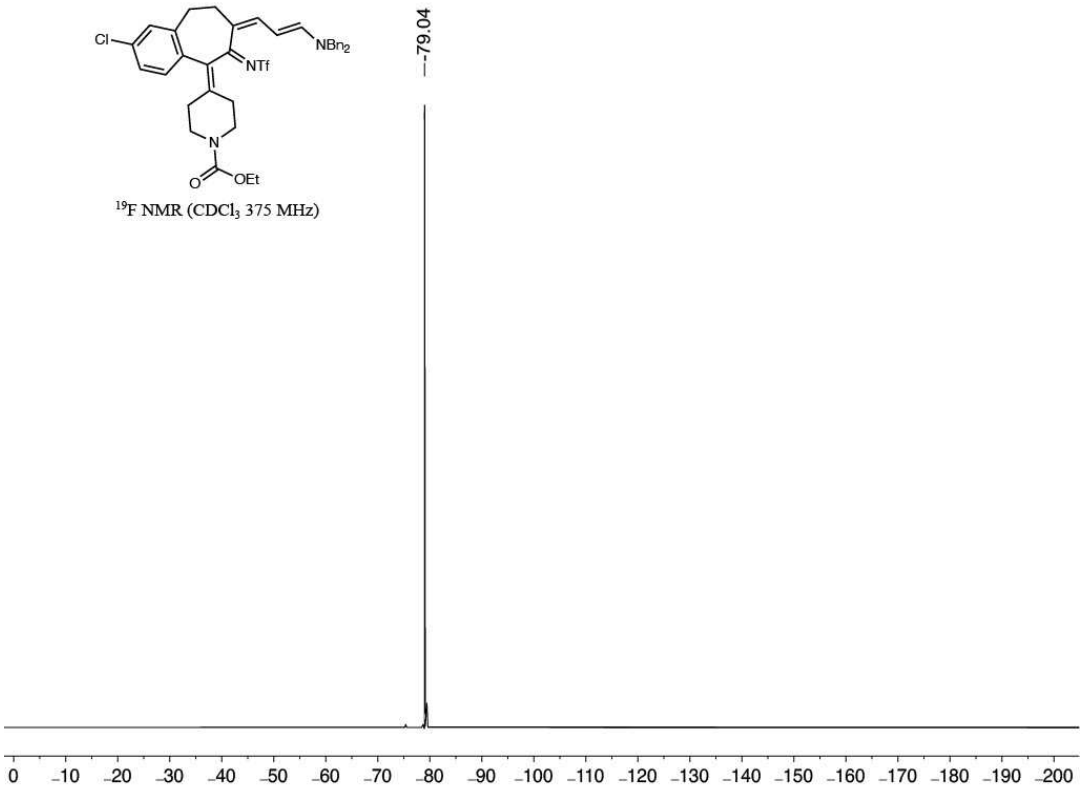

Et
TfN
H
N
Ph
O
N
Bn
S
O
O
O
-80.37
19F NMR (CD3CN 375 MHz)
f1 (ppm)



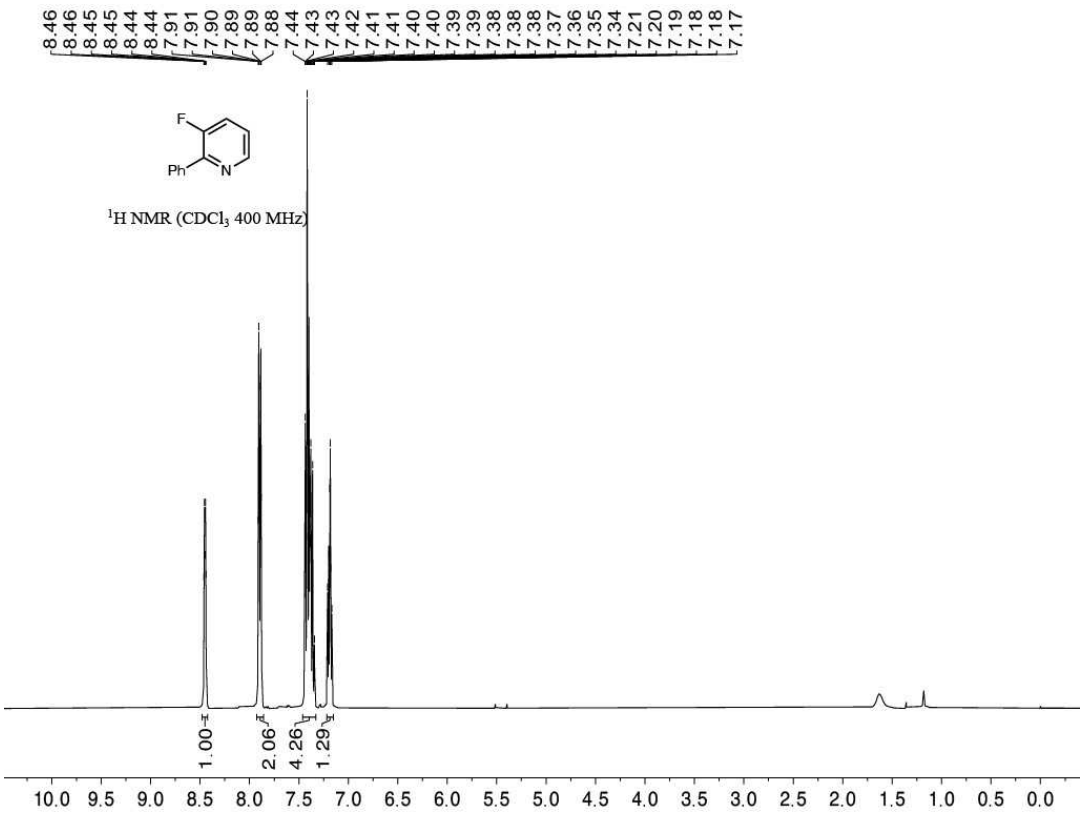
^{13}C NMR (CD_3CN 100 MHz)

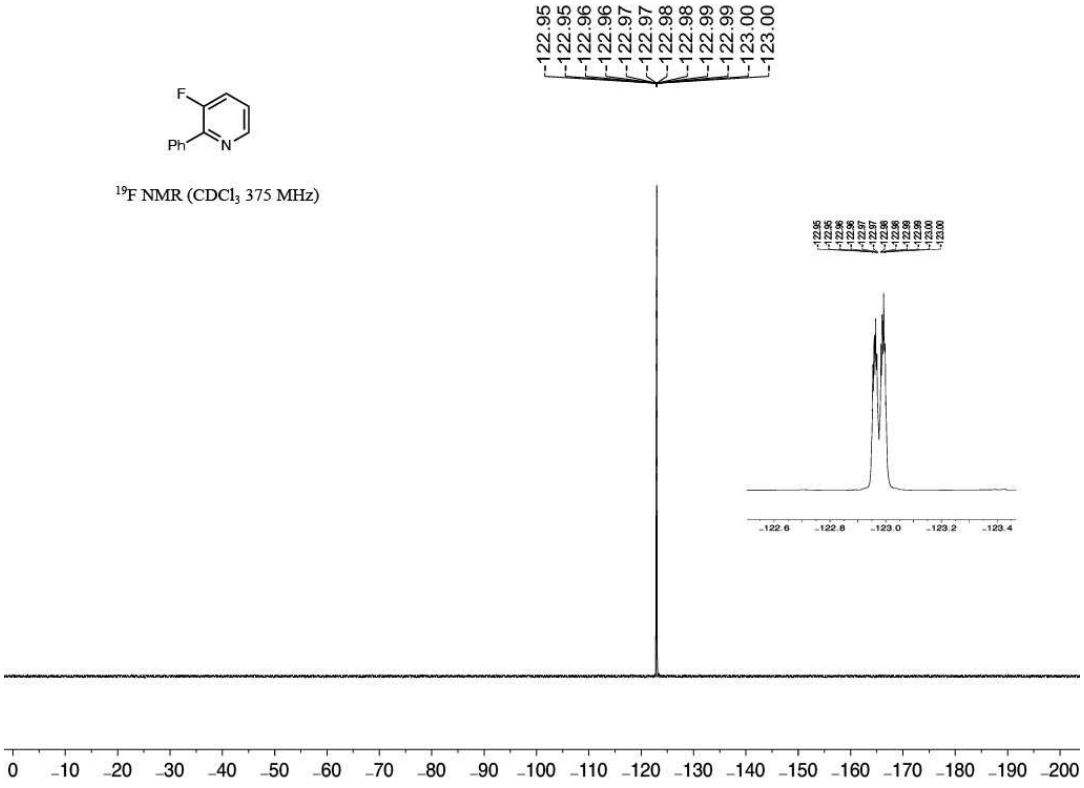


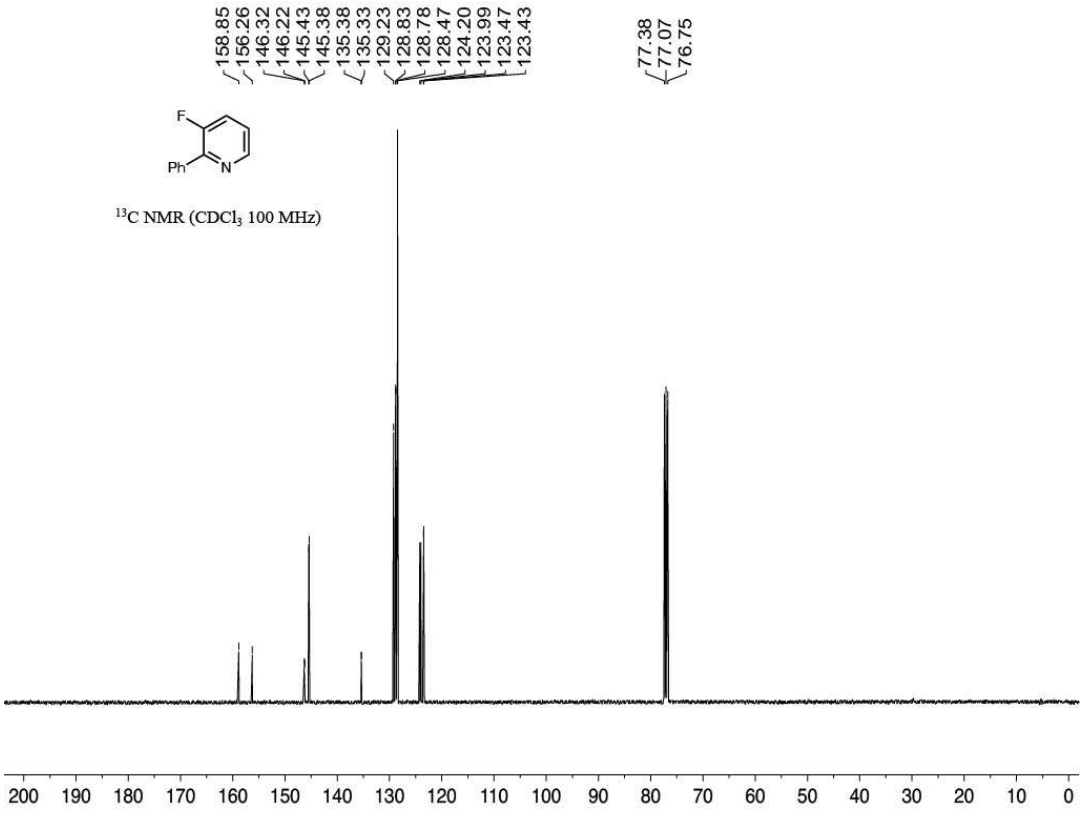
^{1}H NMR ($CDCl_3$ 400 MHz)

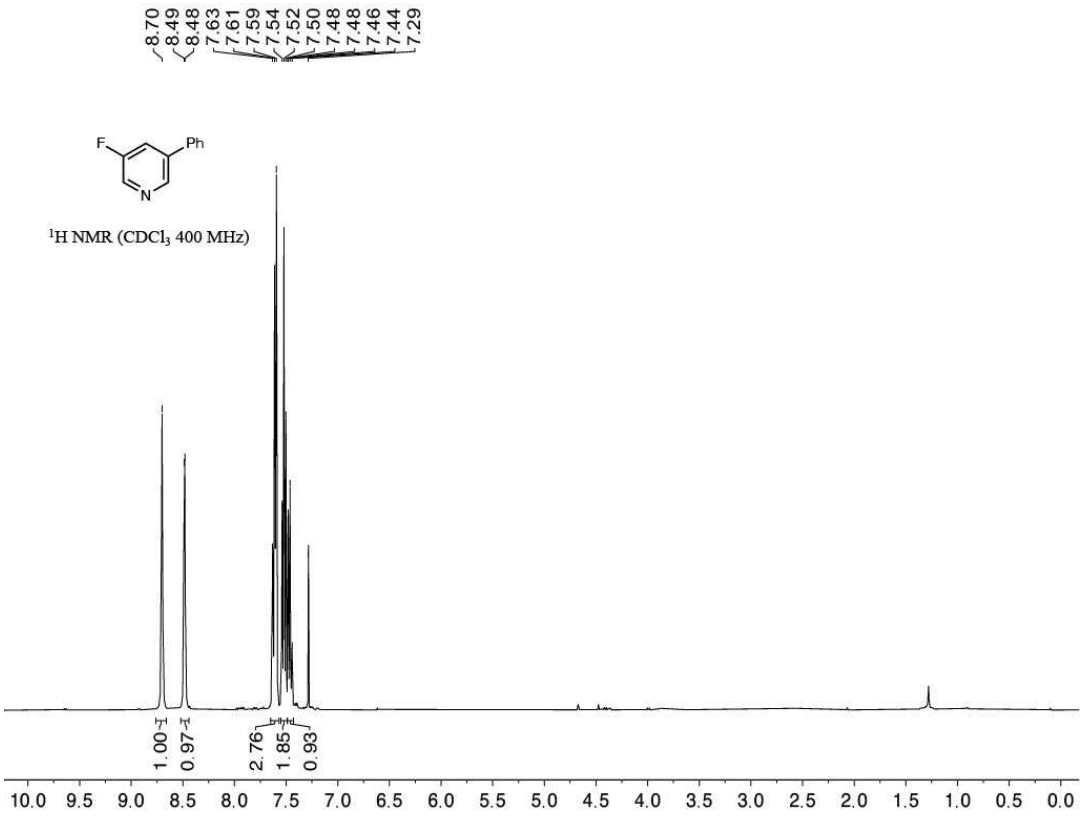


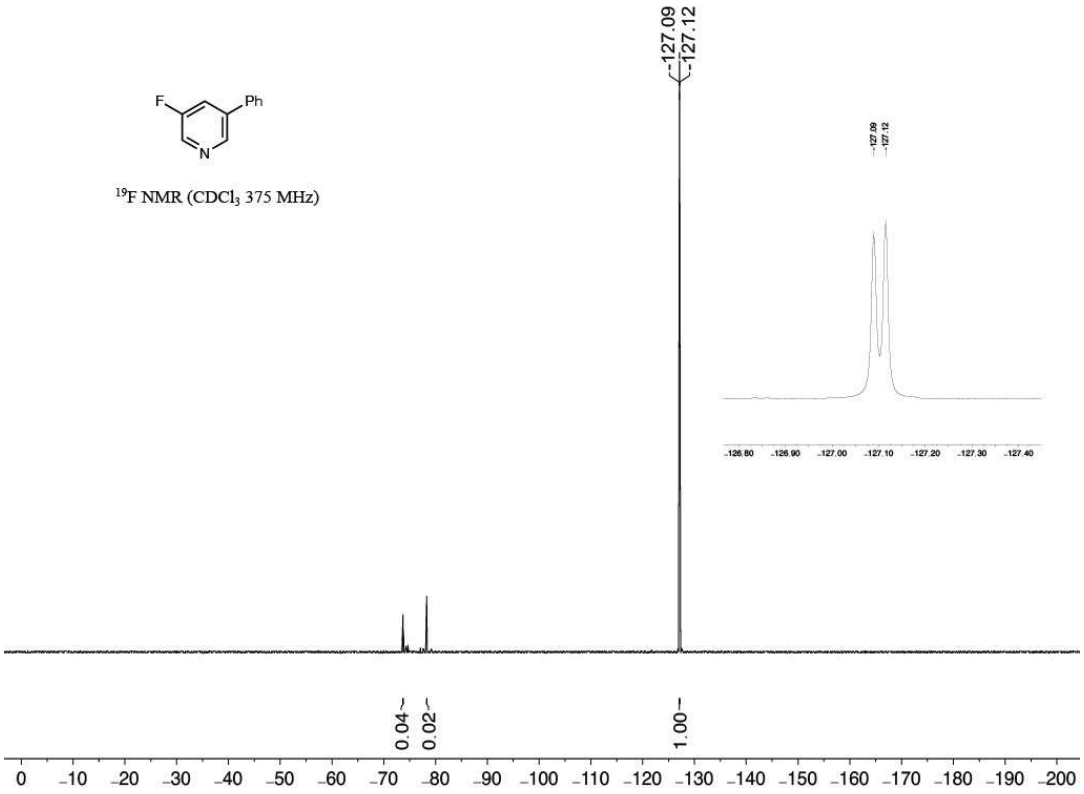
^{19}F NMR ($CDCl_3$ 375 MHz)

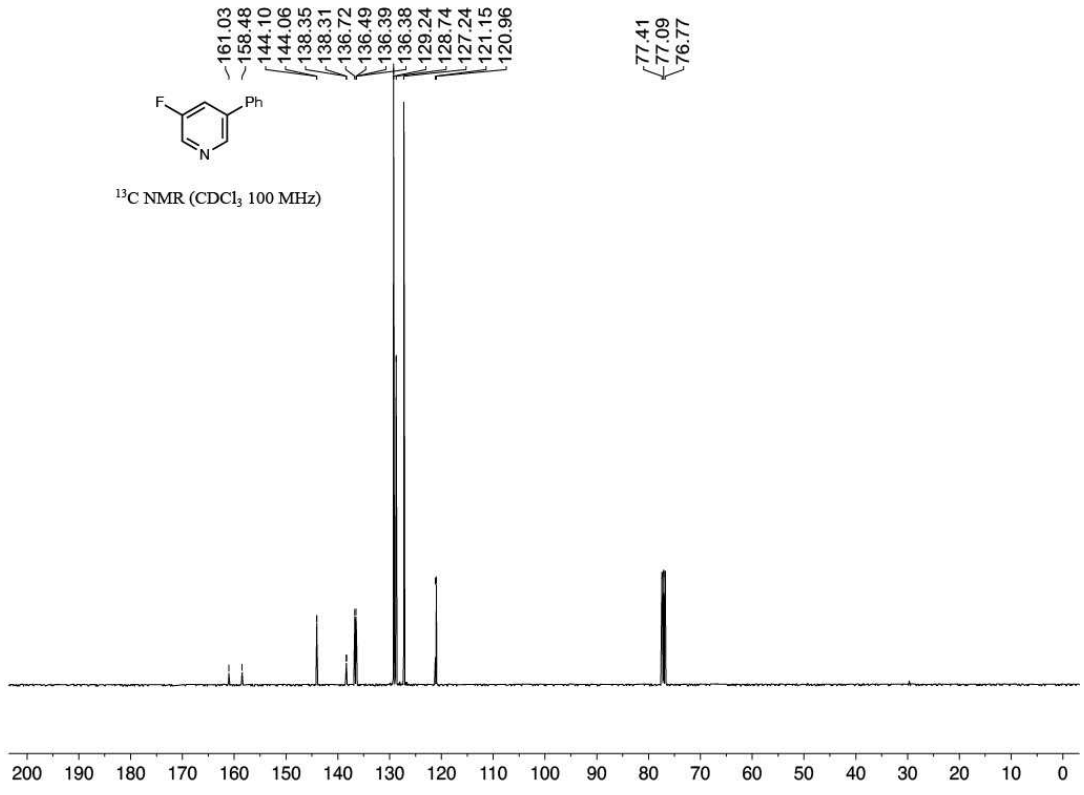

8.46
8.46
8.45
8.45
8.44
8.44
7.91
7.91
7.90
7.89
7.89
7.88
7.44
7.43
7.43
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.36
7.35
7.34
7.21
7.20
7.19
7.18
7.18
7.17
F
Ph
N
1H NMR (CDCl3 400 MHz)
1.00
2.06
4.26
1.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

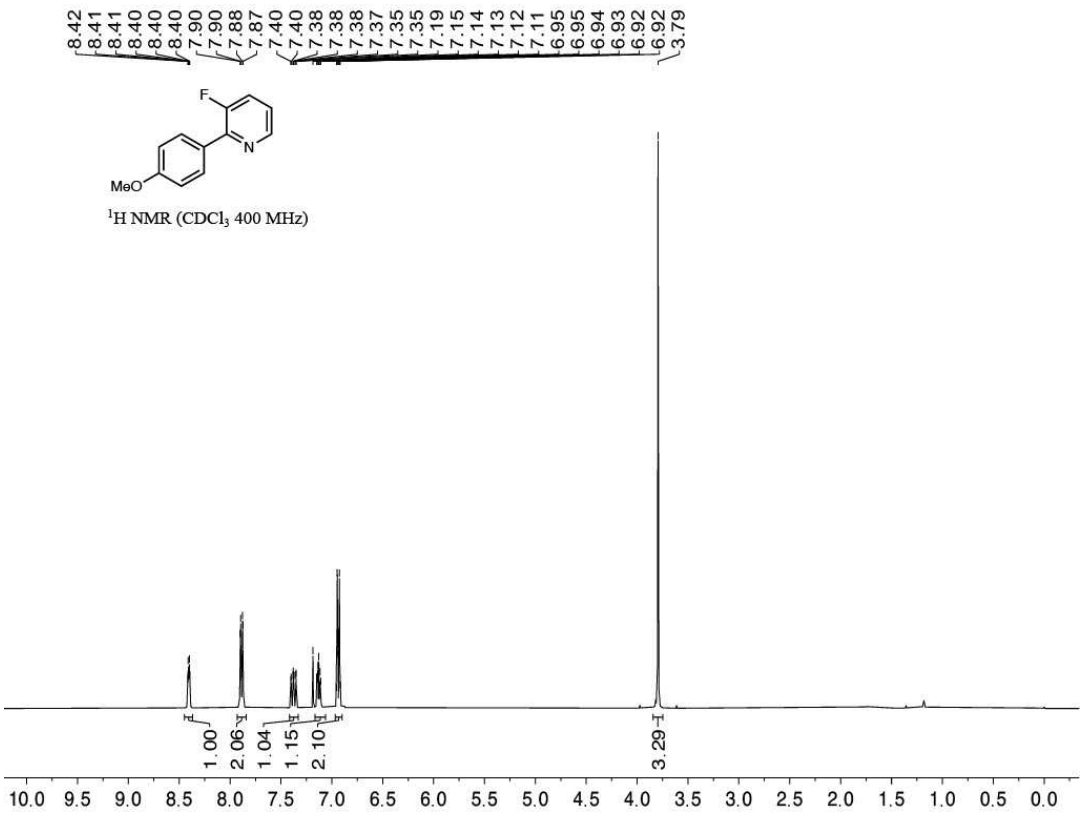

-122.95
-122.95
-122.96
-122.96
-122.97
-122.97
-122.98
-122.98
-122.99
-122.99
-123.00
-123.00
F
Ph
N
19F NMR (CDCl3 375 MHz)
-122.6
-122.8
-123.0
-123.2
-123.4
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200


158.85
156.26
146.32
146.22
145.43
145.38
135.38
135.33
129.23
128.83
128.78
128.47
124.20
123.99
123.47
123.43
77.38
77.07
76.75
F
Ph
N
^{13}C NMR (CDCl$_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

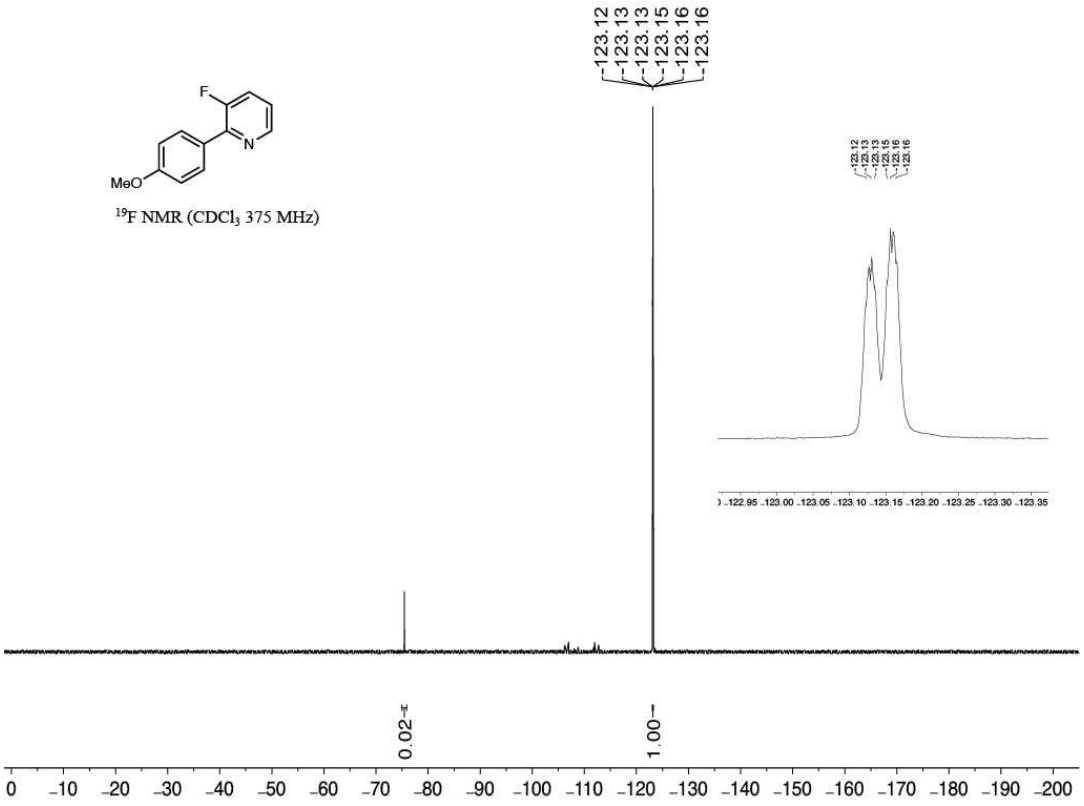

8.70
8.49
8.48
7.63
7.61
7.59
7.54
7.52
7.50
7.48
7.48
7.46
7.44
7.29
F
Ph
N
^{1}H NMR (CDCl$_3$ 400 MHz)
1.00
0.97
2.76
1.85
0.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


F
Ph
N
^{19}F NMR ($CDCl_3$ 375 MHz)
-127.09
-127.12
0.04
0.02
1.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

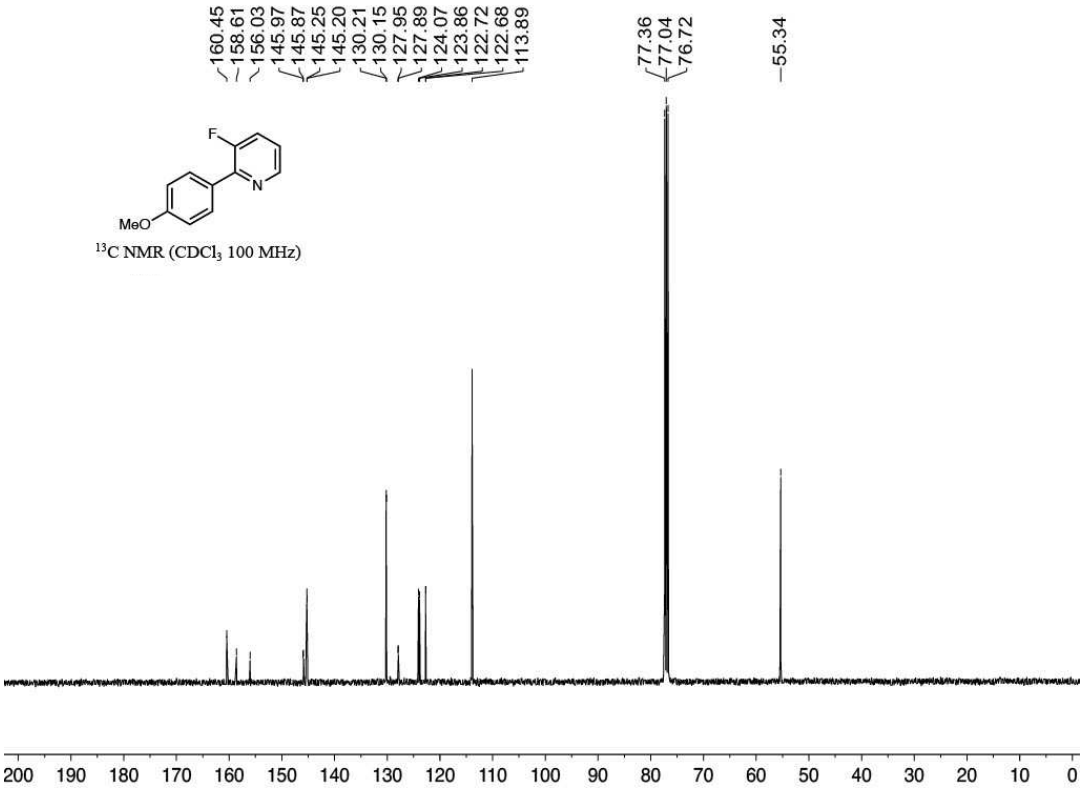

161.03
158.48
144.10
144.06
138.35
138.31
136.72
136.49
136.39
136.38
129.24
128.74
127.24
121.15
120.96
77.41
77.09
76.77
F
Ph
N
^{13}C NMR ($CDCl_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



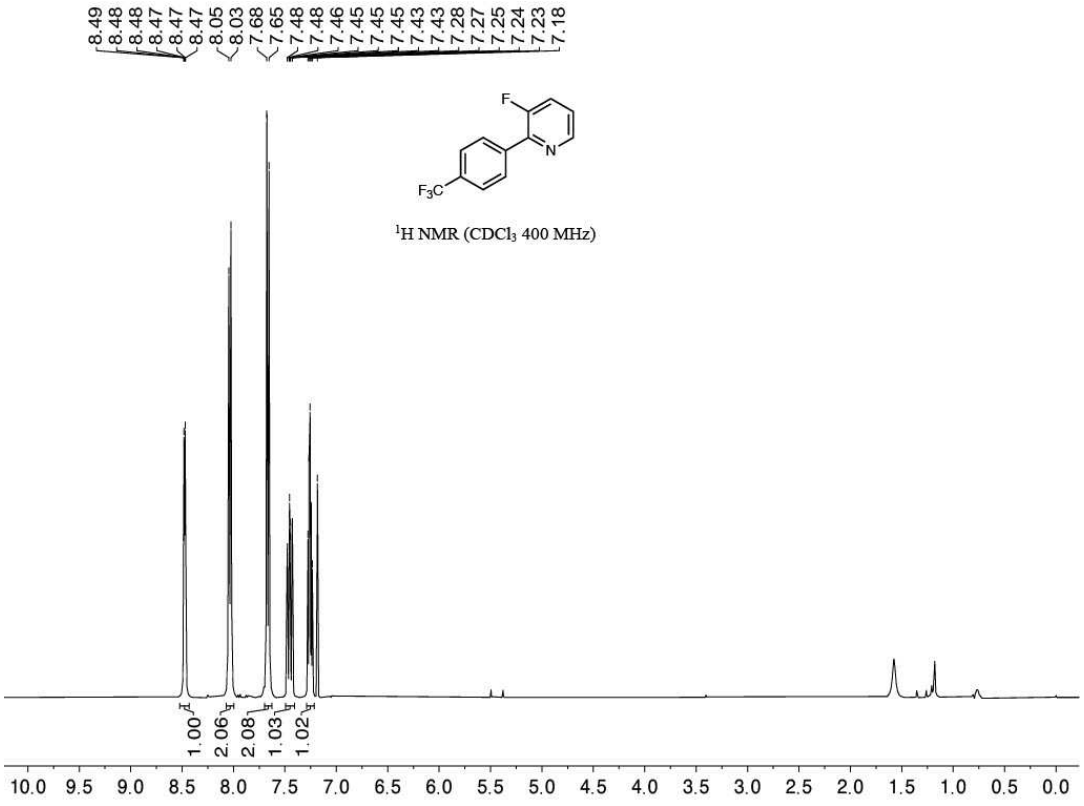
^{1}H NMR ($CDCl_3$ 400 MHz)



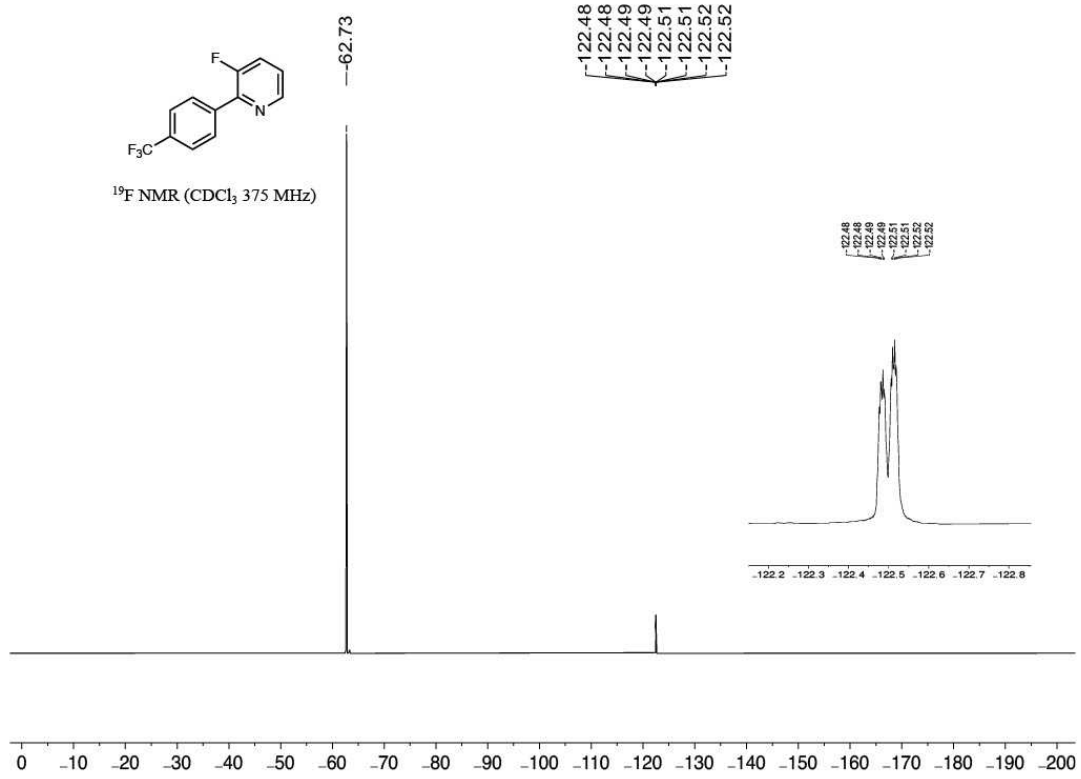
^{19}F NMR ($CDCl_3$ 375 MHz)

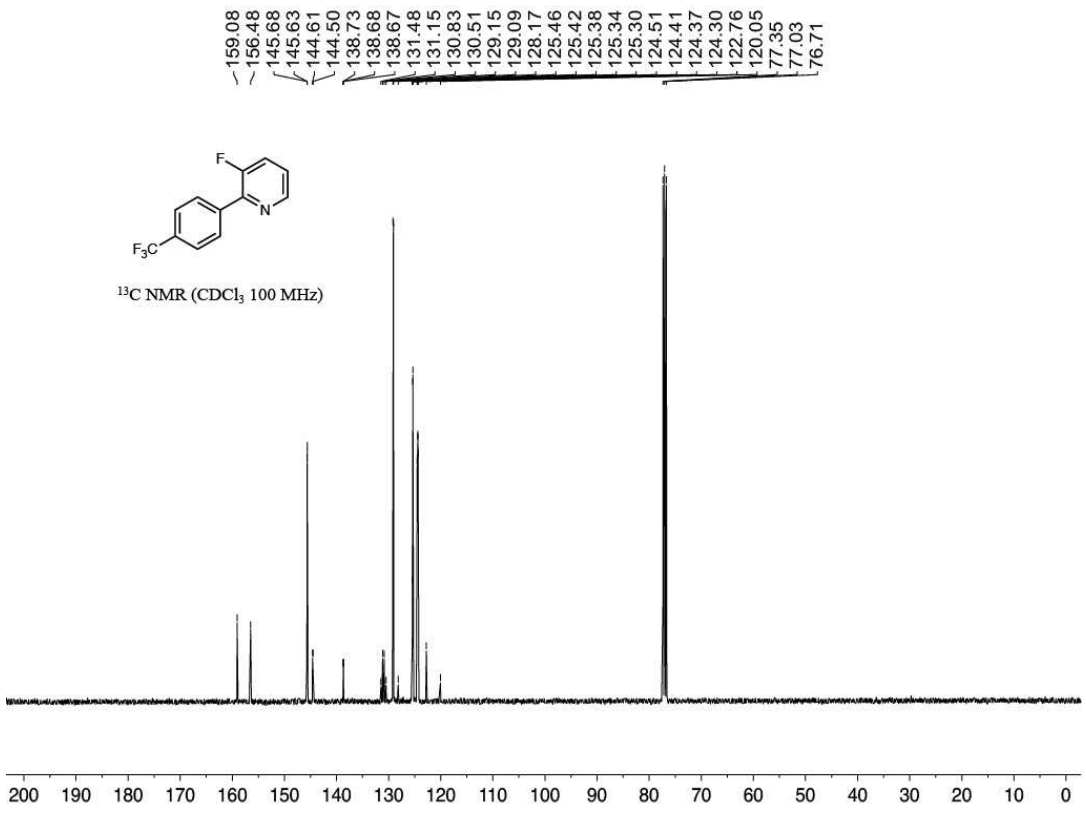


^{13}C NMR ($CDCl_3$ 100 MHz)

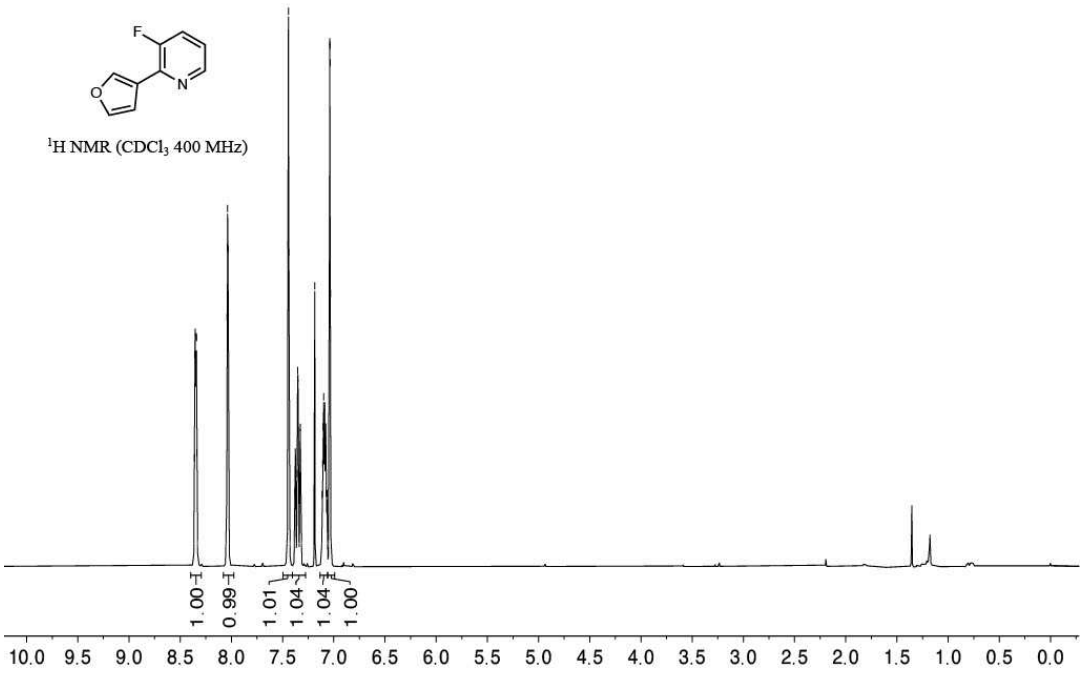


^{1}H NMR ($CDCl_3$ 400 MHz)

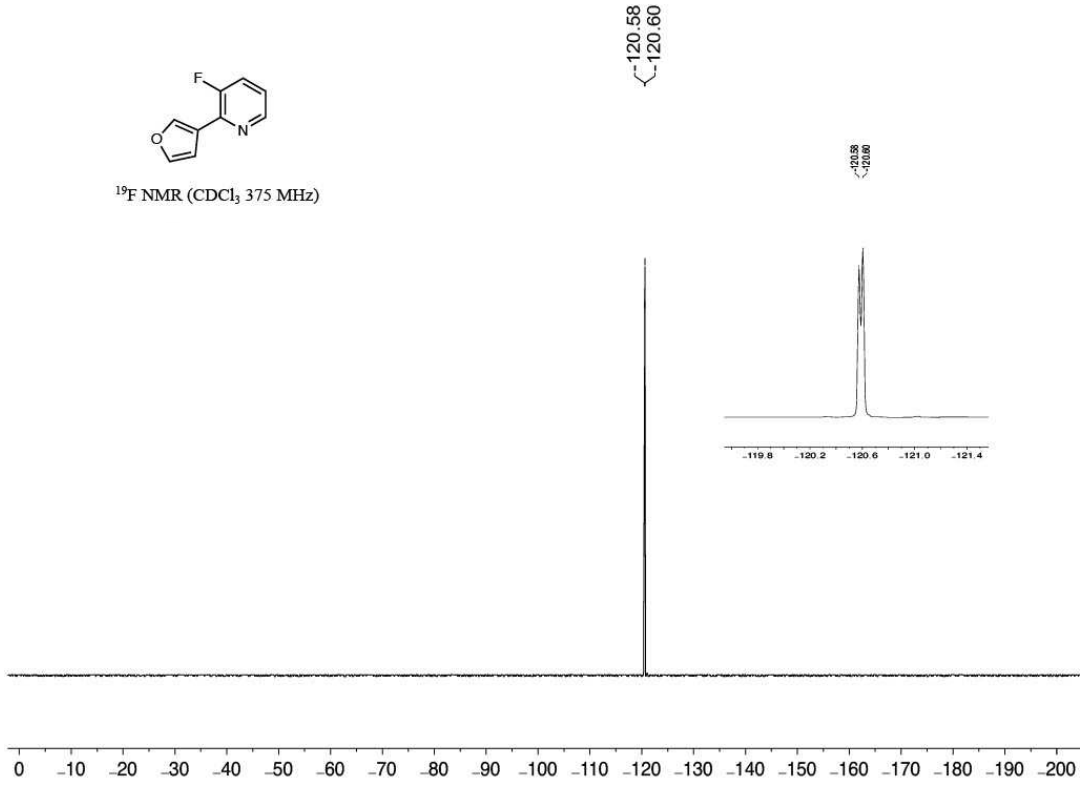

F
N
F3C
19F NMR (CDCl3 375 MHz)
-62.73
-122.48
-122.48
-122.49
-122.49
-122.51
-122.51
-122.52
-122.52
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200


159.08
156.48
145.68
145.63
144.61
144.50
138.73
138.68
138.67
131.48
131.15
130.83
130.51
129.15
129.09
128.17
125.46
125.42
125.38
125.34
125.30
124.51
124.41
124.37
124.30
122.76
120.05
77.35
77.03
76.71
F
N
F3C
13C NMR (CDCl3 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

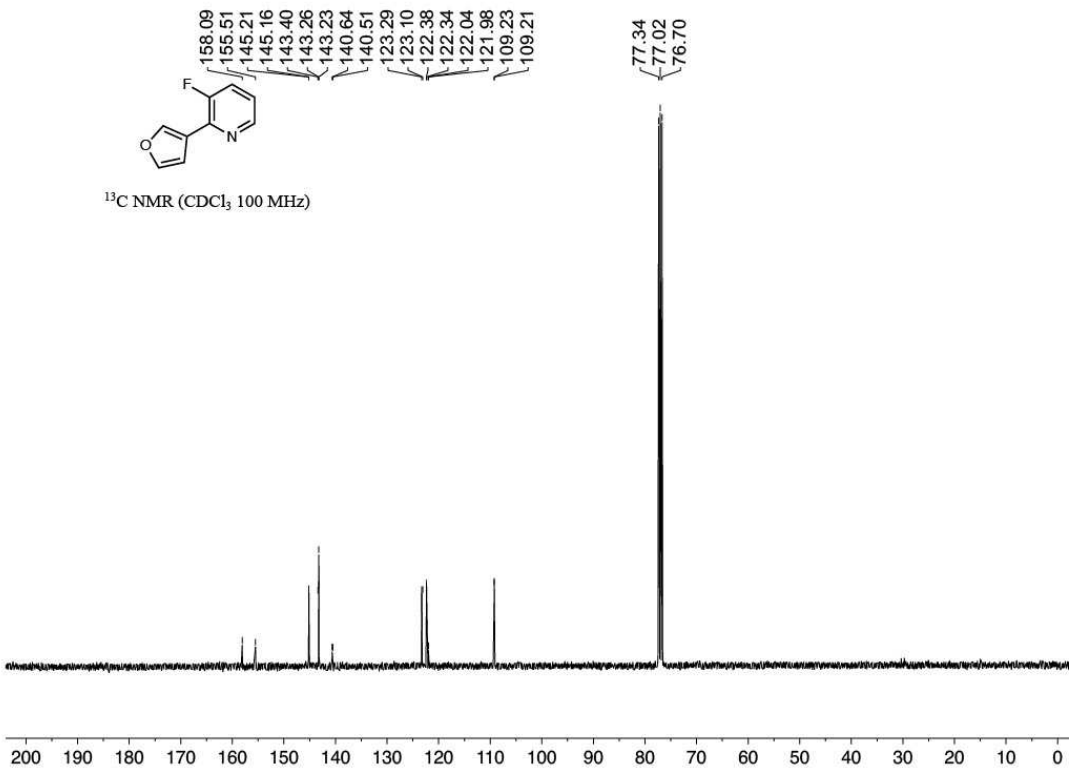




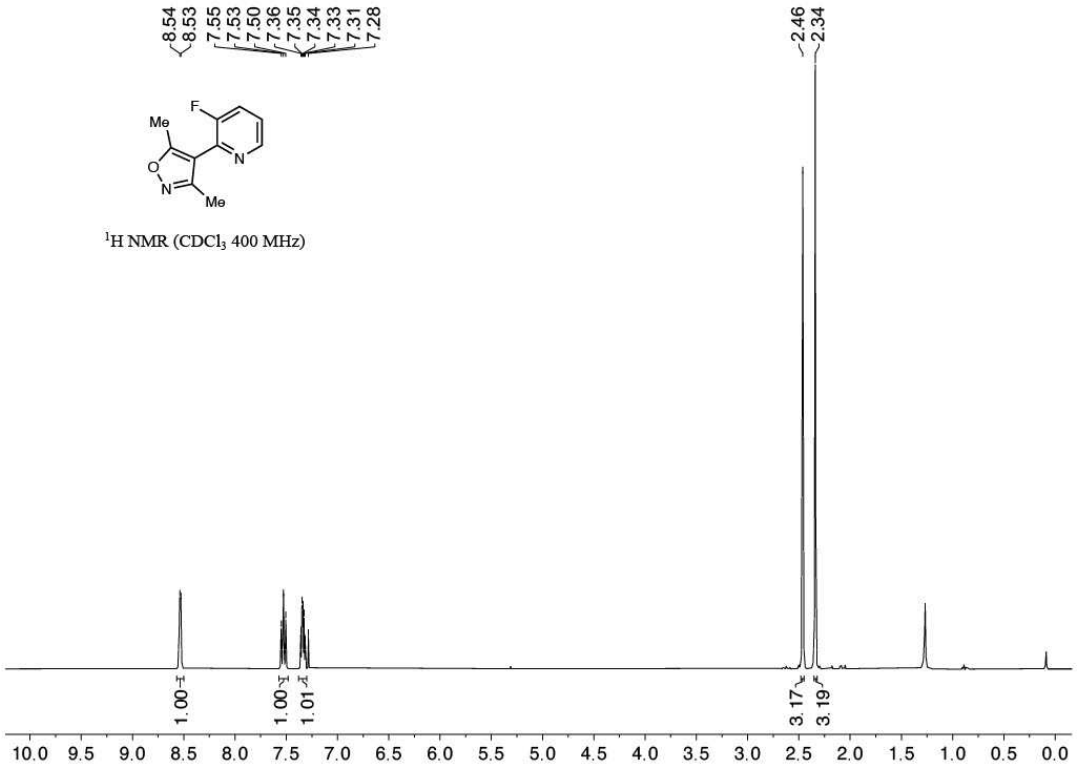
^{1}H NMR ($CDCl_3$ 400 MHz)



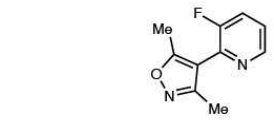
^{19}F NMR ($CDCl_3$ 375 MHz)



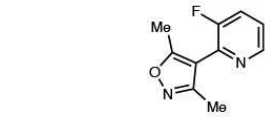
^{13}C NMR ($CDCl_3$ 100 MHz)



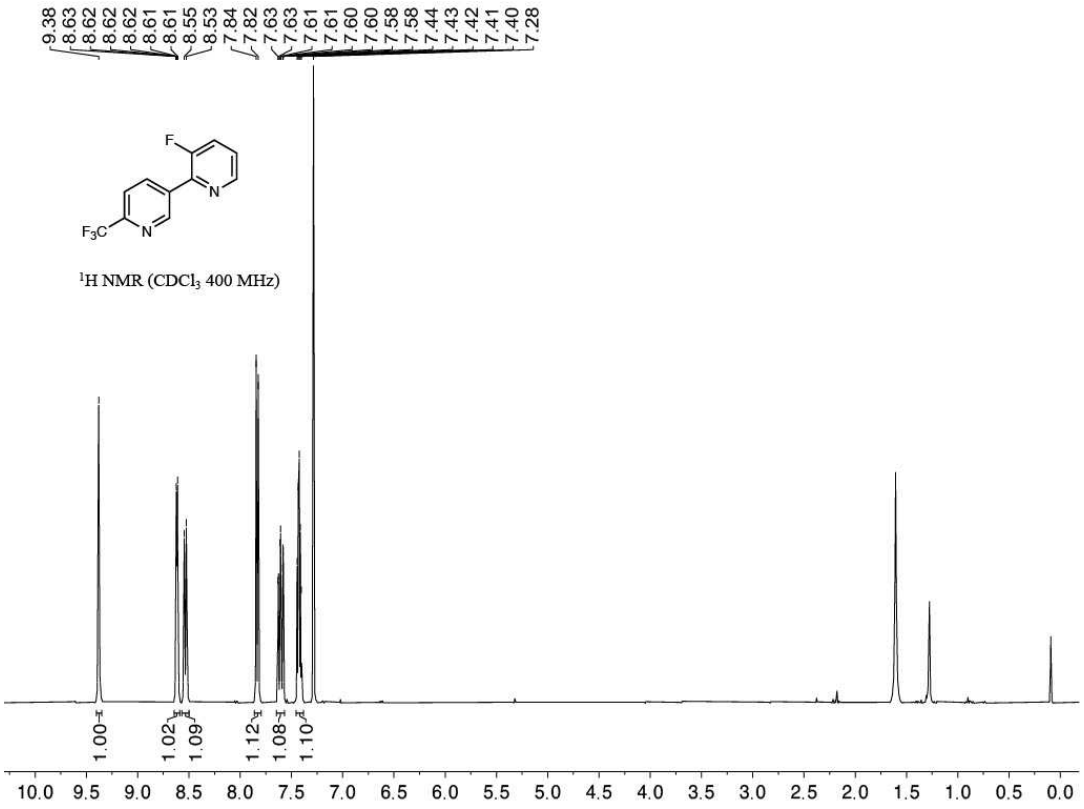
^{1}H NMR ($CDCl_3$ 400 MHz)

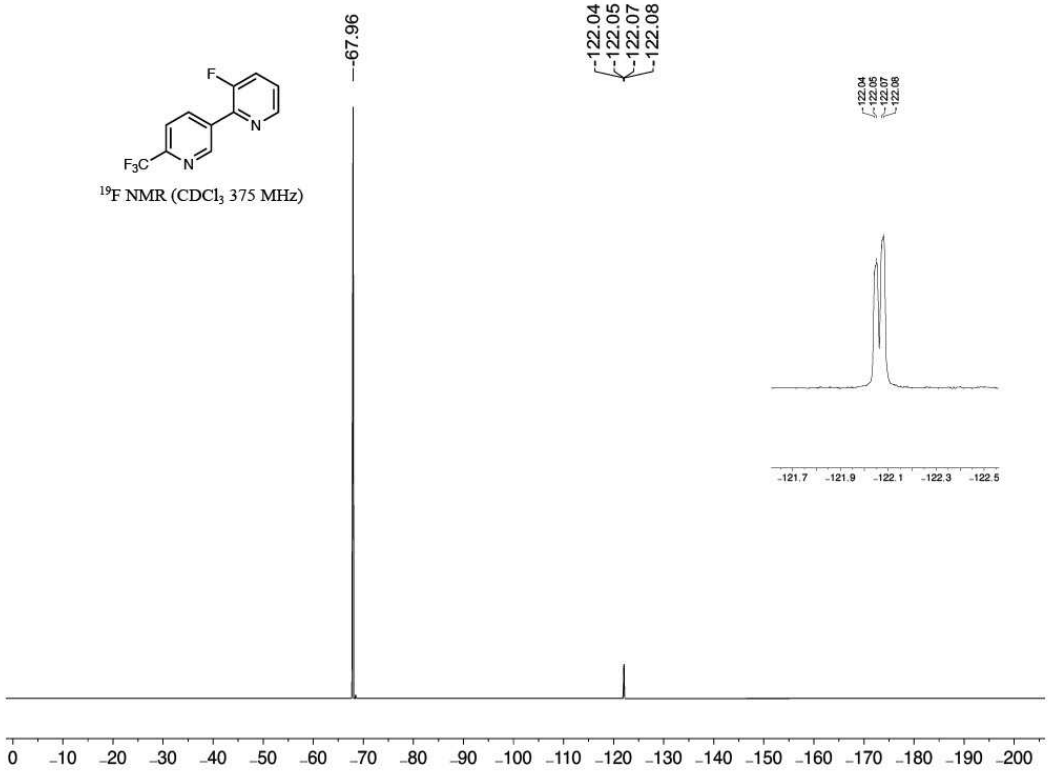


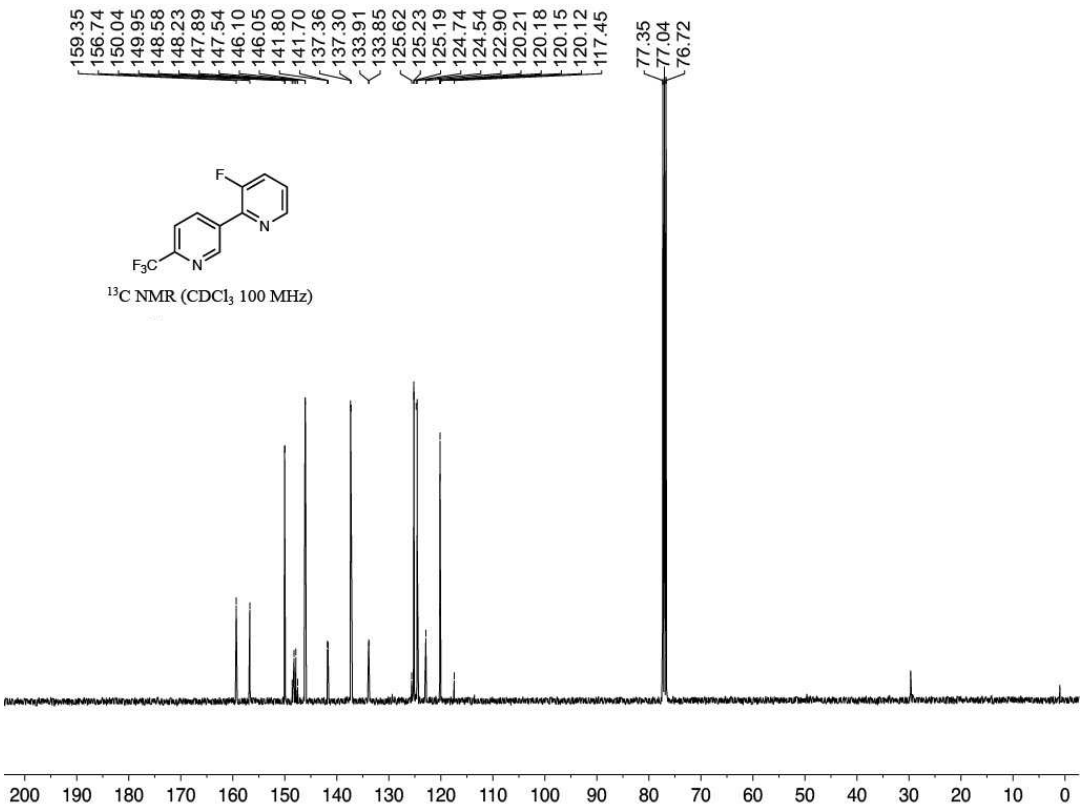
^{19}F NMR ($CDCl_3$ 375 MHz)

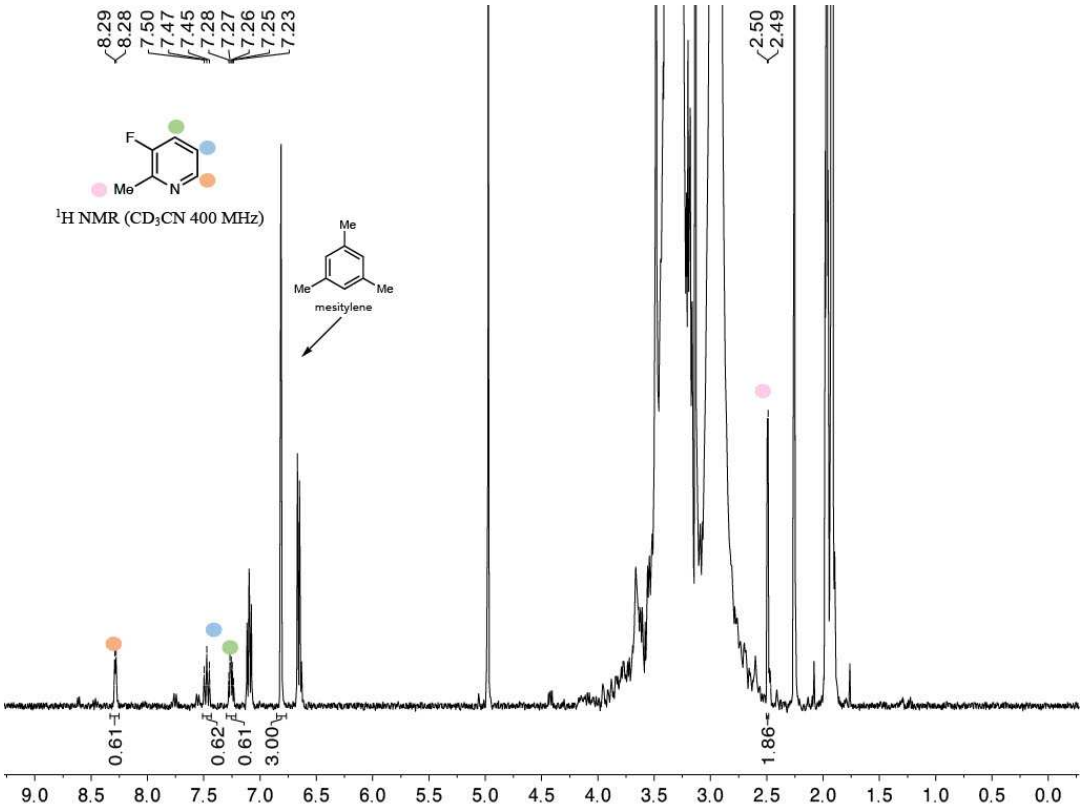


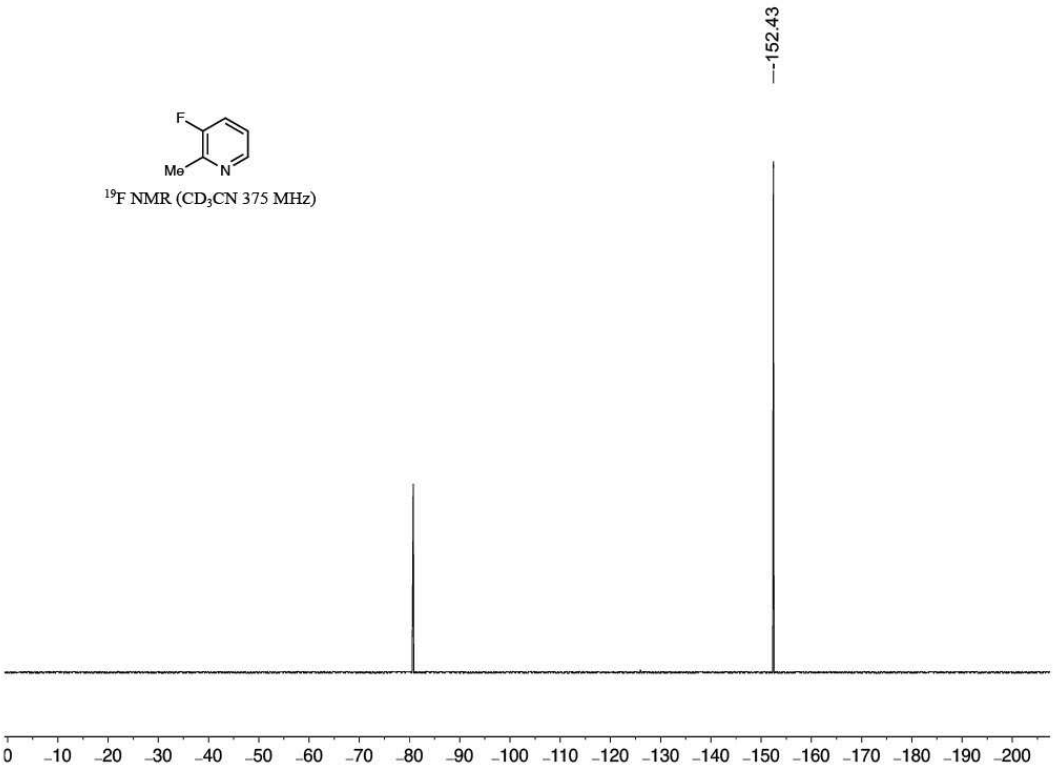
^{13}C NMR ($CDCl_3$ 100 MHz)

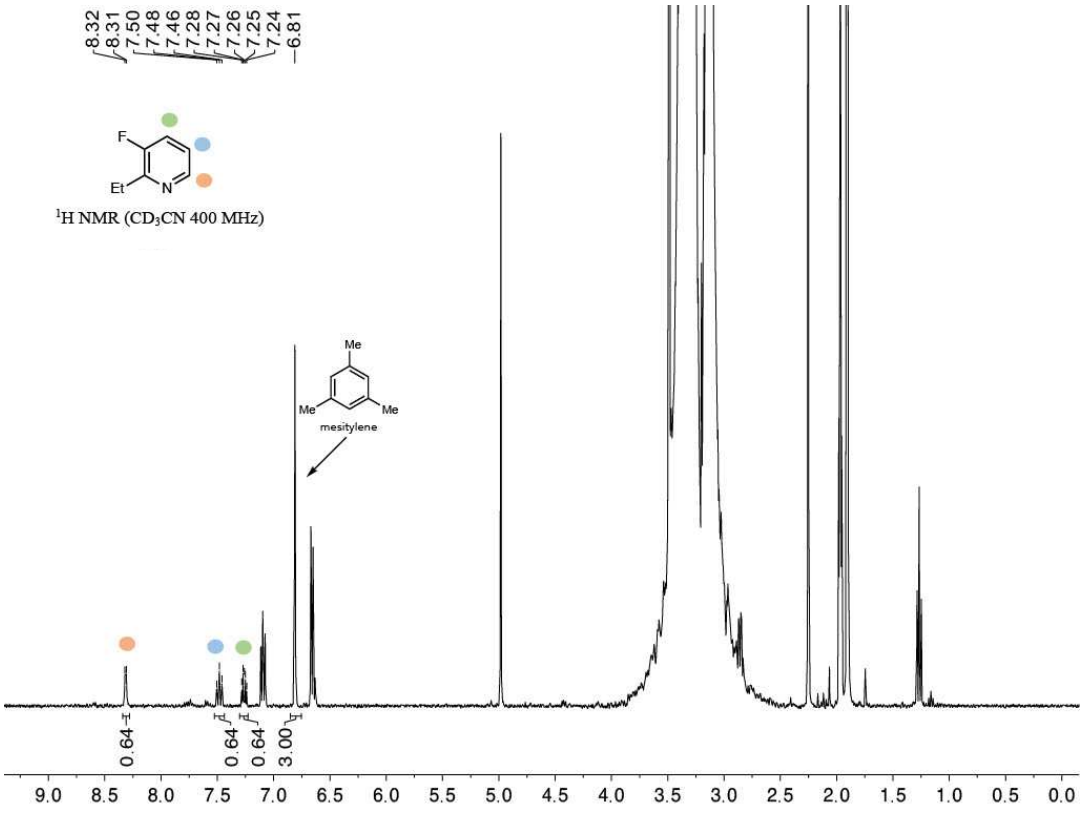

9.38
8.63
8.62
8.62
8.62
8.61
8.61
8.55
8.53
7.84
7.82
7.63
7.63
7.61
7.61
7.60
7.60
7.58
7.58
7.44
7.43
7.42
7.41
7.40
7.28
F
N
F3C
N
1H NMR (CDCl3 400 MHz)
1.00
1.02
1.09
1.12
1.08
1.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

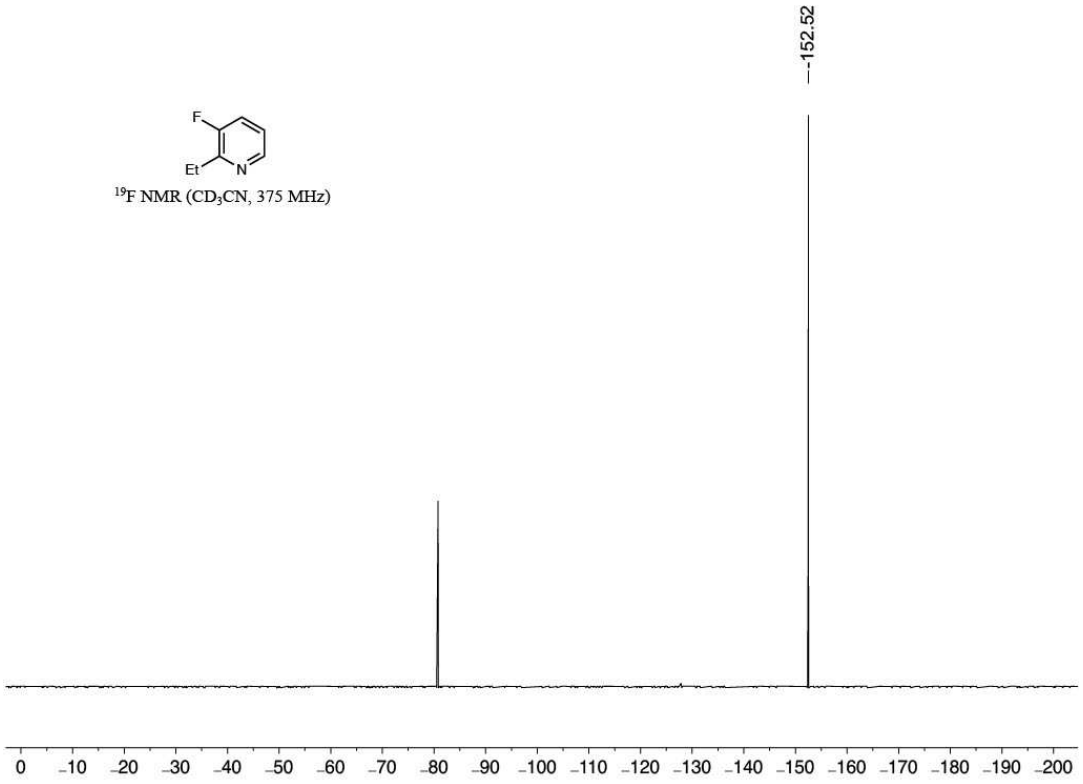

F
N
F3C
N
19F NMR (CDCl3 375 MHz)
-67.96
-122.04
-122.05
-122.07
-122.08
-121.7
-121.9
-122.1
-122.3
-122.5
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200


159.35
156.74
150.04
149.95
148.58
148.23
147.89
147.54
146.10
146.05
141.80
141.70
137.36
137.30
133.91
133.85
125.62
125.23
125.19
124.74
124.54
122.90
120.21
120.18
120.15
120.12
117.45
77.35
77.04
76.72
F
N
F3C
N
13C NMR (CDCl3 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

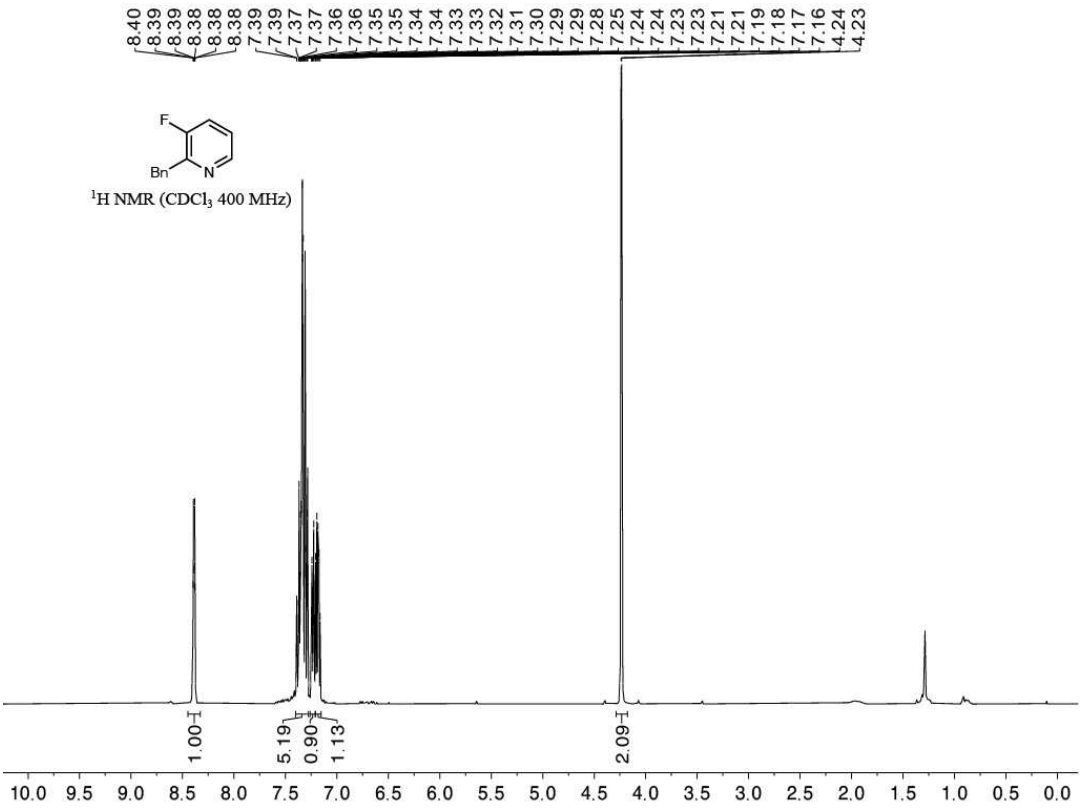

8.29
8.28
7.50
7.47
7.45
7.28
7.27
7.26
7.25
7.23
2.50
2.49
F
Me
N
1H NMR (CD3CN 400 MHz)
Me
Me
Me
mesitylene
0.61
0.62
0.61
3.00
1.86
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


F
Me
N
^{19}F NMR (CD_3CN 375 MHz)
-152.43
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

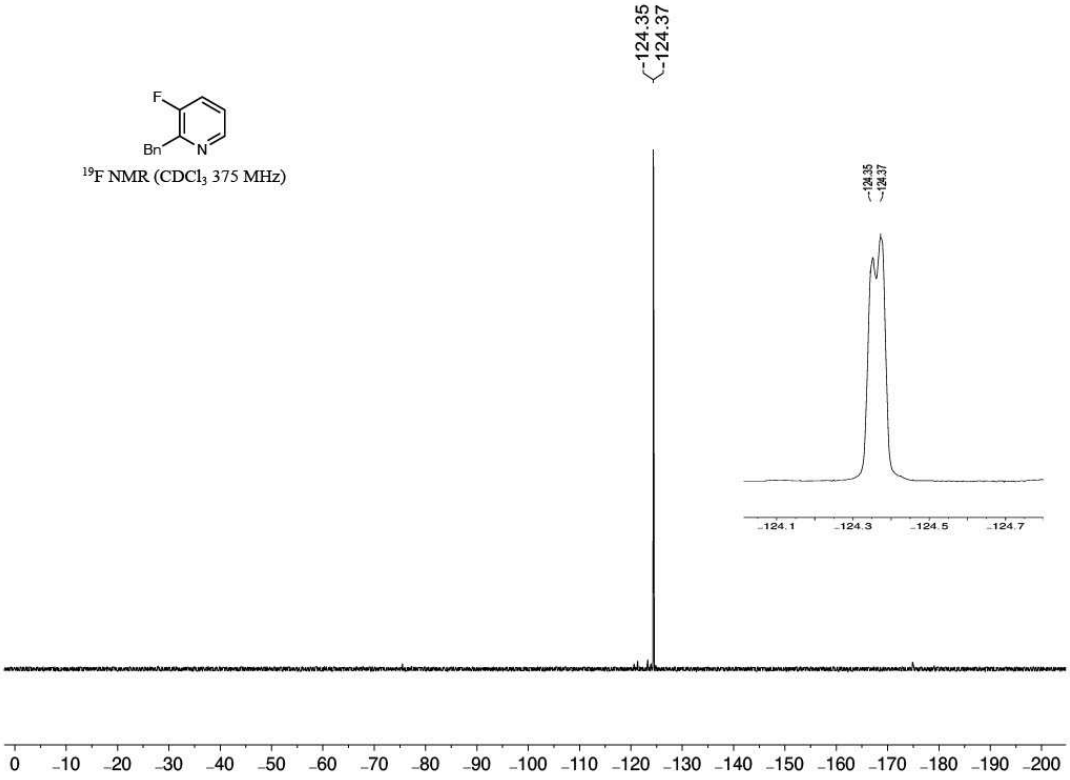

8.32
8.31
7.50
7.48
7.46
7.28
7.27
7.26
7.25
7.24
6.81
F
Et
N
^{1}H NMR (CD_3CN 400 MHz)
Me
Me
Me
mesitylene
0.64
0.64
0.64
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

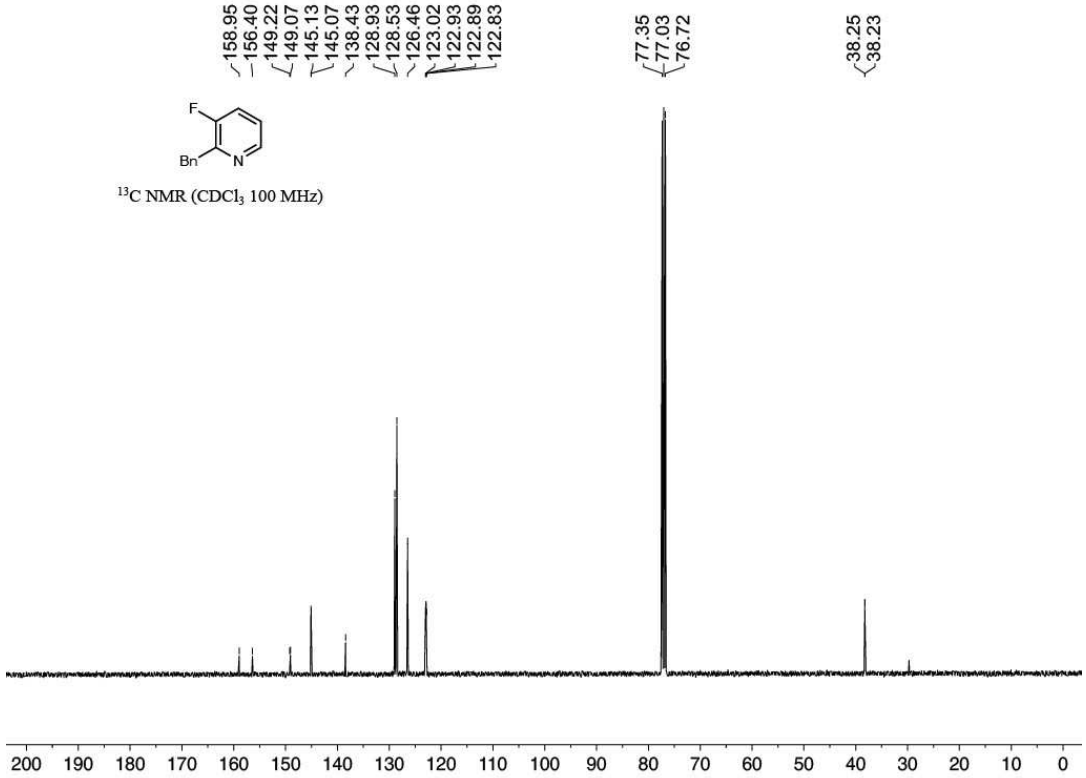


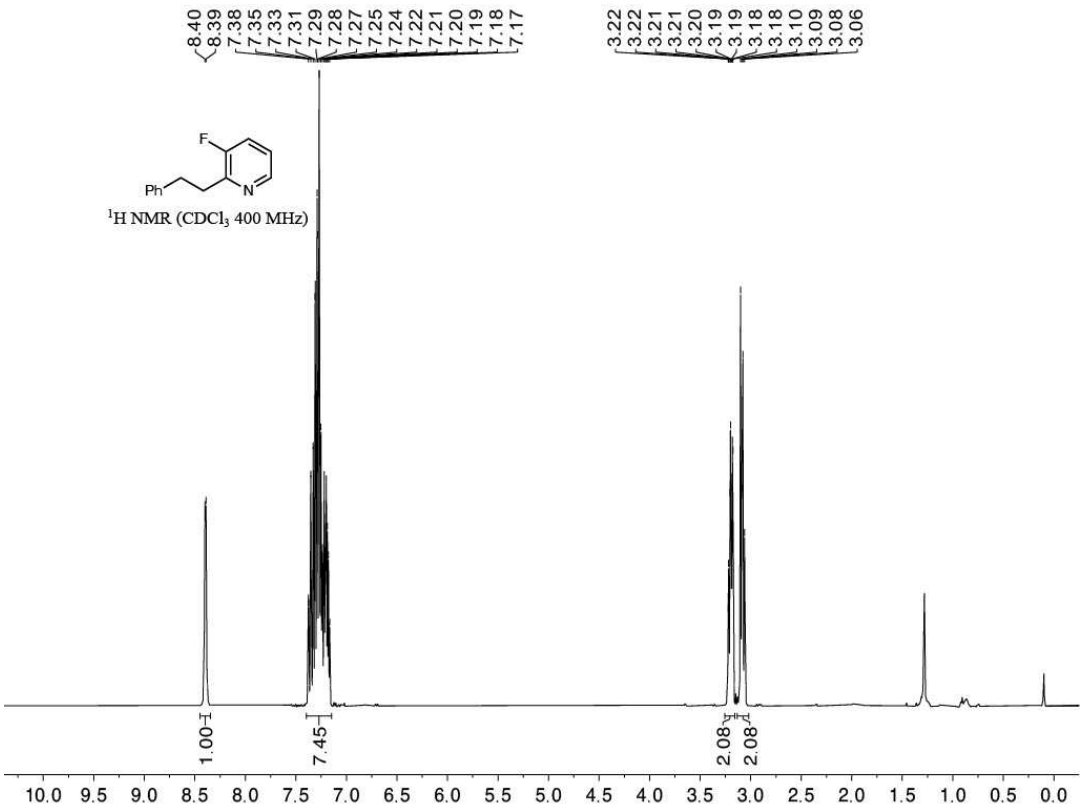
^{19}F NMR (CD_3CN, 375 MHz)

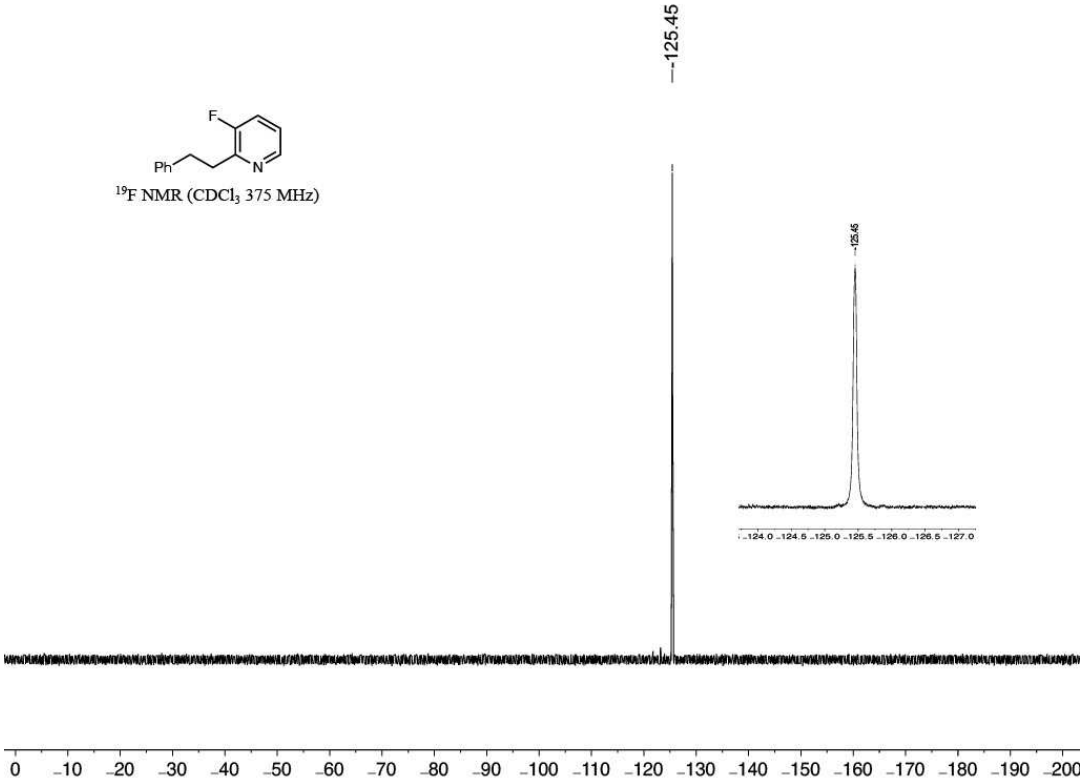


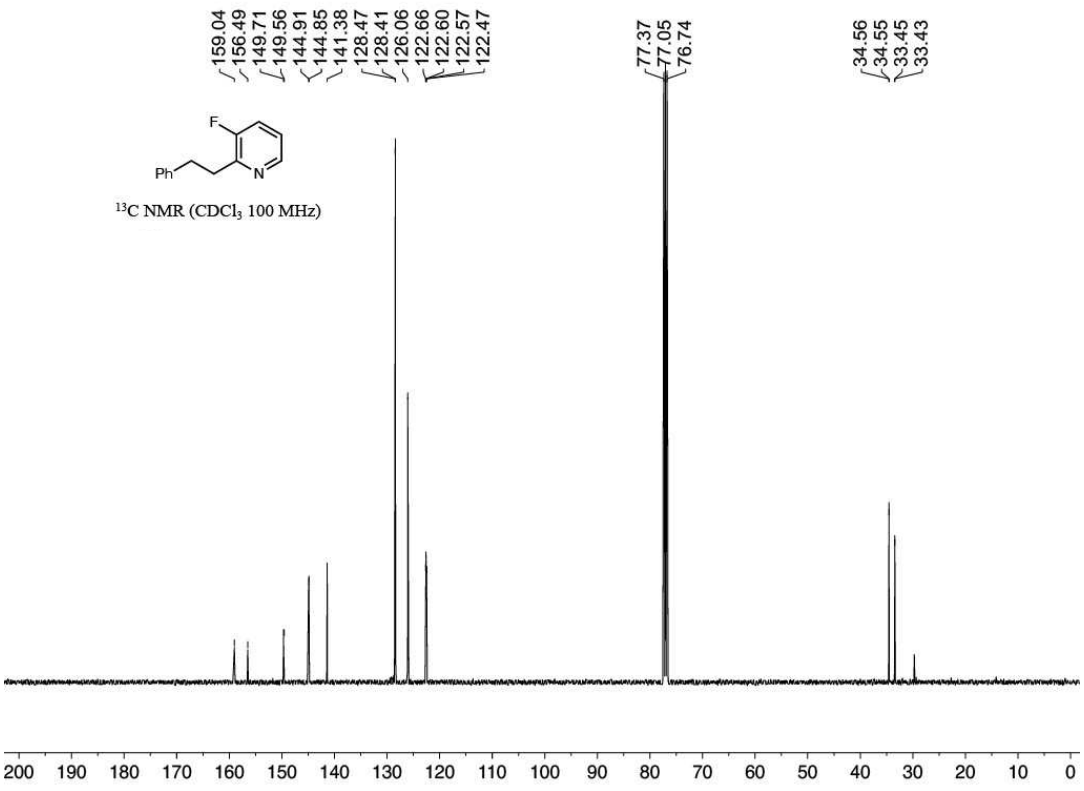
^{1}H NMR ($CDCl_3$ 400 MHz)

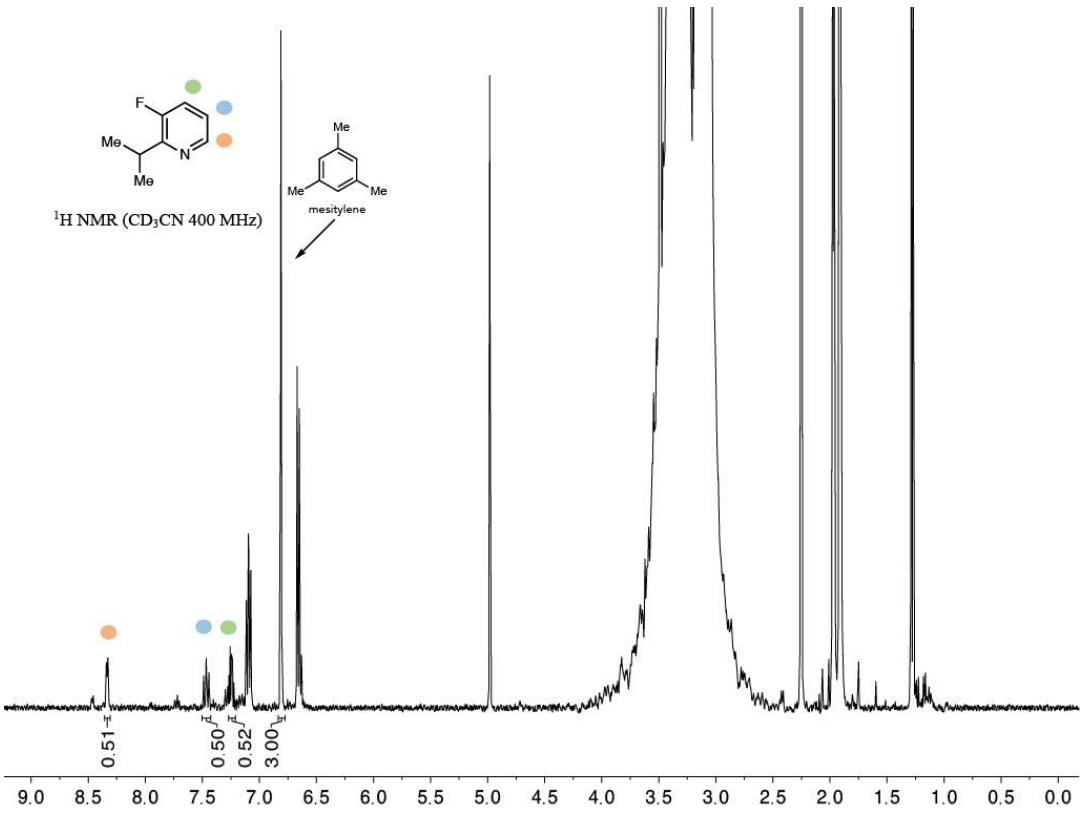

F
Bn
N
^{19}F NMR ($CDCl_3$ 375 MHz)
-124.35
-124.37
-124.1
-124.3
-124.5
-124.7
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

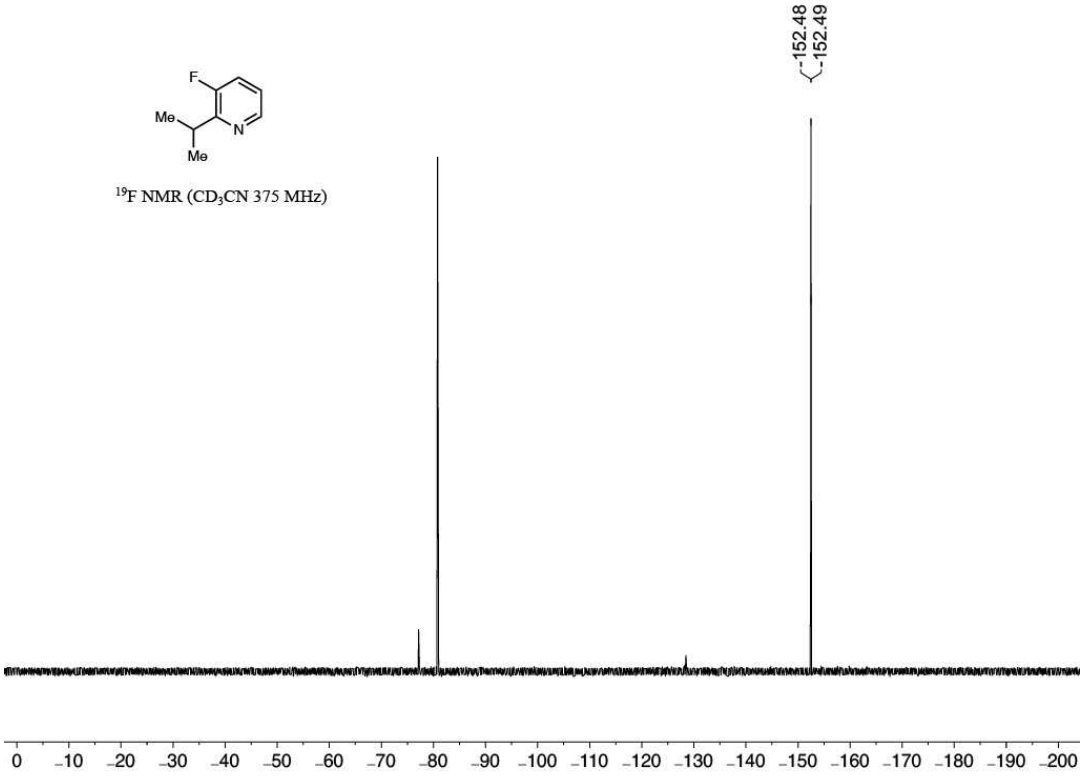

158.95
156.40
149.22
149.07
145.13
145.07
138.43
128.93
128.53
126.46
123.02
122.93
122.89
122.83
77.35
77.03
76.72
38.25
38.23
F
Bn
N
^{13}C NMR ($CDCl_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


8.40
8.39
7.38
7.35
7.33
7.31
7.29
7.28
7.27
7.25
7.24
7.22
7.21
7.20
7.19
7.18
7.17
3.22
3.22
3.21
3.21
3.20
3.19
3.19
3.18
3.18
3.10
3.09
3.08
3.06
F
Ph
N
1H NMR (CDCl3 400 MHz)
1.00
7.45
2.08
2.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

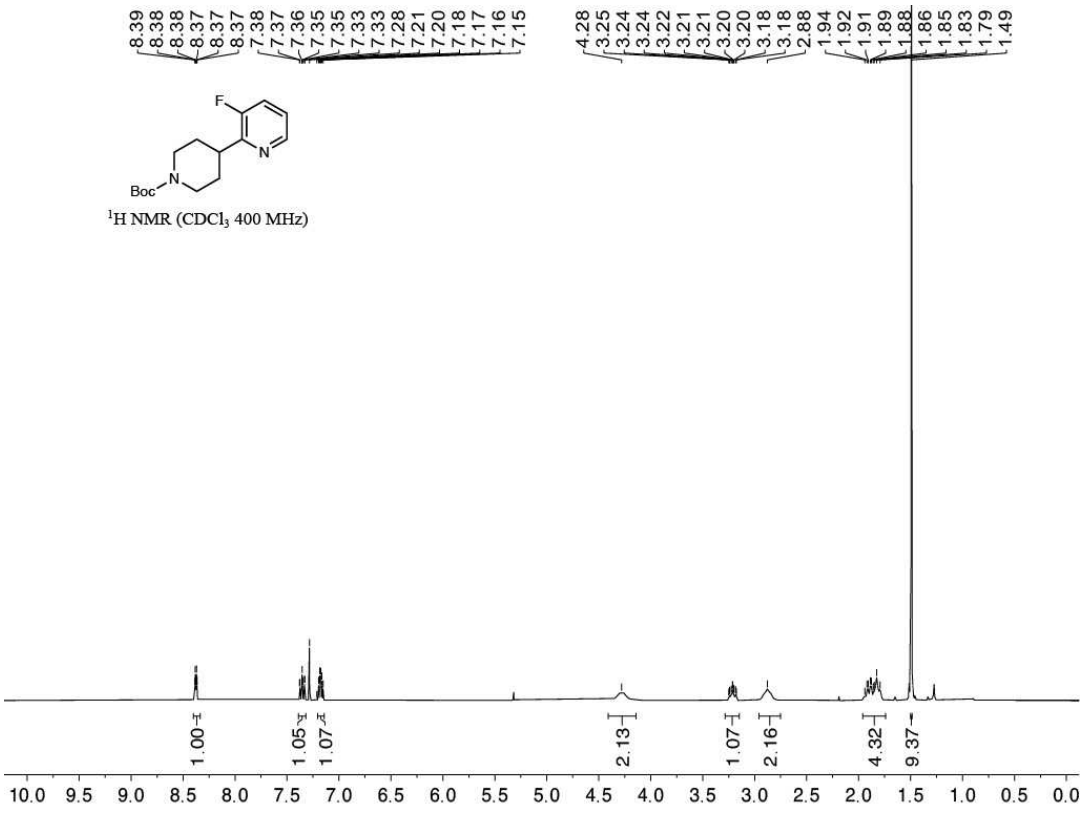

-125.45
F
Ph
N
19F NMR (CDCl3 375 MHz)
-125.45
-124.0 -124.5 -125.0 -125.5 -126.0 -126.5 -127.0
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200


159.04
156.49
149.71
149.56
144.91
144.85
141.38
128.47
128.41
126.06
122.66
122.60
122.57
122.47
77.37
77.05
76.74
34.56
34.55
33.45
33.43
F
Ph
N
^{13}C NMR ($CDCl_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

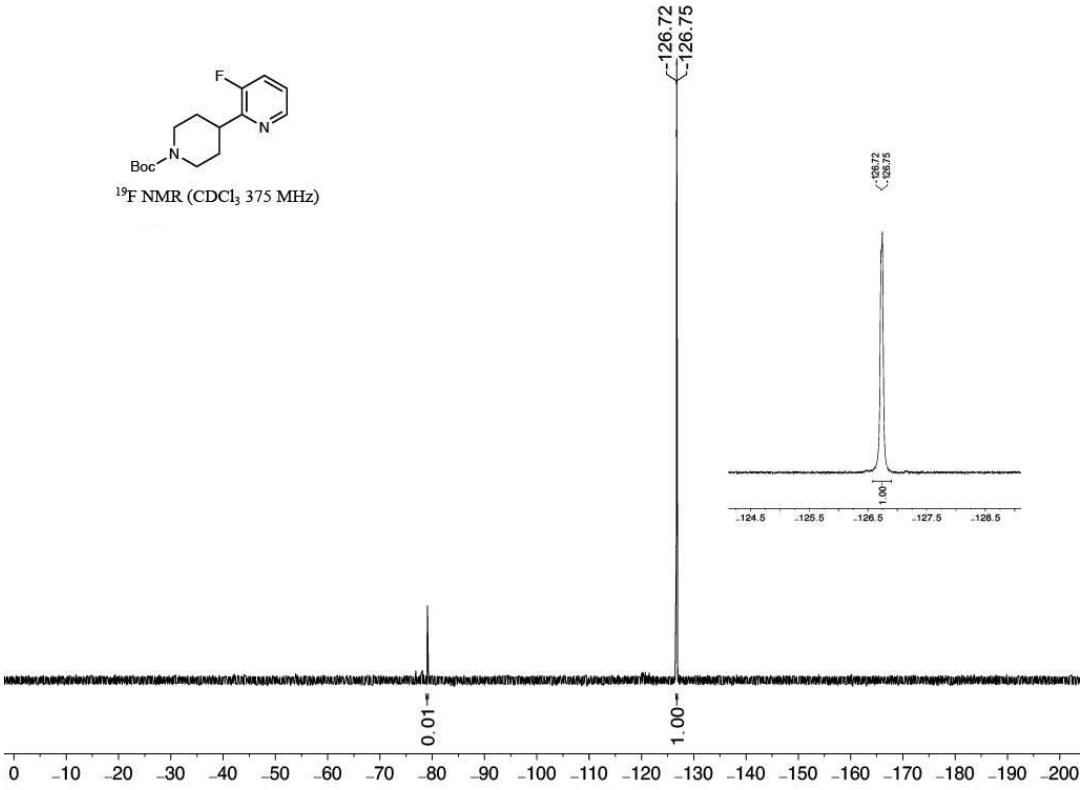

F
Me
N
Me
^{1}H NMR (CD_3CN 400 MHz)
Me
Me
Me
mesitylene
0.51
0.50
0.52
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0



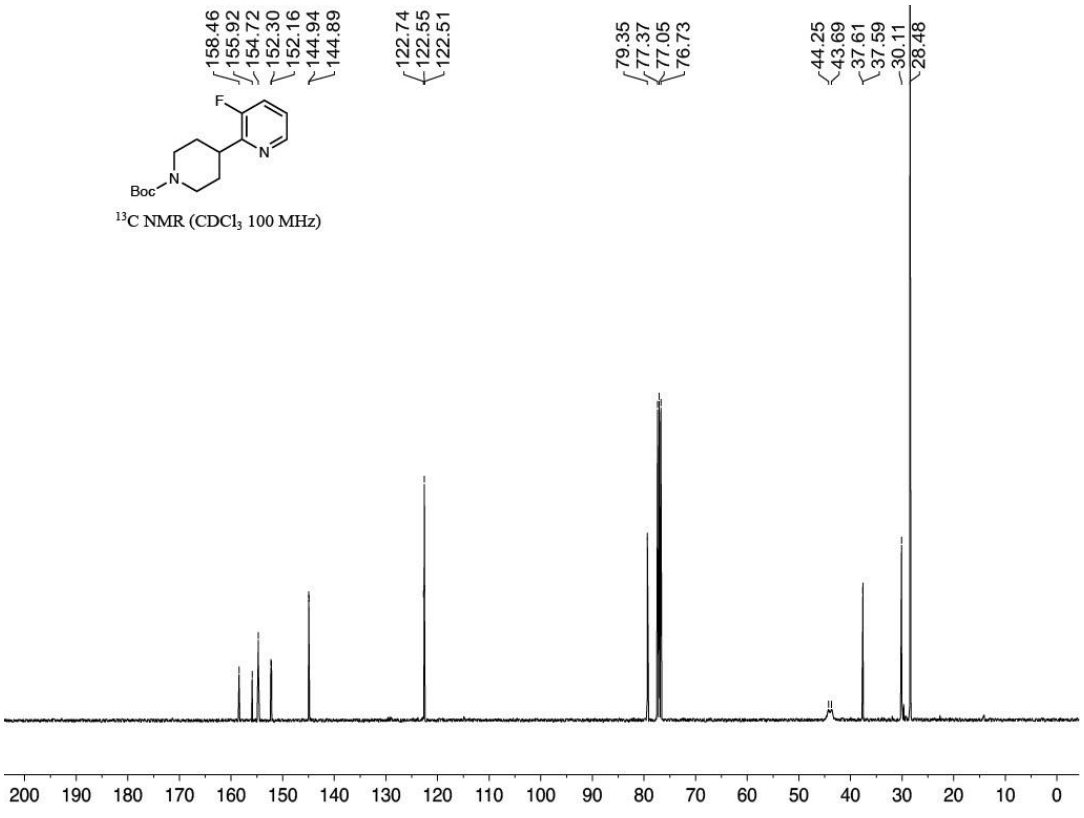
^{19}F NMR (CD_3CN 375 MHz)



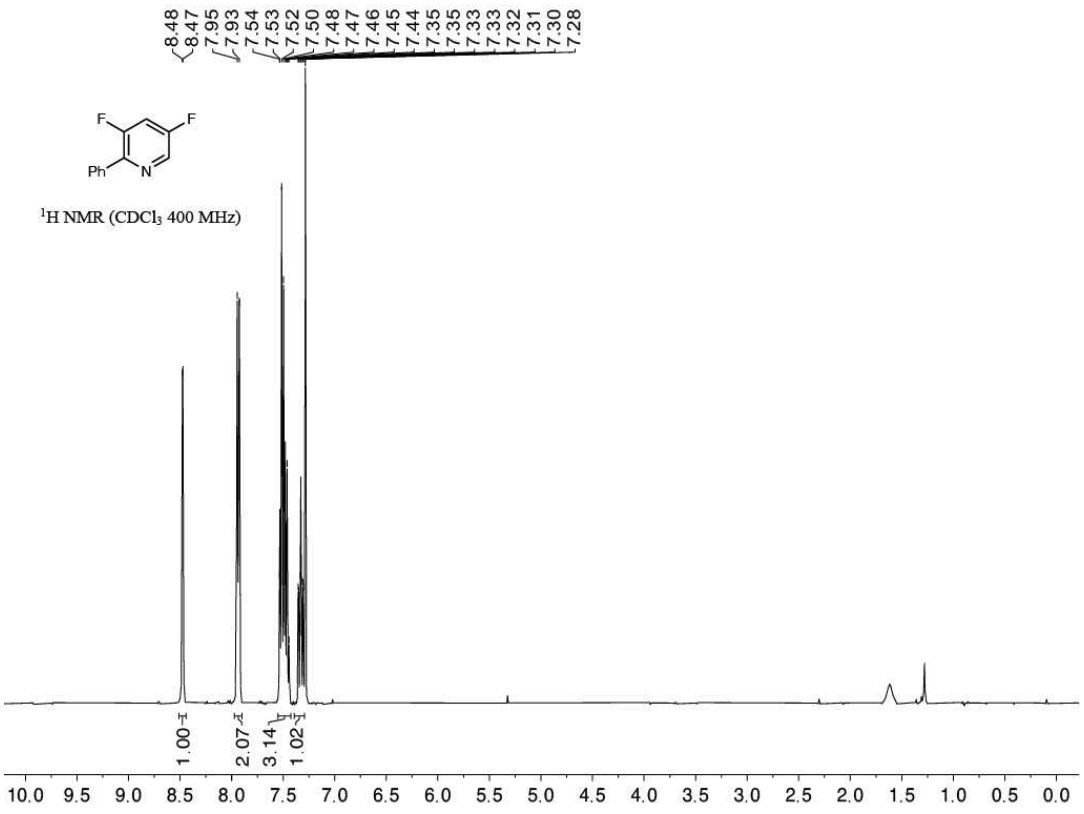
^{1}H NMR ($CDCl_3$ 400 MHz)

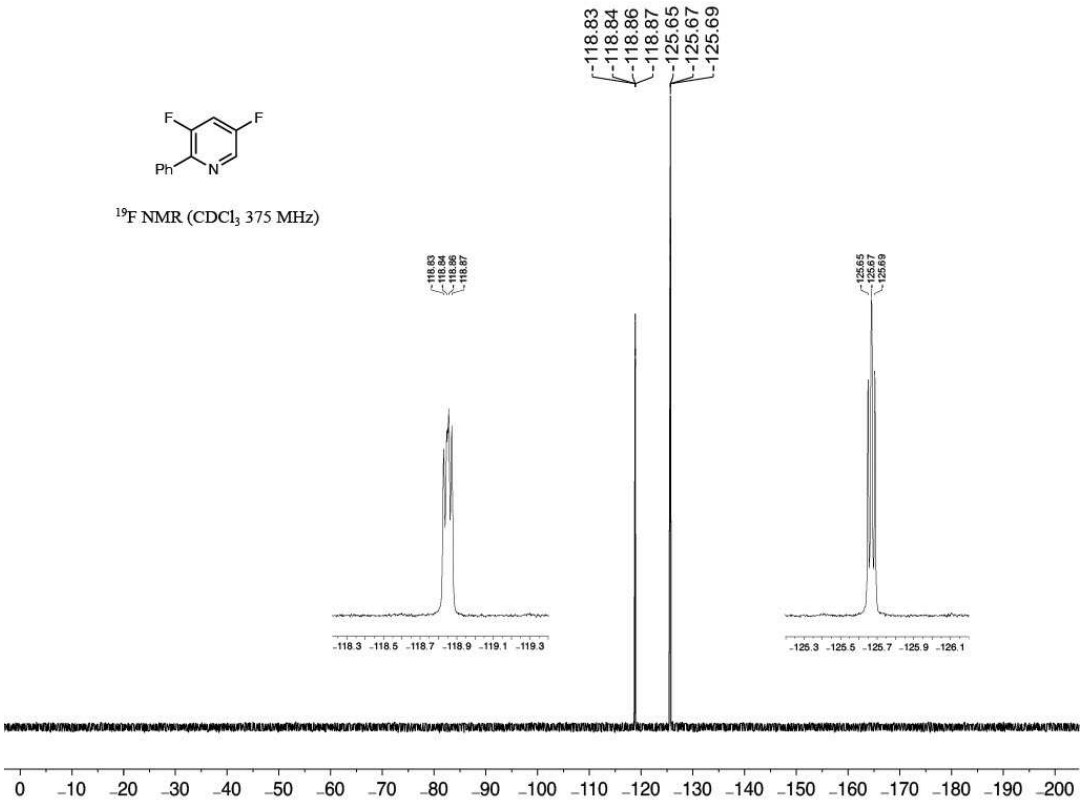


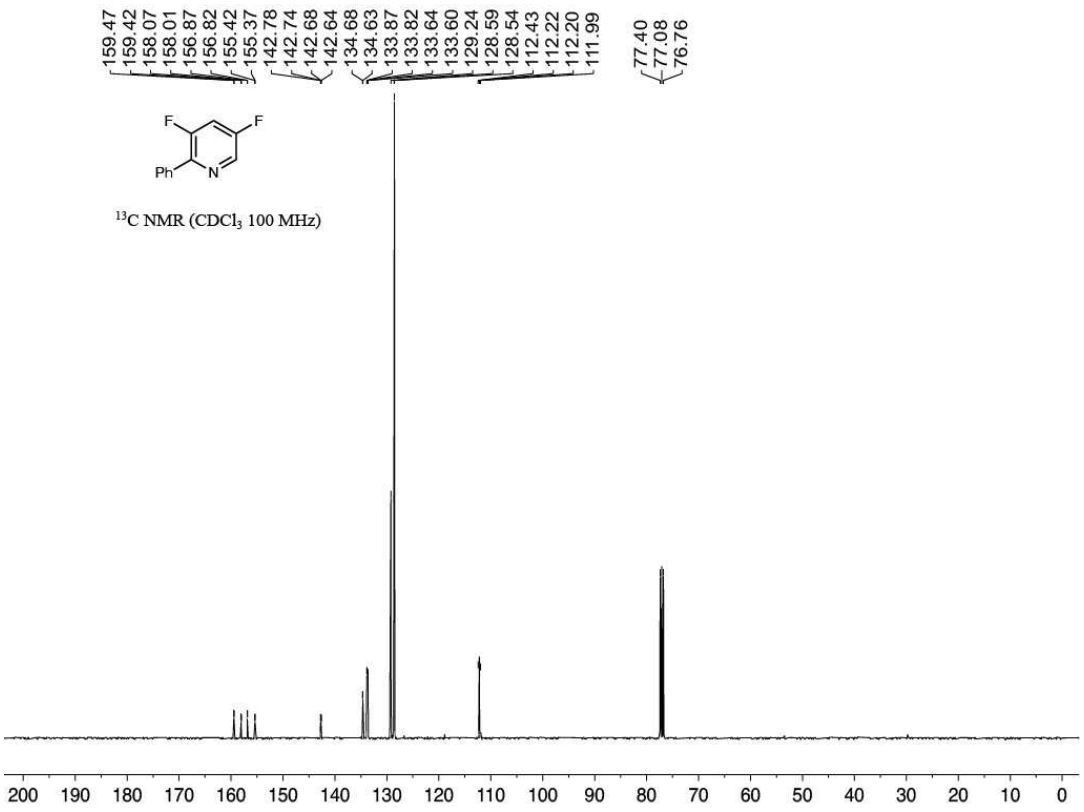
^{19}F NMR ($CDCl_3$ 375 MHz)



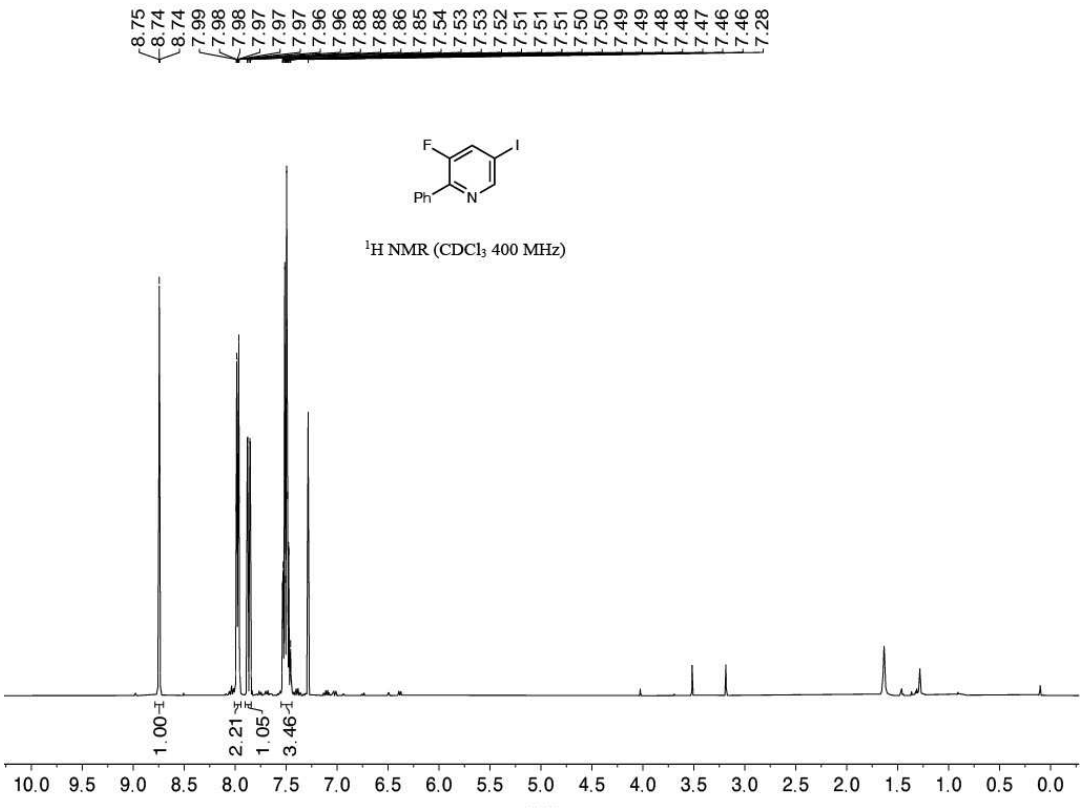
^{13}C NMR ($CDCl_3$ 100 MHz)


8.48
8.47
7.95
7.93
7.54
7.53
7.52
7.50
7.48
7.47
7.46
7.45
7.44
7.35
7.35
7.33
7.33
7.32
7.31
7.30
7.28
F
F
Ph
N
1H NMR (CDCl3 400 MHz)
1.00
2.07
3.14
1.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

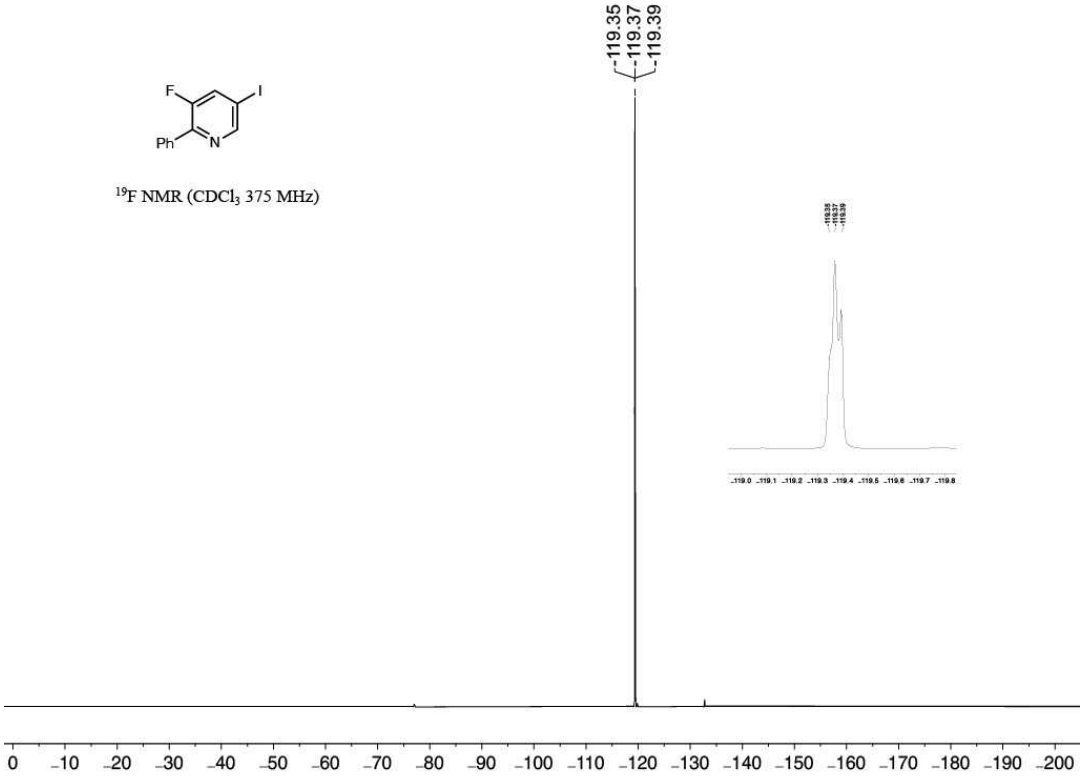

118.83
118.84
118.86
118.87
125.65
125.67
125.69
F
F
Ph
N
19F NMR (CDCl3 375 MHz)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200



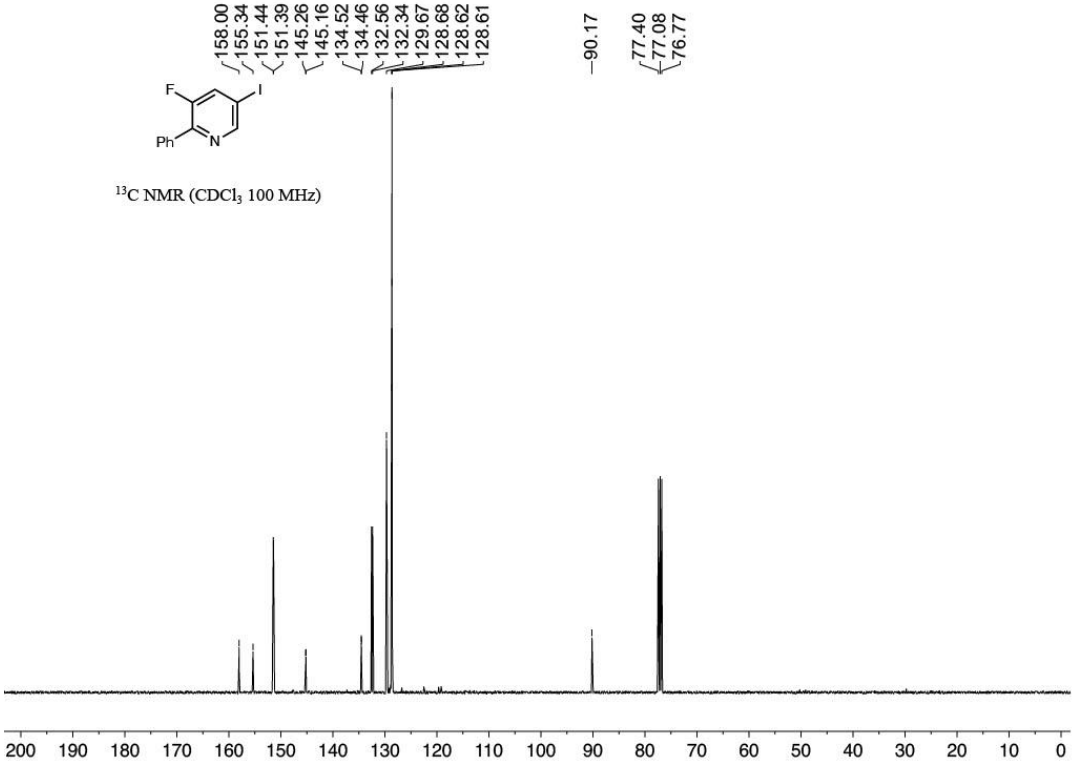
^{13}C NMR ($CDCl_3$ 100 MHz)



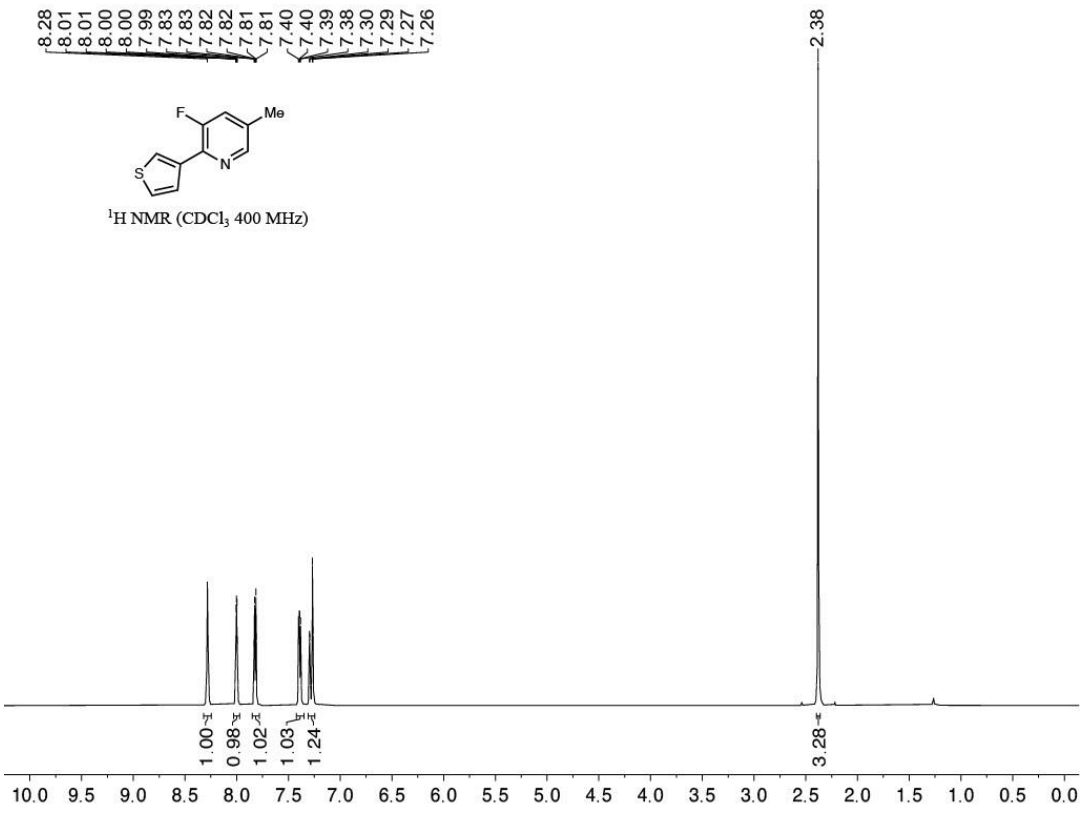
^{1}H NMR ($CDCl_3$ 400 MHz)



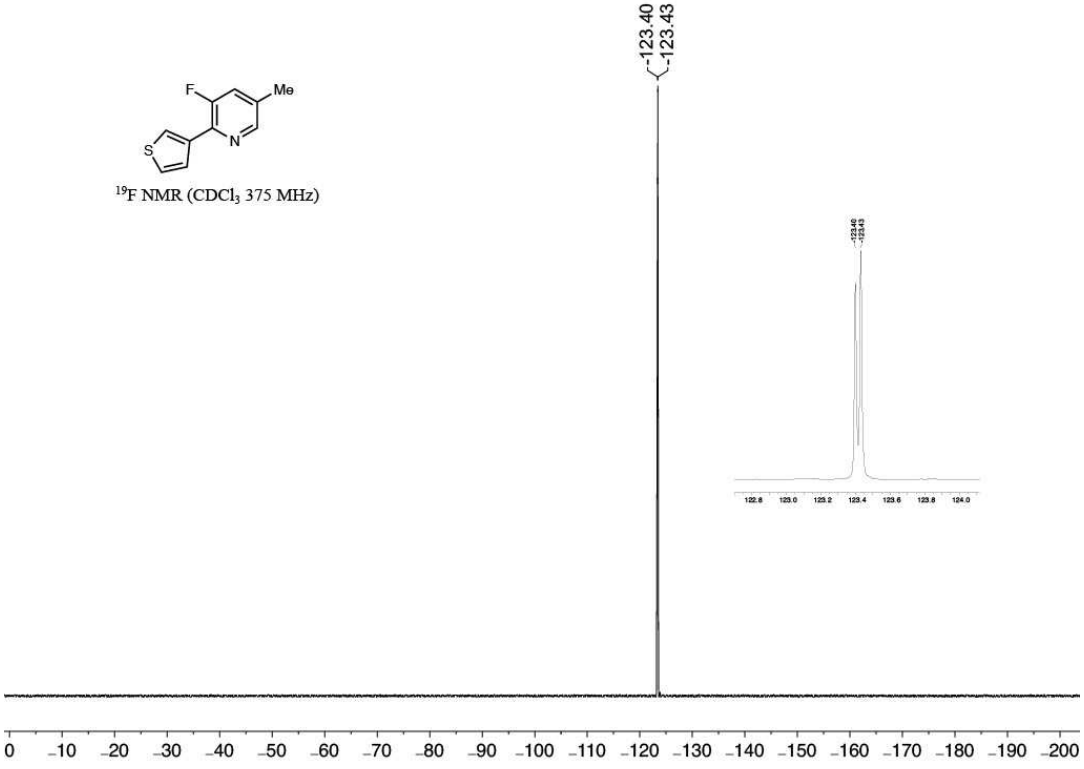
^{19}F NMR ($CDCl_3$ 375 MHz)



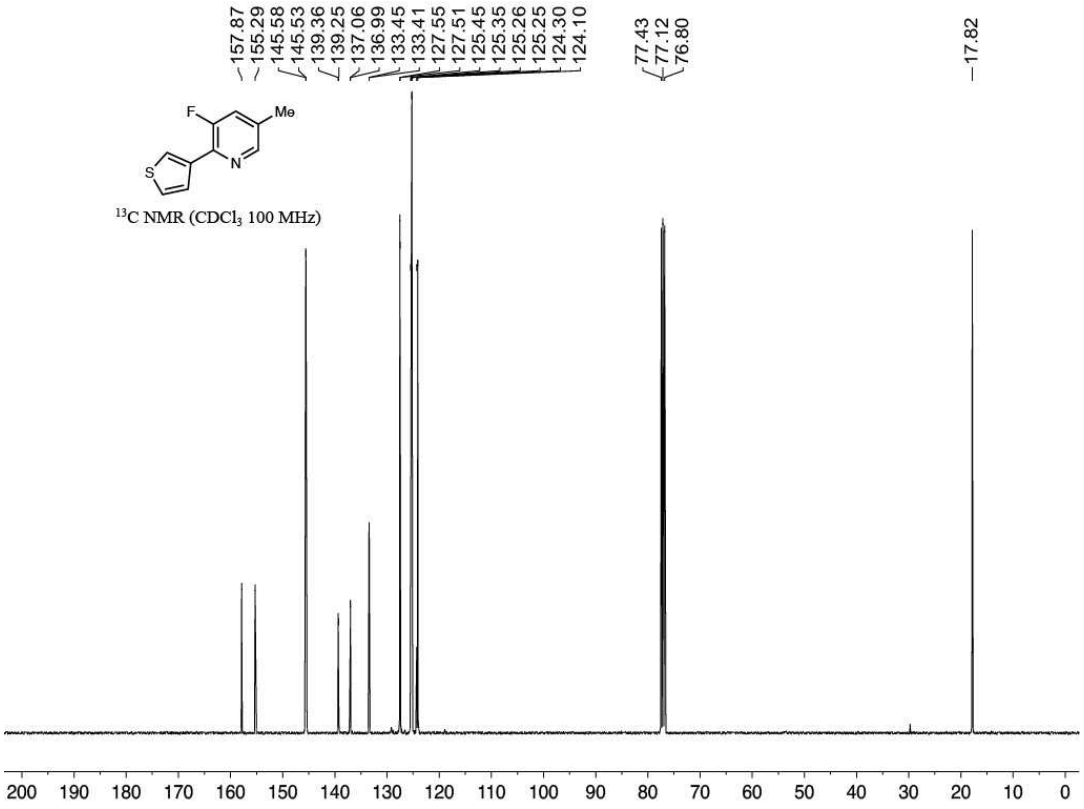
^{13}C NMR ($CDCl_3$ 100 MHz)

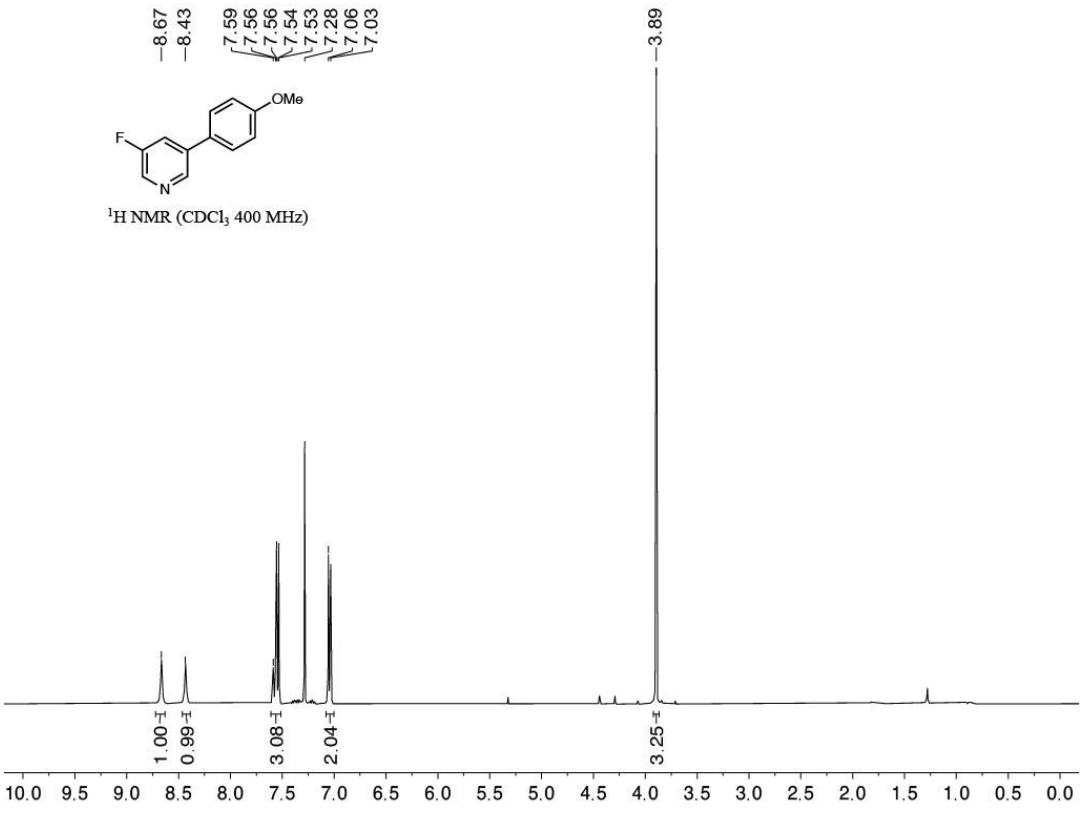


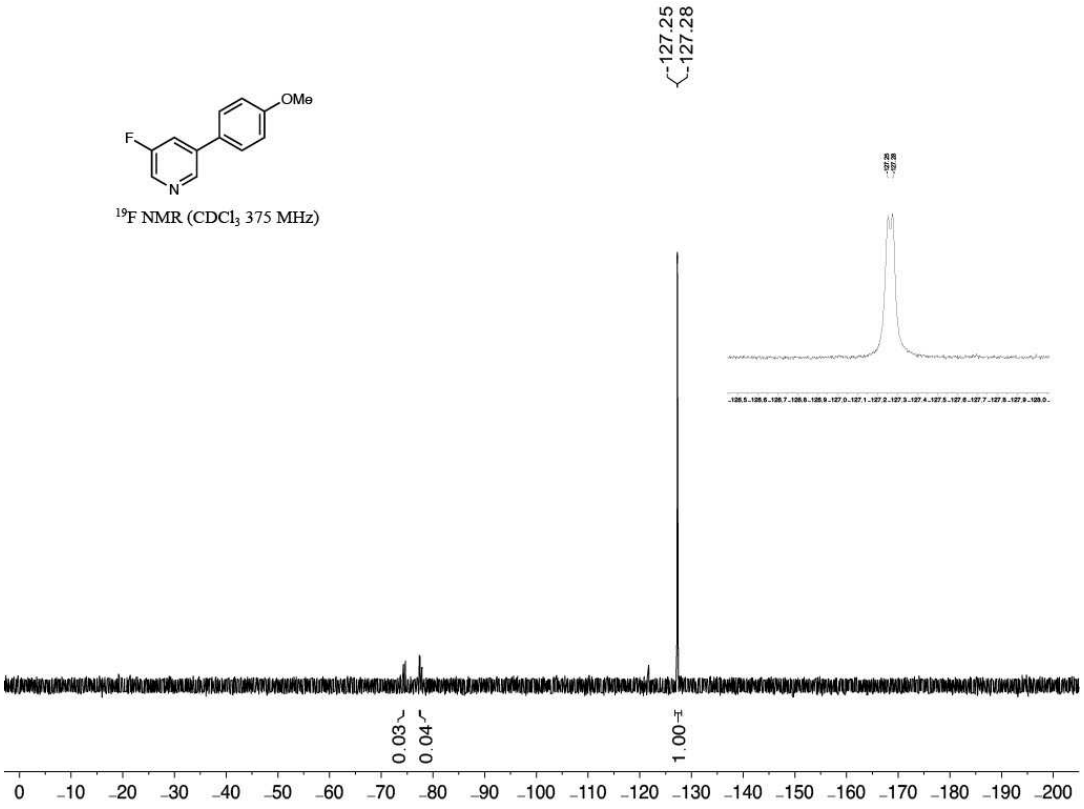
^{1}H NMR ($CDCl_3$ 400 MHz)

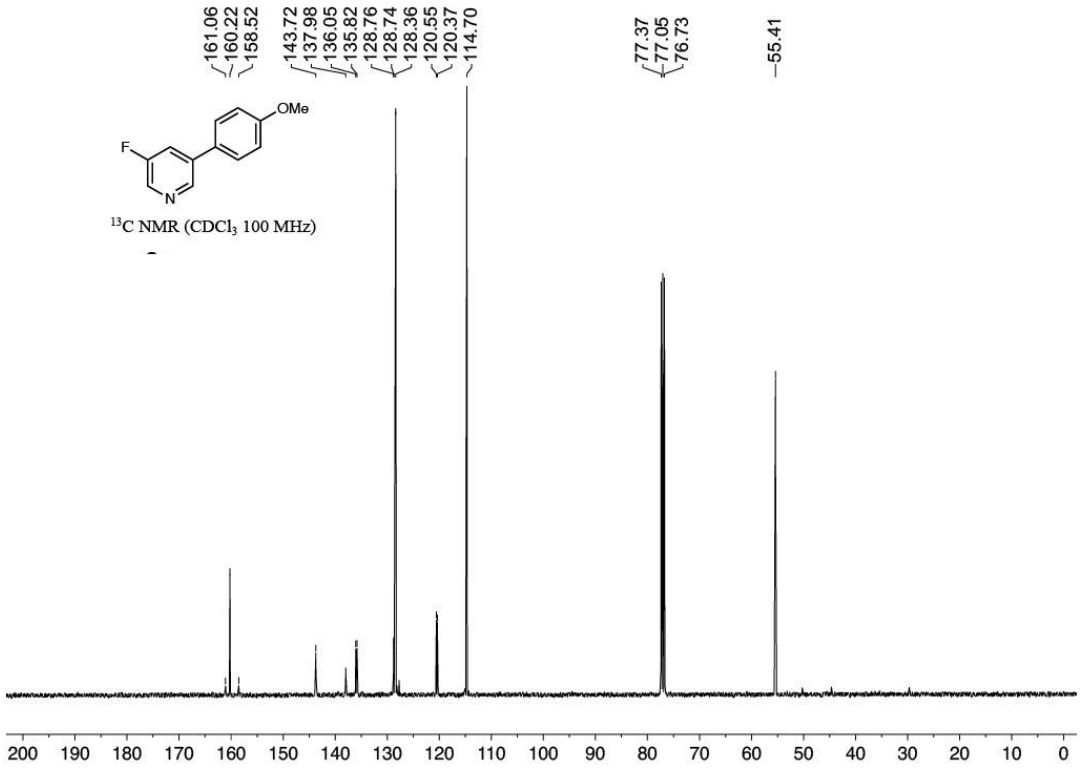


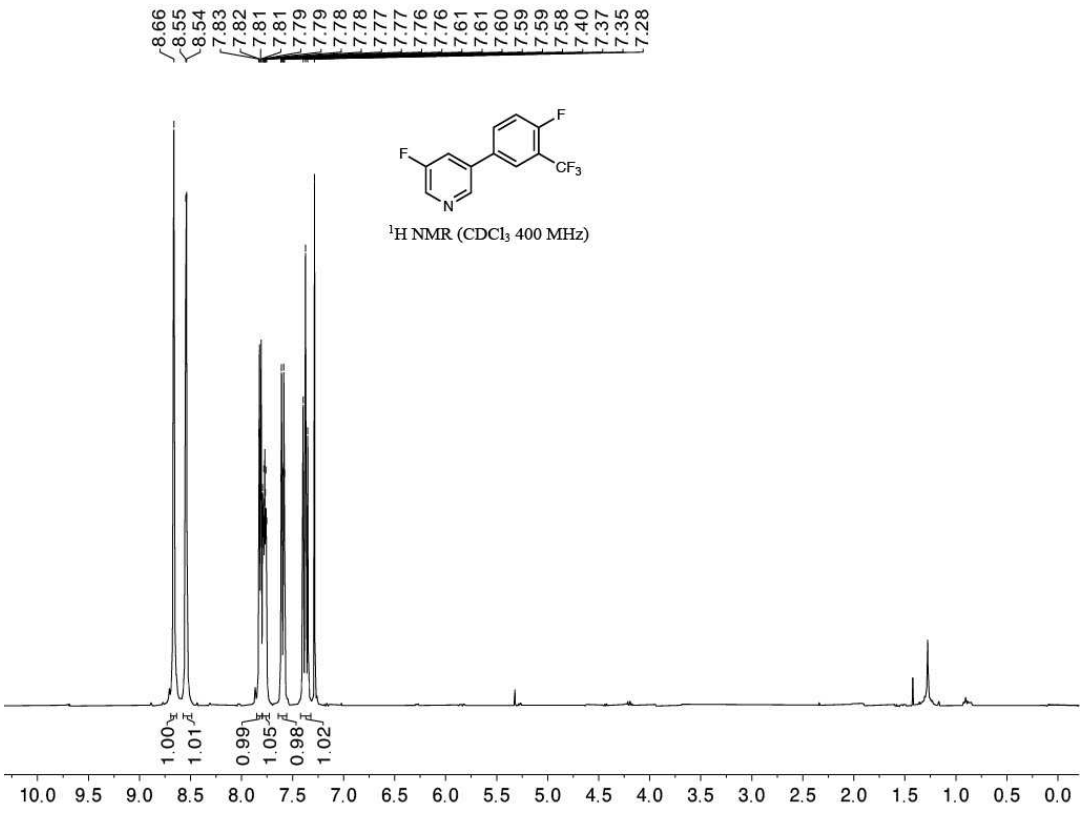
^{19}F NMR ($CDCl_3$ 375 MHz)

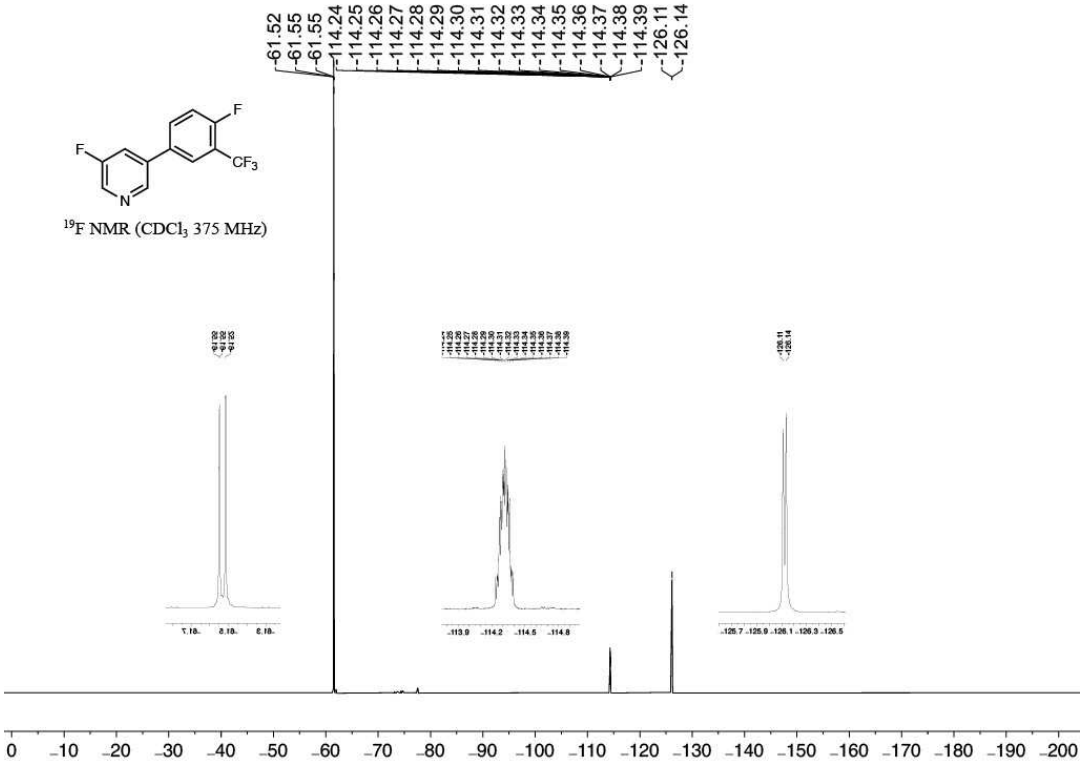

157.87
155.29
145.58
145.53
139.36
139.25
137.06
136.99
133.45
133.41
127.55
127.51
125.45
125.35
125.26
125.25
124.30
124.10
77.43
77.12
76.80
17.82
F
Me
N
S
^{13}C NMR (CDCl$_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

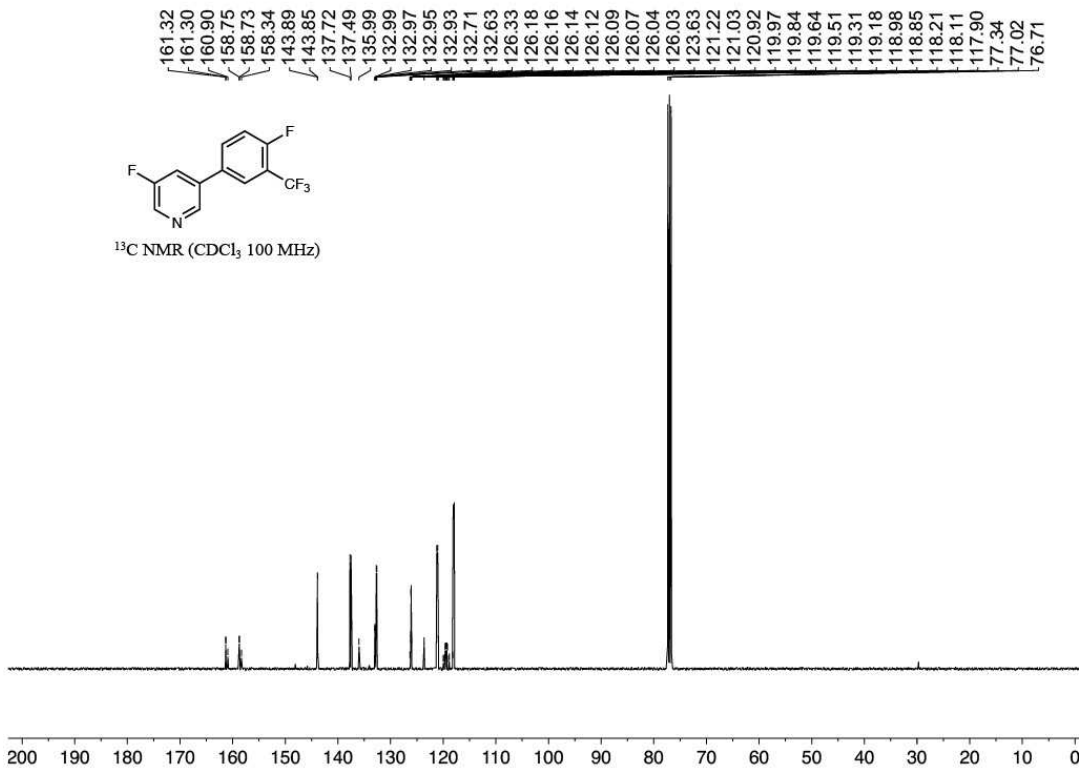

8.67
8.43
7.59
7.56
7.56
7.54
7.53
7.28
7.06
7.03
3.89
OMe
F
N
^{1}H NMR (CDCl$_3$ 400 MHz)
1.00
0.99
3.08
2.04
3.25
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


OMe
F
N
^{19}F NMR ($CDCl_3$ 375 MHz)
-127.25
-127.28
0.03
0.04
1.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

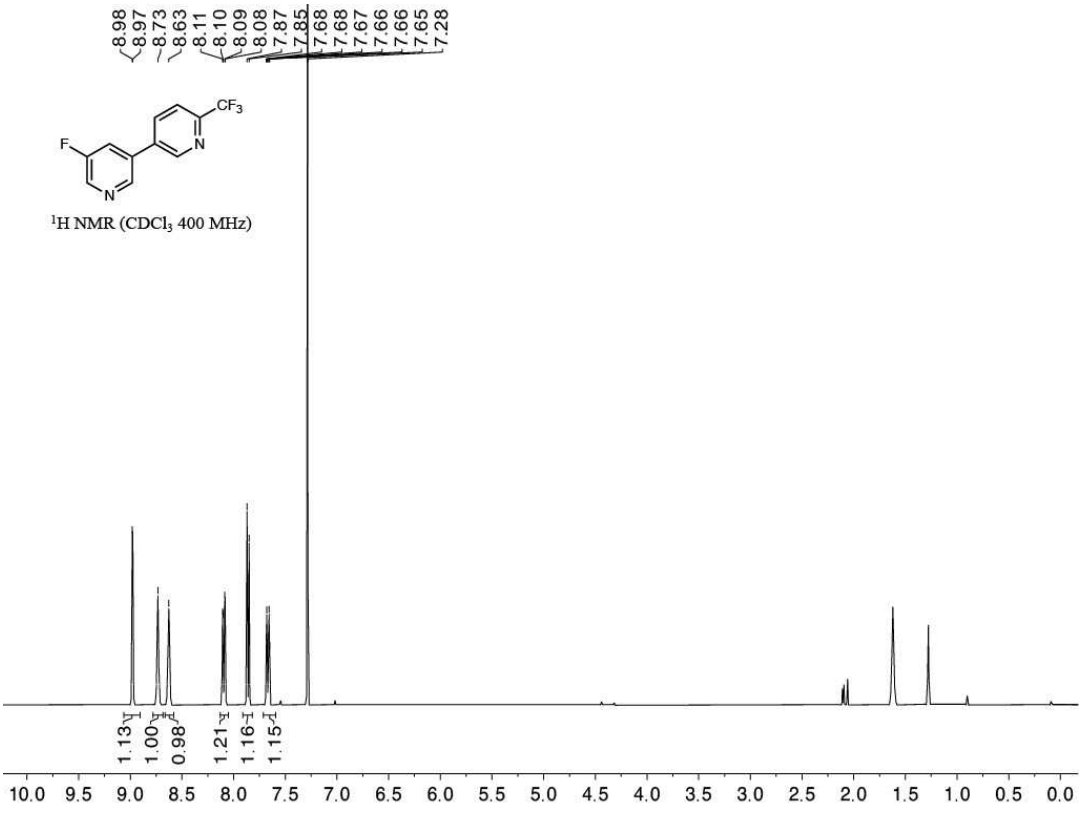

161.06
160.22
158.52
143.72
137.98
136.05
135.82
128.76
128.74
128.36
120.55
120.37
114.70
77.37
77.05
76.73
55.41
OMe
F
N
^{13}C NMR ($CDCl_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


8.66
8.55
8.54
7.83
7.82
7.81
7.81
7.79
7.79
7.78
7.78
7.77
7.77
7.76
7.76
7.61
7.61
7.60
7.59
7.59
7.58
7.40
7.37
7.35
7.28
F
F
CF3
N
1H NMR (CDCl3 400 MHz)
1.00
1.01
0.99
1.05
0.98
1.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

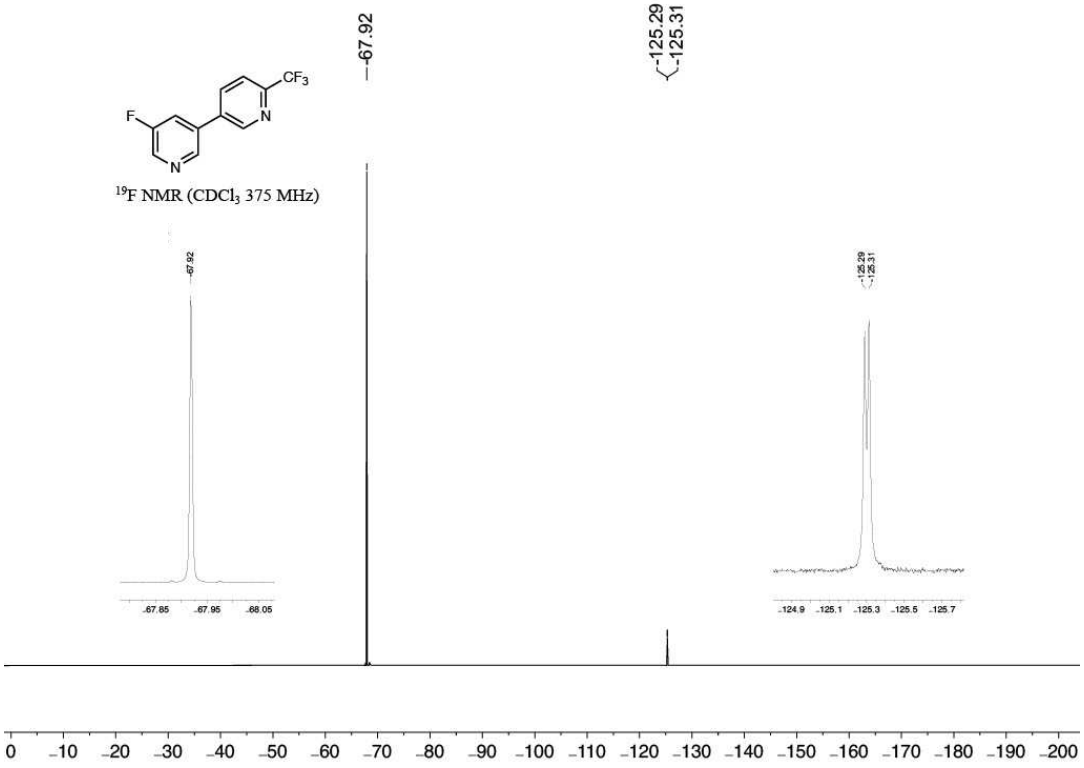

-61.52
-61.55
-61.55
-114.24
-114.25
-114.26
-114.27
-114.28
-114.29
-114.30
-114.31
-114.32
-114.33
-114.34
-114.35
-114.36
-114.37
-114.38
-114.39
-126.11
-126.14
F
F
CF3
N
19F NMR (CDCl3 375 MHz)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

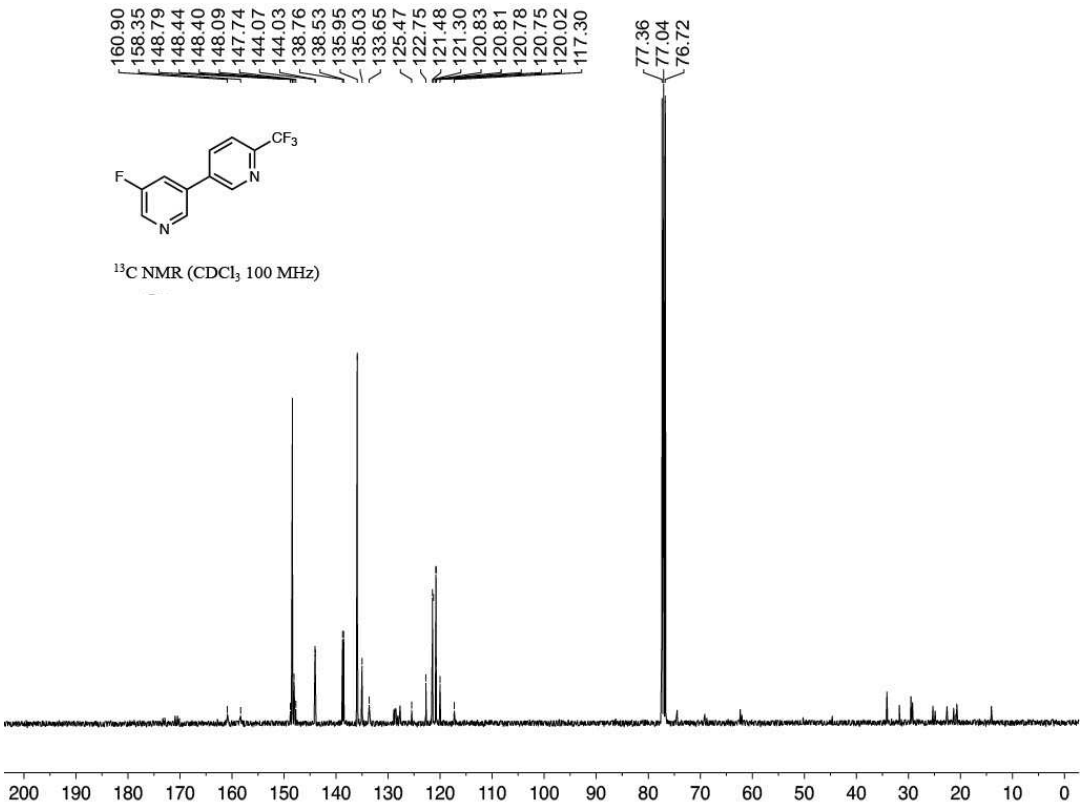


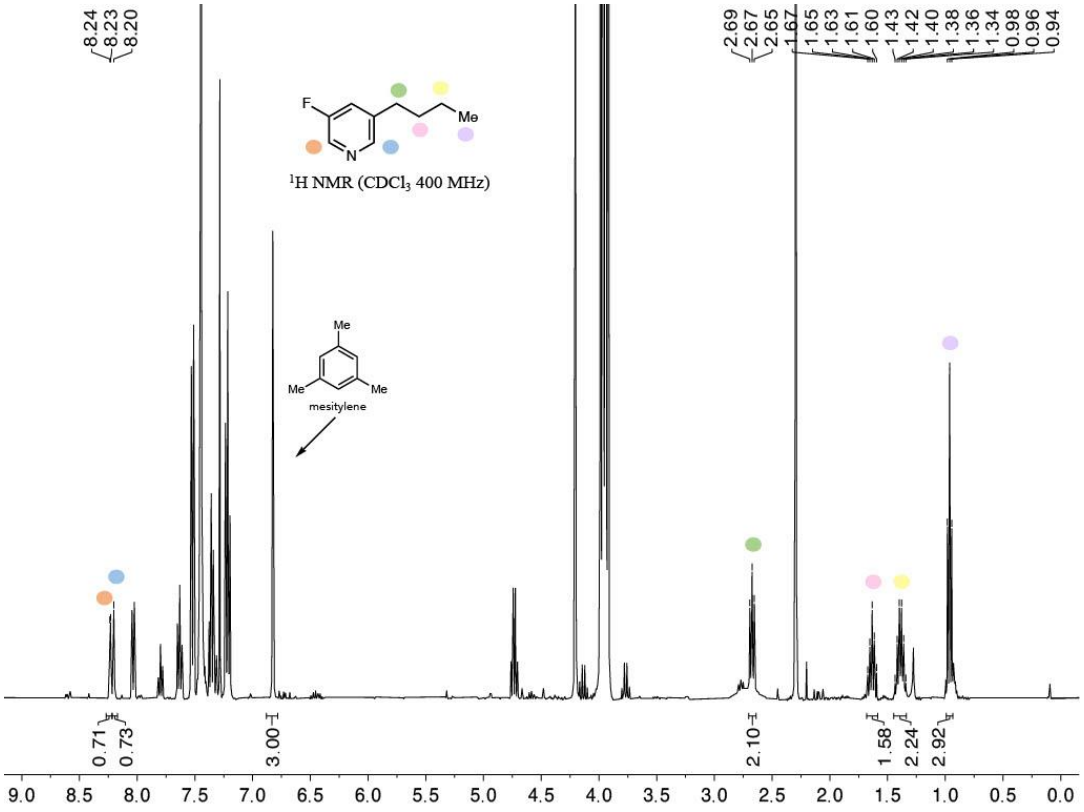
^{13}C NMR ($CDCl_3$ 100 MHz)

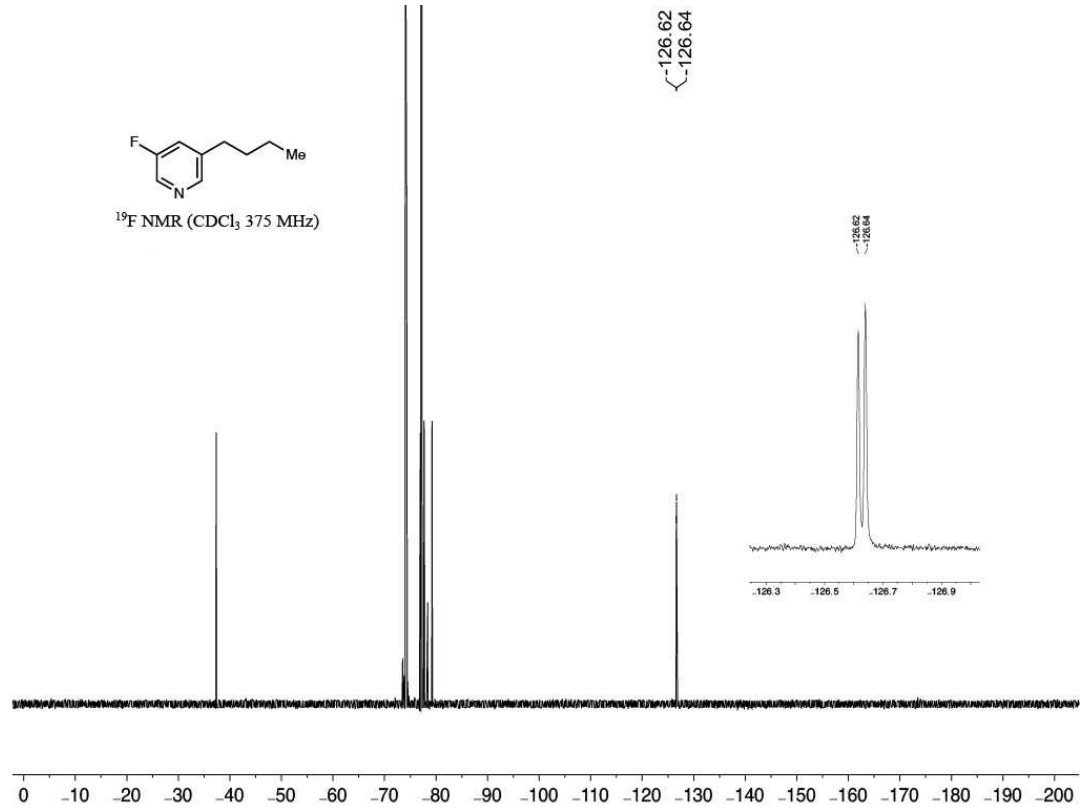


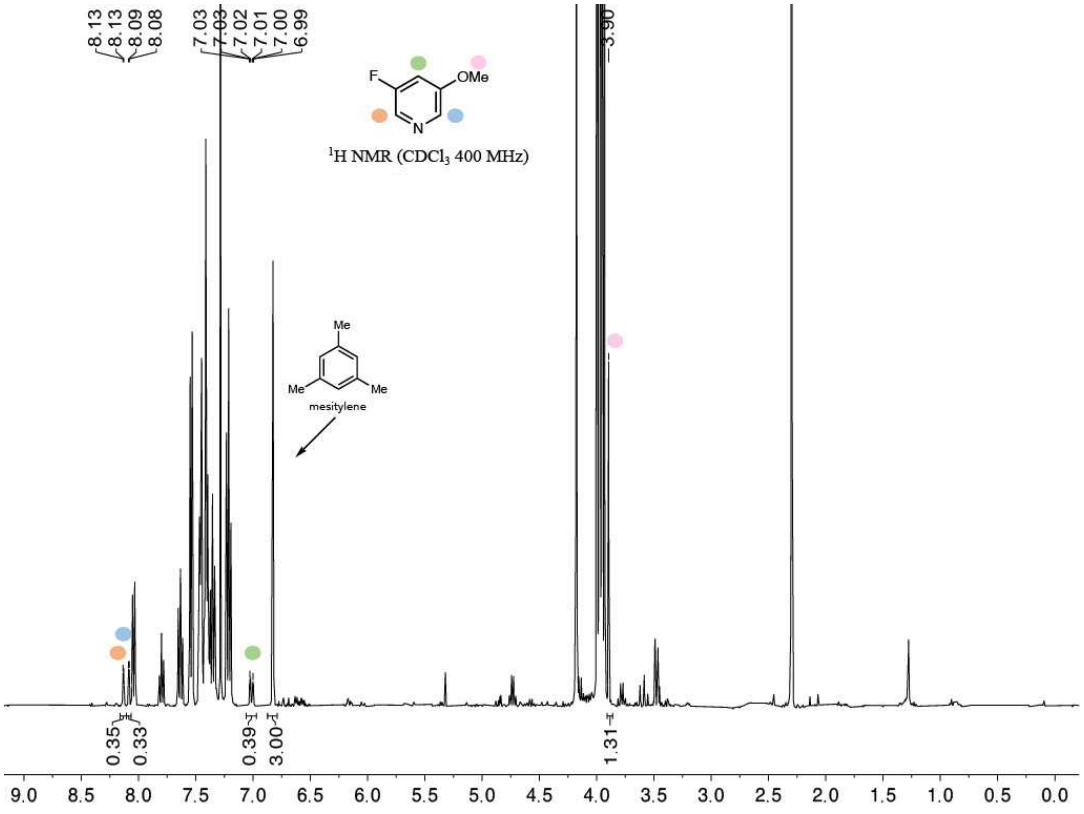
^{1}H NMR ($CDCl_3$ 400 MHz)

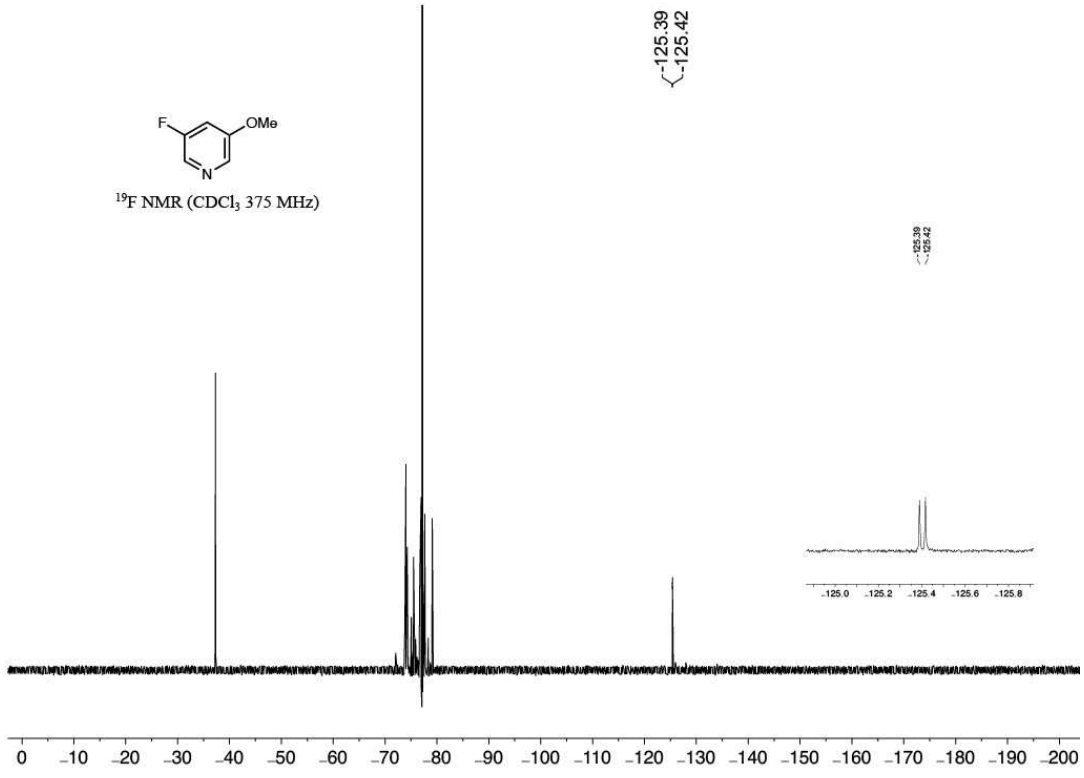

-67.92
-125.29
-125.31
F
CF3
N
N
^{19}F NMR (CDCl$_3$ 375 MHz)
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

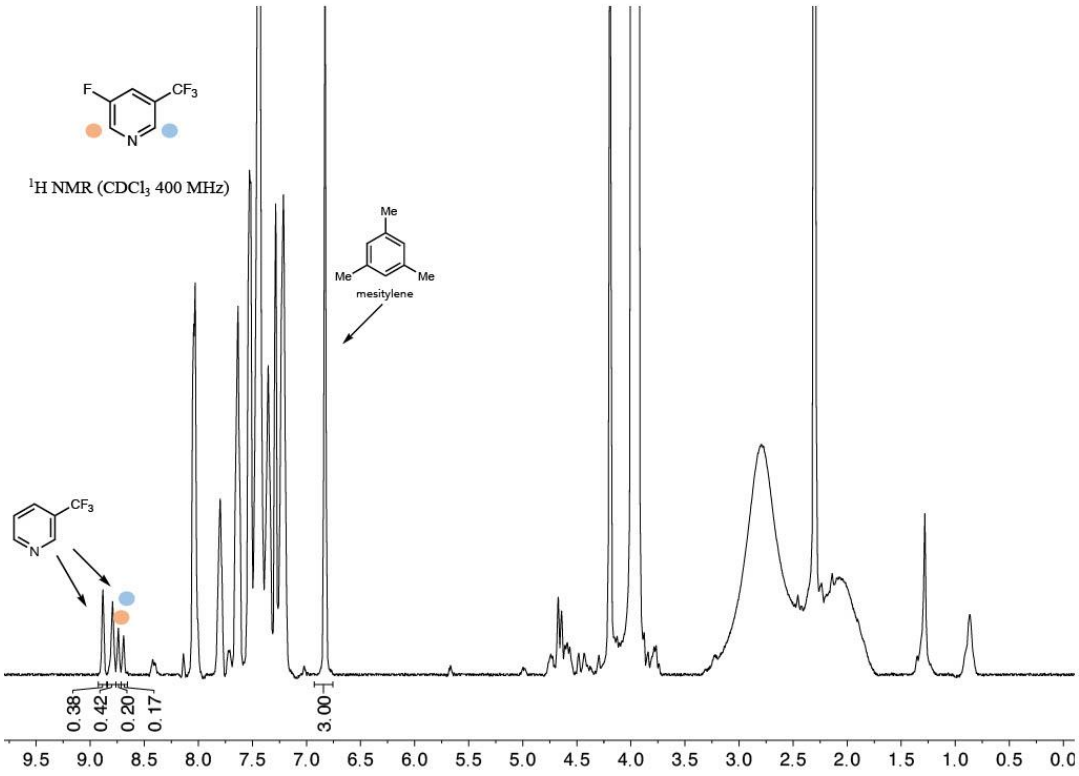

160.90
158.35
148.79
148.44
148.40
148.09
147.74
144.07
144.03
138.76
138.53
135.95
135.03
133.65
125.47
122.75
121.48
121.30
120.83
120.81
120.78
120.75
120.02
117.30
77.36
77.04
76.72
F
CF3
N
N
^{13}C NMR (CDCl$_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

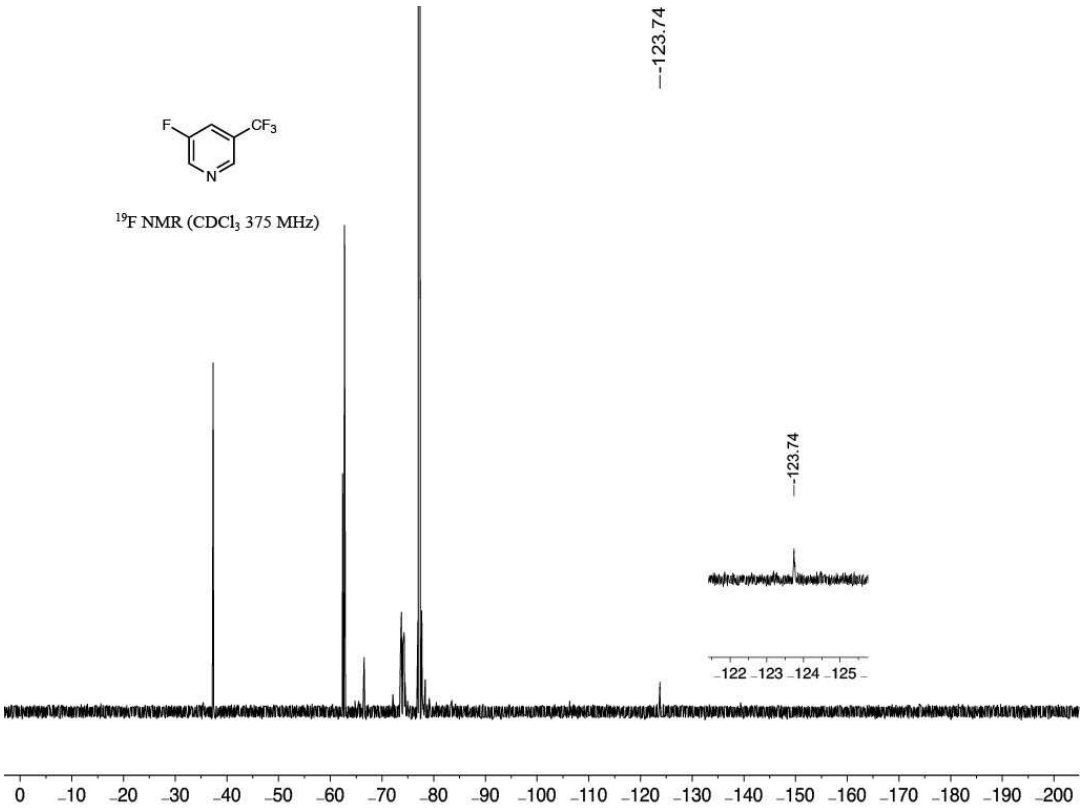

8.24
8.23
8.20
2.69
2.67
2.65
1.67
1.65
1.63
1.61
1.60
1.43
1.42
1.40
1.38
1.36
1.34
0.98
0.96
0.94
F
Me
N
^{1}H NMR ($CDCl_3$ 400 MHz)
Me
Me
Me
mesitylene
0.71
0.73
3.00
2.10
1.58
2.24
2.92
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

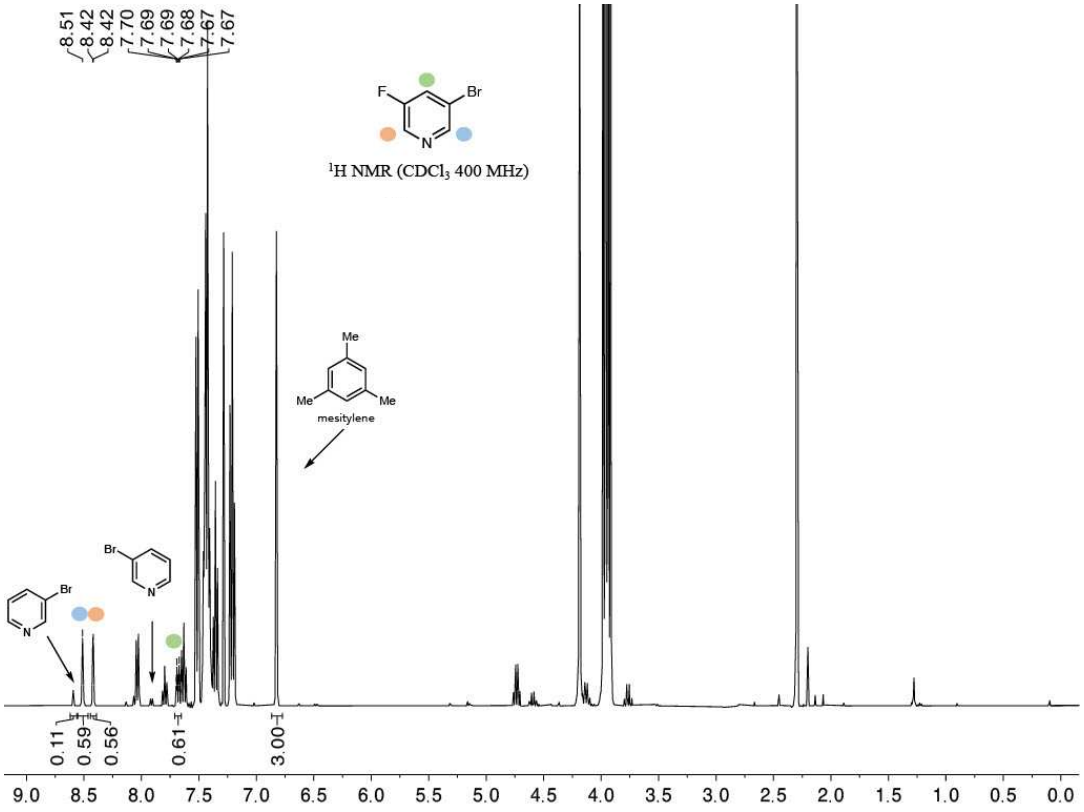

-126.62
-126.64
F
Me
N
^{19}F NMR ($CDCl_3$ 375 MHz)
-126.62
-126.64
-126.3
-126.5
-126.7
-126.9
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

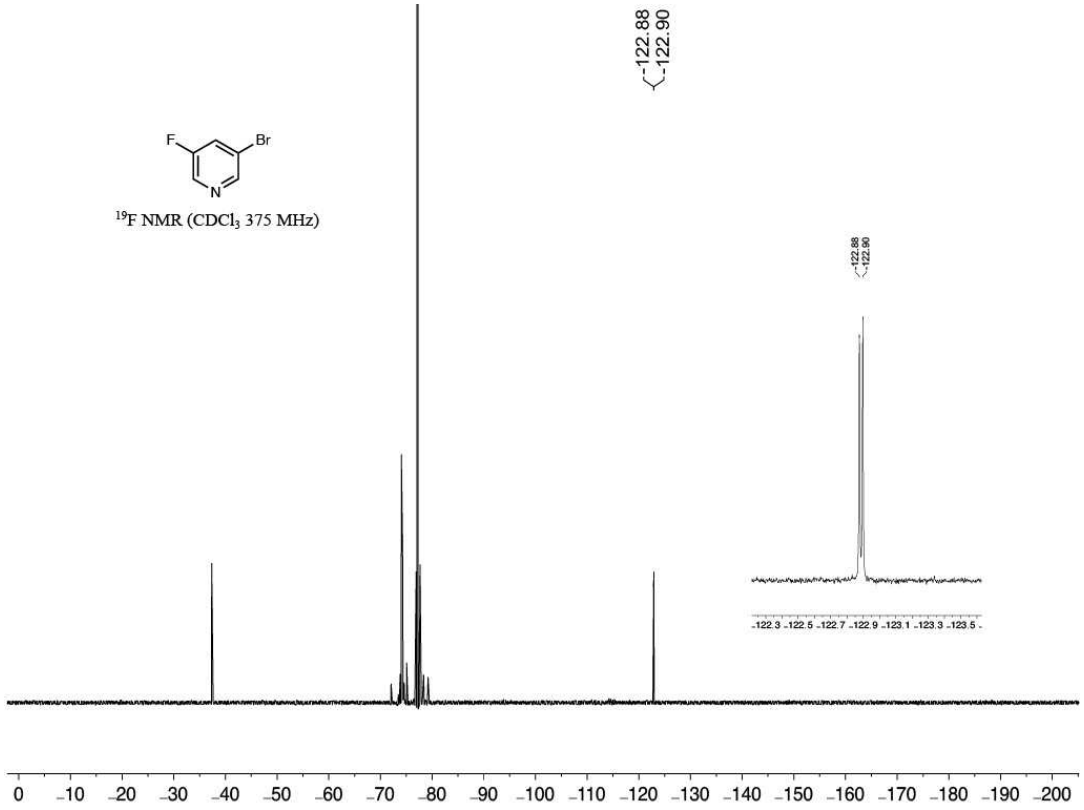

8.13
8.13
8.09
8.08
7.03
7.03
7.02
7.01
7.00
6.99
3.90
F
OMe
N
^{1}H NMR ($CDCl_3$ 400 MHz)
Me
Me
Me
mesitylene
0.35
0.33
0.39
3.00
1.31
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

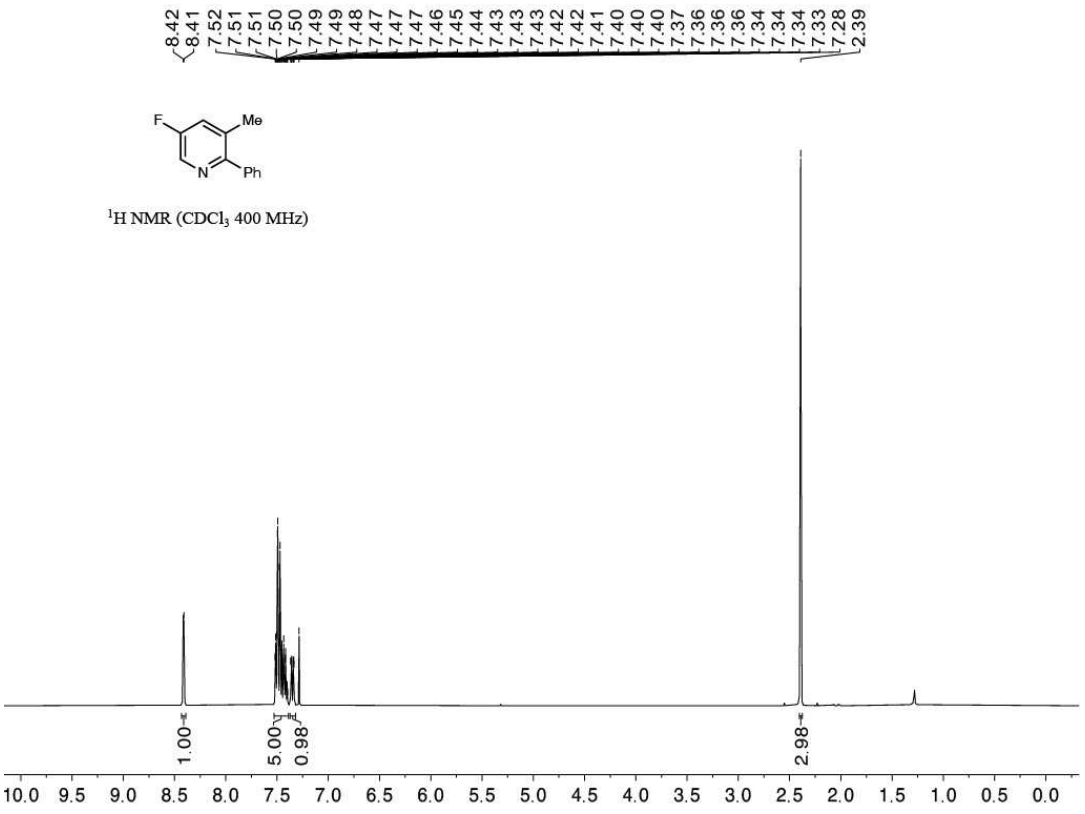

-125.39
-125.42
F
OMe
N
^{19}F NMR ($CDCl_3$ 375 MHz)
-125.0 -125.2 -125.4 -125.6 -125.8
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200


F
CF3
N
1H NMR (CDCl3 400 MHz)
Me
Me
Me
mesitylene
CF3
N
0.38
0.42
0.20
0.17
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

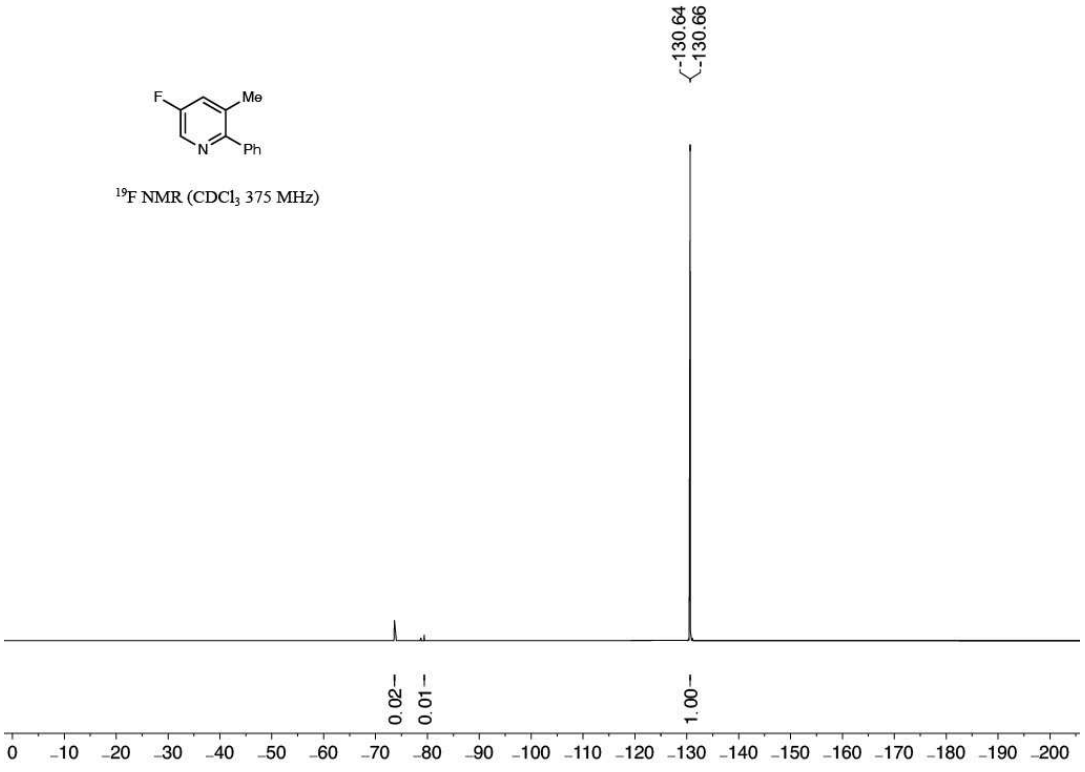

-123.74
F
CF3
N
19F NMR (CDCl3 375 MHz)
-123.74
-122 -123 -124 -125
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200


8.51
8.42
8.42
7.70
7.69
7.69
7.68
7.67
7.67
F
Br
N
^{1}H NMR ($CDCl_3$ 400 MHz)
Me
Me
Me
mesitylene
Br
N
Br
N
0.11
0.59
0.56
0.61
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

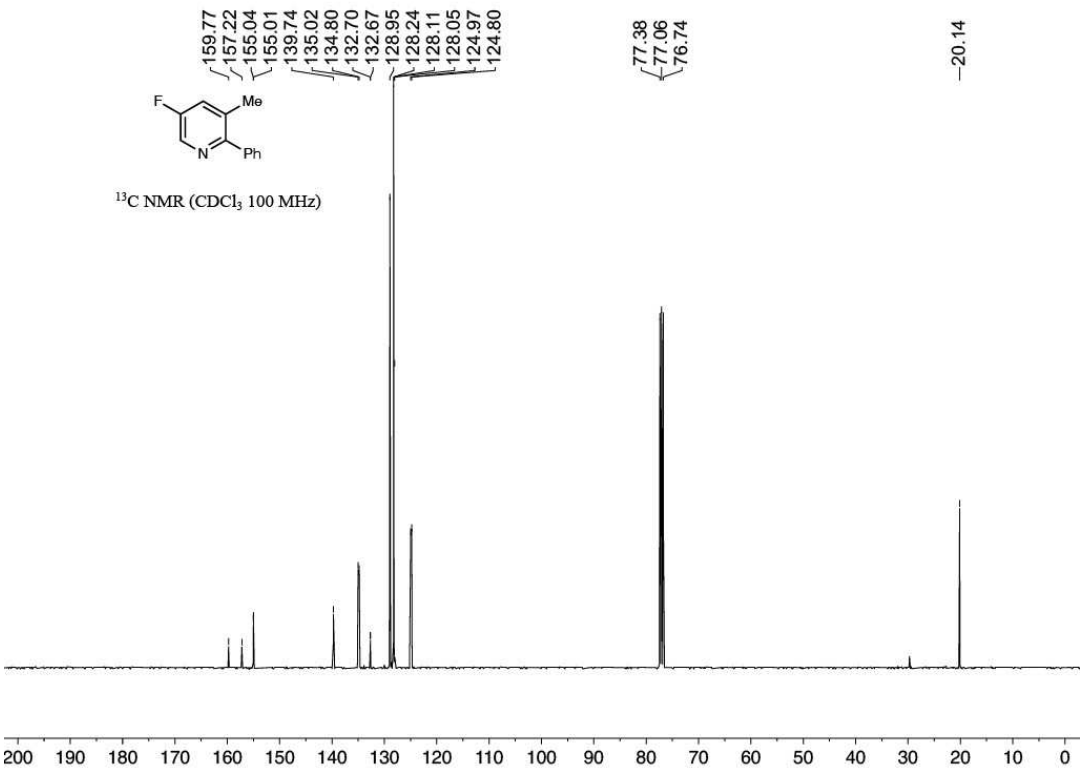

-122.88
-122.90
F
Br
N
^{19}F NMR ($CDCl_3$ 375 MHz)
-122.88
-122.90
-122.3 -122.5 -122.7 -122.9 -123.1 -123.3 -123.5
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200



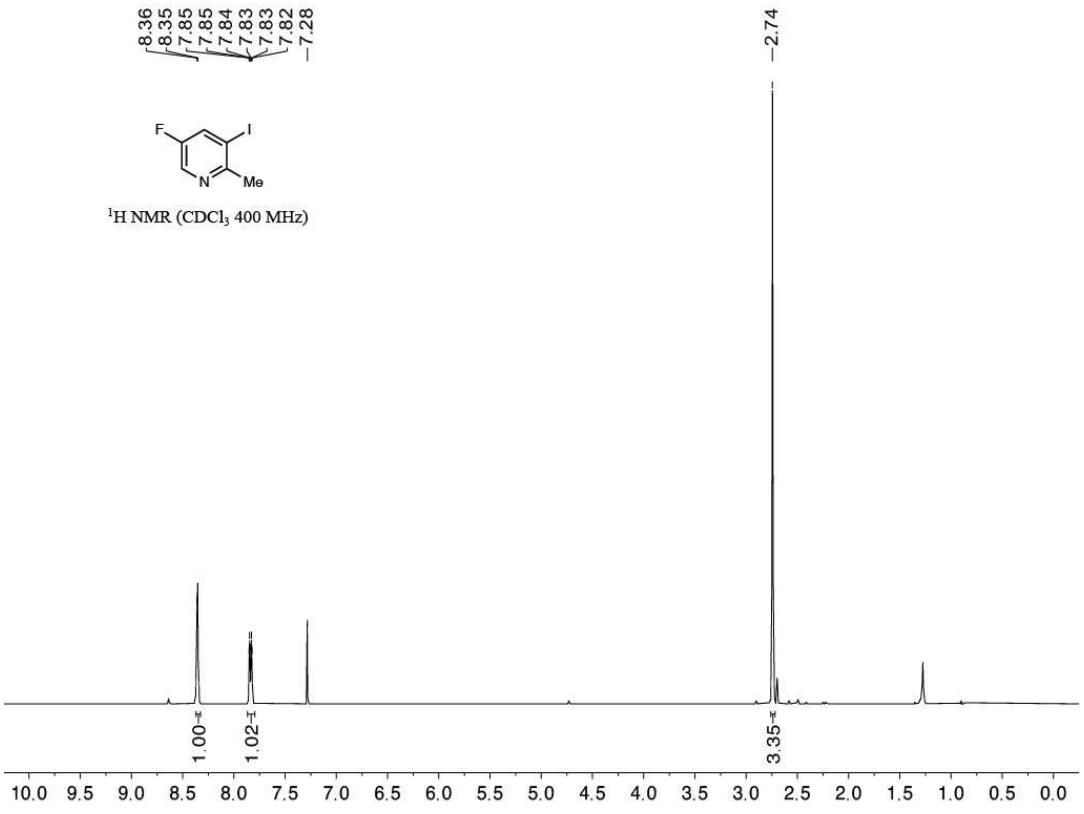
^{1}H NMR ($CDCl_3$ 400 MHz)



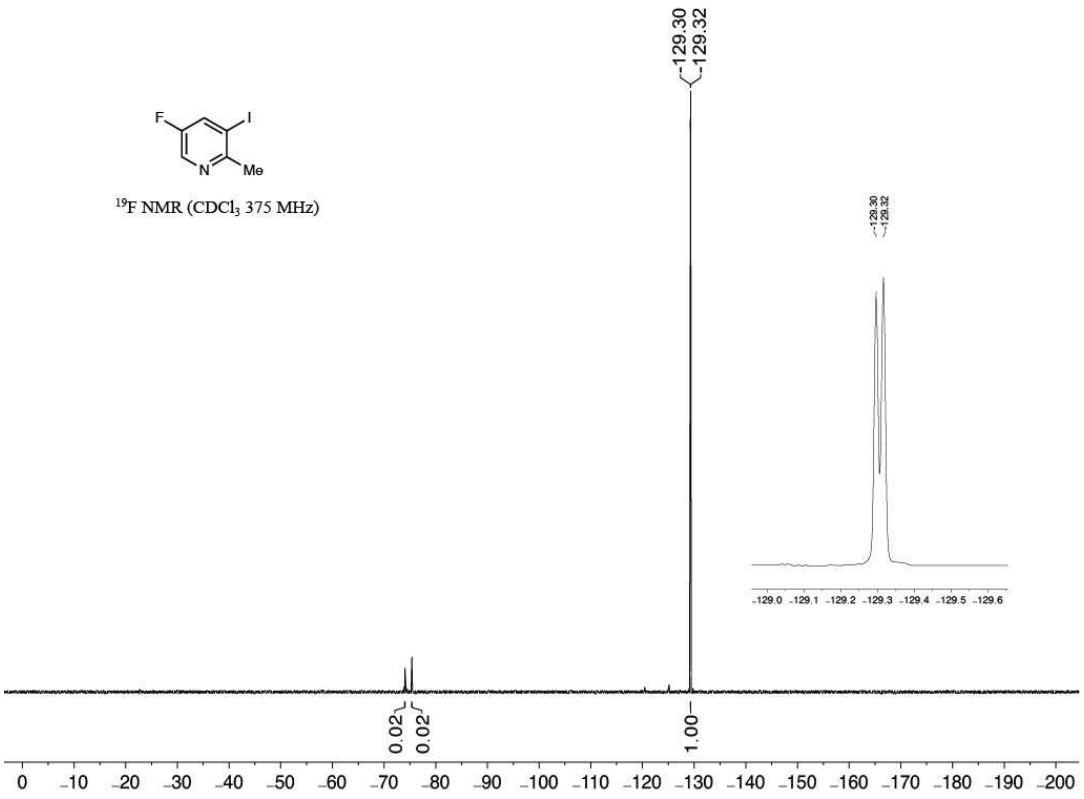
^{19}F NMR ($CDCl_3$ 375 MHz)

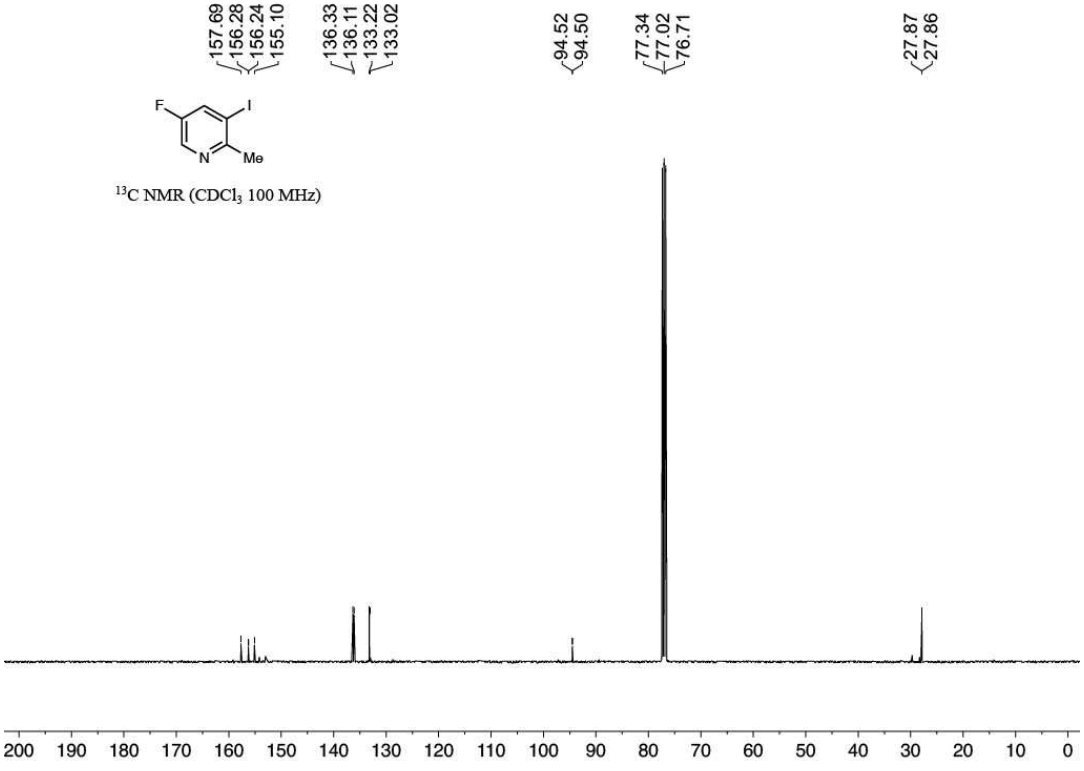


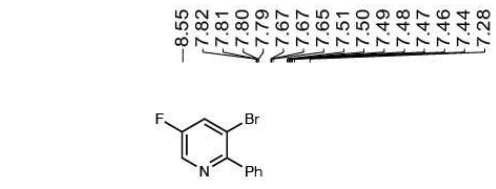
^{13}C NMR ($CDCl_3$ 100 MHz)



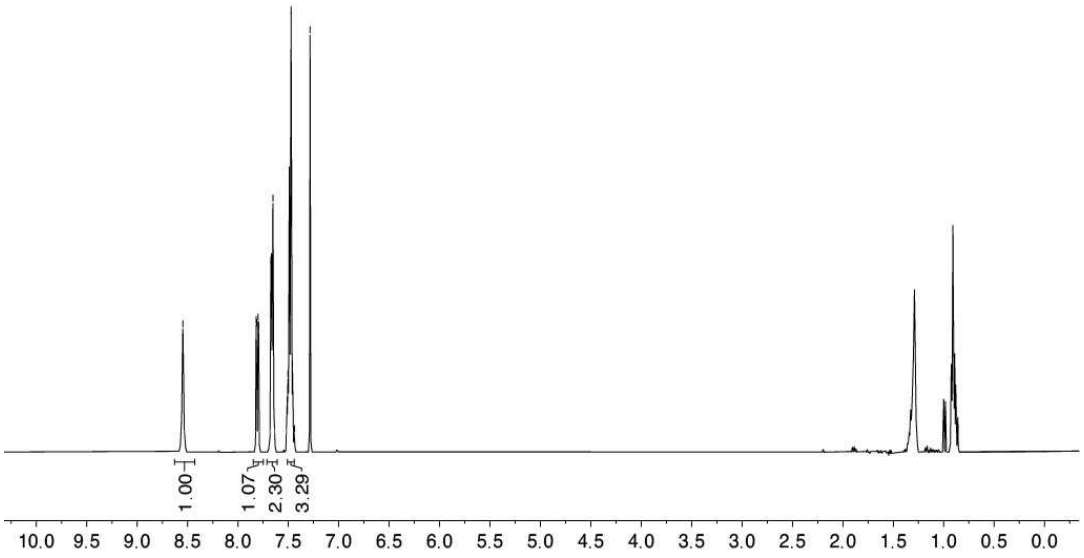
^{1}H NMR ($CDCl_3$ 400 MHz)


F
I
N
Me
^{19}F NMR ($CDCl_3$ 375 MHz)
-129.30
-129.32
-129.0 -129.1 -129.2 -129.3 -129.4 -129.5 -129.6
0.02
0.02
1.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

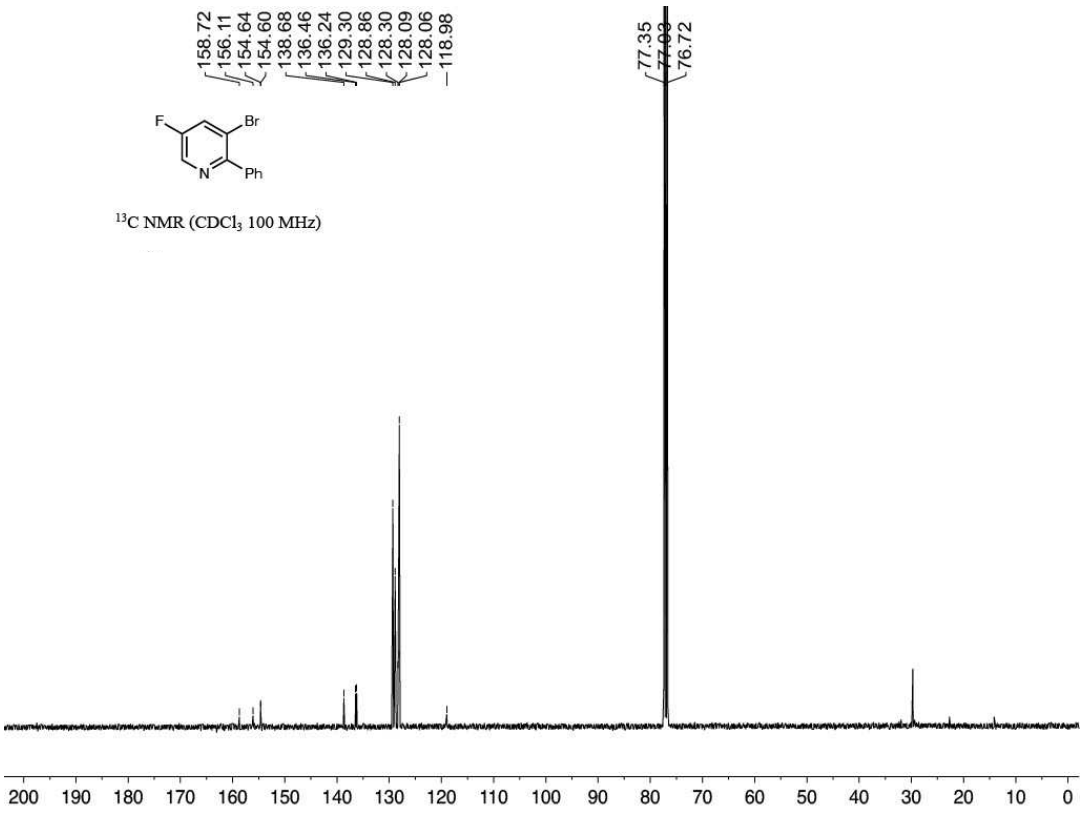

157.69
156.28
156.24
155.10
136.33
136.11
133.22
133.02
94.52
94.50
77.34
77.02
76.71
27.87
27.86
F
I
N
Me
^{13}C NMR ($CDCl_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



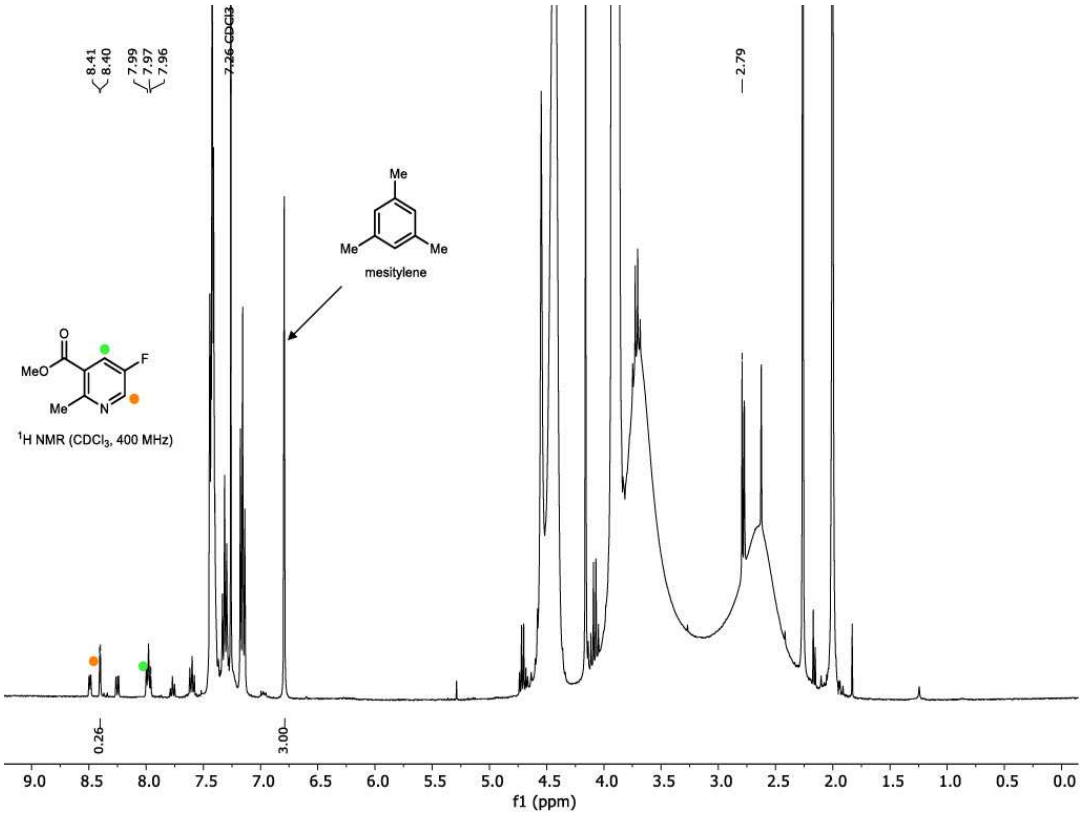
^{1}H NMR ($CDCl_3$ 400 MHz)



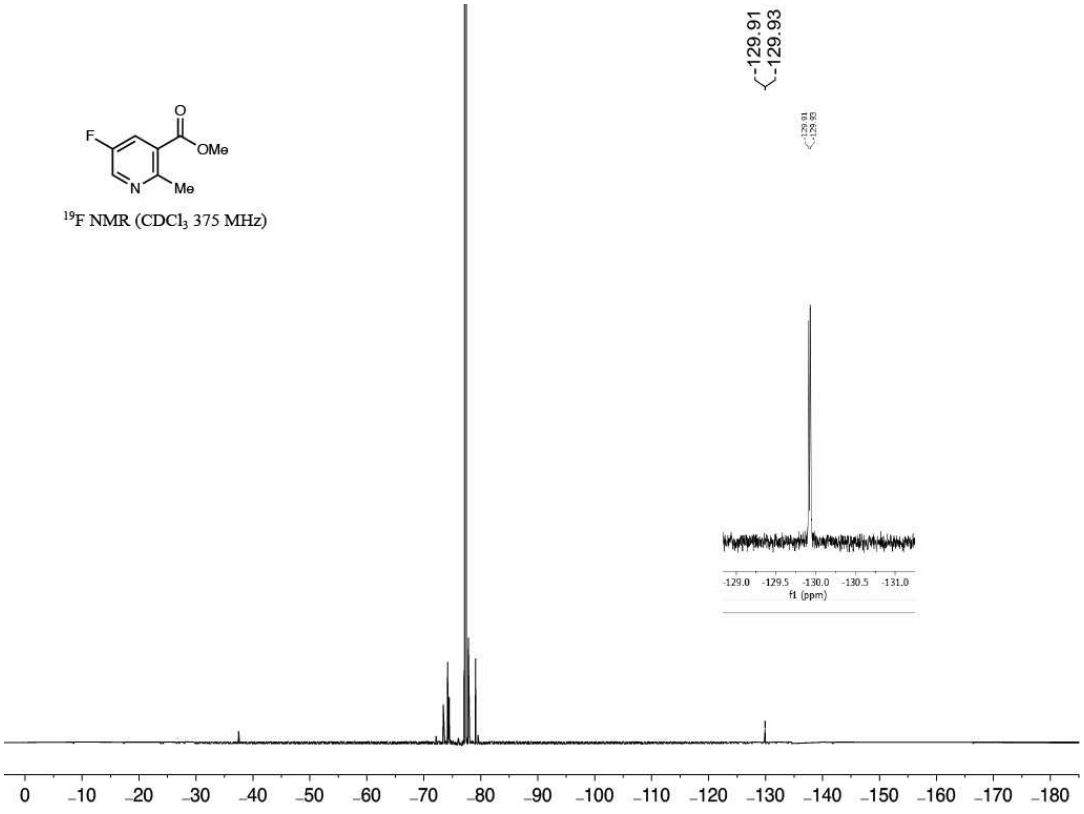
^{19}F NMR ($CDCl_3$ 375 MHz)



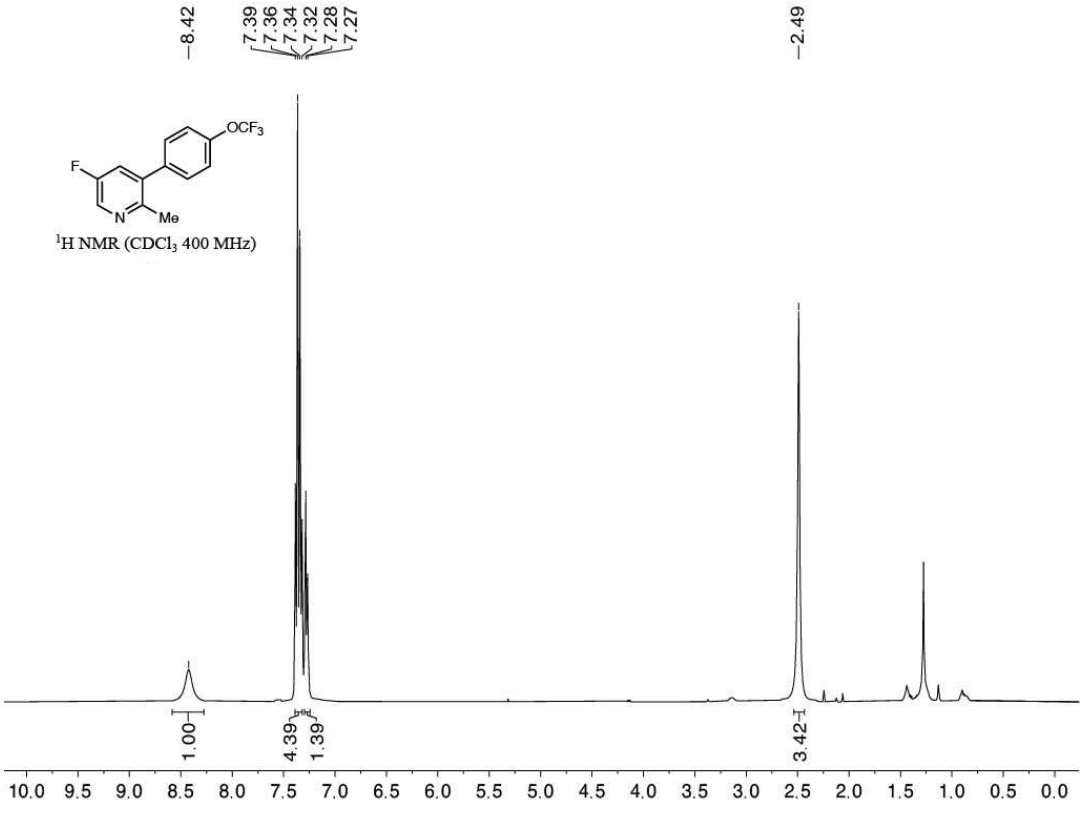
^{13}C NMR ($CDCl_3$ 100 MHz)



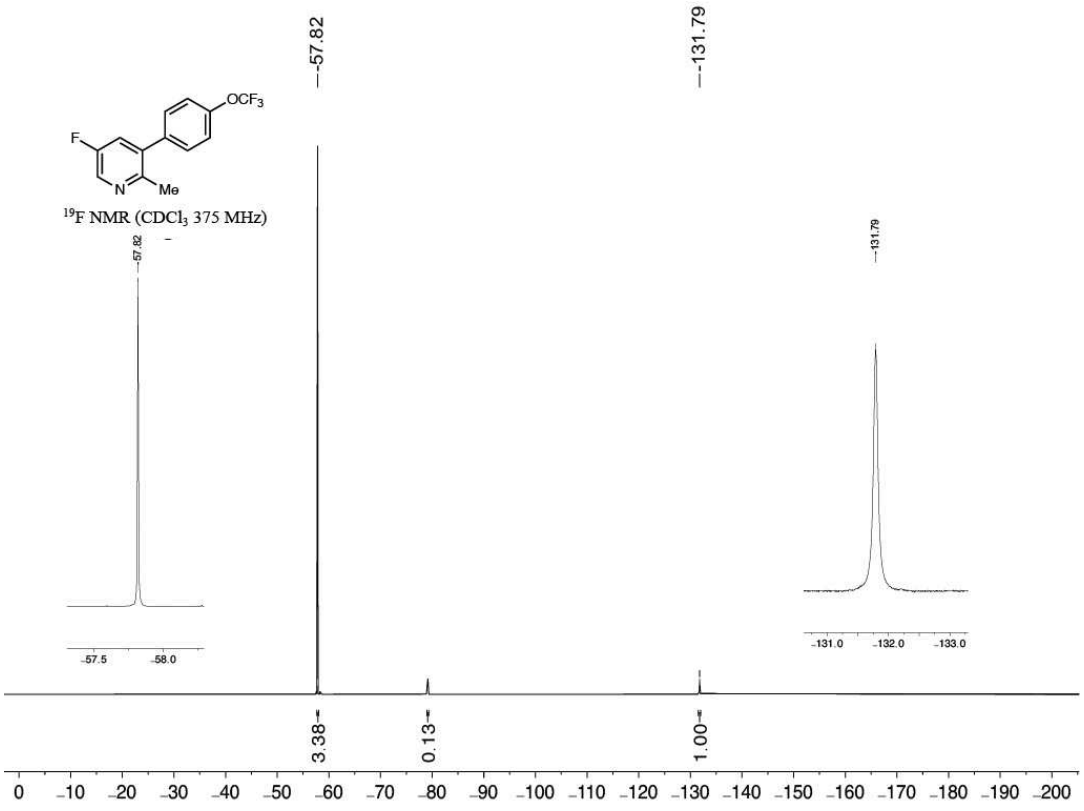
^{1}H NMR ($CDCl_3$, 400 MHz)

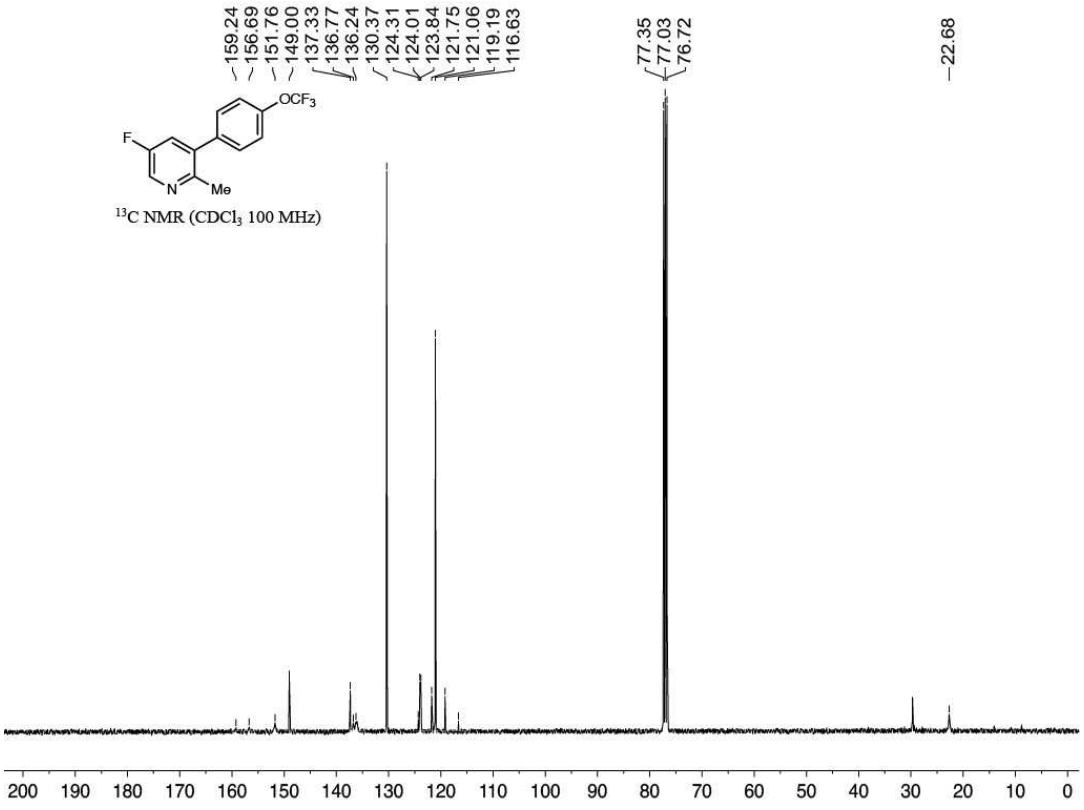


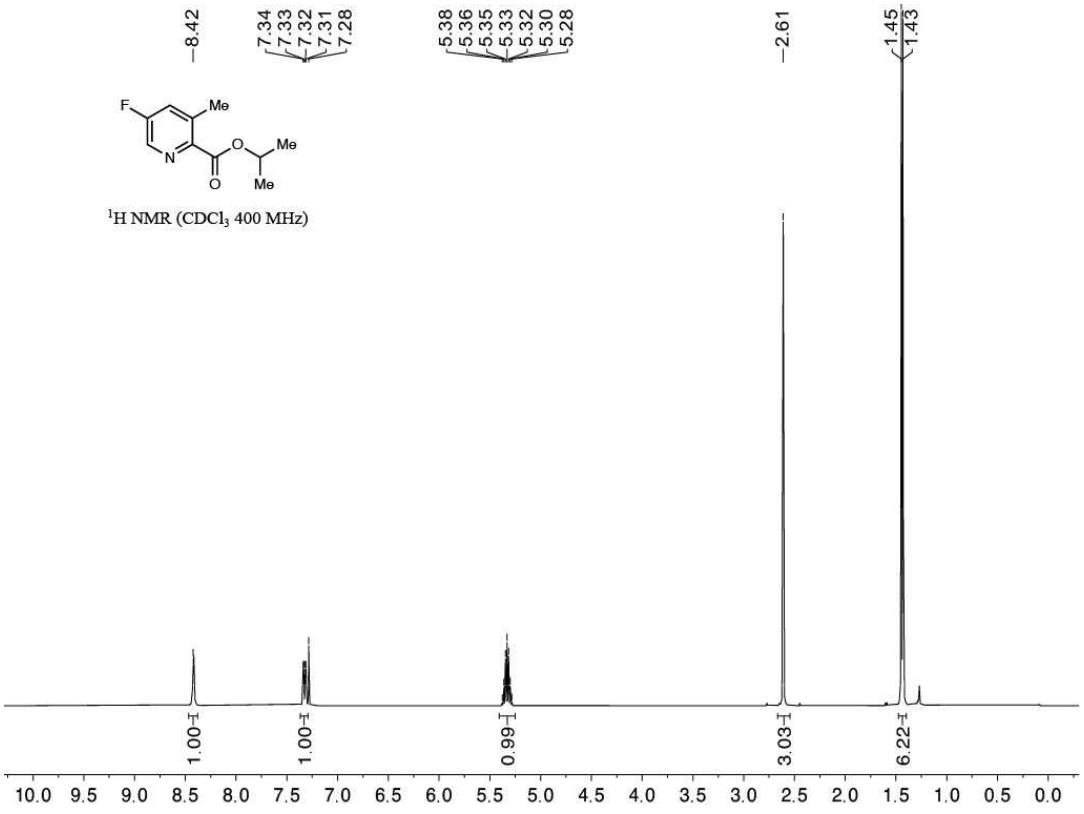
^{19}F NMR ($CDCl_3$ 375 MHz)



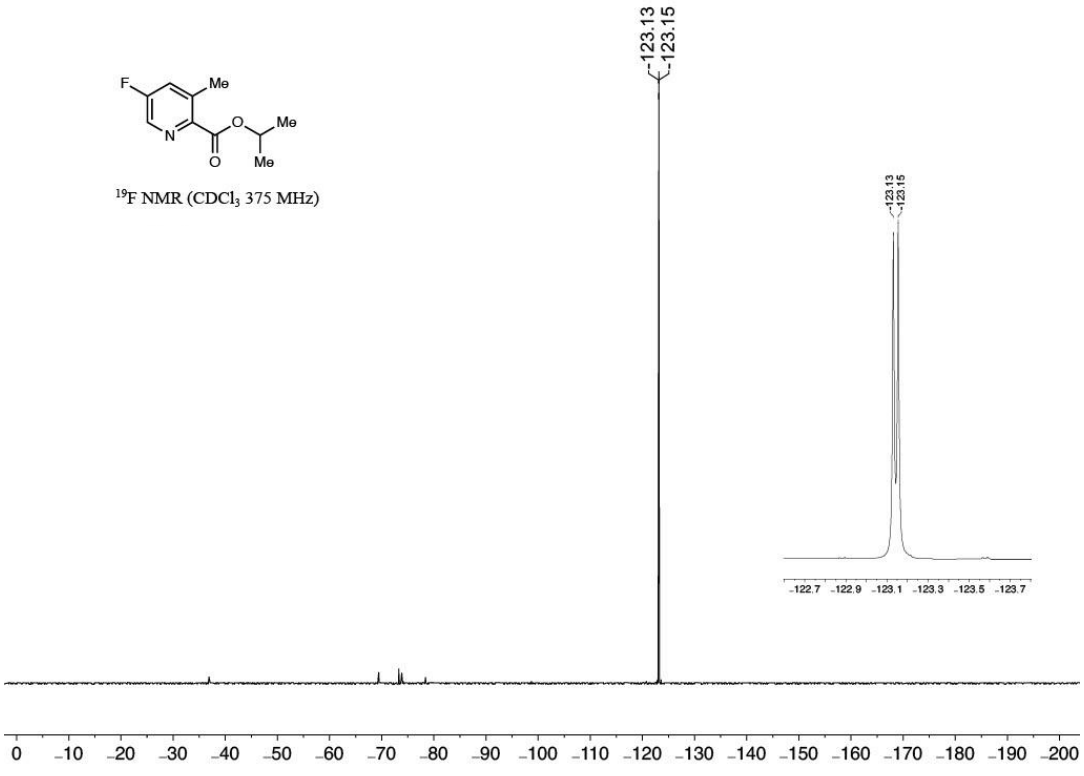
^{1}H NMR ($CDCl_3$ 400 MHz)


-57.82
-131.79
OCF3
F
N
Me
19F NMR (CDCl3 375 MHz)
-57.82
-131.79
-57.5
-58.0
-131.0
-132.0
-133.0
3.38
0.13
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200

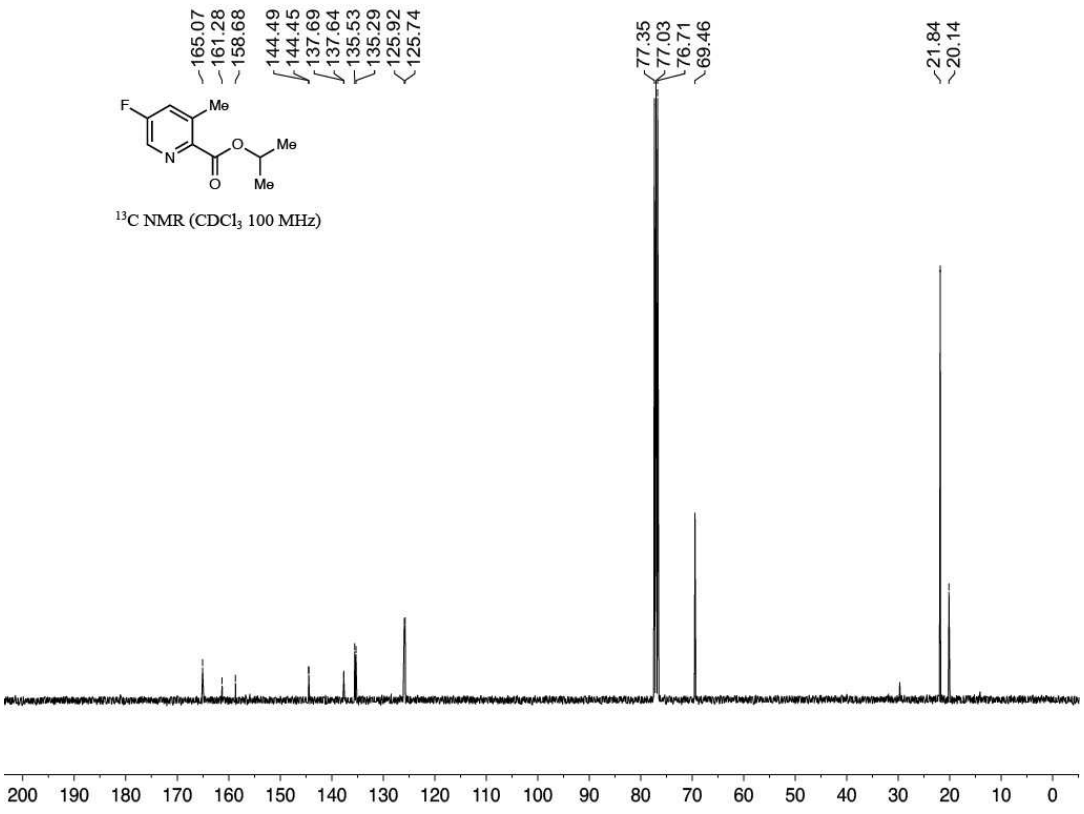

159.24
156.69
151.76
149.00
137.33
136.77
136.24
130.37
124.31
124.01
123.84
121.75
121.06
119.19
116.63
77.35
77.03
76.72
22.68
OCF3
F
N
Me
13C NMR (CDCl3 100 MHz)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



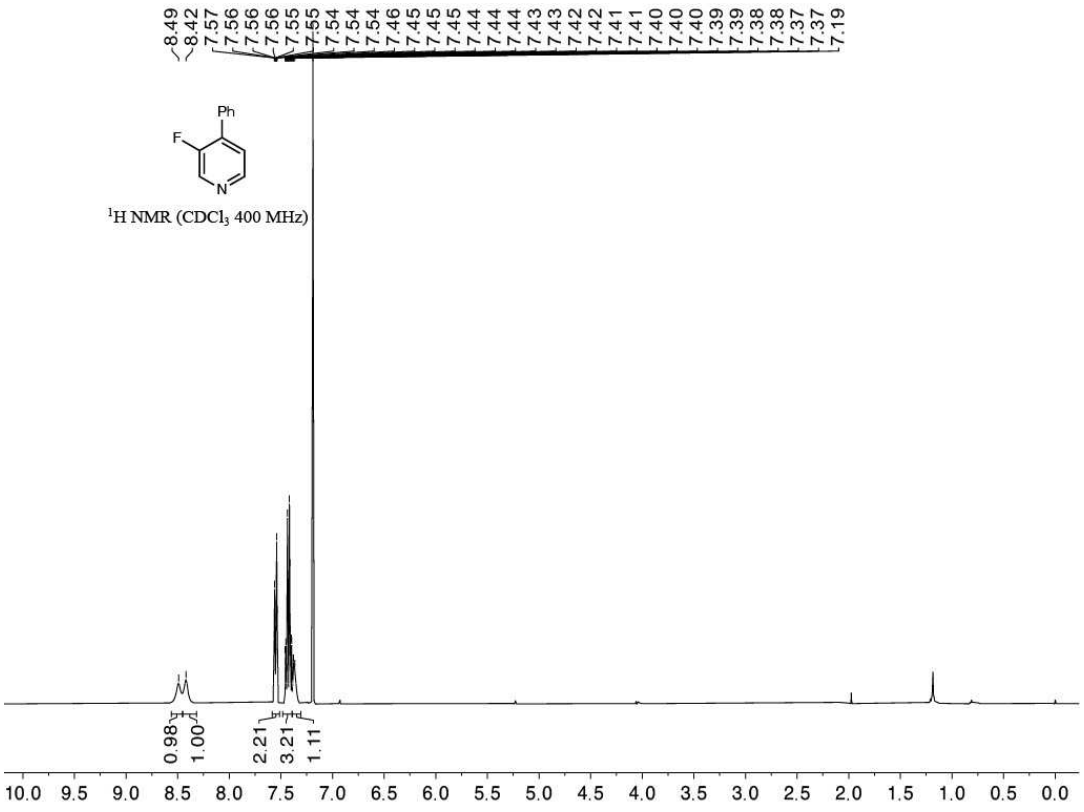
^{1}H NMR ($CDCl_3$ 400 MHz)



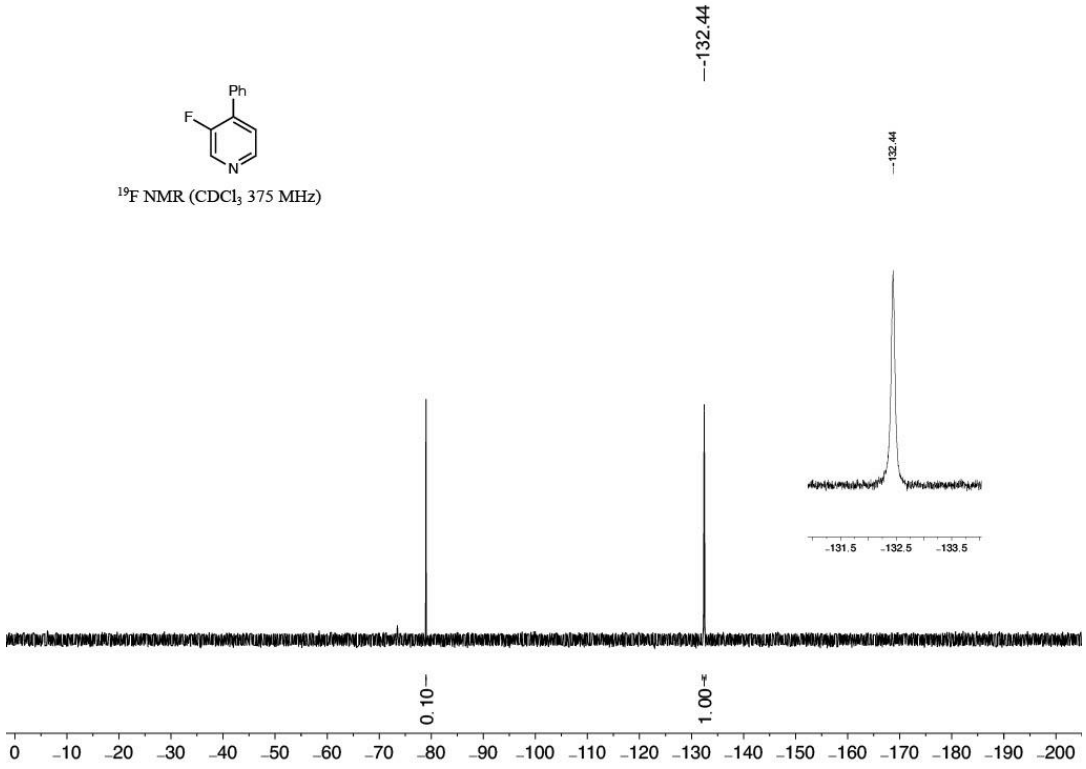
^{19}F NMR ($CDCl_3$ 375 MHz)

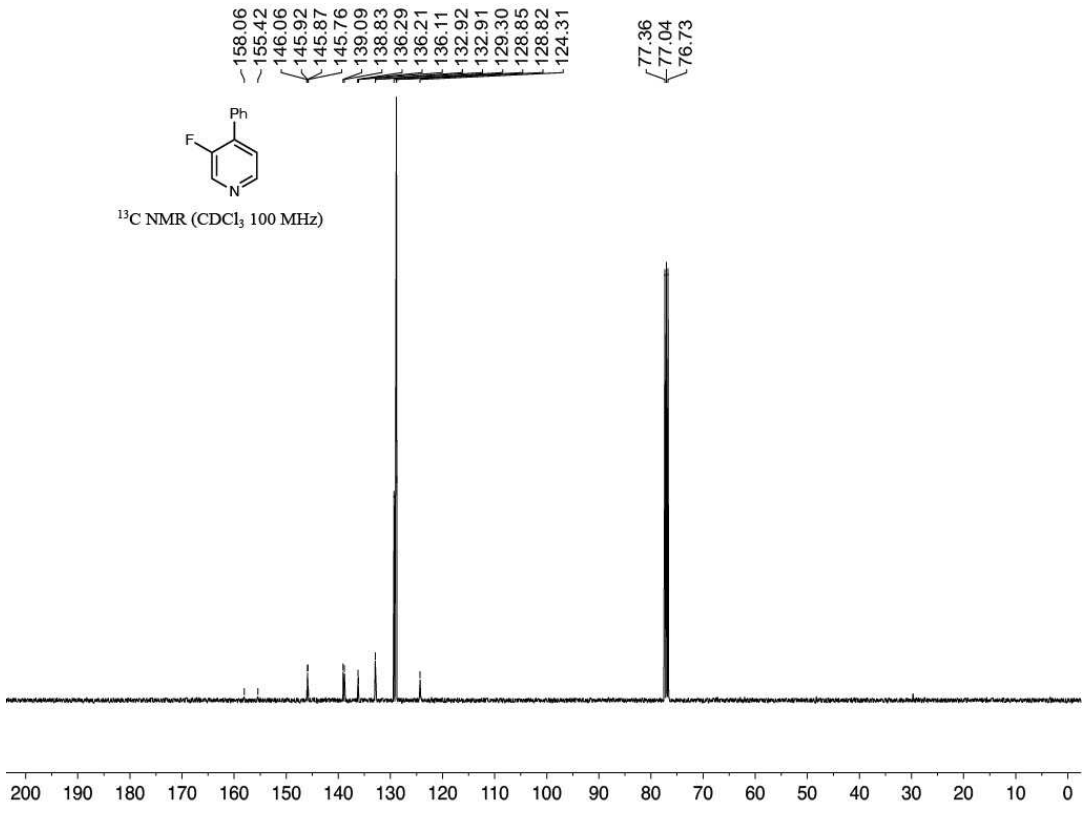


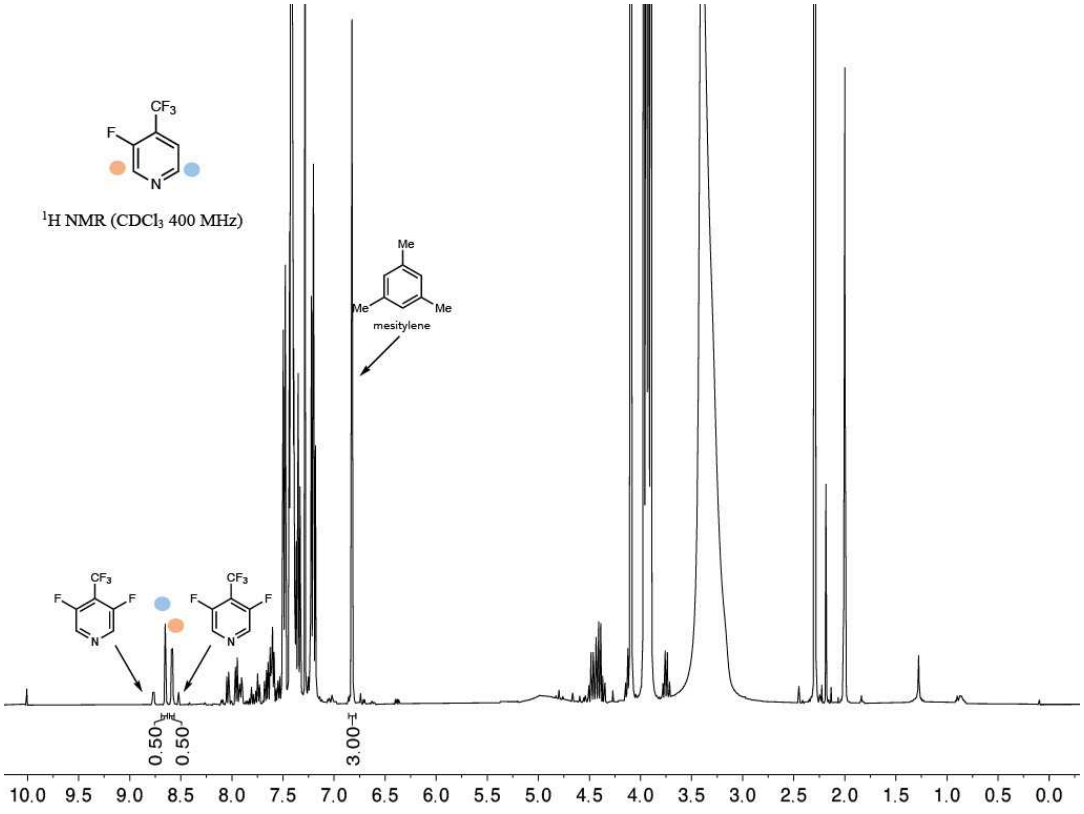
^{13}C NMR ($CDCl_3$ 100 MHz)

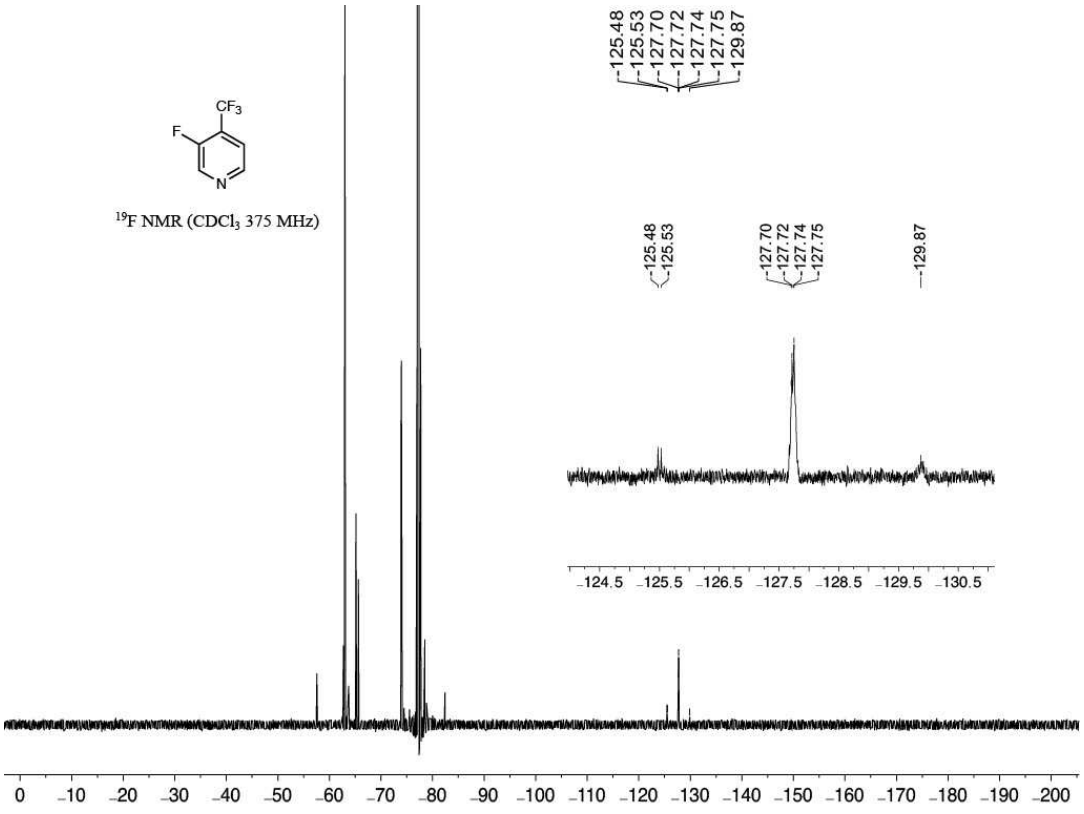


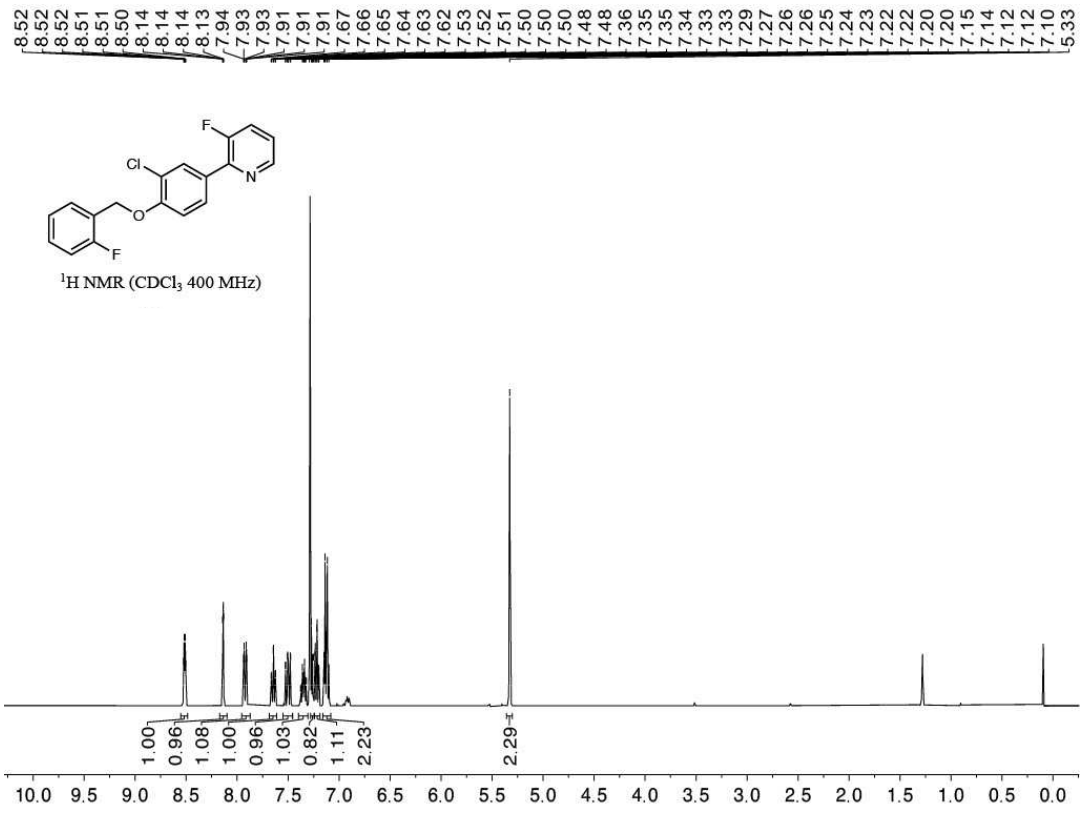
^{1}H NMR ($CDCl_3$ 400 MHz)

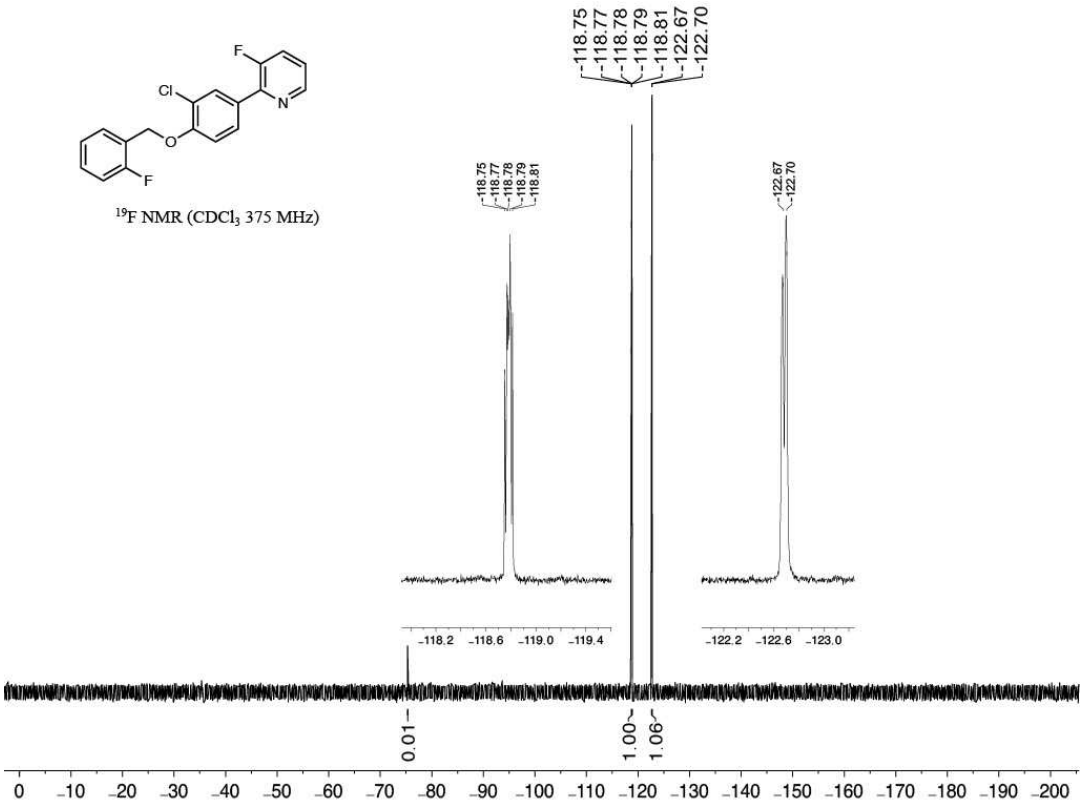

Ph
F
N
^{19}F NMR ($CDCl_3$ 375 MHz)
-132.44
-132.44
-131.5
-132.5
-133.5
0.10
1.00
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

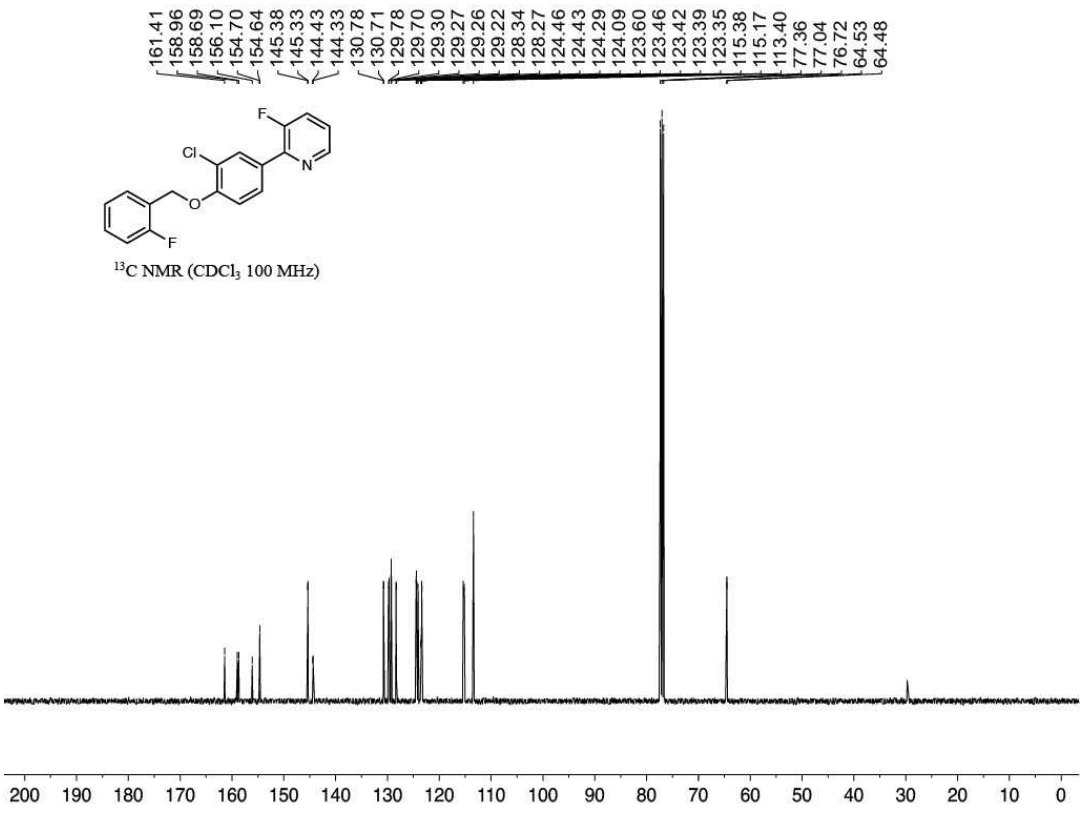

158.06
155.42
146.06
145.92
145.87
145.76
139.09
138.83
136.29
136.21
136.11
132.92
132.91
129.30
128.85
128.82
124.31
77.36
77.04
76.73
Ph
F
N
^{13}C NMR ($CDCl_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


CF3
F
N
1H NMR (CDCl3 400 MHz)
Me
Me
Me
mesitylene
CF3
F
F
N
CF3
F
F
N
0.50
0.50
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

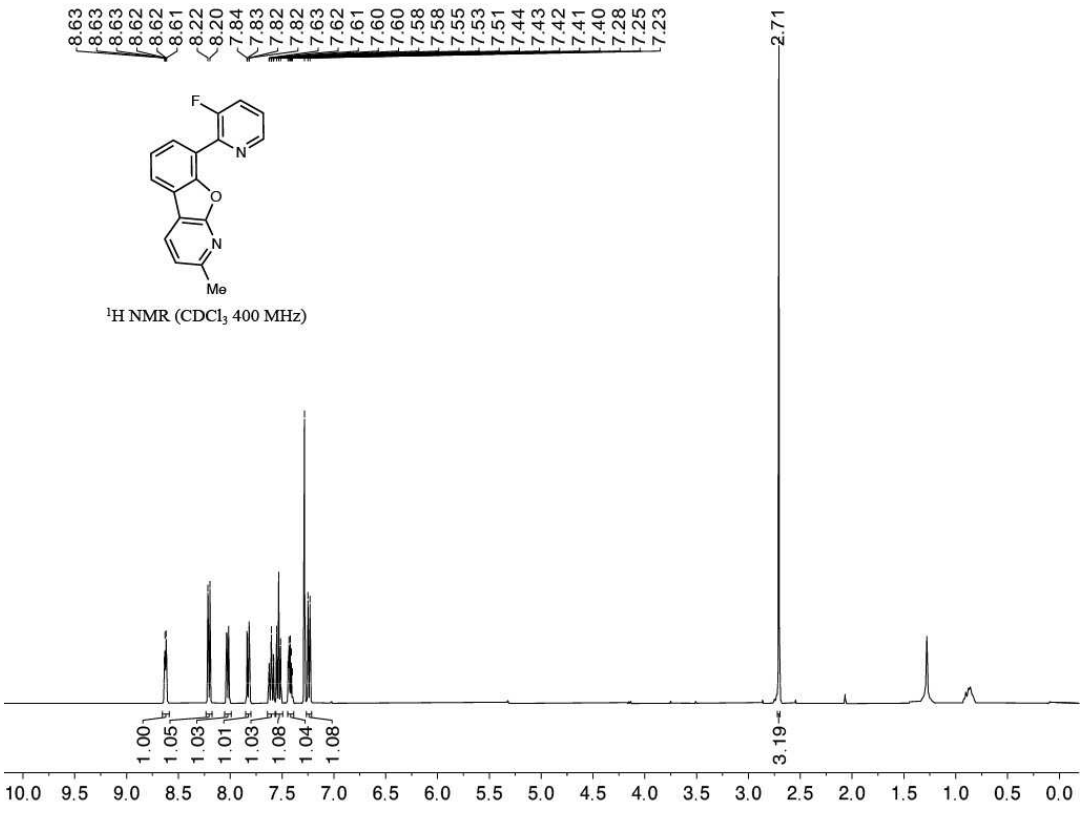

125.48
125.53
127.70
127.72
127.74
127.75
129.87
CF3
F
N
19F NMR (CDCl3 375 MHz)
125.48
125.53
127.70
127.72
127.74
127.75
129.87
124.5 125.5 126.5 127.5 128.5 129.5 130.5
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200


8.52 8.52 8.52 8.51 8.51 8.50 8.14 8.14 8.14 8.13 7.94 7.93 7.93 7.91 7.91 7.91 7.67 7.66 7.65 7.64 7.63 7.62 7.53 7.52 7.51 7.50 7.50 7.50 7.48 7.48 7.36 7.35 7.35 7.34 7.33 7.33 7.29 7.27 7.26 7.26 7.25 7.24 7.23 7.22 7.22 7.20 7.20 7.15 7.14 7.12 7.12 7.10 5.33
F
Cl
N
O
F
1H NMR (CDCl3 400 MHz)
1.00 0.96 1.08 1.00 0.96 1.03 0.82 1.11 2.23
2.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

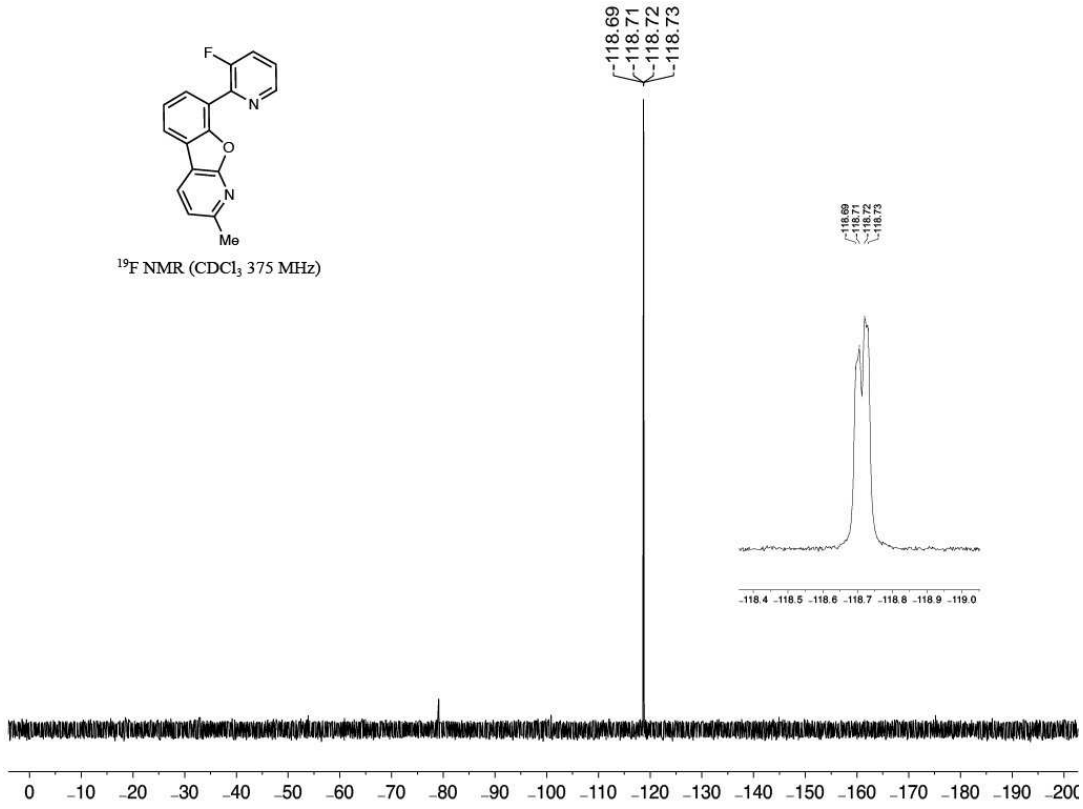

F
Cl
N
O
F
19F NMR (CDCl3 375 MHz)
-118.75 -118.77 -118.78 -118.79 -118.81 -122.67 -122.70
-118.75 -118.77 -118.78 -118.79 -118.81
-122.67 -122.70
-118.2 -118.6 -119.0 -119.4
-122.2 -122.6 -123.0
0.01 1.00 1.06
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200



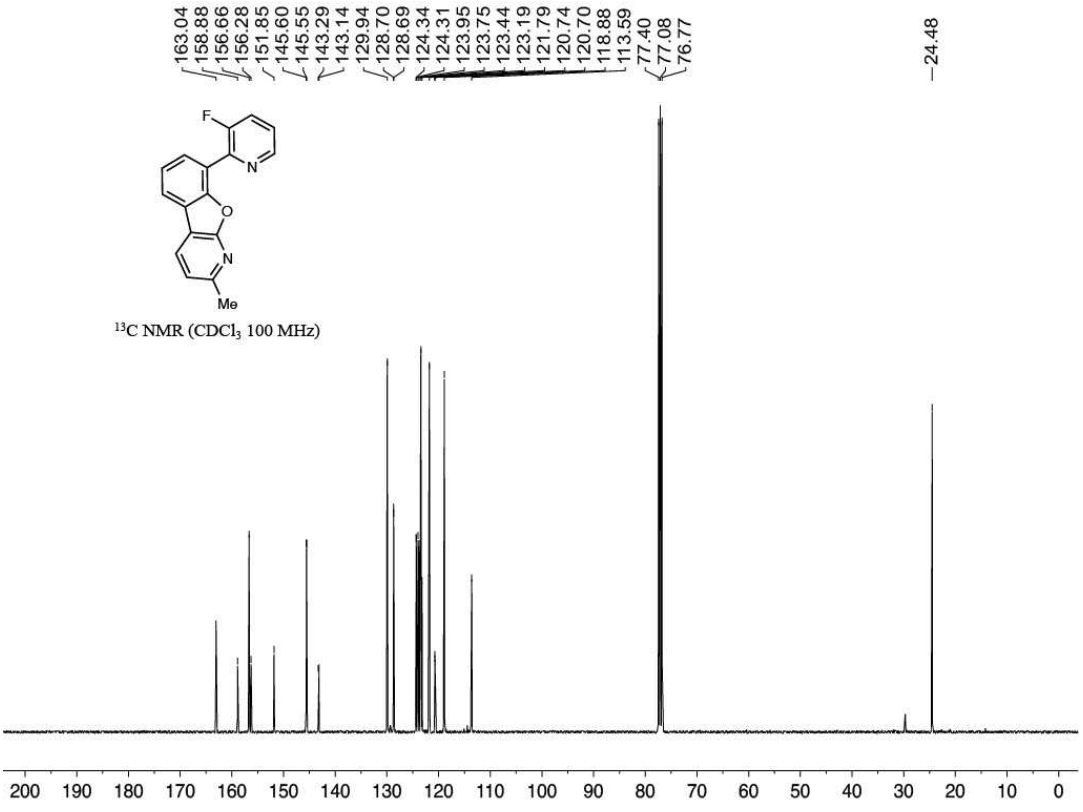
^{13}C NMR ($CDCl_3$ 100 MHz)



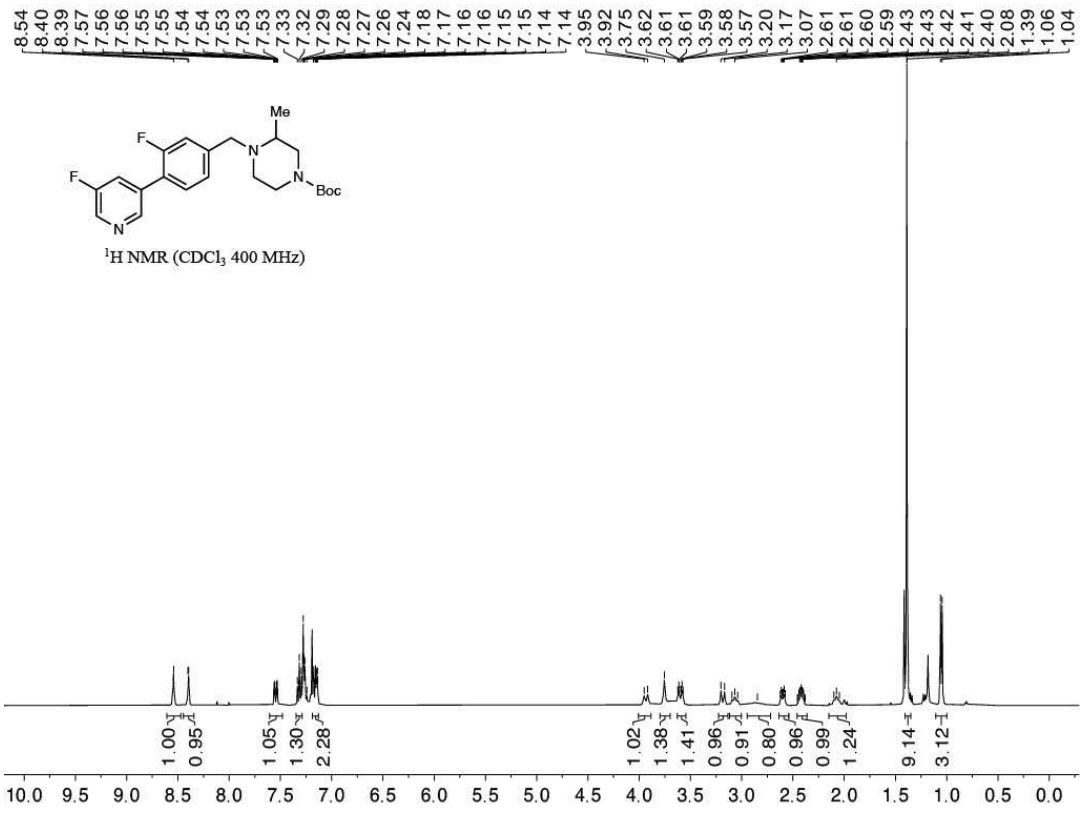
^{1}H NMR ($CDCl_3$ 400 MHz)



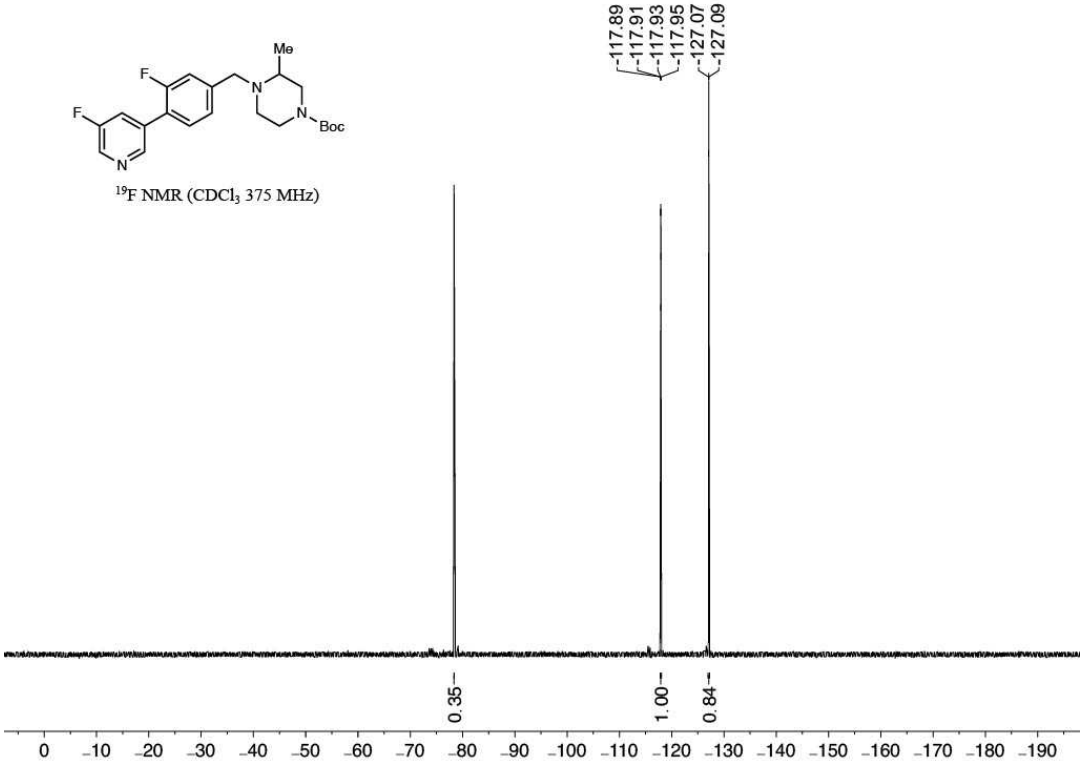
^{19}F NMR ($CDCl_3$ 375 MHz)



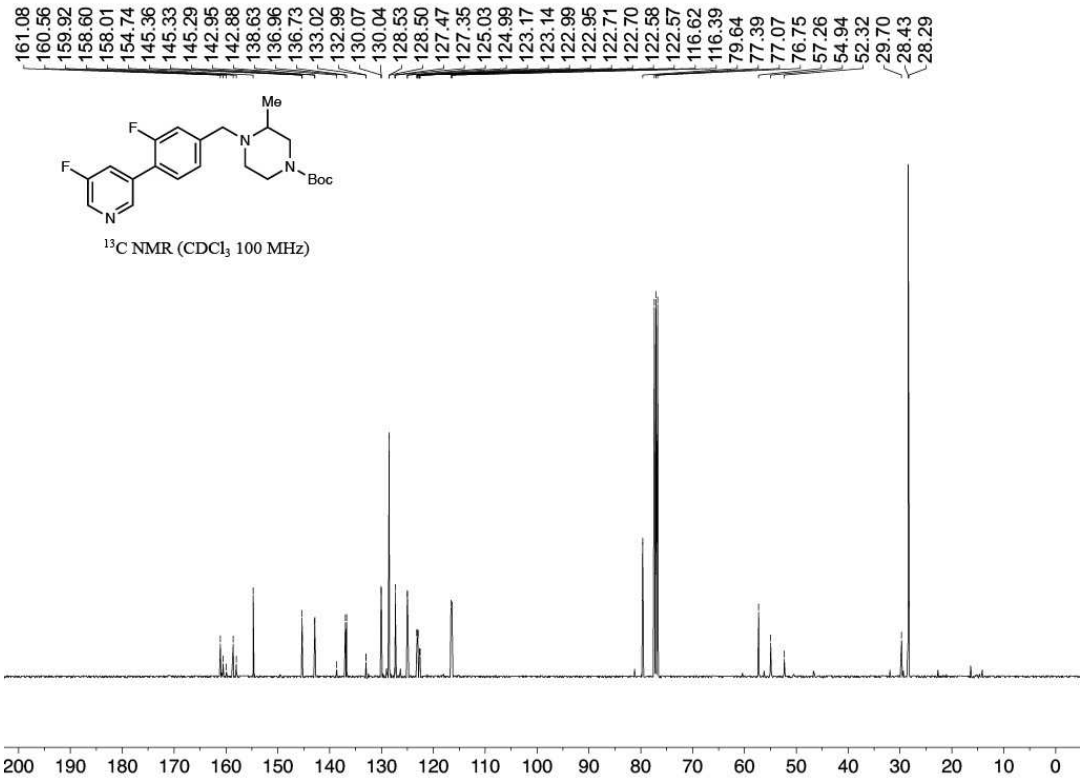
^{13}C NMR ($CDCl_3$ 100 MHz)



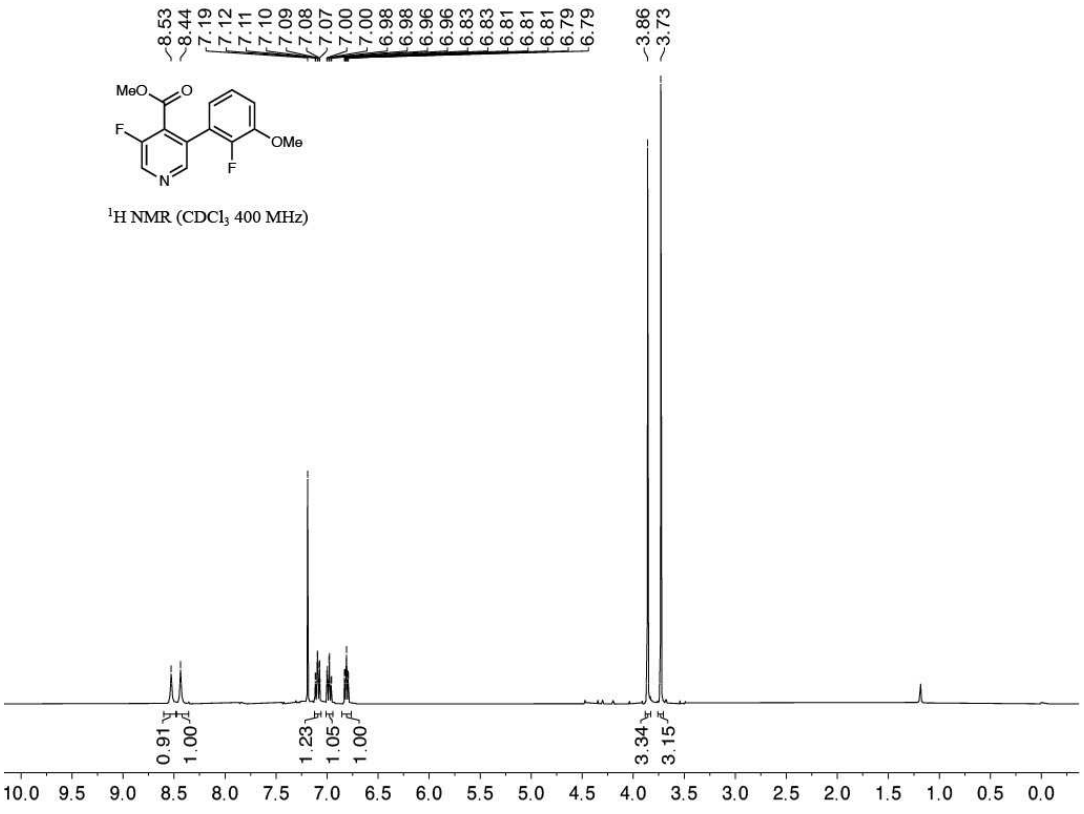
^{1}H NMR ($CDCl_3$ 400 MHz)



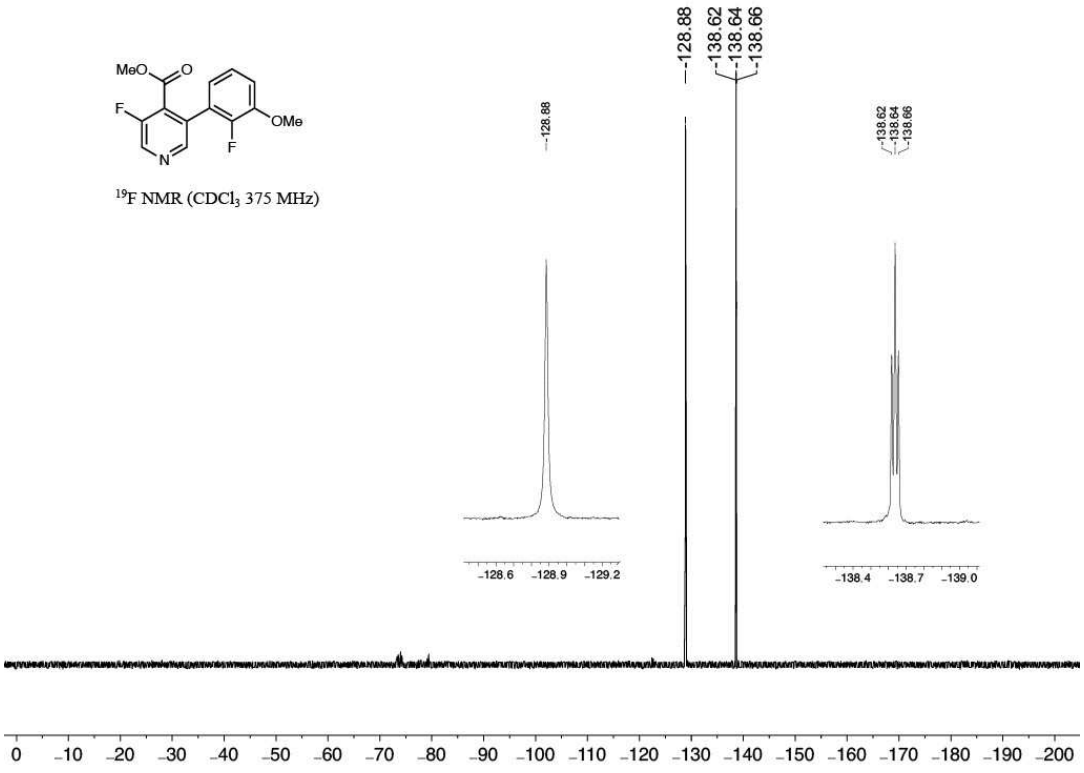
^{19}F NMR ($CDCl_3$ 375 MHz)

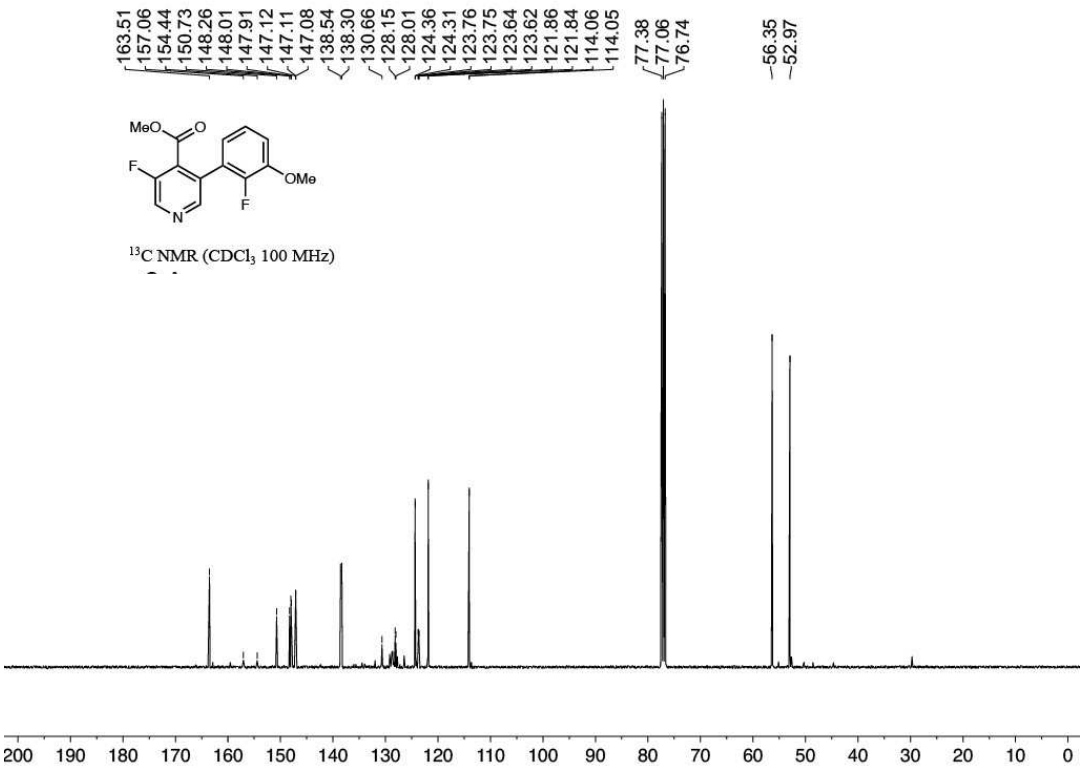


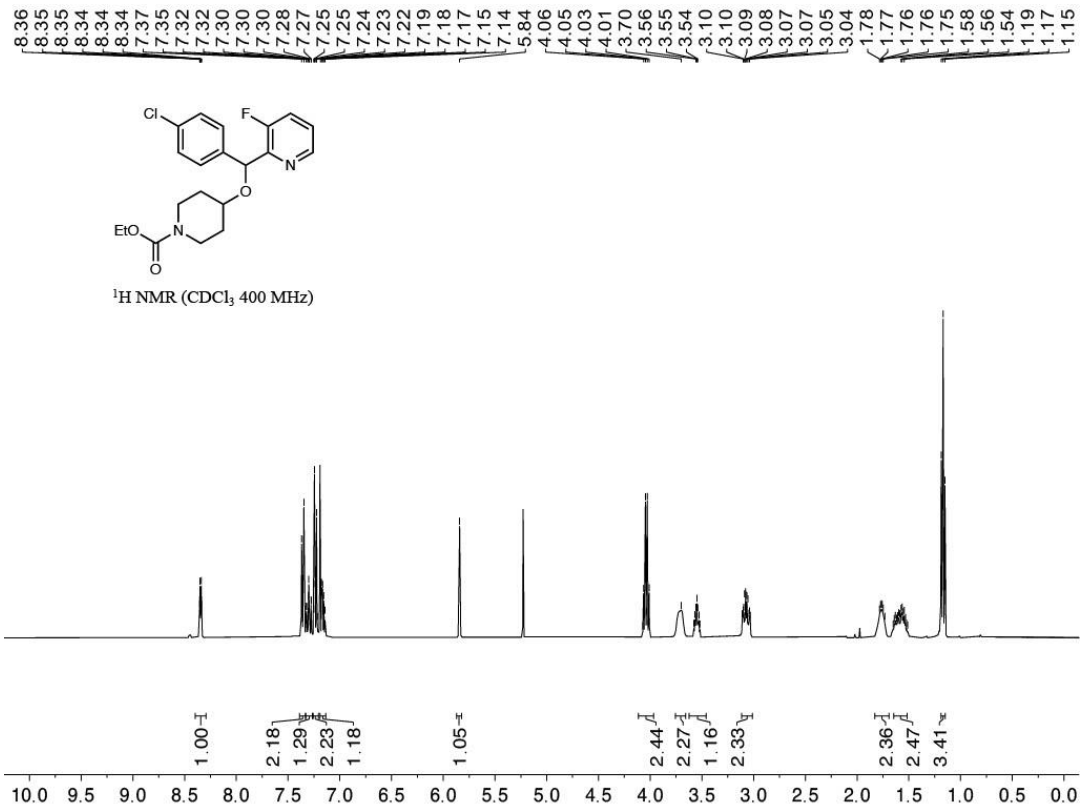
^{13}C NMR ($CDCl_3$ 100 MHz)



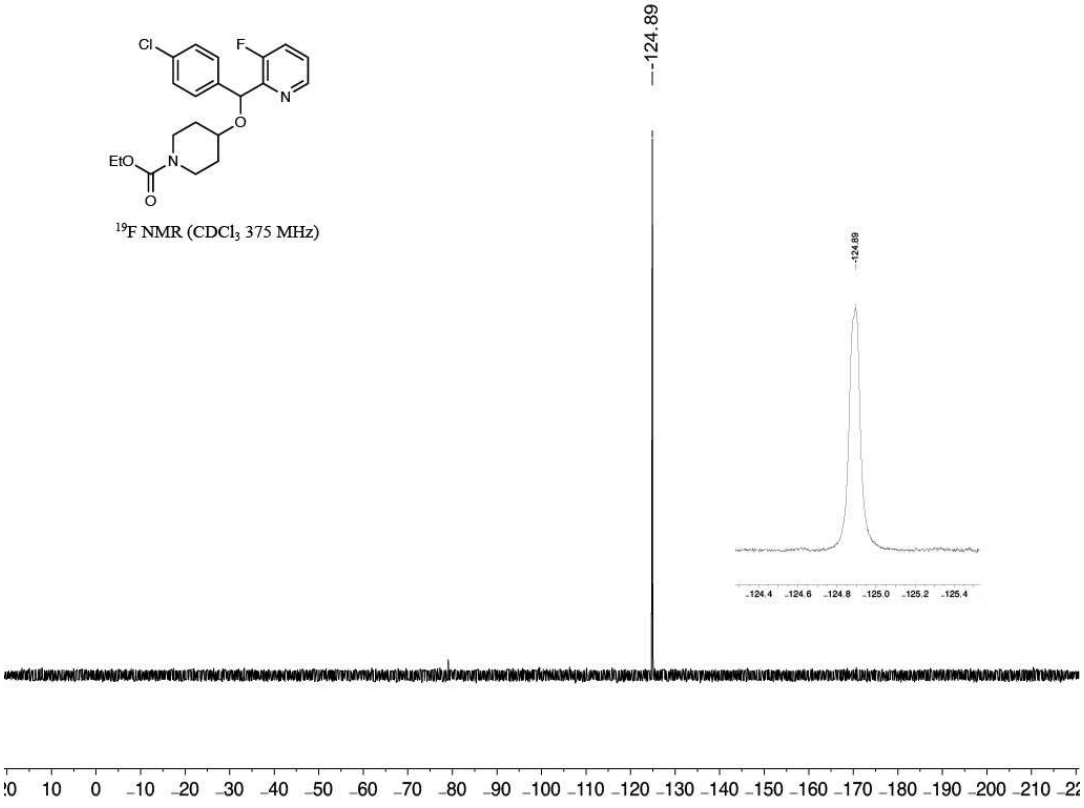
^{1}H NMR ($CDCl_3$ 400 MHz)


MeO
O
F
OMe
F
N
^{19}F NMR ($CDCl_3$ 375 MHz)
-128.88
-138.62
-138.64
-138.66
-128.88
-138.62
-138.64
-138.66
-128.6
-128.9
-129.2
-138.4
-138.7
-139.0
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200

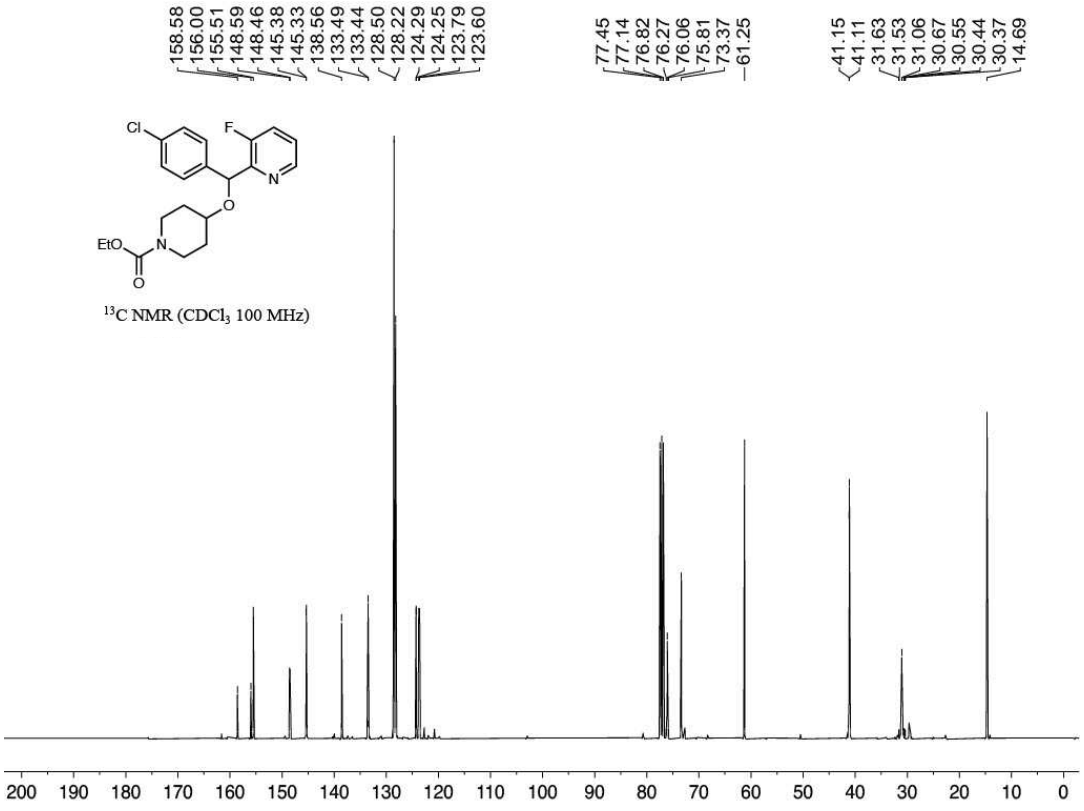

163.51
157.06
154.44
150.73
148.26
148.01
147.91
147.12
147.11
147.08
138.54
138.30
130.66
128.15
128.01
124.36
124.31
123.76
123.75
123.64
123.62
121.86
121.84
114.06
114.05
77.38
77.06
76.74
56.35
52.97
MeO
O
F
OMe
F
N
^{13}C NMR ($CDCl_3$ 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



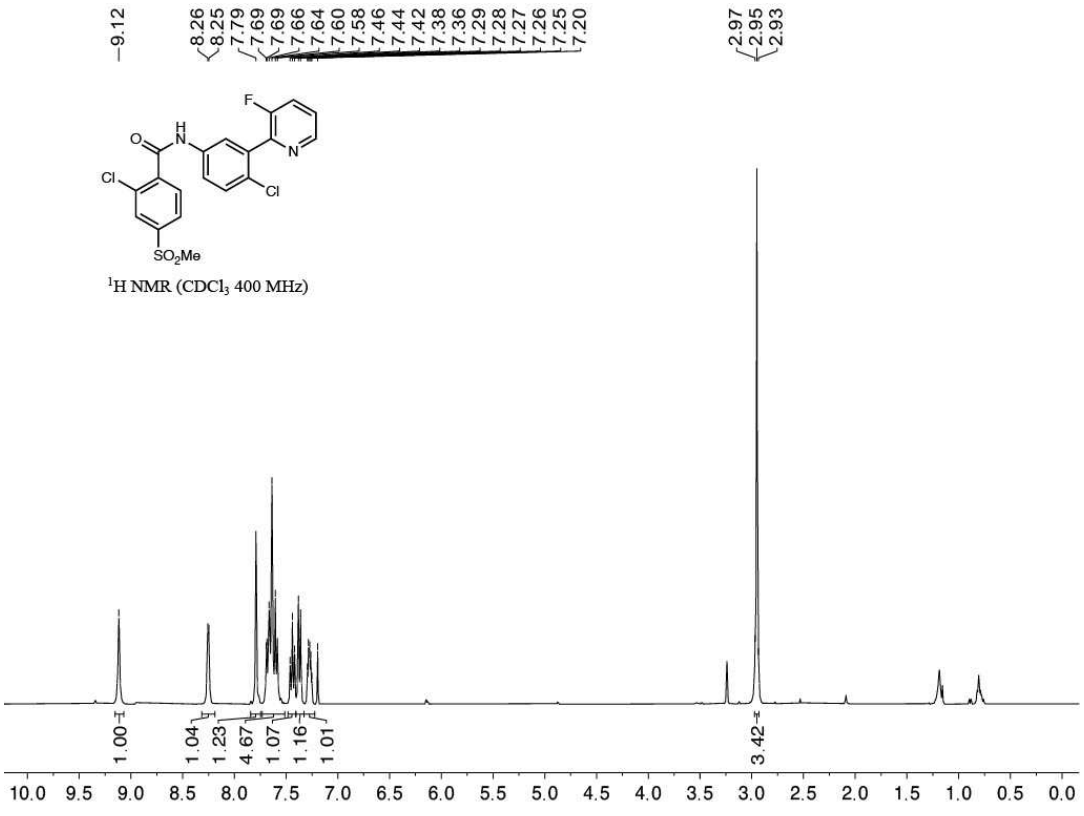
^{1}H NMR ($CDCl_3$ 400 MHz)



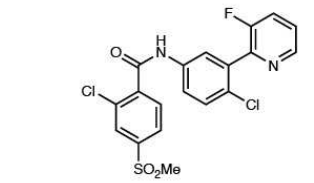
^{19}F NMR ($CDCl_3$ 375 MHz)



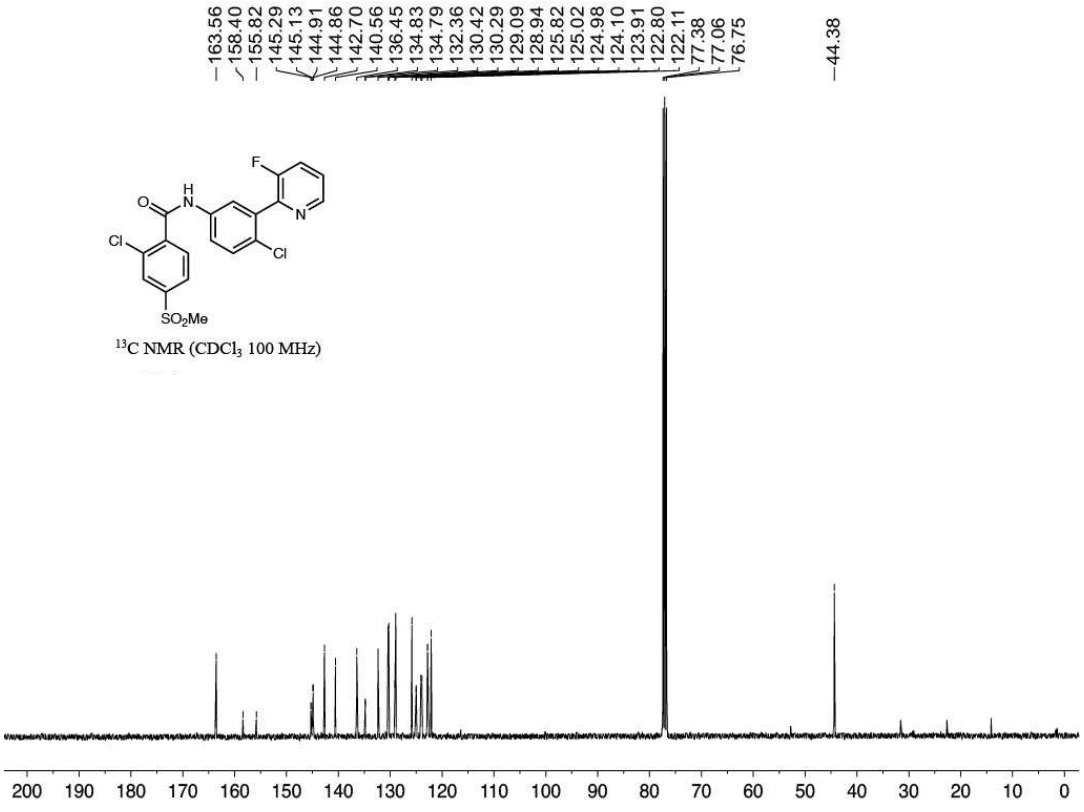
^{13}C NMR ($CDCl_3$ 100 MHz)



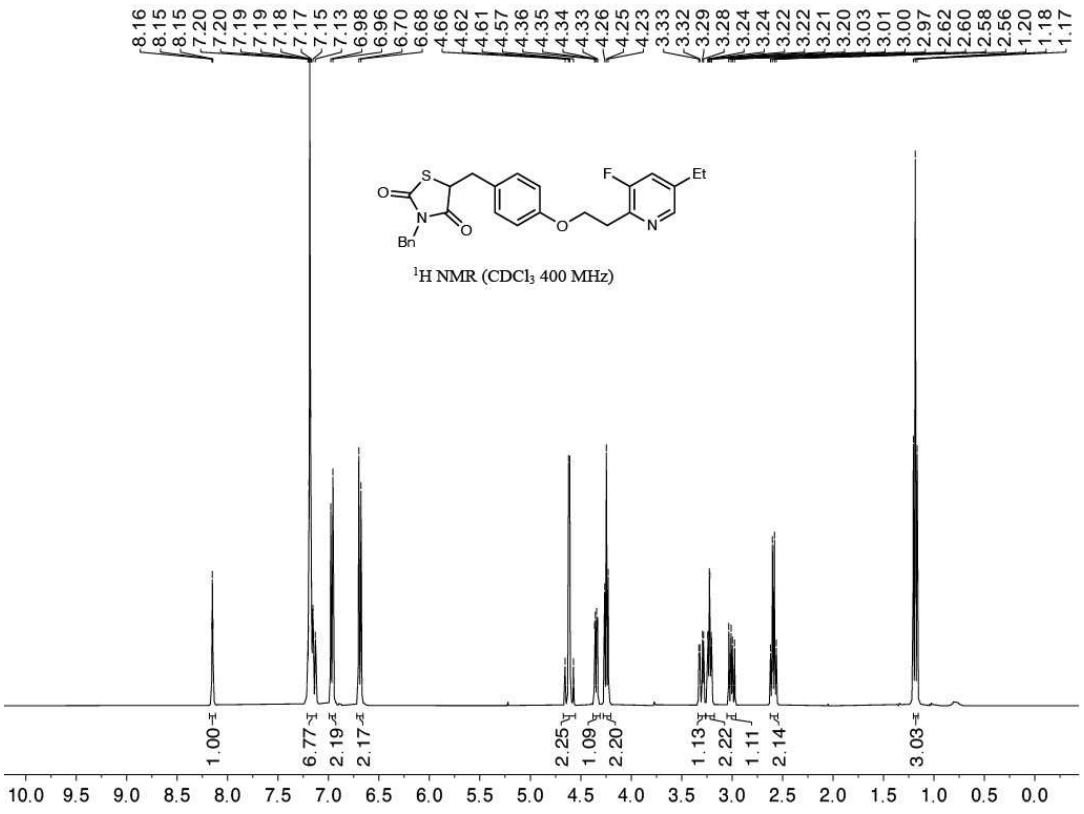
^{1}H NMR ($CDCl_3$ 400 MHz)



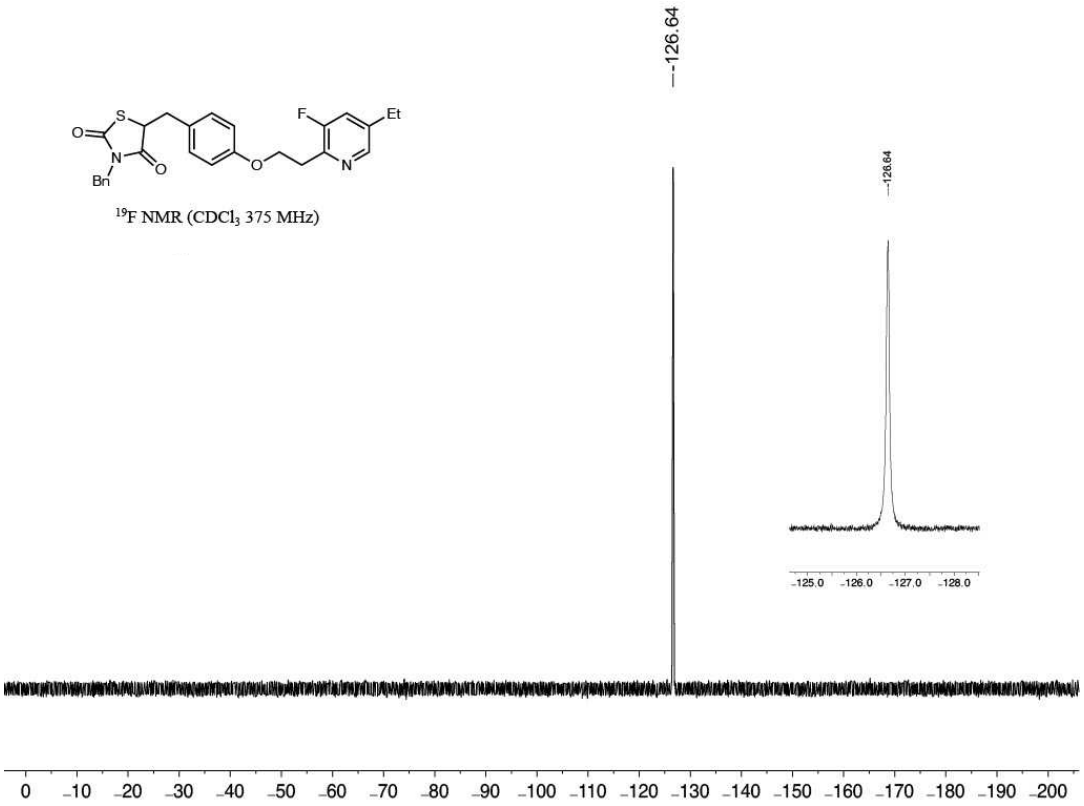
^{19}F NMR ($CDCl_3$ 375 MHz)



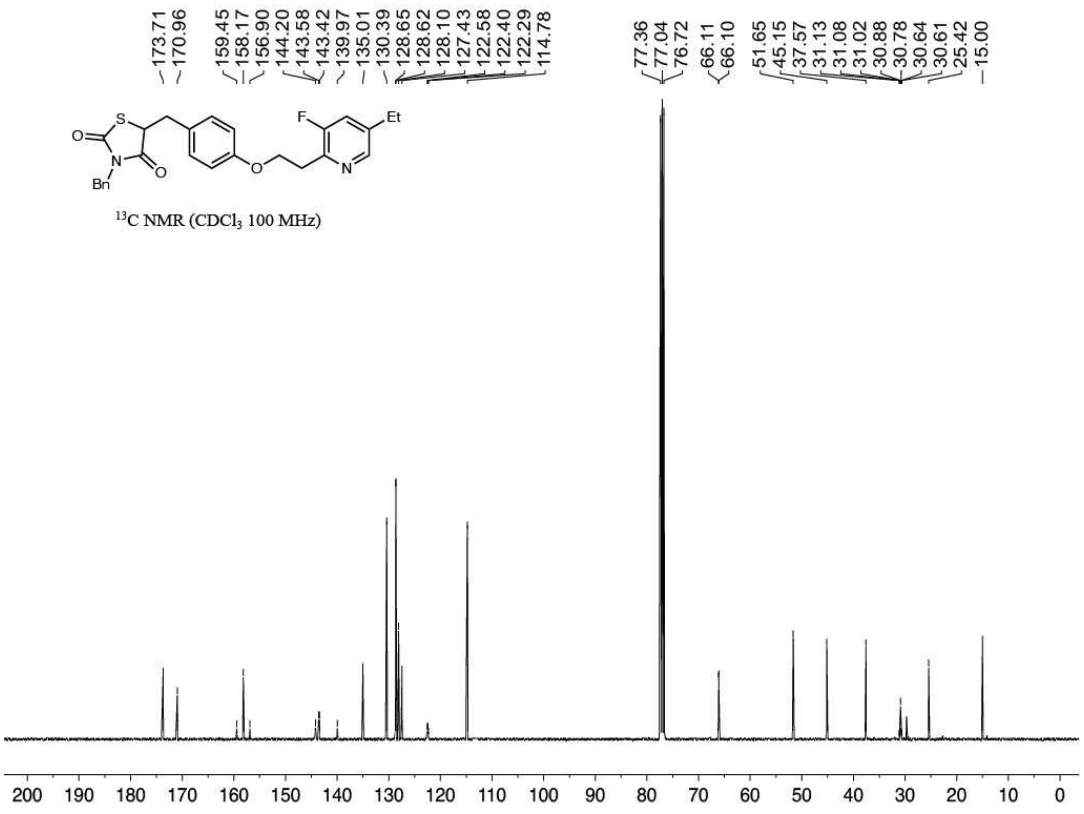
^{13}C NMR ($CDCl_3$ 100 MHz)



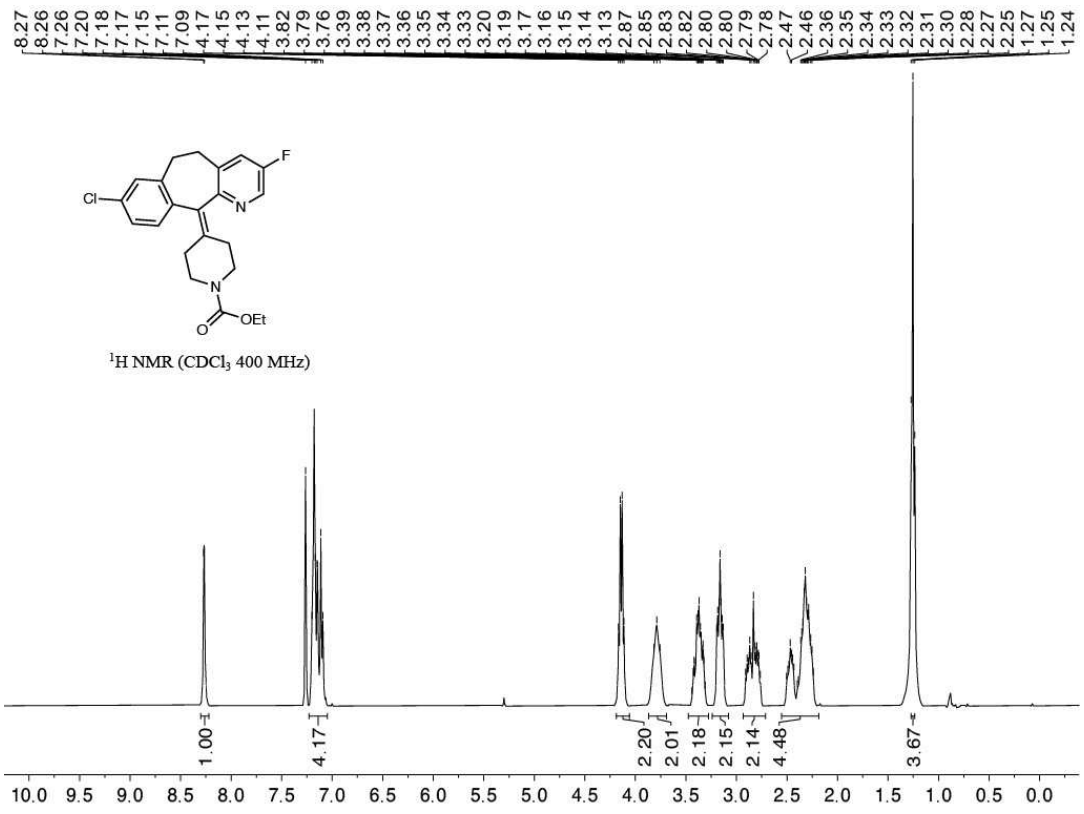
^{1}H NMR ($CDCl_3$ 400 MHz)



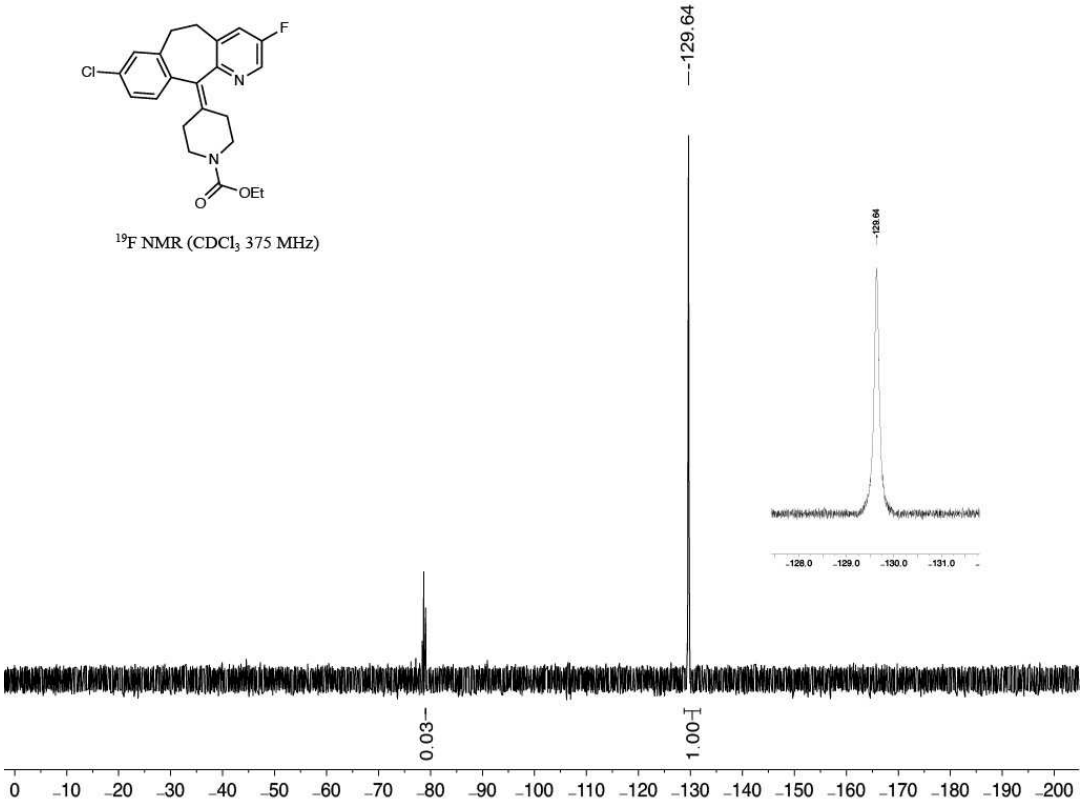
^{19}F NMR ($CDCl_3$ 375 MHz)



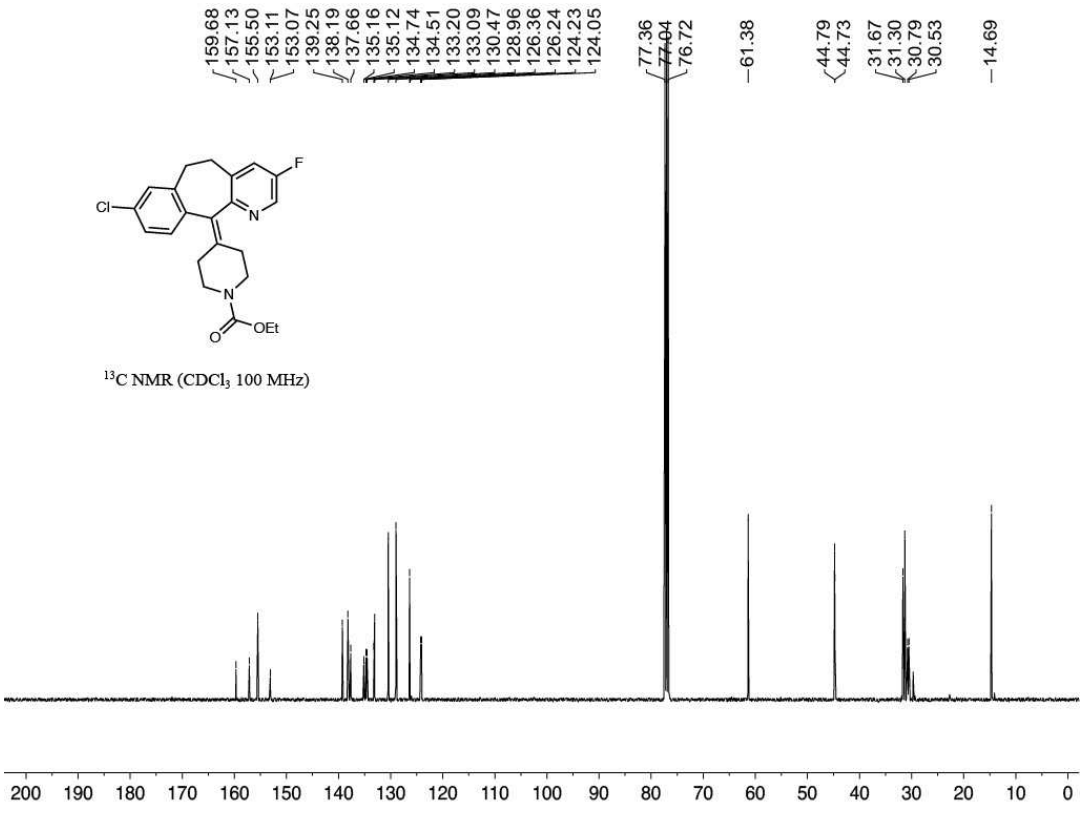
^{13}C NMR ($CDCl_3$ 100 MHz)



^{1}H NMR ($CDCl_3$ 400 MHz)



^{19}F NMR ($CDCl_3$ 375 MHz)



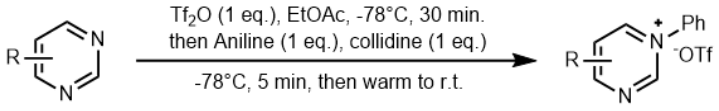
^{13}C NMR ($CDCl_3$ 100 MHz)

APPENDIX TWO

PYRIMIDINE DIVERSIFICATION VIA DECONSTRUCTION-RECONSTRUCTION: EXPERIMENTAL

A 1.5 Preparation of Pyrimidinium Salts

General Procedure G (*N*-Phenyl Pyrimidinium Formation)



An oven-dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the pyrimidine (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.2 M) was added, the reaction vessel was cooled to –78 ºC, and triflic anhydride (Tf_2O) (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before aniline (1.0 equiv) was added dropwise followed by collidine (1.0 equiv). The reaction was stirred for an additional 5 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes.

Isolation A1: The reaction was cooled to 0 ºC and diluted with an equal volume Et_2O. The reaction was stirred for 15 minutes then filtered and washed with ice-cold 1:1 Et_2O:EtOAc to provide pure pyrimidinium.

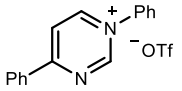
Isolation A2: For products that do not precipitate with the addition of Et_2O, the reaction mixture was transferred to a separatory funnel and washed with a 0.1 M HCl solution (2x) and with brine

(1x), then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was triturated with Et_2O and decanted to provide pure pyrimidinium.

Reaction Notes:

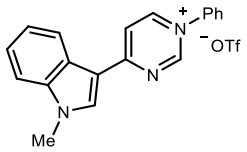
- Isolation procedure applies only to 4-substituted pyrimidines.
- Care must be taken to ensure no aniline freezes to the side of the reaction flask.
- Following aniline addition, reaction mixtures that "gel" or freeze were taken from the cooling bath and swirled by hand until aniline mixed in with the gel before returning to the cooling bath.

1,4-Diphenylpyrimidin-1-ium trifluoromethanesulfonate



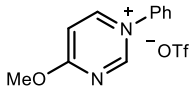
Prepared according to general procedure G using 4-phenylpyrimidine (1.56 g, 10.0 mmol), EtOAc (50 mL), Tf_2O (1.68 mL, 10.0 mmol), aniline (912 µL, 10.0 mmol), and collidine (1.32 mL, 10.0 mmol). Isolation A1 afforded the title compound as a white powder (3.62 g, 9.45 mmol, 95% yield). mp 216-220 °C; IR ν_{max}/cm^{-1} (solid): 3102, 1622, 1589, 1417, 1256, 1146, 1030, 741, 633; ^1H NMR (400 MHz, CD_3CN) δ 9.63 – 9.57 (m, 1H), 9.15 (dd, J = 6.9, 2.1 Hz, 1H), 8.66 (d, J = 6.9 Hz, 1H), 8.46 (d, J = 7.2 Hz, 2H), 7.86 – 7.75 (m, 6H), 7.71 (t, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 171.28, 153.04, 151.69, 140.17, 136.35, 133.77, 132.87, 131.56, 130.86, 130.46, 125.55, 122.02 (q, J = 320.8 Hz), 119.53; ^{19}F NMR (375 MHz, CD_3CN) δ -79.30; *m/z* HRMS (ESI) found $[M+H]^+$ 233.1080, $C_{16}H_{13}N_2^+$ requires 233.1073.

4-(1-Methyl-1H-indol-3-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



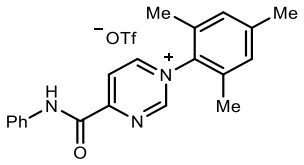
Prepared according to general procedure G using 1-methyl-3-(pyrimidin-4-yl)-1H-indole (72.9 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as a bring-yellow solid (127 mg, 0.29 mmol, 73% yield). mp 106-109 °C; IR ν_{max}/cm^{-1} (solid): 3103, 1630, 1549, 1253, 1221, 1028, 743, 635; ^1H NMR (400 MHz, CD_3CN) δ 9.19 (dd, *J* = 2.1, 1.0 Hz, 1H), 8.61 (s, 1H), 8.56 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.54 (br, 1H), 8.07 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.71 (qd, *J* = 5.5, 3.7 Hz, 5H), 7.65 – 7.59 (m, 1H), 7.50 – 7.43 (m, 2H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 166.20, 152.16, 146.35, 141.98, 140.30, 139.98, 131.86, 131.38, 126.60, 125.52, 125.05, 124.91, 123.59, 122.0 (q, *J* = 318.9 Hz), 115.88, 112.80, 112.56, 34.91; ^{19}F NMR (375 MHz, CD_3CN) δ -79.32; *m/z* HRMS (ESI) found $[M+H]^+$ 286.1348, $C_{19}H_{16}N_3^+$ requires 286.1339.

4-Methoxy-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



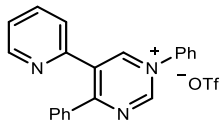
Prepared according to general procedure G using 4-methoxypyrimidine (44.0 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as a white solid (84 mg, 0.25 mmol, 63% yield). mp 131-133 °C; IR ν_{max}/cm^{-1} (solid): 3066, 1633, 1413, 1251, 1139, 1026, 838, 771, 636; ^1H NMR (400 MHz, CD_3CN) δ 9.28 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.80 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.83 – 7.66 (m, 5H), 7.48 (dd, *J* = 7.3, 0.9 Hz, 1H), 4.29 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 173.54, 155.34, 151.02, 139.94, 132.30, 131.34, 125.42, 121.91 (q, *J* = 320.9 Hz), 111.69, 58.37; ^{19}F NMR (375 MHz, CD_3CN) δ -79.21; *m/z* HRMS (ESI) found $[M+H]^+$ 187.0873, $C_{11}H_{11}N_2O^+$ requires 187.0866.

1-Mesityl-4-(phenylcarbamoyl)pyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using N-phenylpyrimidine-4-carboxamide (79.7 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), 2,4,6-trimethylaniline (56 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as a yellow powder (116 mg, 0.25 mmol, 62% yield). mp 228-231 °C; IR ν_{max}/cm^{-1} (solid): 3273, 3034, 1682, 1521, 1447, 1258, 1142, 1029, 742, 635; ^1H NMR (400 MHz, CD_3CN) δ 10.16 (s, 1H), 9.66 (s, 1H), 9.30 (ddd, *J* = 6.4, 1.7, 0.7 Hz, 1H), 8.94 (dt, *J* = 6.4, 0.9 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.52 – 7.43 (m, 2H), 7.29 (ddt, *J* = 7.5, 5.9, 1.0 Hz, 1H), 7.25 (s, 2H), 2.42 (s, 3H), 2.07 (s, 6H); ^{13}C NMR (100 MHz, CD_3CN) δ 164.50, 158.58, 156.88, 154.70, 143.83, 137.84, 136.49, 134.39, 131.05, 130.11, 126.84, 123.64, 121.84, 122.02 (q, *J* = 319.1 Hz), 21.13, 17.65; ^{19}F NMR (375 MHz, CD_3CN) δ -79.29; *m/z* HRMS (ESI) found $[M+H]^+$ 318.1608, $C_{20}H_{20}N_3O^+$ requires 318.1601.

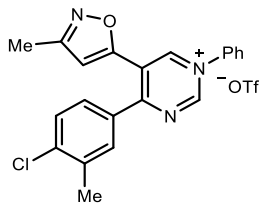
1,4 -Diphenyl-5-(pyridin-2-yl)pyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 4-phenyl-5-(pyridin-2-yl)pyrimidine (700 mg, 3.00 mmol), EtOAc (15 mL), Tf_2O (504 µL, 3.00 mmol), aniline (274 µL, 3.00 mmol), and collidine (396 µL, 3.00 mmol). Isolation A1 afforded the title compound as a pink powder (1.033 g, 2.25 mmol, 75% yield). mp 177-181 °C; IR ν_{max}/cm^{-1} (solid): 3068, 3026, 1623, 1427, 1249, 1167, 1026, 746, 635; ^1H NMR (400 MHz, CD_3CN) δ 9.66 (d, *J* = 1.4 Hz, 1H), 9.32 (s, 1H), 8.70 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.89 – 7.76 (m, 6H), 7.69 – 7.61 (m, 3H), 7.55 – 7.43 (m, 4H); ^{13}C NMR (100 MHz, CD_3CN) δ 171.89, 152.47, 151.93, 151.59, 151.05, 139.99, 138.40, 135.52, 135.04, 134.02, 133.04, 131.61, 131.57, 129.94, 126.13, 125.77, 125.70, 122.02 (q, *J* = 321.0 Hz); ^{19}F

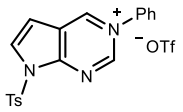
NMR (375 MHz, CD_3CN) δ -79.31; *m/z* HRMS (ESI) found $[M+H]^+$ 310.1348, $C_{21}H_{16}N_3^+$ requires 310.1339.

4-(4-Chloro-3-methylphenyl)-5-(3-methylisoxazol-5-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 5-(4-(4-chloro-3-methylphenyl)pyrimidin-5-yl)-3-methylisoxazole (286 mg, 1.00 mmol), EtOAc (5 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), and collidine (132 µL, 1.00 mmol). Isolation A1 afforded the title compound as a pale-yellow powder (350 mg, 0.68 mmol, 68% yield). mp 205-209 °C; IR ν_{max}/cm^{-1} (solid): 3073, 1616, 1589, 1426, 1250, 1164, 1049, 780, 637; ^1H NMR (400 MHz, CD_3CN) δ 9.64 (d, *J* = 1.8 Hz, 1H), 9.40 (d, *J* = 1.8 Hz, 1H), 7.87 – 7.77 (m, 5H), 7.75 (dt, *J* = 2.2, 0.7 Hz, 1H), 7.59 – 7.45 (m, 2H), 6.69 (s, 1H), 2.44 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 170.22, 162.32, 161.60, 151.99, 151.96, 141.09, 139.70, 138.66, 133.77, 133.35, 133.30, 131.64, 130.85, 129.91, 125.76, 123.61, 122.02 (q, *J* = 318.9 Hz), 109.37, 20.13, 11.42; ^{19}F NMR (375 MHz, CD_3CN) δ -79.30; *m/z* HRMS (ESI) found $[M+H]^+$ 362.1060, $C_{21}H_{17}ClN_3O^+$ requires 362.1055.

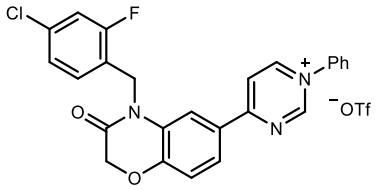
3-Phenyl-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-3-ium trifluoromethanesulfonate



Prepared according to a modified general procedure G with CH_2Cl_2 instead of EtOAc, using 7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (109. mg, 0.40 mmol), CH_2Cl_2 (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the

title compound as a white powder (460 mg, 0.36 mmol, 92% yield). mp 169-174 °C; IR ν_{max}/cm^{-1} (solid): 3109, 1633, 1426, 1256, 1148, 1028, 670, 636; ^{1}H NMR (400 MHz, CD_3CN) δ 9.41 (d, *J* = 1.8 Hz, 1H), 9.32 (d, *J* = 1.8 Hz, 1H), 8.31 (d, *J* = 4.1 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 2H), 7.80 – 7.65 (m, 5H), 7.53 – 7.45 (m, 2H), 7.23 (d, *J* = 4.1 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 151.48, 149.12, 147.82, 146.56, 141.01, 135.14, 134.05, 132.64, 131.53, 131.45, 129.70, 126.08, 122.08, 122.0 (q, *J* = 318.9 Hz), 106.78, 21.77; ^{19}F NMR (375 MHz, CD_3CN) δ -79.34. *m/z* HRMS (ESI) found $[M+H]^+$ 350.0968, $C_{19}H_{16}N_3O_2S^+$ requires 350.0958.

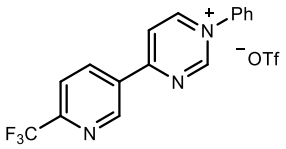
4-(4-(4-Chloro-2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 4-(4-chloro-2-fluorobenzyl)-6-(pyrimidin-4-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (147.9 mg, 0.40 mmol), EtOAc (2.00 mL), Tf_2O (67 µL, 0.40 mmol), aniline (37 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A2 afforded the title compound as a 2:1 mixture of triflate ($^{-}$OTf) and triflamide ($^{-}$NHTf) salts (233 mg, 0.39 mmol, 98% yield). Yield was calculated based on triflate salt, presumed equivalent due to <0.2% difference in product masses. mp 88-92 °C; IRυ_{max}/cm^{-1} (film): 3076, 1687, 1582, 1436, 1381, 1223, 1147, 1027, 894, 636. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (dd, J = 2.0, 1.0 Hz, 1H), 9.19 (dd, J = 7.0, 2.1 Hz, 1H), 8.63 (dd, J = 7.0, 1.0 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 8.03 (dd, J = 8.6, 2.0 Hz, 1H), 7.78 – 7.68 (m, 2H), 7.63 (dd, J = 5.3, 1.9 Hz, 3H), 7.31 – 7.22 (m, 1H), 7.15 – 7.03 (m, 3H), 5.26 (s, 2H), 4.84 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.02, 163.38, 160.50 (d, J = 250.2 Hz), 151.79, 150.46, 138.94, 134.84 (d, J = 10.4 Hz), 132.16, 131.16, 130.43 (d, J = 4.6 Hz),

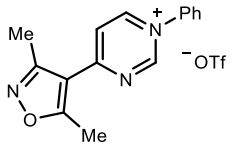
129.17, 127.40, 127.20, 125.34 (d, J = 3.5 Hz), 124.21, 121.02, 120.88, 120.57 (q, J = 318.2 Hz), 118.97, 118.77, 118.51, 116.85, 116.60, 67.56, 38.26 (d, J = 3.9 Hz) . ^{19}F NMR (375 MHz, CD_3CN) δ -79.31 (s, 2F), -80.60 (s, 1F), -116.15 (t, J = 9.3 Hz, 1F). *m/z* HRMS (ESI) found $[M+H]^+$ 446.1072, for $C_{25}H_{18}ClFN_3O_2^+$ requires 446.1066.

1-Phenyl-4-(6-(trifluoromethyl)pyridin-3-yl)pyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 4-(6-(trifluoromethyl)pyridin-3-yl)pyrimidine (225 mg, 1.00 mmol), EtOAc (5 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), and collidine (132 µL, 1.0 mmol). Isolation A1 afforded the title compound as a white powder (325 mg, 0.72 mmol, 95% yield). mp 245-247 °C; IR ν_{max}/cm^{-1} (solid): 3124, 1625, 1463, 1346, 1272, 1250, 1065, 847, 638; ^{1}H NMR (400 MHz, CD_3CN) δ 9.80 – 9.74 (m, 1H), 9.70 (d, *J* = 2.5 Hz, 1H), 9.34 (dd, *J* = 6.8, 1.9 Hz, 1H), 8.98 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.83 (dd, *J* = 6.8, 1.1 Hz, 1H), 8.14 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.83 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.87, 157.94 (d, *J* = 5.1 Hz), 157.47, 156.83, 156.48, 155.84 (d, *J* = 6.4 Hz), 144.51 (d, *J* = 6.7 Hz), 144.33, 137.61, 137.21, 136.04, 131.14 - 121.42 (m), 126.82, 125.67, 125.50. ^{19}F NMR (375 MHz, CD_3CN) δ -68.92, -79.33. HRMS (ESI) found $[M+H]^+$ 302.0955, for $C_{17}H_{11}F_6N_3O_3S^+$ requires 302.0900.

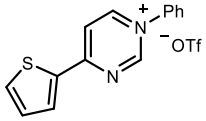
4-(3,5-Dimethylisoxazol-4-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 3,5-dimethyl-4-(pyrimidin-4-yl)isoxazole (526 mg, 3.00 mmol), EtOAc (15 mL), Tf_2O (504 µL, 3.00 mmol), aniline (273 µL, 3.00 mmol), and

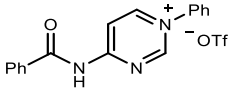
collidine (396 µL, 3.0 mmol). Isolation A1 afforded the title compound as a white powder (3.62 g, 9.45 mmol, 95% yield). mp 175-178 °C; IR ν_{max}/cm^{-1} (solid): 2358, 2049, 1586, 1274, 1226, 1151, 782, 639, 556; ^{1}H NMR (400 MHz, CD_3CN) δ 9.56 (s, 1H), 9.10 (dd, J = 6.9, 2.1 Hz, 1H), 8.25 (d, J = 7.0 Hz, 1H), 7.80 (s, 5H), 2.89 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.15, 169.68, 165.12, 157.16, 155.50, 144.61, 138.35, 135.96, 131.14 - 121.42 (m), 129.98, 124.79 (d, J = 5.1 Hz), 119.17, 19.31, 17.07. ^{19}F NMR (375 MHz, CD_3CN) δ -79.28; HRMS (ESI) found $[M+H]^+$ 252.1220, for $C_{16}H_{14}F_3N_3O_4S^+$ requires 252.1209.

1-Phenyl-4-(thiophen-2-yl)pyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 4-(thiophen-2-yl)pyrimidine (60.0 mg, 0.37 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as a white powder (120 mg, 0.31 mmol, 84% yield). mp 177-180 °C; IR ν_{max}/cm^{-1} (solid): 3123, 1626, 1415, 1253, 1146, 1032, 770, 712, 636; ^{1}H NMR (400 MHz, CD_3CN) δ 9.37 (dd, *J* = 2.0, 1.1 Hz, 1H), 8.94 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.43 – 8.35 (m, 2H), 8.18 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.79 – 7.71 (m, 5H), 7.44 (dd, *J* = 5.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 165.40, 153.26, 150.46, 141.12, 140.22, 139.69, 137.34, 132.70, 132.07, 131.55, 125.38, 122.08 (q, *J* = 321.0 Hz), 117.45; ^{19}F NMR (375 MHz, CD_3CN) δ -79.29; *m/z* HRMS (ESI) found $[M+H]^+$ 239.0645, $C_{14}H_{11}N_2S^+$ requires 239.0637.

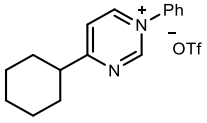
4-Benzamido-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using N-(pyrimidin-4-yl)benzamide (79.7 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53

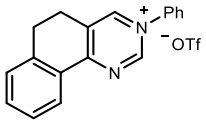
μL, 0.40 mmol). Isolation A1 afforded the title compound as an opaque white solid (160 mg, 37.6 mmol, 94% yield). mp 181-183 °C; IR ν_{max}/cm^{-1} (film): 3387, 3098, 1704, 1632, 1514, 1430, 1247, 1141, 1030, 634. ^{1}H NMR (400 MHz, CD_3CN) δ 10.56 (s, 1H), 9.29 (dd, *J* = 2.1, 1.0 Hz, 1H), 8.93 (dd, *J* = 7.5, 2.1 Hz, 1H), 8.80 (dd, *J* = 7.5, 1.0 Hz, 1H), 8.12 – 7.98 (m, 2H), 7.73 (m, 6H), 7.61 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 168.22, 163.13, 153.60, 151.60, 140.11, 134.93, 132.82, 132.37, 131.42, 129.79, 129.66, 125.36, 121.97 (q, *J* = 320.8 Hz), 111.49; ^{19}F NMR (375 MHz, CD_3CN) δ -79.20; *m/z* HRMS (ESI) found $[M+H]^+$ 267.1133, $C_{17}H_{14}N_3O^+$ requires 267.1140.

4-Cyclohexyl-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



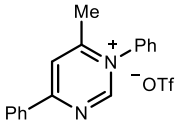
Prepared according to general procedure G using 4-cyclohexylpyrimidine (64.9 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 μL, 0.40 mmol), aniline (36 μL, 0.40 mmol), and collidine (53 μL, 0.40 mmol). Isolation A1 afforded the title compound as a pale-yellow flaky powder (90.3 mg, 0.23 mmol, 58% yield). mp 137-141 °C; IR ν_{max}/cm^{-1} (solid): 3066, 2936, 2855, 1623, 1255, 1154, 1028, 760, 636; ^{1}H NMR (400 MHz, CD_3CN) δ 9.55 (d, *J* = 0.8 Hz, 1H), 9.08 (dd, *J* = 6.7, 2.0 Hz, 1H), 8.14 (dd, *J* = 6.7, 1.1 Hz, 1H), 7.77 (d, *J* = 1.1 Hz, 5H), 3.16 (tt, *J* = 11.7, 3.4 Hz, 1H), 2.06 (ddd, *J* = 12.9, 3.2, 1.5 Hz, 2H), 1.93 (t, *J* = 3.4 Hz, 1H), 1.82 (ddt, *J* = 12.8, 3.4, 1.7 Hz, 1H), 1.68 (qd, *J* = 12.3, 3.1 Hz, 2H), 1.52 (qt, *J* = 12.7, 3.2 Hz, 2H), 1.39 (tt, *J* = 12.5, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 185.96, 152.81, 151.26, 140.30, 132.79, 131.47, 125.63, 122.61, 121.97 (q, *J* = 319.0 Hz), 47.48, 32.11, 26.34, 26.11; ^{19}F NMR (375 MHz, CD_3CN) δ -79.32; *m/z* HRMS (ESI) found $[M+H]^+$ 239.1548, $C_{16}H_{19}N_2^+$ requires 239.1543.

3-Phenyl-5,6-dihydrobenzo[h]quinazolin-3-ium trifluoromethanesulfonate



Prepared according to general procedure G using 5,6-dihydrobenzo[*h*]quinazoline (72.9 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as a white powder (146 mg, 0.37 mmol, 89% yield). mp 179-182 °C; IR ν_{max}/cm^{-1} (solid): 3043, 1624, 1432, 1258, 1028, 758, 635; ^1H NMR (400 MHz, CD_3CN) δ 9.55 (d, *J* = 0.8 Hz, 1H), 9.08 (dd, *J* = 6.7, 2.0 Hz, 3H), 8.14 (dd, *J* = 6.7, 1.1 Hz, 3H), 7.77 (d, *J* = 1.1 Hz, 8H), 3.16 (tt, *J* = 11.7, 3.4 Hz, 3H), 2.06 (ddd, *J* = 12.9, 3.2, 1.5 Hz, 5H), 1.93 (t, *J* = 3.4 Hz, 2H), 1.82 (ddt, *J* = 12.8, 3.4, 1.7 Hz, 2H), 1.68 (qd, *J* = 12.3, 3.1 Hz, 6H), 1.52 (qt, *J* = 12.7, 3.2 Hz, 6H), 1.39 (tt, *J* = 12.5, 3.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 167.18, 151.48, 148.71, 143.75, 140.38, 136.70, 132.73, 132.70, 131.56, 130.47, 130.20, 129.21, 128.76, 125.44, 122.03 (q, *J* = 320.9 Hz), 26.56, 24.86; ^{19}F NMR (375 MHz, CD_3CN) δ -79.32; *m/z* HRMS (ESI) found $[M+H]^+$ 239.1548, $C_{16}H_{19}N_2^+$ requires 239.1543

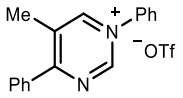
6-Methyl-1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 6-methyl-4-phenylpyrimidine (68 µL, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as an off-white solid (126 mg, 0.32 mmol, 79% yield). mp 202-204 °C. IRυ_{max}/cm^{-1} (solid): 3060, 1623, 1261, 1145, 1028, 739, 639; ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.49 (s, 1H), 8.41 – 8.34 (m, 2H), 7.76 – 7.69 (m, 6H), 7.63 – 7.54 (m, 2H), 2.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.04, 163.65, 151.86, 136.91, 134.90, 132.91, 132.15, 130.92, 129.74, 129.69, 126.17, 125.00 (q, *J* = 320.8 Hz), 120.05, 21.59.

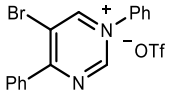
^{19}F NMR (376 MHz, $CDCl_3$) δ -78.31. *m/z* HRMS (ESI) found $[M+H]^+$ 247.1239, $C_{18}H_{15}F_3N_2O_3S^+$ requires 247.1230.

5-Methyl-1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 4-phenyl-5-methylpyrimidine (106 mg, 0.62 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as a peach-colored powder (215 mg, 0.54 mmol, 87% yield). mp 209-213 °C; IR ν_{max}/cm^{-1} (solid): 3074, 3035, 1624, 1438, 1255, 1137, 1032, 764, 690, 636; ^{1}H NMR (400 MHz, CD_3CN) δ 9.51 (d, *J* = 1.9 Hz, 1H), 9.10 (dd, *J* = 1.9, 0.9 Hz, 1H), 8.01 – 7.87 (m, 2H), 7.79 (s, 5H), 7.76 – 7.71 (m, 1H), 7.71 – 7.63 (m, 2H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 173.15, 152.30, 149.96, 140.06, 135.79, 133.61, 133.47, 132.96, 131.61, 131.03, 130.00, 125.57, 122.06 (q, *J* = 320.9 Hz), 18.27; ^{19}F NMR (375 MHz, CD_3CN) δ -79.31; *m/z* HRMS (ESI) found $[M+H]^+$ 247.1238, $C_{17}H_{15}N_2^+$ requires 247.1230.

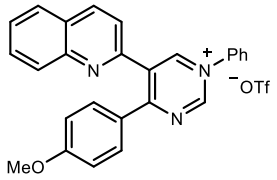
5-Bromo-1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 4-phenyl-5-bromopyrimidine (235.1 mg, 1.00 mmol), EtOAc (5 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), and collidine (132 µL, 1.00 mmol). Isolation A1 afforded the title compound as a white powder (355 mg, 0.77 mmol, 77% yield). mp 238-241 °C; IR ν_{max}/cm^{-1} (solid): 3060, 3003, 1612, 1587, 1439, 1279, 1253, 1225, 1032, 763, 636; ^{1}H NMR (400 MHz, CD_3CN) δ 9.62 (d, *J* = 1.7 Hz, 1H), 9.50 (d, *J* = 1.7 Hz, 1H), 8.16 – 8.09 (m, 2H), 7.85 – 7.76 (m, 6H), 7.70 (ddt, *J* = 8.3, 6.5, 1.3 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 172.28, 154.35, 150.73, 139.28, 135.17, 134.56, 133.34, 131.62,

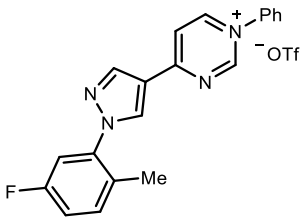
131.28, 129.91, 125.72, 122.01 (d, J = 320.7 Hz), 119.81; ^{19}F NMR (375 MHz, CD_3CN) δ -79.27; *m/z* HRMS (ESI) found $[M+H]^+$ 311.0187, $C_{16}H_{12}BrN_2^+$ requires 311.0178.

4-(4-Methoxyphenyl)-1-phenyl-5-(quinolin-2-yl)pyrimidin-1-ium trifluoromethanesulfonate



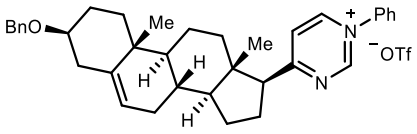
Prepared according to general procedure G using 2-(4-(4-methoxyphenyl)pyrimidin-5-yl)quinoline (125 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A2 afforded the title compound as a bright-orange glass (139 mg, 0.26 mmol, 74% yield). mp 95-99 °C; IR ν_{max}/cm^{-1} (solid): 3062, 1584, 1425, 1252, 1174, 1028, 760, 635; ^{1}H NMR (400 MHz, CD_3CN) δ 9.55 (d, J = 1.9 Hz, 1H), 9.31 (d, J = 1.9 Hz, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.05 – 7.95 (m, 1H), 7.89 – 7.84 (m, 1H), 7.83 – 7.69 (m, 8H), 7.51 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 9.0 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 170.30, 165.48, 152.95, 152.16, 150.58, 149.30, 139.92, 138.46, 134.60, 133.59, 132.78, 131.61, 131.50, 130.21, 129.07, 129.04, 128.60, 127.11, 125.61, 122.59, 121.94 (q, J = 319.0 Hz), 115.64, 56.52; ^{19}F NMR (375 MHz, CD_3CN) δ -79.14; *m/z* HRMS (ESI) found $[M+H]^+$ 390.1610, $C_{26}H_{20}N_3O^+$ requires 390.1601

4-(1-(5-Fluoro-2-methylphenyl)-1H-pyrazol-4-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 4-(1-(5-fluoro-2-methylphenyl)-1H-pyrazol-4-yl)pyrimidine (254.3 mg, 1.0 mmol), EtOAc (5 mL), Tf_2O (168 µL, 1.0 mmol), aniline (91 µL, 1.0 mmol), and collidine (132 µL, 1.0 mmol). Isolation A2 afforded the title compound as a red solid (396 mg, 0.83 mmol, 83% yield). mp 150-154 °C; IR ν_{max}/cm^{-1} (film): 3109, 3055, 1574, 1507, 1269, 1142, 1032; ^1H NMR (400 MHz, CD_3CN) δ 9.41 (d, J = 2.0 Hz, 1H), 8.96 (dd, J = 7.0, 2.0 Hz, 1H), 8.88 (d, J = 0.7 Hz, 1H), 8.62 – 8.59 (s, 1H), 8.31 (dd, J = 7.0, 1.1 Hz, 1H), 7.75 (s, 5H), 7.47 (dd, J = 8.6, 6.1 Hz, 1H), 7.31 (dd, J = 9.1, 2.7 Hz, 1H), 7.25 (td, J = 8.5, 2.7 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 166.08, 161.66 (d, J = 244.1 Hz), 153.33, 150.54, 142.78, 140.33, 140.23 (d, J = 10.1 Hz), 136.84, 133.95 (d, J = 8.6 Hz), 132.63, 131.53, 130.62 (d, J = 3.6 Hz), 125.43, 122.05 (q, J = 319.0 Hz), 121.18, 118.40, 117.41 (d, J = 20.9 Hz), 114.09 (d, J = 24.7 Hz), 17.62; ^{19}F NMR (375 MHz, CD_3CN) δ -79.31 (3F), -117.10 – -117.27 (q, J = 6.9 Hz, 1F); *m/z* HRMS (ESI) found $[M+H]^+$ 331.1359, $C_{20}H_{16}FN_4^+$ requires 331.1354.

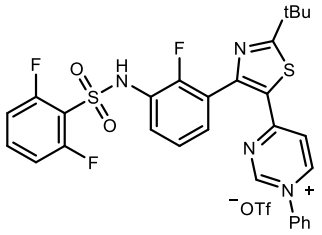
4-((3S,8S,9S,10R,13S,14S,17S)-3-(Benzyloxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to a modified general procedure G using 4-((3S,8S,9S,10R,13S,14S,17S)-3-(benzyloxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)pyrimidine (177.1 mg, 0.4 mmol), CH_2Cl_2 (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as a single diastereomer (white powder, 155 mg, 0.23 mmol, 58% yield). mp 214-218 °C; IR ν_{max}/cm^{-1} (film): 2936, 1627, 1427, 1255, 1030, 736, 637; ^1H NMR (400 MHz,

CD_3CN) δ 9.50 (s, 1H), 8.95 (dd, J = 6.7, 2.0 Hz, 1H), 8.03 (d, J = 6.7 Hz, 1H), 7.84 – 7.63 (m, 5H), 7.34 (d, J = 4.0 Hz, 4H), 7.28 (ddd, J = 8.7, 5.3, 3.5 Hz, 1H), 5.39 (dt, J = 4.1, 1.9 Hz, 1H), 4.54 (s, 2H), 3.25 (td, J = 10.3, 4.7 Hz, 2H), 2.63 – 2.50 (m, 1H), 2.43 (ddd, J = 13.1, 4.7, 2.4 Hz, 1H), 2.29 – 2.17 (m, 1H), 2.11 (d, J = 1.2 Hz, 2H), 2.10 – 2.02 (m, 1H), 1.92 – 1.83 (m, 2H), 1.79 (dt, J = 11.7, 3.3 Hz, 1H), 1.72 – 1.64 (m, 1H), 1.62 (d, J = 7.1 Hz, 1H), 1.59 – 1.54 (m, 1H), 1.53 – 1.43 (m, 4H), 1.16 – 1.05 (m, 2H), 1.03 (s, 3H), 0.64 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 182.72, 152.04, 150.12, 142.13, 140.50, 140.28, 132.85, 131.52, 129.19, 128.49, 128.22, 125.63, 123.92, 122.07 (q, J = 318.9 Hz), 122.00, 79.26, 70.28, 59.99, 58.13, 50.97, 49.35, 39.86, 38.24, 38.03, 37.74, 33.10, 32.54, 29.17, 25.77, 25.52, 21.60, 19.77, 13.31; ^{19}F NMR (375 MHz, CD_3CN) δ -79.33; *m/z* HRMS (ESI) found $[M+H]^+$ 519.3376, $C_{36}H_{43}N_2O^+$ requires 519.3370.

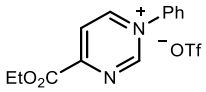
4-(2-(*Tert*-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to a modified general procedure G with CH_2Cl_2 instead of EtOAc, and *N*-{3-(2-(tert-butyl)-5-(pyrimidin-4-yl)thiazol-4-yl)-2-fluorophenyl}-2,6-difluorobenzenesulfonamide (1.00 g, 2.00 mmol), CH_2Cl_2 (10 mL), Tf_2O (336 µL, 2.00 mmol), aniline (182 µL, 1.00 mmol), and collidine (264 µL, 2.00 mmol). Following Isolation A2, the crude material was dissolved in MeOH (10 mL) and NaOTf (688 mg, 4.00 mmol), stirred for 30 minutes at room temperature, and concentrated *in vacuo*. The resulting solid was dissolved in CH_2Cl_2 (50 mL) and filtered. The filtrate was concentrated to afford the title compound as a brown crystalline solid (1.40 g, 1.92 mmol, 96% yield). Product decomposes above 125°C; IR ν_{max}/cm^{-1} (solid): 3097, 2967, 1622,

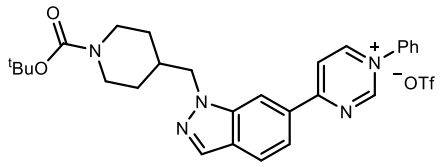
1468, 1250, 1164, 1029, 771, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.98 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.69 (s, 1H), 7.85 – 7.70 (m, 3H), 7.67 – 7.57 (m, 4H), 7.52 (t, *J* = 6.6 Hz, 1H), 7.42 (tt, *J* = 8.4, 5.9 Hz, 1H), 7.31 – 7.22 (m, 1H), 6.89 (t, *J* = 9.0 Hz, 2H), 5.29 (s, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.26, 163.94, 159.47 (dd, *J* = 257.7, 3.5 Hz), 153.64, 150.92, 150.59 (d, *J* = 17.3 Hz), 139.11, 135.05 (t, *J* = 11.3 Hz), 131.83, 130.82, 130.46, 127.96 (d, *J* = 152.5 Hz), 125.62 (d, *J* = 4.1 Hz), 124.79 (d, *J* = 13.0 Hz), 124.27, 122.88 (d, *J* = 13.2 Hz), 122.00 (q, *J* = 329.9 Hz), 121.98, 118.80, 118.24, 117.51 (t, 15.2 Hz), 113.17 (dd, *J* = 23.0, 3.5 Hz), 38.93, 30.50; ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.33 (3F), -107.14 (t, *J* = 9.0 Hz, 2F), -124.76 (1F); *m/z* HRMS (ESI) found $[M+H]^+$ 581.1297, $C_{29}H_{24}F_3N_4O_2S_2^+$ requires 581.1287.

4-(Ethoxycarbonyl)-1-mesitylpyrimidin-1-ium trifluoromethanesulfonate



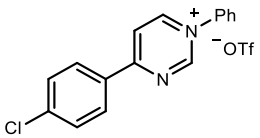
Prepared according to a modified general procedure G using ethyl pyrimidine-4-carboxylate (304 mg, 2.00 mmol), EtOAc (10.0 mL), Tf_2O (336 μL, 2.00 mmol), 2,4,6-trimethylaniline (281 μL, 2.00 mmol), and collidine (264 μL, 2.00 mmol). The reaction was held at -78 °C for an additional 30 minutes, followed by the addition of trifluoromethanesulfonic acid (177 μL, 2.00 mmol), then warming to room temperature. Isolation A2 afforded the title compound as a yellow powder (340 mg, 0.81 mmol, 40% yield). mp 179-183 °C; IR ν_{max}/cm^{-1} (solid): 3096, 1735, 1663, 1320, 1261, 1149, 1032, 636; ^{1}H NMR (400 MHz, CD_3CN) δ 9.64 (s, 1H), 9.33 (dd, J = 6.4, 1.7 Hz, 1H), 8.83 (dd, J = 6.4, 1.1 Hz, 1H), 7.23 (s, 2H), 4.57 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 2.04 (s, 6H), 1.45 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 162.66, 161.65, 157.07, 155.57, 143.87, 134.26, 131.06, 125.74, 121.98 (q, J = 320.7 Hz), 65.06, 21.12, 17.60, 14.21, 1.24; ^{19}F NMR (375 MHz, CD_3CN) δ -79.31; *m/z* HRMS (ESI) found 271.1449, $[M+H]^+$ $C_{16}H_{19}N_2O_2^+$ requires 271.1441.

4-(1-((1-(Tert-butoxycarbonyl)piperidin-4-yl)methyl)-1H-indazol-6-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



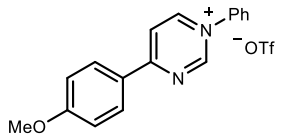
Prepared according to general procedure G using tert-butyl 4-((6-(pyrimidin-4-yl)-1H-indazol-1-yl)methyl)piperidine-1-carboxylate (177.1 mg, 0.45 mmol), EtOAc (2.25 mL), Tf_2O (76 µL, 0.45 mmol), aniline (41 µL, 0.45 mmol), and collidine (60 µL, 0.45 mmol). Isolation A2 afforded the title compound as a 3:1 mixture of triflate ($^-$OTf) and triflamide ($^-$NHTf) salts (219 mg, 0.35 mmol, 78% yield). Yield was calculated based on triflate salt, presumed equivalent due to <0.2% difference in product masses. mp 96-101 $^\circ$C; IRυ_{max}/cm^{-1} (film): 3054, 2985, 1679, 1626, 1427, 1264, 1030, 895, 703, 638. ^{1}H NMR (400 MHz, CD_3CN) δ 9.59 (s, 1H), 9.17 – 9.09 (m, 1H), 8.79 – 8.74 (m, 1H), 8.72 (s, 1H), 8.21 – 8.10 (m, 2H), 8.07 – 7.99 (m, 1H), 7.79 (s, 5H), 4.46 (d, J = 6.4 Hz, 2H), 4.03 (d, J = 13.4 Hz, 2H), 2.66 (s, 2H), 2.42 – 2.02 (m, 3H), 1.53 (d, J = 13.3 Hz, 2H), 1.41 (s, 9H), 1.34 – 1.12 (m, 2H). ^{13}C NMR (100 MHz, CD_3CN) δ 171.84, 155.43, 152.94, 151.41, 141.14, 140.23, 134.33, 132.99, 131.67, 131.44, 128.63, 125.62, 123.69, 121.22, 120.77 (q, J = 318.1 Hz)119.85, 113.64, 79.75, 55.04, 43.09, 38.10, 30.42, 28.58. ^{19}F NMR (375 MHz, CD_3CN) δ -79.31 (s, 2F), -80.60 (s, 1F), -116.15 (t, J = 9.3 Hz, 1F). *m/z* HRMS (ESI) found $[M+H]^+$ 470.2557, for $C_{28}H_{32}N_5O_2^+$ requires 470.2551.

4-(4-Chlorophenyl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 4-(4-chlorophenyl)pyrimidine (76.3 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as a white powder (149 mg, 0.36 mmol, 89% yield). mp 194-198 °C; IR ν_{max}/cm^{-1} (solid): 3125, 3071, 1628, 1588, 1274, 1261, 1152, 1032, 773, 637; ^1H NMR (400 MHz, CD_3CN) δ 9.60 (d, *J* = 1.9 Hz, 1H), 9.16 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.64 (d, *J* = 6.9 Hz, 1H), 8.43 (d, *J* = 8.6 Hz, 2H), 7.78 (s, 5H), 7.72 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 169.97, 153.01, 151.90, 142.22, 140.10, 132.83, 132.47, 131.95, 131.50, 130.97, 125.50, 121.9 (q, *J* = 319.0, 119.58); ^{19}F NMR (375 MHz, CD_3CN) δ -79.14; *m/z* HRMS (ESI) found $[M+H]^+$ 267.0690, $C_{16}H_{12}ClN_2^+$ requires 267.0684.

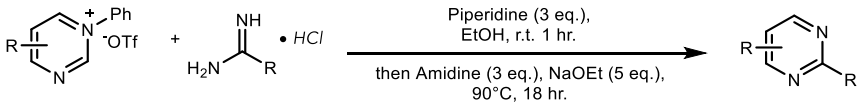
4-(4-Methoxyphenyl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure G using 4-(4-methoxyphenyl)pyrimidine (74.5 mg, 0.4 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), and collidine (53 µL, 0.40 mmol). Isolation A1 afforded the title compound as a yellow powder (150 mg, 0.36 mmol, 91% yield). mp 176-178 °C; IR ν_{max}/cm^{-1} (solid): 3082, 1585, 1465, 1430, 1257, 1150, 1028, 833, 771, 633; ^1H NMR (400 MHz, CD_3CN) δ 9.44 (d, *J* = 2.0 Hz, 1H), 8.96 (dd, *J* = 7.2, 2.0 Hz, 1H), 8.47 (t, *J* = 8.2 Hz, 3H), 7.75 (s, 5H), 7.22 (d, *J* = 9.0 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 169.95, 166.96, 152.54, 150.34, 140.10, 133.04, 132.50, 131.43, 125.91, 125.31, 121.9 (q, *J* = 319.3 Hz), 118.26, 116.38, 56.72; ^{19}F NMR (375 MHz, CD_3CN) δ -79.11; *m/z* HRMS (ESI) found $[M+H]^+$ 263.1187, $C_{17}H_{15}N_2O^+$ requires 263.1179.

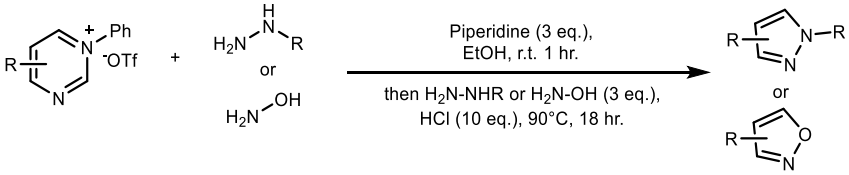
A 1.6 Procedures for Pyrimidine C2-Functionalization and Ring-Conversion

General Procedure H (Pyrimidine C2-Functionalization from Pyrimidinium Salt)



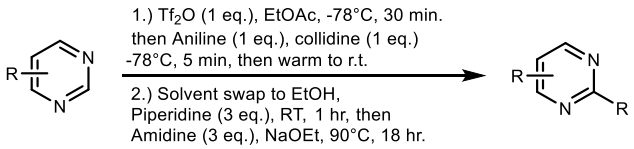
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the pyrimidinium salt (1.0 equiv), EtOH (0.2 M), and piperidine (3.0 equiv). The reaction was stirred for 60 minutes at 25 ºC before amidine (3.0 equiv, HCl salt or free amidine) was added followed by NaOEt (5.0 equiv, 21% soln. in EtOH). The reaction was heated to 90 ºC for 18 hours. After cooling to room temperature, the reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The combined organic extract was washed with brine (1x) and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified with flash column chromatography.

General Procedure I (Pyrimidine Ring-Conversion from Pyrimidinium Salt)



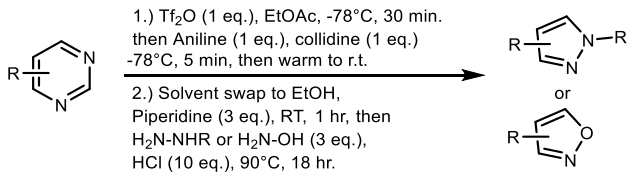
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the pyrimidinium salt (1.0 equiv), EtOH (0.2 M), and piperidine (3.0 equiv). The reaction was stirred for 60 minutes at 25 ºC before hydrazine (3.0 equiv) or hydroxylamine HCl (3.0 equiv) was added followed by concentrated HCl (10 equiv). The reaction was heated to 90 ºC for 18 hours. After cooling to room temperature, the reaction was quenched with sat. $NaHCO_3$, then extracted into EtOAc (3x). The combined organic extract was washed with brine (1x) and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified with flash column chromatography.

General Procedure J (One-Pot C2-Functionalizations from Pyrimidine)



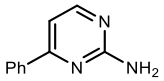
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the pyrimidine (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.2 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before aniline (1.0 equiv) was added dropwise followed by collidine (1.0 equiv). The reaction was stirred for a further 5 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. The reaction was then concentrated with a gentle stream of air (< 0.5 mmol scale) or *in vacuo* at 40 ºC (> 0.5 mmol scale). Then EtOH (0.2 M) and piperidine (3.0 equiv) were added. The reaction was stirred for 60 minutes before amidine (3.0 equiv, HCl salt or free amidine) was added followed by NaOEt (5.0 equiv, 21% soln. in EtOH). The reaction was heated to 90 ºC for 18 hours. After cooling to room temperature, the reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The combined organic extract was washed (1x) with brine and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified with flash column chromatography.

General Procedure K (One-Pot Ring-Conversions from Pyrimidine)



An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the pyrimidine (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.2 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before aniline (1.0 equiv) was added dropwise followed by collidine (1.0 equiv). The reaction was stirred for a further 5 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. The reaction was then concentrated with a gentle stream of air (< 0.5 mmol scale) or *in vacuo* at 40 ºC (> 0.5 mmol scale). Then EtOH (0.2 M) and piperidine (3.0 equiv) were added. The reaction was stirred for 60 minutes before hydrazine (3.0 equiv) or hydroxylamine HCl (3.0 equiv) was added followed by concentrated HCl (10 equiv). The reaction was heated to 90 ºC for 18 hours. After cooling to room temperature, the reaction was quenched with sat. $NaHCO_3$, then extracted into EtOAc (3x). The combined organic extract was washed (1x) with brine and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified with flash column chromatography.

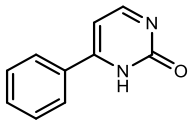
4-Phenylpyrimidin-2-amine



Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), guanidine hydrochloride (115 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 10-30% EtOAc in hexanes with 1% AcOH modifier) to provide the title compound as a pale-yellow powder (57 mg, 0.33 mmol, 83% yield).

To demonstrate comparable yield in a one-pot procedure, 4-phenylpyrimidin-2-amine was also prepared according to general procedure J using 4-phenylpyrimidine (62.5 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 µL, 0.40 mmol), aniline (36 µL, 0.40 mmol), collidine (54 µL, 0.40 mmol). Then, solvent was exchanged for EtOH (2 mL) and piperidine (119 µL, 1.20 mmol), guanidine hydrochloride (115 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH) were added. The crude material was purified by flash chromatography (silica gel: 1:60:39 AcOH:EtOAc:hexanes) to provide the title compound as a pale yellow powder (48 mg, 0.27 mmol, 70% yield). mp 162-165 °C; IR ν_{max}/cm^{-1} (solid): 3264, 3149, 2405, 1654, 1553, 1461, 819, 766; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 5.3 Hz, 1H), 8.17 – 7.81 (m, 2H), 7.66 – 7.42 (m, 3H), 7.05 (d, *J* = 5.3 Hz, 1H), 5.17 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 164.24, 164.07, 159.51, 137.48, 130.93, 129.15, 127.15, 106.28; *m/z* HRMS (DART) found $[M+H]^+$ 172.0879, $C_{10}H_{10}N_3^+$ requires 172.0869. Spectra matched literature values.[13]

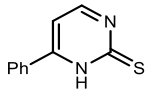
6-Phenylpyrimidin-2(1H)-one



Prepared according to a modified general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), pyrrolidine (164 µL, 2.00 mmol), and stirred for 18 hours at room temperature before adding urea (91.3 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). Following the reaction, AcOH (229 µL, 4.00 mmol) was added at room temperature and saturated $NaHCO_3$ was added until the pH = 8. The aqueous layer was extracted with CH_2Cl_2. The crude material washed with warm Et_2O and filtered to provide the title compound as a brown powder (17 mg, 0.10 mmol, 25% yield). Decomposed above 230 °C; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 11.91 (s, 1H), 8.14 – 8.07 (d, 2H), 8.05 (d, *J* = 6.4 Hz,

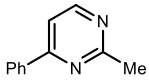
1H), 7.68 – 7.49 (m, 3H), 6.99 (d, J = 6.5 Hz, 1H). m/z HRMS (ESI) found $[M+H]^+$ 173.0716, $C_{10}H_8N_2O^+$ requires 173.0709. Spectra matched literature values.

6-Phenylpyrimidine-2(1H)-thione



Prepared according to a modified general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), thiourea (91.3 mg, 1.20 mmol), and NaOEt (747 µL, 2.0 mmol, as a 21% soln. in EtOH). Following the reaction, AcOH (229 µL, 4.00 mmol) was added at room temperature and saturated $NaHCO_3$ was added until the pH = 8. The aqueous layer was extracted with 3:1 CH_2Cl_2:isopropanol. The crude material was purified by flash chromatography (silica gel: 1:40:59 AcOH:EtOAc:hexanes) to provide the title compound as a brown powder (40 mg, 0.21 mmol, 53% yield). Material decomposes above 275 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.77 (d, J = 5.3 Hz, 1H), 8.08 (d, J = 7.0 Hz, 2H), 7.92 (d, J = 5.3 Hz, 1H), 7.61 – 7.50 (m, 1H), 7.47 (dd, J = 8.3, 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 168.63, 164.20, 159.83, 135.57, 132.22, 129.54, 127.51, 114.68. Spectra matched literature values.

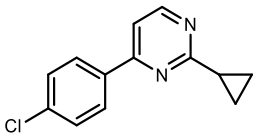
2-Methyl-4-phenylpyrimidine



Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), acetamidine hydrochloride (114 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:40:59 AcOH:EtOAc:hexanes) to afford the title compound as a 17:1 mixture of title compound: 4-

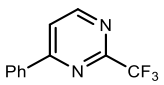
phenylpyrimidine (orange solid, 49 mg, 0.29 mmol, 72% yield). mp 43-46 °C; IR ν_{max}/cm^{-1} (solid): 3060, 2925, 1573, 1547, 1428, 1314, 840, 792, 752, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.3 Hz, 1H), 8.05 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.55 – 7.43 (m, 4H), 2.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.41, 164.05, 157.45, 136.94, 130.81, 128.95, 127.18, 113.93, 26.32; *m/z* HRMS (DART) found $[M+H]^+$ 171.0924, $C_{11}H_{11}N_2^+$ requires 171.0917. Spectra matched literature values.

4-(4-Chlorophenyl)-2-cyclopropylpyrimidine



Prepared according to general procedure H using 4-(4-chlorophenyl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (167 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), cyclopropanecarboximidamide hydrochloride (145 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 0-12% EtOAc in hexanes) to provide the title compound as a brown oil (60 mg, 0.26 mmol, 65% yield). mp 69-72 °C; IR ν_{max}/cm^{-1} (solid): 3065, 3007, 1599, 1542, 1453, 1104, 1014, 915, 856, 867, 791; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 5.3 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 5.3 Hz, 1H), 2.29 (tt, *J* = 8.4, 4.7 Hz, 1H), 1.19 (dt, *J* = 6.2, 3.3 Hz, 2H), 1.11 – 1.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.27, 162.18, 157.45, 136.94, 135.40, 129.06, 128.34, 113.10, 18.37, 10.85; *m/z* HRMS (DART) found $[M+H]^+$ 231.0700, $C_{13}H_{12}ClN_2^+$ requires 231.0684.

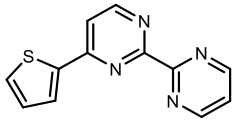
4-Phenyl-2-(trifluoromethyl)pyrimidine



Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol),

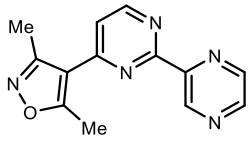
trifluoroacetamidine (135 mg, 1.20 mmol), and NaOEt (747 μL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 0-20% EtOAc in hexanes) to provide the title compound as a white solid (66 mg, 0.30 mmol, 75% yield). mp 44-47 °C; IR ν_{max}/cm^{-1} (solid): 3070, 1583, 1336, 1202, 1136, 873, 767, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 5.3 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 5.3 Hz, 1H), 7.71 – 7.13 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.27, 158.33, 157.00 (q, *J* = 36.4 Hz), 135.00, 132.07, 129.22, 127.44, 122.47-115.61 (q, *J* = 275.8 Hz), 118.28; ^{19}F NMR (375 MHz, $CDCl_3$) δ -70.52; *m/z* HRMS (DART) found $[M+H]^+$ 255.0639, $C_{11}H_8F_3N_2^+$ requires 225.0634. Spectra matched literature values.

4-(Thiophen-2-yl)-2,2'-bipyrimidine



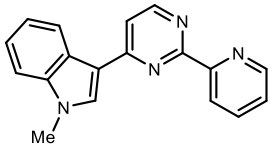
Prepared according to general procedure H using 1-phenyl-4-(thiophen-2-yl)pyrimidin-1-ium trifluoromethanesulfonate (108 mg, 0.28 mmol), EtOH (1.40 mL), piperidine (82 μL, 0.84 mmol), 2-amidinopyrimidine hydrochloride (132 mg, 0.84 mmol), and NaOEt (517 μL, 1.40 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:99 Et_3N:EtOAc followed by 1:19:20:60 Et_3N:hexanes:EtOAc:EtOH)) to provide the title compound as a yellow solid (32 mg, 0.13 mmol, 49% yield). mp 180-183 °C; IR ν_{max}/cm^{-1} (solid): 3066, 3045, 1555, 1426, 1379, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, *J* = 4.9 Hz, 2H), 8.90 (d, *J* = 5.3 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.62 (d, *J* = 5.3 Hz, 1H), 7.57 – 7.50 (m, 1H), 7.40 (t, *J* = 4.8 Hz, 1H), 7.15 (dd, *J* = 5.0, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.78, 162.72, 160.20, 158.18, 157.99, 141.71, 130.65, 128.52, 128.35, 121.34, 115.37; *m/z* HRMS (DART) found $[M+H]^+$ 241.0555, $C_{12}H_9N_4S^+$ requires 241.0542.

3,5-Dimethyl-4-(2-(pyrazin-2-yl)pyrimidin-4-yl)isoxazole



Prepared according to general procedure H using 4-(3,5-dimethylisoxazol-4-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (160.5 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 μL, 1.20 mmol), pyrazine-2-carboximidamide hydrochloride (190.3 mg, 1.20 mmol), and NaOEt (747 μL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:99 AcOH:EtOAc followed by 1:50:25:25 AcOH:hexanes:EtOAc:EtOH) to provide the title compound as a pale-yellow solid (71 mg, 0.28 mmol, 70% yield). mp 173-177 °C; IR ν_{max}/cm^{-1} (film): 3047, 1605, 1564, 1422, 1375, 1012, 845, 713, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, J = 1.6 Hz, 1H), 8.97 (d, J = 5.3 Hz, 1H), 8.81 – 8.76 (m, 1H), 8.70 (d, J = 2.4 Hz, 1H), 7.40 (d, J = 5.3 Hz, 1H), 2.77 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.65, 162.27, 158.97, 158.63, 158.61, 150.09, 145.90, 145.31, 144.68, 118.15, 113.88, 13.70, 12.46; *m/z* HRMS (ESI) found $[M+H]^+$ 254.1043, $C_{13}H_{12}N_5O^+$ requires 254.1036.

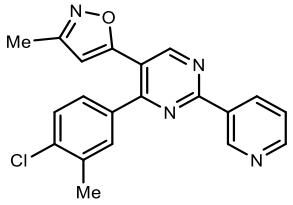
1-Methyl-3-(2-(pyridin-2-yl)pyrimidin-4-yl)-1H-indole



Prepared according to general procedure H using 4-(1-Methyl-1H-indol-3-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (174 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 μL, 1.20 mmol), picolinimidamide hydrochloride (189 mg, 1.20 mmol), and NaOEt (747 μL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:99 Et_3N:EtOAc followed by 1:75:24 Et_3N:EtOAc:EtOH)) to provide the title compound as a brown

solid (63 mg, 0.22 mmol, 55% yield). mp 89-94 °C; IR ν_{max}/cm^{-1} (solid): 3066, 3048, 2927, 2191, 1576, 1389, 1230, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 – 8.81 (m, 1H), 8.75 (d, *J* = 5.4 Hz, 1H), 8.61 (d, *J* = 7.9 Hz, 1H), 8.49 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.89 – 7.82 (m, 2H), 7.47 (d, *J* = 5.4 Hz, 1H), 7.37 (ddd, *J* = 7.7, 4.8, 1.2 Hz, 1H), 7.34 – 7.29 (m, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.38, 161.93, 157.16, 155.57, 149.94, 138.01, 136.84, 131.75, 125.98, 124.61, 123.46, 122.80, 121.73, 121.60, 114.94, 113.52, 109.96, 33.35; *m/z* HRMS (DART) found $[M+H]^+$ 287.1303, $C_{18}H_{15}N_4^+$ requires 287.1291.

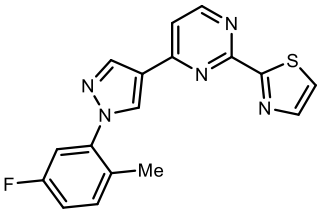
5-(4-(4-Chloro-3-methylphenyl)-2-(pyridin-3-yl)pyrimidin-5-yl)-3-methylisoxazole



Prepared according to general procedure H using 4-(4-chloro-3-methylphenyl)-5-(3-methylisoxazol-5-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (205 mg, 0.40 mmol), piperidine (118 μL, 1.20 mmol), EtOH (2 mL), nicotinimidamide hydrochloride (145 mg, 1.20 mmol), and NaOEt (747 μL, 2.00 mmol, as a 21% soln. in EtOH). The residue was purified by flash chromatography (silica gel: 60% EtOAc in hexanes. A second column was needed (70% EtOAc in hexanes) to provide the pure title compound as a yellow solid (59 mg, 0.16 mmol, 40% yield). mp 142-144 °C. IRυ_{max}/cm^{-1} (solid): 3359, 3146, 1659, 1592, 1412, 1044, 819, 703. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 9.04 (s, 1H), 8.68 (dd, *J* = 12.4, 6.4 Hz, 2H), 7.46 (d, *J* = 1.8 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.26 – 7.19 (m, 1H), 5.86 (s, 1H), 2.36 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.98, 163.09 (d, *J* = 36.4 Hz), 160.25, 157.58, 152.01, 150.29, 136.89 (d, *J* = 14.2 Hz), 135.82, 135.51, 135.50, 132.25, 131.42, 129.31, 128.95, 127.59, 123.46,

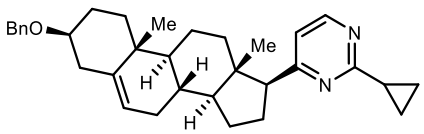
118.58, 105.17, 20.17, 11.49; *m/z* HRMS (ESI) found $[M+H]^+$ 363.1017, $C_{20}H_{15}ClN_4O^+$ requires 363.0934.

2-(4-(1-(5-Fluoro-2-methylphenyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)thiazole



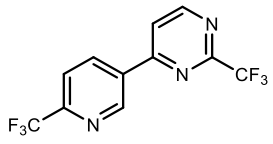
Prepared according to general procedure H using 4-(1-(5-fluoro-2-methylphenyl)-1H-pyrazo l-4-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (192.2 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 μL, 1.20 mmol), thiazole-2-carboximidamide hydrochloride (196.4 mg, 1.20 mmol), and NaOEt (747 μL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:2:97 AcOH:MeOH:CH_2Cl_2) to provide the title compound as a pink solid (87 mg, 0.26 mmol, 64% yield). mp 81-85 °C; IR ν_{max}/cm^{-1} (film): 3076, 1580, 1527, 1430, 1249, 875, 776; ^1H NMR (400 MHz, $CDCl_3$) 1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 5.3 Hz, 1H), 8.40 (s, 1H), 8.29 (s, 1H), 8.02 (d, J = 3.1 Hz, 1H), 7.51 (d, J = 3.2 Hz, 1H), 7.41 (d, J = 5.2 Hz, 1H), 7.35 – 7.24 (m, 1H), 7.12 (dd, J = 8.8, 2.7 Hz, 1H), 7.06 (td, J = 8.3, 2.7 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.36 (q, J = 8.1 Hz); *m/z* HRMS (ESI) found $[M+H]^+$ 338.0873, $C_{17}H_{13}FN_5S^+$ requires 338.0870.

4-((3S,8S,9S,10R,13S,14S,17S)-3-(Benzyloxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-cyclopropylpyrimidine



Prepared according to general procedure H using 4-((3S,8S,9S,10R,13S,14S,17S)-3-(benzyloxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (134 mg, 0.20 mmol), EtOH (1 mL), piperidine (60 μL, 0.60 mmol), cyclopropanecarboximidamide hydrochloride (72.4 mg, 0.60 mmol), and NaOEt (374 μL, 1.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 25% EtOAc in hexanes) to provide the title compound as a pale-yellow solid (51 mg, 0.11 mmol, 53% yield). mp 92-97 °C; IR ν_{max}/cm^{-1} (film): 2932, 2903, 1574, 1551, 1435, 1113, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 5.2 Hz, 1H), 7.40 – 7.30 (m, 4H), 7.29 – 7.19 (m, 1H), 6.83 (d, J = 5.3 Hz, 1H), 5.39 – 5.34 (m, 1H), 4.56 (s, 2H), 3.29 (tt, J = 11.3, 4.5 Hz, 1H), 2.69 (t, J = 9.4 Hz, 1H), 2.43 (tt, J = 7.9, 4.0 Hz, 2H), 2.29 (ddt, J = 13.7, 10.5, 2.7 Hz, 1H), 2.17-2.23 (m, 1H), 2.04 (dtd, J = 13.6, 4.9, 2.3 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.91 – 1.83 (m, 2H), 1.83 – 1.73 (m, 2H), 1.62 (dd, J = 10.5, 2.7 Hz, 1H), 1.59 – 1.51 (m, 3H), 1.49 (d, J = 4.6 Hz, 1H), 1.37 (ddd, J = 13.1, 8.2, 3.8 Hz, 3H), 1.24 (dt, J = 10.1, 5.9 Hz, 1H), 1.15 – 1.08 (m, 2H), 1.06 (d, J = 3.7 Hz, 1H), 1.01-1.03 (m, 1H), 1.00 (s, 3H), 0.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.08, 169.86, 155.64, 141.16, 139.15, 128.45, 127.65, 127.50, 121.47, 117.46, 78.61, 70.03, 57.88, 57.01, 50.39, 45.21, 39.26, 38.16, 37.38, 37.10, 32.26, 32.06, 28.53, 24.79, 24.40, 20.90, 19.52, 18.27, 13.02, 10.63, 10.59; *m/z* HRMS (ESI) found $[M+H]^+$ 483.3379, $C_{33}H_{43}N_2O^+$ requires 483.3370.

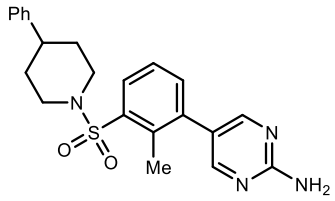
2-(Trifluoromethyl)-4-(6-(trifluoromethyl)pyridin-3-yl)pyrimidine



Prepared according to general procedure H using 1-phenyl-2-(trifluoromethyl)-4-(6-(trifluoromethyl) pyridin-3-yl)pyrimidin-1-ium trifluoromethanesulfonate (160 mg, 0.35 mmol),

EtOH (1.8 mL), piperidine (104 µL, 1.05 mmol), trifluoroacetamidine (118 mg, 1.05 mmol), and NaOEt (654 µL, 1.75 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:39:60 AcOH:EtOAc:hexanes) to provide the title compound as an orange solid (41 mg, 0.14 mmol, 40% yield). mp 89-94 °C; IR ν_{max}/cm^{-1} (solid): 3312, 3158, 1645, 1590, 1512, 1485, 1224, 798, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 9.06 (d, J = 5.3 Hz, 1H), 8.71 (dd, J = 8.3, 2.2 Hz, 1H), 8.00 (d, J = 5.2 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.70, 159.53, 157.69 (q, J = 37.2 Hz), 150.76 (q, J = 35.3 Hz), 148.79, 136.82, 133.67, 121.01 (q, J = 2.8 Hz), 120.90, 120.57 (q, J = 180.4 Hz), 119.01; ^{19}F NMR (375 MHz, CDCl3) δ -68.17 (s, 3F), -70.61 (s, 3F); *m/z* HRMS (ESI) found $[M+H]^+$ 294.0460, $C_{11}H_6F_6N_3^+$ requires 294.0460.

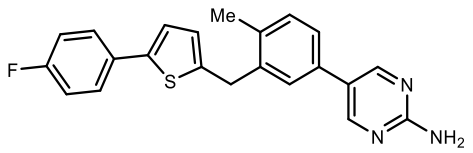
5-(2-Methyl-3-((4-phenylpiperidin-1-yl)sulfonyl)phenyl)pyrimidin-2-amine



Prepared according to a modified general procedure J using 5-(2-methyl-3-((4-phenylpiperidin-1-yl)sulfonyl)phenyl)pyrimidine (79 mg, 0.20 mmol), Tf_2O (34 µL, 0.20 mmol), *p*-NO_2 aniline (28.0 mg, 0.20 mmol), collidine (25 µL, 0.20 mmol), EtOAc (1 mL), then piperidine (59 µL, 0.60 mmol), EtOH (1 mL), guanidine hydrochloride (382 mg, 4.00 mmol) and NaOEt (428 µL, 1.00 mmol, as a 21% soln. in EtOH). The residue was purified by flash chromatography (silica gel: 3% MeOH in dichloromethane) to provide the pure title compound as an off-white solid (31 mg, 0.076 mmol, 38% yield). mp 215-217 °C. IRυ_{max}/cm^{-1} (film): 3675, 2988, 2337, 2161, 1622, 1482, 1161, 1067, 561. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 2H), 7.96 (t, J = 4.7 Hz, 1H), 7.33 (d, J = 4.5 Hz, 2H), 7.24 (t, J = 7.4 Hz, 2H), 7.11 (d, J = 7.0 Hz, 3H), 5.19 (s, 2H), 3.88 – 3.79 (m, 2H), 2.80 (td, J =

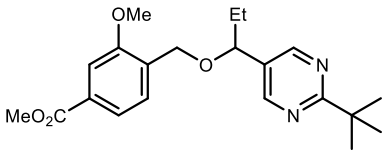
12.5, 2.8 Hz, 2H), 2.57 (dt, J = 12.4, 3.7 Hz, 1H), 2.52 (s, 3H), 1.90 – 1.81 (m, 2H), 1.71 (qd, J = 12.6, 4.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.16, 158.23, 144.88, 138.50, 138.01, 136.20, 134.66, 130.19, 128.64, 126.71, 125.93, 124.50, 45.94, 42.12, 32.91, 17.66. *m/z* HRMS (ESI) found 409.1721, $[M+H]^+$ for $C_{22}H_{24}N_4O_2S^+$ requires 409.1698.

5-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyrimidin-2-amine



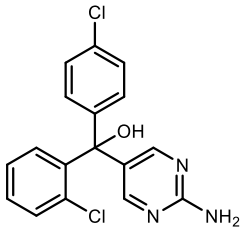
Prepared according to a modified general procedure J using 5-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyrimidine (144 mg, 0.40 mmol), Tf_2O (67 μL, 0.40 mmol), *p*-NO_2 aniline (56.0 mg, 0.40 mmol), collidine (53 μL, 0.40 mmol), EtOAc (2 mL), then piperidine (118 μL, 1.20 mmol), EtOH (2 mL), guanidine hydrochloride (472 mg, 8.00 mmol) and NaOEt (747 μL, 2.00 mmol, as a 21% soln. in EtOH). The residue was purified by flash chromatography (silica gel: 70% EtOAc in hexanes) to provide the pure title compound as an off-white solid (114 mg, 0.30 mmol, 76% yield). mp 120-122 °C. IRυ_{max}/cm^{-1} (film): 3657, 2988, 2358, 2161, 2050, 1506, 1065, 644, 576. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 2H), 7.64 – 7.54 (m, 2H), 7.50 (d, *J* = 2.1 Hz, 1H), 7.40 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.34 – 7.25 (m, 1H), 7.23 – 7.08 (m, 3H), 6.84 (dt, *J* = 3.6, 1.1 Hz, 1H), 5.53 (s, 2H), 4.24 (s, 2H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.40, 160.94, 157.32, 154.78, 142.45, 141.93, 139.57, 137.61, 134.10, 132.22, 131.60, 127.88, 127.18 (d, *J* = 8.0 Hz), 126.26, 125.41, 122.75, 115.87, 34.12, 19.33. ^{19}F NMR (375 MHz, $CDCl_3$) δ -114.94 (dq, J = 9.0, 4.5 Hz). *m/z* HRMS (ESI) found 376.1313, $[M+H]^+$ for $C_{22}H_{18}FN_3S^+$ requires 376.1283.

Methyl 4-((1-(2-(tert-butyl)pyrimidin-5-yl)propoxy)methyl)-3-methoxybenzoate



Prepared according to a modified general procedure J using methyl 3-methoxy-4-((1-(pyrimidin-5-yl)propoxy)methyl)benzoate (50.2 mg, 0.16 mmol), Tf_2O (27 μL, 0.16 mmol), *p*-NO_2 aniline (21.8 mg, 0.16 mmol), collidine (21 μL, 0.16 mmol), EtOAc (0.8 mL), then piperidine (47 μL, 0.48 mmol), MeOH (0.8 mL), pivalimidamide hydrochloride (216 mg, 1.60 mmol), and NaOMe (42.7 mg, 0.80 mmol). The residue was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the pure title compound as a yellow oil (22 mg, 0.06 mmol, 38% yield). IR ν_{max}/cm^{-1} (film): 2958, 1720, 1587, 1432, 1288, 1230, 1103, 1036, 760; ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.51 – 7.44 (m, 2H), 4.46 (s, 2H), 4.28 (t, J = 6.5 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 1.92 (dp, J = 14.6, 7.4 Hz, 1H), 1.82 – 1.67 (dp, J = 14.1, 7.2 Hz, 1H), 1.41 (s, 9H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.89, 167.06, 156.74, 155.49, 131.90, 131.55, 130.61, 128.39, 122.11, 110.81, 79.59, 65.99, 55.51, 52.29, 39.34, 30.85, 29.77, 10.08; *m/z* HRMS (ESI) found $[M+H]^+$ 373.2124, $C_{21}H_{29}N_2O_4^+$ requires 373.2122.

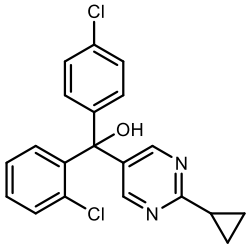
(2-Aminopyrimidin-5-yl)(2-chlorophenyl)(4-chlorophenyl)methanol



Prepared according to a modified general procedure J using (2-chlorophenyl)(4-chlorophenyl)(pyrimidin-5-yl)methanol (132 mg, 0.40 mmol), Tf_2O (67 μL, 0.40 mmol), *p*-NO_2 aniline (56.0 mg, 0.40 mmol), collidine (53 μL, 0.40 mmol), EtOAc (2 mL), then piperidine (118 μL, 1.20 mmol), EtOH (2 mL), guanidine hydrochloride (472 mg, 8.00 mmol) and NaOEt (747

μL, 2.00 mmol, as a 21% soln. in EtOH). The residue was purified by flash chromatography (silica gel: 80% EtOAc in hexanes) to provide the pure title compound as an off-white solid (46 mg, 0.13 mmol, 33% yield). mp 78-80 °C. IRυ_{max}/cm^{-1} (film): 3292, 3157, 1669, 1605, 1496, 1483, 1266, 1131, 813, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.35 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.30 – 7.19 (m, 3H), 7.16 – 7.07 (m, 3H), 6.79 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.27 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.16, 157.90, 143.00, 141.86, 133.88, 132.81, 131.77, 130.75, 129.87, 128.85, 128.53, 128.28, 126.91, 79.76. *m/z* HRMS (ESI) found $[M+H]^+$ 346.0514, for $C_{17}H_{13}Cl_2N_3O^+$ requires 346.0514.

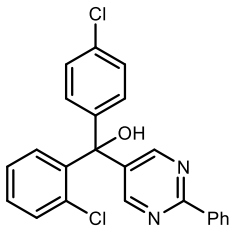
(2-Chlorophenyl)(4-chlorophenyl)(2-cyclopropylpyrimidin-5-yl)methanol



Prepared according to a modified general procedure J using (2-chlorophenyl)(4-chlorophenyl)(pyrimidin-5-yl)methanol (132 mg, 0.40 mmol), Tf_2O (67 μL, 0.40 mmol), *p*-NO_2 aniline (56.0 mg, 0.40 mmol), collidine (53 μL, 0.40 mmol), EtOAc (2 mL), then piperidine (118 μL, 1.20 mmol), EtOH (2 mL), cyclopropanecarboximidamide hydrochloride (960 mg, 8.00 mmol), and NaOEt (747 μL, 2.00 mmol, as a 21% soln. in EtOH). The residue was purified by flash chromatography (silica: 0-30% EtOAc in hexanes. A second column was needed (30% dichloromethane in hexanes)) to provide the pure title compound as a viscous yellow oil (57 mg, 0.15 mmol, 38% yield). IRυ_{max}/cm^{-1} (film): 3168, 1545, 1454, 1190, 1013, 904, 757, 728. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.6 Hz, 3H), 7.11 (dd, *J* = 12.7, 8.1 Hz, 3H), 6.71 (d, 1H), 4.39 (s, 1H), 2.19 (td, *J* = 8.6, 8.1, 4.1 Hz, 1H), 1.13 – 0.98 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.06, 156.15, 142.46, 141.30, 134.79, 134.12, 132.73,

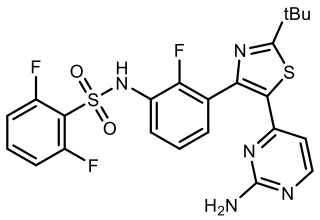
131.85, 130.70, 130.09, 128.79, 128.67, 127.02, 79.75, 17.83, 11.25 (d, J = 3.8 Hz). *m/z* HRMS (ESI) found $[M+H]^+$ 371.0724, $C_{20}H_{16}Cl_2N_2O^+$ requires 371.0718.

(2-Chlorophenyl)(4-chlorophenyl)(2-phenylpyrimidin-5-yl)methanol



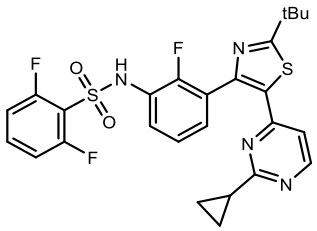
Prepared according to a modified general procedure J using (2-chlorophenyl)(4-chlorophenyl)(pyrimidin-5-yl)methanol (132 mg, 0.40 mmol), Tf_2O (67 µL, 0.40 mmol), *p*-NO_2 aniline (56.0 mg, 0.40 mmol), collidine (53 µL, 0.40 mmol), EtOAc (2 mL), then piperidine (118 µL, 1.20 mmol), EtOH (2 mL), benzimidamide hydrochloride (626 mg, 4.00 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The residue was purified by flash chromatography (silica gel: 20% EtOAc in hexanes. A second column was needed (0 to 10% EtOAc in hexanes)) to provide the pure title compound as a viscous yellow oil (45 mg, 0.11 mmol, 28% yield). IRυ_{max}/cm^{-1} (film): 1651, 1579, 1428, 1163, 1045, 736, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 2H), 8.38 (dd, J = 6.8, 3.1 Hz, 2H), 7.54 – 7.34 (m, 4H), 7.27 (dd, J = 9.0, 2.8 Hz, 3H), 7.22 – 7.08 (m, 3H), 6.75 (d, J = 7.9 Hz, 1H), 4.39 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.62, 156.65, 142.45, 141.33, 137.04, 135.84, 134.19, 132.78, 131.89, 130.97, 130.79, 130.13, 128.89, 128.72, 128.63, 128.23, 127.06, 79.88. *m/z* HRMS (ESI) found $[M+H]^+$ 407.0724, $C_{23}H_{16}Cl_2N_2O^+$ requires 407.0718.

Dabrafenib



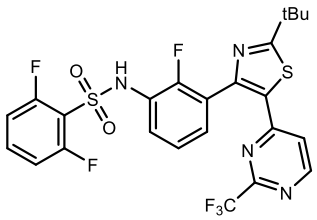
Prepared according to a modified general procedure J, heated to 70 ºC instead of 90 ºC. Used *N*-{3-(2-(*tert*-butyl)-5-(pyrimidin-4-yl)thiazol-4-yl)-2-fluorophenyl}-2,6-difluorobenzenesulfonamide (126 mg, 0.25 mmol), EtOAc (1.25 mL), Tf_2O (42 µL, 0.25 mmol), aniline (23 µL, 0.25 mmol), collidine (33 µL, 0.25 mmol), then EtOH (1.25 mL), piperidine (75 µL, 0.75 mmol), guanidine hydrochloride (71.6 mg, 0.75 mmol), and NaOEt (467 µL, 1.25 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:60:39 AcOH:EtOAc:hexanes) to provide the title compound as a white powder (84 mg, 0.16 mmol, 64% yield). mp 162-165 °C; IR ν_{max}/cm^{-1} (solid): 3467, 3366, 2964, 1612, 1573, 1459, 1356, 1165, 1010, 795, 633; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 5.3 Hz, 1H), 7.49 – 7.38 (m, 1H), 7.31 (ddd, *J* = 14.5, 8.5, 6.0 Hz, 1H), 7.21 – 7.11 (m, 1H), 7.10 – 6.98 (m, 1H), 6.79 (t, *J* = 9.0 Hz, 2H), 5.96 (d, *J* = 5.3 Hz, 1H), 5.30 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, one drop $(CD_3)_2SO$ added for solubility) δ 182.33, 162.81, 159.50 (dd, *J* = 257.7, 3.6 Hz), 158.80, 158.31, 152.33 (d, *J* = 250.5 Hz), 145.88, 134.74 (t, *J* = 11.0 Hz), 133.77, 128.47, 125.52, 124.84 – 124.54 (m, 2C), 124.27 (d, *J* = 14.3 Hz), 117.73 (t, *J* = 15.7 Hz), 112.93 (dd, *J* = 22.9, 3.7 Hz), 107.11, 37.86, 30.60; ^{19}F NMR (375 MHz, $CDCl_3$) δ -106.80 (dt, *J* = 9.9, 4.8 Hz, 2F), -128.81 (td, *J* = 7.0, 3.6 Hz, 1F); *m/z* HRMS (DART) found $[M+H]^+$ 520.1089, $C_{23}H_{21}F_3N_5O_2S_2^+$ requires 520.1083. Spectra matched literature values.

_N_-(3-(2-(*Tert*-butyl)-5-(2-cyclopropylpyrimidin-4-yl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide



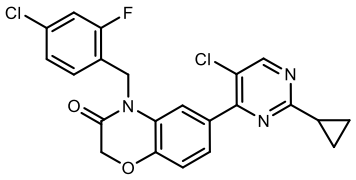
Prepared according to a modified general procedure J, heated to 70 ºC instead of 90 ºC. Used *N*-{3-(2-(*tert*-butyl)-5-(pyrimidin-4-yl)thiazol-4-yl)-2-fluorophenyl}-2,6-difluorobenzenesulfonamide (126 mg, 0.25 mmol), EtOAc (1.25 mL), Tf_2O (42 µL, 0.25 mmol), aniline (23 µL, 0.25 mmol), collidine (33 µL, 0.25 mmol), then EtOH (1.25 mL), piperidine (75 µL, 0.75 mmol), cyclopropanecarboximidamide hydrochloride (90.4 mg, 0.75 mmol), and NaOEt (467. µL, 1.25 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:40:59 AcOH:EtOAc:hexanes) to provide the title compound as a peach-colored powder (83 mg, 0.15 mmol, 61% yield). mp 213-216 °C; IR ν_{max}/cm^{-1} (solid): 2964, 2747, 1568, 1568, 1355, 1171, 1002, 792, 633; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.4 Hz, 1H), 7.72 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 (tt, *J* = 8.5, 5.9 Hz, 1H), 7.39 (s, 1H), 7.30 (ddd, *J* = 8.1, 6.5, 1.7 Hz, 1H), 7.24 – 7.18 (m, 1H), 6.97 (t, *J* = 8.7 Hz, 2H), 6.54 (d, *J* = 5.4 Hz, 1H), 2.19 (tt, *J* = 7.2, 5.7 Hz, 1H), 1.47 (d, *J* = 0.8 Hz, 9H), 1.07 – 0.98 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.38, 172.27, 159.76 (dd, *J* = 259.8, 3.4 Hz), 157.74, 156.78, 150.67 (d, *J* = 247.8 Hz), 146.02, 135.29 (t, *J* = 11.0 Hz), 133.88, 127.96 (d, *J* = 2.3 Hz), 125.29 (d, *J* = 4.5 Hz), 124.46 (dd, *J* = 54.7, 13.3 Hz), 122.73, 116.88, 113.33, 113.24, 113.08 (dd, *J* = 229.9, 3.6 Hz), 38.10, 30.72, 18.06, 10.95; ^{19}F NMR (375 MHz, $CDCl_3$) δ -106.86 (dt, *J* = 9.7, 4.5 Hz, 2F), -130.42 (tt, *J* = 7.1, 3.8 Hz, 1F); *m/z* HRMS (DART) found $[M+H]^+$ 545.1302, $C_{26}H_{24}F_3N_4O_2S_2^+$ requires 545.1287.

_N_-(3-(2-(*Tert*-butyl)-5-(2-(trifluoromethyl)pyrimidin-4-yl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide



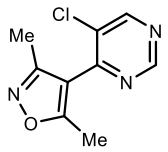
Prepared according to a modified general procedure J, heated to 70 ºC instead of 90 ºC. Used *N*-{3-(2-(*tert*-butyl)-5-(pyrimidin-4-yl)thiazol-4-yl)-2-fluorophenyl}-2,6-difluorobenzenesulfonamide (126 mg, 0.25 mmol), EtOAc (1.25 mL), Tf_2O (42 µL, 0.25 mmol), aniline (23 µL, 0.25 mmol), collidine (33 µL, 0.25 mmol), then EtOH (1.25 mL), piperidine (75 µL, 0.75 mmol), trifluoroacetamidine (85.0 mg, 0.75 mmol), and NaOEt (467 µL, 1.25 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes. A second column was needed (0.25:10:89.75 Et_3N:EtOAc:CH_2Cl_2)) to provide the title compound as a white powder (33 mg, 0.06 mmol, 23% yield). mp 207-211 °C; IR ν_{max}/cm^{-1} (solid): 3068, 2964, 2922, 1613, 1578, 1442, 1418, 1360, 1159, 1006, 816; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.78 (d, *J* = 5.4 Hz, 1H), 7.74 – 7.61 (m, 2H), 7.53 (ddd, *J* = 8.0, 6.4, 1.7 Hz, 1H), 7.36 (td, *J* = 7.9, 1.0 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.20 – 7.09 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 185.15, 160.43 (dd, *J* = 256.2, 3.9 Hz), 160.10, 159.92, 157.00 (d, *J* = 36.3 Hz), 153.46 (d, *J* = 250.0 Hz), 149.02, 136.52 (t, *J* = 11.2 Hz), 132.81, 129.56 (d, *J* = 2.3 Hz), 127.32, 126.44 (d, *J* = 13.1 Hz), 126.04 (d, *J* = 4.6 Hz), 124.77 (d, *J* = 13.7 Hz), 120.54 (q, *J* = 273.4 Hz), 119.85, 118.82 (t, *J* = 16.4 Hz), 114.08 (dd, *J* = 23.3, 3.7 Hz), 38.99, 30.82; ^{19}F NMR (375 MHz, $(CD_3)_2CO$) δ -71.12 (3F), -108.04 (ddd, *J* = 9.2, 6.0, 3.5 Hz, 2F), -126.37 (tt, *J* = 6.4, 3.0 Hz, 1F); *m/z* HRMS (DART) found $[M+H]^+$ 573.0858, $C_{24}H_{19}F_6N_4O_2S_2^+$ requires 573.0848.

6-(5-Chloro-2-cyclopropylpyrimidin-4-yl)-4-(4-chloro-2-fluorobenzyl)-2H-benzo[b][1,4]oxazin-3(4H)-one



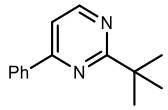
An oven dried 8 mL vial equipped with a stir bar was charged with 4-(4-(4-chloro-2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (119.2 mg, 0.20 mmol), and placed under a nitrogen atmosphere. Then EtOH (1.0 mL, 0.2M) and piperidine (60 µL, 0.60 mmol, 3 equiv) were added. The reaction was stirred for 60 minutes before trifluoroacetic acid (46 µL, 0.60 mmol, 3 equiv) and *N*-chlorosuccinimide (80.1 mg, 0.60 mmol, 3 equiv) was added. The reaction was stirred for an additional 30 minutes before cyclopropanecarboximidamide hydrochloride (72.3 mg, 0.60 mmol, 3 equiv) was added, followed by NaOEt (672 µL, 1.80 mmol, 9.0 equiv, 21% soln. in EtOH). The reaction was heated to 90 ºC for 18 hours. After cooling to room temperature, the reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The combined organic extract was washed (1x) with brine and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel: 0 to 35% EtOAc in hexanes. A second column was required (0 to 3% EtOAc in CH_2Cl_2)) to provide the pure title compound as a white solid (46 mg, 0.10 mmol, 52% yield). IRυ_{max}/cm^{-1} (film): 3088, 1676, 1530, 1389, 1279, 1060, 906, 824. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.62 (dd, J = 8.4, 2.0 Hz, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.20 – 6.83 (m, 4H), 5.22 (s, 2H), 4.80 (s, 2H), 2.23 (tt, J = 7.7, 5.1 Hz, 1H), 1.21 – 0.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.31, 164.57, 160.26 (d, J = 248.2 Hz), 160.07, 157.64, 146.94, 134.50 (d, J = 10.2 Hz), 130.90, 129.33 (d, J = 4.7 Hz), 127.97, 126.10, 125.23 (d, J = 3.6 Hz), 125.03, 121.46 (d, J = 14.2 Hz), 117.02, 116.80, 116.77, 116.56, 67.73, 38.28 (d, J = 4.7 Hz), 17.91, 11.26; ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.49 (dd, J = 9.8, 7.6 Hz). *m/z* HRMS (DART) found 444.0659, $[M+H]^+$ for $C_{22}H_{17}Cl_2FN_3O_2^+$ requires 444.0676

4-(5-Chloropyrimidin-4-yl)-3,5-dimethylisoxazole



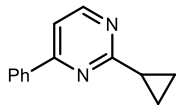
An oven dried 8 mL vial equipped with a stir bar was charged with 4-(3,5-dimethylisoxazol-4-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (160 mg, 0.40 mmol), and placed under a nitrogen atmosphere. Then EtOH (2.0 mL, 0.2 M) and piperidine (120 µL, 1.2 mmol, 3 equiv) were added. The reaction was stirred for 60 minutes before trifluoroacetic acid (88 µL, 1.2 mmol, 3 equiv) and *N*-chlorosuccinimide (160 mg, 1.2 mmol, 3 equiv) was added. The reaction was stirred for an additional 30 minutes before formamidine hydrochloride (96 mg, 1.2 mmol, 3 equiv) was added followed by NaOEt (1.34 mL, 3.6 mmol, 9.0 equiv, 21% soln. in EtOH). The reaction was heated to 90 ºC for 18 hours. After cooling to room temperature, the reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The combined organic extract was washed (1x) with brine and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel: 70% EtOAc in hexanes) to provide the pure title compound as a light orange solid (22 mg, 0.10 mmol, 40% yield). mp 85-87 °C. IRυ_{max}/cm^{-1} (film): 2970, 2323, 2184, 1979, 1729, 1391, 1066, 788, 561. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.76 (s, 1H), 2.37 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.96, 158.91, 157.38, 156.41, 156.13, 130.38, 112.73, 12.82, 10.88. *m/z* HRMS (ESI) found 210.0430, $[M+H]^+$ for $C_9H_8ClN_3O^+$ requires 210.0434.

2-(*Tert*-butyl)-4-phenylpyrimidine



Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), 2,2-dimethylpropanimidamide hydrochloride (164 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 2.5% EtOAc in hexanes) to provide the title compound as a clear oil (55.6 mg, 0.26 mmol, 66% yield). mp 32-34 °C; IR ν_{max}/cm^{-1} (solid): 2975, 2952, 1566, 1544, 1448, 1362, 1177, 768, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 5.2 Hz, 1H), 8.27 – 7.79 (m, 2H), 7.70 – 7.09 (m, 4H), 1.50 (d, *J* = 1.5 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.38, 162.99, 157.21, 137.30, 130.72, 128.87, 127.13, 113.32, 39.64, 29.70; *m/z* HRMS (DART) found $[M+H]^+$ 213.1394, $C_{14}H_{17}N_2^+$ requires 213.1386.

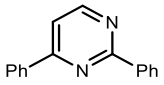
2-Cyclopropyl-4-phenylpyrimidine



Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), cyclopropanecarboximidamide hydrochloride (145 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 0-10% EtOAc in hexanes) to provide the title compound as a pale-yellow oil (55 mg, 0.28 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 3007, 1568, 1546, 1359, 1262, 916, 836, 763, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.3 Hz, 1H), 8.06 (dd, *J* = 6.8, 3.0 Hz, 2H), 7.47 (d, *J* = 3.2 Hz, 3H), 7.40 (d, *J* = 5.3 Hz, 1H), 2.32 (tt, *J* = 8.1, 4.7 Hz, 1H), 1.22 (dt, *J* = 4.7, 3.2 Hz, 2H), 1.17 – 0.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.13, 163.46, 157.28, 137.02, 130.73, 128.85,

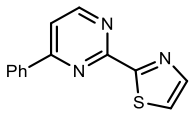
127.08, 113.43, 18.40, 10.76; *m/z* HRMS (DART) found $[M+H]^+$ 197.1119, $C_{13}H_{13}N_2^+$ requires 197.1073. Spectra matched literature values.

2,4-Diphenylpyrimidine



Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), benzamidine hydrochloride (188 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 0-5% EtOAc in hexanes) to provide the title compound as a white solid (48 mg, 0.21 mmol, 52% yield). mp 70-72 °C; IR ν_{max}/cm^{-1} (solid): 3065, 3034, 1541, 1423, 1379, 745, 687; ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 5.3 Hz, 1H), 8.67 – 8.50 (m, 2H), 8.32 – 8.11 (m, 2H), 7.60 (d, *J* = 5.3 Hz, 1H), 7.57 – 7.51 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.61, 163.86, 157.88, 137.93, 136.99, 131.00, 130.76, 128.97, 128.59, 128.35, 127.24, 114.54; *m/z* HRMS (DART) found $[M+H]^+$ 223.1145, $C_{16}H_{13}N_2^+$ requires 233.1073. Spectra matched literature values.

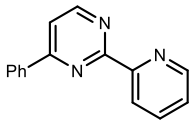
2-(4-Phenylpyrimidin-2-yl)thiazole



Prepared according to a modified general procedure H heating to 60 ºC instead of 90 ºC. 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), thiazole-2-carboximidamide hydrochloride (196 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:70:29 AcOH:EtOAc:hexanes) to provide the title compound as a pale-brown solid (69 mg, 0.29 mmol, 72% yield). mp 88-92 °C; IR ν_{max}/cm^{-1} (solid): 3075, 1570,

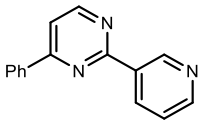
1500, 1430, 1309, 1110, 760, 692, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 5.2 Hz, 1H), 8.19 (dd, *J* = 6.7, 3.1 Hz, 1H), 8.06 (d, *J* = 3.1 Hz, 1H), 7.67 (d, *J* = 5.3 Hz, 1H), 7.60 – 7.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.28, 164.51, 159.64, 158.35, 145.12, 135.79, 131.44, 129.01, 127.32, 123.04, 116.13; *m/z* HRMS (DART) found $[M+H]^+$ 240.0616, $C_{13}H_{10}N_3S^+$ requires 240.0590. Spectra matched literature values.

4-Phenyl-2-(pyridin-2-yl)pyrimidine



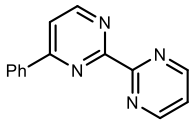
Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), picolinimidamide hydrochloride (189 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:70:29 Et_3N:EtOAc:hexanes followed by 1:75:24 Et_3N:EtOAc:EtOH) to provide the title compound as a brown oil (62 mg, 0.26 mmol, 66% yield). IR ν_{max}/cm^{-1} (film): 3059, 1560, 1543, 1420, 1382, 753, 691, 627; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 5.2 Hz, 1H), 8.85 – 8.75 (m, 1H), 8.61 (d, *J* = 8.0 Hz, 1H), 8.29 – 7.94 (m, 2H), 7.82 (td, *J* = 7.7, 1.8 Hz, 1H), 7.63 (d, *J* = 5.3 Hz, 1H), 7.54 – 7.32 (m, 3H), 7.35 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.21, 163.61, 158.51, 155.01, 150.06, 136.85, 136.56, 131.11, 128.96, 127.27, 124.86, 123.66, 115.80; *m/z* HRMS (DART) found $[M+H]^+$ 234.1081, $C_{15}H_{12}N_3^+$ requires 234.1026. Spectra matched literature values.

4-Phenyl-2-(pyridin-3-yl)pyrimidine



Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), 3-amidinopyridine hydrochloride (189. mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 30-50% EtOAc in hexanes) to provide the title compound as a pink powder (68 mg, 0.29 mmol, 72% yield). mp 89-91 °C; IR ν_{max}/cm^{-1} (solid): 3040, 2921, 1580, 1559, 1543, 1369, 1189, 1020, 758, 685, 614; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.84 – 8.73 (m, 2H), 8.70 (d, *J* = 4.8 Hz, 1H), 8.19 – 8.02 (m, 2H), 7.56 (d, *J* = 5.4 Hz, 1H), 7.53 – 7.43 (m, 3H), 7.38 (dd, *J* = 8.0, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.95, 162.80, 157.95, 151.35, 150.02, 136.44, 135.51, 133.31, 131.22, 129.00, 127.16, 123.33, 115.07; *m/z* HRMS (DART) found $[M+H]^+$ 234.1019, $C_{15}H_{12}N_3^+$ requires 234.1026. Spectra matched literature values.

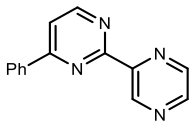
4-Phenyl-2,2'-bipyrimidine



Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), 2-amidinopyrimidine hydrochloride (190 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:70:29 Et_3N:EtOAc:hexanes followed by 1:75:24 Et_3N:EtOAc:EtOH) to provide the title compound as a yellow solid (50 mg, 0.21 mmol, 53% yield). mp 122-125 °C; IR ν_{max}/cm^{-1} (solid): 3073, 2923, 1556, 1419, 1376, 828, 760, 692, 632; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 4.9 Hz, 3H), 8.18 – 8.08 (m, 2H), 7.73 (d, *J* = 5.2 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.35 (t, *J* = 4.8 Hz, 1H); ^{13}C

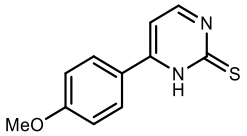
NMR (100 MHz, $CDCl_3$) δ 165.37, 162.92, 162.73, 158.39, 157.97, 136.41, 131.18, 128.98, 127.56, 121.30, 117.12; *m/z* HRMS (ESI) found $[M+H]^+$ 235.0981, $C_{14}H_{11}N_4^+$ requires 235.0983.

4-Phenyl-2-(pyrazin-2-yl)pyrimidine



Prepared according to general procedure H using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), pyrazine-2-carboximidamide hydrochloride (190 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 1:49:50 Et_3N:EtOAc:hexanes followed by 1:75:24 Et_3N:EtOAc:hexanes) to provide the title compound as a pale yellow solid (78 mg, 0.33 mmol, 83% yield). mp 97-99 °C; IR ν_{max}/cm^{-1} (solid): 3056, 1578, 1563, 1541, 1451, 1367, 1323, 1142, 1015, 767, 687; ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (d, *J* = 1.5 Hz, 1H), 9.00 (d, *J* = 5.3 Hz, 1H), 8.87 – 8.75 (m, 1H), 8.72 (s, 1H), 8.39 – 8.01 (m, 2H), 7.78 (d, *J* = 5.3 Hz, 1H), 7.67 – 7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.31, 162.03, 158.56, 150.14, 145.53, 145.43, 144.34, 135.99, 131.36, 129.01, 127.22, 116.28; *m/z* HRMS (DART) found $[M+H]^+$ 235.0996, $C_{14}H_{11}N_4^+$ requires 235.0978.

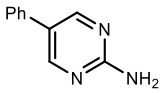
6-(4-Methoxyphenyl)pyrimidine-2(1H)-thione



Prepared according to a modified general procedure H using 4-(4-methoxyphenyl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (165 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), thiourea (91.3 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). Upon completion, AcOH (200 µL, 3.50 mmol) was added to the reaction mixture

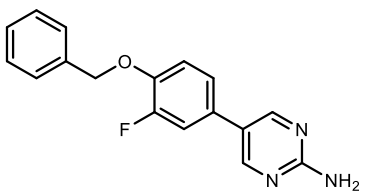
at room temperature. The product was filtered and washed with ice-cold EtOH to provide the title compound as a yellow solid (49 mg, 0.23 mmol, 56% yield). mp 219-225 °C; IR ν_{max}/cm^{-1} (solid): 2889, 1583, 1436, 1264, 1157, 1024, 794; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 13.52 (s, 1H), 8.26 – 8.09 (m, 2H), 8.00 (d, *J* = 6.6 Hz, 1H), 7.38 (d, *J* = 6.7 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 181.14, 165.65, 163.30, 146.85, 130.47, 127.80, 114.90, 105.31, 56.00; *m/z* HRMS (DART) found $[M+H]^+$ 219.0596, $C_{11}H_{11}N_2OS^+$ requires 219.0587.

5-Phenylpyrimidin-2-amine



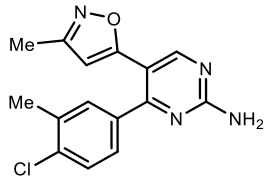
Prepared according to general procedure J using 5-phenylpyrimidine (62.5 mg, 0.40 mmol), Tf_2O (67 μL, 0.40 mmol), *para*-nitro (*p*-NO_2) aniline (56 mg, 0.40 mmol), collidine (53 μL, 0.40 mmol), EtOAc (2 mL), piperidine (118 μL, 1.20 mmol), EtOH (2 mL), guanidine hydrochloride (764 mg, 8.00 mmol), and NaOEt (747 μL, 2.00 mmol, as a 21% soln. in EtOH). The residue was purified by flash chromatography (silica gel: 1:55:44 AcOH:EtOAc:hexanes) to provide the pure title compound as an off-white solid (35 mg, 0.21 mmol, 51% yield). mp 161-164 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 2H), 7.51 – 7.40 (m, 4H), 7.35 (t, *J* = 7.0 Hz, 1H), 5.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.39, 156.50, 135.30, 129.17, 127.57, 126.05, 124.89; m/z HRMS (ESI) found $[M+H]^+$ 172.0869, $C_{10}H_{10}N_3^+$ requires 172.0869. Spectra matched literature values.

5-(4-(Benzyloxy)-3-fluorophenyl)pyrimidin-2-amine



Prepared according to a modified general procedure J using 5-(4-(benzyloxy)-3-fluorophenyl)pyrimidine (112 mg, 0.400 mmol), Tf_2O (67 µL, 0.40 mmol), *p*-NO_2 aniline (56 mg, 0.40 mmol), collidine (53 µL, 0.40 mmol), EtOAc (2 mL), piperidine (118 µL, 1.20 mmol), EtOH (2 mL), guanidine hydrochloride (472 mg, 8.00 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The residue was purified by flash chromatography (silica gel: 60% EtOAc in hexanes) to provide the pure title compound as an off-white solid (53 mg, 0.18 mmol, 45% yield). mp 78-80 °C. IRυ_{max}/cm^{-1} (solid): 3318, 3183, 1615, 1555, 1471, 1091, 820, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 2H), 7.43 – 7.35 (m, 2H), 7.35 – 7.29 (m, 2H), 7.29 – 7.23 (m, 1H), 7.21 – 7.09 (m, 1H), 7.05 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.98 (t, *J* = 8.4 Hz, 1H), 5.23 (s, 2H), 5.10 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.08, 156.18, 154.47, 152.01, 146.30 (d, *J* = 10.9 Hz), 136.33, 128.69, 128.23, 127.44, 123.81 (d, *J* = 2.2 Hz), 121.72 (d, *J* = 3.6 Hz), 116.38 (d, *J* = 2.5 Hz), 114.04 (d, *J* = 19.3 Hz), 71.51. ^{19}F NMR (375 MHz, $CDCl_3$) δ -132.44 (dd, *J* = 11.8, 8.3 Hz). *m/z* HRMS (DART) found $[M+H]^+$ 296.1198, $C_{17}H_{14}FN_3O^+$ requires 296.1199.

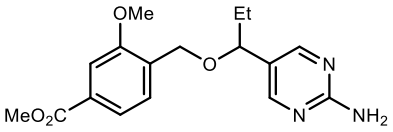
4-(4-Chloro-3-methylphenyl)-5-(3-methylisoxazol-5-yl)pyrimidin-2-amine



Prepared according to general procedure H using 4-(4-chloro-3-methylphenyl)-5-(3-methylisoxazol-5-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (205 mg, 0.40 mmol), piperidine (118 µL, 1.20 mmol), EtOH (2 mL), guanidine hydrochloride (71.0 mg, 1.20 mmol), and NaOEt (747 µL, 2.00 mmol, as a 21% soln. in EtOH). The residue was purified by flash chromatography (silica gel: 60% EtOAc in hexanes. A second column was needed (70% EtOAc in hexanes)) to provide the pure title compound as a light-yellow solid (69 mg, 0.23 mmol, 58% yield). mp 181-183 °C. IRυ_{max}/cm^{-1} (solid): 3361, 3148, 1660, 1577, 1476, 1045, 820, 739. ^{1}H

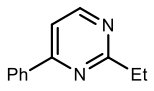
NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 10.5 Hz, 1H), 5.74 (s, 2H), 5.53 (s, 1H), 2.31 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.01, 164.89, 162.71, 159.97, 158.91, 136.63, 136.28, 135.96, 130.81, 129.16, 127.10, 111.12, 103.15, 20.09, 11.46. *m/z* HRMS (ESI) found $[M+H]^+$ 301.0861, $C_{20}H_{15}ClN_4O^+$ requires 301.0778.

Methyl 4-((1-(2-aminopyrimidin-5-yl)propoxy)methyl)-3-methoxybenzoate



Prepared according to a modified general procedure J using methyl 3-methoxy-4-((1-(pyrimidin-5-yl)propoxy)methyl)benzoate (63.3 mg, 0.20 mmol), Tf_2O (34 μL, 0.20 mmol), *p*-NO_2-aniline (27.6 mg, 0.20 mmol), collidine (26 μL, 0.20 mmol), EtOAc (1 mL), then piperidine (60 μL, 0.60 mmol), MeOH (1 mL), guanidine hydrochloride (382 mg, 4.00 mmol), and NaOMe (54.0 mg, 1.00 mmol). The residue was purified by flash chromatography (silica gel: 1:70:29 AcOH:EtOAc:hexanes). A second column was needed (70 to 100% EtOAc in hexanes) to provide the pure title compound as a white solid (17 mg, 0.05 mmol, 26% yield). mp 124-128 °C; IR ν_{max}/cm^{-1} (film): 3319, 3172, 2967, 1717, 1283, 1228, 1077, 761; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.51 – 7.44 (m, 2H), 5.25 (s, 2H), 4.58 – 4.33 (m, 2H), 4.12 (t, J = 6.8 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 1.92 (dp, J = 14.5, 7.3 Hz, 1H), 1.70 (dp, J = 14.1, 7.2 Hz, 1H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.13, 162.99, 157.53, 156.74, 132.18, 130.47, 128.25, 124.85, 122.11, 110.81, 79.56, 65.37, 55.52, 52.29, 30.68, 10.22; *m/z* HRMS (ESI) found $[M+H]^+$ 332.1609, $C_{17}H_{22}N_3O_4^+$ requires 332.1605.

2-Ethyl-4-phenylpyrimidine



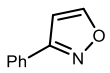
Prepared according to general procedure B using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 μL, 1.20 mmol), propionimidamide hydrochloride (130 mg, 1.20 mmol), and NaOEt (747 μL, 2.00 mmol, as a 21% soln. in EtOH). The crude material was purified by flash chromatography (silica gel: 25% EtOAc in hexanes) to provide the title compound as a clear oil (52 mg, 0.28 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 2972, 1569, 1546, 1432, 840, 764, 690, 627; ^{1}H NMR (400 MHz, $CDCl_3$ δ 8.66 (d, *J* = 5.3 Hz, 1H), 8.11 – 8.05 (m, 2H), 7.79 – 6.76 (m, 4H), 3.05 (q, *J* = 7.6 Hz, 2H), 1.43 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.38, 163.87, 157.50, 137.08, 130.77, 128.92, 127.17, 113.95, 32.85, 12.68; *m/z* HRMS (ESI) found $[M+H]^+$ 185.1078, $C_{12}H_{13}N_2^+$ requires 185.1078.

3-Phenylisoxazole and 5-phenylisoxazole



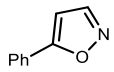
Prepared according to general procedure I using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 μL, 1.20 mmol), hydroxylamine hydrochloride (139 mg, 1.20 mmol), and concentrated aqueous HCl (333 μL, 4.00 mmol). Crude NMR showed 22% of 3-phenyl and 53% of 5-phenyl isoxazole relative to triphenylmethane internal standard. The crude material was purified by flash chromatography (silica gel: 10% hexanes in toluene) to provide pure regioisomers.

3-Phenylisoxazole



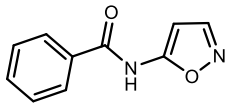
Clear oil (6.00 mg, 0.04 mmol, 10%). IR ν_{max}/cm^{-1} (film): 3124, 3063, 2927, 1552, 1457, 1395, 1123, 878, 762, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 1.7 Hz, 1H), 7.94 – 7.73 (m, 2H), 7.53 – 7.40 (m, 3H), 6.67 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.54, 158.89, 130.06, 128.97, 128.83, 126.93, 102.47. Spectra matched literature values.

5-Phenylisoxazole



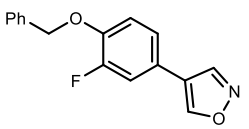
Clear oil (30 mg, 0.21 mmol, 52%). IR ν_{max}/cm^{-1} (film): 3062, 1571, 1458, 1197, 817, 794, 761, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.9 Hz, 1H), 7.84 – 7.71 (m, 2H), 7.49 – 7.37 (m, 3H), 6.51 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.45, 150.92, 130.29, 129.09, 127.36, 125.95, 98.75. Spectra matched literature values.

N-(Isoxazol-5-yl)benzamide



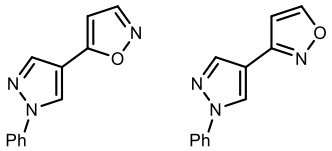
Prepared according to a modified general procedure I using 4-benzamido-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (170 mg, 0.40 mmol), EtOH (2.00 mL), piperidine (119 µL, 1.20 mmol), hydroxylamine hydrochloride (83.4 mg, 1.20 mmol), and concentrated aqueous HCl (333 µL, 4.00 mmol) at 40 °C. The crude material was purified by flash chromatography (silica gel: 0-35% EtOAc in hexanes) to provide the title compound as a white solid (46 mg, 0.25 mmol, 61% yield). mp 134-137 °C; IR ν_{max}/cm^{-1} (solid): 3243, 3216, 3130, 3054, 3006, 1687, 1527, 1499, 1272, 773, 686; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.16 (d, *J* = 1.9 Hz, 1H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.61, 160.71, 152.00, 132.98, 132.42, 128.96, 127.61, 88.59; *m/z* HRMS (DART) found $[M+H]^+$ 189.0667, $C_{10}H_9N_2O_2^+$ requires 189.0659.

4-(4-(Benzyloxy)-3-fluorophenyl)isoxazole



Prepared according to a modified general procedure K using 5-(4-(benzyloxy)-3-fluorophenyl)pyrimidine (112 mg, 0.40 mmol), Tf_2O (67 μL, 0.40 mmol), *p*-NO_2 aniline (56.0 mg, 0.40 mmol), collidine (53 μL, 0.40 mmol), EtOAc (2 mL), piperidine (118 μL, 1.20 mmol), EtOH (2 mL), hydroxylamine hydrochloride (559 mg, 8.00 mmol), and concentrated HCl (333 μL, 4.00 mmol). The residue was purified by flash chromatography (silica gel: 80% EtOAc in hexanes. A second column was needed (15% EtOAc in hexanes)) to provide the pure title compound as a yellow solid (43 mg, 0.16 mmol, 40% yield). mp 102-104 °C. IRυ_{max}/cm^{-1} (solid): 1603, 1513, 1283, 1262, 1114, 986, 811, 753, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.40 (s, 1H), 7.40 – 7.34 (m, 2H), 7.34 – 7.29 (m, 2H), 7.29 – 7.23 (m, 1H), 7.19 – 7.10 (m, 1H), 7.09 – 7.02 (m, 1H), 6.95 (t, *J* = 8.5 Hz, 1H), 5.09 (s, 2H). ^{19}F NMR (375 MHz, $CDCl_3$) δ -132.36 (dd, *J* = 11.8, 8.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.31, 153.07, 151.85, 147.83, 146.53 (d, *J* = 10.7 Hz), 136.20, 128.71, 128.28, 127.45, 122.30 (d, *J* = 3.6 Hz), 116.31 (d, *J* = 2.4 Hz), 114.68, 114.49, 71.46. *m/z* HRMS (DART) found $[M+H]^+$ 270.2727, $C_{16}H_{12}FNO_2^+$ requires 270.2754.

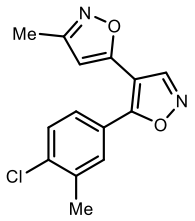
5-(1-Phenyl-1H-pyrazol-4-yl)isoxazole and 3-(1-phenyl-1H-pyrazol-4-yl)isoxazole



Prepared according to general procedure K using 4-(1-phenyl-1H-pyrazol-4-yl)pyrimidine (88.9 mg, 0.40 mmol), EtOAc (2 mL), Tf_2O (67 μL, 0.40 mmol), aniline (36 μL, 0.40 mmol), collidine (53 μL, 0.40 mmol), then EtOH (2 mL), hydroxylamine hydrochloride (139 mg, 2.00 mmol), and concentrated aqueous HCl (333 μL, 10.0 mmol). The crude material was purified by flash chromatography (silica gel: 1:29:70 AcOH:EtOAc:hexanes) to provide the title compounds as a 1:3 mixture of 3-(1-phenyl-1H-pyrazol-4-yl)isoxazole: 5-(1-phenyl-1H-pyrazol-4-yl)isoxazole (tan solid, 44 mg, 0.21 mmol, 52% yield). mp 131-134°C; IR ν_{max}/cm^{-1} (solid): 3111, 3055, 1633,

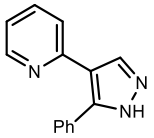
1598, 1501, 1471, 1374, 1214, 1203, 955, 865, 749, 688; *m/z* HRMS (DART) found $[M+H]^+$ 212.0827, $C_{12}H_{10}N_3O^+$ requires 212.0818.

4-(4-Chloro-3-methylphenyl)-3'-methyl-3,5'-biisoxazole



Prepared according to general procedure I using 4-(4-chloro-3-methylphenyl)-5-(3-methylisoxazol-5-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (205 mg, 0.40 mmol), piperidine (118 μL, 1.20 mmol), EtOH (2 mL), hydroxylamine hydrochloride (83.0 mg, 1.20 mmol), and concentrated HCl (333 μL, 4.00 mmol). The residue was purified by flash chromatography (silica gel: 80% dichloromethane in hexanes) to provide the pure title compound as a tan solid (80 mg, 0.30 mmol, 73% yield). mp 69-72 °C. IRυ_{max}/cm^{-1} (solid): 2922, 1650, 1416, 1152, 1045, 922, 781, 674. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.62 (s, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 6.16 (s, 1H), 2.38 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.64, 159.55, 159.24, 149.04, 136.59, 136.14, 129.17, 128.70, 125.47, 123.89, 103.80, 101.72, 19.12, 10.38. *m/z* HRMS (DART) found $[M+H]^+$ 275.7075; $C_{14}H_{11}ClN_2O_2^+$ requires 275.7040.

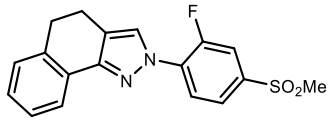
2-(5-Phenyl-1H-pyrazol-4-yl)pyridine



Prepared according to general procedure I using 1,4-diphenyl-5-(pyridin-2-yl)pyrimidin-1-ium trifluoromethanesulfonate (184 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 μL, 1.20 mmol), hydrazine hydrate (58 μL, 1.20 mmol), and concentrated aqueous HCl (333 μL, 4.00 mmol). The

crude material was purified by flash chromatography (silica gel: 50-100% EtOAc in hexanes) to provide the title compound as a white solid (80 mg, 0.36 mmol, 90% yield). IR ν_{max}/cm^{-1} (film): 3139, 2919, 1590, 1509, 1429, 768, 726, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 – 8.48 (m, 1H), 7.92 (s, 1H), 7.47 (qd, *J* = 3.9, 1.8 Hz, 3H), 7.34 – 7.23 (m, 3H), 7.14 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.11 – 7.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.72, 149.51, 145.55, 136.23, 135.15, 131.71, 128.72, 128.62, 128.47, 122.52, 121.21, 119.71; *m/z* HRMS (DART) found $[M+H]^+$ 222.1049, $C_{14}H_{12}N_3^+$ requires 222.1026.

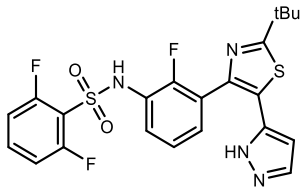
1-(3-Fluoro-4-(methylsulfonyl)phenyl)-4,5-dihydro-1H-benzo[g]indazole



Prepared according to general procedure I using 3-phenyl-5,6-dihydrobenzo[h]quinazolin-3-ium trifluoromethanesulfonate (163 mg, 0.40 mmol), piperidine (118 μL, 1.20 mmol), EtOH (2 mL), (3-fluoro-4-(methylsulfonyl)phenyl)hydrazine (245 mg, 0.40 mmol), and concentrated HCl (333 μL, 4.00 mmol). The residue was purified by flash chromatography (silica gel: 30% EtOAc in hexanes. A second column was needed (29:70:1 EtOAc:hexanes:NEt_3)) to provide the pure title compound as an orange solid (56. mg, 0.16 mmol, 41% yield). mp 145-146 °C. IRυ_{max}/cm^{-1} (solid): 3359, 2921, 1515, 1414, 1312, 1233, 1140, 760, 607. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.75 (dt, *J* = 8.4, 6.9 Hz, 2H), 7.59 (s, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.12 (dd, *J* = 15.0, 1.4 Hz, 1H), 6.98 (td, *J* = 7.6, 1.5 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 3.07 (s, 3H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.71 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.55, 154.96, 141.78 (d, *J* = 5.9 Hz), 139.76, 137.19, 133.98 (d, *J* = 11.9 Hz), 129.79, 128.90, 128.13, 126.77, 126.27, 124.11 (d, *J* = 4.3 Hz), 121.42, 120.39, 116.77 (d, *J* = 22.9 Hz), 44.48, 30.33, 19.69. ^{19}F

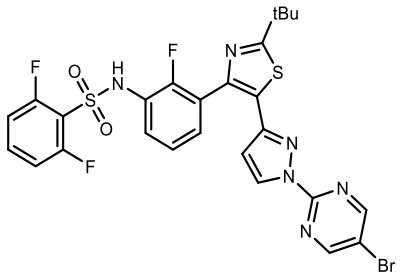
NMR (375 MHz, $CDCl_3$) δ -115.70. *m/z* HRMS (ESI) found $[M+H]^+$ 343.0920, $C_{18}H_{15}FN_2O_2S^+$ requires 343.0916.

_N_-(3-(2-(*Tert*-butyl)-5-(1H-pyrazol-5-yl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide



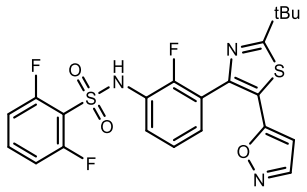
Prepared according to general procedure I using 4-(2-(*tert*-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (183 mg, 0.25 mmol), EtOH (1.25 mL), piperidine (75 µL, 0.75 mmol), hydrazine hydrate (36 µL, 0.75 mmol), and concentrated aqueous HCl (208 µL, 1.25 mmol). The crude material was purified by flash chromatography (silica gel: 55% EtOAc in hexanes) to provide the title compound as a white solid (106 mg, 0.22 mmol, 86% yield). mp 211-214 °C; ; IR ν_{max}/cm^{-1} (solid): 3246, 3154, 2934, 1614, 1589, 1470, 1356, 1185, 1005, 788, 758; ^1H NMR (400 MHz, CD_3CN) δ 11.10 (s, 1H), 8.37 (s, 1H), 7.65 – 7.51 (m, 2H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.28 (ddd, *J* = 8.2, 6.4, 1.9 Hz, 1H), 7.21 (td, *J* = 7.8, 0.9 Hz, 1H), 7.07 (t, *J* = 8.8 Hz, 2H), 5.55 (d, *J* = 2.4 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN) δ 179.82, 160.45 (dd, *J* = 257.7, 3.8 Hz), 154.00 (d, *J* = 248.7 Hz), 143.33, 136.92 (t, *J* = 11.3 Hz), 131.07 (br), 130.66 (d, *J* = 2.8 Hz), 129.14, 127.01, 125.76 (d, *J* = 14.9 Hz), 125.53 (d, *J* = 4.7 Hz), 124.84 (d, *J* = 13.5 Hz), 117.75 (t, *J* = 15.9 Hz), 114.17 (dd, *J* = 23.1, 3.6 Hz), 103.31, 79.10, 38.41, 30.91; ^{19}F NMR (375 MHz, CD_3CN) δ -108.50 (d, *J* = 5.6 Hz, 2F), -127.69 (1F); *m/z* HRMS (DART) found $[M+H]^+$ 493.1028, $C_{22}H_{20}F_3N_4O_2S_2^+$ requires 493.0974.

***N*-(3-(5-(1-(5-Bromopyrimidin-2-yl)-1H-pyrazol-3-yl)-2-(*tert*-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide**



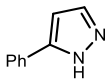
Prepared according to general procedure I using 4-(2-(*tert*-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (183 mg, 0.25 mmol), EtOH (1.25 mL), piperidine (75 µL, 0.75 mmol), 5-bromo-2-hydrazinopyrimidine (142 mg, 0.75 mmol), and concentrated aqueous HCl (208 µL, 1.25 mmol). The crude material was purified by flash chromatography (1:49:50 AcOH: EtOAc: hexanes) followed by a preparative TLC (2% MeOH in dichloromethane) to provide the title compound as a white fluffy solid (77 mg, 0.12 mmol, 47% yield). mp 215-221 °C; IR ν_{max}/cm^{-1} (solid): 3069, 2957, 1613, 1518, 1420, 1171, 1004, 784, 634; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 2H), 7.72 (d, *J* = 1.7 Hz, 1H), 7.49 (dddd, *J* = 10.2, 8.4, 6.6, 2.3 Hz, 2H), 7.17 (s, 1H), 7.05 – 6.88 (m, 4H), 6.40 (d, *J* = 1.7 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.78, 159.74 (dd, *J* = 258.2, 3.5 Hz), 158.86, 158.57, 154.84, 150.05 (d, *J* = 248.9 Hz), 146.00 (d, *J* = 1.9 Hz), 142.32, 135.16 (t, *J* = 11.1 Hz), 134.53 (d, *J* = 1.4 Hz), 127.55 (d, *J* = 2.8 Hz), 124.59 (d, *J* = 12.5 Hz), 124.47 (d, *J* = 4.5 Hz), 123.14 (d, *J* = 13.2 Hz), 121.09, 117.37, 116.79 (t, *J* = 15.2 Hz), 113.19 (dd, *J* = 23.1, 3.7 Hz), 112.59, 38.01, 30.81; ^{19}F NMR (375 MHz, $CDCl_3$) δ -106.92 – -107.03 (m, 2F), -132.07 (tt, *J* = 7.0, 3.6 Hz, 1F); *m/z* HRMS (DART) found $[M+H]^+$ 649.0300, $C_{26}H_{21}BrF_3N_6O_2S_2^+$ requires 649.029

_N_-(3-(2-(*Tert*-butyl)-5-(isoxazol-5-yl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide



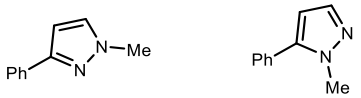
Prepared according to general procedure I using 4-(2-(*tert*-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (183 mg, 0.25 mmol), EtOH (1.25 mL), piperidine (75 µL, 0.75 mmol), hydroxylamine hydrochloride (52.1 mg, 0.75 mmol), and concentrated aqueous HCl (208 µL, 1.25 mmol). The crude material was purified by flash chromatography (silica gel: 35% EtOAc in hexanes) to provide the title compound as a 16:1 mixture of regioisomers (88 mg, 0.18 mmol, 70% yield). Reported spectra are of major isomer. mp 144-147 °C; IR ν_{max}/cm^{-1} (solid): 3081, 1609, 1584, 1461, 1365, 1170, 1004, 792, 634; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 1.9 Hz, 1H), 7.70 (td, *J* = 7.8, 1.7 Hz, 1H), 7.50 (tt, *J* = 8.5, 5.9 Hz, 1H), 7.30 (ddd, *J* = 8.1, 6.5, 1.8 Hz, 1H), 7.19 (td, *J* = 8.0, 1.0 Hz, 1H), 6.99 (t, *J* = 8.7 Hz, 2H), 5.80 (d, *J* = 1.9 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.82, 159.83 (dd, *J* = 259.8, 3.5 Hz), 159.02, 151.00 (d, *J* = 247.5 Hz), 150.70, 146.01, 135.41 (t, *J* = 11.1 Hz), 128.15 (d, *J* = 2.5 Hz), 125.13 (d, *J* = 4.5 Hz), 124.76 (d, *J* = 12.5 Hz), 123.23 (d, *J* = 13.5 Hz), 123.14, 120.59, 116.94 (t, *J* = 15.3 Hz), 113.31 (dd, *J* = 23.2, 3.6 Hz), 100.42, 38.24, 30.79; ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.87 (2F), -130.10 (1F); *m/z* HRMS (DART) found $[M+H]^+$ 494.0826, $C_{22}H_{19}F_3N_3O_3S_2^+$ requires 494.0814.

5-Phenyl-1H-pyrazole



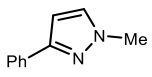
Prepared according to general procedure I using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.400 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), hydrazine hydrate (53 µL, 1.20 mmol), and concentrated aqueous HCl (333 µL, 4.00 mmol). The crude material was purified by flash chromatography (silica gel: 1:50:49 Et_3N:EtOAc:hexanes) to provide the title compound as a white powder (50 mg, 0.35 mmol, 86% yield). mp 72-74 °C; IR ν_{max}/cm^{-1} (solid): 3105, 3065, 2957, 2847, 1498, 1469, 1444, 1095, 958, 826, 755, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 12.06 (s, 1H), 7.77 (d, *J* = 7.0 Hz, 2H), 7.61 (d, *J* = 2.2 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.37 – 7.29 (m, 1H), 6.62 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.22, 133.25, 132.21, 128.81, 128.06, 125.89, 102.68; *m/z* HRMS (DART) found $[M+H]^+$ 145.0799, $C_9H_9N_2^+$ requires 145.0760. Spectra matched literature values.

1-Methyl-3-phenyl-1H-pyrazole and 1-methyl-5-phenyl-1H-pyrazole



Prepared according to general procedure I using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), methylhydrazine (63 µL, 1.20 mmol), and concentrated aqueous HCl (333 µL, 4.00 mmol). Crude NMR showed 30% of 3-phenyl- and 52% of 5-phenyl-1-methyl-1H-pyrazole relative to triphenylmethane internal standard. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in toluene) to provide pure regioisomers.

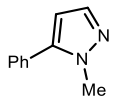
1-Methyl-3-phenyl-1H-pyrazole



Yellow solid (12 mg, 0.07 mmol, 19%). mp 45-57 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.32 – 7.27 (m, 1H), 6.54

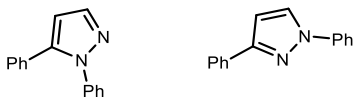
(d, J = 2.3 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.61, 133.56, 131.37, 128.62, 127.55, 125.54, 102.85, 39.05. Spectra matched literature values.

1-Methyl-5-phenyl-1H-pyrazole



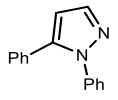
Yellow oil (23 mg, 0.15 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 1.9 Hz, 1H), 7.48 – 7.34 (m, 5H), 6.30 (d, J = 1.9 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.58, 138.53, 130.79, 128.77, 128.68, 128.43, 106.05, 37.49. Spectra matched literature values.

1,5-Diphenyl-1H-pyrazole and 1,3-diphenyl-1H-pyrazole



Prepared according to general procedure I using 1,4-diphenylpyrimidin-1-ium trifluoromethanesulfonate (153 mg, 0.40 mmol), EtOH (2 mL), piperidine (119 µL, 1.20 mmol), phenylhydrazine (118 µL, 1.20 mmol), and concentrated aqueous HCl (333 µL, 4.00 mmol). The crude material was purified by flash chromatography (silica gel: 0-10% EtOAc in toluene) to provide pure regioisomers.

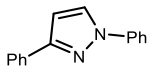
1,5-Diphenyl-1H-pyrazole



Orange solid (27 mg, 0.12 mmol, 30%). mp 79-82 °C IR ν_{max}/cm^{-1} (solid): 3061, 2922, 1598, 1504, 1359, 1045, 954, 749, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 2.5 Hz, 1H), 7.95 – 7.89 (m, 2H), 7.78 (dt, J = 7.8, 1.2 Hz, 2H), 7.51 – 7.40 (m, 4H), 7.37 – 7.32 (m, 1H), 7.32 – 7.27 (m, 1H), 6.79 (d, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.94, 140.26, 133.14, 129.43,

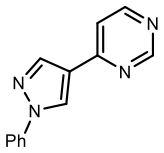
128.66, 128.04, 127.99, 126.34, 125.85, 119.07, 105.04; *m/z* HRMS (DART) found $[M+H]^+$ 221.1129, $C_{15}H_{13}N_2^+$ requires 221.1073. Spectra matched literature values.

1,3-Diphenyl-1H-pyrazole



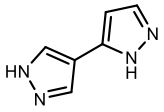
Brown solid (43 mg, 0.20 mmol, 49%). IR ν_{max}/cm^{-1} (solid): 3960, 2998, 1592, 1499, 1450, 1378, 756, 687; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 1.9 Hz, 1H), 7.27 – 7.19 (m, 8H), 7.15 (ddd, *J* = 5.0, 4.3, 2.8 Hz, 2H), 6.42 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.08, 140.24, 140.06, 130.56, 128.93, 128.79, 128.50, 128.27, 127.50, 125.25, 107.88; *m/z* HRMS (DART) found $[M+H]^+$ 221.1124, $C_{15}H_{13}N_2^+$ requires 221.1073. Spectra matched literature values.

4-(1-Phenyl-1H-pyrazol-4-yl)pyrimidine



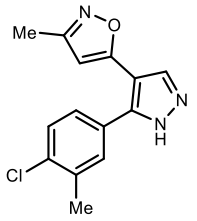
Prepared according to a modified general procedure K using 2,4,6-trimethylaniline instead of aniline. Used 4-5'-bipyrimidine (158 mg, 1.00 mmol), EtOAc (5 mL), Tf_2O (168 µL, 1.00 mmol), 2,4,6-trimethylaniline (421 µL, 1.20 mmol), collidine (132 µL, 1.00 mmol), then EtOH (2 mL), phenylhydrazine (295 µL, 5.00 mmol), and concentrated aqueous HCl (833 µL, 10.0 mmol). The crude material was purified by flash chromatography (silica gel: 0.5:1:98.5 AcOH:MeOH:CH_2Cl_2) to provide the title compound as an orange solid (115 mg, 0.52 mmol, 52% yield). mp 106-112°C; IR ν_{max}/cm^{-1} (solid): 3054, 2922, 1584, 1505, 1388, 1284, 1180, 967, 951, 755, 687, 658; 1H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, *J* = 1.4 Hz, 1H), 8.68 (d, *J* = 5.3 Hz, 1H), 8.61 (s, 1H), 8.24 (s, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.54 – 7.46 (m, 3H), 7.36 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.88, 158.70, 156.87, 139.94, 139.63, 129.77, 127.61, 127.11, 122.91, 119.58, 116.54; *m/z* HRMS (DART) found $[M+H]^+$ 233.0989, $C_{13}H_{11}N_4^+$ requires 223.0978.

1'H, 2H-3,4'-Bipyrazole



Prepared according to a modified general procedure E using 2,4,6-trimethylaniline instead of aniline. Used 4-5'-bipyrimidine (126 mg, 0.80 mmol), EtOAc (4 mL), Tf_2O (270 µL, 1.60 mmol), 2,4,6-trimethylaniline (450 µL, 3.20 mmol), collidine (212 µL, 1.60 mmol), then EtOH (4 mL), hydrazine hydrate (194 µL, 4.00 mmol), and concentrated aqueous HCl (666 µL, 8.00 mmol). The crude material was purified by flash chromatography (silica gel: 1:10:89 AcOH:MeOH:CH_2Cl_2) to provide the title compound as a pale-brown solid (25 mg, 0.19 mmol, 24% yield). mp 233-236°C; IR ν_{max}/cm^{-1} (solid): 3122, 3038, 2884, 2232, 1605, 1373, 765; ^1H NMR (400 MHz, MeOD) δ 7.93 (s, 2H), 7.59 (d, *J* = 2.2 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (HCl salt, 100 MHz, D_2O and 1 equiv. aqueous HCl for solubility) δ 139.63, 134.13, 132.67, 109.08, 104.07; *m/z* HRMS (DART) found $[M+H]^+$ 135.0661, $C_6H_7N_4^+$ requires 135.0665.

5-(4-(4-Chloro-3-methylphenyl)-1H-pyrazol-3-yl)-3-methylisoxazole

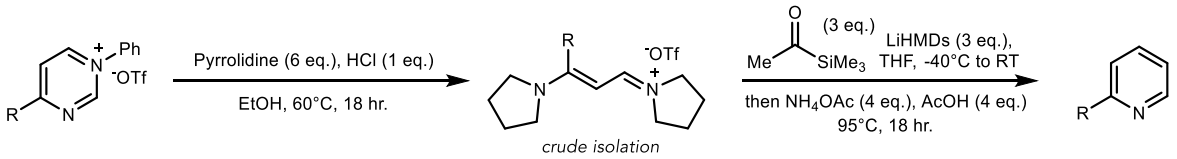


Prepared according to general procedure I using 4-(4-chloro-3-methylphenyl)-5-(3-methylisoxazol-5-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (205 mg, 0.40 mmol), piperidine (118 µL, 1.20 mmol), EtOH (2 mL), hydrazine hydrate (38 µL, 1.20 mmol), and concentrated HCl (333 µL, 4.00 mmol). The residue was purified by flash chromatography (silica gel: 20 to 100% EtOAc in hexanes) to provide the pure title compound as a tan solid (79 mg, 0.29 mmol, 72% yield). mp 100-104 °C. IRυ_{max}/cm^{-1} (solid): 3166, 3119, 2936, 1623, 1436, 1413, 1045,

918, 784, 729. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.34 (dd, *J* = 11.3, 3.1 Hz, 2H), 7.25 (d, *J* = 2.0 Hz, 1H), 5.85 (s, 1H), 2.34 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.62, 160.05, 136.76, 135.53, 134.26, 133.51, 130.89, 129.48, 128.98, 127.22, 108.26, 100.53, 20.09, 11.45. *m/z* HRMS (DART) found $[M+H]^+$ 274.0743, $C_{14}H_{12}ClN_3O^+$ requires 274.0669.

A 1.7 Procedures for Pyrimidine to Pyridine Conversion

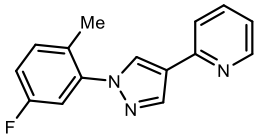
General Procedure L (Pyridine Formation from Pyrimidinium Salt)



An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the pyrimidinium salt (1.0 equiv), EtOH (0.2 M), HCl (1.0 equiv, 4.0M in Dioxane), and pyrrolidine (6.0 equiv). The reaction was stirred for 18 hours at 60 ºC. Next, the reaction was concentrated *in vacuo* and diluted with a 1:3 solution of isopropyl alcohol (iPrOH):CH_2Cl_2 and washed with a 0.1M aqueous solution of HCl (2x). The aqueous layer was extracted with iPrOH:CH_2Cl and the combined organic extract was washed with brine (1x) and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was dissolved in a minimal amount of CH_2Cl_2 and added dropwise to a stirring solution of 1:3 Et_2O:hexanes, then chilled in a -20 ºC freezer (approx. 1 hour) and decanted to provide crude vinamidinium salt. In a separate flask, acetyltrimethylsilane (3.0 equiv) was added to THF (0.2M) and cooled to -40 ºC before adding lithium bis(trimethylsilyl)amide (LiHMDS, 3.0 equiv). The reaction was stirred for 30 minutes before adding vinamidinium (a minimal amount of THF can be used to dissolve the vinamidinium salt if unable to transfer as a solid), then warmed to room temperature under ambient. Next, NH_4OAc (4 equiv) and acetic acid (4 equiv) were added, and the reaction was heated to 95 ºC for 18 hours. After cooling to room temperature, the reaction was quenched with

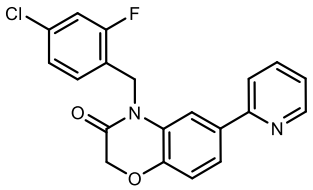
sat. $NaHCO_3$, extracted into EtOAc (3x). The combined organic extract was washed with water (1x), brine (1x), and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified with flash column chromatography.

2-(1-(5-Fluoro-2-methylphenyl)-1H-pyrazol-4-yl)pyridine



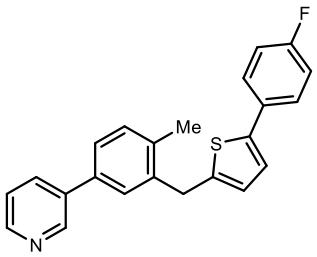
Prepared according to general procedure L using 4-(1-(5-fluoro-2-methylphenyl)-1H-pyrazol-4-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (144 mg, 0.30 mmol), EtOH (1.5 mL), HCl (75 µL, 0.30 mmol), pyrrolidine (150 µL, 1.80 mmol), acetyltrimethylsilane (148 µL, 0.90 mmol), LiHMDS (0.9 mL, 0.90 mmol), THF (1.5 mL), NH_4OAc (92.5 mg, 1.20 mmol), AcOH (69 µL, 1.20 mmol). The crude material was purified by flash chromatography (silica gel: 0-50% EtOAc in hexanes) to provide the pure title compound as a brown oil (37 mg, 0.15 mmol, 49% yield). IRυ_{max}/cm^{-1} (film): 3033, 2910, 1598, 1507, 1415, 1253, 1229, 1112, 828, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 4.9 Hz, 1H), 8.19 (s, J = 1.4 Hz, 2H), 7.71 (tt, J = 7.7, 1.7 Hz, 1H), 7.54 (d, J = 7.9 Hz, 1H), 7.29 (dd, J = 8.5, 6.3 Hz, 1H), 7.20 – 7.12 (m, 2H), 7.06 (tt, J = 8.3, 2.0 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.98 (d, J = 246.0 Hz), 151.61, 149.87, 140.40 (d, J = 9.5 Hz), 138.93, 136.81, 132.58 (d, J = 8.5 Hz), 129.19, 128.99 (d, J = 3.6 Hz), 124.65, 121.61, 119.87, 115.54 (d, J = 20.7 Hz), 113.29 (d, J = 24.0 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.76 (q, J = 7.8 Hz); *m/z* HRMS (ESI) found $[M+H]^+$ 254.1098, for $C_{15}H_{13}FN_3^+$ requires 254.1088.

4-(4-Chloro-2-fluorobenzyl)-6-(pyridin-2-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one



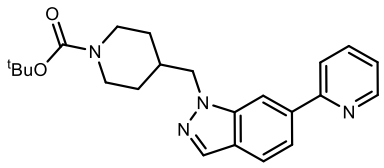
Prepared according to general procedure L using 4-(4-chloro-2-fluorobenzyl)-6-(1-phenyl-1l4-pyrimidin-4-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one trifluoromethanesulfonate (238 mg, 0.4 mmol), EtOH (2 mL), HCl (100 µL, 0.4 mmol), pyrrolidine (197 µL, 2.4 mmol), acetyltrimethylsilane (197 µL, 1.20 mmol), LiHMDS (1.2 mL, 1.20 mmol), THF (2.0 mL), NH_4OAc (123 mg, 1.60 mmol), AcOH (92 µL, 1.60 mmol). The crude material was purified by flash chromatography (silica gel: 0-40% EtOAc in hexanes) to provide the pure title compound as a pale-orange solid (56 mg, 0.15 mmol, 38% yield). mp 152-156 $^{\circ}$C; IRυ_{max}/cm^{-1} (film): 3085, 1607, 1580, 1488, 1420, 1378, 1273, 891, 777, 582. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.54 (m, 1H), 7.71 (td, J = 7.8, 1.8 Hz, 1H), 7.63 (d, J = 7.5 Hz, 2H), 7.55 (dd, J = 8.1, 1.0 Hz, 1H), 7.22 – 6.99 (m, 5H), 5.27 (s, 32H), 4.75 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.76, 160.37 (d, J = 249.5 Hz), 156.18, 149.80, 146.14, 136.92, 134.72, 134.37 (d, J = 10.0 Hz), 129.69 (d, J = 4.7 Hz), 128.50, 125.19 (d, J = 3.6 Hz), 122.99, 122.17, 121.79 (d, J = 14.5 Hz), 119.95, 117.49, 116.50 (d, J = 25.1 Hz), 113.90, 67.79, 38.08 (d, J = 4.5 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.52 (t, J = 3.8 Hz); *m/z* HRMS (ESI) found $[M+H]^+$ 369.0816, for $C_{20}H_{15}ClFN_2O_2^+$ requires 369.0801.

3-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine



Prepared according to modified general procedure H using (Z)-1-(2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (122 mg, 0.20 mmol), acetyltrimethylsilane (33 µL, 0.20 mmol), LiHMDS (200 µL, 0.20 mmol), THF (1.0 mL), NH_4OAc (62 mg, 0.80 mmol), AcOH (46 µL, 0.80 mmol). The crude material was purified by flash column chromatography (silica gel: 0 to 40% EtOAc:Hexanes) to provide the pure title compound as a tan solid (51 mg, 0.14 mmol, 72% yield). mp 51-60 °C. IRυ_{max}/cm^{-1} (film): 2921, 2218, 1571, 1472, 1423, 1230, 906, 799, 728. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 2.4 Hz, 1H), 8.49 (dd, J = 4.9, 1.8 Hz, 1H), 7.78 (dt, J = 8.0, 2.1 Hz, 1H), 7.43 – 7.30 (m, 4H), 7.30 – 7.11 (m, 2H), 7.00 – 6.90 (m, 3H), 6.64 (d, J = 3.7 Hz, 1H), 4.12 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.36, 160.91, 148.19 (d, J = 3.6 Hz), 142.90, 141.76, 139.07, 136.54, 136.44, 135.78, 134.26, 131.28, 130.76, 128.17, 127.16 (d, J = 8.0 Hz), 126.14, 125.61, 123.55, 122.73, 115.74 (d, J = 21.8 Hz), 34.20, 19.26; ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.07 (tt, J = 8.3, 5.2 Hz); *m/z* HRMS (ESI) found $[M+H]^+$ 360.1222, for $C_{23}H_{18}FNS^+$ requires 360.1222.

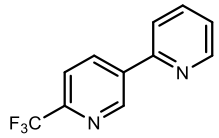
Tert-butyl 4-((6-(pyridin-2-yl)-1H-indazol-1-yl)methyl)piperidine-1-carboxylate



Prepared according to general procedure L using 4-(1-((1-(tert-butoxycarbonyl)piperidin-4-yl)methyl)-1H-indazol-6-yl)-1-phenylpyrimidin-1-ium trifluoromethanesulfonate (214 mg, 0.35 mmol), EtOH (1.7 mL), HCl (86 µL, 0.35 mmol), pyrrolidine (170 µL, 2.07 mmol), acetyltrimethylsilane (170 µL, 1.04 mmol), LiHMDS (1.0 mL, 1.04 mmol), THF (1.7 mL), NH_4OAc (106 mg, 1.38 mmol), AcOH (79 µL, 1.38 mmol). The crude material was purified by flash chromatography (silica gel: 0-60% EtOAc in hexanes) to provide the pure title compound as

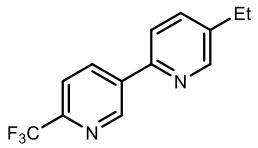
a brown oil (49 mg, 0.13 mmol, 36% yield). mp 60-64 °C; IRυ_{max}/cm^{-1} (film): 3050, 2976, 2930, 1681, 1587, 1425, 1289, 1159, 965, 840. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 4.5 Hz, 1H), 8.09 (s, 1H), 8.02 (s, 1H), 7.81 (dd, J = 9.0, 6.5 Hz, 3H), 7.72 (dd, J = 8.4, 1.4 Hz, 1H), 7.30 – 7.27 (m, 1H), 4.33 (d, J = 7.2 Hz, 2H), 4.09 (s, 2H), 2.64 (t, J = 12.5 Hz, 2H), 2.23 (dqd, J = 11.3, 7.5, 3.5 Hz, 1H), 1.56 (d, J = 13.7 Hz, 2H), 1.43 (s, 9H), 1.33 – 1.18 (m, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 157.97, 155.38, 150.59, 141.42, 138.47, 137.98, 133.51, 125.17, 123.45, 122.03, 121.88, 120.63, 108.62, 79.61, 54.63, 44.18, 38.01, 30.45, 28.55. *m/z* HRMS (ESI) found $[M+H]^+$ 393.2298, for $C_{23}H_{29}N_4O_2^+$ requires 393.2285.

6'-(Trifluoromethyl)-2,3'-bipyridine



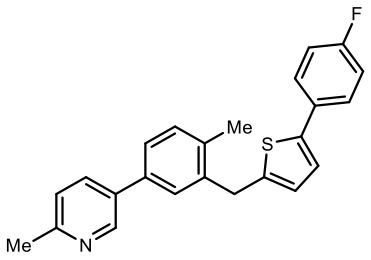
Prepared according to general procedure H using (Z)-1-(3-(pyrrolidin-1-yl)-3-(6-(trifluoromethyl)pyridin-3-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (144 mg, 0.30 mmol), acetyltrimethylsilane (148 µL, 0.90 mmol), LiHMDS (1.5 mL, 0.90 mmol), THF (1.5 mL), NH_4OAc (92.5 mg, 1.20 mmol), AcOH (69 µL, 1.20 mmol). The crude material was purified by flash column chromatography (silica gel: 30% EtOAc in hexanes) to provide the pure title compound as a tan solid (35 mg, 0.14 mmol, 72% yield). mp 66-68 °C. IRυ_{max}/cm^{-1} (film): 2956, 2360, 1589, 1435, 1335, 1247, 1098, 1016, 740. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (d, J = 2.5 Hz, 1H), 8.76 (dt, J = 4.9, 1.5 Hz, 1H), 8.51 (dd, J = 8.2, 2.4 Hz, 1H), 7.89 – 7.76 (m, 3H), 7.35 (ddd, J = 6.6, 4.9, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.25, 150.38, 148.35, 137.47, 137.23, 135.66, 123.67, 122.98, 120.98, 120.45 (q, J = 2.8 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -67.82. *m/z* HRMS (ESI) found $[M+H]^+$ 225.0643, for $C_{11}H_7F_3N_2^+$ requires 225.0639. Spectra matched literature values.

5-Ethyl-6'-(trifluoromethyl)-2,3'-bipyridine



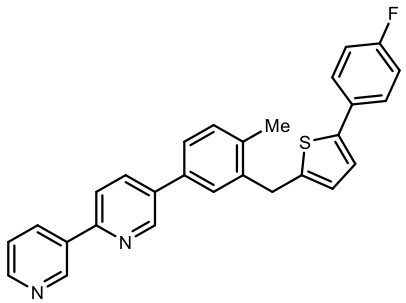
An oven dried 8 mL vial equipped with a stir bar was charged lithium diisopropylamine (2M in hexanes) (300 µL, 0.6 mmol, 3.0 equiv) in THF (0.28M) and cooled to 0 ºC. (E)-2-butylidene-1,1-dimethylhydrazine (80 µL, 0.6 mmol, 3.0 equiv) was added dropwise. The reaction was stirred for 1 hour before adding (Z)-1-(3-(pyrrolidin-1-yl)-3-(6-(trifluoromethyl)pyridin-3-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (122 mg, 0.2 mmol, 1.0 equiv), then warmed to room temperature with stirring for 1 hour. Next, NH_4OAc (4 equiv) and acetic acid (4 equiv) were added, and the reaction stirred at room temperature for 1 hour. The reaction was then heated to 95 ºC for 18 hours. After cooling to room temperature, the reaction was quenched with sat. $NaHCO_3$, extracted into EtOAc (3x). The combined organic extract was washed with water (1x), brine (1x), and dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified with flash column chromatography (silica gel: 0 to 20% EtOAc:Hexanes) to provide the pure title compound as a yellow solid (33 mg, 0.13 mmol, 65% yield). mp 57-59 °C. IRυ_{max}/cm^{-1} (film): 2970, 2933, 1583, 1474, 1265, 1175, 1137, 1089, 1014, 735, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, J = 2.3 Hz, 1H), 8.60 (d, J = 3.0 Hz, 1H), 8.49 (dd, J = 8.1, 2.9 Hz, 1H), 7.80 – 7.69 (m, 2H), 7.66 (dd, J = 8.1, 2.3 Hz, 1H), 2.73 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.75, 150.18, 148.41 - 147.20 (m), 139.65, 137.53, 136.46, 135.33, 120.60, 120.42 (q, J = 2.7 Hz), 25.89, 15.20; ^{19}F NMR (375 MHz, $CDCl_3$) δ -67.78; *m/z* HRMS (ESI) found $[M+H]^+$ 253.0946, for $C_{13}H_{11}F_3N_2^+$ requires 253.0952.

5-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2-methylpyridine



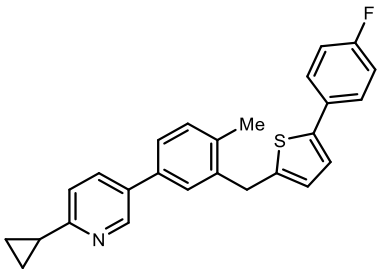
Prepared according to modified general procedure H using (Z)-1-(2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (122 mg, 0.20 mmol), acetone (15 µL, 0.20 mmol), LiHMDS (200 µL, 0.20 mmol), THF (1.0 mL), NH_4OAc (62 mg, 0.80 mmol), AcOH (46 µL, 0.80 mmol). The crude material was purified by flash column chromatography (silica gel: 0 to 40% EtOAc:Hexanes) to provide the pure title compound as an orange oil (46 mg, 0.12 mmol, 61% yield). IRυ_{max}/cm^{-1} (film): 3015, 2921, 1596, 1509, 1478, 1254, 1231, 1097, 820, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 2.8 Hz, 1H), 7.68 (dd, J = 8.0, 2.4 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.37 – 7.28 (m, 2H), 7.23 – 7.16 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.01 – 6.89 (m, 3H), 6.64 (dt, J = 3.6, 1.3 Hz, 1H), 4.12 (s, 2H), 2.51 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.35, 160.90, 157.00, 147.43, 142.98, 141.72, 138.96, 136.13, 135.91, 134.58, 133.49, 131.19, 127.99, 127.15 (d, J = 8.0 Hz), 126.12, 125.41, 123.12, 122.72, 115.73 (d, J = 21.8 Hz), 34.20, 24.10, 19.23; ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.10 (td, J = 8.7, 4.5 Hz); *m/z* HRMS (ESI) found $[M+H]^+$ 374.1375, for $C_{24}H_{20}FNS^+$ requires 374.1378.

5-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2,3'-



Prepared according to modified general procedure H using (Z)-1-(2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (122 mg, 0.20 mmol), 1-(pyridin-3-yl)ethan-1-one (15 µL, 0.20 mmol), LiHMDS (200 µL, 0.20 mmol), THF (1.0 mL), NH_4OAc (62 mg, 0.80 mmol), AcOH (46 µL, 0.80 mmol). The crude material was purified by flash column chromatography (silica gel: 0 to 70% EtOAc:Hexanes) to provide the pure title compound as an tan solid (63 mg, 0.14 mmol, 72% yield). mp 125-127 °C. IRυ_{max}/cm^{-1} (film): 3015, 2921, 1595, 1478, 1445, 1254, 1232, 1179, 903, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.95 (d, J = 2.5 Hz, 1H), 8.66 (d, J = 3.4 Hz, 1H), 8.36 (dt, J = 8.0, 2.0 Hz, 1H), 7.97 (dd, J = 8.3, 2.4 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.54 – 7.45 (m, 4H), 7.42 (dd, J = 8.0, 4.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.08 – 6.97 (m, 3H), 6.74 (d, J = 3.5 Hz, 1H), 4.22 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 163.37, 160.91, 153.26, 149.92, 148.40, 148.19, 142.79, 141.81, 139.20, 136.76, 135.49, 135.26, 135.07, 134.17, 131.36, 130.76 (d, J = 3.6 Hz), 128.00, 127.16 (d, J = 8.0 Hz), 126.21, 125.47, 123.65, 122.75, 120.37, 115.64, 34.19, 19.30; ^{19}F NMR (375 MHz, $CDCl_3$) δ -114.99 (dp, *J* = 8.3, 4.2 Hz); *m/z* HRMS (ESI) found $[M+H]^+$ 437.1485, for $C_{28}H_{21}FN_2S^+$ requires 437.1487.

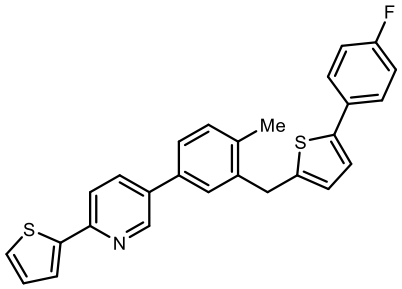
2-Cyclopropyl-5-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine



Prepared according to modified general procedure H using (Z)-1-(2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (122 mg, 0.20 mmol), cyclopropylanone (20 µL, 0.20 mmol),

LiHMDS (200 µL, 0.20 mmol), THF (1.0 mL), NH_4OAc (62 mg, 0.80 mmol), AcOH (46 µL, 0.80 mmol). The crude material was purified by flash column chromatography (silica gel: 0 to 20% EtOAc:Hexanes) to provide the pure title compound as a white solid (50 mg, 0.13 mmol, 65% yield). mp 66-68 °C. IRυ_{max}/cm^{-1} (film): 3015, 2921, 1595, 1509, 1478, 1254, 1213, 1097, 820, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J = 2.4, 0.9 Hz, 1H), 7.71 (dd, J = 8.1, 2.4 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.45 – 7.34 (m, 2H), 7.17 (dd, J = 8.1, 0.9 Hz, 1H), 7.08 – 6.97 (m, 3H), 6.71 (dd, J = 3.6, 1.1 Hz, 1H), 4.18 (s, 2H), 2.37 (s, 3H), 2.12 – 2.01 (m, 1H), 1.09 – 0.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.35, 161.57, 160.90, 147.58, 142.98, 141.72, 138.94, 135.92, 134.14, 133.16, 131.15, 127.86, 127.15 (d, J = 8.0 Hz), 126.14, 125.29, 122.72, 121.08, 115.83, 115.62, 34.17, 19.22, 16.91, 9.88; ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.14 (m); *m/z* HRMS (ESI) found $[M+H]^+$ 400.1526, for $C_{26}H_{22}FNS^+$ requires 400.1535.

5-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-2-(thiophen-2-yl)pyridine

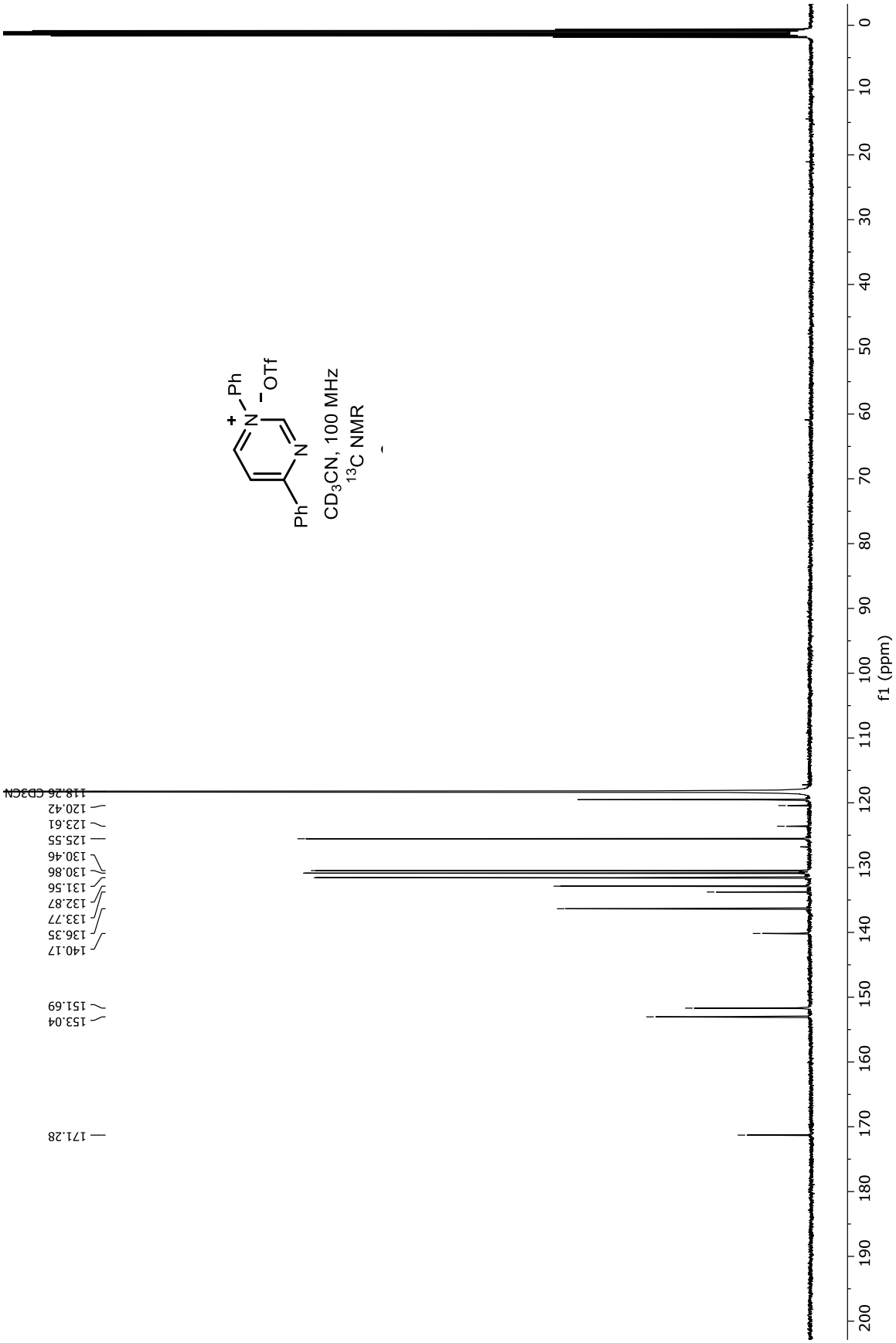


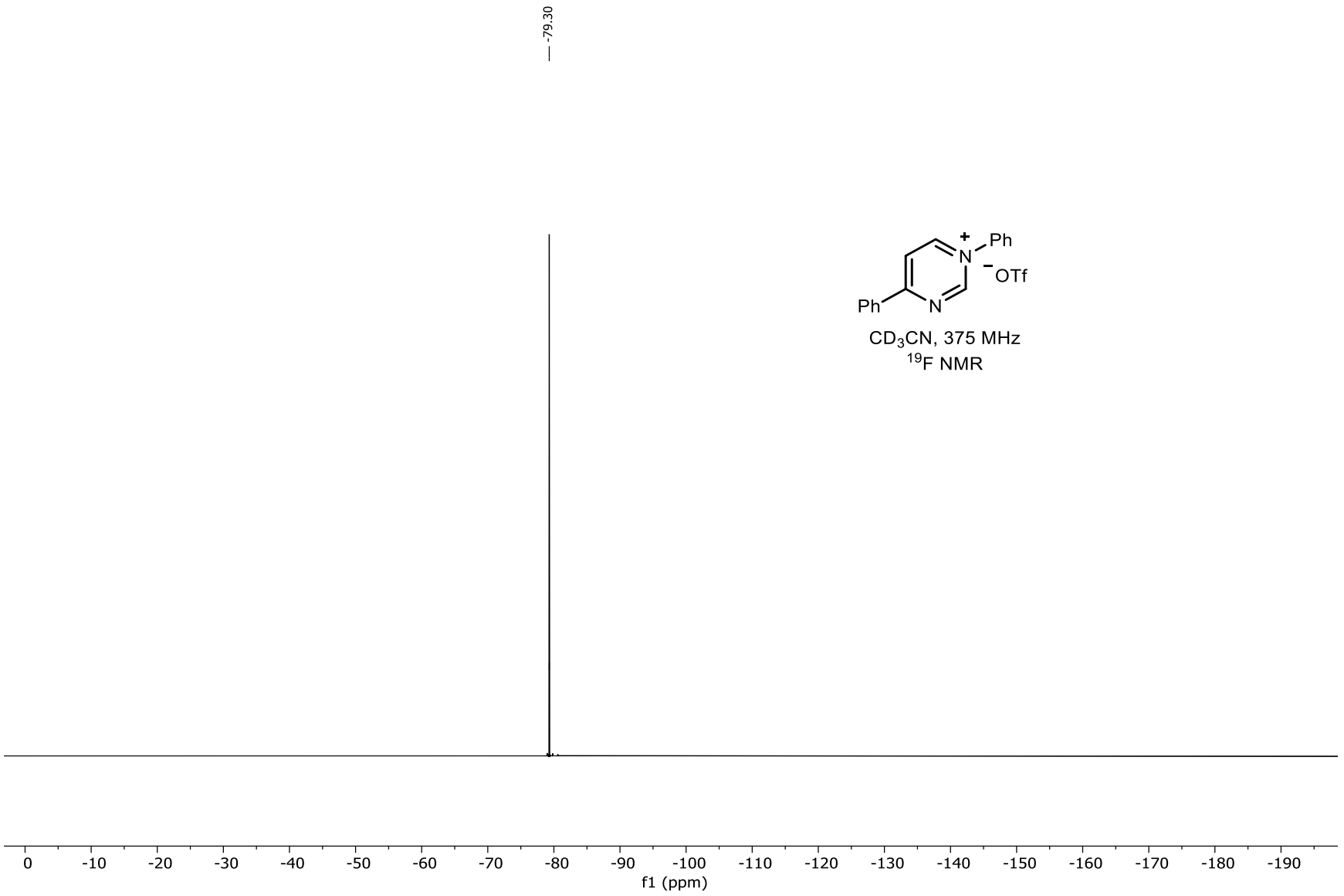
Prepared according to modified general procedure H using (Z)-1-(2-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (122 mg, 0.20 mmol), 1-(thiophen-2-yl)ethan-1-one (22 µL, 0.20 mmol), LiHMDS (200 µL, 0.20 mmol), THF (1.0 mL), NH_4OAc (62 mg, 0.80 mmol), AcOH (46 µL, 0.80 mmol). The crude material was purified by flash column chromatography (silica gel: 0 to 20% EtOAc:hexanes) to provide the pure title compound as yellow solid (49 mg, 0.11 mmol, 55% yield). IRυ_{max}/cm^{-1} (film): 3053, 3001, 1509, 1472, 1264, 895, 802, 723, 703, 659; ^{1}H NMR (400

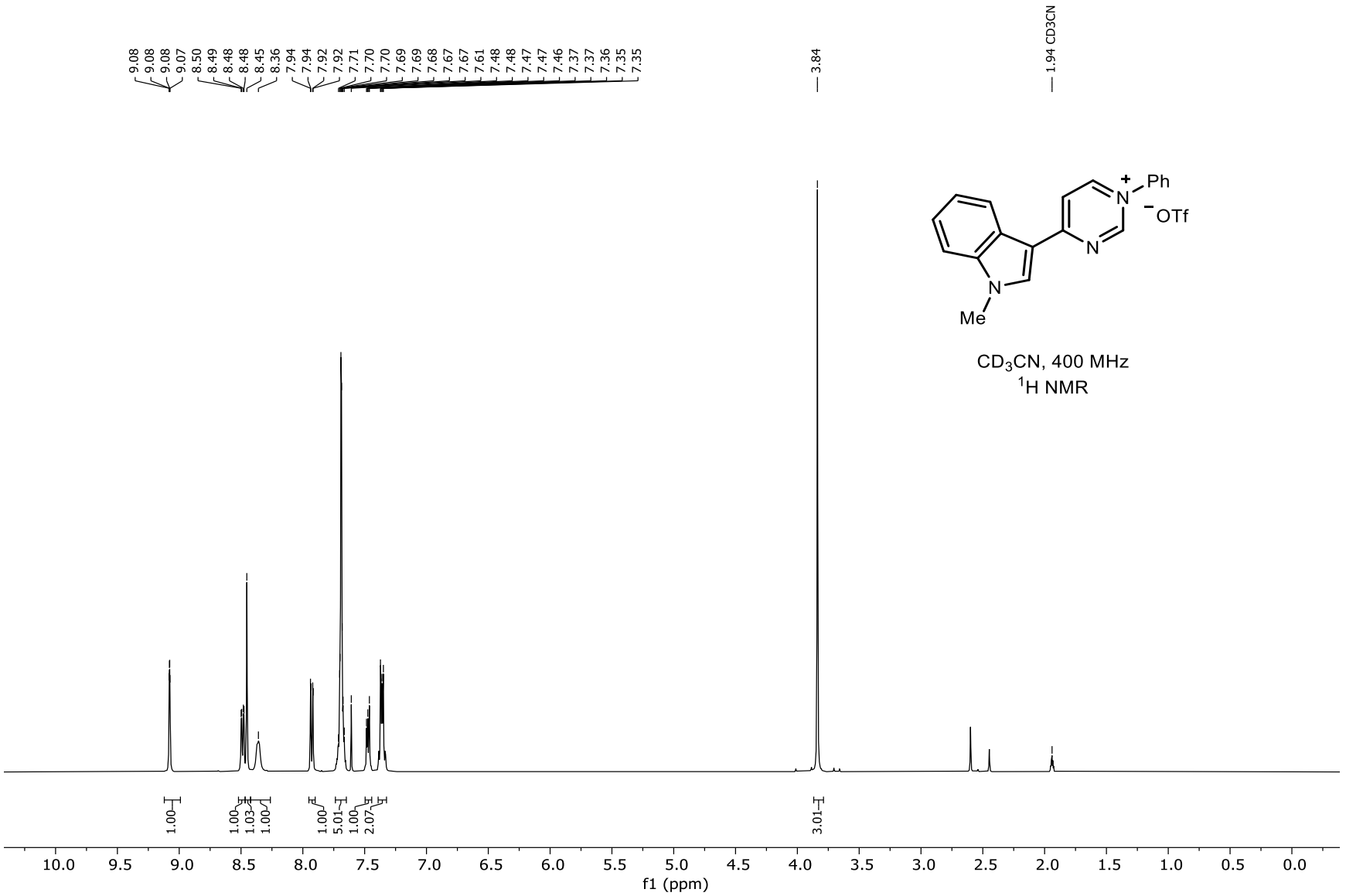
MHz, $CDCl_3$) δ 8.80 (d, J = 2.5 Hz, 1H), 7.87 (dd, J = 8.3, 2.5 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 3.9 Hz, 1H), 7.53 – 7.38 (m, 5H), 7.33 – 7.24 (m, 1H), 7.16 – 7.10 (m, 1H), 7.09 – 6.99 (m, 3H), 6.74 (d, J = 3.8 Hz, 1H), 4.21 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.37, 160.91, 151.21, 147.81, 144.64, 142.83, 141.80, 139.13, 136.46, 135.49, 134.77, 134.50, 131.29, 130.79 (d, *J* = 3.6 Hz), 128.14, 127.68 (d, *J* = 18.2 Hz), 127.21, 126.22, 125.26, 124.50, 122.76, 118.67, 115.74 (d, *J* = 21.8 Hz), 34.17, 19.29; ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.10 (td, J = 8.7, 4.5 Hz). *m/z* HRMS (ESI) found $[M+H]^+$ 442.1092, for $C_{27}H_{21}FNS_2^+$ requires 442.1094.

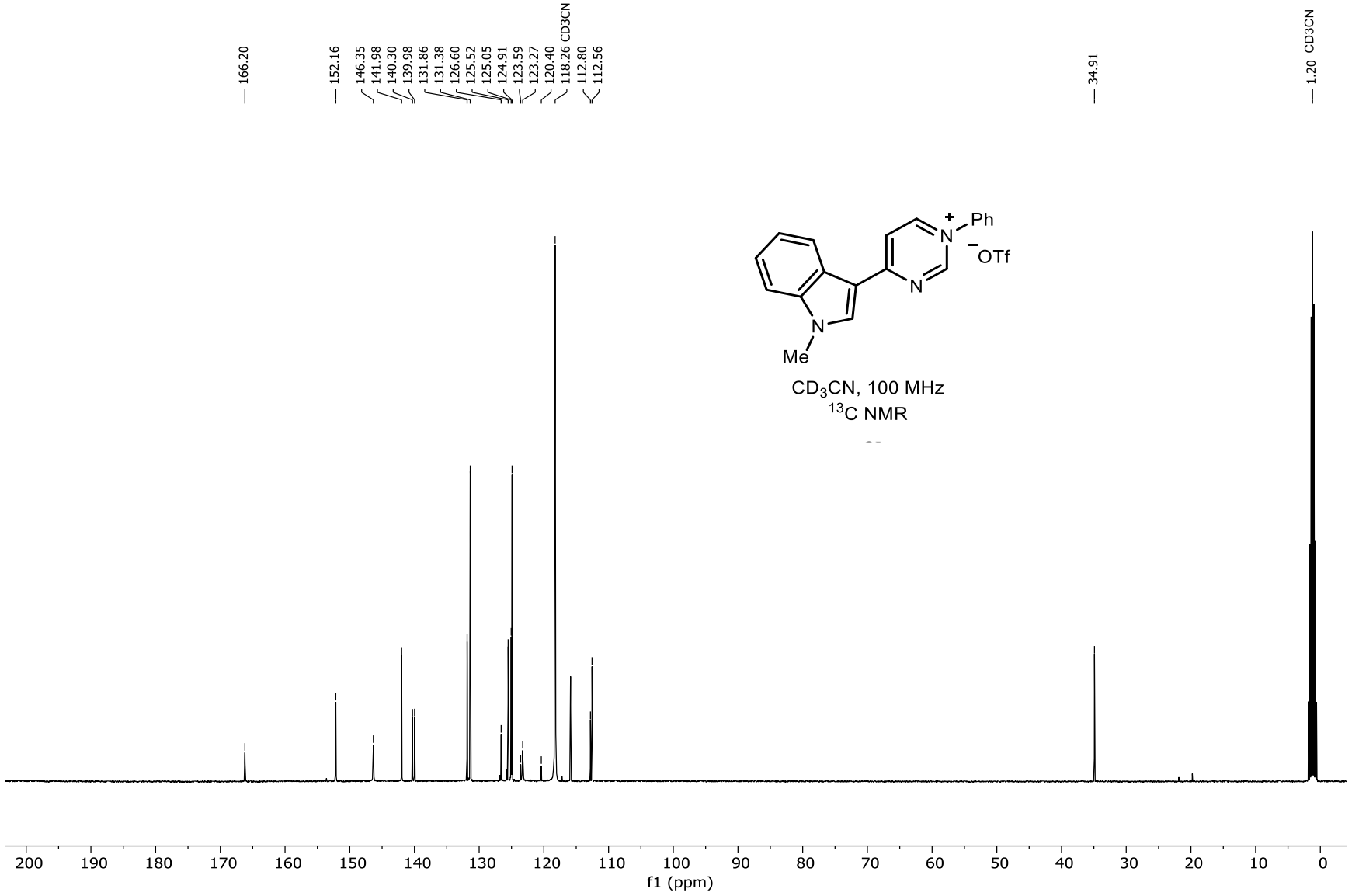
A 1.8 NMR Spectra

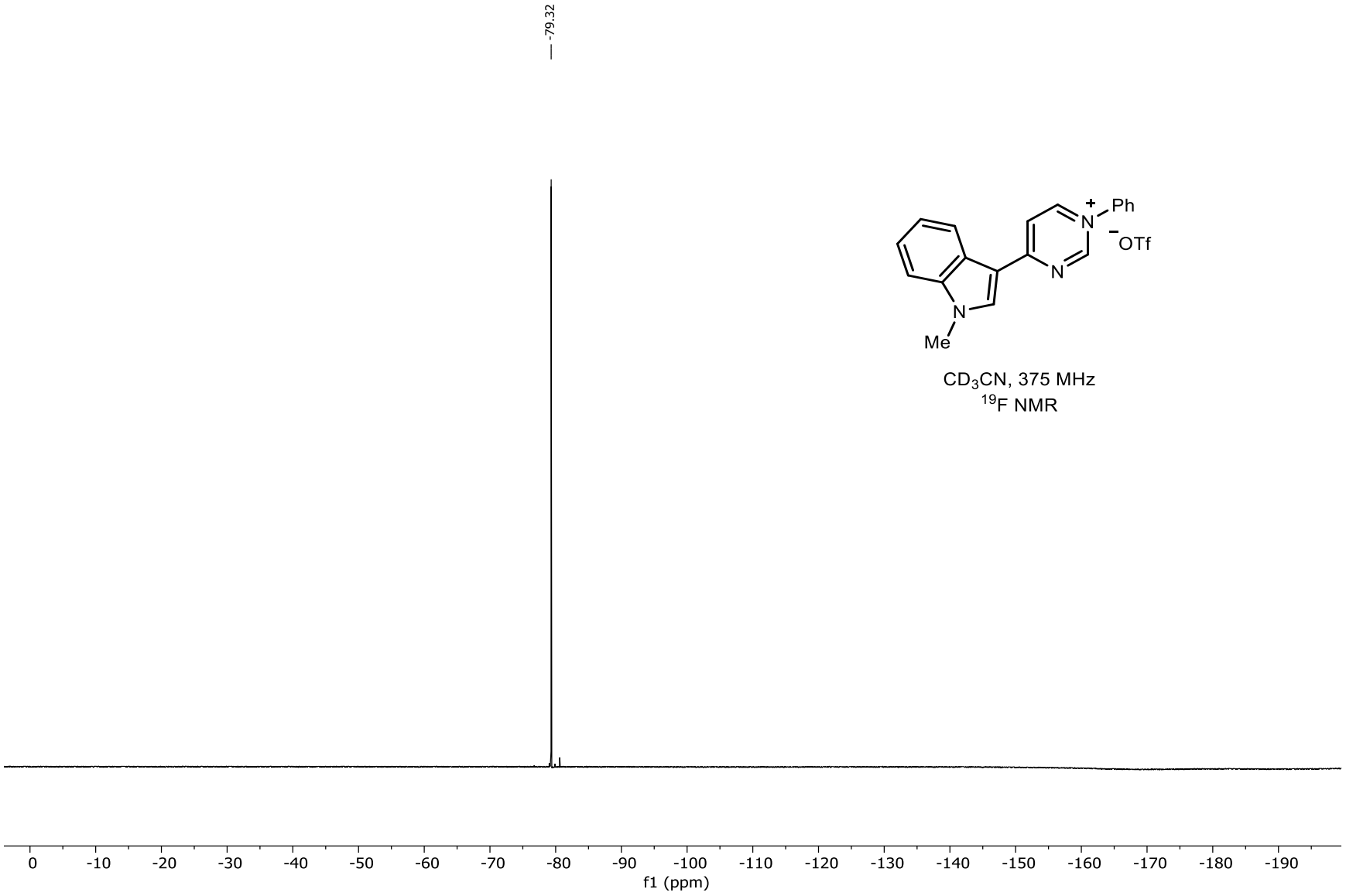
9.60
9.60
9.60
9.16
9.16
9.15
9.14
8.67
8.66
8.47
8.45
7.84
7.82
7.78
7.73
7.71
7.69
0.96
1.00
1.05
2.06
6.02
2.07
2.19 H2O
1.94 CD3CN
Ph
N
OTf
Ph
CD3CN, 400 MHz
1H NMR
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

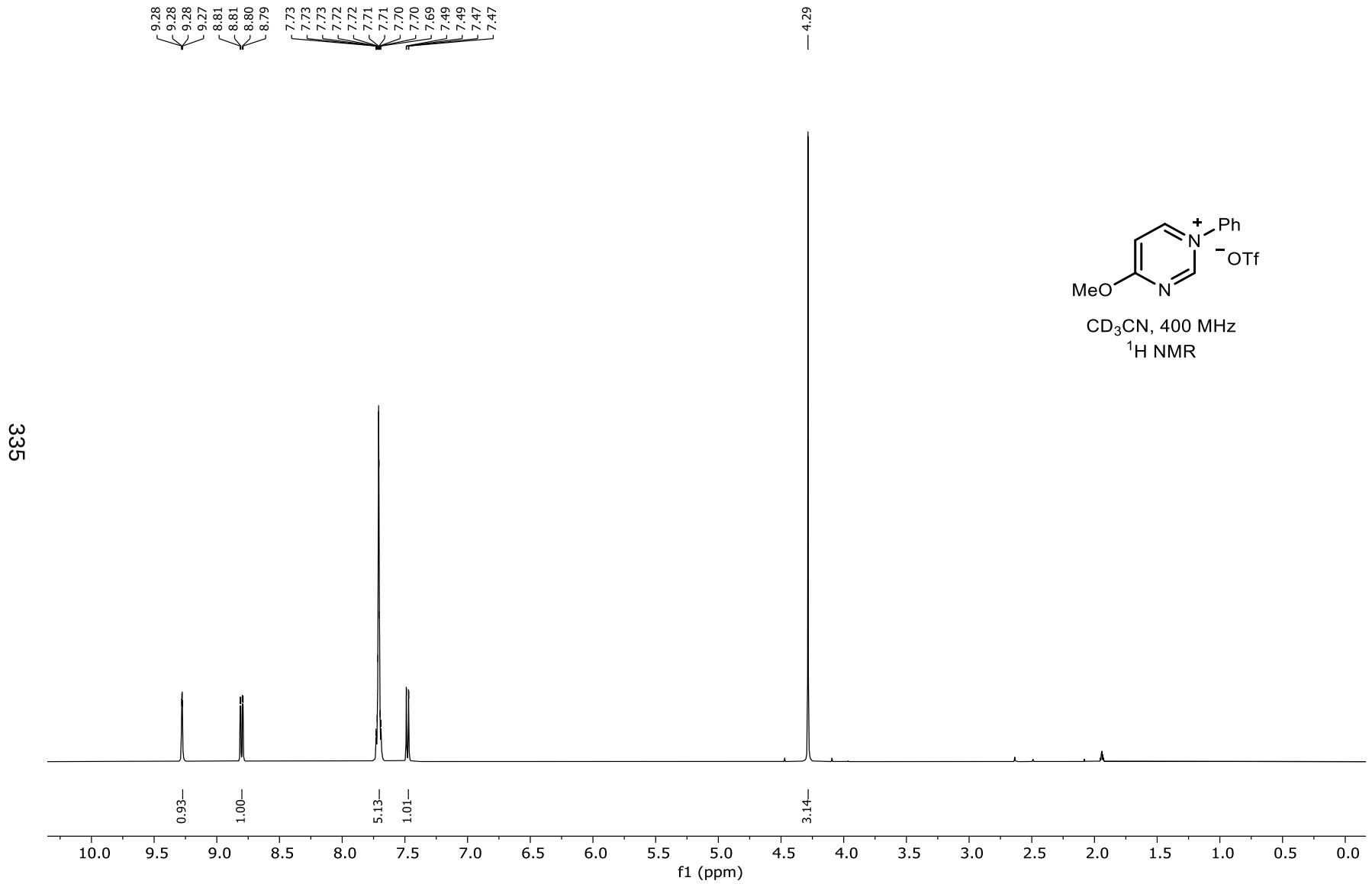

Ph
OTf
Ph
CD3CN, 100 MHz
13C NMR
-
171.28
153.04
151.69
140.17
136.35
133.77
132.87
131.56
130.86
130.46
125.55
123.61
120.42
118.26 CD3CN
f1 (ppm)

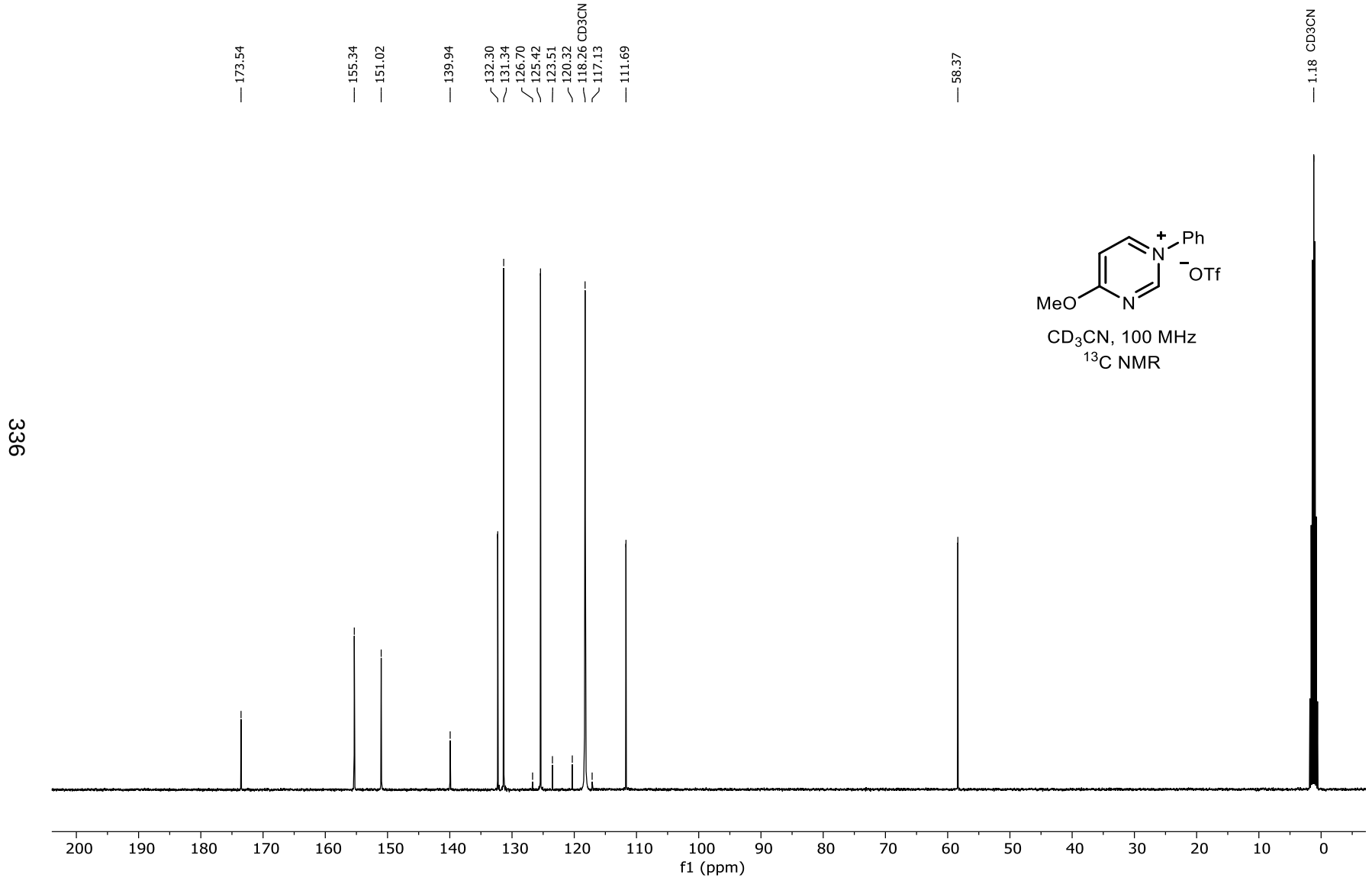

-79.30
Ph
N
OTf
Ph
N
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

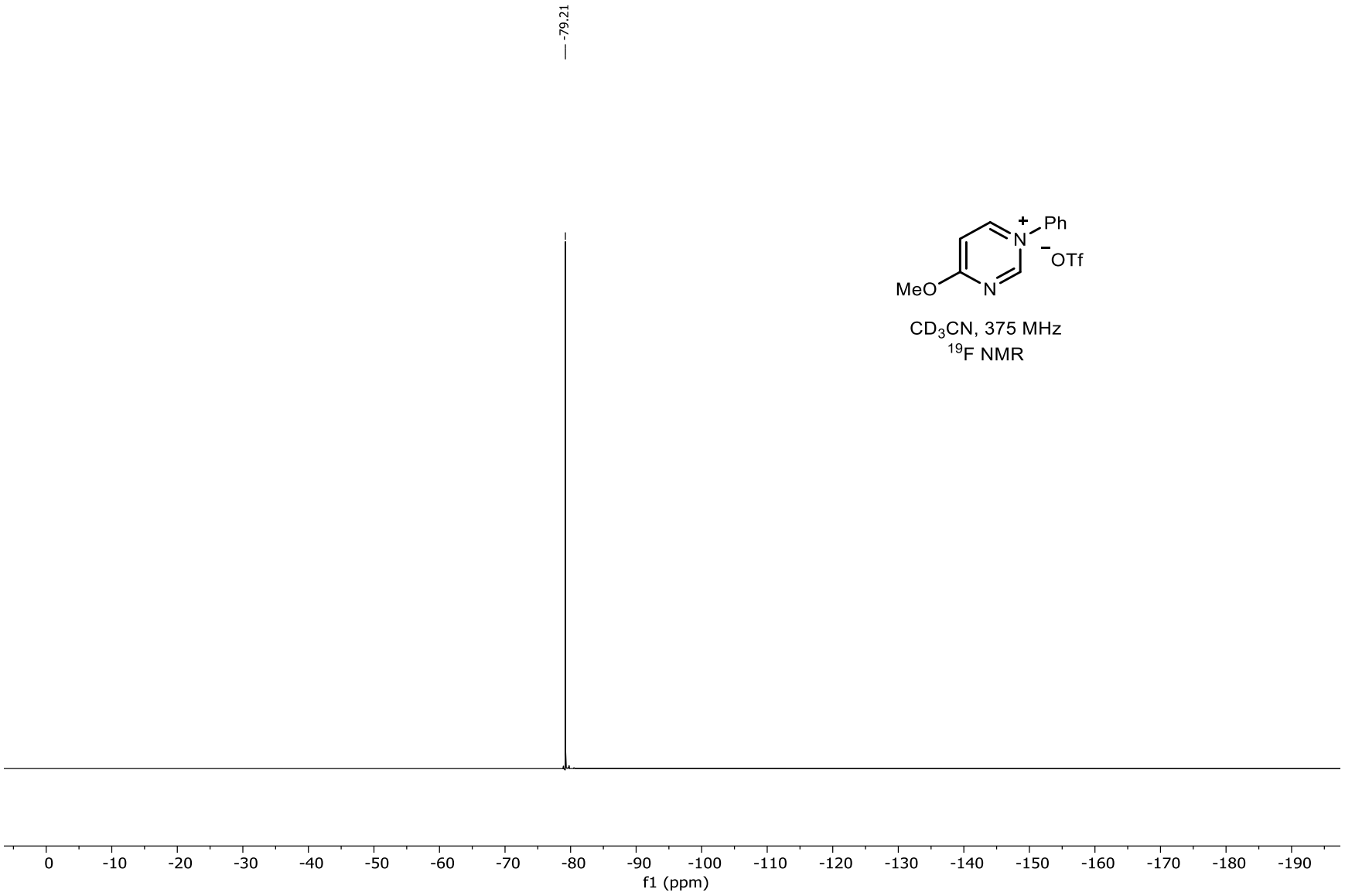

9.08
9.08
9.08
9.07
8.50
8.49
8.48
8.48
8.45
8.36
7.94
7.94
7.92
7.92
7.71
7.70
7.70
7.69
7.69
7.68
7.67
7.67
7.61
7.48
7.48
7.47
7.47
7.46
7.37
7.37
7.36
7.35
7.35
3.84
1.94 CD3CN
Ph
N
OTf
N
N
Me
CD3CN, 400 MHz
1H NMR
1.00
1.00
1.03
1.00
1.00
5.01
1.00
2.07
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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f1 (ppm)

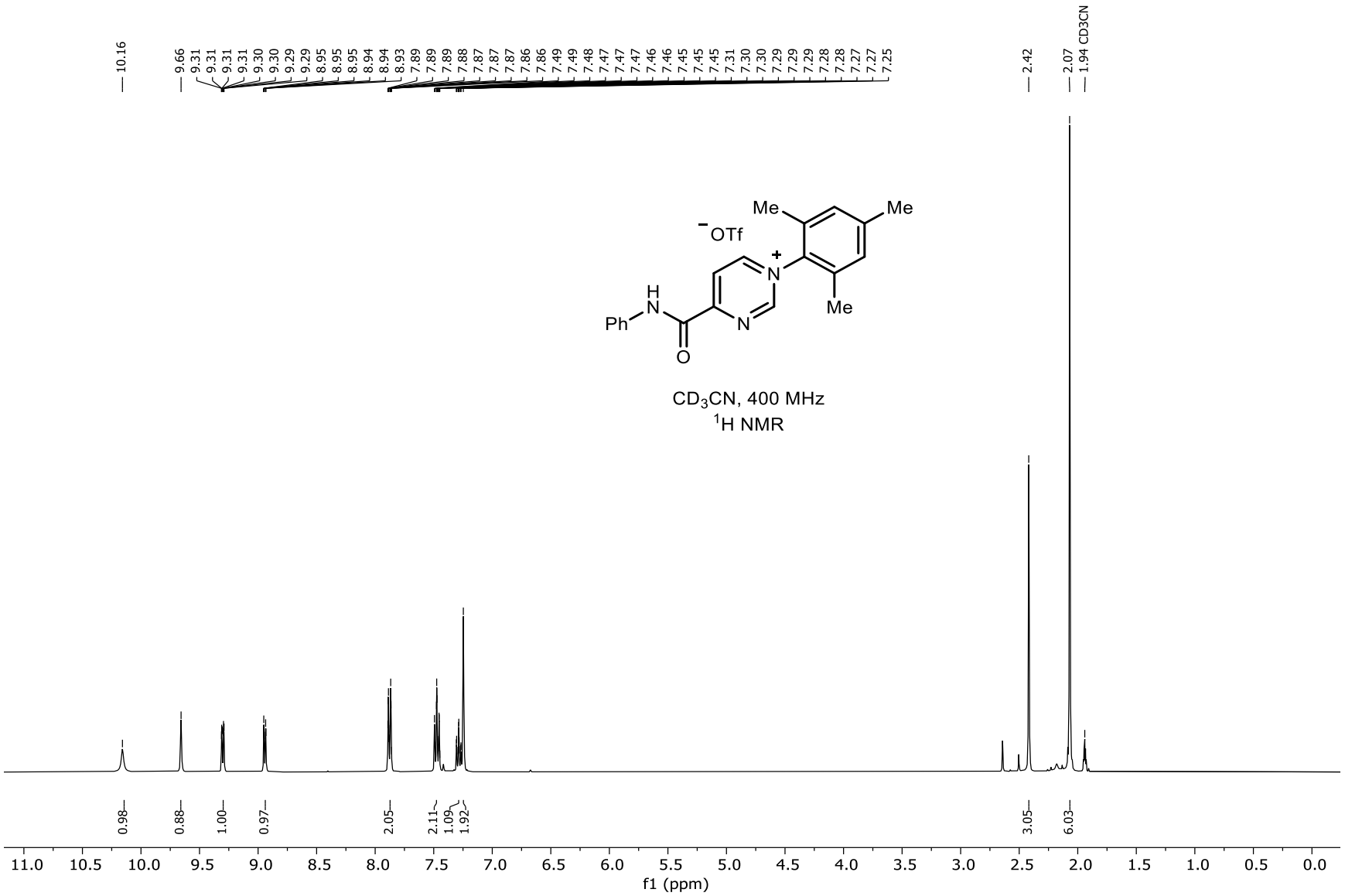

166.20
152.16
146.35
141.98
140.30
139.98
131.86
131.38
126.60
125.52
125.05
124.91
123.59
123.27
120.40
118.26 CD3CN
112.80
112.56
34.91
1.20 CD3CN
Ph
N
OTf
N
N
Me
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

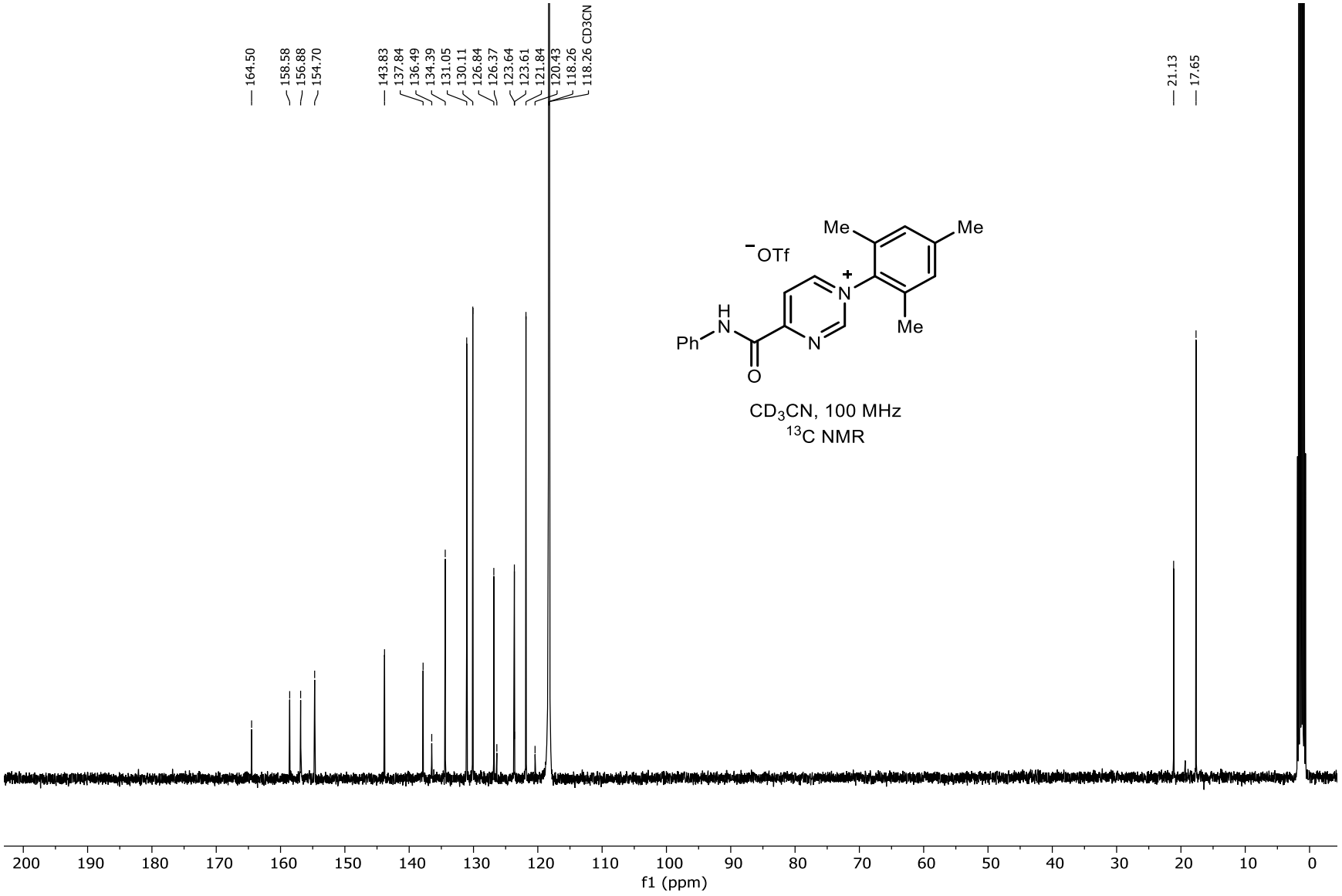

-79.32
Ph
N
OTf
N
N
Me
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

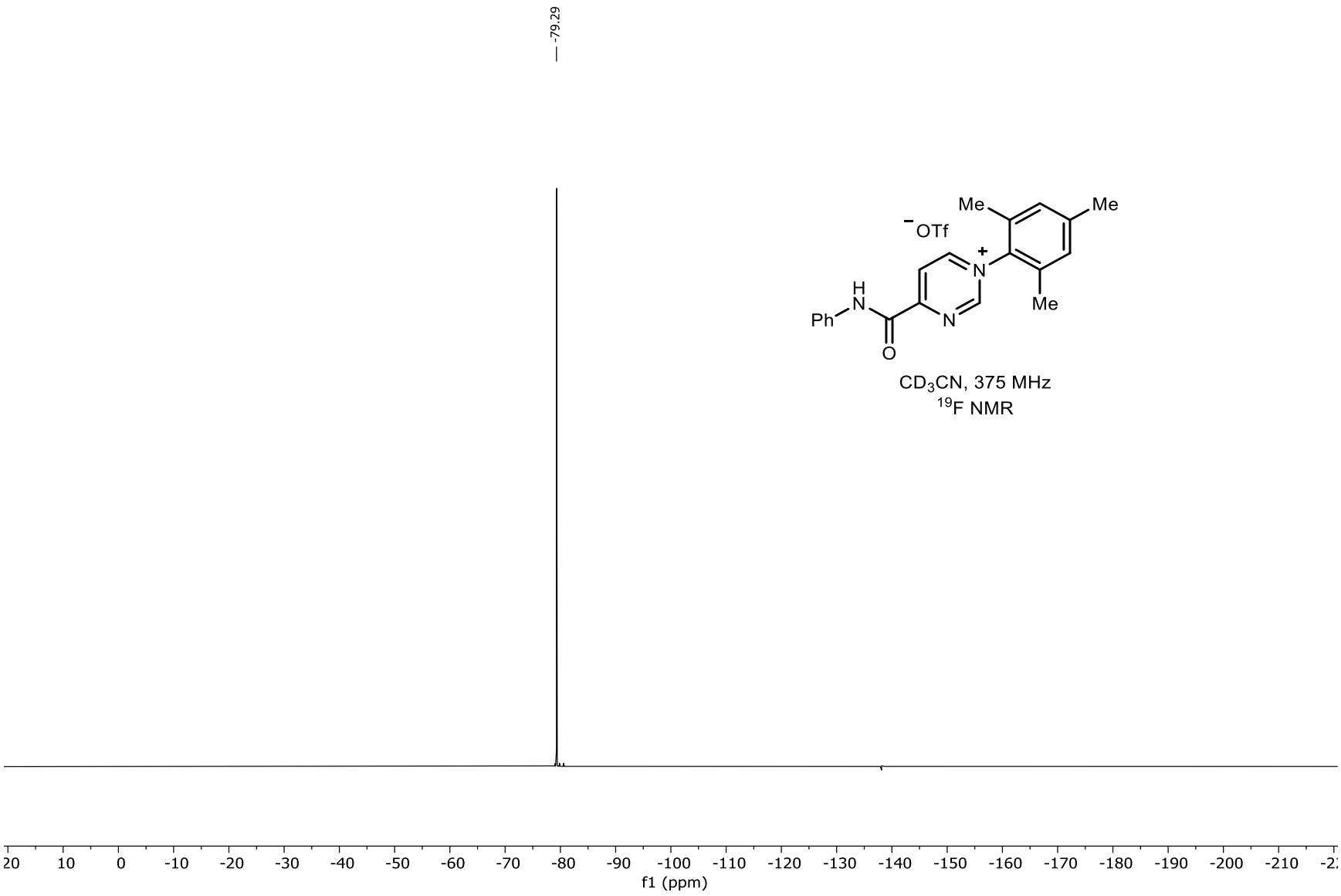

9.28
9.28
9.28
9.27
8.81
8.81
8.80
8.79
7.73
7.73
7.73
7.72
7.72
7.71
7.71
7.70
7.70
7.69
7.49
7.49
7.47
7.47
4.29
Ph
N
OTf
MeO
N
CD3CN, 400 MHz
1H NMR
0.93
1.00
5.13
1.01
3.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

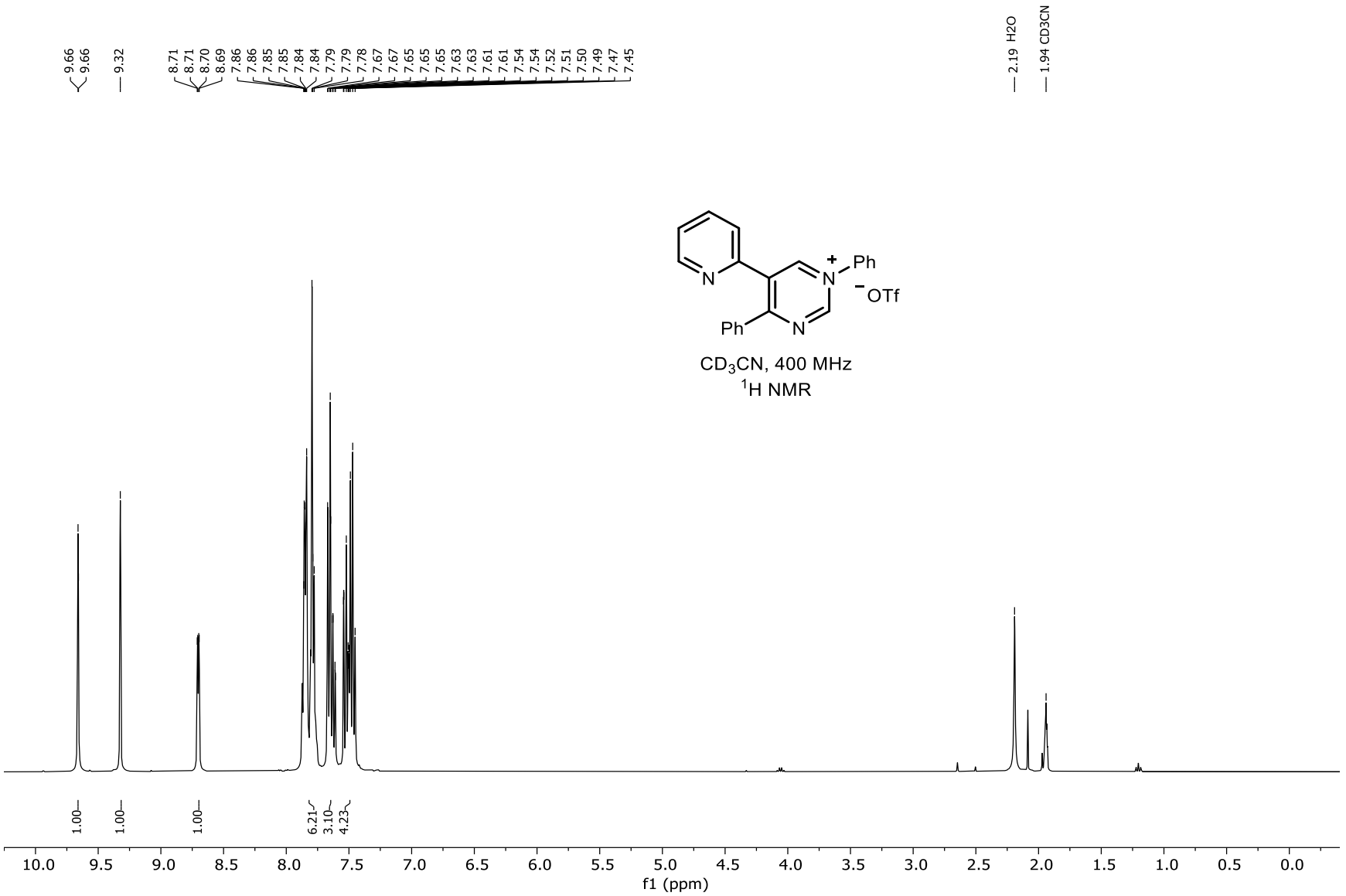

173.54
155.34
151.02
139.94
132.30
131.34
126.70
125.42
123.51
120.32
118.26 CD3CN
117.13
111.69
58.37
1.18 CD3CN
Ph
N
OTf
MeO
N
CD3CN, 100 MHz
13C NMR
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

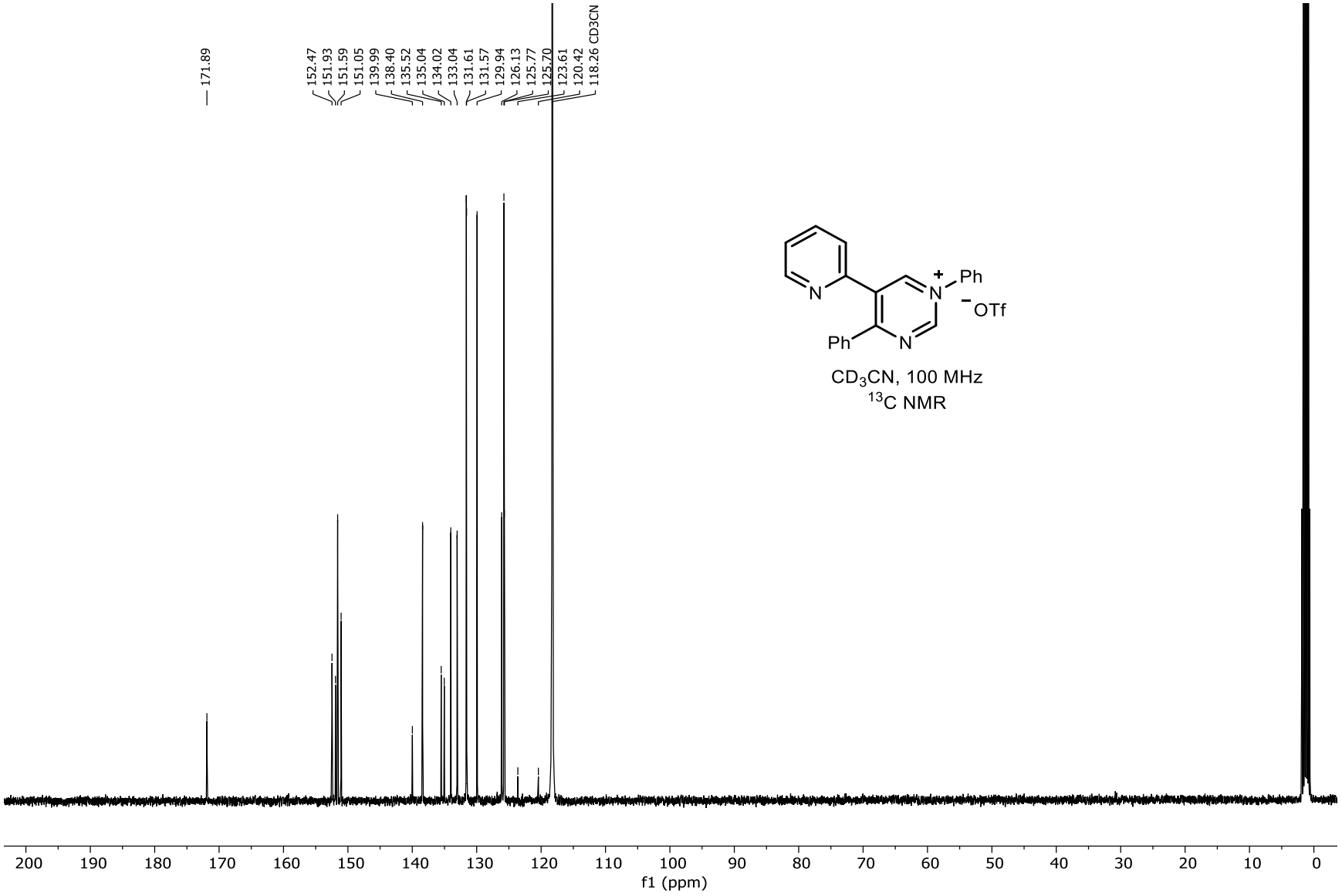

-79.21
Ph
N
OTf
MeO
N
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

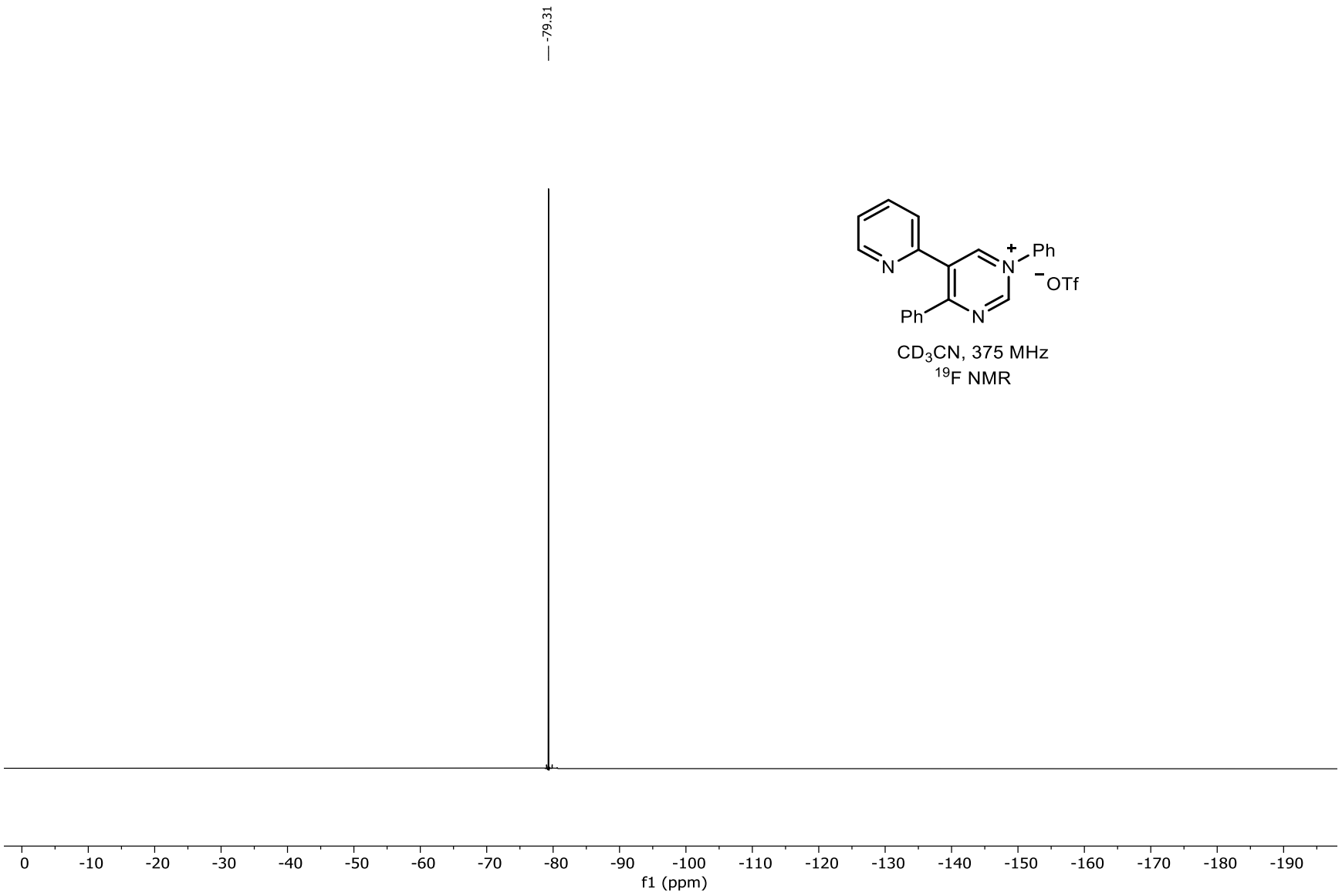

10.16
9.66
9.31
9.31
9.31
9.30
9.30
9.29
9.29
8.95
8.95
8.95
8.94
8.94
8.93
7.89
7.89
7.89
7.88
7.87
7.87
7.87
7.86
7.86
7.49
7.49
7.48
7.47
7.47
7.47
7.46
7.46
7.45
7.45
7.45
7.31
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.25
2.42
2.07
1.94 CD3CN
Me
Me
Me
OTf
N
H
N
Ph
N
O
CD3CN, 400 MHz
1H NMR
0.98
0.88
1.00
0.97
2.05
2.11
1.09
1.92
3.05
6.03
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

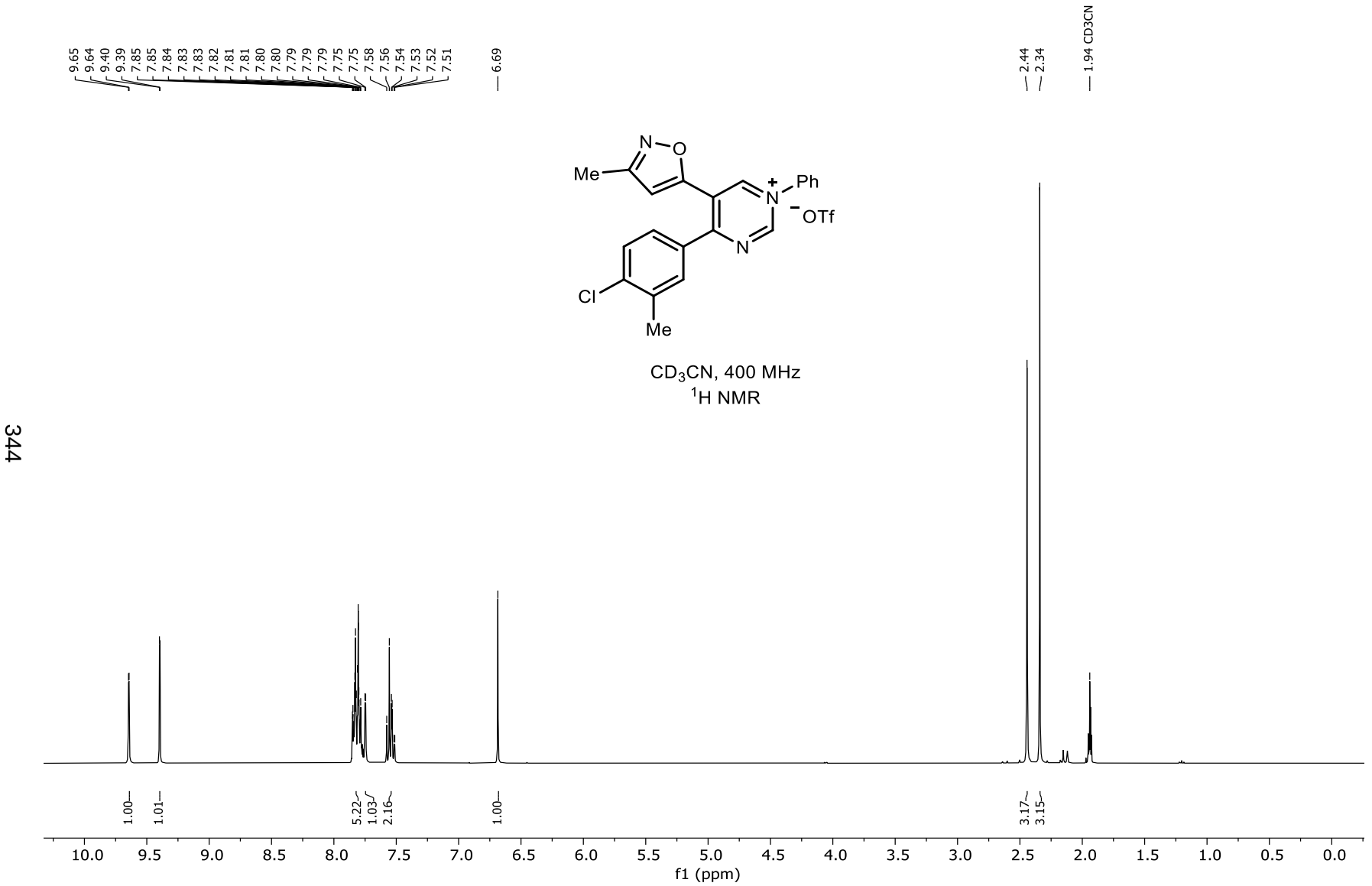

164.50
158.58
156.88
154.70
143.83
137.84
136.49
134.39
131.05
130.11
126.84
126.37
123.64
123.61
121.84
120.43
118.26
118.26 CD3CN
21.13
17.65
Me
Me
Me
OTf
N
H
N
Ph
N
O
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

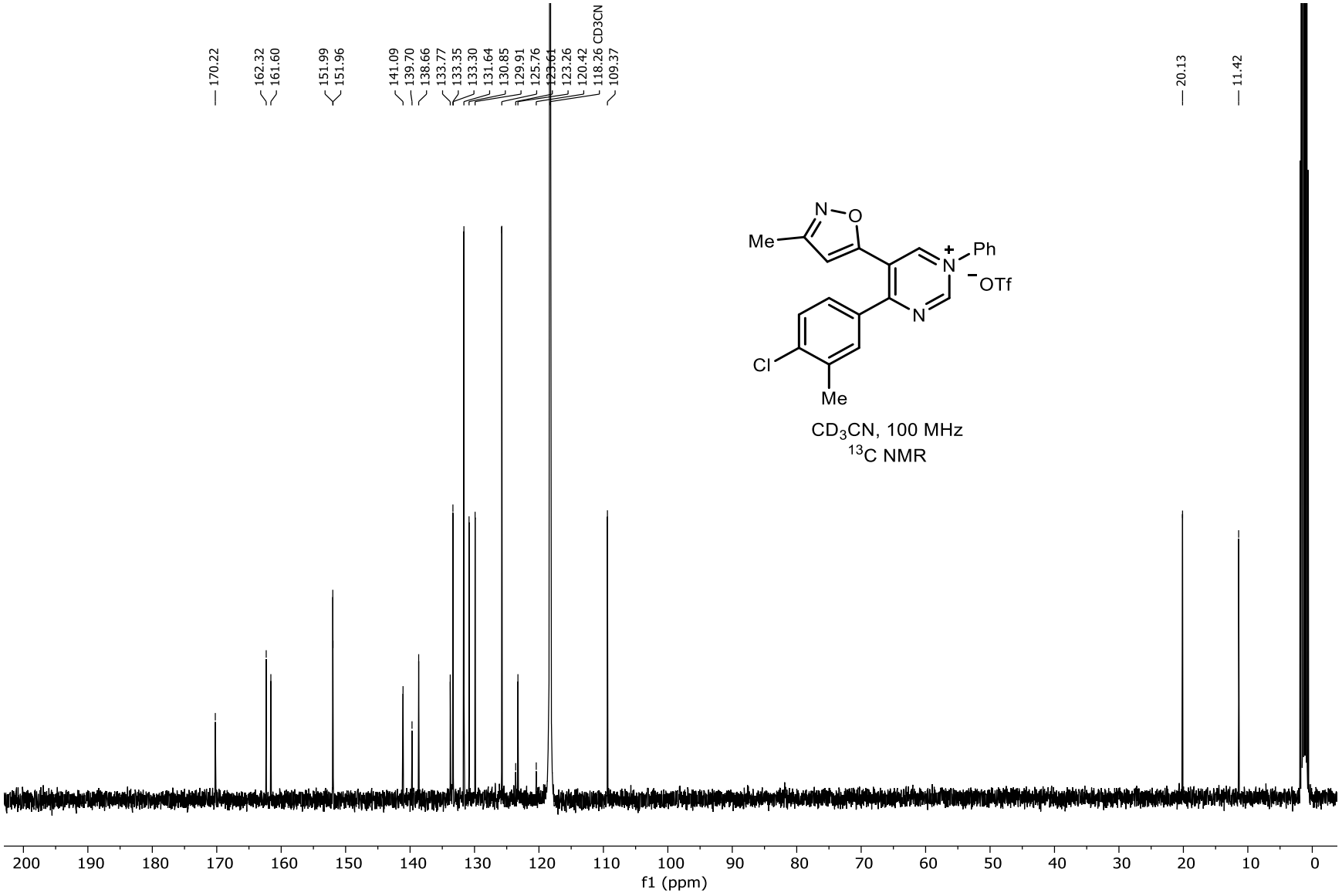

-79.29
Me
Me
OTf
N
H
N
Ph
Me
N
O
CD3CN, 375 MHz
19F NMR
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

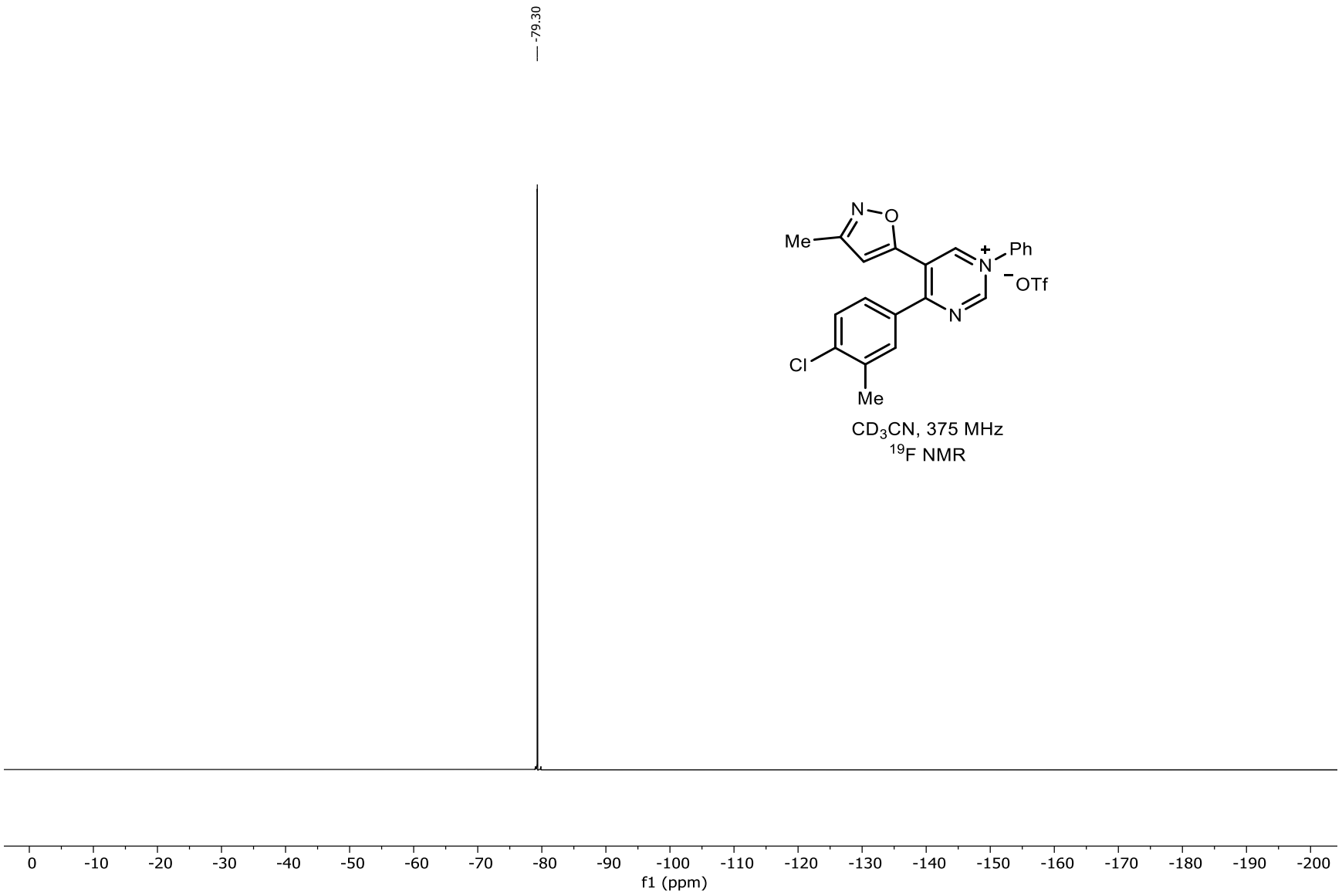

9.66
9.66
9.32
8.71
8.71
8.70
8.69
7.86
7.86
7.85
7.85
7.84
7.84
7.79
7.79
7.78
7.67
7.67
7.65
7.65
7.65
7.63
7.63
7.61
7.61
7.54
7.54
7.52
7.51
7.50
7.49
7.47
7.45
2.19 H2O
1.94 CD3CN
Ph
N
N
OTf
Ph
N
CD3CN, 400 MHz
1H NMR
1.00
1.00
1.00
6.21
3.10
4.23
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

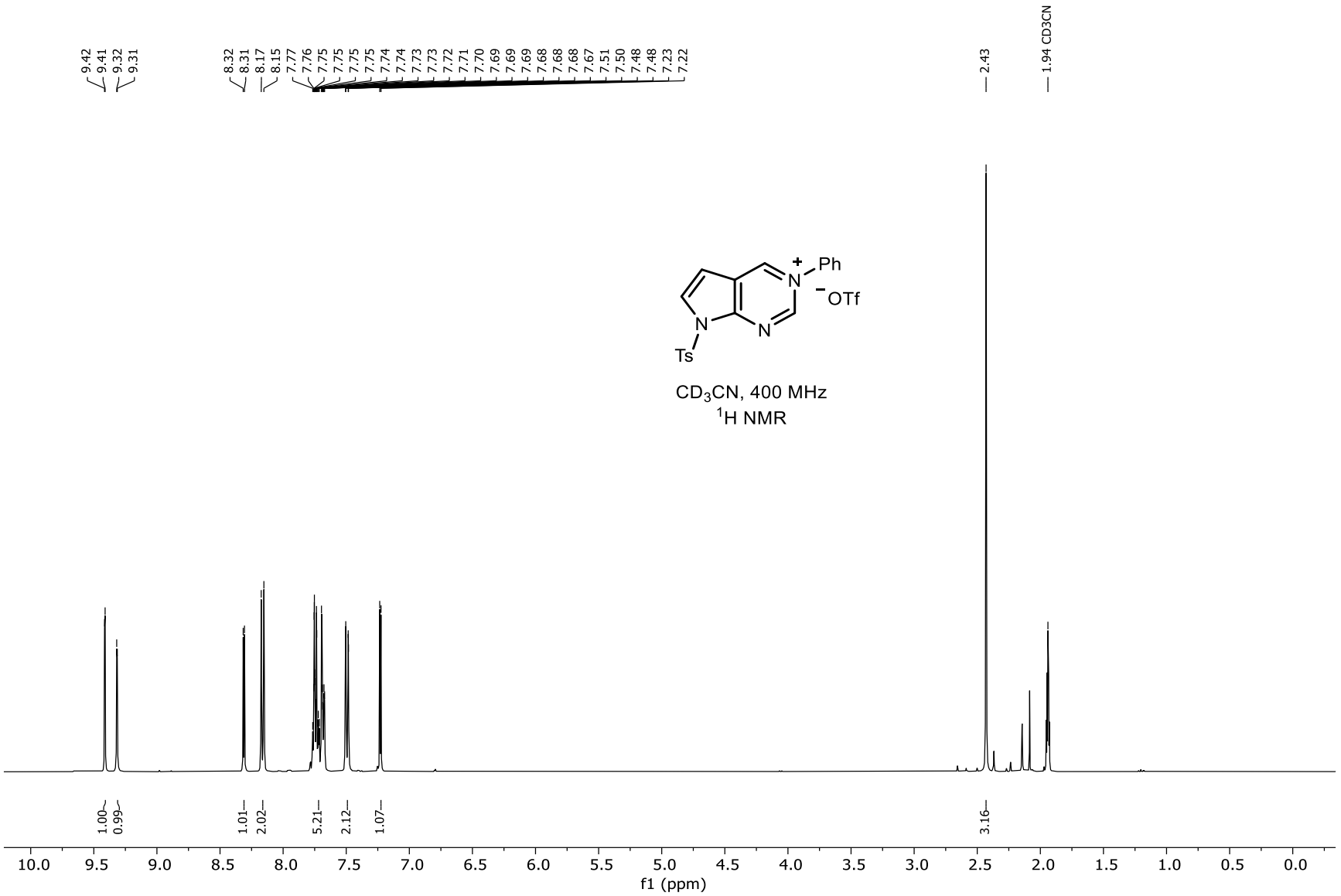

171.89
152.47
151.93
151.59
151.05
139.99
138.40
135.52
135.04
134.02
133.04
131.61
131.57
129.94
126.13
125.77
125.70
123.61
120.42
118.26
CD3CN
Ph
OTf
Ph
N
N
N
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

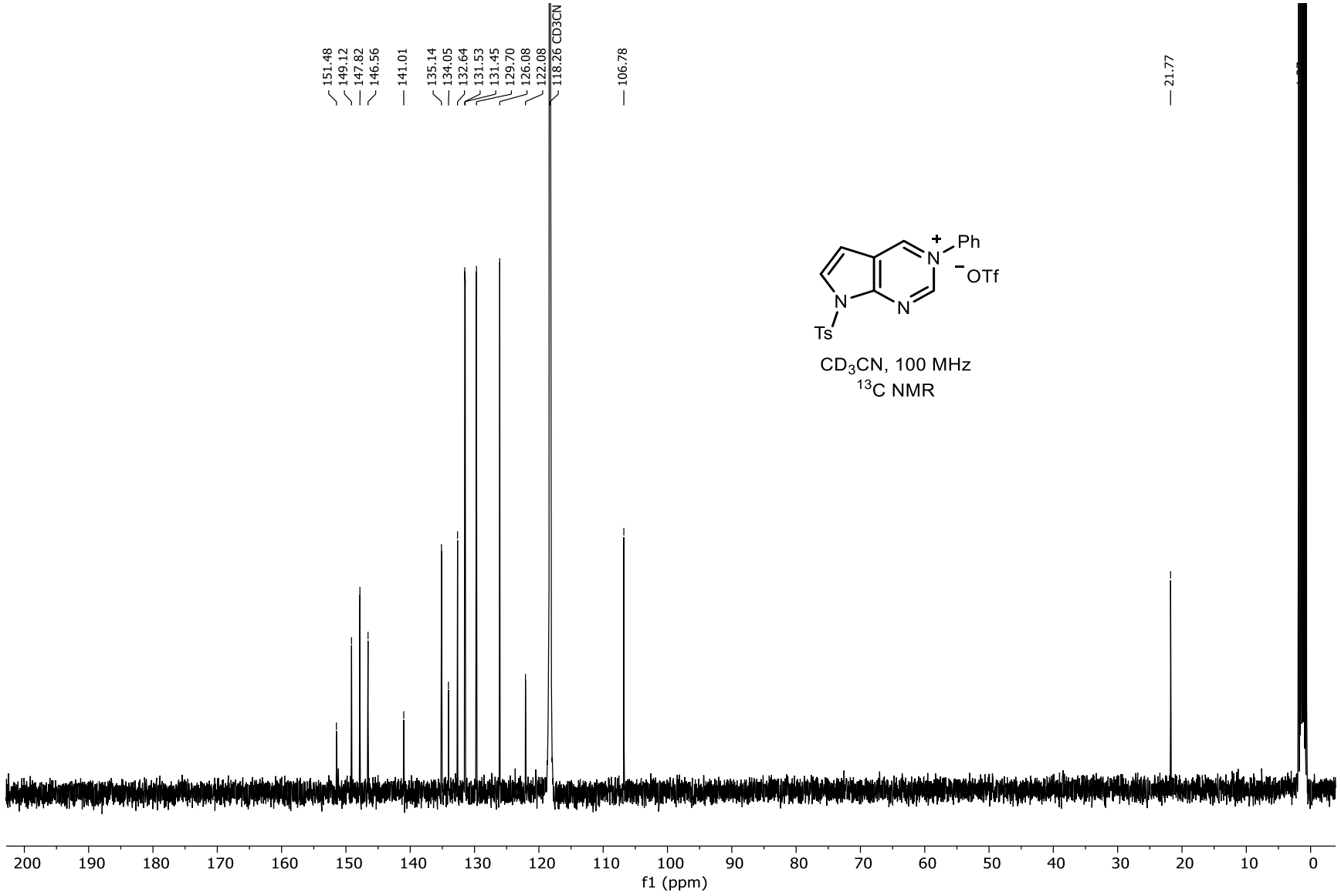

-79.31
Ph
N
N
OTf
Ph
N
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

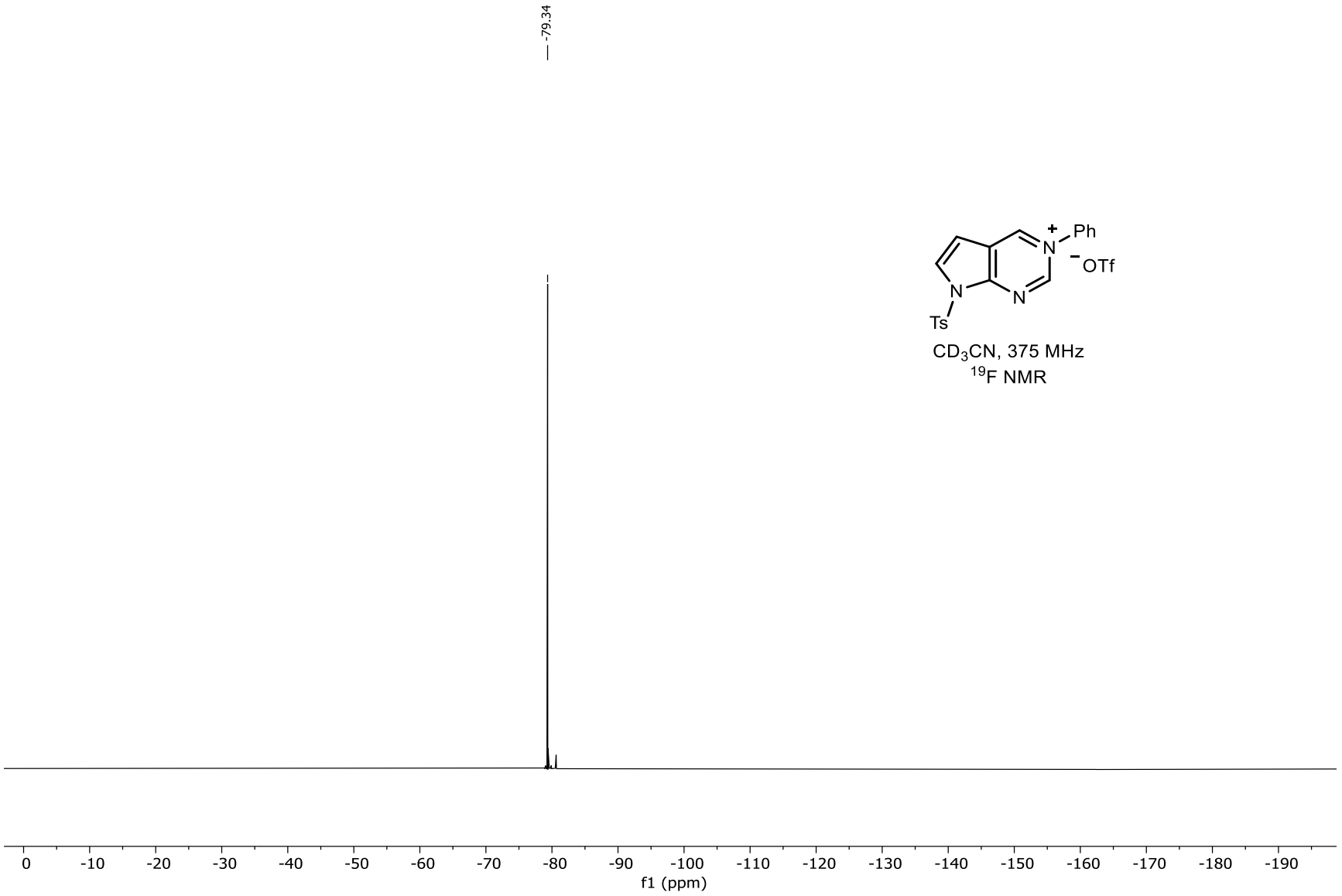

9.65
9.64
9.40
9.39
7.85
7.85
7.84
7.83
7.83
7.82
7.81
7.81
7.80
7.80
7.79
7.79
7.79
7.75
7.75
7.58
7.56
7.54
7.53
7.52
7.51
6.69
2.44
2.34
1.94 CD3CN
N
O
Me
Ph
N
OTf
N
Cl
Me
CD3CN, 400 MHz
1H NMR
1.00
1.01
5.22
1.03
2.16
1.00
3.17
3.15
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

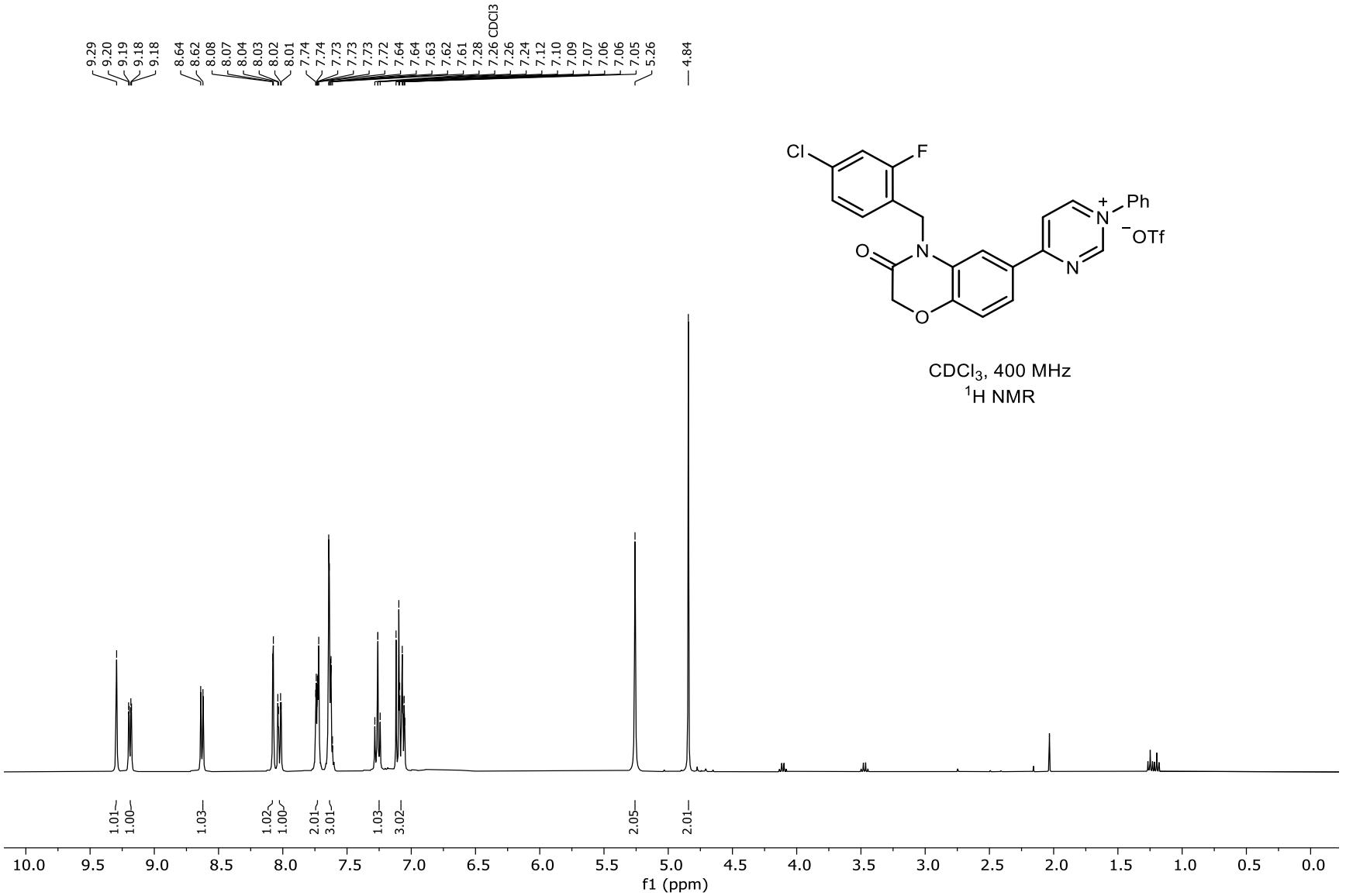

170.22
162.32
161.60
151.99
151.96
141.09
139.70
138.66
133.77
133.35
133.30
131.64
130.85
129.91
125.76
123.61
123.26
120.42
118.26
CD3CN
109.37
20.13
11.42
Me
N
O
Ph
N
OTf
N
Cl
Me
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

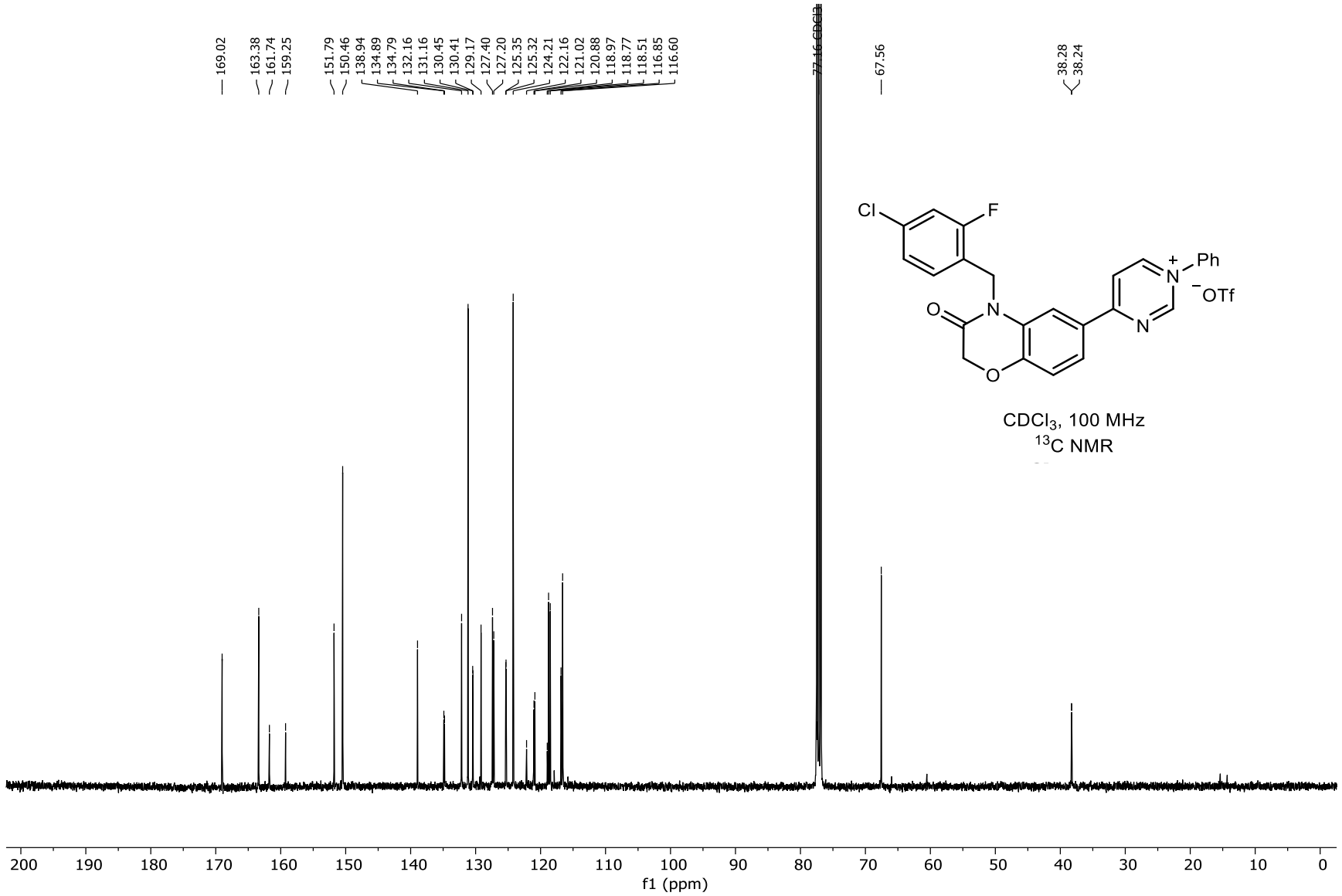

-79.30
N
O
Me
Ph
N
OTf
N
Cl
Me
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

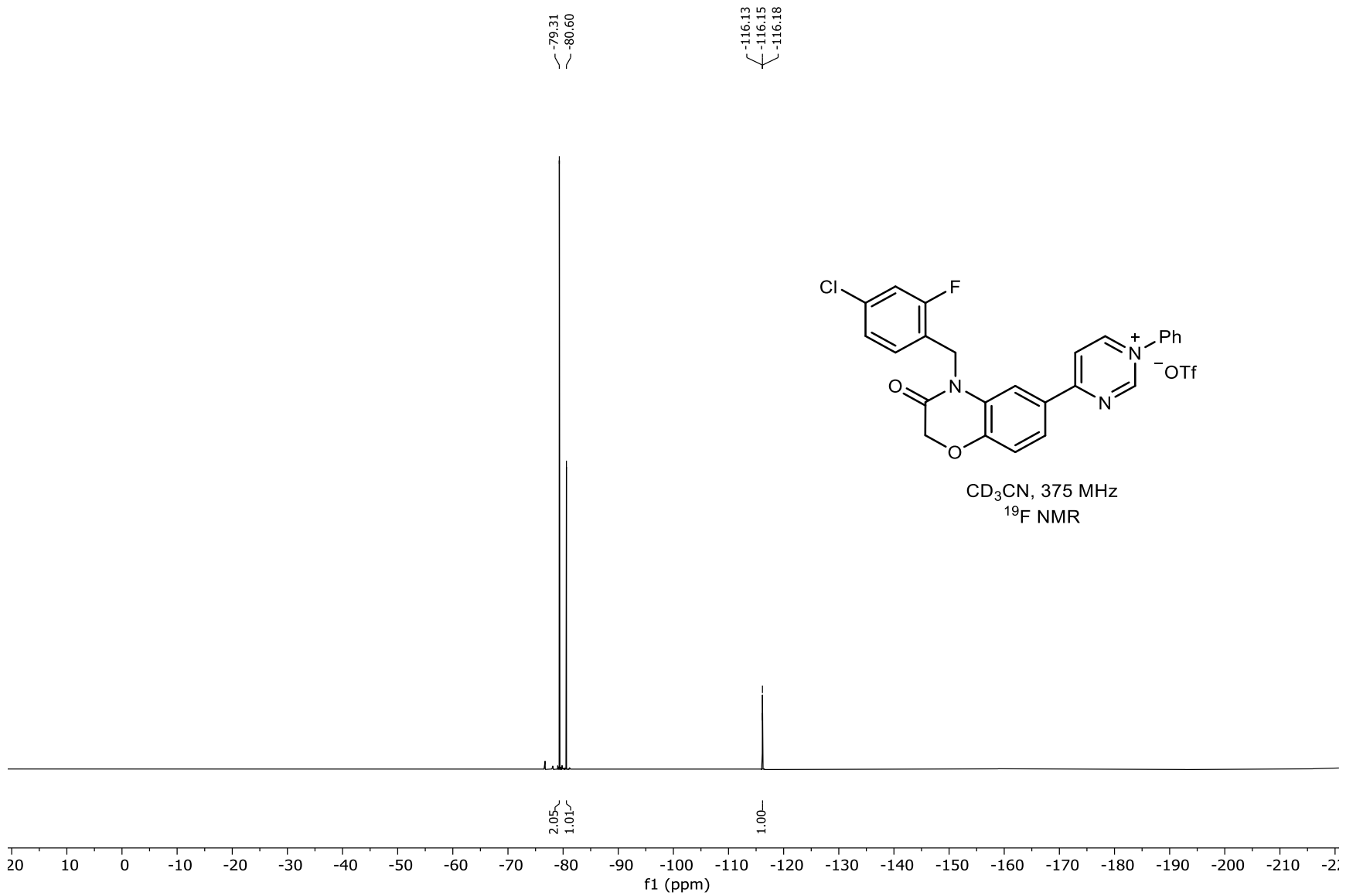

9.42
9.41
9.32
9.31
8.32
8.31
8.17
8.15
7.77
7.76
7.75
7.75
7.75
7.75
7.74
7.74
7.73
7.73
7.72
7.71
7.70
7.69
7.69
7.69
7.68
7.68
7.68
7.67
7.51
7.50
7.48
7.48
7.23
7.22
2.43
1.94 CD3CN
Ph
N
OTf
N
N
Ts
CD3CN, 400 MHz
1H NMR
1.00
0.99
1.01
2.02
5.21
2.12
1.07
3.16
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

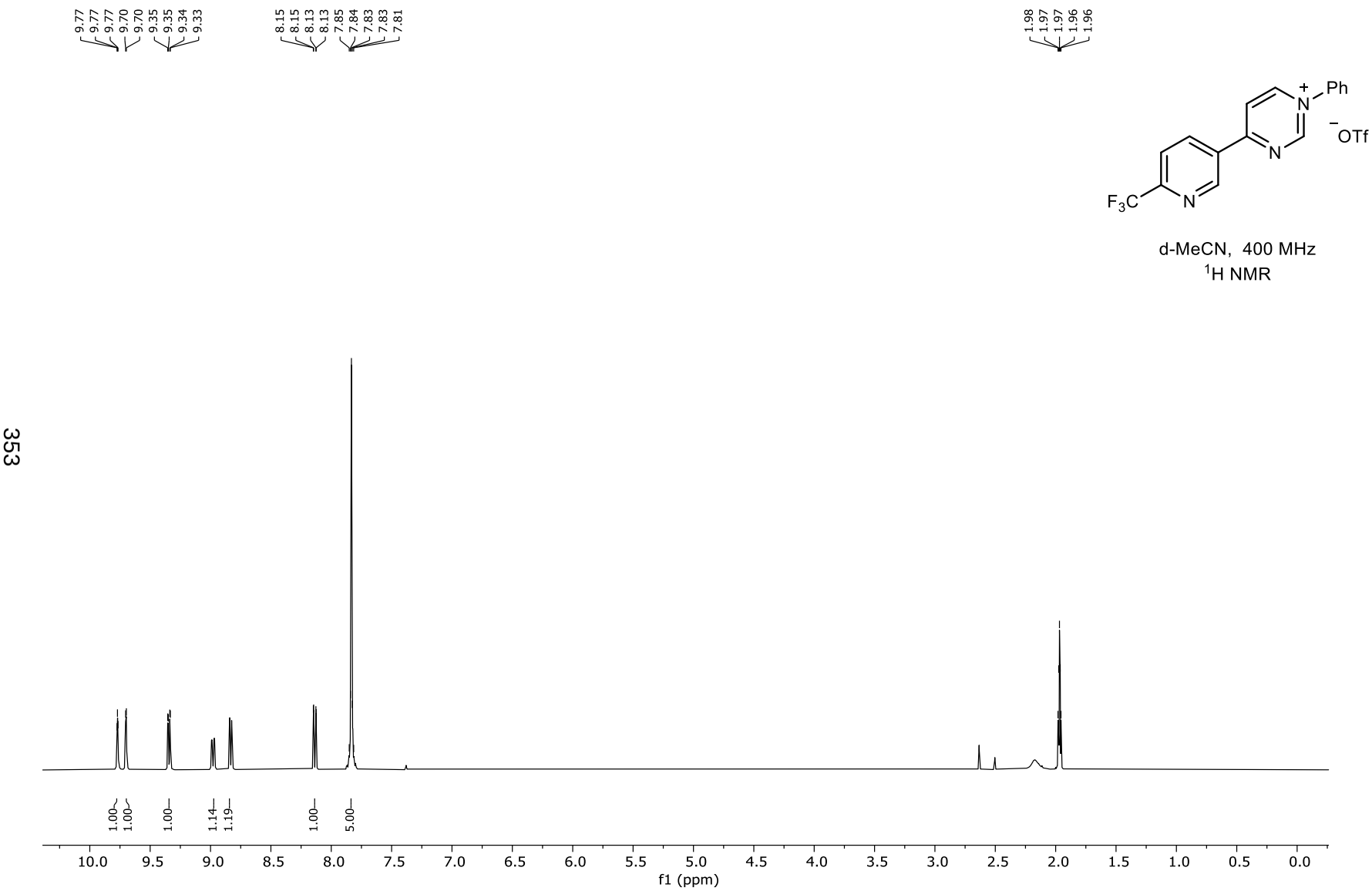

151.48
149.12
147.82
146.56
141.01
135.14
134.05
132.64
131.53
131.45
129.70
126.08
122.08
118.26 CD3CN
106.78
21.77
Ph
OTf
Ts
CD3CN, 100 MHz
13C NMR
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

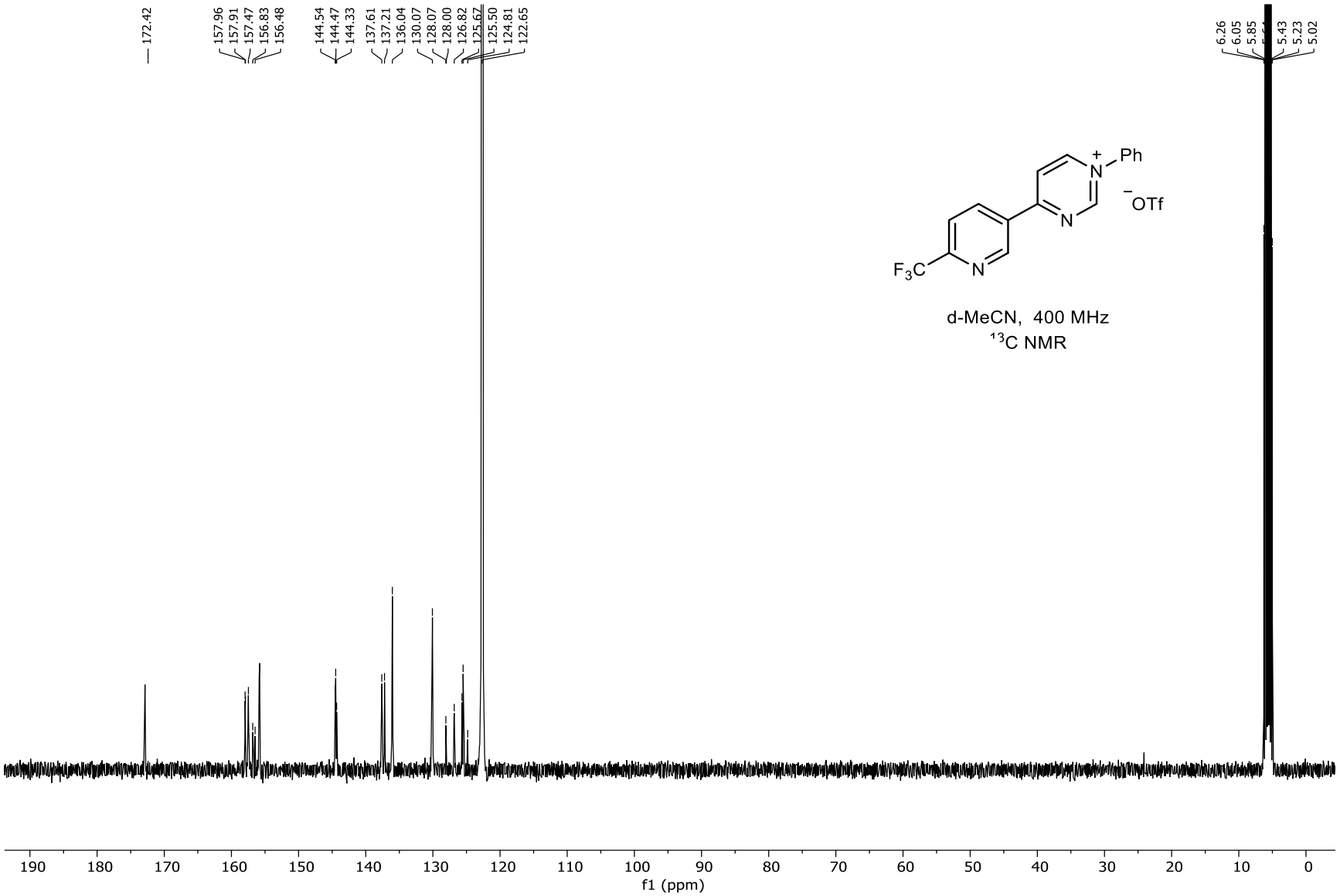

-79.34
Ph
N
OTf
N
N
Ts
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

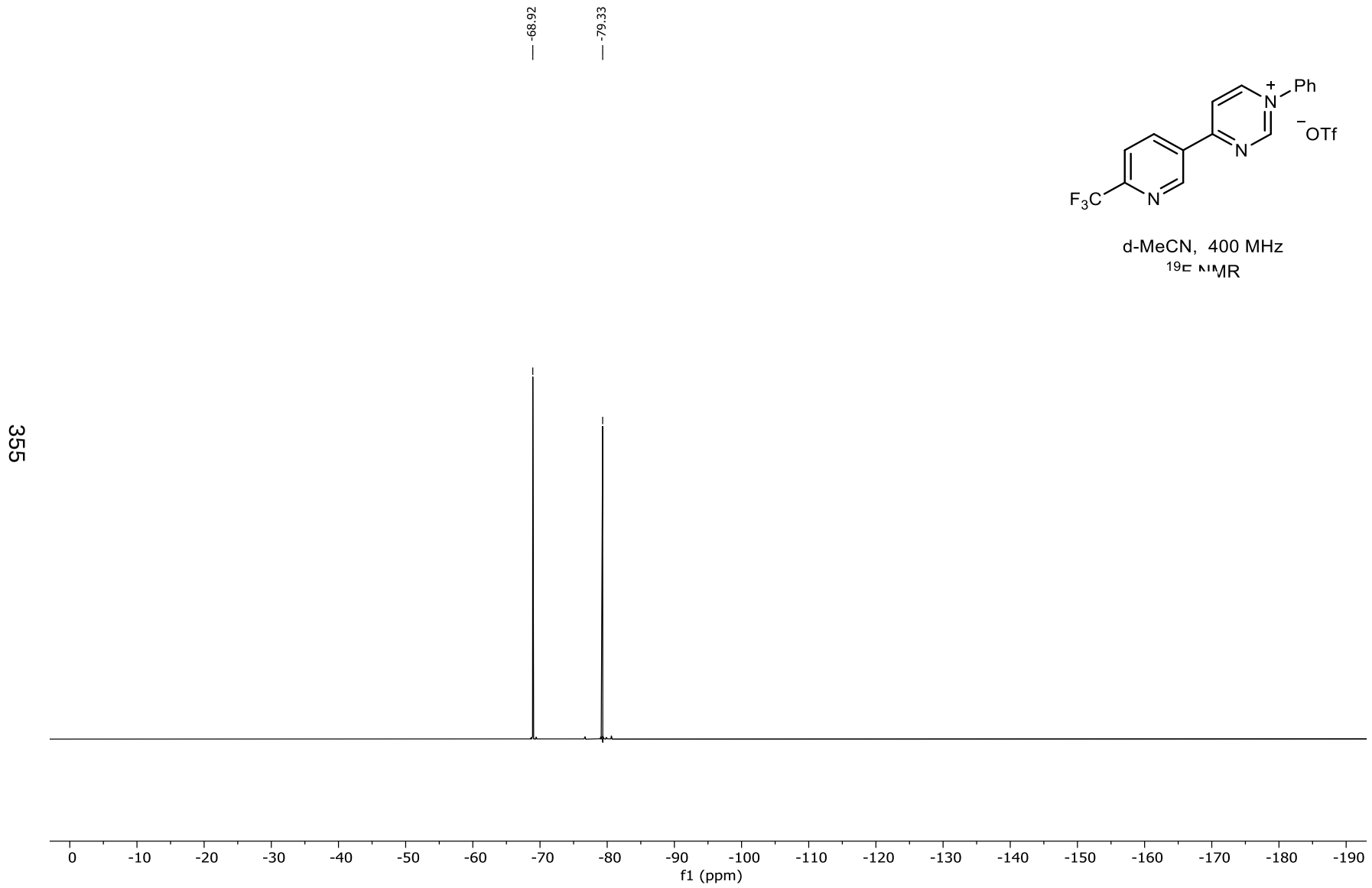

9.29
9.20
9.19
9.18
9.18
8.64
8.62
8.08
8.07
8.04
8.03
8.02
8.01
7.74
7.74
7.73
7.73
7.73
7.72
7.64
7.64
7.63
7.62
7.61
7.28
7.26 CDCl3
7.26
7.24
7.12
7.10
7.09
7.07
7.06
7.06
7.05
5.26
4.84
Cl
F
O
N
N
+
N
Ph
−
OTf
O
CDCl3, 400 MHz
1H NMR
1.01
1.00
1.03
1.02
1.00
2.01
3.01
1.03
3.02
2.05
2.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

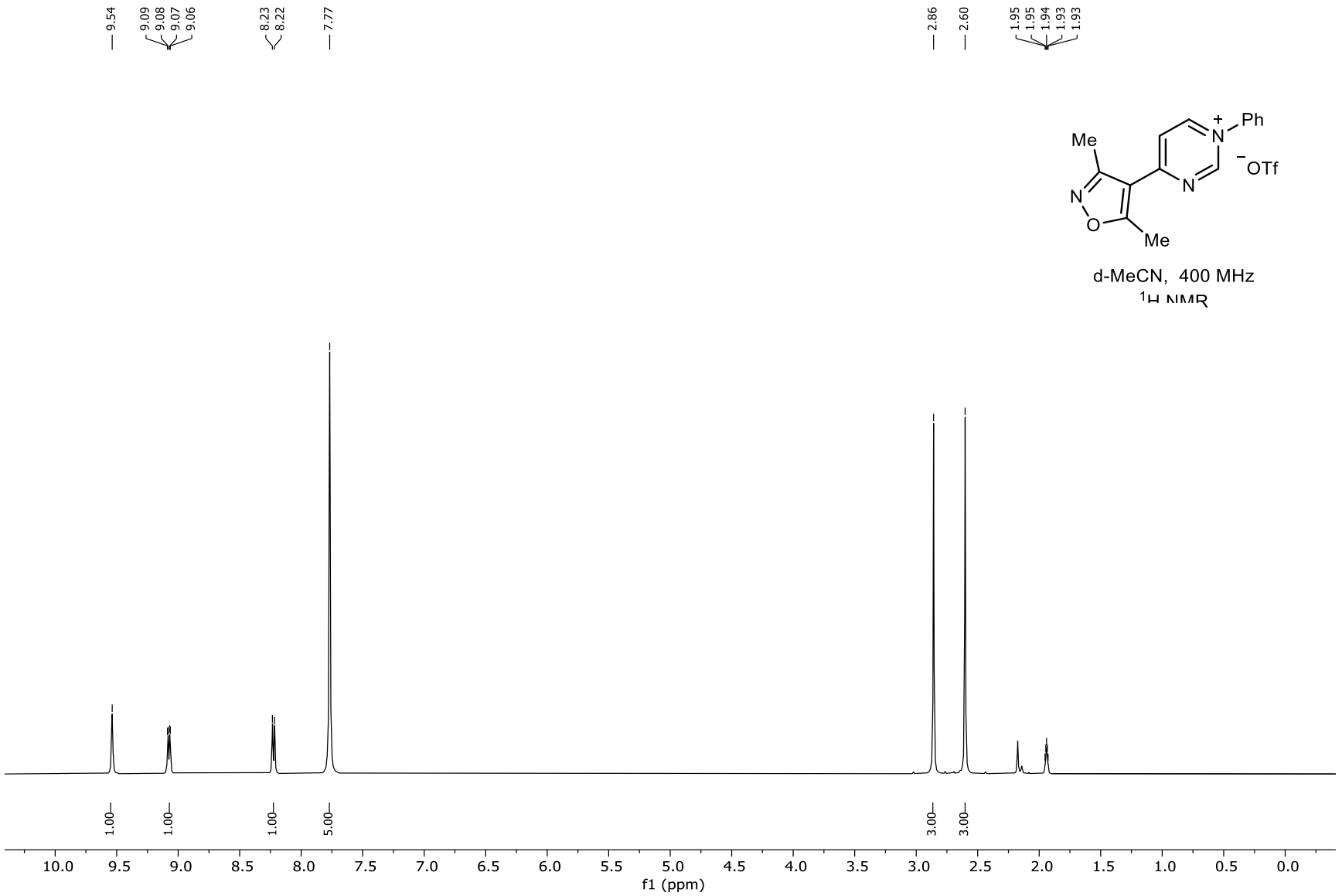

169.02
163.38
161.74
159.25
151.79
150.46
138.94
134.89
134.79
132.16
131.16
130.45
130.41
129.17
127.40
127.20
125.35
125.32
124.21
122.16
121.02
120.88
118.97
118.77
118.51
116.85
116.60
77.16
67.56
38.28
38.24
Cl
F
Ph
OTf
O
N
O
N
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

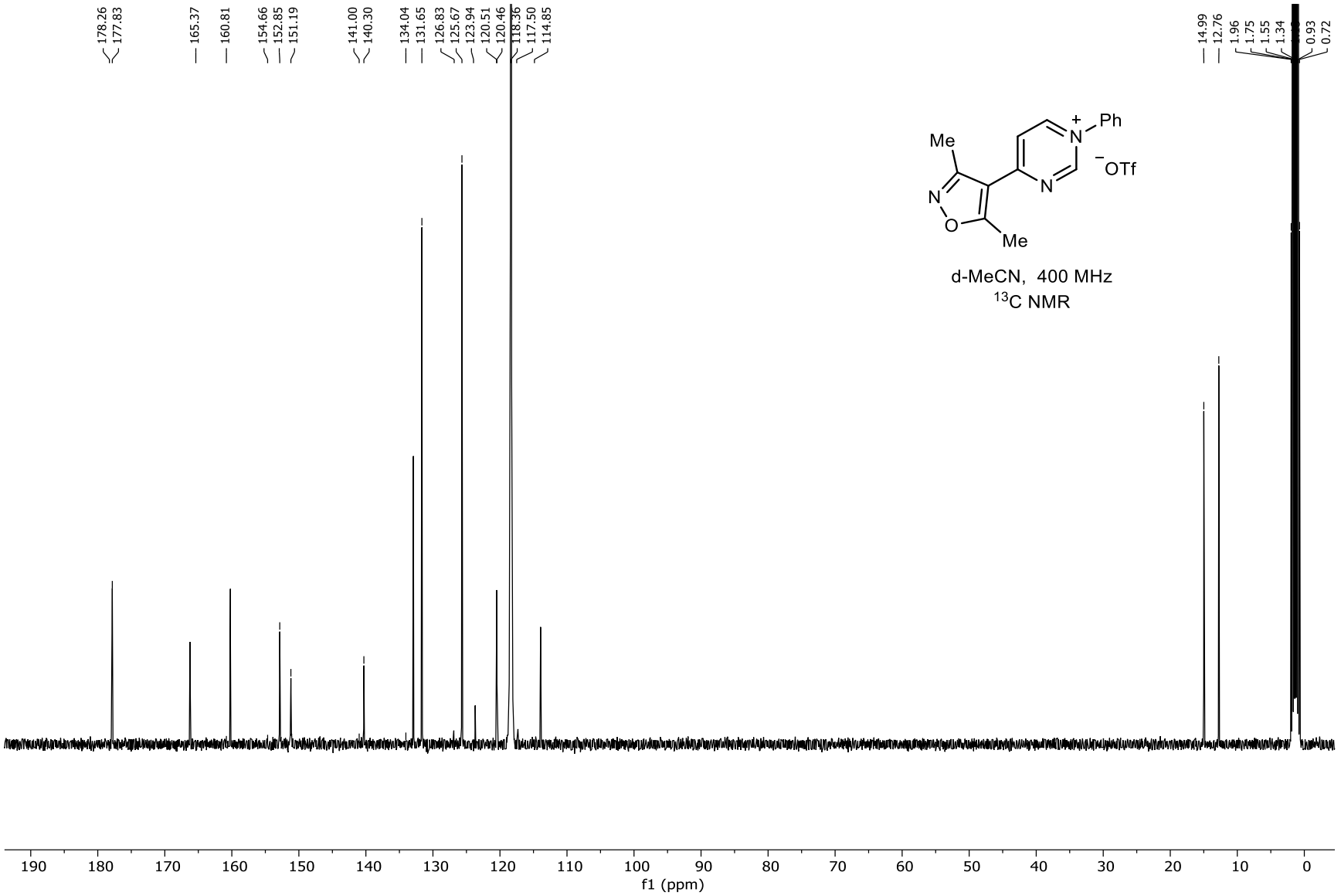

-79.31
-80.60
-116.13
-116.15
-116.18
Cl
F
O
N
O
N
+
N
Ph
−
OTf
CD3CN, 375 MHz
19F NMR
2.05
1.01
1.00
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

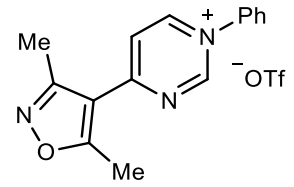

9.77
9.77
9.77
9.70
9.70
9.35
9.35
9.34
9.33
8.15
8.15
8.13
8.13
7.85
7.84
7.83
7.83
7.81
1.98
1.97
1.97
1.96
1.96
Ph
N
OTf
N
F3C
d-MeCN, 400 MHz
1H NMR
1.00
1.00
1.00
1.14
1.19
1.00
5.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


172.42
157.96
157.91
157.47
156.83
156.48
144.54
144.47
144.33
137.61
137.21
136.04
130.07
128.07
128.00
126.82
125.67
125.50
124.81
122.65
6.26
6.05
5.85
5.43
5.23
5.02
Ph
N
OTf
N
F3C
d-MeCN, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-68.92
-79.33
Ph
N
+
OTf
N
F3C
N
d-MeCN, 400 MHz
19F NMR
355
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


9.54
9.09
9.08
9.07
9.06
8.23
8.22
7.77
2.86
2.60
1.95
1.95
1.94
1.93
1.93
Me
N
O
Me
N
+
Ph
N
−
OTf
d-MeCN, 400 MHz
1H NMR
1.00
1.00
1.00
5.00
3.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


178.26
177.83
165.37
160.81
154.66
152.85
151.19
141.00
140.30
134.04
131.65
126.83
125.67
123.94
120.51
120.46
118.36
117.50
114.85
14.99
12.76
1.96
1.75
1.55
1.34
0.93
0.72
Me
N
O
Me
N
+
Ph
N
−
OTf
d-MeCN, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



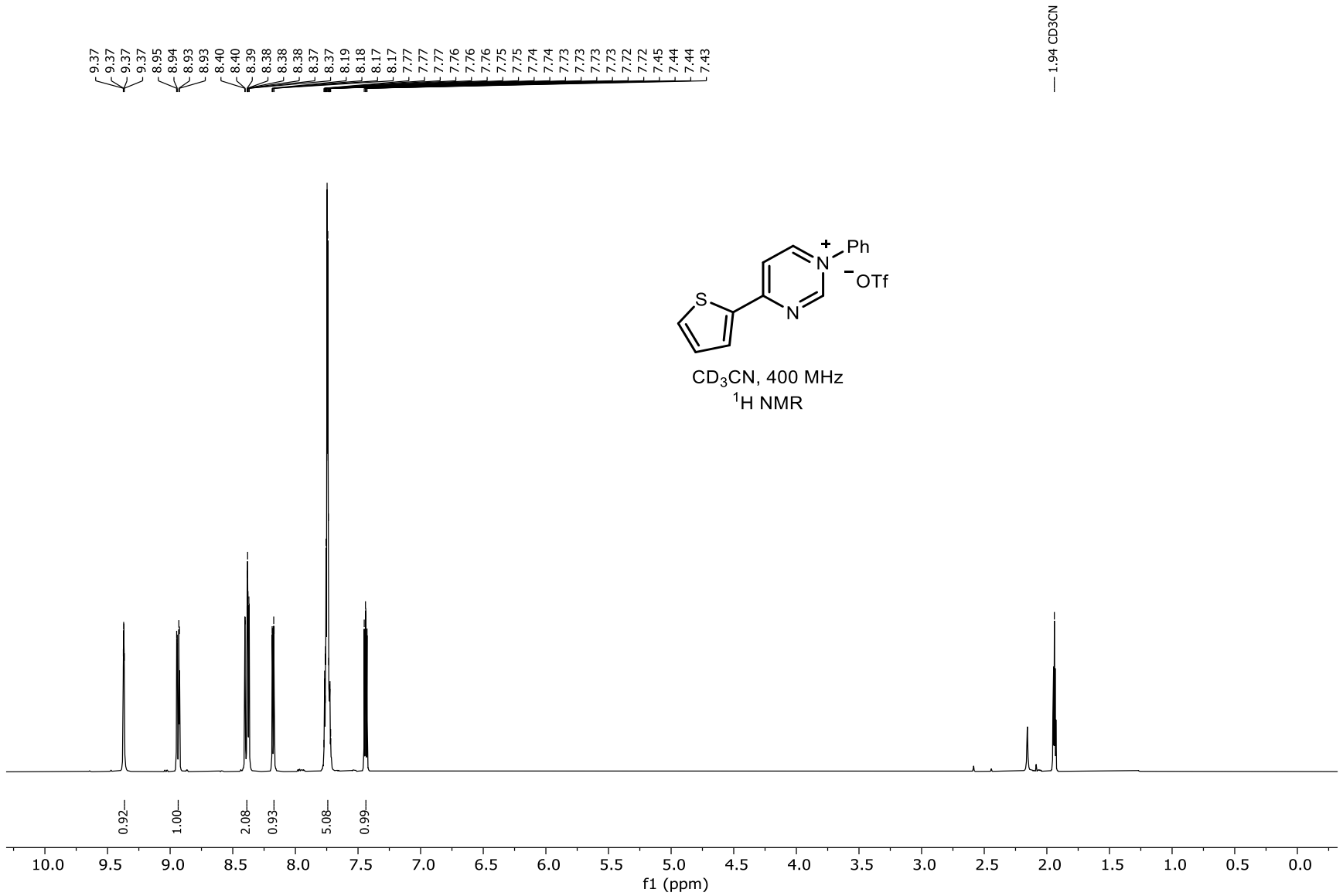
d-MeCN, 400 MHz

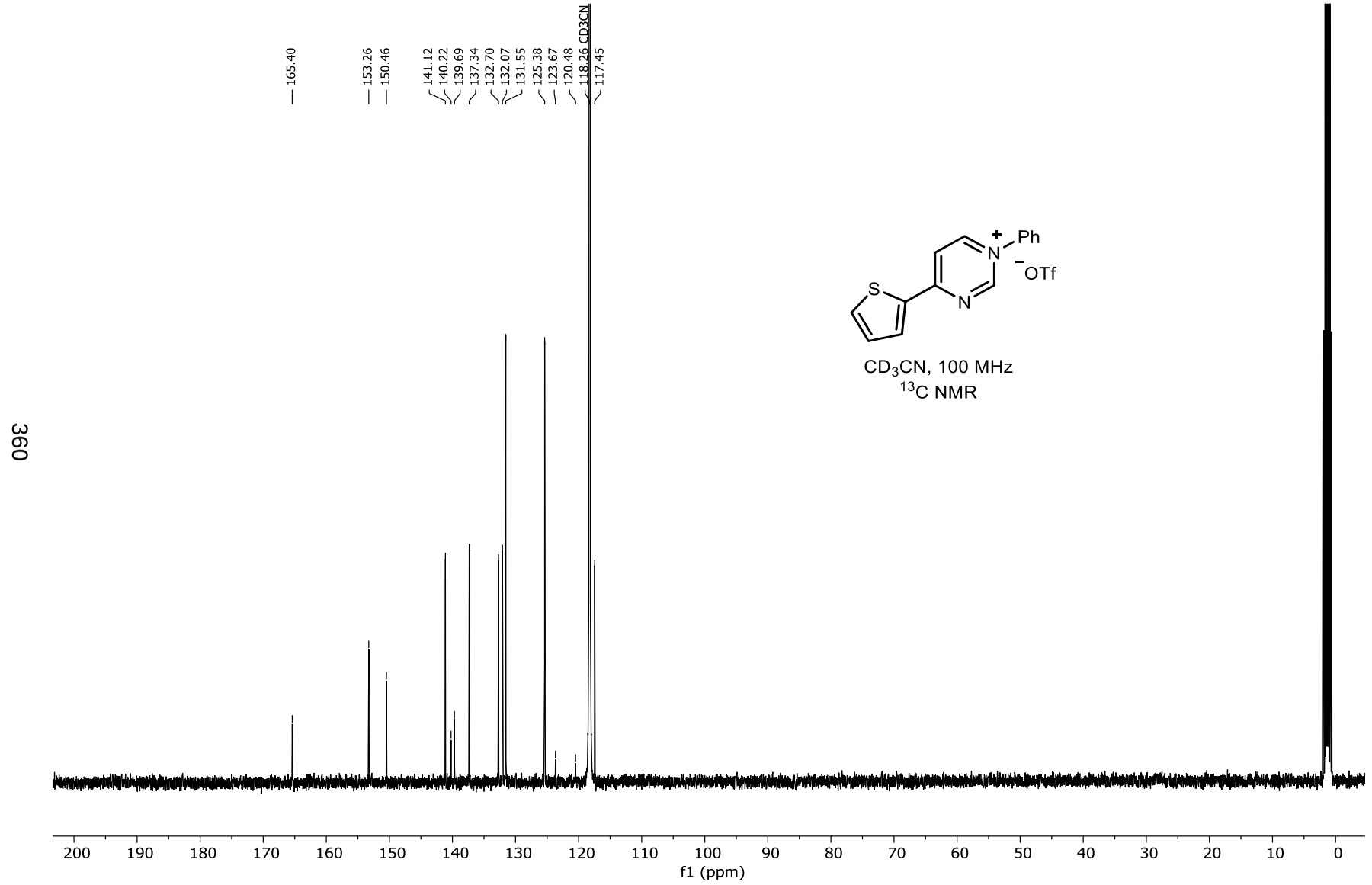
^{19}F NMR

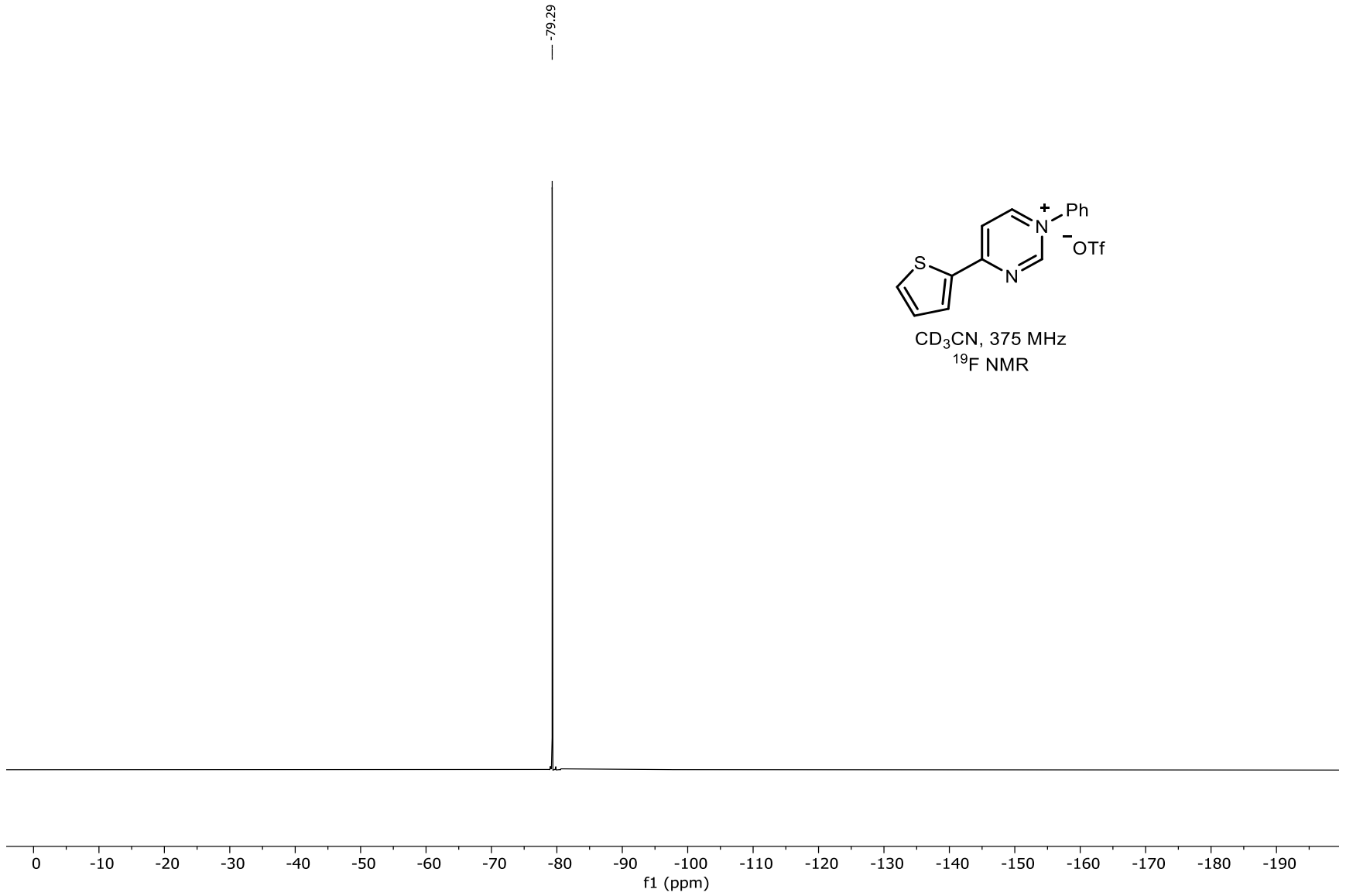
-79.28

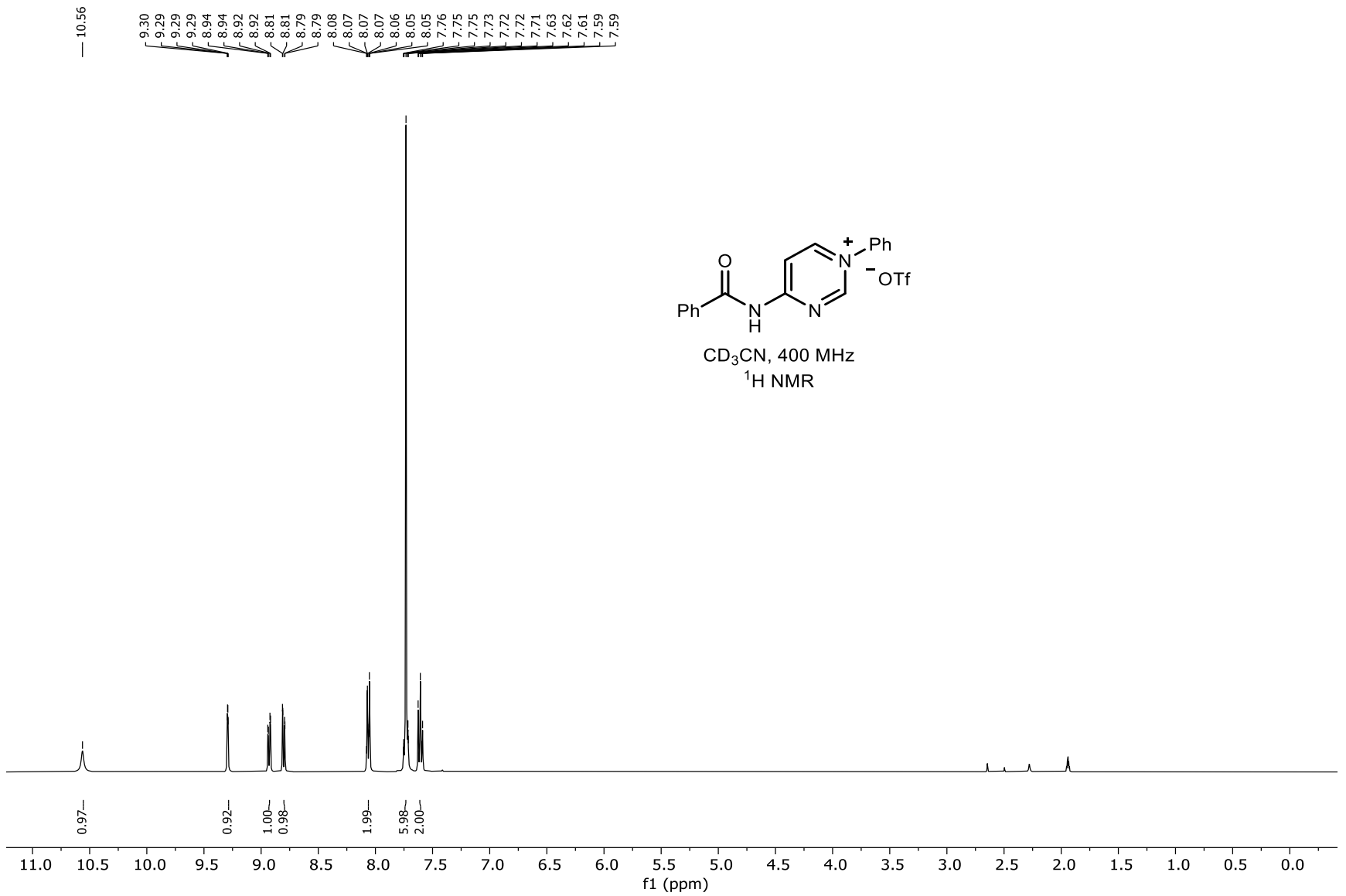
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

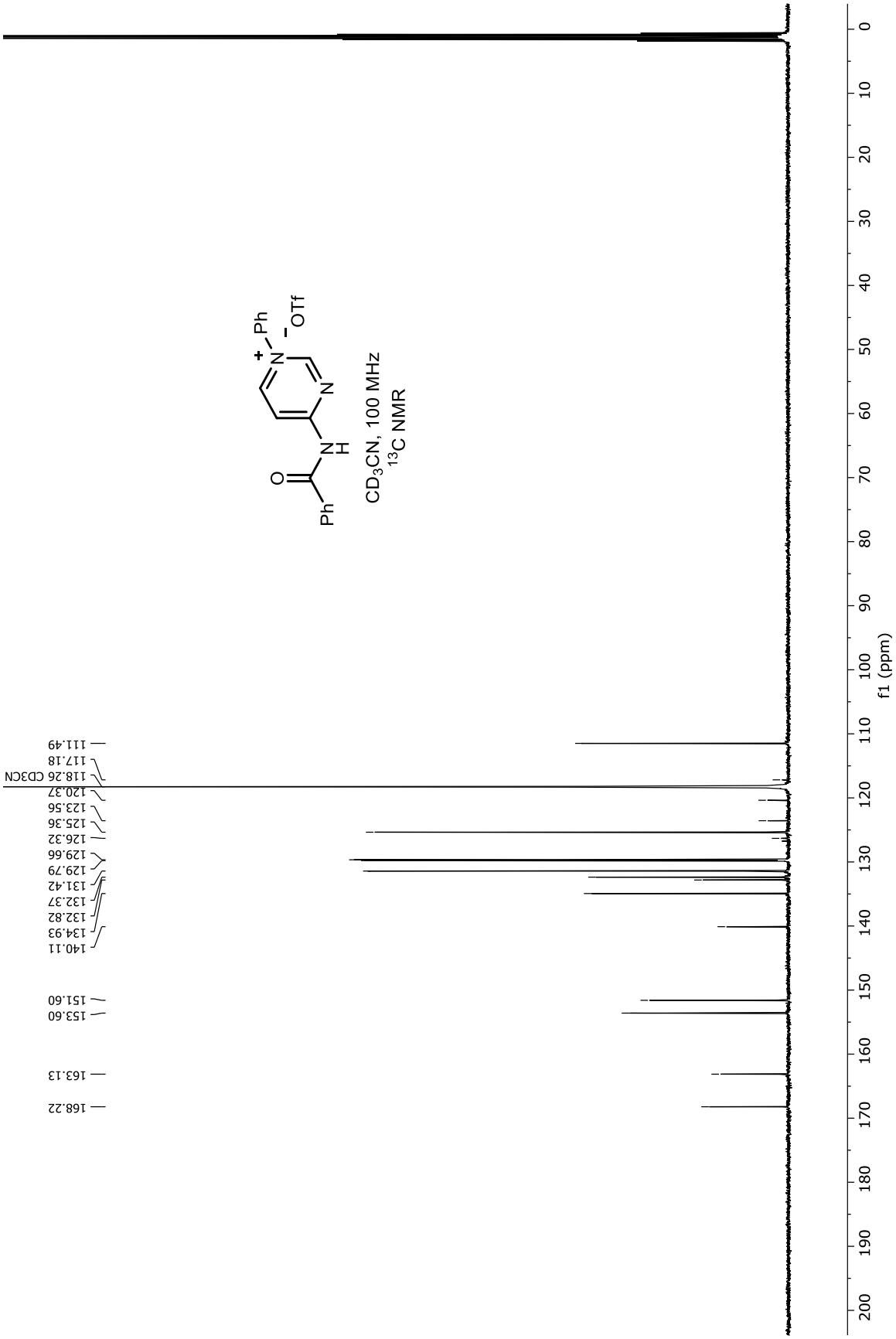
f1 (ppm)


9.37
9.37
9.37
9.37
8.95
8.94
8.93
8.93
8.40
8.40
8.39
8.38
8.38
8.38
8.37
8.37
8.19
8.18
8.17
8.17
7.77
7.77
7.77
7.76
7.76
7.76
7.75
7.75
7.74
7.74
7.73
7.73
7.73
7.73
7.72
7.72
7.45
7.44
7.44
7.43
1.94 CD3CN
Ph
N
OTf
S
N
CD3CN, 400 MHz
1H NMR
0.92
1.00
2.08
0.93
5.08
0.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

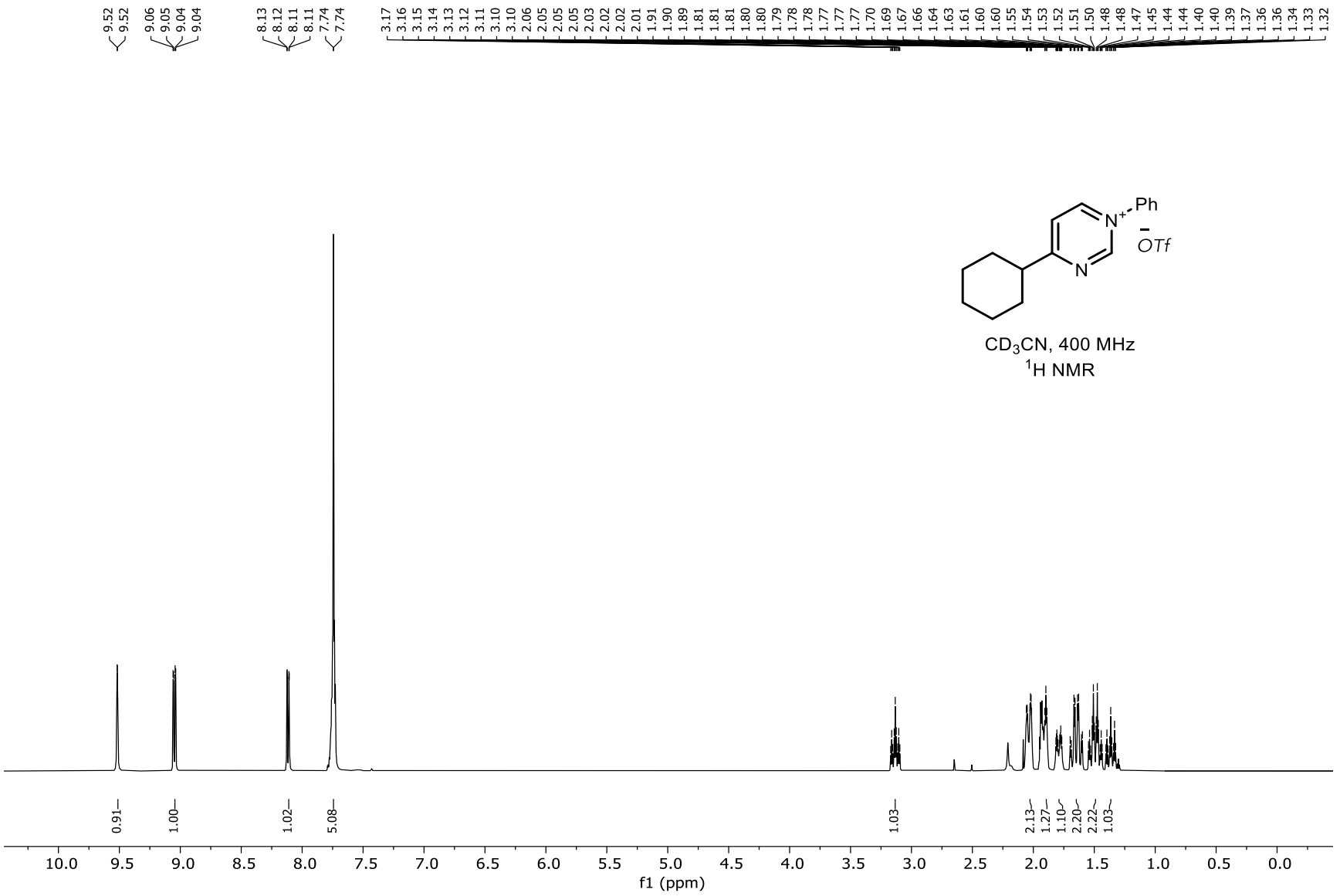

165.40
153.26
150.46
141.12
140.22
139.69
137.34
132.70
132.07
131.55
125.38
123.67
120.48
118.26 CD3CN
117.45
Ph
N
OTf
S
N
CD3CN, 100 MHz
13C NMR
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

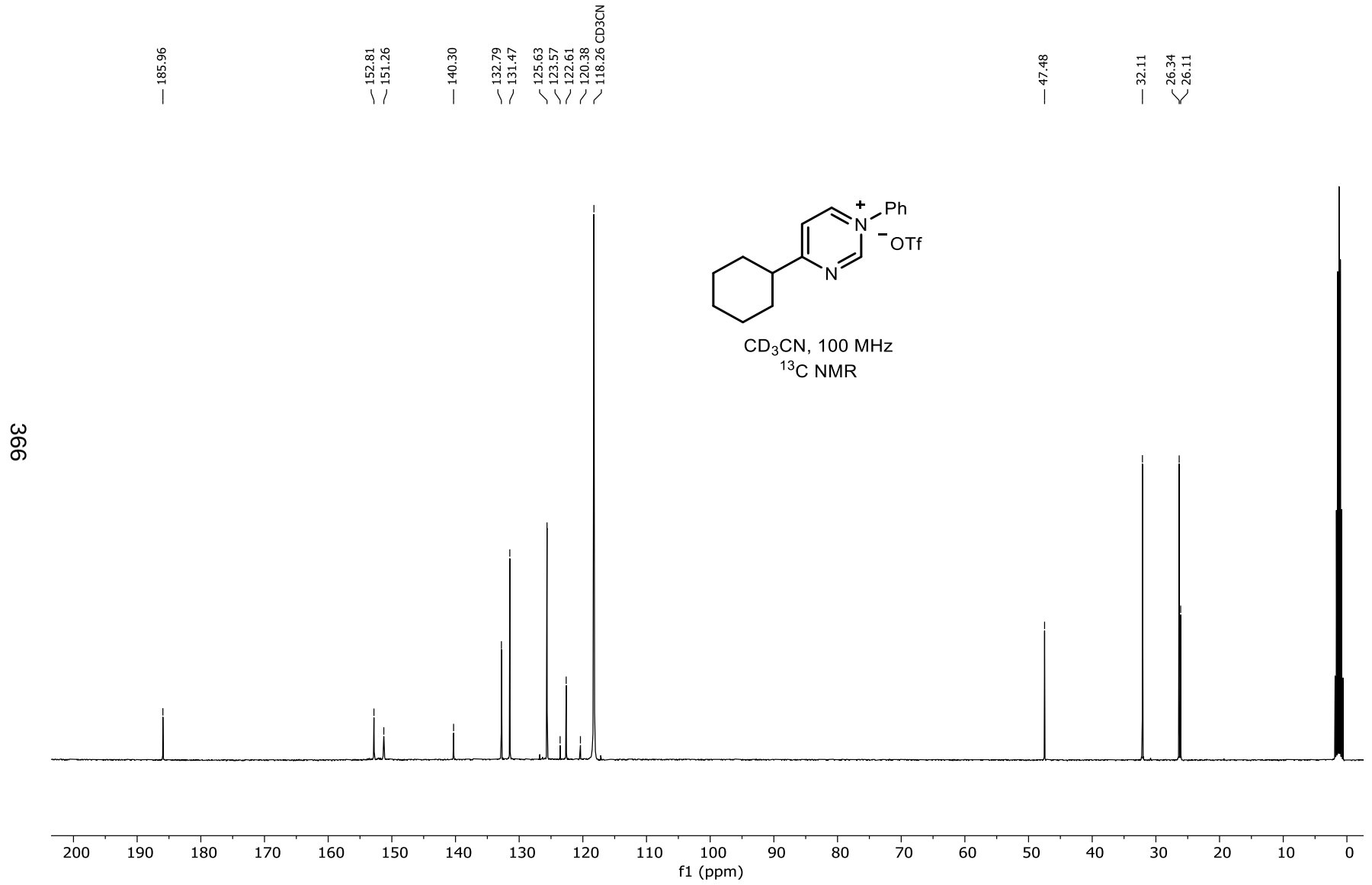

-79.29
Ph
N
OTf
S
N
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

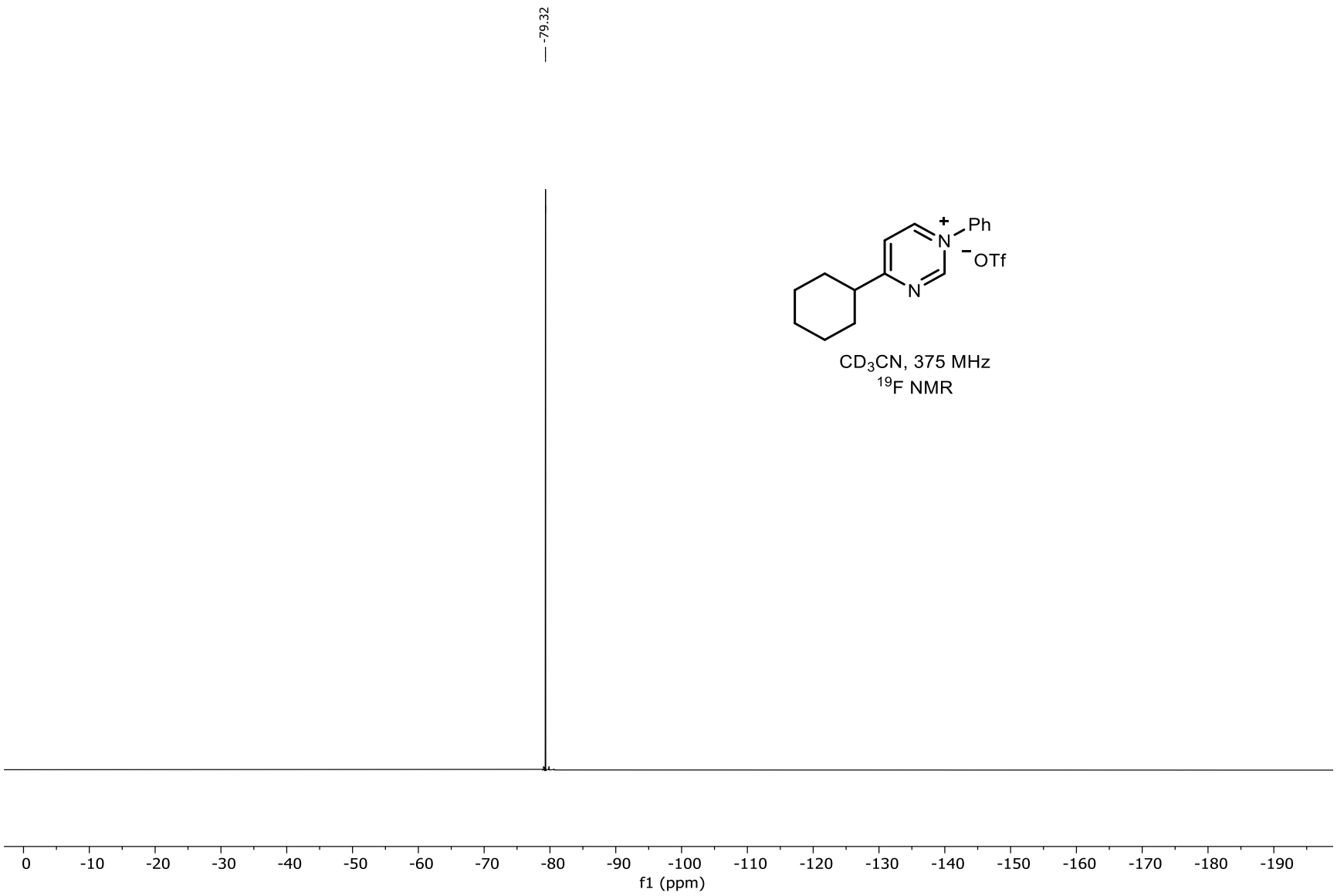

10.56
9.30
9.29
9.29
9.29
8.94
8.92
8.92
8.81
8.81
8.79
8.79
8.08
8.07
8.07
8.07
8.06
8.05
8.05
7.76
7.75
7.75
7.73
7.72
7.72
7.71
7.63
7.62
7.61
7.59
7.59
O
Ph
N
H
N
N
+
Ph
−
OTf
CD3CN, 400 MHz
1H NMR
0.97
0.92
1.00
0.98
1.99
5.98
2.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

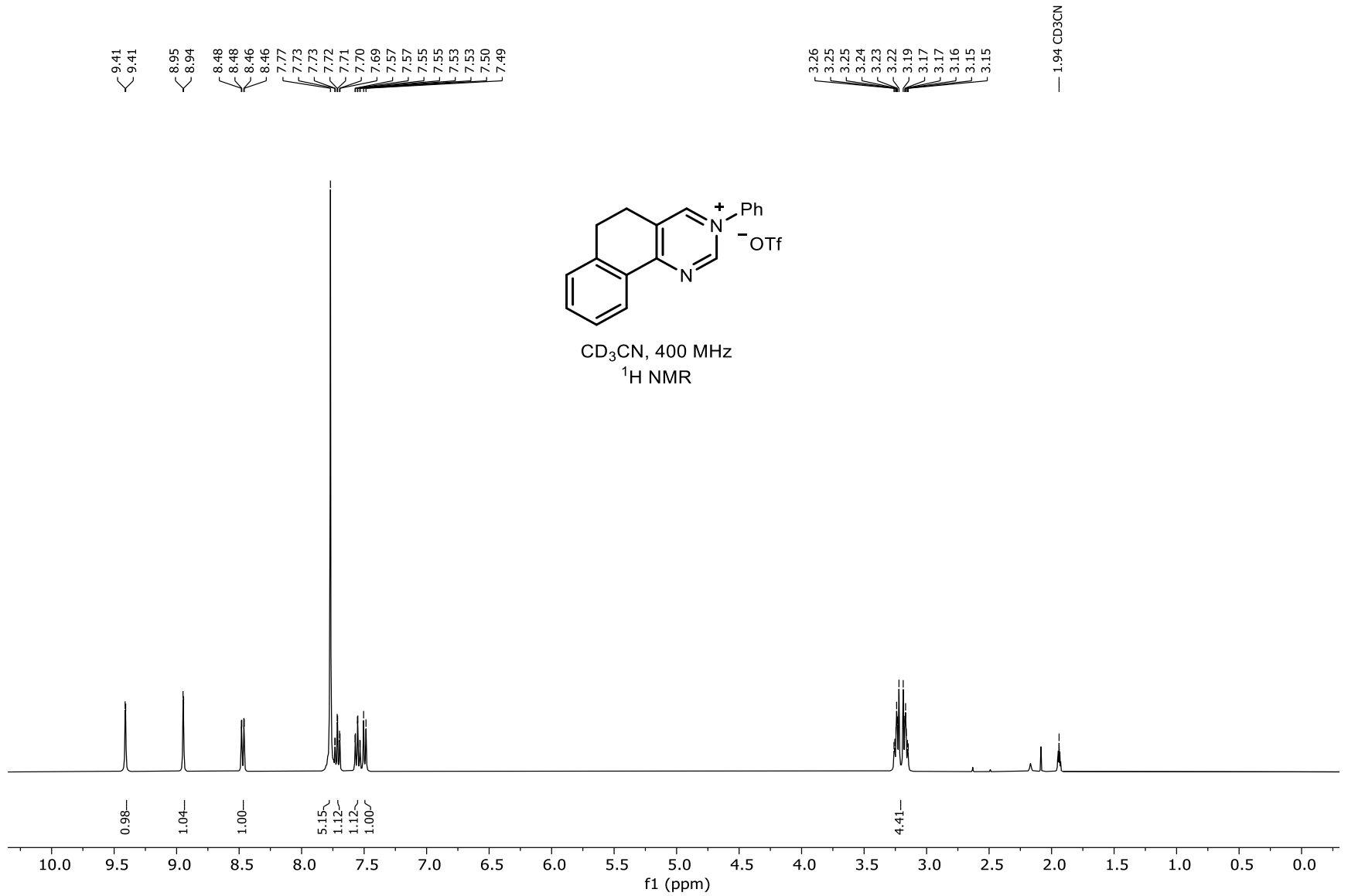

Ph
OTf
O
Ph
CD3CN, 100 MHz
13C NMR
168.22
163.13
153.60
151.60
140.11
134.93
132.82
132.37
131.42
129.79
129.66
126.32
125.36
123.56
120.37
118.26 CD3CN
117.18
111.49
f1 (ppm)

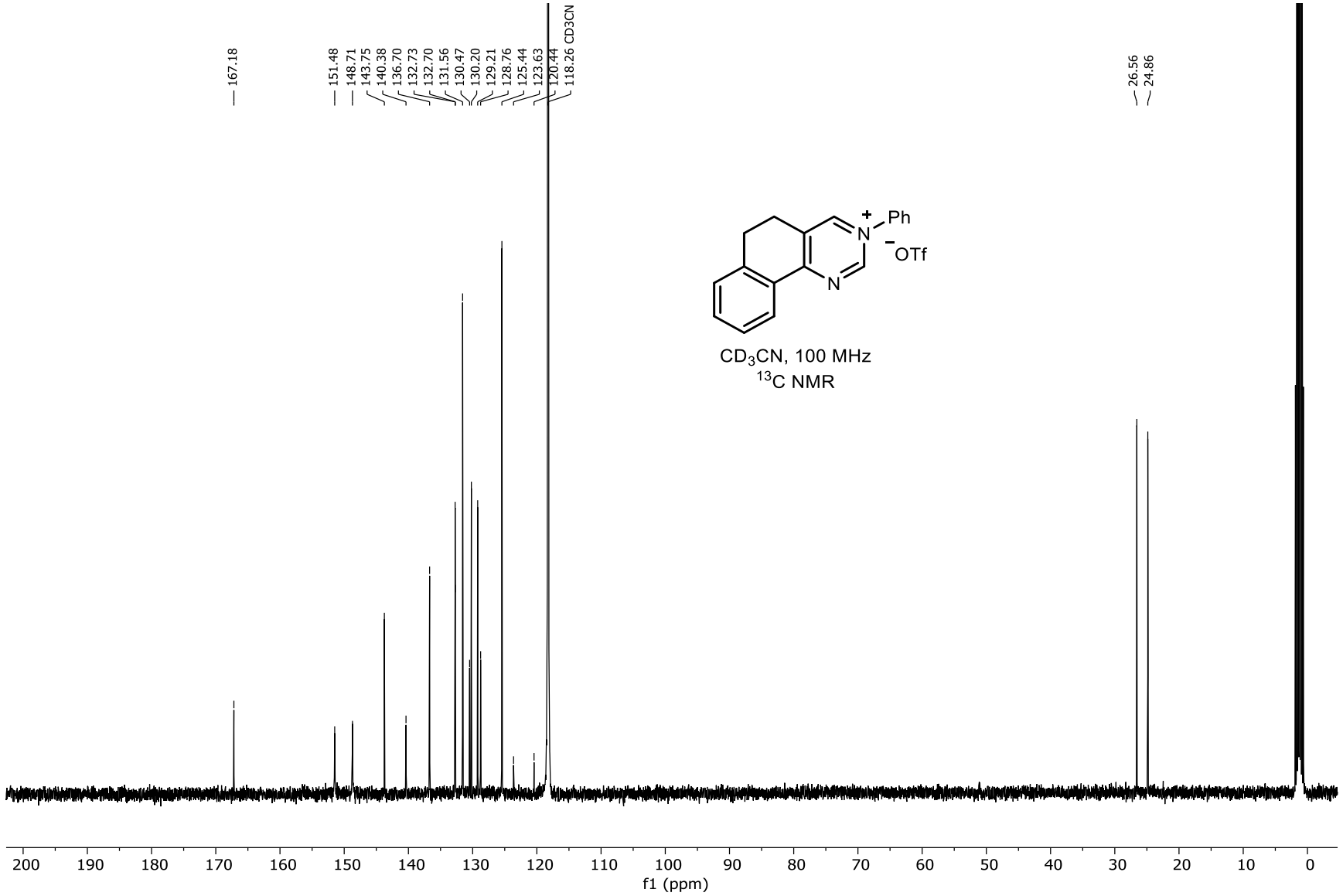

-79.20
O
Ph
N
H
N
N
Ph
OTf
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


9.52
9.52
9.06
9.05
9.04
9.04
8.13
8.12
8.11
8.11
7.74
7.74
3.17
3.16
3.15
3.14
3.13
3.12
3.11
3.10
3.10
2.06
2.05
2.05
2.03
2.02
2.02
2.01
1.91
1.90
1.89
1.81
1.81
1.81
1.80
1.80
1.79
1.78
1.78
1.77
1.77
1.77
1.70
1.69
1.67
1.66
1.64
1.63
1.61
1.60
1.60
1.55
1.54
1.53
1.52
1.51
1.50
1.48
1.48
1.47
1.45
1.44
1.44
1.40
1.40
1.39
1.37
1.36
1.36
1.34
1.33
1.32
Ph
N+
OTf
N
CD3CN, 400 MHz
1H NMR
0.91
1.00
1.02
5.08
1.03
2.13
1.27
1.10
2.20
2.22
1.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

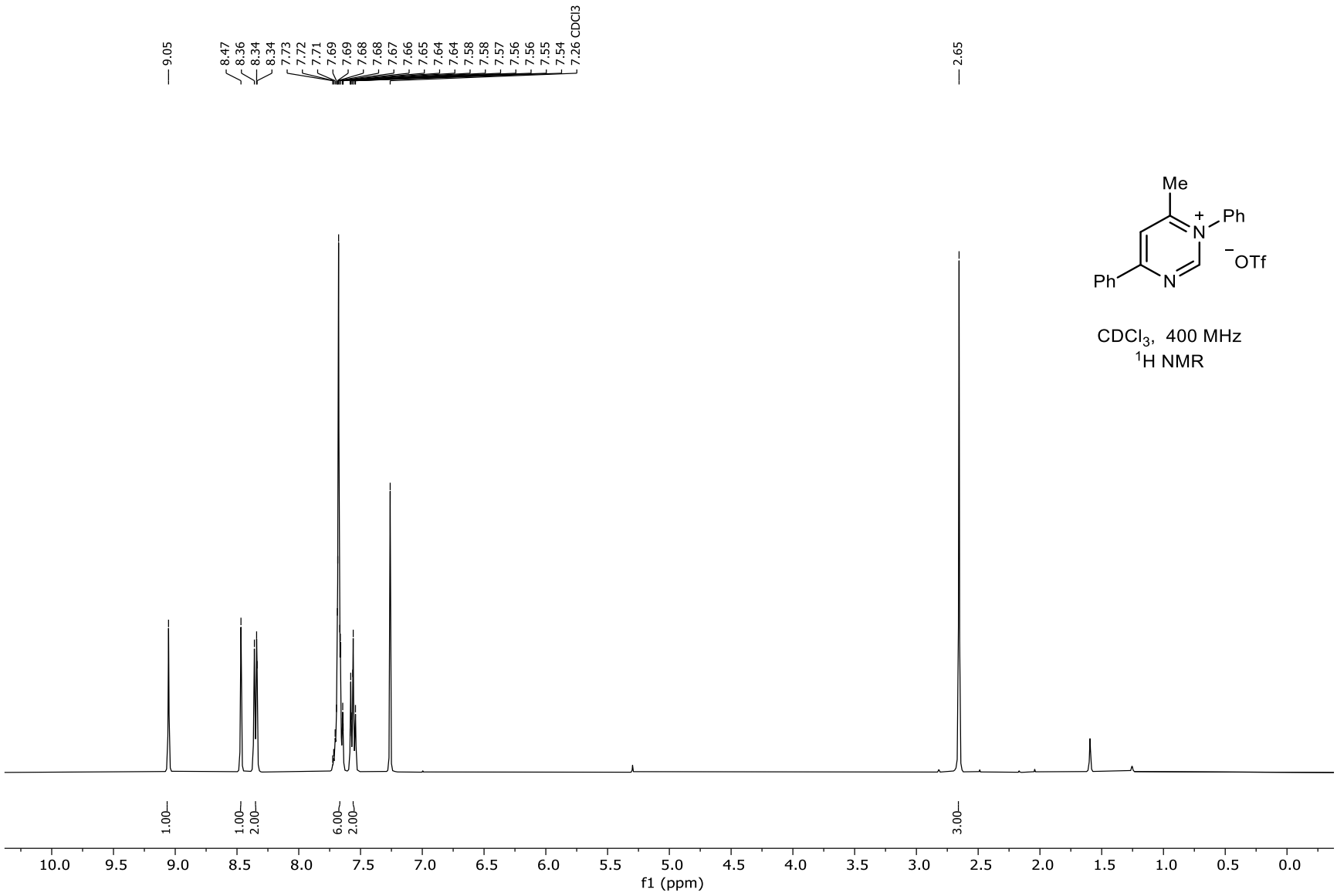

185.96
152.81
151.26
140.30
132.79
131.47
125.63
123.57
122.61
120.38
118.26 CD3CN
47.48
32.11
26.34
26.11
Ph
N
OTf
N
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

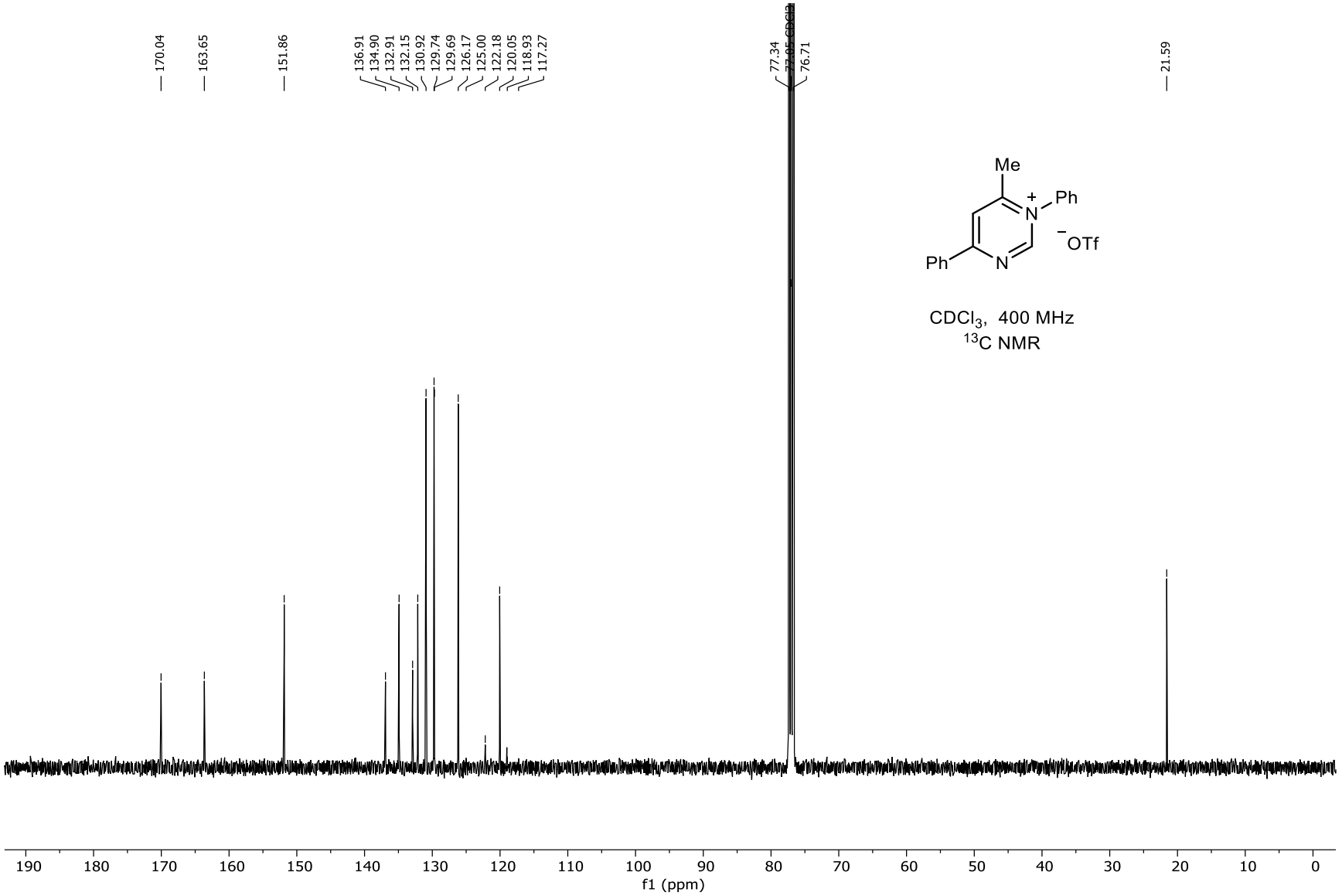

-79.32
Ph
N
OTf
N
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

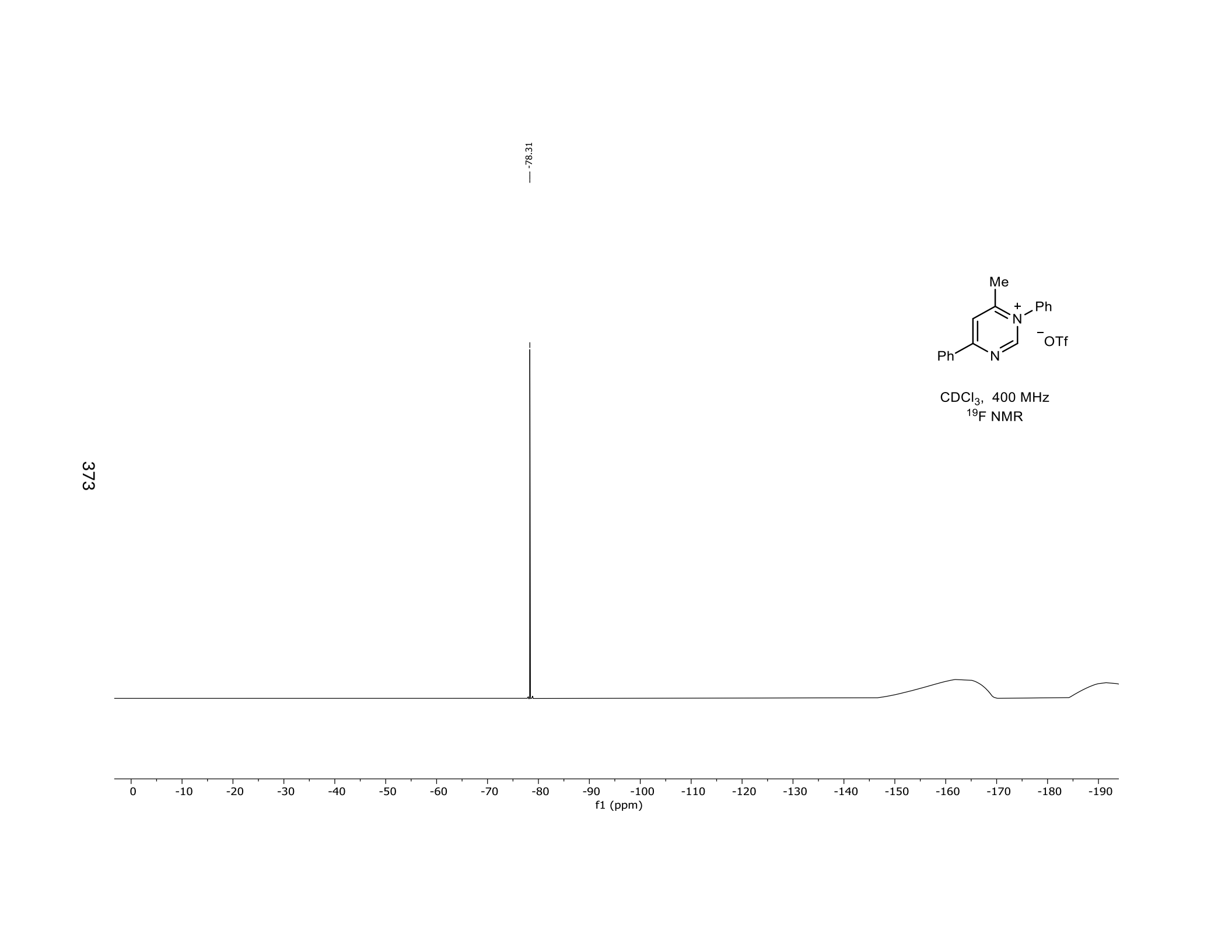

9.41
9.41
8.95
8.94
8.48
8.48
8.46
8.46
7.77
7.73
7.73
7.72
7.71
7.70
7.69
7.57
7.57
7.55
7.55
7.53
7.53
7.50
7.49
3.26
3.25
3.25
3.24
3.23
3.22
3.19
3.17
3.17
3.16
3.15
3.15
1.94 CD3CN
Ph
N
OTf
N
CD3CN, 400 MHz
1H NMR
0.98
1.04
1.00
5.15
1.12
1.12
1.00
4.41
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

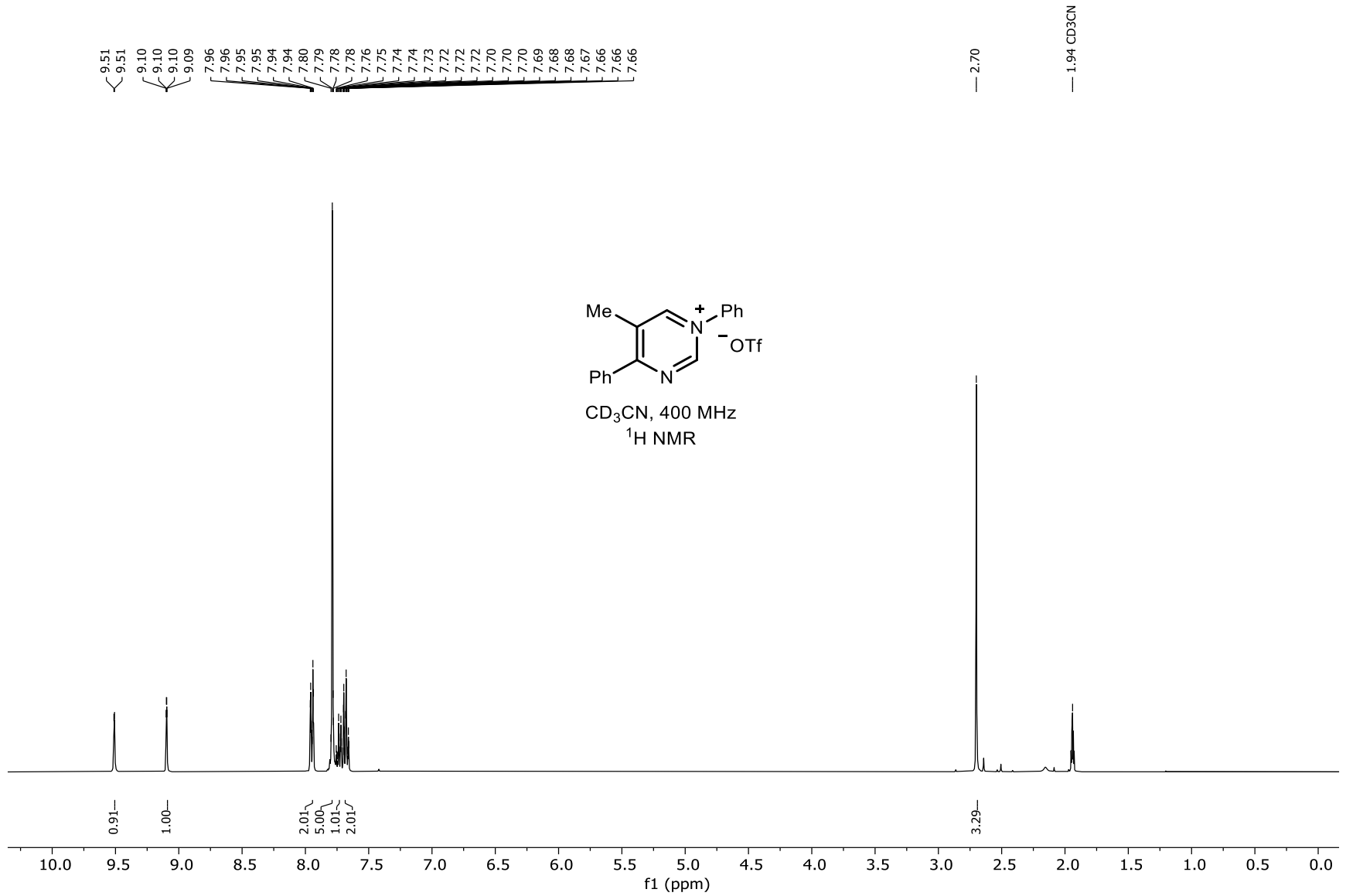

167.18
151.48
148.71
143.75
140.38
136.70
132.73
132.70
131.56
130.47
130.20
129.21
128.76
125.44
123.63
120.44
118.26 CD3CN
26.56
24.86
Ph
N
OTf
N
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

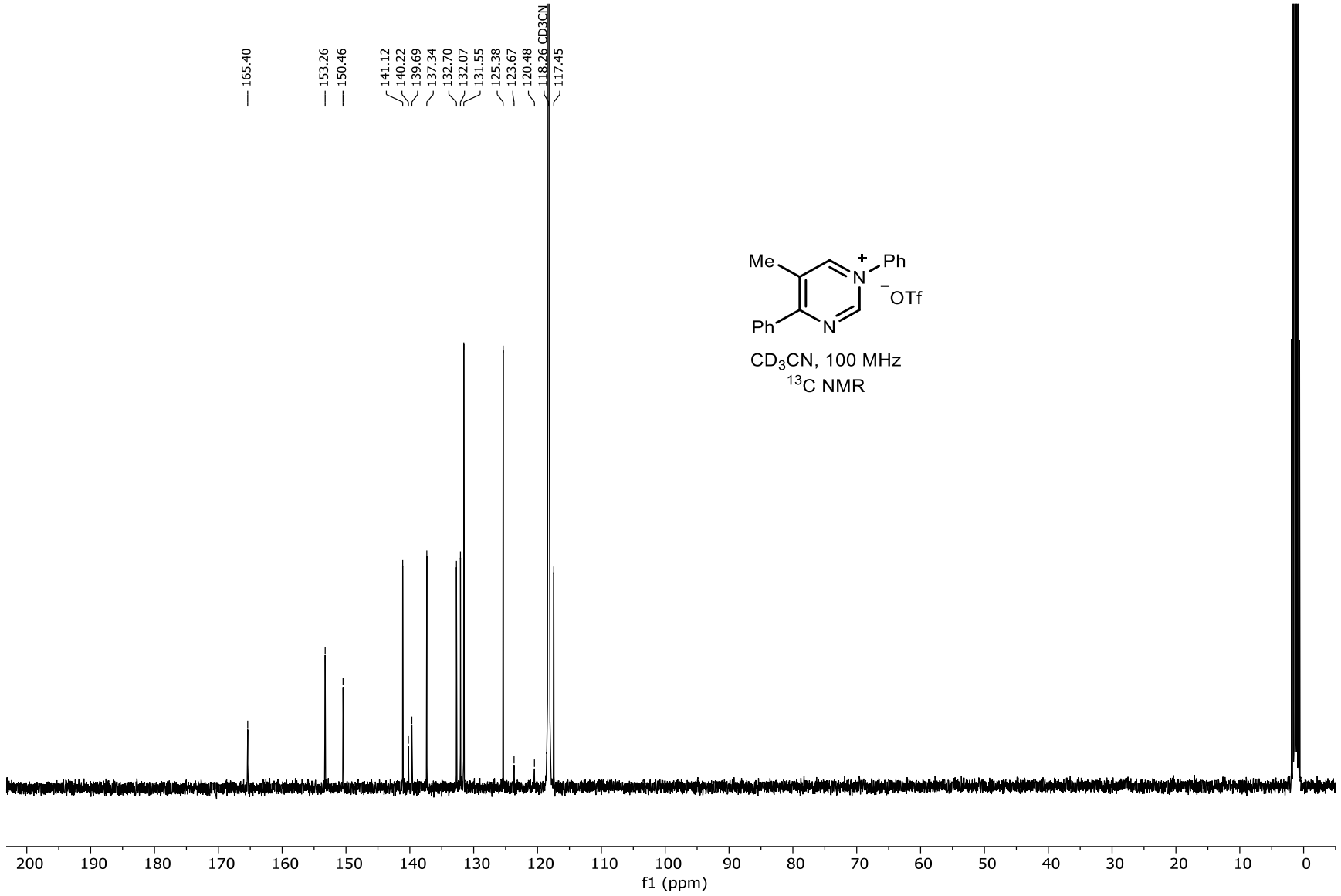

-79.28
Ph
N
OTf
N
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

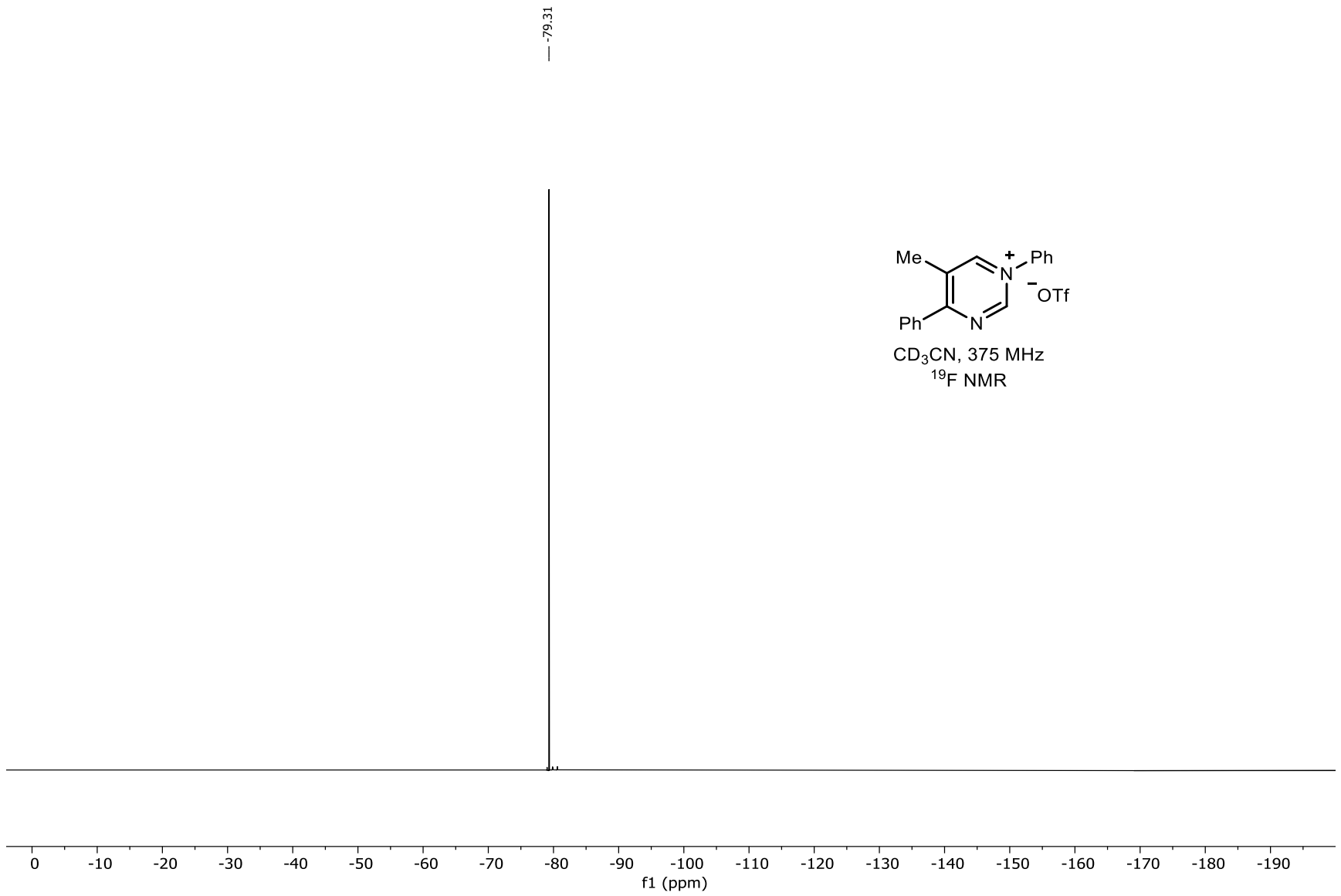

9.05
8.47
8.36
8.34
8.34
7.73
7.72
7.71
7.69
7.69
7.68
7.68
7.67
7.66
7.65
7.64
7.64
7.58
7.58
7.57
7.56
7.56
7.55
7.54
7.26 CDCl3
2.65
Me
Ph
N
Ph
OTf
CDCl3, 400 MHz
1H NMR
1.00
1.00
2.00
6.00
2.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

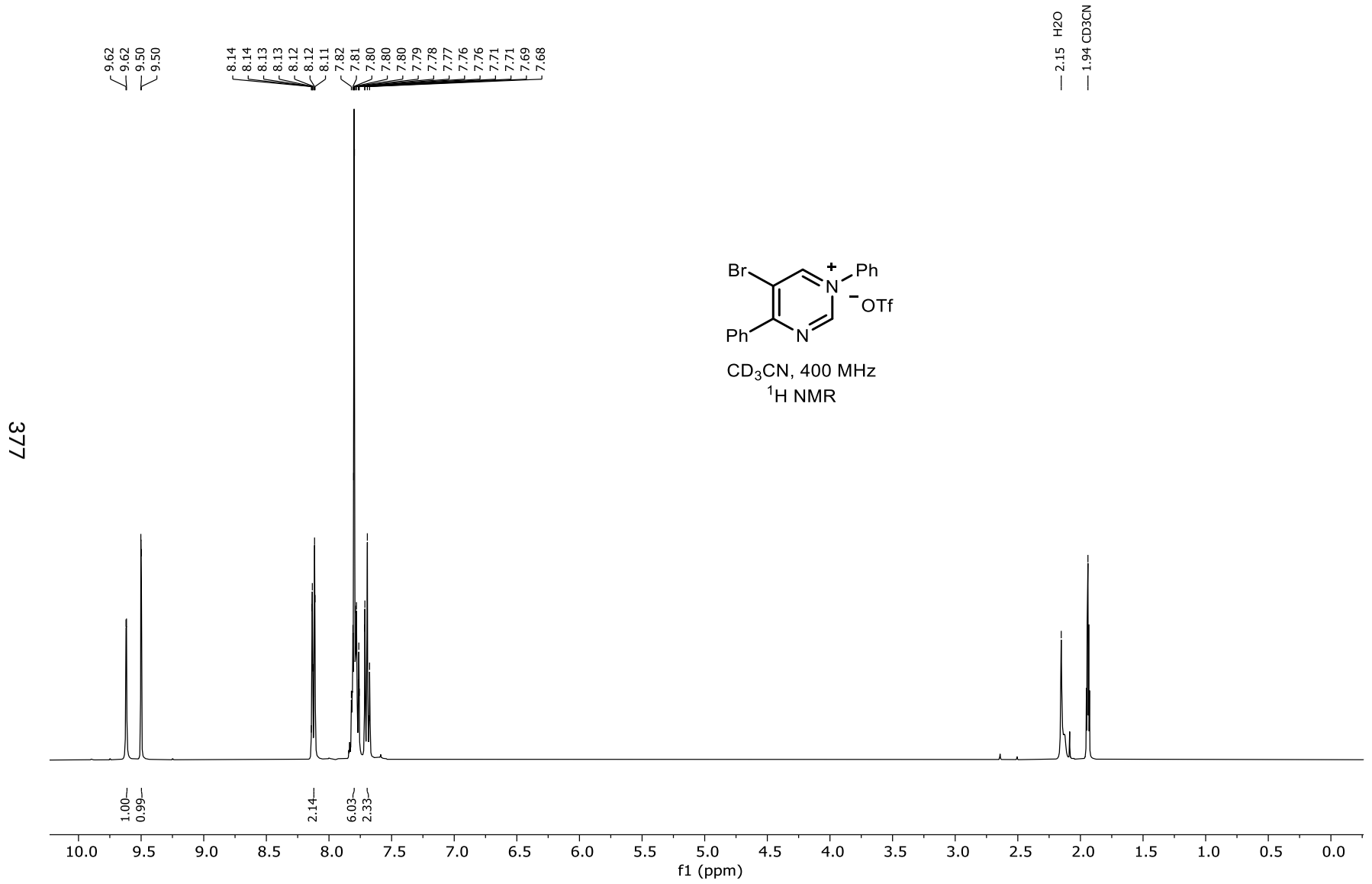

170.04
163.65
151.86
136.91
134.90
132.91
132.15
130.92
129.74
129.69
126.17
125.00
122.18
120.05
118.93
117.27
77.34
77.05
76.71
21.59
Me
Ph
N
OTf
Ph
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

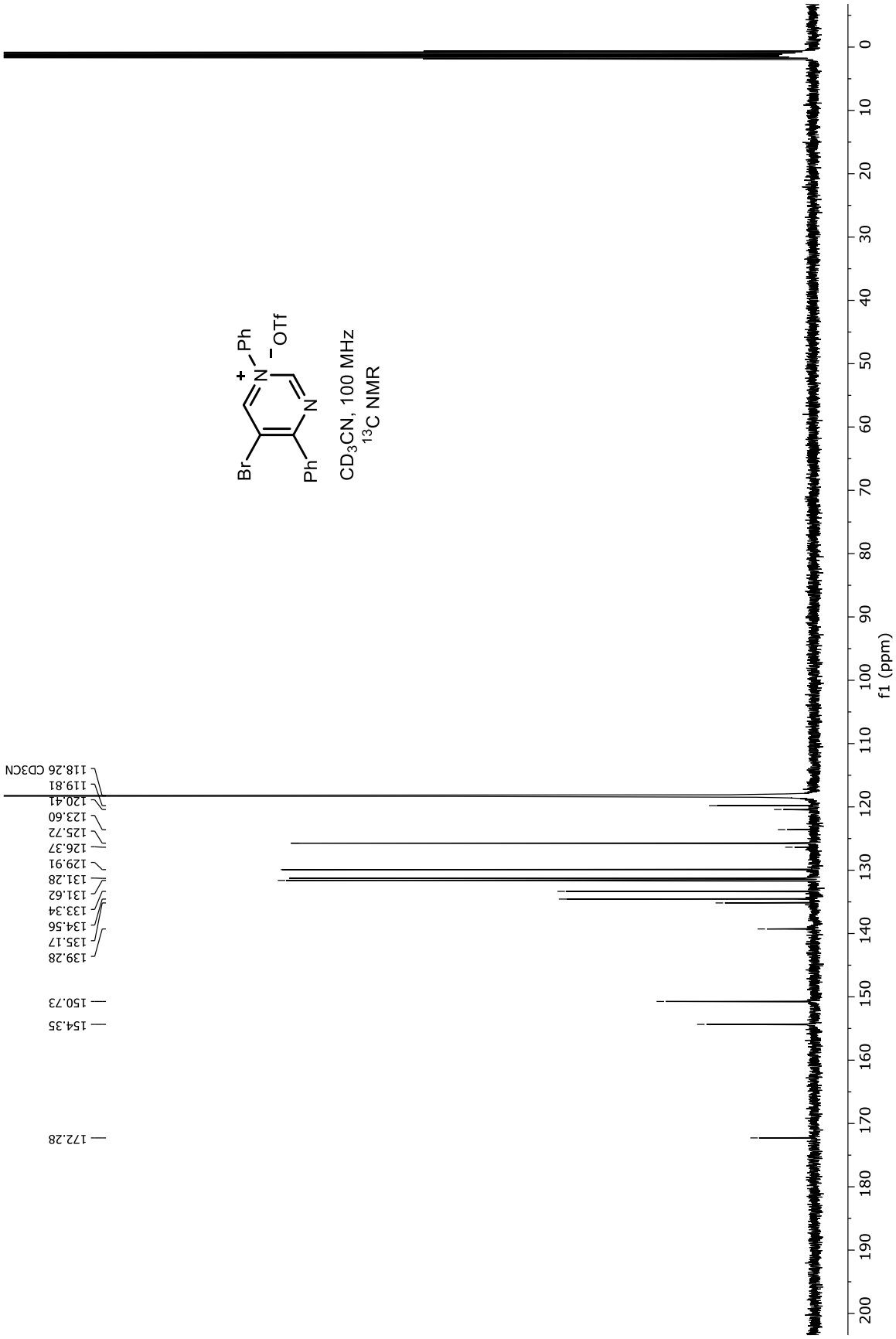

-78.31
Me
Ph
N
OTf
Ph
N
CDCl3, 400 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

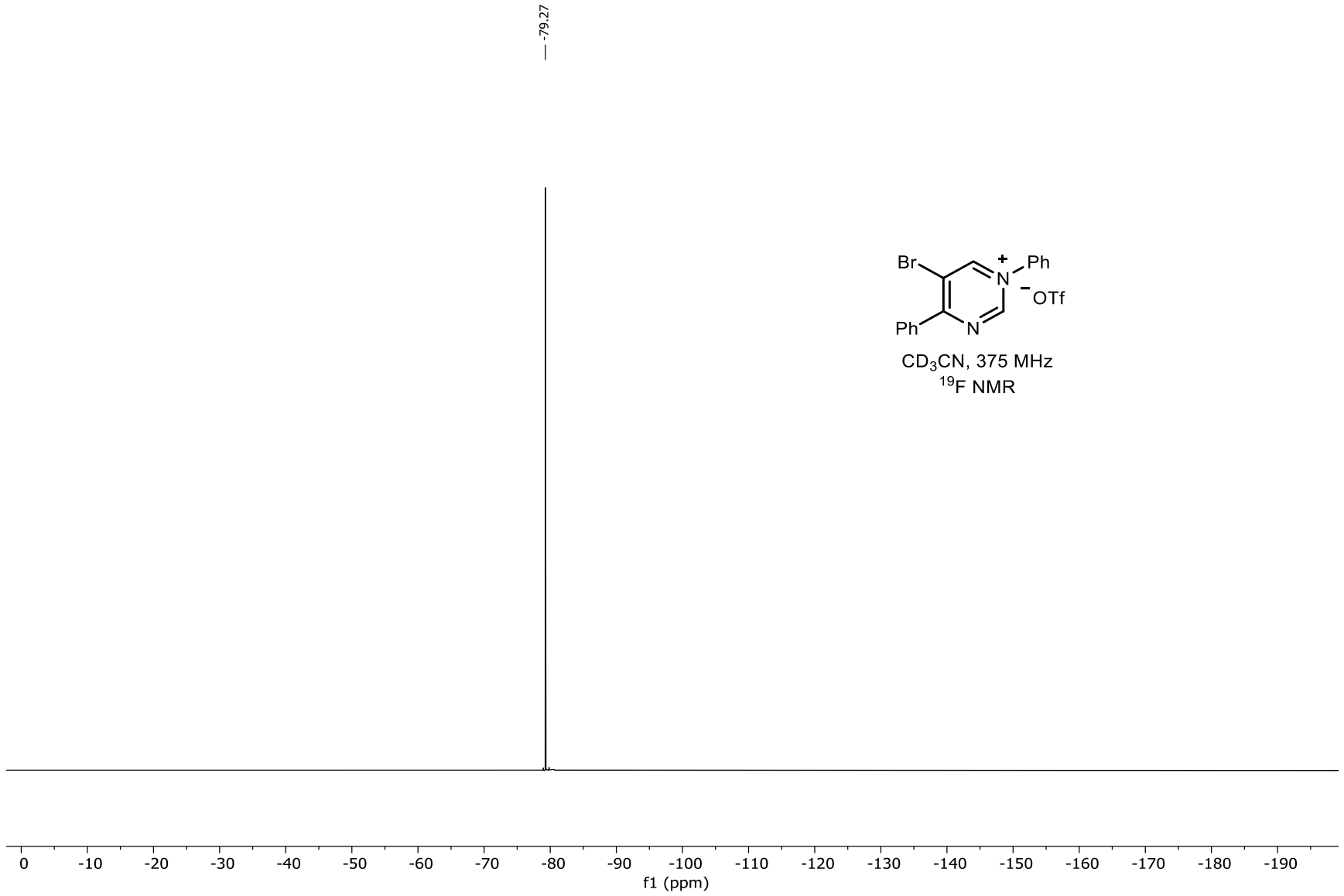

9.51
9.51
9.10
9.10
9.10
9.09
7.96
7.96
7.95
7.95
7.94
7.94
7.80
7.79
7.78
7.78
7.76
7.75
7.74
7.74
7.73
7.72
7.72
7.72
7.70
7.70
7.70
7.69
7.68
7.68
7.67
7.66
7.66
7.66
2.70
1.94 CD3CN
Me
Ph
N
OTf
Ph
N
CD3CN, 400 MHz
1H NMR
0.91
1.00
2.01
5.00
1.01
2.01
3.29
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


165.40
153.26
150.46
141.12
140.22
139.69
137.34
132.70
132.07
131.55
125.38
123.67
120.48
118.26 CD3CN
117.45
Me
Ph
N
OTf
Ph
N
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

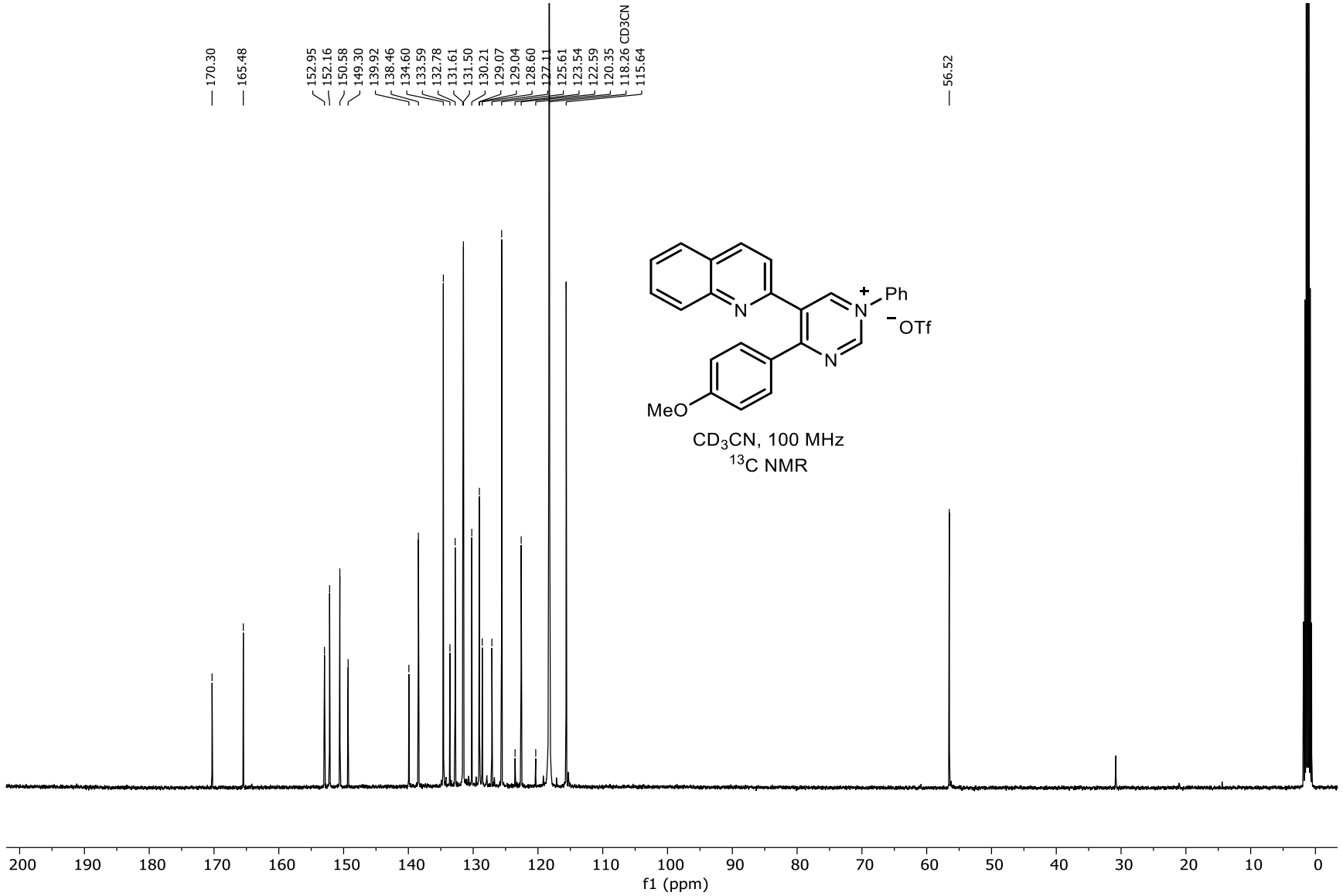

-79.31
Me
Ph
N
OTf
Ph
N
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

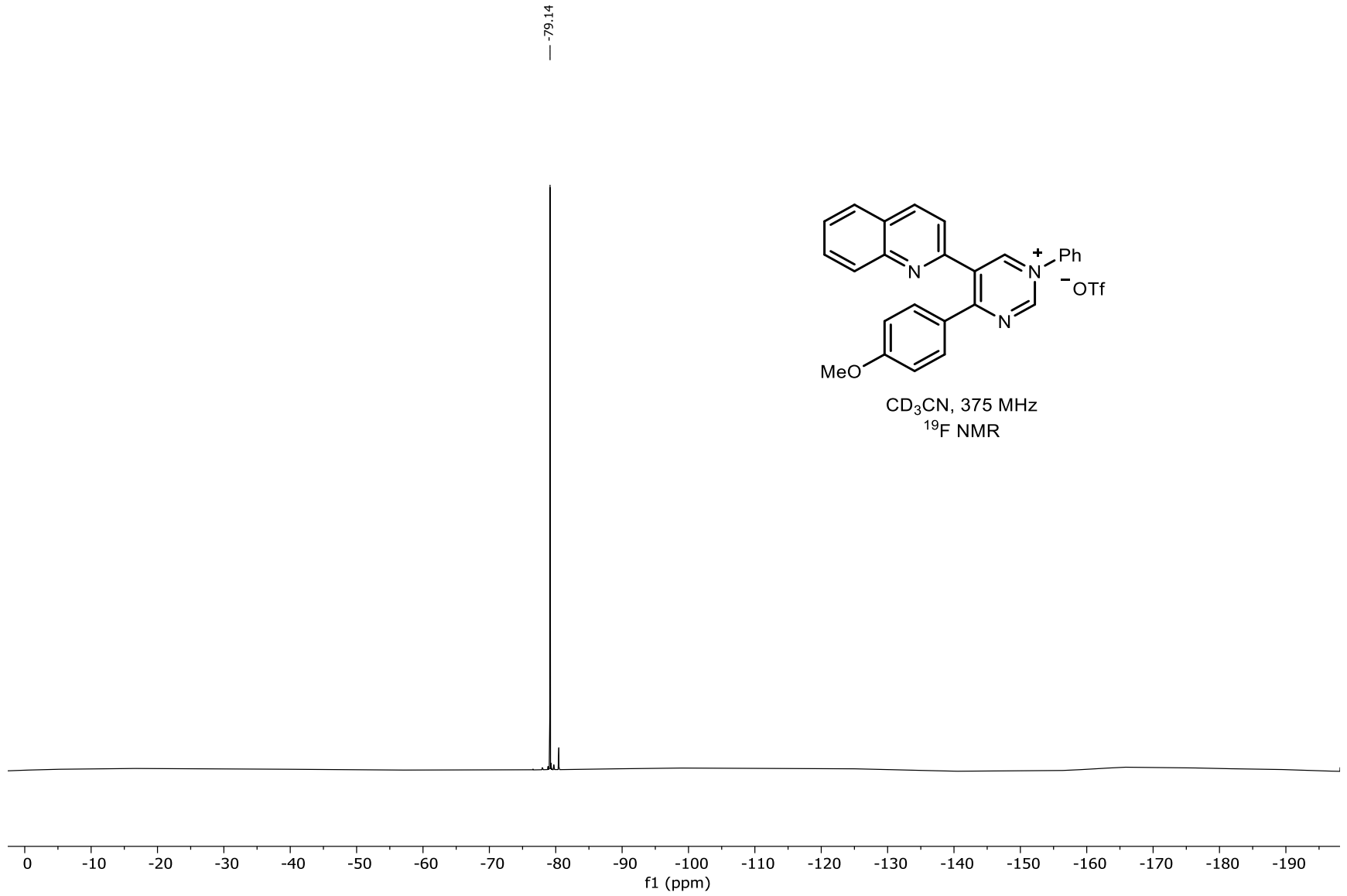

9.62
9.62
9.50
9.50
8.14
8.14
8.13
8.13
8.12
8.12
8.11
7.82
7.81
7.80
7.80
7.80
7.79
7.78
7.77
7.76
7.76
7.71
7.71
7.69
7.68
2.15 H2O
1.94 CD3CN
Br
Ph
N
OTf
Ph
N
CD3CN, 400 MHz
1H NMR
1.00
0.99
2.14
6.03
2.33
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

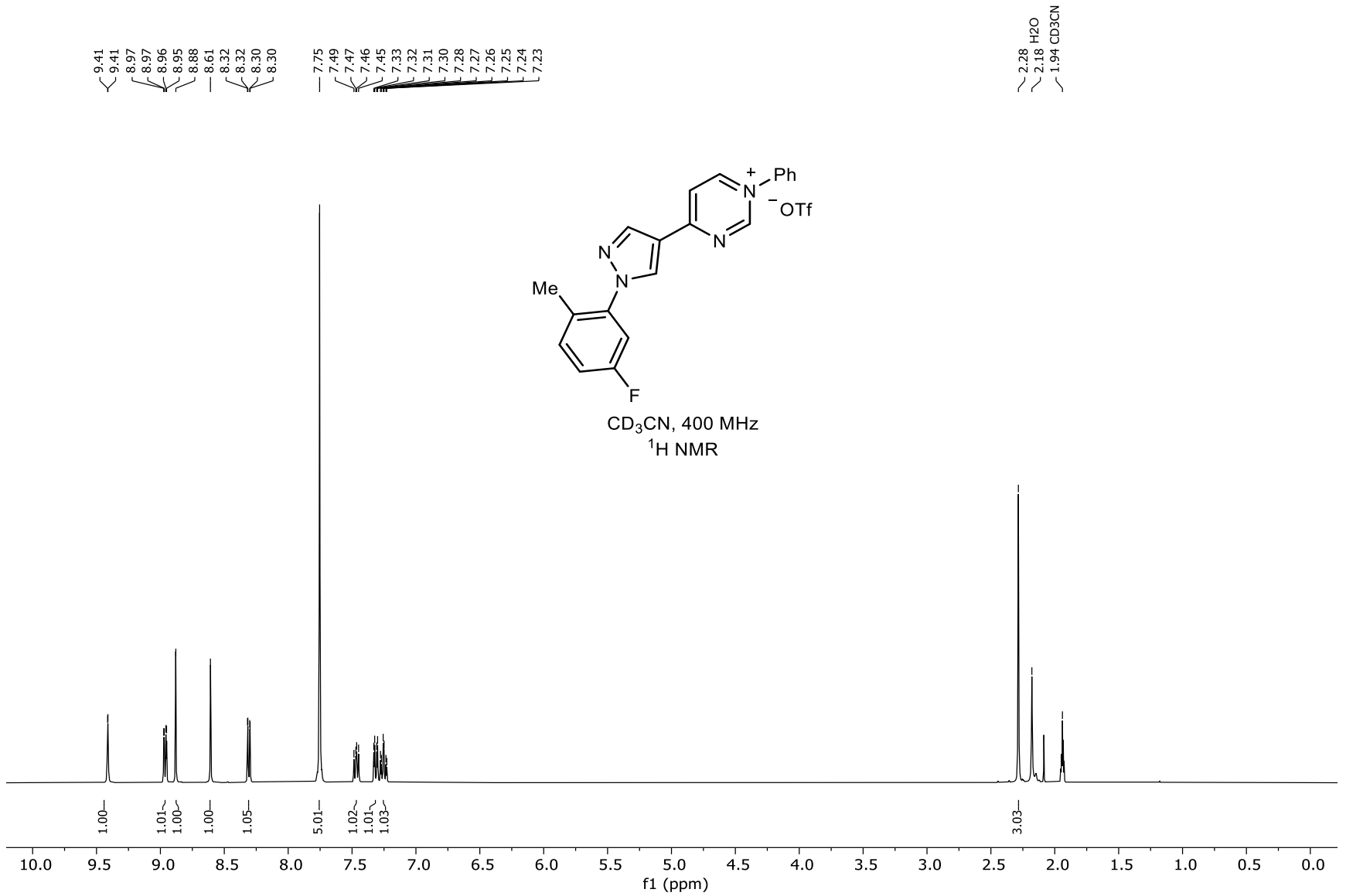

Br
Ph
N
+
N
Ph
OTf
-
CD3CN, 100 MHz
13C NMR
172.28
154.35
150.73
139.28
135.17
134.56
133.34
131.62
131.28
129.91
126.37
125.72
123.60
120.41
119.81
118.26 CD3CN
f1 (ppm)

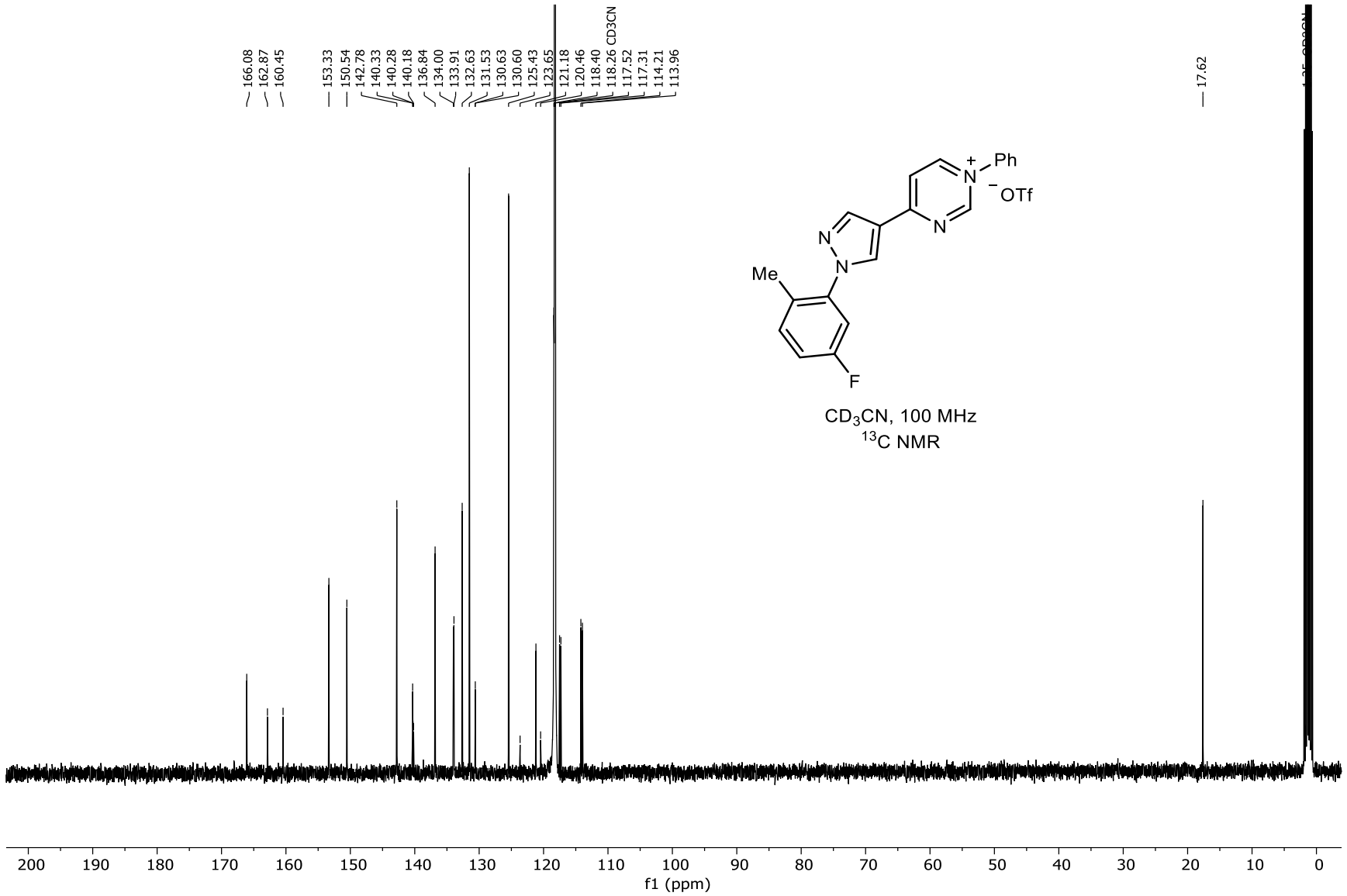

-79.27
Br
Ph
N
OTf
Ph
N
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

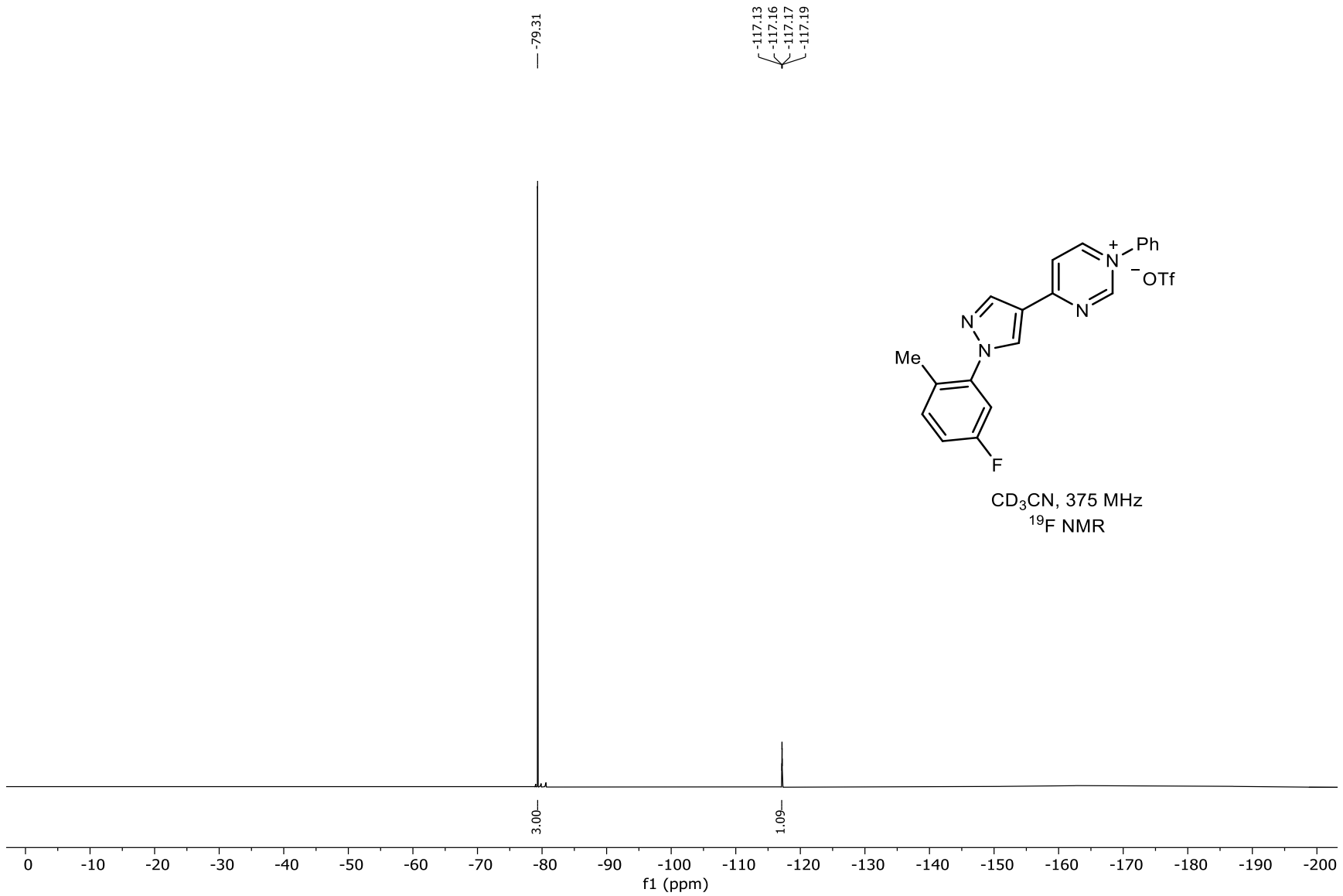
CD3CN, 400 MHz
1H NMR
Ph
OTf
MeO
1.94 CD3CN
3.82
9.59
9.58
9.31
9.31
8.35
8.33
8.11
8.09
8.02
8.00
7.87
7.86
7.85
7.84
7.82
7.78
7.77
7.76
7.75
7.75
7.74
7.73
7.72
7.72
7.70
7.55
7.53
6.92
6.92
6.91
6.90
0.99
1.00
1.02
1.01
1.01
3.01
6.07
1.04
2.01
3.01
f1 (ppm)

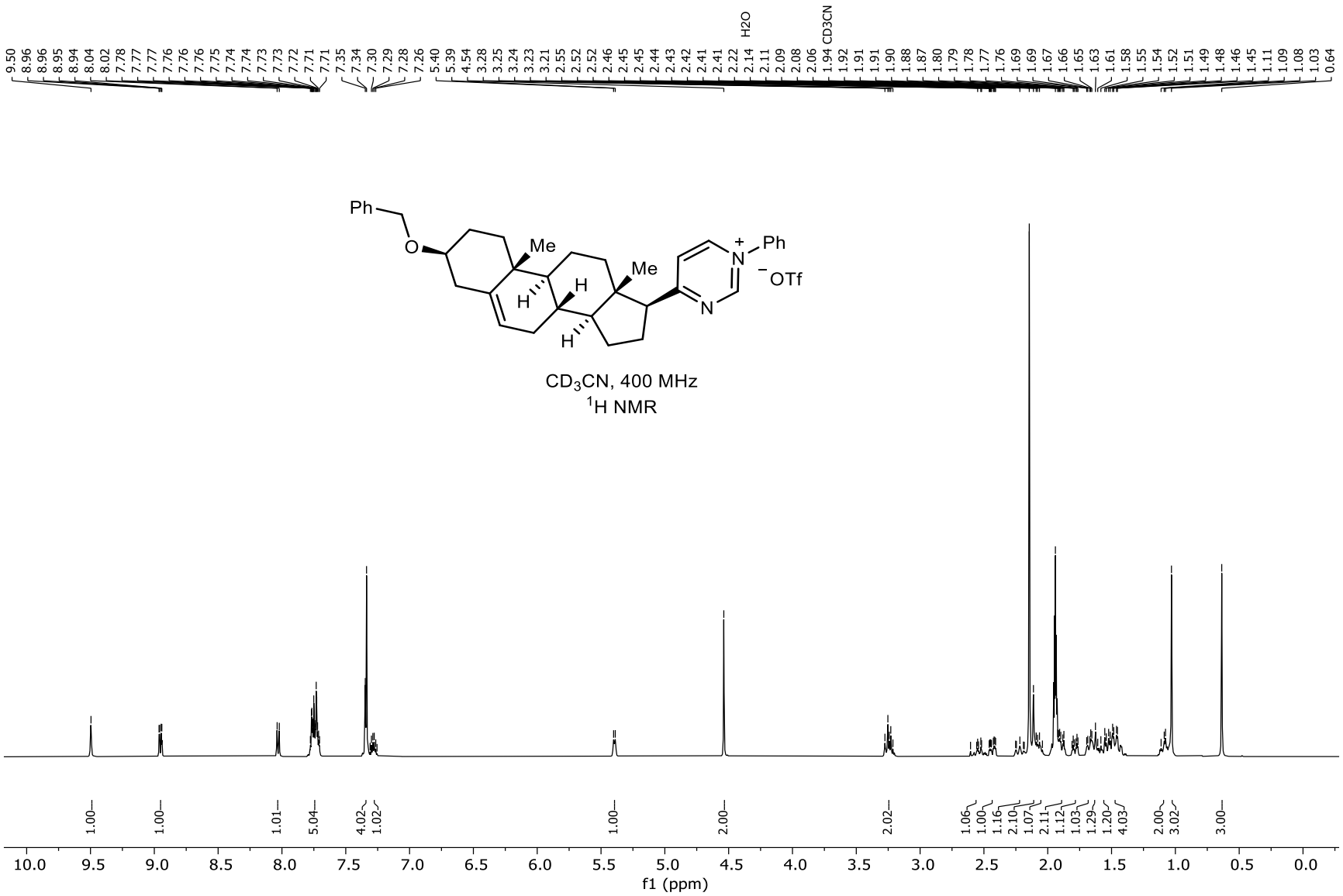

170.30
165.48
152.95
152.16
150.58
149.30
139.92
138.46
134.60
133.59
132.78
131.61
131.50
130.21
129.07
129.04
128.60
122.11
125.61
123.54
122.59
120.35
118.26 CD3CN
115.64
56.52
Ph
OTf
MeO
CD3CN, 100 MHz
13C NMR
f1 (ppm)

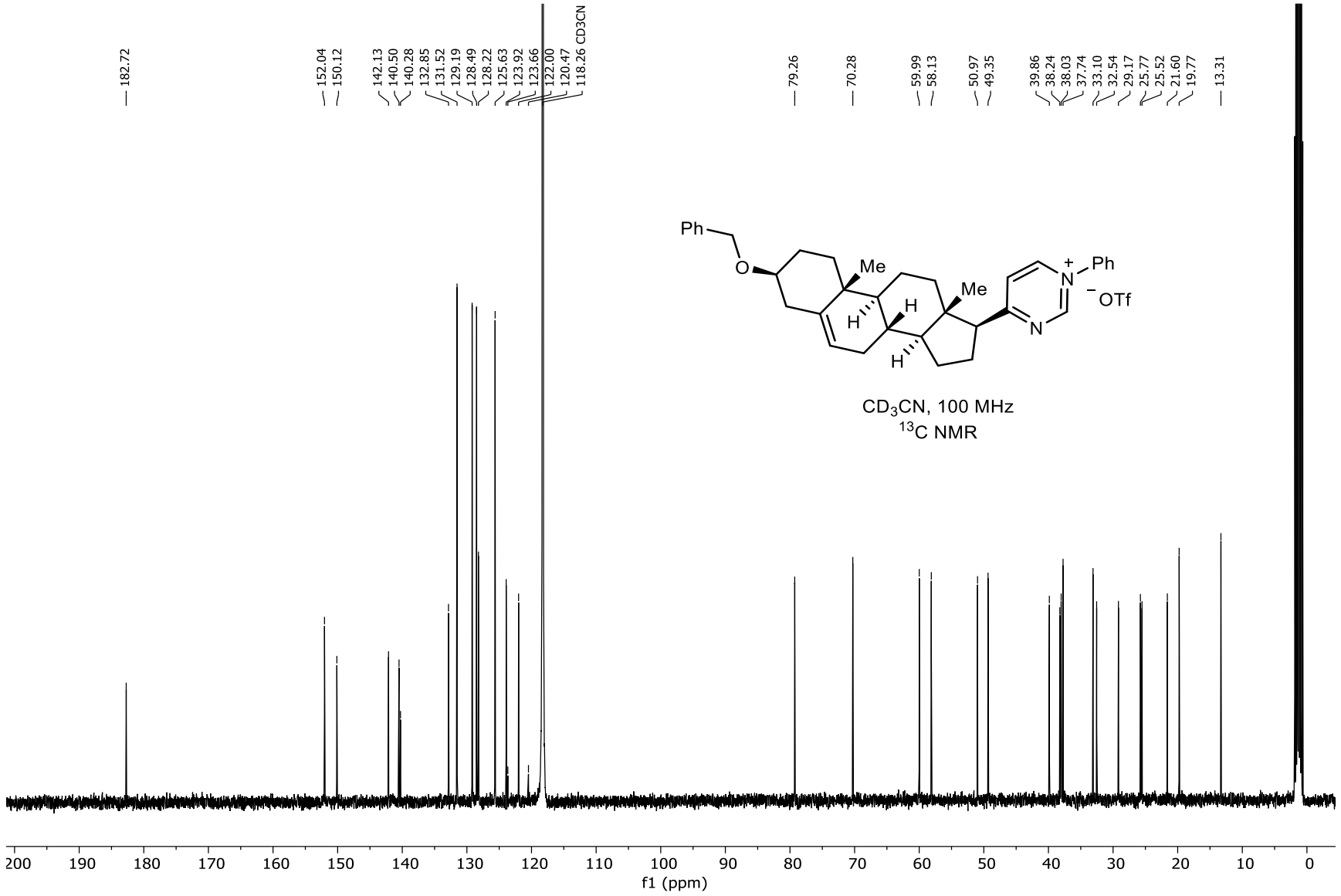

-79.14
Ph
OTf
MeO
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

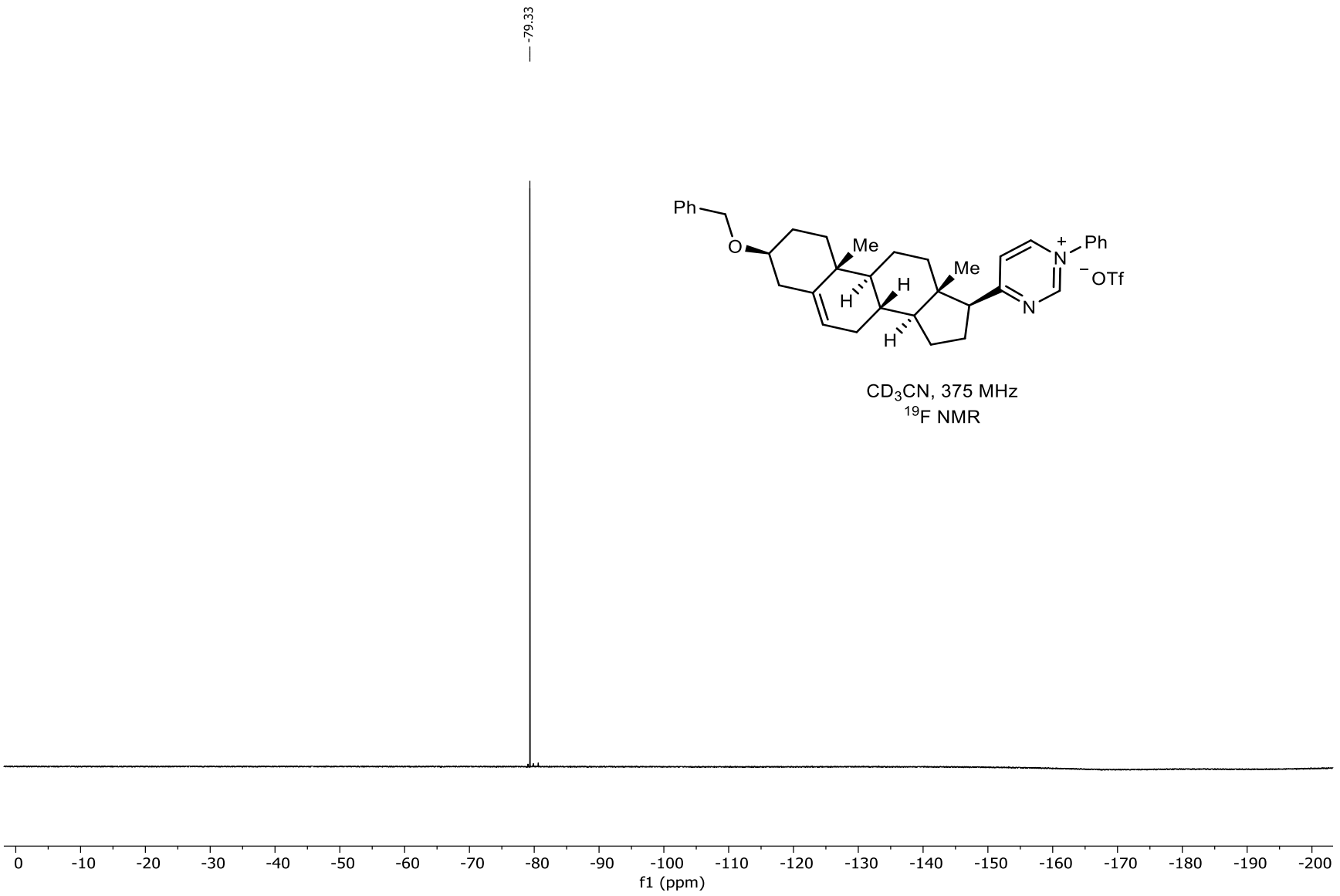

9.41
9.41
8.97
8.97
8.96
8.95
8.88
8.61
8.32
8.32
8.30
8.30
7.75
7.49
7.47
7.46
7.45
7.33
7.32
7.31
7.30
7.28
7.27
7.26
7.25
7.24
7.23
2.28 H2O
2.18
1.94 CD3CN
Ph
N
OTf
N
N
N
Me
F
CD3CN, 400 MHz
1H NMR
1.00
1.01
1.00
1.00
1.05
5.01
1.02
1.01
1.03
3.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

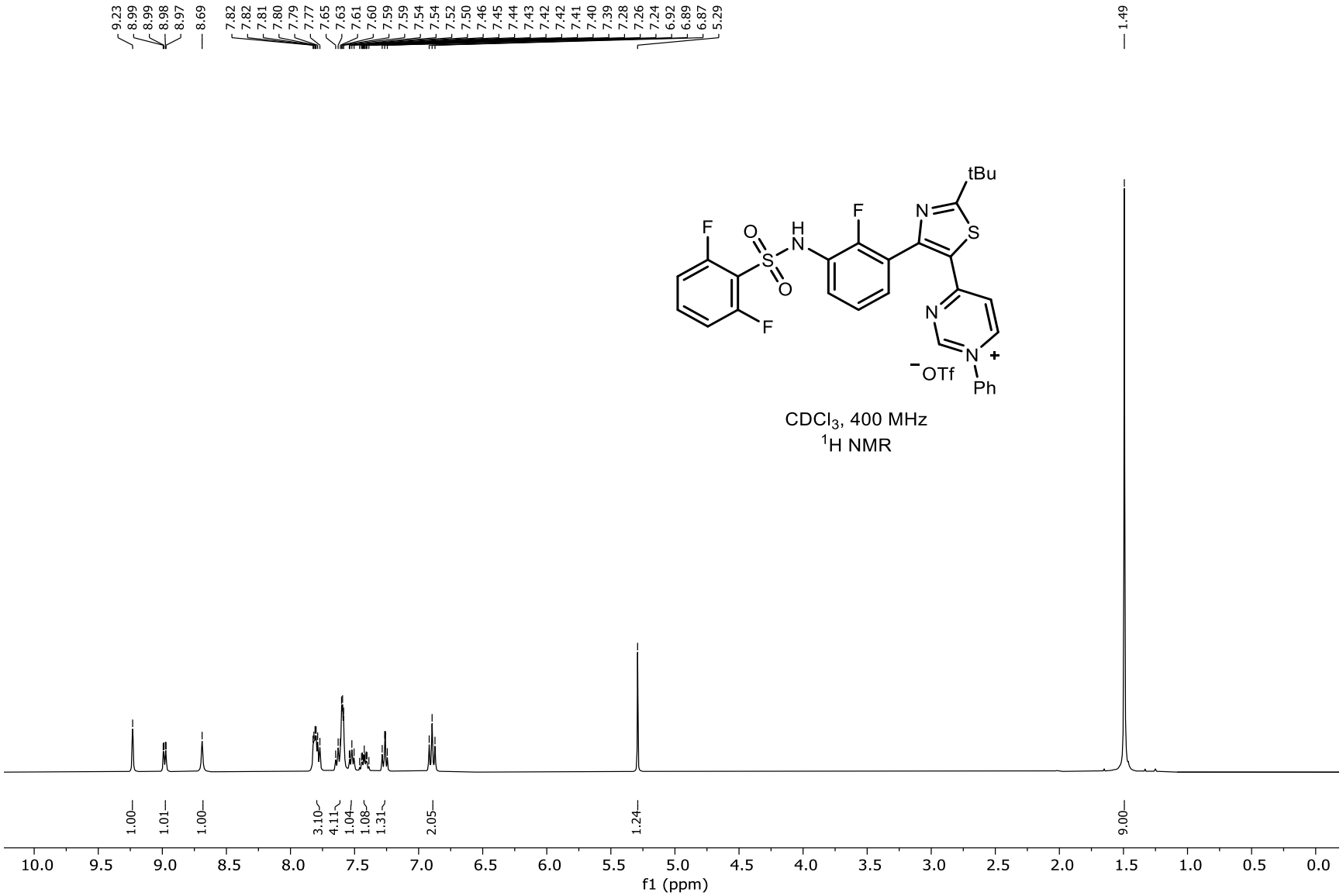

166.08
162.87
160.45
153.33
150.54
142.78
140.33
140.28
140.18
136.84
134.00
133.91
132.63
131.53
130.63
130.60
125.43
123.65
121.18
120.46
118.40
118.26 CD3CN
117.52
117.31
114.21
113.96
17.62
Ph
N
OTf
N
N
N
Me
F
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

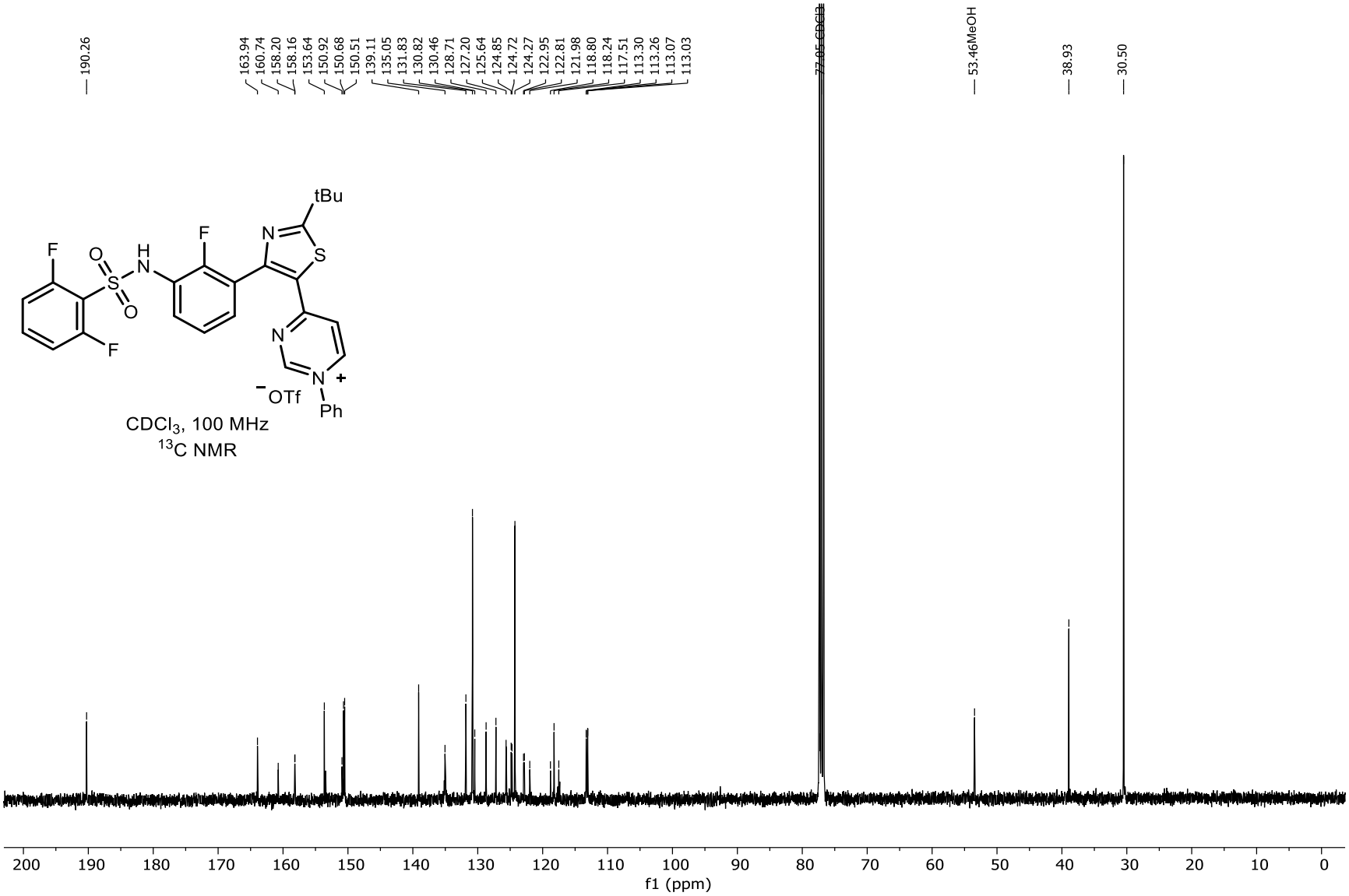

-79.31
-117.13
-117.16
-117.17
-117.19
Ph
N
+
−
OTf
N
N
N
Me
F
CD3CN, 375 MHz
19F NMR
3.00
1.09
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

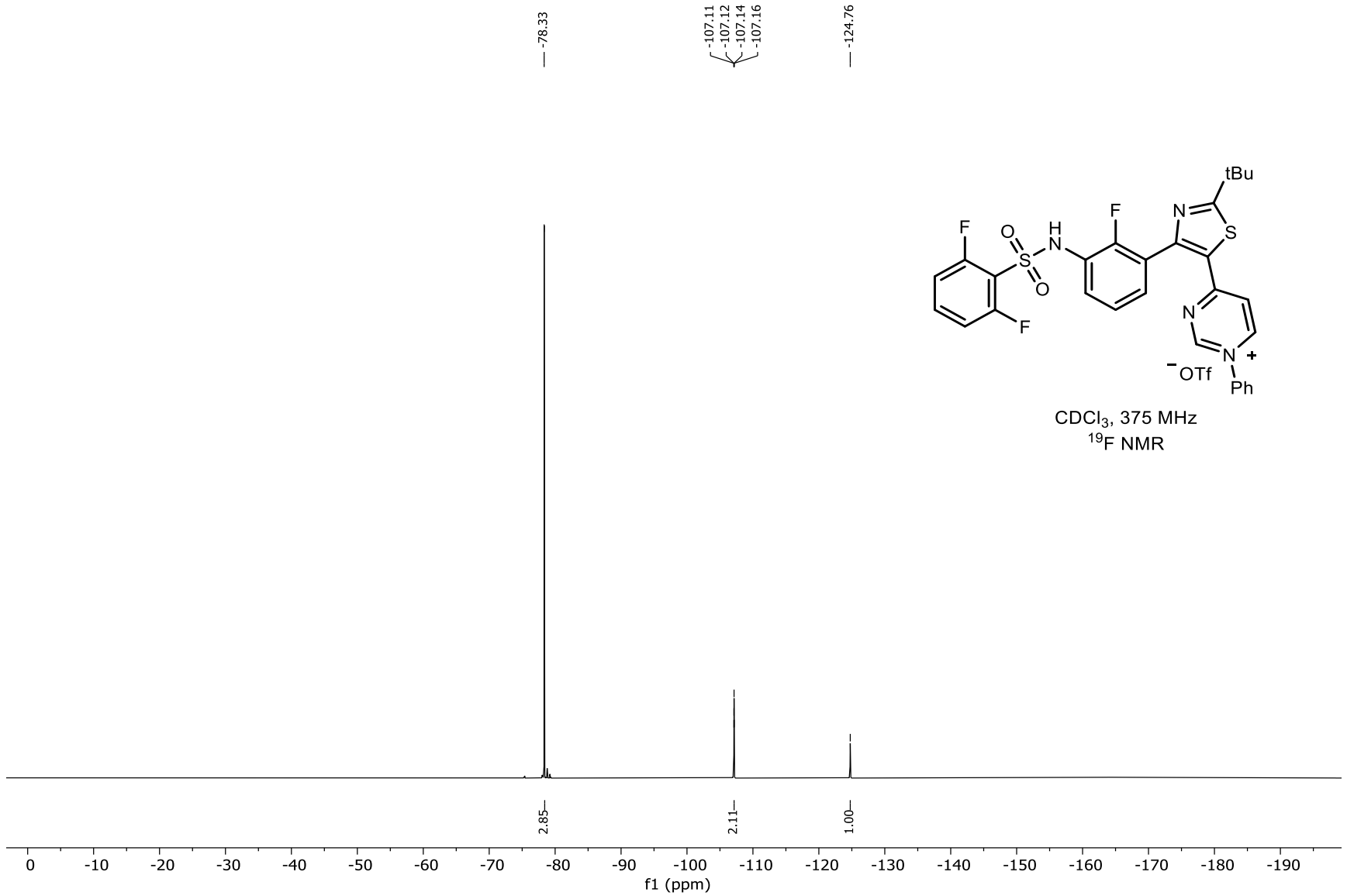

9.50 8.96 8.96 8.95 8.94 8.04 8.02 7.78 7.77 7.77 7.76 7.76 7.76 7.75 7.74 7.74 7.73 7.73 7.72 7.71 7.71 7.35 7.34 7.30 7.29 7.28 7.26 5.40 5.39 4.54 3.28 3.25 3.24 3.23 3.21 2.55 2.52 2.52 2.46 2.45 2.45 2.44 2.43 2.42 2.41 2.41 2.22 H2O 2.14 2.11 2.09 2.08 2.06 CD3CN 1.94 1.92 1.91 1.91 1.90 1.88 1.87 1.80 1.79 1.78 1.77 1.76 1.69 1.69 1.67 1.66 1.65 1.63 1.61 1.58 1.55 1.54 1.52 1.51 1.49 1.48 1.46 1.45 1.11 1.09 1.08 1.03 0.64
Ph
O
Me
H
H
H
Me
N
+
N
Ph
−
OTf
CD3CN, 400 MHz
1H NMR
1.00 1.00 1.01 5.04 4.02 1.02 1.00 2.00 2.02 1.06 1.00 1.16 2.10 1.07 2.11 1.12 1.03 1.29 1.20 4.03 2.00 3.02 3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


182.72
152.04
150.12
142.13
140.50
140.28
132.85
131.52
129.19
128.49
128.22
125.63
123.92
123.66
122.00
120.47
118.26 CD3CN
79.26
70.28
59.99
58.13
50.97
49.35
39.86
38.24
38.03
37.74
33.10
32.54
29.17
25.77
25.52
21.60
19.77
13.31
Ph
O
Me
H
H
H
Me
N
+
N
Ph
−
OTf
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-79.33
Ph
O
Me
H
H
H
Me
N
+
N
Ph
−
OTf
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

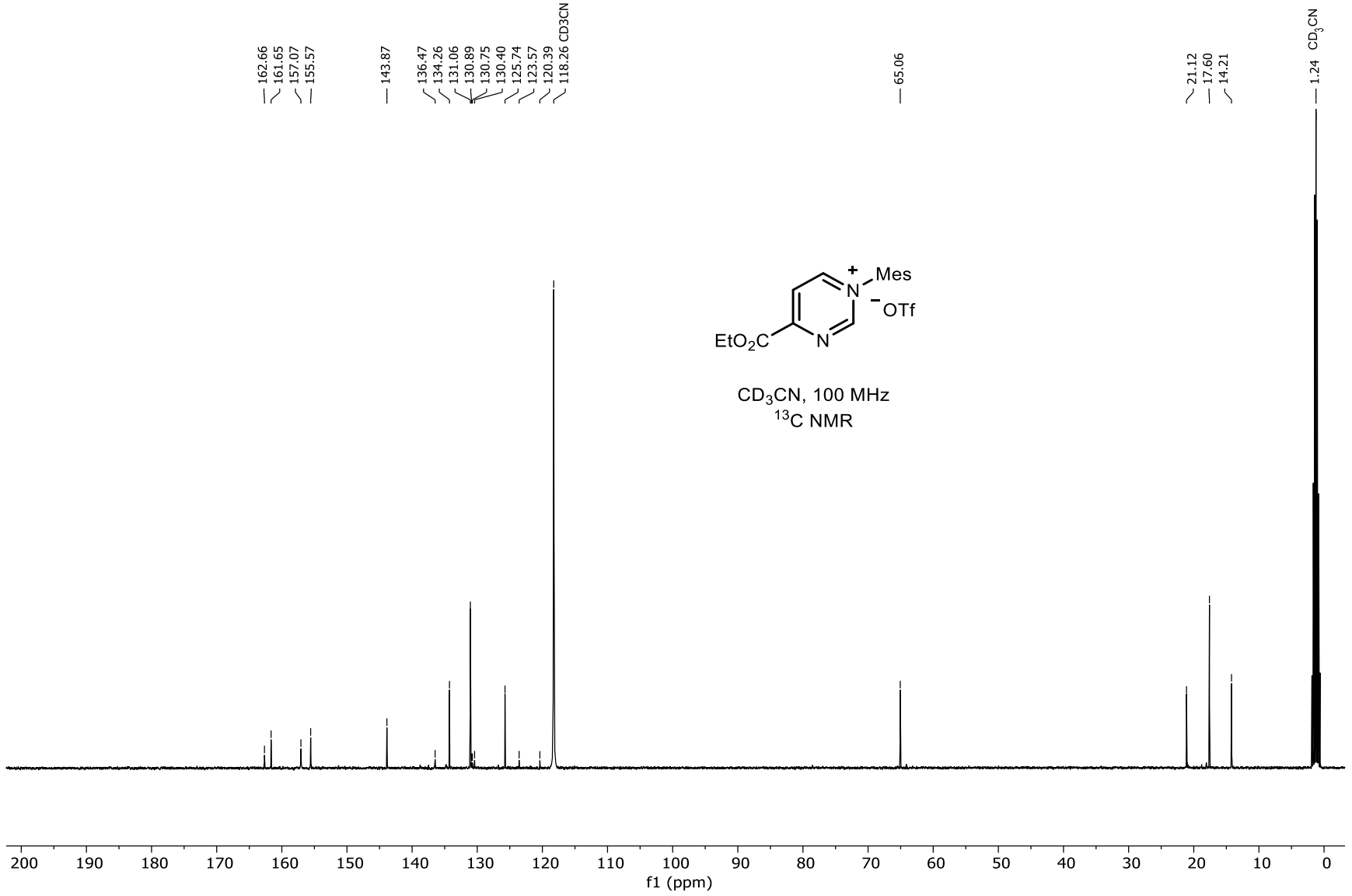

9.23
8.99
8.99
8.98
8.97
8.69
7.82
7.82
7.81
7.80
7.79
7.77
7.65
7.63
7.61
7.60
7.59
7.59
7.54
7.54
7.52
7.50
7.46
7.45
7.44
7.43
7.42
7.42
7.41
7.40
7.39
7.28
7.26
7.24
6.92
6.89
6.87
5.29
1.49
tBu
F
O
H
N
S
F
N
S
O
F
N
N
+
N
OTf
Ph
CDCl3, 400 MHz
1H NMR
1.00
1.01
1.00
3.10
4.11
1.04
1.08
1.31
2.05
1.24
9.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

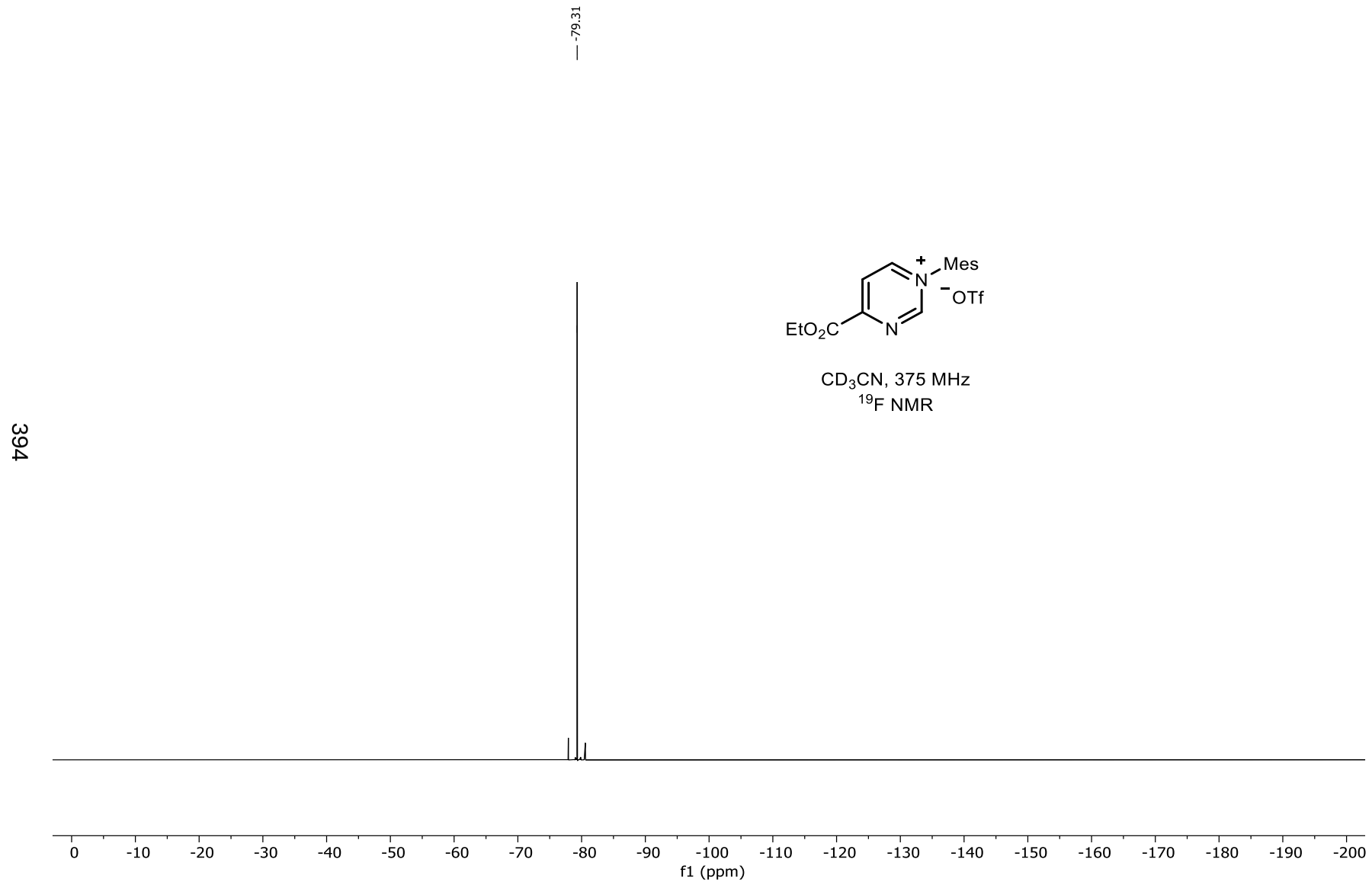

190.26
163.94
160.74
158.20
158.16
153.64
150.92
150.68
150.51
139.11
135.05
131.83
130.82
130.46
128.71
127.20
125.64
124.85
124.72
124.27
122.95
122.81
121.98
118.80
118.24
117.51
113.30
113.26
113.07
113.03
77.05 CDCl3
53.46MeOH
38.93
30.50
tBu
F
O
H
N
S
F
N
S
O
F
N
N
+
OTf
Ph
CDCl3, 100 MHz
13C NMR
f1 (ppm)

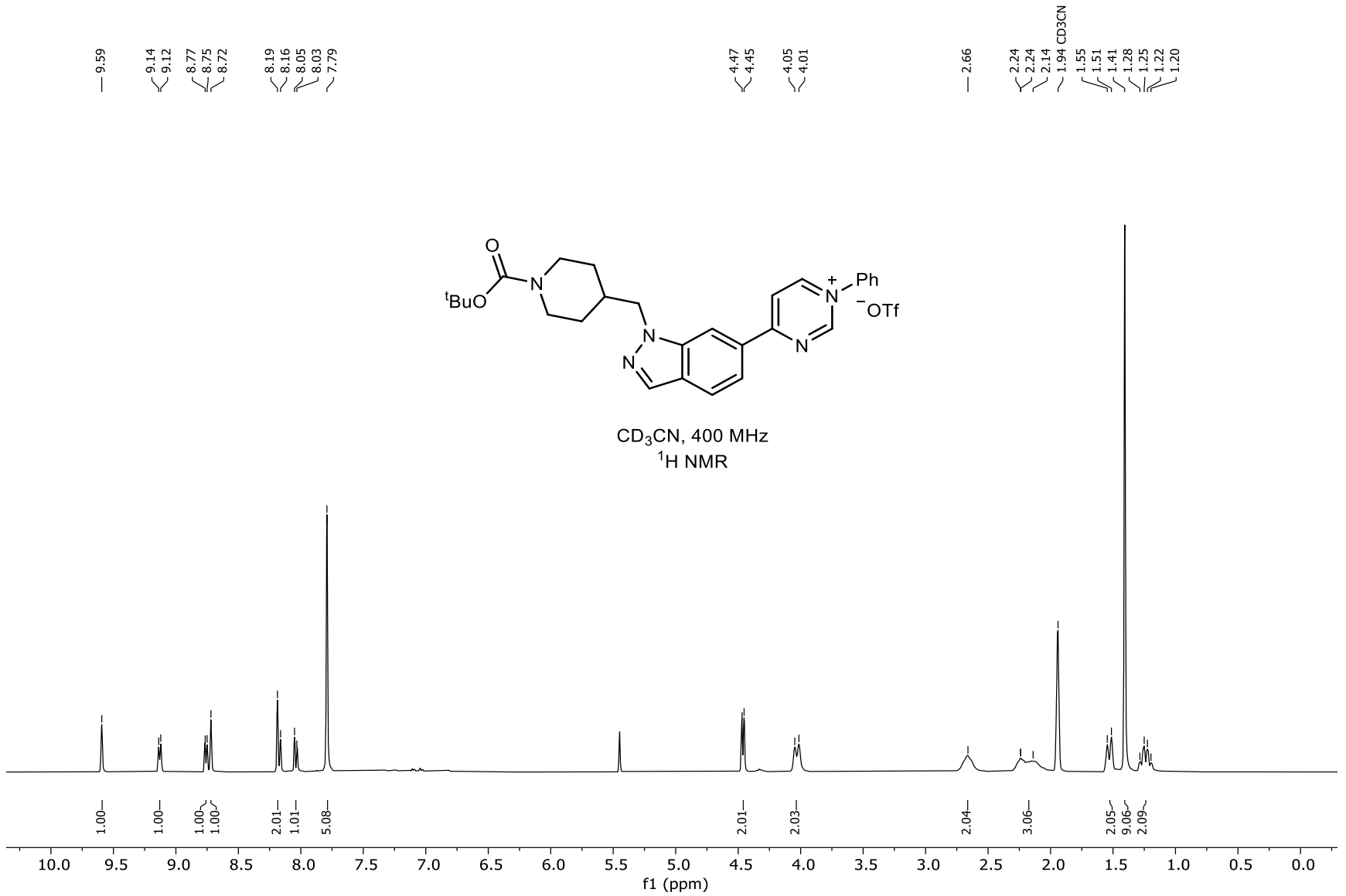


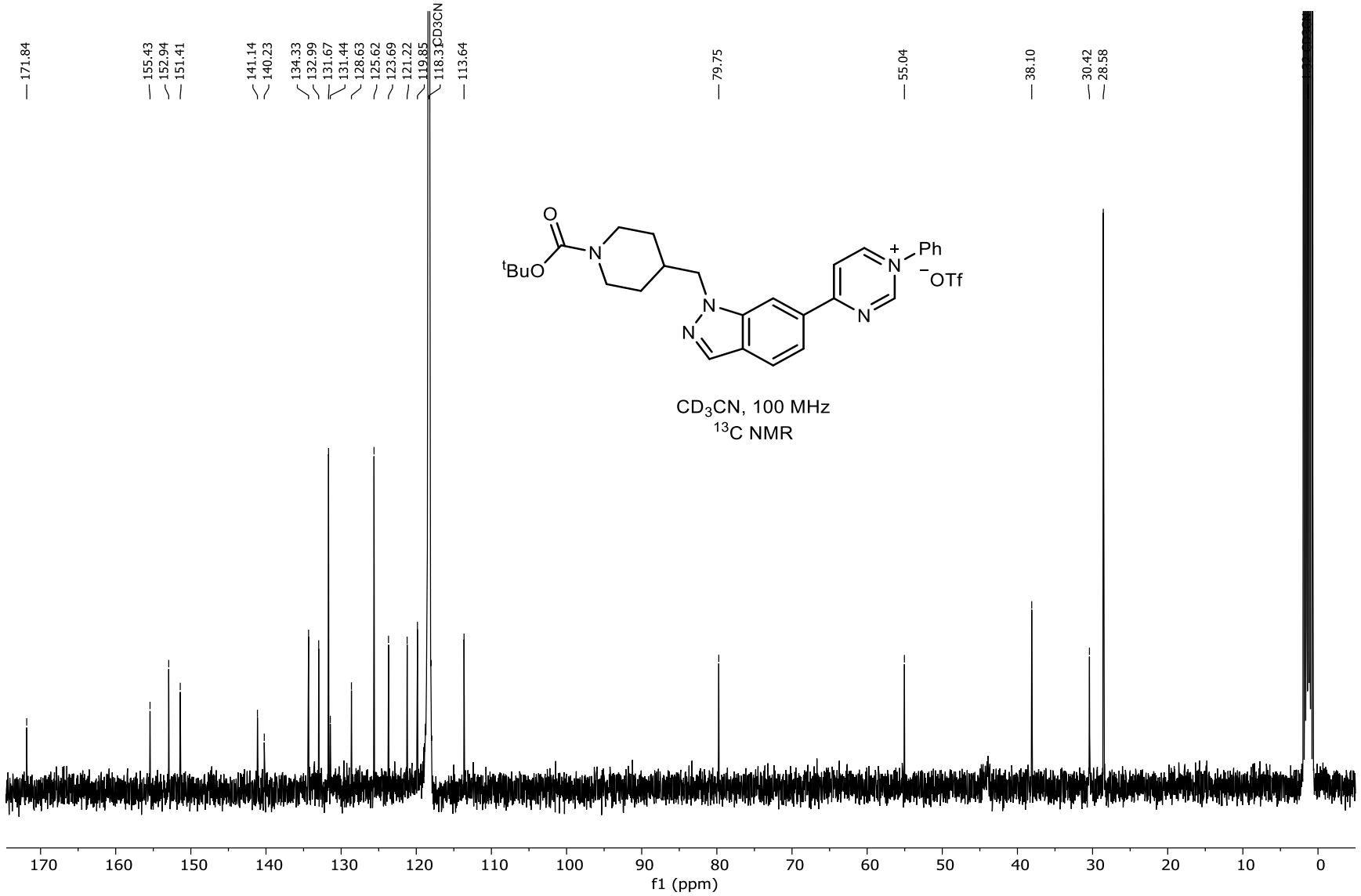
$CDCl_3$, 375 MHz
^{19}F NMR

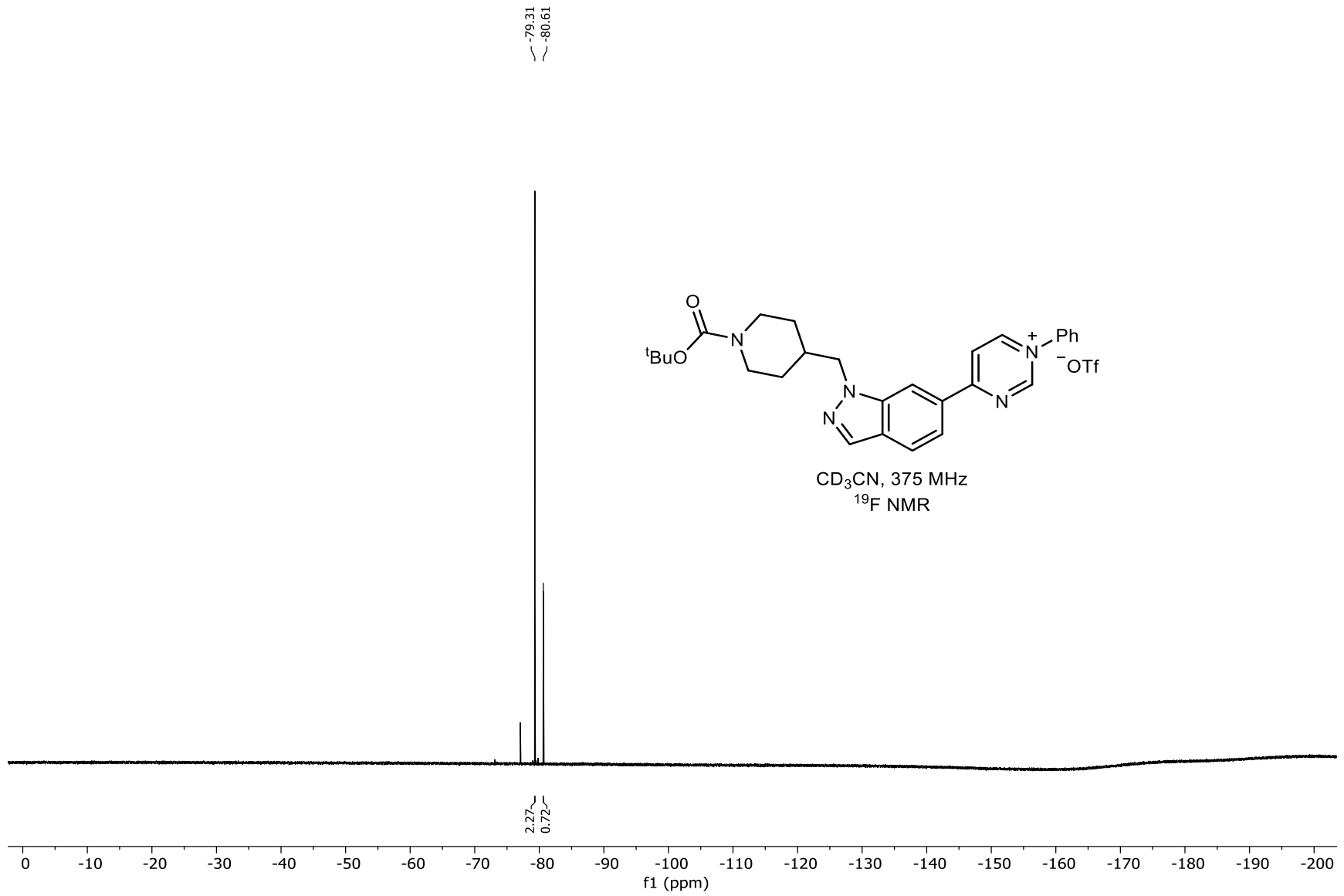
9.64
9.34
9.34
9.33
9.32
8.84
8.84
8.82
8.82
7.23
4.60
4.58
4.56
4.54
2.41
2.04
1.94 CD3CN
1.47
1.45
1.43
0.93
1.00
1.00
2.01
2.07
3.04
6.01
3.07
f1 (ppm)
Mes
OTf
N
N
EtO2C
CD3CN, 400 MHz
1H NMR

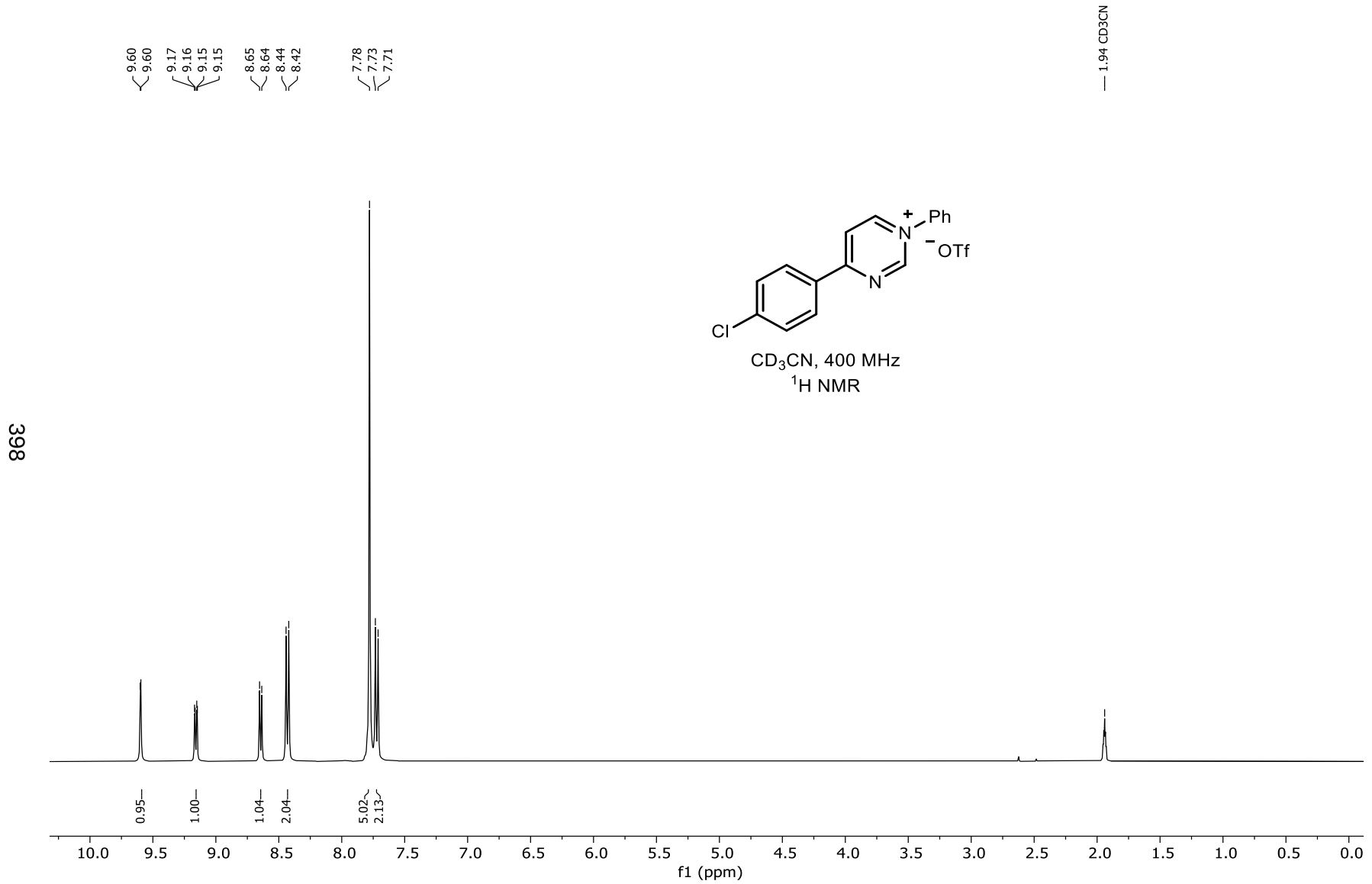

162.66
161.65
157.07
155.57
143.87
136.47
134.26
131.06
130.89
130.75
130.40
125.74
123.57
120.39
118.26 CD3CN
65.06
21.12
17.60
14.21
1.24 CD3CN
Mes
OTf
EtO2C
N
CD3CN, 100 MHz
13C NMR
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

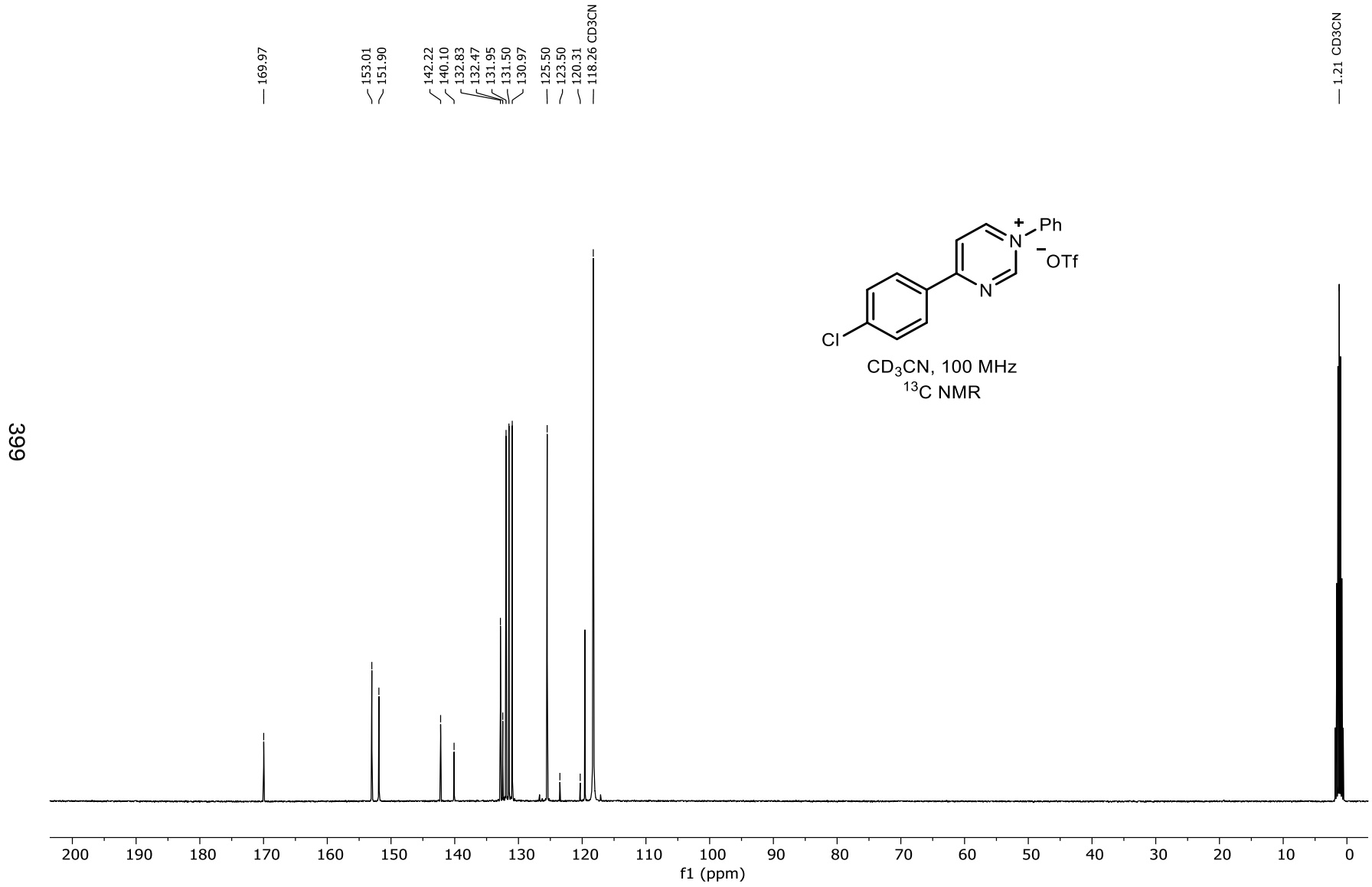

-79.31
Mes
OTf
EtO2C
N
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


9.59
9.14
9.12
8.77
8.75
8.72
8.19
8.16
8.05
8.03
7.79
4.47
4.45
4.05
4.01
2.66
2.24
2.24
2.14
1.94 CD3CN
1.55
1.51
1.41
1.28
1.25
1.22
1.20
O
tBuO
N
N
N
N
+
Ph
−
OTf
CD3CN, 400 MHz
1H NMR
1.00
1.00
1.00
1.00
2.01
1.01
5.08
2.01
2.03
2.04
3.06
2.05
9.06
2.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


171.84
155.43
152.94
151.41
141.14
140.23
134.33
132.99
131.67
131.44
128.63
125.62
123.69
121.22
119.85
118.31CD3CN
113.64
79.75
55.04
38.10
30.42
28.58
O
tBuO
N
N
N
N
+
Ph
OTf
CD3CN, 100 MHz
13C NMR
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

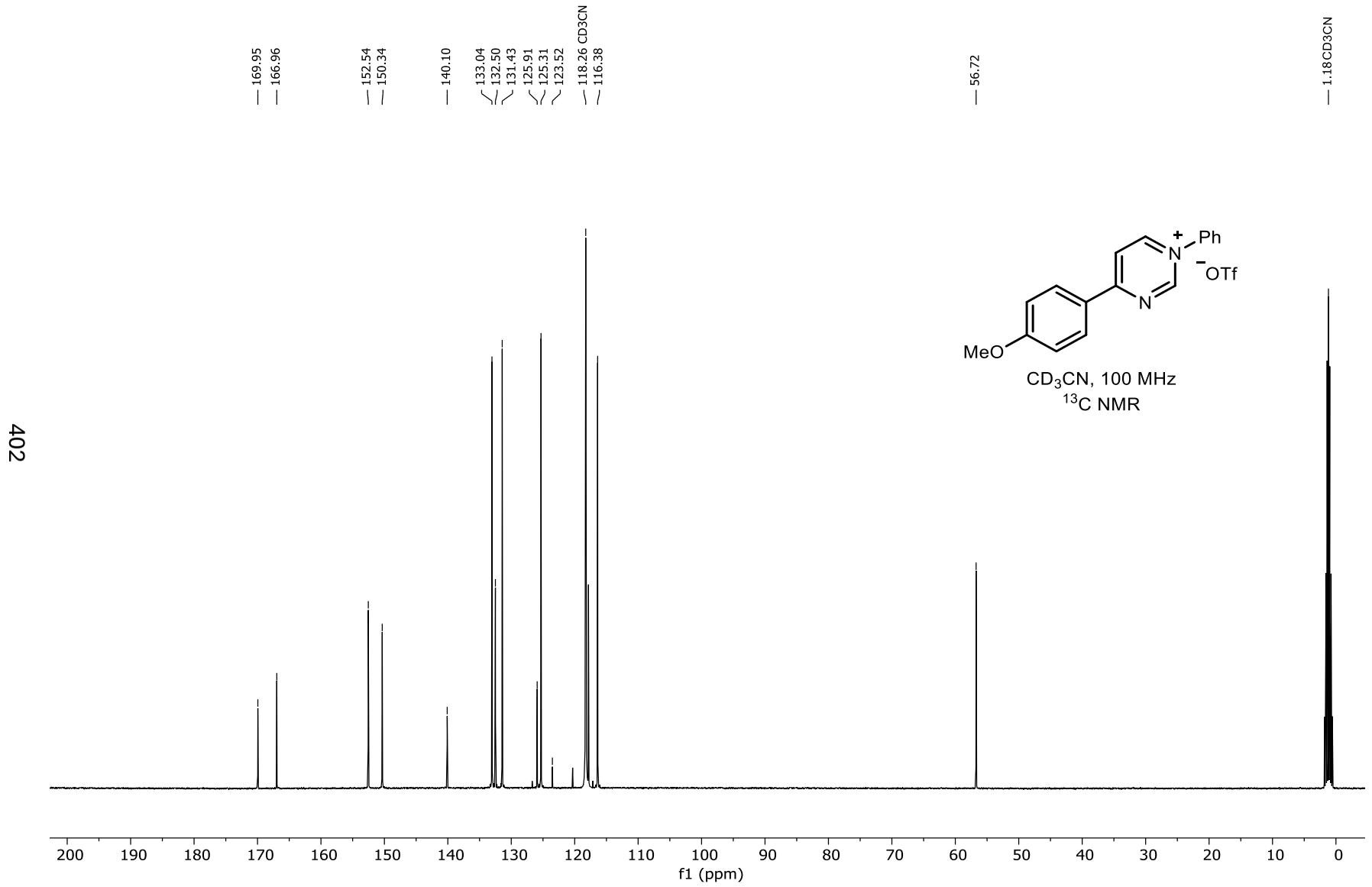

-79.31
-80.61
O
tBuO
N
N
N
N
+
Ph
−
OTf
CD3CN, 375 MHz
19F NMR
2.27
0.72
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


9.60
9.60
9.17
9.16
9.15
9.15
8.65
8.64
8.44
8.42
7.78
7.73
7.71
1.94 CD3CN
Ph
N
OTf
N
Cl
CD3CN, 400 MHz
1H NMR
0.95
1.00
1.04
2.04
5.02
2.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

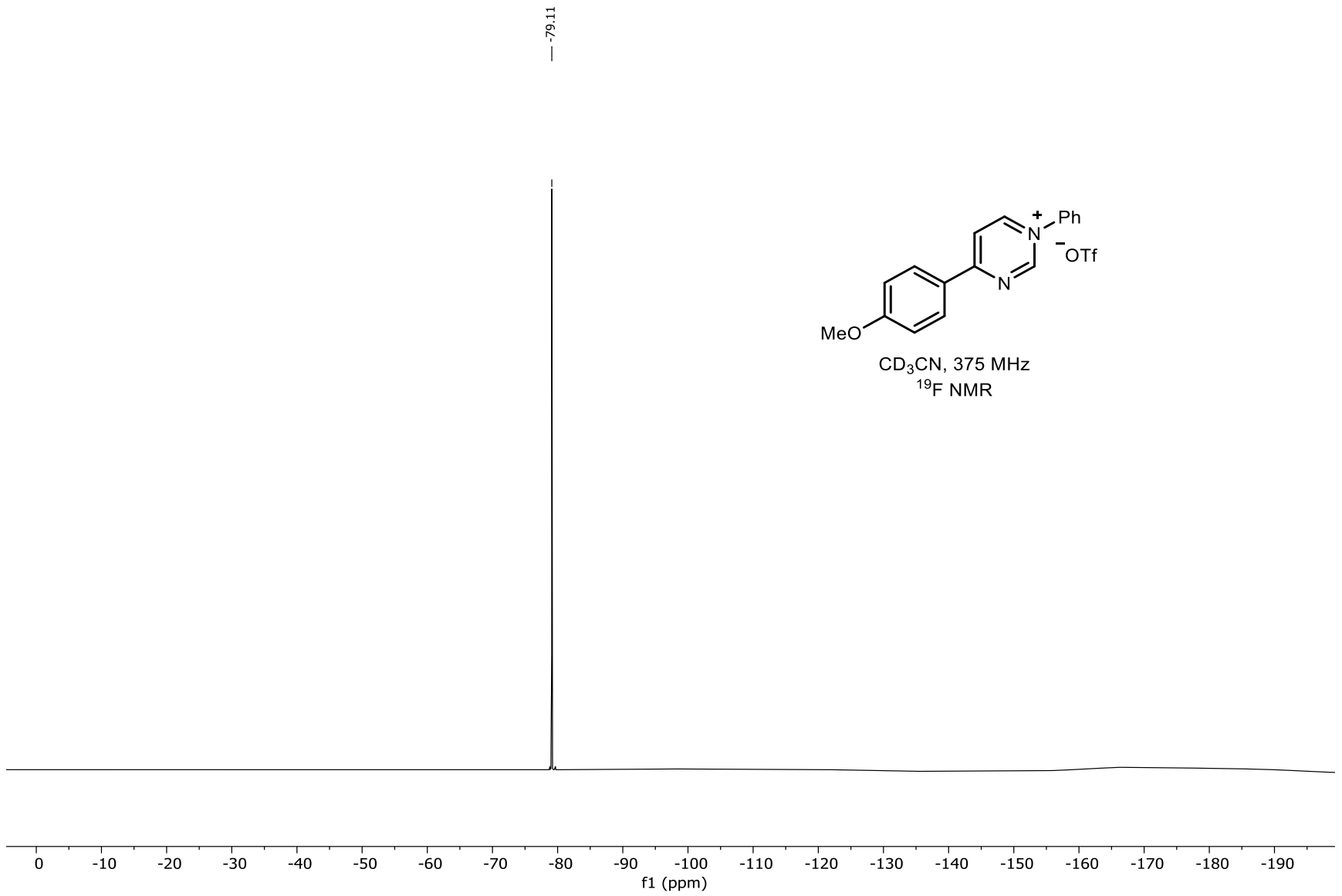

169.97
153.01
151.90
142.22
140.10
132.83
132.47
131.95
131.50
130.97
125.50
123.50
120.31
118.26 CD3CN
1.21 CD3CN
Ph
N
OTf
N
Cl
CD3CN, 100 MHz
13C NMR
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

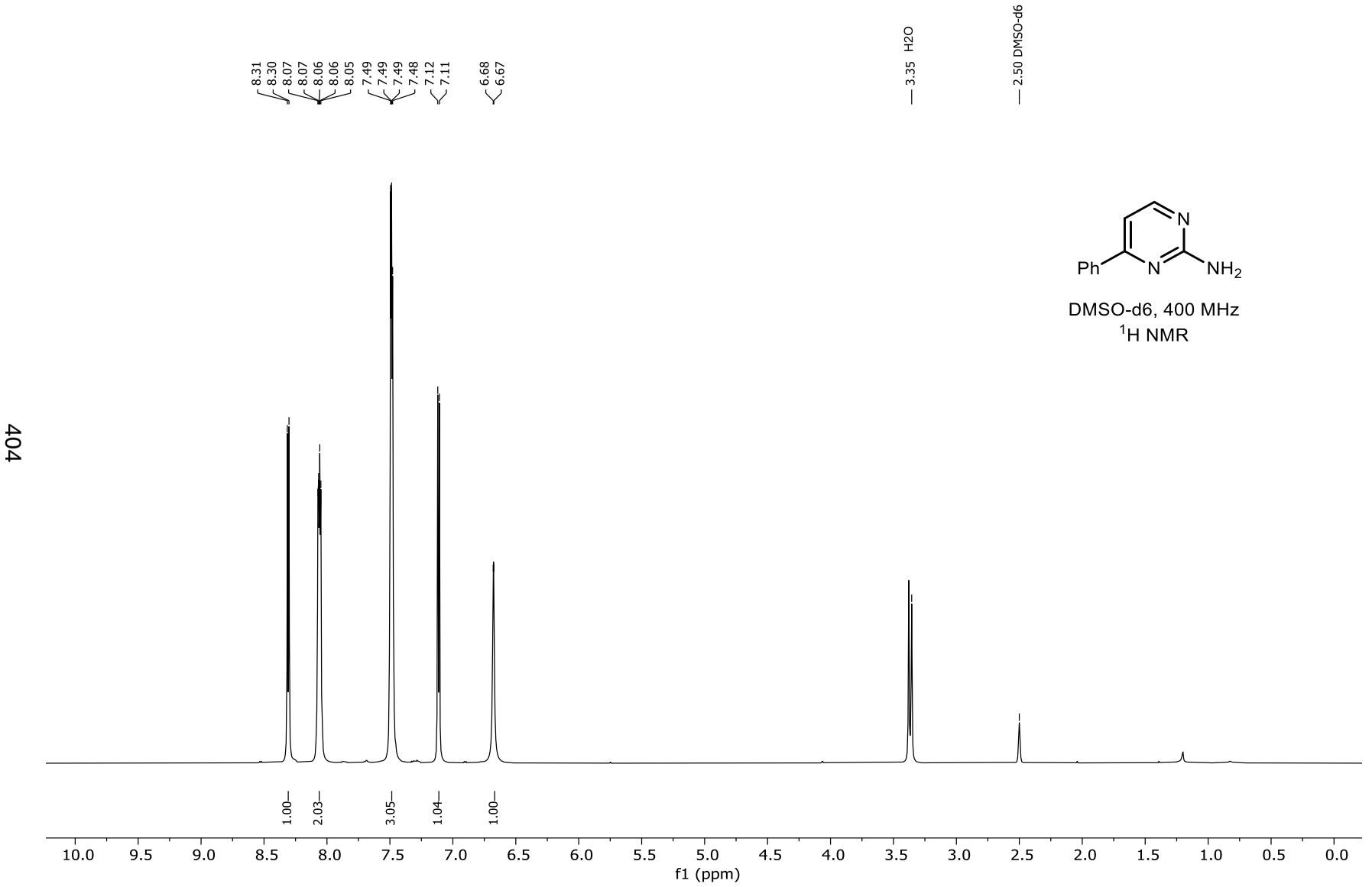

-79.14
Ph
N
OTf
N
Cl
CD3CN, 375 MHz
19F NMR
400
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

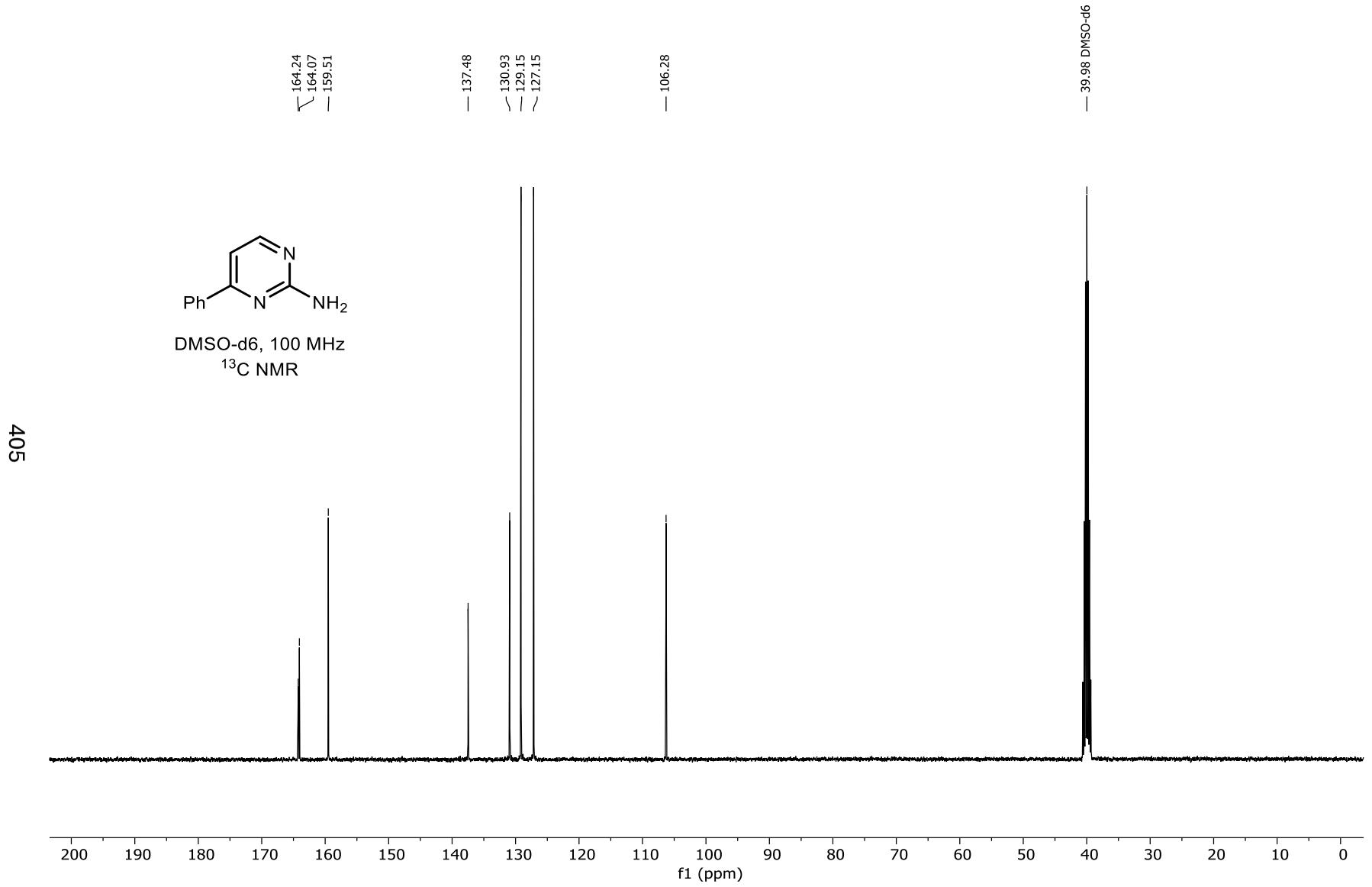
CD3CN, 400 MHz
1H NMR
Ph
OTf
MeO
9.44
9.43
8.97
8.97
8.95
8.95
8.49
8.49
8.47
8.47
8.45
8.45
7.75
7.73
7.23
7.20
3.96
1.94 CD3CN
0.97
1.00
3.08
5.07
2.01
3.00
f1 (ppm)

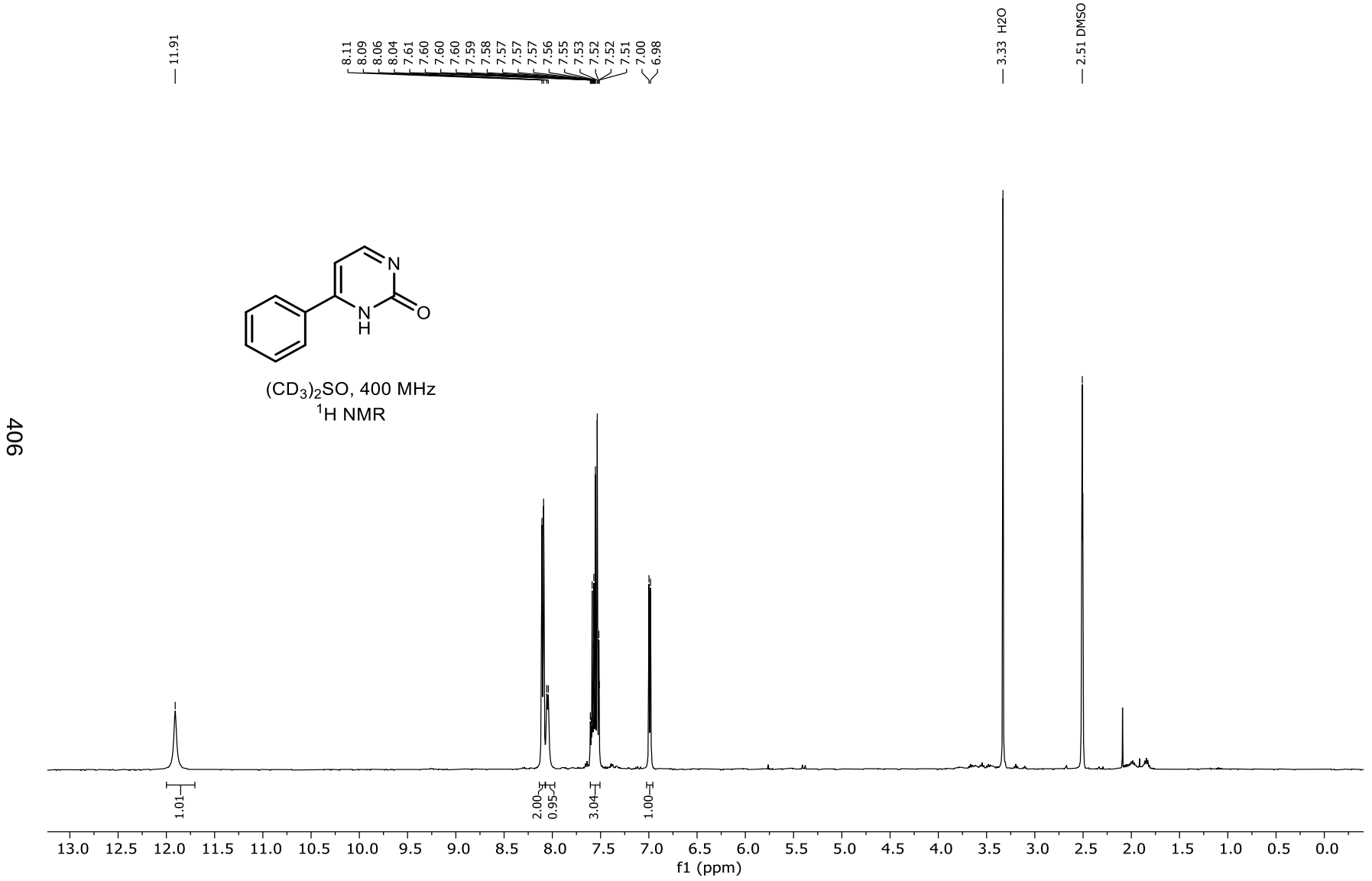

169.95
166.96
152.54
150.34
140.10
133.04
132.50
131.43
125.91
125.31
123.52
118.26 CD3CN
116.38
56.72
1.18 CD3CN
Ph
N
OTf
N
MeO
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

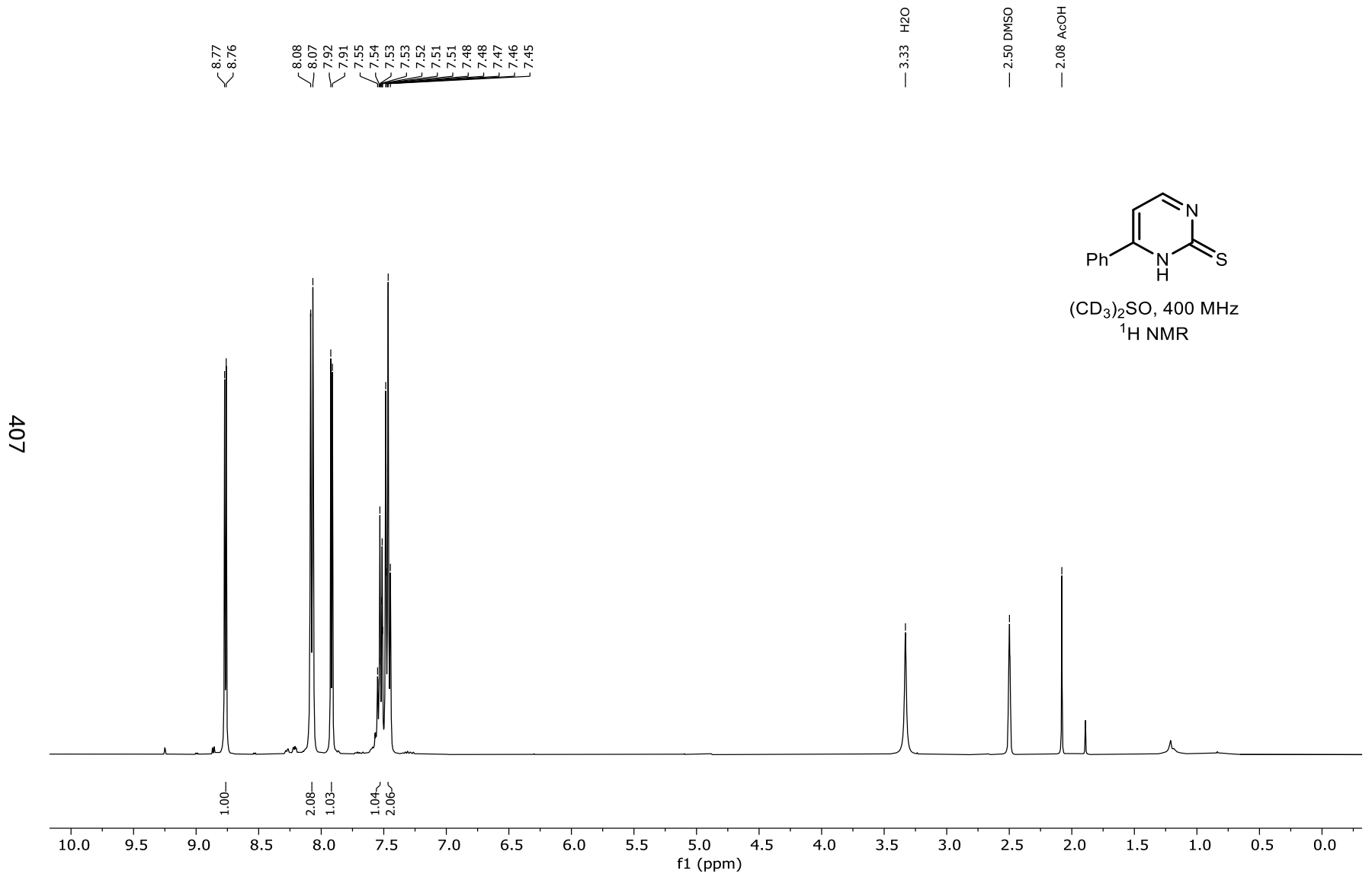
403

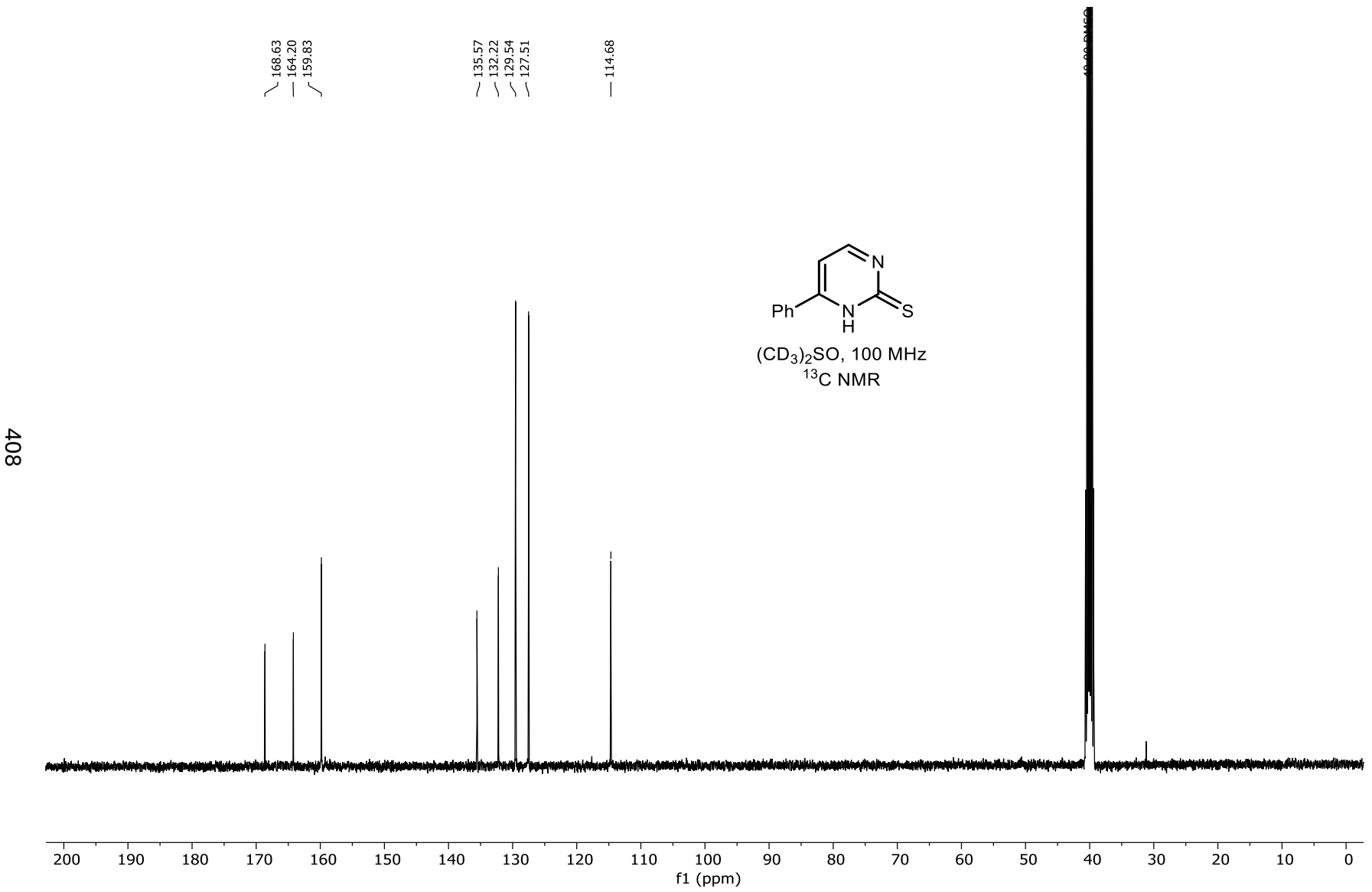

-79.11
Ph
N
OTf
N
MeO
CD3CN, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

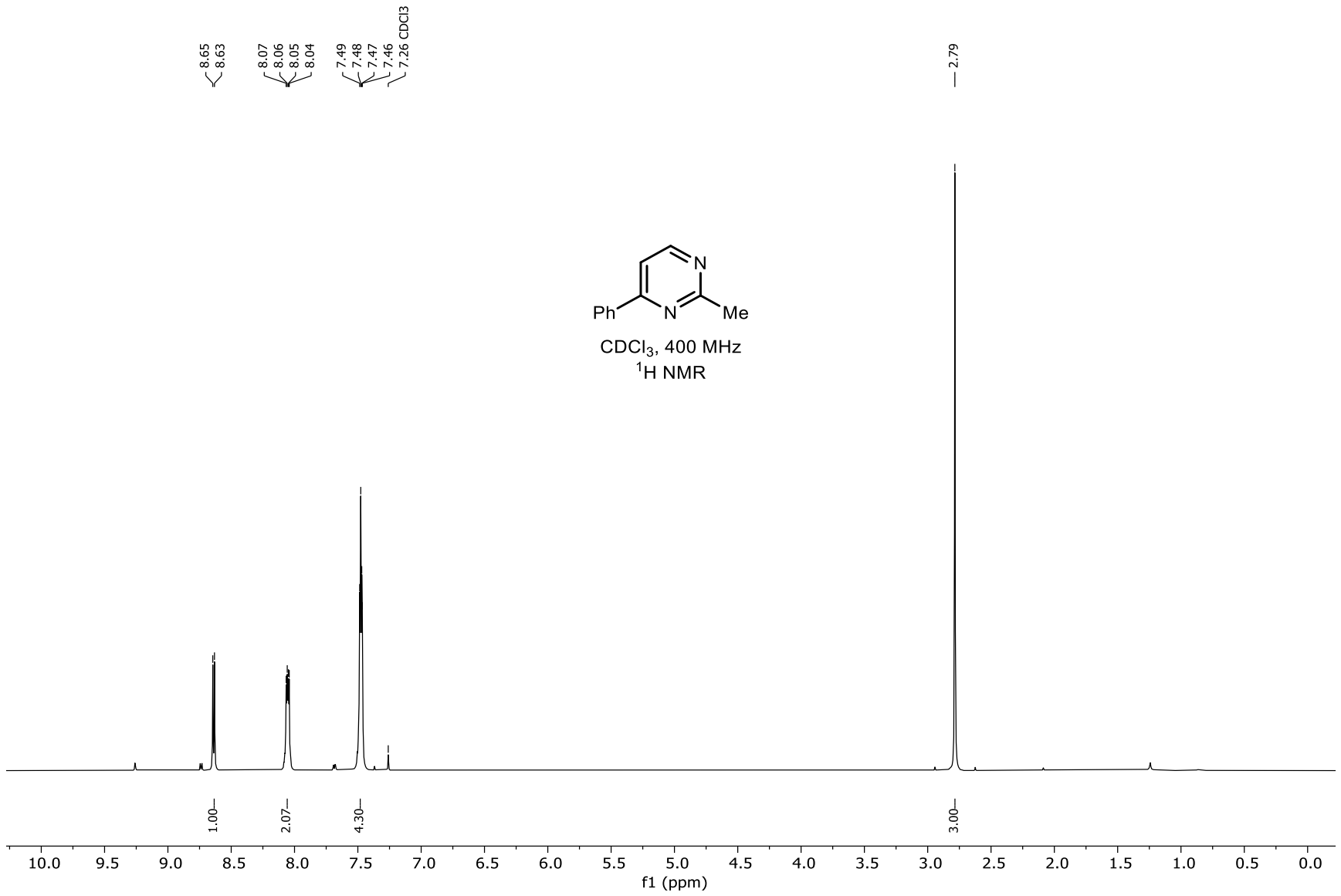

8.31
8.30
8.07
8.07
8.06
8.06
8.05
7.49
7.49
7.49
7.48
7.12
7.11
6.68
6.67
3.35 H2O
2.50 DMSO-d6
Ph
N
N
NH2
DMSO-d6, 400 MHz
1H NMR
1.00
2.03
3.05
1.04
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

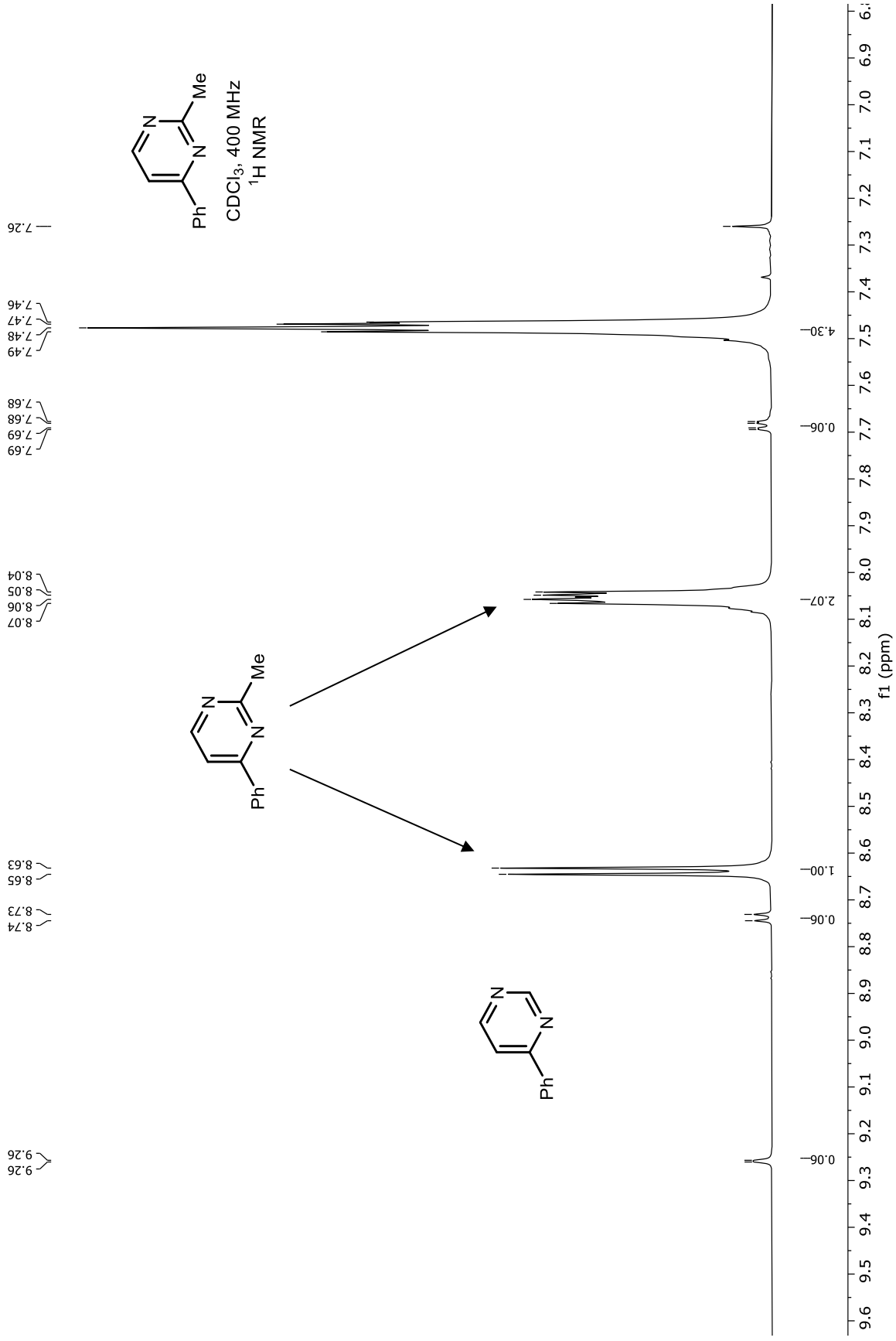

164.24
164.07
159.51
137.48
130.93
129.15
127.15
106.28
39.98 DMSO-d6
Ph
N
N
NH2
DMSO-d6, 100 MHz
13C NMR
405
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

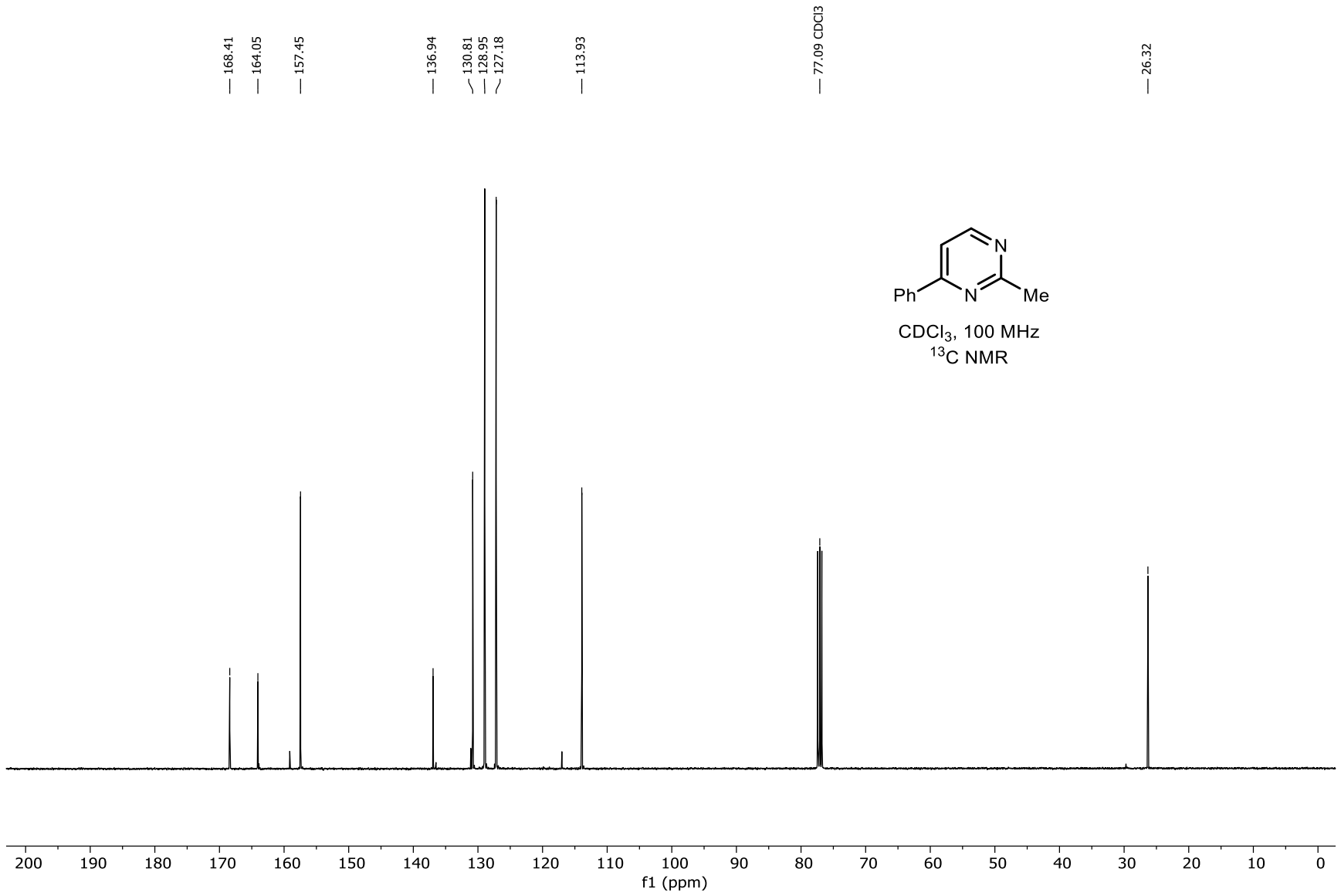

11.91
8.11
8.09
8.06
8.04
7.61
7.60
7.60
7.60
7.59
7.58
7.57
7.57
7.57
7.56
7.55
7.53
7.52
7.52
7.51
7.00
6.98
3.33 H2O
2.51 DMSO
N
N
H
O
(CD3)2SO, 400 MHz
1H NMR
1.01
2.00
0.95
3.04
1.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


8.77
8.76
8.08
8.07
7.92
7.91
7.55
7.54
7.53
7.53
7.52
7.51
7.51
7.48
7.48
7.47
7.46
7.45
3.33 H2O
2.50 DMSO
2.08 AcOH
Ph
N
H
N
S
(CD3)2SO, 400 MHz
1H NMR
1.00
2.08
1.03
1.04
2.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

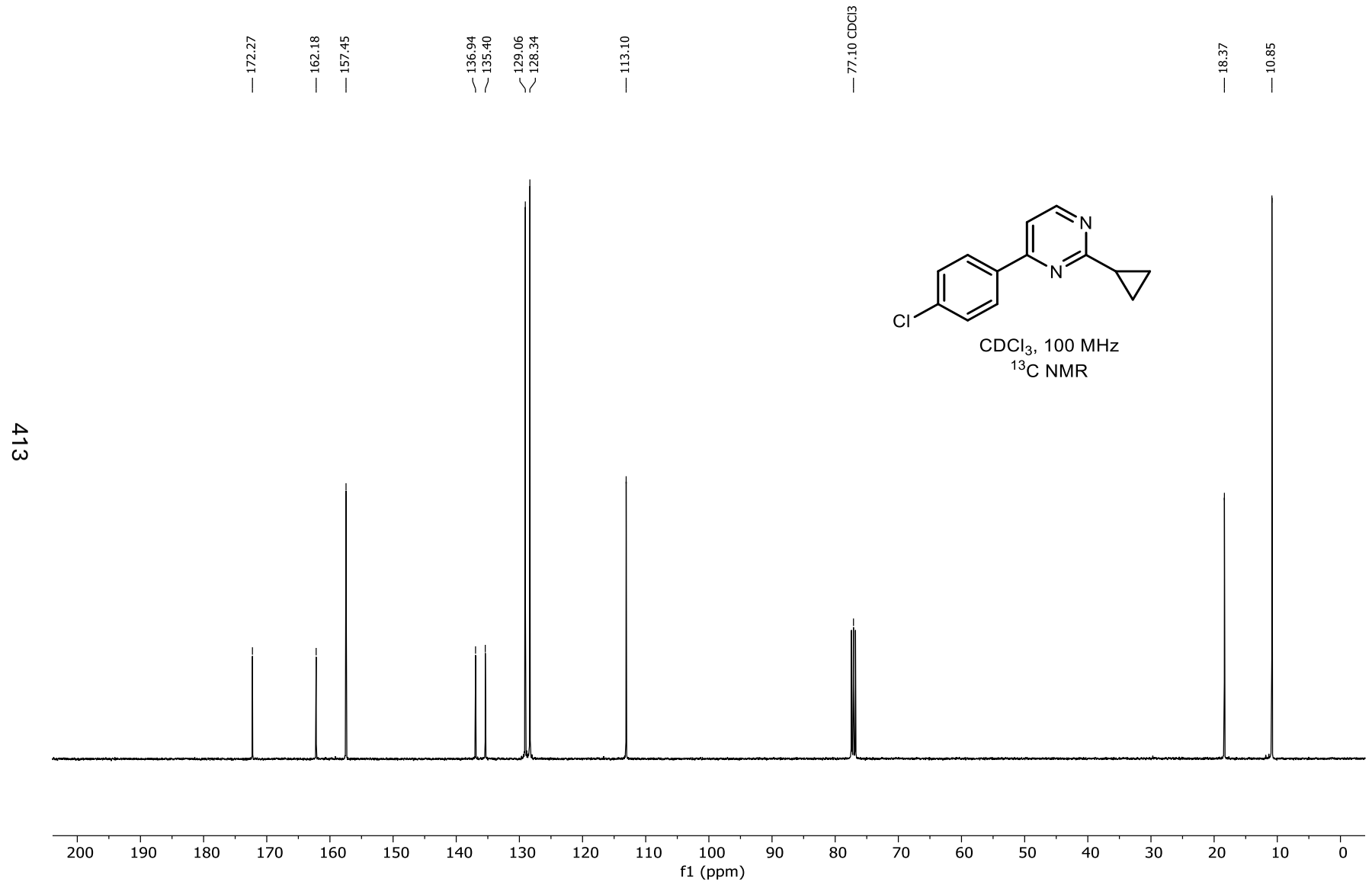

168.63
164.20
159.83
135.57
132.22
129.54
127.51
114.68
40.00 DMSO
Ph
N
H
S
(CD3)2SO, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

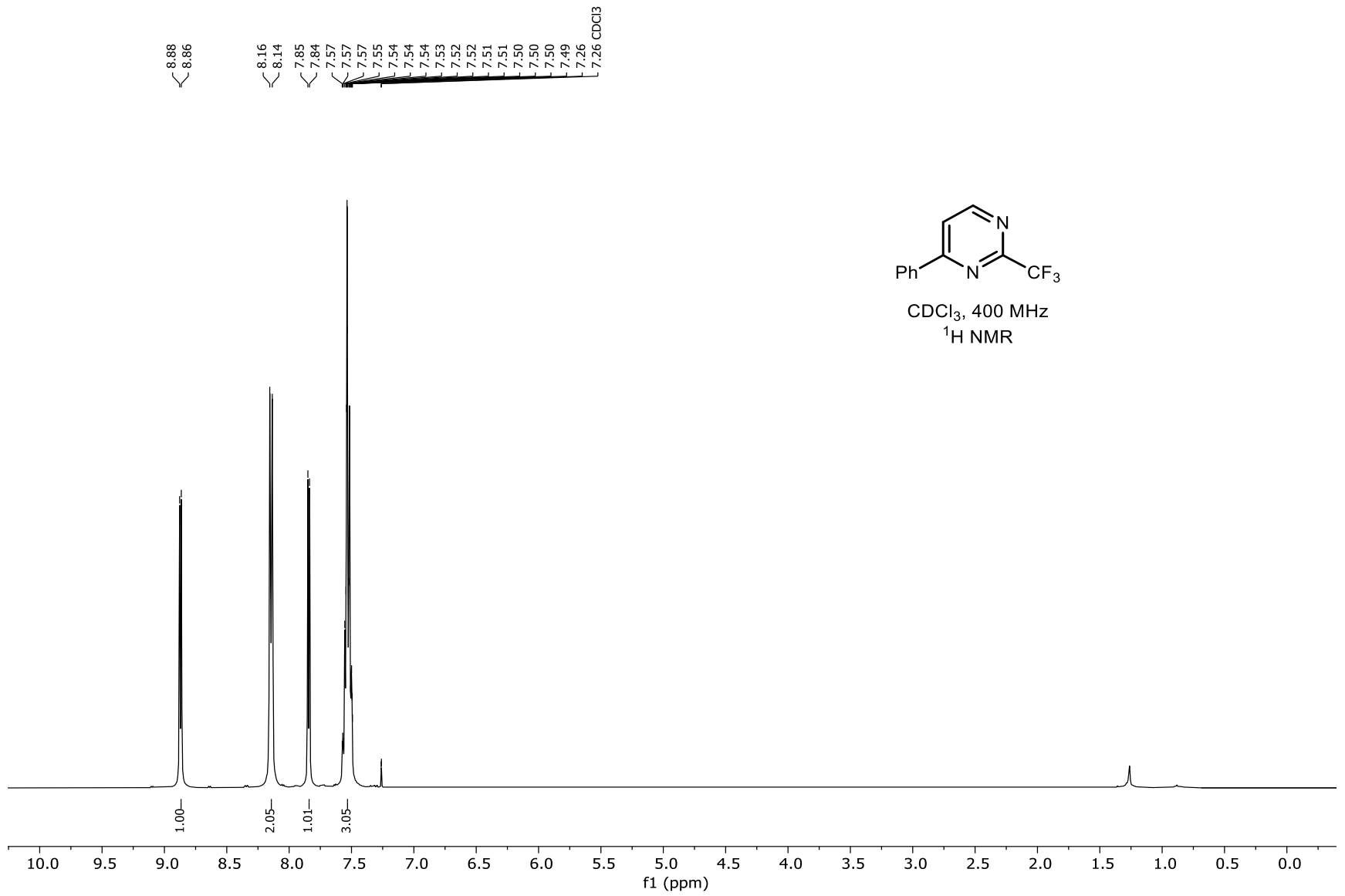

8.65
8.63
8.07
8.06
8.05
8.04
7.49
7.48
7.47
7.46
7.26 CDCl3
2.79
Ph
N
N
Me
CDCl3, 400 MHz
1H NMR
1.00
2.07
4.30
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

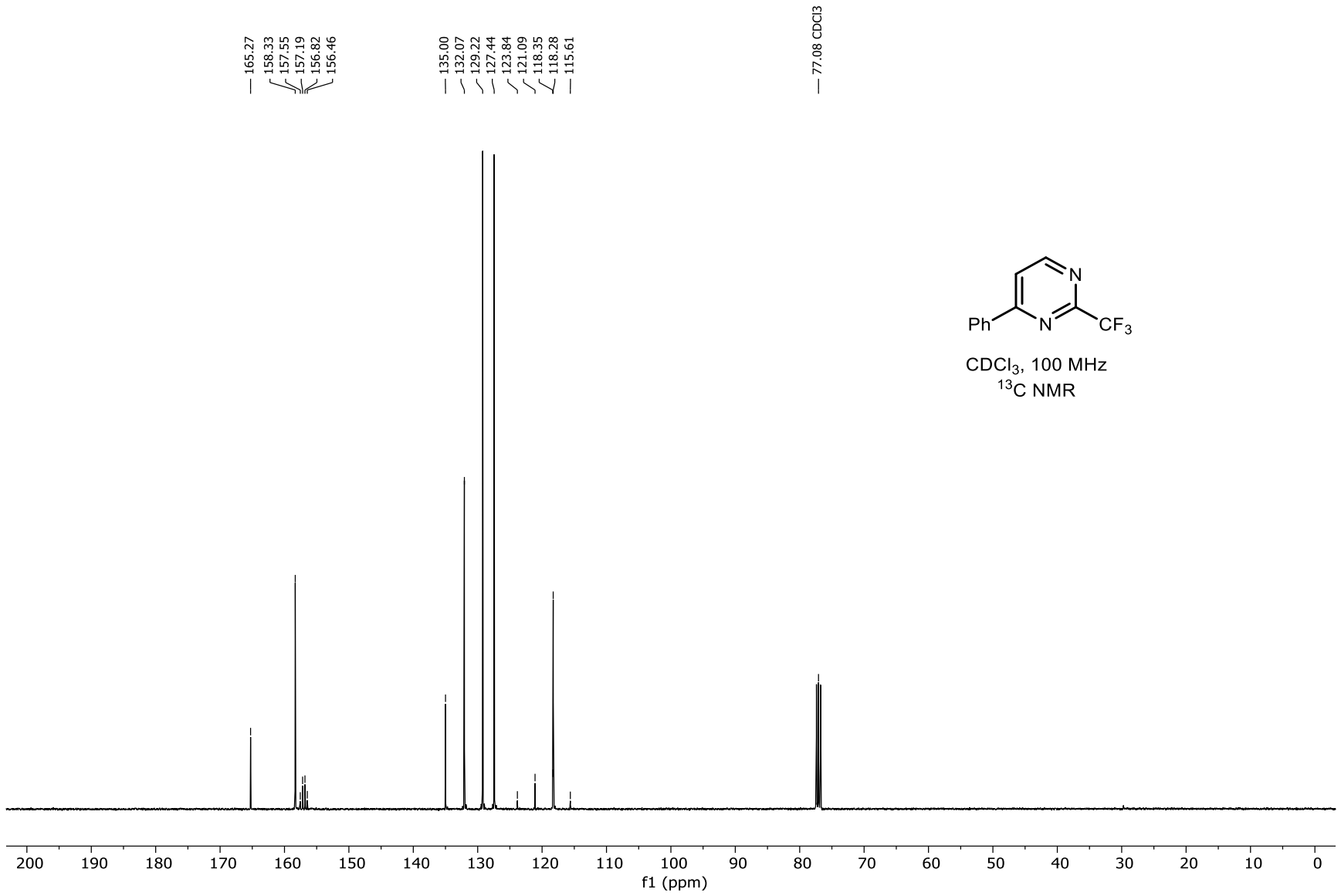

CDCl3, 400 MHz
1H NMR
Me
N
N
Ph
f1 (ppm)
9.6
9.5
9.4
9.3
9.2
9.1
9.0
8.9
8.8
8.7
8.6
8.5
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
9.26
8.74
8.73
8.65
8.63
8.07
8.06
8.05
8.04
7.69
7.69
7.68
7.68
7.49
7.48
7.47
7.46
7.26
0.06
1.00
0.06
2.07
0.06
4.30


168.41
164.05
157.45
136.94
130.81
128.95
127.18
113.93
77.09 CDCl3
26.32
Ph
N
N
Me
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

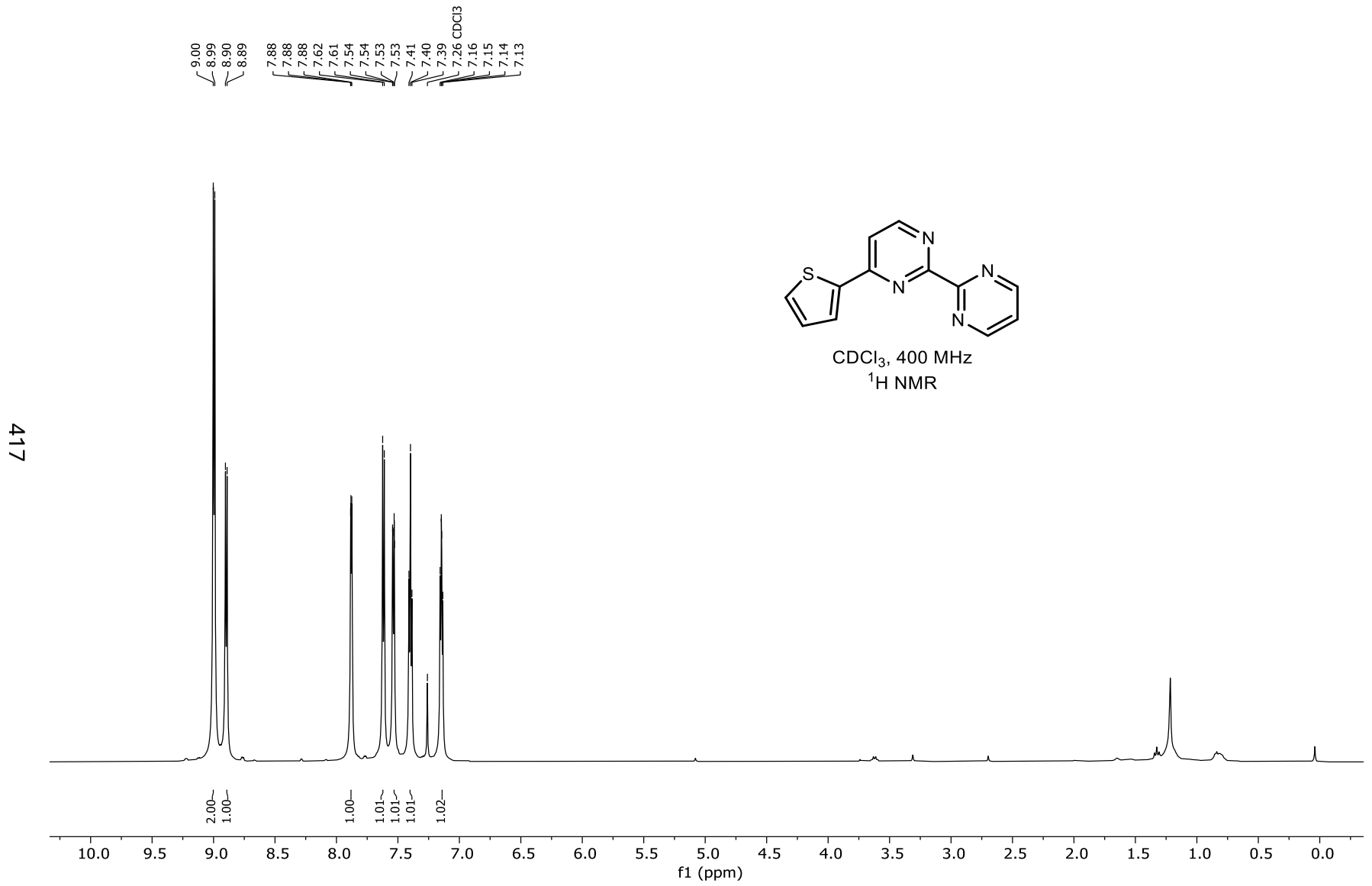
CDCl3, 400 MHz
1H NMR
Cl
N
N
f1 (ppm)
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
2.06
2.01
1.03
1.02
2.03
2.18
8.56
8.55
7.99
7.97
7.42
7.40
7.35
7.34
7.26 CDCl3
2.32
2.31
2.30
2.29
2.28
2.27
2.26
1.21
1.20
1.19
1.19
1.18
1.17
1.09
1.08
1.08
1.07
1.06
1.05
1.04

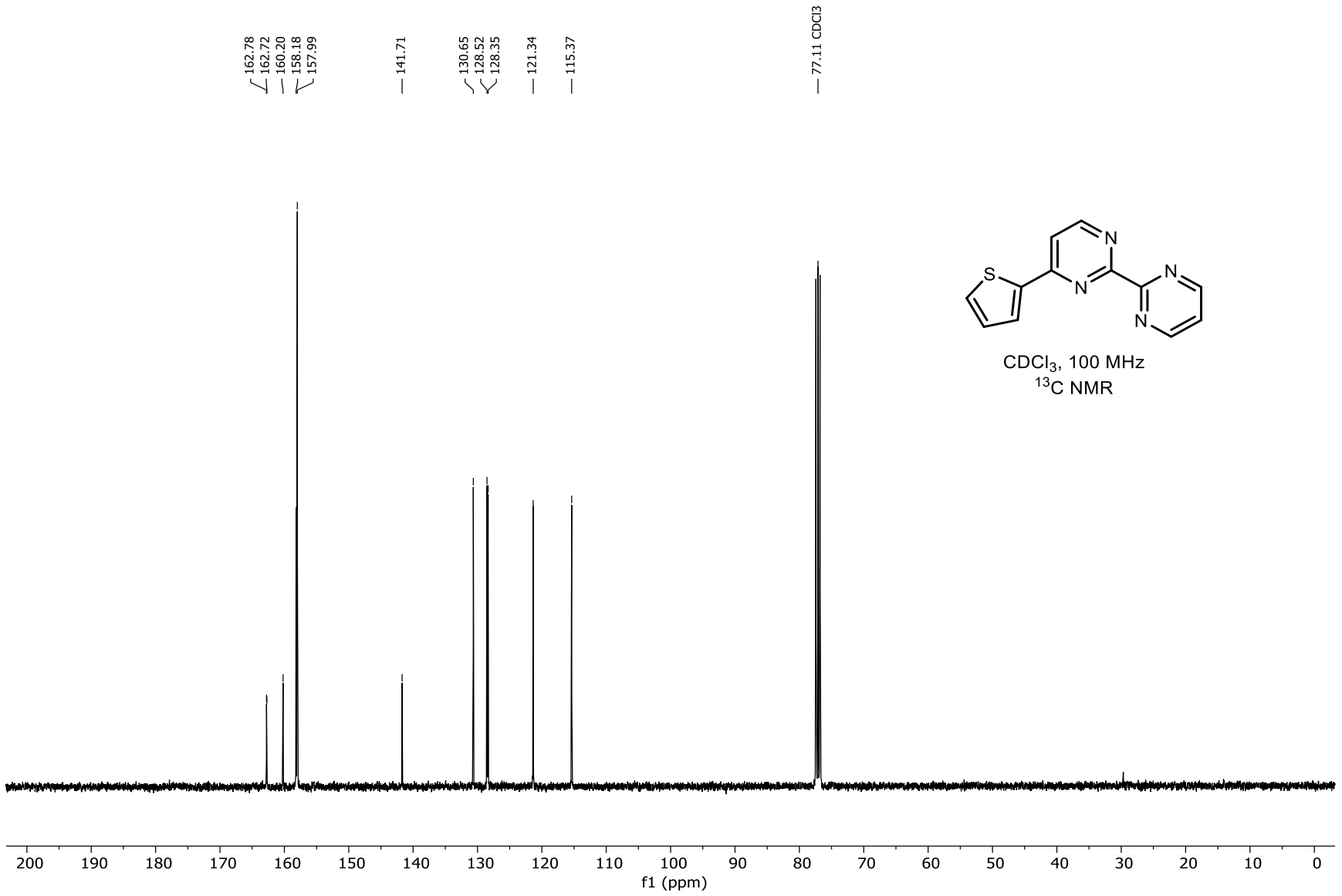

172.27
162.18
157.45
136.94
135.40
129.06
128.34
113.10
77.10 CDCl3
18.37
10.85
N
N
Cl
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.88
8.86
8.16
8.14
7.85
7.84
7.57
7.57
7.57
7.55
7.54
7.54
7.54
7.53
7.52
7.52
7.51
7.51
7.50
7.50
7.50
7.49
7.26
7.26 CDCl3
N
Ph
N
CF3
CDCl3, 400 MHz
1H NMR
1.00
2.05
1.01
3.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

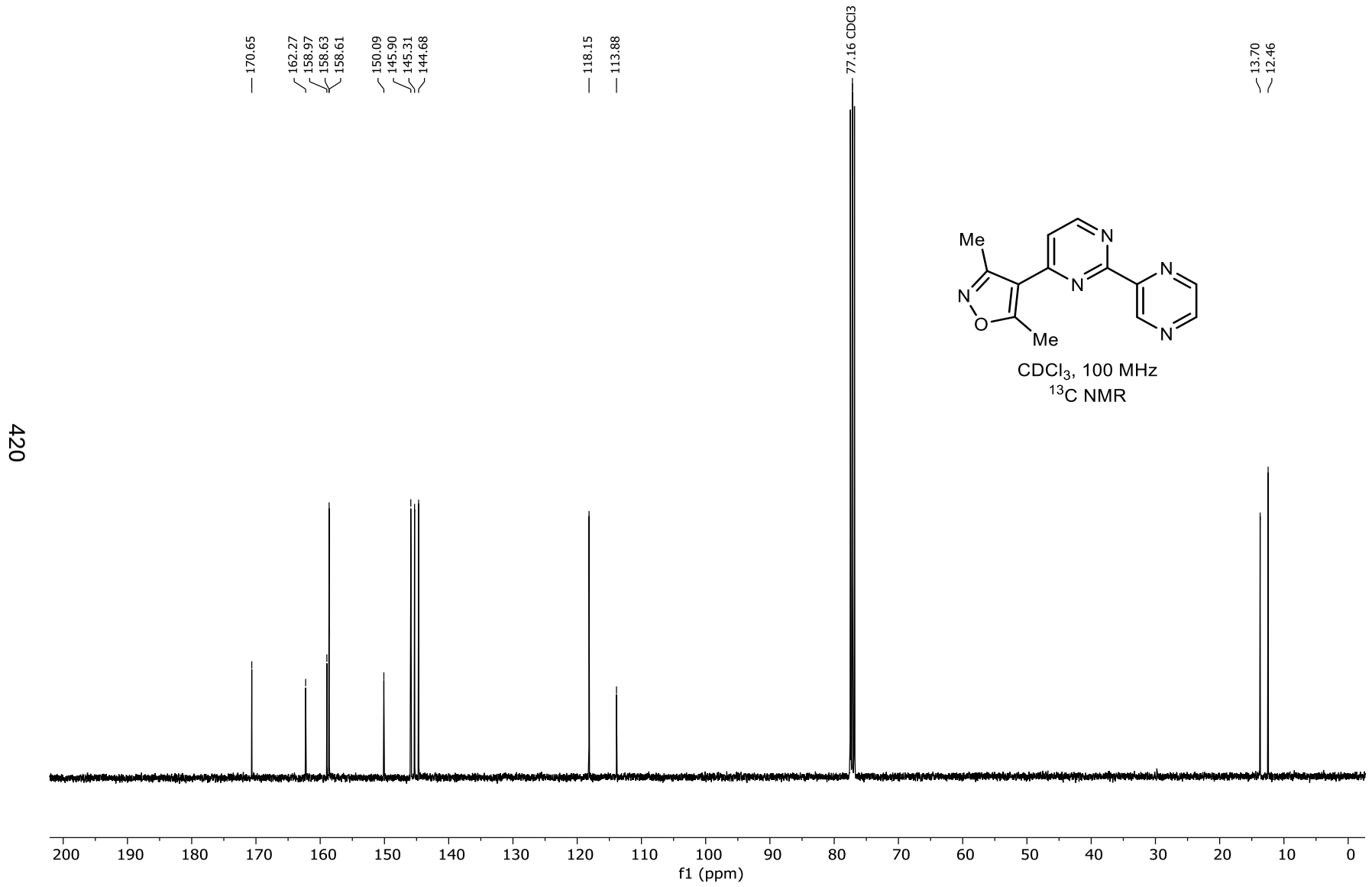

165.27
158.33
157.55
157.19
156.82
156.46
135.00
132.07
129.22
127.44
123.84
121.09
118.35
118.28
115.61
77.08 CDCl3
Ph
N
N
CF3
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

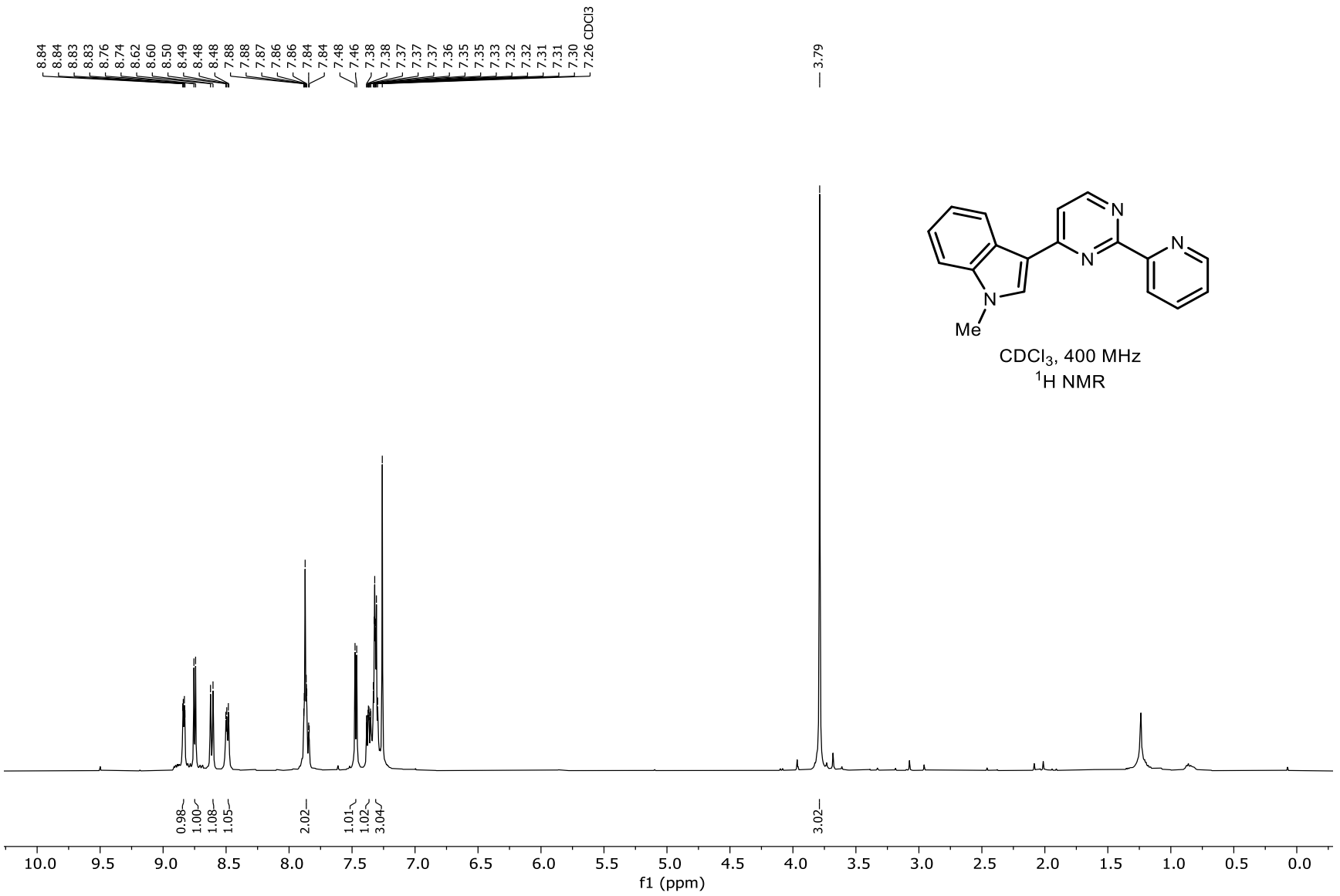

-70.52
Ph
N
N
CF3
CDCl3, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

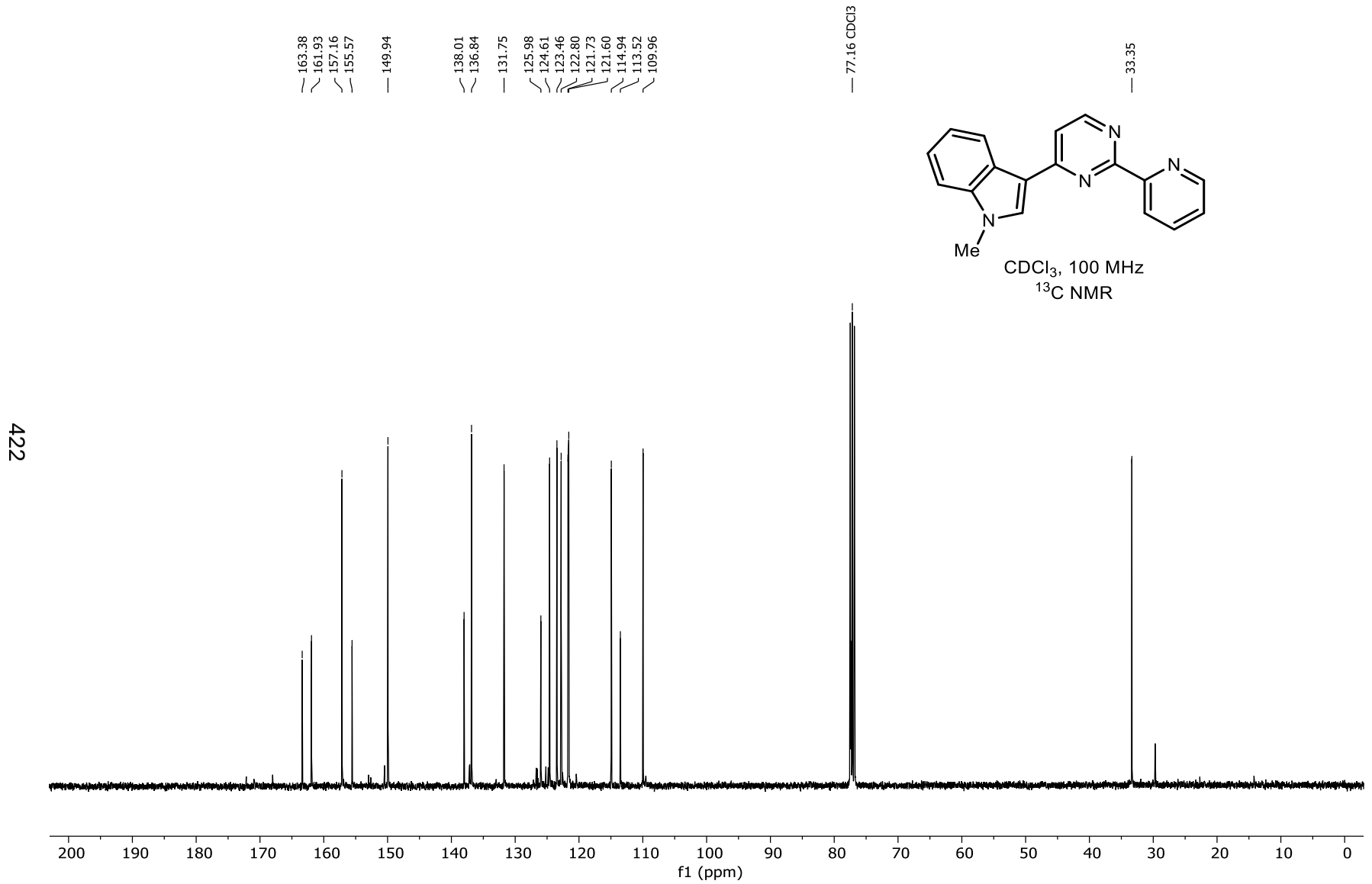

9.00
8.99
8.90
8.89
7.88
7.88
7.88
7.62
7.61
7.54
7.54
7.53
7.53
7.41
7.40
7.39
7.26 CDCl3
7.16
7.15
7.14
7.13
S
N
N
N
N
CDCl3, 400 MHz
1H NMR
2.00
1.00
1.00
1.01
1.01
1.01
1.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

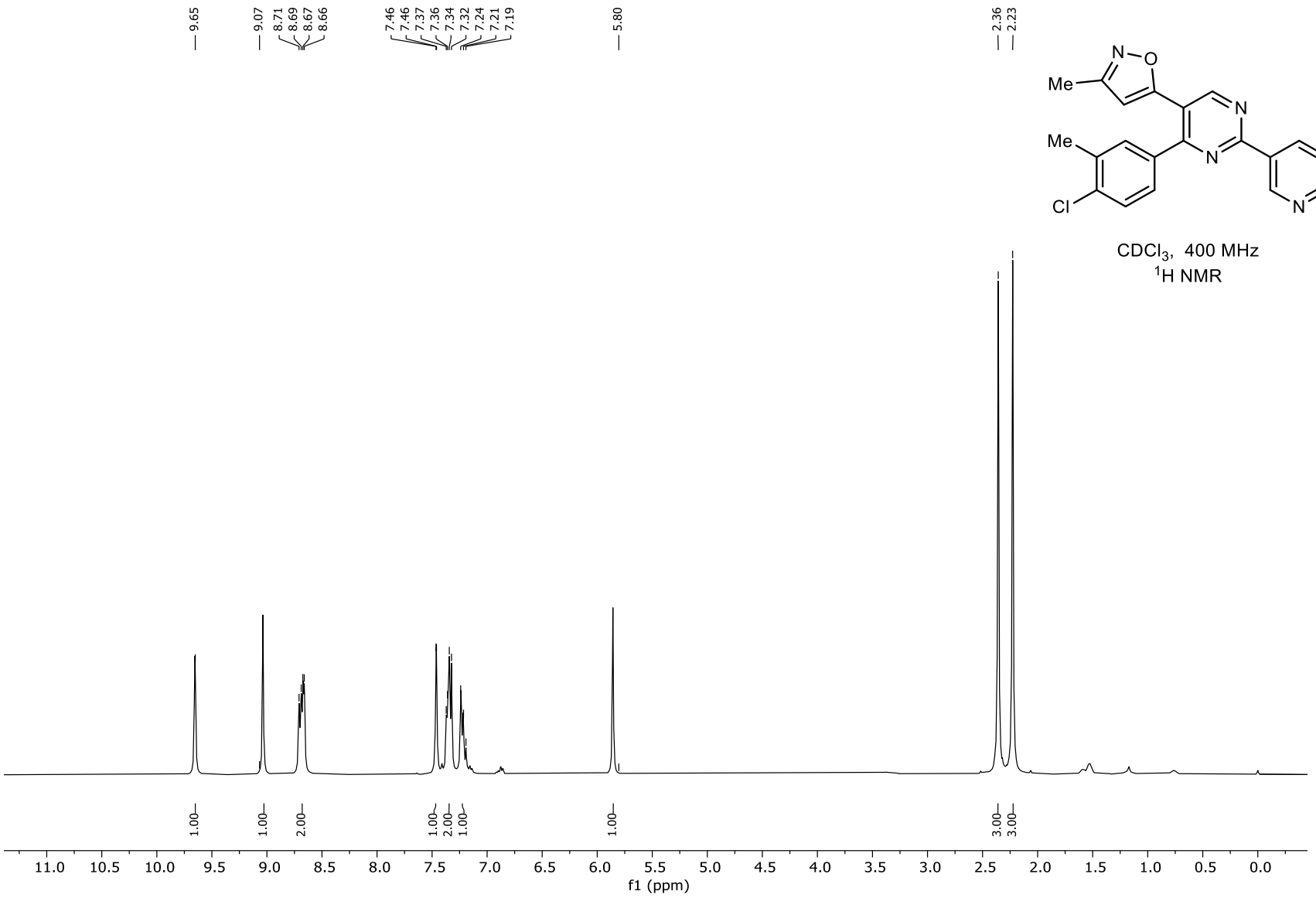

162.78
162.72
160.20
158.18
157.99
141.71
130.65
128.52
128.35
121.34
115.37
77.11 CDCl3
S
N
N
N
N
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

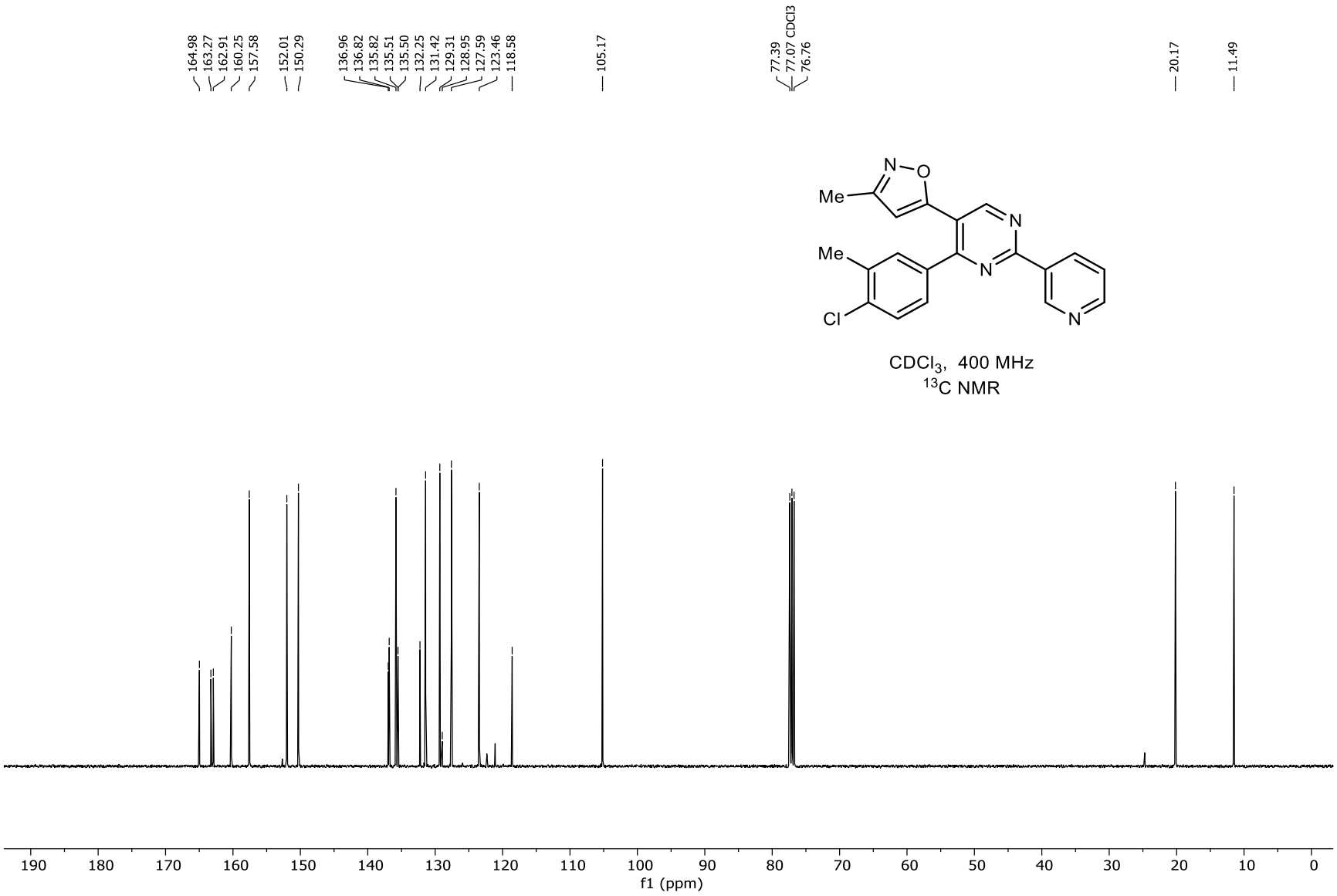
9.70
9.70
8.98
8.97
8.79
8.71
8.70
7.41
7.40
7.26 CDCl3
2.77
2.58
1.00
1.02
1.00
0.99
1.02
3.00
3.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
CDCl3, 400 MHz
1H NMR
Me
Me
N
N
N
N
N
O

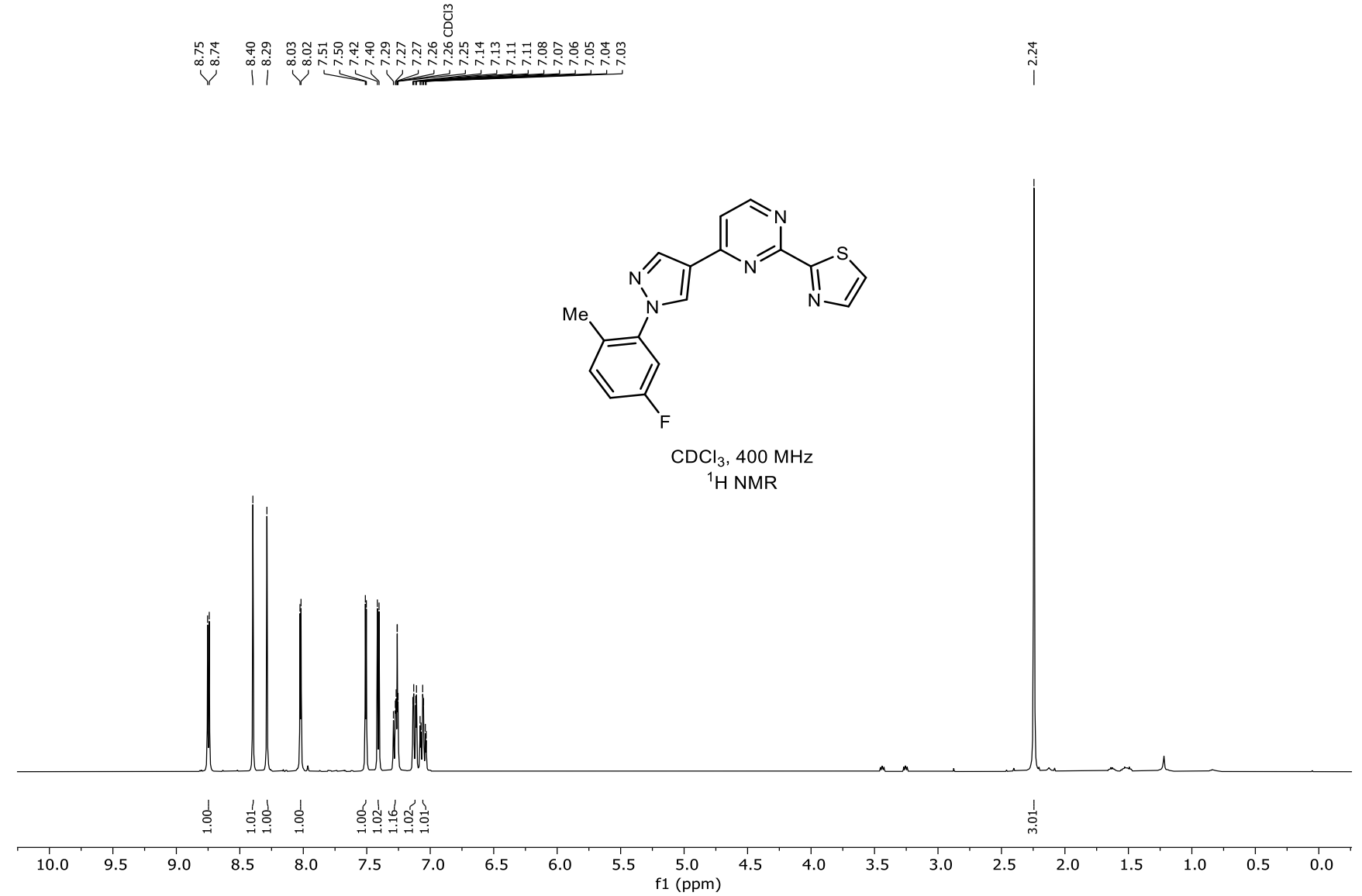

170.65
162.27
158.97
158.63
158.61
150.09
145.90
145.31
144.68
118.15
113.88
77.16 CDCl3
13.70
12.46
Me
N
N
N
N
O
Me
N
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

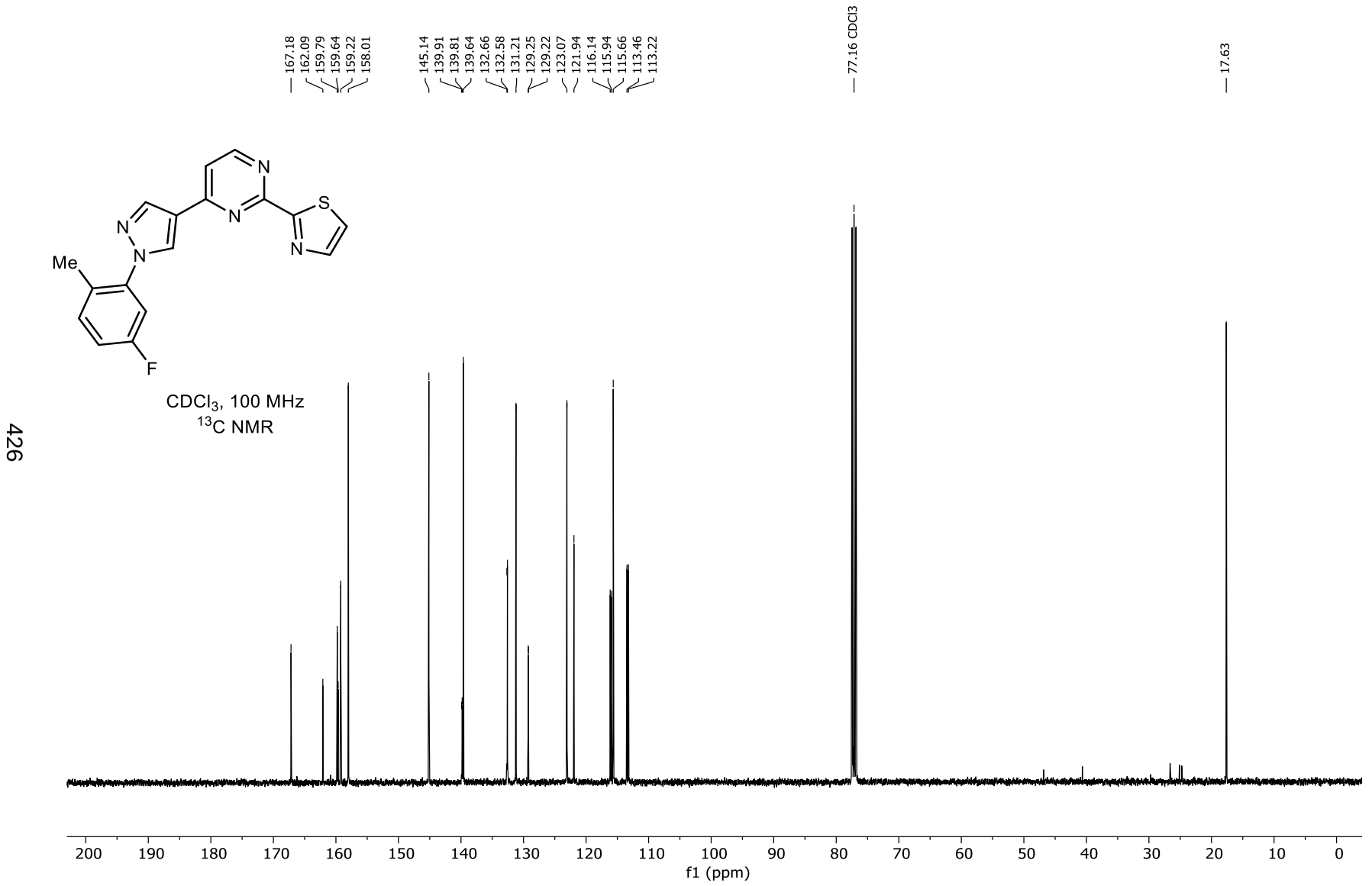

8.84
8.84
8.83
8.83
8.76
8.74
8.62
8.60
8.50
8.49
8.48
8.48
7.88
7.88
7.87
7.86
7.86
7.84
7.84
7.48
7.46
7.38
7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.33
7.32
7.32
7.31
7.31
7.30
7.26 CDCl3
3.79
N
N
N
N
Me
CDCl3, 400 MHz
1H NMR
0.98
1.00
1.08
1.05
2.02
1.01
1.02
3.04
3.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

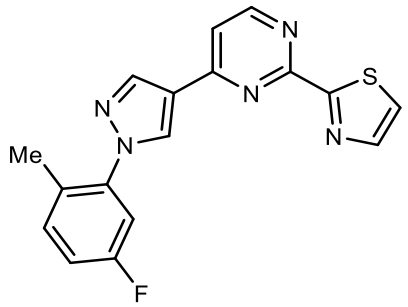

163.38
161.93
157.16
155.57
149.94
138.01
136.84
131.75
125.98
124.61
123.46
122.80
121.73
121.60
114.94
113.52
109.96
77.16 CDCl3
33.35
N
N
N
N
Me
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.65
9.07
8.71
8.69
8.67
8.66
7.46
7.46
7.37
7.36
7.34
7.32
7.24
7.21
7.19
5.80
2.36
2.23
Me
N
O
N
Me
N
Cl
N
CDCl3, 400 MHz
1H NMR
1.00
1.00
2.00
1.00
2.00
1.00
1.00
3.00
3.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.98
163.27
162.91
160.25
157.58
152.01
150.29
136.96
136.82
135.82
135.51
135.50
132.25
131.42
129.31
128.95
127.59
123.46
118.58
105.17
77.39
77.07 CDCl3
76.76
20.17
11.49
Me
N
O
N
Me
N
Cl
N
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

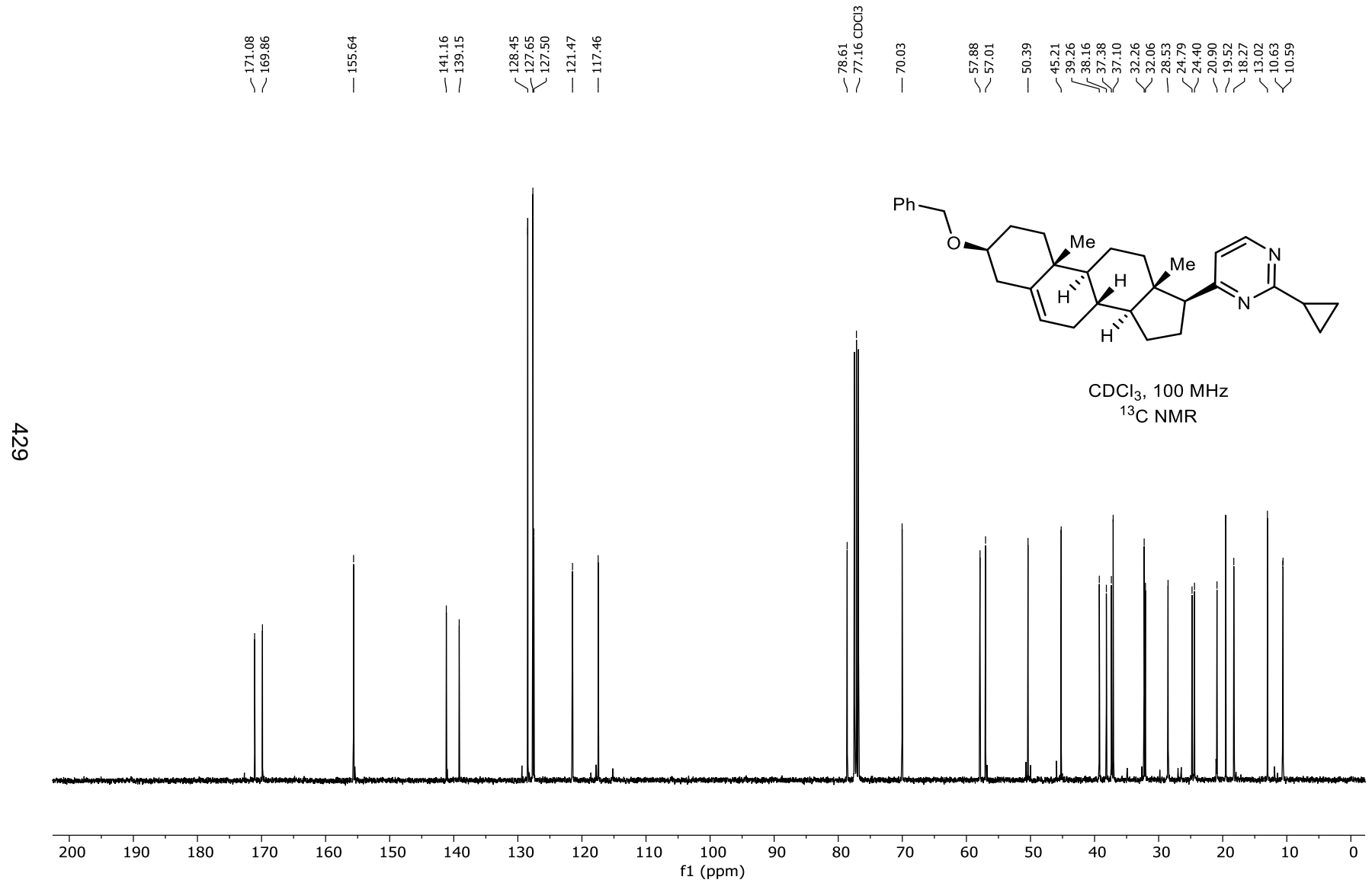

8.75
8.74
8.40
8.29
8.03
8.02
7.51
7.50
7.42
7.40
7.29
7.27
7.27
7.26
7.26 CDCl3
7.25
7.14
7.13
7.11
7.11
7.08
7.07
7.06
7.05
7.04
7.03
2.24
N
N
S
N
N
Me
F
CDCl3, 400 MHz
1H NMR
1.00
1.01
1.00
1.00
1.00
1.02
1.16
1.02
1.01
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

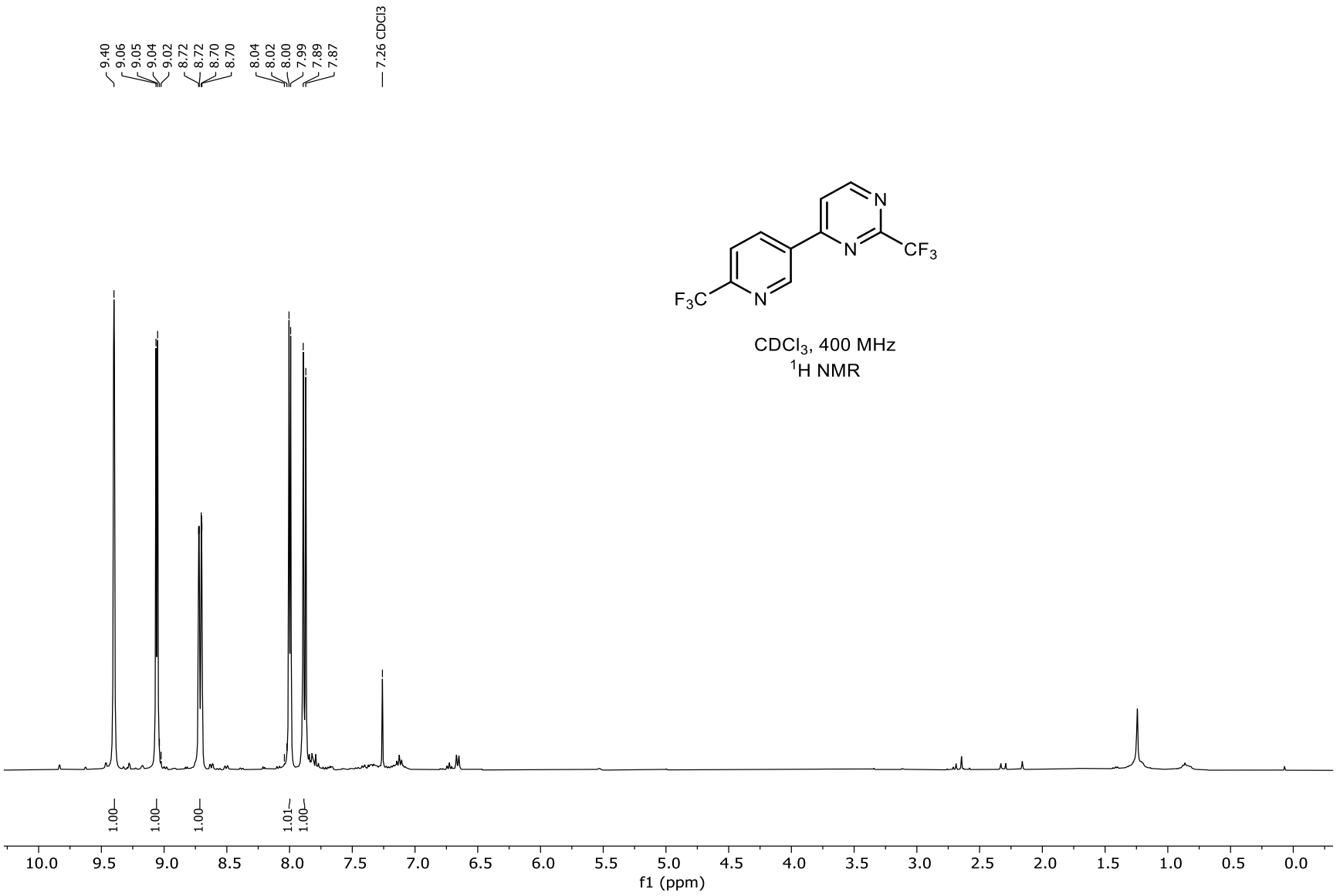

167.18
162.09
159.79
159.64
159.22
158.01
145.14
139.91
139.81
139.64
132.66
132.58
131.21
129.25
129.22
123.07
121.94
116.14
115.94
115.66
113.46
113.22
77.16 CDCl3
17.63
N
N
S
N
N
N
Me
F
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

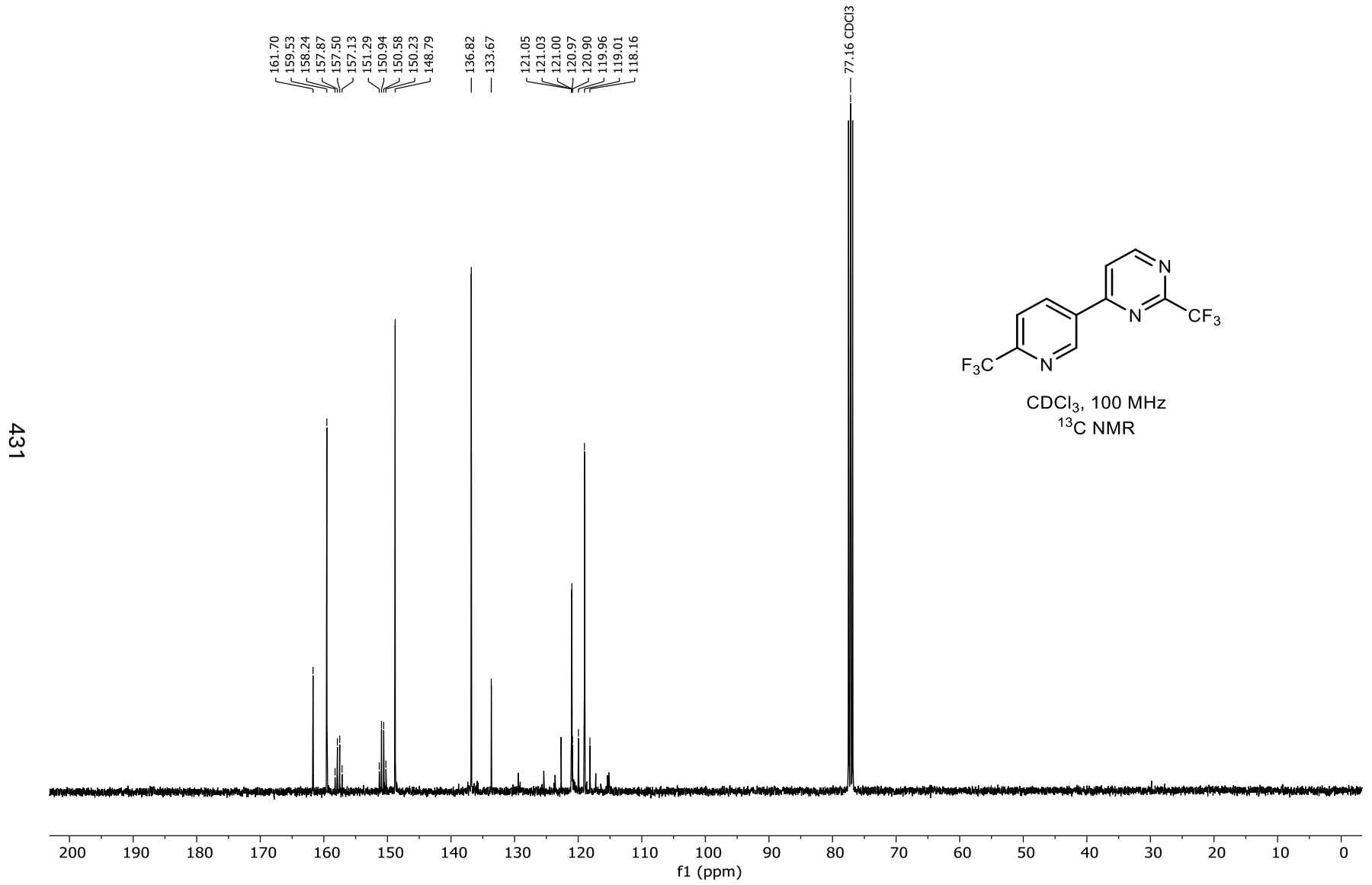


$CDCl_3$, 375 MHz
^{19}F NMR

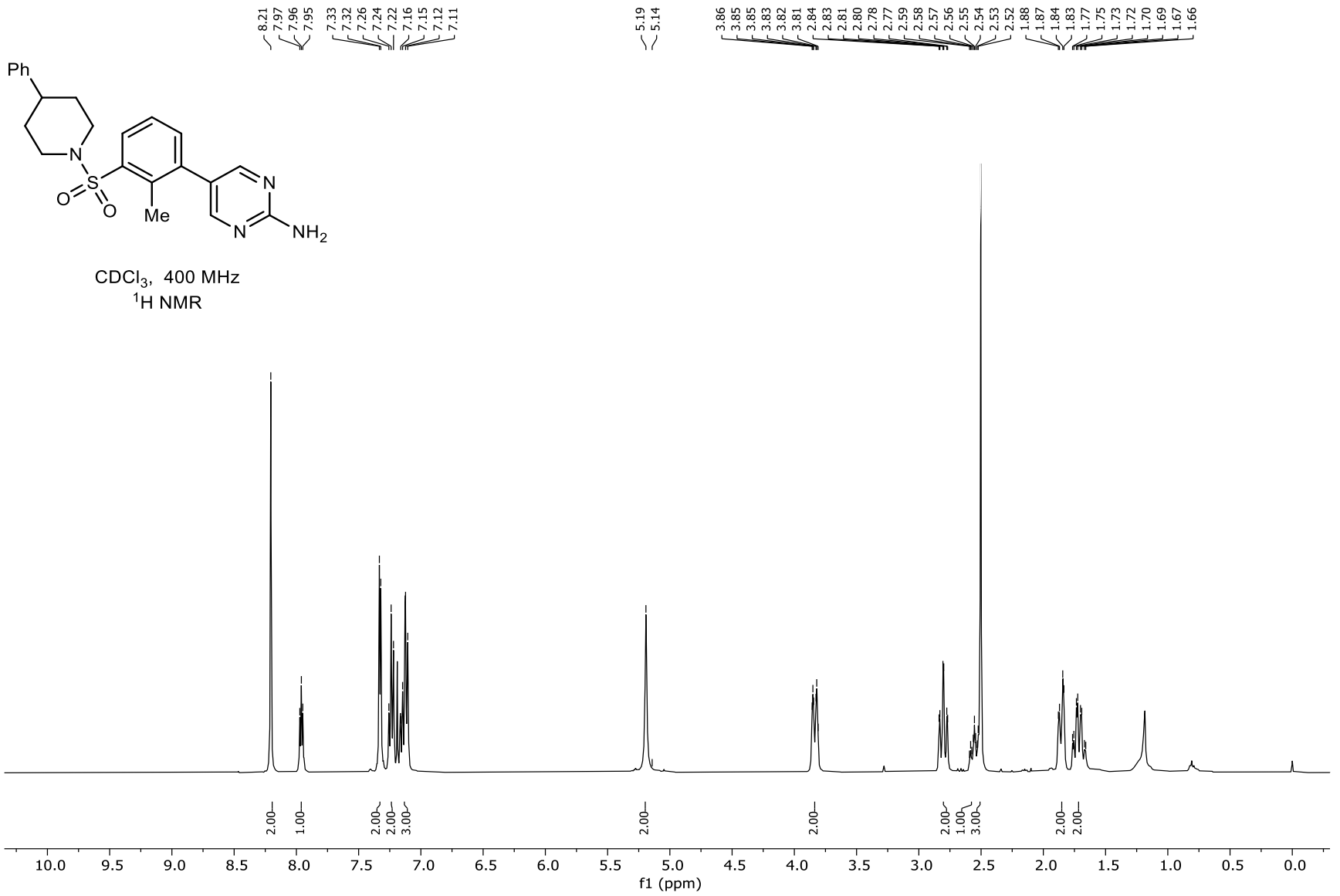
CDCl3, 400 MHz
1H NMR
Me
Me
H
H
H
N
N
O
Ph
f1 (ppm)

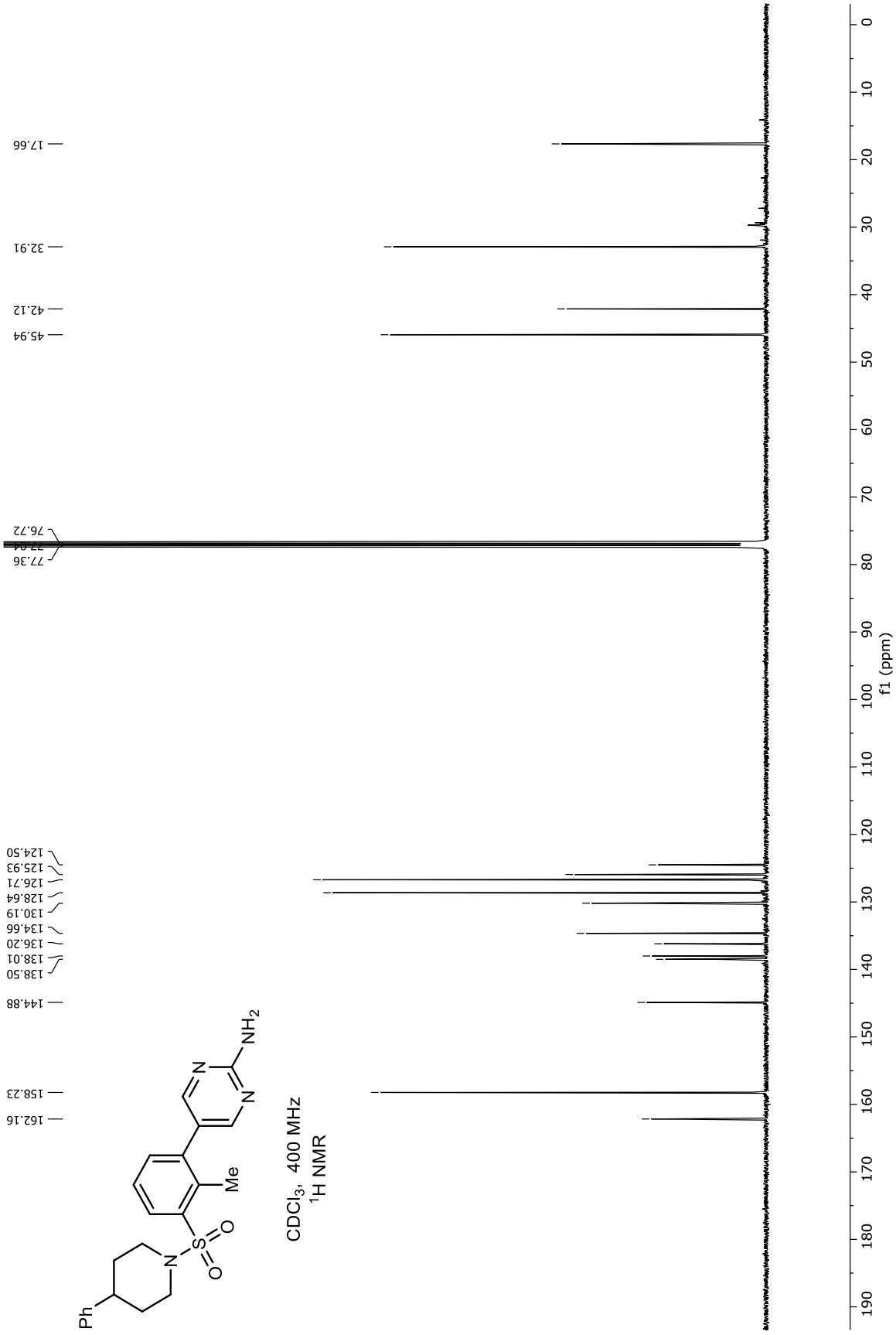

171.08
169.86
155.64
141.16
139.15
128.45
127.65
127.50
121.47
117.46
78.61
77.16 CDCl3
70.03
57.88
57.01
50.39
45.21
39.26
38.16
37.38
37.10
32.26
32.06
28.53
24.79
24.40
20.90
19.52
18.27
13.02
10.63
10.59
Ph
O
Me
Me
H
H
H
N
N
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

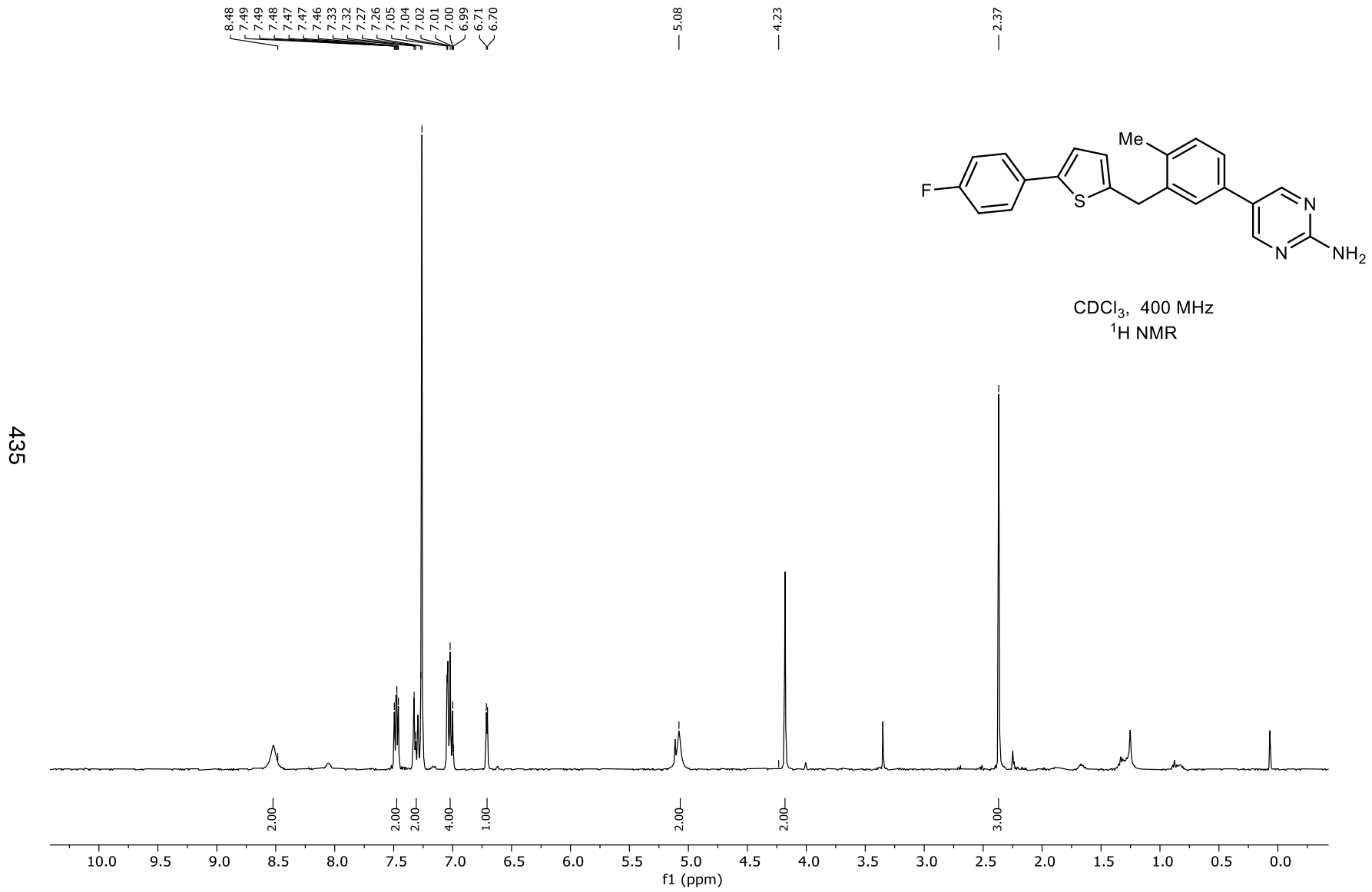

9.40
9.06
9.05
9.04
9.02
8.72
8.72
8.70
8.70
8.04
8.02
8.00
7.99
7.89
7.87
7.26 CDCl3
N
N
CF3
F3C
N
CDCl3, 400 MHz
1H NMR
1.00
1.00
1.00
1.01
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

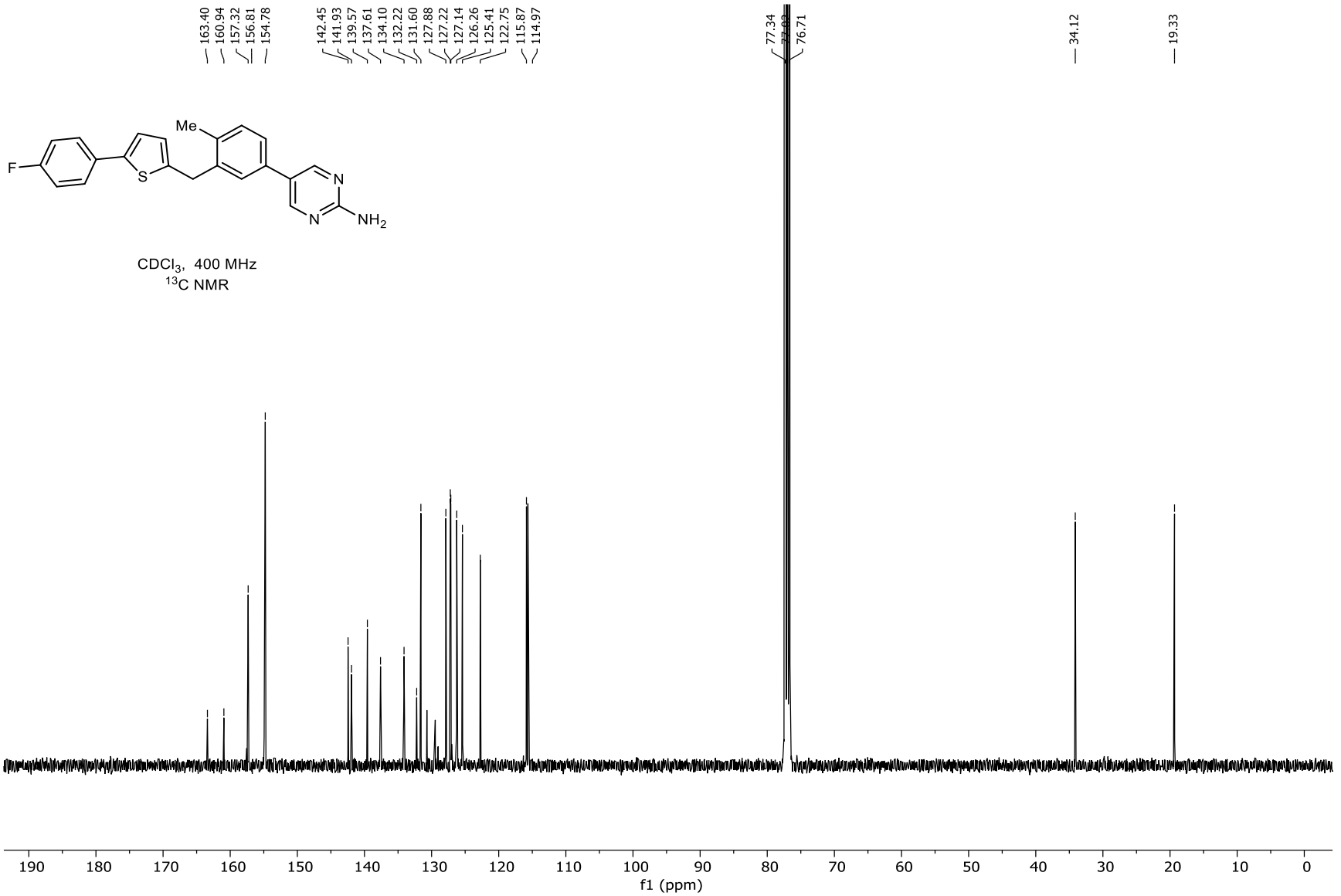

161.70
159.53
158.24
157.87
157.50
157.13
151.29
150.94
150.58
150.23
148.79
136.82
133.67
121.05
121.03
121.00
120.97
120.90
119.96
119.01
118.16
77.16 CDCl3
N
N
CF3
F3C
N
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

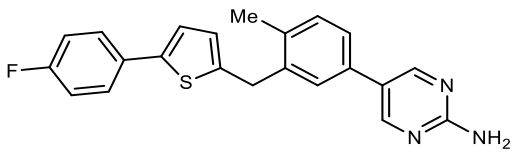

-68.17
-70.61
N
N
CF3
F3C
N
CDCl3, 375 MHz
19F NMR
3.02
3.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


8.21
7.97
7.96
7.95
7.33
7.32
7.26
7.24
7.22
7.16
7.15
7.12
7.11
5.19
5.14
3.86
3.85
3.85
3.83
3.82
3.81
2.84
2.83
2.81
2.80
2.78
2.77
2.59
2.58
2.57
2.56
2.55
2.54
2.53
2.52
1.88
1.87
1.84
1.83
1.77
1.75
1.73
1.72
1.70
1.69
1.67
1.66
Ph
N
S
O
O
Me
N
N
NH2
CDCl3, 400 MHz
1H NMR
2.00
1.00
2.00
2.00
3.00
2.00
2.00
2.00
1.00
3.00
2.00
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CDCl3, 400 MHz
1H NMR
Ph
N
S
O
O
Me
N
N
NH2
162.16
158.23
144.88
138.50
138.01
136.20
134.66
130.19
128.64
126.71
125.93
124.50
77.36
76.72
45.94
42.12
32.91
17.66
f1 (ppm)

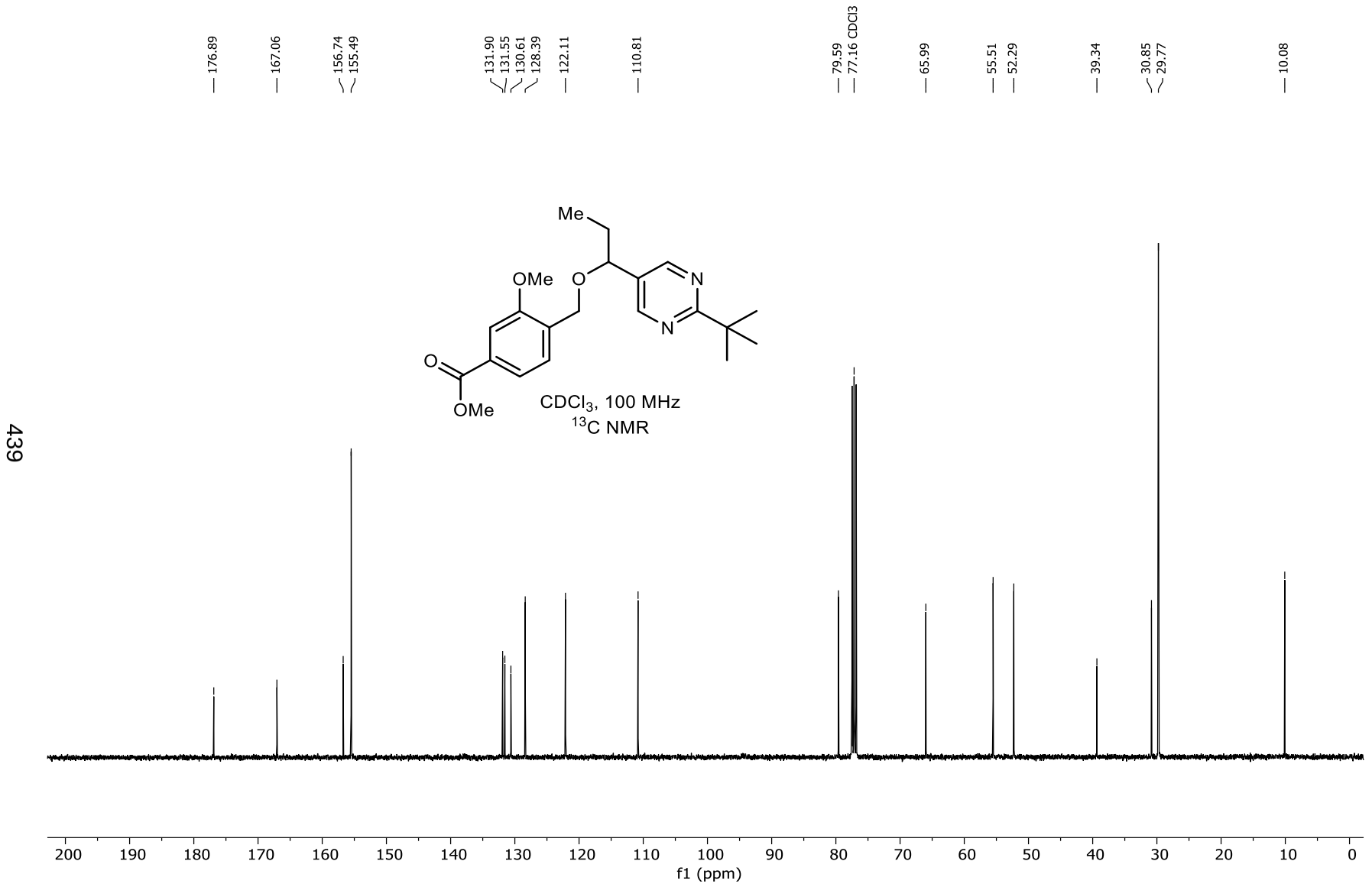

8.48
7.49
7.49
7.48
7.47
7.47
7.46
7.33
7.32
7.27
7.26
7.05
7.04
7.02
7.01
7.00
6.99
6.71
6.70
5.08
4.23
2.37
Me
F
S
N
N
NH2
CDCl3, 400 MHz
1H NMR
2.00
2.00
2.00
4.00
1.00
2.00
2.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

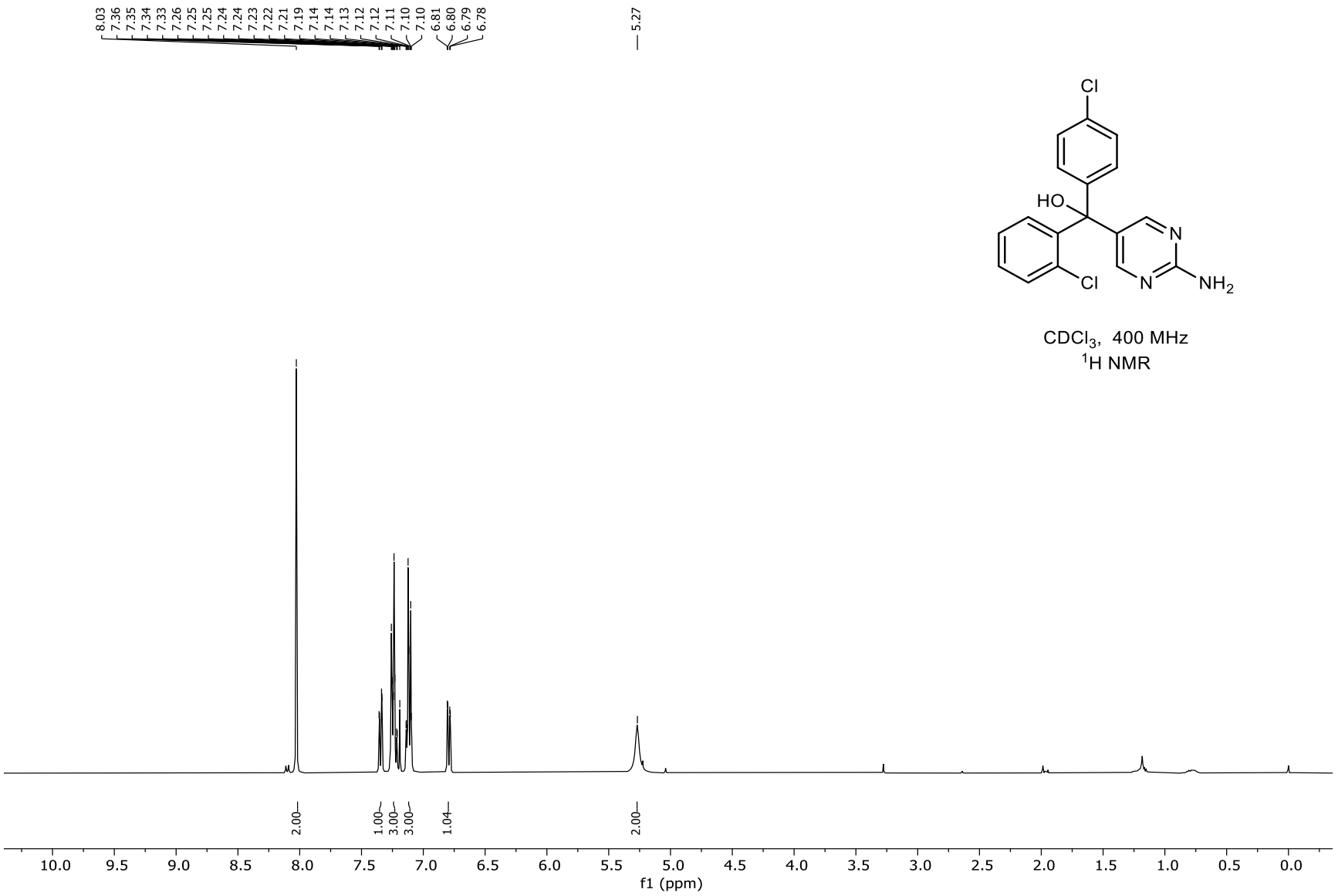

163.40
160.94
157.32
156.81
154.78
142.45
141.93
139.57
137.61
134.10
132.22
131.60
127.88
127.22
127.14
126.26
125.41
122.75
115.87
114.97
77.34
77.03
76.71
34.12
19.33
Me
F
S
N
N
NH2
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

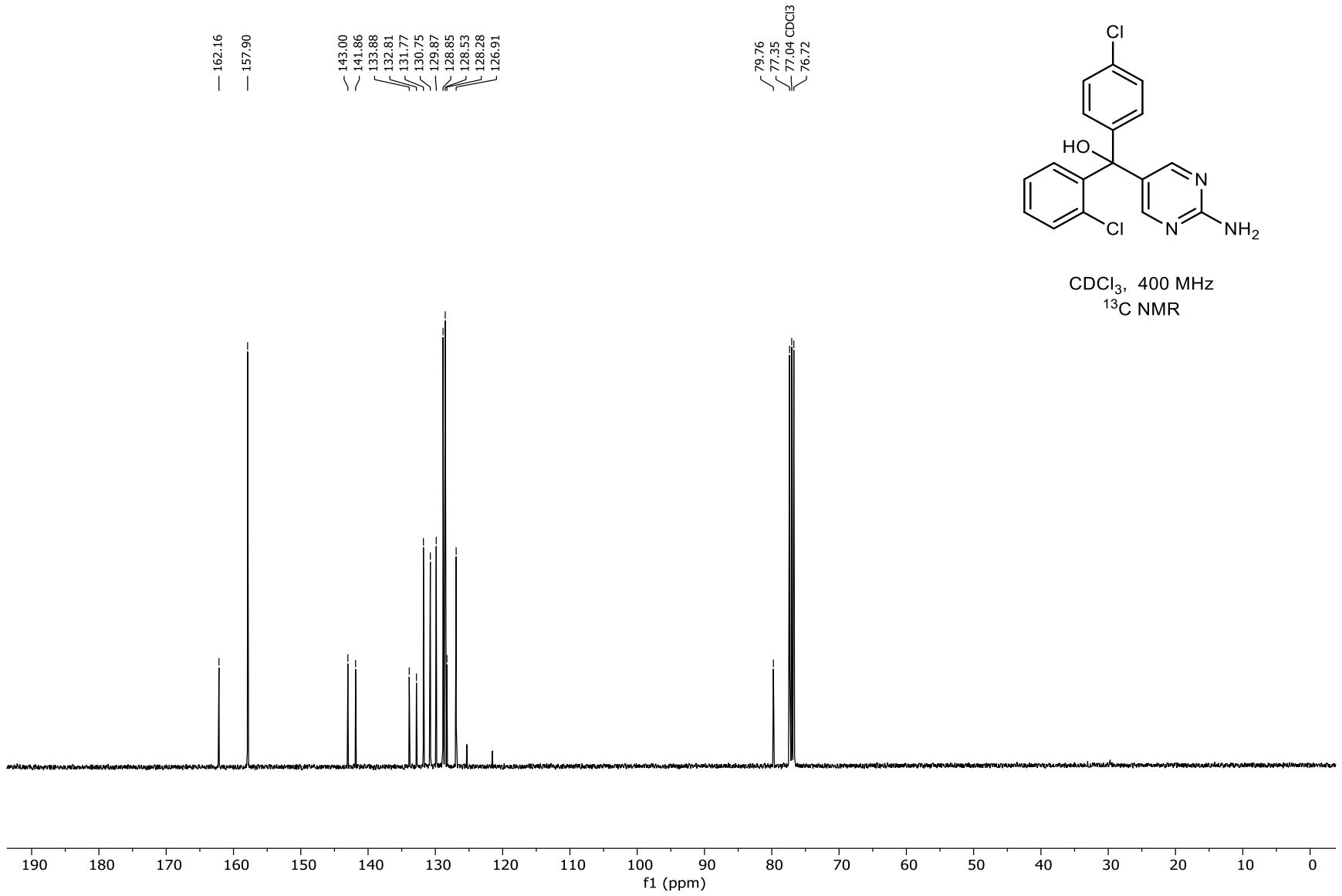


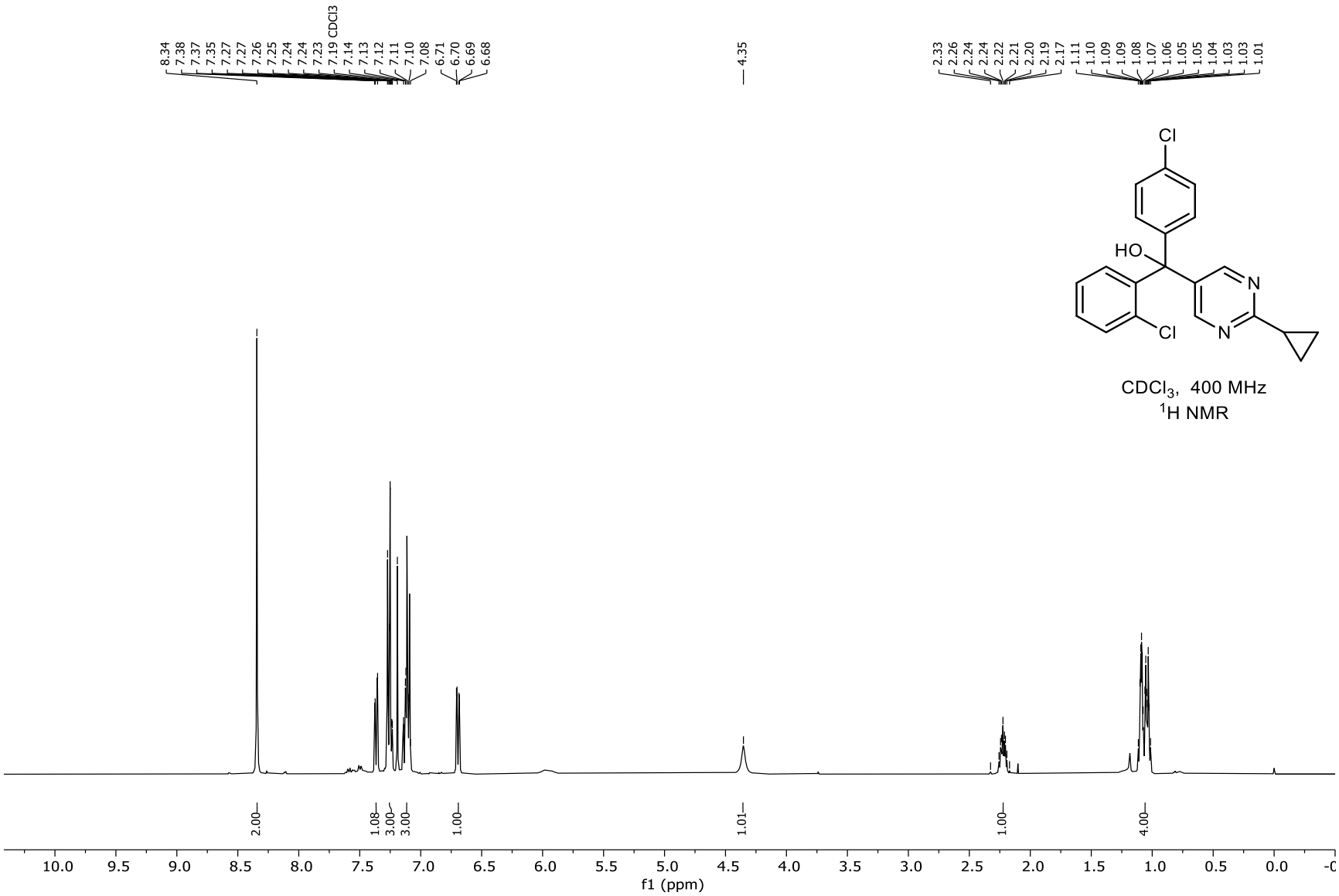
$CDCl_3$, 400 MHz
^{19}F NMR

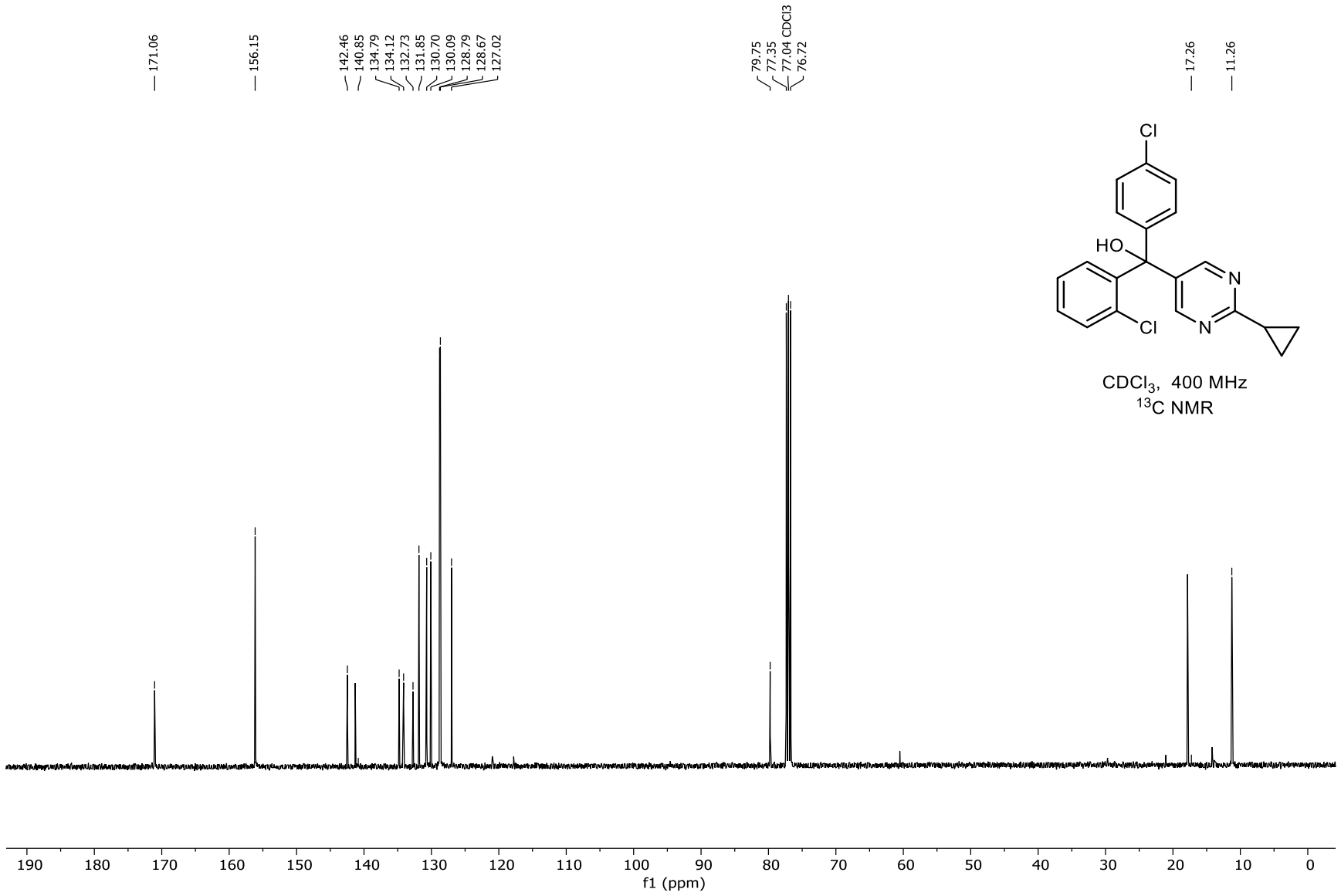
8.62
7.65
7.63
7.48
7.46
7.26 CDCl3
4.46
4.29
4.28
4.26
3.90
3.82
1.98
1.96
1.94
1.92
1.91
1.89
1.87
1.79
1.78
1.76
1.74
1.72
1.71
1.69
1.41
0.95
0.93
0.91
2.00
1.00
2.00
2.02
1.03
3.06
3.05
1.02
1.02
9.06
3.01
Me
O
OMe
OMe
O
N
N
CDCl3, 400 MHz
1H NMR
f1 (ppm)


176.89
167.06
156.74
155.49
131.90
131.55
130.61
128.39
122.11
110.81
79.59
77.16 CDCl3
65.99
55.51
52.29
39.34
30.85
29.77
10.08
Me
OMe
O
N
N
O
OMe
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

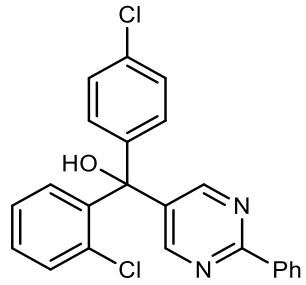

8.03
7.36
7.35
7.34
7.33
7.26
7.25
7.25
7.24
7.24
7.23
7.22
7.21
7.19
7.14
7.14
7.13
7.12
7.12
7.11
7.10
7.10
6.81
6.80
6.79
6.78
5.27
Cl
HO
N
Cl
N
NH2
CDCl3, 400 MHz
1H NMR
2.00
1.00
3.00
3.00
1.04
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


162.16
157.90
143.00
141.86
133.88
132.81
131.77
130.75
129.87
128.85
128.53
128.28
126.91
79.76
77.35
77.04 CDCl3
76.72
Cl
HO
N
Cl
N
NH2
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

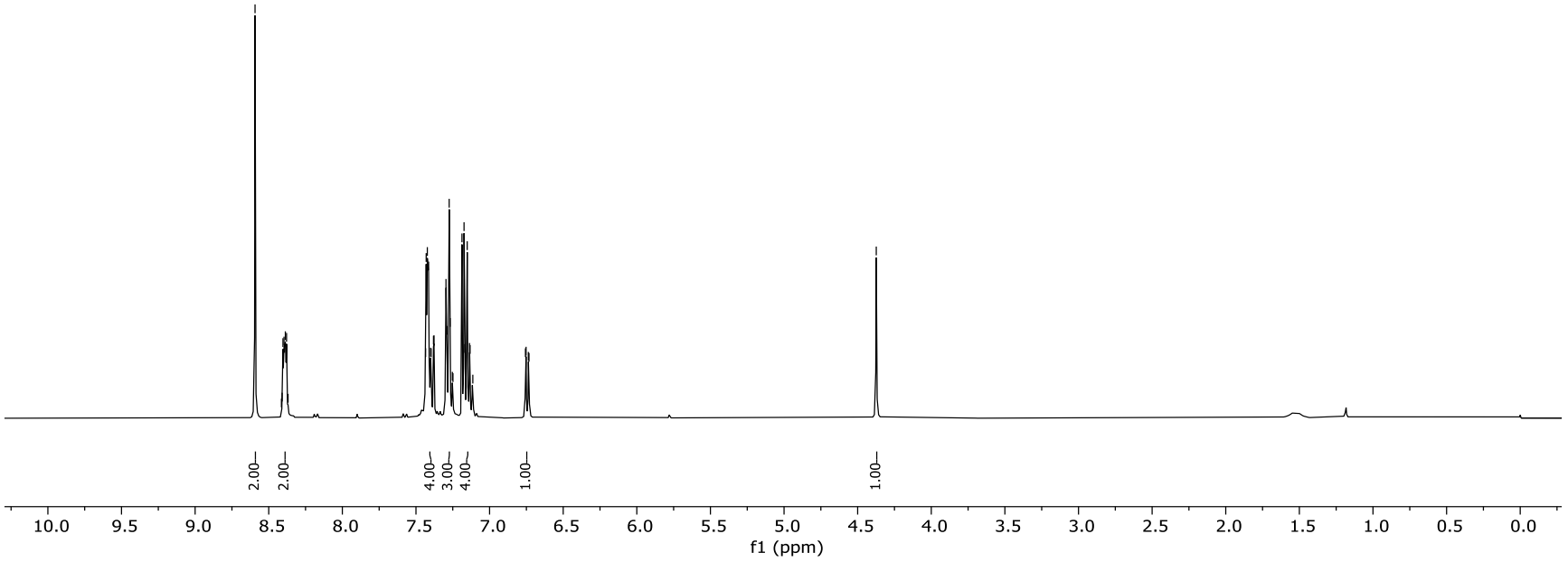

8.34
7.38
7.37
7.35
7.27
7.27
7.26
7.25
7.24
7.24
7.23
7.19 CDCl3
7.14
7.13
7.12
7.11
7.10
7.08
6.71
6.70
6.69
6.68
4.35
2.33
2.26
2.24
2.24
2.22
2.21
2.20
2.19
2.17
1.11
1.10
1.09
1.09
1.08
1.07
1.06
1.05
1.05
1.04
1.03
1.03
1.01
Cl
HO
N
N
Cl
CDCl3, 400 MHz
1H NMR
2.00
1.08
3.00
3.00
1.00
1.01
1.00
4.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

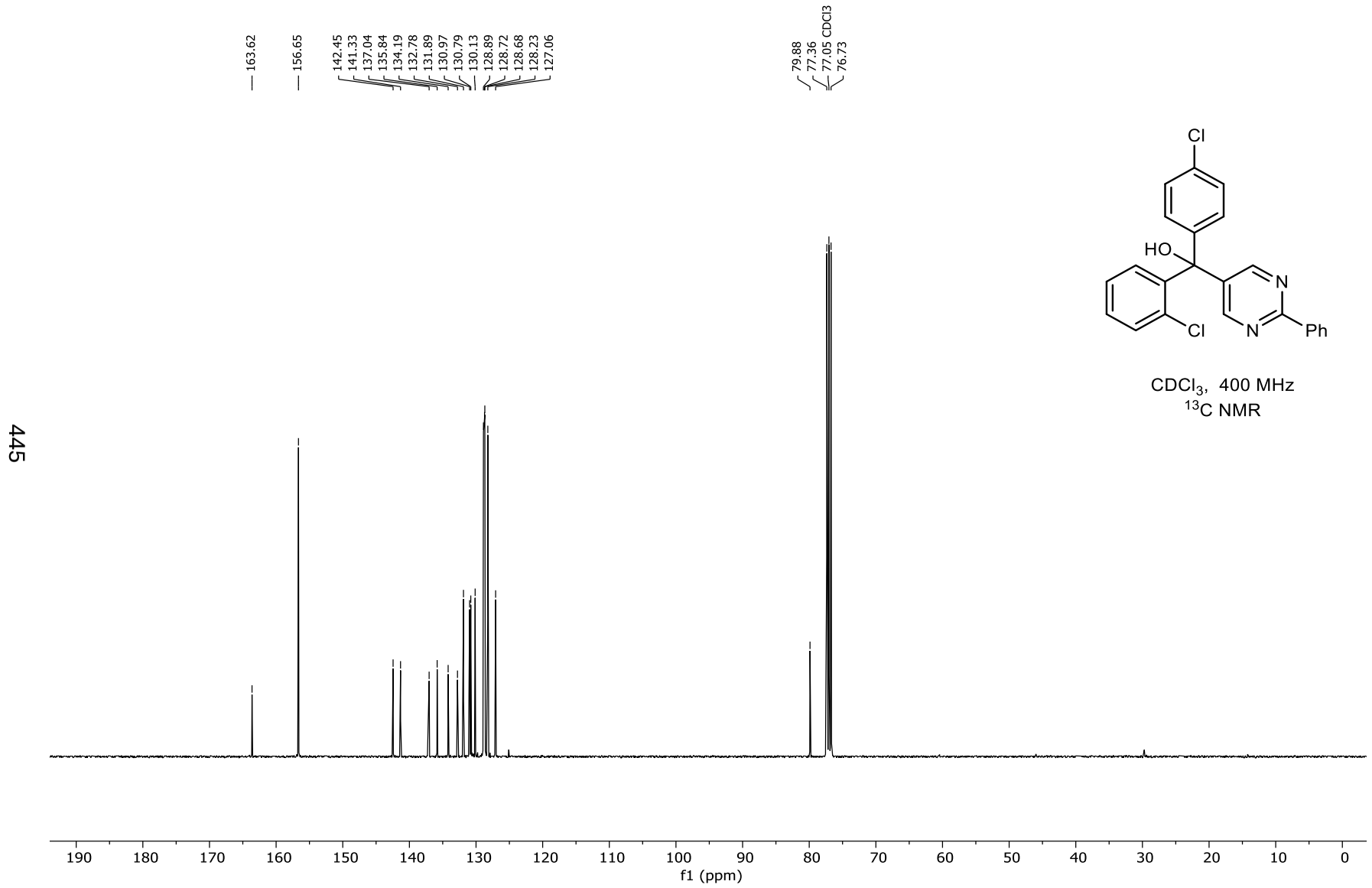

171.06
156.15
142.46
140.85
134.79
134.12
132.73
131.85
130.70
130.09
128.79
128.67
127.02
79.75
77.35
77.04 CDCl3
76.72
17.26
11.26
Cl
HO
N
N
Cl
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

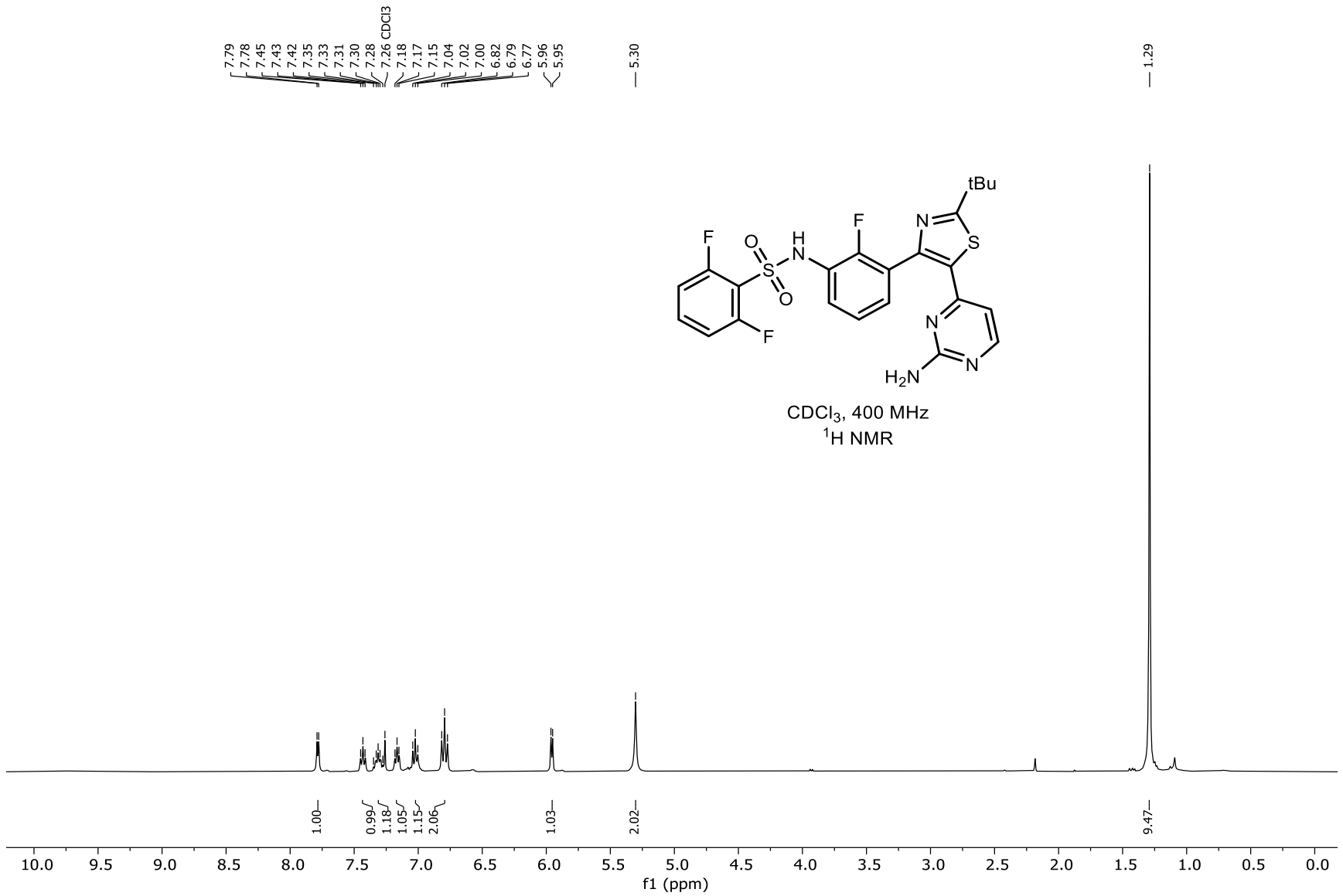


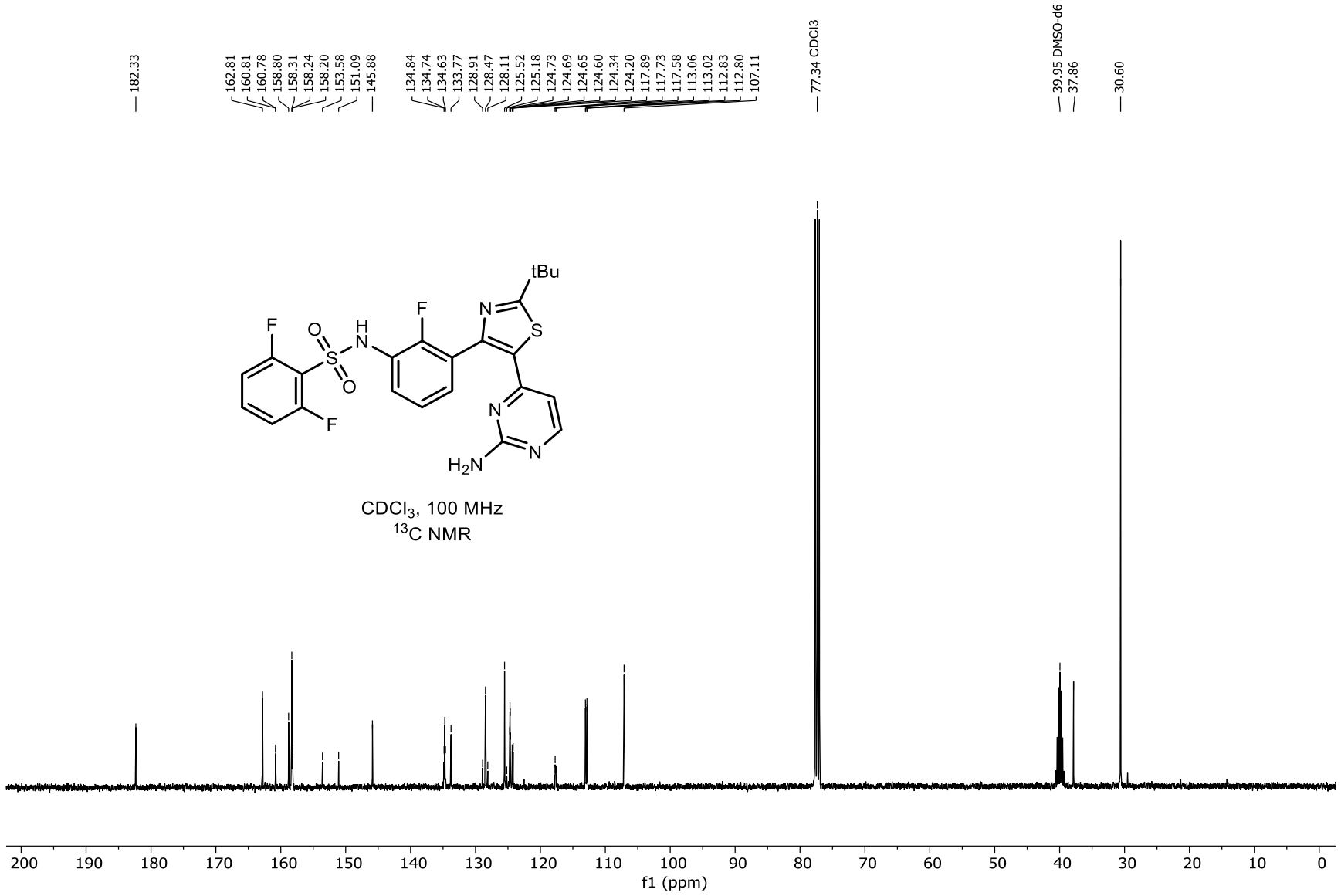


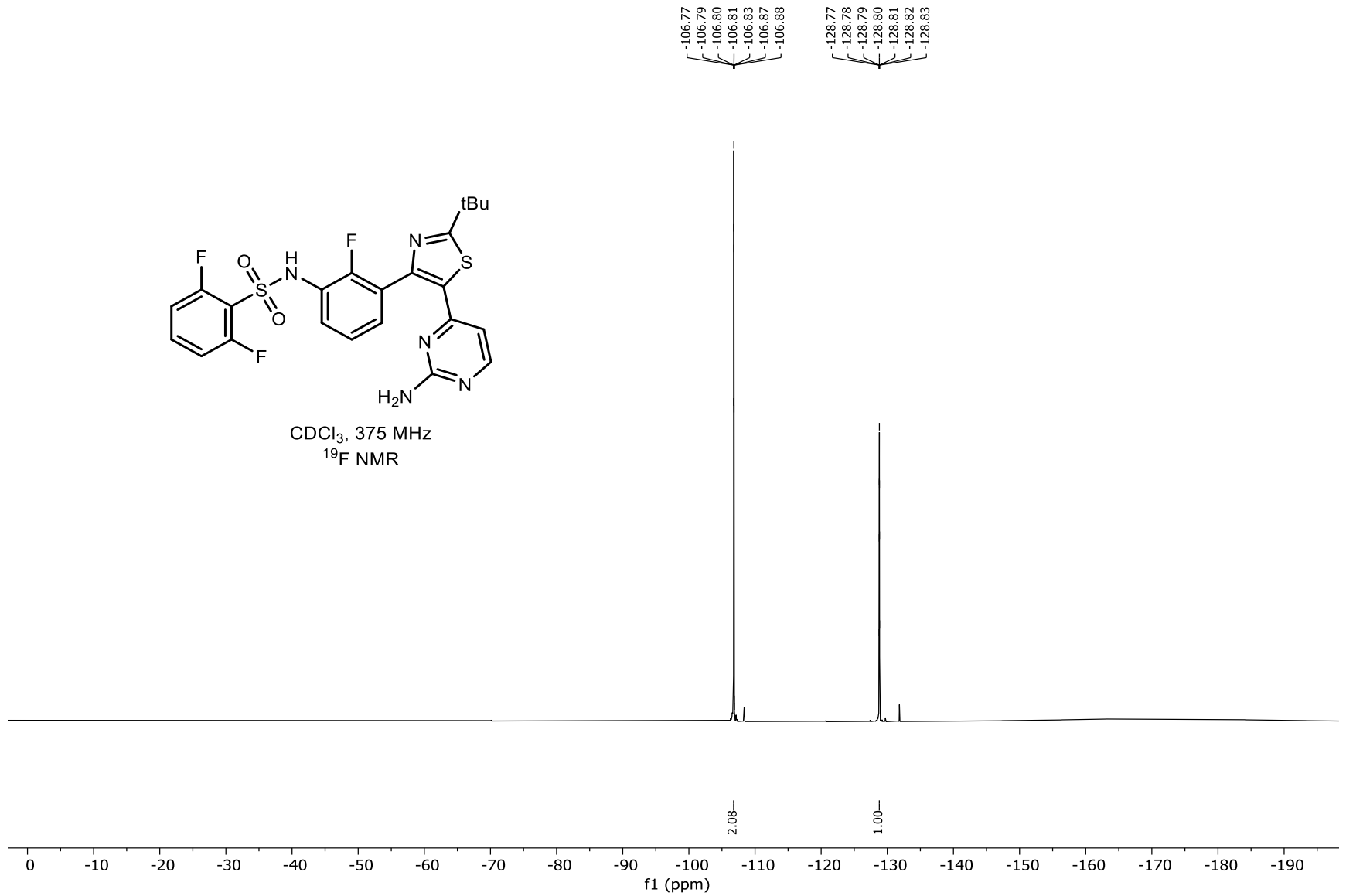
$CDCl_3$, 400 MHz
^1H NMR

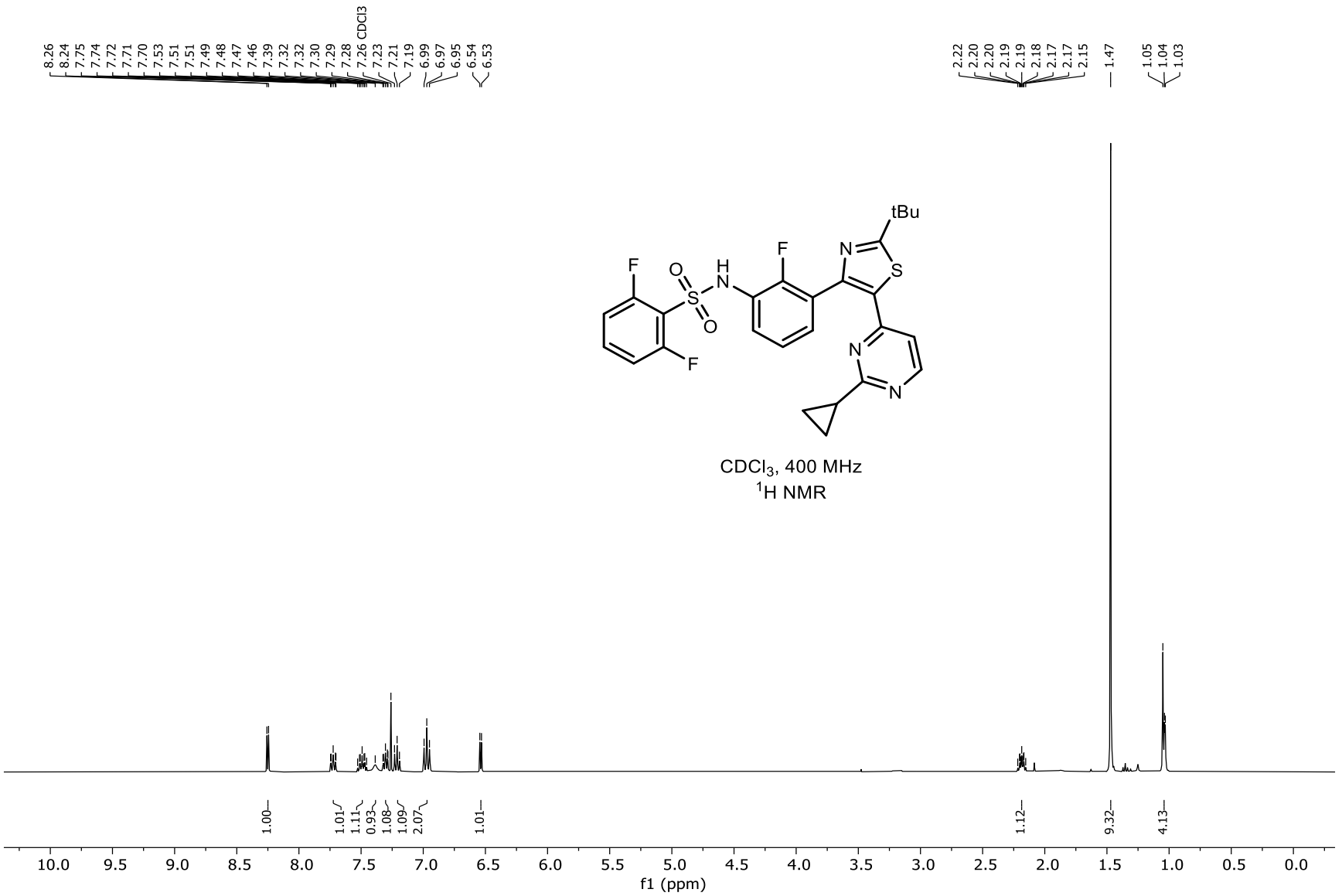


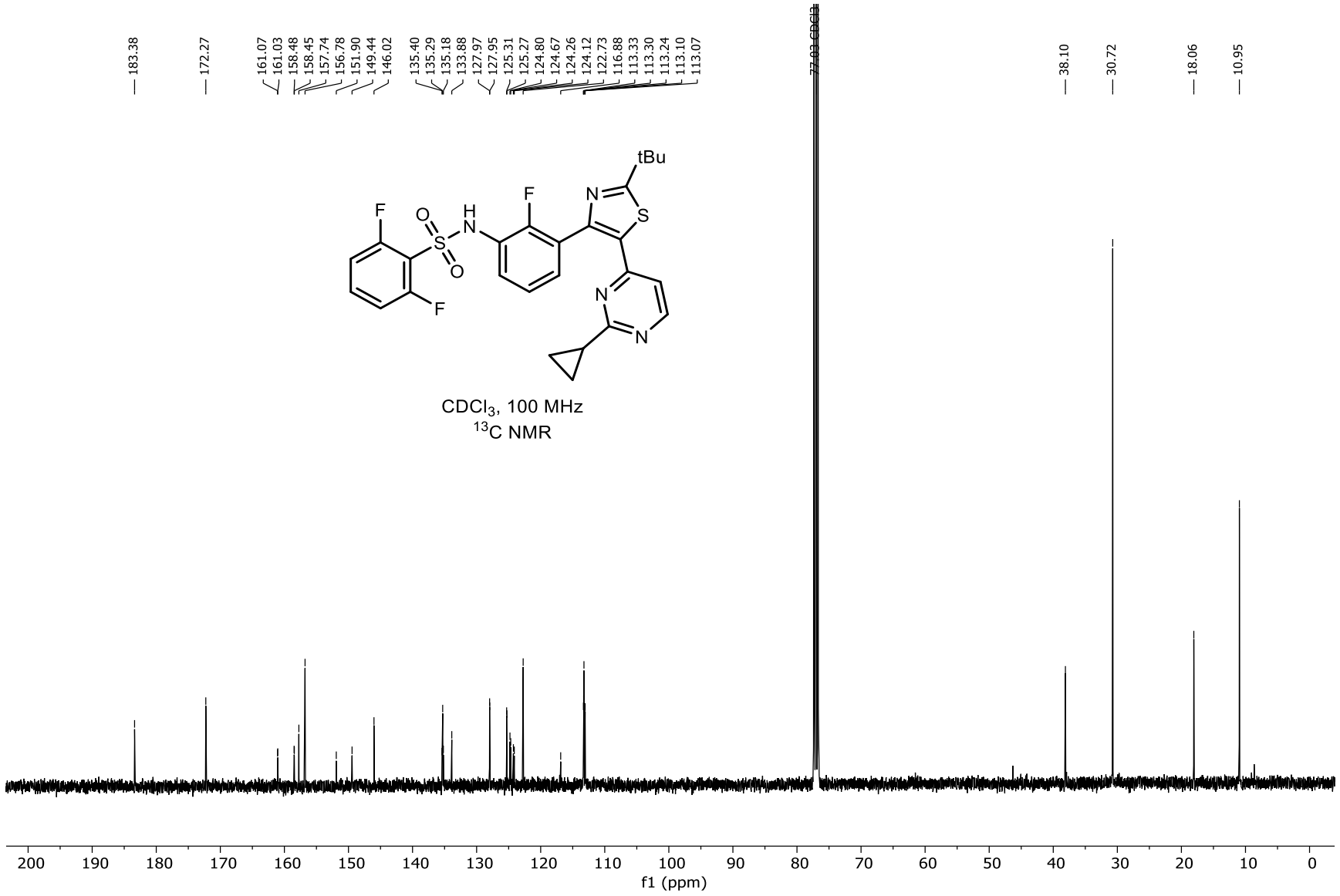

163.62
156.65
142.45
141.33
137.04
135.84
134.19
132.78
131.89
130.97
130.79
130.13
128.89
128.72
128.68
128.23
127.06
79.88
77.36
77.05 CDCl3
76.73
Cl
HO
N
Cl
N
Ph
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

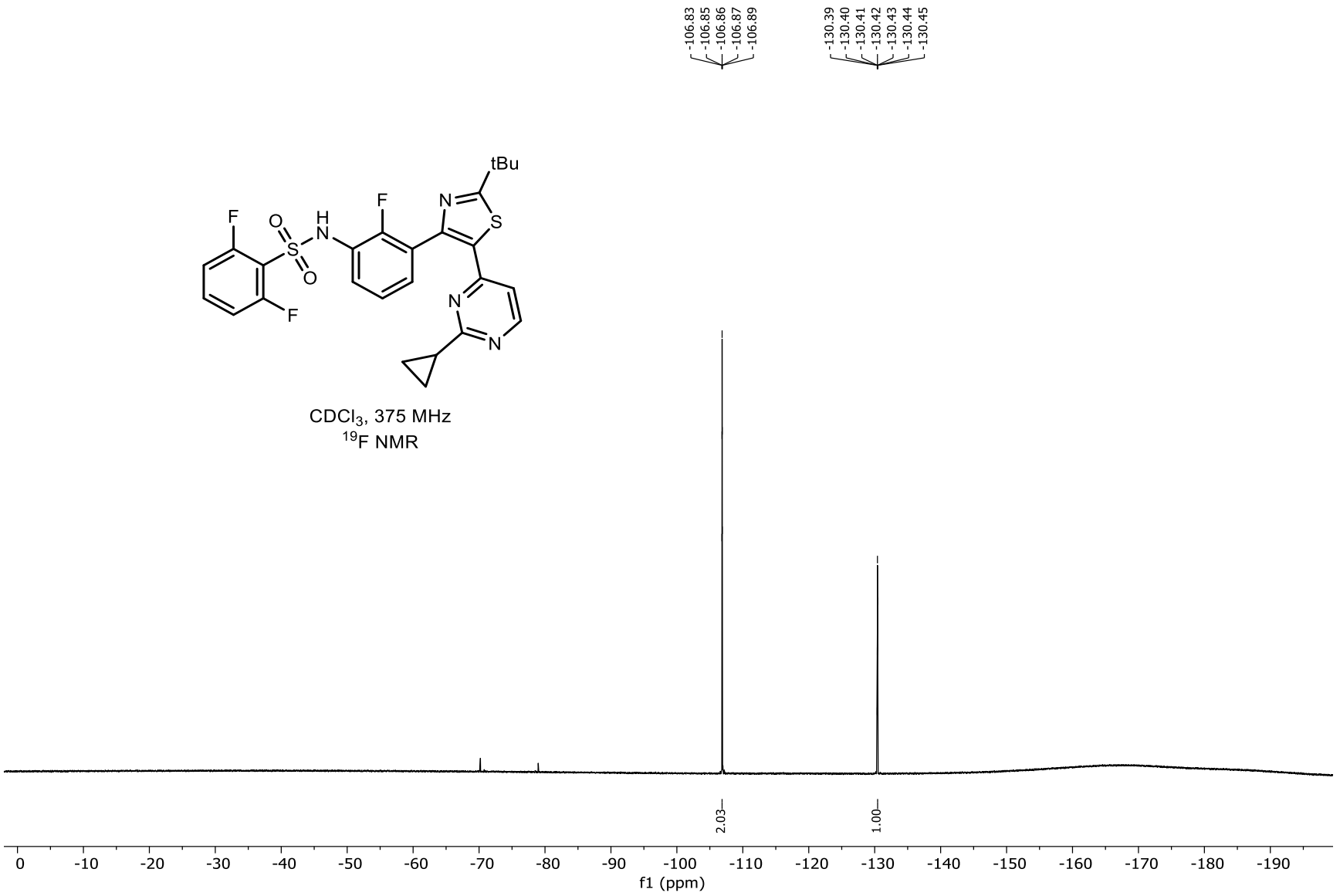

7.79
7.78
7.45
7.43
7.42
7.35
7.33
7.31
7.30
7.28
7.26 CDCl3
7.18
7.17
7.15
7.04
7.02
7.00
6.82
6.79
6.77
5.96
5.95
5.30
1.29
tBu
F
O
H
N
F
N
S
S
O
F
N
N
H2N
CDCl3, 400 MHz
1H NMR
1.00
0.99
1.18
1.05
1.15
2.06
1.03
2.02
9.47
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

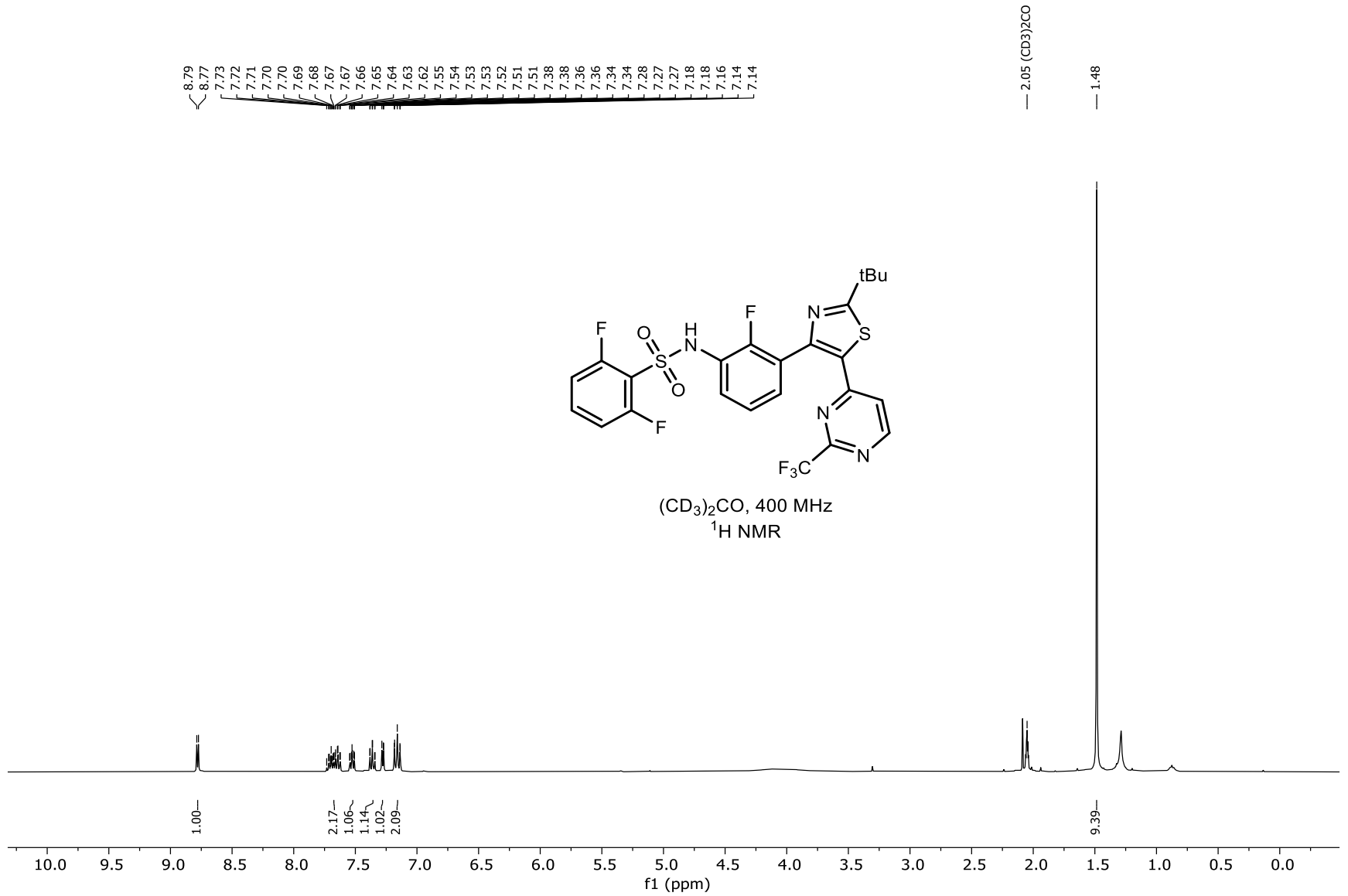

182.33
162.81
160.81
160.78
158.80
158.31
158.24
158.20
153.58
151.09
145.88
134.84
134.74
134.63
133.77
128.91
128.47
128.11
125.52
125.18
124.73
124.69
124.65
124.60
124.34
124.20
117.89
117.73
117.58
113.06
113.02
112.83
112.80
107.11
77.34 CDCl3
39.95 DMSO-d6
37.86
30.60
tBu
F
O
H
N
F
N
S
S
O
O
F
N
N
H2N
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

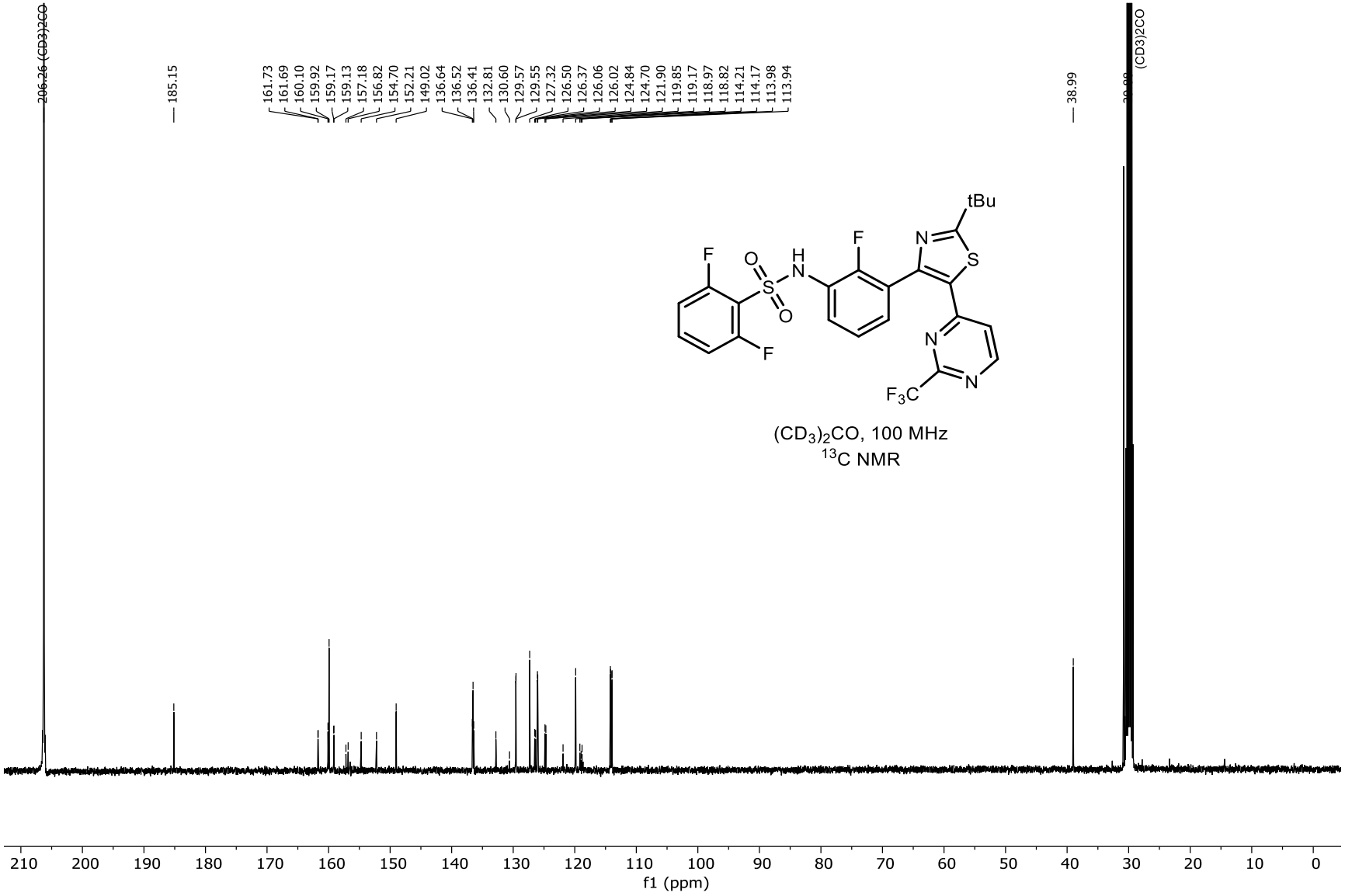

-106.77
-106.79
-106.80
-106.81
-106.83
-106.87
-106.88
-128.77
-128.78
-128.79
-128.80
-128.81
-128.82
-128.83
tBu
F
O
S
O
H
N
F
N
S
N
N
F
H_2N
$CDCl_3$, 375 MHz
^{19}F NMR
2.08
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

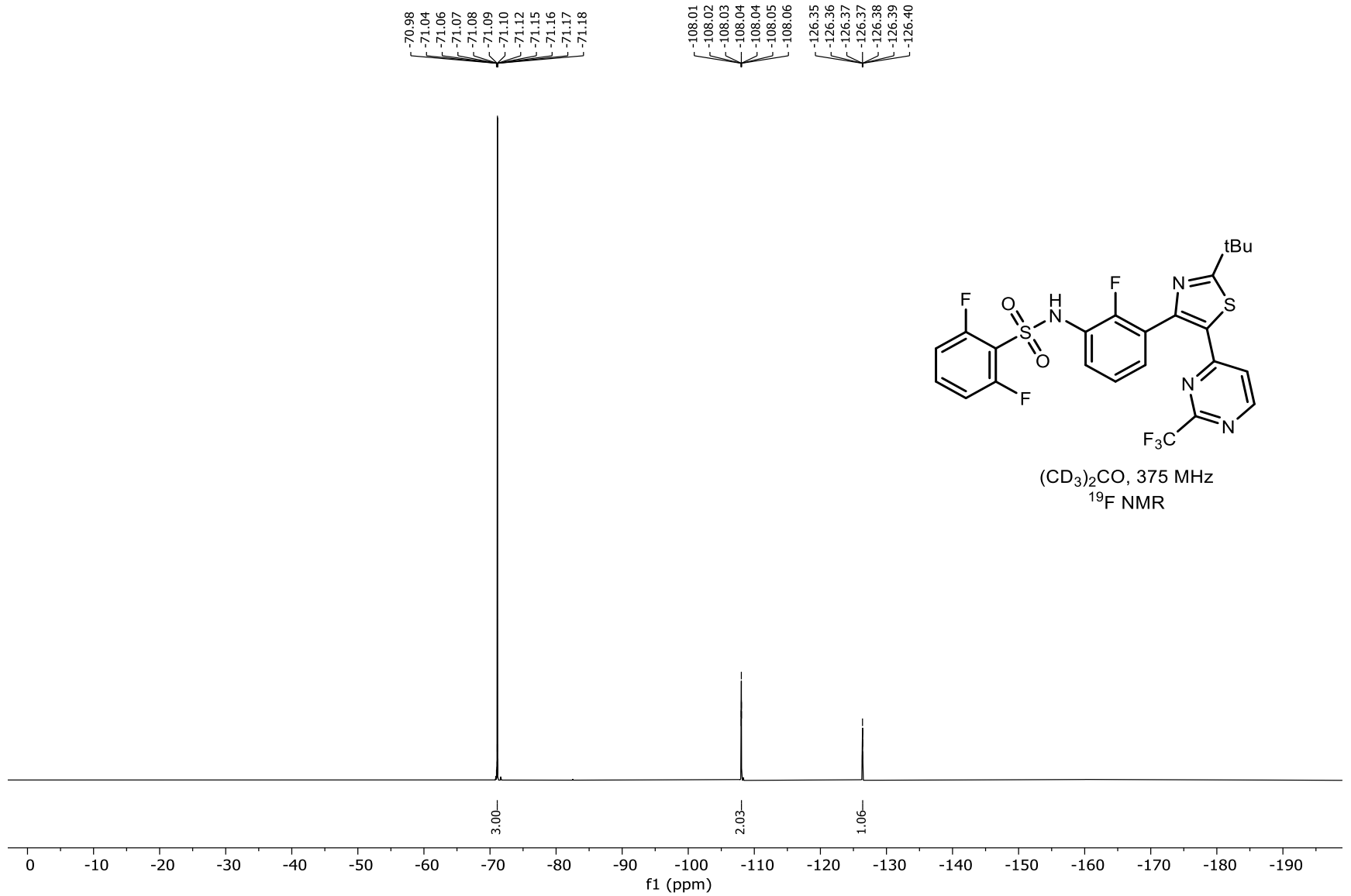

8.26
8.24
7.75
7.74
7.72
7.71
7.70
7.53
7.51
7.51
7.49
7.48
7.47
7.46
7.39
7.32
7.32
7.30
7.29
7.28
7.26 CDCl3
7.23
7.21
7.19
6.99
6.97
6.95
6.54
6.53
2.22
2.20
2.20
2.19
2.19
2.18
2.17
2.17
2.15
1.47
1.05
1.04
1.03
tBu
F
N
S
F
O
H
N
S
O
F
N
N
CDCl3, 400 MHz
1H NMR
1.00
1.01
1.11
0.93
1.08
1.09
2.07
1.01
1.12
9.32
4.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


183.38
172.27
161.07
161.03
158.48
158.45
157.74
156.78
151.90
149.44
146.02
135.40
135.29
135.18
133.88
127.97
127.95
125.31
125.27
124.80
124.67
124.26
124.12
122.73
116.88
113.33
113.30
113.24
113.10
113.07
77.03 CDCl3
38.10
30.72
18.06
10.95
tBu
F
O
S
O
H
N
F
N
S
N
N
F
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

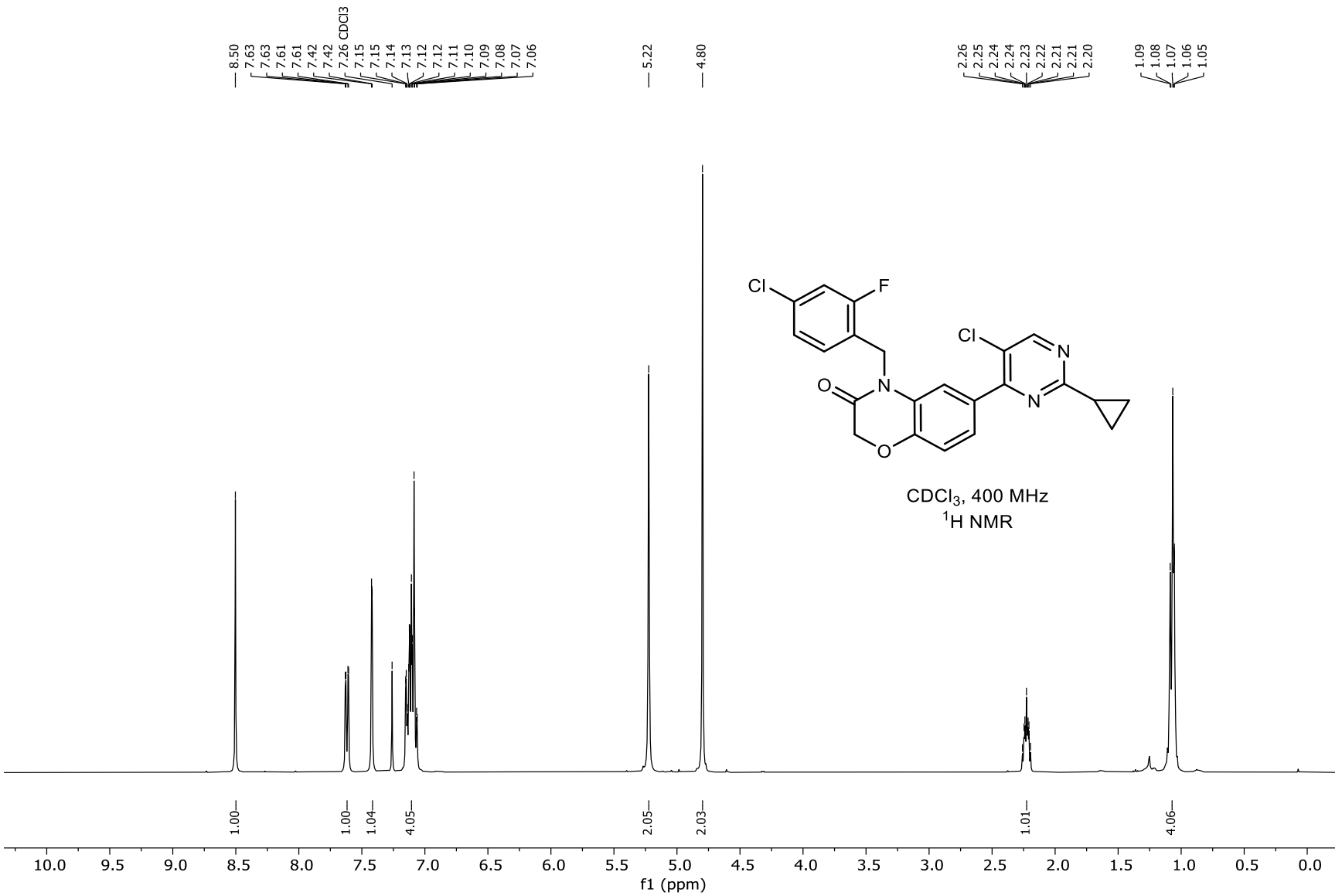

-106.83
-106.85
-106.86
-106.87
-106.89
-130.39
-130.40
-130.41
-130.42
-130.43
-130.44
-130.45
tBu
F
O
H
N
S
O
F
F
N
S
N
N
CDCl3, 375 MHz
19F NMR
2.03
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

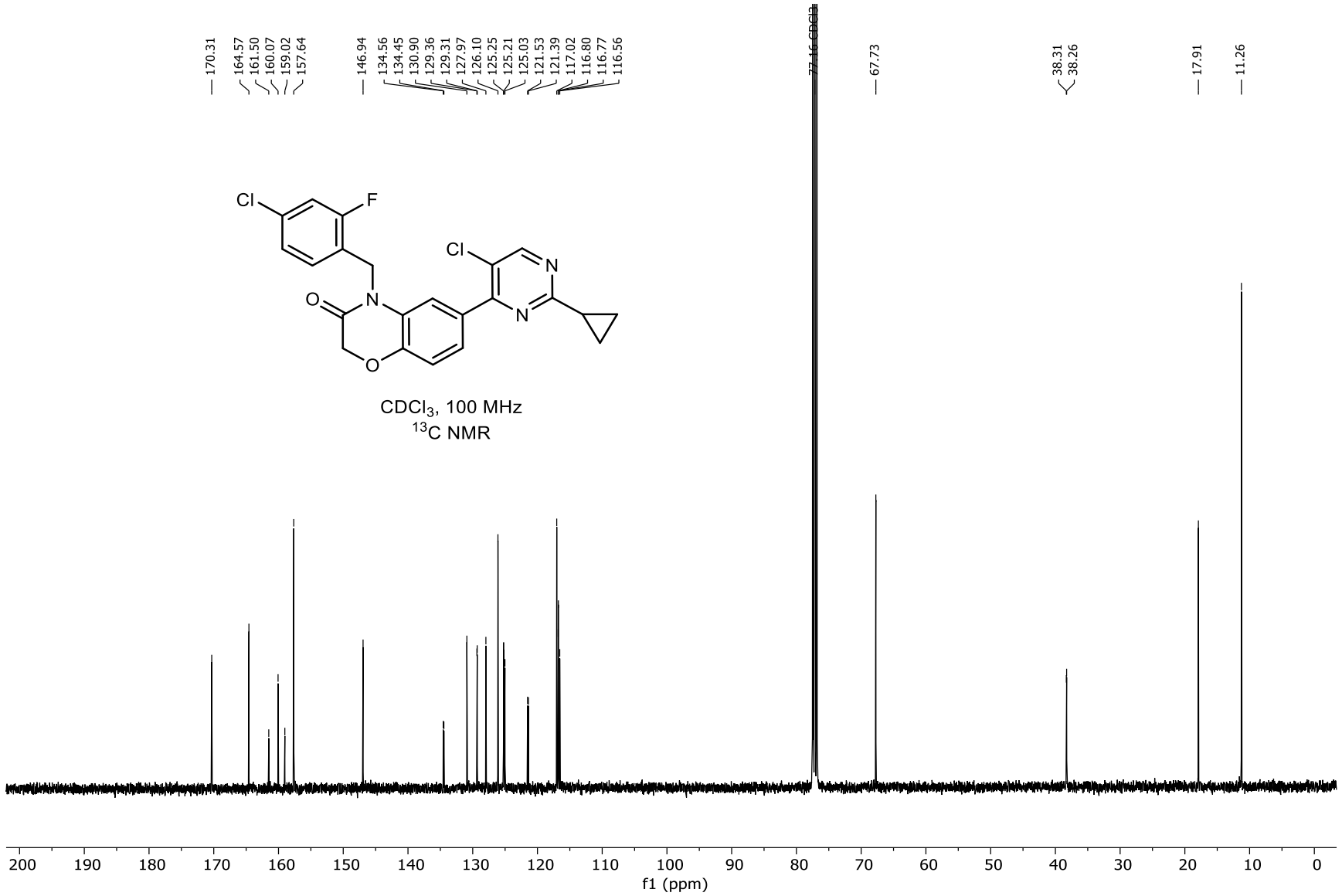

8.79
8.77
7.73
7.72
7.71
7.70
7.70
7.69
7.68
7.67
7.67
7.66
7.65
7.64
7.63
7.62
7.55
7.54
7.53
7.53
7.52
7.51
7.51
7.38
7.38
7.36
7.36
7.34
7.34
7.28
7.27
7.27
7.18
7.18
7.16
7.14
7.14
2.05 (CD3)2CO
1.48
tBu
F
O
H
N
F
N
S
S
O
O
N
F
N
F3C
(CD3)2CO, 400 MHz
1H NMR
1.00
2.17
1.06
1.14
1.02
2.09
9.39
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


206.26 (CD3)2CO
185.15
161.73
161.69
160.10
159.92
159.17
159.13
157.18
156.82
154.70
152.21
149.02
136.64
136.52
136.41
132.81
130.60
129.57
129.55
127.32
126.50
126.37
126.06
126.02
124.84
124.70
121.90
119.85
119.17
118.97
118.82
114.21
114.17
113.98
113.94
38.99
(CD3)2CO
tBu
F
N
S
O
H
N
F
F
O
S
F
N
N
F3C
(CD3)2CO, 100 MHz
13C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

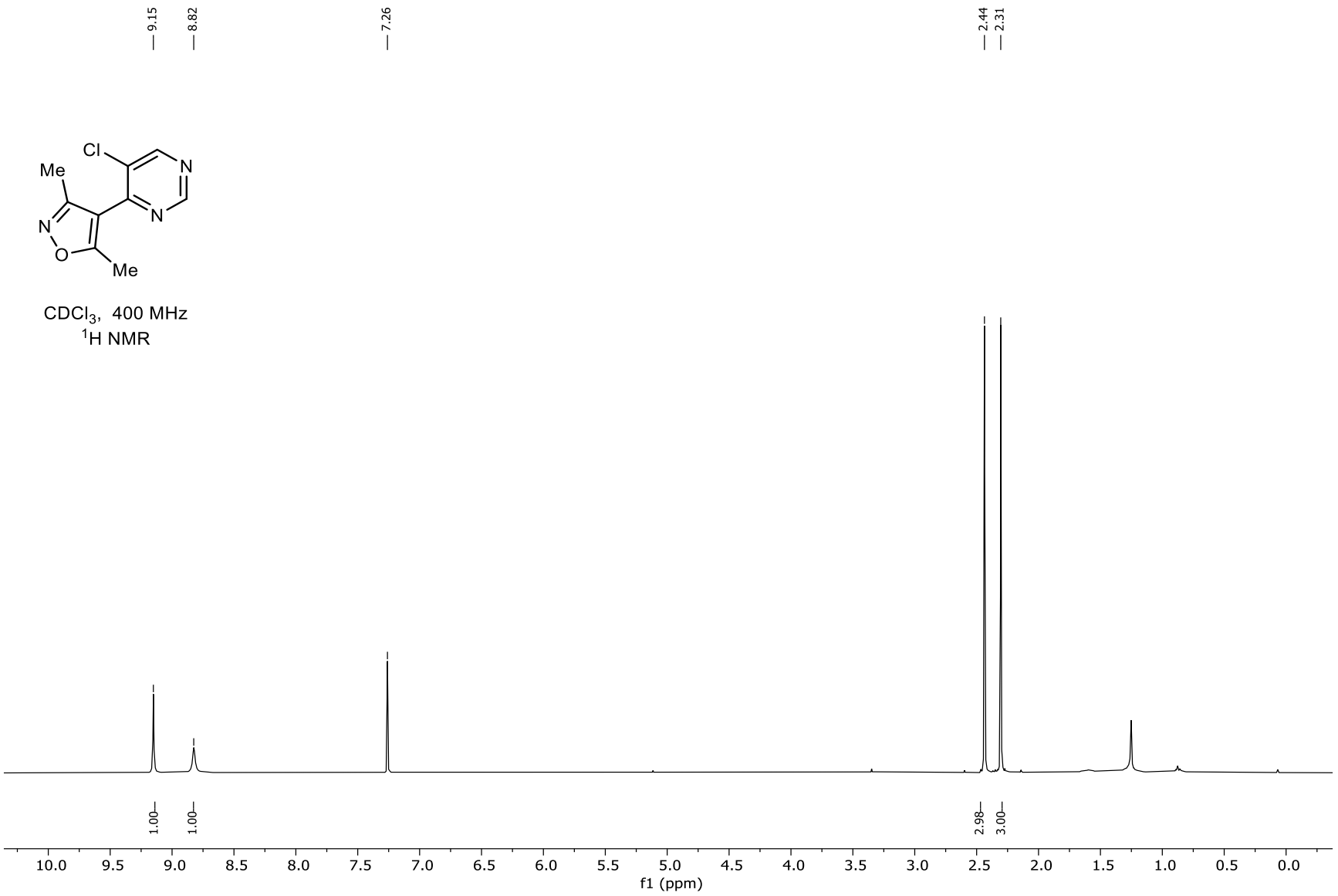


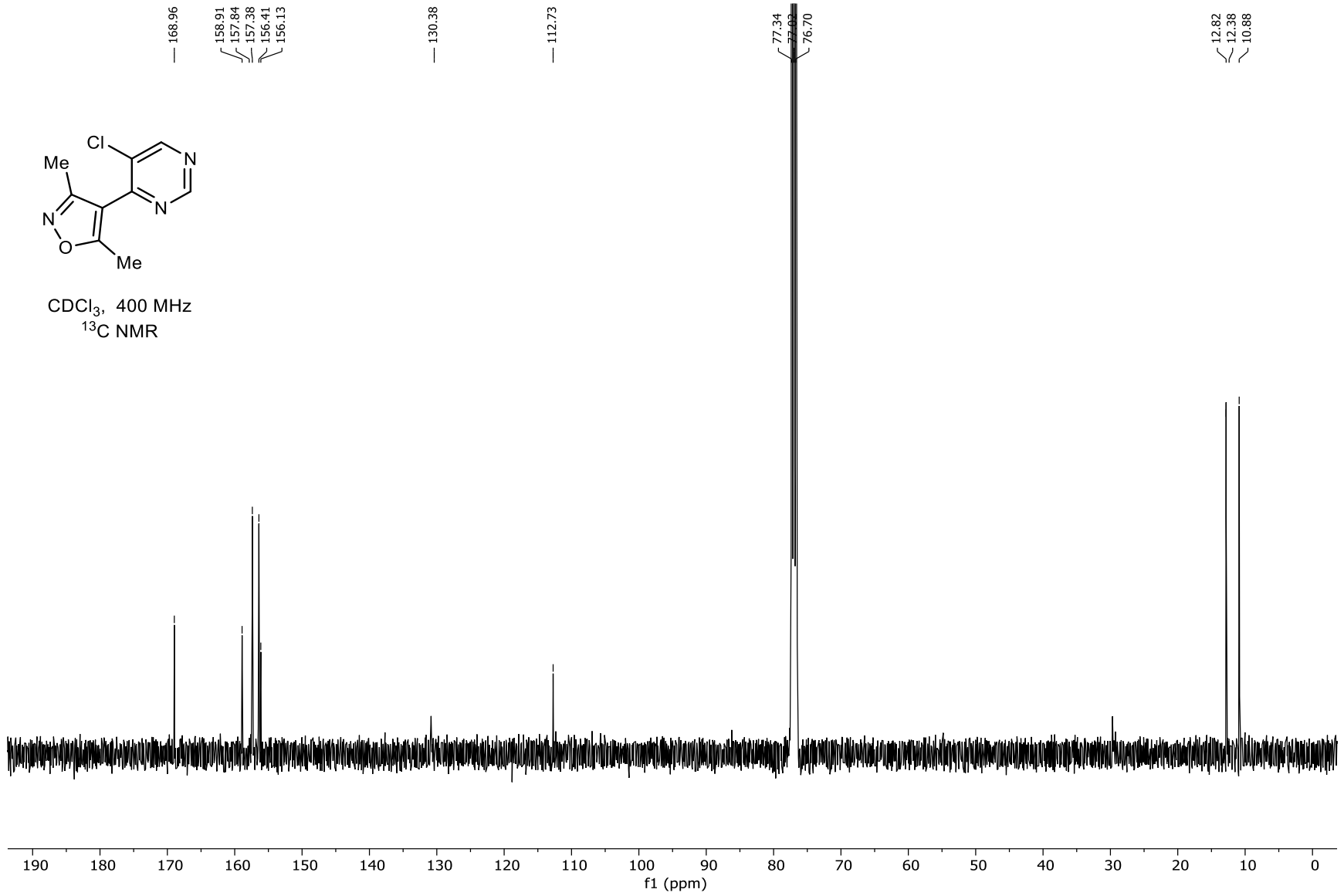
$(CD_3)_2CO$, 375 MHz
^{19}F NMR

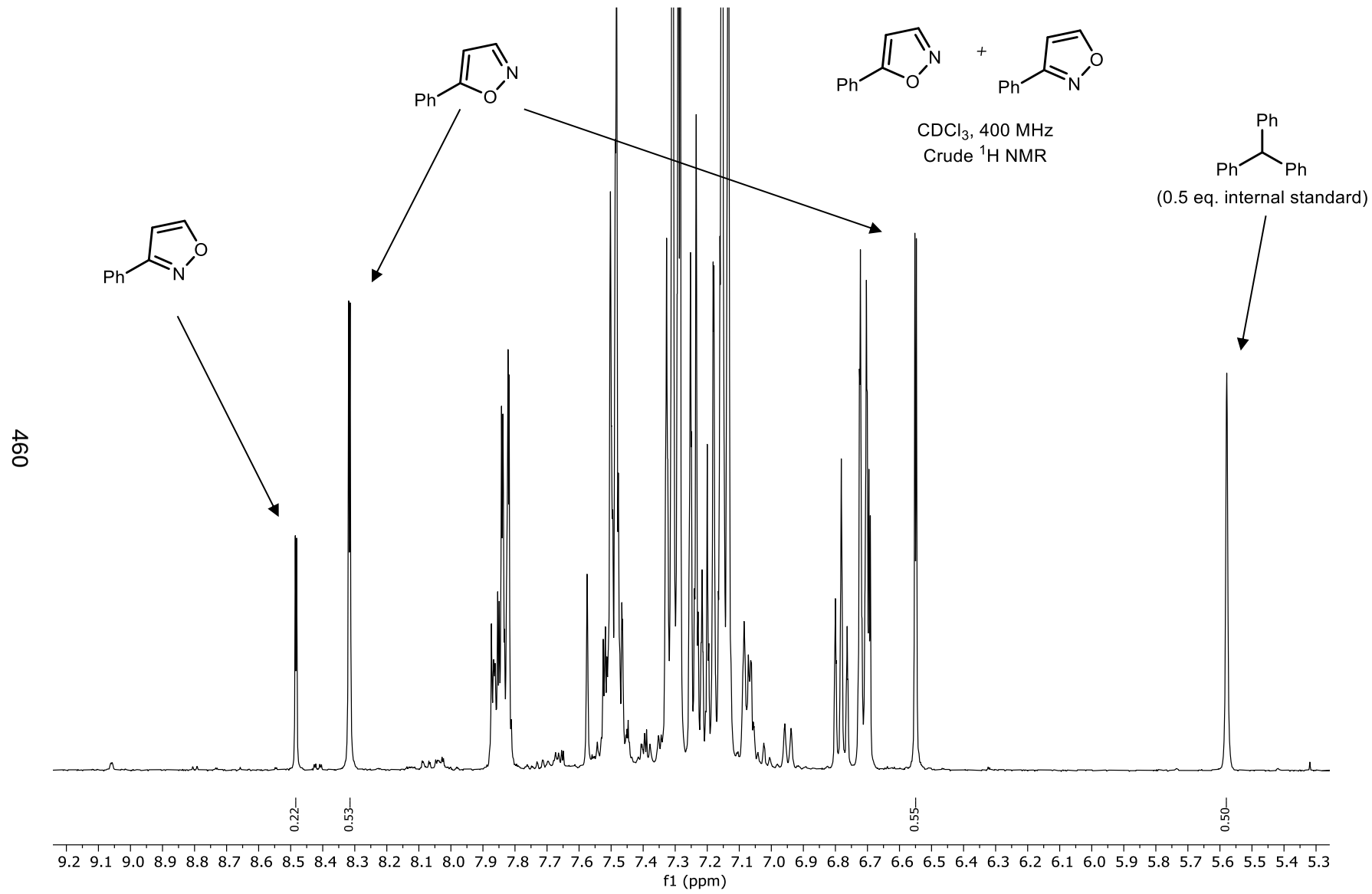

8.50
7.63
7.63
7.61
7.61
7.42
7.42
7.26 CDCl3
7.15
7.15
7.14
7.13
7.12
7.12
7.11
7.10
7.09
7.08
7.07
7.06
5.22
4.80
2.26
2.25
2.24
2.24
2.23
2.22
2.21
2.21
2.20
1.09
1.08
1.07
1.06
1.05
Cl
F
Cl
N
O
N
N
O
CDCl3, 400 MHz
1H NMR
1.00
1.00
1.04
4.05
2.05
2.03
1.01
4.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

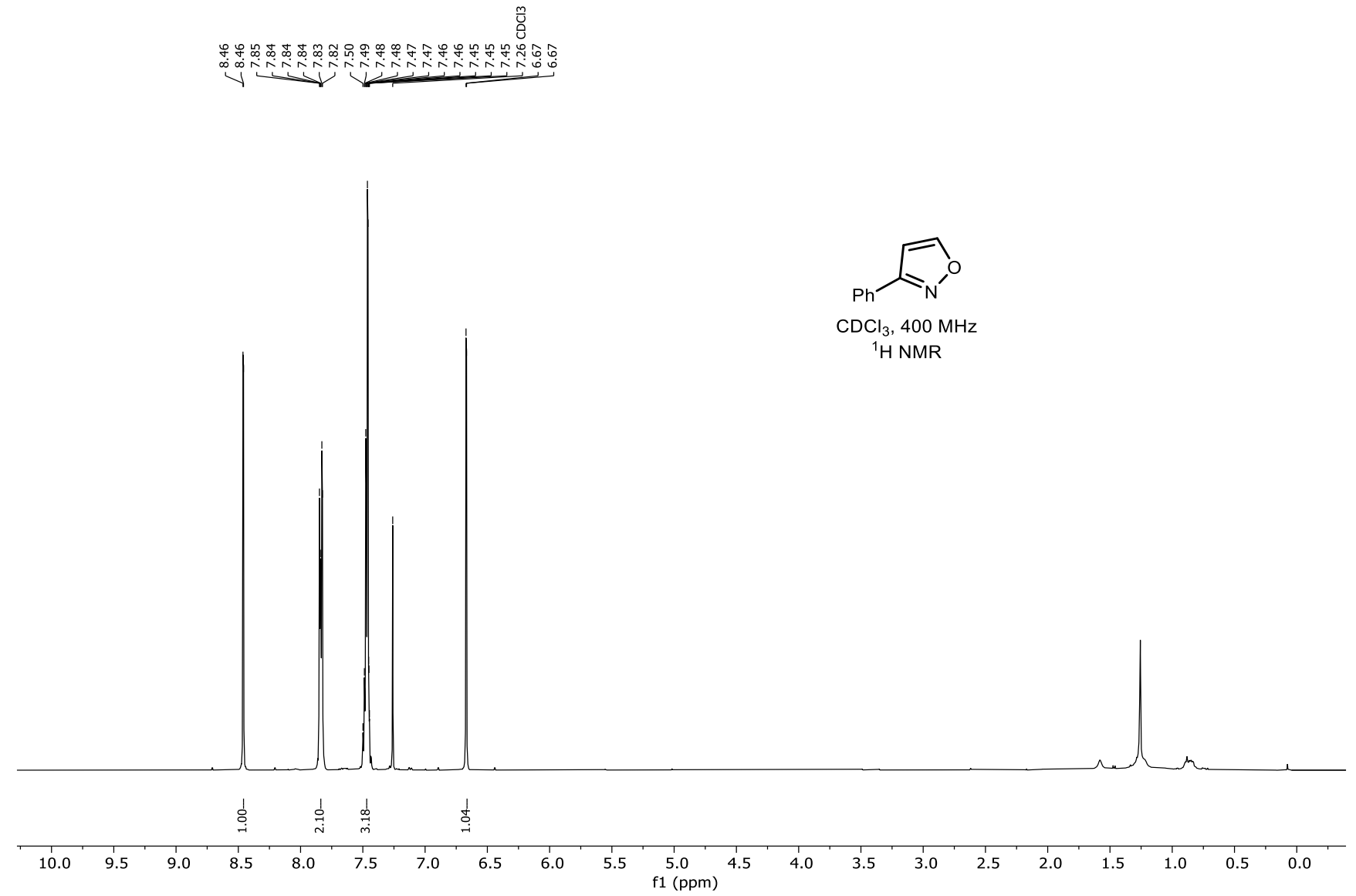

170.31
164.57
161.50
160.07
159.02
157.64
146.94
134.56
134.45
130.90
129.36
129.31
127.97
126.10
125.25
125.21
125.03
121.53
121.39
117.02
116.80
116.77
116.56
77.16 CDCl3
67.73
38.31
38.26
17.91
11.26
Cl
F
Cl
N
O
N
N
O
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

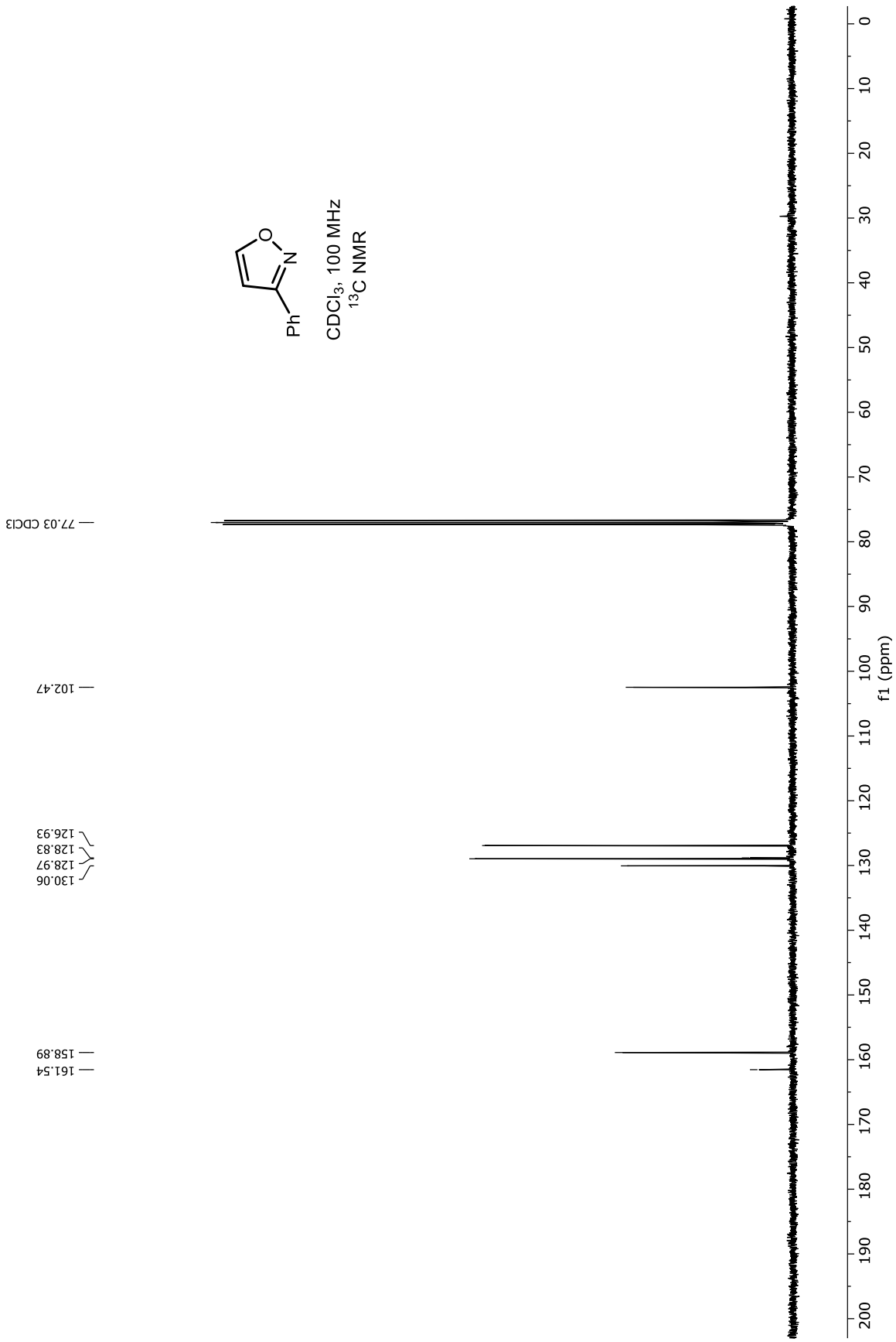

-115.46
-115.48
-115.49
-115.51
Cl
F
Cl
N
O
N
N
O
CDCl3, 375 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

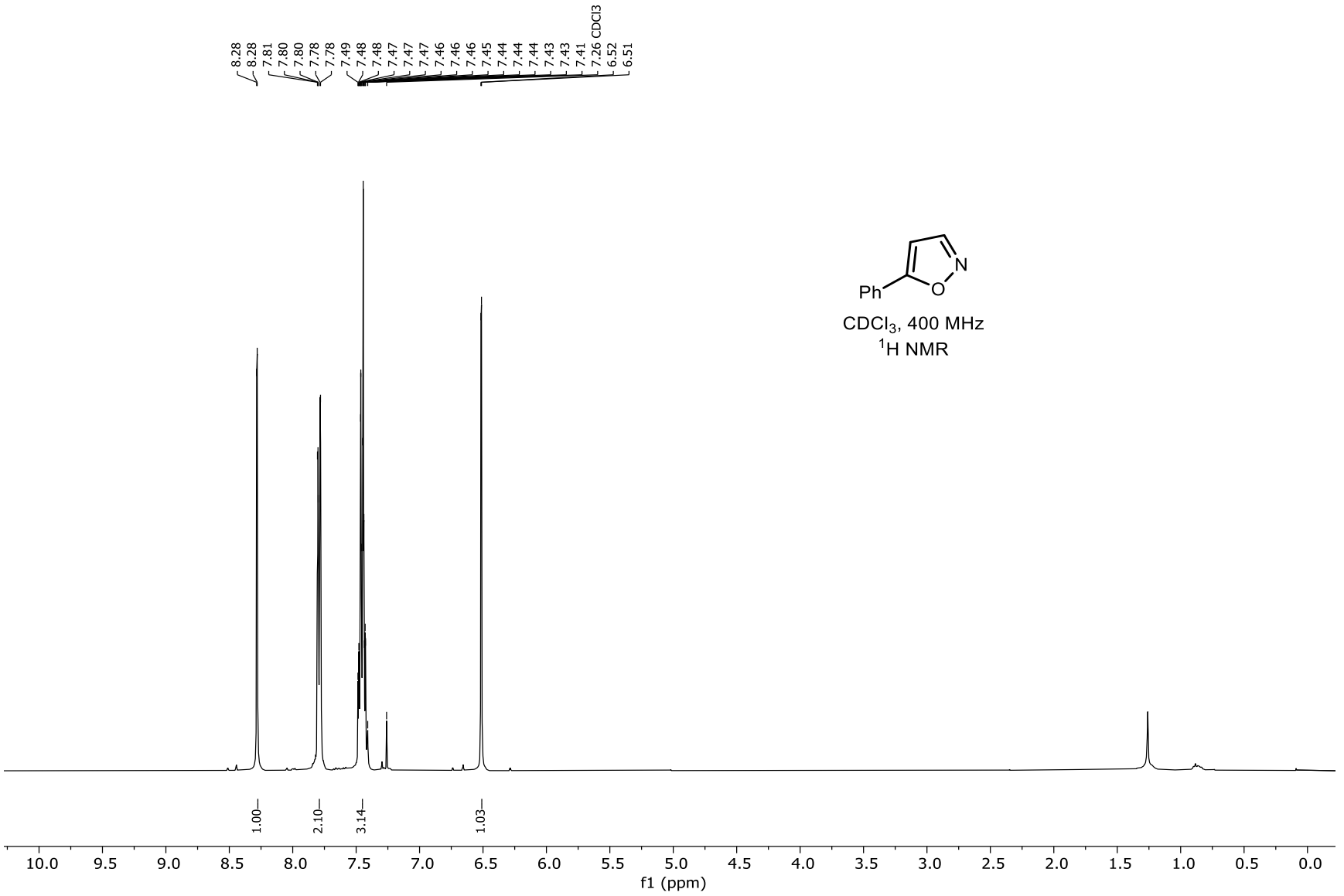

9.15
8.82
7.26
2.44
2.31
Cl
Me
N
N
N
O
Me
CDCl3, 400 MHz
1H NMR
1.00
1.00
2.98
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

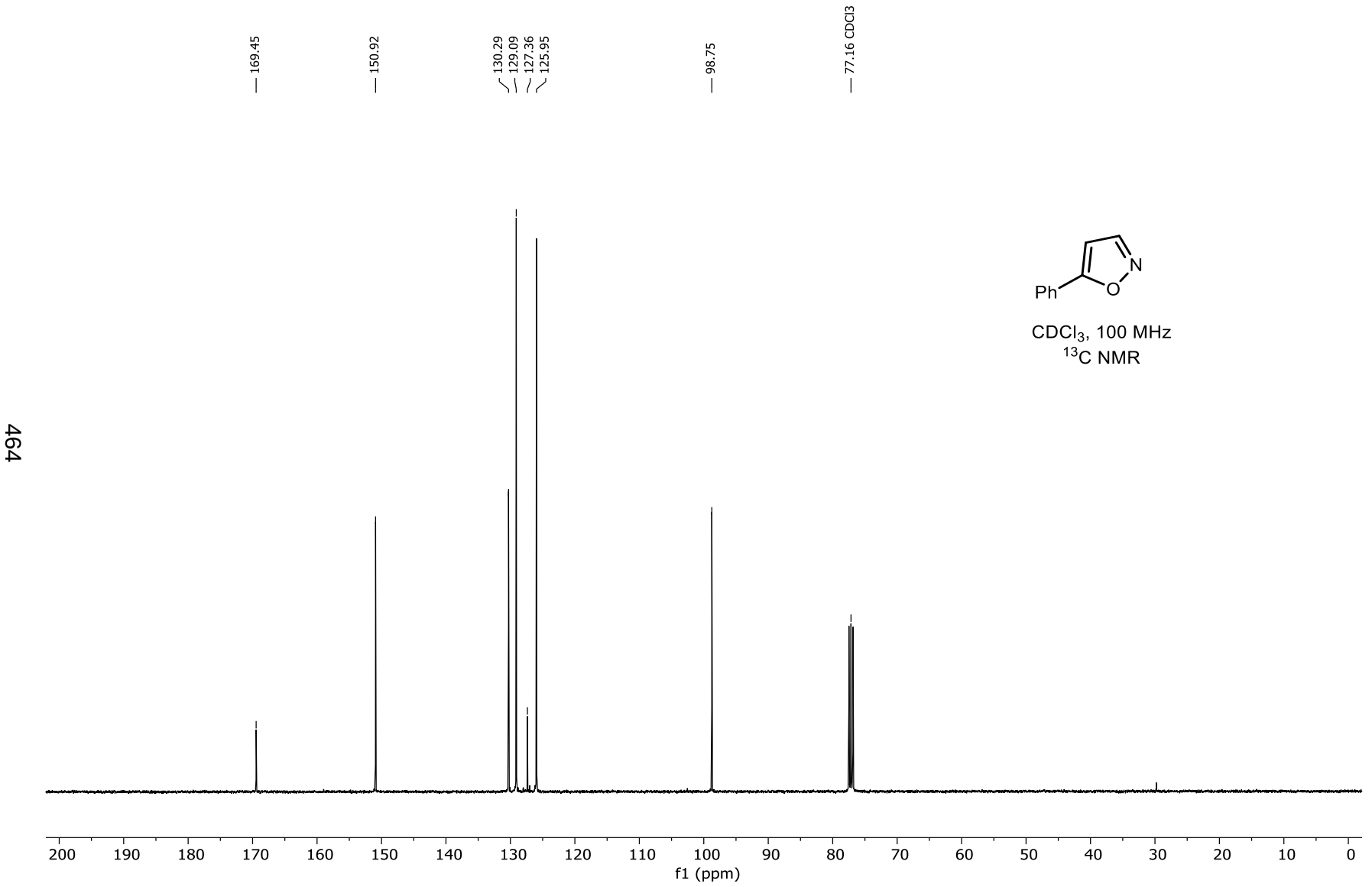

168.96
158.91
157.84
157.38
156.41
156.13
130.38
112.73
77.34
77.02
76.70
12.82
12.38
10.88
Cl
N
Me
N
N
O
Me
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

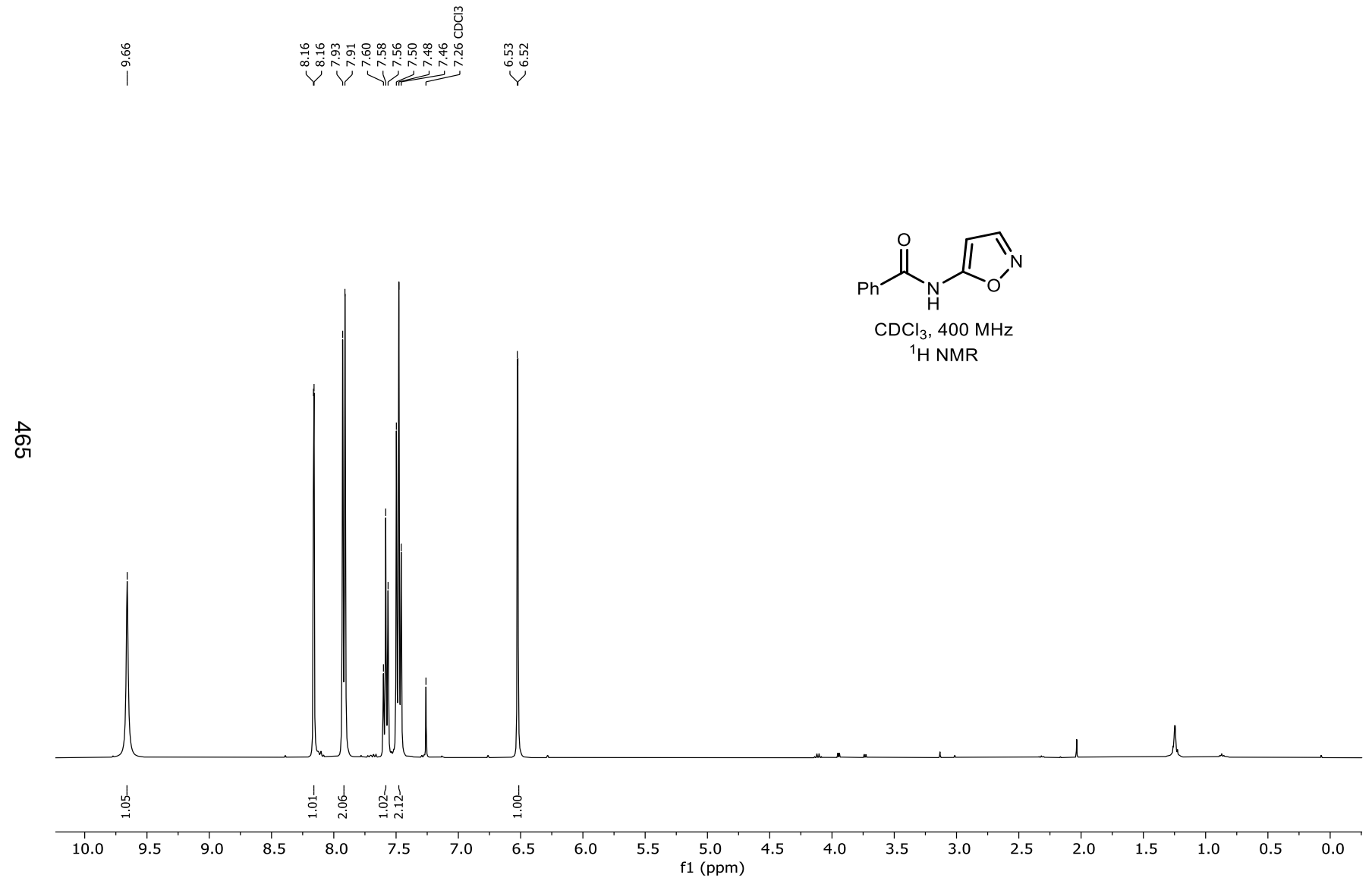

Ph
N
O
Ph
N
O
+
Ph
O
N
CDCl3, 400 MHz
Crude 1H NMR
Ph
Ph
Ph
(0.5 eq. internal standard)
0.22
0.53
0.55
0.50
9.2 9.1 9.0 8.9 8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3
f1 (ppm)

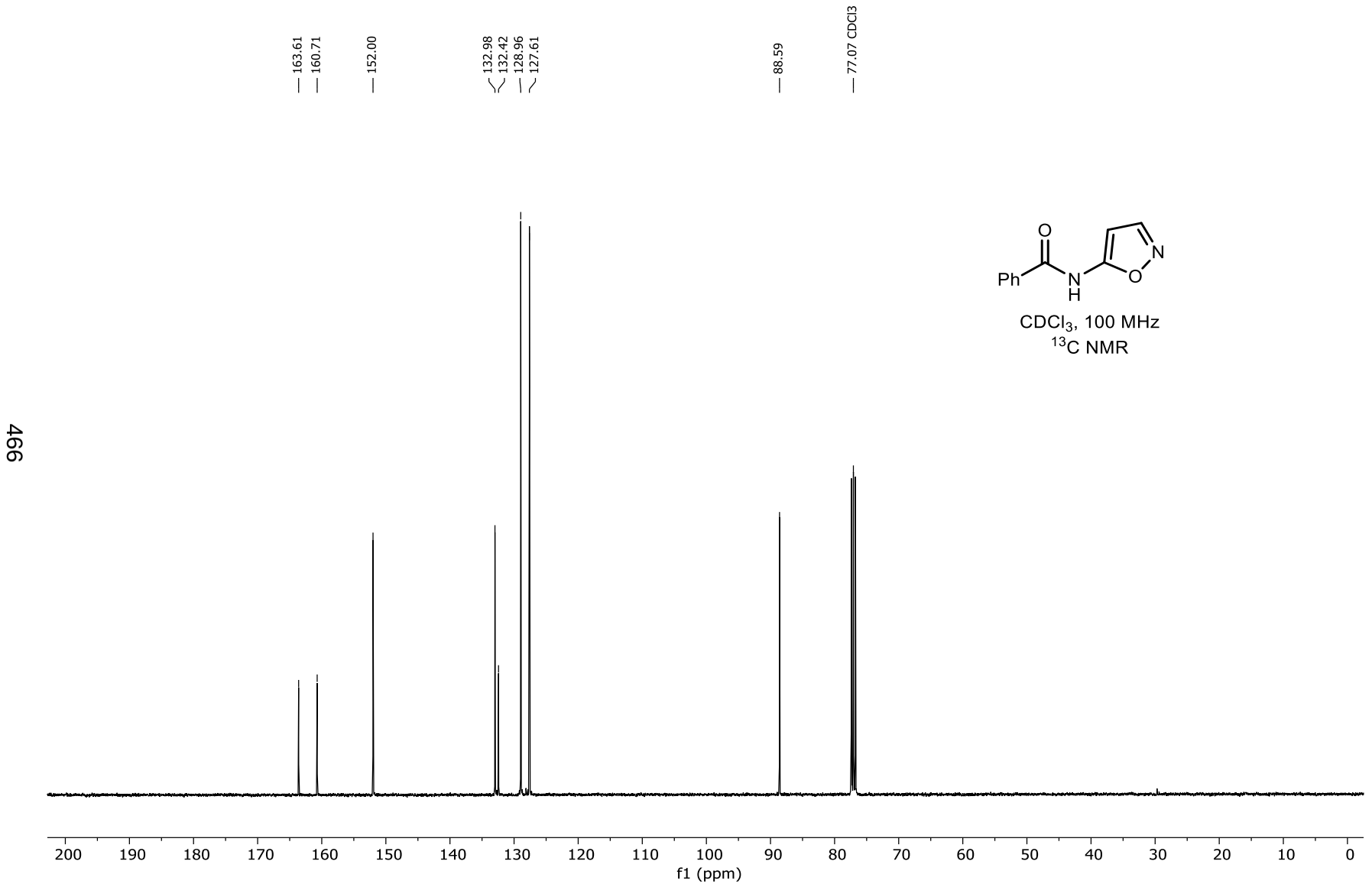

8.46
8.46
7.85
7.84
7.84
7.84
7.83
7.82
7.50
7.49
7.48
7.48
7.47
7.47
7.46
7.46
7.45
7.45
7.45
7.26 CDCl3
6.67
6.67
Ph
O
N
CDCl3, 400 MHz
1H NMR
1.00
2.10
3.18
1.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

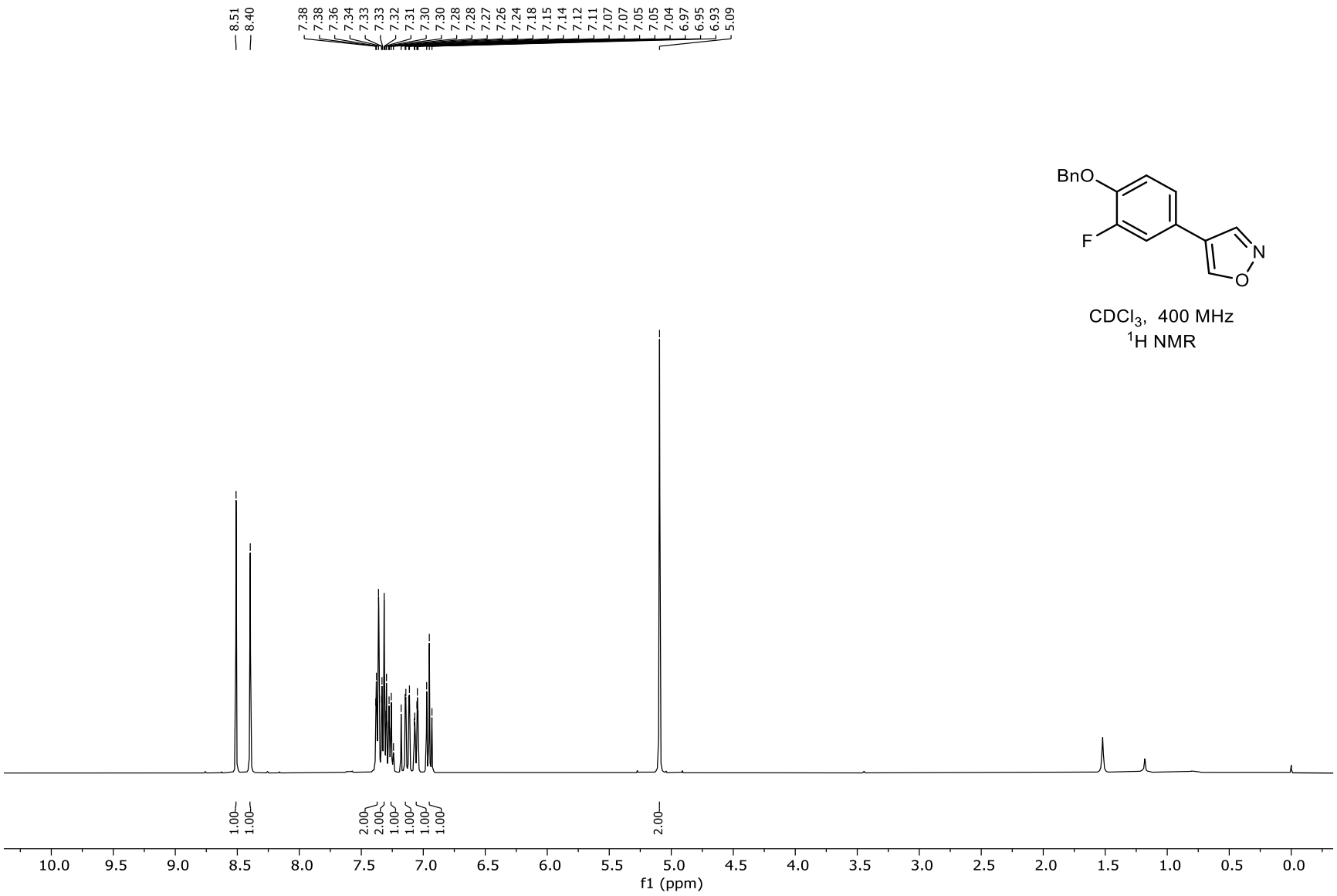

Ph
CDCl3, 100 MHz
13C NMR
77.03 CDCl3
102.47
130.06
128.97
128.83
126.93
161.54
158.89
f1 (ppm)

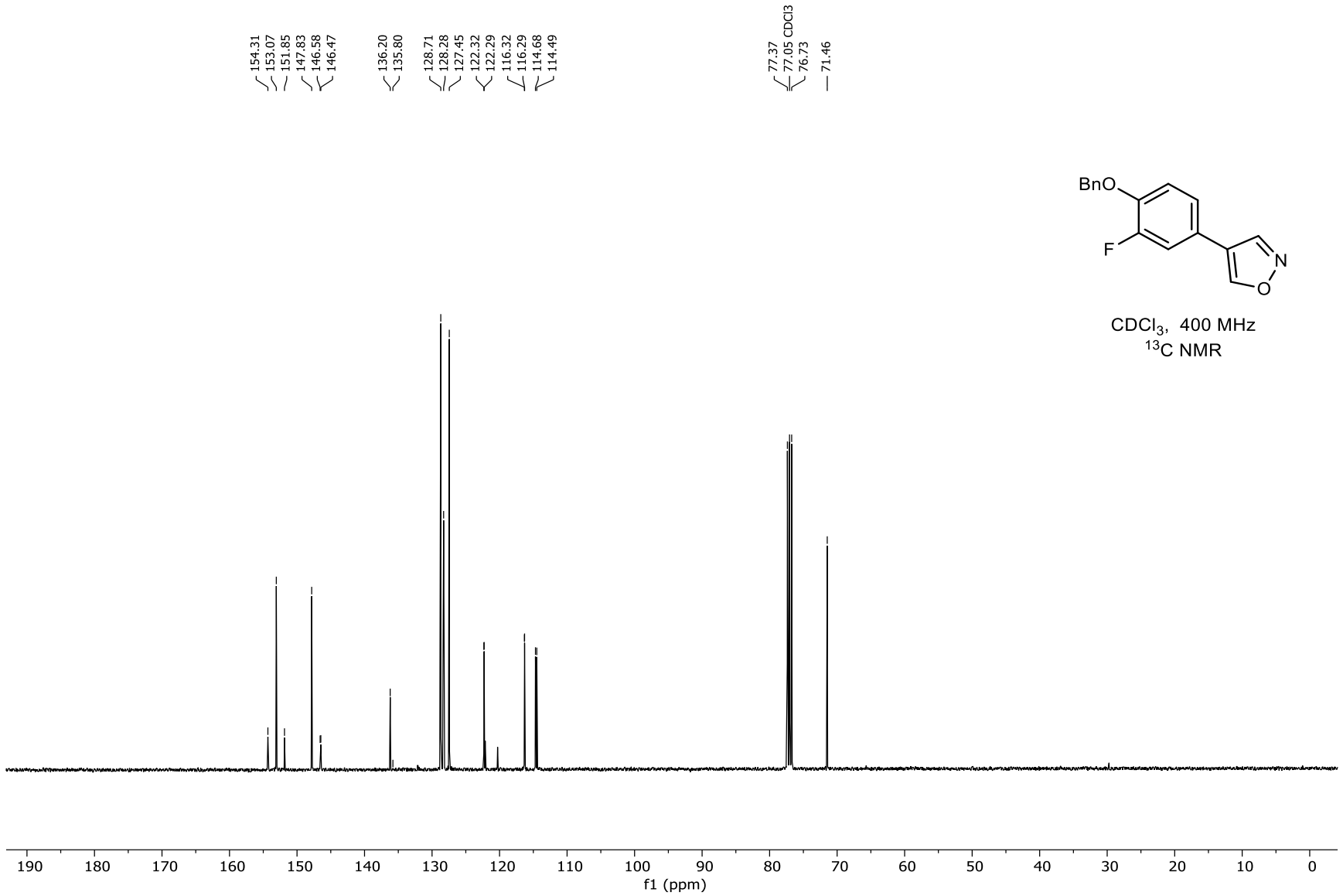

8.28
8.28
7.81
7.80
7.80
7.78
7.78
7.49
7.48
7.48
7.47
7.47
7.47
7.46
7.46
7.46
7.45
7.44
7.44
7.44
7.43
7.43
7.41
7.26 CDCl3
6.52
6.51
Ph
N
O
CDCl3, 400 MHz
1H NMR
1.00
2.10
3.14
1.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

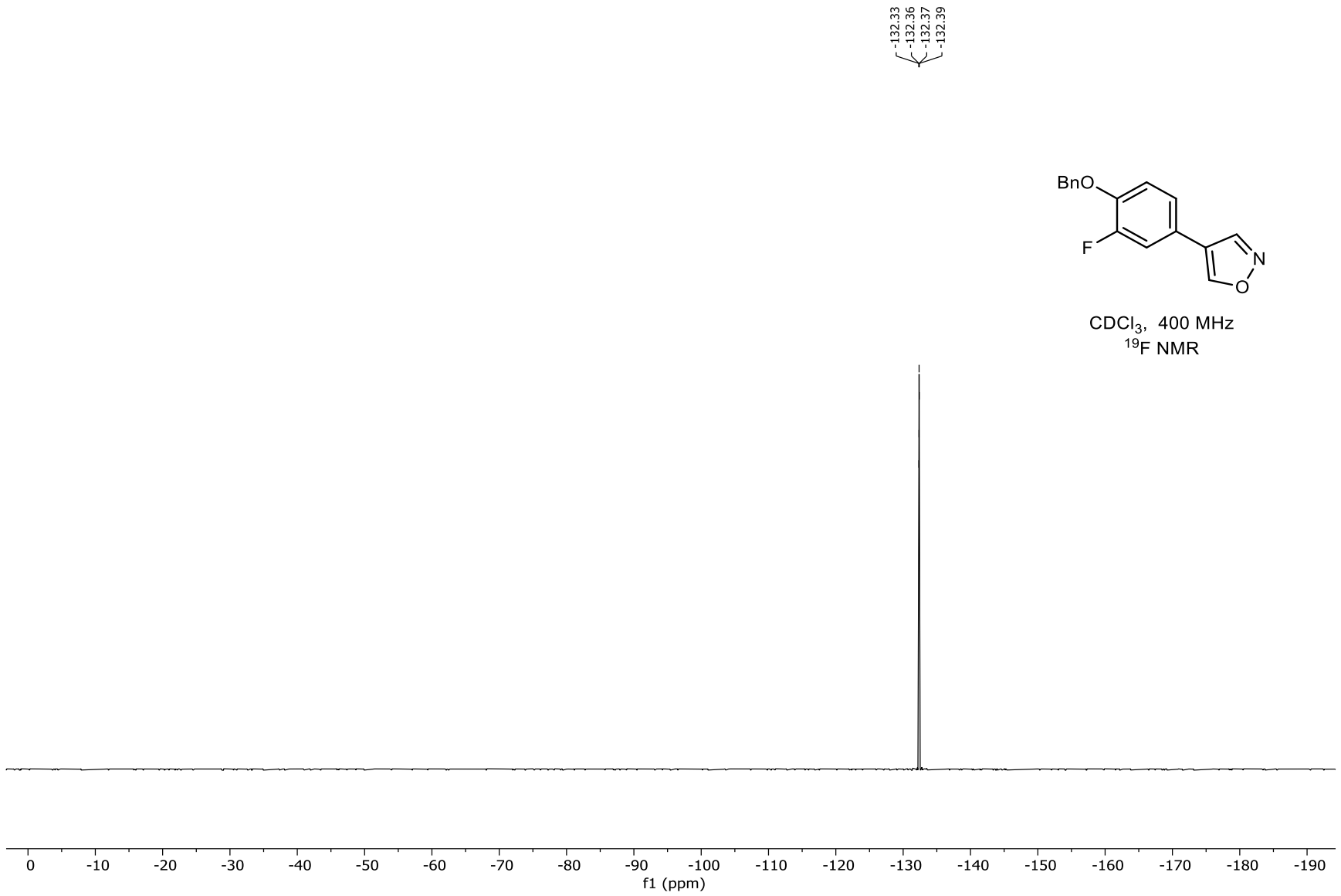

169.45
150.92
130.29
129.09
127.36
125.95
98.75
77.16 CDCl3
Ph
N
O
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.66
8.16
8.16
7.93
7.91
7.60
7.58
7.56
7.50
7.48
7.46
7.26 CDCl3
6.53
6.52
O
N
Ph
N
H
O
CDCl3, 400 MHz
1H NMR
1.05
1.01
2.06
1.02
2.12
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

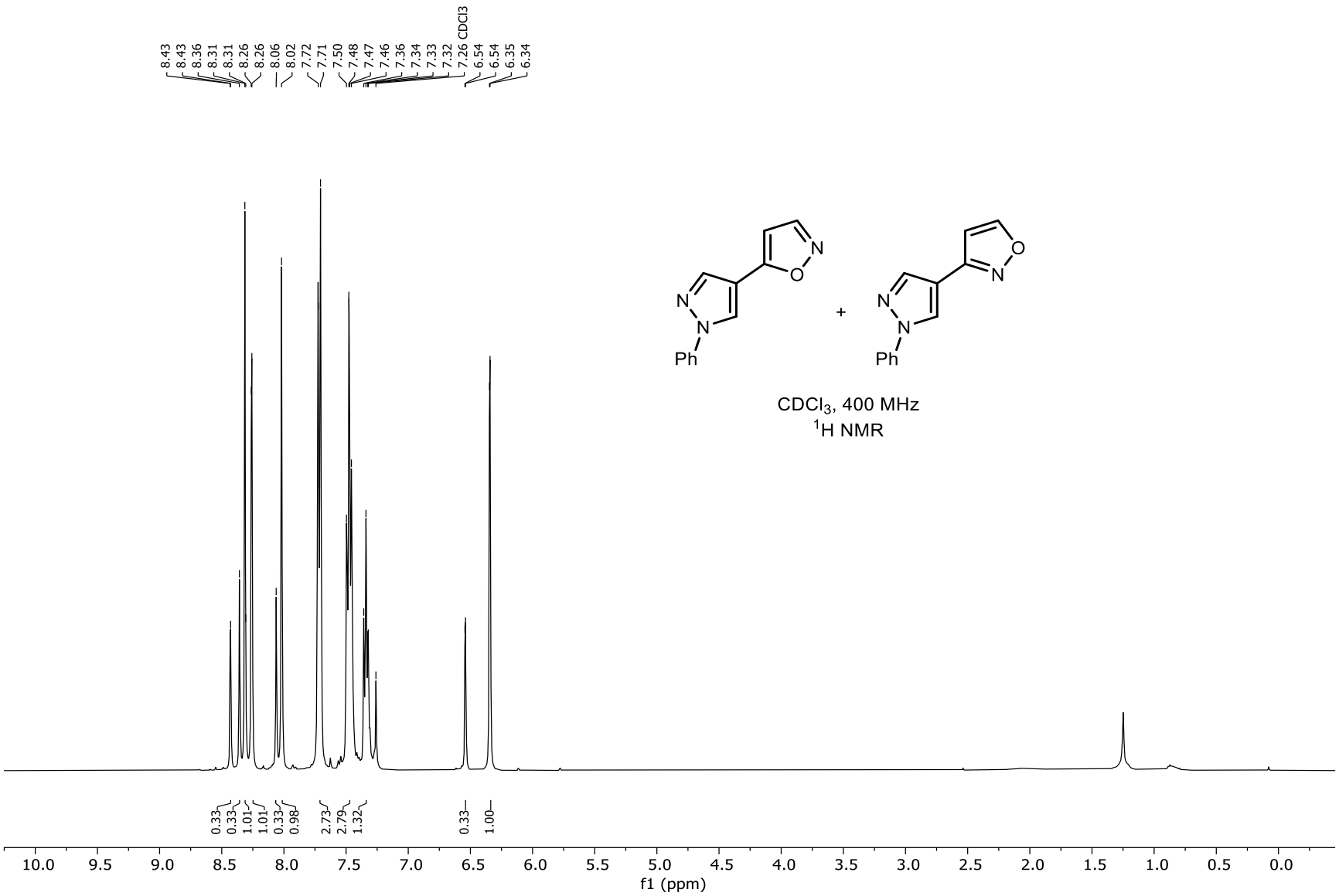

163.61
160.71
152.00
132.98
132.42
128.96
127.61
88.59
77.07 CDCl3
O
N
Ph
N
H
O
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

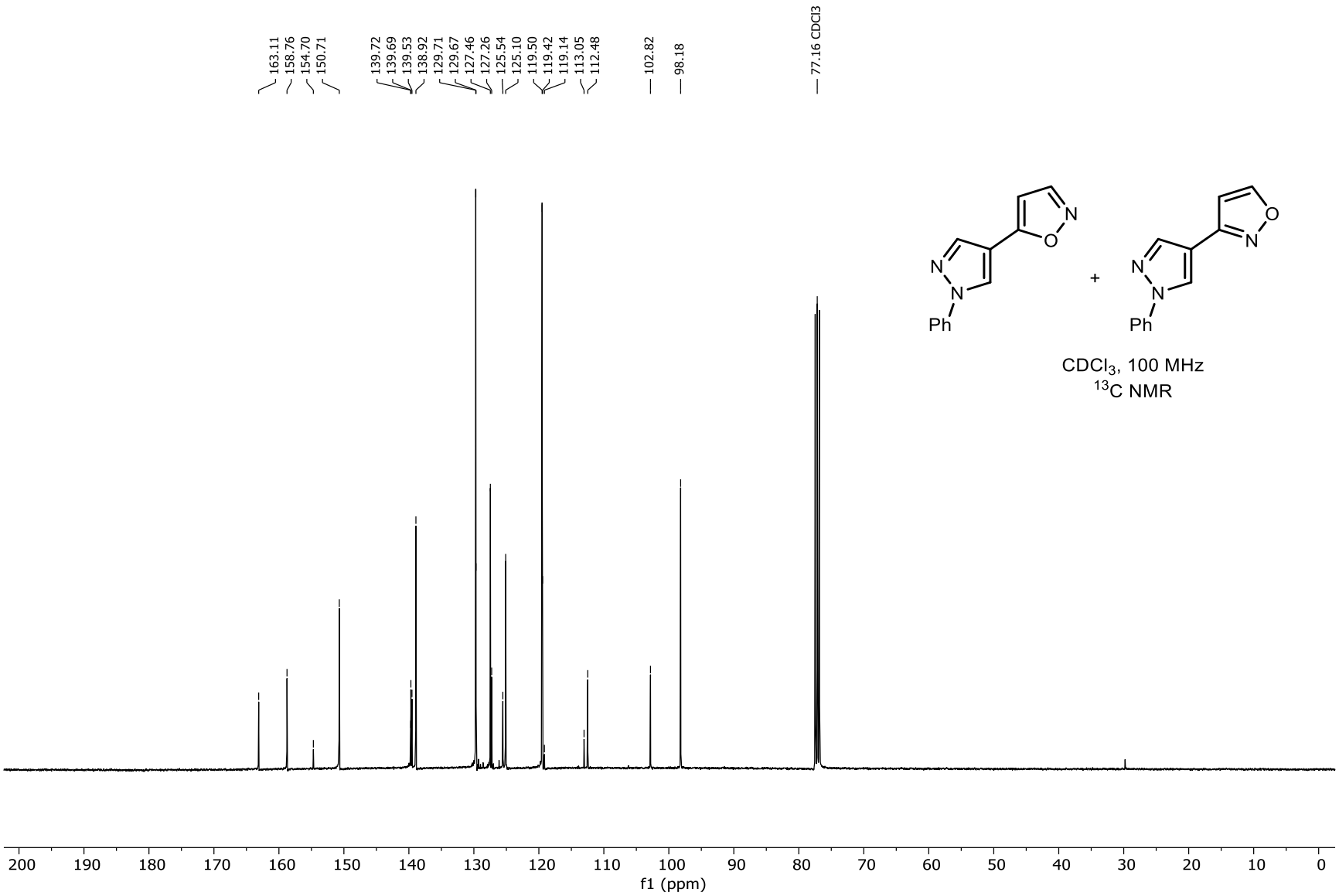

8.51
8.40
7.38
7.38
7.36
7.34
7.33
7.33
7.32
7.31
7.30
7.30
7.28
7.28
7.27
7.26
7.24
7.18
7.15
7.14
7.12
7.11
7.07
7.07
7.05
7.05
7.04
6.97
6.95
6.93
5.09
BnO
F
N
O
CDCl3, 400 MHz
1H NMR
1.00
1.00
2.00
2.00
1.00
1.00
1.00
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

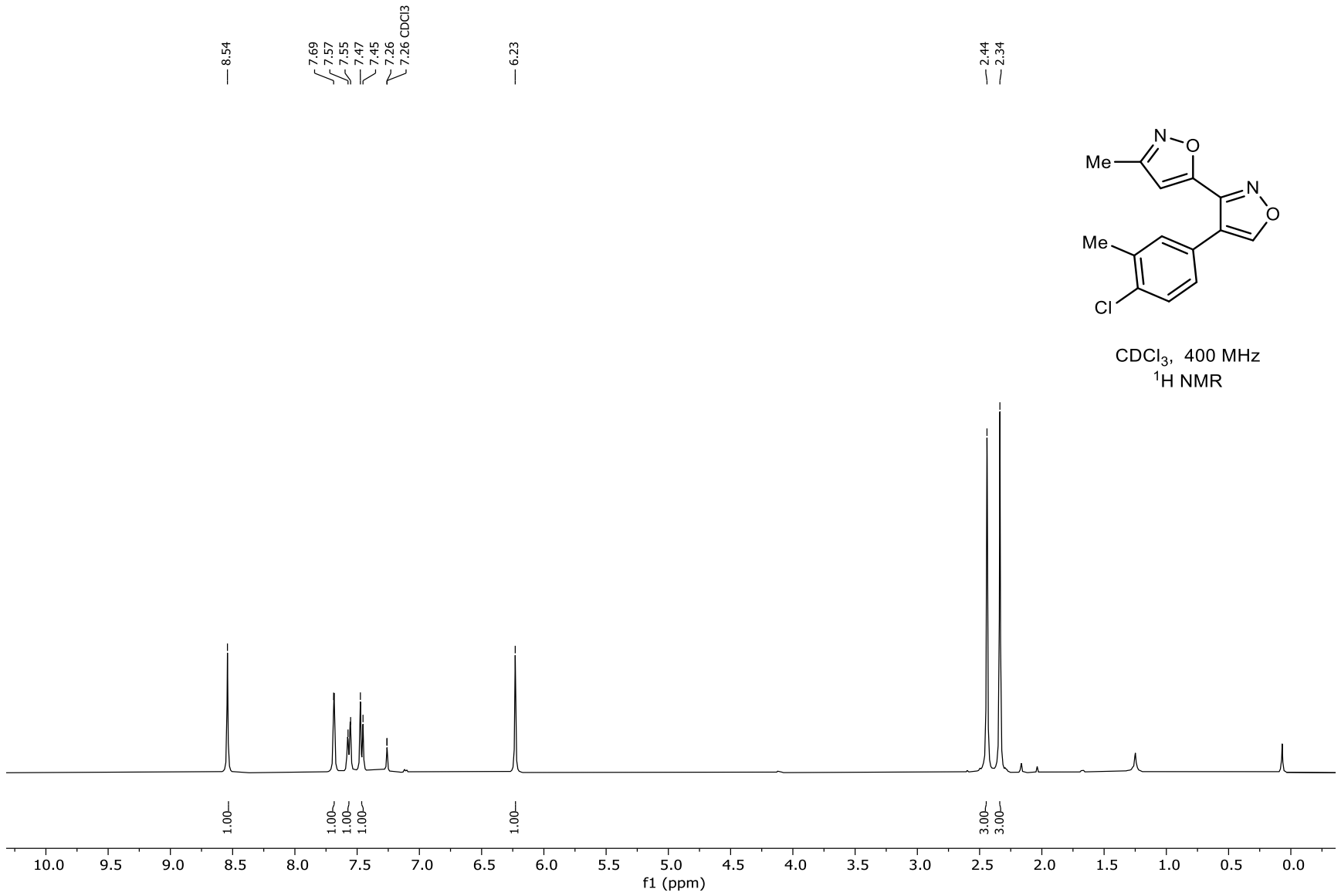

154.31
153.07
151.85
147.83
146.58
146.47
136.20
135.80
128.71
128.28
127.45
122.32
122.29
116.32
116.29
114.68
114.49
77.37
77.05 CDCl3
76.73
71.46
BnO
F
N
O
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

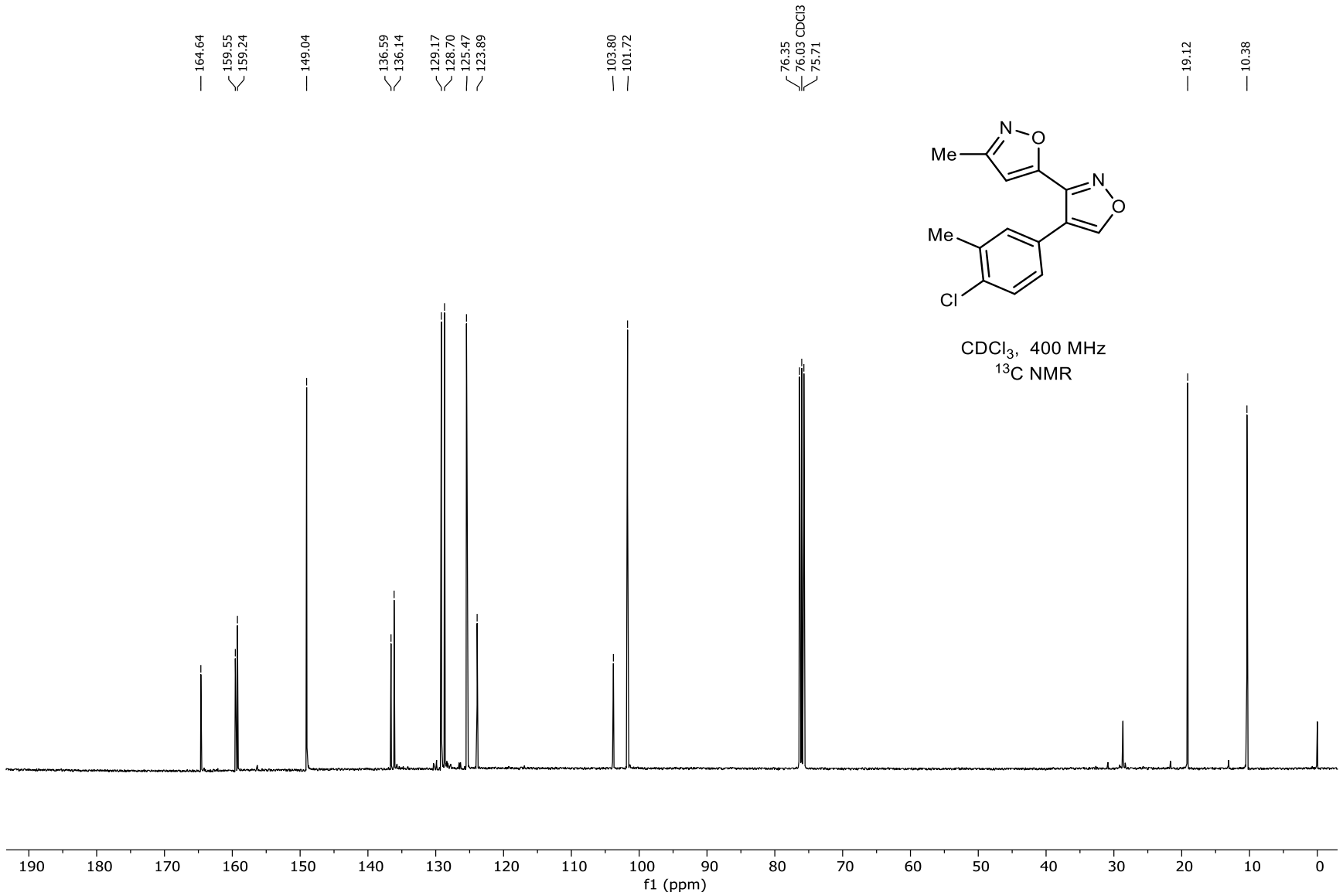

-132.33
-132.36
-132.37
-132.39
BnO
F
N
O
CDCl3, 400 MHz
19F NMR
469
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

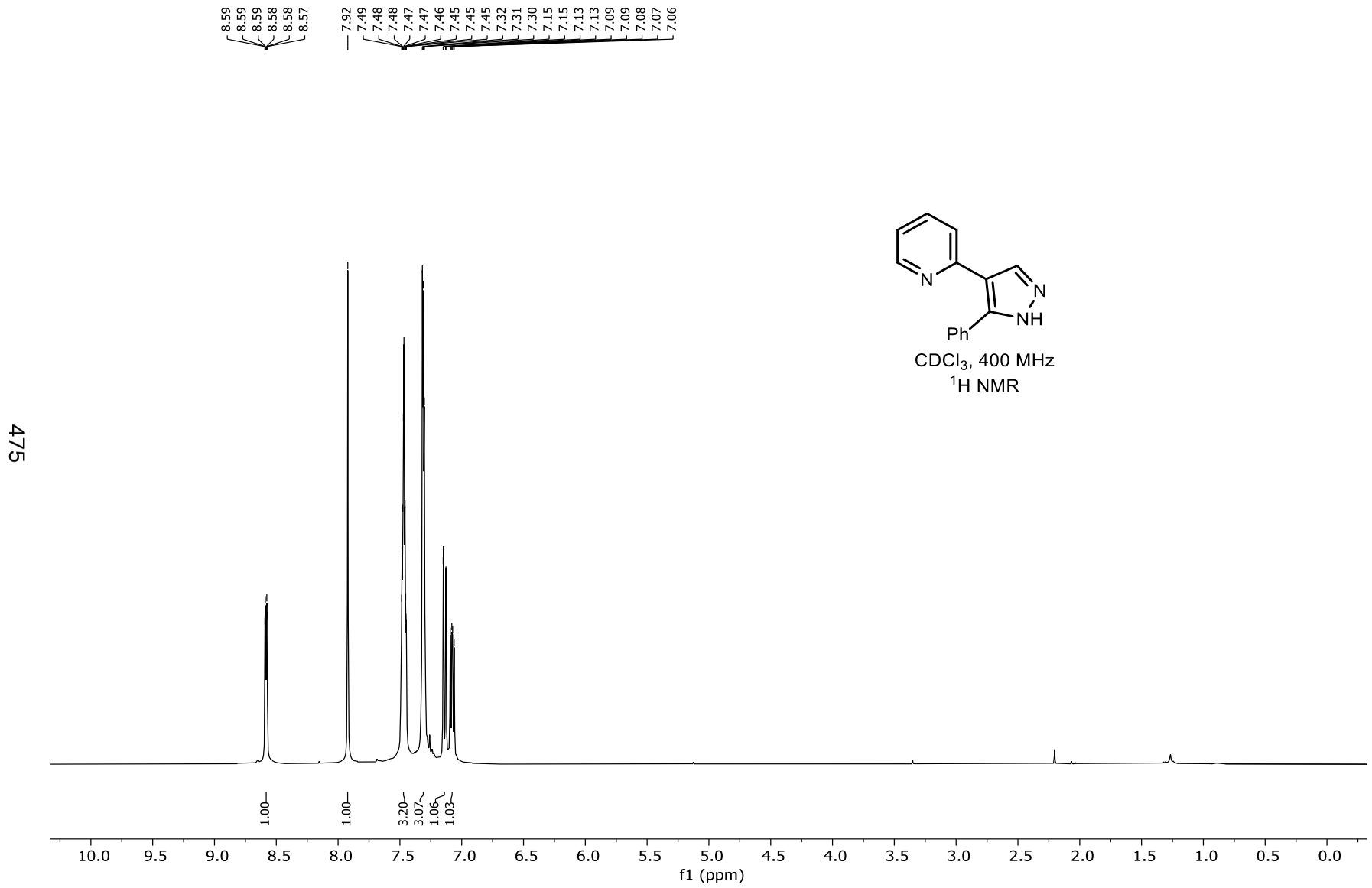
CDCl3, 400 MHz
1H NMR
Ph
Ph
Ph
f1 (ppm)
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.
0.33
1.01
0.33
1.01
0.33
0.98
2.73
2.79
1.32
1.00
0.33
8.43
8.43
8.36
8.31
8.31
8.26
8.26
8.06
8.02
7.73
7.72
7.71
7.50
7.48
7.47
7.46
7.36
7.34
7.33
7.32
7.26
6.54
6.54
6.35
6.34

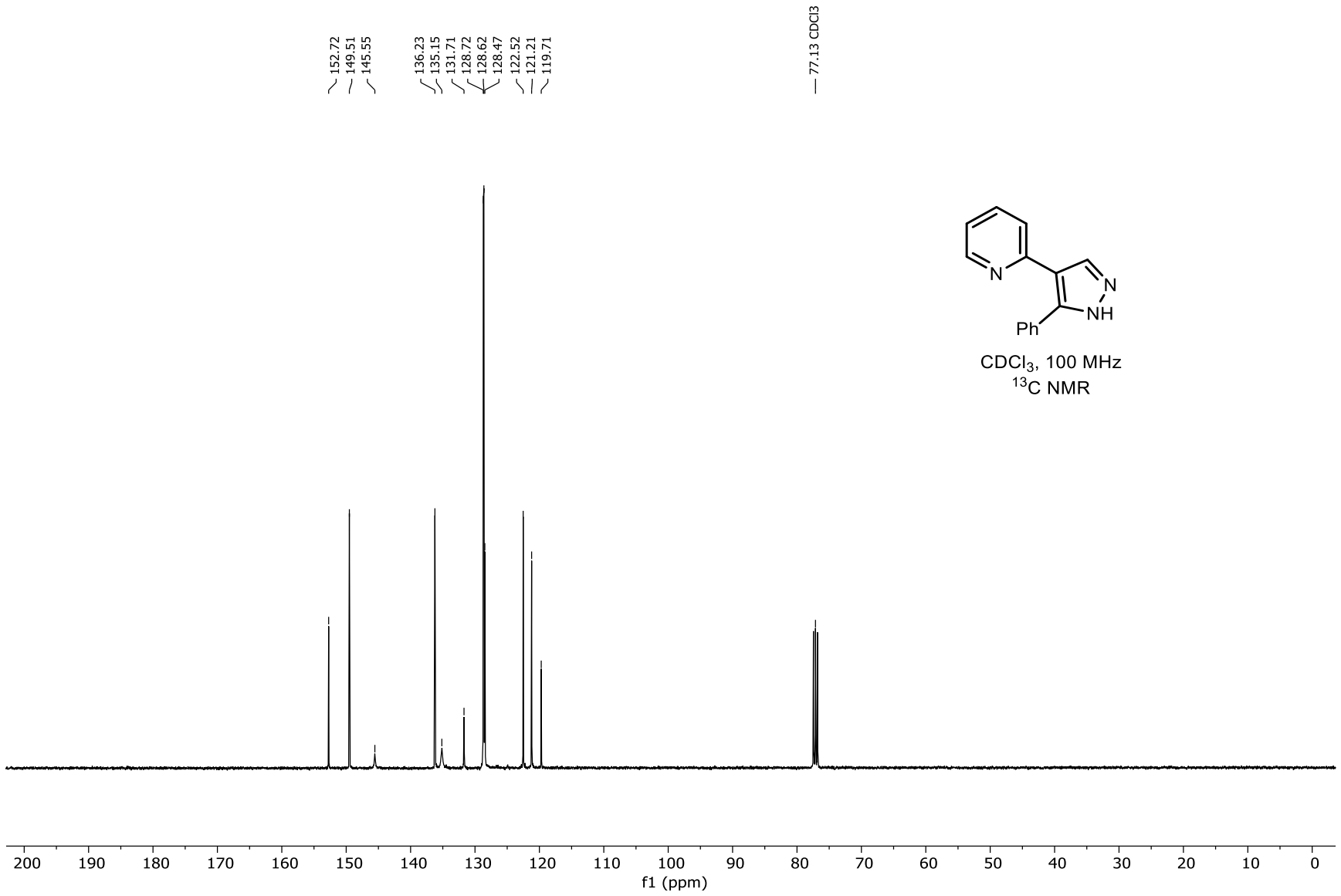

8.43
8.43
8.36
8.31
8.31
8.26
8.26
8.06
8.02
7.72
7.71
7.50
7.48
7.47
7.46
7.36
7.34
7.33
7.32
7.26 CDCl3
6.54
6.54
6.35
6.34
N
O
N
N
Ph
+
O
N
N
N
Ph
CDCl3, 400 MHz
1H NMR
0.33
0.33
1.01
1.01
0.33
0.98
2.73
2.79
1.32
0.33
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

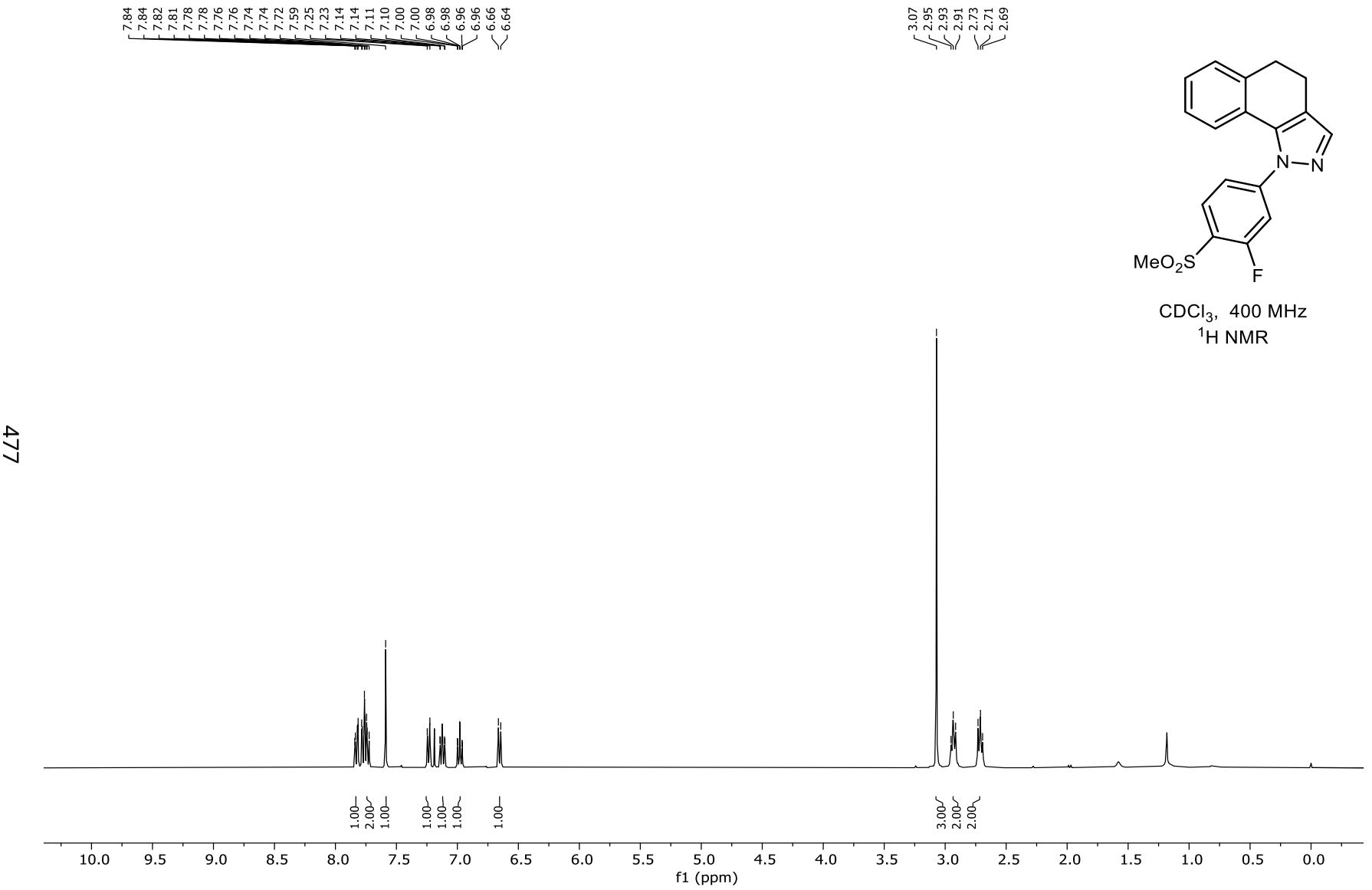

163.11
158.76
154.70
150.71
139.72
139.69
139.53
138.92
129.71
129.67
127.46
127.26
125.54
125.10
119.50
119.42
119.14
113.05
112.48
102.82
98.18
77.16 CDCl3
N
O
N
N
Ph
+
O
N
N
N
Ph
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

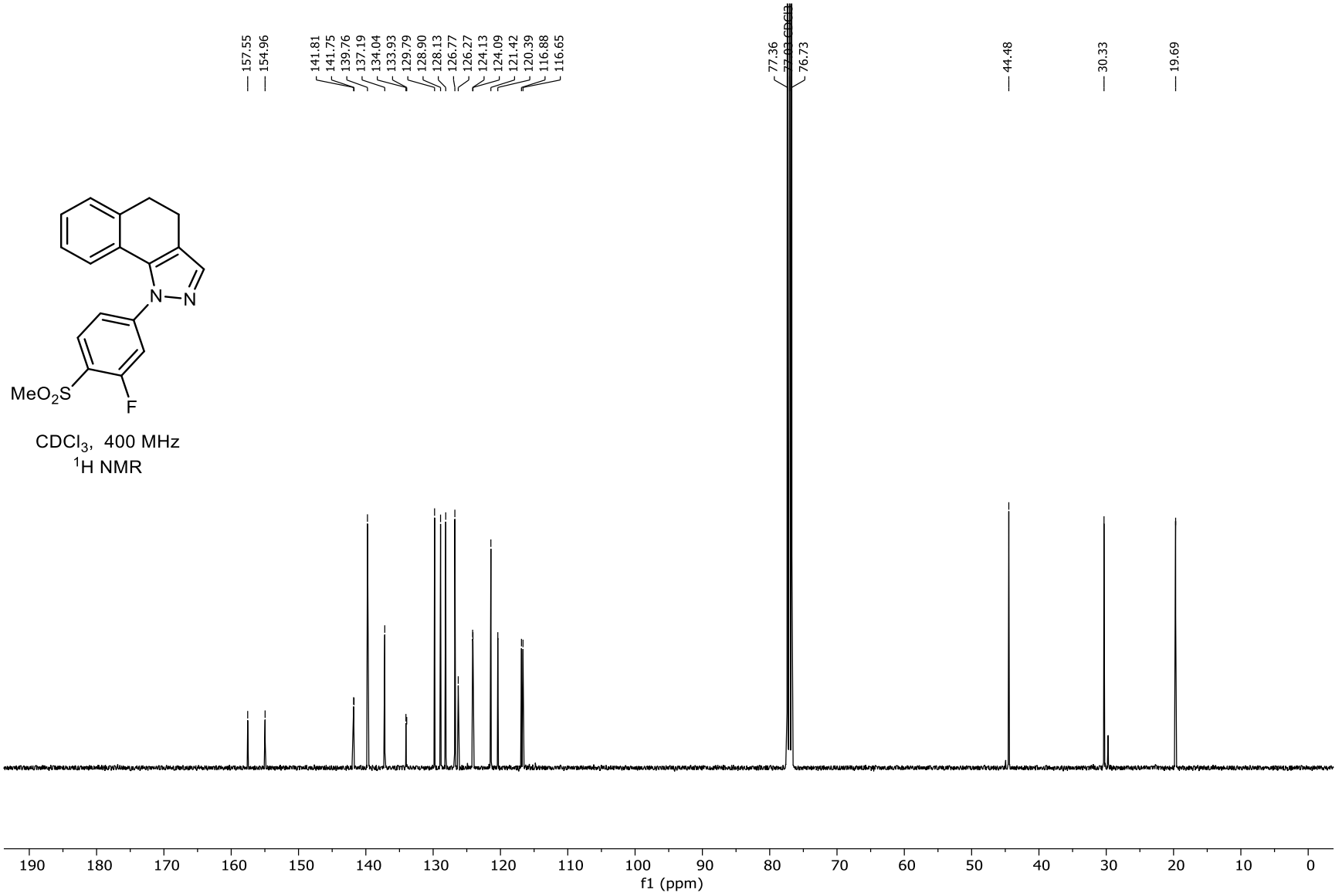

8.54
7.69
7.57
7.55
7.47
7.45
7.26
7.26 CDCl3
6.23
2.44
2.34
Me
N
O
N
O
Me
Cl
CDCl3, 400 MHz
1H NMR
1.00
1.00
1.00
1.00
3.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

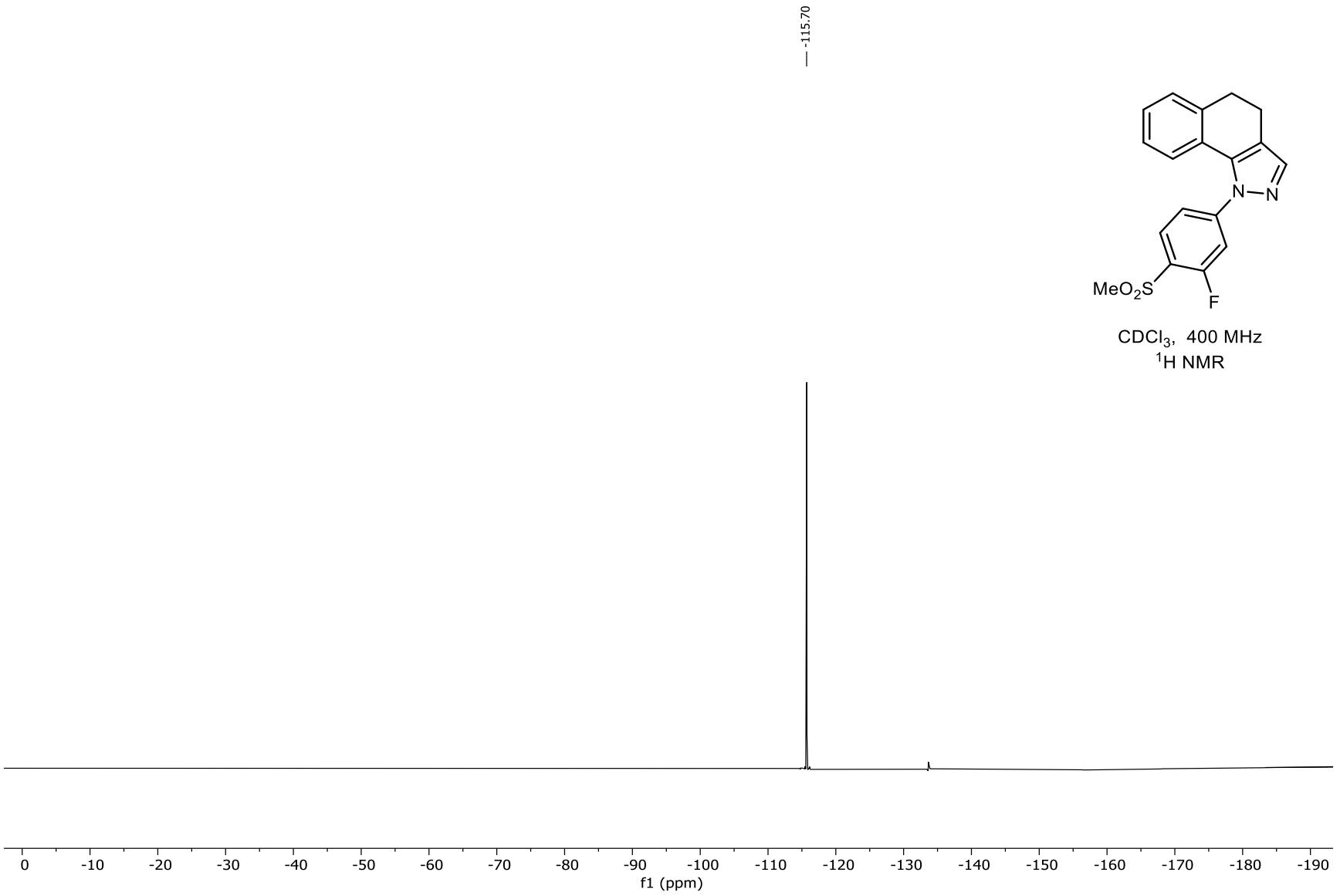

164.64
159.55
159.24
149.04
136.59
136.14
129.17
128.70
125.47
123.89
103.80
101.72
76.35
76.03 CDCl3
75.71
19.12
10.38
Me
N
O
N
O
Me
Cl
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

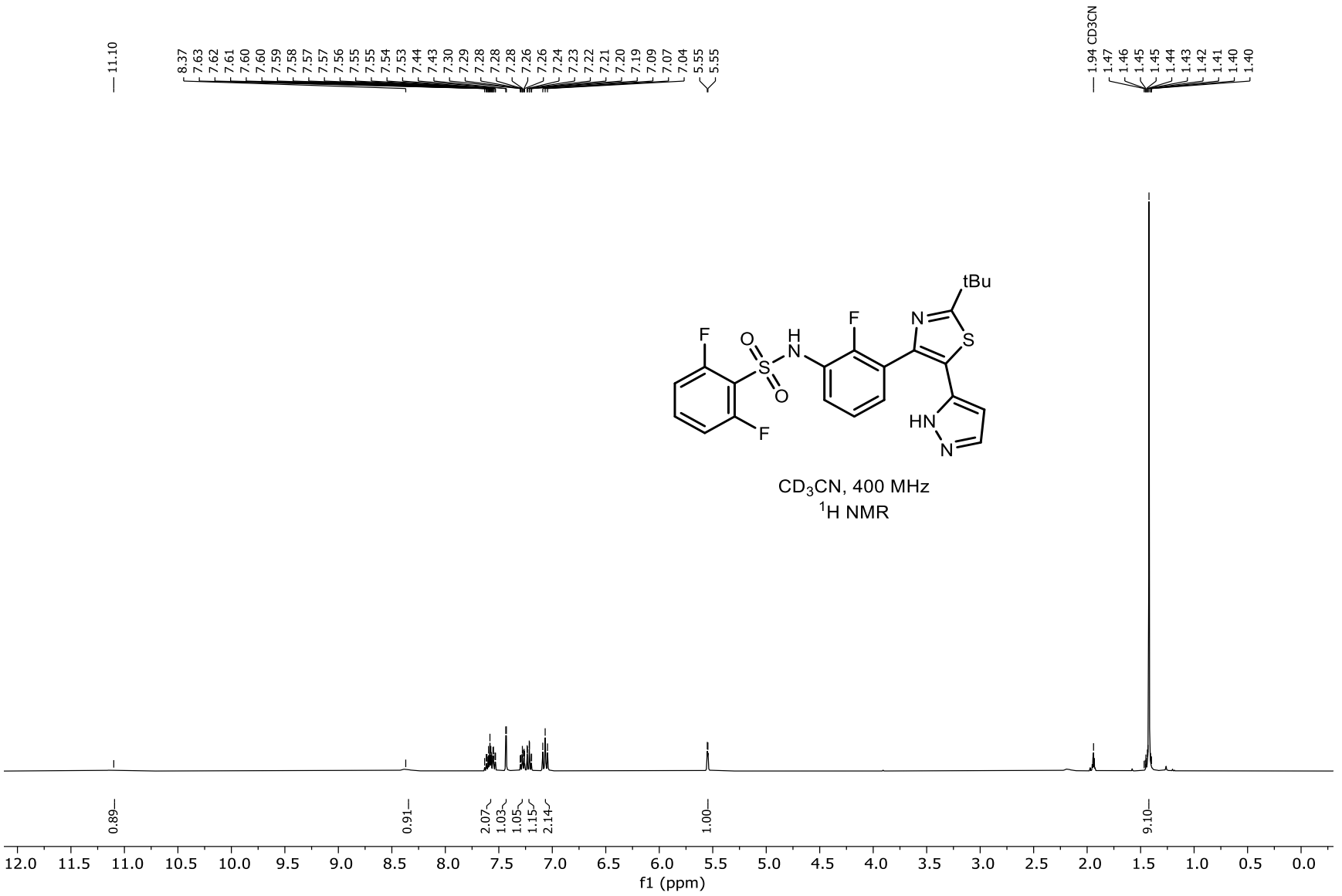

8.59
8.59
8.59
8.58
8.58
8.57
7.92
7.49
7.48
7.48
7.47
7.47
7.46
7.45
7.45
7.45
7.32
7.31
7.30
7.15
7.15
7.13
7.13
7.09
7.09
7.08
7.07
7.06
N
N
NH
Ph
CDCl3, 400 MHz
1H NMR
1.00
1.00
3.20
3.07
1.06
1.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

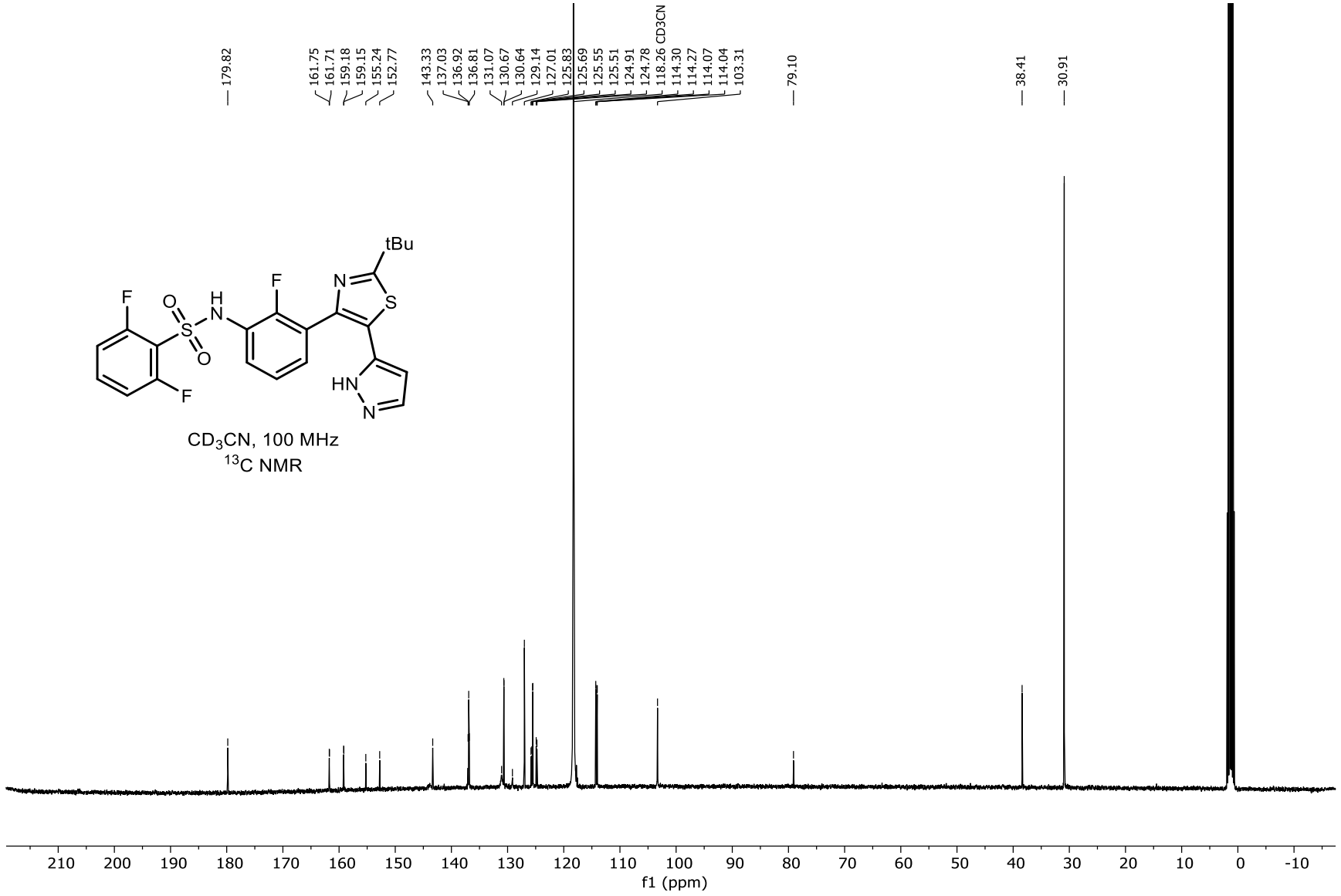

152.72
149.51
145.55
136.23
135.15
131.71
128.72
128.62
128.47
122.52
121.21
119.71
77.13 CDCl3
N
N
NH
Ph
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

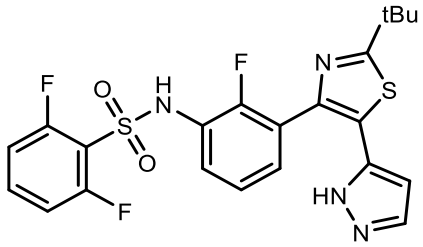

7.84
7.84
7.82
7.81
7.78
7.78
7.76
7.76
7.74
7.74
7.72
7.59
7.25
7.23
7.14
7.14
7.11
7.10
7.00
7.00
6.98
6.98
6.96
6.96
6.66
6.64
3.07
2.95
2.93
2.91
2.73
2.71
2.69
MeO2S
F
CDCl3, 400 MHz
1H NMR
1.00
2.00
1.00
1.00
1.00
1.00
1.00
3.00
2.00
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


157.55
154.96
141.81
141.75
139.76
137.19
134.04
133.93
129.79
128.90
128.13
126.77
126.27
124.13
124.09
121.42
120.39
116.88
116.65
77.36
77.03 CDCl3
76.73
44.48
30.33
19.69
MeO2S
F
CDCl3, 400 MHz
1H NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-115.70
N
N
MeO2S
F
CDCl3, 400 MHz
1H NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

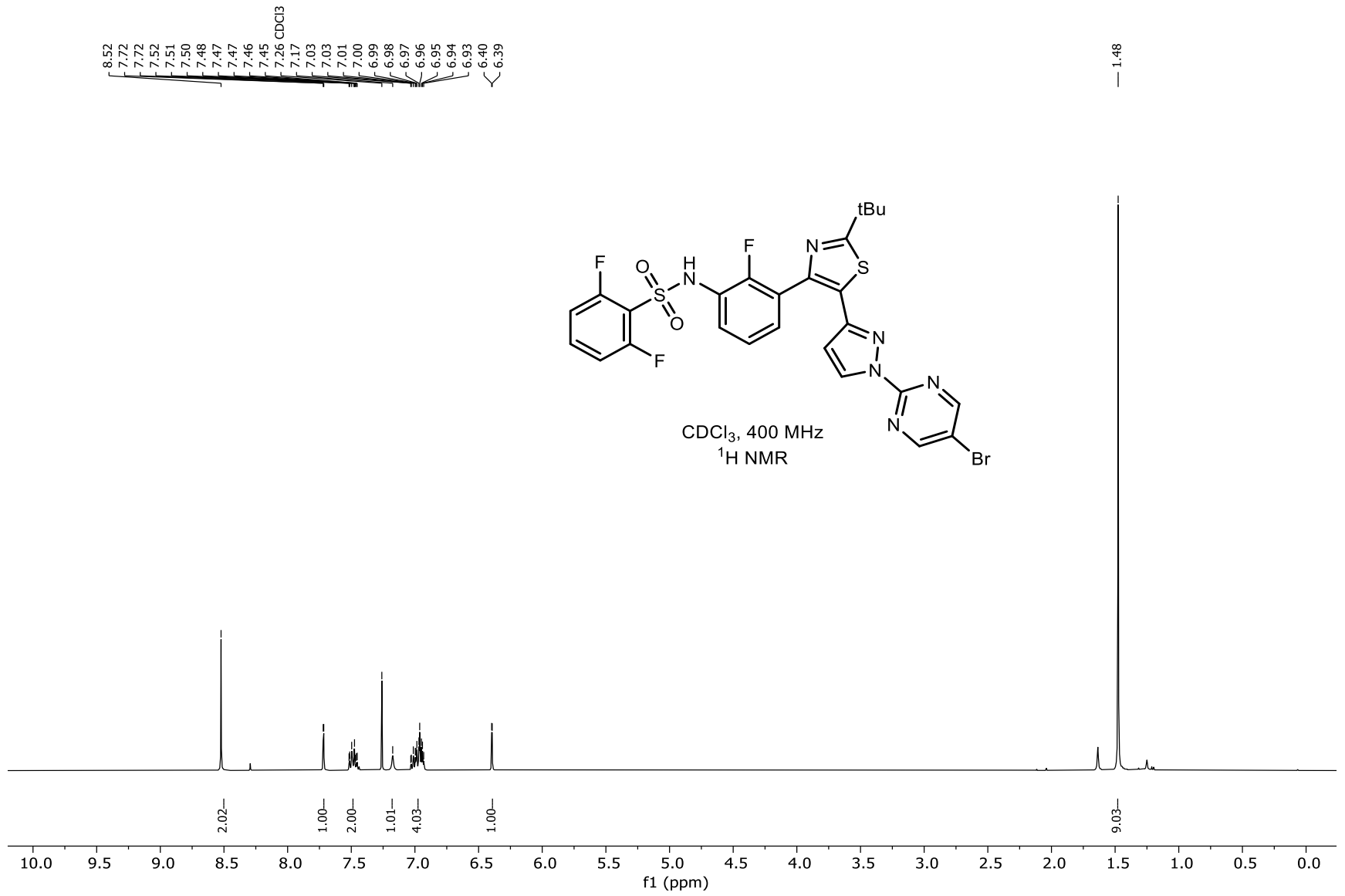

11.10
8.37
7.63
7.62
7.61
7.60
7.60
7.59
7.58
7.57
7.57
7.56
7.55
7.55
7.54
7.53
7.44
7.43
7.30
7.29
7.28
7.28
7.28
7.26
7.26
7.24
7.23
7.22
7.21
7.20
7.19
7.09
7.07
7.04
5.55
5.55
1.94 CD3CN
1.47
1.46
1.45
1.45
1.44
1.43
1.42
1.41
1.40
1.40
tBu
F
O
H
N
S
O
F
F
N
S
HN
N
CD3CN, 400 MHz
1H NMR
0.89
0.91
2.07
1.03
1.05
1.15
2.14
1.00
9.10
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

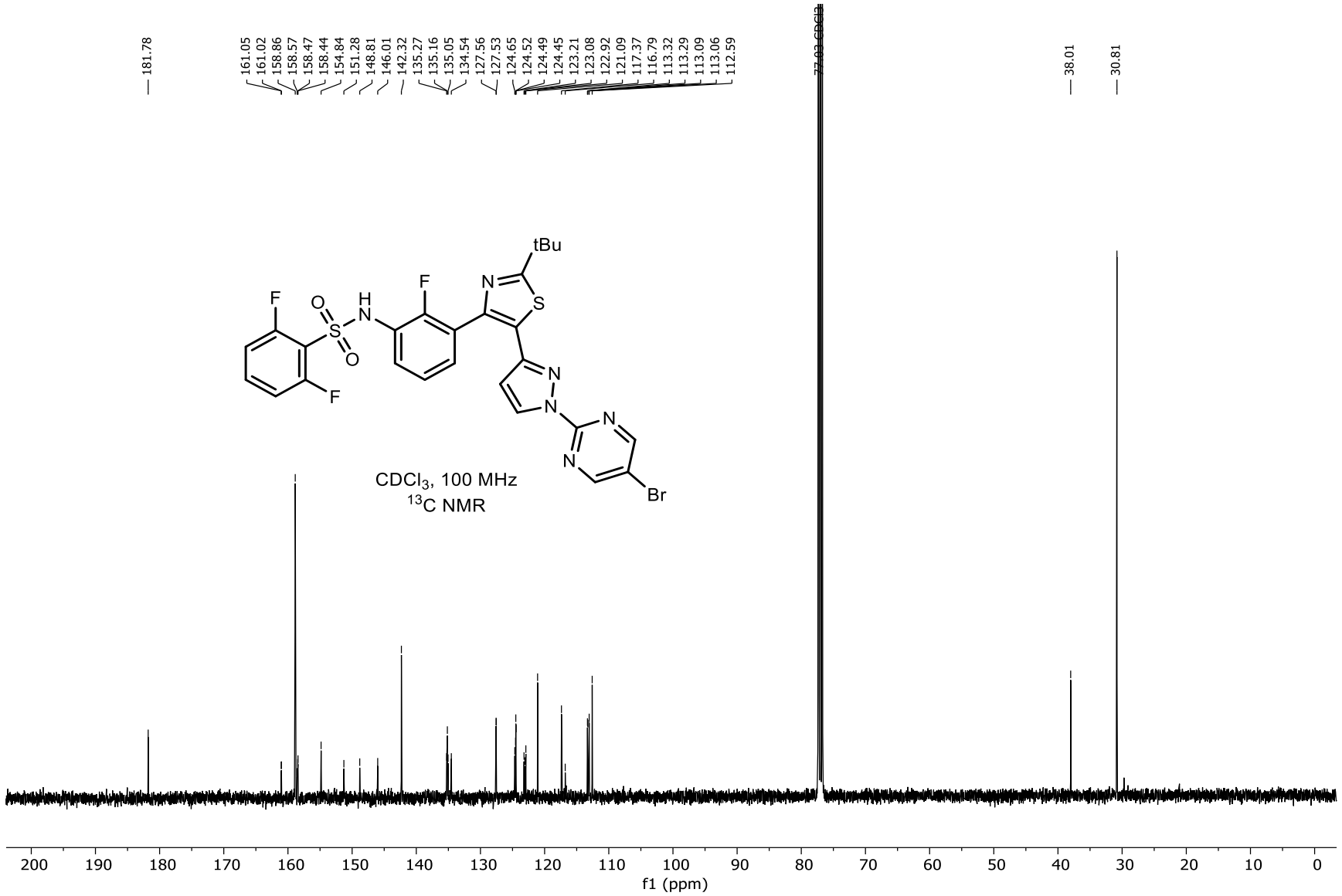

179.82
161.75
161.71
159.18
159.15
155.24
152.77
143.33
137.03
136.92
136.81
131.07
130.67
130.64
129.14
127.01
125.83
125.69
125.55
125.51
124.91
124.78
118.26 CD3CN
114.30
114.27
114.07
114.04
103.31
79.10
38.41
30.91
tBu
F
O
H
N
S
O
F
F
N
S
HN
N
CD3CN, 100 MHz
13C NMR
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

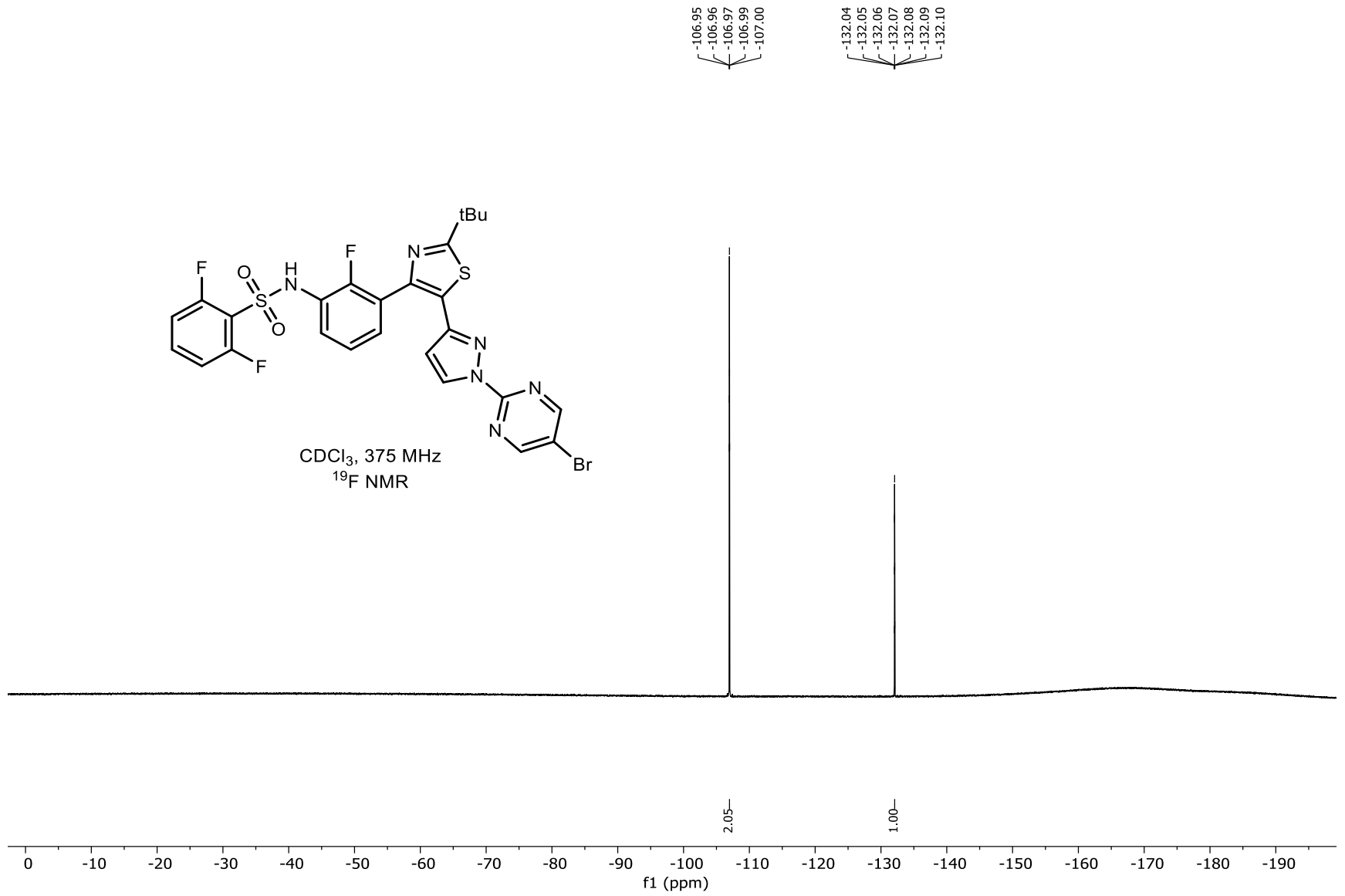


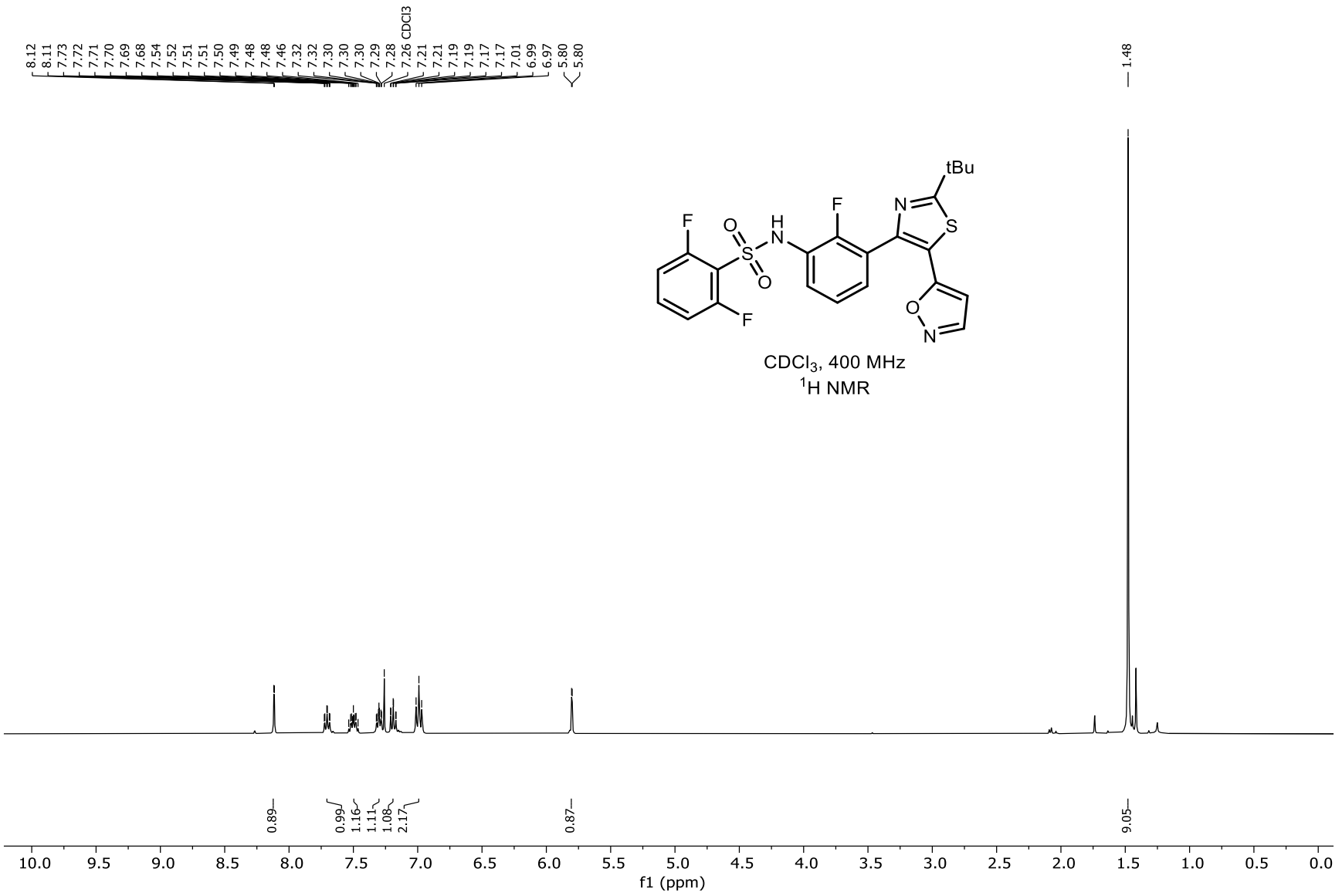
CD_3CN, 375 MHz

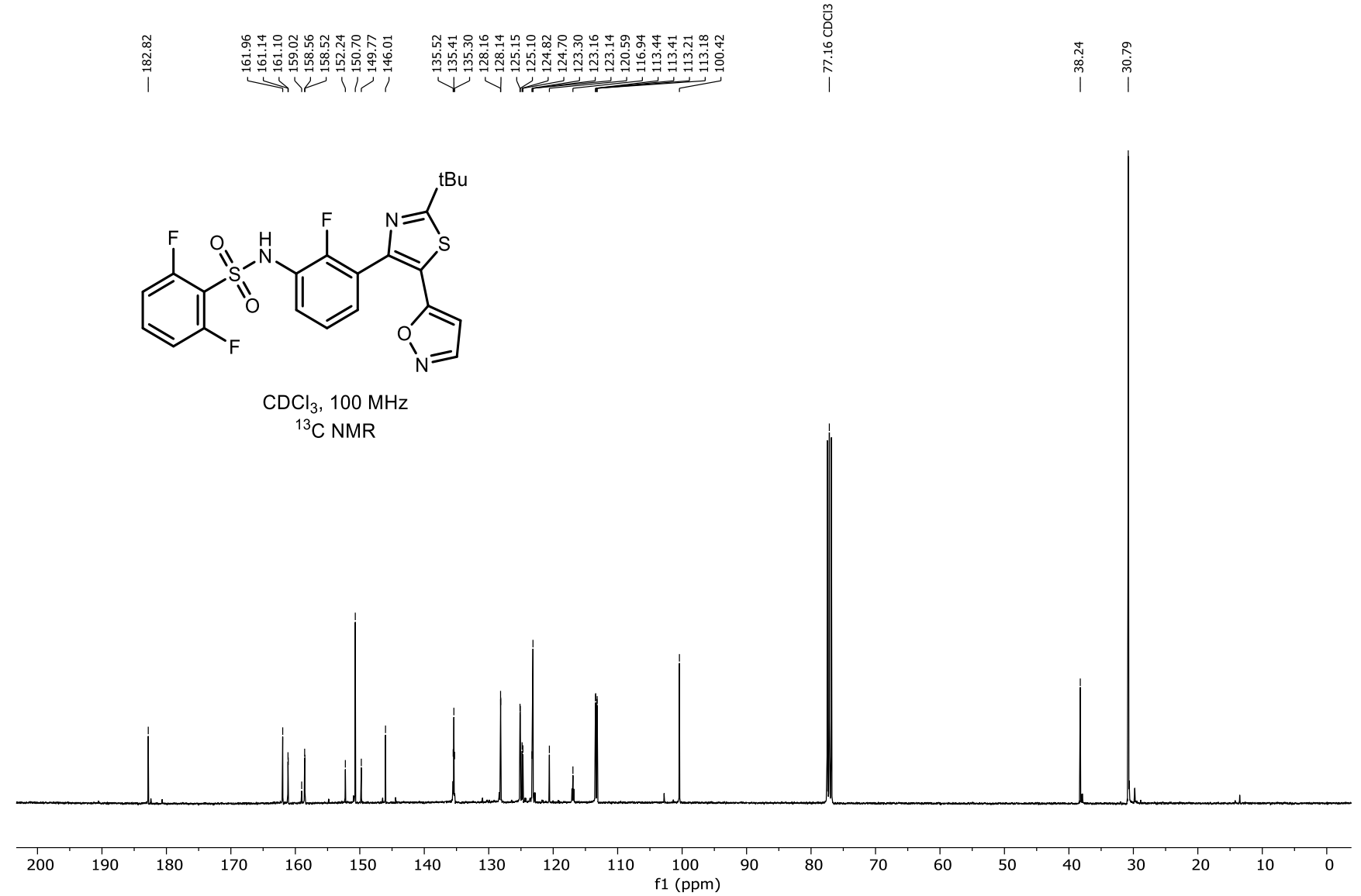
^{19}F NMR

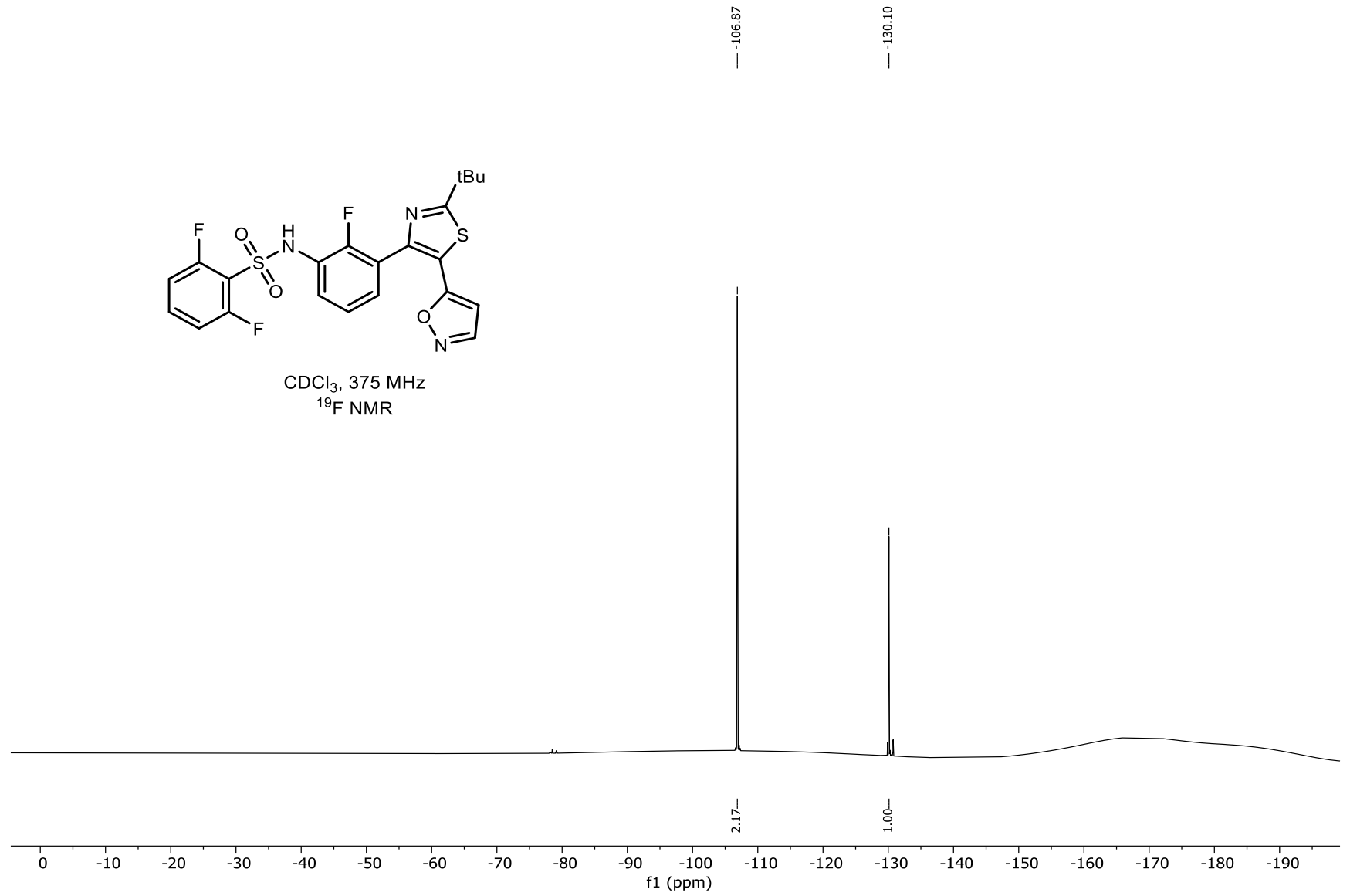

8.52
7.72
7.72
7.52
7.51
7.50
7.48
7.47
7.47
7.46
7.45
7.26 CDCl3
7.17
7.03
7.03
7.01
7.00
6.99
6.98
6.97
6.96
6.95
6.94
6.93
6.40
6.39
1.48
tBu
F
O
H
N
S
F
N
S
O
F
N
N
N
N
Br
CDCl3, 400 MHz
1H NMR
2.02
1.00
2.00
1.01
4.03
1.00
9.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

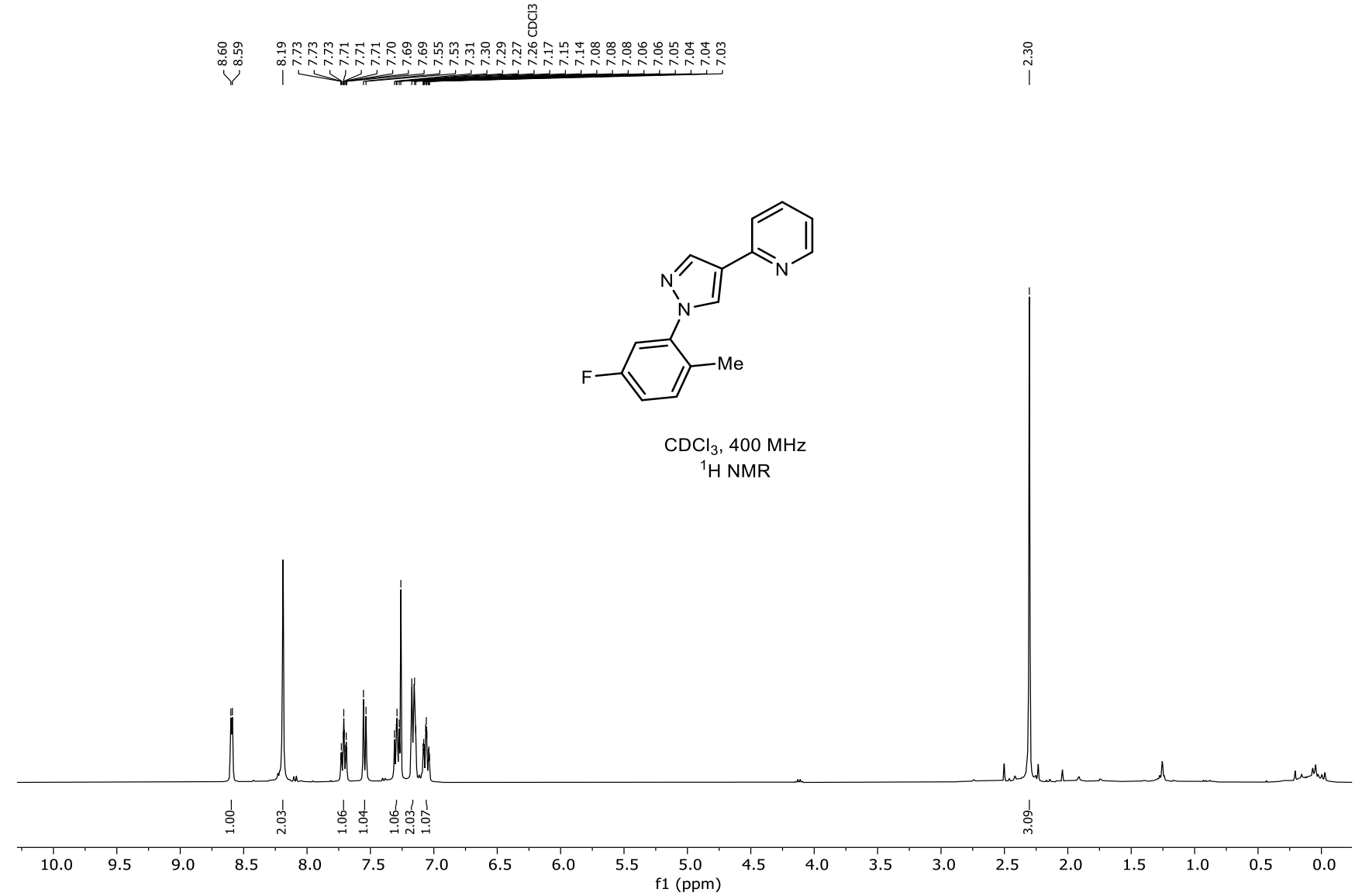

181.78
161.05
161.02
158.86
158.57
158.47
158.44
154.84
151.28
148.81
146.01
142.32
135.27
135.16
135.05
134.54
127.56
127.53
124.65
124.52
124.49
124.45
123.21
123.08
122.92
121.09
117.37
116.79
113.32
113.29
113.09
113.06
112.59
77.03 CDCl3
38.01
30.81
tBu
F
O
H
N
F
N
S
S
O
O
F
N
N
N
N
Br
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

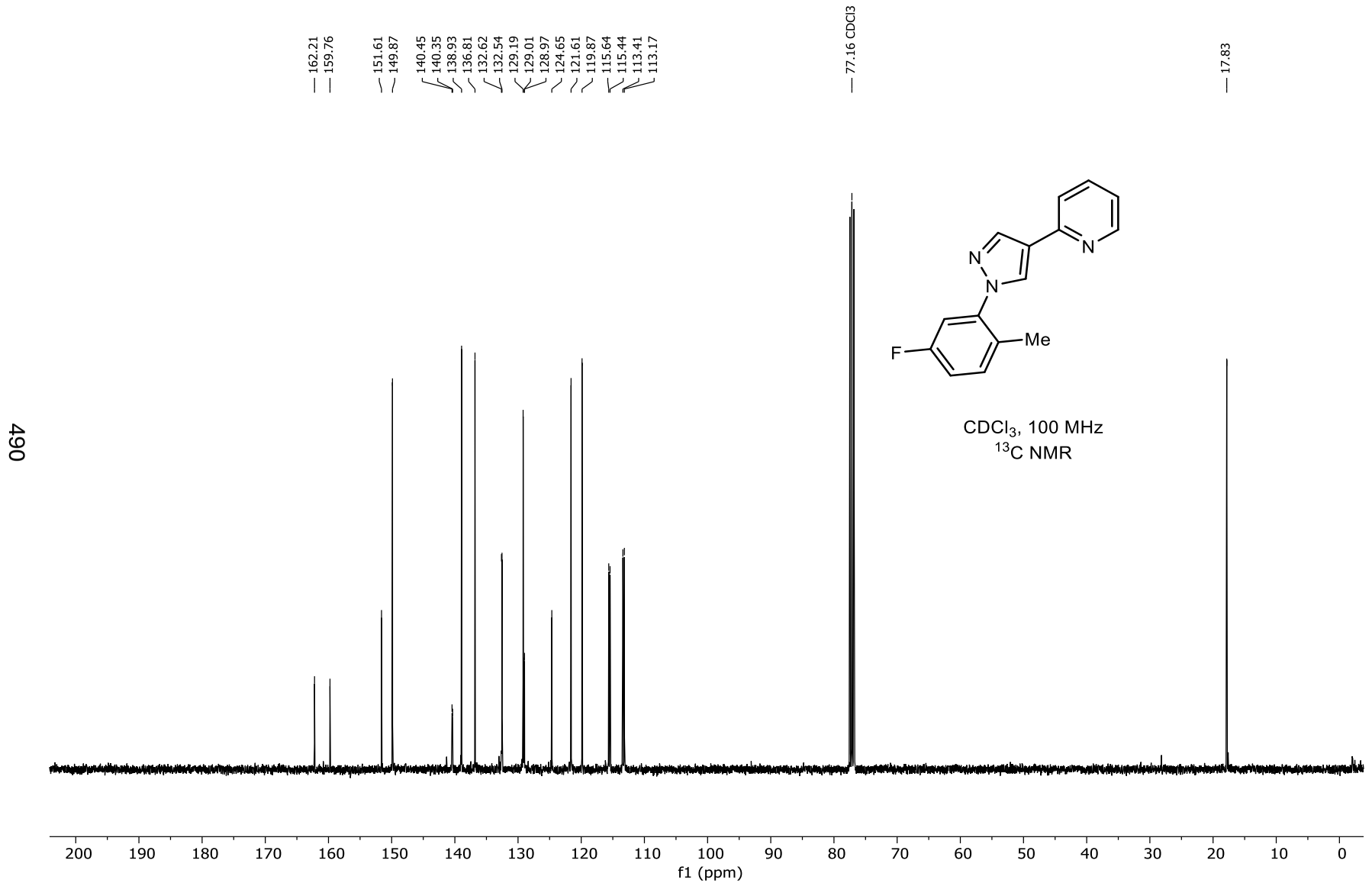

-106.95
-106.96
-106.97
-106.99
-107.00
-132.04
-132.05
-132.06
-132.07
-132.08
-132.09
-132.10
tBu
F
O
H
N
S
F
N
S
O
F
N
N
N
N
Br
CDCl3, 375 MHz
19F NMR
2.05
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

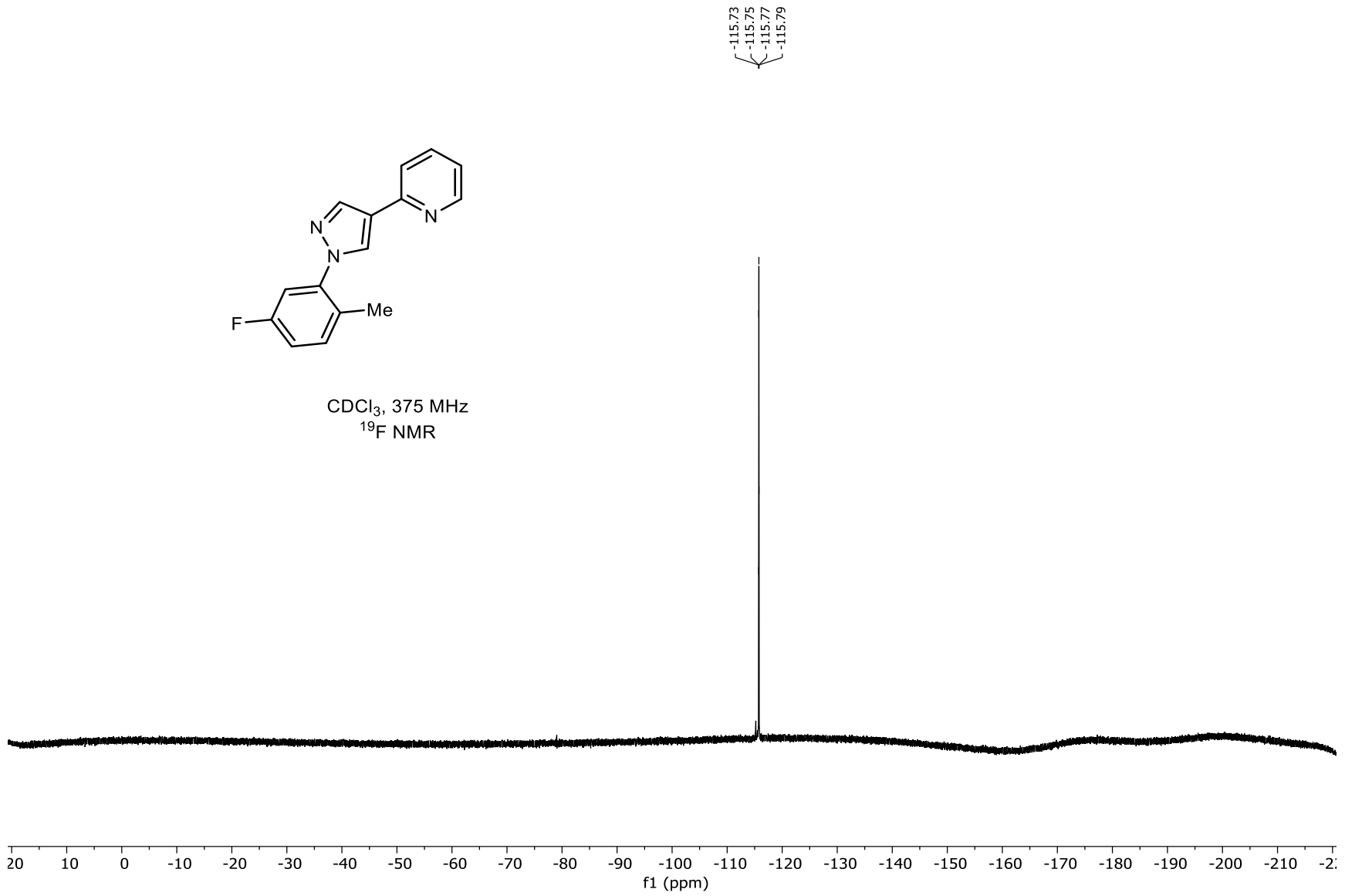

8.12
8.11
7.73
7.72
7.71
7.70
7.69
7.68
7.54
7.52
7.51
7.51
7.50
7.49
7.48
7.48
7.46
7.32
7.32
7.30
7.30
7.30
7.29
7.28
7.26 CDCl3
7.21
7.21
7.19
7.19
7.17
7.17
7.01
6.99
6.97
5.80
5.80
1.48
F
O
S
O
H
N
F
F
N
S
tBu
O
N
CDCl3, 400 MHz
1H NMR
0.89
0.99
1.16
1.11
1.08
2.17
0.87
9.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

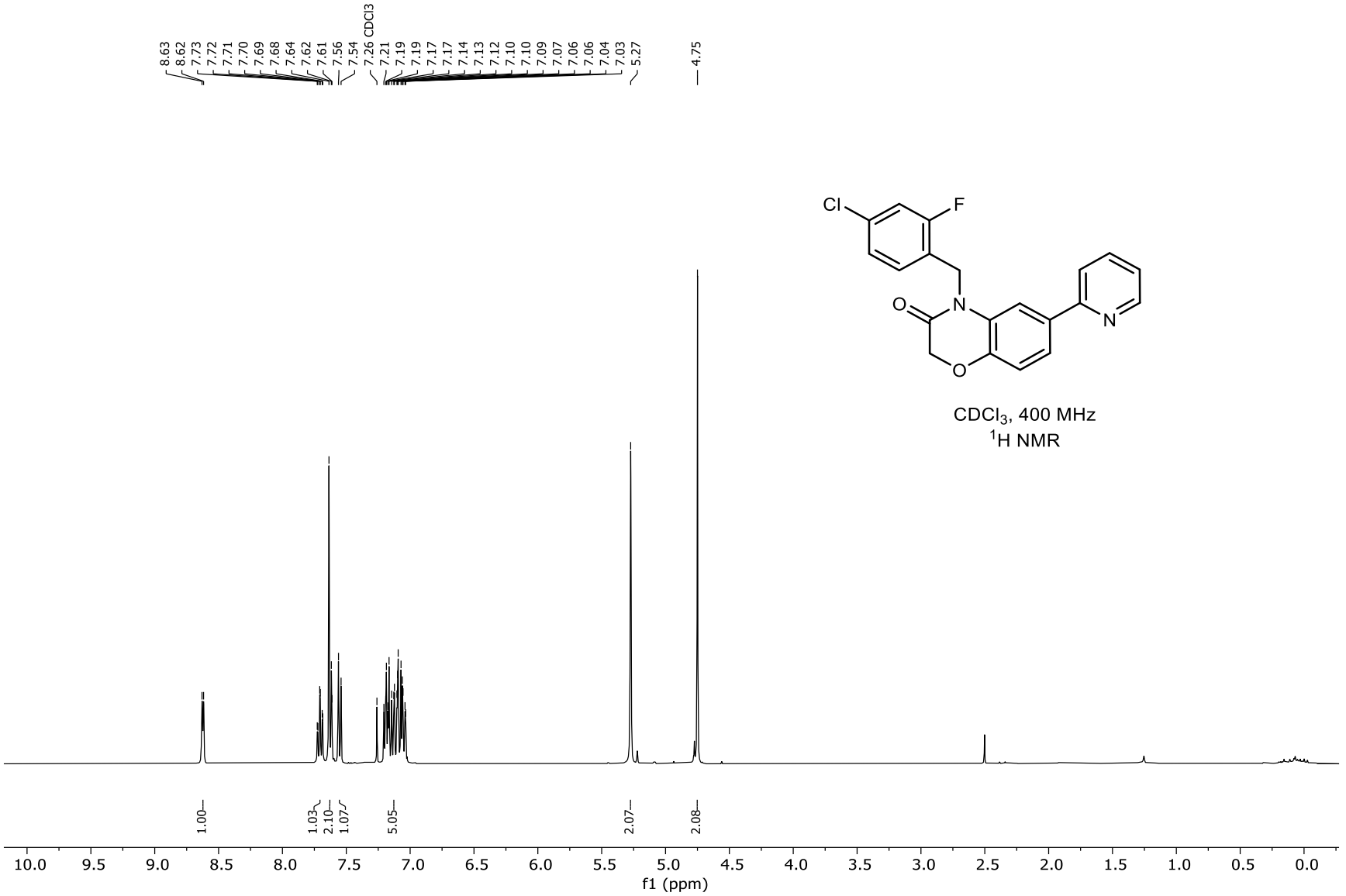

182.82
161.96
161.14
161.10
159.02
158.56
158.52
152.24
150.70
149.77
146.01
135.52
135.41
135.30
128.16
128.14
125.15
125.10
124.82
124.70
123.30
123.16
123.14
120.59
116.94
113.44
113.41
113.21
113.18
100.42
77.16 CDCl3
38.24
30.79
tBu
F
O
H
N
F
N
S
S
O
O
F
O
N
CDCl3, 100 MHz
13C NMR
f1 (ppm)

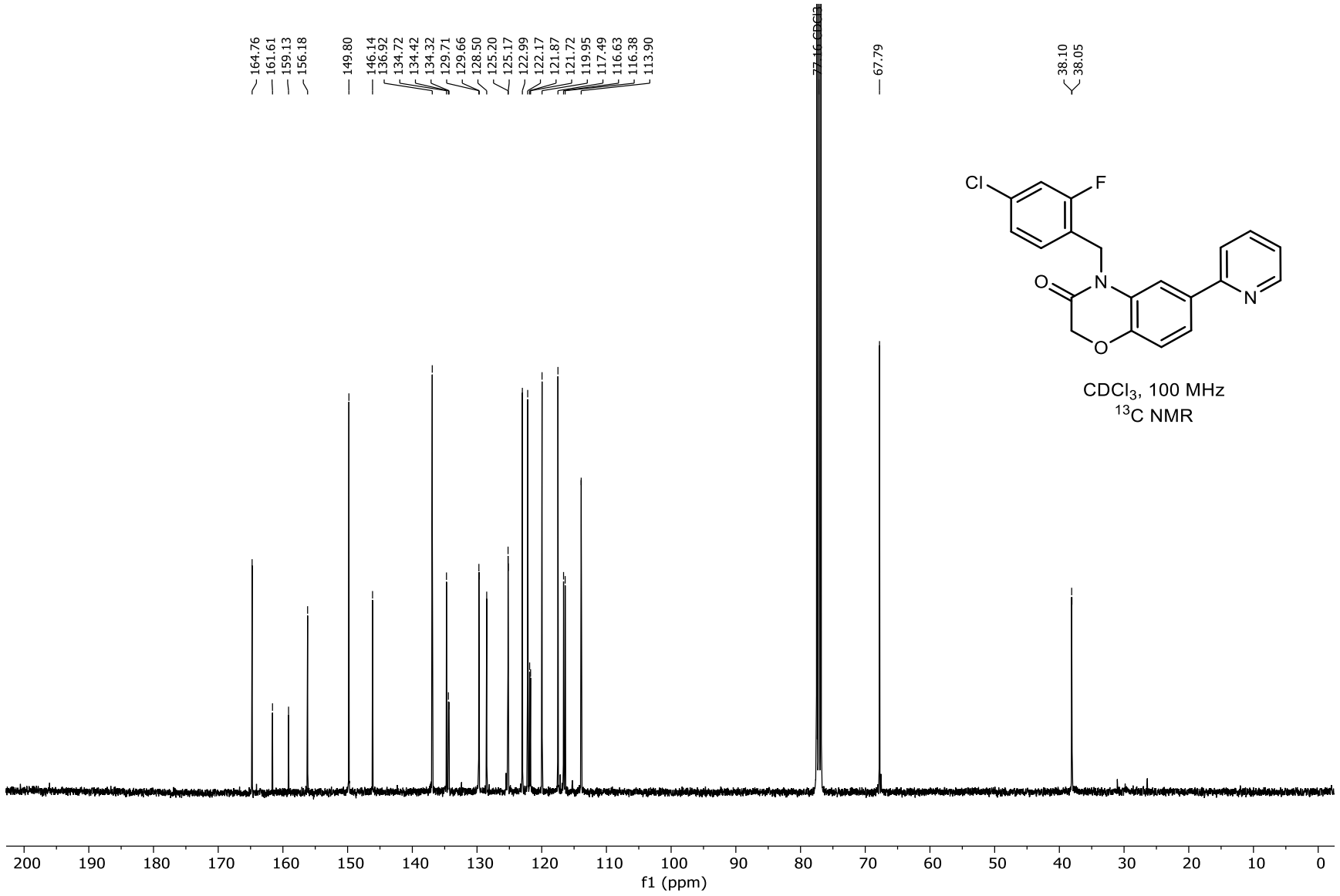

-106.87
-130.10
tBu
F
O
H
N
F
N
S
S
O
F
O
N
CDCl3, 375 MHz
19F NMR
2.17
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

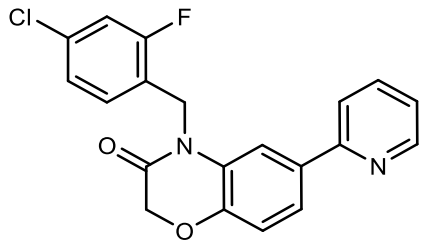

8.60
8.59
8.19
7.73
7.73
7.73
7.71
7.71
7.71
7.70
7.69
7.69
7.55
7.53
7.31
7.30
7.29
7.27
7.26 CDCl3
7.17
7.15
7.14
7.08
7.08
7.08
7.06
7.06
7.05
7.04
7.04
7.03
2.30
N
N
N
F
Me
CDCl3, 400 MHz
1H NMR
1.00
2.03
1.06
1.04
1.06
2.03
1.07
3.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


162.21
159.76
151.61
149.87
140.45
140.35
138.93
136.81
132.62
132.54
129.19
129.01
128.97
124.65
121.61
119.87
115.64
115.44
113.41
113.17
77.16 CDCl3
17.83
N
N
N
F
Me
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

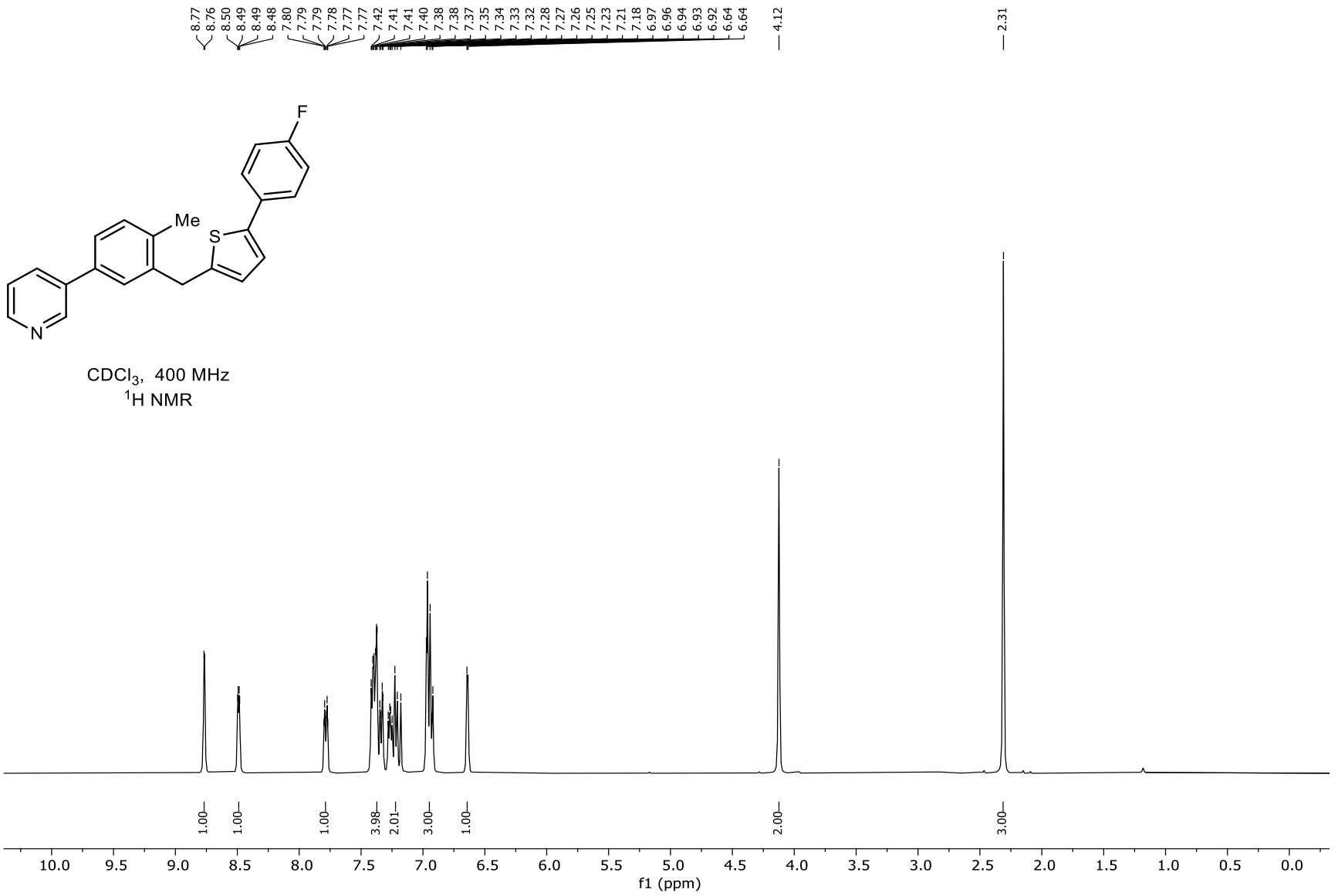

-115.73
-115.75
-115.77
-115.79
N
N
N
F
Me
CDCl3, 375 MHz
19F NMR
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

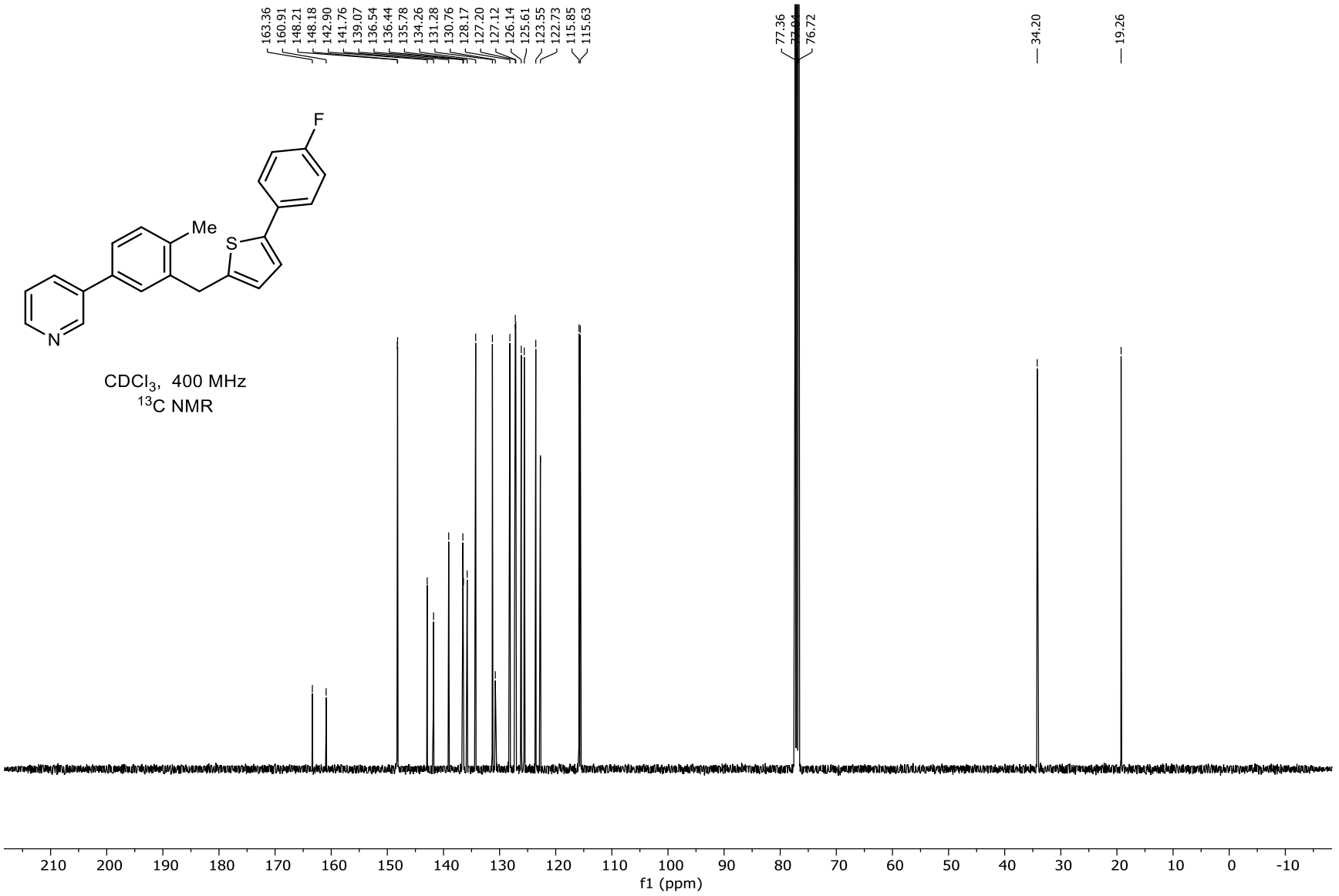

8.63
8.62
7.73
7.72
7.71
7.70
7.69
7.68
7.64
7.62
7.61
7.56
7.54
7.26 CDCl3
7.21
7.19
7.19
7.17
7.17
7.14
7.13
7.12
7.10
7.10
7.09
7.07
7.06
7.06
7.04
7.03
5.27
4.75
Cl
F
O
N
N
O
CDCl3, 400 MHz
1H NMR
1.00
1.03
2.10
1.07
5.05
2.07
2.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

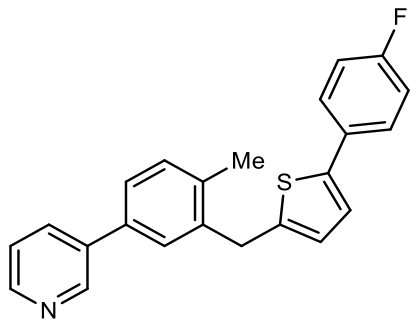

164.76
161.61
159.13
156.18
149.80
146.14
136.92
134.72
134.42
134.32
129.71
129.66
128.50
125.20
125.17
122.99
122.17
121.87
121.72
119.95
117.49
116.63
116.38
113.90
77.16 CDCl3
67.79
38.10
38.05
Cl
F
O
N
N
O
CDCl3, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



$CDCl_3$, 375 MHz
^{19}F NMR

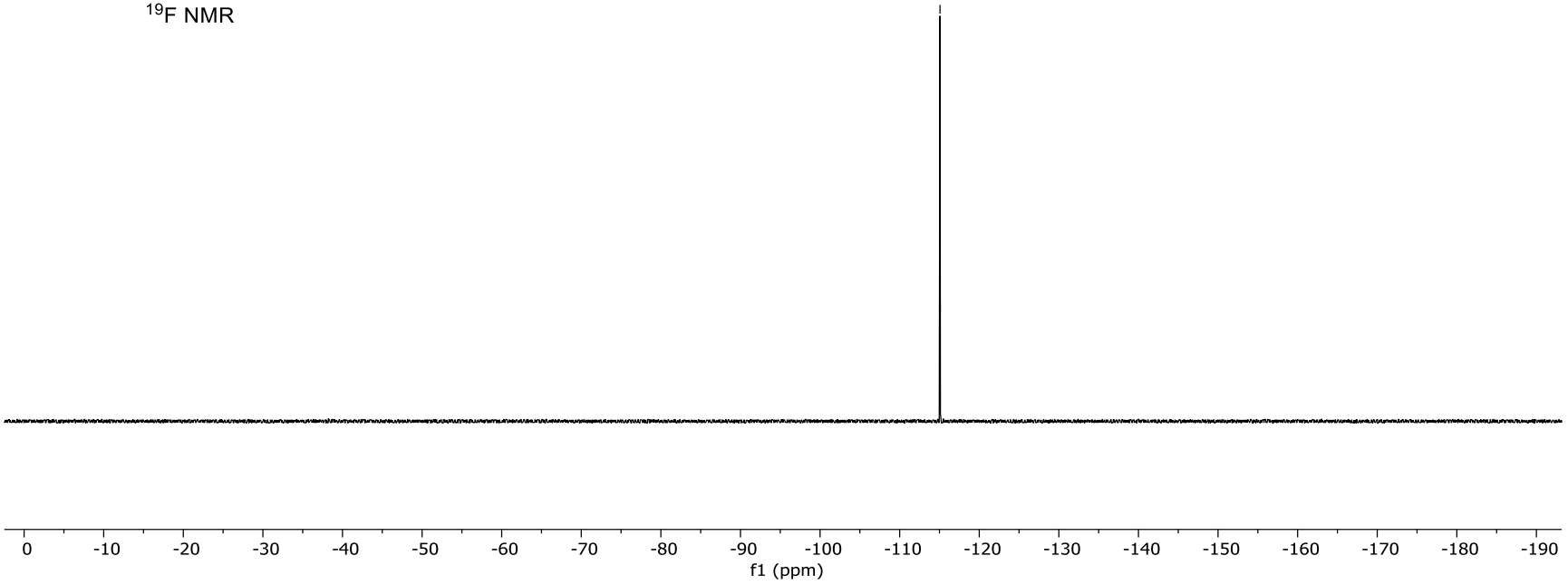

8.77
8.76
8.50
8.49
8.49
8.48
7.80
7.79
7.79
7.78
7.77
7.77
7.42
7.41
7.41
7.40
7.38
7.38
7.37
7.35
7.34
7.33
7.32
7.28
7.27
7.26
7.25
7.23
7.21
7.18
6.97
6.96
6.94
6.93
6.92
6.64
6.64
4.12
2.31
F
Me
S
N
CDCl3, 400 MHz
1H NMR
1.00
1.00
1.00
3.98
2.01
3.00
1.00
2.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

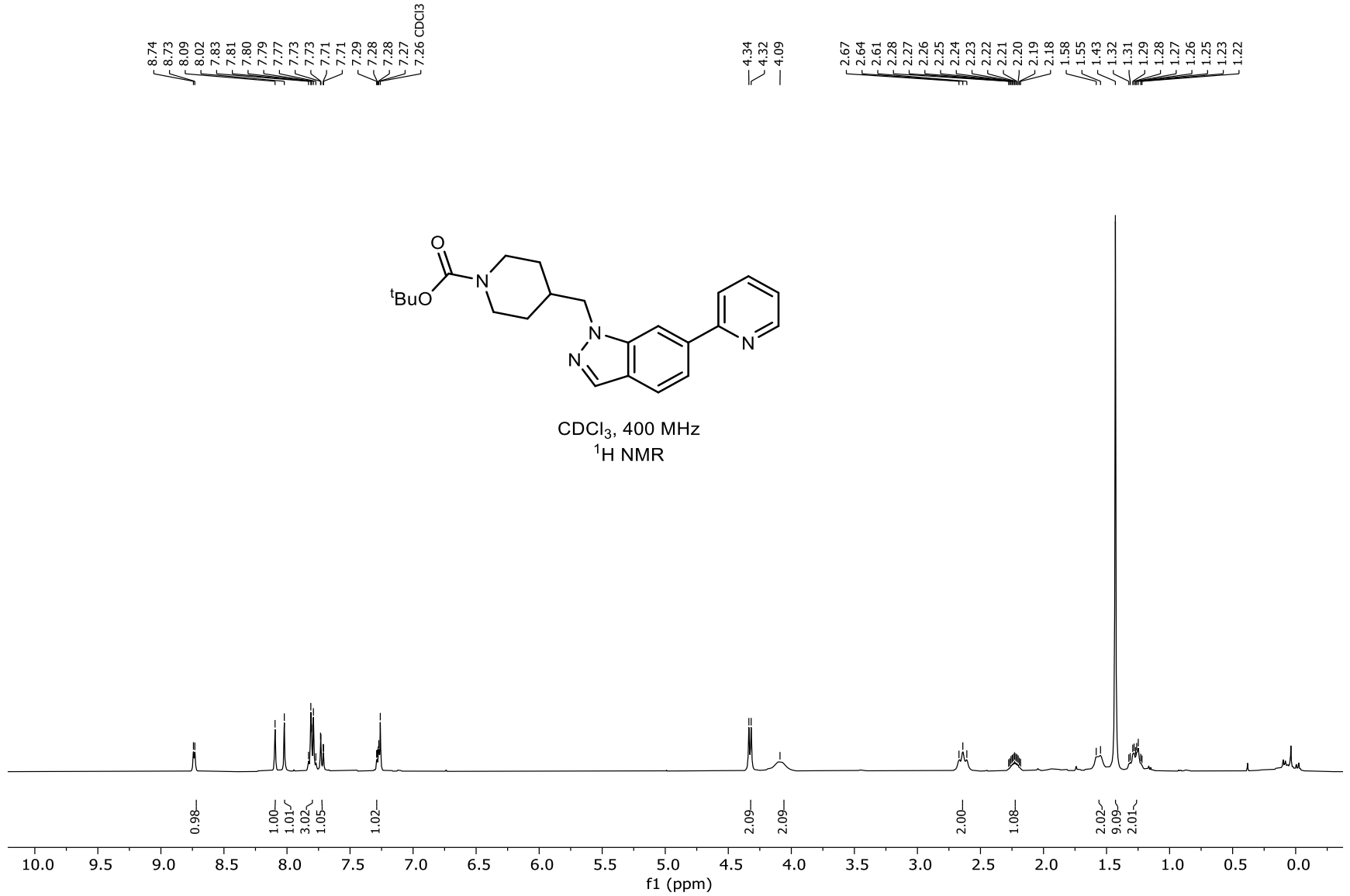

163.36
160.91
148.21
148.18
142.90
141.76
139.07
136.54
136.44
135.78
134.26
131.28
130.76
128.17
127.20
127.12
126.14
125.61
123.55
122.73
115.85
115.63
77.36
77.04
76.72
34.20
19.26
F
Me
S
N
CDCl3, 400 MHz
13C NMR
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

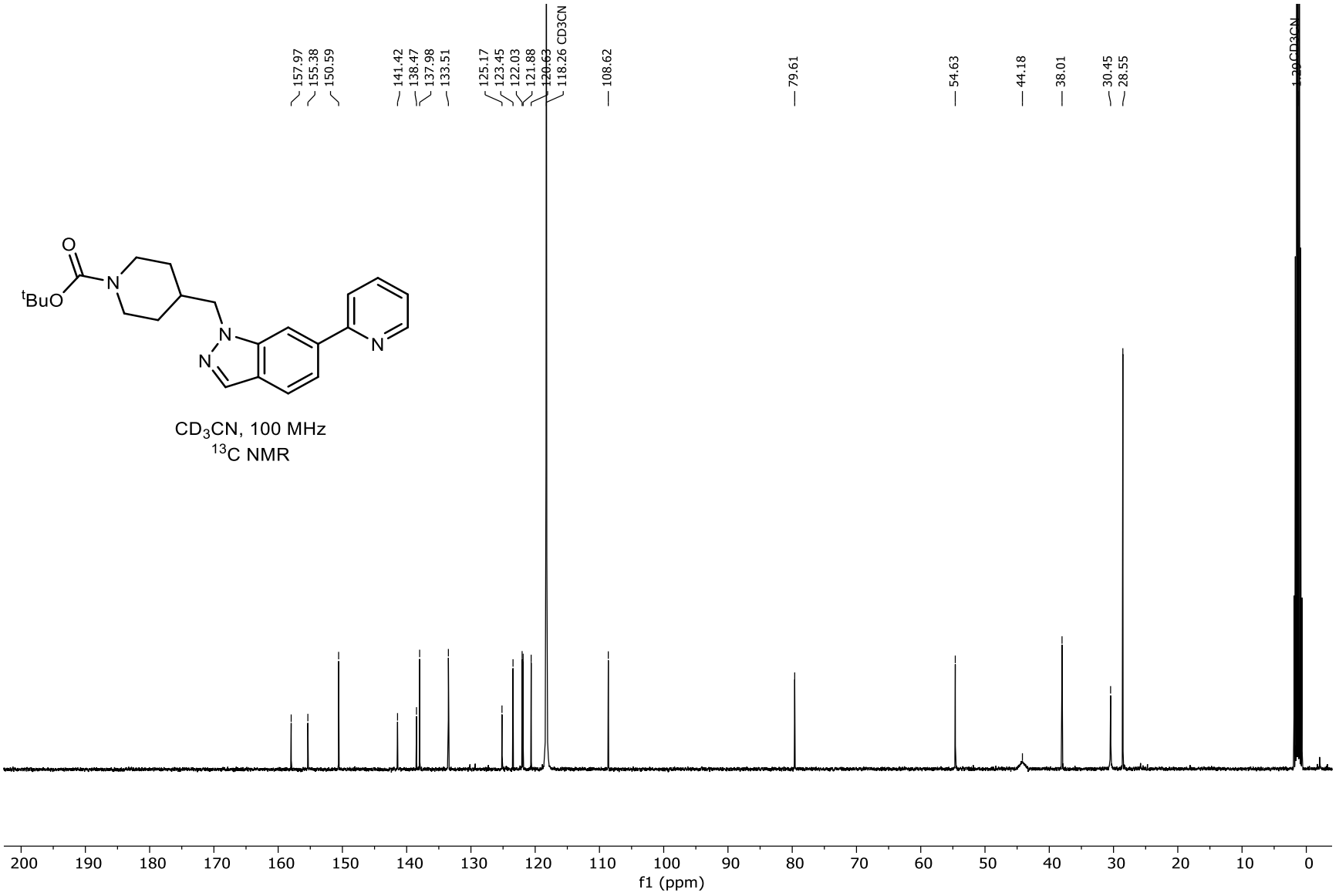


$CDCl_3$, 400 MHz
^{19}F NMR

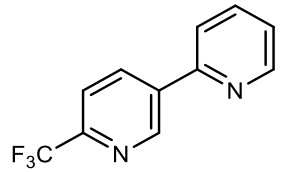
-115.03
-115.05
-115.06
-115.06
-115.07
-115.08
-115.08
-115.09
-115.11




8.74
8.73
8.09
8.02
7.83
7.81
7.80
7.79
7.77
7.73
7.73
7.71
7.71
7.29
7.28
7.28
7.27
7.26 CDCl3
4.34
4.32
4.09
2.67
2.64
2.61
2.28
2.27
2.26
2.25
2.24
2.23
2.22
2.21
2.20
2.19
2.18
1.58
1.55
1.43
1.32
1.31
1.29
1.28
1.27
1.26
1.25
1.23
1.22
O
tBuO
N
N
N
N
CDCl3, 400 MHz
1H NMR
0.98
1.00
1.01
3.02
1.05
1.02
2.09
2.09
2.00
1.08
2.02
9.09
2.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

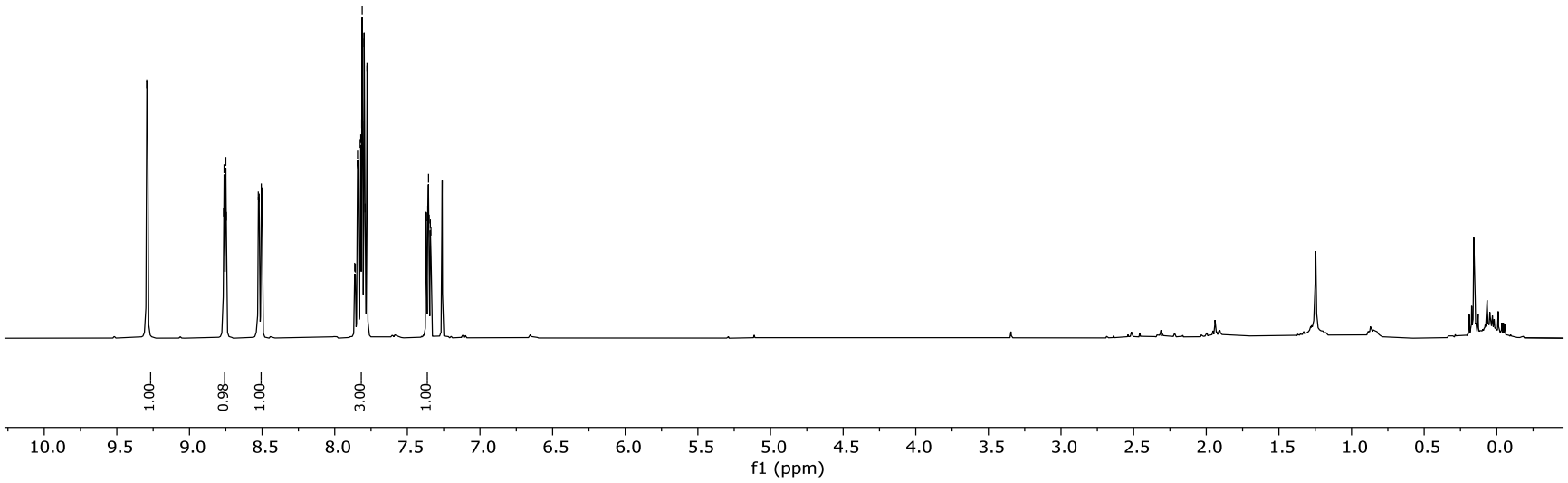

157.97
155.38
150.59
141.42
138.47
137.98
133.51
125.17
123.45
122.03
121.88
120.63
118.26 CD3CN
108.62
79.61
54.63
44.18
38.01
30.45
28.55
1.39CD3CN
O
tBuO
N
N
N
N
CD3CN, 100 MHz
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

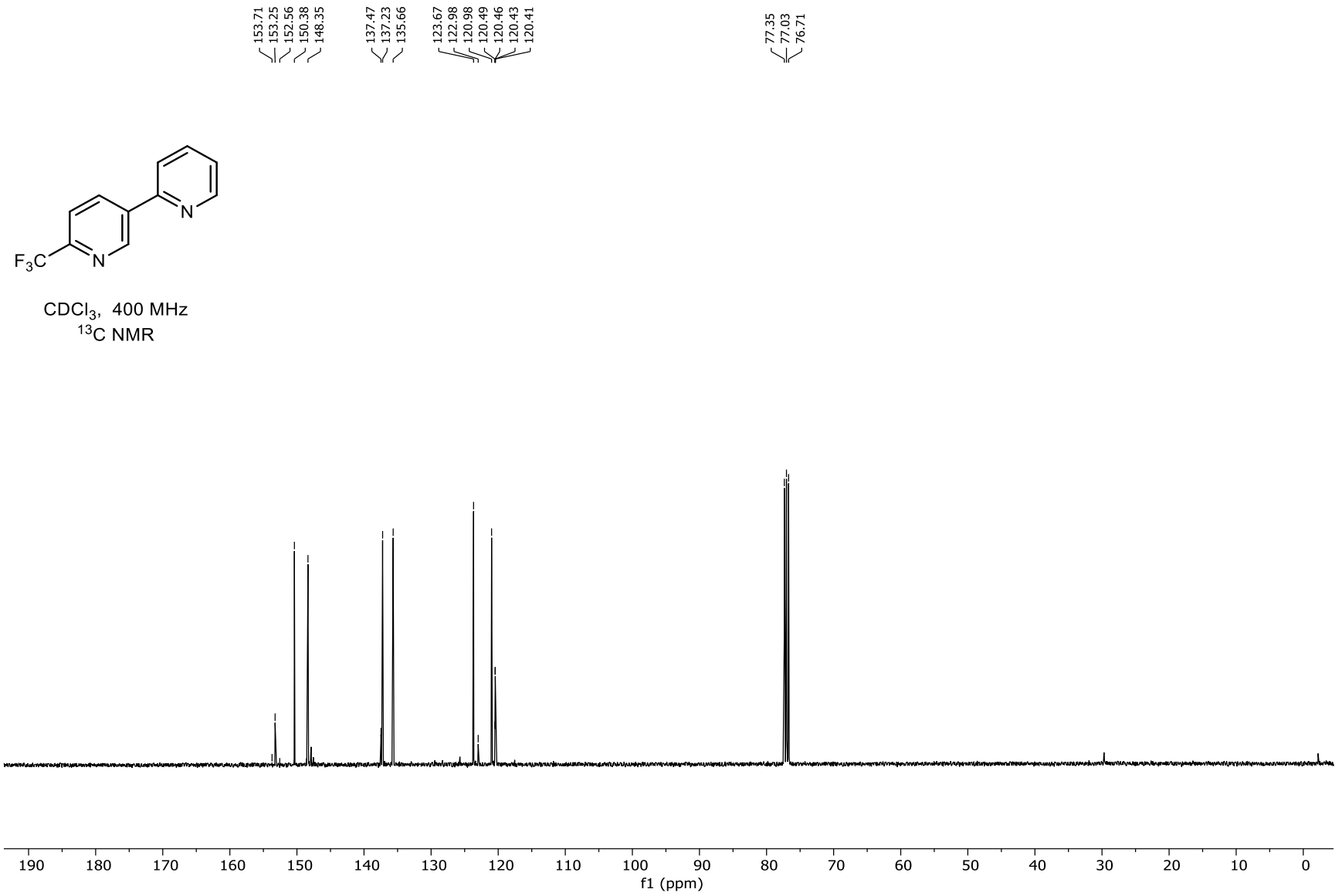




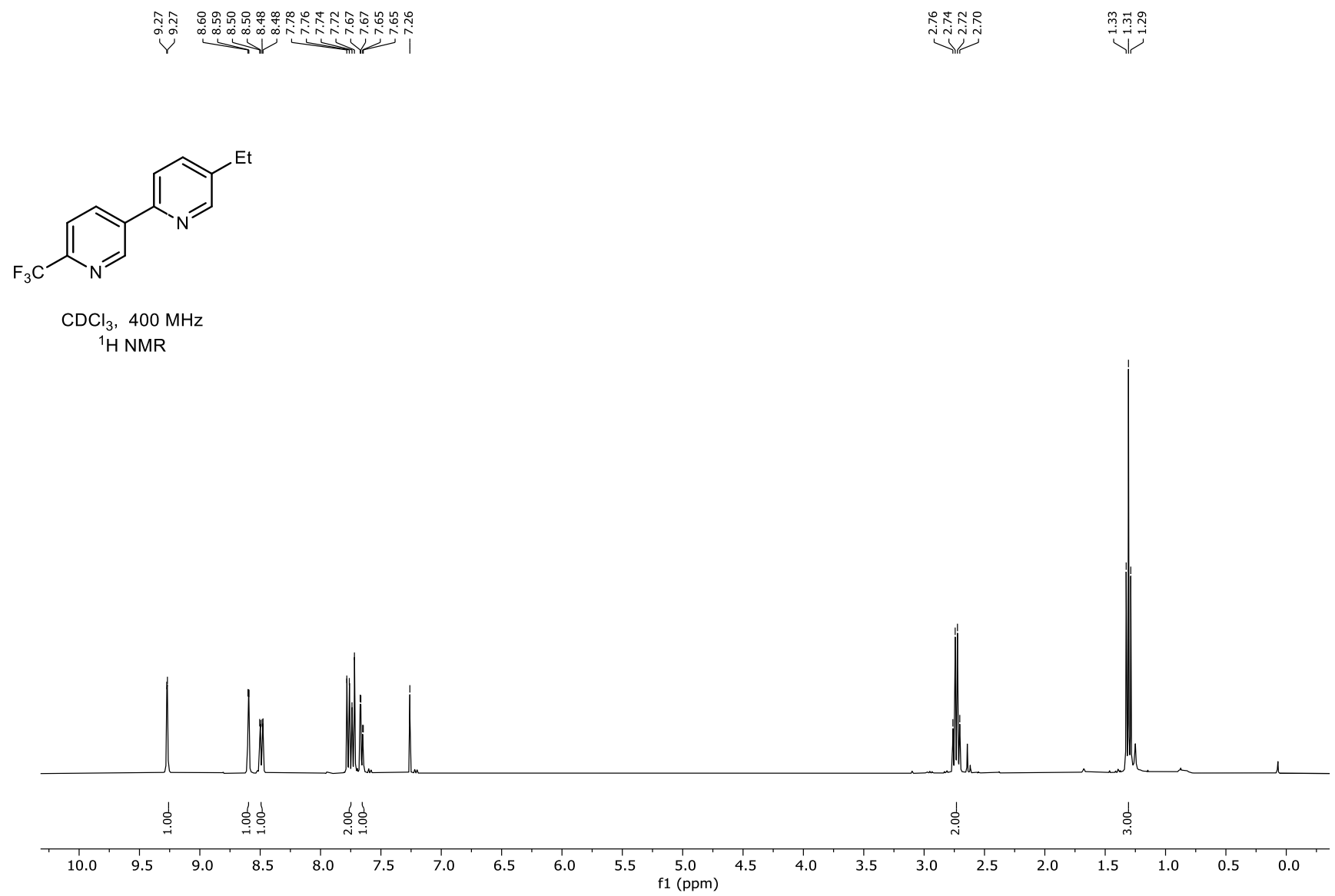
$CDCl_3$, 400 MHz
^1H NMR

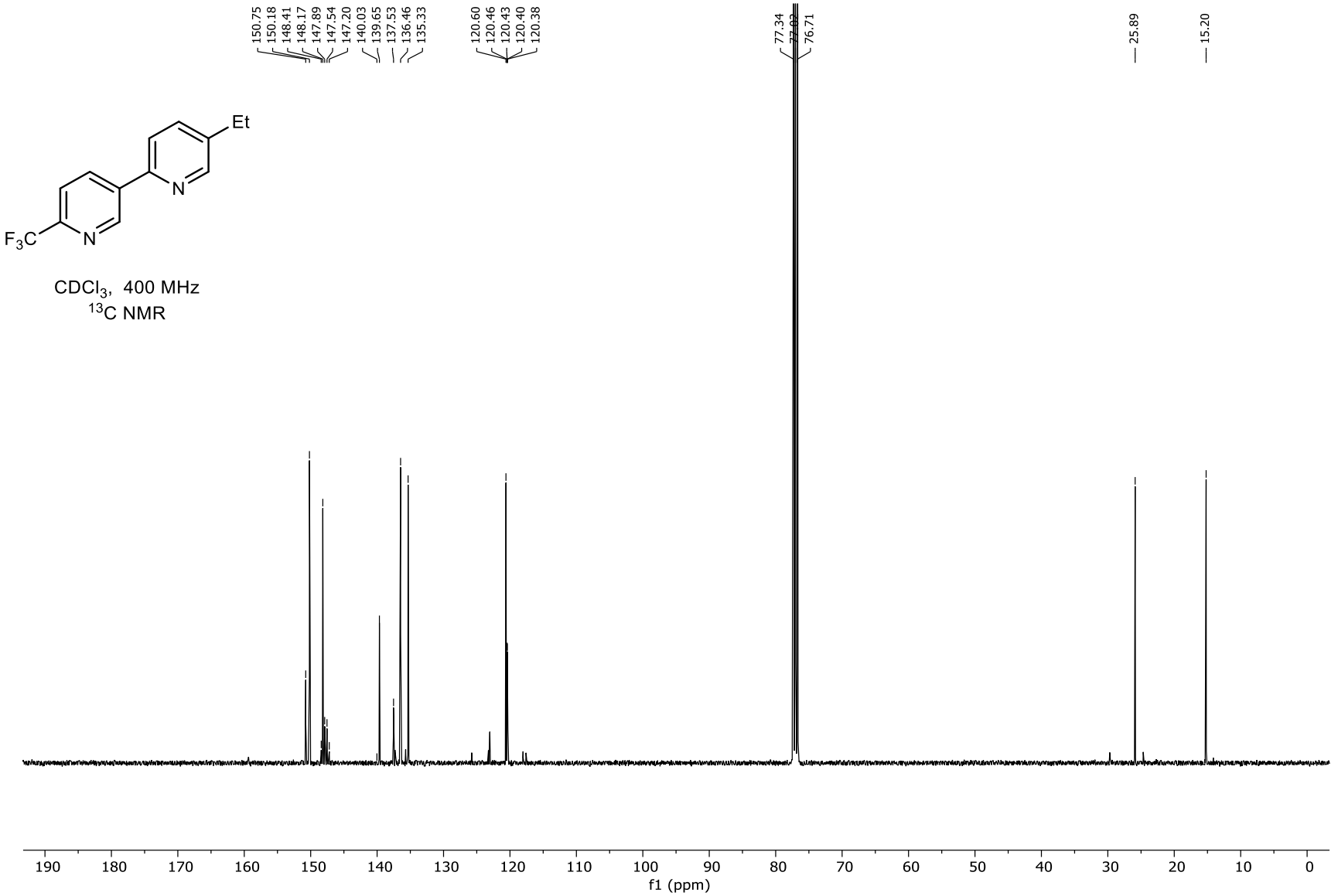
500

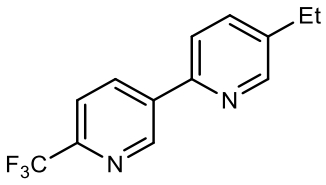



153.71
153.25
152.56
150.38
148.35
137.47
137.23
135.66
123.67
122.98
120.98
120.49
120.46
120.43
120.41
77.35
77.03
76.71
N
N
F3C
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

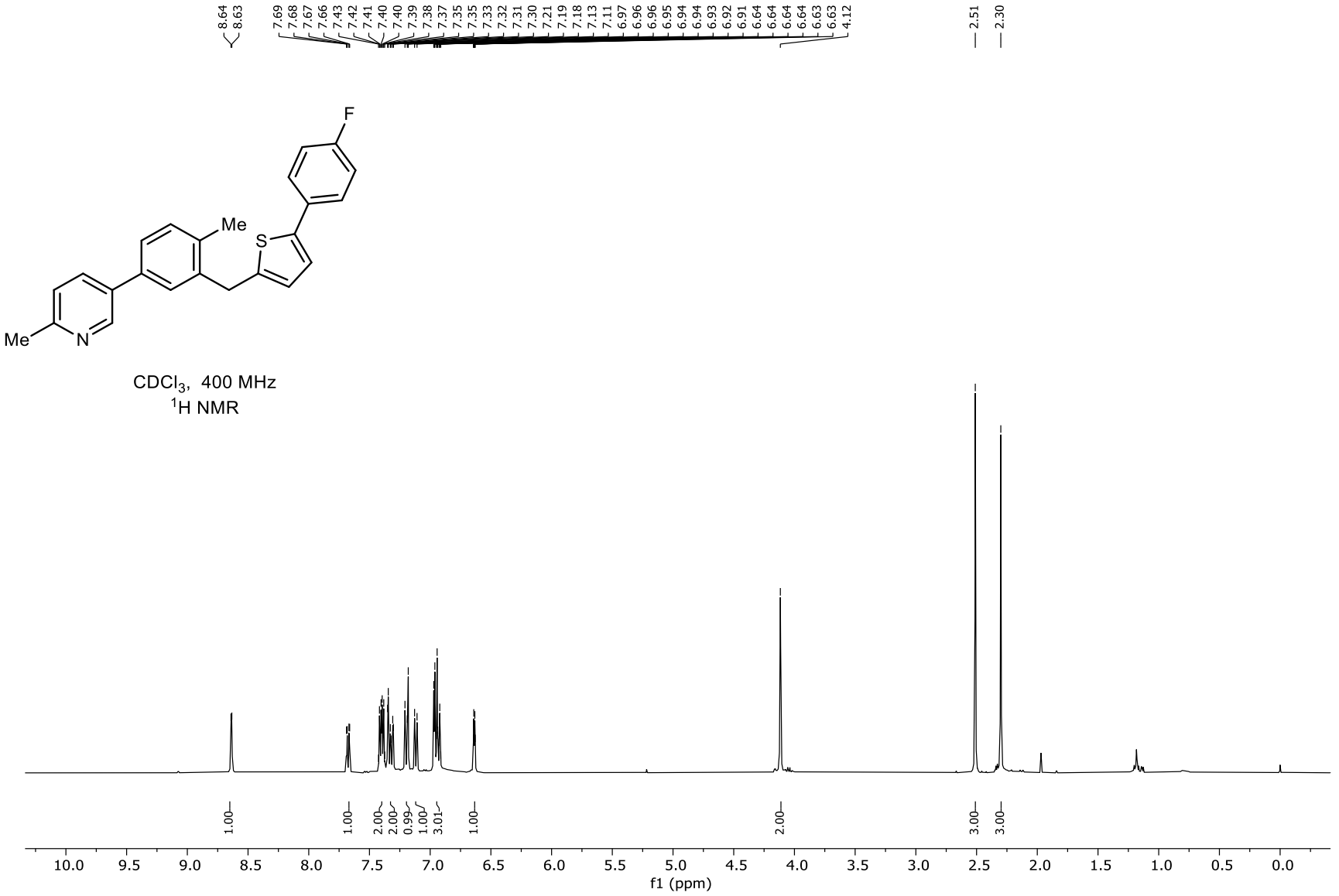
501

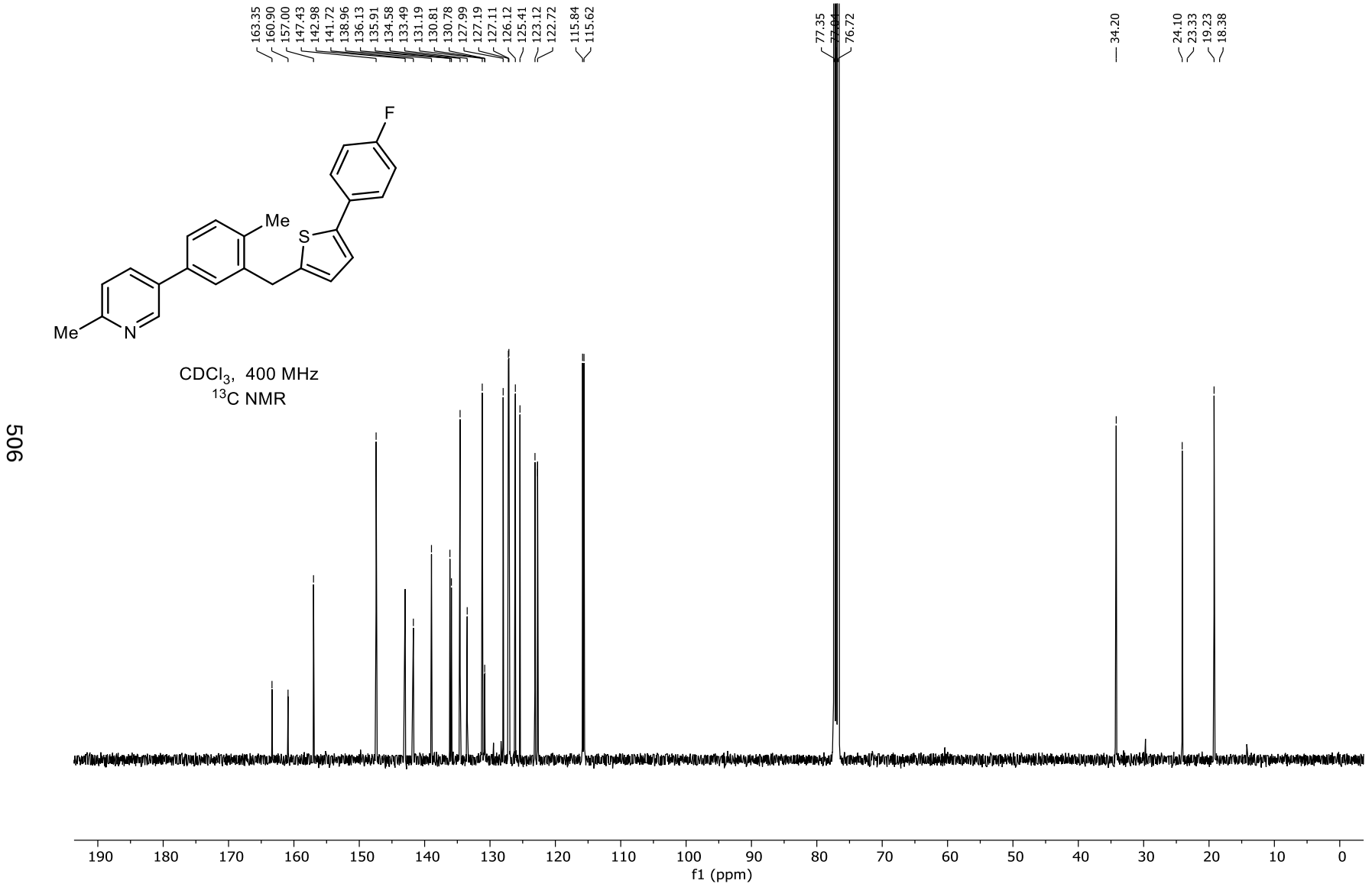

9.27
9.27
8.60
8.59
8.50
8.50
8.48
8.48
7.78
7.76
7.74
7.72
7.67
7.67
7.65
7.65
7.26
2.76
2.74
2.72
2.70
1.33
1.31
1.29
Et
N
N
F3C
CDCl3, 400 MHz
1H NMR
1.00
1.00
1.00
2.00
1.00
2.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

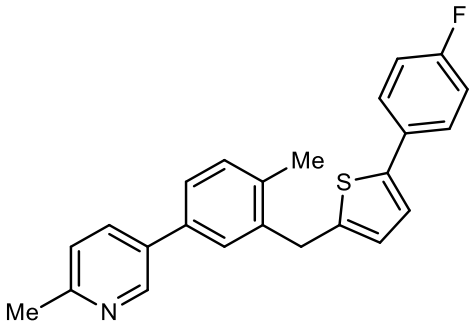

150.75
150.18
148.41
148.17
147.89
147.54
147.20
140.03
139.65
137.53
136.46
135.33
120.60
120.46
120.43
120.40
120.38
77.34
77.02
76.71
25.89
15.20
Et
N
F3C
N
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



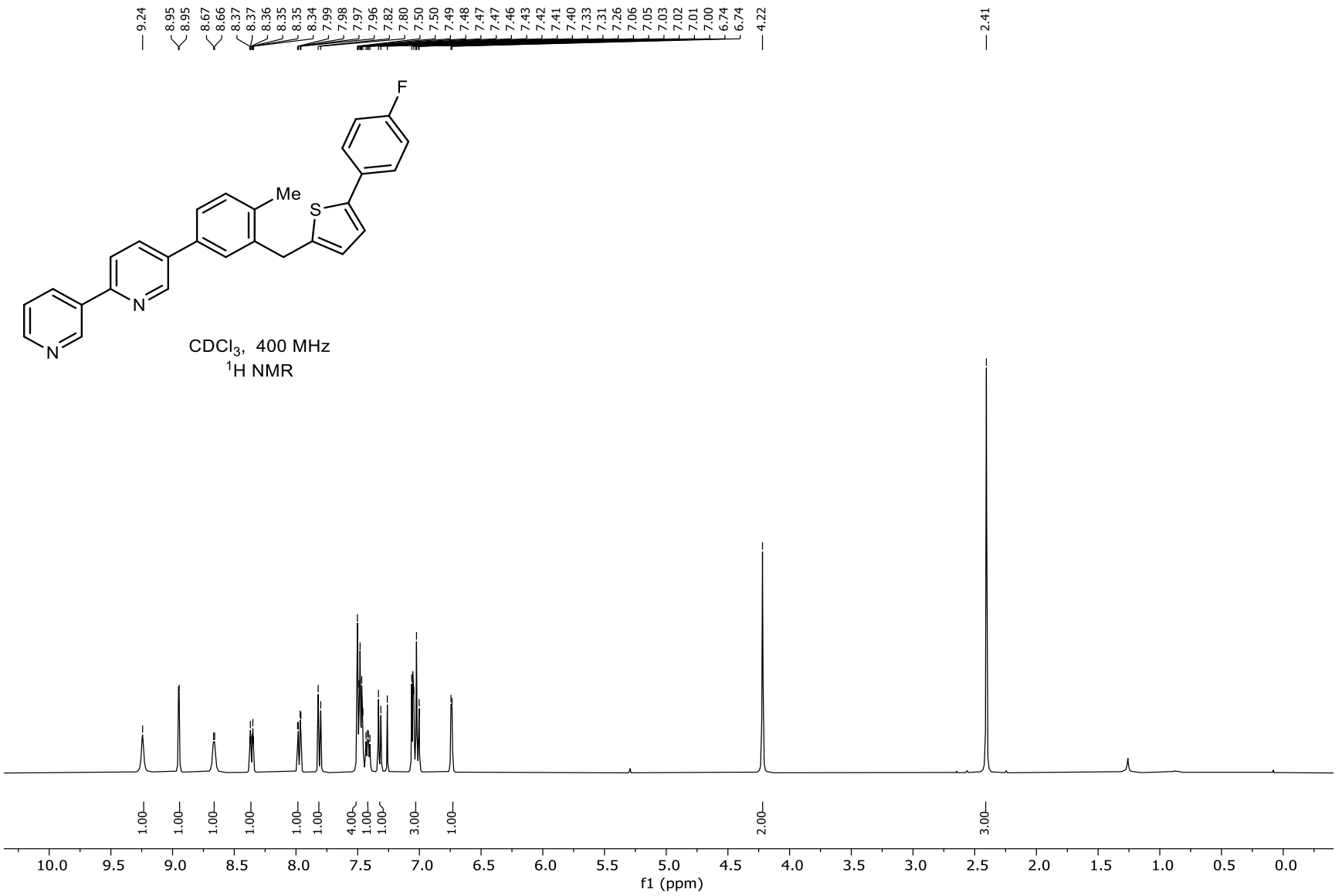
$CDCl_3$, 400 MHz
^{19}F NMR

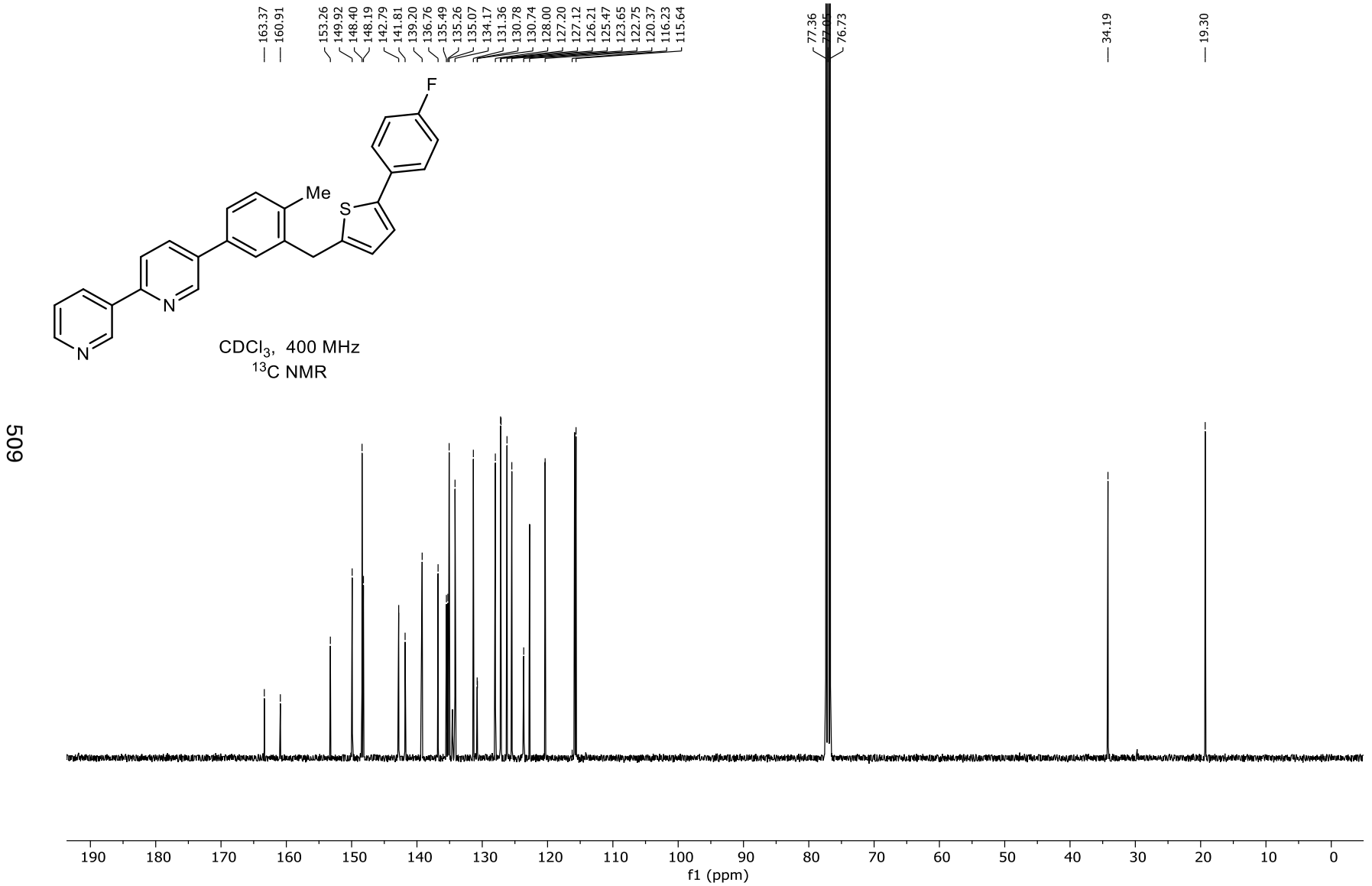

8.64
8.63
7.69
7.68
7.67
7.66
7.43
7.42
7.41
7.40
7.40
7.39
7.38
7.37
7.35
7.35
7.33
7.32
7.31
7.30
7.21
7.19
7.18
7.13
7.11
6.97
6.96
6.96
6.95
6.94
6.94
6.93
6.92
6.91
6.64
6.64
6.64
6.64
6.63
6.63
4.12
2.51
2.30
F
Me
S
Me
N
CDCl3, 400 MHz
1H NMR
1.00
1.00
2.00
2.00
0.99
1.00
3.01
1.00
2.00
3.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


163.35
160.90
157.00
147.43
142.98
141.72
138.96
136.13
135.91
134.58
133.49
131.19
130.81
130.78
127.99
127.19
127.11
126.12
125.41
123.12
122.72
115.84
115.62
77.35
77.04
76.72
34.20
24.10
23.33
19.23
18.38
F
Me
S
Me
N
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

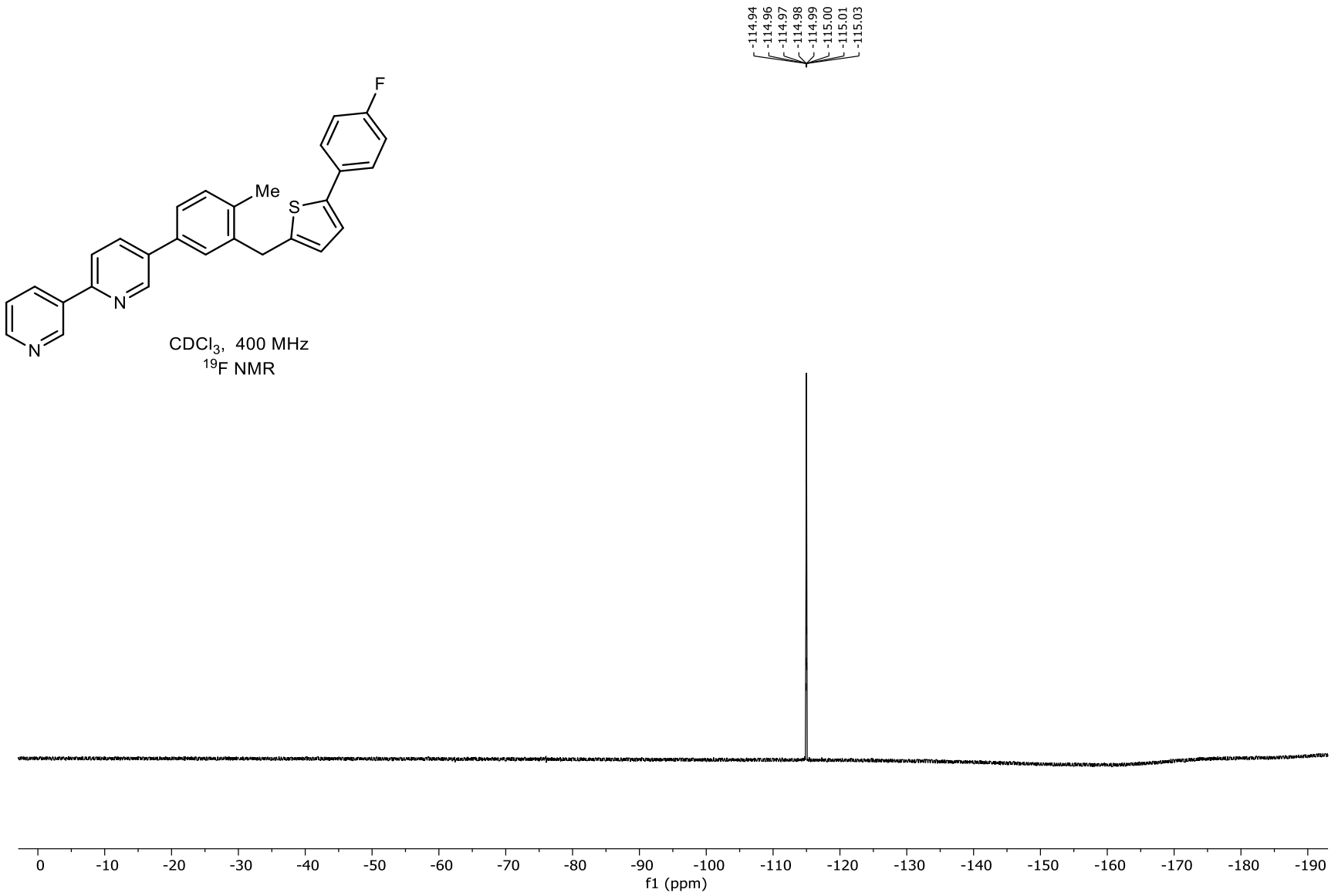


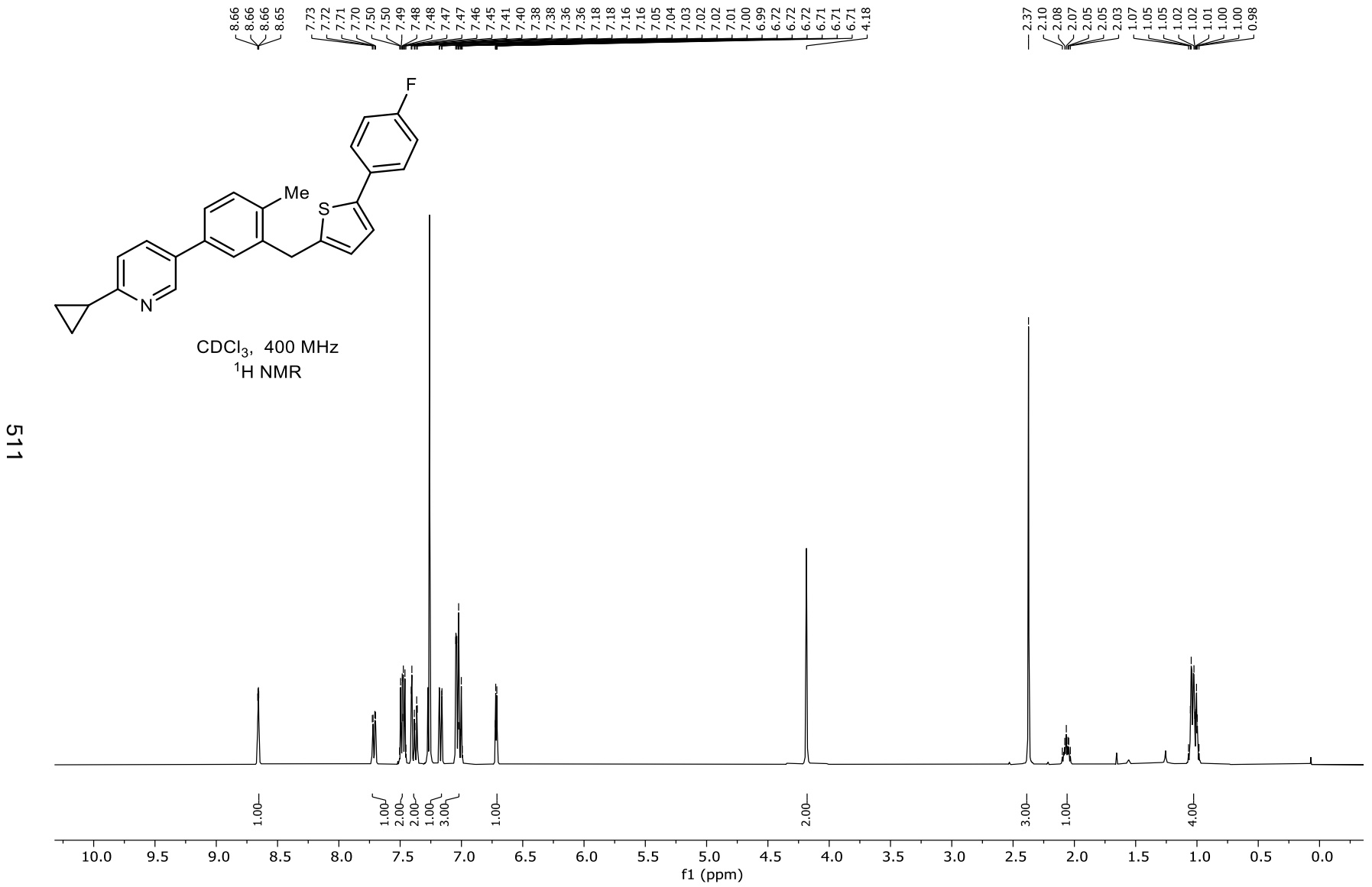
$CDCl_3$, 400 MHz
^{19}F NMR

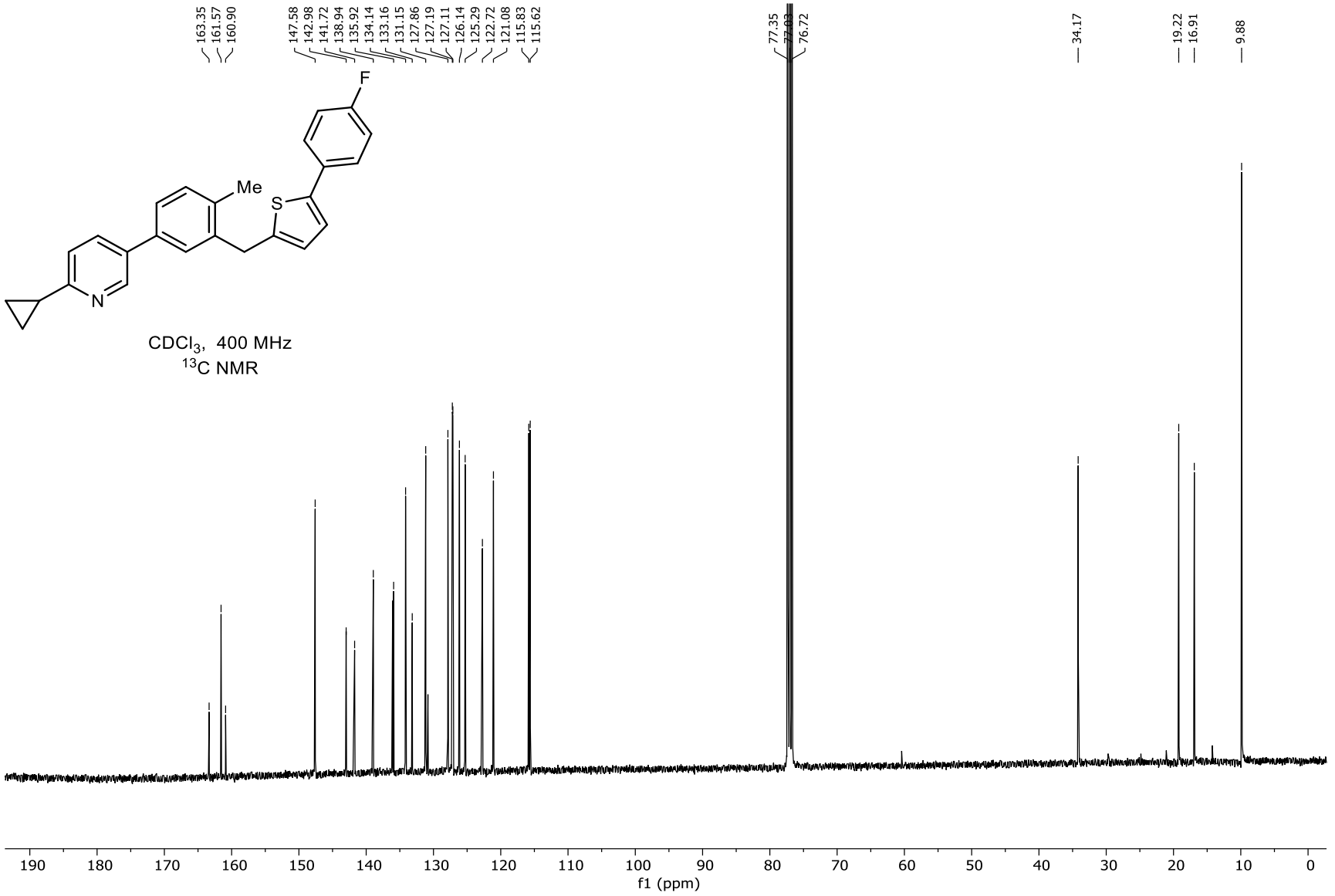

9.24
8.95
8.95
8.67
8.66
8.37
8.37
8.36
8.35
8.35
8.34
7.99
7.98
7.97
7.96
7.82
7.80
7.50
7.50
7.49
7.48
7.47
7.47
7.46
7.43
7.42
7.41
7.40
7.33
7.31
7.26
7.06
7.05
7.03
7.02
7.01
7.00
6.74
6.74
4.22
2.41
F
Me
S
N
N
CDCl3, 400 MHz
1H NMR
1.00
1.00
1.00
1.00
1.00
1.00
4.00
1.00
1.00
3.00
1.00
2.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
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0.5
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f1 (ppm)

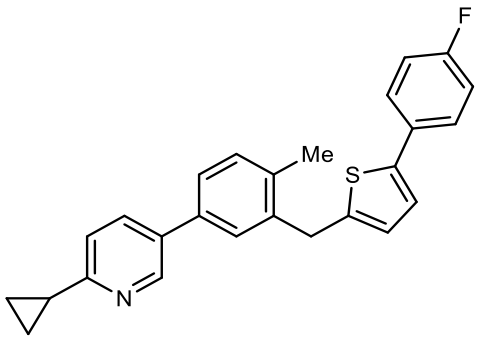

163.37
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153.26
149.92
148.40
148.19
142.79
141.81
139.20
136.76
135.49
135.26
135.07
134.17
131.36
130.78
130.74
128.00
127.20
127.12
126.21
125.47
123.65
122.75
120.37
116.23
115.64
77.36
77.05
76.73
34.19
19.30
F
Me
S
N
N
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

509

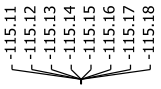

-114.94
-114.96
-114.97
-114.98
-114.99
-115.00
-115.01
-115.03
F
Me
S
N
N
CDCl3, 400 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
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-160
-170
-180
-190
f1 (ppm)

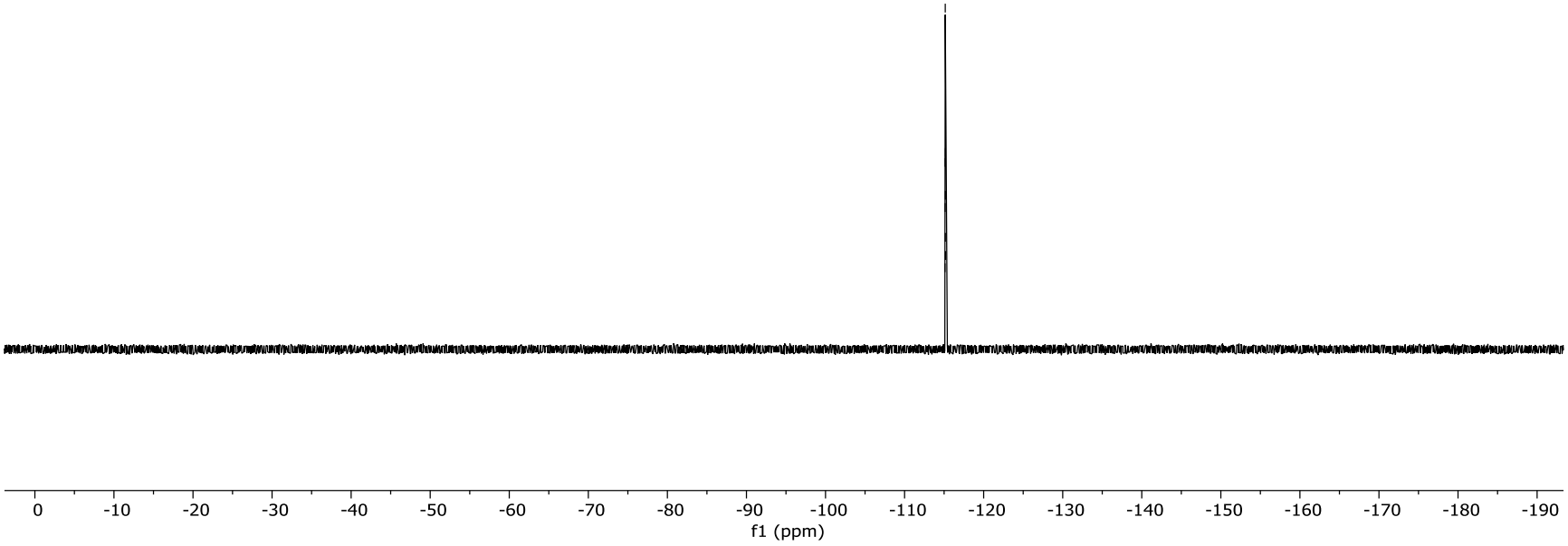

8.66
8.66
8.66
8.65
7.73
7.72
7.71
7.70
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7.48
7.47
7.47
7.46
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7.05
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7.01
7.00
6.99
6.72
6.72
6.72
6.71
6.71
6.71
4.18
2.37
2.10
2.08
2.07
2.05
2.05
2.03
1.07
1.05
1.05
1.02
1.02
1.01
1.00
1.00
0.98
F
Me
S
N
CDCl3, 400 MHz
1H NMR
1.00
1.00
2.00
2.00
1.00
3.00
1.00
2.00
3.00
1.00
4.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

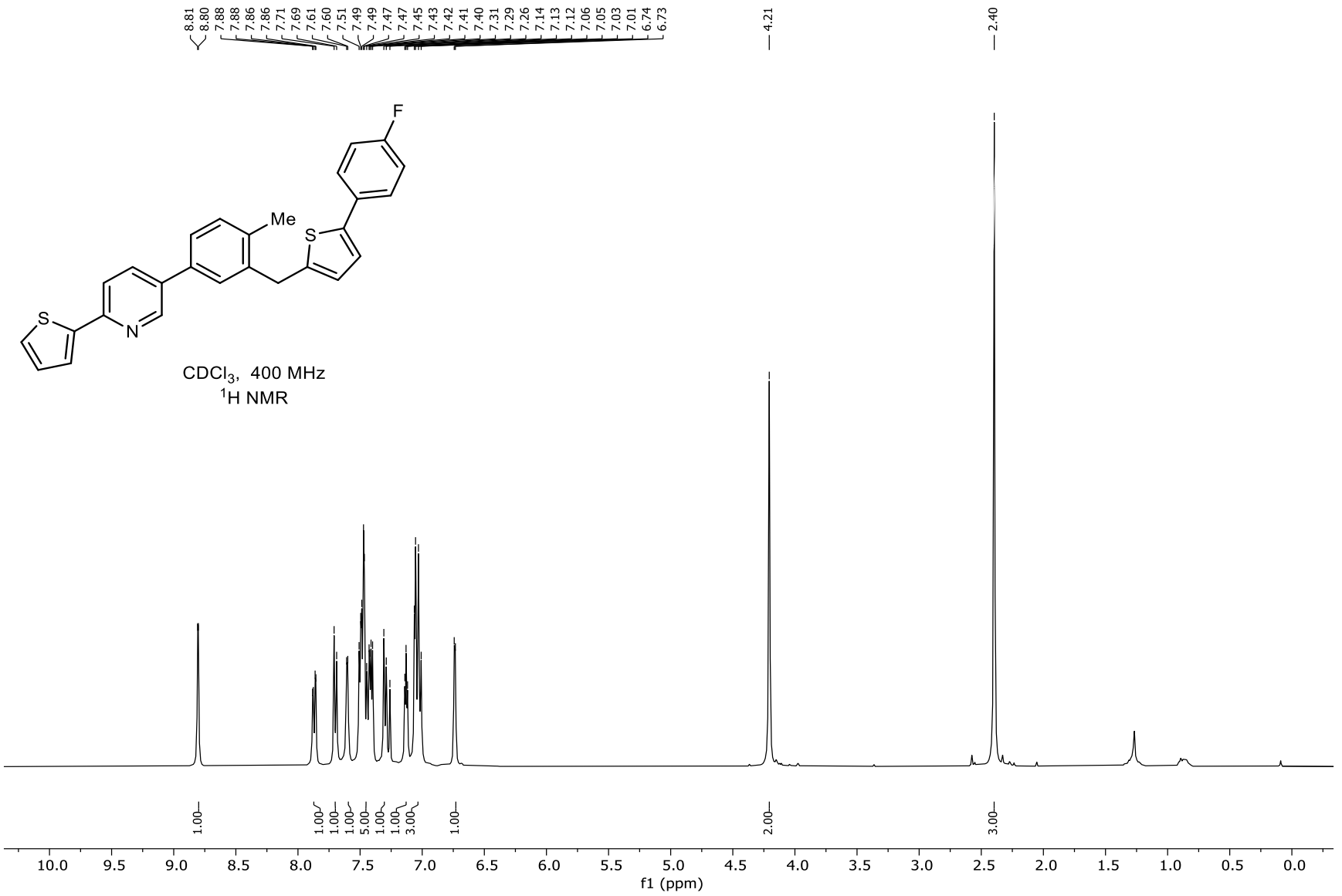

163.35
161.57
160.90
147.58
142.98
141.72
138.94
135.92
134.14
133.16
131.15
127.86
127.19
127.11
126.14
125.29
122.72
121.08
115.83
115.62
77.35
77.03
76.72
34.17
19.22
16.91
9.88
F
Me
S
N
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

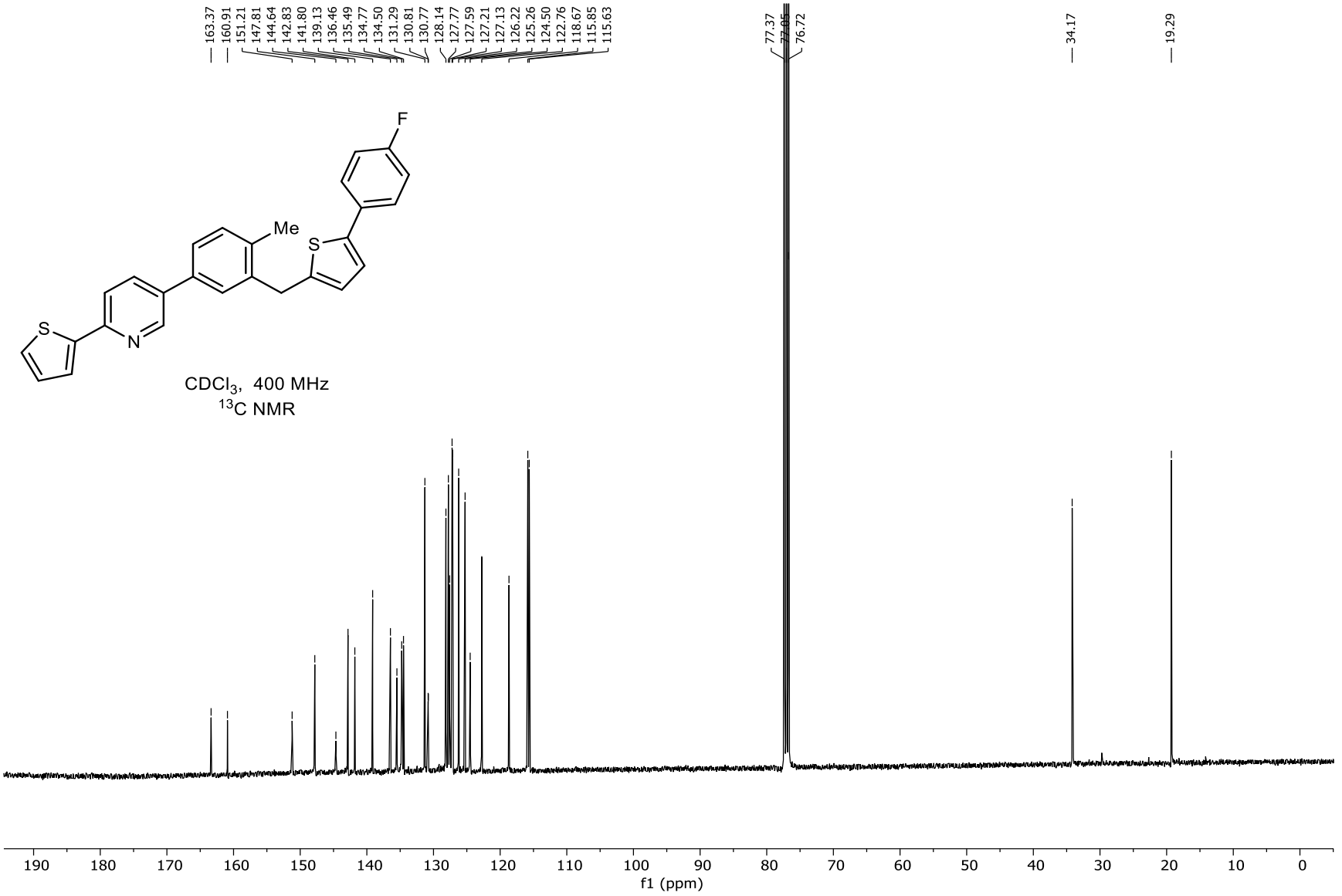


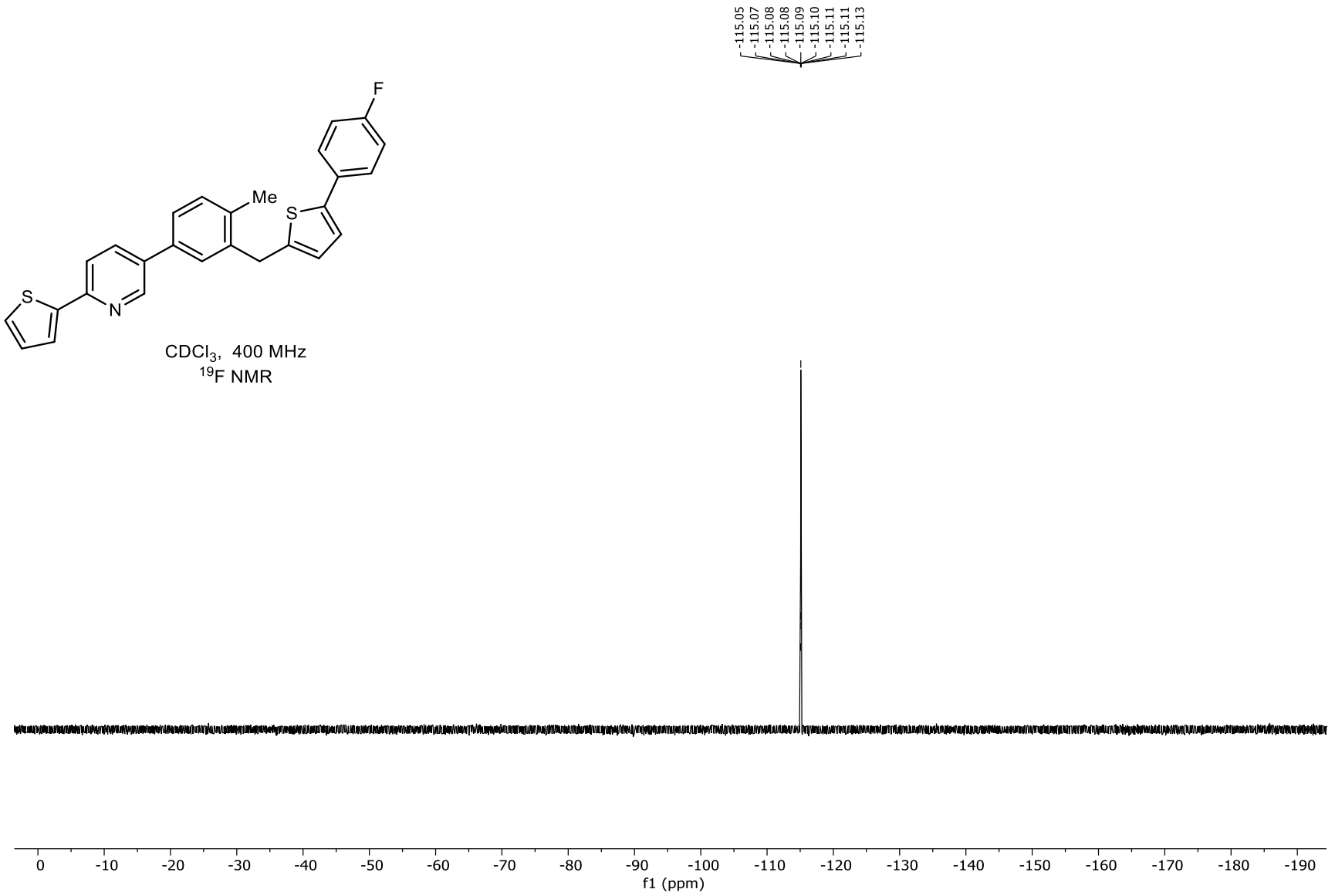
$CDCl_3$, 400 MHz
^{19}F NMR






8.81
8.80
7.88
7.88
7.86
7.86
7.71
7.69
7.61
7.60
7.51
7.49
7.49
7.47
7.47
7.45
7.43
7.42
7.41
7.40
7.31
7.29
7.26
7.14
7.13
7.12
7.06
7.05
7.03
7.01
6.74
6.73
4.21
2.40
F
Me
S
S
N
CDCl3, 400 MHz
1H NMR
1.00
1.00
1.00
5.00
1.00
3.00
1.00
2.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

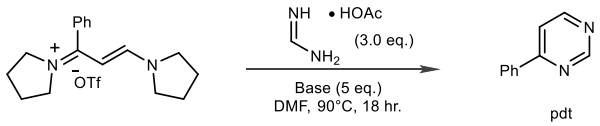

163.37
160.91
151.21
147.81
144.64
142.83
141.80
139.13
136.46
135.49
134.77
134.50
131.29
130.81
130.77
128.14
127.77
127.59
127.21
127.13
126.22
125.26
124.50
122.76
118.67
115.85
115.63
77.37
77.05
76.72
34.17
19.29
F
Me
S
S
N
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-115.05
-115.07
-115.08
-115.08
-115.09
-115.10
-115.11
-115.11
-115.13
F
Me
S
S
N
CDCl3, 400 MHz
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

APPENDIX THREE

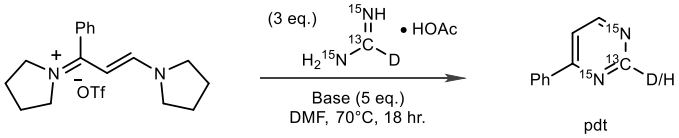
PYRIMIDINE STABLE ISOTOPE INCORPORATION: EXPERIMENTAL

A 1.9 Optimization and Isotopic Enrichment Calculation Guidelines for Isotopic Enrichment of Pyrimidines



entry	base	pdt yield
1	NaOEt	74
2	Cs_2CO_3	74
3	Et_3N	83
4	DBU	85
5	DMAP	84
6	collidine	42

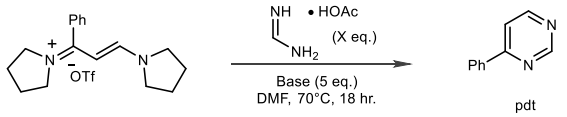
Scheme A1: Optimization of base for cyclization with formamidine acetate. Note: Et_3N had variable results and was not always reproducible.



entry	base	pdt yield	% D/H
1	DBU	85	93
2	DMAP	84	99

Scheme A2: Optimization of base for improved C2-D incorporation. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

To summarize Scheme 1 and 2, DMAP was selected as the base for this transformation. DBU performs similarly in a majority of cases, but DBU resulted in losses of deuterium incorporation at the pyrimidine C2-position.



pdt

entry	base	equiv. FA	pdt yield
1	DBU	1	73
2	DBU	2	89
3	DBU	3	91
4	DMAP	2	86

Scheme 3: Reduced equivalents of isotopically-enriched formamidines. Yields determined by ^{1}H NMR using triphenylmethane as an internal standard. Note: Using reduced equivalents of formamidine acetate (FA) can still result in high yields, particularly when using DBU as a base. 3.0 equiv. was selected for consistency.

Isotopic Enrichment Calculation Guidelines

Isotopic enrichment was calculated as a weighted average based on the desired total number of isotopes incorporated into the pyrimidine.

M+2 Pyrimidines: IE = (0.5 x %[M+2]) + %[M+3]

M+3 Pyrimidines: IE = (0.33 x %[M+2]) + (0.66 x %[M+3]) + %[M+4]

M+4 Pyrimidines: IE = (0.25 x %[M+2]) + (0.50 x %[M+3]) + (0.75 x (%[M+4]) + %[M+5]

M+5 Pyrimidines: IE = (0.20 x %[M+2]) + (0.40 x %[M+3]) + (0.60 x (%[M+4]) + (0.80 x %[M+5]) + %[M+6]

Abundance percentages of each isotopolog were calculated using the formulas below. Corrections were made to account for natural abundance of higher-mass isotopes in target molecules, and

corrections were made to correct for off-target deuteration on a small number of products. Note: Corrections which would change the abundance percentage by < 0.1% were considered negligible.

Abbreviations in Abundance Percentage Calculations

0.011 = natural abundance of ^{13}C
0.242 = natural abundance of ^{37}Cl
0.042 = natural abundance of ^{34}S
0.493 = natural abundance of ^{81}Br

N_C = Number of carbons in the molecule
N_{Br} = Number of bromines in the molecule
N_{Cl} = Number of chlorines in the molecule
N_S = Number of sulfurs in the molecule
N_D = Fraction of off-target deuteration determined by ^1H-NMR

A_{M+1} = Observed abundance of parent pyrimidine
A_{M+2} = Observed abundance of pyrimidine + 1 isotope
A_{M+3} = Observed abundance of pyrimidine + 2 isotopes
A_{M+X} = Observed abundance of pyrimidine + (X-1) isotopes

C_{M+1} = Calculated abundance of parent pyrimidine correcting for natural isotope abundance
C_{M+X} = Calculated abundance of pyrimidine + (X-1) isotopes correcting for natural isotope abundance

Cor_{All} = All appropriate corrections for the natural abundance of isotopes.

Corrections in Abundance Percentage Calculations

All molecules:

Cor_{C13} = Correction for natural ^{13}C abundance = (N_C x 0.011)

When molecule contains Cl, Br, or S:

Corrections for Cl, Br, or S
Cor_{Cl37} = Correction for natural ^{37}Cl abundance = (N_{Cl} x 0.319)
Cor_{S34} = Correction for natural ^{34}S abundance = (N_S x 0.042)
Cor_{Br81} = Correction for natural ^{81}Br abundance = (N_{Br} x 0.973)

Corrections for two natural isotope abundances
Cor_{CCl} = Correction for natural ^{13}C and ^{37}Cl abundance = (N_C x 0.011 x N_{Cl} x 0.319)
Cor_{CS} = Correction for natural ^{13}C and ^{34}S abundance = (N_C x 0.011 x N_S x 0.042)
Cor_{CBr} = Correction for natural ^{13}C and ^{81}Br abundance = (N_C x 0.011 x N_{Br} x 0.973)

When molecule contains multiple Cl, Br, or S:

Cor_{SCl} = Correction for natural ^{34}S and ^{37}Cl abundance = (N_S x 0.042 x N_{Cl} x 0.319)
Cor_{SBr} = Correction for natural ^{34}S and ^{81}Br abundance = (N_S x 0.042 x N_{Br} x 0.973)

When off-target deuteration was observed:

Cor_D = Correction for additional deuterium isotopes present = N_D
Cor_{DX} = Correction for additional deuterium and other natural isotope abundance =
N_D x ($Corr_{C13}$ + $Corr_{Cl37}$ + Cor_{S34} + Cor_{Br81} + $Corr_{CCl}$ + $Corr_{CS}$ + $Corr_{CBr}$ + $Corr_{SCl}$ + $Corr_{SBr}$)

Equations used in Abundance Calculations

For Pyrimidines-[$^{15}N_2$] where target product has M+3:

$C_{M+1} = A_{M+1} + A_{M+1}(Cor_{All})$
$C_{M+2} = A_{M+2} - A_{M+1}(Cor_{C13}) + A_{M+2}(Cor_{All})$
$C_{M+3} = A_{M+3} - A_{M+1}(Cor_{Cl37} + Cor_{S34} + Cor_{Br81}) - A_{M+2}(Cor_{C13})$
$C_{M+4} = A_{M+4} - A_{M+1}(Cor_{CCl} + Cor_{CS} + Cor_{CBr}) - A_{M+2}(Cor_{Cl37} + Cor_{S34} + Cor_{Br81})$
$C_{M+5} = A_{M+5} - A_{M+1}(Cor_{SCl} + Cor_{SBr}) - A_{M+2}(Cor_{CCl} + Cor_{CS} + Cor_{CBr})$
$C_{M+6} = A_{M+6} - A_{M+2}(Cor_{SCl} + Cor_{SBr})$

For Pyrimidines-[$^{15}N_3$] or other where target product has M+4:

$C_{M+1} = A_{M+1} + A_{M+1}(Cor_{All})$
$C_{M+2} = A_{M+2} - A_{M+1}(Cor_{C13}) + A_{M+2}(Cor_{All})$
$C_{M+3} = A_{M+3} - A_{M+1}(Cor_{Cl37} + Cor_{S34} + Cor_{Br81}) - A_{M+2}(Cor_{C13}) + A_{M+3}(Cor_{All})$
$C_{M+4} = A_{M+4} - A_{M+1}(Cor_{CCl} + Cor_{CS} + Cor_{CBr}) - A_{M+2}(Cor_{Cl37} + Cor_{S34} + Cor_{Br81}) - A_{M+3}(Cor_{C13})$
$C_{M+5} = A_{M+5} - A_{M+1}(Cor_{SCl} + Cor_{SBr}) - A_{M+2}(Cor_{CCl} + Cor_{CS} + Cor_{CBr}) - A_{M+3}(Cor_{Cl37} + Cor_{S34} + Cor_{Br81})$
$C_{M+6} = A_{M+6} - A_{M+2}(Cor_{SCl} + Cor_{SBr}) - A_{M+3}(Cor_{CCl} + Cor_{CS} + Cor_{CBr})$
$C_{M+7} = A_{M+7} - A_{M+3}(Cor_{SCl} + Cor_{SBr})$

For Pyrimidines-[$^{15}N_2{}^{13}C_1D_1$] or other where target product has M+5:

$C_{M+1} = A_{M+1} + A_{M+1}(Cor_{All})$
$C_{M+2} = A_{M+2} - A_{M+1}(Cor_{C13}) + A_{M+2}(Cor_{All})$
$C_{M+3} = A_{M+3} - A_{M+1}(Cor_{Cl37} + Cor_{S34} + Cor_{Br81}) - A_{M+2}(Cor_{C13}) + A_{M+3}(Cor_{All})$
$C_{M+4} = A_{M+4} - A_{M+1}(Cor_{CCl} + Cor_{CS} + Cor_{CBr}) - A_{M+2}(Cor_{Cl37} + Cor_{S34} + Cor_{Br81}) - A_{M+3}(Cor_{C13}) + A_{M+4}(Cor_{All})$
$C_{M+5} = A_{M+5} - A_{M+1}(Cor_{SCl} + Cor_{SBr}) - A_{M+2}(Cor_{CCl} + Cor_{CS} + Cor_{CBr}) - A_{M+3}(Cor_{Cl37} + Cor_{S34} + Cor_{Br81}) - A_{M+4}(Cor_{C13})$
$C_{M+6} = A_{M+6} - A_{M+2}(Cor_{SCl} + Cor_{SBr}) - A_{M+3}(Cor_{CCl} + Cor_{CS} + Cor_{CBr}) - A_{M+4}(Cor_{Cl37} + Cor_{S34} + Cor_{Br81})$
$C_{M+7} = A_{M+7} - A_{M+3}(Cor_{SCl} + Cor_{SBr}) - A_{M+4}(Cor_{CCl} + Cor_{CS} + Cor_{CBr})$
$C_{M+8} = A_{M+8} - A_{M+4}(Cor_{SCl} + Cor_{SBr})$

Notes:

- Corrections resulting in < 0.2% change in abundance were ignored for simplicity.
- Off-target deuterium corrections were omitted for clarity.
- Only two examples of mono-deuterated pyrimidines and one example of a pyrimidine-[$^{15}N_2{}^{13}C_1D_2$] are reported, specific calculations for those cases can be found in the supporting information.

Equations used in Percentage Calculations

$$\%[M+1] = \frac{C_{M+1}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\%$$

$$\%[M+2] = \frac{C_{M+2}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\%$$

For M+2 isotopologs:

$$\%[M+3] = \frac{C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\%$$

For > M+2 isotopologs:

$$\%[M+3] = \frac{C_{M+3}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\%$$

For M+3 isotopologs:

$$\%[M+4] = \frac{C_{M+4} + C_{M+5} + C_{M+6} + \text{etc..}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\%$$

For M+4 isotopologs:

$$\%[M+5] = \frac{C_{M+5} + C_{M+6} + C_{M+7} + \text{etc..}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\%$$

For > M+3 isotopologs:

$$\%[M+4] = \frac{C_{M+4}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\%$$

For > M+4 isotopologs:

$$\%[M+5] = \frac{C_{M+5}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\%$$

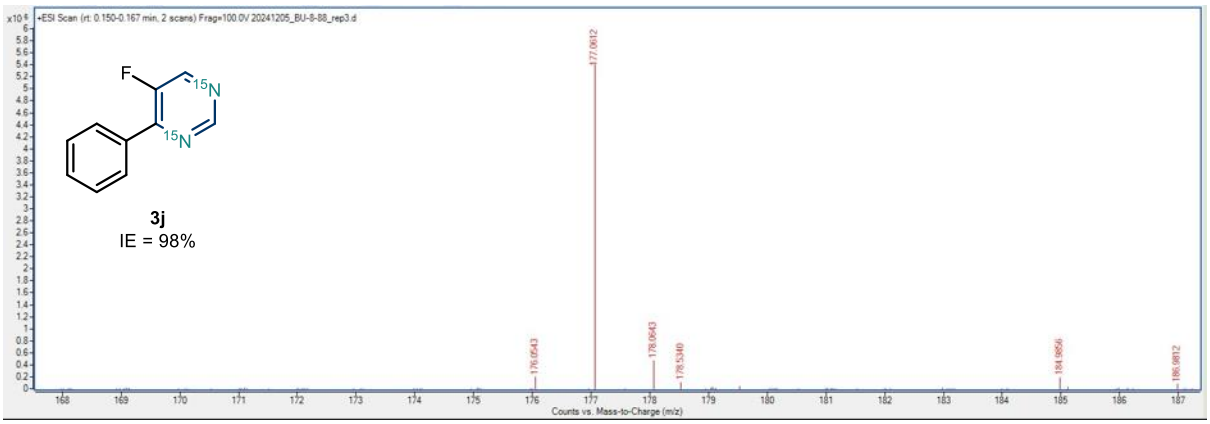
For M+5 isotopologs:

$$\%[M+6] = \frac{C_{M+6} + C_{M+7} + C_{M+8} + \text{etc..}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\%$$

Examples of Isotopic Enrichment Calculations

are two examples of isotopic enrichment calculations to demonstrate the formulas used.

Example 1:



Observed abundances:

	m/z	mass observed	abundance	
parent pyrimidine mass	M+1	none	0	A_{M+1}
pyrimidine-$^{15}N_1$	M+2	176.0543	202299	A_{M+2}
target mass (pyrimidine-$^{15}N_2$)	M+3	177.0612	5415403	A_{M+3}
pyrimidine-$^{15}N_2$ + natural ^{13}C	M+4	178.0643	474245	A_{M+4}

Calculations for corrected abundances:

$C_{M+1} = 0$

N_C (Natural ^{13}C abundance)

$C_{M+2} = A_{M+2} - A_{M+1}(Cor_{C13}) + A_{M+2}(Cor_{C13}) = 202299 - 0 + 202299(10 \times 0.011) =$ **224552**

$C_{M+3} = A_{M+3} - A_{M+2}(Cor_{C13}) = 5415403 - 202299(10 \times 0.011) =$ **5393150**

$C_{M+4} = A_{M+4} =$ **474245**

Calculations for percents of each isotopolog:

%[M+1] = 0

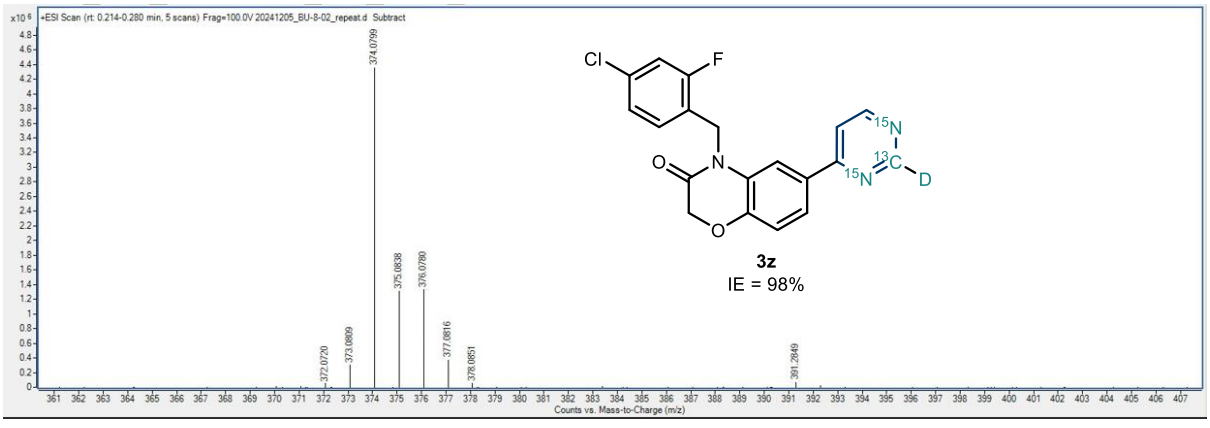
$$\%[M+2] = \frac{C_{M+2}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\% = \frac{224552}{0 + 224552 + 5393150 + 474245} \times 100\% = 3.69\%$$

$$\%[M+3] = \frac{C_{M+3} + C_{M+4}}{C_{M+1} + C_{M+2} + C_{M+3} + C_{M+4} + C_{M+5} + \text{etc..}} \times 100\% = \frac{5393150 + 474245}{0 + 224552 + 5393150 + 474245} \times 100\% = 96.31\%$$

Weighted isotopic enrichment calculations:

IE = (0.5 x %[M+2]) + %[M+3] = (0.5 x 3.69) + 96.31 = **98.2%**

Example 2:



3z
IE = 98%

Observed abundances:

	m/z	mass observed	abundance	
parent pyrimidine mass	M+1	none	0	A_{M+1}
	M+2	none	0	A_{M+2}
	M+3	372.0720	49265	A_{M+3}
	M+4	373.0809	302227	A_{M+4}
target mass (pyrimidine-$^{15}N_2$)	M+5	374.0799	4353501	A_{M+5}
various natural ^{13}C and ^{37}Cl isotopologs	M+6	375.0838	1307813	A_{M+6}
	M+7	376.0780	1334503	A_{M+7}
	M+8	377.0816	375476	A_{M+8}
	M+9	378.0851	55469	A_{M+9}

Calculations for corrected abundances:

$C_{M+1} = 0$

$C_{M+2} = 0$

Correction ommitted, changes total by 0.04%

Natural ^{13}C abundance

N_C

N_{Cl}

Relative natural ^{37}Cl abundance

$C_{M+3} = A_{M+3} + A_{M+3}(Cor_{C13} + Cor_{Cl37} + \cancel{Cor_{CCl}}) = 49265 + 49265([18 \times 0.011] + [1 \times 0.319]) =$ **74733**

$C_{M+4} = A_{M+4} - A_{M+3}(Cor_{C13}) + A_{M+4}(Cor_{C13} + Cor_{Cl37} + Cor_{CCl})$
$= 302227 - 49265(18 \times 0.011) + 302227([18 \times 0.011] + [1 \times 0.319] + [18 \times 1 \times 0.011 \times 0.319]) =$ **467813**

$C_{M+5} = A_{M+5} - A_{M+3}(Cor_{Cl37}) - A_{M+4}(Cor_{C13}) = 4353501 - 49263(1 \times 0.319) - 302227(18 \times 0.011) =$ **4277945**

$C_{M+6} = A_{M+6} - A_{M+4}(Cor_{Cl37}) = 1307813 - 302227(1 \times 0.319) =$ **1211403**

$C_{M+7} = A_{M+7} - A_{M+4}(Cor_{CCl}) = 1334503 - 302227(18 \times 1 \times 0.011 \times 0.319) =$ **1315414**

$C_{M+8} = A_{M+8} =$ **375476**

$C_{M+9} = A_{M+9} =$ **55469**

Calculations for percents of each isotopolog:

For simplicity: $\mathbf{C_{All}} = (74733 + 467813 + 4277945 + 1211403 + 1315414 + 375476 + 55469) =$ **7778251**

%[M+1] = 0

%[M+2] = 0

$$\%[M+3] = \frac{C_{M+3}}{C_{All}} \times 100\% = \frac{74733}{7778251} \times 100\% = 0.96\%$$

$$\%[M+4] = \frac{C_{M+4}}{C_{All}} \times 100\% = \frac{467813}{7778251} \times 100\% = 6.01\%$$

$$\%[M+5] = \frac{C_{M+5} + C_{M+6} + C_{M+7} + C_{M+8} + C_{M+9}}{C_{All}} \times 100\% = \frac{4277945 + 1211403 + 1315414 + 375476 + 55469}{7778251} \times 100\% = 93.02\%$$

Weighted isotopic enrichment calculations:

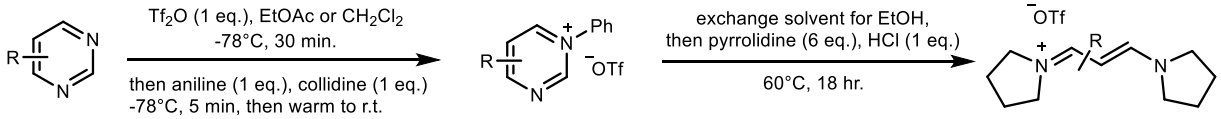
IE = (0.25 x %[M+2]) + (0.50 x %[M+3]) + (0.75 x (%[M+4]) + %[M+5]

= (0.25 x 0) + (0.50 x 0.96) + (0.75 x 6.01) + 93.02

= 98.02%

A 1.10 Preparation of Vinamidinium Salt Intermediates

General Procedure M



An oven-dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the pyrimidine (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc or CH_2Cl_2 (0.2 M) was added, the reaction vessel was cooled to –78 ºC, and triflic anhydride (Tf_2O) (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before aniline (1.0 equiv) was added dropwise followed by collidine (1.0 equiv). The reaction was stirred for an additional 5 minutes at –78 ºC. The cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. The resulting mixture was then concentrated *in vacuo*, then EtOH (0.2M), pyrrolidine (6.0 equiv), and HCl (1.0 equiv, as a 12 M solution in water) was added before heating to 60 ºC for 18 hours. Upon completion, as determined by ^{1}H-NMR, the mixture was cooled to room temperature and concentrated *in vacuo*. The resulting oil was diluted with CH_2Cl_2 and transferred to a separatory funnel before washing (3x) with 0.1 M aqueous HCl. The combined aqueous layers were extracted (x2) with CH_2Cl_2, and the combined organic layers were washed (1x) with H_2O, then dried over $MgSO_4$ and concentrated *in vacuo*. Additional purification details below.

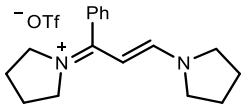
Isolation A1: The crude product was dissolved in a minimal amount of CH_2Cl_2 and added dropwise to a stirring solution of Et_2O and hexanes (3:1, 100 mL per mmol). The suspension was chilled for 3-18 hours in a –20 ºC freezer and filtered over a frit to yield pure vinamidinium salt.

Isolation A2: Products that still had significant impurities following Isolation A1 were purified by column chromatography (silica gel plug, 1% Et_3N in EtOAc followed by 5% MeOH in CH_2Cl_2) to yield pure vinamidinium salt.

Reaction Notes:

- Care must be taken to ensure no aniline freezes to the side of the reaction flask.
- Following aniline addition, reaction mixtures that "gel" or freeze were taken from the cooling bath and swirled by hand until aniline mixed in with the gel before returning to the cooling bath.
- Minor changes to General Procedure M due to substituents and substitution pattern are described in procedural details. In general, 5-aryl substrates use 4-CF_3-aniline instead of aniline and do not use HCl, and 4-alkyl pyrimidines or pyrimidines with electron rich 4-aryl substrates required elevated temperatures or additional reaction time.

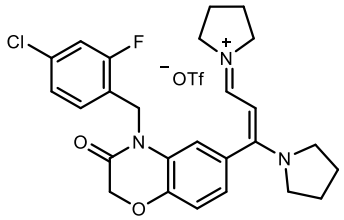
(*E*)-1-(1-Phenyl-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure M using 4-phenylpyrimidine (781 mg, 5.00 mmol), EtOAc (25 mL), Tf_2O (841 µL, 5.00 mmol), aniline (457 µL, 5.00 mmol), collidine (661 µL, 5.00 mmol), EtOH (25 mL), pyrrolidine (2.46 mL, 30.0 mmol), and concentrated HCl (455 µL, 5.00 mmol). Isolation A1 afforded the title compound as an orange solid (1.69 g, 4.17 mmol, 84% yield). mp 104-107 °C. IRυ_{max}/cm^{-1} (film): 2979, 1618, 1534, 1399, 1252, 1140, 1028, 634. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.47 (m, 3H), 7.34 – 7.29 (m, 2H), 6.93 (d, J = 11.8 Hz, 1H), 5.42 (d, J = 11.9 Hz, 1H), 3.78 (t, J = 7.2 Hz, 2H), 3.67 – 3.53 (m, 2H), 3.51 (t, J = 6.9 Hz, 2H), 3.24 (t, J = 6.9

Hz, 2H), 2.17 (p, J = 7.0 Hz, 2H), 2.13 – 2.03 (m, 2H), 1.99 – 1.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.28, 156.41, 132.52, 130.72, 129.44, 128.02, 121.04 (q, J = 321.0 Hz), 94.14, 54.29, 52.82, 50.42, 48.76, 25.15, 24.95, 24.93, 24.89; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.17; HRMS (ESI) found $[M+H]^+$ 255.1814, for $C_{17}H_{23}N_2^+$ requires 255.1856.

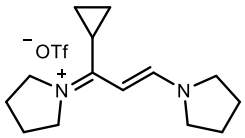
(*E*)-1-(3-(4-(4-Chloro-2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure M using 4-(4-chloro-2-fluorobenzyl)-6-(pyrimidin-4-yl)-2H-benzo[*b*][1,4]oxazin-3(4*H*)-one (740 mg, 2.00 mmol), EtOAc (10 mL), Tf_2O (336 µL, 2.00 mmol), aniline (182 µL, 2.00 mmol), collidine (264 µL, 2.00 mmol), EtOH (10 mL), pyrrolidine (985 µL, 12.0 mmol), and concentrated HCl (182 µL, 2.00 mmol). Isolation A1 did not sufficiently purify the material, and additional precipitations (3:1 Et_2O:hexanes, then repeated with 100% Et_2O) afforded the title compound as an orange solid (1.02 g, 1.66 mmol, 83% yield). mp 185-190 °C. IRυ_{max}/cm^{-1} (film): 2972, 1688, 1552, 1383, 1262, 1029, 634. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 8.2 Hz, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.08 – 7.01 (m, 2H), 7.00 (d, J = 1.9 Hz, 1H), 6.93 (d, J = 11.9 Hz, 1H), 6.89 (dd, J = 8.2, 1.9 Hz, 1H), 5.44 – 5.01 (m, 3H), 4.87 – 4.66 (m, 2H), 3.77 (dt, J = 13.7, 7.0 Hz, 1H), 3.67 – 3.52 (m, 2H), 3.48 (q, J = 6.4 Hz, 3H), 3.07 (dt, J = 13.1, 6.9 Hz, 1H), 2.86 (dt, J = 12.9, 7.0 Hz, 1H), 2.11 (dtd, J = 14.8, 12.3, 6.3 Hz, 4H), 1.95 (pd, J = 6.8, 2.7 Hz, 2H), 1.85 (p, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.29, 164.26, 160.59 (d, J = 251.1 Hz), 156.54, 147.14, 134.35 (d, J = 10.1 Hz), 131.04 (d, J = 4.8 Hz), 128.71, 126.78, 124.85 (d, J = 3.6 Hz), 124.01, 121.45 (d, J = 14.2 Hz), 120.96 (q, J = 319.0 Hz), 118.02, 116.38

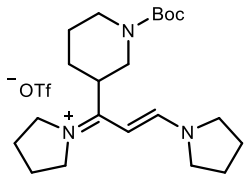
(d, J = 24.7 Hz), 115.82, 94.13, 67.64, 54.20, 52.49, 50.32, 48.66, 38.42 (d, J = 3.3 Hz), 25.06, 25.00, 24.92, 24.90; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.24 (s, 3F), -114.23 (t, J = 8.9 Hz, 1F); HRMS (ESI) found $[M+H]^+$ 468.1883, for $C_{26}H_{28}ClFN_3O_2^+$ requires 468.1849.

(*E*)-1-(1-Cyclopropyl-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



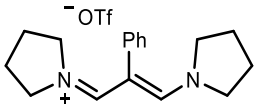
Prepared according to a modified general procedure A using 4-cyclopropylpyrimidine (120 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 μL, 1.00 mmol), aniline (91 μL, 1.00 mmol), collidine (132 μL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 μL, 6.00 mmol), and concentrated HCl (91 μL, 1.00 mmol). A 0.1M solution of AcOH was used instead of HCl during the aqueous workup. Isolation A1 did not sufficiently purify the material, and an additional precipitation (3:1 Et_2O:hexanes) afforded the title compound as a tan solid (269 mg, 0.73 mmol, 73% yield). mp 71-75 °C. IRυ_{max}/cm^{-1} (film): 2987, 1615, 1546, 1406, 1255, 1028, 634. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 12.1 Hz, 1H), 4.89 (d, J = 12.1 Hz, 1H), 3.86 (t, J = 6.6 Hz, 2H), 3.77 (t, J = 6.8 Hz, 2H), 3.51 (t, J = 6.8 Hz, 2H), 3.40 (t, J = 7.2 Hz, 2H), 2.15 – 1.93 (m, 8H), 1.80 (ddd, J = 14.6, 8.7, 6.1 Hz, 1H), 1.29 – 1.17 (m, 2H), 0.80 (td, J = 6.3, 4.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.07, 154.87, 120.84 (q, J = 321.2 Hz), 92.17, 54.11, 51.20, 50.59, 47.98, 25.10, 24.86, 24.76, 24.49, 12.80, 7.88; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.25; LRMS (ESI + APCI) found $[M+H]^+$ 219.2, for $C_{14}H_{23}N_2^+$ requires 219.2.

(*E*)-1-(1-(1-(*tert*-Butoxycarbonyl)piperidin-3-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



Prepared according to a modified general procedure M using tert-butyl 3-(pyrimidin-4-yl)piperidine-1-carboxylate (263 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), HCl (250 µL, 1.00 mmol, 4M solution in *p*-dioxane), and heated to 60 ºC for 24 hours. The reaction was determined to be incomplete by ^{1}H-NMR and was heated to 90 ºC for an additional 24 hours. Isolation A1 using a 0.1M solution of AcOH instead of HCl afforded the title compound as a sticky brown gum (294 mg, 0.57 mmol, 57% yield). IRυ_{max}/cm^{-1} (film): 2976, 1610, 1549, 1252, 1143, 1029, 636. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 12.7 Hz, 1H), 4.82 (d, J = 12.6 Hz, 1H), 4.14 (d, J = 13.1 Hz, 2H), 3.89 (t, J = 6.8 Hz, 2H), 3.82 (s, 1H), 3.71 (s, 3H), 3.41 (t, J = 7.2 Hz, 2H), 2.93 (t, J = 12.1 Hz, 1H), 2.76 (s, 1H), 2.09 (q, J = 6.8 Hz, 6H), 2.01 (q, J = 6.7 Hz, 3H), 1.83 (dt, J = 13.8, 3.0 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.64, 154.36, 129.37, 128.55, 120.95 (d, J = 320.8 Hz), 115.20, 90.87, 80.37, 54.56, 53.44, 51.58, 47.99, 28.51, 25.04, 24.83; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.31; LRMS (ESI + APCI) found $[M+H]^+$ 362.4, for $C_{21}H_{36}N_3O_2^+$ requires 362.3.

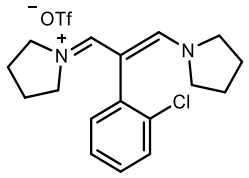
(*E*)-1-(2-Phenyl-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



Prepared according to a modified general procedure M using 5-phenylpyrimidine (78.1 mg, 0.50 mmol), EtOAc (2.5 mL), Tf_2O (84.1 µL, 0.50 mmol), 4-CF_3-aniline (62.8 µL, 0.50 mmol), collidine (66.1 µL, 0.50 mmol), EtOH (2.5 mL), pyrrolidine (246 µL, 3.00 mmol), and heated to 60 ºC for 2 hours. Isolation A1 did not sufficiently purify the material, so flash column

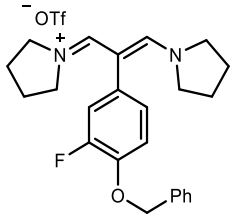
chromatography (silica gel: 1% MeOH in EtOAc, then 0-5% MeOH in CH_2Cl_2) afforded the title compound as a yellow solid (97.2 mg, 0.24 mmol, 48% yield). mp 112-116 °C. IRυ_{max}/cm^{-1} (film): 2920, 1566, 1424, 1261, 1144, 1028, 634. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 2H), 7.42 – 7.37 (m, 1H), 7.36 – 7.30 (m, 2H), 7.28 – 7.21 (m, 2H), 3.83 (t, J = 6.6 Hz, 4H), 2.61 (t, J = 6.8 Hz, 4H), 1.87 – 1.70 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.20, 133.13, 132.84, 129.10, 128.08, 120.95 (q, J = 320.4 Hz), 106.78, 56.55, 49.31, 26.12, 23.83; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.24; HRMS (ESI) found $[M+H]^+$ 255.1864, for $C_{17}H_{23}N_2^+$ requires 255.1856.

(*E*)-1-(2-(2-Chlorophenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



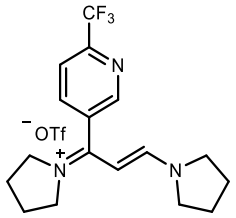
Prepared according to a modified general procedure M using 5-(2-chlorophenyl)pyrimidine (114 mg, 0.60 mmol), EtOAc (3.0 mL), Tf_2O (101 µL, 0.60 mmol), 4-CF_3-aniline (75 µL, 0.60 mmol), collidine (79 µL, 0.60 mmol), EtOH (3.0 mL), pyrrolidine (296 µL, 3.60 mmol) and heated to 60 ºC for 2 hours. Isolation A1 did not sufficiently purify the material, but flash column chromatography (silica gel: 1% MeOH in EtOAc, then 0-5% MeOH in CH_2Cl_2) afforded the title compound as an orange solid (98.9 mg, 0.23 mmol, 38% yield). mp 108-114 °C. IRυ_{max}/cm^{-1} (film): 2883, 1562, 1423, 1263, 1148, 1028, 635. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 2H), 7.44 – 7.34 (m, 2H), 7.30 (qd, J = 6.9, 2.0 Hz, 2H), 3.82 (qd, J = 6.9, 3.9 Hz, 4H), 2.76 – 2.64 (m, 2H), 2.58 (dt, J = 13.0, 6.7 Hz, 2H), 1.88 – 1.71 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.17, 136.85, 134.81, 132.47, 131.13, 129.29, 126.64, 120.88 (q, J = 320.4 Hz), 103.35, 56.61, 48.32, 26.07, 23.83; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.23; LRMS (ESI + APCI) found $[M+H]^+$ 289.1, for $C_{17}H_{22}ClN_2^+$ requires 289.1.

(*E*)-1-(2-(4-(Benzyloxy)-3-fluorophenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



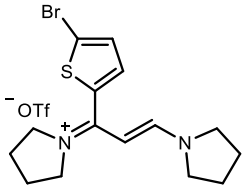
Prepared according to a modified general procedure M using 5-(4-(benzyloxy)-3-fluorophenyl)pyrimidine (240 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), 4-CF_3-aniline (126 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), and heated to 60 ºC for 2 hours. Isolation A1 did not sufficiently purify the material, but flash column chromatography (silica gel: 1% MeOH in EtOAc, then 0-5% MeOH in CH_2Cl_2) afforded the title compound as a yellow flaky solid (257 mg, 0.49 mmol, 49% yield). mp 152-158 °C. IRυ_{max}/cm^{-1} (film): 2977, 2883, 1564, 1425, 1297, 1030, 636. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 2H), 7.47 – 7.41 (m, 2H), 7.41 – 7.30 (m, 3H), 7.04 – 6.89 (m, 3H), 5.17 (s, 2H), 3.87 – 3.74 (m, 4H), 2.67 (t, J = 6.1 Hz, 4H), 1.89 – 1.70 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.42, 151.65 (d, *J* = 250.6 Hz), 147.31 (d, J = 10.4 Hz), 135.87, 129.07 (d, J = 3.5 Hz), 128.77, 128.52, 127.80, 125.84 (d, J = 6.6 Hz), 120.94 (q, J = 318 Hz), 120.46 (d, J = 17.5 Hz), 114.93 (d, J = 2.5 Hz), 105.13, 71.52, 56.62, 49.34, 26.13, 23.80; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.24 (s, 3F), -132.01 (dd, *J* = 11.0, 7.8 Hz, 1F); HRMS (ESI) found $[M+H]^+$ 379.2193, for $C_{24}H_{28}FN_2O^+$ requires 379.2180.

(*E*)-1-(3-(Pyrrolidin-1-yl)-1-(6-(trifluoromethyl)pyridin-3-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure M using 4-(6-(trifluoromethyl)pyridin-3-yl)pyrimidine (225 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), and concentrated HCl (91 µL, 1.00 mmol). Isolation A1 afforded the title compound as a yellow flaky solid along with a 14% triflylated aniline (Tf-NHPh) impurity (407 mg, 0.86 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 2.1 Hz, 1H), 8.36 (dd, J = 8.1, 2.1 Hz, 1H), 7.92 (dd, J = 8.1, 0.9 Hz, 1H), 6.94 (d, J = 12.0 Hz, 1H), 5.43 (d, J = 12.0 Hz, 1H), 3.89 (dt, J = 13.7, 7.1 Hz, 1H), 3.77 – 3.58 (m, 3H), 3.51 (dq, J = 14.3, 7.2 Hz, 2H), 3.37 – 3.11 (m, 2H), 2.32 – 1.80 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.31, 156.19, 148.54, 139.02, 131.73, 128.30, 121.40 (d, J = 2.9 Hz), 121.13 (q, J = 272.9 Hz), 120.93 (q, J = 319.0 Hz), 94.83, 54.51, 53.09, 50.82, 48.91, 25.23, 24.88, 24.84, 24.73; ^{19}F NMR (375 MHz, $CDCl_3$) δ -68.13 (s, 3F), -78.31 (s, 3F).

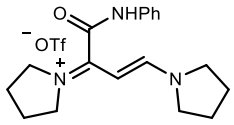
(*E*)-1-(1-(5-Bromothiophen-2-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



Prepared according to general procedure M using 4-(5-bromothiophen-2-yl)pyrimidine (241 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), and concentrated HCl (91 µL, 1.00 mmol). Isolation A1 afforded the title compound as a red glass (378 mg, 0.77 mmol, 77%

yield). mp 91-94 °C. IRυ_{max}/cm^{-1} (film): 2977, 2878, 1615, 1550, 1442, 1252, 1029, 635. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 11.6 Hz, 1H), 7.14 (t, J = 2.7 Hz, 2H), 5.44 (d, J = 11.7 Hz, 1H), 3.73 (t, J = 7.1 Hz, 2H), 3.62 (dt, J = 15.5, 7.1 Hz, 4H), 3.46 (t, J = 6.9 Hz, 2H), 2.22 – 2.06 (m, 4H), 1.98 (dt, J = 10.9, 6.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.84, 156.27, 132.59, 132.23, 130.94, 120.87 (q, J = 319.1 Hz), 117.23, 95.31, 54.53, 53.13, 50.89, 48.96, 25.17, 24.86, 24.85, 24.81; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.25; LRMS (ESI + APCI) found $[M+H]^+$ 339.1, for $C_{15}H_{20}BrN_2S^+$ requires 339.1.

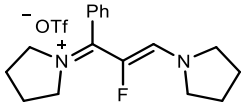
(*E*)-1-(1-Oxo-1-(phenylamino)-4-(pyrrolidin-1-yl)but-3-en-2-ylidene)pyrrolidin-1-ium trifluoromethanesulfonate



Prepared according to a modified general procedure M using *N*-phenylpyrimidine-4-carboxamide (199 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), 2,4,6-trimethylaniline (132 µL, 1.00 mmol), and collidine (132 µL, 1.00 mmol). The mixture was stirred for 30 minutes at –78 ºC for 30 minutes before adding TfOH (88 µL, 1.00 mmol) and warming to room temperature. Solvent was exchanged for EtOH (5.0 mL), then added pyrrolidine (493 µL, 6.00 mmol) and heated to 60 ºC for 18 hours. The mixture was cooled to room temperature and concentrated *in vacuo*. The resulting oil was diluted with CH_2Cl_2 and transferred to a separatory funnel before washing (3x) with 0.1 M aqueous AcOH. The combined aqueous layers were extracted (x2) with CH_2Cl_2, and the combined organic layers were washed (1x) with H_2O, then dried over $MgSO_4$ and concentrated *in vacuo.* Flash column chromatography (silica gel: 1% MeOH in EtOAc, then 0–5% MeOH in CH_2Cl_2) followed by precipitation in (1:1 Et_2O:hexanes) afforded the title compound as a brown oil (184 mg, 0.41 mmol, 41% yield) along with minor ^{1}H and ^{13}C impurities. The product

was used in the isotope labeling procedure without additional purification. IRυ_{max}/cm^{-1} (film): 2979, 1564, 1443, 1242, 1028, 635. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 12.2 Hz, 1H), 7.33 (t, J = 7.8 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 4.99 (d, J = 12.2 Hz, 1H), 3.84 – 3.49 (m, 6H), 3.46 – 3.30 (m, 2H), 2.26 – 1.82 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.17, 159.83, 155.24, 137.02, 129.07, 125.49, 120.53 (q, J = 318.0 Hz), 120.33, 90.42, 54.46, 51.54, 49.75, 48.50, 25.03, 24.85, 24.79, 24.42; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.36; LRMS (ESI + APCI) found $[M+H]^+$ 298.2, for $C_{18}H_{24}N_3O^+$ requires 298.2.

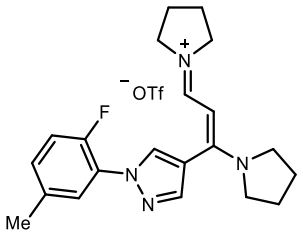
(Z)-1-(2-Fluoro-1-phenyl-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-iumtrifluoromethanesulfonate



Prepared according to general procedure M using 4-phenyl-5-fluoropyrimidine (175 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 μL, 1.00 mmol), aniline (91 μL, 1.00 mmol), collidine (132 μL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 μL, 6.00 mmol), and concentrated HCl (250 μL, 1.00 mmol, 4.0 M solution in dioxane). Isolation A1 using a 0.1 M solution of AcOH instead of HCl followed by column chromatography (silica gel: 1% MeOH in EtOAc, then 5% MeOH in CH_2Cl_2) afforded the title compound as a dark red oil (170 mg, 0.40 mmol, 40% yield). IRυ_{max}/cm^{-1} (film): 2978, 1632, 1536, 1441, 1259, 1029, 635. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 5.0, 2.0 Hz, 3H), 7.46 (dd, J = 6.5, 2.9 Hz, 2H), 6.61 (d, J = 26.4, 1H), 4.09 (dd, J = 9.6, 4.3 Hz, 2H), 3.88 (q, J = 6.6 Hz, 2H), 3.53 (t, J = 7.0 Hz, 2H), 3.21 (t, J = 7.0 Hz, 2H), 2.13 (p, J = 6.9 Hz, 2H), 2.05 (h, J = 6.6 Hz, 2H), 1.96 – 1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.79 (d, J = 6.7 Hz), 145.10 (d, J = 7.8 Hz), 134.20, 131.41, 131.18 (d, J = 4.5 Hz), 129.72, 128.94, 121.09 (d, J = 321.2 Hz), 56.27, 54.95, 52.90, 52.77, 50.51 (d, J = 9.8 Hz), 26.09 (d, J = 4.0 Hz), 25.95 (d, J

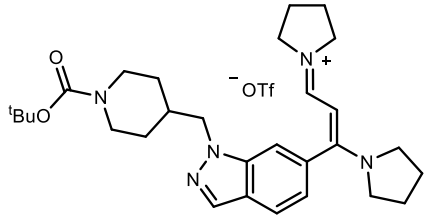
= 2.6 Hz), 24.23 (d, J = 2.4 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.19 (s, 3F), -159.02 (dp, J = 26.2, 5.9 Hz, 1F); LRMS (ESI + APCI) found $[M+H]^+$ 273.2, for $C_{17}H_{22}FN_2^+$ requires 273.2.

(*E*)-1-(3-(1-(2-Fluoro-5-methylphenyl)-1H-pyrazol-4-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



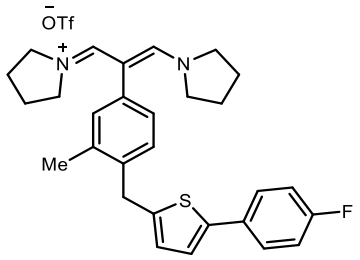
Prepared according to general procedure M using 4-(1-(5-fluoro-2-methylphenyl)-1H-pyrazol-4-yl)pyrimidine (254 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), and concentrated HCl (91 µL, 1.00 mmol). Isolation A1 afforded the title compound as a red solid (400 mg, 0.80 mmol, 80% yield). mp 46-49 °C. IRυ_{max}/cm^{-1} (film): 2976, 1613, 1545, 1409, 1252, 1028, 635. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 0.7 Hz, 1H), 7.74 (d, J = 0.7 Hz, 1H), 7.38 (d, J = 11.8 Hz, 1H), 7.29 (dd, J = 8.6, 6.0 Hz, 1H), 7.21 (dd, J = 8.9, 2.7 Hz, 1H), 7.07 (td, J = 8.2, 2.7 Hz, 1H), 5.31 (d, J = 11.8 Hz, 1H), 3.71 (t, J = 7.1 Hz, 2H), 3.65 (t, J = 6.8 Hz, 2H), 3.59 (t, J = 6.9 Hz, 2H), 3.56 – 3.51 (m, 2H), 2.28 (s, 3H), 2.20 (dq, J = 13.8, 6.3 Hz, 2H), 2.11 (td, J = 7.1, 1.4 Hz, 2H), 2.06 – 1.93 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.91 (d, 244.9 Hz), 160.24, 156.01, 140.08, 139.35 (d, J = 9.7 Hz), 133.23, 132.73 (d, J = 8.4 Hz), 128.54 (d, J = 3.6 Hz), 120.82 (q, J = 320.8 Hz), 116.00 (d, J = 20.7 Hz), 113.92, 113.26 (d, J = 24.5 Hz), 94.33, 54.21, 53.11, 50.60, 48.60, 25.19, 24.91, 24.89, 17.78 (Note: One pyrrolidine methylene unit is missing, we believe the signal at 24.89 ppm contains two unresolved ^{13}C signals); ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.32 (s, 3F), -115.23 – -115.34 (m, 1F); LRMS (ESI + APCI) found $[M+H]^+$ 353.3, for $C_{21}H_{26}FN_4^+$ requires 353.2.

(*E*)-1-(3-(1-((1-(*tert*-Butoxycarbonyl)piperidin-4-yl)methyl)-1H-indazol-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



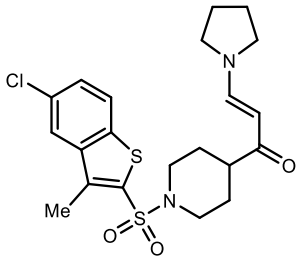
Prepared according to a general procedure M using *tert*-butyl 4-((6-(pyrimidin-2-yl)-1H-indazol-1-yl)methyl) piperidine-1-carboxylate (394 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), and concentrated HCl (91 µL, 1.00 mmol). Isolation A1 using a 0.1M solution of AcOH instead of HCl afforded the title compound as a pale pink solid (363 mg, 0.57 mmol, 57% yield). mp 72-77 °C. IRυ_{max}/cm^{-1} (film): 2976, 1616, 1589, 1251, 1148, 1029, 635. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.00 – 6.91 (m, 2H), 5.36 (d, J = 11.9 Hz, 1H), 4.47 – 4.26 (m, 2H), 4.05 (d, J = 13.2 Hz, 2H), 3.82 (dt, J = 13.9, 7.3 Hz, 1H), 3.74 – 3.34 (m, 6H), 3.25 (hept, J = 6.3 Hz, 2H), 2.63 (s, 2H), 2.29 – 1.78 (m, 8H), 1.54 (t, J = 10.5 Hz, 2H), 1.40 (s, 9H), 1.29 – 1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.35, 156.55, 154.87, 139.47, 133.18, 130.08, 124.51, 122.28, 120.97 (q, J = 319.0 Hz), 119.65, 110.66, 94.19, 79.44, 67.16, 54.30, 54.23, 52.89, 50.45, 48.70, 37.28, 29.67, 28.50, 25.18, 24.92, 24.86.; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.16; LRMS (ESI + APCI) found $[M+H]^+$ 492.3324, for $C_{29}H_{42}N_5O_2^+$ requires 492.3333.

(*E*)-1-(2-(4-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-3-methylphenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



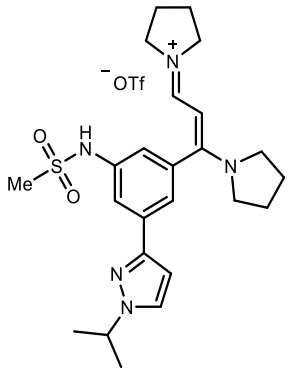
Prepared according to a modified general procedure M using 5-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyrimidine (361 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), 4-CF_3-aniline (126 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), and heated to 60 ºC for 2 hours. Following the aqueous workup described under Isolation A1, the oil was dissolved in EtOAc (5.0 mL) and stored at room temperature for 10 minutes. The product precipitated and filtration afforded the title compound as a pale-yellow solid (297 mg, 0.49 mmol, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 2H), 7.47 – 7.38 (m, 2H), 7.14 (d, J = 7.8 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 7.06 – 6.98 (m, 4H), 6.75 – 6.69 (m, 1H), 4.13 (s, 2H), 3.82 (t, J = 6.8 Hz, 4H), 2.70 – 2.61 (m, 4H), 2.38 (s, 3H), 1.85 – 1.67 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.25, 142.89, 141.84, 138.33, 137.25, 133.64, 131.18, 130.86, 130.53 (d, J = 3.3 Hz), 130.13, 126.99 (d, J = 8.0 Hz), 126.07, 122.71, 115.99, 115.77, 106.40, 56.37, 49.35, 33.96, 25.96, 23.73, 19.36; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.24 (3F), -114.53 (ddd, J = 13.9, 8.3, 5.6 Hz, 1F); Spectra matched literature values.

(*E*)-1-(1-((5-Chloro-3-methylbenzo[b]thiophen-2-yl)sulfonyl)piperidin-4-yl)-3-(pyrrolidin-1-yl)prop-2-en-1-one



Prepared according to a modified general procedure M using 4-(1-((5-chloro-3-methylbenzo[b]thiophen-2-yl)sulfonyl)piperidin-4-yl)pyrimidine (408 mg, 1.00 mmol), CH_2Cl_2 (7.5 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (821 µL, 10.0 mmol), concentrated HCl (91 µL, 1.00 mmol), and heated to 90 ºC for 96 hours. Following the aqueous workup described under Isolation A1 using 0.1 M AcOH instead of HCl, purification by column chromatography (silica gel: 90% EtOAc in hexanes) afforded the title compound as a white powder (298 mg, 0.66 mmol, 66% yield). Note: Enaminone formation is not typical and has not been observed on a significant number of pyrimidines. mp 176-181 °C. IRυ_{max}/cm^{-1} (film): 2867, 1644, 1564, 1339, 1153, 1080, 932, 719. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 8.6 Hz, 1H), 7.43 (dd, J = 8.6, 2.0 Hz, 1H), 4.91 (d, J = 12.4 Hz, 1H), 3.84 (dt, J = 11.6, 3.6 Hz, 2H), 3.45 (t, J = 6.9 Hz, 2H), 3.10 (t, J = 7.0 Hz, 2H), 2.71 (td, J = 11.5, 3.2 Hz, 2H), 2.66 (s, 3H), 2.25 (tt, J = 10.6, 4.0 Hz, 1H), 1.97 (q, J = 6.9 Hz, 2H), 1.91 – 1.70 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.86, 148.81, 141.05, 137.77, 136.19, 134.67, 131.55, 127.78, 123.70, 123.47, 93.75, 52.33, 46.90, 46.08, 28.42, 25.27, 12.91; LRMS (ESI + APCI) found $[M+H]^+$ 453.2, for $C_{21}H_{26}ClN_2O_3S_2^+$ requires 453.1.

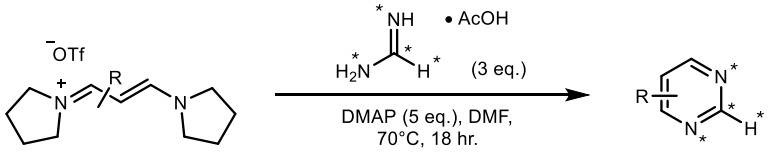
(*E*)-1-(3-(3-(1-Isopropyl-1H-pyrazol-3-yl)-5-(methylsulfonamido)phenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate



Prepared according to a modified general procedure M using *N*-(3-(1-isopropyl-4-(pyrimidin-4-yl)-1H-pyrazol-3-yl)phenyl)methanesulfonamide (257 mg, 1.00 mmol), CH_2Cl_2 (20 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (821 µL, 10.0 mmol), concentrated HCl (91 µL, 1.00 mmol) and heated to 90 ºC for 18 hours. Isolation A1 afforded the title compound as an orange solid (441 mg, 0.73 mmol, 73% yield). mp 87-93 °C. IRυ_{max}/cm^{-1} (film): 2979, 1614, 1545, 1254, 1148, 1030, 636. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.40 (ddt, J = 7.8, 6.7, 1.2 Hz, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 12.2 Hz, 1H), 7.17 (t, J = 1.9 Hz, 1H), 5.29 (d, J = 11.7 Hz, 1H), 4.58 (hept, J = 6.7 Hz, 1H), 4.01 (ddd, J = 12.5, 8.0, 4.7 Hz, 1H), 3.67 – 3.48 (m, 2H), 3.43 (dt, J = 13.0, 7.8 Hz, 1H), 3.31 (dq, J = 11.6, 6.5 Hz, 2H), 3.18 (dt, J = 12.4, 6.0 Hz, 1H), 2.95 (s, 3H), 2.91 (t, J = 6.4 Hz, 1H), 2.00 (hept, J = 6.4 Hz, 2H), 1.95 – 1.78 (m, 4H), 1.76 – 1.59 (m, 3H), 1.55 (dd, J = 6.7, 2.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.10, 155.88, 148.72, 143.03, 133.30, 130.39, 129.81, 120.93 (q, J = 318.8 Hz), 120.19, 119.64, 118.70, 109.98, 94.72, 54.75, 54.01, 52.19, 50.31, 48.46, 38.41, 24.95, 24.92, 24.90, 22.93, 22.83; ^{19}F NMR (375 MHz, $CDCl_3$) δ -78.25; LRMS (ESI + APCI) found $[M+H]^+$ 456.3, for $C_{24}H_{34}N_5O_2S^+$ requires 456.2.

A 1.10 Preparation of Isotopically-Labeled Pyrimidines

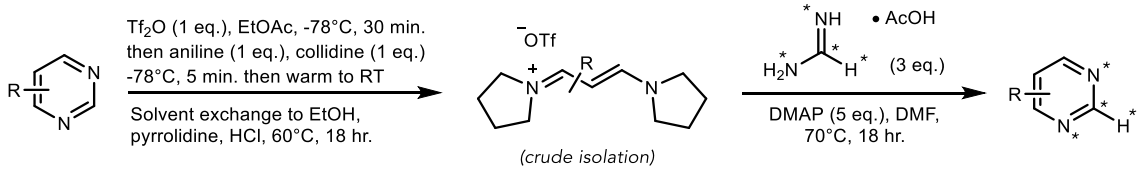
General Procedure N (Higher Mass Pyrimidine Formation from Vinamidinium Salts)



An oven-dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the vinamidinium salt (1.0 equiv), formamidine acetate (3.0 equiv, enriched with ^{15}N, ^{13}C, or D), 4-dimethylaminopyridine (DMAP) (5.0 equiv), and DMF (0.2 M).

The reaction was heated to 70 ºC for 18 hours. Upon completion, as determined by ^{1}H-NMR, the mixture was cooled to room temperature and diluted with H_2O, then extracted (3x) with EtOAc. The combined organic layers were washed (1x) with brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography.

General Procedure O (Higher Mass Pyrimidine Formation from Pyrimidines)



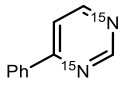
An oven-dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the pyrimidine (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.2 M) was added, the reaction vessel was cooled to –78 ºC, and triflic anhydride (Tf_2O) (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before aniline (1.0 equiv) was added dropwise followed by collidine (1.0 equiv). The reaction was stirred for an additional 5 minutes at –78 ºC. The cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. The resulting mixture was then concentrated *in vacuo*, then EtOH (0.2M), pyrrolidine (6.0 equiv), and HCl (1.0 equiv, as a 12M solution in water) was added before heating to 60 ºC for 18 hours. The mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting oil was diluted with CH_2Cl_2 and transferred to a separatory funnel before washing (3x) with 0.1M aqueous HCl. The combined aqueous layers were extracted (x2) with CH_2Cl_2, and the combined organic layers were washed (1x) with H_2O, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was then dissolved in a minimal amount of CH_2Cl_2 and added dropwise to a stirring solution of Et_2O:hexanes (3:1, approx.. 100 mL/mmol of starting material), then chilled in a -20 ºC freezer for 3 hours before filtering to yield crude vinamidinium salt.

Note: The following reagent quantities were calculated relative to crude vinamidinium salt, not starting material pyrimidine. The crude vinamidinium salt was then added to an oven-dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar. Next was added formamidine acetate (3.0 equiv, enriched with ^{15}N, ^{13}C, or D), DMAP (5.0 equiv), and DMF (0.2 M). The reaction was heated to 70 ºC for 18 hours. Upon completion, as determined by ^{1}H-NMR, the mixture was cooled to room temperature and diluted with H_2O, then extracted (3x) with EtOAc. The combined organic layers were washed (1x) with brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography.

Reaction Notes:

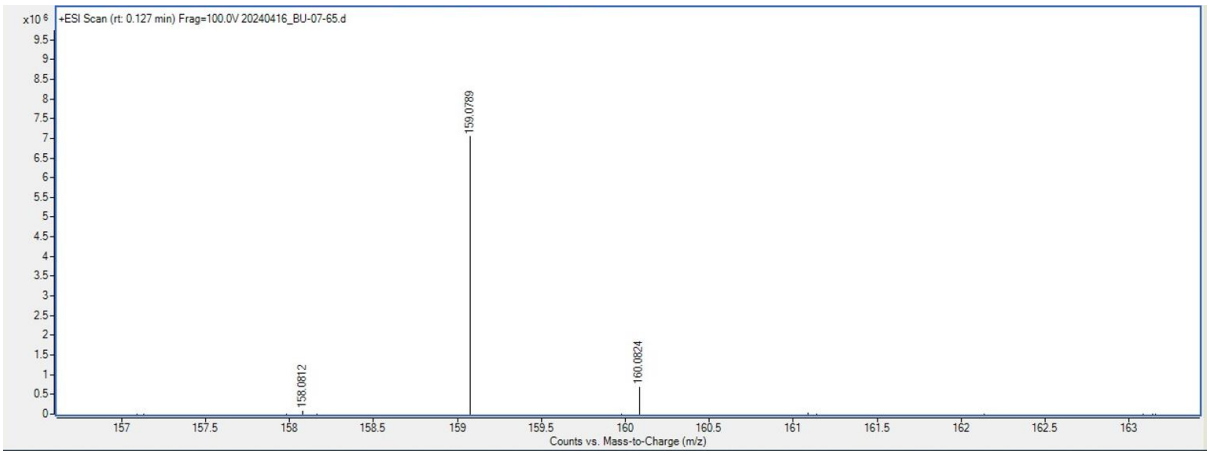
For high isotopic enrichment, vinamidinium salts must be separated completely from pyrimidine starting materials, iminoenamines, and amidine cleavage byproducts. Some impurities (i.e. triflylated aniline) can be carried forward without significantly impacting yield or isotopic enrichment. Yields reported "over two steps" (General Procedure C) are from vinamidinium salts containing significant impurities.

4-Phenylpyrimidine-1,3-$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(1-phenyl-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (80.9 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DBU (149 µL, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 10-40% EtOAc in hexanes) afforded the title compound as a white solid (27 mg, 0.17 mmol, 85% yield). mp 59-62 °C. IRυ_{max}/cm^{-1} (film): 3021, 1563, 1534, 1461, 1377, 738, 687. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (td, J = 14.5, 1.4 Hz, 1H), 8.77 (dd, J = 10.4,

5.4 Hz, 1H), 8.14 – 8.04 (m, 2H), 7.72 (dq, J = 5.4, 1.2 Hz, 1H), 7.58 – 7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.97 (d, J = 4.7 Hz), 159.18 (t, J = 3.2 Hz), 157.55 (d, J = 4.1 Hz), 136.59 (d, J = 7.2 Hz), 131.19, 129.13, 127.22 (d, J = 2.5 Hz), 117.11 (t, J = 2.1 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 285.86; HRMS (ESI) found $[M+H]^+$ 159.0789, for $C_{10}H_9{}^{15}N_2{}^+$ requires 159.0701. Isotopic enrichment >99% determined by HRMS.

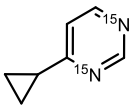


m/z	abundance
M+1	0
M+2	95586
M+3	7049768
M+4	694505

M+1	M+2	M+3
0%	1.35%	98.65%

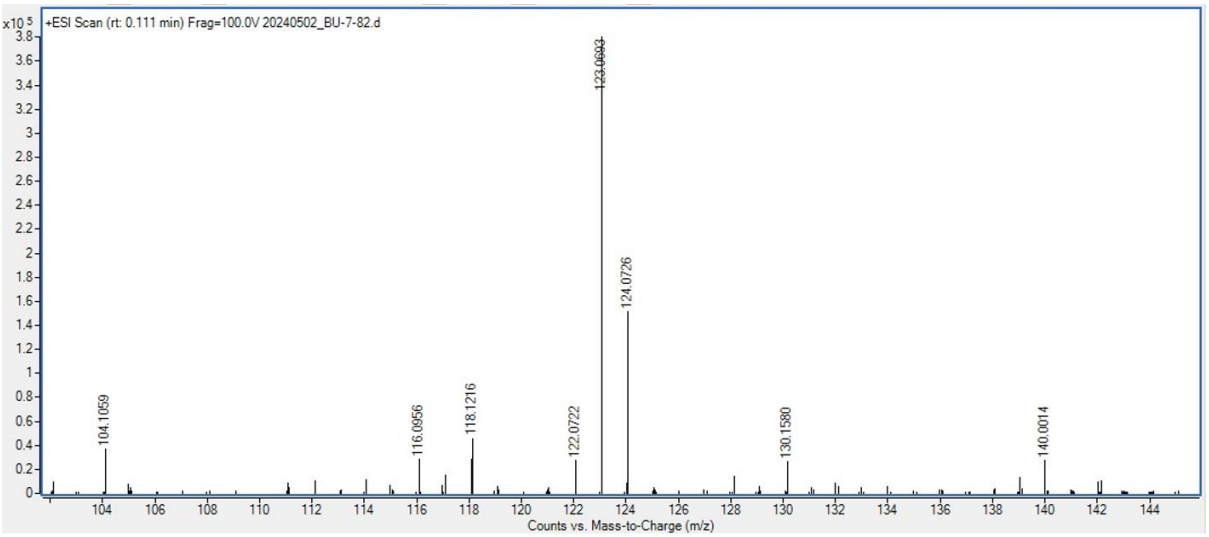
Isotopic Enrichment > 99%

4-Cyclopropylpyrimidine-1,3-$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(1-Cyclopropyl-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (73.7 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 10-50% EtOAc in hexanes) afforded the title compound as a white solid (14 mg, 0.11 mmol, 57% yield). mp 38-40 °C. IRυ_{max}/cm^{-1} (film): 3036, 1577, 1533, 1394,

1295, 1229, 897. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (td, J = 14.5, 1.4 Hz, 1H), 8.46 (dd, J = 10.4, 5.3 Hz, 1H), 7.13 (dd, J = 5.2, 1.2 Hz, 1H), 1.94 (dtd, J = 12.7, 5.5, 3.1 Hz, 1H), 1.17 – 1.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.97 (d, J = 4.6 Hz), 158.76 (t, J = 3.0 Hz), 155.74 (d, J = 4.0 Hz), 119.24 (t, J = 2.0 Hz), 17.01 (d, J = 7.9 Hz), 11.50 (d, J = 1.5 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 281.66, 280.24; HRMS (ESI) found $[M+H]^+$ 123.0693, for $C_7H_9{}^{15}N_2{}^+$ requires 123.0701. Isotopic enrichment >99% determined by HRMS.

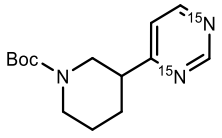


m/z	abundance
M+1	0
M+2	27753
M+3	1916130
M+4	151644

M+1	M+2	M+3
0%	1.43%	98.57%

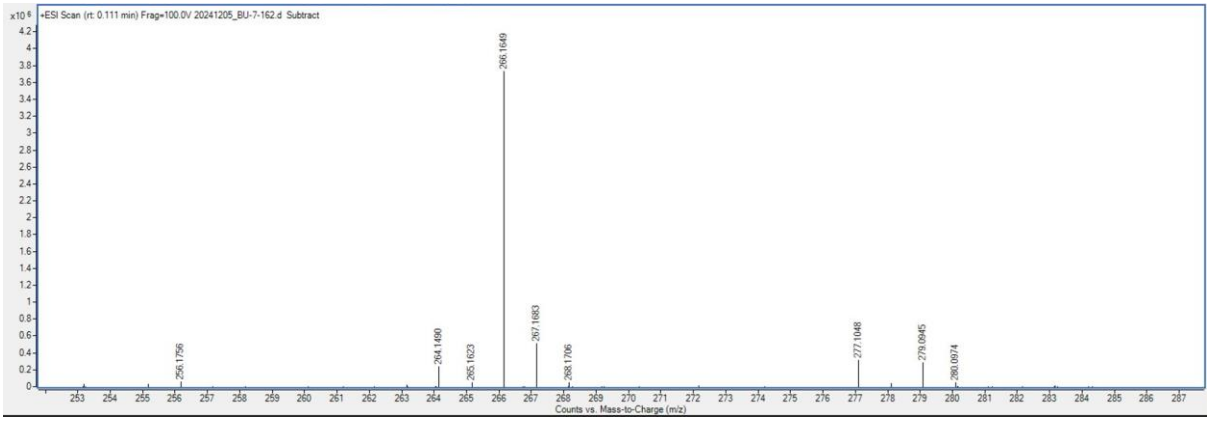
Isotopic Enrichment > 99%

***tert*-Butyl 3-(pyrimidin-4-yl-$^{15}N_2$)piperidine-1-carboxylate**



Prepared according to a modified general procedure N using (*E*)-1-(1-(1-(*tert*-butoxycarbonyl)piperidin-3-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (102.3 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60

mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL), and heating to 90 °C for 18 hours. Flash column chromatography (silica gel: 10-60% EtOAc in hexanes) afforded the title compound as a clear oil (43 mg, 0.16 mmol, 81% yield). IRυ_{max}/cm^{-1} (film): 2933, 1685, 1573, 1417, 1365, 1147. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (tt, J = 14.4, 1.0 Hz, 1H), 8.63 (dd, J = 10.4, 5.2 Hz, 1H), 7.21 (d, J = 5.4 Hz, 1H), 4.20 (s, 1H), 4.07 (s, 1H), 3.05 (s, 1H), 2.92 – 2.67 (m, 2H), 2.03 (td, J = 8.2, 3.8 Hz, 1H), 1.89 – 1.72 (m, 2H), 1.68 – 1.51 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.04 (d, J = 4.8 Hz), 158.81 (t, J = 3.3 Hz), 157.08 (d, J = 4.2 Hz), 154.89, 119.87, 79.86, 77.36, 43.77, 43.73, 30.18, 28.57, 24.88; ^{15}N NMR (40 MHz, $CDCl_3$) δ 291.33, 287.08; HRMS (ESI) found $[M+H]^+$ 266.1649, for $C_{14}H_{22}N^{15}N_2O_2^+$ requires 266.1647. Isotopic enrichment >99% determined by HRMS.

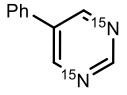


m/z	abundance
M+1	0
M+2	46232
M+3	3731303
M+4	513764

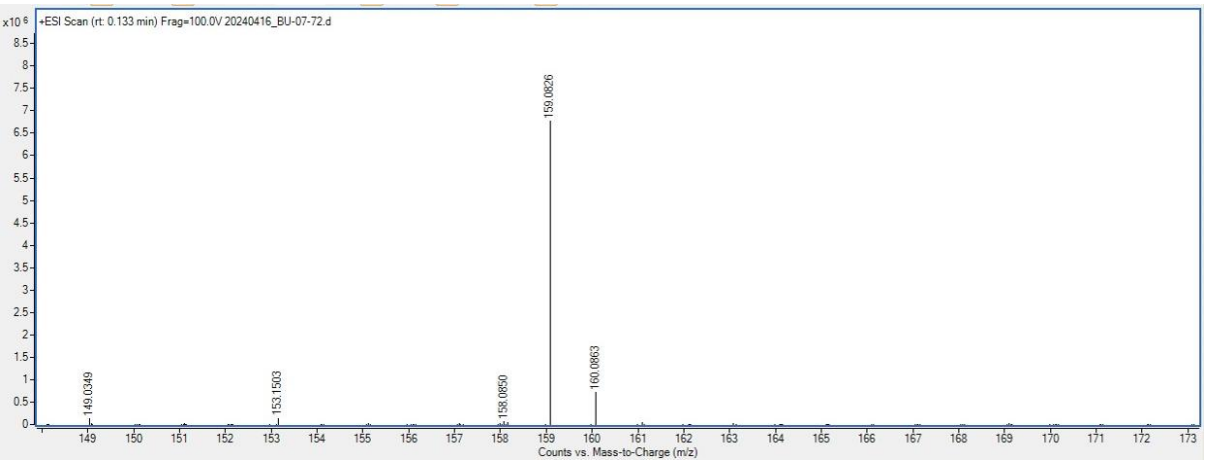
M+1	M+2	M+3
0%	1.23%	98.77%

Isotopic Enrichment > 99%

5-Phenylpyrimidine-1,3-$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(2-phenyl-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (80.9 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 20-60% EtOAc in hexanes) afforded the title compound as a yellow solid (24 mg, 0.15 mmol, 75% yield). mp 34-37 °C. IRυ_{max}/cm^{-1} (film): 3041, 1548, 1408, 1389, 758, 695, 626. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (t, J = 14.4 Hz, 1H), 8.94 (d, J = 9.5 Hz, 2H), 7.61 – 7.56 (m, 2H), 7.52 (t, J = 7.3 Hz, 2H), 7.49 – 7.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.60 (t, J = 3.4 Hz), 155.02 (d, J = 4.4 Hz), 134.44 (t, J = 2.7 Hz), 134.40, 129.54, 129.12, 127.11; ^{15}N NMR (40 MHz, CDCl3) δ 292.53; HRMS (ESI) found $[M+H]^+$ 159.0700, for $C_{10}H_9{}^{15}N_2^+$ requires 159.0701. Isotopic enrichment >99% determined by HRMS.

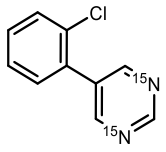


m/z	abundance
M+1	0
M+2	78097
M+3	6779983
M+4	714670

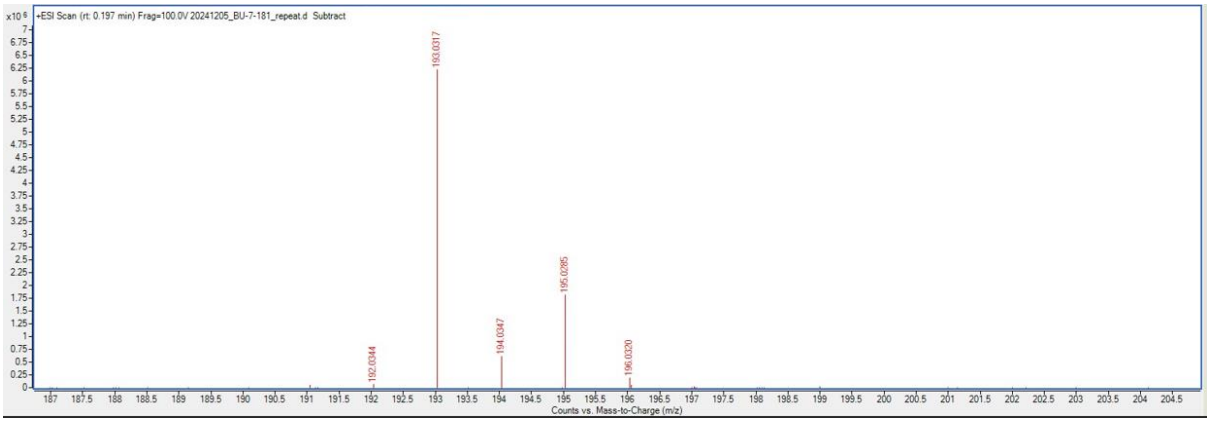
M+1	M+2	M+3
0%	0.62%	99.38%

Isotopic Enrichment > 99%

5-(2-Chlorophenyl)pyrimidine-1,3-$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(2-(2-chlorophenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (83.7 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 10-40% EtOAc in hexanes) afforded the title compound as a white solid (31 mg, 16 mmol, 84% yield). mp 49-51 °C. IRυ_{max}/cm^{-1} (film): 3037, 1542, 1388, 751, 719, 617. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (t, J = 14.5 Hz, 1H), 8.87 – 8.82 (m, 2H), 7.60 – 7.46 (m, 1H), 7.44 – 7.35 (m, 2H), 7.38 – 7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.80 (t, J = 3.6 Hz), 156.98 (d, J = 3.9 Hz), 133.57, 133.25 (t, J = 2.2 Hz), 132.94, 131.21, 130.53, 130.46, 127.62; ^{15}N NMR (40 MHz, $CDCl_3$) δ 291.62; HRMS (ESI) found $[M+H]^+$ 193.0317, for $C_{10}H_8Cl^{15}N_2^+$ requires 193.0311. Isotopic enrichment >99% determined by HRMS.

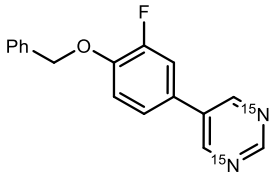


m/z	abundance
M+1	0
M+2	68720
M+3	6213528
M+4	605029
M+5	1816074
M+6	186763

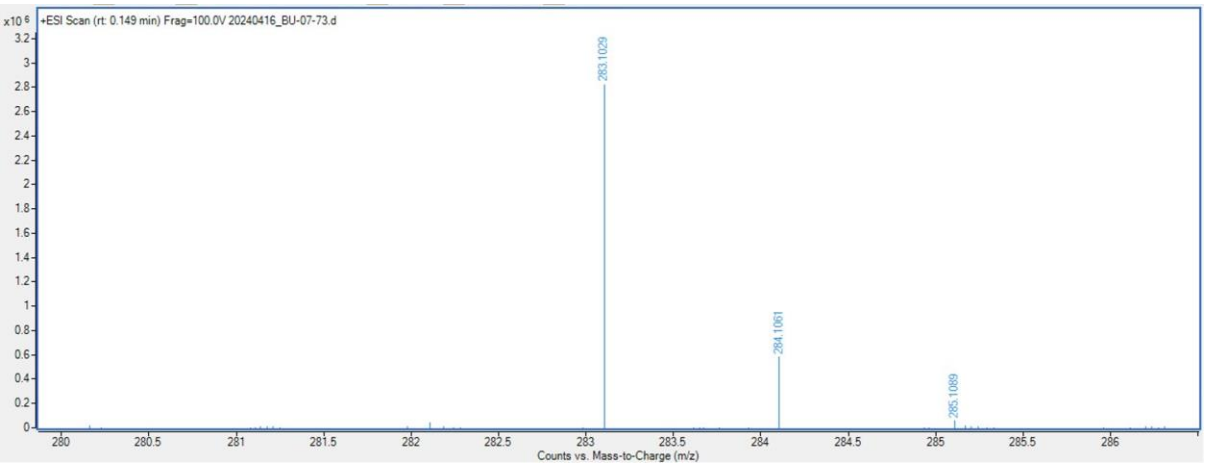
M+1	M+2	M+3
0%	1.13%	98.87%

Isotopic Enrichment > 99%

5-(4-(Benzyloxy)-3-fluorophenyl) pyrimidine-1,3--$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(2-(4-(benzyloxy)-3-fluorophenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (105.7 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 10-50% EtOAc in hexanes) afforded the title compound as a pale-yellow solid (49 mg, 0.17 mmol, 87% yield). mp 104-108 °C. IRυ_{max}/cm^{-1} (film): 3049, 1520, 1387, 1275, 814, 749, 715. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (t, J = 14.4 Hz, 1H), 8.94 – 8.85 (m, 2H), 7.49 – 7.44 (m, 2H), 7.40 (ddd, J = 7.9, 6.9, 1.0 Hz, 2H), 7.38 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 7.13 (t, J = 8.4 Hz, 1H), 5.21 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.43 (t, J = 3.5 Hz), 154.54 (d, J = 4.2 Hz), 152.09, 147.59 (d, J = 10.6 Hz), 136.12, 133.02 (q, J = 2.1 Hz), 128.80, 128.40, 127.61 (d, J = 6.7 Hz), 127.48, 122.92 (d, J = 3.6 Hz), 116.35 (d, J = 2.4 Hz), 114.91 (d, J = 19.7 Hz), 71.42; ^{19}F NMR (375 MHz, $CDCl_3$) δ -131.81 (dd, J = 11.7, 8.4 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 292.80; HRMS (ESI) found $[M+H]^+$ 283.1029, for $C_{17}H_{14}F^{15}N_2O^+$ requires 283.1025. Isotopic enrichment >99% determined by HRMS.

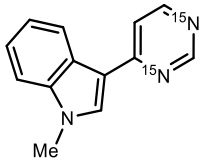


m/z	abundance
M+1	0
M+2	0
M+3	2826020
M+4	582626
M+5	59445

M+1	M+2	M+3
0%	0%	100.0%

Isotopic Enrichment > 99%

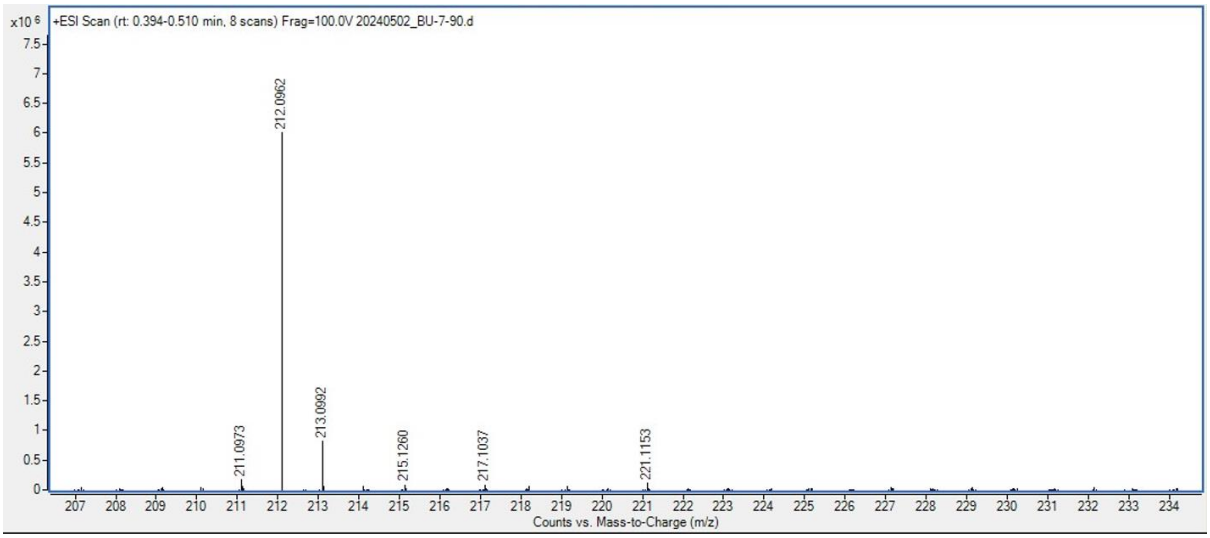
1-Methyl-3-(pyrimidin-4-yl-$^{15}N_2$)-1H-indole



Prepared according to a modified general procedure O using 1-methyl-3-(pyrimidin-4-yl)-1H-indole (209.3 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), and concentrated HCl (91 µL, 1.00 mmol). The reaction was determined to be incomplete by ^{1}H-NMR after 18 hours at 60 ºC and additional pyrrolidine (493 µL, 6.00 mmol) was added and the reaction heated to 90 ºC for 24 hours. Isolation A1 afforded crude (*E*)-1-(3-(1-methyl-1H-indol-3-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate as an orange powder (358 mg, 0.78 mmol, 78% yield) along with impurities.

The procedure continued with a portion of the crude vinamidinium salt (91.5 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). The reaction was heated to 60 ºC for 18 hours, then 90 ºC for 24 hours. Flash column chromatography (silica gel: 60-100% EtOAc in hexanes, followed by a second column using 90% EtOAc in hexanes) afforded the title compound as a yellow solid (36 mg, 0.17 mmol, 84% yield; 66% combined yield over two steps). mp 84-87 °C. IRυ_{max}/cm^{-1} (film): 3014, 1571, 1360, 1233, 745. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 – 9.05 (m, 1H), 8.60 (dd, J = 10.3, 5.5 Hz, 1H), 8.43 –

8.30 (m, 1H), 7.89 (s, 1H), 7.59 (dd, J = 5.5, 1.1 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.36 – 7.28 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.60 (d, J = 4.6 Hz), 159.06 (t, J = 3.1 Hz), 156.34 (d, J = 4.0 Hz), 138.17, 131.62 (d, J = 3.3 Hz), 125.98, 122.96, 121.75, 121.59, 116.28 (t, J = 2.0 Hz), 113.58 (d, J = 7.8 Hz), 110.11, 33.53; ^{15}N NMR (40 MHz, $CDCl_3$) δ 280.52, 278.44; HRMS (ESI) found $[M+H]^+$ 212.0962, for $C_{13}H_{12}N^{15}N_2^+$ requires 212.0966. Isotopic enrichment = 99% determined by HRMS.

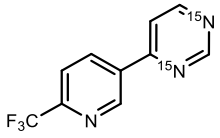


m/z	abundance
M+1	0
M+2	165877
M+3	6013889
M+4	818642

M+1	M+2	M+3
0%	2.71%	97.29%

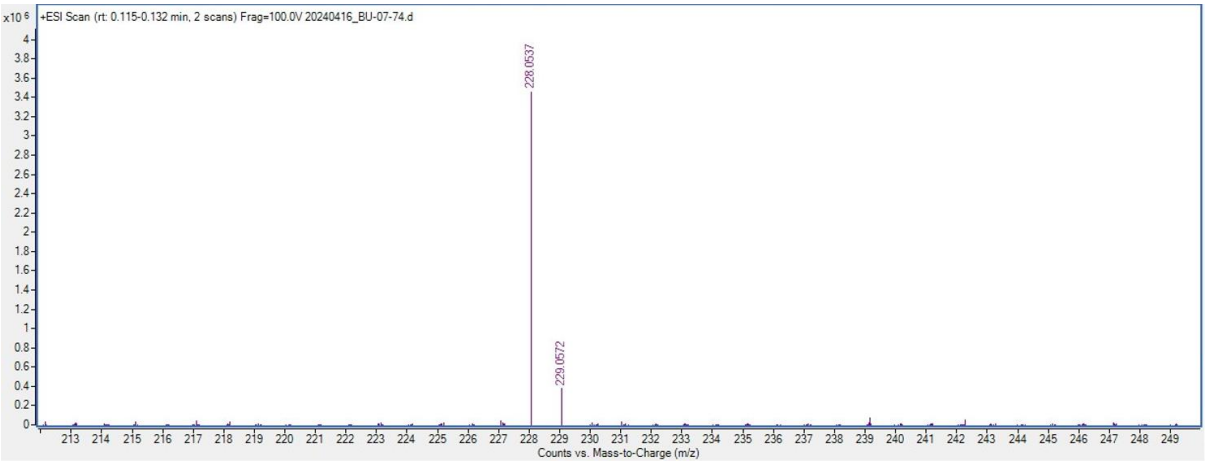
Isotopic Enrichment = 99%

4-(6-(Trifluoromethyl)pyridin-3-yl)pyrimidine-1,3-$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(3-(pyrrolidin-1-yl)-1-(6-(trifluoromethyl)pyridin-3-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (94.7 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and

DMF (1.0 mL). Flash column chromatography (silica gel: 10-60% EtOAc in hexanes) afforded the title compound as a white solid (39 mg, 0.17 mmol, 85% yield). mp 92-94 °C. IRυ_{max}/cm^{-1} (film): 3076, 1568, 1339, 1123, 1091, 836. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 – 9.29 (m, 2H), 8.90 (dd, J = 10.4, 5.3 Hz, 1H), 8.62 (dd, J = 8.3, 2.2 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.15 (d, J = 4.7 Hz), 159.59 (t, J = 3.4 Hz), 158.38 (d, J = 4.1 Hz), 149.95 (q, J = 35.1 Hz), 148.70 (d, J = 2.8 Hz), 136.26 (d, J = 2.7 Hz), 134.97 (d, J = 7.5 Hz), 121.43 (q, J = 272.6 Hz), 120.78 (q, J = 2.7 Hz), 117.54 (t, J = 2.1 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -68.05; ^{15}N NMR (40 MHz, $CDCl_3$) δ 292.75, 287.89; HRMS (ESI) found $[M+H]^+$ 228.0537, for $C_{10}H_7F_3N^{15}N_2^+$ requires 228.0527. Isotopic enrichment >99% determined by HRMS.

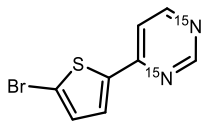


m/z	abundance
M+1	0
M+2	0
M+3	3460908
M+4	382012

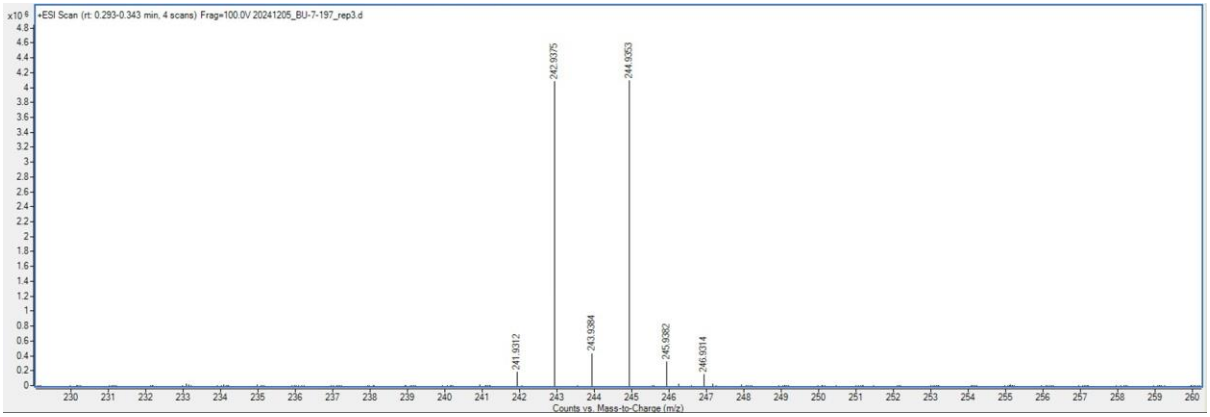
M+1	M+2	M+3
0%	0%	100.0%

Isotopic Enrichment > 99%

4-(5-Bromothiophen-2-yl)pyrimidine-1,3-$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(1-(5-bromothiophen-2-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (97.0 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 0-50% EtOAc in hexanes) afforded the title compound as a yellow powder (42 mg, 0.17 mmol, 86% yield). mp 46-50 °C. IRυ_{max}/cm^{-1} (film): 3075, 1572, 1455, 1422, 1369, 964, 831, 757. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (td, J = 14.5, 1.4 Hz, 1H), 8.69 (dd, J = 10.4, 5.4 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.13 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.09 (t, J = 3.1 Hz), 158.14 (d, J = 3.5 Hz), 157.29 (d, J = 4.1 Hz), 143.48 (d, J = 8.9 Hz), 131.63, 127.91 (d, J = 2.8 Hz), 118.88, 114.65 (t, J = 2.1 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 286.36, 280.87; HRMS (ESI) found $[M+H]^+$ 242.9375, for $C_8H_6Br^{15}N_2S^+$ requires 242.9370. Isotopic enrichment >99% determined by HRMS.

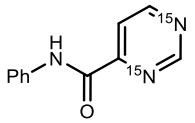


m/z	abundance
M+1	0
M+2	183832
M+3	4083712
M+4	43544
M+5	4097696
M+6	320047
M+7	148341

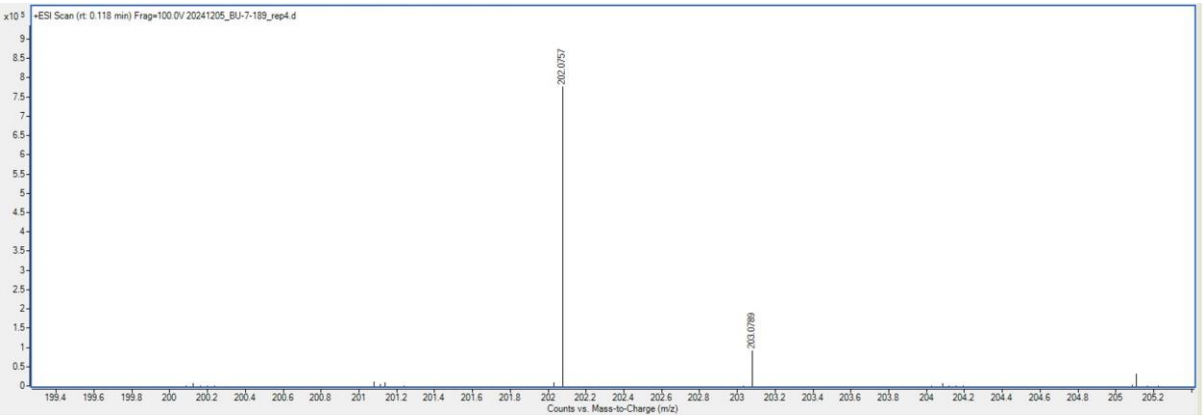
M+1	M+2	M+3
0%	0.89%	99.11%

Isotopic Enrichment > 99%

_N_-Phenylpyrimidine-1,3-$^{15}N_2$-4-carboxamide



Prepared according to general procedure N using (*E*)-1-(1-oxo-1-(phenylamino)-4-(pyrrolidin-1-yl)but-3-en-2-ylidene)pyrrolidin-1-ium trifluoromethanesulfonate (89.5 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 0-40% EtOAc in hexanes) afforded the title compound as a pale-yellow solid (18 mg, 0.09 mmol, 45% yield). mp 86-92 °C. IRυ_{max}/cm^{-1} (film): 3337, 3055, 1682, 1526, 1441, 752, 655. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 9.31 (td, J = 14.3, 1.5 Hz, 1H), 9.03 (dd, J = 10.7, 5.0 Hz, 1H), 8.26 – 8.19 (m, 1H), 7.77 (d, J = 7.4 Hz, 2H), 7.41 (dd, J = 8.5, 7.4 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.32 (d, J = 7.6 Hz), 159.71 (d, J = 4.2 Hz), 157.78 (dd, J = 3.8, 2.3 Hz), 156.42 (d, J = 4.4 Hz), 137.12, 129.36, 125.19, 120.01, 118.74 (t, J = 2.2 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 301.90, 279.33; HRMS (ESI) found $[M+H]^+$ 202.0757, for $C_{11}H_{10}N^{15}N_2O^+$ requires 202.0759. Isotopic enrichment >99% determined by HRMS.

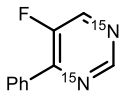


m/z	abundance
M+1	0
M+2	0
M+3	777062
M+4	91902

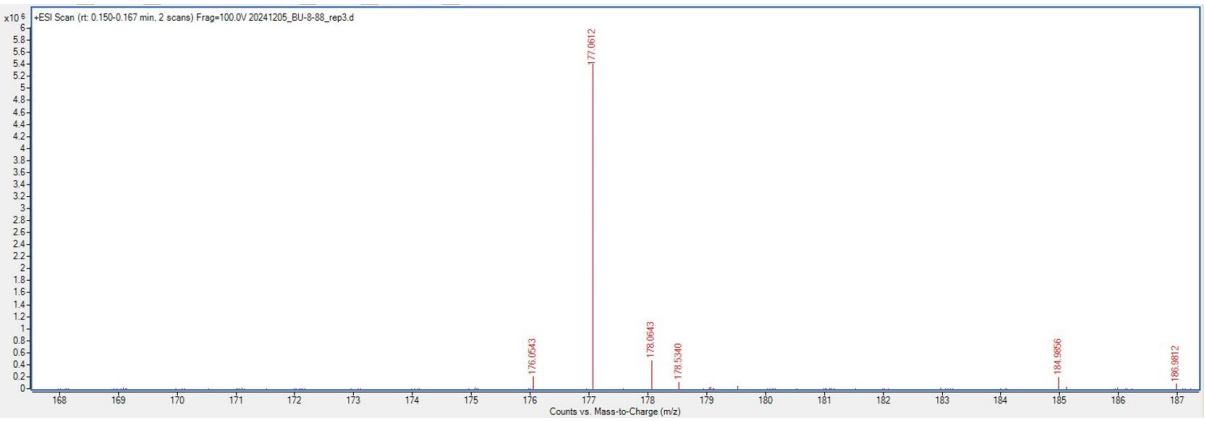
M+1	M+2	M+3
0%	0%	100.0%

Isotopic Enrichment > 99%

4-Phenyl-5-fluoropyrimidine-1,3-$^{15}N_2$



Prepared according to a modified general procedure N using (Z)-1-(2-fluoro-1-phenyl-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-iumtrifluoromethanesulfonate (84.5 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 6% EtOAc in hexanes) afforded the title compound as a white solid (24 mg, 0.13 mmol, 67% yield). mp 67-70 °C. IRυ_{max}/cm^{-1} (film): 3030, 2921, 1571, 1376, 1270, 735, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (td, J = 15.2, 3.0 Hz, 1H), 8.63 (dd, J = 9.8, 3.6 Hz, 1H), 8.14 (ddd, J = 7.3, 3.2, 1.4 Hz, 2H), 7.65 – 7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.94 (dt, J = 264.5, 3.0 Hz), 154.65 (td, J = 5.8, 2.9 Hz), 152.03 (dd, *J* = 7.4, 4.1 Hz), 146.10 (dd, J = 23.8, 3.8 Hz), 132.93 (dd, J = 6.9, 5.3 Hz), 131.36, 129.25 (dd, J = 6.5, 2.5 Hz), 128.93; ^{19}F NMR (375 MHz, $CDCl_3$) δ -134.55 – -134.59 (m); ^{15}N NMR (40 MHz, $CDCl_3$) δ 294.69 (d, J = 3.5 Hz); HRMS (ESI) found $[M+H]^+$ 177.0612, for $C_{10}H_8F^{15}N_2^+$ requires 177.0607. Isotopic enrichment = 98% determined by HRMS.

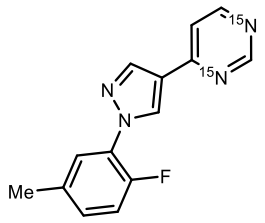


m/z	abundance
M+1	0
M+2	202299
M+3	5415403
M+4	474245

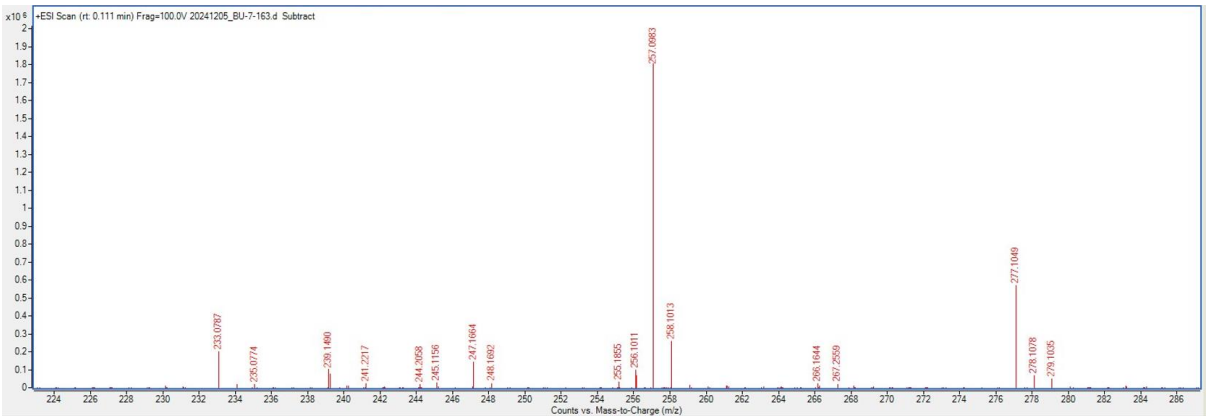
M+1	M+2	M+3
0%	3.69%	96.31%

Isotopic Enrichment = 98%

4-(1-(2-Fluoro-5-methylphenyl)-1H-pyrazol-4-yl)pyrimidine-1,3-$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(3-(1-(2-Fluoro-5-methylphenyl)-1H-pyrazol-4-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (100.5 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 75% EtOAc in hexanes) afforded the title compound as a pale-yellow powder (45 mg, 0.18 mmol, 88% yield). mp 131-134 °C. IRυ_{max}/cm^{-1} (film): 3101, 3051, 1587, 1513, 1361, 967, 714. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 – 9.03 (m, 1H), 8.69 (dd, J = 10.4, 5.3 Hz, 1H), 8.29 (s, 1H), 8.25 (s, 1H), 7.47 (d, J = 5.3 Hz, 1H), 7.30 (dd, J = 8.5, 6.0 Hz, 1H), 7.15 (dd, J = 8.8, 2.7 Hz, 1H), 7.08 (td, J = 8.3, 2.7 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.02 (d, J = 246.6 Hz), 159.32 (t, J = 3.2 Hz), 158.45 (d, J = 4.7 Hz), 157.30 (d, J = 4.2 Hz), 140.00 (d, J = 9.5 Hz), 139.52 (d, J = 2.2 Hz), 132.75 (d, J = 8.4 Hz), 130.76 (d, J = 2.4 Hz), 129.08 (d, J = 3.7 Hz), 122.44 (d, J = 8.1 Hz), 116.50, 116.06 (d, J = 20.7 Hz), 113.37 (d, J = 24.1 Hz), 17.78; ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.37 (q, J = 7.8 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 281.69; HRMS (ESI) found $[M+H]^+$ 257.0983, for $C_{14}H_{12}FN_2{}^{15}N_2{}^+$ requires 257.0981. Isotopic enrichment = 97% determined by HRMS.

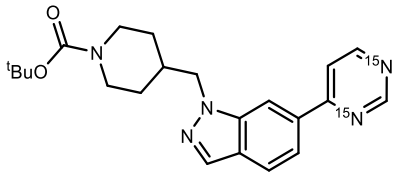


m/z	abundance
M+1	0
M+2	97496
M+3	1809420
M+4	259046
M+5	22235

M+1	M+2	M+3
0%	5.19%	94.81%

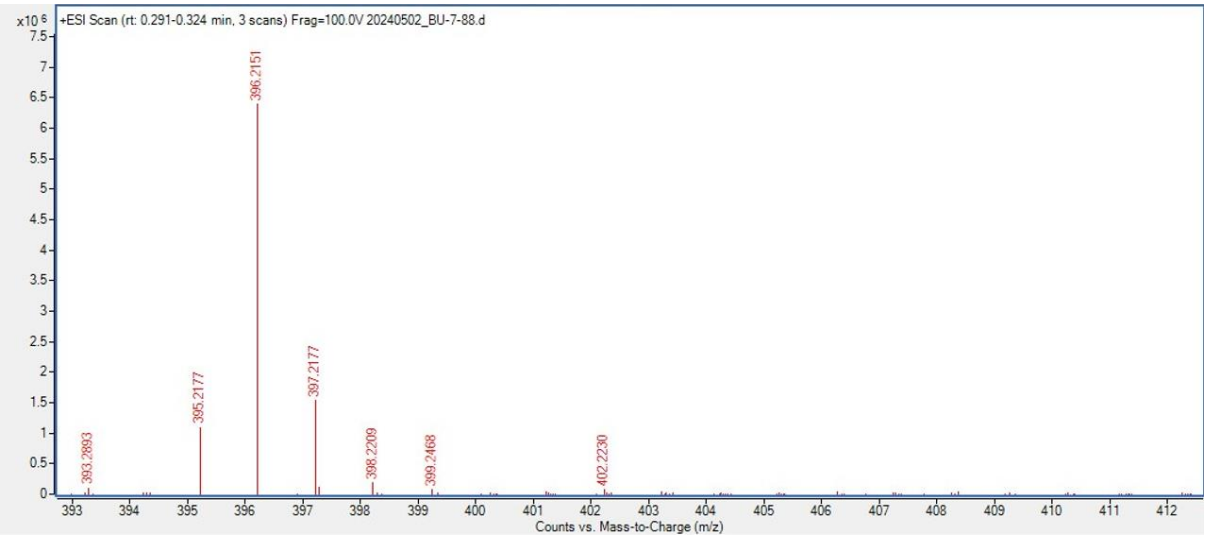
Isotopic Enrichment = 97%

***tert*-Butyl 4-((6-(pyrimidin-4-yl-$^{15}N_2$)-1H-indazol-1-yl)methyl)piperidine-1-carboxylate**



Prepared according to general procedure N using (*E*)-1-(3-(1-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methyl)-1H-indazol-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (128.4 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 20-100% EtOAc in hexanes, followed by a second column using 90% EtOAc in hexanes) afforded the title compound as a white solid (66 mg, 0.17 mmol, 84% yield). mp 98-100 °C. IRυ_{max}/cm^{-1} (film): 2929, 1680, 1569, 1421, 1365, 1158, 767. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 – 9.09 (m, 1H), 8.80 (dd, J = 10.4, 5.3 Hz, 1H), 8.26 (s, 1H), 8.05 (s, 1H), 7.87 – 7.72 (m, 3H), 4.34 (d, J = 7.2 Hz, 2H), 4.10 (s, 2H), 2.64 (t, J = 12.8 Hz, 2H), 2.22 (ttt, J = 11.1, 7.2, 3.7 Hz, 1H),

1.61 – 1.50 (m, 2H), 1.42 (s, 9H), 1.35 – 1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.99 (d, J = 4.6 Hz), 159.20 (t, J = 3.3 Hz), 157.74 (d, J = 3.7 Hz), 154.82, 140.46, 134.78 (d, J = 7.3 Hz), 133.27, 125.48, 121.88, 119.37 (d, J = 2.1 Hz), 117.63, 108.37 (d, J = 3.0 Hz), 79.57, 77.36, 54.38, 37.46, 30.00, 28.54; ^{15}N NMR (40 MHz, $CDCl_3$) δ 285.55; HRMS (ESI) found $[M+H]^+$ 396.2151, for $C_{22}H_{28}N_3{}^{15}N_2O_2^+$ requires 396.2178. Isotopic enrichment = 92% determined by HRMS.

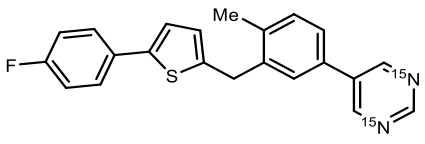


m/z	abundance
M+1	0
M+2	1101597
M+3	6405492
M+4	1538472
M+5	127481
M+6	198451
M+7	74353

M+1	M+2	M+3
0%	14.80%	85.20%

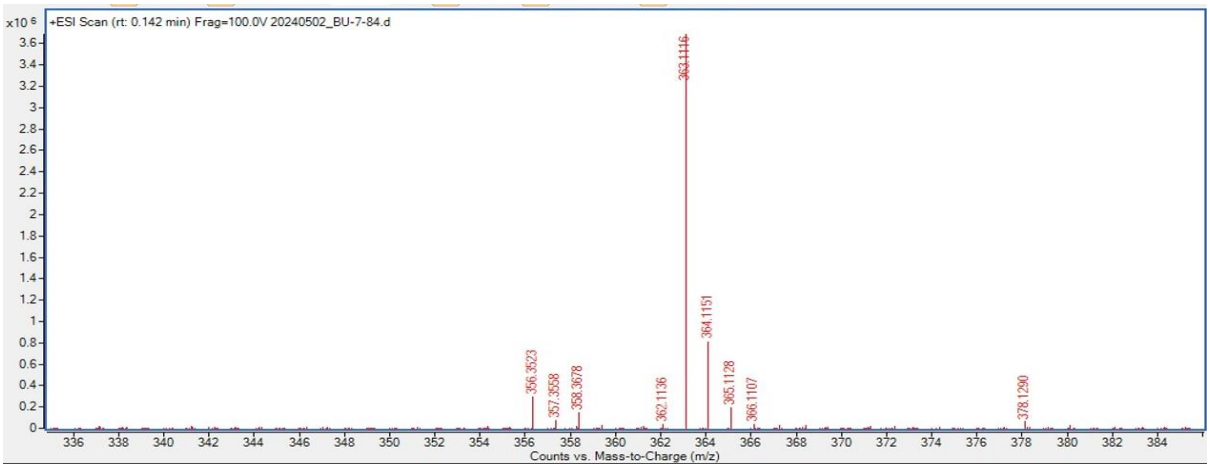
Isotopic Enrichment = 93%

5-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyrimidine-1,3-$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(2-(4-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-3-methylphenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium

trifluoromethanesulfonate (121.7 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a white solid (67 mg, 0.18 mmol, 92% yield). mp 108-111 °C. IRυ_{max}/cm^{-1} (film): 2912, 1508, 1389, 1229, 828, 801. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (t, J = 14.4 Hz, 1H), 8.97 – 8.89 (m, 2H), 7.51 – 7.45 (m, 2H), 7.45 – 7.39 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.10 – 6.98 (m, 3H), 6.72 (d, J = 3.6 Hz, 1H), 4.21 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.26 (d, J = 246.8 Hz), 157.38 (t, J = 3.3 Hz), 154.85 (d, J = 4.4 Hz), 142.55, 142.03, 139.67, 137.70, 134.20 (t, J = 2.3 Hz), 132.32, 131.70, 130.79 (d, J = 3.4 Hz), 127.97, 127.27 (d, J = 8.0 Hz), 126.37, 125.50, 122.85 (d, J = 1.2 Hz), 115.86 (d, J = 21.8 Hz), 34.22, 19.43; ^{19}F NMR (375 MHz, $CDCl_3$) δ -114.83 – -115.07 (m); ^{15}N NMR (40 MHz, $CDCl_3$) δ 292.43; HRMS (ESI) found $[M+H]^+$ 363.1116, for $C_{22}H_{18}F^{15}N_2S^+$ requires 363.1110. Isotopic enrichment >99% determined by HRMS.

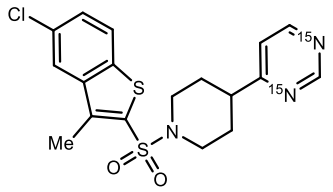


m/z	abundance
M+1	0
M+2	41744
M+3	3686414
M+4	814811
M+5	189856
M+6	39132

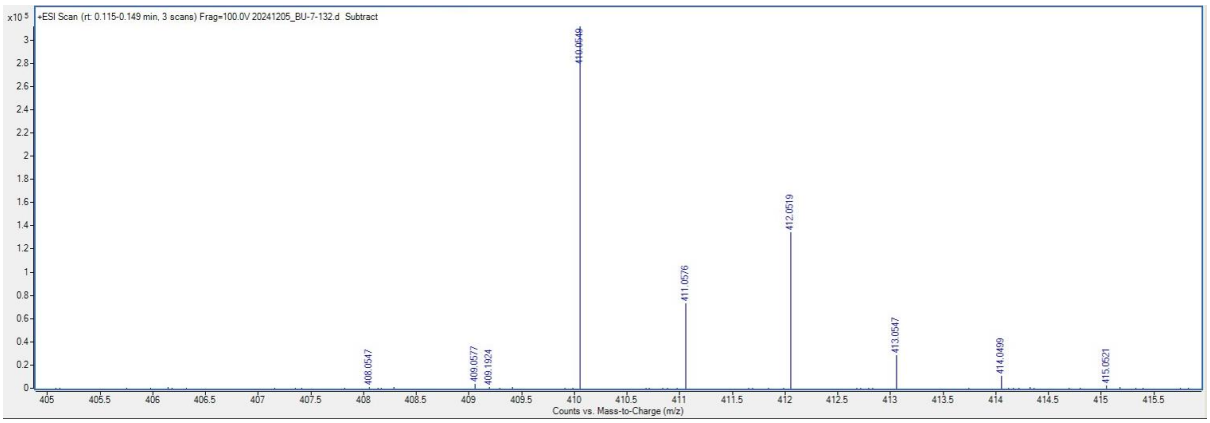
M+1	M+2	M+3
0%	1.14%	98.86%

Isotopic Enrichment > 99%

4-(1-((5-Chloro-3-methylbenzo[b]thiophen-2-yl)sulfonyl)piperidin-4-yl)pyrimidine-1,3-$^{15}N_2$



Prepared according to a modified general procedure N using (*E*)-1-(1-((5-chloro-3-methylbenzo[b]thiophen-2-yl)sulfonyl)piperidin-4-yl)-3-(pyrrolidin-1-yl)prop-2-en-1-one (90.6 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL), and heated to 90 ºC for 24 hours. Flash column chromatography (silica gel: 75% EtOAc in hexanes) afforded the title compound as a white solid (70.2 mg, 0.17 mmol, 86% yield). mp 201-203 °C. IRυ_{max}/cm^{-1} (film): 2918, 1574, 1354, 1155, 931, 735, 554. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (td, J = 14.4, 1.4 Hz, 1H), 8.64 (dd, J = 10.4, 5.2 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.47 (dd, J = 8.6, 2.0 Hz, 1H), 7.15 (d, J = 5.2 Hz, 1H), 4.05 (dt, J = 12.6, 3.4 Hz, 2H), 2.74 (dd, J = 12.1, 2.7 Hz, 3H), 2.70 (s, 3H), 2.10 – 2.01 (m, 2H), 1.99 – 1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.59 (d, J = 4.4 Hz), 158.86 (t, J = 3.4 Hz), 157.38 (d, J = 4.1 Hz), 141.04, 137.80, 136.53, 134.34, 131.73, 128.00, 123.76, 123.57, 118.77, 46.31, 42.91 (d, J = 7.5 Hz), 30.43 (d, J = 1.5 Hz), 12.97; ^{15}N NMR (40 MHz, $CDCl_3$) δ 291.50; HRMS (ESI) found $[M+H]^+$ 410.0549, for $C_{18}H_{19}ClN^{15}N_2O_2S_2^+$ requires 410.0542. Isotopic enrichment >99% determined by HRMS.

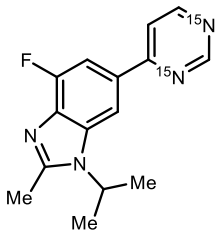


m/z	abundance
M+1	913
M+2	3557
M+3	311451
M+4	73290
M+5	134243
M+6	28592
M+7	10500
M+8	2370

M+1	M+2	M+3
0.16%	0.98%	98.86%

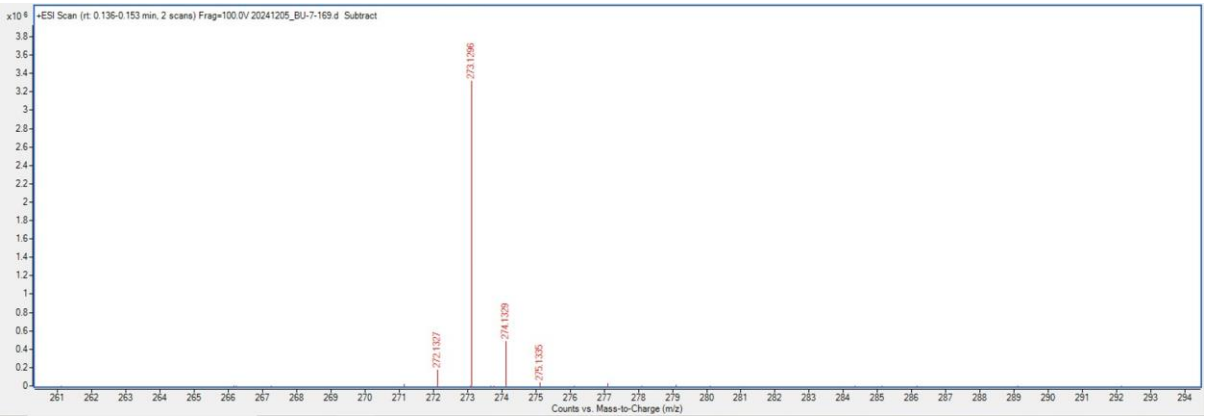
Isotopic Enrichment > 99%

4-Fluoro-1-isopropyl-2-methyl-6-(pyrimidin-4-yl-$^{15}N_2$)-1H-benzo[d]imidazole



Prepared according to general procedure O using 4-fluoro-1-isopropyl-2-methyl-6-(pyrimidin-4-yl)-1H-benzo[d]imidazole (270.3 mg, 1.00 mmol), EtOAc (5.0 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), and concentrated HCl (91 µL, 1.00 mmol). Isolation A1 followed by a second precipitation in Et_2O afforded crude (*E*)-1-(3-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazol-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate as an orange powder (235 mg, 0.45 mmol, 45% yield) along with impurities.

The procedure continued with a portion of the crude vinamidinium salt (103.7 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 60-100% EtOAc in hexanes, followed by a second column using 90% EtOAc in hexanes) afforded the title compound as a yellow solid (35 mg, 0.13 mmol, 65% yield; 29% combined yield over two steps). mp 128-135 °C. IRυ_{max}/cm^{-1} (film): 2989, 2962, 1573, 1373, 1335, 1261, 1193, 830, 634. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (ddd, J = 15.4, 14.4, 1.5 Hz, 1H), 8.74 (dd, J = 10.4, 5.4 Hz, 1H), 8.18 (d, J = 1.4 Hz, 1H), 7.69 (dq, J = 5.6, 1.0 Hz, 1H), 7.57 (dd, J = 11.3, 1.4 Hz, 1H), 4.73 (hept, J = 7.0 Hz, 1H), 2.67 (s, 3H), 1.69 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.42, 159.08 (t, J = 3.2 Hz), 157.59 (d, J = 3.9 Hz), 153.74 (d, J = 250.6 Hz), 153.63, 137.18 (d, J = 9.3 Hz), 134.14 (d, J = 17.0 Hz), 130.99 (t, J = 7.2 Hz), 116.96 (t, J = 2.1 Hz), 106.51 (t, J = 3.3 Hz), 106.26 (dd, J = 19.4, 2.4 Hz), 48.72, 21.63, 15.30; ^{19}F NMR (375 MHz, $CDCl_3$) δ -128.13 (d, J = 11.3 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 284.57; HRMS (ESI) found $[M+H]^+$ 273.1296, for $C_{15}H_{16}FN_2{}^{15}N_2^+$ requires 273.1294. Isotopic enrichment = 97% determined by HRMS.

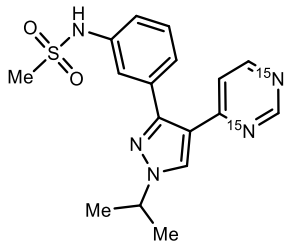


m/z	abundance
M+1	0
M+2	173356
M+3	3313139
M+4	484990
M+5	36282

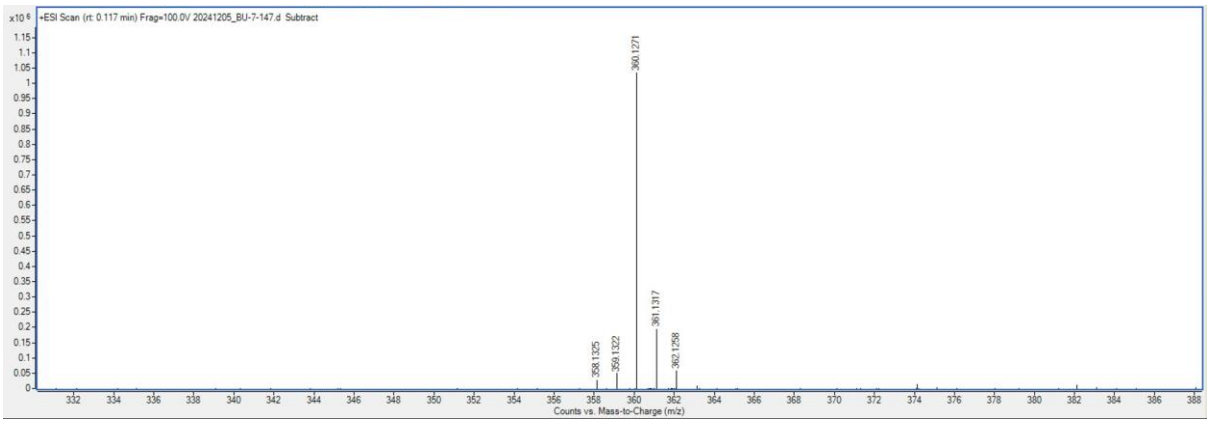
M+1	M+2	M+3
0%	5.04%	94.96%

Isotopic Enrichment = 97%

***N*-(3-(1-Isopropyl-4-(pyrimidin-4-yl-$^{15}N_2$)-1H-pyrazol-3-yl)phenyl)methanesulfonamide**



Prepared according to a modified general procedure N using (*E*)-1-(3-(3-(1-isopropyl-1H-pyrazol-3-yl)-5-(methylsulfonamido)phenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (121.7 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL), and heated to 90 ºC for 24 hours. Flash column chromatography (silica gel: 90% EtOAc in hexanes) afforded the title compound as a white solid (50 mg, 0.14 mmol, 69% yield). mp 191-195 °C. IRυ_{max}/cm^{-1} (film): 2923, 1579, 1323, 1147, 961, 800. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 – 9.02 (m, 1H), 8.46 (dd, J = 10.4, 5.4 Hz, 1H), 8.14 (s, 1H), 7.44 – 7.38 (m, 1H), 7.37 – 7.30 (m, 3H), 7.09 (dd, J = 5.4, 1.2 Hz, 1H), 7.01 (s, 1H), 4.58 (hept, J = 6.7 Hz, 1H), 3.02 (s, 3H), 1.59 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.50, 158.99, 156.67, 149.27, 137.38, 135.09, 130.21, 129.49, 125.95, 121.11, 120.46, 118.17, 118.09, 54.74, 39.83, 22.98; ^{15}N NMR (40 MHz, $CDCl_3$) δ 284.00, 283.64; HRMS (ESI) found $[M+H]^+$ 360.1271, for $C_{17}H_{20}N_3{}^{15}N_2O_2S^+$ requires 360.1273. Isotopic enrichment = 95% determined by HRMS.

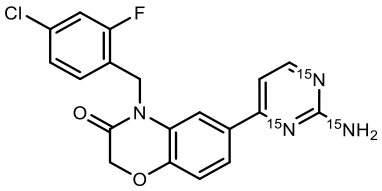


m/z	abundance
M+1	28041
M+2	48710
M+3	1034831
M+4	195538
M+5	58109

M+1	M+2	M+3
2.64%	4.19%	93.17%

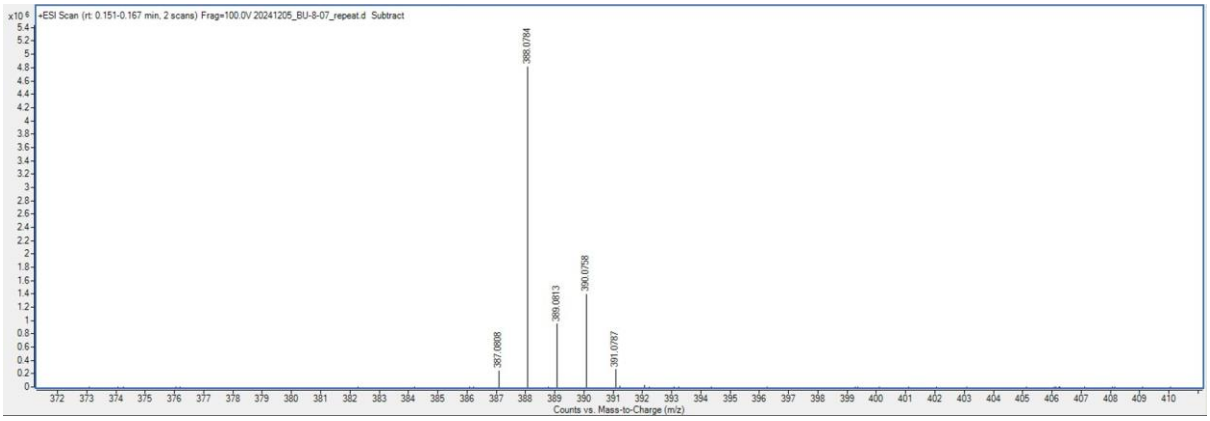
Isotopic Enrichment = 95%

6-(2-(Amino-^{15}N)pyrimidin-4-yl-1,3-$^{15}N_2$)-4-(4-chloro-2-fluorobenzyl)-2H-benzo[*b*][1,4]oxazin-3(4*H*)-one



To an oven-dried 8 mL vial equipped with a stir bar was added (*E*)-1-(3-(4-(4-chloro-2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (123.3 mg, 0.20 mmol), guanidine-$^{15}N_3$ hydrochloride (59.1 mg, 0.60 mmol), DBU (149 µL, 1.00 mmol), and DMF (1.0 mL) and the suspension was heated to 90 °C for 18 hours. Upon completion, the mixture was diluted with water, neutralized with 0.1M HCl and saturated $NaHCO_3$, then extracted with EtOAc. The combined organic extracts were washed with brine and dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 90% EtOAc in hexanes) afforded the title

compound as a yellow solid (57 mg, 0.15 mmol, 74% yield). mp 201-205 °C. IRυ_{max}/cm^{-1} (film): 3275, 3153, 1677, 1550, 1437, 1275, 801. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, J = 10.9, 5.3 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.64 (dd, J = 8.4, 1.9 Hz, 1H), 7.18 (t, J = 8.3 Hz, 1H), 7.14 (dd, J = 10.0, 2.1 Hz, 1H), 7.09 – 7.02 (m, 2H), 6.89 (dt, J = 5.3, 1.1 Hz, 1H), 5.26 (s, 2H), 5.12 (dt, J = 87.6, 3.1 Hz, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.53, 160.39 (d, *J* = 249.3 Hz), 158.68, 147.49, 134.61 (d, J = 10.3 Hz), 132.10 (d, J = 7.9 Hz), 129.91 (d, J = 4.7 Hz), 128.44, 125.34 (d, J = 3.6 Hz), 123.40 (d, J = 2.7 Hz), 121.73, 121.59, 117.51, 116.67, 116.42, 114.07, 107.03, 67.74, 37.93 (d, J = 4.4 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.69 – -115.79 (m); ^{15}N NMR (40 MHz, $CDCl_3$) δ 76.23 (t, J = 6.9 Hz); HRMS (ESI) found $[M+H]^+$ 388.0784, for $C_{19}H_{15}ClFN^{15}N_3O_2^+$ requires 388.0773. Isotopic enrichment = 98% determined by HRMS.

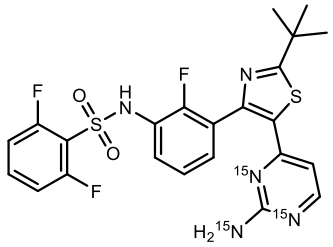


m/z	abundance
M+1	0
M+2	0
M+3	248529
M+4	4818602
M+5	955206
M+6	1400503
M+7	268157

M+1	M+2	M+3	M+4
0%	0%	5.15%	94.85%

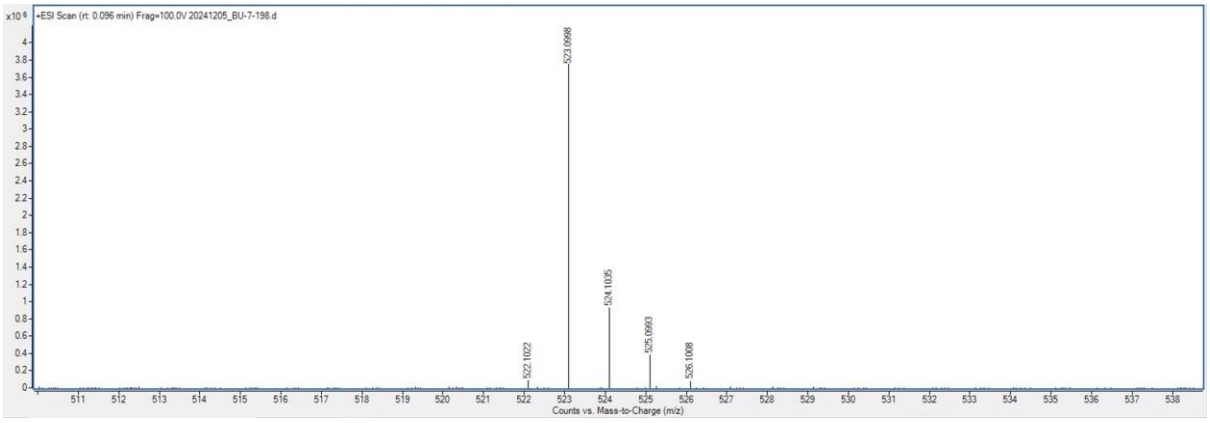
Isotopic Enrichment = 98%

Dabrafenib-$^{15}N_3$ (3r)



To an oven-dried 8 mL vial equipped with a stir bar was added N-{3-(2-(tert-Butyl)-5-(pyrimidin-4-yl)thiazol-4-yl)-2-fluorophenyl}-2,6-difluorobenzenesulfonamide (202 mg, 0.40 mmol) and placed under a nitrogen atmosphere. CH_2Cl_2 (2.0 mL) was added, the reaction vessel was cooled to -78 ºC, and Tf_2O (67 µL, 0.40 mmol) was added dropwise. The reaction was stirred for 30 minutes before aniline (37 µL, 0.40 mmol) was added dropwise followed by collidine (53 µL, 0.40 mmol). The reaction was stirred for an additional 5 minutes at -78 ºC before removing the cooling bath and allowing the reaction to warm to room temperature while stirring for approximately 30 minutes. The resulting mixture was then concentrated *in vacuo*, then EtOH (2.0 mL), and pyrrolidine (197 µL, 2.40 mmol) were added before heating to 40 ºC for 120 hours. The mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting oil was diluted with CH_2Cl_2 and transferred to a separatory funnel before washing (3x) with 0.1M aqueous HCl. The combined aqueous layers were extracted (x2) with CH_2Cl_2, and the combined organic layers were washed (1x) with H_2O, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was then dissolved in a minimal amount of CH_2Cl_2 and added dropwise to a stirring solution of Et_2O:hexanes (3:1), then chilled in a -20 ºC freezer for 3 hours before filtering. The crude material was precipitated again using 100% Et_2O, then purified by column chromatography (silica gel: 1% Et_3N in EtOAc followed by 6% MeOH in CH_2Cl_2) to yield crude vinamidinium salt (89 mg) with a mixture of counterions. The crude vinamidinium salt was then added to an oven-dried 8 mL vial equipped with a stir bar. Next was added guanidine-$^{15}N_3$ hydrochloride (38.4 mg, 0.39 mmol), DBU (97 µL, 0.65 mmol), and DMF (0.65 mL). The reaction was heated to 90 ºC for 18 hours

before diluting with water, neutralizing with 0.1M AcOH and saturated $NaHCO_3$ to pH = 8, and extracting with EtOAc. The combined organic extracts were washed with brine and dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 3.5% MeOH in CH_2Cl_2) afforded the title compound as a yellow solid (24.1 mg, 0.46 mmol, 12% yield over two steps). mp 209-213 °C. IRυ_{max}/cm^{-1} (film): 3520, 3412, 2963, 1564, 1464, 1173, 1001, 794. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 10.7, 5.3 Hz, 1H), 7.71 (td, J = 7.8, 1.7 Hz, 1H), 7.47 (tt, J = 8.5, 5.9 Hz, 1H), 7.35 (ddd, J = 8.0, 6.5, 1.7 Hz, 1H), 7.21 (td, J = 8.0, 1.0 Hz, 1H), 6.95 (t, J = 8.7 Hz, 2H), 6.14 (d, J = 5.3 Hz, 1H), 5.20 (d, J = 88.1 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.22, 162.59 (d, J = 24.7 Hz), 159.88 (dd, J = 259.8, 3.4 Hz), 159.50, 158.02, 151.39 (d, J = 248.8 Hz), 146.03 (d, J = 2.1 Hz), 135.29 (t, J = 11.1 Hz), 133.79 (d, J = 9.1 Hz), 128.51 (d, J = 2.2 Hz), 125.30 (d, J = 4.6 Hz), 124.48 (dd, J = 38.0, 13.4 Hz), 124.04, 117.28 (d, J = 15.5 Hz), 113.40 (d, J = 3.8 Hz), 113.17 (d, J = 3.6 Hz), 107.50, 38.18, 30.82; ^{19}F NMR (375 MHz, $CDCl_3$) δ -106.82 (dt, J = 9.8, 4.7 Hz, 2F), -129.34 (td, J = 7.1, 3.8 Hz, 1F); ^{15}N NMR (40 MHz, $CDCl_3$) δ 76.82 (t, J = 6.7 Hz); HRMS (ESI) found $[M+H]^+$ 523.0998, for $C_{23}H_{21}F_3N_2{}^{15}N_3O_2S_2^+$ requires 523.0994. Isotopic enrichment >99% determined by HRMS.

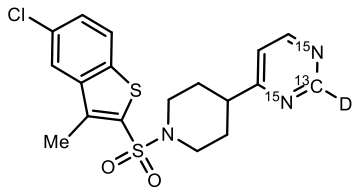


m/z	abundance
M+1	0
M+2	0
M+3	87140
M+4	3757847
M+5	932682
M+6	381617
M+7	81571

M+1	M+2	M+3	M+4
0%	0%	2.26%	97.74%

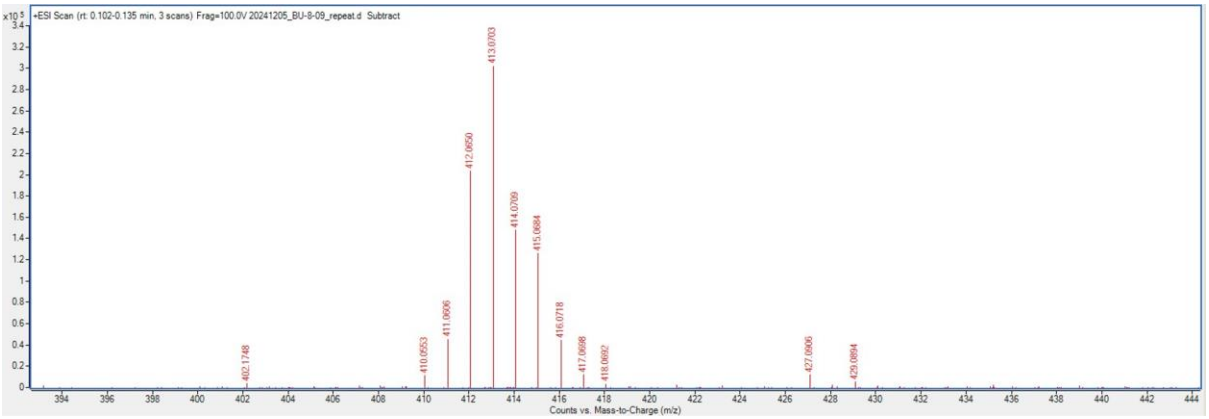
Isotopic Enrichment > 99%

4-(1-((5-Chloro-3-methylbenzo[b]thiophen-2-yl)sulfonyl)piperidin-4-yl)pyrimidine-2-^{13}C-2-d-1,3-$^{15}N_2$



Prepared according to a modified general procedure N using (*E*)-1-(1-((5-chloro-3-methylbenzo[b]thiophen-2-yl)sulfonyl)piperidin-4-yl)-3-(pyrrolidin-1-yl)prop-2-en-1-one (90.6 mg, 0.20 mmol), formimidamide-^{13}C-1-d-$^{15}N_2$ acetate (64.9 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL), and heated to 90 ºC for 40 hours. Flash column chromatography (silica gel: 75% EtOAc in hexanes) afforded the title compound as a white solid (60 mg, 0.14 mmol, 72% yield). Note: 58% undesired deuteration occurred on the benzothiophene, IE calculations corrected accordingly. mp 199-202 °C. IRυ_{max}/cm^{-1} (film): 2919, 2851, 1550, 1344, 1156, 930, 735, 556. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (t, J = 10.4 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.45 (dd, J = 8.6, 2.0 Hz, 1H), 7.14 (d, J = 5.2 Hz, 1H), 4.03 (dt, J = 12.6, 3.4 Hz, 2H), 2.73 (dd, J = 12.1, 2.7 Hz, 3H), 2.69 (s, 3H), 2.10 – 1.99 (m, 2H), 1.99 – 1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.53 (d, J = 5.5 Hz), 158.79 (dt, J = 6.4, 3.2 Hz), 158.28 (dd, J = 30.8, 3.1 Hz), 157.31, 141.00, 137.76, 136.50, 134.29, 131.69, 127.96, 123.63 (d, J = 19.9 Hz), 118.80 (d, J = 16.7 Hz), 46.28, 42.81 (dd, J = 7.7, 4.3 Hz), 30.39 (d, J = 1.5 Hz), 12.94; ^{15}N

NMR (40 MHz, $CDCl_3$) δ 291.48; HRMS (ESI) found $[M+H]^+$ 412.0650, for $C_{17}{}^{13}CH_{18}DClN^{15}N_2O_2S_2^+$ requires 412.0639. Isotopic enrichment = 96% determined by HRMS.

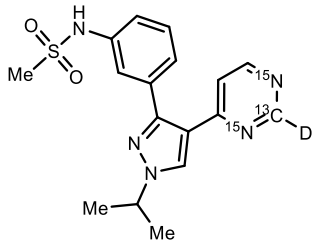


m/z	abundance
M+1	0
M+2	0
M+3	11648
M+4	45546
M+5	203554
M+6	301961
M+7	148136
M+8	126147
M+9	44770
M+10	12255

M+1	M+2	M+3	M+4	M+5
0%	0%	4.01%	12.62%	84.11%

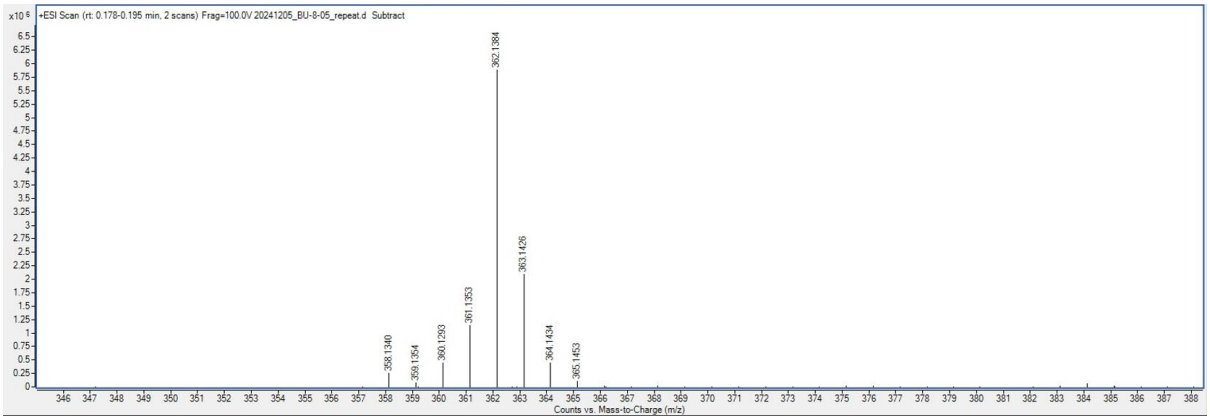
Isotopic Enrichment = 96%

_N_-(3-(1-Isopropyl-4-(pyrimidin-4-yl-2-^{13}C-2-d-1,3-$^{15}N_2$)-1H-pyrazol-3-yl)phenyl)methanesulfonamide



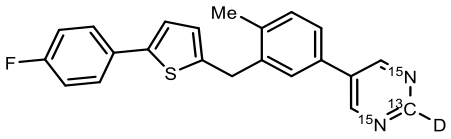
Prepared according to a modified general procedure N (*E*)-1-(3-(3-(1-isopropyl-1H-pyrazol-3-yl)-5-(methylsulfonamido)phenyl)-3-(pyrrolidin-1-yl)allylidene)-pyrrolidine-1-ium trifluoromethanesulfonate (121.7 mg, 0.20 mmol), formimidamide-^{13}C-1-d-$^{15}N_2$ acetate (64.9 mg,

0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL), and heated to 90 ºC for 48 hours. Flash column chromatography (silica gel: 90% EtOAc in hexanes) afforded the title compound as a white solid (39 mg, 0.11 mmol, 54% yield). mp 191-195 °C. IRυ_{max}/cm^{-1} (film): 2923, 1571, 1322, 1149, 961, 803, 762. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (td, J = 10.4, 5.3 Hz, 1H), 8.14 (s, 1H), 7.44 – 7.38 (m, 1H), 7.37 – 7.33 (m, 3H), 7.19 (s, 1H), 7.09 (dt, J = 5.4, 1.0 Hz, 1H), 4.58 (hept, J = 6.7 Hz, 1H), 3.01 (s, 3H), 1.59 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.51, 159.13 – 158.88 (m), 158.51 (d, J = 30.4 Hz), 156.68, 149.26, 137.38, 135.10, 130.21, 129.49, 125.94, 121.11, 120.43, 118.05, 54.74, 39.81 (d, J = 3.9 Hz), 22.99; ^{15}N NMR (40 MHz, $CDCl_3$) δ 283.49.; HRMS (ESI) found $[M+H]^+$ 362.1384, for $C_{16}{}^{13}CH_{19}DN_3{}^{15}N_2O_2S^+$ requires 362.1369. Isotopic enrichment = 91% determined by HRMS.

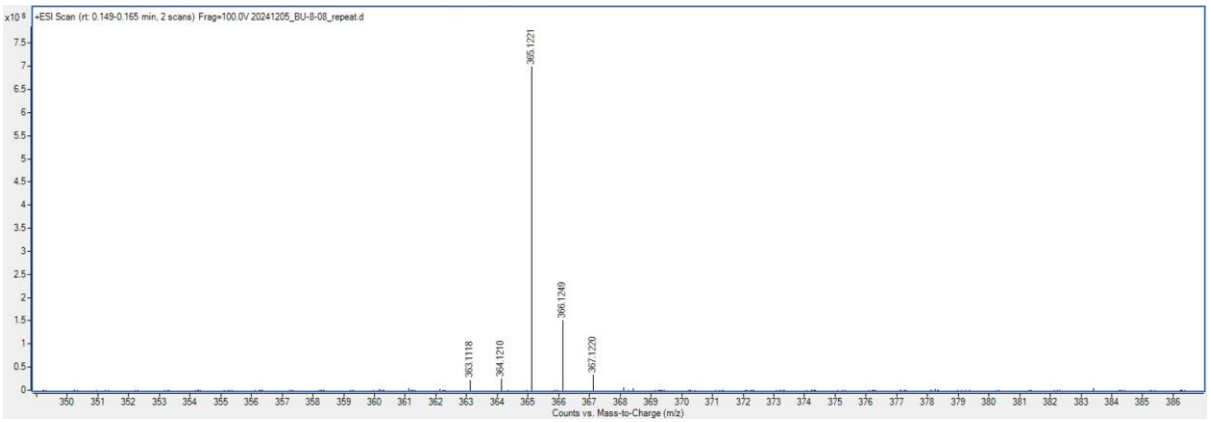


m/z	abundance	M+1	M+2	M+3	M+4	M+5
M+1	251907	2.93	0.49%	5.05%	12.57%	79.01%
M+2	78608					
M+3	446526	Isotopic Enrichment = 91%				
M+4	1140114					
M+5	5891232					
M+6	2096106					
M+7	446526					
M+8	111293					

5-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyrimidine-2-^{13}C-2-d-1,3 -$^{15}N_2$



Prepared according to general procedure N using (*E*)-1-(2-(4-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-3-methylphenyl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (121.7 mg, 0.20 mmol), formimidamide-^{13}C-1-d-$^{15}N_2$ acetate (64.9 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a white solid (65 mg, 0.18 mmol, 90% yield). mp 109-112 °C. IRυ_{max}/cm^{-1} (film): 2912, 1507, 1387, 1229, 828, 800, 656. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 – 8.81 (m, 2H), 7.53 – 7.45 (m, 2H), 7.45 – 7.38 (m, 2H), 7.34 (d, J = 7.7 Hz, 1H), 7.07 – 6.93 (m, 3H), 6.73 (dd, J = 3.6, 1.1 Hz, 1H), 4.21 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.29 (d, J = 246.9 Hz), 156.95 (dd, J = 32.5, 29.2 Hz), 155.48 – 154.64 (m), 142.56, 142.06, 139.71, 137.76, 134.29 (d, J = 17.0 Hz), 132.30, 131.73, 130.81 (d, J = 3.4 Hz), 128.00, 127.30 (d, J = 8.0 Hz), 126.39, 125.53, 122.88, 115.89 (d, J = 21.8 Hz), 34.24, 19.46; ^{19}F NMR (375 MHz, $CDCl_3$) δ -114.92 (ddd, J = 13.8, 8.5, 5.1 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 292.05; HRMS (ESI) found $[M+H]^+$ 365.1215, for $C_{21}{}^{13}CH_{17}DF^{15}N_2S^+$ requires 365.1206. Isotopic enrichment = 98% determined by HRMS.

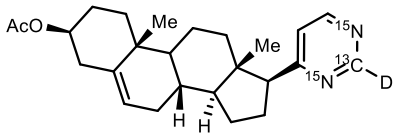


m/z	abundance
M+1	0
M+2	0
M+3	220930
M+4	247729
M+5	6996911
M+6	1516834
M+7	327231

M+1	M+2	M+3	M+4	M+5
0%	0%	3.04%	2.87%	94.07%

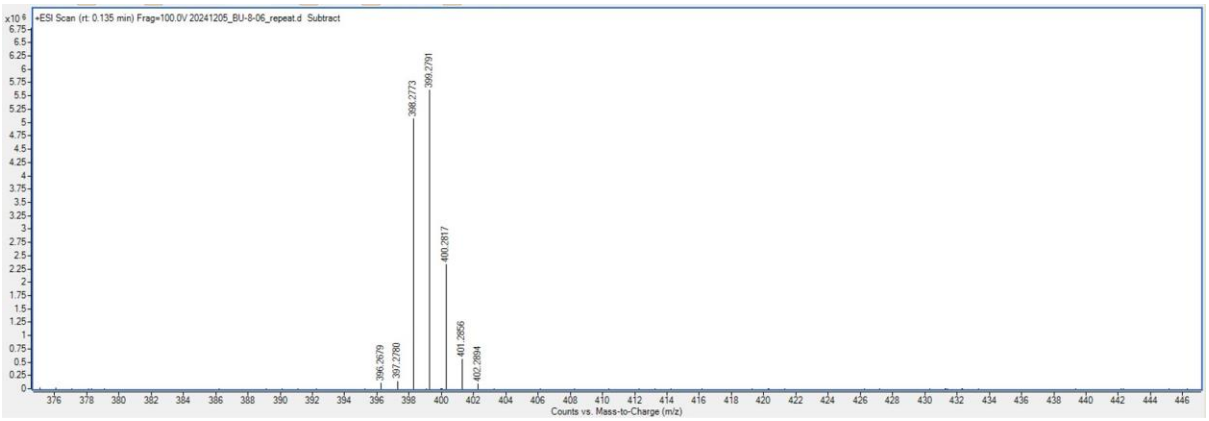
Isotopic Enrichment = 98%

(3S,8S,10R,13S,14S,17S)-10,13-Dimethyl-17-(pyrimidin-4-yl-2-^{13}C-2-d-1,3-$^{15}N_2$)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate



Prepared according to a modified general procedure O using (3S,8S,10R,13S,14S,17S)-10,13-dimethyl-17-(pyrimidin-4-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (394.6 mg, 1.00 mmol), CH_2Cl_2 (5.0 mL), Tf_2O (168 µL, 1.00 mmol), aniline (91 µL, 1.00 mmol), collidine (132 µL, 1.00 mmol), EtOH (5.0 mL), pyrrolidine (493 µL, 6.00 mmol), 0.4M HCl in dioxanes (250 µL, 1.00 mmol), and heated to 90 ºC for 144 hours. Isolation A1 using 0.1M AcOH instead of HCl, followed by column chromatography (silica gel: 1% Et_3N in EtOAc followed by 5% MeOH in CH_2Cl_2) yielded crude vinamidinium salt (133 mg) afforded crude 1-((*E*)-3-((3S,8S,10R,13S,14S,17S)-3-acetoxy-10,13-

dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate as a red solid (133 mg, 0.21 mmol, 21% yield) along with impurities. The crude vinamidinium salt was then added to an oven-dried 8 mL vial equipped with a stir bar. Next was added formimidamide-^{13}C-1-d-$^{15}N_2$ acetate (64.9 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL), and the reaction was heated to 90 °C for 48 hours. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a 5:1 mixture of diastereomers (white powder, 41.6 mg, 0.10 mmol, 10% yield over two steps). Reported spectroscopy are of the major diastereomer. mp 180-189 °C. IRυ_{max}/cm^{-1} (film): 2930, 1719, 1565, 1366, 1239, 1035. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (td, J = 10.4, 5.2 Hz, 1H), 7.14 (d, J = 5.2 Hz, 1H), 5.40 – 5.31 (m, 1H), 4.66 – 4.53 (m, 1H), 2.79 (t, J = 9.5 Hz, 1H), 2.51 – 2.37 (m, 1H), 2.36 – 2.24 (m, 2H), 2.06 (td, J = 5.1, 2.3 Hz, 1H), 2.02 (s, 3H), 1.98 – 1.89 (m, 1H), 1.84 (dtq, J = 8.7, 6.1, 2.8 Hz, 2H), 1.76 (dt, J = 8.0, 3.5 Hz, 1H), 1.68 – 1.46 (m, 5H), 1.45 – 1.33 (m, 3H), 1.33 – 1.21 (m, 1H), 1.15 (td, J = 14.2, 4.4 Hz, 1H), 1.04 (dd, J = 11.0, 5.0 Hz, 1H), 0.99 (s, 3H), 0.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.64, 170.27, 158.42 – 157.24 (m), 155.91 (d, J = 6.3 Hz), 139.87, 122.47, 121.20 (d, J = 17.0 Hz), 73.97, 58.02 (q, J = 3.4 Hz), 56.95, 50.17, 45.47, 45.39, 38.20, 38.01, 37.13, 36.79, 32.24, 31.98, 27.85, 24.80, 24.52, 21.55, 19.44, 13.02; ^{15}N NMR (40 MHz, $CDCl_3$) ^{15}N NMR (40 MHz, CDCl3) δ 293.85, 283.81; HRMS (ESI) found $[M+H]^+$ 399.2791, for $C_{24}{}^{13}CH_{34}D^{15}N_2O_2^+$ requires 399.2730. Isotopic enrichment = 87% determined by HRMS.

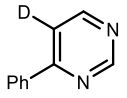


m/z	abundance
M+1	0
M+2	106647
M+3	146195
M+4	5069029
M+5	5608104
M+6	2337302
M+7	556839
M+8	89522

M+1	M+2	M+3	M+4	M+5
0%	0.97%	1.13%	45.77%	52.13%

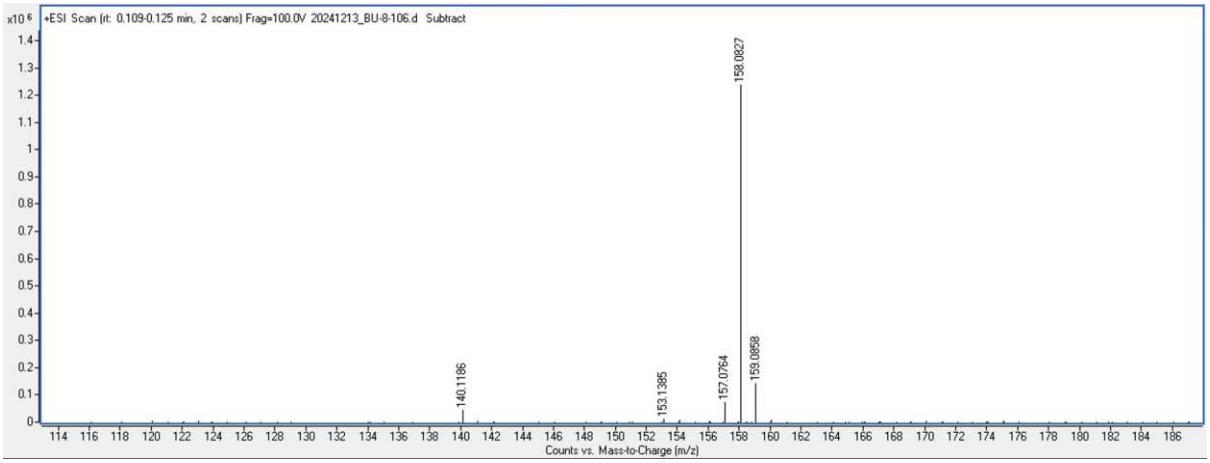
Isotopic Enrichment = 88%

4-Phenylpyrimidine-5-d



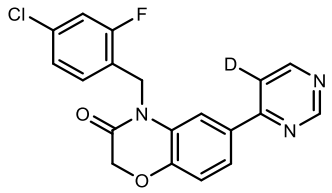
To an oven-dried 8 mL vial equipped with a stir bar was added (*E*)-1-(1-phenyl-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (80.9 mg, 0.20 mmol), ethanol-OD (1.0 mL), acetyl chloride (3 µL, 0.04 mmol), and heated to 50 ºC for 1 hour. The reaction was then cooled to room temperature and DBU (149 µL, 1.00 mmol) was added. The solvent was removed *in vacuo*, and formamidine acetate (62.5 mg, 0.60 mmol) and DMF (1.0 mL) were added. The reaction was heated to 70 ºC for 18 hours before cooling to room temperature and diluting with water and extracting with EtOAc. The combined organic extracts were washed with brine and dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 10-45% EtOAc in hexanes) afforded the title compound as a white powder (24 mg, 0.15

mmol, 76% yield). mp 59-62 °C. IRυ_{max}/cm^{-1} (film): 3023, 1529, 1436, 1388, 1152, 740, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.76 (s, 1H), 8.15 – 8.03 (m, 2H), 7.51 (tt, J = 3.5, 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.97, 159.24, 157.50, 136.59, 131.21, 129.16, 127.24, 117.21 – 116.32 (m); HRMS (ESI) found $[M+H]^+$ 158.0827, for $C_{10}H_8DN_2^+$ requires 158.0823. Isotopic enrichment = 94% determined by HRMS. Deuterium incorporation = 94% by ^{1}H-NMR.



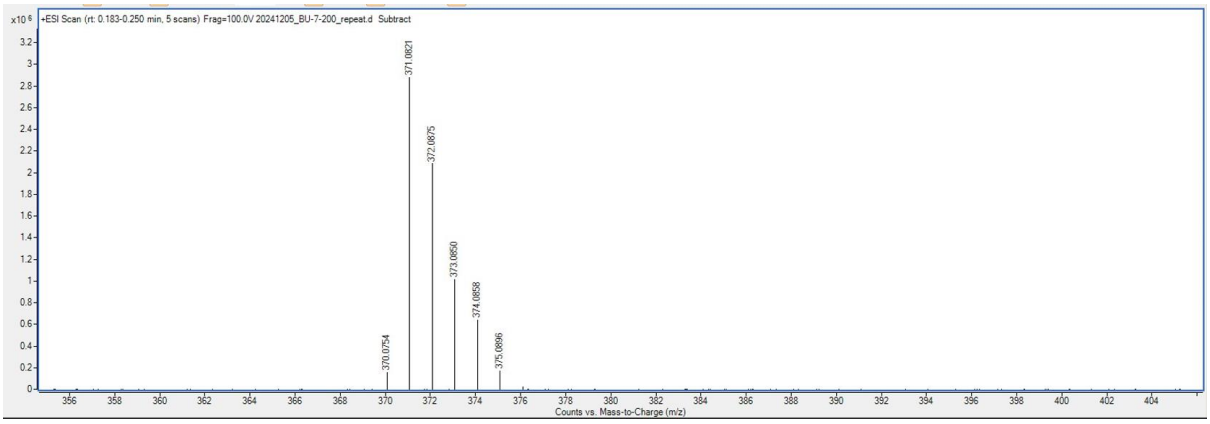
m/z	abundance	M+1	M+2
M+1	72430	5.53%	94.47%
M+2	1237819		
M+3	143766	Isotopic Enrichment = 94%	

4-(4-Chloro-2-fluorobenzyl)-6-(pyrimidin-4-yl-5-d)-2H-benzo[*b*][1,4]oxazin-3(4*H*)-one



To an oven-dried 8 mL vial equipped with a stir bar was added (*E*)-1-(3-(4-(4-chloro-2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (123.2 mg, 0.20 mmol), ethanol-OD (1.0 mL), acetyl chloride (3 µL, 0.04 mmol), and heated to 70 ºC for 1 hour. The reaction was then cooled to room temperature and DBU (149 µL, 1.00 mmol) was added. The solvent was removed

in vacuo, and formamidine acetate (62.5 mg, 0.60 mmol) and DMF (1.0 mL) were added. The reaction was heated to 70 ºC for 18 hours before cooling to room temperature and diluting with water and extracting with EtOAc. The combined organic extracts were washed with brine and dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the title compound as a white powder (66 mg, 0.18 mmol, 90% yield). Note: 20% undesired deuteration occurred at the α-amide protons, IE calculations corrected accordingly. mp 164-167 °C. IRυ_{max}/cm^{-1} (film): 2922, 1674, 1566, 1447, 1384, 893, 785. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.72 (s, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.4, 2.0 Hz, 1H), 7.18 (t, J = 8.2 Hz, 1H), 7.13 (dd, J = 10.1, 2.1 Hz, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.06 (ddd, J = 8.4, 2.1, 0.8 Hz, 1H), 5.27 (s, 2H), 4.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.39, 162.55, 160.40 (d, J = 248.5 Hz), 159.15, 157.48, 147.82, 134.65 (d, J = 10.3 Hz), 131.50, 129.90 (d, J = 4.7 Hz), 128.72, 125.31 (d, J = 3.6 Hz), 123.44, 121.58, 121.44, 117.81, 116.60 (d, J = 25.1 Hz), 114.08 (d, J = 2.1 Hz), 67.70, 38.01 (d, J = 4.3 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.57 (t, J = 9.0 Hz); HRMS (ESI) found $[M+H]^+$ 371.0821, for $C_{19}H_{13}DClFN_3O_2^+$ requires 371.0816. Isotopic enrichment = 96% determined by HRMS. Deuterium incorporation = 94% by ^{1}H-NMR.

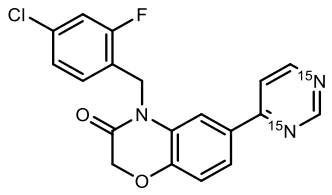


m/z	abundance
M+1	154866
M+2	2878290
M+3	2081184
M+4	1014944
M+5	642741
M+6	168825

M+1	M+2
4.33%	95.67%

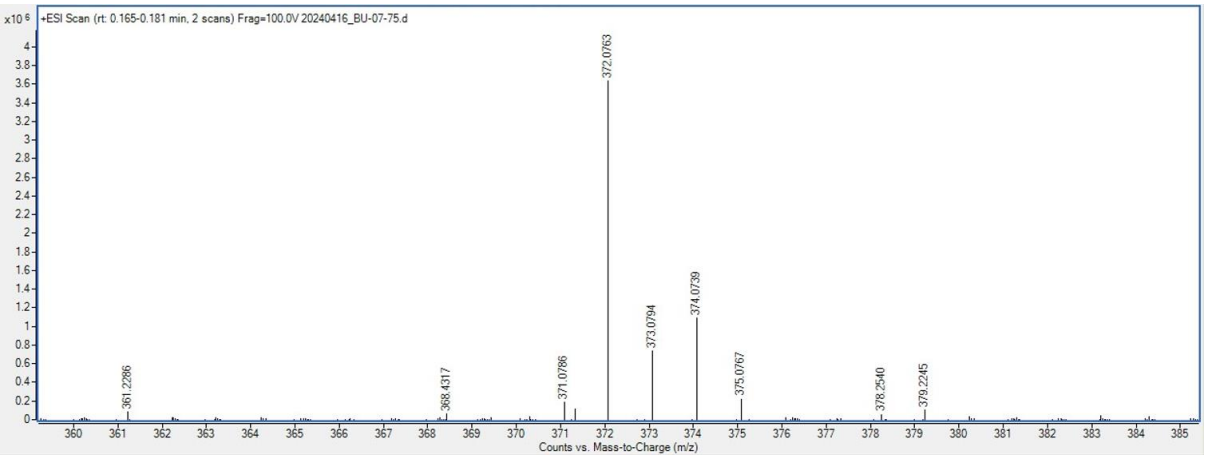
Isotopic Enrichment = 96%

4-(4-Chloro-2-fluorobenzyl)-6-(pyrimidin-4-yl-$^{15}N_2$)-2H-benzo[*b*][1,4]oxazin-3(4*H*)-one



Prepared according to general procedure N using (*E*)-1-(3-(4-(4-chloro-2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (123.2 mg, 0.20 mmol), formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the title compound as a white powder (69 mg, 0.19 mmol, 93% yield). mp 162-165 °C. IRυ_{max}/cm^{-1} (film): 3051, 2990, 1677, 1433, 1385, 1275, 817. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (td, J = 14.5, 1.4 Hz, 1H), 8.73 (dd, J = 10.4, 5.4 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 8.4, 2.0 Hz, 1H), 7.56 (d, J = 5.5 Hz, 1H), 7.19 (t, J = 8.2 Hz, 1H), 7.14 (dd, J = 10.0, 2.1 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.3, 2.0 Hz, 1H), 5.28 (s, 2H), 4.79 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.41, 162.59 (d, J = 4.4 Hz), 160.42 (d, J = 248.2 Hz), 159.13 (d, *J* = 3.2 Hz), 157.58 (d, J = 4.1 Hz), 147.83, 134.67 (d, J = 10.4 Hz), 131.56 (d, J = 7.4 Hz), 129.92 (d, J = 4.6 Hz), 128.73, 125.33 (d, J = 3.6 Hz), 123.45 (d, J = 2.6 Hz), 121.53 (d, J = 14.2 Hz), 117.83, 116.62 (d, J = 25.1 Hz), 116.35, 114.10 (t, J = 2.6 Hz), 67.72, 38.02 (d, J = 4.4 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.57 (t, J = 9.0 Hz); ^{15}N NMR (40 MHz,

$CDCl_3$) δ 284.54; HRMS (ESI) found $[M+H]^+$ 372.0763, for $C_{19}H_{14}ClFN^{15}N_2O_2^+$ requires 372.0694. Isotopic enrichment = 98% determined by HRMS.

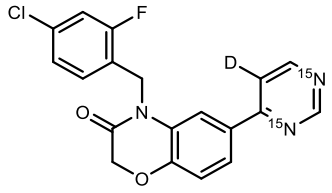


m/z	abundance
M+1	0
M+2	188059
M+3	3635591
M+4	741892
M+5	1094420
M+6	226969

M+1	M+2	M+3
0%	5.83%	94.17%

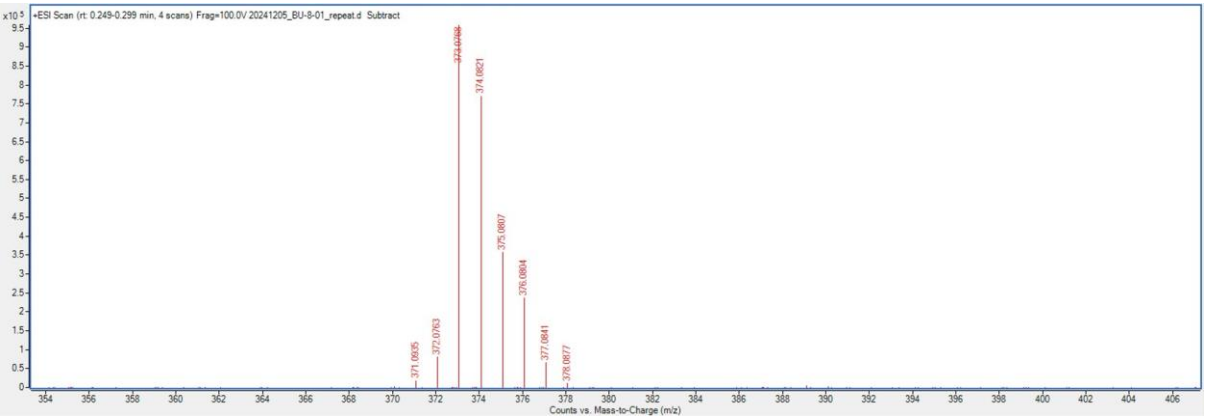
Isotopic Enrichment = 97%

4-(4-Chloro-2-fluorobenzyl)-6-(pyrimidin-4-yl-5-d-1,3-$^{15}N_2$)-2H-benzo[*b*][1,4]oxazin-3(4*H*)-one



To an oven-dried 8 mL vial equipped with a stir bar was added (*E*)-1-(3-(4-(4-chloro-2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (123.2 mg, 0.20 mmol), ethanol-OD (1.0 mL), acetyl chloride (3 µL, 0.04 mmol), and heated to 70 ºC for 1 hour. The reaction was then cooled to room temperature and DBU (149 µL, 1.00 mmol) was added. The solvent was removed *in vacuo*, and formamidine-$^{15}N_2$ acetate (63.7 mg, 0.60 mmol) and DMF (1.0 mL) were added.

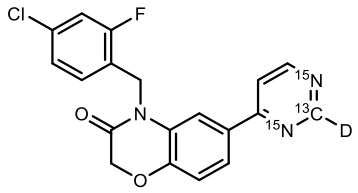
The reaction was heated to 70 ºC for 18 hours before cooling to room temperature and diluting with water and extracting with EtOAc. The combined organic extracts were washed with brine and dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the title compound as a white powder (67 mg, 0.18 mmol, 89% yield). Note: 23% undesired deuteration occurred at the α-amide protons, IE were calculations corrected accordingly. mp 167-169 °C. IRυ_{max}/cm^{-1} (film): 3055, 1677, 1563, 1441, 1370, 893, 784. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (t, J = 14.6 Hz, 1H), 8.71 (d, J = 10.4 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.4, 2.0 Hz, 1H), 7.18 (t, J = 8.2 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.10 (d, J = 8.6 Hz, 1H), 7.06 (dd, J = 8.3, 2.0 Hz, 1H), 5.27 (s, 2H), 4.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.37, 162.48 (d, J = 4.4 Hz), 160.38 (d, J = 248.0 Hz), 159.14 (t, J = 3.2 Hz), 157.49 (d, J = 4.0 Hz), 147.78, 134.62 (d, J = 10.2 Hz), 131.49 (d, J = 7.5 Hz), 129.88 (d, J = 4.7 Hz), 128.70, 125.29 (d, J = 3.6 Hz), 123.40 (d, J = 2.5 Hz), 121.50 (d, J = 14.3 Hz), 117.78, 116.71, 116.46, 114.05 (t, J = 2.6 Hz), 67.68, 37.99 (d, J = 4.3 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.56 (t, J = 9.0 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 286.65, 284.48; HRMS (ESI) found $[M+H]^+$ 373.0773, for $C_{19}H_{13}DClFN^{15}N_2O_2^+$ requires 373.0757. Isotopic enrichment = 98% determined by HRMS.



Note: 371.0935 m/z not included in calculations due to >10 ppm error.

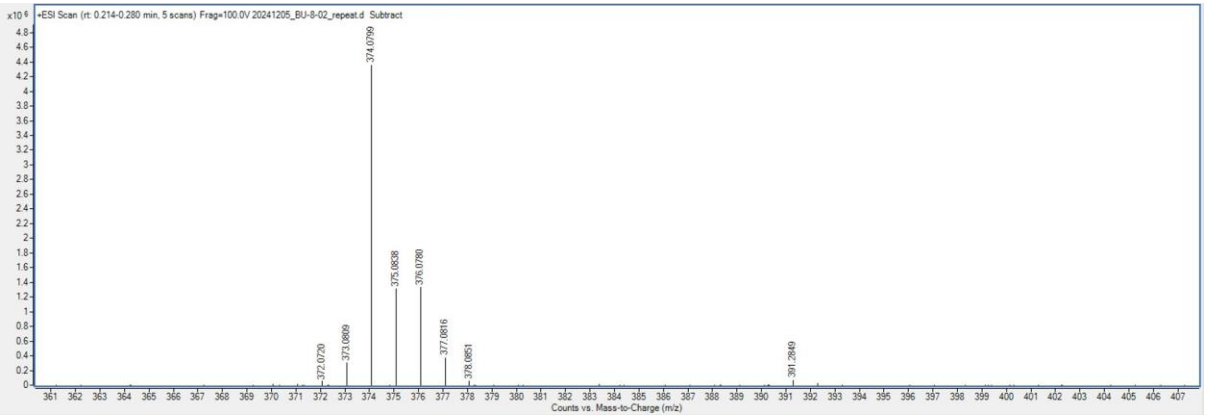
m/z	abundance	M+1	M+2	M+3	M+4
M+1	0	0%	0%	6.53%	93.65%
M+2	0				
M+3	80027	Isotopic Enrichment = 98%			
M+4	957676				
M+5	771397				
M+6	358303				
M+7	236218				
M+8	66433				

4-(4-Chloro-2-fluorobenzyl)-6-(pyrimidin-4-yl-2-^{13}C-2-d-1,3-$^{15}N_2$)-2H-benzo[*b*][1,4]oxazin-3(4*H*)-one



Prepared according to general procedure N using (*E*)-1-(3-(4-(4-chloro-2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (123.2 mg, 0.20 mmol), formimidamide-^{13}C-1-d-$^{15}N_2$ acetate (64.9 mg, 0.60 mmol), DMAP (122 mg, 1.00 mmol), and DMF (1.0 mL). Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the title compound as a white powder (68 mg, 0.18 mmol, 91% yield). mp 163-167 °C. IRυ_{max}/cm^{-1} (film): 3054, 1677, 1561, 1453, 1276, 892, 824. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (td, J = 10.5, 5.4 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.4, 2.0 Hz, 1H), 7.55 (d, J = 5.4 Hz, 1H), 7.18 (t, J = 8.2 Hz, 1H), 7.15 – 7.11 (m, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.07 – 7.03 (m, 1H), 5.27 (s, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.36, 162.50 (d, J = 5.1 Hz), 160.37 (d, J = 248.5 Hz), 158.74 (t, J = 30.7 Hz), 157.57 (d, J = 5.6 Hz), 147.78, 134.61 (d, J = 10.3 Hz), 131.51 (dd, J = 7.6, 5.4 Hz), 129.87 (d, J = 4.6 Hz), 128.69, 125.28 (d, J = 3.6 Hz), 123.40 (d, J = 2.5 Hz), 121.49 (d, J = 14.4 Hz), 117.77, 116.57 (d, J = 25.1 Hz), 116.33 (d, J = 16.3 Hz), 114.05 (t, J = 2.7 Hz), 67.67, 37.98 (d, J = 4.4 Hz); ^{19}F NMR

(375 MHz, $CDCl_3$) δ -115.55 (t, J = 9.0 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 286.23; HRMS (ESI) found $[M+H]^+$ 374.0799, for $C_{18}{}^{13}CH_{13}DClFN^{15}N_2O_2^+$ requires 374.0790. Isotopic enrichment = 98% determined by HRMS.

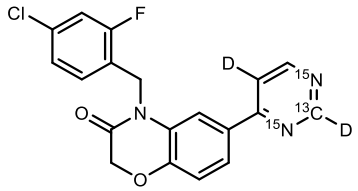


m/z	abundance
M+1	0
M+2	0
M+3	49265
M+4	302227
M+5	4353501
M+6	1307813
M+7	1334503
M+8	375476
M+9	55369

M+1	M+2	M+3	M+4	M+5
0%	0%	0.69%	6.01%	93.02%

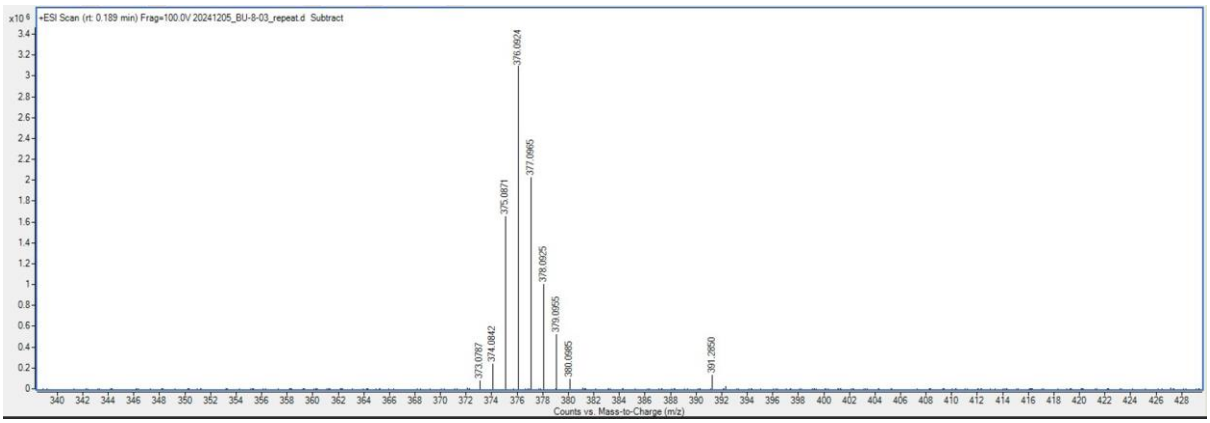
Isotopic Enrichment = 98%

4-(4-Chloro-2-fluorobenzyl)-6-(pyrimidin-4-yl-2-^{13}C-2,5-d_2-1,3-$^{15}N_2$)-2H-benzo[*b*][1,4]oxazin-3(4*H*)-one



To an oven-dried 8 mL vial equipped with a stir bar was added (*E*)-1-(3-(4-(4-chloro-2-fluorobenzyl)-3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-6-yl)-3-(pyrrolidin-1-yl)allylidene)pyrrolidin-1-ium trifluoromethanesulfonate (123.2 mg, 0.20 mmol), ethanol-OD (1.0

mL), acetyl chloride (3 µL, 0.04 mmol), and heated to 70 ºC for 1 hour. The reaction was then cooled to room temperature and DBU (149 µL, 1.00 mmol) was added. The solvent was removed *in vacuo*, and formamidine-^{13}C-1-d-$^{15}N_2$ acetate (64.9 mg, 0.60 mmol) and DMF (1.0 mL) were added. The reaction was heated to 70 ºC for 18 hours before cooling to room temperature and diluting with water and extracting with EtOAc. The combined organic extracts were washed with brine and dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the title compound as a white powder (69 mg, 0.18 mmol, 91% yield). Note: 50% undesired deuteration occurred at the α-amide proton, IE calculations were corrected accordingly. mp 168-170 °C. IRυ_{max}/cm^{-1} (film): 3039, 1676, 1550, 1452, 1379, 892. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (t, J = 10.5 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.72 (dd, J = 8.4, 2.0 Hz, 1H), 7.18 (t, J = 8.2 Hz, 1H), 7.16 – 7.09 (m, 1H), 7.10 (d, J = 8.4 Hz, 1H), 7.09 – 7.02 (m, 1H), 5.27 (s, 2H), 4.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.35, 162.49 (d, J = 5.0 Hz), 160.36 (d, J = 248.5 Hz), 159.22 – 157.65 (m), 157.71 – 157.11 (m), 147.77, 134.60 (d, J = 10.4 Hz), 132.17 – 130.92 (m), 129.87 (d, J = 4.7 Hz), 128.68, 125.28 (d, J = 3.6 Hz), 123.39 (d, J = 2.5 Hz), 121.49 (d, J = 14.4 Hz), 117.77, 116.69, 116.44, 114.04 (t, J = 2.5 Hz), 70.48 – 63.94 (m), 37.97 (d, J = 4.3 Hz); ^{19}F NMR (375 MHz, $CDCl_3$) δ -115.55 (t, J = 9.0 Hz); ^{15}N NMR (40 MHz, $CDCl_3$) δ 286.22, 284.47; HRMS (ESI) found $[M+H]^+$ 375.0867, for $C_{18}{}^{13}CH_{12}D_2ClFN^{15}N_2O_2^+$ requires 375.0853. Isotopic enrichment = 98% determined by HRMS.

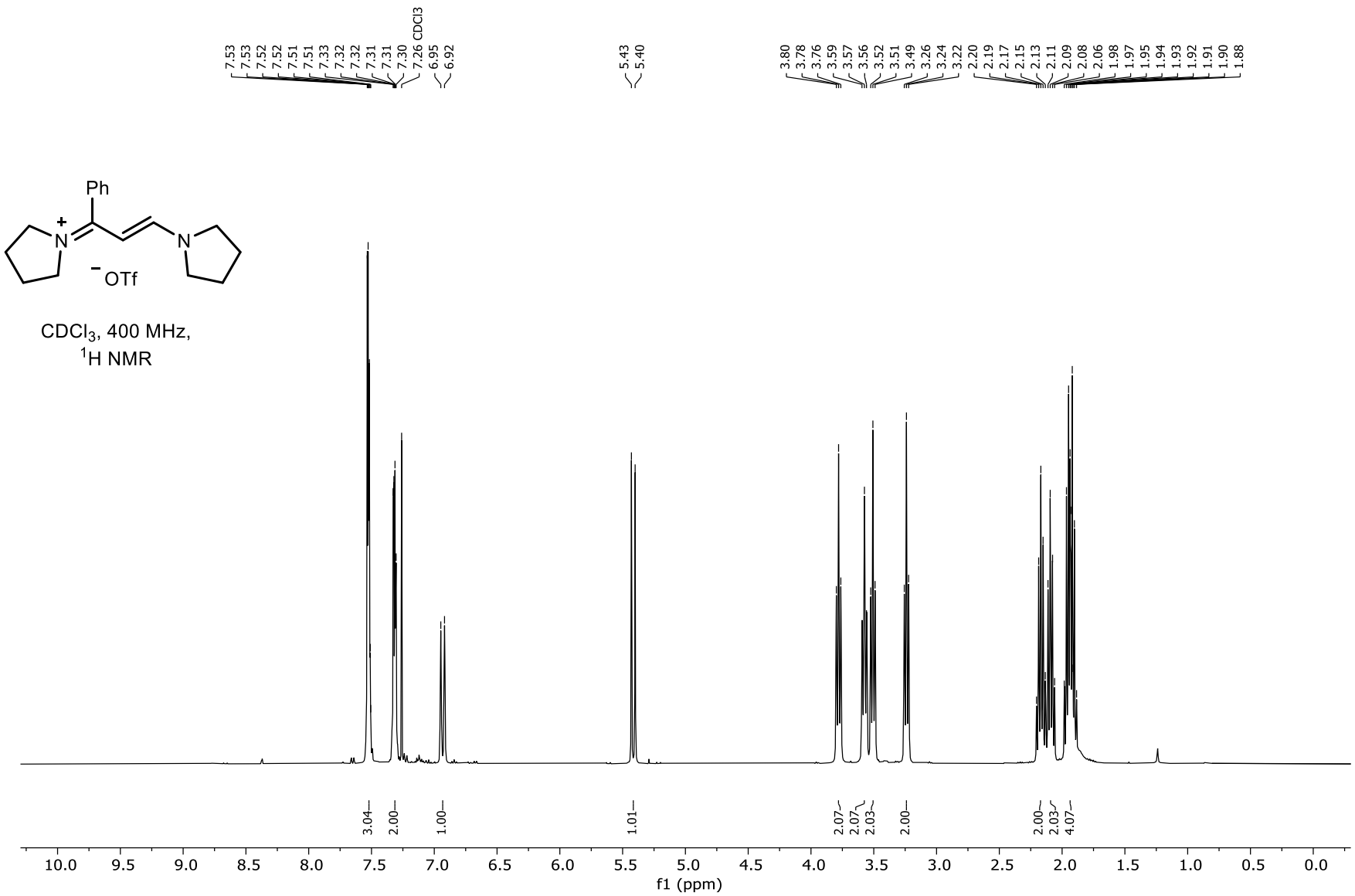


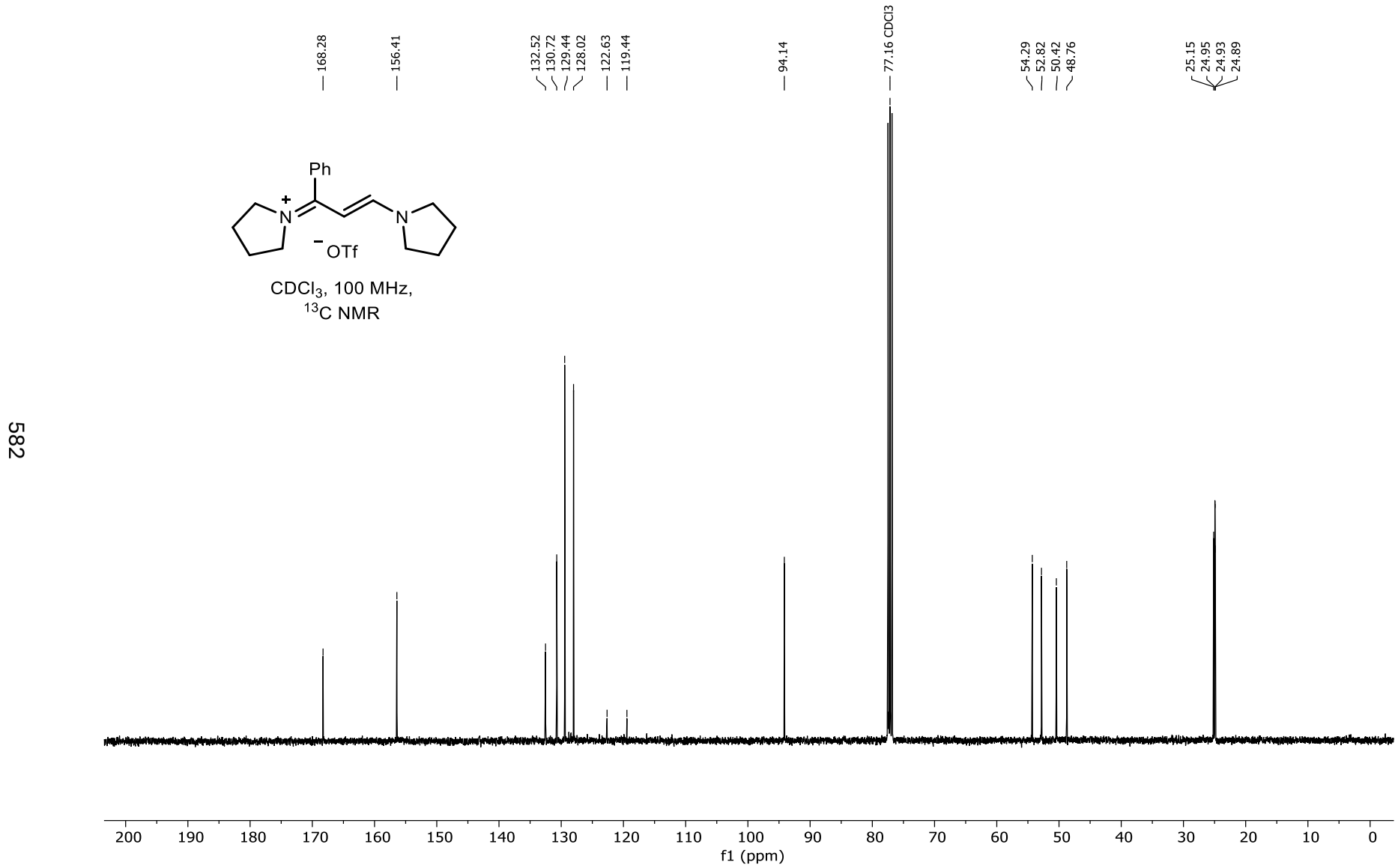
m/z	abundance
M+1	0
M+2	0
M+3	0
M+4	78034
M+5	241528
M+6	1653162
M+7	3094176
M+8	2028305
M+9	1004670
M+10	523769
M+11	91841

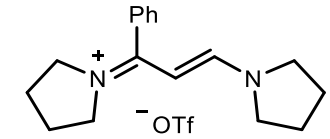
M+1	M+2	M+3	M+4	M+5	M+6
0%	0%	0%	2.03%	5.93%	92.04%

Isotopic Enrichment = 98%

A 1.11 NMR Spectra

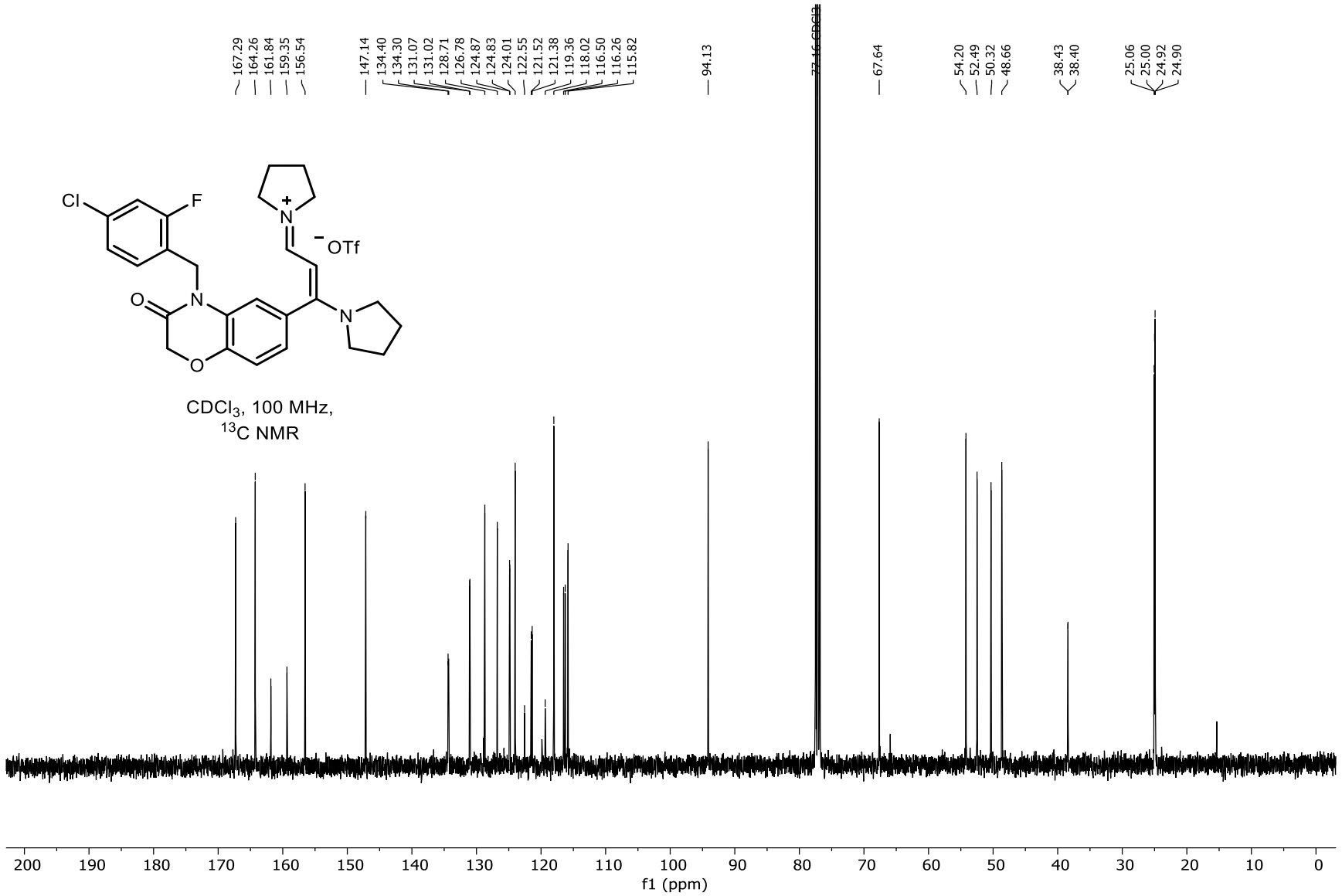

7.53
7.53
7.52
7.52
7.51
7.51
7.33
7.32
7.32
7.31
7.31
7.30
7.26 CDCl3
6.95
6.92
5.43
5.40
3.80
3.78
3.76
3.59
3.57
3.56
3.52
3.51
3.49
3.26
3.24
3.22
2.20
2.19
2.17
2.15
2.13
2.11
2.09
2.08
2.06
1.98
1.97
1.95
1.94
1.93
1.92
1.91
1.90
1.88
Ph
N
N
OTf
CDCl3, 400 MHz,
1H NMR
3.04
2.00
1.00
1.01
2.07
2.07
2.03
2.00
2.00
2.03
4.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


168.28
156.41
132.52
130.72
129.44
128.02
122.63
119.44
94.14
77.16 CDCl3
54.29
52.82
50.42
48.76
25.15
24.95
24.93
24.89
Ph
N
N
OTf
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



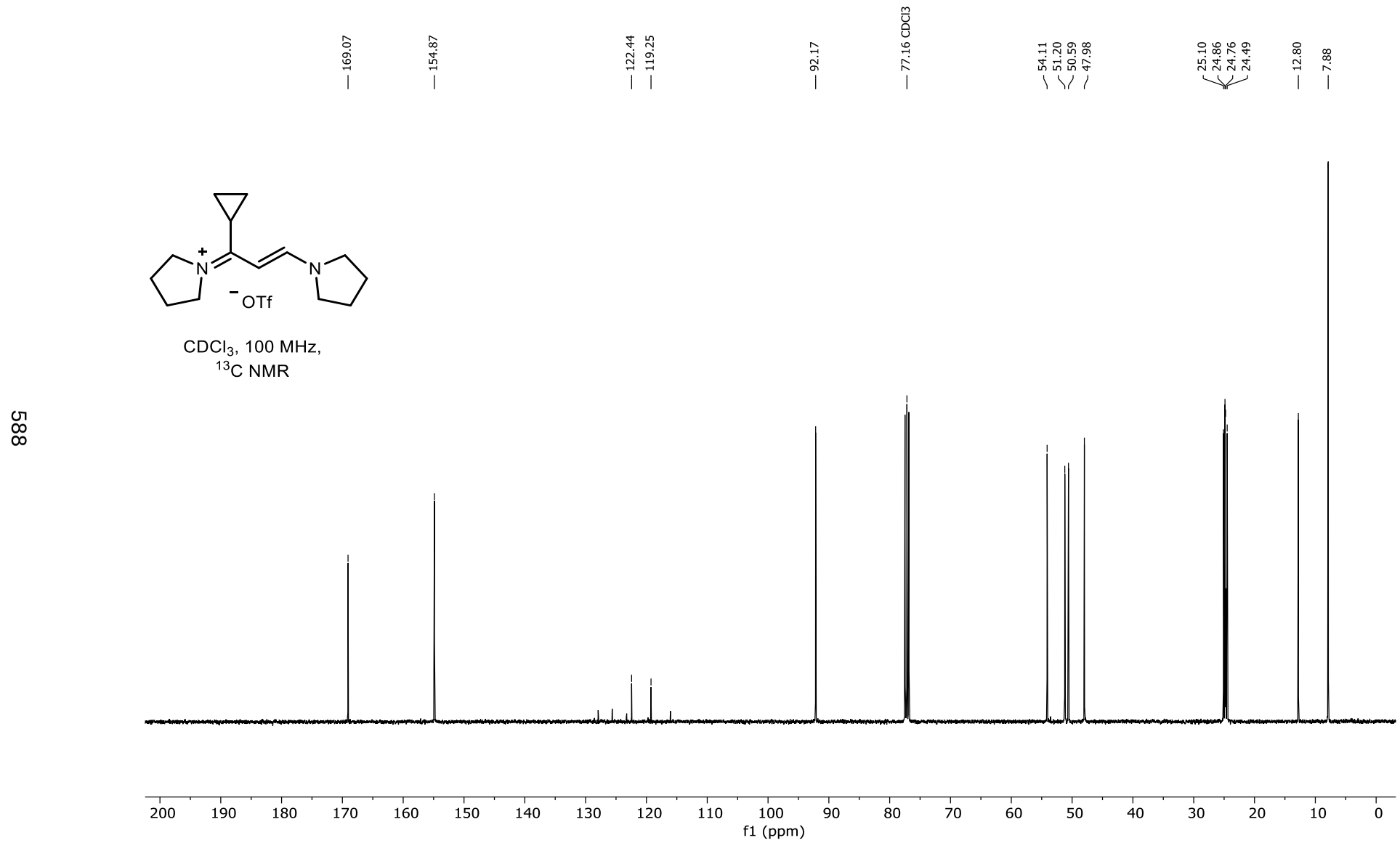
$CDCl_3$, 375 MHz,
^{19}F NMR

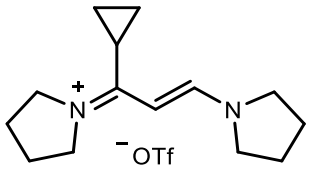
CDCl3, 400 MHz,
1H NMR
f1 (ppm)


167.29
164.26
161.84
159.35
156.54
147.14
134.40
134.30
131.07
131.02
128.71
126.78
124.87
124.83
124.01
122.55
121.52
121.38
119.36
118.02
116.50
116.26
115.82
94.13
77.16 CDCl3
67.64
54.20
52.49
50.32
48.66
38.43
38.40
25.06
25.00
24.92
24.90
Cl
F
N
O
N
O
N
OTf
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

-78.24
-114.21
-114.23
-114.25
3.03
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)
CDCl3, 375 MHz,
19F NMR
F
Cl
O
N
N
O
N
OTf

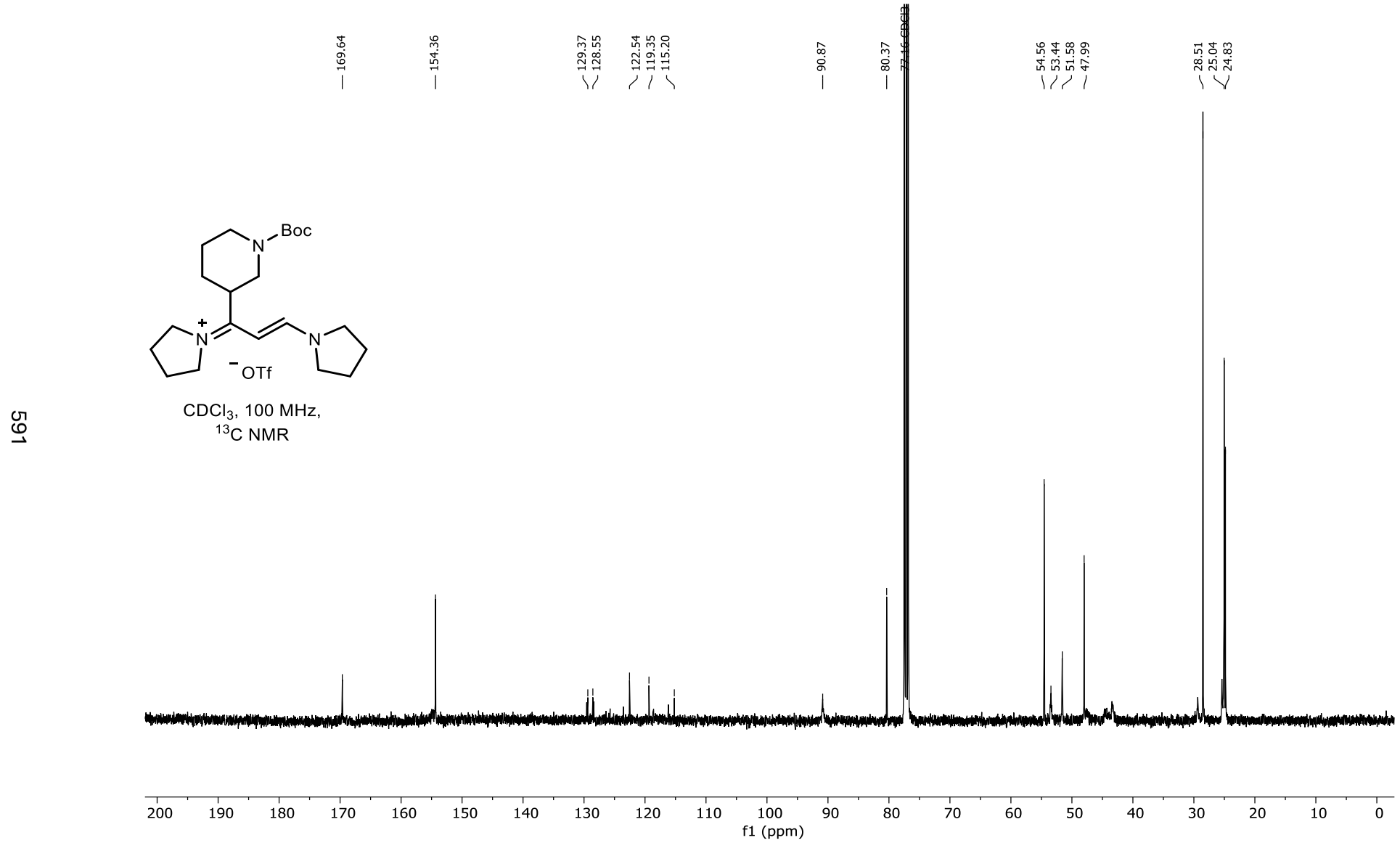
CDCl3, 400 MHz,
1H NMR
OTf
f1 (ppm)

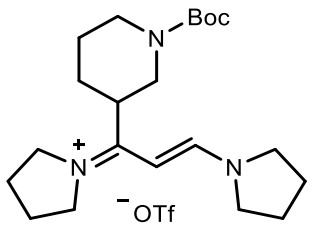

169.07
154.87
122.44
119.25
92.17
77.16 CDCl3
54.11
51.20
50.59
47.98
25.10
24.86
24.76
24.49
12.80
7.88
N
N
OTf
CDCl3, 100 MHz,
13C NMR
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



$CDCl_3$, 375 MHz,
^{19}F NMR

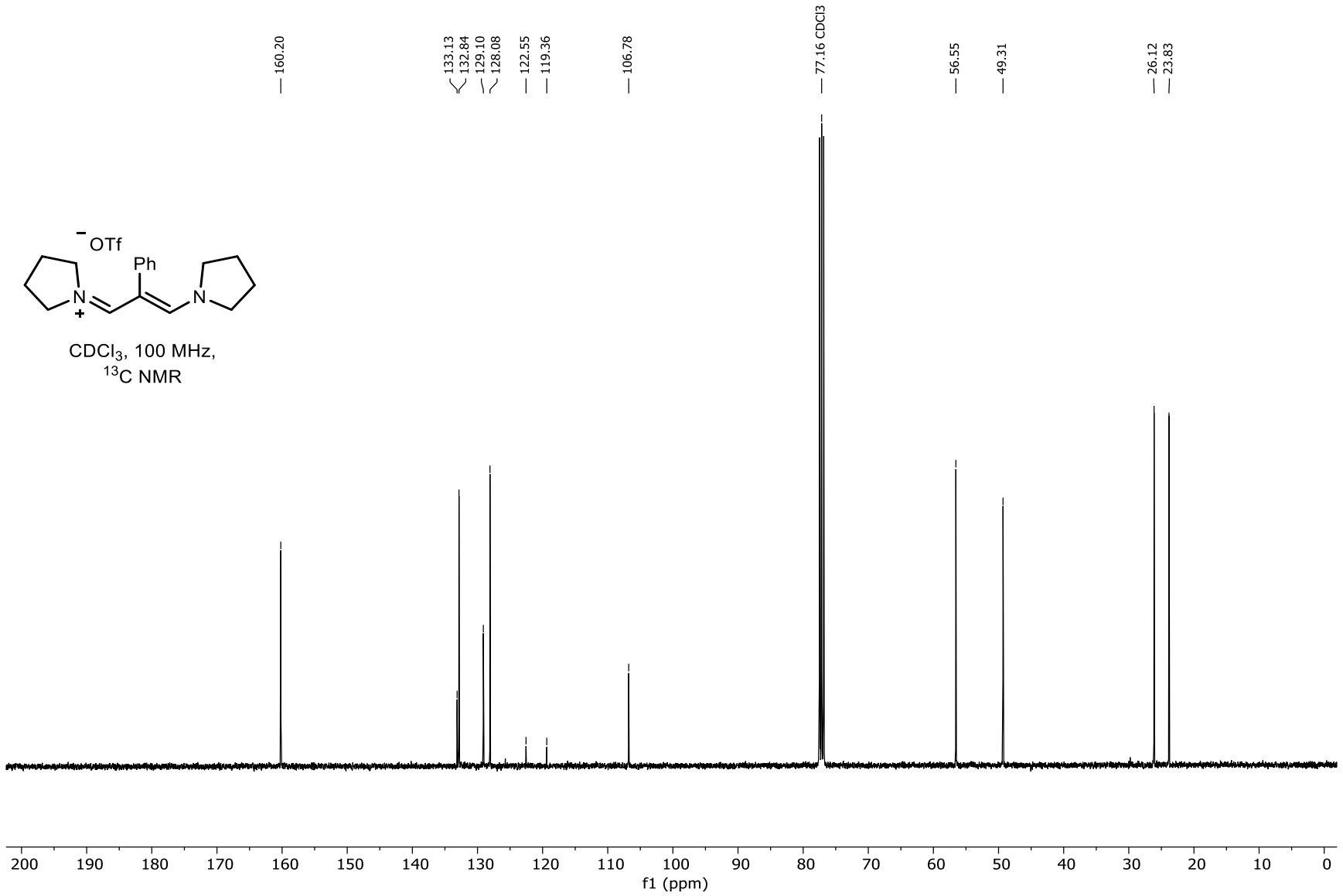
Boc
N
N
N
+
OTf
-
CDCl3, 400 MHz,
1H NMR
8.30
8.27
7.26 CDCl3
4.84
4.80
4.16
4.12
3.91
3.89
3.87
3.82
3.71
3.70
3.43
3.41
3.39
2.96
2.93
2.90
2.76
2.13
2.11
2.09
2.08
2.06
2.04
2.02
2.01
1.99
1.85
1.84
1.84
1.82
1.81
1.80
1.47
1.46
1.44
1.00
1.01
2.00
1.12
2.05
3.09
2.00
1.98
1.05
6.30
3.10
2.10
9.13
f1 (ppm)

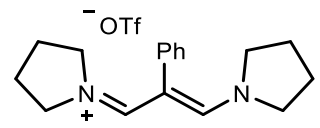

169.64
154.36
129.37
128.55
122.54
119.35
115.20
90.87
80.37
77.16 CDCl3
54.56
53.44
51.58
47.99
28.51
25.04
24.83
Boc
N
+
N
N
−
OTf
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



$CDCl_3$, 375 MHz,
^{19}F NMR

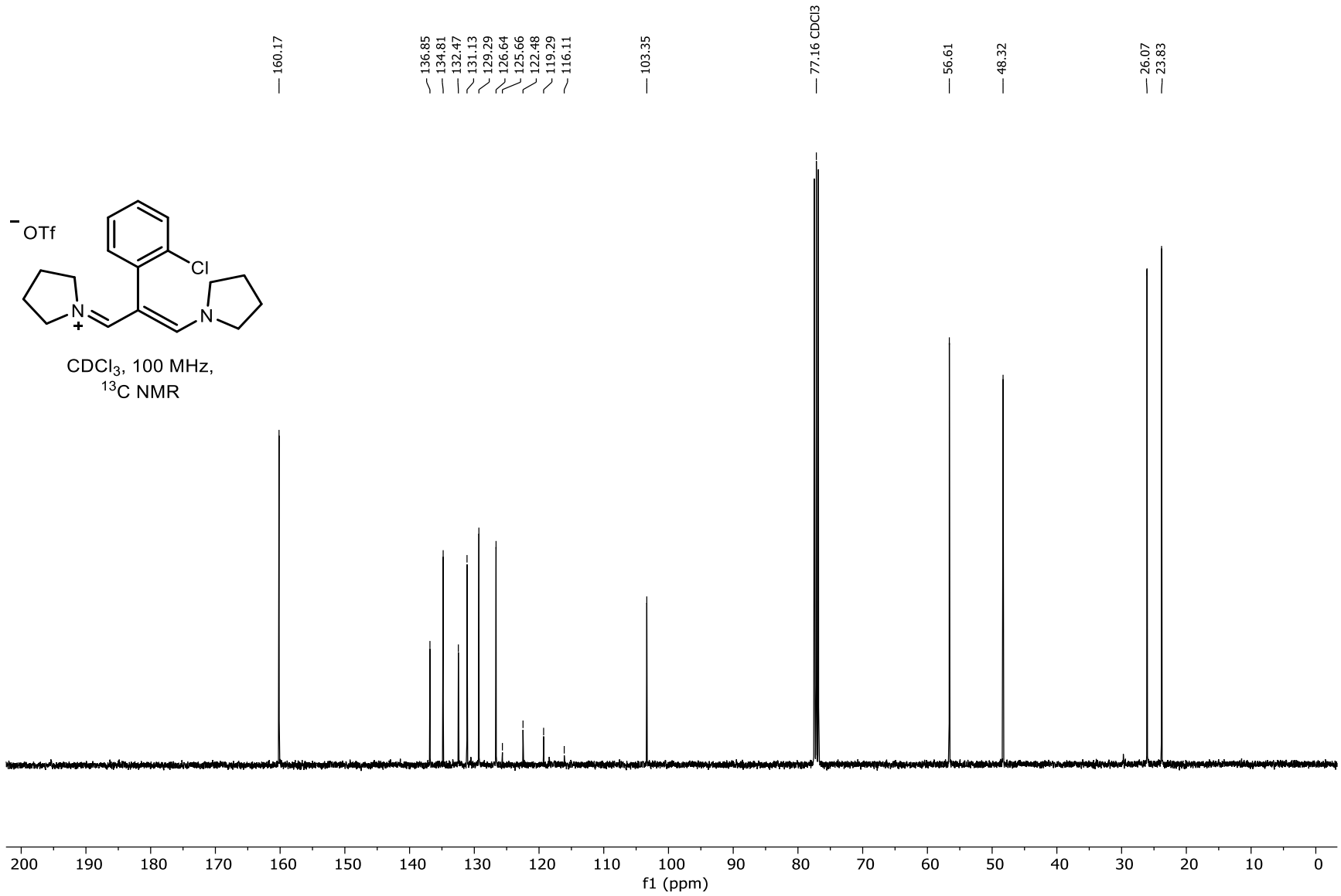
CDCl3, 400 MHz,
1H NMR
Ph
OTf
f1 (ppm)

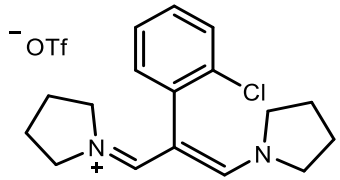

160.20
133.13
132.84
129.10
128.08
122.55
119.36
106.78
77.16 CDCl3
56.55
49.31
26.12
23.83
OTf
Ph
N
N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



$CDCl_3$, 375 MHz,
^{19}F NMR

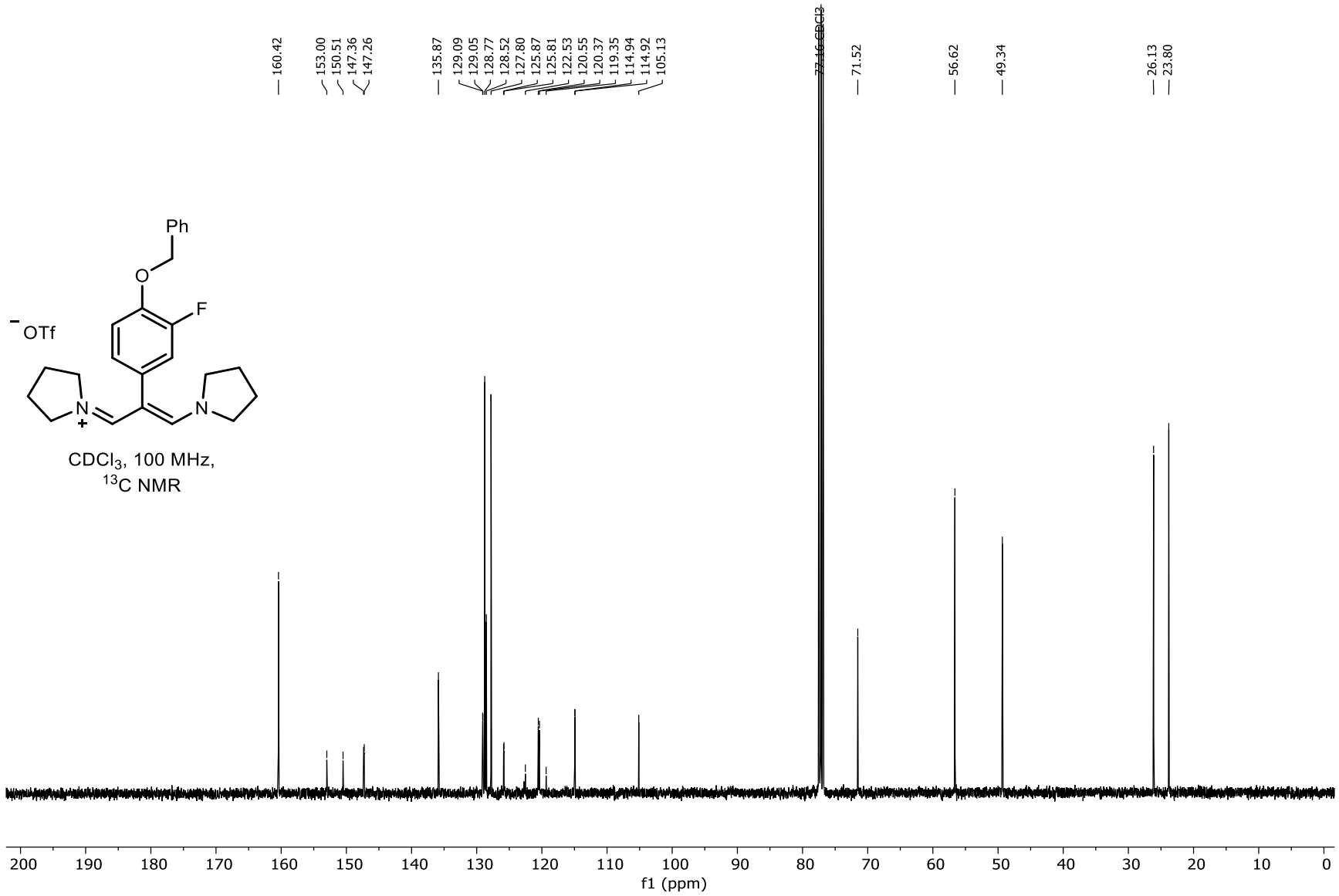
Cl
N
N+
OTf
CDCl3, 400 MHz,
1H NMR
8.13
7.42
7.41
7.40
7.39
7.38
7.37
7.37
7.35
7.35
7.32
7.32
7.30
7.30
7.29
7.29
7.28
7.27
7.26 CDCl3
3.84
3.83
3.82
3.81
2.72
2.70
2.68
2.67
2.66
2.65
2.62
2.60
2.58
2.57
2.55
1.83
1.82
1.81
1.80
1.79
1.78
1.78
2.00
2.01
2.09
4.05
2.05
2.08
8.09
f1 (ppm)


160.17
136.85
134.81
132.47
131.13
129.29
126.64
125.66
122.48
119.29
116.11
103.35
77.16 CDCl3
56.61
48.32
26.07
23.83
OTf
Cl
N
N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

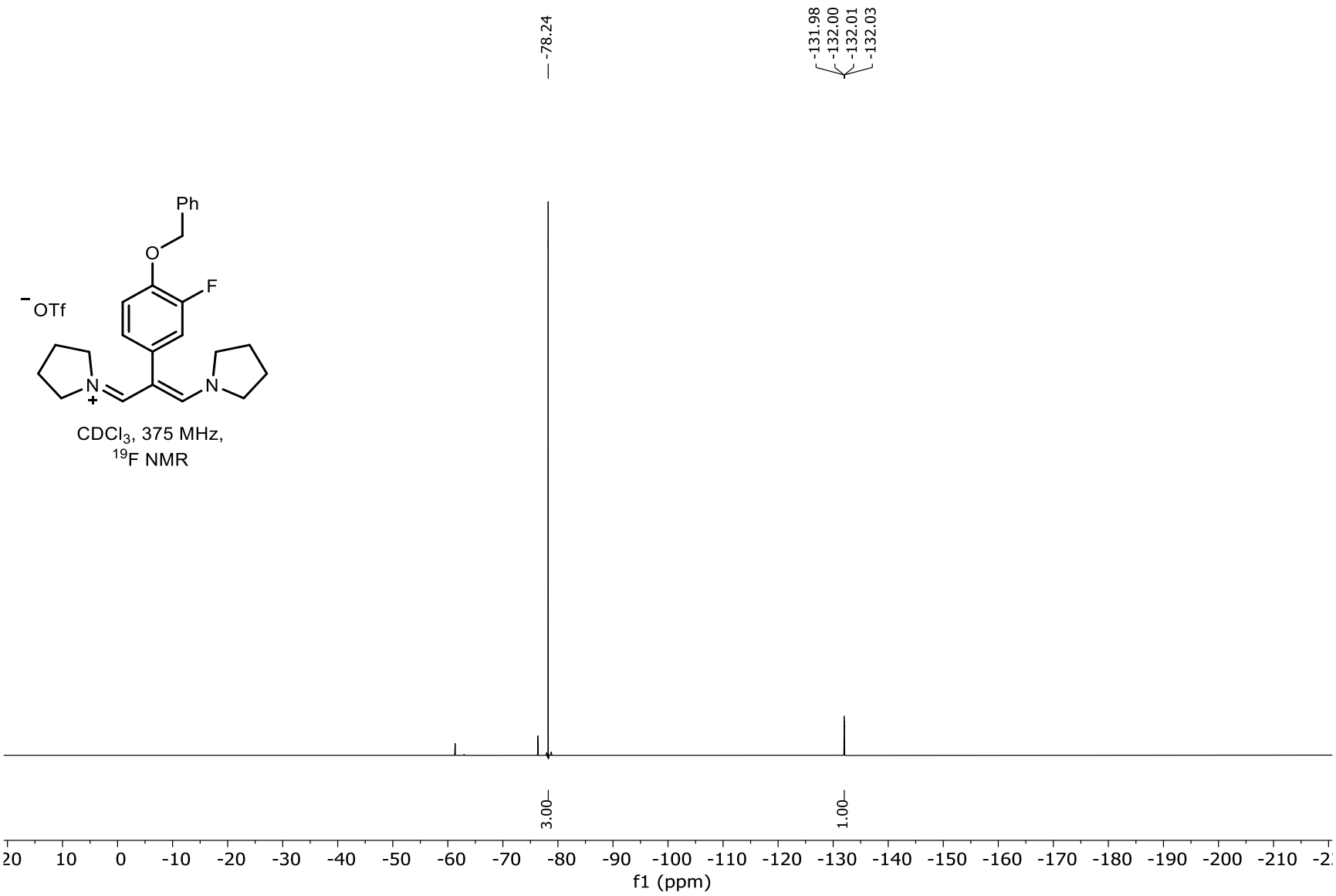


$CDCl_3$, 375 MHz,
^{19}F NMR

Ph
O
F
N
N+
-OTf
CDCl3, 400 MHz,
1H NMR
8.08
7.44
7.43
7.40
7.40
7.38
7.36
7.35
7.35
7.35
7.33
7.26 CDCl3
7.01
7.00
6.99
6.97
6.97
6.97
6.96
6.96
6.94
6.94
5.17
3.83
3.81
3.80
2.68
2.67
2.65
1.83
1.81
1.81
1.80
1.78
2.00
3.00
2.01
3.03
2.02
4.03
4.07
8.06
f1 (ppm)

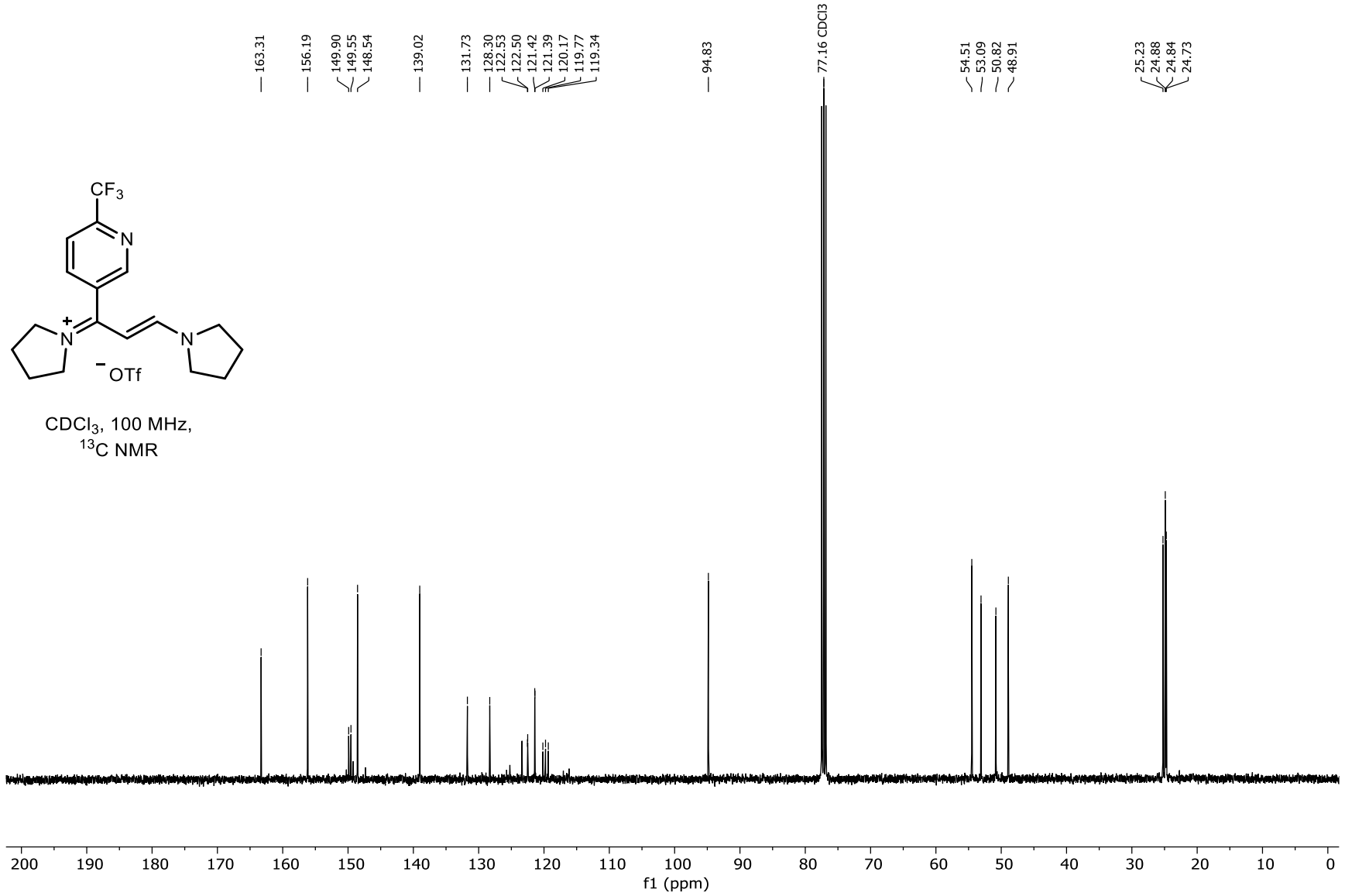

160.42
153.00
150.51
147.36
147.26
135.87
129.09
129.05
128.77
128.52
127.80
125.87
125.81
122.53
120.55
120.37
119.35
114.94
114.92
105.13
77.16 CDCl3
71.52
56.62
49.34
26.13
23.80
Ph
O
F
OTf
N
N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

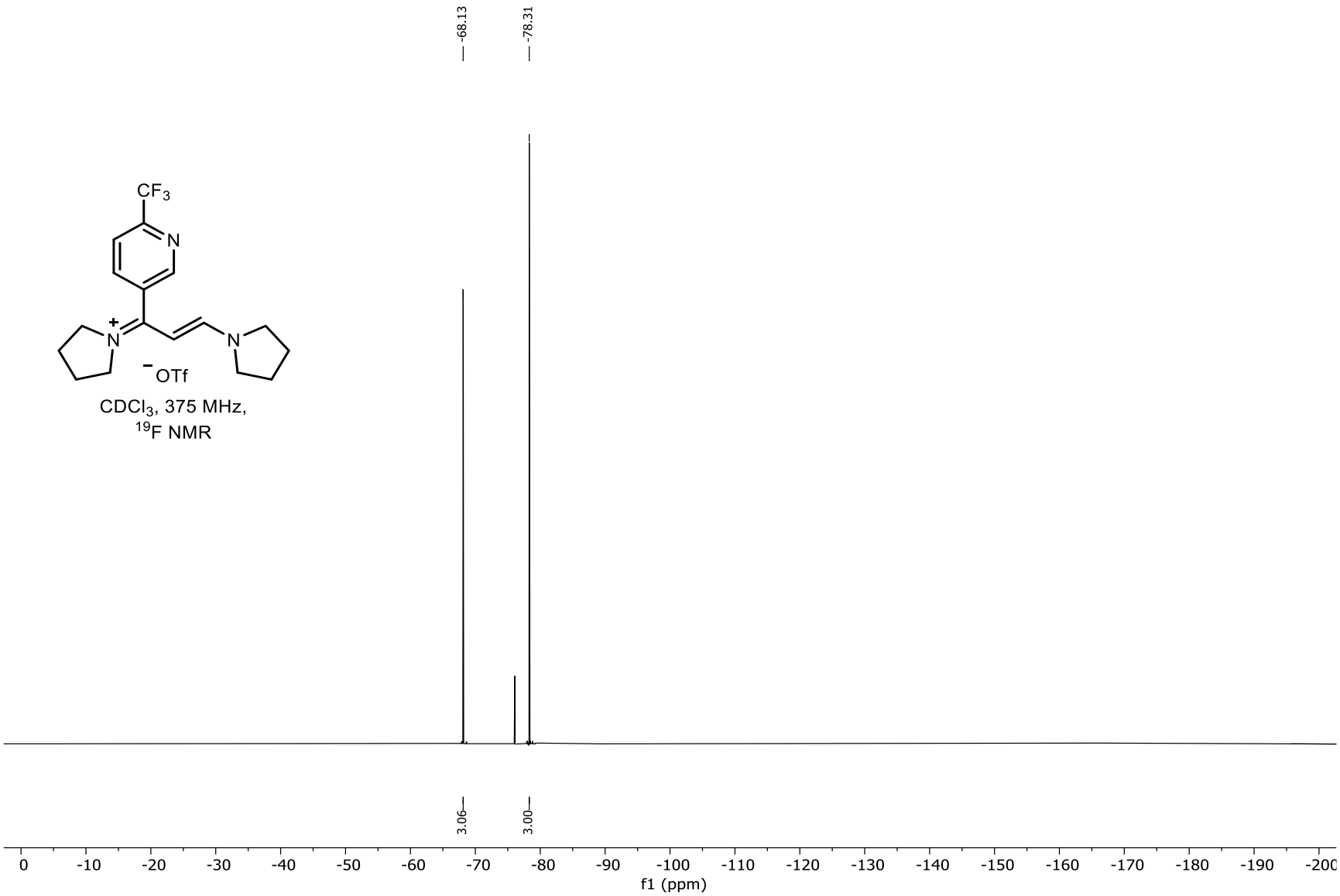
601


Ph
O
F
OTf
N
N
CDCl3, 375 MHz,
19F NMR
-78.24
-131.98
-132.00
-132.01
-132.03
3.00
1.00
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

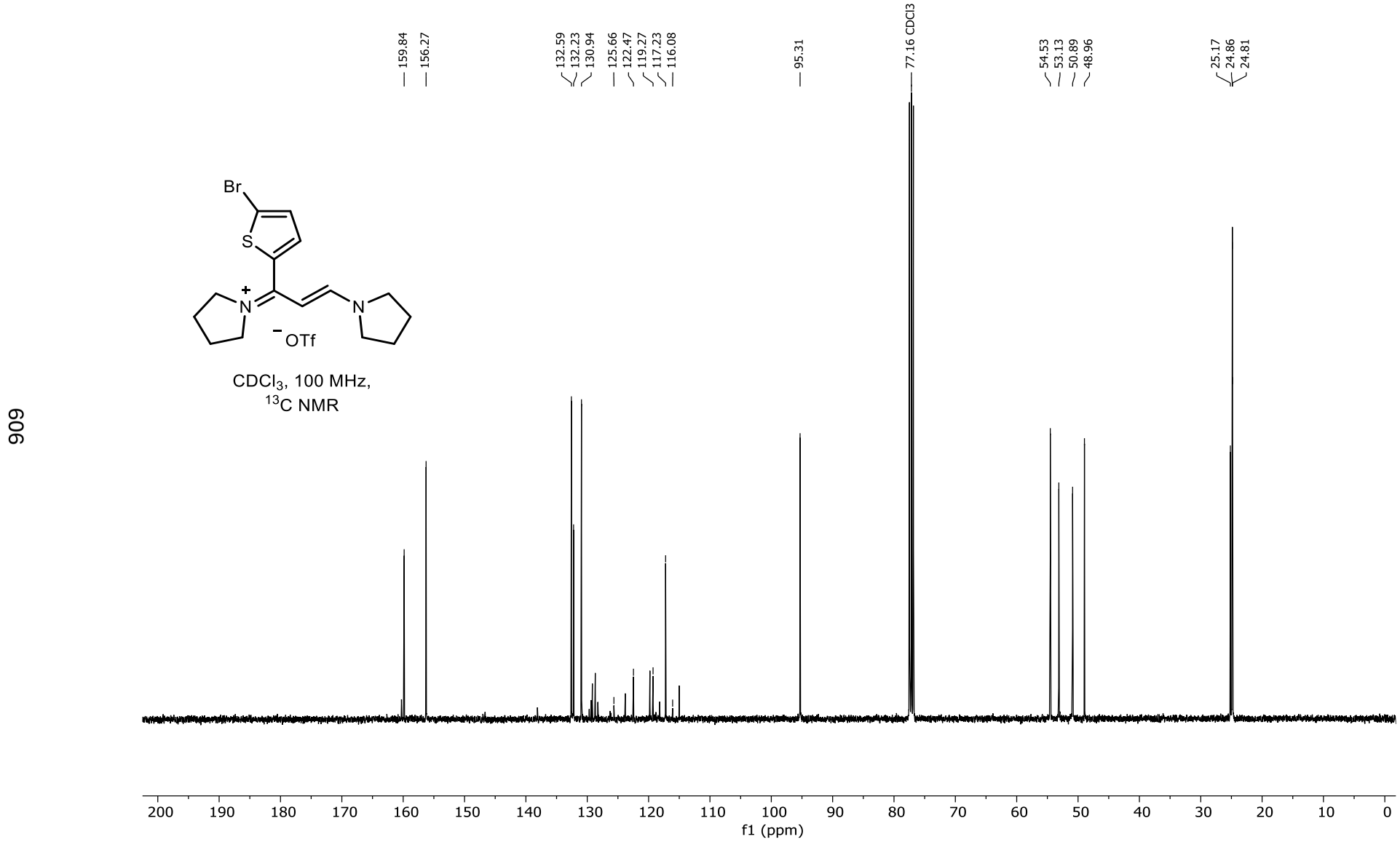
CF3
N
N
N
+
- OTf
CDCl3, 400 MHz,
1H NMR
8.66
8.66
8.37
8.37
8.35
8.35
7.93
7.91
7.26 CDCl3
6.96
6.93
5.44
5.41
3.92
3.91
3.89
3.87
3.86
3.74
3.72
3.70
3.69
3.67
3.66
3.64
3.63
3.61
3.55
3.54
3.52
3.50
3.49
3.47
3.34
3.32
3.31
3.29
3.27
3.25
3.23
3.22
3.20
3.19
2.24
2.23
2.16
2.14
2.14
2.13
2.13
2.12
2.11
2.09
2.07
2.05
2.04
2.02
2.01
2.00
2.00
1.99
1.98
1.97
1.96
1.94
1.92
1.01
1.01
1.00
1.02
1.00
8.06
2.11
2.06
3.07
1.05
f1 (ppm)

603


163.31
156.19
149.90
149.55
148.54
139.02
131.73
128.30
122.53
122.50
121.42
121.39
120.17
119.77
119.34
94.83
77.16 CDCl3
54.51
53.09
50.82
48.91
25.23
24.88
24.84
24.73
CF3
N
+
N
N
−
OTf
CDCl3, 100 MHz,
13C NMR
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CF3
N
N
N
OTf
CDCl3, 375 MHz,
19F NMR
-68.13
-78.31
3.06
3.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

Br
S
N
+
N
- OTf
CDCl3, 400 MHz,
1H NMR
7.31
7.29
7.26 CDCl3
7.16
7.15
7.15
7.15
7.14
5.45
5.42
3.75
3.73
3.71
3.66
3.64
3.62
3.60
3.59
3.47
3.46
3.44
2.20
2.18
2.16
2.14
2.13
2.11
2.10
2.08
2.03
2.01
1.99
1.98
1.98
1.97
1.95
1.93
1.02
2.01
1.00
2.06
4.06
2.07
4.09
4.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

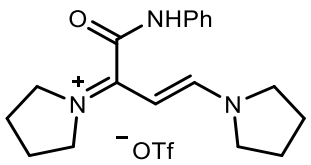

159.84
156.27
132.59
132.23
130.94
125.66
122.47
119.27
117.23
116.08
95.31
77.16 CDCl3
54.53
53.13
50.89
48.96
25.17
24.86
24.81
Br
S
N
N
OTf
CDCl3, 100 MHz,
13C NMR
f1 (ppm)

609

-78.25
Br
S
N
N
OTf
CDCl3, 375 MHz,
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

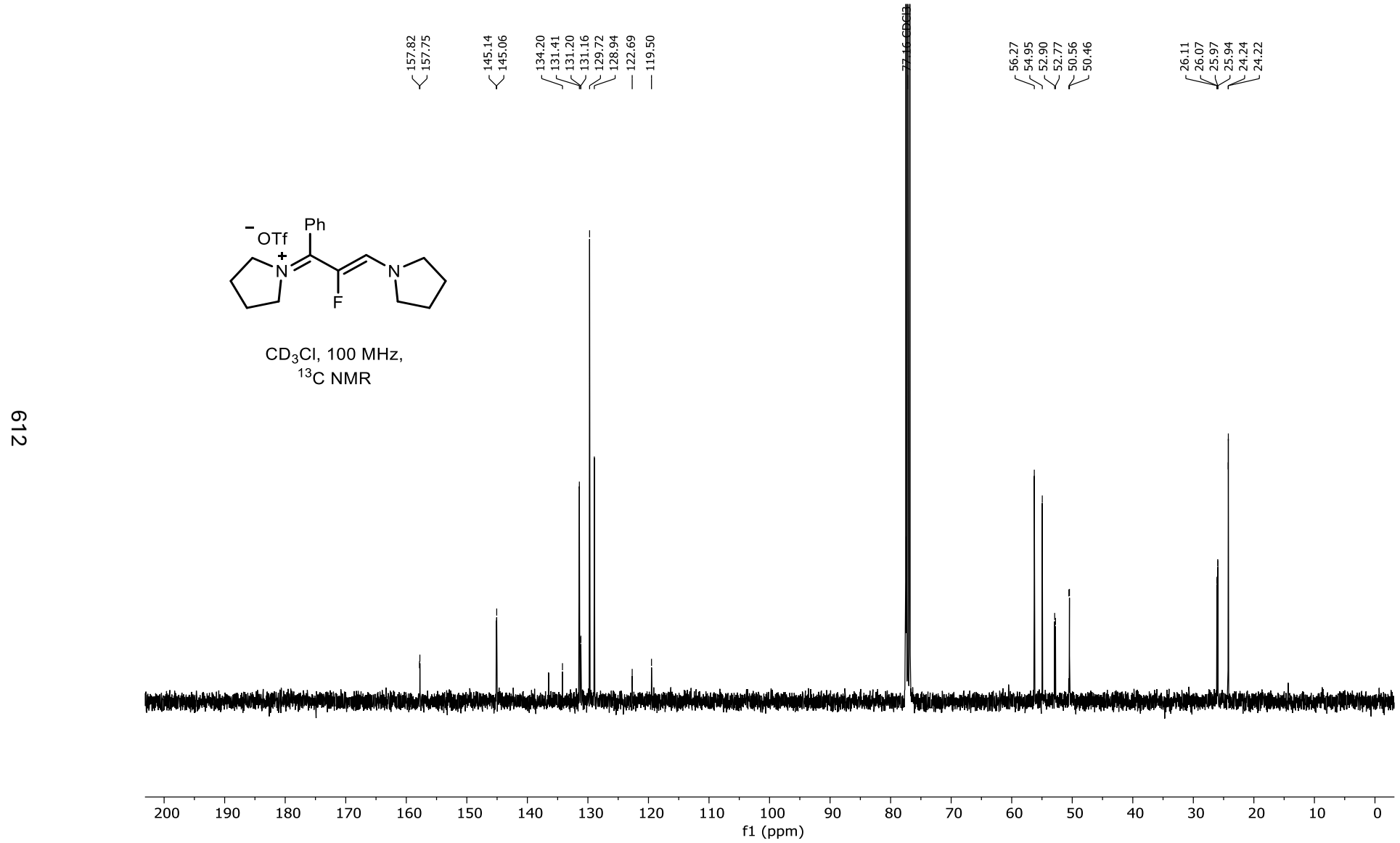
10.34
7.77
7.75
7.58
7.55
7.35
7.33
7.31
7.26 CDCl3
7.17
7.15
7.13
5.00
4.97
3.77
3.75
3.74
3.70
3.67
3.62
3.54
3.41
2.21
2.19
2.17
2.12
2.09
2.07
2.03
2.01
1.97
1.96
NHPh
OTf
CDCl3, 400 MHz,
1H NMR
1.01
2.03
1.00
2.01
1.01
1.04
6.02
2.06
8.09
f1 (ppm)

162.17
159.83
155.24
137.02
129.07
125.49
125.30
122.12
120.33
118.94
115.76
90.42
77.16 CDCl3
54.46
51.54
49.75
48.50
25.03
24.85
24.79
24.42
NHPh
O
N
+
N
OTf
CDCl3, 100 MHz,
13C NMR
f1 (ppm)



$CDCl_3$, 375 MHz,
^{19}F NMR

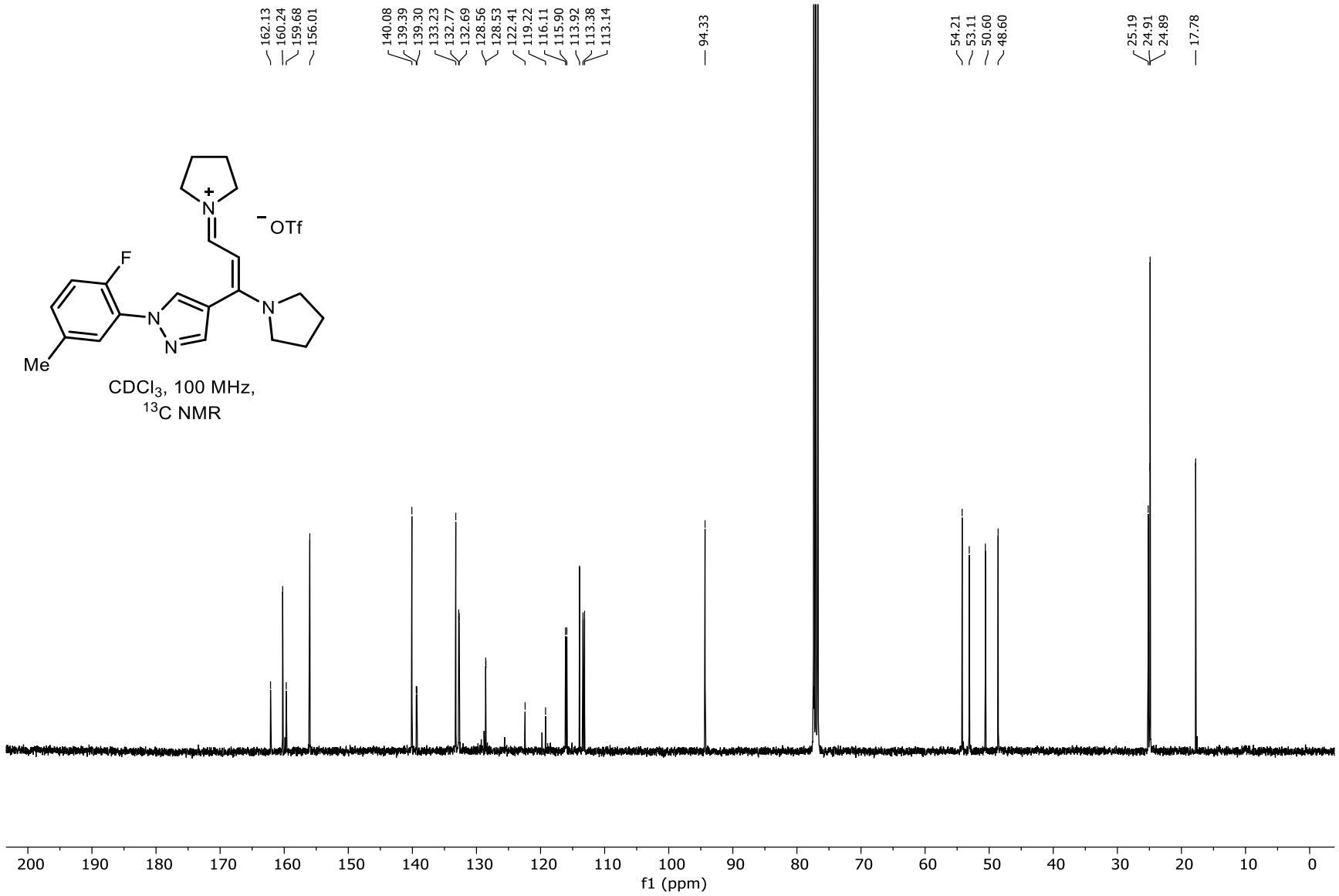
7.55
7.54
7.53
7.53
7.52
7.47
7.47
7.46
7.45
7.26 CDCl3
6.61
6.54
4.12
4.12
4.11
4.10
4.09
4.07
3.90
3.89
3.87
3.85
3.55
3.53
3.52
3.23
3.21
3.20
2.17
2.15
2.13
2.12
2.10
2.09
2.07
2.05
2.04
2.03
2.02
1.94
1.92
1.91
1.89
1.87
1.86
1.84
1.82
Ph
F
N
N
OTf
CD3Cl, 400 MHz,
1H NMR
3.04
2.04
1.00
2.04
2.05
2.00
2.03
2.08
2.09
4.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

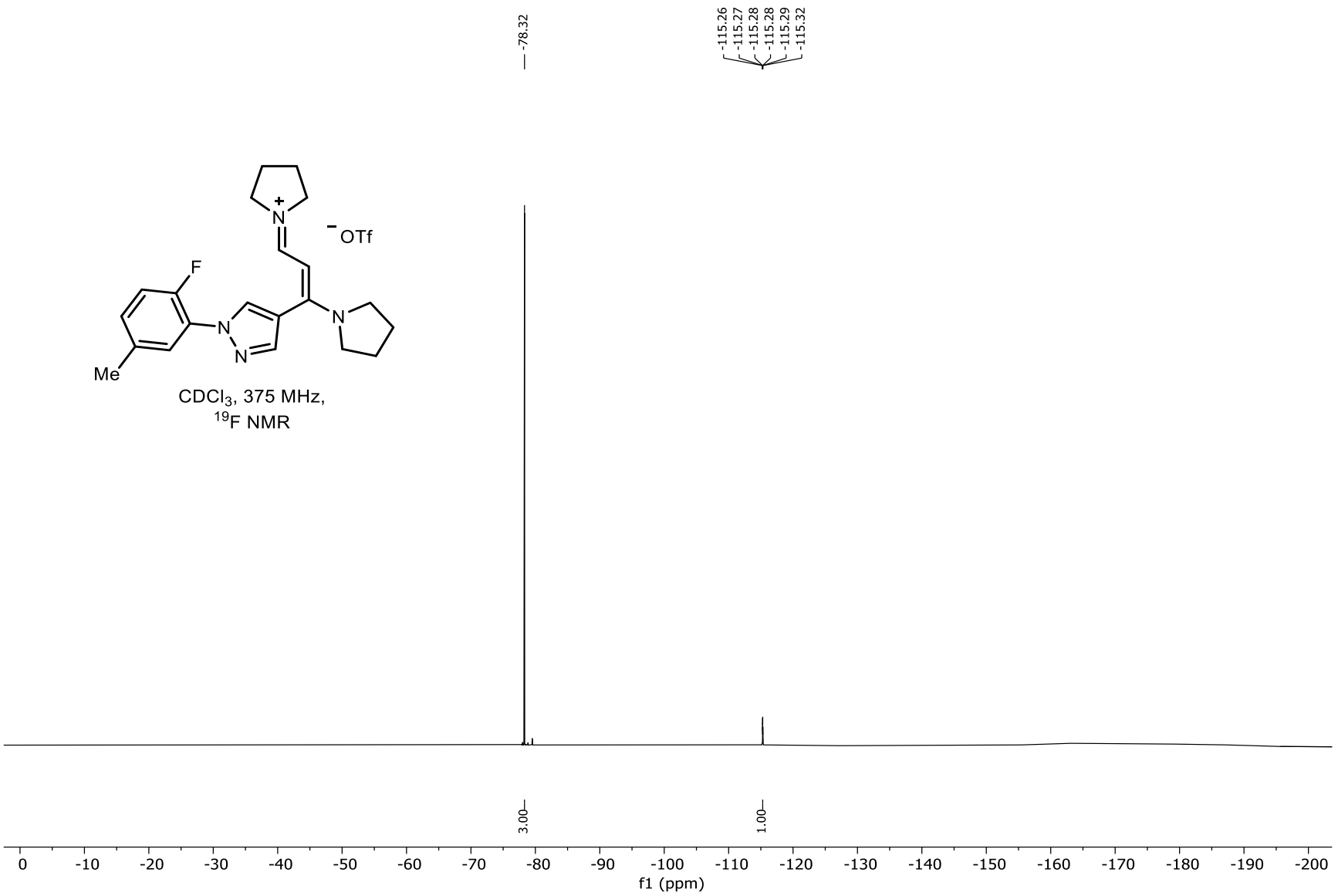

157.82
157.75
145.14
145.06
134.20
131.41
131.20
131.16
129.72
128.94
122.69
119.50
77.16 CDCl3
56.27
54.95
52.90
52.77
50.56
50.46
26.11
26.07
25.97
25.94
24.24
24.22
Ph
OTf
N
N
F
CD3Cl, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

612

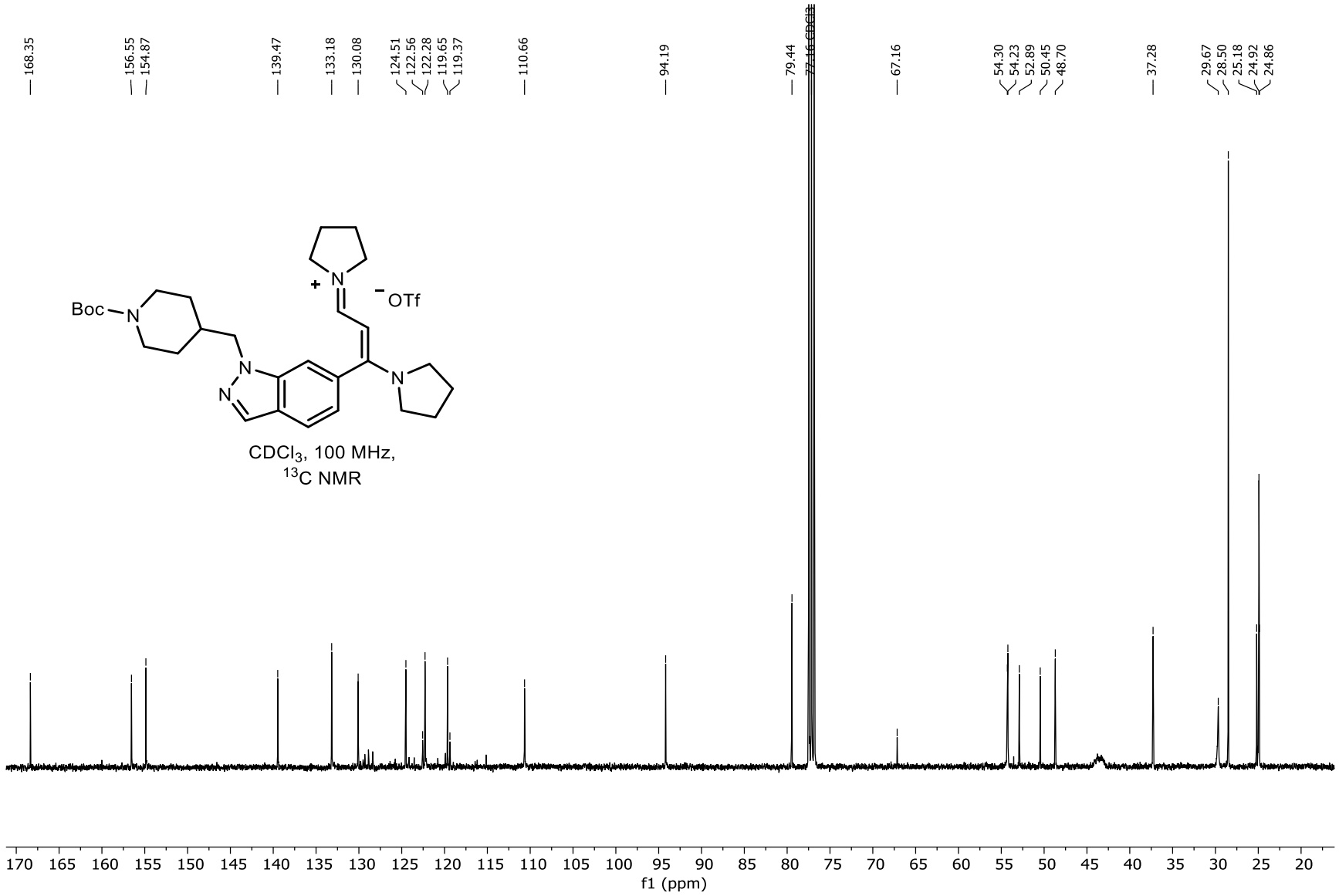
-78.19
-158.96
-158.97
-158.99
-159.00
-159.02
-159.03
-159.04
-159.06
-159.07
-159.09
3.06
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)
Ph
OTf
F
N
N
CDCl3, 375 MHz,
19F NMR

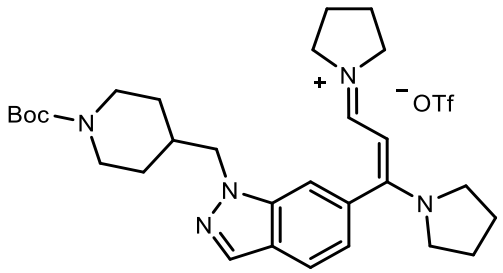
CDCl3, 400 MHz,
1H NMR
OTf
F
Me
CDCl3
f1 (ppm)


162.13
160.24
159.68
156.01
140.08
139.39
139.30
133.23
132.77
132.69
128.56
128.53
122.41
119.22
116.11
115.90
113.92
113.38
113.14
94.33
54.21
53.11
50.60
48.60
25.19
24.91
24.89
17.78
OTf
F
Me
CDCl3, 100 MHz,
13C NMR
f1 (ppm)

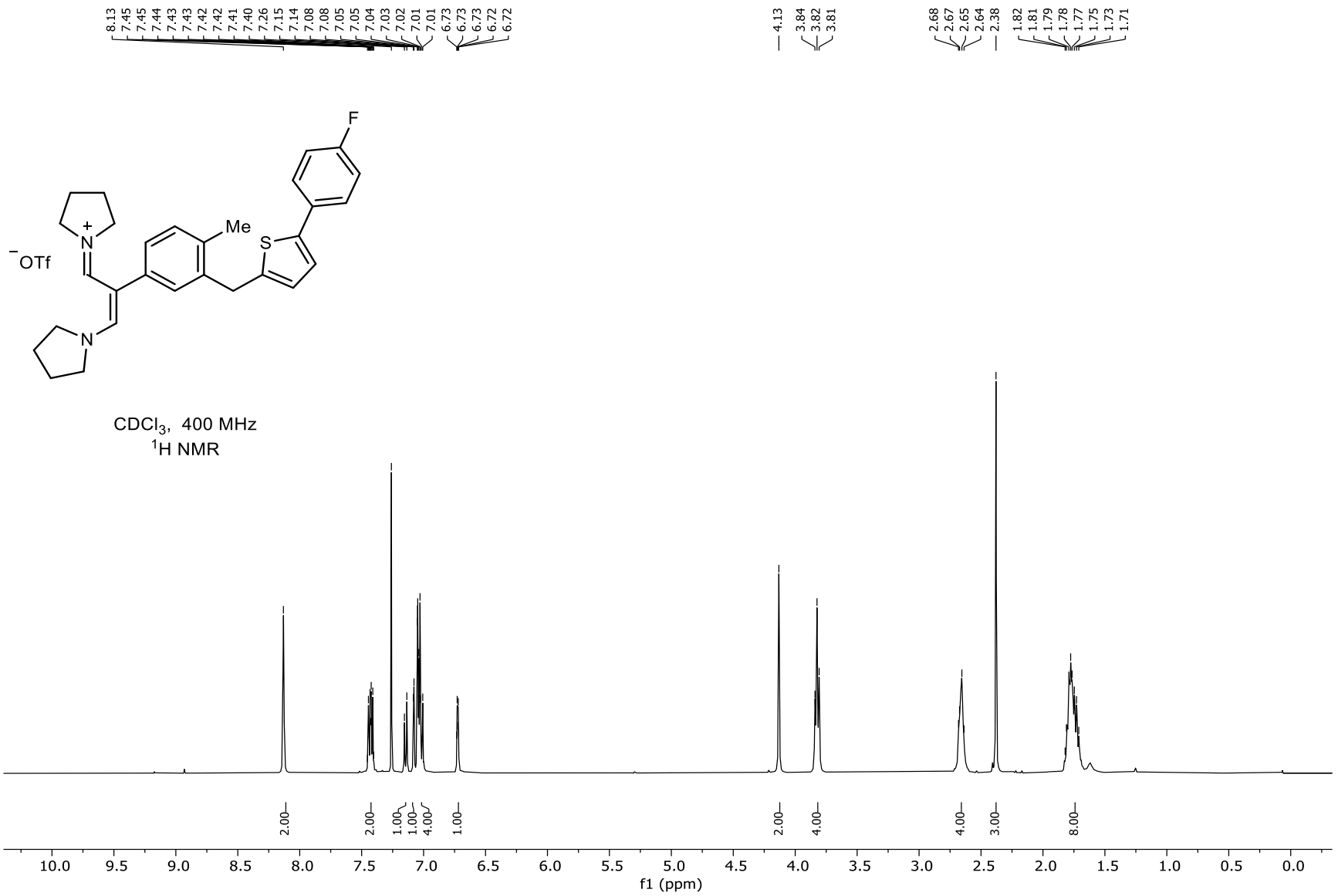

-78.32
-115.26
-115.27
-115.28
-115.28
-115.29
-115.32
OTf
F
Me
N
N
N
N
CDCl3, 375 MHz,
19F NMR
3.00
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

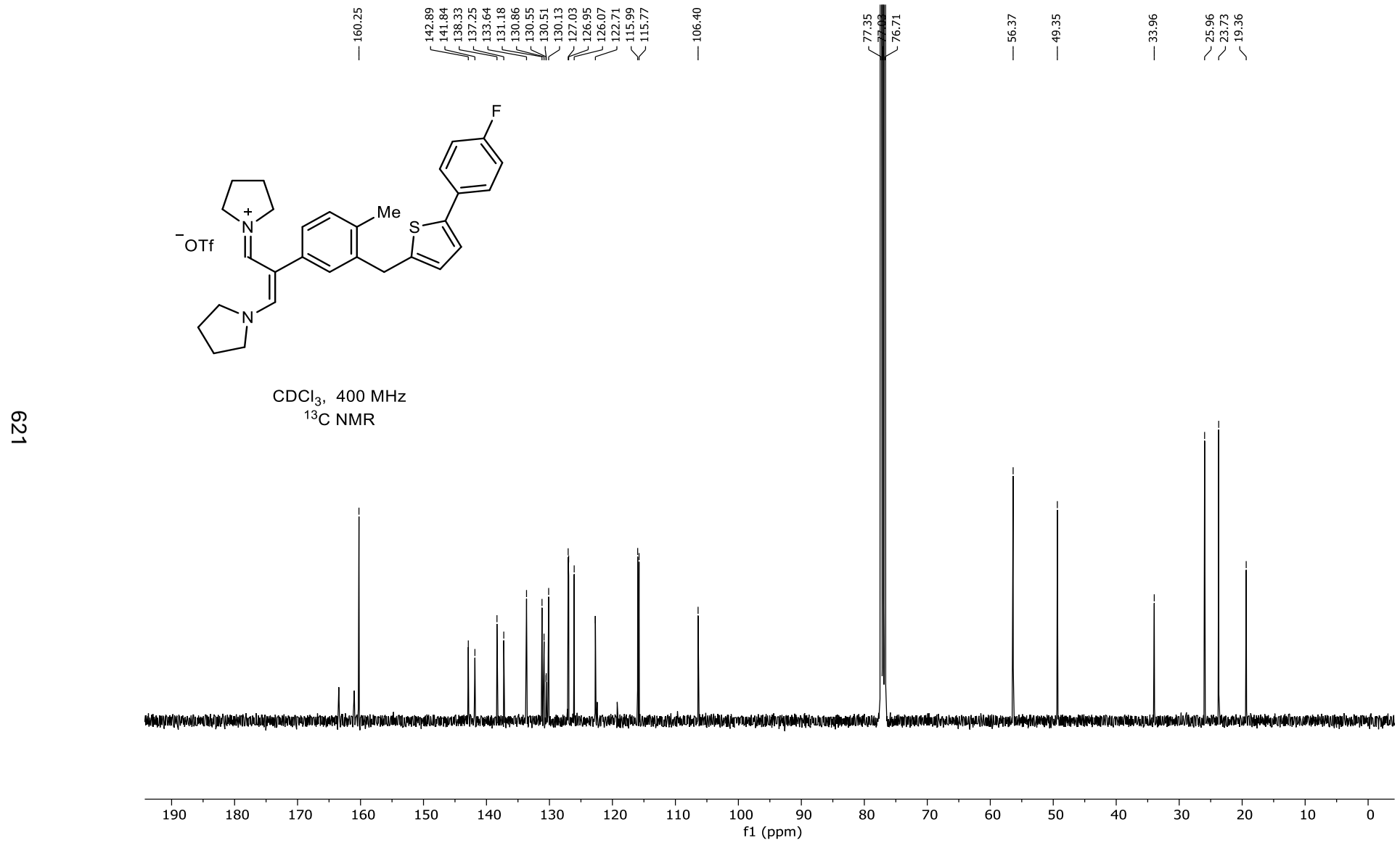
CDCl3, 400 MHz,
1H NMR
f1 (ppm)


168.35
156.55
154.87
139.47
133.18
130.08
124.51
122.56
122.28
119.65
119.37
110.66
94.19
79.44
77.16 CDCl3
67.16
54.30
54.23
52.89
50.45
48.70
37.28
29.67
28.50
25.18
24.92
24.86
Boc
N
N
N
N
+
OTf
CDCl3, 100 MHz,
13C NMR
170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

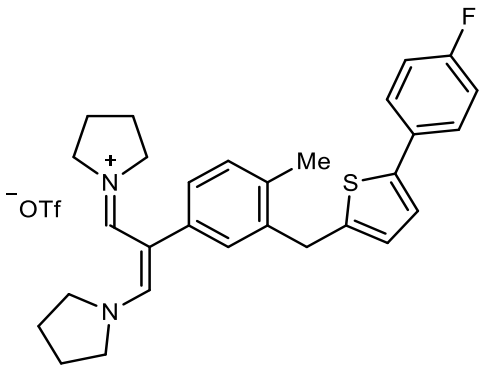


$CDCl_3$, 375 MHz,
^{19}F NMR


8.13
7.45
7.45
7.44
7.43
7.43
7.42
7.42
7.41
7.40
7.26
7.15
7.14
7.08
7.08
7.05
7.05
7.04
7.03
7.02
7.01
7.01
6.73
6.73
6.72
6.72
4.13
3.84
3.82
3.81
2.68
2.67
2.65
2.64
2.38
1.82
1.81
1.79
1.78
1.77
1.75
1.73
1.71
F
Me
S
N
N
OTf
CDCl3, 400 MHz
1H NMR
2.00
2.00
1.00
1.00
4.00
1.00
2.00
4.00
4.00
3.00
8.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

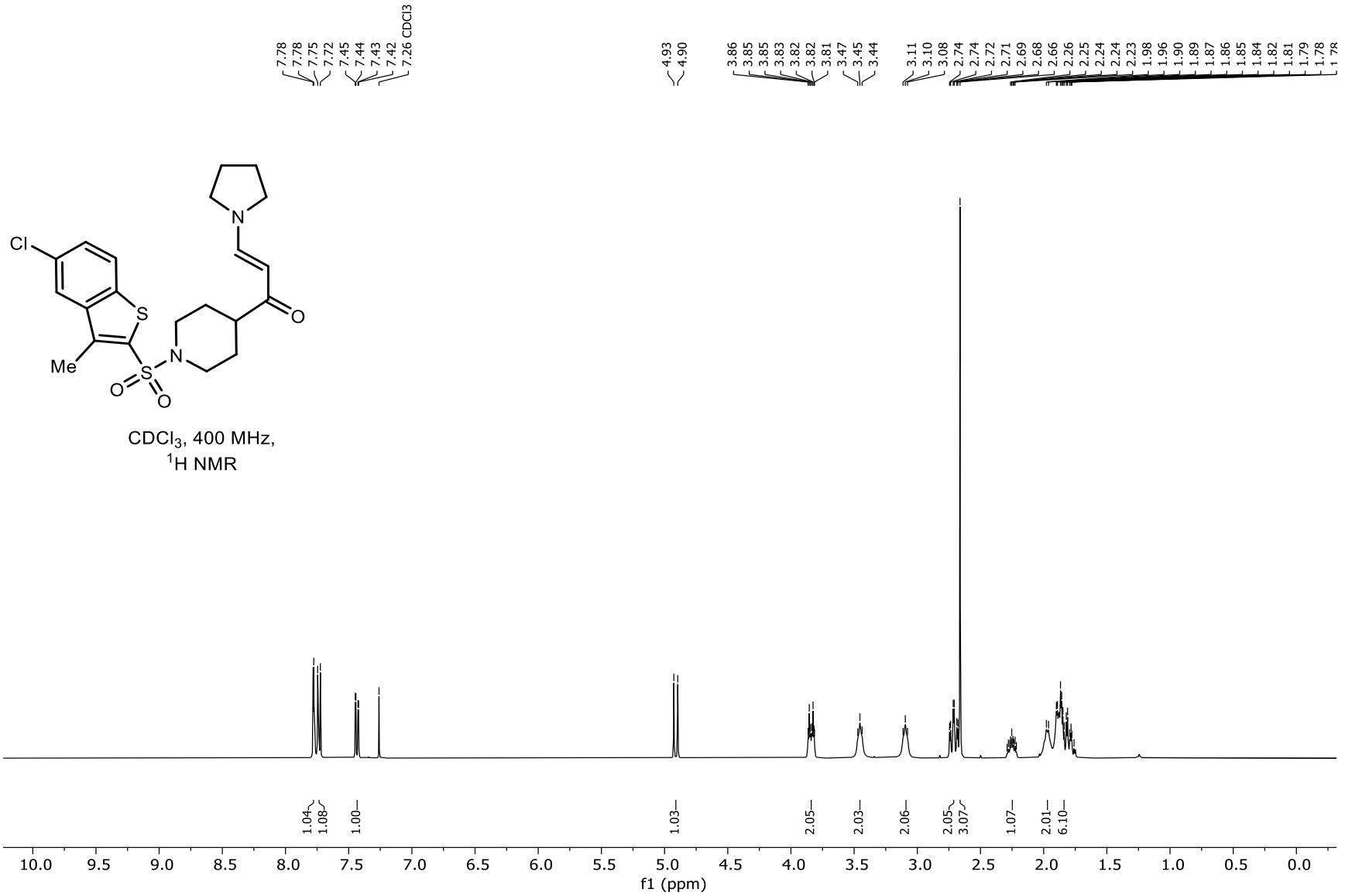

160.25
142.89
141.84
138.33
137.25
133.64
131.18
130.86
130.55
130.51
130.13
127.03
126.95
126.07
122.71
115.99
115.77
106.40
77.35
77.03
76.71
56.37
49.35
33.96
25.96
23.73
19.36
F
Me
S
N
N
OTf
CDCl3, 400 MHz
13C NMR
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

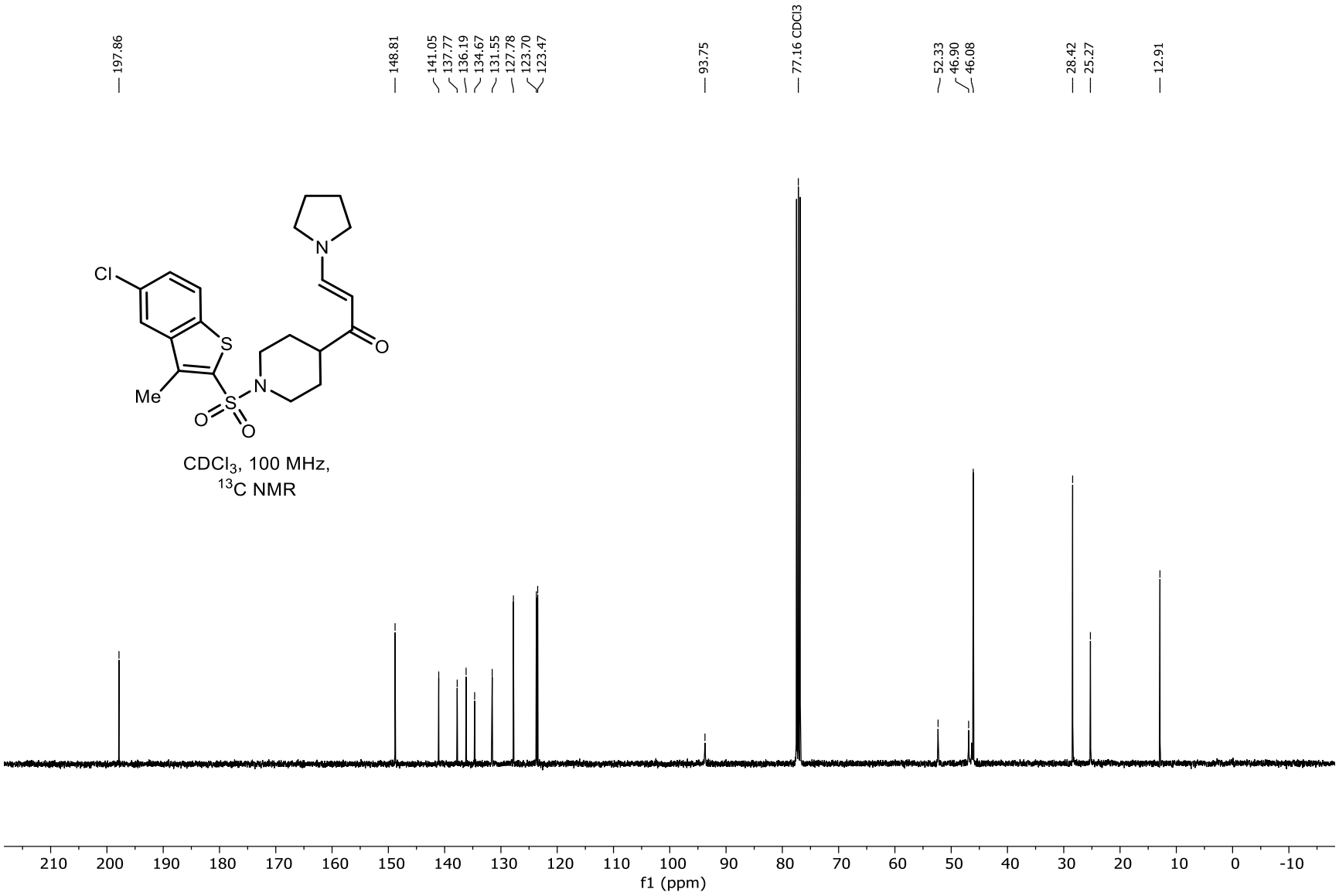
621



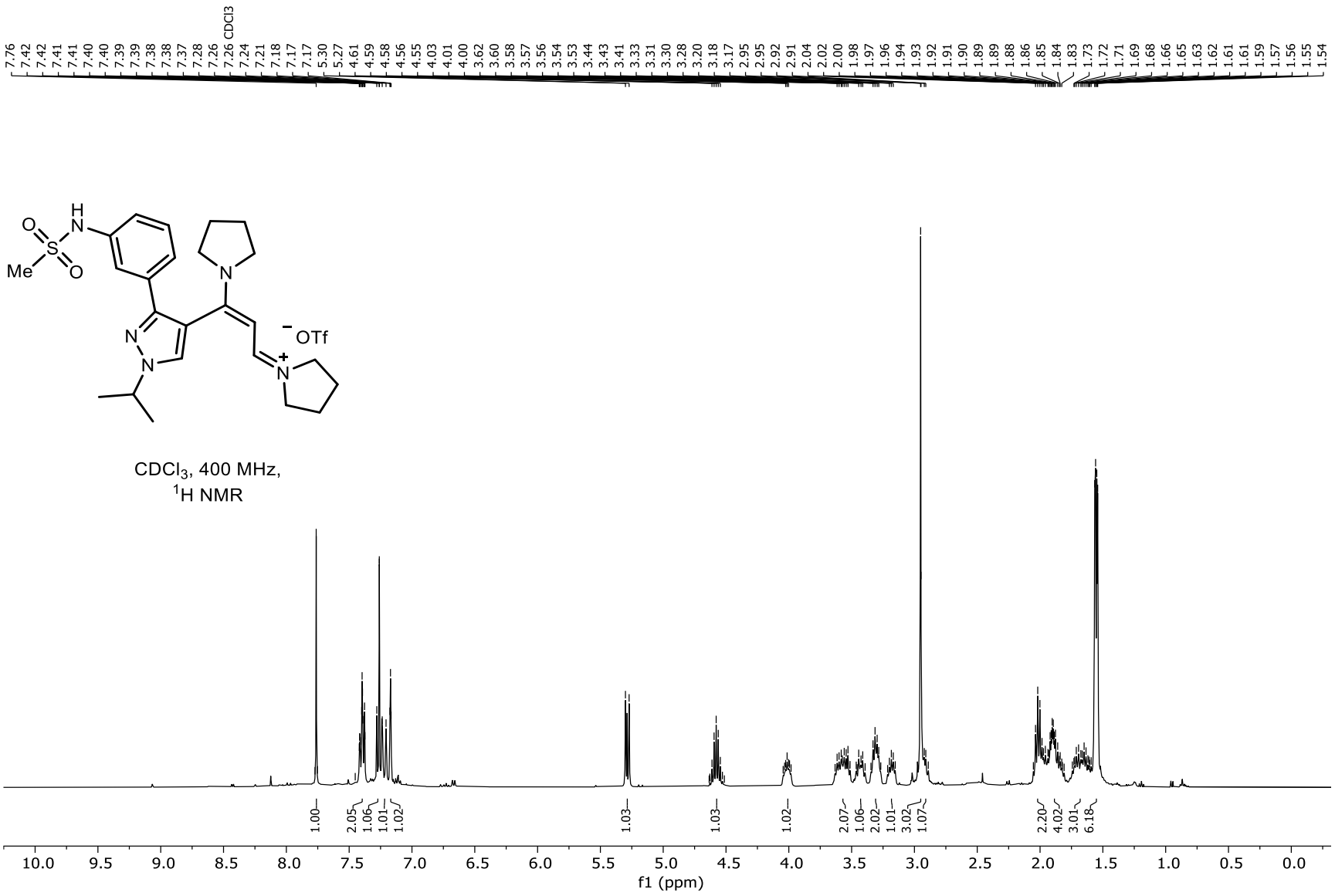
$CDCl_3$, 400 MHz
^{19}F NMR

623

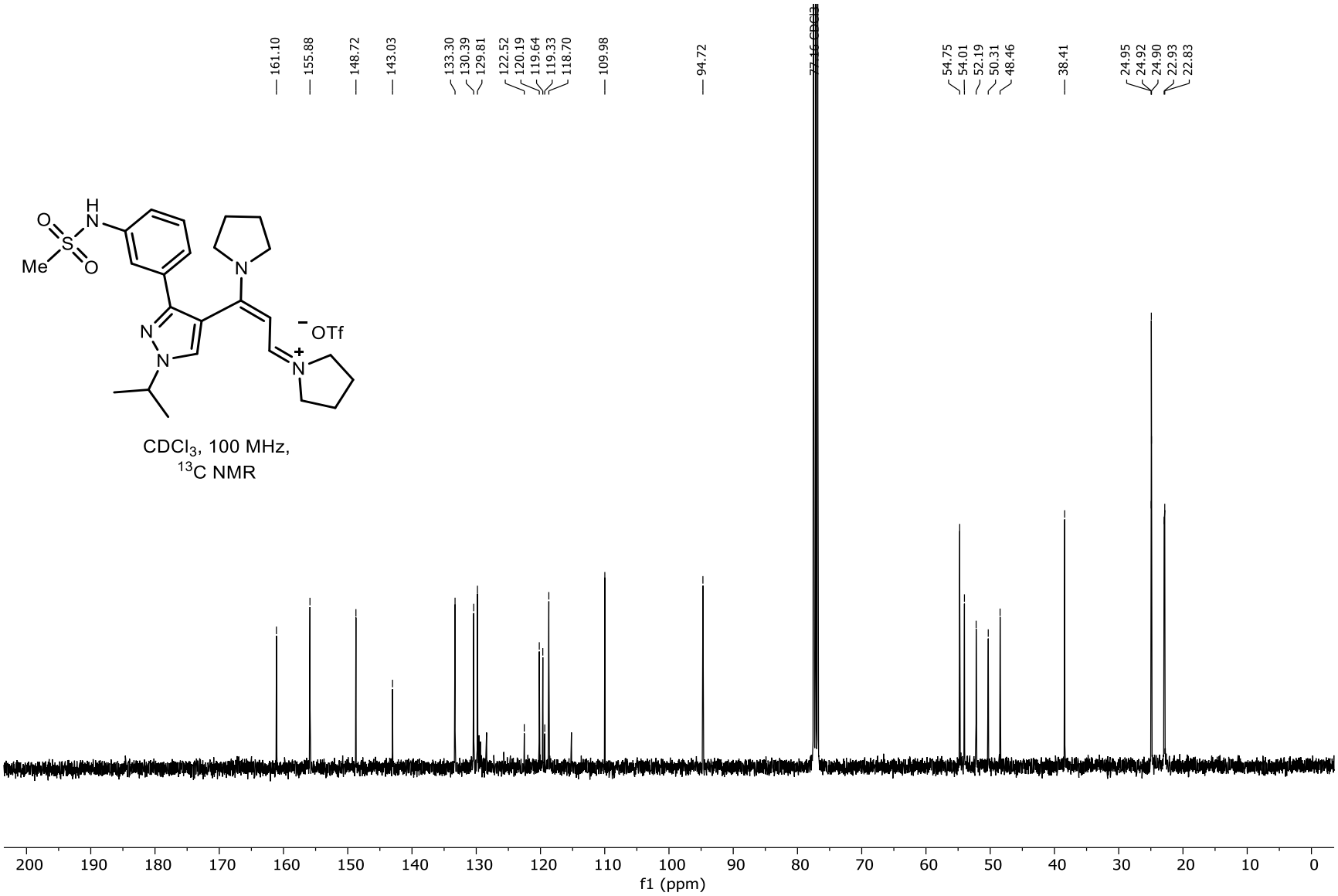

7.78
7.78
7.75
7.72
7.45
7.44
7.43
7.42
7.26 CDCl3
4.93
4.90
3.86
3.85
3.85
3.83
3.82
3.82
3.81
3.47
3.45
3.44
3.11
3.10
3.08
2.74
2.74
2.72
2.71
2.69
2.68
2.66
2.26
2.25
2.24
2.24
2.23
1.98
1.96
1.90
1.89
1.87
1.86
1.85
1.84
1.82
1.81
1.79
1.78
Cl
S
N
O
Me
S
N
O
O
CDCl3, 400 MHz,
1H NMR
1.04
1.08
1.00
1.03
2.05
2.03
2.06
2.05
3.07
1.07
2.01
6.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


197.86
148.81
141.05
137.77
136.19
134.67
131.55
127.78
123.70
123.47
93.75
77.16 CDCl3
52.33
46.90
46.08
28.42
25.27
12.91
Cl
S
Me
N
O
S
O
O
N
O
CDCl3, 100 MHz,
13C NMR
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

624

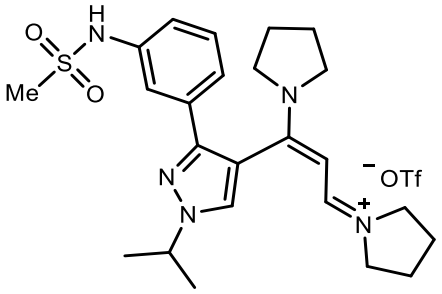

7.76 7.42 7.42 7.41 7.41 7.40 7.40 7.39 7.39 7.38 7.38 7.37 7.28 7.26 CDCl3 7.24 7.21 7.18 7.17 7.17 5.30 5.27 4.61 4.59 4.58 4.56 4.55 4.03 4.01 4.00 3.62 3.60 3.58 3.57 3.56 3.54 3.53 3.44 3.43 3.41 3.33 3.31 3.30 3.28 3.20 3.18 3.17 2.95 2.95 2.92 2.91 2.04 2.02 2.00 1.98 1.97 1.96 1.94 1.93 1.92 1.91 1.90 1.89 1.89 1.88 1.86 1.85 1.84 1.83 1.73 1.72 1.71 1.69 1.68 1.66 1.65 1.63 1.62 1.61 1.61 1.59 1.57 1.56 1.55 1.54
H
N
O
S
Me
O
O
N
N
N
OTf
N
CDCl3, 400 MHz,
1H NMR
1.00 2.05 1.06 1.01 1.02 1.03 1.03 1.02 2.07 1.06 2.02 1.01 3.02 1.07 2.20 4.02 3.01 6.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

625

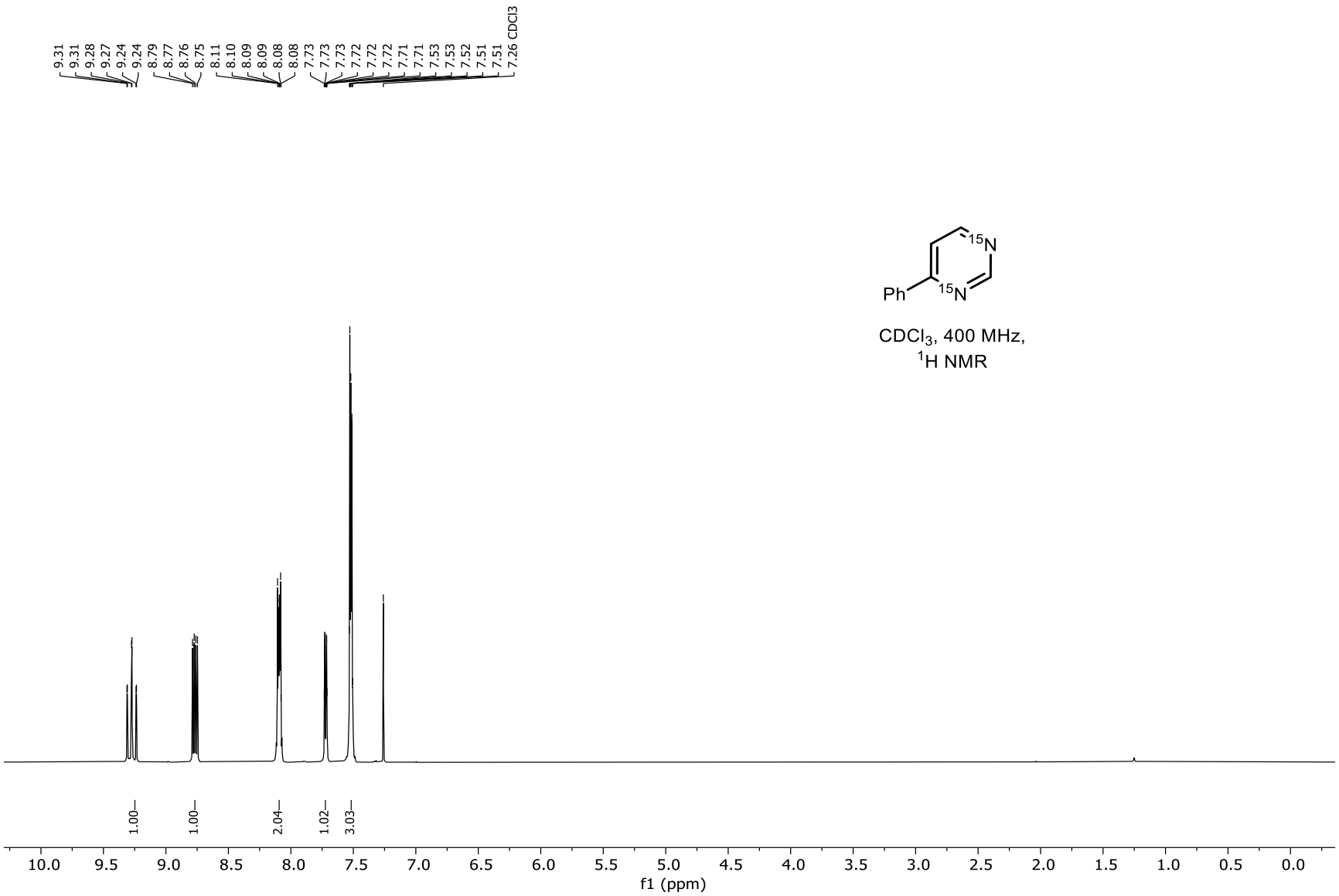

161.10
155.88
148.72
143.03
133.30
130.39
129.81
122.52
120.19
119.64
119.33
118.70
109.98
94.72
77.16 CDCl3
54.75
54.01
52.19
50.31
48.46
38.41
24.95
24.92
24.90
22.93
22.83
OTf
CDCl3, 100 MHz,
13C NMR
f1 (ppm)

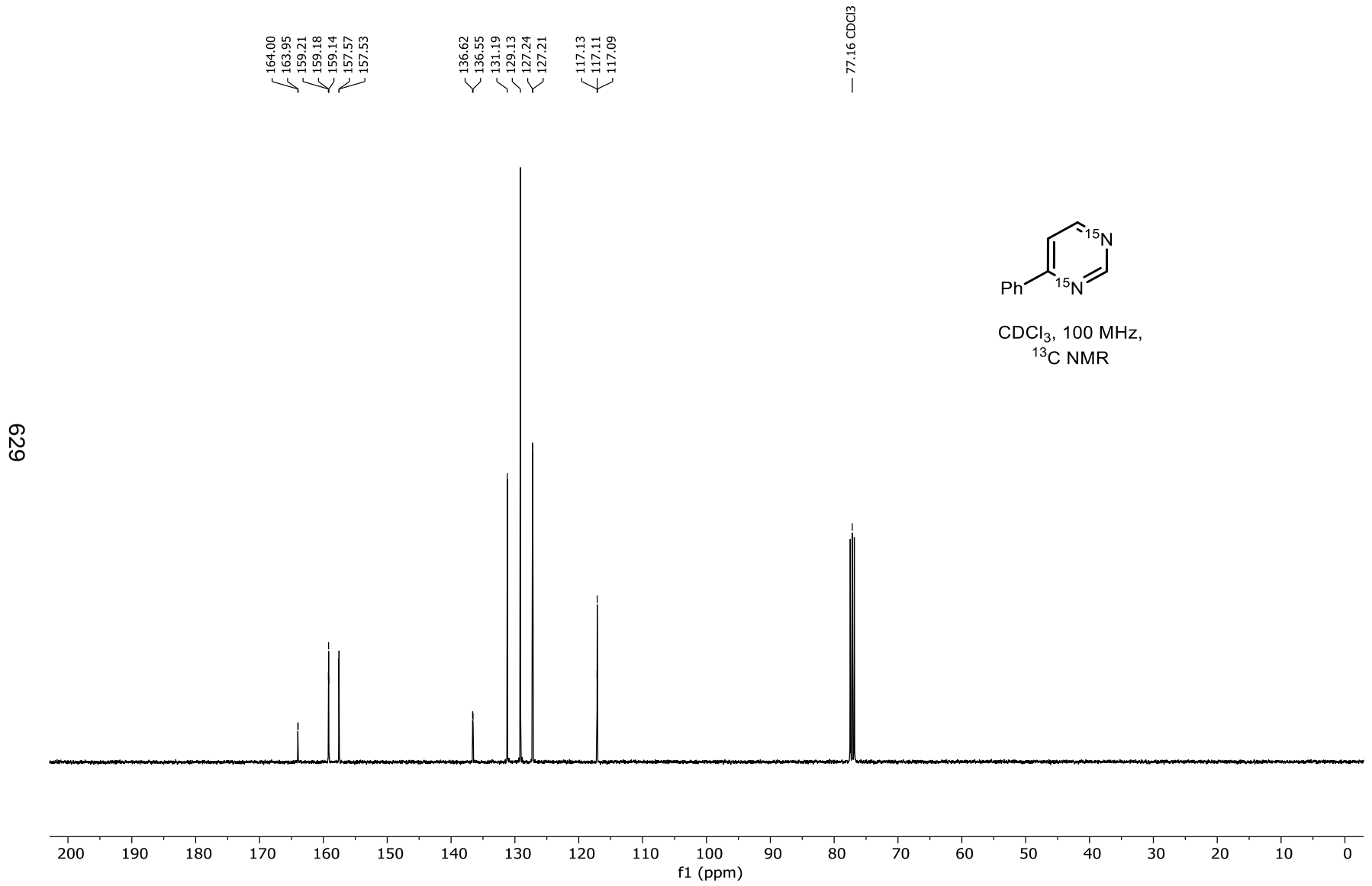
626

627

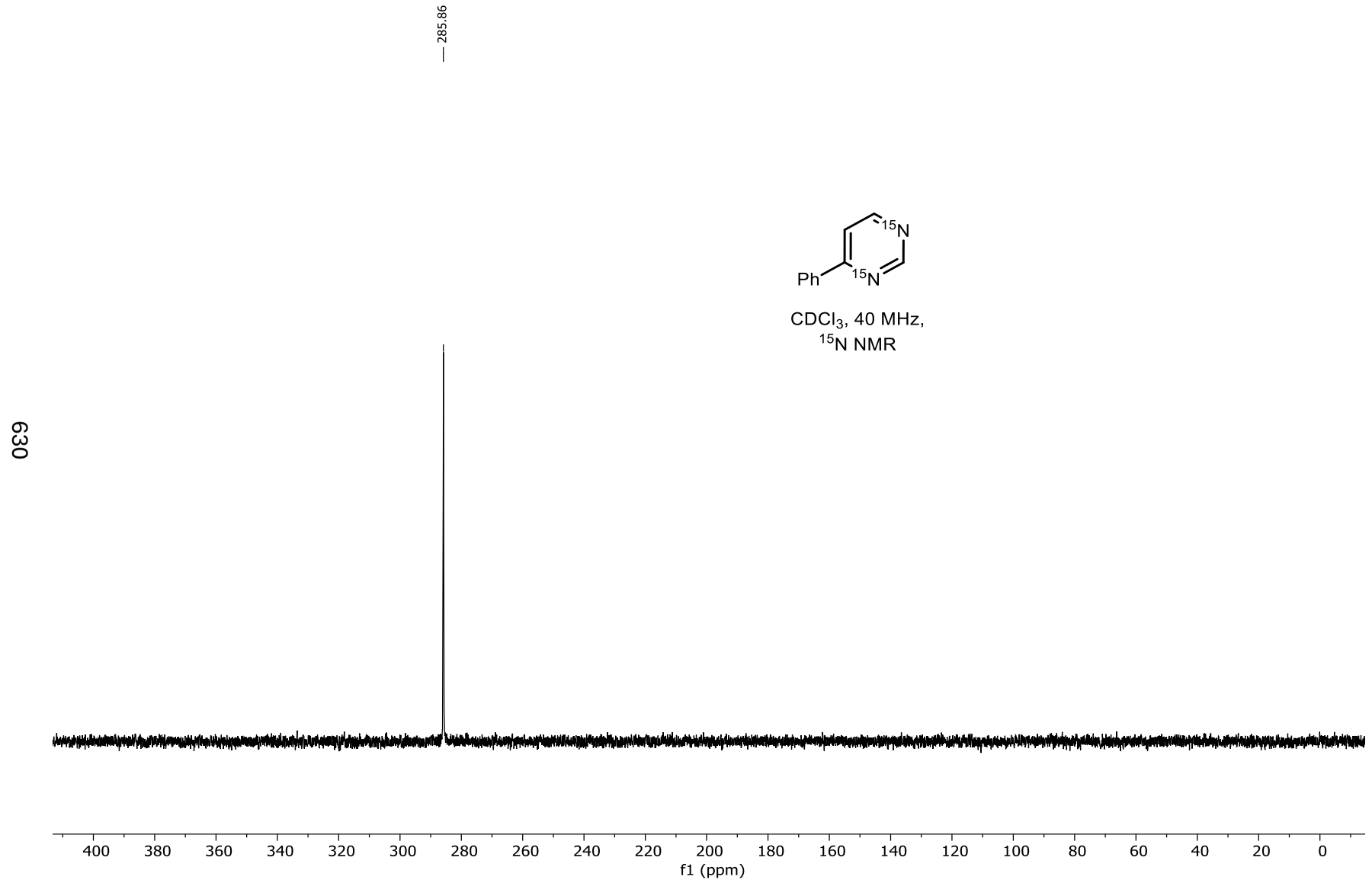


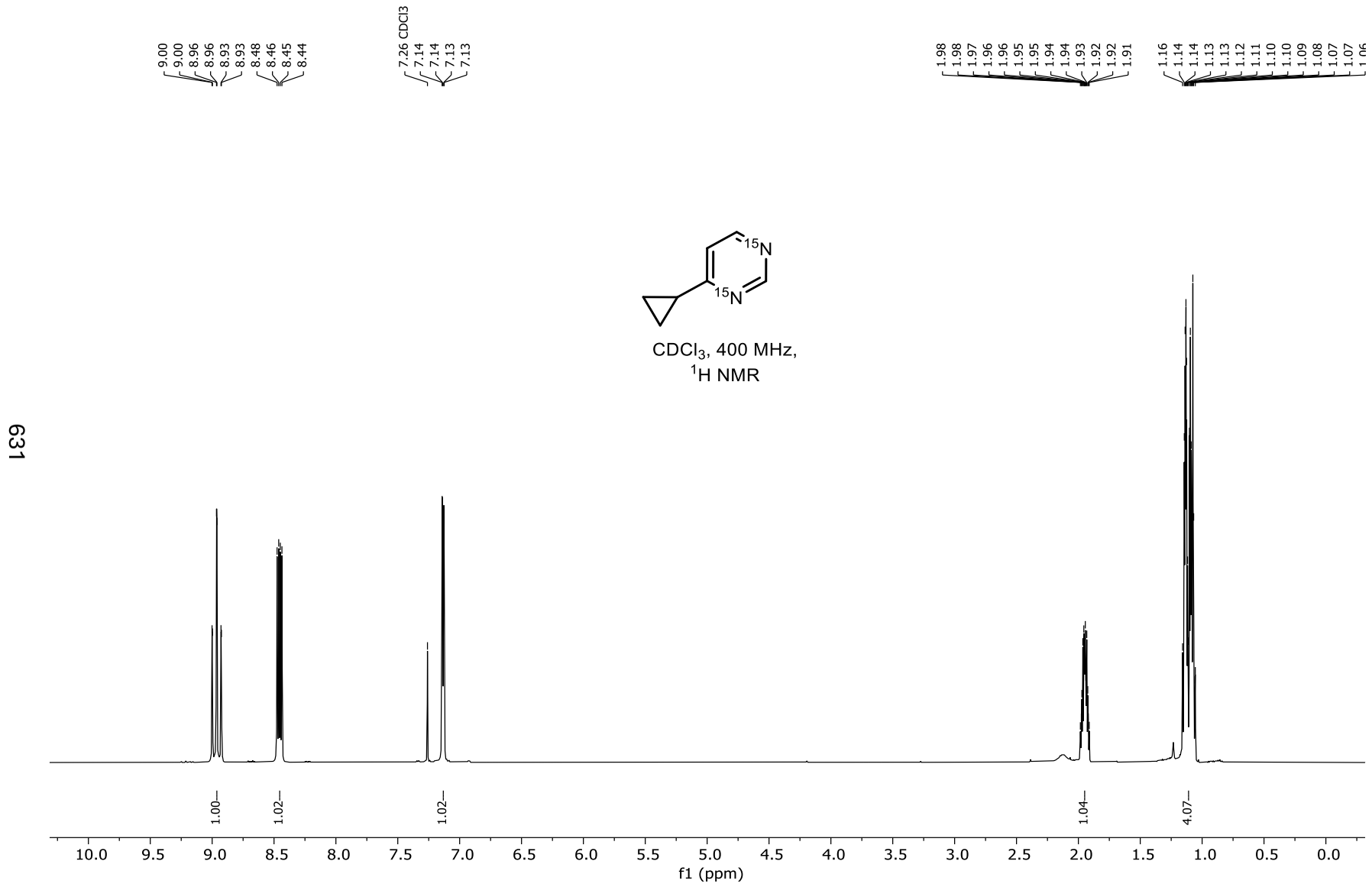
$CDCl_3$, 375 MHz,
^{19}F NMR


9.31
9.31
9.28
9.27
9.24
9.24
8.79
8.77
8.76
8.75
8.11
8.10
8.09
8.09
8.08
8.08
7.73
7.73
7.73
7.72
7.72
7.72
7.71
7.71
7.53
7.53
7.52
7.51
7.51
7.26 CDCl3
Ph
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
1.00
2.04
1.02
3.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.00
163.95
159.21
159.18
159.14
157.57
157.53
136.62
136.55
131.19
129.13
127.24
127.21
117.13
117.11
117.09
77.16 CDCl3
15N
Ph
15N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

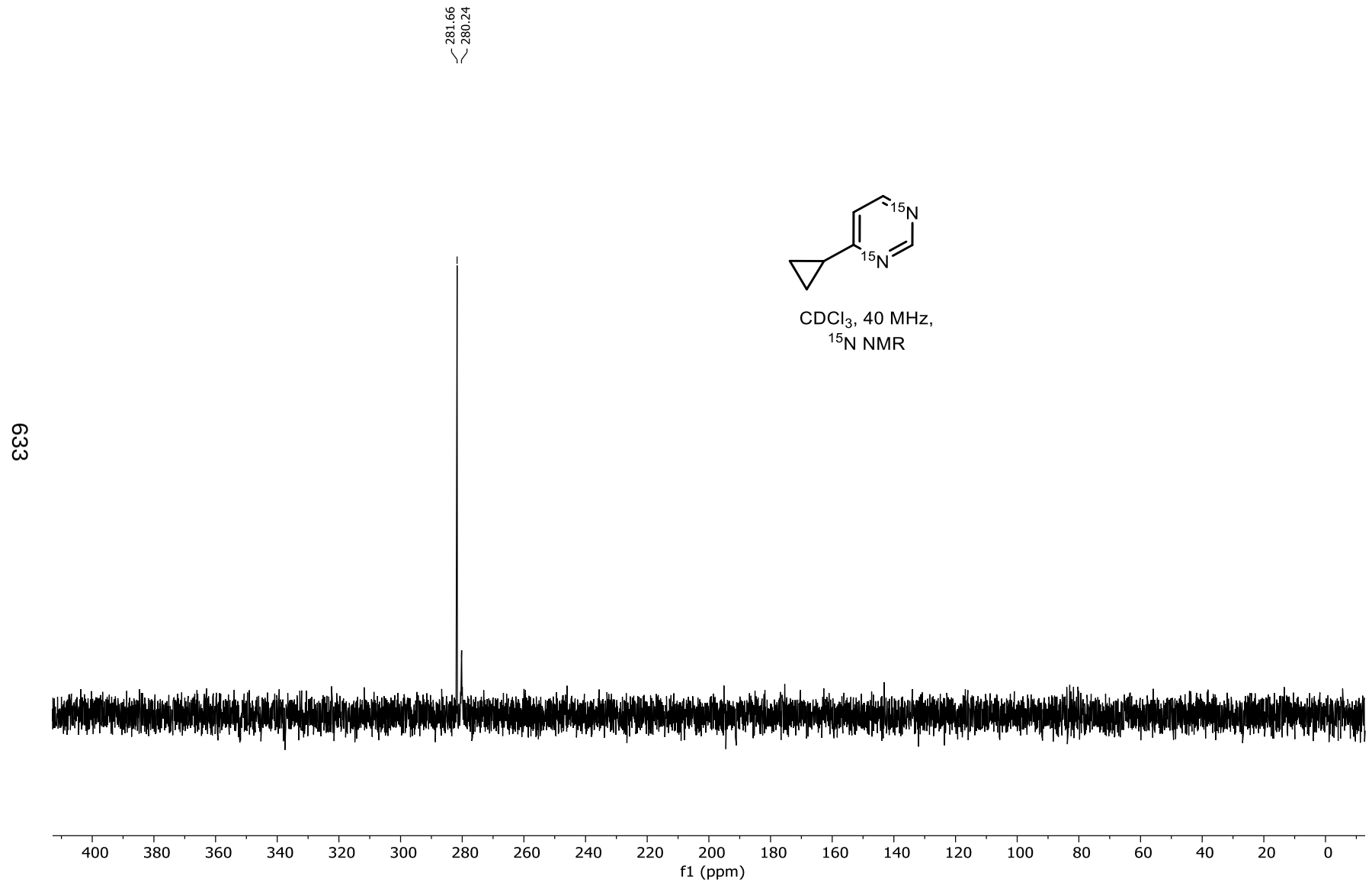
629


285.86
15N
Ph
15N
CDCl3, 40 MHz,
15N NMR
630
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


9.00
9.00
8.96
8.96
8.93
8.93
8.48
8.46
8.45
8.44
7.26 CDCl3
7.14
7.14
7.13
7.13
1.98
1.98
1.97
1.96
1.96
1.95
1.95
1.94
1.94
1.93
1.92
1.92
1.91
1.16
1.14
1.14
1.13
1.13
1.12
1.11
1.10
1.10
1.09
1.08
1.07
1.07
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
1.02
1.02
1.04
4.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

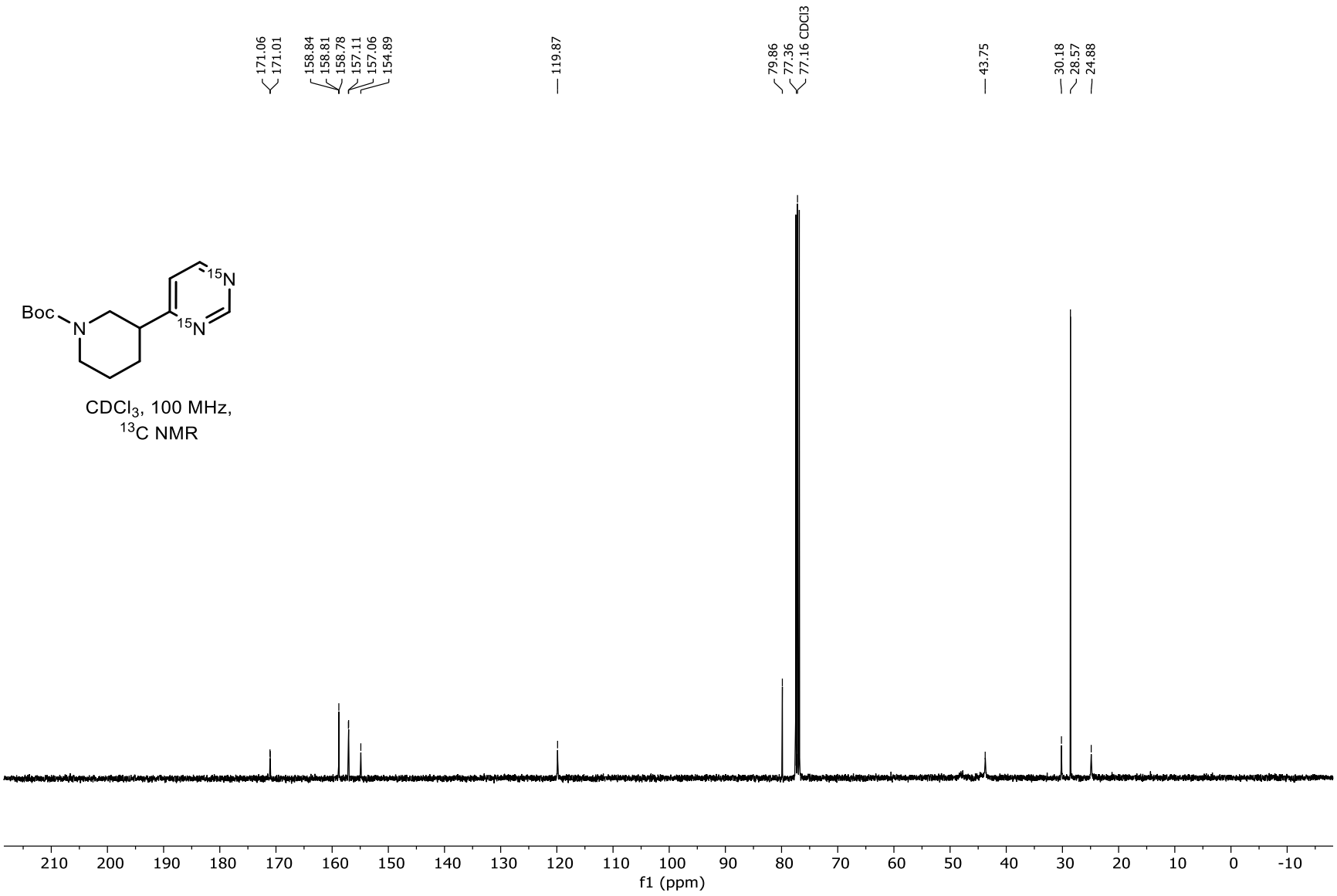
$CDCl_3$, 100 MHz,
^{13}C NMR
^{15}N
^{15}N
11.49
11.50
16.97
17.05
77.16 CDCl3
119.22
119.24
119.26
155.72
155.76
158.73
158.76
158.79
171.95
171.99
f1 (ppm)

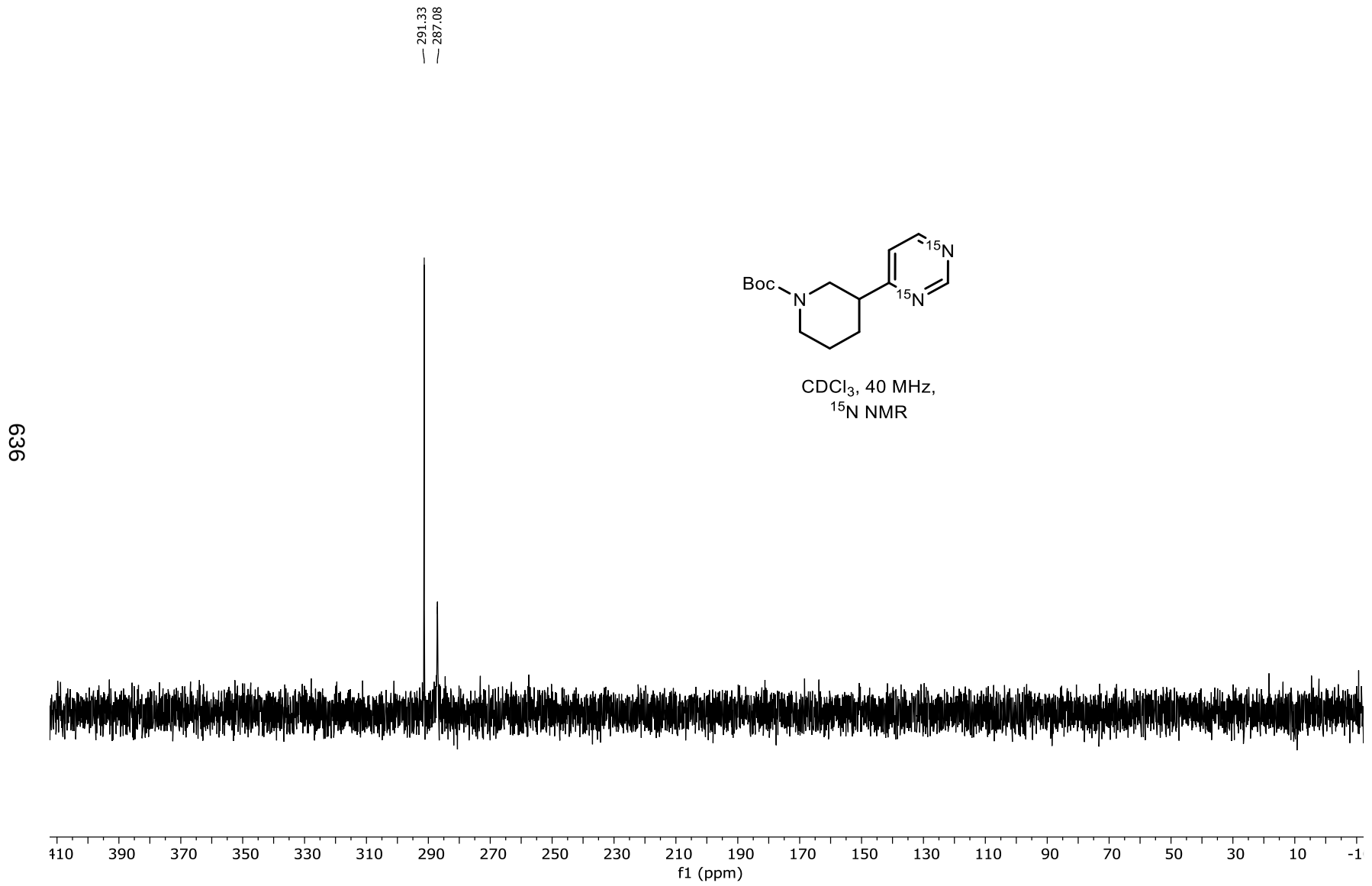
633

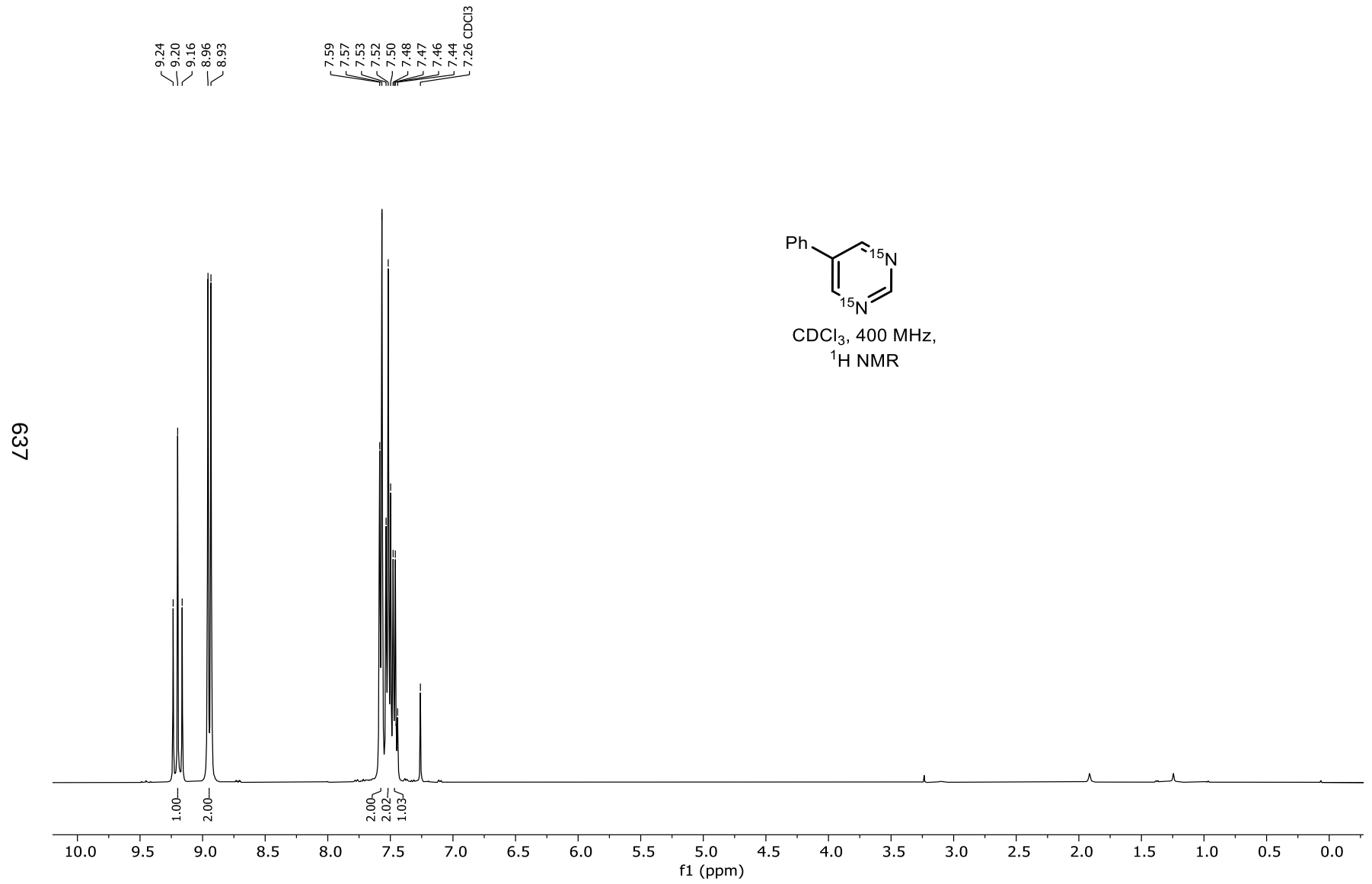

281.66
280.24
15N
15N
CDCl3, 40 MHz,
15N NMR
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

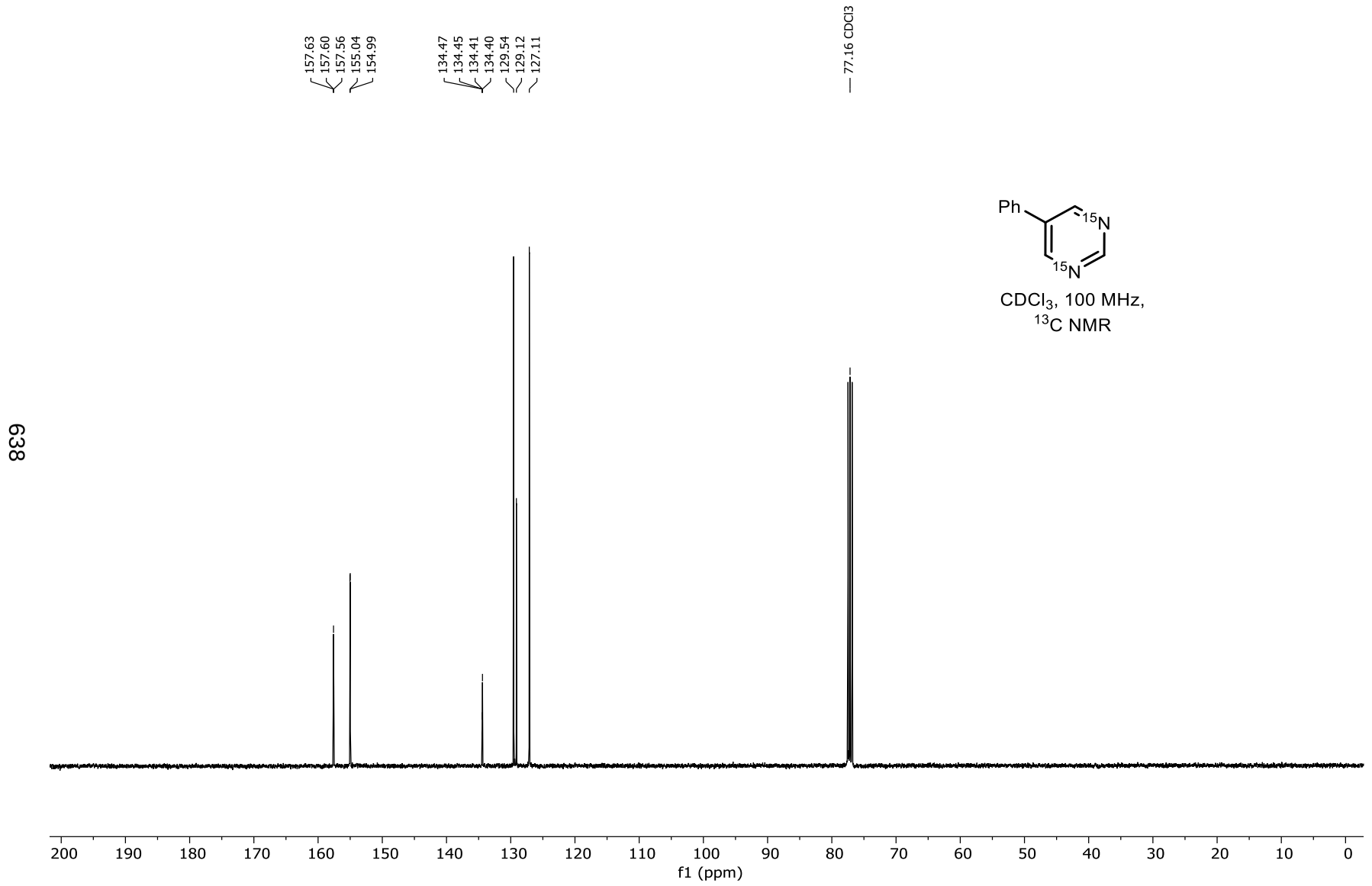
9.17
9.17
9.16
9.13
9.13
9.13
9.10
9.10
9.09
8.65
8.63
8.62
8.61
7.26 CDCl3
7.21
7.20
4.20
4.07
3.05
2.83
2.82
2.81
2.80
2.05
2.03
2.03
2.02
2.01
1.84
1.81
1.77
1.74
1.73
1.61
1.58
1.55
1.46
1.02
1.00
1.01
1.07
2.00
1.01
1.00
1.01
2.07
1.05
9.04
Boc
15N
15N
CDCl3, 400 MHz,
1H NMR
f1 (ppm)

635

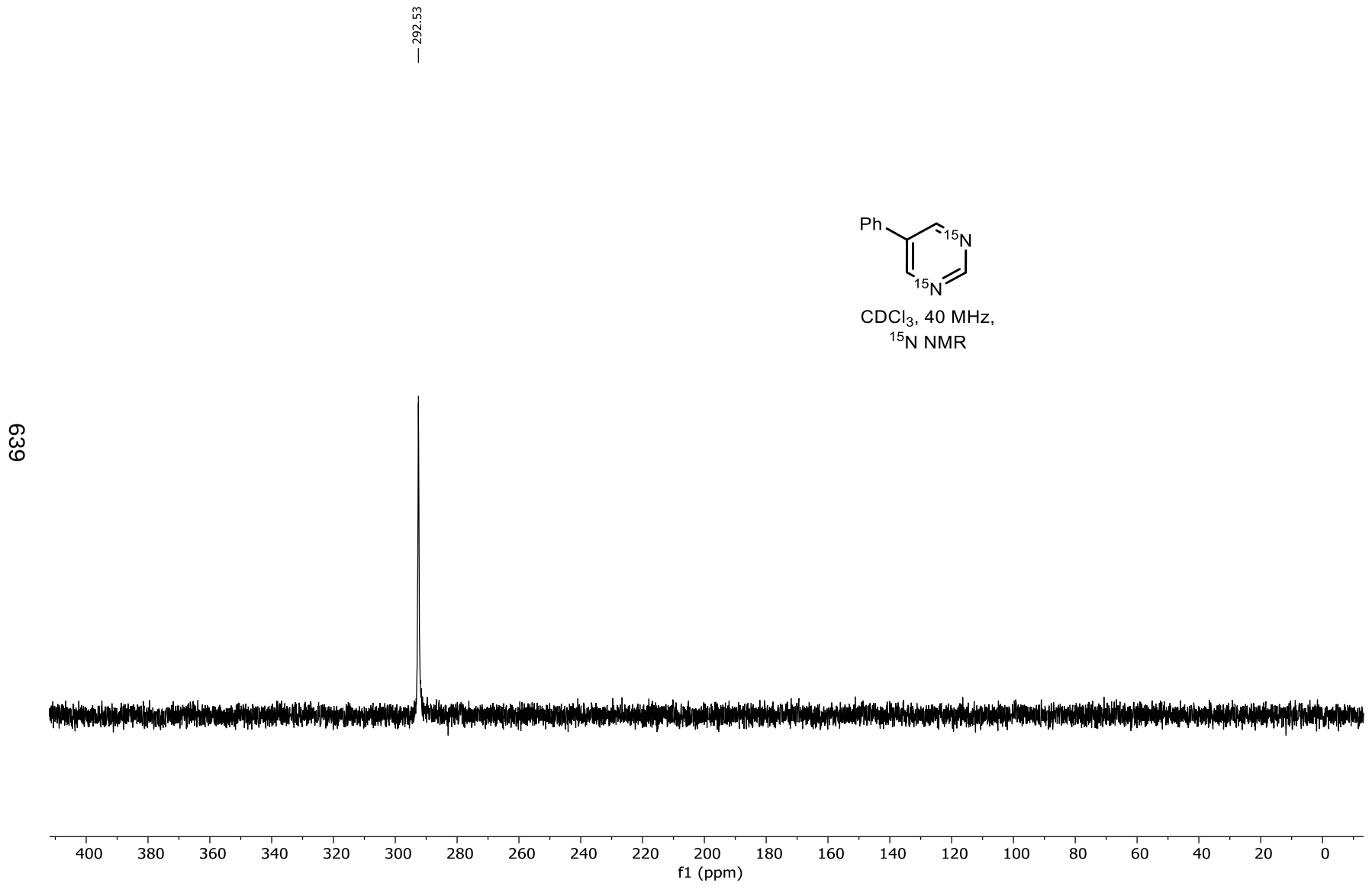

171.06
171.01
158.84
158.81
158.78
157.11
157.06
154.89
119.87
79.86
77.36
77.16 CDCl3
43.75
30.18
28.57
24.88
Boc
N
15N
15N
CDCl3, 100 MHz,
13C NMR
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

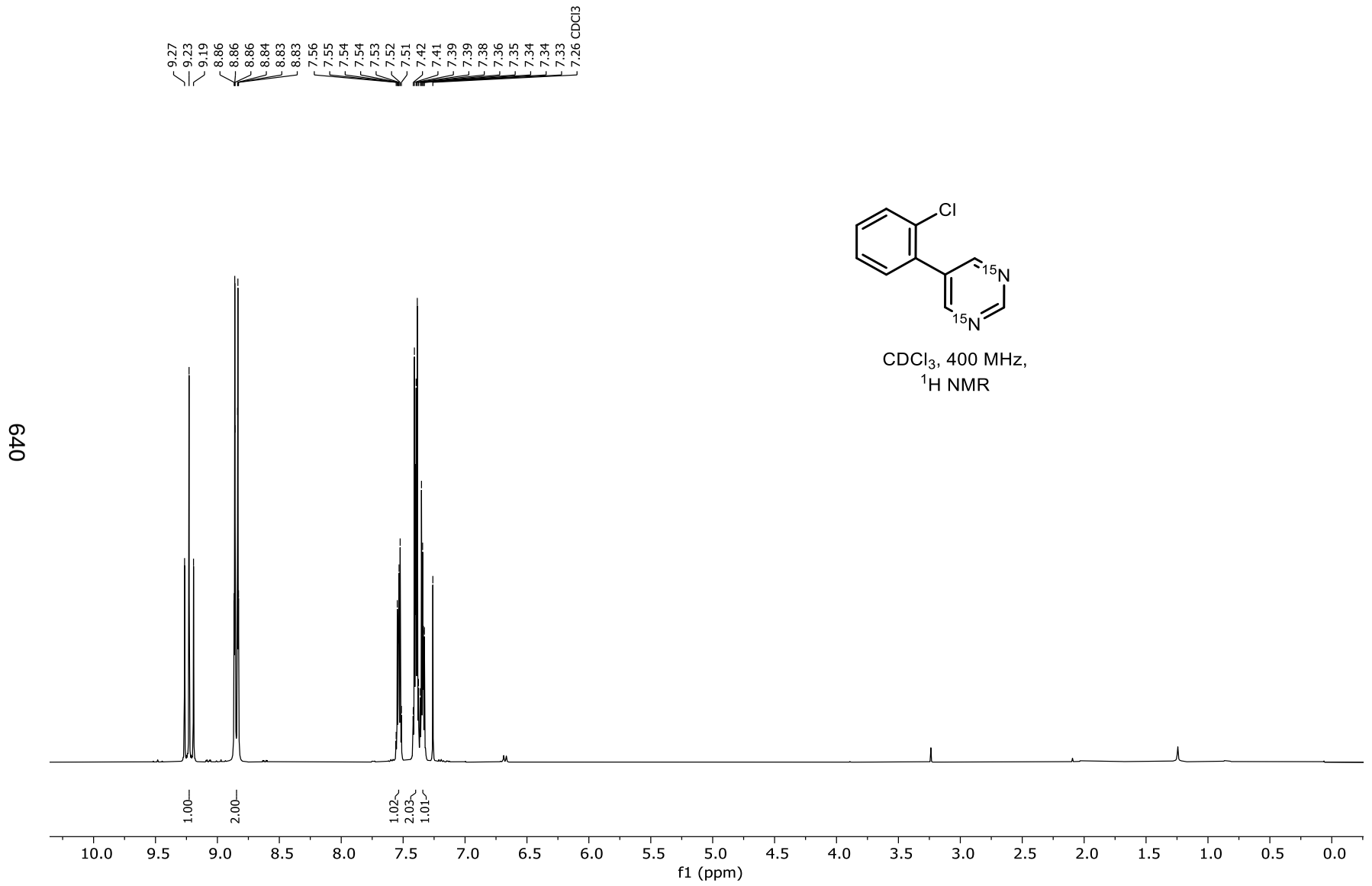

291.33
287.08
Boc
N
15N
15N
CDCl3, 40 MHz,
15N NMR
636
410
390
370
350
330
310
290
270
250
230
210
190
170
150
130
110
90
70
50
30
10
-1
f1 (ppm)


9.24
9.20
9.16
8.96
8.93
7.59
7.57
7.53
7.52
7.50
7.48
7.47
7.46
7.44
7.26 CDCl3
Ph
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
2.00
2.00
2.02
1.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


157.63
157.60
157.56
155.04
154.99
134.47
134.45
134.41
134.40
129.54
129.12
127.11
77.16 CDCl3
Ph
15N
15N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

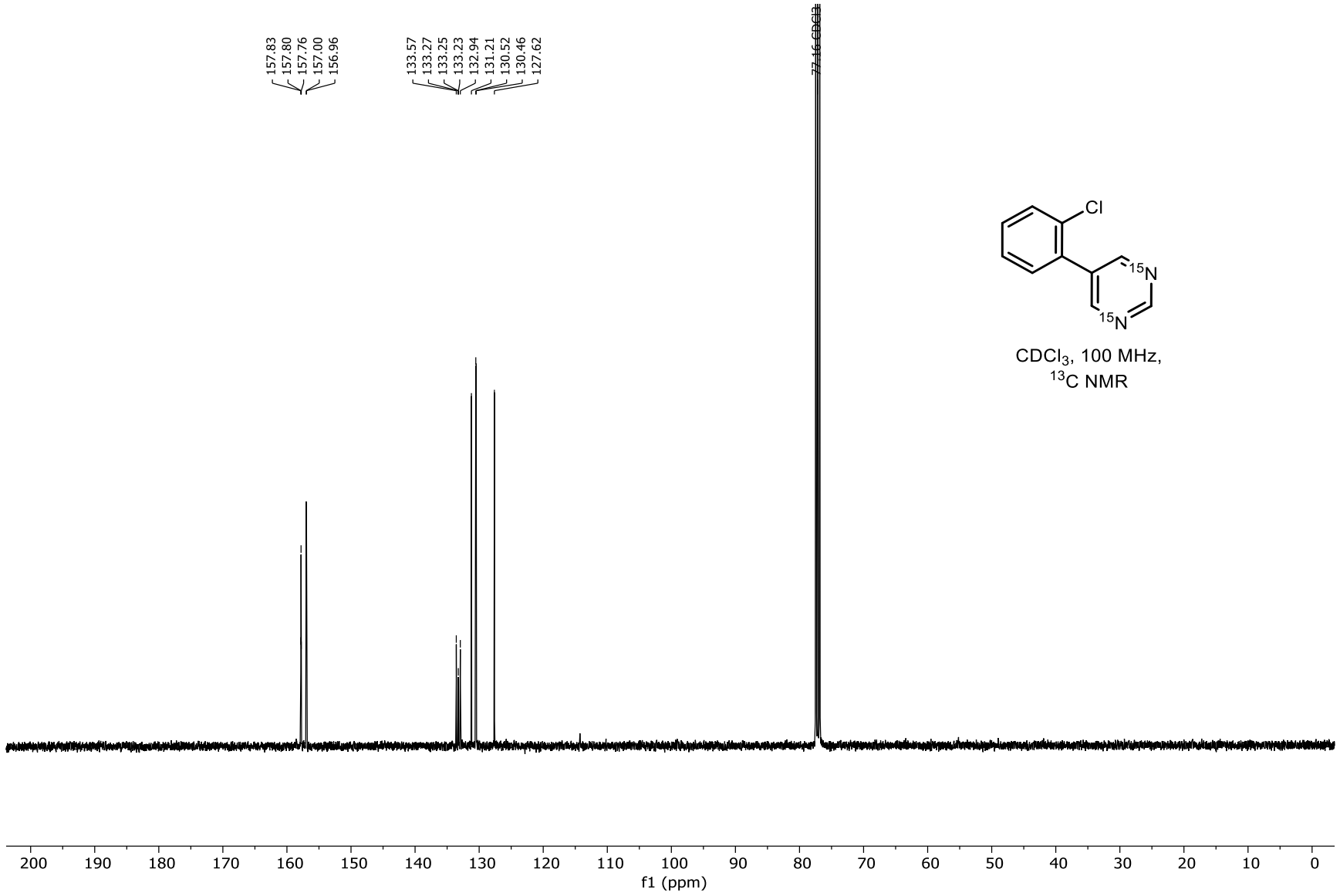
638


292.53
Ph
15N
15N
CDCl3, 40 MHz,
15N NMR
639
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

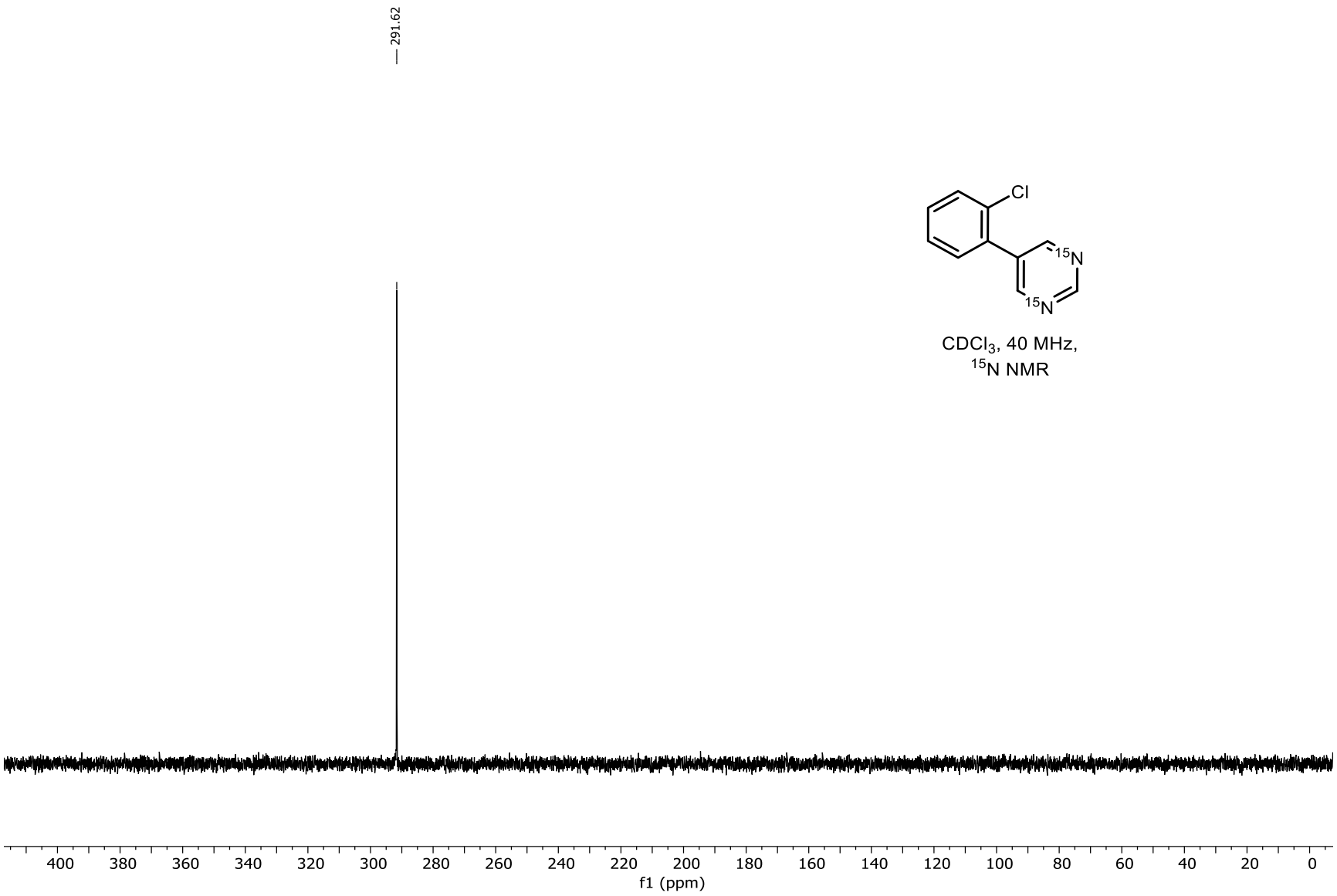

9.27
9.23
9.19
8.86
8.86
8.86
8.84
8.83
8.83
7.56
7.55
7.54
7.54
7.53
7.52
7.51
7.42
7.41
7.39
7.39
7.38
7.36
7.35
7.34
7.34
7.33
7.26 CDCl3
Cl
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
2.00
1.02
2.03
1.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

640

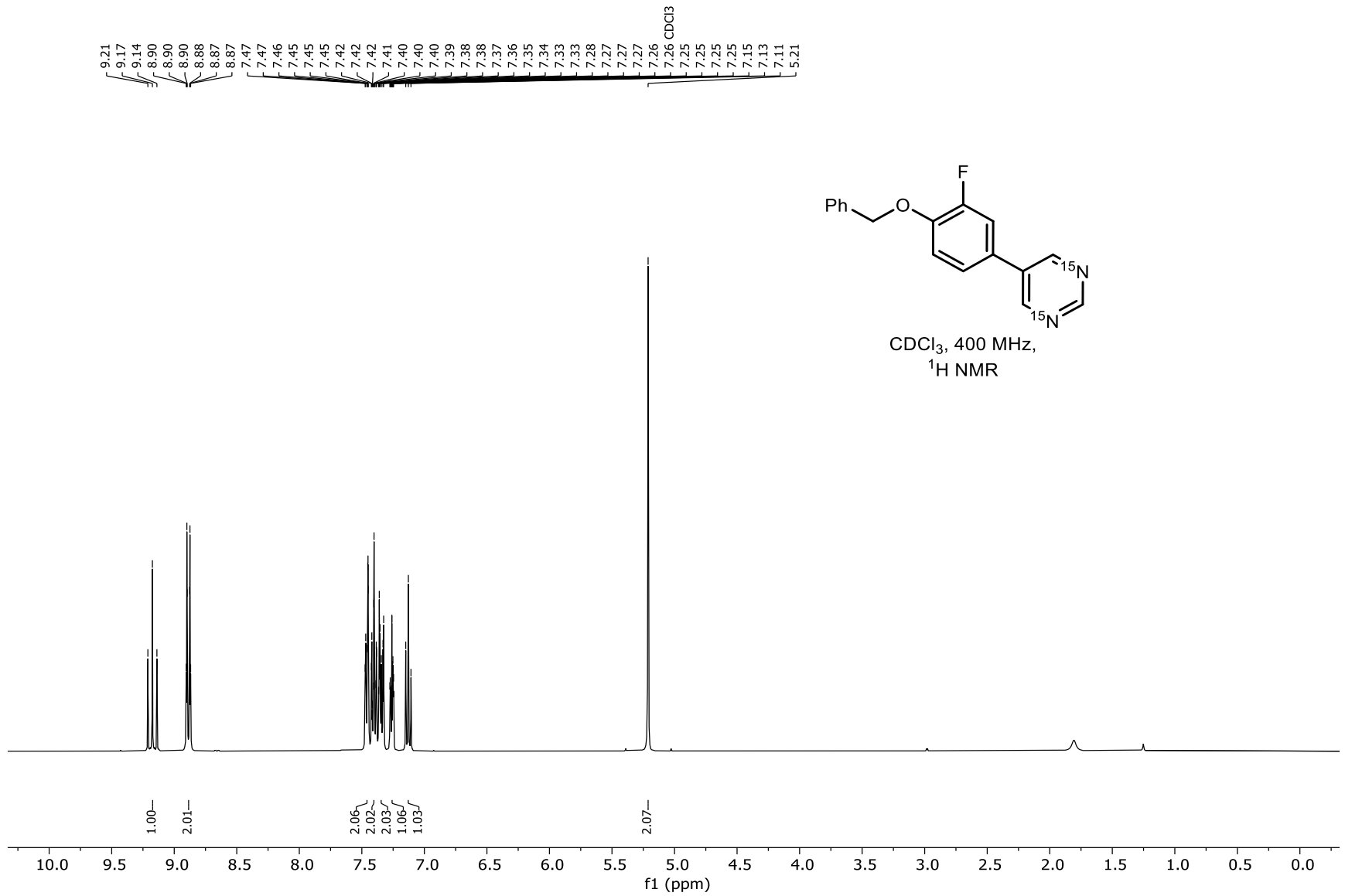
641


157.83
157.80
157.76
157.00
156.96
133.57
133.27
133.25
133.23
132.94
131.21
130.52
130.46
127.62
77.16 CDCl3
Cl
15N
15N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

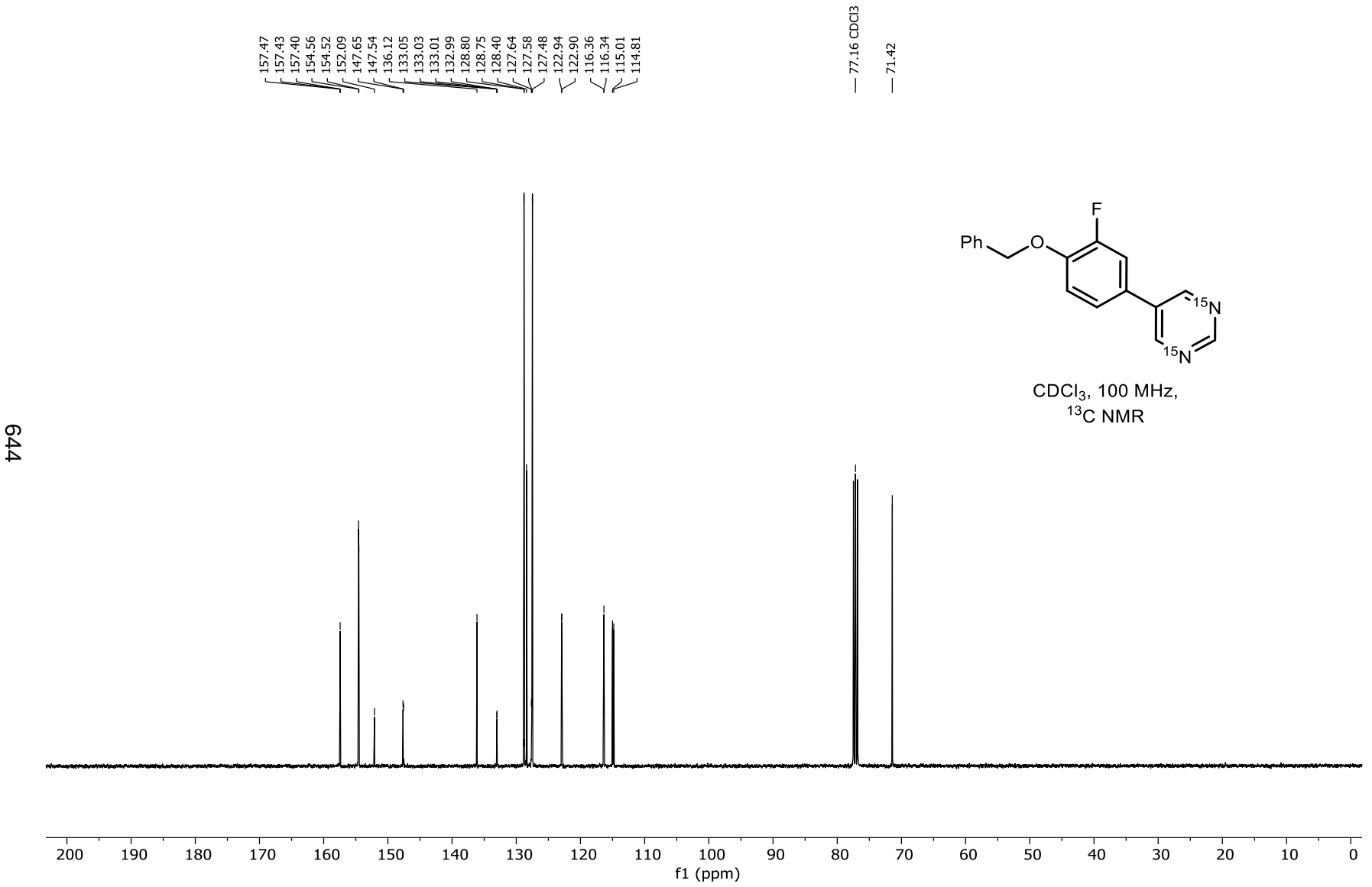
642


291.62
Cl
15N
15N
CDCl3, 40 MHz,
15N NMR
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

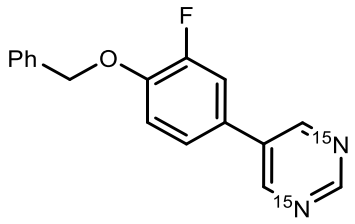
643


9.21
9.17
9.14
8.90
8.90
8.90
8.88
8.87
8.87
7.47
7.47
7.46
7.45
7.45
7.45
7.42
7.42
7.42
7.41
7.40
7.40
7.40
7.39
7.38
7.38
7.37
7.36
7.35
7.34
7.33
7.33
7.28
7.27
7.27
7.27
7.26
7.26 CDCl3
7.25
7.25
7.25
7.25
7.15
7.13
7.11
5.21
F
Ph
O
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
2.01
2.06
2.02
2.03
1.06
1.03
2.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

644


157.47
157.43
157.40
154.56
154.52
152.09
147.65
147.54
136.12
133.05
133.03
133.01
132.99
128.80
128.75
128.40
127.64
127.58
127.48
122.94
122.90
116.36
116.34
115.01
114.81
77.16 CDCl3
71.42
F
Ph
O
15N
15N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

645

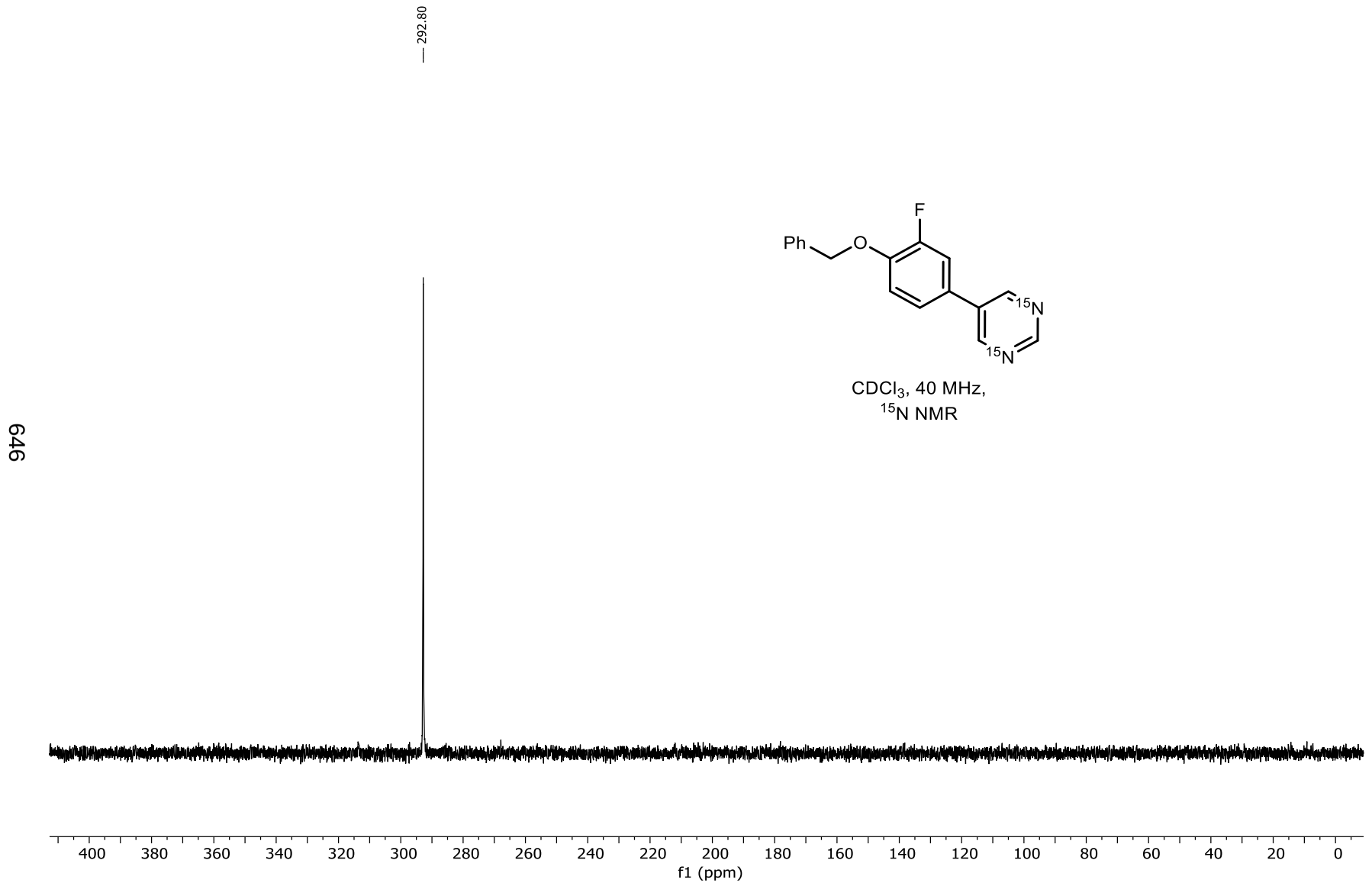


$CDCl_3$, 375 MHz,
^{19}F NMR

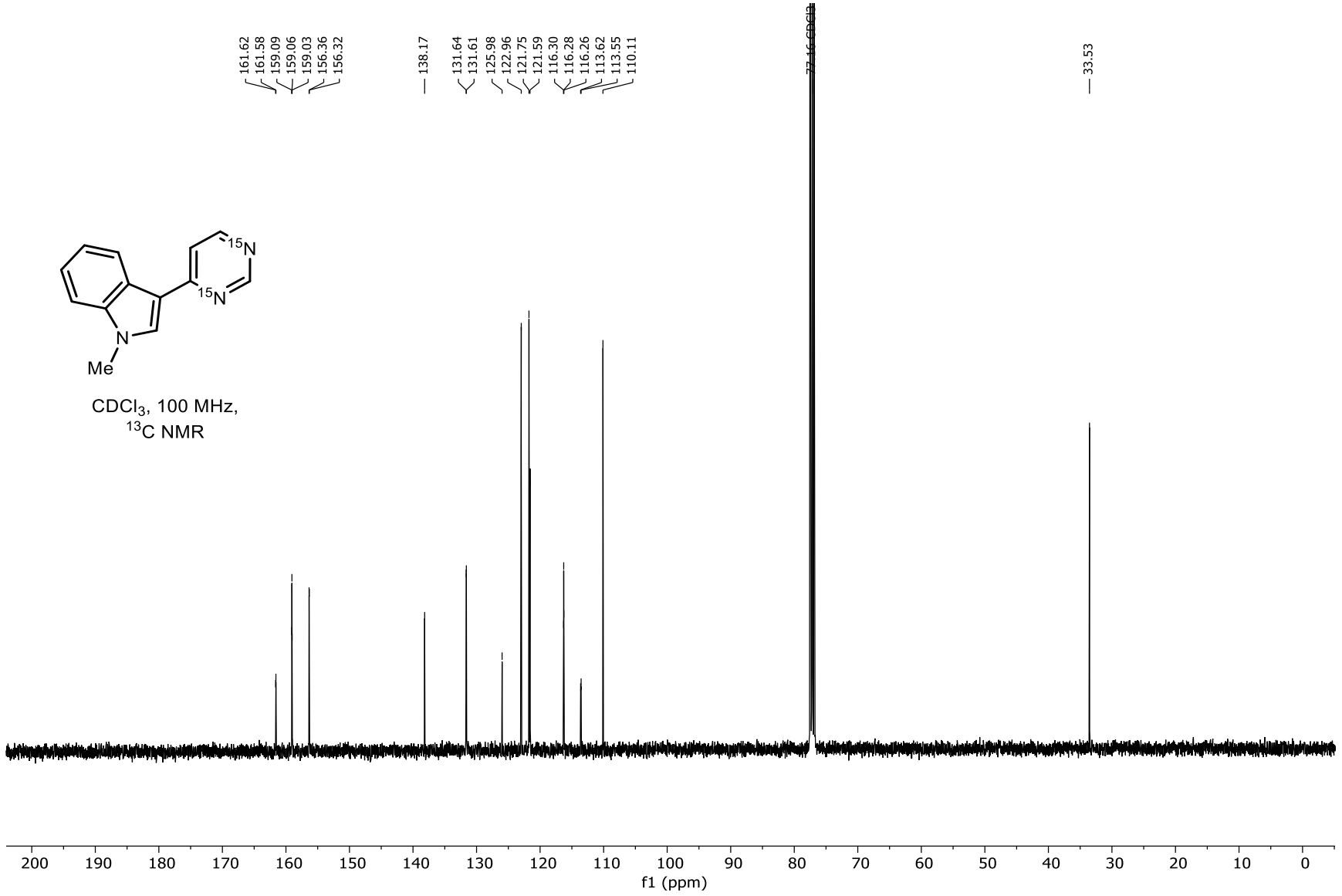
-131.78
-131.80
-131.81
-131.83

0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -20(

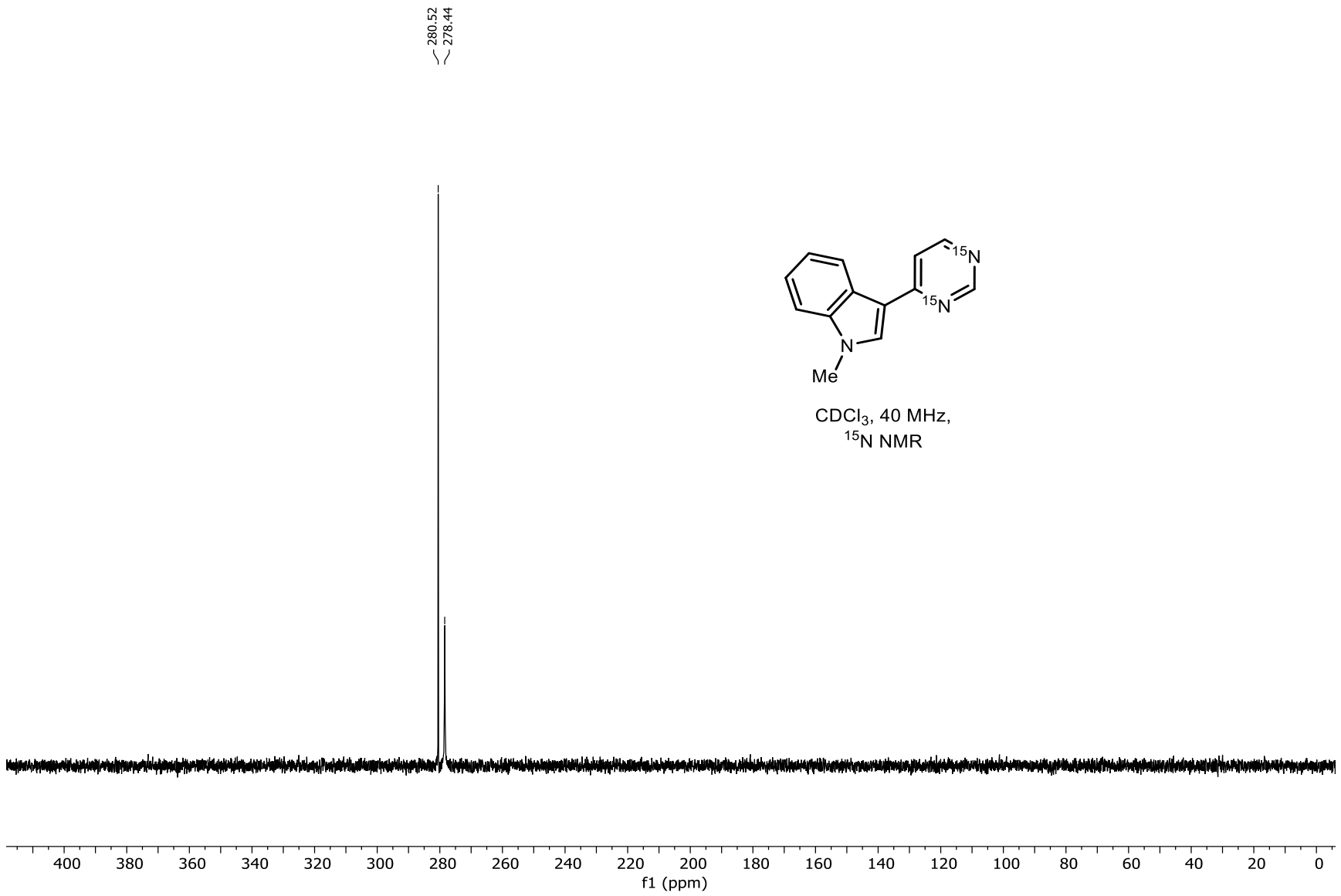
f1 (ppm)


292.80
F
Ph
O
15N
15N
CDCl3, 40 MHz,
15N NMR
6446
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

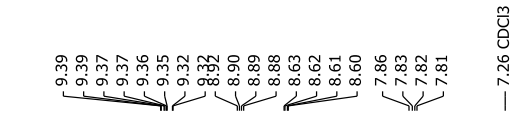
^{15}N
^{15}N
N
Me
CDCl$_3$, 400 MHz,
^{1}H NMR
9.18
9.18
9.14
9.14
9.11
9.10
8.62
8.61
8.60
8.58
8.40
8.39
8.38
8.38
8.38
8.37
8.36
8.36
8.35
7.89
7.60
7.60
7.59
7.59
7.41
7.41
7.40
7.39
7.39
7.38
7.38
7.36
7.35
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.29
7.29
7.26 CDCl3
3.88
3.05
2.04
1.05
1.02
1.00
1.03
1.00
1.00
f1 (ppm)

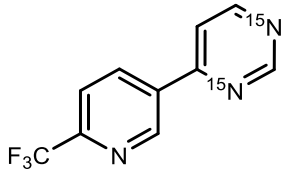

161.62
161.58
159.09
159.06
159.03
156.36
156.32
138.17
131.64
131.61
125.98
122.96
121.75
121.59
116.30
116.28
116.26
113.62
113.55
110.11
77.16 CDCl3
33.53
15N
15N
N
Me
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

649

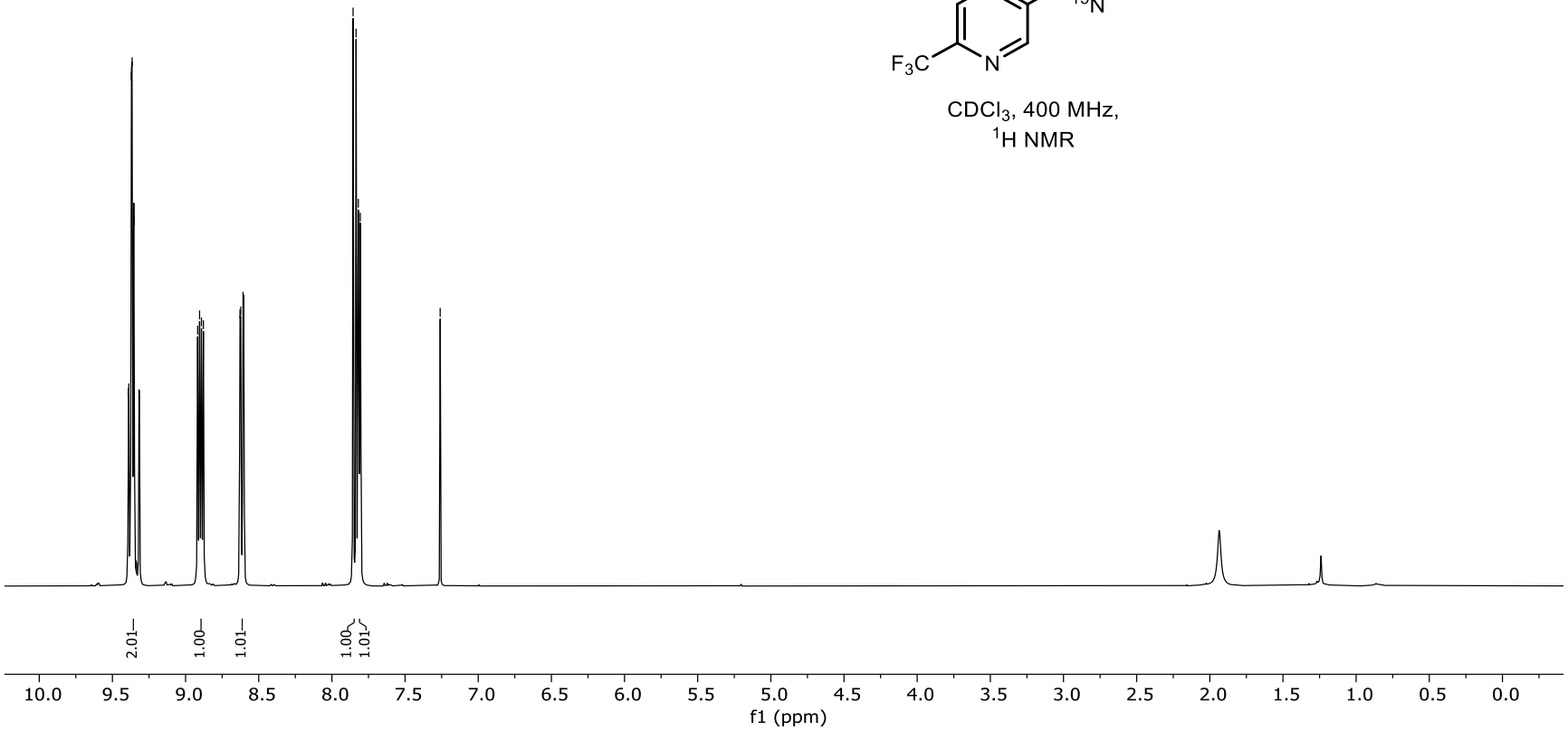

280.52
278.44
15N
15N
N
Me
CDCl3, 40 MHz,
15N NMR
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

650

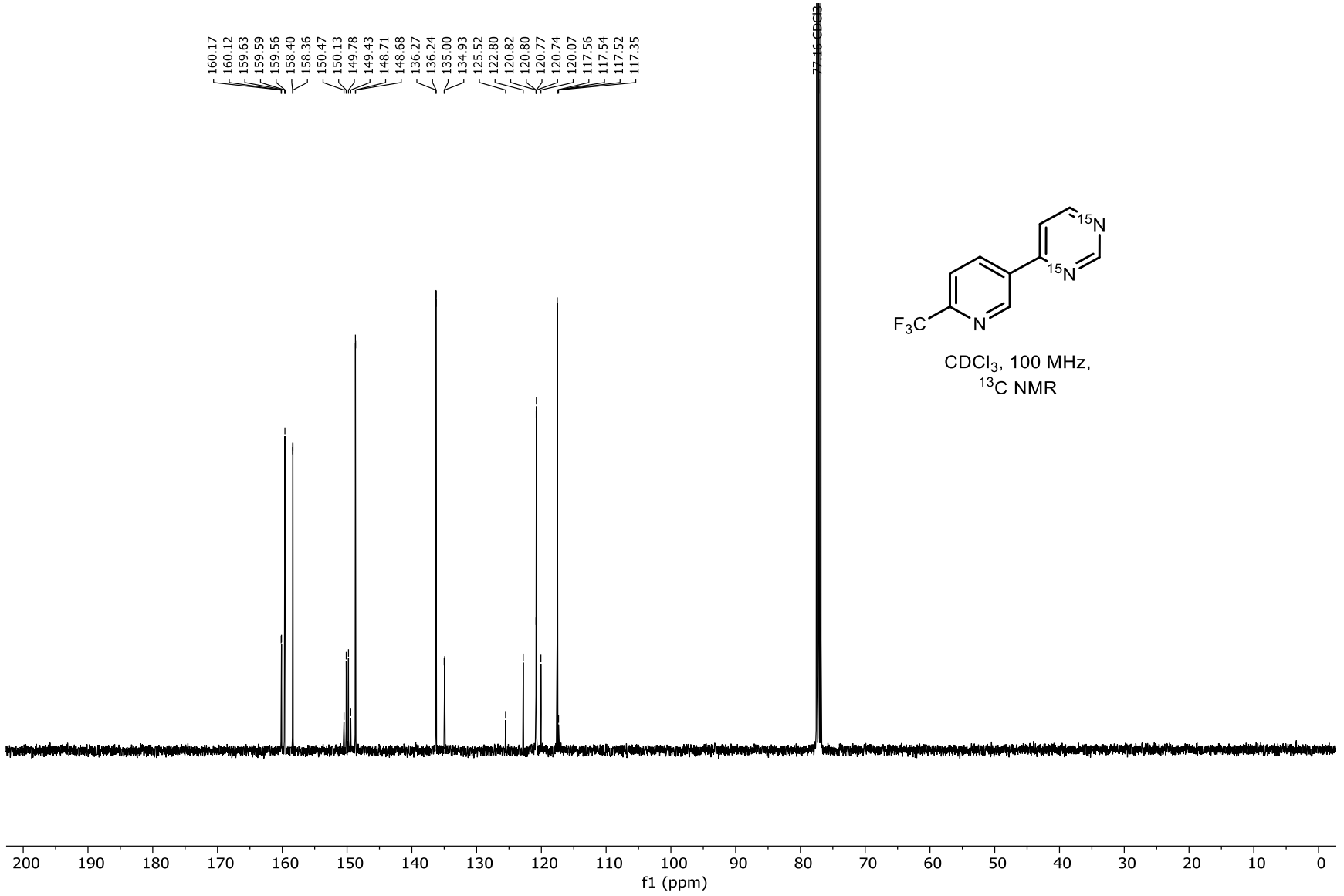




$CDCl_3$, 400 MHz,
^1H NMR



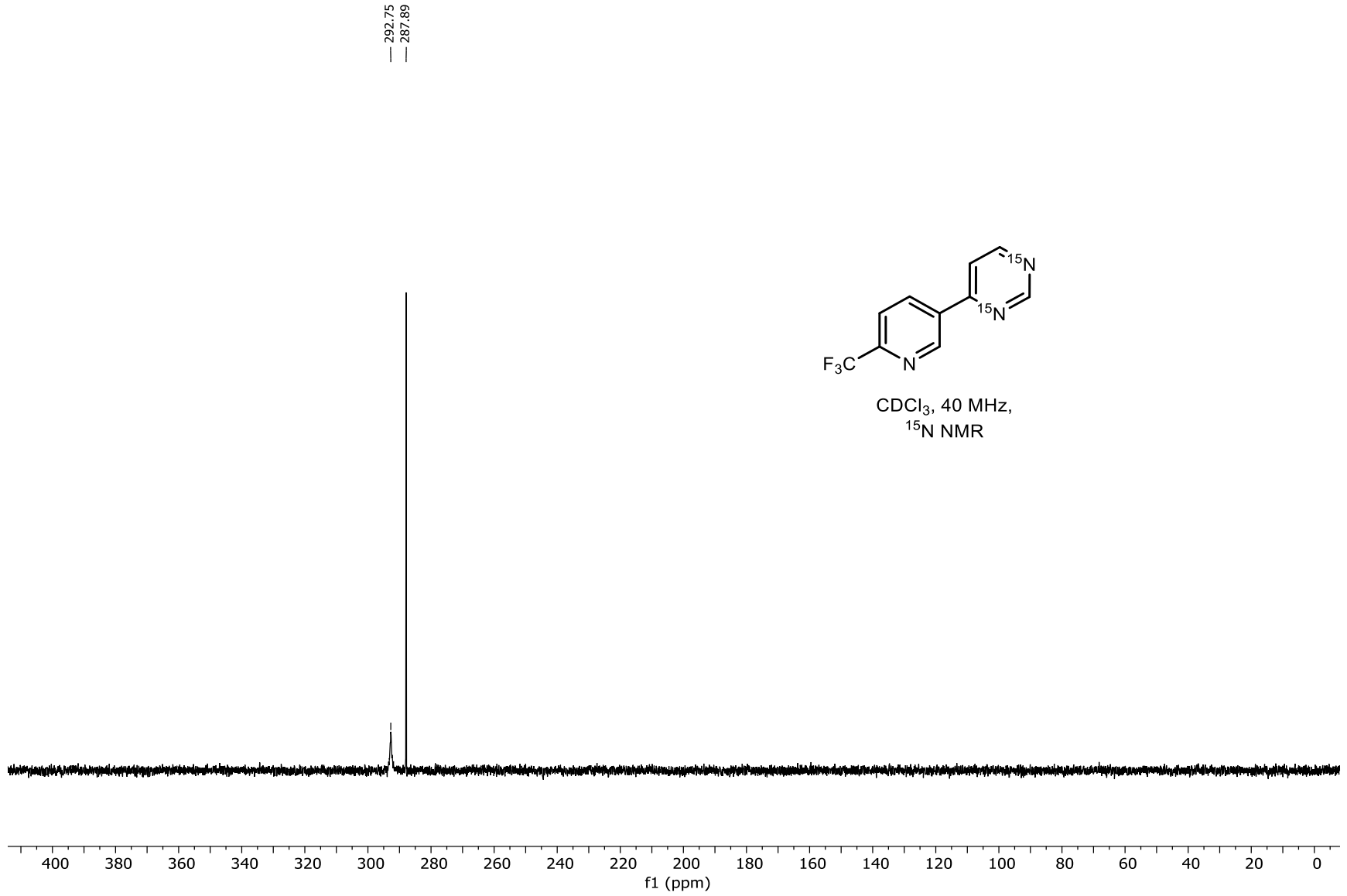
651

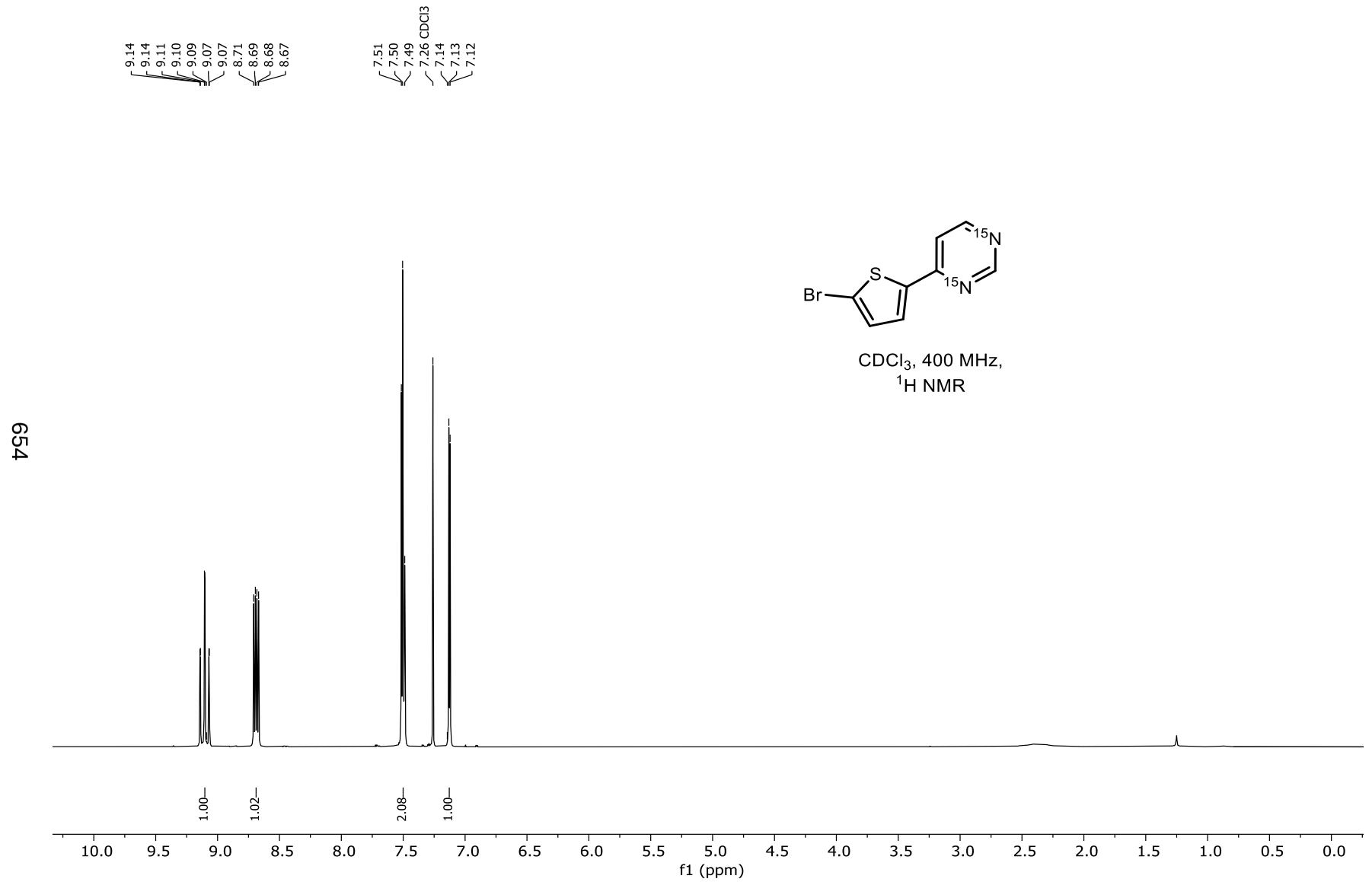

160.17
160.12
159.63
159.59
159.56
158.40
158.36
150.47
150.13
149.78
149.43
148.71
148.68
136.27
136.24
135.00
134.93
125.52
122.80
120.82
120.80
120.77
120.74
120.07
117.56
117.54
117.52
117.35
77.16 CDCl3
15N
15N
F3C
N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

652

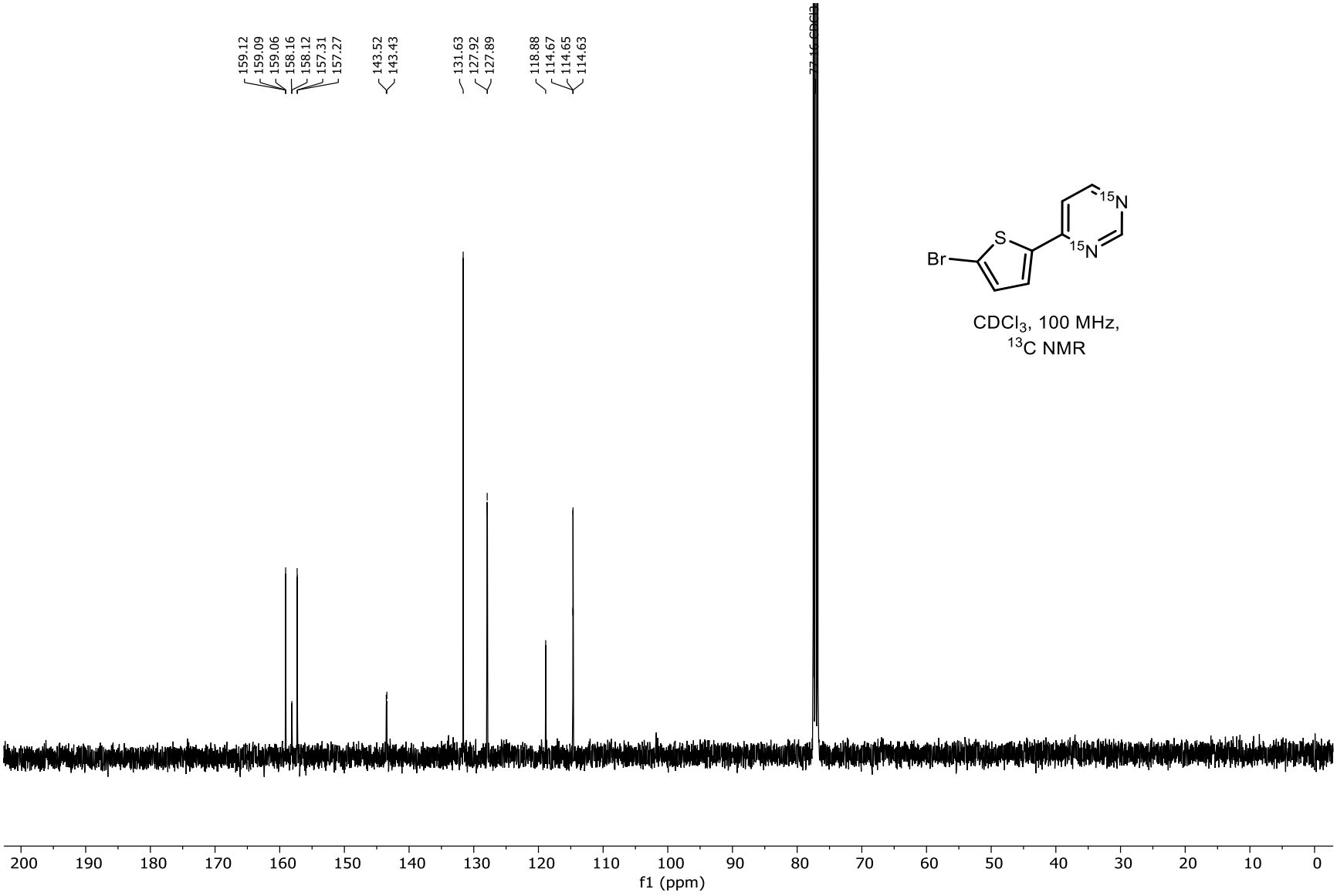

-68.05
^{15}N
^{15}N
F_3C
N
$CDCl_3$, 375 MHz,
^{19}F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

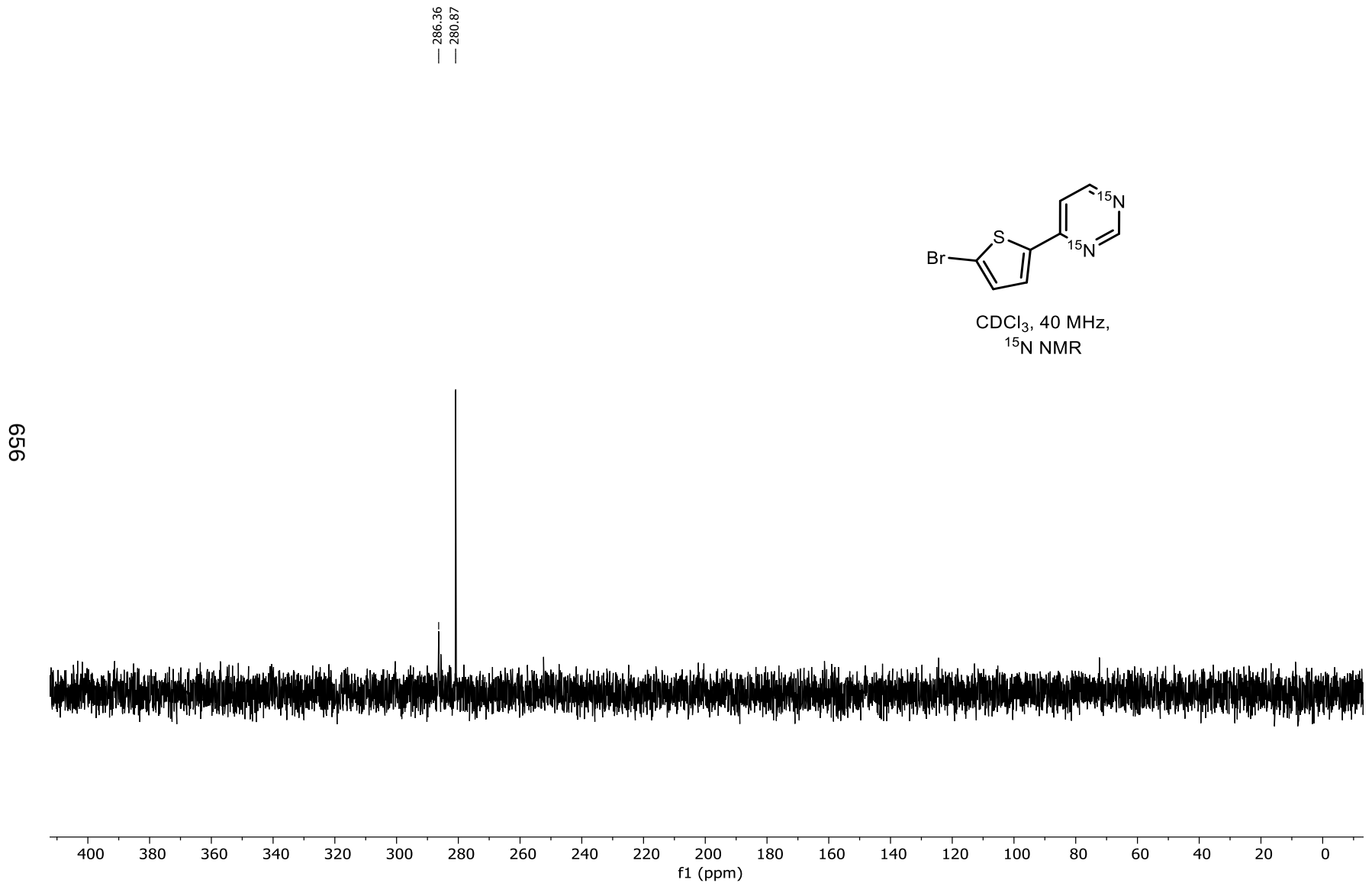
653

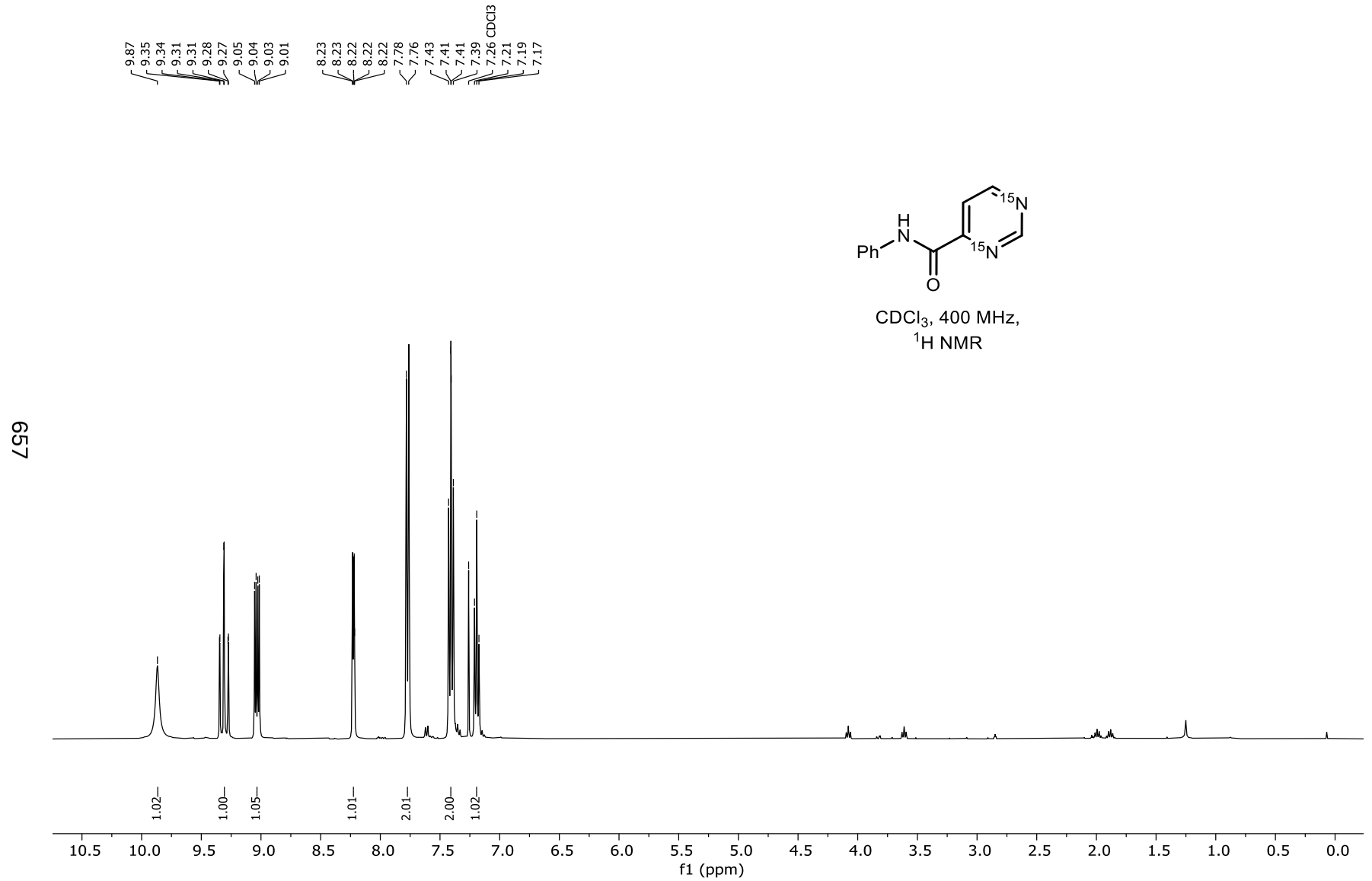

292.75
287.89
15N
15N
F3C
N
CDCl3, 40 MHz,
15N NMR
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

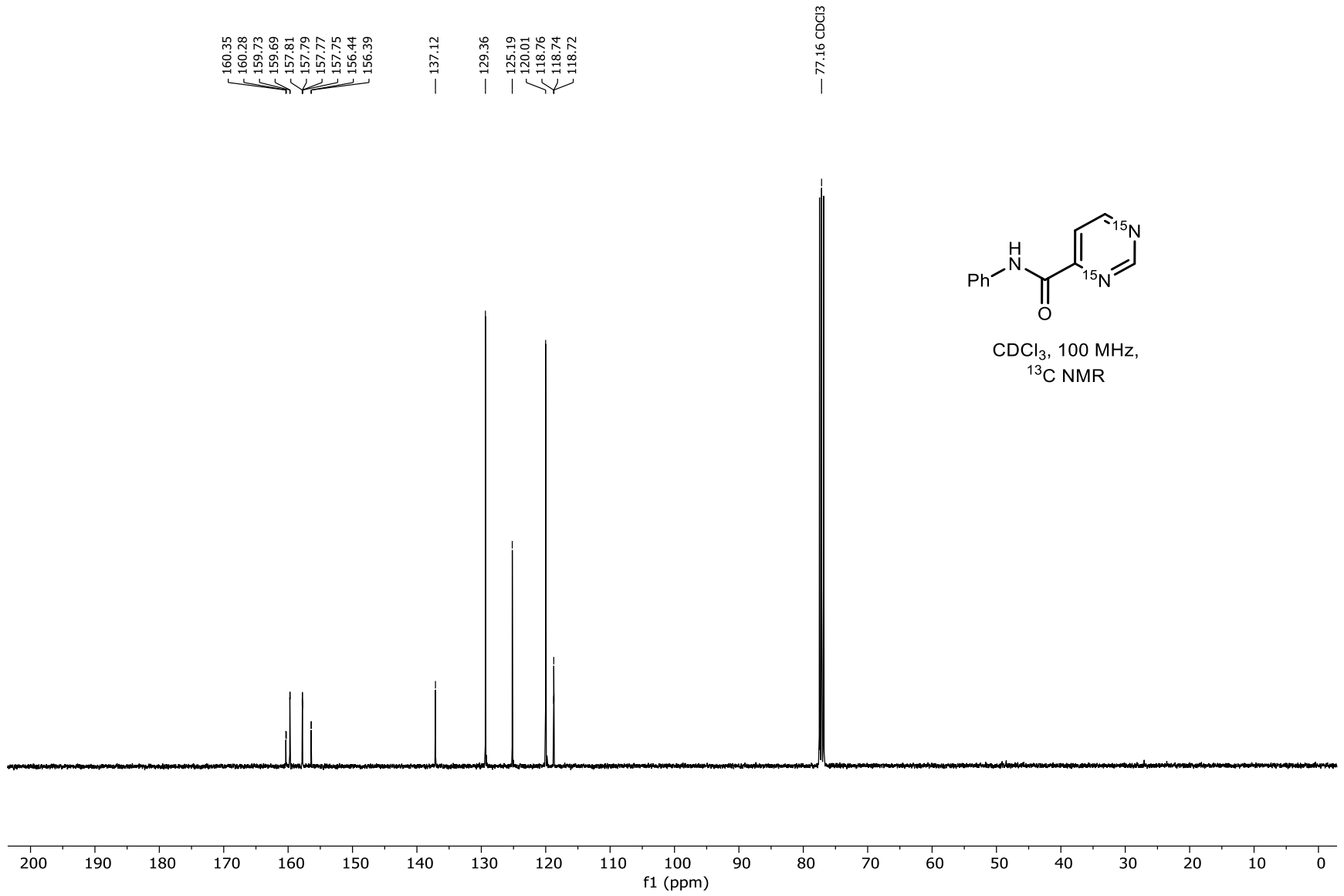

9.14
9.14
9.11
9.10
9.09
9.07
9.07
8.71
8.69
8.68
8.67
7.51
7.50
7.49
7.26 CDCl3
7.14
7.13
7.12
Br
S
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
1.02
2.08
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

655

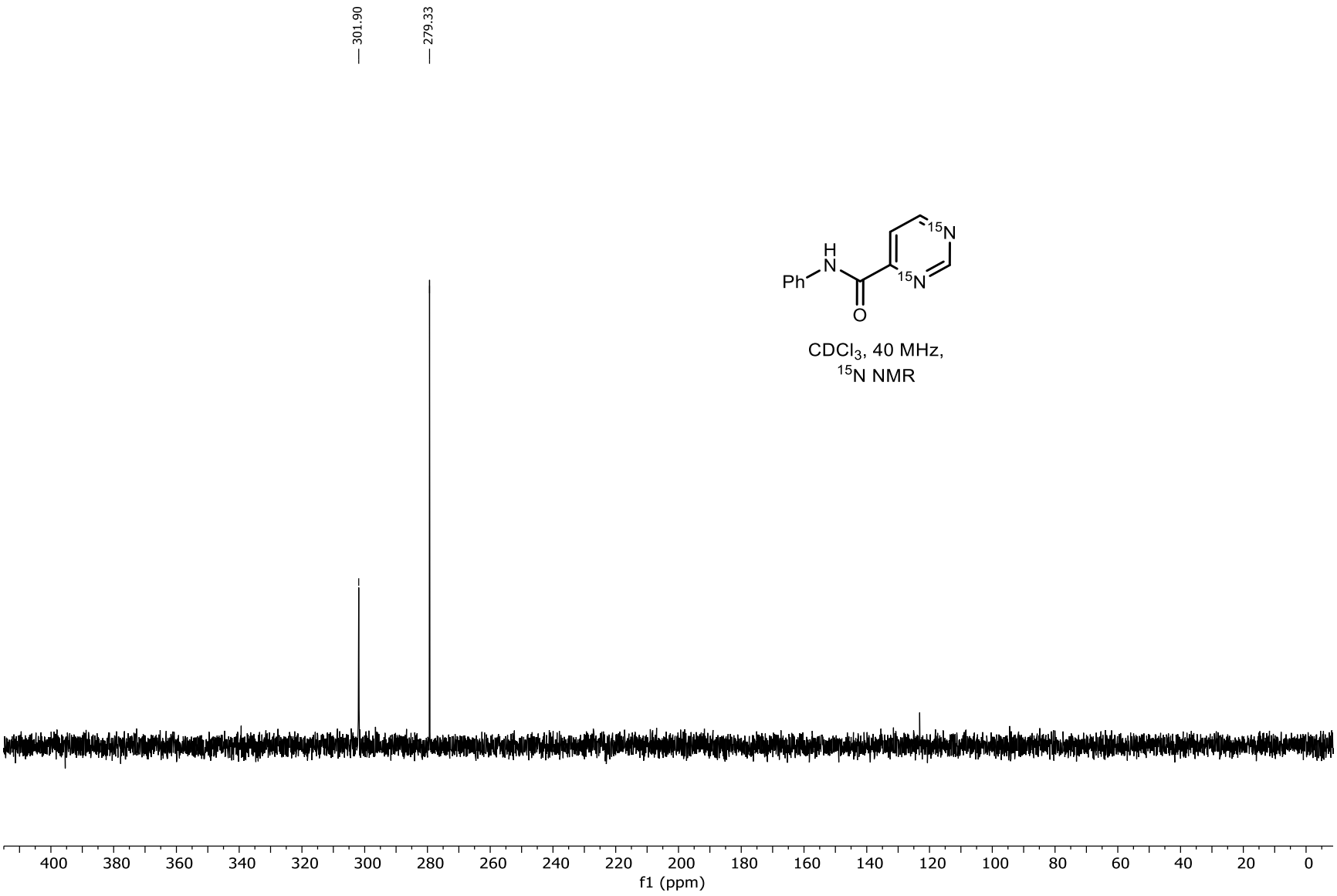

159.12
159.09
159.06
158.16
158.12
157.31
157.27
143.52
143.43
131.63
127.92
127.89
118.88
114.67
114.65
114.63
77.16 CDCl3
Br
S
15N
15N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


286.36
280.87
Br
S
15N
15N
CDCl3, 40 MHz,
15N NMR
656
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

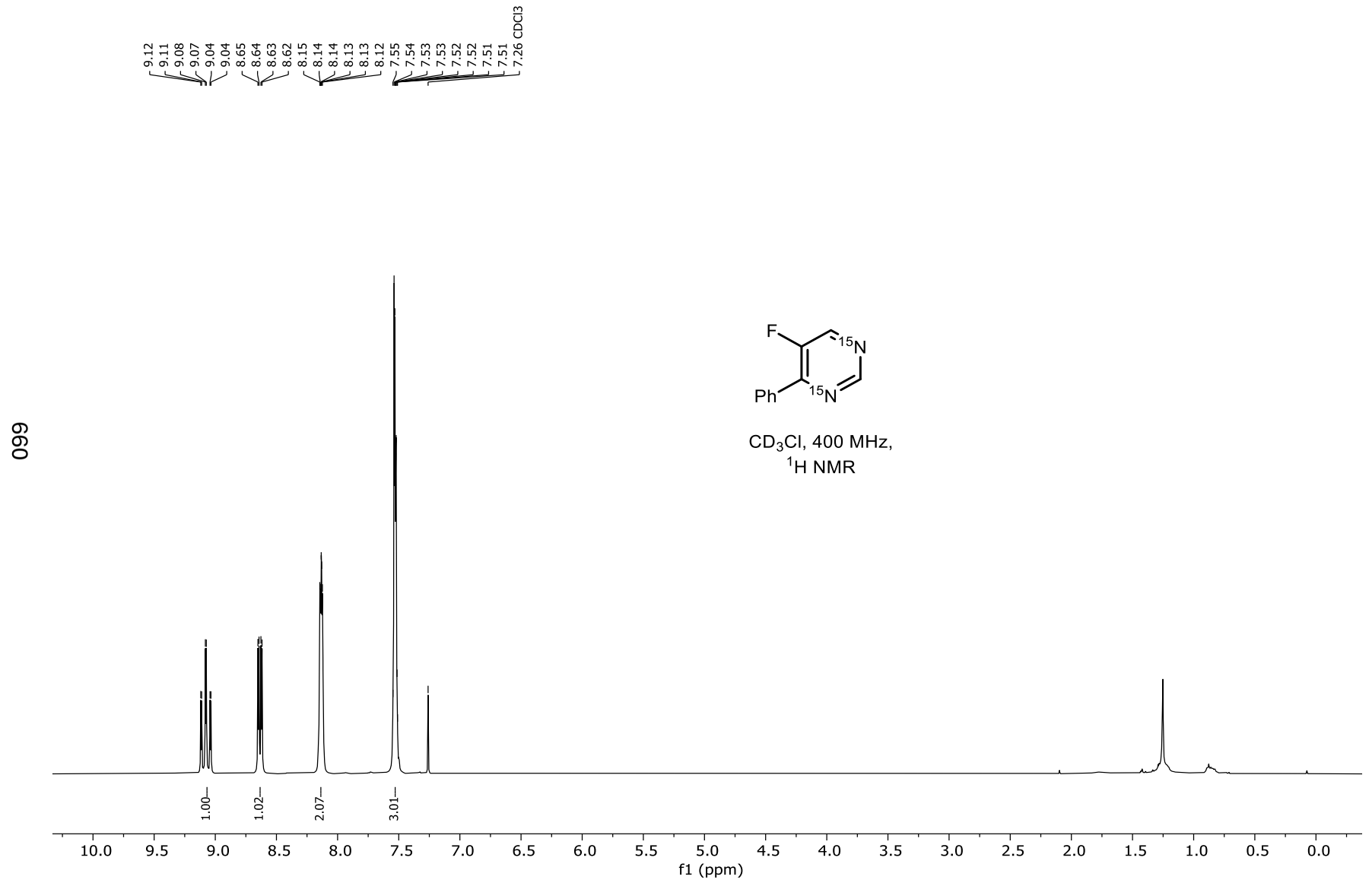

9.87
9.35
9.34
9.31
9.31
9.28
9.27
9.05
9.04
9.03
9.01
8.23
8.23
8.22
8.22
8.22
7.78
7.76
7.43
7.41
7.41
7.39
7.26 CDCl3
7.21
7.19
7.17
15N
H
N
Ph
15N
O
CDCl3, 400 MHz,
1H NMR
1.02
1.00
1.05
1.01
2.01
2.00
1.02
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

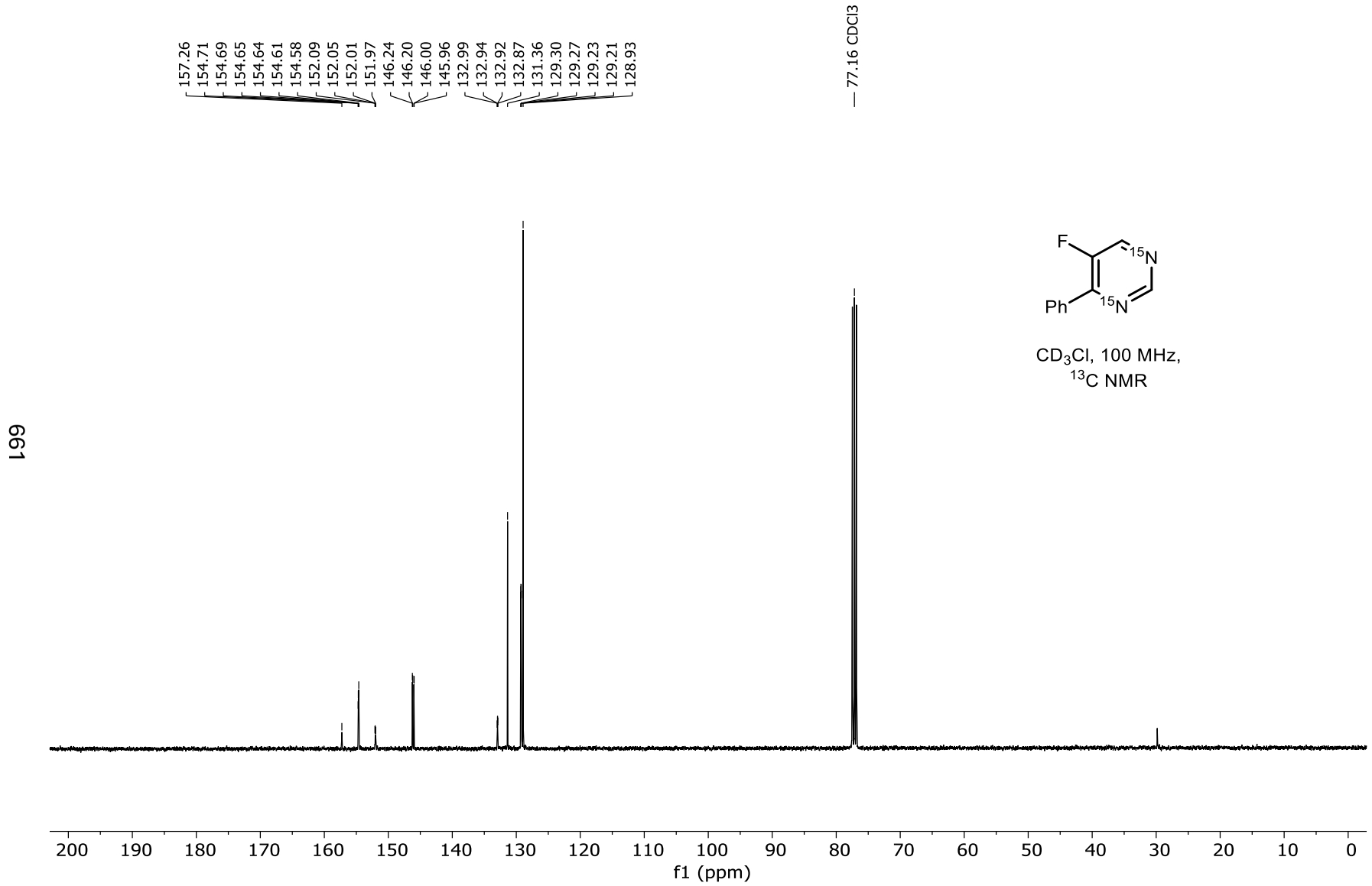

160.35
160.28
159.73
159.69
157.81
157.79
157.77
157.75
156.44
156.39
137.12
129.36
125.19
120.01
118.76
118.74
118.72
77.16 CDCl3
Ph
N
H
O
15N
15N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

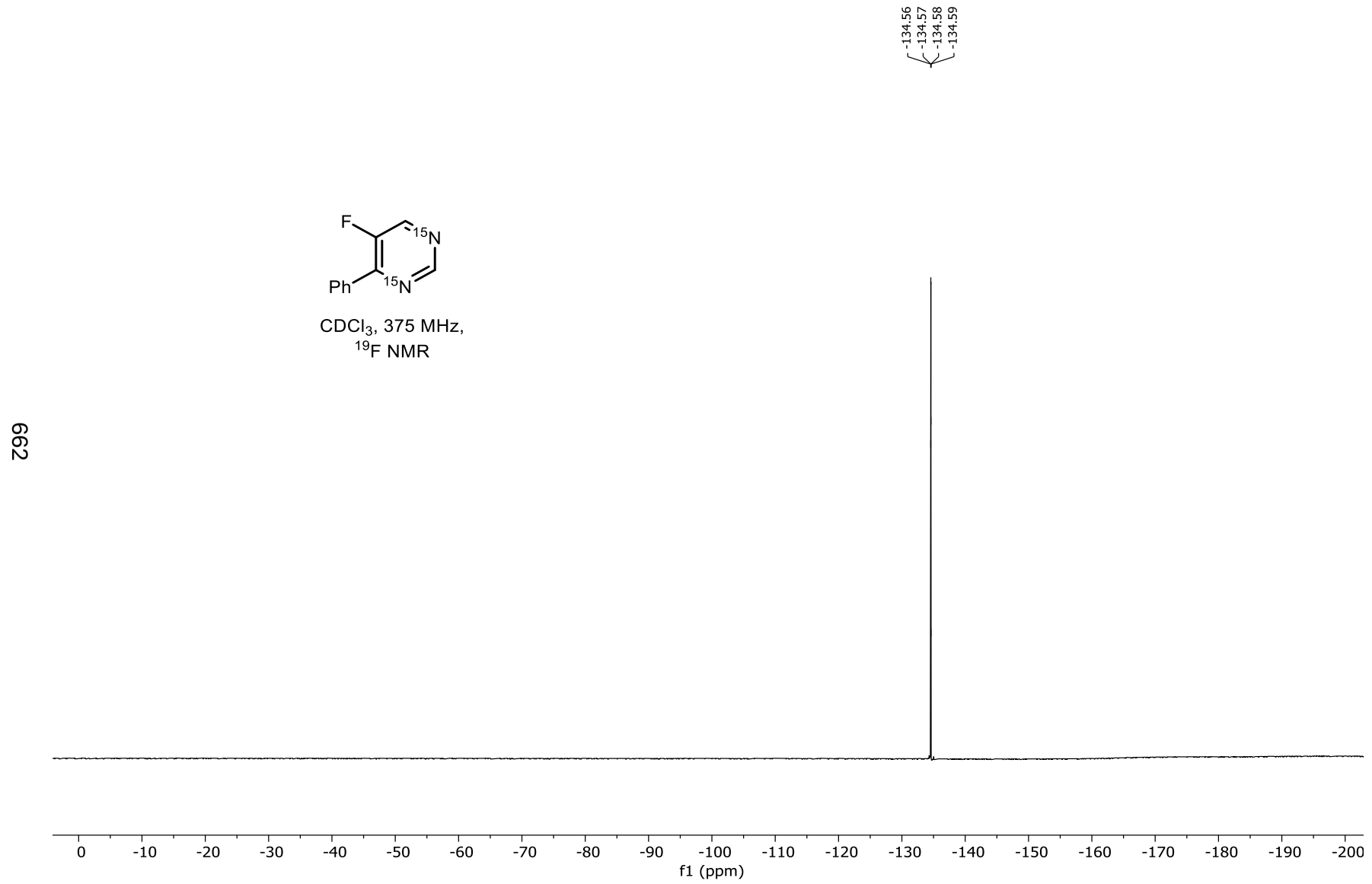
659



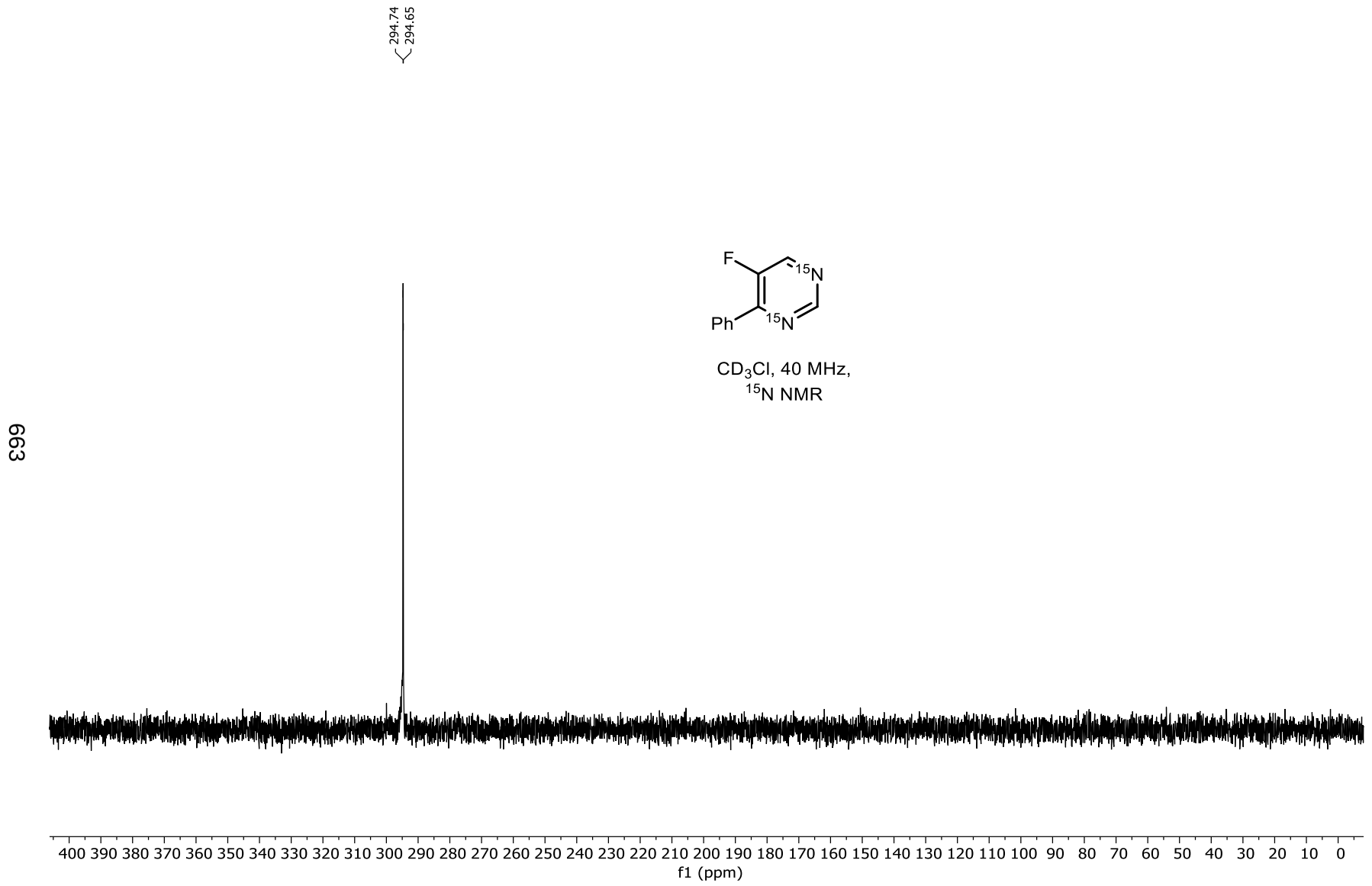
$CDCl_3$, 40 MHz,
^{15}N NMR

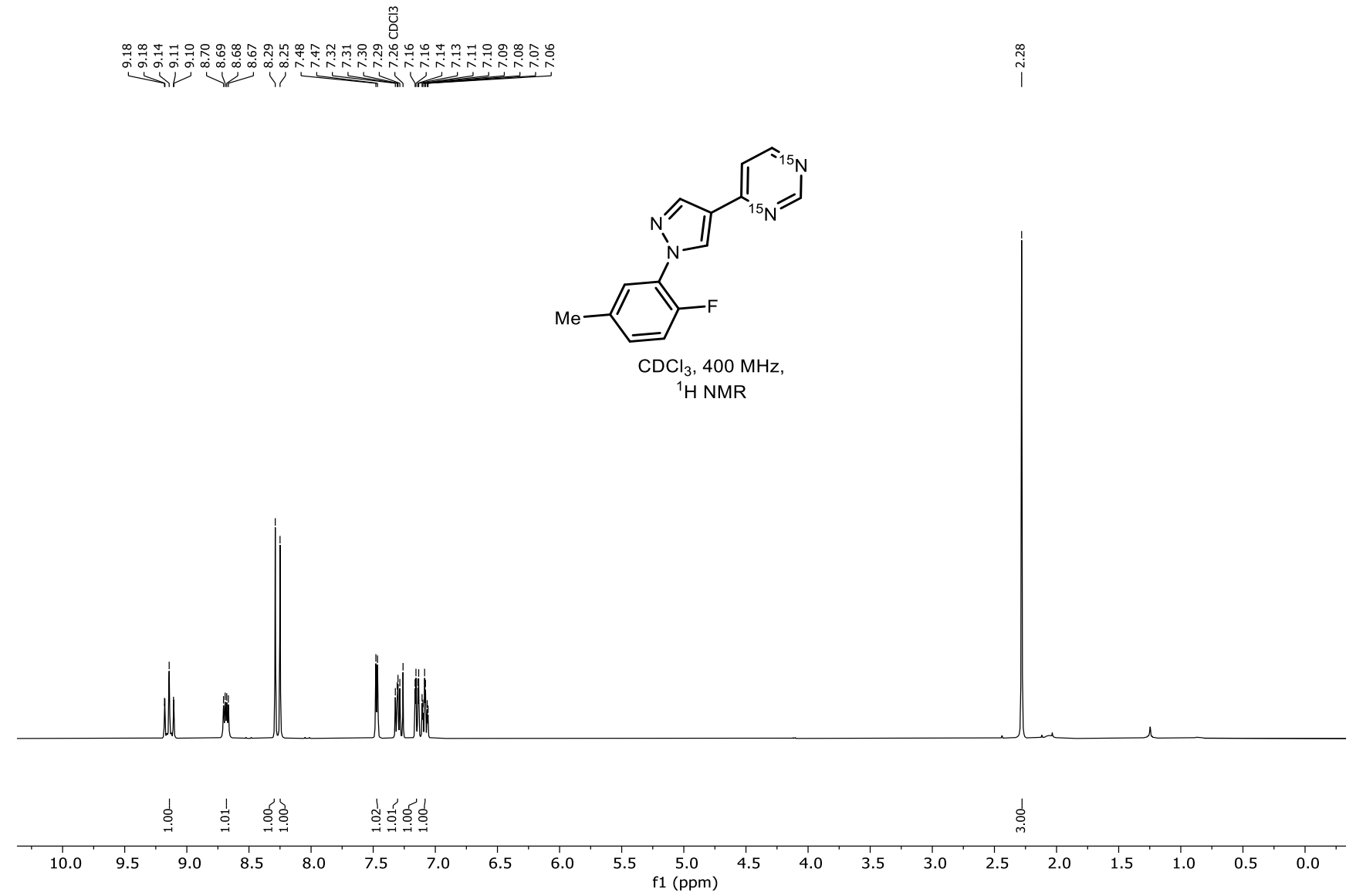

9.12
9.11
9.08
9.07
9.04
9.04
8.65
8.64
8.63
8.62
8.15
8.14
8.14
8.13
8.13
8.12
7.55
7.54
7.53
7.53
7.52
7.52
7.51
7.51
7.26 CDCl3
F
15N
Ph
15N
CD3Cl, 400 MHz,
1H NMR
099
1.00
1.02
2.07
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

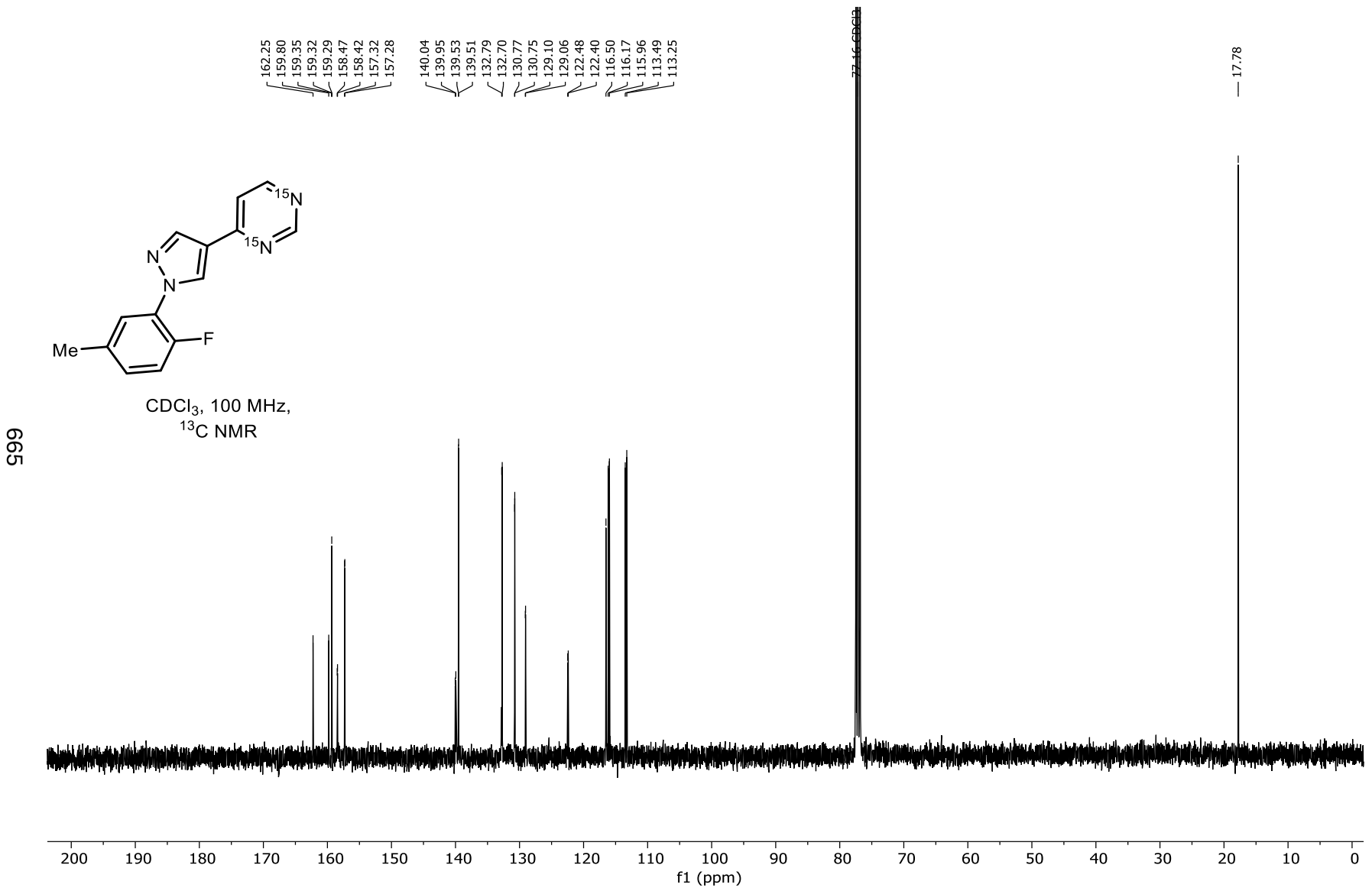

157.26
154.71
154.69
154.65
154.64
154.61
154.58
152.09
152.05
152.01
151.97
146.24
146.20
146.00
145.96
132.99
132.94
132.92
132.87
131.36
129.30
129.27
129.23
129.21
128.93
77.16 CDCl3
F
15N
Ph
15N
CD3Cl, 100 MHz,
13C NMR
f1 (ppm)


-134.56
-134.57
-134.58
-134.59
F
15N
Ph
15N
CDCl3, 375 MHz,
19F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

662

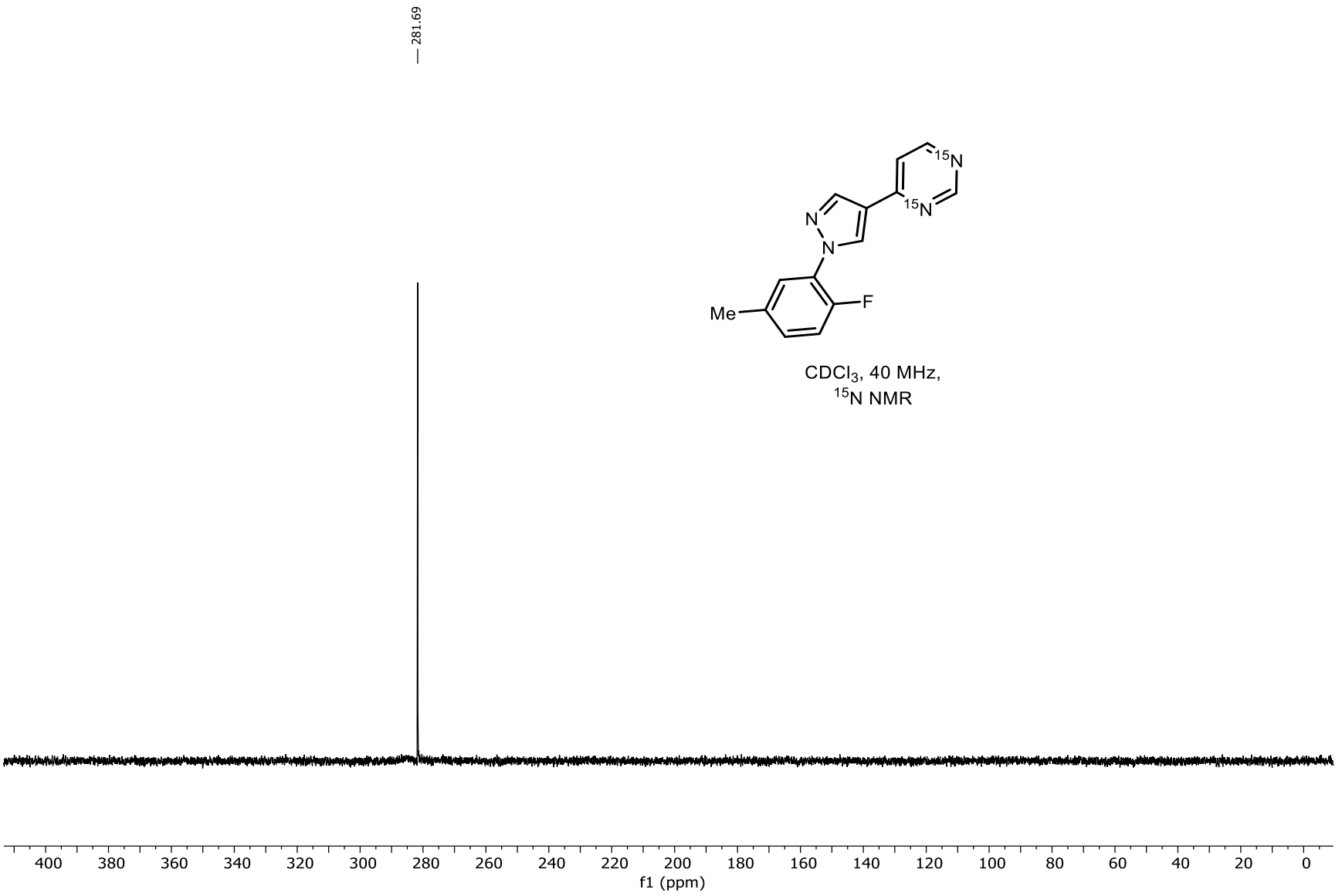

294.74
294.65
F
15N
Ph
15N
CD3Cl, 40 MHz,
15N NMR
663
400 390 380 370 360 350 340 330 320 310 300 290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


9.18
9.18
9.14
9.11
9.10
8.70
8.69
8.68
8.67
8.29
8.25
7.48
7.47
7.32
7.31
7.30
7.29
7.26 CDCl3
7.16
7.16
7.14
7.13
7.11
7.10
7.09
7.08
7.07
7.06
2.28
15N
15N
N
N
Me
F
CDCl3, 400 MHz,
1H NMR
1.00
1.01
1.00
1.00
1.02
1.01
1.00
1.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

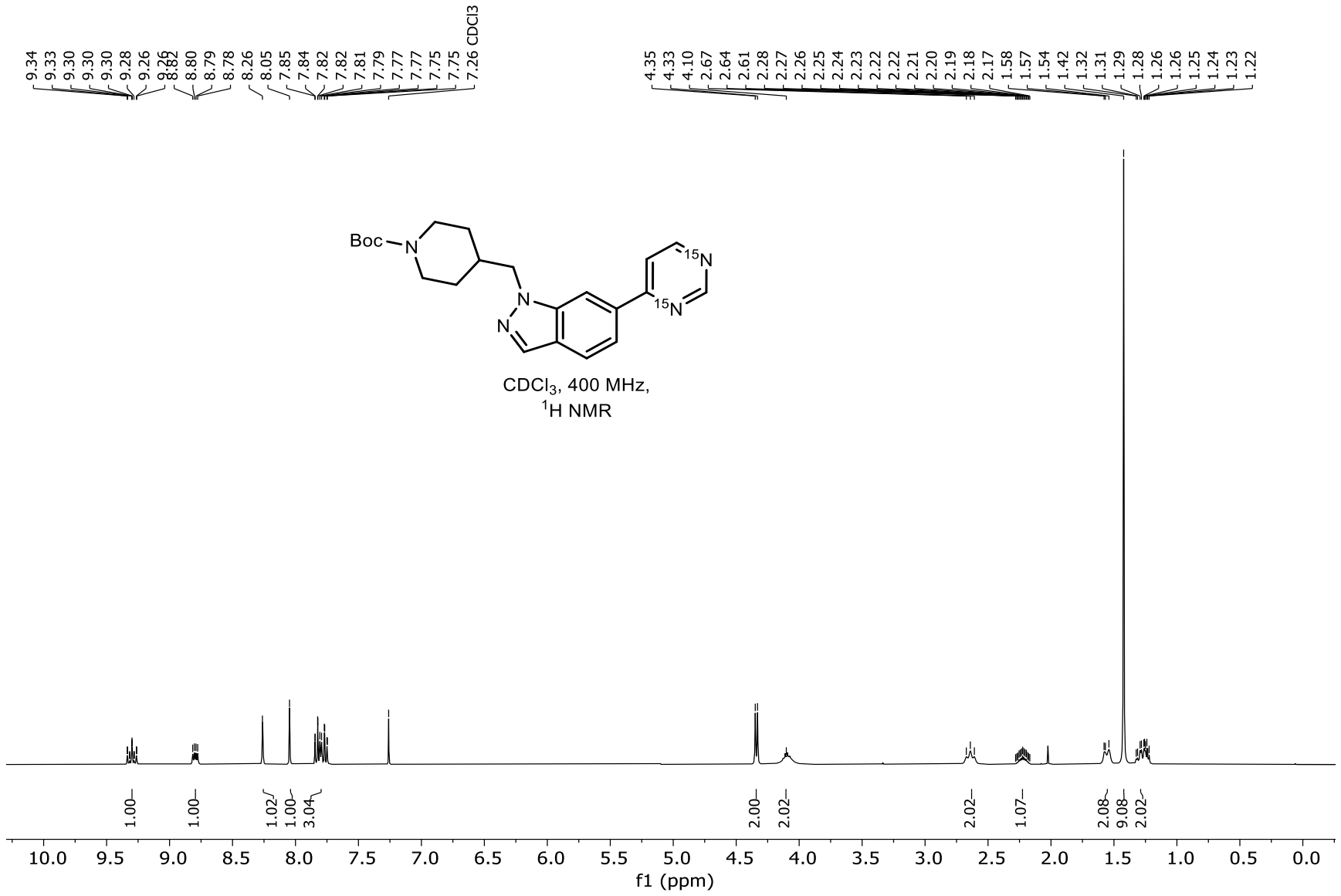

162.25
159.80
159.35
159.32
159.29
158.47
158.42
157.32
157.28
140.04
139.95
139.53
139.51
132.79
132.70
130.77
130.75
129.10
129.06
122.48
122.40
116.50
116.17
115.96
113.49
113.25
77.16 CDCl3
17.78
15N
15N
N
N
Me
F
CDCl3, 100 MHz,
13C NMR
695
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

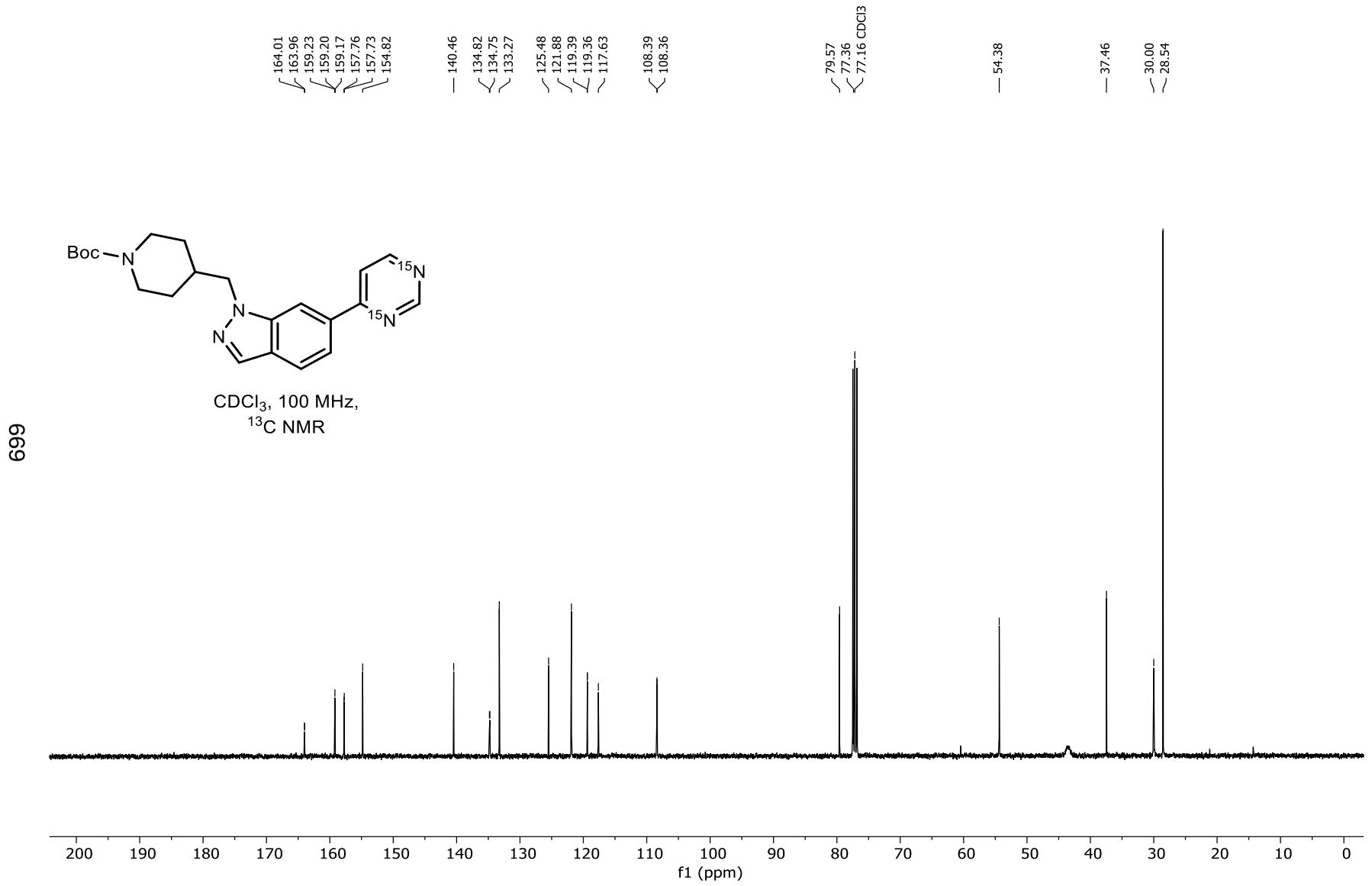

-115.34
-115.36
-115.38
-115.40
15N
15N
N
N
Me
F
CDCl3, 375 MHz,
19F NMR
999
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

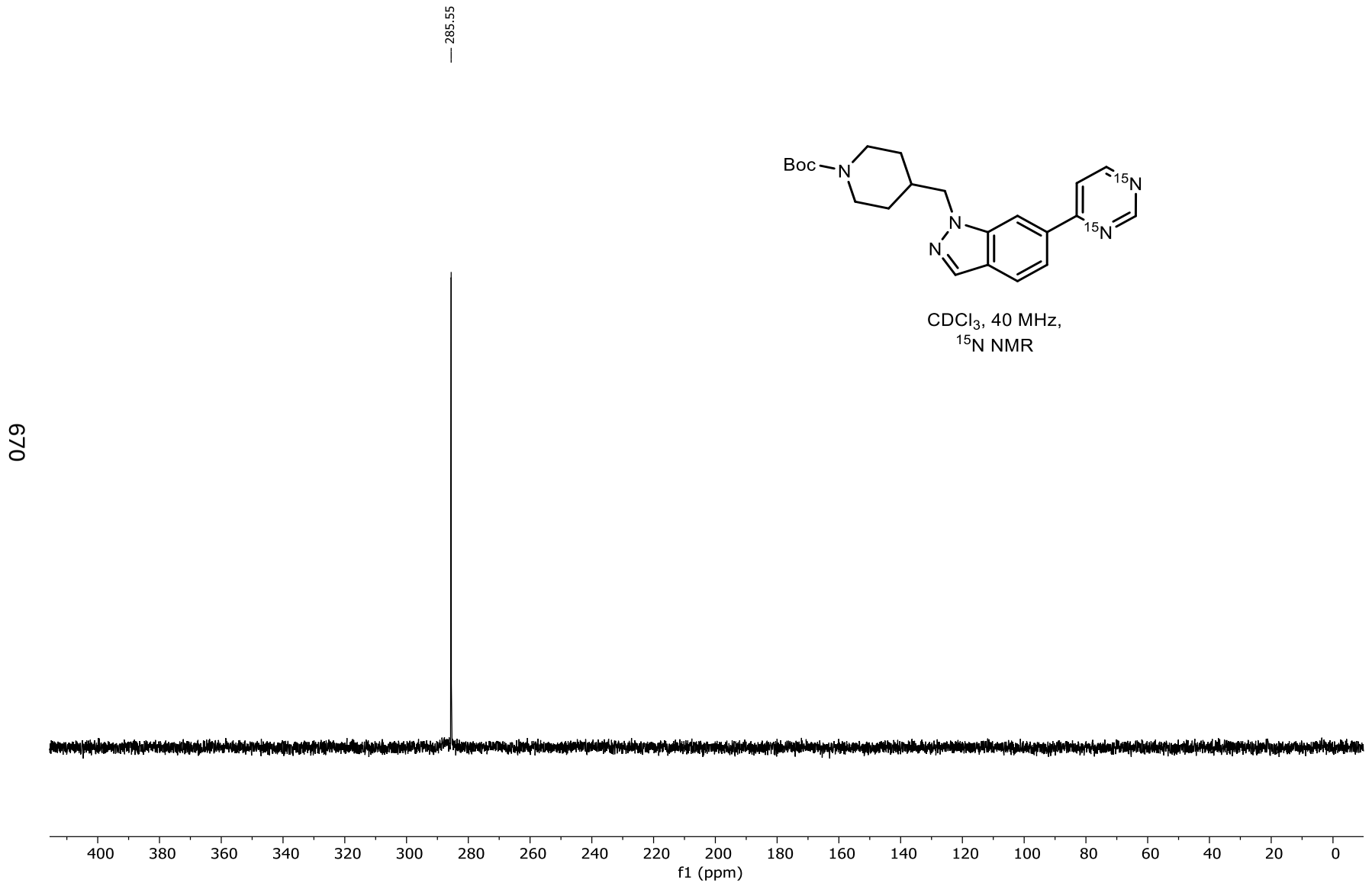
667

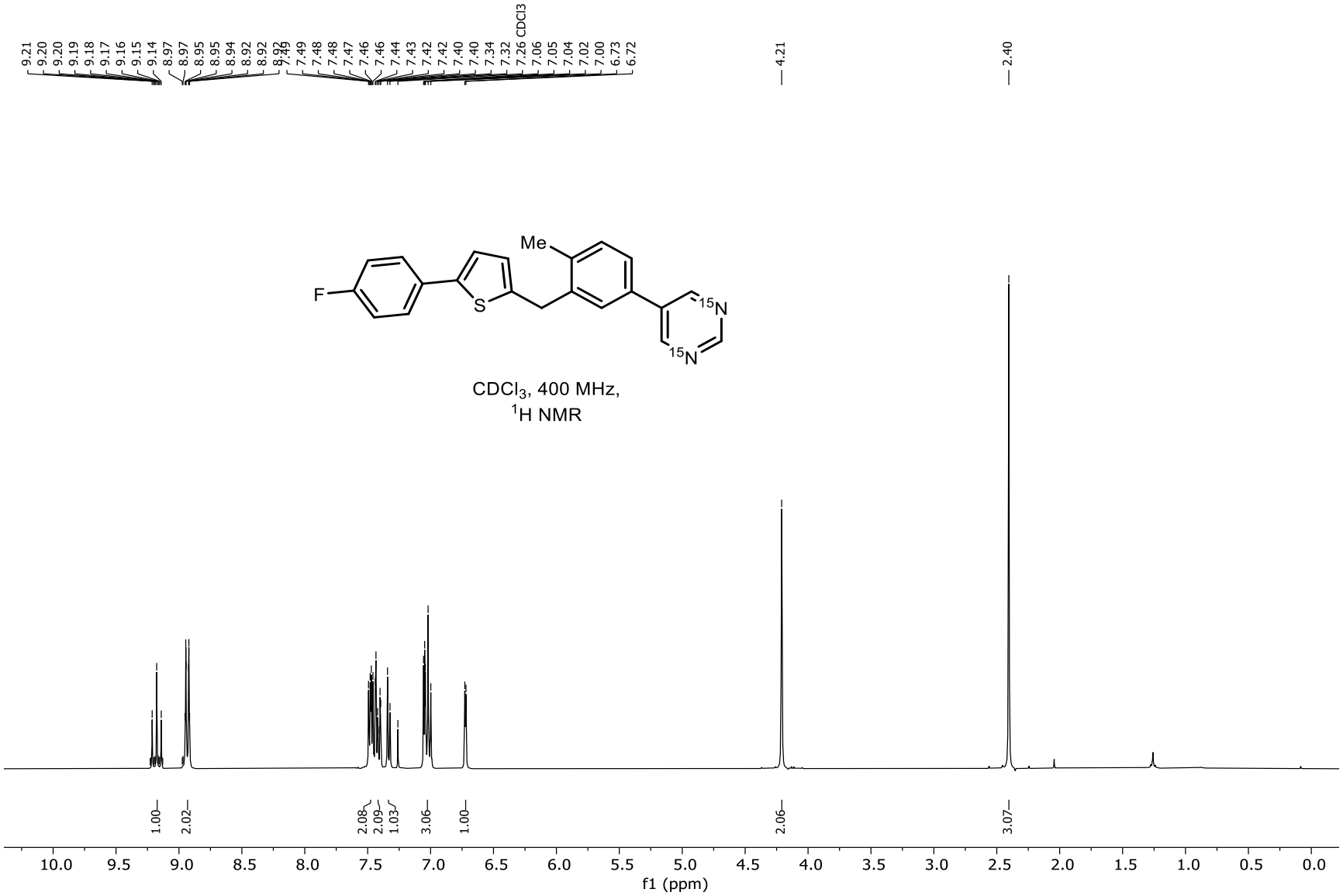

281.69
15N
15N
N
N
Me
F
CDCl3, 40 MHz,
15N NMR
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

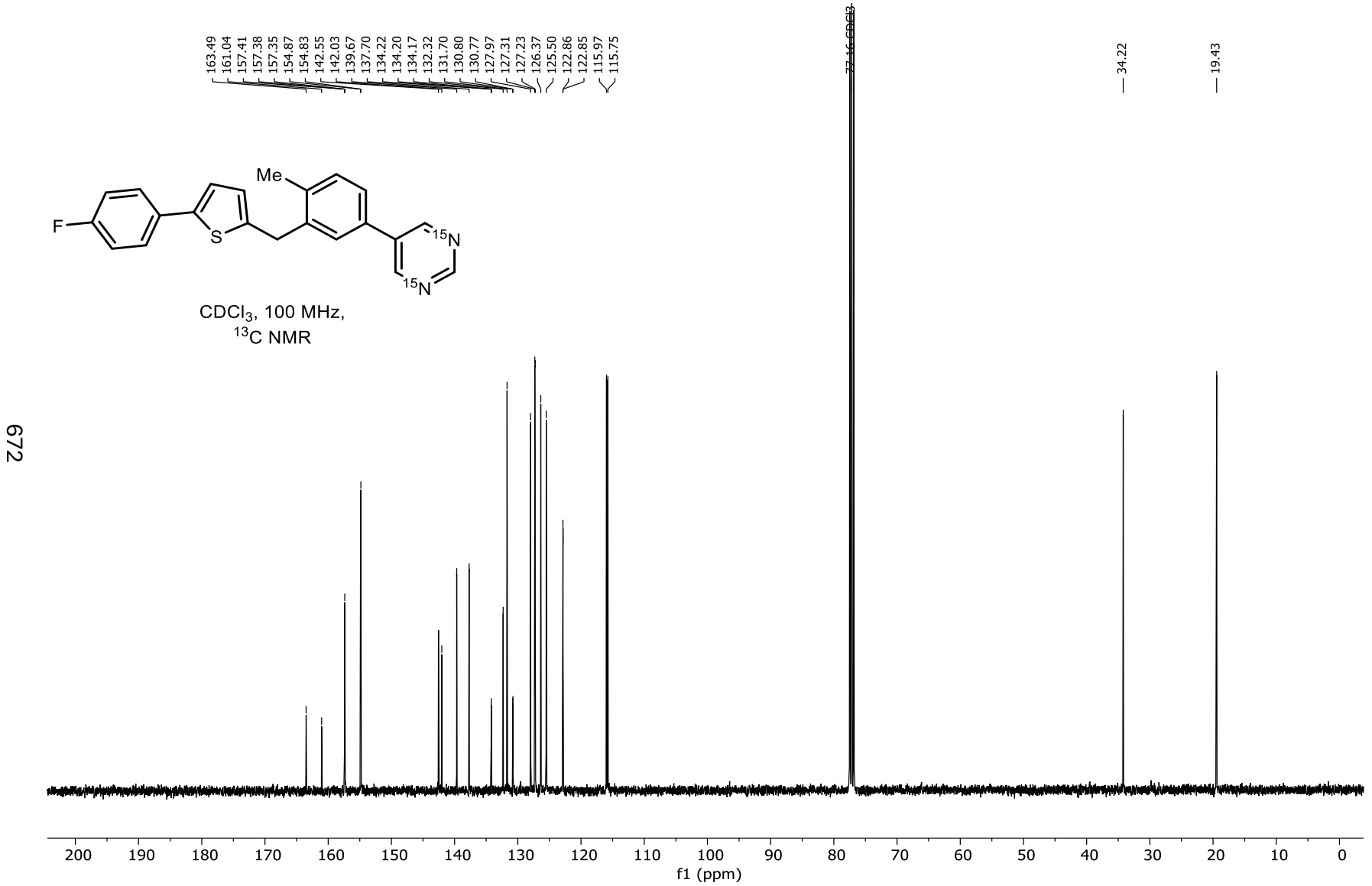
899


9.34
9.33
9.30
9.30
9.30
9.28
9.26
8.82
8.80
8.79
8.78
8.26
8.05
7.85
7.84
7.82
7.82
7.81
7.79
7.77
7.77
7.75
7.75
7.26 CDCl3
4.35
4.33
4.10
2.67
2.64
2.61
2.28
2.27
2.26
2.25
2.24
2.23
2.22
2.22
2.21
2.20
2.19
2.18
2.17
1.58
1.57
1.54
1.42
1.32
1.31
1.29
1.28
1.26
1.26
1.25
1.24
1.23
1.22
Boc
N
N
N
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
1.00
1.02
1.00
3.04
2.00
2.02
2.02
1.07
2.08
9.08
2.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.01
163.96
159.23
159.20
159.17
157.76
157.73
154.82
140.46
134.82
134.75
133.27
125.48
121.88
119.39
119.36
117.63
108.39
108.36
79.57
77.36
77.16 CDCl3
54.38
37.46
30.00
28.54
Boc
N
N
N
15N
15N
CDCl3, 100 MHz,
13C NMR
699
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

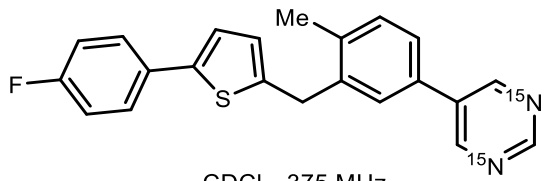

285.55
Boc
N
N
N
15N
15N
CDCl3, 40 MHz,
15N NMR
670
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


9.21
9.20
9.20
9.19
9.18
9.17
9.16
9.15
9.14
8.97
8.97
8.95
8.95
8.94
8.92
8.92
7.49
7.48
7.48
7.47
7.46
7.46
7.44
7.43
7.42
7.42
7.40
7.40
7.34
7.32
7.26 CDCl3
7.06
7.05
7.04
7.02
7.00
6.73
6.72
4.21
2.40
Me
F
S
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
2.02
2.08
2.09
1.03
3.06
1.00
2.06
3.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


163.49
161.04
157.41
157.38
157.35
154.87
154.83
142.55
142.03
139.67
137.70
134.22
134.20
134.17
132.32
131.70
130.80
130.77
127.97
127.31
127.23
126.37
125.50
122.86
122.85
115.97
115.75
77.16 CDCl3
34.22
19.43
Me
F
S
15N
15N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

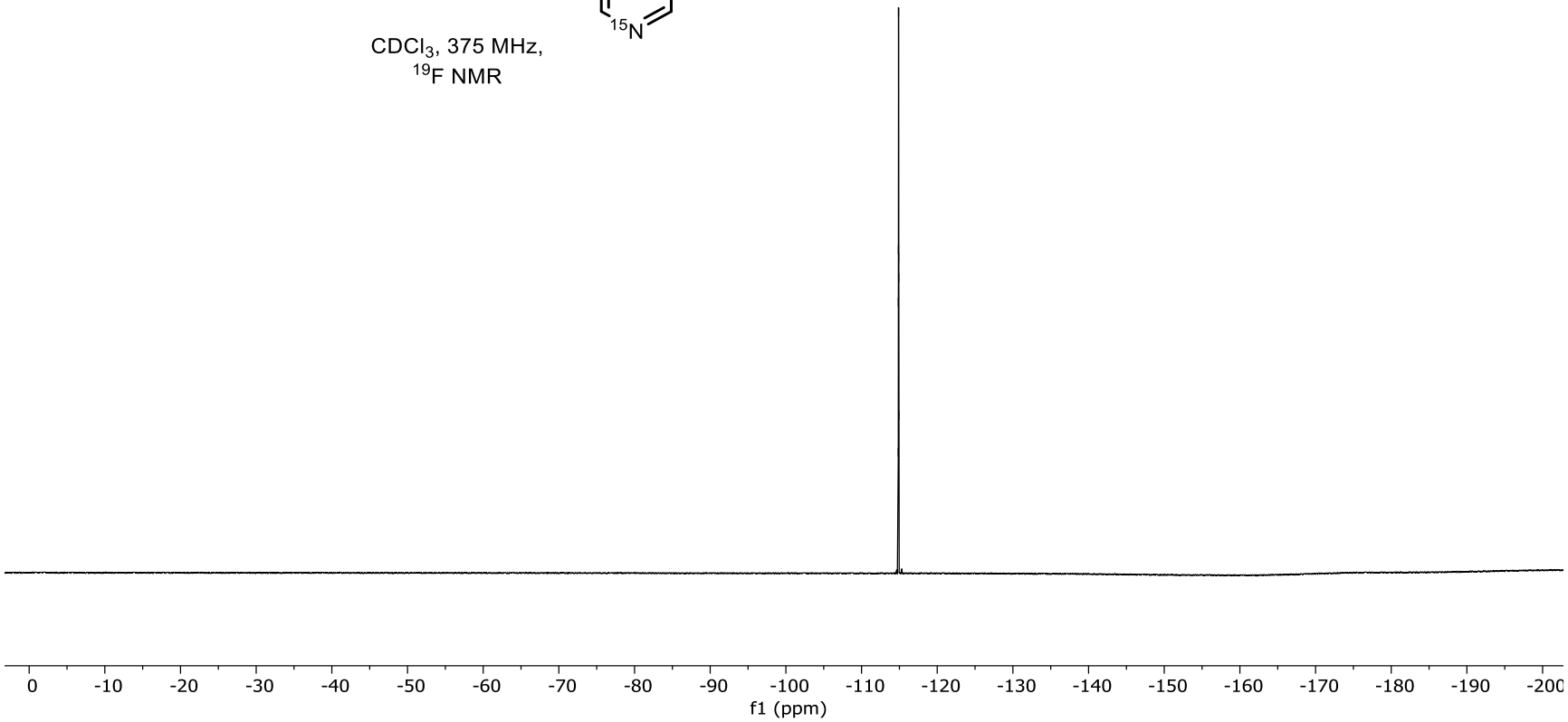
672

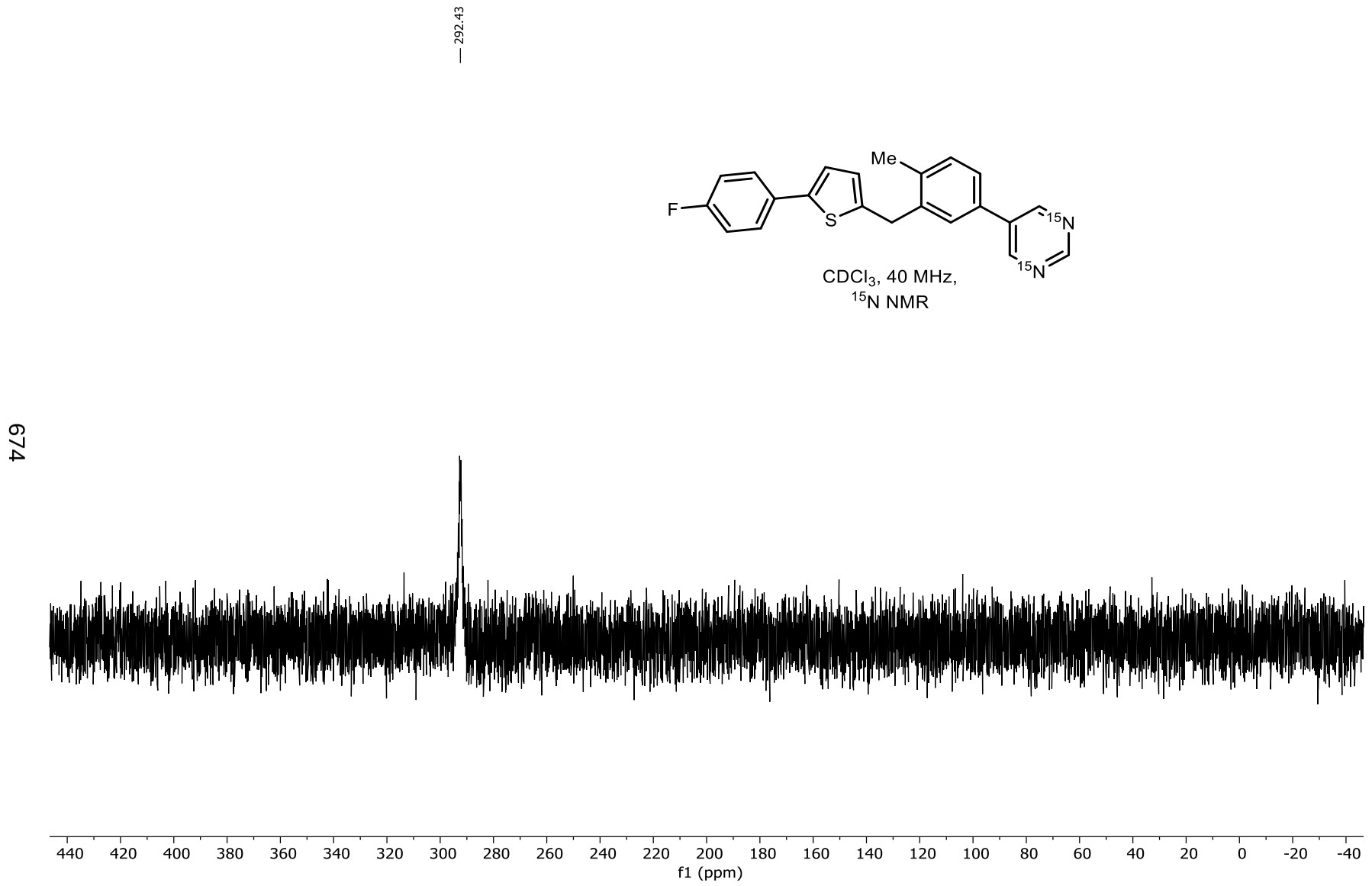
673

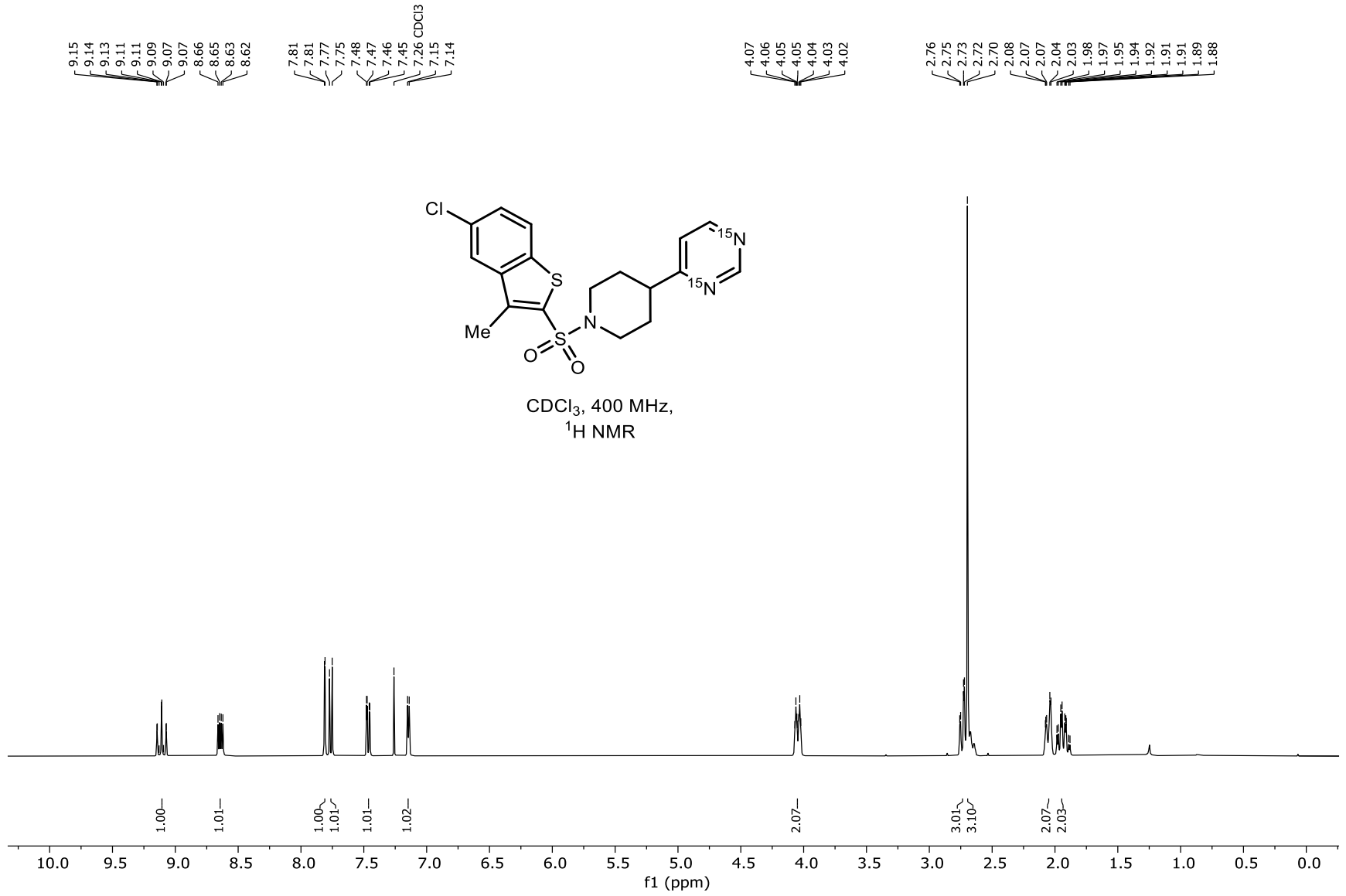


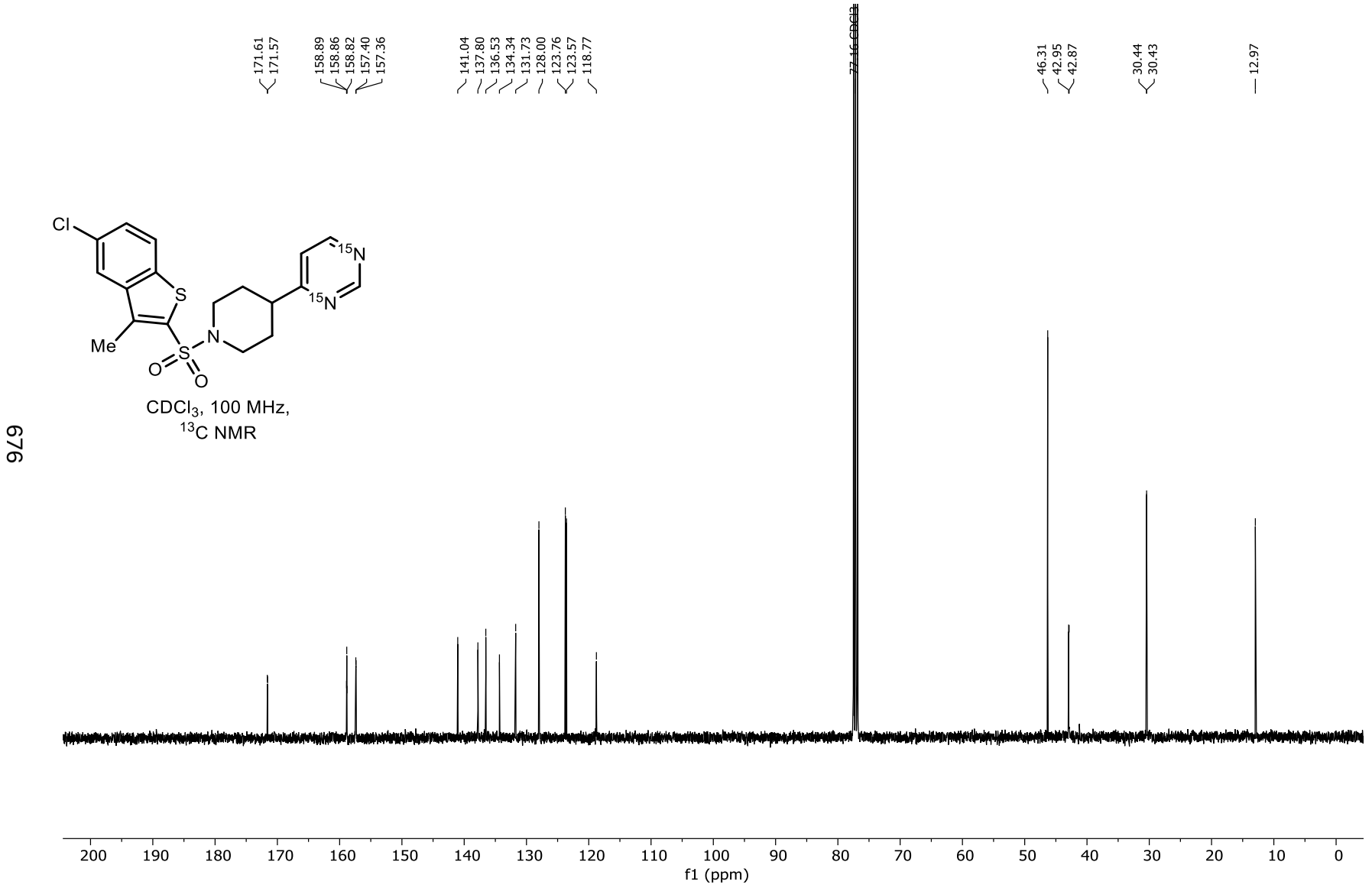
$CDCl_3$, 375 MHz,
^{19}F NMR

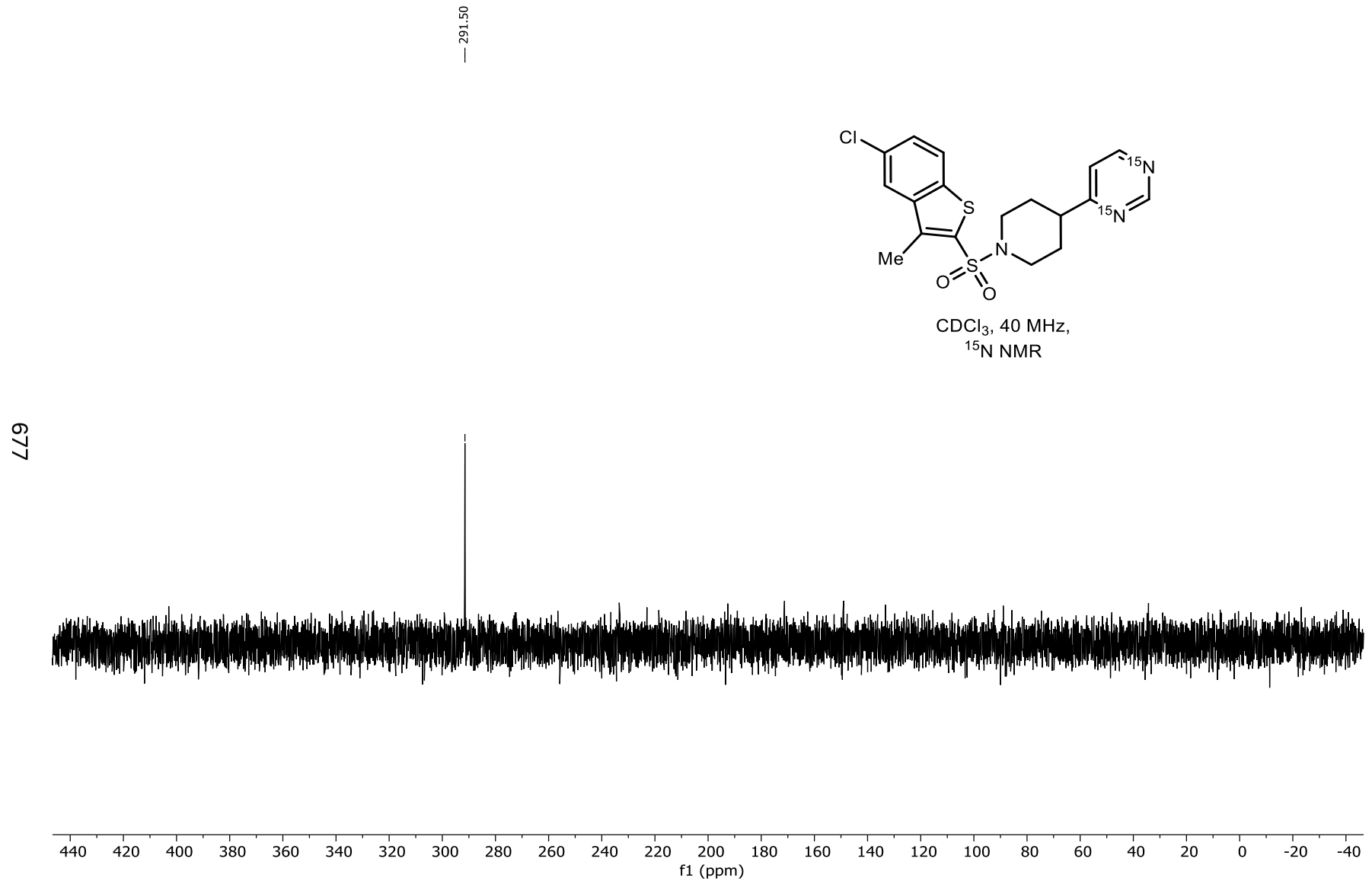
-114.85
-114.87
-114.88
-114.89
-114.90
-114.91
-114.93




292.43
Me
F
S
15N
15N
CDCl3, 40 MHz,
15N NMR
674
440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40
f1 (ppm)

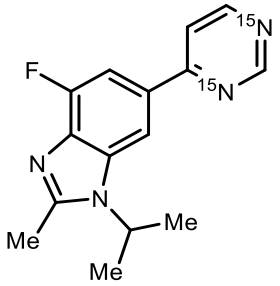

9.15
9.14
9.13
9.11
9.11
9.09
9.07
9.07
8.66
8.65
8.63
8.62
7.81
7.81
7.77
7.75
7.48
7.47
7.46
7.45
7.26 CDCl3
7.15
7.14
4.07
4.06
4.05
4.05
4.04
4.03
4.02
2.76
2.75
2.73
2.72
2.70
2.08
2.07
2.07
2.04
2.03
1.98
1.97
1.95
1.94
1.92
1.91
1.91
1.89
1.88
Cl
S
Me
N
S
O
O
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
1.01
1.00
1.01
1.01
1.02
2.07
3.01
3.10
2.07
2.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


171.61
171.57
158.89
158.86
158.82
157.40
157.36
141.04
137.80
136.53
134.34
131.73
128.00
123.76
123.57
118.77
77.16 CDCl3
46.31
42.95
42.87
30.44
30.43
12.97
Cl
S
Me
S
O
O
N
15N
15N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


291.50
677
Cl
S
Me
S
O
O
N
15N
15N
CDCl3, 40 MHz,
15N NMR
440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40
f1 (ppm)

9.27
9.27
9.24
9.23
9.23
9.20
9.20
8.76
8.75
8.74
8.72
8.18
8.18
7.70
7.69
7.58
7.58
7.55
7.55
7.26 CDCl3
4.79
4.77
4.75
4.73
4.72
4.70
4.68
2.67
2.64
1.70
1.68
0.99
1.00
1.01
1.00
1.00
1.02
3.06
6.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
CDCl3, 400 MHz,
1H NMR
F
N
N
15N
15N
Me
Me
Me

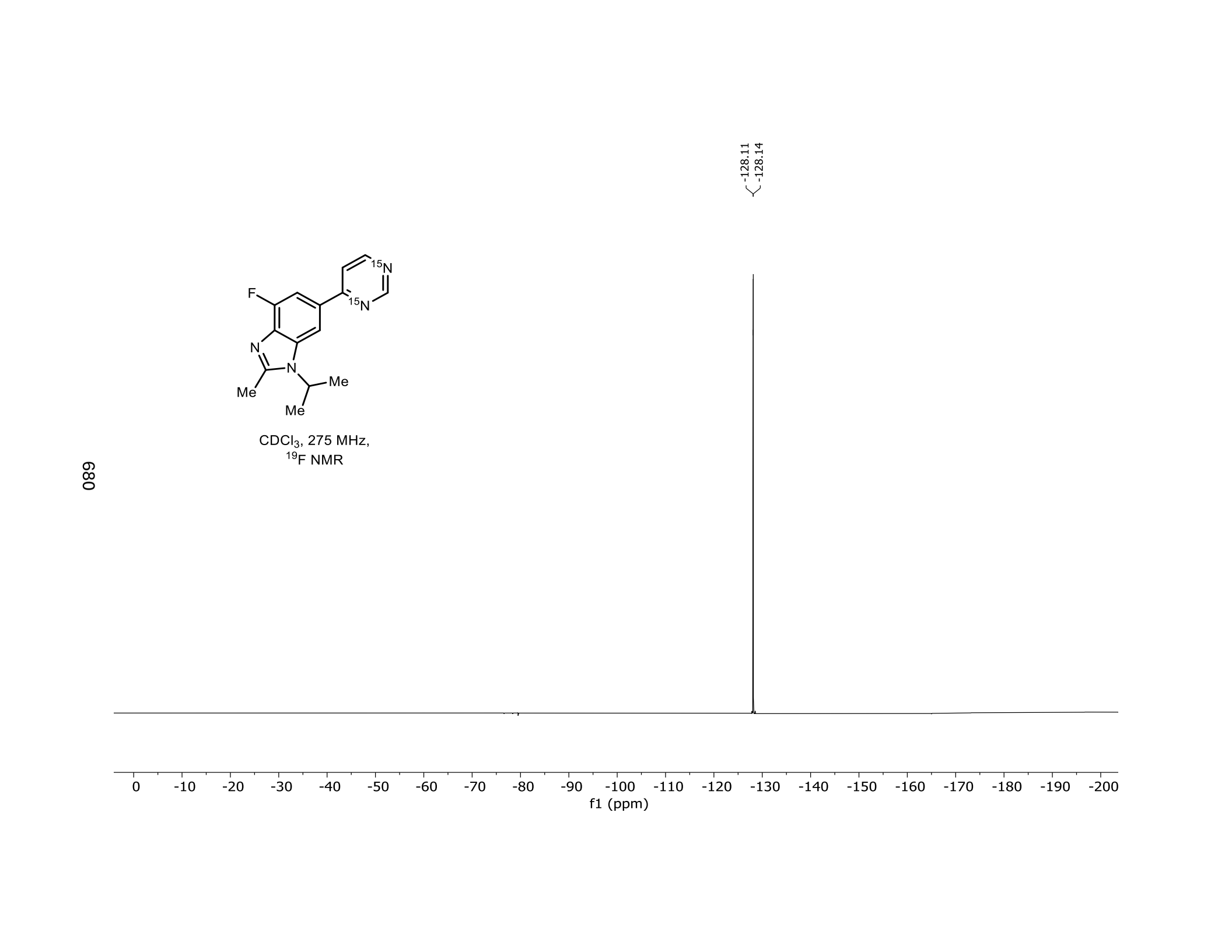
679



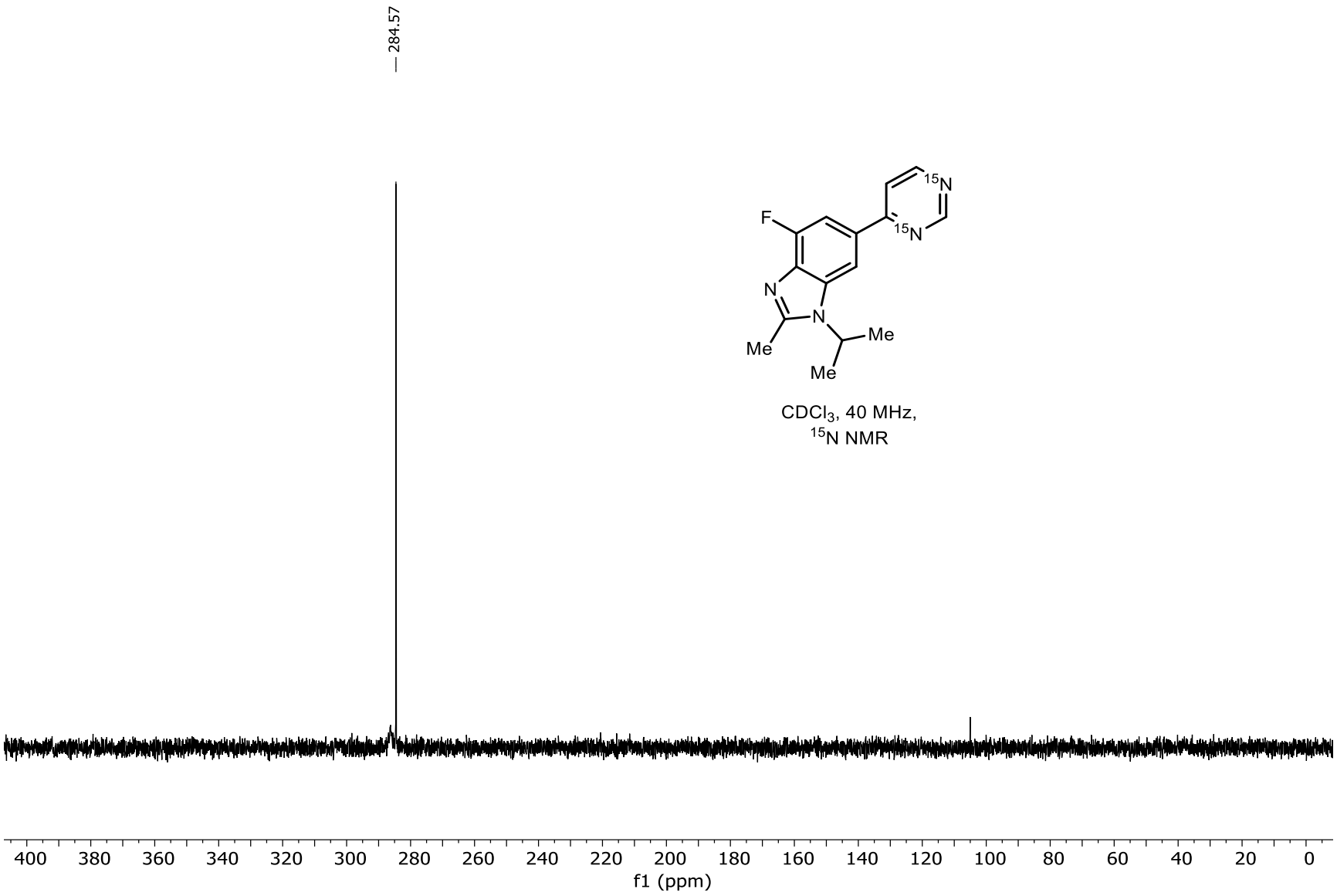
$CDCl_3$, 100 MHz,
^{13}C NMR

163.42
159.11
159.08
159.05
157.61
157.57
154.99
153.63
152.49
137.22
137.13
134.23
134.06
131.06
130.99
130.92
116.98
116.96
116.94
106.55
106.51
106.48
106.37
106.35
106.18
106.15
77.16 CDCl3
48.72
21.63
15.30

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

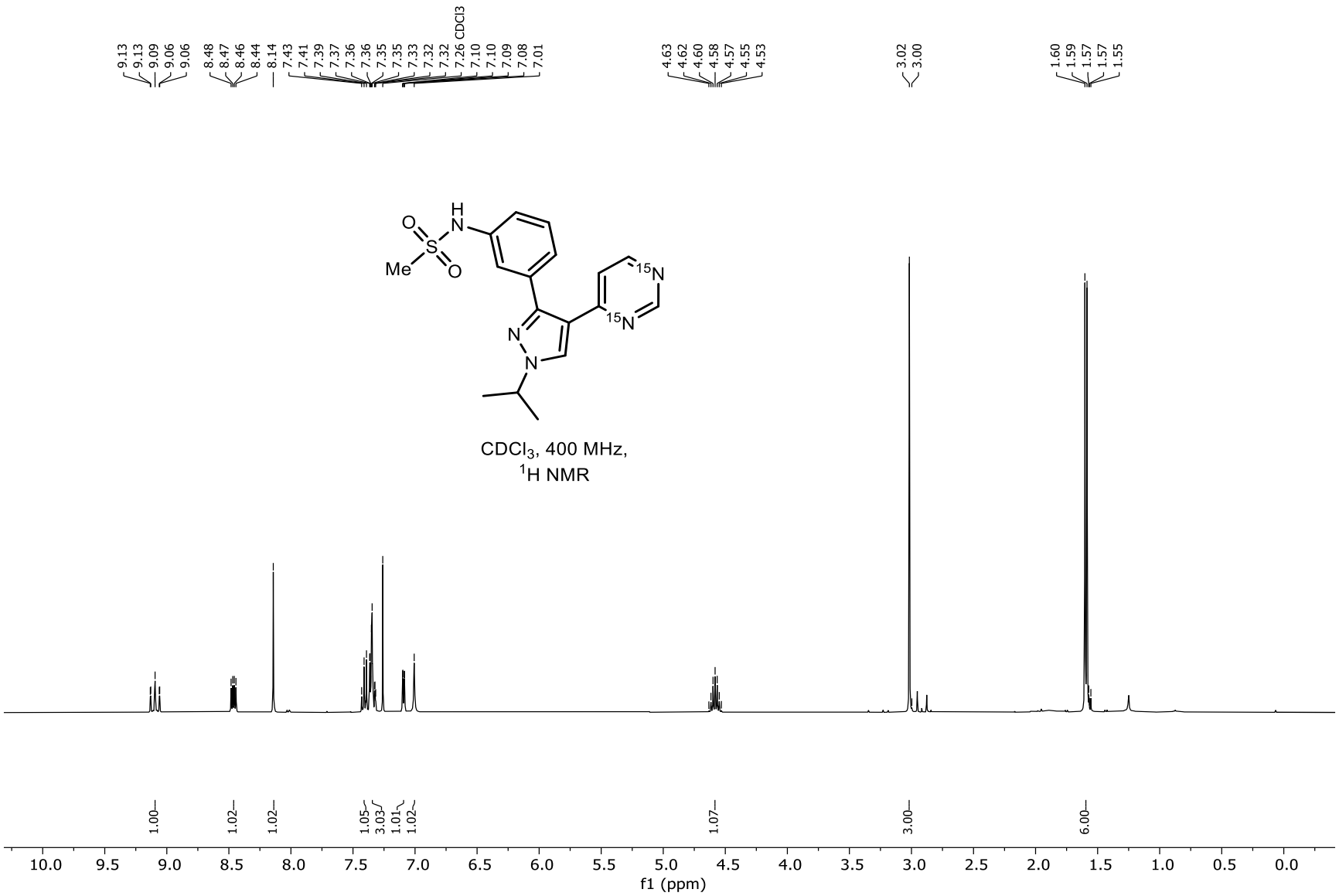

-128.11
-128.14
F
15N
15N
N
N
Me
Me
Me
CDCl3, 275 MHz,
19F NMR
680
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

681

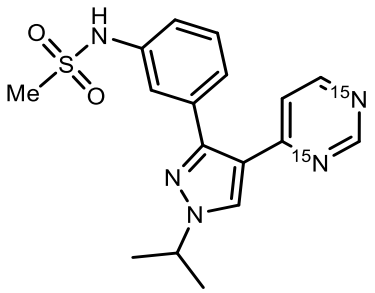


$CDCl_3$, 40 MHz,
^{15}N NMR

682


9.13
9.13
9.09
9.06
9.06
8.48
8.47
8.46
8.44
8.14
7.43
7.41
7.39
7.37
7.36
7.36
7.35
7.35
7.33
7.32
7.32
7.26 CDCl3
7.10
7.10
7.09
7.08
7.01
4.63
4.62
4.60
4.58
4.57
4.55
4.53
3.02
3.00
1.60
1.59
1.57
1.57
1.55
H
N
O
S
O
Me
N
N
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
1.02
1.02
1.05
3.03
1.01
1.02
1.07
3.00
6.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

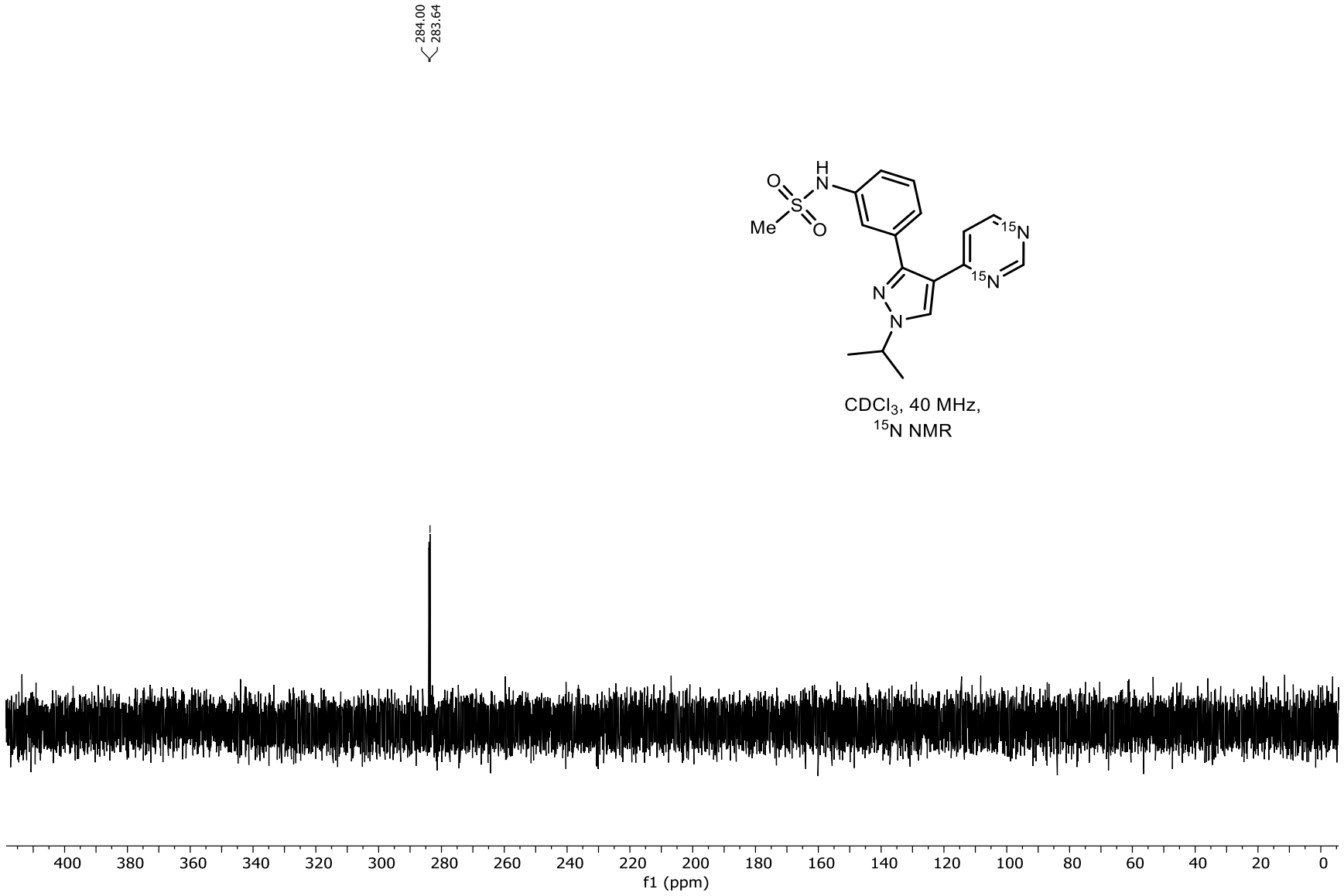
683



$CDCl_3$, 100 MHz,
^{13}C NMR

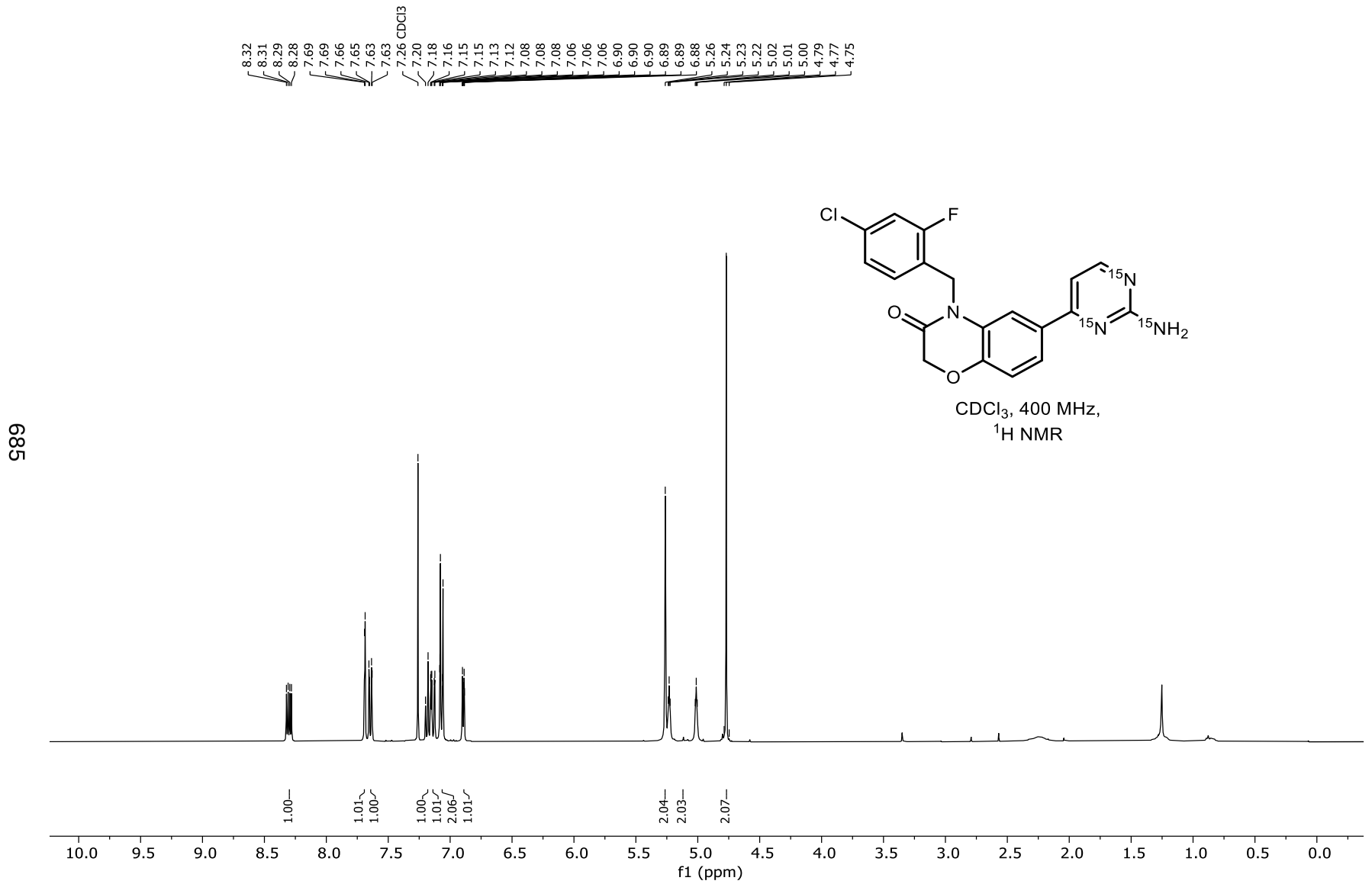
159.50
158.99
156.67
149.27
137.38
135.09
130.21
129.49
125.95
121.11
120.46
118.09
77.16 CDCl3
54.74
39.83
22.98

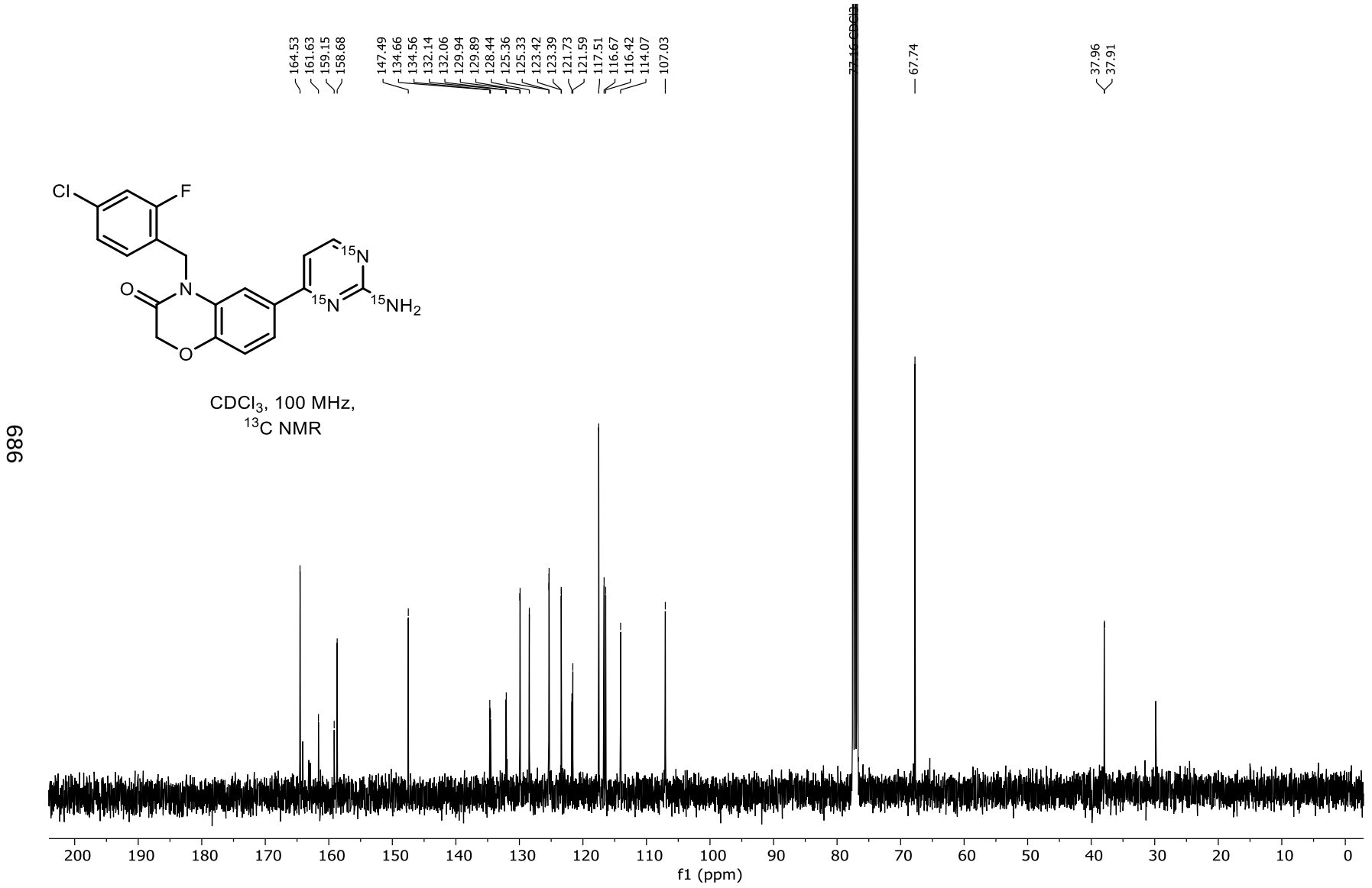
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



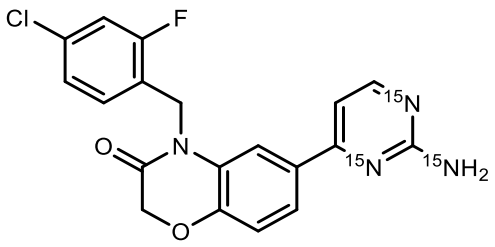
$CDCl_3$, 40 MHz,
^{15}N NMR

685


8.32
8.31
8.29
8.28
7.69
7.69
7.66
7.65
7.63
7.63
7.26 CDCl3
7.20
7.18
7.16
7.15
7.15
7.13
7.12
7.08
7.08
7.08
7.06
7.06
7.06
6.90
6.90
6.90
6.89
6.89
6.88
5.26
5.24
5.23
5.22
5.02
5.01
5.00
4.79
4.77
4.75
Cl
F
O
N
O
15N
15N
15NH2
CDCl3, 400 MHz,
1H NMR
1.00
1.01
1.00
1.00
1.01
2.06
1.01
2.04
2.03
2.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.53
161.63
159.15
158.68
147.49
134.66
134.56
132.14
132.06
129.94
129.89
128.44
125.36
125.33
123.42
123.39
121.73
121.59
117.51
116.67
116.42
114.07
107.03
77.16 CDCl3
67.74
37.96
37.91
Cl
F
O
N
O
15N
15N
15NH2
CDCl3, 100 MHz,
13C NMR
989
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

687

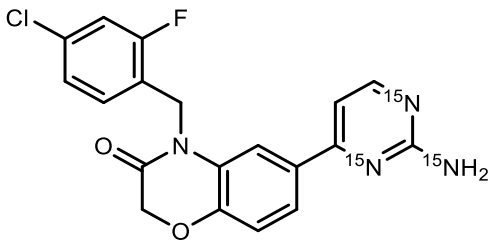


$CDCl_3$, 375 MHz,
^{19}F NMR

-115.71
-115.74
-115.76

0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -20(

f1 (ppm)



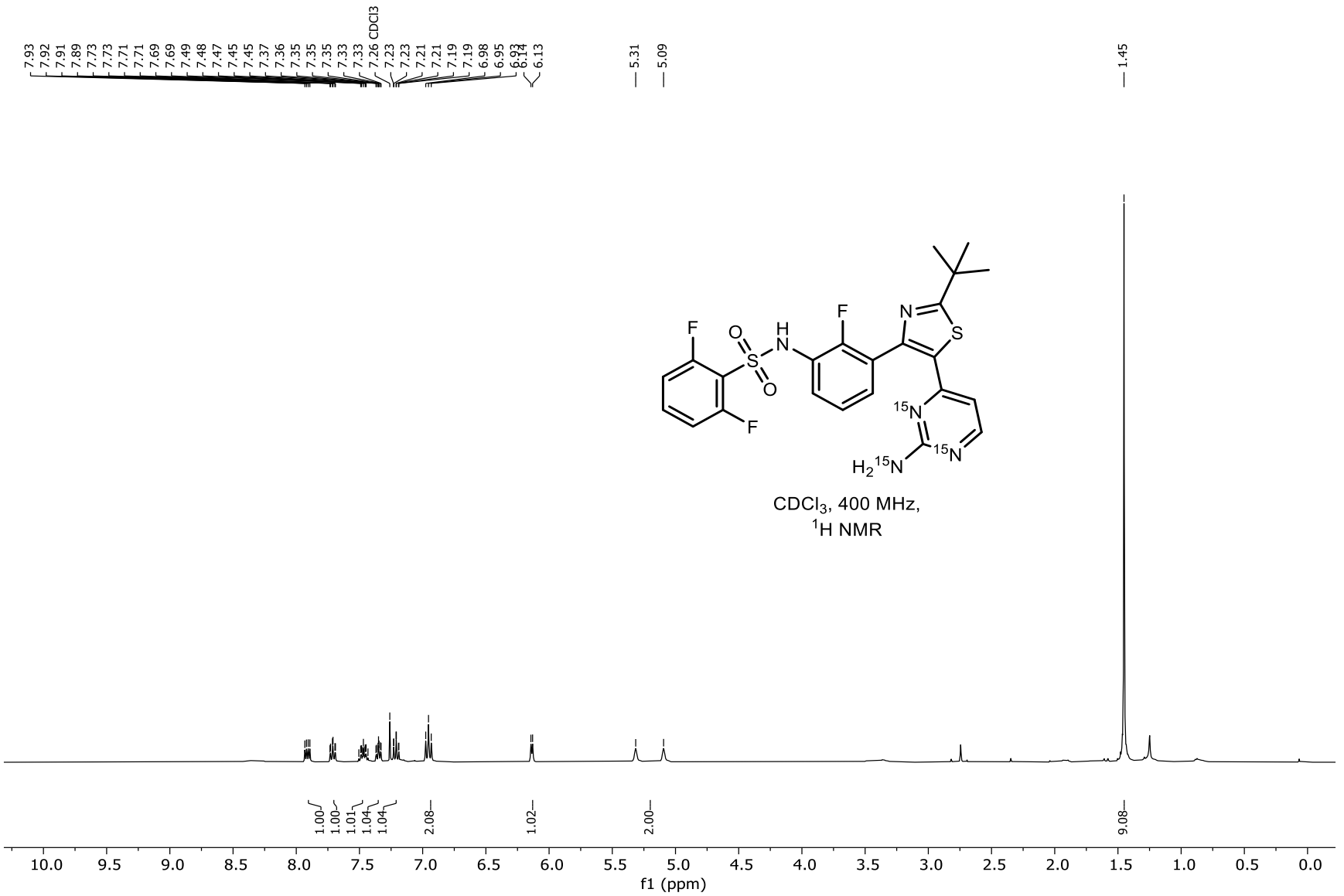
$CDCl_3$, 40 MHz,
^{15}N NMR

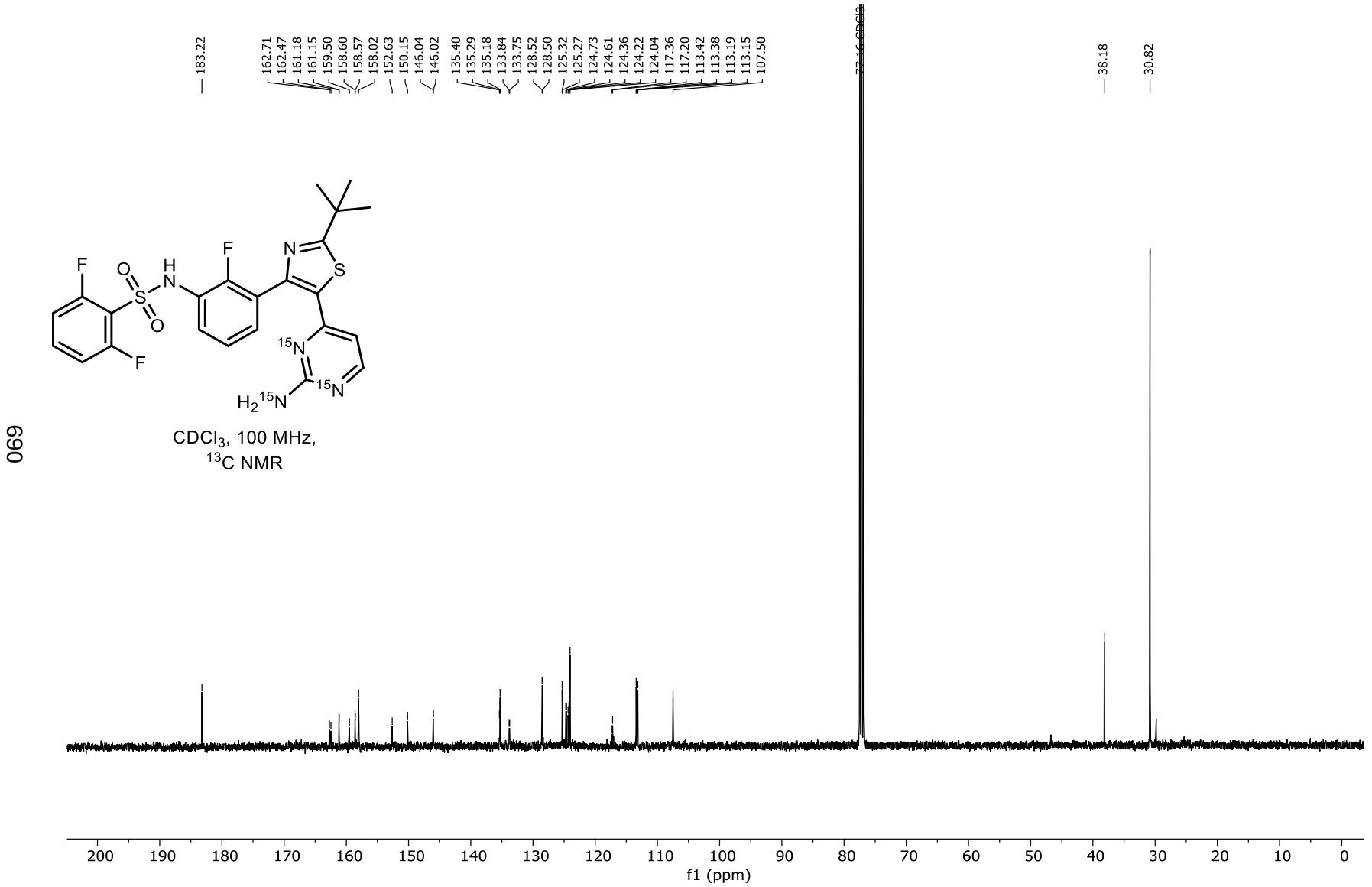
688

76.40
76.23
76.06

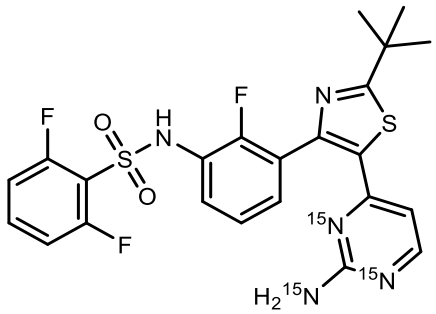
400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)

689


7.93
7.92
7.91
7.89
7.73
7.73
7.71
7.71
7.69
7.69
7.49
7.48
7.47
7.45
7.45
7.37
7.36
7.35
7.35
7.35
7.33
7.33
7.26 CDCl3
7.23
7.23
7.21
7.21
7.19
7.19
6.98
6.95
6.93
6.14
6.13
5.31
5.09
1.45
F
O
H
N
F
N
S
S
O
F
15N
15N
H2 15N
CDCl3, 400 MHz,
1H NMR
1.00
1.00
1.01
1.04
1.04
2.08
1.02
2.00
9.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

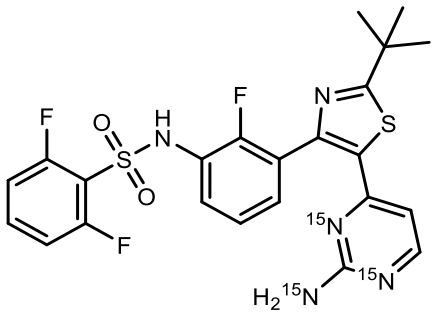

183.22
162.71
162.47
161.18
161.15
159.50
158.60
158.57
158.02
152.63
150.15
146.04
146.02
135.40
135.29
135.18
133.84
133.75
128.52
128.50
125.32
125.27
124.73
124.61
124.36
124.22
124.04
117.36
117.20
113.42
113.38
113.19
113.15
107.50
77.16 CDCl3
38.18
30.82
F
O
H
N
S
O
F
F
N
S
15N
15N
H2 15N
CDCl3, 100 MHz,
13C NMR
069
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

691



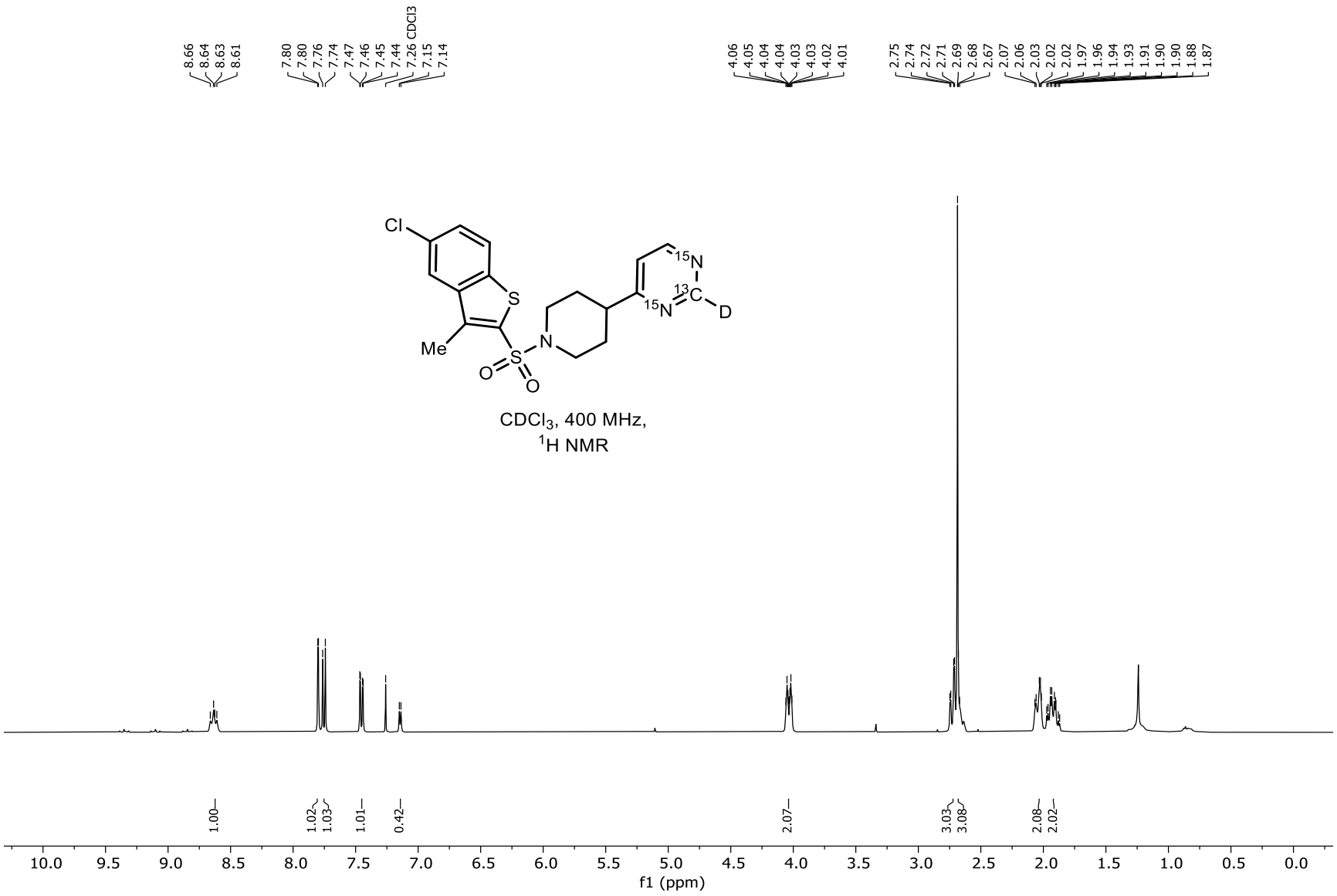
$CDCl_3$, 375 MHz,
^{19}F NMR

692

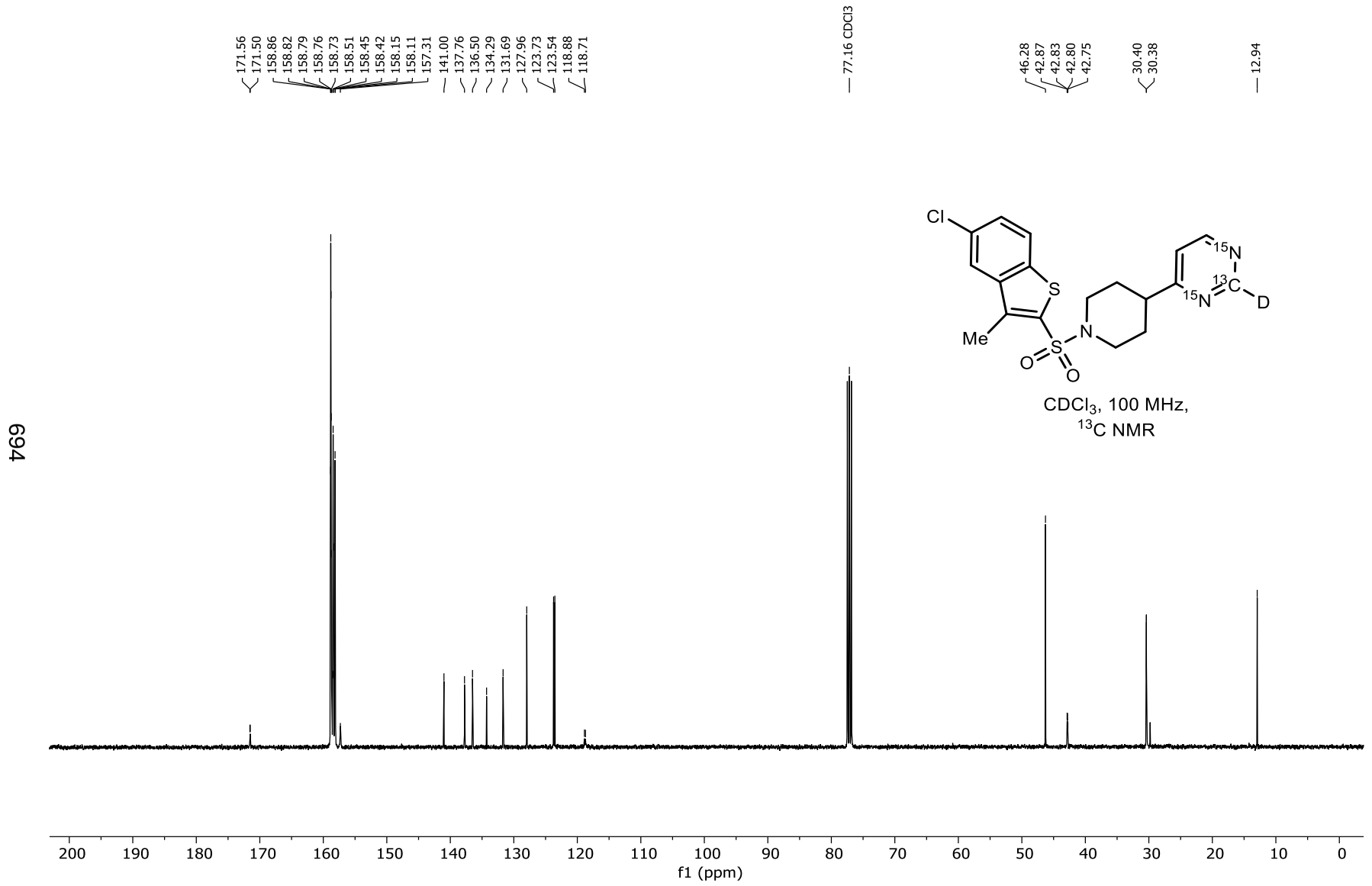


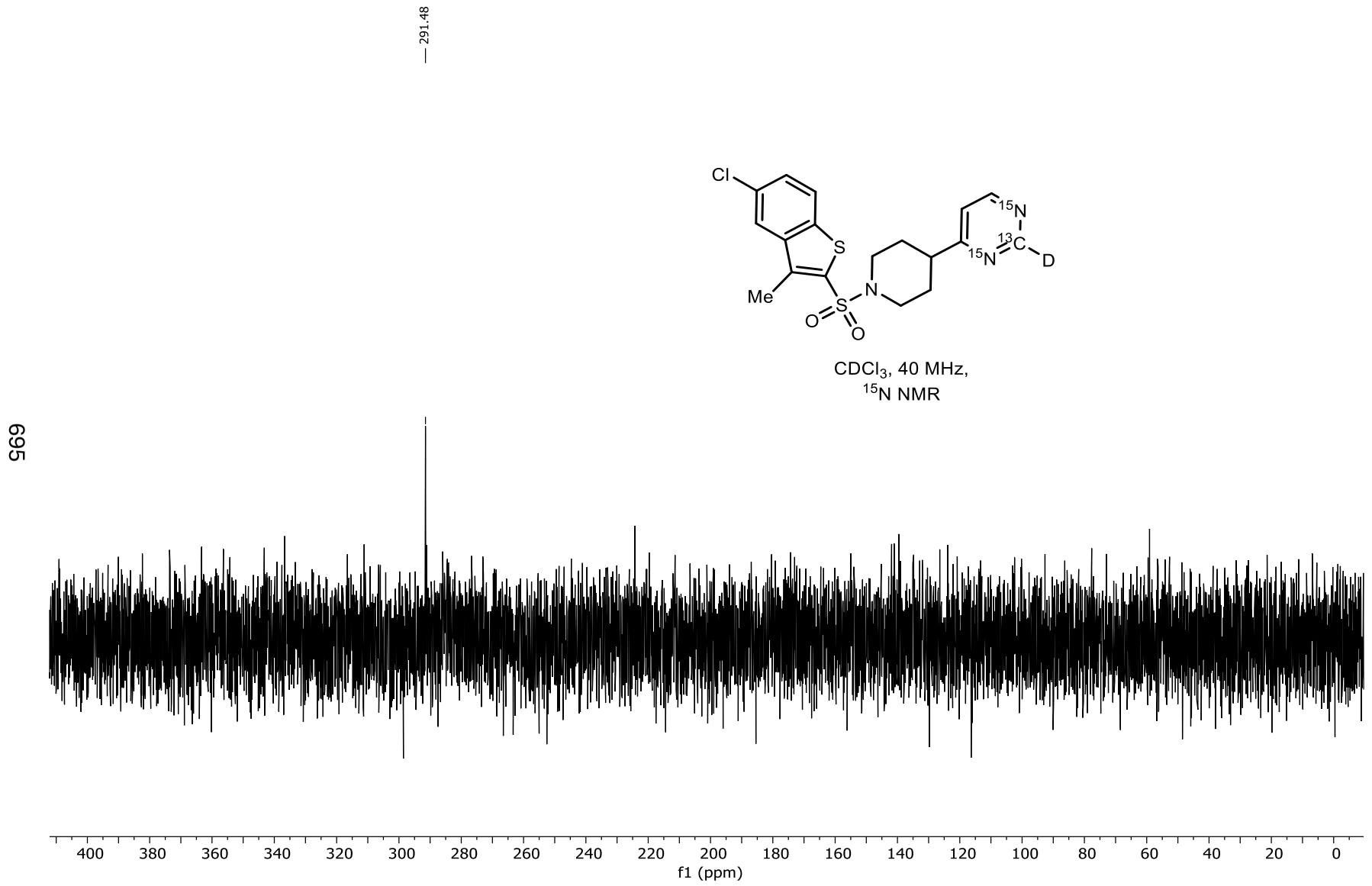
$CDCl_3$, 40 MHz,
^{15}N NMR

693

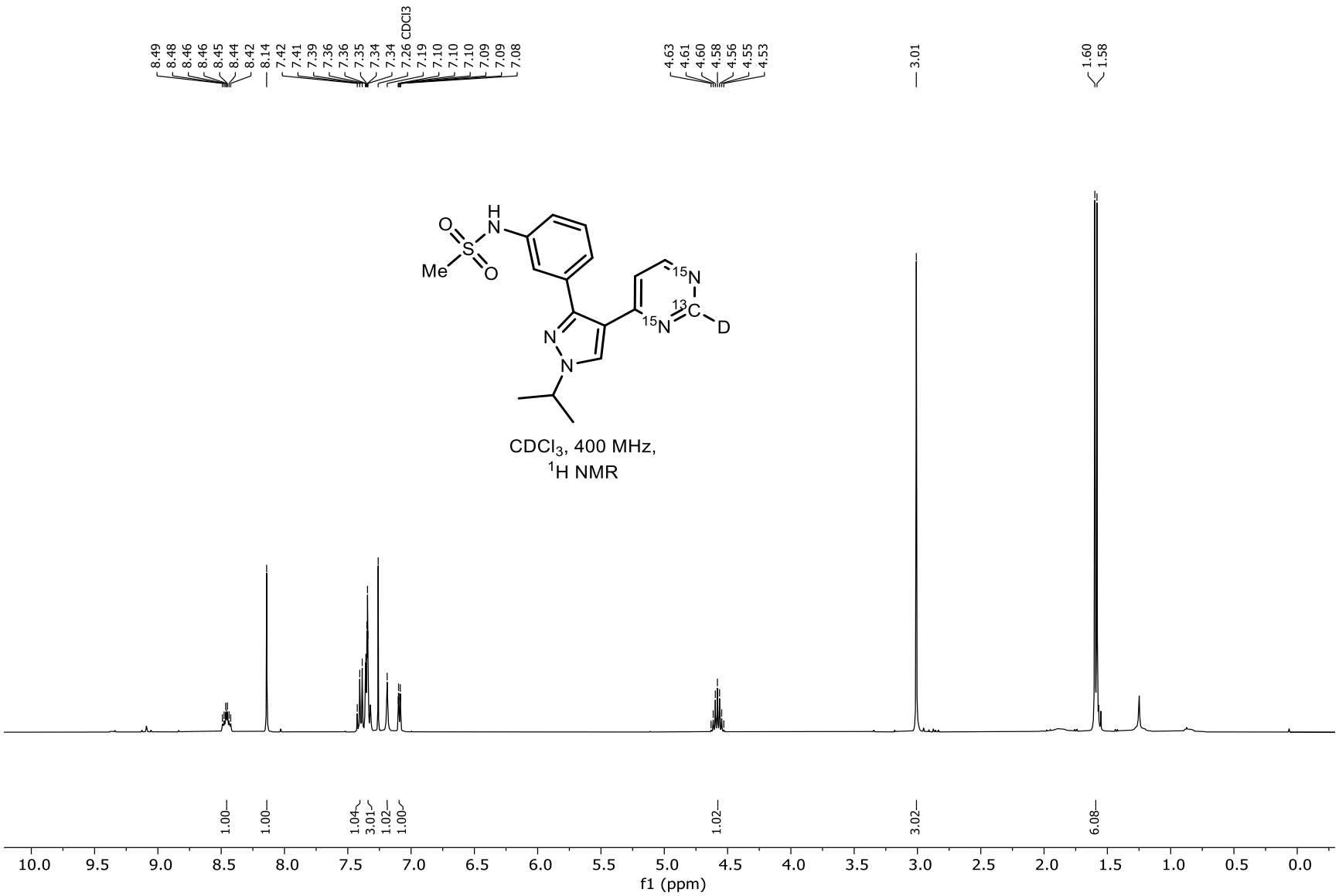

8.66
8.64
8.63
8.61
7.80
7.80
7.76
7.74
7.47
7.46
7.45
7.44
7.26 CDCl3
7.15
7.14
4.06
4.05
4.04
4.04
4.03
4.03
4.02
4.01
2.75
2.74
2.72
2.71
2.69
2.68
2.67
2.07
2.06
2.03
2.02
2.02
1.97
1.96
1.94
1.93
1.91
1.90
1.90
1.88
1.87
Cl
S
Me
S
O
O
N
15N
13C
15N
D
CDCl3, 400 MHz,
1H NMR
1.00
1.02
1.03
1.01
0.42
2.07
3.03
3.08
2.08
2.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

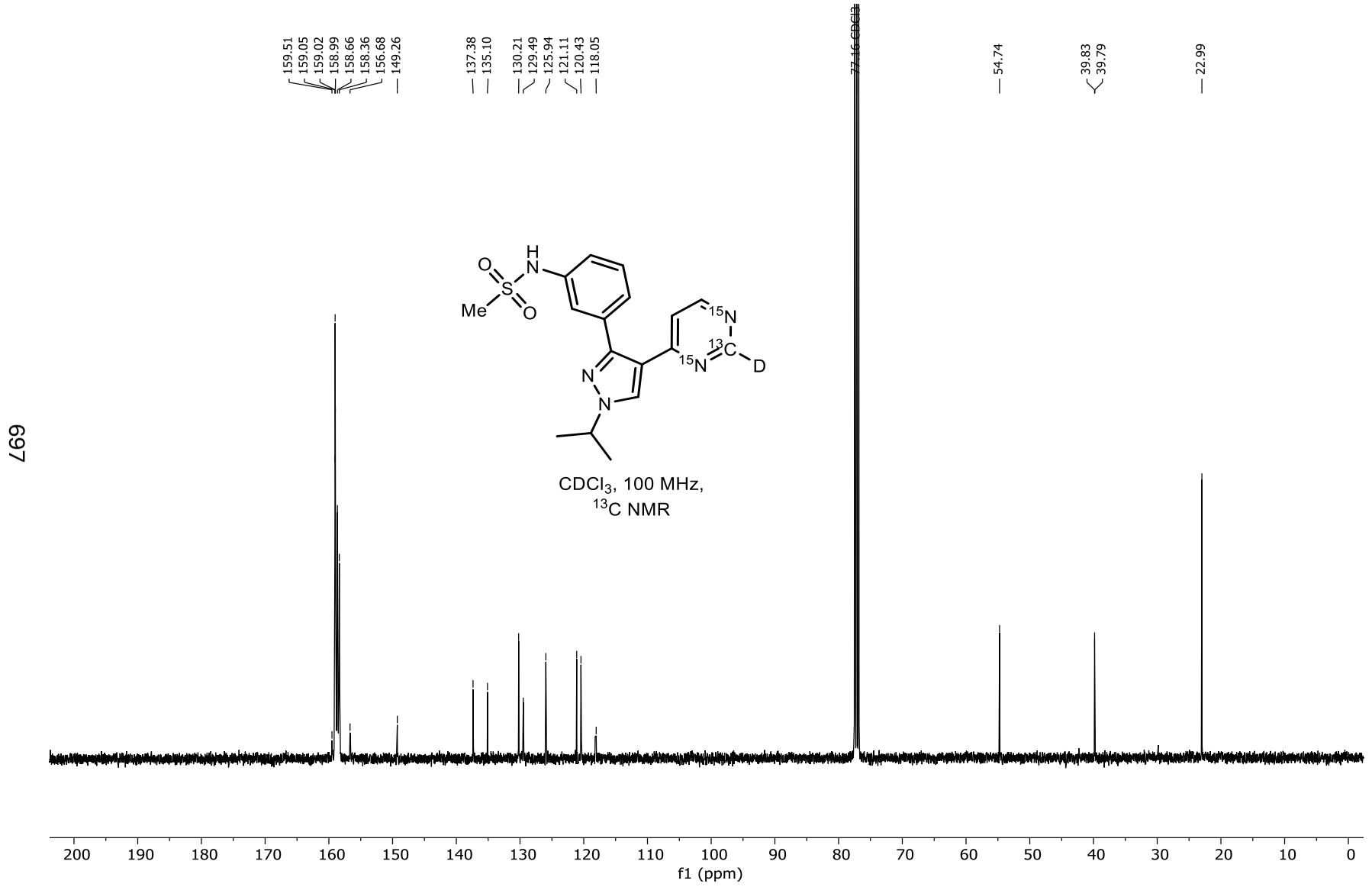
694


171.56
171.50
158.86
158.82
158.79
158.76
158.73
158.51
158.45
158.42
158.15
158.11
157.31
141.00
137.76
136.50
134.29
131.69
127.96
123.73
123.54
118.88
118.71
77.16 CDCl3
46.28
42.87
42.83
42.80
42.75
30.40
30.38
12.94
Cl
S
Me
N
S
O
O
15N
13C
15N
D
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

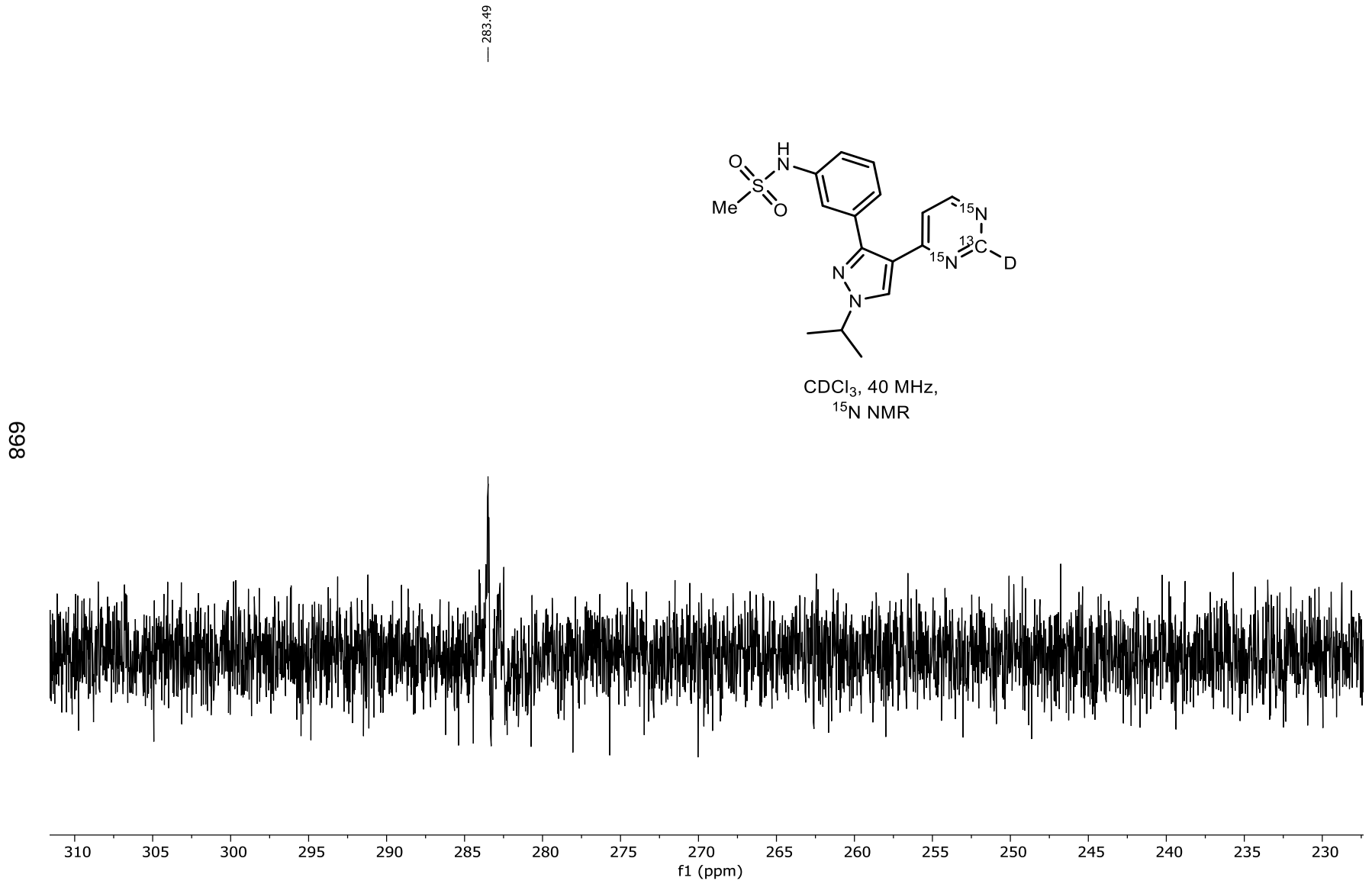

291.48
Cl
S
Me
S
O
O
N
15N
13C
15N
D
CDCl3, 40 MHz,
15N NMR
695
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

969

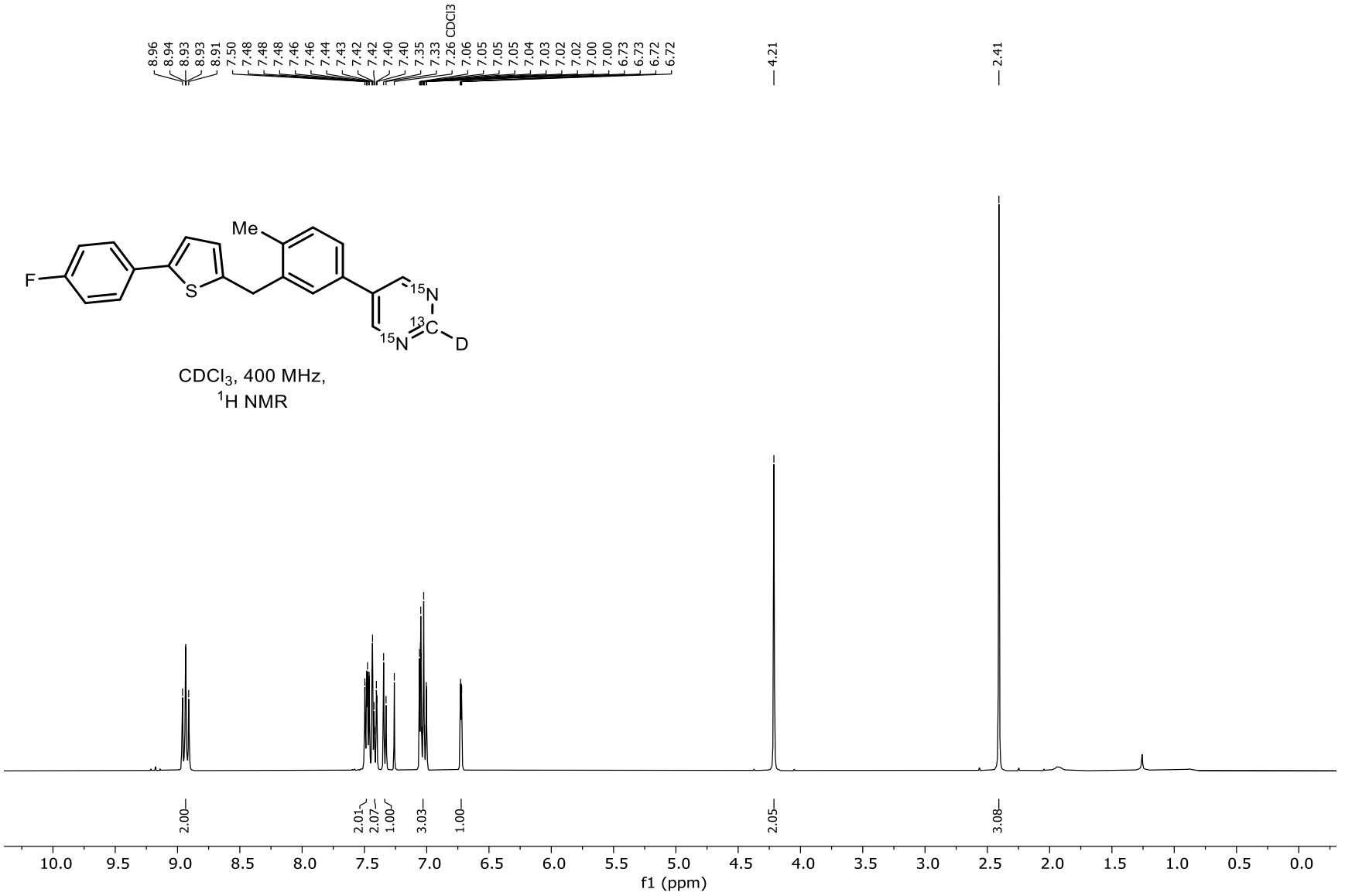

8.49
8.48
8.46
8.46
8.45
8.44
8.42
8.14
7.42
7.41
7.39
7.36
7.36
7.35
7.34
7.34
7.26 CDCl3
7.19
7.10
7.10
7.10
7.09
7.09
7.08
4.63
4.61
4.60
4.58
4.56
4.55
4.53
3.01
1.60
1.58
O
S
O
Me
H
N
N
N
15N
13C
15N
D
CDCl3, 400 MHz,
1H NMR
1.00
1.00
1.04
3.01
1.02
1.00
1.02
3.02
6.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

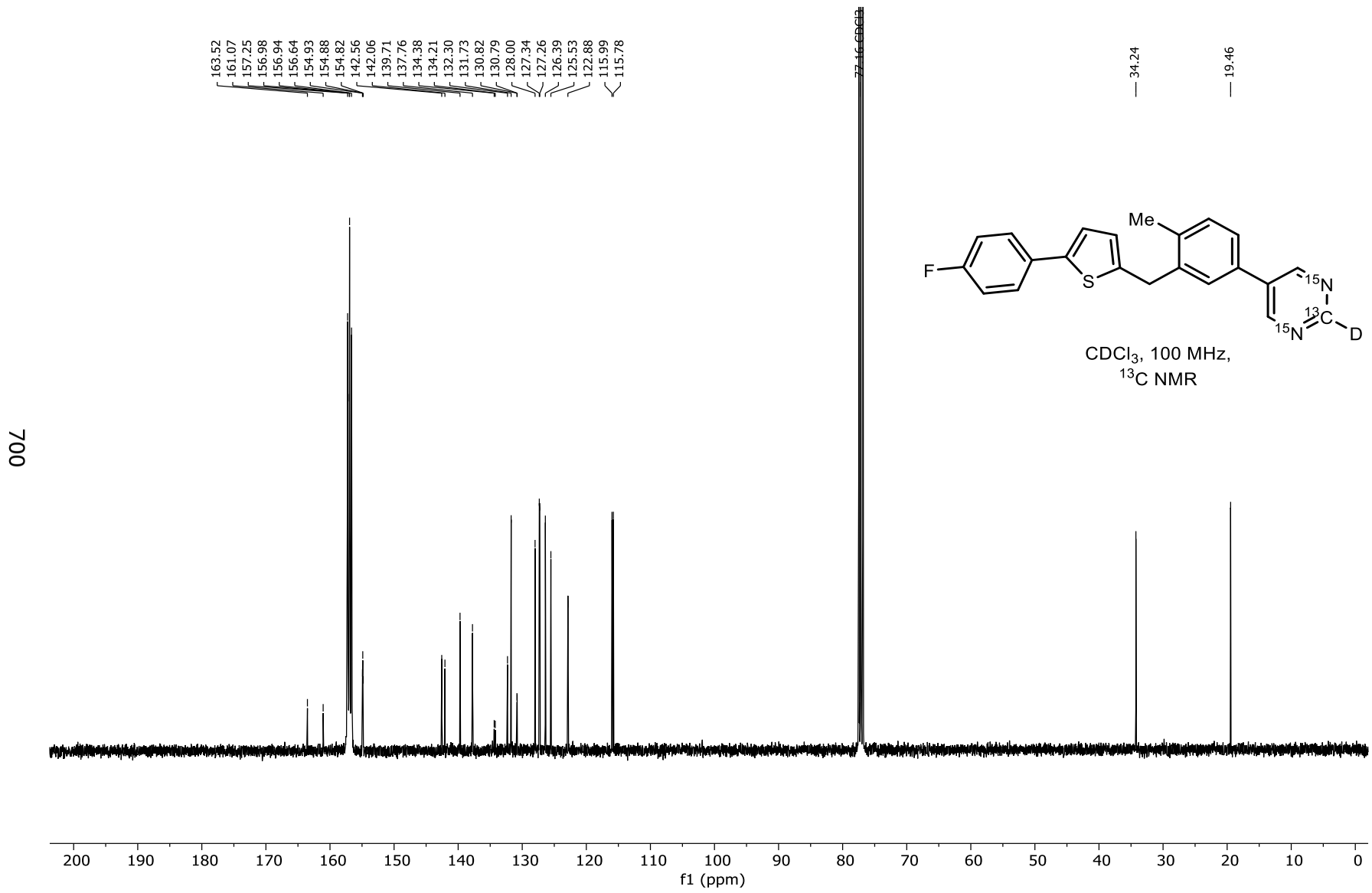

159.51
159.05
159.02
158.99
158.66
158.36
156.68
149.26
137.38
135.10
130.21
129.49
125.94
121.11
120.43
118.05
77.16 CDCl3
54.74
39.83
39.79
22.99
O
S
N
H
Me
O
N
N
15N
13C
15N
D
CDCl3, 100 MHz,
13C NMR
f1 (ppm)

697

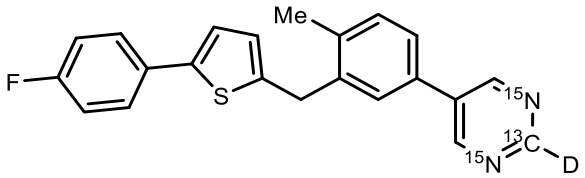

283.49
869
CDCl3, 40 MHz,
15N NMR
310
305
300
295
290
285
280
275
270
265
260
255
250
245
240
235
230
f1 (ppm)

669


8.96
8.94
8.93
8.93
8.91
7.50
7.48
7.48
7.48
7.46
7.46
7.44
7.43
7.42
7.42
7.40
7.40
7.35
7.33
7.26 CDCl3
7.06
7.05
7.05
7.05
7.04
7.03
7.02
7.02
7.00
7.00
6.73
6.73
6.72
6.72
4.21
2.41
Me
F
S
15N
13C
15N
D
CDCl3, 400 MHz,
1H NMR
2.00
2.01
2.07
1.00
3.03
1.00
2.05
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

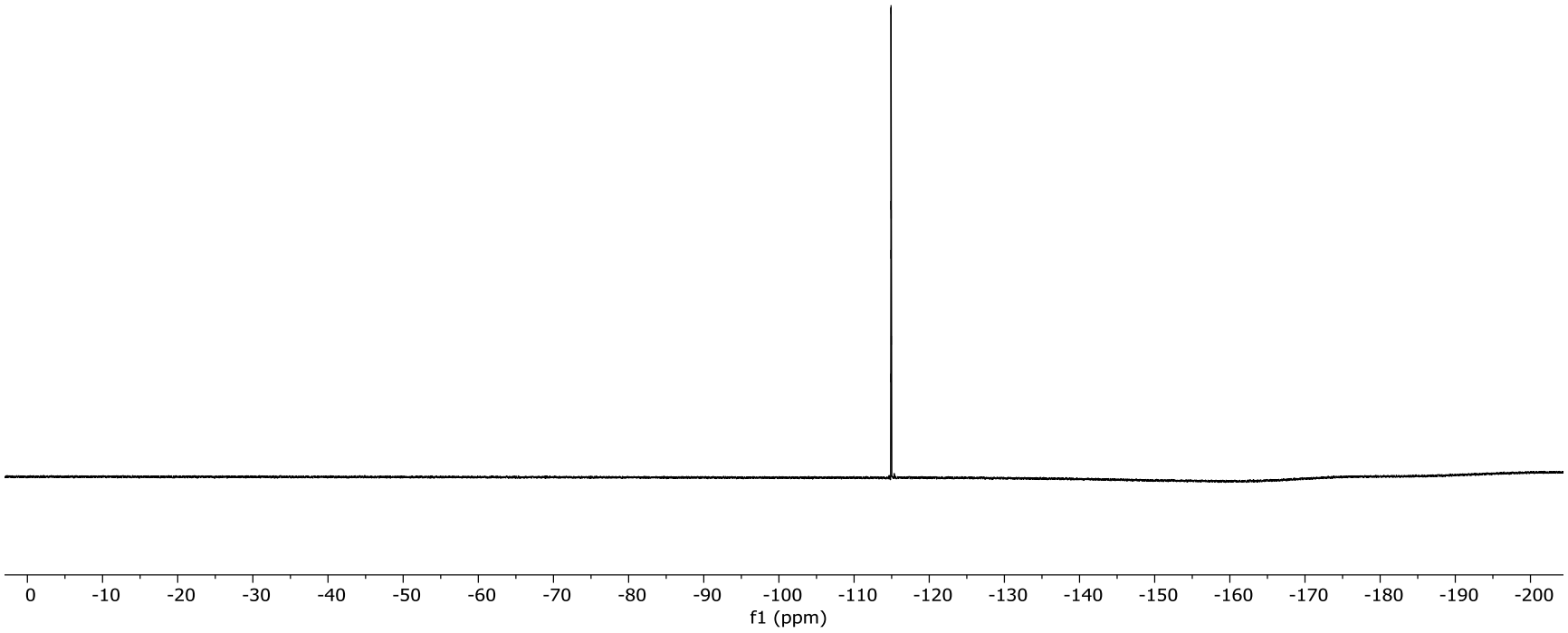

163.52
161.07
157.25
156.98
156.94
156.64
154.93
154.88
154.82
142.56
142.06
139.71
137.76
134.38
134.21
132.30
131.73
130.82
130.79
128.00
127.34
127.26
126.39
125.53
122.88
115.99
115.78
77.16 CDCl3
34.24
19.46
Me
F
S
15N
13C
15N
D
CDCl3, 100 MHz,
13C NMR
700
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

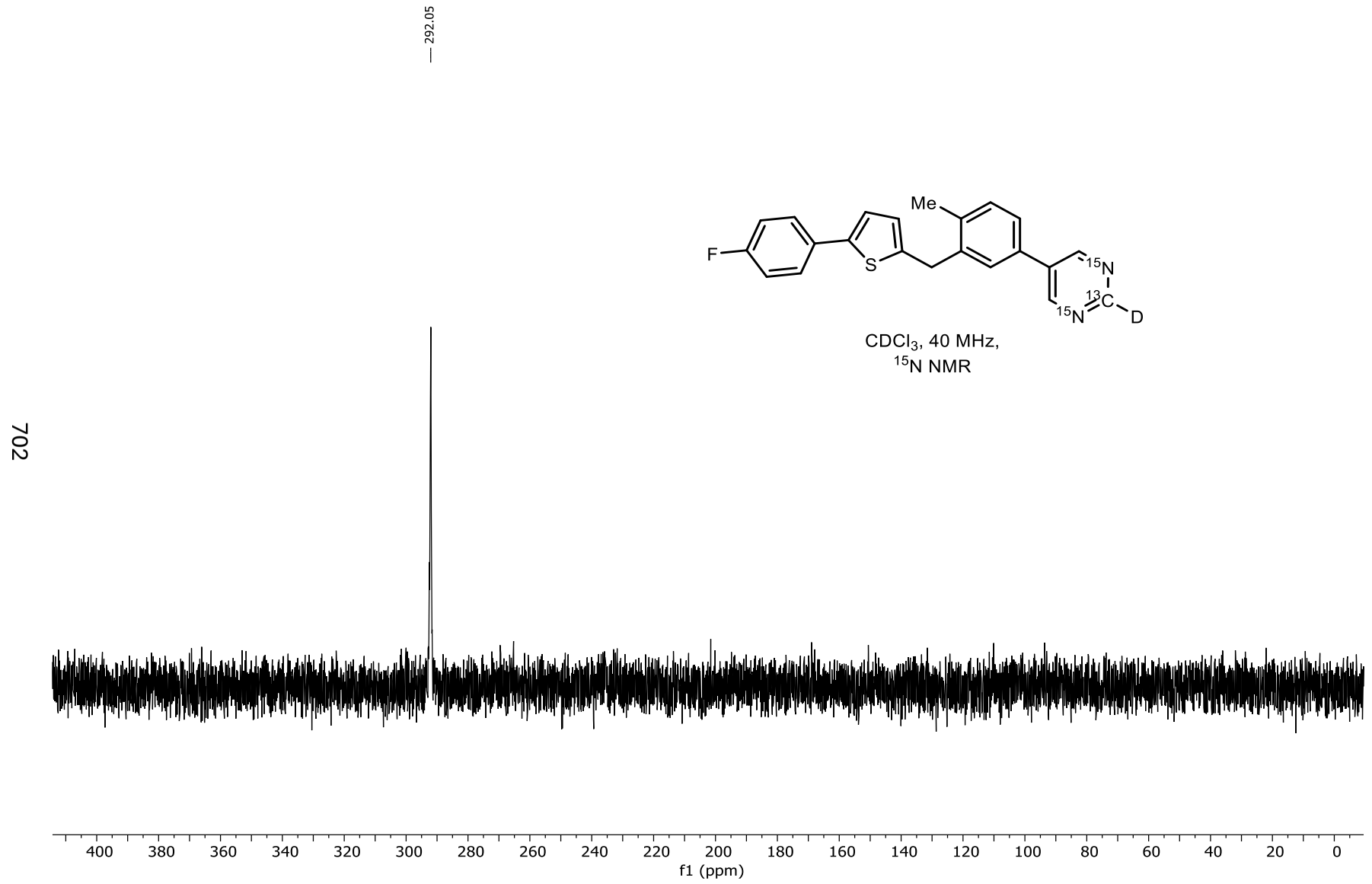
-114.88
-114.90
-114.91
-114.92
-114.93
-114.94
-114.96

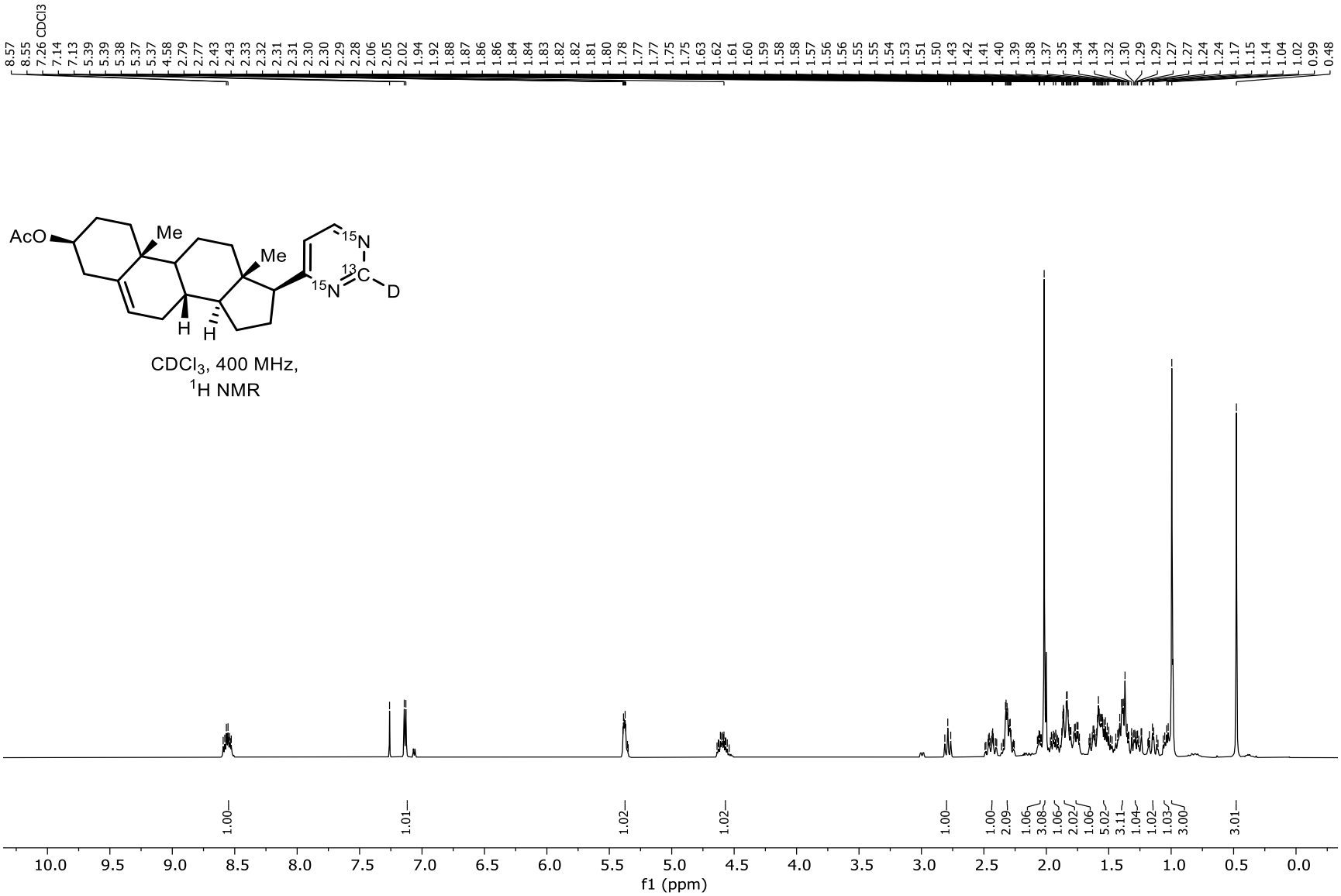


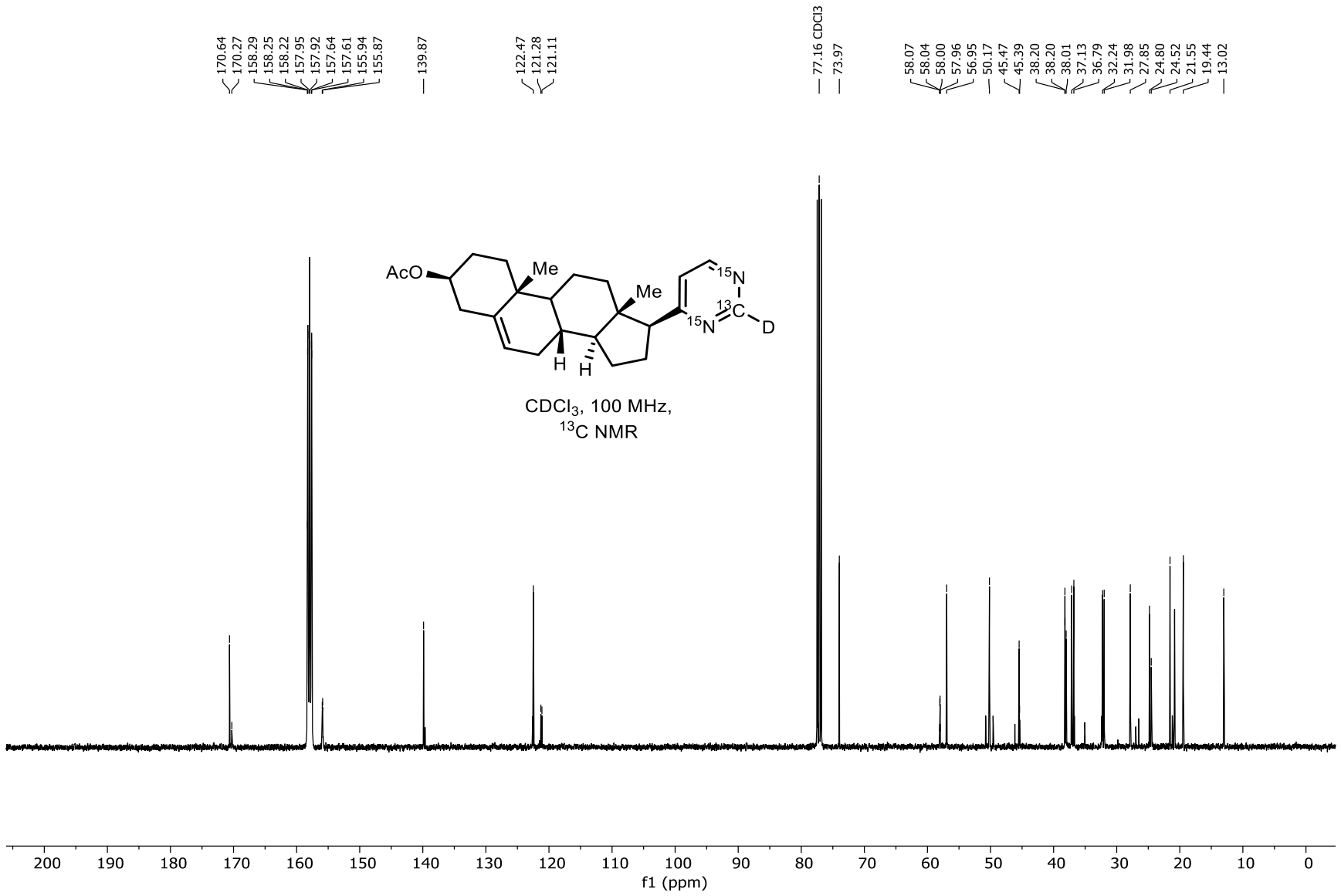
$CDCl_3$, 375 MHz,
^{19}F NMR

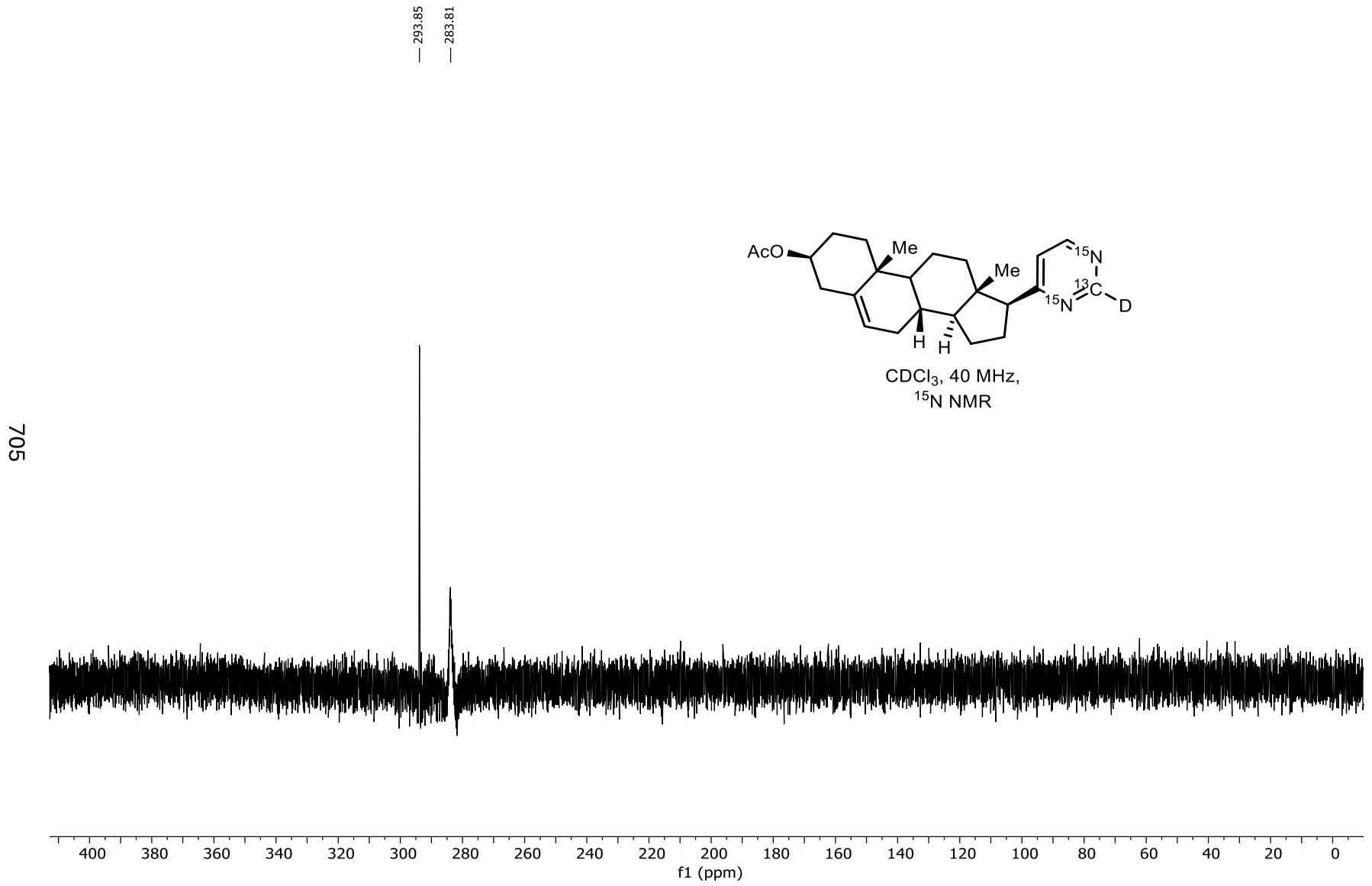
701

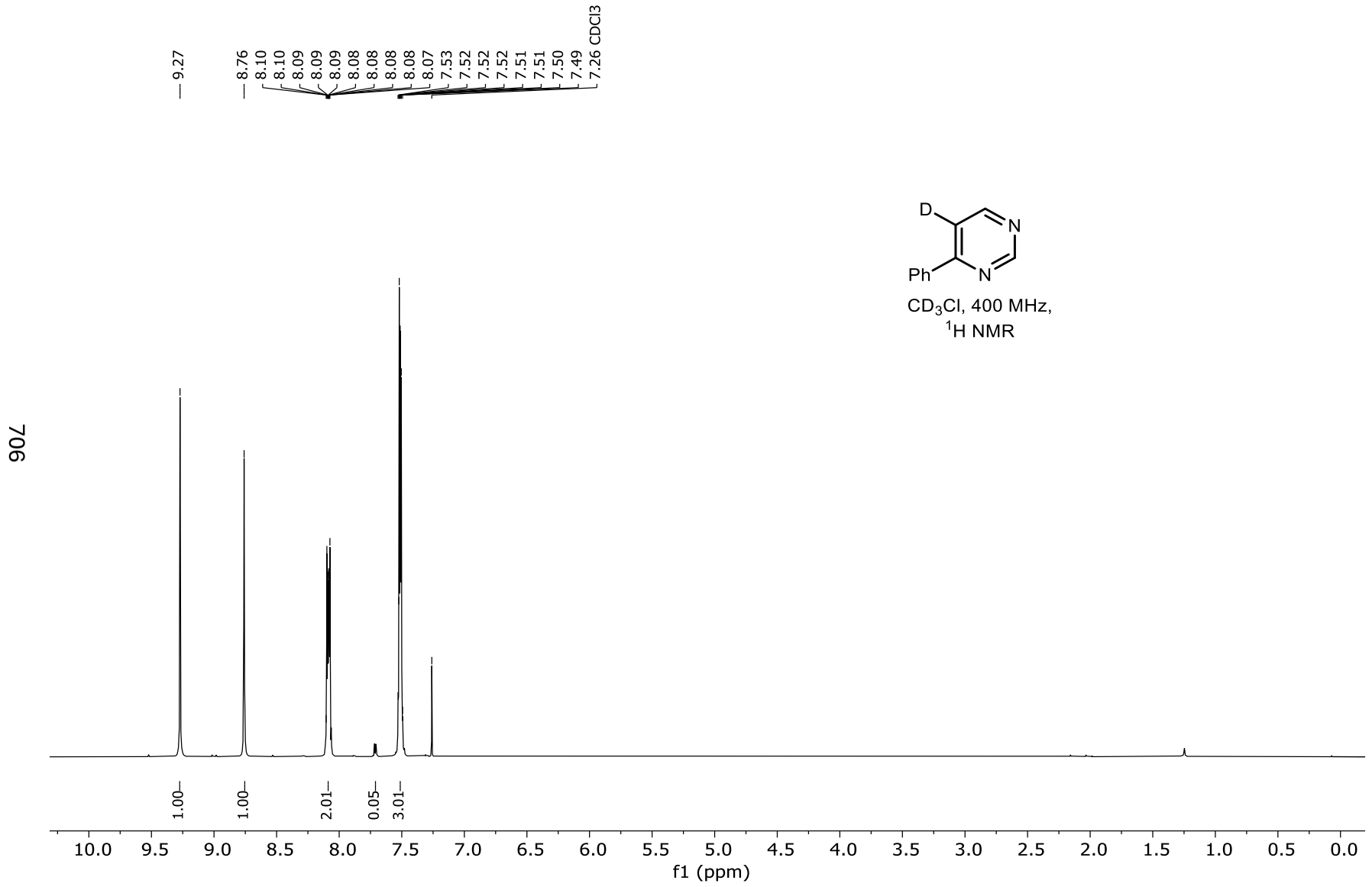


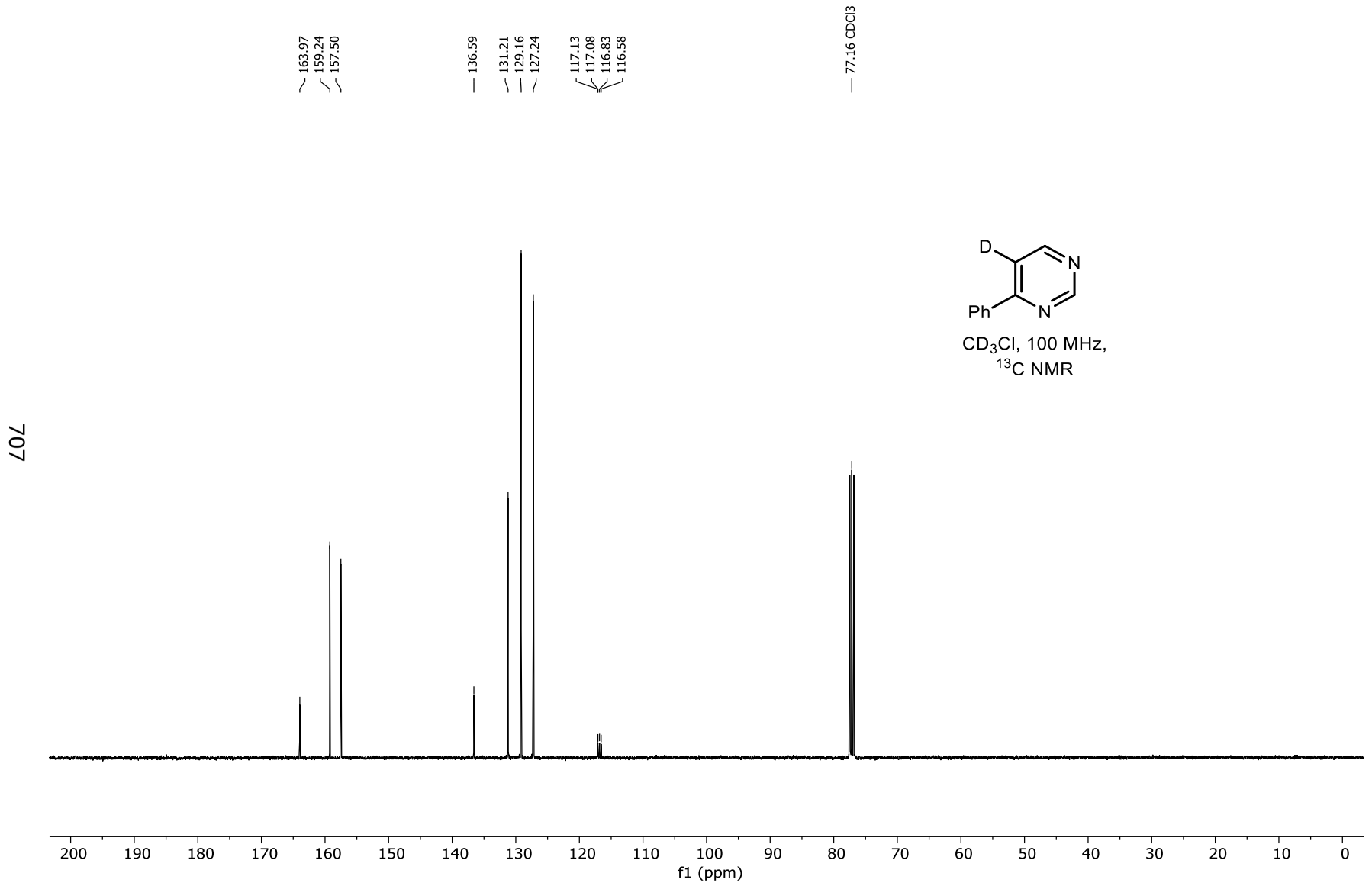

292.05
Me
F
S
^{15}N
^{13}C
^{15}N
D
$CDCl_3$, 40 MHz,
^{15}N NMR
702
400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)

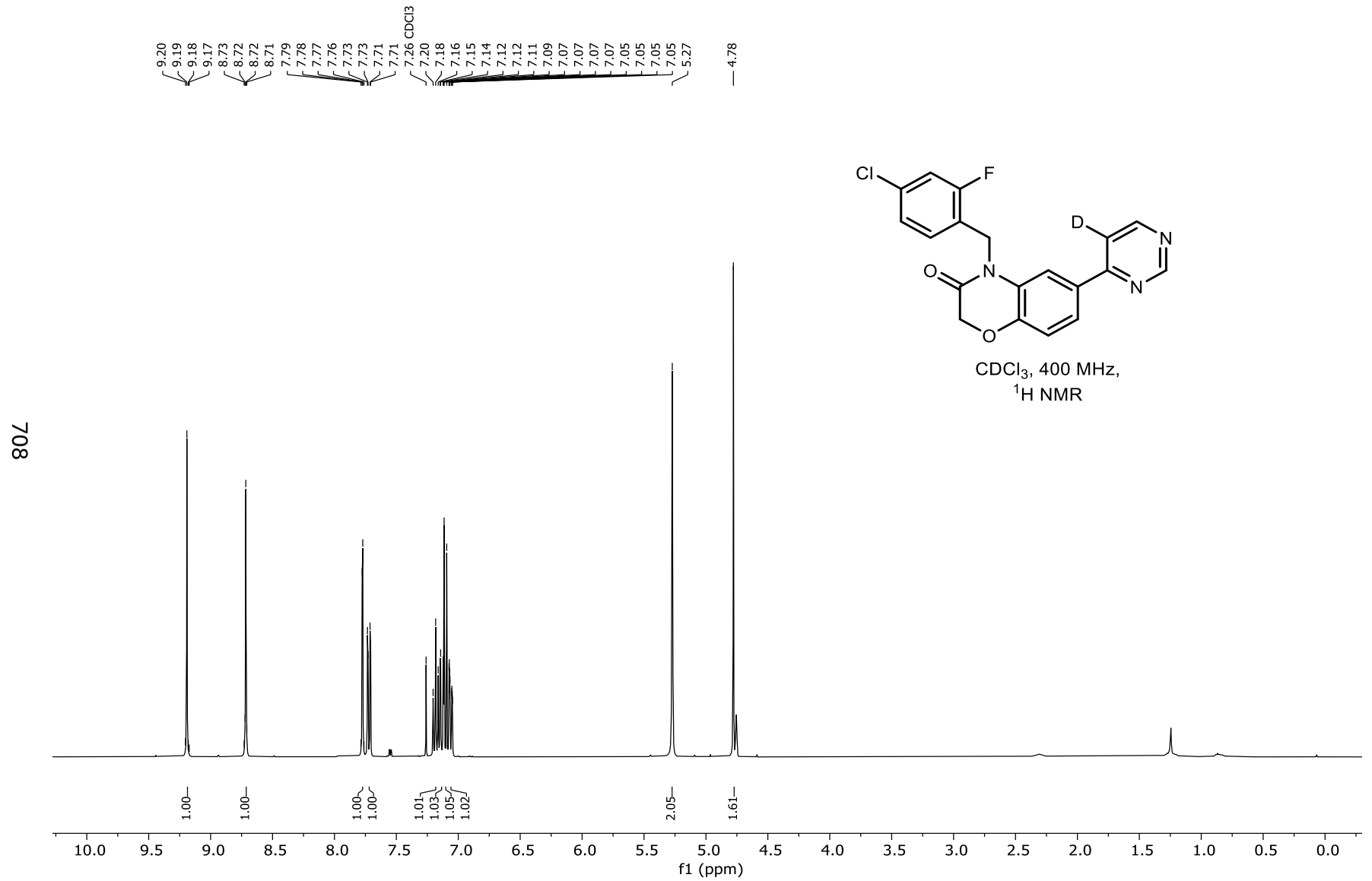

8.57 8.55 7.26 CDCl3 7.14 7.13 5.39 5.39 5.38 5.37 5.37 4.58 2.79 2.77 2.43 2.43 2.33 2.32 2.31 2.31 2.30 2.30 2.29 2.28 2.06 2.05 2.02 1.94 1.92 1.88 1.87 1.86 1.86 1.84 1.84 1.83 1.82 1.82 1.81 1.80 1.78 1.77 1.77 1.75 1.75 1.63 1.62 1.61 1.60 1.59 1.58 1.58 1.57 1.56 1.56 1.55 1.55 1.54 1.53 1.51 1.50 1.43 1.42 1.41 1.40 1.39 1.38 1.37 1.35 1.34 1.34 1.32 1.30 1.29 1.29 1.27 1.27 1.24 1.24 1.17 1.15 1.14 1.04 1.02 0.99 0.48
AcO
Me
Me
15N
13C
15N
D
H
H
CDCl3, 400 MHz,
1H NMR
1.00
1.01
1.02
1.02
1.00
1.00
2.09
1.06
3.08
1.06
2.02
1.06
5.02
3.11
1.04
1.02
1.03
3.00
3.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

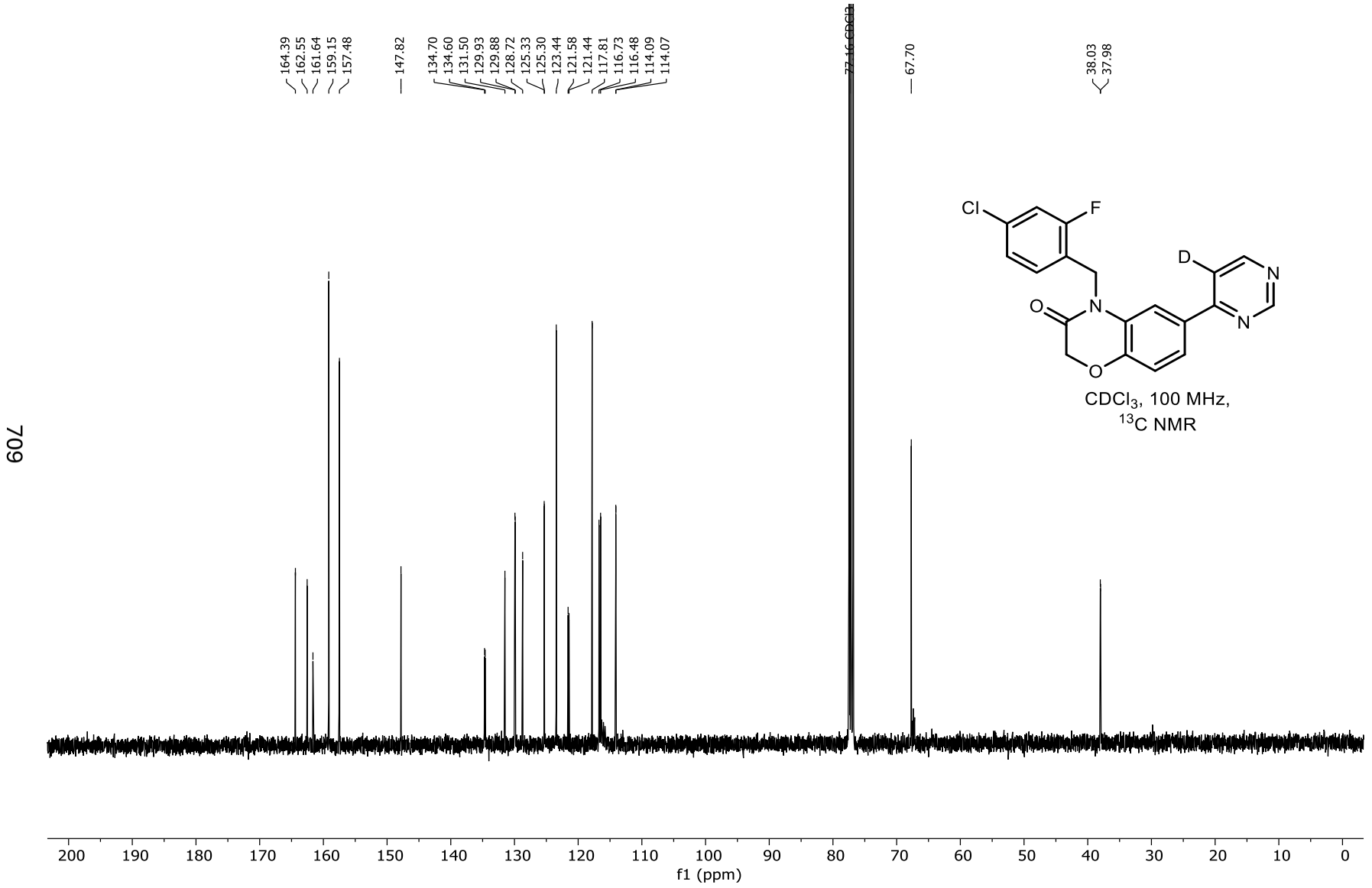

170.64
170.27
158.29
158.25
158.22
157.95
157.92
157.64
157.61
155.94
155.87
139.87
122.47
121.28
121.11
77.16 CDCl3
73.97
58.07
58.04
58.00
57.96
56.95
50.17
45.47
45.39
38.20
38.20
38.01
37.13
36.79
32.24
31.98
27.85
24.80
24.52
21.55
19.44
13.02
AcO
Me
Me
H
H
15N
13C
15N
D
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

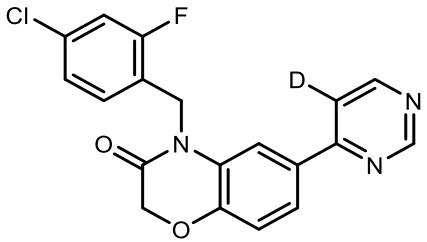

293.85
283.81
AcO
Me
Me
15N
13C
15N
D
H
H
CDCl3, 40 MHz,
15N NMR
705
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)


9.27
8.76
8.10
8.10
8.09
8.09
8.09
8.08
8.08
8.08
8.08
8.07
7.53
7.52
7.52
7.52
7.51
7.51
7.50
7.49
7.26 CDCl3
D
N
Ph
N
CD3Cl, 400 MHz,
1H NMR
706
1.00
1.00
2.01
0.05
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

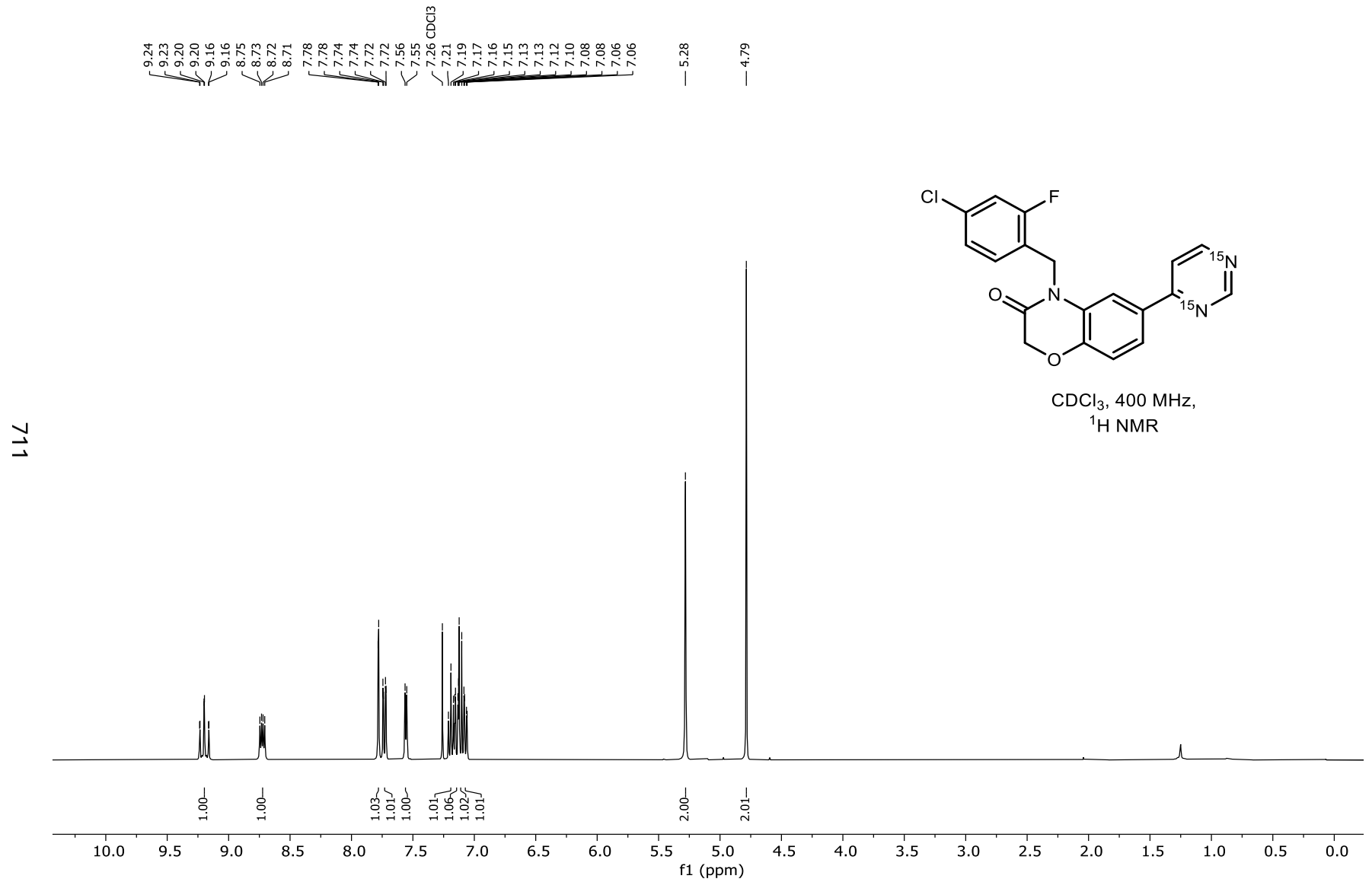

163.97
159.24
157.50
136.59
131.21
129.16
127.24
117.13
117.08
116.83
116.58
77.16 CDCl3
D
N
Ph
N
CD3Cl, 100 MHz,
13C NMR
707
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

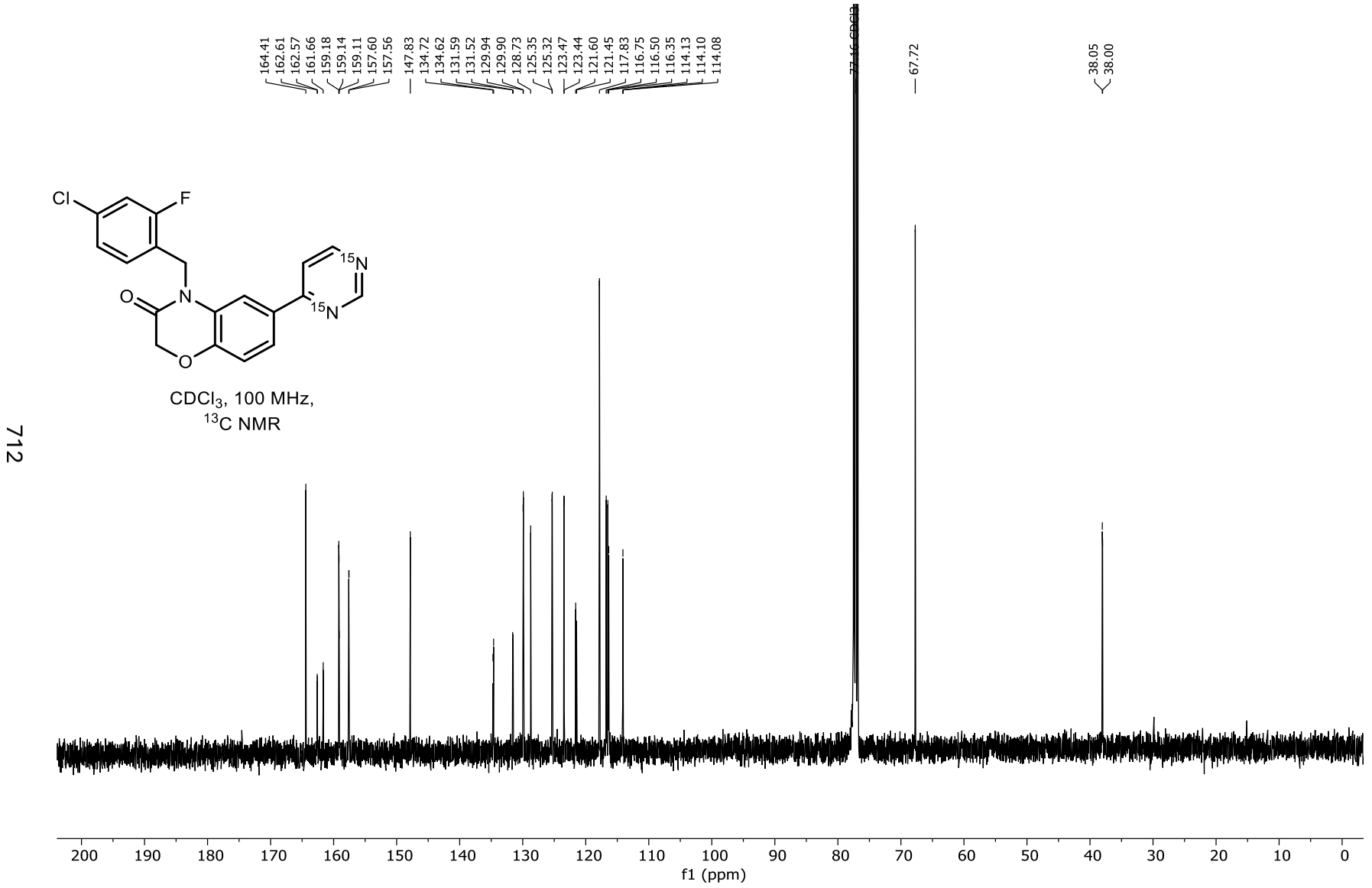

9.20
9.19
9.18
9.17
8.73
8.72
8.72
8.71
7.79
7.78
7.77
7.76
7.73
7.73
7.71
7.71
7.26 CDCl3
7.20
7.18
7.16
7.15
7.14
7.12
7.12
7.11
7.09
7.07
7.07
7.07
7.07
7.05
7.05
7.05
7.05
5.27
4.78
Cl
F
D
N
N
O
N
O
CDCl3, 400 MHz,
1H NMR
1.00
1.00
1.00
1.00
1.01
1.03
1.05
1.02
2.05
1.61
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.39
162.55
161.64
159.15
157.48
147.82
134.70
134.60
131.50
129.93
129.88
128.72
125.33
125.30
123.44
121.58
121.44
117.81
116.73
116.48
114.09
114.07
77.16 CDCl3
67.70
38.03
37.98
Cl
F
D
N
N
O
N
O
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

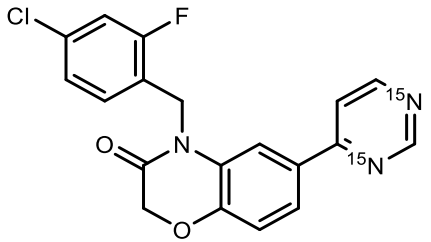


$CDCl_3$, 375 MHz,
^{19}F NMR

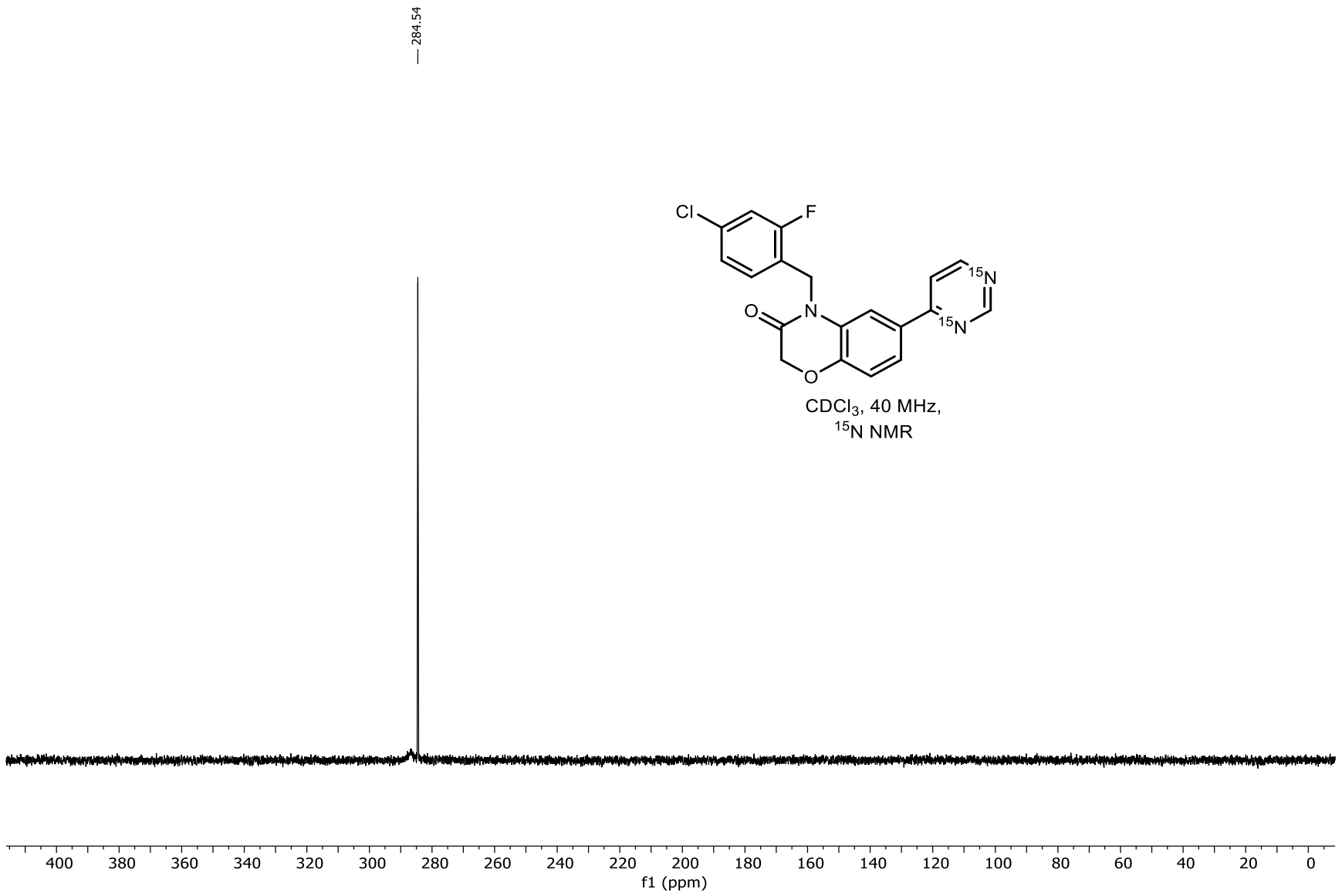

9.24
9.23
9.20
9.20
9.16
9.16
8.75
8.73
8.72
8.71
7.78
7.78
7.74
7.74
7.72
7.72
7.56
7.55
7.26 CDCl3
7.21
7.19
7.17
7.16
7.15
7.13
7.13
7.12
7.10
7.08
7.08
7.06
7.06
5.28
4.79
Cl
F
O
N
O
15N
15N
CDCl3, 400 MHz,
1H NMR
1.00
1.00
1.03
1.01
1.00
1.01
1.06
1.02
1.01
2.00
2.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.41
162.61
162.57
161.66
159.18
159.14
159.11
157.60
157.56
147.83
134.72
134.62
131.59
131.52
129.94
129.90
128.73
125.35
125.32
123.47
123.44
121.60
121.45
117.83
116.75
116.50
116.35
114.13
114.10
114.08
77.16 CDCl3
67.72
38.05
38.00
Cl
F
O
N
O
15N
15N
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

712

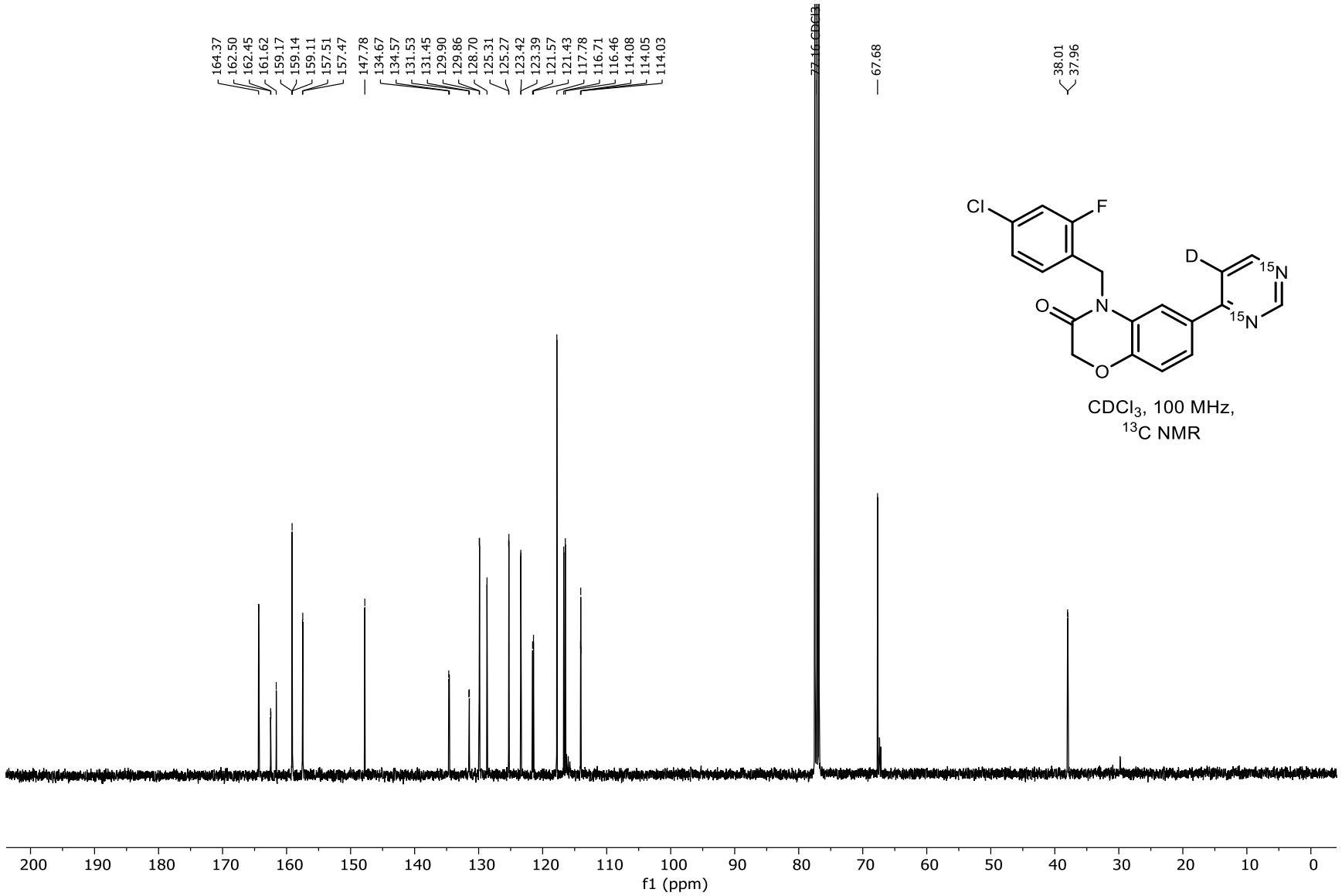


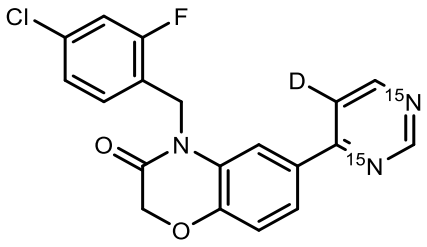
$CDCl_3$, 375 MHz,
^{19}F NMR


284.54
Cl
F
O
N
O
^{15}N
^{15}N
$CDCl_3$, 40 MHz,
^{15}N NMR
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

714

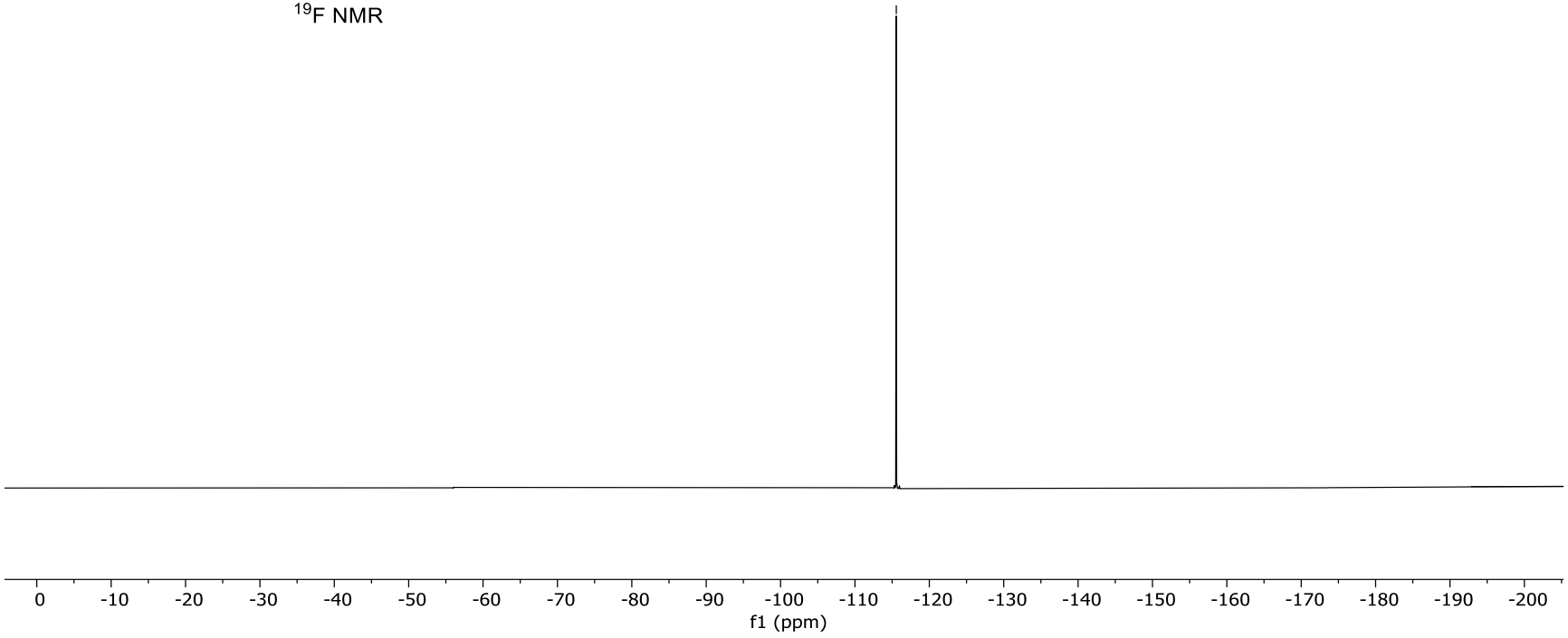
CDCl3, 400 MHz,
1H NMR
F
Cl
O
N
O
D
15N
15N
9.23
9.19
9.15
8.73
8.70
7.77
7.77
7.73
7.73
7.71
7.71
7.26 CDCl3
7.20
7.18
7.16
7.15
7.14
7.12
7.11
7.11
7.09
7.07
7.07
7.05
7.05
5.27
4.78
1.00
1.00
1.05
1.01
1.03
1.01
1.04
1.01
2.07
1.54
f1 (ppm)


164.37
162.50
162.45
161.62
159.17
159.14
159.11
157.51
157.47
147.78
134.67
134.57
131.53
131.45
129.90
129.86
128.70
125.31
125.27
123.42
123.39
121.57
121.43
117.78
116.71
116.46
114.08
114.05
114.03
77.16 CDCl3
67.68
38.01
37.96
Cl
F
D
15N
O
N
15N
O
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

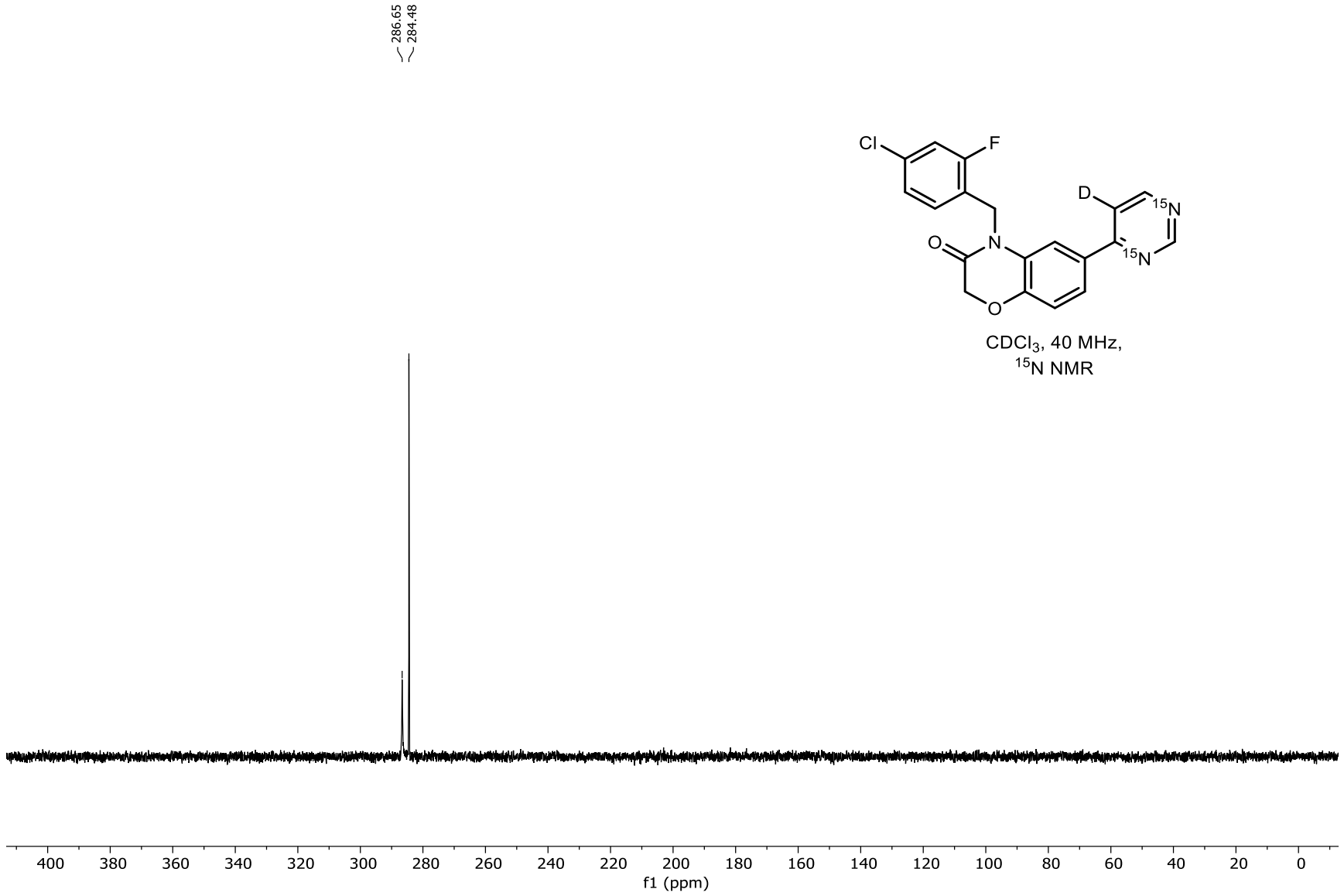


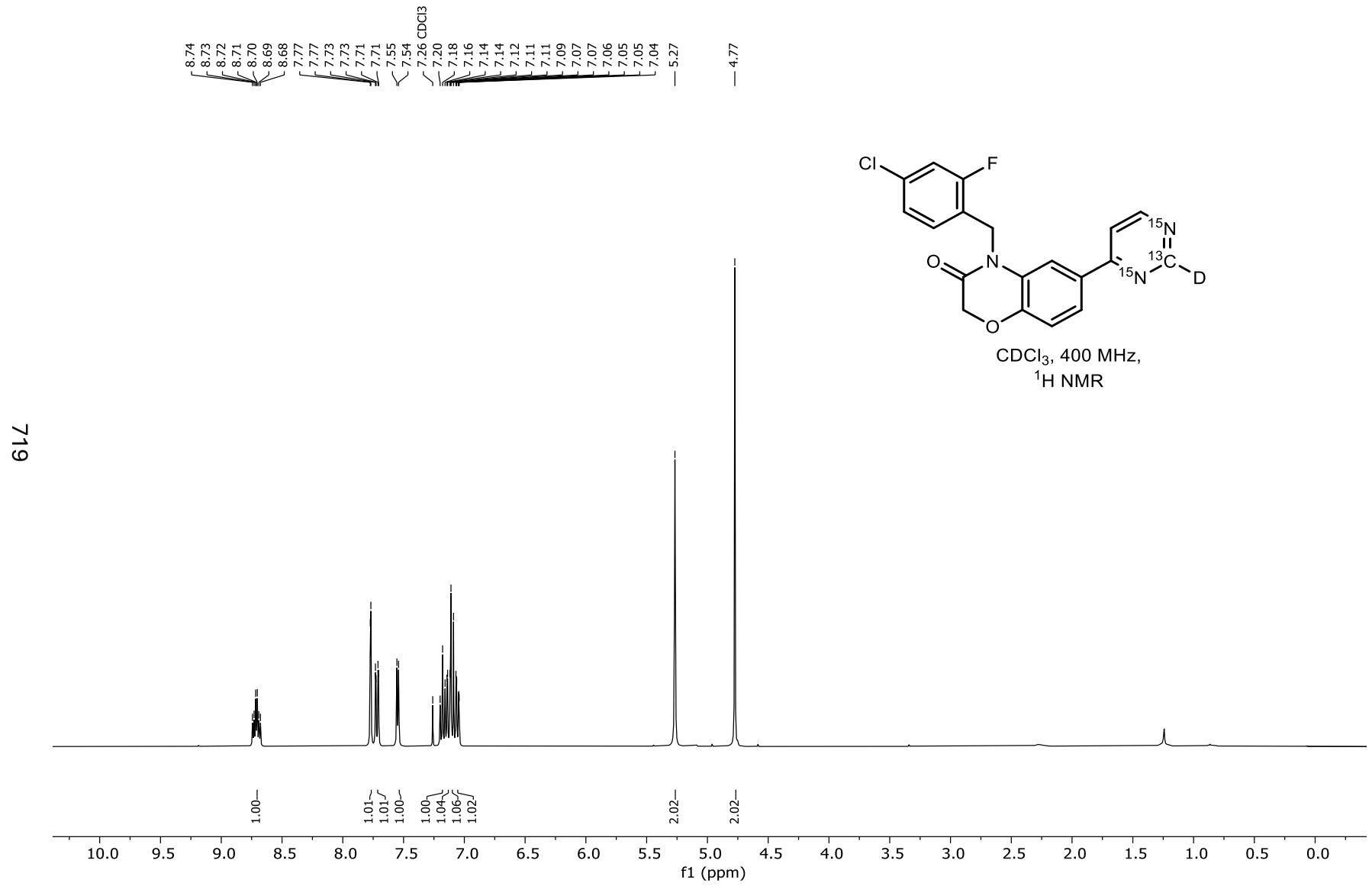
$CDCl_3$, 375 MHz,
^{19}F NMR

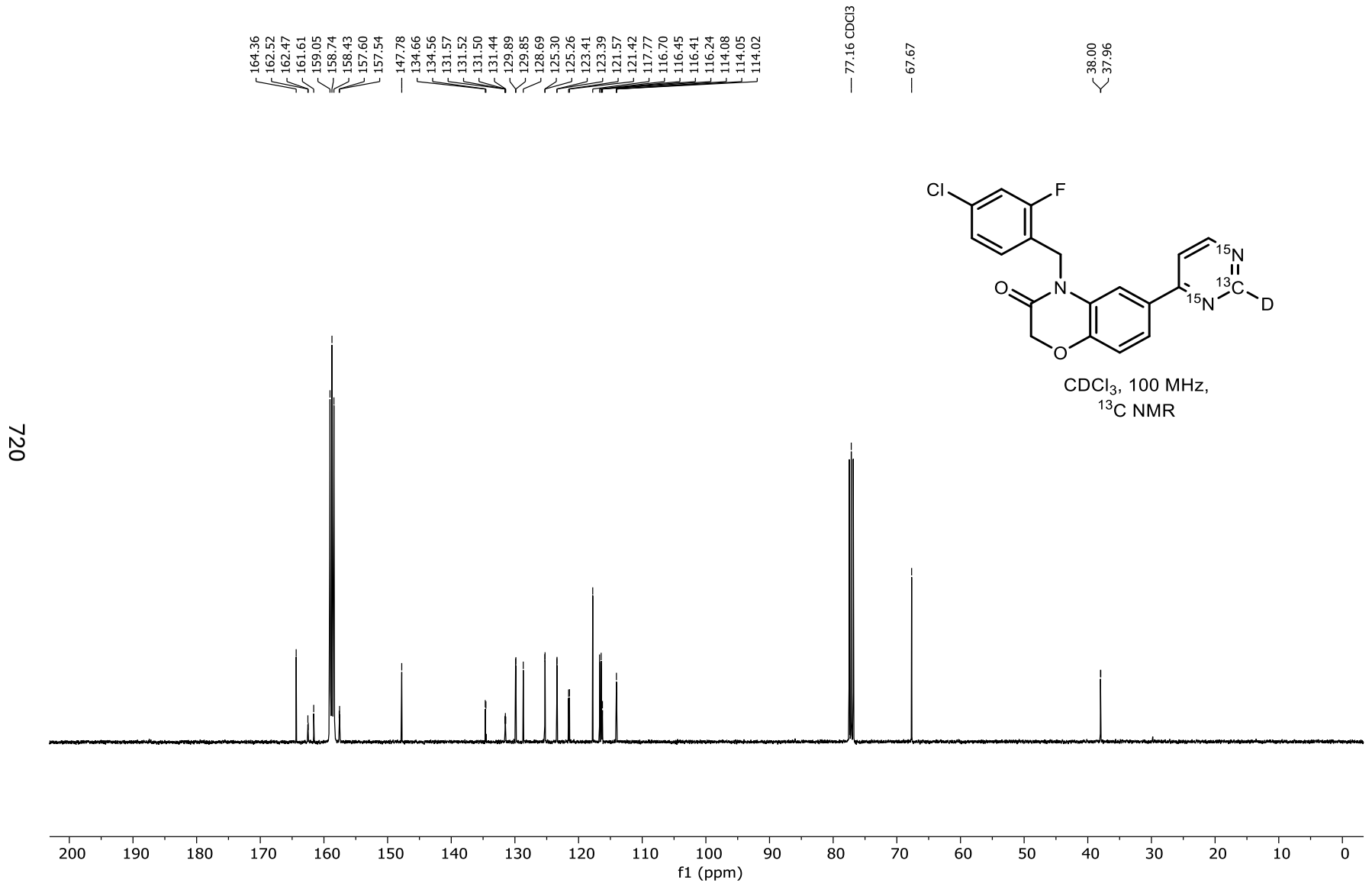
-115.53
-115.56
-115.58



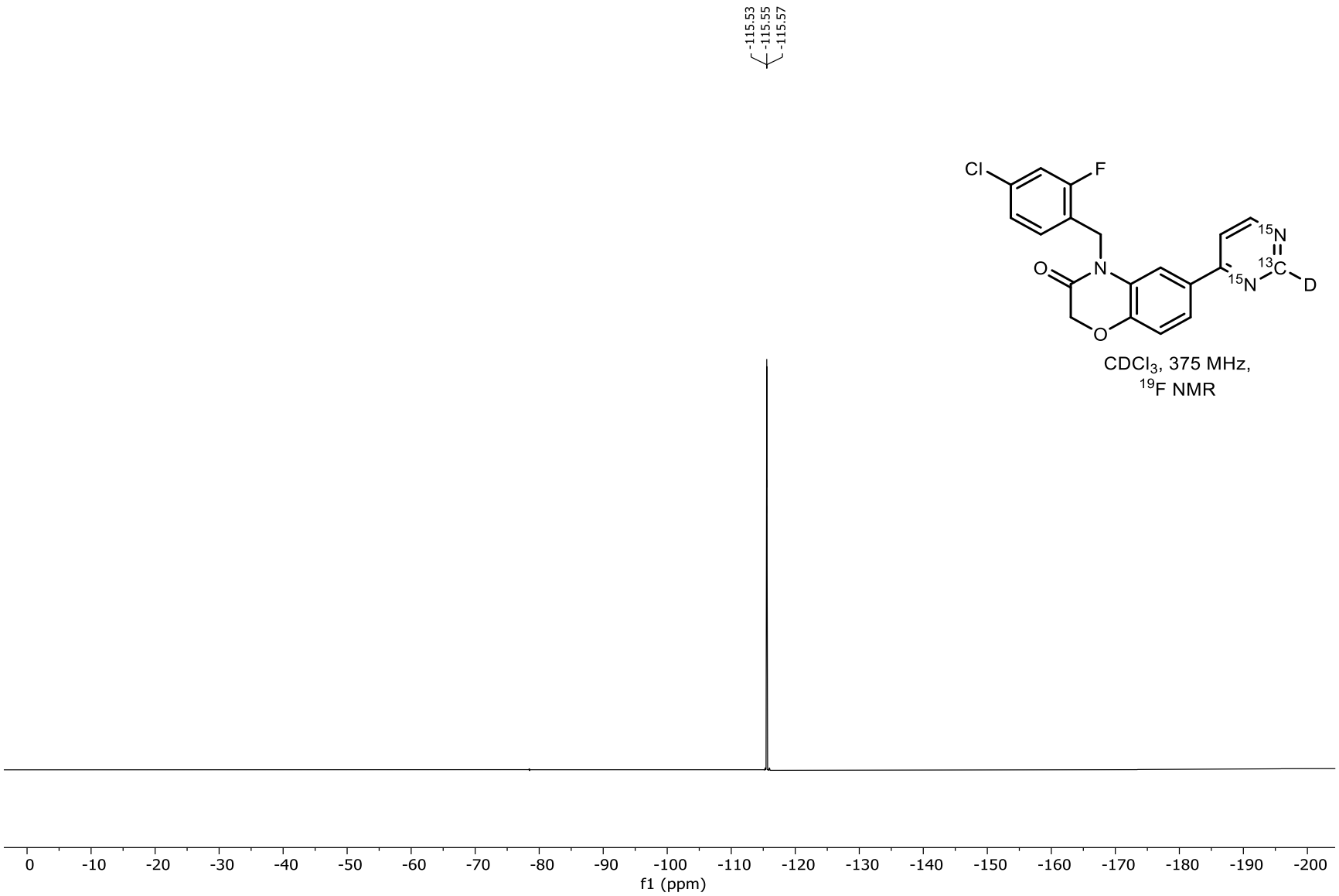
718


286.65
284.48
Cl
F
D
^{15}N
O
N
^{15}N
O
$CDCl_3$, 40 MHz,
^{15}N NMR
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

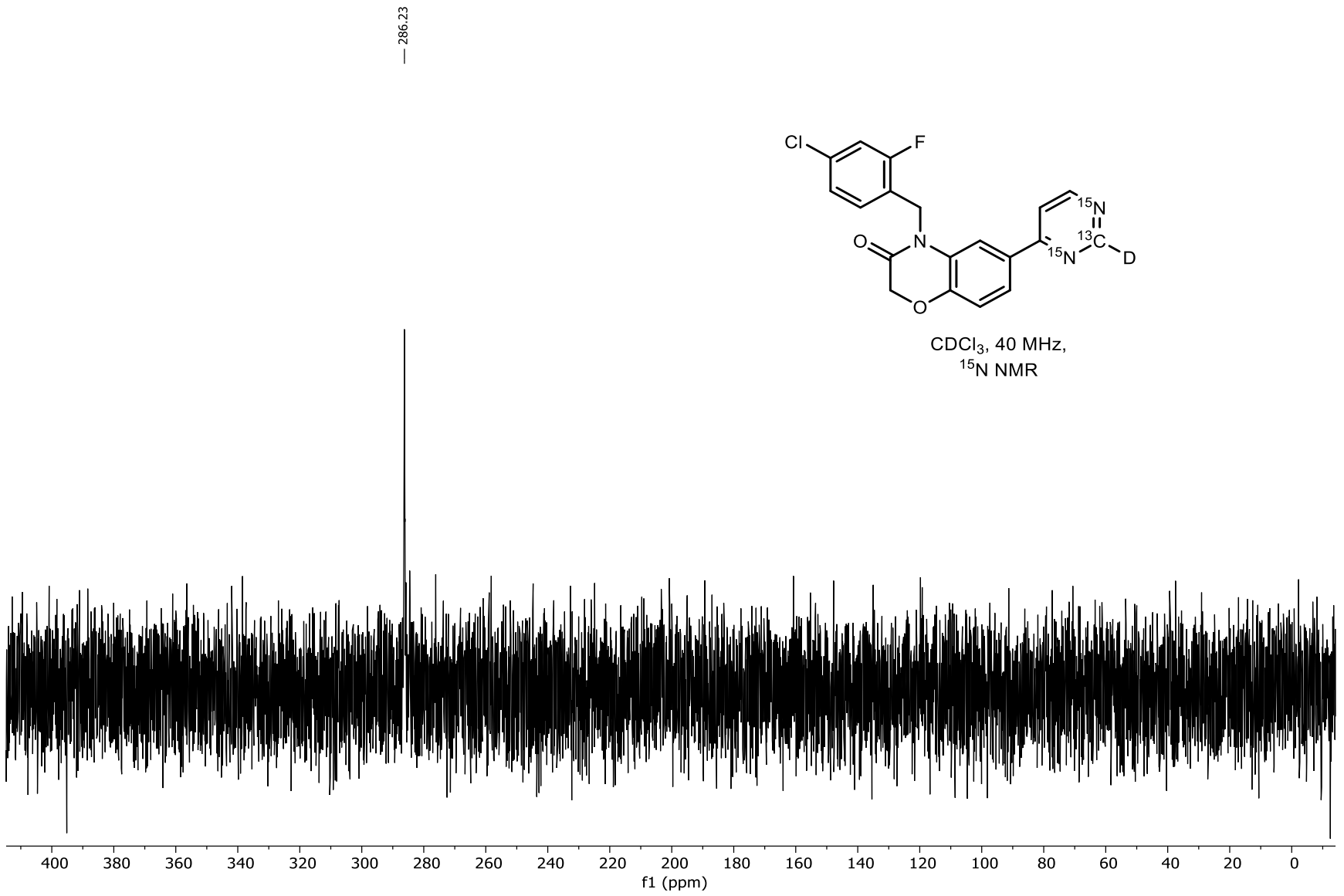

8.74
8.73
8.72
8.71
8.70
8.69
8.68
7.77
7.77
7.73
7.73
7.71
7.71
7.55
7.54
7.26 CDCl3
7.20
7.18
7.16
7.14
7.14
7.12
7.11
7.11
7.09
7.07
7.07
7.06
7.05
7.05
7.04
5.27
4.77
Cl
F
O
N
O
15N
13C
15N
D
CDCl3, 400 MHz,
1H NMR
1.00
1.01
1.01
1.00
1.00
1.04
1.06
1.02
2.02
2.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.36
162.52
162.47
161.61
159.05
158.74
158.43
157.60
157.54
147.78
134.66
134.56
131.57
131.52
131.50
131.44
129.89
129.85
128.69
125.30
125.26
123.41
123.39
121.57
121.42
117.77
116.70
116.45
116.41
116.24
114.08
114.05
114.02
77.16 CDCl3
67.67
38.00
37.96
Cl
F
O
N
O
15N
13C
15N
D
CDCl3, 100 MHz,
13C NMR
720
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

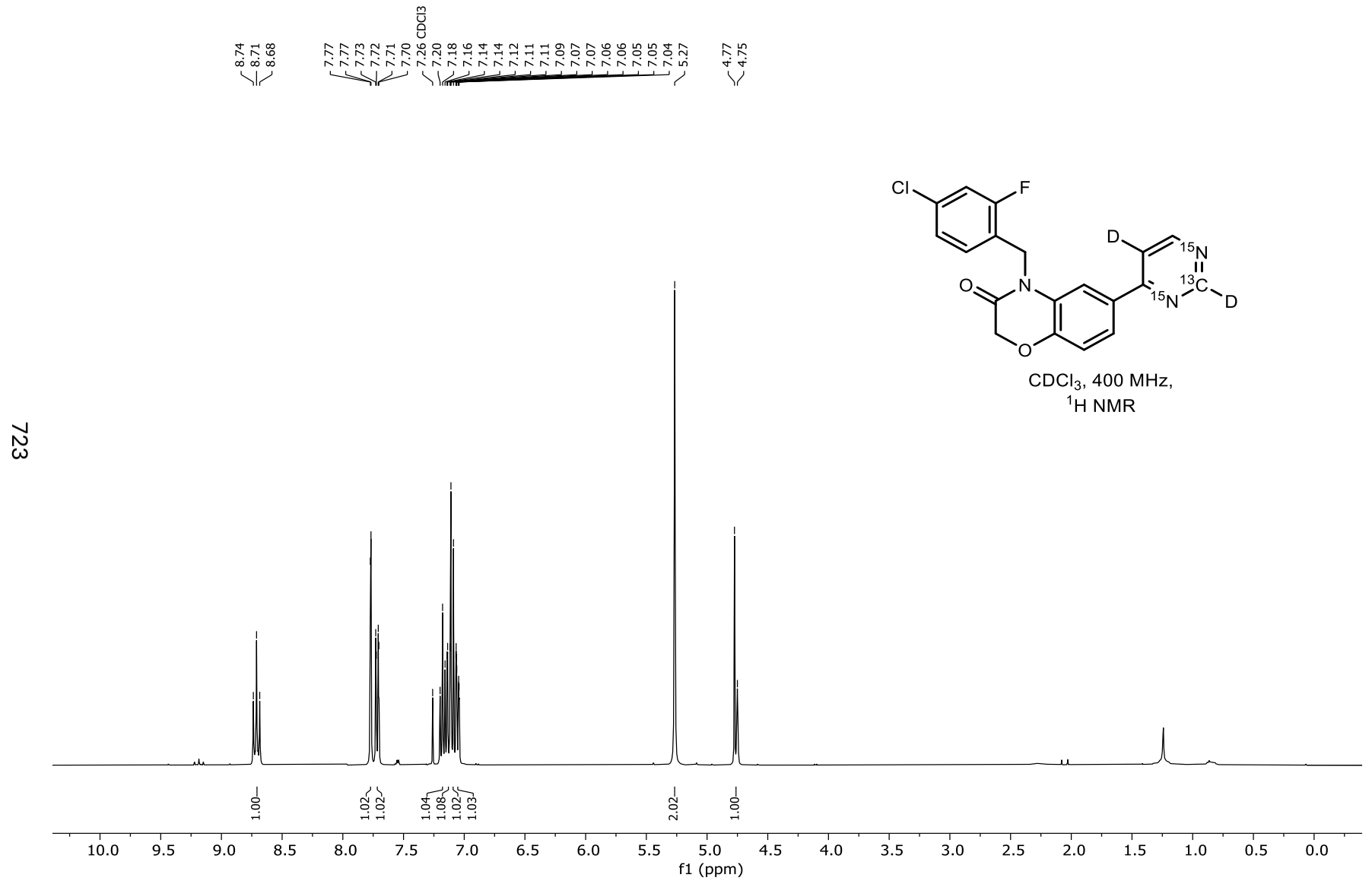
721

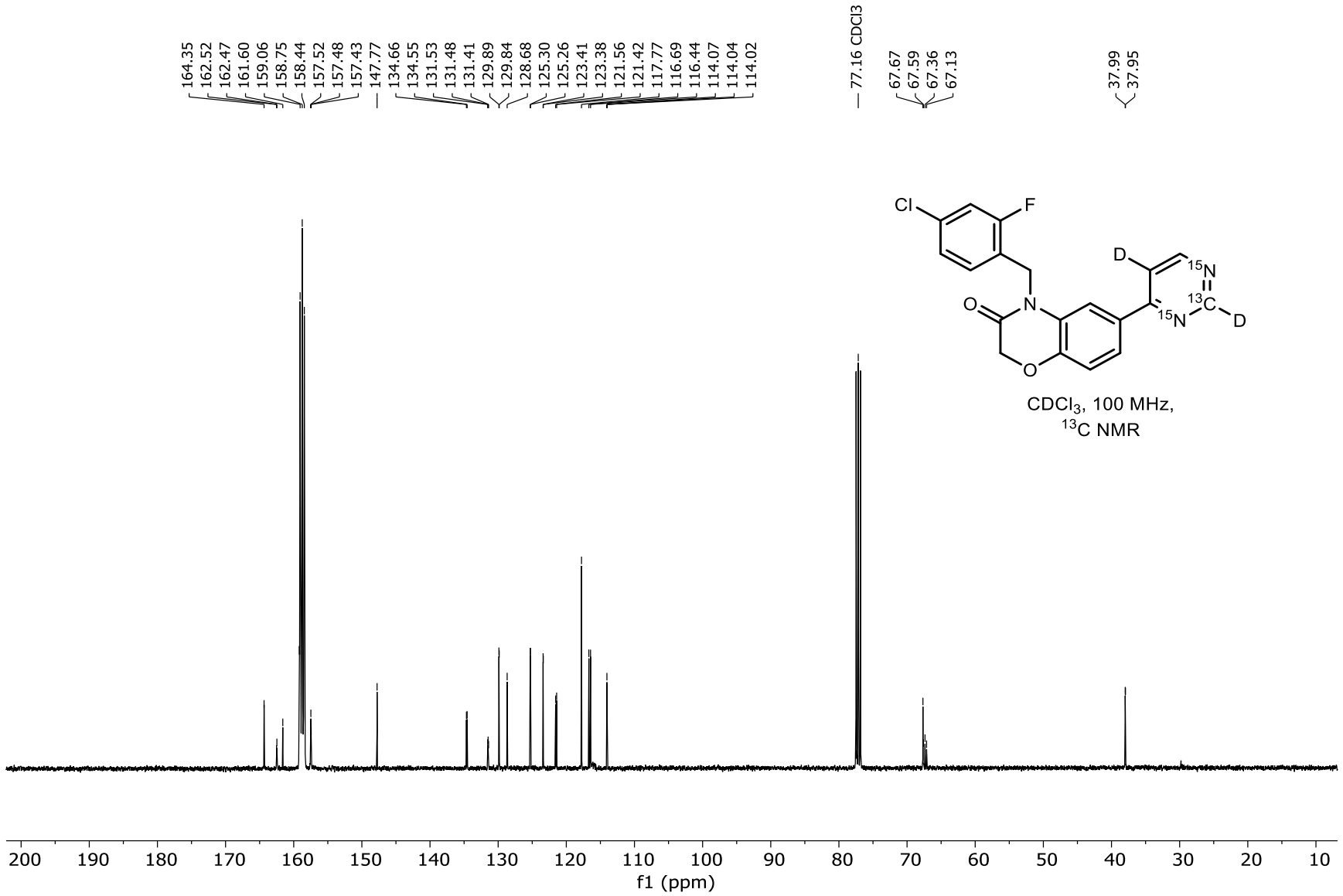

-115.53
-115.55
-115.57
Cl
F
O
N
O
^{15}N
^{13}C
^{15}N
D
$CDCl_3$, 375 MHz,
^{19}F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

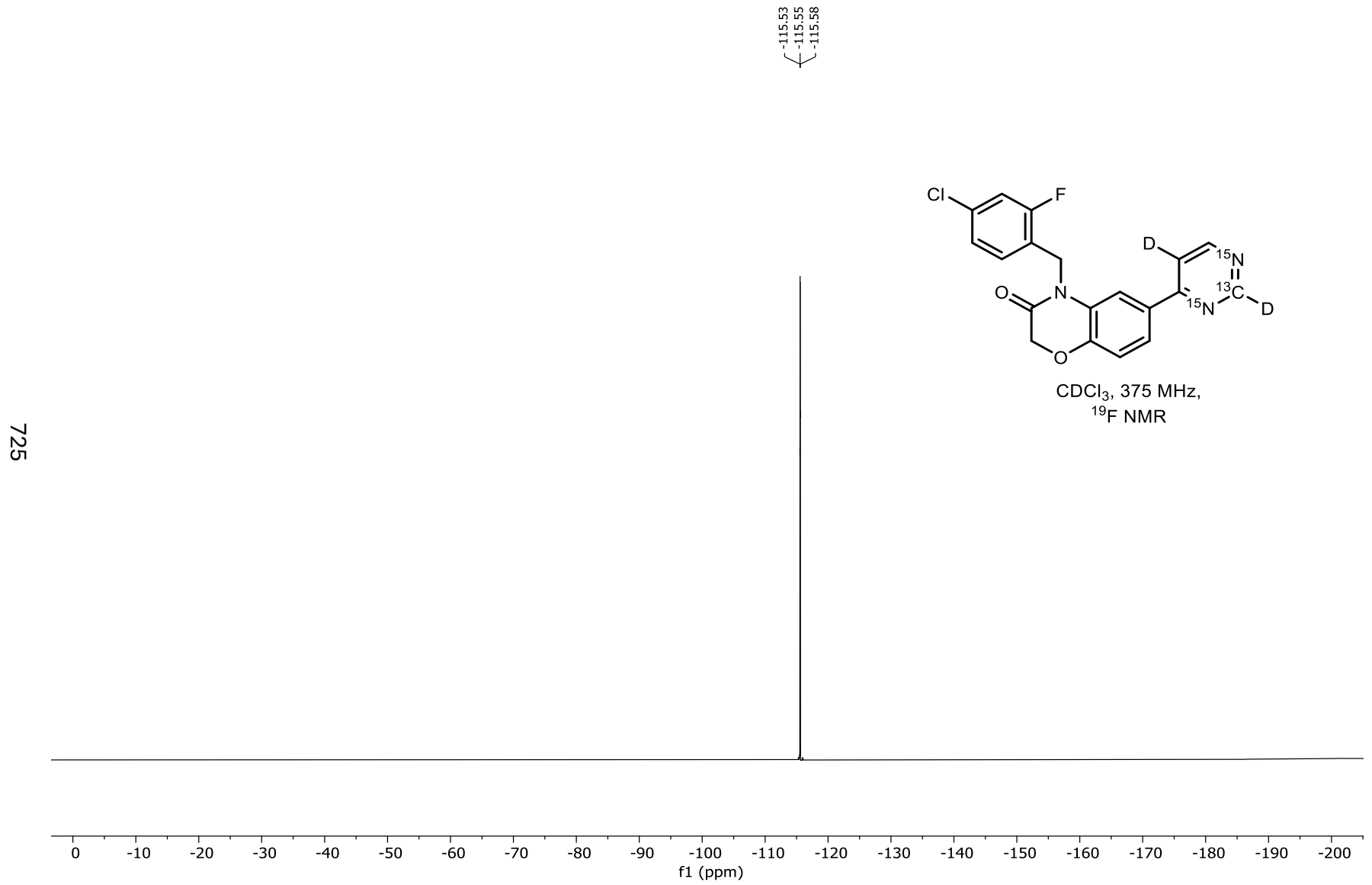
722

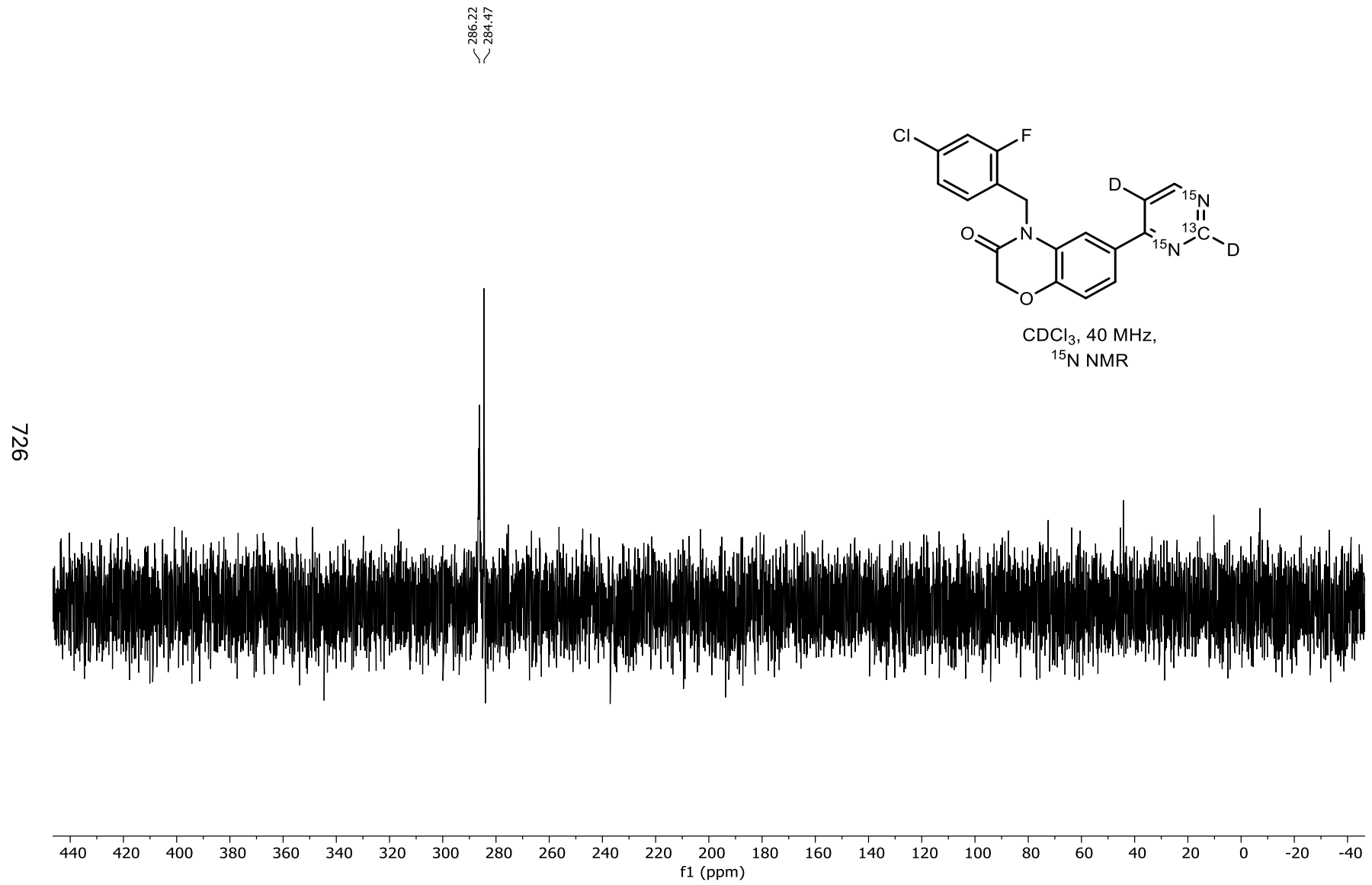


$CDCl_3$, 40 MHz,
^{15}N NMR


8.74
8.71
8.68
7.77
7.77
7.73
7.72
7.71
7.70
7.26 CDCl3
7.20
7.18
7.16
7.14
7.14
7.12
7.11
7.11
7.09
7.07
7.07
7.06
7.06
7.05
7.05
7.04
5.27
4.77
4.75
Cl
F
D
15N
13C
15N
D
O
N
O
CDCl3, 400 MHz,
1H NMR
1.00
1.02
1.02
1.04
1.08
1.02
1.03
2.02
1.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.35
162.52
162.47
161.60
159.06
158.75
158.44
157.52
157.48
157.43
147.77
134.66
134.55
131.53
131.48
131.41
129.89
129.84
128.68
125.30
125.26
123.41
123.38
121.56
121.42
117.77
116.69
116.44
114.07
114.04
114.02
77.16 CDCl3
67.67
67.59
67.36
67.13
37.99
37.95
Cl
F
D
15N
13C
15N
D
O
N
O
CDCl3, 100 MHz,
13C NMR
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


-115.53
-115.55
-115.58
Cl
F
D
^{15}N
O
N
^{13}C
^{15}N
D
O
$CDCl_3$, 375 MHz,
^{19}F NMR
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


286.22
284.47
Cl
F
D
^{15}N
O
N
^{13}C
D
^{15}N
O
$CDCl_3$, 40 MHz,
^{15}N NMR
726
440 420 400 380 360 340 320 300 280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 -20 -40
f1 (ppm)