DISSERTATION

NEW METHODS TO ACCESS FUNCTIONALIZED N-HETEROCYCLES

Submitted by
Chirag Patel
Department of Chemistry

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Doctoral Committee:

Advisor: Andrew McNally

Jeffrey Bandar
Melissa Reynolds
Matthew Kipper

ABSTRACT

NEW METHODS TO ACCESS FUNCTIONALIZED N-HETEROCYCLES

N-heterocycles are ubiquitous in pharmaceuticals and agrochemicals. Their prevalence is due to the unique properties they can impart to a molecule. Due to their ubiquity, it is vital that synthetic chemists be able to modify the structure of these valuable scaffolds. Despite a great deal of literature on the functionalization of these important motifs, challenges toward the functionalization of N-heterocycles remain.

Chapter 1 will highlight the importance of azaarenes in pharmaceuticals and explain the properties that make these structures so prevalent in drugs. Classical and modern methods to functionalize pyridines and diazines will also be discussed. Chapter 2 will describe the development of the phosphonium salt chemistry in the McNally lab and the use of these reactive intermediates to aminate pyridines and diazines via the Staudinger reaction.

Chapter 3 will introduce the concept of phosphorus ligand-coupling and briefly describe its previous application toward the synthesis of bis-heterobiaryls. This chapter will also cover the importance of fluoroalkyl groups in both the pharmaceutical and agrochemical industries. Current methods to fluoroalkylate azaarenes will be discussed, and the development of a novel fluoroalkylation strategy via a phosphorus ligand-coupling reaction will be explained. Finally, chapter 4 covers ongoing research into the synthesis of N-alkyl/aryl pyridiniums and their hydrogenation to N-substituted piperidines. The importance of N-substituted piperidines and the limitations to their synthesis are described.

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CHAPTER ONE

THE IMPORTANCE OF AZAARENES AND METHODS FOR THEIR FUNCTIONALIZATION

1.1 The Importance of Pyridines and Diazines in Pharmaceuticals

Nitrogen-containing heterocycles (N-heterocycles) are among the most prevalent motifs found in FDA-approved pharmaceuticals, naturally occurring biomolecules, and agrochemicals.[1,2] Pyridine, a 6-membered aromatic N-heterocycle, is the second most prominent heterocycle found in small-molecule therapeutics. In 2014, 59% of all FDA-approved pharmaceuticals contained at least one N-heterocycle, and of these 640 molecules, 62 contained at least one pyridine, Other aromatic N-heterocycles such as quinolines, pyrimidines, and other diazines are also widespread in the pharmaceutical industry.[2]

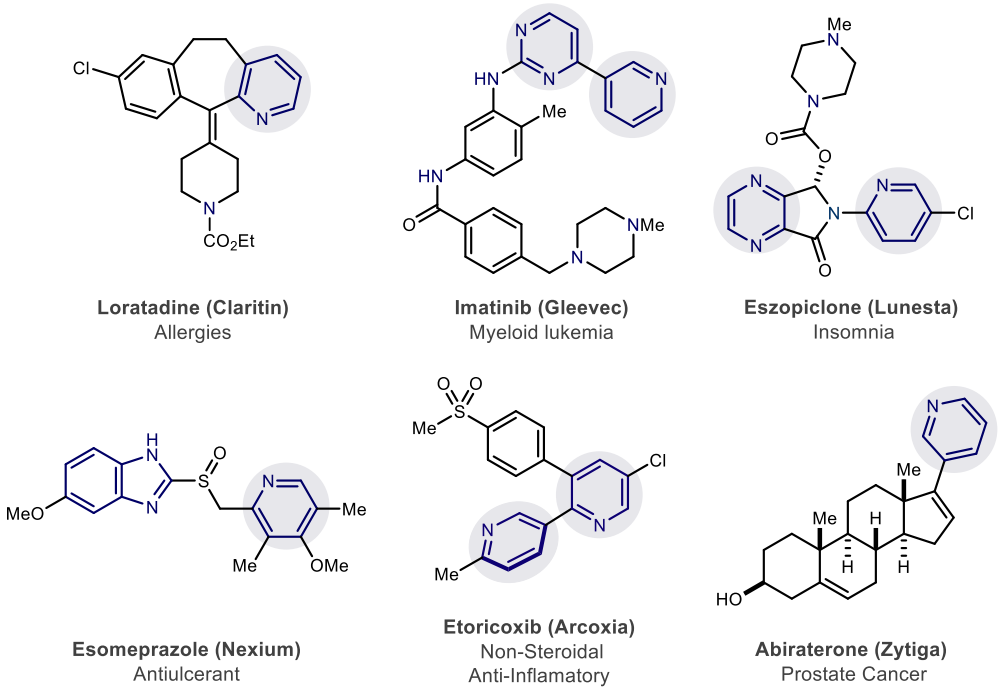


Figure 1.1. Examples of aromatic N-heterocycles in pharmaceuticals.

The prevalence of pyridine and related azaarenes in pharmaceuticals is due to the unique physical and chemical properties they can impart on a molecule.[2–4] Azaarenes are structurally similar to benzene, with at least one carbon atom replaced by a nitrogen atom. This small change can drastically alter the characteristics of the aromatic ring. The Nitrogen atom being more electronegative than carbon causes the entire π-system to be electron-deficient. The electronegative nature of nitrogen also causes an induced dipole toward the nitrogen atom. These properties cause the heterocycle to be more soluble in aqueous media and are often used in pharmaceuticals to render the drug molecule more water-soluble and thus more bioavailable.[5]

In addition to rendering the π-system electron-deficient and polarized, the nitrogen atom also has an sp^2 hybridized lone pair perpendicular to the heterocycle's π-system. The lone pair can impact how the molecule binds and interacts with biological targets. The nitrogen lone pair can act as a hydrogen bond acceptor and make key binding interactions inside an enzyme binding pocket. In 2011, medicinal chemists at Amgen published on the optimization of a benzothiazole phosphoinositide 3-kinase (PI3K) inhibitor.[6] The replacement of a phenyl linker with pyridine caused a 30 fold increase in potency toward the target enzyme. They rationalized that this increase in potency was due to a hydrogen bonding interaction between the pyridine nitrogen and an ordered water molecule between Asp841 and Tyr867 (**Figure 1.2**).

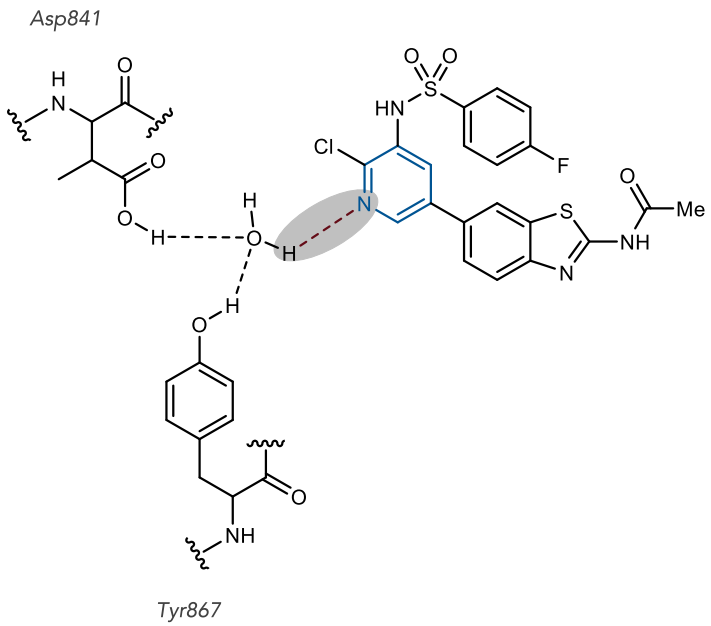


Figure 1.2. Hydrogen bond interaction between Asp841 and Tyr867 of Phosphoinositide 3-kinase ∝ (PI3K∝) and pyridine nitrogen through an ordered water molecule.

During the drug discovery process, medicinal chemists make systematic alterations to the molecular structure to tune the properties of the drug candidate, such as efficacy, stability, and bioavailability. Drugs that must pass through the liver are often oxidized by cytochrome P-450 (CYP-450).[7–9] This enzyme class will oxidize weak C-H bonds into hydroxyl groups, increasing the metabolite's water solubility. The metabolite can then be more easily excreted from the body. The C-H bonds of electron-rich arenes are often susceptible to this form of metabolism, and medicinal chemists must find ways to limit this form of metabolic clearance. One technique commonly used is to swap a functional group in the molecule with a corresponding bioisostere that can make similar interactions but change the overall characteristics of the molecule. Azaarenes are often used as bioisosteres of arenes. The more electron-deficient nature of these N-heterocycles makes them less susceptible to oxidative metabolism by CYP-450 enzymes, thereby

allowing the drug molecule to remain in the body for a longer duration before being excreted. In this way, N-heterocycles are installed in drug molecules to regulate their metabolic stability.

1.2 Classical Methods for Direct Pyridine and Azaarene Functionalization

Given the prevalence of N-heterocycles in pharmaceuticals, methods that allow for the functionalization of these important motifs are highly desirable. Functionalization strategies can be categorized as either indirect or direct methods. Indirect methods require a pre-installed functional handle on the N-heterocycle, which can be derivatized into the desired functional group. Direct methods allow for the installation of the functional group directly from the C-H bond. The latter strategies are most desirable, but several limitations exist for the direct functionalization of azaarenes (**Figure 1.3**).[10] As previously stated, pyridines have an electron-deficient π-system due to the electronegativity of the nitrogen atom. This electron deficiency makes electrophilic aromatic substitution (EAS) reactions far more difficult for pyridines than their more electron-rich benzene counterparts. The nitrogen lone pair can also make metal-catalyzed processes difficult, as it can ligate to the metal catalyst and shut down the catalytic cycle. Radical additions to pyridines, Minisci reactions, allow for the direct functionalization of pyridines; however, these methods often lead to undesired regioisomers and multiple-addition products, which can be challenging to separate.

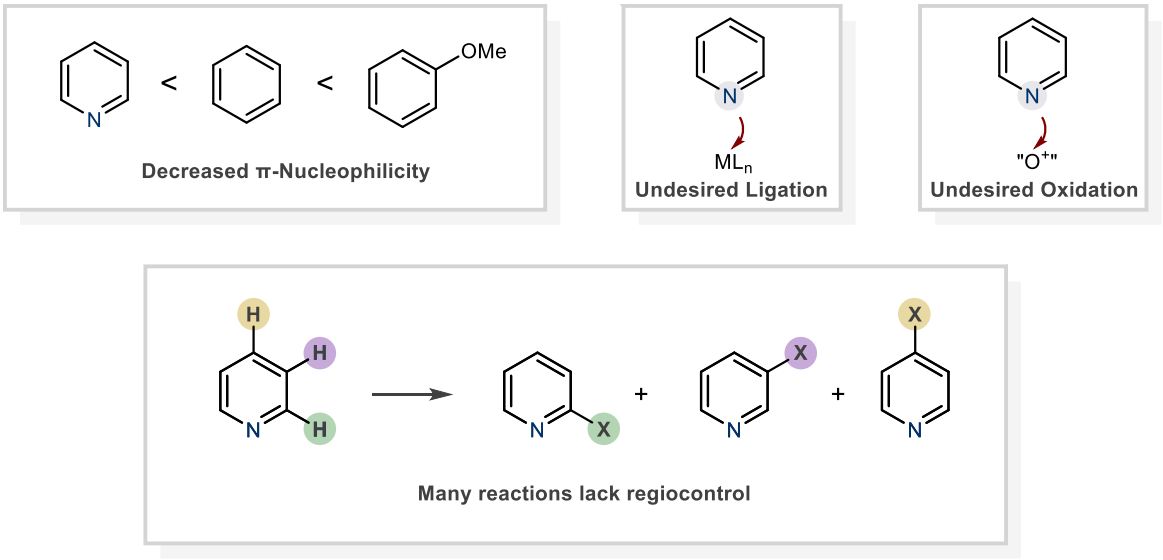


Figure 1.3. Challenges toward functionalizing pyridines.

Despite their difficulty, EAS reactions to directly functionalize pyridines have been developed, such as halogenation. Halogenation is achieved by reaction between the aromatic π-system of the pyridine and an electrophilic halogen source. The resulting carbon-halogen bond is highly desirable as it can be used as a functional handle for several different bond-forming reactions such as cross-coupling reactions, nucleophilic aromatic substitution reactions, and radical processes. As stated above, EAS reactions are far more difficult on N-heterocycles. While these reactions can typically be run at room temperature for electron-rich aromatic systems, the conditions required to halogenate pyridines are considerably harsher. Halogenation requires heating the pyridine in sulfuric acid with elemental bromine as the halogen source, resulting in a mixture of mono and polybrominated pyridine (**Figure 1.4**).[11] The forceful conditions of this reaction limit the scope to simple building block pyridines and would be challenging to use on more complex molecules.

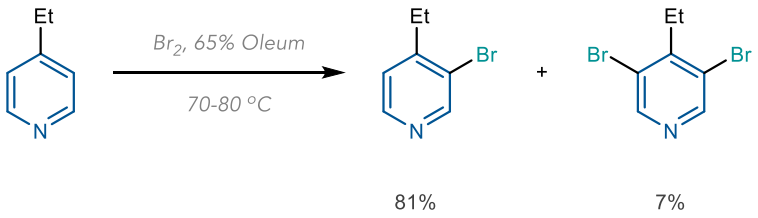


Figure 1.4. EAS bromination of pyridine.

The Chichibabin reaction represents another classical method for direct pyridine functionalization.[12] Pyridine is refluxed with sodium amide in xylene to install an amine at the 2-position selectively. This process starts with the amine attacking pyridine at the 2-position to form a Meisenheimer intermediate. The intermediate then eliminates a hydride and regains aromaticity (**Figure 1.5**). This method allows access to valuable aminated heterocycles with complete selectivity for the 2-position; however, a significant drawback is the use of $NaNH_2$, which is strongly basic and limits the functional group tolerance of this method.

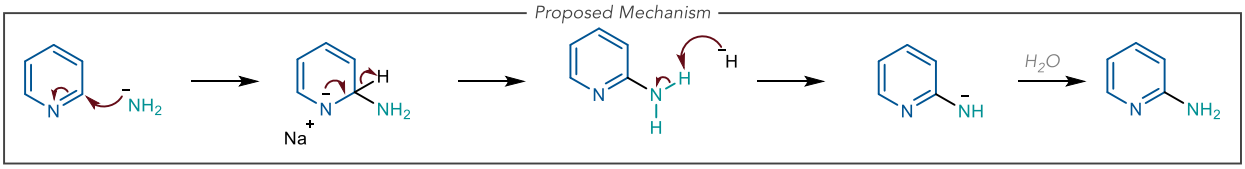


Figure 1.5. Chichibabin amination of pyridine with proposed mechanism.

Among the most common direct functionalization strategies for pyridines is the metalation-trapping process.[13] In these processes, a magnesium or lithium base is used to deprotonate the n-heterocycle, and the subsequent anion is trapped with an electrophile (**Figure 1.6**).[14] Regio-selectivity can be controlled by the presence of a directing group pre-installed on the pyridine. The directing group can coordinate to the base and guide it to metalate at a specific position on the

ring. An alternative strategy to control regioselectivity was recently reported by Knochel, in which a bulky Lewis acid can coordinate to the Lewis basic nitrogen lone pair and sterically shield the 2- and 3-positions, leading to selective metalation at the 4-position of the ring.[15] These metalated intermediates can then be used to trap electrophiles or can be used in a Negishi cross-coupling reaction to furnish 4-functionalized pyridines.[16]

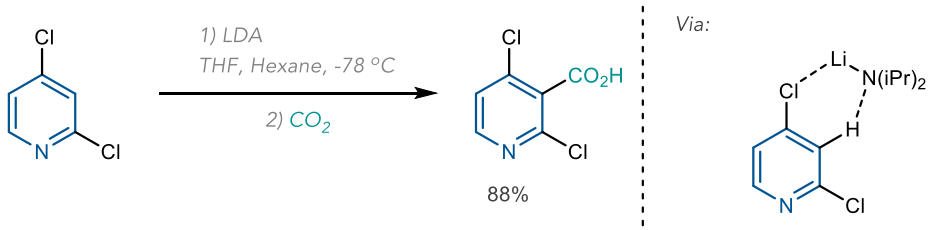


Figure 1.6. Carboxylation of pyridine via directed metalation.

1.3 Recent Advances in Direct Pyridine and Azaarene Functionalization

A recent development in direct pyridine functionalization has been the application of photoredox catalysis to the Minisci reaction. By utilizing a photocatalyst excited by light, chemists have generated radical species in a much milder fashion than the typically strong oxidants and high temperatures previously required. The Merck process group used such an approach to accomplish a late-stage N-heterocycle alkylation.[17] Using an iridium photocatalyst excited by blue (450 nm) light, Ir^{III} was excited to Ir^{III*}. *Tert*-butyl peracetate (*t*PBA) decomposes to *tert*-butoxy radical via a proton-coupled electron transfer (PCET) event with the Ir^{III*} photocatalyst. The resulting *tert*-butoxy radical then undergoes β-scission to give a methyl radical which adds to the protonated pyridine. The Ir^{IV} oxidizes the amino-radical cation to give alkylated azaarene product and regenerate the active catalyst. To illustrate the method's applicability to late-stage N-heterocycle alkylation, the group showed the alkylation on several FDA-approved pharmaceuticals, including

Eszopiclone, Varenicline, and Loratadine (**Figure 1.7**). The method still gave mixtures of regioisomers but showed excellent functional group tolerance.

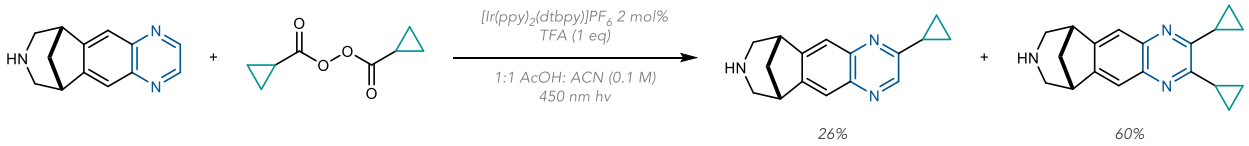


Figure 1.7. Photoredox alkylation of Varenicline.

John Hartwig recently developed a 2-selective fluorination reaction for azaarenes based on the Chichibabin reaction previously discussed.[18] The desired transformation is achieved by reacting the azaarene with commercially available silver difluoride (AgF_2). The AgF_2 first coordinates with the nitrogen lone pair to form an activated intermediate. Addition of a fluoride anion to the 2-position of the activated azaarene and subsequent hydride abstraction by a second equivalent of AgF_2 forms the desired fluorinated azaarene product (**Figure 1.8**). These fluorinated products are highly valuable, as S_NAr with a range of nucleophiles allows access to a variety of 2-substituted azaarenes.

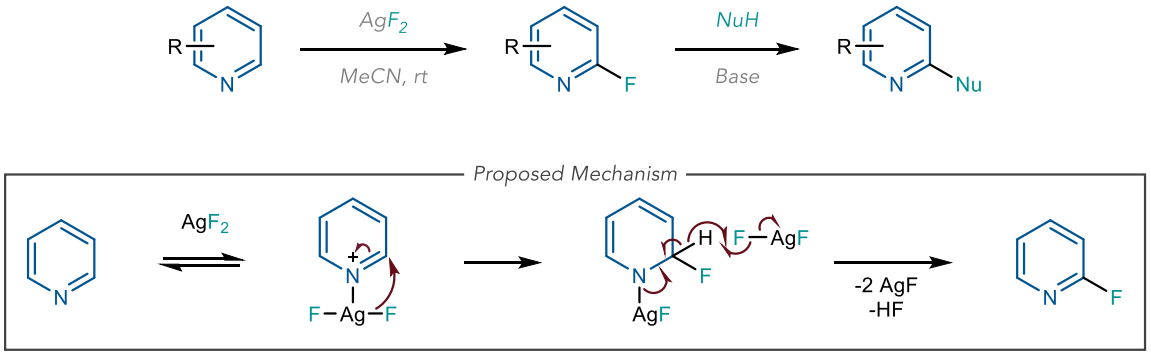


Figure 1.8. AgF_2 mediated 2-selective fluorination of pyridine.

An additional 2-selective functionalization strategy for azaarenes was published by Patrick Fier.[19] This process allows for the direct nucleophilic addition to the 2-position of pyridines and

diazines by activation with a bifunctional aldoxime reagent. The azaarene is first activated by reaction through the nitrogen lone-pair with the ∝-chloro *O*-methylsulfonyl aldoxime. The resulting pyridinium salt then undergoes nucleophilic attack at the 2-position. Treatment with a base and decomposition of the activating group gives the desired 2-functionalized azaarene (**Figure 1.9**). Here, Fier utilizes NaCN as the nucleophile on a broad range of azaarenes to demonstrate the scope of the reaction but also shows preliminary results on several other nucleophiles such as Grignard reagents, organozinc reagents, and alkoxides.

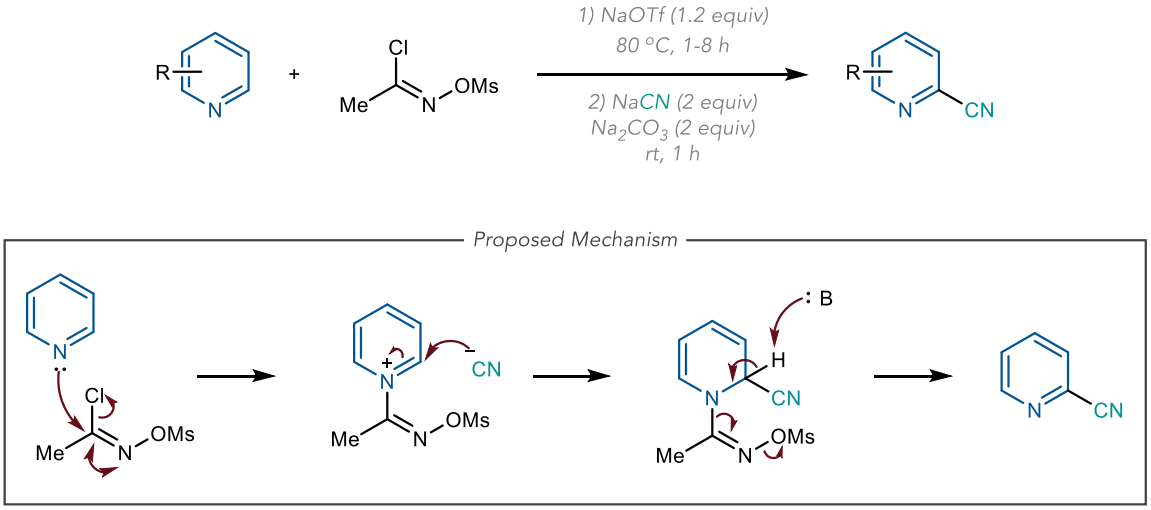


Figure 1.9. Patrick Fier's 2-selective cyanation of pyridine and proposed mechanism.

A highly desirable transformation for azaarenes is the iridium-catalyzed C-H borylation developed by Ishiyama, Miyaura, and Hartwig.[20] Using bis(pinacolato)-diboron (B_2pin_2), an Iridium catalyst, and a bipyridine ligand, Hartwig and coworkers were able to accomplish the desired borylation selectively at the 3-position. C-H activation occurs selectively at the 3-position, and subsequent reductive elimination furnishes the borylated azaarene. Although the reaction is generally 3-selective, mixtures of 2, 3, and 4-borylated pyridines were obtained in some cases depending on the substitution pattern of the pyridine.

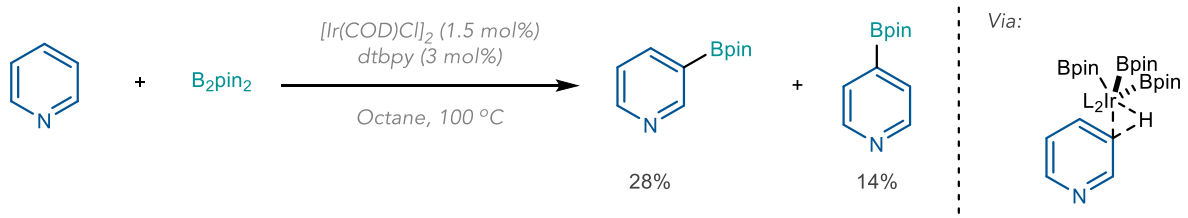


Figure 1.10. Iridium-catalyzed borylation of pyridine.

1.4 4-Selective Strategies for Pyridine Functionalization

Most methods, both classical and modern, for direct pyridine functionalization are either 2- or 3-selective. Methods that directly functionalize the 4-position are comparatively rare. One strategy for the 4-selective functionalization of pyridine is first to react the pyridine nitrogen with an electrophile to form a pyridinium. This activation makes the ring more electrophilic. The addition of a nucleophile followed by oxidation can allow for the 4-selective functionalization of azaarenes. Daniel Comins used such a strategy to achieve the 4-selective alkylation of nicotine.[21] Nicotine is first reacted with pivaloyl chloride to form an acyl pyridinium. An alkyl cuprate, generated from the corresponding alkyl Grignard and copper (I) bromide, then adds to the 4-position. Refluxing the dearomatized intermediate in the presence of elemental sulfur then gives the 4-alkylated nicotine product.

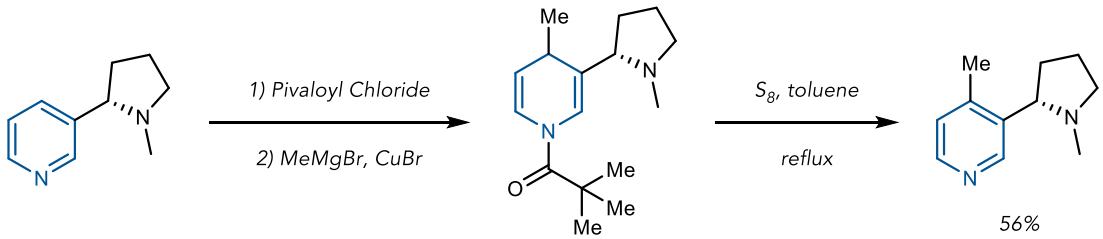


Figure 1.11. Comins' 4-selective methylation of nicotine.

Kanai developed a similar strategy for the 4-selective fluoroalkylation of pyridines.[22] A bulky boron Lewis acid is used to activate the pyridine for nucleophilic attack and sterically shield the 2- and 6-positions to maintain 4-selectivity. Tetrabutylammonium difluorotriphenylsilicate reacts

with trimethylsilyl trifluoromethane (Rupert's reagent) to form trifluoromethyl anion that selectively adds to the 4-position of the activated pyridine. An iodonium salt is used to oxidize the dearomatized intermediate to give the fluoroalkylated pyridine. Despite the steric shielding of the bulky boron Lewis acid, in the case of 3-substituted pyridines, significant amounts of the 2- and 6-regioisomers were obtained.

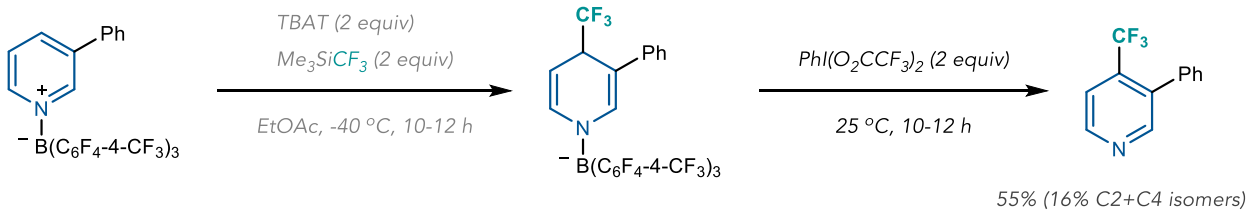


Figure 1.12. Kanai's 4-trifluoromethylation of 3-phenyl pyridine.

Nakao used a similar steric shielding approach for his 4-selective alkylation of pyridines.[23] Here, a bulky aluminum Lewis acid is used to activate the pyridine and block the 2- and 3-positions from nucleophilic attack. The pyridine nitrogen coordinates to methylaluminum bis (2, 6-di-t-butyl4-methylphenoxide) (MAD), and then a nickel catalyst can oxidatively insert into the 4-position C-H bond. Subsequent migratory insertion of an alkene and reductive elimination give the alkylated products (**Figure 1.13**). The secondary isomer is formed in some cases as a minor product.

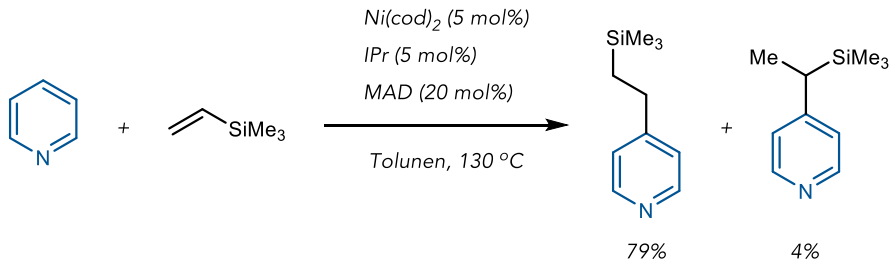


Figure 1.13. Nakao's nickel/Lewis acid-catalyzed 4-alkylation of pyridines.

In 2019, Martin reported a reaction that selectively installs a silyl group at the 4-positon of azaarenes using a silylborane reagent.[24] The silylborane reagent, $Me_2PhSiBpin$, is activated by potassium hexamethyldisilazane (KHMDS), and the pyridine nitrogen is activated through coordination with the Potassium cation. The resulting boronate species adds the silyl group to the activated pyridine to form the 4-silylated product. Interestingly, when the reaction is run in DME, the silylation occurs selectively at the 4-position of pyridine, but when the solvent is changed to dioxane, the selectivity switches to the 2-position.

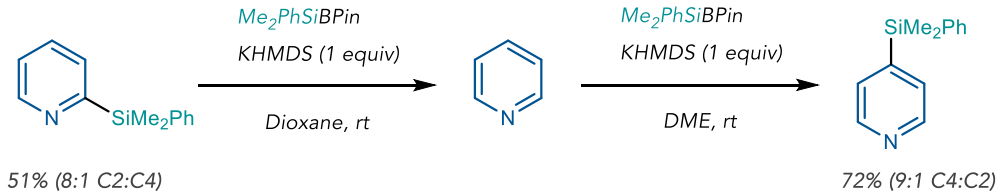


Figure 1.14. Martin's site-selective C-H sialylation of pyridine.

1.5 Conclusion

Due to their prevalence in pharmaceuticals, pyridines and related diazines remain of synthetic interest. Current methods to functionalize these valuable motifs are discussed. While 2- and 3-selective strategies are numerous and well explored, 4-selective functionalization strategies remain underexplored. The McNally group provides a solution to this problem by installing phosphonium salts to the 4-position of azaarenes and performing subsequent derivatizations.

REFERENCES

(1) Baumann, M.; Baxendale, I. R. An Overview of the Synthetic Routes to the Best Selling Drugs Containing 6-Membered Heterocycles. *Beilstein J. Org. Chem.* **2013**, *9* (1), 2265–2319. https://doi.org/10.3762/bjoc.9.265.

(2) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57* (24), 10257–10274. https://doi.org/10.1021/jm501100b.

(3) Smith, D. A. *Metabolism, Pharmacokinetics and Toxicity of Functional Groups*; 2010. https://doi.org/10.1039/9781849731102.

(4) Thomas, G. Medicinal Chemistry: An Introduction, 2nd Edition | Wiley https://www.wiley.com/en-us/Medicinal+Chemistry%3A+An+Introduction%2C+2nd+Edition-p-9780470025970 (accessed 2021 -08 -16).

(5) Patrick, G. L. Introduction to Medicinal Chemistry 5th edition https://www.textbooks.com/Introduction-to-Medicinal-Chemistry-5th-Edition/9780199697397/Graham-L-Patrick.php (accessed 2021 -08 -16).

(6) D'Angelo, N. D.; Kim, T.-S.; Andrews, K.; Booker, S. K.; Caenepeel, S.; Chen, K.; D'Amico, D.; Freeman, D.; Jiang, J.; Liu, L.; McCarter, J. D.; San Miguel, T.; Mullady, E. L.; Schrag, M.; Subramanian, R.; Tang, J.; Wahl, R. C.; Wang, L.; Whittington, D. A.; Wu, T.; Xi, N.; Xu, Y.; Yakowec, P.; Yang, K.; Zalameda, L. P.; Zhang, N.; Hughes, P.; Norman, M. H. Discovery and Optimization of a Series of Benzothiazole Phosphoinositide

3-Kinase (PI3K)/Mammalian Target of Rapamycin (MTOR) Dual Inhibitors. *J. Med. Chem.* **2011**, *54* (6), 1789–1811. https://doi.org/10.1021/jm1014605.

(7) Zanger, U. M.; Schwab, M. Cytochrome P450 Enzymes in Drug Metabolism: Regulation of Gene Expression, Enzyme Activities, and Impact of Genetic Variation. *Pharmacology & Therapeutics* **2013**, *138* (1), 103–141. https://doi.org/10.1016/j.pharmthera.2012.12.007.

(8) St. Jean, D. J.; Fotsch, C. Mitigating Heterocycle Metabolism in Drug Discovery. *J. Med. Chem.* **2012**, *55* (13), 6002–6020. https://doi.org/10.1021/jm300343m.

(9) Lin, J. H.; Lu, A. Y. H. Role of Pharmacokinetics and Metabolism in Drug Discovery and Development. *Pharmacol Rev* **1997**, *49* (4), 403–449.

(10) Brahmachari, G. Green Synthetic Approaches for Biologically Relevant Heterocycles - 1st Edition https://www.elsevier.com/books/green-synthetic-approaches-for-biologically-relevant-heterocycles/brahmachari/978-0-12-800070-0 (accessed 2021 -08 -16).

(11) Grimmett, M. R. Halogenation of Heterocycles: II. Six- and Seven-Membered Rings. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press, 1993; Vol. 58, pp 271–345. https://doi.org/10.1016/S0065-2725(08)60288-3.

(12) Mcgill, C. K.; Rappa, A. Advances in the Chichibabin Reaction. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press, 1988; Vol. 44, pp 1–79. https://doi.org/10.1016/S0065-2725(08)60261-5.

(13) Schlosser, M.; Mongin, F. Pyridine Elaboration through Organometallic Intermediates: Regiochemical Control and Completeness. *Chem. Soc. Rev.* **2007**, *36* (7), 1161–1172. https://doi.org/10.1039/B706241A.

(14) Marzi, E.; Bigi, A.; Schlosser, M. Strategies for the Selective Functionalization of Dichloropyridines at Various Sites. *European Journal of Organic Chemistry* **2001**, *2001* (7), 1371–1376. https://doi.org/10.1002/1099-0690(200104)2001:7<1371::AID-EJOC1371>3.0.CO;2-E.

(15) Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. Highly Selective Metalations of Pyridines and Related Heterocycles Using New Frustrated Lewis Pairs or Tmp-Zinc and Tmp-Magnesium Bases with BF3·OEt2. *Angewandte Chemie International Edition* **2010**, *49* (32), 5451–5455. https://doi.org/10.1002/anie.201002031.

(16) Luzung, M. R.; Patel, J. S.; Yin, J. A Mild Negishi Cross-Coupling of 2-Heterocyclic Organozinc Reagents and Aryl Chlorides. *J. Org. Chem.* **2010**, *75* (23), 8330–8332. https://doi.org/10.1021/jo1018798.

(17) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. Late-Stage Functionalization of Biologically Active Heterocycles Through Photoredox Catalysis. *Angewandte Chemie International Edition* **2014**, *53* (19), 4802–4806. https://doi.org/10.1002/anie.201402023.

(18) Fier, P. S.; Hartwig, J. F. Selective C-H Fluorination of Pyridines and Diazines Inspired by a Classic Amination Reaction. *Science* **2013**, *342* (6161), 956–960. https://doi.org/10.1126/science.1243759.

(19) Fier, P. S. A Bifunctional Reagent Designed for the Mild, Nucleophilic Functionalization of Pyridines. *J. Am. Chem. Soc.* **2017**, *139* (28), 9499–9502. https://doi.org/10.1021/jacs.7b05414.

(20) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. Mild Iridium-Catalyzed Borylation of Arenes. High Turnover Numbers, Room Temperature

Reactions, and Isolation of a Potential Intermediate. *J. Am. Chem. Soc.* **2002**, *124* (3), 390–391. https://doi.org/10.1021/ja0173019.

(21) Comins, D. L.; King, L. S.; Smith, E. D.; Février, F. C. Synthesis of C-4 Substituted Nicotine Derivatives via an N-Acylpyridinium Salt of (S)-Nicotine. *Org. Lett.* **2005**, *7* (22), 5059–5062. https://doi.org/10.1021/ol0520469.

(22) Nagase, M.; Kuninobu, Y.; Kanai, M. 4-Position-Selective C–H Perfluoroalkylation and Perfluoroarylation of Six-Membered Heteroaromatic Compounds. *J. Am. Chem. Soc.* **2016**, *138* (19), 6103–6106. https://doi.org/10.1021/jacs.6b01753.

(23) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. Selective C-4 Alkylation of Pyridine by Nickel/Lewis Acid Catalysis. *J. Am. Chem. Soc.* **2010**, *132* (39), 13666–13668. https://doi.org/10.1021/ja106514b.

(24) Gu, Y.; Shen, Y.; Zarate, C.; Martin, R. A Mild and Direct Site-Selective Sp2 C–H Silylation of (Poly)Azines. *J. Am. Chem. Soc.* **2019**, *141* (1), 127–132. https://doi.org/10.1021/jacs.8b12063.

CHAPTER TWO

AMINATION OF PYRIDINES AND DIAZINES VIA HETEROCYCLIC PHOSPHONIUM SALTS

2.1 The Importance of Amines in Pharmaceuticals

The amine functional group consists of a nitrogen atom with 1, 2, or 3 alkyl groups bound to it. These motifs are highly sought after in small-molecule pharmaceuticals for their unique properties.[1,2] The nitrogen lone pair can make key binding interactions in an enzymatic pocket by acting as a hydrogen bond acceptor. Additionally, in the case of primary and secondary amines, the N-H bond can act as a hydrogen bond donor, making additional interactions that can increase the binding affinity of the drug molecule. In addition to binding to target molecules, the nitrogen atom's electronegativity makes the functional group polar. The polar character of this functional group can increase the water solubility of the drug, thereby allowing chemists to use it as a tool to tune a molecule's bioavailability. Making the drug molecule more water-soluble facilitates excretion from the body, lowering the potentially dangerous build-up of a drug in one's system. For these reasons, amine functional groups are prevalent in many small-molecule therapeutics and can be found directly bound to N-heterocycles specifically. They are present in molecules designed to treat a broad range of disease states. Lamotrigine and Valacyclovir have been used to treat seizures and herpes viral infections, respectively. Hydroxychloroquine has been used as an immunosuppressant to help treat malaria, and Methotrexate has been used as a potent chemotherapy for treating multiple cancer types, including leukemia and non-Hodgkin's lymphoma **(Figure 2.1)**.

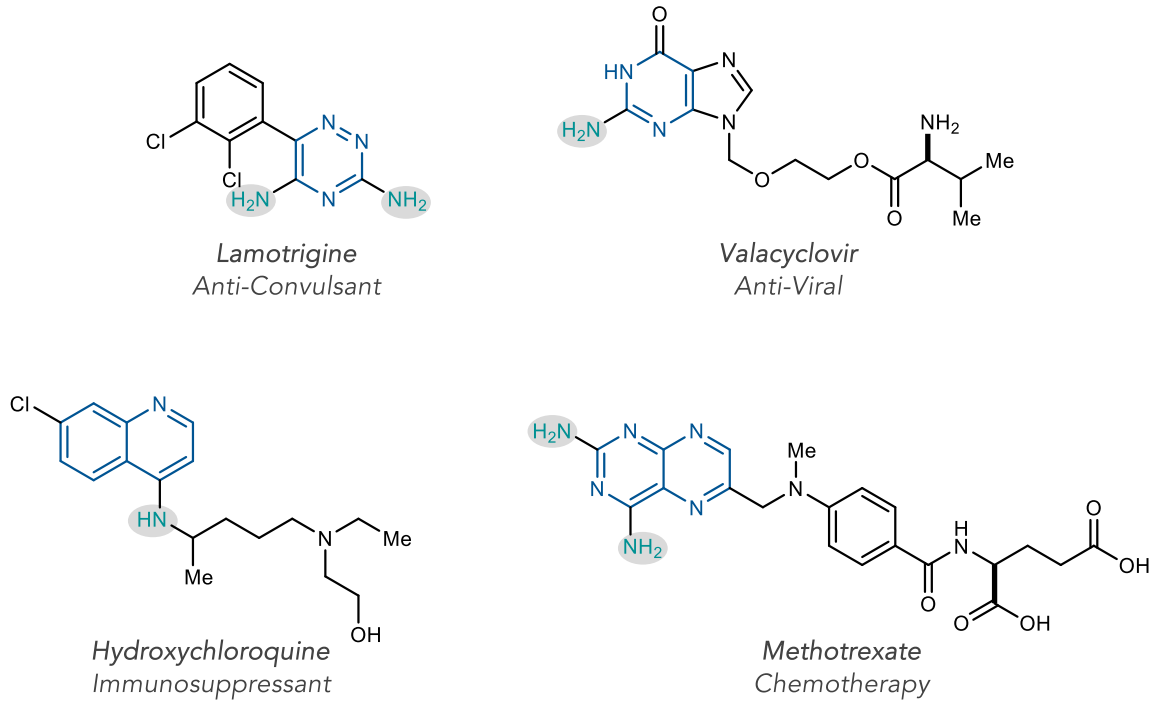


Figure 2.1. Examples of N-heterocyclic amines in pharmaceuticals.

2.2 Direct Methods for N-Heterocycle Amination

Given the prevalence of amines in small-molecule therapeutics, several strategies have been developed to aminate N-heterocycles. These strategies can be classified as either direct or indirect methods. Direct methods are those that directly convert a C-H bond to the desired C-N bond. Indirect methods require a preinstalled functional handle, typically a C-halogen bond, which can then be converted to the desired C-N bond. One of the oldest direct methods to aminate pyridines and diazines is the Chichibabin reaction discussed in chapter one.[3] Here, sodium amide is used to aminate the 2-positon of pyridines selectively.

Abramovitch, and more recently, Davies have shown that pyridine N-oxides can also undergo direct, 2-selective amination.[4,5] The pyridine is first oxidized to the corresponding pyridine N-oxide. Activation with p-toluenesulfonic anhydride (Ts_2O) and nucleophilic attack by

tert-butylamine gives the aminated pyridine. Deprotection of the amine with trifluoroacetic acid (TFA) gives the free amine selectively at the 2-positon of pyridine. Davies' method is amenable to both electron-rich and electron-deficient pyridines and can be extended to quinolines as well. While directly converting C-H bonds to C-N bonds, this strategy requires prefunctionalization of the starting pyridine via oxidation to the pyridine N-oxide. Conditions to accomplish this transformation can be harsh and can limit the scope of this strategy to simple building-block N-heterocycles **(Figure 2.2)**.

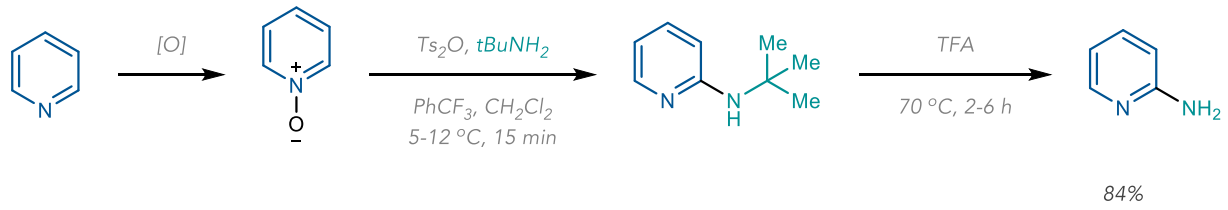


Figure 2.2. Davies' 2-selective amination of pyridine N-oxides.

An additional direct amination strategy for azaarenes was recently developed by Patrick Fier.[6] In this strategy, a multifunctional reagent is used to activate the azaarene and act as the amine source. First, the pyridine attacks the *tert*-butyl ((3-chloro-5,6-dicyanopyrazin-2-yl)oxy)carbamate activating group to form the activated pyridinium, followed by intramolecular delivery of the amine. Base mediated rearomatization through N-O bond cleavage gives the aminated pyridinium. Zinc-mediated pyrazine cleavage is used to install the amine selectively at the 2-positon **(Figure 2.3)**.

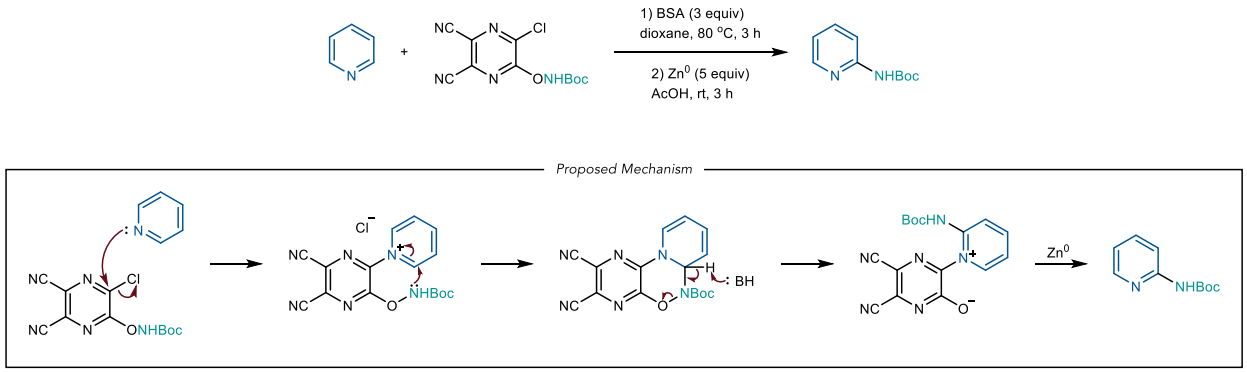


Figure 2.3. Fier's 2-selective amination of pyridines with proposed mechanism.

2.3 Indirect Methods for Azaarene Amination.

Among the indirect methods for azaarene amination, nucleophilic aromatic substitution (S_NAr) is one of the most common strategies.[7] An amine anion attacks the bromopyridine to form a dearomatized Meisenheimer intermediate. The Meisenheimer intermediate then rearomatizes and displaces the bromide leaving group to give the 2-aminopyridine product (**Figure 2.4**). The major drawback of this method is the reliance on prefunctionalized starting materials. A good leaving group such as a halide of triflate is required for the reaction to occur. These functionalities can be challenging to install and often require preplanning to use this amination strategy at a late stage in a synthesis. The reaction also requires forcing conditions to accomplish the desired transformation, further limiting the scope of this amination strategy.

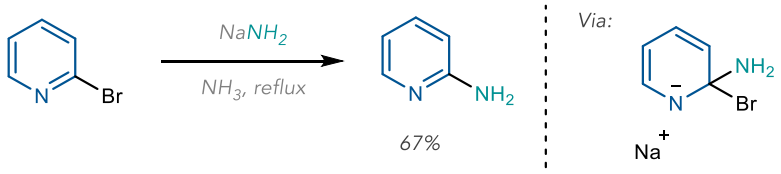


Figure 2.4. S_NAr strategy for indirect amination of 2-bromopyridine.

Several metal-catalyzed processes for the indirect amination of azaarenes have been developed. Chan, Evans, and Lam each published their oxidative, copper-catalyzed cross-coupling

reactions in May of 1998.[8–10] The amine nucleophile first coordinates to the copper (II) catalyst followed by transmetallation of the azaarene boronic acid or ester. The resulting copper (II) species undergoes disproportionation with a second copper (II) species to generate a copper (III) species. Reductive elimination from this copper (III) center gives the aminated N-heterocycle, and the copper (I) is oxidized to copper (II) by O_2 to regenerate the active catalyst.[11] The Chan-Lam coupling reaction allows for the oxidative, copper-catalyzed cross-coupling of aryl and heteroaryl boronic acids with heteroatom nucleophiles such as alcohols and amines **(Figure 2.5)**.[12]

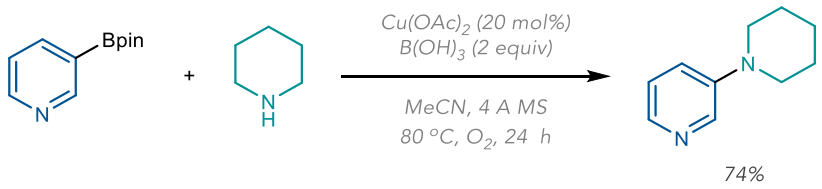


Figure 2.5. Chan-Lam coupling of piperidine with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine.

One of the most common methods to aminate azaarenes is the Buchwald-Hartwig coupling reaction: this palladium-catalyzed reaction couples (hetero)aryl-halides and pseudo halides with primary or secondary amines.[13] The palladium (0) inserts into the heteroaryl halide bond to form a palladium (II) species. The amine then adds to the catalyst to form an amide bond. Subsequent reductive elimination from this palladium (II) species forms the aminated azaarene and regenerates the palladium (0) catalyst **(Figure 2.6)**. Since its initial development, several advances have been made with new ligands and catalyst systems which have expanded the scope of the coupling reaction to tolerate a wide range of (hetero)aryl halides and amines, but conditions for each substrate can vary greatly.[14] In order to find adequate coupling conditions, both coupling partners' steric and electronic properties must be considered. This can be tedious and time-consuming, especially for medicinal chemists whose aim is to synthesize as many drug analogues as possible.

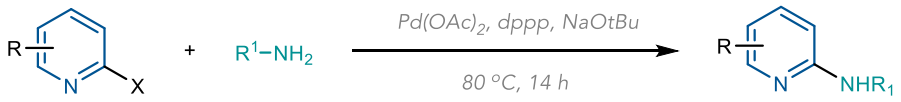


Figure 2.6. Buchwald-Hartwig amination of heteroaryl halides.

Buchwald and Hartwig published a novel nickel catalyzed photoredox amination strategy for (hetero)aryl halides in Science in 2016.[15] Typical metal-catalyzed amination reactions such as the Buchwald-Hartwig reaction rely on specialized ligands to destabilize the metal amido complexes and facilitate reductive elimination[13]. Instead, this strategy uses photoredox catalysis to destabilize the metal amido complex, thus presenting a complimentary amination process for arenes and azaarenes. The nickel (II) is first reduced to nickel (0) by the excited state photocatalyst. The nickel (0) oxidatively inserts into the C-Halogen bond on the arene or heteroarene to form a nickel (II) species to which the amine can add. The resulting nickel (II) species undergoes a single electron transfer event with the photocatalyst to form a nickel (III) species. Reductive elimination from this nickel (III) species gives the aminated product and nickel (I), which is reduced by the photocatalyst to regenerate the active nickel (0) species **(Figure 2.7)**.

Figure 2.7. MacMillan and Buchwald's nickel-catalyzed photoredox amination of arenes and azaarenes.

2.4 Introduction to Heterocyclic Phosphonium Salts

As discussed in the previous chapter, there have been several advancements toward the direct functionalization of azaarenes. Most methods are either 2- or 3-selective, while 4-selective strategies remain rare. Many of the existing strategies to directly functionalize the 4-position, such as Kanai's perfluoroalkylation and Nakao's alkylation reactions, are limited to the formation of C-C bonds. While these transformations are important, there are a variety of bond types that would be useful for medicinal chemists to install selectively at the 4-position besides C-C bonds. An alternative strategy would be to selectively install a versatile, functional handle at the 4-position of azaarenes which could then be derivatized into multiple bond types (**Figure 2.8**).

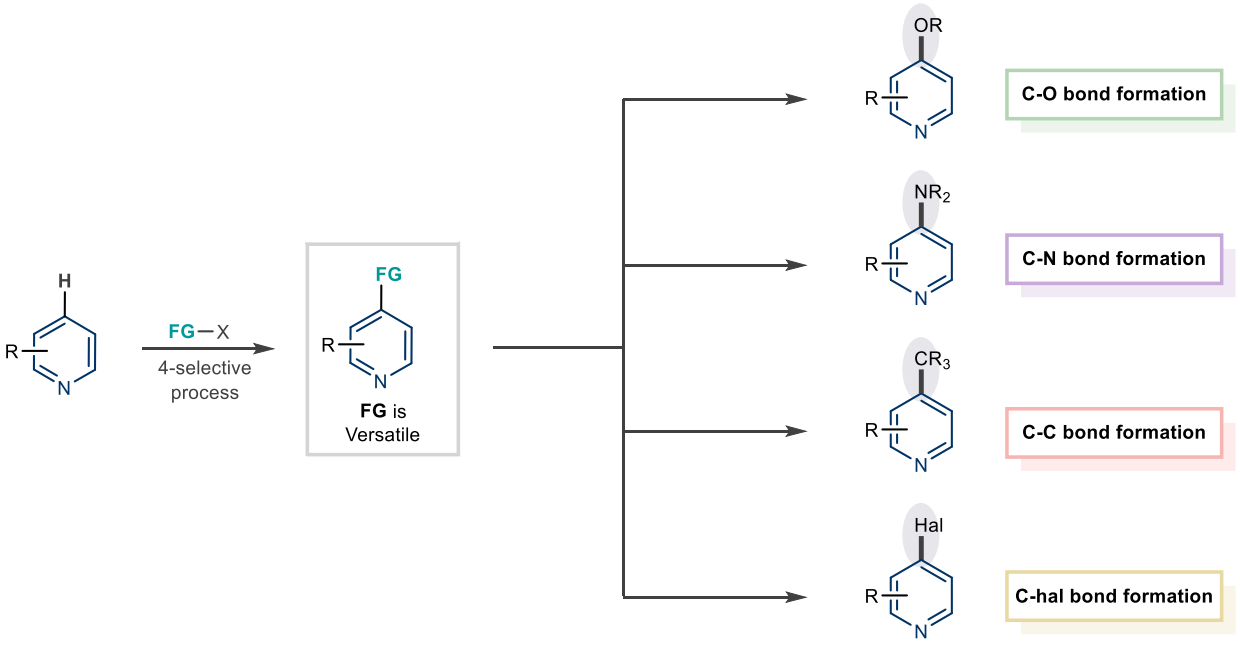


Figure 2.8. A strategy for 4-selective functionalization of azaarenes via a versatile, functional handle.

The McNally group sought to develop a strategy for the 4-selective functionalization of azaarenes. Their approach focused on adding a nucleophile selectively to the 4-position of an activated pyridinium. Base mediated elimination would then give the rearomatized, functionalized

azaarene. While developing this strategy, they became aware of a report from Ernst Anders, in which pyridine is activated with triflic anhydride, and triphenylphosphine adds selectively to the activated pyridinium. Deprotonation with triethylamine (Et_3N) gave the heterocyclic phosphonium salat with exquisite 4-selectivity **(Figure 2.9)**.[16]

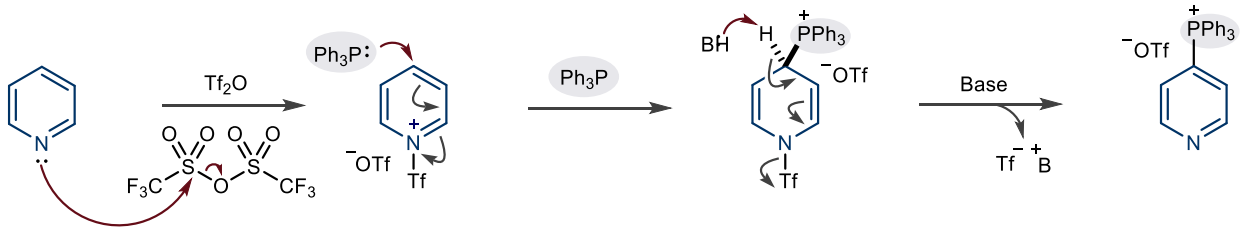


Figure 2.9. Proposed mechanism for heterocyclic phosphonium salt formation.

While this report demonstrated the viability of the McNally group's approach, the transformation was only shown on a limited number of examples. The McNally group explored the scope of the reaction and found that 3-substituted pyridines were not amenable to this process. After reaction optimization, the McNally group found that switching the base from Et_3N to 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) significantly enhanced the reaction scope. For example, 3-methyl pyridine gave no conversion to the phosphonium salt when using Et_3N as the base. By switching the base to DBU, a 78% yield of the phosphonium salt was obtained on the same substrate while maintaining 4-selectivity **(Figure 2.10)**.[17] These optimized conditions developed by the McNally lab allow for the 4-selective installation of the phosphonium group on pyridines of any substitution pattern besides 2,6-disubstituted pyridines. To date, the McNally lab has developed a number of transformations from these heterocyclic phosphonium salts.[17–30]

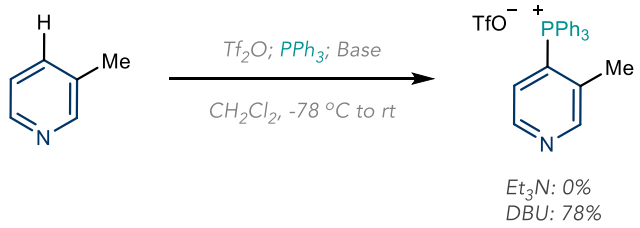


Figure 2.10. Effects of base in phosphonium salt-forming reaction. Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

2.5 The Staudinger Reaction

In 1919, Hermann Staudinger reported on the formation of iminophosphoranes from the addition of triarylphosphines to organoazides.[31] These iminophosphoranes can then be hydrolyzed to obtain the primary amine product. First, the terminal nitrogen of the azide is attacked by the phosphine to form a phosphazide intermediate. This intermediate undergoes an intramolecular cyclization and decomposition to give the iminophosphorane and diatomic nitrogen (**Figure 2.11**). The iminophosphorane is a versatile, functional handle that can be derivatized into many valuable functionalities. As previously stated, the iminophosphorane can be hydrolyzed to give the primary amine, but it can also undergo an aza-Wittig reaction with aldehydes and ketones to generate the corresponding imine products.[32] The iminophosphorane can also react with carbon dioxide or carbon disulfide to access isocyanate and isothiocyanate products, respectively.[33] Reaction with alkyl or allyl halides and subsequent hydrolysis can give access to secondary amine products as well.[34]

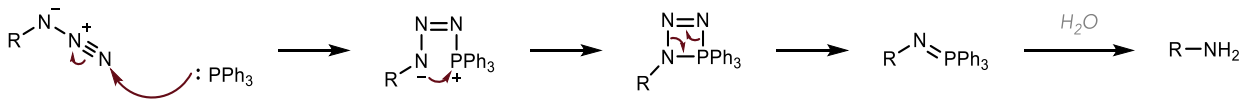


Figure 2.11. Proposed mechanism for the Staudinger reaction.

In his initial report on the formation of heterocyclic phosphonium salts, Anders demonstrated several derivatizations which could be accomplished from these reactive intermediates. The reaction of the bis-phosphonium salt with methanol (MeOH) in the presence of triethylamine (Et_3N) gave the alkoxylated product in 73% yield. The bis-phosphonium salt also gave a good yield of the iminophosphorane product when reacted with sodium azide in dimethylsulfoxide (DMSO). The same reaction on the pyridyl phosphonium salt only gave trace amounts of the iminophosphorane product **(Figure 2.12)**. Despite the low yield, this result demonstrates that the Staudinger reaction is possible on these heterocyclic phosphonium salts and could serve as a 4-selective amination strategy for pyridines and diazines.

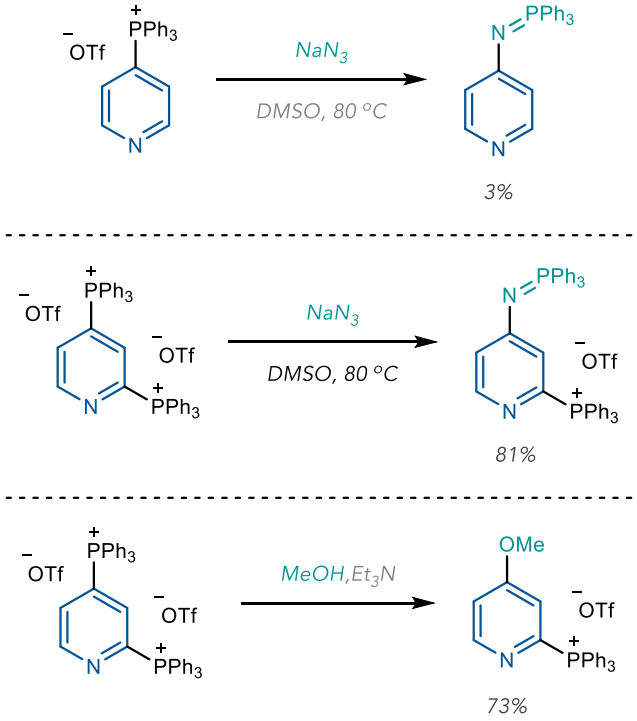


Figure 2.12. Derivatizations of N-heterocyclic phosphonium salts from Anders' initial report.

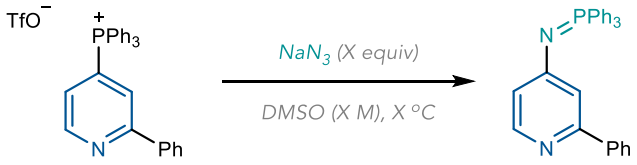
2.6 Results and Discussion

2.6.1 Reaction Optimization

The initial report on the conversion of heterocyclic phosphonium salts to iminophosphoranes from Anders showed only trace conversion to the desired product in the case of the mono-phosphonium salt and was only demonstrated on unsubstituted pyridine. Given that the McNally lab had previously shown that these phosphonium salts could be installed on a broad range of pyridines and diazines, we proposed that the Staudinger reaction could provide a valuable method for the 4-selective amination of these important motifs. First, the conversion of the phosphonium salt to the iminophosphorane had to be optimized to ensure the reaction could be applied to a broad range of azaarenes. Optimization on the 2-phenyl pyridyl phosphonium salt was accomplished **(Table 2.1)**.

Temperature played a significant role in the yield of the reaction (**Table 2.1, Entries 1-5**). Increasing the reaction temperature from 100 ^{o}C to 120 ^{o}C lead to a significant increase in yield. Further elevation of the temperature beyond 120 ^{o}C did not further improve the yield. The equivalents of sodium azide (NaN_3) were also explored (**Table 2.1, entries 6-9**). Increasing NaN_3 from 1 to 1.25 equivalents improved the yield to 88%, but further increase in the yield was not observed beyond 1.25 equivalents. Next, the concentration of the reaction was adjusted (**Table 2.1, entries 11-18**). A concentration of 1.5 M was found to be optimal. Various solvents beyond DMSO were tested using the optimized reaction conditions, but none improved the reaction yield (**Table 2.1, entries 19-21**). The optimized conditions (**Table 2.1, entry 14**) were used to explore the scope of the reaction.

Table 2.1. Optimization of azide reaction with 2-phenyl pyridyl phosphonium salt.[a]



Entry	NaN_3 (equiv)	Concentration (M)	Solvent	Temperature (°C)	% Yield
1	1.0	1.0	DMSO	100	39
2	1.0	1.0	DMSO	110	51
3	1.0	1.0	DMSO	120	81
4	1.0	1.0	DMSO	130	74
5	1.0	1.0	DMSO	140	79
6	0.8	1.0	DMSO	120	70
7	1.25	1.0	DMSO	120	88
8	1.5	1.0	DMSO	120	84
9	2.0	1.0	DMSO	120	85
11	1.25	0.25	DMSO	120	72
12	1.25	0.5	DMSO	120	79
13	1.25	0.75	DMSO	120	86
14	**1.25**	**1.5**	**DMSO**	**120**	**91**
15	1.25	2.0	DMSO	120	88
16	1.25	3.0	DMSO	120	84
17	1.25	4.0	DMSO	120	80
18	1.25	5.0	DMSO	120	77
19	1.25	1.5	DMF	120	66
20	1.25	1.5	NMP	120	68
21	1.25	1.5	DCE	80	0

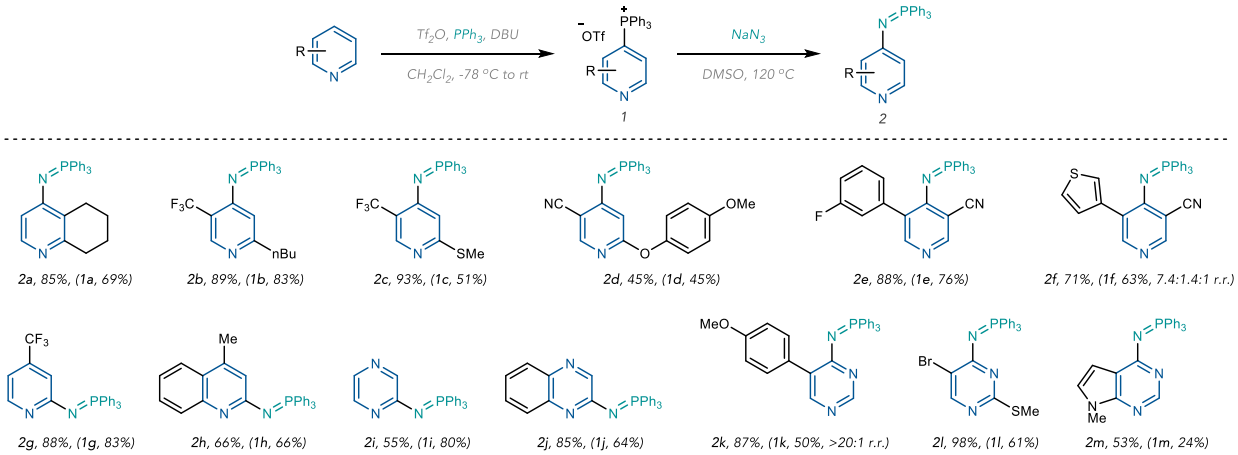
[a]Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

2.6.2 Reaction Scope

With optimized conditions in hand, we next sought to explore the scope of heterocyclic phosphonium salts that would be compatible with the iminophosphorane reaction (**Table 2.2**).[21] The regiocontrol of the Staudinger reaction is solely determined by the phosphonium salt. In all but two cases, complete regiocontrol for the 4-position was observed. In cases where the 4-position was blocked, the phosphonium salt and iminophosphorane were formed at the 2-position. We observed that the Staudinger reaction was tolerant of multiple substitution patterns, including 2,3-

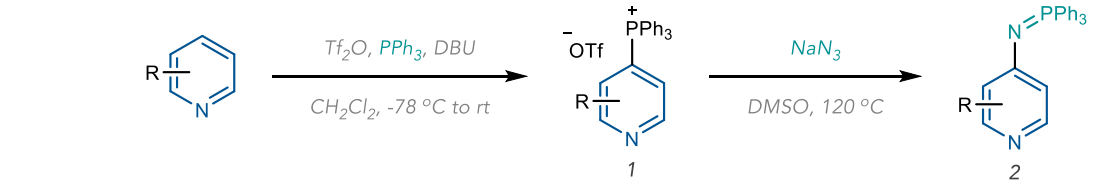
disubstituted pyridines (**2a**) and 2,5-disubstituted pyridines (**2b-2d**). Despite the sterically hindered environment around the phosphonium salt, 3,5-disubstituted pyridines (**2e & 2f**) were well tolerated in the reaction and provided the desired product in good yields. The reaction conditions were amenable to 4-substituted heterocycles (**2g & 2h**) as well. A range of pyrazines and pyrimidines (**2i-2m**) were also converted into the desired iminophosphorane in moderate to good yields. This amination strategy works well on neutral and electron-deficient azaarenes.

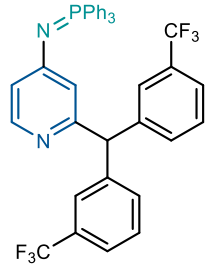
Table 2.2. Building-block scope of iminophosphorane reaction. r.r. = regiomeric ratio. Isolated yields are shown. Phosphonium salt yields in parentheses.



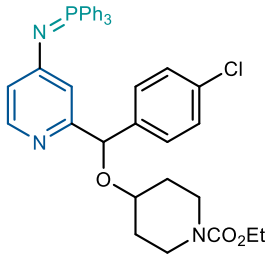
To demonstrate the versatility of this amination process, we sought to expand the reaction scope to more complex pyridine and diazine-containing drug-like fragments (**Table 2.3**). These more complex fragments were converted to the iminophosphoranes smoothly in two steps with moderate to good yields. Benzhydryl stereocenters are accommodated in this reaction (**2n**). Pyrimidine-containing fragments (**2q & 2r**) are also converted to the corresponding iminophosphoranes in good yields. Interestingly, fragments with multiple sites of reactivity (**2p & 2s**) were isolated as single isomers.

Table 2.3. Complex fragment scope of iminophosphorane reaction. r.r. = regiomeric ratio. Isolated yields are shown. Phosphonium salt yields in parentheses.

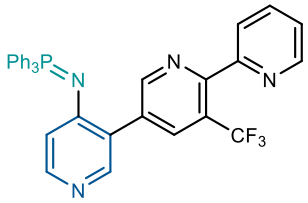




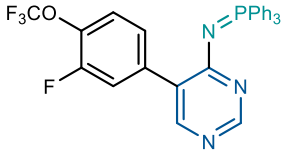
2n, 74%, (1n, 87%)



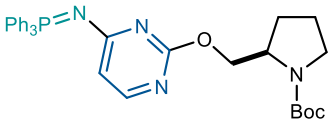
2o, 68%, (1o, 73%)



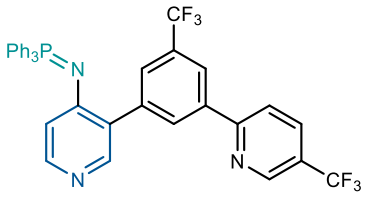
2p, 75%, (1p, 78%, 9.6:1.3:1 r.r.)



2q, 95%, (1q, 68%)



2r, 90%, (1r, 77%)

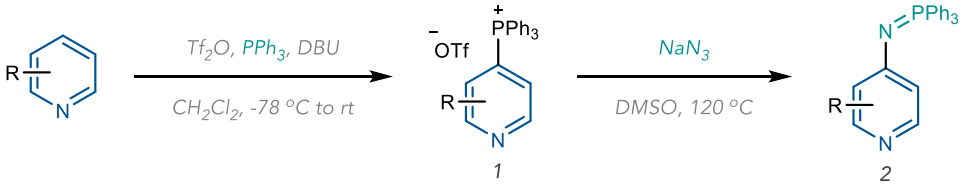


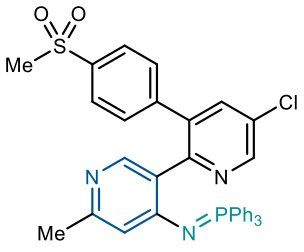
2s, 70%, (1s, 66%)

Having demonstrated that this amination strategy can be applied to a broad range of building block pyridines and diazines, as well as to more complicated drug-like fragments, we next turned our attention to pharmaceuticals (**Table 2.4**). Loratadine (**2u**) and Chlorphenamine (**2v**) are converted to the iminophosphorane over two steps in usable yields. Quinazoline containing Chantix (**2w**) is also aminated successfully using this strategy. Both Imatinib and Etoricoxib contain multiple sites for possible phosphonium salt formation. Despite this, the salt reaction on etoricoxib gave only one regioisomer on the 2,5-substituted pyridine, and the salt reaction on Imatinib is highly selective for the pyridine ring over the pyrimidine. Etoricoxib (**2t**) is smoothly converted to the iminophosphorane in moderate yield. When attempting to form the iminophosphorane on Imatinib, we observed significant hydrolysis to the primary amine under the

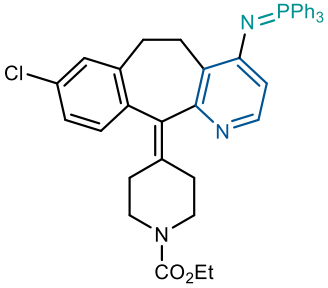
reaction conditions. After the phosphonium salt starting material was consumed, water was added to the reaction mixture to hydrolyze the iminophosphorane to give the aminated Imatinib (**2x**).

Table 2.4. Pharmaceutical scope of iminophosphorane reaction. r.r. = regiomeric ratio. Isolated yields are shown. Phosphonium salt yields in parentheses.

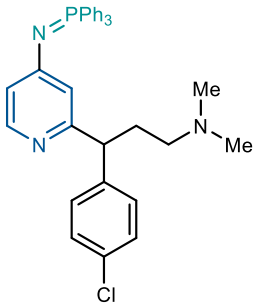




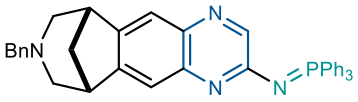
2t, 60%, (1t, 73%)
From Etoricoxib



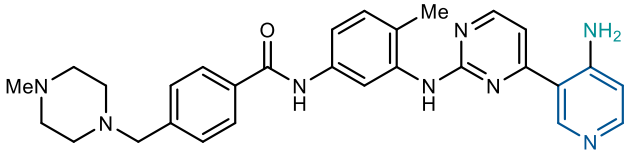
2u, 41%, (1u, 88%)
From Loratadine



2v, 28%, (1v, 40%)
From Chlorphenamine



2w, 51%, (1w, 58%)
From N-Bn Varenicline



2x, 40%, (1x, 75%, 20:1 r.r.)
From Imatinib

2.6.3 Derivatization of Iminophosphorane

Having shown that this amination strategy is effective on a broad range of pyridines and diazines, we then focused on demonstrating the versatility of the iminophosphorane as a functional handle. Using 5,6,7,8-tetrahydroquinoline iminophosphorane, we demonstrated three derivatizations that can be accomplished **(Figure 2.13)**. Hydrolysis with water in dimethylformamide (DMF) at 100 °C gives the heteroaryl aniline (**3aa**) in good yield. An aza-Wittig reaction with carbon disulfide (CS_2) provides access to the valuable isothiocyanate product

(**3ab**). The iminophosphorane intermediate can also react with allyl iodide, and subsequent hydrolysis forms the secondary amine product (**3ac**).

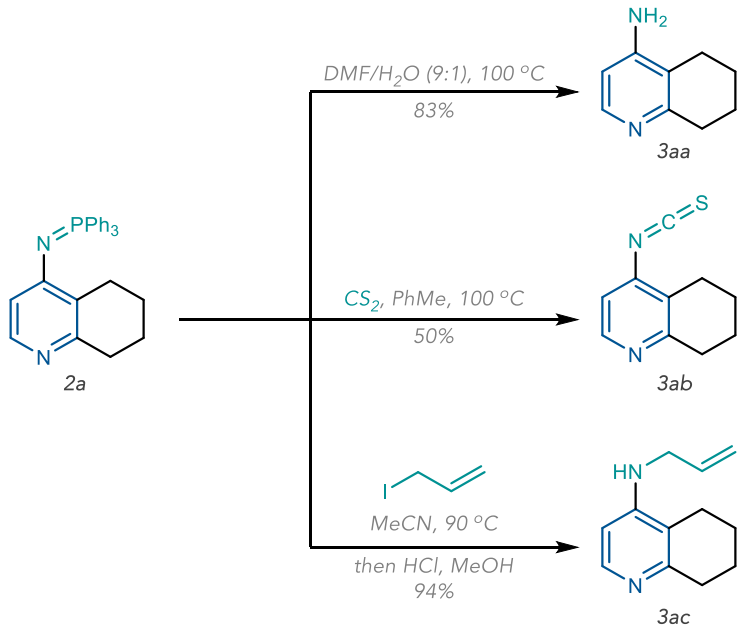


Figure 2.13. Derivatizations of 5,6,7,8-tetrahydroquinoline iminophosphorane.

2.6.4 Reaction Mechanism

Two mechanistic pathways are possible for this reaction to occur (**Figure 2.14 A**). The first involves a nucleophilic attack at the phosphorus atom by sodium azide. A ligand-coupling event at the phosphorus center can then generate the organoazide intermediate and displace triphenylphosphine (PPh_3). The phosphine can react with the azide in a Staudinger reaction to generate the desired iminophosphorane product. An alternative reaction pathway would involve an S_NAr reaction in which the azide attacks the ipso-carbon of the phosphonium salt to generate a Meisenheimer intermediate. Rearomatization and elimination of PPh_3 will give the organoazide intermediate, and a Staudinger reaction will form the iminophosphorane. Evidence of a discreet organoazide intermediate was shown via a trapping experiment **(Figure 2.14 B)**. The reaction to

form the iminophosphorane was run under the optimized conditions with an equivalent of tritolyl phosphine ($PTol_3$) added. Two iminophosphorane products were observed with masses and ^{31}P phosphorus peaks corresponding to the iminophosphoranes of PPh_3 and $PTol_3$.

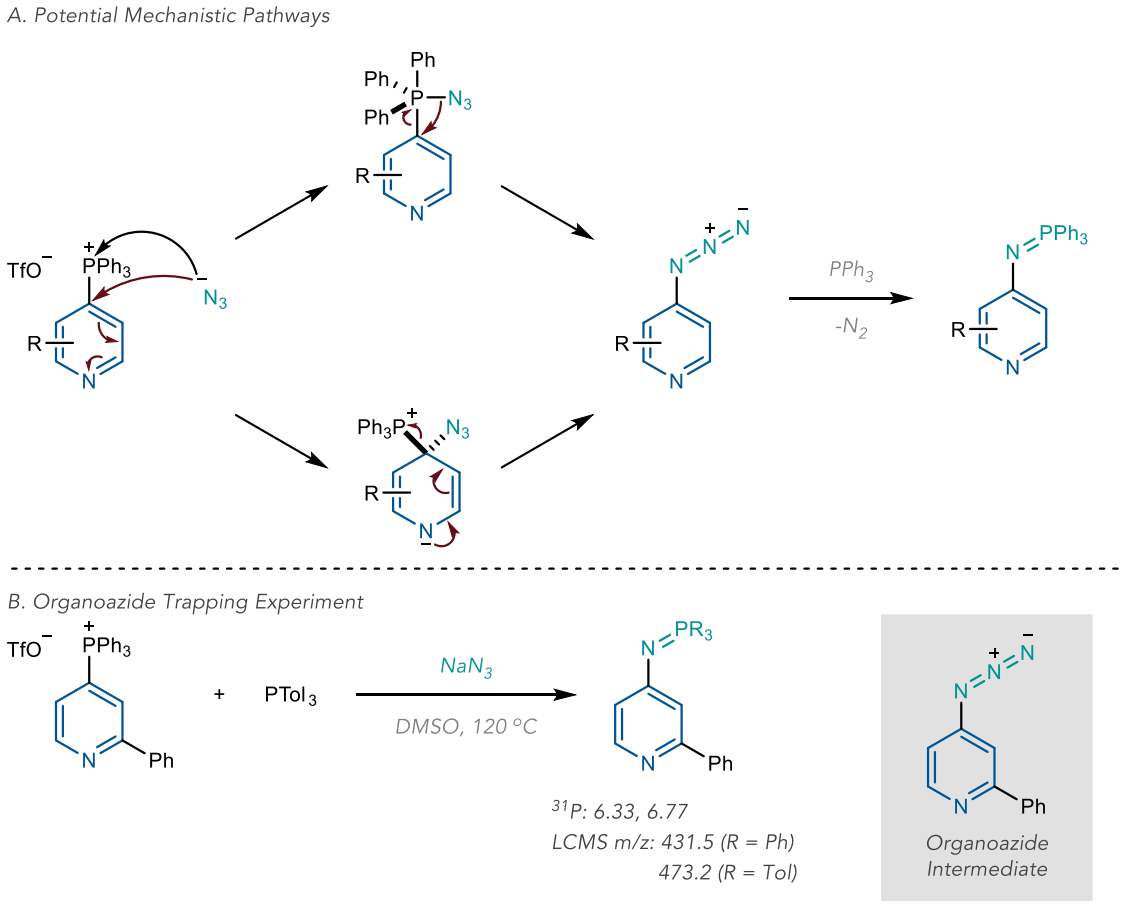


Figure 2.14. A. Potential mechanistic pathways for iminophosphorane reaction. B. Organoazide trapping experiment with tritolyl phosphine.

2.7 Conclusion

This two-step strategy for the amination of pyridines and diazines provides synthetic chemists with a valuable tool for the direct, 4-selective installation of C-N bonds on a broad range of azaarenes. This method applies not only to a broad range of pyridines and diazines but also to more complex drug-like fragments and pharmaceuticals, highlighting it as an effective late-stage

amination strategy. This strategy also circumvents the need for prefunctionalized starting materials such as halogens or pseudo-halogens. The mechanism of this reaction is believed to be either an S_NAr or a ligand coupling event leading to a discreet organoazide.

REFERENCES

(1) Hall, D. G. Amines: Synthesis, Properties and Applications By Stephen A. Lawrence (Mimas Ltd.). Cambridge University Press: Cambridge, U.K. x + 372 Pp. $180.00. ISBN 0-521-78284-8. *J. Am. Chem. Soc.* **2005**, *127* (26), 9655–9655. https://doi.org/10.1021/ja041026j.

(2) Corbet, J.-P.; Mignani, G. Selected Patented Cross-Coupling Reaction Technologies. *Chem. Rev.* **2006**, *106* (7), 2651–2710. https://doi.org/10.1021/cr0505268.

(3) Mcgill, C. K.; Rappa, A. Advances in the Chichibabin Reaction. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press, 1988; Vol. 44, pp 1–79. https://doi.org/10.1016/S0065-2725(08)60261-5.

(4) Abramovitch, R. A.; Singer, G. M. Direct Alkyl and Aryl Amination of Heteroaromatic Nitrogen Compounds. *J. Am. Chem. Soc.* **1969**, *91* (20), 5672–5673. https://doi.org/10.1021/ja01048a059.

(5) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. A General and Efficient 2-Amination of Pyridines and Quinolines. *J. Org. Chem.* **2007**, *72* (12), 4554–4557. https://doi.org/10.1021/jo070189y.

(6) Fier, P. S.; Kim, S.; Cohen, R. D. A Multifunctional Reagent Designed for the Site-Selective Amination of Pyridines. *J. Am. Chem. Soc.* **2020**, *142* (19), 8614–8618. https://doi.org/10.1021/jacs.0c03537.

(7) HAUSER, C. R.; WEISS, M. J. SUBSTITUTIONS AT THE α- OR γ-POSITIONS IN PYRIDYL RING SYSTEMS BY BASIC REAGENTS1. *J. Org. Chem.* **1949**, *14* (2), 310–321. https://doi.org/10.1021/jo01154a019.

(8) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New N- and O-Arylations with Phenylboronic Acids and Cupric Acetate. *Tetrahedron Letters* **1998**, *39* (19), 2933–2936. https://doi.org/10.1016/S0040-4039(98)00503-6.

(9) Evans, D. A.; Katz, J. L.; West, T. R. Synthesis of Diaryl Ethers through the Copper-Promoted Arylation of Phenols with Arylboronic Acids. An Expedient Synthesis of Thyroxine. *Tetrahedron Letters* **1998**, *39* (19), 2937–2940. https://doi.org/10.1016/S0040-4039(98)00502-4.

(10) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New Aryl/Heteroaryl C□N Bond Cross-Coupling Reactions via Arylboronic Acid/Cupric Acetate Arylation. *Tetrahedron Letters* **1998**, *39* (19), 2941–2944. https://doi.org/10.1016/S0040-4039(98)00504-8.

(11) West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J. B. Mechanistic Development and Recent Applications of the Chan–Lam Amination. *Chem. Rev.* **2019**, *119* (24), 12491–12523. https://doi.org/10.1021/acs.chemrev.9b00491.

(12) Vantourout, J. C.; Miras, H. N.; Isidro-Llobet, A.; Sproules, S.; Watson, A. J. B. Spectroscopic Studies of the Chan–Lam Amination: A Mechanism-Inspired Solution to Boronic Ester Reactivity. *J. Am. Chem. Soc.* **2017**, *139* (13), 4769–4779. https://doi.org/10.1021/jacs.6b12800.

(13) Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M.; Malmir, M. Buchwald-Hartwig Reaction: An Overview. *Journal of Organometallic Chemistry* **2018**, *861*, 17–104. https://doi.org/10.1016/j.jorganchem.2018.02.023.

(14) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald–Hartwig Amination After 25 Years. *Angewandte Chemie International Edition* **2019**, *58* (48), 17118–17129. https://doi.org/10.1002/anie.201904795.

(15) Corcoran, E. B.; Pirnot, M. T.; Lin, S.; Dreher, S. D.; DiRocco, D. A.; Davies, I. W.; Buchwald, S. L.; MacMillan, D. W. C. Aryl Amination Using Ligand-Free Ni(II) Salts and Photoredox Catalysis. *Science* **2016**, *353* (6296), 279–283. https://doi.org/10.1126/science.aag0209.

(16) Anders, E.; Markus, F. Neue Methode Zur Regiospezifischen Substitution Einiger Reaktionsträcer N-Heteroaromatischer Ringsysteme. *Tetrahedron Letters* **1987**, *28* (24), 2675–2676. https://doi.org/10.1016/S0040-4039(00)96178-1.

(17) Hilton, M. C.; Dolewski, R. D.; McNally, A. Selective Functionalization of Pyridines via Heterocyclic Phosphonium Salts. *J. Am. Chem. Soc.* **2016**, *138* (42), 13806–13809. https://doi.org/10.1021/jacs.6b08662.

(18) Zhang, X.; McNally, A. Phosphonium Salts as Pseudohalides: Regioselective Nickel-Catalyzed Cross-Coupling of Complex Pyridines and Diazines. *Angewandte Chemie International Edition* **2017**, *56* (33), 9833–9836. https://doi.org/10.1002/anie.201704948.

(19) Anderson, R. G.; Jett, B. M.; McNally, A. Selective Formation of Heteroaryl Thioethers via a Phosphonium Ion Coupling Reaction. *Tetrahedron* **2018**, *74* (25), 3129–3136. https://doi.org/10.1016/j.tet.2017.12.040.

(20) Koniarczyk, J. L.; Hesk, D.; Overgard, A.; Davies, I. W.; McNally, A. A General Strategy for Site-Selective Incorporation of Deuterium and Tritium into Pyridines, Diazines, and Pharmaceuticals. *J. Am. Chem. Soc.* **2018**, *140* (6), 1990–1993. https://doi.org/10.1021/jacs.7b11710.

(21) Patel, C.; Mohnike, M.; Hilton, M. C.; McNally, A. A Strategy to Aminate Pyridines, Diazines, and Pharmaceuticals via Heterocyclic Phosphonium Salts. *Org. Lett.* **2018**, *20* (9), 2607–2610. https://doi.org/10.1021/acs.orglett.8b00813.

(22) Anderson, R. G.; Jett, B. M.; McNally, A. A Unified Approach to Couple Aromatic Heteronucleophiles to Azines and Pharmaceuticals. *Angewandte Chemie International Edition* **2018**, *57* (38), 12514–12518. https://doi.org/10.1002/anie.201807322.

(23) Hilton, M. C.; Zhang, X.; Boyle, B. T.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. Heterobiaryl Synthesis by Contractive C–C Coupling via P(V) Intermediates. *Science* **2018**, *362* (6416), 799–804. https://doi.org/10.1126/science.aas8961.

(24) Zhang, X.; McNally, A. Cobalt-Catalyzed Alkylation of Drug-Like Molecules and Pharmaceuticals Using Heterocyclic Phosphonium Salts. *ACS Catal.* **2019**, *9* (6), 4862–4866. https://doi.org/10.1021/acscatal.9b00851.

(25) Koniarczyk, J. L.; Greenwood, J. W.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. A Pyridine–Pyridine Cross-Coupling Reaction via Dearomatized Radical Intermediates. *Angewandte Chemie International Edition* **2019**, *58* (42), 14882–14886. https://doi.org/10.1002/anie.201906267.

(26) Boyle, B. T.; Hilton, M. C.; McNally, A. Nonsymmetrical Bis-Azine Biaryls from Chloroazines: A Strategy Using Phosphorus Ligand-Coupling. *J. Am. Chem. Soc.* **2019**, *141* (38), 15441–15449. https://doi.org/10.1021/jacs.9b08504.

(27) Levy, J. N.; Alegre-Requena, J. V.; Liu, R.; Paton, R. S.; McNally, A. Selective Halogenation of Pyridines Using Designed Phosphine Reagents. *J. Am. Chem. Soc.* **2020**, *142* (25), 11295–11305. https://doi.org/10.1021/jacs.0c04674.

(28) Greenwood, J. W.; Boyle, B. T.; McNally, A. Pyridylphosphonium Salts as Alternatives to Cyanopyridines in Radical–Radical Coupling Reactions. *Chem. Sci.* **2021**, *12* (31), 10538–10543. https://doi.org/10.1039/D1SC02324A.

(29) Zhang, X.; Nottingham, K. G.; Patel, C.; Alegre-Requena, J. V.; Levy, J. N.; Paton, R. S.; McNally, A. Phosphorus-Mediated Sp2–Sp3 Couplings for C–H Fluoroalkylation of Azines. *Nature* **2021**, *594* (7862), 217–222. https://doi.org/10.1038/s41586-021-03567-3.

(30) Fricke, P. J.; Dolewski, R. D.; McNally, A. 4-Selective Pyridine Alkylation via Wittig Olefination of Dearomatized Pyridylphosphonium Ylides. *Angewandte Chemie International Edition n/a* (n/a). https://doi.org/10.1002/anie.202109271.

(31) Staudinger, H.; Meyer, J. Über Neue Organische Phosphorverbindungen III. Phosphinmethylenderivate Und Phosphinimine. *Helvetica Chimica Acta* **1919**, *2* (1), 635–646. https://doi.org/10.1002/hlca.19190020164.

(32) Staudinger, H.; Hauser, E. Über Neue Organische Phosphorverbindungen IV Phosphinimine. *Helvetica Chimica Acta* **1921**, *4* (1), 861–886. https://doi.org/10.1002/hlca.19210040192.

(33) Friant-Michel, P.; Marsura, A.; Kovacs, J.; Pintér, I.; Rivail, J.-L. PM3 Study of Cyclization of α- and β-d-Glucosyl Azides into 1,2-Cyclic Carbamates. *Journal of Molecular Structure: THEOCHEM* **1997**, *395–396*, 61–69. https://doi.org/10.1016/S0166-1280(97)00092-4.

(34) Palacios, F.; Aparicio, D.; García, J. A Simple Strategy for the Preparation of 4-Aminoquinolines from β-Functionalized Enamines. *Tetrahedron* **1998**, *54* (8), 1647–1656. https://doi.org/10.1016/S0040-4020(97)10372-6.

CHAPTER THREE

4-SELECTIVE FLUOROALKYLATION OF PYRIDINES AND DIAZINES VIA PHOSPHORUS LIGAND-COUPLING

3.1 The Importance of Fluoroalkyl Groups in Pharmaceuticals

Since the FDA approval of the first fluorinated pharmaceutical, fludrocortisone, in 1955, nearly 150 additional fluorinated drugs have reached the market. The fluoroalkyl groups have gained prominence in pharmaceuticals due to the unique properties they can endow a molecule with (**Figure 3.1**). They have been shown to influence almost all metrics involved in pharmacokinetic and pharmacodynamic studies.[1–4] The presence of fluorine atoms can lower the susceptibility of nearby moieties to cytochrome P-450 metabolic oxidation.[5] In addition, the presence of fluoroalkyl groups can result in increased binding affinity, increased cell-membrane permeability and can modulate a drug's ability to cross the blood-brain barrier.[2] The difluoromethyl group can act as both a hydrogen bond donor and acceptor, allowing it to behave as a bioisostere for hydroxyl, thiol, and amine groups. The unique properties of fluoroalkyl groups are beneficial in the pharmaceutical space and extend to agrochemicals, with trifluoromethylated pyridines being highly valued in crop protection.[6,7] Despite their importance, methods to fluoroalkylate complex pharmaceuticals and agrochemicals are limited to radical addition processes. Here, we describe a new method for the direct, late-stage trifluoromethylation and difluoromethylation of complex drugs and agrochemicals.

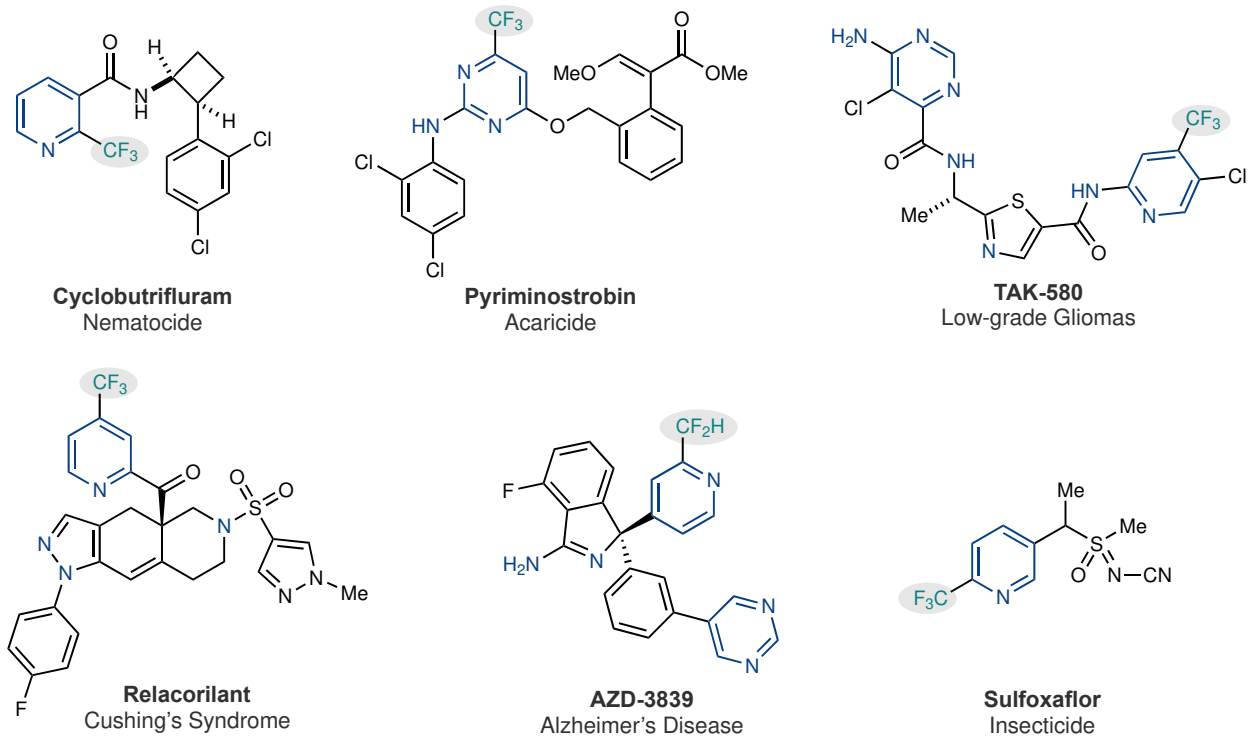


Figure 3.1. Examples of fluoroalkylated pharmaceuticals.

3.2 Methods for Direct Fluoroalkylation of Azaarenes

Due to their importance in pharmaceuticals and agrochemicals, several methods have been developed for the direct fluoroalkylation of azaarenes. The major strategies to accomplish the direct fluoroalkylation of N-heterocycles can be divided into two subcategories. The first method involves activation the N-heterocycle, addition of a fluoroalkyl anion, and subsequent oxidation to give the fluoroalkylated products. Such a strategy was employed by Kanai to selectively fluoroalkylate the 4-position of azaarenes.[8] The second strategy involves the generation of a fluoroalkyl radical species, which can then add to an activated pyridine or diazine in a Minisci reaction. Several methods to access the fluoroalkyl radical species have been developed by the labs of MacMillan, Stephenson, and Baran.[9–11]

Phil Baran and co-workers developed a direct trifluoromethylation strategy that uses sulfinates as a trifluoromethyl radical source as an alternative to dangerous trifluoromethyl iodide, which had previously been used to accomplish this transformation.[12] In 2011, Baran published on the use of sodium trifluoromethylsulfinate (Langlois' reagent) as a trifluoromethyl radical source for the direct fluoroalkylation of heterocycles.[13] First, *tert*-butyl hydroperoxide (*t*BuOOH) reacts with trace metal to generate the *tert*-butoxy radical which can then react with Langlois' reagent to give the corresponding trifluoromethyl sulfinyl radical. This transient radical then undergoes disproportionation to give sulfur dioxide and trifluoromethyl radical. The trifluoromethyl radical then combines with an azaarene, and an additional equivalent of tBuOOH oxidizes the resulting radical. Deprotonation gives the trifluoromethylated azaarene (**Figure 3.2, A**). This fluoroalkylation strategy applies to a broad range of heterocycles and can even be extended to complex pharmaceuticals such as Varenicline. The trifluoromethylation typically occurs at the most electron rich positions, however, one disadvantage of this method is the possibility of obtaining multiple regioisomers. Interestingly, by changing the solvent system from DCM/H_2O to DMSO/H_2O, the inherent selectivity for the 2-positon of pyridine can be switched to the 3-position (**Figure 3.2, B**).

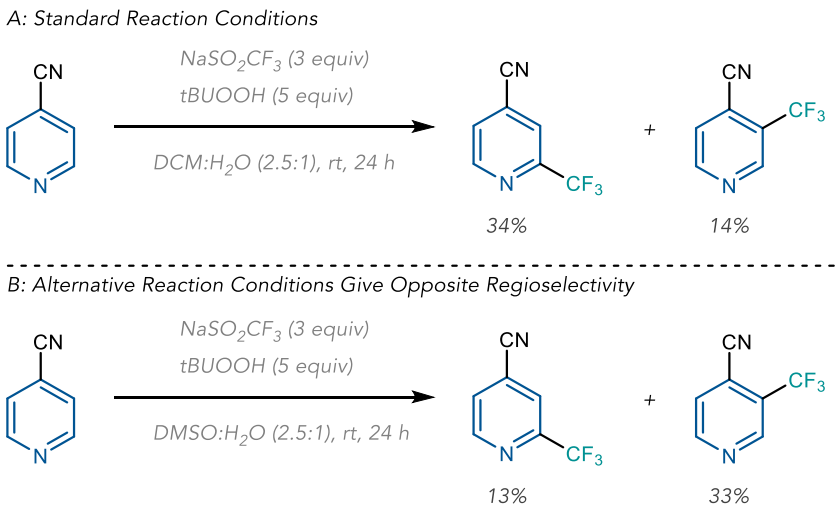


Figure 3.2. Baran's radical trifluoromethylation of azaarenes and alternative conditions.

In 2012, the Baran group extended their sulfinate chemistry to affect the difluoromethylation of heterocycles.[14] Initial attempts to access the difluoromethyl radical species with sodium difluoromethylsulfinate were unsuccessful. Through experimentation, it was found that zinc difluoromethylsulfinate (DFMS) was able to generate the desired nucleophilic radical. The reaction proceeds similarly to the previously discussed trifluoromethylation reaction. *t*BuOOH reacts with trace metal to generate *tert*-butoxy radical, which can react with the sulfinate to give the desired difluoromethyl radical. This radical species then adds to the heterocycle, and deprotonation gives the desired product (**Figure 3.4, A**). Conversely to the trifluoromethylation reaction, difluoromethylation occurs typically at the most electron-poor positions. Changing the solvent system from DCM/H_2O to DMSO/H_2O switches the inherent selectivity from the 2-position to the 3-position of pyridine just as was observed in the trifluoromethylation strategy (**Figure 3.3, B**).

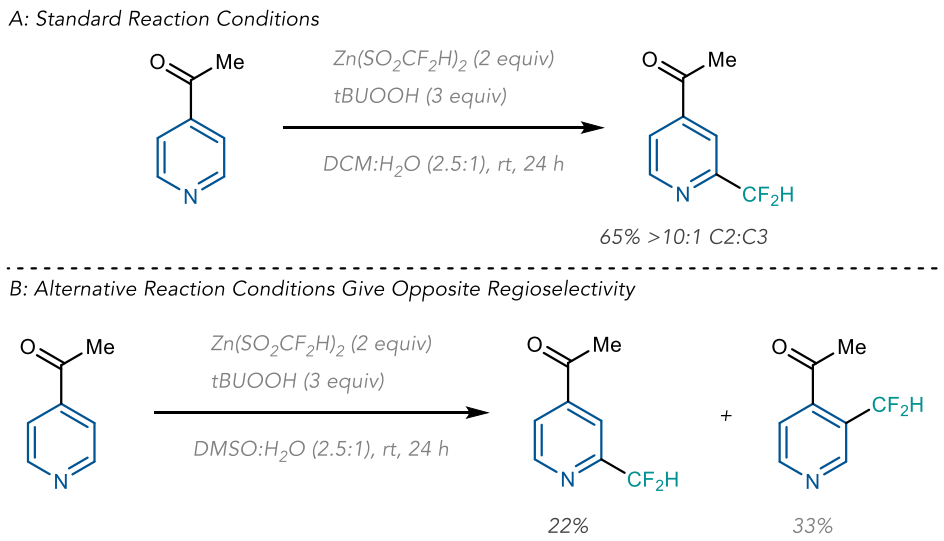


Figure 3.3. Baran's radical difluoromethylation of azaarenes and alternative conditions.

In 2011, MacMillan reported on a photoredox trifluoromethylation of arenes and azaarenes via a Minisci reaction.[9] In this reaction, a ruthenium (II) photocatalyst is excited by visible light and reduces trifluoromethylsuflonyl chloride in a single electron transfer event which decomposes to give trifluoromethyl radical. The trifluoromethyl radical then combines with the azaarene. The fluoroalkylated intermediate undergoes a single electron transfer event with the ruthenium (III) species to regenerate the active ruthenium (II) catalyst and form a carbocation. Deprotonation gives the 3-fluoroalkylated azaarene. MacMillan showed that this reaction could be applied to a number of azaarenes, including pyridines, pyrimidines, and pyrazines, but did give mixtures of regioisomers in some cases (**Figure 3.4**). One advantage of the Minisci approaches is their broad functional group tolerance, which allows them to be applied toward late-stage fluoroalkylation. To demonstrate this, MacMillan applied his fluoroalkylation strategy to the cholesterol medication Lipitor.

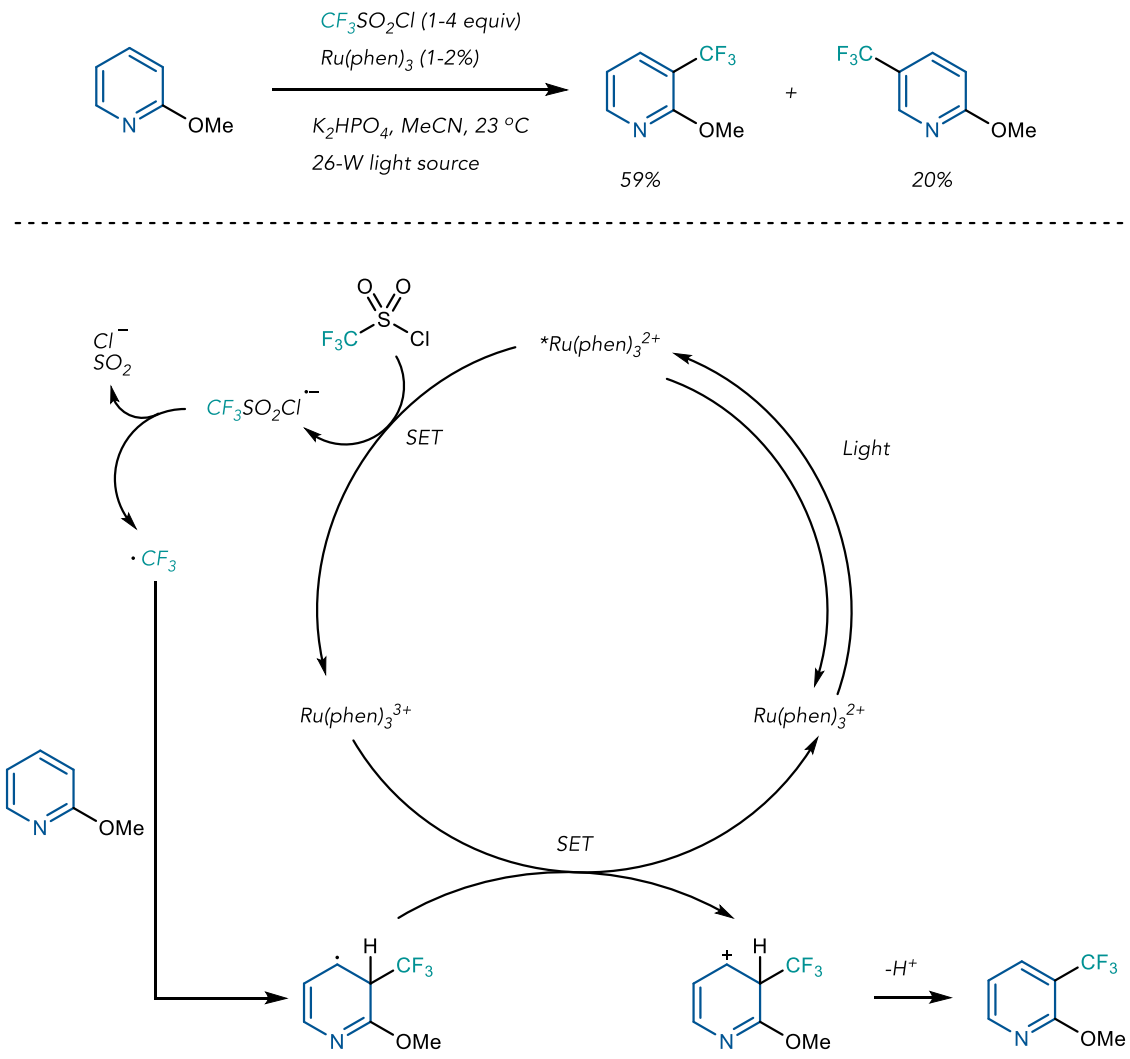


Figure 3.4. MacMillan's photoredox trifluoromethylation of azaarenes.

Corey Stephenson's group was interested in developing a scalable trifluoromethylation strategy for vinyl, aryl, and heteroaryl substrates.[10] Their aim was to utilize trifluoroacetic anhydride (TFAA) as a cheap trifluoromethyl radical source. The decarboxylation of trifluoroacetic acid (TFA) typically requires forcing temperatures or strong oxidants, limiting the scope of the reaction. To circumvent these limitations, the Stephenson group accomplished facile decarboxylation of TFAA by appending a sacrificial redox auxiliary to alter the electrochemical potential of the reagent. Pyridine N-oxide adds to the TFAA to form the corresponding adduct.

This adduct is then reduced by the excited state ruthenium (II) photocatalyst. The reduced adduct decarboxylates to generate pyridine, carbon dioxide, and trifluoromethyl radical. The trifluoromethyl radical reacts with the (hetero)arene, and the resulting radical is oxidized by the photocatalyst. Deprotonation gives the desired fluoroalkylated product. While this method is not directly applicable to pyridines, it can be accomplished on 2-pyridones, which can then be converted to the corresponding 2-halo-3-trifluoromethyl pyridine (**Figure 3.5**).

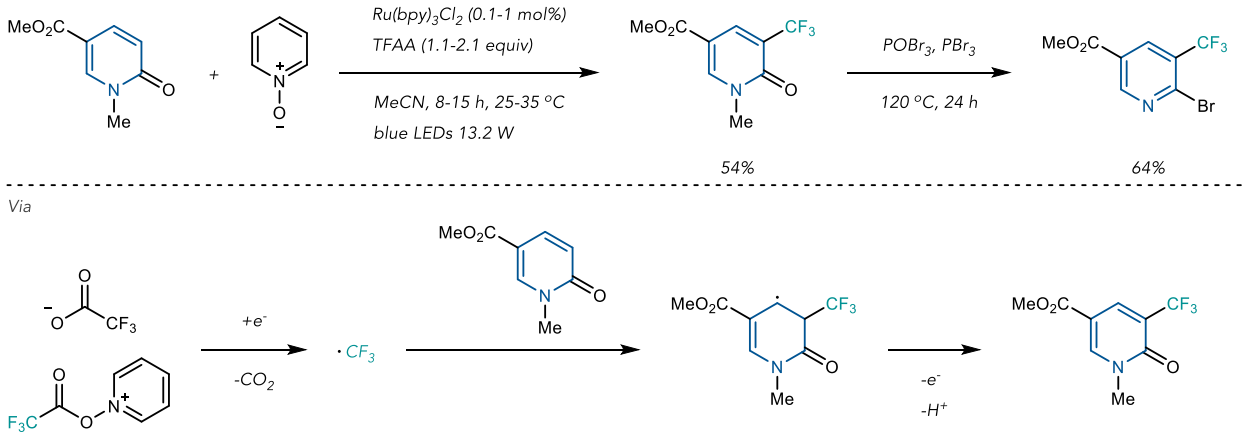


Figure 3.5. Stephenson's trifluoromethylation of 2-pyridone and conversion to trifluoromethylated pyridine.

Kanai's strategy for the direct fluoroalkylation of azaarenes represents one of the few, 4-selective fluoroalkylation reactions for azaarenes.[8] The selectivity is achieved via steric-shielding by a bulky boron Lewis acid, which activates the azaarene and blocks the 2- and 3-positions from attack. The azaarene is first reacted with $B(C_6F_4\text{-}4\text{-}CF_3)_3$ to form the pyridinium-borane complex, which can be isolated via column chromatography. Trifluoromethyltrimethylsilane and tetrabutylammonium difluorotriphenylsilicate (TBAT) react to generate the corresponding trifluoromethyl anion, which adds to the 4-position of the activated pyridinium-borane complex to form a dihydropyridine intermediate. Oxidation of the dearomatized intermediate with phenyl-λ3-iodanediyl bis(2,2,2-trifluoroacetate) (PIFA) gives the fluoroalkylated product (**Figure 3.6**).

While this fluoroalkylation reaction is mostly 4-selective, varying amounts of the 2-regioisomer are obtained depending on the substrate. In addition, the method requires multiple isolations to achieve the desired transformation, which can make the process challenging to apply toward late-stage fluoroalkylation.

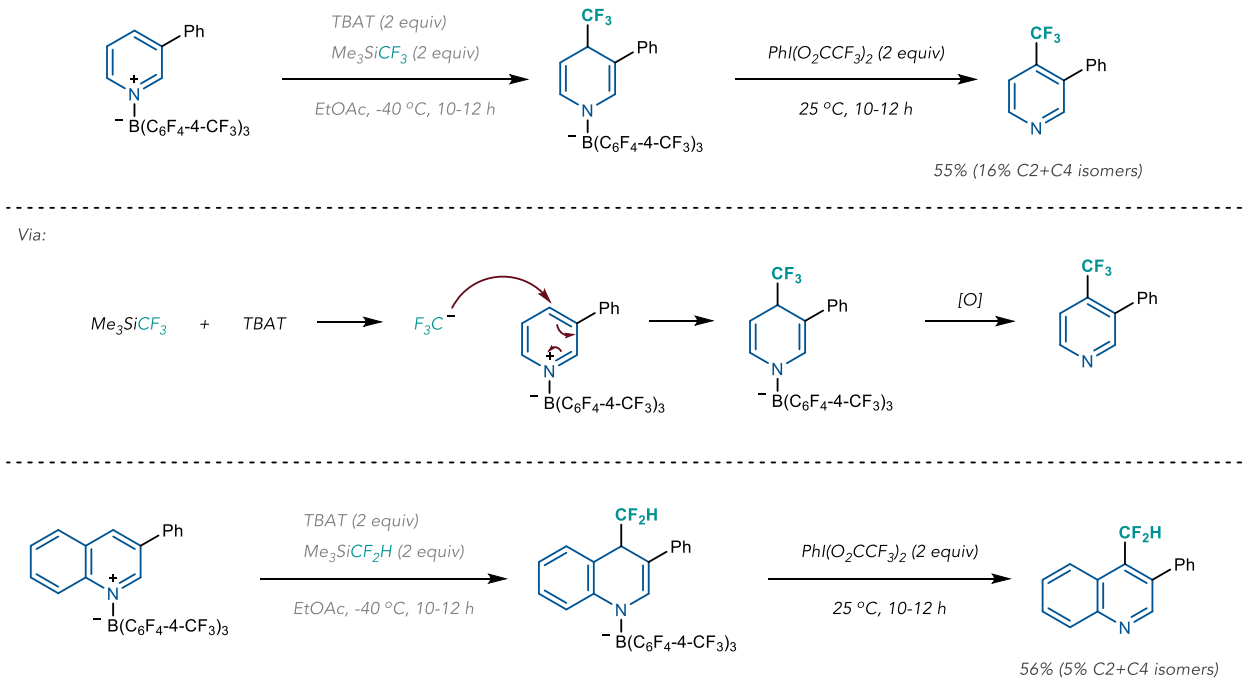


Figure 3.6. Kanai's strategy for trifluoromethylation and difluoromethylation of azaarenes.

In 2021, Tobias Ritter published his work on the development of a novel trifluoromethylation reagent, trifluoromethyl thianthrenium triflate (TT-CF_3^+ OTf^-), which can behave as a source of trifluoromethyl radical, trifluoromethyl anion, and trifluoromethyl cation. Utilizing this unique reagent as a trifluoromethyl radical source allowed the Ritter group to trifluoromethylate N-heterocycles. An excess of the azaarene is mixed with TT-CF_3^+ OTf^- in acetonitrile at room temperature under blue light irradiation. The TT-CF_3^+ OTf^-, under these conditions, will generate trifluoromethyl radical that then reacts with the N-heterocycle to give the trifluoromethylated azaarene (**Figure 3.7**). The group demonstrated this on a 2,6-disubstituted

pyridine and observed trifluoromethylation at the 3-position. As shown in the publication, the reaction can also be applied to more complex azaarenes such as caffeine.

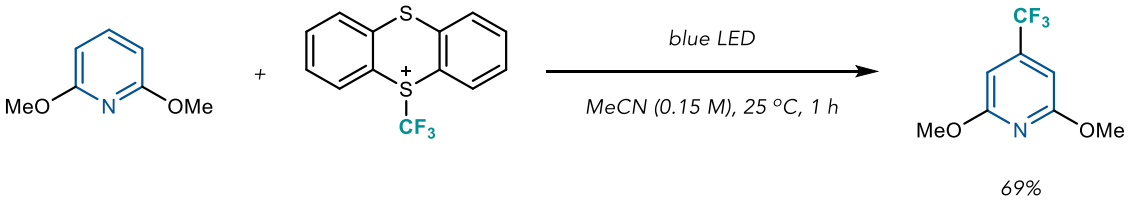


Figure 3.7. Ritter's trifluoromethyl thianthrenium triflate reagent for the radical trifluoromethylation of azaarenes.

3.3 Methods for Indirect Fluoroalkylation of Azaarenes

In 2012, Hartwig reported a method for the fluoroalkylation of (hetero)arenes and (hetero)aryl halides using stoichiometric copper.[15] The heteroarene or (hetero)aryl halide is first converted to the corresponding (hetero)arylboronate ester through iridium-catalyzed borylation or palladium-catalyzed borylation, respectively. The (phen)$CuCF_3$ then undergoes oxidative arylation with the (hetero)arylboronate ester in the presence of air to give the fluoroalkylated azaarene.[16] This method extends to other perfluoroalkyl groups to accomplish perfluoroethylation and perfluoropropylation. In this report, Hartwig only showed one example of pyridine fluoroalkylation. 2,6-di-tert-butyl pyridine is borylated at the 4-position via iridium-catalyzed borylation. The borylated intermediate is then subjected to the reaction conditions to give 2,6-di-tert-butyl-4-(trifluoromethyl)pyridine (**Figure 3.8, A**). Two major drawbacks of this strategy are the need to use stoichiometric amounts of copper and having to first form the boronic ester in the reaction. In the initial report, the Hartwig group was unable to directly convert (hetero)aryl bromides to the corresponding fluoroalkylated azaarenes, but in a subsequent publication in 2014, they demonstrated the conversion of heteroaryl bromides to fluoroalkylated heteroarenes using stoichiometric amounts of the same (phen)$CuCF_3$ catalyst. Here, the copper (I) species oxidatively

inserts into the heteroaryl bromide bond to generate a copper (III) species. This copper (III) species then undergoes reductive elimination to give the desired product (**Figure 3.8, B**). Despite allowing the reaction to be accomplished directly on the heteroaryl bromide, this reaction still requires the use of stoichiometric copper.

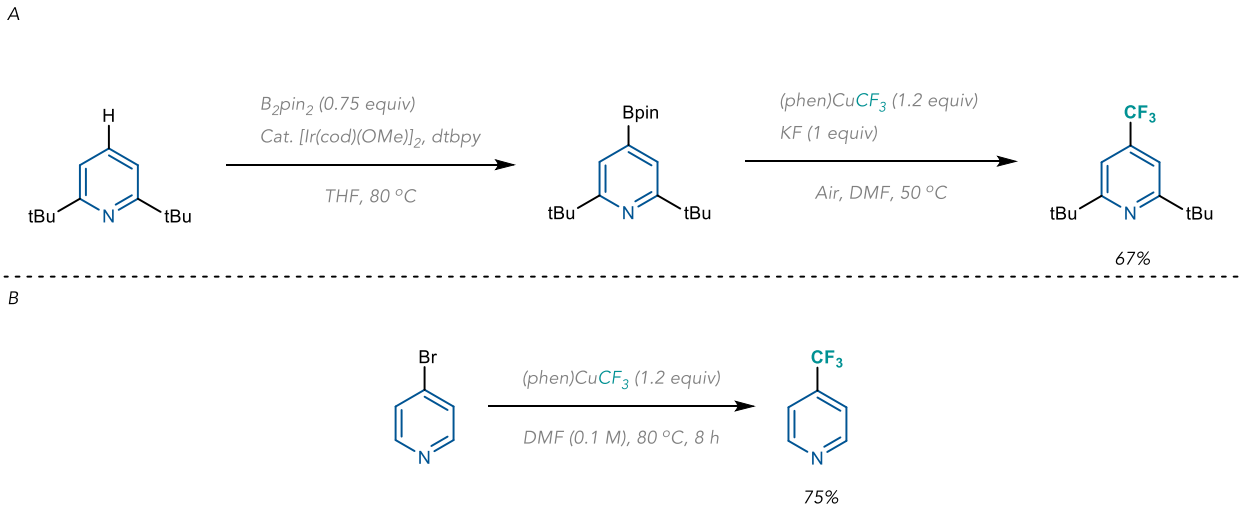


Figure 3.8. Hartwig's fluoroalkylation of borylated and halogenated (hetero)arenes.

The Sanford group published a catalytic trifluoromethylation of (hetero)aryl boronic acids, which utilizes a copper catalyst and a ruthenium (II) photocatalyst. They used the same photoredox strategy previously employed by MacMillan to access the trifluoromethyl radical under mild conditions from trifluoroiodomethane.[17] The ruthenium (II) is excited by visible light and undergoes a single electron transfer event with copper (I) to give copper (II) and ruthenium (I). Reduction of the trifluoroiodomethane by the ruthenium (I) regenerates ruthenium (II) and gives trifluoromethyl radical, which then adds to the copper (II) species to give a copper (III) intermediate. This intermediate reacts with the (hetero)aryl boronic acid in a base-promoted transmetalation. A subsequent reductive elimination gives the trifluoromethylated (hetero)arene and copper (I) to complete the catalytic cycle (**Figure 3.9**).

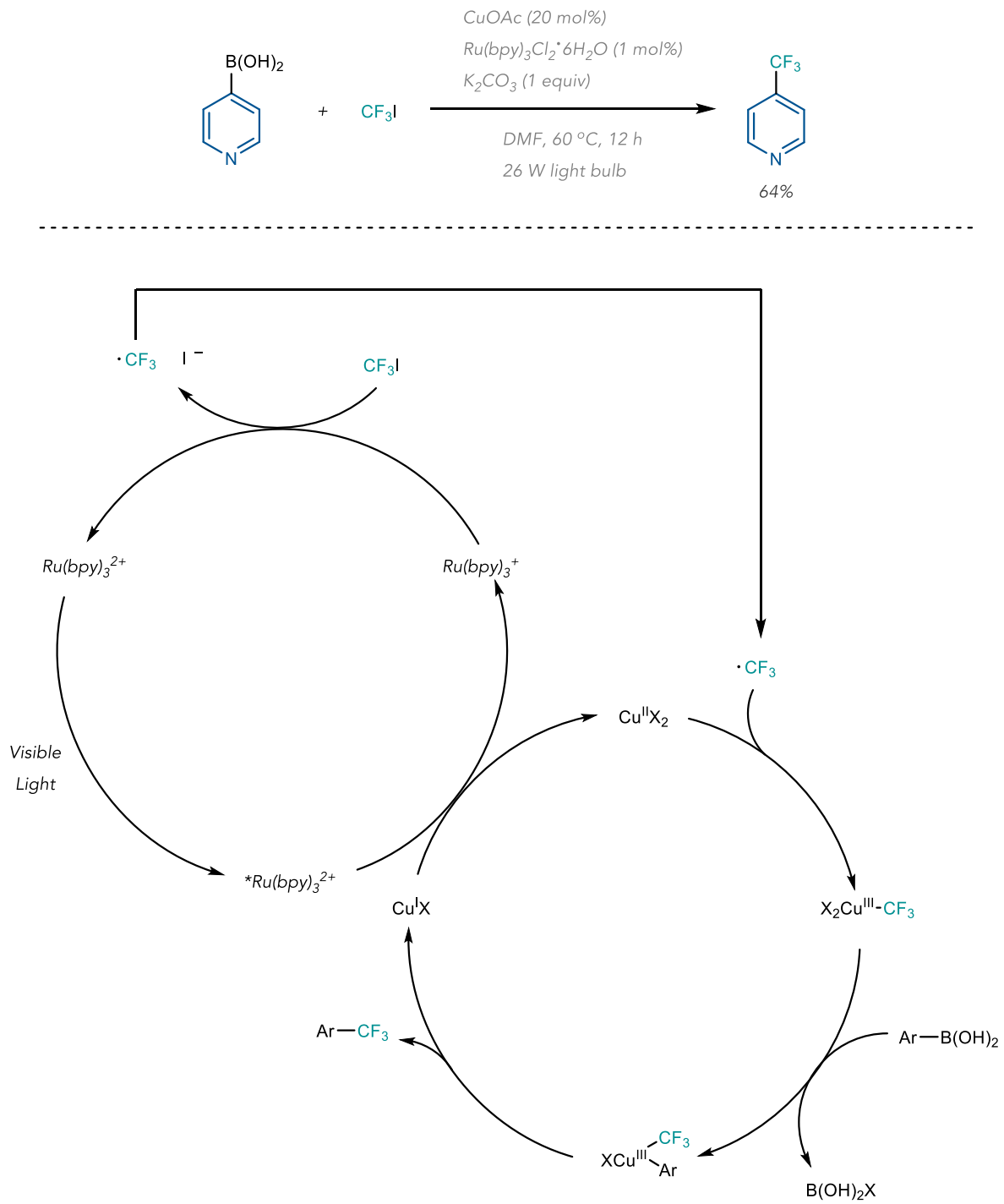


Figure 3.9. Sanford's copper-catalyzed photoredox trifluoromethylation of (hetero)arenes.

In 2018, MacMillan and co-workers published a photoredox difluoromethylation of (hetero)aryl halides.[18] This silyl-radical mediated difluoromethylation strategy uses an iridium

photocatalyst and a nickel catalyst to accomplish the desired transformation. The iridium (III) photocatalyst is excited by visible light. In a single electron transfer event, the excited state iridium (III) then oxidizes bromine anion to bromine radical. The bromine radical then abstracts a hydrogen atom from tris(trimethylsilyl)silane ($(TMS)_3SiH$) to form the corresponding silyl radical, which then abstracts a hydrogen atom from bromodifluoromethane to generate difluoromethyl radical. Concurrently to the photocatalytic cycle, nickel (0) undergoes oxidative addition into the (hetero)aryl bromide to generate a nickel (II) species. The difluoromethyl radical then adds to the nickel (II) species to generate the corresponding nickel (III) species. Reductive elimination gives the difluoromethylated (hetero)arene and a nickel (I) species which is reduced by iridium (II) to regenerate the active catalyst, nickel (0), and the iridium (III) photocatalyst (**Figure 3.10**).

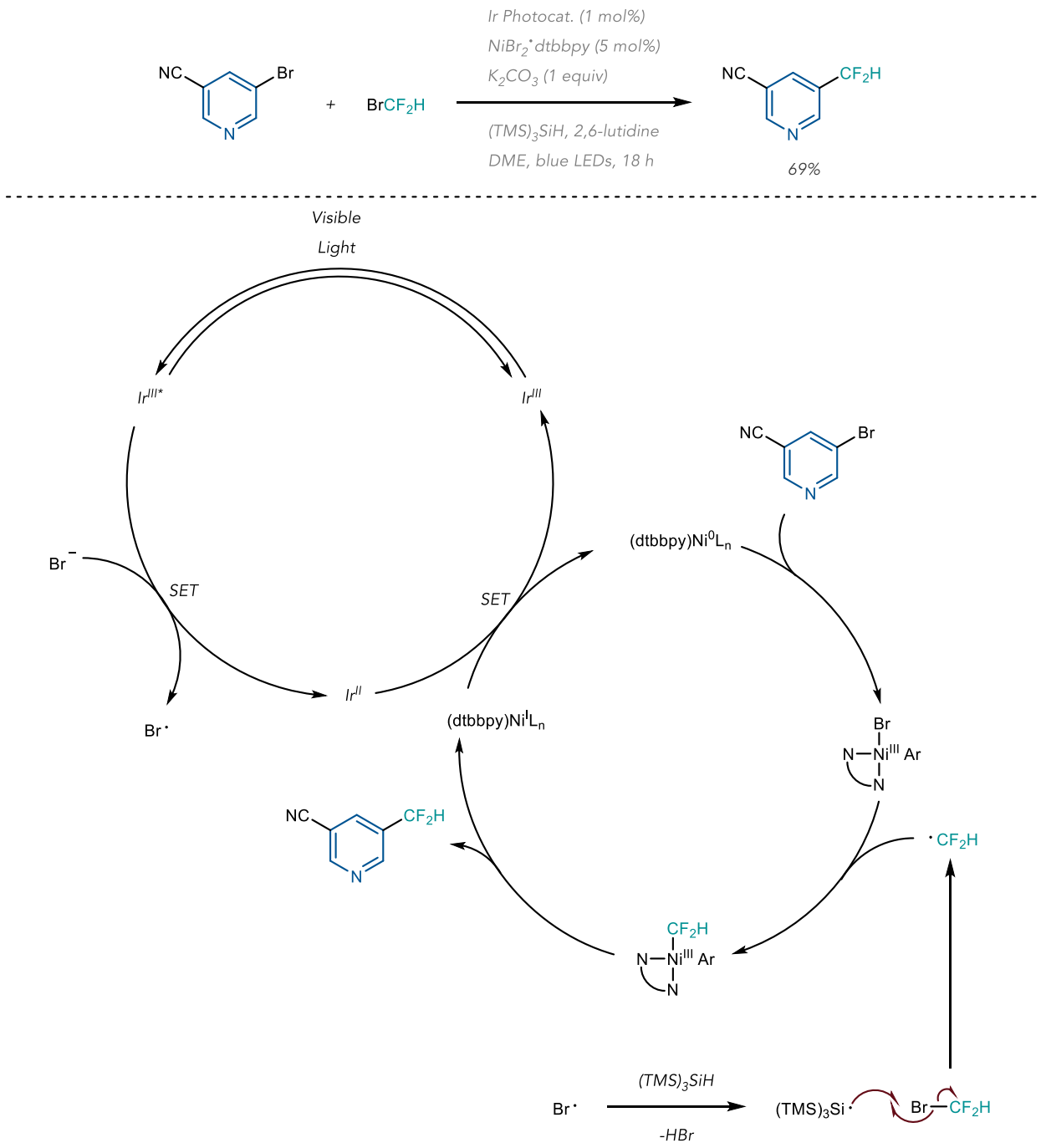


Figure 3.10. MacMillan's nickel-catalyzed photoredox difluoromethylation of (hetero)arenes.

3.4 Introduction to Phosphorus Ligand-Coupling

Heteroaryl-Heteroaryl couplings had been previously demonstrated in the literature by several groups, but the inability to form the necessary bis-heterobiaryl phosphonium salt in a generic manner on a broad range of azaarenes greatly limited this strategy to access bis-azaarenes.[19–23] In 2018, the McNally lab published on the synthesis of these valuable bis-heterobiaryls via pentavalent phosphorus ligand-coupling.[24] The lab was able to employ the phosphonium salt chemistry it had previously developed to form the necessary bis-heterobiaryl phosphonium salts on a broad range of azaarenes. This transformation was accomplished by utilizing a designed, fragmentable phosphine in the phosphonium salt-forming reaction. Upon addition of excess DBU, deprotonation of the phosphonium salt eliminates methyl acrylate and gives the corresponding pyridyl phosphine. This pyridyl phosphine can then be used in a subsequent phosphonium salt-forming reaction to generate the desired bis-heterobiaryl phosphonium salt (**Figure 3.11**). Utilizing this strategy, the McNally lab was able to form the previously elusive bis-heterobiaryl phosphonium salts on a broad range of pyridines and diazines. Heating the bis-heterobiaryl phosphonium salt in an alcoholic solvent in the presence of acid gives the desired bis-heterobiaryl product. This strategy allows for the formation of 4,4'- 2,4-, and 2,2'-bis-heterobiaryl products. Not only is this strategy shown on a broad range of building-block azaarenes, but it is also shown to be capable of coupling complex, drug-like fragments, and pharmaceuticals. This strategy allows for the rapid formation of complex bipyridine scaffolds through a previously under-exploited phosphorus ligand-coupling mechanism.

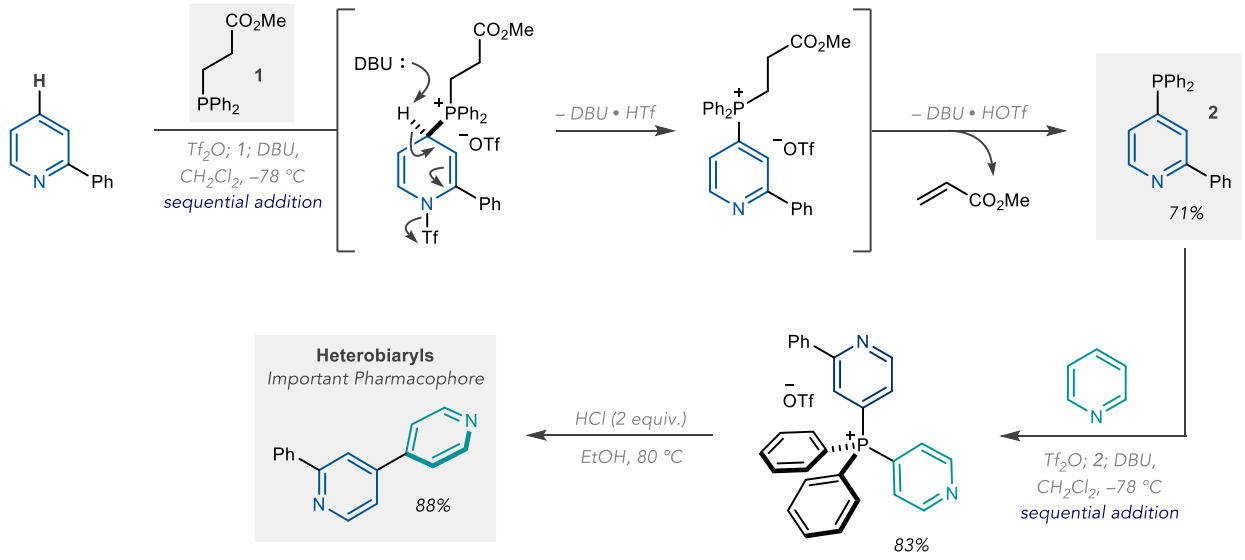


Figure 3.11. Phosphorus ligand-coupling strategy for bis-heterobiaryl synthesis.

Through computational calculations done by the Paton lab, the McNally lab was able to determine a great deal about the pentavalent phosphorus ligand-coupling reaction mechanism. Both pyridines on the bis-heterobiaryl phosphonium salt are first protonated. This protonation lowers the barrier for ligand-coupling and increases the electrophilicity of the phosphonium salt. Next, a nucleophile, methanol (MeOH), adds to the phosphorus center to form a pentavalent phosphorane intermediate. In this pentavalent phosphorane intermediate, the orientation of the ligands was shown to be very important for productive ligand-coupling to occur. One pyridine will adopt the apical position, and the other will adopt the equatorial position. The apical pyridine will experience the trans effect, an elongation of the carbon-phosphorus bond, and subsequent negative charge build-up on the ipso-carbon. The more electron-deficient pyridine will adopt the apical position as it can better stabilize this build-up of negative charge. The apical pyridine will then migrate to the equatorial pyridine, which acts as an electron sink in an asynchronous ligand-coupling event. Rearomatization and displacement of phosphine oxide gives the desired bis-heterobiaryl product (**Figure 3.12**).

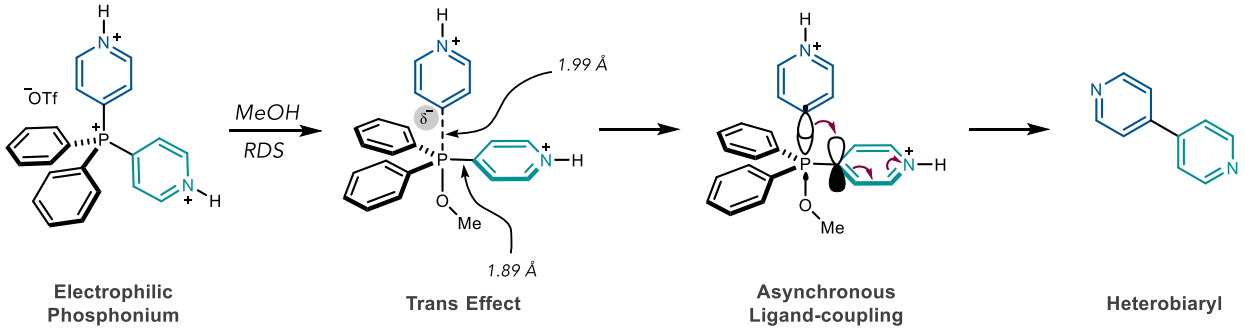


Figure 3.12. Phosphorus ligand-coupling mechanism for bis-heterobiaryl synthesis.

3.5 Initial Reaction Development

Following the bis-heterobiaryl synthesis, we wanted to expand the scope of the phosphorous ligand-coupling reaction from sp^2-sp^2 coupling to sp^2-sp^3 coupling. There is only one example of sp^2-sp^3 coupling from a phosphorus center previously reported in the literature. In 1989, Uchida reacted benzyldi(pyridin-2-yl)phosphine oxide with a benzyl Grignard and observed small amounts of sp^2-sp^3 coupled product. Given the level of understanding gained from the bis-heterobiaryl project about the pentavalent phosphorus ligand-coupling mechanism, we understood several criteria needed to be met in order for productive sp^2-sp^3 ligand-coupling to occur. As previously stated, the orientation of the ligands is vital for the reaction to give the desired product. For productive ligand-coupling to occur, the pyridine must adopt the equatorial position so that it may act as an electron sink and allow for asynchronous ligand-coupling to occur. This is because apical-equatorial coupling in a concerted mechanism is symmetry disallowed. This also necessitates that the sp^3 group must adopt the apical position. If the pyridine were to adopt the apical position, it would be unable to migrate to the sp^3 center and will eventually be protonated to give undesired C-H pyridine. To ensure that the sp^3 group adopts the apical position, it must stabilize the build-up of negative charge that occurs due to the trans effect (**Figure 3.13**).

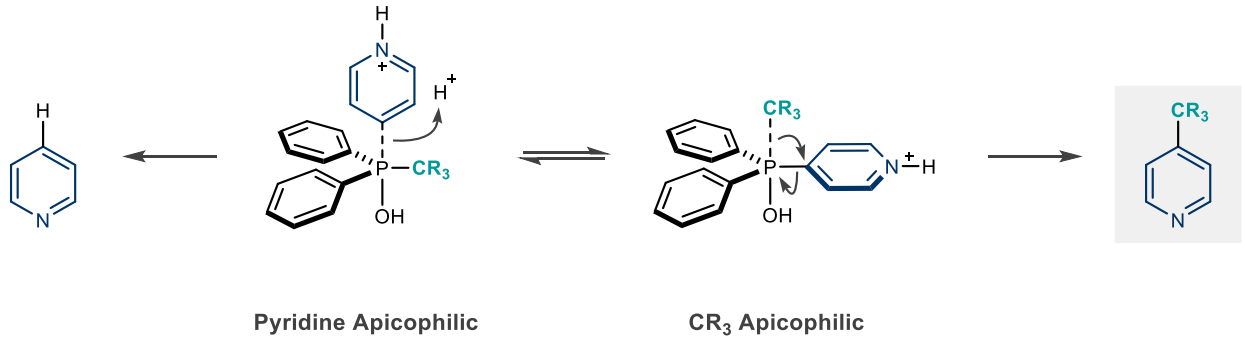


Figure 3.13. Potential ligand orientations for sp^2-sp^3 ligand-coupling on pentavalent phosphorus.

Fluoroalkyl groups represent an ideal sp^3 center for this ligand-coupling reaction for several reasons. Fluoroalkylated azaarenes are valuable motifs in pharmaceuticals and agrochemicals. Additionally, the electron-deficient nature of the fluoroalkyl groups is well suited to stabilize the build-up of negative charge and are therefore likely to adopt the apical position in the pentavalent phosphorane intermediate. For these reasons, we hypothesized that the fluoroalkyl groups would make ideal coupling partners for an sp^2-sp^3 ligand-coupling from a pentavalent phosphorus center. We wished to develop a one-pot fluoroalkylation strategy that would allow for the 4-selective fluoroalkylation of pyridines and diazines. First, we would synthesize fluoroalkyl phosphines and use them in the phosphonium salt-forming reaction our lab had previously developed. After the salt had been formed, we would then add acid and a nucleophile to trigger the ligand-coupling event to generate the desired fluoroalkylated azaarene. Initial calculations from the Paton group indicated that the sp^2-sp^3 ligand-coupling had a ΔG of 19 Kcal/mol for the trifluoromethyl and difluoromethyl groups which suggests the process would be facile at room temperature (**Figure 3.14**).

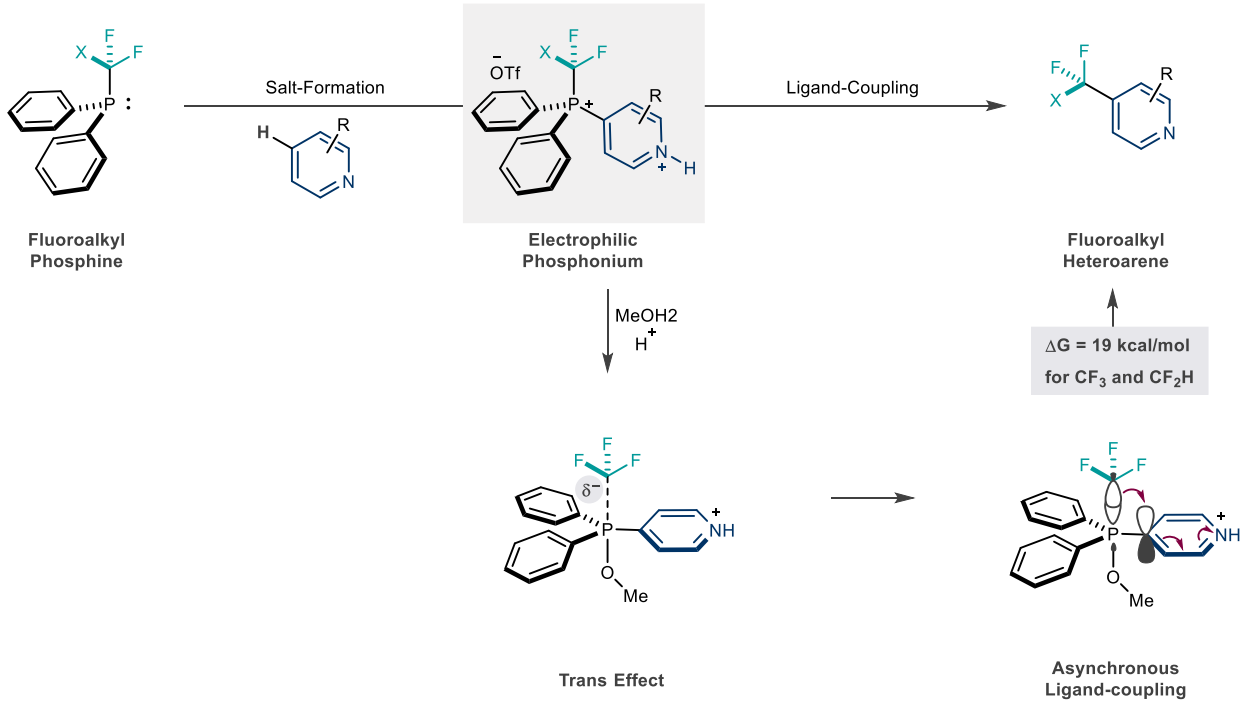


Figure 3.14. Initial plan for one-pot fluoroalkylation of pyridines and diazines via phosphorus ligand-coupling.

To determine if this strategy was feasible, we first sought to synthesize the trifluoromethyl phosphonium salt. We attempted to use our standard phosphonium salt-forming reaction with 2-phenyl pyridine using diphenyl(trifluoromethyl)phosphine. Unexpectedly, none of the desired trifluoromethyl phosphonium salt was detected after an aqueous workup. However, we observed trace amounts of 2-phenyl-4-(trifluoromethyl)pyridine (**Figure 3.15**). Although the reaction did not give the expected product, we hypothesized that the ligand-coupling is very facile and occurred during the aqueous workup. Only small amounts of phosphonium salt are being made under these reaction conditions. This is most likely due to the decreased nucleophilicity of the diphenyl(trifluoromethyl)phosphine compared to triphenylphosphine.

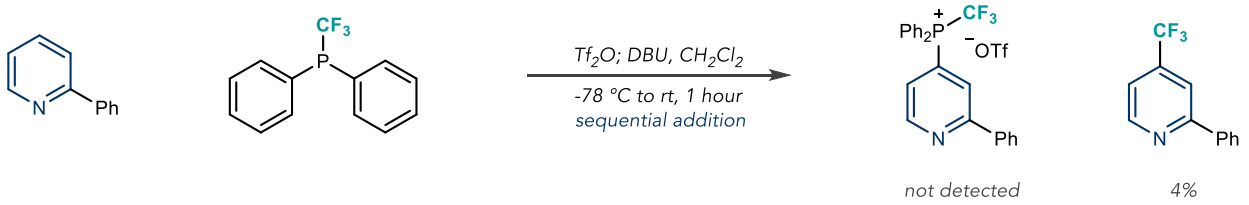


Figure 3.15. Initial attempt at forming trifluoromethyl phosphonium slat on 2-phenyl pyridine. Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

3.6 Reaction Optimization

Based on the initial attempt to form the phosphonium salt, it was determined that more nucleophilic phosphines were needed in order to improve the yield of the phosphonium salt reaction. In 2019, the Prakash lab published on the synthesis of fluoroalkylated phosphines. Interestingly, using this strategy, both the trifluoromethyl phosphine and the difluoromethyl phosphine oxide can be accessed using trifluoromethyltrimethylsilane (Rupert's reagent) as the fluoroalkyl source in both cases.[25] After some reaction optimization, this strategy allowed for the synthesis of several more nucleophilic trifluoromethyl and difluoromethyl phosphines, which were then applied to the phosphonium salt-forming reaction (**Figure 3.16**).

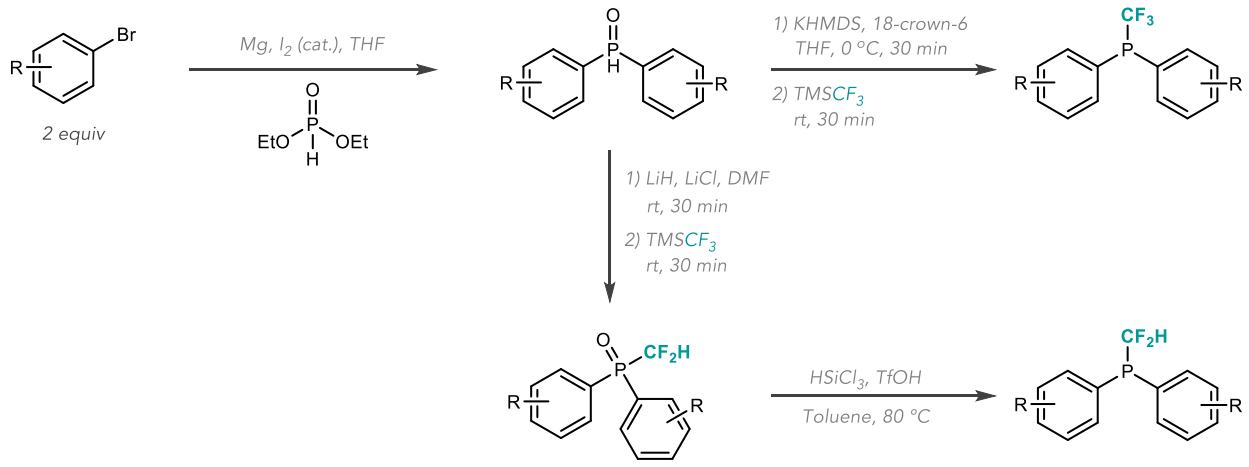
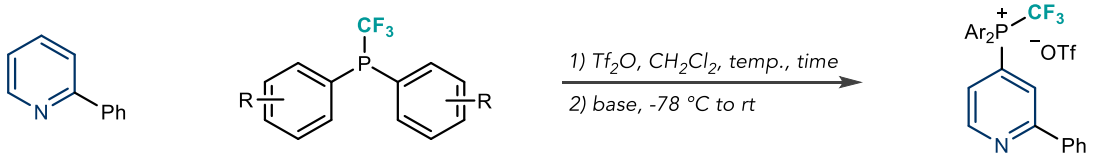


Figure 3.16. Synthetic route for trifluoromethyl and difluoromethyl phosphines.

With an efficient synthesis in hand, a number of more nucleophilic phosphines were synthesized by varying the substituents at the para-position of the aryl rings. As previously hypothesized, the more nucleophilic the phosphine, the higher the yield of the corresponding phosphonium salt. In the case of the trifluoromethyl phosphines, 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine gave the highest yield. The temperature was also explored, but the standard -78 °C proved optimal (**Table 3.1**).

Table 3.1. Optimization of heteroaryl phosphonium salt formation for trifluoromethylphosphines.[a]

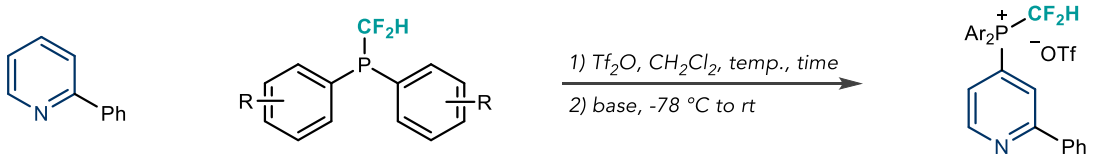


Entry	R	temp. (°C)	Time (min)	base	T.M. % Yield[a]
1	H	-78	30	DBU	n.d.
2	OMe	-78	30	DBU	54
3	NMe_2	-78	30	DBU	81
4	N-pyrrolidinyl	-30	30	DBU	76
5	N-pyrrolidinyl	-50	30	DBU	81
6	N-pyrrolidinyl	-78	30	DBU	85

[a]Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

A similar optimization was performed on the difluoromethyl phosphines. In this case, the difluoromethyl group is not as withdrawing as the trifluoromethyl group, and thus the (difluoromethyl)bis(4-methoxyphenyl)phosphane proved to be nucleophilic enough to increase the yield of the phosphonium salt reaction into a suitable range. The time and temperature of the reaction were also explored, and it was found that 30 minutes at -78 °C was sufficient to give good conversion to the phosphonium salt. Alternative bases were also explored, but it was found that the standard DBU gave the highest yield and was most consistent (**Table 3.2**).

Table 3.2. Optimization of heteroaryl phosphonium salt formation for difluoromethylphosphines.[a]

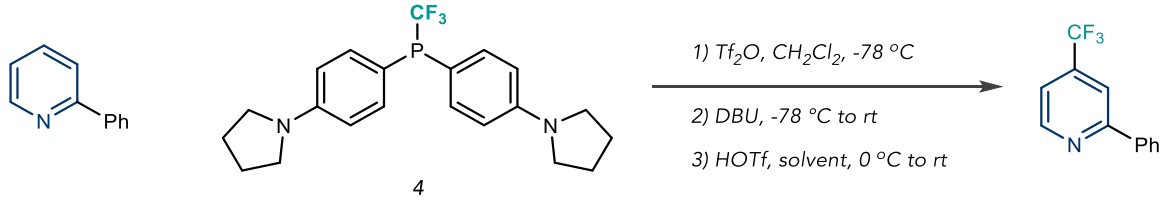


Entry	R	temp. (°C)	Time (min)	base	T.M. % Yield[a]
1	H	-50	60	DBU	65
2	OMe	-50	60	DBU	68
3	Me	-50	60	DBU	83
4	Me	-30	60	DBU	66
5	Me	-78	60	DBU	84
6	Me	-78	30	DBU	85
7	Me	-78	15	DBU	79
8	Me	-78	30	Et_3N	79
9	Me	-78	30	TBD	51
10	Me	-78	30	MTBD	82
11	Me	-78	30	TMG	70
12	OMe	-78	30	DBU	90

[a]Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Having optimized the phosphonium salt formation, we then turned our attention to the ligand-coupling step of the reaction. We sought to develop several different conditions to trigger the ligand-coupling to suit sensitive functionalities in potential substrates. Based on the bis-heterobiaryl synthesis project, we hypothesized that the desired coupling reaction could be accomplished under acidic conditions in alcoholic solvents. For acidic conditions, it was found that 1.5 equivalents of triflic acid in MeOH with 10 equivalents of water gave the desired ligand-coupled product after stirring for 12 hours at room temperature. In the case of substrates with acid-sensitive functionalities such as esters, neutral conditions were also developed. Stirring for 24 hours at room temperature in the presence of methanol and 10 equivalents of water gave the fluoroalkylated product in good yields (**Table 3.3**).

Table 3.3. Optimization of acidic coupling conditions for trifluoromethylation of azaarenes.[a]

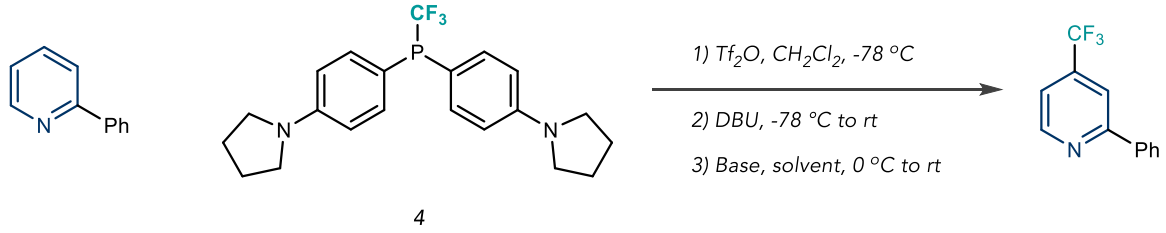


Entry	HOTf (equiv)	Solvent	Time (h)	T.M. % Yield[a]
1	1	MeOH/H_2O = 1/1	18	76
2	1	MeOH/H_2O = 4/1	18	79
3	1	MeOH/H_2O = 9/1	18	71
4	1	MeOH (0.5 mL), H_2O (10 equiv)	18	80
5	1.5	MeOH (0.5 mL), H_2O (10 equiv)	12	84
6	2	MeOH (0.5 mL), H_2O (10 equiv)	12	81
7	1.5	MeOH (1.0 mL), H_2O (10 equiv)	12	85
8	1.5	MeOH (0.25 mL), H_2O (10 equiv)	12	82
9	1.5	THF (0.5 mL), H_2O (10 equiv)	12	79
10	1.5	EtOH (0.5 mL), H_2O (10 equiv)	12	80
11	1.5	IPA (0.5 mL), H_2O (10 equiv)	12	75
12	1.5	TFE (0.5 mL), H_2O (10 equiv)	12	---
13	0	MeOH (0.5 mL), H_2O (10 equiv)	24	77

[a]Yields determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard.

In addition to acidic and neutral conditions, basic conditions to trigger ligand-coupling were also explored. These conditions give slightly lower yields than the acidic conditions; however, they provide the desired products in significantly less time. Using 3 equivalents of sodium bicarbonate in tetrahydrofuran (THF) with 10 equivalents of water gave the fluoroalkylated product in good yield in only 30 minutes. This is significantly faster than the acidic conditions, which typically require 12-24 hours to reach completion. In addition, sodium bicarbonate can be used without any water for water-sensitive substrates, albeit the reaction is significantly slower, taking 24 hours to reach completion (**Table 3.4**).

Table 3.4. Optimization of basic coupling conditions for trifluoromethylation of azaarenes.[a]



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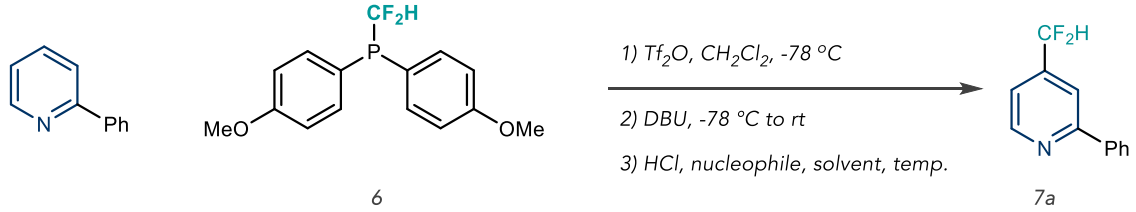
Entry	Base (equiv)	Solvent	Time	T.M. % Yield[a]
1	NaOMe (3)	MeOH	30 min	0
2	NaOMe (3)	THF	30 min	12
3	$NaHCO_3$ (3)	THF	24 h	73
4	Na_2CO_3 (3)	THF	24 h	13
5	NaO^tBu (3)	THF	30 min	0
6	$NaHCO_3$ (3)	CH_3CN	20 h	57
7	$NaHCO_3$ (3)	DMF	20 h	0
8	$NaHCO_3$ (3)	THF (0.5 mL), H_2O (10 equiv)	30 min	78

[a]Yields determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Coupling conditions were also explored for the difluoromethylation reaction. For this coupling, acidic, basic, and anhydrous conditions were developed to accommodate a variety of substrates. For the acidic conditions, HCl is used to protonate the azaarene nitrogen, water is used as the nucleophilic trigger, and the reaction is complete in 24 hours after heating to 40 °C in ethanol (EtOH). Basic conditions using potassium carbonate as the nucleophilic trigger in water and THF gives the coupled product after 15 minutes at room temperature. In the case of substrates that are water sensitive, fluoride can also act as the nucleophilic trigger. Treating the phosphonium salt with TBAF at 40 °C in THF for 14 hours gives good conversion to the fluoroalkylated product (**Table 3.5**).

Table 3.5. Optimization of coupling conditions for difluoromethylation of azaarenes.[a]



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Entry	nucleophile	temp. (°C)	Solvent	time	T.M. % Yield[a]
1	MeOH	rt	MeOH	>48 h	---
2	MeOH	40	MeOH	>48 h	---
3	H_2O	rt	MeOH	>48 h	---
4	H_2O	40	MeOH	36 h	79
5	H_2O	40	EtOH	24 h	81
6	H_2O	40	THF	24 h	79
7	H_2O	40	iPrOH	24 h	80
8	CsF	rt	THF	>48 h	---
9	TBAF	40	THF	14 h	75
10	TBAF	rt	THF	14 h	61
11	K_2CO_3[b]	rt	H_2O/THF	15 min	64
12	$NaHCO_3$[b]	rt	H_2O/THF	15 min	43

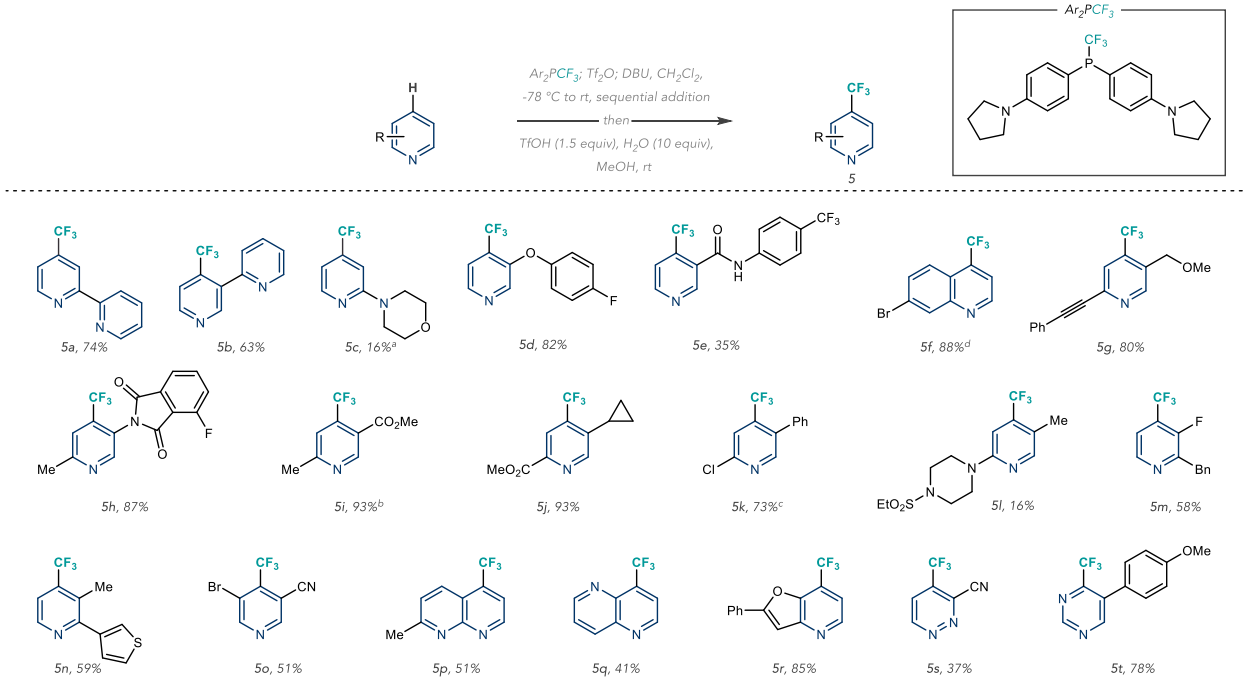
[a]Yields determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard.

3.7 Reaction Scope

With optimized conditions for the phosphonium salt formation and multiple conditions for the ligand-coupling step, we set out to determine the scope of this fluoroalkylation strategy. We began by exploring the building-block scope for the trifluoromethylation reaction. The reaction is amenable to a variety of substitution patterns, including 2-substituted (**5a & 5c**), 2,3-disubstituted (**5m & 5n**), 2,5-disubstituted pyridines (**5g-5l**), and even sterically encumbered 3,5-disubstituted pyridines (**5o**) are amenable. In all these cases, selectivity for the 4-position is maintained. This process can also be extended to diazines, with pyridazine (**5s**) and pyrimidine (**5t**) both transformed to the corresponding fluoroalkylated products. Both electron-donating groups such as morpholine (**5c**) and withdrawing groups such as esters, halides, and nitriles are also well tolerated under the reaction conditions (**Table 3.6**).

Several notable limitations to this approach to trifluoromethylation should be noted. One limitation is 2,6-disubstituted N-heterocycles, and 2-trifluoromethyl N-heterocycles are not amenable as they are unreactive toward triflic anhydride. Free alcohols and amides other than N-aryl amides are not suited to this reaction, as those functionalities can react with triflic anhydride over the heterocyclic nitrogen. Alkoxides and alkylamines at the 2- or 3-position tend to give low yields due to protodephosphination.

Table 3.6. Building-block azaarene scope for trifluoromethylation.

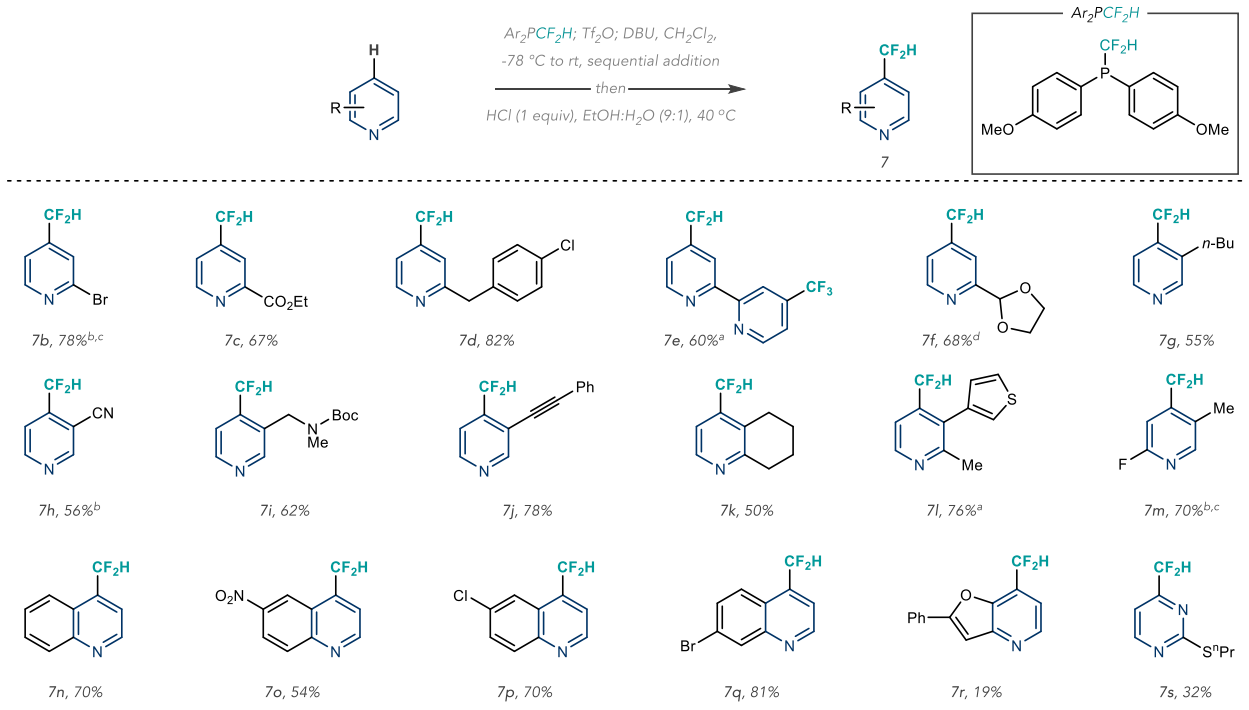


The building-block scope for the difluoromethylation reaction was also explored (**Table 3.7**). While not as general as the trifluoromethylation reaction, the difluoromethylation strategy still applies to a broad range of N-heterocycles and compares favorably to other direct difluoromethylation strategies. The reaction can tolerate 2-substituted (**7b-7d**), 3-substituted (**7g-7j**), 2,3-disubstituted (**7k & 7l**), and 2,5-disubstituted azaarenes (**7m**). 2-Halopyridines are well tolerated; however, basic conditions are required for ligand-coupling to occur. Under acidic

conditions, the phosphonium salt is unreactive toward the water nucleophile. We hypothesized that this is due to insufficient activation of the pyridine nitrogen in these substrates. The reaction tolerates neutral and deficient groups well and can be extended to diazines such as pyrimidine (**7s**).

The difluoromethylation does have several limitations which should be noted. Similar to the trifluoromethylation reaction, 2,6-disubstituted pyridines and 2-trifluoromethyl pyridines are unreactive for the phosphonium salt formation. Alcohols and N-alkyl amides are also unreactive in this system. 3-Halopyridines, 3-esters, 3,5-disubstituted pyridines, as well as alkoxylated and aminated pyridines suffer from poor conversion from phosphonium salt to fluoroalkylated pyridines due to protodephosphination.

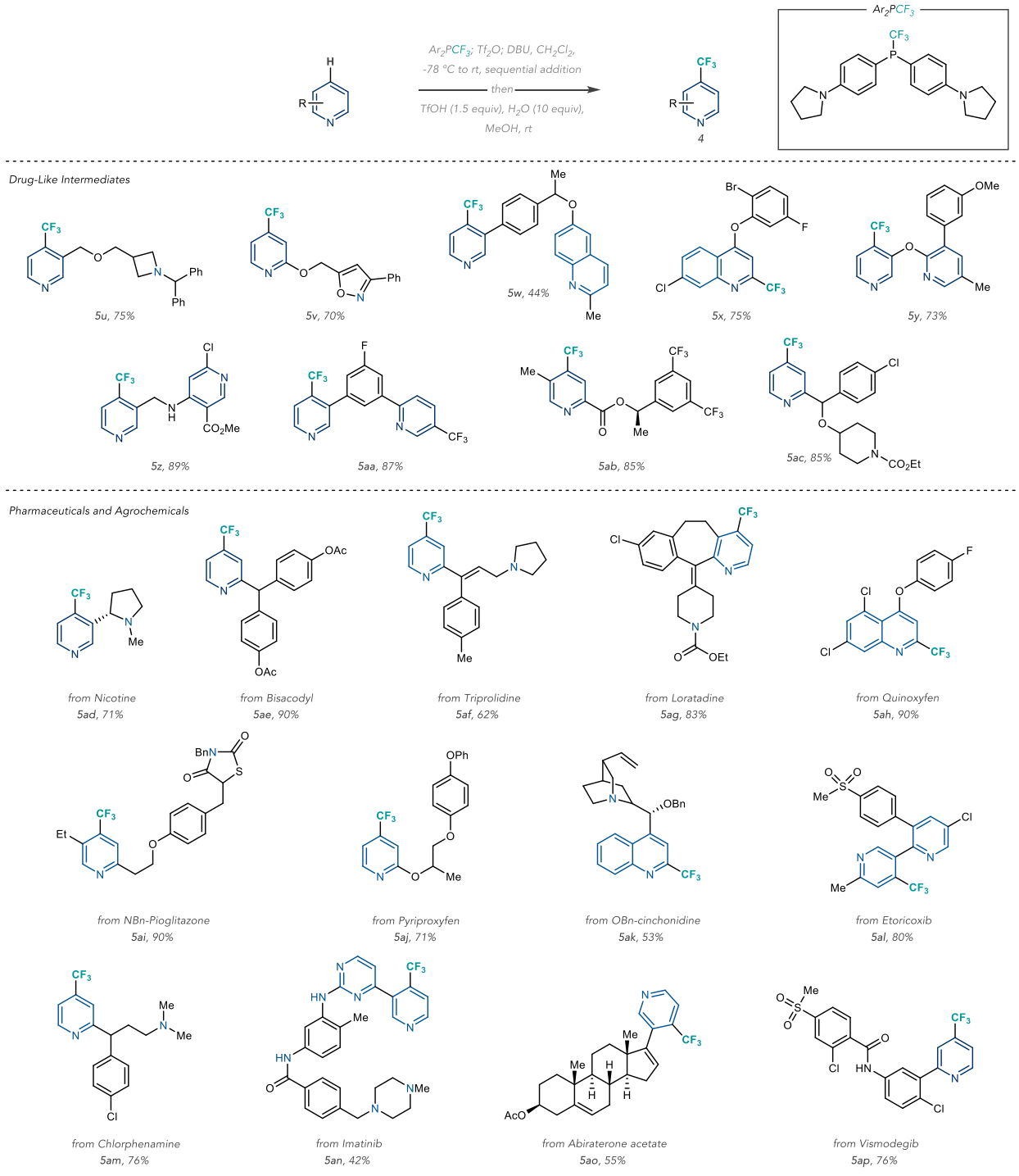
Table 3.7. Building-block azaarene scope for difluoromethylation.



After exploring the building-block scope of the reaction, more complex drug-like intermediates, pharmaceuticals, and agrochemicals were explored (**Table 3.8**). The

trifluoromethylation reaction can be extended to a number of complex examples. Even in cases such as **5aa** and **5an**, where there are multiple sites of reactivity, only a single regioisomer is obtained in both cases. This can be considered advantageous over other fluoroalkylation strategies such as Minisci reactions which tend to give mixtures of regioisomers. The broad range of pharmaceuticals and agrochemicals shown illustrates that this strategy is viable for the direct, late-stage fluoroalkylation of complex molecules.

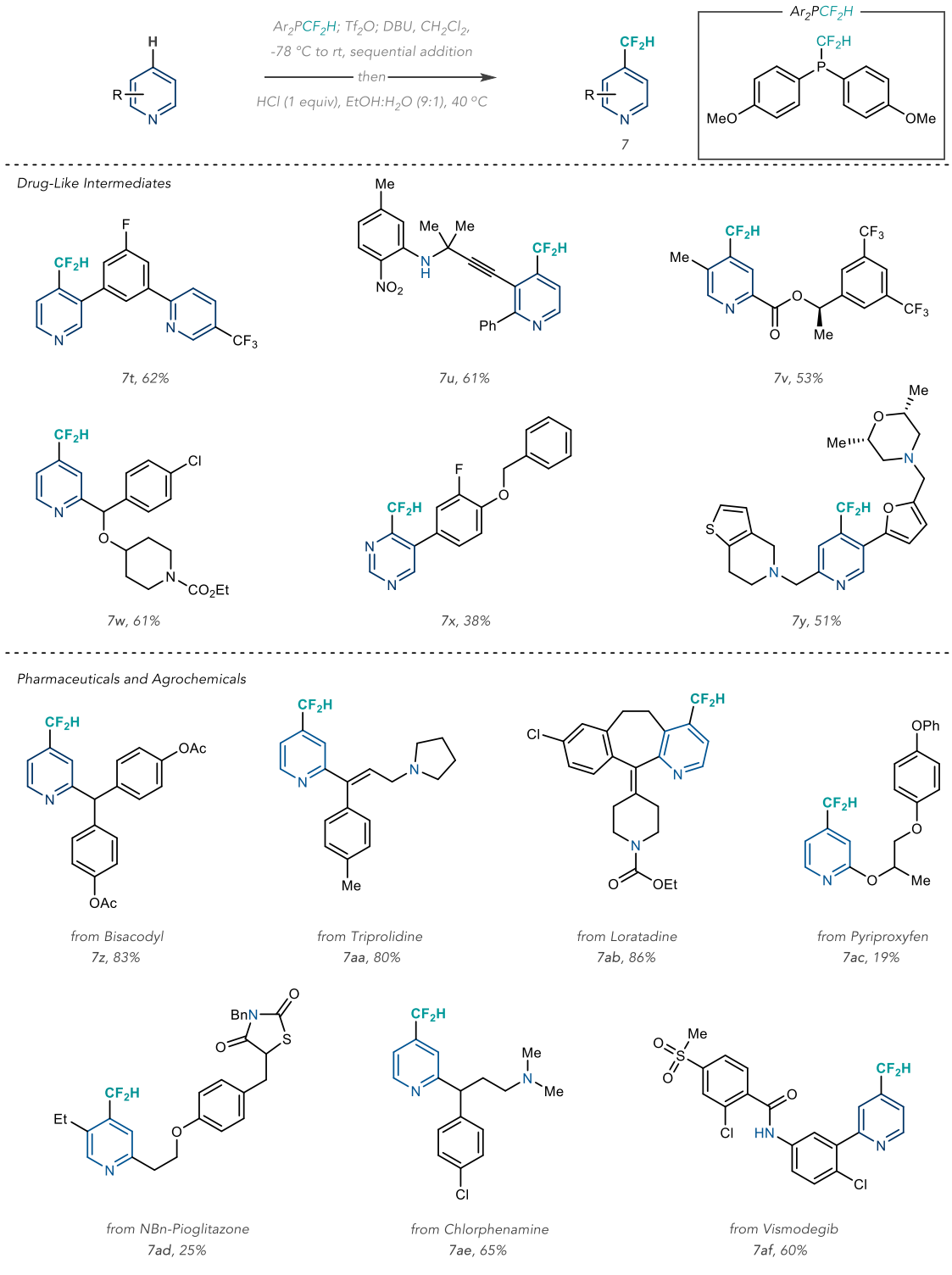
Table 3.8. Drug-like intermediate, pharmaceutical, and agrochemical azaarene scope for trifluoromethylation.



The difluoromethylation strategy maintains the excellent regioselectivity observed in the case of the trifluoromethylation reaction as illustrated by **7t**. While more limited than the

trifluoromethylation scope, this difluoromethylation strategy can also be applied to complex pharmaceuticals and agrochemicals, making it a powerful method for the late-stage difluoromethylation of complex azaarenes (**Table 3.9**). Molecules with acid-sensitive functionalities such as bisacodyl (**7z**) and loratadine (**7ab**) are successfully difluoromethylated under these reaction conditions.

Table 3.9. Drug-like intermediate, pharmaceutical, and agrochemical azaarene scope for difluoromethylation.



Having shown that this fluoroalkylation strategy is amenable to a broad range of simple and complex pyridines and diazines, we sought to exploit the site-selective switching conditions previously developed by members of our lab.[26] Under the standard reaction conditions, using DBU as the base, the phosphonium salt, and subsequent ligand-coupling, will occur on the pyridine with less steric hindrance about the nitrogen (**Figure 3.17, A**). However, if Et_3N is used as the base with an excess of the activating group and phosphine, then the dearomatized intermediate will be formed on both pyridines. Unlike DBU, Triethylamine cannot deprotonate pyridines with 3-carbon bearing substituents and will instead only deprotonate the 2-substituted pyridine. The 3-substituted dihydropyridine will be hydrolyzed back to the pyridine during the workup, effectively switching the selectivity for the fluoroalkylation reaction (**Figure 3.17, B**). This was also extended to a Loratadine derivative to demonstrate that the site-selective switching strategy is still amenable to late-stage fluoroalkylation (**Figure 3.17, C**).

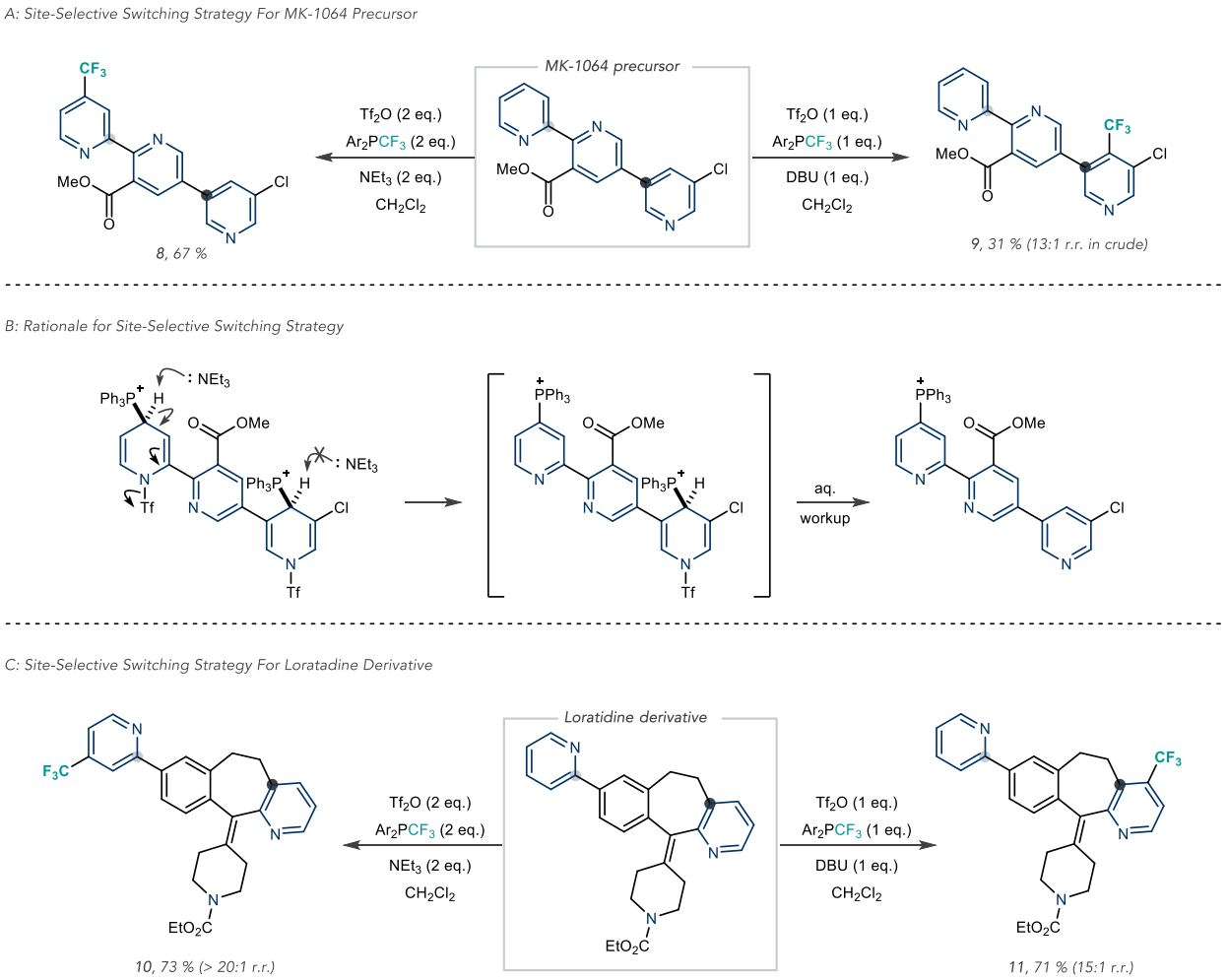


Figure 3.17. Site-selective switching strategy for MK-1064 precursor and Loratadine derivative.

3.8 Conclusion

We have developed a one-pot strategy for the 4-selective fluoroalkylation of pyridines and diazines. This reaction accomplishes the desired C-C bond forming reaction via a pentavalent phosphorus ligand-coupling event using designed fluoroalkyl phosphines. The reaction is amenable to a broad range of pyridines and diazines and can form trifluoromethylated and difluoromethylated azaarenes. The strategy works well for building-block azaarenes as well as for more complex pharmaceuticals and agrochemicals. The inherent selectivity of the reaction on

polyazines is well understood and can be switched using previously developed conditions from our lab.

REFERENCES

(1) Fluorine in Pharmaceuticals: Looking Beyond Intuition | Science https://science.sciencemag.org/content/317/5846/1881 (accessed 2021 -08 -11).

(2) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51* (15), 4359–4369. https://doi.org/10.1021/jm800219f.

(3) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116* (2), 422–518. https://doi.org/10.1021/acs.chemrev.5b00392.

(4) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept. *J. Med. Chem.* **2017**, *60* (2), 797–804. https://doi.org/10.1021/acs.jmedchem.6b01691.

(5) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. Metabolism of Fluorine-Containing Drugs. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41* (1), 443–470. https://doi.org/10.1146/annurev.pharmtox.41.1.443.

(6) Jeschke, P. The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection. *ChemBioChem* **2004**, *5* (5), 570–589. https://doi.org/10.1002/cbic.200300833.

(7) Burriss, A.; Edmunds, A. J.; Emery, D.; Hall, R. G.; Jacob, O.; Schaetzer, J. The Importance of Trifluoromethyl Pyridines in Crop Protection. *Pest Management Science* **2018**, *74* (6), 1228–1238. https://doi.org/10.1002/ps.4806.

(8) Nagase, M.; Kuninobu, Y.; Kanai, M. 4-Position-Selective C–H Perfluoroalkylation and Perfluoroarylation of Six-Membered Heteroaromatic Compounds. *J. Am. Chem. Soc.* **2016**, *138* (19), 6103–6106. https://doi.org/10.1021/jacs.6b01753.

(9) Nagib, D. A.; MacMillan, D. W. C. Trifluoromethylation of Arenes and Heteroarenes by Means of Photoredox Catalysis. *Nature* **2011**, *480* (7376), 224–228. https://doi.org/10.1038/nature10647.

(10) Beatty, J. W.; Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. A Scalable and Operationally Simple Radical Trifluoromethylation. *Nat Commun* **2015**, *6* (1), 7919. https://doi.org/10.1038/ncomms8919.

(11) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. Practical and Innate Carbon–Hydrogen Functionalization of Heterocycles. *Nature* **2012**, *492* (7427), 95–99. https://doi.org/10.1038/nature11680.

(12) Kino, T.; Nagase, Y.; Ohtsuka, Y.; Yamamoto, K.; Uraguchi, D.; Tokuhisa, K.; Yamakawa, T. Trifluoromethylation of Various Aromatic Compounds by CF3I in the Presence of Fe(II) Compound, H2O2 and Dimethylsulfoxide. *Journal of Fluorine Chemistry* **2010**, *131* (1), 98–105. https://doi.org/10.1016/j.jfluchem.2009.09.007.

(13) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. Innate C-H Trifluoromethylation of Heterocycles. *PNAS* **2011**, *108* (35), 14411–14415. https://doi.org/10.1073/pnas.1109059108.

(14) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. A New Reagent for Direct Difluoromethylation. *J. Am. Chem. Soc.* **2012**, *134* (3), 1494–1497. https://doi.org/10.1021/ja211422g.

(15) Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. A General Strategy for the Perfluoroalkylation of Arenes and Arylbromides by Using Arylboronate Esters and [(Phen)CuRF]. *Angewandte Chemie International Edition* **2012**, *51* (2), 536–539. https://doi.org/10.1002/anie.201106668.

(16) Qi, Q.; Shen, Q.; Lu, L. Copper-Mediated Aerobic Fluoroalkylation of Arylboronic Acids with Fluoroalkyl Iodides at Room Temperature. *J. Am. Chem. Soc.* **2012**, *134* (15), 6548–6551. https://doi.org/10.1021/ja301705z.

(17) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. Enantioselective α-Trifluoromethylation of Aldehydes via Photoredox Organocatalysis. *J. Am. Chem. Soc.* **2009**, *131* (31), 10875–10877. https://doi.org/10.1021/ja9053338.

(18) Bacauanu, V.; Cardinal, S.; Yamauchi, M.; Kondo, M.; Fernández, D. F.; Remy, R.; MacMillan, D. W. C. Metallaphotoredox Difluoromethylation of Aryl Bromides. *Angewandte Chemie International Edition* **2018**, *57* (38), 12543–12548. https://doi.org/10.1002/anie.201807629.

(19) MANN, F. G.; WATSON, J. CONDITIONS OF SALT FORMATION IN POLYAMINES AND KINDRED COMPOUNDS. SALT FORMATION IN THE TERTIARY 2-PYRIDYLAMINES, PHOSPHINES AND ARSINES. *J. Org. Chem.* **1948**, *13* (4), 502–531. https://doi.org/10.1021/jo01162a007.

(20) Newkome, G. R.; Hager, D. C. A New Contractive Coupling Procedure. Convenient Phosphorus Expulsion Reaction. *J. Am. Chem. Soc.* **1978**, *100* (17), 5567–5568. https://doi.org/10.1021/ja00485a053.

(21) Uchida, Y.; Onoue, K.; Tada, N.; Nagao, F.; Oae, S. Ligand Coupling Reaction on the Phosphorus Atom. *Tetrahedron Letters* **1989**, *30* (5), 567–570. https://doi.org/10.1016/S0040-4039(00)95256-0.

(22) Uchida, Y.; Kozawa, H. Formation of 2,2′-Bipyridyl by Ligand Coupling on the Phosphorus Atom. *Tetrahedron Letters* **1989**, *30* (46), 6365–6368. https://doi.org/10.1016/S0040-4039(01)93895-X.

(23) Uchida, Y.; Echikawa, N.; Oae, S. Reactions of Heteroaryllithium Compounds with Phosphorus Trichloride, Phosphorus Oxychloride, and Thionyl Chloride. Formation of Heterocyclic Biaryls. *Heteroatom Chemistry* **1994**, *5* (4), 409–413. https://doi.org/10.1002/hc.520050414.

(24) Hilton, M. C.; Zhang, X.; Boyle, B. T.; Alegre-Requena, J. V.; Paton, R. S.; McNally, A. Heterobiaryl Synthesis by Contractive C–C Coupling via P(V) Intermediates. *Science* **2018**, *362* (6416), 799–804. https://doi.org/10.1126/science.aas8961.

(25) Krishnamurti, V.; Barrett, C.; Prakash, G. K. S. Siladifluoromethylation and Deoxo-Trifluoromethylation of PV–H Compounds with TMSCF3: Route to PV–CF2– Transfer Reagents and P–CF3 Compounds. *Org. Lett.* **2019**, *21* (5), 1526–1529. https://doi.org/10.1021/acs.orglett.9b00381.

(26) Dolewski, R. D.; Fricke, P. J.; McNally, A. Site-Selective Switching Strategies to Functionalize Polyazines. *J. Am. Chem. Soc.* **2018**, *140* (25), 8020–8026. https://doi.org/10.1021/jacs.8b04530.

CHAPTER FOUR

SYNTHESIS AND HYDROGENATION OF N-SUBSTITUTED PYRIDINIUMS TO ACCESS N-SUBSTITUTED PIPERIDINES

4.1 Introduction to Piperidines

Piperidines are considered privileged scaffolds in medicinal chemistry and are ubiquitous in pharmaceuticals and natural products (**Figure 4.1**).[1–3] They represented the most prominent N-heterocycle in FDA-approved small-molecule therapeutics in 2014.[4] These N-heterocycles are so prevalent in pharmaceuticals because they can often play a key role in how the drugs function within the body. They can make critical binding interactions through the nitrogen lone pair.[4] Additionally, these saturated N-heterocycles offer more structural complexity than their planar, aromatic counterpart, pyridine. This saturation allows for a greater number of isomers to be explored. In addition, the ability to install out-of-plane substituents and adjust the molecular shape of the ring can allow for greater specificity between the molecule and the target enzyme.[5] Given the prevalence and importance of these saturated N-heterocycles, methods to synthesize these motifs are highly sought after.

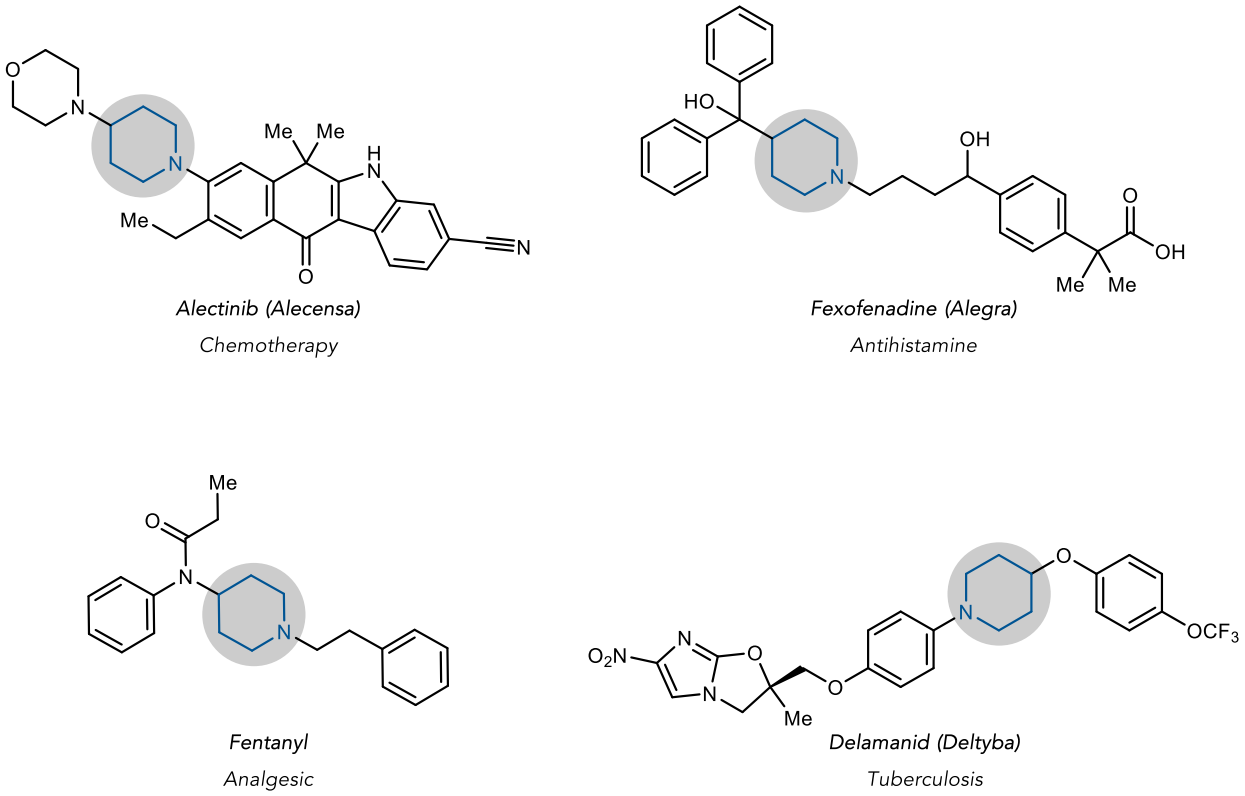


Figure 4.1. FDA-approved pharmaceuticals containing N-substituted piperidines.

The most appealing strategy to synthesize piperidines is via hydrogenation of the corresponding pyridine. Functionalization of the piperidine C-H bonds can be challenging to accomplish, but pyridine functionalization is far more accessible and has been extensively studied. Pyridine functionalization, followed by hydrogenation to the corresponding piperidine, allows access to a broad range of substituted piperidines. There are three main strategies for pyridine hydrogenation to piperidines: catalyst activation, relay catalysis, and substrate activation (**Figure 4.2**).[6] Catalyst activation involves introducing additives that can form more active catalyst species by tuning the steric and electronic effects of the ligands.[7] Relay catalysis consists of using two hydrogenation catalysts to achieve the full hydrogenation of the heterocycle.[8] The first catalyst performs a partial hydrogenation, and the second hydrogenates the intermediate to the fully saturated product. Substrate activation typically involves protonation or alkylation of the

heterocycle to destabilize the aromatic system and render it more susceptible to hydrogenation.[9–12] Zhou demonstrated this in his 2012 publication in which he was able to accomplish the asymmetric hydrogenation of N-benzyl pyridiniums using an iridium catalyst.[12]

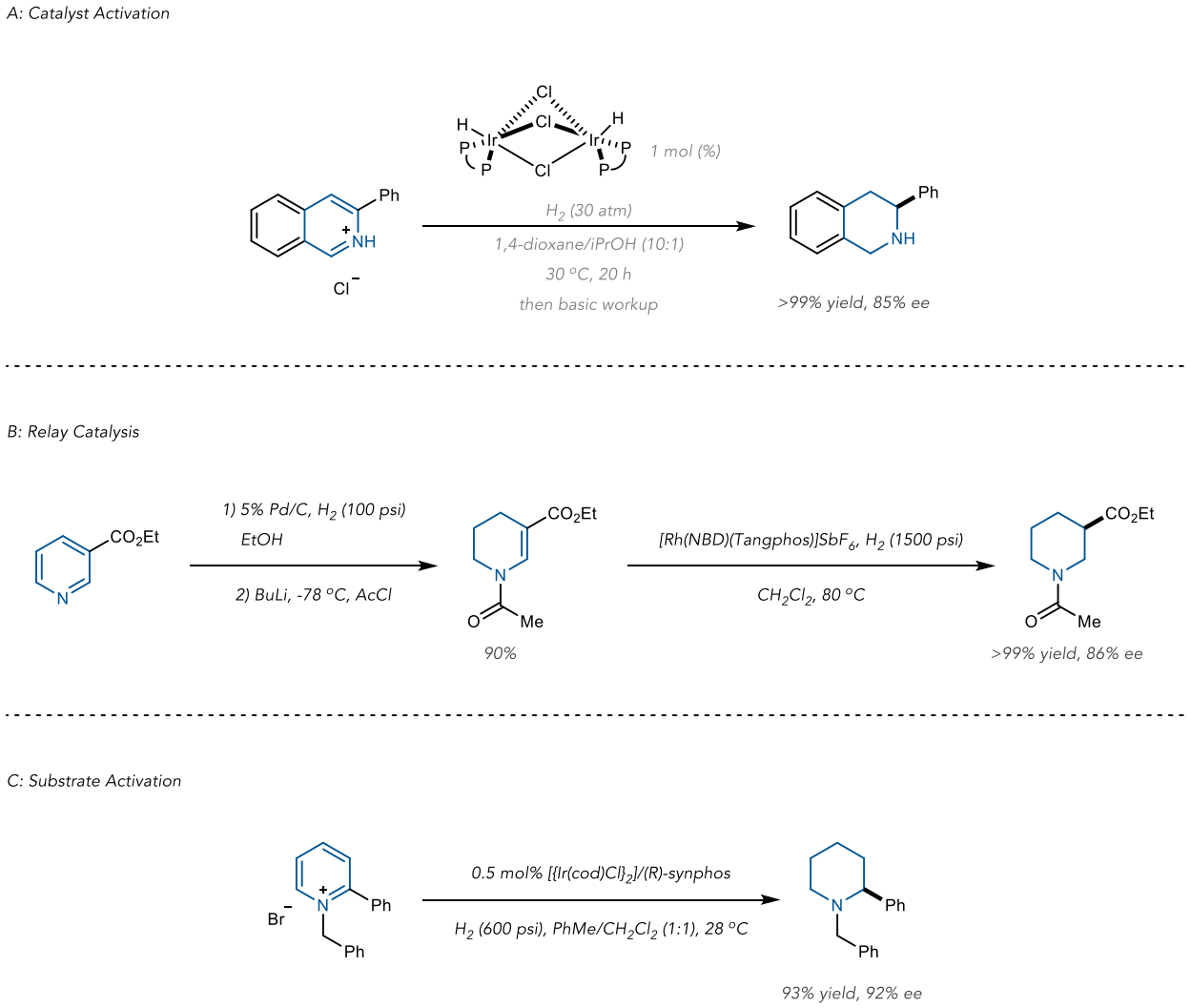


Figure 4.2. Three strategies for N-heterocycle hydrogenation.

4.2 Existing Methods to Synthesize Pyridiniums

Substrate activation represents a desirable method for the hydrogenation of pyridine to the corresponding piperidines. In addition to activating the aromatic π-system, the activating group can prevent undesired ligation between the nitrogen lone pair and the hydrogenation catalyst.[13] Such coordination can poison the catalyst and shut down the hydrogenation process.[6] An additional benefit to this strategy is that hydrogenation gives N-functionalized piperidines, commonly found throughout pharmaceuticals. However, one major drawback of this method comes from the limitations of forming the necessary N-substituted pyridiniums on a broad range of pyridines. Typical strategies to synthesize N-alkyl pyridiniums involve S_N2 type reactions between the pyridine and the corresponding alkyl halide.[14] These reactions work well on unsubstituted pyridine; however, the introduction of electron-withdrawing groups on the heterocycle or steric hindrance greatly diminishes the yields of these reactions, limiting the scope of this method.

An alternative approach to form these valuable N-substituted pyridiniums is through the Zincke reaction. Here, pyridine reacts with 1-chloro-2,4-dinitrobenzene to form the corresponding N-aryl pyridinium. This N-aryl pyridinium can then react with other amines, which will add to the 2-position and open the ring. Displacement of 2,4-dinitroaniline and rearomatization gives the desired pyridinium product (**Figure 4.3**).[15] The major drawback to this method is that the initial formation of the N-aryl pyridinium does not tolerate 2-substituted pyridines. The inability of this strategy to tolerate 2-substituted pyridines dramatically reduces the scope and generality of this strategy.

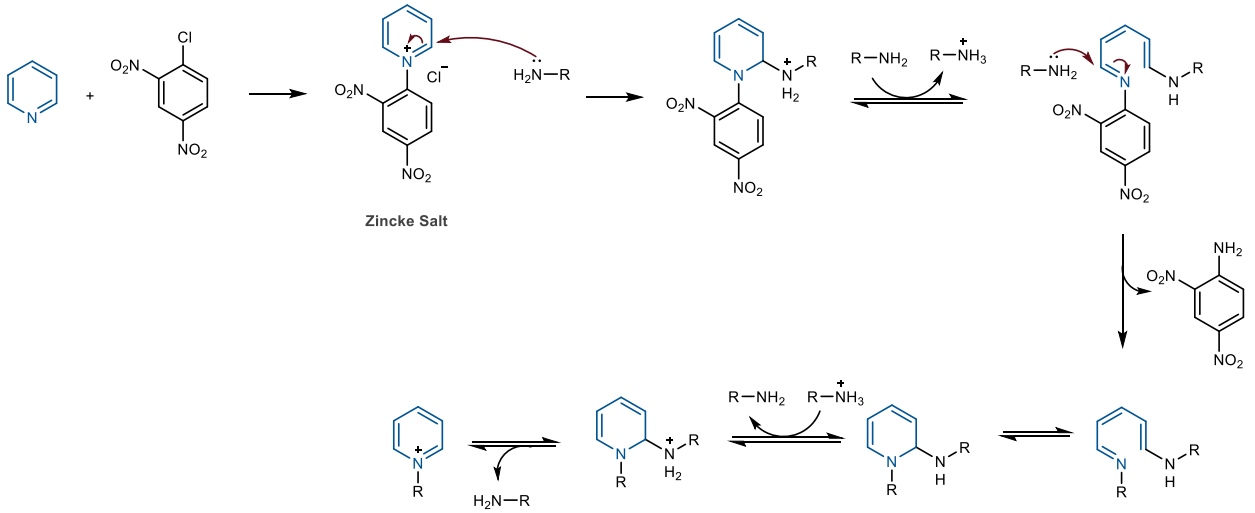


Figure 4.3. Pyridinium synthesis via Zincke Salt.

4.3 Results and Discussion

Given the synthetic challenge of synthesizing 2-substituted N-alkyl/aryl pyridiniums and their importance as precursors to piperidines, we sought to develop a novel strategy to synthesize these valuable motifs with tolerance for 2-substituents. Our lab has had experience with pyridine activation from our phosphonium salt chemistry. Triflic anhydride was used as an activating group and proved effective on a broad range of pyridines and diazines, including most 2-substituted substrates. With this knowledge, our lab sought to develop a strategy to open the pyridine from an electron-deficient, aromatic system to a ring-opened series of electron-rich alkenes. This would significantly alter the reactivity of these molecules and allow access to a new set of functionalization strategies. The envisioned system was first to activate the pyridine nitrogen using triflic anhydride to form the N-triflyl pyridinium. Next, a secondary amine would add to the 2-position and dearomatize the ring. A subsequent ring-opening would give the Zincke imine product. One byproduct of the reaction was the Zincke iminium, occurring from the displacement of the triflimide by a second equivalent of amine. After reaction optimization, the desired

transformation was accomplished, and the Zincke iminium product was suppressed by using triflic anhydride as the activating group, dibenzylamine as the secondary amine, and collidine as the base. These Zincke adducts can be crashed out in hexanes to give pure products as solids or highly viscous oils, depending on the substrate.

Our lab is developing several strategies to functionalize these ring-opened adducts followed by a ring-closing step to obtained functionalized pyridines. The ring-closing step of the reaction involves heating the adduct with ammonia in alcoholic solvents. It was hypothesized that an alkyl amine could be used in place of ammonia to form pyridiniums from the ring-closing reaction. To determine if these Zincke adducts could be used to access the corresponding N-alkyl pyridiniums, we initially reacted 4-phenyl Zincke adduct with *n*-butylamine in methanol at 50 °C for 1.5 hours. The reaction resulted in the quantitative conversion of the Zincke Adduct to the corresponding pyridinium product (**Figure 4.4**).

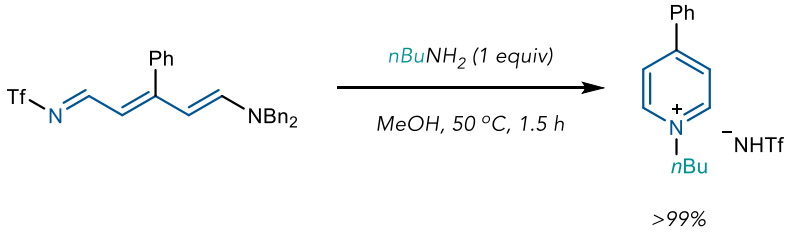
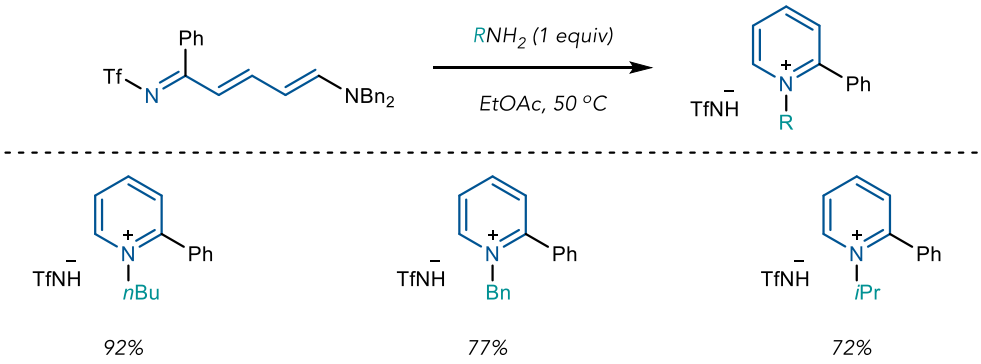


Figure 4.4. Initial result for the conversion of 4-phenyl Zincke adduct to N-alkyl pyridinium. Yields determined by ^{1}H NMR with triphenylmethane as an internal standard.

Having shown that the Zincke adducts can be converted to the corresponding pyridiniums, we sought to expand this reaction to pyridines with a 2-substituent as this represents the major limitation of typical Zincke strategies. Our strategy is a two-step process. In the first step, the pyridine is converted to the ring-opened Zincke adduct. The adduct is heated with an alkylamine in the second step to form the corresponding pyridinium product. 2-phenyl pyridine was used as

a model substrate, and the reaction can be extended to several different alkyl amines. *N*-butylamine, benzylamine, and sterically hindered isopropyl amine are all amenable to the pyridinium synthesis and give good yields (**Table 4.1**). The reaction with *n*-butylamine and benzylamine proceeds at room temperature; however, the reaction is significantly slower and requires 24 hours to go to completion. Heating to 50 °C significantly lowers reaction time, with the *n*-butyl pyridinium reaction being complete in 5 hours and the N-benzyl pyridinium being formed in 3 hours. The isopropyl pyridinium reaction only gives trace product at room temperature, and heating to 50 °C provides complete conversion after 24 hours. This is due to the increased steric hindrance of this amine compared to the *n*-butylamine and benzylamine. Ethyl acetate was chosen as the reaction solvent for several reasons. First, it proved to be general for most amines, and it is the same solvent used in the Zincke adduct formation reaction. This would allow for the development of a one-pot process to convert amines to N-alkyl pyridiniums.

Table 4.1. Optimized conditions for N-alkyl pyridinium synthesis for 2-phenyl Zincke adduct.[a]



[a]Yields determined by ^{1}H NMR with triphenylmethane as an internal standard.

Having developed optimized reaction conditions for the synthesis of N-alkyl pyridiniums, we turned our attention to similarly forming N-aryl pyridiniums. Using anilines in place of alkyl amines under similar reaction conditions, it was hypothesized, would give the corresponding N-aryl pyridiniums. An initial attempt to form the N-aryl pyridinium using aniline and 2-phenyl

Zincke adduct gave none of the desired product after heating to 50 °C overnight. The reaction mainly gave unreacted Zincke adduct and small amounts of the ring-opened adduct where the aniline had displaced triflimide (**Figure 4.5**). It was theorized that the aniline is significantly less nucleophilic than the alkyl amines, so the addition to the adduct is more challenging. In addition, the observation of ring-opened adduct indicates that the cyclization is also more difficult.

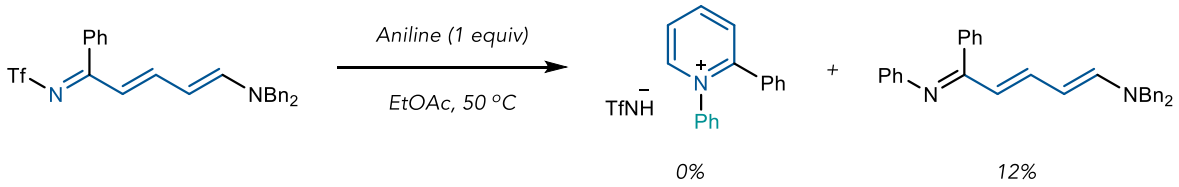
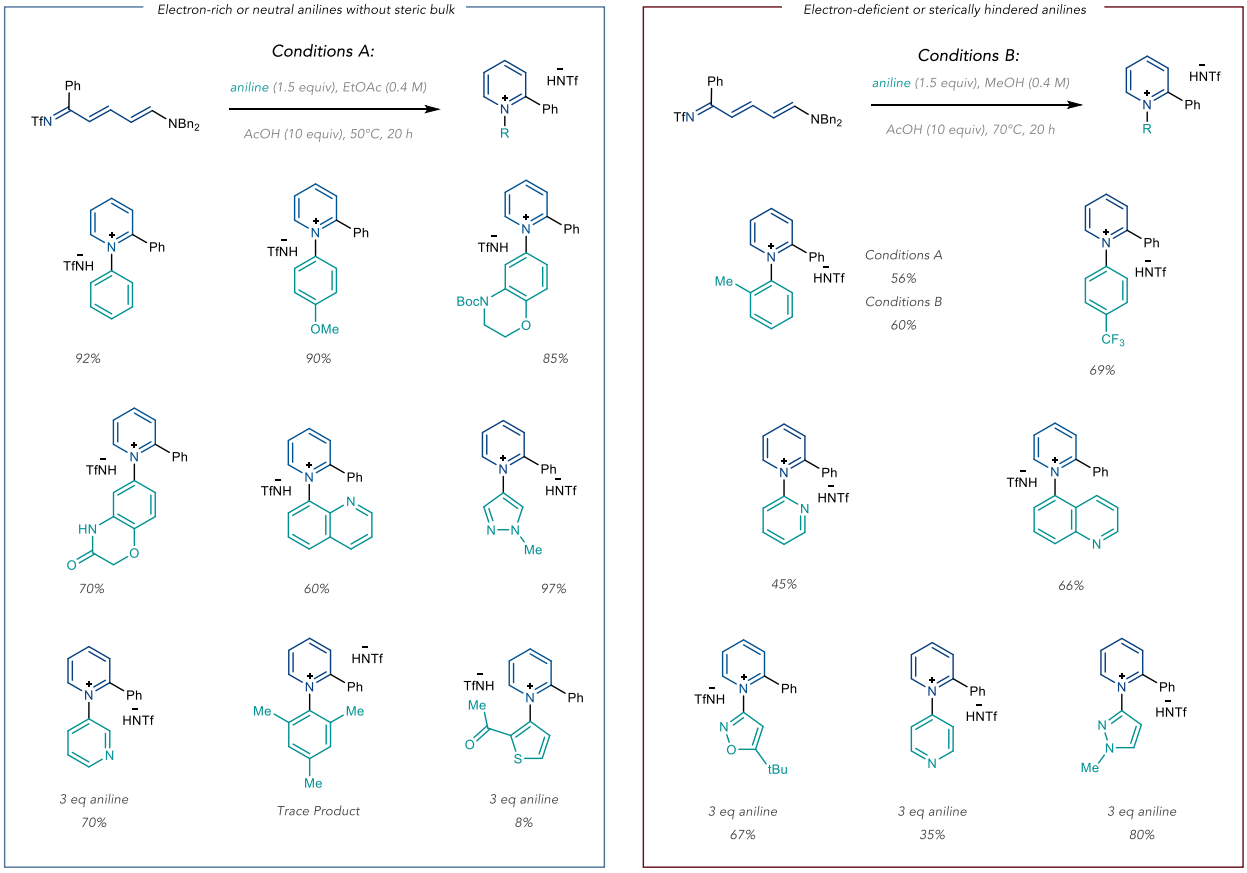


Figure 4.5. Initial attempt at forming N-phenyl pyridinium on 2-phenyl Zincke Adduct. Yields determined by ^{1}H NMR with triphenylmethane as an internal standard.

Two significant modifications to the reaction conditions proved vital for the synthesis of the N-aryl pyridiniums. First, the addition of acetic acid to the reaction significantly improves the yield. It is hypothesized that the acid could protonate the triflimide, making displacement by the aniline more facile. The acid may also play a role in facilitating the ring-closing step of the reaction. The second modification was increasing the concentration from 0.1 molar to 0.4 molar. This significantly increased the rate of the reaction, allowing good conversion to the pyridinium overnight. With optimized conditions in hand, we then tested various anilines to determine the generality of this approach. Electron-rich anilines and sterically unencumbered anilines work well in this reaction, and the reactions can be run at 50 °C in ethyl acetate to give the desired product. Anilines that are sterically hindered or electron-deficient required heating to 70 °C in methanol to provide good conversion to the desired product (**Table 4.2**).

Table 4.2. Optimized reaction conditions and aniline scope for N-aryl Pyridinium synthesis on 2-Phenyl Zincke adduct.[a]

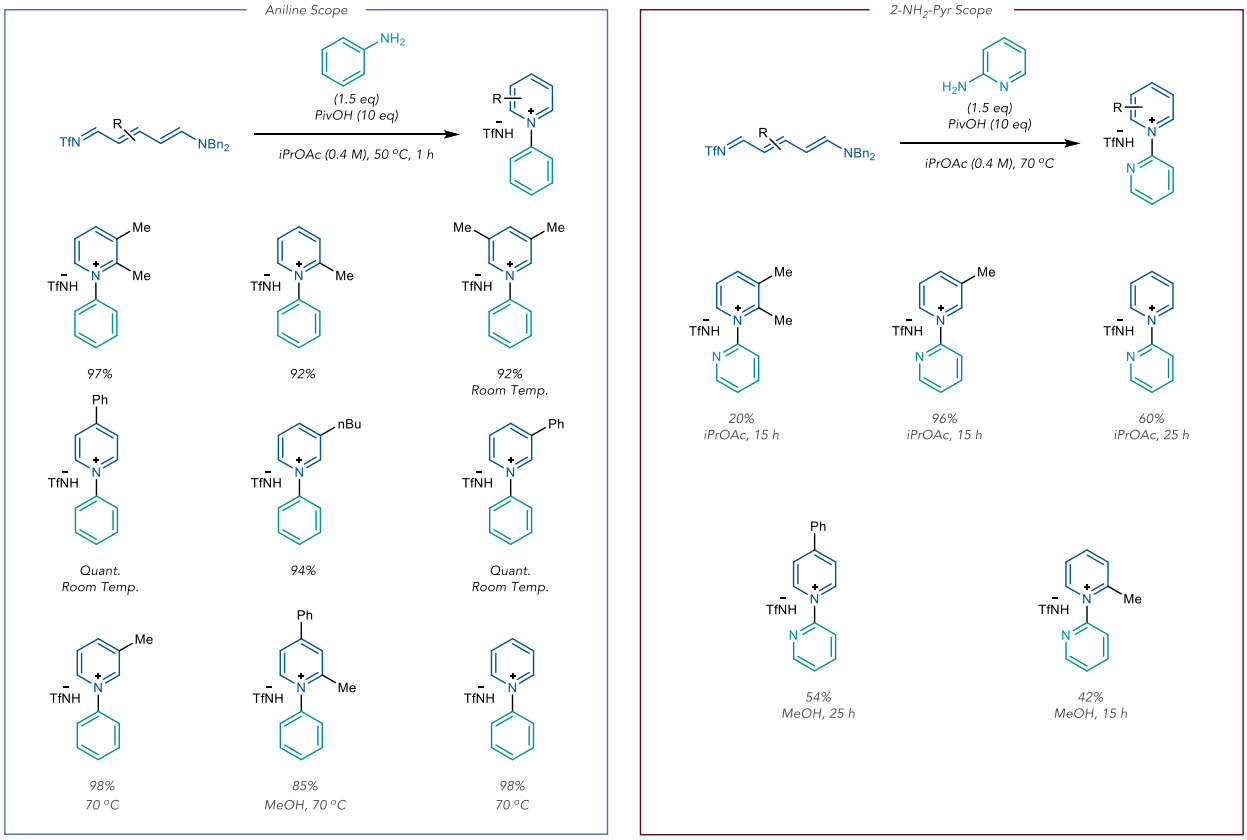


[a]Yields determined by ^{1}H NMR with triphenylmethane as an internal standard.

After developing two sets of conditions for the synthesis of N-aryl pyridiniums, we then explored different Zincke adducts with varying substitution patterns. Aniline and 2-aminopyridine were chosen to test the generality of this reaction. Pyridinium synthesis was more facile on pyridines with decreased sterics at the 2-position compared to 2-phenyl Zincke adduct. For aniline, 4-substituted, 3-substituted, and 3,5-disubstituted Zincke adducts proved to be most amenable to form the pyridinium with the reaction going to completion in 1 hour at room temperature. Somewhat surprisingly, unsubstituted pyridine required heating to 70 °C for the reaction to give

complete conversion. These results lead us to investigate the effects of substitution patterns on the pyridinium synthesis reaction **(Table 4.3)**.

Table 4.3. Scope of Zincke adducts for N-aryl Pyridinium synthesis with aniline and 2-aminopyridine.[a]



[a]Yields determined by ^{1}H NMR with triphenylmethane as an internal standard.

For aniline, increasing the number of steric interactions increased the observed rate of cyclization. We hypothesize that, for the synthesis of N-phenyl pyridiniums, ring-closing is the rate-determining step. Increasing the steric interactions along the alkene chain encourages the Zincke adduct to adopt a configuration more amenable to ring closure to minimize the steric interactions. For 2-aminopyridine, the rate of the reaction is more heavily impacted by sterics at the 2-position. For this weaker nucleophile, addition to the adduct may be the rate-determining

step, so increasing sterics at the 2-position decreases the observed rate of the pyridinium synthesis. This hypothesis is further supported by the comparison of unsubstituted Zincke adduct with 4-phenyl adduct. In both cases, there are no 2-substituents, and now, the adduct with more steric interactions is observed to form the pyridinium at a higher rate than the unsubstituted adduct **(Figure 4.6)**.

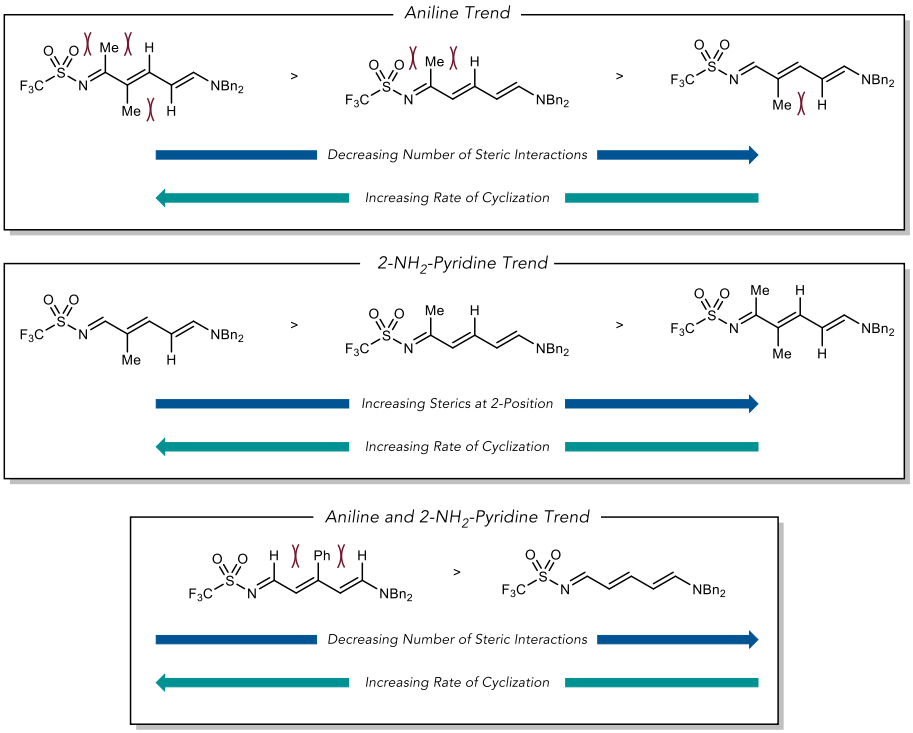


Figure 4.6. Observed trend in rates of cyclization for pyridinium synthesis with aniline and 2-aminopyridine.

Having established a protocol for converting pyridines to the corresponding N-alkyl/aryl pyridiniums, we then briefly explored hydrogenation conditions to convert these pyridiniums to the corresponding N-alkyl/aryl piperidines. Using Pt_2O (Adam's Catalyst) with hydrogen gas (H_2) in methanol proved effective, giving good conversion in both cases. In the case of the N-phenyl pyridinium, 17% of the over-reduced product was observed where the N-phenyl ring was reduced to the cyclohexane. A one-pot strategy was also developed to convert 2-phenyl pyridine directly

to N-butyl-2-phenylpiperidine (**Figure 4.7**). This reaction gave only 50% of the desired product, with the remainder of the mass balance remaining as unreduced pyridinium. It is most likely that byproducts from previous steps poisoned the hydrogenation catalyst and shut down the reaction prematurely.

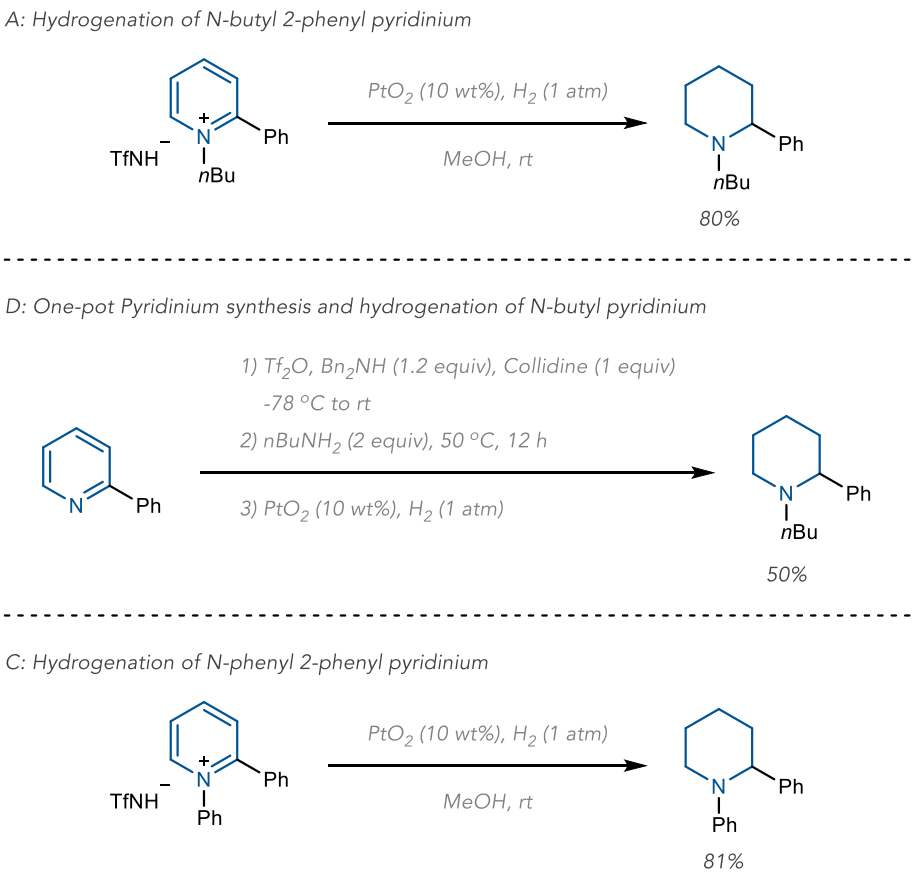


Figure 4.7. Hydrogenation of N-butyl and N-phenyl 2-phenyl pyridinium and one-pot strategy for Piperidine synthesis. Yields determined by ^{1}H NMR with triphenylmethane as an internal standard

4.4 Conclusion

We have developed a strategy to synthesize 2-substituted N-alkyl/aryl pyridiniums via a Zincke adduct intermediate. For N-aryl pyridiniums, two sets of conditions have been developed. One set of conditions apply to electron-rich and sterically unencumbered anilines, and the second

set of conditions are well suited for electron-deficient or sterically hindered anilines. The hydrogenation of these pyridiniums has also been demonstrated. One-pot conditions to convert the pyridine directly to the N-substituted piperidine have been explored, and further investigation is ongoing in our lab to further develop this chemistry.

SUMMARY

The work described in chapters 2 and 3 of this dissertation highlight the use of heterocyclic phosphonium salts to accomplish the 4-selective functionalization of pyridines and diazines. These motifs are ubiquitous in pharmaceuticals and agrochemicals, and strategies to functionalize them are appealing to medicinal chemists. Through methods developed during my time in the McNally lab, these phosphonium slats can be installed on a broad range of pyridines and diazines and can be used as versatile, functional handles to form a number of useful bonds. Chapter 2 describes the conversion of these heterocyclic phosphonium salts to valuable iminophosphorane products via the Staudinger reaction. These iminophosphoranes can be used to access aminated pyridines, a highly desirable product for medicinal chemists. Chapter 3 extends the ligand-coupling reaction on pentavalent phosphoranes from sp^2-sp^2 couplings to sp^2-sp^3 couplings. Designed fluoroalkyl phosphines were used in a one-pot reaction to form fluoroalkylated azaarenes. Not only does this reaction expand the phosphorus ligand-coupling reaction, but it also provides very desirable fluoroalkylated azaarene products, which have become more prevalent in pharmaceuticals and agrochemicals in recent years.

Chapter 4 describes ongoing work toward the synthesis of N-alkyl/aryl pyridiniums via Zincke imines. Conditions to form pyridiniums with both alkyl amines and aryl amines have been developed. These pyridiniums can be made on 2-substituted Zincke adducts, circumventing a major limitation of previous methods. Preliminary hydrogenations of these pyridinium products are promising and demonstrate this strategy's viability to access valuable N-substituted piperidine products.

REFERENCES

(1) 1 - Piperidine. A General Survey. In *Studies in Organic Chemistry*; Rubiralta, M., Giralt, E., Diez, A., Eds.; Piperidine; Elsevier, 1991; Vol. 43, pp 1–23. https://doi.org/10.1016/B978-0-444-88348-3.50005-2.

(2) Bailey, P. D.; Millwood, P. A.; Smith, P. D. Asymmetric Routes to Substituted Piperidines. *Chem. Commun.* **1998**, No. 6, 633–640. https://doi.org/10.1039/A709071D.

(3) Escolano, C.; Amat, M.; Bosch, J. Chiral Oxazolopiperidone Lactams: Versatile Intermediates for the Enantioselective Synthesis of Piperidine-Containing Natural Products. *Chemistry – A European Journal* **2006**, *12* (32), 8198–8207. https://doi.org/10.1002/chem.200600813.

(4) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57* (24), 10257–10274. https://doi.org/10.1021/jm501100b.

(5) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52* (21), 6752–6756. https://doi.org/10.1021/jm901241e.

(6) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. Asymmetric Hydrogenation of Heteroarenes and Arenes. *Chem. Rev.* **2012**, *112* (4), 2557–2590. https://doi.org/10.1021/cr200328h.

(7) Kita, Y.; Yamaji, K.; Higashida, K.; Sathaiah, K.; Iimuro, A.; Mashima, K. Enhancing Effects of Salt Formation on Catalytic Activity and Enantioselectivity for Asymmetric Hydrogenation of Isoquinolinium Salts by Dinuclear Halide-Bridged Iridium Complexes Bearing Chiral Diphosphine Ligands. *Chemistry – A European Journal* **2015**, *21* (5), 1915–1927. https://doi.org/10.1002/chem.201405408.

(8) Lei, A.; Chen, M.; He, M.; Zhang, X. Asymmetric Hydrogenation of Pyridines: Enantioselective Synthesis of Nipecotic Acid Derivatives. *European Journal of Organic Chemistry* **2006**, *2006* (19), 4343–4347. https://doi.org/10.1002/ejoc.200600558.

(9) Grozavu, A.; Hepburn, H. B.; Smith, P. J.; Potukuchi, H. K.; Lindsay-Scott, P. J.; Donohoe, T. J. The Reductive C3 Functionalization of Pyridinium and Quinolinium Salts through Iridium-Catalysed Interrupted Transfer Hydrogenation. *Nature Chem* **2019**, *11* (3), 242–247. https://doi.org/10.1038/s41557-018-0178-5.

(10) Heusler, A.; Fliege, J.; Wagener, T.; Glorius, F. Substituted Dihydropyridine Synthesis by Dearomatization of Pyridines. *Angewandte Chemie International Edition* **2021**, *60* (25), 13793–13797. https://doi.org/10.1002/anie.202104115.

(11) Qu, B.; Mangunuru, H. P. R.; Tcyrulnikov, S.; Rivalti, D.; Zatolochnaya, O. V.; Kurouski, D.; Radomkit, S.; Biswas, S.; Karyakarte, S.; Fandrick, K. R.; Sieber, J. D.; Rodriguez, S.; Desrosiers, J.-N.; Haddad, N.; McKellop, K.; Pennino, S.; Lee, H.; Yee, N. K.; Song, J. J.; Kozlowski, M. C.; Senanayake, C. H. Enantioselective Synthesis of α-(Hetero)Aryl Piperidines through Asymmetric Hydrogenation of Pyridinium Salts and Its Mechanistic Insights. *Org. Lett.* **2018**, *20* (5), 1333–1337. https://doi.org/10.1021/acs.orglett.8b00067.

(12) Ye, Z.-S.; Chen, M.-W.; Chen, Q.-A.; Shi, L.; Duan, Y.; Zhou, Y.-G. Iridium-Catalyzed Asymmetric Hydrogenation of Pyridinium Salts. *Angewandte Chemie International Edition* **2012**, *51* (40), 10181–10184. https://doi.org/10.1002/anie.201205187.

(13) Balakrishna, B.; Núñez-Rico, J. L.; Vidal-Ferran, A. Substrate Activation in the Catalytic Asymmetric Hydrogenation of N-Heteroarenes. *European Journal of Organic Chemistry* **2015**, *2015* (24), 5293–5303. https://doi.org/10.1002/ejoc.201500588.

(14) Lim, C.; Kim, S.-H.; Yoh, S.-D.; Fujio, M.; Tsuno, Y. The Menschutkin Reaction of 1-Arylethyl Bromides with Pyridine: Evidence for the Duality of Clean SN1 and SN2 Mechanisms. *Tetrahedron Letters* **1997**, *38* (18), 3243–3246. https://doi.org/10.1016/S0040-4039(97)00574-1.

(15) Cheng, W.-C.; Kurth, M. J. The Zincke Reaction. a Review. *Organic Preparations and Procedures International* **2002**, *34* (6), 585–608. https://doi.org/10.1080/00304940209355784.

APPENDIX ONE

Amination of Pyridines and Diazines via Heterocyclic Phosphonium Salts: Experimental
(Combined work of Chirag Patel, Maga Mohnike, and Michael Hilton)

A 1.1 General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz), an Agilent Inova 400 (400 MHz) spectrometer, an Agilent Inova 500 (500 MHz) spectrometer or 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), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants, proton assignment). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity was 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 Varian 400 MR spectrometer (100 MHz), an Agilent Inova 400 (100 MHz) spectrometer, an Agilent Inova 500 (125 MHz) spectrometer or a Bruker AV-111 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in $CDCl_3$ (77.00 ppm), C_6D_6 (128.06 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32 ppm). DEPT135, NOE experiments and 2-dimensional experiments (COSY, HMBC and HSQC) were used to support assignments where appropriate.

Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 27 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 Merck glass-backed

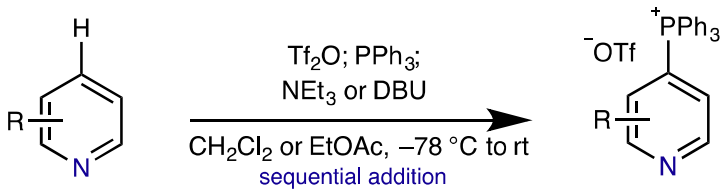
silica gel plates (Silicagel 60 F254) or foil-backed basic aluminum oxide plates (Baker-flex 4467). Flash column chromatography was undertaken on Fluka or Material Harvest silica gel (230–400 mesh) or Sigma-Aldrich aluminum oxide (activated, basic) under a positive pressure of air. Preparative thin layer chromatography was performed using pre-coated Silicycle glass-backed silica gel plates (Siliaplate 60Å, 20 cm×20 cm, 2000 μm, TLG–R10011B–353). Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate.

Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] 1,2-Dichloroethane (DCE), 1,4-dioxane, chloroform, chlorobenzene and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality and used without further purification. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^{1}H NMR spectra taken from reaction samples, gas chromatography (GC) and gas chromatography-mass spectrometry (GCMS) using an Agilent 5977A fitted with an Agilent J&W HP-5ms Ultra Inert Column (30 m, 0.25 mm, 0.25 μm film) for MS analysis and an Agilent J&W VF-5ms column (10 m, 0.15 mm, 0.15 μm film) for FID analysis or liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

PPh_3 (99%) was purchased from Oakwood Chemical and is most effective when crushed to a powder before use. Tf_2O (99%) was purchased from Oakwood Chemical and used without further purification and was routinely stored in a –20 ºC fridge. NEt_3 and DBU were distilled before use. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and were used without further purification. ACS reagent grade DMSO (≥99.9%) was purchased from Sigma Aldrich, distilled, and stored under nitrogen atmosphere in a –20 ºC fridge. ReagentPlus grade sodium azide (≥99.5%) was purchased from Sigma Aldrich and used without further purification.

A 1.2 Preparation of Heterocyclic Phosphonium Salts

General Procedure A



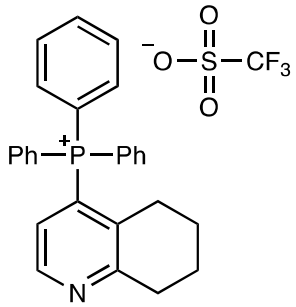
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) or EtOAc (0.4 M) was added, the reaction vessel cooled to –78 ºC, and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before PPh_3 (1.1 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 ºC. The stated organic base (NEt_3 or DBU, 1.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (approximately 15-30 minutes). The reaction mixture was quenched with H_2O (approximately the same volume as CH_2Cl_2) and the mixture was transferred to a separatory funnel. The mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Approximately 2-10 mL (depending on the scale of the reaction) of CH_2Cl_2 was added to reaction mixture and was then added dropwise to an excess of chilled Et_2O (0 ºC). The flask was then placed in a –20 ºC refrigerator for approximately 1 h. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC), and dried *in vacuo* to provide the pure phosphonium salt.

Notes.

1) PPh_3 was crushed into a powder prior to use.
2) Certain substrates require longer periods for the precipitation step and specific cases are indicated below.
3) In a small number of cases, residual CH_2Cl_2 can become trapped in the phosphonium salt products. In these cases, heating the salts under vacuum (50-100 ºC) removed the solvent.

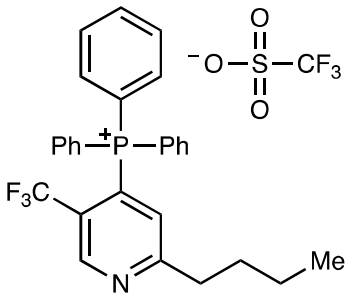
4) In order to evaluate regioselectivity from the crude reaction mixtures, a duplicate reaction was performed and aliquots taken after addition of the organic base and warming to room temperature. These aliquots were concentrated *in vacuo* and analyzed by ^{1}H and ^{31}P NMR.

Triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (1a)



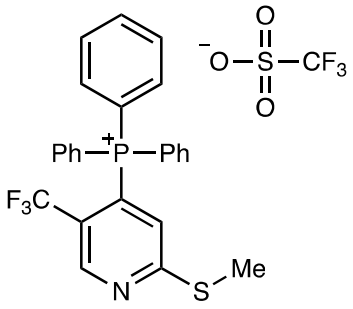
Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.74 (1H, app t, *J* = 5.1 Hz), 8.07-7.93 (3H, m), 7.92-7.71 (12H, m), 6.94 (1H, dd, *J* = 15.3, 5.1 Hz), 3.12-2.97 (2H, m), 2.21-2.04 (2H, m), 1.84-1.71(2H, m), 1.60-1.44 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.25 (d, *J* = 8.4 Hz), 148.20 (d, *J* = 11.4 Hz), 135.48 (d, *J* = 7.6 Hz), 135.27 (d, *J* = 3.1 Hz), 134.06 (d, *J* = 10.7 Hz), 130.50 (d, *J* = 13.0 Hz), 126.18 (d, *J* = 9.9 Hz), 125.51 (d, *J* = 82.4 Hz), 120.40 (q, *J* = 322.0 Hz), 116.34 (d, *J* = 87.7 Hz), 32.01 (d, *J* = 2.3 Hz), 29.66 (d, *J* = 5.3 Hz), 21.03, 20.54. The spectroscopic data is in agreement with our reported synthesis.[2]

(2-Butyl-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1b)



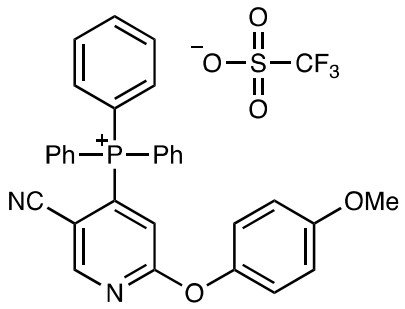
Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$): 9.16 (1H, d, *J* = 6.8 Hz), 7.92–7.87 (3H, m), 7.80–7.76 (6H, m), 7.73–7.67 (6H, m), 7.18 (1H, d, *J* = 17.2 Hz), 2.93 (2H, t, *J* = 7.6 Hz, H_6), 1.69–1.62 (2H, m), 1.37–1.27 (2H, m), 0.88 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.99 (d, *J* = 9.7 Hz), 150.06 (m), 135.96 (d, *J* = 3.1 Hz), 134.41 (d, *J* = 10.4 Hz), 130.74 (d, *J* = 13.0 Hz), 129.77 (d, *J* = 8.5 Hz), 125.90 (d, *J* = 80.1, 1.0 Hz), 124.42 (qd, *J* = 33.1, 4.0 Hz), 122.49 (qd, *J* = 275.1, 2.9 Hz), 120.76 (q, *J* = 321.2 Hz), 116.40 (d, *J* = 90.4 Hz), 37.93, 30.35, 22.11, 13.63; ^{19}F NMR (365 MHz, $CDCl_3$): –78.27, –53.55; ^{31}P NMR (162 MHz, $CDCl_3$): 27.4 (d, *J* = 2.3 Hz). The spectroscopic data is in agreement with our reported synthesis.[2]

(2-(Methylthio)-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1c)



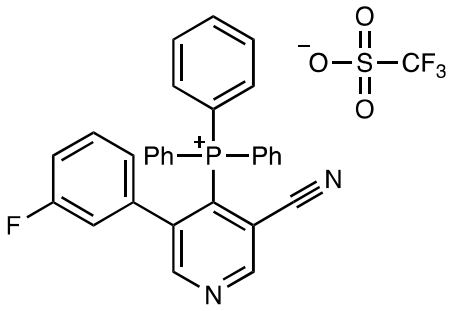
Prepared according to general procedure A using 2-(methylthio)-5-(trifluoromethyl)pyridine (850 mg, 4.40 mmol), Tf_2O (0.74 mL, 4.40 mmol), PPh_3 (1.27 g, 4.84 mmol), DBU (0.66 mL, 4.40 mmol) and CH_2Cl_2 (45 mL). After the purification procedure, the title compound was isolated as a white solid (1.34 g, 2.22 mmol, 51% yield). mp 183-184 ºC; IR ν_{max}/cm^{-1} (film): 3062, 3006, 1570, 1443, 1438, 1271, 1262, 1155, 1140, 1128, 1109, 1029, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, d, *J* = 6.8 Hz), 7.94-7.85 (3H, m), 7.83-7.74 (6H, m), 7.72-7.62 (6H, m), 7.00 (1H, d, *J* = 17.1 Hz), 2.56 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.71 (d, *J* = 10.3 Hz), 150.40-150.08 (m), 136.09 (d, *J* = 3.1 Hz), 134.45 (d, *J* = 10.6 Hz), 130.83 (d, *J* = 13.4 Hz), 128.61 (d, *J* = 9.5 Hz), 125.29 (d, *J* = 79.0 Hz), 122.74 (qd, *J* = 274.4, 2.1 Hz), 121.14 (qd, *J* = 33.7, 4.0 Hz), 120.85 (q, *J* = 321.2 Hz), 116.28 (d, *J* = 89.9 Hz), 13.64; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –53.37, –78.18; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 27.57; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 454.2, $C_{25}H_{20}F_3NPS^+$ requires 454.1.

(5-Cyano-2-(4-methoxyphenoxy)pyridin-4-yl)triphenylphosphonium (1d)



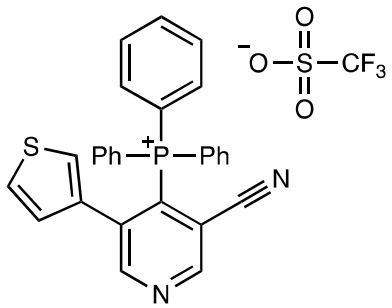
Prepared according to general procedure A using 6-(4-methoxyphenoxy)nicotinonitrile (1.23 g, 5.44 mmol), Tf_2O (0.91 mL, 5.44 mmol), PPh_3 (1.57 g, 5.98 mmol), DBU (0.81 mL, 5.44 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a yellow solid (1.28 g, 2.01 mmol, 45% yield). mp 112-114 ºC; IR ν_{max}/cm^{-1} (film): 3061, 2989, 2226, 1575, 1502, 1467, 1438, 1357, 1261, 1236, 1223, 1147, 1106, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, d, *J* = 6.0 Hz), 7.96-7.71 (15H, m), 7.15 (2H, d, *J* = 8.9 Hz), 6.98 (1H, d, *J* = 16.0 Hz), 6.87 (2H, d, *J* = 8.9 Hz), 3.76 (3H, s); ^{13}C NMR (100 MHz, CDCl3) δ: 166.57 (d, *J* = 14.6 Hz), 157.51, 155.51 (d, *J* = 7.5 Hz), 145.30, 136.30 (d, *J* = 3.1 Hz), 134.75 (d, *J* = 10.8 Hz), 133.60 (d, *J* = 83.8 Hz), 131.00 (d, *J* = 13.4 Hz), 122.41, 120.76 (q, *J* = 321.3 Hz), 120.74 (d, *J* = 9.5 Hz), 114.77, 114.46 (d, *J* = 90.0 Hz), 114.06 (d, *J* = 4.5 Hz), 104.60 (d, *J* = 4.2 Hz), 55.49; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.10; ^{31}P NMR (162 MHz, $CDCl_3$) δ:22.91; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 487.3, $C_{31}H_{24}N_2O_2P^+$ requires 487.2.

(3-Cyano-5-(3-fluorophenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1e)



Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, CDCl3) δ: 9.10 (1H, dd, *J* = 4.9, 1.2 Hz), 8.83 (1H, dd, *J* = 5.5, 1.1 Hz), 7.92-7.44 (15H, m), 7.02-6.92 (1H, m), 6.84-6.73 (2H, m), 6.70 (1H, d, *J* = 8.9 Hz); ^{13}C NMR (100 MHz, CDCl3) δ: 162.59 (d, *J* = 247.8 Hz), 152.82, 147.29, 140.07, 137.63 (d, *J* = 7.9 Hz), 135.63, 130.31 (d, *J* = 8.4 Hz), 128.95, 128.72, 127.93, 125.41 (d, *J* = 3.1 Hz), 116.68 (d, *J*, 22.5 Hz), 115.98 (d, *J* = 21.0 Hz), 115.08. The spectroscopic data is in agreement with our reported synthesis.[3]

(3-Cyano-5-(thiophen-3-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1f)



Major

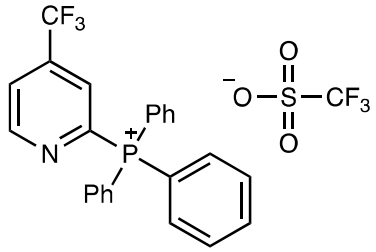
11.4:1 Mixture of Regioisomers

Prepared according to general procedure A using 5-(thiophen-3-yl)nicotinonitrile (1.86 g, 10.00 mmol), Tf_2O (1.68 mL, 10.00 mmol), PPh_3 (2.88 g, 11.00 mmol), DBU (1.49 mL, 10.00 mmol) and CH_2Cl_2 (100 mL). After the purification procedure, the title compound (11.4:1 mixture of regioisomers as determined by ^{1}H NMR)* was isolated as a white solid (3.73 g, 6.25 mmol, 63% yield). Mixture of isomers, IR ν_{max}/cm^{-1} (film): 3066, 2227, 1586, 1441, 1261, 1223, 1149, 1102, 1079, 1030, 996, 720; Major isomer, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.45 (1H, d, *J* = 5.0 Hz), 9.07 (1H, d, *J* = 5.5 Hz), 7.98-7.84 (9H, m), 7.77-7.67 (6H, m), 7.21-7.16 (1H, m), 7.13 (1H, br s), 6.57 (1H, d, *J* = 4.9 Hz); Major isomer, ^{13}C NMR† (100 MHz, DMSO-d_6) δ: 157.02 (d, *J* = 6.9 Hz), 154.74 (d, *J* = 5.8 Hz), 140.22 (d, *J* = 5.5 Hz), 135.30 (d, *J* = 3.0 Hz), 134.48 (d, *J* = 10.8 Hz), 130.35 (d, *J* = 13.3 Hz), 128.47, 128.33 (d, *J* = 84.5 Hz), 128.27, 127.78, 120.69 (q, *J* = 322.4 Hz), 117.00 (d, *J* = 88.5 Hz), 113.91 (d, *J* = 6.0 Hz), 113.21 (d, *J* = 4.4 Hz); Both isomers, ^{19}F NMR (365 MHz, DMSO-d_6) δ: –77.67; Major isomer, ^{31}P NMR (162 MHz, DMSO-d_6) δ: 20.26; Minor isomer, ^{31}P NMR (162 MHz, DMSO-d_6) δ: 19.73; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 447.3, $C_{28}H_{20}N_2PS^+$ requires 447.1.

Triphenyl(4-(trifluoromethyl)pyridin-2-yl)phosphonium trifluoromethanesulfonate (1g)

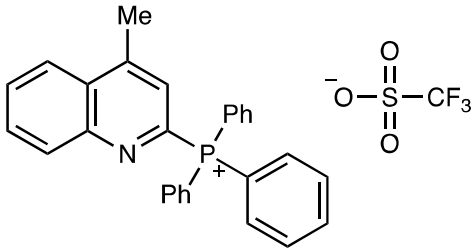
* In a separate reaction, the reaction mixture was concentrated *in vacuo* and the crude regiomeric ratio was 7.4:1.4:1 determined by analysis of the crude ^{1}H NMR spectrum.

† 1 ^{13}C resonance cannot be clearly identified from the mixture.



Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.33 (1H, d, *J* = 2.8 Hz), 8.02 (1H, m), 7.92 (3H, m), 7.82–7.69 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.20 (d, *J* = 19.9 Hz), 147.00 (d, *J* = 121.0 Hz), 139.92 (qd, *J* = 35.8 Hz, 11.3 Hz), 136.02 (d, *J* = 2.9 Hz), 134.55 (d, *J* = 10.2 Hz), 130.70 (d, *J* = 13.1 Hz), 126.05 (dq, *J* = 25.9, 3.6 Hz), 124.36 (m), 121.47 (qd, *J* = 274.1, 3.0 Hz), 120.70 (q, *J* = 320.5 Hz), 115.93 (d, *J* = 90.0 Hz). The spectroscopic data is in agreement with our reported synthesis.[2]

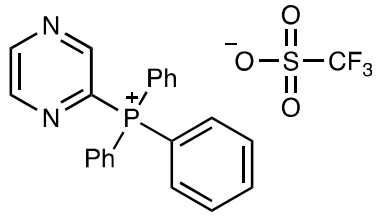
(4-Methylquinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (1h)



Prepared according to general procedure A (except that the reaction was warmed to -50 ºC before the addition of PPh_3 and was stirred at -50 ºC for 30 minutes) using 4-methylquinoline (793 μL, 6.00 mmol), Tf_2O (1.01 mL, 6.00 mmol), PPh_3 (1.73 g, 6.60 mmol), DBU (0.90 mL, 6.00 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (2.18 g, 3.94 mmol, 66% yield). mp 171-174 ºC; IR ν_{max}/cm^{-1} (film): 3067, 2989, 1576, 1439, 1259, 1223, 1144, 1109, 1028, 997, 765, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22-8.12 (2H, m), 7.94-7.65 (17H, m), 7.53, (1H, d, *J* = 4.6 Hz), 2.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.52 (d, *J* = 10.6 Hz), 148.50 (d, *J* = 22.6 Hz), 144.376 (d, *J* = 117.2 Hz), 135.63 (d, *J* = 3.1 Hz), 134.60 (d, *J* = 10.1 Hz), 131.63, 130.63 (d, *J* = 1.2 Hz), 130.49 (d, *J* = 12.9 Hz), 130.39, 128.77, 125.14

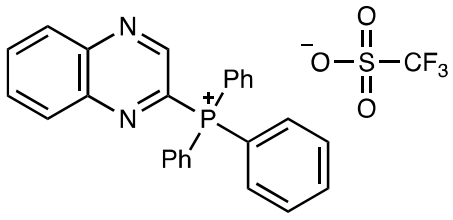
(d, J = 26.4 Hz), 124.43 (d, J = 1.3 Hz), 120.83 (q, J = 321.2 Hz), 117.30 (d, J = 88.2 Hz), 19.18 (d, J = 1.5 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.07; ^{31}P NMR (162 MHz, $CDCl_3$) δ:14.41; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 404.3, $C_{28}H_{23}NP^+$ requires 404.2.

Triphenyl(pyrazin-2-yl)phosphonium trifluoromethanesulfonate (1i)



Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, CDCl3) δ: 9.09 (1H, br s), 9.06 (1H, br s), 8.86 (1H, br s), 7.91 (3H, m), 7.82– 7.71 (12H, m); ^{13}C NMR (100 MHz, CDCl3) δ: 149.72 (d, J = 24.0 Hz), 149.51 (d, J = 3.4 Hz), 147.25 (d, J = 14.7 Hz), 141.37 (d, J = 115.4 Hz), 136.02 (d, J = 3.1 Hz), 134.54 (d, J = 10.4 Hz), 130.71 (d, J = 13.1 Hz), 120.69 (q, J = 321.1 Hz), 115.71 (d, J = 89.3 Hz). The spectroscopic data is in agreement with our reported synthesis.[2]

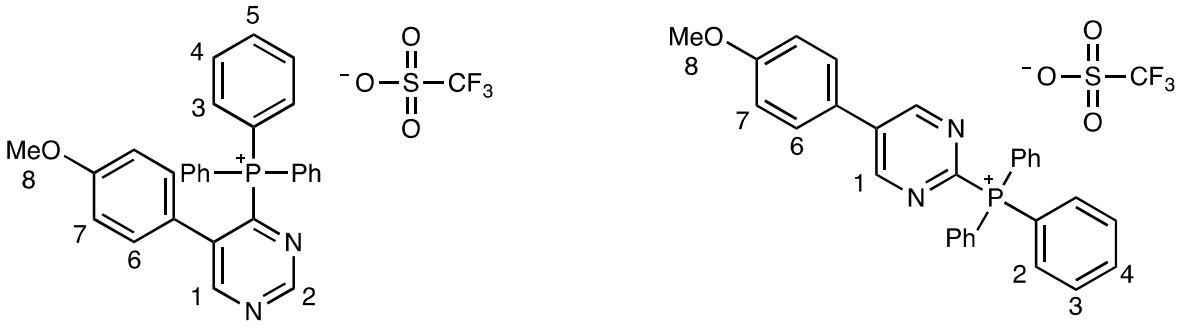
Triphenyl(quinoxalin-2-yl)phosphonium (1j)



Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, s), 8.27-8.22 (2H, m), 8.09-8.01 (2H, m), 7.93-7.90 (3H, m), 7.79-7.72 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.86 (d, J = 25.4 Hz), 143.38 (d, J = 2.8 Hz), 142.70 (d, J = 17.3 Hz), 140.83 (d, J = 111.6 Hz), 136.16 (d, J = 3.1 Hz), 134.98, 134.66 (d, J = 10.5 Hz), 133.08, 130.86 (d, J = 13.0 Hz), 130.19 (d, J = 2.0 Hz), 129.85 (d, J = 2.3 Hz), 120.76 (q, J = 319.5 Hz), 116.03 (d, J = 88.1 Hz).

The spectroscopic data is in agreement with our reported synthesis.[3]

(5-(4-Methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1k)

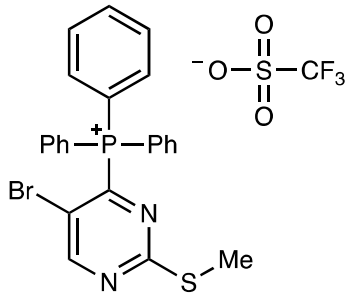


Major Minor

24:1 Mixture of Regioisomers

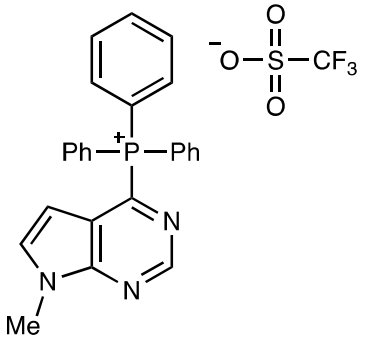
Prepared according to our previous report.[2] Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.44 (1H, s, H_2), 8.98 (1H, d, J = 9.0 Hz, H_1), 7.80-7.70 (3H, m, H_5), 7.67-7.56 (12H, m, H_3 and H_4), 6.91 (2H, d, J = 8.7 Hz, H_6), 6.55 (2H, d, J = 8.7 Hz, H_7), 3.72 (3H, s, H_8); Minor isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.23 (2H, s, H_1), 7.80-7.70 (3H, m, H_4), 7.70 (2H, d, J = 8.7 Hz, H_5), 7.67-7.56 (12H, m, H_2 and H_3), 7.09 (2H, d, J = 8.6 Hz, H_6), 3.88 (3H, s, H_7); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.84 (d, J = 5.3 Hz), 160.53, 156.97 (d, J = 16.8 Hz), 149.74 (d, J = 114.5 Hz), 142.72 (d, J = 19.2 Hz), 135.22 (d, J = 3.1 Hz), 134.67 (d, J = 10.2 Hz), 130.60, 130.25 (d, J = 13.1 Hz), 123.61, 120.82 (q, J = 321.3 Hz), 117.10 (d, J = 88.6 Hz), 114.37, 55.42; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.01; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ; 17.84; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 447.2, $C_{29}H_{24}N_2OP^+$ requires 447.2. The spectroscopic data is in agreement with our reported synthesis.[2]

(5-Bromo-2-(methylthio)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1l)



Prepared according to general procedure A using 5-bromo-2-(methylthio)pyrimidine (820 mg, 4.00 mmol), Tf_2O (0.67 mL, 4.00 mmol), PPh_3 (1.15 g, 4.40 mmol), DBU (0.60 mL, 4.00 mmol) and EtOAc (10 mL). After the purification procedure, the title compound was isolated as a white solid (1.51 g, 2.45 mmol, 61% yield). mp 168-169 ºC; IR ν_{max}/cm^{-1} (film): 3058, 2989, 1530, 1442, 1379, 1261, 1220, 1201, 1184, 1162, 1107, 1027, 724; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, d, *J* = 7.9 Hz), 7.97-7.85 (3H, m), 7.83-7.66 (12H, m), 2.15 (3H, s); ^{13}C NMR (100 MHz, CDCl3) δ: 173.86 (d, *J* = 17.2 Hz), 161.98 (d, *J* = 4.1 Hz), 151.47 (d, *J* = 118.7 Hz), 136.06 (d, *J* = 3.1 Hz), 134.75 (d, *J* = 10.4 Hz), 130.74 (d, *J* = 13.3 Hz), 120.86 (q, *J* = 321.2 Hz), 120.85 (d, *J* = 17.1 Hz), 115.00 (d, *J* = 89.9 Hz), 14.43; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.08; ^{31}P NMR (162 MHz, $CDCl_3$) δ:24.37; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 465.2, $C_{23}H_{19}BrN_2PS^+$ requires 465.0.

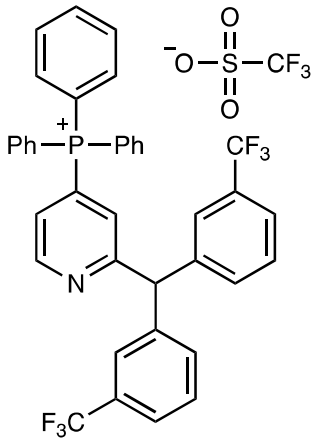
(7-Methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1m)



Prepared according to general procedure A using 7-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (592 mg,

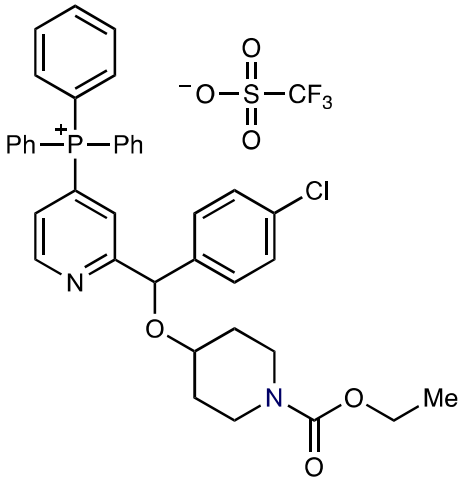
4.45 mmol), Tf_2O (0.75 mL, 4.45 mmol), PPh_3 (1.28 g, 4.89 mmol), DBU (0.67 mL, 4.45 mmol) and CH_2Cl_2 (45 mL). After the purification procedure, the title compound was isolated as a purple crystalline solid (0.57 g, 1.05 mmol, 24% yield); mp 184-189 ºC; IR ν_{max}/cm^{-1} (film): 3061, 2972, 1539, 1514, 1436, 1407, 1335, 1263, 1240, 1225, 1139, 1108, 1099, 1030, 728; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.12 (1H, s), 7.99-7.86 (3H, m), 7.81-7.66 (12H, m), 7.63 (1H, d, *J* = 3.6 Hz), 5.31(1H, d, *J* = 3.6 Hz), 3.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.64 (d, *J* = 9.9 Hz), 150.62 (d, *J* = 18.5 Hz), 142.07 (d, *J* = 118.7 Hz), 136.55, 136.04 (d, *J* = 3.1 Hz), 134.83 (d, *J* = 10.3 Hz), 130.63 (d, *J* = 13.0 Hz), 123.49 (d, *J* = 24.4 Hz), 120.88 (q, *J* = 321.0 Hz), 116.67 (d, *J* = 88.7), 98.28, 31.65; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.13; ^{31}P NMR (162 MHz, $CDCl_3$) δ:13.29; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 394.3, $C_{25}H_{21}N_3P^+$ requires 394.2.

(2-(Bis(3-(trifluoromethyl)phenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1n)



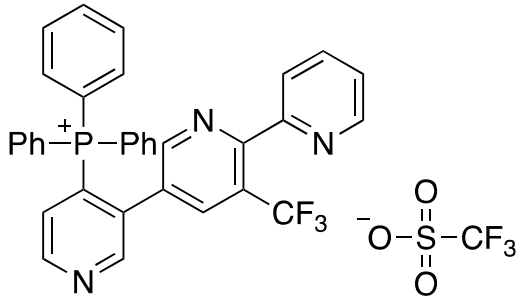
Prepared according to general procedure A (except the reaction was warmed to −30 ºC before the addition of triphenylphosphine and the reaction was then stirred at −30 ºC for 30 minutes instead −78 ºC) using 2-(bis(3-(trifluoromethyl)phenyl)methyl)pyridine (762 mg, 2.00 mmol), Tf_2O (336 μL, 2.00 mmol), PPh_3 (576 mg, 2.10 mmol), DBU (299 μL, 2.0 mmol) and CH_2Cl_2 (20 mL). After the purification procedure, the title compound was isolated as a pale orange solid (1.37 g, 1.73 mmol, 87% yield). mp 64-69 ºC; IR ν_{max}/cm^{-1} (film): 3065, 1577, 1439, 1327, 1259, 1224, 1153, 1109, 1075, 1029, 725, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, app t, *J* = 5.1 Hz), 7.91-7.80 (3H, m), 7.78-7.66 (6H, m), 7.63-7.37 (15H, m), 7.29 (1H, d, *J* = 13.8 Hz), 5.97 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.02 (d, *J* = 9.8), 151.56 (d, *J* = 10.4 Hz), 141.69, 136.10 (d, *J* = 3.1 Hz), 134.31 (d, *J* = 10.5 Hz), 132.90 (d, *J* = 1.1 Hz), 130.89 (d, *J* = 13.1 Hz), 130.73 (q, *J* = 32.2 Hz), 129.99, 129.57 (d, *J* = 83.7 Hz), 126.99 (d, *J* = 8.7 Hz), 125.65-125.39 (2C, m), 124.04 (q, *J* = 3.8 Hz), 123.83 (q, *J* = 272.5 Hz), 120.78 (q, *J* = 321.2 Hz), 115.44 (d, *J* = 89.5 Hz), 57.75; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −62.46, −78.13; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.38; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 642.4, $C_{38}H_{27}F_6NP^+$ requires 642.2.

(2-((4-Chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl) triphenylphosphonium trifluoromethanesulfonate (1o)



Prepared according to general procedure A (except that the reaction was warmed to –50 ºC before the addition of PPh_3 and was stirred at –50 ºC for 30 minutes) using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (750 mg, 2.00 mmol), Tf_2O (0.34 mL, 2.00 mmol), PPh_3 (0.58 g, 2.20 mmol), DBU (0.30 mL, 2.00 mmol) and CH_2Cl_2 (20 mL). After the purification procedure, the title compound was isolated as a white solid (1.15 g, 1.47 mmol, 73% yield). mp 95-98 ºC; IR ν_{max}/cm^{-1} (film): 3063, 2928, 1686, 1438, 1382, 1261, 1223, 1146, 1108, 1084, 1029, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, t, *J* = 5.1 Hz), 7.94-7.86 (3H, m), 7.82-7.73 (6H, m), 7.71-7.59 (7H, m), 7.49 (1H, ddd, *J* = 12.6, 5.0, 1.1 Hz), 7.34-7.25 (4H, m), 5.71 (1H, s), 4.11 (2H, q, *J* = 7.1 Hz), 3.70-3.60 (1H, m), 3.55-3.42 (2H, m), 3.25-3.12 (2H, m), 1.79-1.56 (2H, m), 1.54-1.37 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.37 (d, *J* = 9.6 Hz), 155.43, 151.10 (d, *J* =10.5 Hz), 138.68, 136.16 (d, *J* = 3.1 Hz), 134.53 (d, *J* = 10.5 Hz), 134.01, 130.95 (d, *J* = 13.1 Hz), 129.28 (d, *J* = 84.1 Hz), 128.81, 128.47, 125.92 (d, *J* = 8.4 Hz), 123.86 (d, *J* = 9.1 Hz), 120.83 (q, *J* = 321.2 Hz), 115.80 (d, *J* = 89.4 Hz), 79.94, 72.82, 61.29, 40.69 (rot), 40.66, 31.29, 30.35 (rot), 14.68; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ:22.67; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 635.3, $C_{38}H_{37}ClN_2O_3P^+$ requires 635.2.

Triphenyl(3'-(trifluoromethyl)-[2,2':5',3''-terpyridin]-4''-yl)phosphonium trifluoromethanesulfonate (1p)

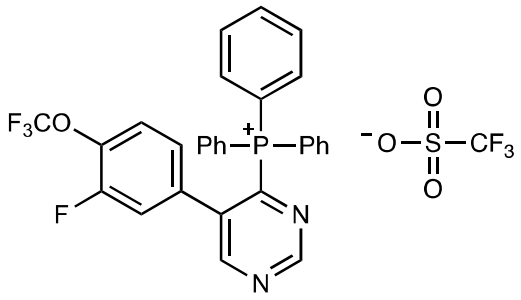


13.4:1:1 Mixture of Regioisomers

Prepared according to general procedure A (except that the reaction was warmed to –30 ºC before the addition of PPh_3 and was stirred at –30 ºC for 30 minutes) using 3'-(trifluoromethyl)-2,2':5',3''-terpyridine (407 mg, 1.35 mmol), Tf_2O (0.23 mL, 1.35 mmol), PPh_3 (0.39 g, 1.49 mmol), DBU (0.20 mL, 1.35 mmol) and CH_2Cl_2 (13.5 mL). After the purification procedure, the title compound (13.4:1:1 mixture of regioisomers determined by ^{31}P NMR)‡ was isolated as a white solid (0.75 g, 1.06 mmol, 78% yield). Mixture of isomers, IR ν_{max}/cm^{-1} (film): 3064, 1588, 1438, 1262, 1224, 1141, 1108, 1030, 721; Major Isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.08 (1H, app t, J = 4.7 Hz), 8.79 (1H, d, J = 6.8 Hz), 8.70 (1H, d, J = 4.7 Hz), 8.27 (1H, d, J = 1.7 Hz), 7.87-7.58 (18H, m), 7.55 (1H, d, J = 7.8 Hz), 7.39 (1H, dd, J = 7.8, 4.7 Hz); Major Isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.12, 155.29, 153.09 (d, J = 7.3 Hz), 151.27 (d, J = 9.9 Hz), 150.97, 150.56, 148.83, 136.40, 136.24-136.07(m), 135.86 (d, J = 6.5 Hz), 135.65 (d, J = 2.8 Hz), 134.18 (d, J = 10.3 Hz), 130.70 (d, J = 13.0 Hz), 128.73 (d, J = 9.0 Hz), 127.45 (d, J = 83.1 Hz), 123.95 (q, J = 33.8 Hz), 123.77, 123.39, 122.19 (q, J = 273.7 Hz), 120.57 (q, J = 321.3 Hz), 116.19 (d, J = 88.6 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –57.97, –78.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.05; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 562.2, $C_{34}H_{24}F_3N_3P^+$ requires 562.2.

‡ The crude regiomeric ratio was determined prior to precipitation by taking a portion of the crude mixture, concentrating *in vacuo* and analyzing by ^{31}P NMR to be 9.6:1.3:1.

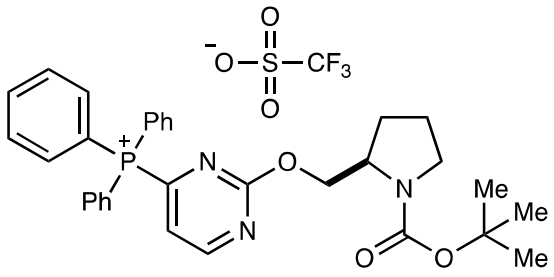
(5-(3-Fluoro-4-(trifluoromethoxy)phenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1q)



An oven dried round bottom flask equipped with a stir bar was charged with 5-(3-fluoro-4-(trifluoromethoxy)phenyl)pyrimidine (307 mg, 1.19 mmol) and PPh_3 (344 mg, 1.31 mmol). The round bottom flask was placed under a nitrogen atmosphere, EtOAc (6 mL) was added, and the reaction vessel was cooled to –50 ºC before Tf_2O (200 µL, 1.19 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before DBU (178 µL, 1.19 mmol) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (approximately 15-30 minutes). The reaction mixture was quenched with H_2O (approximately the same volume as CH_2Cl_2) and the mixture was transferred to a separatory funnel. The mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed six times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Approximately 2 mL of CH_2Cl_2 was added to the crude mixture which was then added dropwise to an excess of 1:1 Et_2O:hexanes to give a fine suspension. The flask was then placed in a –20 ºC refrigerator until a viscous oil settled at the bottom of the flask. The excess solvent was poured off and additional 1:1 Et_2O:hexanes was added, the mixture was stirred and decanted. This process was repeated twice more, and the resulting viscous oil was concentrated *in vacuo* to give the pure phosphonium salt as a tan solid (538 g, 0.81 mmol, 68% yield). mp 61-65 ºC; IR ν_{max}/cm^{-1} (film): 3065, 1624, 1439, 1400, 1257, 1217, 1147, 721, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.50 (1H, s), 8.90 (1H, d, *J* = 8.8 Hz), 7.82-7.51 (16H, m), 6.98, (1H, d, *J* = 8.6 Hz), 6.35 (1H, d, *J* = 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.00 (d, *J* = 5.3 Hz), 158.21 (d, *J* = 248.49 Hz), 157.73 (d, *J* = 16.6 Hz), 151.69 (d, *J* = 116.9 Hz), 150.75 (dd, *J* = 10.8, 1.6 Hz), 135.26 (d, *J* = 3.0 Hz), 135.04, 134.85 (d, *J* = 10.3 Hz), 132.95 (d, *J* = 2.4 Hz), 129.93 (d, *J* = 13.2 Hz), 120.54 (q, *J* = 321.1 Hz), 119.84 (q, *J* = 259.5 Hz), 118.78 (d, *J* = 15.1 Hz), 117.36. 116.46 (d, *J* = 88.8), 107.87

(d, J = 25.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –57.70, –78.30, –107.25 (t, J = 10.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.12; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 519.3, $C_{29}H_{20}F_4N_2OP^+$ requires 519.1.

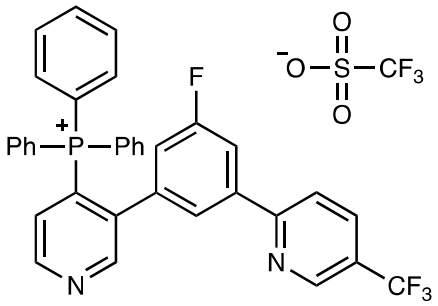
(*R*)-(2-((1-(*Tert*-butoxycarbonyl)pyrrolidin-2-yl)methoxy)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1r)



An oven dried round bottom flask equipped with a stir bar was charged with *tert*-butyl (*R*)-2-((pyrimidin-2-yloxy)methyl)pyrrolidine-1-carboxylate (249 mg, 0.89 mmol) and PPh_3 (257 mg, 0.98 mmol). The round bottom flask was placed under a nitrogen atmosphere, EtOAc (4.5 mL) was added, and the reaction vessel was cooled to –50 ºC before Tf_2O (150 μL, 0.89 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before DBU (133 μL, 0.89 mmol) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (approximately 15-30 minutes). The reaction mixture was quenched with H_2O (approximately the same volume as CH_2Cl_2) and the mixture was transferred to a separatory funnel. The mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Approximately 2 mL of CH_2Cl_2 was added to reaction mixture and was then added dropwise to an excess of chilled Et_2O (0 ºC). The flask was then placed in a –20 ºC refrigerator for approximately 4.5 h. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC), and dried *in vacuo* to provide the pure phosphonium salt. After the purification procedure, the title compound was isolated as a white solid (471 mg, 0.68 mmol, 77% yield). mp 51-54 ºC; IR ν_{max}/cm^{-1} (film): 3064, 2976, 1684, 1560, 1544, 1424, 1393, 1367, 1260, 1149, 1029, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91, (1H, dd, J = 8.2, 4.8 Hz), 7.90-7.80

(3H, m), 7.77-7.59 (12H, m), 7.49 (1H, br s), 4.45-4.30 (1H, m), 4.29-4.15 (1H, m), 4.14-4.03 (1H, m), 3.29 (2H, s), 2.05-1.69 (4H, m), 1.43-1.24 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.06 (d, *J* = 19.3 Hz), 163.16 (d, *J* = 8.6 Hz), 156.69-154.78 (m), 154.63-153.87 (m), 135.97 (d, *J* = 2.9 Hz), 134.58 (d, *J* = 10.3 Hz), 130.56 (d, *J* = 13.1 Hz), 121.43 (d, *J* = 19.9 Hz), 120.60 (q, *J* = 321.2 Hz), 115.05 (d, *J* = 88.9 Hz), 79.63-78.90 (m), 68.93 (rot), 68.55, 55.20, 46.64, 46.23 (rot), 28.72-27.47 (2C, m), 23.47-22.71 (rot); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.10; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 540.4, $C_{32}H_{35}N_3O_3P^+$ requires 540.2.

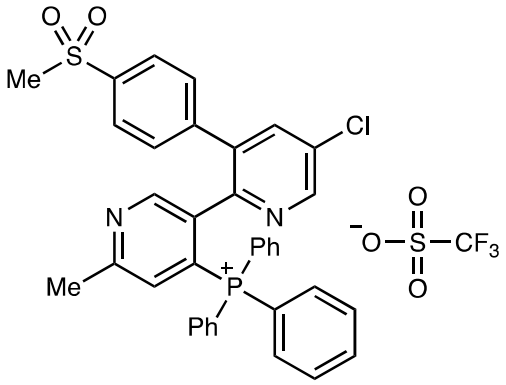
(3-(3-Fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1s)



Prepared according to general procedure A using 2-(3-fluoro-5-(pyridin-3-yl)phenyl)-5-(trifluoromethyl)pyridine (1.27 g, 4.00 mmol), Tf_2O (0.67 mL, 4.00 mmol), PPh_3 (1.15 g, 4.40 mmol), DBU (0.60 mL, 4.00 mmol) and CH_2Cl_2 (40 mL). After the purification procedure, the title compound was isolated as a white solid (1.92 g, 2.64 mmol, 66% yield). mp 209-211 ºC; IR ν_{max}/cm^{-1} (film): 3067, 1595, 1445, 1439, 1328, 1262, 1138, 1124, 1110, 1101, 1082, 1030, 719, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98 (1H, app t, *J* = 4.8 Hz), 8.78 (1H, d, *J* = 6.8 Hz), 8.72 (1H, br s), 7.98 (1H, dd, *J* = 8.3, 1.8 Hz), 7.77-7.56 (17H, m), 7.51-7.42 (2H, m), 6.53 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.25 (d, *J* = 249.6 Hz), 156.95, 153.34, 150.62 (d, *J* = 10.3 Hz), 146.22 (q, *J* = 4.1 Hz), 139.97 (d, *J* = 8.1 Hz), 139.84 (dd, *J* = 6.7, 2.1 Hz), 137.12 (dd, *J* = 8.3, 4.2 Hz), 135.42 (d, *J* = 3.1 Hz),134.66-134.28 (2C, m), 130.65 (d, *J* = 13.1 Hz), 128.45 (d, *J* = 9.3 Hz), 126.68 (d, *J* = 83.3 Hz), 125.79 (q, *J* = 33.2 Hz), 124.82-124.63 (m), 123.41 (q, *J* = 272.3 Hz), 120.81 (q, *J* = 321.0 Hz), 120.50, 117.49 (d, *J* = 23.1 Hz), 116.89 (d, *J* = 88.8 Hz), 114.59 (d, *J* = 23.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.35, –78.20, –110.86; ^{31}P NMR (162

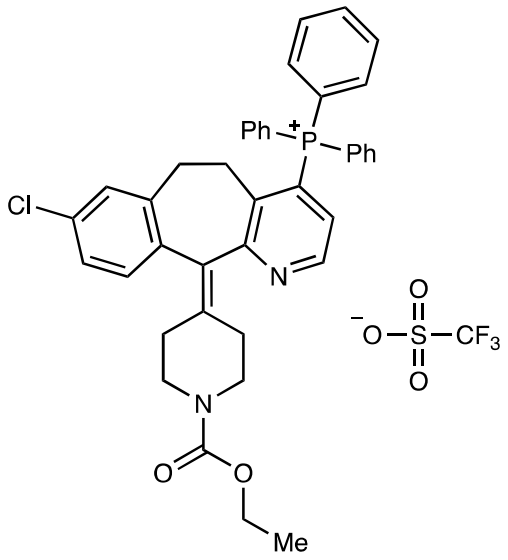
MHz, $CDCl_3$) δ: 21.30; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 579.2, $C_{35}H_{24}F_4N_2P^+$ requires 579.2.

(5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)triphenylphosphonium trifluoromethanesulfonate (1t)



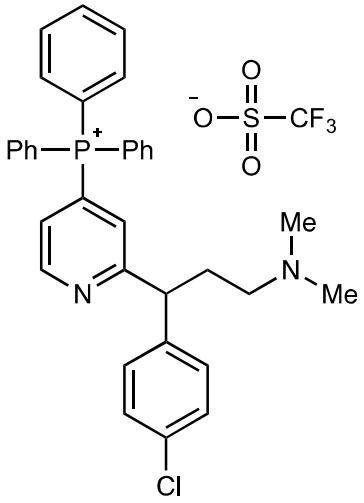
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, d, *J* = 7.1 Hz), 8.10 (2H, d, *J* = 8.2 Hz), 7.86-7.62 (16H, m), 7.51-7.45 (3H, m), 7.20 (1H, d, *J* = 16.5 Hz), 3.14 (3H, s), 2.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.84 (d, *J* = 11.2 Hz), 152.42 (d, *J* = 7.3 Hz), 147.53 (d, *J* = 2.2 Hz), 146.09, 141.53, 141.02, 138.92, 135.62, 134.84 (d, *J* = 2.9 Hz), 134.17 (d, *J* = 10.0 Hz), 133.29 (d, *J* = 3.6 Hz), 132.10, 130.76 (d, *J* = 10.2 Hz), 130.03 (d, *J* = 13.1 Hz), 129.86, 128.55, 128.19 (d, *J* = 86.2 Hz), 120.77 (q, *J* = 321.1 Hz), 119.34 (d, *J* = 91.8 Hz), 43.96, 24.55. The spectroscopic data is in agreement with our reported synthesis.[3]

(8-Chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5Hbenzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1u)



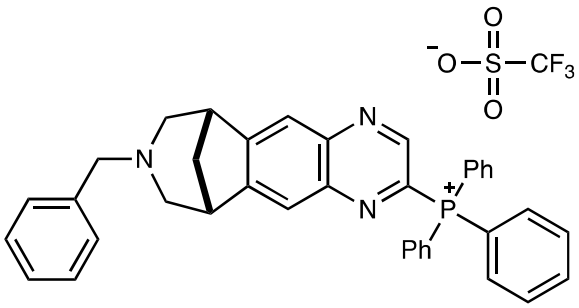
Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, app t, *J* = 5.0 Hz), 7.97-7.87 (3H, m), 7.86-7.74 (6H, m), 7.73-7.60 (6H, m), 7.16-7.01 (3H, m), 6.71 (1H, s), 4.14 (2H, q, *J* = 7.0 Hz), 3.84-3.61 (2H, m), 3.45- 3.20 (3H, m), 2.75 (1H, dt, *J* = 17.4, 4.7 Hz), 2.58 (1H, dt, *J* = 14.9, 4.7 Hz), 2.53-2.30 (3H, m), 2.26-2.09 (1H, m), 1.60-1.43 (1H, m), 1.25 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.64 (d, *J* = 8.3 Hz), 155.37, 149.08 (d, *J* = 11.4 Hz), 139.23, 136.84, 136.66 (d, *J* = 6.8 Hz), 136.06 (d, *J* = 3.1 Hz), 134.21 (d, *J* = 10.7 Hz), 133.95, 133.57, 132.37, 131.58, 131.13 (d, *J* = 13.0 Hz), 129.85, 127.22 (d, *J* = 10.0 Hz), 127.01 (d, *J* = 82.2 Hz), 126.43, 120.78 (q, *J* = 321.3 Hz), 116.42 (d, *J* = 88.5 Hz), 61.39, 44.65, 44.41, 30.74, 30.46, 30.39, 29.39, 14.59. The spectroscopic data is in agreement with our reported synthesis.[2]

(2-(1-(4-chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1v)



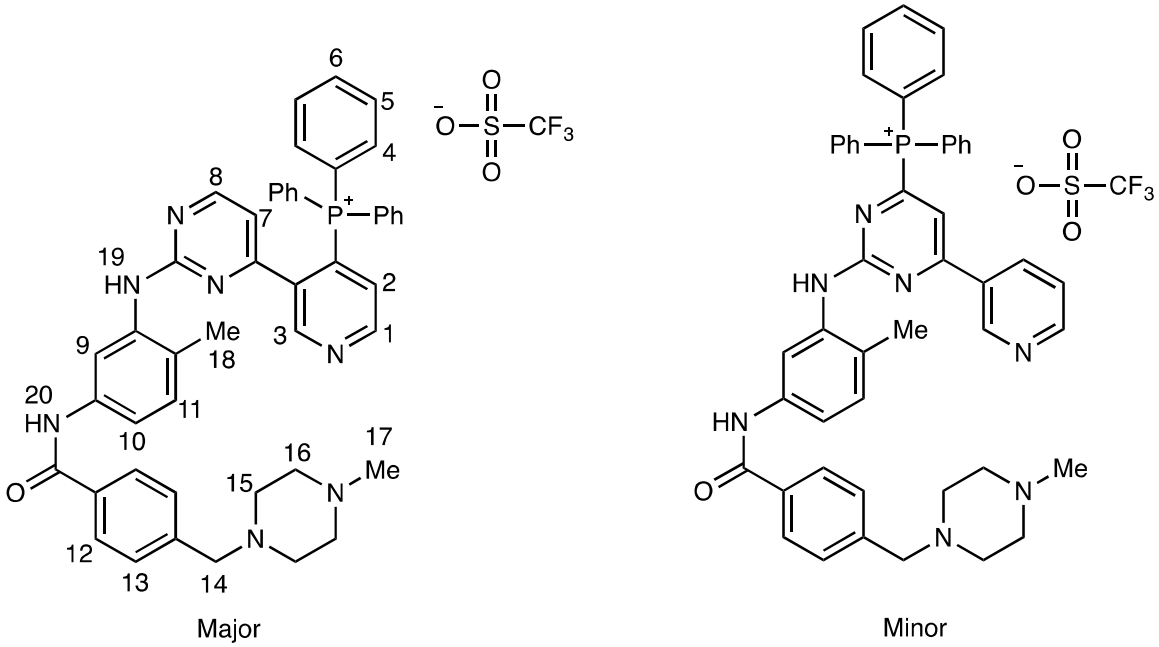
Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.97 (1H, app t, J = 5.1 Hz, H_1), 7.93-7.86 (3H, m, H_6), 7.80-7.70 (6H, m, H_5), 7.61-7.50 (6H, m, H_4), 7.39 (1H, ddd, J = 12.8, 5.1, 1.5 Hz, H_2), 7.25-7.16 (5H, m, H_3, H_7, and H_8), 4.28 (1H, app t, J = 6.8 Hz, H_9), 2.56-2.43 (1H, m, H_{10}), 2.32-2.11 (9H, m, H_{10}, H_{11}, and H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.55 (d, J = 9.9 Hz), 150.97 (d, J = 9.9 Hz), 140.26, 135.82 (d, J = 3.1 Hz), 134.02 (d, J = 10.7 Hz), 132.25, 130.61 (d, J = 13.0 Hz), 128.92 (d, J = 85.5 Hz), 128.75, 127.92, 126.26 (d, J = 8.4 Hz), 124.42 (d, J = 7.6 Hz), 120.46 (q, J = 321.2 Hz), 115.31 (d, J = 89.3 Hz), 56.73, 49.77, 44.88, 31.99. The spectroscopic data is in agreement with our reported synthesis.[2]

((6*S*,10*R*)-8-Benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxalin-2-yl)triphenylphosphonium (1w)



Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, s), 8.10-7.72 (17H, m), 7.20-7.05 (3H, m), 6.92-6.80 (2H, m), 3.55-3.27 (4H, m), 3.03-2.87 (2H, m), 2.66-2.42 (2H, m), 2.29-2.15 (1H, m), 1.87 (1H, d, *J* = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.90 (d, *J* = 23.5 Hz), 144.21, 143.45 (d, *J* = 16.9 Hz), 137.51 (br s), 136.00 (d, *J* = 2.9 Hz), 134.55 (d, *J* = 10.9 Hz), 130.72 (d, *J* = 13.0 Hz), 129.20-126.21 (3C, m,), 120.69 (br s), 120.67 (q, *J* = 321.5 Hz), 116.42 (d, *J* = 88.3 Hz), 61.29, 57.90-56.06 (2C, m), 43.14-40.43 (3C, m). The spectroscopic data is in agreement with our reported synthesis.[2]

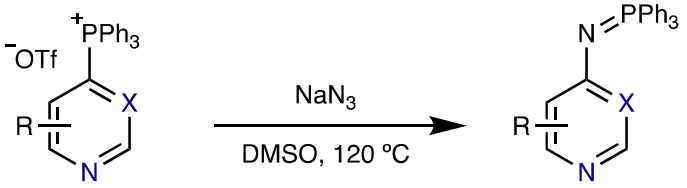
(3-(2-((2-Methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate and (2-((2-Methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)-6-(pyridin-3-yl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1x)



Prepared according to our previous report.[4] Major isomer, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.14 (1H, s, H_{20}), 9.55 (1H, d, J = 6.7 Hz, H_3), 9.09 (1H, app t, J = 4.6 Hz, H_1), 8.31 (1H, d, J = 5.1 Hz, H_8), 8.00-7.55 (18H, m, H_4, H_5, H_6, H_9, and H_{12}), 7.52-7.20 (5H, m, H_2, H_7, H_{10}, and H_{13}), 7.08 (1H, d, J = 8.3 Hz, H_{11}), 6.10 (1H, br, H_{19}), 3.55 (2H, s, H_{14}), 2.70-2.13 (11H, m, H_{15}, H_{16}, and H_{18}), 1.74 (3H, s, H_{17}); Major isomer, ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.15, 159.79, 159.72 (d, J = 2.0 Hz), 158.29, 152.67 (d, J = 11.4 Hz), 151.77 (d, J = 6.8 Hz), 141.14 (br), 137.28, 136.16, 135.81 (d, J = 3.8 Hz), 134.70 (d, J = 2.3 Hz), 133.91 (d, J = 10.0 Hz), 130.75 (d, J = 10.2 Hz), 129.96, 129.95 (d, J = 13.4 Hz), 128.74, 127.70, 125.67 (d, J = 86.2 Hz), 125.48, 120.67 (q, J = 322.8 Hz), 119.54 (d, J = 92.3 Hz), 117.03, 117.00, 115.56, 110.34, 60.65, 53.15, 50.09, 43.09, 16.99. The spectroscopic data is in agreement with our reported synthesis.[4]

A 1.3 Preparation of Heterocyclic Iminophosphoranes

General procedure B

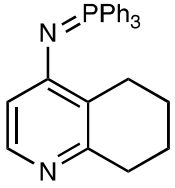


Care should be taken when handling sodium azide. We recommend conducting these reactions behind a blast shield. For proper storage, handling, and waste protocols, see the CDC's International Chemical Safety Card.[*]

An oven-dried 8 mL vial equipped with a stir bar and septa cap was charged with the phosphonium salt (1.0 equiv), sodium azide (1.25 equiv), and placed under a nitrogen atmosphere. DMSO (1.5 M) was added, the cap was wrapped with parafilm and the reaction mixture was heated for the stated time at 120 ºC. The reaction was cooled to room temperature, diluted with EtOAc and a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted a further three times with EtOAc and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography under the stated conditions to provide the iminophosphorane product.

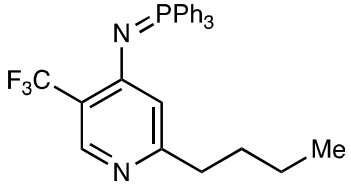
[*] Center for Disease Control and Prevention: Sodium Azide International Chemical Safety Card. https://www.cdc.gov/niosh/ipcsneng/neng0950.html (accessed Apr 4, 2018).

1,1,1-triphenyl-N-(5,6,7,8-tetrahydroquinolin-4-yl)- λ^5-phosphanimine (2a)



Prepared according to general procedure B using triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (272 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 23 h. Flash column chromatography (basic alumina: 50% EtOAc in Hexanes) afforded the title compound as a light brown crystalline solid (174 mg, 0.43 mmol, 85% yield). mp 77-80 ºC; IR ν_{max}/cm^{-1} (film): 3084, 3051, 2989, 2954, 1442, 1439, 1270, 1260, 1221, 1145, 1106, 1029, 758, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (1H, d, *J* = 6.5 Hz), 7.74-7.59 (9H, m), 7.53 (6H, td, *J* = 7.7, 3.2 Hz), 6.02 (1H, d, *J* = 6.5 Hz), 2.98-2.84 (4H, m), 1.91-1.80 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.54, 154.56, 143.78, 132.46 (d, *J* = 9.9 Hz), 132.21 (d, *J* = 2.9 Hz), 129.87 (d, *J* = 100.3 Hz), 128.86 (d, *J* = 12.2 Hz), 127.44 (d, *J* = 23.6 Hz), 113.09 (d, *J* = 11.2 Hz), 31.69, 24.94, 23.01, 22.91; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 6.85; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 409.4, $C_{27}H_{26}N_2P^+$ requires 409.2.

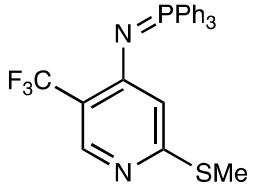
N-(2-butyl-5-(trifluoromethyl)pyridin-4-yl)-1,1,1-triphenyl- λ^5-phosphanimine (2b)



Prepared according to general procedure B using (2-butyl-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (307 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 21.25 h. Flash column chromatography (basic alumina: 30% EtOAc in hexanes) afforded the title compound as a white solid (214 mg, 0.45 mmol, 89% yield). mp 145-147 ºC; IR ν_{max}/cm^{-1} (film): 3075, 2963, 2927, 1592, 1520, 1491, 1484, 1442, 1434, 1324,

1200, 1182, 1108, 1057, 1024, 718, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (1H, d, *J* = 2.4 Hz), 7.77 (6H, dd, *J* = 8.2, 7.2 Hz), 7.58 (3H, td, *J* = 7.7, 1.6 Hz), 7.49 (6H, td, *J* = 7.7, 3.0 Hz), 6.03 (1H, s), 2.37 (2H, t, *J* = 7.5 Hz), 1.33 (2H, pent, *J* = 7.5 Hz), 1.11 (2H, pent, *J* = 7.6 Hz), 0.77 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.45, 157.38, 147.18 (qd, *J* = 6.0, 2.5 Hz), 132.44 (d, *J* = 10.0 Hz), 132.21 (d, *J* = 2.9 Hz), 129.38 (d, *J* = 101.7 Hz), 128.81 (d, *J* = 12.3 Hz), 125.35 (q, *J* = 272.3 Hz), 118.45-117.19 (m), 115.05 (d, *J* = 11.8 Hz), 37.56, 31.18, 21.97, 13.79; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.27; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 6.25; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 479.3, $C_{28}H_{27}F_3N_2P^+$ requires 479.2.

N-(2-(methylthio)-5-(trifluoromethyl)pyridin-4-yl)-1,1,1-triphenyl- λ^5-phosphanimine (2c)

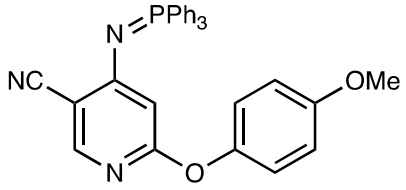


Prepared according to general procedure B using (2-(methylthio)-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (301 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 6 h. Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a white solid (219 mg, 0.47 mmol, 93% yield). mp 172-174 ºC; IR ν_{max}/cm^{-1} (film): 2989, 2901, 1578, 1569, 1516, 1468, 1434, 1418, 1326, 1103, 1058, 1019, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (1H, d, *J* = 2.5 Hz), 7.80-7.72 (6H, m), 7.59 (3H, tdd, *J* = 6.7, 1.7, 1.4 Hz), 7.54-7.47 (6H, m), 5.99 (1H, s), 2.15 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.87, 156.89, 147.19 (qd, *J* = 6.2, 2.5 Hz), 132.47 (d, *J* = 10.1 Hz), 132.38 (d, *J* = 3.0 Hz), 129.21 (d, *J* = 101.3 Hz), 128.94 (d, *J* = 12.4 Hz), 125.25 (q, *J* = 272.2 Hz), 117.11 (qd, *J* = 27.4, 23.2 Hz), 111.68 (d, *J* = 12.0 Hz), 13.29; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.23; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 6.45; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 469.2, $C_{25}H_{21}F_3N_2PS^+$ requires 469.1.

N-(2-(methylthio)-5-(trifluoromethyl)pyridin-4-yl)-1,1,1-triphenyl- λ^5-phosphanimine (2c) (Large Scale Procedure)

An oven-dried 8 mL vial equipped with a stir bar and septa cap was charged with (2-(methylthio)-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (603 mg, 1.00 mmol), sodium azide (81 mg, 1.25 mmol), and placed under a nitrogen atmosphere. DMSO (1.5 M) was added, the cap was wrapped with parafilm and the reaction mixture was heated for 15 h at 120 ºC. The reaction was cooled to room temperature, diluted with EtOAc and a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted a further three times with EtOAc and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) which afforded the title compound as a white solid (421 mg, 0.90 mmol, 90% yield).

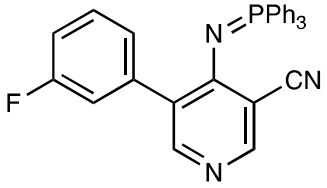
6-(4-methoxyphenoxy)-4-((triphenyl- λ^5-phosphaneylidene)amino)nicotinonitrile (2d)



Prepared according to general procedure B using (5-cyano-2-(4-methoxyphenoxy)pyridin-4-yl)triphenylphosphonium (318 mg, 0.50 mmol), sodium azide (41 mg, 0.625 mmol) and DMSO (0.33 mL) for 8 h. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a yellow solid (112 mg, 0.22 mmol, 45% yield). mp 212-214 ºC; IR ν_{max}/cm^{-1} (film): 2989, 2214, 1582, 1502, 1471, 1418, 1206, 1176, 1105, 1033; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.20 (1H, d, J = 2.6 Hz), 7.74-7.67 (6H, m), 7.59 (3H, tdd, J = 7.3, 2.0, 1.9 Hz), 7.52-7.44 (6H, m), 6.85-6.80 (2H, m), 6.79-6.74 (2H, m), 5.55 (1H, s), 3.79 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.02, 163.28, 156.51, 153.08 (d, J = 2.4 Hz), 146.82, 132.56, 132.54 (d, J = 10.0 Hz), 129.00 (d, J = 12.4 Hz), 128.07 (d, J = 101.1 Hz), 122.26, 118.63, 114.56, 102.15, (d, J = 26.4 Hz), 99.39

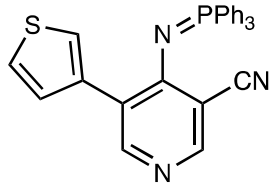
(d, J = 11.9 Hz), 55.54; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 9.18; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 502.3, $C_{31}H_{25}N_3O_2P^+$ requires 502.2.

5-(3-fluorophenyl)-4-((triphenyl- λ^5-phosphaneylidene)amino)nicotinonitrile (2e)



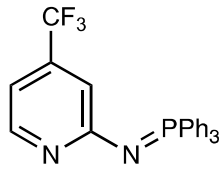
Prepared according to general procedure B using (3-cyano-5-(3-fluorophenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (304 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 23.75 h. Flash column chromatography (basic alumina: 20% EtOAc in hexanes) afforded the title compound as a yellow amorphous solid (208 mg, 0.44 mmol, 88% yield). mp 43-45 ºC; IR ν_{max}/cm^{-1} (film): 3058, 3012, 2919, 2220, 1614, 1582, 1565, 1468, 1434, 1254, 1198, 1149, 1109, 1043, 908, 716; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (1H, s), 8.22 (1H, d, J = 1.7 Hz), 7.55-7.34 (9H, m), 7.39 (6H, td, J = 7.7, 3.4 Hz), 7.21 (1H, m), 7.08 (1H, d, J = 7.6 Hz), 6.97 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.34 (d, J = 245.8 Hz), 157.63 (d, J = 2.2 Hz), 154.08 (d, J = 0.9 Hz), 151.84, 139.90 (d, J = 8.1 Hz), 133.05 (d, J = 12.0 Hz), 132.40 (d, J = 10.55 Hz), 132.02 (d, J = 3.0 Hz), 130.08 (d, J = 105.3 Hz), 129.44 (d, J = 8.4 Hz), 128.55 (d, J = 12.7 Hz), 125.53 (d, J = 2.9 Hz), 119.1 (d, J = 1.0 Hz), 116.95 (d, J = 21.6 Hz), 113.94 (d, J = 21.0 Hz), 105.22 (d, J = 7.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –113.76; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 4.88; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 474.3, $C_{30}H_{22}FN_3P^+$ requires 474.2.

5-(thiophen-3-yl)-4-((triphenyl- λ^5-phosphaneylidene) amino)nicotinonitrile (2f)



Prepared according to general procedure B using (3-cyano-5-(thiophen-3-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (298 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 21 h. Flash column chromatography (basic alumina: 50% EtOAc in hexanes) afforded the title compound as a yellow oil (164 mg, 0.35 mmol, 71% yield). IR ν_{max}/cm^{-1} (film): 3058, 3011, 2218, 1566, 1464, 1435, 1372, 1245, 1152, 1108, 1043, 1025, 748, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34, (1H, d, *J* = 1.8 Hz), 8.32 (1H, s), 7.58-7.48 (9H, m), 7.42 (6H, td, *J* = 7.5, 3.3 Hz), 7.25 (1H, dd, *J* = 3.0, 1.7 Hz), 7.22 (1H, dd, *J* = 5.0, 3.0 Hz), 7.17 (1H, dd, *J* = 5.0, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.61 (d, *J* = 1.8 Hz), 153.67 (d, *J* = 1.0 Hz), 151.83, 137.77, 132.51 (d, *J* = 10.6 Hz), 132.03 (d, *J* = 2.9 Hz), 130.31 (d, *J* = 105.2 Hz), 129.42, 129.31, 128.56 (d, *J* = 12.8 Hz), 124.53, 123.73, 119.28 (d, *J* = 0.8 Hz), 104.76 (d, *J* = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 5.00; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 462.2, $C_{28}H_{21}N_3PS^+$ requires 462.1.

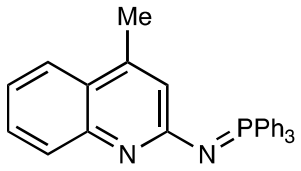
1,1,1-triphenyl-N-(4-(trifluoromethyl)pyridin-2-yl)- λ^5-phosphanimine (2g)



Prepared according to general procedure B using triphenyl(4-(trifluoromethyl)pyridin-2-

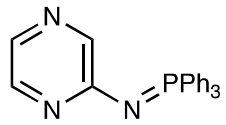
yl)phosphonium trifluoromethanesulfonate (279 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 25 h. Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a pale yellow solid (186 mg, 0.44 mmol, 88% yield). mp 159-160 ºC; IR ν_{max}/cm^{-1} (film): 3055, 2995, 1595, 1546, 1469, 1422,1335, 1305, 1271, 1162, 1128, 1111, 1073, 1034, 1022, 998, 720, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89, (1H, d, *J* = 5.4 Hz), 7.81 (6H, m), 7.52 (3H, td, *J* = 7.5, 1.4 Hz), 7.13 (1H, s), 7.44 (6H, td, *J* = 7.8, 2.9 Hz), 6.60 (1H, d, *J* = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.25 (d, *J* = 6.3 Hz), 147.97, 138.73 (qd, *J* = 32.7, 5.3 Hz), 133.08 (d, *J* = 9.7 Hz), 131.69 (d, *J* = 2.9 Hz), 129.61 (d, *J* = 100.1 Hz), 128.7 (d, *J* = 12.2 Hz), 123.52 (qd, *J* = 272.9, 1.5 Hz), 113.42 (dq, *J* = 26.0, 4.0 Hz), 107.10 (q, *J* = 3.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –65.10; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 14.85; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 423.3 $C_{24}H_{19}F_3N_2P^+$ requires 423.1.

N-(4-methylquinolin-2-yl)-1,1,1-triphenyl- λ^5-phosphanimine (2h)



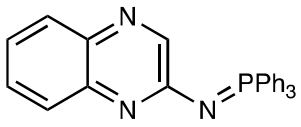
Prepared according to general procedure B using (4-methylquinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (277 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 22.67 h. Flash column chromatography (basic alumina: 25% EtOAc in hexanes) afforded the title compound as a yellow solid (277 mg, 0.33 mmol, 66% yield). mp 193-195 ºC; IR ν_{max}/cm^{-1} (film): 3077, 3046, 2989, 1602, 1541, 1456, 1438, 1386, 1355, 1321, 1308, 1243, 1206, 1188, 1108, 1073, 1058, 914, 854, 718; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95-7.85 (6H, m), 7.70 (1H, d, *J* = 8.2 Hz), 7.53-7.46 (3H, m), 7.41 (6H, td, *J* = 7.7, 2.9 Hz), 7.36-7.24 (2H, m), 7.11 (1H, ddd, *J* = 8.1, 6.7, 1.5 Hz), 7.05 (1H, s), 2.52 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.64 (d, *J* = 6.8 Hz), 147.96, 143.38 (d, *J* = 4.8 Hz), 133.29 (d, *J* = 9.5 Hz), 131.40 (d, *J* = 2.8 Hz), 130.12 (d, *J* = 99.3 Hz), 128.17 (d, *J* = 12.1 Hz), 127.85, 126.13, 123.68, 123.25, 120.87, 120.55 (d, *J* = 25.1 Hz), 18.42 (d, *J* = 0.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.97; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 419.3, $C_{28}H_{24}N_2P^+$ requires 419.2.

1,1,1-triphenyl-N-(pyrazin-2-yl)- λ^5-phosphanimine (2i)



Prepared according to general procedure B using triphenyl(pyrazin-2-yl)phosphonium trifluoromethanesulfonate (245 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 21.5 h. Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a brown solid (98 mg, 0.28 mmol, 55% yield). mp 174-176 ºC; IR ν_{max}/cm^{-1} (film): 3061, 1573, 1492, 1471, 1435, 1410, 1344, 1109, 996, 718, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (1H, s), 7.80 (6H, dd, *J* = 8.3, 7.2 Hz), 7.70-7.64 (2H, m), 7.53 (3H, td, *J* = 7.8, 1.6 Hz), 7.44 (6H, td, *J* = 7.6, 2.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.19 (d, *J* = 6.4 Hz), 141.89 (d, *J* = 25.8 Hz), 140.99, 131.82 (d, *J* = 2.9 Hz), 133.02 (d, *J* = 9.8 Hz), 131.82 (d, *J* = 2.9 Hz), 129.34 (d, *J* = 100.1 Hz), 128.44 (d, *J* = 12.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.85; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 356.2, $C_{22}H_{19}N_3P^+$ requires 356.1.

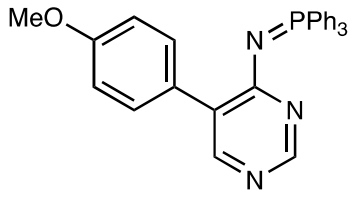
1,1,1-triphenyl-N-(quinoxalin-2-yl)- λ^5-phosphanimine (2j)



Prepared according to general procedure B using triphenyl(quinoxalin-2-yl)phosphonium (270 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 22.5 h. Flash column

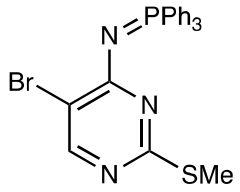
chromatography (basic alumina: 30% EtOAc in hexanes) afforded the title compound as a yellow solid (172 mg, 0.42 mmol, 85% yield). mp 125-128 ºC; IR ν_{max}/cm^{-1} (film): 3061, 2989, 1534, 1437, 1432, 1407, 1375, 1352, 1305, 1237, 1106, 1033, 1023, 1011, 946, 904, 728, 720.3, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, s), 7.93-7.85 (6H, m), 7.80 (1H, dd, *J* = 8.1, 1.4 Hz), 7.54 (3H, tdd, *J* = 6.7, 1.7, 1.4 Hz), 7.49-7.42 (6H, m), 7.37 (1H, ddd, *J* = 8.3, 6.8, 1.4 Hz), 7.31-7.22 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.17 (d, *J* = 6.7 Hz), 147.00 (d, *J* = 26.8 Hz), 142.21, 136.82, 133.21 (d, *J* = 9.8 Hz), 131.41 (d, *J* = 2.9 Hz), 129.34-128.22 (4C, m), 125.80, 123.30; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.83; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 406.2, $C_{26}H_{21}N_3P^+$ requires 406.2.

N-(5-(4-methoxyphenyl)pyrimidin-4-yl)-1,1,1-triphenyl- λ^5-phosphanimine (2k)



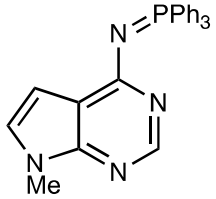
Prepared according to general procedure B using 5-(4-methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (298 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 21.75 h. Flash column chromatography (basic alumina: 75% EtOAc in hexanes) afforded the title compound as a yellow solid (201 mg, 0.43 mmol, 87% yield). mp 139-141 ºC; IR ν_{max}/cm^{-1} (film): 3058, 2989, 1578, 1567, 1517, 1506, 1451, 1432, 1411, 1391, 1354, 1293, 1239, 1176, 1116, 1108, 1101, 1028, 1018, 824, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22-8.18 (2H, m), 7.88-7.76 (8H, m), 7.52 (3H, td, *J* = 7.7, 1.5 Hz), 7.43 (6H, td, *J* = 7.7, 2.9 Hz), 7.01 (2H, d, *J* = 8.6 Hz), 3.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.22 (d, *J* = 6.7 Hz), 158.59, 155.84, 153.10 (d, *J* = 3.0 Hz), 133.04 (d, *J* = 9.8 Hz), 131.67 (d, *J* = 2.8 Hz), 130.38, 129.65, 129.07 (d, *J* = 100.4 Hz), 128.22 (d, *J* = 12.2 Hz), 125.47 (d, *J* = 22.0 Hz), 113.11, 55.12; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.78; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 462.3, $C_{29}H_{25}N_3OP^+$ requires 462.2.

N-(5-bromo-2-(methylthio)pyrimidin-4-yl)-1,1,1-triphenyl- λ^5-phosphanimine (2l)



Prepared according to general procedure B using (5-bromo-2-(methylthio)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (308 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 18 h. Flash column chromatography (basic alumina: 30% EtOAc in hexanes) afforded the title compound as a white solid (235 mg, 0.49 mmol, 98% yield). mp 176-178 ºC; IR ν_{max}/cm^{-1} (film): 3061, 2989, 1541, 1495, 1482, 1426, 1350, 1316, 1301, 1174, 1109, 1061, 1028, 1005; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (1H, d, *J* = 2.9 Hz), 7.82-7.74 (6H, m), 7.57 (3H, tdd, *J* = 7.2, 1.6, 1.4 Hz), 7.51-7.44 (6H, m), 1.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.16, (d, *J* = 0.5 Hz), 163.96, (d, *J* = 4.6 Hz), 155.57 (d, *J* = 2.6 Hz), 132.88 (d, *J* = 10.0 Hz), 132.17 (d, *J* = 2.9 Hz), 128.54 (d, *J* = 12.4 Hz), 128.38 (d, *J* = 101.2 Hz), 109.14 (d, *J* = 26.2 Hz), 13.50; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 480.1, $C_{23}H_{20}BrN_3PS^+$ requires 480.0.

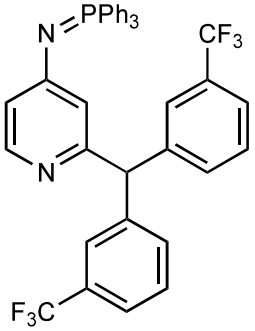
N-(7-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,1,1-triphenyl- λ^5-phosphanimine (2m)



Prepared according to general procedure B using (7-methyl-*7H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (272 mg, 0.50 mmol), sodium azide (41 mg, 0.63 mmol) and DMSO (0.33 mL) for 8 h. Flash column chromatography (basic alumina: 50% EtOAc in hexanes) afforded the title compound as a yellow solid (108 mg, 0.26 mmol, 53% yield). mp 236-238 ºC; IR ν_{max}/cm^{-1} (film): 3051, 2919, 2850, 1567, 1555, 1482, 1443, 1431, 1375, 1334, 1293, 1245, 1107, 1063, 715; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (1H, s), 7.92-7.84 (6H, m), 7.52

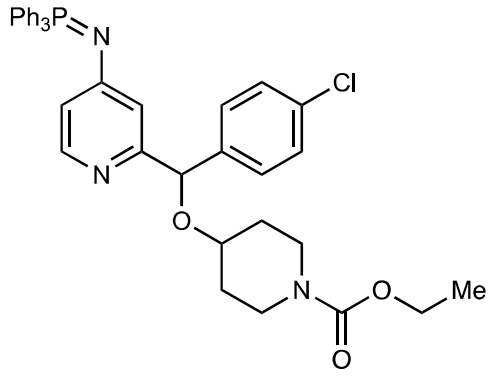
(3H, tdd, J = 7.6, 1.6, 1.4 Hz), 7.47-7.40 (6H, m), 6.86 (1H, d, J = 3.4 Hz), 6.75 (1H, d, J = 3.4 Hz), 3.76 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.46 (d, J = 6.9 Hz), 151.14, 150.62 (d, J = 5.3 Hz), 133.42 (d, J = 9.8 Hz), 131.68 (d, J = 2.9 Hz), 129.65 (d, J = 100.0 Hz), 128.29 (d, J = 12.2 Hz), 123.90, 111.16 (d, J = 25.2 Hz), 99.94, 31.08; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.13; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 409.3, $C_{25}H_{22}N_4P^+$ requires 409.2.

***N*-(2-(bis(3-(trifluoromethyl)phenyl)methyl)-5-methylpyridin-4-yl)-1,1,1-triphenyl-λ^5-phosphanimine (2n)**



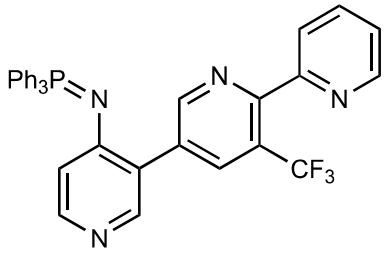
Prepared according to general procedure B (except the reaction was diluted and extracted with CH_2Cl_2 instead of EtOAc during the workup) using (2-(bis(3-(trifluoromethyl)phenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (198 mg, 0.25 mmol), sodium azide (20 mg, 0.31 mmol) and DMSO (0.17 mL) for 17 h. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then: 40% EtOAc, 1% NEt_3 in hexanes to 60% EtOAc, 1% NEt_3 in hexanes) afforded the title compound as a white solid (122 mg, 0.19 mmol, 74% yield). mp 44-46 ºC; IR ν_{max}/cm^{-1} (film): 3058, 2989, 1582, 1477, 1438, 1352, 1327, 1157, 1115, 1074, 1049, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (1H, d, *J* = 5.5 Hz), 7.58-7.48 (6H, m), 7.47-7.39 (3H, m), 7.39-7.26 (8H, m), 7.24-7.14 (4H, m), 7.10-7.00 (2H, m), 6.52 (1H, dd, *J* = 5.5, 1.8 Hz), 6.11 (1H, s), 5.45 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.55 (d, *J* = 1.5 Hz), 159.53 (d, *J* = 2.5 Hz), 149.62 (d, *J* = 2.2 Hz), 143.32, 132.67, (d, *J* = 0.9 Hz), 132.37 (d, *J* = 9.8 Hz), 132.17 (d, *J* = 2.8 Hz), 130.49 (q, *J* = 32.0 Hz), 129.06 (d, *J* = 99.4 Hz), 128.78 (d, *J* = 12.1 Hz), 128.67, 125.82 (q, *J* = 3.8 Hz), 124.06 (q, *J* = 272.4, Hz), 123.32 (q, *J* = 3.8 Hz), 118.41 (d, *J* = 18.1 Hz), 117.66 (d, *J* = 21.0 Hz), 58.75; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.41; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 8.97; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 657.3, $C_{38}H_{28}F_6N_2P^+$ requires 657.2.

Ethyl 4-((4-chlorophenyl)(4-((triphenyl-λ^5-phosphaneylidene)amino)pyridin-2-yl)methoxy)piperidine-1-carboxylate (2o)



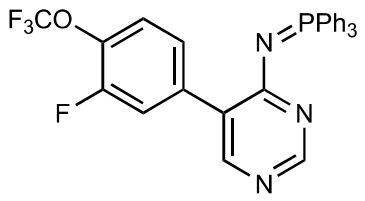
Prepared according to general procedure B using (2-((4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl) triphenylphosphonium trifluoromethanesulfonate (196 mg, 0.25 mmol), sodium azide (20 mg, 0.31 mmol) and DMSO (0.17 mL) for 24.75 h. Flash column chromatography (silica gel, gradient elution: 2% MeOH in CH_2Cl_2 to 4% MeOH in CH_2Cl_2) afforded the title compound as a light yellow oil (110 mg, 0.17 mmol, 68% yield). IR ν_{max}/cm^{-1} (film): 3057, 2928, 1692, 1585, 1477, 1437, 1354, 1230, 1108, 1088, 1028, 752, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (1H, d, *J* = 5.7 Hz), 7.73-7.64 (6H, m), 7.62-7.55 (3H, m), 7.52-7.43 (6H, m), 7.20-7.14 (4H, m), 6.68 (1H, d, *J* = 1.8 Hz), 6.60 (1H, dd, *J* = 5.8, 1.9 Hz), 5.46 (1H, s), 4.11 (2H, q, *J* = 7.1 Hz), 3.64-3.47 (3H, m), 3.21-3.04 (2H, m), 1.78-1.67 (1H, m), 1.61-1.35 (3H, m), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.11, 159.51, 155.42, 146.62, 140.10, 132.98, 132.57-132.30 (2C, m), 128.93 (d, *J* = 12.2 Hz), 128.76 (d, J = 99.6 Hz), 128.27, 128.07, 118.42 (d, *J* = 22.15), 114.54 (d, *J* = 18.4 Hz), 79.76, 72.12, 61.13, 40.87, 40.83 (rot), 30.89 (rot), 30.80, 14.66; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 650.3, $C_{38}H_{38}ClN_3O_3P^+$ requires 650.2.

1,1,1-Triphenyl-*N*-(3'-(trifluoromethyl)-[2,2':5',3''-terpyridin]-4''-yl)-λ^5-phosphanimine (2p)



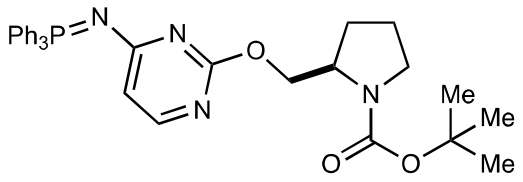
Prepared according to general procedure B using triphenyl(3'-(trifluoromethyl)-[2,2':5',3''-terpyridin]-4''-yl)phosphonium trifluoromethanesulfonate (178 mg, 0.25 mmol), sodium azide (20 mg, 0.31 mmol) and DMSO (0.17 mL) for 20 h. Flash column chromatography (silica gel packed in hexanes and neutralized with NEt_3, gradient elution: 100% EtOAc to 5% MeOH in CH_2Cl_2) afforded the title compound as a light yellow oil (108 mg, 0.19 mmol, 75% yield). IR ν_{max}/cm^{-1} (film): 3055, 2989, 2928, 1580, 1489, 1476, 1452, 1439, 1419, 1386, 1355, 1331, 1133, 1109, 1036, 753, 718; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.11 (1H, d, *J* = 1.7 Hz), 8.80 (1H, d, *J* = 1.9 Hz), 8.75 (1H, ddd, *J* = 4.9, 1.7, 0.9 Hz), 8.38 (1H, d, *J* = 2.6 Hz), 7.95 (1H, d, *J* = 5.7 Hz), 7.85 (1H, ddd, *J* = 9.5, 7.5, 1.8 Hz), 7.74 (1H, d, *J* = 7.8 Hz), 7.71-7.63 (6H, m), 7.60-7.54 (3H, m), 7.48 (6H, td, *J* = 7.6, 3.1 Hz), 7.38, (1H, ddd, *J* = 7.5, 4.9, 1.2 Hz), 6.34 (1H, d, *J* = 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.29, 156.49, 153.96 (q, *J* = 1.6 Hz), 151.86, 149.98 (d, *J* = 2.4 Hz), 149.62, 149.01, 136.70 (q, *J* = 5.0 Hz), 136.29, 134.19, 132.49-132.31 (2C, m), 129.20 (d, *J* = 100.36 Hz), 128.97 (d, *J* = 12.2 Hz), 126.61 (d, *J* = 23.7 Hz), 123.90 (q, *J* = 273.4 Hz), 123.84 (q, *J* = 32.3 Hz), 123.80 (d, *J* = 1.3 Hz), 123.27, 116.75 (d, *J* = 12.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –57.33; ^{31}P NMR (162 MHz, $CDCl_3$) δ:8.68; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 577.3, $C_{34}H_{25}F_3N_4P^+$ requires 577.2.

***N*-(5-(3-fluoro-4-(trifluoromethoxy)phenyl)pyrimidin-4-yl)-1,1,1-triphenyl-λ^5-phosphanimine (2q)**



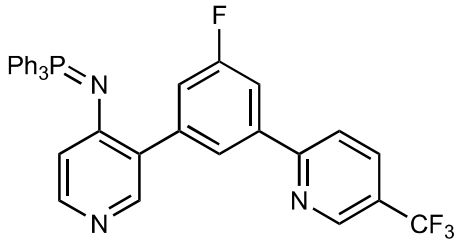
Prepared according to general procedure B (except the reaction was diluted and extracted with CH_2Cl_2 instead of EtOAc during the workup) using (*R*)-(2-((1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)methoxy)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (167 mg, 0.25 mmol), sodium azide (20 mg, 0.31 mmol) and DMSO (0.17 mL) for 8 h. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then: 50% EtOAc in hexanes to 55% EtOAc in hexanes) afforded the title compound as a off-white solid (126 mg, 0.24 mmol, 95% yield). mp 44-47 ºC; IR ν_{max}/cm^{-1} (film): 3057, 3010, 1571, 1516, 1450, 1435, 1419, 1398, 1250, 1214, 1168, 1106, 1020, 997, 716, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (1H, s), 8.20 (1H, br s), 7.85-7.66 (7H, m), 7.57-7.47 (3H, m), 7.47-7.37 (6H, m), 7.19-7.05 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.55 (d, *J* = 5.9 Hz), 160.27 (d, *J* = 250.8 Hz), 157.50, 154.42, 148.68 (dd, *J* = 11.0, 2.1 Hz), 133.04 (d, *J* = 9.8 Hz), 132.80 (d, *J* = 5.1 Hz), 131.91 (d, *J* = 2.8 Hz), 128.82 (d, *J* = 100.9 Hz), 128.37 (d, *J* = 12.2 Hz), 124.45 (d, *J* = 15.3 Hz), 120.46 (d, *J* = 23.3 Hz), 120.42 (q, *J* = 257.7 Hz), 115.95 (d, *J* = 3.2 Hz), 100.87 (d, *J* = 26.5 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –57.99, –108.65 (t, *J* = 9.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.32; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 534.3, $C_{29}H_{21}F_4N_3OP^+$ requires 534.1

***Tert*-butyl (*R*)-2-(((4-((triphenyl-λ^5-phosphaneylidene)amino)pyrimidin-2-yl)oxy)methyl)pyrrolidine-1-carboxylate (2r)**



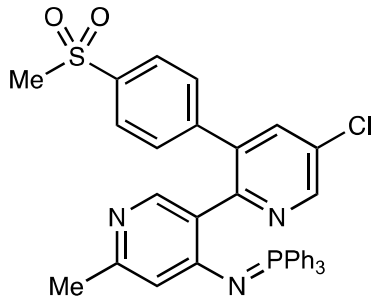
Prepared according to general procedure B (except the reaction was diluted and extracted with CH_2Cl_2 instead of EtOAc during the workup) using triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (172 mg, 0.25 mmol), sodium azide (20 mg, 0.31 mmol) and DMSO (0.17 mL) for 12 h. Flash column chromatography (silica gel, gradient elution: 1% MeOH in CH_2Cl_2 to 2.5% MeOH in CH_2Cl_2) afforded the title compound as an off white solid (125 mg, 0.23 mmol, 90% yield). mp 156-159 ºC; IR ν_{max}/cm^{-1} (film): 3052, 2997, 2980, 1681, 1578, 1571, 15.27, 1456, 1446, 1440, 1435, 1400, 1360, 1344, 1330, 1282, 1111, 1036, 942, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96-7.84 (1H, m), 7.77-7.59 (6H, m), 7.56-7.46 (3H, m), 7.45-7.34 (6H, m), 6.52-6.39 (1H, m), 3.92-3.79 (1H, m), 3.74-3.45 (1H, m), 3.39-2.80 (3H, m), 1.83-1.25 (13H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.25 (rot), 170.17, 163.97, 156.53, 156.29 (rot), 154.15, 133.08-132.40 (m), 131.84 (d, *J* = 2.6 Hz), 129.59-128.19 (2C, m), 108.16 (d, *J* = 23.9 Hz), 78.97, 78.64 (rot), 65.97, 55.61 (rot), 55.42, 46.58 (rot), 46.01, 28.64-27.56 (2C, m), 23.56 (rot), 22.22; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.78; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 555.4, $C_{32}H_{36}N_4O_3P^+$ requires 555.3.

***N*-(3-(3-fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridin-4-yl)-1,1,1-triphenyl-λ^5-phosphanimine (2s)**



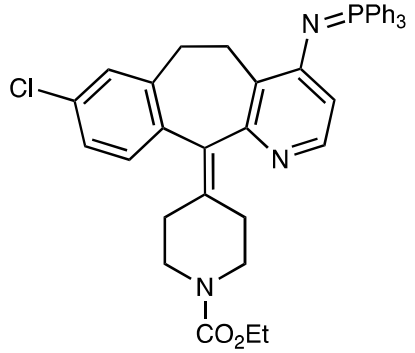
Prepared according to general procedure B using (3-(3-Fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (182 mg, 0.25 mmol), sodium azide (20 mg, mmol) and DMSO (0.17 mL) for 8 h. Flash column chromatography (silica gel packed in hexanes and neutralized with NEt_3, gradient elution: 50% EtOAc in hexanes to 75% EtOAc in hexanes) afforded the title compound as a white solid (104 mg, 0.17 mmol, 70% yield). mp 80-83 ºC; IR ν_{max}/cm^{-1} (film): 3056, 2989, 2925, 1579, 1484, 1401, 1355, 1327, 1131, 1108, 1082, 1040, 753, 718, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94-8.91 (1H, m), 8.38 (1H, d, *J* = 2.9 Hz), 8.18 (1H, t, *J* = 1.5 Hz), 7.95-7.89 (2H, m), 7.82-7.75 (2H, m), 7.70-7.60 (7H, m), 7.57-7.49 (3H, m), 7.41 (6H, td, *J* = 7.8, 3.0 Hz), 6.33 (1H, d, *J* = 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.95 (d, *J* = 244.1 Hz), 159.74 (q, *J* = 1.6 Hz), 155.86, 150.02 (d, *J* = 2.2 Hz), 148.93, 146.54 (q, *J* = 4.1 Hz), 141.80 (d, *J* = 8.5 Hz), 139.00 (d, *J* = 8.2 Hz), 133.89 (q, *J* = 3.5 Hz), 132.45 (d, *J* = 10.0 Hz), 132.17 (d, *J* = 2.9 Hz), 130.41, 129.69 (d, *J* = 100.5 Hz), 128.82 (d, *J* = 12.2 Hz), 125.00 (q, *J* = 33.1 Hz), 124.69 (d, *J* = 2.4 Hz), 123.68 (q, *J* = 272.1 Hz), 119.93, 118.75 (d, *J* = 22.1 Hz), 116.89 (d, *J* = 11.1 Hz), 112.10 (d, *J* = 23.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.25, –114.34; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 6.60; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 594.3, $C_{35}H_{25}F_4N_3P^+$ requires 594.2.

***N*-(5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)-1,1,1-triphenyl-λ^5-phosphanimine (2t)**



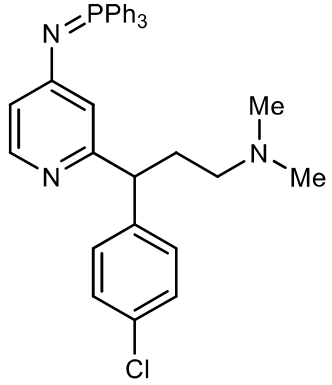
Prepared according to general procedure B using (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)triphenylphosphonium trifluoromethanesulfonate (192 mg, 0.25 mmol), sodium azide (20 mg, 0.31 mmol) and DMSO (0.17 mL) for 39.75 h. Flash column chromatography (silica gel packed in hexanes and neutralized with NEt_3: 5% MeOH in CH_2Cl_2) afforded the title compound as a yellow crystalline solid (94 mg, 0.15 mmol, 60% yield). mp 116-120 ºC; IR ν_{max}/cm^{-1} (film): 3055, 2989, 2923, 1589, 1494, 1438, 1413, 1312, 1150, 1109, 719; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, d, *J* = 2.3 Hz), 8.34 (1H, d, *J* = 3.0 Hz), 7.64 (1H, d, *J* = 2.3 Hz), 7.59-7.50 (5H, m), 7.41 (6H, td, *J* = 7.9, 3.0 Hz), 7.24-7.16 (8H, m), 5.78 (1H, s), 2.99 (3H, s), 2.15 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.41, 156.47, 154.99, 148.79, 147.48, 144.96, 139.05, 137.40, 136.08, 132.27, (d, *J* = 2.9 Hz), 132.14 (d, *J* = 10.0 Hz), 130.15, 129.50, 129.00 (d, *J* = 100.4 Hz), 128.75 (d, *J* = 12.2 Hz), 128.19 (d, *J* = 24.8 Hz), 126.85, 115.06 (d, *J* = 11.3 Hz), 44.48, 23.83; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 6.76; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 634.2, $C_{36}H_{30}ClN_3O_2PS^+$ requires 634.2

Ethyl 4-(8-chloro-4-((triphenyl-λ^5-phosphaneylidene)amino)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (2u)



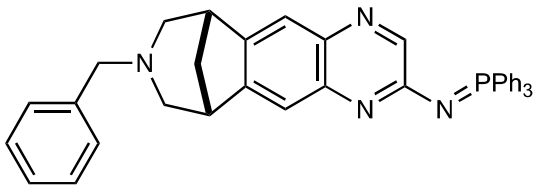
Prepared according to general procedure B using (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5Hbenzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (198 mg, 0.25 mmol), sodium azide (20 mg, 0.31 mmol) and DMSO (0.17 mL) for 15.25 h. Flash column chromatography (silica gel packed in hexanes and neutralized with NEt_3: 6% MeOH in CH_2Cl_2) followed by filtration through a neutralized plug of silica (NEt_3) eluting with 5% MeOH in hexanes afforded the title compound as a yellow crystalline solid (68 mg, 0.10 mmol, 41% yield). mp 166-170 ºC; IR ν_{max}/cm^{-1} (film): 3054, 2989, 2912, 1693, 1560, 1465, 1434, 1367, 1339, 1230, 1121, 718; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (1H, d, *J* = 5.6 Hz), 7.75-7.66 (6H, m), 7.57 (3H, td, *J* = 7.2, 1.6 Hz), 7.48 (6H, td, *J* = 7.7, 3.0 Hz), 7.19 (1H, s), 7.13-7.10 (2H, m), 6.08 (1H, dd, *J* = 5.6, 0.9 Hz), 4.12 (2H, q, *J* = 7.1 Hz), 3.84 (2H, br s,), 3.44-3.26 (3H, m), 3.12-3.00 (2H, m), 2.91-2.81 (1H, m), 2.81-2.37 (2H, m), 2.34-2.25 (2H, m), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.57 (br), 155.24, 147.49 (br), 141.55 (br), 140.21, 138.19 (br), 137.80, 133.20, 133.03 (d, *J* = 2.6 Hz), 132.28 (d, *J* = 10.1 Hz), 130.11, 129.26 (d, *J* = 12.4 Hz), 128.41 (d, *J* = 23.71 Hz), 128.12, 127.56 (d, *J* = 101.6 Hz), 127.50 (br), 126.31, 113.16 (d, *J* =12.3 Hz), 61.16, 45.57, 44.05, 43.97, 31.06, 30.51, 28.15, 14.57; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 5.25; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 658.3, $C_{40}H_{38}ClN_3O_2P^+$ requires 658.2.

3-(4-Chlorophenyl)-N,N-dimethyl-3-(4-((triphenyl-λ5-phosphanylidene)amino)pyridin-2-yl)propan-1-amine (2v)



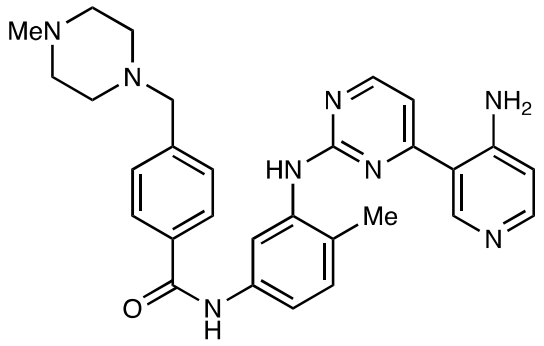
Prepared according to general procedure B using (2-(1-(4-chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (137 mg, 0.20 mmol), sodium azide (16 mg, 0.25 mmol) and DMSO (0.13 mL) for 20.5 h. Flash column chromatography (silica gel packed in hexanes and neutralized with NEt_3, gradient elution: 5% MeOH in CH_2Cl_2 to 5% MeOH in CH_2Cl_2 with 1% NH_4OH) afforded the title compound as a Yellow Oil (31 mg, 0.06 mmol, 28% yield). IR ν_{max}/cm^{-1} (film): 3057, 2938, 2857, 2815, 2766, 1582, 1475, 1437, 1351, 1180, 1107, 1043, 1026, 1014, 750; (400 MHz, $CDCl_3$) δ: 8.00 (1H, d, J = 5.6 Hz), 7.70-7.60 (6H, m), 7.59-7.51 (3H, m), 7.49-7.40 (6H, m), 7.16-7.06 (4H, m), 6.45 (1H, d, J = 5.6 Hz), 6.40 (1H, s), 3.81 (1H, t, J = 7.3 Hz), 2.33-2.06 (9H, m), 2.02-1.90 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.63, 159.23, 148.81, 142.46, 132.49 (d, J = 9.8 Hz), 132.13 (d, J = 2.8 Hz), 131.56, 129.47 (d, J = 99.3 Hz), 129.41, 128.80 (d, J = 12.1 Hz), 128.24, 117.00 (d, J = 19.1 Hz), 116.89 (d, J = 19.7 Hz), 57.95, 50.69, 45.44, 32.55; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 8.10; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 550.3, $C_{34}H_{34}ClN_3P^+$ requires 550.2.

_N_-((6_S_,10_R_)-8-benzyl-7,8,9,10-tetrahydro-6_H_-6,10-methanoazepino[4,5-_g_]quinoxalin-2-yl)-1,1,1-triphenyl-λ^5-phosphanimine (2w)



Prepared according to general procedure B using ((6*S*,10*R*)-8-benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxalin-2-yl)triphenylphosphonium trifluoromethanesulfonate (178 mg, 0.25 mmol), sodium azide (20 mg, 0.31 mmol) and DMSO (0.17 mL) for 42.25 h. Flash column chromatography (silica gel packed in hexanes and neutralized with NEt_3: 40% EtOAc in hexanes) followed by filtration through a neutralized plug of silica (NEt_3) eluting with 20% EtOAc in hexanes to afford the title compound as a dark yellow oil (73 mg, 0.13 mmol, 51% yield). IR ν_{max}/cm^{-1} (film): 3059, 2945, 2787, 1532, 1467, 1438, 1389, 1303, 1216, 1108, 951, 906, 718; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (1H, s), 7.98-7.85 (6H, m), 7.59-7.51 (4H, m), 7.46 (6H, td, *J* = 7.6, 2.8 Hz), 7.16-7.04 (4H, m), 6.86 (2H, d, *J* = 6.7 Hz), 3.47 (2H, s), 3.19 (1H, m), 3.10 (1H, m), 2.91 (1H, dd, *J* = 10.3, 2.4 Hz), 2.85 (1H, dd, *J* = 10.3, 2.5 Hz), 2.51 (1H, d, *J* = 9.9 Hz), 2.44 (1H, d, *J* = 10.0 Hz), 2.25-2.16 (1H, m), 1.17 (1H, d, *J* = 10.5 Hz); ^{13}C NMR of this compound is poorly resolved, containing several broad and overlapping peaks (see S172); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.75; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 577.3, $C_{38}H_{34}N_4P^+$ requires 577.3.

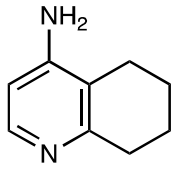
***N*-(3-((4-(4-aminopyridin-3-yl)pyrimidin-2-yl)amino)-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (2x)**



An 8 mL vial equipped with a screw cap and septa was charged with (3-(2-((2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate and (2-((2-Methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)-6-(pyridin-3-yl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (20:1 mixture of regioisomers, 90 mg, 0.10 mmol), sodium azide (8 mg, 0.13 mmol) and DMSO (0.07 mL) and heated for 13.75 h at 100 ºC. The reaction was cooled to room temperature and an additional 70 μL of DMSO and 20 μL of H_2O were added and the mixture stirred for 52 h. Flash column chromatography (silica gel packed in hexanes and neutralized with NEt_3, gradient elution: 10% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2 with 1% NEt_3) afforded the title compound as a dark yellow solid (20 mg, 0.04 mmol, 40% yield). mp 226-229 ºC; IR ν_{max}/cm^{-1} (film): 3285, 2935, 2804, 1609, 1562, 1530, 1507, 1457, 1290, 1241, 1211, 1163, 1139, 1053, 1010, 816; ^1H NMR (400 MHz, CD_3OD) δ: 8.62 (1H, br s), 8.30 (1H, d, *J* = 5.6 Hz), 7.88-7.81(3H, m), 7.76 (1H, d, *J* = 2.0 Hz), 7.53 (1H, dd, *J* = 8.3, 2.1 Hz), 7.42 (2H, d, *J* = 8.2 Hz), 7.24 (1H, d, *J* = 8.3 Hz), 7.19 (1H, d, *J* = 5.6 Hz), 6.56 (1H, d, *J* = 6.0 Hz), 3.55 (2H, s), 2.46 (8H, br s), 2.26-2.19 (6H, m); ^{13}C NMR (100 MHz CD_3OD) δ: 168.55, 166.56, 162.09, 159.23, 156.38, 150.48, 149.65, 142.96, 139.05, 138.48, 135.31, 131.88, 131.61, 130.55, 128.67, 120.32, 119.87, 114.44, 112.52, 107.48, 63.27, 55.74, 53.59, 45.98, 17.84; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 509.3, $C_{29}H_{33}N_8O^+$ requires 509.3

A 1.4 Derivatization Reactions

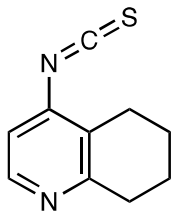
5,6,7,8-Tetrahydroquinolin-4-amine (3aa)



An 8mL vial equipped with a screw cap and septa was charged with 1,1,1-triphenyl-*N*-(5,6,7,8-tetrahydroquinolin-4-yl)- λ^5-phosphanimine (204 mg, 0.5 mmol) and 0.5 mL of a 9:1 mixture of DMF/H_2O. The vial was sealed and heated at 100 ºC for 44 h before the reaction was loaded directly onto a silica gel column. Flash column chromatography (silica gel packed in hexanes and neutralized with NEt_3, gradient elution: 5% MeOH in CH_2Cl_2 to 1% MeOH in basified[§] CH_2Cl_2 to 2.5% MeOH in basified CH_2Cl_2 followed by filtration through a plug of basic alumina by gradient elution: 1% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) followed by filtration through a plug of basic alumnia eluting with 5% MeOH in CH_2Cl_2 to afford the title compound as a white crystalline solid (61 mg, 0.41 mmol, 83% yield). mp 121-125 ºC; IR ν_{max}/cm^{-1} (film): 3329, 3190, 2930, 1637, 1589, 1481, 1452, 1351, 1164, 1066, 820; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.97 (1H, d, J = 5.3 Hz), 6.33 (1H, d, J = 5.4 Hz), 4.16 (2H, br s), 2.84-2.72 (2H, m), 2.44-2.31 (2H, m), 1.88-172 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.86, 150.90, 146.59, 115.71, 106.98, 32.65, 22.79, 22.67, 22.39; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 149.2, $C_9H_{13}N_2^+$ requires 149.1.

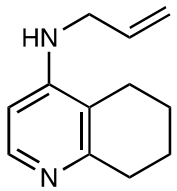
[§] CH_2Cl_2 was basified by shaking in a seperatory funnel with aqueous ammonium hydroxide.

4-Isothiocyanato-5,6,7,8-tetrahydroquinoline (3ab)



An 8 mL vial equipped with a screw cap and septa was charged with 1,1,1-triphenyl-*N*-(5,6,7,8-tetrahydroquinolin-4-yl)-λ^5-phosphanimine (102 mg, 0.25 mmol), carbon disulfide (375 μL) and toluene (1.25 mL). The vial was sealed and heated at 100 ºC for 64 h until consumption of starting material was observed by LCMS analysis. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the crude material was directly purified by flash column chromatography (silica gel: 10% EtOAc in hexanes) to afford title compound as a yellow oil (24 mg, 0.13 mmol, 50% yield). IR ν_{max}/cm^{-1} (film): 2938, 2052, 1566, 1460, 1437, 1408, 1066, 832, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (1H, d, *J* = 5.2 Hz), 6.90 (1H, d, *J* = 5.2 Hz), 2.95-2.87 (2H, m), 2.83-2.75 (2H, m), 1.93-1.80 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.73, 147.49, 138.95, 138.35, 128.59, 117.42, 32.70, 24.90, 22.51, 22.03; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 191.1, $C_{10}H_{11}N_2S^+$ requires 191.1

***N*-allyl-5,6,7,8-tetrahydroquinolin-4-amine (3ac)**



An 8 mL vial equipped with a screw cap and septa was charged with 1,1,1-triphenyl-*N*-(5,6,7,8-tetrahydroquinolin-4-yl)-λ^5-phosphanimine (102 mg, 0.25 mmol), allyl iodide (34 μl, 0.38 mmol) and MeCN (3.33 mL). The vial was sealed and heated at 90 ºC for 41 h before additional allyl

iodide (34 μl, 0.38 mmol) was added. The reaction was heated at 90 ºC for a further 21 h before being concentrated *in vacuo*, dissolved in MeOH (2 mL) and added to a chilled (0 ºC) solution of MeOH (15 mL) and acetyl chloride (0.35 mL, 5.0 mmol). The reaction mixture was stirred for 1 h at room temperature and then concentrated *in vacuo*. The crude material was directly purified by flash column chromatography (neutral alumina activated, gradient elution: 1% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2 with 1% NEt_3) followed by filtration through a plug of activated basic alumina eluting with 10% MeOH in CH_2Cl_2. A second round of flash column chromatography (neutral alumina activated, gradient elution: 1% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) provided the title compound as a yellow solid (44 mg, 0.23 mmol, 94% yield). mp 204-206 ºC; IR ν_{max}/cm^{-1} (film): 3291, 3157, 2939, 1639, 1500, 1450, 1428, 1214, 1182, 845; ^{1}H NMR (400 MHz, CD_3OD) δ: 7.98 (1H, d, J = 7.2 Hz), 6.81 (1H, d, J = 7.2 Hz), 6.11-6.00 (1H, m), 5.34 (1H, d, J = 10.5), 5.00 (1H, d, J = 17.2 Hz), 4.87-4.80 (2H, m), 2.93-2.85 (2H, m), 2.54-2.46 (2H, m), 1.96-1.82 (4H, m); ^{13}C NMR (100 MHz, CD_3OD) δ: 159.22, 151.62, 143.15, 133.27, 119.47, 118.76, 108.64, 57.06, 27.40, 24.27, 22.43, 21.70; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 189.1, $C_{12}H_{17}N_2^+$ requires 189.1

A 1.5 Phosphine Competition Experiment

The reaction was conducted in accordance with general experimental B using Triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate, except that tri-*p*-tolylphosphane (76 mg, 0.25 mmol) was also added at the start of the reaction. After the work up procedure, the reaction was analyzed by ^{31}P NMR and LCMS analysis.

References

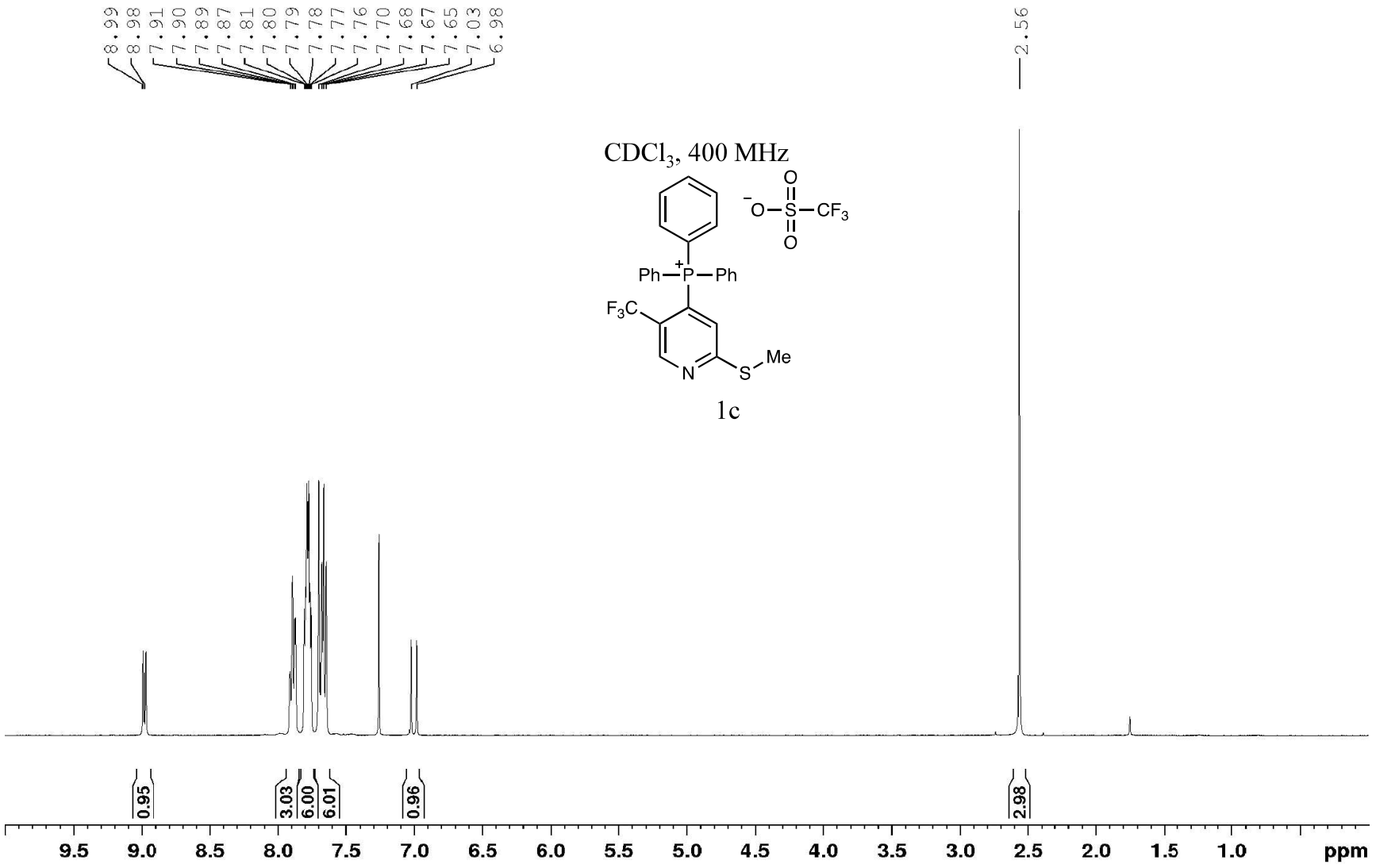
S1. D. D. Perrin, W. L. F. Amarego, Purification of Laboratory Chemicals (Pergamon, Press, Oxford. ed. 3, 1988).

S2. Hilton, M.; Dolewski, R.; McNally, A. Selective Functionalization of Pyridines via Heterocyclic Phosphonium Salts. *J. Am. Chem. Soc*., 2016, 138 (42), pp 13806–13809.

S3. Anderson, R.; Jett, B.; McNally, A. Selective Formation of Heteroaryl Thioethers via a Phosphonium Ion Coupling Reaction. *Tetrahedron*, 2017, https://doi.org/10.1016/j.tet.2017.12.040

S4. Koniarczyk, J.; Hesk, D.; Overgard, A.; Davies, I.W.; McNally, A. A General Strategy for Site-Selective Incorporation of Deuterium and Tritium into Pyridines, Diazines and Pharmaceuticals, *J. Am. Chem. Soc.*, 2018, doi.org/10.1021/jacs.7b11710

A 1.6 Spectra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7.68
7.67
7.65
7.03
6.98
2.56
CDCl3, 400 MHz
Ph
P
Ph
F3C
N
S
Me
O
O
S
CF3
O
1c
0.95
3.03
6.00
6.01
0.96
2.98
9.5
9.0
8.5
8.0
7.5
7.0
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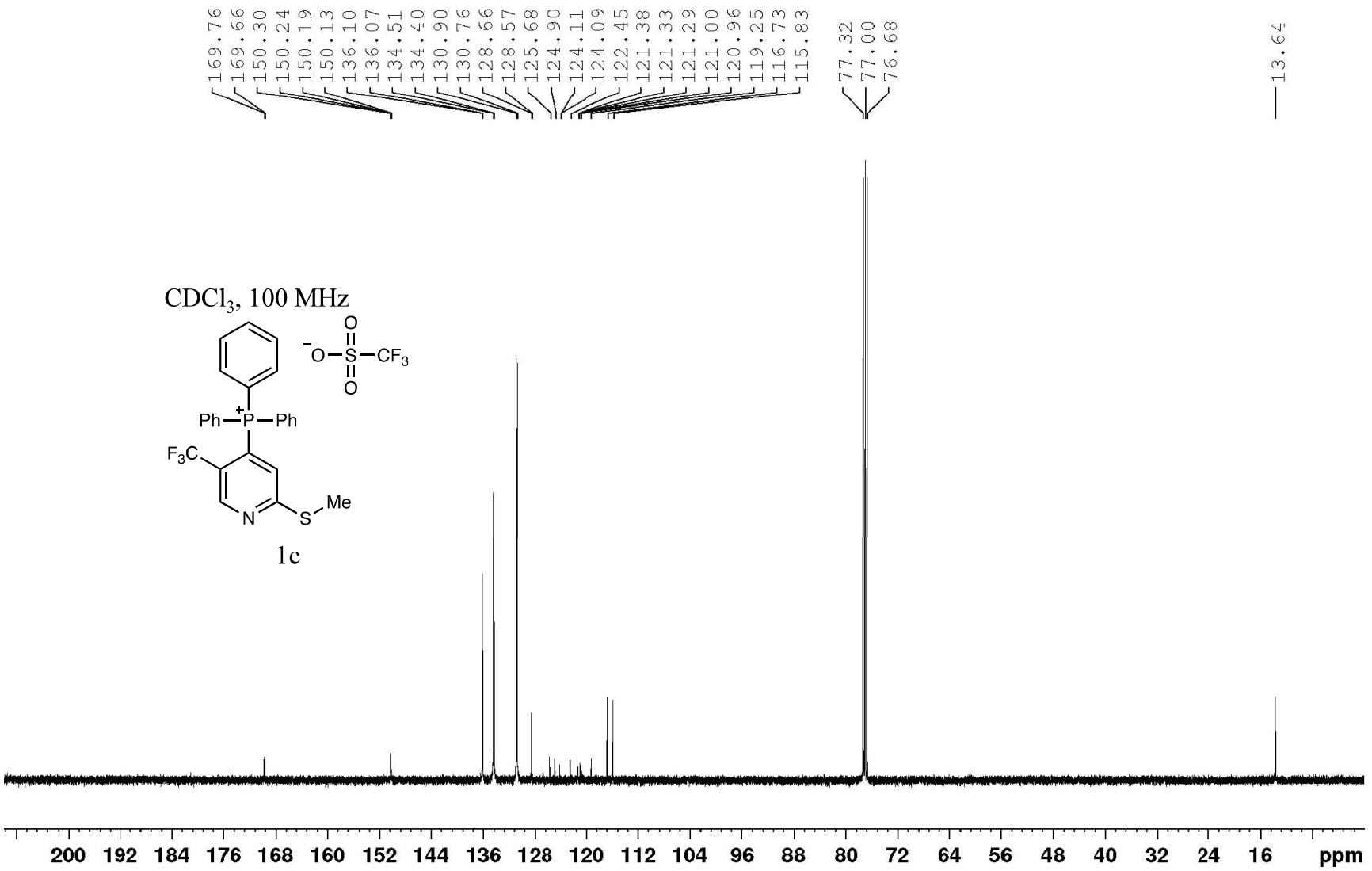
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150.13
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128.57
125.68
124.90
124.11
124.09
122.45
121.38
121.33
121.29
121.00
120.96
119.25
116.73
115.83
77.32
77.00
76.68
13.64
CDCl3, 100 MHz
1c
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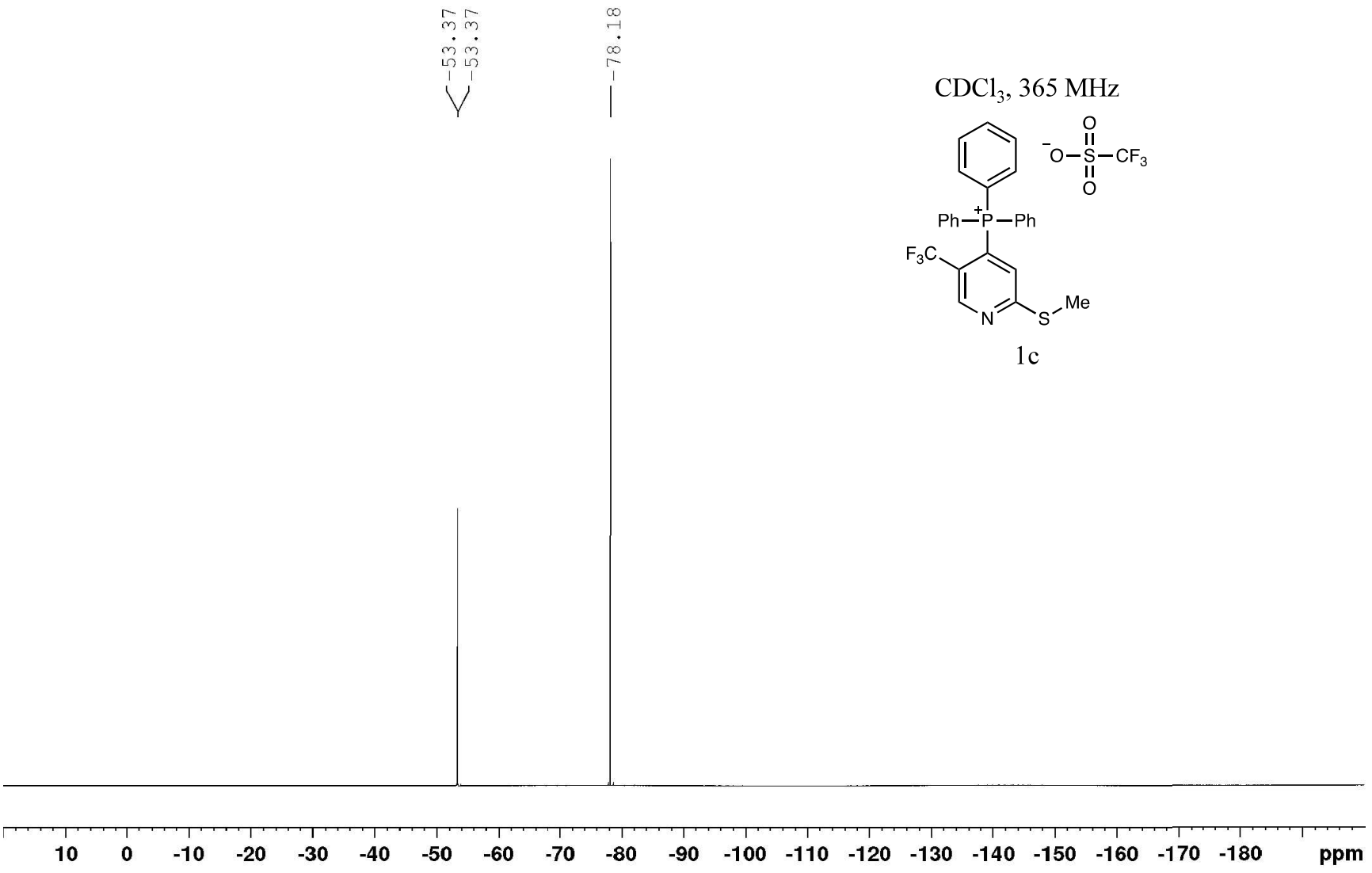
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P
Ph
F3C
N
S
Me
O
S
CF3
1c
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0
-10
-20
-30
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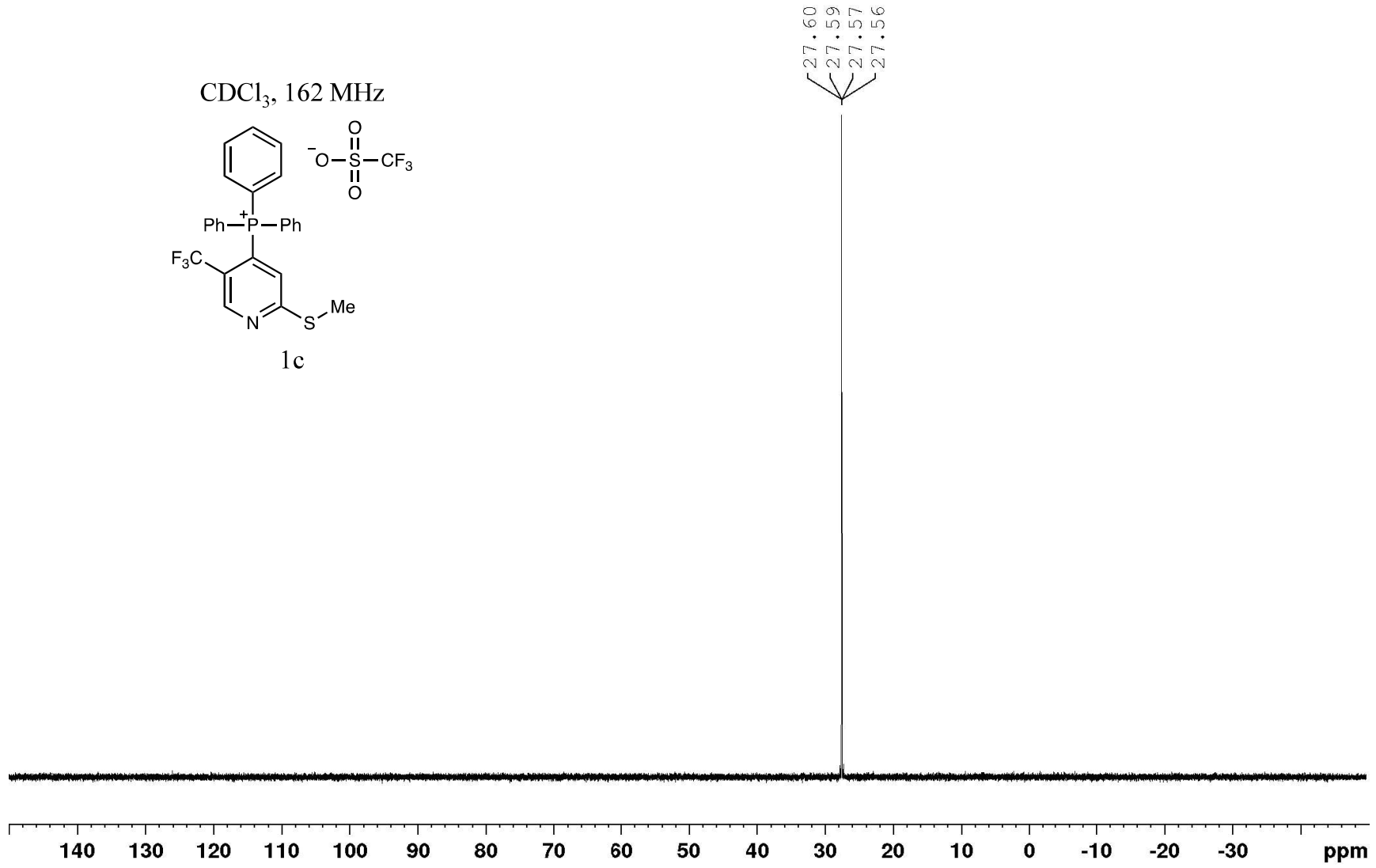
ppm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27.56
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S
Me
O
S
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1c
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100
90
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60
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30
20
10
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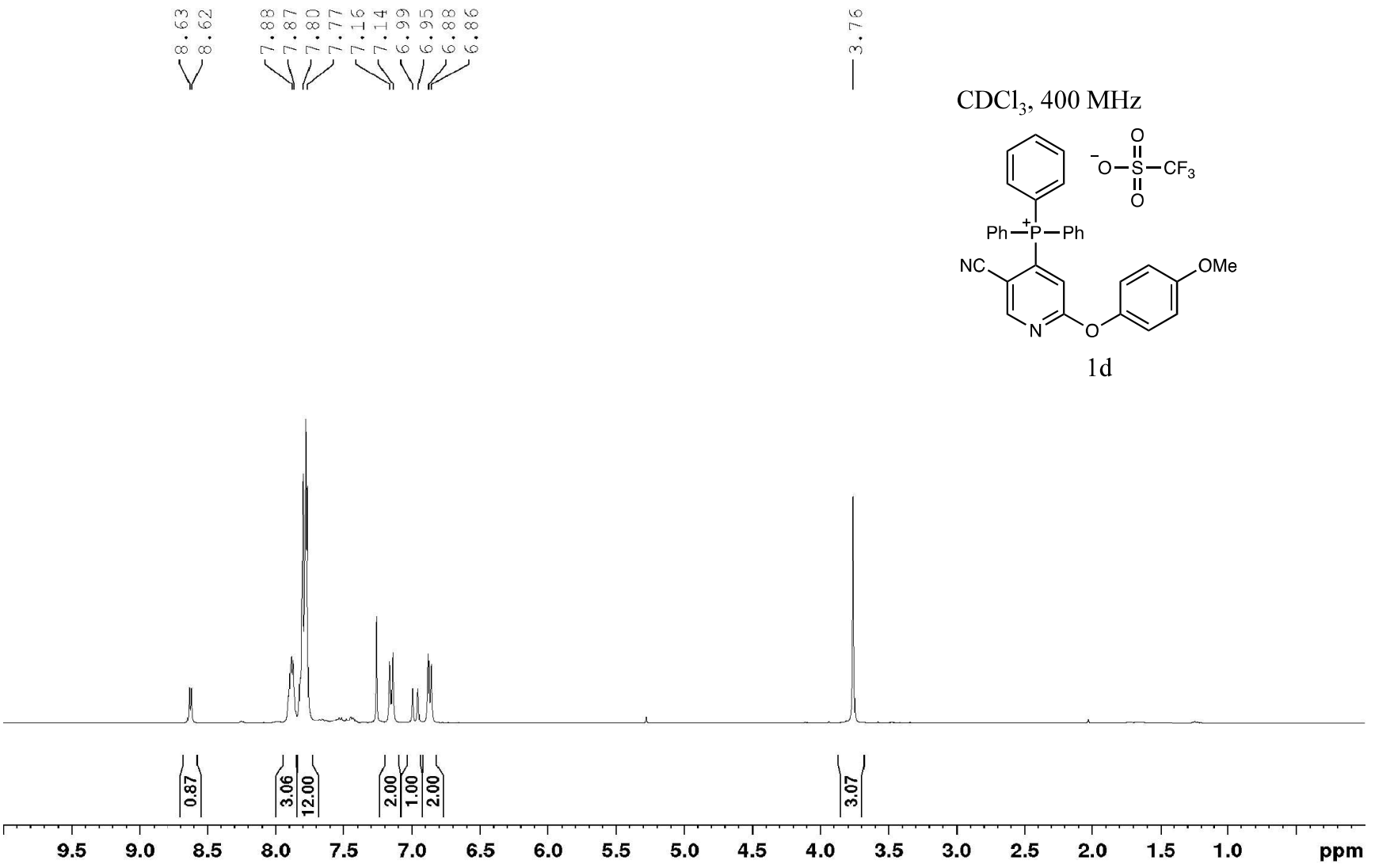
ppm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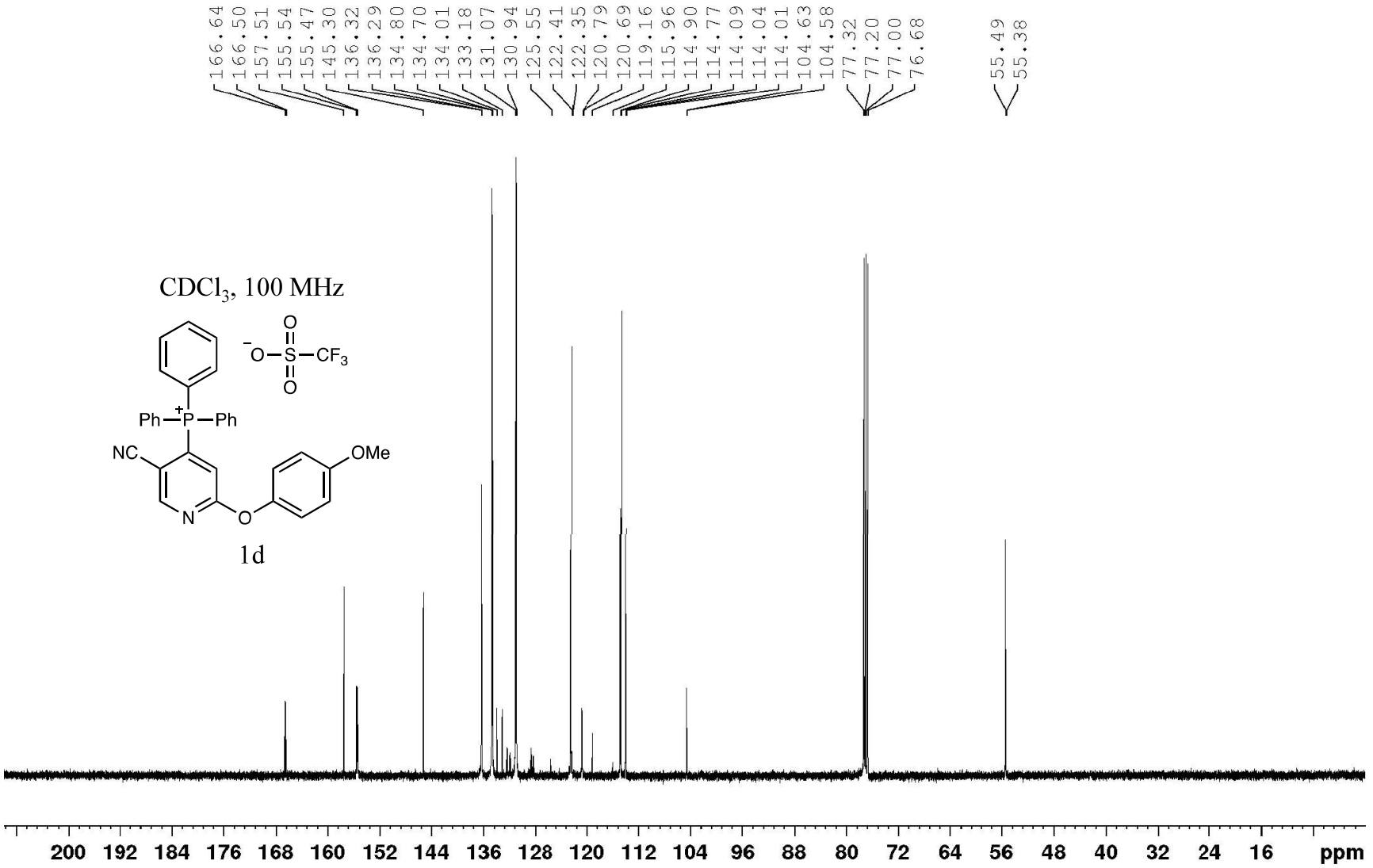
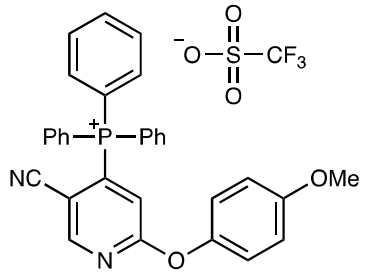
7.77
7.16
7.14
6.99
6.95
6.88
6.86
3.76
CDCl3, 400 MHz
Ph
P
Ph
NC
OMe
N
O
O
S
CF3
1d
0.87
3.06
12.00
2.00
1.00
2.00
3.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

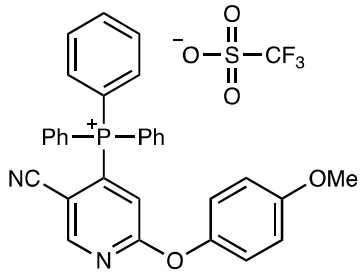

166.64
166.50
157.51
155.54
155.47
145.30
136.32
136.29
134.80
134.70
134.01
133.18
131.07
130.94
125.55
122.41
122.35
120.79
120.69
119.16
115.96
114.90
114.77
114.09
114.04
114.01
104.63
104.58
77.32
77.20
77.00
76.68
55.49
55.38
CDCl3, 100 MHz
Ph
P
Ph
NC
OMe
N
O
O
S
CF3
1d
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

$CDCl_3$, 365 MHz

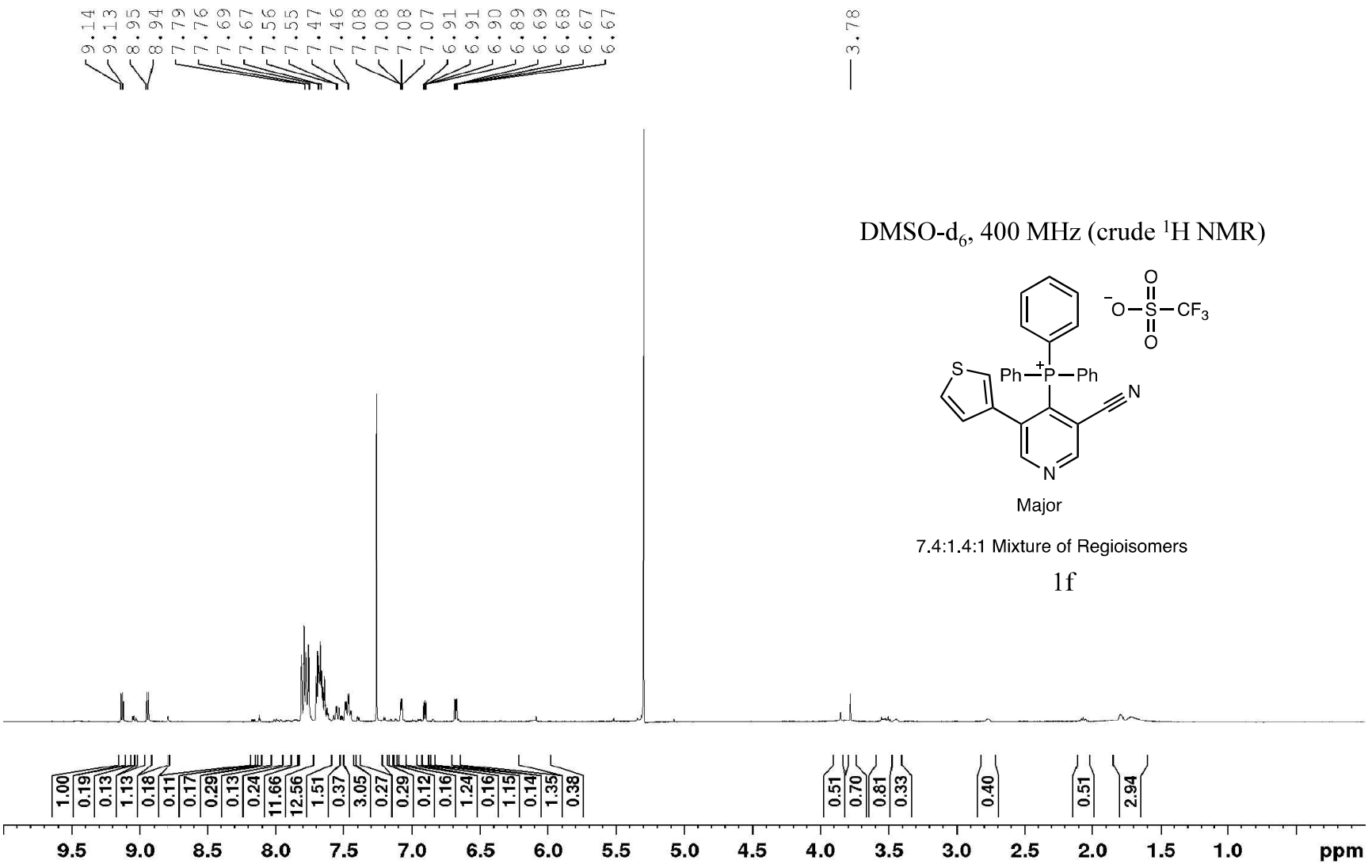


1d

$CDCl_3$, 162 MHz



1d

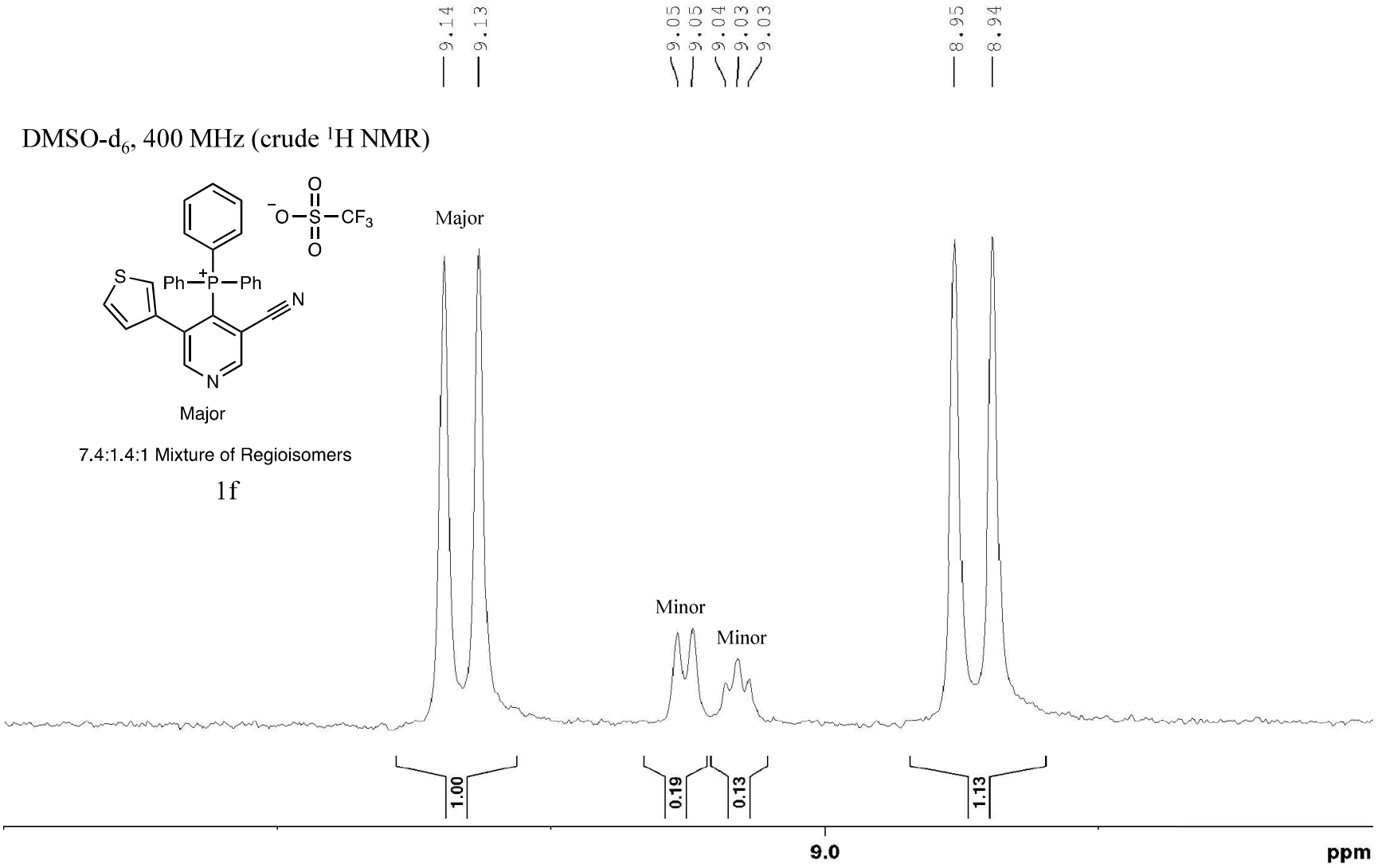


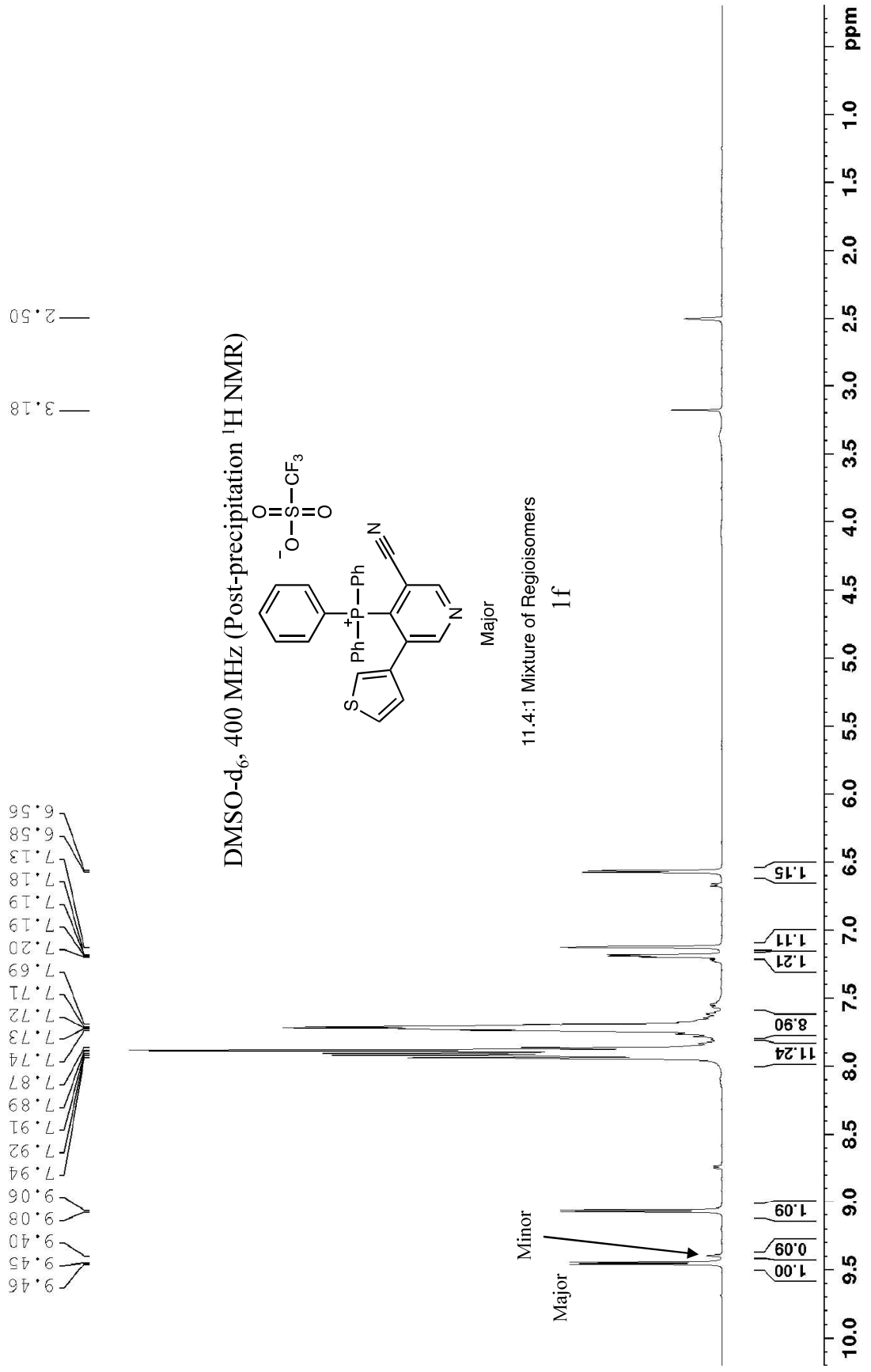
DMSO-d_6, 400 MHz (crude ^{1}H NMR)

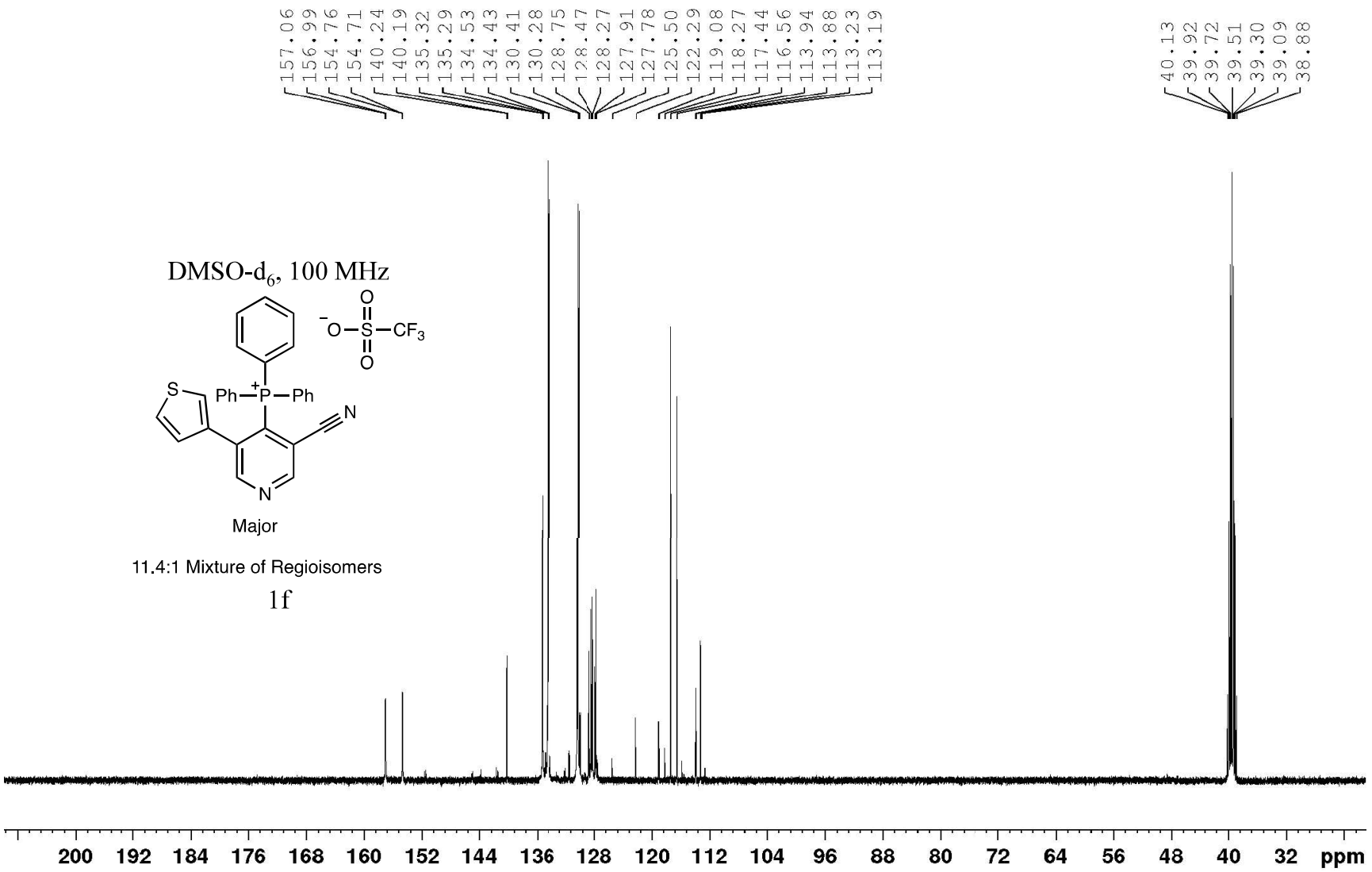
Major

7.4:1.4:1 Mixture of Regioisomers

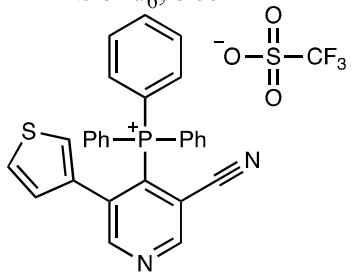
1f


9.14
9.13
9.05
9.05
9.04
9.03
9.03
8.95
8.94
DMSO-d6, 400 MHz (crude 1H NMR)
Major
Minor
Minor
1.00
0.19
0.13
1.13
9.0
ppm
Major
7.4:1.4:1 Mixture of Regioisomers
1f


DMSO-d6, 400 MHz (Post-precipitation 1H NMR)
11.4:1 Mixture of Regioisomers
1f
Major
Minor
Major
2.50
3.18
9.46
9.45
9.40
9.08
9.06
7.94
7.92
7.91
7.89
7.87
7.74
7.73
7.72
7.71
7.69
7.20
7.19
7.19
7.18
7.13
6.58
6.56
1.00
0.09
1.09
11.24
8.90
1.21
1.11
1.15
ppm


157.06
156.99
154.76
154.71
140.24
140.19
135.32
135.29
134.53
134.43
130.41
130.28
128.75
128.47
128.27
127.91
127.78
125.50
122.29
119.08
118.27
117.44
116.56
113.94
113.88
113.23
113.19
40.13
39.92
39.72
39.51
39.30
39.09
38.88
DMSO-d6, 100 MHz
Major
11.4:1 Mixture of Regioisomers
1f
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
ppm

DMSO-d_6, 365 MHz

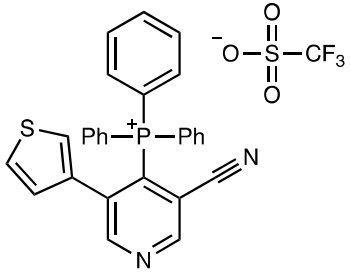


Major

11.4:1 Mixture of Regioisomers

1f

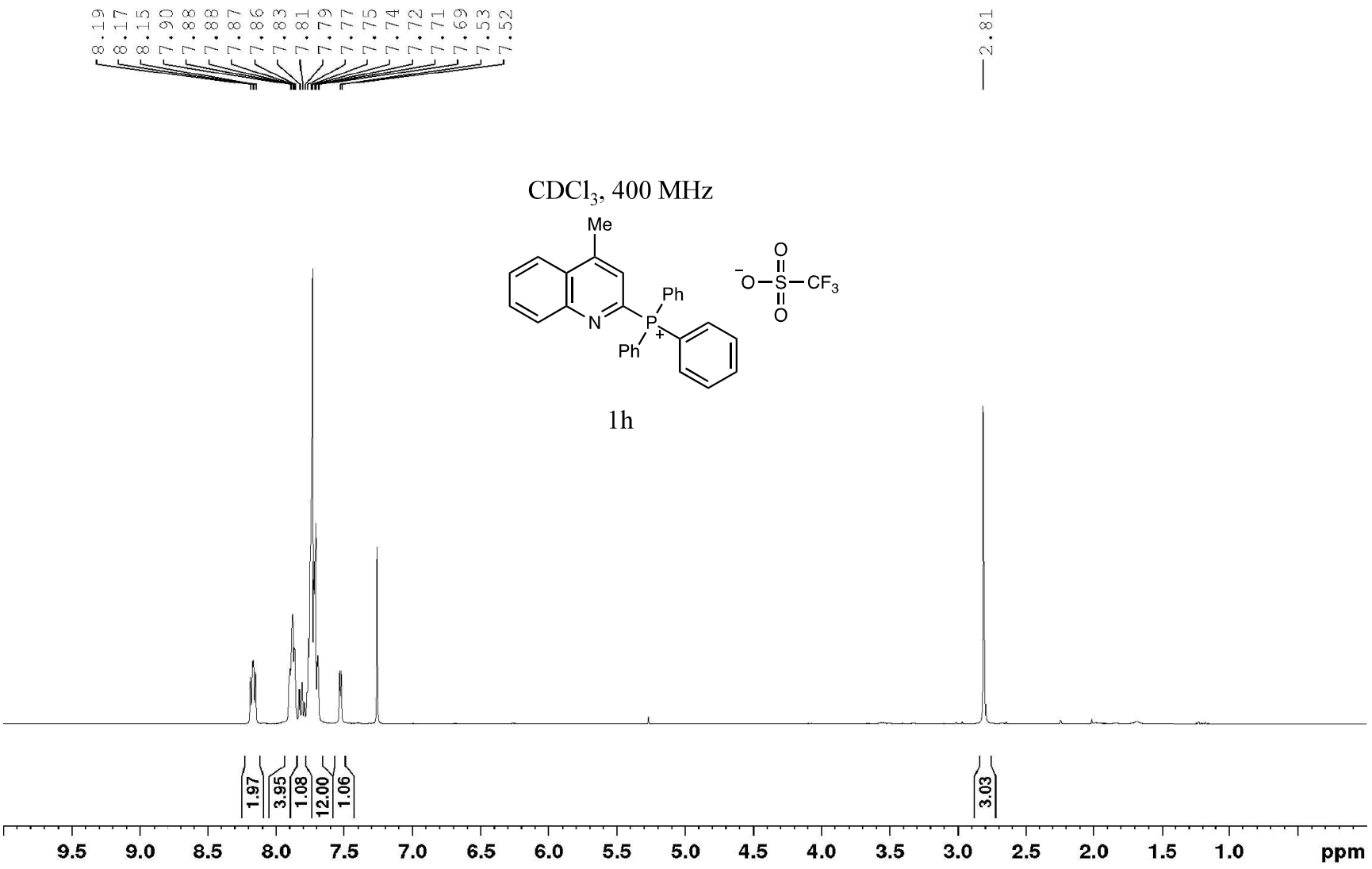
DMSO-d_6, 162MHz

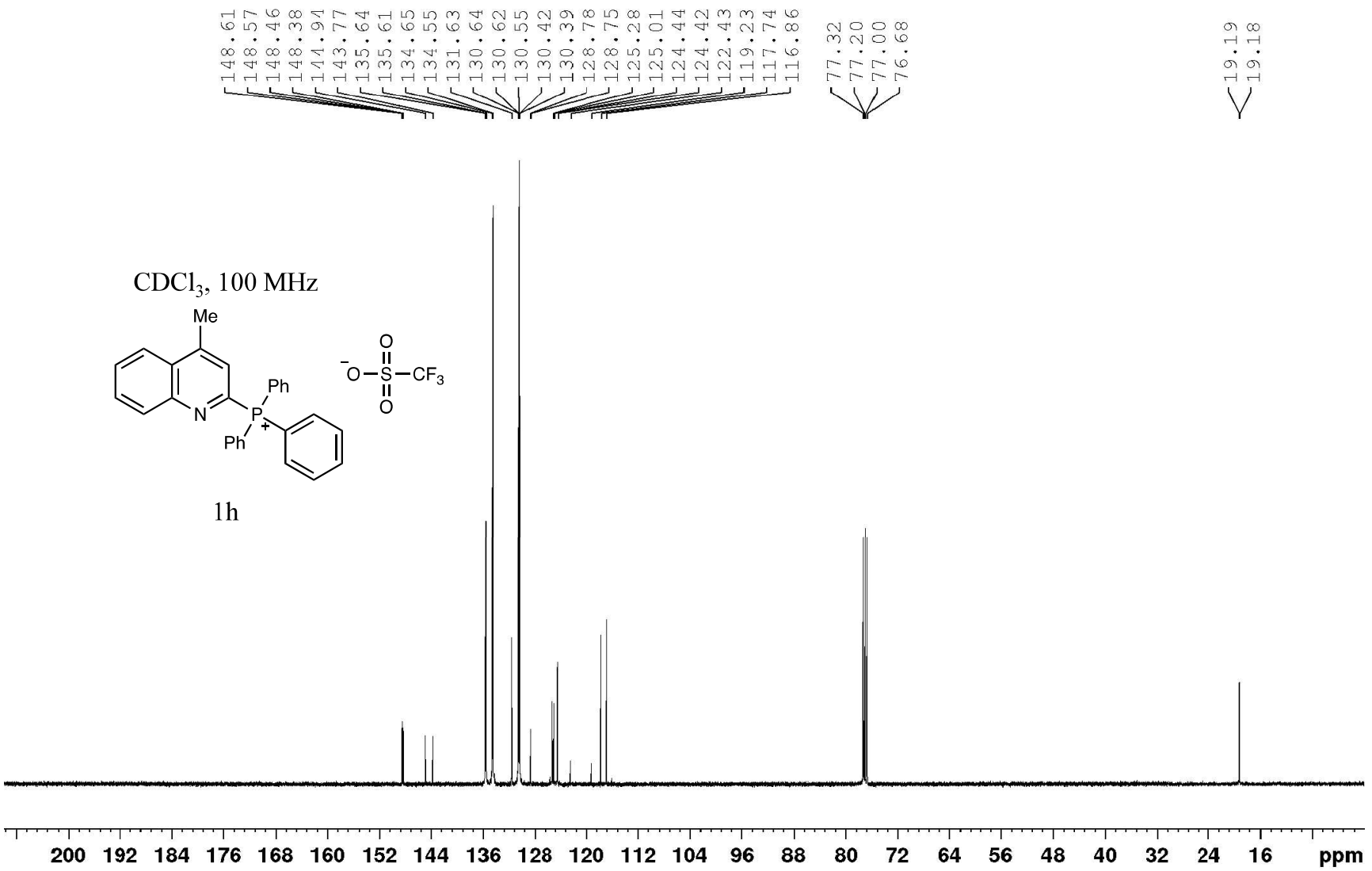


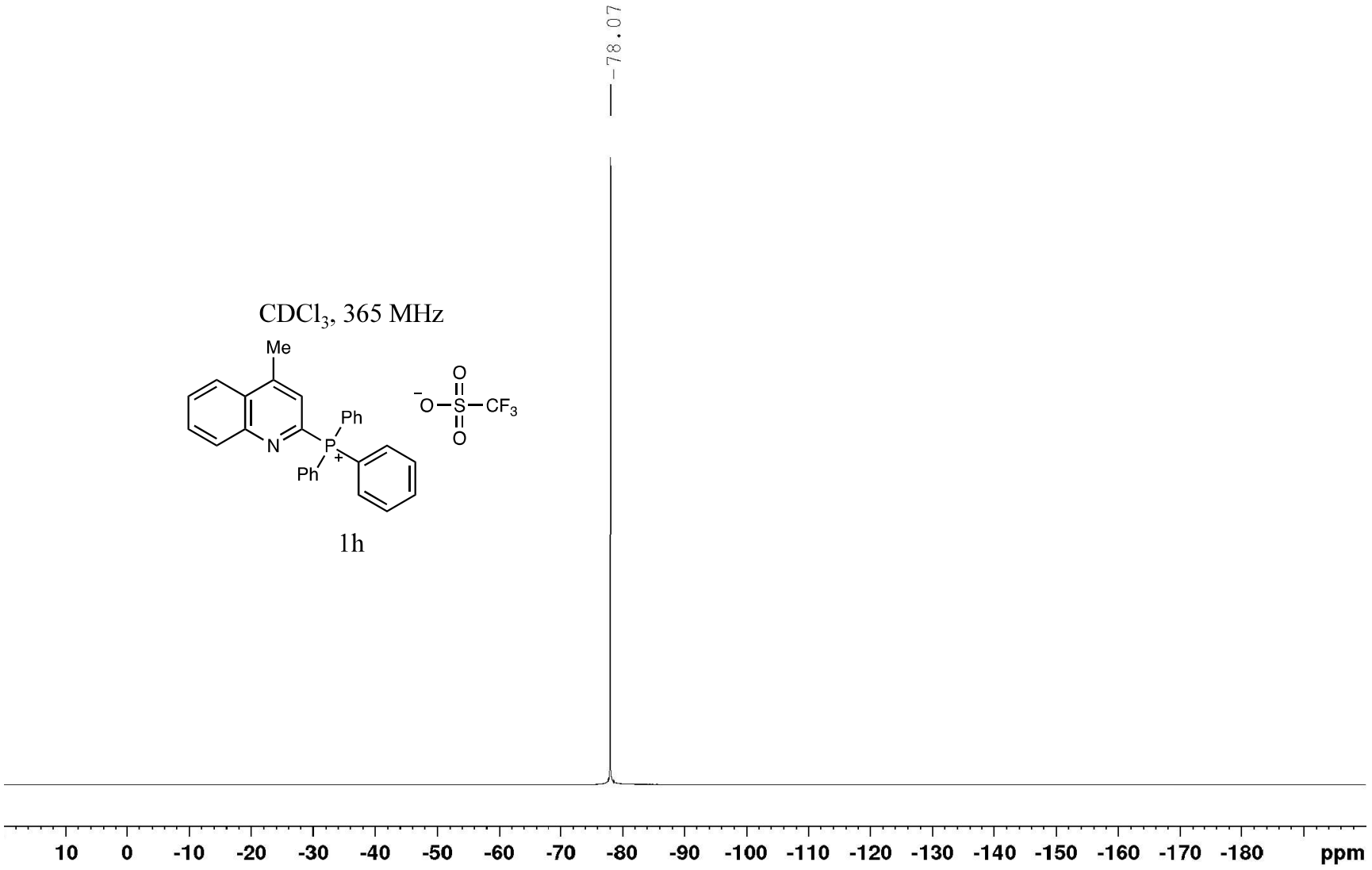
Major

11.4:1 Mixture of Regioisomers

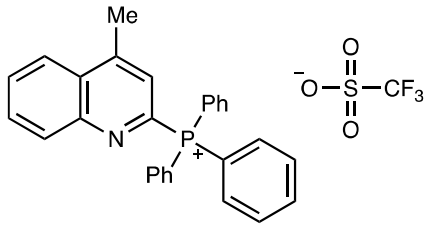
1f


8.19
8.17
8.15
7.90
7.88
7.88
7.87
7.86
7.83
7.81
7.79
7.77
7.75
7.74
7.72
7.71
7.69
7.53
7.52
2.81
CDCl3, 400 MHz
Me
Ph
Ph
N
P
+
O
S
CF3
1h
1.97
3.95
1.08
12.00
1.06
3.03
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
ppm

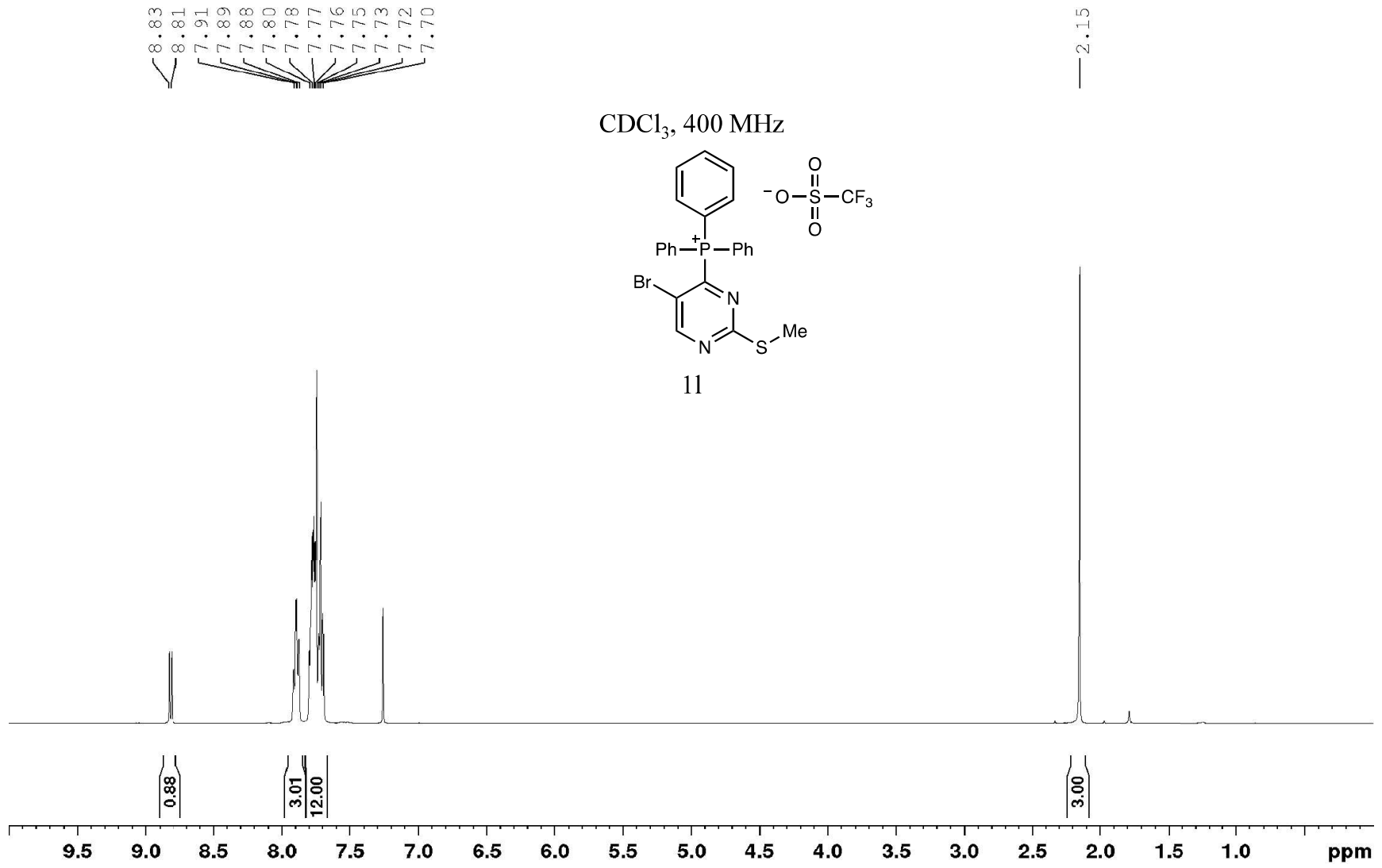

148.61
148.57
148.46
148.38
144.94
143.77
135.64
135.61
134.65
134.55
131.63
130.64
130.62
130.55
130.42
130.39
128.78
128.75
125.28
125.01
124.44
124.42
122.43
119.23
117.74
116.86
77.32
77.20
77.00
76.68
19.19
19.18
CDCl3, 100 MHz
Me
Ph
Ph
N
P
O
O
S
O
CF3
1h
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

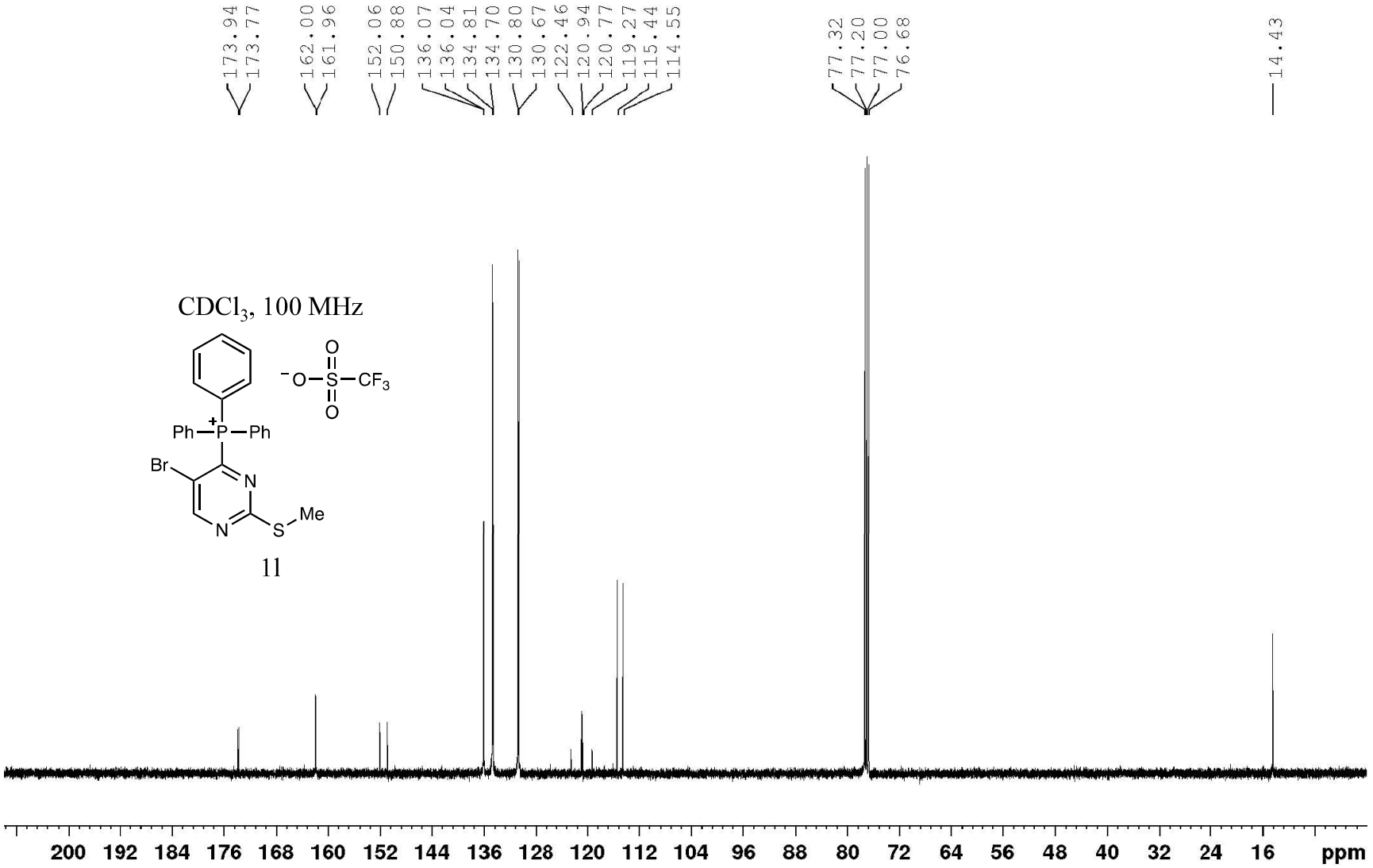

-78.07
CDCl3, 365 MHz
Me
Ph
Ph
N
P
+
O
S
CF3
O
O
O
1h
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

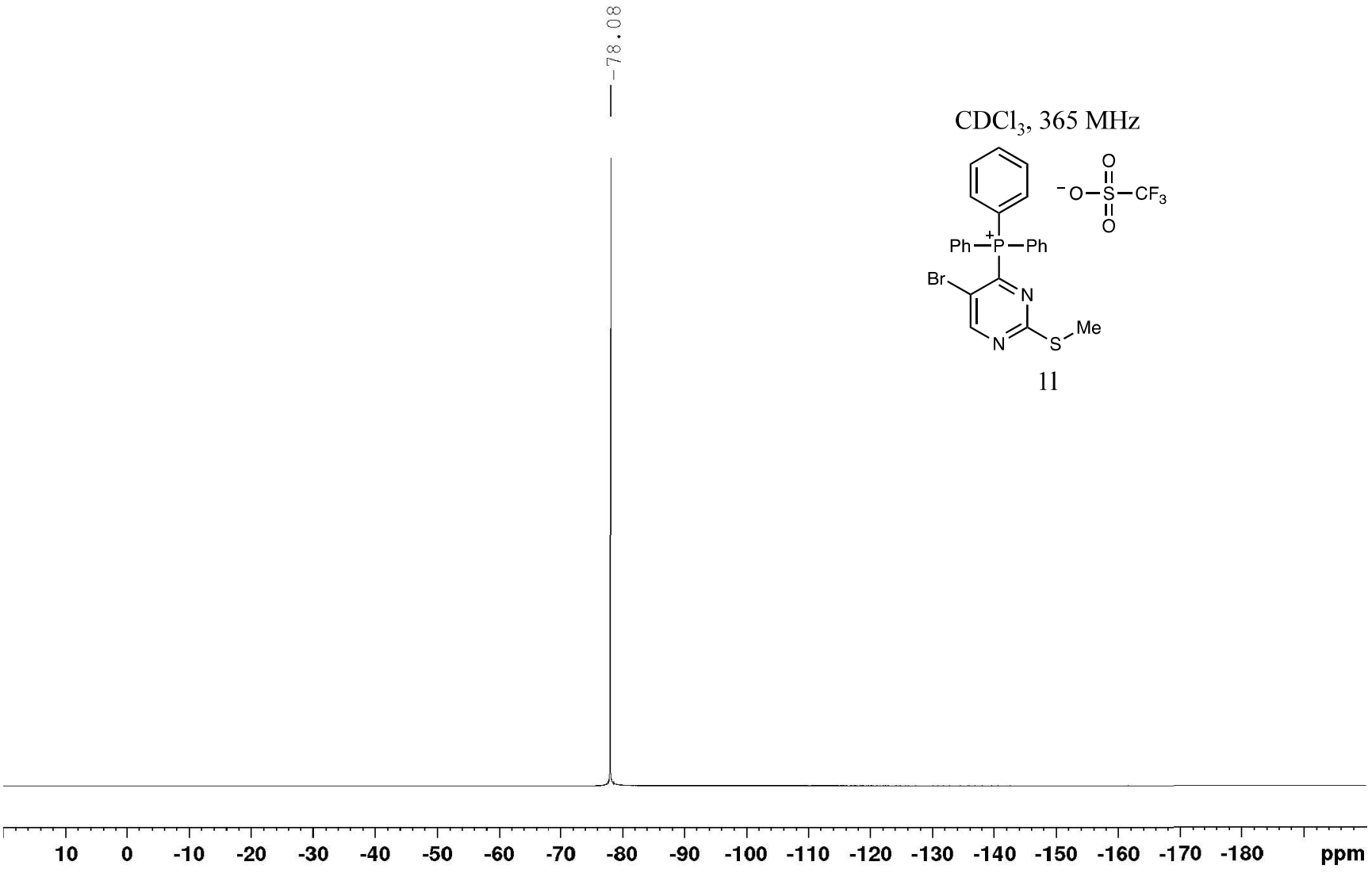
$CDCl_3$, 162 MHz



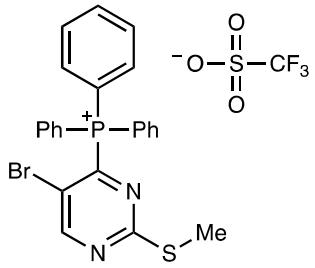
1h


8.83
8.81
7.91
7.89
7.88
7.80
7.78
7.77
7.76
7.75
7.73
7.72
7.70
2.15
CDCl3, 400 MHz
Ph
P
Ph
Br
N
N
S
Me
O
O
O
-O-S-CF3
11
0.88
3.01
12.00
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
ppm

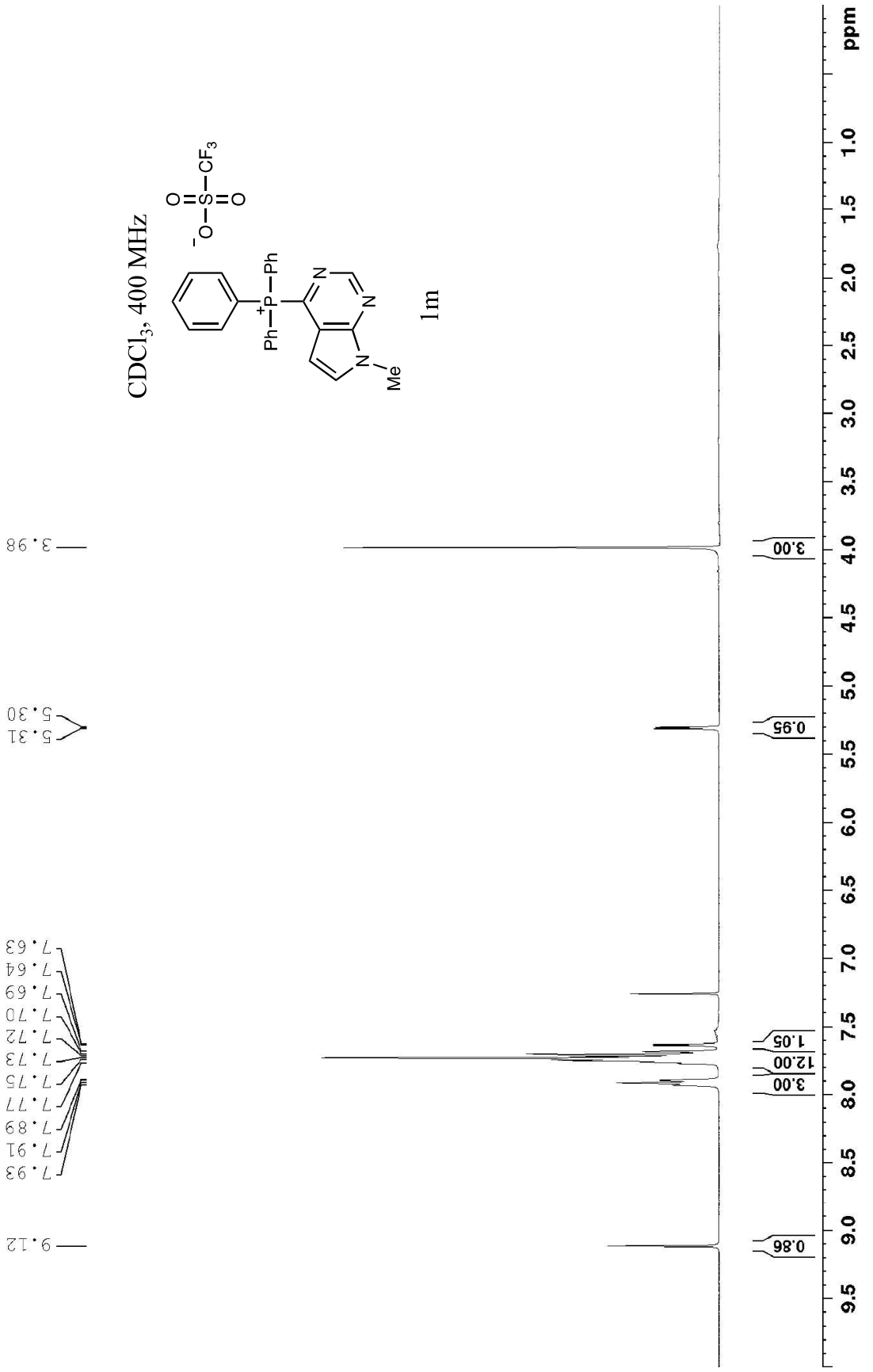

173.94
173.77
162.00
161.96
152.06
150.88
136.07
136.04
134.81
134.70
130.80
130.67
122.46
120.94
120.77
119.27
115.44
114.55
77.32
77.20
77.00
76.68
14.43
CDCl3, 100 MHz
Ph
P
Ph
Br
N
N
S
Me
O
O
S
CF3
O
11
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

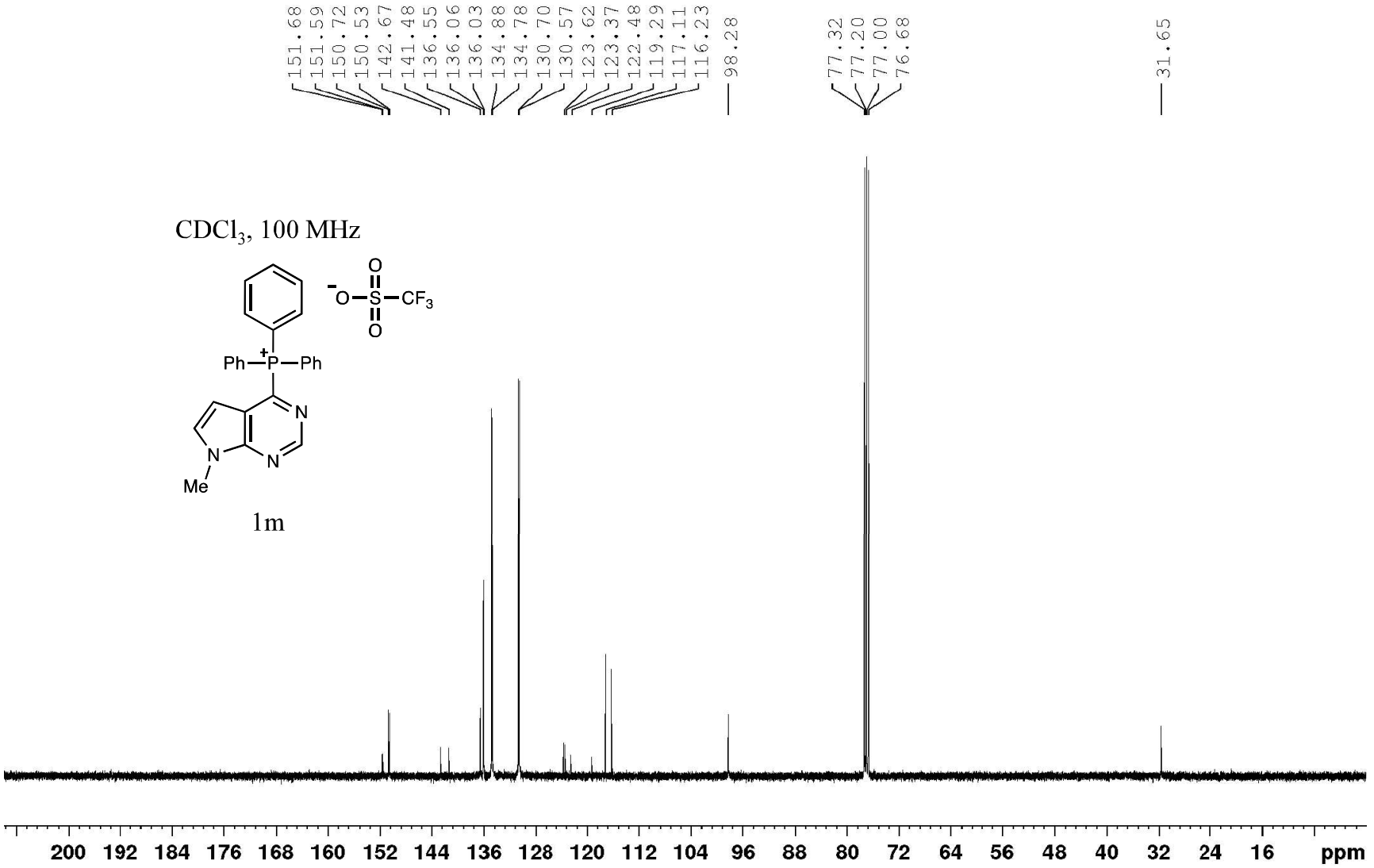

-78.08
CDCl3, 365 MHz
Ph
P
Ph
Br
N
N
Me
S
O
O
O
O
CF3
11
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

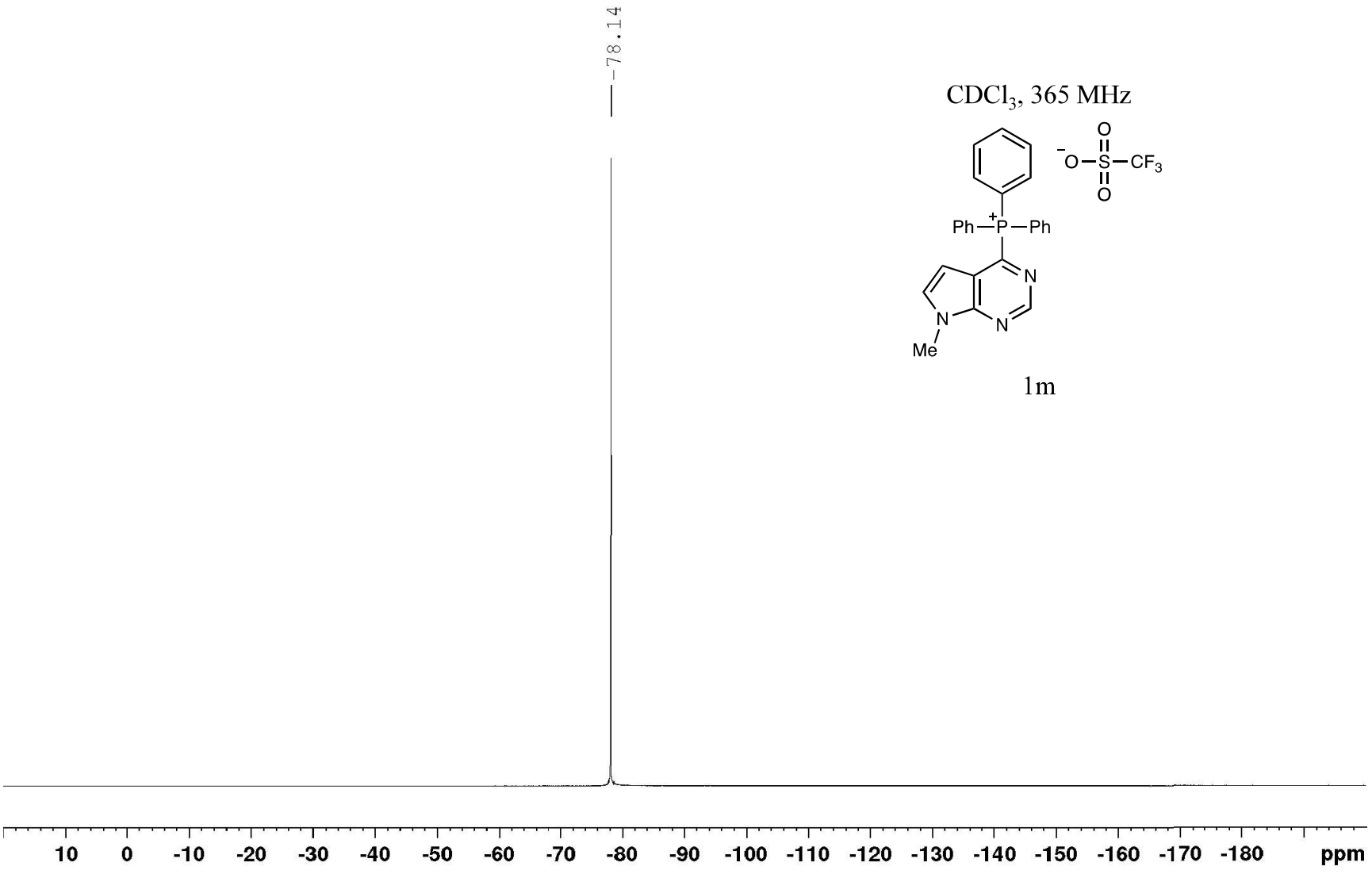
$CDCl_3$, 162 MHz



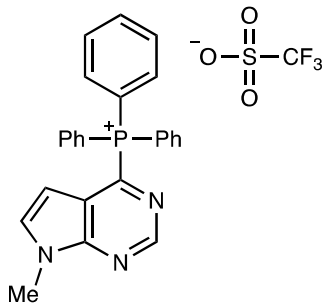
11


CDCl3, 400 MHz
1m
Ph
P
Ph
N
N
N
Me
O
S
CF3
3.98
5.31
5.30
7.93
7.91
7.89
7.77
7.75
7.73
7.72
7.70
7.69
7.64
7.63
9.12
3.00
0.95
1.05
12.00
3.00
0.86
ppm

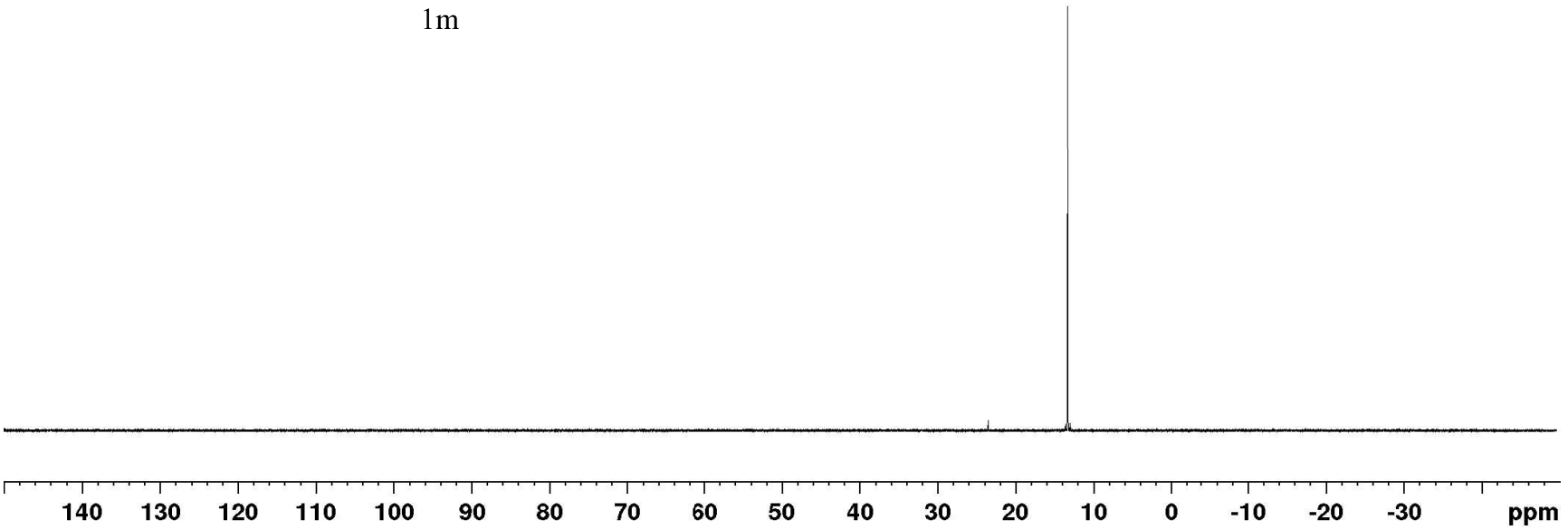

151.68
151.59
150.72
150.53
142.67
141.48
136.55
136.06
136.03
134.88
134.78
130.70
130.57
123.62
123.37
122.48
119.29
117.11
116.23
98.28
77.32
77.20
77.00
76.68
31.65
CDCl3, 100 MHz
Ph
P
Ph
N
N
N
Me
O
O
S
O
CF3
1m
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

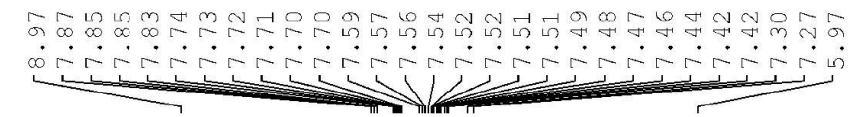

-78.14
CDCl3, 365 MHz
Ph
P
Ph
N
N
N
Me
O
O
S
CF3
1m
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

$CDCl_3$, 162 MHz

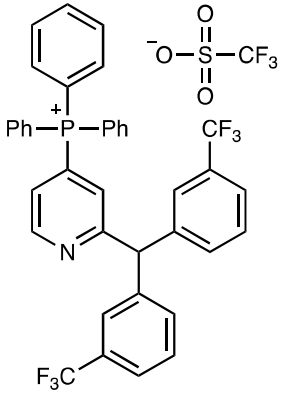


1m

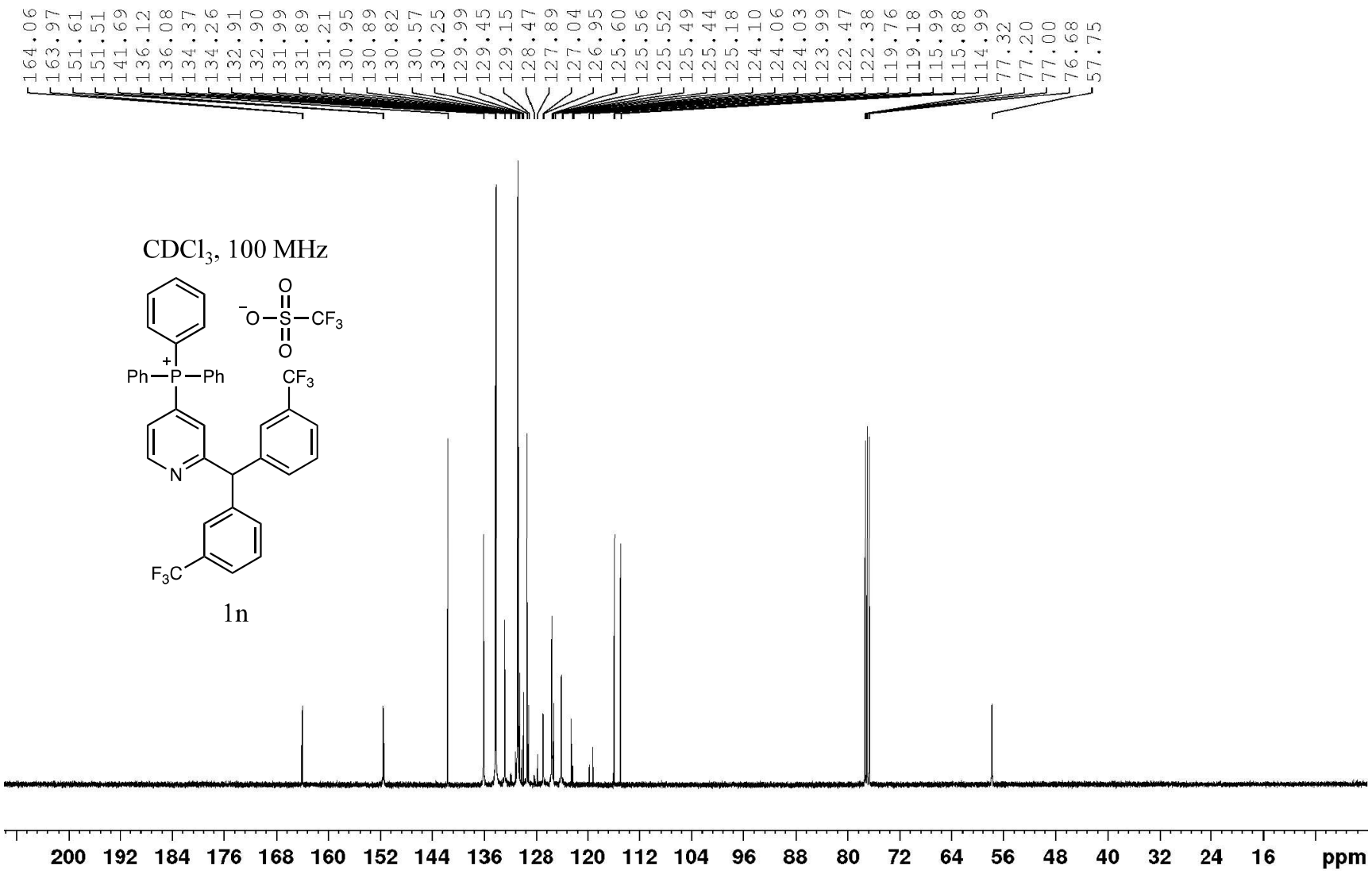




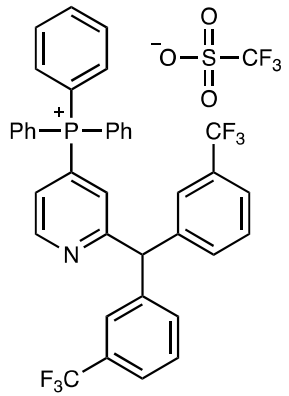
$CDCl_3$, 400 MHz



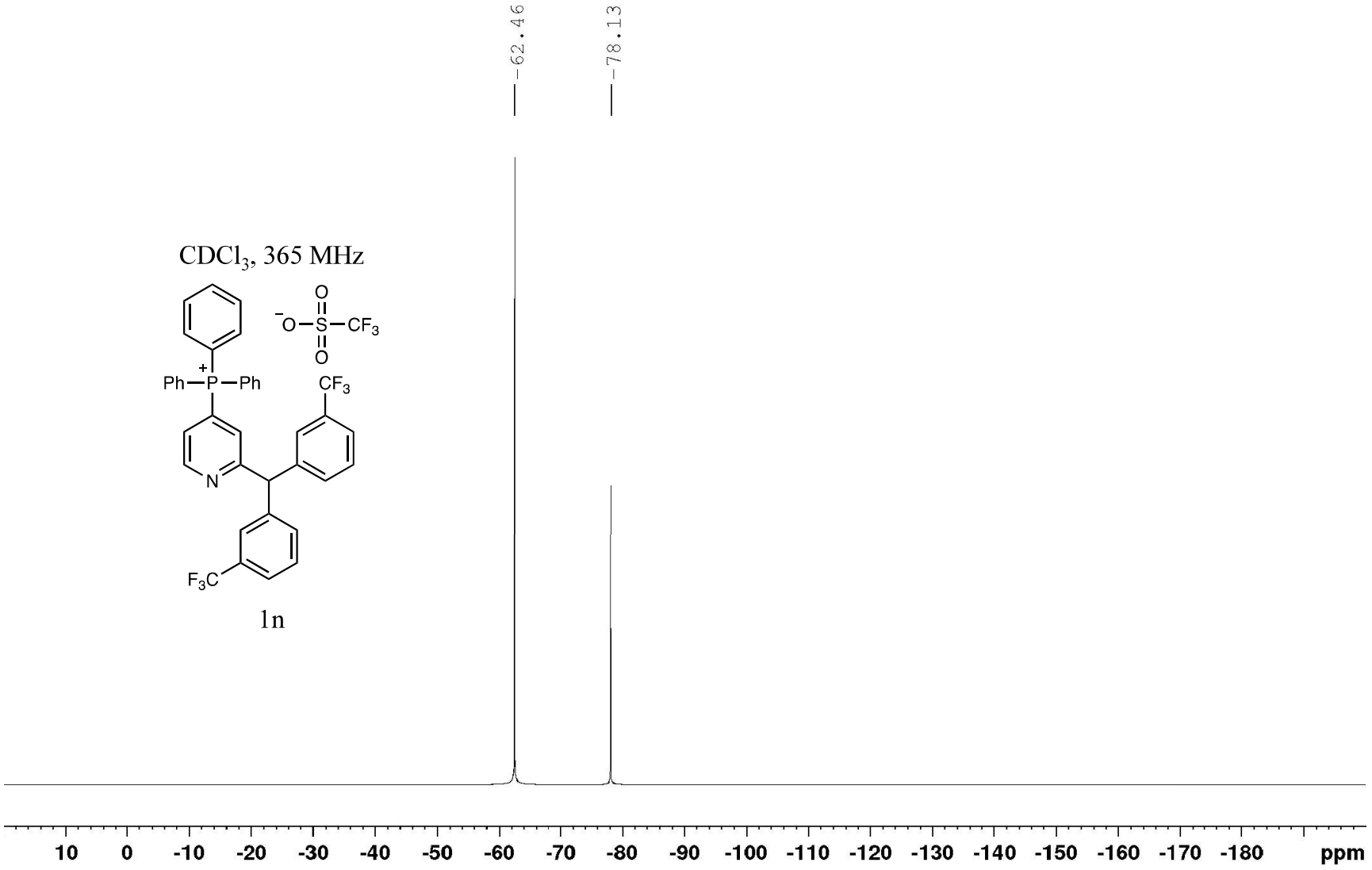
1n

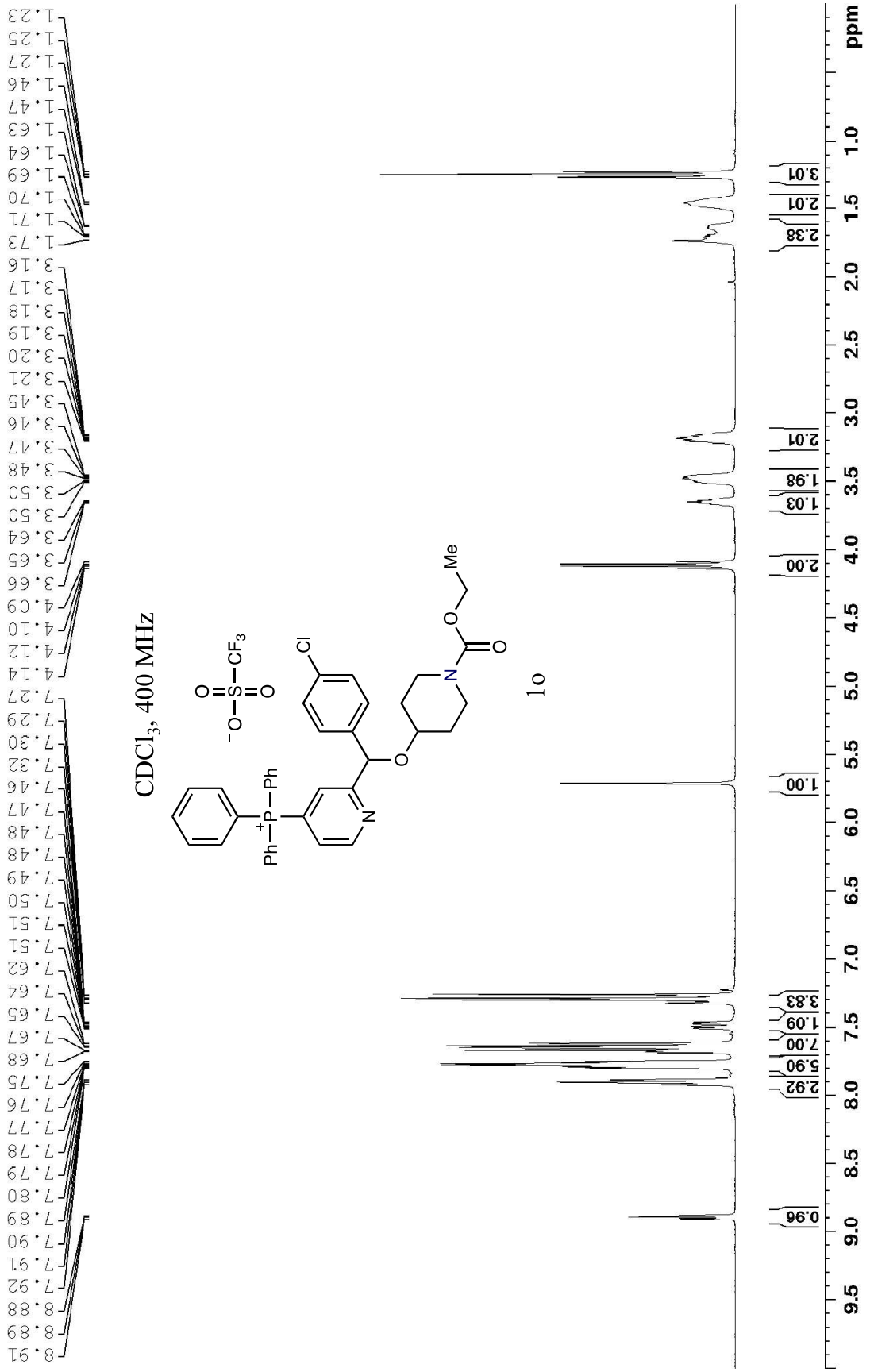

164.06
163.97
151.61
151.51
141.69
136.12
136.08
134.37
134.26
132.91
132.90
131.99
131.89
131.21
130.95
130.89
130.82
130.57
130.25
129.99
129.45
129.15
128.47
127.89
127.04
126.95
125.60
125.56
125.52
125.49
125.44
125.18
124.10
124.06
124.03
123.99
122.47
122.38
119.76
119.18
115.99
115.88
114.99
77.32
77.20
77.00
76.68
57.75
CDCl3, 100 MHz
1n
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

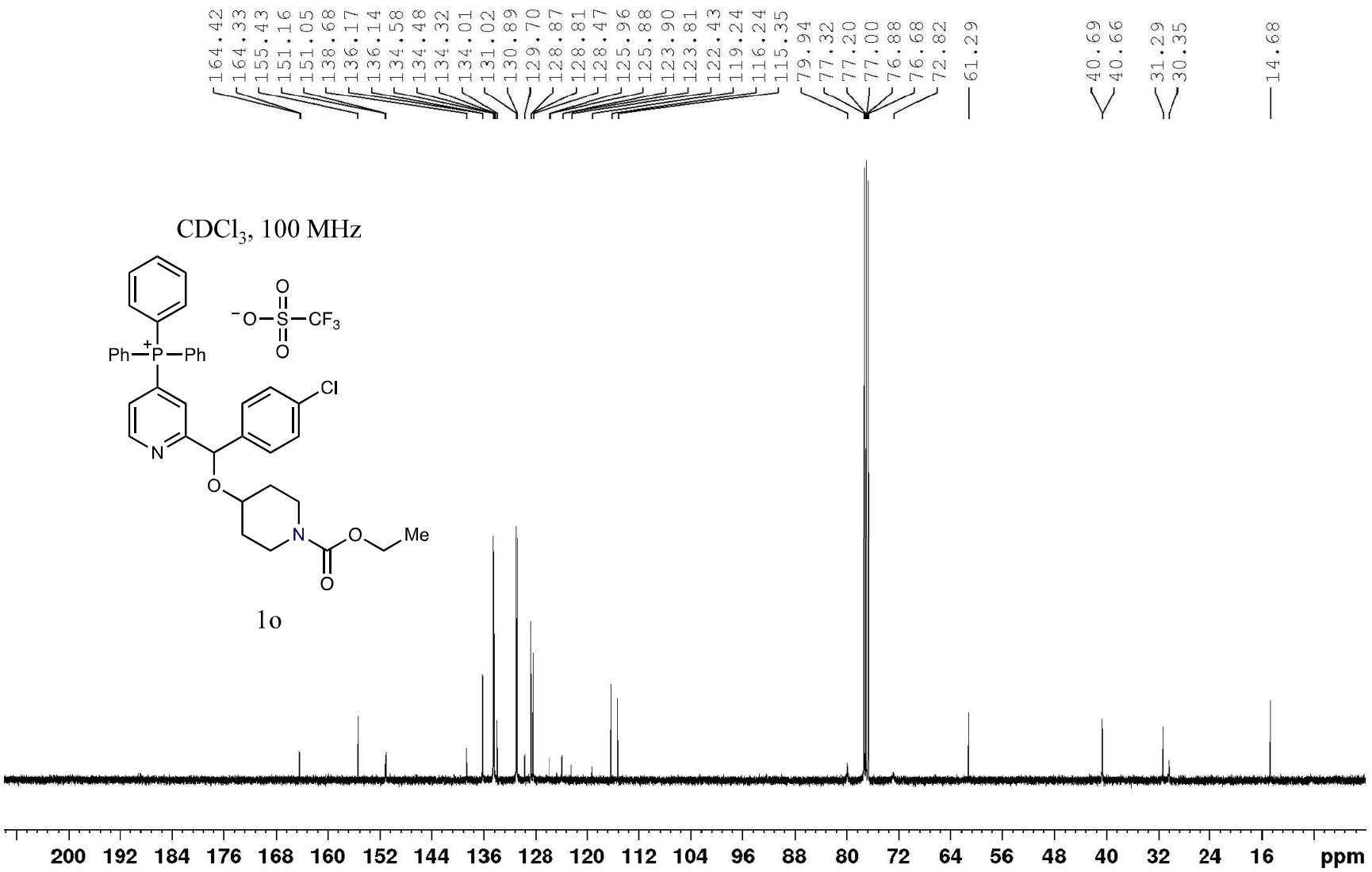
$CDCl_3$, 162 MHz

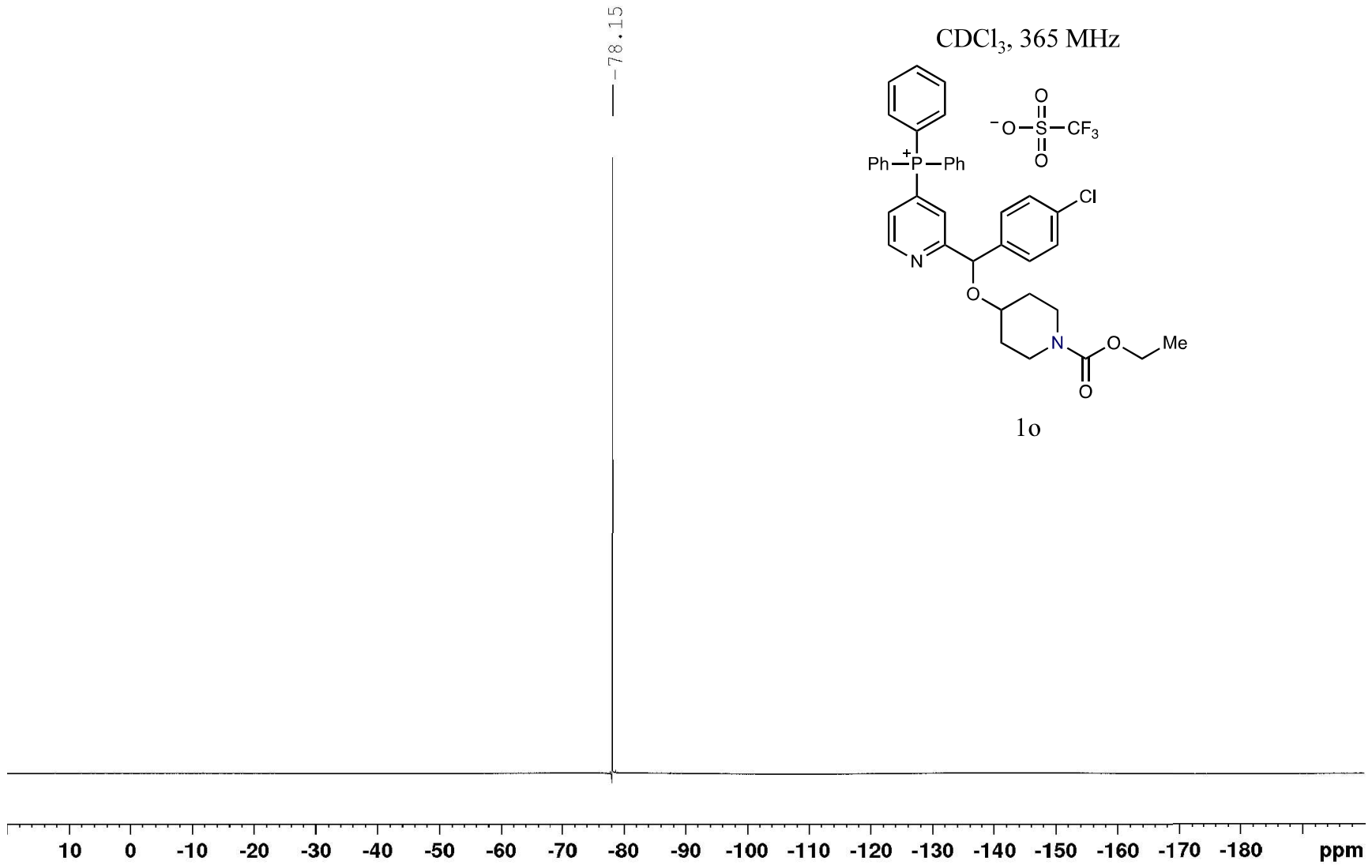


1n


-62.46
-78.13
CDCl3, 365 MHz
Ph—P—Ph
CF3
F3C
1n
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

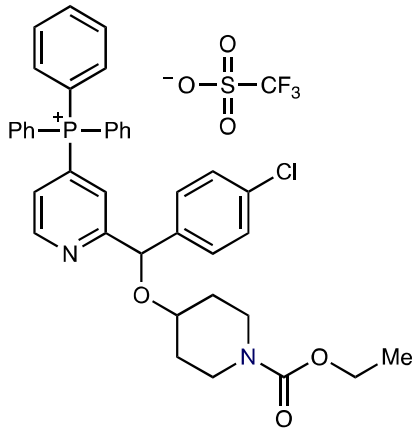

CDCl3, 400 MHz
1o
ppm


164.42
164.33
155.43
151.16
151.05
138.68
136.17
136.14
134.58
134.48
134.32
134.01
131.02
130.89
129.70
128.87
128.81
128.47
125.96
125.88
123.90
123.81
122.43
119.24
116.24
115.35
79.94
77.32
77.20
77.00
76.88
76.68
72.82
61.29
40.69
40.66
31.29
30.35
14.68
CDCl3, 100 MHz
Ph
P
Ph
O
S
CF3
Cl
N
O
N
O
O
Me
O
1o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


-78.15
CDCl3, 365 MHz
Ph
P
Ph
O
S
CF3
Cl
N
O
N
O
Me
O
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

1o

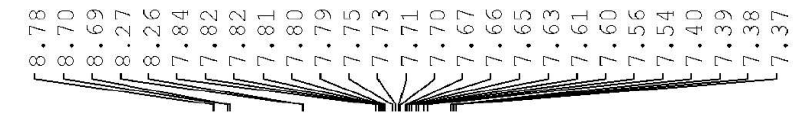
$CDCl_3$, 162 MHz



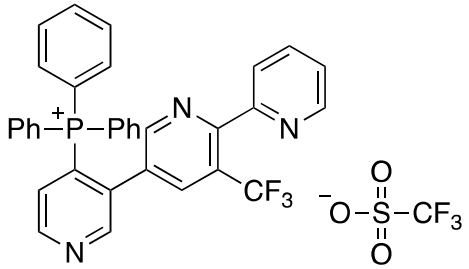
1o

22.67

140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 ppm

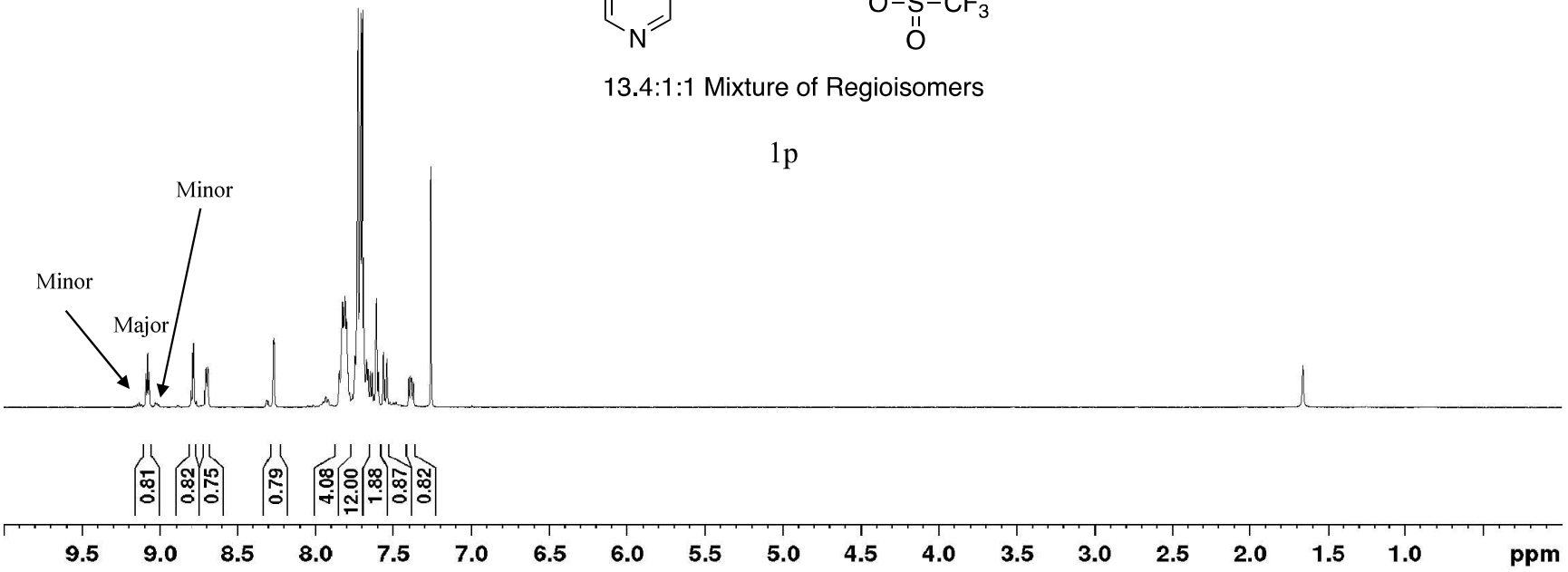


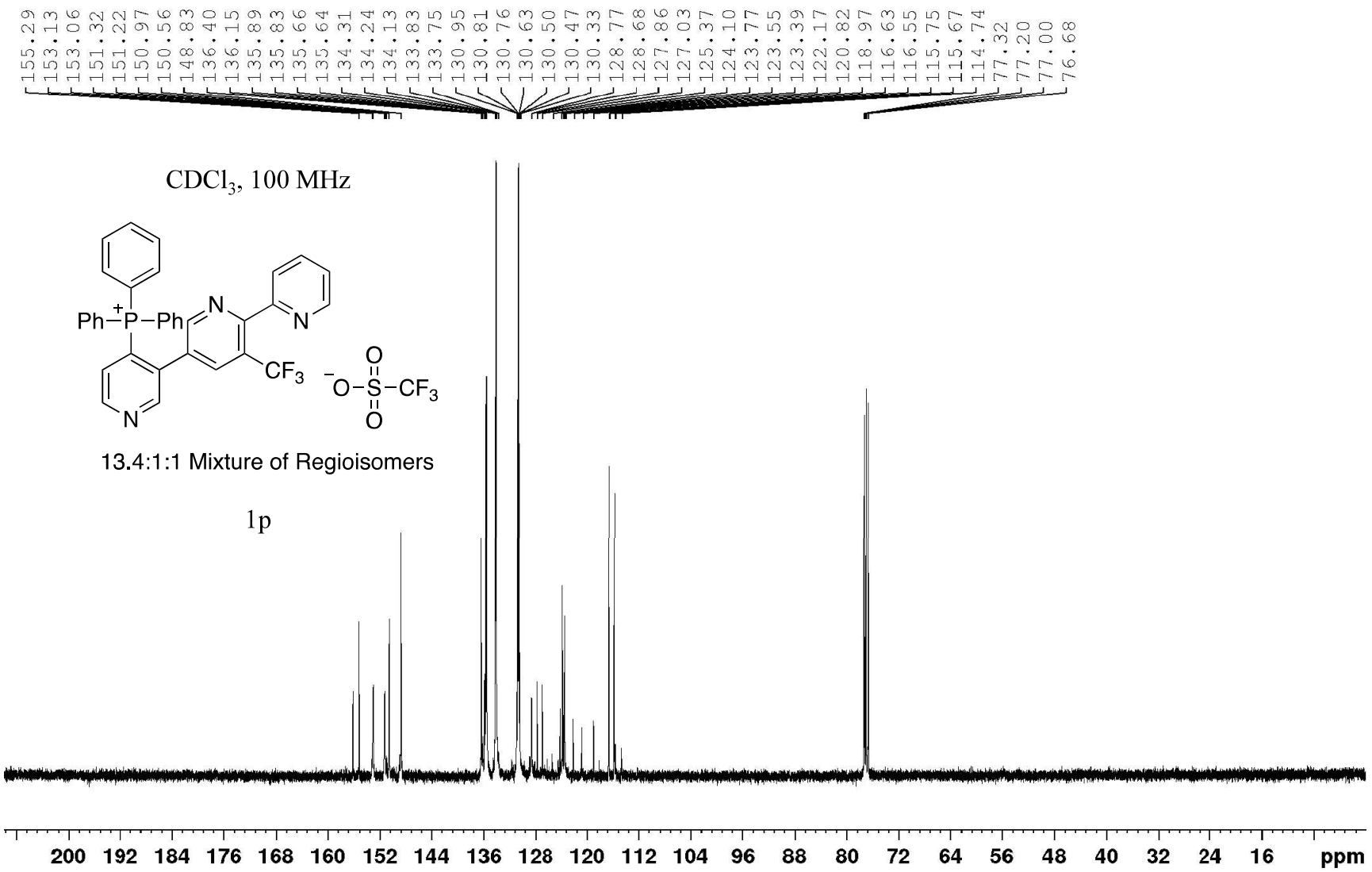
$CDCl_3$, 400 MHz

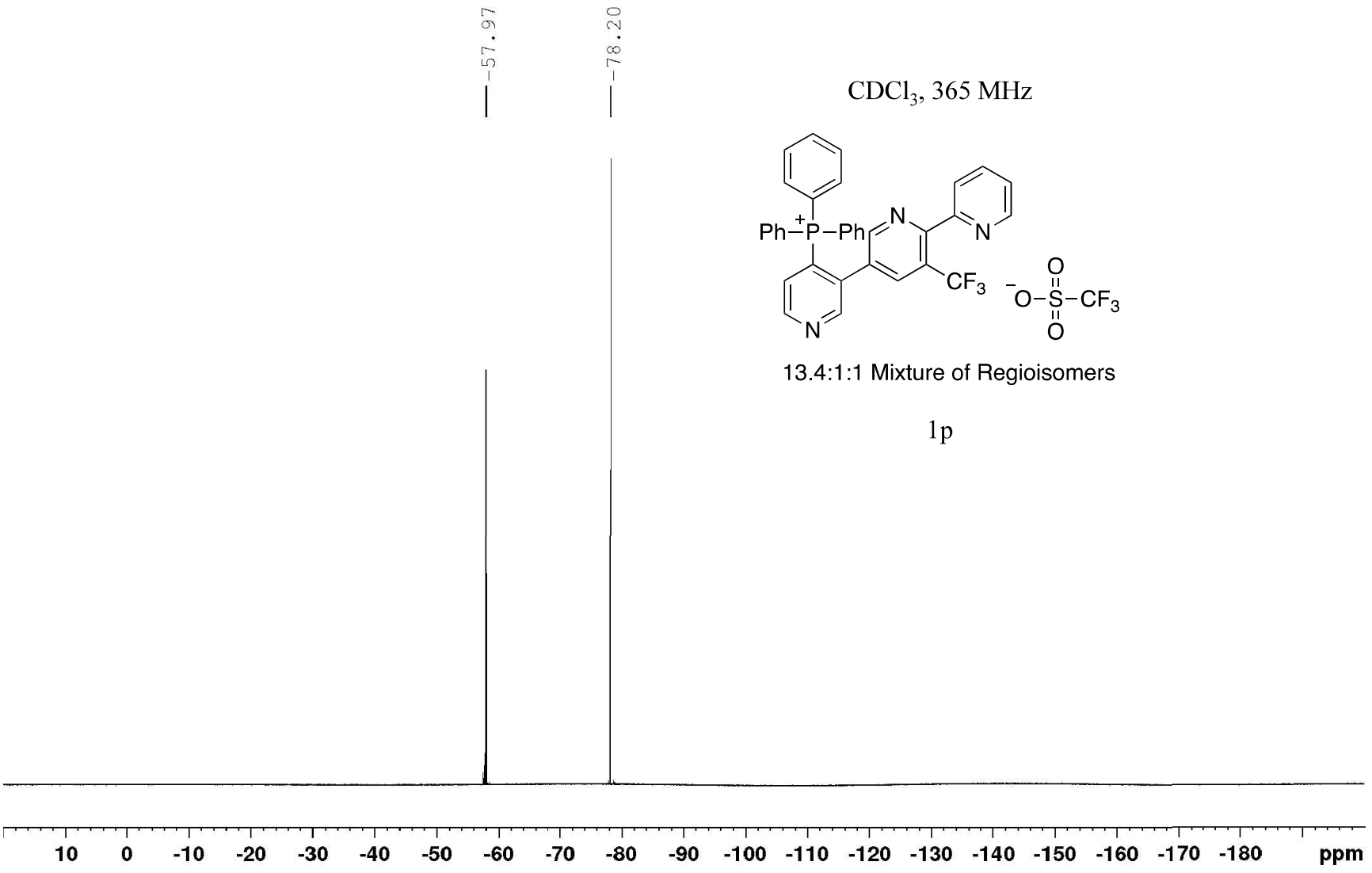


13.4:1:1 Mixture of Regioisomers

1p




155.29
153.13
153.06
151.32
151.22
150.97
150.56
148.83
136.40
136.15
135.89
135.83
135.66
135.64
134.31
134.24
134.13
133.83
133.75
130.95
130.81
130.76
130.63
130.50
130.47
130.33
128.77
128.68
127.86
127.03
125.37
124.10
123.77
123.55
123.39
122.17
120.82
118.97
116.63
116.55
115.75
115.67
114.74
77.32
77.20
77.00
76.68
CDCl3, 100 MHz
Ph
P
Ph
N
N
CF3
O
O
S
CF3
O
N
13.4:1:1 Mixture of Regioisomers
1p
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

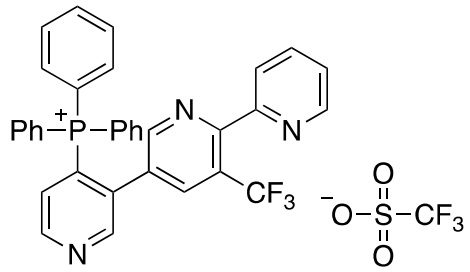


$CDCl_3$, 365 MHz

13.4:1:1 Mixture of Regioisomers

1p

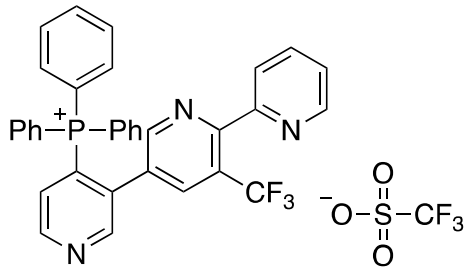
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



9.6:1.3:1 Mixture of Regioisomers

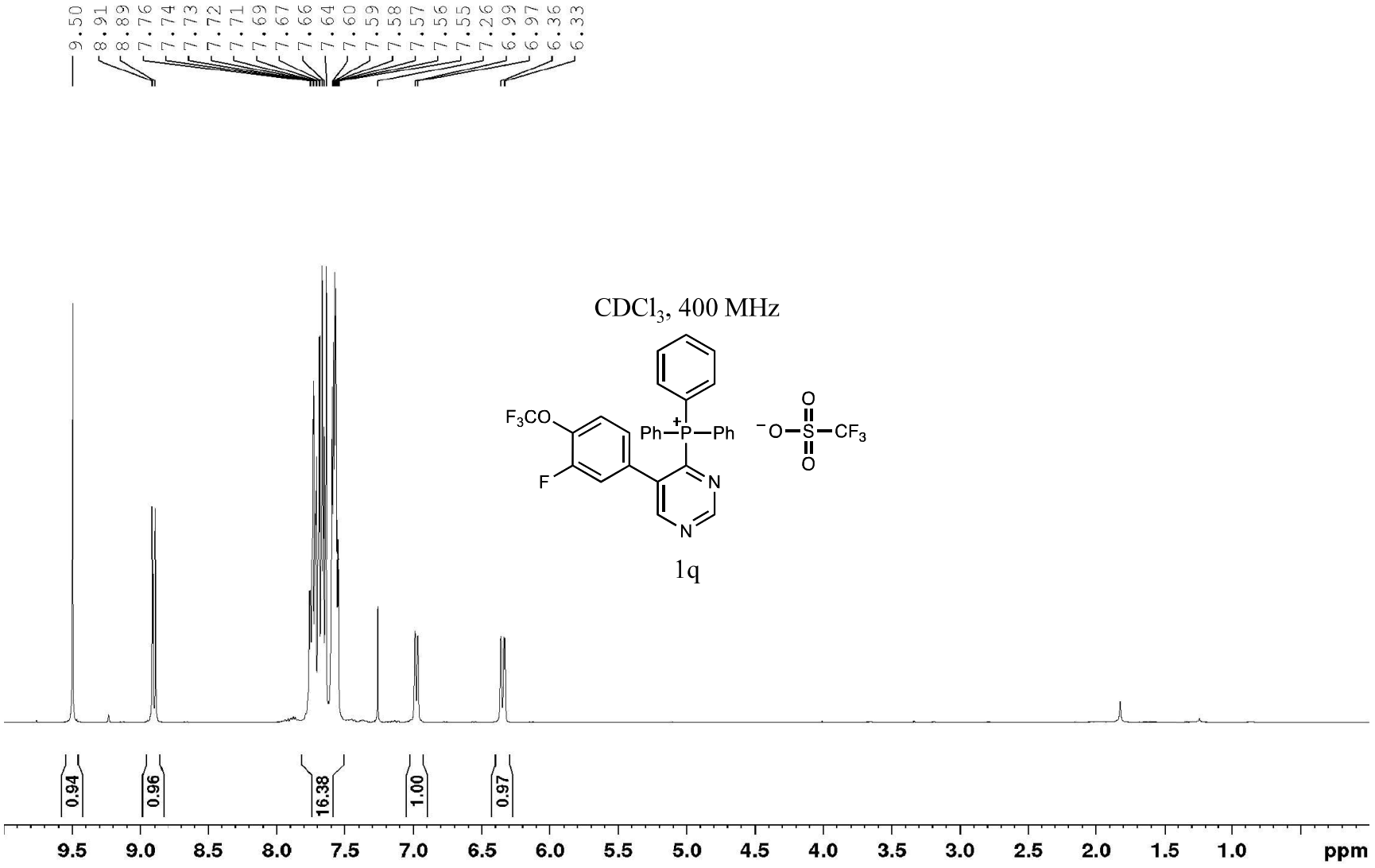
1p

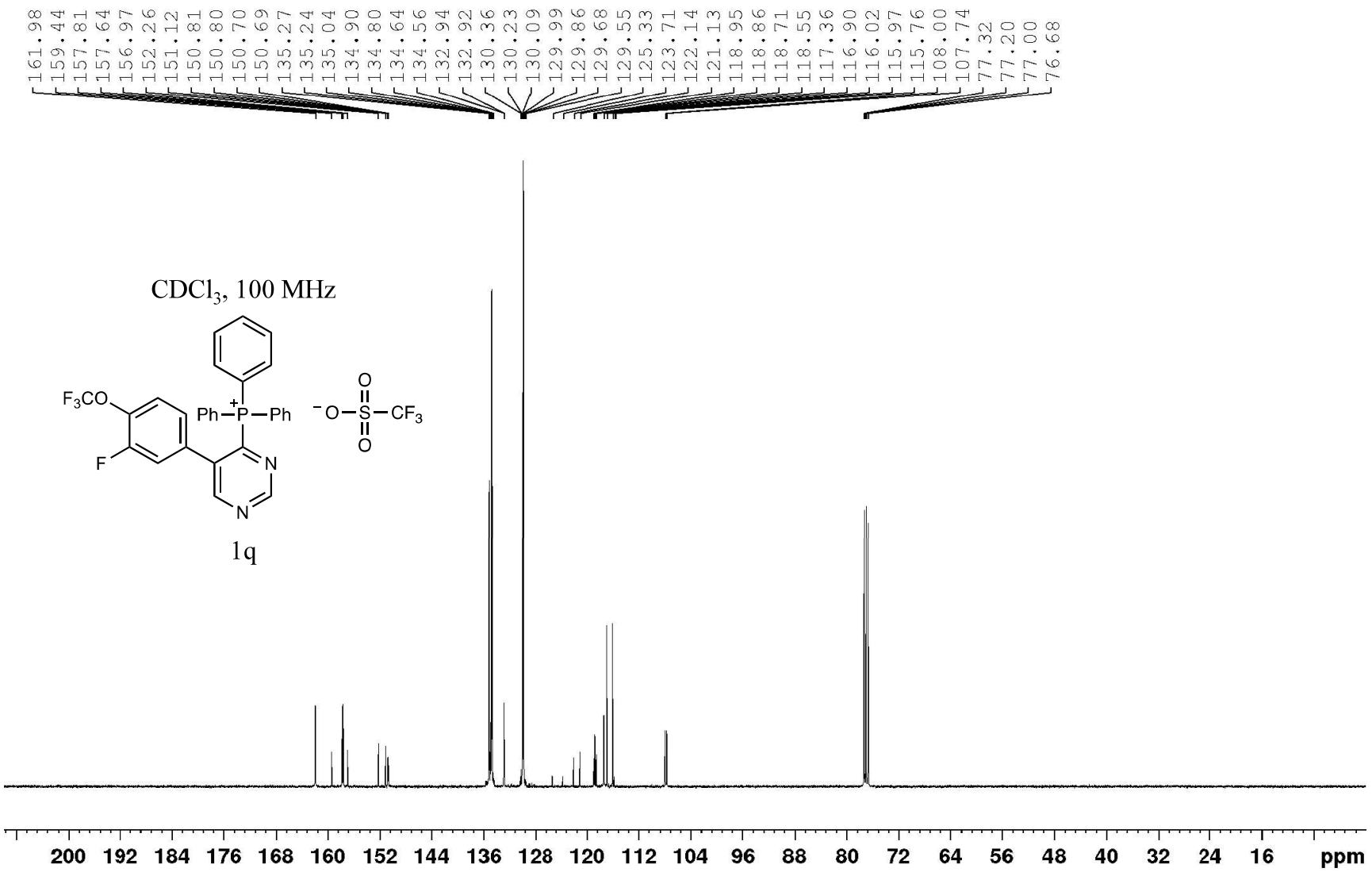
$CDCl_3$, 162 MHz (Post-precipitate ^{31}P NMR)

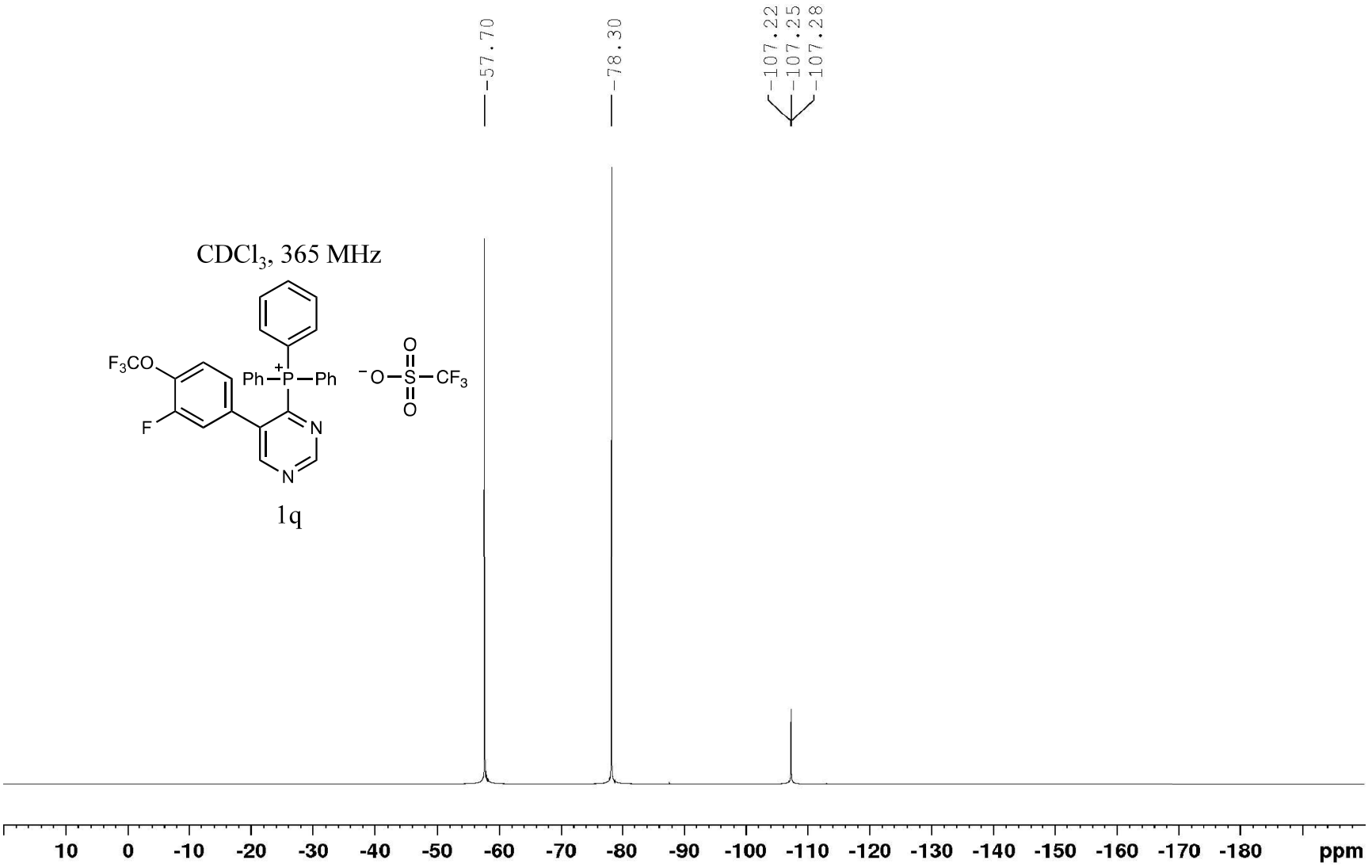


13.4:1:1 Mixture of Regioisomers

1p

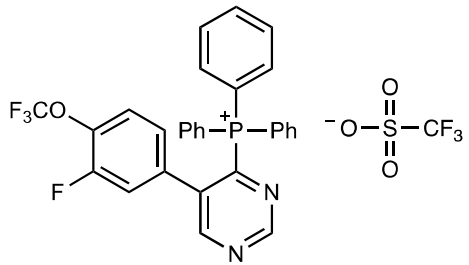

9.50
8.91
8.89
7.76
7.74
7.73
7.72
7.71
7.69
7.67
7.66
7.64
7.60
7.59
7.58
7.57
7.56
7.55
7.26
6.99
6.97
6.36
6.33
CDCl3, 400 MHz
F3CO
F
Ph–P–Ph
+
N
N
−O–S–CF3
O
O
O
1q
0.94
0.96
16.38
1.00
0.97
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


161.98
159.44
157.81
157.64
156.97
152.26
151.12
150.81
150.80
150.70
150.69
135.27
135.24
135.04
134.90
134.80
134.64
134.56
132.94
132.92
130.36
130.23
130.09
129.99
129.86
129.68
129.55
125.33
123.71
122.14
121.13
118.95
118.86
118.71
118.55
117.36
116.90
116.02
115.97
115.76
108.00
107.74
77.32
77.20
77.00
76.68
CDCl3, 100 MHz
F3CO
Ph
P
Ph
O
S
CF3
F
N
N
1q
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

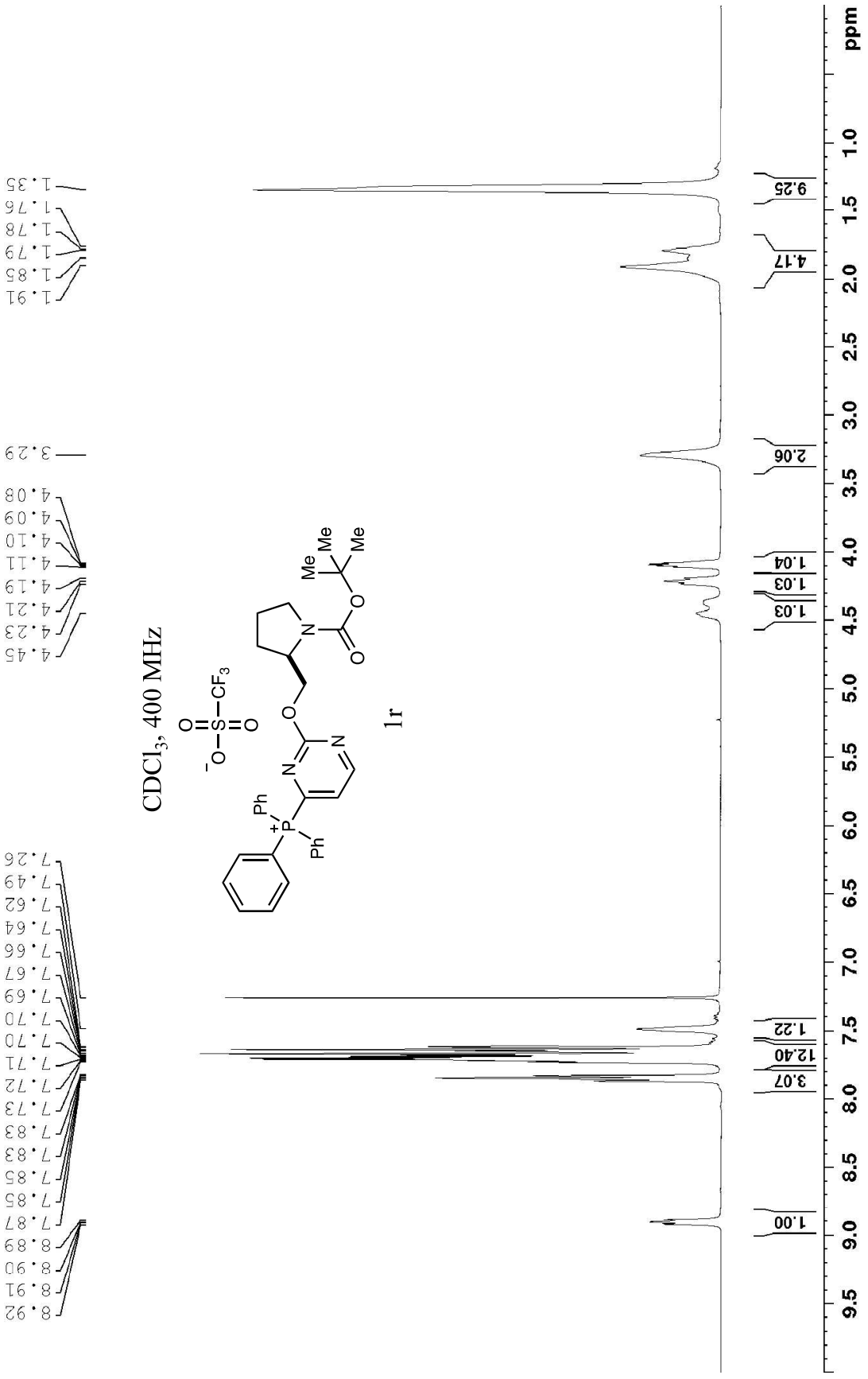

-57.70
-78.30
-107.22
-107.25
-107.28
CDCl3, 365 MHz
F3CO
Ph–P–Ph
O–S–CF3
F
N
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

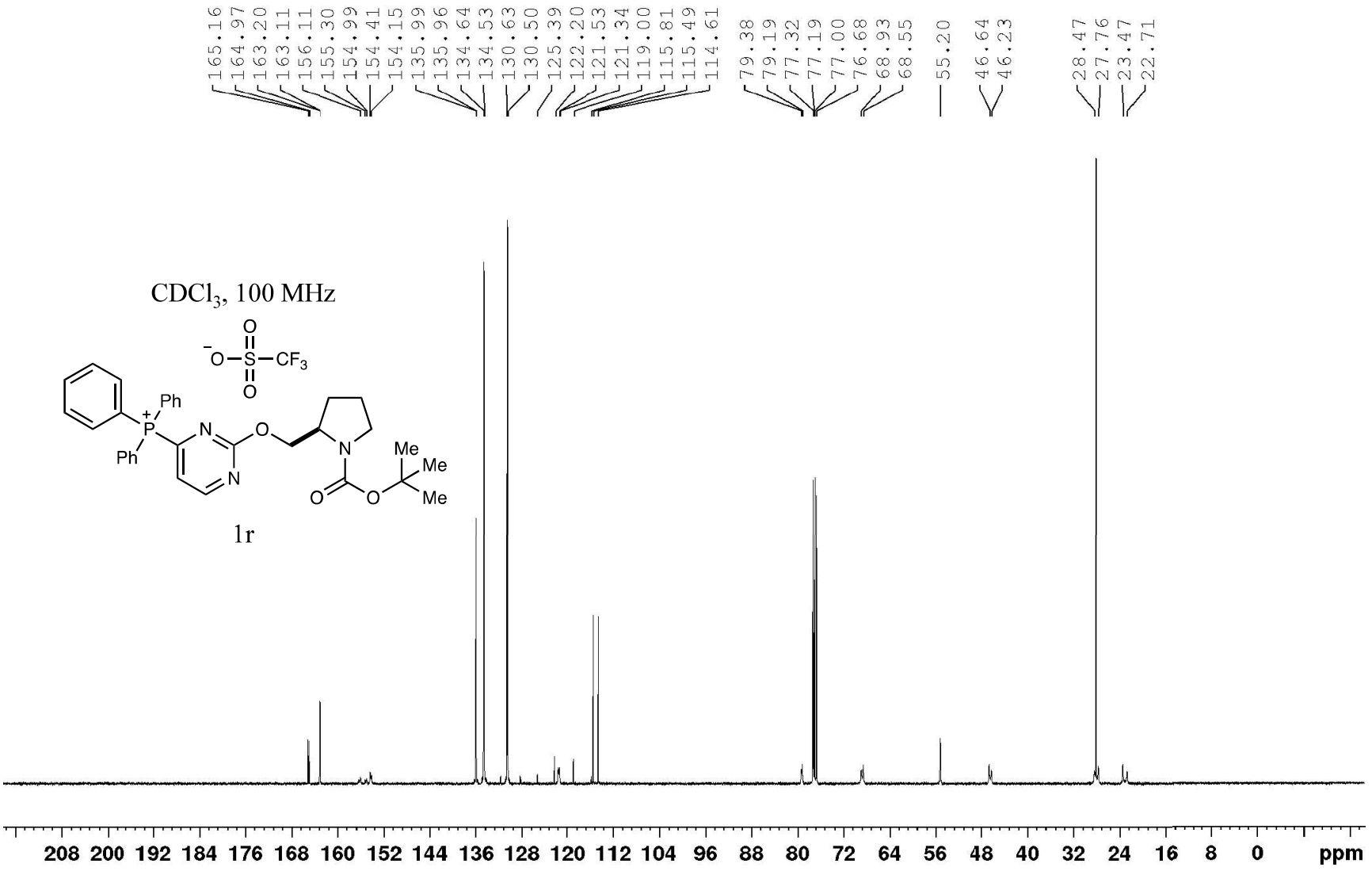
1q

$CDCl_3$, 162 MHz

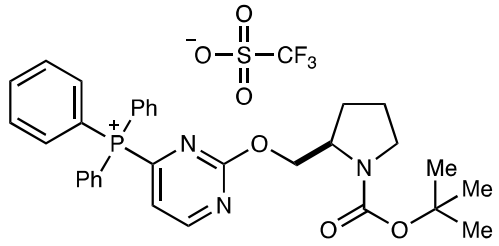


1q


CDCl3, 400 MHz
1r
ppm

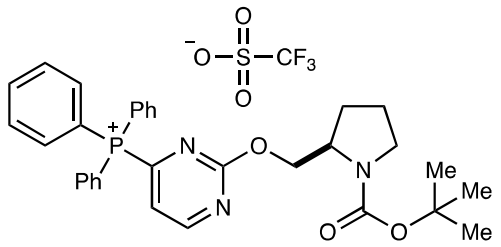

165.16
164.97
163.20
163.11
156.11
155.30
154.99
154.41
154.15
135.99
135.96
134.64
134.53
130.63
130.50
125.39
122.20
121.53
121.34
119.00
115.81
115.49
114.61
79.38
79.19
77.32
77.19
77.00
76.68
68.93
68.55
55.20
46.64
46.23
28.47
27.76
23.47
22.71
CDCl3, 100 MHz
Ph
Ph
Me
Me
Me
1r
208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 ppm

$CDCl_3$, 365 MHz

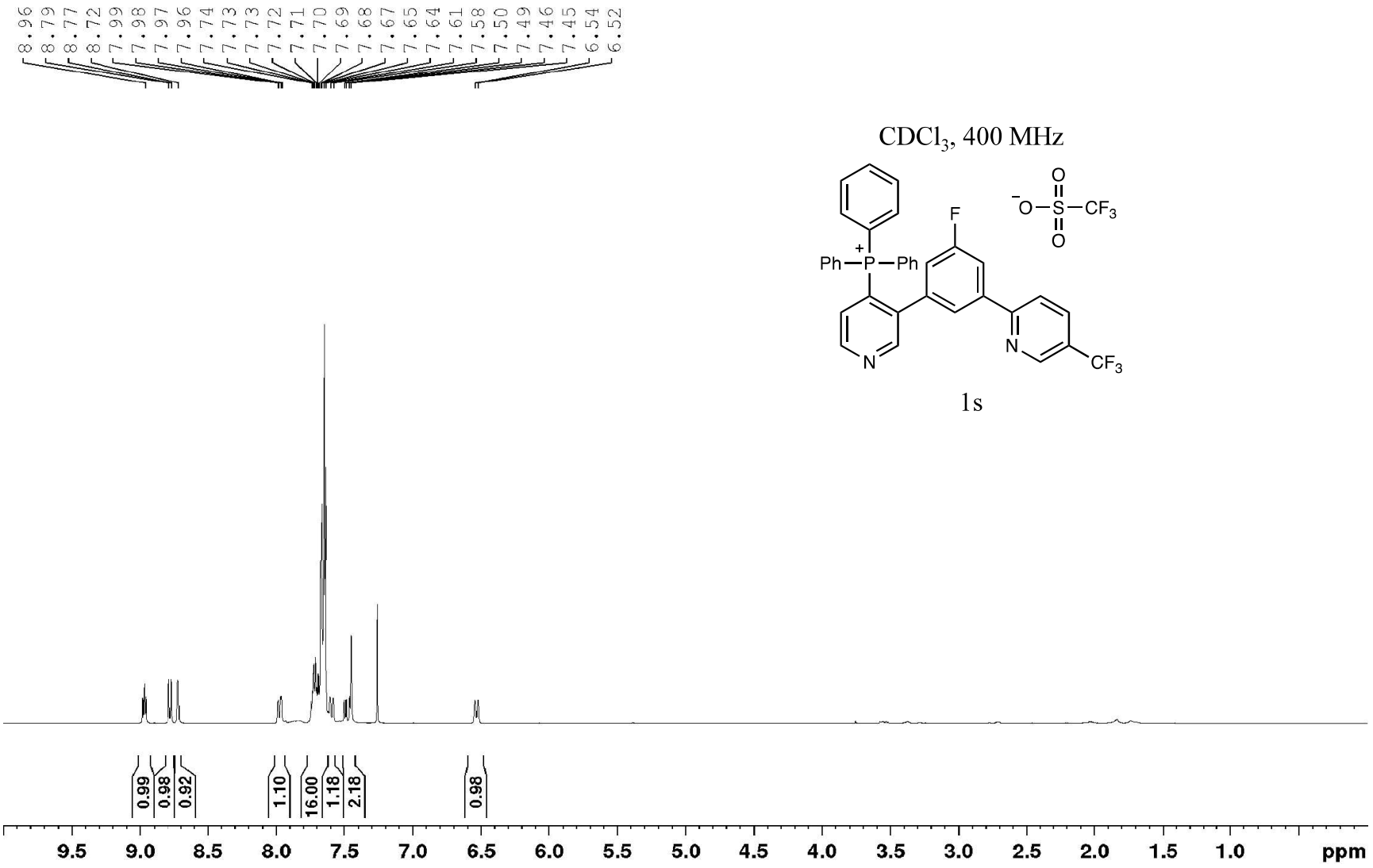


1r

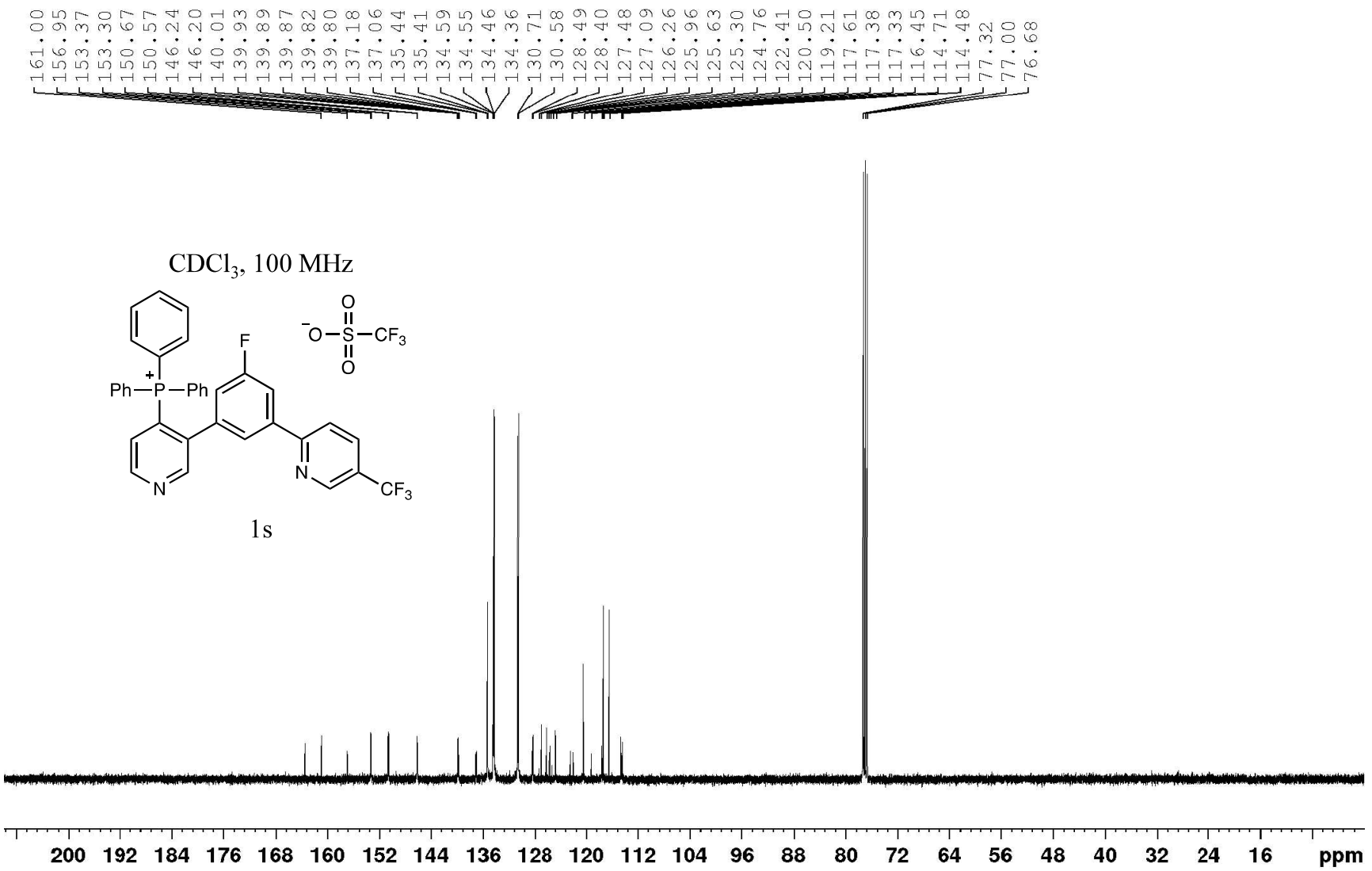
$CDCl_3$, 162 MHz

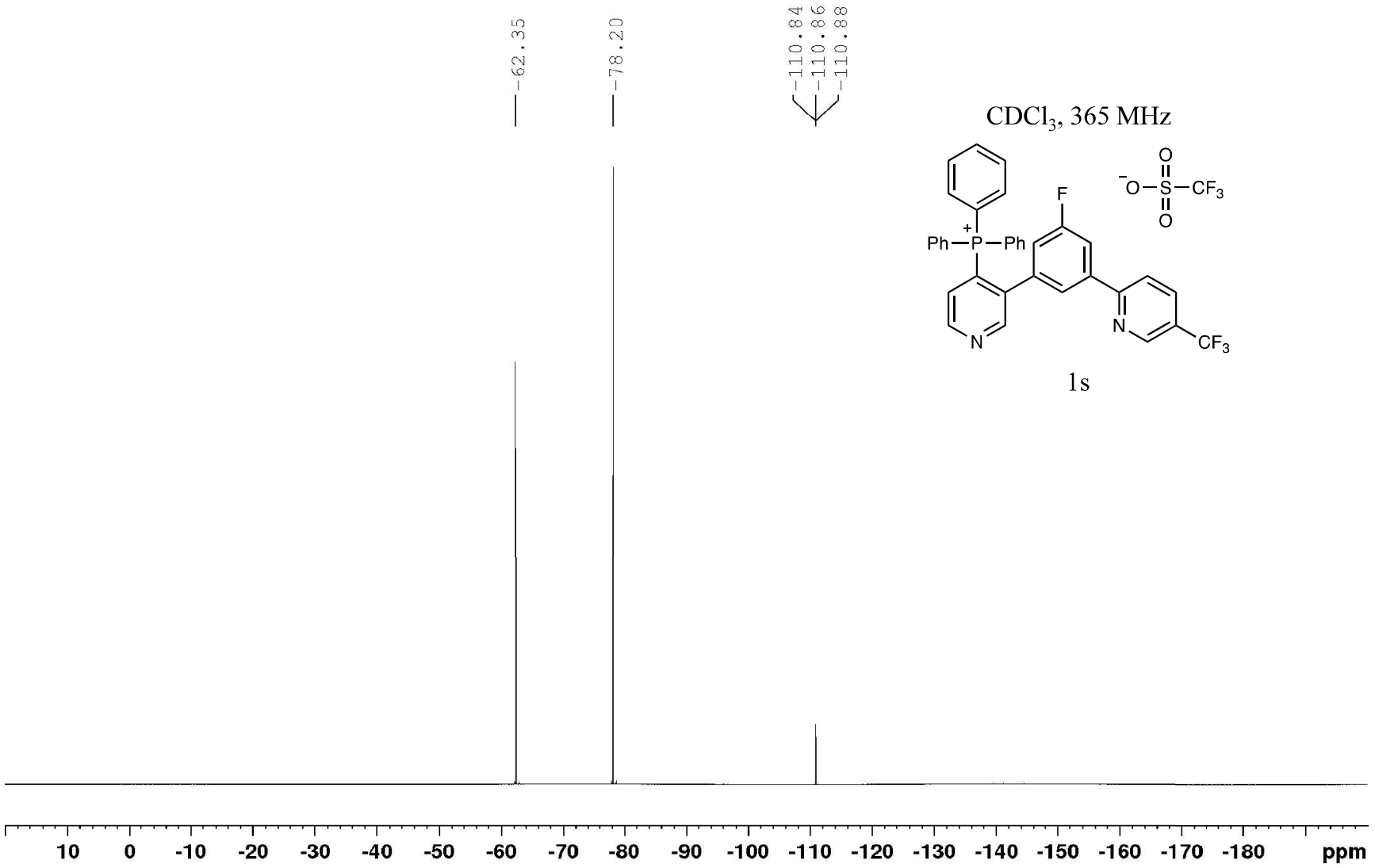


1r

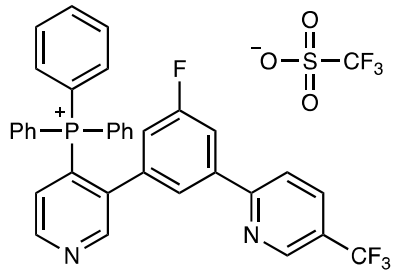

8.96
8.79
8.77
8.72
7.99
7.98
7.97
7.96
7.74
7.73
7.73
7.72
7.71
7.70
7.69
7.68
7.67
7.65
7.64
7.61
7.58
7.50
7.49
7.46
7.45
6.54
6.52
CDCl3, 400 MHz
F
Ph
P
Ph
O
S
CF3
N
N
CF3
0.99
0.98
0.92
1.10
16.00
1.18
2.18
0.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

1s

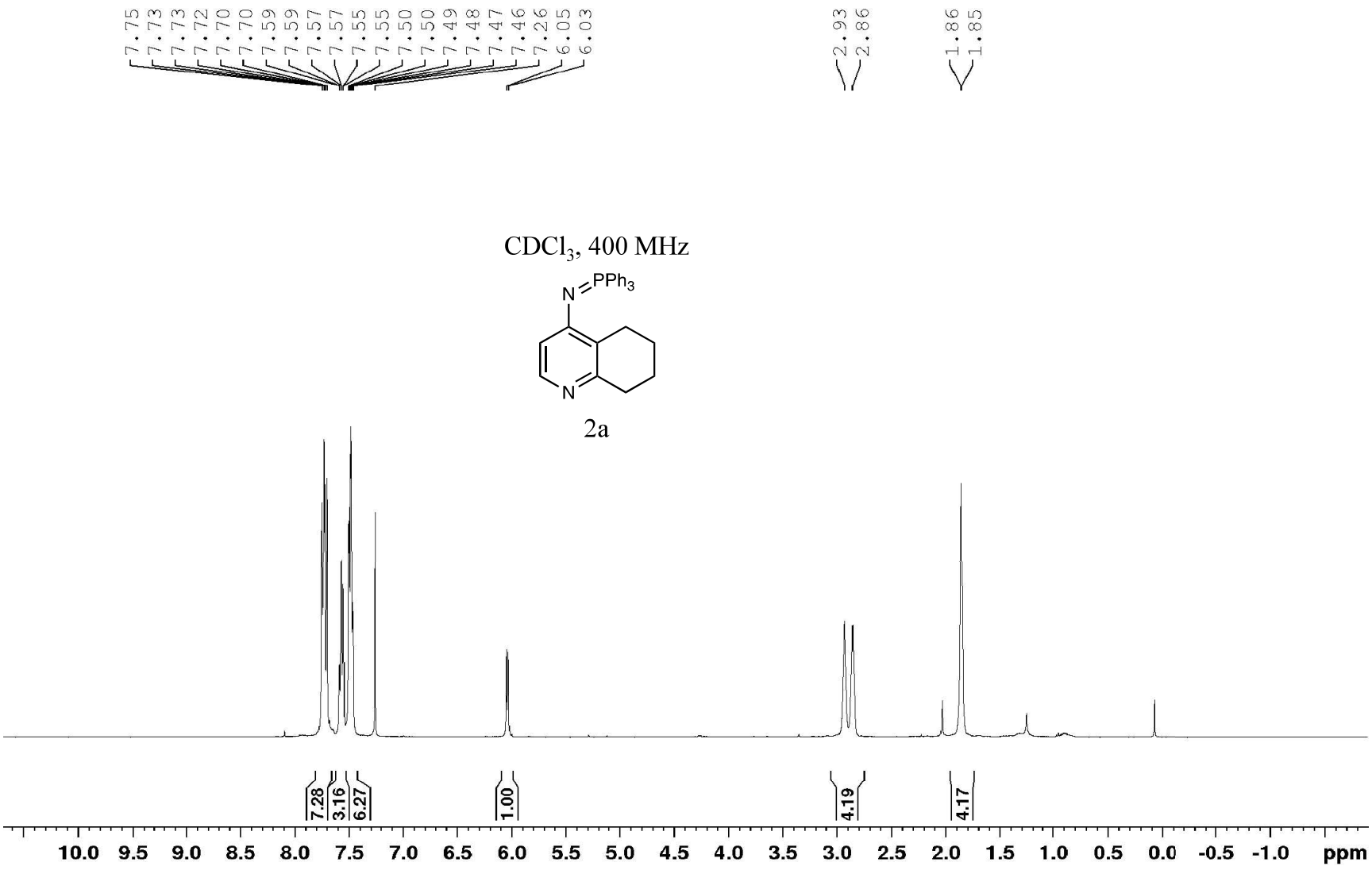

161.00
156.95
153.37
153.30
150.67
150.57
146.24
146.20
140.01
139.93
139.89
139.87
139.82
139.80
137.18
137.06
135.44
135.41
134.59
134.55
134.46
134.36
130.71
130.58
128.49
128.40
127.48
127.09
126.26
125.96
125.63
125.30
124.76
122.41
120.50
119.21
117.61
117.38
117.33
116.45
114.71
114.48
77.32
77.00
76.68
CDCl3, 100 MHz
Ph—P—Ph
F
O
O—S—CF3
O
N
N
CF3
1s
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

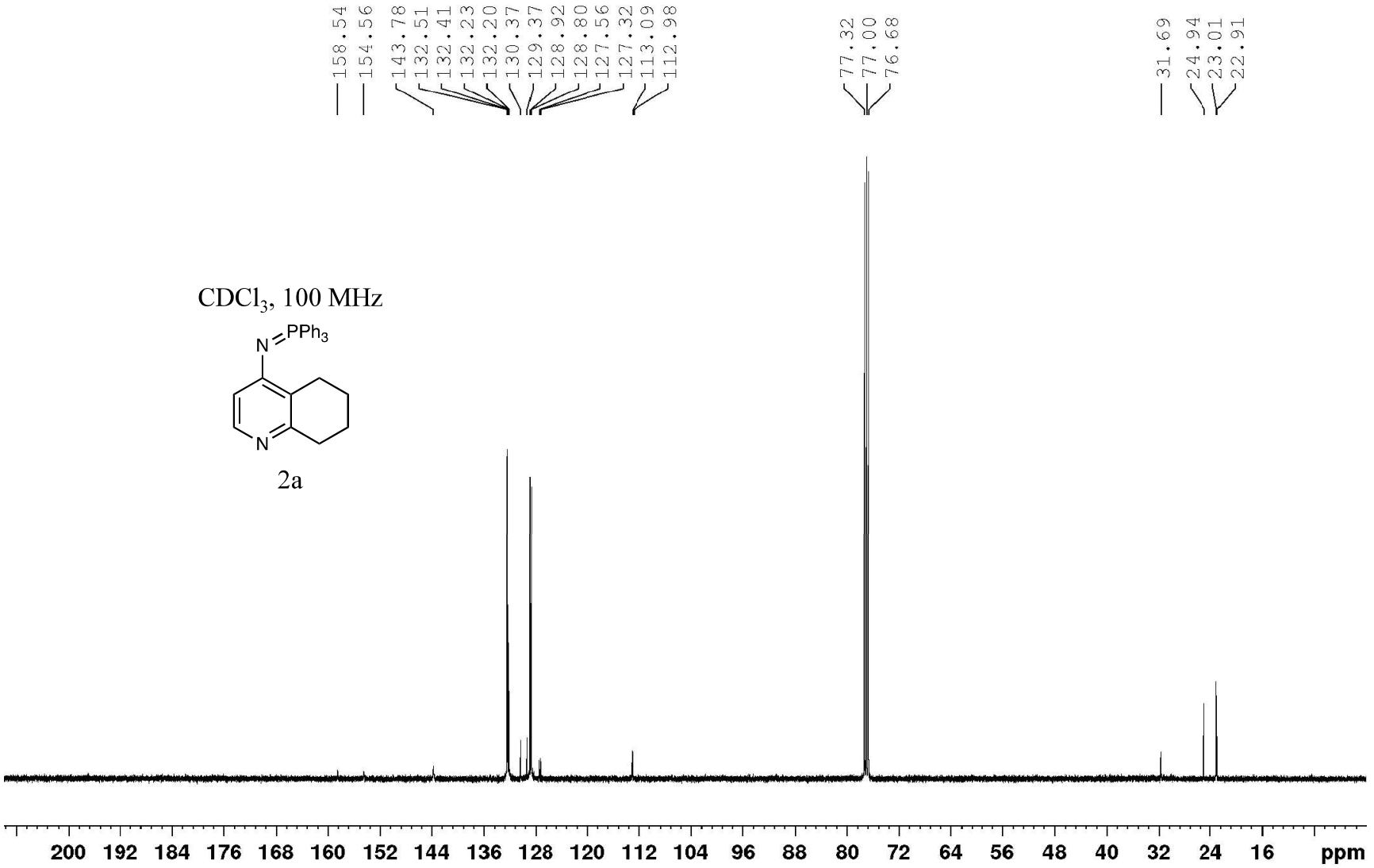

-62.35
-78.20
-110.84
-110.86
-110.88
CDCl3, 365 MHz
F
Ph
P
Ph
N
N
CF3
O
O
S
O
CF3
1s
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

$CDCl_3$, 162 MHz

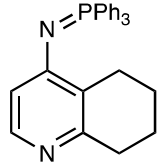


1s

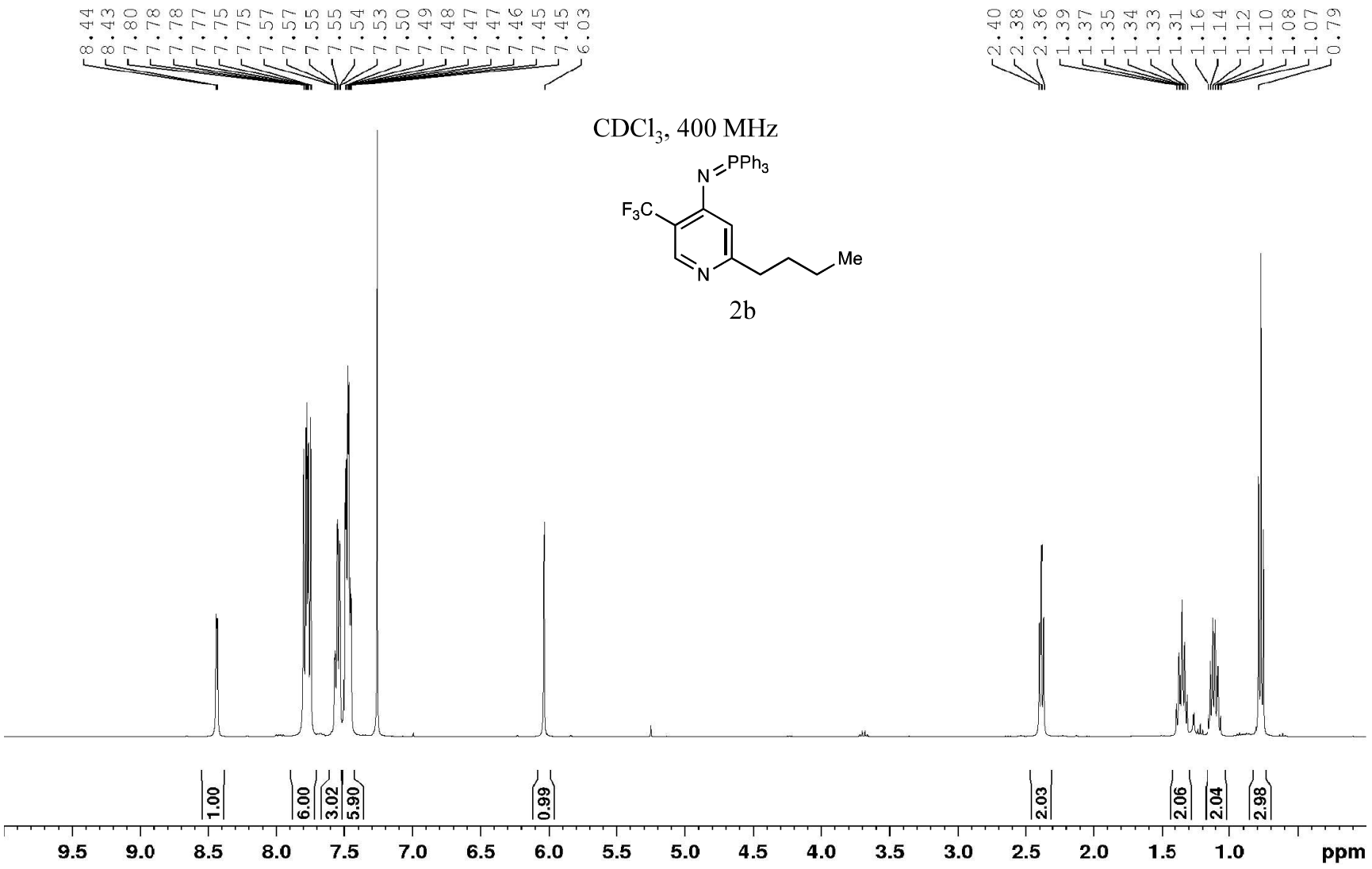

7.75
7.73
7.73
7.72
7.70
7.70
7.59
7.59
7.57
7.57
7.55
7.55
7.50
7.50
7.49
7.48
7.47
7.46
7.26
6.05
6.03
2.93
2.86
1.86
1.85
CDCl3, 400 MHz
N
PPh3
N
2a
7.28
3.16
6.27
1.00
4.19
4.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 ppm

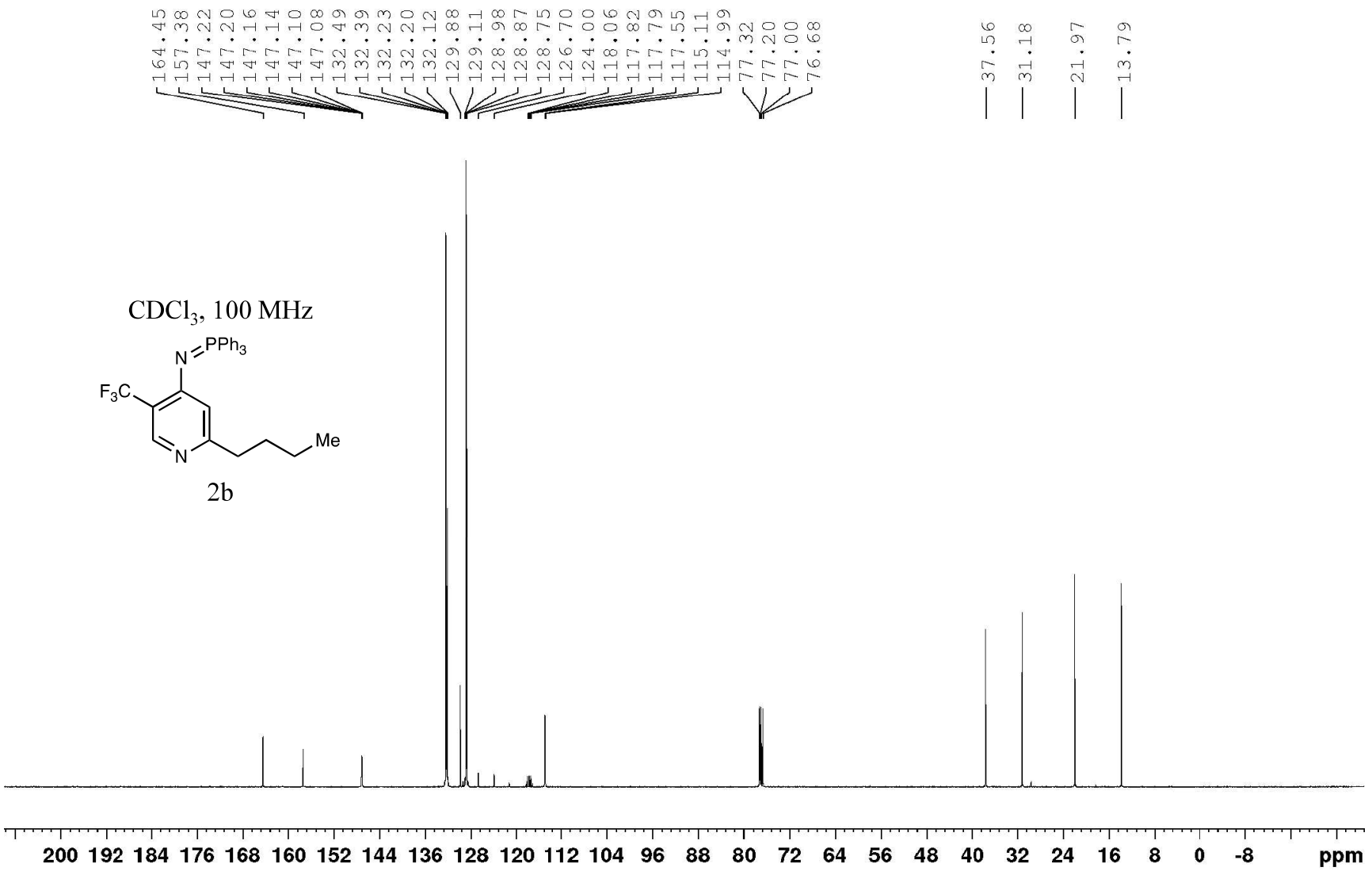

158.54
154.56
143.78
132.51
132.41
132.23
132.20
130.37
129.37
128.92
128.80
127.56
127.32
113.09
112.98
77.32
77.00
76.68
31.69
24.94
23.01
22.91
CDCl3, 100 MHz
N
PPh3
N
2a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

$CDCl_3$, 162 MHz

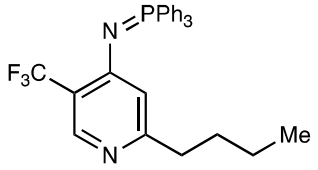


2a

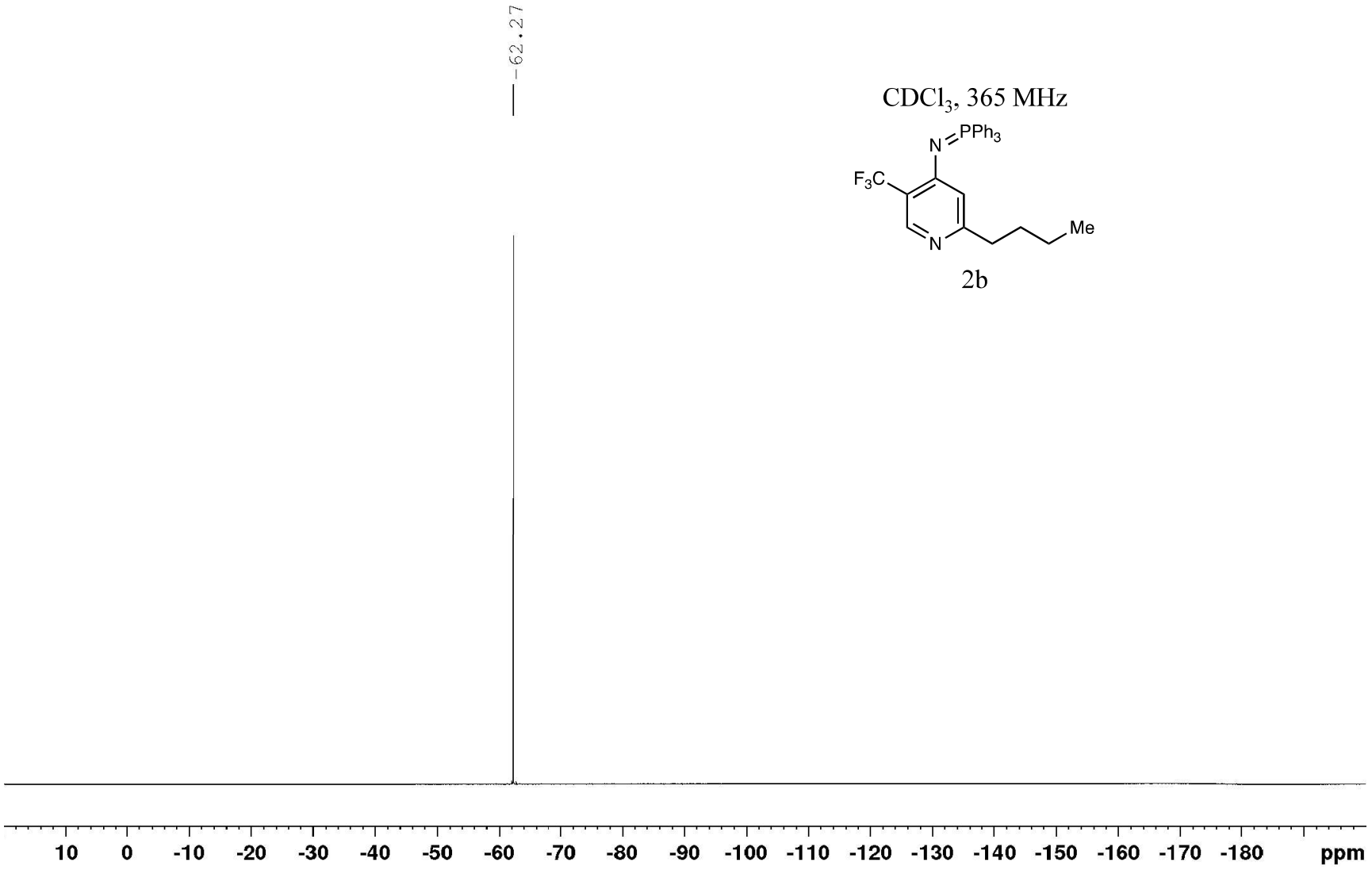

8.44
8.43
7.80
7.78
7.78
7.77
7.75
7.75
7.57
7.57
7.55
7.55
7.54
7.53
7.50
7.49
7.48
7.47
7.47
7.46
7.45
7.45
6.03
2.40
2.38
2.36
1.39
1.37
1.35
1.34
1.33
1.31
1.16
1.14
1.12
1.10
1.08
1.07
0.79
CDCl3, 400 MHz
N=PPh3
F3C
N
Me
2b
1.00
6.00
3.02
5.90
0.99
2.03
2.06
2.04
2.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

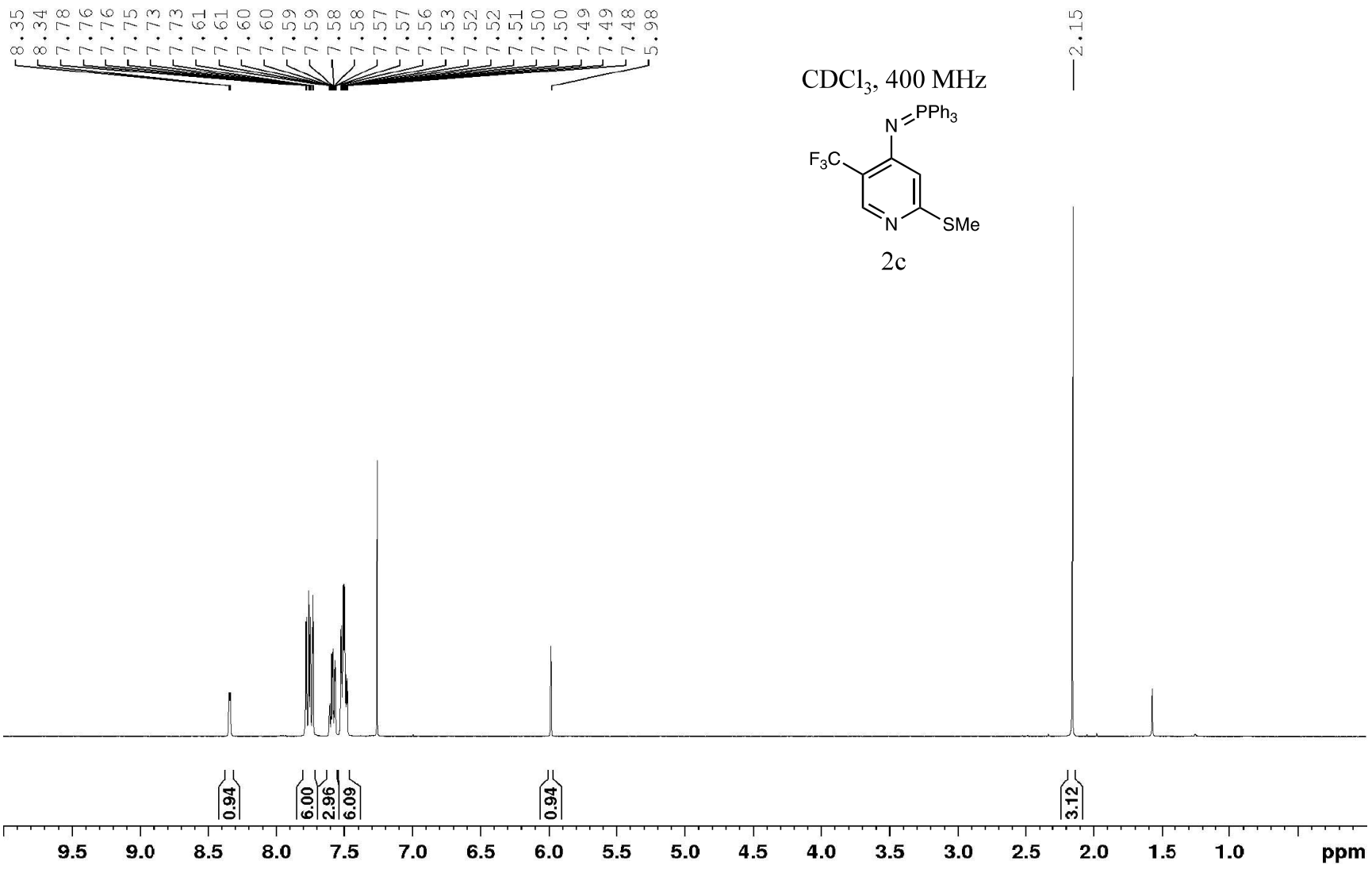

164.45
157.38
147.22
147.20
147.16
147.14
147.10
147.08
132.49
132.39
132.23
132.20
132.12
129.88
129.11
128.98
128.87
128.75
126.70
124.00
118.06
117.82
117.79
117.55
115.11
114.99
77.32
77.20
77.00
76.68
37.56
31.18
21.97
13.79
CDCl3, 100 MHz
N
PPh3
F3C
Me
2b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8
ppm

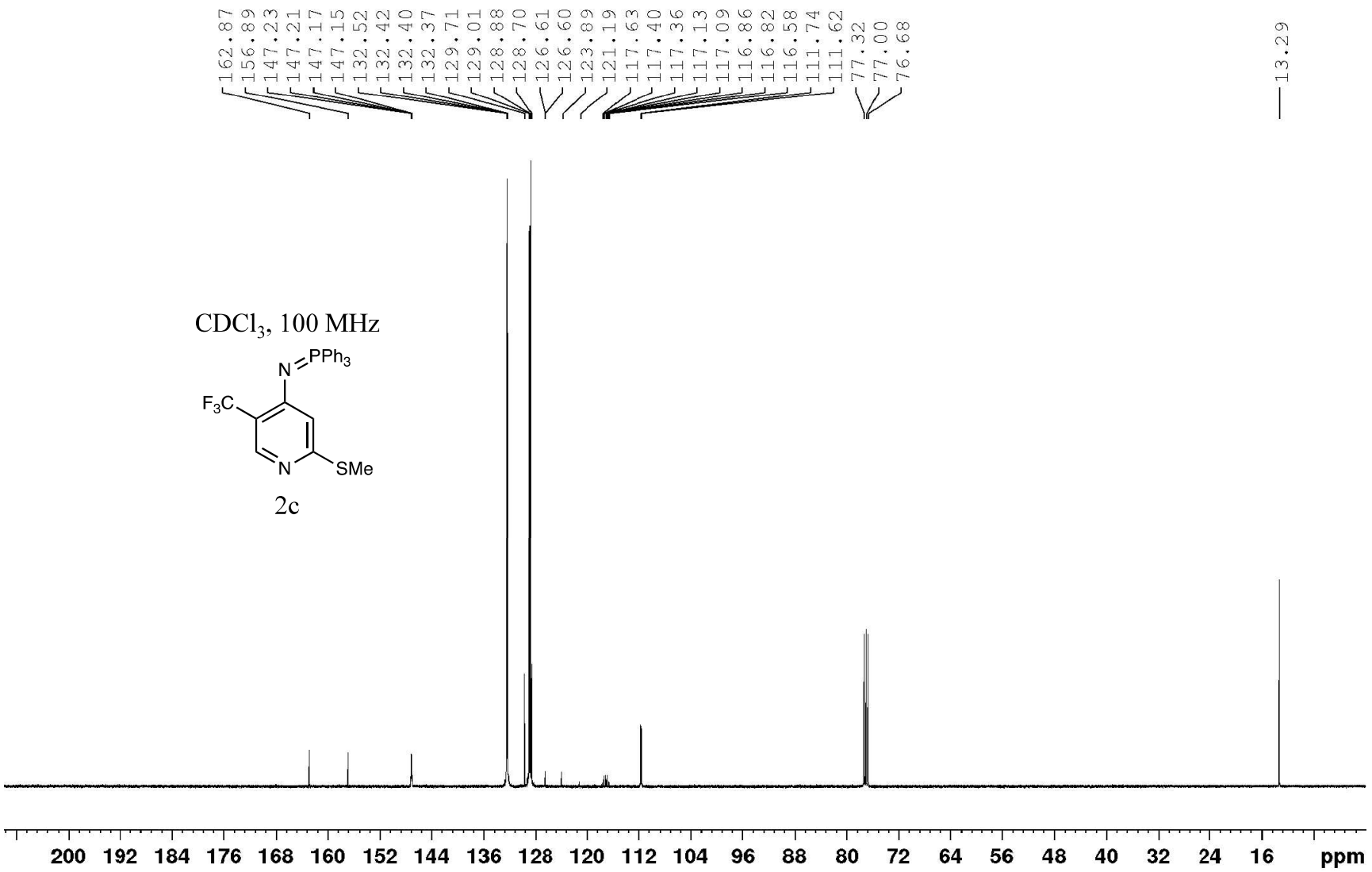
$CDCl_3$, 162 MHz

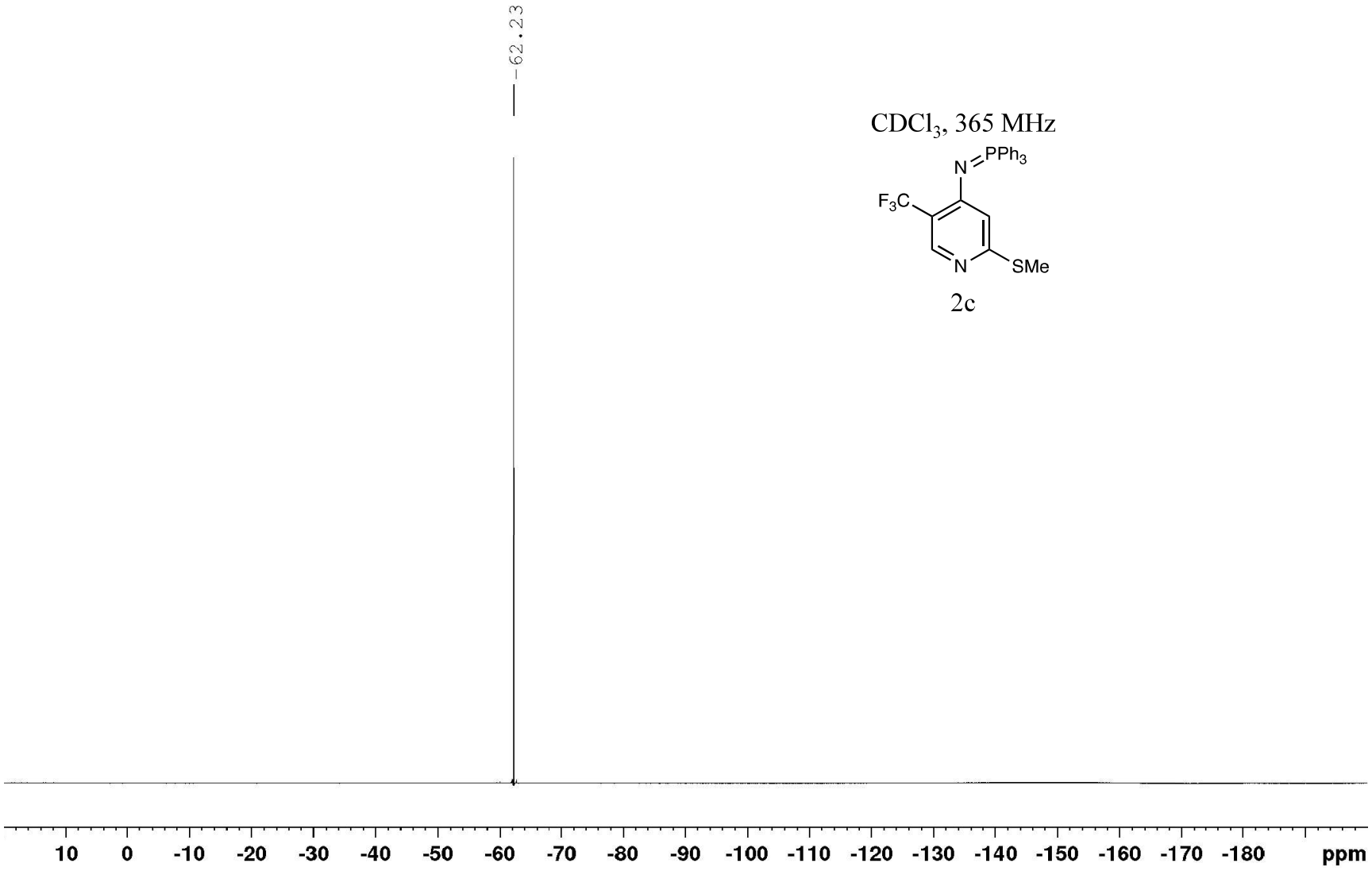


2b

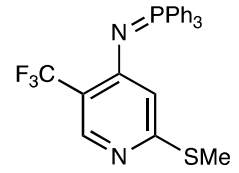

-62.27
CDCl3, 365 MHz
N
PPh3
F3C
N
Me
2b
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm


8.35
8.34
7.78
7.76
7.76
7.75
7.73
7.73
7.61
7.61
7.60
7.60
7.59
7.59
7.58
7.58
7.57
7.57
7.56
7.53
7.52
7.52
7.51
7.50
7.50
7.49
7.49
7.48
5.98
2.15
CDCl3, 400 MHz
N
PPh3
F3C
N
SMe
2c
0.94
6.00
2.96
6.09
0.94
3.12
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
ppm

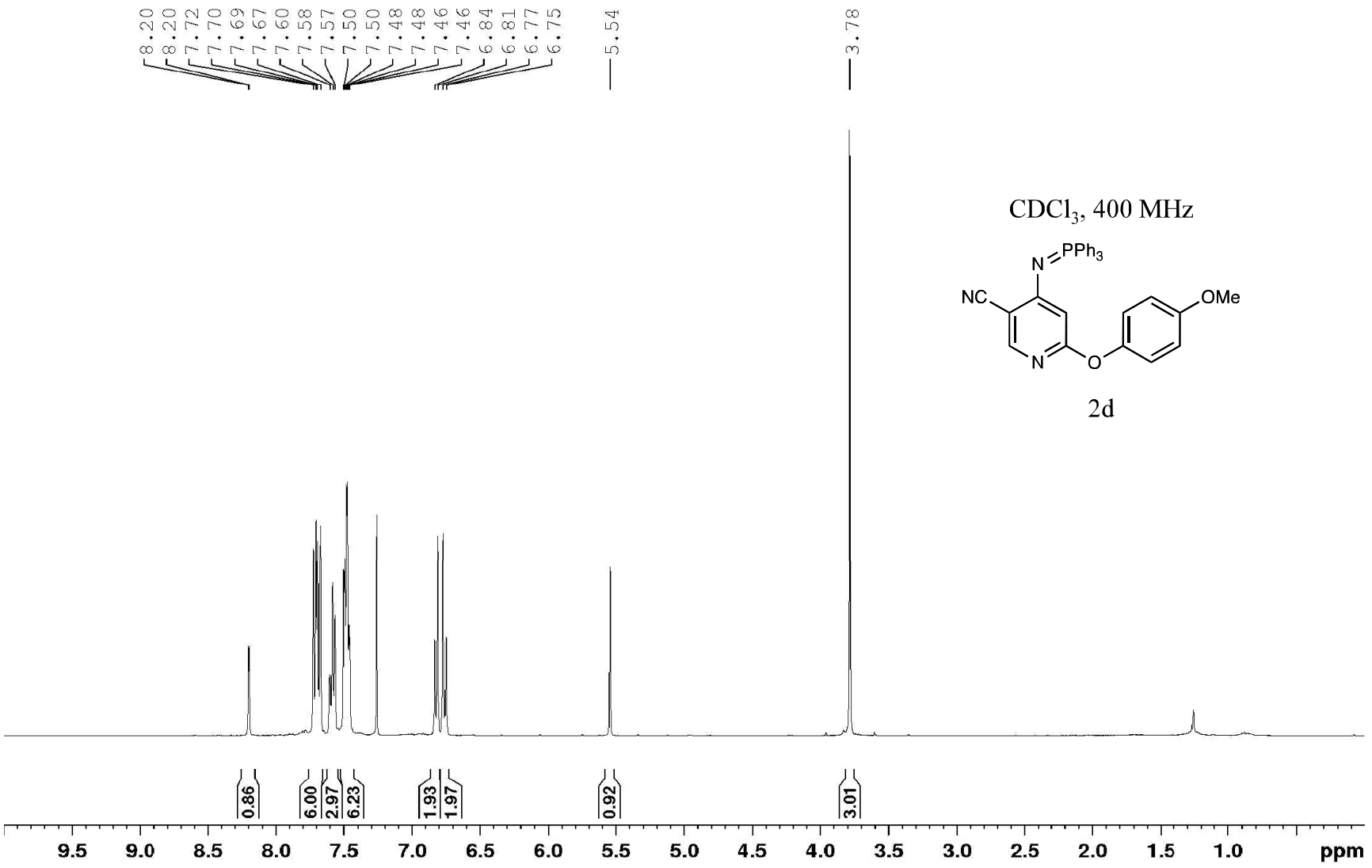

162.87
156.89
147.23
147.21
147.17
147.15
132.52
132.42
132.40
132.37
129.71
129.01
128.88
128.70
126.61
126.60
123.89
121.19
117.63
117.40
117.36
117.13
117.09
116.86
116.82
116.58
111.74
111.62
77.32
77.00
76.68
13.29
CDCl3, 100 MHz
N=PPh3
F3C
N
SMe
2c
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

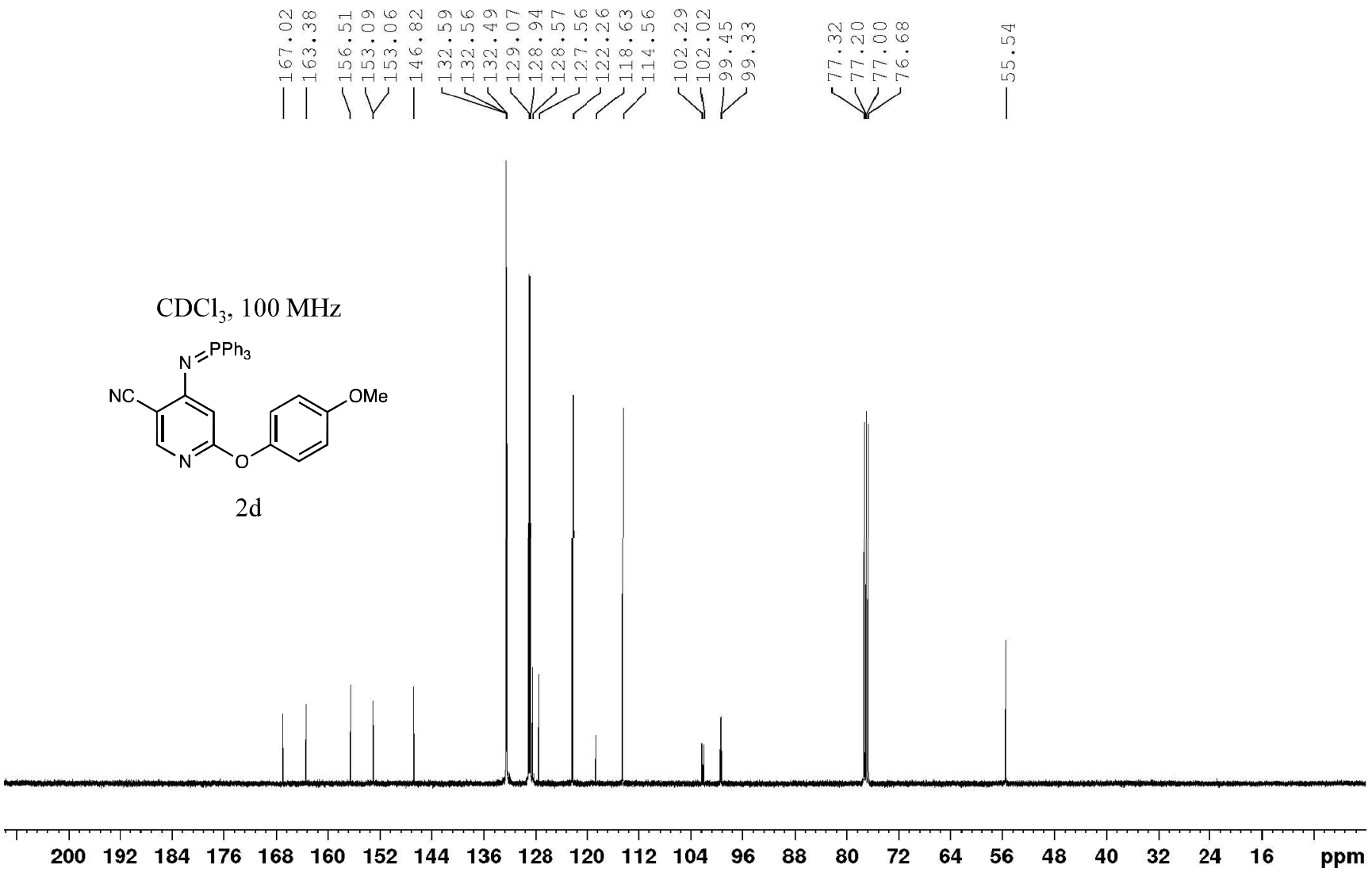

-62.23
CDCl3, 365 MHz
N
PPh3
F3C
N
SMe
2c
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

$CDCl_3$, 162 MHz

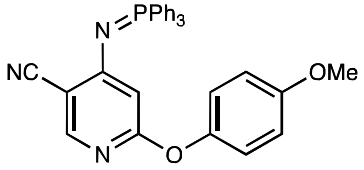


2c

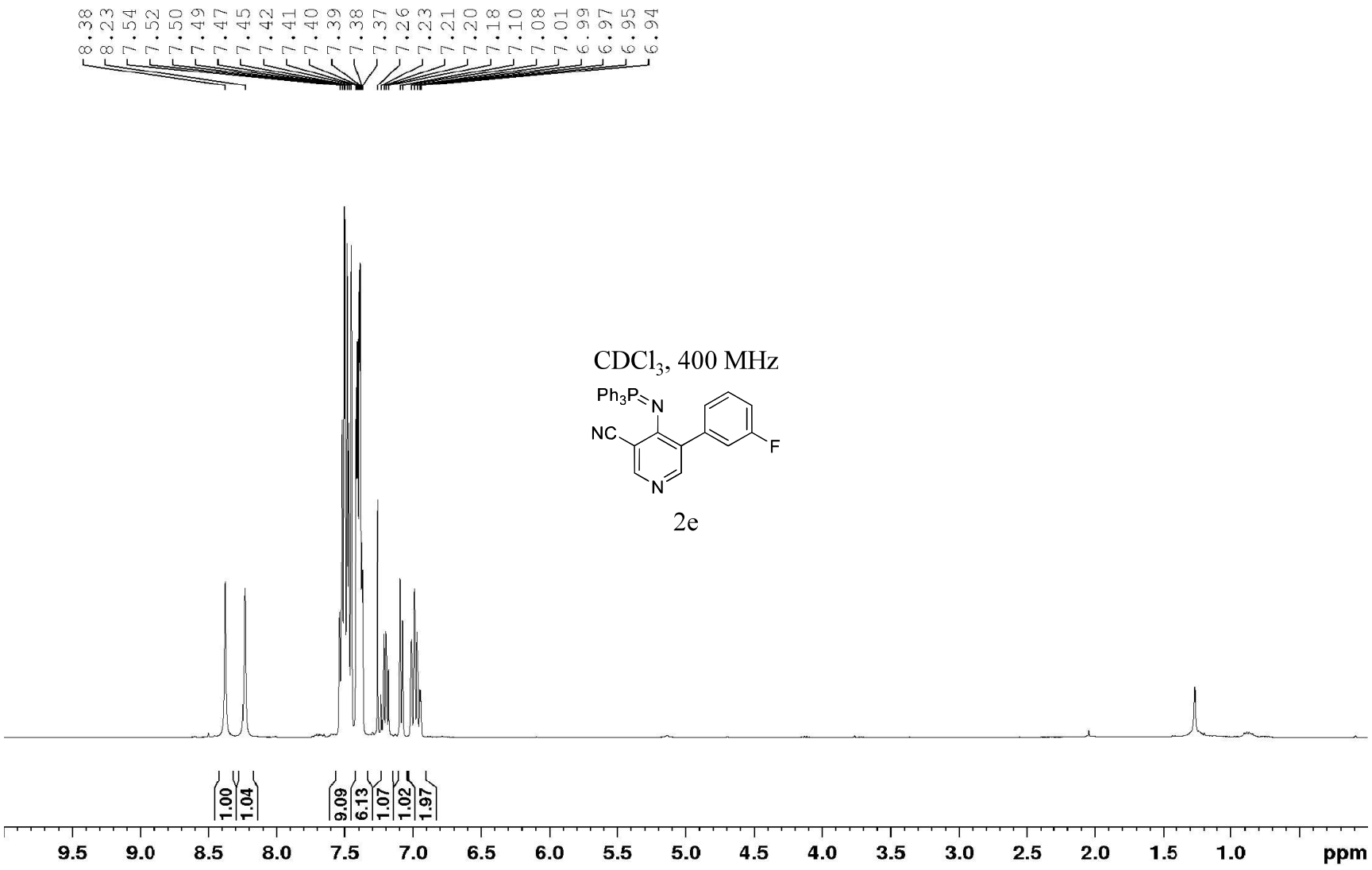

8.20
8.20
7.72
7.70
7.69
7.67
7.60
7.58
7.57
7.50
7.50
7.48
7.48
7.46
7.46
6.84
6.81
6.77
6.75
5.54
3.78
CDCl3, 400 MHz
N=PPh3
NC
OMe
N
O
2d
0.86
6.00
2.97
6.23
1.93
1.97
0.92
3.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


167.02
163.38
156.51
153.09
153.06
146.82
132.59
132.56
132.49
129.07
128.94
128.57
127.56
122.26
118.63
114.56
102.29
102.02
99.45
99.33
77.32
77.20
77.00
76.68
55.54
CDCl3, 100 MHz
N=PPh3
NC
OMe
N
O
2d
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

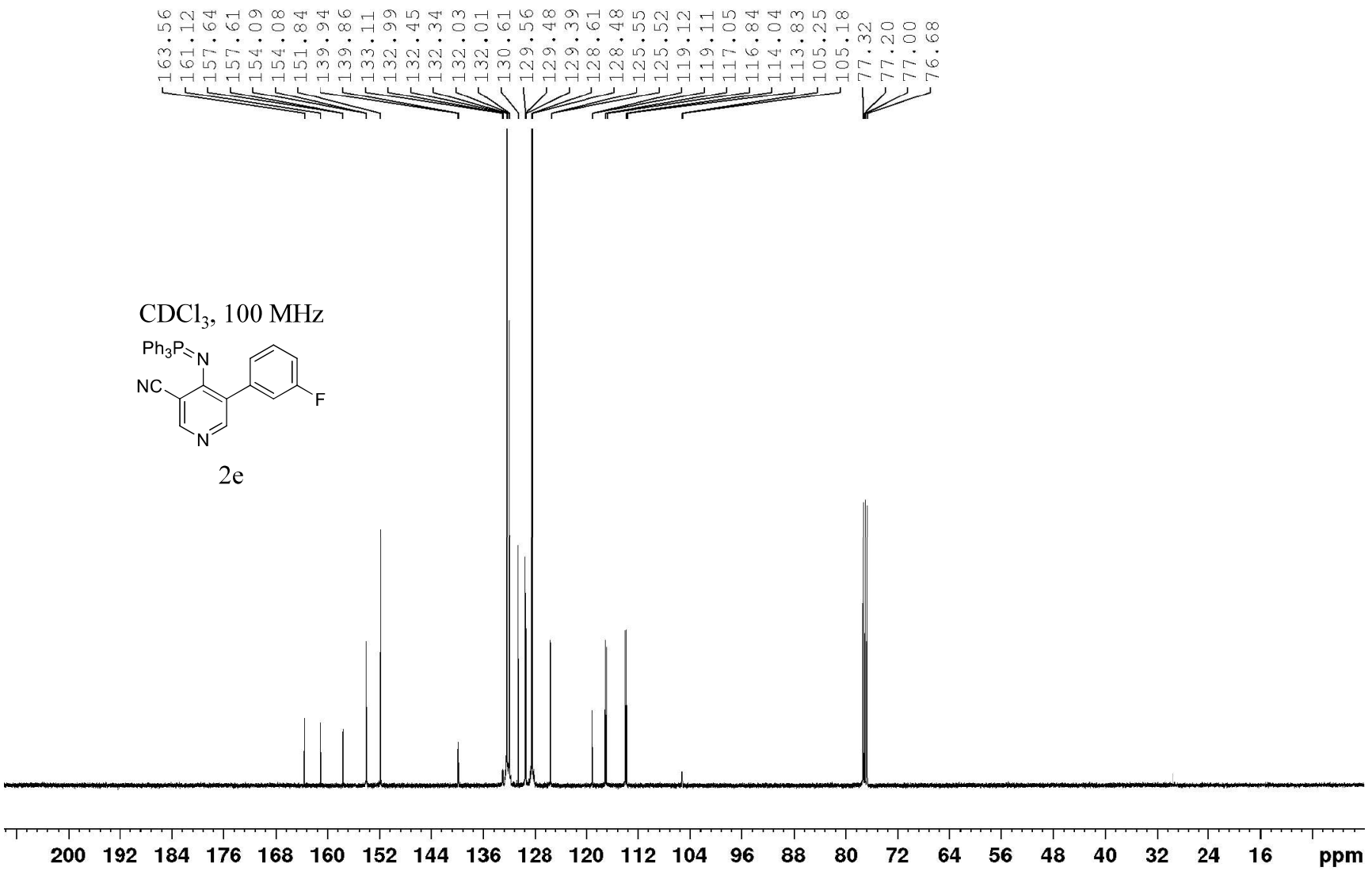
$CDCl_3$, 162 MHz

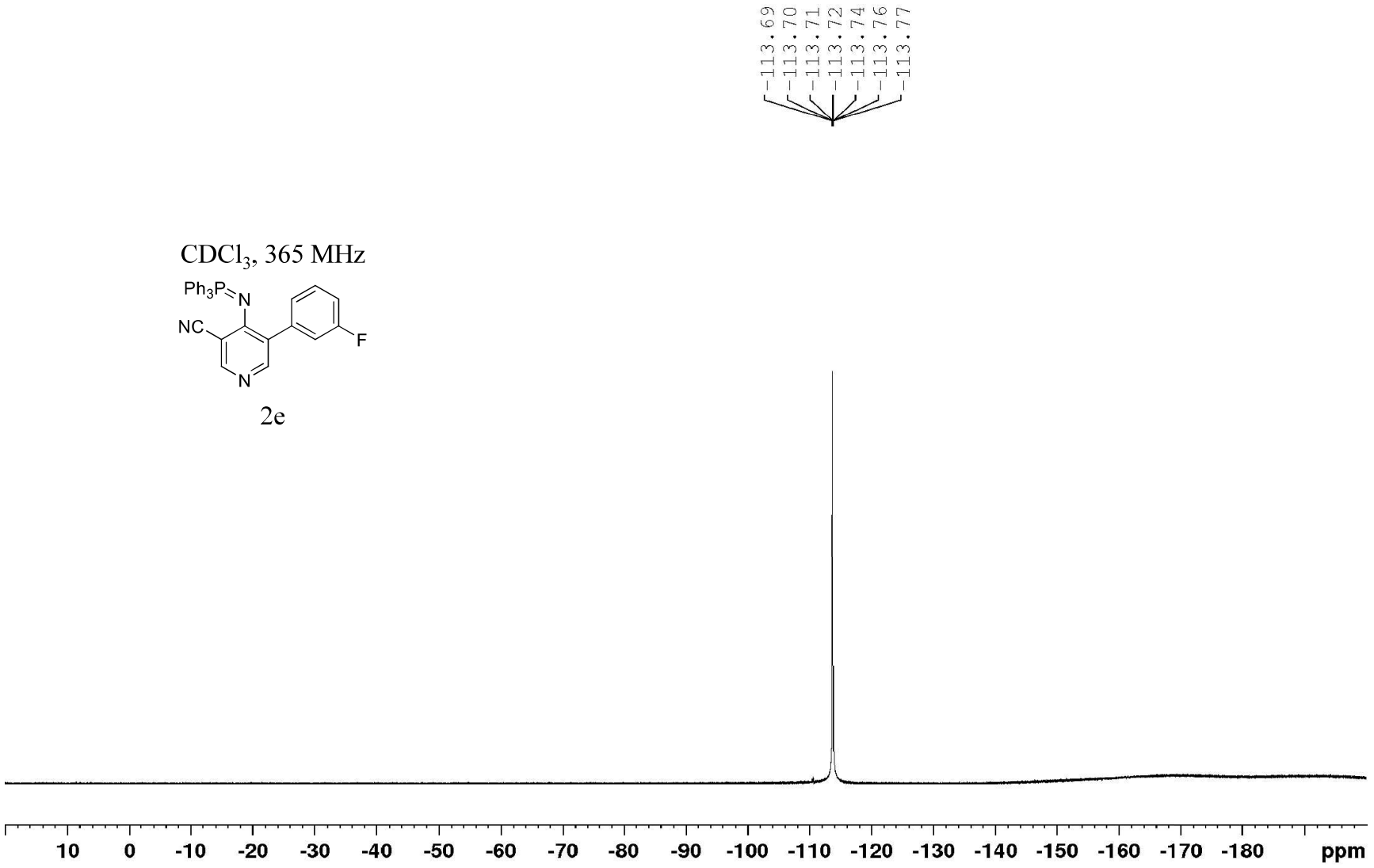


2d

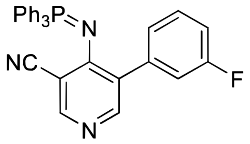

8.38
8.23
7.54
7.52
7.50
7.49
7.47
7.45
7.42
7.41
7.40
7.39
7.38
7.37
7.26
7.23
7.21
7.20
7.18
7.10
7.08
7.01
6.99
6.97
6.95
6.94
CDCl3, 400 MHz
Ph3P=N
NC
F
N
1.00
1.04
9.09
6.13
1.07
1.02
1.97
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

2e

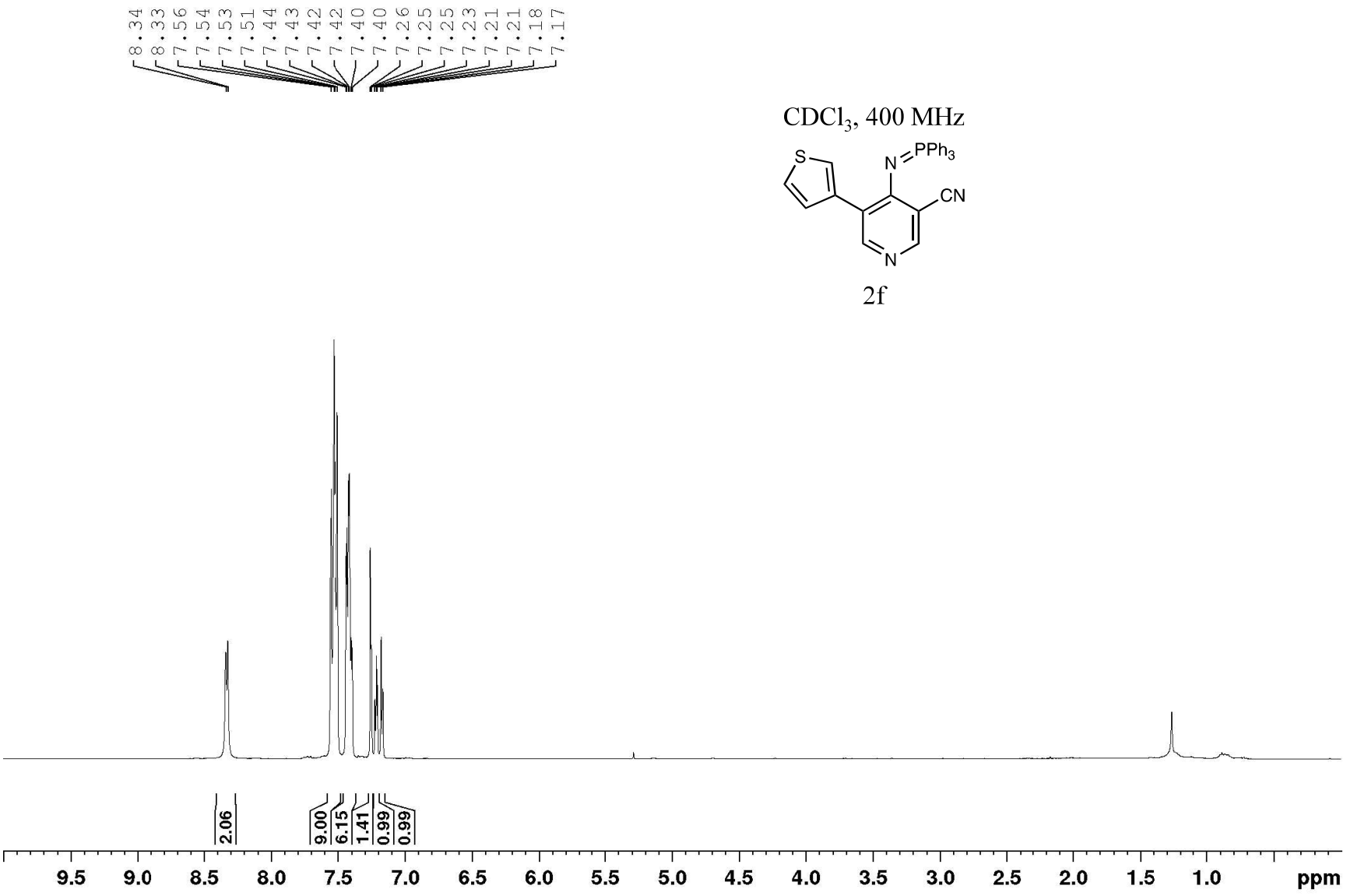

163.56
161.12
157.64
157.61
154.09
154.08
151.84
139.94
139.86
133.11
132.99
132.45
132.34
132.03
132.01
130.61
129.56
129.48
129.39
128.61
128.48
125.55
125.52
119.12
119.11
117.05
116.84
114.04
113.83
105.25
105.18
77.32
77.20
77.00
76.68
CDCl3, 100 MHz
Ph3P=N
NC
F
N
2e
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

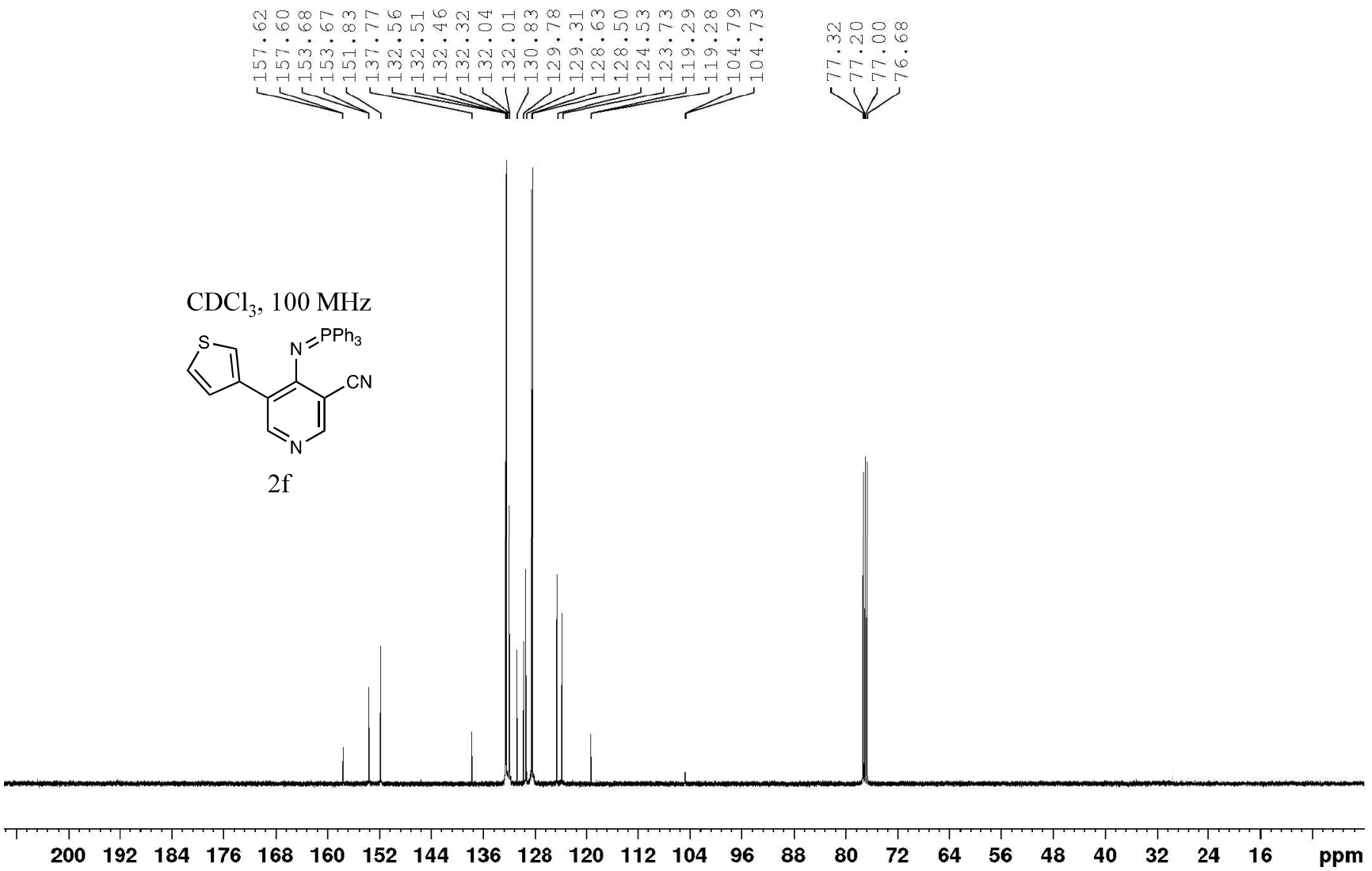

-113.69
-113.70
-113.71
-113.72
-113.74
-113.76
-113.77
CDCl3, 365 MHz
Ph3P=N
NC
F
N
2e
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

$CDCl_3$, 162 MHz

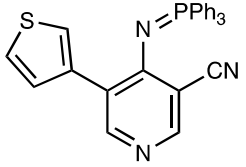


2e

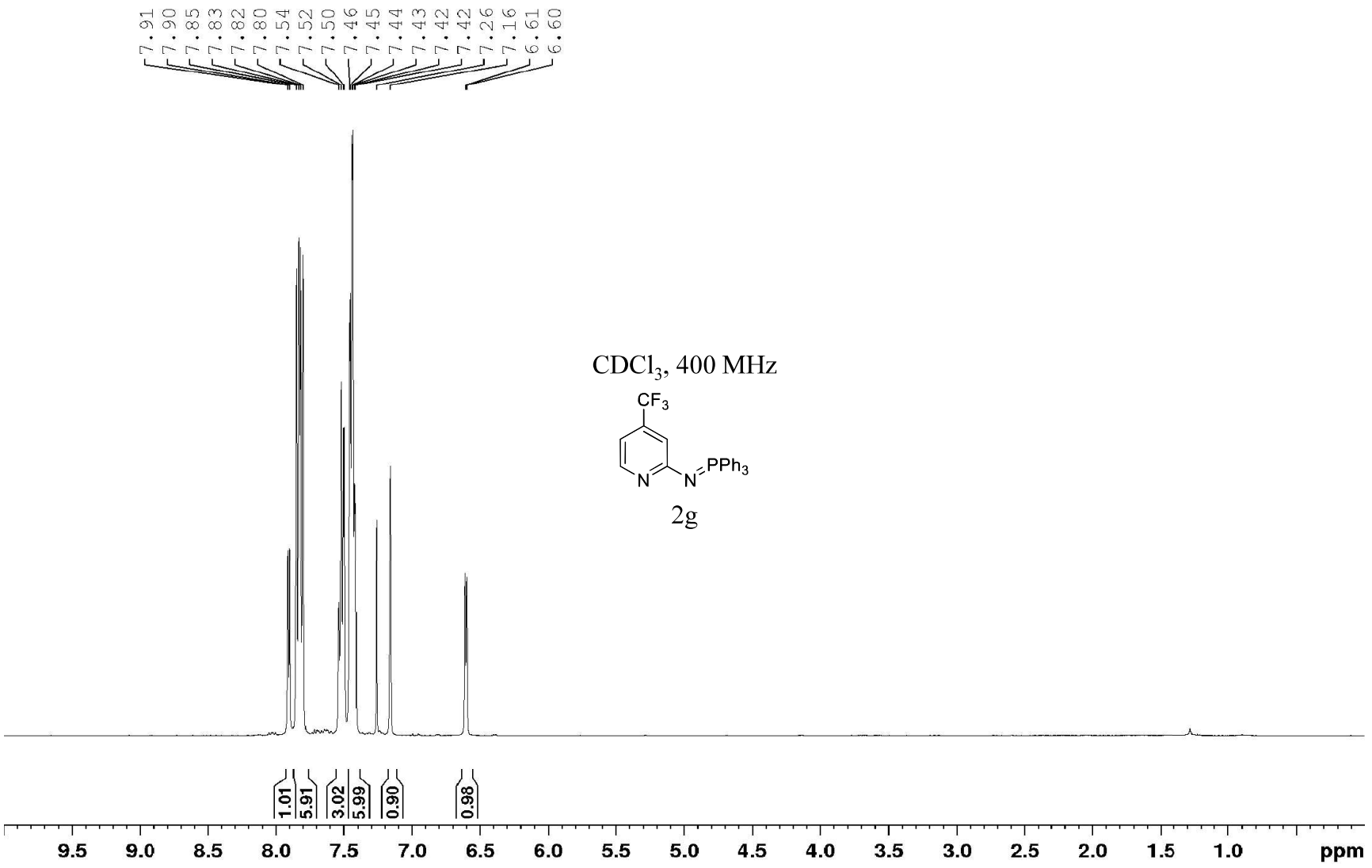

8.34
8.33
7.56
7.54
7.53
7.51
7.44
7.43
7.42
7.42
7.40
7.40
7.26
7.25
7.25
7.23
7.21
7.21
7.18
7.17
CDCl3, 400 MHz
S
N=PPh3
CN
N
2f
2.06
9.00
6.15
1.41
0.99
0.99
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

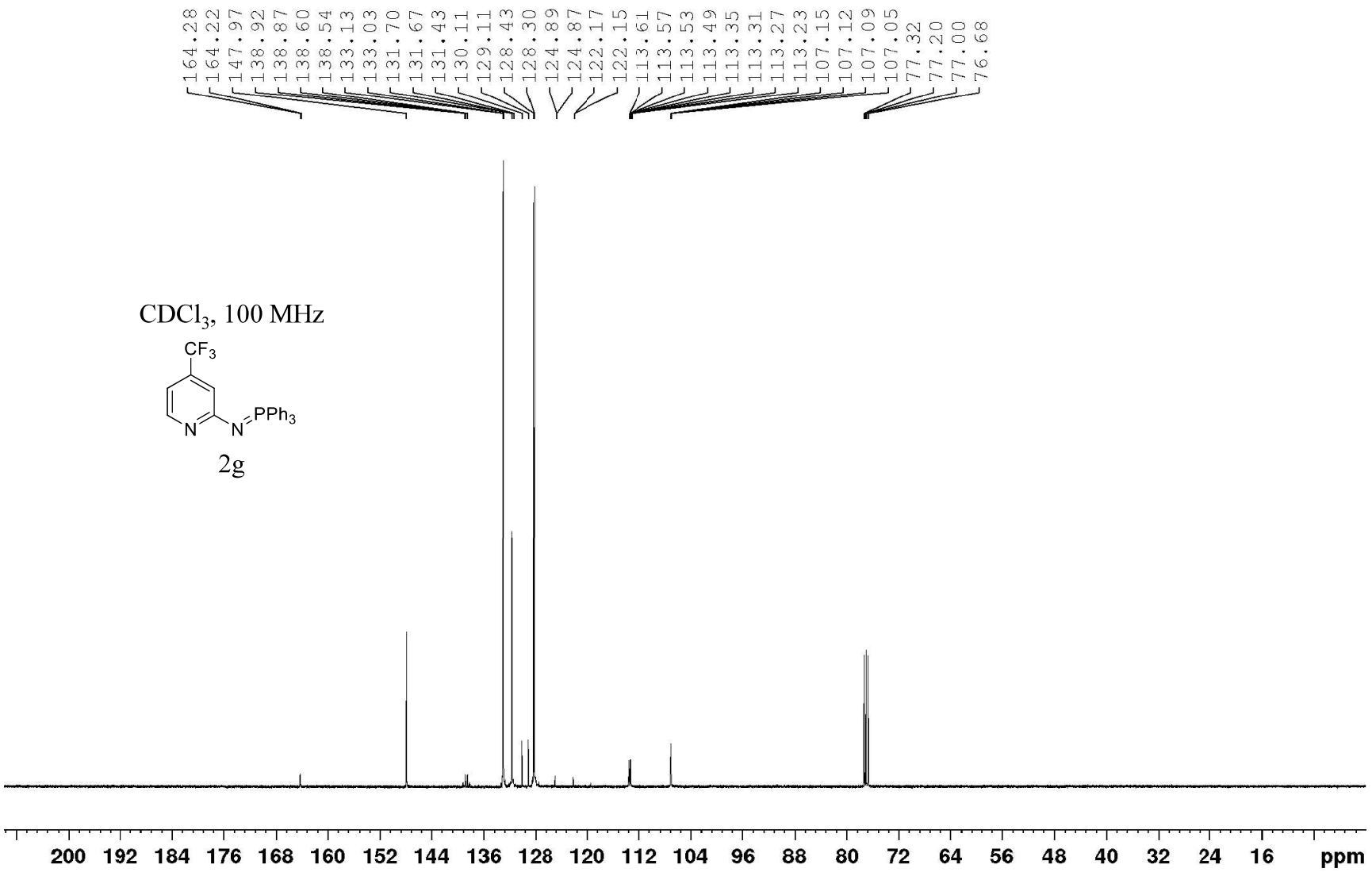

157.62
157.60
153.68
153.67
151.83
137.77
132.56
132.51
132.46
132.32
132.04
132.01
130.83
129.78
129.31
128.63
128.50
124.53
123.73
119.29
119.28
104.79
104.73
77.32
77.20
77.00
76.68
CDCl3, 100 MHz
S
N
PPh3
CN
N
2f
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

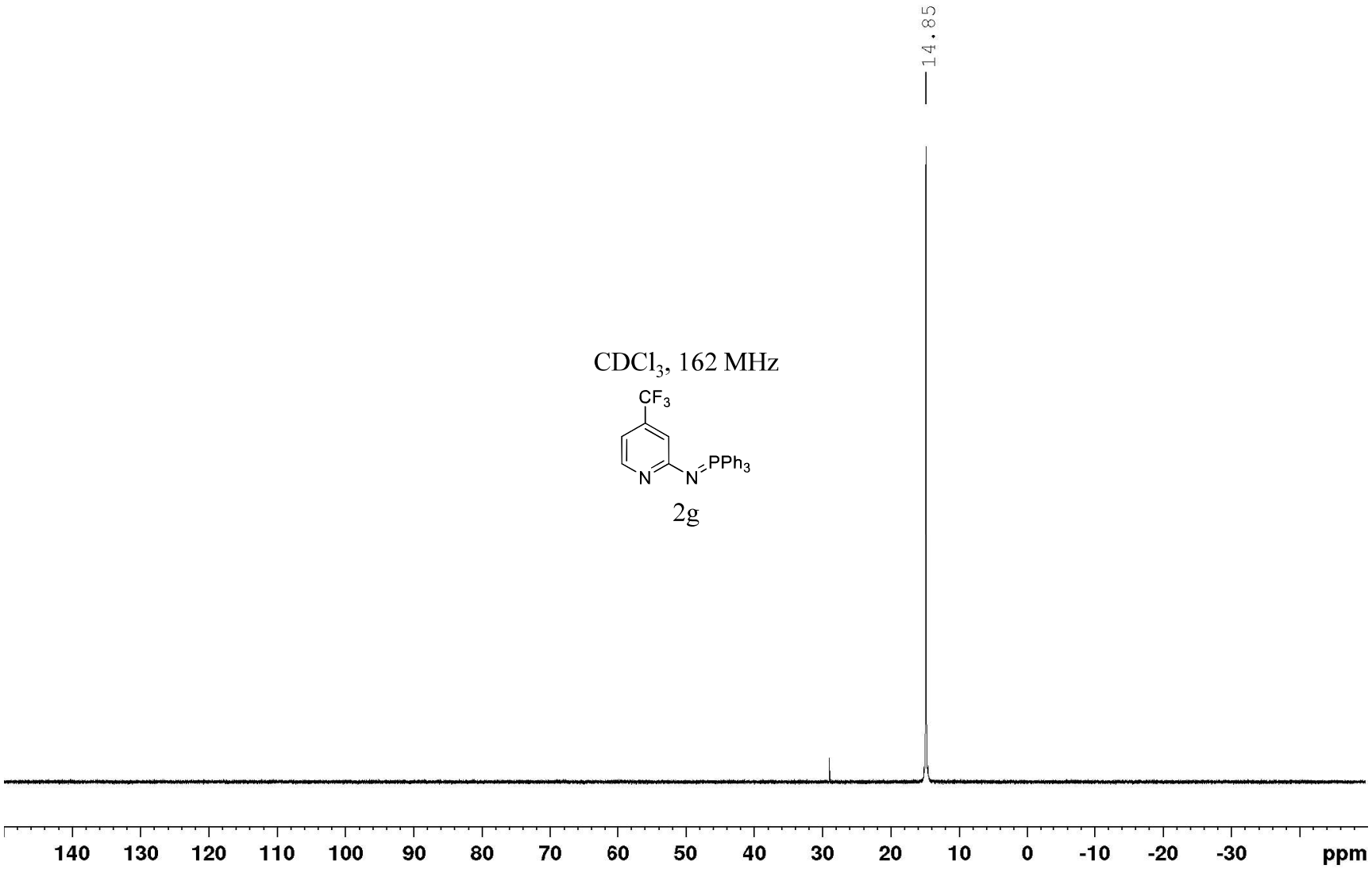
$CDCl_3$, 162 MHz

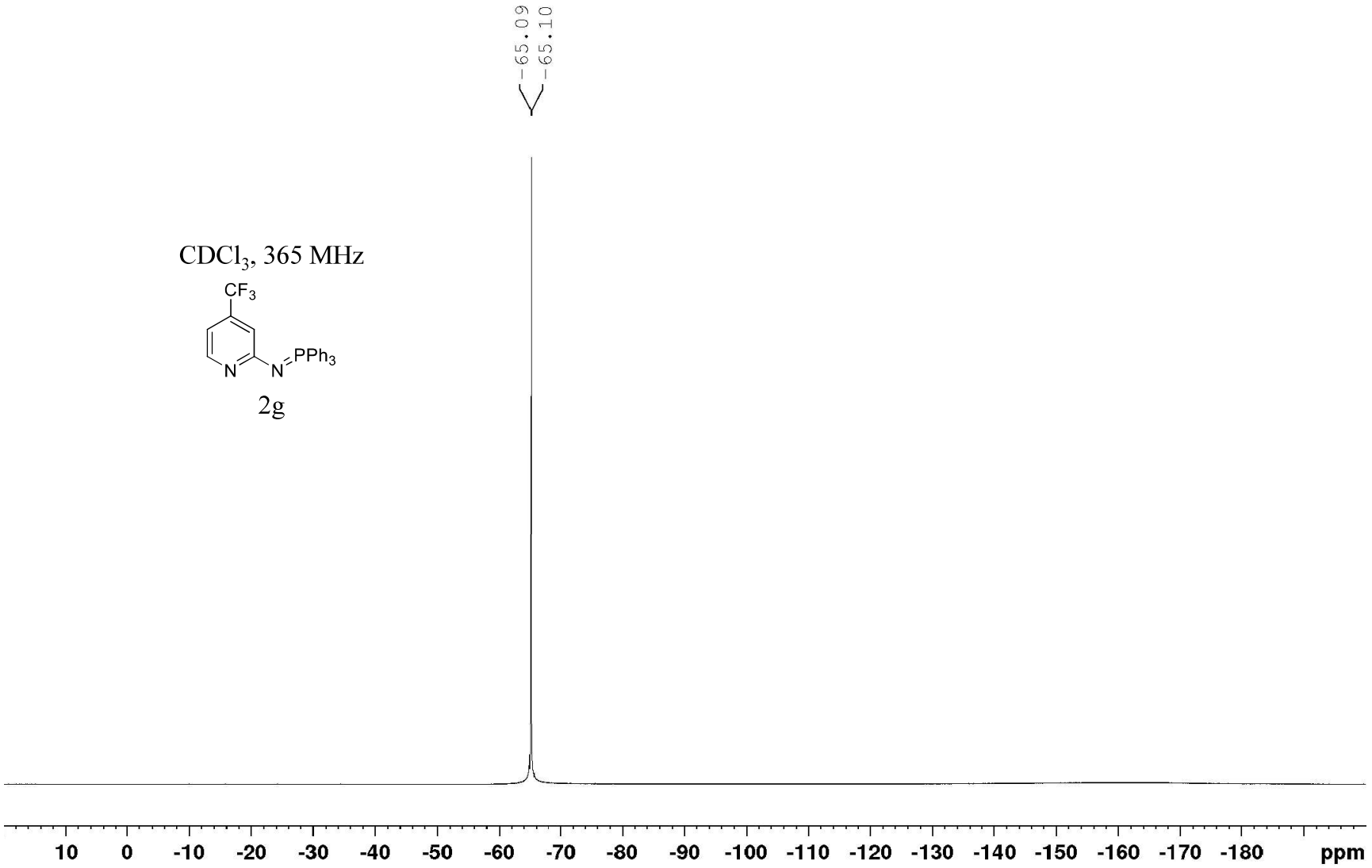


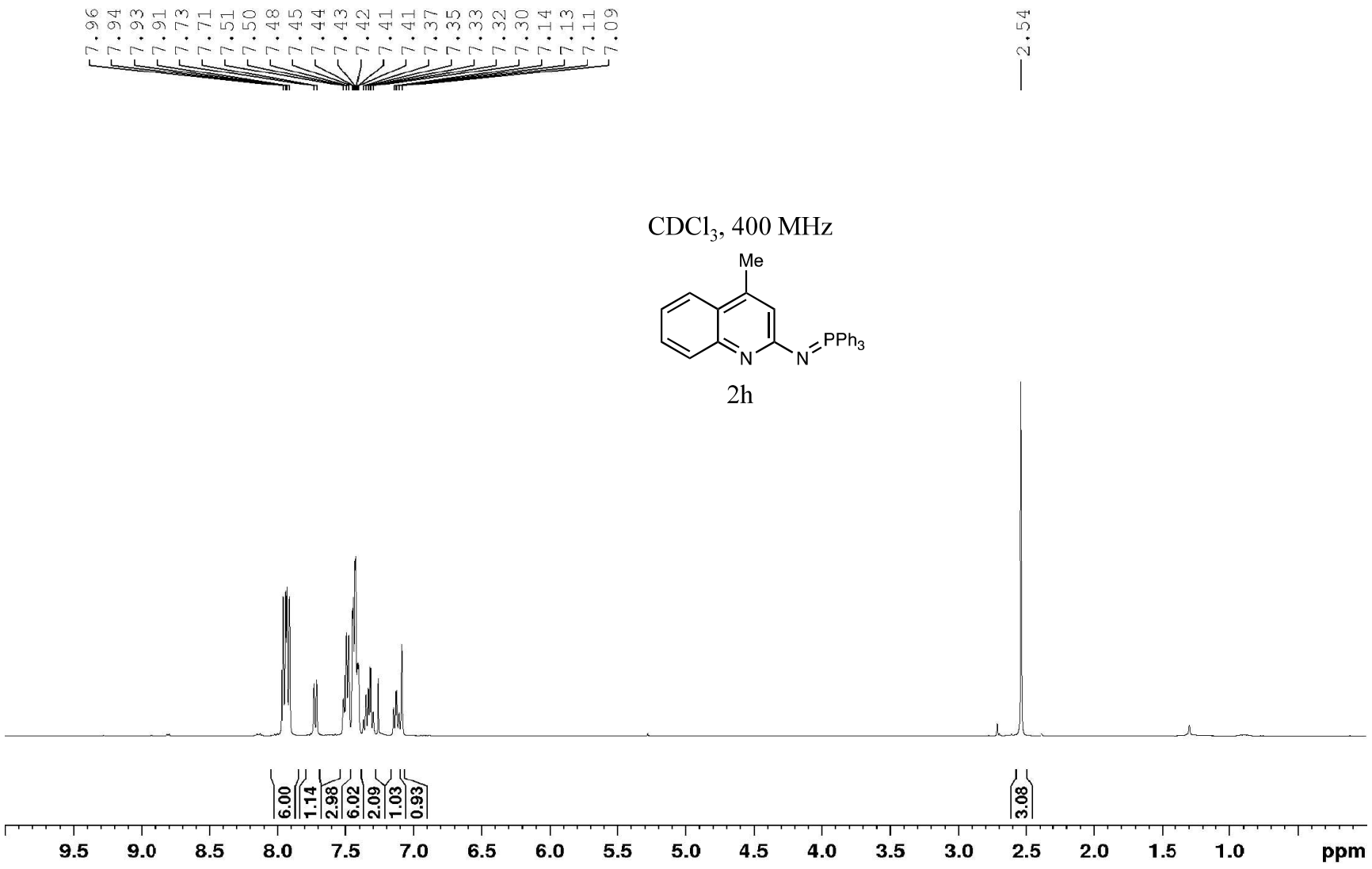
2f

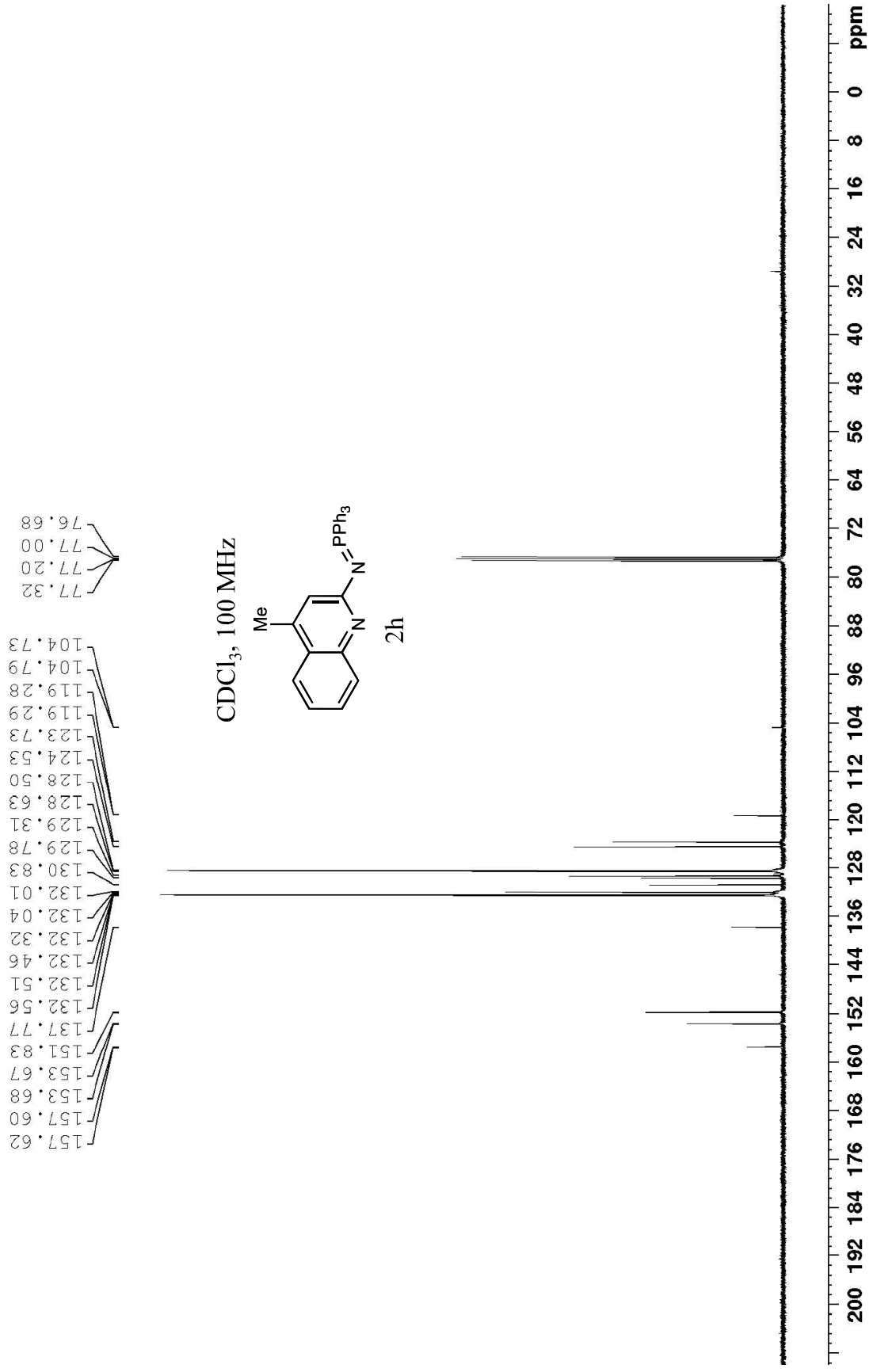

7.91
7.90
7.85
7.83
7.82
7.80
7.54
7.52
7.50
7.46
7.45
7.44
7.43
7.42
7.42
7.26
7.16
6.61
6.60
CDCl3, 400 MHz
CF3
PPh3
N
N
2g
1.01
5.91
3.02
5.99
0.90
0.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


164.28
164.22
147.97
138.92
138.87
138.60
138.54
133.13
133.03
131.70
131.67
131.43
130.11
129.11
128.43
128.30
124.89
124.87
122.17
122.15
113.61
113.57
113.53
113.49
113.35
113.31
113.27
113.23
107.15
107.12
107.09
107.05
77.32
77.20
77.00
76.68
CDCl3, 100 MHz
CF3
N
N
PPh3
2g
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

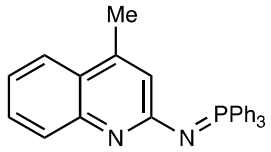

14.85
CDCl3, 162 MHz
CF3
N
N
PPh3
2g
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
ppm


-65.09
-65.10
CDCl3, 365 MHz
CF3
PPh3
N
N
2g
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

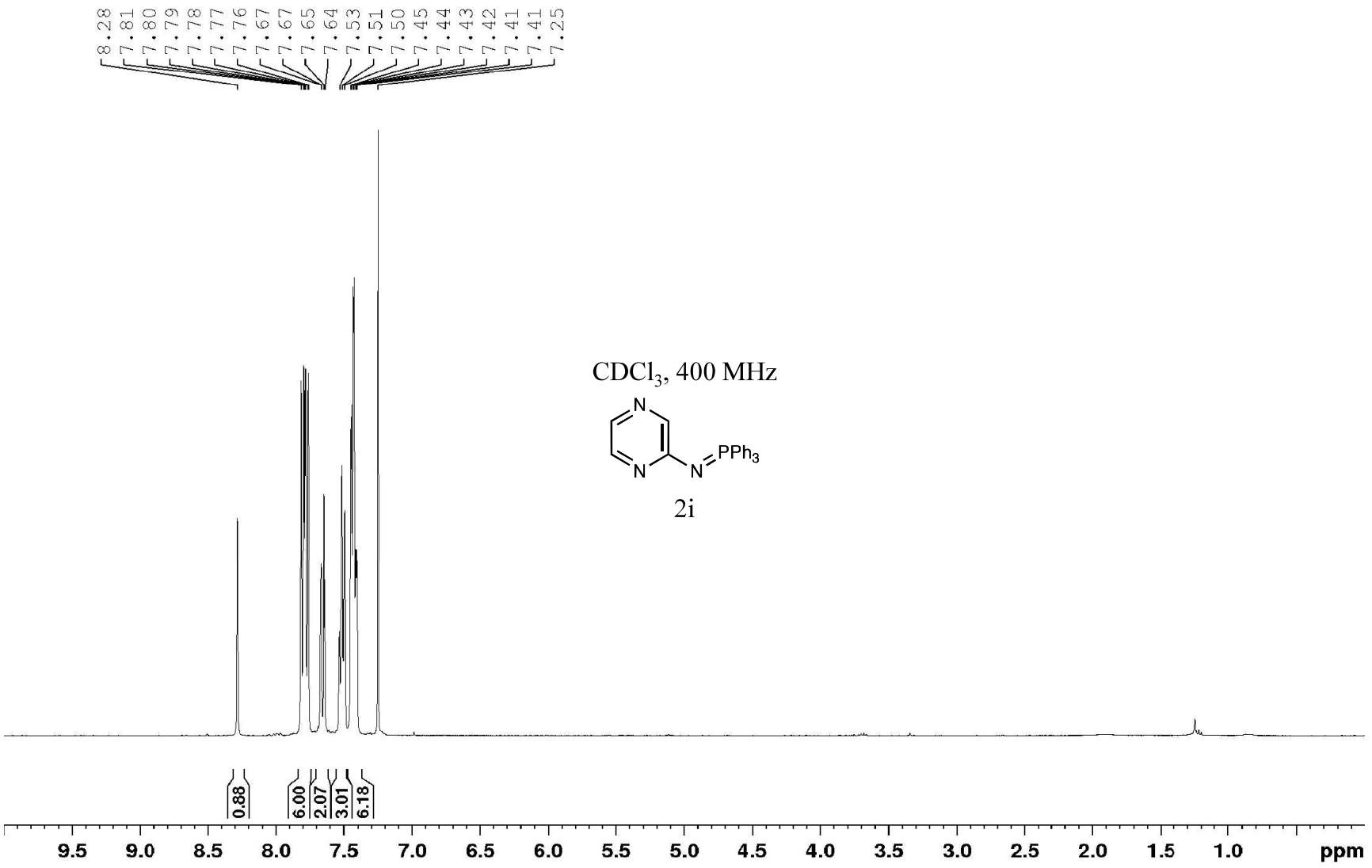

7.96
7.94
7.93
7.91
7.73
7.71
7.51
7.50
7.48
7.45
7.44
7.43
7.42
7.41
7.41
7.37
7.35
7.33
7.32
7.30
7.14
7.13
7.11
7.09
2.54
CDCl3, 400 MHz
Me
N
N
PPh3
2h
6.00
1.14
2.98
6.02
2.09
1.03
0.93
3.08
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


157.62
157.60
153.68
153.67
151.83
137.77
132.56
132.51
132.46
132.32
132.04
132.01
130.83
129.78
129.31
128.63
128.50
124.53
123.73
119.29
119.28
104.79
104.73
77.32
77.20
77.00
76.68
CDCl3, 100 MHz
Me
PPh3
N
N
2h
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 ppm

$CDCl_3$, 162 MHz

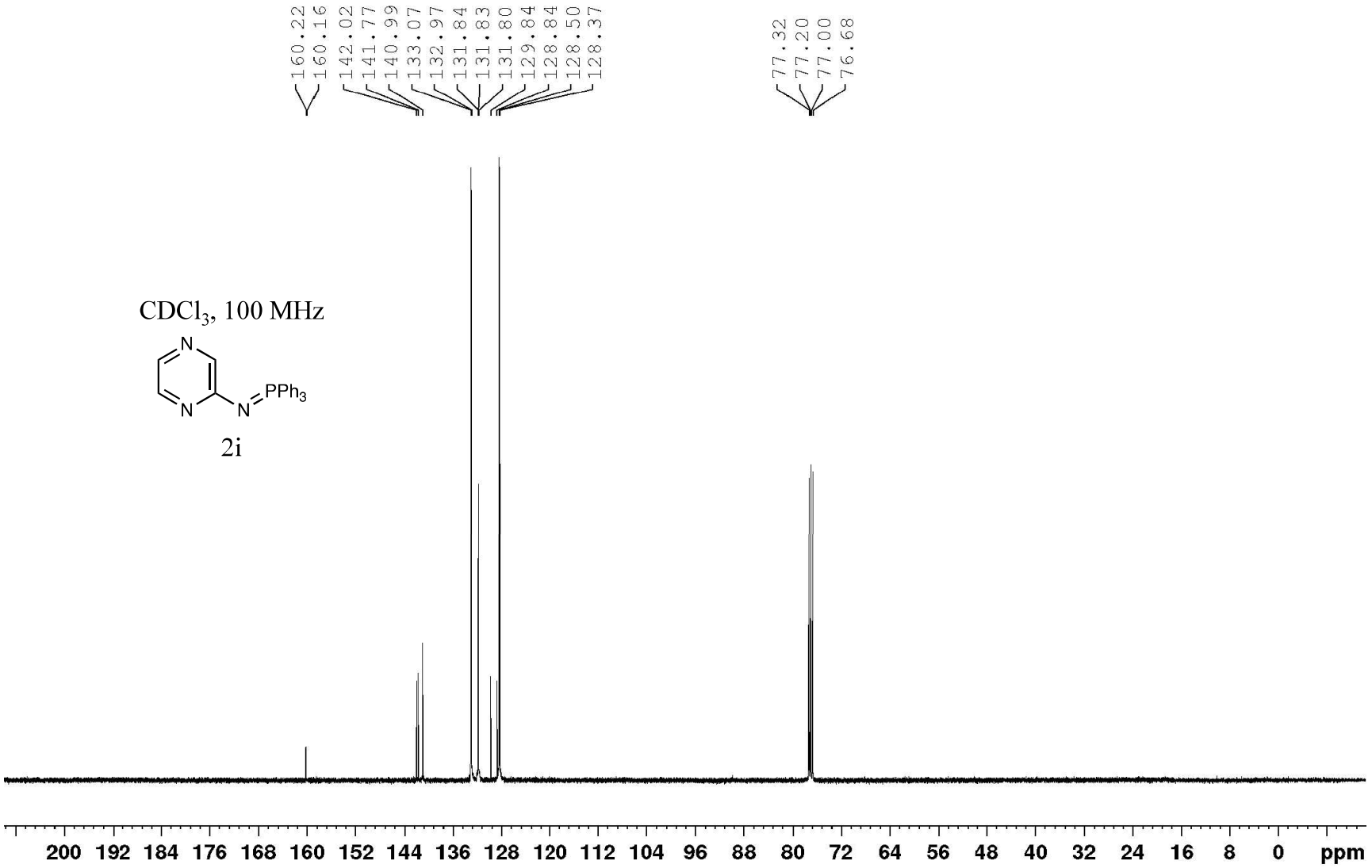


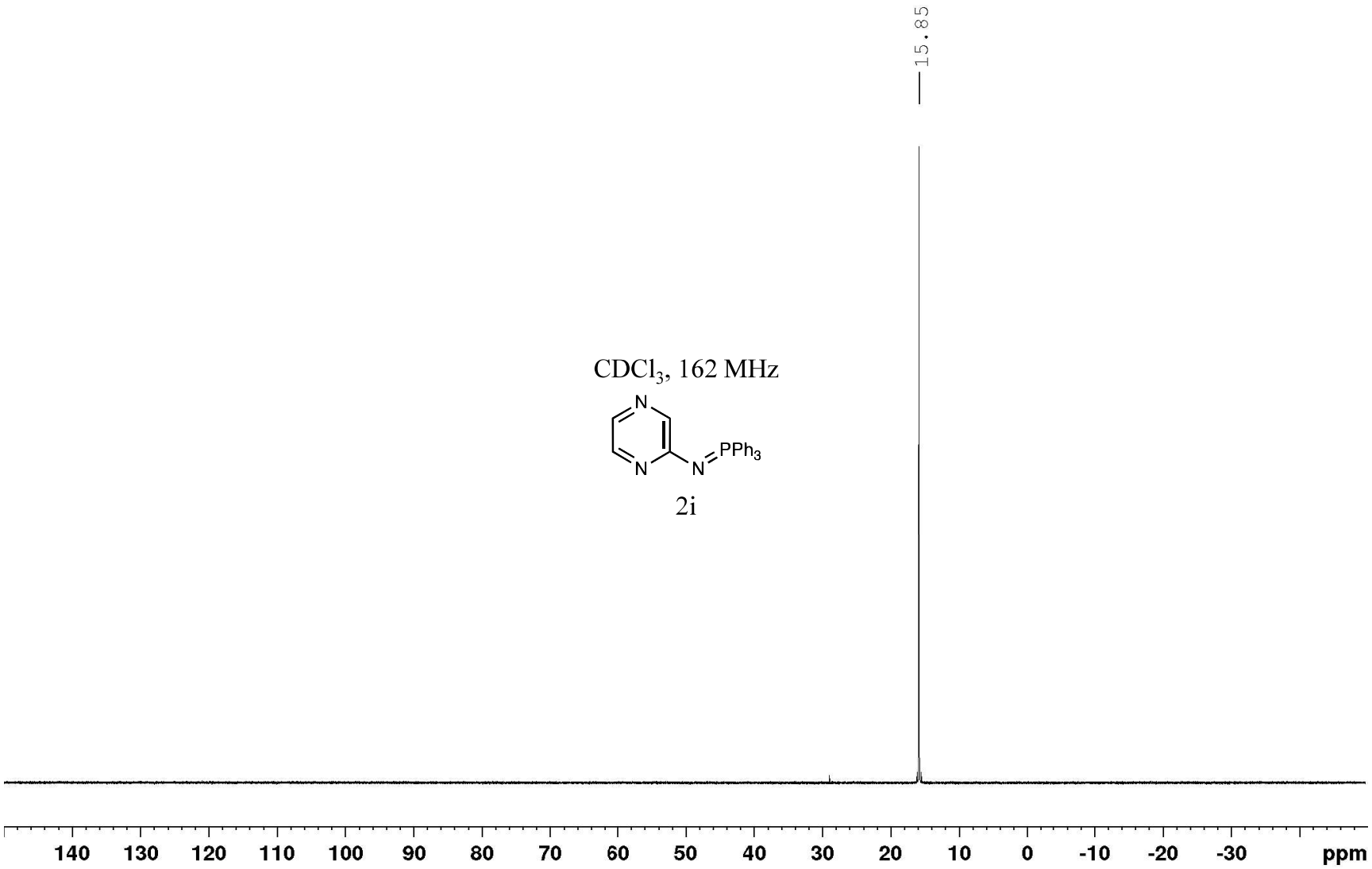
2h

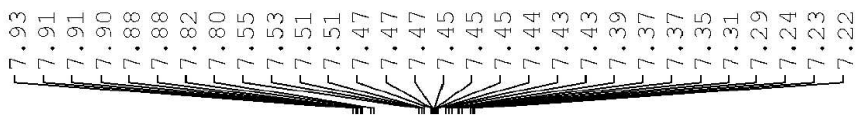


$CDCl_3$, 400 MHz

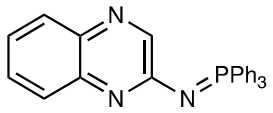
2i


160.22
160.16
142.02
141.77
140.99
133.07
132.97
131.84
131.83
131.80
129.84
128.84
128.50
128.37
77.32
77.20
77.00
76.68
CDCl3, 100 MHz
N
N
N
PPh3
2i
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 ppm

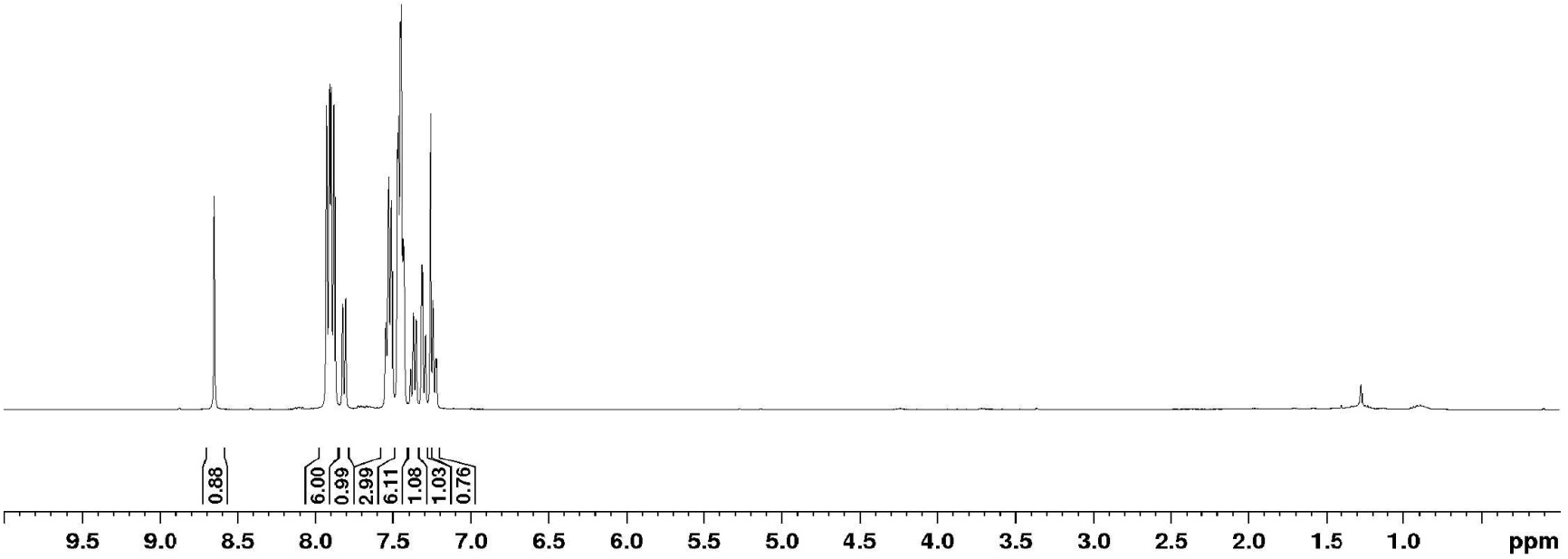

15.85
CDCl3, 162 MHz
N
N
N
PPh3
2i
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
ppm

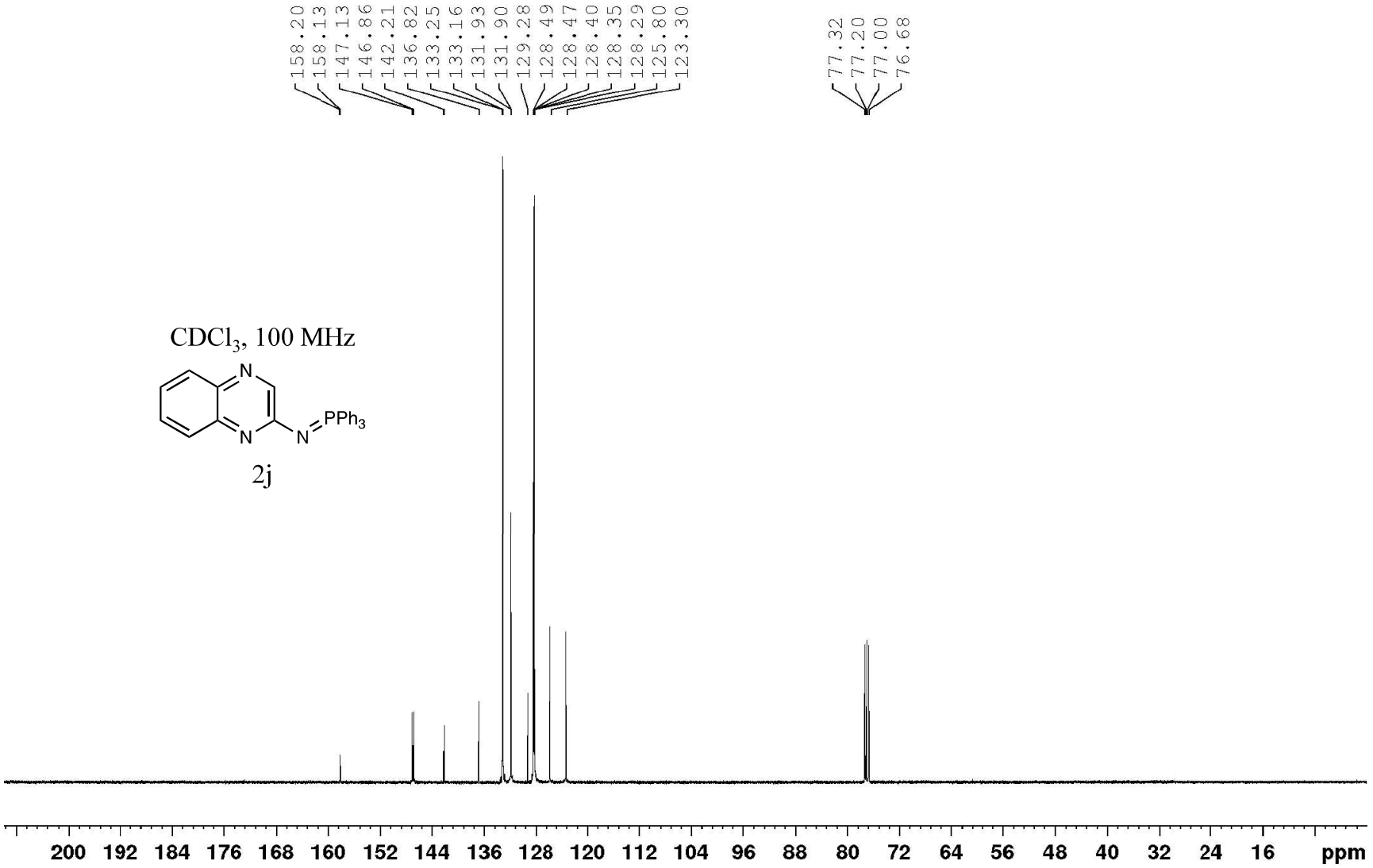


$CDCl_3$, 400 MHz

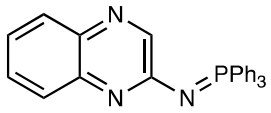


2j

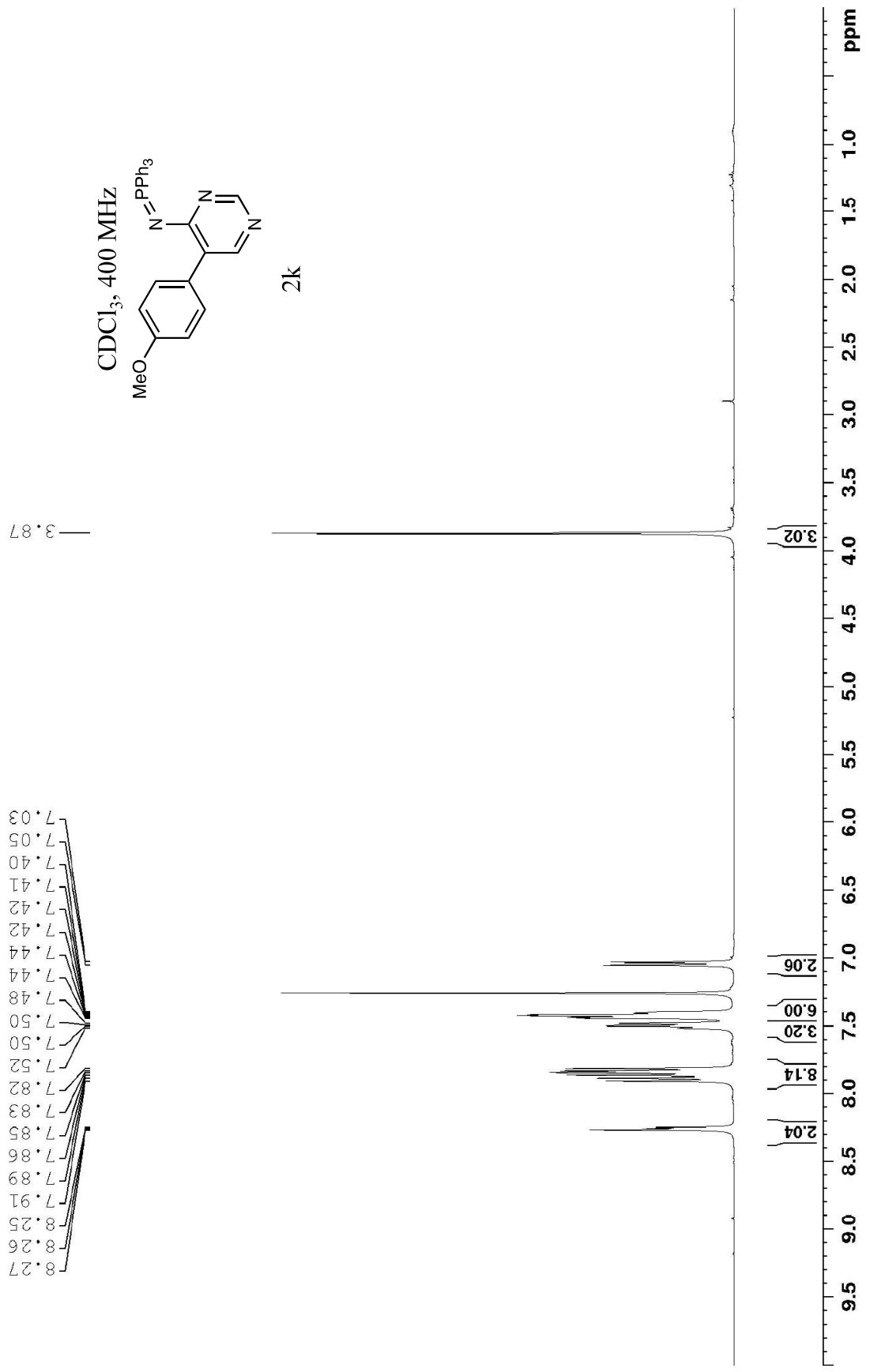


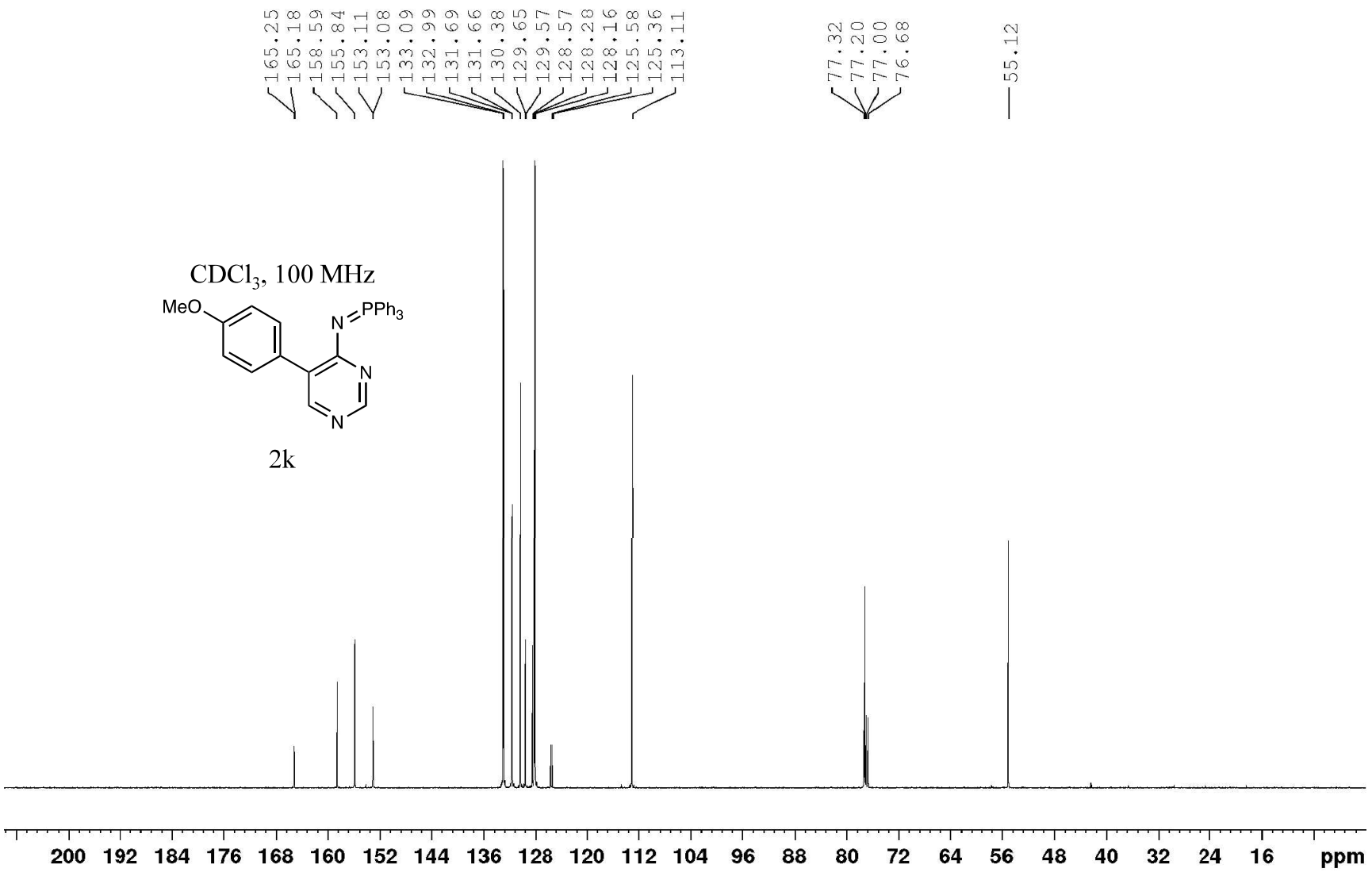

158.20
158.13
147.13
146.86
142.21
136.82
133.25
133.16
131.93
131.90
129.28
128.49
128.47
128.40
128.35
128.29
125.80
123.30
77.32
77.20
77.00
76.68
CDCl3, 100 MHz
N
N
N
PPh3
2j
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

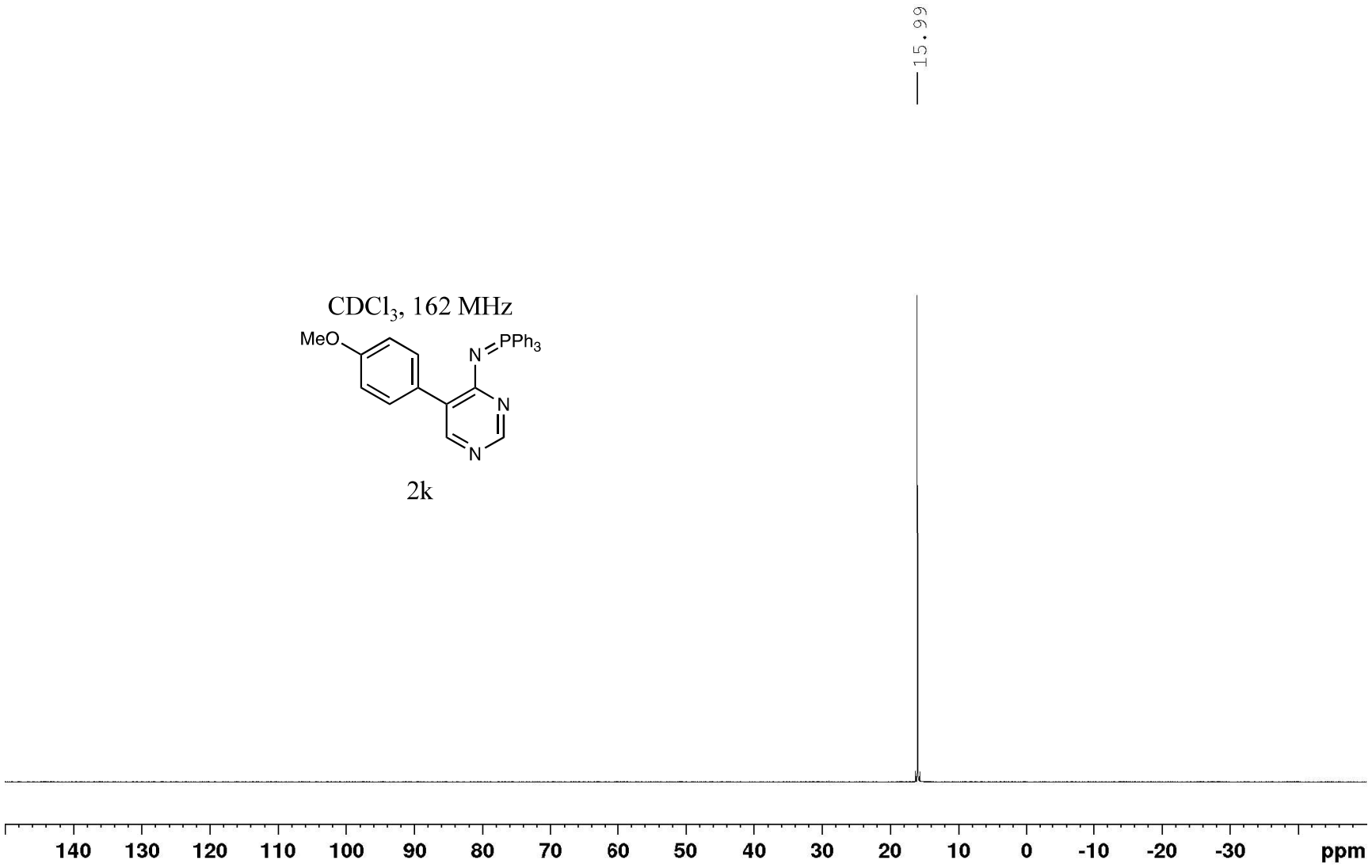
$CDCl_3$, 162 MHz

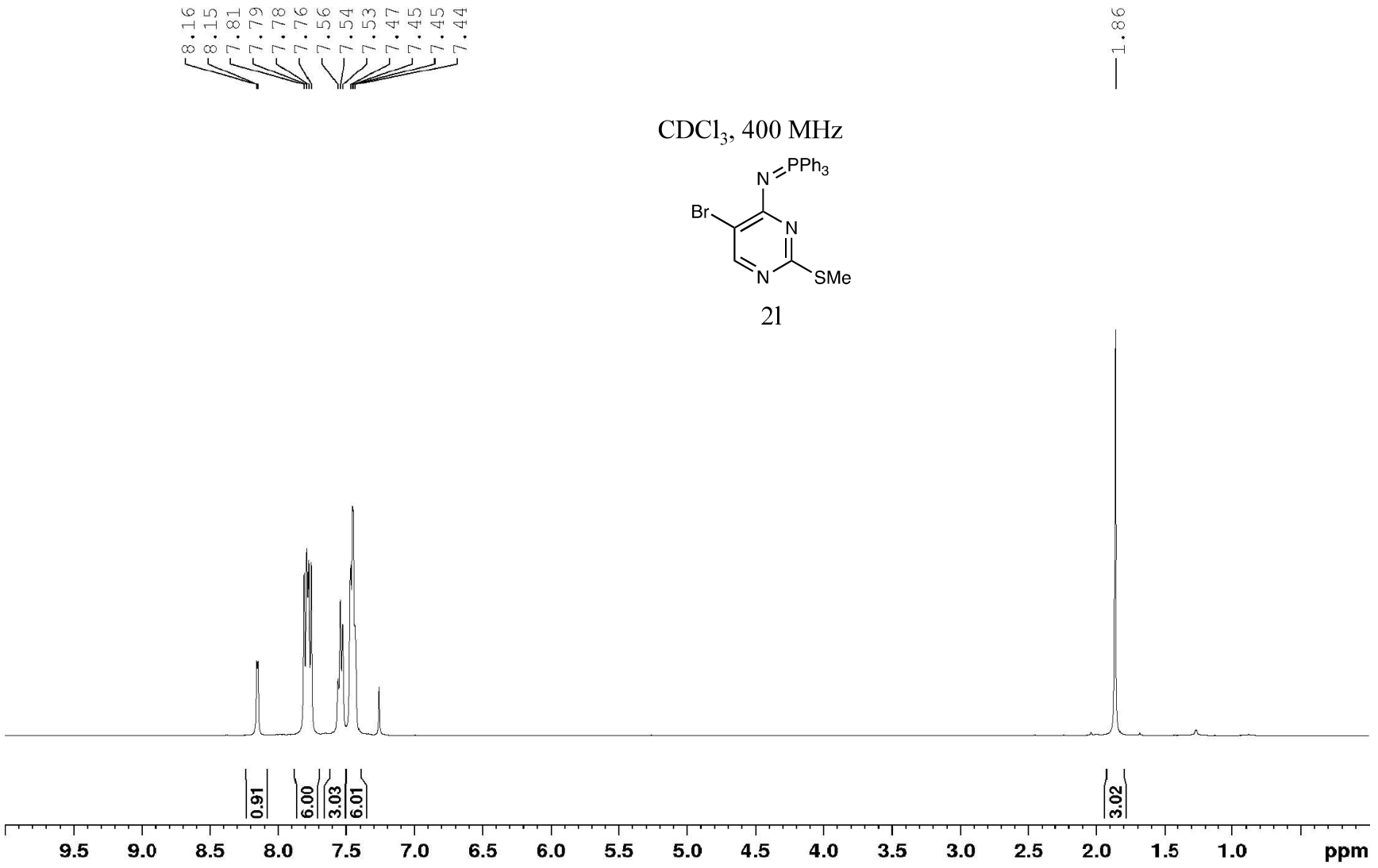


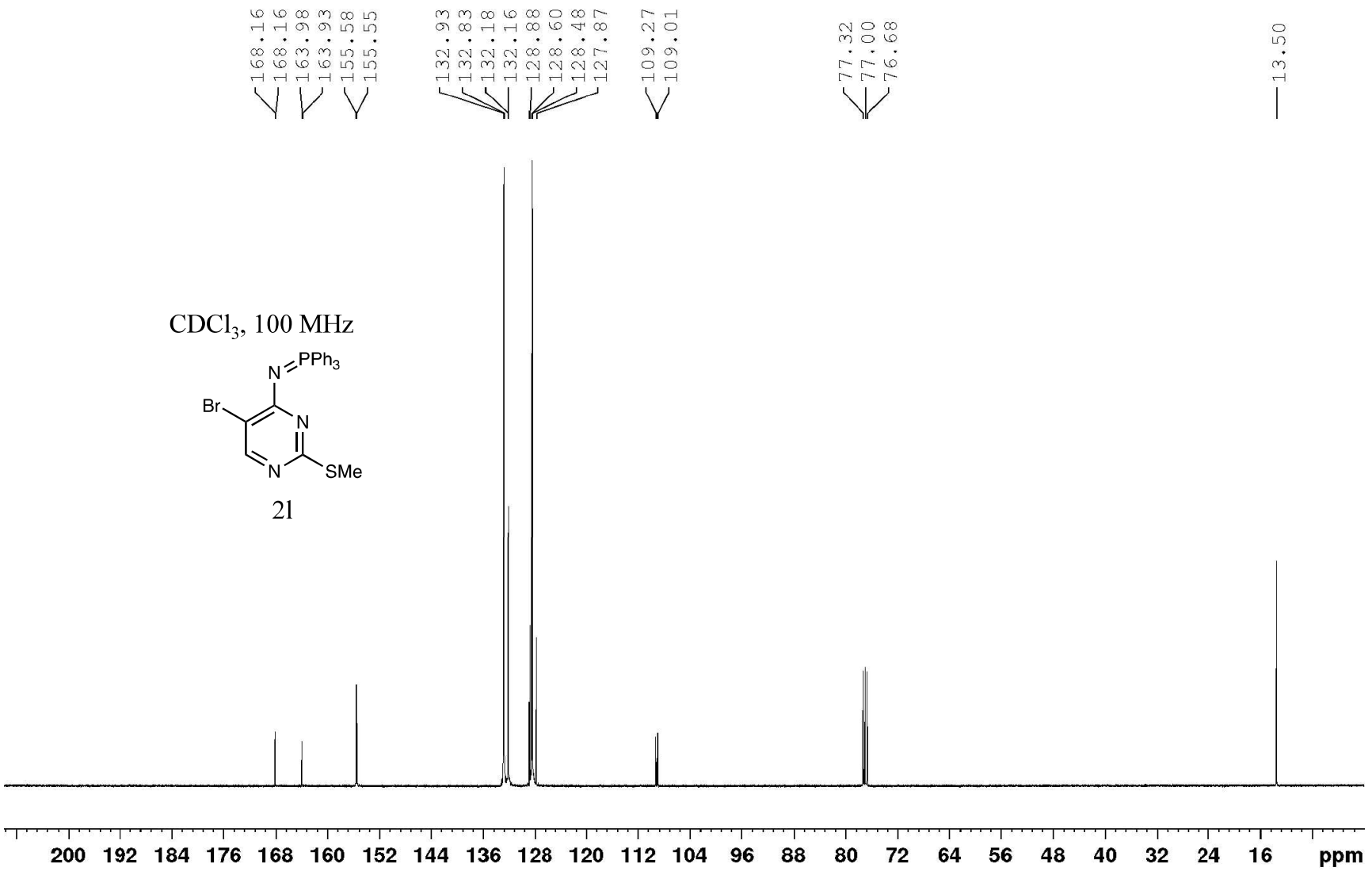
2j


CDCl3, 400 MHz
MeO
N
N
N
PPh3
2k
3.87
8.27
8.26
8.25
7.91
7.89
7.86
7.85
7.83
7.82
7.52
7.50
7.50
7.48
7.44
7.44
7.42
7.42
7.41
7.40
7.05
7.03
3.02
2.06
6.00
3.20
8.14
2.04
ppm


165.25
165.18
158.59
155.84
153.11
153.08
133.09
132.99
131.69
131.66
130.38
129.65
129.57
128.57
128.28
128.16
125.58
125.36
113.11
77.32
77.20
77.00
76.68
55.12
CDCl3, 100 MHz
MeO
N
PPh3
N
N
2k
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

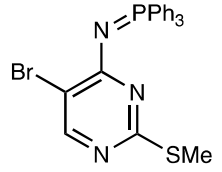

15.99
CDCl3, 162 MHz
MeO
N
PPh3
N
N
2k
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
ppm


8.16
8.15
7.81
7.79
7.78
7.76
7.56
7.54
7.53
7.47
7.45
7.45
7.44
1.86
CDCl3, 400 MHz
N
PPh3
Br
N
N
SMe
21
0.91
6.00
3.03
6.01
3.02
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
ppm

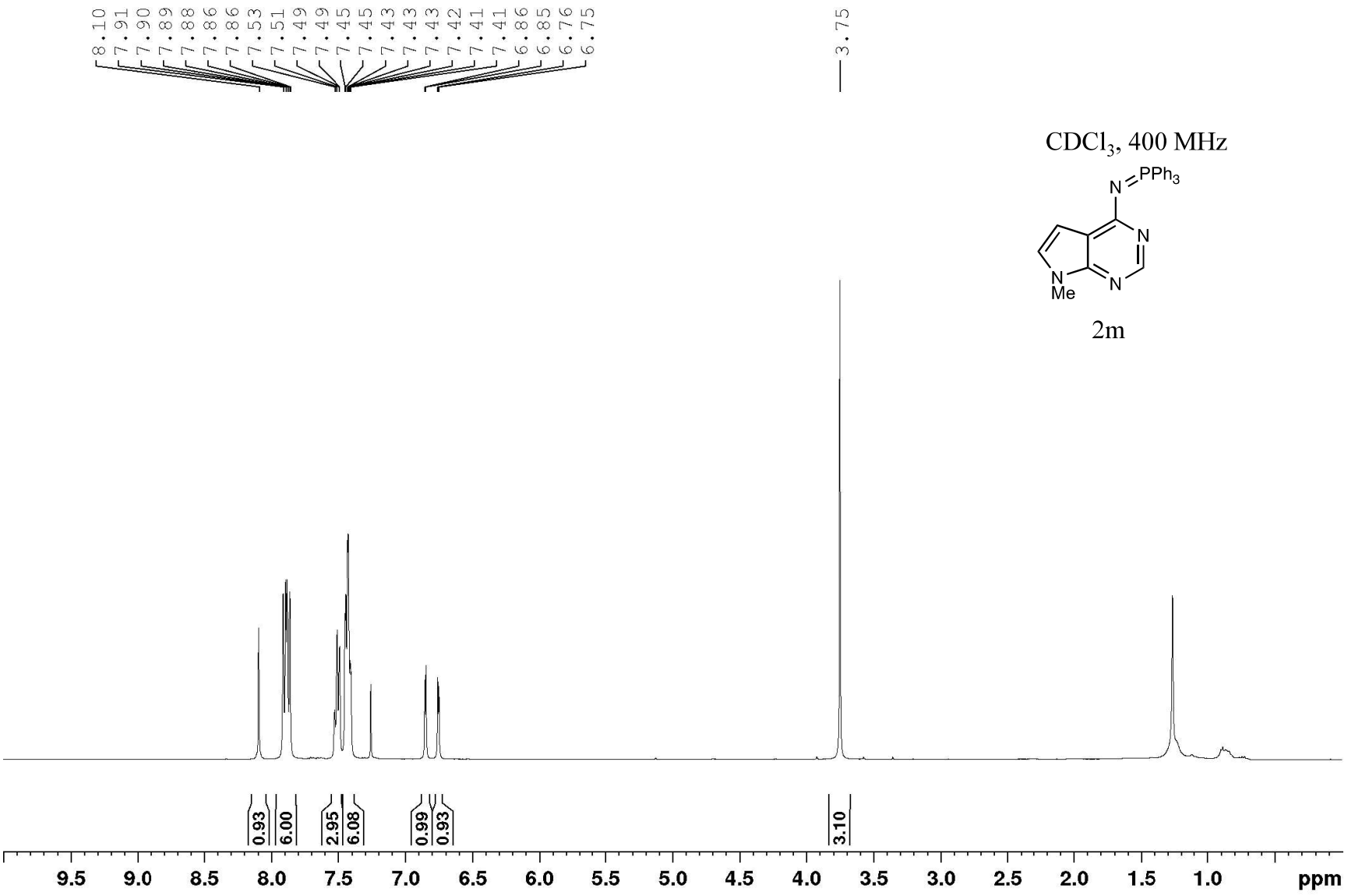

168.16
168.16
163.98
163.93
155.58
155.55
132.93
132.83
132.18
132.16
128.88
128.60
128.48
127.87
109.27
109.01
77.32
77.00
76.68
13.50
CDCl3, 100 MHz
N=PPh3
Br
N
N
SMe
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

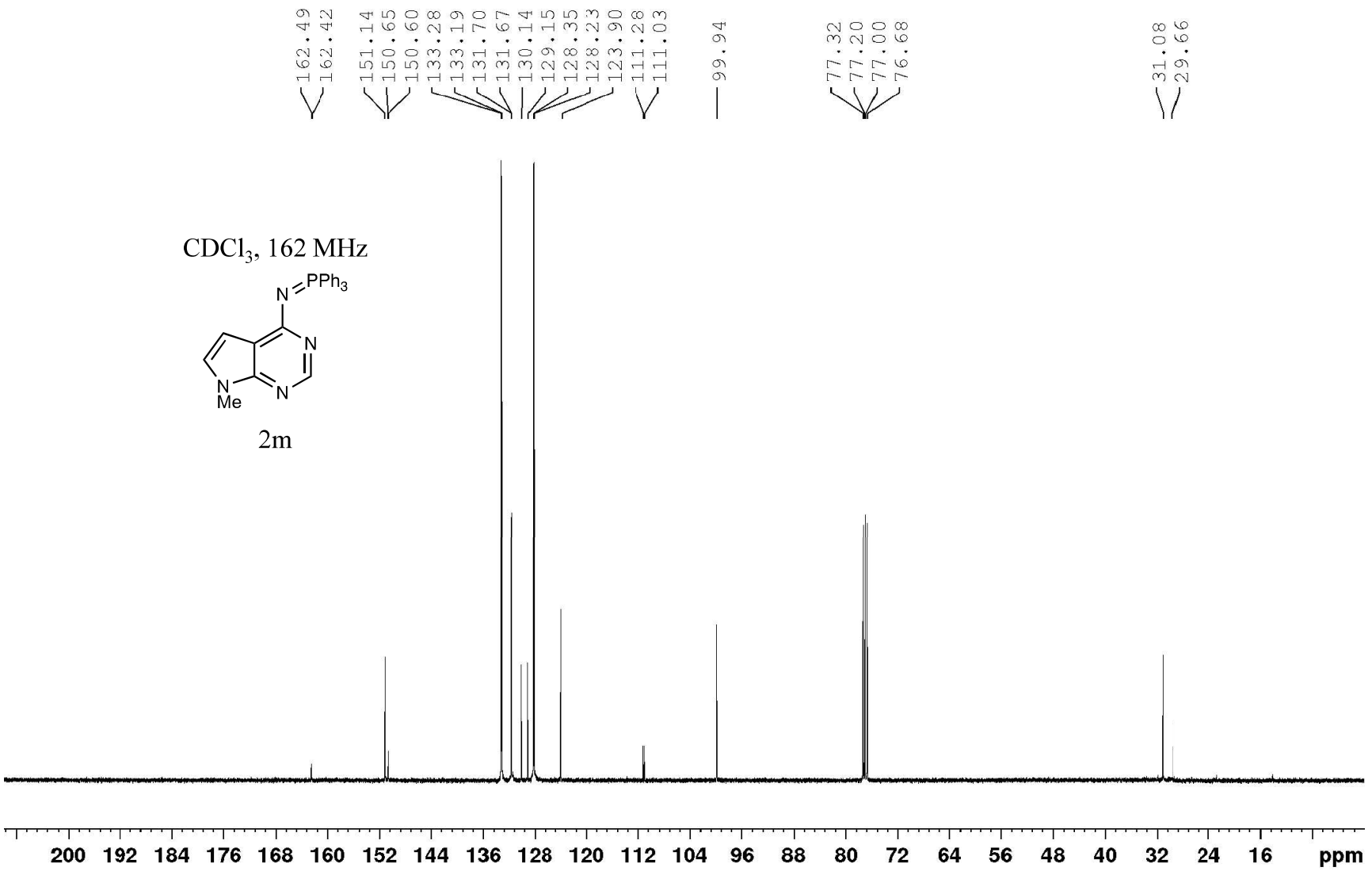
21

$CDCl_3$, 162 MHz

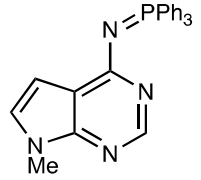


21

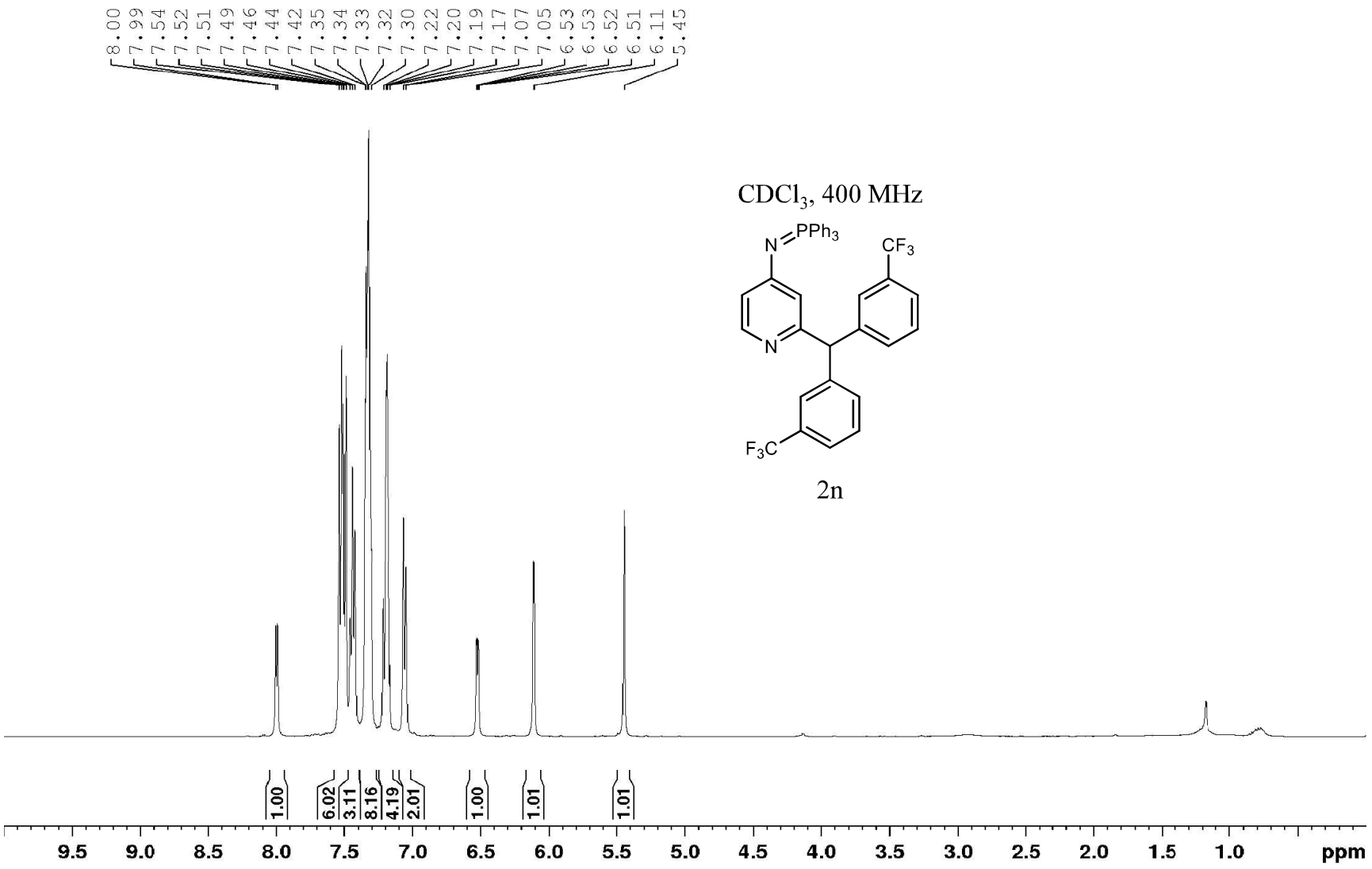

8.10
7.91
7.90
7.89
7.88
7.86
7.86
7.53
7.51
7.49
7.49
7.45
7.45
7.43
7.43
7.43
7.42
7.41
7.41
6.86
6.85
6.76
6.75
3.75
CDCl3, 400 MHz
PPh3
N
N
N
Me
2m
0.93
6.00
2.95
6.08
0.99
0.93
3.10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


162.49
162.42
151.14
150.65
150.60
133.28
133.19
131.70
131.67
130.14
129.15
128.35
128.23
123.90
111.28
111.03
99.94
77.32
77.20
77.00
76.68
31.08
29.66
CDCl3, 162 MHz
N=PPh3
N
N
N
Me
2m
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

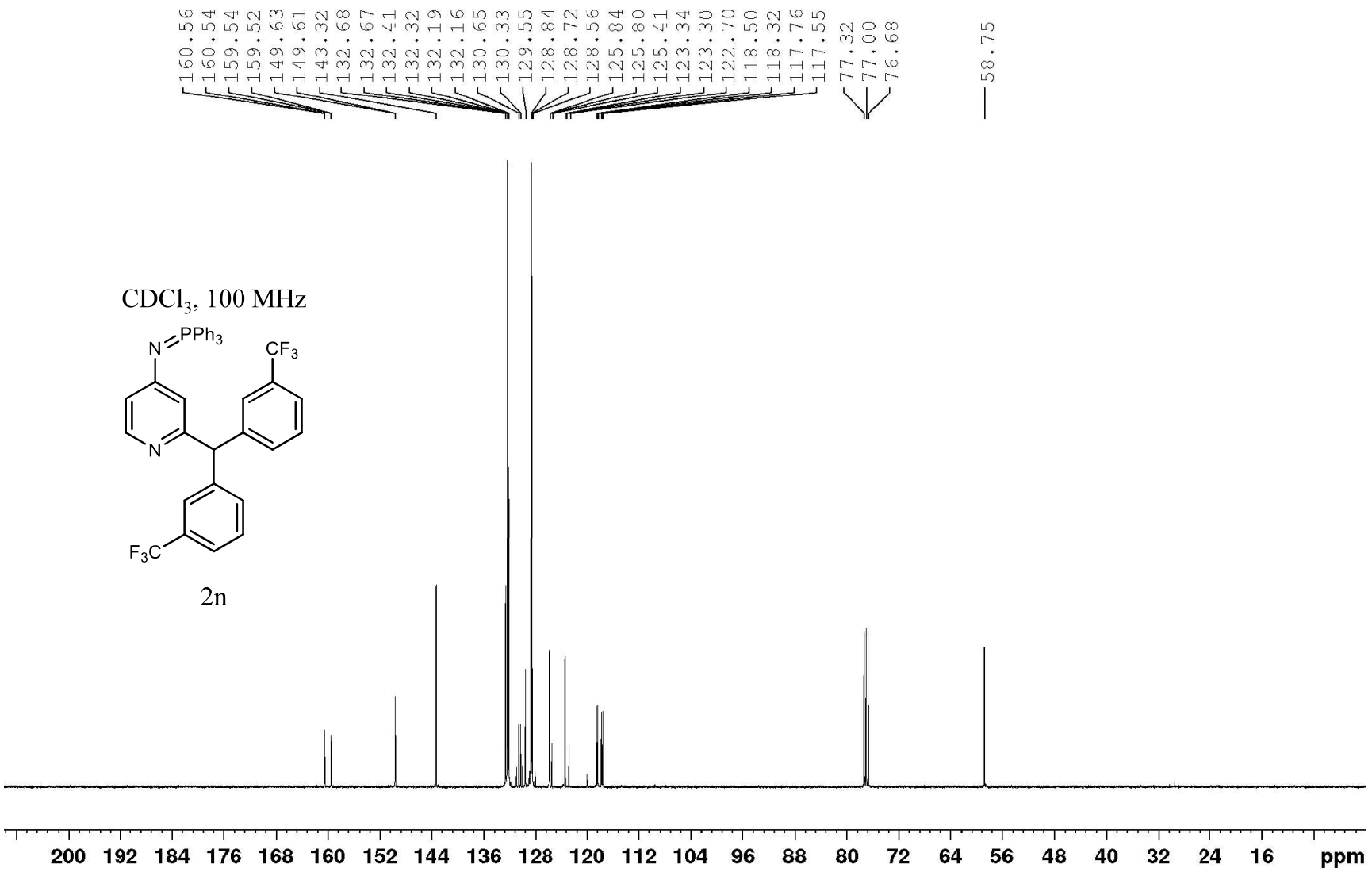
$CDCl_3$, 162 MHz



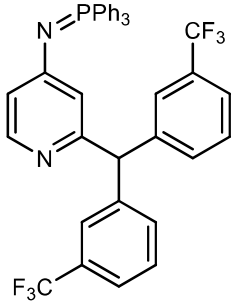
2m


8.00
7.99
7.54
7.52
7.51
7.49
7.46
7.44
7.42
7.35
7.34
7.33
7.32
7.30
7.22
7.20
7.19
7.17
7.07
7.05
6.53
6.53
6.52
6.51
6.11
5.45
CDCl3, 400 MHz
N=PPh3
CF3
N
F3C
1.00
6.02
3.11
8.16
4.19
2.01
1.00
1.01
1.01
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
ppm

2n

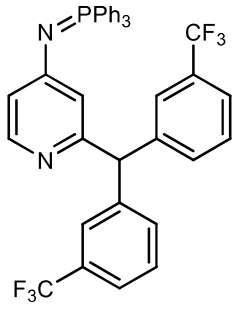

160.56
160.54
159.54
159.52
149.63
149.61
143.32
132.68
132.67
132.41
132.32
132.19
132.16
130.65
130.33
129.55
128.84
128.72
128.56
125.84
125.80
125.41
123.34
123.30
122.70
118.50
118.32
117.76
117.55
77.32
77.00
76.68
58.75
CDCl3, 100 MHz
N
PPh3
CF3
N
F3C
2n
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

$CDCl_3$, 162 MHz

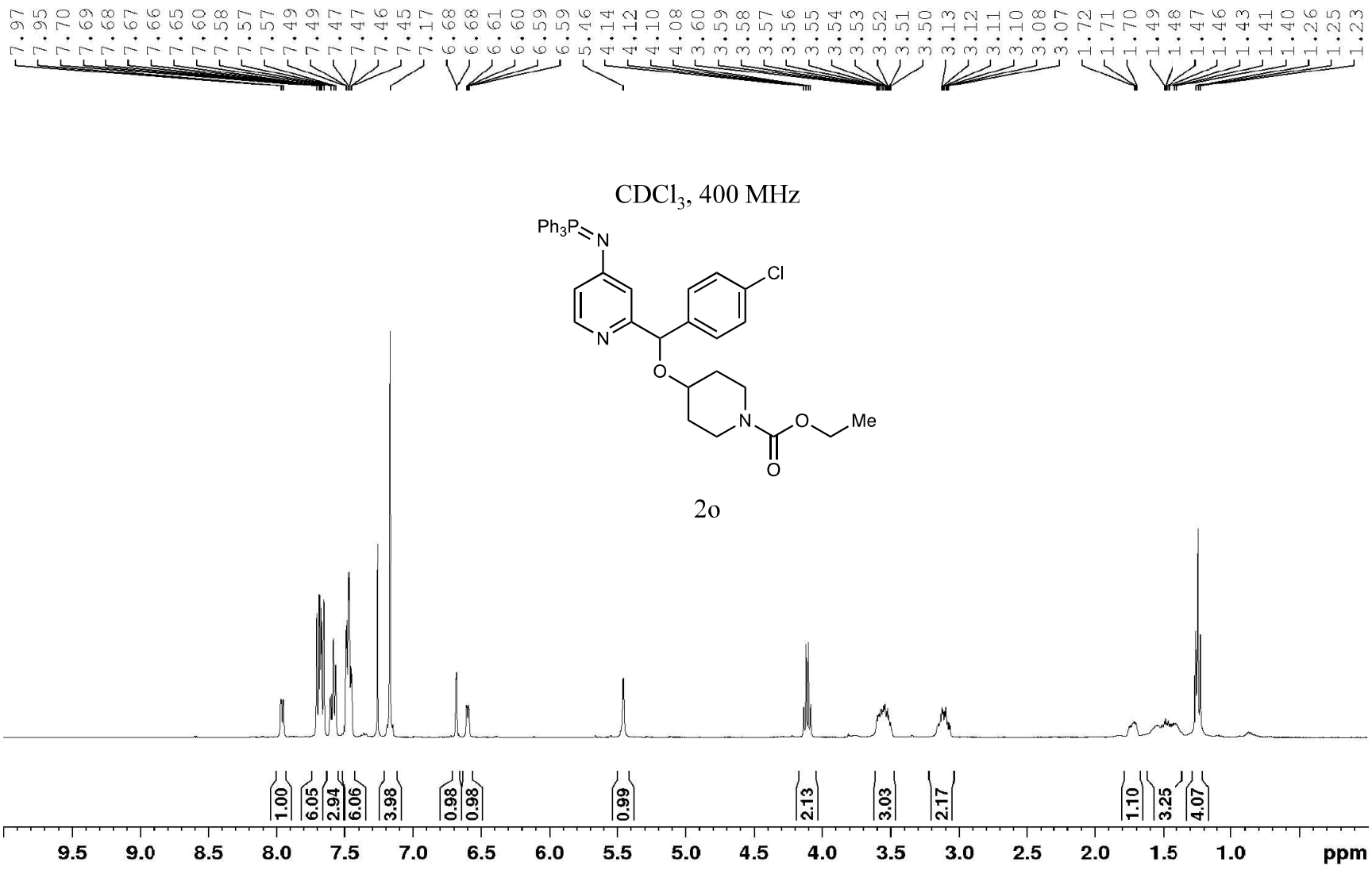


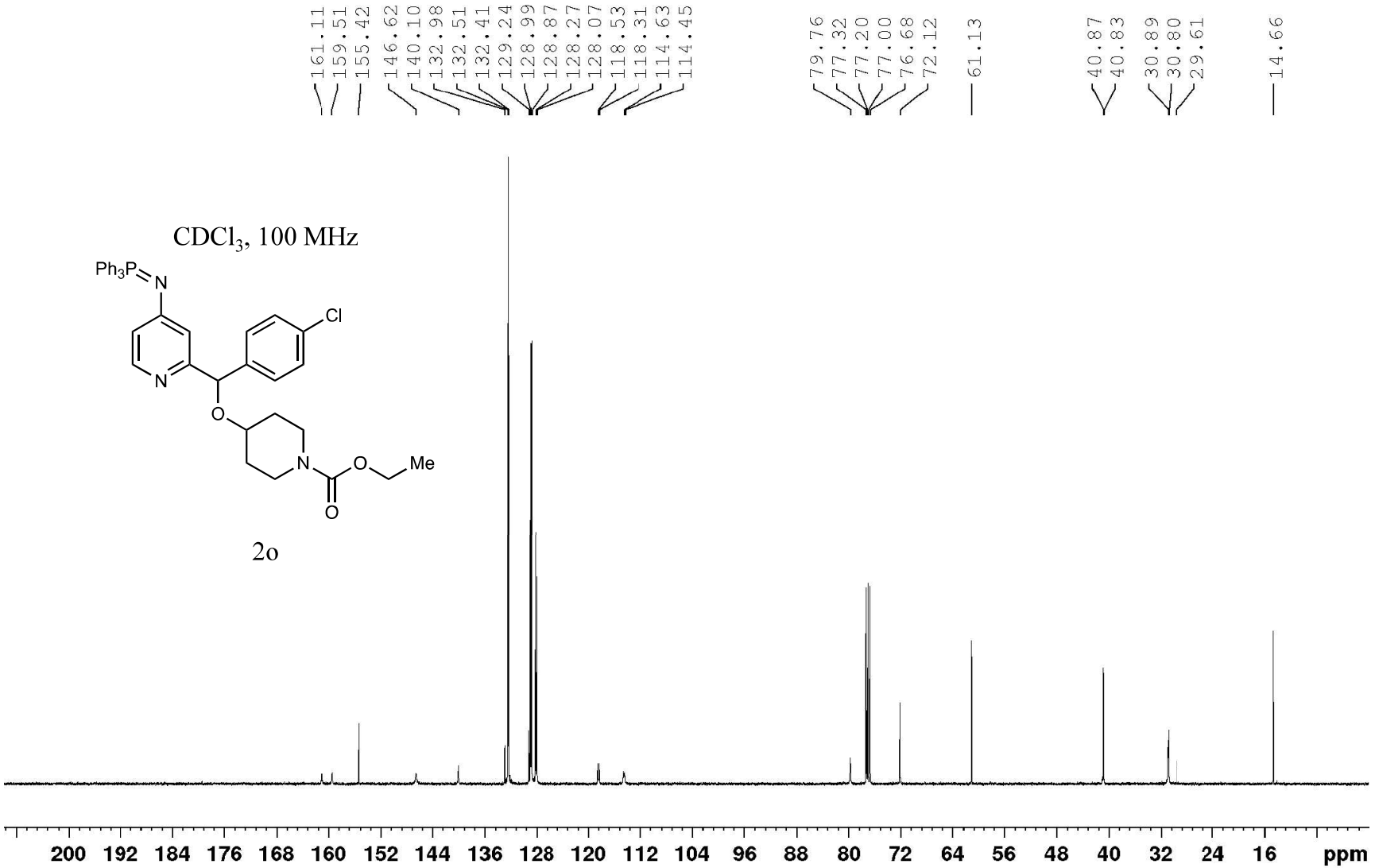
2n

$CDCl_3$, 365 MHz

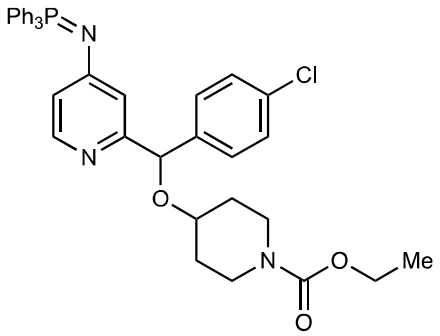


2n

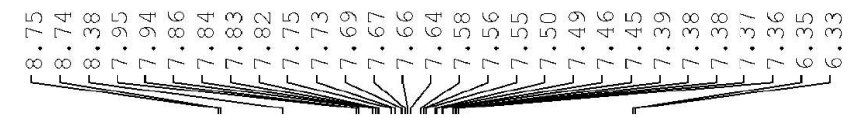

7.97
7.95
7.70
7.69
7.68
7.67
7.66
7.65
7.60
7.58
7.57
7.57
7.49
7.49
7.47
7.47
7.46
7.45
7.17
6.68
6.68
6.61
6.60
6.59
6.59
5.46
4.14
4.12
4.10
4.08
3.60
3.59
3.58
3.57
3.56
3.55
3.54
3.53
3.52
3.51
3.50
3.13
3.12
3.11
3.10
3.08
3.07
1.72
1.71
1.70
1.49
1.48
1.47
1.46
1.43
1.41
1.40
1.26
1.25
1.23
CDCl3, 400 MHz
Ph3P=N
Cl
N
O
N
O
O
Me
O
2o
1.00
6.05
2.94
6.06
3.98
0.98
0.98
0.99
2.13
3.03
2.17
1.10
3.25
4.07
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
ppm


161.11
159.51
155.42
146.62
140.10
132.98
132.51
132.41
129.24
128.99
128.87
128.27
128.07
118.53
118.31
114.63
114.45
79.76
77.32
77.20
77.00
76.68
72.12
61.13
40.87
40.83
30.89
30.80
29.61
14.66
CDCl3, 100 MHz
Ph3P=N
Cl
N
O
N
O
Me
O
2o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

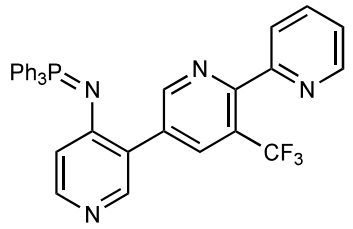
$CDCl_3$, 162 MHz



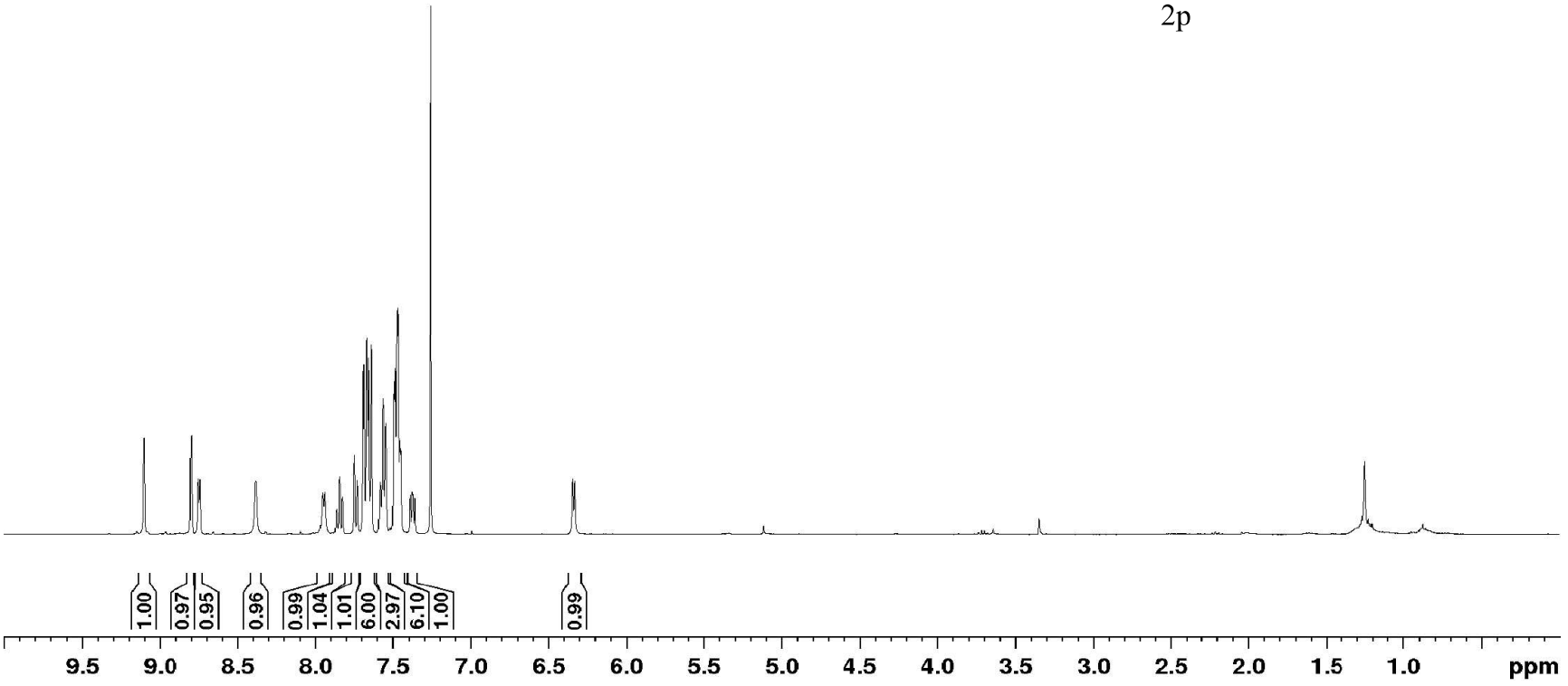
2o

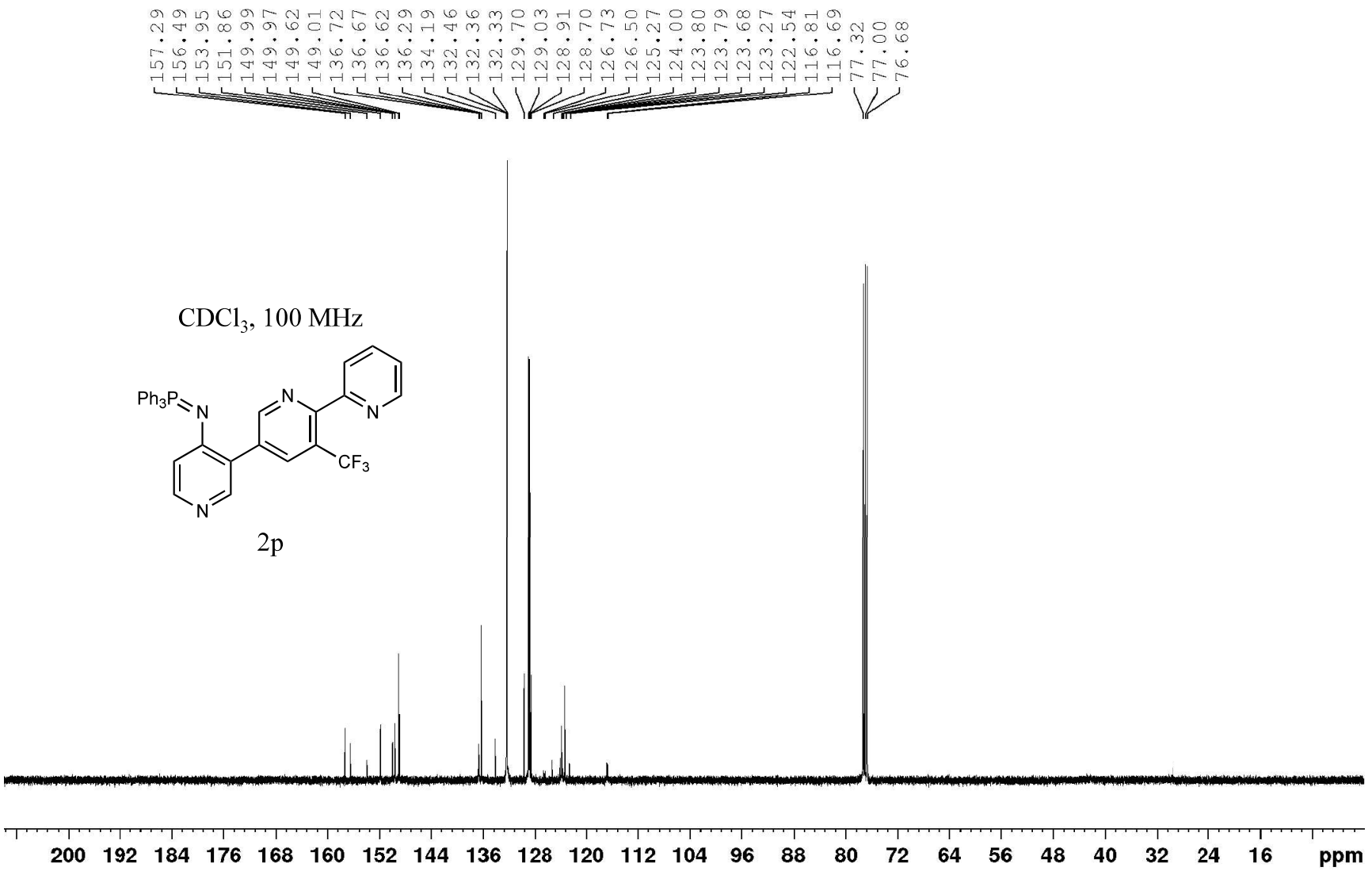


$CDCl_3$, 400 MHz

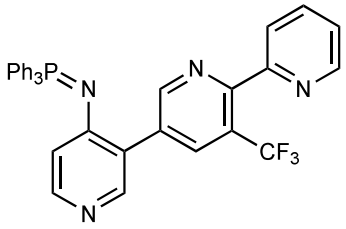


2p

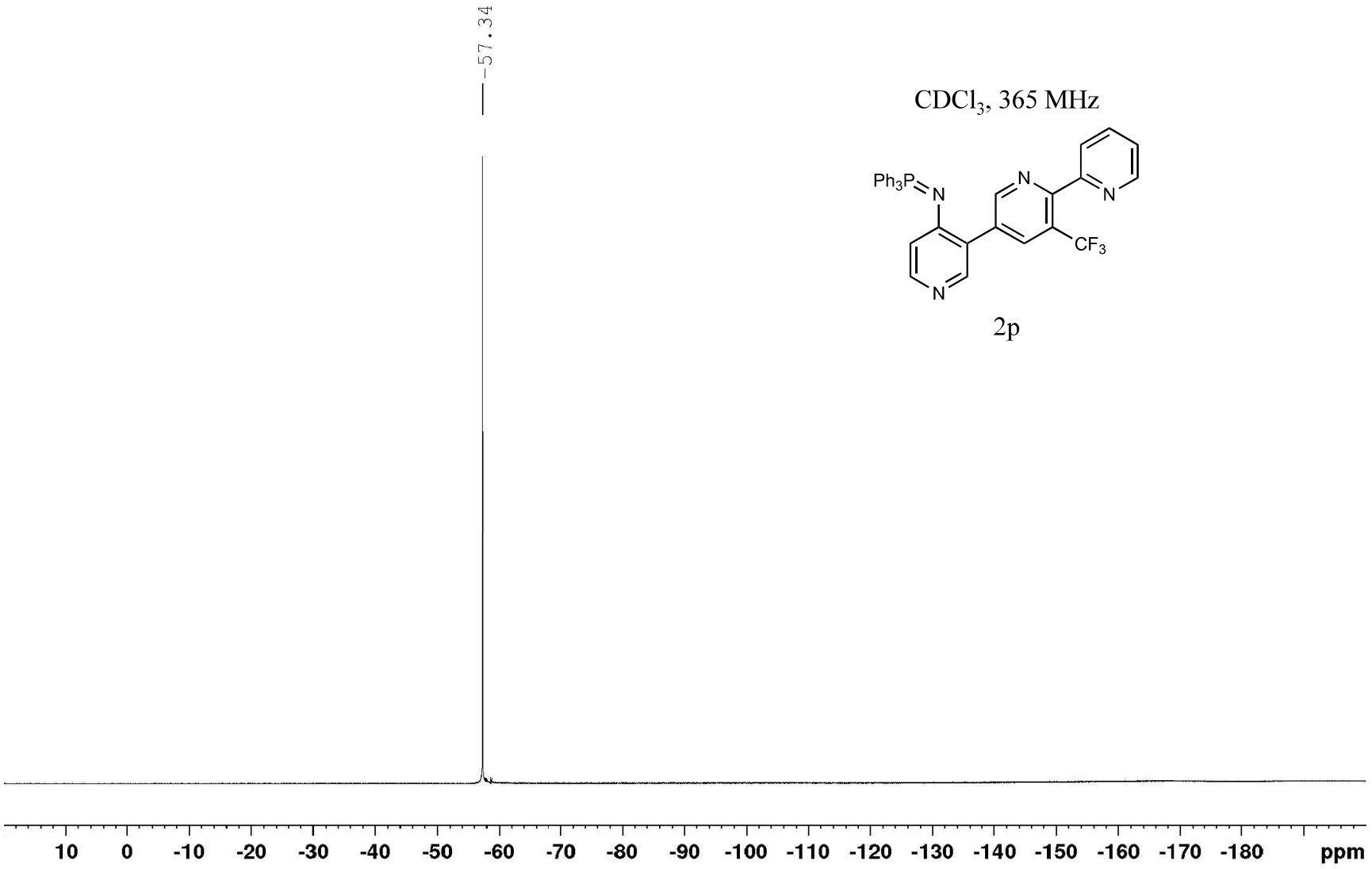


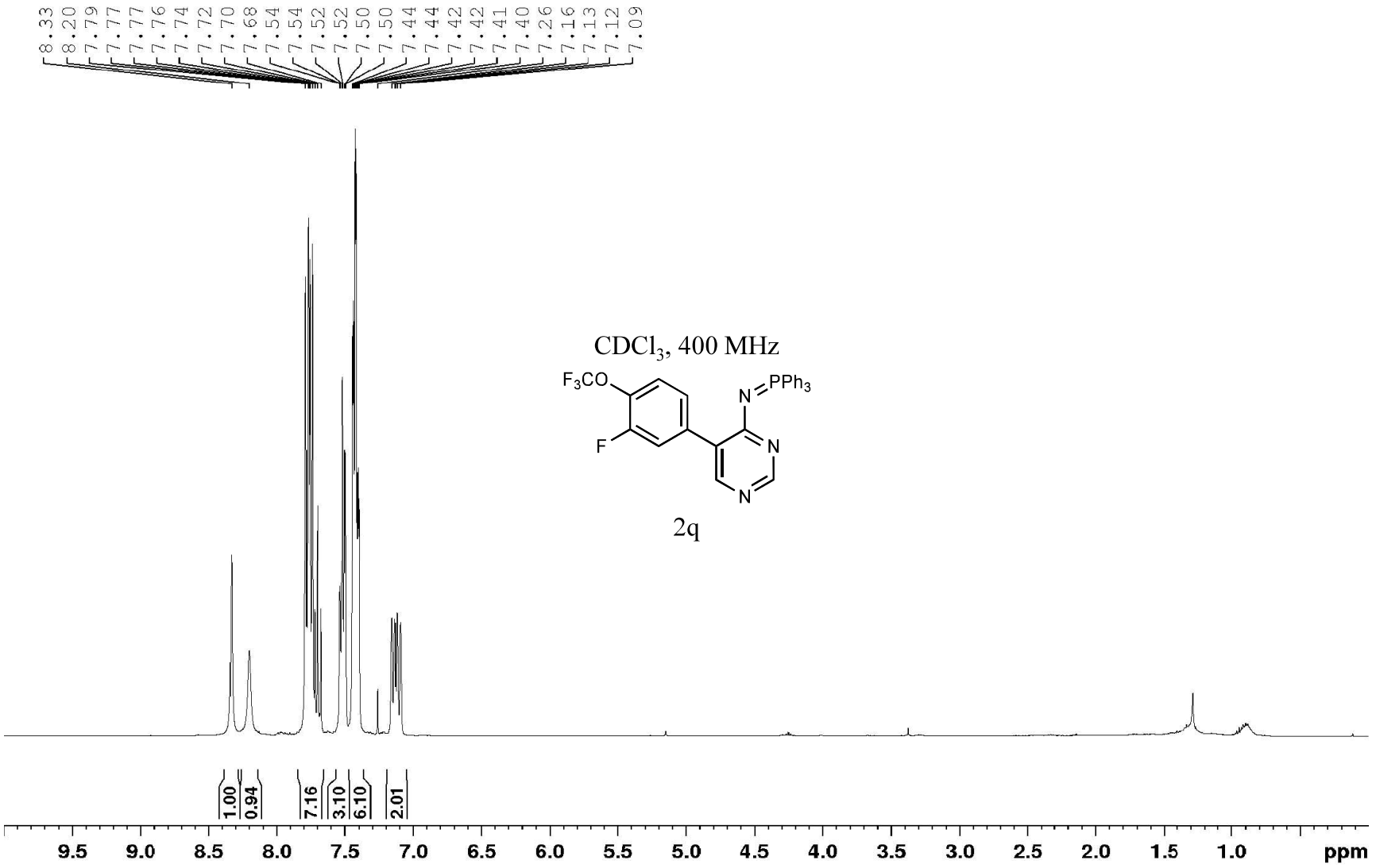

157.29
156.49
153.95
151.86
149.99
149.97
149.62
149.01
136.72
136.67
136.62
136.29
134.19
132.46
132.36
132.33
129.70
129.03
128.91
128.70
126.73
126.50
125.27
124.00
123.80
123.79
123.68
123.27
122.54
116.81
116.69
77.32
77.00
76.68
CDCl3, 100 MHz
Ph3P=N
N
N
N
CF3
2p
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

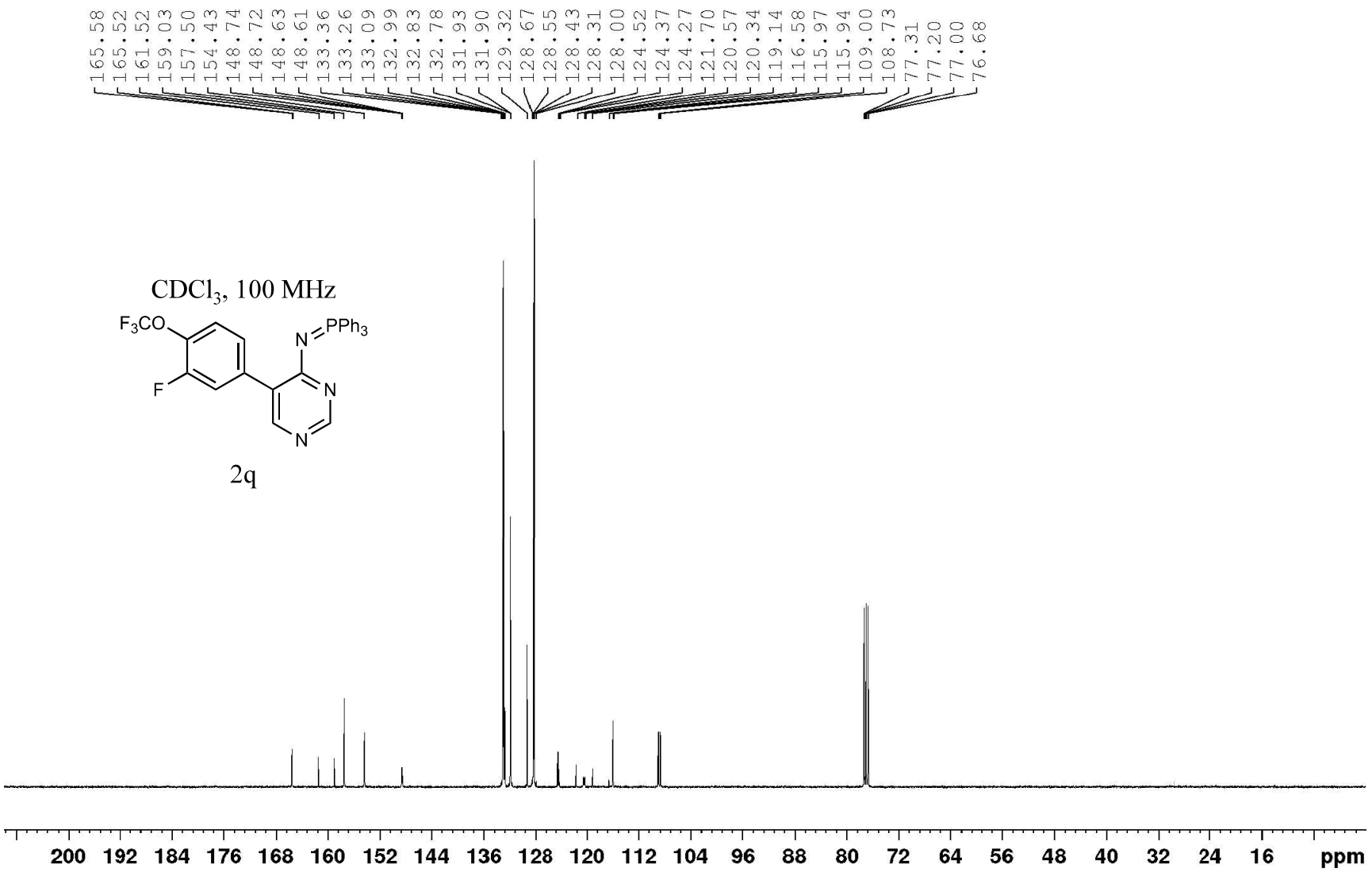
$CDCl_3$, 162 MHz



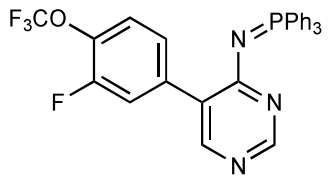
2p


-57.34
CDCl3, 365 MHz
Ph3P=N
N
N
N
CF3
2p
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

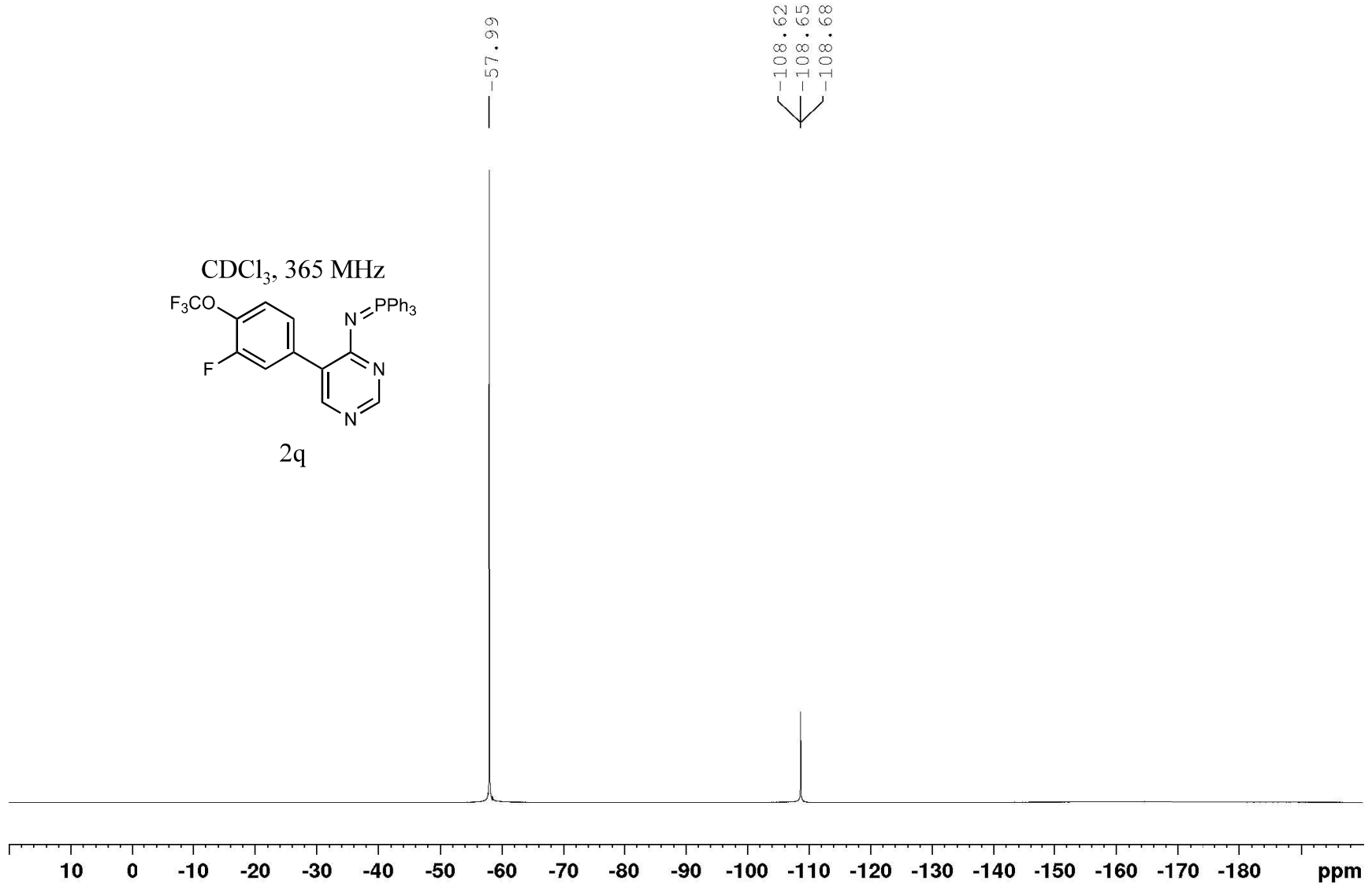

8.33
8.20
7.79
7.77
7.77
7.76
7.74
7.72
7.70
7.68
7.54
7.54
7.52
7.52
7.50
7.50
7.44
7.44
7.42
7.42
7.41
7.40
7.26
7.16
7.13
7.12
7.09
CDCl3, 400 MHz
F3CO
F
N
PPh3
N
N
2q
1.00
0.94
7.16
3.10
6.10
2.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

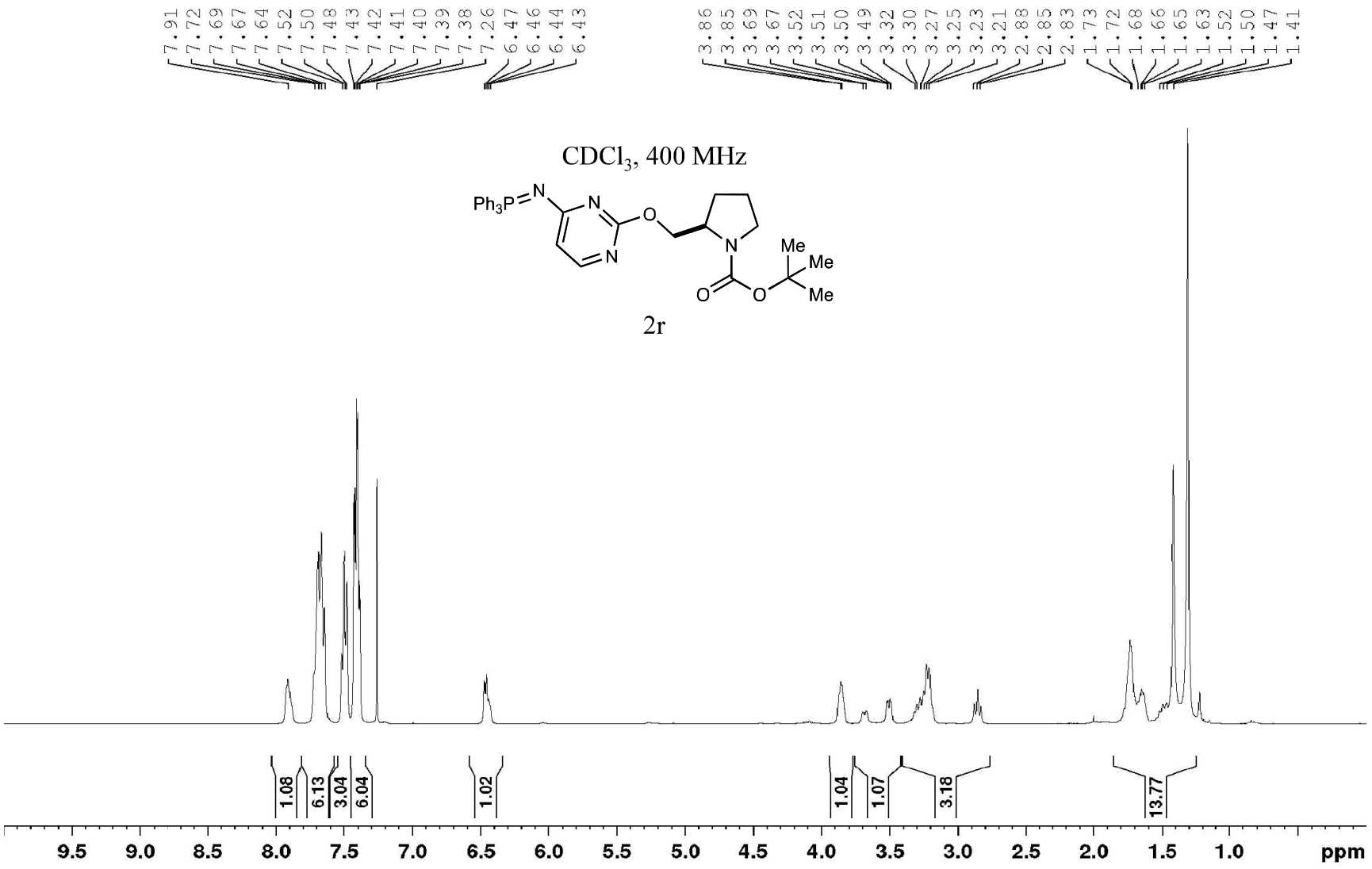

165.58
165.52
161.52
159.03
157.50
154.43
148.74
148.72
148.63
148.61
133.36
133.26
133.09
132.99
132.83
132.78
131.93
131.90
129.32
128.67
128.55
128.43
128.31
128.00
124.52
124.37
124.27
121.70
120.57
120.34
119.14
116.58
115.97
115.94
109.00
108.73
77.31
77.20
77.00
76.68
CDCl3, 100 MHz
F3CO
N=PPh3
F
N
N
2q
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

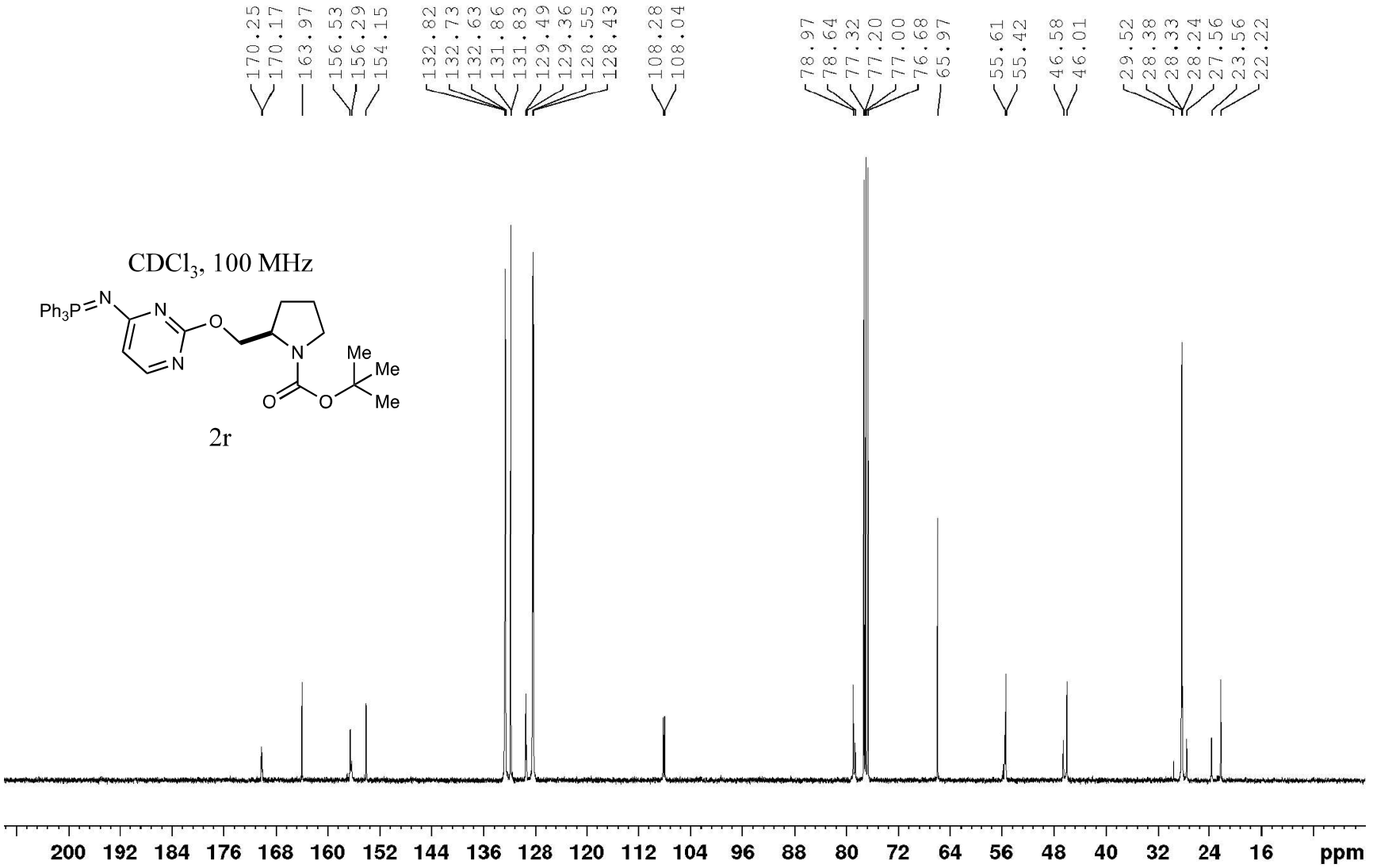
$CDCl_3$, 162 MHz



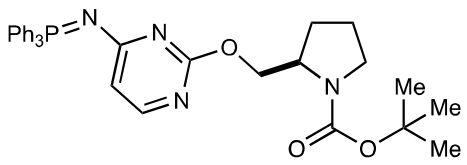
2q


-57.99
-108.62
-108.65
-108.68
CDCl3, 365 MHz
F3CO
F
N
PPh3
N
N
2q
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

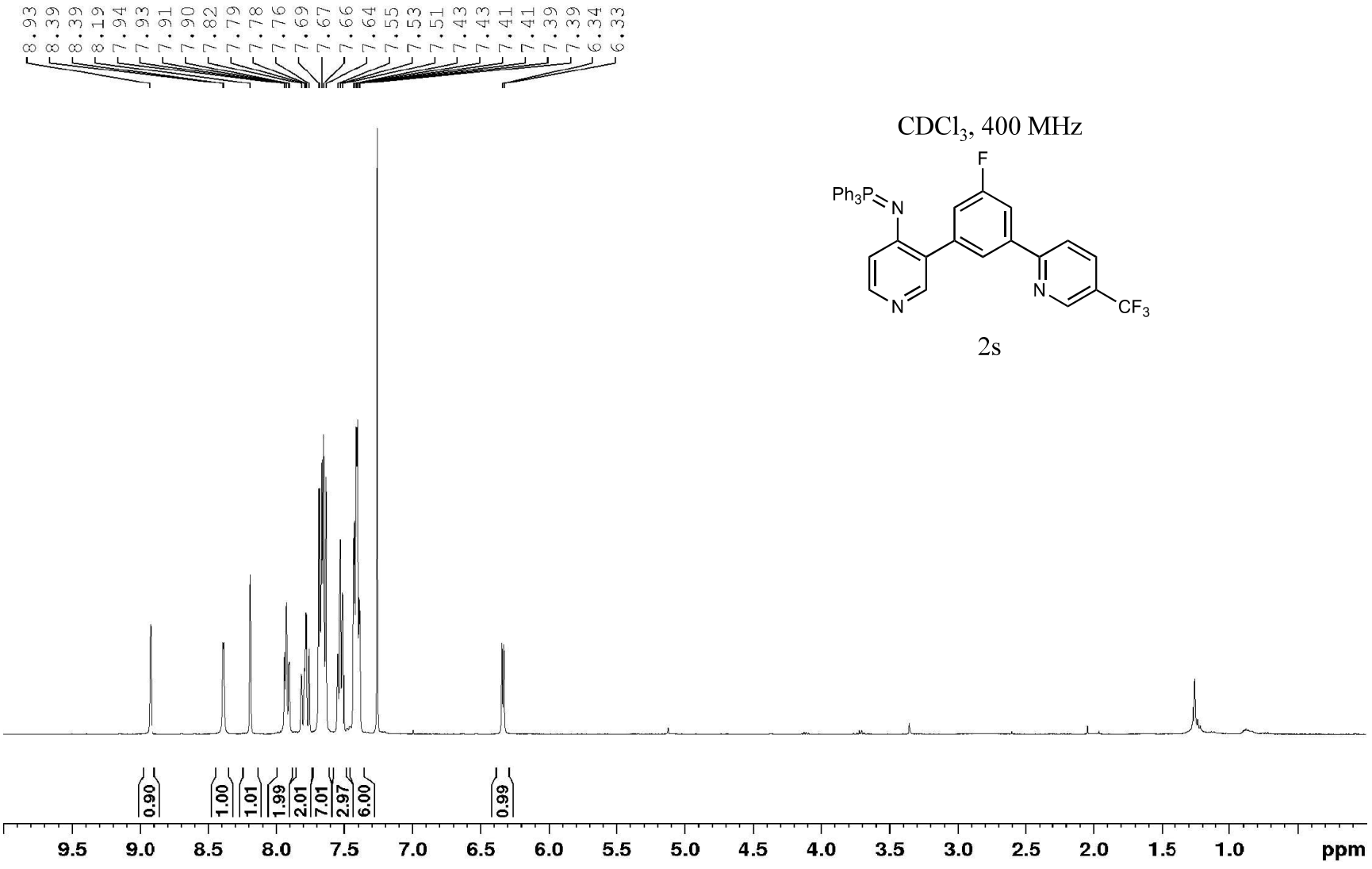

7.91
7.72
7.69
7.67
7.64
7.52
7.50
7.48
7.43
7.42
7.41
7.40
7.39
7.38
7.26
6.47
6.46
6.44
6.43
3.86
3.85
3.69
3.67
3.52
3.51
3.50
3.49
3.32
3.30
3.27
3.25
3.23
3.21
2.88
2.85
2.83
1.73
1.72
1.68
1.66
1.65
1.63
1.52
1.50
1.47
1.41
CDCl3, 400 MHz
Ph3P=N
N
N
O
N
Me
Me
Me
O
O
2r
1.08
6.13
3.04
6.04
1.02
1.04
1.07
3.18
13.77
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
ppm


170.25
170.17
163.97
156.53
156.29
154.15
132.82
132.73
132.63
131.86
131.83
129.49
129.36
128.55
128.43
108.28
108.04
78.97
78.64
77.32
77.20
77.00
76.68
65.97
55.61
55.42
46.58
46.01
29.52
28.38
28.33
28.24
27.56
23.56
22.22
CDCl3, 100 MHz
Ph3P=N
N
N
O
N
Me
Me
Me
O
O
2r
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

$CDCl_3$, 162 MHz

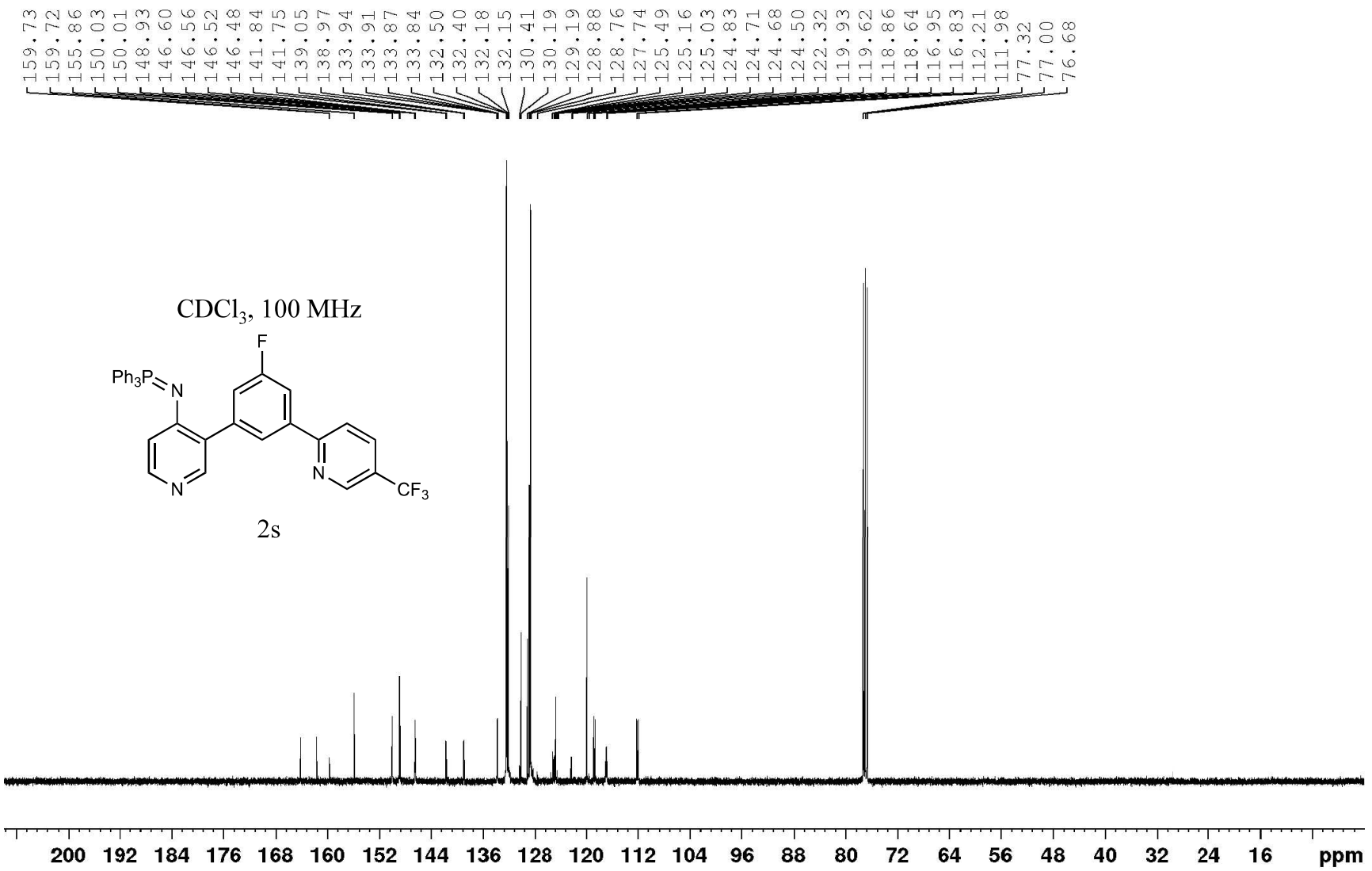


2r

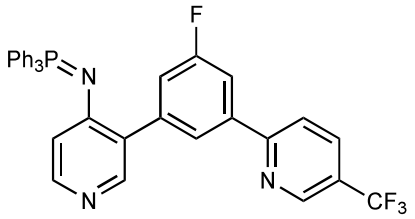


$CDCl_3$, 400 MHz

2s

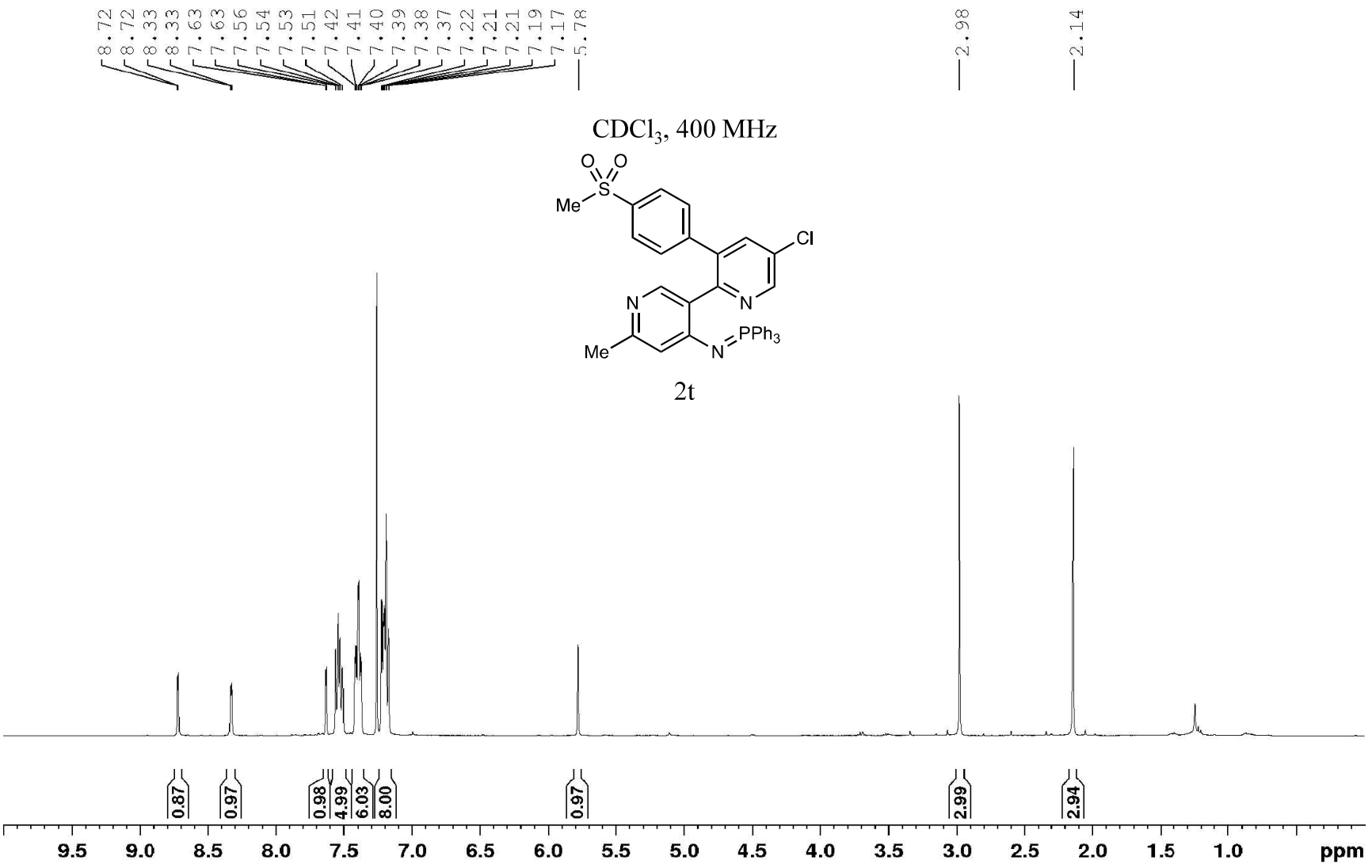

159.73
159.72
155.86
150.03
150.01
148.93
146.60
146.56
146.52
146.48
141.84
141.75
139.05
138.97
133.94
133.91
133.87
133.84
132.50
132.40
132.18
132.15
130.41
130.19
129.19
128.88
128.76
127.74
125.49
125.16
125.03
124.83
124.71
124.68
124.50
122.32
119.93
119.62
118.86
118.64
116.95
116.83
112.21
111.98
77.32
77.00
76.68
CDCl3, 100 MHz
F
Ph3P=N
N
N
CF3
2s
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

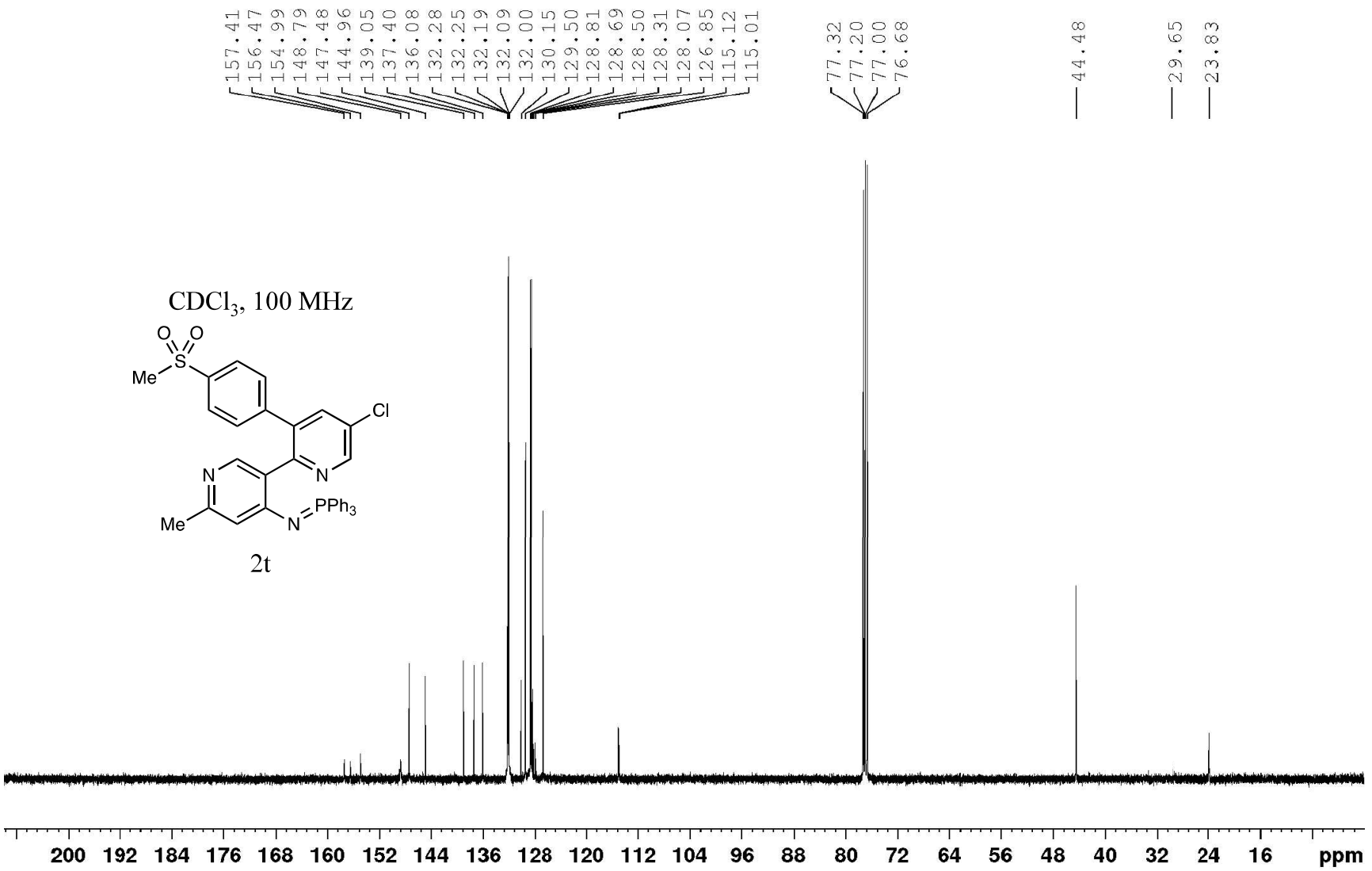
$CDCl_3$, 162 MHz



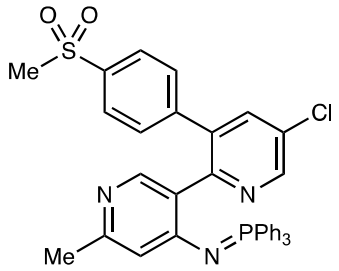
2s


-62.26
-114.31
-114.34
-114.37
CDCl3, 365 MHz
F
Ph3P=N
N
N
CF3
2s
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
ppm

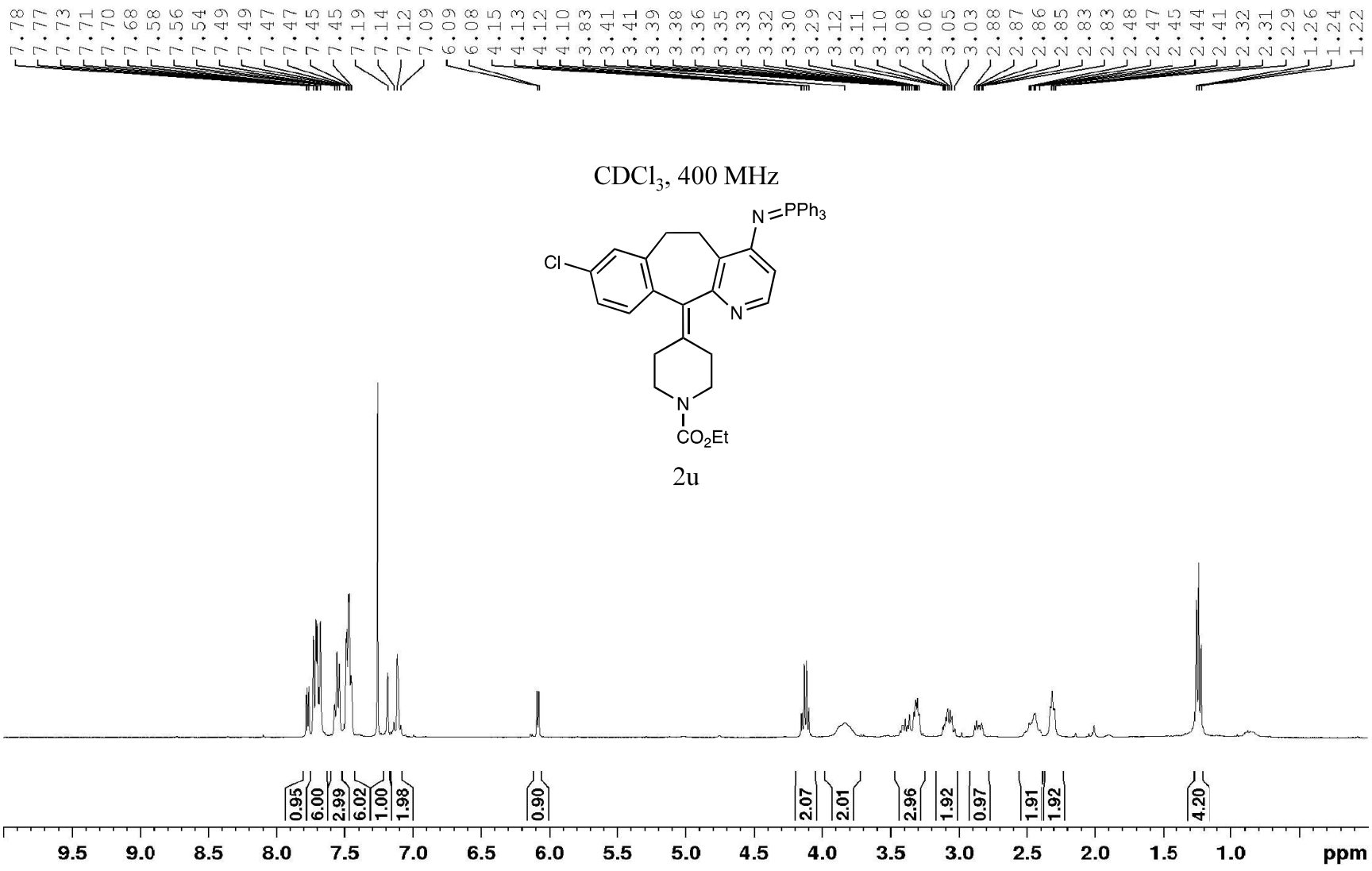

8.72
8.72
8.33
8.33
7.63
7.63
7.56
7.54
7.53
7.51
7.42
7.41
7.40
7.39
7.38
7.37
7.22
7.21
7.21
7.19
7.17
5.78
2.98
2.14
CDCl3, 400 MHz
Me
S
O
O
Cl
N
N
Me
N
PPh3
2t
0.87
0.97
0.98
4.99
6.03
8.00
0.97
2.99
2.94
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

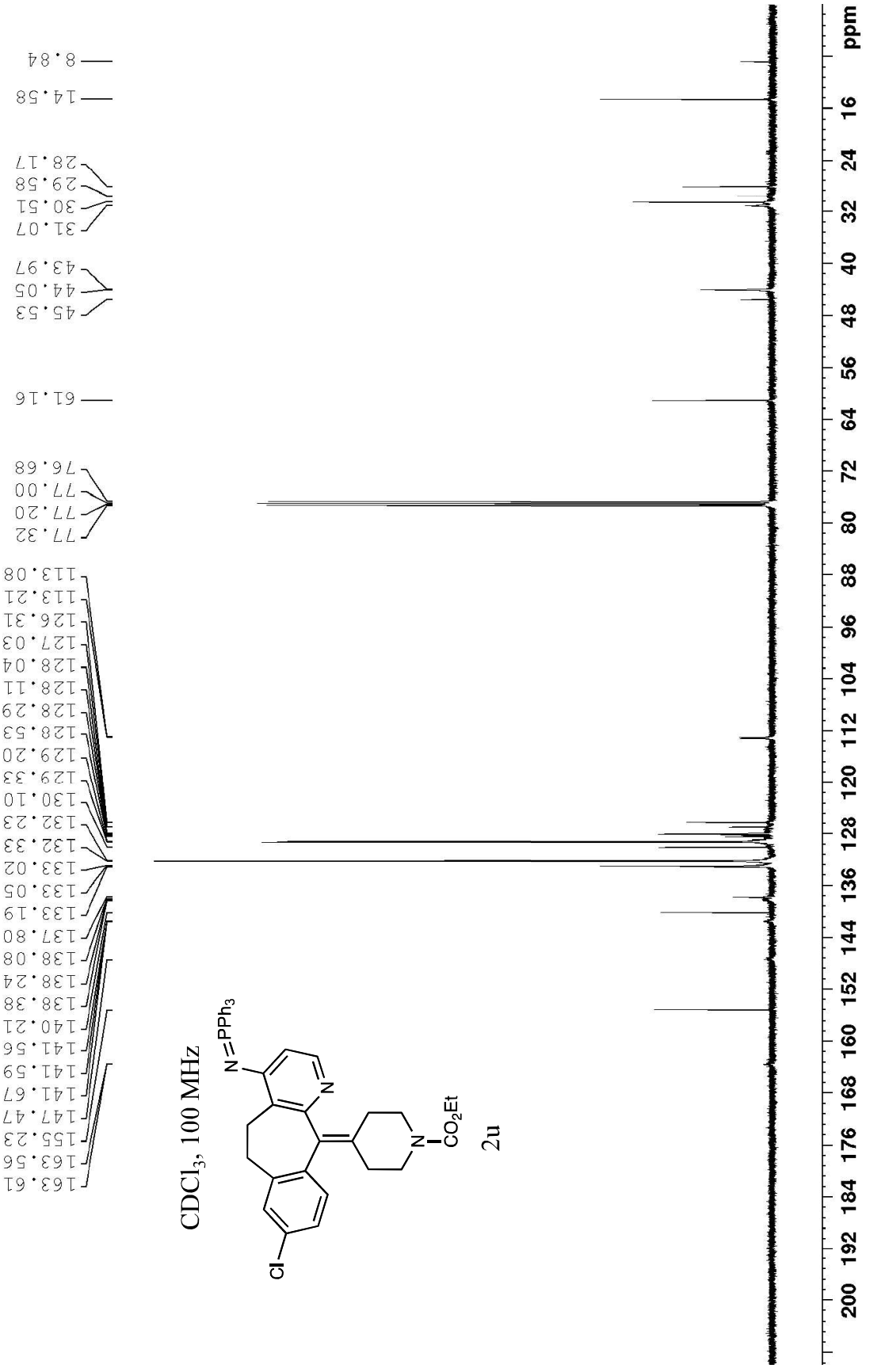

157.41
156.47
154.99
148.79
147.48
144.96
139.05
137.40
136.08
132.28
132.25
132.19
132.09
132.00
130.15
129.50
128.81
128.69
128.50
128.31
128.07
126.85
115.12
115.01
77.32
77.20
77.00
76.68
44.48
29.65
23.83
CDCl3, 100 MHz
Me
S
O
O
Cl
N
N
Me
N
PPh3
2t
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

$CDCl_3$, 162 MHz

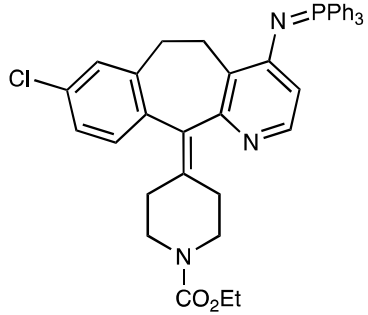


2t

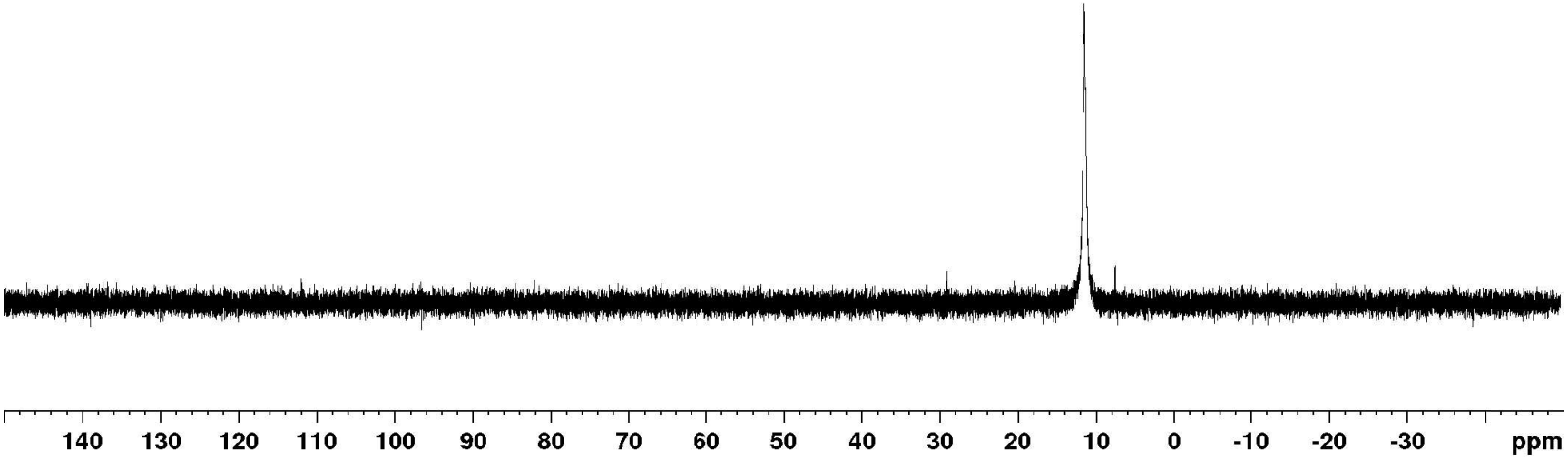

7.78
7.77
7.73
7.71
7.70
7.68
7.58
7.56
7.54
7.49
7.49
7.47
7.47
7.45
7.45
7.19
7.14
7.12
7.09
6.09
6.08
4.15
4.13
4.12
4.10
3.83
3.41
3.41
3.39
3.38
3.36
3.35
3.33
3.32
3.30
3.29
3.12
3.11
3.10
3.08
3.06
3.05
3.03
2.88
2.87
2.86
2.85
2.83
2.83
2.48
2.47
2.45
2.44
2.41
2.32
2.31
2.29
1.26
1.24
1.22
CDCl3, 400 MHz
N=PPh3
Cl
N
N
CO2Et
2u
0.95
6.00
2.99
6.02
1.00
1.98
0.90
2.07
2.01
2.96
1.92
0.97
1.91
1.92
4.20
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
ppm

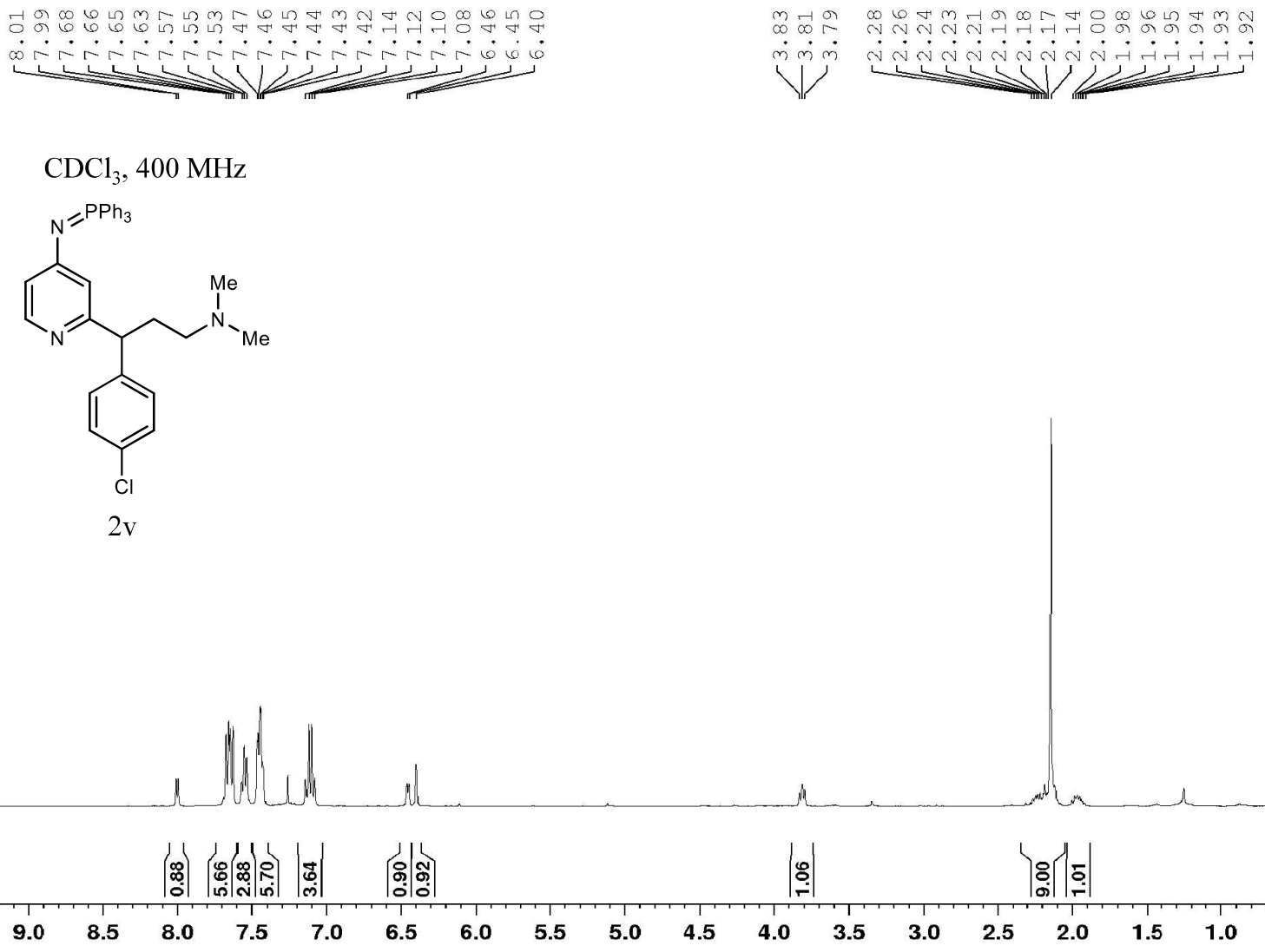

CDCl3, 100 MHz
N=PPh3
N
N
CO2Et
Cl
2u
ppm
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16
8.84
14.58
28.17
29.58
30.51
31.07
43.97
44.05
45.53
61.16
76.68
77.00
77.20
77.32
113.08
113.21
126.31
127.03
128.04
128.11
128.29
128.53
129.20
129.33
130.10
132.23
132.33
133.02
133.05
133.19
137.80
138.08
138.24
138.38
140.21
141.56
141.59
141.67
147.47
155.23
163.56
163.61

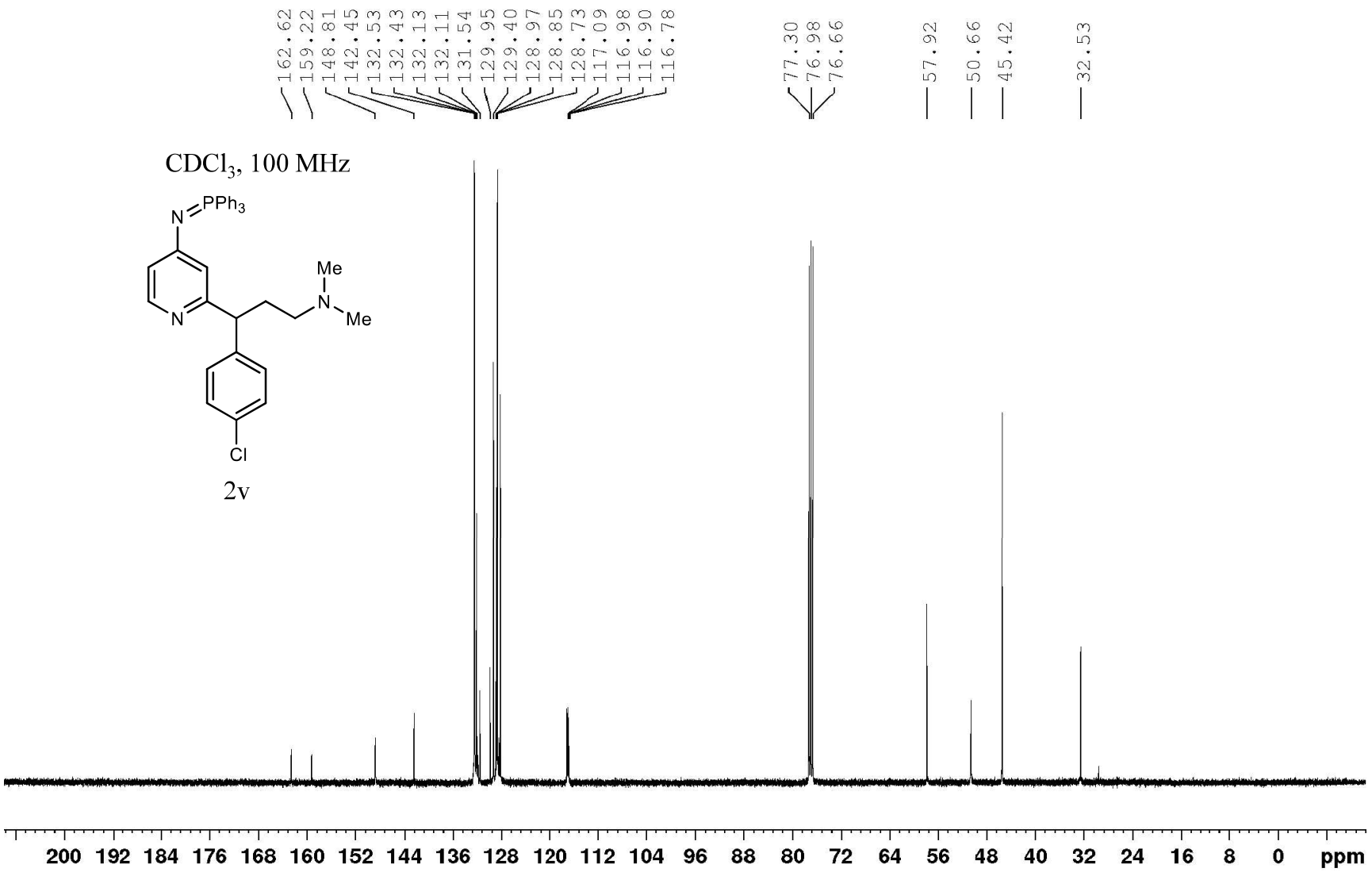
$CDCl_3$, 162 MHz



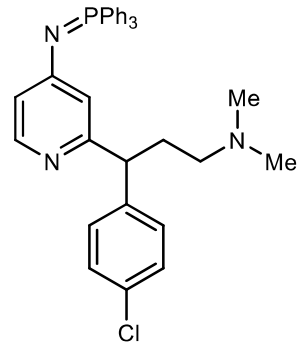
2u



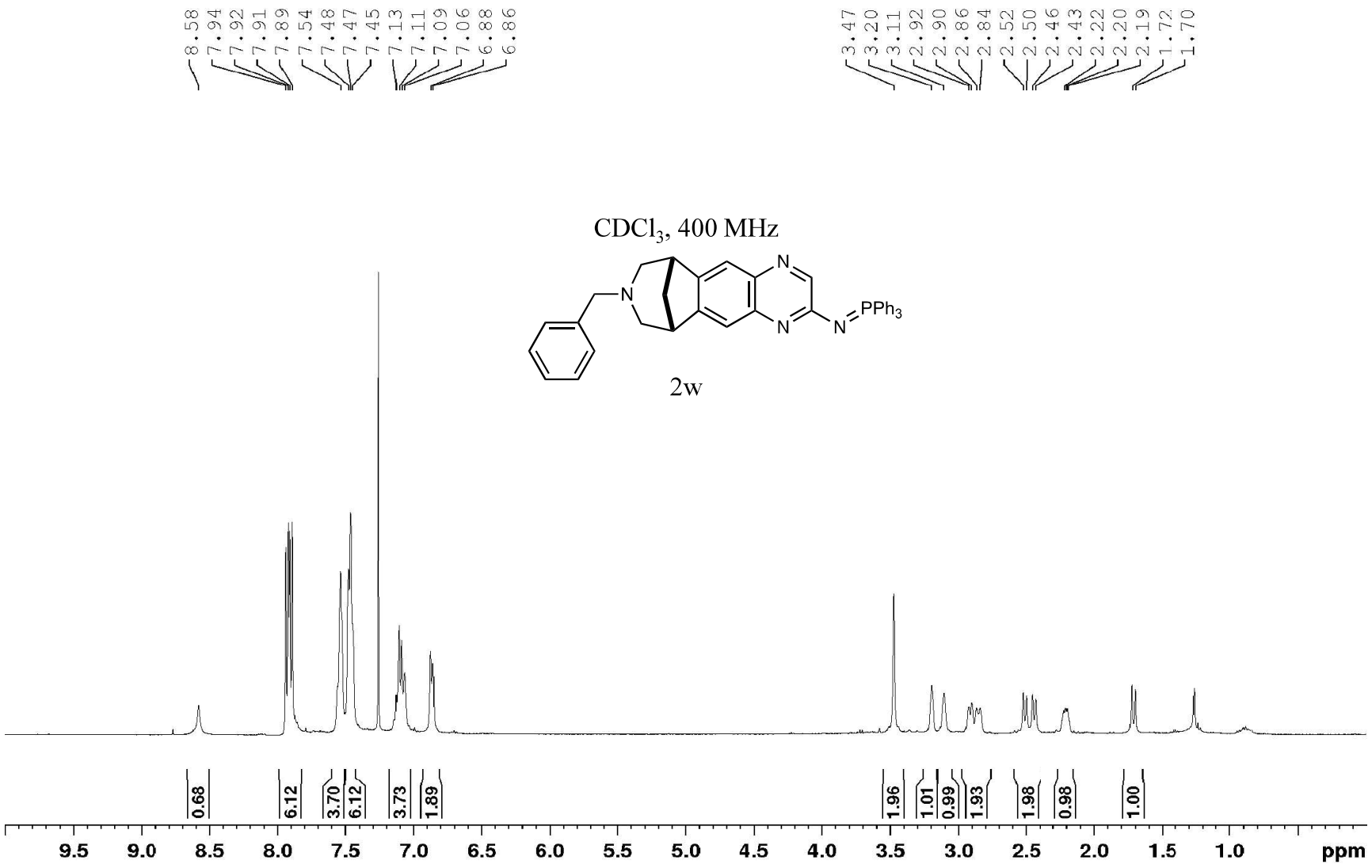

8.01
7.99
7.68
7.66
7.65
7.63
7.57
7.55
7.53
7.47
7.46
7.45
7.44
7.43
7.42
7.14
7.12
7.10
7.08
6.46
6.45
6.40
3.83
3.81
3.79
2.28
2.26
2.24
2.23
2.21
2.19
2.18
2.17
2.14
2.00
1.98
1.96
1.95
1.94
1.93
1.92
CDCl3, 400 MHz
N
PPh3
Me
N
Me
N
Cl
2v
0.88
5.66
2.88
5.70
3.64
0.90
0.92
1.06
9.00
1.01
9.5
9.0
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
ppm

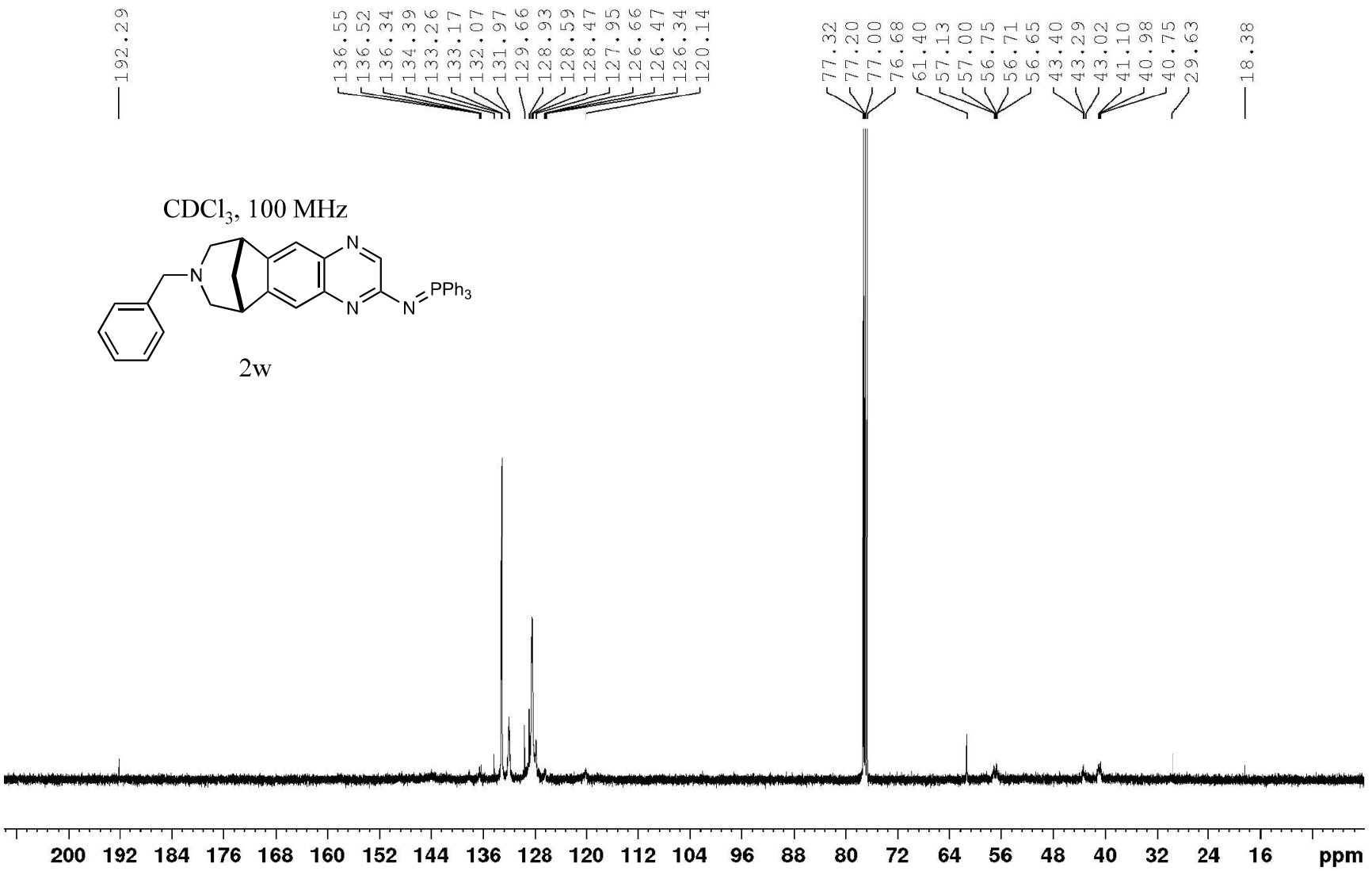

162.62
159.22
148.81
142.45
132.53
132.43
132.13
132.11
131.54
129.95
129.40
128.97
128.85
128.73
117.09
116.98
116.90
116.78
77.30
76.98
76.66
57.92
50.66
45.42
32.53
CDCl3, 100 MHz
N=PPh3
Me
N
Me
N
Cl
2v
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 ppm

$CDCl_3$, 162 MHz

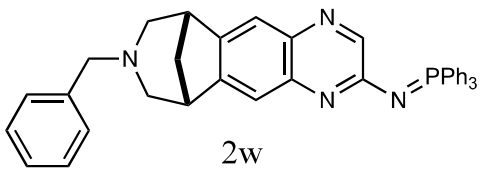


2v

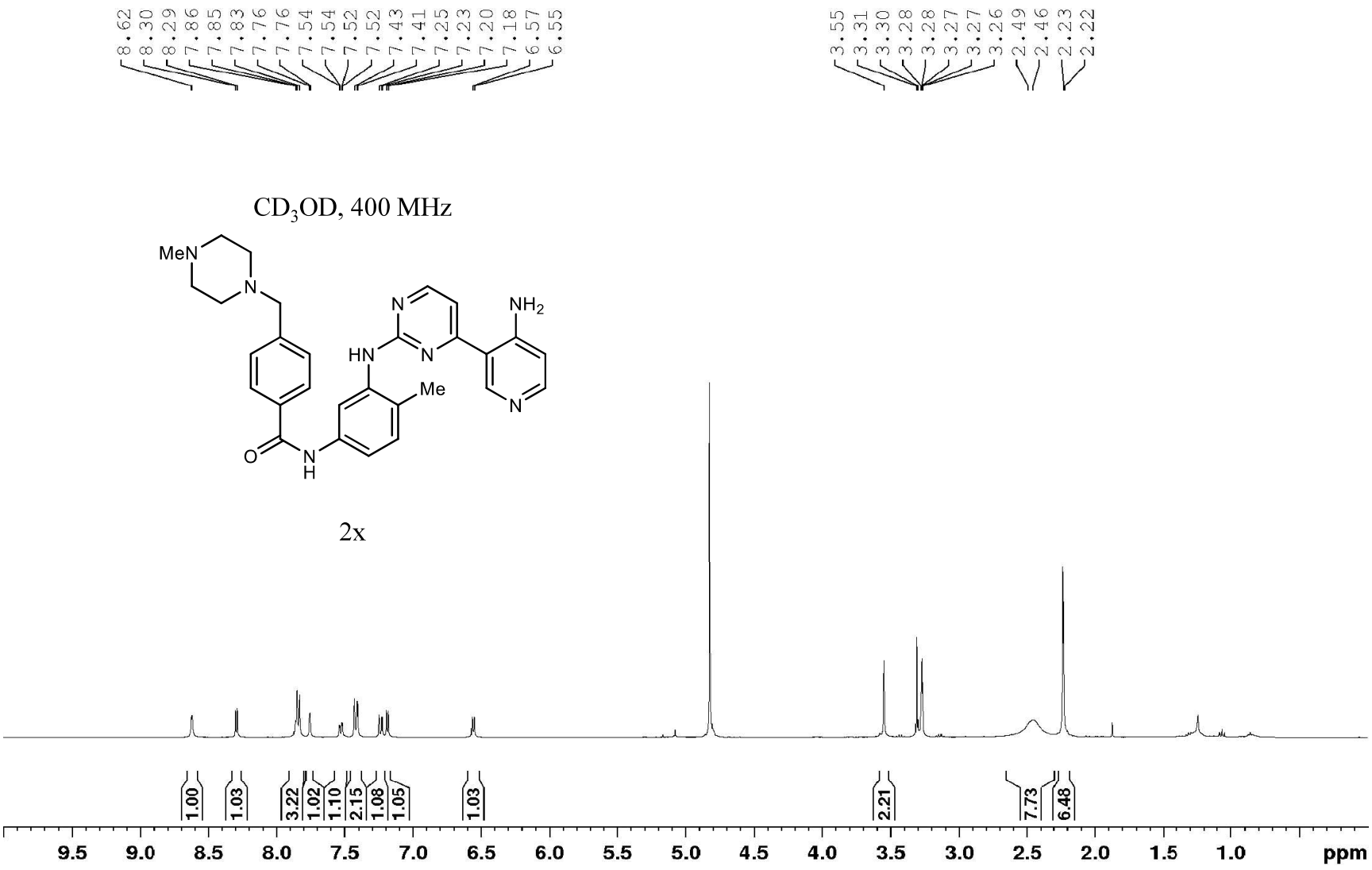

8.58
7.94
7.92
7.91
7.89
7.54
7.48
7.47
7.45
7.13
7.11
7.09
7.06
6.88
6.86
3.47
3.20
3.11
2.92
2.90
2.86
2.84
2.52
2.50
2.46
2.43
2.22
2.20
2.19
1.72
1.70
CDCl3, 400 MHz
N
N
N
N
PPh3
2w
0.68
6.12
3.70
6.12
3.73
1.89
1.96
1.01
0.99
1.93
1.98
0.98
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

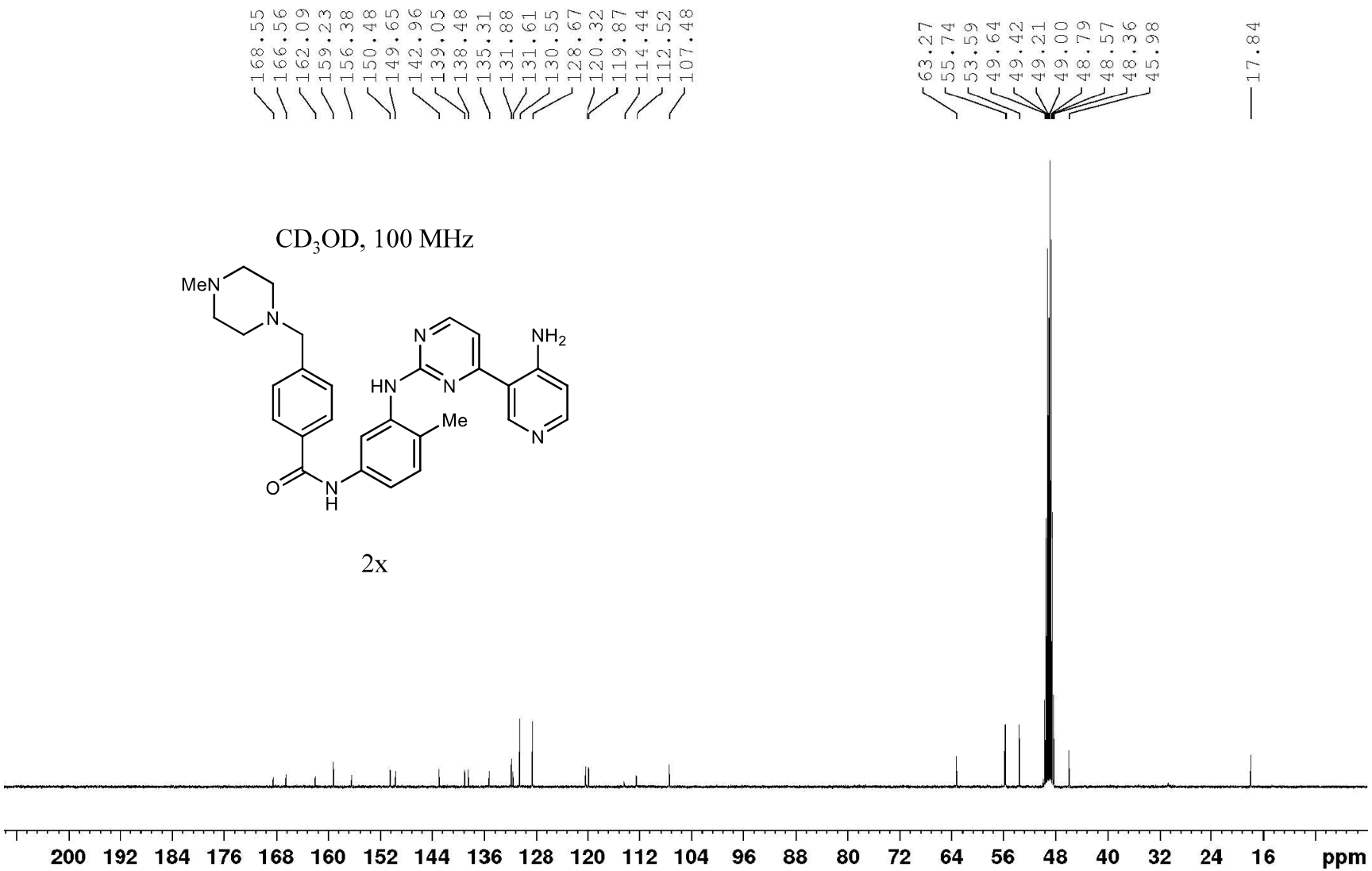

192.29
136.55
136.52
136.34
134.39
133.26
133.17
132.07
131.97
129.66
128.93
128.59
128.47
127.95
126.66
126.47
126.34
120.14
77.32
77.20
77.00
76.68
61.40
57.13
57.00
56.75
56.71
56.65
43.40
43.29
43.02
41.10
40.98
40.75
29.63
18.38
CDCl3, 100 MHz
N
N
N
N
PPh3
2w
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

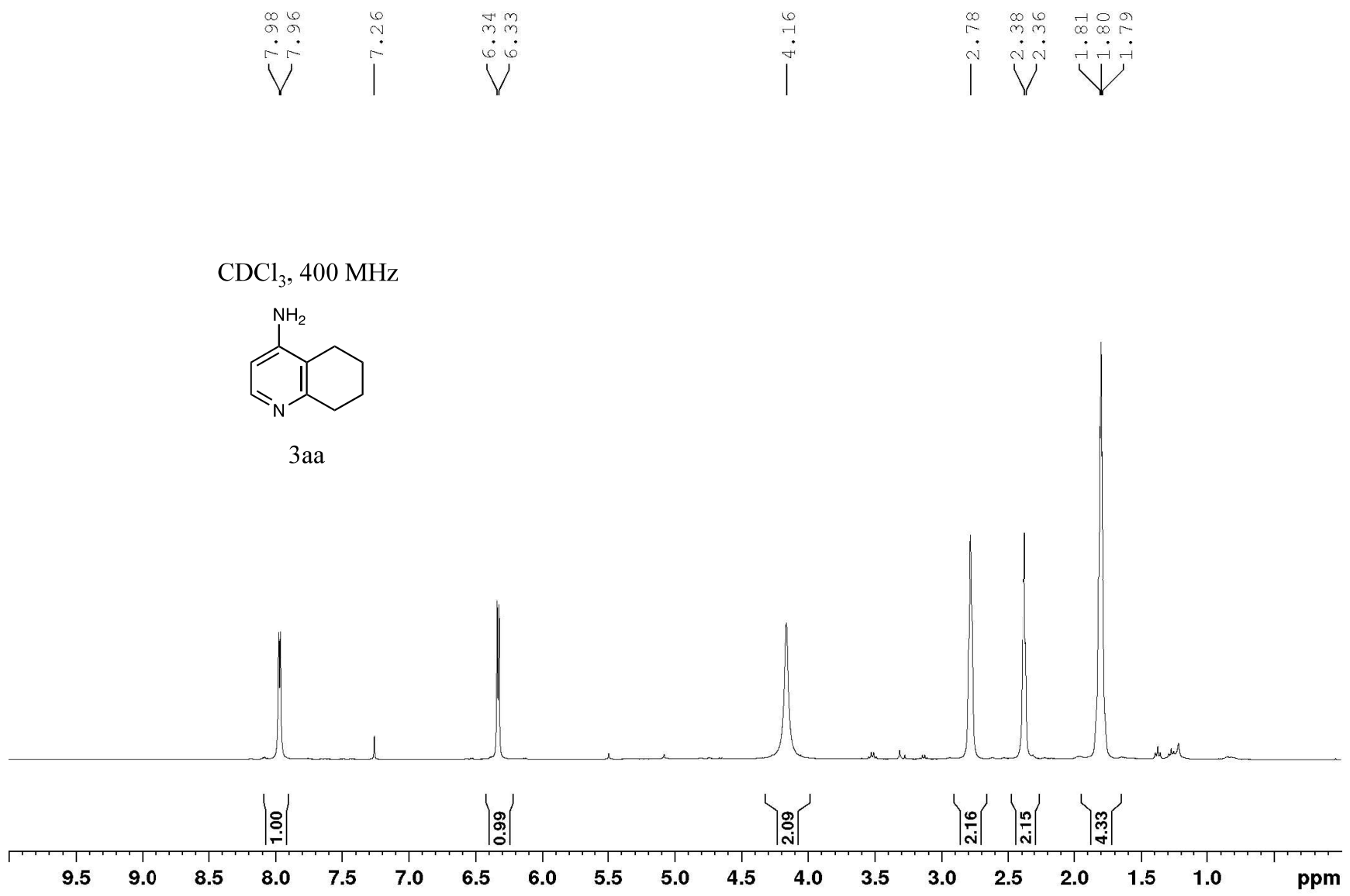
$CDCl_3$, 162 MHz

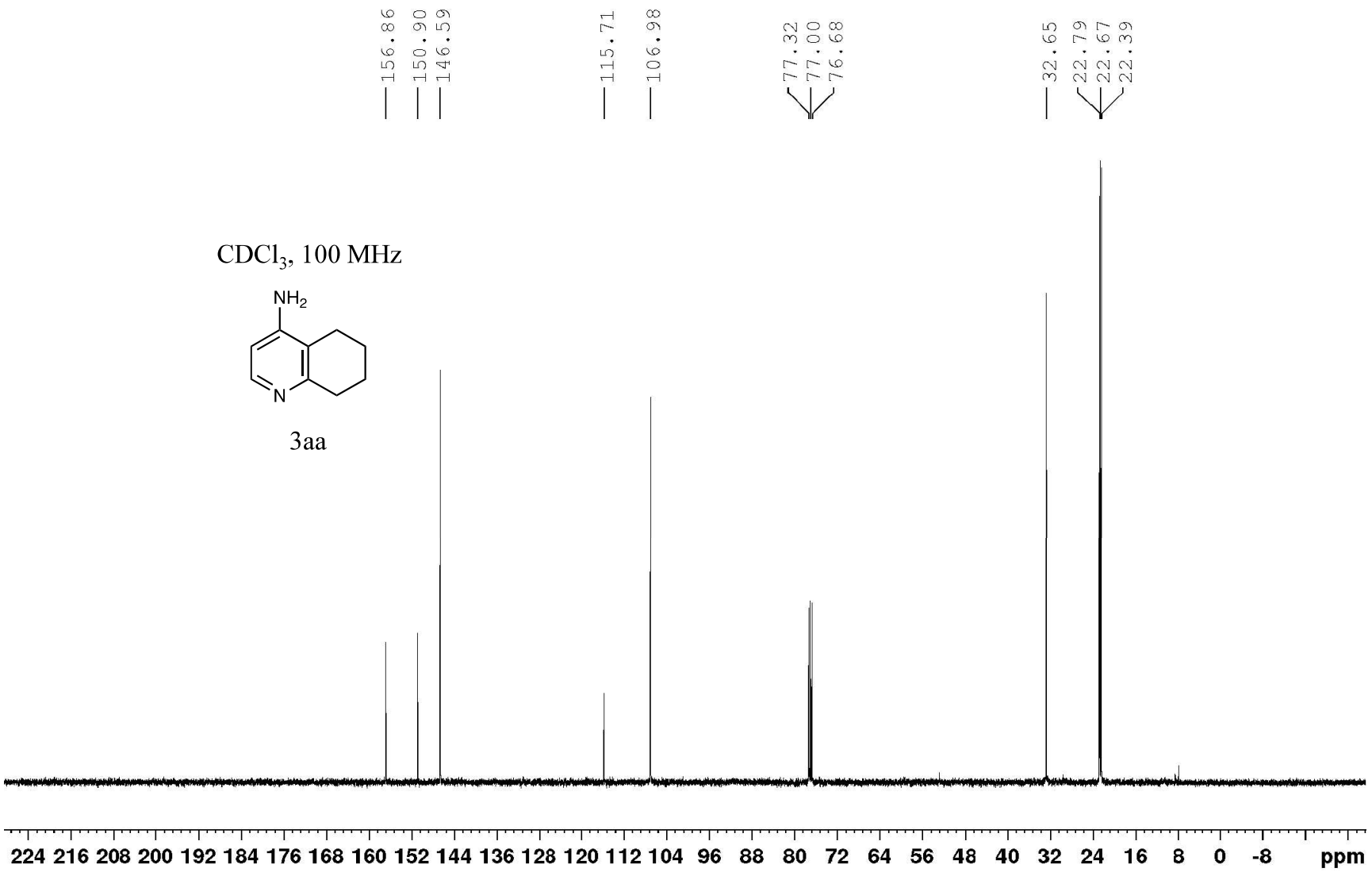


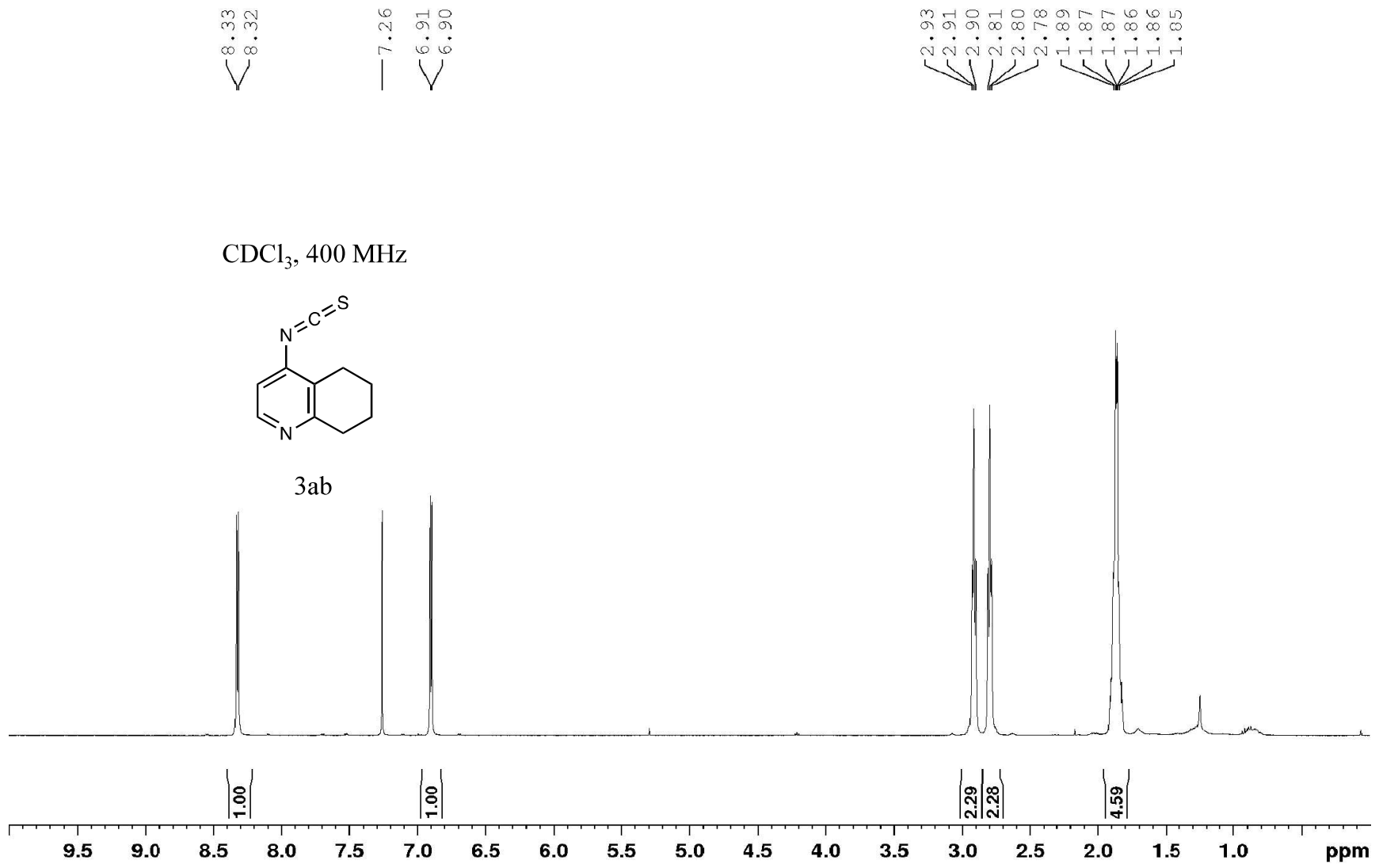
2w

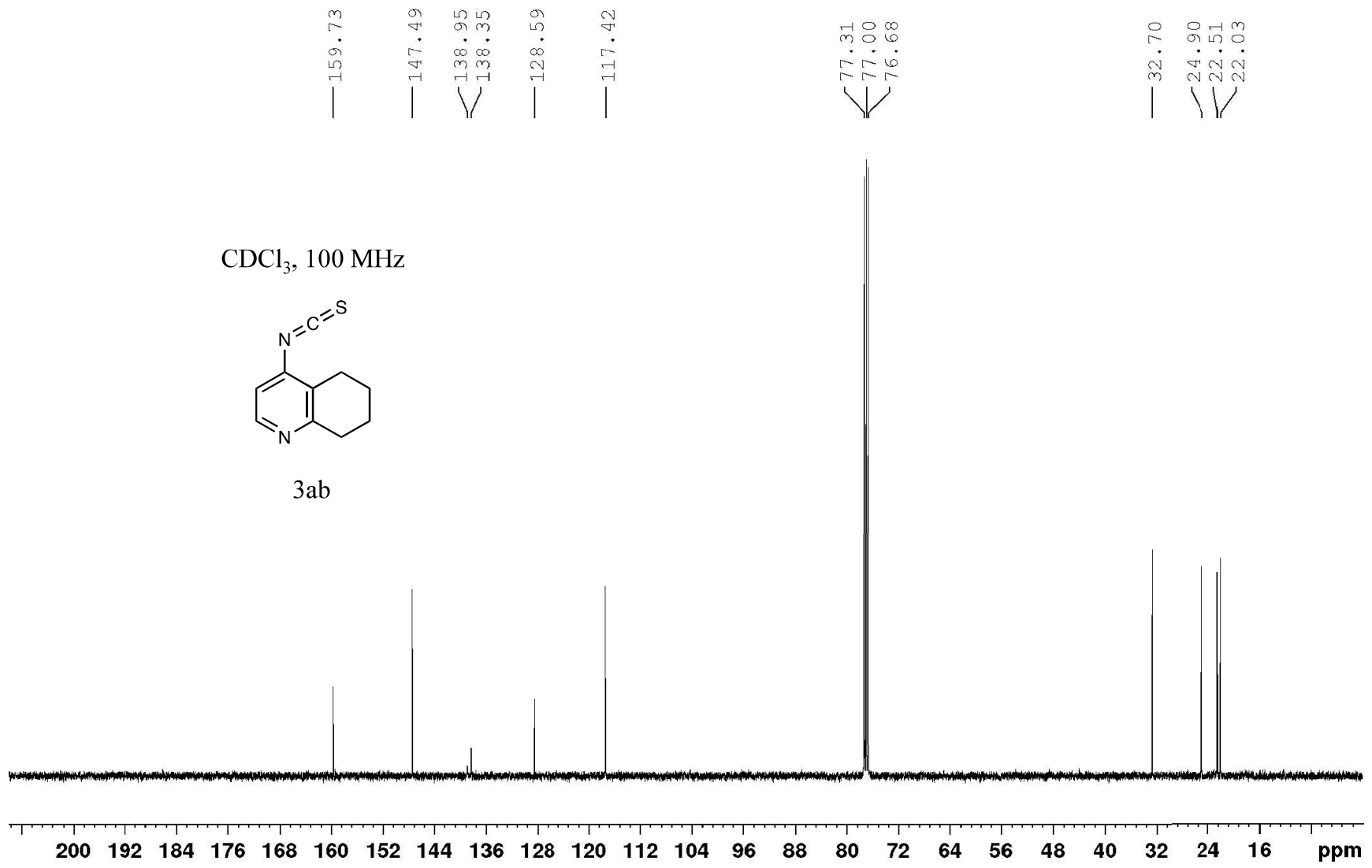

8.62
8.30
8.29
7.86
7.85
7.83
7.76
7.76
7.54
7.54
7.52
7.52
7.43
7.41
7.25
7.23
7.20
7.18
6.57
6.55
3.55
3.31
3.30
3.28
3.28
3.27
3.27
3.26
2.49
2.46
2.23
2.22
CD3OD, 400 MHz
MeN
N
HN
N
N
NH2
Me
N
O
N
H
2x
1.00
1.03
3.22
1.02
1.10
2.15
1.08
1.05
1.03
2.21
7.73
6.48
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

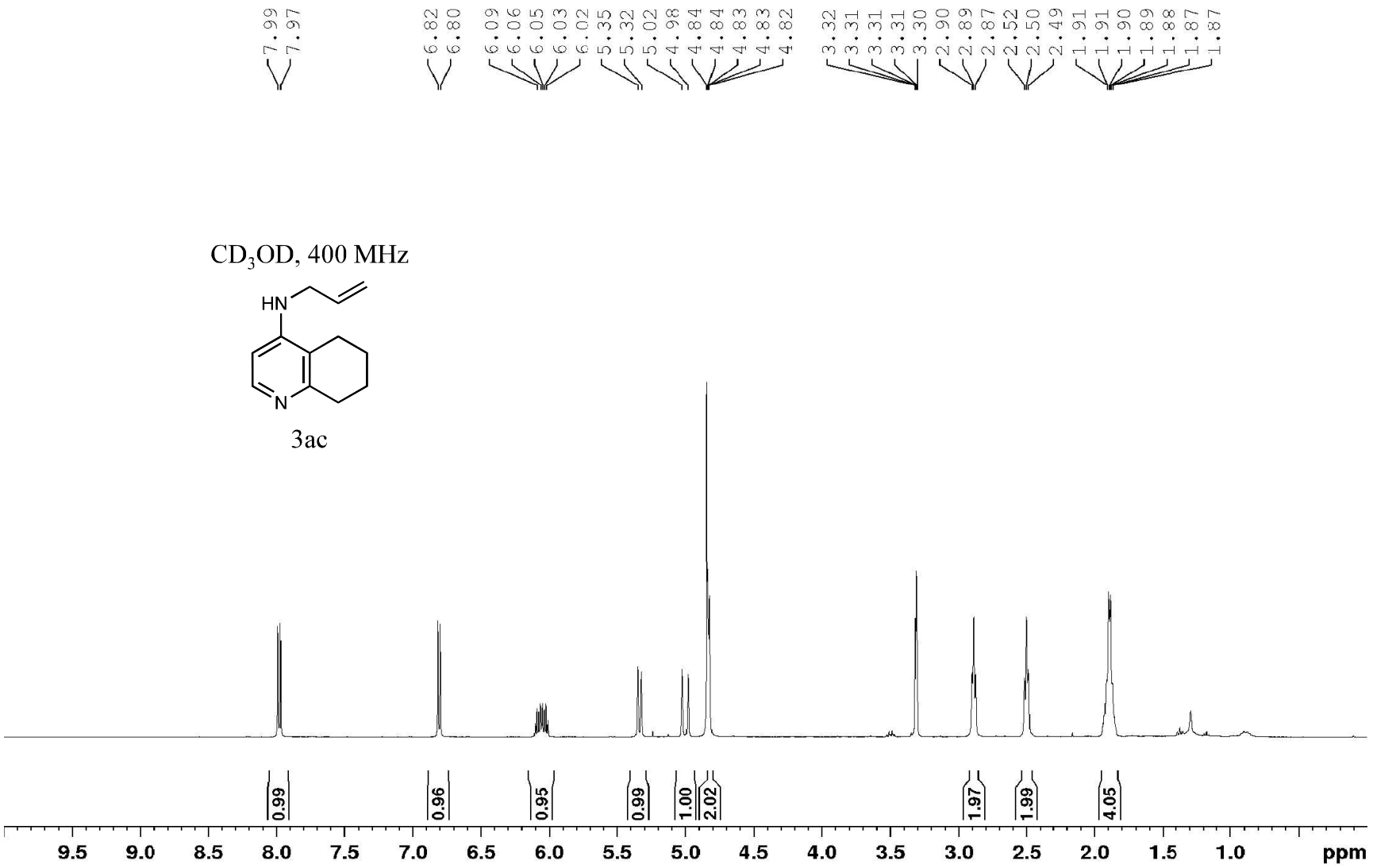

168.55
166.56
162.09
159.23
156.38
150.48
149.65
142.96
139.05
138.48
135.31
131.88
131.61
130.55
128.67
120.32
119.87
114.44
112.52
107.48
63.27
55.74
53.59
49.64
49.42
49.21
49.00
48.79
48.57
48.36
45.98
17.84
CD3OD, 100 MHz
MeN
N
HN
N
N
NH2
Me
N
O
N
H
2x
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

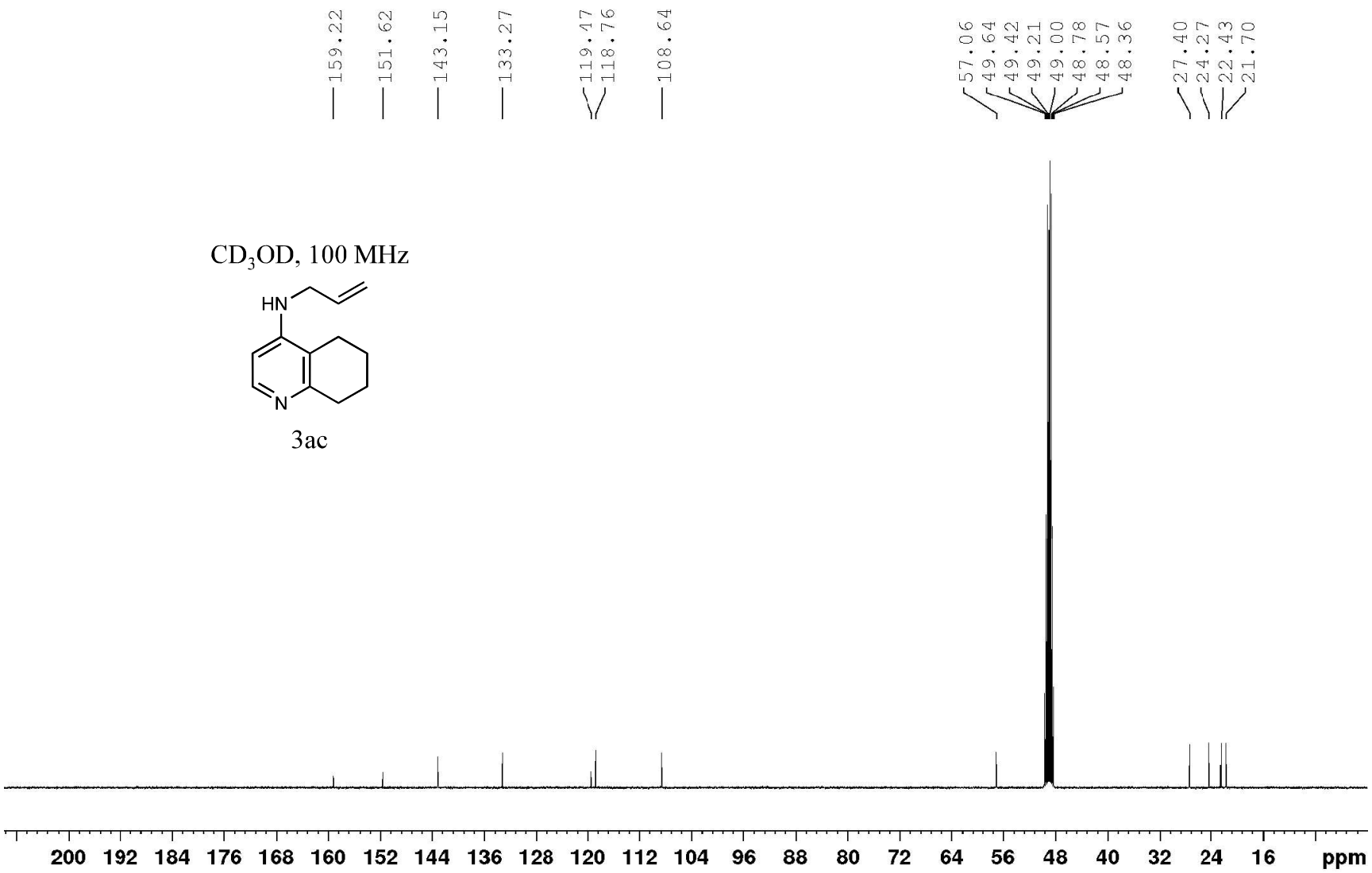

7.98
7.96
7.26
6.34
6.33
4.16
2.78
2.38
2.36
1.81
1.80
1.79
CDCl3, 400 MHz
NH2
N
3aa
1.00
0.99
2.09
2.16
2.15
4.33
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


156.86
150.90
146.59
115.71
106.98
77.32
77.00
76.68
32.65
22.79
22.67
22.39
CDCl3, 100 MHz
NH2
N
3aa
224 216 208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8 ppm


8.33
8.32
7.26
6.91
6.90
2.93
2.91
2.90
2.81
2.80
2.78
1.89
1.87
1.87
1.86
1.86
1.85
CDCl3, 400 MHz
N=C=S
N
3ab
1.00
1.00
2.29
2.28
4.59
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
ppm


159.73
147.49
138.95
138.35
128.59
117.42
77.31
77.00
76.68
32.70
24.90
22.51
22.03
CDCl3, 100 MHz
N
C
S
N
3ab
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


7.99
7.97
6.82
6.80
6.09
6.06
6.05
6.03
6.02
5.35
5.32
5.02
4.98
4.84
4.84
4.83
4.83
4.82
3.32
3.31
3.31
3.31
3.30
2.90
2.89
2.87
2.52
2.50
2.49
1.91
1.91
1.90
1.89
1.88
1.87
1.87
CD3OD, 400 MHz
HN
N
3ac
0.99
0.96
0.95
0.99
1.00
2.02
1.97
1.99
4.05
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
ppm


159.22
151.62
143.15
133.27
119.47
118.76
108.64
57.06
49.64
49.42
49.21
49.00
48.78
48.57
48.36
27.40
24.27
22.43
21.70
CD3OD, 100 MHz
HN
N
3ac
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

APPENDIX TWO

4-Selective Fluoroalkylation of Pyridines and Diazines via Phosphorus Ligand-Coupling: Experimental

(Combined work of Xuan Zhang, Kyle Nottingham, Chirag Patel, and Jeffrey Levy)

A 2.1 General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz), an Agilent Inova 400 (400 MHz) spectrometer, an Agilent Inova 500 (500 MHz) spectrometer, or a Bruker AV-111 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.1 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm) or $(CD_3)_2SO$ (2.05 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 Varian 400 MR spectrometer (100 MHz), an Agilent Inova 400 (100 MHz) spectrometer, an Agilent Inova 500 spectrometer (125 MHz) or 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), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32 ppm).

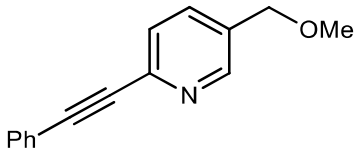
Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. High-resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF LC/MS ("OTOF") interfaced to an Agilent 1200 HPLC with multi-mode (combined ESI and APCI) and Direct Analysis in Real Time (DART) sources. (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 CHCl3, 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). Flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 um (230-400 mesh) under a positive pressure of air unless otherwise stated. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with

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.

Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Methanol, 1,2-dichloroethane (DCE), 1,4-dioxane, ethyl acetate, chloroform, and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality and used without further purification. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^{1}H NMR spectra taken from reaction samples, and liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer for MS analysis. Tf_2O (99%) was purchased from Oakwood Chemical and used without further purification but was routinely stored in a –20 °C fridge. DBU was distilled before use. 200 proof ethanol was purchased from PHARMCO-AAPER and used without further purification. HCl (4.0 M in dioxanes) and trifluoromethanesulfonic acid (98%) were purchased from Sigma Aldrich chemical company and used without further purification but were routinely stored in a –20 °C fridge.

A 2.2 Preparation of Heterocyclic Precursors

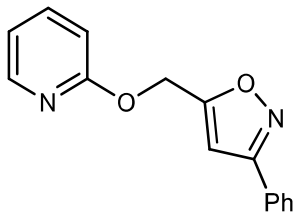
5-(Methoxymethyl)-2-(phenylethynyl)pyridine



A 100 mL flask equipped with a magnetic stirring bar was charged with $PdCl_2(PPh_3)_2$ (140 mg, 0.20 mmol) and CuI (76 mg, 0.40 mmol) dissolved in diisopropylamine (20 mL) and *N*,*N*-dimethylformamide (15 mL). The resultant solution was stirred under nitrogen at room temperature for 10 minutes before adding 2-bromo-5-(methoxymethyl)pyridine (2.02 g, 10.00 mmol) in diisopropylamine (10 mL) and phenylacetylene (1.22 g, 12.00 mmol). Then, stirring was continued at room temperature for an additional hour. After this time, the reaction mixture was diluted with EtOAc and washed with a saturated NH_4Cl solution and with brine. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a light brown oil (2.12 g, 9.50 mmol, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, J = 2.2 Hz, 1H), 7.69 (dd, J = 2.2, 8.0 Hz, 1H), 7.62–7.59 (m, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.40–7.33 (m, 3H), 4.50 (s, 2H), 3.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.33, 142.74, 135.60, 133.05, 132.12, 129.06, 128.47, 126.93, 122.32, 89.38, 88.58, 71.87, 58.52; IR υ_{max}/cm^{-1} (film): 3055, 2986, 2926, 2892, 2817, 2220, 1725, 1590, 1559, 1491, 1470, 1442, 1394, 1356, 1314, 1279, 1191, 1153, 1098, 1024,

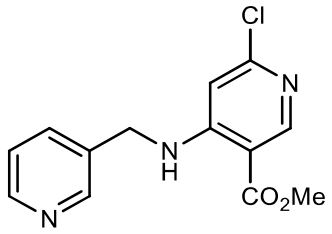
966, 914, 863, 839, 755, 689; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{14}NO^+$ = 224.1070, found 224.1079.

3-Phenyl-5-((pyridin-2-yloxy)methyl)isoxazole



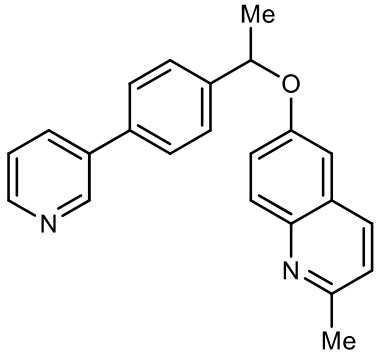
(3-Phenylisoxazol-5-yl)methanol (1.75 g, 10.00 mmol) was added portion wise under N_2 to a suspension of NaH (60%) (480 mg, 12.00 mmol) in anhydrous DMF (25 mL). After stirring at rt for 30 min, 2-fluoropyridine (1.03 mL, 12.00 mmol) was added dropwise and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with cold H_2O and extracted with EtOAc (3 x 50 mL). The organic extracts were washed with H_2O (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes) to provide the title compound as a yellow oil (2.26 g, 8.90 mmol, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (dd, *J* = 1.6, 5.1 Hz, 1H), 7.82–7.79 (m, 2H), 7.64–7.60 (m, 1H), 7.48–7.43 (m, 3H), 6.95–6.92 (m, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.64 (s, 1H), 5.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.15, 162.61, 162.55, 146.85, 139.14, 130.14, 129.12, 129.03, 126.99, 117.80, 111.38, 101.67, 58.30; IR υ_{max}/cm^{-1} (film): 3128, 3059, 2961, 1611, 1600, 1573, 1469, 1433, 1422, 1403, 1365, 1309, 1284, 1263, 1249, 1221, 1167, 1140, 1044, 1014, 993, 946, 910, 826, 772, 759, 738, 731, 689, 678; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{13}N_2O_2^+$ = 253.0972, found 253.0971.

Methyl 6-chloro-4-((pyridin-3-ylmethyl)amino)nicotinate



An oven dried 50 mL flask was charged with pyridin-3-ylmethanamine (611 μL, 6.00 mmol), methyl 4,6-dichloronicotinate (1.03 g, 5.00 mmol), *N*,*N*-diisopropylethylamine (2.09 mL, 12.00 mmol) and EtOH (10 mL). The mixture was stirred at reflux for overnight. After cooling to room temperature, the mixture was poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: EtOAc) to provide the title compound as a white solid (1.19 g, 3.55 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 8.62–8.57 (m, 3H), 7.66–7.63 (m, 1H), 7.32 (ddd, J = 0.9, 4.8, 7.2 Hz, 1H), 6.53 (s, 1H), 4.47 (d, J = 5.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.06, 156.21, 155.84, 153.22, 149.46, 148.86, 134.99, 132.45, 124.04, 107.33, 105.14, 52.20, 44.24; IR υ_{max}/cm^{-1} (film): 3320, 3070, 3036, 2961, 1687, 1592, 1576, 1565, 1501, 1484, 1465, 1442, 1428, 1408, 1363, 1324, 1297, 1280, 1223, 1191, 1113, 1065, 1026, 928, 842, 791, 712, 607; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{13}ClN_3O_2^+$ = 278.0691, found 278.0704.

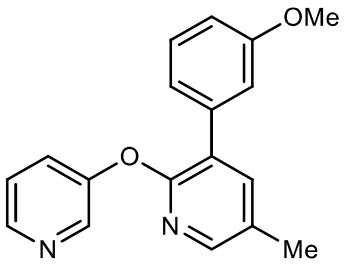
2-Methyl-6-(1-(4-(pyridin-3-yl)phenyl)ethoxy)quinoline



To a mixture of 1-(4-(pyridin-3-yl)phenyl)ethan-1-ol (598 mg, 3.00 mmol), Et_3N (544 μL, 3.30 mmol) and CH_2Cl_2 (6.6 mL) was added MsCl (256 μL, 3.30 mmol) in one portion at –10 °C for 30 minutes under nitrogen. After the reaction completed, the mixture was poured into cold water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the product 1-(4-(pyridin-3-yl)phenyl)ethyl methanesulfonate, which was used without further purification.

2-methylquinolin-6-ol (477 mg, 3.00 mmol) was added portion wise under N_2 to a suspension of NaH (60%) (144 mg, 3.60 mmol) in anhydrous DMF (4.5 mL). After stirring at room temperature for 30 min, 1-(4-(pyridin-3-yl)phenyl)ethyl methanesulfonate (prepared accordingly) in anhydrous DMF (4.5 mL) was added dropwise and the mixture was stirred at rt overnight. The reaction mixture was quenched with cold H_2O and extracted with EtOAc (3 x 50 mL). The organic extracts were washed with H_2O (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: EtOAc) to provide the title compound as a colorless oil (130 mg, 0.38 mmol, 13% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (dd, *J* = 0.8, 2.4 Hz, 1H), 8.58 (dd, *J* = 1.6, 4.8 Hz, 1H), 7.90 (d, J = 9.2 Hz, 1H), 7.86–7.81 (m, 2H), 7.58–7.52 (m, 4H), 7.40 (dd, *J* = 2.8, 9.2 Hz, 1H), 7.34 (ddd, *J* = 0.9, 4.8, 8.0 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 2.8 Hz, 1H), 5.50 (q, *J* = 6.4 Hz, 1H), 2.67 (s, 3H), 1.74 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.54, 155.37, 148.59, 148.33, 143.78, 142.94, 137.22, 136.25, 135.25, 134.32, 130.08, 127.60, 127.25, 126.40, 123.64, 122.71, 122.23, 108.58, 76.05, 25.06, 24.53; IR υ_{max}/cm^{-1} (film): 3029, 2976, 2925, 1621, 1599, 1497, 1476, 1429, 1395, 1376, 1342, 1304, 1266, 1223, 1167, 1112, 1071, 1023, 1000, 967, 940, 897, 832, 802, 710; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{21}N_2O^+$ = 341.1648, found 341.1662.

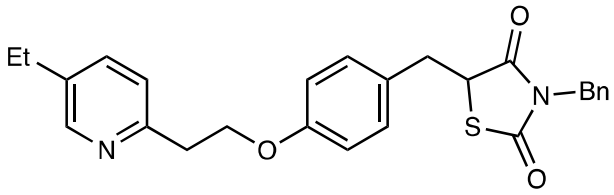
3-(3-Methoxyphenyl)-5-methyl-2-(pyridin-3-yloxy)pyridine



To a mixture of (3-methoxyphenyl)boronic acid (547 mg, 3.60 mmol), 3-bromo-5-methyl-2-(pyridin-3-yloxy)pyridine (795 mg, 3.00 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) and Na_2CO_3 (636 mg, 6.00 mmol) was added a degassed mixture of THF (14.4 mL) and H_2O (3.6 mL). The mixture was stirred at 70 °C for 24 hours under nitrogen. After cooling to room temperature, the mixture was poured into water (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 67% EtOAc in hexanes to 75% EtOAc in hexanes) to provide the title compound as a colorless oil (778 mg, 2.64 mmol, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (d, *J* = 2.6 Hz, 1H), 8.40 (dd, *J* = 1.4, 4.7 Hz, 1H), 7.94 (dd, *J* = 0.7, 2.4 Hz, 1H), 7.61 (dd, *J* = 0.7, 2.4 Hz, 1H), 7.47–7.44 (m, 1H), 7.43 (dd, *J* = 2.8, 9.2 Hz, 1H), 7.37 (ddd, *J* = 0.9, 4.8, 8.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 2.8 Hz, 1H), 5.53 (q, *J*

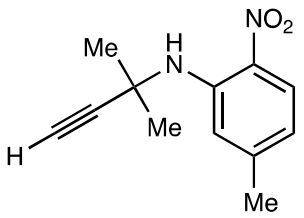
= 6.4 Hz, 1H), 2.69 (s, 3H), 1.76 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.61, 157.67, 151.37, 146.00, 145.14, 143.27, 140.98, 137.32, 129.51, 129.33, 128.28, 125.36, 123.94, 121.61, 115.09, 113.37, 55.37, 17.57. IR υ_{max}/cm^{-1} (film): 3029, 2976, 2925, 1621, 1599, 1497, 1476, 1429, 1395, 1376, 1342, 1304, 1266, 1223, 1167, 1112, 1071, 1023, 1000, 967, 940, 897, 832, 802, 710; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{17}N_2O_2^+$ = 293.3414, found 293.3428.

3-benzyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione



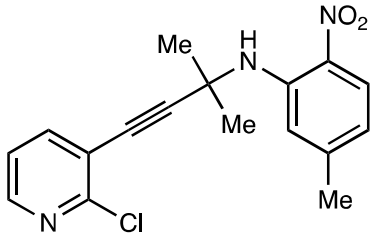
To a mixture of 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (535 mg, 1.5 mmol) in DMF (15 mL) was added NaH (60% dispersion in oil) (66 mg, 1.65 mmol) at 0 °C. The reaction was warmed to room temperature over 15 minutes, then benzyl bromide (196 μL, 1.65 mmol) was added. The reaction was stirred at room temperature for 25 hours and then concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: hexanes to 25% EtOAc in hexanes) to provide the title compound as a light-yellow solid (625 mg, 1.40 mmol, 93% yield). m.p. 94-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, J= 2.2 Hz, 1H), 7.48 (dd, J = 7.9, 2.3 Hz, 1H), 7.32 –7.23 (m, 5H), 7.21 (d, J = 7.9 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 4.79 –4.59 (m, 2H), 4.43 (dd, J = 8.7, 4.0 Hz, 1H), 4.31 (t, J = 6.6 Hz, 2H), 3.38 (dd, J = 14.1, 4.0 Hz, 1H), 3.24 (t, J = 6.6 Hz, 2H), 3.09 (dd, J = 14.1, 8.7 Hz, 1H), 2.64 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.78, 171.03, 158.32, 155.73, 149.02, 137.24, 136.01, 135.09, 130.49, 128.72, 128.16, 127.45, 123.47, 115.98, 114.83, 67.32, 51.73, 45.22, 37.64, 37.62, 25.82, 15.44. IR υ_{max}/cm^{-1} (film): 3033, 2966, 2931, 2874, 2360, 2342, 1749, 1680, 1611, 1512, 1490, 1430, 1382, 1330, 1247, 1179, 1146, 1029, 908, 730, 700. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{26}H_{27}N_2O_3S^+$= 447.1737, found 447.1748.

5-methyl-*N*-(2-methylbut-3-yn-2-yl)-2-nitroaniline



To a mixture of 2-fluoro-4-methyl-1-nitrobenzene (776 mg, 5 mmol) and K_2CO_3 (1.38 g, 10 mmol) in DMF was added 2-methylbut-3-yn-2-amine (2.63 mL, 25 mmol), and the reaction was heated to 60 °C for 72 hours. After cooling to room temperature, the reaction was poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 5% CH_2Cl_2 in hexanes) to provide the title compound as a yellow solid (562 mg, 2.57 mmol, 51% yield). m.p. 104-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 – 8.20 (m, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.34 (dd, J = 1.8, 0.9 Hz, 1H), 6.51 (dd, J = 8.8, 1.7 Hz, 1H), 2.47 (s, 1H), 2.37 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.01, 143.60, 131.22, 127.03, 117.81, 116.26, 86.22, 71.92, 47.61, 30.51, 22.42. IR υ_{max}/cm^{-1} (film): 3331, 3288, 2994, 2979, 2938, 2360, 2342, 1619, 1582, 1486, 1414, 1334, 1276, 1237, 1209, 1177, 1076, 988, 940, 753, 679, 647. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_{15}N_2O_2^+$ = 219.1128, found 219.1119.

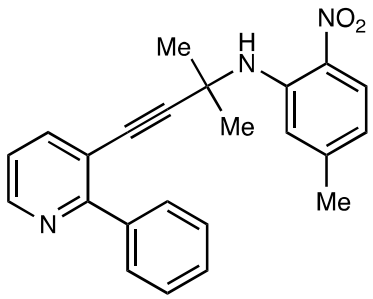
***N*-(4-(2-chloropyridin-3-yl)-2-methylbut-3-yn-2-yl)-5-methyl-2-nitroaniline**



To a mixture of 3-bromo-2-chloropyridine (620 mg, 3.22 mmol), CuI (37 mg, 0.19 mmol), $PdCl_2(PPh_3)_2$ (68 mg, 0.097 mmol) and Et_3N (6.5 mL) was added 5-methyl-*N*-(2-methylbut-3-yn-2-yl)-2-nitroaniline (704 mg, 3.22 mmol). The reaction was heated to 100 °C for 24 hours. After cooling to room temperature, EtOAc (20 mL) and water (20 mL) was added, the organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a yellow oil (692 mg, 2.10 mmol, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (s, 1H), 8.30 (dd, J = 4.9, 1.8 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.72

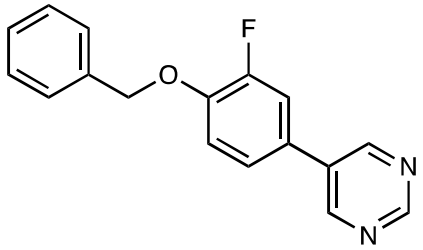
(dd, J = 7.7, 2.0 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.19 (dd, J = 7.6, 4.8 Hz, 1H), 6.51 (dd, J = 8.7, 1.7 Hz, 1H), 2.36 (s, 3H), 1.83 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 152.48, 148.57, 147.11, 143.42, 141.51, 131.20, 126.92, 121.97, 119.95, 117.93, 116.31, 99.29, 78.80, 48.28, 30.32, 22.39. IR υ_{max}/cm^{-1} (film): 3352, 2984, 2938, 2360, 2342, 2253, 1618, 1578, 1491, 1394, 1335, 1270, 1236, 1215, 1188, 1079, 908, 754, 730. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{17}ClN_3O_2^+$ = 330.1004, found 330.1011.

5-methyl-*N*-(2-methyl-4-(2-phenylpyridin-3-yl)but-3-yn-2-yl)-2-nitroaniline



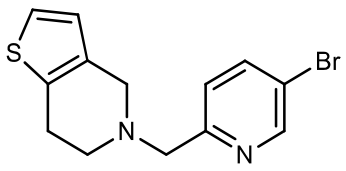
To a mixture of *N*-(4-(2-chloropyridin-3-yl)-2-methylbut-3-yn-2-yl)-5-methyl-2-nitroaniline (241 mg, 0.73 mmol), phenylboronic acid (98 mg, 0.80 mmol), $Pd(PPh_3)_4$ (85 mg, 0.073 mmol) and Na_2CO_3 (164 mg, 1.55 mmol) was added toluene (6 mL) and EtOH (6 mL). The reaction was heated to 110 °C for 24 hours. After cooling to room temperature, the reaction was filtered through celite, EtOAc (20 mL) and water (20 mL) was added, the organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 10% CH_2Cl_2 in hexanes) to provide the title compound as a yellow oil (252 mg, 0.678 mmol, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, 1H), 8.32 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.88 (dd, J = 6.7, 2.9 Hz, 2H), 7.78 (dd, J = 7.8, 1.8 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.21 (dd, J = 7.8, 4.8 Hz, 1H), 7.15 (s, 1H), 6.52 – 6.39 (m, 1H), 2.13 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.97, 148.89, 146.99, 143.57, 140.99, 139.26, 131.05, 129.21, 129.08, 127.89, 126.93, 121.46, 117.73, 117.32, 116.14, 96.73, 81.84, 48.30, 30.18, 22.29. IR υ_{max}/cm^{-1} (film): 3351, 3058, 2980, 2932, 2360, 2342, 1618, 1578, 1490, 1422, 1334, 1265, 1237, 1186, 1077, 743. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{22}N_3O_2^+$ = 372.1707, found 372.1719.

5-(4-(benzyloxy)-3-fluorophenyl)pyrimidine



To a mixture of 5-bromopyrimidine (795 mg, 5.0 mmol), (4-(benzyloxy)-3-fluorophenyl)boronic acid (1.85 g, 7.5 mmol), Pd/C (10 % w/w) (160 mg, 0.15 mmol) and K_2CO_3 (691 mg, 5.0 mmol) was added EtOH (30 mL) and H_2O (10 mL). The reaction was heated to 80 °C for 18 hours. After cooling to room temperature, the reaction was filtered through celite, EtOAc (50 mL) and water (50 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a white solid (1.135 g, 4.05 mmol, 81 % yield). m.p. 103-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.18 (s, 1H), 8.89 (s, 2H), 7.49 – 7.44 (m, 2H), 7.41 (ddd, J = 8.0, 6.9, 1.1 Hz, 2H), 7.38 – 7.34 (m, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.13 (t, J = 8.4 Hz, 1H), 5.22 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.54, 154.64, 152.18, 147.67 (d, J = 10.7 Hz), 136.17, 133.12 (d, J = 1.9 Hz), 128.87, 128.47, 127.70 (d, J = 6.8 Hz), 127.55, 122.99 (d, J = 3.6 Hz), 116.45 (d, J = 2.4 Hz), 114.99 (d, J = 19.6 Hz), 71.52; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -131.81 (dd, J = 11.8, 8.4 Hz). IR υ_{max}/cm^{-1} (film): 3050, 3035, 2941, 2883, 2578, 2360, 2341, 1618, 1585, 1559, 1522, 1417, 1403, 1389, 1302, 1275, 1257, 1203, 1146, 1052, 1012, 1001, 898, 873, 855, 791, 749, 722, 699, 635, 625. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{14}FN_2O^+$ = 281.1085, found 281.1105.

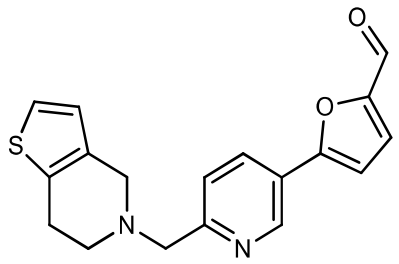
5-((5-bromopyridin-2-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine



An oven-dried 200 mL round bottom flask was charged with 5-bromopicolinaldehyde (2.68 g, 14.4 mmol), 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (2.20 g, 15.8 mmol), and sodium triacetoxyhydroborate (6.1 g, 28.8 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill. DCM (72 mL) was added to the reaction flask along with glacial AcOH (1.65 mL). After 19 hours at room temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL), diluted with CH_2Cl_2, and the organic layer

was separated. The aqueous layer was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 40 % EtOAc in hexanes) to provide the title compound as a white solid (4.17 g, 13.5 mmol, 94 % yield). mp 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (d, J = 2.2 Hz, 1H), 7.79 (dd, J = 8.3, 2.4 Hz, 1H), 7.43 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 5.1 Hz, 1H), 6.69 (d, J = 5.1 Hz, 1H), 3.83 (s, 2H), 3.62 (s, 2H), 2.95 – 2.88 (m, 2H), 2.88 – 2.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.67, 150.33, 139.28, 133.71, 133.42, 125.30, 124.54, 122.88, 119.22, 63.16, 53.31, 50.98, 25.57. IR υ_{max}/cm^{-1} (film): 2962, 2901, 2826, 2771, 2360, 2342, 1573, 1468, 1446, 1376, 1365, 1320, 1171, 1108, 1086, 1001, 982, 843, 703, 652. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{14}BrN_2S^+$ = 309.0056, found 309.0041.

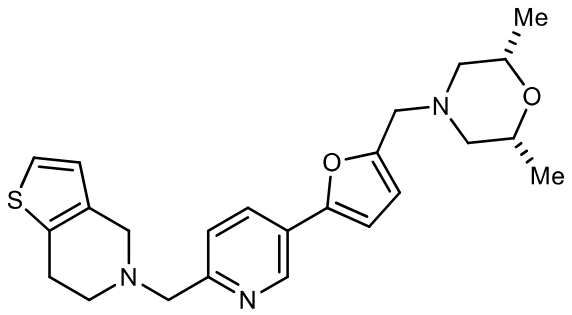
5-(6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-carbaldehyde



An oven dried 200 mL pressure tube was charged with 5-((5-bromopyridin-2-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (4.02 g, 13.0 mmol), (5-formylfuran-2-yl)boronic acid (1.65 g, 11.8 mmol), K_2CO_3 (4.89 g, 35.4 mmol), $Pd(OAc)_2$ (132 mg, 0.59 mmol), triphenylphosphine (619 mg, 2.36 mmol) and subjected to three cycles of vacuum/nitrogen backfill. H_2O (43 mL) and dimethoxyethane (41 mL) were charged to the tube. The mixture was heated at 85 ºC for 18 hours then diluted with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted 2x with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 2 % MeOH in CH_2Cl_2) to provide the title compound as a slightly impure white solid. Further purification was achieved by dissolving the compound in CH_2Cl_2 and adding an excess of 1M HCl. The aqueous phase was extracted with CH_2Cl_2, separated, and treated with sat. aq. $NaHCO_3$. The aqueous phase was then extracted with CH_2Cl_2 and the combined organic layers were washed with brine then dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as pure white solid (1.45 g, 4.5 mmol, 38 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 8.99 (d, J = 2.1 Hz, 1H), 8.10 (dd, J = 8.2, 2.3 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 3.7 Hz, 1H), 7.08 (d, J = 5.1 Hz, 1H), 6.92 (d, J = 3.7 Hz, 1H), 6.70 (d, J = 5.1 Hz, 1H), 3.94 (s, 2H), 3.68 (s, 2H), 3.00 – 2.83 (m, 4H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 177.43, 160.18, 156.71, 152.67, 146.18, 133.69, 133.42, 133.03, 125.31, 123.96, 123.28, 122.91, 108.62, 63.55, 53.36, 51.04, 25.55. IR υ_{max}/cm^{-1} (film): 3109, 2913, 2813, 2360, 2342, 1690, 1600, 1584, 1519, 1467, 1403, 1376, 1357, 1340, 1259, 1019, 965, 797, 768, 754, 700, 637. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{17}N_2O_2S^+$ = 325.1005, found 325.1014.

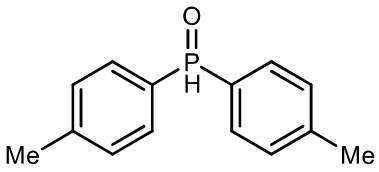
5-(6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-carbaldehyde



An oven-dried 100 mL round bottom flask was charged with 5-(6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-carbaldehyde (0.973 g, 3.00 mmol), *cis*-2,6,-dimethylmorpholine (0.406 mL, 3.30 mmol), and sodium triacetoxyhydroborate (1.27 g, 6.00 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill. DCM (15 mL) was added to the reaction flask along with glacial AcOH (0.343 mL). After 3 hours stirring at room temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, gradient elution: 90 % EtOAc in hexanes to 5 % MeOH in CH_2Cl_2) to provide the title compound as an amber oil (1.17 g, 2.8 mmol, 92 % yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.85 (d, *J* = 1.9 Hz, 1H), 7.91 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 5.1 Hz, 1H), 6.68 (dd, *J* = 10.6, 4.2 Hz, 2H), 6.33 (d, *J* = 3.3 Hz, 1H), 3.89 (s, 2H), 3.71 (ddq, *J* = 12.5, 6.3, 3.1, 1.7 Hz, 2H), 3.63 (d, *J* = 17.5 Hz, 4H), 2.99 – 2.83 (m, 4H), 2.78 (d, *J* = 10.5 Hz, 2H), 1.86 (t, *J* = 10.8 Hz, 2H), 1.15 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.28, 152.06, 150.82, 144.70, 133.73, 133.34, 131.39, 125.48, 125.21, 122.94, 122.66, 111.19, 106.81, 71.63, 63.52, 58.94, 54.81, 53.20, 50.85, 25.47, 19.15. IR υ_{max}/cm^{-1} (film): 2970, 2929, 2811, 2771, 2360, 2342, 1591, 1566, 1477, 1453, 1397, 1374, 1300, 1197, 1141, 1082, 1065, 1018, 981, 837, 788, 733, 700. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{24}H_{30}N_3O_2S^+$ = 424.2053, found 424.2062.

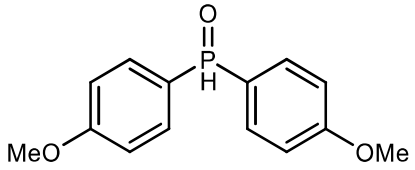
A 2.3 Preparation of Phosphines

Di-p-tolylphosphine oxide



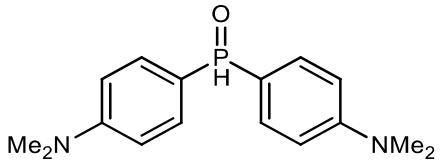
An oven-dried 200 mL round bottom flask was charged with 4-bromotoluene (11.4 g, 66.6 mmol) and 70 mL THF. The resulting solution was added dropwise to a separate oven-dried 200 mL round bottom flask containing magnesium turnings (1.70 g, 70 mmol) at 0 °C. Upon completion of the addition, the flask was allowed to warm to room temperature. After stirring for 2 hours at room temperature the mixture was cooled with an ice bath and a solution of diethyl phosphite (2.6 mL, 20 mmol) in 7.0 mL THF was added. The mixture was allowed to warm to room temperature and stirred for two hours. Subsequently 60 mL 0.1 N HCl was added drop wise over a period of 5 minutes at 0 °C, followed by addition of 60 mL methyl *tert*-butyl ether (MTBE) and stirring for further 5 minutes. The upper organic phase was decanted from the formed gel. 60 mL CH_2Cl_2 was added to the remaining gel and the mixture agitated well for additional 5 minutes. The resultant mixture was then filtered through a frit equipped with Celite. After washing the Celite with CH_2Cl_2 (2 x 60 mL) the organic phases were combined, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica gel: 90 % EtOAc in Hexanes) to give the product di-p-tolylphosphine oxide as a white solid (4.35 g, 18.9 mmol, 94 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, J = 480 Hz, 1H), 7.57 (dd, J = 13.5, 7.9 Hz, 4H), 7.29 (dd, J = 8.0, 2.7 Hz, 4H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.04 (d, J = 3.2 Hz), 130.70 (d, J = 11.9 Hz), 129.56 (d, J = 13.4 Hz), 128.32 (d, J = 104.0 Hz), 21.64 (d, J = 1.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.53. The spectroscopic data is in agreement with the previous reported synthesis.[2]

Bis(4-methoxyphenyl)phosphine oxide



An oven-dried 200 mL round bottom flask was charged with 4-bromoanisole (8.3 mL, 66.6 mmol) and 70 mL THF. The resulting solution was added dropwise to a separate oven-dried 200 mL round bottom flask containing magnesium turnings (1.70 g, 70 mmol) at 0 °C. Upon completion of the addition, the flask was allowed to warm to room temperature. After stirring for 2 hours at room temperature the mixture was cooled with an ice bath and a solution of diethyl phosphite (2.6 mL, 20 mmol) in 7.0 mL THF was added. The mixture was allowed to warm to room temperature and stirred for two hours. Subsequently 60 mL 0.1 N HCl was added drop wise over a period of 5 minutes at 0 °C, followed by addition of 60 mL methyl *tert*-butyl ether (MTBE) and stirring for further 5 minutes. The upper organic phase was decanted from the formed gel. 60 mL CH_2Cl_2 was added to the remaining gel and the mixture agitated well for additional 5 minutes. The resultant mixture was then filtered through a frit equipped with Celite. After washing the Celite with CH_2Cl_2 (2 x 60 mL) the organic phases were combined, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica gel: 1 % MeOH in EtOAc) to give the product bis(4-methoxyphenyl)phosphine oxide as a white solid (4.72 g, 18.0 mmol, 90 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J = 476 Hz, 1H), 7.61 (dd, J = 13.2, 8.6 Hz, 4H), 6.99 (dd, J = 8.7, 2.3 Hz, 4H), 3.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.88 (d, J = 2.8 Hz), 132.63 (d, J = 12.9 Hz), 123.01 (d, J = 107.9 Hz), 114.43 (d, J = 13.9 Hz), 55.36; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.56. The spectroscopic data is in agreement with the previous reported synthesis.[2]

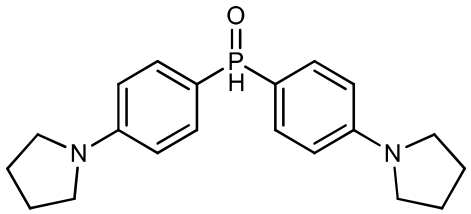
Bis(4-(dimethylamino)phenyl)phosphine oxide



An oven-dried 100 mL round bottom flask was charged with 4-bromo-*N*,*N*-dimethylaniline (4.00 g, 20.00 mmol) and 20 mL THF. The resulting solution was added dropwise to a separate oven-dried 100 mL round bottom flask containing magnesium turnings (504 mg, 21.00 mmol) at 0 °C. After stirring for four hours at room temperature, the mixture was cooled with an ice bath and a solution of diethyl phosphite (773 µL, 6.00 mmol) in 2 mL THF was added. The mixture was allowed to warm to room temperature and stirred

for two hours. Subsequently 16 mL 0.1 N HCl was added drop wise over a period of 5 minutes at 0 °C, followed by addition of 16 mL methyl *tert*-butyl ether (MTBE) and stirring for further 5 minutes. The upper organic phase was decanted from the formed gel. 20 mL CH_2Cl_2 were added to the remaining gel and the mixture agitated well for additional 5 minutes. The resultant mixture was then filtered through a frit equipped with Celite. After washing the Celite with CH_2Cl_2 (2 x 30 mL) the organic phases were combined, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica gel: EtOAc to 2% MeOH in EtOAc) to give the product bis(4-(dimethylamino)phenyl)phosphine oxide as a white solid (1.38 g, 16 .00mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J = 468 Hz, 1H), 7.50 (dd, J = 13.0, 8.8 Hz, 4H), 6.71 (dd, J = 8.9, 2.2 Hz, 4H), 3.01 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.64 (d, J = 2.4 Hz), 132.21 (d, J = 12.6 Hz), 117.18 (d, J = 111.9 Hz), 111.41 (d, J = 13.4 Hz), 39.96; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.11. The spectroscopic data is in agreement with previous reported synthesis.[2]

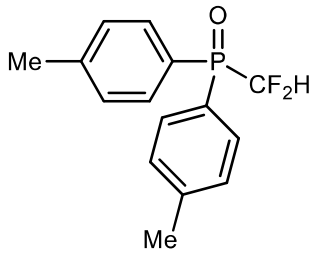
Bis(4-(pyrrolidin-1-yl)phenyl)phosphine oxide



An oven-dried 500 mL round bottom flask was charged with 1-(4-bromophenyl)pyrrolidine (31.0 g, 137 mmol) and 140 mL THF. The resulting solution was added dropwise to a separate oven-dried 500 mL round bottom flask containing magnesium turnings (3.51 g, 144 mmol) at 0 °C. Upon completion of the addition, the flask was allowed to warm to room temperature. After stirring for 2 hours at room temperature the mixture was cooled with an ice bath and a solution of diethyl phosphite (5.31 mL, 41.2 mmol) in 14.0 mL THF was added. The mixture was allowed to warm to room temperature and stirred for two hours. Subsequently 140 mL 0.1 N HCl was added drop wise over a period of 5 minutes at 0 °C, followed by addition of 140 mL methyl *tert*-butyl ether (MTBE) and stirring for further 5 minutes. The upper organic phase was decanted from the formed gel. 140 mL CH_2Cl_2 was added to the remaining gel and the mixture agitated well for additional 5 minutes. The resultant mixture was then filtered through a frit equipped with Celite. After washing the Celite with CH_2Cl_2 (2 x 100 mL) the organic phases were combined, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica gel: 3 % MeOH in CH_2Cl_2) to give the product bis(4-(pyrrolidin-1-yl)phenyl)phosphine oxide as a white solid (11.9 g, 34.8 mmol, 84 % yield). mp 176-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, J = 468.6 Hz, 1H), 7.48 (dd, J = 13.0, 8.7 Hz, 4H), 6.56 (dd, J = 8.8, 2.3 Hz, 4H), 3.40 – 3.20 (m, 8H), 2.11 –

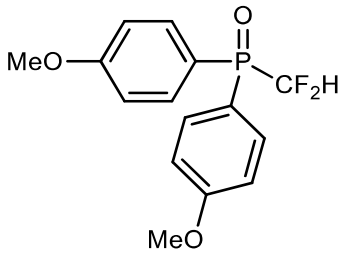
1.92 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.27 (d, *J* = 2.3 Hz), 132.50 (d, *J* = 12.9 Hz), 116.72 (d, *J* = 112.6 Hz), 111.45 (d, *J* = 13.6 Hz), 47.57, 25.56; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.61. IR υ_{max}/cm^{-1} (film): 2953, 2850, 2270, 1594, 1542, 1482, 1459, 1385, 1283, 1175, 1125, 1003, 961, 927, 802, 708. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{26}N_2OP^+$ = 341.1777, found 341.1769.

(Difluoromethyl)di-p-tolylphosphine oxide



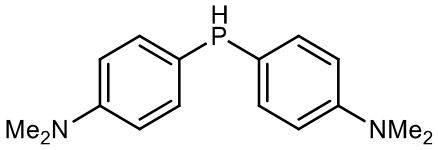
Prepared according to a previous report.[3] An oven-dried 300 mL round bottom flask was charged with di-p-tolylphosphine oxide (3.45 g, 15 mmol) and K_2CO_3 (10.4 g, 75 mmol) and subjected to three cycles of vacuum/nitrogen backfill. CH_2Cl_2 (30 mL) and H_2O (90 mL) were added and the mixture was stirred until all solids dissolved. The flask was cooled to 0 °C and a solution of bromodifluoromethyl)trimethylsilane (6.92 mL, 45 mmol) in CH_2Cl_2 (15 mL) was added. After being stirred at 0 °C for 16 h, the reaction was quenched by adding water (150 mL), followed by extraction with EtOAc (2 × 100 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and filtered. After removal of the solvents *in vacuo*, the crude material was purified by flash chromatography (silica gel: 50 % EtOAc in petroleum ether) to provide the title compound as a white solid (2.92 g, 10.4 mmol, 69 % yield). mp 127-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (dd, *J* = 11.6, 8.0 Hz, 4H), 7.35 (dd, *J* = 7.9, 2.5 Hz, 4H), 6.29 (td, *J* = 49.2, 22.0 Hz, 1H), 2.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.20 (d, *J* = 2.9 Hz), 132.20 (d, *J* = 10.0 Hz), 129.80 (d, *J* = 12.7 Hz), 123.45 (d, *J* = 104.8 Hz), 115.51 (td, *J* = 266.1, 104.6 Hz), 21.85 (d, *J* = 1.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -132.25 (dd, *J* = 69.5, 49.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.08 (t, *J* = 69.4 Hz). IR υ_{max}/cm^{-1} (film): 3041, 2967, 2360, 2342, 1602, 1384, 1347, 1220, 1200, 1194, 1121, 1080, 1040, 805, 664, 641, 629. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{16}F_2OP^+$ = 281.0901, found 281.0913.

(Difluoromethyl)bis(4-methoxyphenyl)phosphine oxide



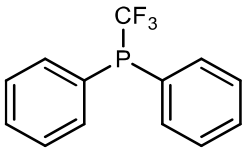
Prepared according to a modified version of a previous report.[4] An oven-dried round 100 mL round bottom flask was charged with bis(4-methoxyphenyl)phosphine oxide (13.1 g, 50 mmol) and brought into a nitrogen-filled glovebox. LiH (0.48 g, 60 mmol) and LiCl (8.5 g, 200 mmol) were added and the flask was brought out of the glovebox and equipped with a nitrogen line. After cooling to 0 °C, the flask was charged with DMF while stirring and allowed to warm to room temperature. After 30 minutes, trifluoromethyltrimethylsilane (30 mL, 200 mmol) was added dropwise at 0 °C, and the reaction mixture was allowed to warm to room temperature. After 20 minutes, the solution was cooled to 0 °C and a 1M solution of aqueous K_2CO_3 was added slowly, and the reaction was allowed to warm to room temperature. After 2 hours, the solution was treated with 60 mL of 1M HCl and extracted (3x) with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo.* The crude material was purified by flash chromatography (silica gel: 25 % EtOAc in CH_2Cl_2) to provide the title compound as white solid (12.3 g, 39.5 mmol, 79 % yield). mp 87-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (dd, J = 11.1, 8.7 Hz, 4H), 7.04 (dd, J = 8.8, 2.2 Hz, 4H), 6.27 (td, J = 49.3, 21.9 Hz, 1H), 3.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.62 (d, J = 2.9 Hz), 134.15 (d, J = 10.9 Hz), 117.74 (d, J = 109.4 Hz), 115.58 (td, J = 265.7, 105.7 Hz), 114.67 (d, J = 13.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -132.26 (dd, J = 69.4, 49.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.84 (t, J = 69.4 Hz). IR υ_{max}/cm^{-1} (film): 3012, 2964, 2845, 2360, 2342, 1594, 1567, 1499, 1458, 1411, 1318, 1294, 1256, 1199, 1185, 1123, 1107, 1081, 1024, 828, 815, 800, 670, 640, 575. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{16}F_2O_3P^+$ = 313.0800, found 313.0812.

4,4'-Phosphanediylbis(N,N-dimethylaniline)



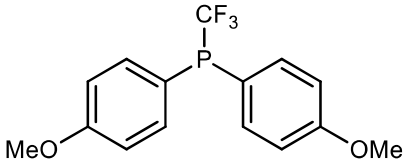
A 100 mL flask was equipped with a gas inlet, a bubbler and an addition funnel. The addition funnel was charged with a solution of the bis(4-(dimethylamino)phenyl)phosphine oxide (577 mg, 2.00 mmol) in 4 mL THF. This solution was added over a period of 15 minutes to a 1M solution of DIBAL-H in hexane (6 mL, 6.00 mmol) and stirred for overnight at room temperature (caution: gas evolution). Subsequently 7 mL freshly degassed MTBE was added via the addition funnel over ten minutes. After cooling the solution to 0 °C, 4 mL 2N aq. NaOH (freshly degassed) was added via the addition funnel over 15 minutes (caution: vigorous gas evolution), followed by 2 mL sat. aq. NaCl over 5 minutes. The solution was stirred for additional 5 minutes and warmed to room temperature. Stirring was subsequently stopped, and the layers allowed to separate. The organic layer was then transferred via cannula to a second 250 mL flask charged with Na_2SO_4 (4.00 g). After stirring for 10 minutes the mixture was filtered under N_2 atmosphere and the solvent removed *in vacuo* yielding 4,4'-phosphanediylbis(N,N-dimethylaniline) as a white solid (495 mg, 1.82 mmol, 91% yield) (caution: the phosphine is air sensitive and stored in glovebox). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (t, J = 7.8 Hz, 4H), 6.67 (d, J = 7.1 Hz, 4H), 5.16 (d, J = 218.8 Hz, 1H), 2.94 (s, 12H). ^{31}P NMR (162 MHz, $CDCl_3$) δ: -46.13. The spectroscopic data is in agreement with previous reported synthesis.[2]

Diphenyl(trifluoromethyl)phosphane



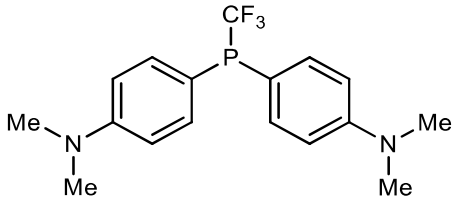
Prepared according to a previous report.[5] An oven dried 100 mL round bottom flask was charged with CsF, diethyl ether, and phenoxydiphenylphosphane under nitrogen. Trifluoromethyltrimethylsilane was added and the reaction was stirred for 16 hours at room temperature, then the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica gel: 2 % EtOAc in hexanes) to yield the title compound as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (t, J = 8.2 Hz, 4H), 7.40 – 7.27 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.09 (d, J = 21.0 Hz), 130.52, 129.54 (dq, J = 9.9, 3.2 Hz), 128.90 (d, J = 7.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 2.54 (q, J = 73.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -55.16 (d, J = 73.4 Hz). The spectroscopic data is in agreement with previous reported synthesis.[5]

Bis(4-methoxyphenyl)(trifluoromethyl)phosphane



Prepared according to a modified version of a previous report.[4] An oven-dried 300 mL round bottom flask was charged with bis(4-methoxyphenyl)phosphine oxide (5.24 g, 20.0 mmol) and 18-crown-6 (6.34 g, 24.0 mmol) and then subjected to 3 cycles of vacuum/nitrogen backfill. THF (400 mL) was added and the reaction was cooled to 0 °C. KH (2.65 g, 24.0 mmol, 36% dispersion in paraffin) was added in one portion, and the reaction was stirred at room temperature for 30 minutes. Trimethyl(trifluoromethyl)silane (12.0 mL, 80.0 mmol) was added dropwise, and the reaction was stirred at room temperature for 10 minutes. The reaction was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20 % CH_2Cl_2 in hexanes) to provide the title compound as a pale yellow oil (1.34 g, 4.2 mmol, 21 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 – 7.49 (m, 4H), 7.00 – 6.92 (m, 4H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.54, 135.74 (d, J = 22.1 Hz), 120.36 (dq, J = 6.7, 3.3 Hz), 114.57 (d, J = 9.1 Hz), 55.24; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -0.54 (q, J = 73.3 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ: -56.23 (d, J = 72.8 Hz). The spectroscopic data is in agreement with previous reported synthesis.[6]

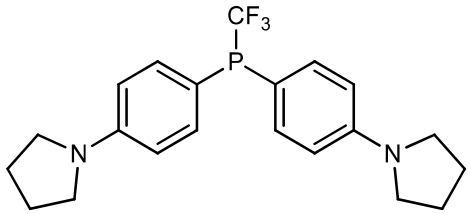
4,4'-((Trifluoromethyl)phosphanediyl)bis(*N*,*N*-dimethylaniline)



To a stirred solution of 4,4'-phosphanediylbis(*N*,*N*-dimethylaniline) (495 mg, 1.82 mmol) and pyridine (147 µL, 1.82 mmol) in 7.5 mL of DMF was added 2,8-difluoro-*S*-(trifluoromethyl) dibenzothiophenium triflate (760 mg, 1.73 mmol) under N_2 atmosphere. The mixture was stirred at rt for overnight. After the reaction was completed, the mixture was poured into water (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 5% EtOAc in Hexanes) to give 4,4'-((trifluoromethyl)phosphanediyl)bis(*N*,*N*-dimethylaniline) as a white powder (366 mg, 1.07 mmol, 62% yield). mp 79–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (t, *J* = 8.5 Hz, 4H), 6.72 (dd, *J* = 1.2, 9.0 Hz, 4H), 2.99 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.68, 135.54 (d, *J* = 22.3 Hz), 131.65 (dq, *J* = 33.0,

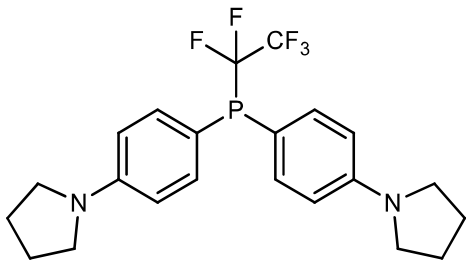
319.9 Hz), 114.89, 112.21 (d, J = 8.8 Hz), 40.11; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -56.54 (d, J = 71.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -1.02 (q, J = 71.3 Hz); IR υ_{max}/cm^{-1} (film): 3087, 2895, 2820, 1593, 1544, 1513, 1481, 1443, 1365, 1230, 1199, 1176, 1144, 1100, 1078, 999, 946, 800; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{21}F_3N_2P^+$ = 341.1389, found 341.1360.

1,1'-(((Trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (4)



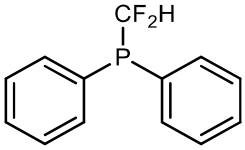
Prepared according to a modified version of a previous report.[4] An oven-dried 300 mL round bottom flask was charged with bis(4-(pyrrolidin-1-yl)phenyl)phosphine oxide (6.81 g, 20.0 mmol) and 18-crown-6 (6.34 g, 24.0 mmol) and then subjected to 3 cycles of vacuum/nitrogen backfill. THF (136 mL) was added and the reaction was cooled to 0 °C. KHMDS (1.0 M in THF) (24 mL, 24.0 mmol) was added dropwise, and the reaction was stirred at room temperature for 30 minutes. Trimethyl(trifluoromethyl)silane (11.82 mL, 80.0 mmol) was added dropwise, and the reaction was stirred at room temperature for 10 minutes. The reaction was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20 % CH_2Cl_2 in hexanes) to provide the title compound as a peach solid (5.08 g, 12.9 mmol, 65 % yield). m.p. 163-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (t, J = 8.4 Hz, 4H), 6.58 (d, J = 8.3 Hz, 4H), 3.38 – 3.22 (m, 8H), 2.07 – 1.94 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.13, 135.66 (d, J = 22.5 Hz), 113.82 – 113.51 (m), 47.56, 25.62; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -0.42 (q, J = 71.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -56.83 (d, J = 71.4 Hz). IR υ_{max}/cm^{-1} (film): 2974, 2847, 1594, 1543, 1511, 1484, 1460, 1381, 1277, 1148, 1100, 1084, 1000, 962, 803, 716, 698. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{25}F_3N_2P^+$ = 393.1702, found 393.1702.

1,1'-(((Perfluoroethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine



Prepared according to a modified version of a previous report.[4] An oven-dried 300 mL round bottom flask was charged with bis(4-(pyrrolidin-1-yl)phenyl)phosphine oxide (681 mg, 2.0 mmol) and 18-crown-6 (634 mg, 2.4 mmol) and then subjected to 3 cycles of vacuum/nitrogen backfill. THF (13.6 mL) was added and the reaction was cooled to 0 °C. KHMDS (1.0 M in THF) (2.4 mL, 2.4 mmol) was added dropwise, and the reaction was stirred at room temperature for 30 minutes. Trimethyl(perfluoroethyl)silane (1.41 mL, 8.0 mmol) was added dropwise, and the reaction was stirred at room temperature for 10 minutes. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20 % CH_2Cl_2 in hexanes) to provide the title compound as a yellow solid (93 mg, 0.210 mmol, 11 % yield). m.p. 149-150 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (t, J = 8.6 Hz, 4H), 6.70 – 6.50 (m, 4H), 3.43 – 3.22 (m, 8H), 2.09 – 1.96 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.23, 136.51 (d, J = 24.3 Hz), 122.37 – 119.90 (m), 119.32 – 118.33 (m), 112.60 (q, J = 4.0 Hz), 111.77 (d, J = 9.8 Hz), 47.48, 25.59; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -4.89 (td, J = 56.5, 17.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ: -80.51 (dt, J = 17.2, 3.4 Hz), -113.74 (dq, J = 56.5, 3.4 Hz). IR υ_{max}/cm^{-1} (film): 2847, 1593, 1543, 1510, 1484, 1384, 1323, 1279, 1248, 1229, 1187, 1098, 1077, 947, 809, 742, 714, 699. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{22}H_{25}F_5N_2P^+$ = 443.1670, found 443.1689.

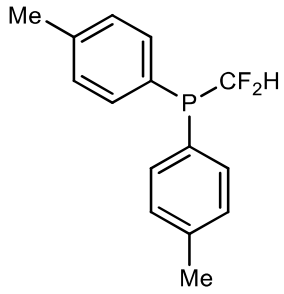
(Difluoromethyl)diphenylphosphane



An oven-dried 300 mL round bottom flask was charged with $LiBF_4$ (1.12 g, 12.0 mmol), LiH (95 mg, 12.0 mmol), DMF (50 mL) and then subjected to 3 cycles of vacuum/nitrogen backfill. The reaction was cooled to 0 °C, then diphenylphosphane (1.74 mL, 10.0 mmol) was added and the reaction was stirred for 5

minutes. Trimethyl(trifluoromethyl)silane (7.4 mL, 50.0 mmol) was added, and the reaction was stirred at room temperature for 24 hours. TBAF (1 M in THF) (40 mL, 40 mmol) was added, and the reaction was stirred at room temperature for 10 minutes. The reaction was quenched with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with water (3 x 200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 100 % hexanes) to provide the title compound as a colorless oil (1.075 g, 4.55 mmol, 46 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 – 7.52 (m, 4H), 7.51 – 7.39 (m, 6H), 6.55 (td, *J* = 51.7, 14.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.92 (d, *J* = 18.9 Hz), 131.41 (dt, *J* = 10.3, 5.8 Hz), 130.05, 128.95 (d, *J* = 7.1 Hz), 122.35 (td, *J* = 264.7, 12.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -10.09 (t, *J* = 117.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.40 (dd, *J* = 117.5, 51.7 Hz). IR υ_{max}/cm^{-1} (film): 3075, 3056, 2933, 2360, 2342, 1483, 1435, 1307, 1288, 1064, 1022, 734, 692. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{12}F_2P^+$ = 237.0639, found 237.0638.

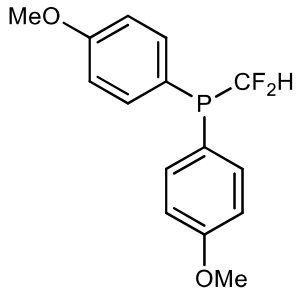
(Difluoromethyl)di-p-tolylphosphine



An oven-dried 300 mL round bottom flask was charged with (difluoromethyl)di-p-tolylphosphine oxide (2.80 g, 10 mmol) and subjected to 3 cycles of vacuum/nitrogen backfill. Toluene (120 mL) was added and the flask was cooled to 0 °C. Trichlorosilane (4.04 mL, 40 mmol) and TfOH (0.132 mL, 1.5 mmol) were added and the reaction was immediately warmed to 70 °C. After 22 h, the reaction was quenched with saturated aqueous sodium carbonate (500 mL) at 0 °C while stirring vigorously. The mixture was allowed to warm to room temperature and filtered through a pad of celite, rinsing liberally with EtOAc. The organic layer was separated and dried with anhydrous MgSO4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 10 % EtOAc in hexanes) to provide the title compound as a colorless oil (2.28 g, 8.6 mmol, 86 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (t, *J* = 7.8 Hz, 4H), 7.28 – 7.21 (m, 4H), 6.49 (td, *J* = 51.9, 13.9 Hz, 1H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.20, 133.90 (d, *J* = 19.2 Hz), 129.75 (d, *J* = 7.4 Hz), 128.00 (dt, *J* = 8.9, 5.8 Hz), 122.56 (td, *J* = 264.6, 12.7 Hz), 21.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.62 (dd, *J* = 117.5, 51.9 Hz); ^{31}P NMR (162 MHz,

$CDCl_3$) δ: -11.58 (t, *J* = 117.5 Hz). IR υ_{max}/cm^{-1} (film): 3073, 3019, 2922, 2866, 2361, 2342, 1599, 1498, 1448, 1398, 1307, 1287, 1188, 1094, 1065, 1019, 804, 627. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{16}F_2P^+$ = 265.0952, found 265.0968.

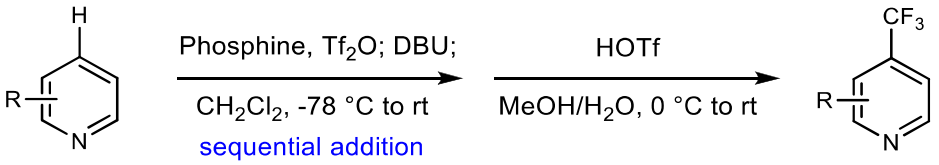
(Difluoromethyl)bis(4-methoxyphenyl)phosphine (6)



An oven-dried 2 L round bottom flask was charged with (difluoromethyl)bis(4-methoxyphenyl)phosphine oxide (20.6 g, 66 mmol) and subjected to 3 cycles of vacuum/nitrogen backfill. Toluene (800 mL) was added and the flask was cooled to 0 °C. Trichlorosilane (26.7 mL, 264 mmol) and TfOH (0.874 mL, 9.9 mmol) were added and the reaction was immediately warmed to 70 °C. After 22 h, the reaction was quenched with saturated aqueous sodium carbonate (1 L) at 0 °C while stirring vigorously. The mixture was allowed to warm to room temperature and filtered through a pad of celite, rinsing liberally with EtOAc. The organic layer was separated and dried with anhydrous MgSO4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 7.5 % EtOAc in hexanes) to provide the title compound as a white solid (13.8 g, 46.5 mmol, 70 % yield). mp 34-35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (tt, *J* = 7.5, 2.3 Hz, 4H), 7.01 – 6.85 (m, 4H), 6.45 (td, *J* = 51.9, 14.9 Hz, 1H), 3.83 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.21, 135.48 (d, *J* = 20.6 Hz), 122.59 (td, *J* = 264.8, 13.5 Hz), 122.17 (q, *J* = 6.0 Hz), 114.65 (d, *J* = 8.1 Hz), 55.32; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -118.06 (dd, *J* = 116.0, 51.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -12.74 (t, *J* = 116.0 Hz). IR υ_{max}/cm^{-1} (film): 3012, 2969, 2947, 2932, 2840, 2361, 2342, 1590, 1568, 1497, 1281, 1249, 1217, 1186, 1108, 1095, 1066, 1024, 842, 827, 812, 798. *m/z*

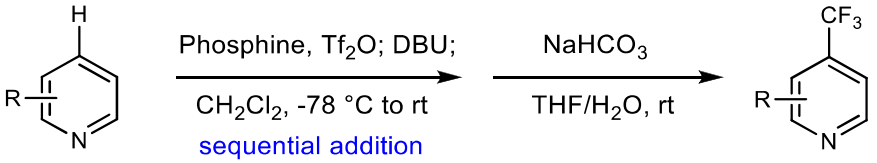
A 2.4 Trifluoromethylation of Heterocycles

General Procedure A



An oven dried 8 mL vial (≤ 0.30 mmol scale) or a round bottom flask (> 0.30 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 °C and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 1 hour before DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction warmed to room temperature while stirring (approximately 15–30 minutes). Then, the reaction mixture was cooled to 0 °C, HOTf (1.5 equiv), MeOH (0.2 M) and H_2O (10 equiv) were added sequentially. The mixture was warmed to room temperature and stirred for 12 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the trifluoromethylated heterocycle.

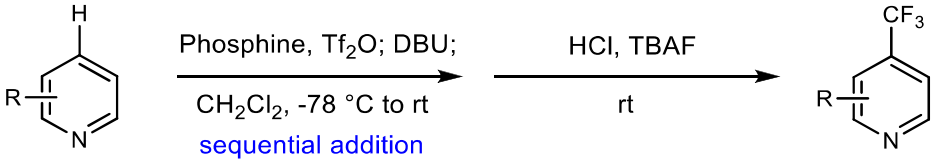
General Procedure B



An oven dried 8 mL vial (≤ 0.30 mmol scale) or a round bottom flask (> 0.30 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 °C and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 1 hour before DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction warmed to room temperature while stirring (approximately 15–30 minutes). Then, the mixture was stirred for additional 30 minutes after $NaHCO_3$ (3 equiv), THF (0.2 M) and H_2O (10 equiv) were added sequentially. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous

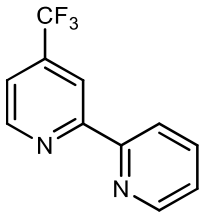
solution of brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the trifluoromethylated heterocycle.

General Procedure C



An oven dried 8 mL vial (≤ 0.30 mmol scale) or a round bottom flask (> 0.30 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 °C and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 1 hour before DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction warmed to room temperature while stirring (approximately 15–30 minutes). Then, the reaction mixture was cooled to 0 °C, HOTf (1.5 equiv) and TBAF (1M in THF, 1 equiv) were added sequentially. The mixture was warmed to room temperature and stirred for 12 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the trifluoromethylated heterocycle.

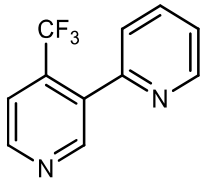
4-(Trifluoromethyl)-2,2'-bipyridine (5a)



Prepared according to general procedure A using 2,2'-bipyridine (78 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 µL, 0.50 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (111 µL, 1.25 mmol), MeOH (2.5 mL) and H_2O (90 µL, 5.00 mmol) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as a white solid (83 mg, 0.37 mmol, 74% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.83 (d, J = 5.0 Hz, 1H), 8.71–8.68 (m,

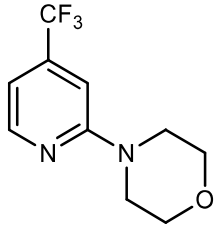
2H), 8.44 (td, J = 1.2, 7.9 Hz, 1H), 7.84 (dt, J = 1.8, 7.7 Hz, 1H), 7.51 (dd, J = 1.7, 5.1 Hz, 1H), 7.35 (ddd, J = 1.2, 4.8, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.69, 154.81, 150.16, 149.47, 139.39 (q, J = 33.9 Hz), 137.19, 124.60, 123.11 (q, J = 271.6 Hz), 121.40, 119.17 (q, J = 3.5 Hz), 116.98 (q, J = 3.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.78. The spectroscopic data is in agreement with previous reported synthesis.[7]

4'-(Trifluoromethyl)-2,3'-bipyridine (5b)



Prepared according to general procedure A using 2,3'-bipyridine (78 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 µL, 0.50 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (111 µL, 1.25 mmol), MeOH (2.5 mL) and H_2O (90 µL, 5.00 mmol) at rt for 24 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as a light-yellow oil (83 mg, 0.37 mmol, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83–8.81 (m, 2H), 8.72 (td, *J* = 1.4, 4.8 Hz, 1H), 7.79 (dt, *J* = 1.8, 7.8 Hz, 1H), 7.63 (d, *J* = 5.2 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.38–7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.52, 152.45, 150.27, 149.74, 136.45, 135.81 (q, *J* = 32.3 Hz), 134.18 (q, *J* = 0.9 Hz), 124.34 (q, *J* = 2.2 Hz), 123.27, 122.88 (q, *J* = 273.2 Hz), 119.73 (q, *J* = 4.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.29. The spectroscopic data is in agreement with previous reported synthesis.[8]

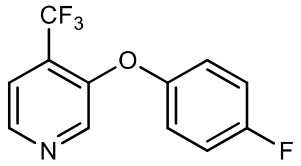
4-(4-(Trifluoromethyl)pyridin-2-yl)morpholine (5c)



Prepared according to general procedure A (except that the reaction was done in a pressure tube), using 4-(pyridin-2-yl)morpholine (82 mg, 0.50 mmol), Tf_2O (84 µL, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (68 µL, 0.77 mmol), MeOH (2.5 mL), and H_2O (90 µL, 5.00 mmol) at 60 °C for 12 hours. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a colorless oil (19 mg, 0.08 mmol, 16% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (d, *J* = 5.1 Hz, 1H), 6.82 (d, *J* = 5.2 Hz, 1H), 6.79 (s, 1H), 3.85 – 3.81 (m , 4H), 3.59 – 3.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.73, 149.37, 139.94 (q, *J* = 32.9 Hz), 123.30 (q, *J* = 273.0 Hz), 108.87 (q, *J* = 3.3 Hz), 102.51 (q, *J* = 4.4 Hz), 66.75, 45.43; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -

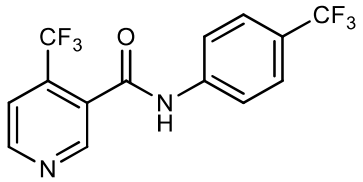
65.16, IR υ_{max}/cm^{-1} (film): 2925, 1610, 1320, 1040, 957, 761, 667, 531. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_{12}F_3N_2O^+$ = 233.0902, found 233.0898.

3-(4-Fluorophenoxy)-4-(trifluoromethyl)pyridine (5d)



Prepared according to general procedure A using 3-(4-fluorophenoxy)pyridine (95 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 12 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes) to provide the title compound as a light-yellow oil (106 mg, 0.41 mmol, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (d, *J* = 5.0 Hz, 1H), 8.29 (s, 1H), 7.55 (d, *J* = 4.9 Hz, 1H), 7.13–7.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.80 (d, *J* = 242.7 Hz), 151.56 (d, *J* = 2.7 Hz), 151.23, 144.49, 141.39, 127.97 (q, *J* = 32.8 Hz), 122.21 (q, *J* = 272.1 Hz), 121.02 (d, *J* = 8.4 Hz), 120.44 (q, *J* = 3.1 Hz), 117.00 (d, *J* = 23.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.66, -117.55; IR υ_{max}/cm^{-1} (film): 3047, 1599, 1572, 1501, 1489, 1411, 1322, 1290, 1257, 1218, 1181, 1138, 1090, 1069, 1057, 1011, 881, 832, 823, 769, 732, 649, 617; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_8F_4NO^+$ = 258.0537, found 258.0551.

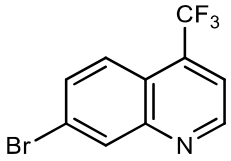
4-(Trifluoromethyl)-N-(4-(trifluoromethyl)phenyl)nicotinamide (5e)



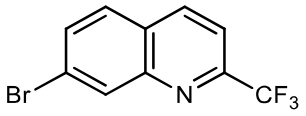
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using *N*-(4-(trifluoromethyl)phenyl)nicotinamide (133 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (20 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a light-yellow solid (58 mg, 0.18 mmol, 35% yield). mp 167–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.93 (br s, 2H), 7.88 (s, 1H), 7.73 (d, *J* = 8.4

Hz, 2H), 7.66–7.64 (m, 3H); ^{13}C NMR (100 MHz, d_6-Acetone) δ: 164.61, 153.24, 150.29, 143.05, 135.40 (q, J = 33.3 Hz), 130.86, 127.11–127.07 (m), 126.40 (q, J = 32.3 Hz), 125.35 (q, J = 269.1 Hz), 123.64 (q, J = 272.4 Hz), 121.08–120.92 (m), 120.72–120.53 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.24, -62.31; IR υ_{max}/cm^{-1} (film): 3255, 1649, 1605, 1548, 1413, 1404, 1317, 1289, 1272, 1190, 1141, 1065, 1048, 1019, 898, 841, 703, 658; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{14}H_9F_6N_2O^+$ = 335.0614, found 335.0621.

7-Bromo-4-(trifluoromethyl)quinoline (5f)



16.8



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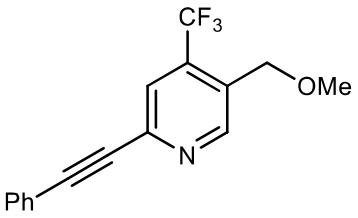
Prepared according to general procedure A using 7-bromoquinoline (104 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), THF (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes to 50% EtOAc in hexanes) to provide the mixture of compounds as a light-brown solid (122 mg, 0.44 mmol, 88% yield). Major, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (d, J = 4.4 Hz, 1H), 8.40 (s, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 4.1 Hz, 1H); Major, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.75, 149.68, 134.60 (d, J = 32.0 Hz), 132.87, 132.01, 125.44 (q, J = 2.3 Hz), 124.74, 123.27 (q, J = 273.0 Hz), 121.71, 118.31 (d, J = 5.2 Hz); Major, ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.44; IR υ_{max}/cm^{-1} (film): 3055, 3023, 2923, 1606, 1499, 1443, 1347, 1323, 1287, 1271, 1252, 1187, 1145, 1113, 1092, 1062, 977, 886, 856, 824, 775, 739, 653, 623, 610; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_6BrF_3N^+$ = 275.9630, found 275.9616.

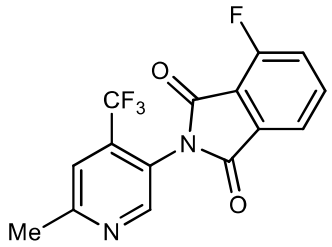
5-(Methoxymethyl)-2-(phenylethynyl)-4-(trifluoromethyl)pyridine (5g)



Prepared according to general procedure A using 5-(methoxymethyl)-2-(phenylethynyl)pyridine (112 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol),

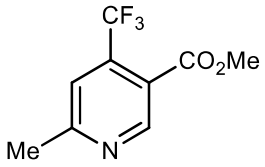
Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 20 hours. The crude material was purified by flash chromatography (silica gel: 9% EtOAc in hexanes to 17% EtOAc in hexanes) to provide the title compound as an off-white solid (117 mg, 0.40 mmol, 80% yield). mp 65–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (s, 1H), 7.72 (s, 1H), 7.62–7.60 (m, 2H), 7.42–7.35 (m, 3H), 4.67 (s, 2H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.37, 143.72, 135.75 (q, J = 32.7 Hz), 132.24, 129.95 (q, J = 1.6 Hz), 129.51, 128.56, 122.81 (q, J = 273.5 Hz), 122.62 (q, J = 5.2 Hz), 121.75, 91.04, 87.71, 68.69 (q, J = 2.5 Hz), 58.98; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.62; IR υ_{max}/cm^{-1} (film): 3064, 2984, 2920, 2888, 2825, 2226, 1600, 1496, 1471, 1458, 1445, 1392, 1299, 1283, 1270, 1204, 1185, 1165, 1136, 1117, 1054, 971, 932, 922, 905, 894, 760, 690, 678; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{16}H_{13}F_3NO^+$ = 292.0944, found 292.0973.

4-Fluoro-2-(6-methyl-4-(trifluoromethyl)pyridin-3-yl)isoindoline-1,3-dione (5h)



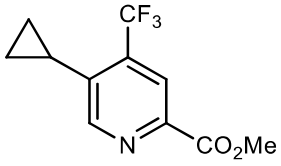
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 4-fluoro-2-(6-methylpyridin-3-yl)isoindoline-1,3-dione (128 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 43 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes to 50% EtOAc in hexanes) to provide the title compound as an off-white solid (141 mg, 0.44 mmol, 87% yield). mp 163–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.86–7.78 (m, 2H), 7.58 (s, 1H), 7.49 (dt, J = 1.1, 8.4 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.76 (d, J = 2.9 Hz), 163.45 (d, J = 1.5 Hz), 162.17, 158.05 (d, J = 265.7 Hz), 151.58, 137.51 (d, J = 7.7 Hz), 137.21 (q, J = 32.4 Hz), 133.84 (d, J = 1.3 Hz), 123.19 (d, J = 19.4 Hz), 122.21 (q, J = 2.0 Hz), 121.86 (q, J = 273.0 Hz), 120.64 (q, J = 4.2 Hz), 120.46 (d, J = 3.8 Hz), 117.74 (d, J = 12.4 Hz), 24.58; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.14, -110.89; IR υ_{max}/cm^{-1} (film): 3501, 3083, 1784, 1724, 1664, 1610, 1495, 1479, 1442, 1391, 1294, 1267, 1251, 1216, 1197, 1169, 1135, 1099, 1062, 1040, 968, 915, 892, 869, 822,794, 781, 743, 704, 670, 635, 607, 557; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_9F_4N_2O_2^+$ = 325.0595, found 325.0621.

Methyl 6-methyl-4-(trifluoromethyl)nicotinate (5i)



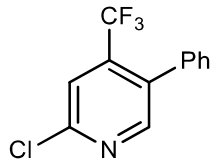
Prepared according to general procedure B using methyl 6-methylnicotinate (76 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), $NaHCO_3$ (126 mg, 1.50 mmol), THF (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 30 minutes. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a light-yellow solid (92 mg, 0.42 mmol, 84% yield). mp 31–33 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (s, 1H), 7.49 (s, 1H), 3.96 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.19, 163.59, 151.53, 137.10 (q, J = 34.0 Hz), 122.30 (q, J = 1.7 Hz), 122.26 (q, J = 272.8 Hz), 119.96 (q, J = 5.1 Hz), 53.09, 24.90; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.98; IR υ_{max}/cm^{-1} (film): 3453, 3078, 2964, 2858, 1733, 1694, 1602, 1569, 1442, 1384, 1367, 1257, 1232, 1214, 1147, 1125, 1050, 956, 890, 817, 790, 732, 671; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_9H_9F_3NO_2^+$ = 220.0580, found 220.0587.

Methyl 5-cyclopropyl-4-(trifluoromethyl)picolinate (5j)



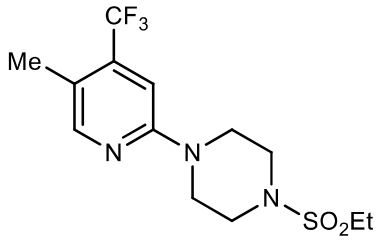
Prepared according to general procedure A using methyl 5-cyclopropylpicolinate (89 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 48 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as a white solid (115 mg, 0.47 mmol, 93% yield). mp 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (s, 1H), 8.29 (s, 1H), 4.02 (s, 3H), 2.25–2.19 (m, 1H), 1.25–1.20 (m, 2H), 1.00–0.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.73, 148.52, 146.02, 140.71, 138.10 (q, J = 31.9 Hz), 123.05 (q, J = 273.3 Hz), 120.78 (q, J = 5.1 Hz), 53.11, 10.87, 9.67; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.60; IR υ_{max}/cm^{-1} (film): 3424, 3029, 2963, 1718, 1680, 1601, 1558, 1491, 1456, 1442, 1323, 1310, 1258, 1154, 1124, 1069, 1042, 1017, 986, 923, 909, 879, 863, 806, 788, 754, 746, 669, 629; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{11}H_{11}F_3NO_2^+$ = 246.0736, found 246.0752.

2-Chloro-5-phenyl-4-(trifluoromethyl)pyridine (5k)



Prepared according to general procedure A using 2-chloro-5-phenylpyridine (95 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), THF (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 80 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 33% CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (92 mg, 0.37 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 7.67 (s, 1H), 7.48–7.43 (m, 3H), 7.34–7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.64, 151.36, 138.59 (q, J = 32.1 Hz), 134.67 (q, J = 1.8 Hz), 134.55, 129.26 (q, J = 1.5 Hz), 128.94, 128.44, 122.19 (q, J = 273.7 Hz), 120.67 (q, J = 5.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.70; IR υ_{max}/cm^{-1} (film): 3061, 1586, 1463, 1445, 1303, 1284, 1253, 1215, 1122, 1076, 1035, 885, 840, 775, 757, 699, 684, 665; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_8ClF_3N^+$ = 258.0292, found 258.0297.

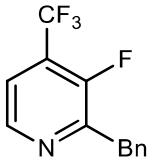
1-(Ethylsulfonyl)-4-(5-methyl-4-(trifluoromethyl)pyridin-2-yl)piperazine (5l)



Prepared according to general procedure A using 1-(ethylsulfonyl)-4-(5-methylpyridin-2-yl)piperazine (135 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as an off-white solid (28 mg, 0.08 mmol, 16% yield). mp 103–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 6.83 (s, 1H), 3.65–3.63 (m, 4H), 3.41–3.38 (m, 4H), 2.98 (q, J = 7.4 Hz, 2H), 2.30 (q, J = 1.8 Hz, 3H), 1.38 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.79, 150.94, 138.26 (q, J = 30.7 Hz), 123.55 (q, J = 273.0 Hz), 119.74 (q, J = 1.6 Hz), 103.46 (d, J = 5.5 Hz), 45.63, 45.54, 44.10, 15.18 (q, J = 1.5 Hz), 7.88;

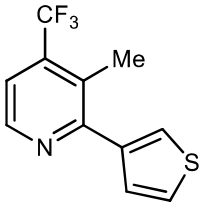
^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.34; IR υ_{max}/cm^{-1} (film): 2980, 2926, 2870, 1726, 1612, 1499, 1433, 1386, 1354, 1342, 1326, 1303, 1276, 1244, 1219, 1193, 1138, 1117, 1067, 1048, 1005, 957, 937, 868, 847, 837, 779, 753, 715, 678; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{19}F_3N_3O_2S^+$ = 338.1145, found 338.1149.

2-Benzyl-3-fluoro-4-(trifluoromethyl)pyridine (5m)



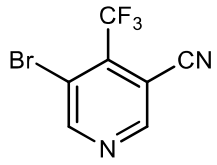
Prepared according to general procedure B, using 2-benzyl-3-fluoropyridine (94 mg, 0.50 mmol), Tf_2O (84 µL, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (5 mL), $NaHCO_3$ (126 mg, 1.50 mmol), H_2O (90 µL, 5.00 mmol), THF (2.5 mL) at rt for 30 minutes. The crude material was purified by flash chromatography (silica gel: 50% EtOAc in hexanes) to provide the title compound as a colorless oil (75 mg, 0.29 mmol, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, J = 4.9 Hz, 1H), 7.39 – 7.21 (m, 6H), 4.27 (d, J = 3.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.77 (dq, J = 267.0, 2.3 Hz), 151.46 (d, J = 15.0 Hz), 145.54 (d, J = 7.2 Hz), 137.51, 129.12, 128.81, 126.94, 125.64 (qd, J = 34.0, 11.1 Hz), 121.62 (q, J = 273.6 Hz), 119.0 (qd, J = 4.0, 1.2 Hz), 38.08; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.72 (J = 12.5 Hz, 3F), -127.75 – (-127.61) (m, 1F), IR υ_{max}/cm^{-1} (film): 3032, 2932, 1430, 1226, 1149, 907, 728. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{10}F_4N^+$ = 256.0749, found 256.0772.

3-Methyl-2-(thiophen-3-yl)-4-(trifluoromethyl)pyridine (5n)



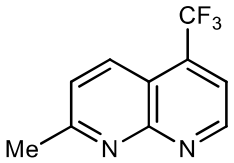
Prepared according to general procedure A, using 3-methyl-2-(thiophen-3-yl)pyridine (88 mg, 0.50 mmol), Tf_2O (84 µL, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (68 µL, 0.77 mmol), H_2O (90 µL, 5.00 mmol), MeOH (2.5 mL) at rt for 20 hours. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a colorless oil (72 mg, 0.29 mmol, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (d, J = 5.0 Hz, 1H), 7.55 (dd, J = 3.0, 1.3 Hz, 1H), 7.46 (d, J = 5.0 Hz, 1H), 7.43 (dd, J = 5.0, 3.0 Hz, 1H), 7.36 (dd, J = 5.0, 1.3 Hz, 1H), 2.53 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.79, 147.37, 140.62, 137.76 (q, J = 30.8 Hz), 128.84 (m), 128.78, 125.87, 125.61, 123.50 (q, J = 275.1 Hz), 118.23 (q, J = 5.3 Hz), 16.24 (q, J = 1.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.10, IR υ_{max}/cm^{-1} (film): 2928, 2359, 1425, 1317, 1129, 1057, 907, 732, 530. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{11}H_9F_3NS^+$ = 244.0408, found 244.0404.

5-Bromo-4-(trifluoromethyl)nicotinonitrile (5o)



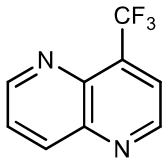
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –30 °C) using 5-bromonicotinonitrile (92 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 80% CH_2Cl_2 in hexanes) to provide the title compound as a white solid (65 mg, 0.26 mmol, 51% yield). mp 40–43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 8.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.07, 153.44, 138.75 (q, J = 32.9 Hz), 122.71 (q, J = 275.9 Hz), 119.11, 113.23, 108.54 (q, J = 1.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -60.76; IR υ_{max}/cm^{-1} (film): 3070, 2923, 2240, 1547, 1535, 1407, 1277, 1233, 1208, 1196, 1171, 1148, 1057, 916, 850, 757, 687, 609; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_7H_3BrF_3N_2^+$ = 250.9426, found 250.9429.

2-Methyl-5-(trifluoromethyl)-1,8-naphthyridine (5p)



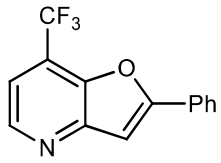
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 2-methyl-1,8-naphthyridine (72 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (111 μL, 1.25 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 2% Et_3N in hexanes) to provide the title compound as a brown solid (55 mg, 0.26 mmol, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.21 (d, J = 4.4 Hz, 1H), 8.39 (qd, J = 1.9, 8.7 Hz, 1H), 7.72 (d, J = 4.4 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.21, 156.26, 152.75, 135.34 (q, J = 32.2 Hz), 133.18 (q, J = 2.2 Hz), 124.43, 123.01 (q, J = 272.8 Hz), 118.13 (q, J = 5.0 Hz), 116.13 (q, J = 0.5 Hz), 25.67; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -60.81. The spectroscopic data is in agreement with previous reported synthesis.[8]

4-(Trifluoromethyl)-1,5-naphthyridine (5q)



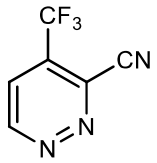
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 1,5-naphthyridine (65 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (111 μL, 1.25 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 16 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a white solid (41 mg, 0.21 mmol, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15–9.13 (m, 2H), 8.51 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.93 (d, *J* = 4.3 Hz, 1H), 7.77 (dd, *J* = 4.2, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.22, 150.77, 144.75, 139.46, 137.86, 135.58 (q, *J* = 31.2 Hz), 125.32, 122.97 (q, *J* = 273.1 Hz), 121.29 (q, *J* = 5.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.68. The spectroscopic data is in agreement with previous reported synthesis.[8]

2-Phenyl-7-(trifluoromethyl)furo[3,2-b]pyridine (5r)



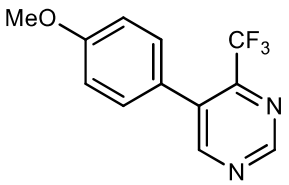
Prepared according to general procedure A using 2-phenylfuro[3,2-b]pyridine (98 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as a light yellow solid (112 mg, 0.43 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (d, *J* = 5.0 Hz, 1H), 7.95–7.92 (m, 2H), 7.53–7.43 (m, 3H), 7.38 (d, *J* = 5.0 Hz, 1H), 7.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.36, 151.27, 146.32, 142.78, 130.28, 129.06, 128.84, 125.64, 122.28 (q, *J* = 271.4 Hz), 120.71 (q, *J* = 35.6 Hz), 114.36, 102.21; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.06. The spectroscopic data is in agreement with previous reported synthesis.[8]

4-(Trifluoromethyl)pyridazine-3-carbonitrile (5s)



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using pyridazine-3-carbonitrile (53 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), THF (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a light-yellow oil (32 mg, 0.19 mmol, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.64 (d, J = 5.4 Hz, 1H), 7.93 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.62, 135.72 (q, J = 0.9 Hz), 132.56 (q, J = 36.2 Hz), 122.85 (q, J = 4.1 Hz), 120.65 (q, J = 273.6 Hz), 112.47; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.21; IR υ_{max}/cm^{-1} (film): 3078, 1555, 1435, 1344, 1307, 1194, 1149, 1108, 1072, 1028, 867, 834, 783, 750, 663; *m*/*z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_6H_3F_3N_3^+$ = 174.0, found 174.0.

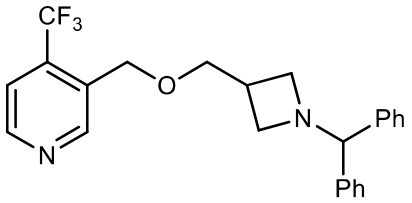
5-(4-Methoxyphenyl)-4-(trifluoromethyl)pyrimidine (5t)



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 5-(4-methoxyphenyl)pyrimidine (93 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 30 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as an off-white solid (100 mg, 0.39 mmol, 78% yield). mp 66–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.31 (s, 1H), 8.84 (s, 1H), 7.29–7.26 (m, 2H), 7.02–6.98 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.97, 160.48, 156.98, 151.96 (q, J = 33.9 Hz), 133.64, 130.29 (q, J = 1.6 Hz), 125.31, 121.05 (q, J = 275.2 Hz), 114.23, 55.42; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.60; IR υ_{max}/cm^{-1} (film): 3021, 2966, 2934, 2839, 1612, 1572, 1548, 1515, 1459, 1450, 1440, 1416, 1398, 1326, 1308, 1294, 1251, 1231, 1180, 1166, 1132, 1110, 1085, 1032,

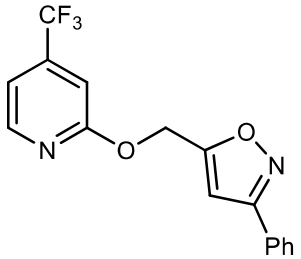
1018, 997, 930, 833, 819, 800, 786, 730, 658; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_{10}F_3N_2O^+$ = 255.0740, found 255.0739.

3-(((1-Benzhydrylazetidin-3-yl)methoxy)methyl)-4-(trifluoromethyl)pyridine (5u)



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 3-(((1-benzhydrylazetidin-3-yl)methoxy)methyl)pyridine (86 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 2% Et_3N in hexanes) to provide the title compound as an off-white solid (77 mg, 0.19 mmol, 75% yield). mp 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (s, 1H), 8.70 (d, *J* = 5.1 Hz, 1H), 7.48 (d, *J* = 5.1 Hz, 1H), 7.40–7.37 (m, 4H), 7.27–7.23 (m, 4H), 7.18–7.13 (m, 2H), 4.69 (s, 2H), 4.33 (s, 1H), 3.69 (d, *J* = 6.5 Hz, 2H), 3.29 (t, *J* = 7.5 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.81–2.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.16, 149.83, 142.32, 135.37 (q, *J* = 32.5 Hz), 131.02 (q, *J* = 1.7 Hz), 128.50, 127.60, 127.13, 123.12 (q, *J* = 273.2 Hz), 119.23 (q, *J* = 5.1 Hz), 78.13, 73.70, 67.31 (q, *J* = 2.2 Hz), 56.43, 29.82; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.39; IR υ_{max}/cm^{-1} (film): 3031, 2942, 2911, 2853, 1731, 1724, 1596, 1489, 1451, 1404, 1368, 1348, 1318, 1301, 1235, 1205, 1181, 1151, 1129, 1067, 1036, 976, 840, 821, 808, 780, 747, 707, 659, 638, 614; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{24}H_{24}F_3N_2O^+$ = 413.1835, found 413.1864.

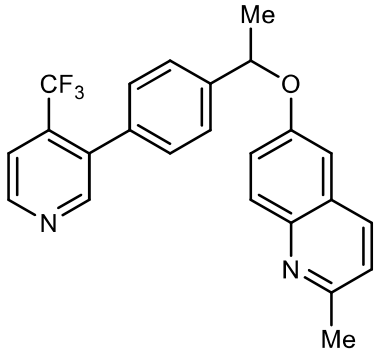
3-Phenyl-5-(((4-(trifluoromethyl)pyridin-2-yl)oxy)methyl)isoxazole (5v)



Prepared according to general procedure A using 3-phenyl-5-((pyridin-2-yloxy)methyl)isoxazole (63 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28

mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (90 μL, 5.00 mmol) at 80 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: CH_2Cl_2) to provide the title compound as an off-white solid (56 mg, 0.18 mmol, 70% yield). mp 56–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (d, J = 5.4 Hz, 1H), 7.83–7.79 (m, 2H), 7.49–7.43 (m, 3H), 7.16 (dd, J = 1.0, 5.4 Hz, 1H), 7.08 (s, 1H), 6.65 (s, 1H), 5.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.32, 162.96, 162.64, 148.31, 141.49 (q, J = 33.8 Hz), 130.23, 129.05, 128.94, 126.96, 122.64 (q, J = 271.6 Hz), 113.42 (q, J = 3.2 Hz), 108.07 (q, J = 4.0 Hz), 101.90, 58.81; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.96; IR υ_{max}/cm^{-1} (film): 3120, 3053, 2920, 2850, 1622, 1569, 1490, 1473, 1426, 1407, 1337, 1289, 1271, 1231, 1170, 1160, 1131, 1081, 1037, 1002, 985, 951, 908, 884, 838, 826, 786, 766, 689, 667; m/z HRMS (DART): $[M+H]^+$ calculated for $C_{16}H_{12}F_3N_2O_2^+$ = 321.0845, found 321.0862.

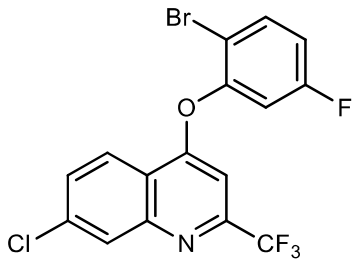
2-Methyl-6-(1-(4-(4-(trifluoromethyl)pyridin-3-yl)phenyl)ethoxy)quinoline (5w)



Prepared according to general procedure A using 2-methyl-6-(1-(4-(pyridin-3-yl)phenyl)ethoxy)quinoline (85 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 2% Et_3N in hexanes to 33% EtOAc, 5% Et_3N in hexanes) to provide the title compound as a colorless oil (45 mg, 0.11 mmol, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, J = 5.2 Hz, 1H), 8.63 (s, 1H), 7.91 (d, J = 9.2 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 5.2 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.40 (dd, J = 2.8, 9.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 2.8 Hz, 1H), 5.50 (q, J = 6.4 Hz, 1H), 2.67 (s, 3H), 1.74 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.64, 155.35, 152.70, 149.48, 143.95, 143.37, 135.91 (q, J = 31.6 Hz), 135.18, 135.05, 130.18, 129.67 (q, J = 1.7 Hz), 127.30, 125.52, 122.94 (q, J = 273.3 Hz), 122.71, 122.29, 119.55 (q, J = 4.8 Hz), 108.69, 76.13, 25.14, 24.33; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.25; IR υ_{max}/cm^{-1} (film): 3031, 2979, 2929, 1622, 1601, 1563, 1497, 1478, 1443, 1398, 1376, 1342, 1320, 1304, 1255, 1224, 1179,

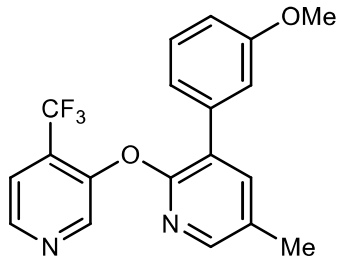
1134, 1064, 1001, 968, 940, 908, 831, 730, 659, 615; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{24}H_{20}F_3N_2O^+$ = 409.1522, found 409.1541.

4-(2-Bromo-5-fluorophenoxy)-7-chloro-2-(trifluoromethyl)quinoline (5x)



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 4-(2-bromo-5-fluorophenoxy)-7-chloroquinoline (88 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (33 μL, 0.38 mmol), THF (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 22 hours. The crude material was purified by flash chromatography (silica gel: 5% EtOAc in hexanes) to provide the title compound as a white solid (90 mg, 0.22 mmol, 86% yield). mp 150–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, *J* = 8.9 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 7.75–7.67 (m, 2H), 7.08–7.03 (m, 2H), 6.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.60 (d, *J* = 249.8 Hz), 161.89, 151.01 (d, *J* = 10.5 Hz), 150.11 (q, *J* = 34.8 Hz), 149.40, 138.05, 135.33 (d, *J* = 9.0 Hz), 129.58, 128.97, 123.40, 121.09 (q, *J* = 273.9 Hz), 119.74, 115.73 (d, *J* = 22.2 Hz), 111.36 (d, *J* = 24.8 Hz), 110.83 (d, *J* = 4.2 Hz), 99.91 (q, *J* = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -67.87, -109.55; IR υ_{max}/cm^{-1} (film): 3101, 3081, 1614, 1588, 1569, 1478, 1438, 1424, 1412, 1372, 1285, 1244, 1197, 1158, 1147, 1128, 1118, 1102, 1073, 1038, 963, 950, 925, 914, 880, 865, 842, 829, 815, 739, 621, 600; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{16}H_8BrClF_4NO^+$ = 419.9408, found 419.9420.

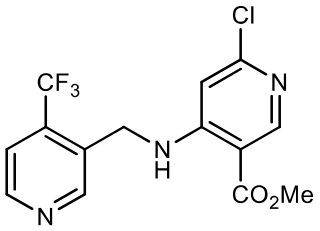
3-(3-Methoxyphenyl)-5-methyl-2-((4-(trifluoromethyl)pyridin-3-yl)oxy)pyridine (5y)



Prepared according to general procedure A using 3-(3-methoxyphenyl)-5-methyl-2-(pyridin-3-yloxy)pyridine (73 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-

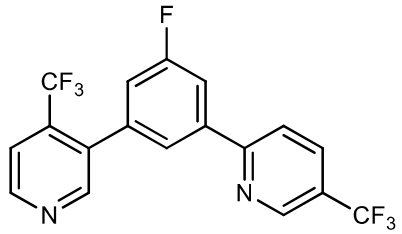
phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 2% Et_3N in hexanes) to provide the title compound as a colorless oil (66 mg, 0.18 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55–8.53 (m, 2H), 7.90 (dd, *J* = 0.8, 2.4 Hz, 1H), 7.63 (dd, *J* = 0.8, 2.4 Hz, 1H), 7.56 (d, *J* = 5.0 Hz, 1H), 7.39–7.35 (m, 1H), 7.22–7.20 (m, 2H), 6.94 (ddd, *J* = 1.4, 2.2, 8.2 Hz, 1H), 3.85 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.62, 157.51, 147.69, 146.57, 145.82, 145.53, 141.19, 136.95, 129.83 (q, *J* = 32.6 Hz), 129.73, 129.51, 125.05, 122.28 (q, *J* = 272.2 Hz), 121.66, 120.26 (q, *J* = 4.5 Hz), 114.69, 114.09, 55.31, 17.54; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.10; IR υ_{max}/cm^{-1} (film): 2938, 2836, 1571, 1490, 1456, 1440, 1407, 1322, 1288, 1231, 1184, 1137, 1068, 1056, 1040, 937, 869, 836, 820, 784, 743, 698, 649, 615; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{19}H_{16}F_3N_2O_2^+$ = 361.1158, found 361.1173.

Methyl 6-chloro-4-(((4-(trifluoromethyl)pyridin-3-yl)methyl)amino)nicotinate (5z)



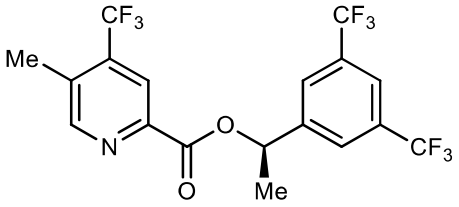
Prepared according to general procedure A using methyl 6-chloro-4-((pyridin-3-ylmethyl)amino)nicotinate (70 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes to 33% EtOAc, 2% Et_3N in hexanes) to provide the title compound as a white solid (77 mg, 0.22 mmol, 89% yield). mp 115–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78–8.73 (m, 3H), 8.66 (t, *J* = 5.9 Hz, 1H), 7.59 (d, *J* = 5.1 Hz, 1H), 6.47 (s, 1H), 4.67 (d, *J* = 5.9 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.89, 156.25, 155.61, 153.19, 150.53, 150.44, 135.99 (q, *J* = 32.5 Hz), 129.21, 123.05 (q, *J* = 273.2 Hz), 119.81 (q, *J* = 5.0 Hz), 107.44, 104.89, 52.18, 41.25 (q, *J* = 2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.47; IR υ_{max}/cm^{-1} (film): 3310, 3009, 2955, 2846, 1710, 1586, 1559, 1500, 1448, 1436, 1419, 1393, 1358, 1309, 1275, 1261, 1244, 1215, 1182, 1152, 1109, 1062, 977, 960, 934, 888, 838, 786, 776, 750, 717, 661, 613; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{14}H_{12}ClF_3N_3O_2^+$ = 346.0565, found 346.0570.

2-(3-Fluoro-5-(4-(trifluoromethyl)pyridin-3-yl)phenyl)-5-(trifluoromethyl)pyridine (5aa)



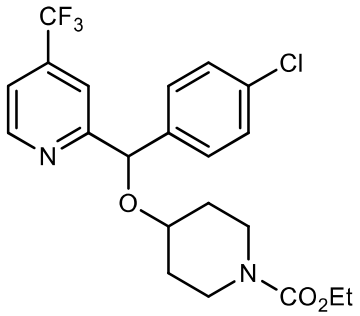
Prepared according to general procedure A using 2-(3-fluoro-5-(pyridin-3-yl)phenyl)-5-(trifluoromethyl)pyridine (80 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a white solid (84 mg, 0.22 mmol, 87% yield). mp 87–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96–8.95 (m, 1H), 8.86 (d, *J* = 5.2 Hz, 1H), 8.73 (s, 1H), 8.02 (dd, *J* = 2.4, 4.4 Hz, 1H), 7.91–7.83 (m, 3H), 7.67 (d, *J* = 5.1 Hz, 1H), 7.19 (dt, *J* = 8.5, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.14, 161.67, 158.56 (m), 152.36, 150.31, 146.93 (q, J = 4.0 Hz), 140.25 (d, J = 8.1 Hz), 138.39 (d, J = 8.3 Hz), 136.05 (q, J = 32.0 Hz), 134.37 (q, J = 3.5 Hz), 133.83, 125.88 (q, J = 33.2 Hz), 124.01 (d, J = 1.5 Hz), 119.68 (q, J = 4.6 Hz), 118.02 (dd, J = 22.9, 1.6 Hz), 114.59 (d, J = 23.1 Hz), 77.16 (t, *J* = 32.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.27, -62.37, -111.82; IR υ_{max}/cm^{-1} (film): 3046, 2924, 2360, 1599, 1573, 1492, 1430, 1399, 1384, 1330, 1316, 1279, 1239, 1183, 1170, 1153, 1135, 1113, 1081, 1067, 1042, 1014, 938, 922, 882, 840, 769, 697, 658, 633, 616; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{10}F_7N_2^+$ = 387.0727, found 387.0748.

(*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl 5-methyl-4-(trifluoromethyl)picolinate (5ab)



Prepared according to general procedure A using (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl 5-methylpicolinate (76 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (18 μL, 0.20 mmol), TBAF (0.2 mL, 0.20 mmol, 1M in THF) at rt for 24 hours. The crude material was purified by flash chromatography (silica gel: 50% DCM in hexanes to 80% DCM in hexanes) to provide the title compound as a white solid (76 mg, 0.17 mmol, 85% yield). mp 55–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (s, 1H), 8.28 (s, 1H), 7.93 (s, 2H), 7.83 (s, 1H), 6.28 (q, *J* = 6.7 Hz, 1H), 2.57 (s, 3H), 1.80 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.59, 153.46, 146.63, 143.76, 137.73 (q, *J* = 32.2 Hz), 135.51 (q, *J* = 1.7 Hz), 132.23 (q, *J* = 33.2 Hz), 126.72 (q, *J* = 3.8 Hz), 123.28 (q, *J* = 271.0 Hz), 122.87 (q, *J* = 273.1 Hz), 122.42–122.23 (m), 121.18 (q, *J* = 5.1 Hz), 72.93, 22.05, 16.51 (q, *J* = 1.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.90, -64.10; IR υ_{max}/cm^{-1} (film): 1746, 1382, 1370, 1361, 1321, 1303, 1283, 1268, 1243, 1200, 1163, 1114, 1103, 1067, 1059, 1005, 915, 900, 857, 841, 816, 787, 744, 728, 707, 683, 677; LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{13}F_9NO_2^+$ = 446.1, found 446.2.

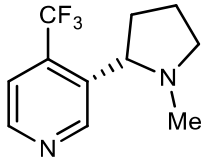
Ethyl 4-((4-chlorophenyl)(4-(trifluoromethyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (5ac)



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (94 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (33 μL, 0.38 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a colorless oil (85

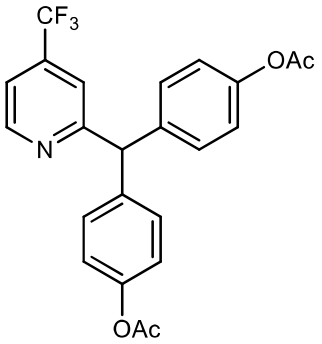
mg, 0.19 mmol, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (d, *J* = 5.1 Hz, 1H), 7.77 (s, 1H), 7.39–7.35 (m, 3H), 7.32–7.28 (m, 2H), 5.67 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.80–3.76 (m, 2H), 3.66–3.60 (m, 1H), 3.22–3.15 (m, 2H), 1.87–1.81 (m, 2H), 1.71–1.62 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.79, 155.59, 150.05, 139.35, 139.34 (q, *J* = 33.8 Hz), 133.94, 128.90, 128.31, 122.87 (q, *J* = 271.7 Hz), 118.21 (q, *J* = 3.6 Hz), 116.08 (q, *J* = 3.7 Hz), 80.60, 73.08, 61.40, 41.18, 41.09, 31.39, 30.89, 14.76; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.73; IR υ_{max}/cm^{-1} (film): 2931, 1692, 1488, 1473, 1432, 1407, 1383, 1331, 1273, 1227, 1204, 1167, 1135, 1083, 1029, 1014, 964, 921, 832, 767, 723, 665; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{23}ClF_3N_2O_3^+$ = 443.1344, found 443.1347.

(*S*)-3-(1-Methylpyrrolidin-2-yl)-4-(trifluoromethyl)pyridine (5ad)



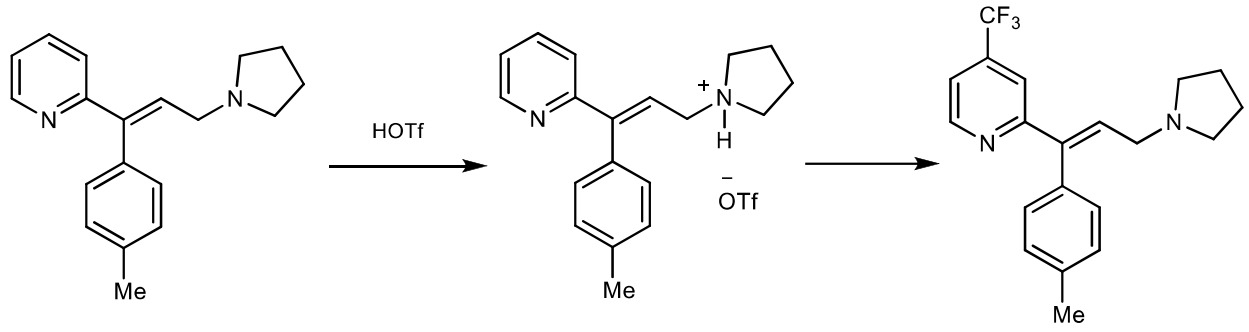
Prepared according to general procedure A using (*S*)-3-(1-methylpyrrolidin-2-yl)pyridine (33 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (44 μL, 0.50 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: EtOAc) to provide the title compound as a light-yellow oil (30 mg, 0.13 mmol, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.18 (s, 1H), 8.64 (s, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 3.53 (t, *J* = 7.9 Hz, 1H), 3.27 (t, *J* = 7.9 Hz, 1H), 2.38–2.24 (m, 2H), 2.18 (m, 3H), 2.05–1.93 (m, 1H), 1.88–1.78 (m, 1H), 1.71–1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.88, 148.71, 137.15, 136.03 (q, *J* = 31.5 Hz), 123.34 (q, *J* = 273.2 Hz), 118.57, 64.85, 56.88, 40.39, 35.91, 23.04; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -60.50; IR υ_{max}/cm^{-1} (film): 2944, 2779, 1454, 1409, 1315, 1290, 1235, 1170, 1128, 1062, 1043, 900, 835, 659, 614; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{11}H_{14}F_3N_2^+$ = 231.1104, found 231.1106.

((4-(Trifluoromethyl)pyridin-2-yl)methylene)bis(4,1-phenylene) diacetate (5ae)



Prepared according to general procedure B using (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (72 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), $NaHCO_3$ (50 mg, 0.60 mmol), THF (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 50 minutes. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a white solid (78 mg, 0.18 mmol, 90% yield). mp 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78 (d, J = 5.0 Hz, 1H), 7.39–7.37 (m, 2H), 7.19 (d, J = 8.6 Hz, 4H), 7.05 (d, J = 8.6 Hz, 4H), 5.71 (s, 1H), 2.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.49, 164.31, 150.80, 149.68, 139.25, 139.06 (q, J = 33.7 Hz), 130.32, 122.86 (q, J = 271.7 Hz), 121.80, 119.31 (q, J = 3.6 Hz), 117.48 (q, J = 3.5 Hz), 58.14, 21.23; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.65; IR υ_{max}/cm^{-1} (film): 3053, 2926, 1749, 1607, 1570, 1503, 1479, 1403, 1367, 1330, 1269, 1216, 1201, 1162, 1140, 1107, 1087, 1046, 1015, 958, 919, 879, 862, 848, 838, 800, 777, 750, 697, 677, 657, 644, 630, 593; HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{19}F_3NO_4^+$ = 430.1261, found 430.1271.

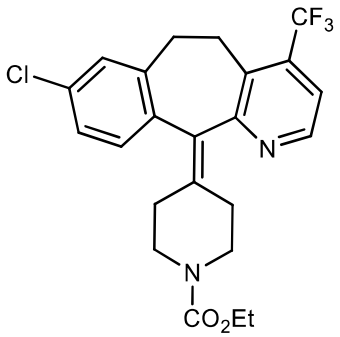
(*E*)-2-(3-(Pyrrolidin-1-yl)-1-(p-tolyl)prop-1-en-1-yl)-4-(trifluoromethyl)pyridine (5af)



(*E*)-2-(3-(pyrrolidin-1-yl)-1-(p-tolyl)prop-1-en-1-yl)pyridine (56 mg, 0.20 mmol) was dissolved in Et2O (1 mL) and cooled to 0 °C. Trifluoromethanesulfonic acid (18 μL, 0.20 mmol) was added dropwise, the ice bath was removed, and the solution was stirred for 10 minutes at room temperature. The solution was concentrated *in vacuo* and the resulting acid salt was subjected to general procedure A (except that after

Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 µL, 0.20 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (2 mL), HOTf (44 µL, 0.50 mmol), MeOH (1 mL) and H_2O (36 µL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 2% Et_3N in EtOAc) to provide the title compound as a light-yellow solid (43 mg, 0.12 mmol, 62% yield). mp 39–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (d, *J* = 5.0 Hz, 1H), 7.31 (dd, *J* = 1.6, 5.1 Hz, 1H), 7.24–7.22 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 6.8 Hz, 1H), 3.23 (d, *J* = 6.9 Hz, 2H), 2.56–2.51 (m, 4H), 2.40 (s, 3H), 1.79–1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.26, 150.18, 141.11, 138.65 (q, *J* = 33.4 Hz), 137.55, 134.64, 132.76, 129.76, 129.48, 123.01 (q, *J* = 271.5 Hz), 117.40 (q, *J* = 3.7 Hz), 117.25 (q, *J* = 3.4 Hz), 54.84, 54.29, 23.64, 21.42; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.83; IR υ_{max}/cm^{-1} (film): 3386, 3024, 2969, 2877, 2790, 1630, 1605, 1568, 1512, 1460, 1434, 1397, 1327, 1233, 1168, 1139, 1083, 957, 932, 902, 878, 839, 816, 782, 750, 729, 711, 690, 659, 641; HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{22}F_3N_2^+$ = 347.1730, found 347.1735.

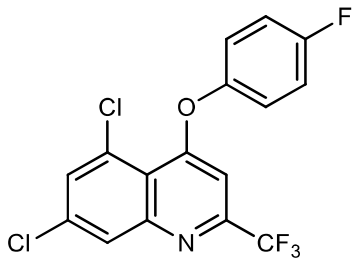
Ethyl 4-(8-chloro-4-(trifluoromethyl)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (5ag)



Prepared according to general procedure A using ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (77 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 µL, 0.20 mmol), DBU (30 µL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (27 µL, 0.30 mmol), MeOH (1 mL) and H_2O (36 µL, 2.00 mmol) at rt for 16 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes to 50% EtOAc in hexanes) to provide the title compound as a colorless oil (75 mg, 0.17 mmol, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, *J* = 5.2 Hz, 1H), 7.41 (d, *J* = 5.2 Hz, 1H), 7.11–7.09 (m, 3H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.82–3.75 (m, 2H), 3.44–3.36 (m, 2H), 3.29–3.13 (m, 3H), 2.97–2.88 (m, 1H), 2.51–2.33 (m, 3H), 2.14–2.08 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.47, 155.57, 147.72, 138.37, 137.83, 136.35 (q, *J* = 31.4 Hz), 134.63, 133.64, 133.47, 131.89,

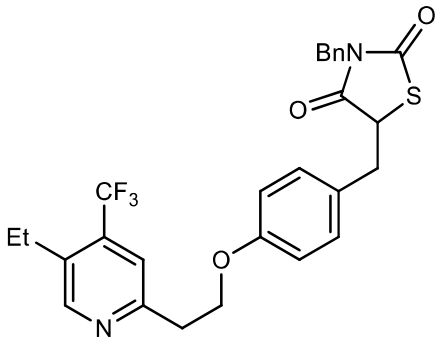
131.31, 130.32, 126.23, 123.33 (q, J = 273.5 Hz), 118.59 (q, J = 5.2 Hz), 61.52, 44.89, 44.64, 31.92, 30.86, 30.62, 26.18, 14.77; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.88; IR υ_{max}/cm^{-1} (film): 2980, 2909, 1692, 1590, 1476, 1430, 1406, 1326, 1300, 1278, 1222, 1155, 1119, 1092, 1061, 1028, 999, 981, 907, 844, 813, 766, 729, 690, 682; HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{23}ClF_3N_2O_2^+$ = 451.1395, found 451.1412.

5,7-Dichloro-4-(4-fluorophenoxy)-2-(trifluoromethyl)quinoline (5ah)



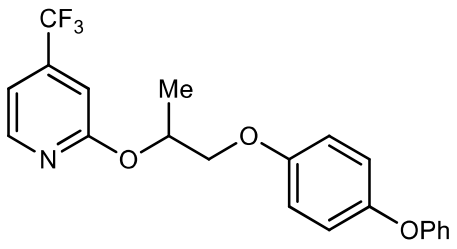
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 5,7-dichloro-4-(4-fluorophenoxy)quinoline (62 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (27 μL, 0.30 mmol), THF (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 22 hours. The crude material was purified by flash chromatography (silica gel: 5% EtOAc in hexanes) to provide the title compound as a white solid (68 mg, 0.18 mmol, 90% yield). mp 82–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.70 (s, 1H), 7.26–7.15 (m, 4H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.61, 160.67 (d, J = 244.6 Hz), 150.88, 150.39 (q, J = 35.0 Hz), 149.15 (d, J = 2.8 Hz), 136.63, 131.53, 130.68, 128.55, 122.61 (d, J = 8.5 Hz), 120.85 (q, J = 274.0 Hz), 118.50, 117.68 (q, J = 23.4 Hz), 102.15 (q, J = 2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -68.35, -115.41; IR υ_{max}/cm^{-1} (film): 3103, 1750, 1599, 1586, 1565, 1503, 1431, 1386, 1366, 1330, 1316, 1266, 1241, 1214, 1186, 1139, 1123, 1099, 1070, 1014, 964, 926, 855, 835, 770, 738, 724, 694, 611; HRMS (DART): $[M+H]^+$ calculated for $C_{16}H_8Cl_2F_4NO^+$ = 375.9914, found 375.9930.

3-Benzyl-5-(4-(2-(5-ethyl-4-(trifluoromethyl)pyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (5ai)



Prepared according to general procedure B using 3-benzyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (89 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 µL, 0.20 mmol), DBU (30 µL, 0.20 mmol), CH_2Cl_2 (2 mL), $NaHCO_3$ (50 mg, 0.60 mmol), THF (1 mL) and H_2O (36 µL, 2.00 mmol) at rt for 30 minutes. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a white solid (50 mg, 0.10 mmol, 49% yield). mp 111–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 7.45 (s, 1H), 7.25 (s, 5H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 4.72–4.64 (m, 2H), 4.42 (dd, *J* = 4.0, 8.8 Hz, 1H), 4.32 (t, *J* = 6.4 Hz, 2H), 3.38 (dd, *J* = 4.0, 14.2 Hz, 1H), 3.28 (t, *J* = 6.4 Hz, 2H), 3.38 (dd, *J* = 8.8, 14.2 Hz, 1H), 2.81 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.79, 171.02, 158.17, 157.13, 152.07, 136.14 (q, *J* = 31.0 Hz), 135.12, 134.66 (q, *J* = 1.6 Hz), 130.55, 128.73, 128.17, 127.70, 123.52 (q, *J* = 273.1 Hz), 119.50 (q, *J* = 5.2 Hz), 114.83, 66.82, 51.70, 45.24, 37.68, 37.62, 23.14 (q, *J* = 1.8 Hz), 15.76; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.14; IR υ_{max}/cm^{-1} (film): 3032, 2921, 1740, 1679, 1610, 1582, 1514, 1493, 1467, 1456, 1436, 1380, 1335, 1324, 1308, 1296, 1279, 1265, 1247, 1198, 1180, 1146, 1122, 1080, 1069, 1054, 1029, 964, 899, 879, 824, 810, 790, 745, 722, 696, 678, 668, 626, 601; HRMS (DART): $[M+H]^+$ calculated for $C_{27}H_{26}F_3N_2O_3S^+$ = 515.1611, found 515.1646.

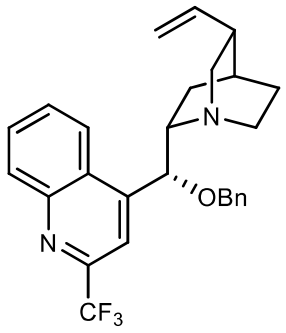
2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)-4-(trifluoromethyl)pyridine (5aj)



Prepared according to general procedure A using 2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (64 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22

mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (27 μL, 0.30 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at 60 °C for 68 hours. The crude material was purified by flash chromatography (silica gel: 33% CH_2Cl_2 in hexanes to 50% CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (55 mg, 0.14 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (d, *J* = 5.3 Hz, 1H), 7.33–7.28 (m, 2H), 7.08–7.03 (m, 2H), 7.00–6.90 (m, 7H), 5.67–5.62 (m, 1H), 4.20 (dd, *J* = 5.6, 10.0 Hz, 1H), 4.09 (dd, *J* = 4.6, 10.0 Hz, 1H), 1.50 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.78, 158.57, 155.18, 150.60, 148.33, 141.17 (q, *J* = 33.6 Hz), 129.76, 122.80 (q, *J* = 271.6 Hz), 122.64, 120.90, 117.81, 115.90, 112.42 (q, *J* = 3.2 Hz), 108.46 (q, *J* = 4.0 Hz), 71.01, 70.54, 16.93; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -65.01; IR υ_{max}/cm^{-1} (film): 3041, 2934, 1615, 1589, 1569, 1503, 1488, 1416, 1335, 1306, 1217, 1171, 1135, 1073, 1045, 989, 966, 872, 826, 767, 748, 690, 668; HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{19}F_3NO_3^+$ = 390.1312, found 390.1338.

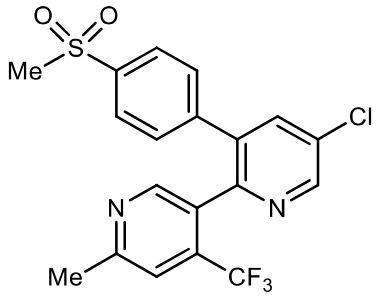
(1*R*,4*R*,5*R*)-2-((*R*)-(Benzyloxy)(2-(trifluoromethyl)quinolin-4-yl)methyl)-5-vinylquinuclidine (5ak)



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using (1*R*,4*R*,5*R*)-2-((*R*)-(benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (77 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (44 μL, 0.50 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at 40 °C for 20 hours. The crude material was purified by flash chromatography (silica gel: 2% Et_3N in EtOAc) to provide the title compound as a colorless oil (48 mg, 0.11 mmol, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 8.1 Hz, 1H), 8.22 (d, *J* = 8.6 Hz, 1H), 7.86–7.81 (m, 2H), 7.72–7.68 (m, 1H), 7.37–7.27 (m, 5H), 5.79–5.70 (m, 1H), 5.33 (s, 1H), 4.98–4.90 (m, 2H), 4.42 (dd, *J* = 1.1, 13.1 Hz, 2H), 3.38–3.31 (m, 1H), 3.18–3.03 (m, 2H), 2.71–2.57 (m, 2H), 2.29–2.24 (m, 1H), 1.84–1.65 (s, 4H), 1.55–1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.87, 147.86 (q, *J* = 34.2 Hz), 147.77, 141.88, 137.41, 131.33, 130.54, 128.79, 128.66, 128.15, 128.14, 127.35, 123.41, 121.78 (q, *J* = 273.8 Hz), 119.89, 114.51, 81.06, 72.00, 61.14, 57.09, 43.19, 40.03, 27.93, 27.79, 22.85; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -67.43; IR υ_{max}/cm^{-1} (film): 3066, 2934, 2864, 1636, 1596, 1569, 1511, 1467, 1454, 1423,

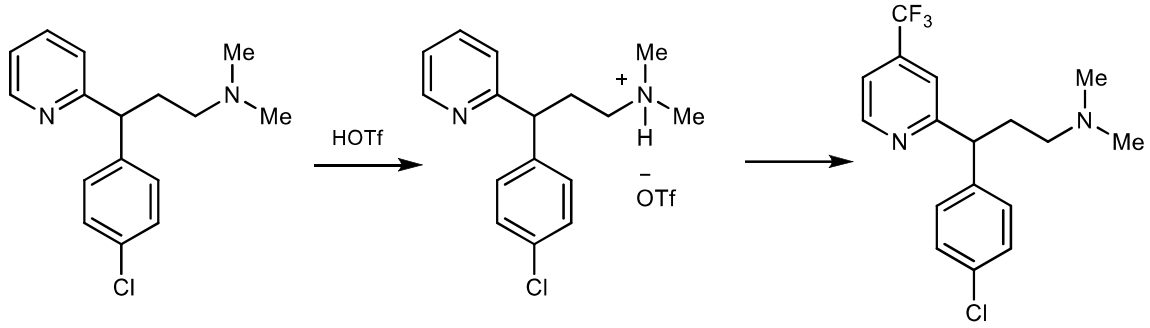
1363, 1320, 1251, 1212, 1180, 1132, 1095, 1046, 1027, 990, 905, 807, 761, 732, 698, 669; HRMS (DART): $[M+H]^+$ calculated for $C_{27}H_{28}F_3N_2O^+$ = 453.2148, found 453.2177.

5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-4'-(trifluoromethyl)-2,3'-bipyridine (5al)



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (72 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 µL, 0.20 mmol), DBU (30 µL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (44 µL, 0.50 mmol), MeOH (1 mL) and H_2O (36 µL, 2.00 mmol) at rt for 60 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in CH_2Cl_2 to 33% EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (68 mg, 0.16 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (d, *J* = 1.9 Hz, 1H), 8.25 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.42 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.02 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.09, 151.81, 150.96, 148.02, 142.68, 140.36, 137.47, 136.81 (q, *J* = 32.0 Hz), 136.59, 132.15, 130.33, 129.04, 127.82, 122.77 (q, *J* = 273.5 Hz), 120.04 (q, *J* = 3.5 Hz), 44.48, 24.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -60.13; IR υ_{max}/cm^{-1} (film): 3054, 2926, 1601, 1573, 1538, 1493, 1431, 1386, 1367, 1310, 1268, 1218, 1140, 1089, 1033, 1012, 956, 906, 888, 836, 790, 771, 728, 674, 661, 646, 593; HRMS (DART): $[M+H]^+$ calculated for $C_{19}H_{15}ClF_3N_2O_2S^+$ = 427.0489, found 427.0503.

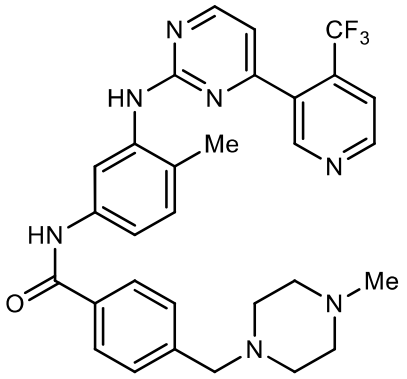
3-(4-Chlorophenyl)-N,N-dimethyl-3-(4-(trifluoromethyl)pyridin-2-yl)propan-1-amine (5am)



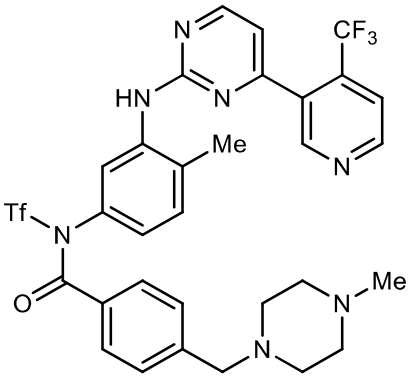
3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine (55 mg, 0.20 mmol) was dissolved in Et2O (1 mL) and cooled to 0 °C. Trifluoromethanesulfonic acid (18 µL, 0.20 mmol) was added dropwise, the ice bath was removed, and the solution was stirred for 10 minutes at room temperature. The solution

was concentrated *in vacuo* and the resulting acid salt was subjected to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 µL, 0.20 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (2 mL), HOTf (44 µL, 0.50 mmol), MeOH (1 mL) and H_2O (36 µL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 5% Et_3N in EtOAc) to provide the title compound as a light-yellow oil (52 mg, 0.15 mmol, 76% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, J = 5.2 Hz, 1H), 7.37–7.26 (m, 6H), 4.25–4.22 (m, 1H), 2.48–2.36 (m, 1H), 2.26–2.15 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.86, 150.54, 141.35, 138.80 (q, J = 33.7 Hz), 132.73, 129.57, 128.91, 122.93 (q, J = 271.6 Hz), 118.64 (q, J = 3.7 Hz), 117.22 (q, J = 3.5 Hz), 57.45, 50.57, 45.52, 33.05; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.75; IR υ_{max}/cm^{-1} (film): 2943, 2858, 2817, 2767, 1609, 1570, 1490, 1460, 1403, 1328, 1264, 1238, 1167, 1135, 1088, 1043, 1014, 895, 842, 828, 744, 721, 667; HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{19}ClF_3N_2^+$ = 343.1183, found 343.1187.

_N_-(4-Methyl-3-((4-(4-(trifluoromethyl)pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (5an)



13

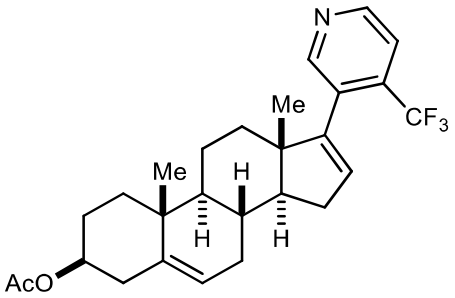


1

An oven dried 8 mL vial with a stir bar was charged with *N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (74 mg, 0.15 mmol) and placed under a nitrogen atmosphere. CH_2Cl_2 (3.8 mL) was added, the reaction vessel cooled to –78 °C and Tf_2O (26 µL, 0.15 mmol) was added dropwise over 5 minutes. The reaction was stirred for 2 hours before 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (65 mg, 0.17 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred further for 1 hour at –50 °C. The DBU (23 µL, 0.15 mmol) was added dropwise via syringe at the same temperature and stirred for another 2 hours. Then HOTf (47 µL, 0.53 mmol), MeOH (0.75 mL) and H_2O (27 µL, 1.50 mmol) were added sequentially at –50 °C, the cooling bath was removed and the reaction was allowed to

warm to room temperature and stirred for 5 additional hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 30% toluene, 3% MeOH and 2% Et_3N in CH_2Cl_2) to provide the mixture of compounds as a yellow oil (36 mg, 0.06 mmol, 42% yield). Major, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87–8.86(m, 2H), 8.52 (d, *J* = 5.0 Hz, 1H), 8.25 (s, 1H), 7.89 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 5.2 Hz, 1H), 7.50 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.10 (s, 1H), 6.87 (d, *J* = 5.0 Hz, 1H), 3.55 (s, 2H), 2.47 (br s, 8H), 2.30–2.29 (m, 6H); Major, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.61, 163.29, 160.37, 158.67, 151.87, 151.21, 142.60, 137.38, 136.70, 135.71 (d, *J* = 32.6 Hz), 133.97, 132.11 (q, *J* = 2.0 Hz), 130.99, 129.37, 127.13, 124.94, 122.77 (q, *J* = 273.2 Hz), 119.95 (d, *J* = 4.9 Hz), 116.18, 113.74, 112.58, 62.61, 55.18, 53.18, 46.08, 17.64; Major, ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.03; IR υ_{max}/cm^{-1} (film): 3246, 2937, 2801, 1656, 1572, 1505, 1449, 1402, 1316, 1185, 1136, 1066, 1009, 908, 815, 727, 660, 613; *m*/*z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{30}H_{31}F_3N_7O^+$ = 562.3, found 562.3.

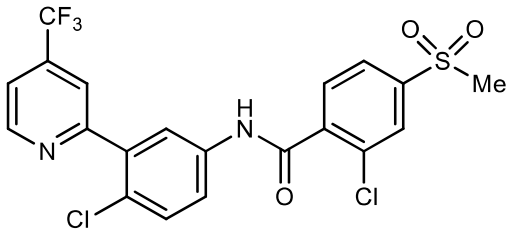
(3*S*,9*S*,10*R*,13*S*,14*S*)-10,13-Dimethyl-17-(4-(trifluoromethyl)pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (5ao)



Prepared according to general procedure A using (3*S*,9*S*,10*R*,13*S*,14*S*)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (78 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (18 μL, 0.20 mmol), TBAF (0.2 mL, 0.20 mmol, 1M in THF) at rt for 24 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a white solid (51 mg, 0.11 mmol, 55% yield). mp 145–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64–8.61 (m, 2H), 7.53 (d, *J* = 5.0 Hz, 1H), 5.81 (s, 1H), 5.41 (d, *J* = 5.1 Hz, 1H), 4.64–4.56 (m, 1H), 2.37–2.69 (m, 3H), 2.14–2.01 (m, 5H), 1.88–1.44 (m, 10H), 1.18–1.04 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.64, 151.30, 148.59, 147.95, 140.13, 136.59 (q, *J* = 30.5 Hz), 133.13 (q, *J* = 2.5 Hz), 131.89, 123.01 (q, *J* = 273.2 Hz), 122.40, 119.97 (q, *J* = 4.9 Hz), 73.97,

57.06, 50.36, 49.67, 38.24, 37.02, 36.93, 34.56, 32.57, 31.65, 30.83, 27.84, 21.53, 20.77, 19.34, 17.10; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -58.61; IR υ_{max}/cm^{-1} (film): 3060, 2941, 2912, 2853, 2836, 1731, 1724, 1597, 1429, 1402, 1368, 1317, 1291, 1236, 1181, 1152, 1135, 1061, 1036, 963, 876, 839, 821, 808, 739, 653; HRMS (DART): $[M+H]^+$ calculated for $C_{27}H_{33}F_3NO_2^+$ = 460.2458, found 460.2446.

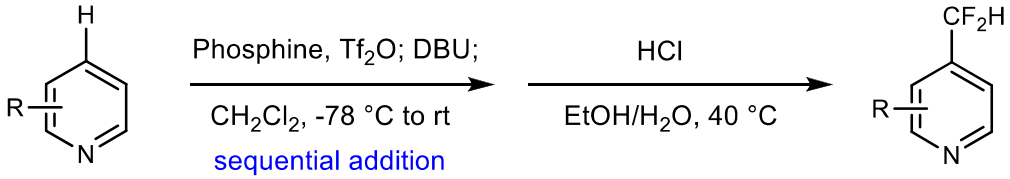
2-Chloro-*N*-(4-chloro-3-(4-(trifluoromethyl)pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (5ap)



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (84 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 µL, 0.20 mmol), DBU (30 µL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (27 µL, 0.30 mmol), MeOH (1 mL) and H_2O (36 µL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in CH_2Cl_2 to 25% EtOAc in CH_2Cl_2) to provide the title compound as a white solid (75 mg, 0.15 mmol, 76% yield). mp 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (s, 1H), 8.82 (d, *J* = 5.2 Hz, 1H), 7.92–7.90 (m, 2H), 7.83 (t, *J* = 1.1 Hz, 1H), 7.76 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.70 (d, *J* = 1.1 Hz, 2H), 7.52 (dd, *J* = 0.9, 5.1 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 1H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.68, 157.54, 150.49, 142.63, 140.62, 138.61 (q, *J* = 34.1 Hz), 138.24, 136.83, 132.51, 131.09, 130.50, 128.97, 127.90, 125.86, 123.04, 122.77 (q, *J* = 271.8 Hz), 122.16, 120.84 (q, *J* = 3.8 Hz), 118.46 (q, *J* = 3.4 Hz), 44.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.70; IR υ_{max}/cm^{-1} (film): 3299, 3066, 3025, 2926, 1675, 1605, 1584, 1534, 1485, 1462, 1430, 1371, 1335, 1301, 1280, 1246, 1211, 1167, 1150, 1137, 1098, 1084, 1049, 1032, 965, 883, 851, 817, 795, 757, 725, 667, 642, 591, 559; HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{14}Cl_2F_3N_2O_3S^+$ = 489.0049, found 489.0062.

A 2.5 Difluoromethylation of Heterocycles

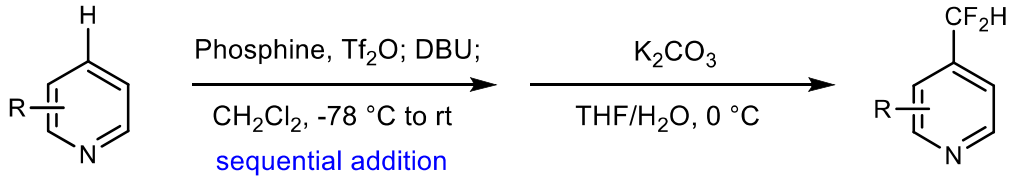
General Procedure A



An oven dried 8 mL vial or 25 mL round bottom flask was charged with the heterocycle (1.0 equiv) and phosphine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 °C and Tf_2O (1.0 equiv) was added dropwise

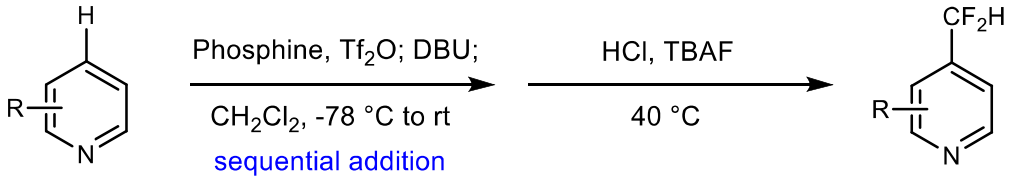
over 5 minutes. The reaction was stirred for 30 minutes before DBU (1.0 equiv) was added dropwise (note – addition should be performed with vigorous stirring to ensure the DBU is readily homogenized; at –78 °C it tends to freeze and stick to the stir bar, preventing stirring). After the addition was complete, the reaction was warmed to 0 °C in an ice bath over 5 minutes. A 10 % H_2O in EtOH (v/v) solution was added to the reaction, bringing the final concentration to 0.05 M, and HCl in dioxane was added (1.0 equiv). The reaction was heated to 40 °C and allowed to run for 24 h, then quenched with a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography to provide the difluoromethylated heteroarene.

General Procedure B



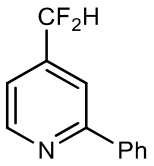
An oven dried 8 mL vial or 25 mL round bottom flask was charged with the heterocycle (1.0 equiv) and phosphine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 °C and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before DBU (1.0 equiv) was added dropwise (note – addition should be performed with vigorous stirring to ensure the DBU is readily homogenized; at –78 °C it tends to freeze and stick to the stir bar, preventing stirring). After the addition was complete, the reaction was warmed to 0 °C in an ice bath over 5 minutes. The solvent was removed under vacuum, and THF and H_2O (1:1, 0.1 M) were added to the residue. The solution was vigorously stirred and solid K_2CO_3 (1.5 eq.) was added in one portion. After 1 h, the reaction mixture was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography to provide the difluoromethylated heteroarene.

General Procedure C



An oven dried 8 mL vial or 25 mL round bottom flask was charged with the heterocycle (1.0 equiv) and phosphine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 °C and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before DBU (1.0 equiv) was added dropwise (note – addition should be performed with vigorous stirring to ensure the DBU is readily homogenized; at –78 °C it tends to freeze and stick to the stir bar, preventing stirring). After the addition was complete, the reaction was warmed to 0 °C in an ice bath over 5 minutes. HCl in dioxane was added (1.0 equiv), followed by TBAF (1.0 equiv.), and the reaction was heated to 40 °C for 24 h, then quenched with a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography to provide the difluoromethylated heteroarene.

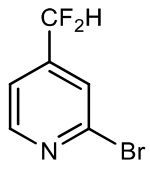
4-(Difluoromethyl)-2-phenylpyridine (7a)



Prepared according to general procedure A using 2-phenylpyridine (71.5 µL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 60 % CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (83 mg, 0.40 mmol, 80 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, J = 5.3 Hz, 1H), 8.09 – 7.91 (m, 2H), 7.84 (s, 1H), 7.60 – 7.39 (m, 3H), 7.39 – 7.31 (m, 1H), 6.69 (t, J = 55.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.43, 150.38, 142.97 (t, J = 23.3 Hz), 138.48, 129.57, 128.90, 127.00, 118.20 (t, J = 5.7 Hz), 116.62 (t, J = 6.0 Hz), 113.14 (t, J = 240.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.56 (d, J = 55.8 Hz). IR υ_{max}/cm^{-1} (film): 3054, 2360,

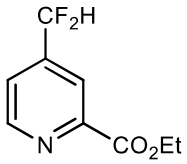
1609, 1583, 1564, 1476, 1409, 1380, 1302, 1198, 1114, 1038, 837, 774, 692, 635, 548. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_{10}F_2N^+$ = 206.0776, found 206.0792.

2-Bromo-4-(difluoromethyl)pyridine (7b)



Prepared according to general procedure B using 2-bromopyridine (48.6 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), K_2CO_3 (69 mg, 0.5 mmol), THF (2.5 mL) and H_2O (2.5 mL) at rt for 16 hours. The crude material was purified by flash chromatography (silica gel: 75 % CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (68 mg, 0.33 mmol, 65 % iso. yield, 78 % ^{1}H NMR yield). Note that the product evaporates during solvent evaporation. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, J = 5.1 Hz, 1H), 7.62 (s, 1H), 7.38 (d, J = 5.1 Hz, 1H), 6.60 (t, J = 55.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.09, 144.83 (t, J = 23.7 Hz), 142.91, 124.87 (t, J = 6.2 Hz), 119.17 (t, J = 5.6 Hz), 112.01 (t, J = 242.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.15 (d, J = 55.4 Hz). IR υ_{max}/cm^{-1} (film): 3067, 2979, 1598, 1557, 1464, 1397, 1363, 1286, 1218, 1125, 1078, 1043, 830, 739, 708, 671. *m/z* LRMS (ESI + APCI): $[M]^+$ calculated for $C_6H_4BrF_2N$ = 208.0, found 208.0.

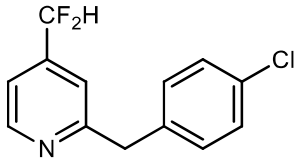
Ethyl 4-(difluoromethyl)picolinate (7c)



Prepared according to general procedure A using ethyl picolinate (67.5 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 30 % EtOAc in hexanes) to provide the title compound as a colorless oil (67 mg, 0.33 mmol, 67 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (d, J = 4.6 Hz, 1H), 8.23 (s, 1H), 7.59 (d, J = 4.0 Hz, 1H), 6.69 (t, J = 55.4 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.53, 150.74, 149.37, 143.62 (t, J = 23.9 Hz), 123.02 (t, J = 5.7 Hz), 121.63 (t, J = 6.0 Hz), 112.56 (t, J = 241.6 Hz),

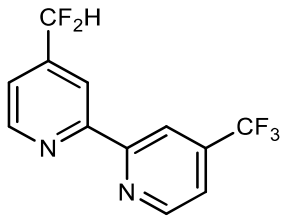
62.47, 14.40; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.95 (d, J = 55.5 Hz). IR υ_{max}/cm^{-1} (film): 2985, 2940, 2360, 1720, 1609, 1471, 1367, 1300, 1275, 1206, 1131, 1040, 1022, 913, 863, 783, 668. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_9H_{10}F_2NO_2^+$ = 202.0674, found 202.0689.

2-(4-Chlorobenzyl)-4-(difluoromethyl)pyridine (7d)



Prepared according to general procedure A using 2-(4-chlorobenzyl)pyridine (74 µL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (104 mg, 0.41 mmol, 82 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, J = 5.1 Hz, 1H), 7.34 – 7.24 (m, 3H), 7.24 – 7.13 (m, 3H), 6.58 (t, J = 55.7 Hz, 1H), 4.18 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.68, 150.37, 142.98 (t, J = 23.3 Hz), 137.35, 132.71, 130.57, 128.99, 119.29 (t, J = 5.9 Hz), 117.83 (t, J = 5.7 Hz), 113.06 (t, J = 240.9 Hz), 44.07; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.63 (d, J = 55.7 Hz). IR υ_{max}/cm^{-1} (film): 3028, 2928, 2360, 2341, 2222, 1611, 1570, 1491, 1407, 1365, 1174, 1089, 1043, 1016, 907, 848, 797, 729, 686. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{11}ClF_2N^+$ = 254.0543, found 254.0563.

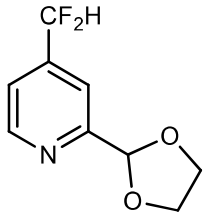
4-(Difluoromethyl)-4'-(trifluoromethyl)-2,2'-bipyridine (7e)



Prepared according to general procedure A using 4-(trifluoromethyl)-2,2'-bipyridine (112 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 60 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 3 % EtOAc in CH_2Cl_2) to provide the title compound as a white solid (83 mg, 0.30 mmol, 60 % yield). mp 74-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (dd, J = 14.3, 4.2 Hz, 2H), 8.72 (s, 1H), 8.60 (s, 1H), 7.53 (dd, J =

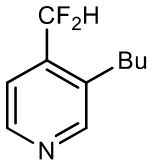
24.8, 4.5 Hz, 2H), 6.73 (t, J = 55.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.70, 155.82, 150.29 (d, J = 11.7 Hz), 143.62 (t, J = 23.6 Hz), 139.69 (q, J = 34.2 Hz), 124.39, 121.67, 121.18 – 120.39 (m), 119.82, 117.97 (t, J = 6.3 Hz), 117.25 (d, J = 3.7 Hz), 113.15 (t, J = 241.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.85, -115.58 (d, J = 55.7 Hz). IR υ_{max}/cm^{-1} (film): 3080, 2925, 2360, 2342, 1603, 1568, 1465, 1392, 1367, 1332, 1287, 1263, 1164, 1129, 1080, 1068, 1038, 908, 849, 667. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_8F_5N_2^+$ = 275.0602, found 275.0608.

4-(Difluoromethyl)-2-(1,3-dioxolan-2-yl)pyridine (7f)



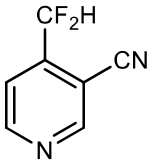
Prepared according to general procedure C using 2-(1,3-dioxolan-2-yl)pyridine (76 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), and TBAF (1 M in THF, 500 μL, 0.5 mmol), at 60 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 10 % EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (68 mg, 0.34 mmol, 68 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (d, J = 5.0 Hz, 1H), 7.66 (s, 1H), 7.40 (d, J = 4.8 Hz, 1H), 6.64 (t, J = 55.7 Hz, 1H), 5.89 (s, 1H), 4.23 – 4.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.44, 150.22, 143.18 (t, J = 23.5 Hz), 120.26 (t, J = 5.7 Hz), 117.23 (t, J = 6.0 Hz), 112.97 (t, J = 241.2 Hz), 103.30, 65.80; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.73 (d, J = 55.7 Hz). IR υ_{max}/cm^{-1} (film): 2962, 2893, 2360, 2341, 2252, 1614, 1383, 1173, 1119, 1080, 1041, 982, 907, 855, 728, 647. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_9H_{10}F_2NO_2^+$ = 202.0674, found 202.0687.

3-Butyl-4-(difluoromethyl)pyridine (7g)



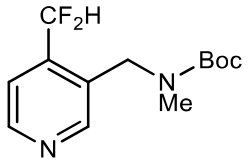
Prepared according to general procedure A using 3-butylpyridine (74 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15 % EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (56 mg, 0.28 mmol, 55 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 – 8.37 (m, 2H), 7.41 (d, *J* = 5.0 Hz, 1H), 6.77 (t, *J* = 54.8 Hz, 1H), 2.80 – 2.63 (m, 2H), 1.60 (tt, *J* = 7.9, 6.4 Hz, 2H), 1.41 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.68, 148.01, 139.36 (t, *J* = 22.0 Hz), 135.36, 119.37 (t, *J* = 6.6 Hz), 112.20 (t, *J* = 239.6 Hz), 33.45, 29.32, 22.55, 13.77; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -114.97 (d, *J* = 55.0 Hz). IR υ_{max}/cm^{-1} (film): 2960, 2934, 2874, 1466, 1411, 1379, 1347, 1237, 1166, 1089, 1035, 833, 730. *m/z* LRMS (ESI-APCI): $[M]^+$ calculated for $C_{10}H_{13}F_2N$ = 186.1, found 186.2.

4-(Difluoromethyl)nicotinonitrile (7h)



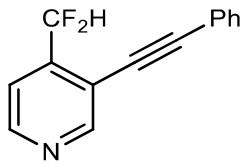
Prepared according to general procedure A using 3-cyanopyridine (52 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 2 % EtOAc in CH_2Cl_2) to provide the title compound as a white solid (13 mg, 0.08 mmol, 17 % iso. yield, 40 % ^{1}H NMR yield). Note that the product evaporates during solvent evaporation. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 (s, 1H), 8.98 (d, *J* = 4.8 Hz, 1H), 7.68 (d, *J* = 5.1 Hz, 1H), 6.89 (t, *J* = 54.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.72, 147.33, 139.88 (t, *J* = 21.5 Hz), 129.96, 117.17 (t, *J* = 7.1 Hz), 112.61 (t, *J* = 239.6 Hz), 33.05, 24.90, 22.52, 22.32; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.21 (d, *J* = 54.0 Hz). IR υ_{max}/cm^{-1} (film): 3037, 2924, 2236, 1593, 1407, 1381, 1235, 1191, 1164, 1090, 1042, 836, 790, 734, 660. *m/z* LRMS (ESI-APCI): $[M]^+$ calculated for $C_7H_4F_2N_2$ = 154.0, found 154.0.

Tert-butyl ((4-(difluoromethyl)pyridin-3-yl)methyl)(methyl)carbamate (7i)



Prepared according to general procedure A using tert-butyl methyl(pyridin-3-ylmethyl)carbamate (111 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 55 % EtOAc in hexanes) to provide the title compound as a colorless oil (85 mg, 0.31 mmol, 62 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, J = 5.0 Hz, 1H), 8.57 (s, 1H), 7.48 (d, J = 5.0 Hz, 1H), 6.91 (br t, J = 54.1 Hz, 1H), 4.58 (s, 2H), 2.82 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.06 – 154.49 (m), 152.70 – 150.30 (m), 149.93, 141.44 – 138.84 (m), 130.85, 119.89, 112.22 (t, J = 239.2 Hz), 80.67, 51.80 – 44.51 (m), 34.13, 29.82, 28.43; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.47 (d, J = 53.3 Hz). IR υ_{max}/cm^{-1} (film): 2978, 2933, 2360, 2341, 1686, 1480, 1414, 1391, 1367, 1240, 1147, 1084, 1038, 980, 911, 730, 663. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{19}F_2N_2O_2^+$ = 273.1409, found 273.1417.

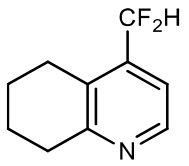
4-(Difluoromethyl)-3-(phenylethynyl)pyridine (7j)



Prepared according to general procedure A using 3-(phenylethynyl)pyridine (90 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 20 % EtOAc in hexanes) to provide the title compound as a yellow solid (89 mg, 0.39 mmol, 78 % yield). mp 44-45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (s, 1H), 8.68 (d, J = 5.1 Hz, 1H), 7.59 – 7.52 (m, 3H), 7.40 (qd, J = 4.7, 1.6 Hz, 3H), 7.00 (t, J = 54.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.21, 149.37, 142.40 (t, J = 23.2 Hz), 131.90, 129.57, 128.70, 121.90, 119.01 (t, J = 5.1 Hz), 118.44 (t, J = 5.7 Hz), 111.98 (t, J = 239.8 Hz), 98.26, 81.91; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.10 (d, J = 54.7 Hz). IR υ_{max}/cm^{-1} (film): 3068, 3021, 3001, 2926, 2854, 2360, 2341, 2221, 1598, 1496, 1442, 1365, 1233, 1211, 1168, 1143, 1076,

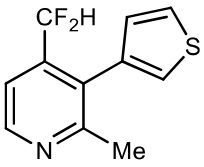
1031, 869, 848, 825, 749, 720, 686, 664. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{14}H_{10}F_2N^+$ = 230.0776, found 230.0787.

4-(Difluoromethyl)-5,6,7,8-tetrahydroquinoline (7k)



Prepared according to general procedure A using 5,6,7,8-tetrahydroquinoline (64.7 µL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol) (125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 40 % EtOAc in hexanes) to provide the title compound as a colorless oil (46 mg, 0.25 mmol, 50 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (d, *J* = 5.0 Hz, 1H), 7.24 (d, *J* = 5.0 Hz, 1H), 6.71 (t, *J* = 54.7 Hz, 1H), 2.99 (t, *J* = 6.2 Hz, 2H), 2.84 (t, *J* = 6.1 Hz, 2H), 1.98 – 1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.56, 147.18, 139.72 (t, *J* = 21.5 Hz), 129.80, 117.01 (t, *J* = 7.1 Hz), 112.46 (t, *J* = 239.6 Hz), 32.89, 24.74, 22.36, 22.17; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.77 (d, *J* = 54.7 Hz). IR υ_{max}/cm^{-1} (film): 2941, 2864, 2360, 2341, 2213, 1574, 1438, 1412, 1374, 1263, 1249, 1232, 1112, 1036, 908, 872, 843, 728, 644. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_{12}F_2N^+$ = 184.0932, found 184.0941.

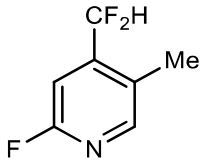
4-(Difluoromethyl)-2-methyl-3-(thiophen-3-yl)pyridine (7l)



Prepared according to general procedure A using 2-methyl-3-(thiophen-3-yl)pyridine (87.6 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 60 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 25 % EtOAc in hexanes) to provide the title compound as a colorless oil (86 mg, 0.38 mmol, 76 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, *J* = 5.1 Hz, 1H), 7.56 – 7.37 (m, 2H), 7.22 (dd, *J* = 2.9, 1.1 Hz, 1H), 7.01 (dd, *J* = 4.9, 1.1 Hz, 1H), 6.29 (t, *J* = 54.7 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.60, 148.98, 140.76 (t, *J* = 22.8 Hz), 134.91, 130.22 (t, *J* = 6.3 Hz), 128.80, 126.73, 125.17, 116.69 (t,

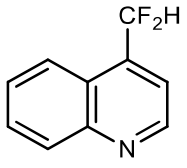
J = 5.1 Hz), 111.98 (t, J = 238.4 Hz), 23.52; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -106.33 – -117.12 (m). IR υ_{max}/cm^{-1} (film): 3107, 2997, 2220, 1576, 1423, 1394, 1355, 1268, 1242, 1105, 1038, 908, 860, 845, 785, 729, 705, 658. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{11}H_{10}F_2NS^+$ = 226.0497, found 226.0518.

4-(Difluoromethyl)-2-fluoro-5-methylpyridine (7m)



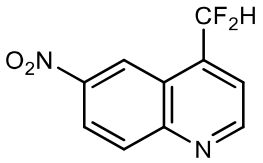
Prepared according to general procedure B using 2-fluoro-5-methylpyridine (52 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), K_2CO_3 (69 mg, 0.5 mmol), THF (2.5 mL) and H_2O (2.5 mL) at rt for 2 hours. The crude material was purified by flash chromatography (silica gel: 80 % CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (44 mg, 0.27 mmol, 27 % iso. yield, 70 % ^{1}H NMR yield) Note that the product evaporates during solvent evaporation. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.05 (d, J = 2.4 Hz, 1H), 6.69 (t, J = 54.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.69 (d, J = 238.1 Hz), 149.46 (d, J = 14.2 Hz), 145.18 (td, J = 22.2, 7.2 Hz), 128.49 (q, J = 4.6 Hz), 111.85 (td, J = 240.9, 2.9 Hz), 106.06 (dt, J = 40.1, 7.7 Hz), 14.85; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.09, -118.49 (d, J = 54.4 Hz). IR υ_{max}/cm^{-1} (film): 2973, 2360, 2342, 1612, 1582, 1490, 1456, 1387, 1348, 1269, 1156, 1049, 967, 881, 820, 735, 691. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_7H_7F_3N^+$ = 162.0525, found 162.0535.

4-(Difluoromethyl)quinoline (7n)



Prepared according to general procedure A using quinoline (59.2 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in CH_2Cl_2) to provide the title compound as colorless crystals (69 mg, 0.39 mmol, 77 % yield). mp 53-55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (d, *J* = 4.3 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.12 – 8.01 (m, 2H), 7.78 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (d, *J* = 4.3 Hz, 1H), 7.15 (t, *J* = 54.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.11, 148.75, 137.88 (t, *J* = 21.8 Hz), 130.55, 130.03, 127.92, 124.25 (t, *J* = 2.5 Hz), 123.40, 118.05 (t, *J* = 7.7 Hz), 113.41 (t, *J* = 240.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.10 (d, *J* = 54.5 Hz). IR υ_{max}/cm^{-1} (film): 3059, 2983, 2923, 2851, 2360, 2342, 1602, 1515, 1501, 1466, 1407, 1359, 1310, 1245, 1171, 1147, 1115, 1074, 1031, 1022, 999, 986, 865, 851, 767, 816, 777, 752, 665, 625. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_8F_2N^+$ = 180.0619, found 180.0632.

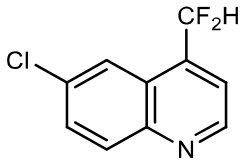
4-(Difluoromethyl)-6-nitroquinoline (7o)



Prepared according to general procedure A using 6-nitroquinoline (87 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 4 % EtOAc in CH_2Cl_2) to provide the title compound as a white solid (61 mg, 0.27 mmol, 54 % yield). mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.20 (d, *J* = 4.4 Hz, 1H), 9.05 (s, 1H), 8.55 (dd, *J* = 9.2, 2.4 Hz, 1H), 8.35 (d, *J* = 9.2 Hz, 1H), 7.74 (d, *J* = 4.3 Hz, 1H), 7.20 (t, *J* = 54.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.58, 150.63, 146.30, 139.97 (t, *J* = 22.5 Hz), 132.49, 123.61, 123.21 (t, *J* = 2.5 Hz), 120.71 (t, *J* = 1.9 Hz), 120.06 (t, *J* = 7.6 Hz), 112.95 (t, *J* = 241.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -114.34 (d, *J* = 54.1 Hz). IR υ_{max}/cm^{-1} (film): 3118, 3084, 3059, 3027, 2923, 2840, 2359, 2342, 1620, 1609, 1574, 1421, 1392,

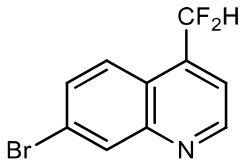
1344, 1300, 1264, 1235, 1221, 1145, 1120, 1100, 1046, 1009, 910, 894, 867, 805, 742, 736, 657. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_7F_2N_2O_2^+$ = 225.047, found 225.0478.

6-Chloro-4-(difluoromethyl)quinoline (7p)



Prepared according to general procedure A using 6-chloroquinoline (82 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in CH_2Cl_2) to provide the title compound as pale yellow crystals (75 mg, 0.35 mmol, 70 % yield). mp 65-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (d, *J* = 4.3 Hz, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 8.06 (d, *J* = 1.7 Hz, 1H), 7.72 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.58 (d, *J* = 4.3 Hz, 1H), 7.07 (t, *J* = 54.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.27, 147.17, 137.20 (t, *J* = 22.1 Hz), 134.09, 132.09, 131.11, 124.81 (t, *J* = 2.8 Hz), 122.66, 119.00 (t, *J* = 7.7 Hz), 113.25 (t, *J* = 240.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -114.91 (d, *J* = 54.3 Hz). IR υ_{max}/cm^{-1} (film): 2925, 2360, 2342, 1602, 1498, 1453, 1386, 1346, 1301, 1240, 1119, 1068, 1036, 851, 790. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_7ClF_2N^+$ = 214.023, found 214.0233.

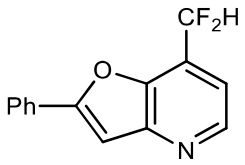
7-Bromo-4-(difluoromethyl)quinoline (7q)



Prepared according to general procedure A using 8-bromoquinoline (104 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 3 % EtOAc in CH_2Cl_2) to provide the title compound as colorless crystals (104 mg, 0.40 mmol, 81 % yield). mp 77-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (d, *J* = 4.3 Hz, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 7.94 (dt, *J* = 9.0, 1.3 Hz, 1H), 7.72 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.57 (d, *J* = 4.3 Hz, 1H), 7.09 (t, *J* = 54.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.13, 149.39, 138.11 (t, *J* = 22.0 Hz), 132.83, 131.44, 124.88, 124.33, 122.84 (t, *J* = 2.9

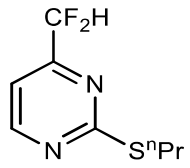
Hz), 118.46 (t, J = 7.7 Hz), 113.29 (t, J = 240.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -114.66 (d, J = 54.4 Hz). IR υ_{max}/cm^{-1} (film): 3068, 3040, 2975, 2923, 2852, 2360, 2333, 1600, 1494, 1442, 1362, 1305, 1238, 1166, 1120, 1080, 1066, 1041, 1001, 899, 858, 821, 778, 769, 672. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_7BrF_2N^+$ = 257.9724, found 257.9745.

7-(Difluoromethyl)-2-phenylfuro[3,2-b]pyridine (7r)



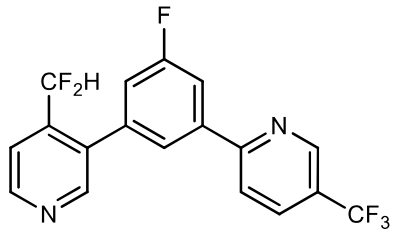
Prepared according to general procedure A using 2-phenylfuro[3,2-b]pyridine (195 mg, 1.0 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (326 mg, 1.1 mmol), Tf_2O (168 μL, 1.0 mmol), DBU (150 μL, 1.0 mmol), CH_2Cl_2 (10 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (9 mL) and H_2O (1.0 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in CH_2Cl_2) to provide the title compound as a pale yellow solid (46 mg, 0.19 mmol, 19 % yield). mp 93-94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (d, J = 4.4 Hz, 1H), 7.96 – 7.85 (m, 2H), 7.56 – 7.39 (m, 3H), 7.35 (d, J = 4.9 Hz, 1H), 7.27 (s, 1H), 7.15 (t, J = 54.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.92, 150.48, 146.60, 144.71 – 143.57 (m), 130.21, 129.21, 129.15, 125.66, 124.47 (t, J = 24.9 Hz), 115.32 – 114.04 (m), 110.90 (t, J = 240.0 Hz), 102.49; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.04 (d, J = 54.7 Hz). IR υ_{max}/cm^{-1} (film): 3117, 3068, 3037, 2979, 2924, 2853, 2360, 2341, 1577, 1494, 1448, 1398, 1375, 1362, 1282, 1267, 1257, 1215, 1114, 1080, 1034, 1015, 992, 917, 840, 800, 771, 756, 698, 686, 659. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{14}H_{10}F_2NO^+$ = 246.0725, found 246.0748.

4-(Difluoromethyl)-2-(propylthio)pyrimidine (7s)



Prepared according to general procedure A using 2-(propylthio)pyrimidine (77 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 10 % EtOAc in hexanes) to provide the title compound as a colorless oil (32 mg, 0.16 mmol, 32 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (d, *J* = 5.0 Hz, 1H), 7.22 (d, *J* = 5.0 Hz, 1H), 6.44 (t, *J* = 54.8 Hz, 1H), 3.23 – 3.05 (m, 2H), 1.77 (h, *J* = 7.3 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.68, 160.52 (t, *J* = 26.9 Hz), 159.00, 112.59 (t, *J* = 242.3 Hz) 111.64 (t, *J* = 2.9 Hz), 33.09, 22.55, 13.58; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -119.57 (d, *J* = 54.8 Hz). IR υ_{max}/cm^{-1} (film): 2966, 2933, 2874, 2360, 2342, 1560, 1458, 1436, 1363, 1325, 1262, 1202, 1182, 1110, 1052, 835, 751, 735. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_8H_{11}F_2N_2S^+$ = 205.0606, found 205.0624.

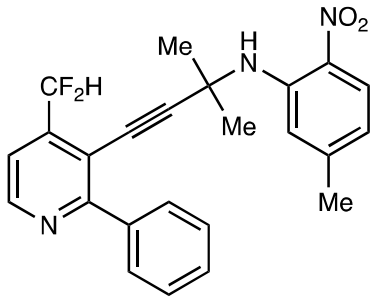
2-(3-(4-(Difluoromethyl)pyridin-3-yl)-5-fluorophenyl)-5-(trifluoromethyl)pyridine (7t)



Prepared according to general procedure A using 2-(3-fluoro-5-(pyridin-3-yl)phenyl)-5-(trifluoromethyl)pyridine (80 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 µL, 0.25 mmol), DBU (37 µL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 µL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 23 hours. The crude material was purified by flash chromatography (silica gel: 20 % EtOAc in toluene) to provide the title compound as a white solid (57 mg, 0.155 mmol, 62 % yield). m.p. 120-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 – 8.92 (m, 1H), 8.83 (d, *J* = 5.1 Hz, 1H), 8.72 (s, 1H), 8.04 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.94 – 7.83 (m, 3H), 7.69 (d, *J* = 5.1 Hz, 1H), 7.22 (dt, *J* = 8.5, 2.0 Hz, 1H), 6.58 (t, *J* = 54.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.53, 162.05, 159.25 – 157.72 (m), 151.00, 150.37, 147.02 (d, *J* = 4.0 Hz), 140.89 (d, *J* = 8.1 Hz), 139.35

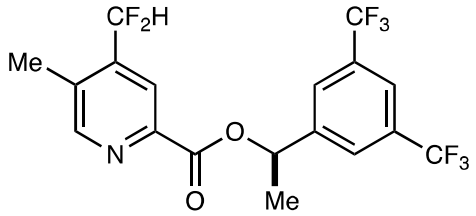
(t, J = 23.1 Hz), 137.73 (d, J = 8.1 Hz), 134.67 – 134.33 (m), 126.05 (q, J = 33.2 Hz), 124.98, 124.29, 120.28, 119.53 (t, J = 5.3 Hz), 118.20 (d, J = 22.6 Hz), 114.77 (d, J = 23.0 Hz), 111.65 (t, J = 239.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ: -62.38, -110.80 (t, J = 9.1 Hz), -111.59 (d, J = 54.1 Hz). IR υ_{max}/cm^{-1} (film): 3080, 3036, 2923, 1600, 1571, 1492, 1432, 1046, 1329, 1237, 1164, 1177, 1138, 1076, 1020, 920, 886, 842, 771, 697, 670, 553, 532. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{11}F_6N_2^+$ = 369.0821, found 369.0846.

_N_-(4-(4-(Difluoromethyl)-2-phenylpyridin-3-yl)-2-methylbut-3-yn-2-yl)-5-methyl-2-nitroaniline (7u)



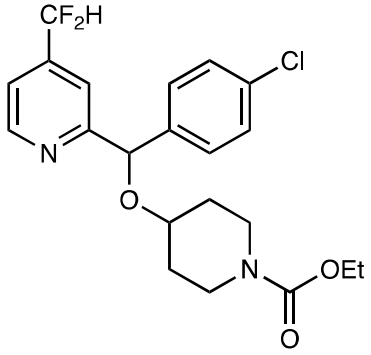
Prepared according to general procedure A using 5-methyl-*N*-(2-methyl-4-(2-phenylpyridin-3-yl)but-3-yn-2-yl)-2-nitroaniline (70 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 µL, 0.25 mmol), DBU (37 µL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 µL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in hexanes) to provide the title compound as a yellow oil (64 mg, 0.152 mmol, 61 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, J = 5.0 Hz, 1H), 8.31 (s, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.83 (dd, J = 7.6, 2.0 Hz, 2H), 7.50 (d, J = 4.9 Hz, 1H), 7.43 – 7.31 (m, 3H), 7.08 (d, J = 1.6 Hz, 1H), 6.91 (t, J = 54.8 Hz, 1H), 6.49 (dd, J = 8.7, 1.7 Hz, 1H), 2.19 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.31, 149.15, 147.37, 144.16 (t, J = 22.9 Hz), 143.34, 138.57, 131.18, 129.47, 129.34, 127.99, 127.04, 118.01, 117.33 (t, J = 5.4 Hz), 115.71, 115.19 (d, J = 5.8 Hz), 112.20 (t, J = 240.0 Hz), 103.06, 48.35, 29.99, 22.14; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.97 (d, J = 54.8 Hz). IR υ_{max}/cm^{-1} (film): 3352, 2983, 2932, 2360, 2342, 1617, 1578, 1491, 1405, 1335, 1237, 1187, 1128, 1073, 1048, 908, 843, 751, 732, 697. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{24}H_{22}F_2N_3O_2^+$ = 422.1675, found 422.1682.

(*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl 4-(difluoromethyl)-5-methylpicolinate (7v)



Prepared according to general procedure A using (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl 5-methylpicolinate (94 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 µL, 0.25 mmol), DBU (37 µL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 µL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 60 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 1 % EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (57 mg, 0.133 mmol, 53 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (t, *J* = 0.9 Hz, 1H), 8.20 (s, 1H), 7.92 (d, *J* = 1.7 Hz, 2H), 7.82 (t, *J* = 1.7 Hz, 1H), 6.76 (t, *J* = 54.4 Hz, 1H), 6.27 (q, *J* = 6.7 Hz, 1H), 2.49 (d, *J* = 1.6 Hz, 3H), 1.78 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.78, 152.49, 146.39, 143.75, 140.99 (t, *J* = 22.4 Hz), 135.33 (t, *J* = 4.3 Hz), 132.05 (q, *J* = 33.4 Hz), 126.58 (q, *J* = 3.6 Hz), 123.15 (q, *J* = 272.8 Hz), 122.38 – 122.00 (m), 121.30 (t, *J* = 7.1 Hz), 112.20 (t, *J* = 240.9 Hz), 72.59, 21.97, 15.81; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -62.90, -117.64 (d, *J* = 54.7 Hz). IR υ_{max}/cm^{-1} (film): 2989, 2360, 2342, 1726, 1456, 1384, 1278, 1247, 1222, 1174, 1134, 1054, 907, 845, 755, 730, 705, 682, 669. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{14}F_8NO_2^+$ = 428.0891, found 428.0907.

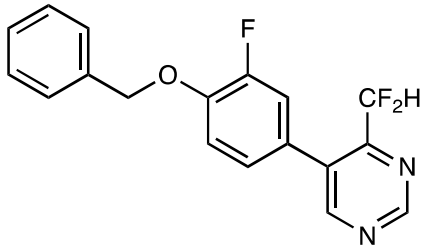
Ethyl 4-((4-chlorophenyl)(4-(difluoromethyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (7w)



Prepared according to general procedure A using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (94 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 µL, 0.25 mmol), DBU (37 µL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 µL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C

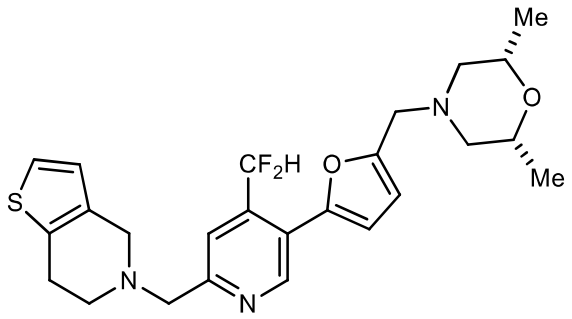
for 45 hours. The crude material was purified by flash chromatography (silica gel: 30 % EtOAc in toluene) to provide the title compound as a colorless oil (69 mg, 0.162 mmol, 65 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, *J* = 5.1 Hz, 1H), 7.62 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.28 – 7.21 (m, 3H), 6.58 (t, *J* = 55.7 Hz, 1H), 5.62 (s, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.82 – 3.66 (m, 2H), 3.59 (tt, *J* = 7.7, 3.7 Hz, 1H), 3.21 – 3.08 (m, 2H), 1.89 – 1.72 (m, 2H), 1.61 (td, *J* = 8.4, 4.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.25, 155.60, 149.79, 143.28 (t, *J* = 23.4 Hz), 139.63, 133.79, 128.83, 128.28, 118.80 (t, *J* = 5.7 Hz), 116.77 (t, *J* = 6.1 Hz), 113.05 (t, *J* = 241.1 Hz), 80.75, 72.96, 61.40, 41.15 (d, *J* = 7.4 Hz), 31.16 (d, *J* = 34.4 Hz), 14.79; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.57 (dd, *J* = 55.8, 10.1 Hz). IR υ_{max}/cm^{-1} (film): 2982, 2931, 2870, 1687, 1609, 1571, 1489, 1474, 1433, 1383, 1274, 1229, 1164, 1113, 1077, 1032, 1015, 828, 751, 666, 548, 531. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{24}ClF_2N_2O_3^+$ = 425.1438, found 425.1463.

5-(4-(Benzyloxy)-3-fluorophenyl)-4-(difluoromethyl)pyrimidine (7x)



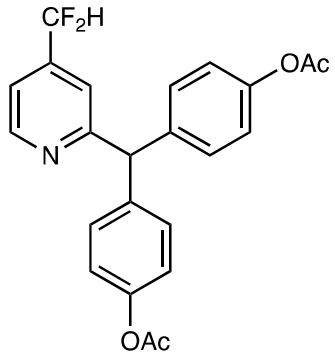
Prepared according to general procedure A using 5-(4-(benzyloxy)-3-fluorophenyl)pyrimidine (70 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 17 hours. The crude material was purified by flash chromatography (silica gel: 30 % EtOAc in hexanes) to provide the title compound as a white solid (32 mg, 0.096 mmol, 39 % yield). m.p. 73-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.81 (s, 1H), 7.51 – 7.33 (m, 5H), 7.22 – 7.04 (m, 3H), 6.58 (t, *J* = 53.6 Hz, 1H), 5.22 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.46, 157.84, 155.64 (t, *J* = 23.5 Hz), 153.97, 151.50, 147.90 (d, *J* = 10.5 Hz), 136.08, 132.83 (d, *J* = 2.2 Hz), 128.90, 128.52, 127.57, 125.96 – 125.44 (m), 117.53 (dt, *J* = 19.7, 1.8 Hz), 115.78 (d, *J* = 2.5 Hz), 111.90 (t, *J* = 242.5 Hz), 71.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -114.77 (d, *J* = 53.8 Hz), -131.97 (dd, *J* = 11.4, 8.1 Hz). IR υ_{max}/cm^{-1} (film): 3038, 2923, 2851, 1618, 1573, 1555, 1520, 1511, 1455, 1435, 1384, 1371, 1348, 1300, 1272, 1211, 1134, 1093, 1059, 1009, 993, 926, 906, 883, 817, 756, 746, 698, 668, 637, 630, 558. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{14}F_3N_2O^+$ = 331.1053, found 331.1058.

(2R,6S)-4-((5-(4-(Difluoromethyl)-6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-yl)methyl)-2,6-dimethylmorpholine (7y)



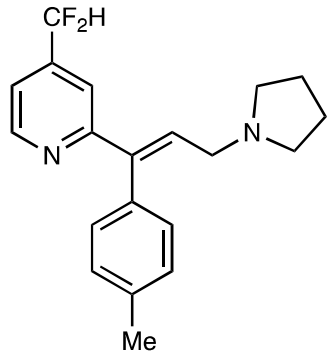
Prepared according to general procedure A except the reaction was allowed to warm to –50 °C after DBU addition and stirred for 5 minutes, then HCl was added and the reaction heated to 60 °C using (2R,6S)-4-((5-(6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-yl)methyl)-2,6-dimethylmorpholine (106 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (81.5 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 190 μL, 0.75 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 60 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 1 % MeOH in CH_2Cl_2) to provide the title compound as a pale yellow oil (60 mg, 0.13 mmol, 52 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (s, 1H), 7.82 (s, 1H), 7.08 (d, J = 5.1 Hz, 1H), 7.02 (t, J = 54.6 Hz, 1H), 6.70 (dd, J = 11.2, 4.2 Hz, 2H), 6.38 (d, J = 3.3 Hz, 1H), 3.94 (s, 2H), 3.77 – 3.66 (m, 4H), 3.62 (s, 2H), 2.99 – 2.85 (m, 4H), 2.77 (d, J = 10.5 Hz, 2H), 1.86 (t, J = 10.7 Hz, 2H), 1.16 (d, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.92, 153.65, 148.50, 148.20, 137.64 (t, J = 22.8 Hz), 133.74, 133.48, 125.36, 123.32 (t, J = 5.8 Hz), 122.85, 118.84 (t, J = 6.8 Hz), 111.82 (t, J = 239.0 Hz), 111.53, 111.45 – 111.16 (m), 71.80, 63.44, 59.06, 54.84, 53.38, 50.98, 25.54, 19.27; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.13 (d, J = 54.6 Hz). IR υ_{max}/cm^{-1} (film): 2971, 2931, 2871, 2813, 2360, 2342, 1474, 1454, 1376, 1355, 1321, 1162, 1142, 1080, 1044, 1023, 906, 837, 795, 730, 702. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{25}H_{30}F_2N_3O_2S^+$ = 474.2021, found 474.2025.

((4-(Difluoromethyl)pyridin-2-yl)methylene)bis(4,1-phenylene) diacetate (7z)



Prepared according to general procedure C using (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (90 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), and TBAF (1 M in THF, 250 μL, 0.25 mmol) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 20 % EtOAc in toluene) to provide the title compound as a yellow oil (86 mg, 0.208 mmol, 83 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (d, *J* = 5.0 Hz, 1H), 7.29 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.23 (s, 1H), 7.21 – 7.15 (m, 4H), 7.08 – 7.00 (m, 4H), 6.58 (t, *J* = 55.7 Hz, 1H), 5.70 (s, 1H), 2.28 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.52, 163.85, 150.53, 149.60, 142.97 (t, *J* = 23.3 Hz), 139.53, 130.36, 121.74, 120.04 (t, *J* = 6.1 Hz), 117.99 (t, *J* = 5.7 Hz), 113.04 (t, *J* = 241.0 Hz), 58.20, 21.26; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.50 (d, *J* = 55.9 Hz). IR υ_{max}/cm^{-1} (film): 3023, 1754, 1608, 1571, 1504, 1412, 1369, 1165, 1044, 1018, 909, 847, 751, 730, 665, 650, 549, 531. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{20}F_2NO_4^+$ = 412.1355, found 412.1367.

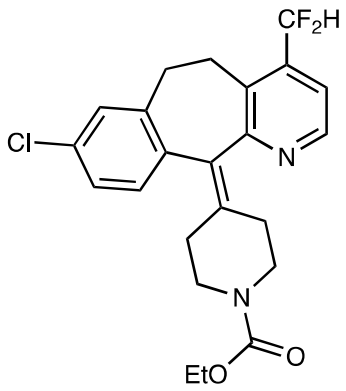
(*E*)-4-(Difluoromethyl)-2-(3-(pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridine (7aa)



Prepared according to general procedure A (except (*E*)-2-(3-(pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridine was protonated using TfOH (22 μL, 0.25 mmol) before the salt reaction) using (*E*)-2-(3-

(pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridine (70 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 25 hours. The crude material was purified by flash chromatography (silica gel: 5 % MeOH in CH_2Cl_2) to provide the title compound as a brown oil (66 mg, 0.200 mmol, 80 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (d, *J* = 4.9 Hz, 1H), 7.33 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.11 – 7.00 (m, 4H), 6.52 (t, *J* = 55.6 Hz, 1H), 3.79 (d, *J* = 7.3 Hz, 2H), 3.25 (s, 4H), 2.43 (s, 3H), 2.15 – 2.01 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.67, 150.02, 142.50 (t, *J* = 23.2 Hz), 141.90, 137.50, 134.80, 131.15, 129.76, 129.46, 118.33 (t, *J* = 6.2 Hz), 117.93 (t, *J* = 5.6 Hz), 113.23 (t, *J* = 240.7 Hz), 54.63, 54.11, 23.63, 21.43; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.28 (d, *J* = 55.9 Hz). IR υ_{max}/cm^{-1} (film): 2966, 2927, 2878, 2796, 1605, 1568, 1513, 1462, 1413, 1379, 1216, 1157, 1110, 1046, 908, 823, 731, 666, 549, 531. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{23}F_2N_2^+$ = 329.1824, found 329.1832.

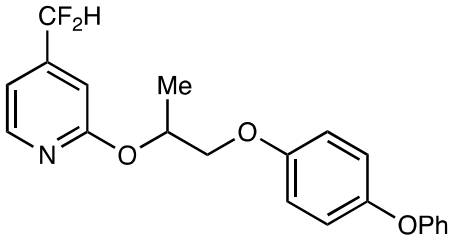
Ethyl 4-(8-chloro-4-(difluoromethyl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (7ab)



Prepared according to general procedure A using ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (96 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 20 hours. The crude material was purified by flash chromatography (silica gel: 50 % EtOAc in toluene) to provide the title compound as a yellow oil (93 mg, 0.216 mmol, 86 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (d, *J* = 5.0 Hz, 1H), 7.32 (d, *J* = 5.1 Hz, 1H), 7.12 (d, *J* = 2.5 Hz, 3H), 6.76 (t, *J* = 54.7 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.80 (d, *J* = 12.5 Hz, 2H), 3.49 – 3.30 (m, 2H), 3.26 – 3.11 (m, 2H), 3.10 – 2.99 (m, 1H), 2.94 – 2.83 (m, 1H), 2.53 – 2.32 (m, 3H), 2.27 – 2.10 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.34, 155.48, 147.54, 139.97 (t, *J* = 21.8 Hz), 138.65,

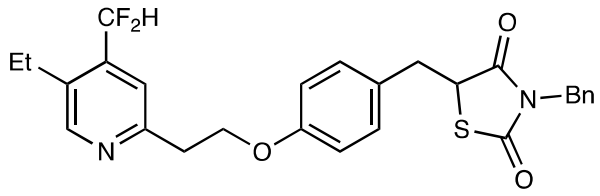
137.80, 135.81, 133.75, 133.25, 131.24, 131.11 (t, J = 4.0 Hz), 129.69, 126.24, 118.79 (t, J = 7.2 Hz), 112.71 (t, J = 240.4 Hz), 61.40, 44.71 (d, J = 15.6 Hz), 31.59, 30.66 (d, J = 7.2 Hz), 26.31, 14.69; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -112.76 – -118.16 (m). IR υ_{max}/cm^{-1} (film): 2981, 2911, 2870, 1734, 1591, 1478, 1434, 1386, 1374, 1227, 1119, 1043, 909, 757, 733, 561. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{24}ClF_2N_2O_2^+$ = 433.1489, found 433.1515.

4-(Difluoromethyl)-2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (7ac)



Prepared according to general procedure B using 2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (80 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 µL, 0.25 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (2.5 mL), K_2CO_3 (35 mg, 0.25 mmol), THF (0.625 mL) and H_2O (0.625 mL) at rt for 30 minutes. The crude material was purified by flash chromatography (silica gel: 100 % toluene) to provide the title compound as a colorless oil (18 mg, 0.048 mmol, 19 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, J = 5.2 Hz, 1H), 7.29 (dd, J = 8.6, 7.3 Hz, 2H), 7.08 – 7.01 (m, 1H), 7.01 – 6.88 (m, 7H), 6.87 (s, 1H), 6.56 (t, J = 55.8 Hz, 1H), 5.67 – 5.56 (m, 1H), 4.13 (ddd, J = 42.4, 9.9, 5.1 Hz, 2H), 1.48 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.74, 158.59, 155.25, 150.54, 147.97, 145.21, 129.76, 122.62, 120.91, 117.79, 115.92, 115.54 – 110.51 (m), 108.68, 71.09, 70.20, 17.01; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.62 (d, J = 55.8 Hz). IR υ_{max}/cm^{-1} (film): 2985, 1617, 1590, 1569, 1504, 1489, 1422, 1380, 1317, 1221, 1078, 1047, 909, 759, 734, 582, 560. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{20}F_2NO_3^+$ = 372.1406, found 372.1420.

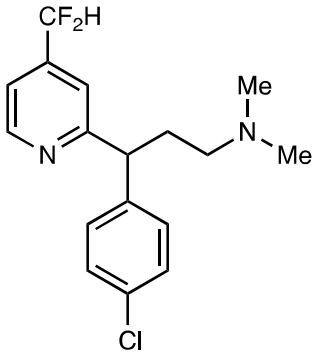
3-Benzyl-5-(4-(2-(4-(difluoromethyl)-5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (7ad)



Prepared according to general procedure A using 3-benzyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (112 mg, 0.25 mmol), (difluoromethyl)bis(4-

methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 15 % EtOAc in toluene) to provide the title compound as a colorless oil (31 mg, 0.061 mmol, 25 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (s, 1H), 7.40 (s, 1H), 7.26 (d, *J* = 1.2 Hz, 6H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.91 – 6.61 (m, 3H), 4.78 – 4.60 (m, 2H), 4.42 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.32 (t, *J* = 6.5 Hz, 2H), 3.38 (dd, *J* = 14.2, 3.9 Hz, 1H), 3.27 (t, *J* = 6.5 Hz, 2H), 3.08 (dd, *J* = 14.2, 8.7 Hz, 1H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.82, 171.05, 158.26, 157.12, 150.97, 139.71 (t, *J* = 21.8 Hz), 135.12, 134.58, 130.53, 128.76, 128.20, 127.63, 119.55 (t, *J* = 6.8 Hz), 114.87, 112.58 (d, *J* = 238.9 Hz), 67.01, 51.75, 45.27, 37.81, 37.68, 22.65, 15.74; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.09 (d, *J* = 54.8 Hz). IR υ_{max}/cm^{-1} (film): 3017, 2971, 2935, 2878, 1749, 1679, 1610, 1512, 1382, 1330, 1302, 1244, 1216, 1179, 1147, 1036, 908, 699, 667, 561, 530. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{27}H_{27}F_2N_2O_3S^+$ = 497.1705, found 497.1720.

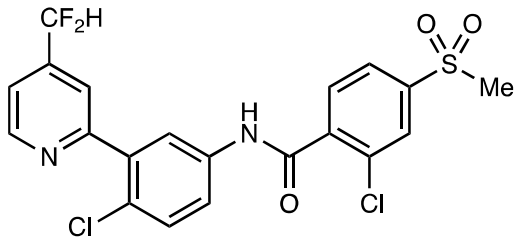
3-(4-Chlorophenyl)-3-(4-(difluoromethyl)pyridin-2-yl)-*N*,*N*-dimethylpropan-1-amine (7ae)



Prepared according to general procedure A (except 3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine was protonated using TfOH (22 μL, 0.25 mmol) before the salt reaction) using 3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine (69 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 20 hours. The crude material was purified by flash chromatography (neutral silica gel: 2 % MeOH in CH_2Cl_2) to provide the title compound as a brown oil (53 mg, 0.163 mmol, 65 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (d, *J* = 5.0 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 7H), 6.54 (t, *J* = 55.7 Hz, 1H), 4.24 (t, *J* = 6.6 Hz, 1H), 2.68 (s, 3H), 2.57 (s, 6H), 2.47 – 2.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.69, 150.25, 143.10 (t, *J* = 23.3 Hz), 140.45, 133.21, 129.42, 129.20, 119.80 (t, *J* = 6.0 Hz), 118.27 (t, *J* = 5.7 Hz), 112.92 (t, *J* = 241.1 Hz), 56.89, 50.04, 43.90, 30.44.; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.59 (dd, *J* = 55.6,

3.7 Hz). IR υ_{max}/cm^{-1} (film): 2953, 1681, 1611, 1570, 1420, 1410, 1383, 1090, 1039, 1015, 832. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{20}ClF_2N_2^+$ = 325.1278, found 325.1297.

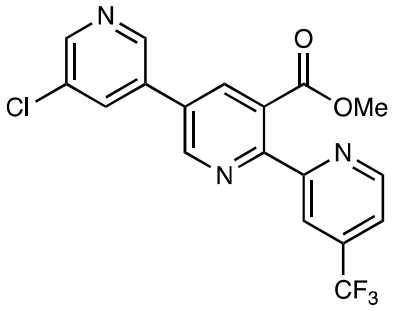
2-Chloro-N-(4-chloro-3-(4-(difluoromethyl)pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (7af)



Prepared according to general procedure A using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (105 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 µL, 0.25 mmol), DBU (37 µL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 µL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 25 hours. The crude material was purified by flash chromatography (silica gel: 60 % EtOAc in toluene) to provide the title compound as a yellow solid (71 mg, 0.151 mmol, 60 % yield). m.p. 124-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.21 (s, 1H), 8.63 (d, *J* = 5.1 Hz, 1H), 7.90 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.83 (d, *J* = 1.7 Hz, 1H), 7.80 (s, 1H), 7.78 (d, *J* = 2.7 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.32 (m, 1H), 6.71 (t, *J* = 55.7 Hz, 1H), 3.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.02, 157.28, 150.30, 143.54 – 142.75 (m), 140.92, 138.63, 137.31, 132.71, 131.54, 130.70, 129.33, 128.03, 126.22, 123.25, 122.40, 121.92 (t, *J* = 6.1 Hz), 119.50 (t, *J* = 5.7 Hz), 113.15 (t, *J* = 241.4 Hz), 44.75; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.15 (d, *J* = 55.8 Hz). IR υ_{max}/cm^{-1} (film): 3015, 2932, 1678, 1609, 1546, 1488, 1469, 1367, 1310, 1155, 1095, 1033, 959, 892, 875, 749, 676, 607, 550. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{15}Cl_2F_2N^+$ = 471.0143, found 471.0138.

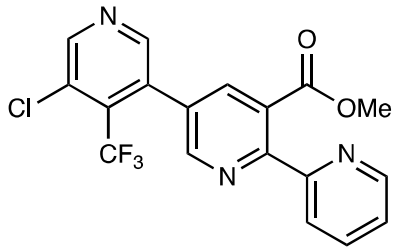
A 2.6 Site-Selective Trifluoromethylation of Heterocycles

Methyl 5''-chloro-4-(trifluoromethyl)-[2,2':5',3''-terpyridine]-3'-carboxylate (8)



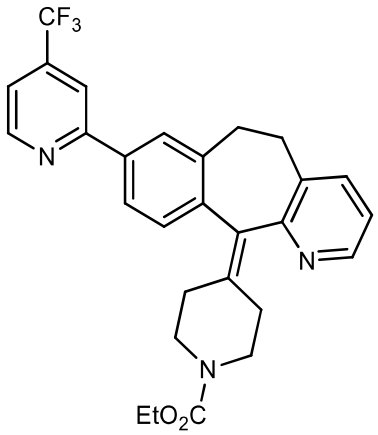
An oven dried 8 mL vial equipped with a stir bar was charged with methyl 5''-chloro-[2,2':5',3''-terpyridine]-3'-carboxylate (65 mg, 0.20 mmol), 1,1'-(((trifluoromethyl) phosphanediyl)bis(4,1-phenylene))dipyrrolidine (157 mg, 0.40 mmol), and placed under a nitrogen atmosphere. CH_2Cl_2 (2 mL) was added, the reaction vessel was cooled to –50 °C and Tf_2O (67 µL, 0.40 mmol) was added dropwise. After stirring for 1 hour, the reaction was cooled to –78 °C and Et_3N (56 µL, 0.40 mmol) was added dropwise via syringe. The cooling bath was removed, and the reaction was allowed to warm 0 °C while stirring (approximately 20-30 minutes). At 0 °C, TfOH (27 µL mg, 0.31 mmol), H_2O (36 µL, 2.00 mmol), MeOH (1 mL) were added and the reaction was stirred at room temperature for 40 hours. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 25% EtOAc in hexanes) to provide the title compound as a yellow solid (53 mg, 0.13 mmol, 67% yield). mp 185 – 189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98 (d, J = 2.2 Hz, 1H), 8.82 – 8.79 (m, 2H), 8.68 (d, J = 2.2 Hz, 1H), 8.51 (s, 1H), 8.16 (d, J = 2.3 Hz, 1H), 7.96 (app t, J = 2.1 Hz, 1H), 7.57 (dd, J = 5.0, 1.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.76, 156.77, 153.68, 149.56, 149.01, 148.54, 145.95, 139.54 (q, J = 34.1 Hz), 135.60, 134.26, 133.32, 132.83, 132.14, 129.20, 122.91 (q, J = 273.5 Hz), 119.64 (q, J = 3.6 Hz), 118.90 (q, J = 3.8 Hz), 52.86; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.76, IR υ_{max}/cm^{-1} (film): 3021, 2925, 1733, 1336, 1262, 1142, 891, 667. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{12}ClF_3N_3O_2^+$ = 394.0570, found 394.0559.

Methyl 5''-chloro-4''-(trifluoromethyl)-[2,2':5',3''-terpyridine]-3'-carboxylate (9)



Prepared according to trifluoromethylation general procedure A using methyl 5''-chloro-[2,2':5',3''-terpyridine]-3'-carboxylate (65 mg, 0.20 mmol), Tf_2O (34 µL, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (84 mg, 0.22 mmol), DBU (30 µL, 0.20 mmol), CH_2Cl_2 (2 mL), then TfOH (27 µL mg, 0.31 mmol), H_2O (36 µL, 2.00 mmol), MeOH (1 mL) were added at 0 °C and the reaction was stirred at room temperature for 24 hours. The crude material was purified by flash chromatography (silica gel: 35% EtOAc in hexanes) to provide the title compound as an amorphous solid (25 mg, 0.06 mmol, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (s, 1H), 8.69 – 8.63 (m, 2H), 8.51 (s, 1H), 8.23 (d, J = 7.9 Hz, 1H), 7.93 – 7.85 (m, 2H), 7.36 (ddd, J = 7.6, 5.0, 0.9 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.43, 155.51, 155.36, 152.17, 150.71, 149.47 (d, J = 2.0 Hz), 148.68, 137.17, 136.95 (d, J = 1.5 Hz), 133.92 (q, J = 30.8 Hz), 132.49 (q, J = 2.0 Hz), 131.42, 130.40 (q, J = 1.4 Hz), 128.16, 124.25, 123.02, 122.10 (q, J = 276.2 Hz), 52.79; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -55.55, IR υ_{max}/cm^{-1} (film): 2950, 2359, 1728, 1284, 1144, 1034, 750, 667. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{12}ClF_3N_3O_2^+$ = 394.0570, found 394.0590.

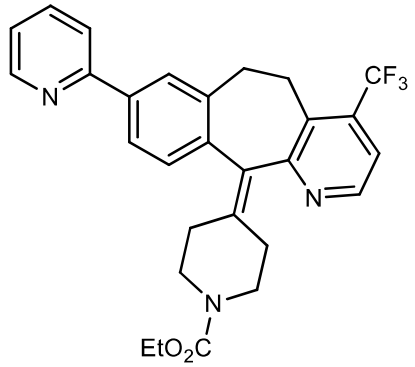
Ethyl 4-(8-(4-(trifluoromethyl)pyridin-2-yl)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (10)



An oven dried 8 mL vial with a stir bar was charged with ethyl 4-(8-(pyridin-2-yl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (85 mg, 0.20 mmol) and placed under a nitrogen atmosphere. CH_2Cl_2 (3.8 mL) was added, the reaction vessel cooled to –78 ºC and Tf_2O (68 μL, 0.40 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (157 mg, 0.40 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 °C. Then Et_3N (56 μL, 0.40 mmol) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (approximately 15 minutes). Then, the reaction mixture was cooled to 0 ºC, HOTf (45 μL, 0.5 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) were added sequentially. The mixture was warmed to room temperature and stirred for 12 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 10% Et_3N in hexanes) to provide the title compound as a light-yellow oil (72 mg, 0.15 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (d, *J* = 5.1 Hz, 1H), 8.41 (dd, *J* = 1.7, 4.8 Hz, 1H), 7.88 (s, 2H), 7.79 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.45 (dd, *J* = 1.7, 7.7 Hz, 1H), 7.42 (dd, *J* = 0.7, 5.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 4.8, 7.7 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.83 (br s, 2H), 3.55–3.47 (m, 1H), 3.44–3.36 (m, 1H), 3.19–3.12 (m, 2H), 2.99–2.87 (m, 2H), 2.55–2.48 (m, 1H), 2.42–2.32 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.55, 157.13, 155.61, 150.71, 146.79, 141.19, 139.20 (q, *J* = 33.7 Hz), 138.69, 137.66, 137.59, 137.23, 134.90, 133.70, 130.05, 127.83, 124.80, 123.02 (q, *J* = 271.6 Hz), 122.35, 117.56 (q, *J* = 3.6 Hz), 115.98 (q, *J* = 3.7 Hz), 61.40, 44.95, 44.93, 32.04, 31.83, 30.95, 30.67, 14.78; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.84; IR υ_{max}/cm^{-1} (film): 2911, 1690, 1608, 1570, 1471, 1423, 1384, 1333, 1277, 1227, 1168, 1134, 1113,

1088, 1059, 1026, 996, 889, 835, 790, 766, 726, 666; HRMS (DART): $[M+H]^+$ calculated for $C_{28}H_{27}F_3N_3O_2^+$ = 494.2050, found 494.2084.

Ethyl 4-(8-(pyridin-2-yl)-4-(trifluoromethyl)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (11)

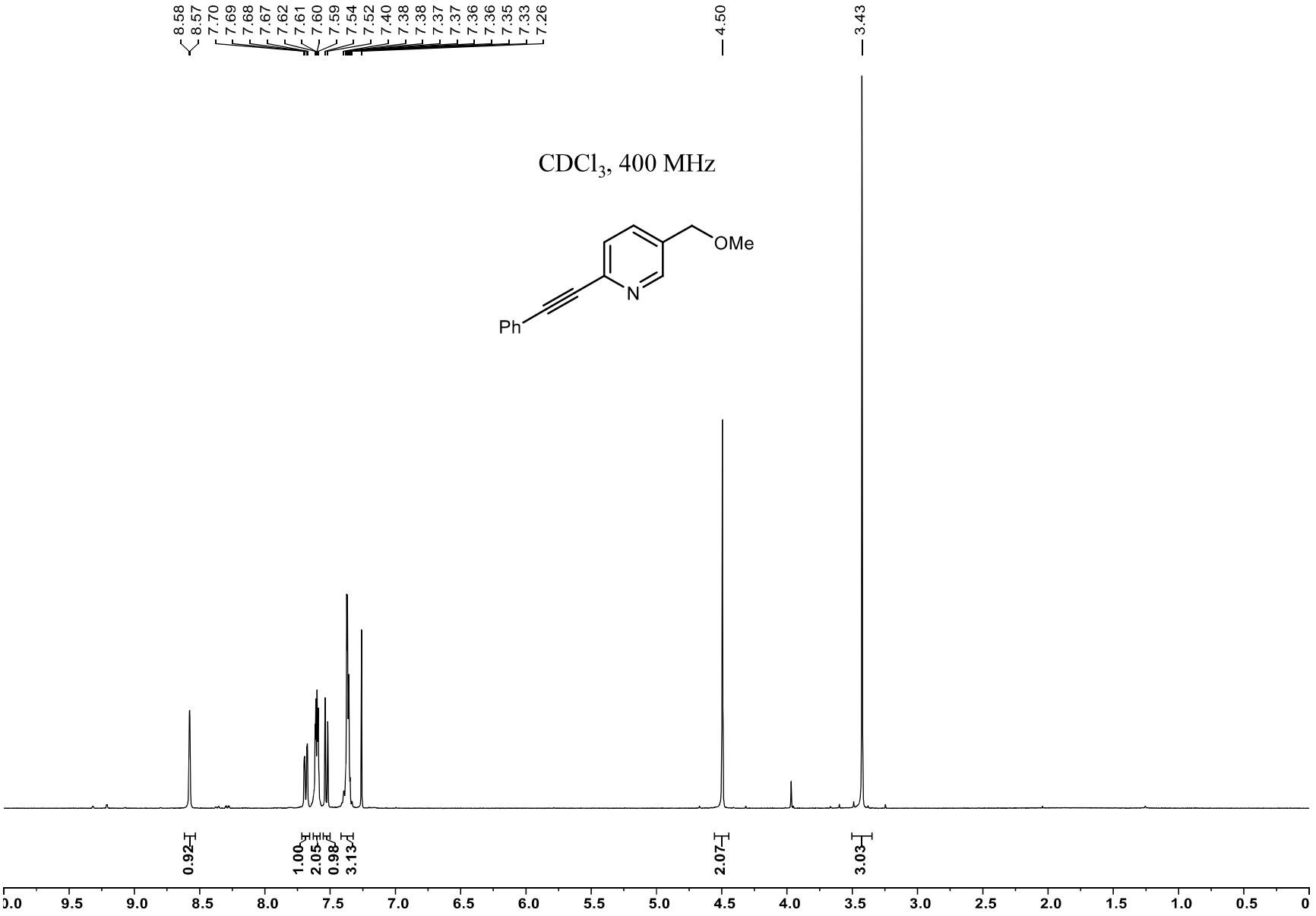


Prepared according to trifluoromethylation general procedure A using ethyl 4-(8-(pyridin-2-yl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (85 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (79 mg, 0.20 mmol), Tf_2O (34 µL, 0.20 mmol), DBU (30 µL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (45 µL, 0.50 mmol), MeOH (1 mL) and H_2O (36 µL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 10% Et_3N in hexanes) to provide the title compound as a colorless oil (70 mg, 0.14 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (d, *J* = 4.6 Hz, 1H), 8.56 (d, *J* = 5.1 Hz, 1H), 7.78 (s, 1H), 7.74–7.65 (m, 3H), 7.40 (d, *J* = 5.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.21–7.18 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.83–3.80 (m, 2H), 3.56–3.42 (m, 2H), 3.30–3.16 (m, 3H), 3.11–3.02 (m, 1H), 2.55–2.52 (m, 2H), 2.44–2.37 (m, 1H), 2.18–2.12 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.61, 156.86, 155.57, 149.76, 147.56, 138.84, 137.48, 137.00, 136.92, 136.83, 136.27 (q, *J* = 31.1 Hz), 134.42, 131.62, 131.04, 128.98, 124.45, 123.37 (q, *J* = 273.2 Hz), 122.28, 120.47, 118.46 (q, *J* = 5.1 Hz), 61.45, 44.95, 44.70, 32.15, 30.88, 30.69, 26.45, 14.76; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.86; IR υ_{max}/cm^{-1} (film): 2911, 2868, 1708, 1585, 1484, 1463, 1431, 1407, 1328, 1302, 1279, 1215, 1149, 1122, 1065, 1028, 1000, 985, 893, 857, 781, 759, 736, 687; HRMS (DART): $[M+H]^+$ calculated for $C_{28}H_{27}F_3N_3O_2^+$ = 494.2050, found 494.2080.

References

1. Perrin, D. D. & Amarego, W. L. F. *Purification of Laboratory Chemicals* (Pergamon Press, Oxford. ed. 3, 1988).
2. Busacca, C. A. et al. A Superior Method for the Reduction of Secondary Phosphine Oxides. *Org. Lett.* **7**, 4277–4280 (2005). doi:10.1021/ol0517832
3. Li, L., Wang, F., Ni, C., & Hu, J. Synthesis of *gem*-Difluorocyclopropa(e)nes and O-, S-, N-, and P-Difluoromethylated Compounds with $TMSCF_2Br$. *Angew. Chem. Int. Ed.* **52**, 12390–12394 (2013). doi:10.1002/anie.201306703
4. Krishnamurti, V., Barrett, C., & Prakash, G. K. S. Siladifluoromethylation and Deoxo-trifluoromethylation of P^V–H Compounds with $TMSCF_3$: Route to P^V–CF_2– Transfer Reagents and P–CF_3 Compounds. *Org. Lett.* **21**, 1526–1529 (2019). doi:10.1021/acs.orglett.9b00381
5. Murphy-Jolly, M. B., Lewis, L. C., & Caffyn, A. J. M. The Synthesis of Tris(perfluoroalkyl)phosphines. *Chem. Commun.* **35**, 4479–4480 (2005). doi:10.1039/B507752D

A 2.7 Spectra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4.50
3.43
CDCl3, 400 MHz
OMe
N
Ph
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1.00
2.05
0.98
3.13
2.07
3.03
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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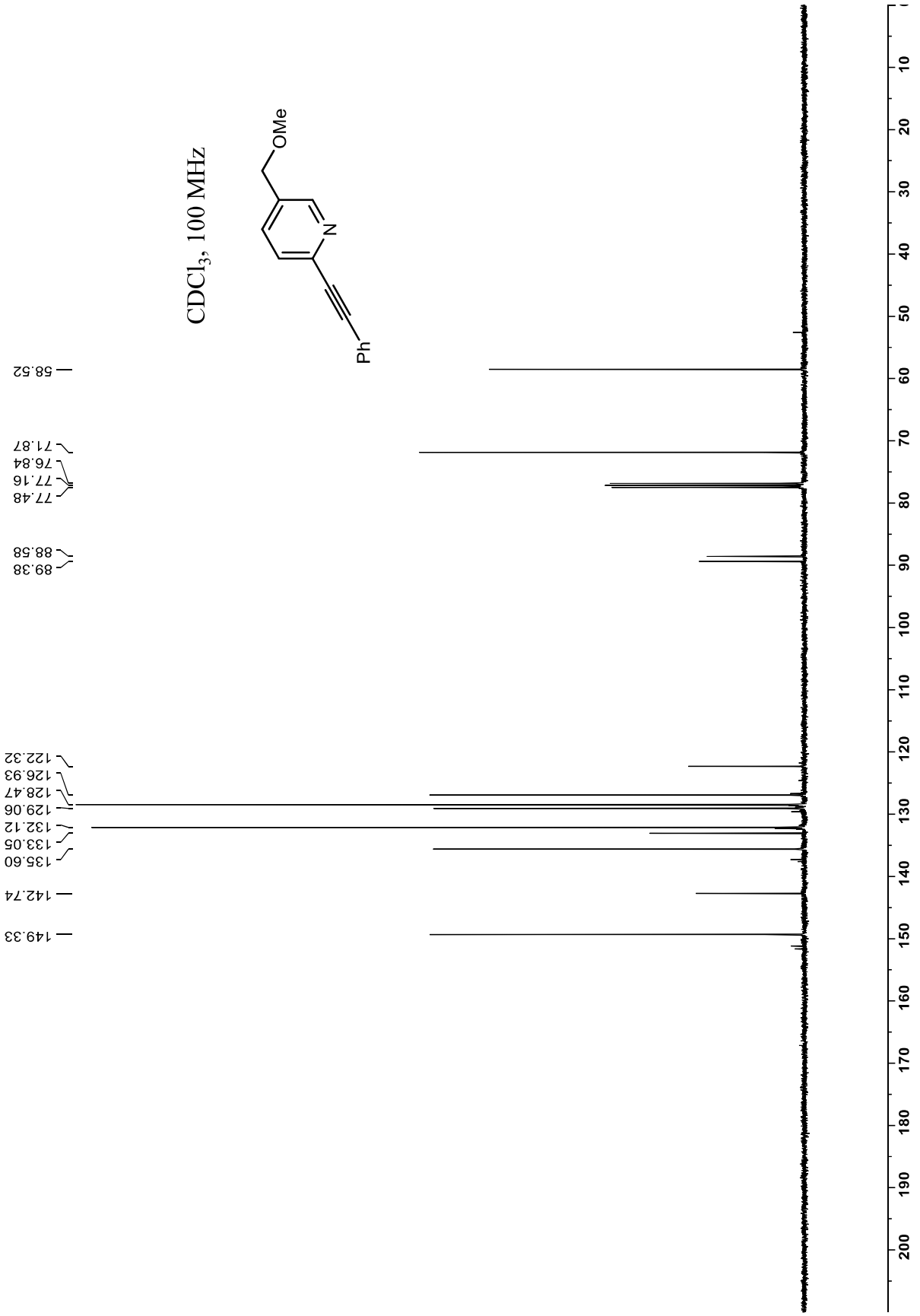
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126.93
128.47
129.06
132.12
133.05
135.60
142.74
149.33

CDCl3, 400 MHz
Ph
O
N
O
N
1.00
2.08
1.07
3.06
1.02
1.01
1.04
2.17
8.19
8.18
8.18
8.17
7.82
7.82
7.81
7.81
7.80
7.79
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7.64
7.63
7.62
7.62
7.62
7.61
7.60
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7.45
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7.44
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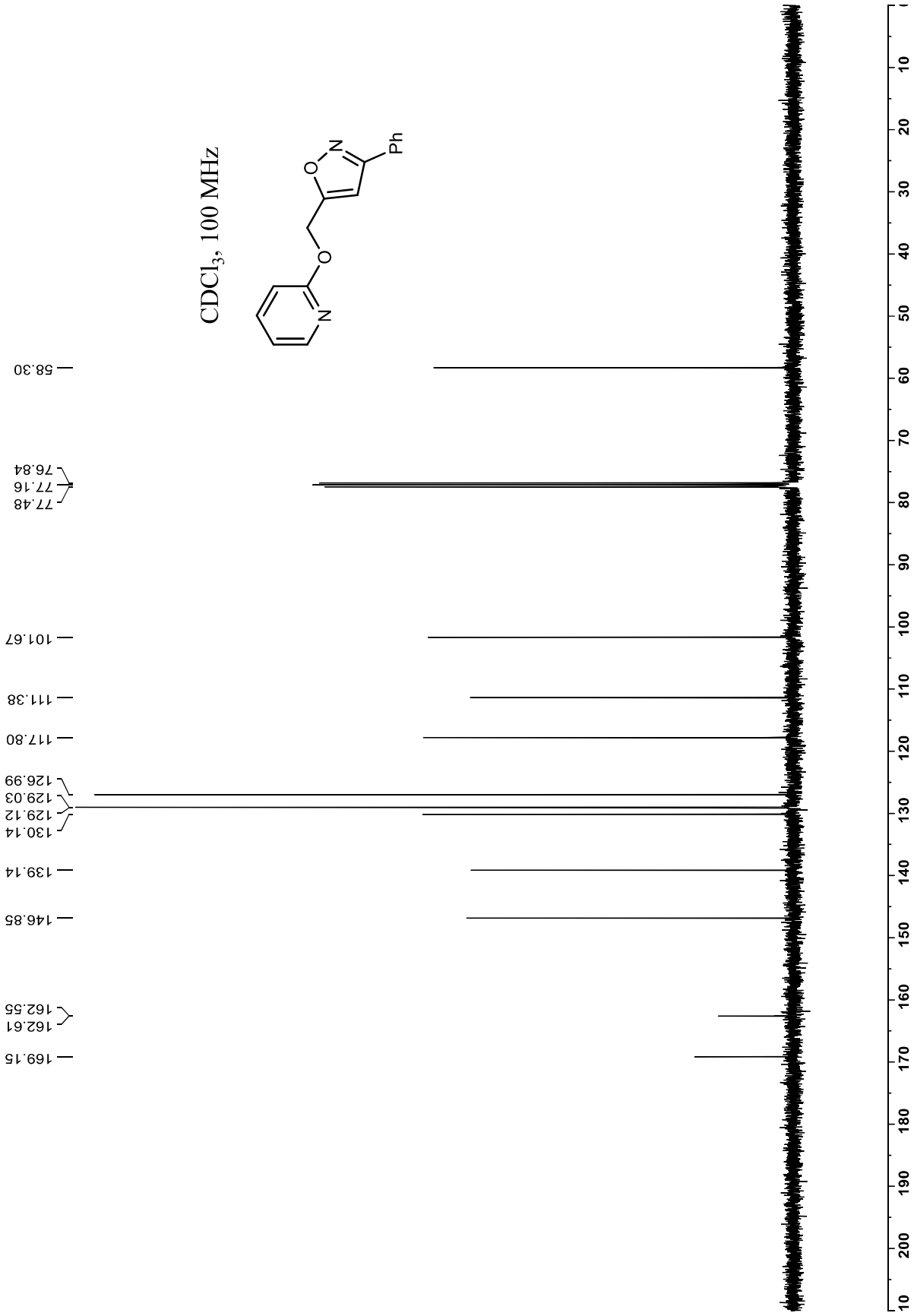
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126.99
129.03
129.12
130.14
139.14
146.85
162.55
162.61
169.15
10
20
30
40
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60
70
80
90
100
110
120
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140
150
160
170
180
190
200
10

CDCl3, 400 MHz
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CO2Me
NH
N
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8.62
8.61
8.60
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8.59
8.58
8.57
7.66
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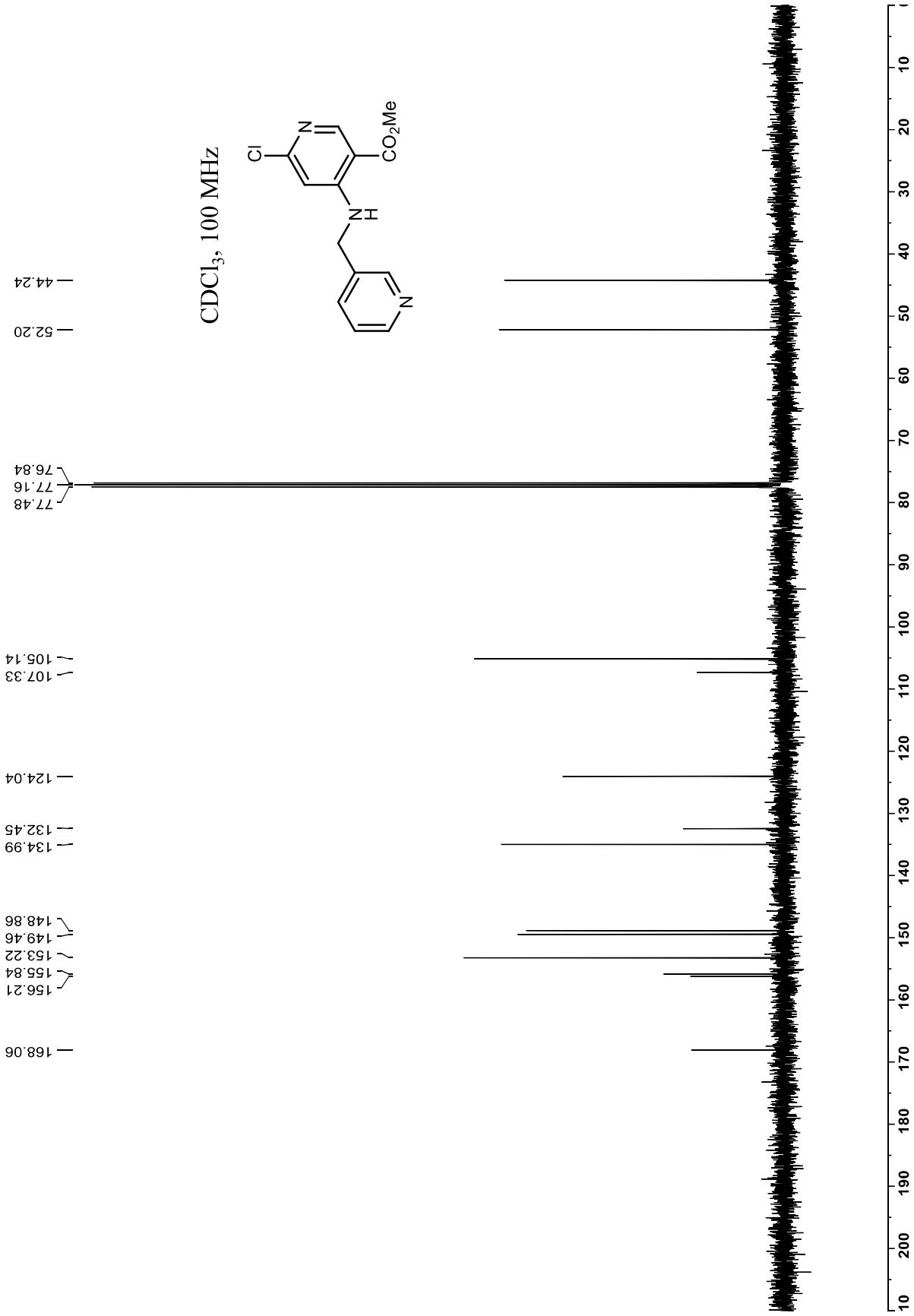
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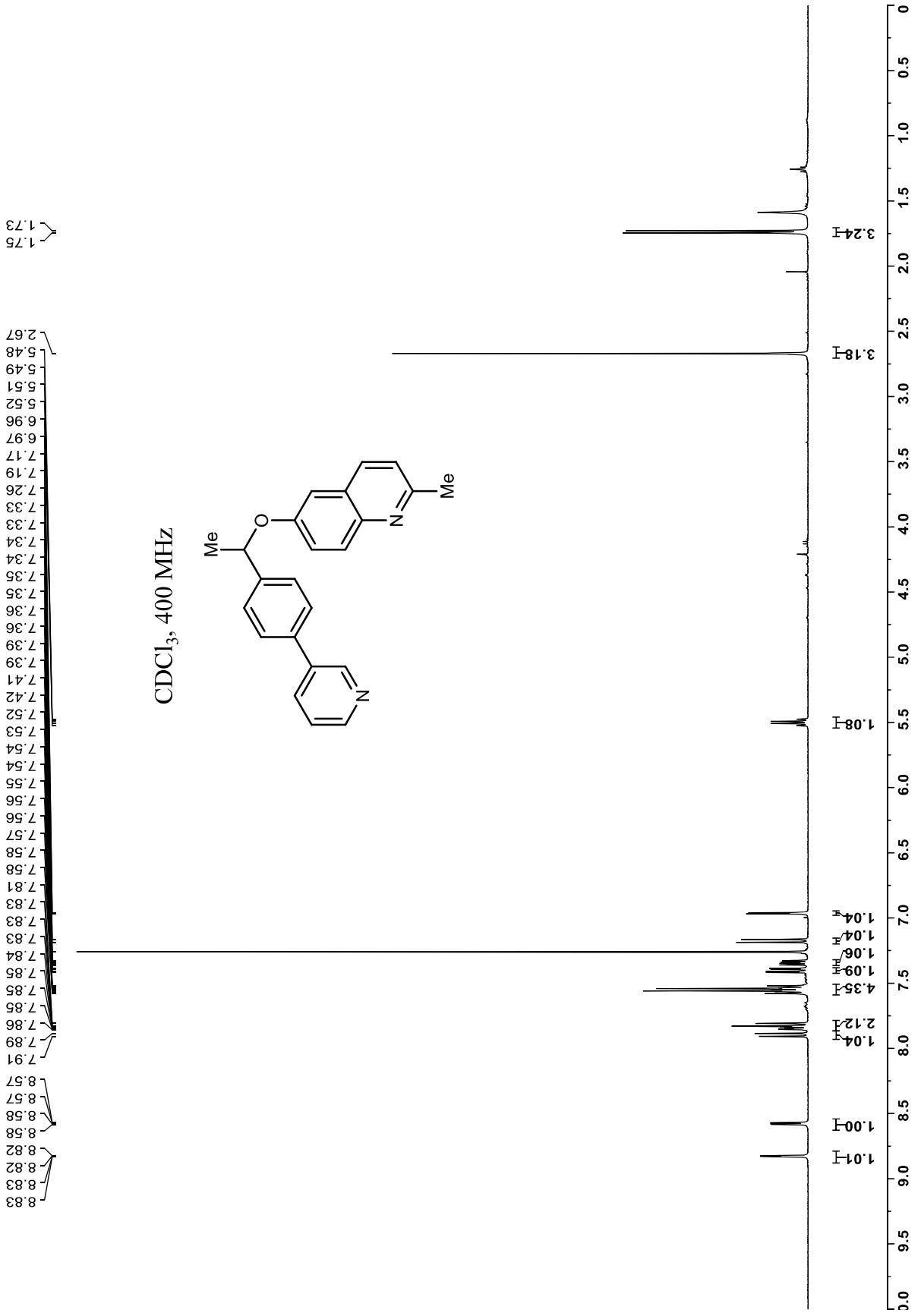
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7.84
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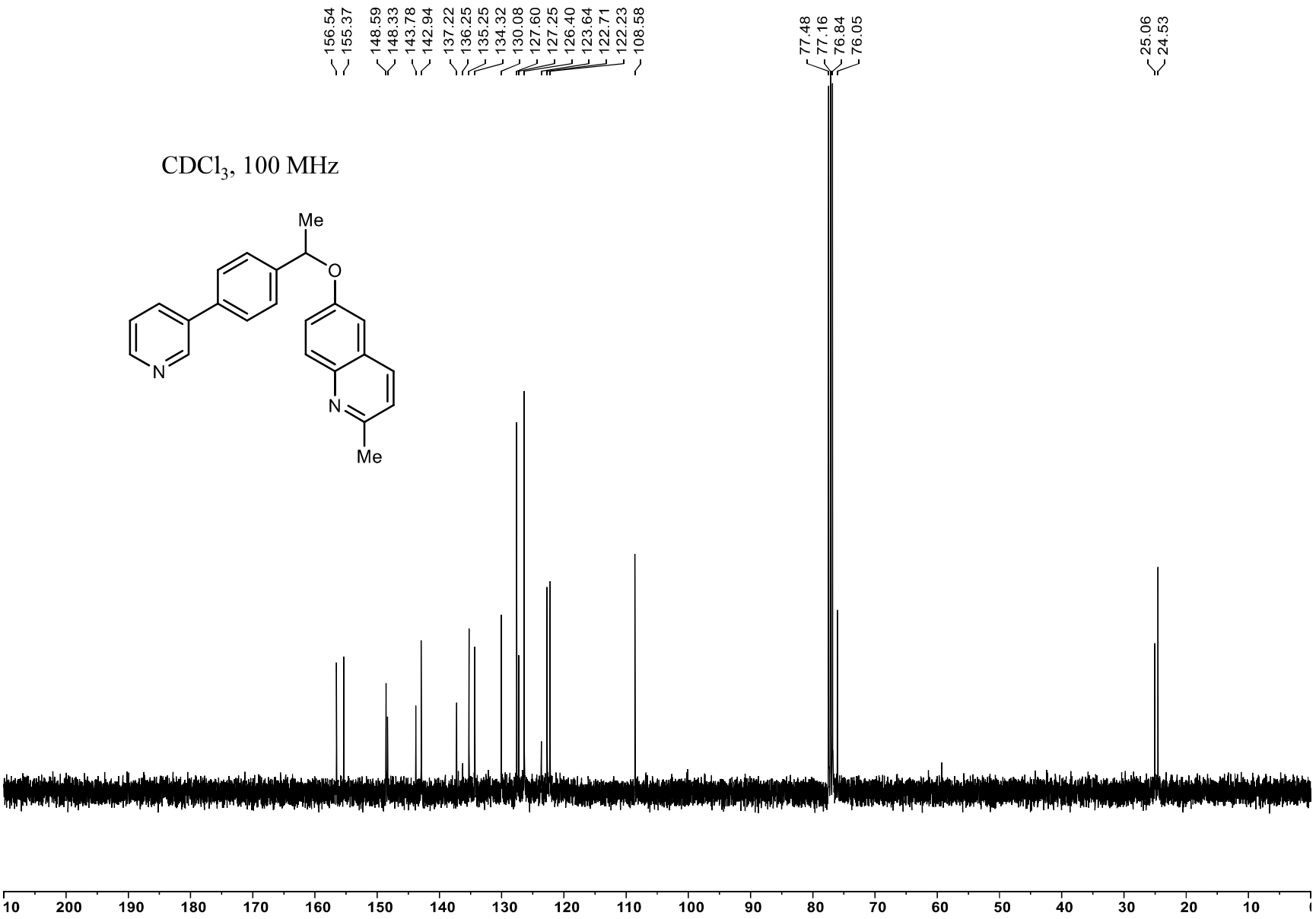
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77.16
76.84
76.05
25.06
24.53
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N
N
Me
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150
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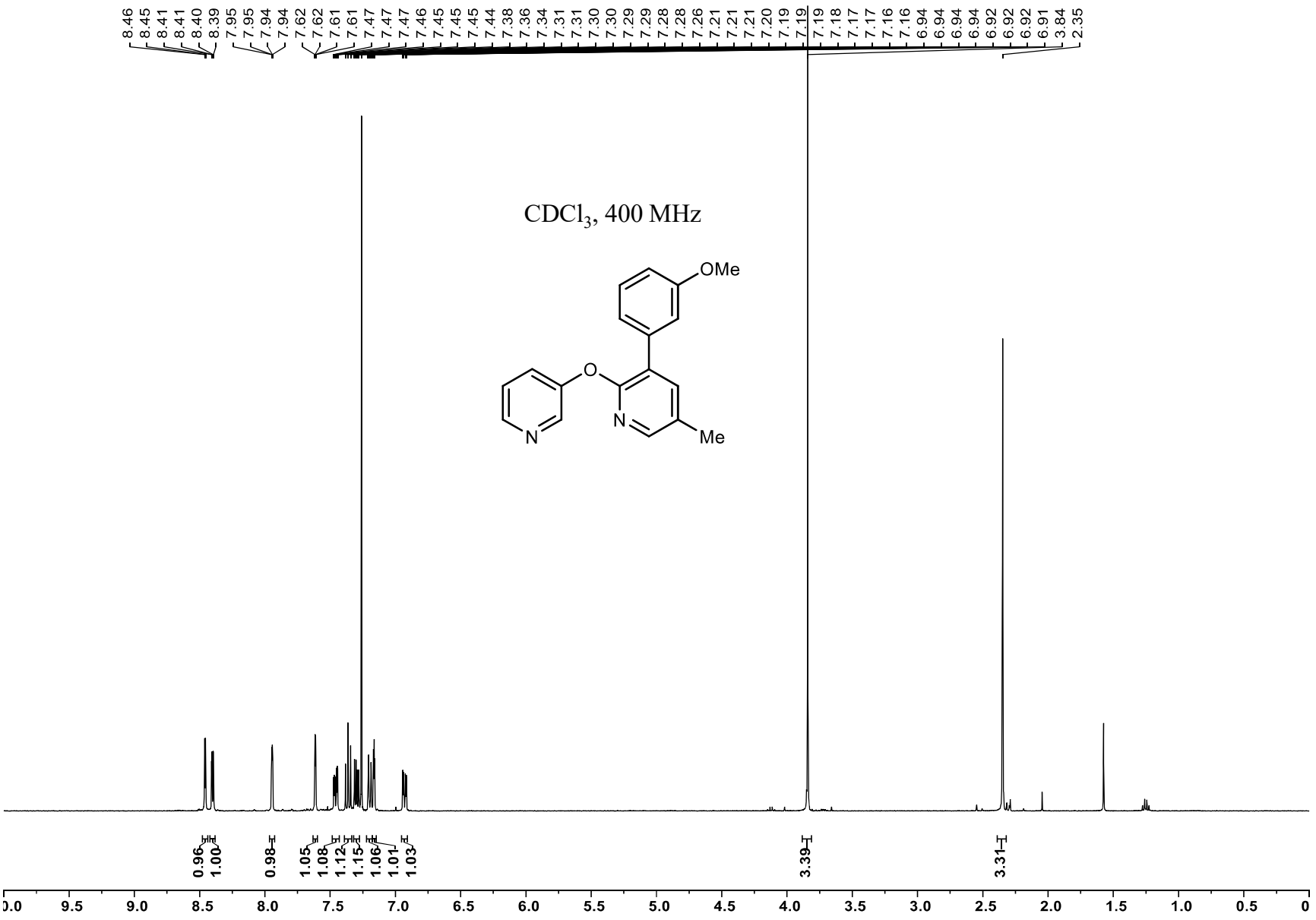
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OMe
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N
N
Me
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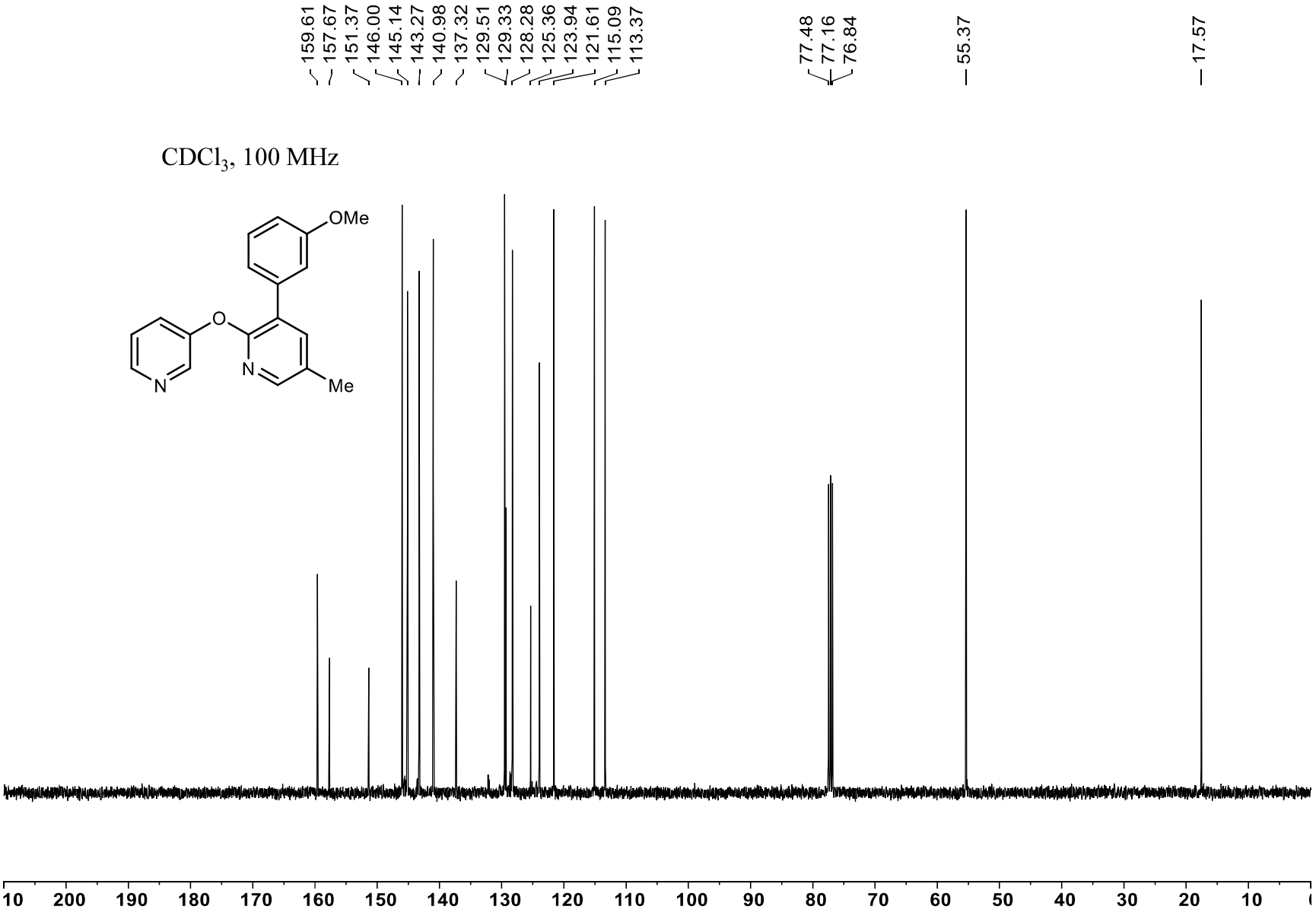
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Me
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200
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180
170
160
150
140
130
120
110
100
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70
60
50
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20
10

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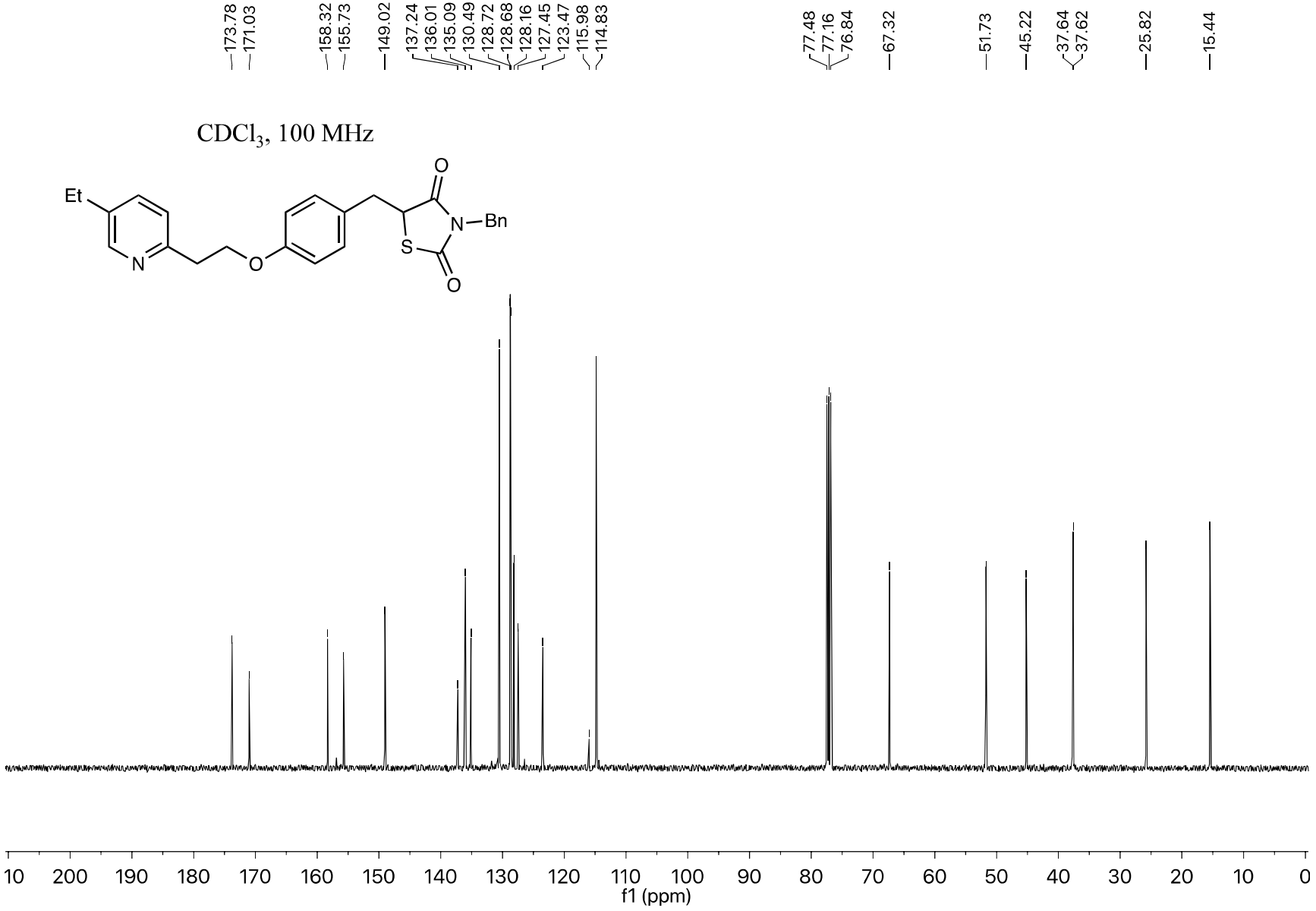
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Et
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O
S
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Bn
O
O
f1 (ppm)

CDCl3, 400 MHz
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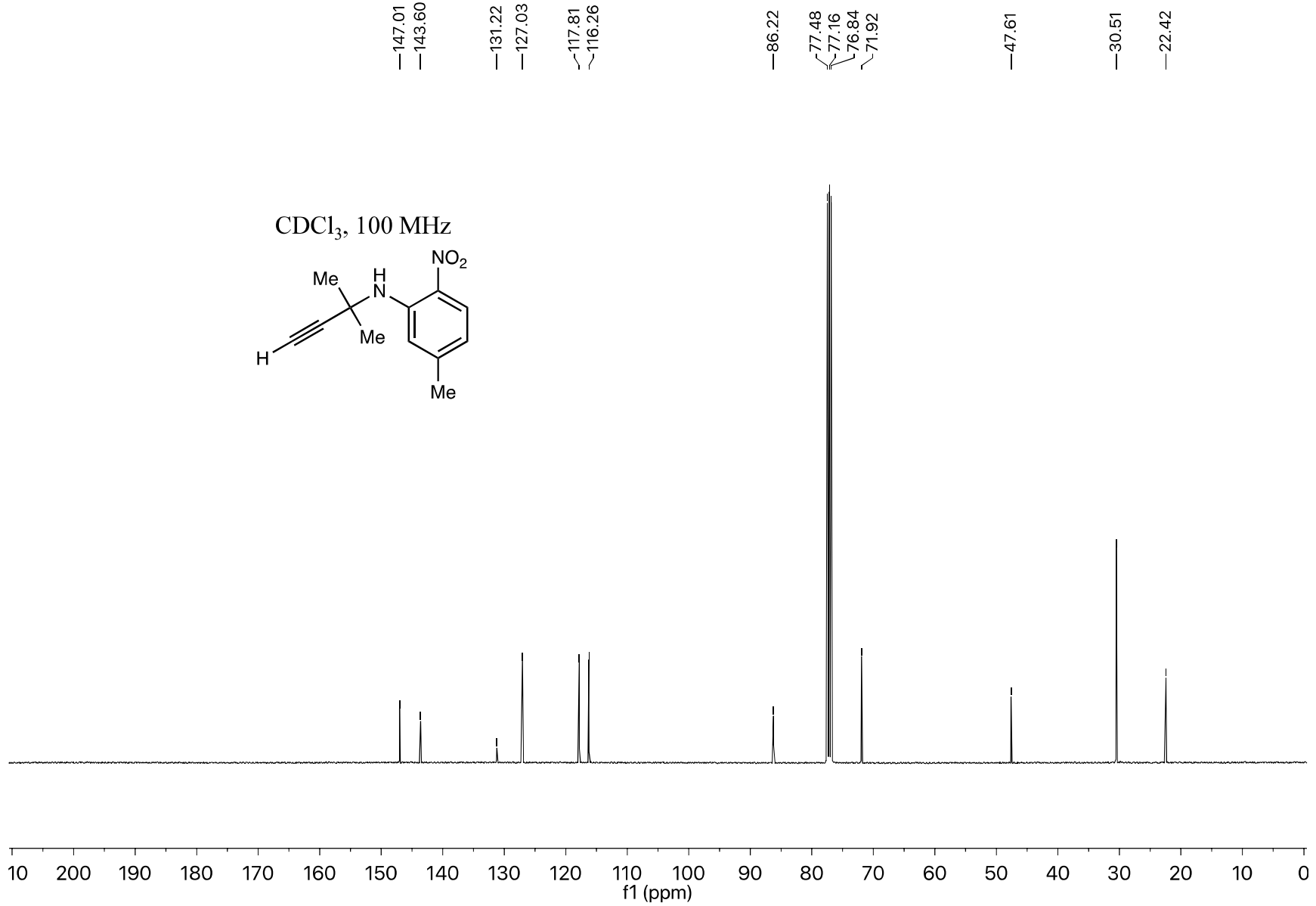
f1 (ppm)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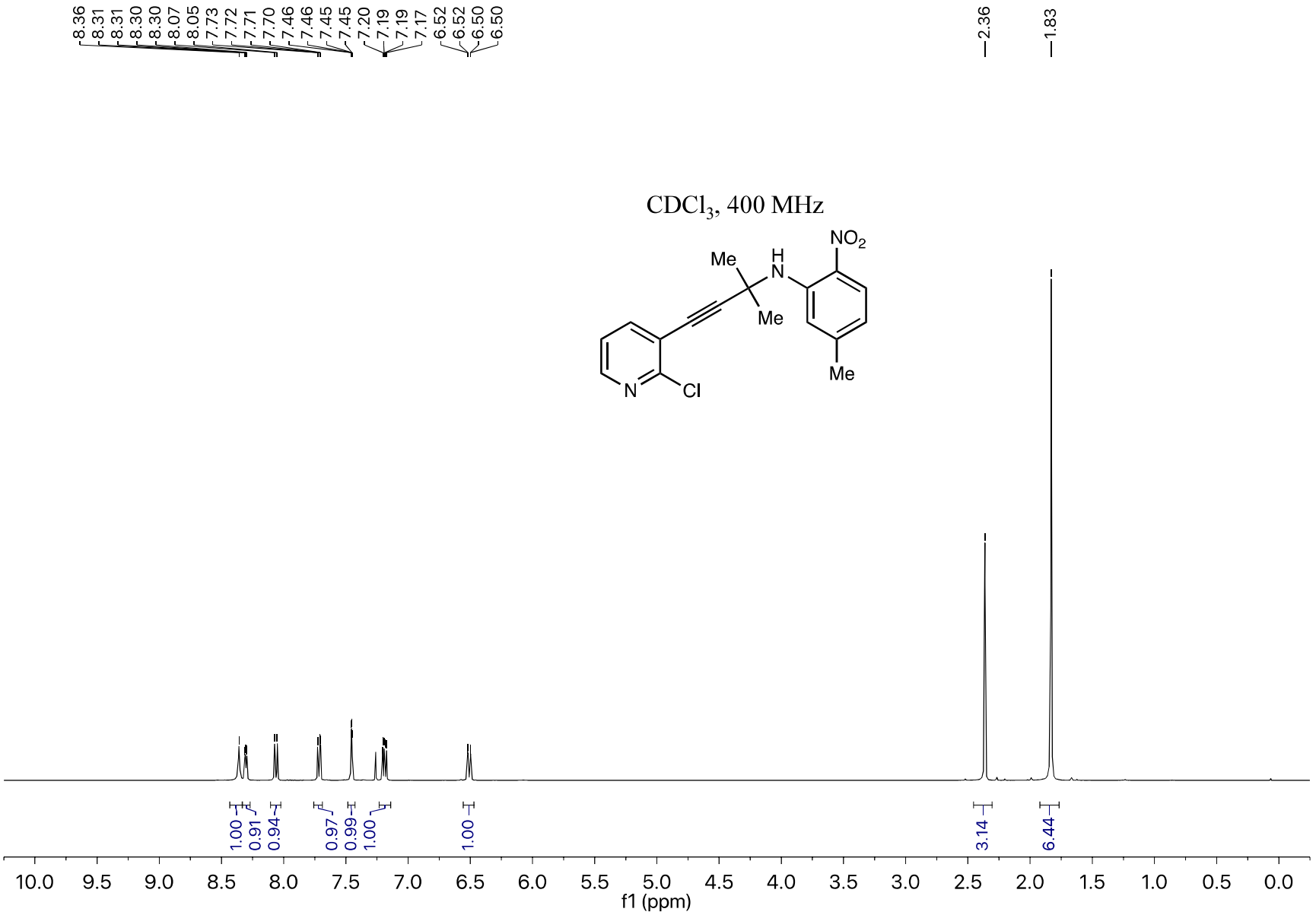
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7.17
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6.50
6.50
2.36
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NO2
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H
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Me
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N
Cl
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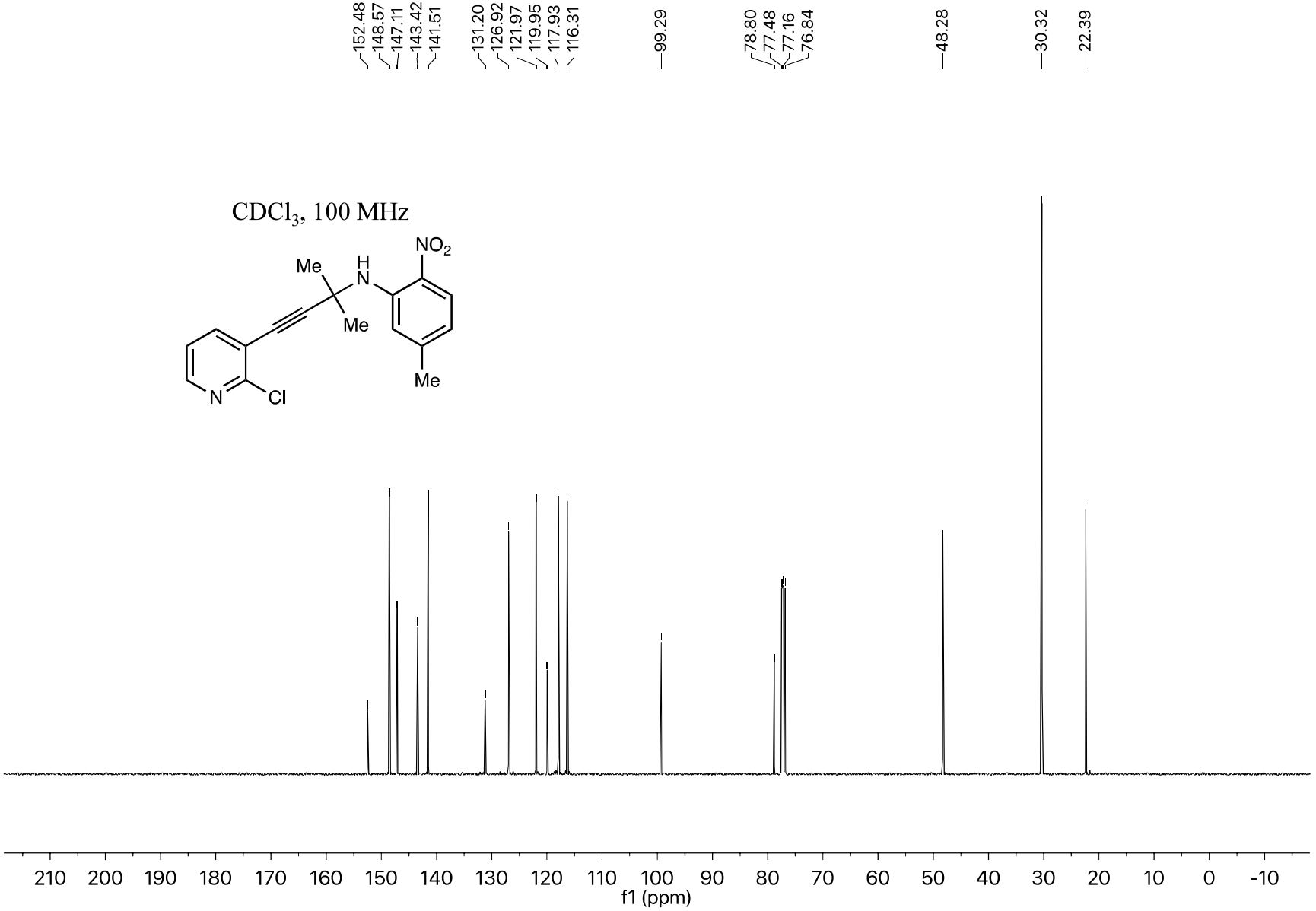
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77.16
76.84
48.28
30.32
22.39
CDCl3, 100 MHz
NO2
Me
H
N
Me
Me
N
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

CDCl3, 400 MHz
NO2
Me
H
N
Me
Me
N
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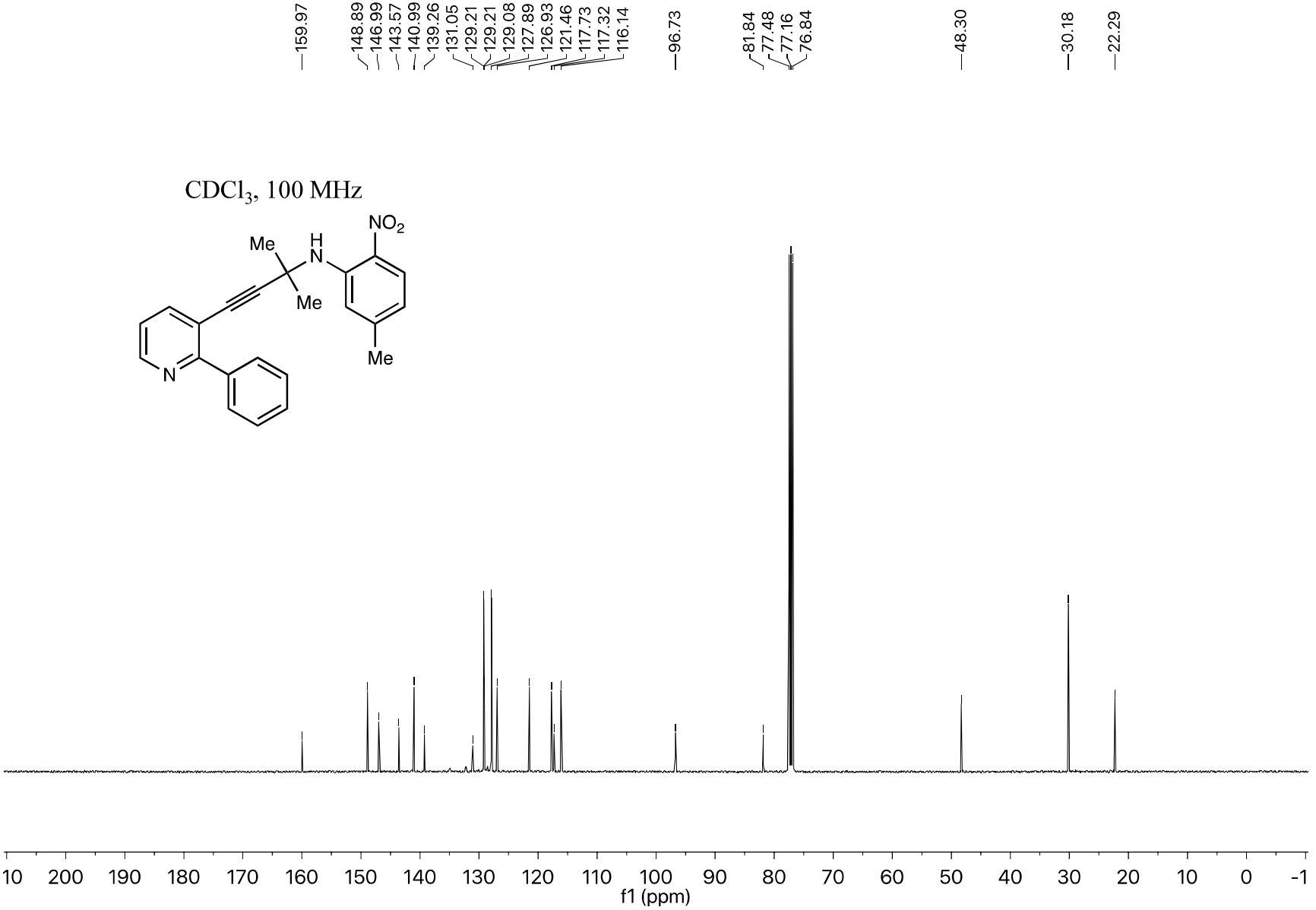
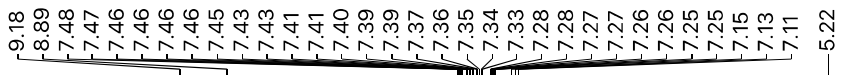
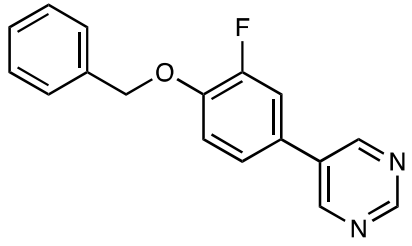
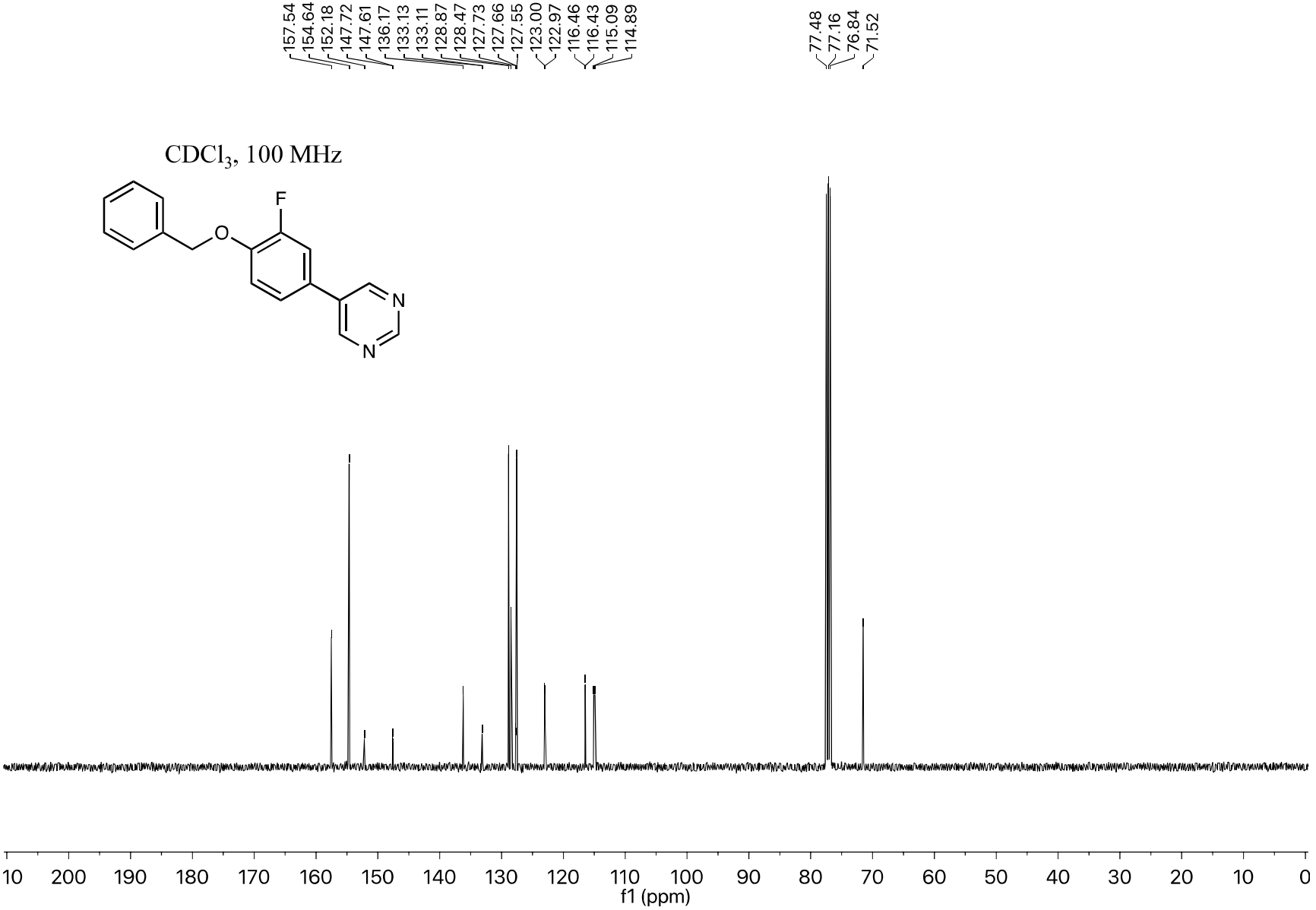
1.12
1.01
1.03
6.27
3.12
f1 (ppm)

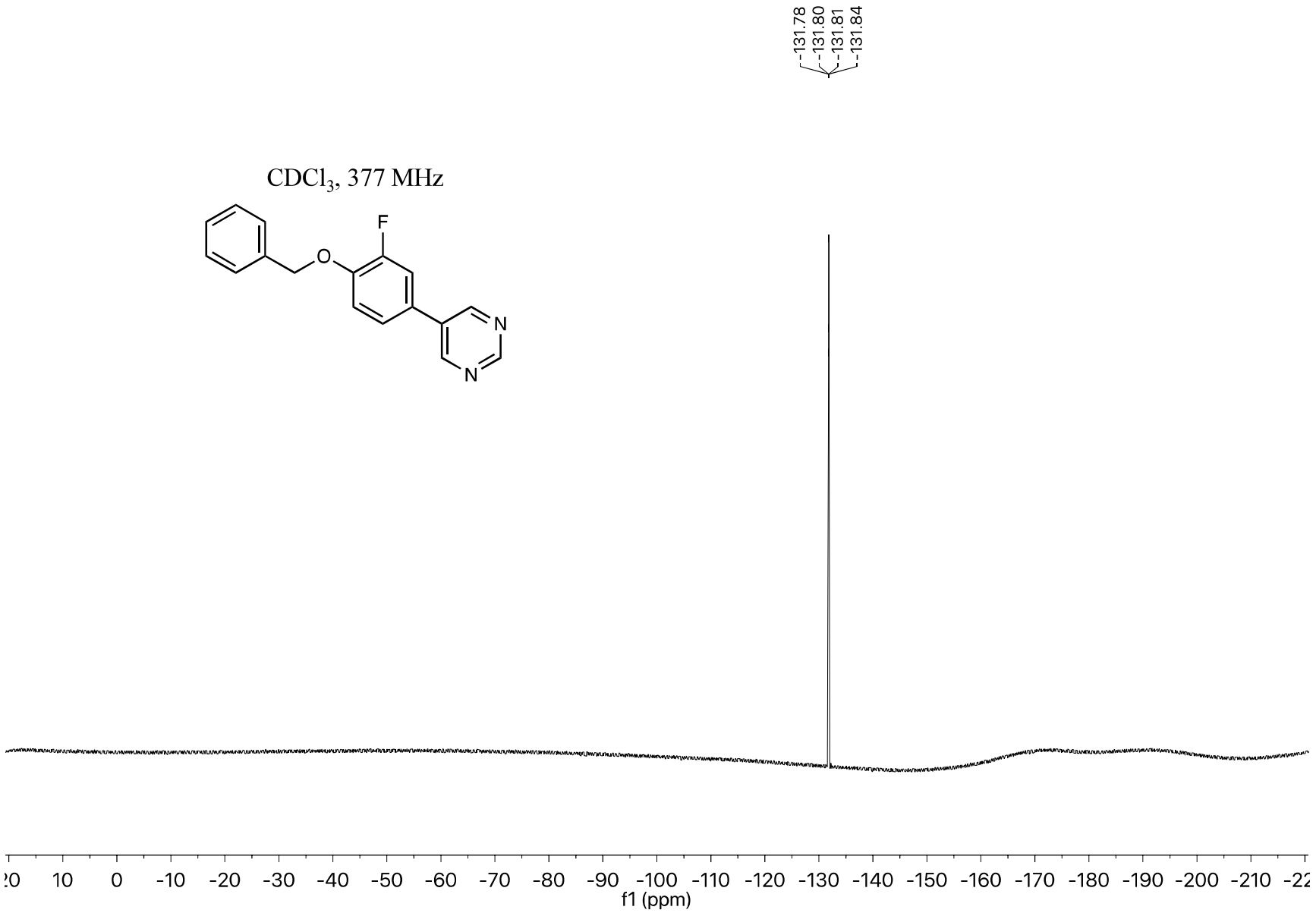

159.97
148.89
146.99
143.57
140.99
139.26
131.05
129.21
129.21
129.08
127.89
126.93
121.46
117.73
117.32
116.14
96.73
81.84
77.48
77.16
76.84
48.30
30.18
22.29
CDCl3, 100 MHz
NO2
H
N
Me
Me
Me
N
f1 (ppm)

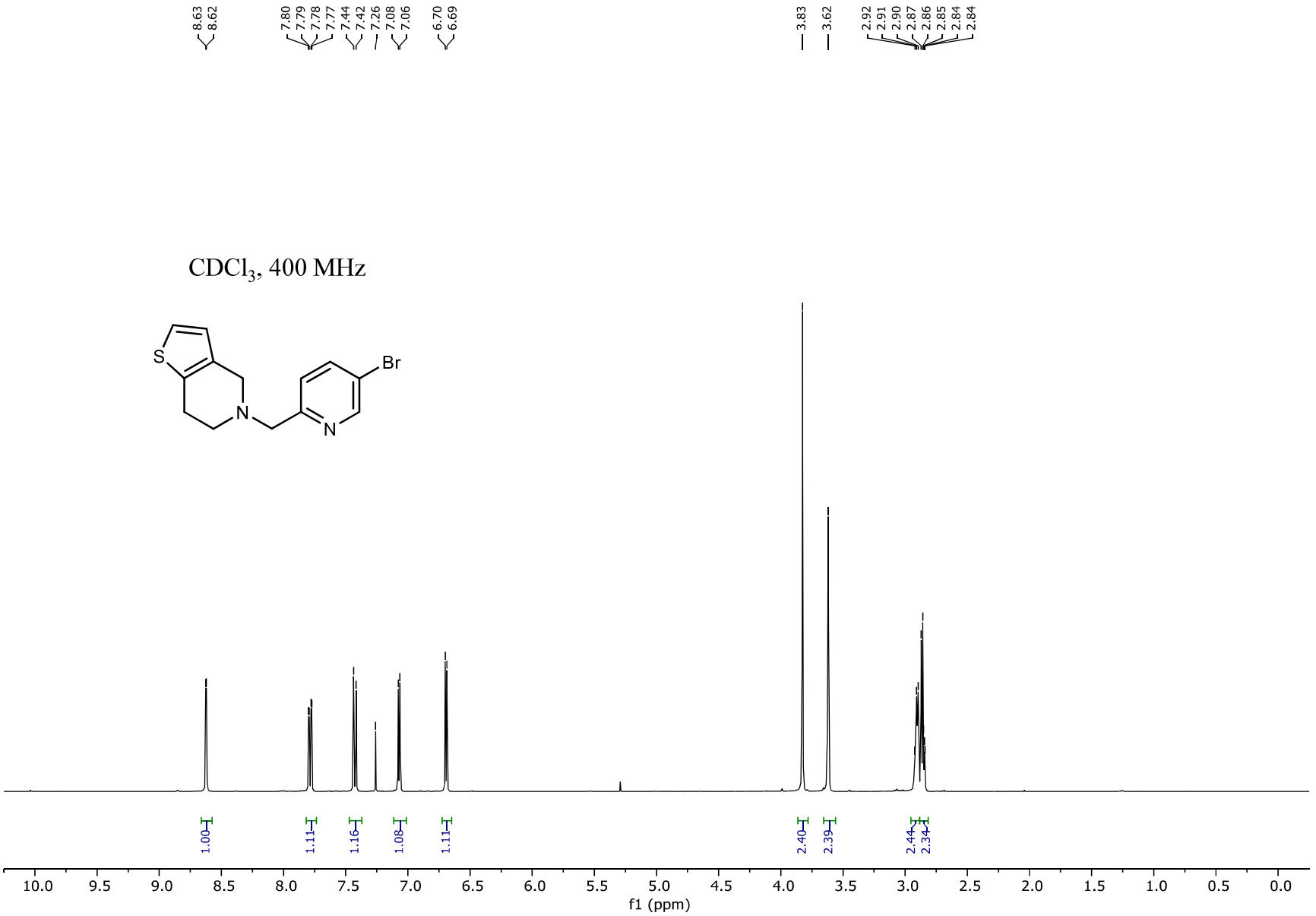


$CDCl_3$, 400 MHz



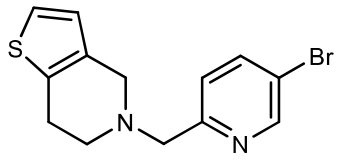

157.54
154.64
152.18
147.72
147.61
136.17
133.13
133.11
128.87
128.47
127.73
127.66
127.55
123.00
122.97
116.46
116.43
115.09
114.89
77.48
77.16
76.84
71.52
CDCl3, 100 MHz
F
O
N
N
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-131.78
-131.80
-131.81
-131.84
CDCl3, 377 MHz
F
O
N
N
f1 (ppm)

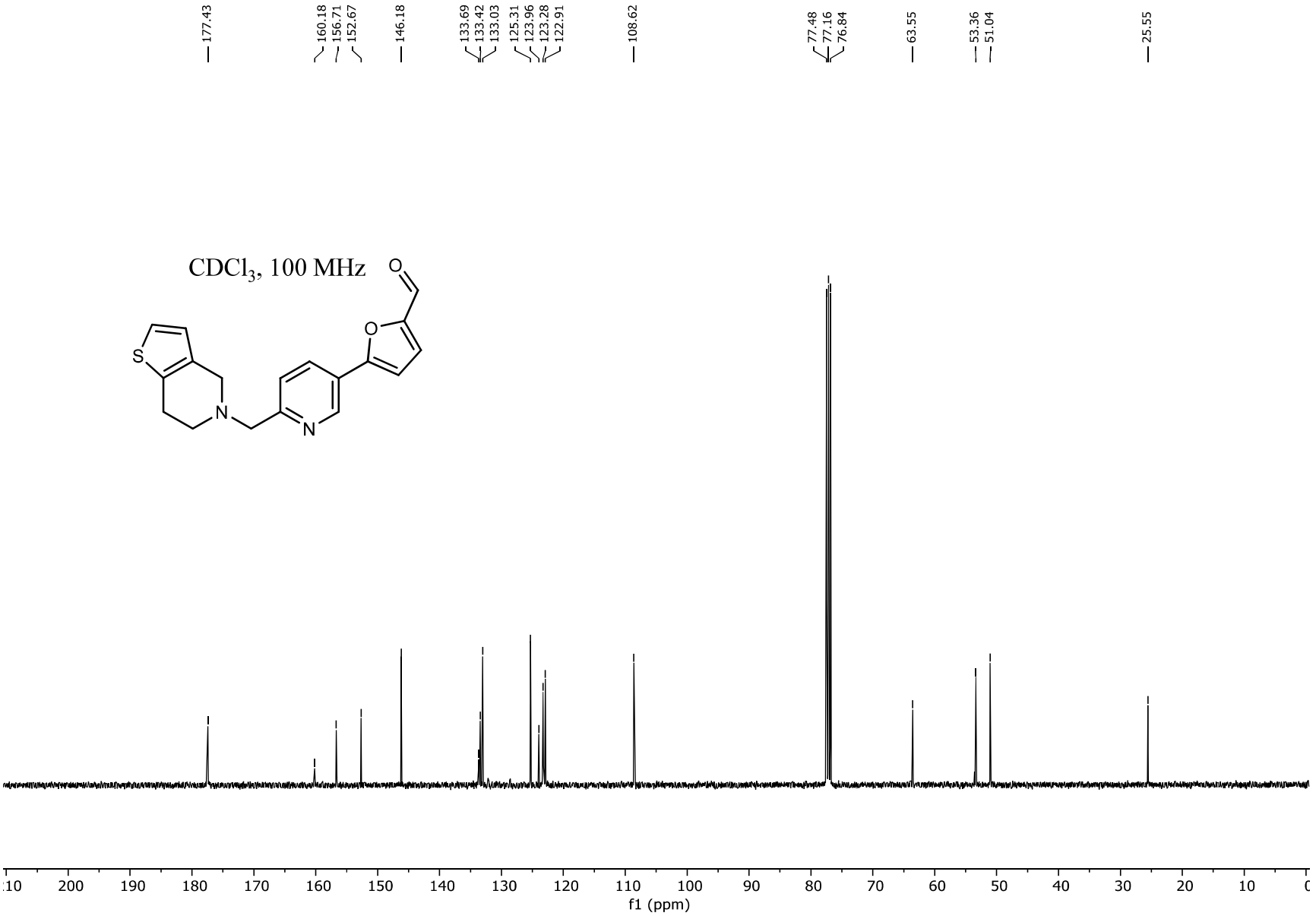

8.63
8.62
7.80
7.79
7.78
7.77
7.44
7.42
7.26
7.08
7.06
6.70
6.69
3.83
3.62
2.92
2.91
2.90
2.87
2.86
2.85
2.84
2.84
CDCl3, 400 MHz
S
N
N
Br
1.00
1.11
1.16
1.08
1.11
2.40
2.39
2.44
2.34
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

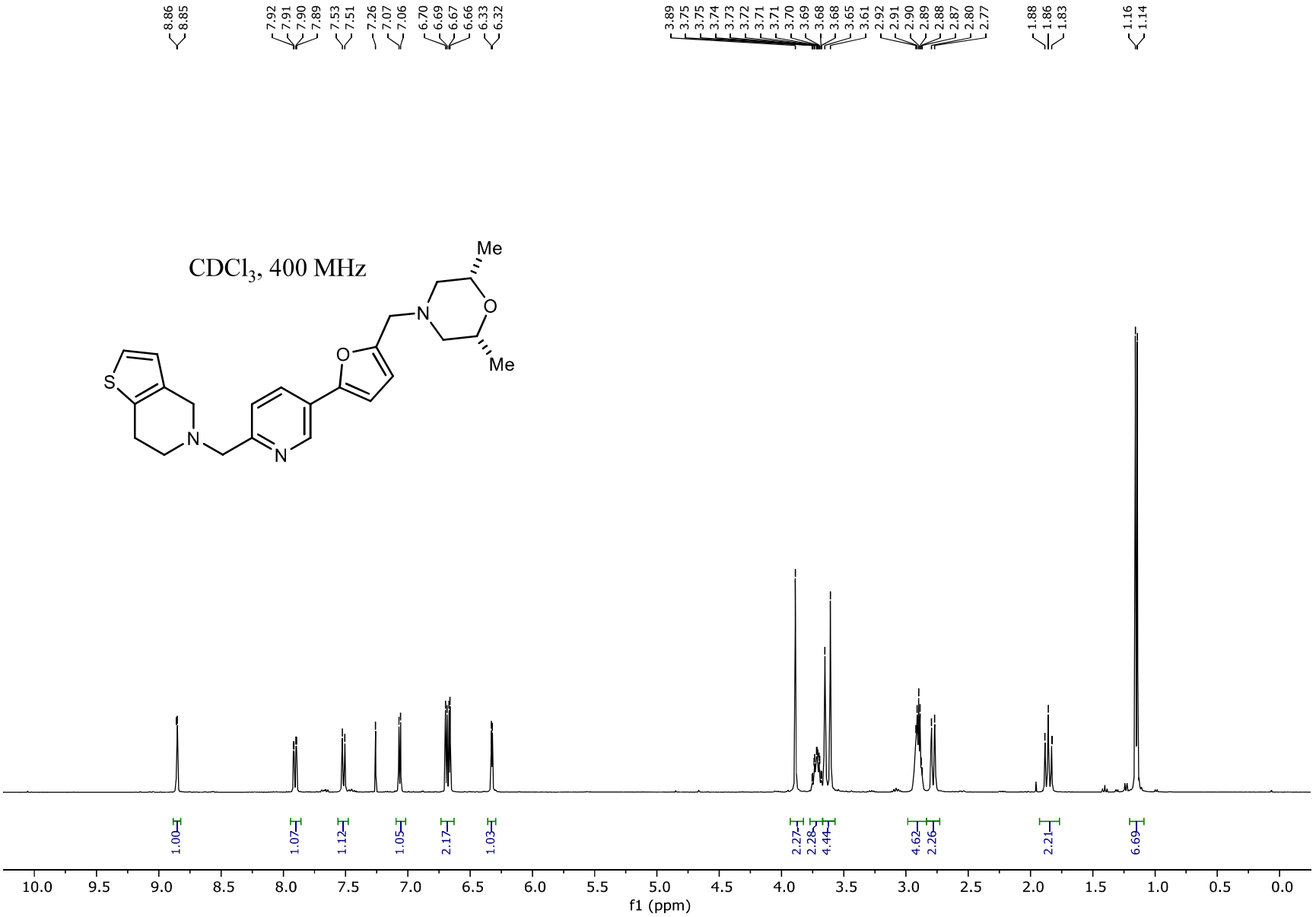
157.67
150.33
139.28
133.71
133.42
125.30
124.54
122.88
119.22
77.48
77.16
76.84
63.16
53.31
50.98
25.57

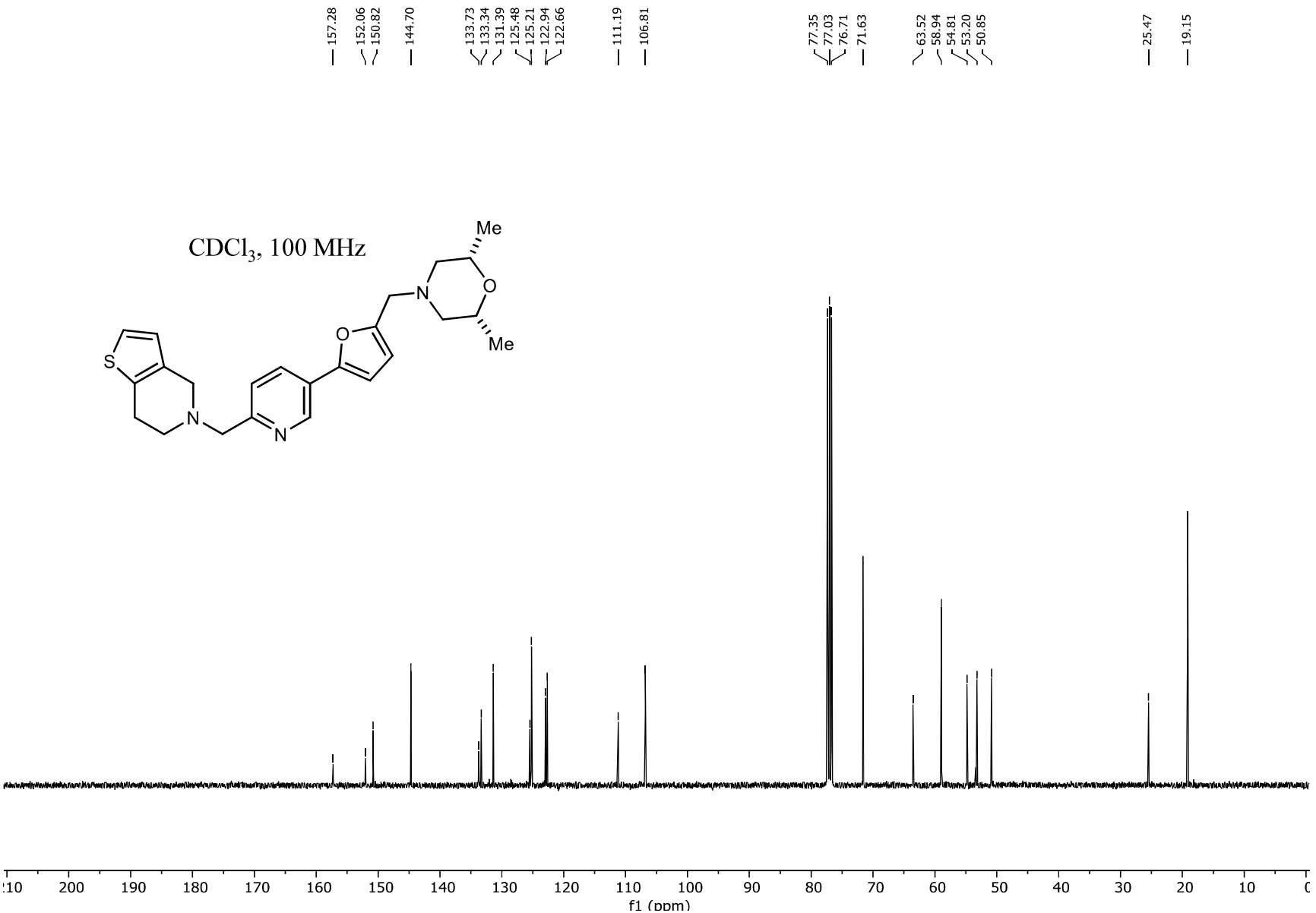
$CDCl_3$, 100 MHz

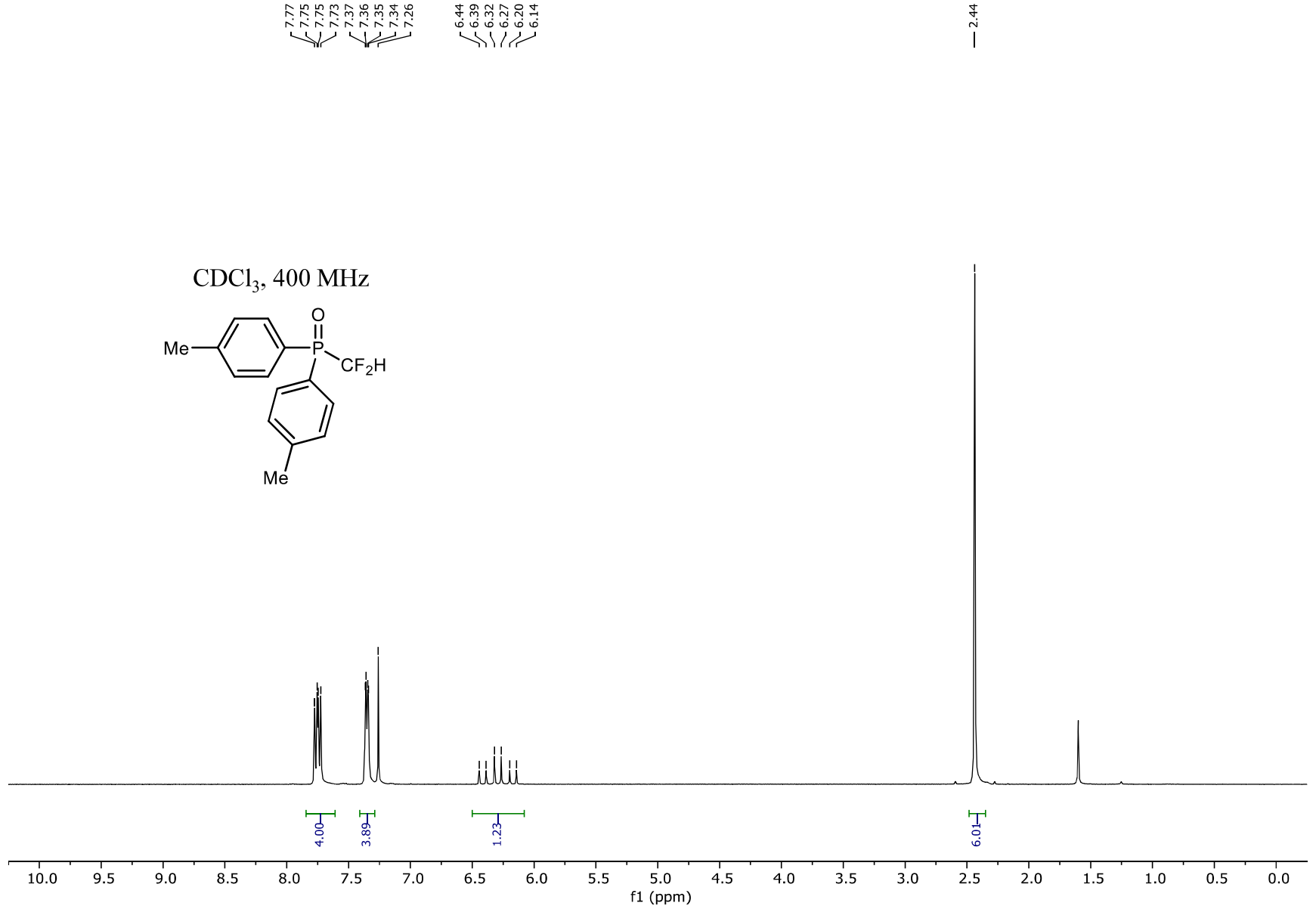


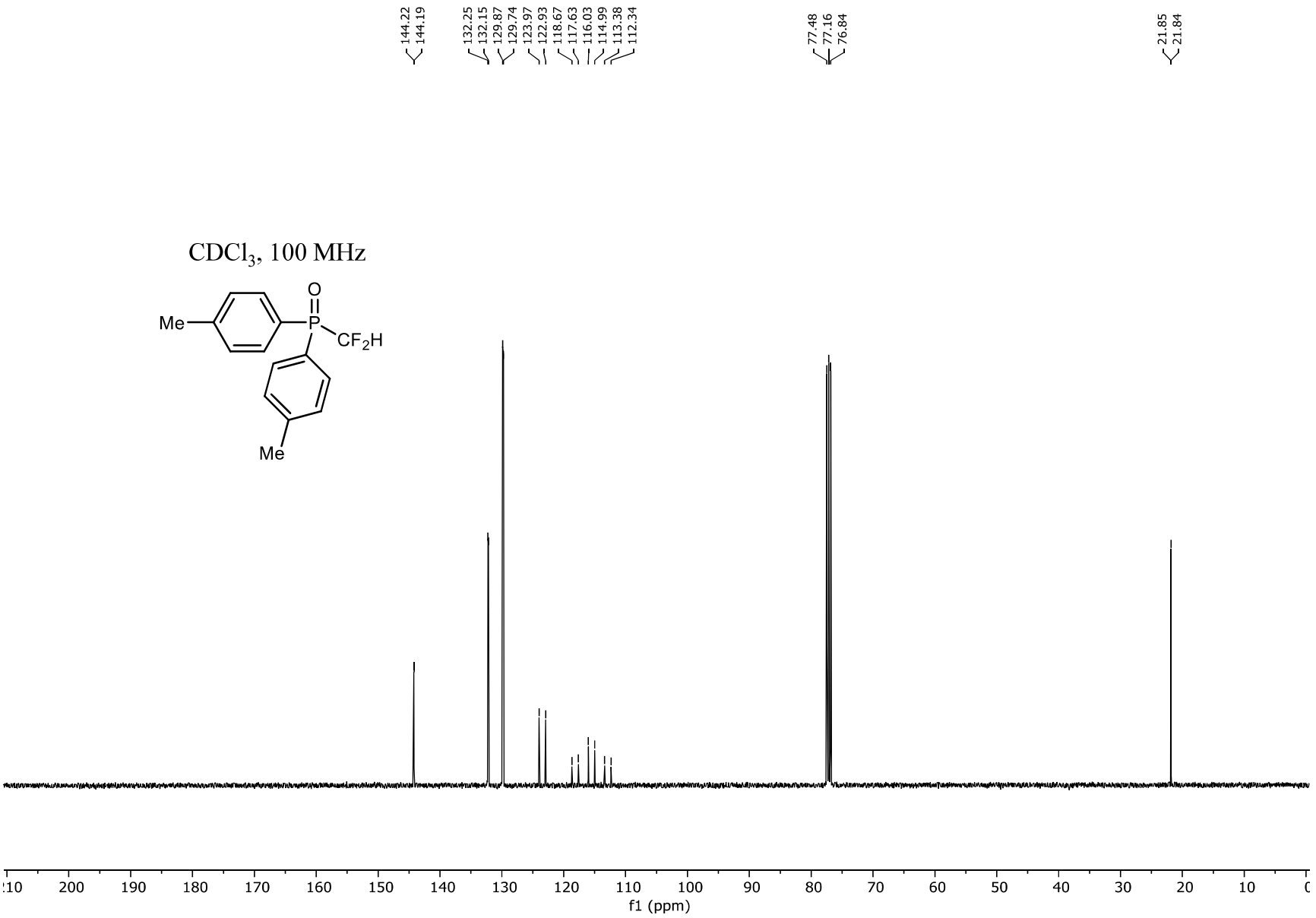
CDCl3, 400 MHz
O
O
N
N
S
9.68
8.99
8.99
8.11
8.10
8.09
8.08
7.65
7.63
7.34
7.34
7.26
7.09
7.07
6.93
6.92
6.71
6.69
3.94
3.68
2.93
2.92
2.91
2.90
1.00
1.09
1.13
1.33
1.20
1.17
1.16
1.18
2.41
2.37
4.80
f1 (ppm)

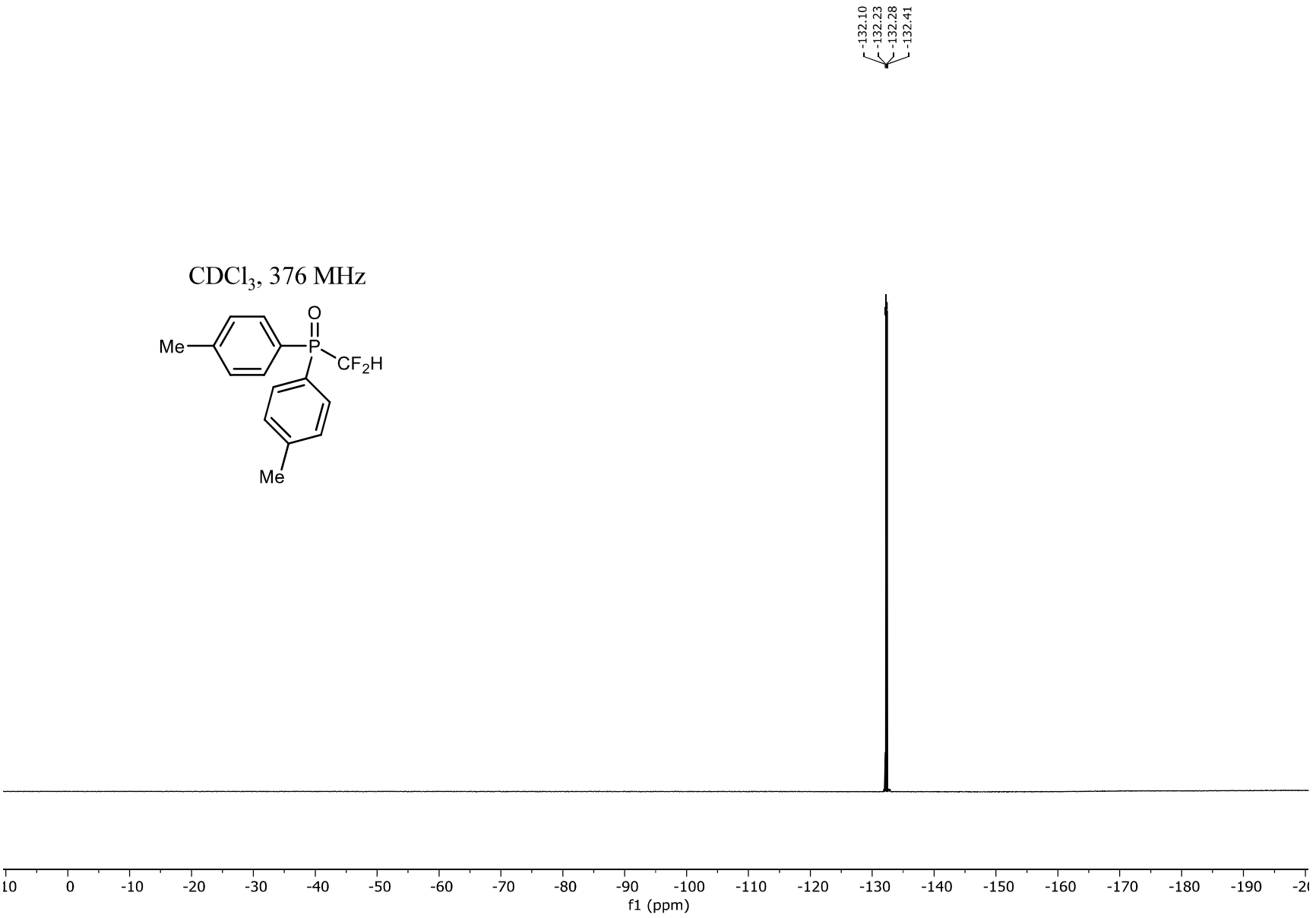

177.43
160.18
156.71
152.67
146.18
133.69
133.42
133.03
125.31
123.96
123.28
122.91
108.62
77.48
77.16
76.84
63.55
53.36
51.04
25.55
CDCl3, 100 MHz
O
O
S
N
N
f1 (ppm)


8.86
8.85
7.92
7.91
7.90
7.89
7.53
7.51
7.26
7.07
7.06
6.70
6.69
6.67
6.66
6.33
6.32
3.89
3.75
3.75
3.74
3.73
3.72
3.71
3.71
3.70
3.69
3.68
3.68
3.65
3.61
2.92
2.91
2.90
2.89
2.88
2.87
2.80
2.77
1.88
1.86
1.83
1.16
1.14
CDCl3, 400 MHz
Me
Me
S
N
N
O
O
N
1.00
1.07
1.12
1.05
2.17
1.03
2.27
2.28
4.44
4.62
2.26
2.21
6.69
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)

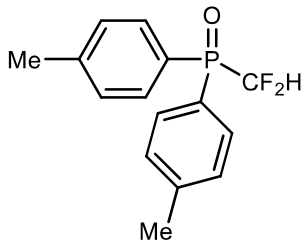

157.28
152.06
150.82
144.70
133.73
133.34
131.39
125.48
125.21
122.94
122.66
111.19
106.81
77.35
77.03
76.71
71.63
63.52
58.94
54.81
53.20
50.85
25.47
19.15
CDCl3, 100 MHz
Me
Me
O
N
O
S
N
N
f1 (ppm)

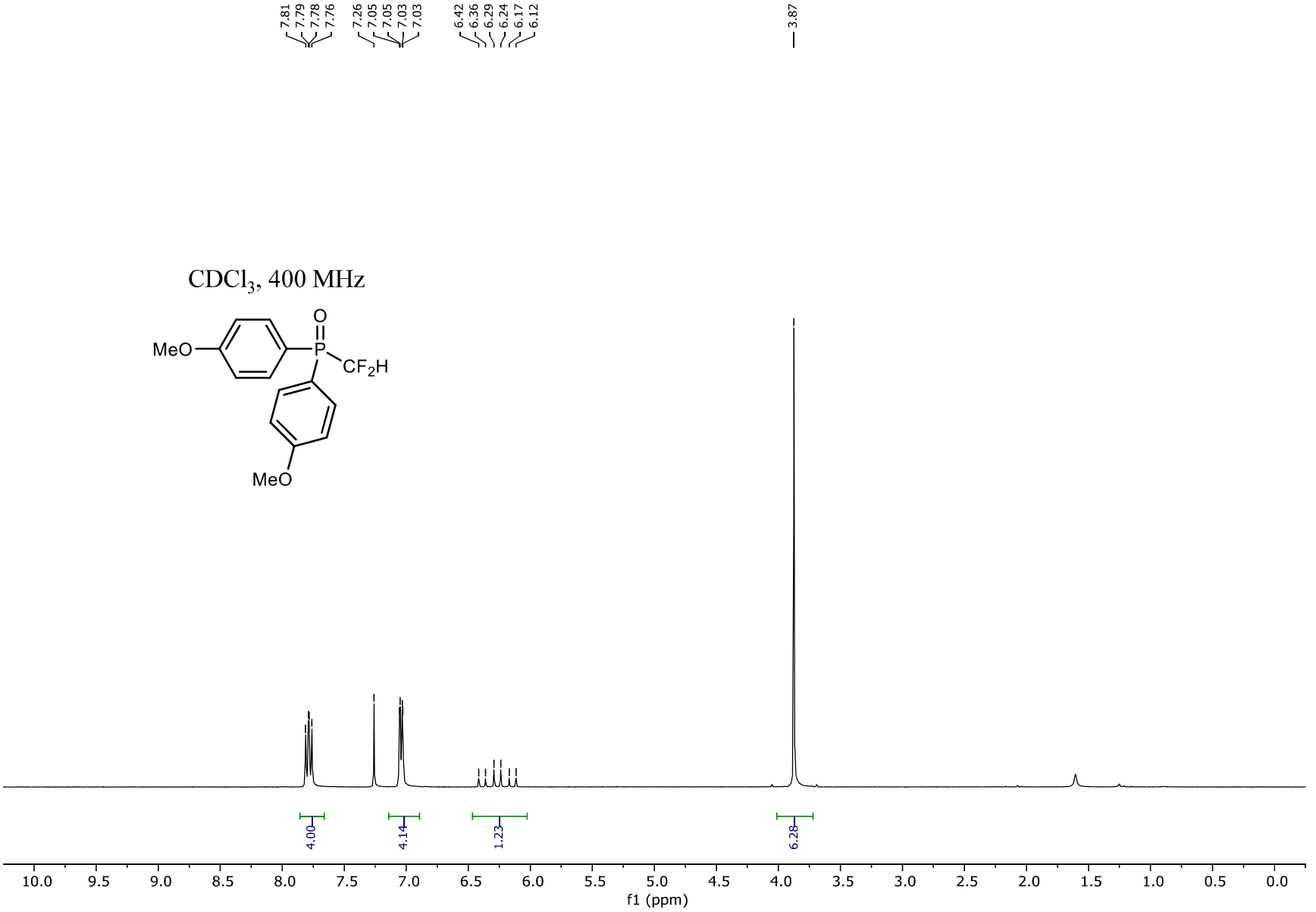

7.77
7.75
7.75
7.73
7.37
7.36
7.35
7.34
7.26
6.44
6.39
6.32
6.27
6.20
6.14
2.44
CDCl3, 400 MHz
O
Me
P
CF2H
Me
4.00
3.89
1.23
6.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

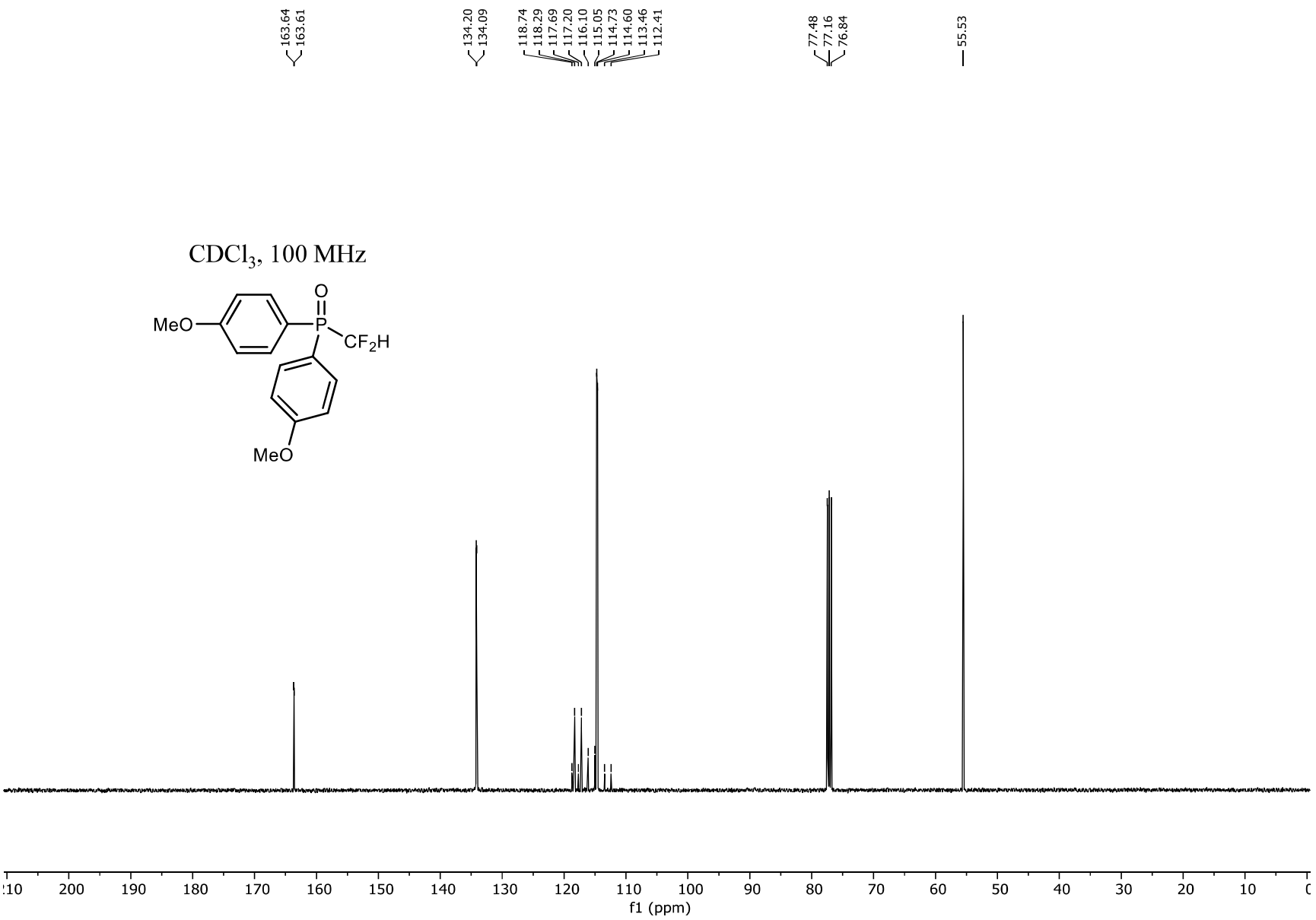

144.22
144.19
132.25
132.15
129.87
129.74
123.97
122.93
118.67
117.63
116.03
114.99
113.38
112.34
77.48
77.16
76.84
21.85
21.84
CDCl3, 100 MHz
O
Me
P
CF2H
Me
f1 (ppm)


-132.10
-132.23
-132.28
-132.41
CDCl3, 376 MHz
O
Me
P
CF2H
Me
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

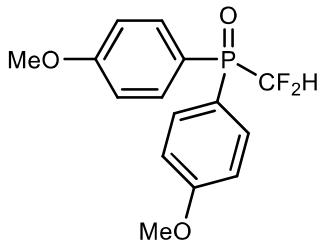
$CDCl_3$, 162 MHz

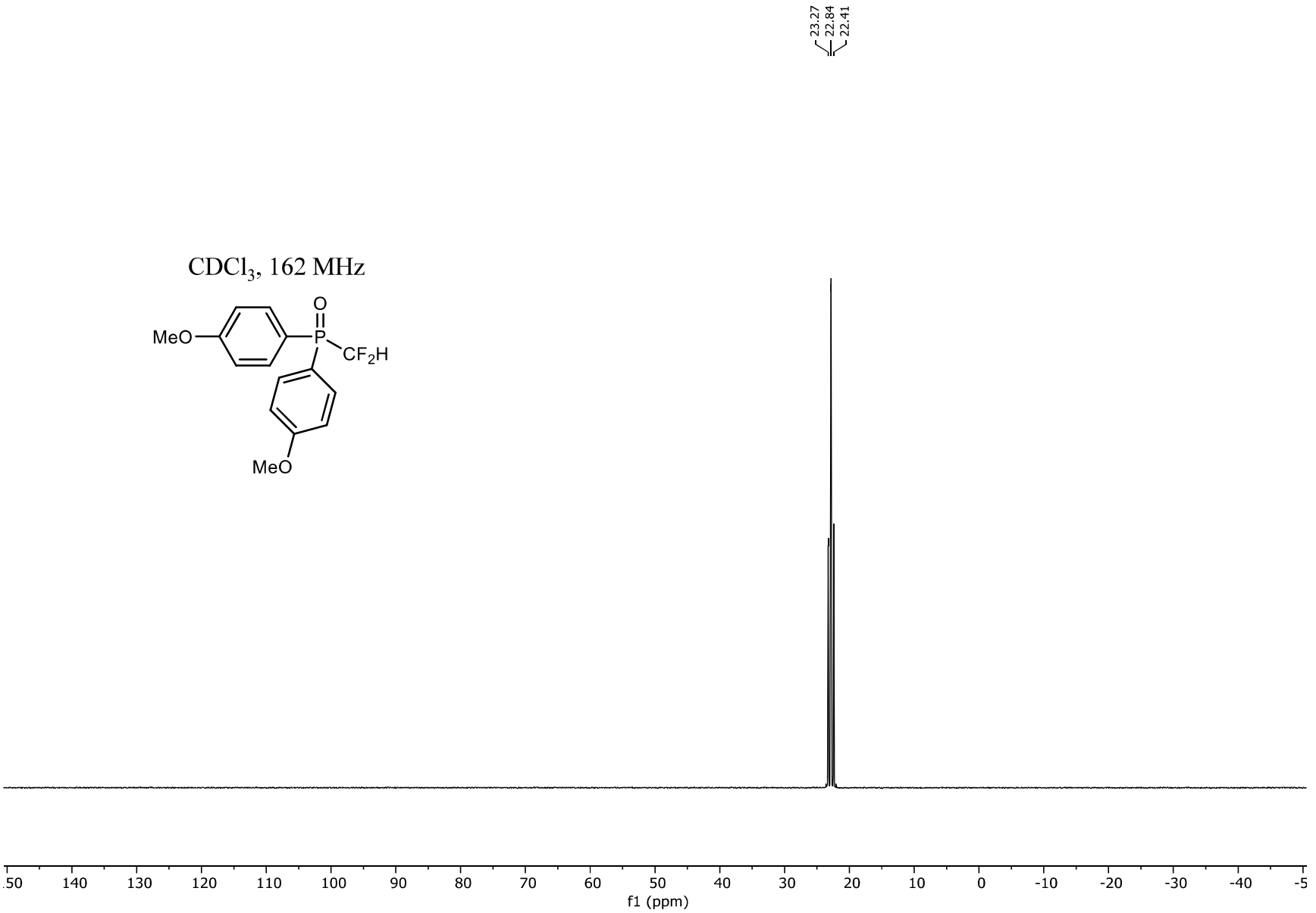


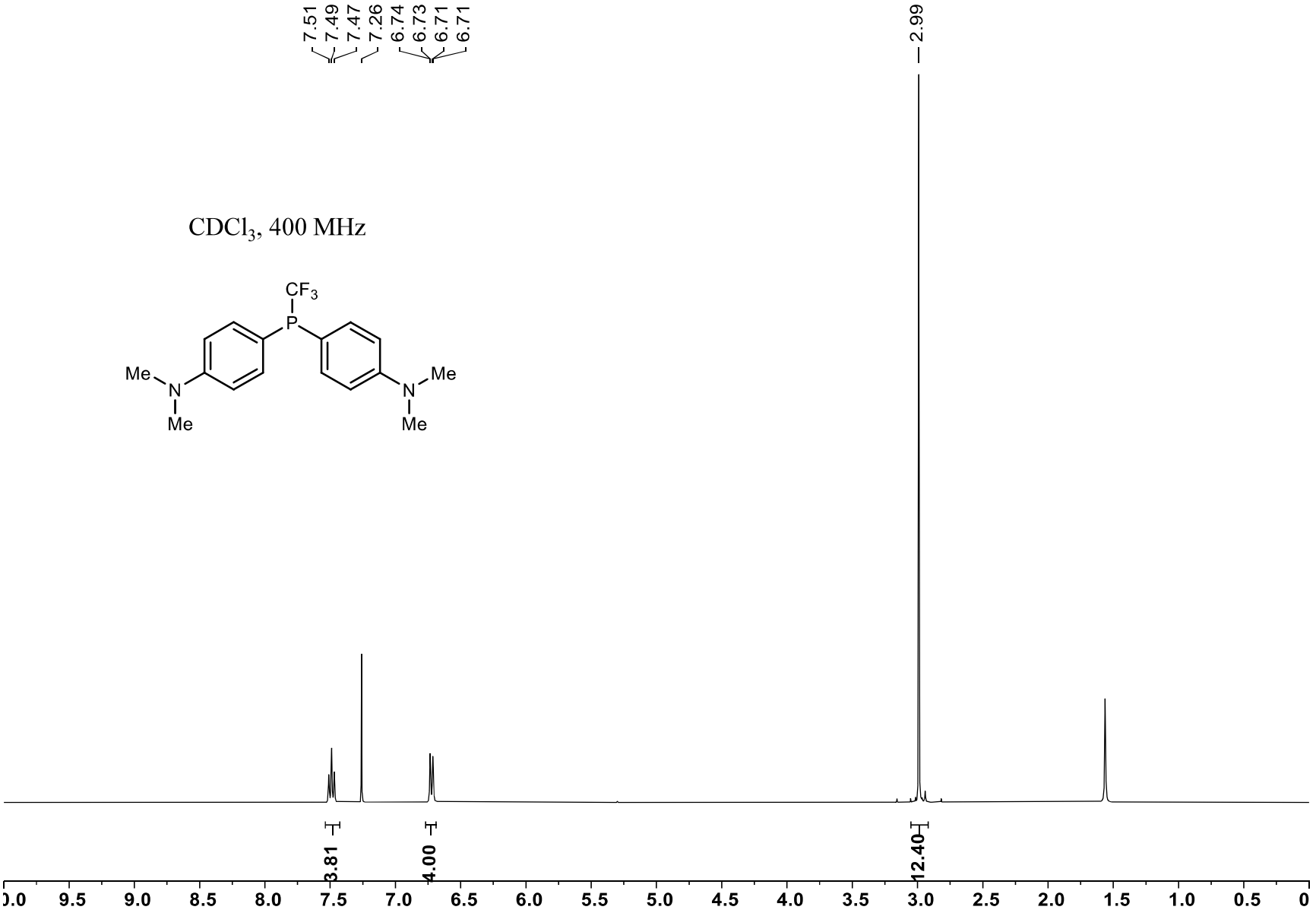

7.81
7.79
7.78
7.76
7.26
7.05
7.05
7.03
7.03
6.42
6.36
6.29
6.24
6.17
6.12
3.87
CDCl3, 400 MHz
O
MeO
P
CF2H
MeO
4.00
4.14
1.23
6.28
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

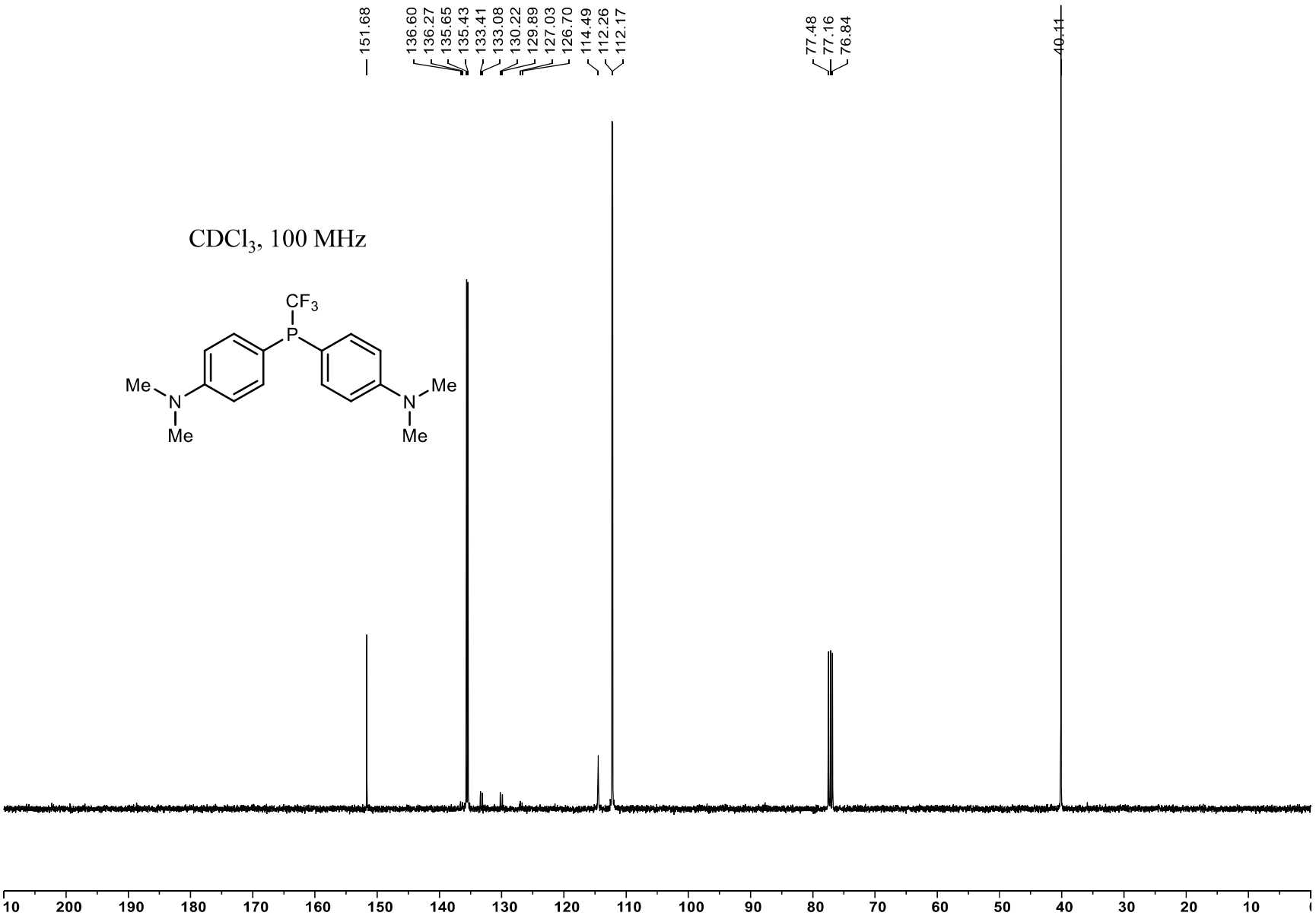

163.64
163.61
134.20
134.09
118.74
118.29
117.69
117.20
116.10
115.05
114.73
114.60
113.46
112.41
77.48
77.16
76.84
55.53
CDCl3, 100 MHz
MeO
O
P
CF2H
MeO
f1 (ppm)

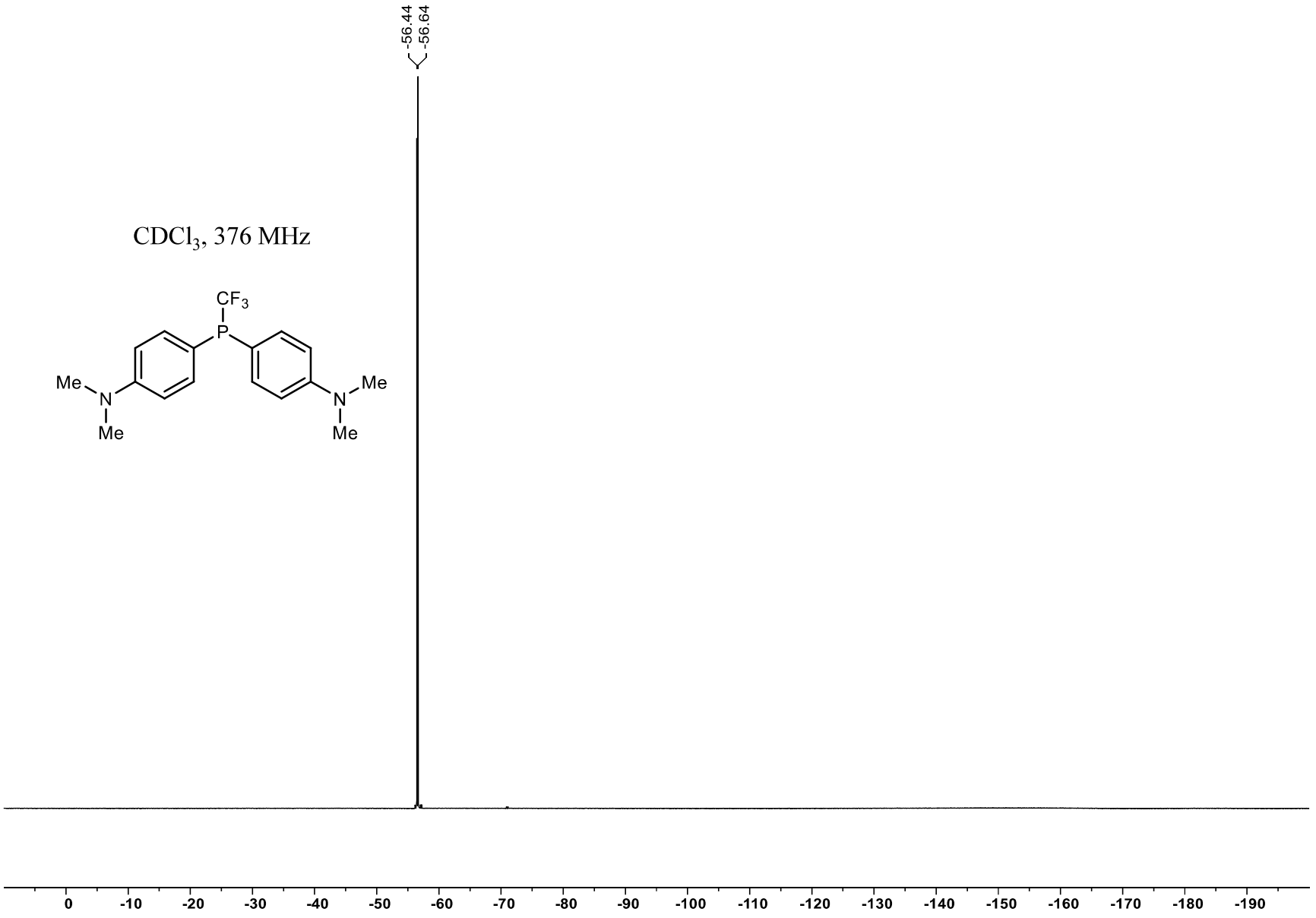
$CDCl_3$, 376 MHz



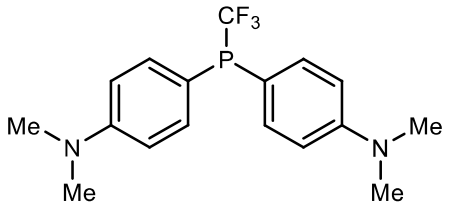

23.27
22.84
22.41
CDCl3, 162 MHz
O
MeO
P
CF2H
MeO
f1 (ppm)

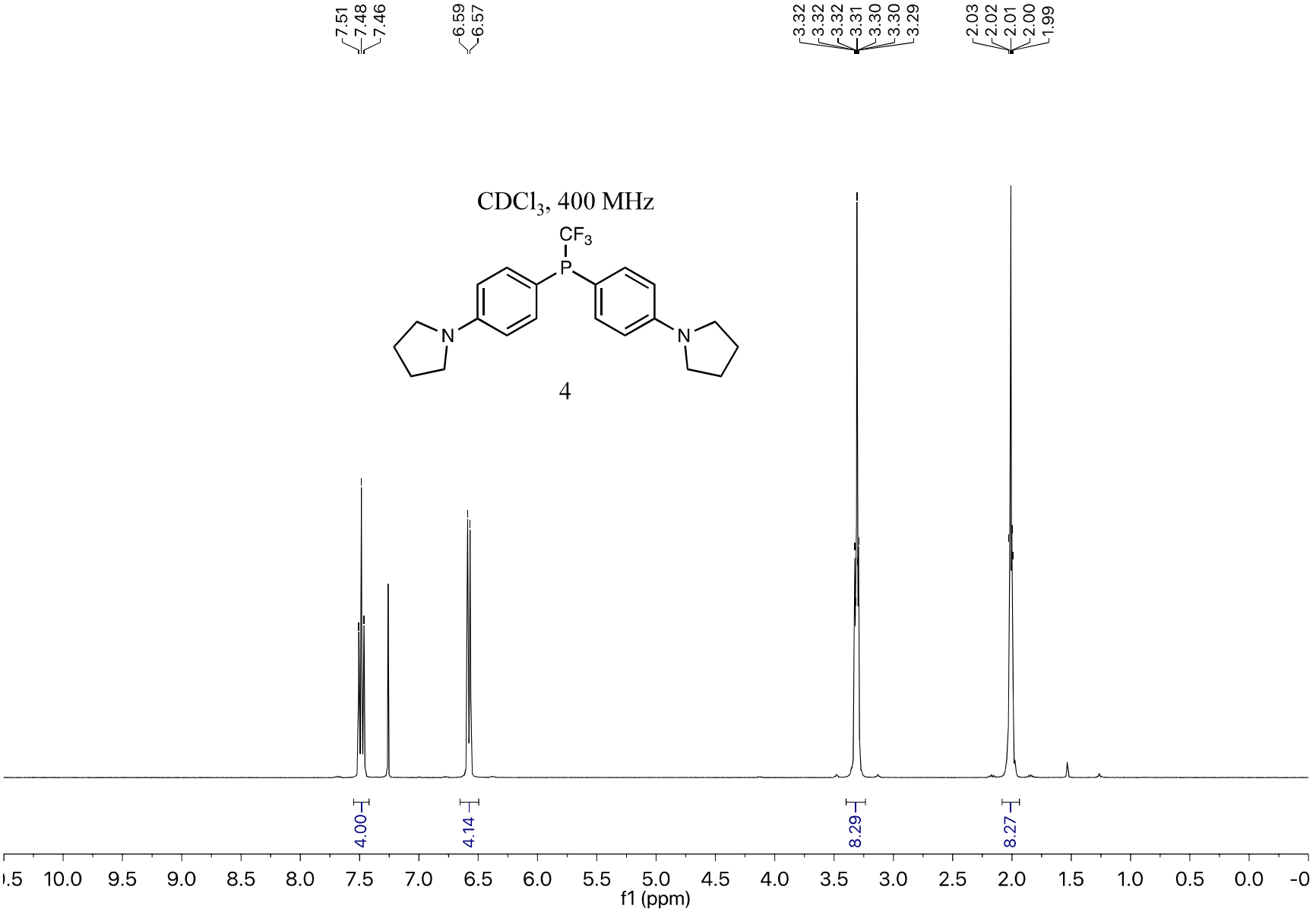

7.51
7.49
7.47
7.26
6.74
6.73
6.71
6.71
2.99
CDCl3, 400 MHz
CF3
P
Me
N
Me
Me
N
Me
3.81
4.00
12.40
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


151.68
136.60
136.27
135.65
135.43
133.41
133.08
130.22
129.89
127.03
126.70
114.49
112.26
112.17
77.48
77.16
76.84
40.11
CDCl3, 100 MHz
CF3
P
Me
N
Me
Me
N
Me
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

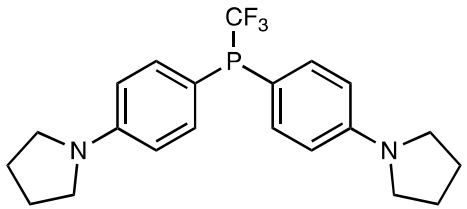

-56.44
-56.64
CDCl3, 376 MHz
CF3
P
Me
N
Me
Me
N
Me
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

$CDCl_3$, 162 MHz

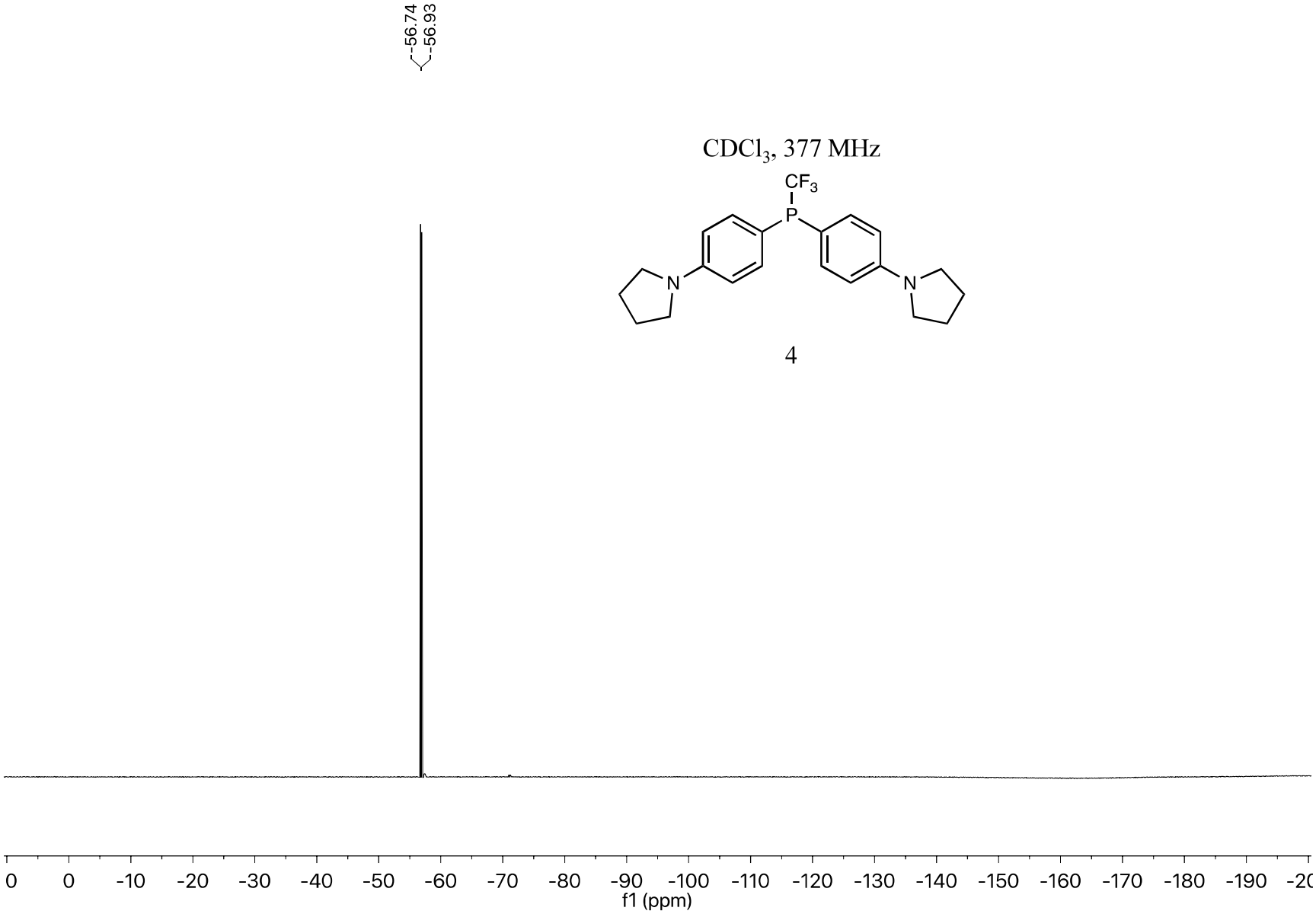


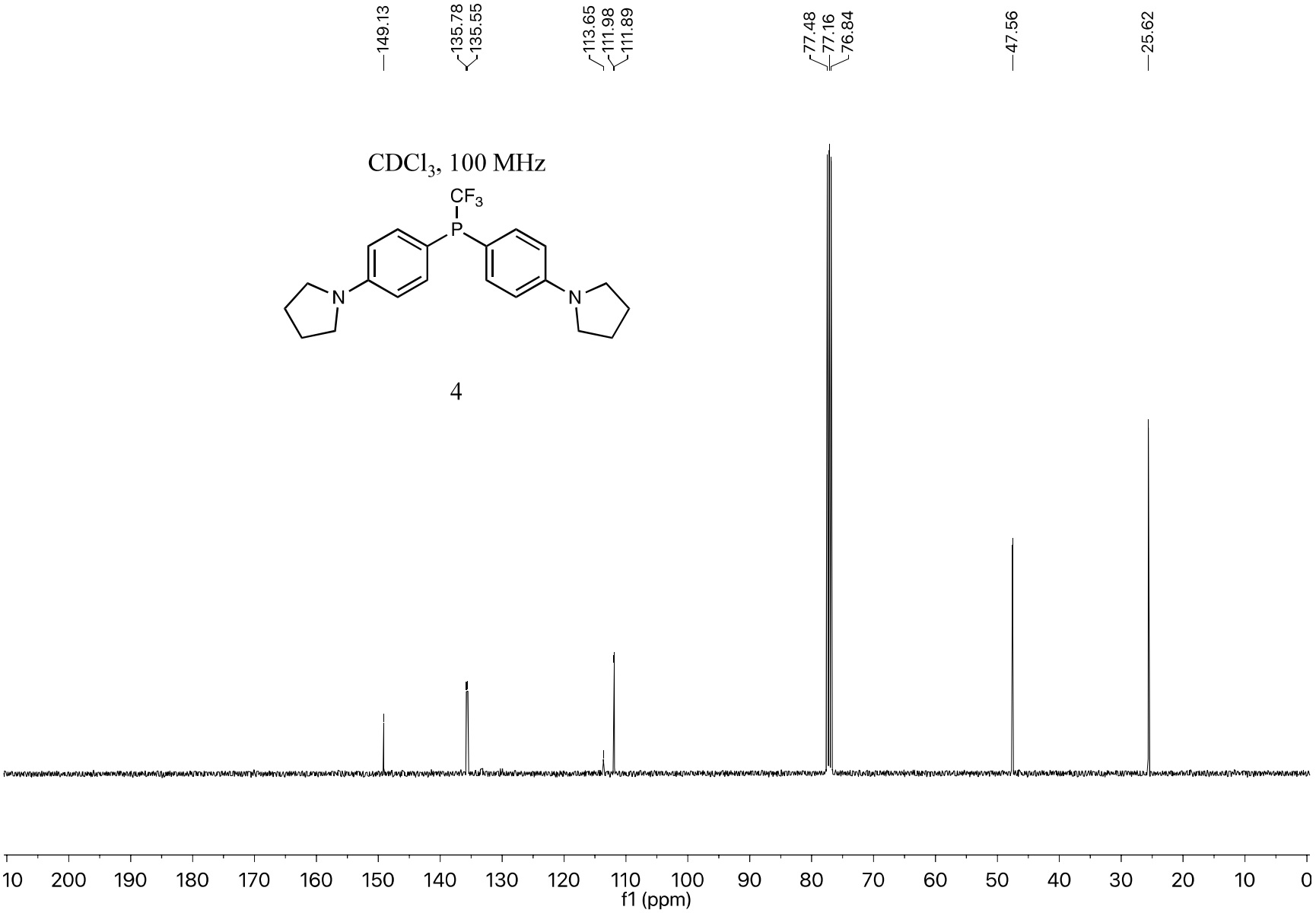

7.51
7.48
7.46
6.59
6.57
3.32
3.32
3.32
3.31
3.30
3.30
3.29
2.03
2.02
2.01
2.00
1.99
CDCl3, 400 MHz
CF3
P
N
N
4
4.00
4.14
8.29
8.27
f1 (ppm)

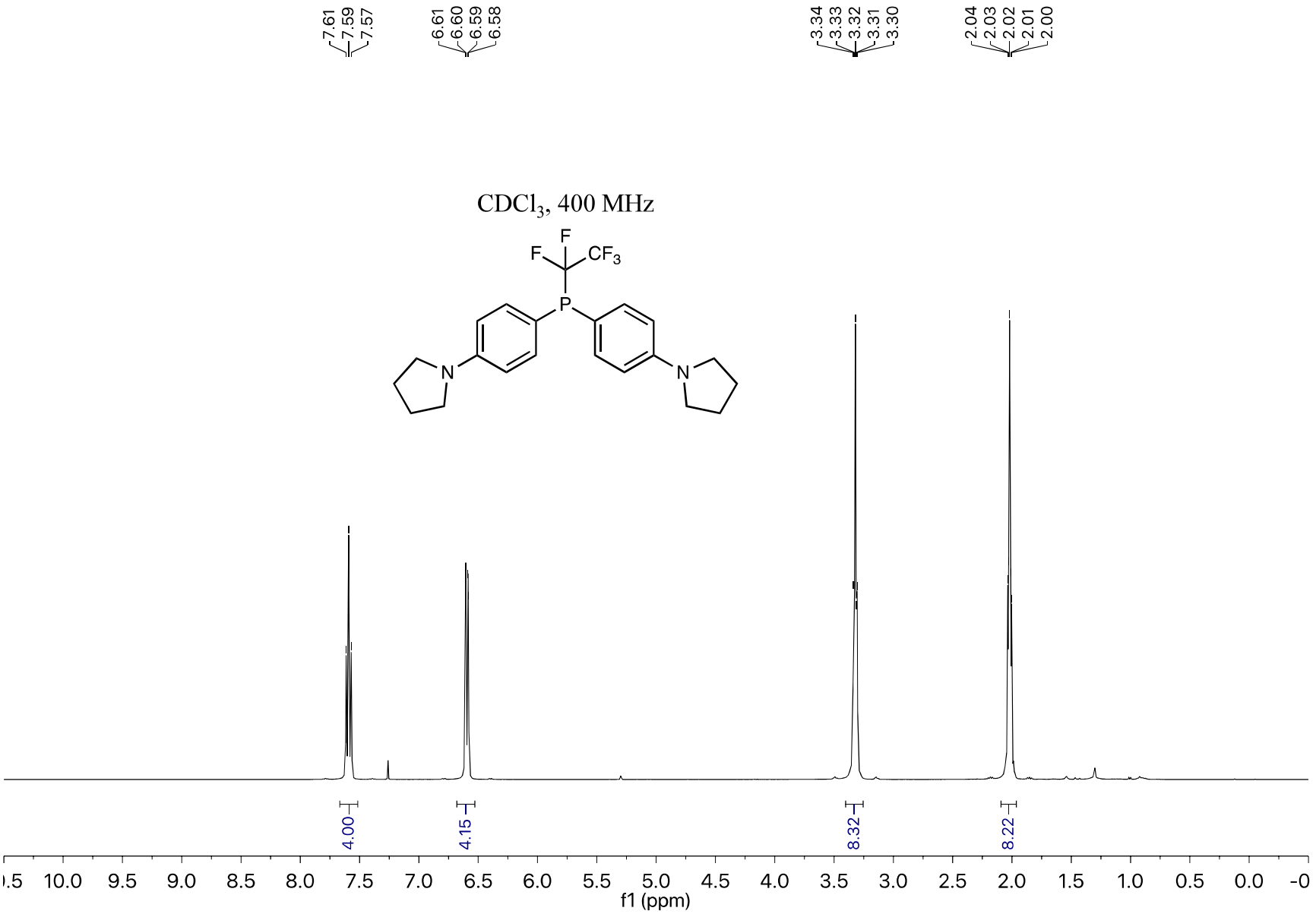
$CDCl_3$, 162 MHz

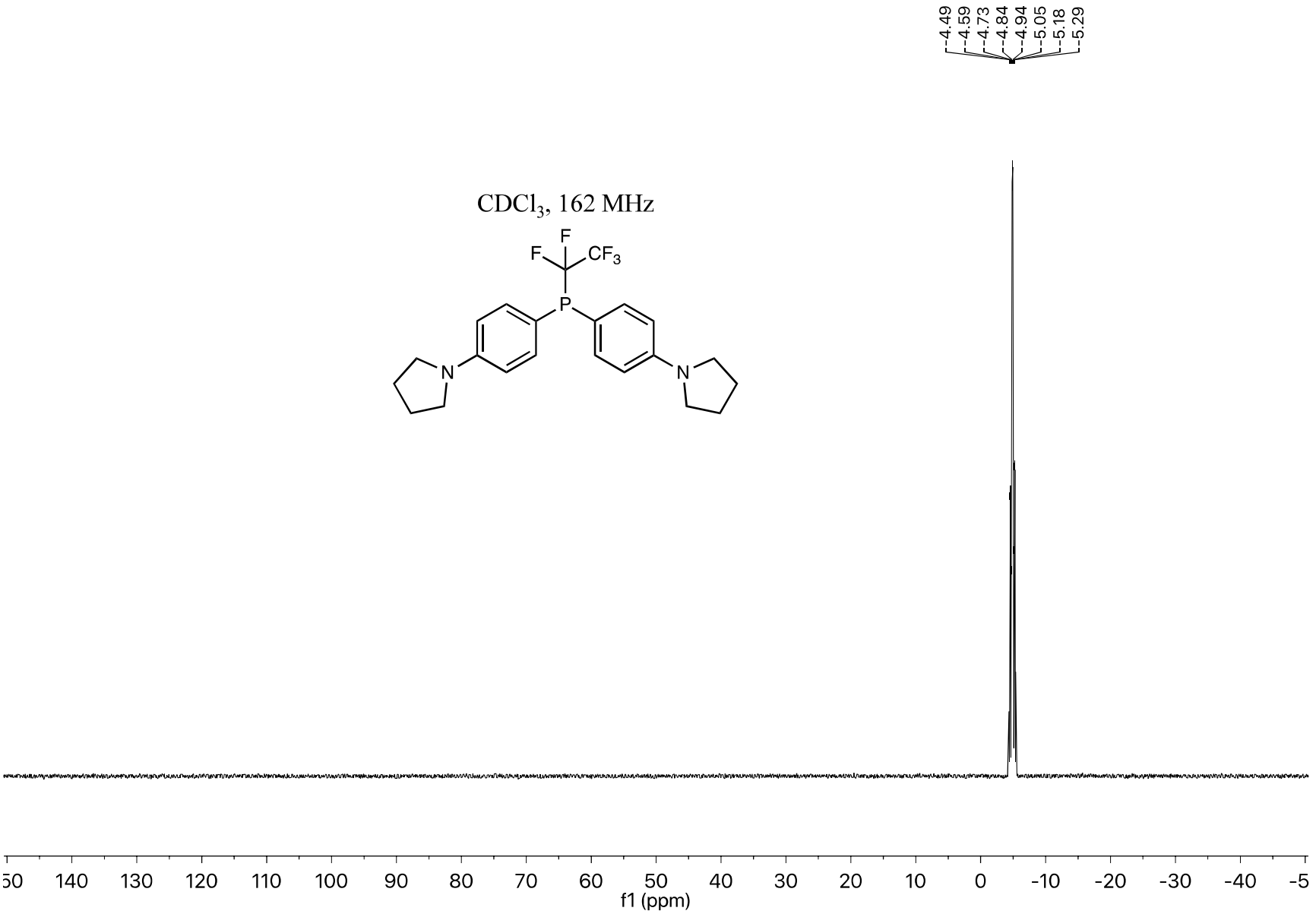


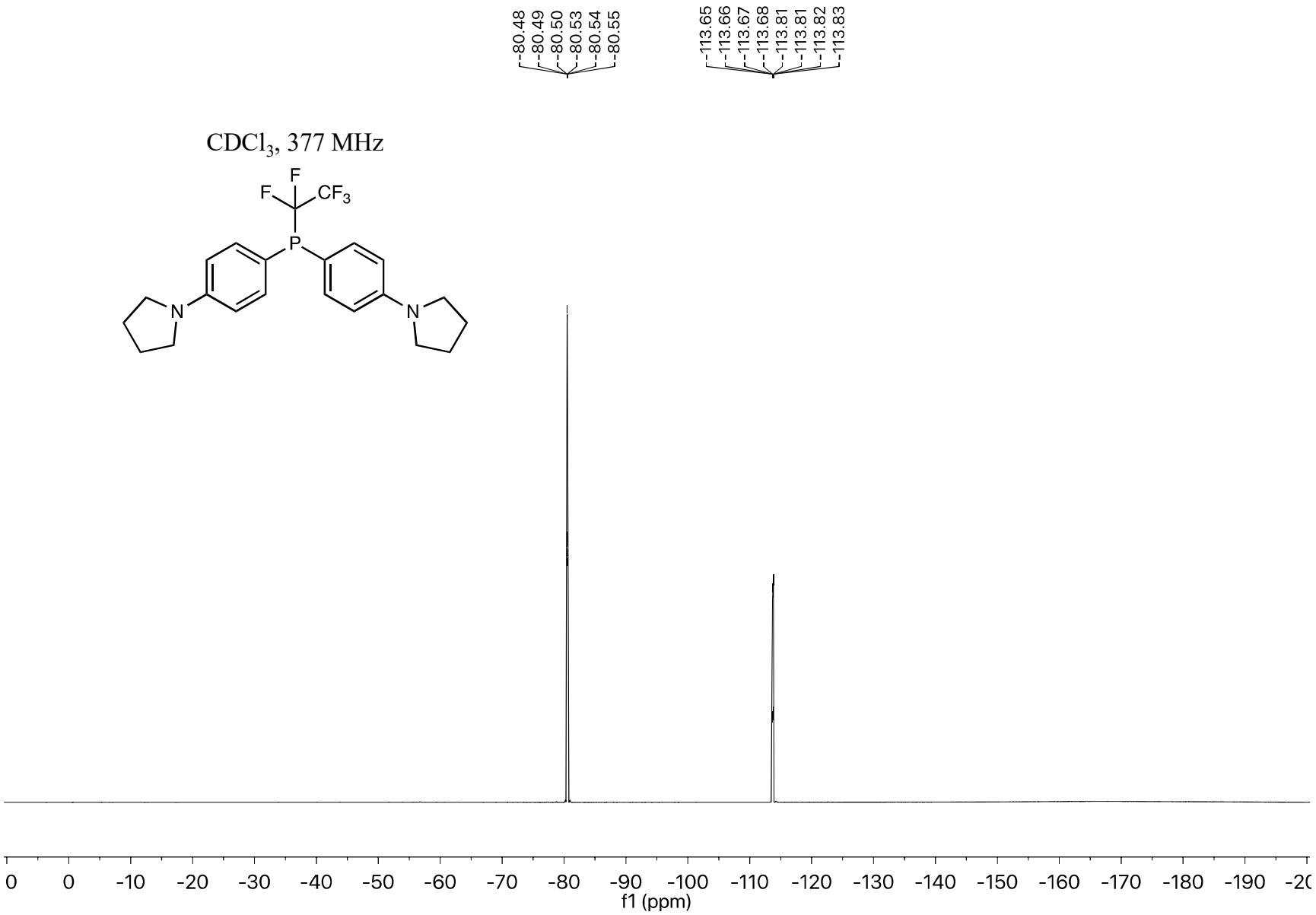
4

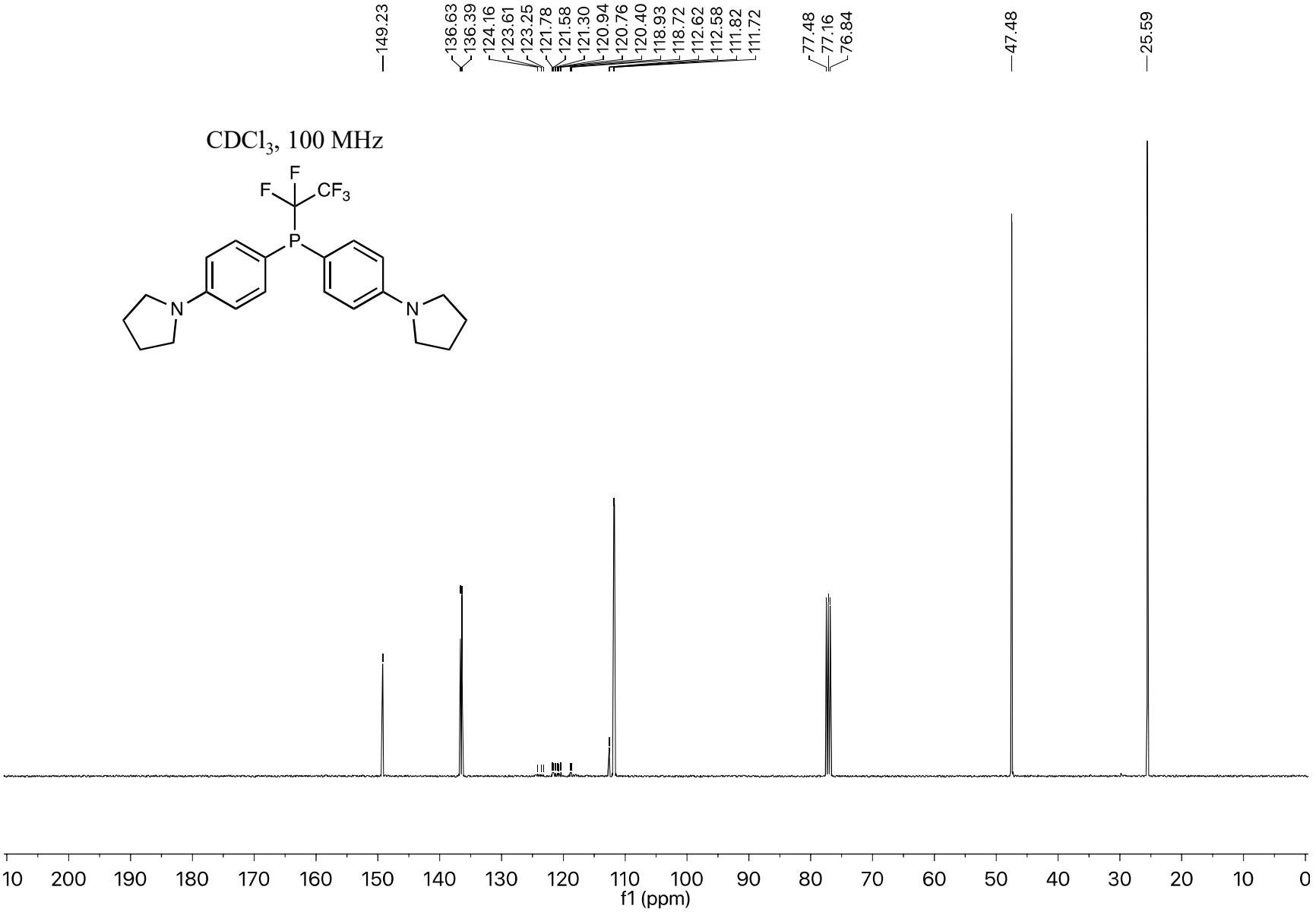

-56.74
-56.93
CDCl3, 377 MHz
CF3
P
N
N
4
0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

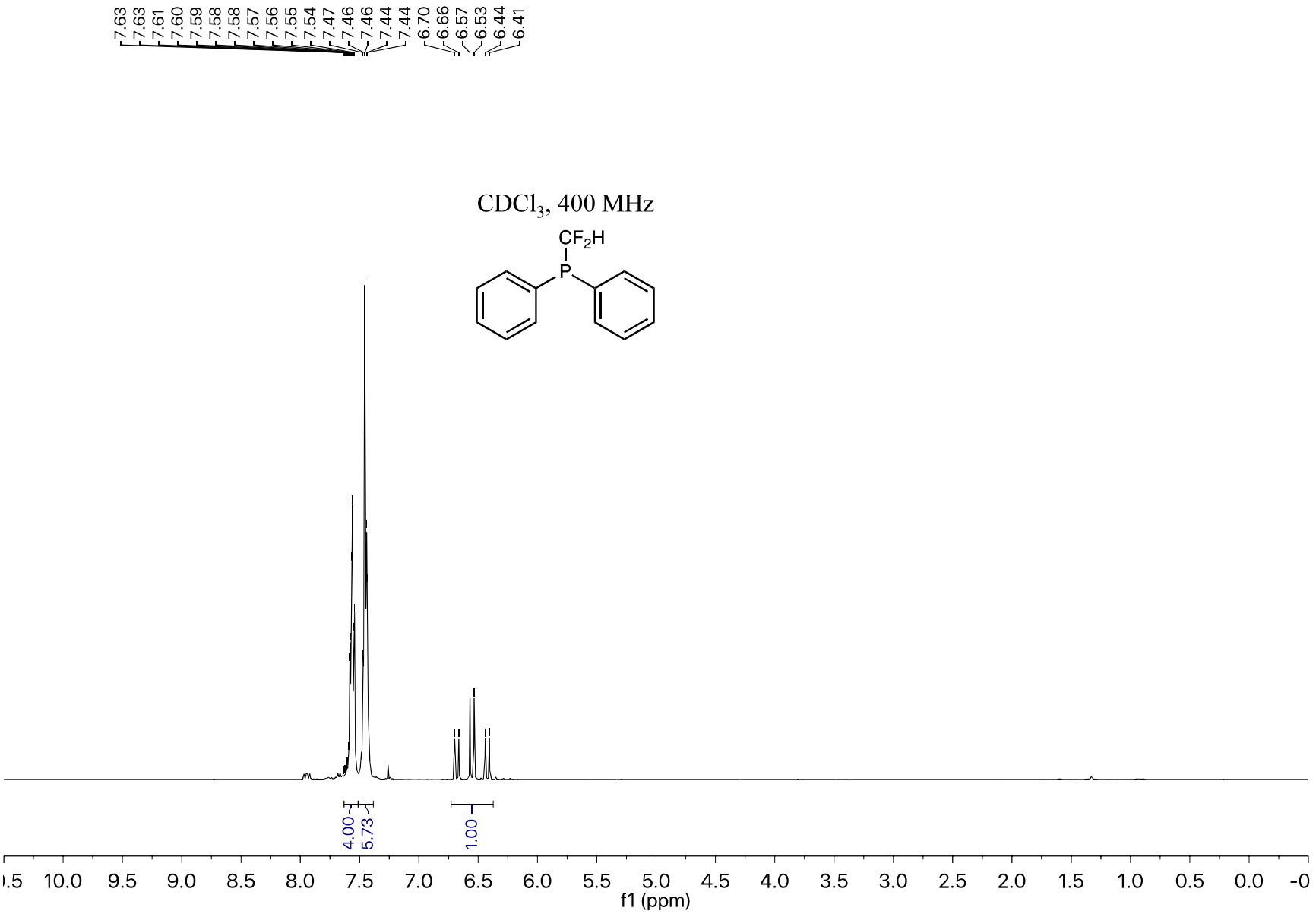

149.13
135.78
135.55
113.65
111.98
111.89
77.48
77.16
76.84
47.56
25.62
CDCl3, 100 MHz
CF3
P
N
N
4
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

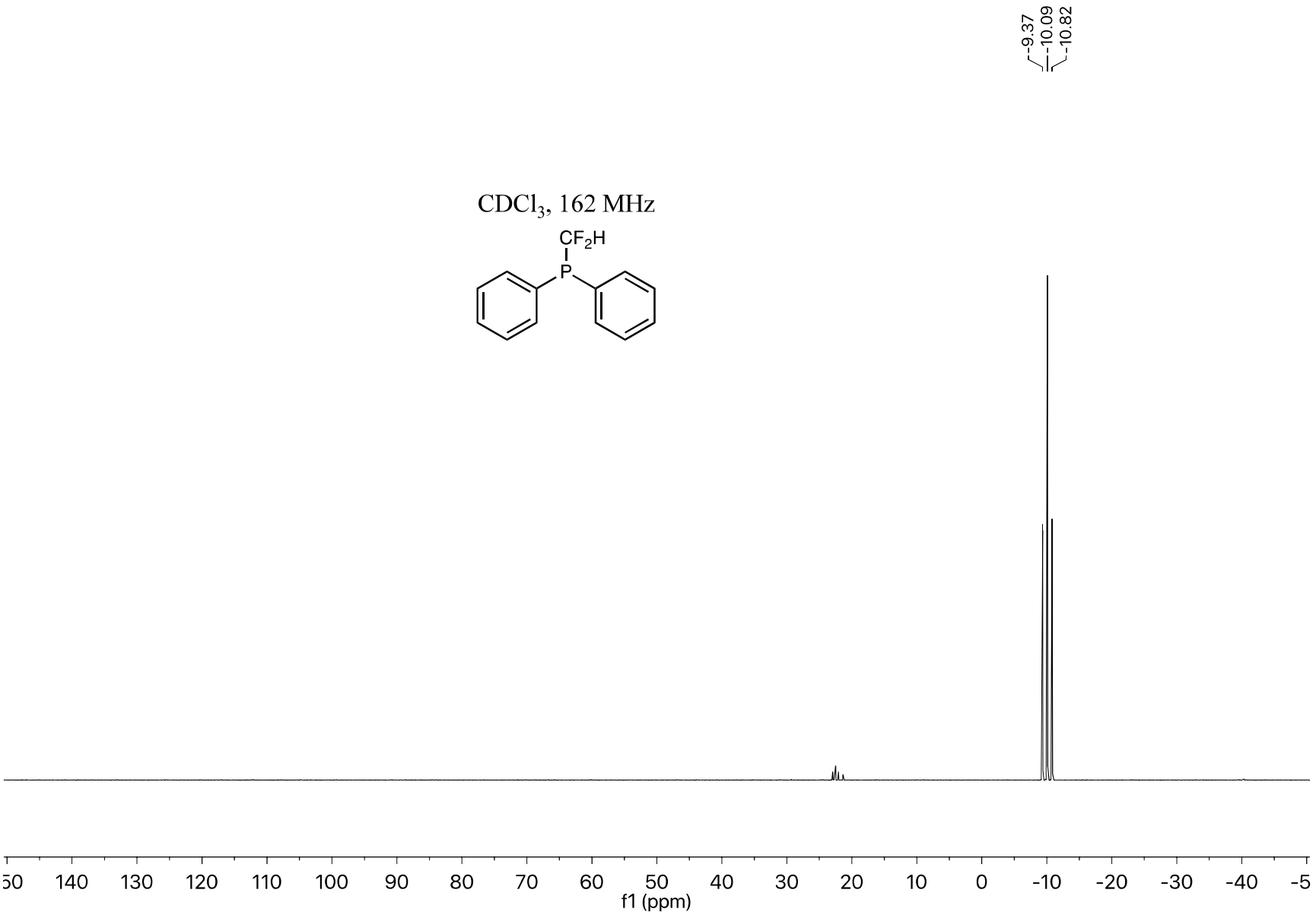

7.61
7.59
7.57
6.61
6.60
6.59
6.58
3.34
3.33
3.32
3.31
3.30
2.04
2.03
2.02
2.01
2.00
CDCl3, 400 MHz
F
F
CF3
P
N
N
4.00
4.15
8.32
8.22
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

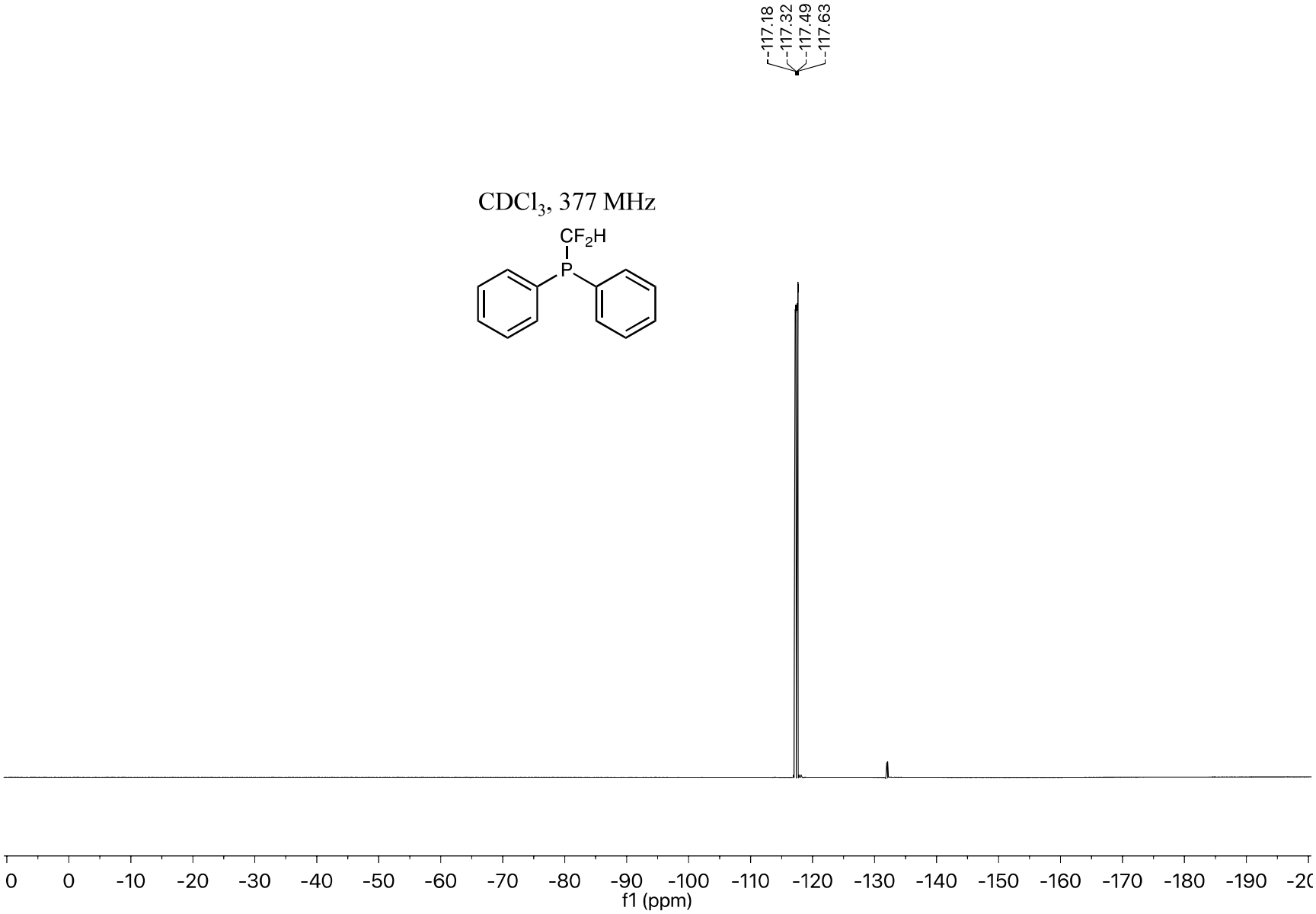

4.49
4.59
4.73
4.84
4.94
5.05
5.18
5.29
CDCl3, 162 MHz
F
F
CF3
P
N
N
50
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-5
f1 (ppm)

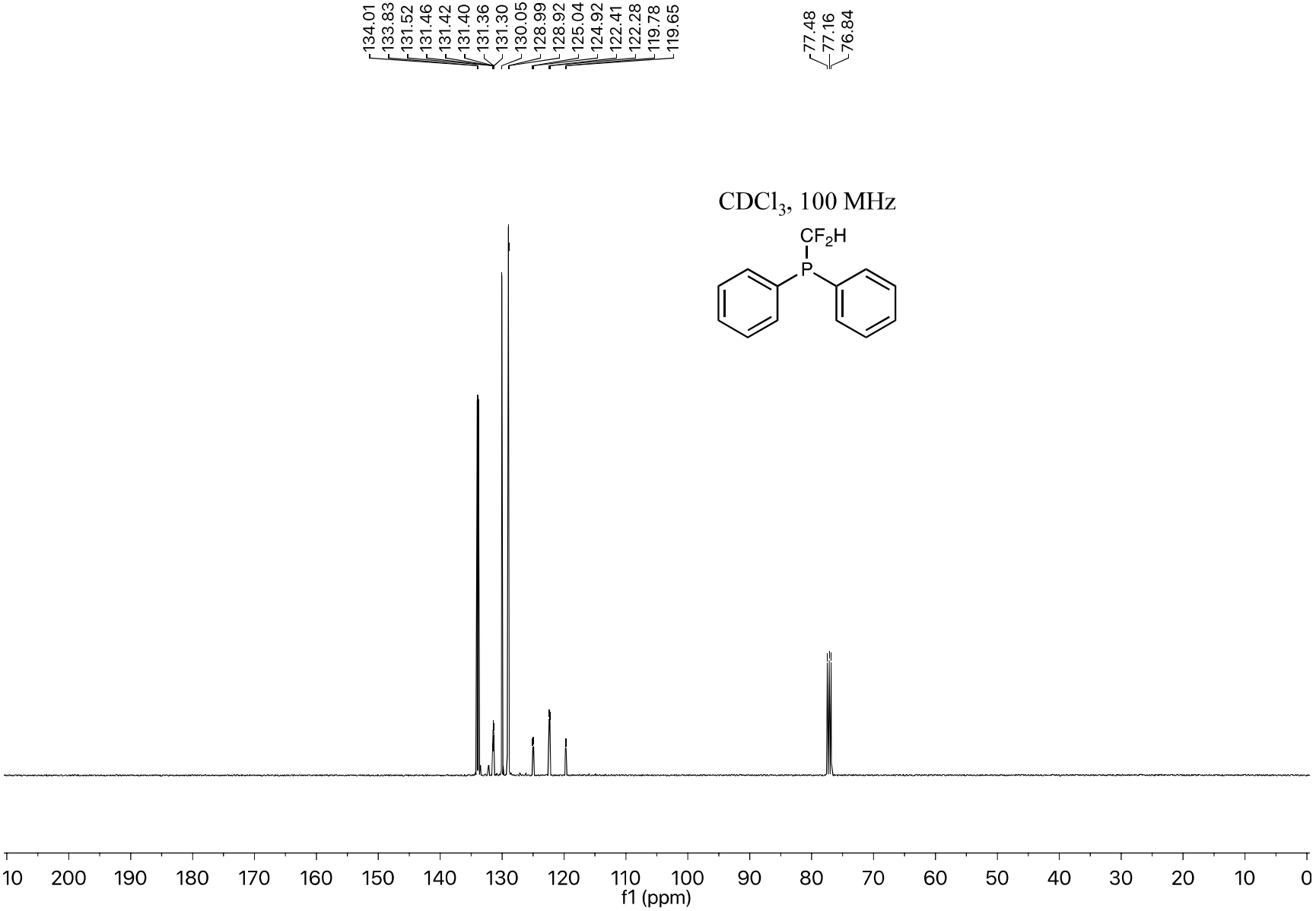

-80.48
-80.49
-80.50
-80.53
-80.54
-80.55
-113.65
-113.66
-113.67
-113.68
-113.81
-113.81
-113.82
-113.83
CDCl3, 377 MHz
F
F
CF3
P
N
N
0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

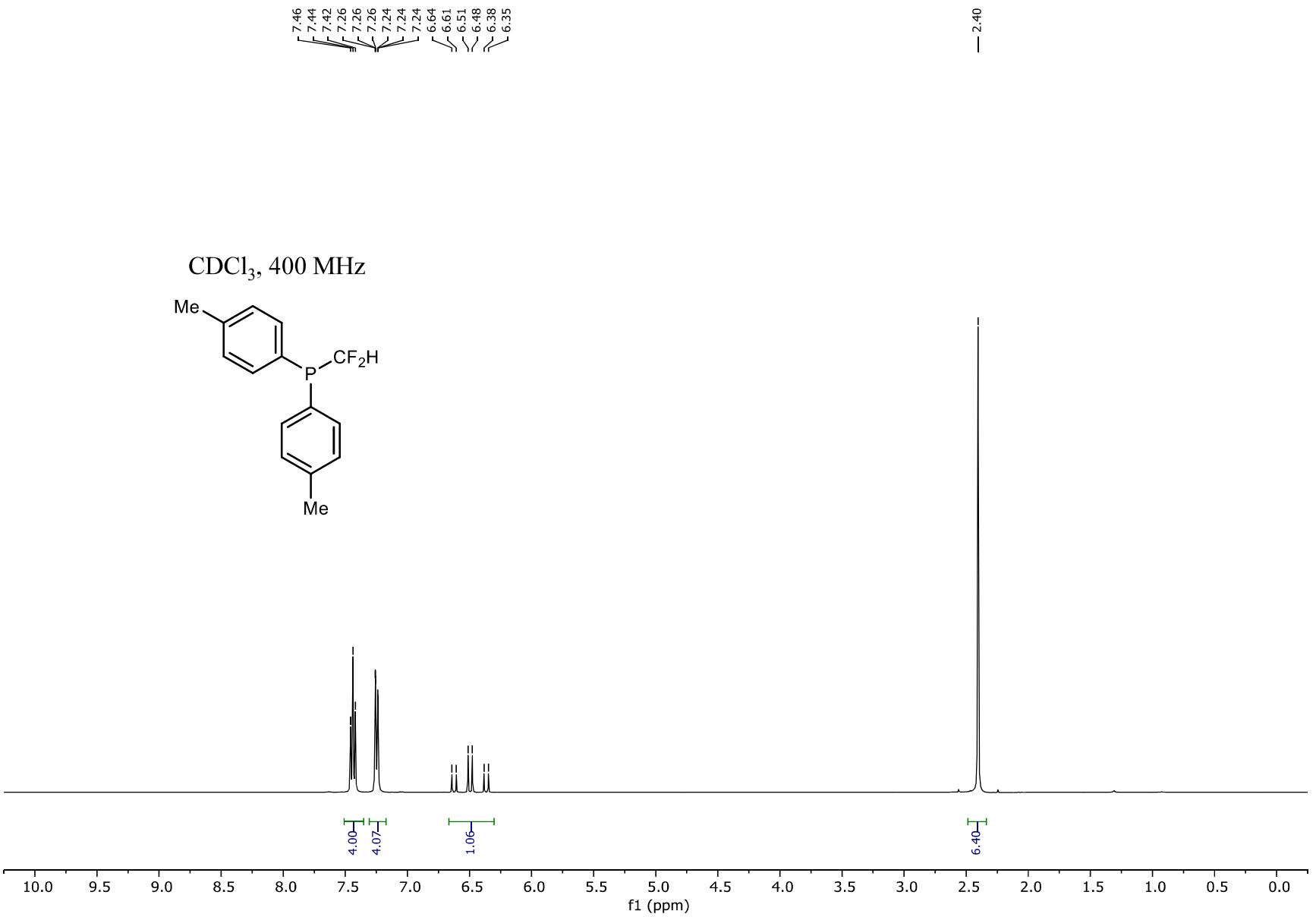

149.23
136.63
136.39
124.16
123.61
123.25
121.78
121.58
121.30
120.94
120.76
120.40
118.93
118.72
112.62
112.58
111.82
111.72
77.48
77.16
76.84
47.48
25.59
CDCl3, 100 MHz
F
F
CF3
P
N
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

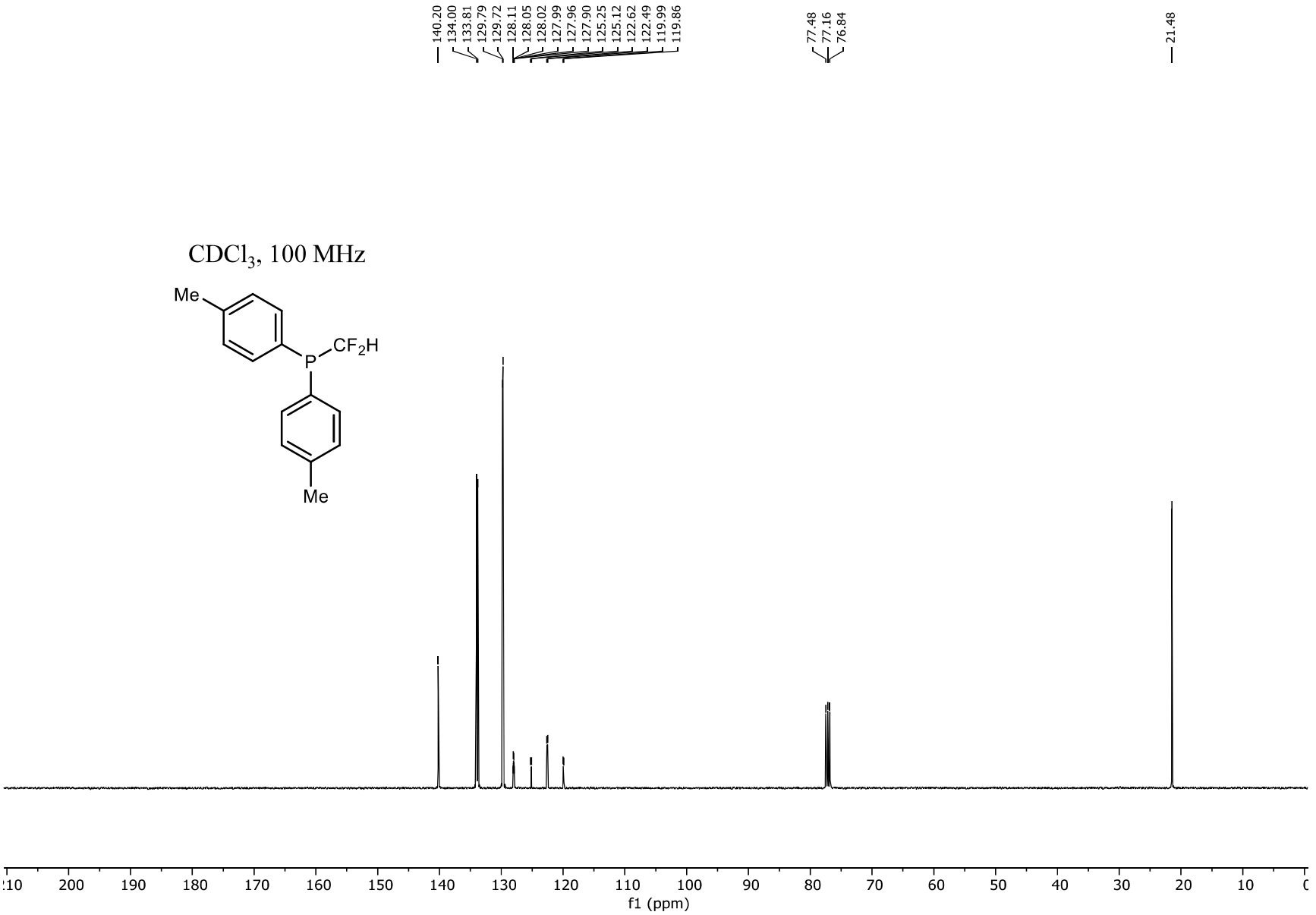

7.63
7.63
7.61
7.60
7.59
7.58
7.58
7.57
7.56
7.55
7.54
7.47
7.46
7.46
7.44
7.44
6.70
6.66
6.57
6.53
6.44
6.41
CDCl3, 400 MHz
CF2H
P
4.00
5.73
1.00
f1 (ppm)


-9.37
-10.09
-10.82
CDCl3, 162 MHz
CF2H
P
50
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-5
f1 (ppm)


-117.18
-117.32
-117.49
-117.63
CDCl3, 377 MHz
CF2H
P
0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

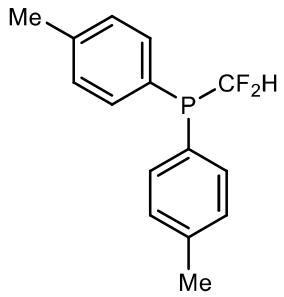

134.01
133.83
131.52
131.46
131.42
131.40
131.36
131.30
130.05
128.99
128.92
125.04
124.92
122.41
122.28
119.78
119.65
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
P
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

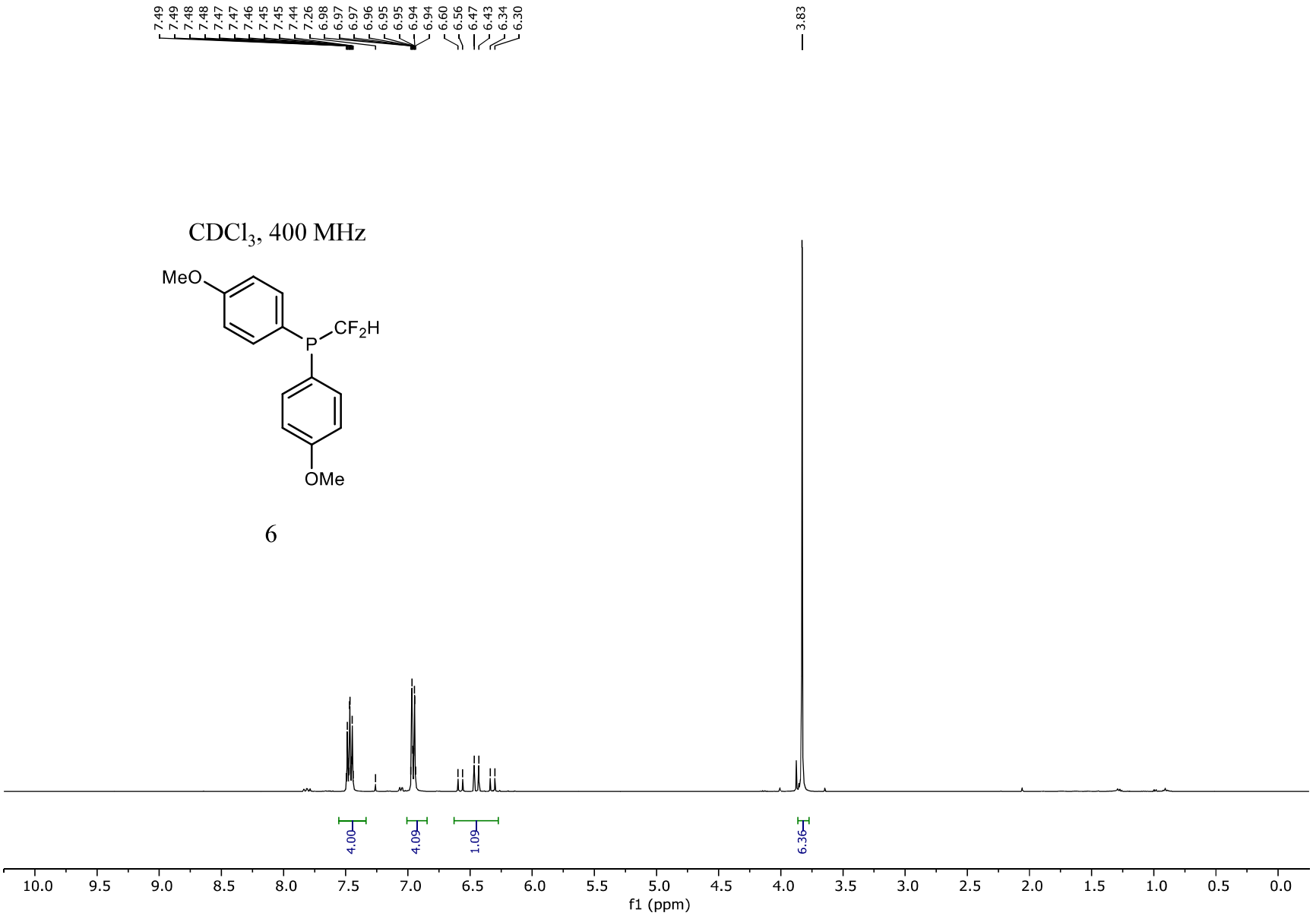

7.46
7.44
7.42
7.26
7.26
7.26
7.24
7.24
7.24
6.64
6.61
6.51
6.48
6.38
6.35
2.40
CDCl3, 400 MHz
Me
P
CF2H
Me
4.00
4.07
1.06
6.40
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

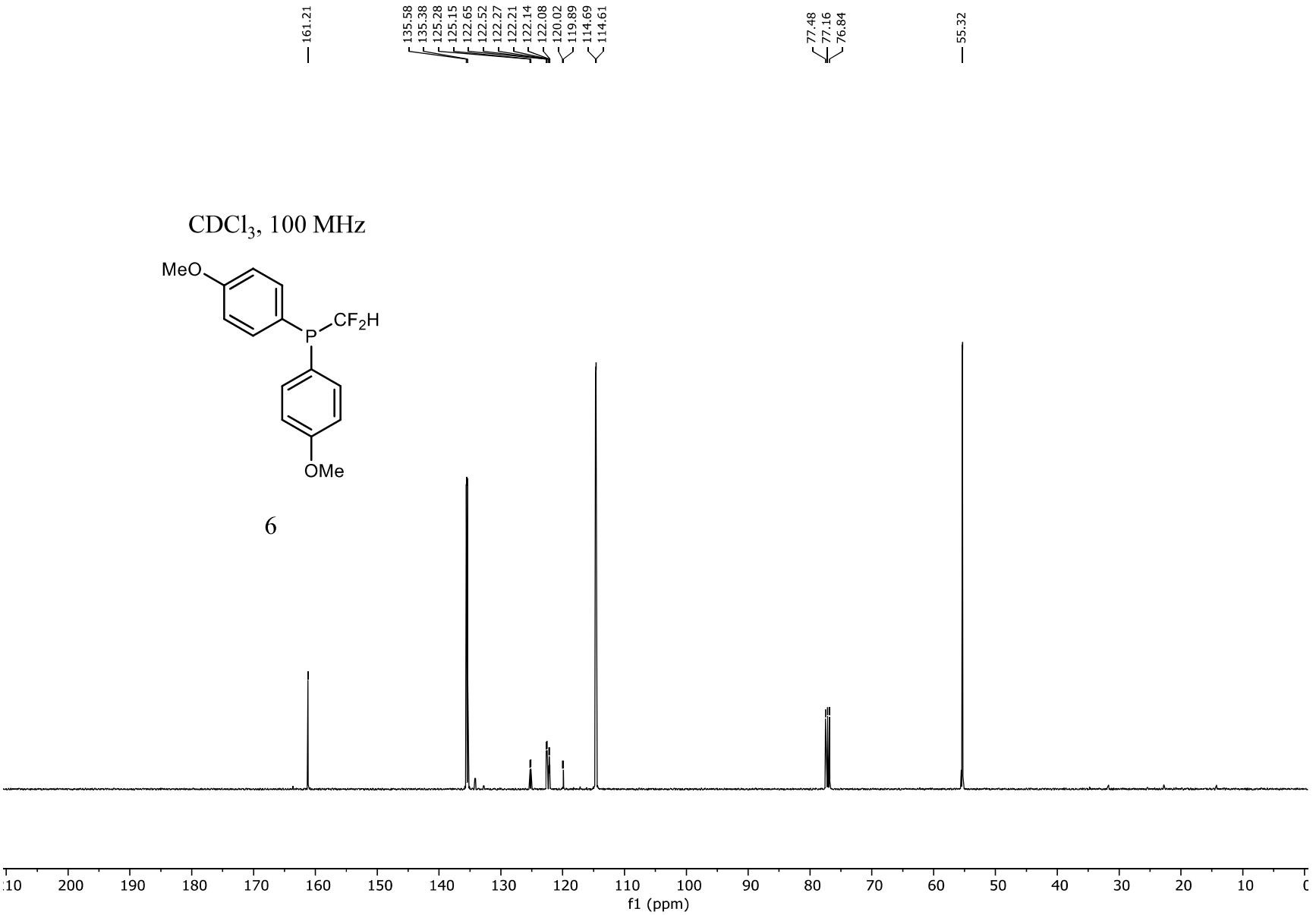

140.20
134.00
133.81
129.79
129.72
128.11
128.05
128.02
127.99
127.96
127.90
125.25
125.12
122.62
122.49
119.99
119.86
77.48
77.16
76.84
21.48
CDCl3, 100 MHz
Me
P
CF2H
Me
f1 (ppm)


-117.39
-117.53
-117.70
-117.84
CDCl3, 376 MHz
Me
P
CF2H
Me
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

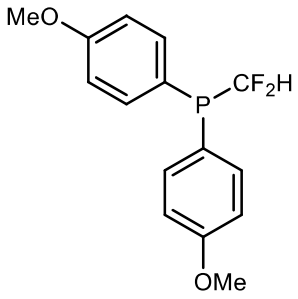
$CDCl_3$, 162 MHz




7.49
7.49
7.48
7.48
7.47
7.47
7.46
7.45
7.45
7.44
7.26
6.98
6.97
6.97
6.96
6.95
6.95
6.94
6.94
6.60
6.56
6.47
6.43
6.34
6.30
3.83
CDCl3, 400 MHz
MeO
P
CF2H
OMe
6
4.00
4.09
1.09
6.36
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)

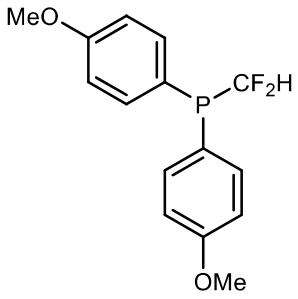

161.21
135.58
135.38
125.28
125.15
122.65
122.52
122.27
122.21
122.14
122.08
120.02
119.89
114.69
114.61
77.48
77.16
76.84
55.32
CDCl3, 100 MHz
MeO
P
CF2H
OMe
6
f1 (ppm)

$CDCl_3$, 376 MHz

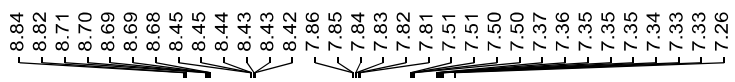


6

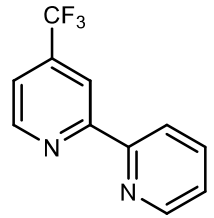
$CDCl_3$, 162 MHz



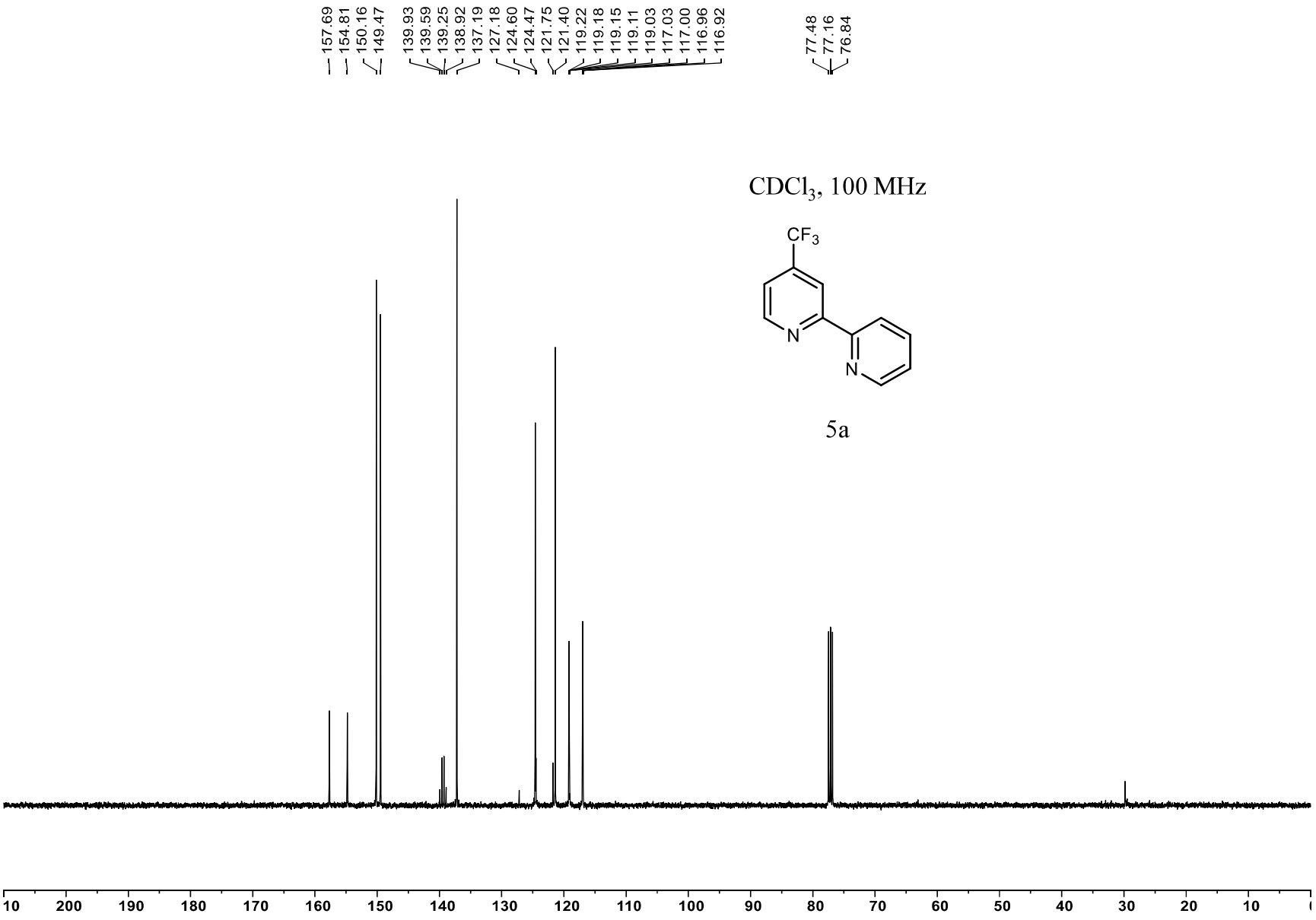
6

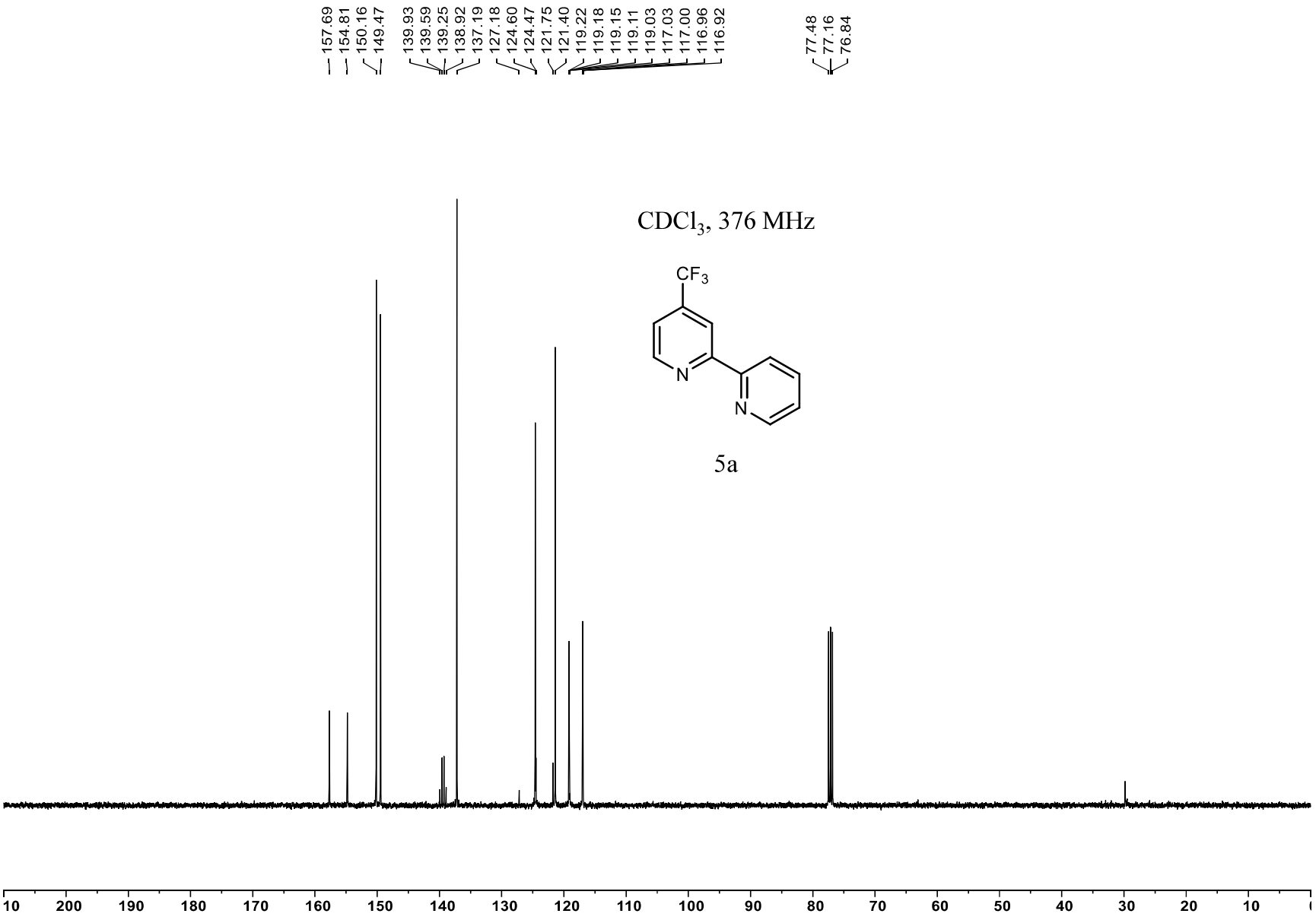


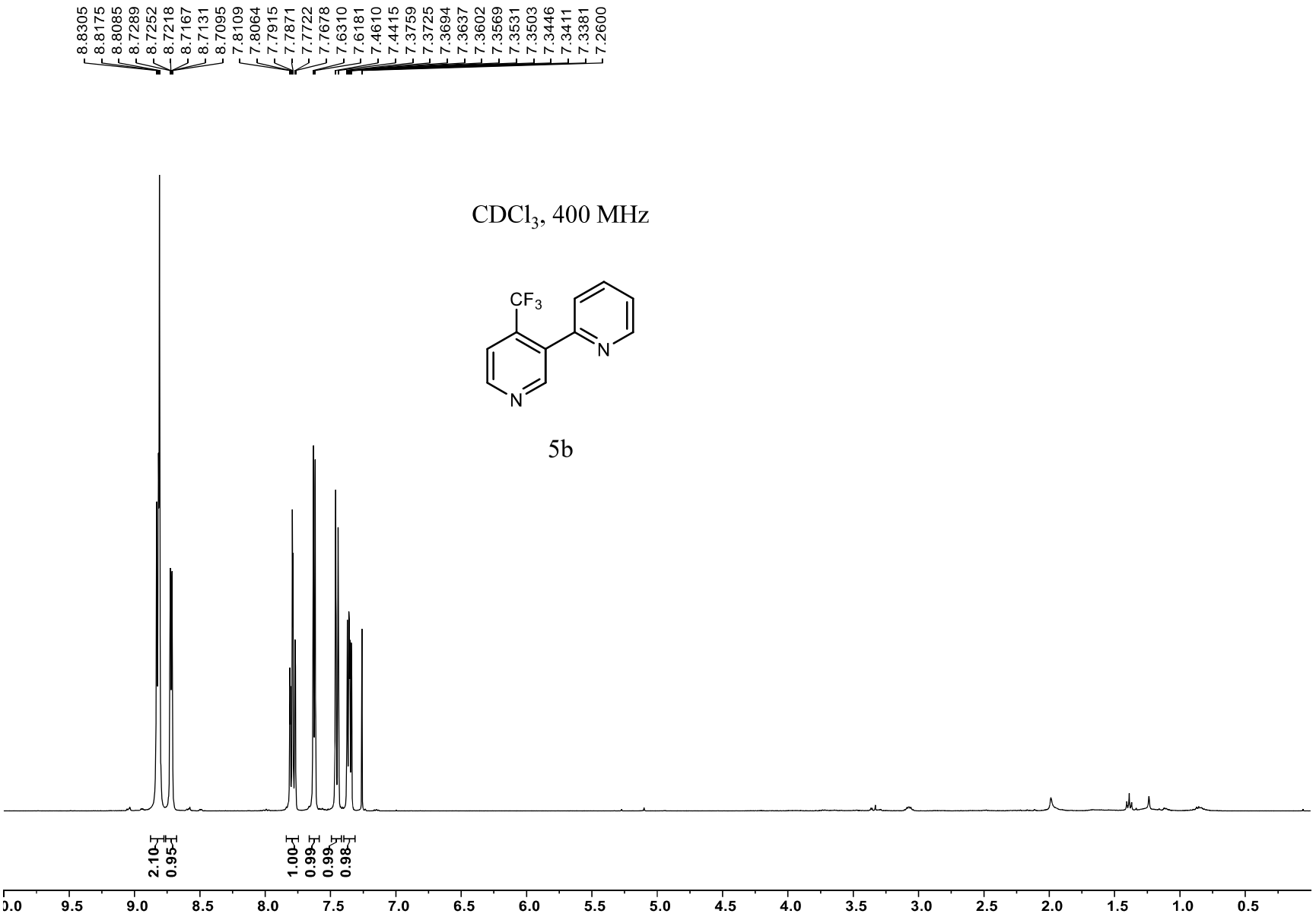
$CDCl_3$, 400 MHz

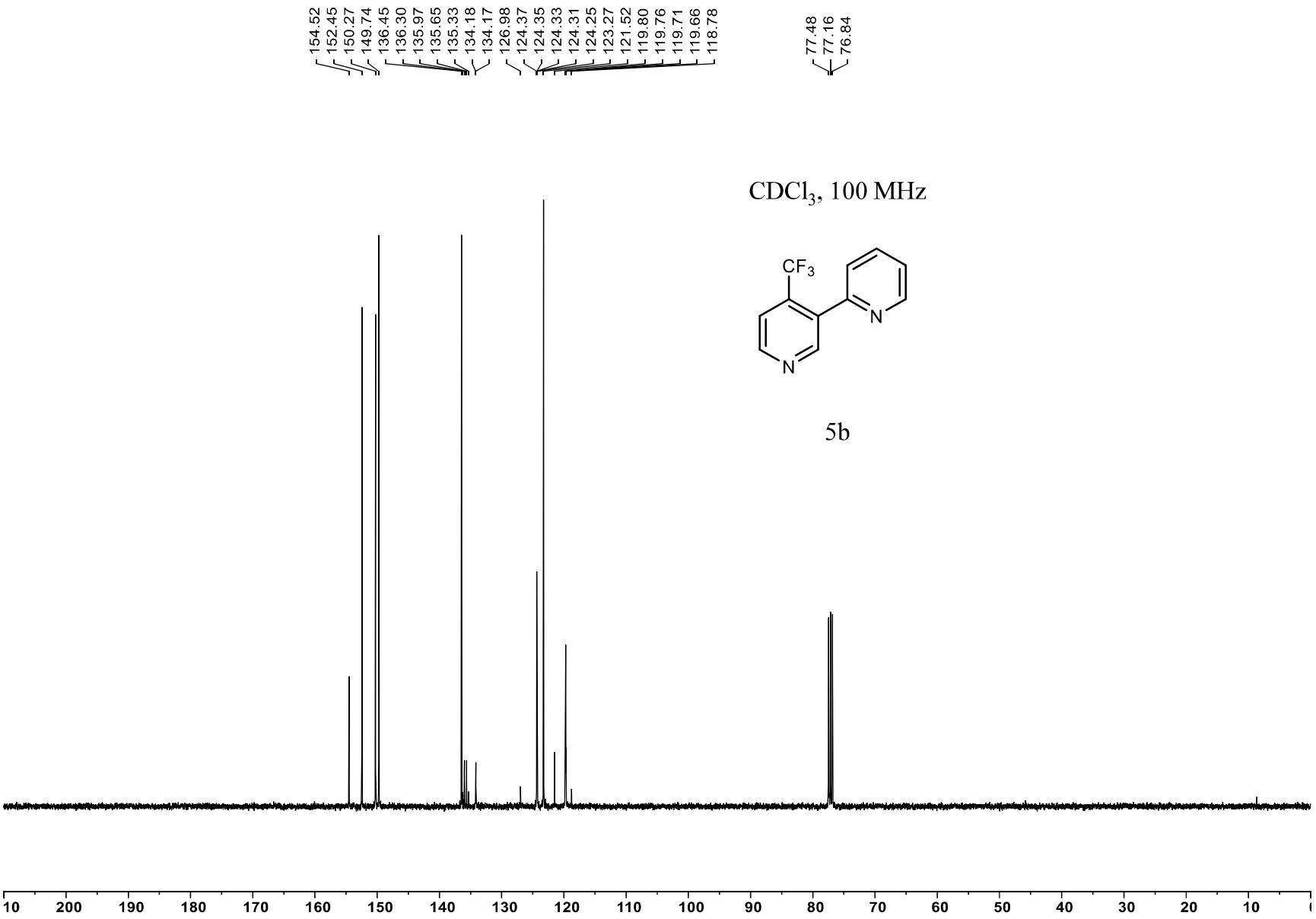


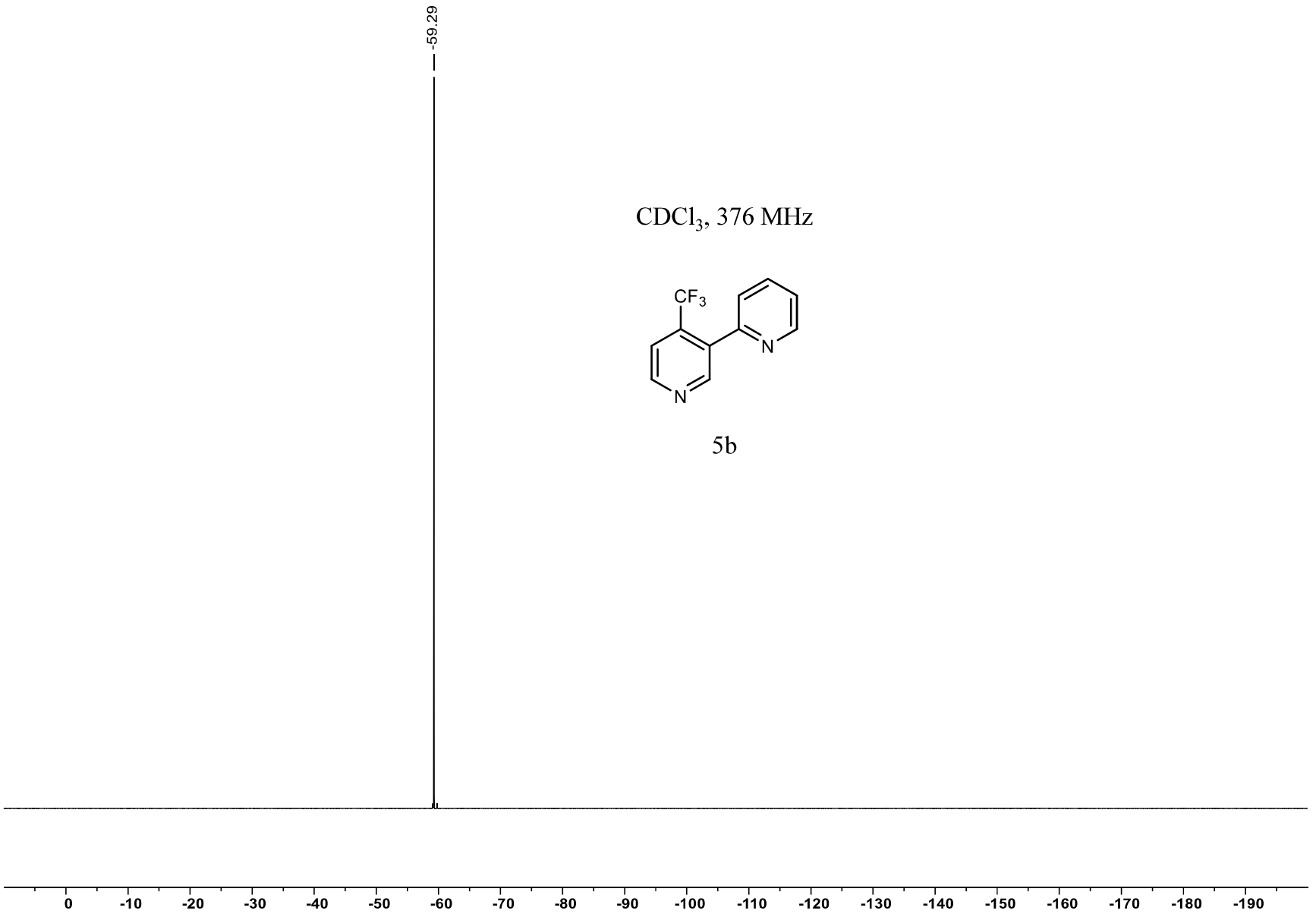
5a


157.69
154.81
150.16
149.47
139.93
139.59
139.25
138.92
137.19
127.18
124.60
124.47
121.75
121.40
119.22
119.18
119.15
119.11
119.03
117.03
117.00
116.96
116.92
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
N
N
5a
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


157.69
154.81
150.16
149.47
139.93
139.59
139.25
138.92
137.19
127.18
124.60
124.47
121.75
121.40
119.22
119.18
119.15
119.11
119.03
117.03
117.00
116.96
116.92
77.48
77.16
76.84
CDCl3, 376 MHz
CF3
N
N
5a
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

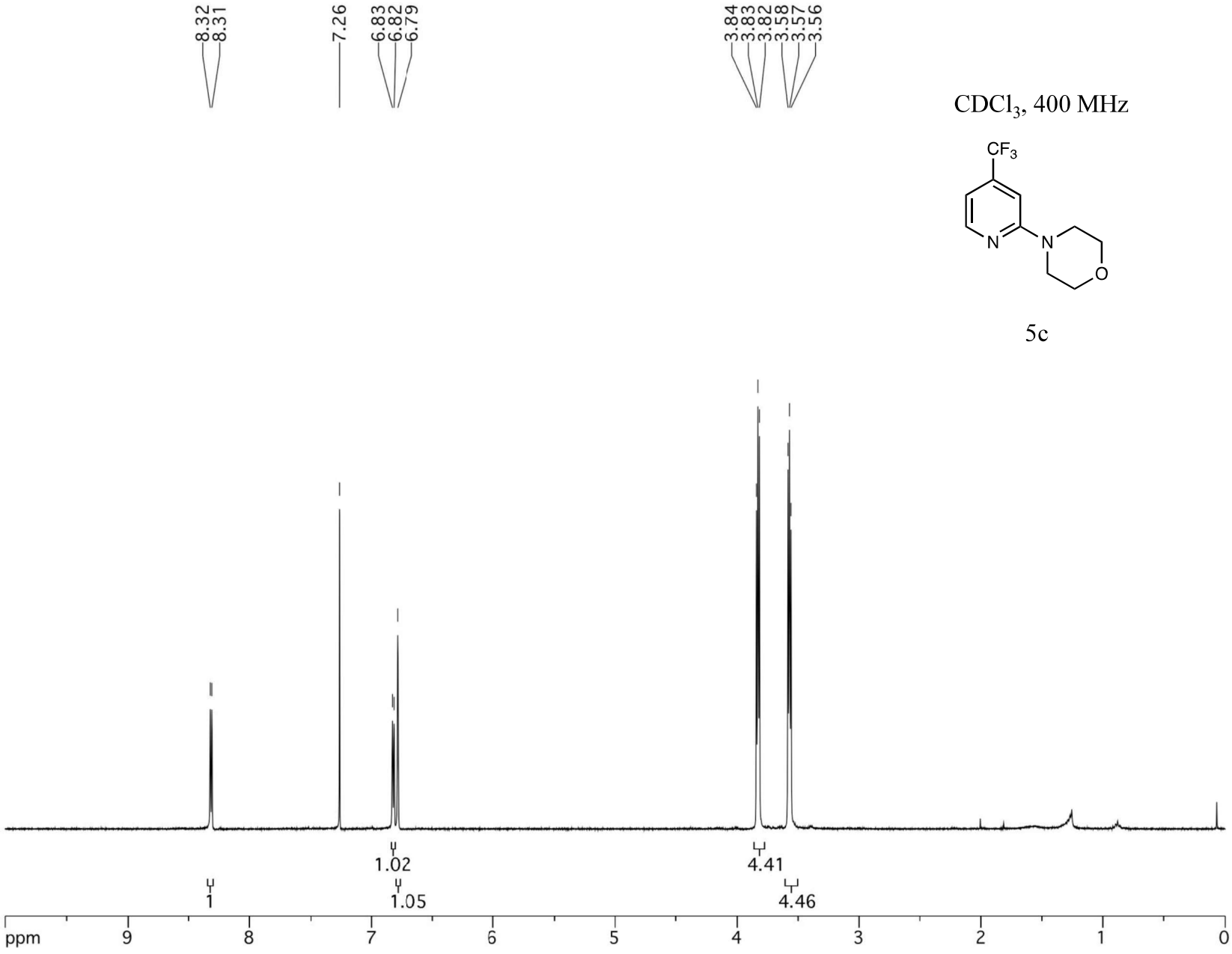

8.8305
8.8175
8.8085
8.7289
8.7252
8.7218
8.7167
8.7131
8.7095
7.8109
7.8064
7.7915
7.7871
7.7722
7.7678
7.6310
7.6181
7.4610
7.4415
7.3759
7.3725
7.3694
7.3637
7.3602
7.3569
7.3531
7.3503
7.3446
7.3411
7.3381
7.2600
CDCl3, 400 MHz
CF3
N
N
5b
2.10
0.95
1.00
0.99
0.99
0.98
0.0
9.5
9.0
8.5
8.0
7.5
7.0
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


154.52
152.45
150.27
149.74
136.45
136.30
135.97
135.65
135.33
134.18
134.17
126.98
124.37
124.35
124.33
124.31
124.25
123.27
121.52
119.80
119.76
119.71
119.66
118.78
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
N
N
5b
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

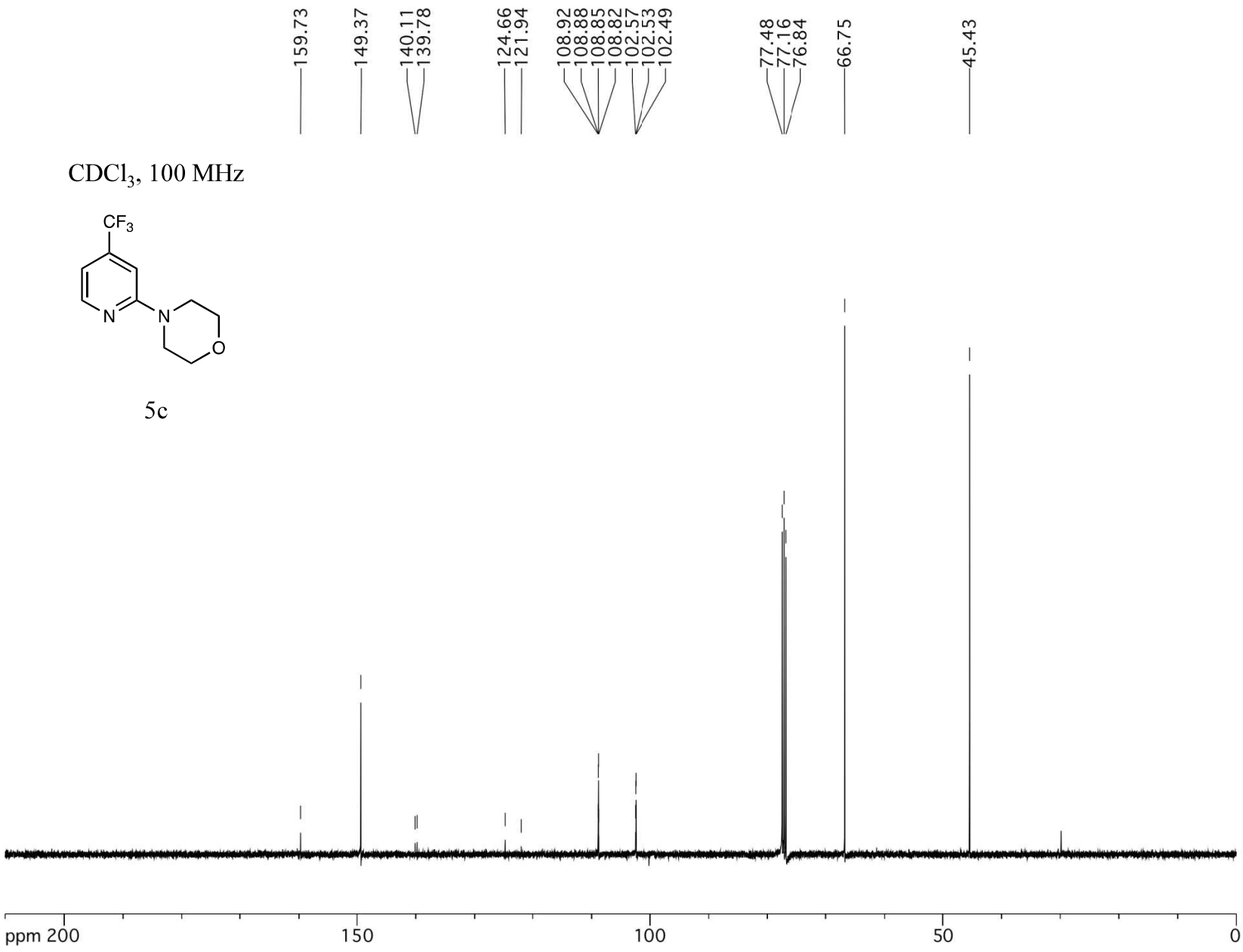


$CDCl_3$, 376 MHz

5b


8.32
8.31
7.26
6.83
6.82
6.79
3.84
3.83
3.82
3.58
3.57
3.56
CDCl3, 400 MHz
CF3
N
N
O
1.02
4.41
1
1.05
4.46
ppm
9
8
7
6
5
4
3
2
1
0

5c

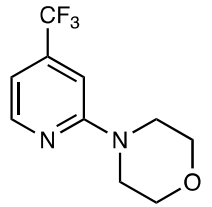


$CDCl_3$, 100 MHz

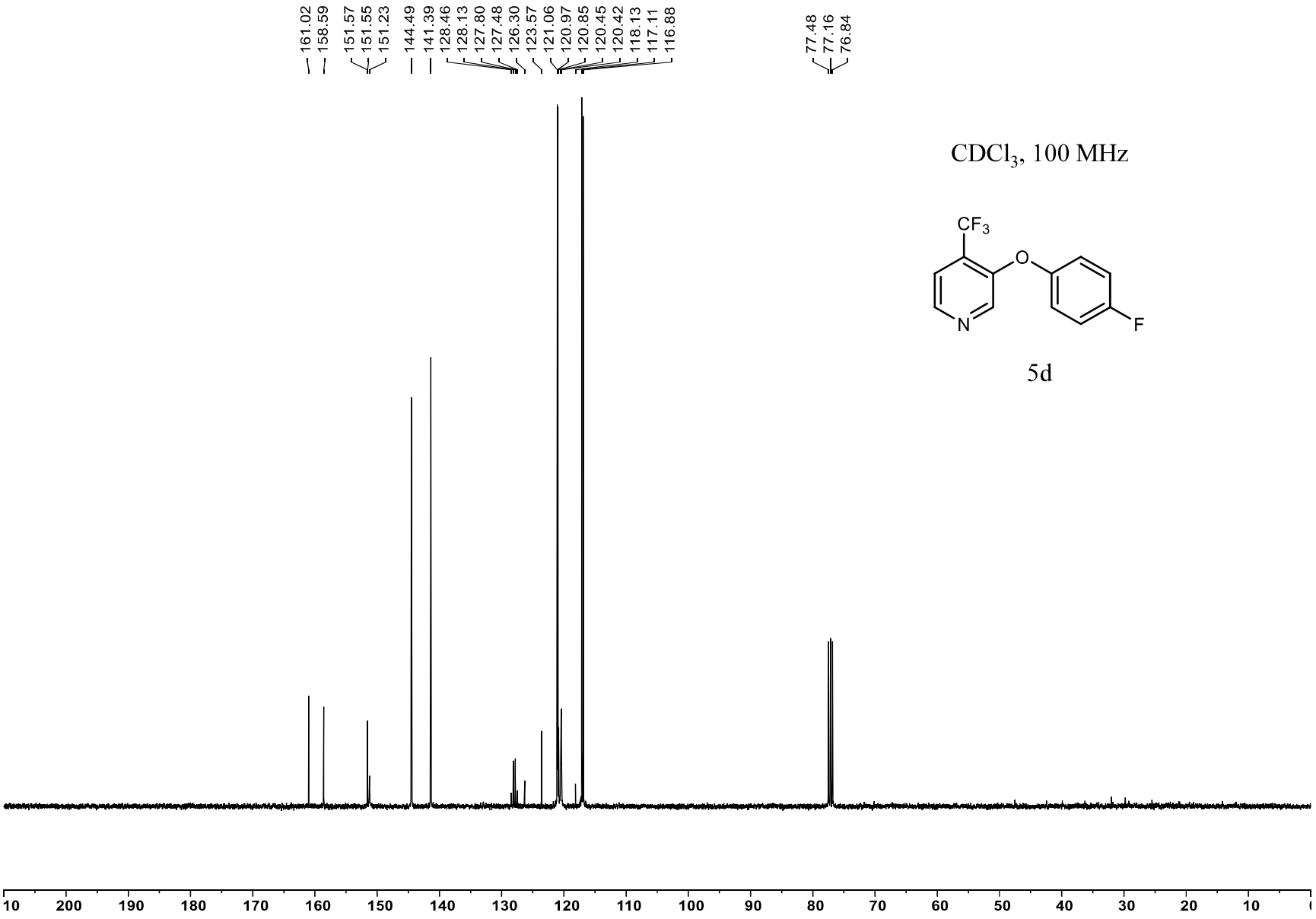
5c

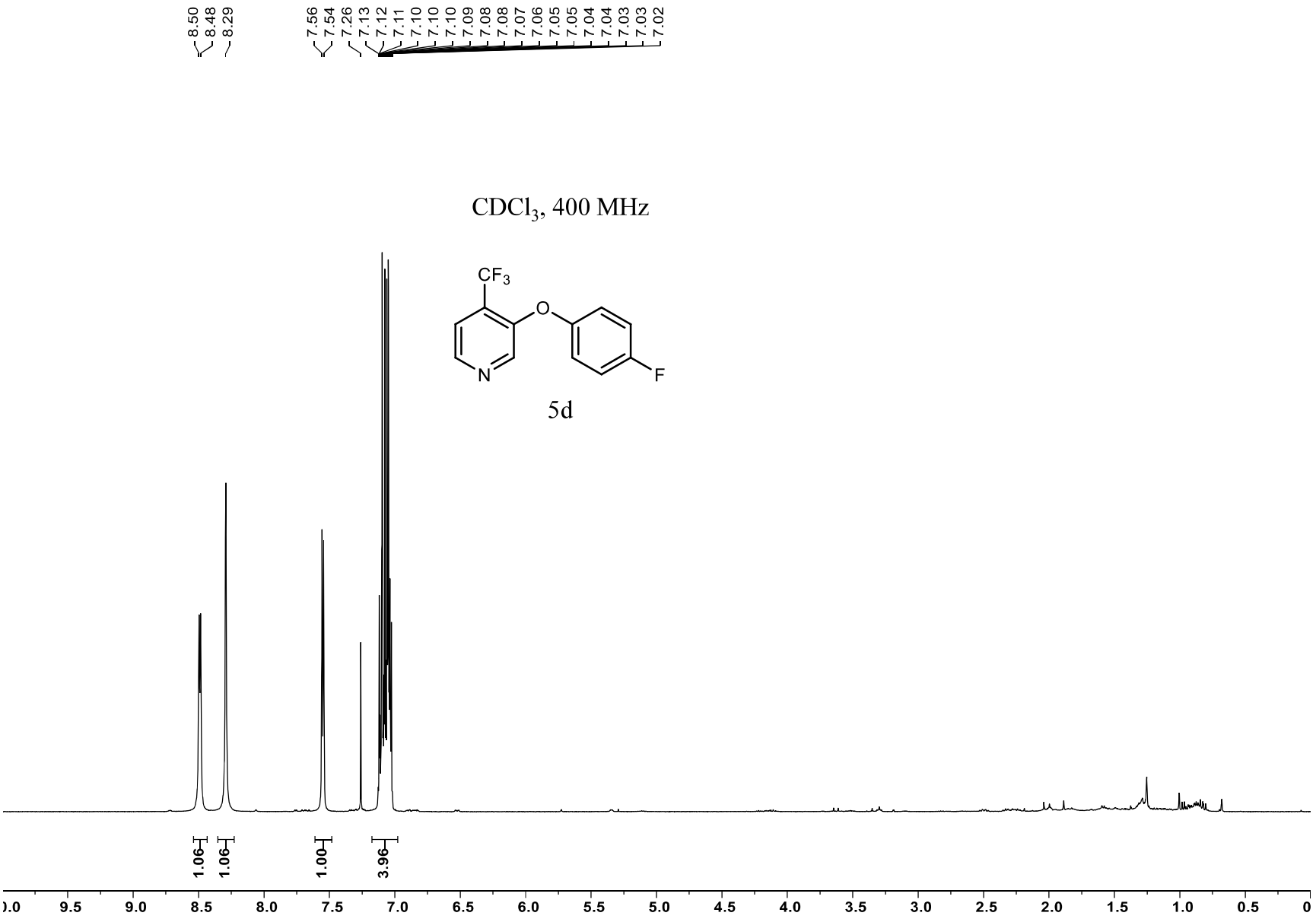
-65.16

$CDCl_3$, 376 MHz

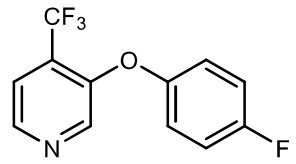


5c

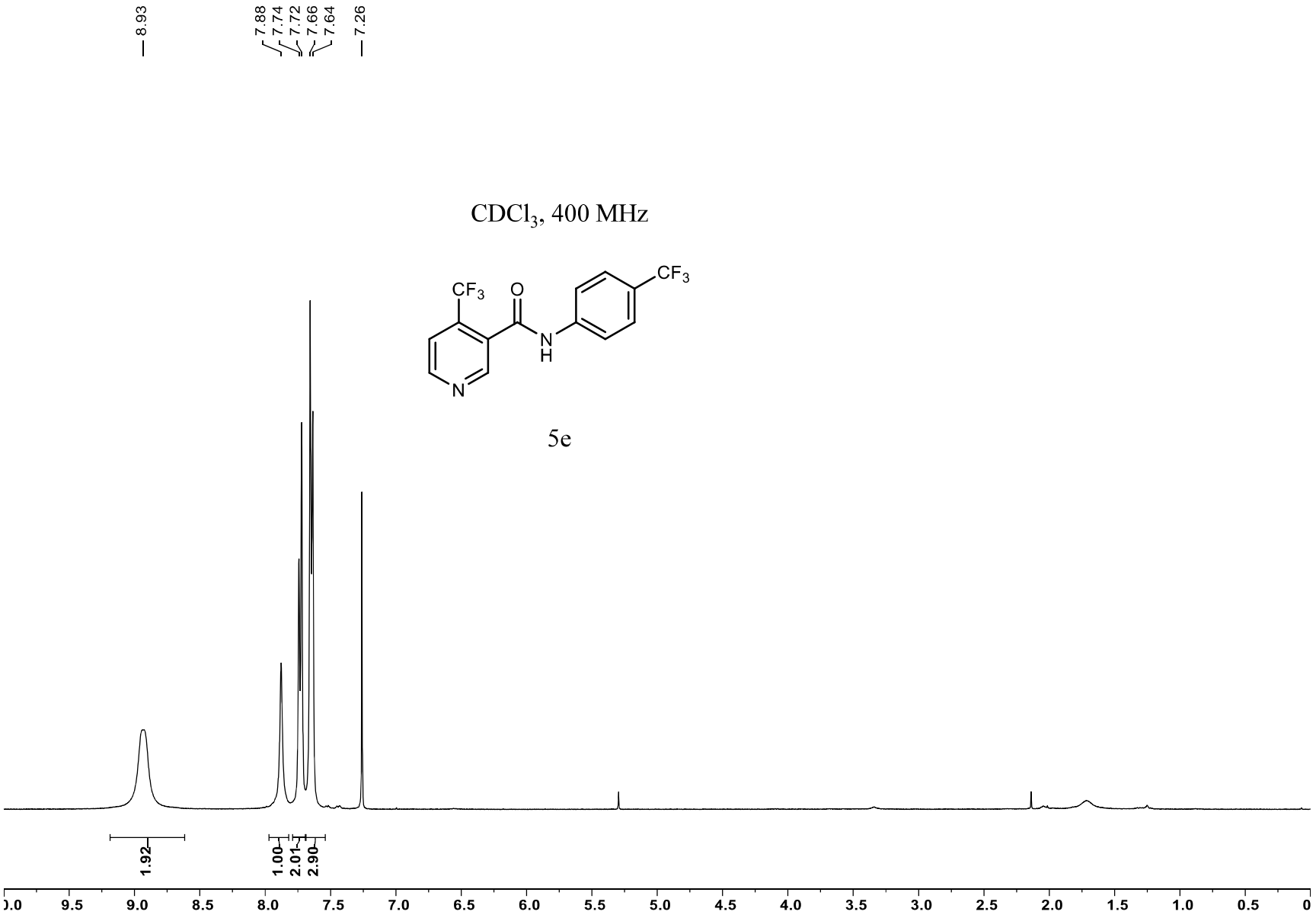

161.02
158.59
151.57
151.55
151.23
144.49
141.39
128.46
128.13
127.80
127.48
126.30
123.57
121.06
120.97
120.85
120.45
120.42
118.13
117.11
116.88
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
O
N
F
5d
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

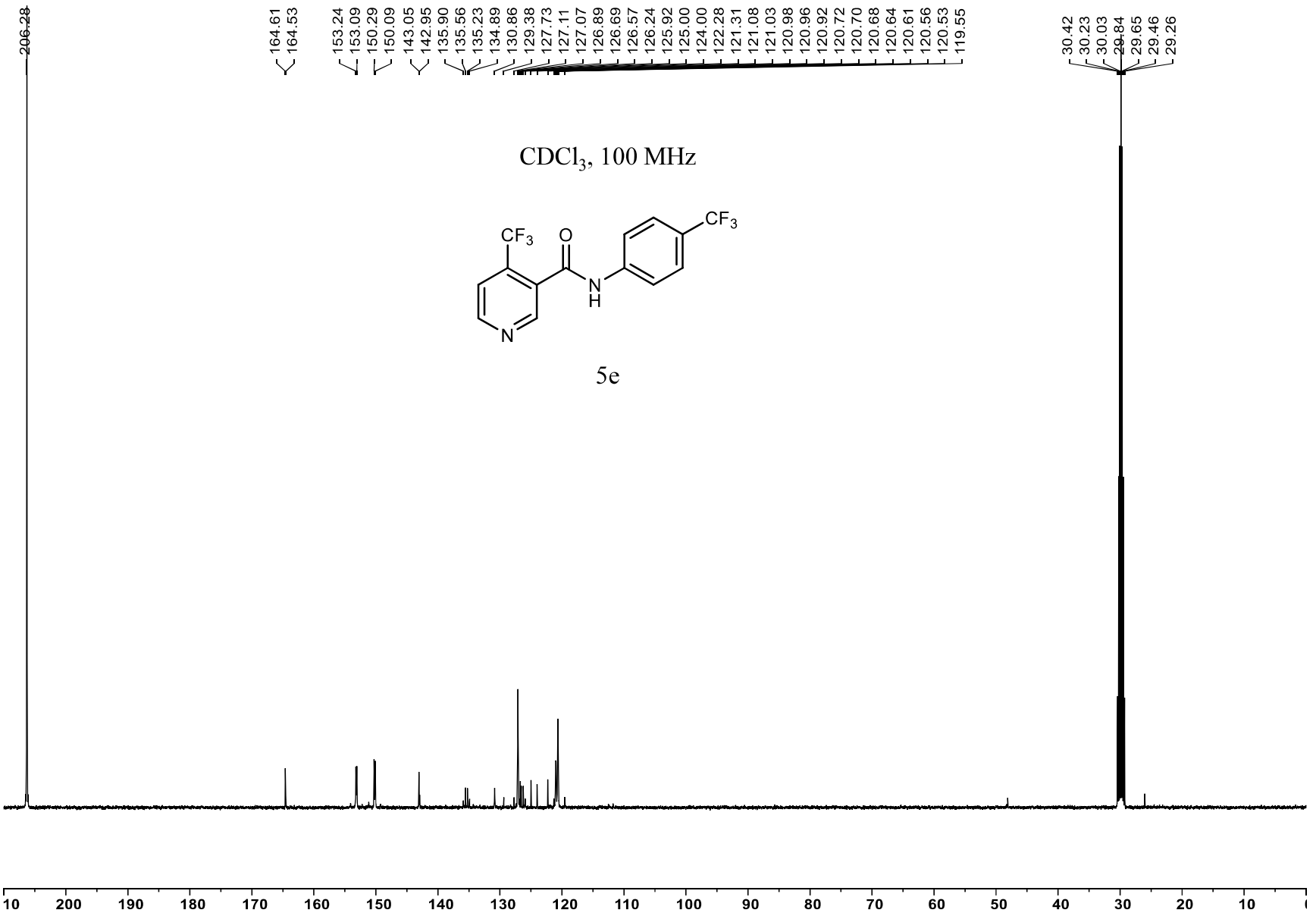

8.50
8.48
8.29
7.56
7.54
7.26
7.13
7.12
7.11
7.10
7.10
7.10
7.09
7.08
7.08
7.07
7.06
7.05
7.05
7.04
7.04
7.03
7.03
7.02
CDCl3, 400 MHz
CF3
O
N
F
5d
1.06
1.06
1.00
3.96
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

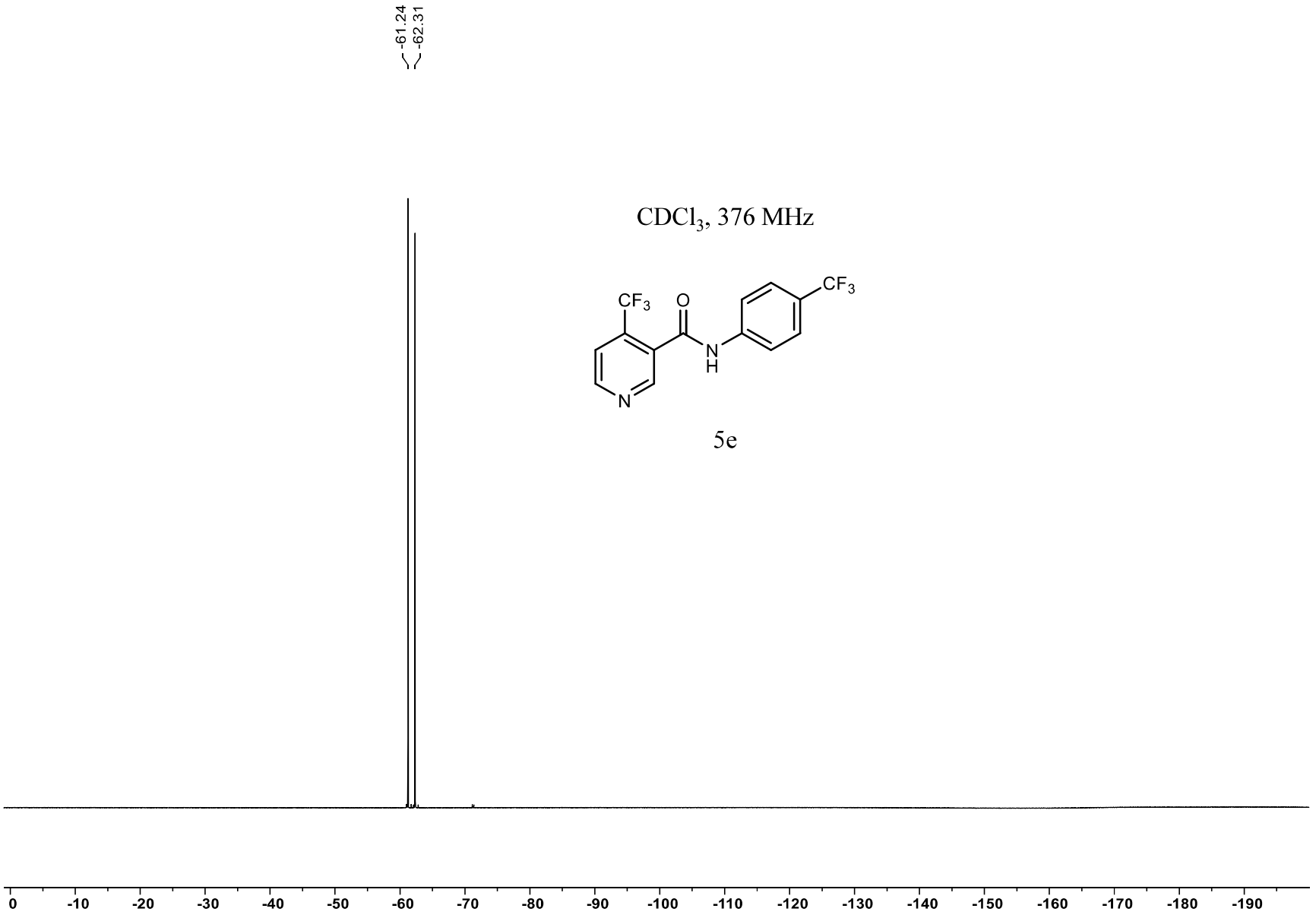
$CDCl_3$, 376 MHz

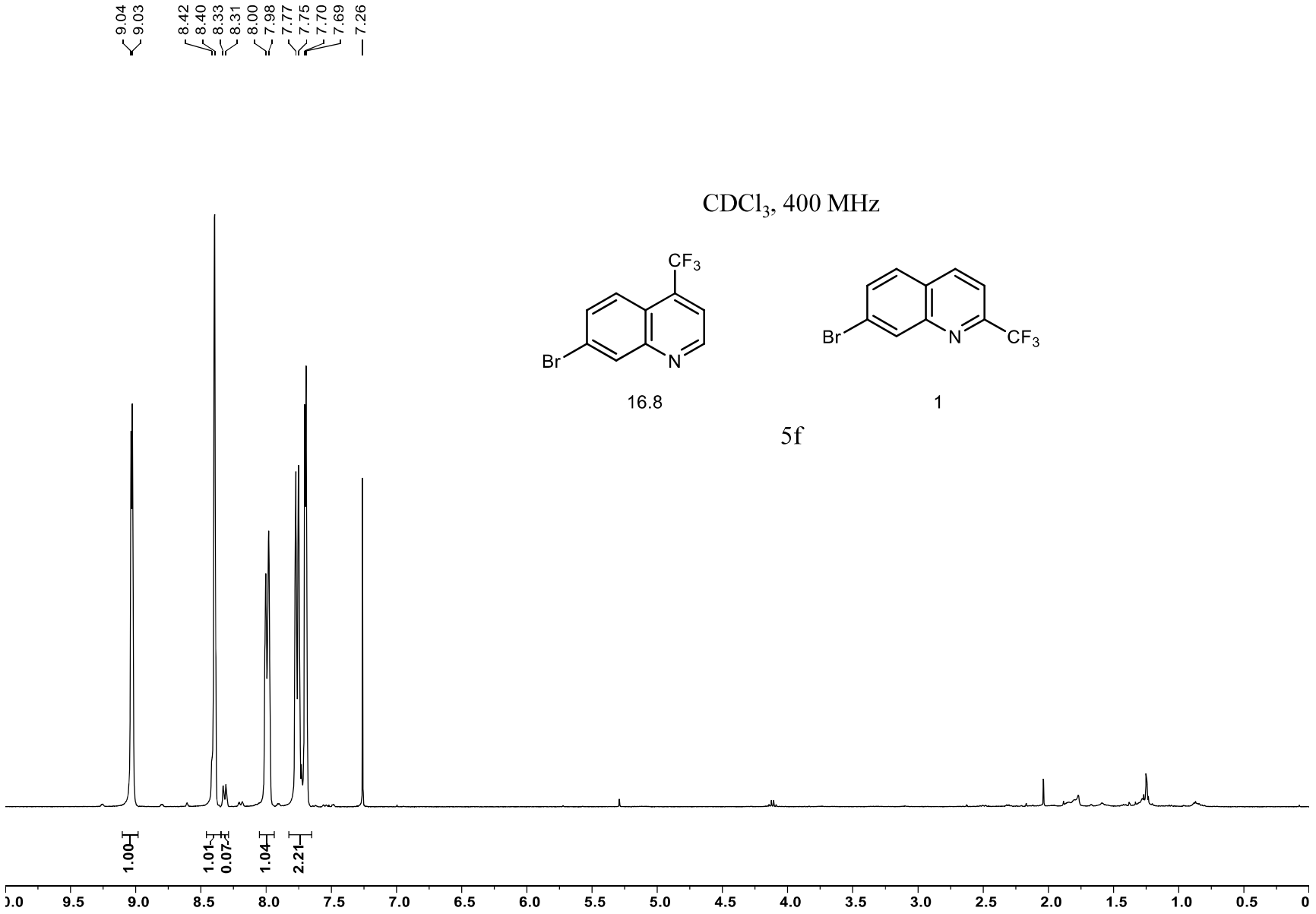


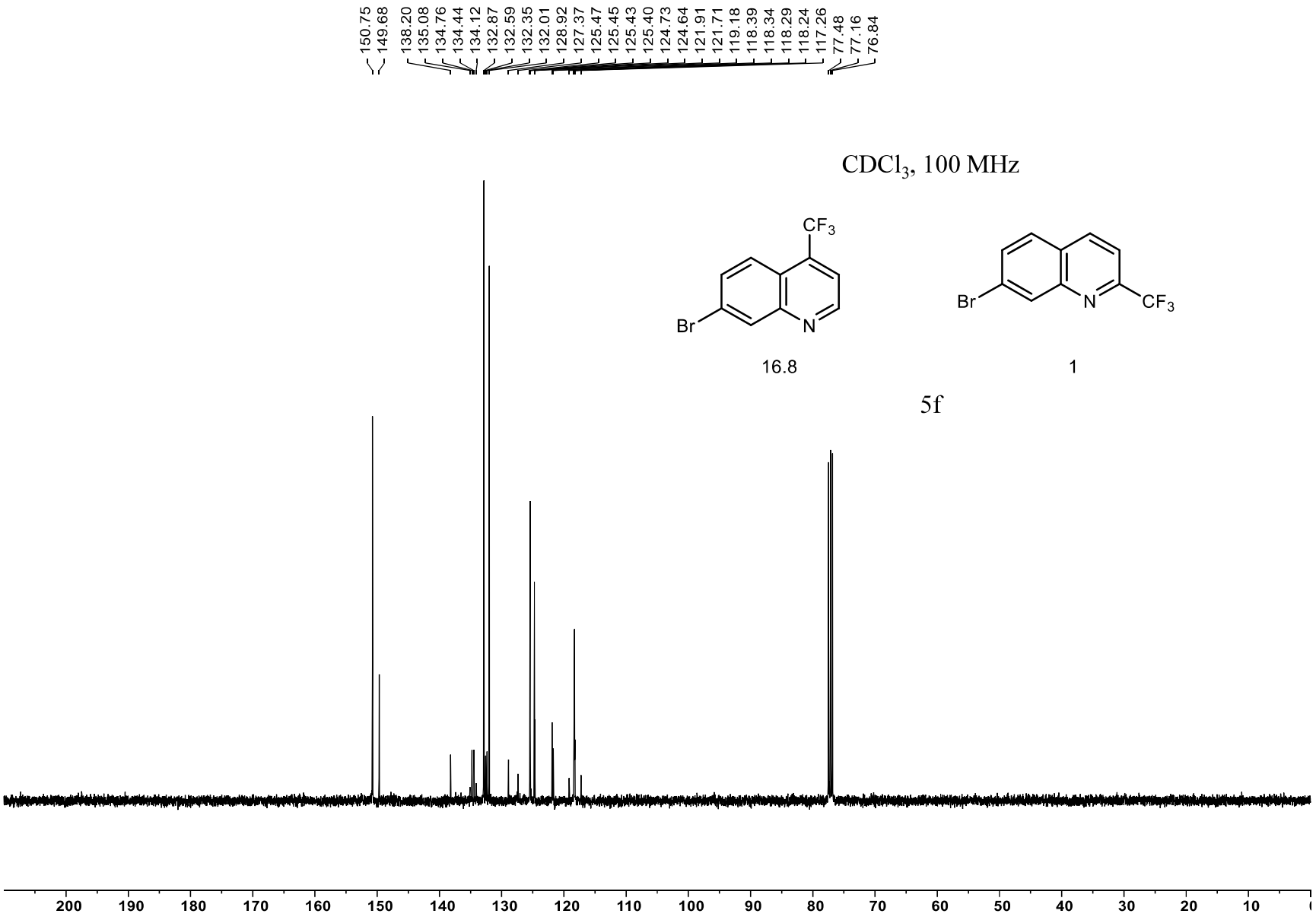
5d

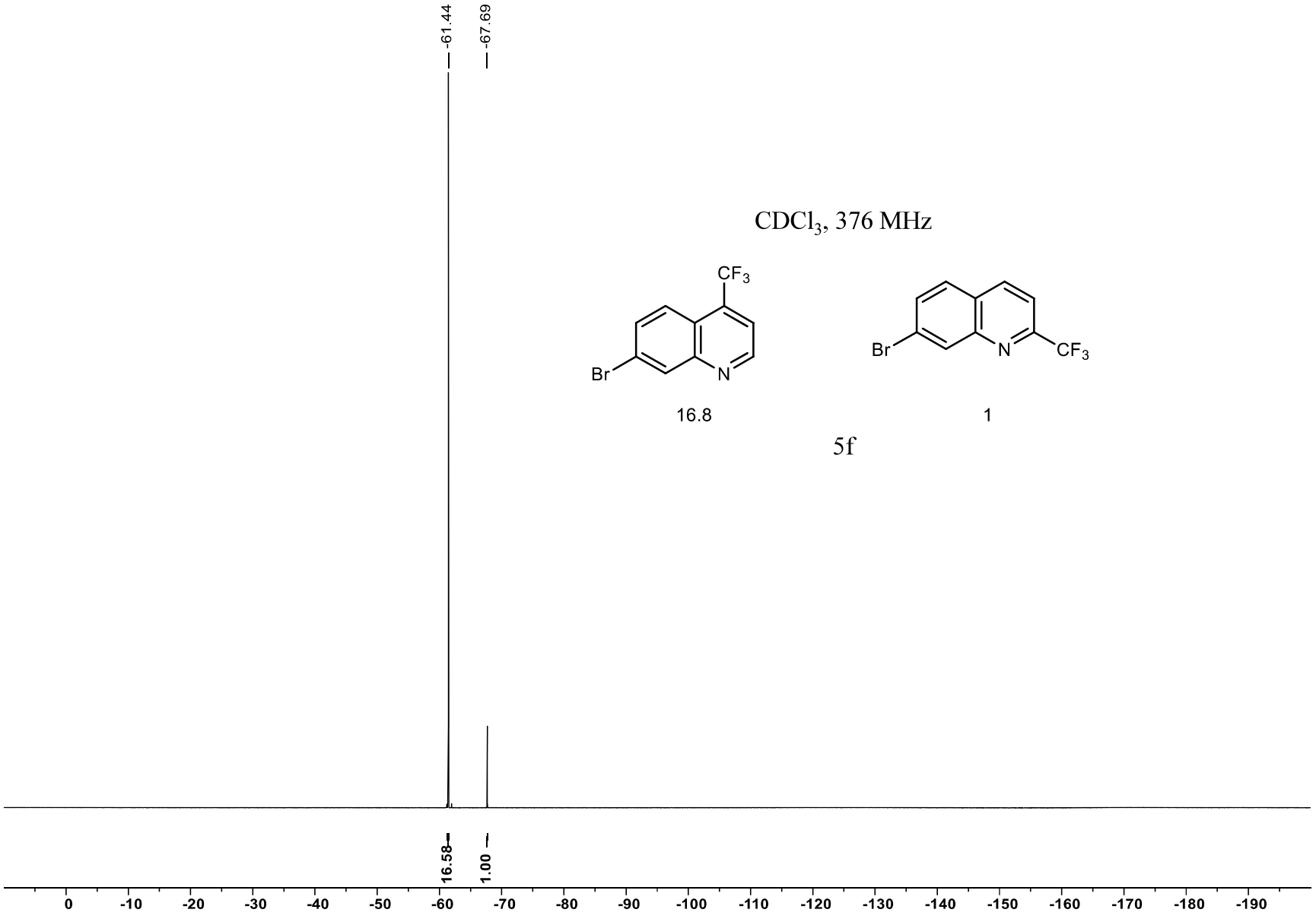

8.93
7.88
7.74
7.72
7.66
7.64
7.26
CDCl3, 400 MHz
CF3
O
N
H
N
CF3
5e
1.92
1.00
2.01
2.90
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


206.28
164.61
164.53
153.24
153.09
150.29
150.09
143.05
142.95
135.90
135.56
135.23
134.89
130.86
129.38
127.73
127.11
127.07
126.89
126.69
126.57
126.24
125.92
125.00
124.00
122.28
121.31
121.08
121.03
120.98
120.96
120.92
120.72
120.70
120.68
120.64
120.61
120.56
120.53
119.55
30.42
30.23
30.03
29.84
29.65
29.46
29.26
CDCl3, 100 MHz
CF3
O
N
H
CF3
N
5e
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


-61.24
-62.31
CDCl3, 376 MHz
CF3
O
N
H
N
CF3
5e
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190


9.04
9.03
8.42
8.40
8.33
8.31
8.00
7.98
7.77
7.75
7.70
7.69
7.26
CDCl3, 400 MHz
CF3
Br
N
16.8
Br
N
CF3
1
5f
1.00
1.01
0.07
1.04
2.21
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


150.75
149.68
138.20
135.08
134.76
134.44
134.12
132.87
132.59
132.35
132.01
128.92
127.37
125.47
125.45
125.43
125.40
124.73
124.64
121.91
121.71
119.18
118.39
118.34
118.29
118.24
117.26
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
Br
N
16.8
Br
N
CF3
1
5f
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

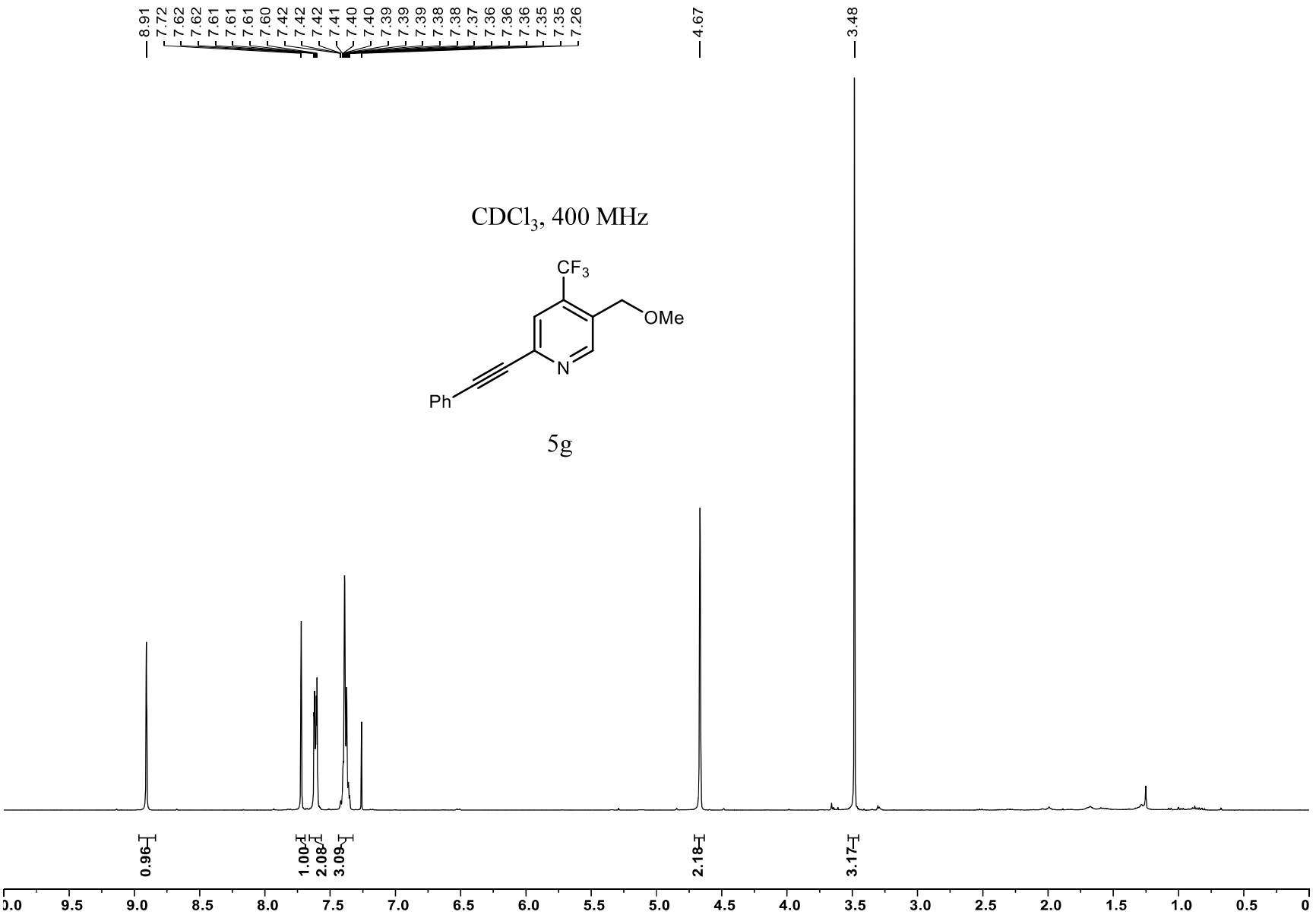


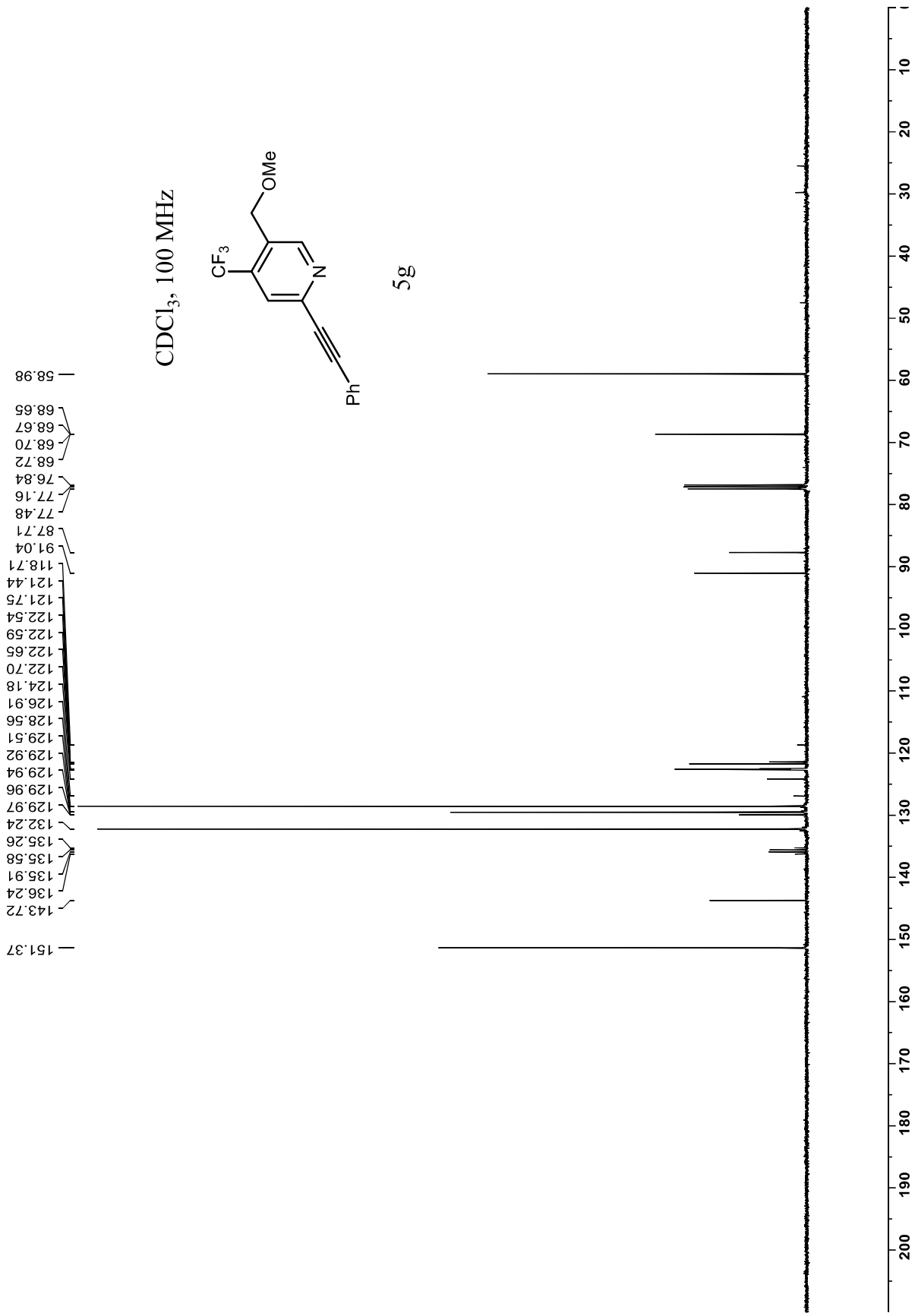
$CDCl_3$, 376 MHz

16.8

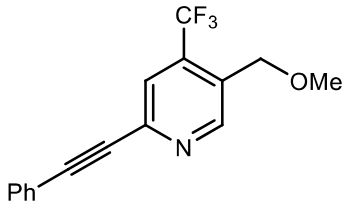
1

5f

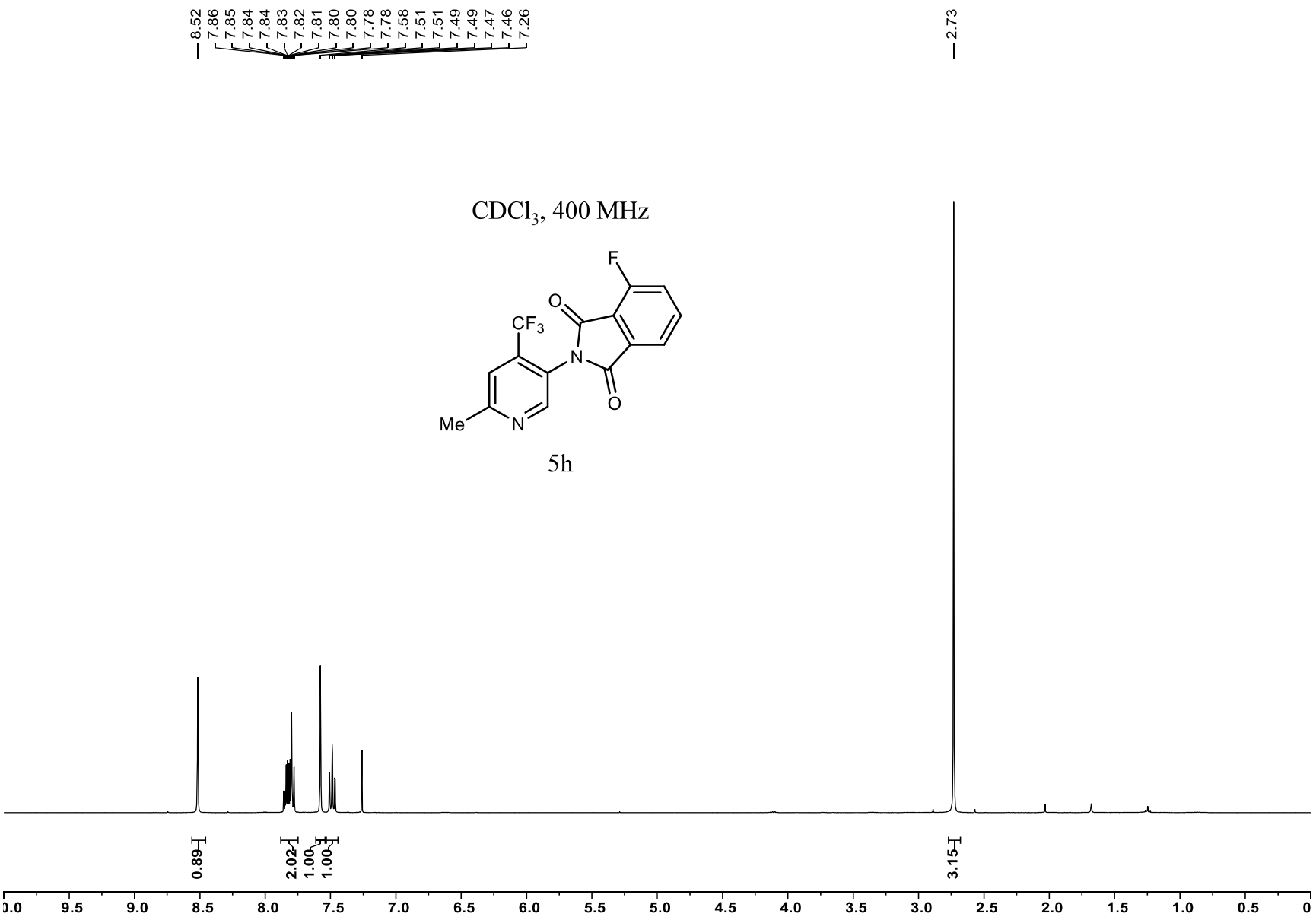

8.91
7.72
7.62
7.62
7.61
7.61
7.61
7.60
7.42
7.42
7.42
7.41
7.40
7.40
7.39
7.39
7.39
7.38
7.38
7.37
7.36
7.36
7.36
7.35
7.35
7.26
4.67
3.48
CDCl3, 400 MHz
CF3
OMe
N
Ph
5g
0.96
1.00
2.08
3.09
2.18
3.17
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


CDCl3, 100 MHz
5g
CF3
OMe
N
Ph
58.98
68.65
68.67
68.70
68.72
76.84
77.16
77.48
87.71
91.04
118.71
121.44
121.75
122.54
122.59
122.65
122.70
124.18
126.91
128.56
129.51
129.92
129.94
129.96
129.97
132.24
135.26
135.58
135.91
136.24
143.72
151.37

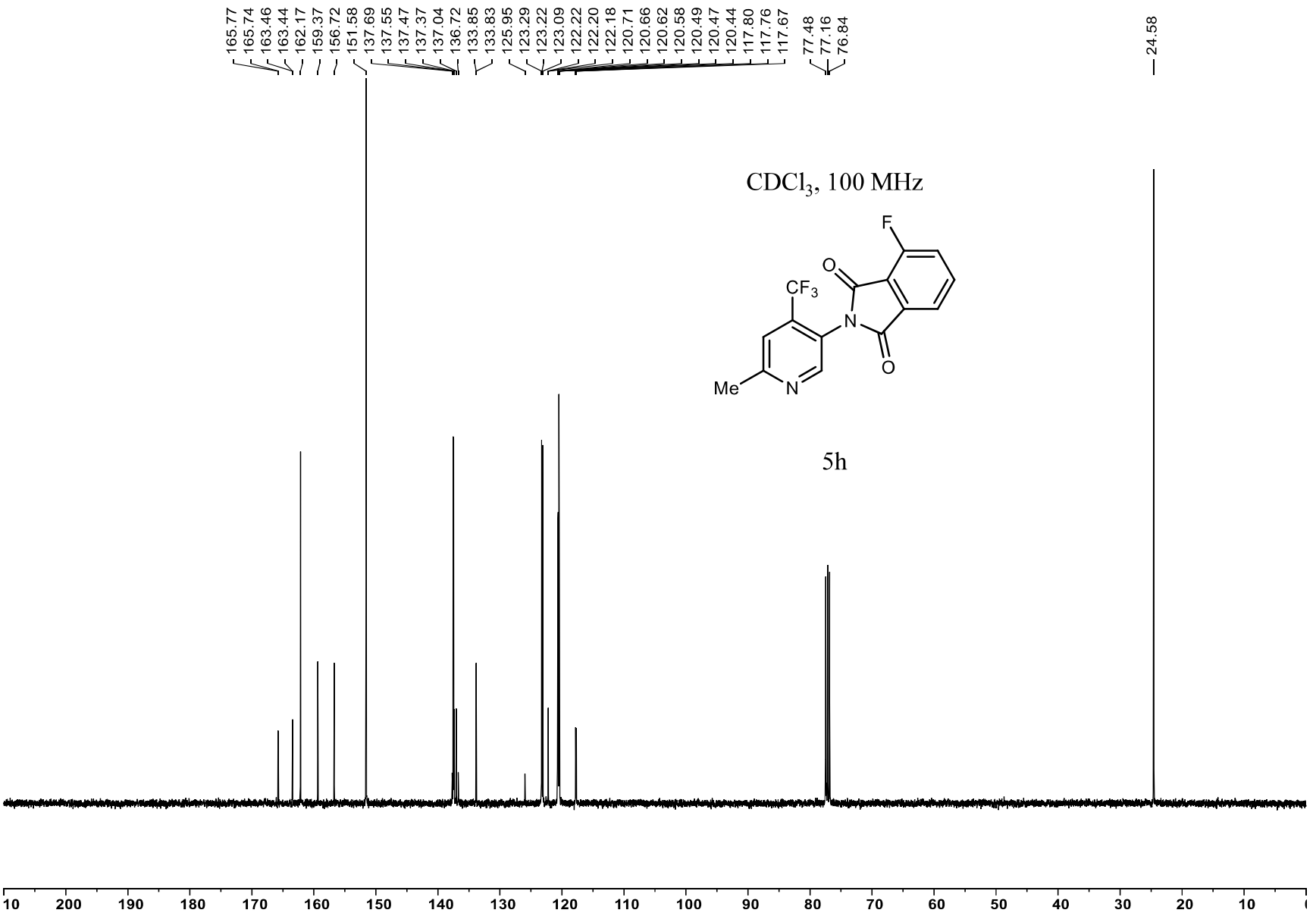
$CDCl_3$, 376 MHz

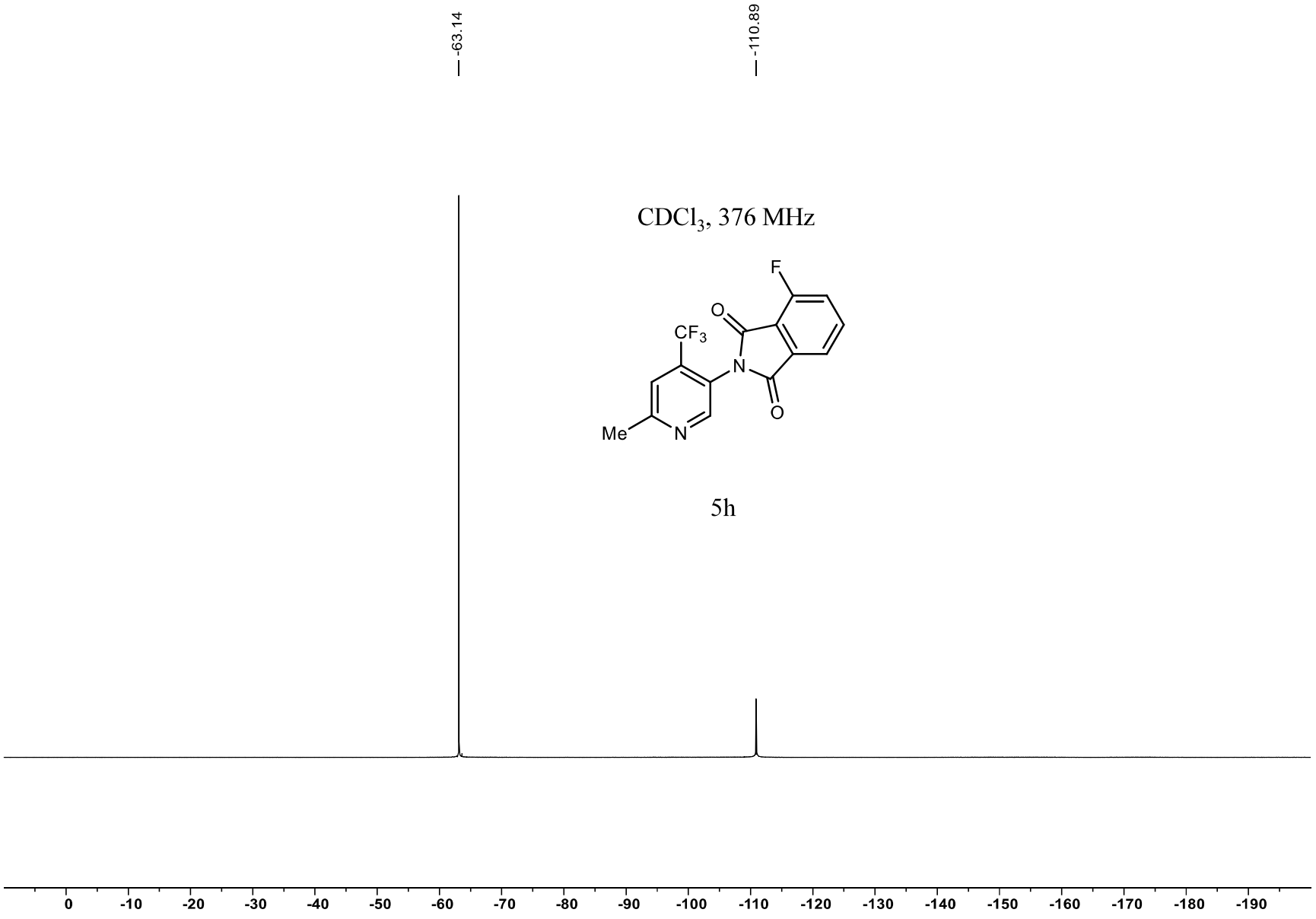


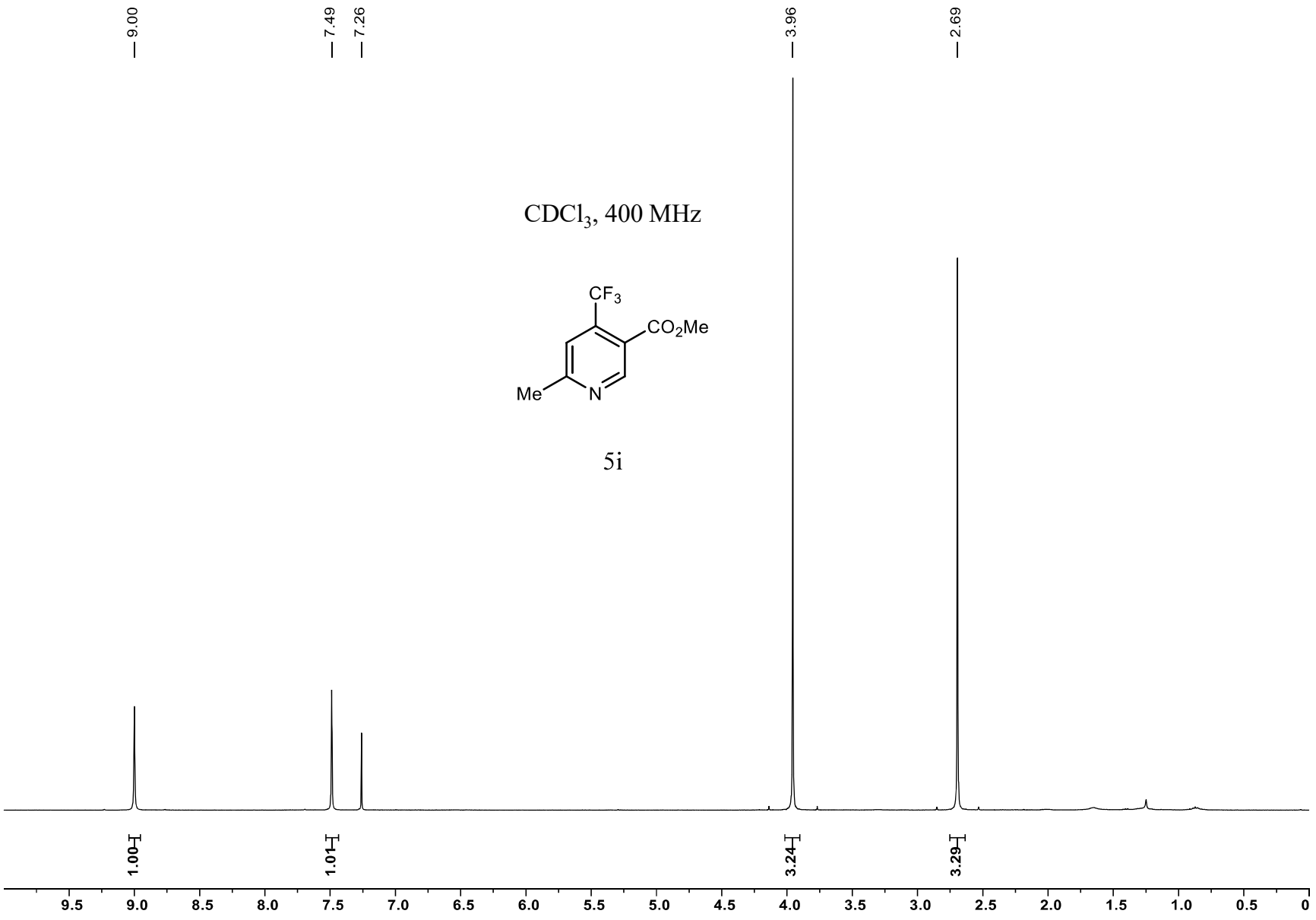
5g

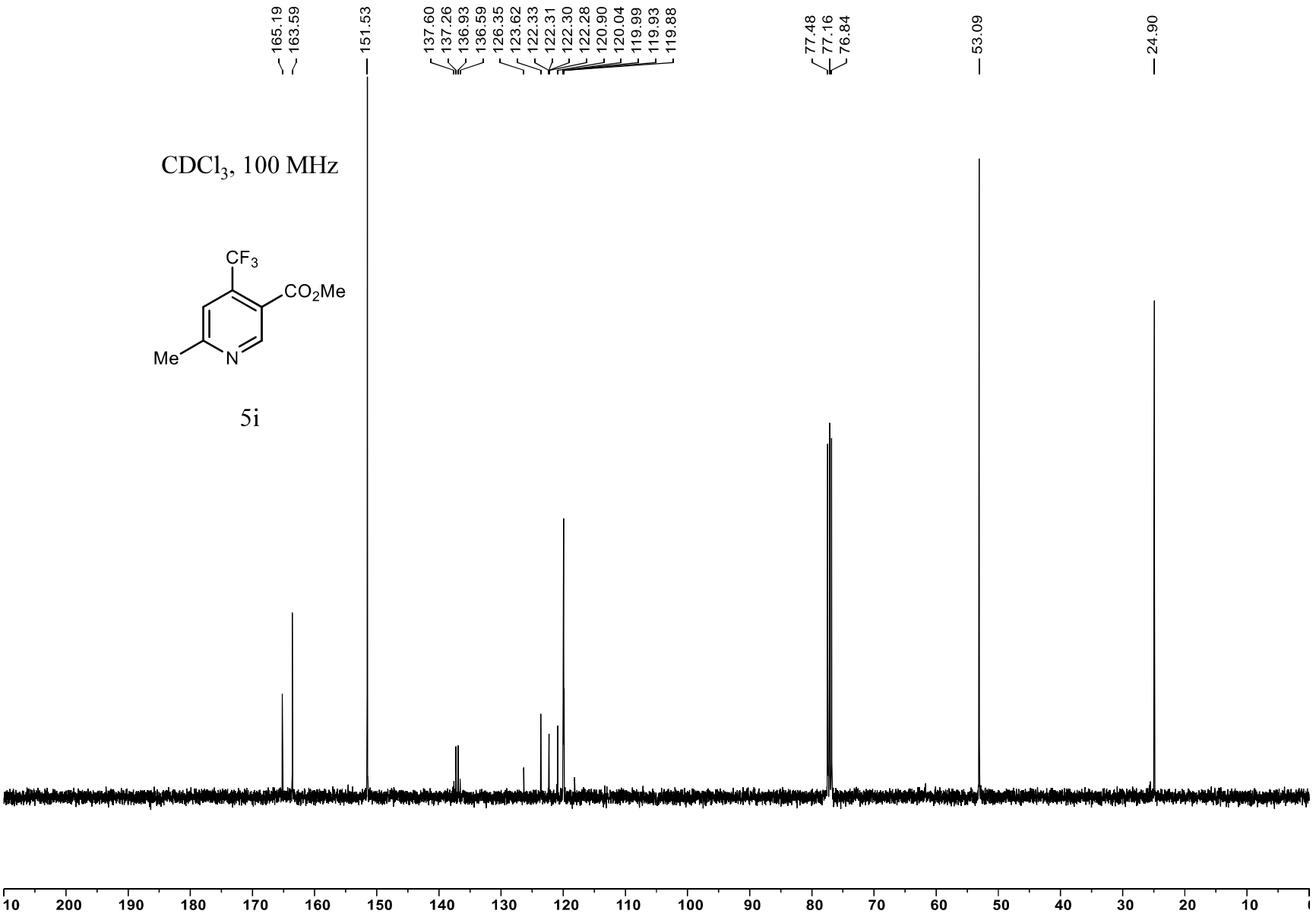

8.52
7.86
7.85
7.84
7.84
7.83
7.82
7.81
7.80
7.80
7.78
7.78
7.58
7.51
7.51
7.49
7.49
7.47
7.46
7.26
2.73
CDCl3, 400 MHz
F
O
CF3
N
O
Me
N
0.89
2.02
1.00
1.00
3.15
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

5h

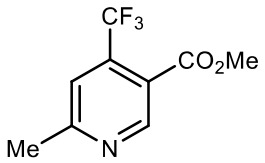

165.77
165.74
163.46
163.44
162.17
159.37
156.72
151.58
137.69
137.55
137.47
137.37
137.04
136.72
133.85
133.83
125.95
123.29
123.22
123.09
122.22
122.20
122.18
120.71
120.66
120.62
120.58
120.49
120.47
120.44
117.80
117.76
117.67
77.48
77.16
76.84
24.58
CDCl3, 100 MHz
F
O
CF3
N
O
Me
N
5h
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


-63.14
-110.89
CDCl3, 376 MHz
F
O
CF3
N
O
Me
N
5h
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

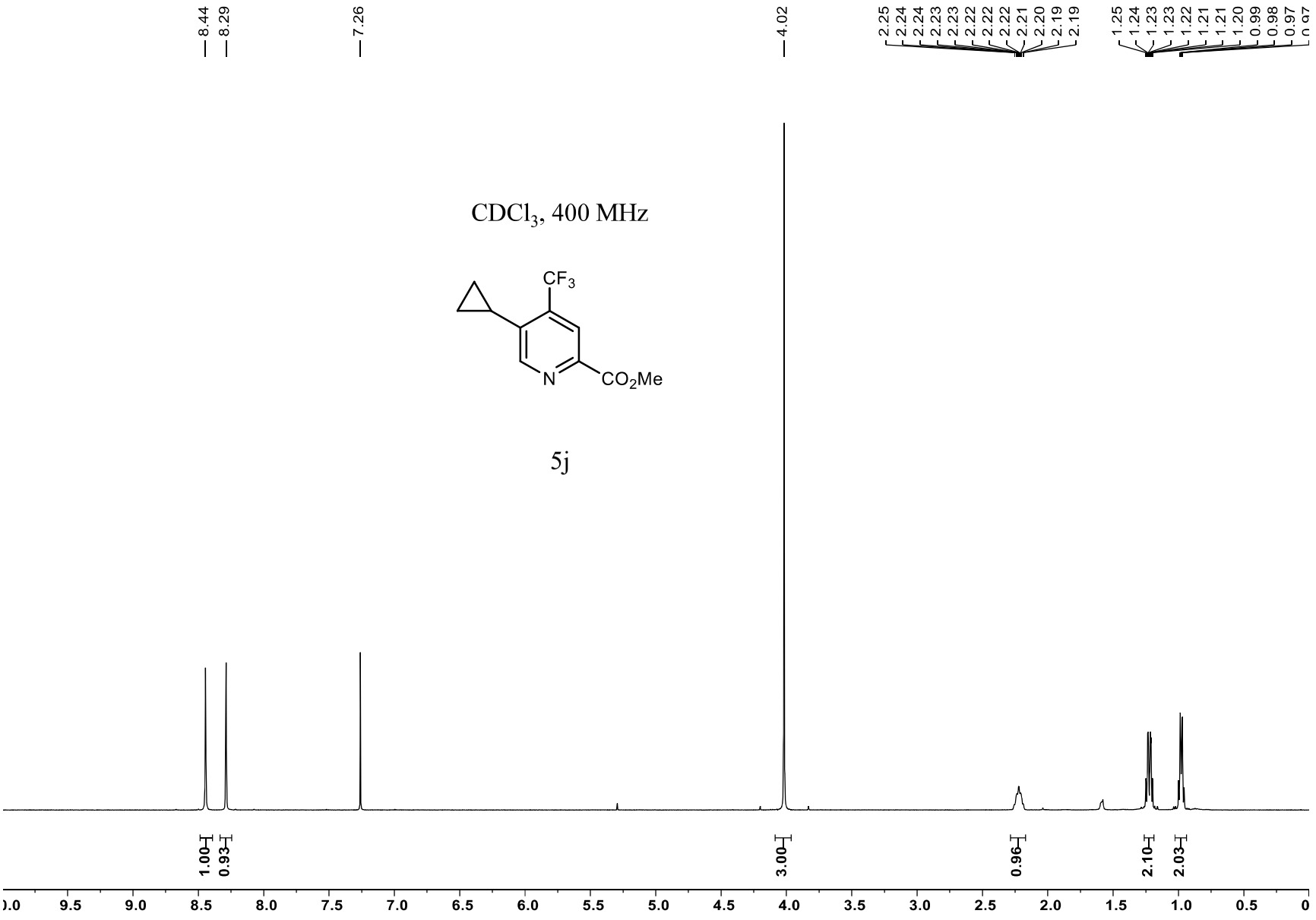

9.00
7.49
7.26
3.96
2.69
CDCl3, 400 MHz
CF3
CO2Me
Me
N
5i
1.00
1.01
3.24
3.29
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

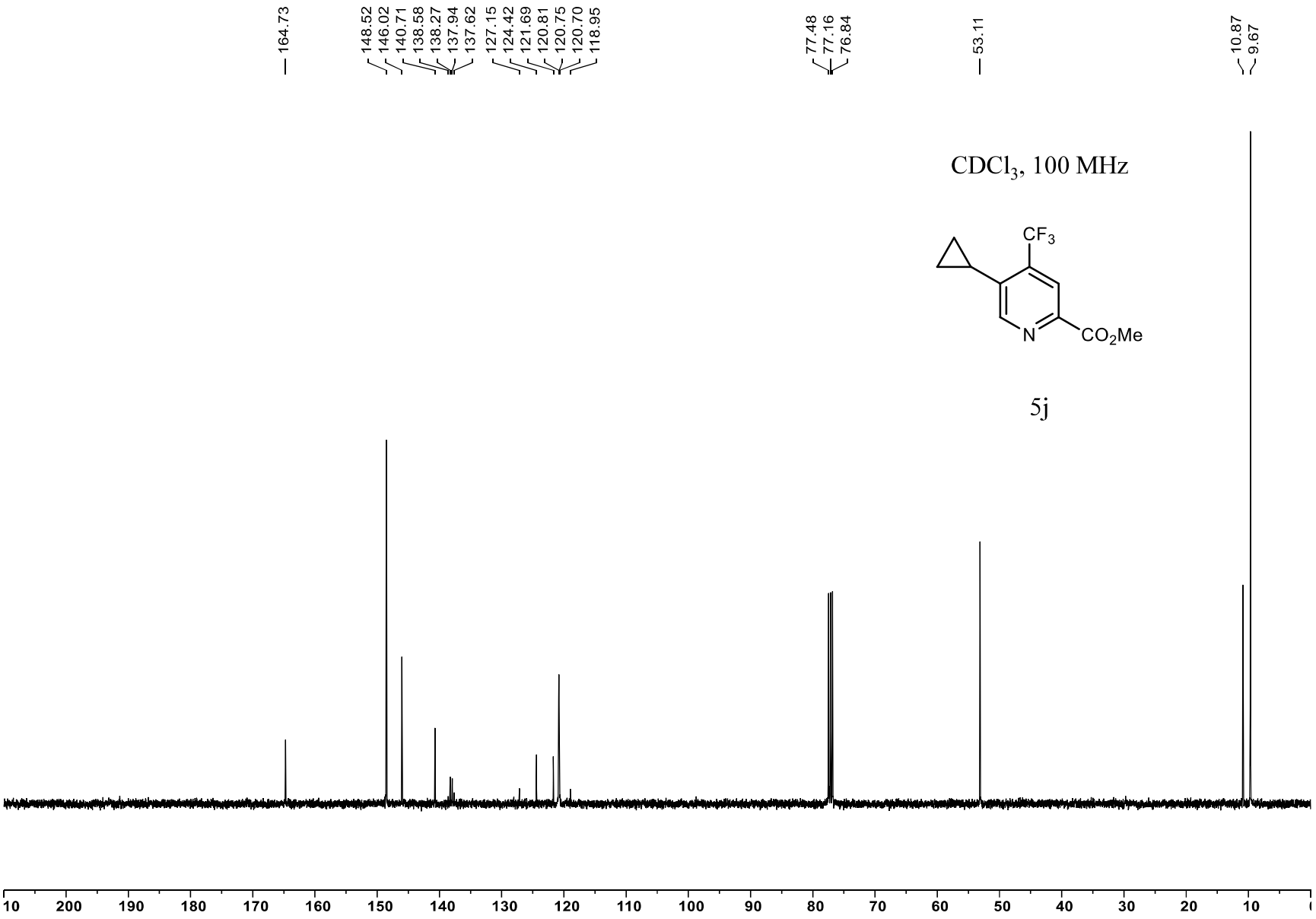

165.19
163.59
151.53
137.60
137.26
136.93
136.59
126.35
123.62
122.33
122.31
122.30
122.28
120.90
120.04
119.99
119.93
119.88
77.48
77.16
76.84
53.09
24.90
CDCl3, 100 MHz
CF3
CO2Me
Me
N
5i
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

$CDCl_3$, 376 MHz

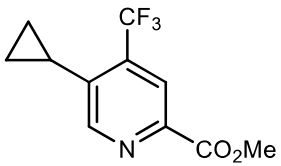


5i

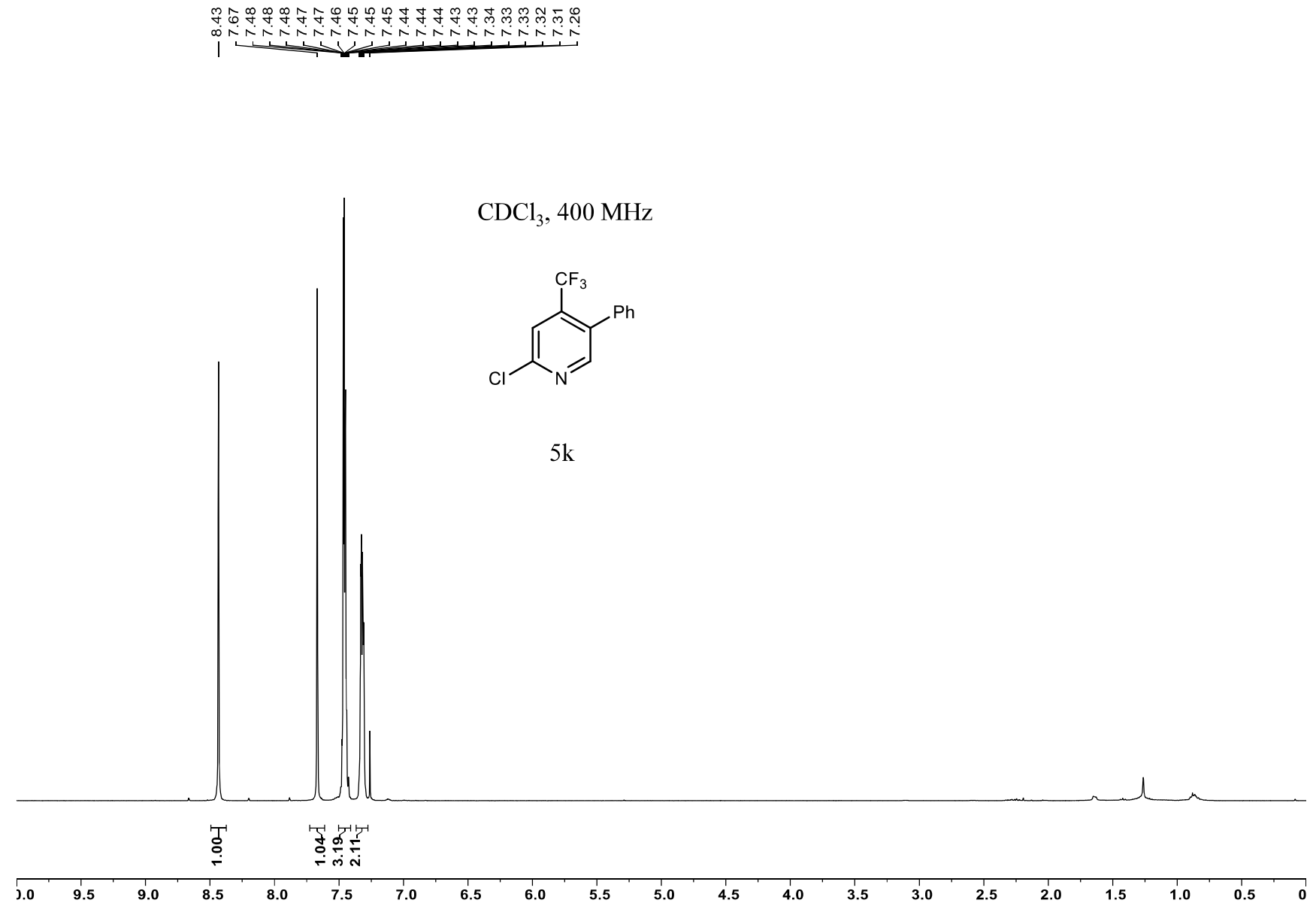

8.44
8.29
7.26
4.02
2.25
2.24
2.24
2.23
2.23
2.22
2.22
2.22
2.21
2.20
2.19
2.19
1.25
1.24
1.23
1.23
1.22
1.21
1.21
1.20
0.99
0.98
0.97
CDCl3, 400 MHz
CF3
N
CO2Me
5j
1.00
0.93
3.00
0.96
2.10
2.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

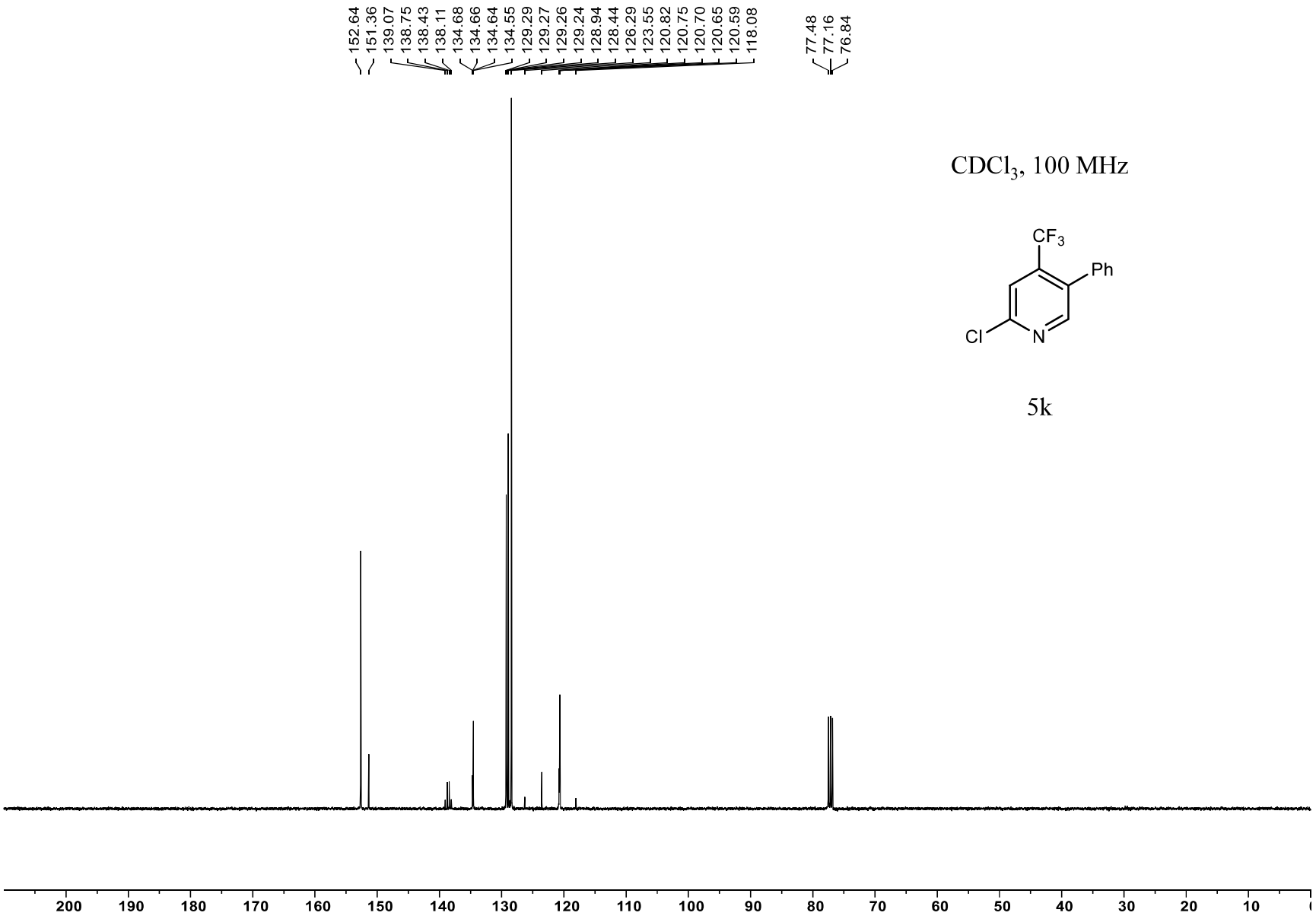

164.73
148.52
146.02
140.71
138.58
138.27
137.94
137.62
127.15
124.42
121.69
120.81
120.75
120.70
118.95
77.48
77.16
76.84
53.11
10.87
9.67
CDCl3, 100 MHz
CF3
N
CO2Me
5j
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

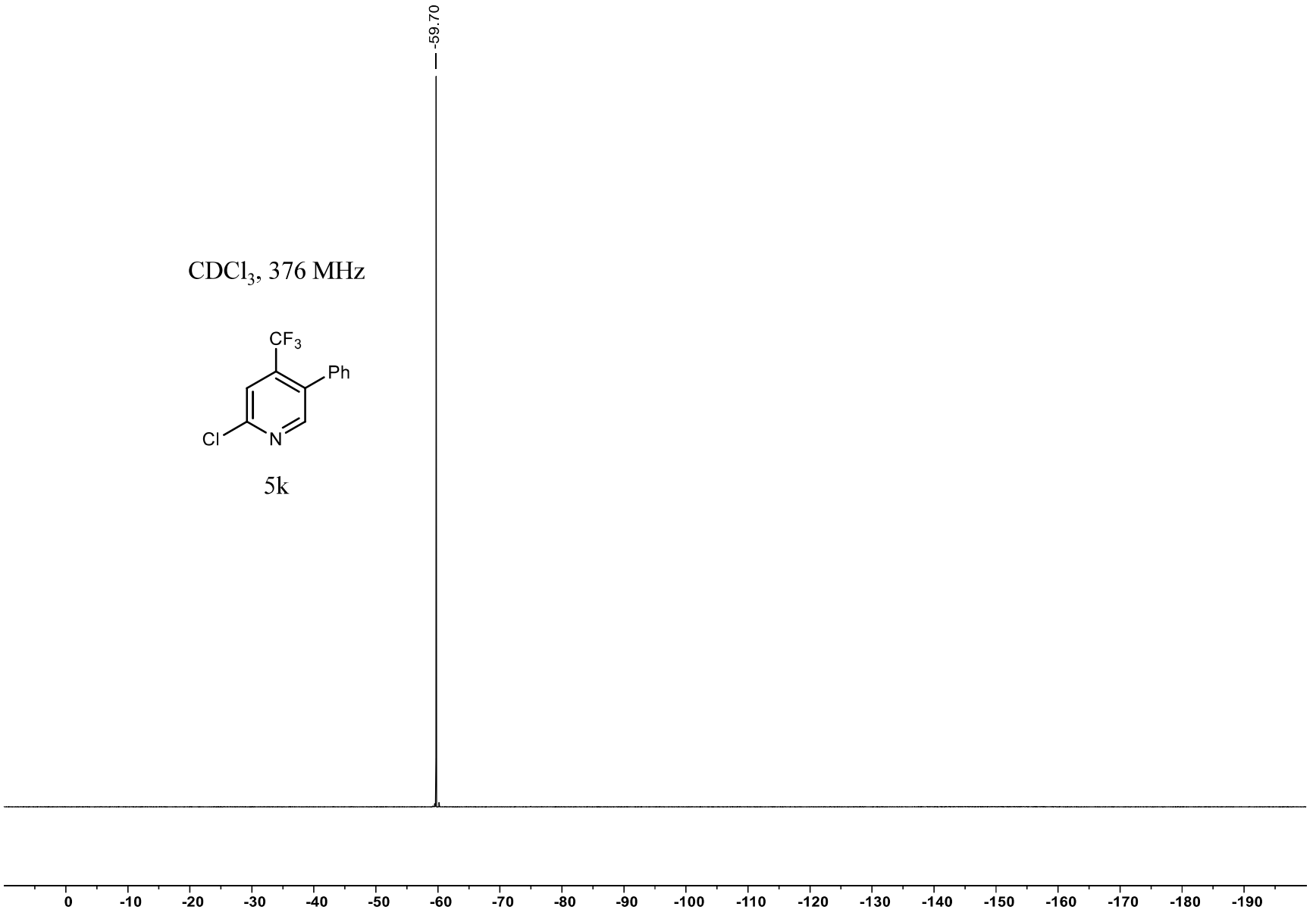
$CDCl_3$, 376 MHz

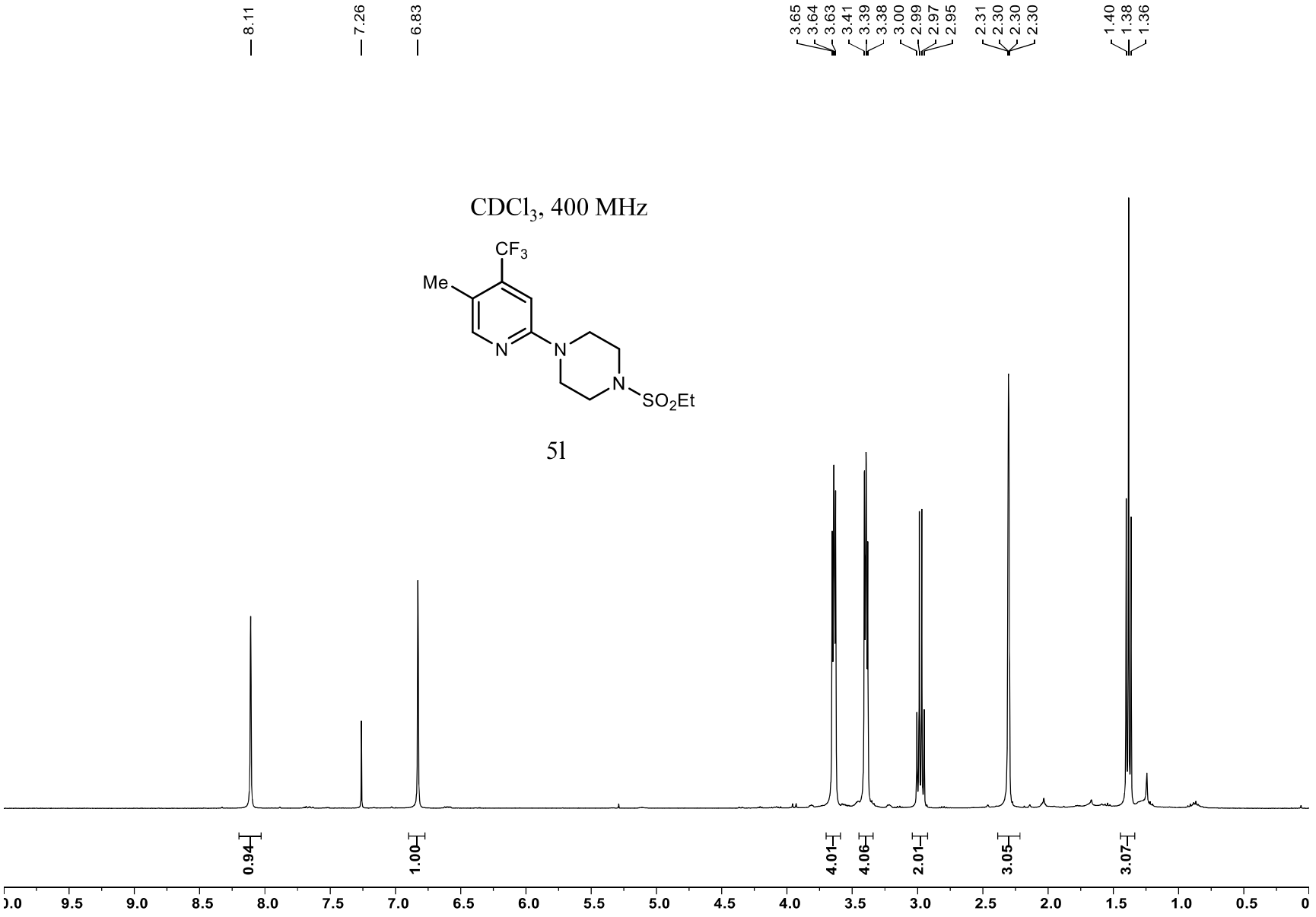


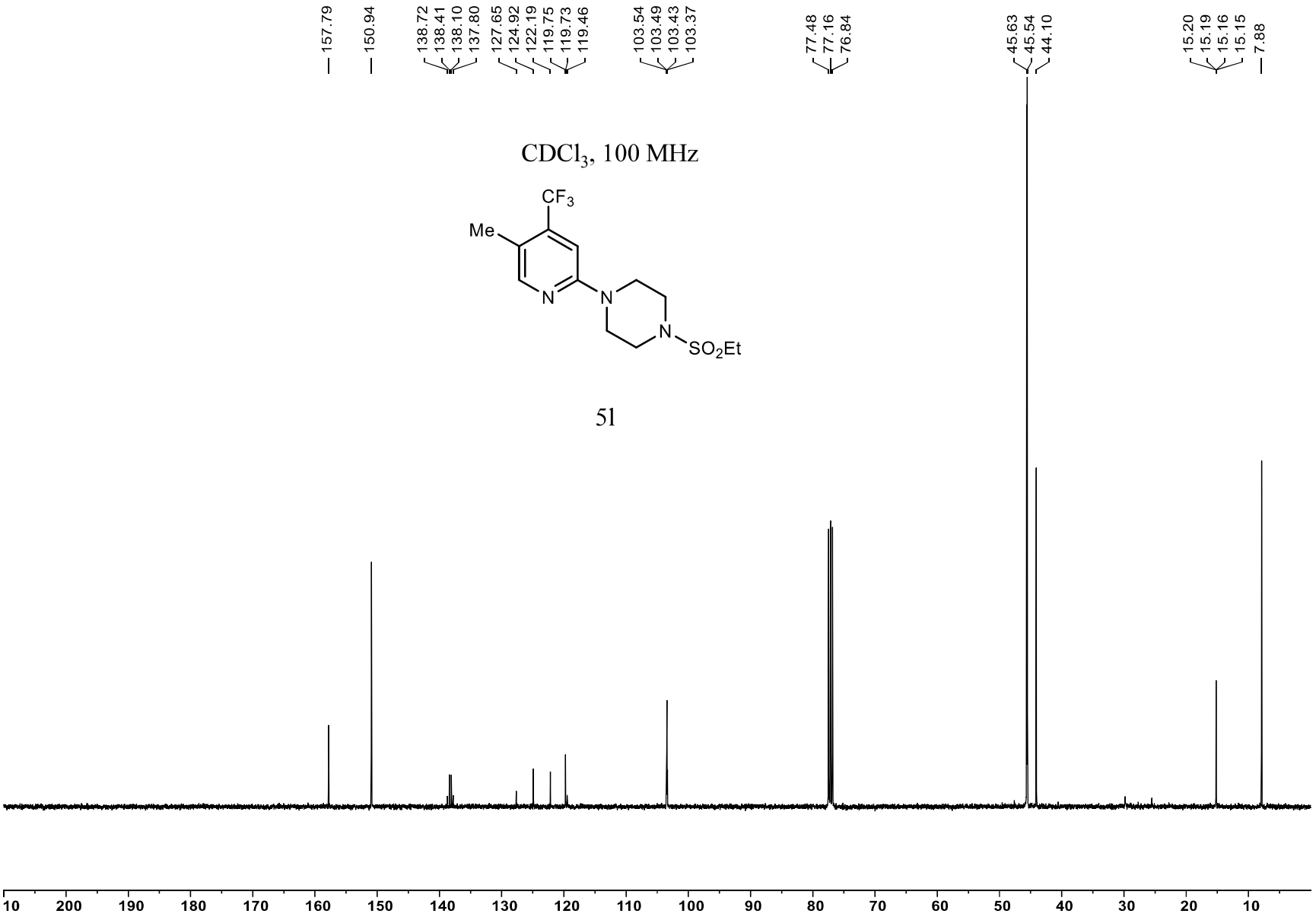
5j


8.43
7.67
7.48
7.48
7.48
7.47
7.47
7.46
7.45
7.45
7.45
7.44
7.44
7.44
7.43
7.43
7.34
7.33
7.33
7.32
7.31
7.26
CDCl3, 400 MHz
CF3
Ph
Cl
N
5k
1.00
1.04
3.19
2.11
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


152.64
151.36
139.07
138.75
138.43
138.11
134.68
134.66
134.64
134.55
129.29
129.27
129.26
129.24
128.94
128.44
126.29
123.55
120.82
120.75
120.70
120.65
120.59
118.08
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
Ph
Cl
N
5k
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


-59.70
CDCl3, 376 MHz
CF3
Ph
Cl
N
5k
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

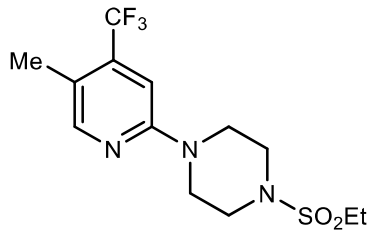

8.11
7.26
6.83
3.65
3.64
3.63
3.41
3.39
3.38
3.00
2.99
2.97
2.95
2.31
2.30
2.30
2.30
1.40
1.38
1.36
CDCl3, 400 MHz
CF3
Me
N
N
N
SO2Et
51
0.94
1.00
4.01
4.06
2.01
3.05
3.07


157.79
150.94
138.72
138.41
138.10
137.80
127.65
124.92
122.19
119.75
119.73
119.46
103.54
103.49
103.43
103.37
77.48
77.16
76.84
45.63
45.54
44.10
15.20
15.19
15.16
15.15
7.88
CDCl3, 100 MHz
CF3
Me
N
N
N
SO2Et
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

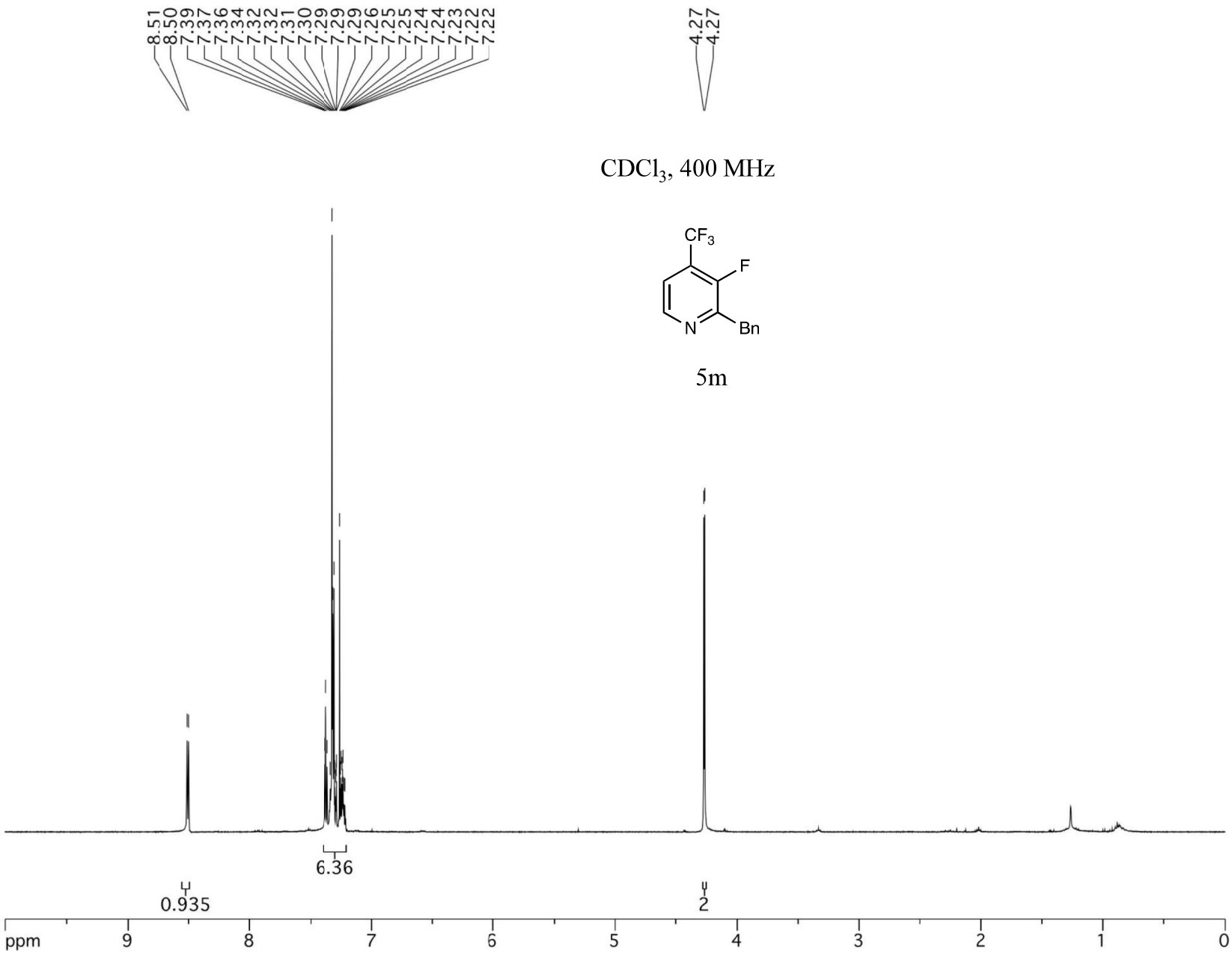
51

-64.34

$CDCl_3$, 376 MHz

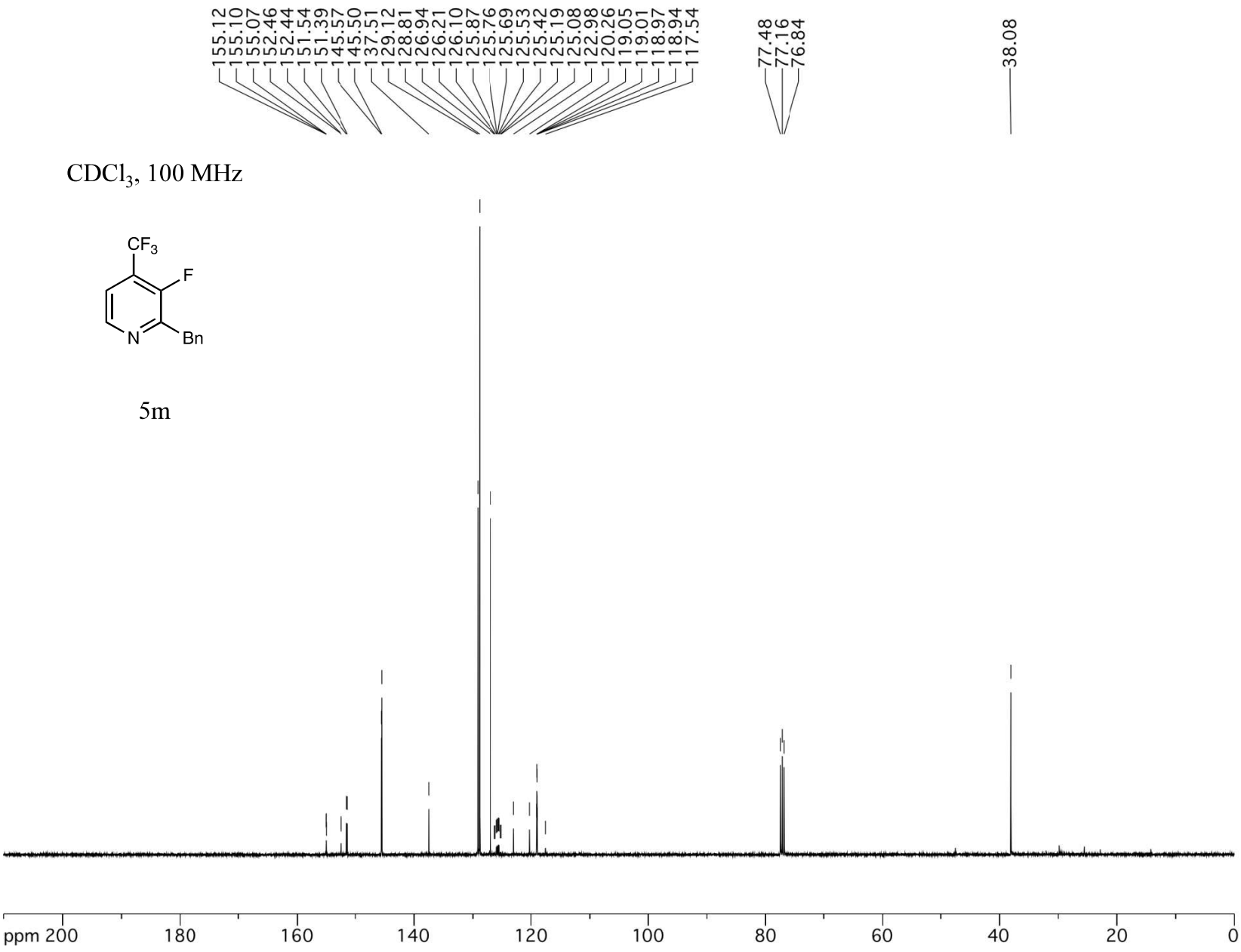


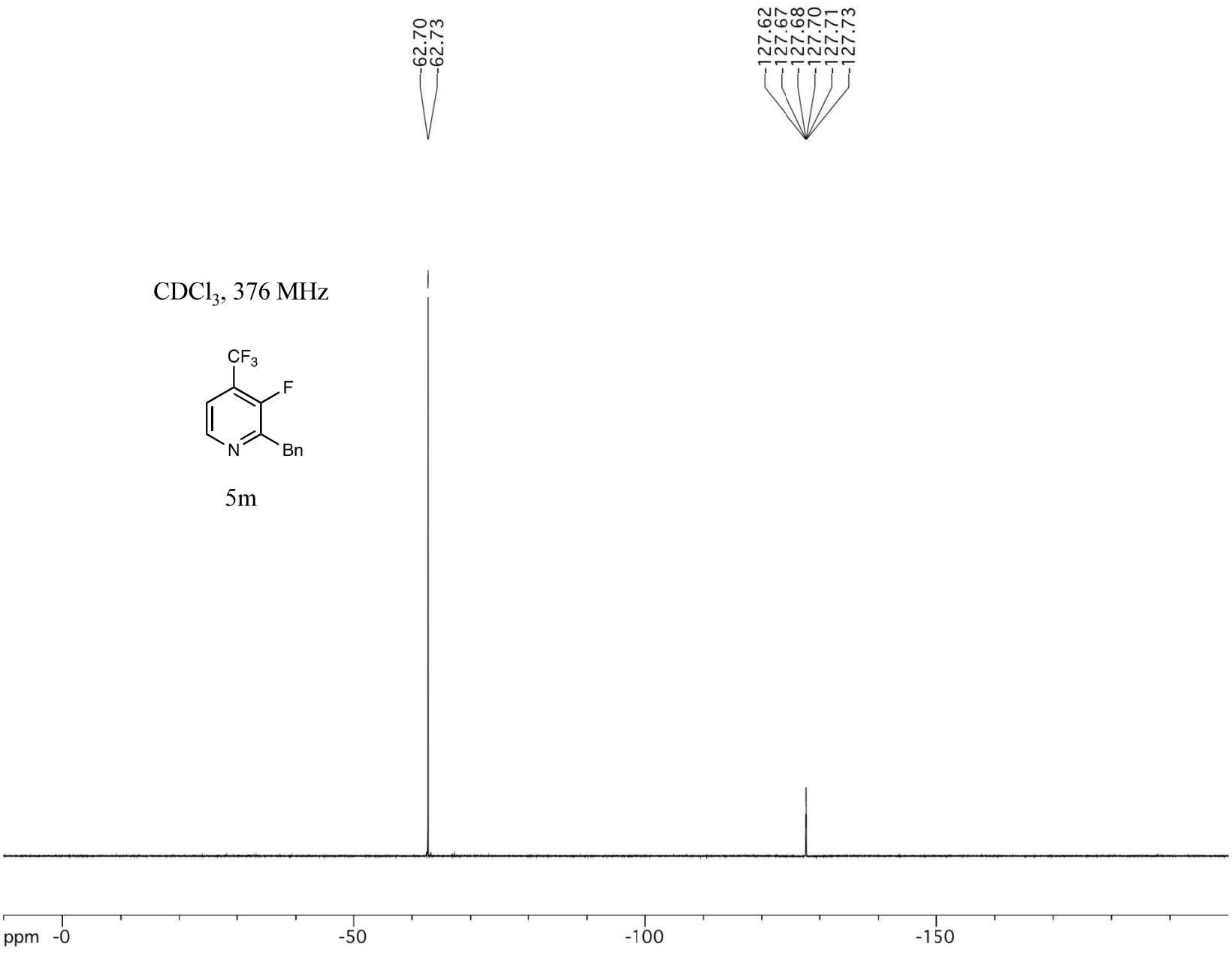
51

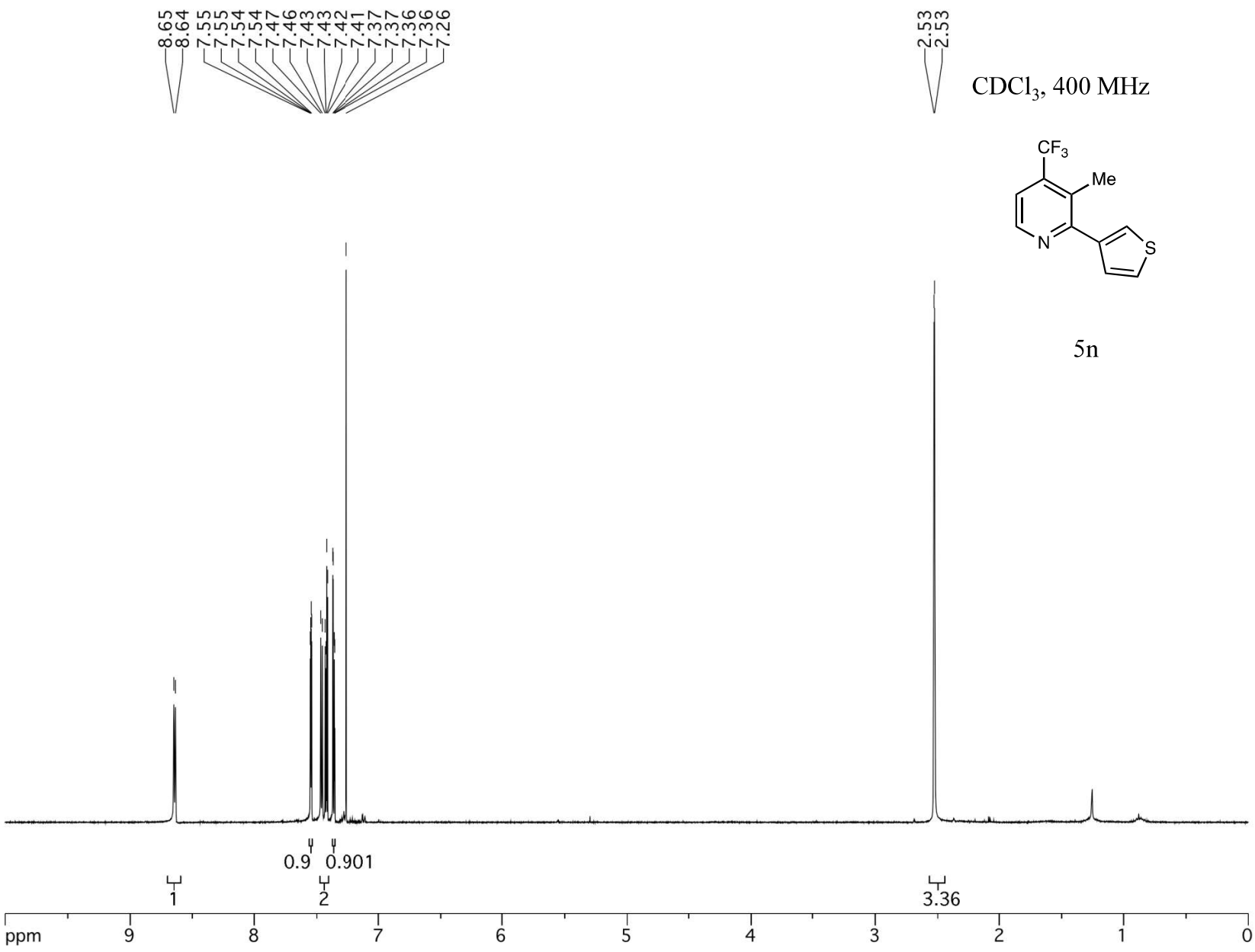


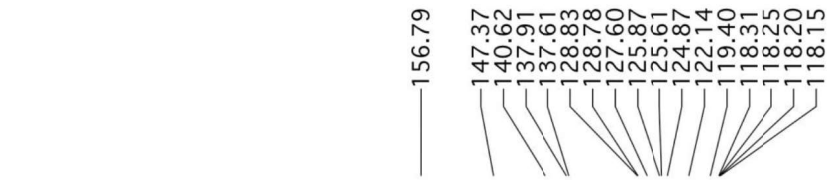
$CDCl_3$, 400 MHz

5m

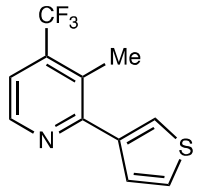

155.12
155.10
155.07
152.46
152.44
151.54
151.39
145.57
145.50
137.51
129.12
128.81
126.94
126.21
126.10
125.87
125.76
125.69
125.53
125.42
125.19
125.08
122.98
120.26
119.05
119.01
118.97
118.94
117.54
77.48
77.16
76.84
38.08
CDCl3, 100 MHz
CF3
F
N
Bn
5m
ppm 200
180
160
140
120
100
80
60
40
20
0


62.70
62.73
127.62
127.67
127.68
127.70
127.71
127.73
CDCl3, 376 MHz
CF3
F
N
Bn
5m
ppm -0
-50
-100
-150

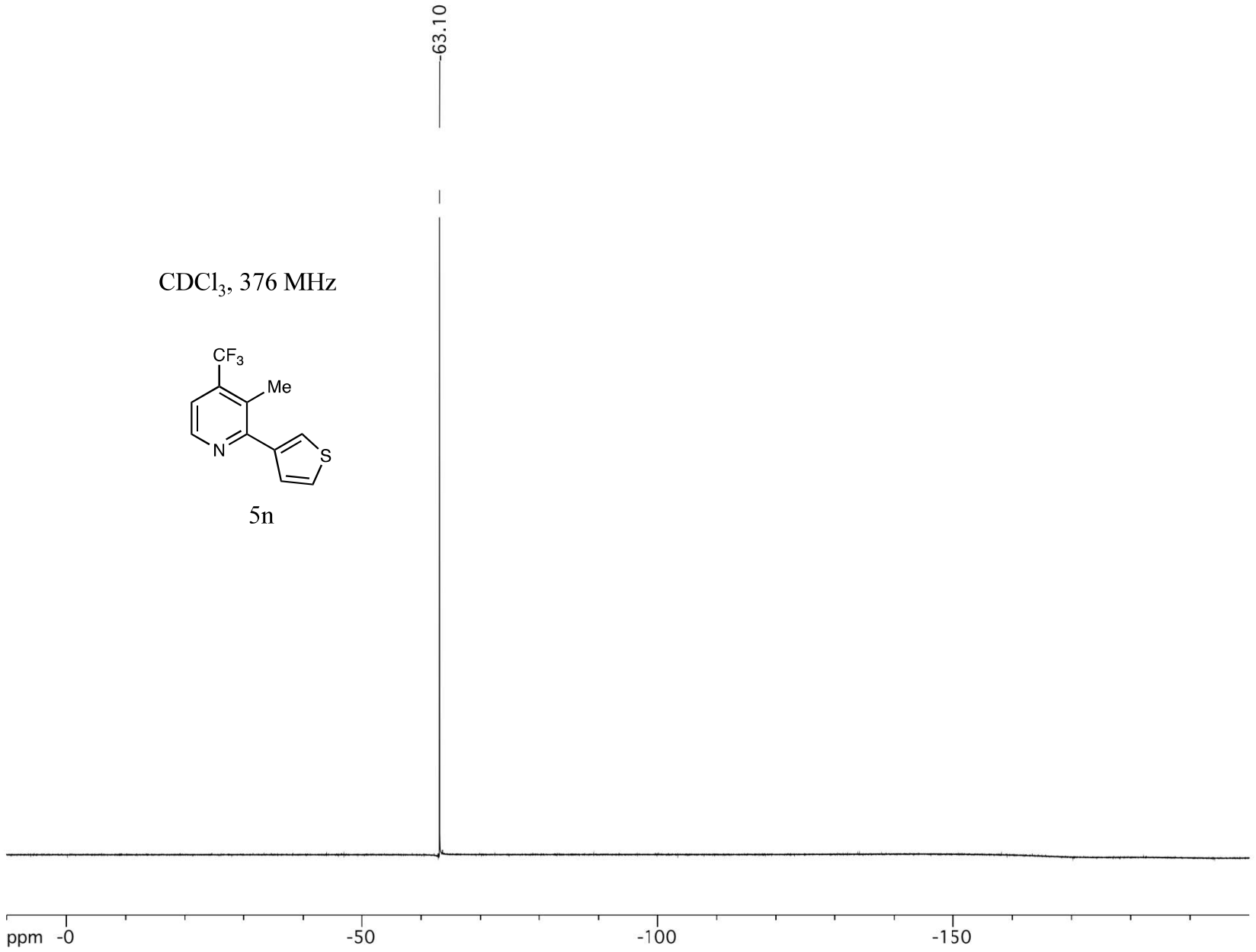

8.65
8.64
7.55
7.55
7.54
7.54
7.47
7.46
7.43
7.43
7.42
7.41
7.37
7.37
7.36
7.36
7.26
2.53
2.53
CDCl3, 400 MHz
CF3
Me
N
S
5n
0.9
0.901
1
2
3.36
ppm
9
8
7
6
5
4
3
2
1
0

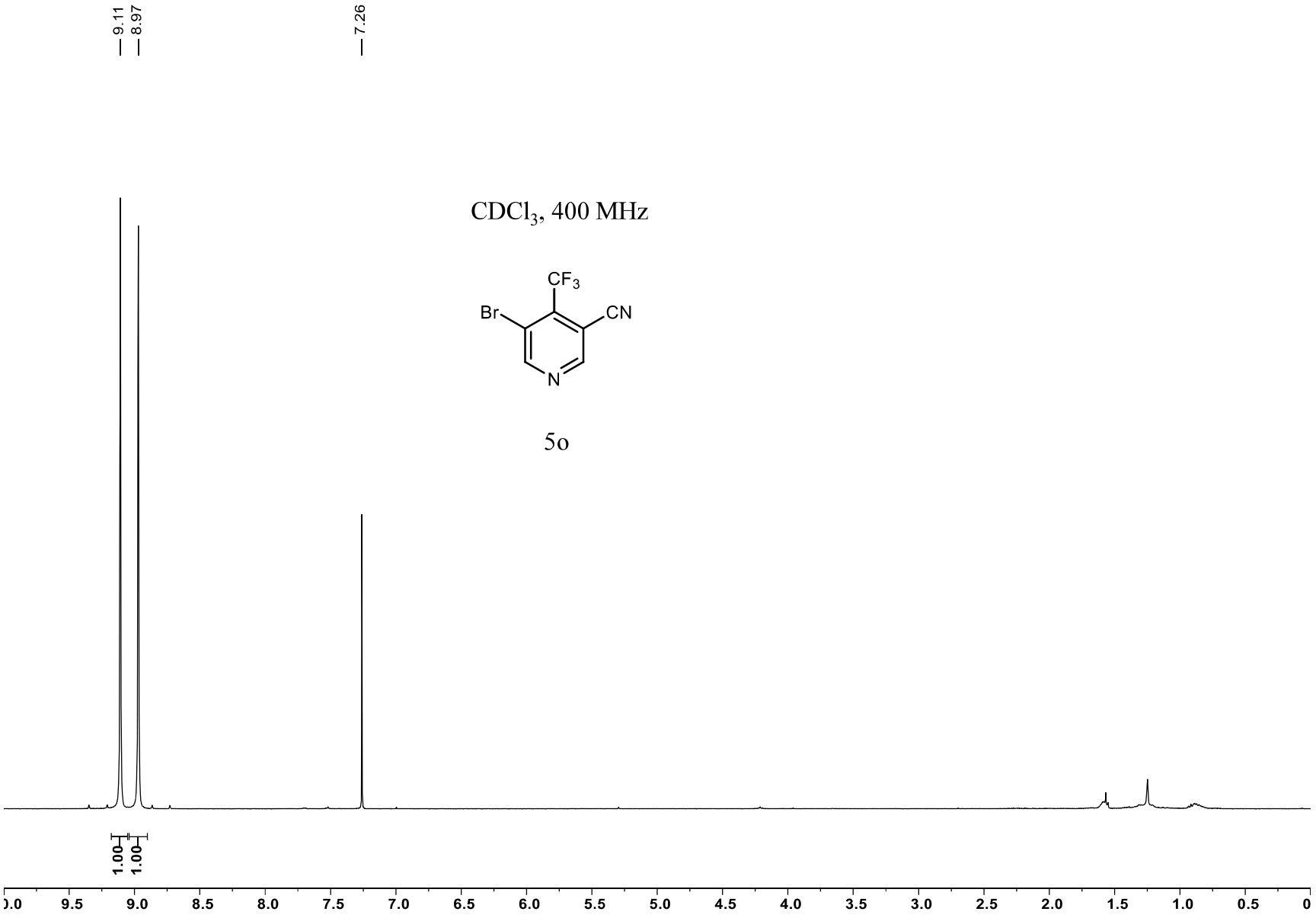


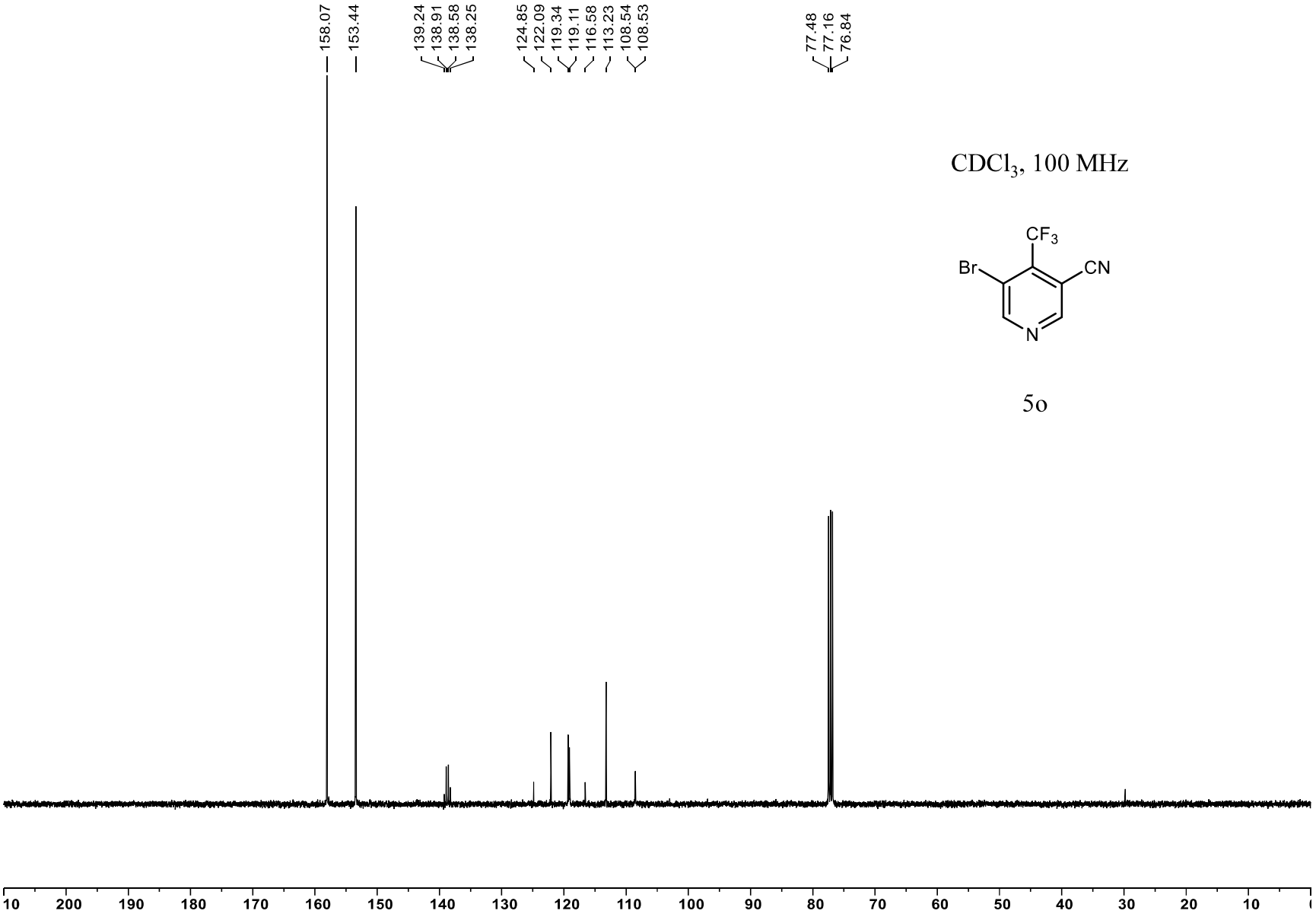
$CDCl_3$, 100 MHz

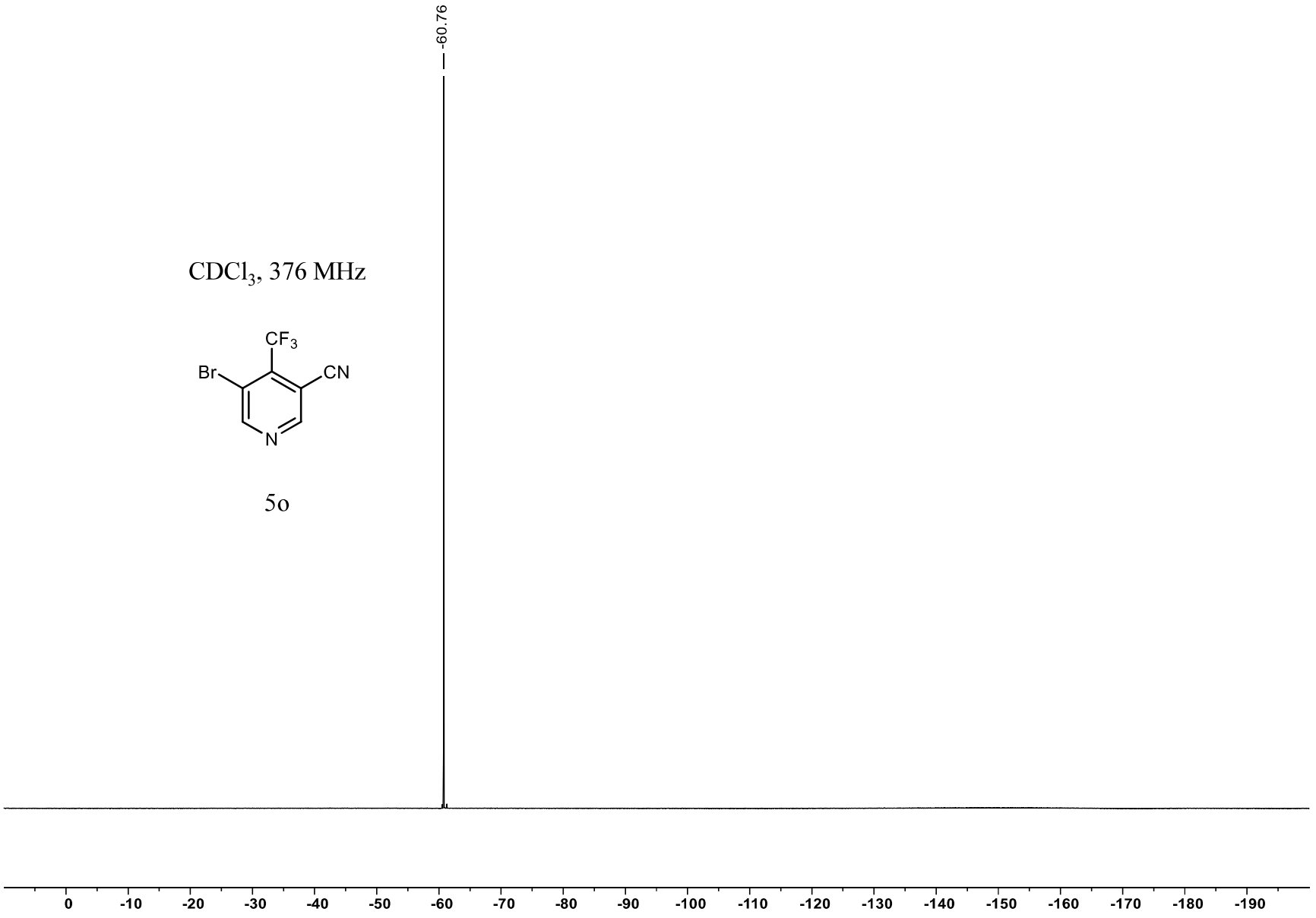


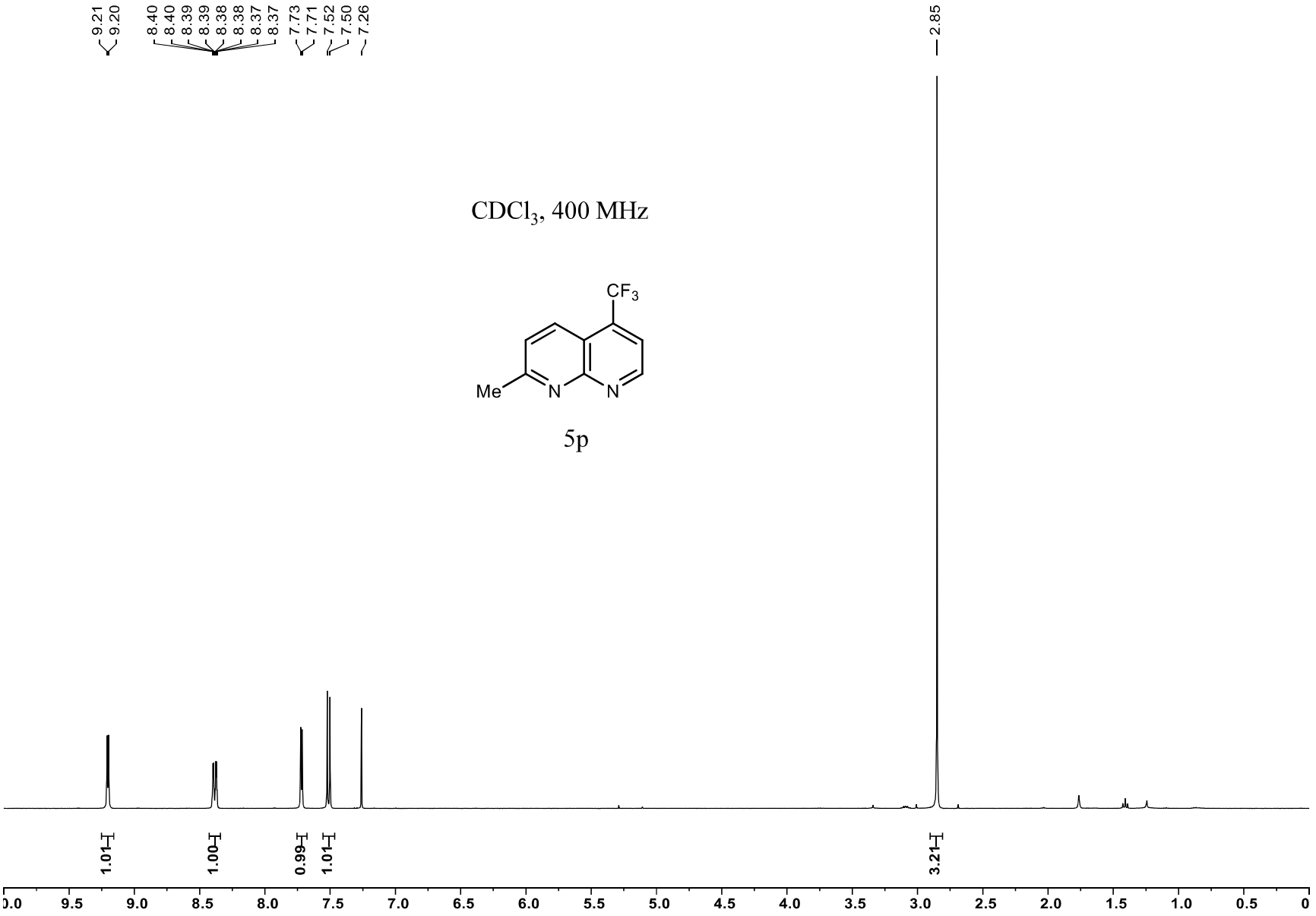
5n

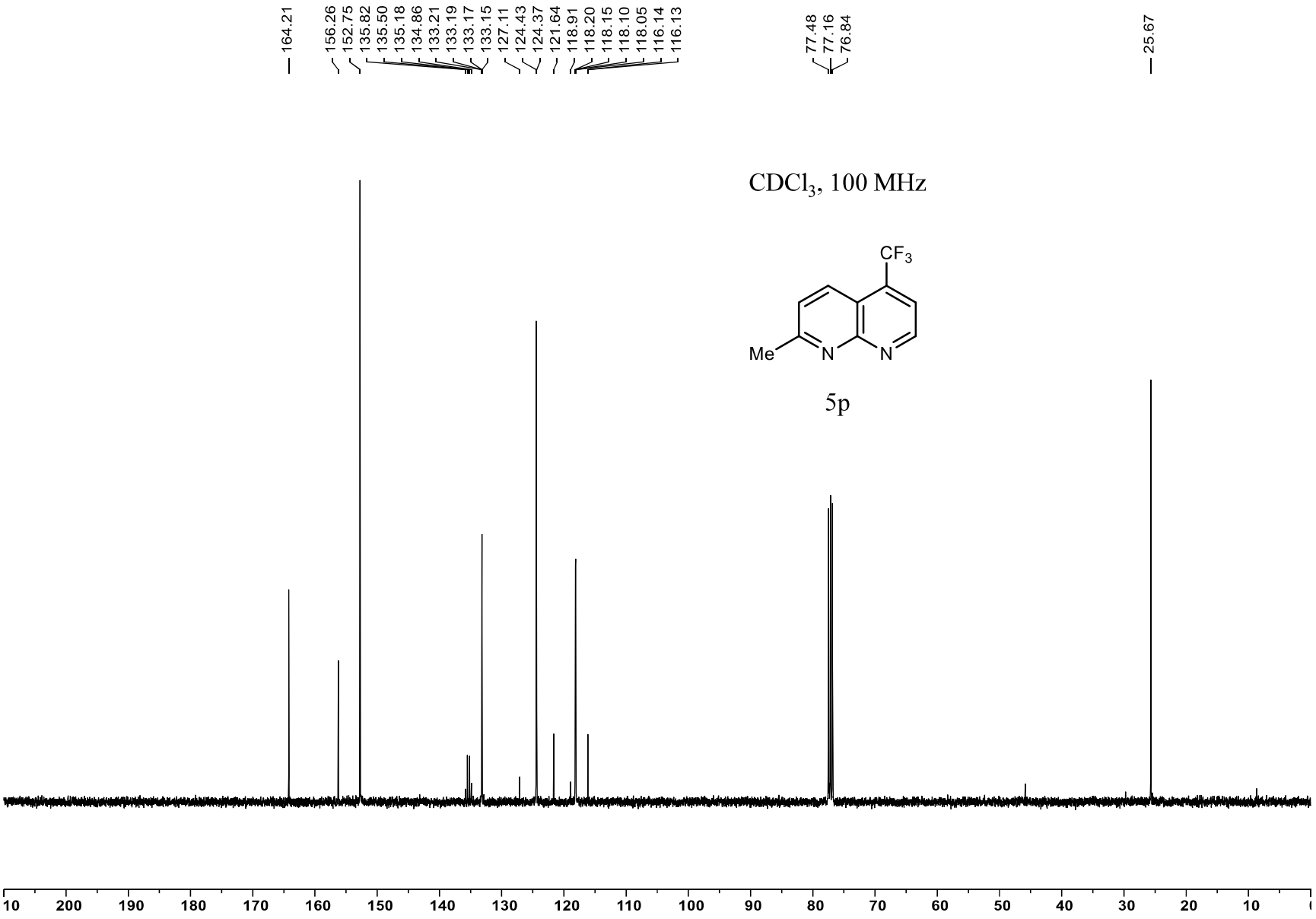

-63.10
CDCl3, 376 MHz
CF3
Me
N
S
5n
ppm -0
-50
-100
-150

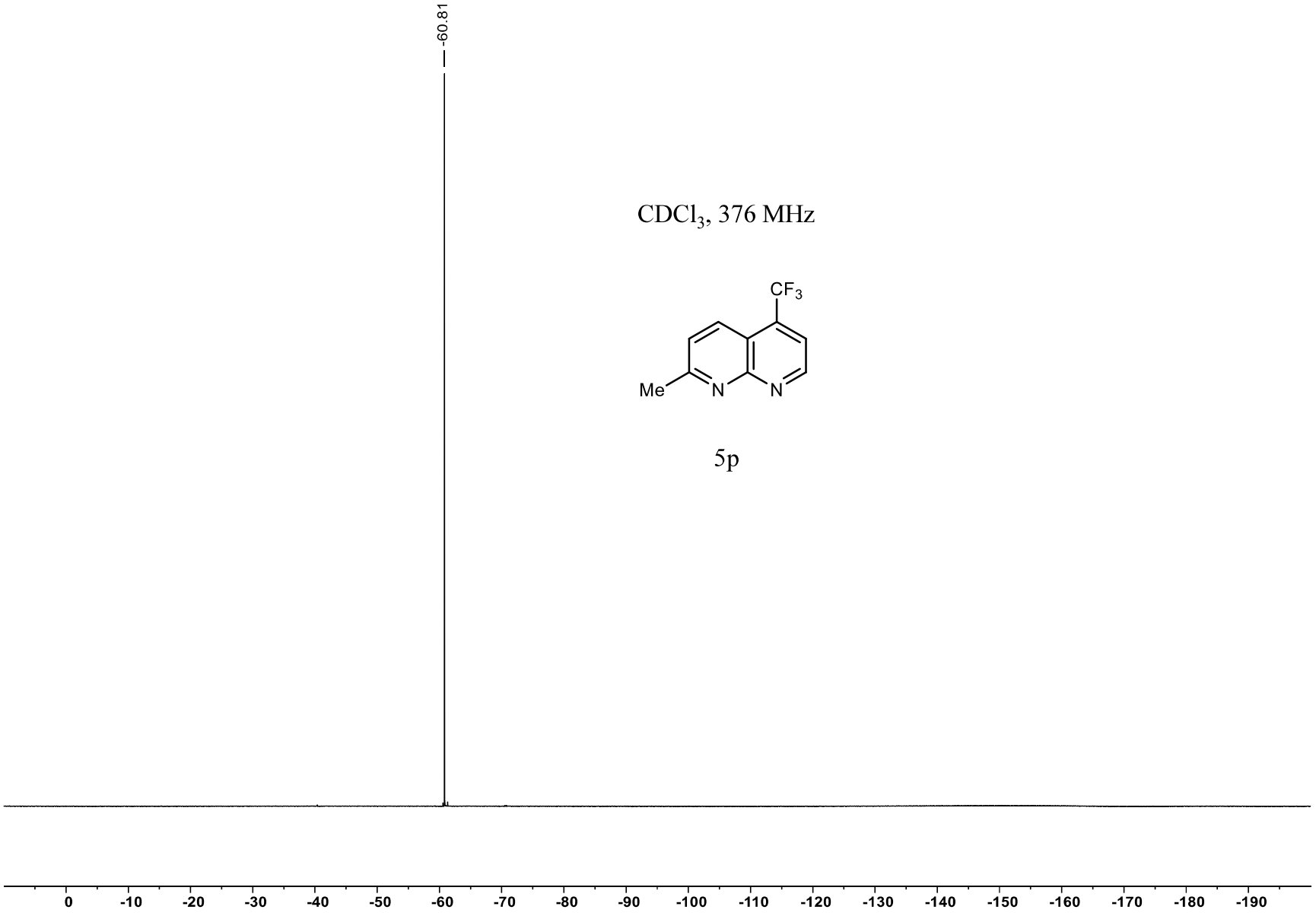

9.11
8.97
7.26
CDCl3, 400 MHz
CF3
Br
CN
N
5o
1.00
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


158.07
153.44
139.24
138.91
138.58
138.25
124.85
122.09
119.34
119.11
116.58
113.23
108.54
108.53
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
Br
CN
N
5o
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


-60.76
CDCl3, 376 MHz
CF3
Br
CN
N
5o
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

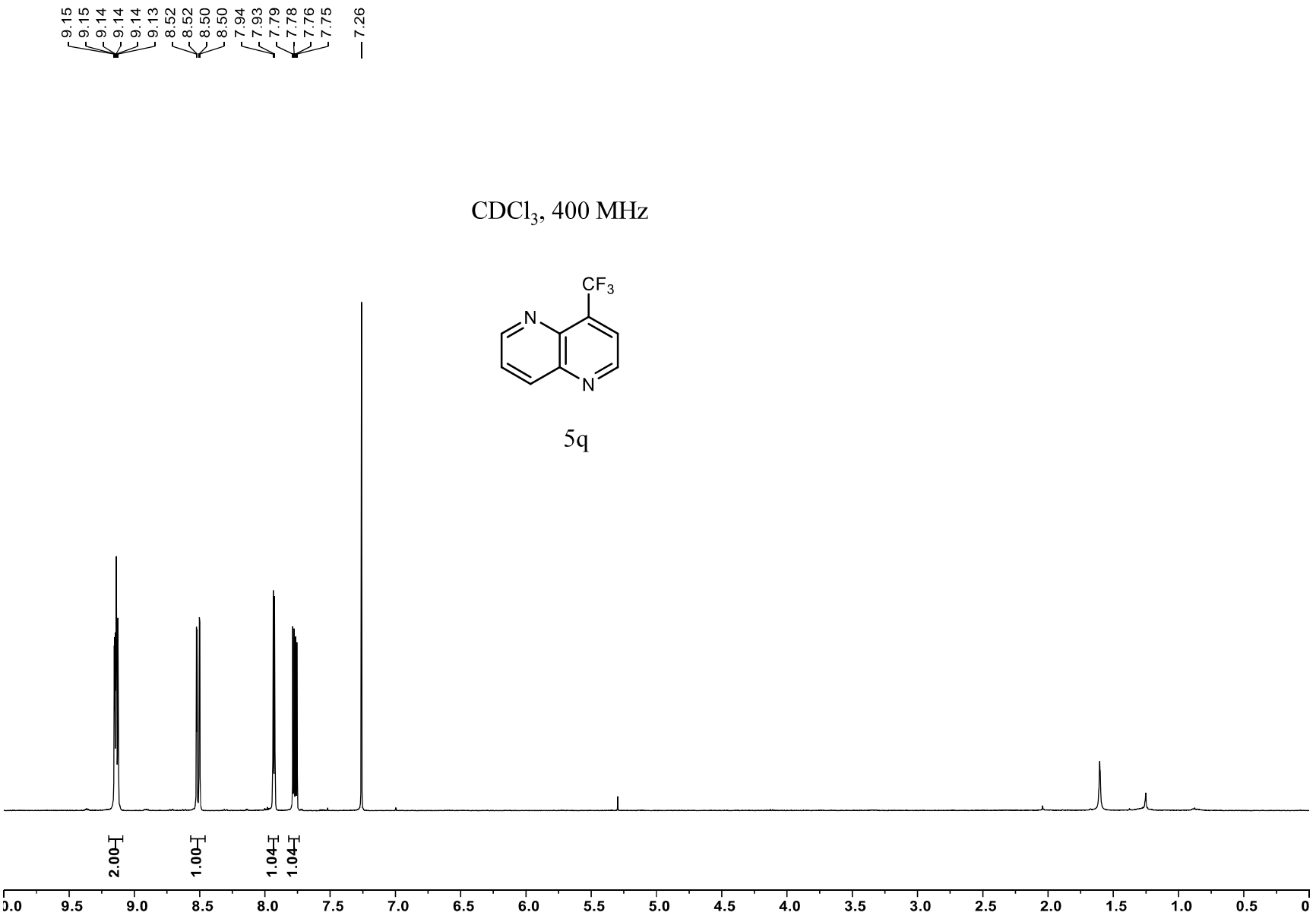

9.21
9.20
8.40
8.40
8.39
8.39
8.38
8.38
8.37
8.37
7.73
7.71
7.52
7.50
7.26
2.85
CDCl3, 400 MHz
CF3
Me
N
N
5p
1.01
1.00
0.99
1.01
3.21
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

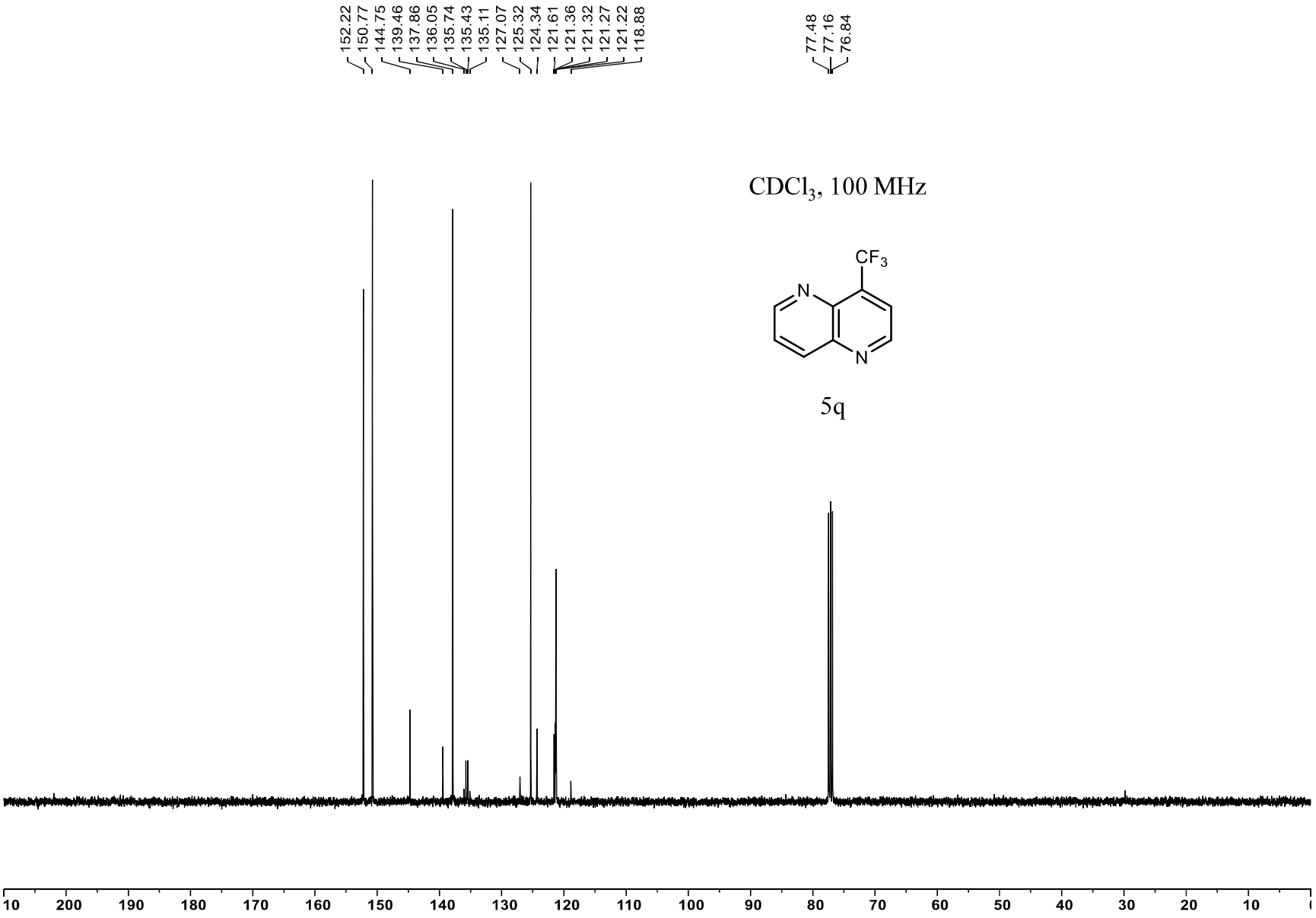

164.21
156.26
152.75
135.82
135.50
135.18
134.86
133.21
133.19
133.17
133.15
127.11
124.43
124.37
121.64
118.91
118.20
118.15
118.10
118.05
116.14
116.13
77.48
77.16
76.84
25.67
CDCl3, 100 MHz
CF3
Me
N
N
5p
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

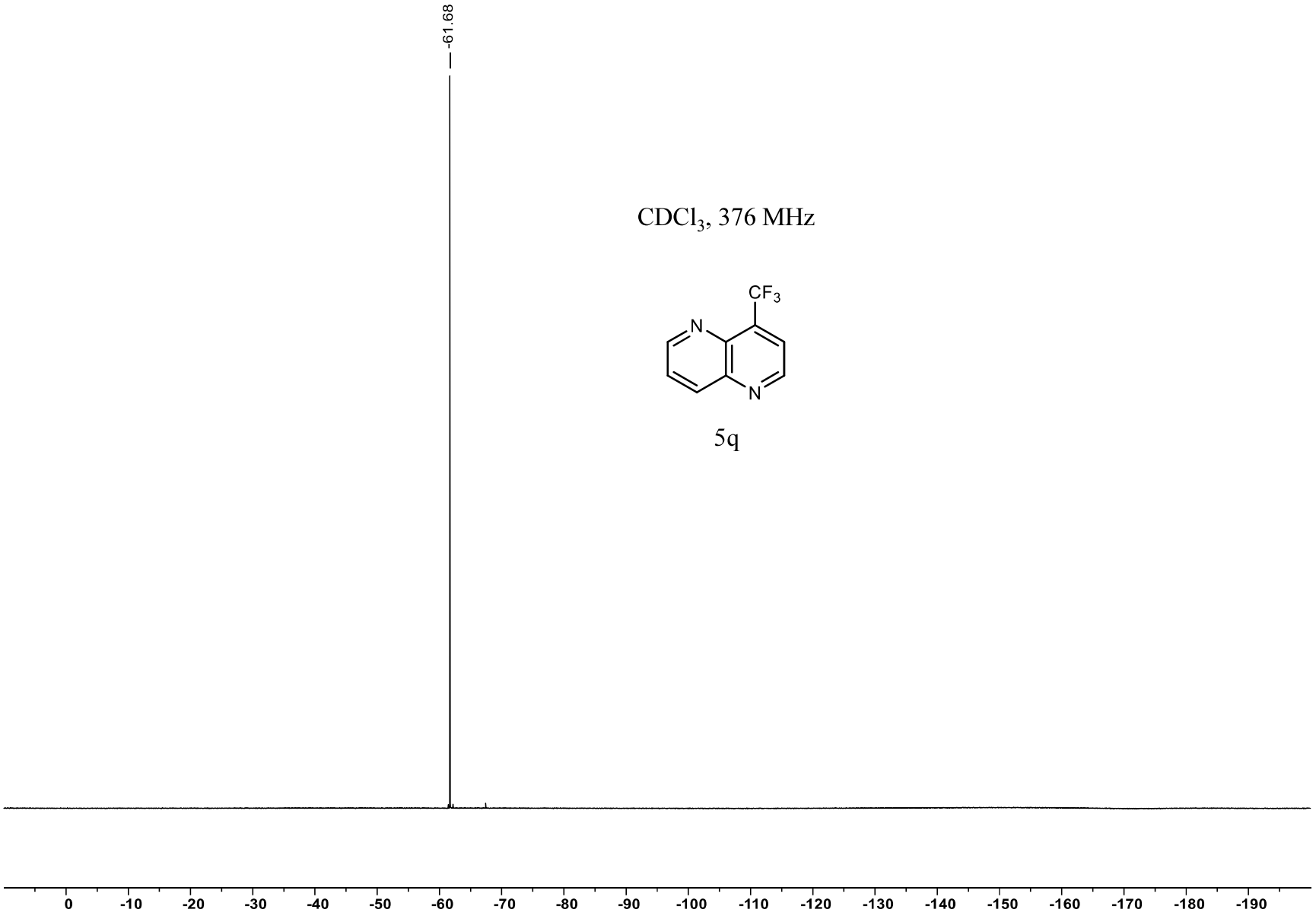


$CDCl_3$, 376 MHz

5p

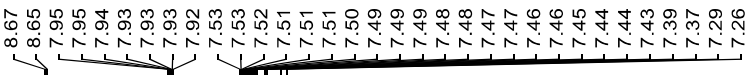

9.15
9.15
9.14
9.14
9.14
9.13
8.52
8.52
8.50
8.50
7.94
7.93
7.79
7.78
7.76
7.75
7.26
CDCl3, 400 MHz
CF3
N
N
5q
2.00
1.00
1.04
1.04
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


152.22
150.77
144.75
139.46
137.86
136.05
135.74
135.43
135.11
127.07
125.32
124.34
121.61
121.36
121.32
121.27
121.22
118.88
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
N
N
5q
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

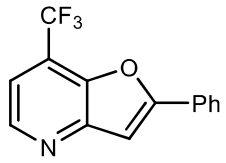


$CDCl_3$, 376 MHz

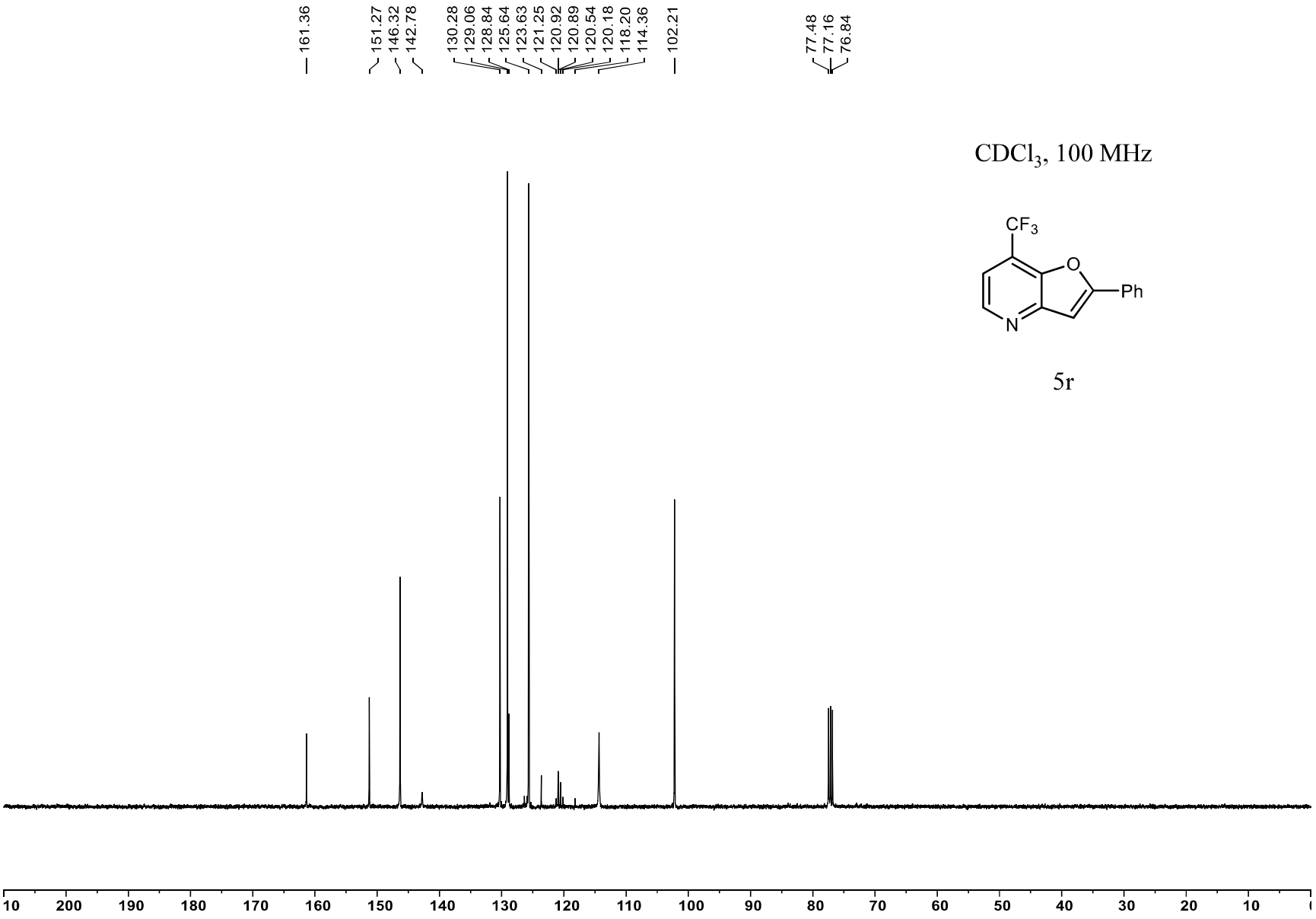
5q

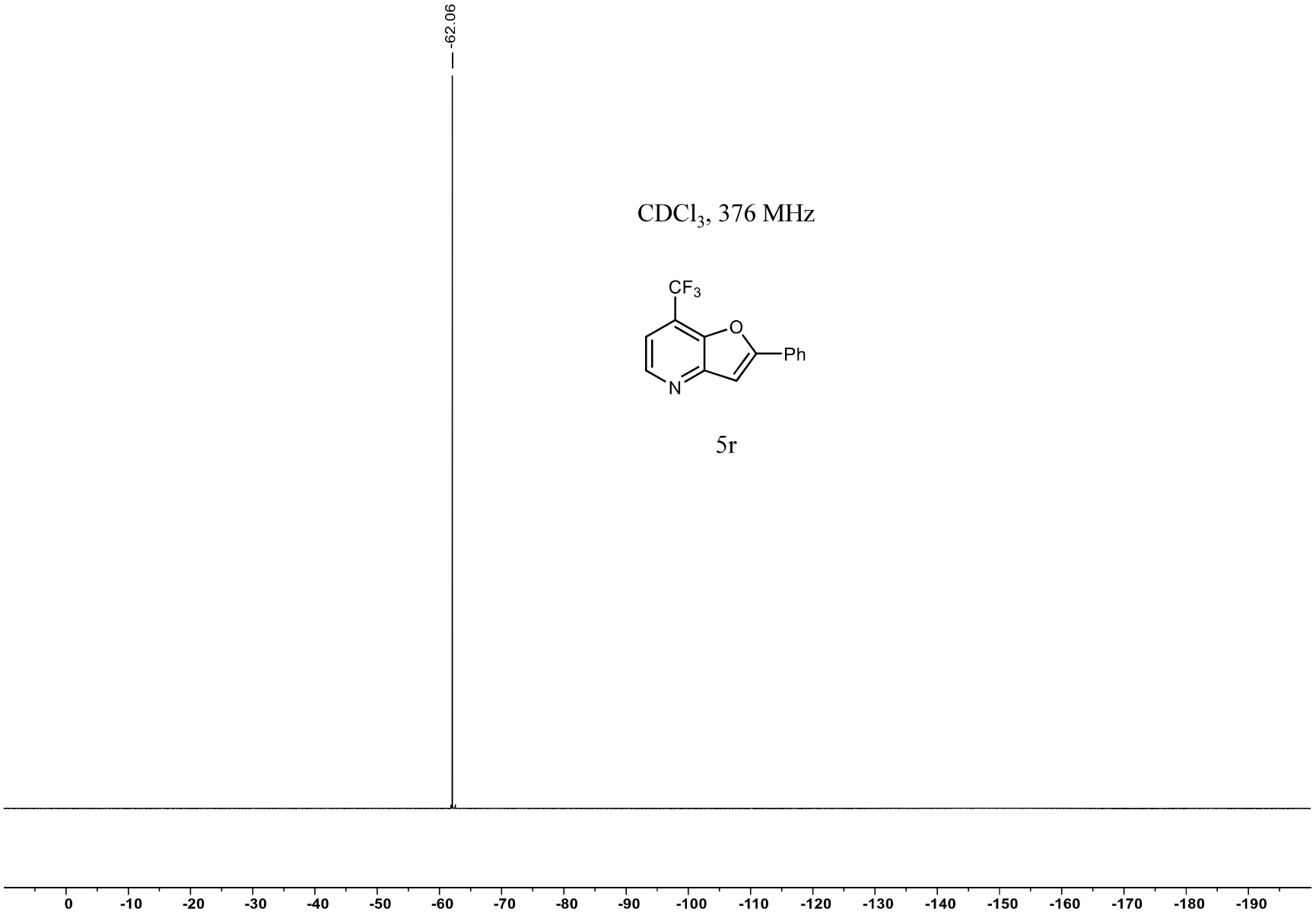


$CDCl_3$, 400 MHz



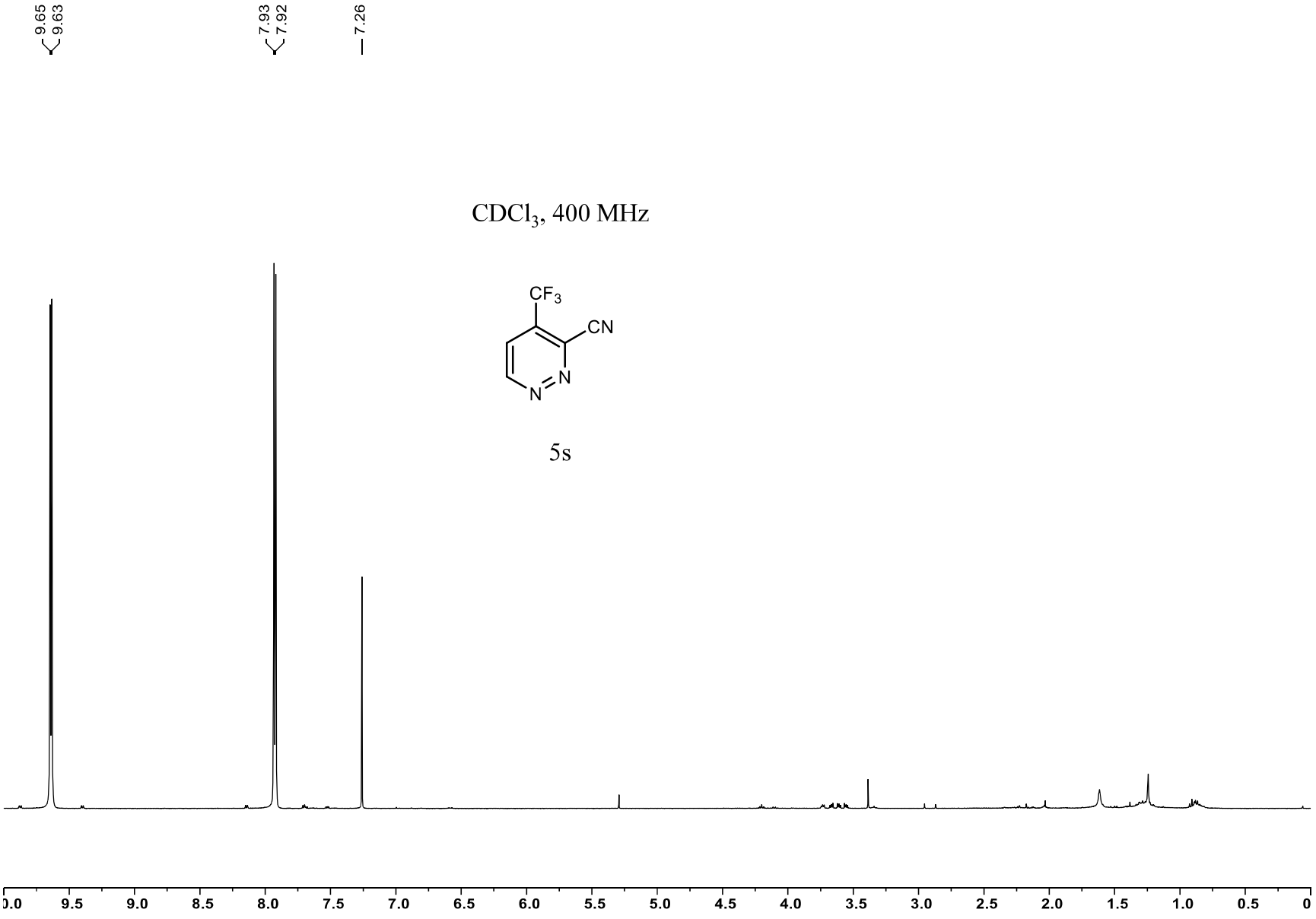
5r


161.36
151.27
146.32
142.78
130.28
129.06
128.84
125.64
123.63
121.25
120.92
120.89
120.54
120.18
118.20
114.36
102.21
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
O
Ph
N
5r
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



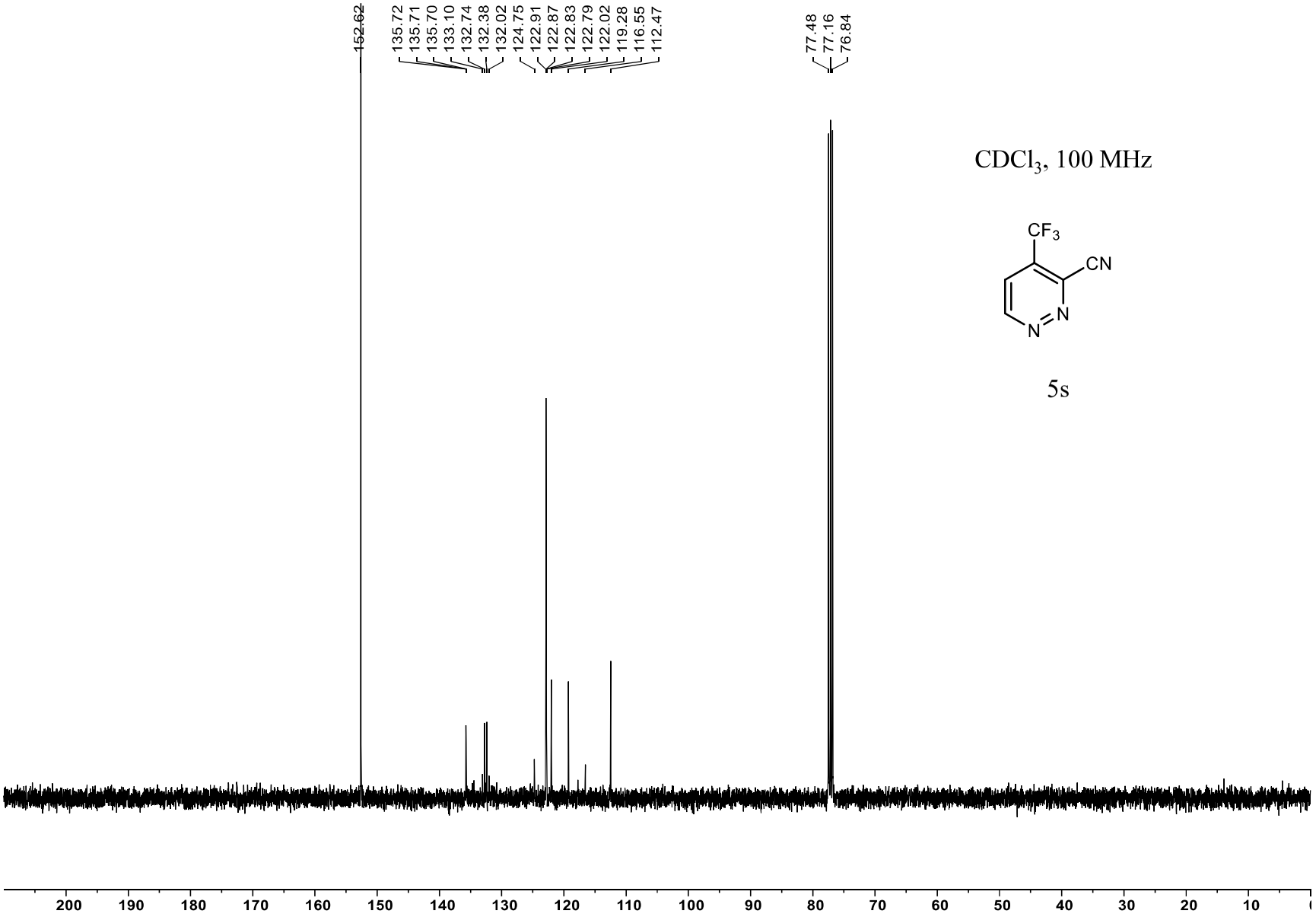
$CDCl_3$, 376 MHz

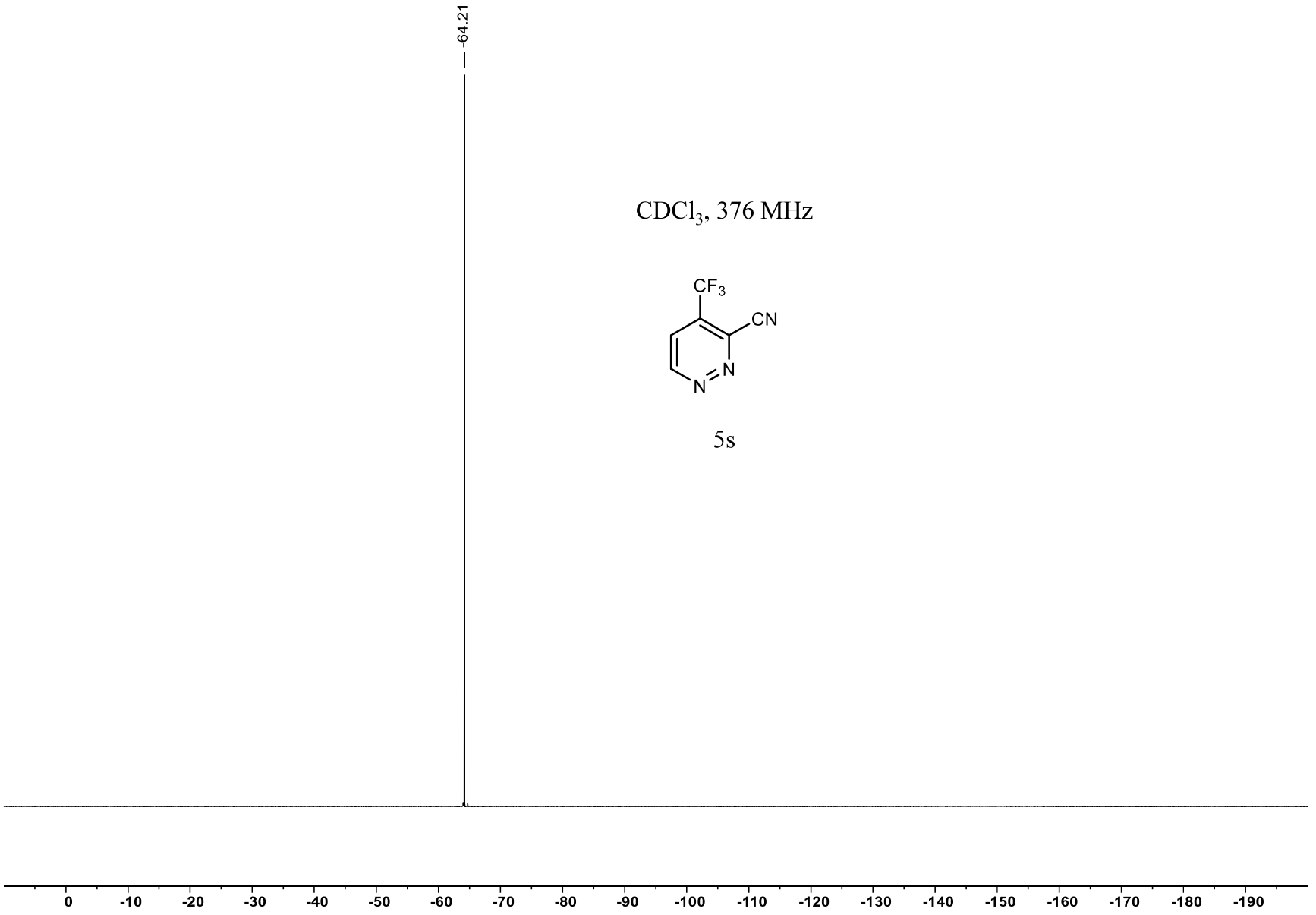
5r



$CDCl_3$, 400 MHz

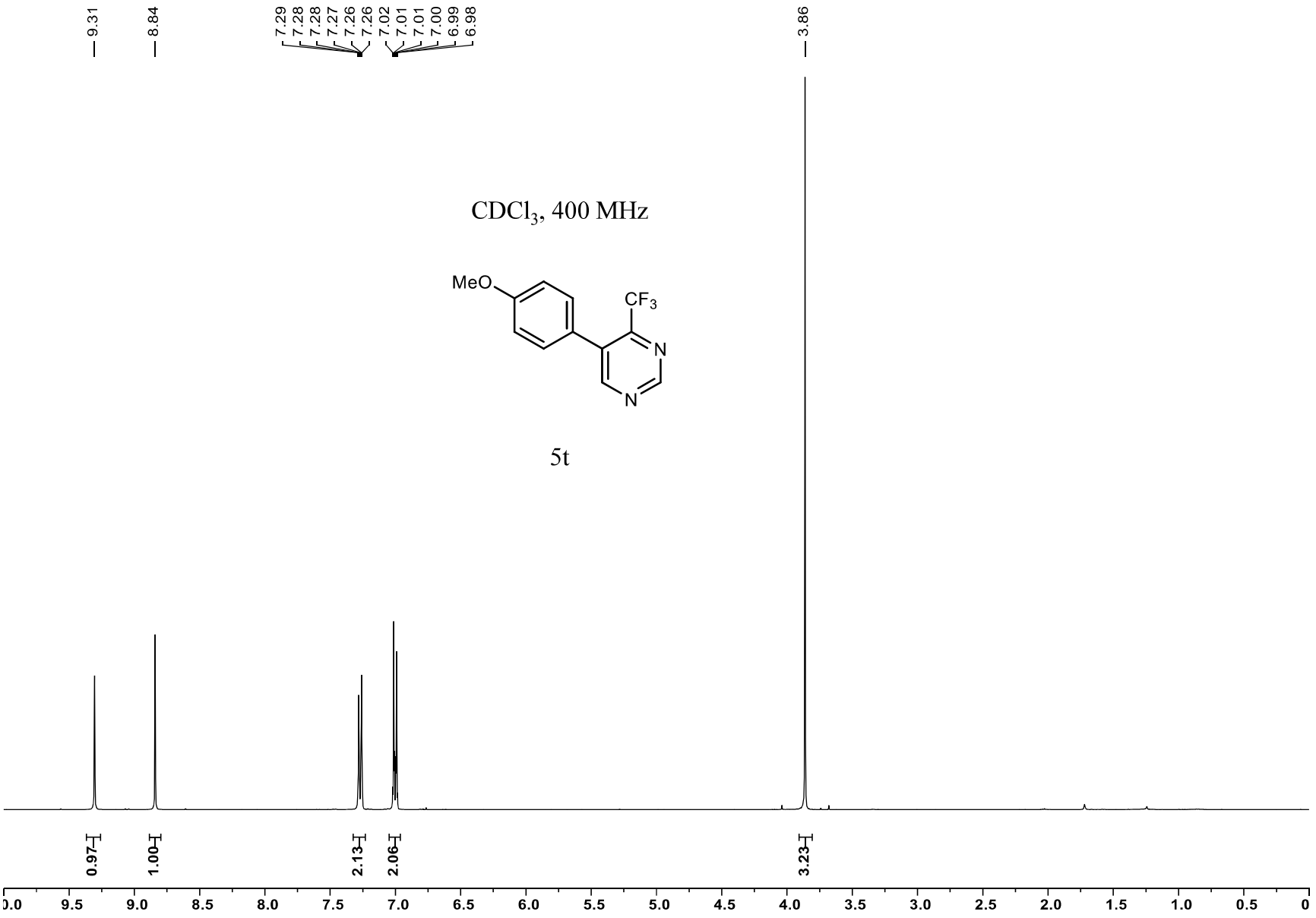
5s

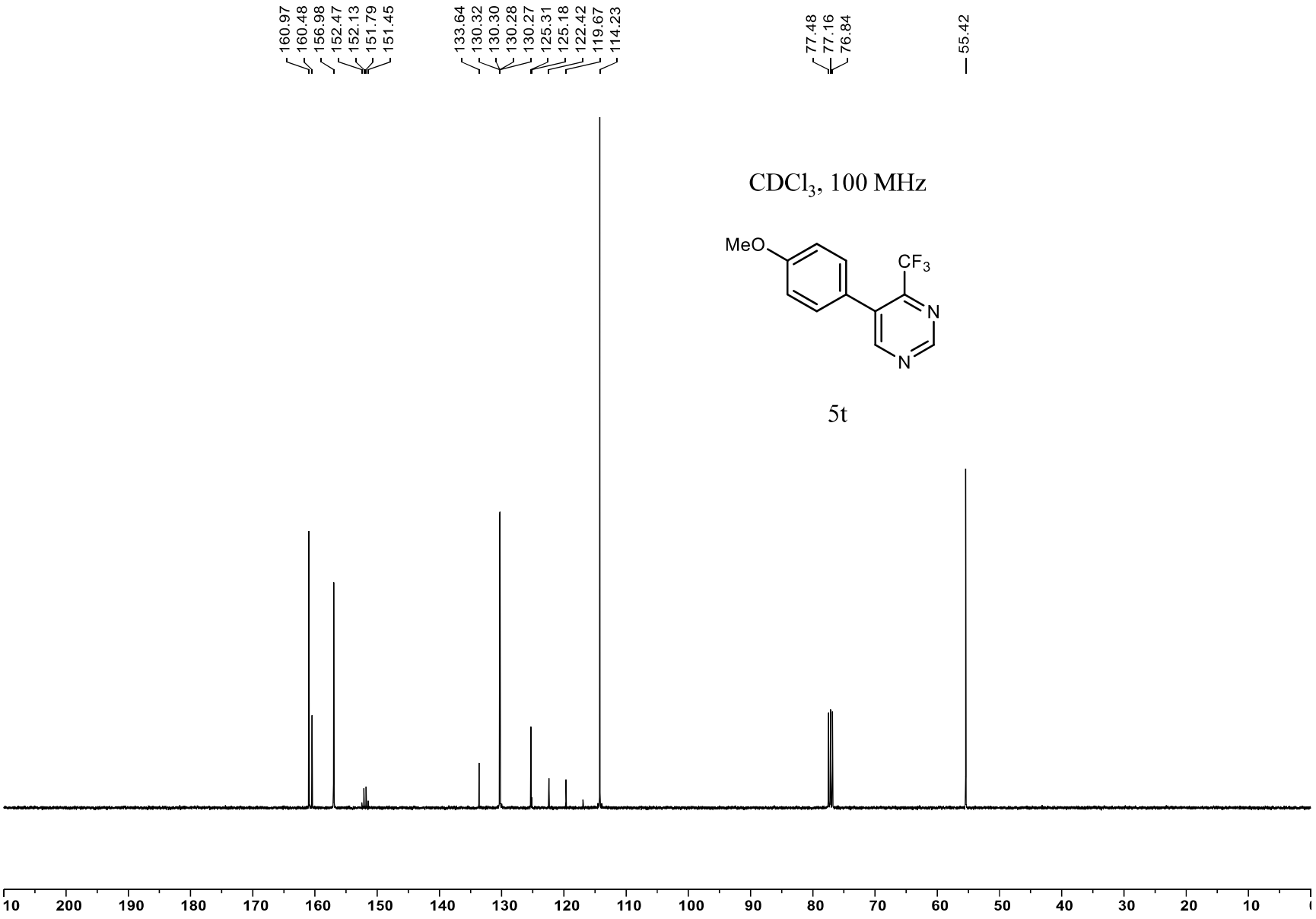

152.62
135.72
135.71
135.70
133.10
132.74
132.38
132.02
124.75
122.91
122.87
122.83
122.79
122.02
119.28
116.55
112.47
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
CN
N
N
5s
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

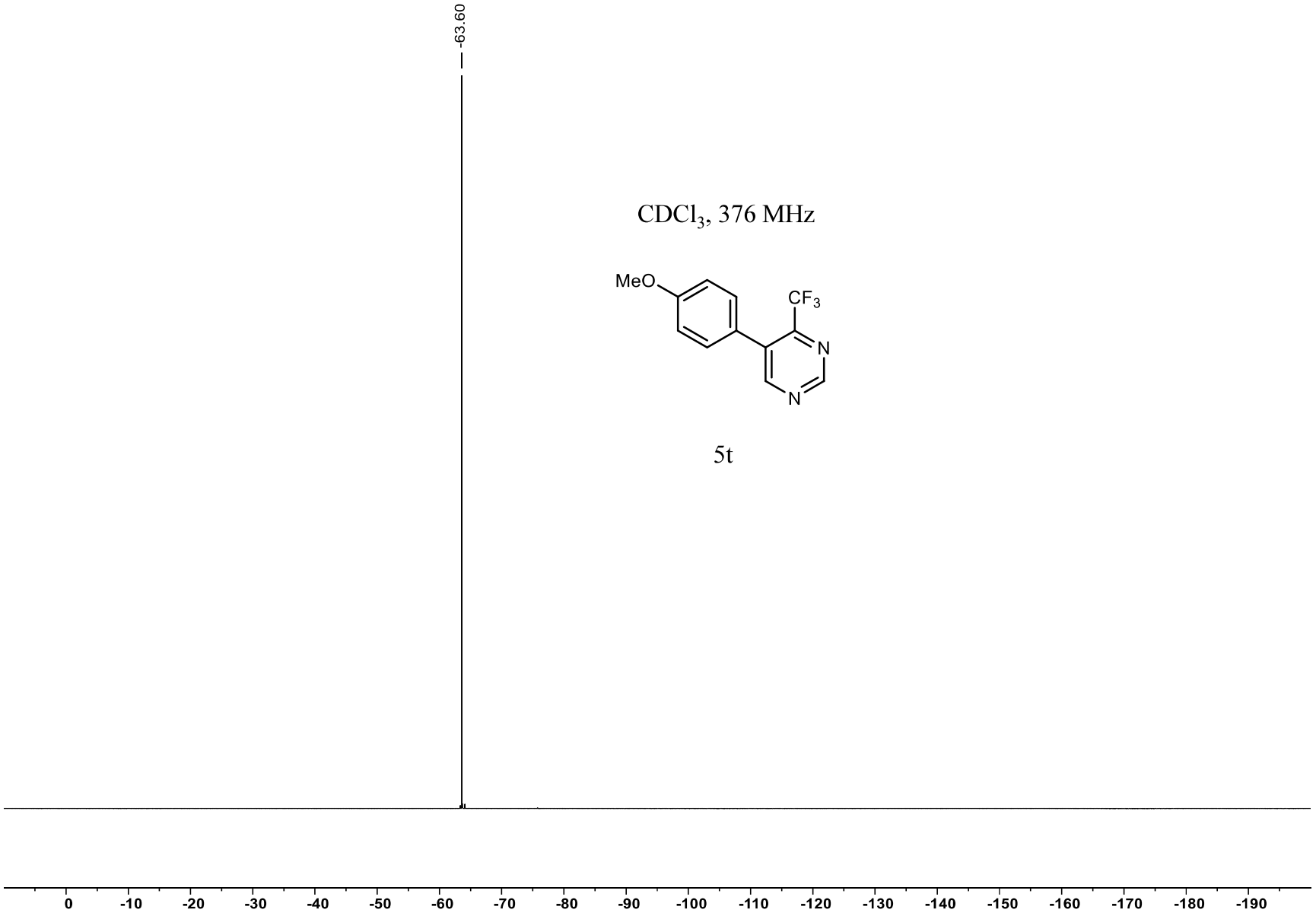


$CDCl_3$, 376 MHz

5s


9.31
8.84
7.29
7.28
7.28
7.27
7.26
7.26
7.02
7.01
7.01
7.00
6.99
6.98
3.86
CDCl3, 400 MHz
MeO
CF3
N
N
5t
0.97
1.00
2.13
2.06
3.23
0.0
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

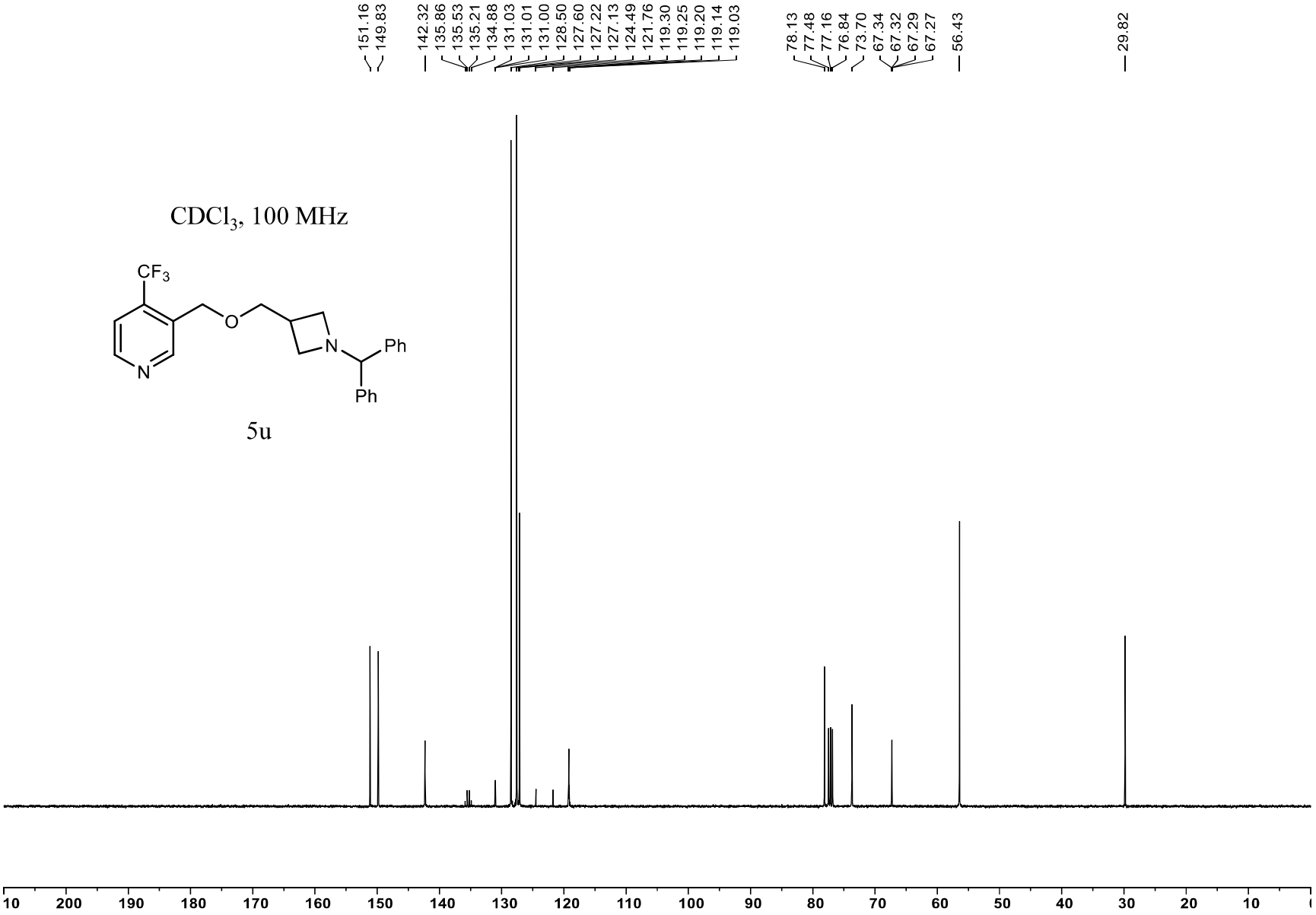

160.97
160.48
156.98
152.47
152.13
151.79
151.45
133.64
130.32
130.30
130.28
130.27
125.31
125.18
122.42
119.67
114.23
77.48
77.16
76.84
55.42
CDCl3, 100 MHz
MeO
CF3
N
N
5t
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

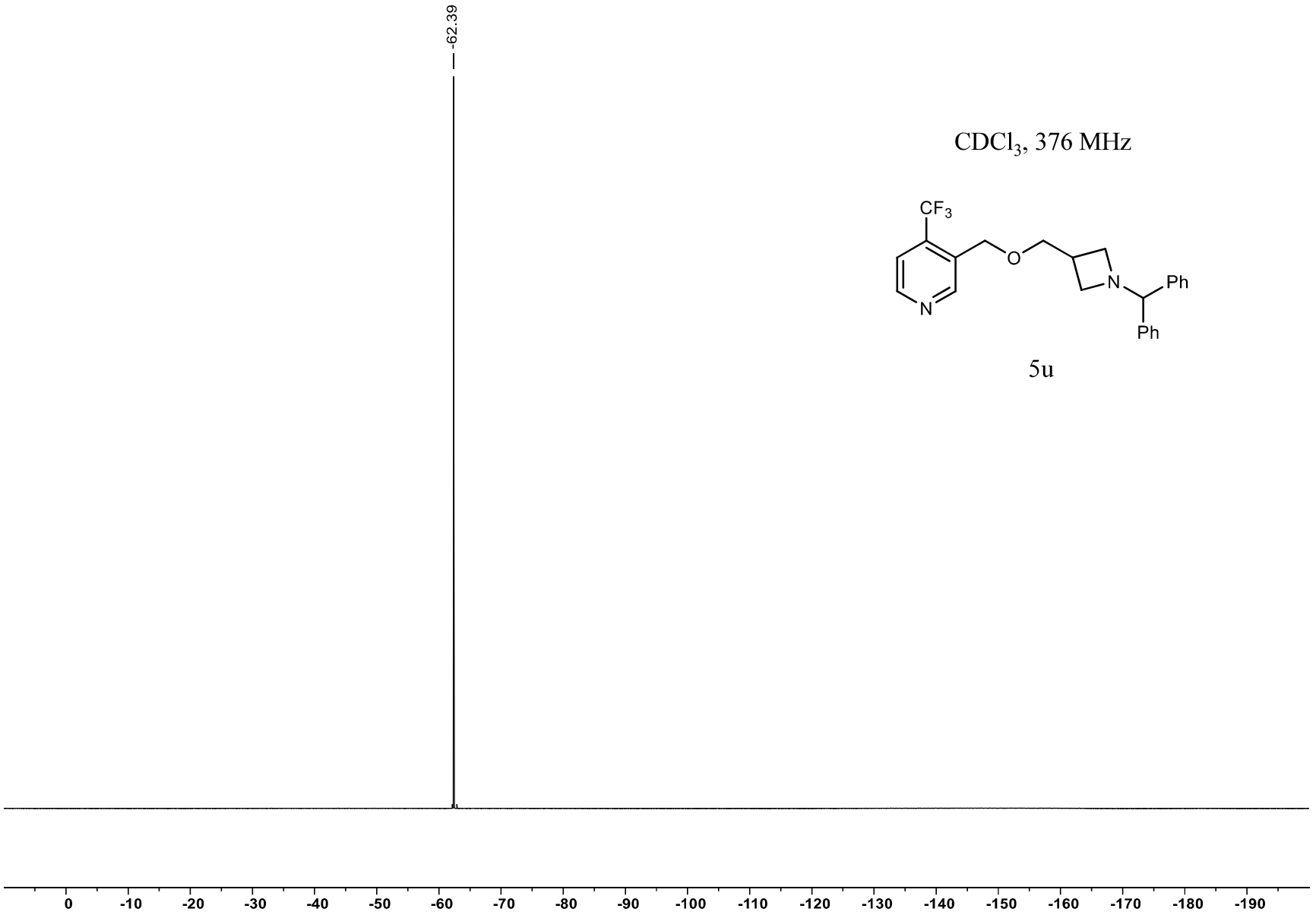


$CDCl_3$, 376 MHz

5t

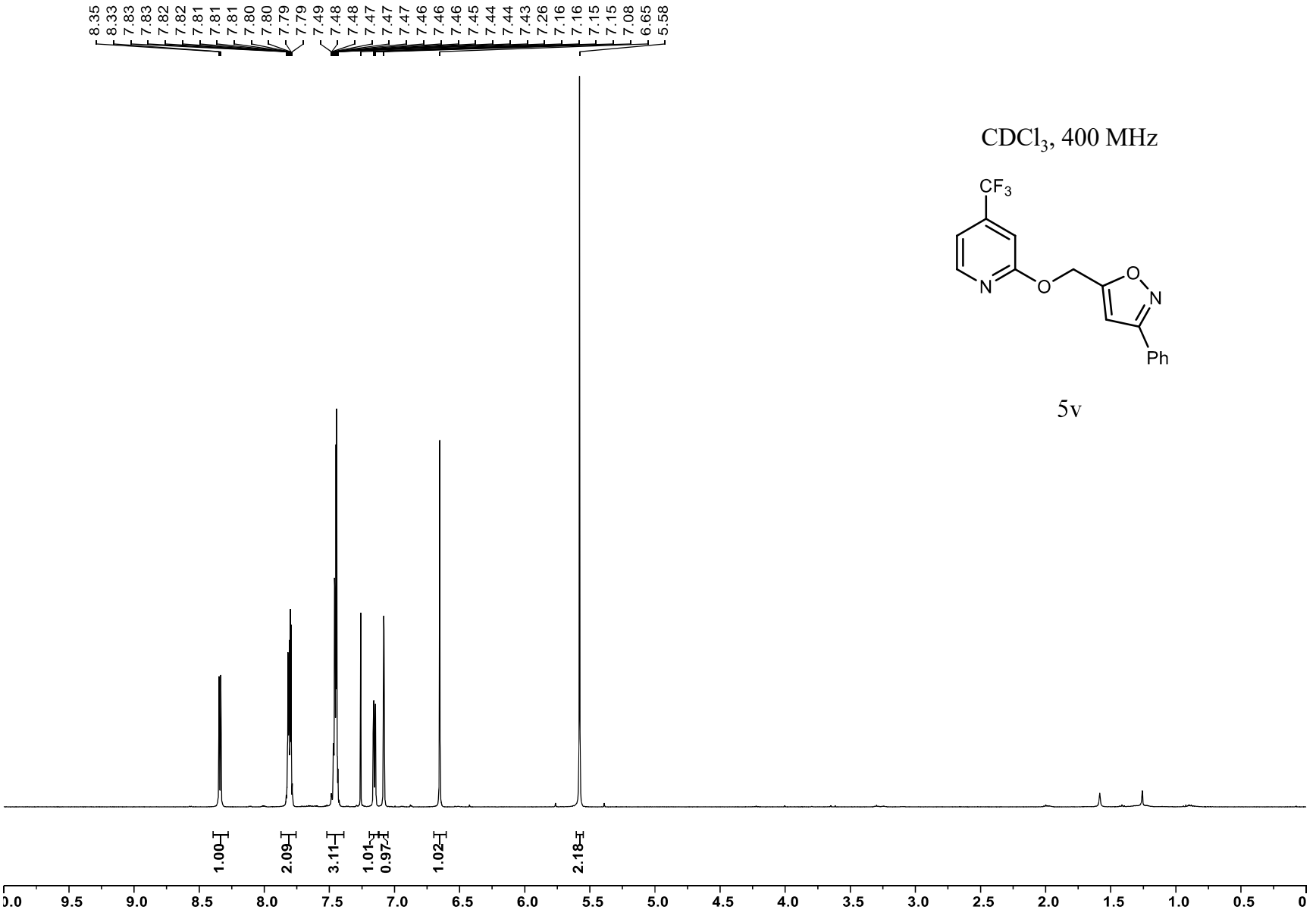
CDCl3, 400 MHz
5u
CF3
N
O
N
Ph
Ph
8.90
8.70
8.69
7.48
7.47
7.40
7.39
7.39
7.38
7.37
7.37
7.37
7.27
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.18
7.17
7.17
7.16
7.16
7.15
7.14
7.14
7.13
4.69
4.33
3.69
3.68
3.31
3.29
3.27
2.94
2.93
2.91
2.81
2.79
2.78
2.77
2.76
2.74
2.72
2.71
0.97
0.97
1.00
4.11
4.24
2.02
2.11
1.05
2.12
2.09
2.08
1.05


151.16
149.83
142.32
135.86
135.53
135.21
134.88
131.03
131.01
131.00
128.50
127.60
127.22
127.13
124.49
121.76
119.30
119.25
119.20
119.14
119.03
78.13
77.48
77.16
76.84
73.70
67.34
67.32
67.29
67.27
56.43
29.82
CDCl3, 100 MHz
CF3
O
N
Ph
Ph
N
5u
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



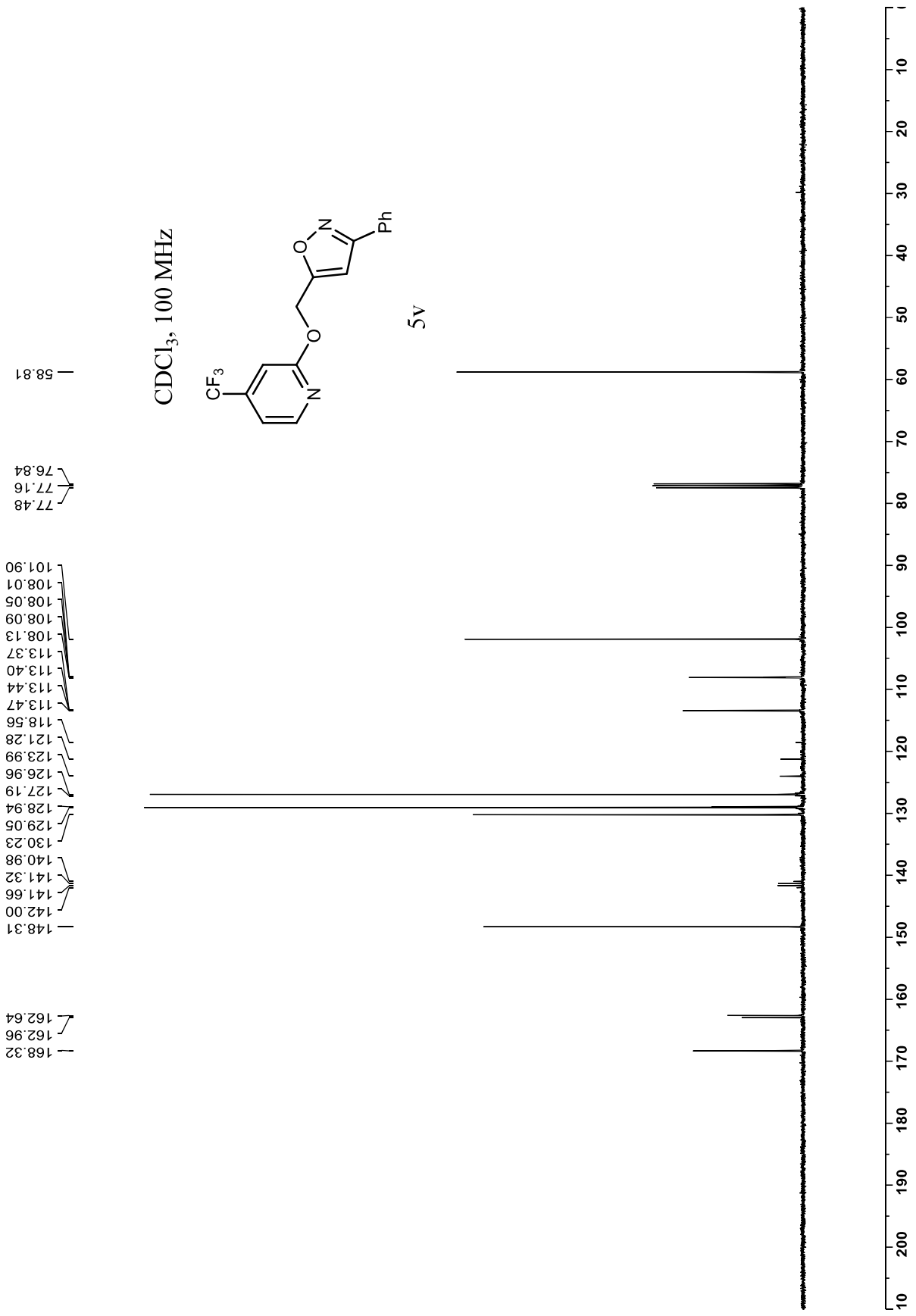
$CDCl_3$, 376 MHz

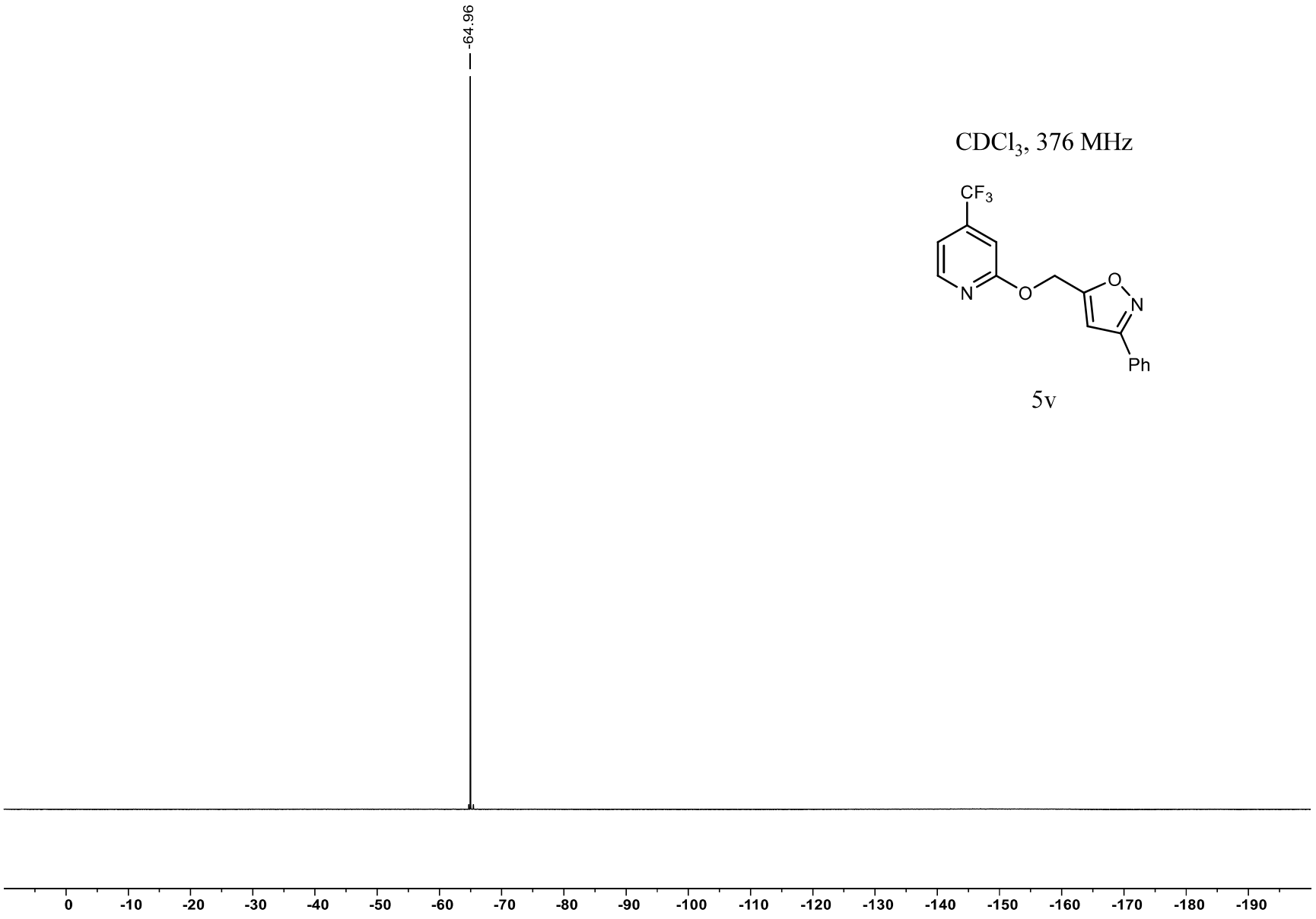
5u



$CDCl_3$, 400 MHz

5v

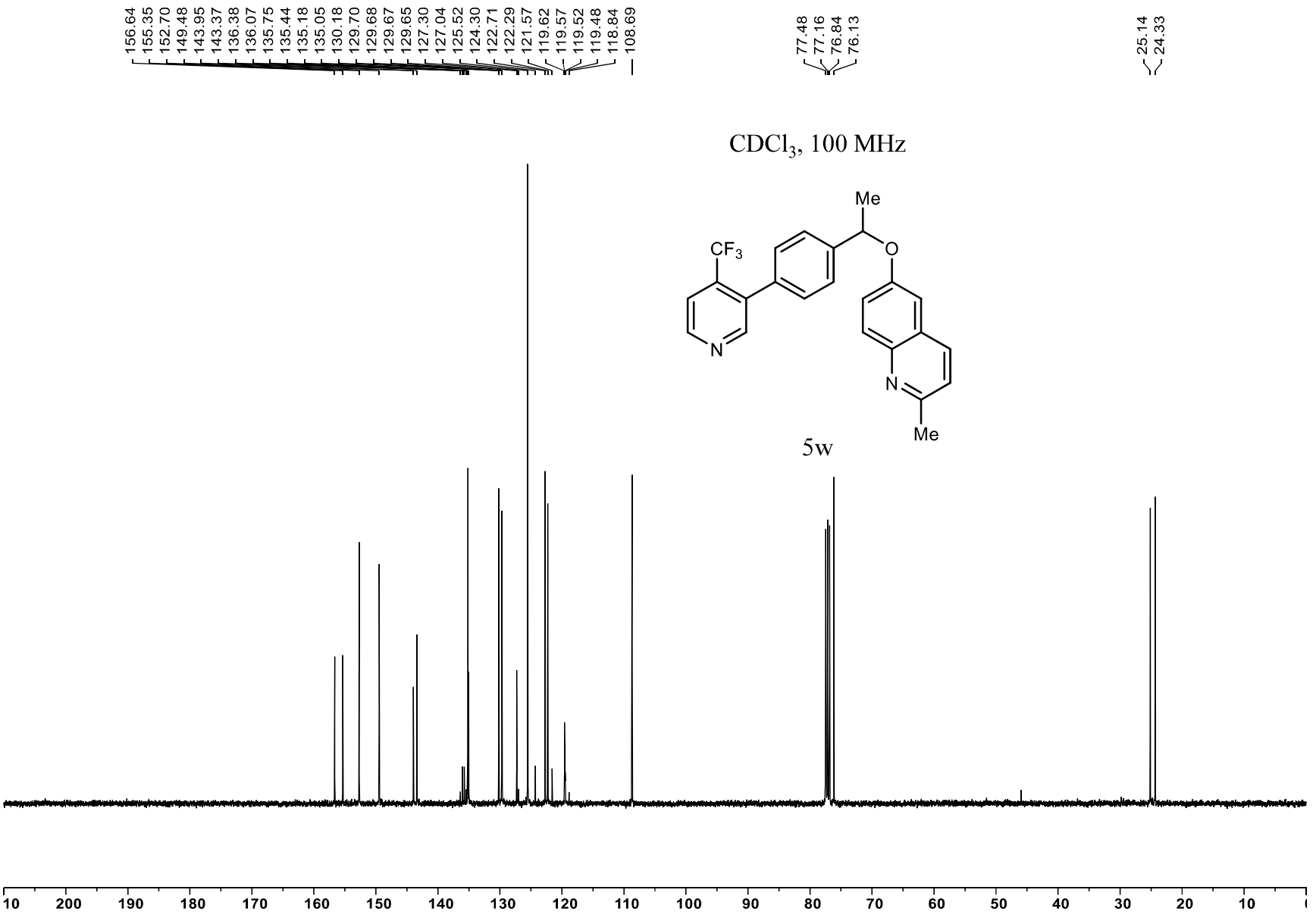

CDCl3, 100 MHz
5v
CF3
N
O
O
N
Ph
58.81
76.84
77.16
77.48
101.90
108.01
108.05
108.09
108.13
113.37
113.40
113.44
113.47
118.56
121.28
123.99
126.96
127.19
128.94
129.05
130.23
140.98
141.32
141.66
142.00
148.31
162.64
162.96
168.32

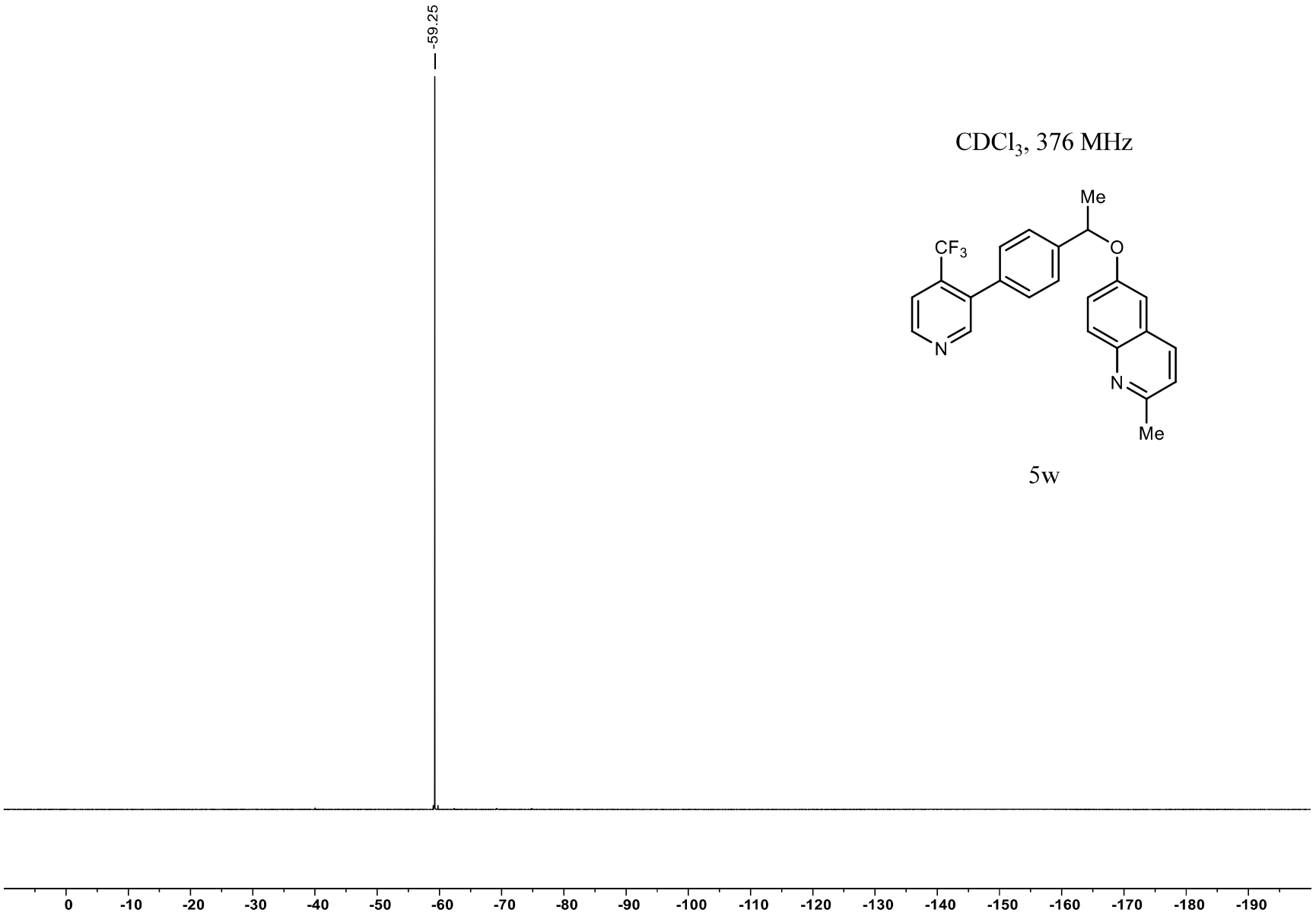


$CDCl_3$, 376 MHz

5v

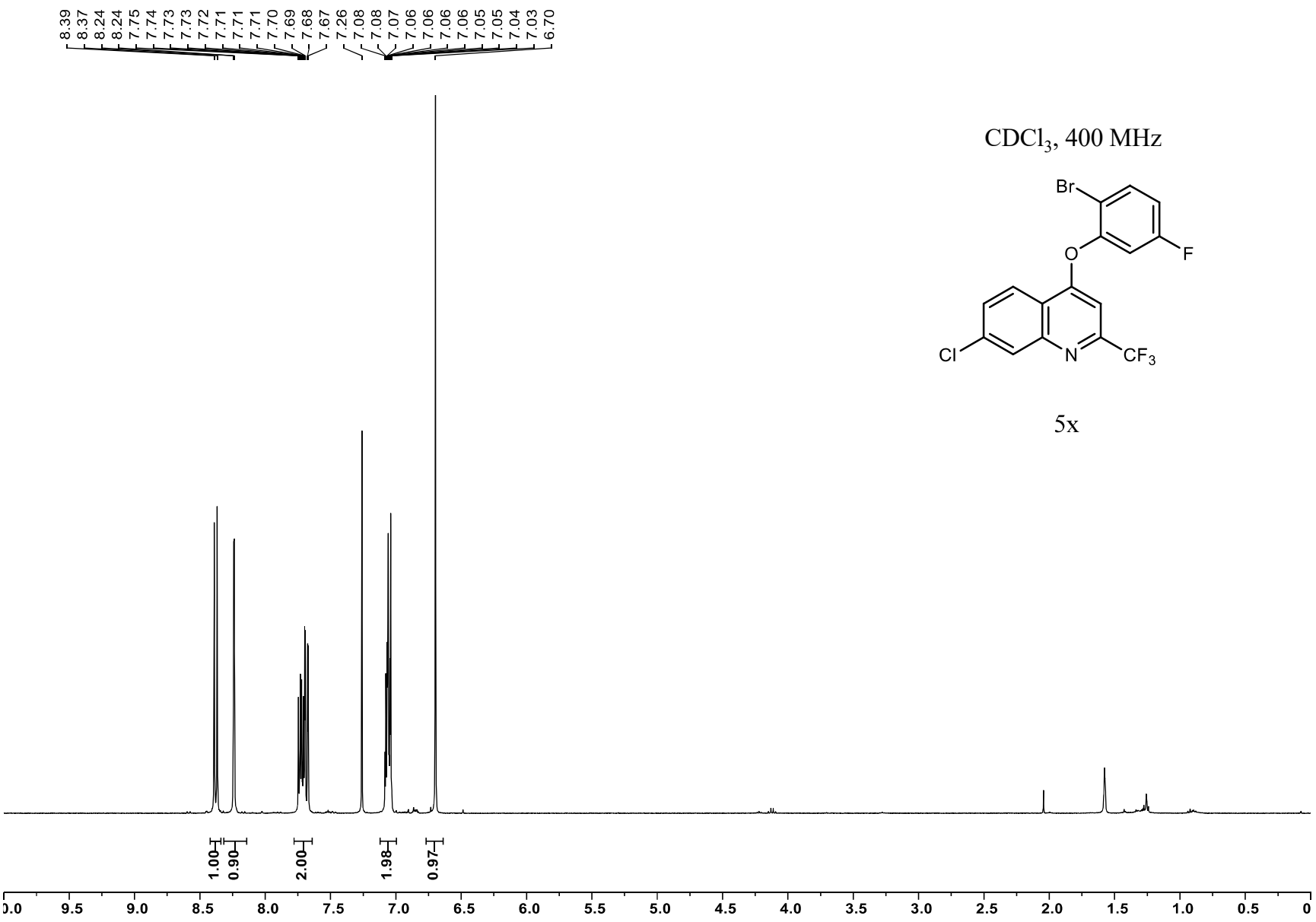
CDCl3, 400 MHz
5w
Me
O
N
Me
CF3
N
8.76
8.74
8.63
7.92
7.89
7.83
7.81
7.59
7.58
7.51
7.49
7.41
7.41
7.39
7.38
7.33
7.31
7.26
7.19
7.16
6.97
6.96
5.52
5.50
5.49
5.47
2.67
1.74
1.73
1.00
1.00
0.97
1.01
0.98
2.04
1.05
1.99
1.00
1.01
1.01
3.02
3.13


156.64
155.35
152.70
149.48
143.95
143.37
136.38
136.07
135.75
135.44
135.18
135.05
130.18
129.70
129.68
129.67
129.65
127.30
127.04
125.52
124.30
122.71
122.29
121.57
119.62
119.57
119.52
119.48
118.84
108.69
77.48
77.16
76.84
76.13
25.14
24.33
CDCl3, 100 MHz
Me
CF3
O
N
N
Me
5w
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



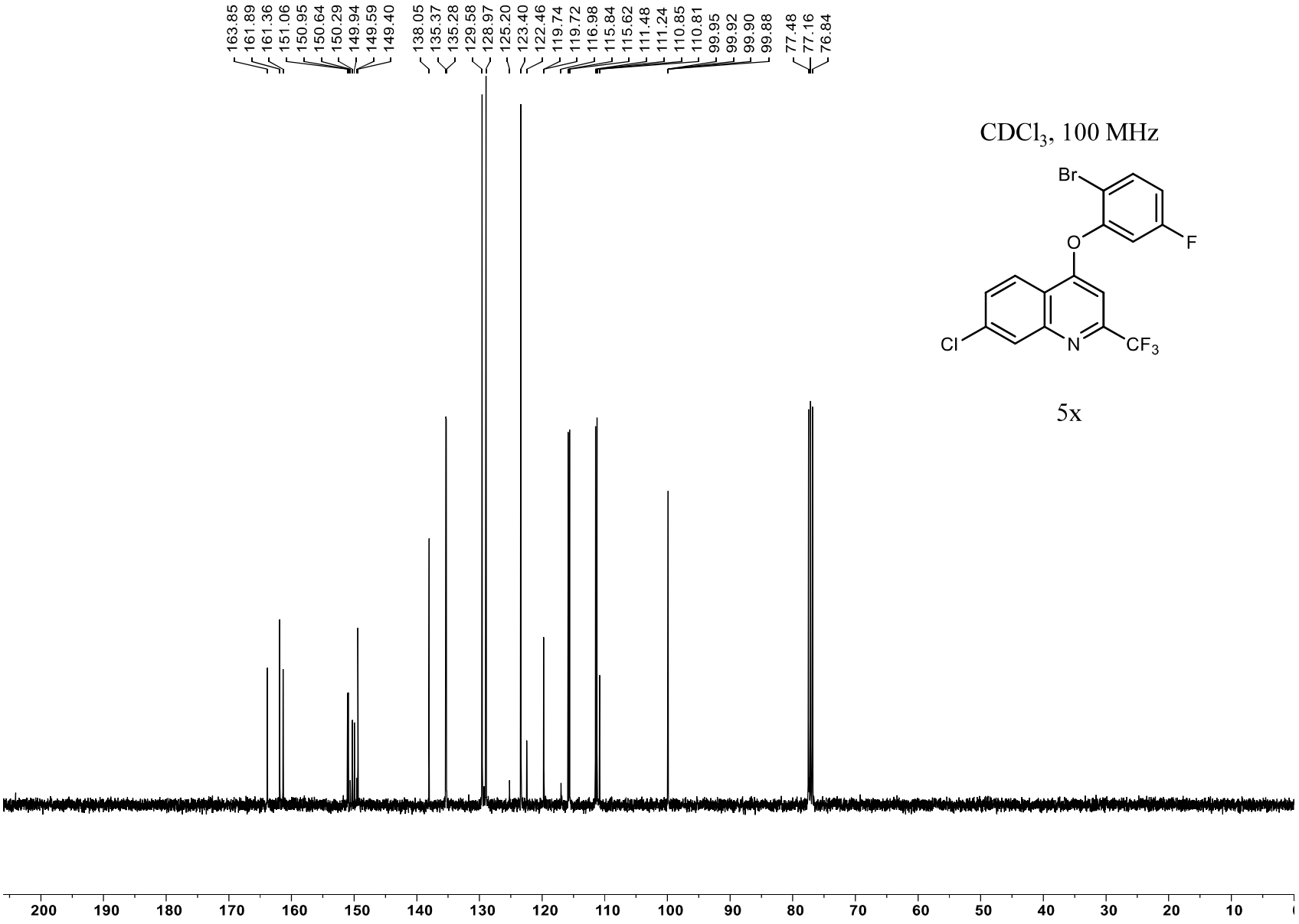
$CDCl_3$, 376 MHz

5w



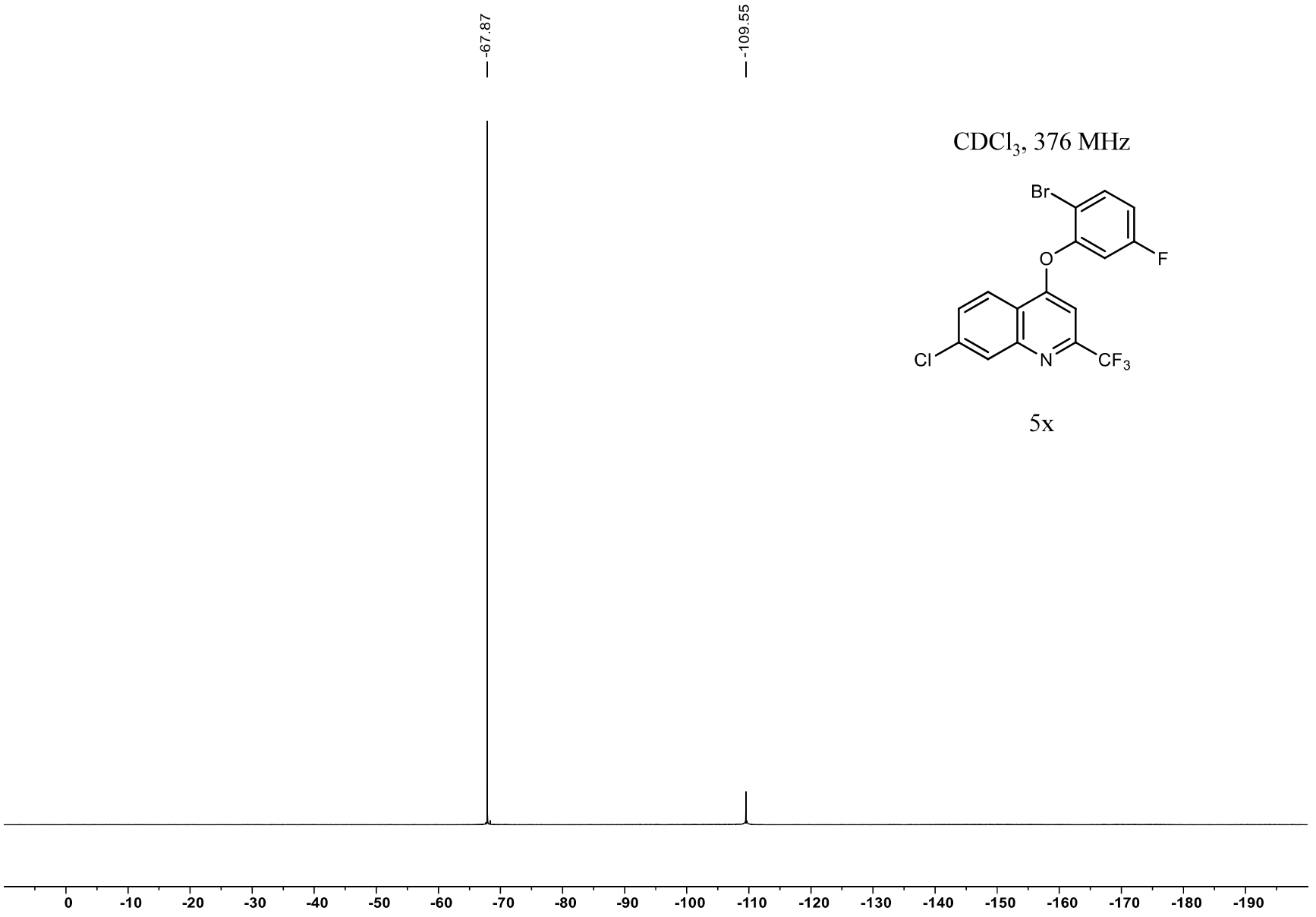
$CDCl_3$, 400 MHz

5x



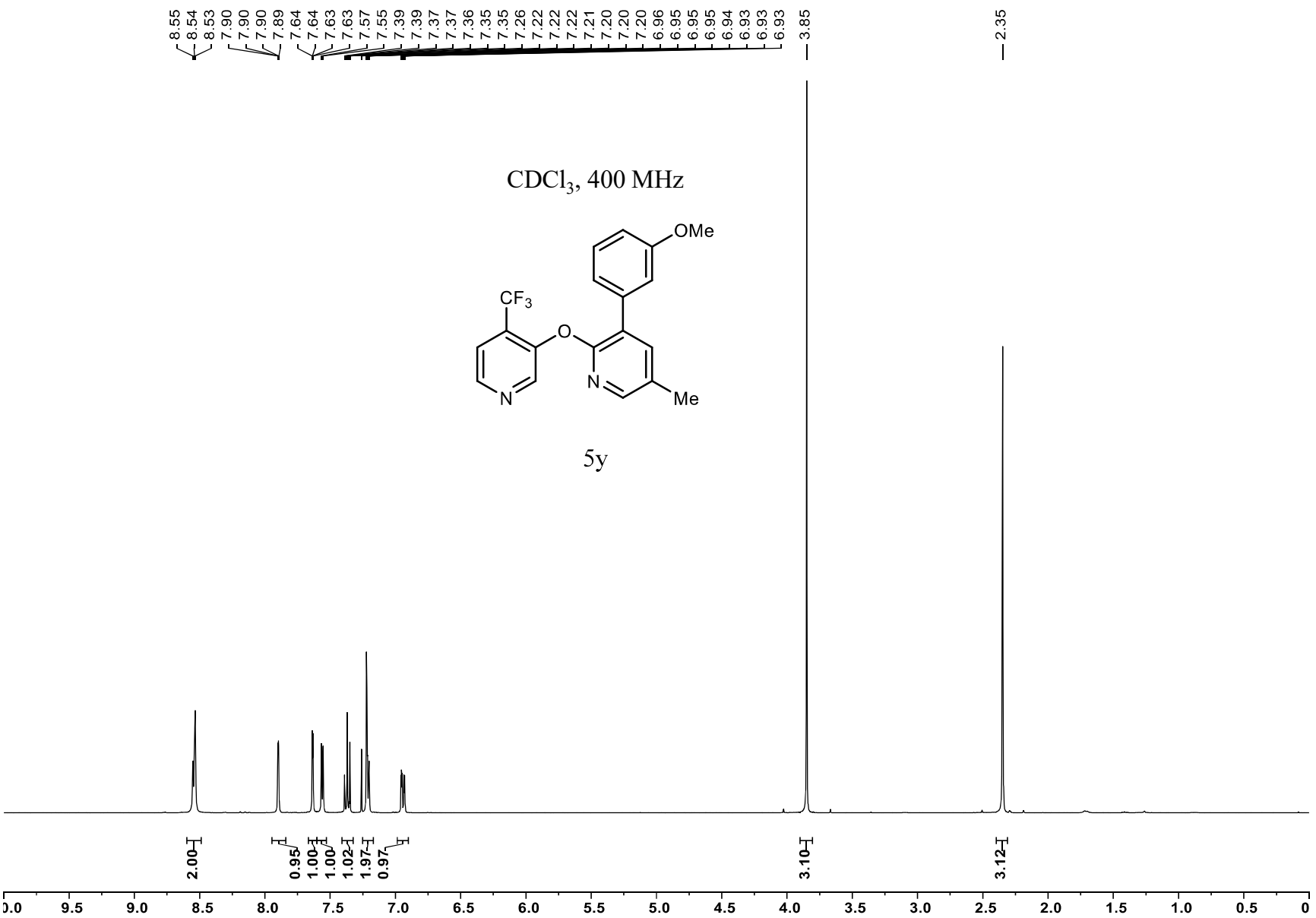
$CDCl_3$, 100 MHz

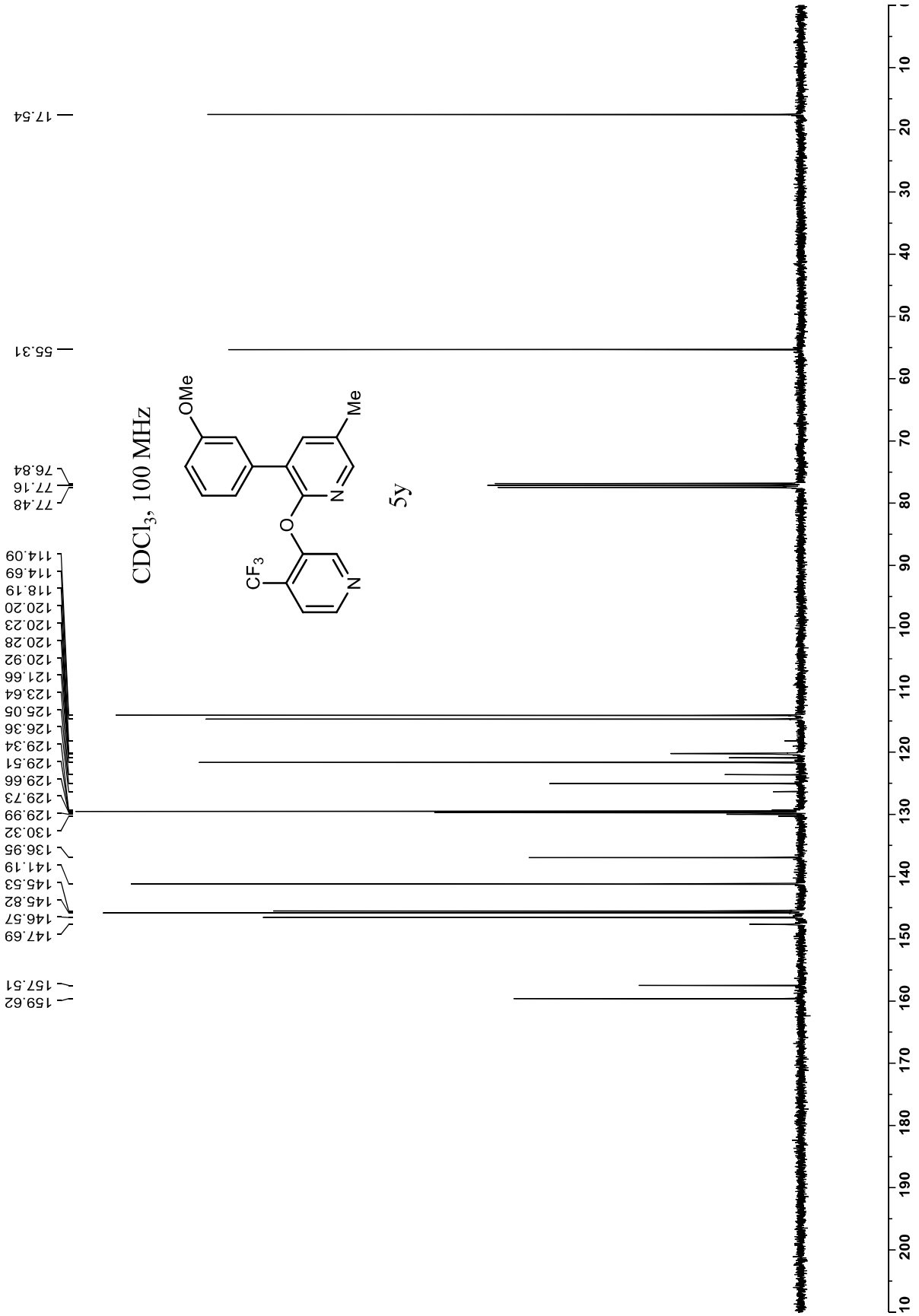
5x

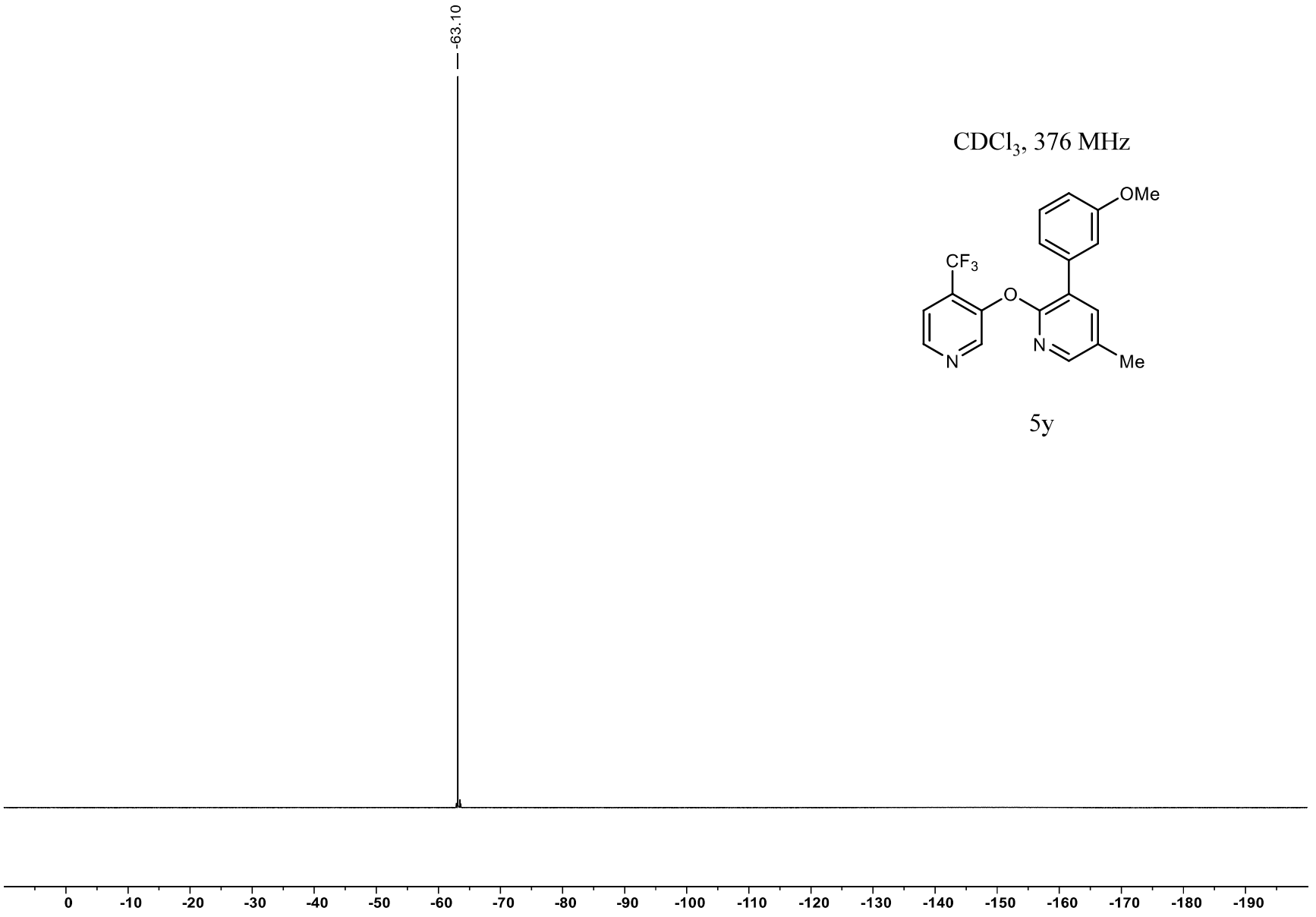


$CDCl_3$, 376 MHz

5x

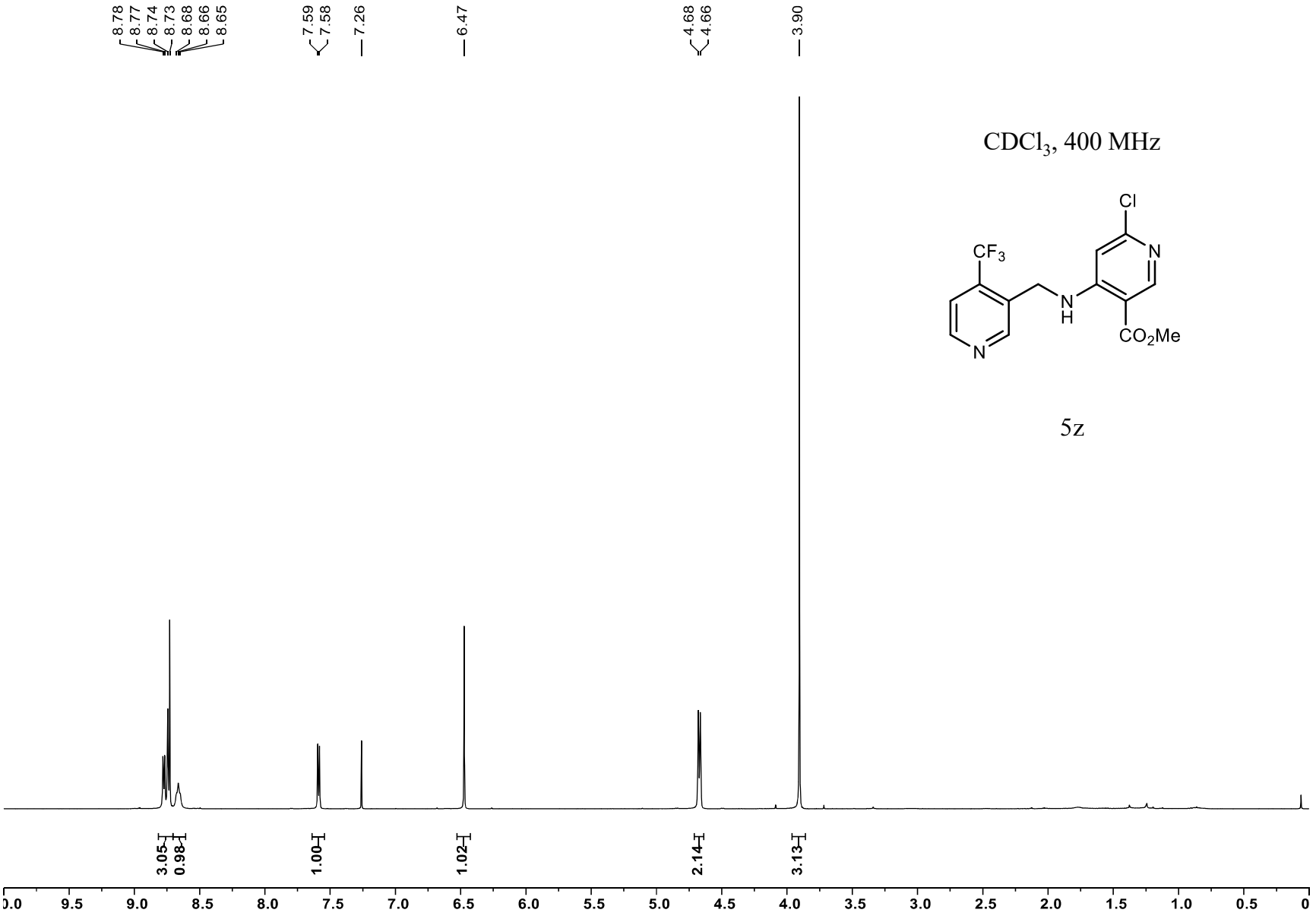

8.55
8.54
8.53
7.90
7.90
7.90
7.89
7.64
7.64
7.63
7.63
7.57
7.55
7.39
7.39
7.37
7.37
7.36
7.35
7.35
7.26
7.22
7.22
7.22
7.21
7.20
7.20
7.20
6.96
6.95
6.95
6.94
6.93
6.93
6.93
3.85
2.35
CDCl3, 400 MHz
OMe
CF3
O
N
N
Me
5y
2.00
0.95
1.00
1.00
1.02
1.97
0.97
3.10
3.12
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


17.54
55.31
76.84
77.16
77.48
114.09
114.69
118.19
120.20
120.23
120.28
120.92
121.66
123.64
125.05
126.36
129.34
129.51
129.66
129.73
129.99
130.32
136.95
141.19
145.53
145.82
146.57
147.69
157.51
159.62
CDCl3, 100 MHz
OMe
Me
N
O
CF3
N
5y
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
10

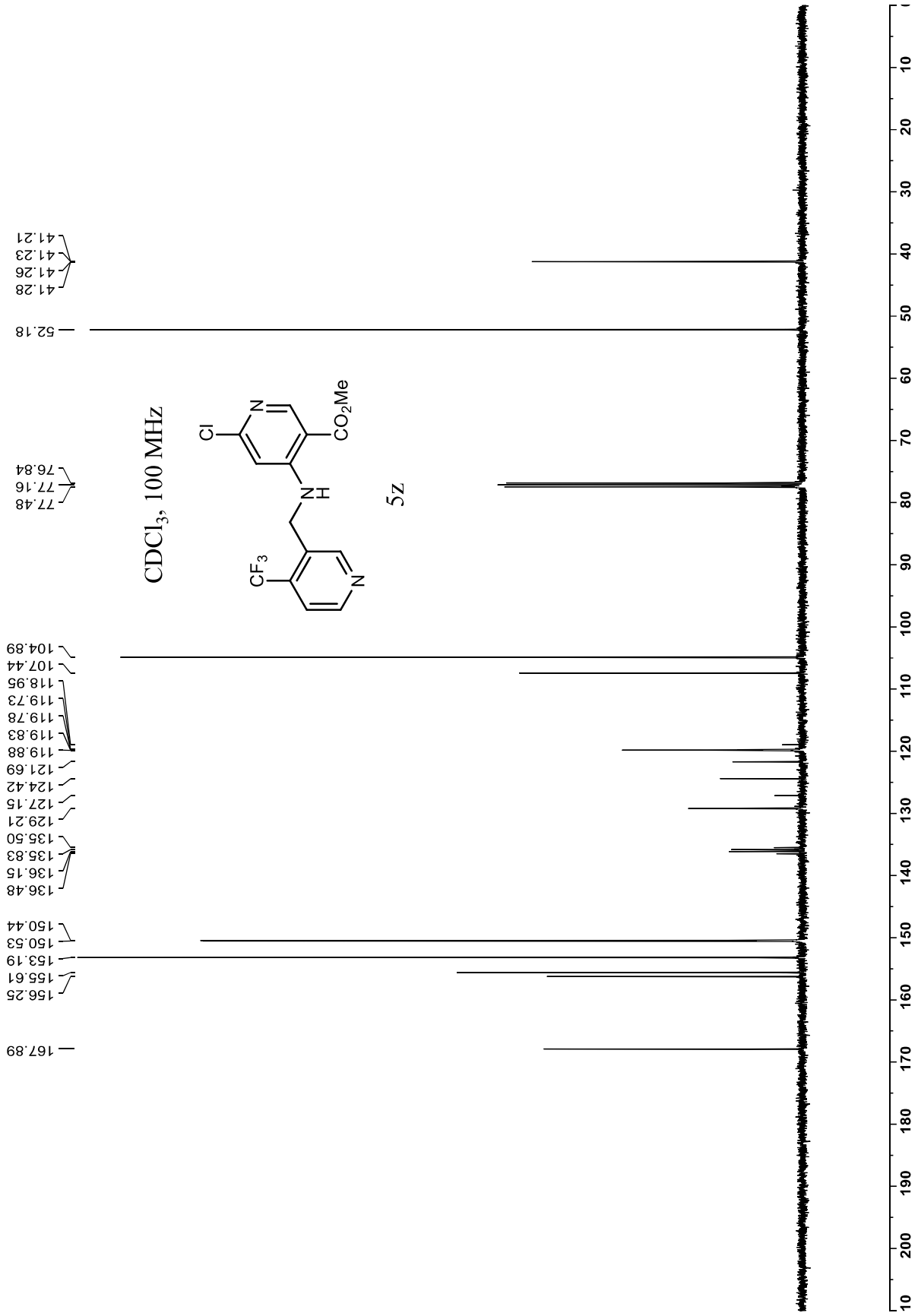


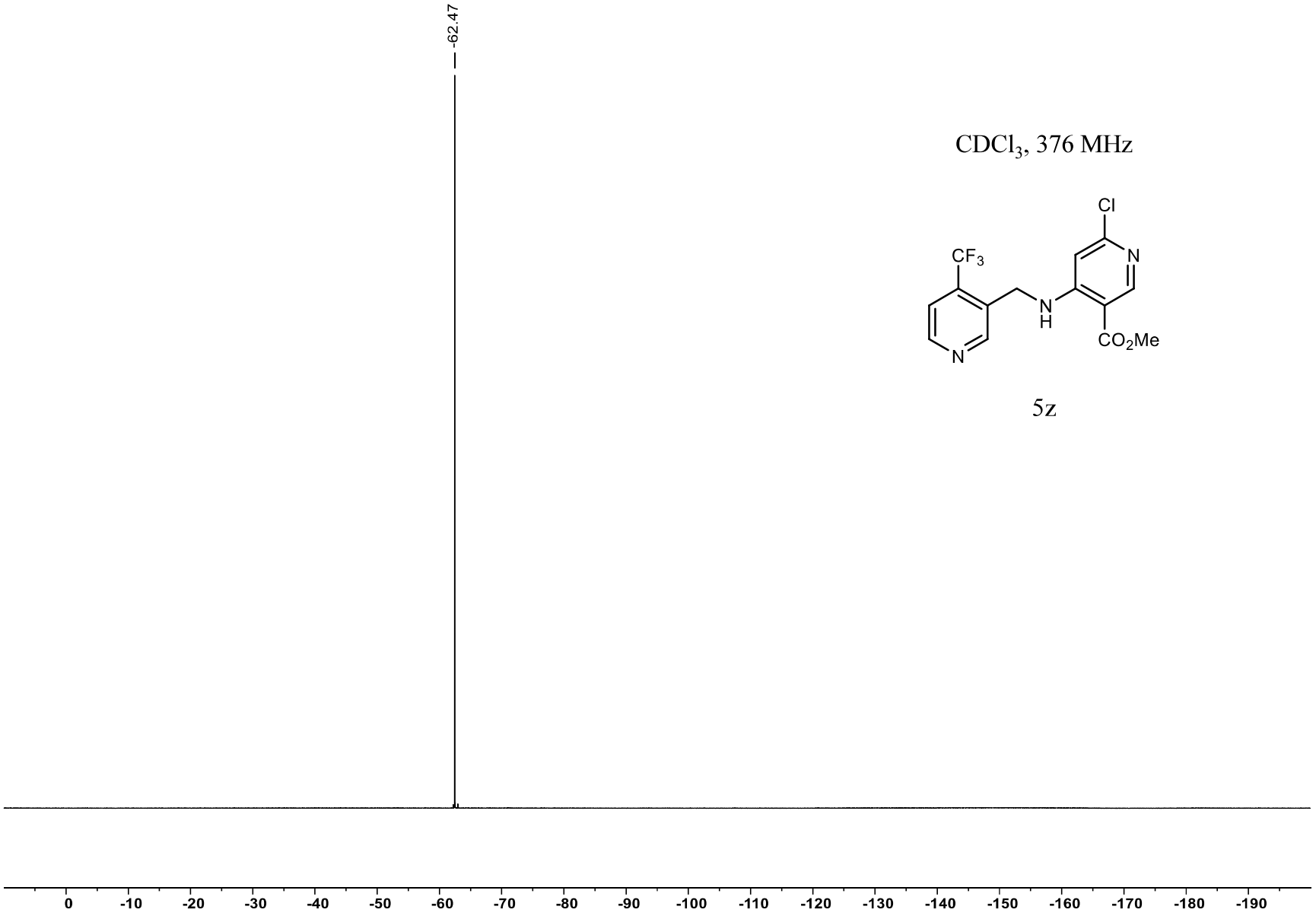
$CDCl_3$, 376 MHz

5y


8.78
8.77
8.74
8.73
8.68
8.66
8.65
7.59
7.58
7.26
6.47
4.68
4.66
3.90
CDCl3, 400 MHz
Cl
CF3
N
N
H
N
CO2Me
3.05
0.98
1.00
1.02
2.14
3.13
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

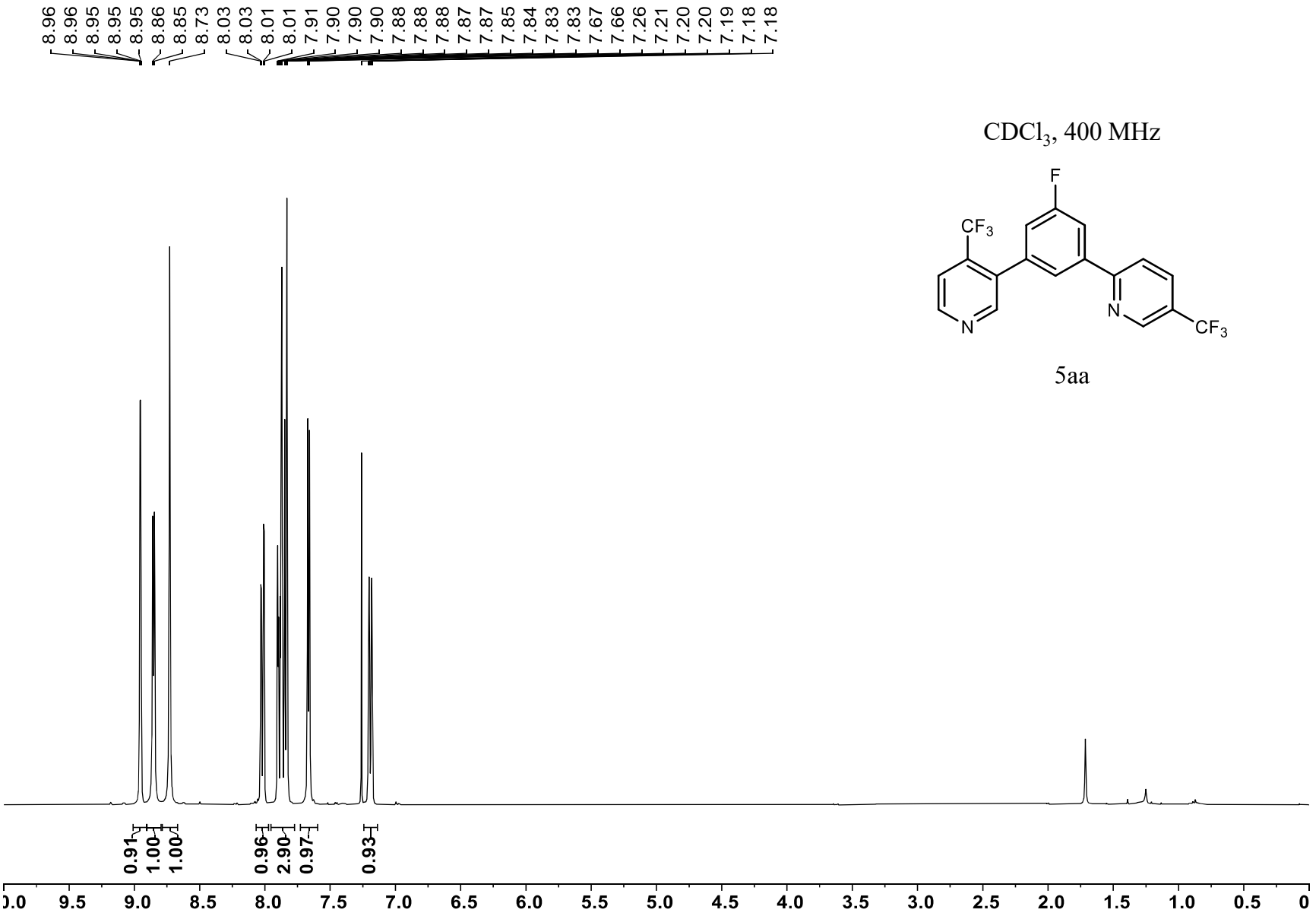
5z

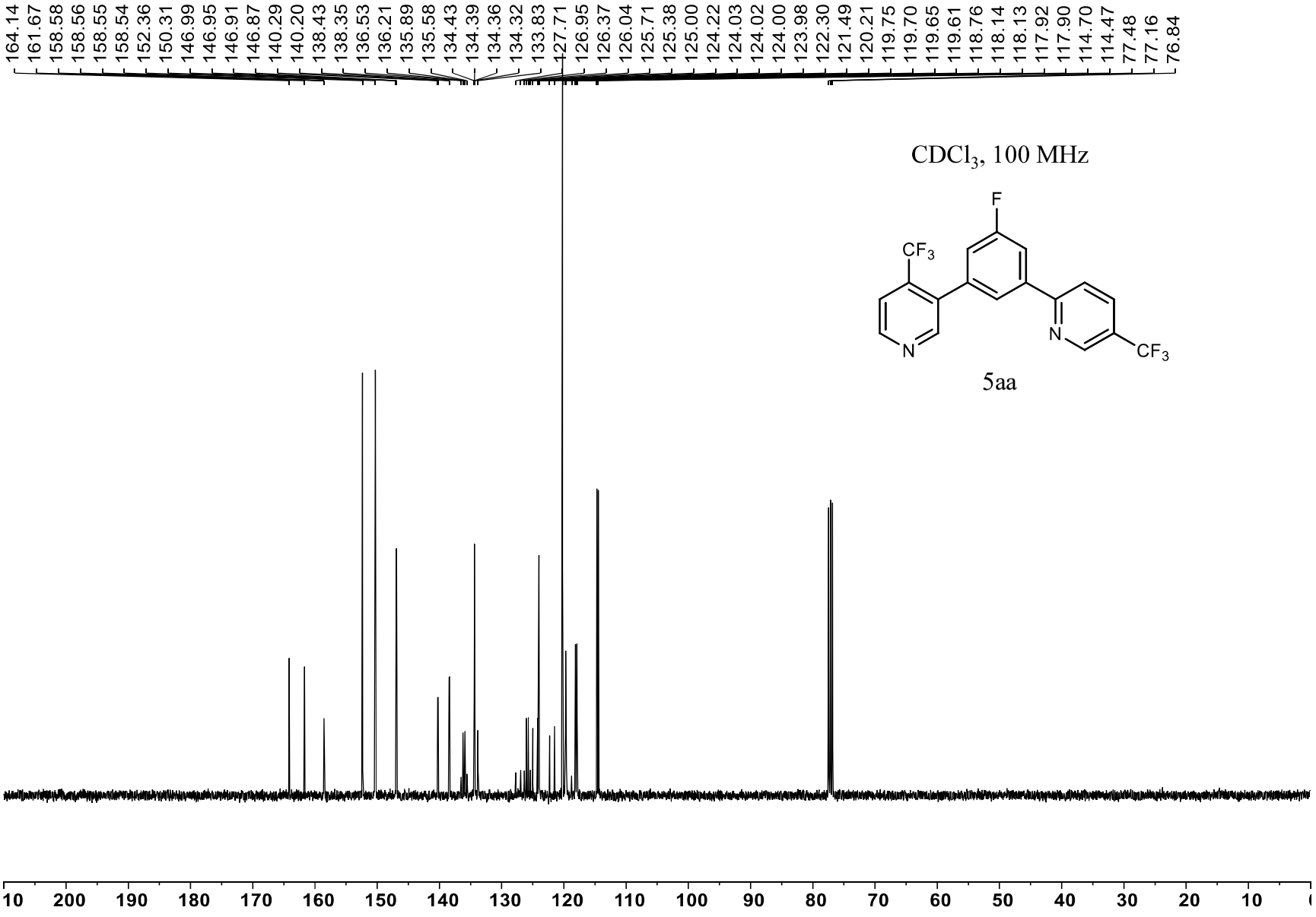

41.21
41.23
41.26
41.28
52.18
76.84
77.16
77.48
104.89
107.44
118.95
119.73
119.78
119.83
119.88
121.69
124.42
127.15
129.21
135.50
135.83
136.15
136.48
150.44
150.53
153.19
155.61
156.25
167.89
CDCl3, 100 MHz
Cl
N
CO2Me
N
H
CF3
N
5z

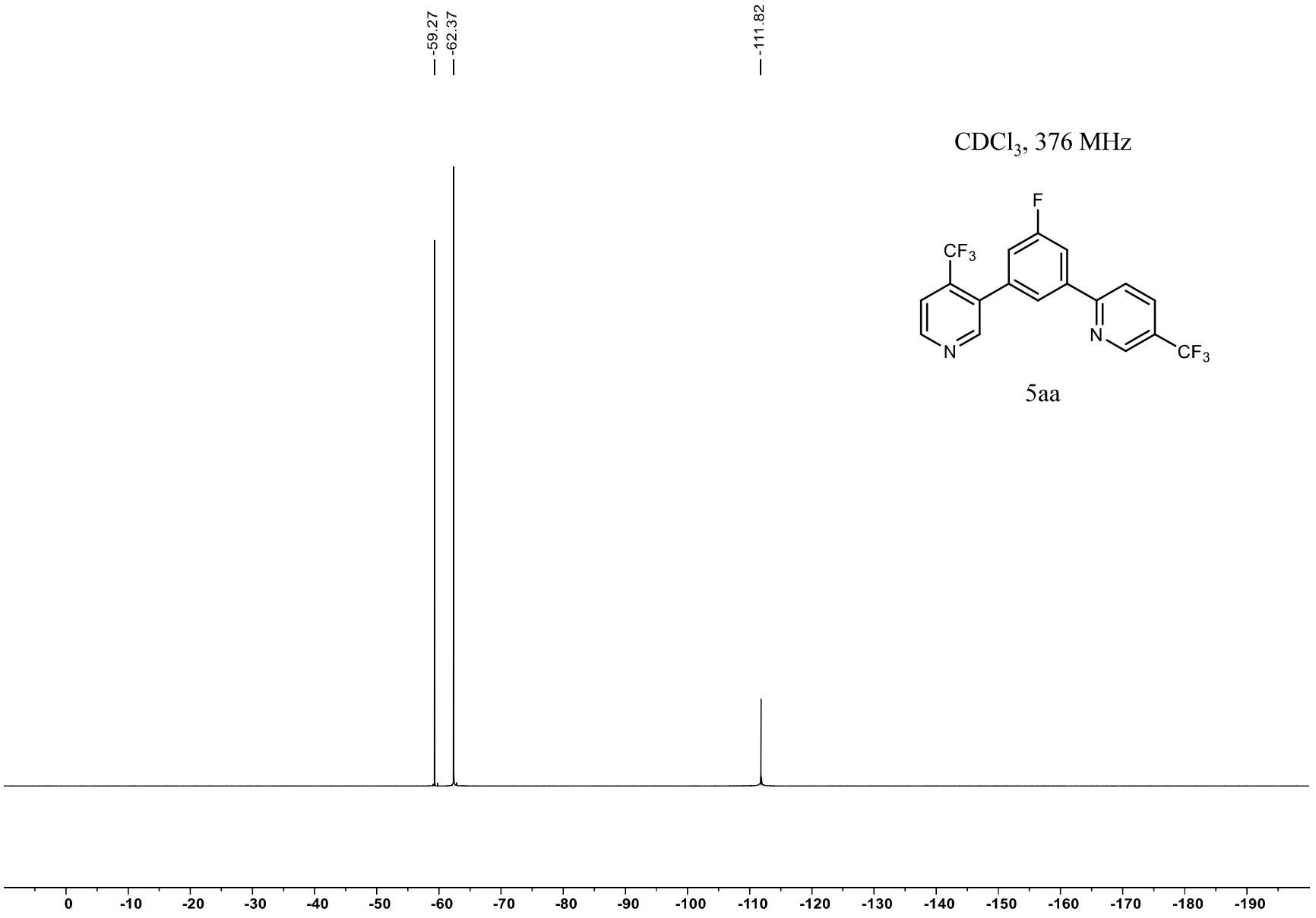


$CDCl_3$, 376 MHz

5z


8.96
8.96
8.95
8.95
8.95
8.86
8.85
8.73
8.03
8.03
8.01
8.01
7.91
7.90
7.90
7.90
7.88
7.88
7.88
7.87
7.87
7.85
7.84
7.83
7.83
7.67
7.66
7.26
7.21
7.20
7.20
7.19
7.18
7.18
CDCl3, 400 MHz
F
CF3
N
N
CF3
5aa
0.91
1.00
1.00
0.96
2.90
0.97
0.93
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


164.14
161.67
158.58
158.56
158.55
158.54
152.36
150.31
146.99
146.95
146.91
146.87
140.29
140.20
138.43
138.35
136.53
136.21
135.89
135.58
134.43
134.39
134.36
134.32
133.83
127.71
126.95
126.37
126.04
125.71
125.38
125.00
124.22
124.03
124.02
124.00
123.98
122.30
121.49
120.21
119.75
119.70
119.65
119.61
118.76
118.14
118.13
117.92
117.90
114.70
114.47
77.48
77.16
76.84
CDCl3, 100 MHz
F
CF3
N
N
CF3
5aa
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

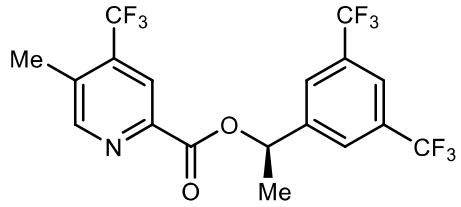


$CDCl_3$, 376 MHz

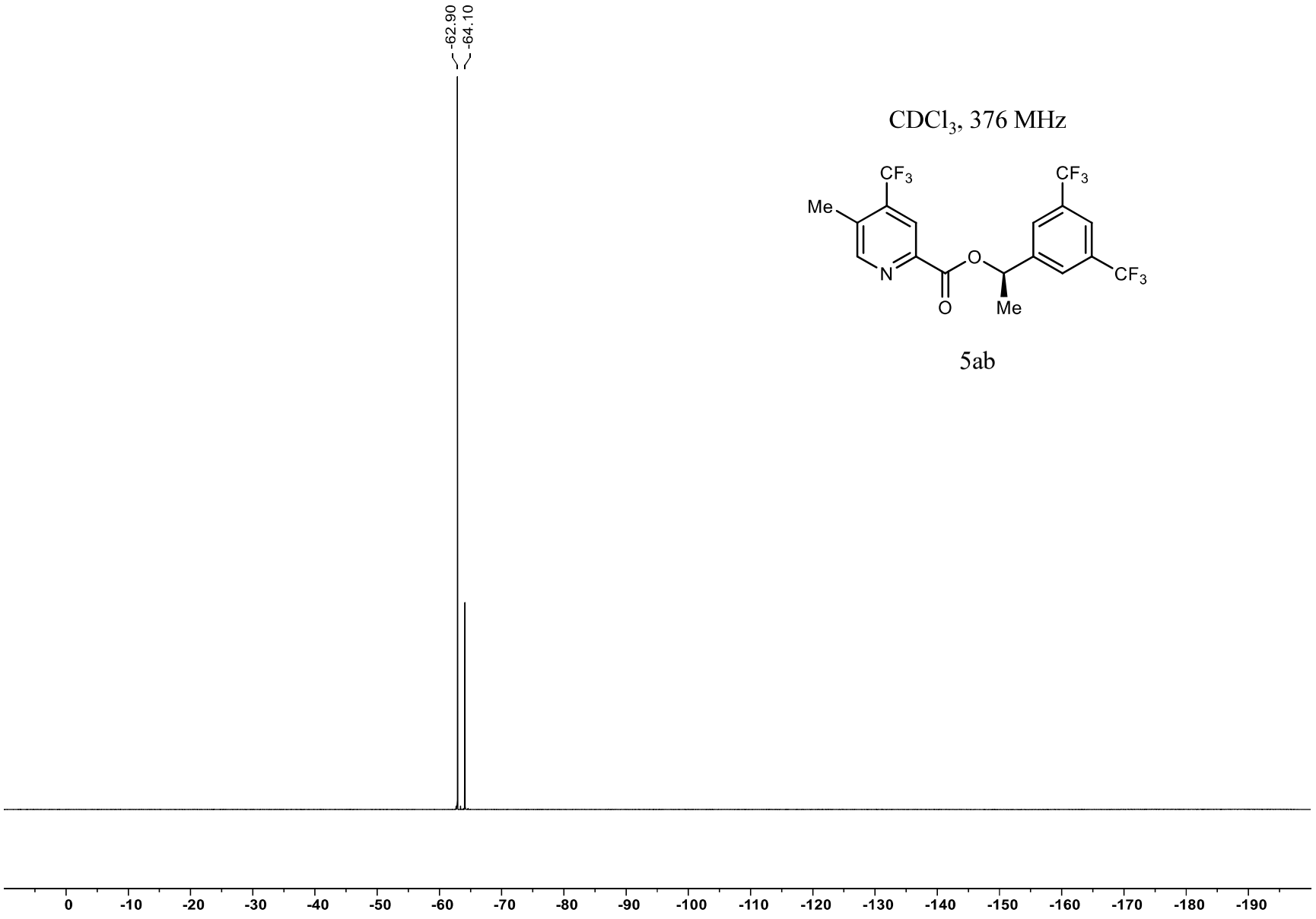
5aa

CDCl3, 400 MHz
5ab
CF3
CF3
Me
O
O
N
CF3
Me
8.75
8.28
7.93
7.83
7.26
6.30
6.29
6.27
6.25
2.57
1.80
1.79
1.00
0.96
1.97
0.97
1.02
3.10
3.15

$CDCl_3$, 100 MHz

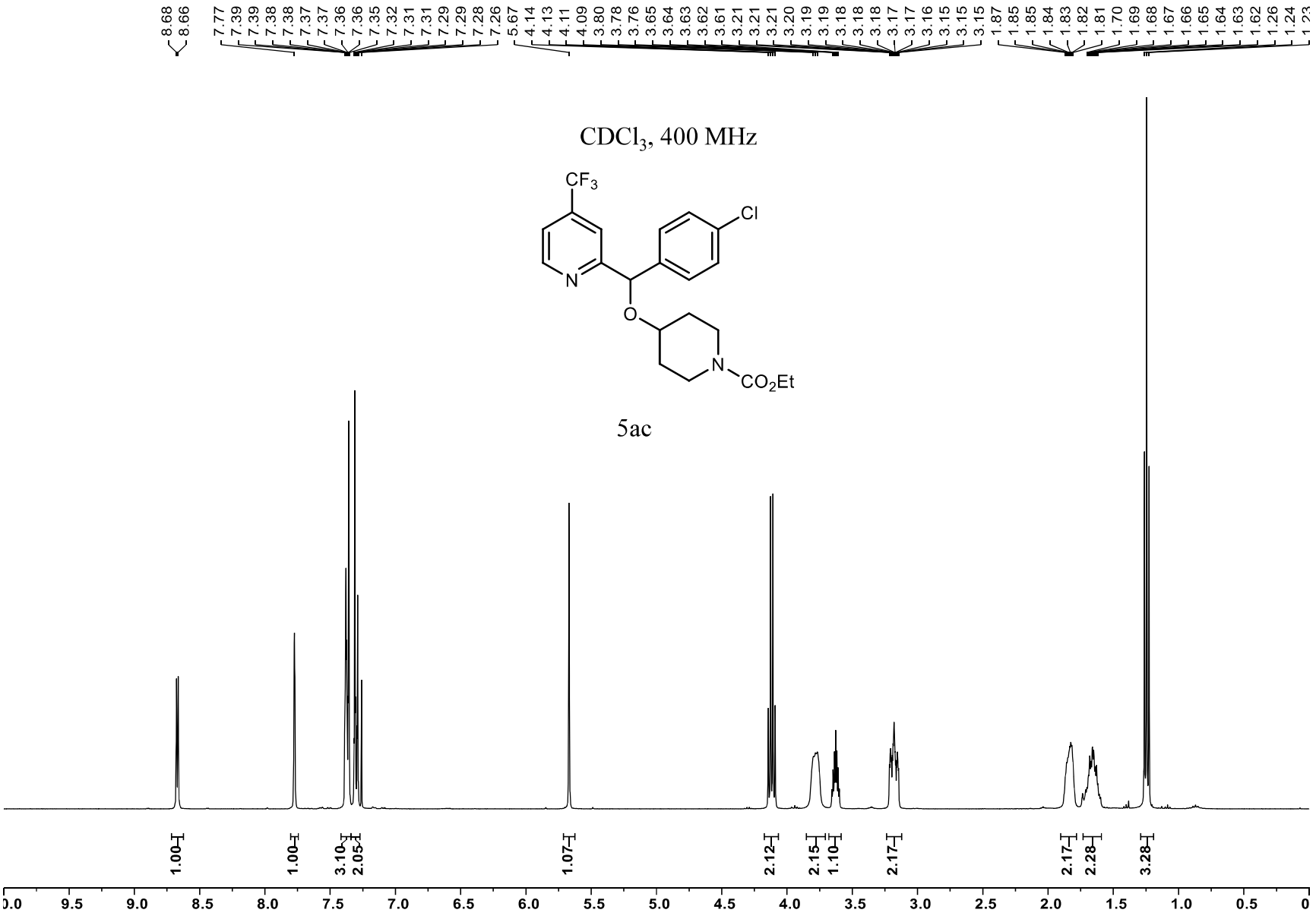


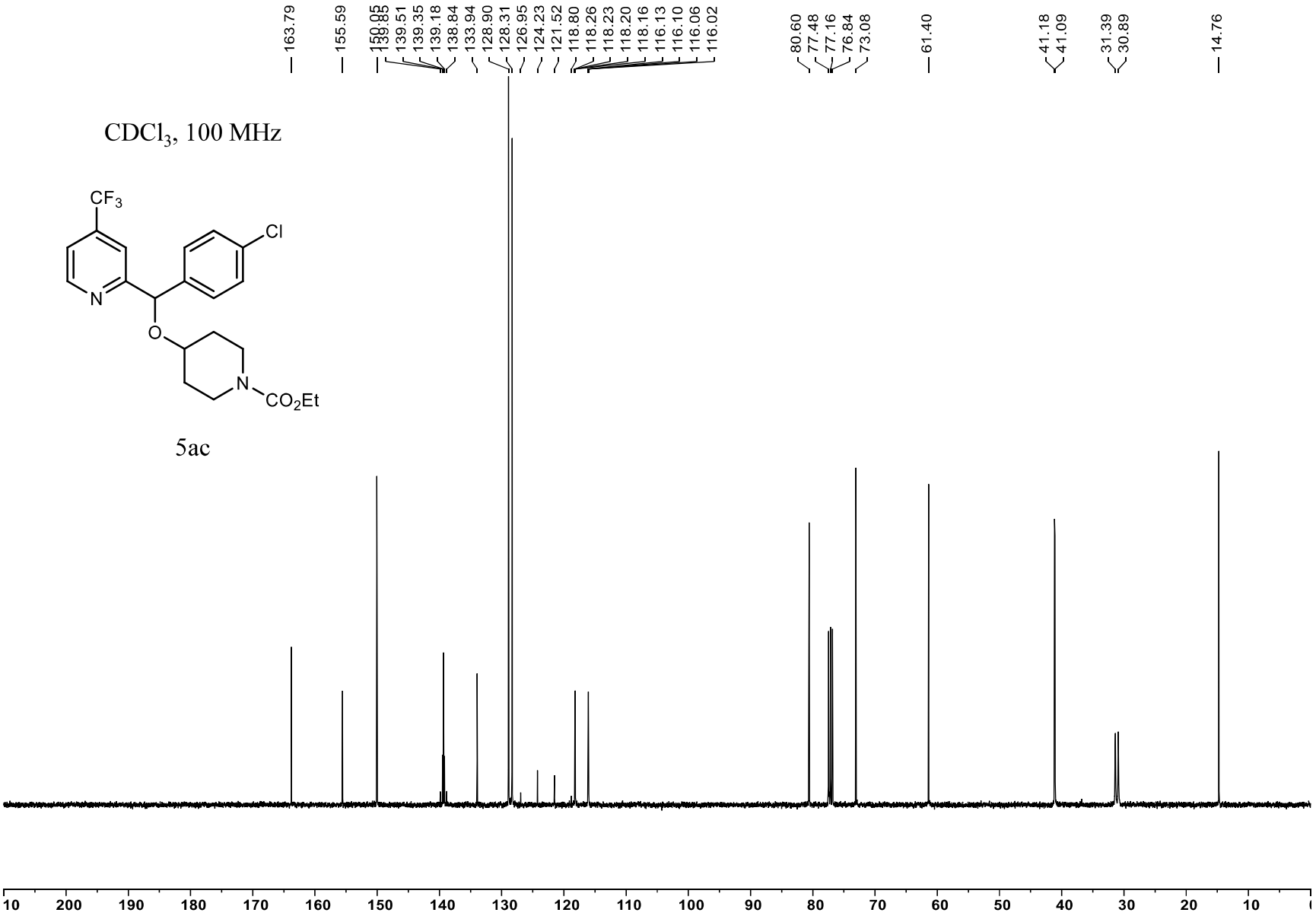
5ab

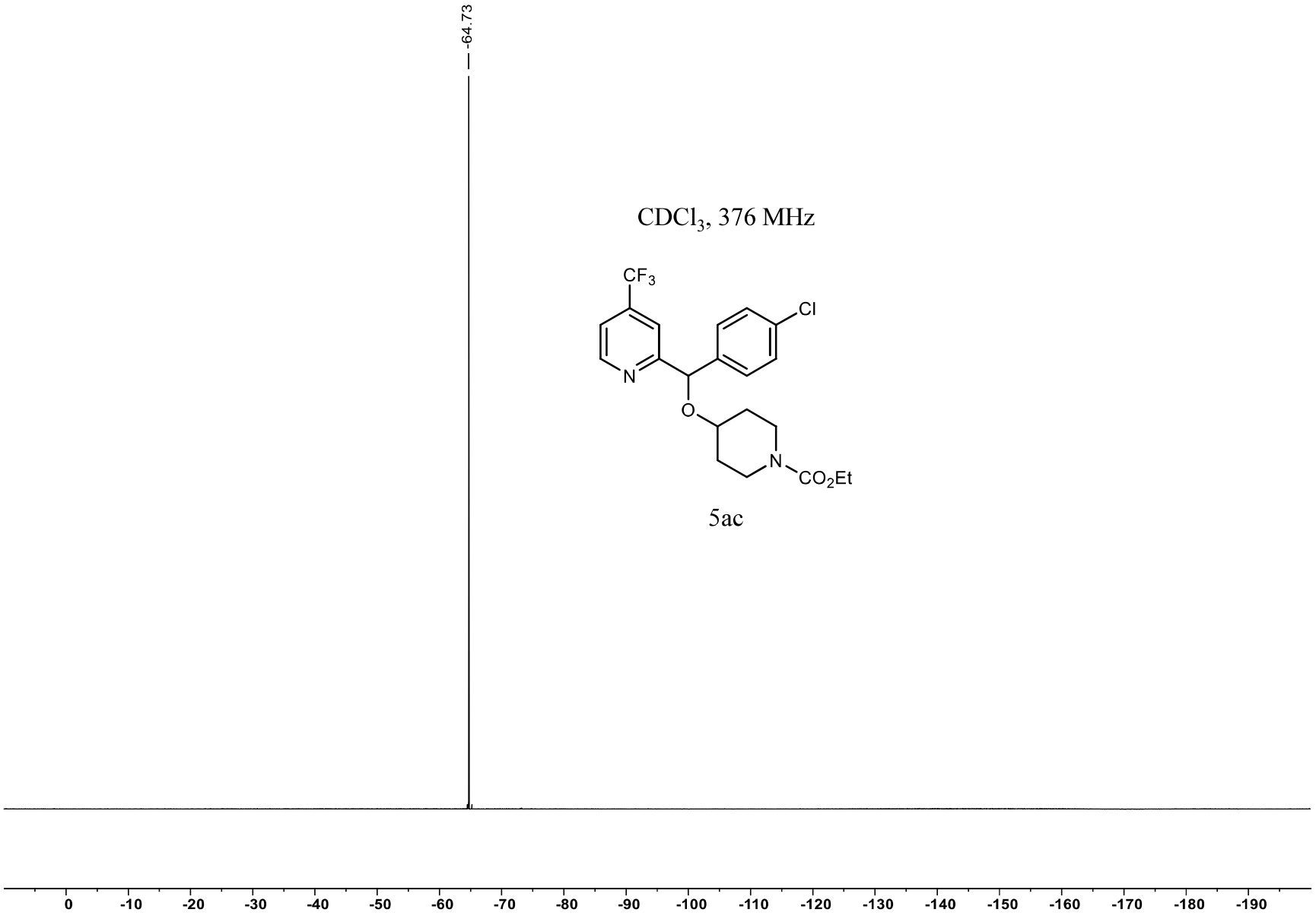


$CDCl_3$, 376 MHz

5ab

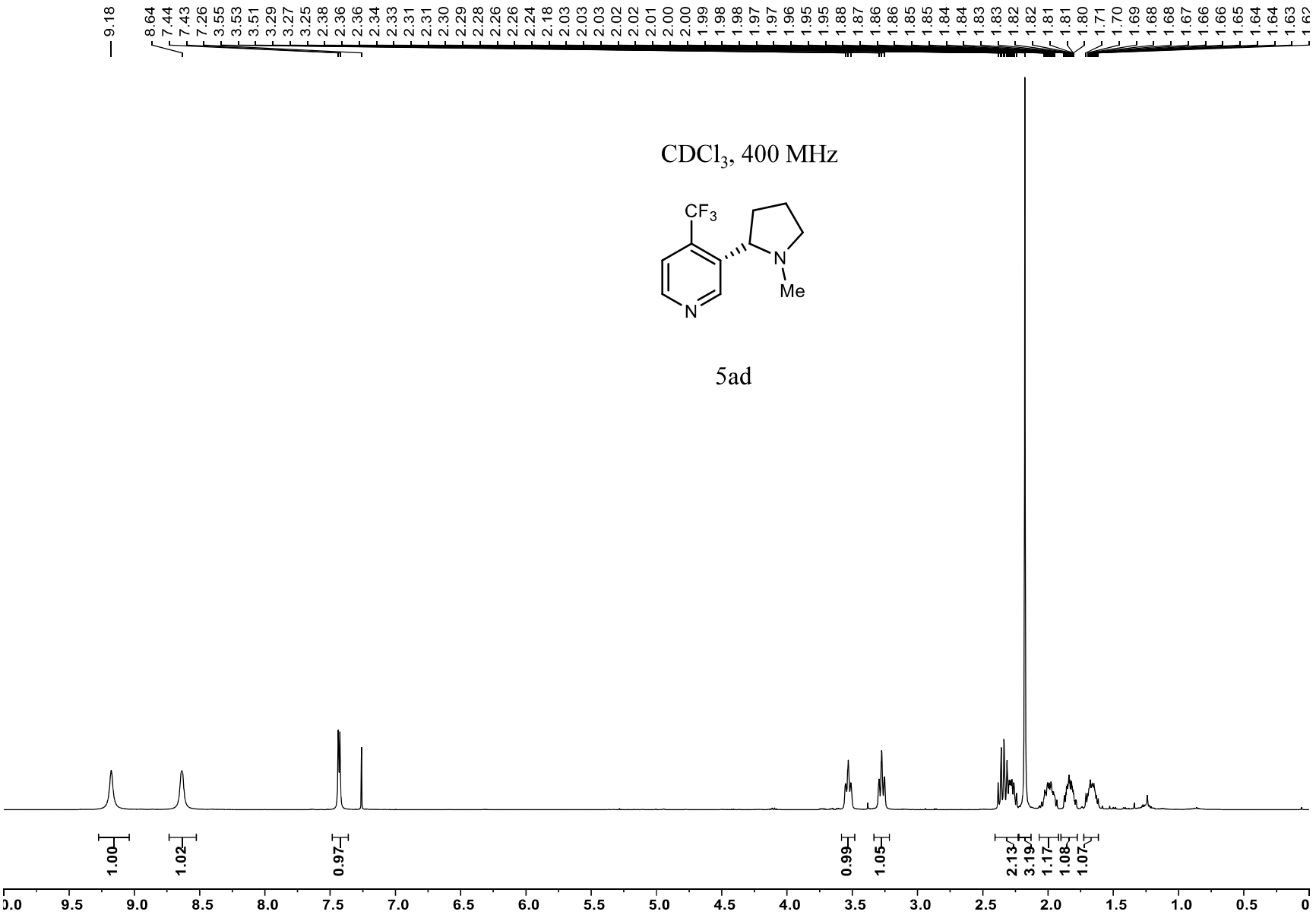

8.68
8.66
7.77
7.39
7.39
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.32
7.31
7.31
7.29
7.29
7.28
7.26
5.67
4.14
4.13
4.11
4.09
3.80
3.78
3.76
3.65
3.64
3.63
3.62
3.61
3.21
3.21
3.20
3.19
3.19
3.18
3.18
3.17
3.17
3.16
3.15
3.15
1.87
1.85
1.85
1.84
1.83
1.82
1.81
1.70
1.69
1.68
1.67
1.66
1.65
1.64
1.63
1.62
1.26
1.24
CDCl3, 400 MHz
CF3
Cl
N
O
N
CO2Et
5ac
1.00
1.00
3.10
2.05
1.07
2.12
2.15
1.10
2.17
2.17
2.28
3.28
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

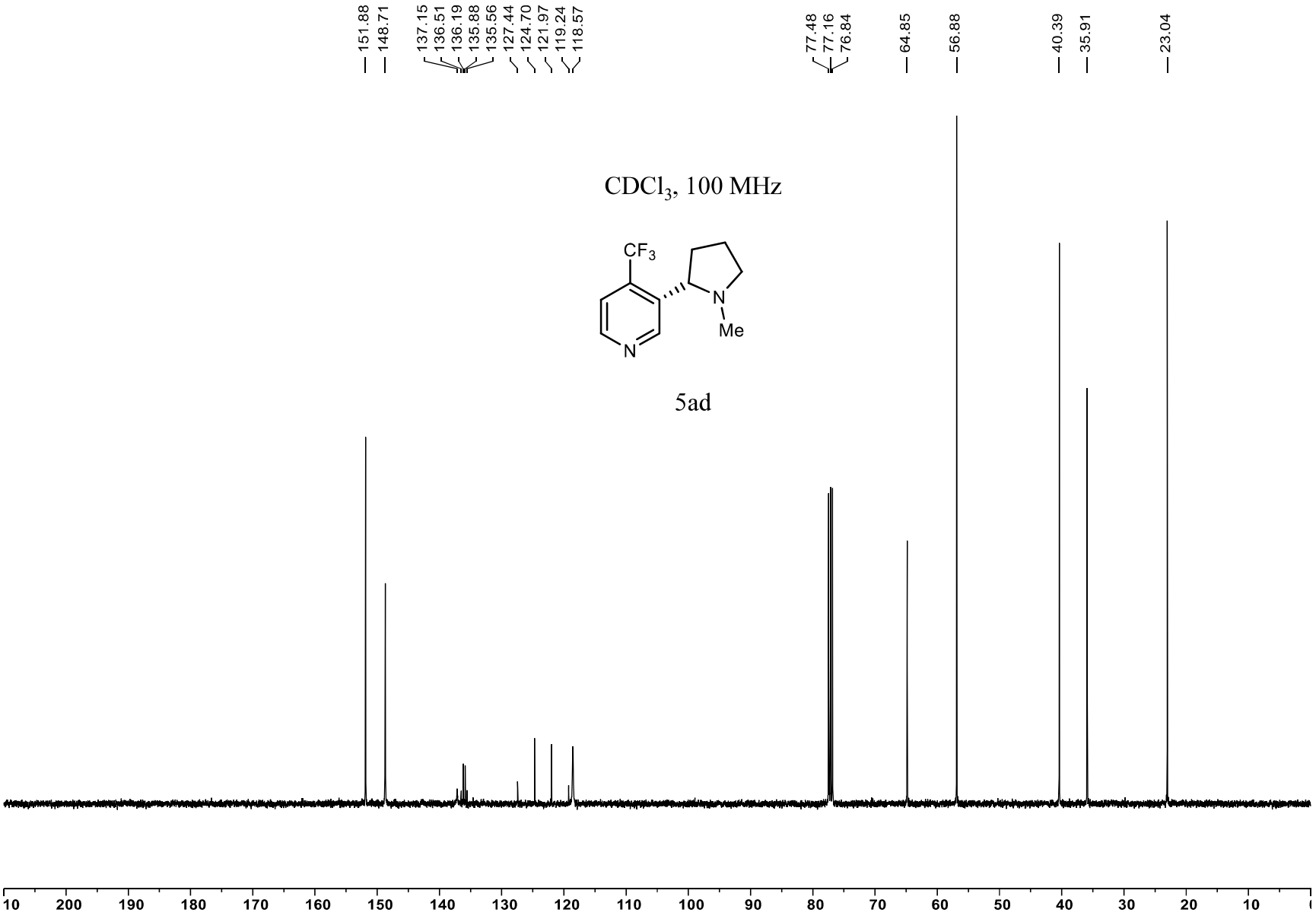

163.79
155.59
150.05
139.51
139.35
139.18
138.84
133.94
128.90
128.31
126.95
124.23
121.52
118.80
118.26
118.23
118.20
118.16
116.13
116.10
116.06
116.02
80.60
77.48
77.16
76.84
73.08
61.40
41.18
41.09
31.39
30.89
14.76
CDCl3, 100 MHz
CF3
Cl
N
O
N
CO2Et
5ac
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

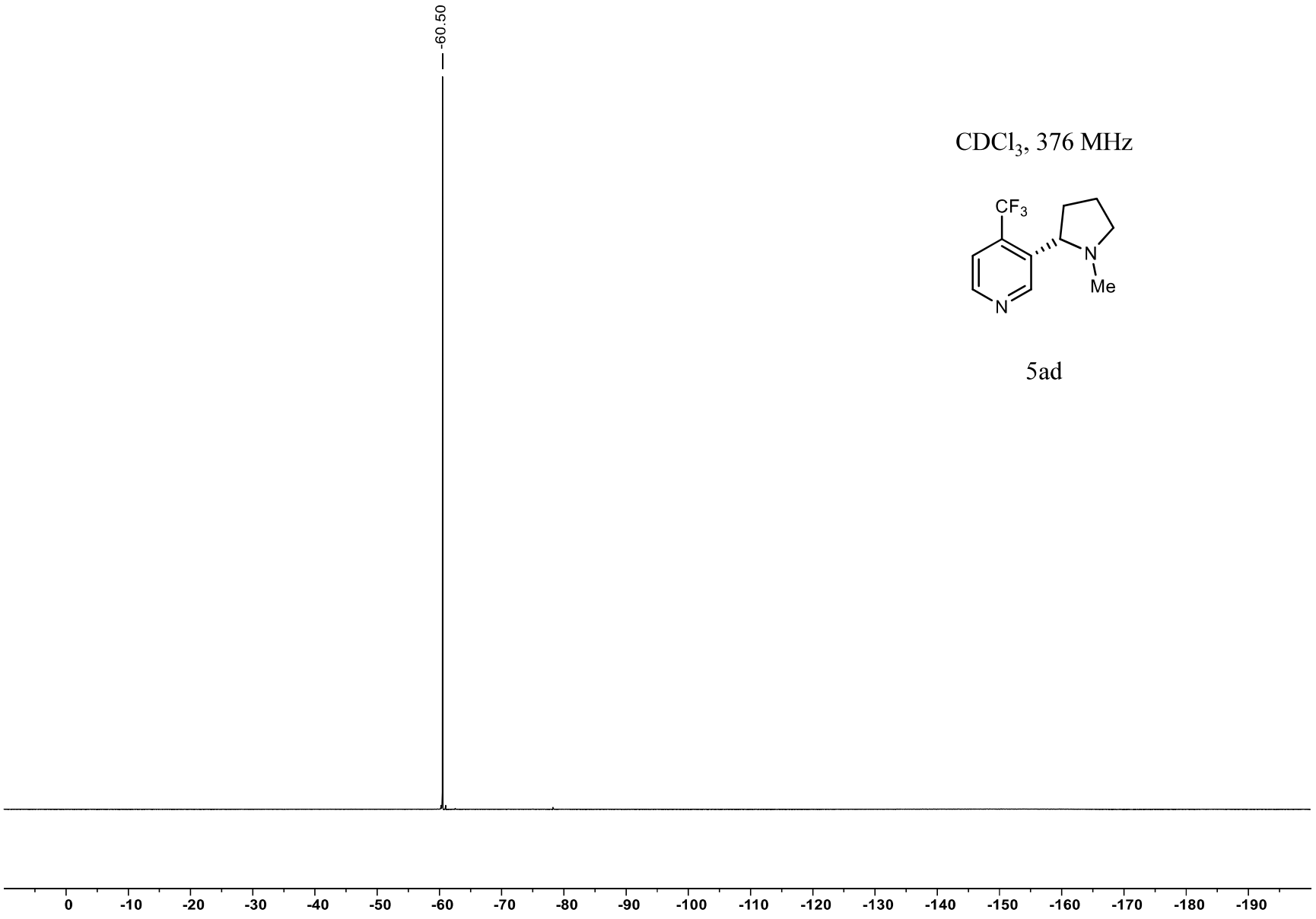


$CDCl_3$, 376 MHz

5ac

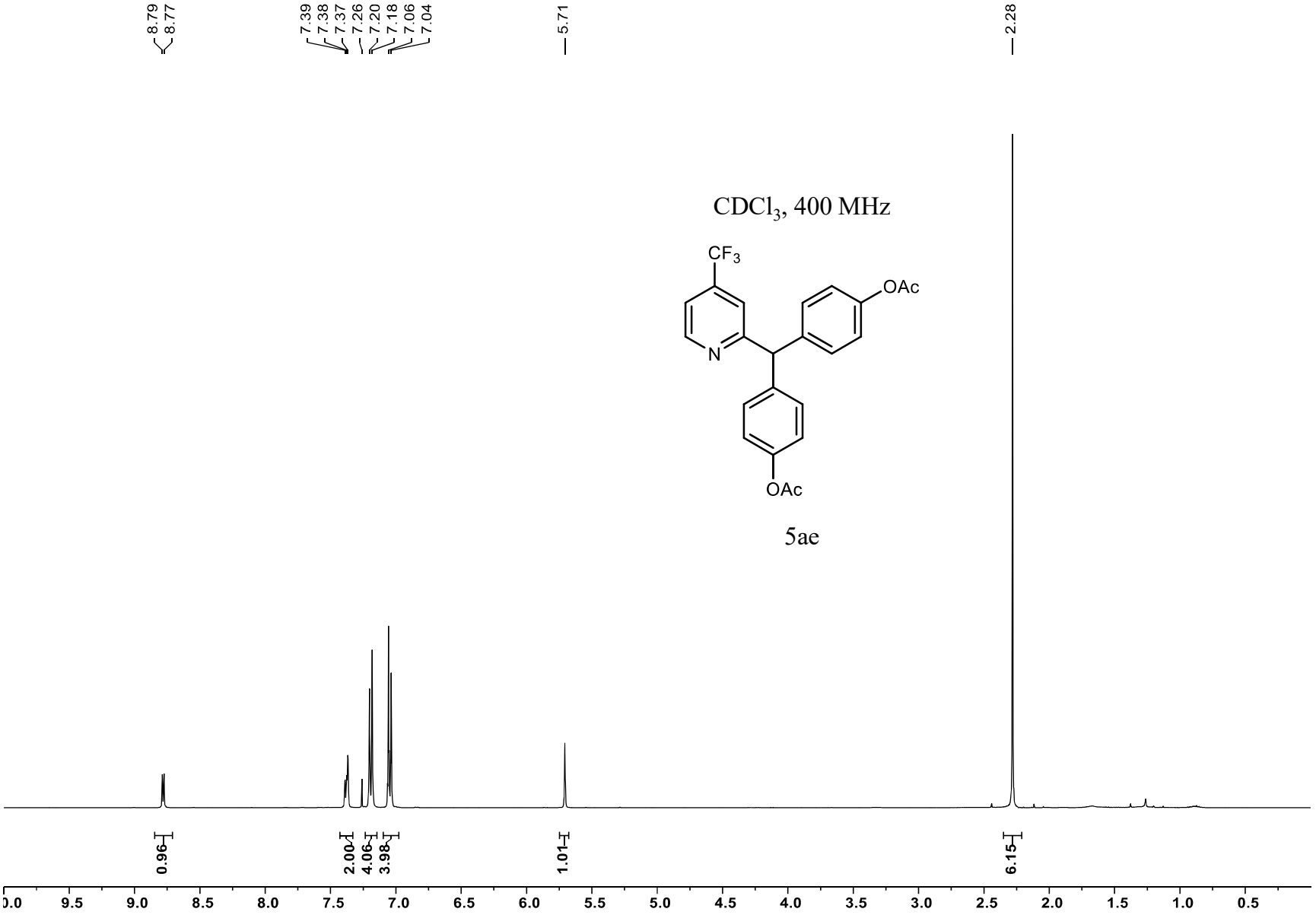

9.18
8.64
7.44
7.43
7.26
3.55
3.53
3.51
3.29
3.27
3.25
2.38
2.36
2.36
2.34
2.33
2.31
2.31
2.30
2.29
2.28
2.26
2.26
2.24
2.18
2.03
2.03
2.03
2.02
2.02
2.01
2.00
2.00
1.99
1.98
1.98
1.97
1.97
1.96
1.95
1.95
1.88
1.87
1.86
1.86
1.85
1.85
1.84
1.84
1.83
1.83
1.82
1.82
1.81
1.81
1.80
1.71
1.70
1.69
1.68
1.68
1.67
1.66
1.66
1.65
1.64
1.64
1.63
CDCl3, 400 MHz
CF3
N
Me
N
5ad
1.00
1.02
0.97
0.99
1.05
2.13
3.19
1.17
1.08
1.07
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


151.88
148.71
137.15
136.51
136.19
135.88
135.56
127.44
124.70
121.97
119.24
118.57
77.48
77.16
76.84
64.85
56.88
40.39
35.91
23.04
CDCl3, 100 MHz
CF3
N
Me
N
5ad
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

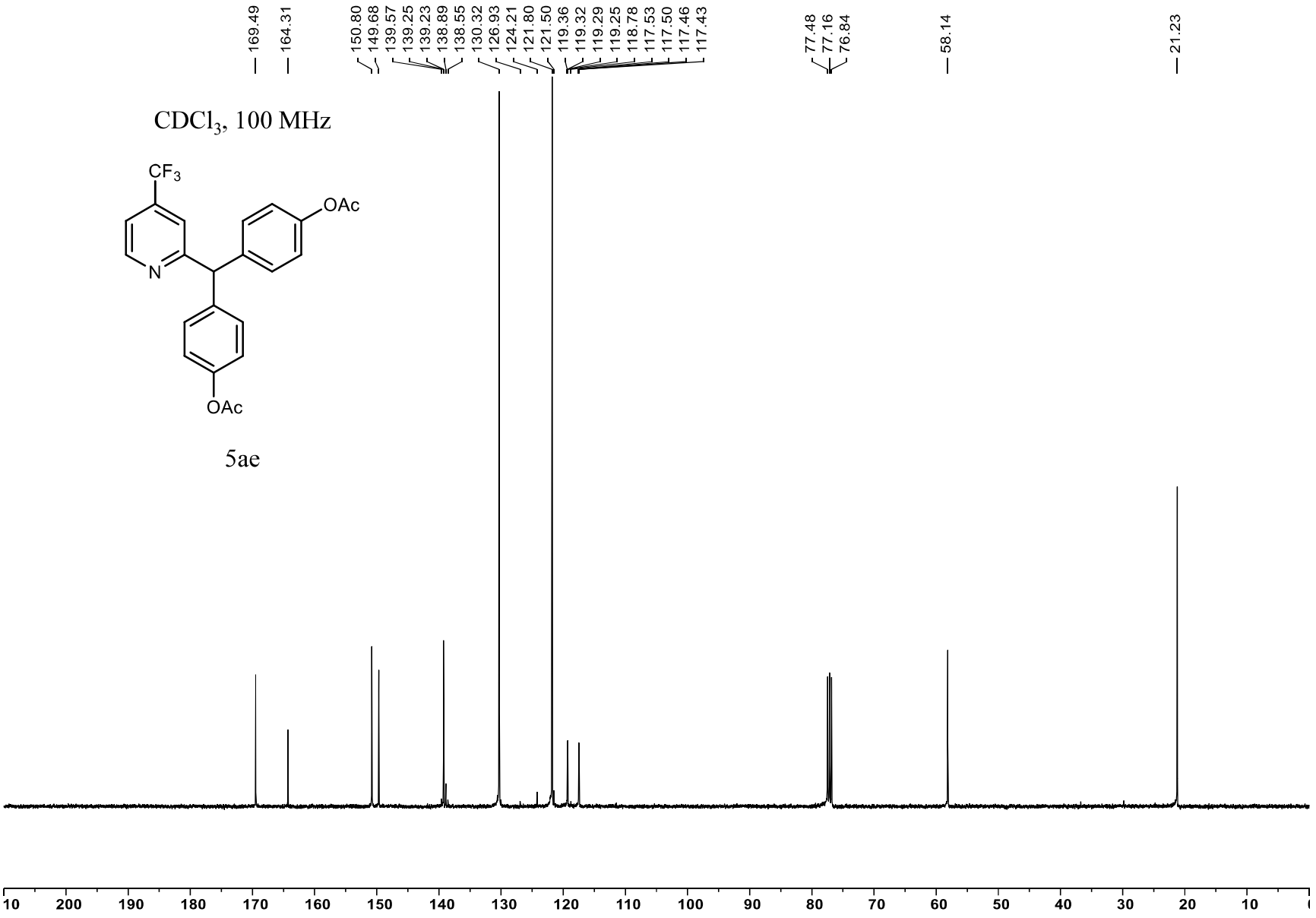


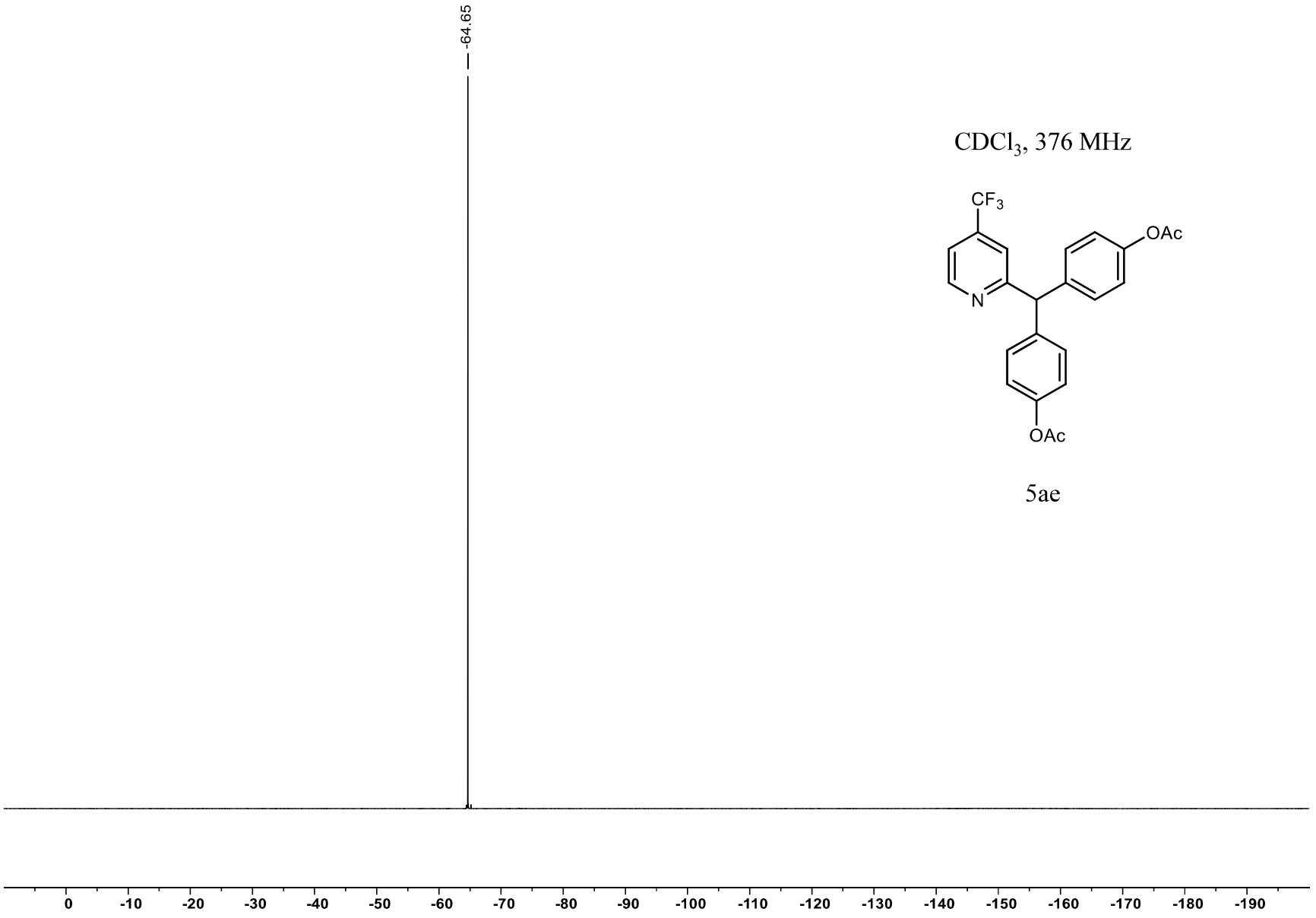
$CDCl_3$, 376 MHz

5ad


8.79
8.77
7.39
7.38
7.37
7.26
7.20
7.18
7.06
7.04
5.71
2.28
CDCl3, 400 MHz
CF3
OAc
N
OAc
0.96
2.00
4.06
3.98
1.01
6.15
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

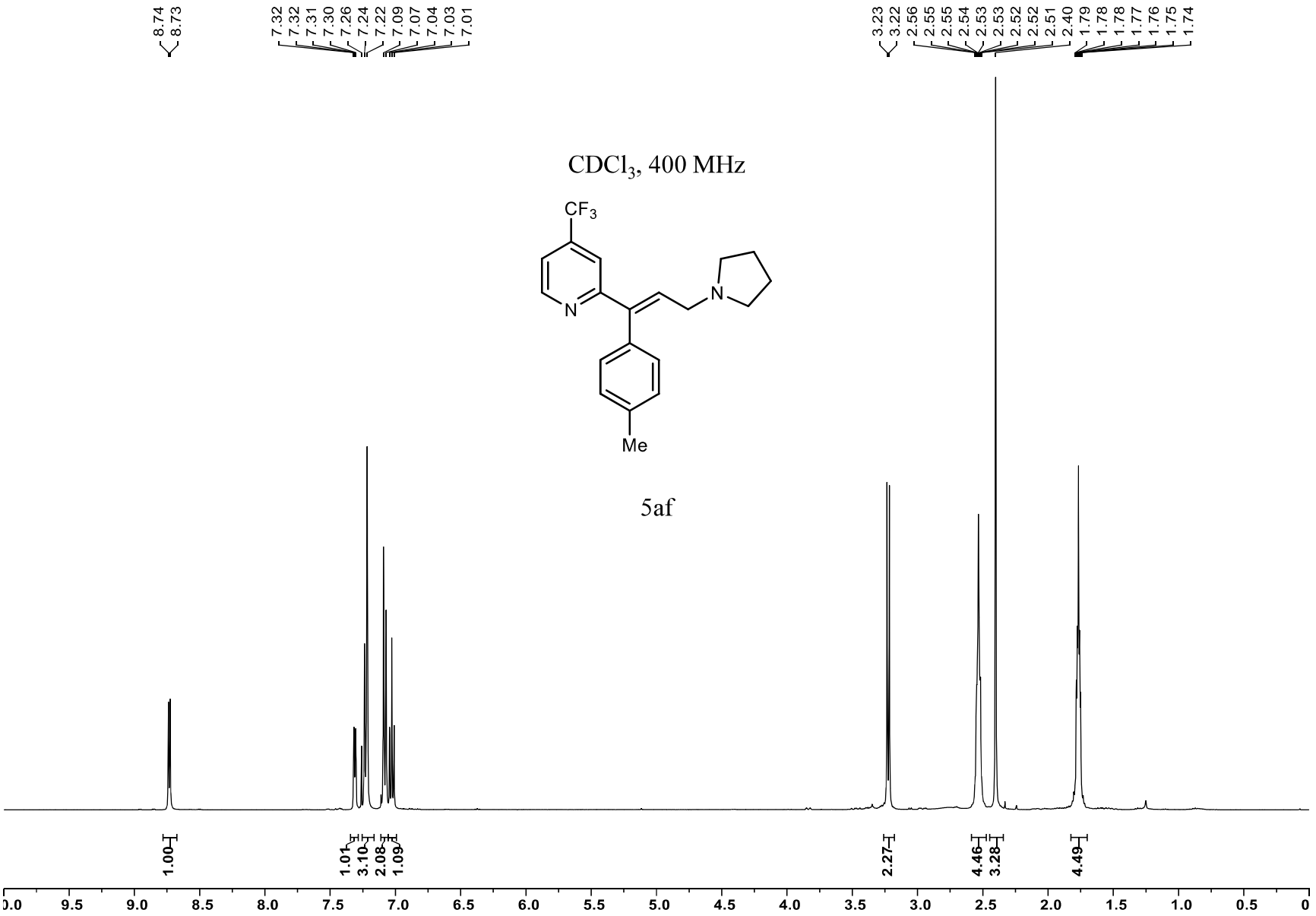
5ae

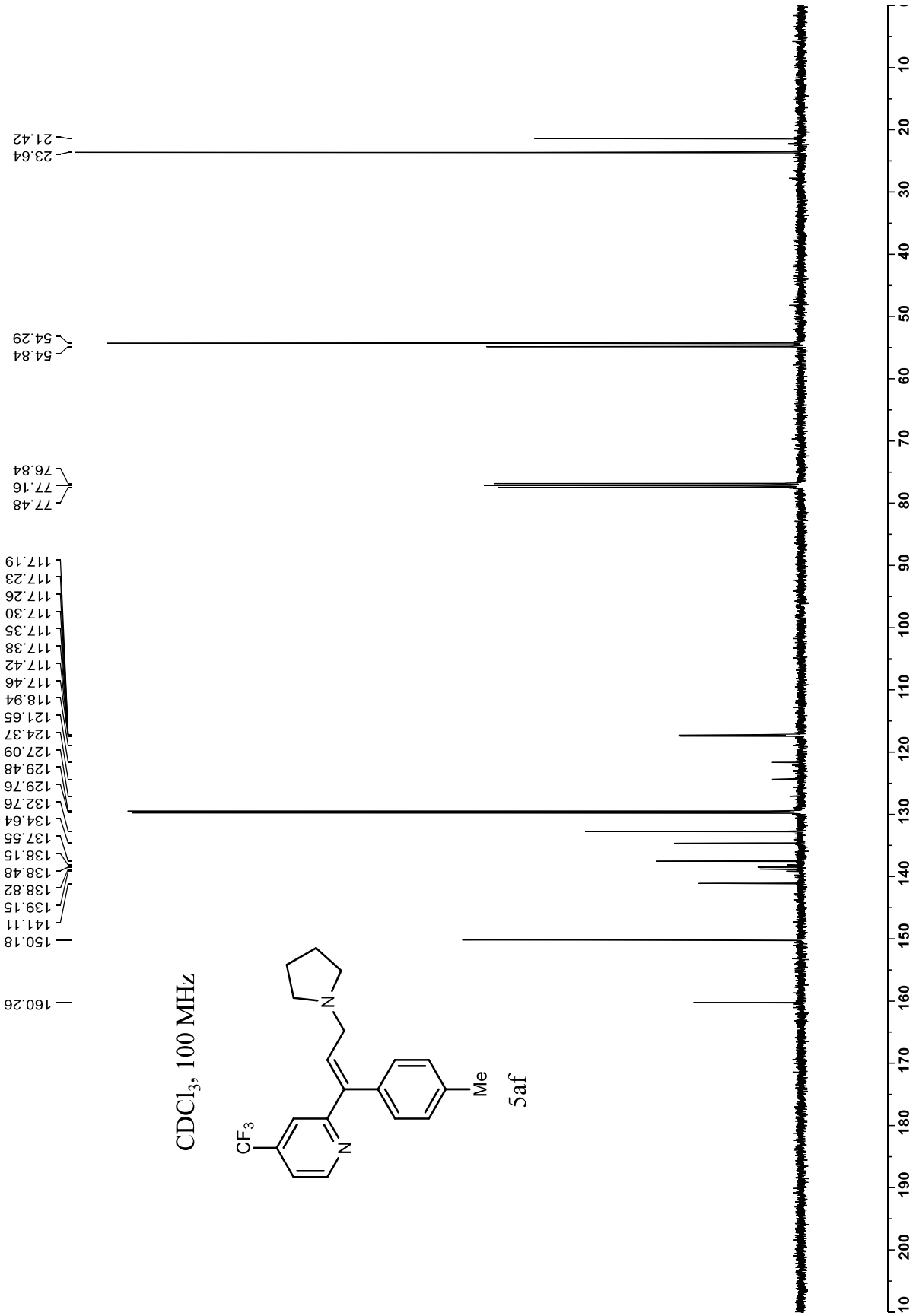

169.49
164.31
150.80
149.68
139.57
139.25
139.23
138.89
138.55
130.32
126.93
124.21
121.80
121.50
119.36
119.32
119.29
119.25
118.78
117.53
117.50
117.46
117.43
77.48
77.16
76.84
58.14
21.23
CDCl3, 100 MHz
CF3
OAc
N
OAc
5ae
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

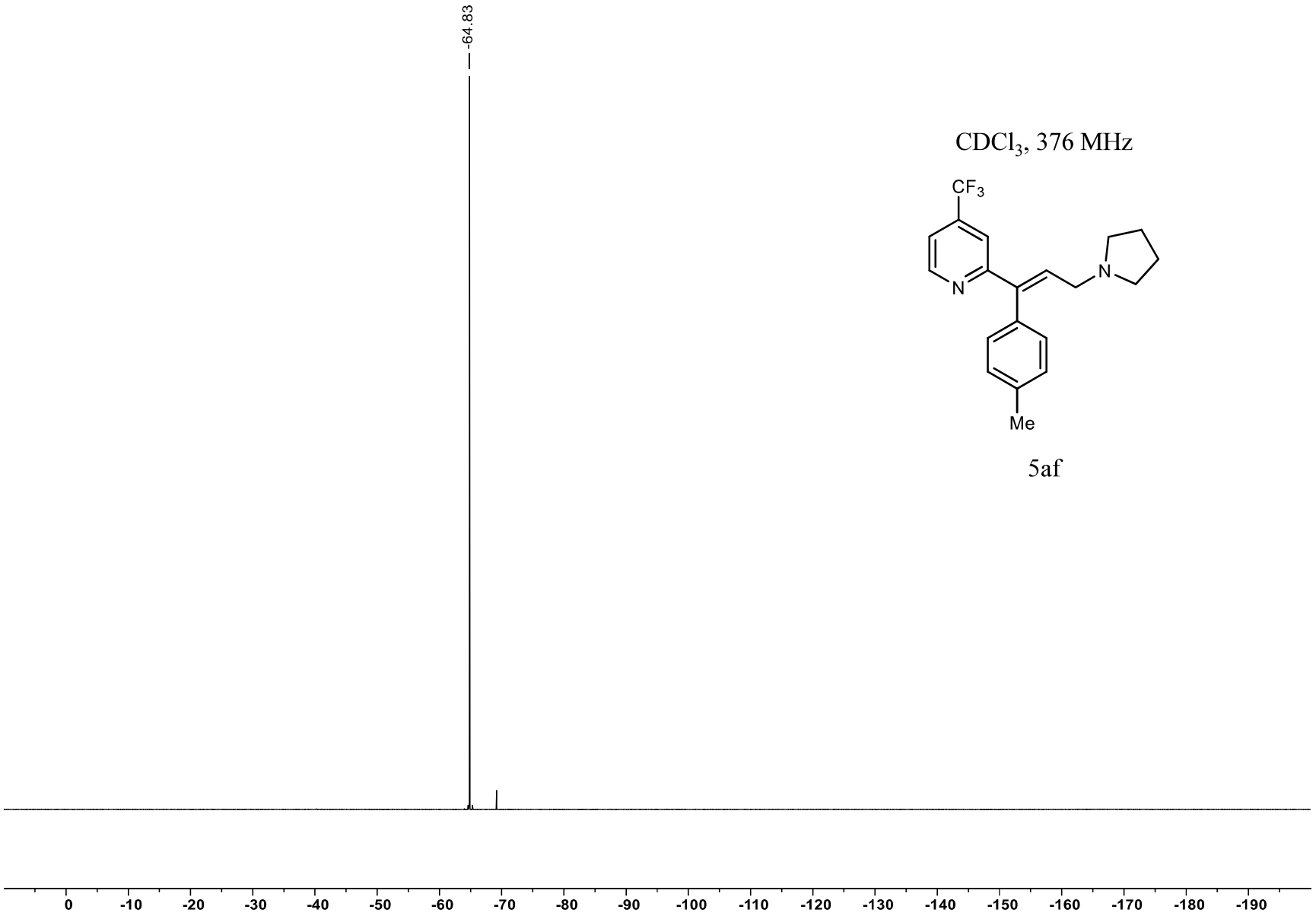


$CDCl_3$, 376 MHz

5ae

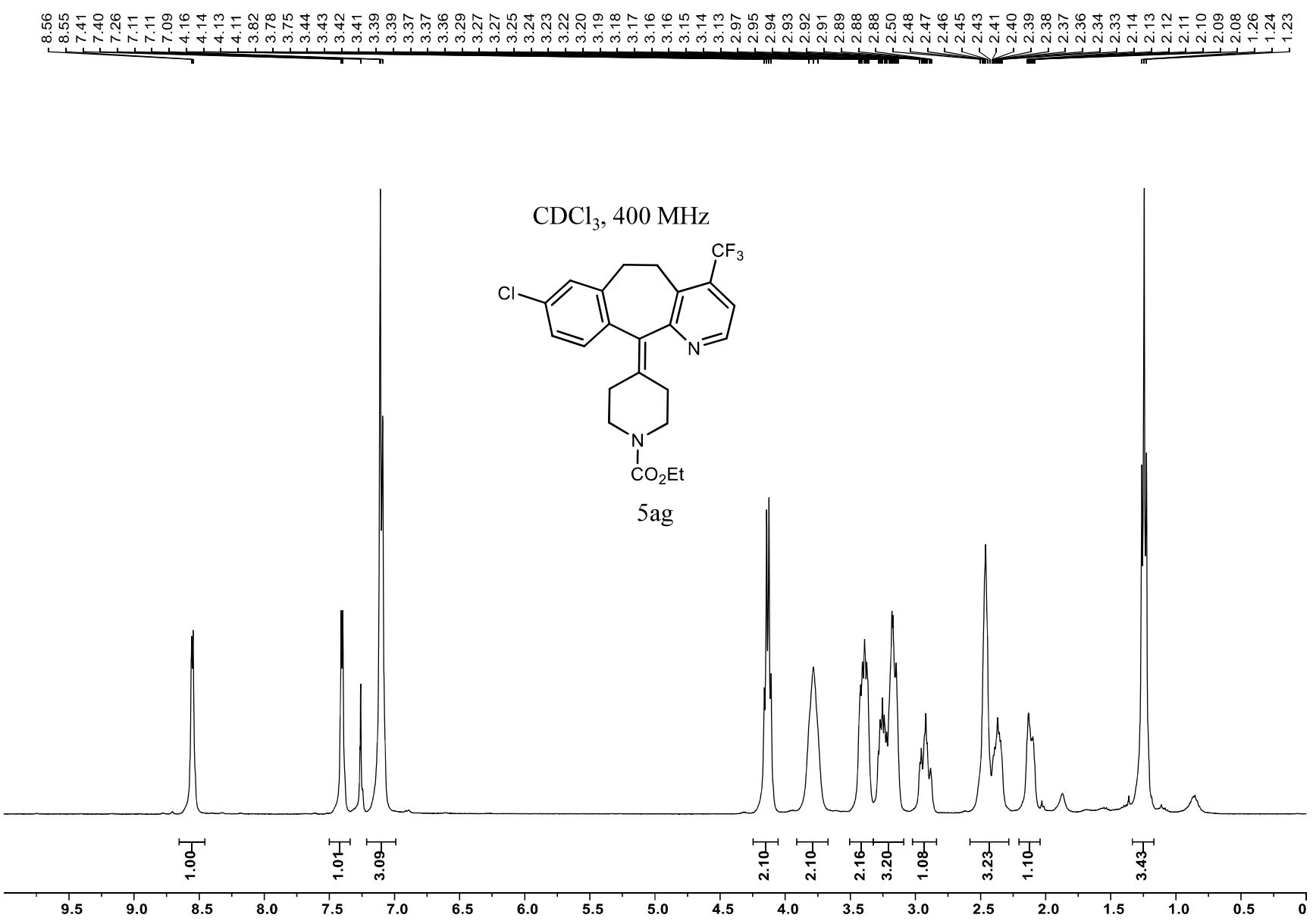

8.74
8.73
7.32
7.32
7.31
7.30
7.26
7.24
7.22
7.09
7.07
7.04
7.03
7.01
3.23
3.22
2.56
2.55
2.55
2.54
2.53
2.53
2.52
2.52
2.51
2.40
1.79
1.78
1.78
1.77
1.76
1.75
1.74
CDCl3, 400 MHz
CF3
N
N
Me
5af
1.00
1.01
3.10
2.08
1.09
2.27
4.46
3.28
4.49
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

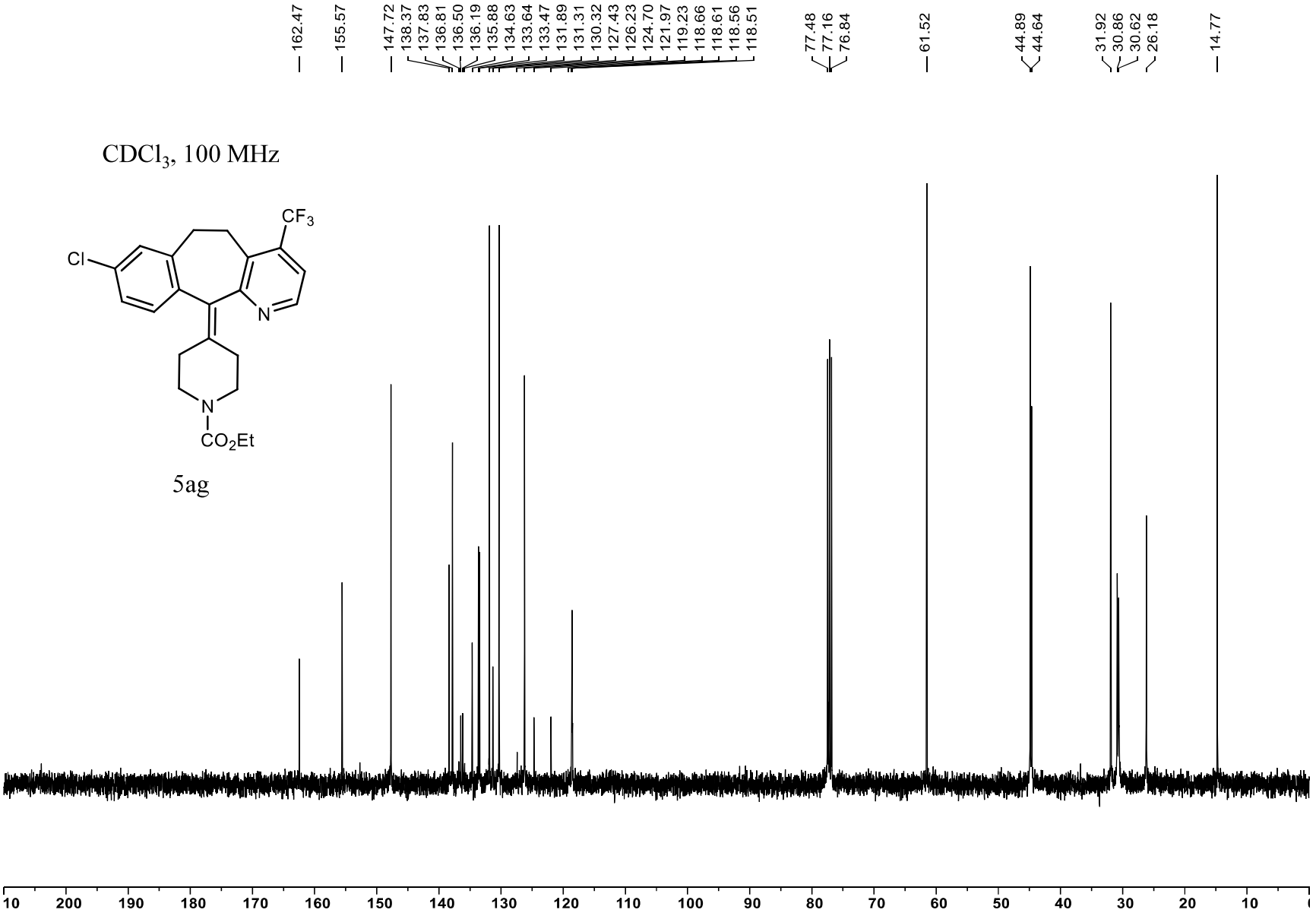

21.42
23.64
54.29
54.84
76.84
77.16
77.48
117.19
117.23
117.26
117.30
117.35
117.38
117.42
117.46
118.94
121.65
124.37
127.09
129.48
129.76
132.76
134.64
137.55
138.15
138.48
138.82
139.15
141.11
150.18
160.26
CDCl3, 100 MHz
CF3
N
N
Me
5af
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
10

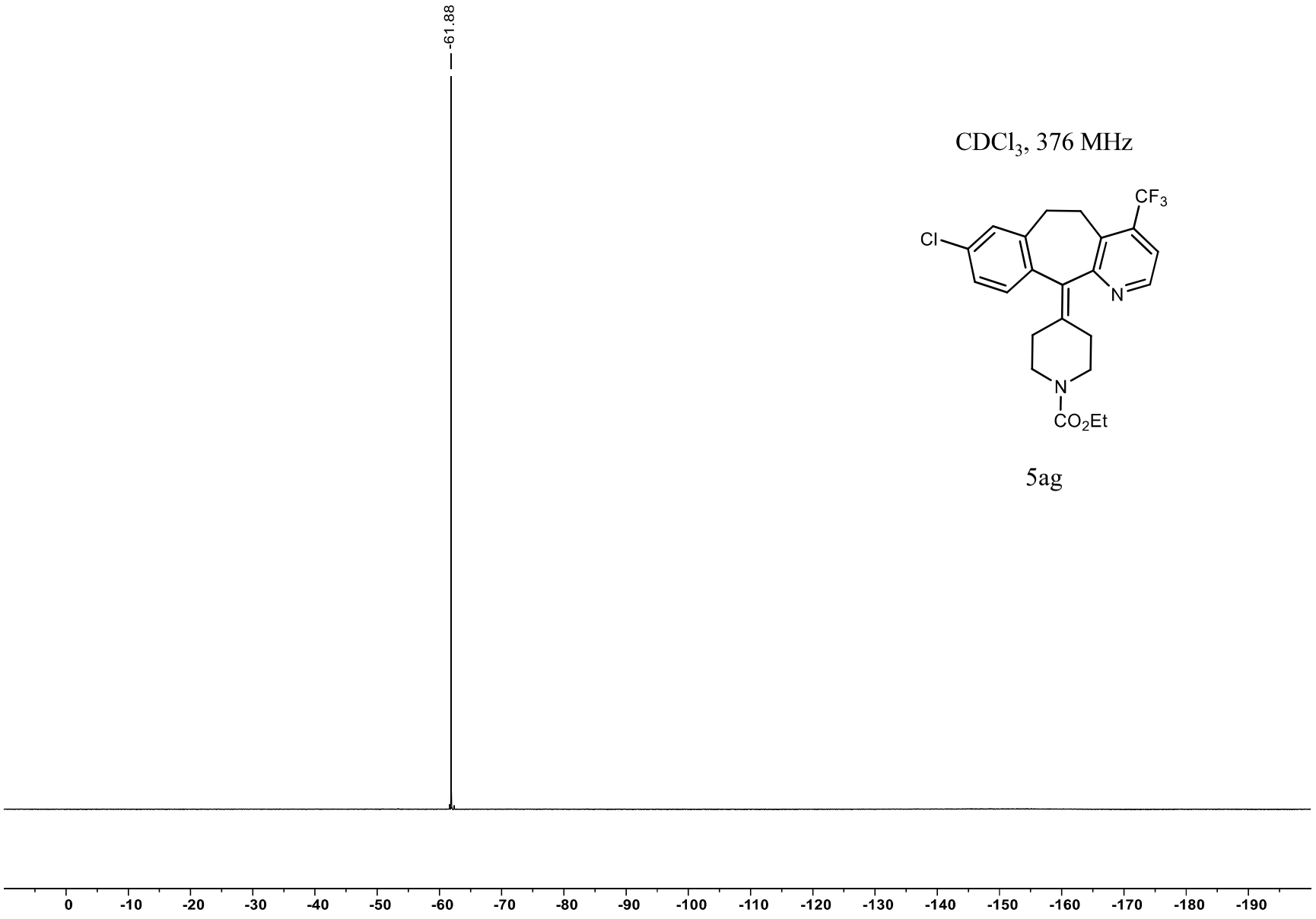


$CDCl_3$, 376 MHz

5af

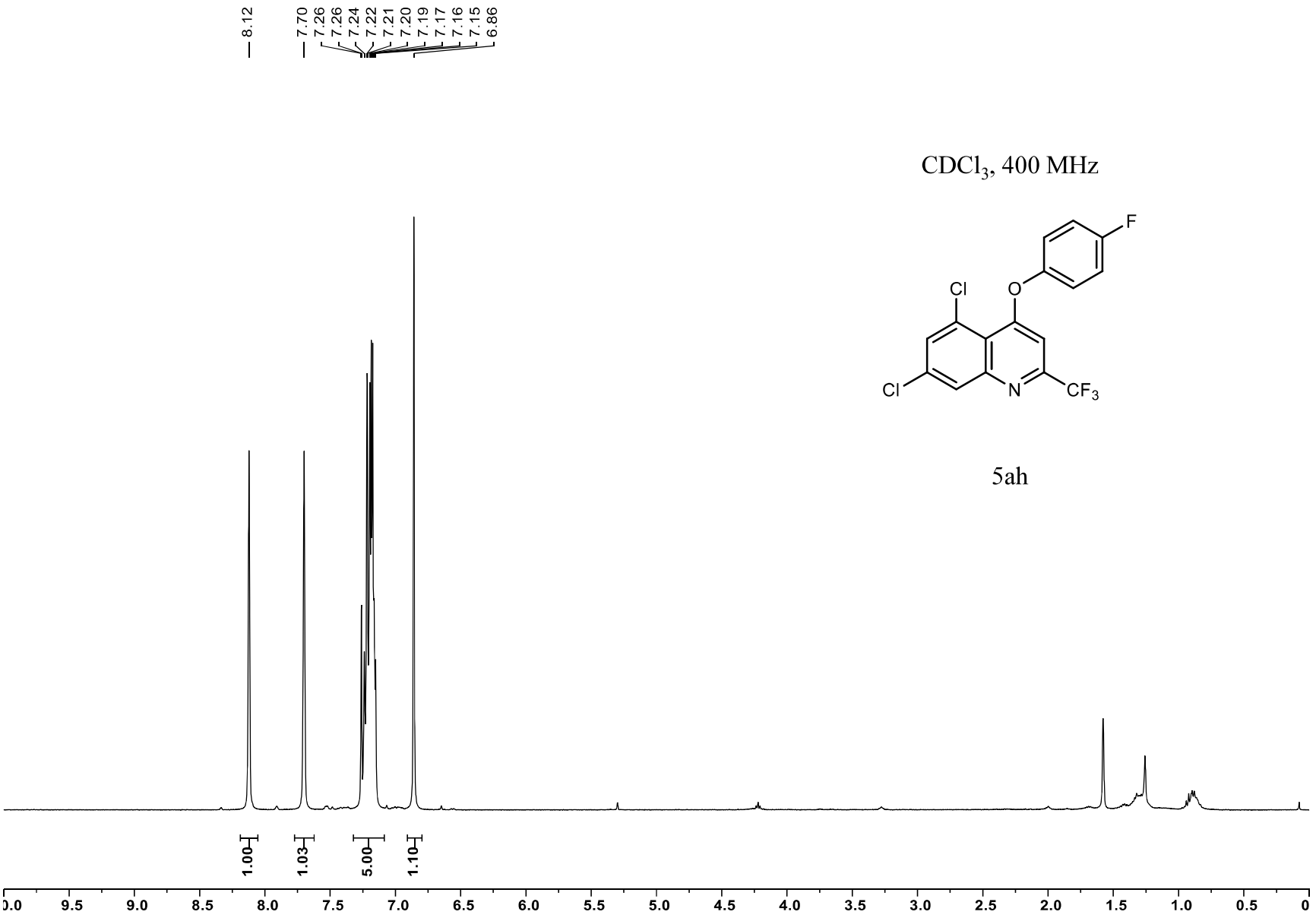

8.56 8.55 7.41 7.40 7.26 7.11 7.11 7.09 4.16 4.14 4.13 4.11 3.82 3.78 3.75 3.44 3.43 3.42 3.41 3.39 3.39 3.37 3.37 3.36 3.29 3.27 3.27 3.25 3.24 3.23 3.22 3.20 3.19 3.18 3.17 3.16 3.16 3.15 3.14 3.13 2.97 2.95 2.94 2.93 2.92 2.91 2.89 2.88 2.88 2.50 2.48 2.47 2.46 2.45 2.43 2.41 2.40 2.39 2.38 2.37 2.36 2.34 2.33 2.14 2.13 2.12 2.11 2.10 2.09 2.08 1.26 1.24 1.23
CDCl3, 400 MHz
CF3
Cl
N
N
CO2Et
5ag
1.00 1.01 3.09 2.10 2.10 2.16 3.20 1.08 3.23 1.10 3.43
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


162.47
155.57
147.72
138.37
137.83
136.81
136.50
136.19
135.88
134.63
133.64
133.47
131.89
131.31
130.32
127.43
126.23
124.70
121.97
119.23
118.66
118.61
118.56
118.51
77.48
77.16
76.84
61.52
44.89
44.64
31.92
30.86
30.62
26.18
14.77
CDCl3, 100 MHz
CF3
Cl
N
N
CO2Et
5ag
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



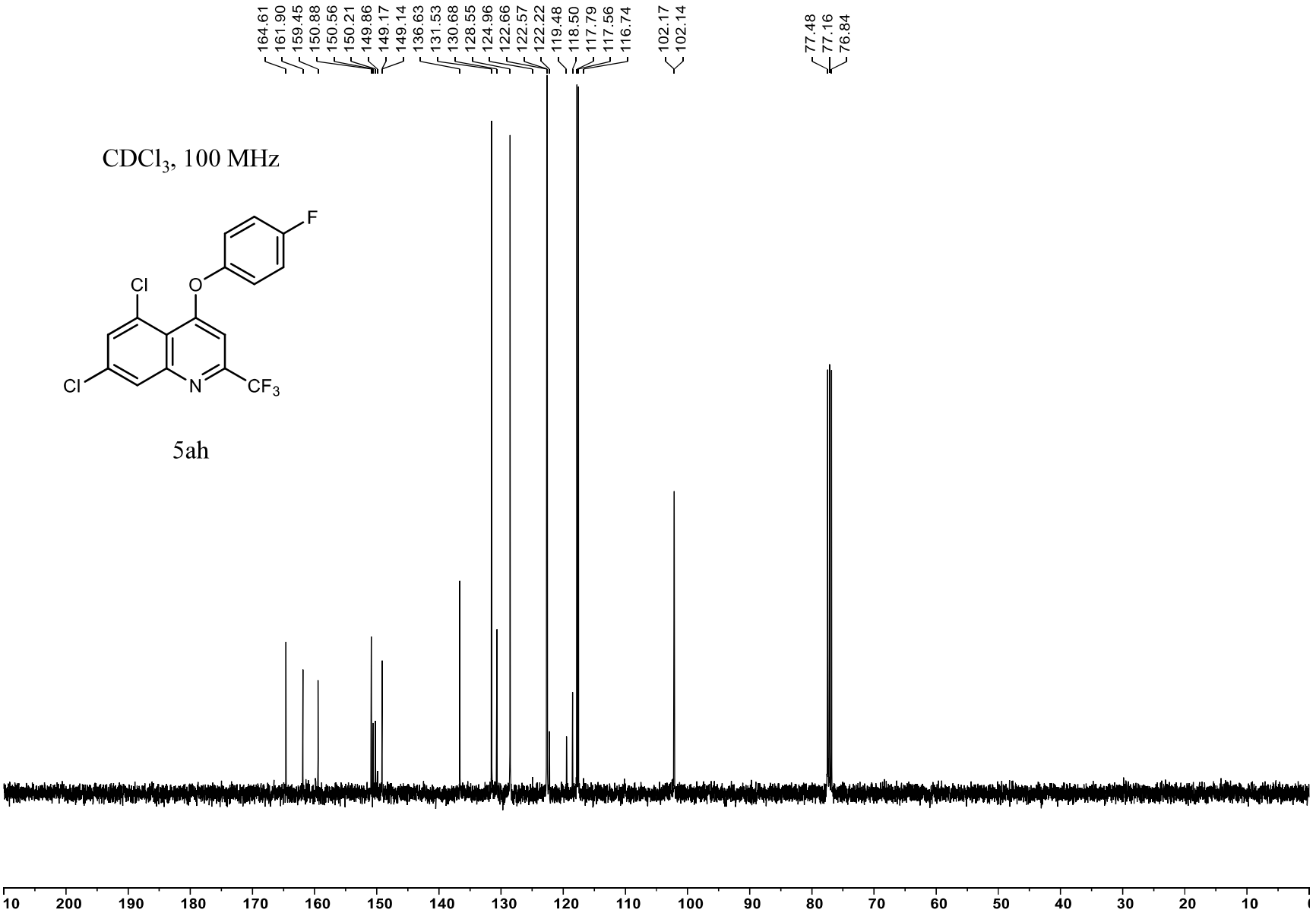
$CDCl_3$, 376 MHz

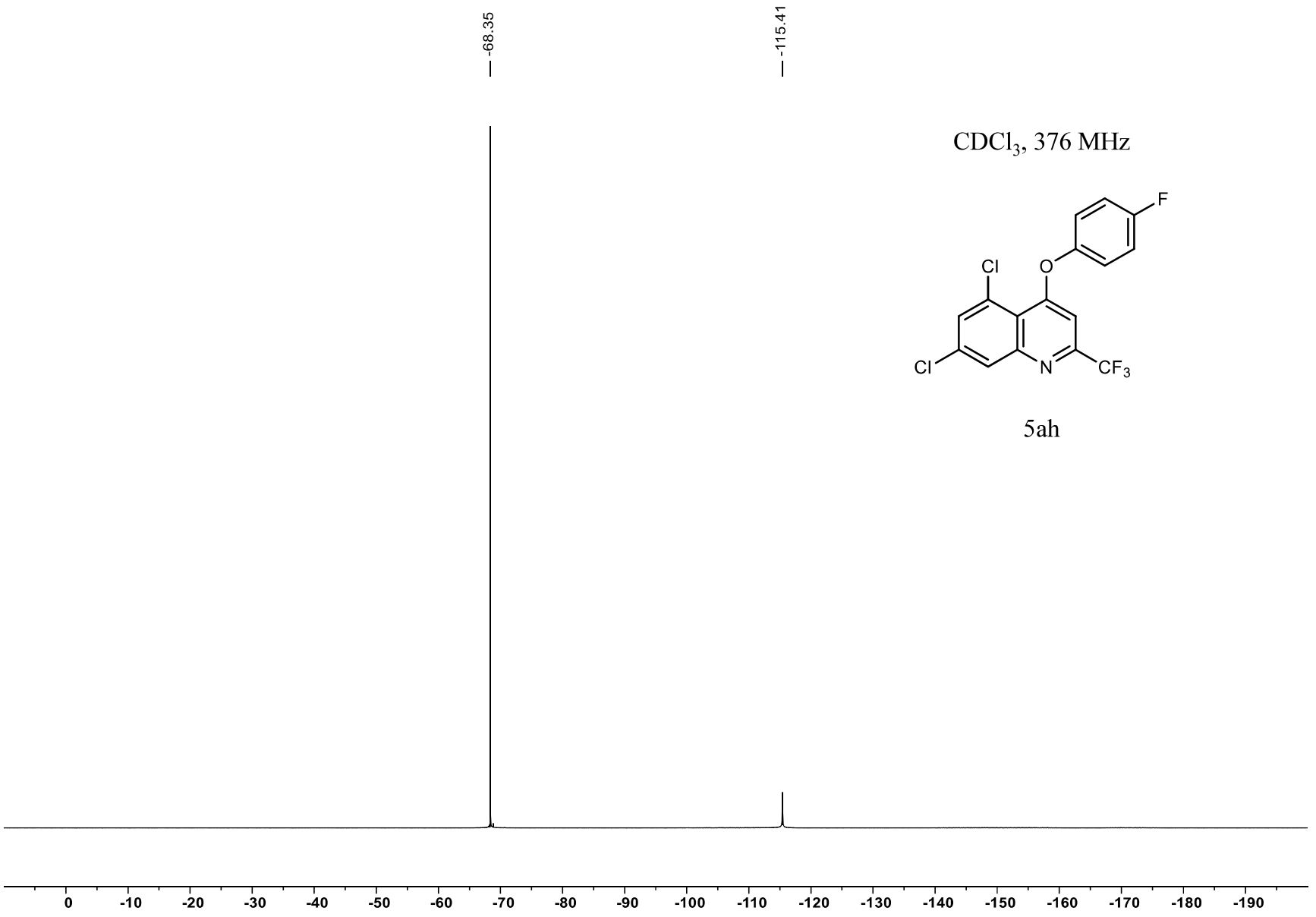
5ag



$CDCl_3$, 400 MHz

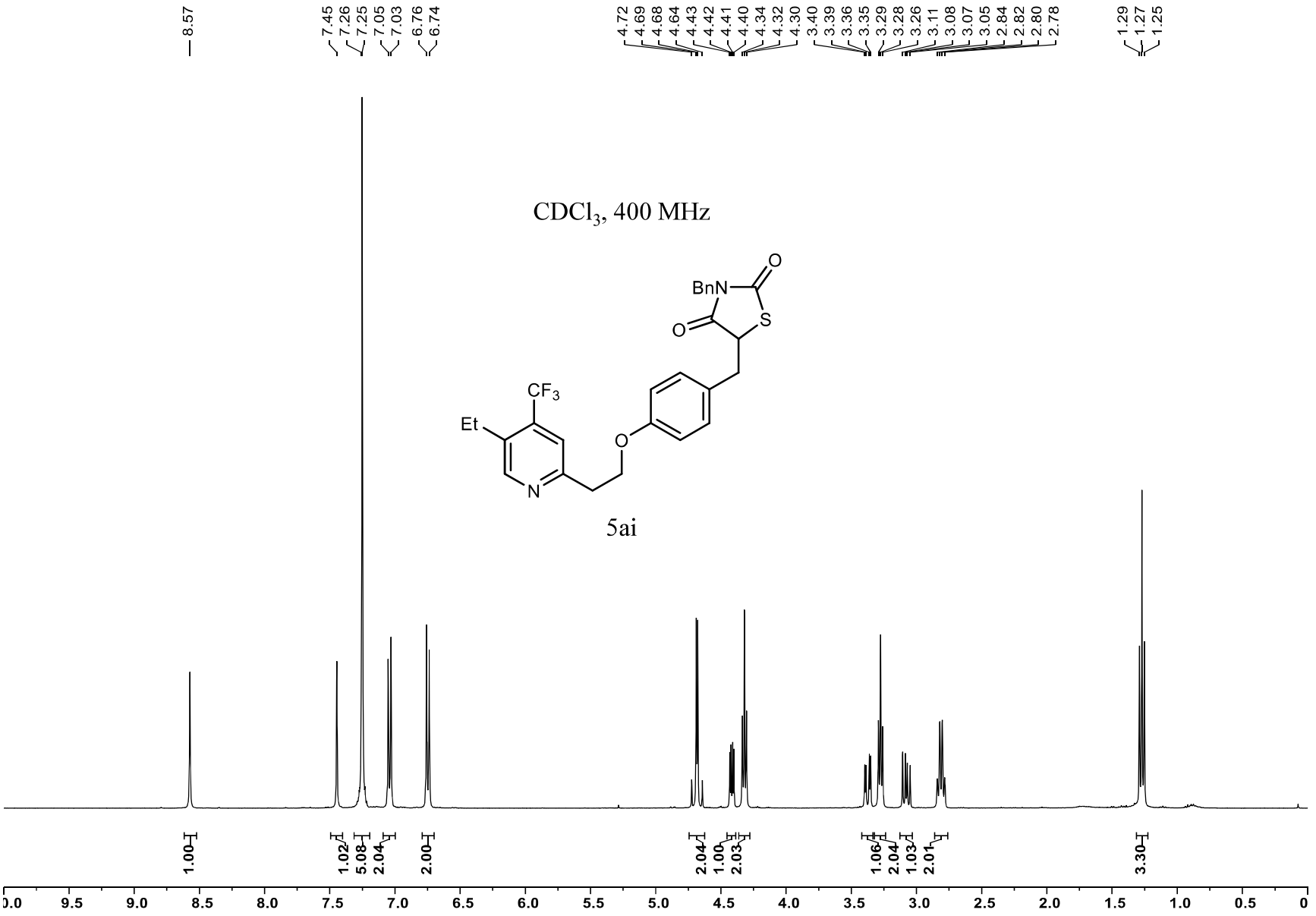
5ah

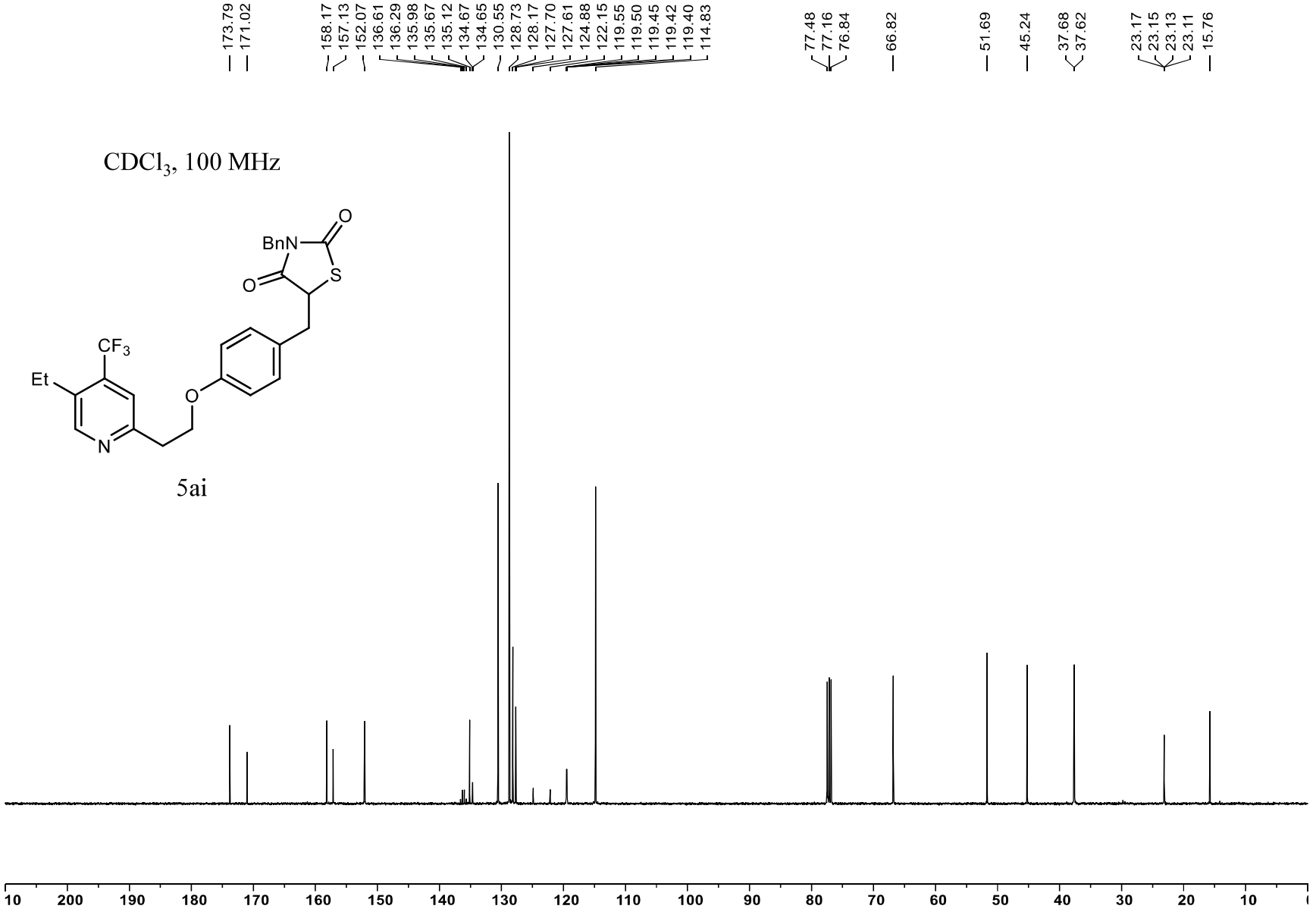

164.61
161.90
159.45
150.88
150.56
150.21
149.86
149.17
149.14
136.63
131.53
130.68
128.55
124.96
122.66
122.57
122.22
119.48
118.50
117.79
117.56
116.74
102.17
102.14
77.48
77.16
76.84
CDCl3, 100 MHz
F
Cl
O
Cl
N
CF3
5ah
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

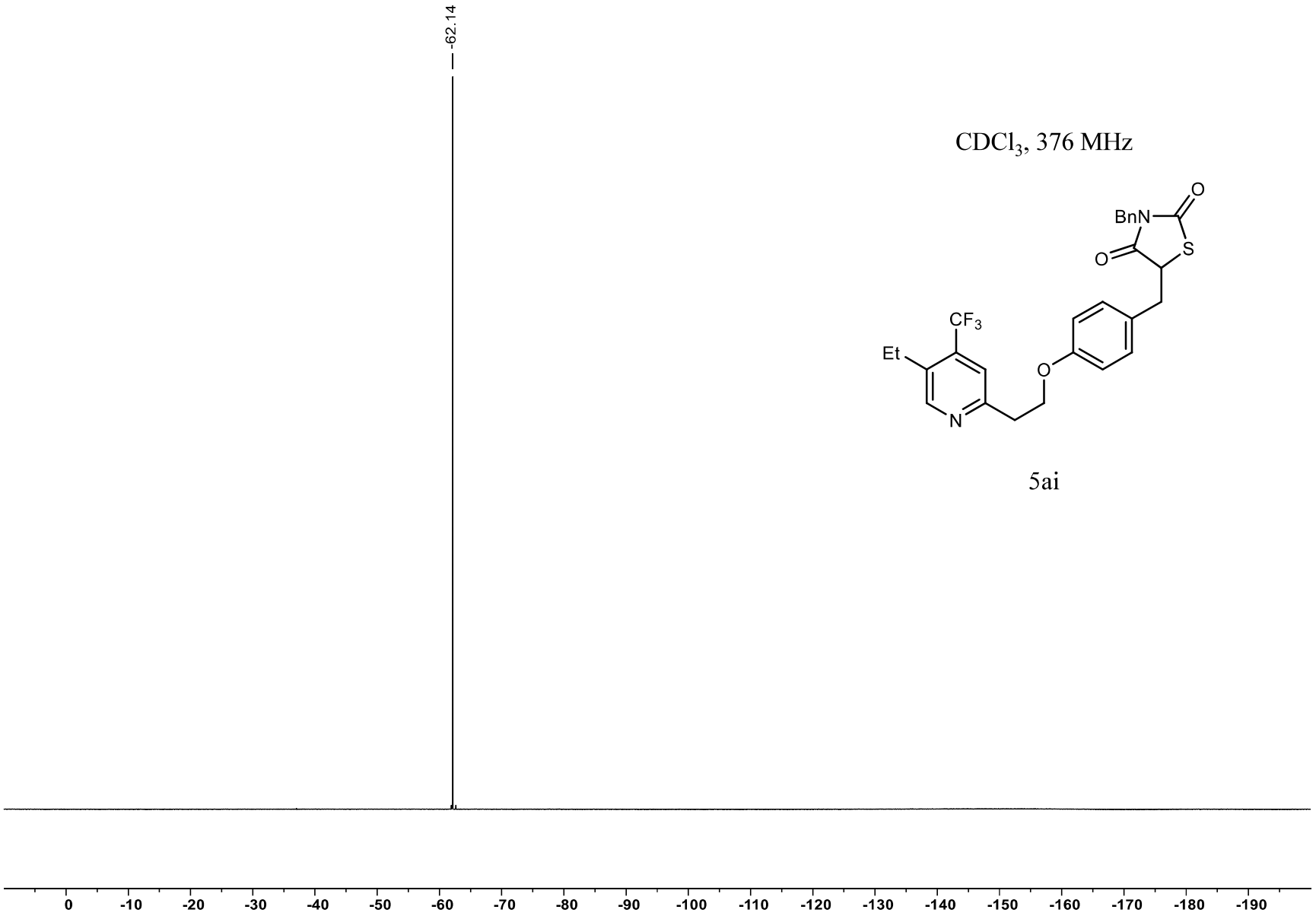


$CDCl_3$, 376 MHz

5ah

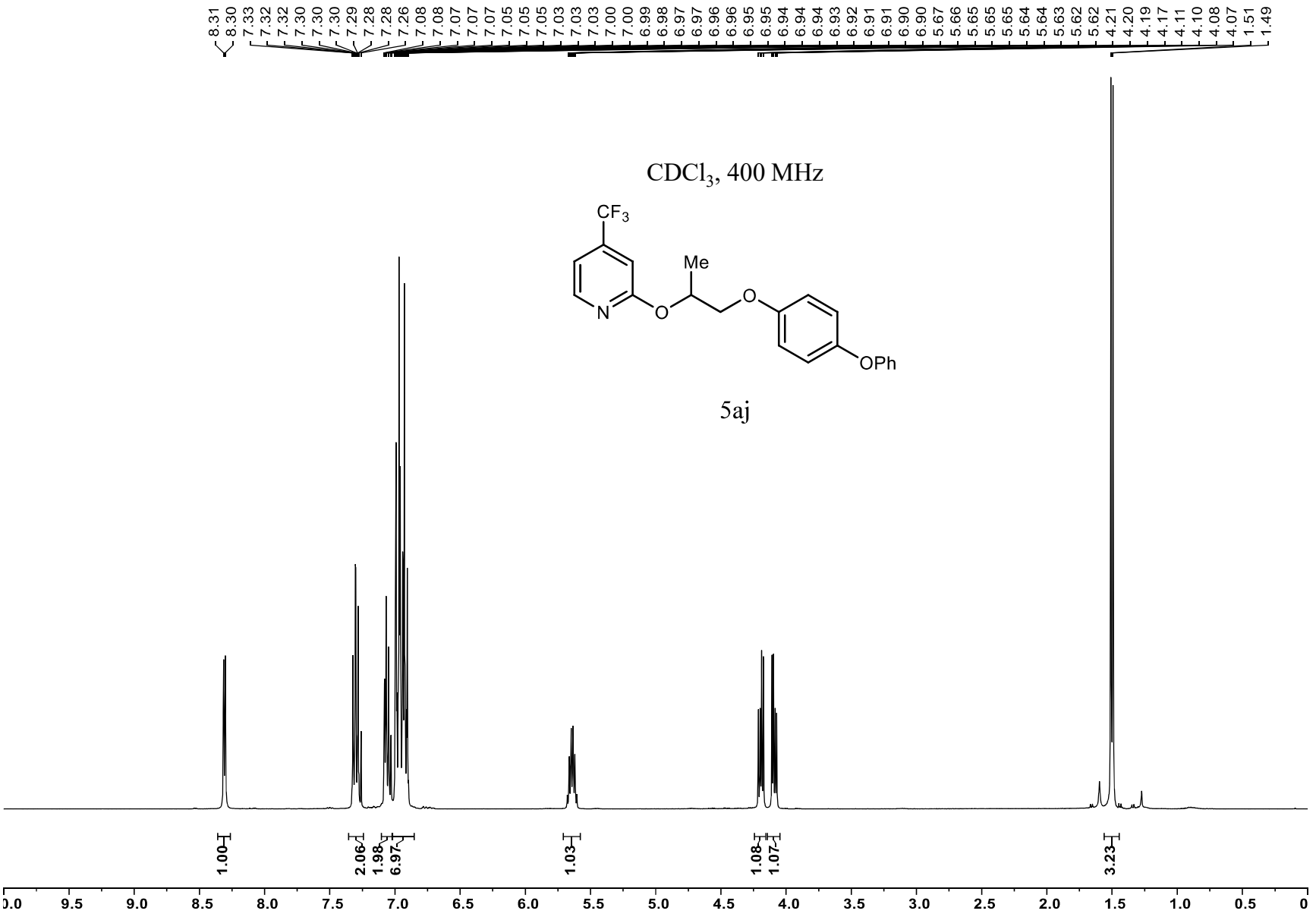

8.57
7.45
7.26
7.25
7.05
7.03
6.76
6.74
4.72
4.69
4.68
4.64
4.43
4.42
4.41
4.40
4.34
4.32
4.30
3.40
3.39
3.36
3.35
3.29
3.28
3.26
3.11
3.08
3.07
3.05
2.84
2.82
2.80
2.78
1.29
1.27
1.25
CDCl3, 400 MHz
BnN
O
O
S
CF3
Et
O
N
5ai
1.00
1.02
5.08
2.04
2.00
2.04
1.00
2.03
1.06
2.04
1.03
2.01
3.30
0.0
9.5
9.0
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

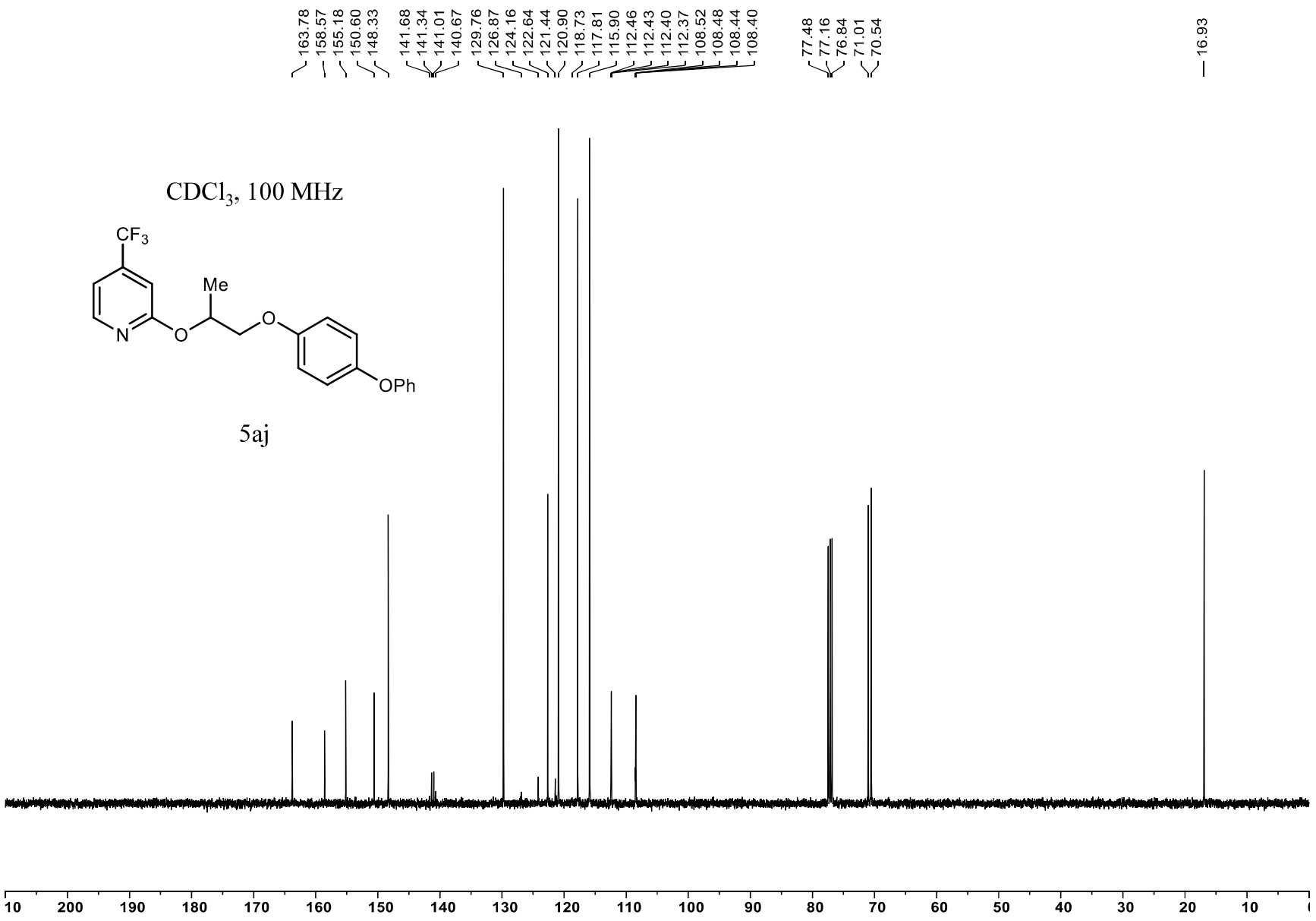

173.79
171.02
158.17
157.13
152.07
136.61
136.29
135.98
135.67
135.12
134.67
134.65
130.55
128.73
128.17
127.70
127.61
124.88
122.15
119.55
119.50
119.45
119.42
119.40
114.83
77.48
77.16
76.84
66.82
51.69
45.24
37.68
37.62
23.17
23.15
23.13
23.11
15.76
CDCl3, 100 MHz
BnN
O
O
S
CF3
Et
O
N
5ai
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

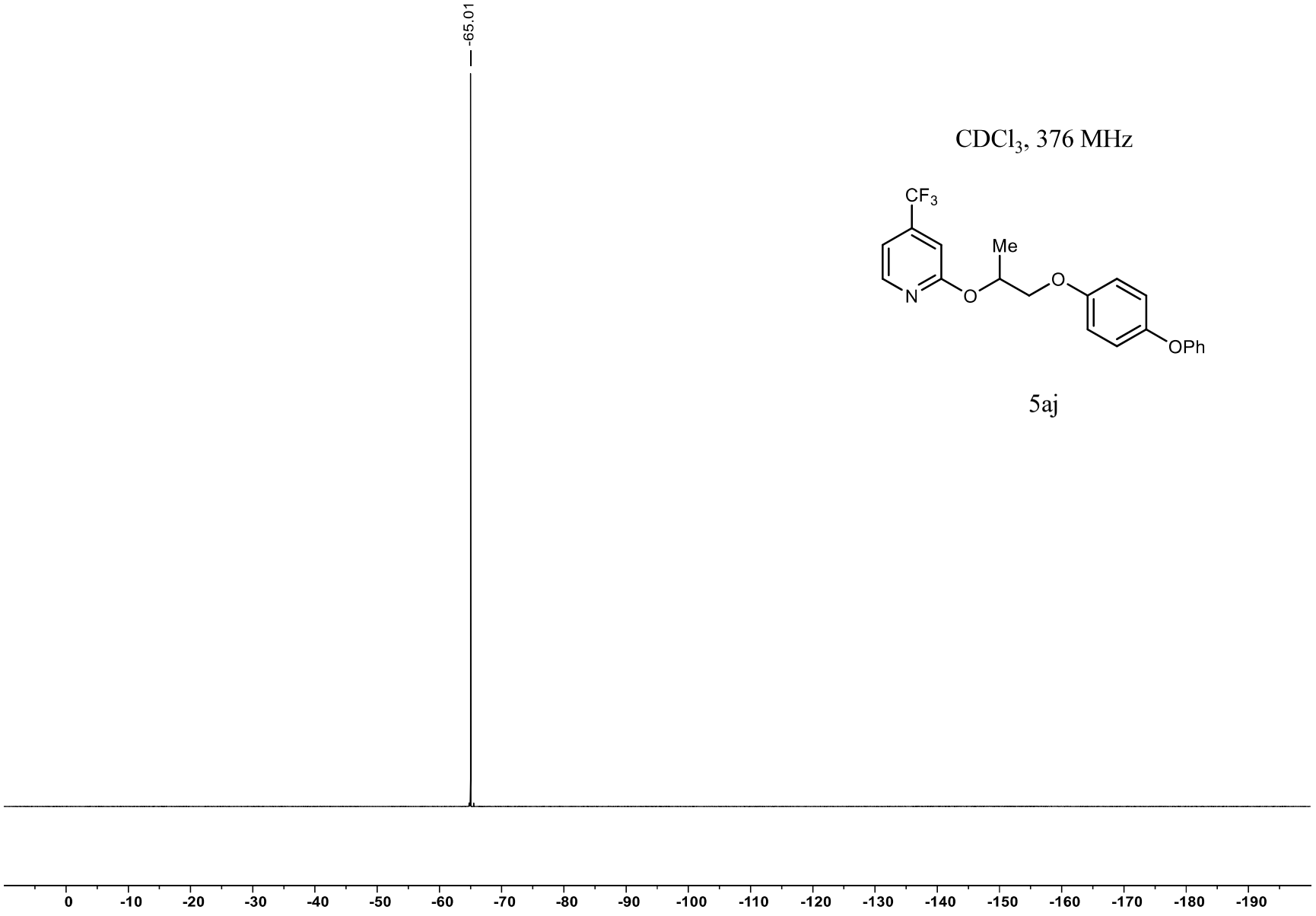


$CDCl_3$, 376 MHz

5ai

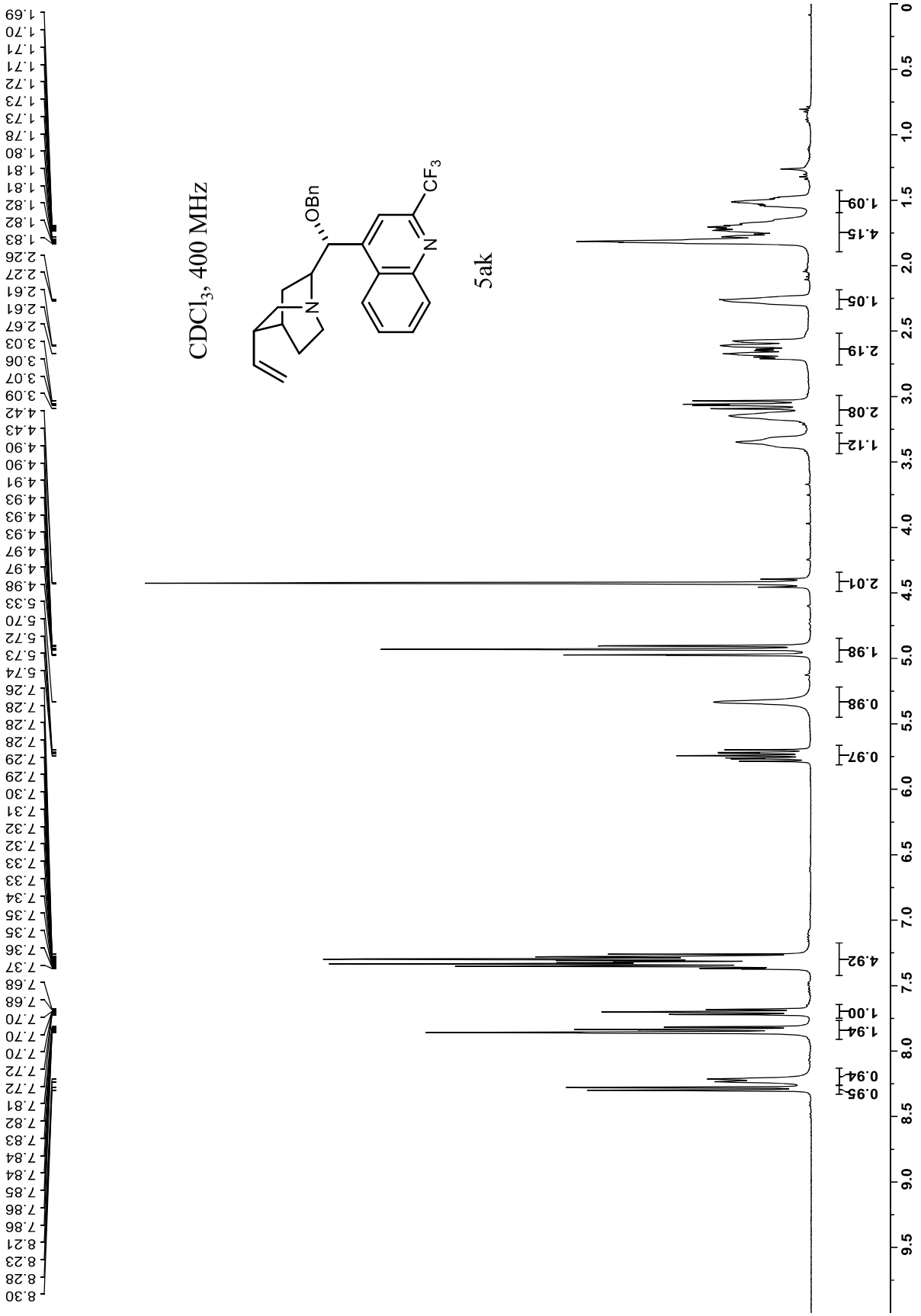

8.31
8.30
7.33
7.32
7.32
7.30
7.30
7.30
7.29
7.28
7.28
7.26
7.08
7.08
7.07
7.07
7.07
7.05
7.05
7.05
7.03
7.03
7.03
7.00
7.00
6.99
6.98
6.97
6.97
6.96
6.96
6.95
6.95
6.94
6.94
6.94
6.93
6.92
6.91
6.91
6.90
6.90
5.67
5.66
5.65
5.65
5.65
5.64
5.64
5.63
5.62
5.62
4.21
4.20
4.19
4.17
4.11
4.10
4.08
4.07
1.51
1.49
CDCl3, 400 MHz
CF3
Me
N
O
O
O
OPh
5aj
1.00
2.06
1.98
6.97
1.03
1.08
1.07
3.23
0.0
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

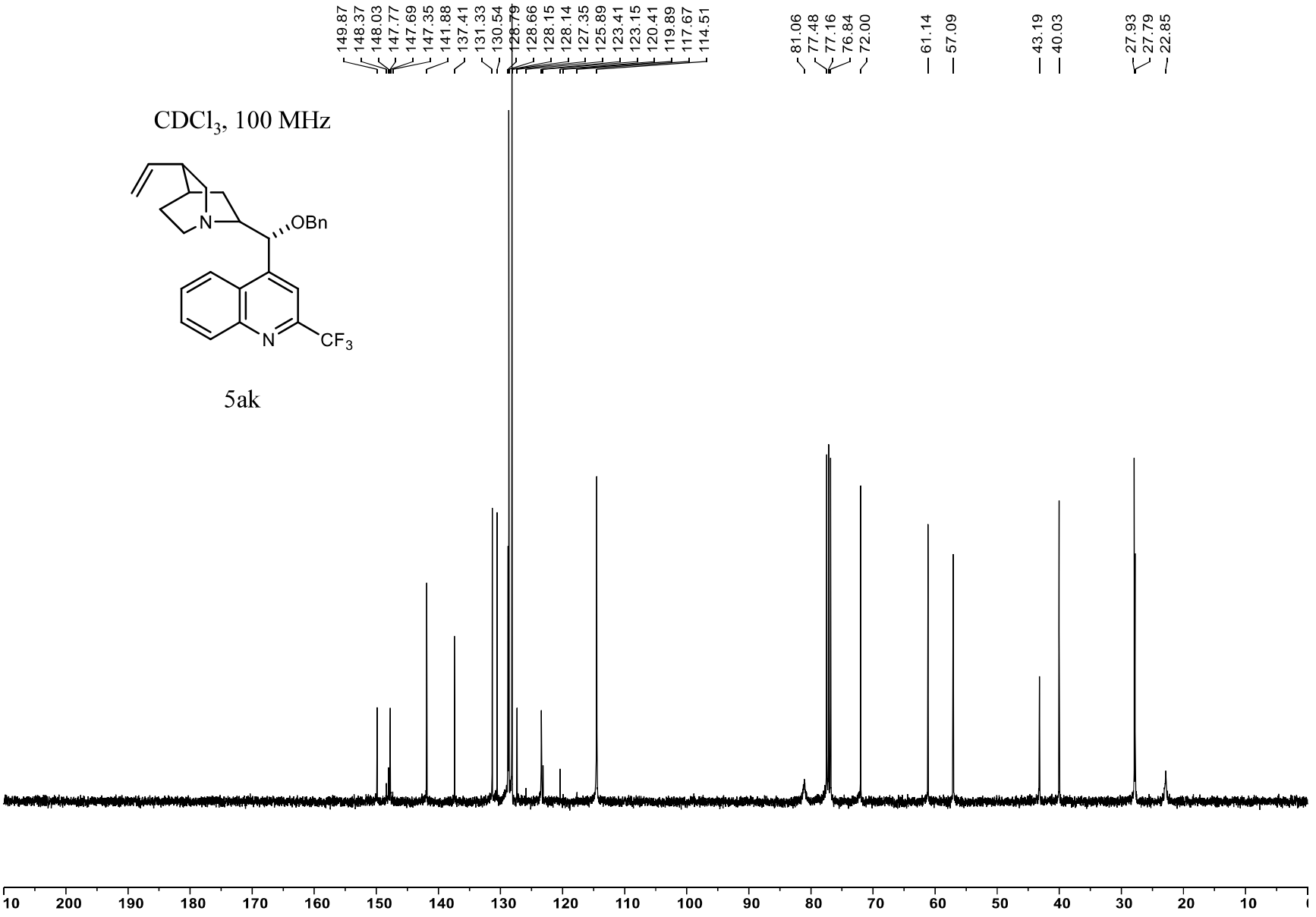

163.78
158.57
155.18
150.60
148.33
141.68
141.34
141.01
140.67
129.76
126.87
124.16
122.64
121.44
120.90
118.73
117.81
115.90
112.46
112.43
112.40
112.37
108.52
108.48
108.44
108.40
77.48
77.16
76.84
71.01
70.54
16.93
CDCl3, 100 MHz
CF3
Me
N
O
O
O
OPh
5aj
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

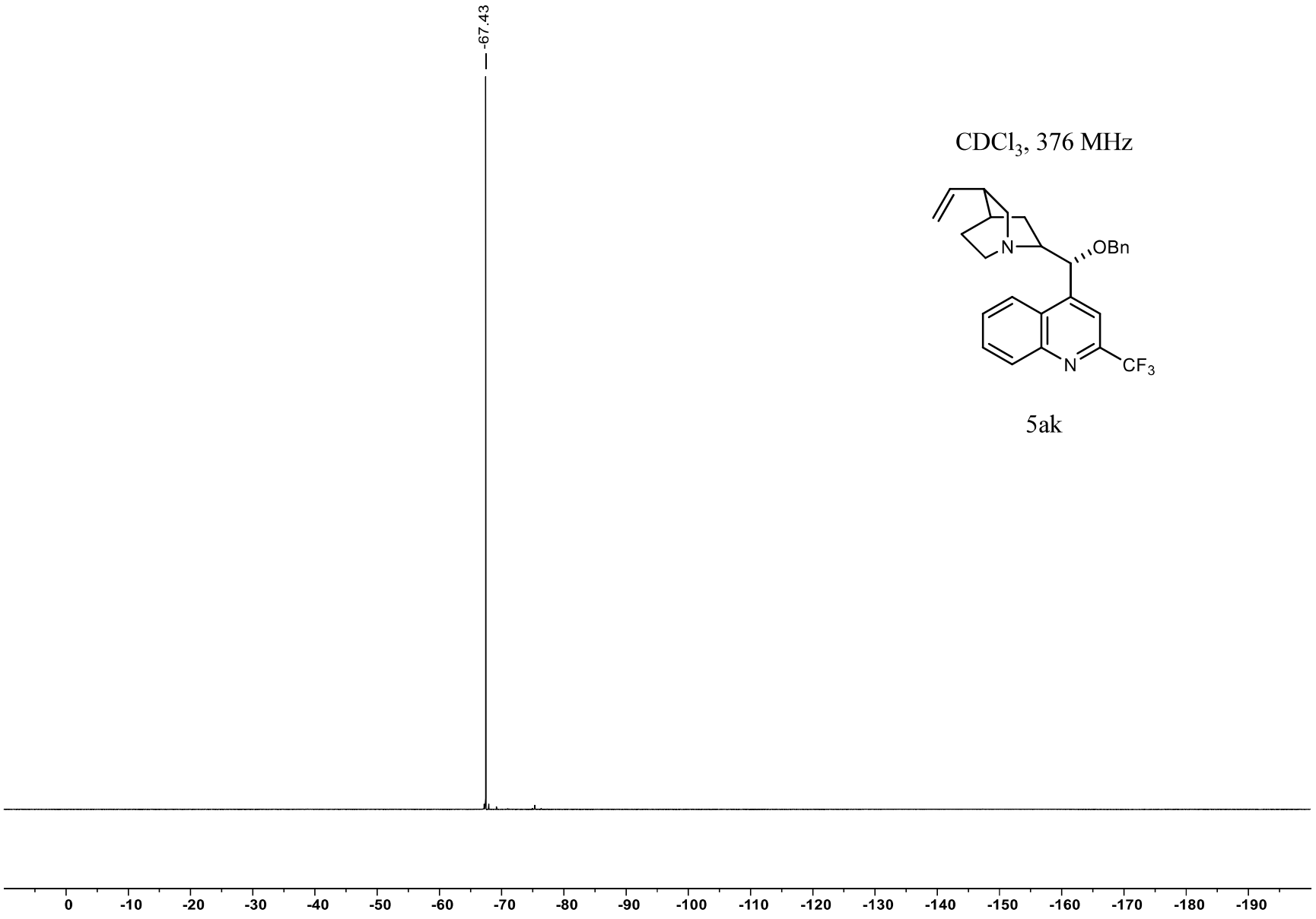


$CDCl_3$, 376 MHz

5aj

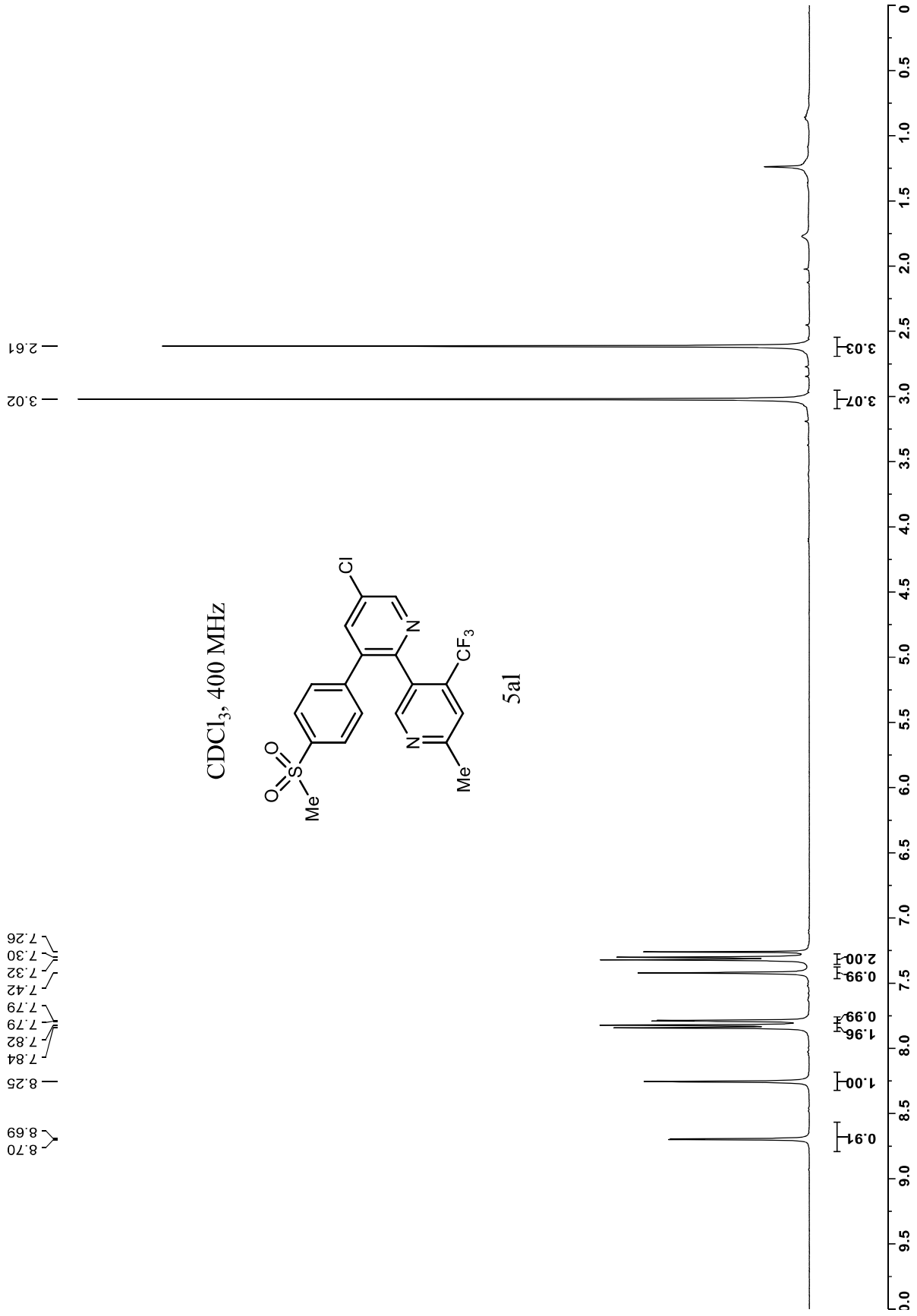

CDCl3, 400 MHz
OBn
CF3
N
N
5ak

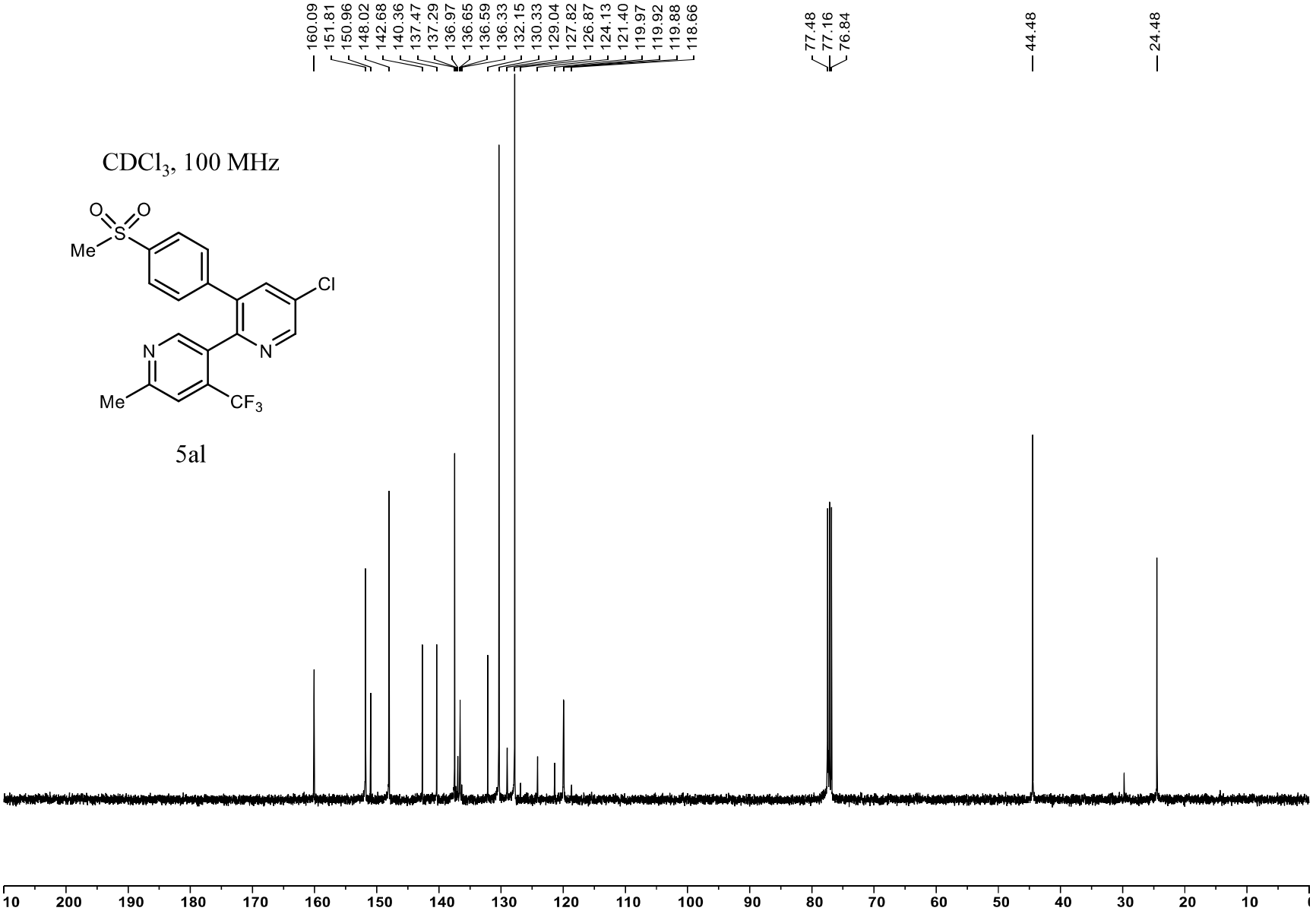

149.87
148.37
148.03
147.77
147.69
147.35
141.88
137.41
131.33
130.54
128.79
128.66
128.15
128.14
127.35
125.89
123.41
123.15
120.41
119.89
117.67
114.51
81.06
77.48
77.16
76.84
72.00
61.14
57.09
43.19
40.03
27.93
27.79
22.85
CDCl3, 100 MHz
N
OBn
N
CF3
5ak
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

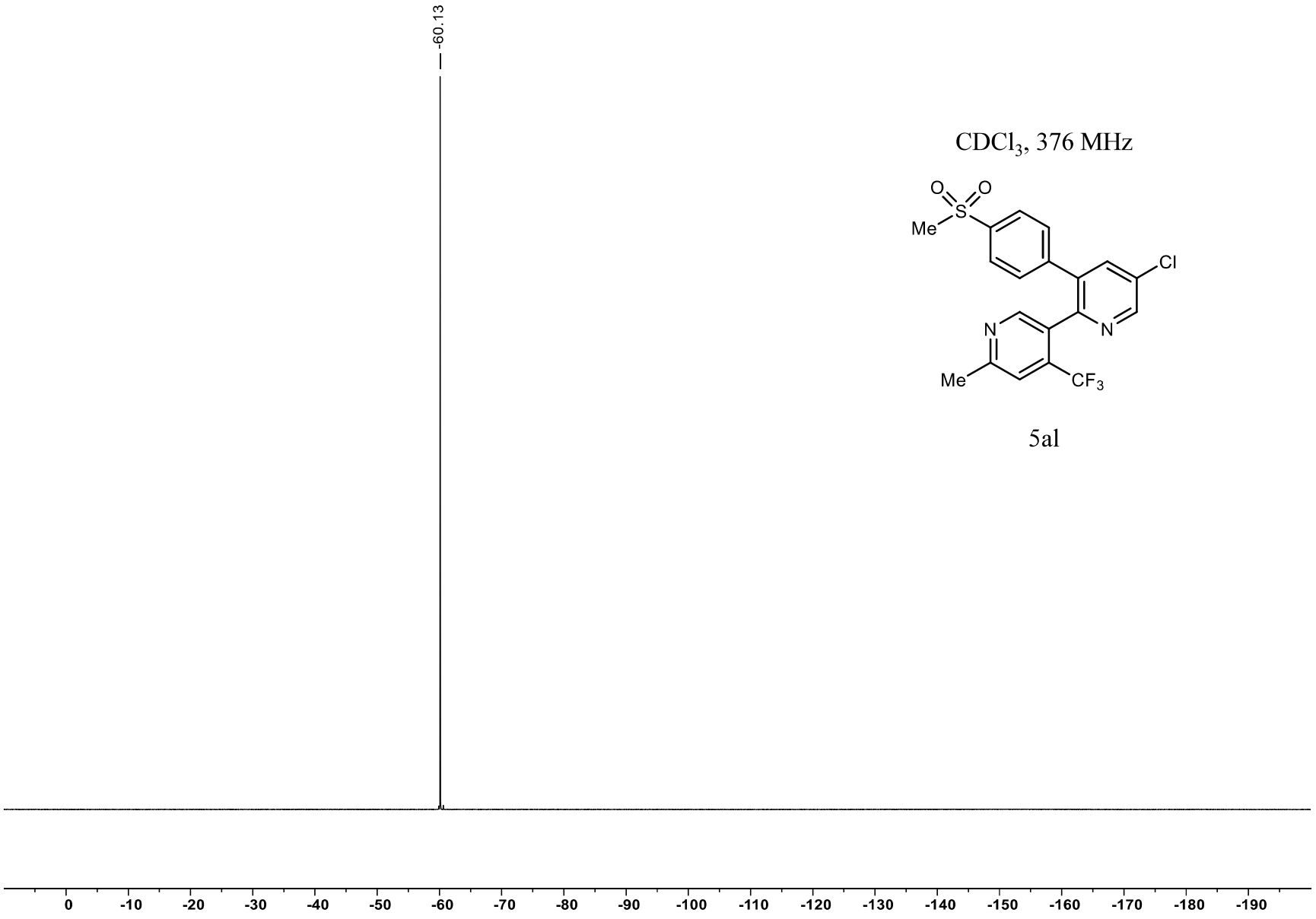


$CDCl_3$, 376 MHz

5ak

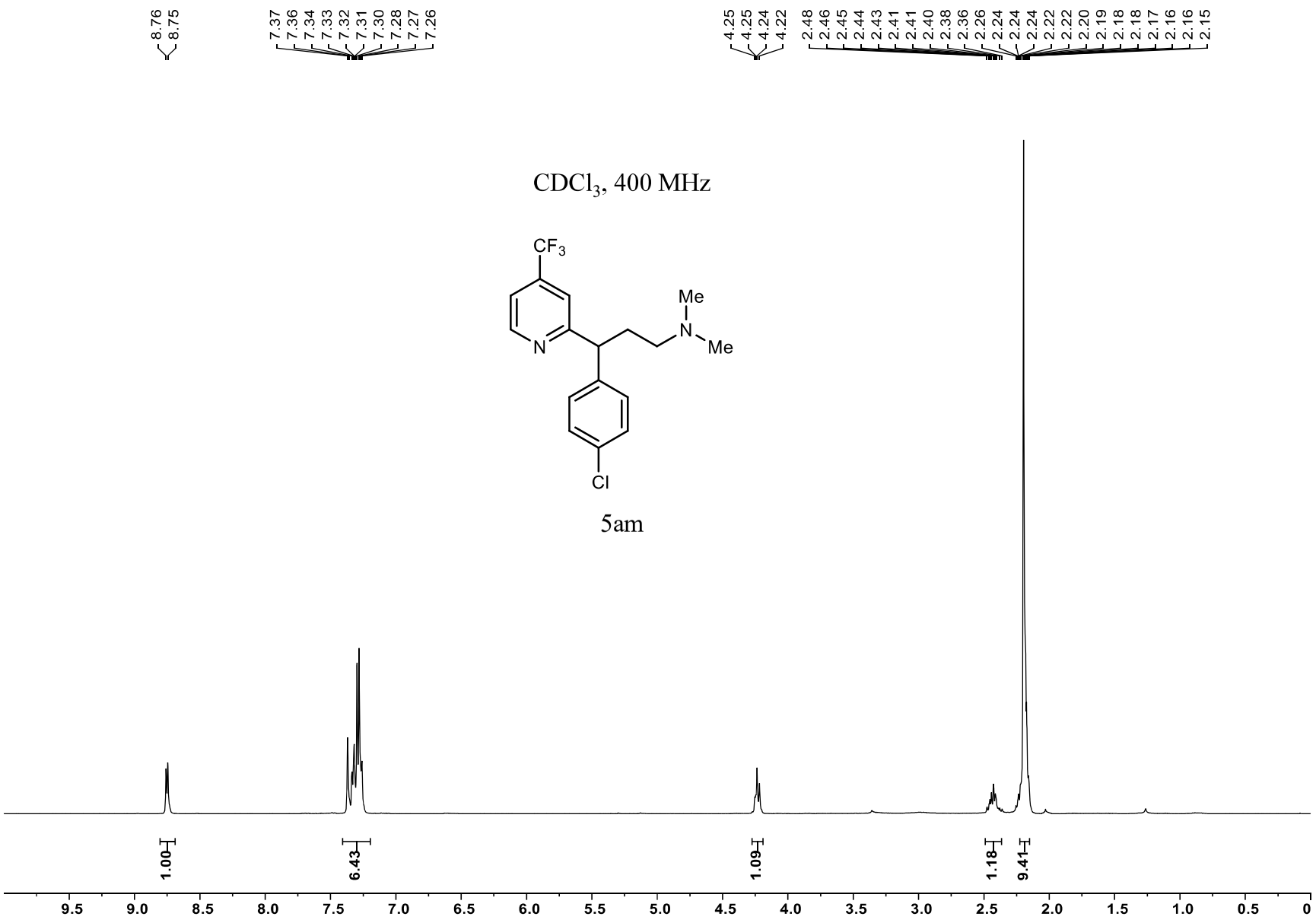

CDCl3, 400 MHz
5al
Cl
N
CF3
N
Me
O
O
S
Me
2.61
3.02
8.70
8.69
8.25
7.84
7.82
7.79
7.79
7.42
7.32
7.30
7.26
0.91
1.00
1.96
0.99
0.99
2.00
3.07
3.03

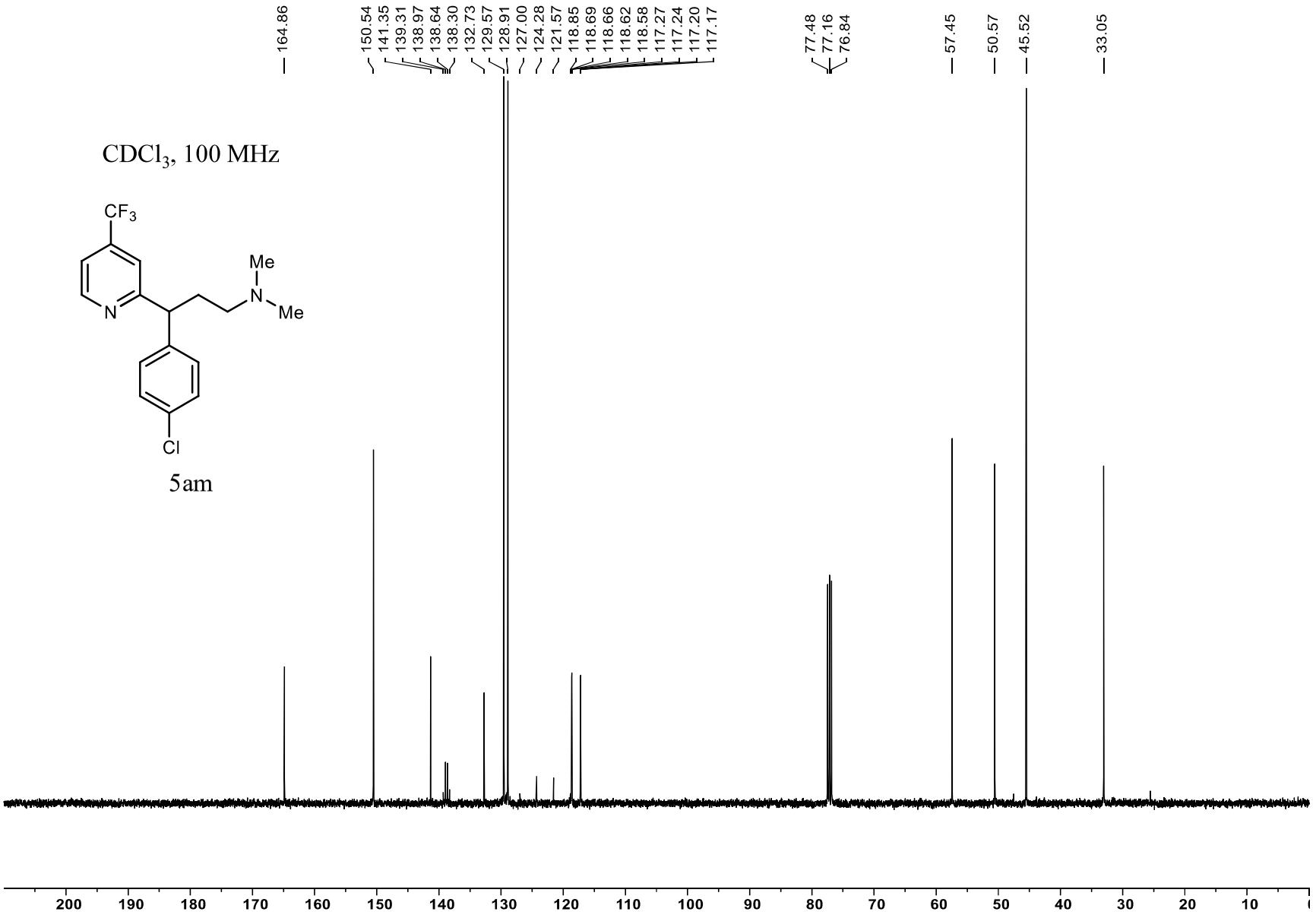

160.09
151.81
150.96
148.02
142.68
140.36
137.47
137.29
136.97
136.65
136.59
136.33
132.15
130.33
129.04
127.82
126.87
124.13
121.40
119.97
119.92
119.88
118.66
77.48
77.16
76.84
44.48
24.48
CDCl3, 100 MHz
O
O
S
Me
Cl
N
N
Me
CF3
5al
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

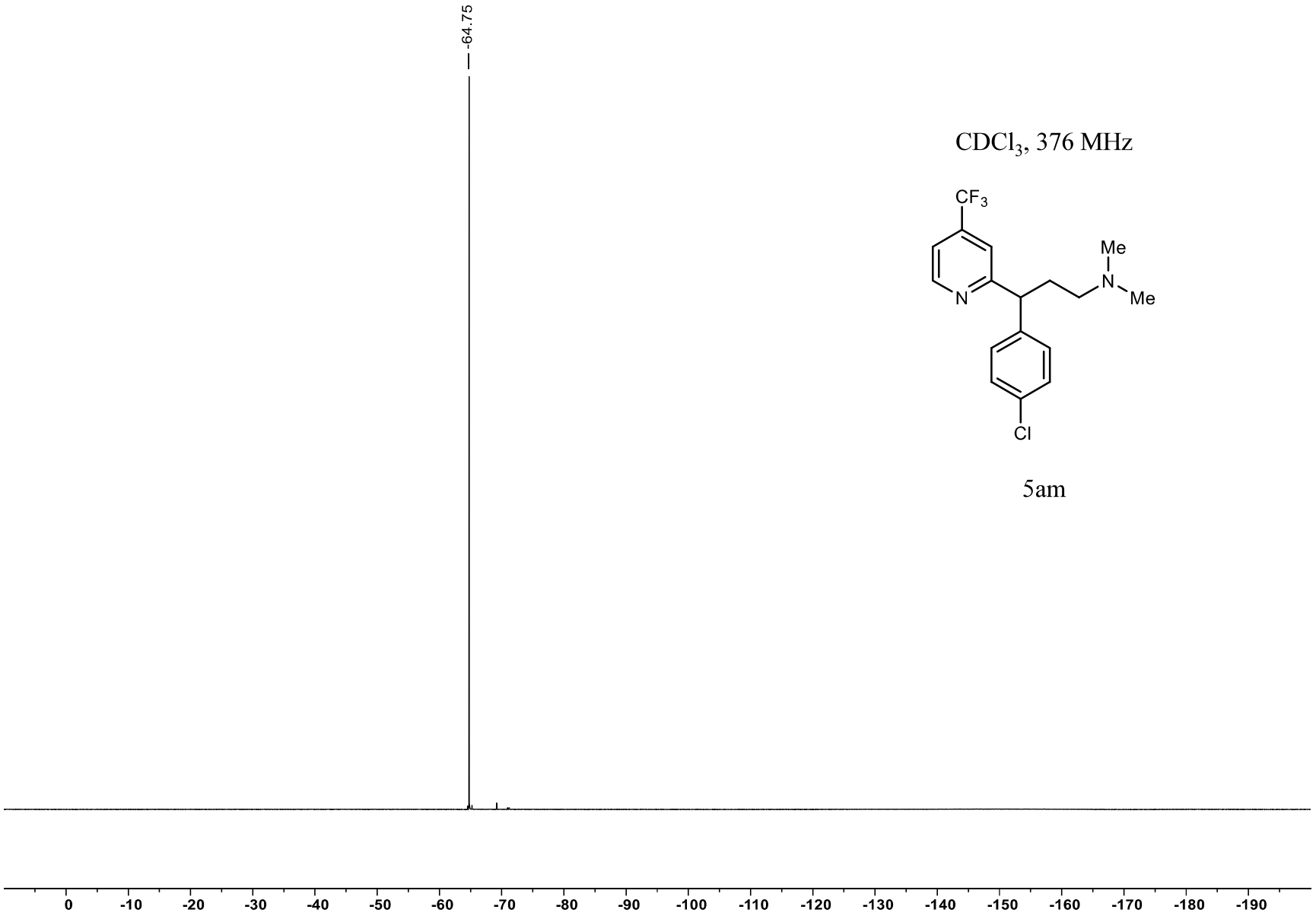


$CDCl_3$, 376 MHz

5al

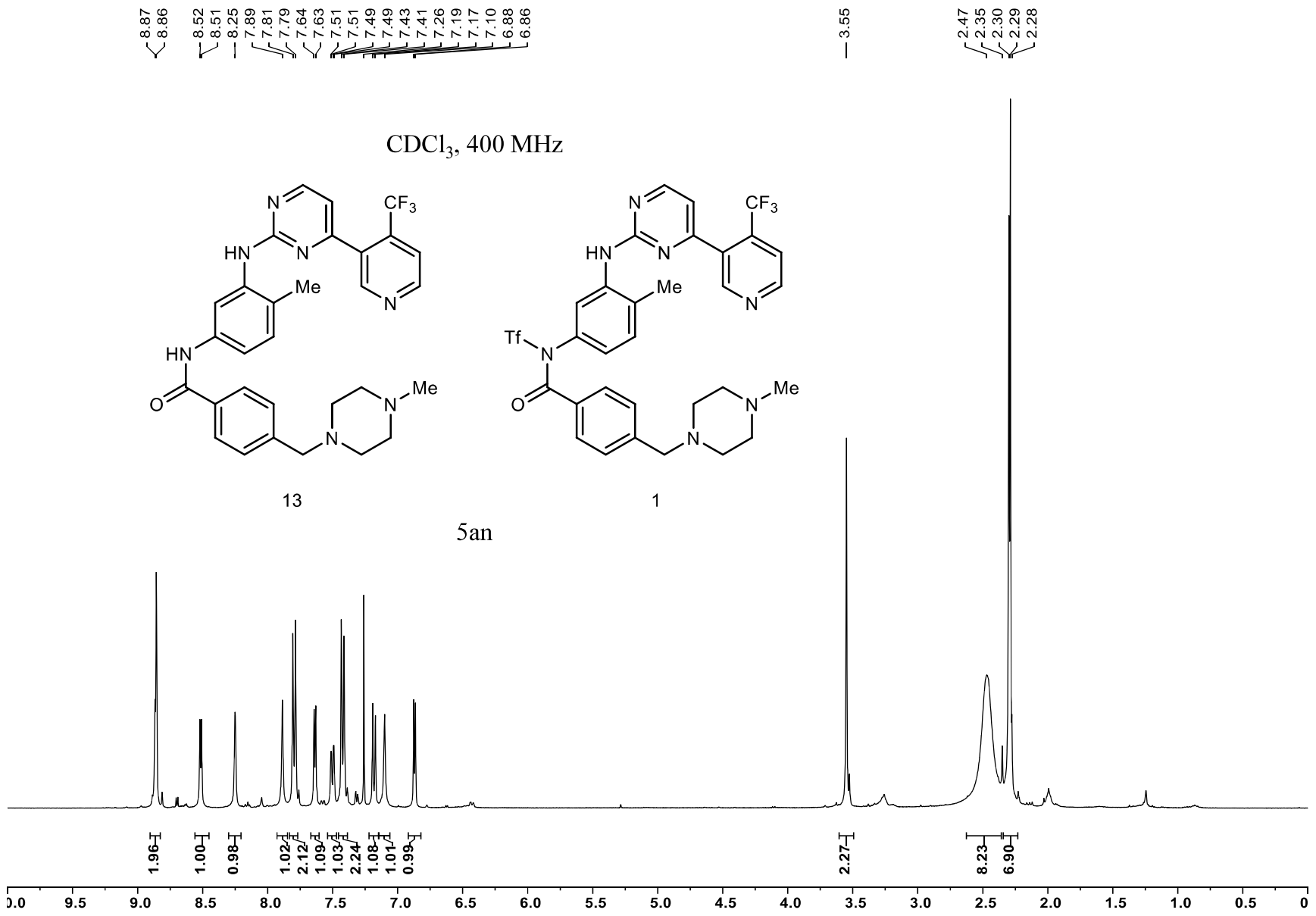

8.76
8.75
7.37
7.36
7.34
7.33
7.32
7.31
7.30
7.28
7.27
7.26
4.25
4.25
4.24
4.22
2.48
2.46
2.45
2.44
2.43
2.41
2.41
2.40
2.38
2.36
2.26
2.24
2.24
2.24
2.22
2.22
2.20
2.19
2.18
2.18
2.17
2.16
2.16
2.15
CDCl3, 400 MHz
CF3
Me
N
Me
N
Cl
5am
1.00
6.43
1.09
1.18
9.41
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

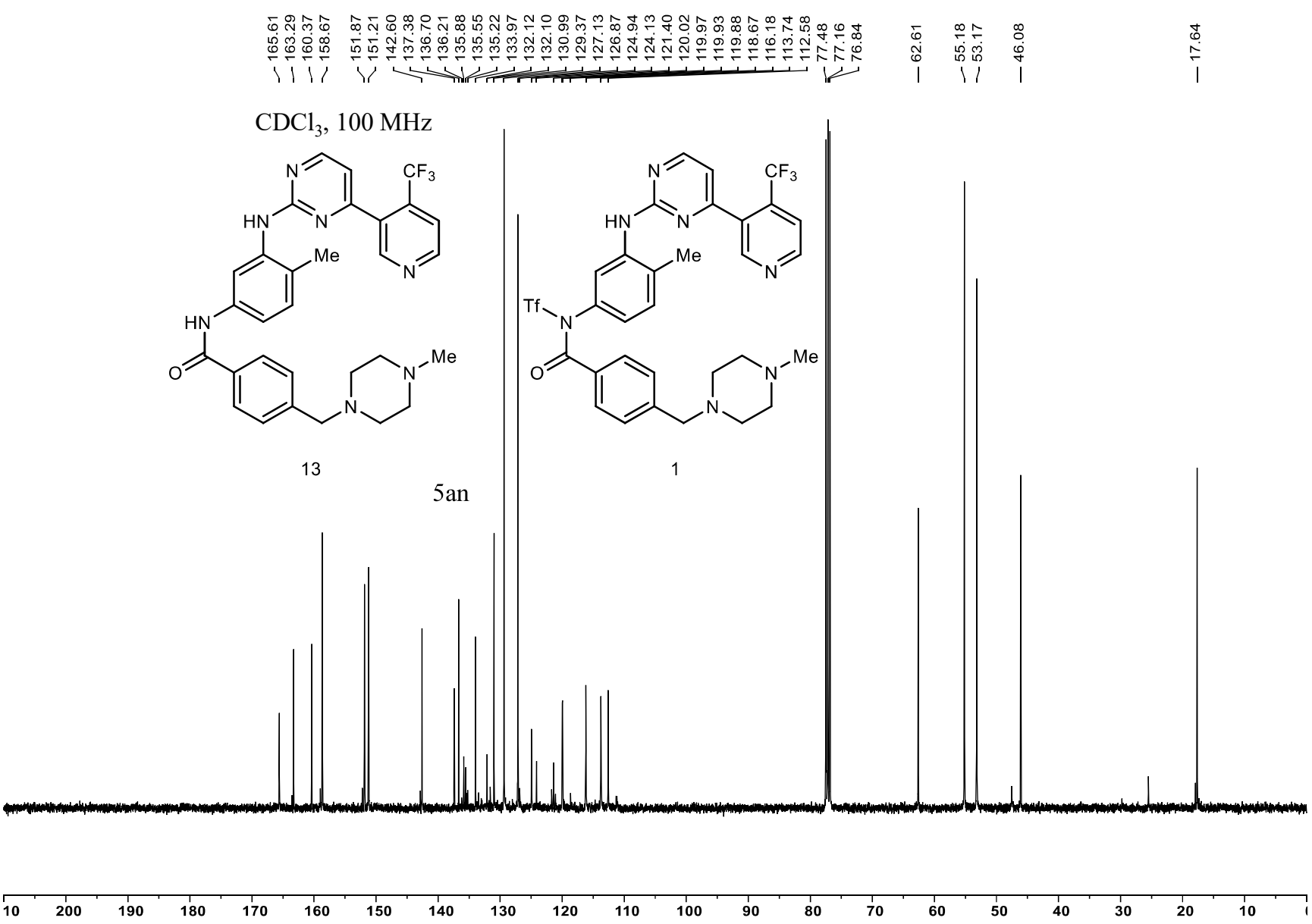

164.86
150.54
141.35
139.31
138.97
138.64
138.30
132.73
129.57
128.91
127.00
124.28
121.57
118.85
118.69
118.66
118.62
118.58
117.27
117.24
117.20
117.17
77.48
77.16
76.84
57.45
50.57
45.52
33.05
CDCl3, 100 MHz
CF3
Me
N
Me
N
Cl
5am
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

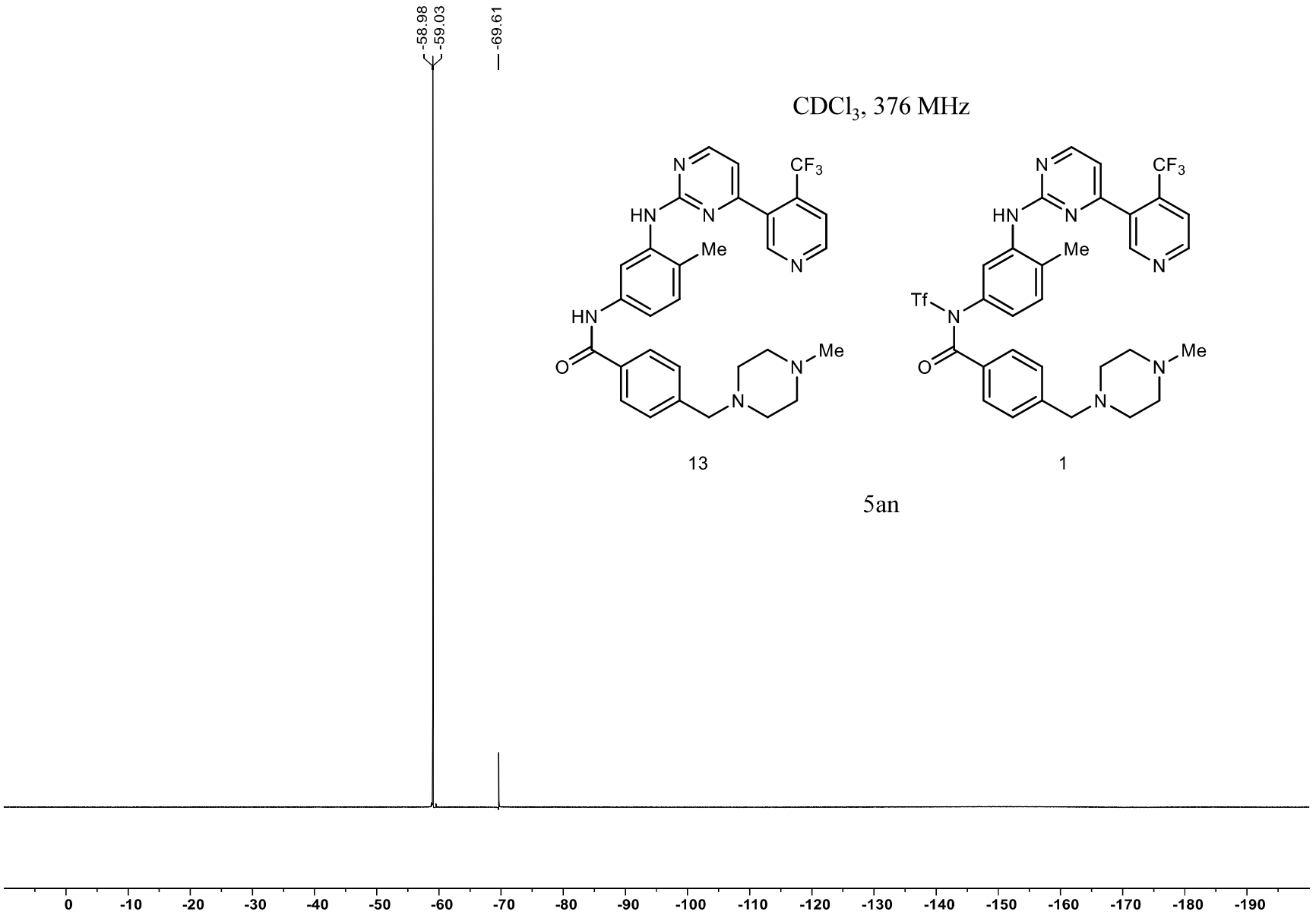


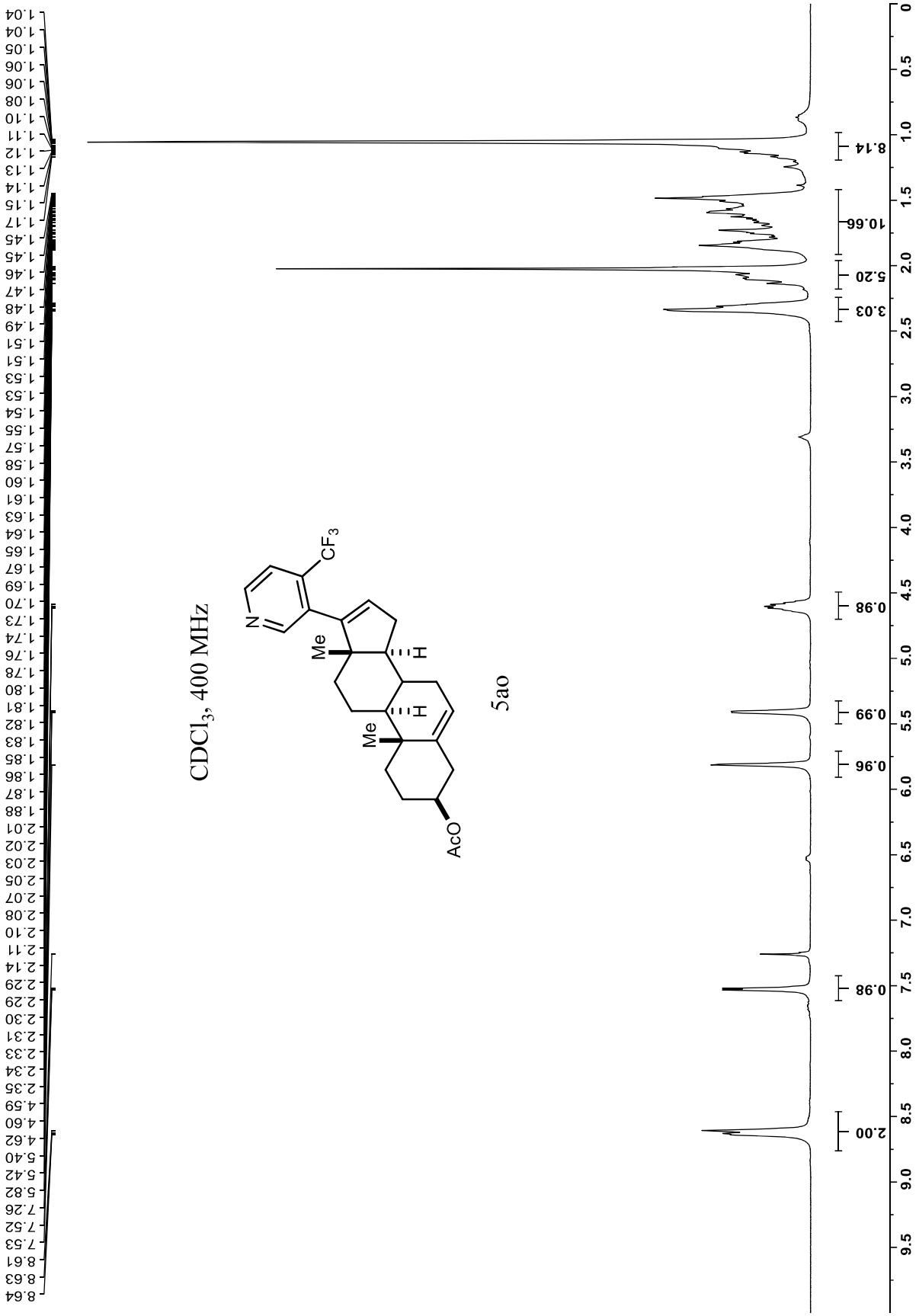
$CDCl_3$, 376 MHz

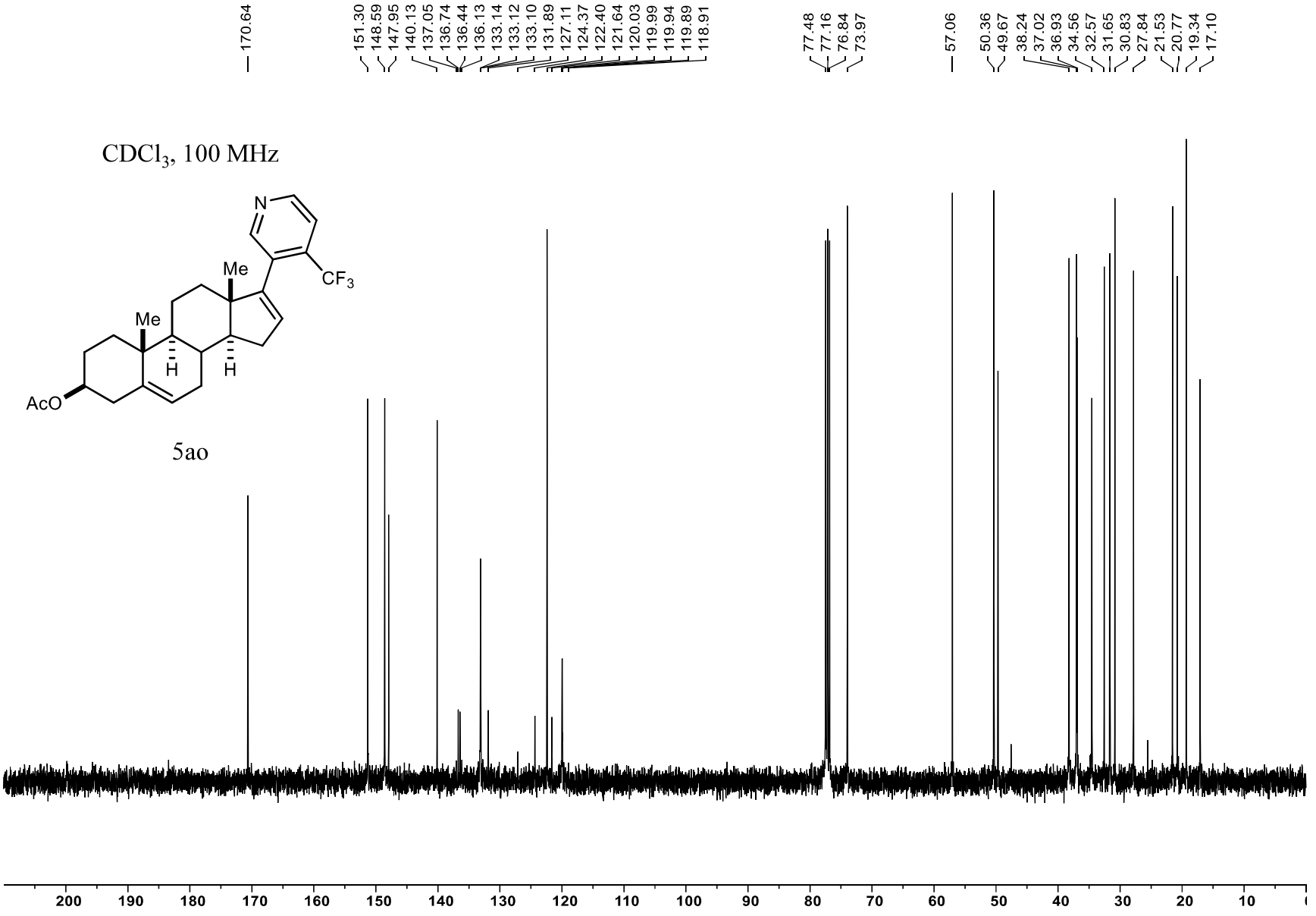
5am

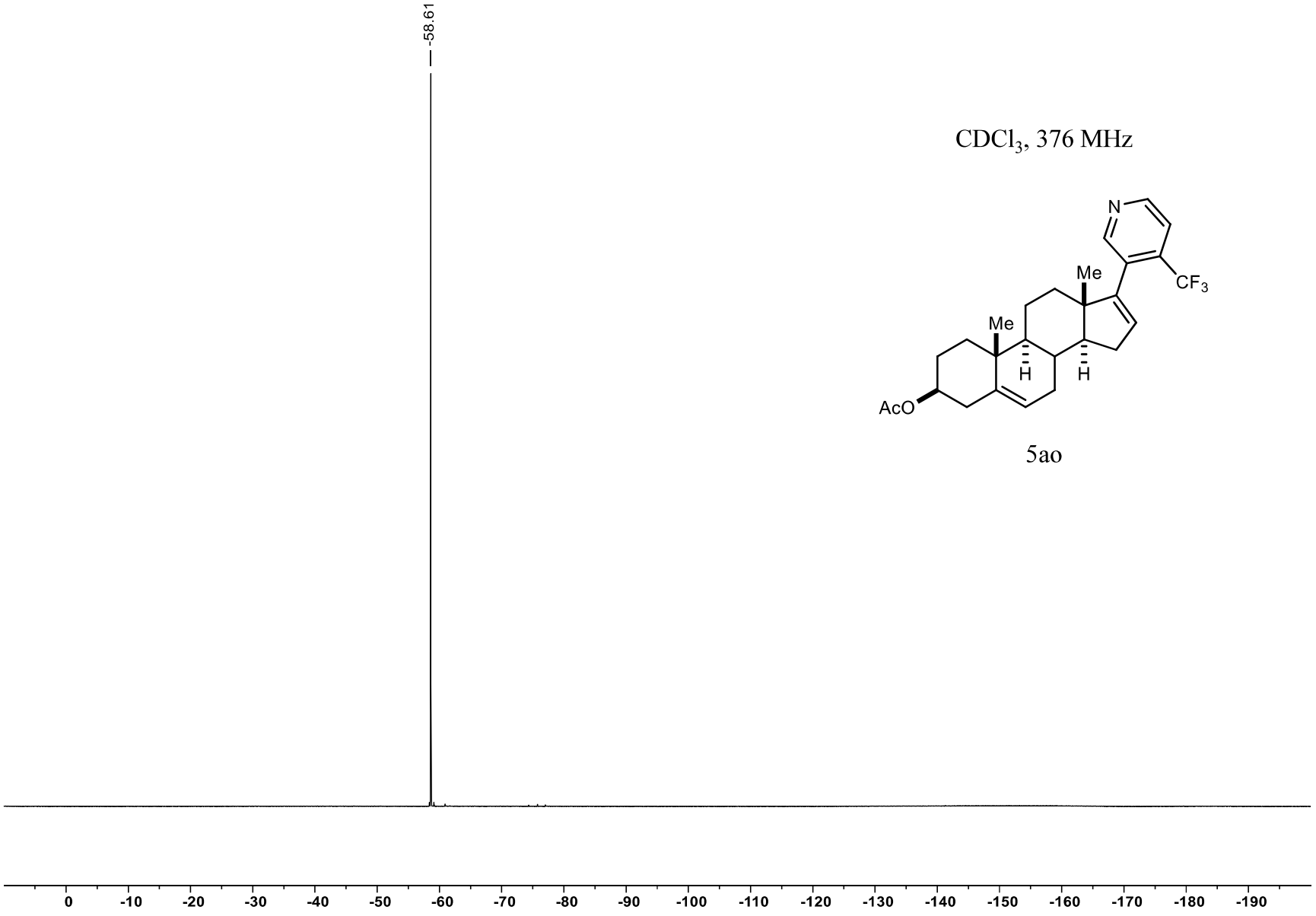

8.87
8.86
8.52
8.51
8.25
7.89
7.81
7.79
7.64
7.63
7.51
7.51
7.49
7.49
7.43
7.41
7.26
7.19
7.17
7.10
6.88
6.86
3.55
2.47
2.35
2.30
2.29
2.28
CDCl3, 400 MHz
13
1
5an
1.96
1.00
0.98
1.02
2.12
1.09
1.03
2.24
1.08
1.01
0.99
2.27
8.23
6.90


165.61
163.29
160.37
158.67
151.87
151.21
142.60
137.38
136.70
136.21
135.88
135.55
135.22
133.97
132.12
132.10
130.99
129.37
127.13
126.87
124.94
124.13
121.40
120.02
119.97
119.93
119.88
118.67
116.18
113.74
112.58
77.48
77.16
76.84
62.61
55.18
53.17
46.08
17.64
CDCl3, 100 MHz
13
1
5an
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


-58.98
-59.03
-69.61
CDCl3, 376 MHz
13
1
5an
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

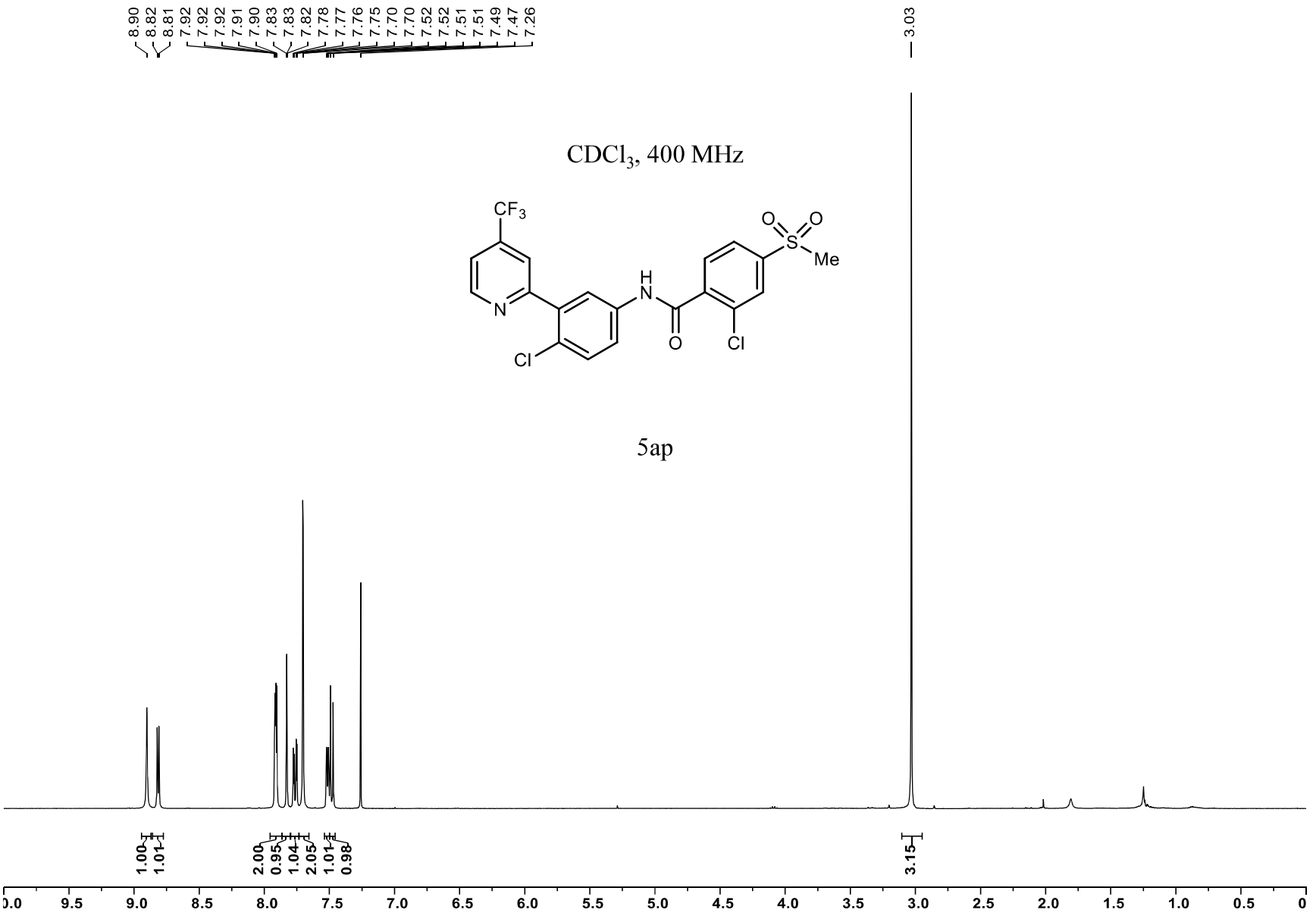

CDCl3, 400 MHz
5ao
CF3
N
Me
H
H
Me
AcO
8.14
10.66
5.20
3.03
0.98
0.99
0.96
0.98
2.00

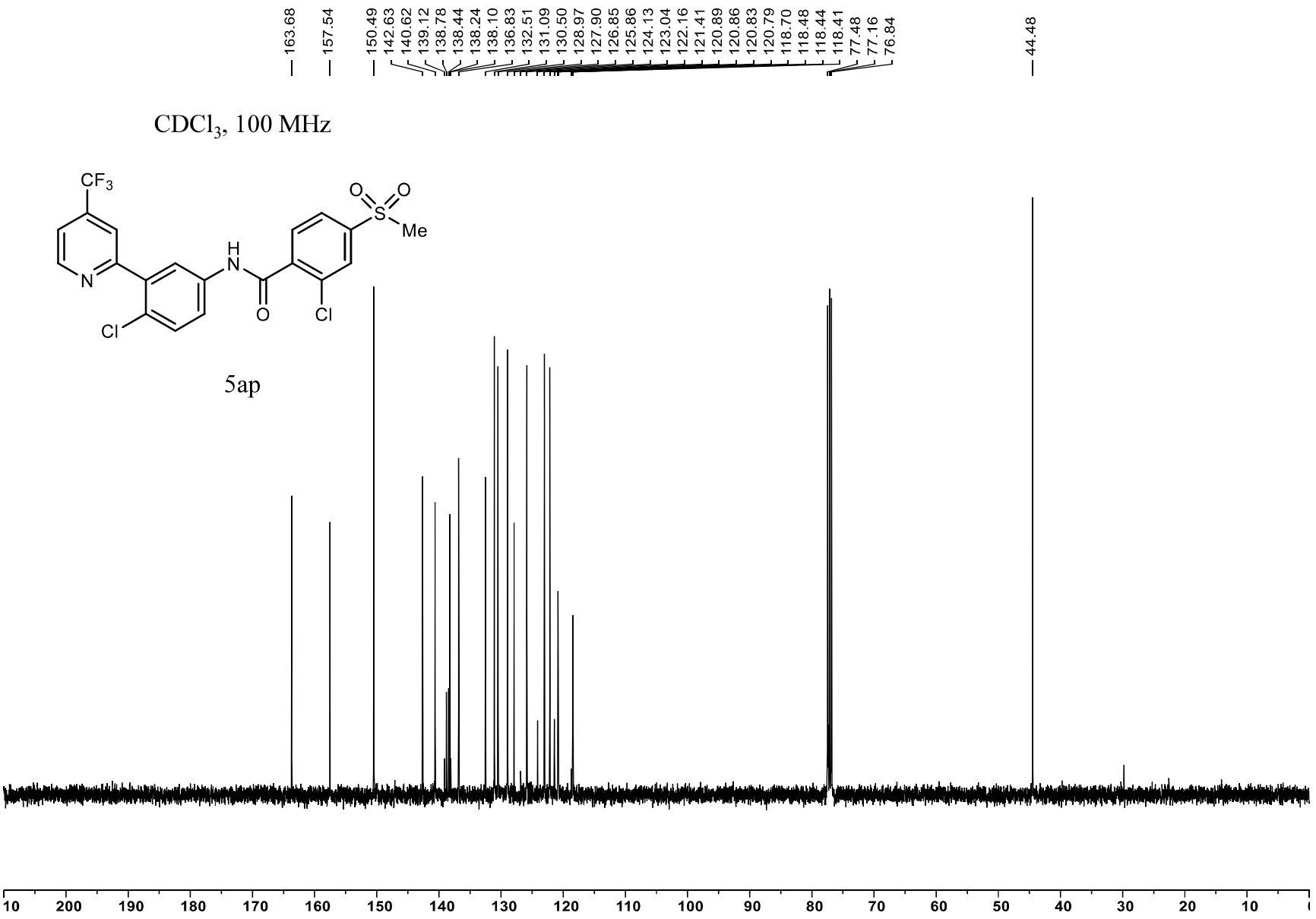

170.64
151.30
148.59
147.95
140.13
137.05
136.74
136.44
136.13
133.14
133.12
133.10
131.89
127.11
124.37
122.40
121.64
120.03
119.99
119.94
119.89
118.91
77.48
77.16
76.84
73.97
57.06
50.36
49.67
38.24
37.02
36.93
34.56
32.57
31.65
30.83
27.84
21.53
20.77
19.34
17.10
CDCl3, 100 MHz
N
Me
CF3
Me
H
H
AcO
5ao
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

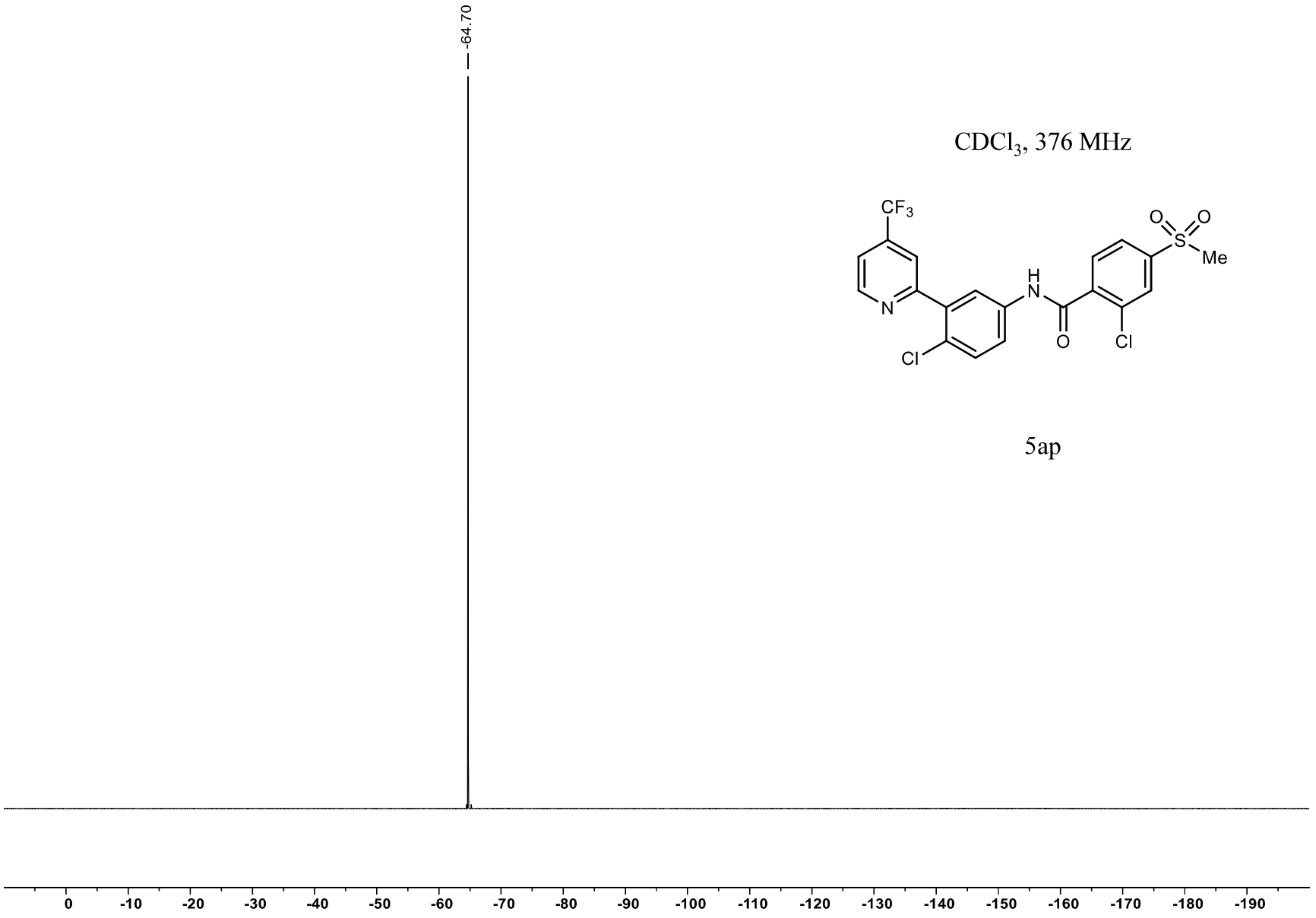


$CDCl_3$, 376 MHz

5ao

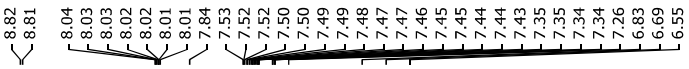

8.90
8.82
8.81
7.92
7.92
7.92
7.91
7.90
7.83
7.83
7.82
7.78
7.77
7.76
7.75
7.70
7.70
7.52
7.52
7.51
7.51
7.49
7.47
7.26
3.03
CDCl3, 400 MHz
CF3
O
O
S
Me
H
N
N
O
Cl
Cl
5ap
1.00
1.01
2.00
0.95
1.04
2.05
1.01
0.98
3.15
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


163.68
157.54
150.49
142.63
140.62
139.12
138.78
138.44
138.24
138.10
136.83
132.51
131.09
130.50
128.97
127.90
126.85
125.86
124.13
123.04
122.16
121.41
120.89
120.86
120.83
120.79
118.70
118.48
118.44
118.41
77.48
77.16
76.84
44.48
CDCl3, 100 MHz
CF3
O
O
S
Me
H
N
N
O
Cl
Cl
5ap
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

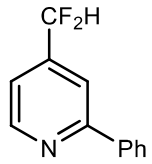


$CDCl_3$, 376 MHz

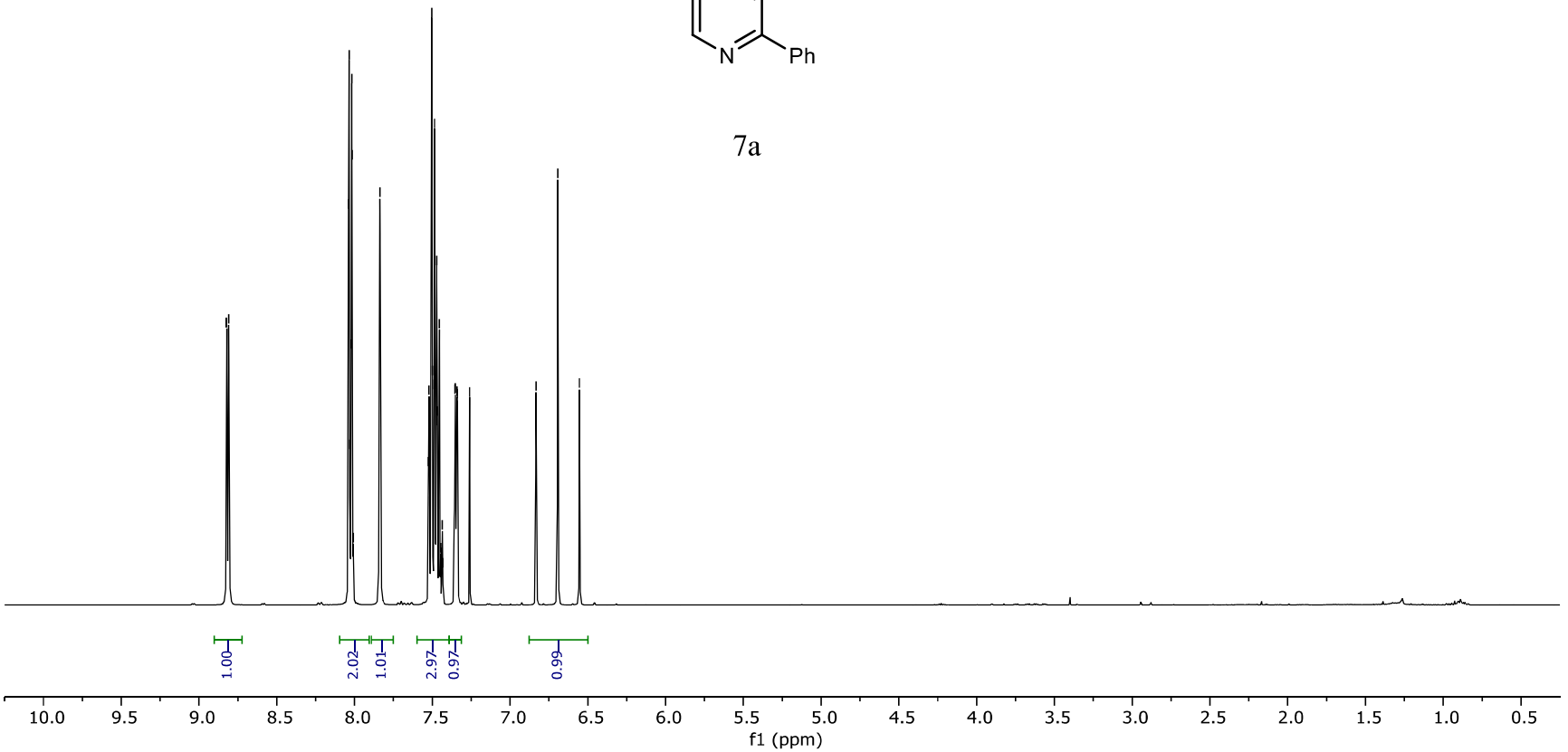
5ap

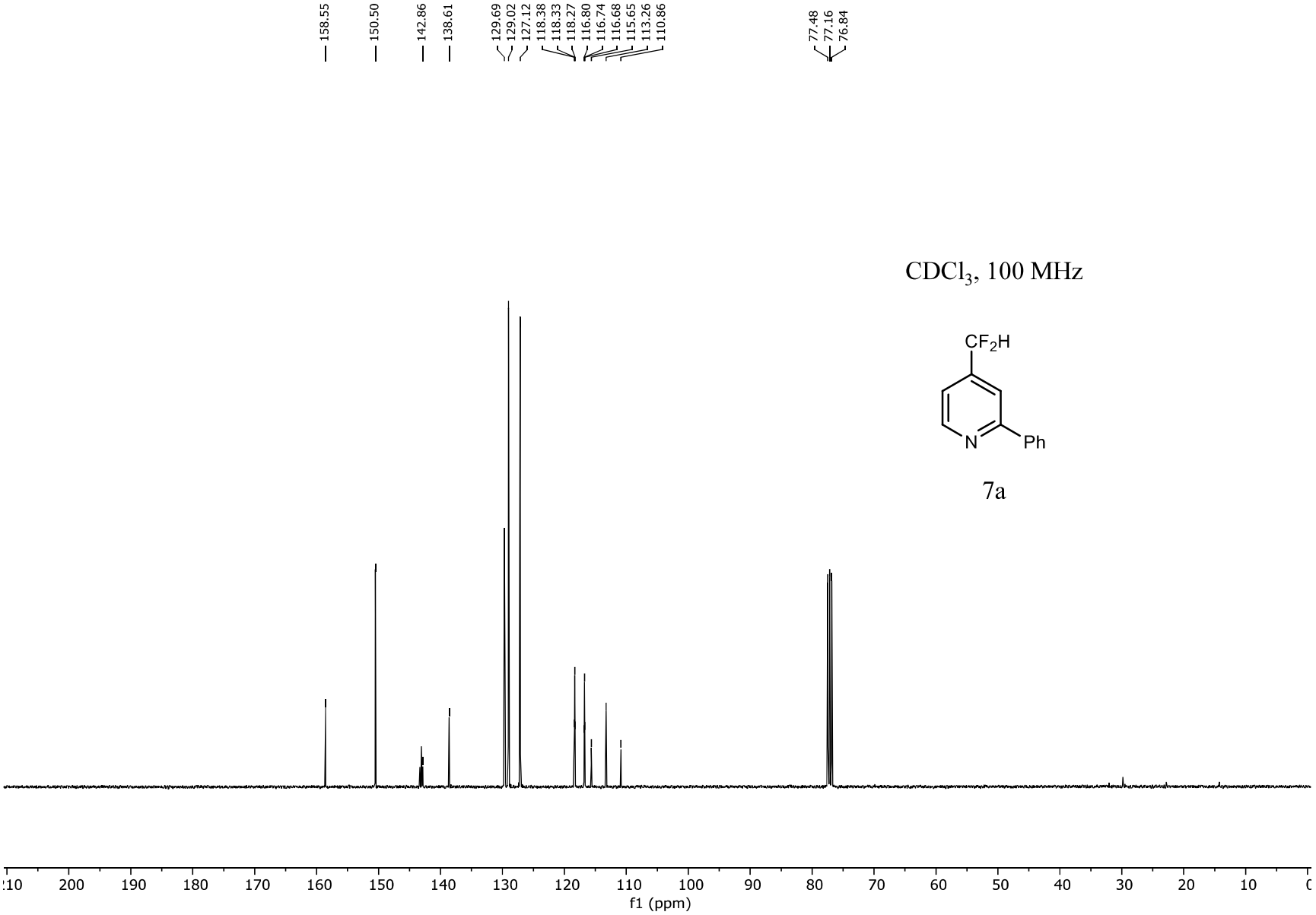


$CDCl_3$, 400 MHz

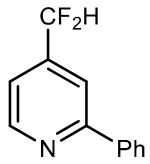


7a

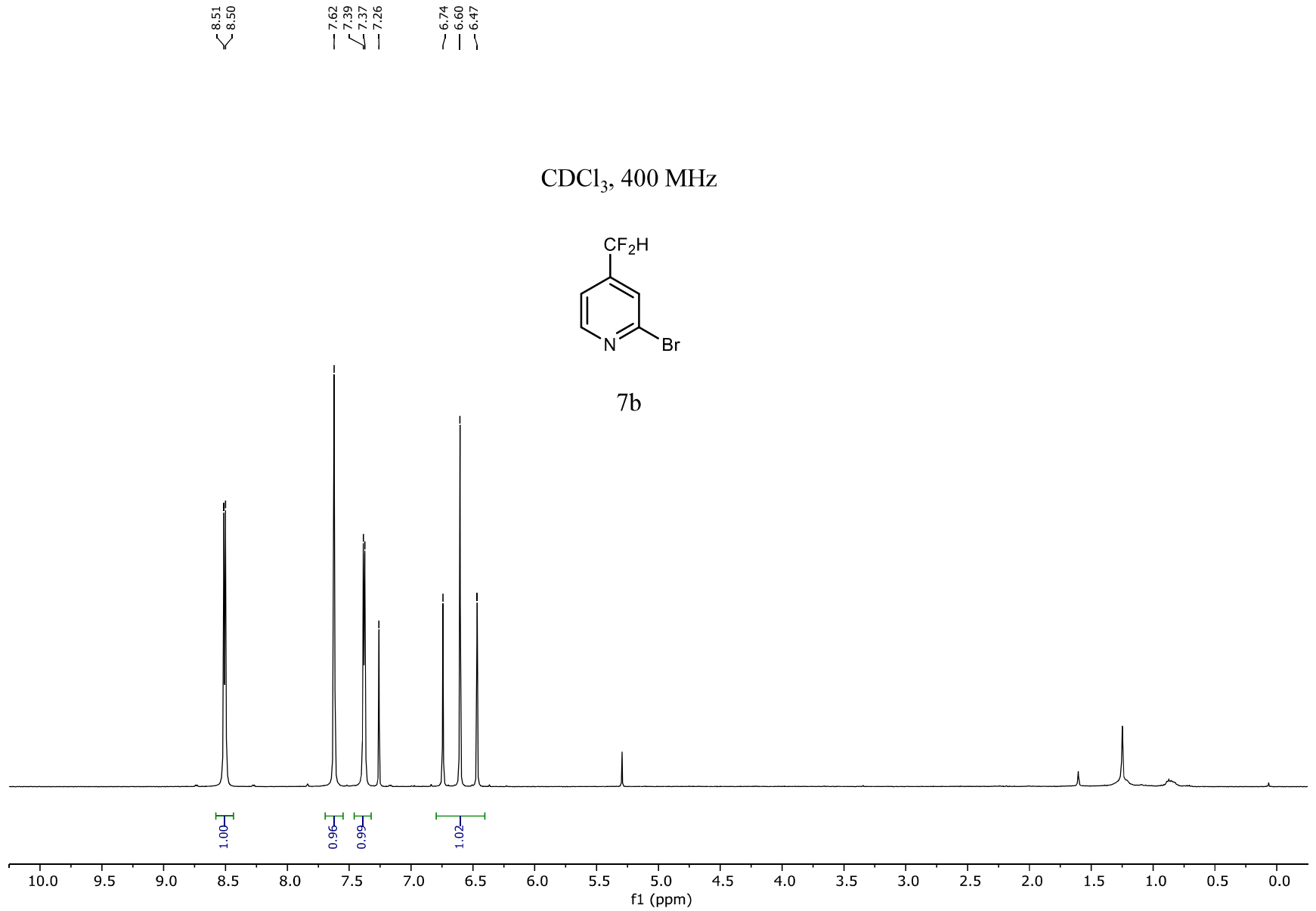


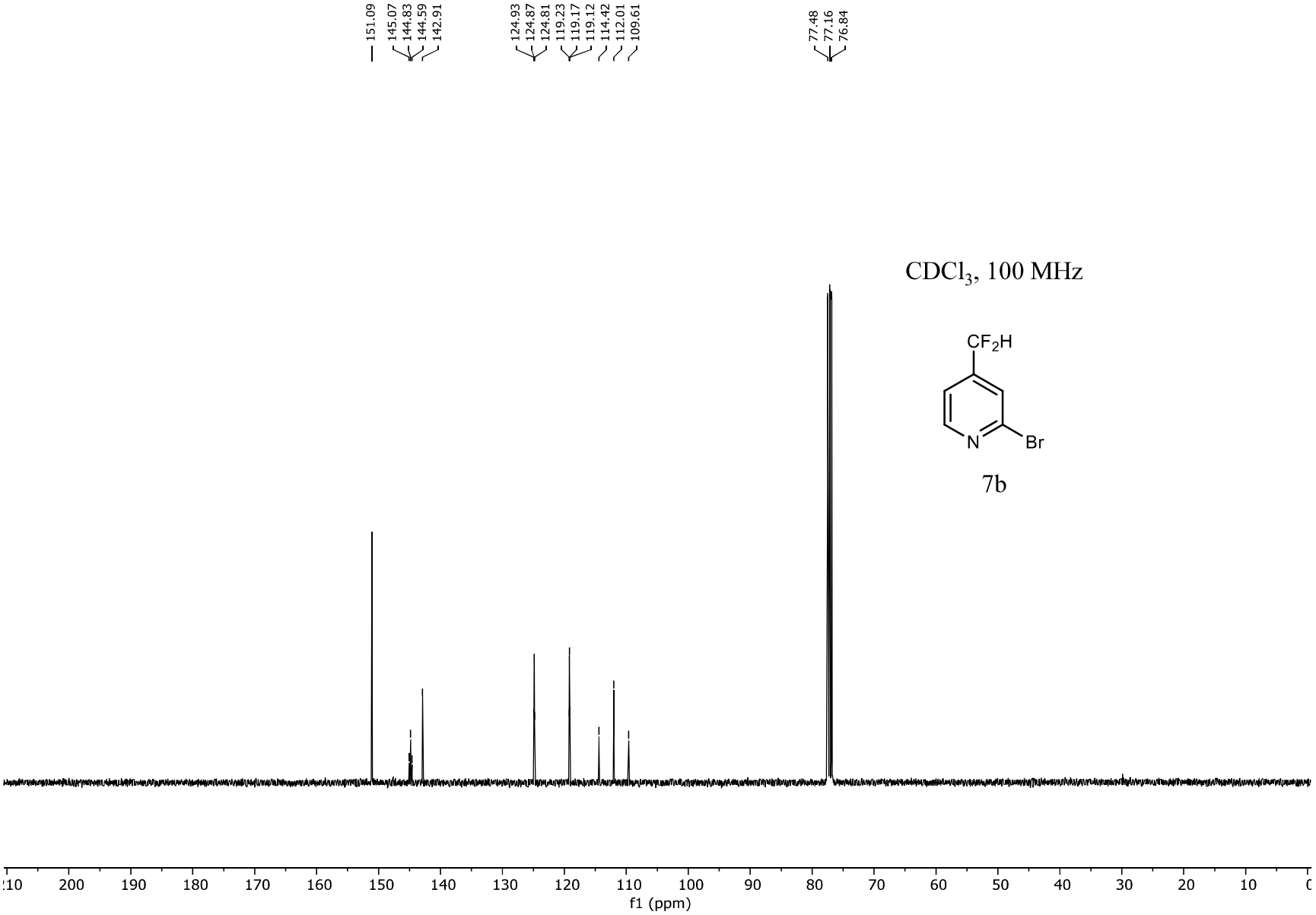

158.55
150.50
142.86
138.61
129.69
129.02
127.12
118.38
118.33
118.27
116.80
116.74
116.68
115.65
113.26
110.86
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
N
Ph
7a
f1 (ppm)

$CDCl_3$, 376 MHz

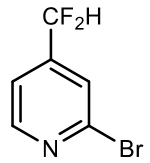


7a

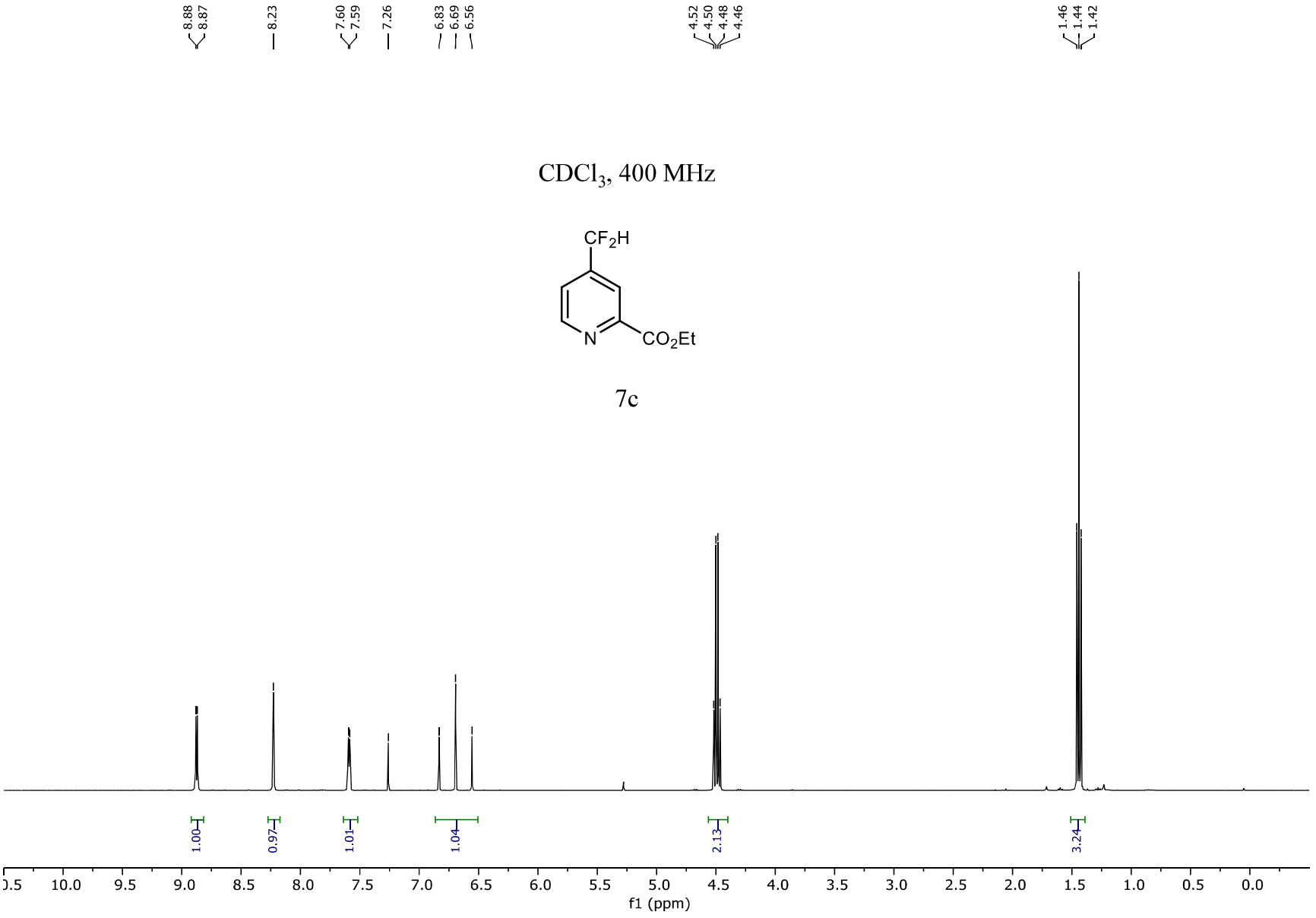

8.51
8.50
7.62
7.39
7.37
7.26
6.74
6.60
6.47
CDCl3, 400 MHz
CF2H
N
Br
7b
1.00
0.96
0.99
1.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

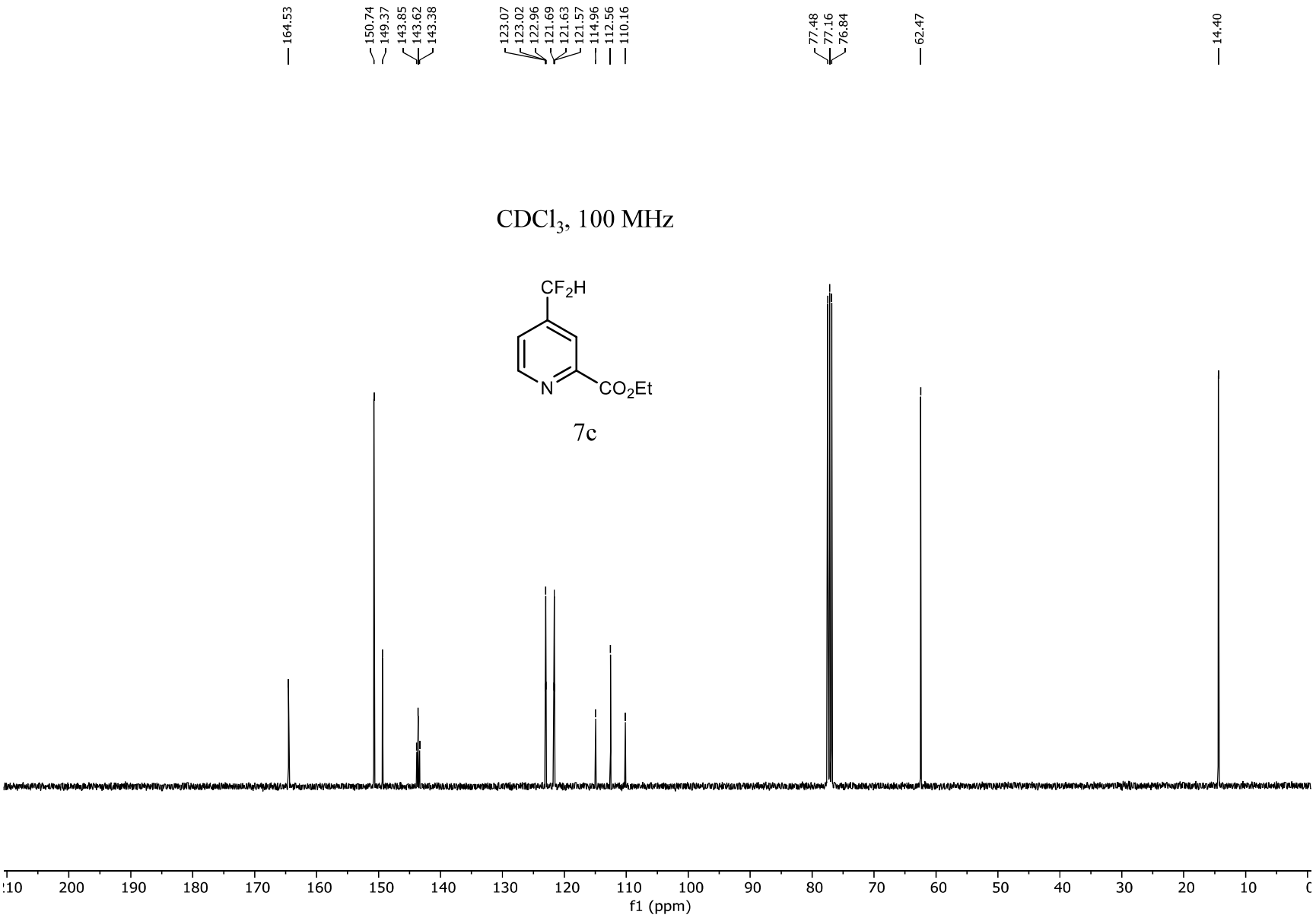

151.09
145.07
144.83
144.59
142.91
124.93
124.87
124.81
119.23
119.17
119.12
114.42
112.01
109.61
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
N
Br
7b
f1 (ppm)

$CDCl_3$, 376 MHz

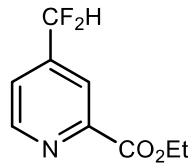


7b

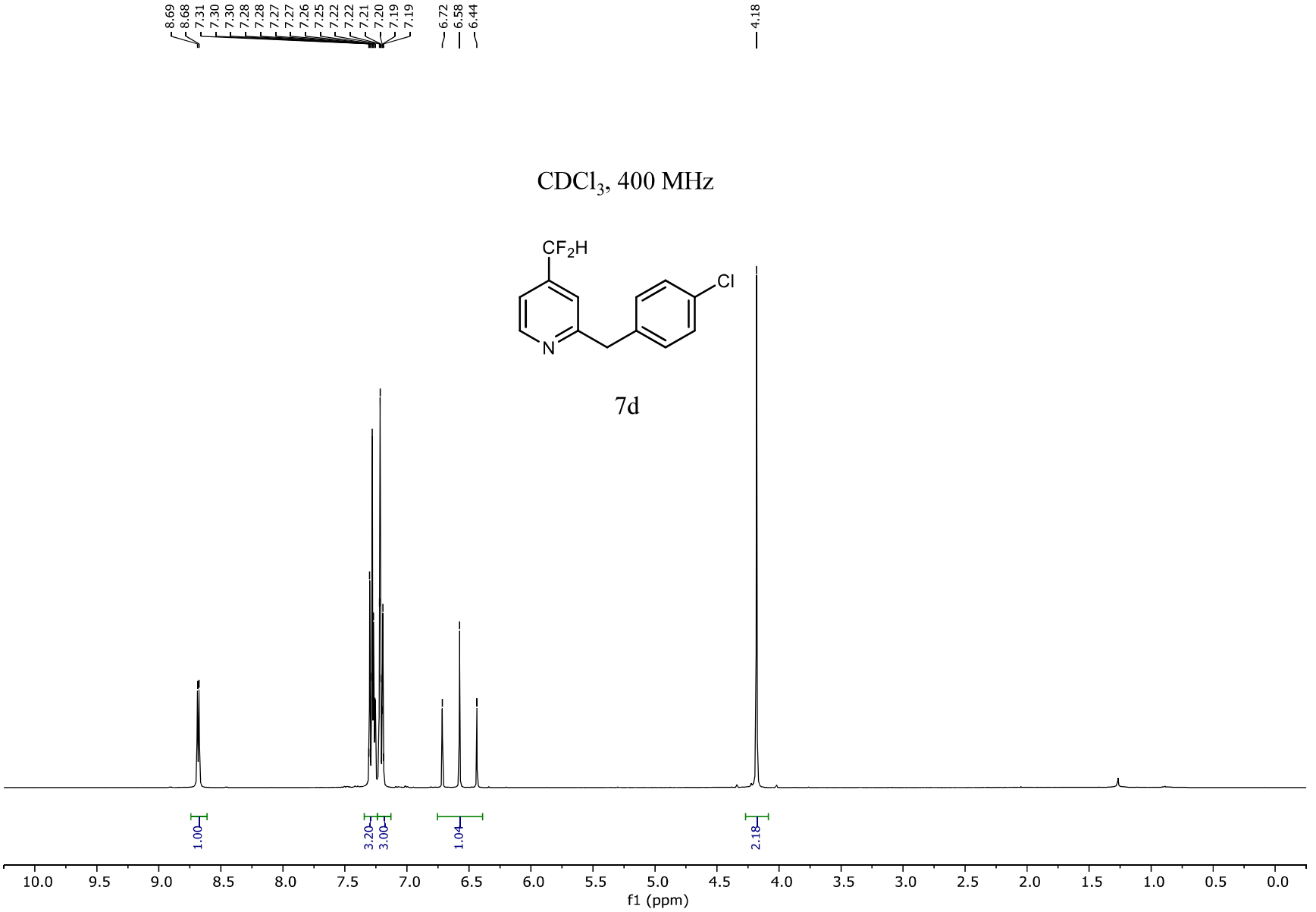

8.88
8.87
8.23
7.60
7.59
7.26
6.83
6.69
6.56
4.52
4.50
4.48
4.46
1.46
1.44
1.42
CDCl3, 400 MHz
CF2H
N
CO2Et
7c
1.00
0.97
1.01
1.04
2.13
3.24
f1 (ppm)

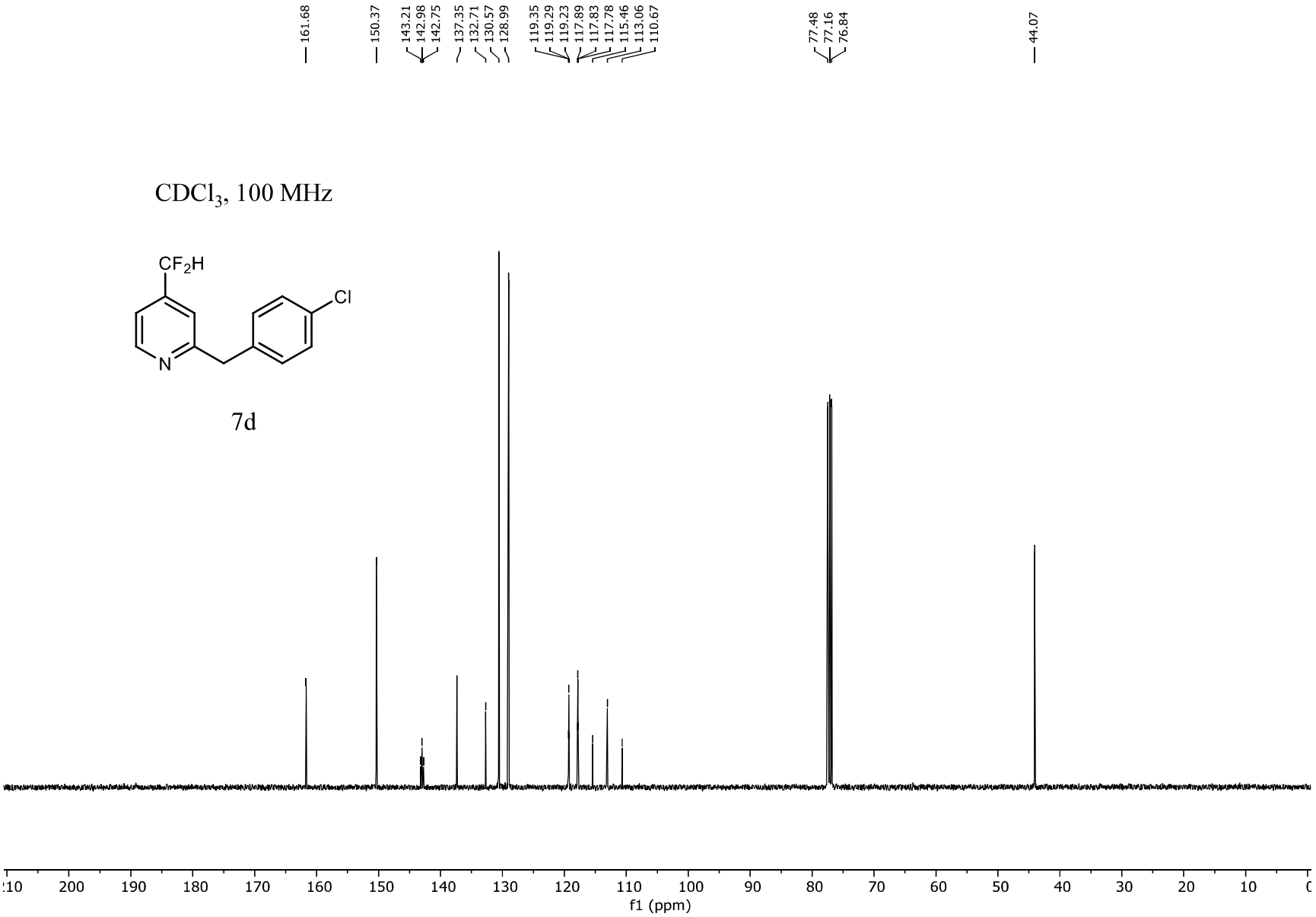

164.53
150.74
149.37
143.85
143.62
143.38
123.07
123.02
122.96
121.69
121.63
121.57
114.96
112.56
110.16
77.48
77.16
76.84
62.47
14.40
CDCl3, 100 MHz
CF2H
N
CO2Et
7c
f1 (ppm)

$CDCl_3$, 376 MHz

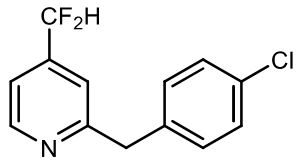


7c

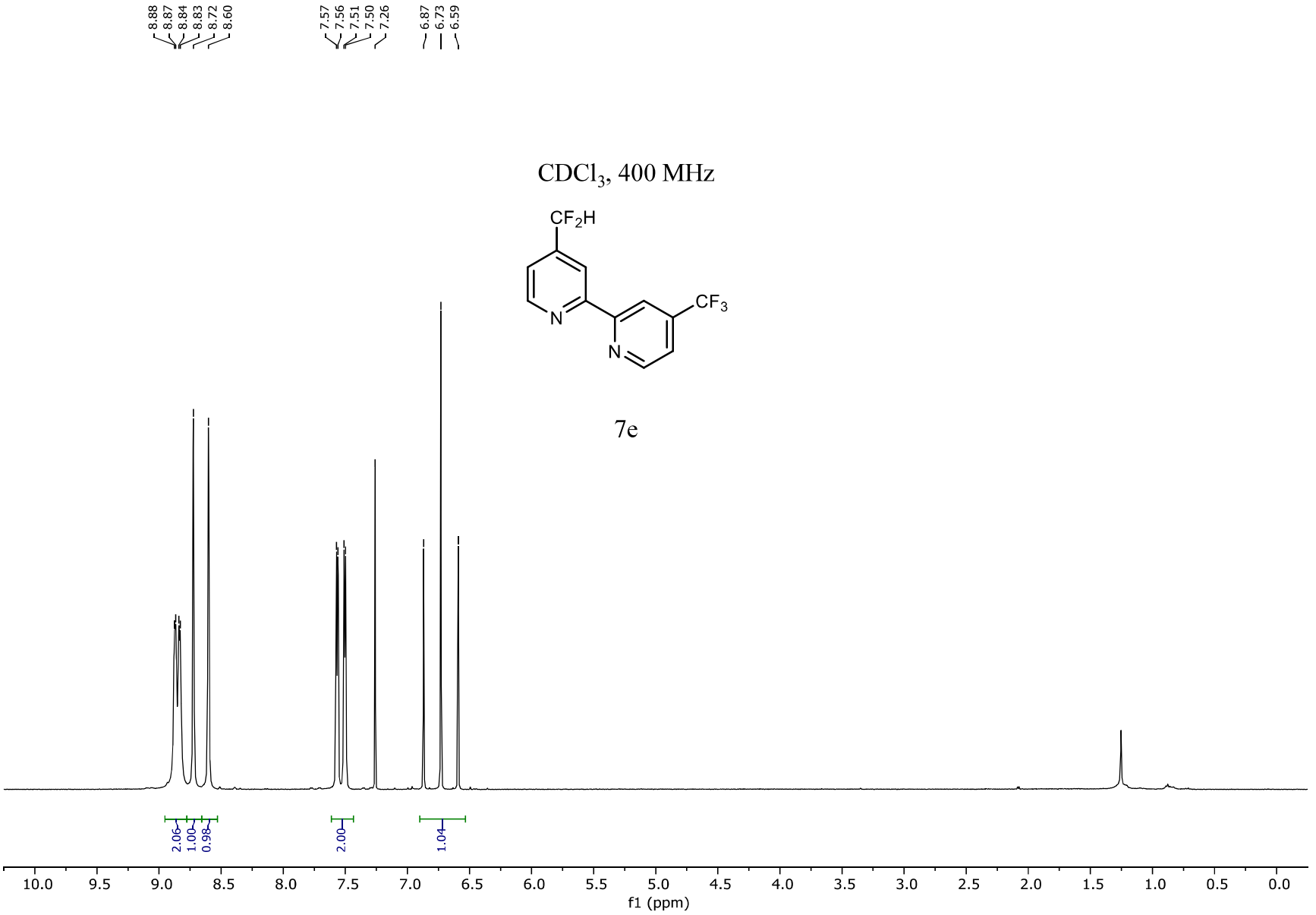

8.69
8.68
7.31
7.30
7.30
7.28
7.28
7.27
7.27
7.26
7.25
7.22
7.22
7.21
7.20
7.19
7.19
6.72
6.58
6.44
4.18
CDCl3, 400 MHz
CF2H
Cl
N
7d
1.00
3.20
3.00
1.04
2.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

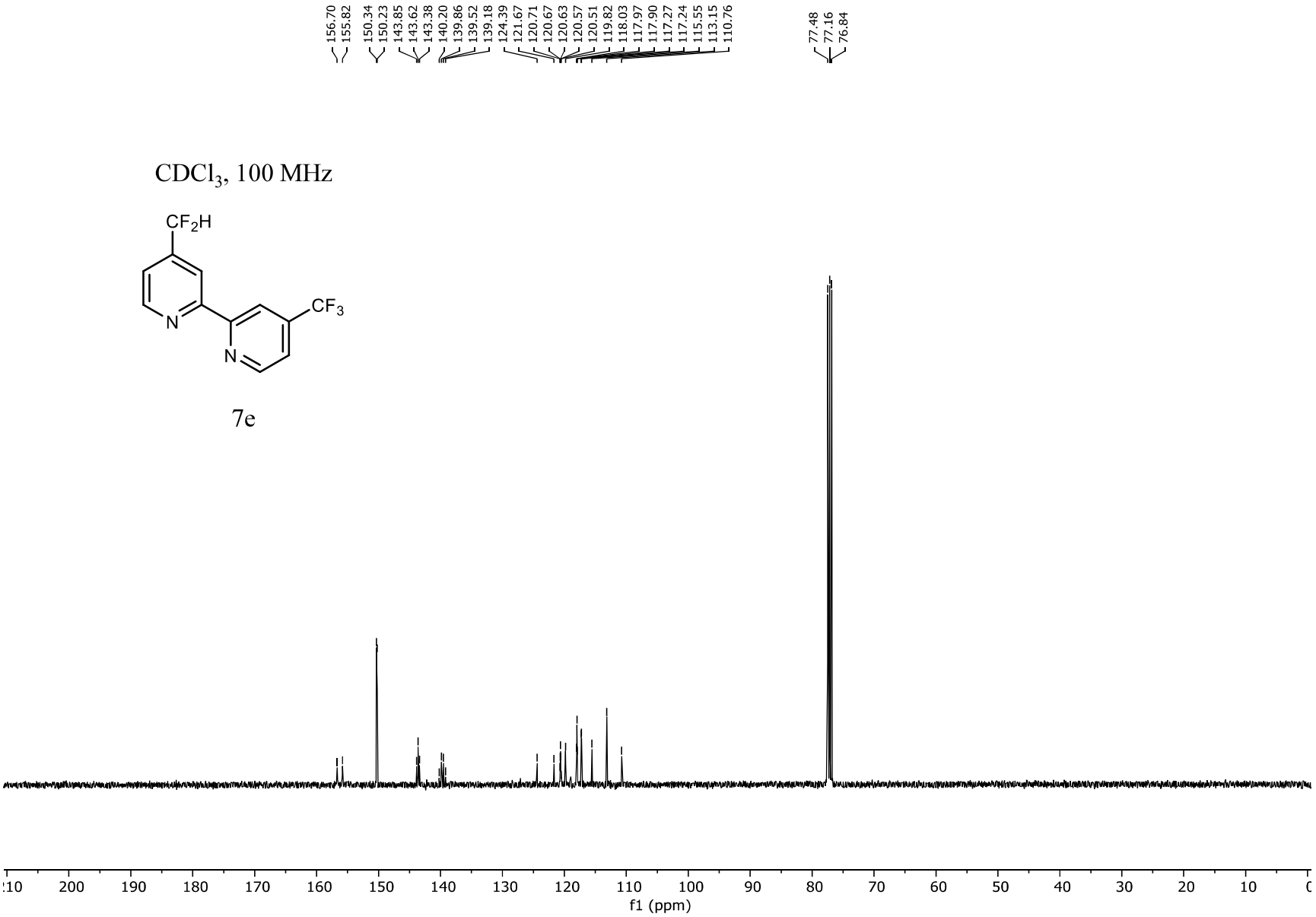

161.68
150.37
143.21
142.98
142.75
137.35
132.71
130.57
128.99
119.35
119.29
119.23
117.89
117.83
117.78
115.46
113.06
110.67
77.48
77.16
76.84
44.07
CDCl3, 100 MHz
CF2H
Cl
N
7d
f1 (ppm)

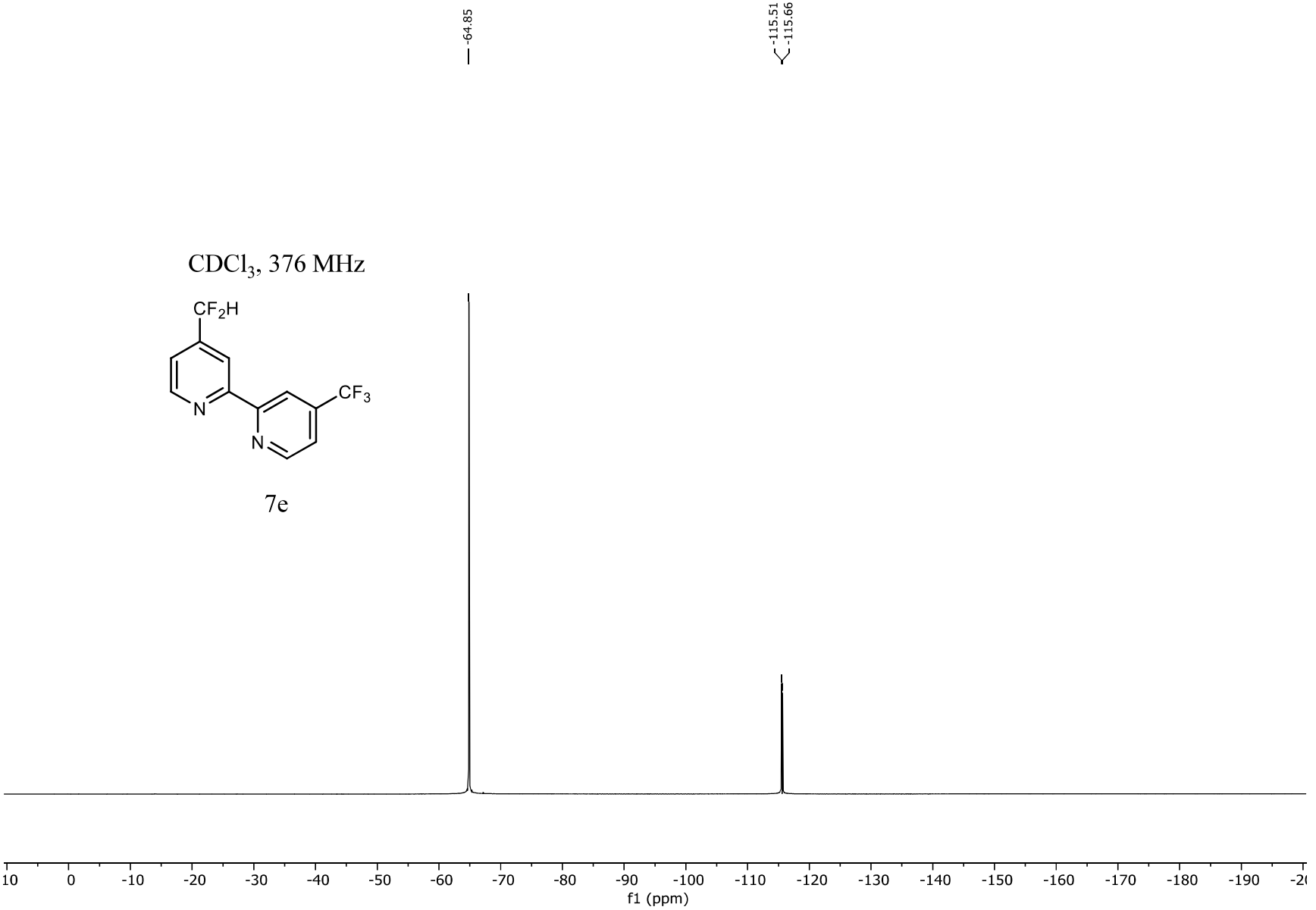
$CDCl_3$, 376 MHz

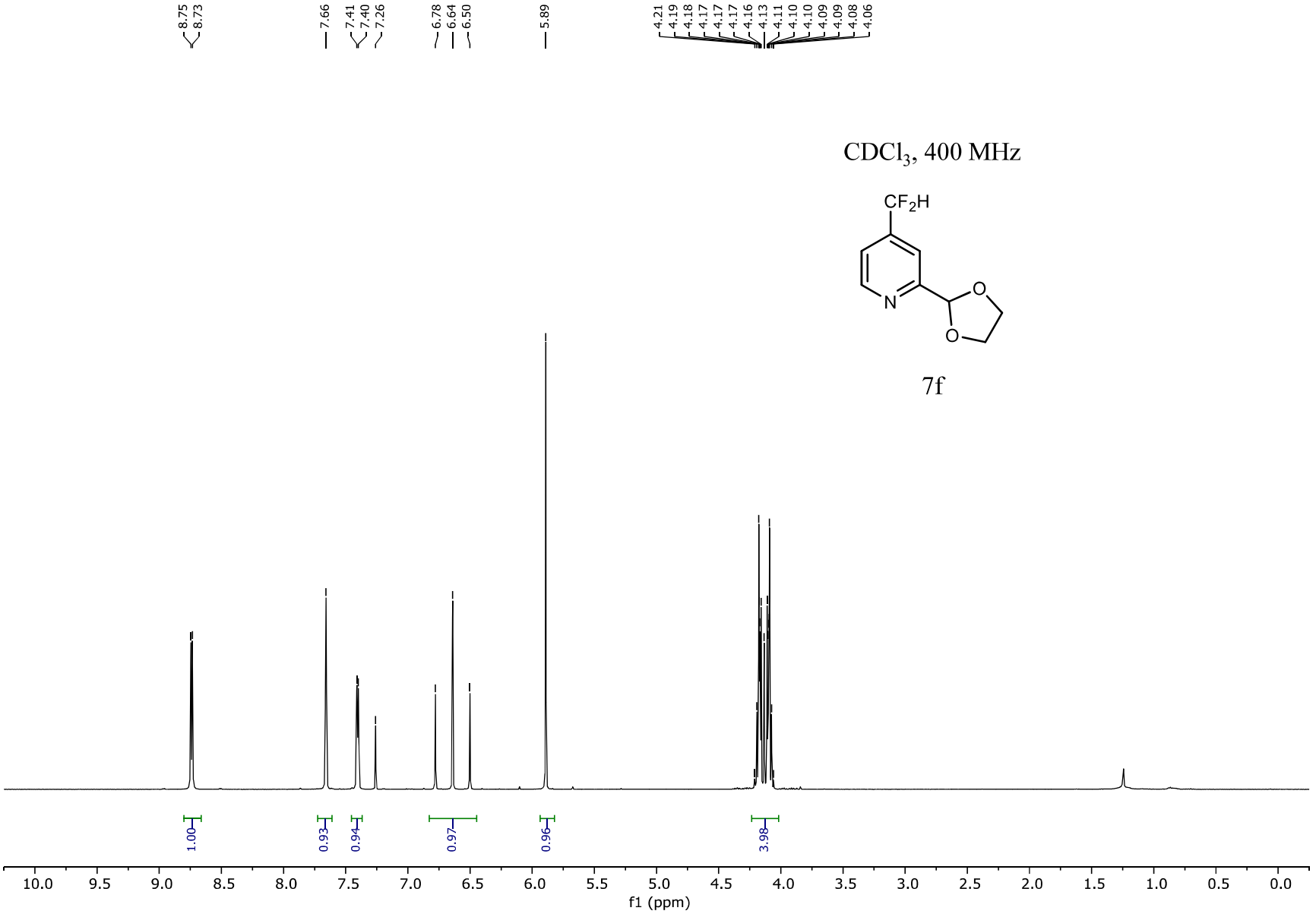


7d


8.88
8.87
8.84
8.83
8.72
8.60
7.57
7.56
7.51
7.50
7.26
6.87
6.73
6.59
CDCl3, 400 MHz
CF2H
CF3
N
N
7e
2.06
1.00
0.98
2.00
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)

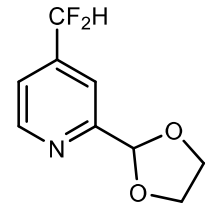

156.70
155.82
150.34
150.23
143.85
143.62
143.38
140.20
139.86
139.52
139.18
124.39
121.67
120.71
120.67
120.63
120.57
120.51
119.82
118.03
117.97
117.90
117.27
117.24
115.55
113.15
110.76
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
CF3
N
N
7e
f1 (ppm)


-64.85
-115.51
-115.66
CDCl3, 376 MHz
CF2H
CF3
N
N
7e
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


8.75
8.73
7.66
7.41
7.40
7.26
6.78
6.64
6.50
5.89
4.21
4.19
4.18
4.17
4.17
4.17
4.16
4.13
4.11
4.10
4.10
4.09
4.09
4.08
4.06
CDCl3, 400 MHz
CF2H
N
O
O
7f
1.00
0.93
0.94
0.97
0.96
3.98
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)

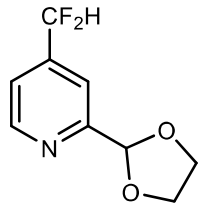
158.44
150.22
143.42
143.18
142.95
120.32
120.26
120.21
117.29
117.23
117.17
115.37
112.97
110.58
103.30
77.48
77.16
76.84
65.80

$CDCl_3$, 100 MHz

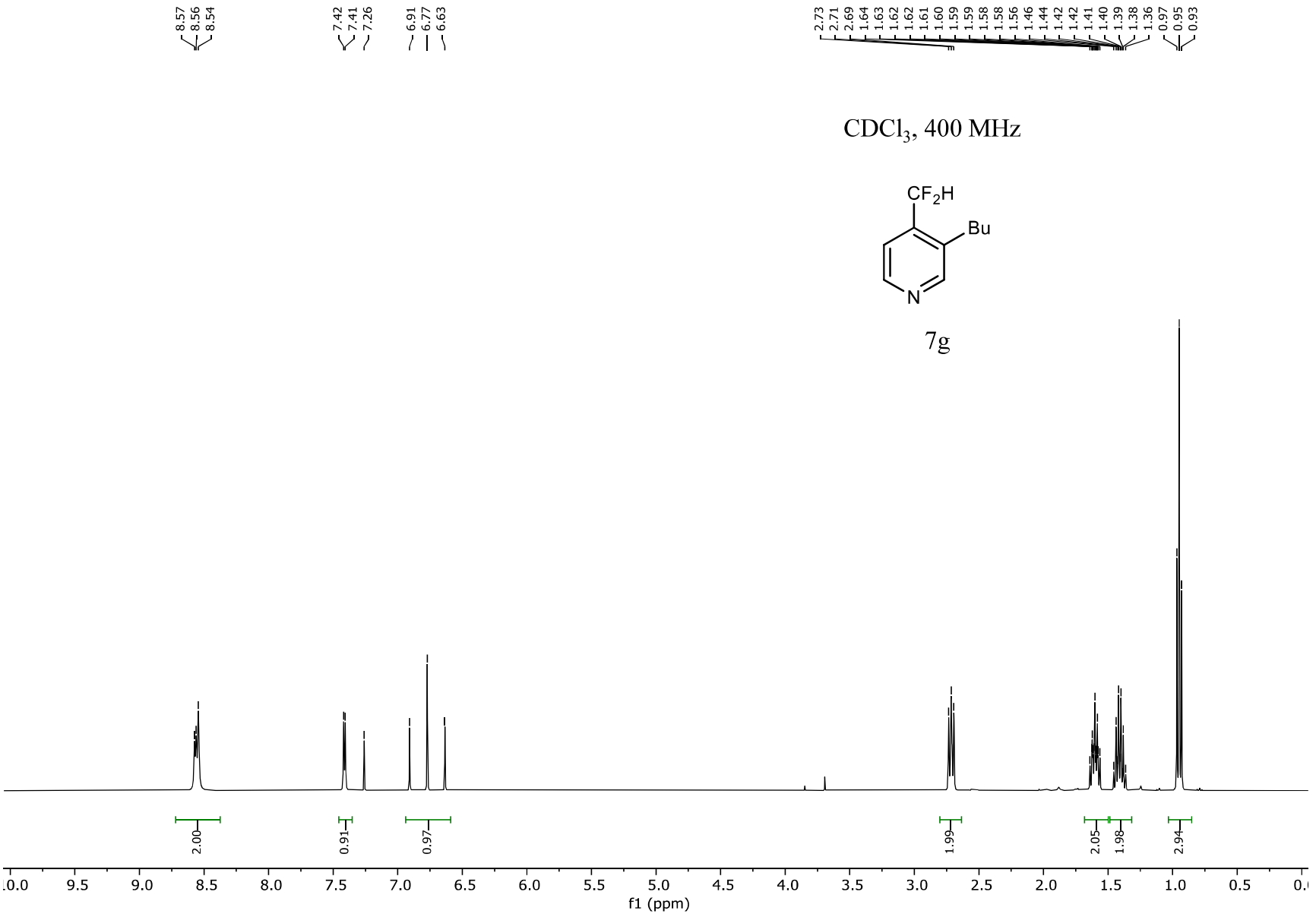


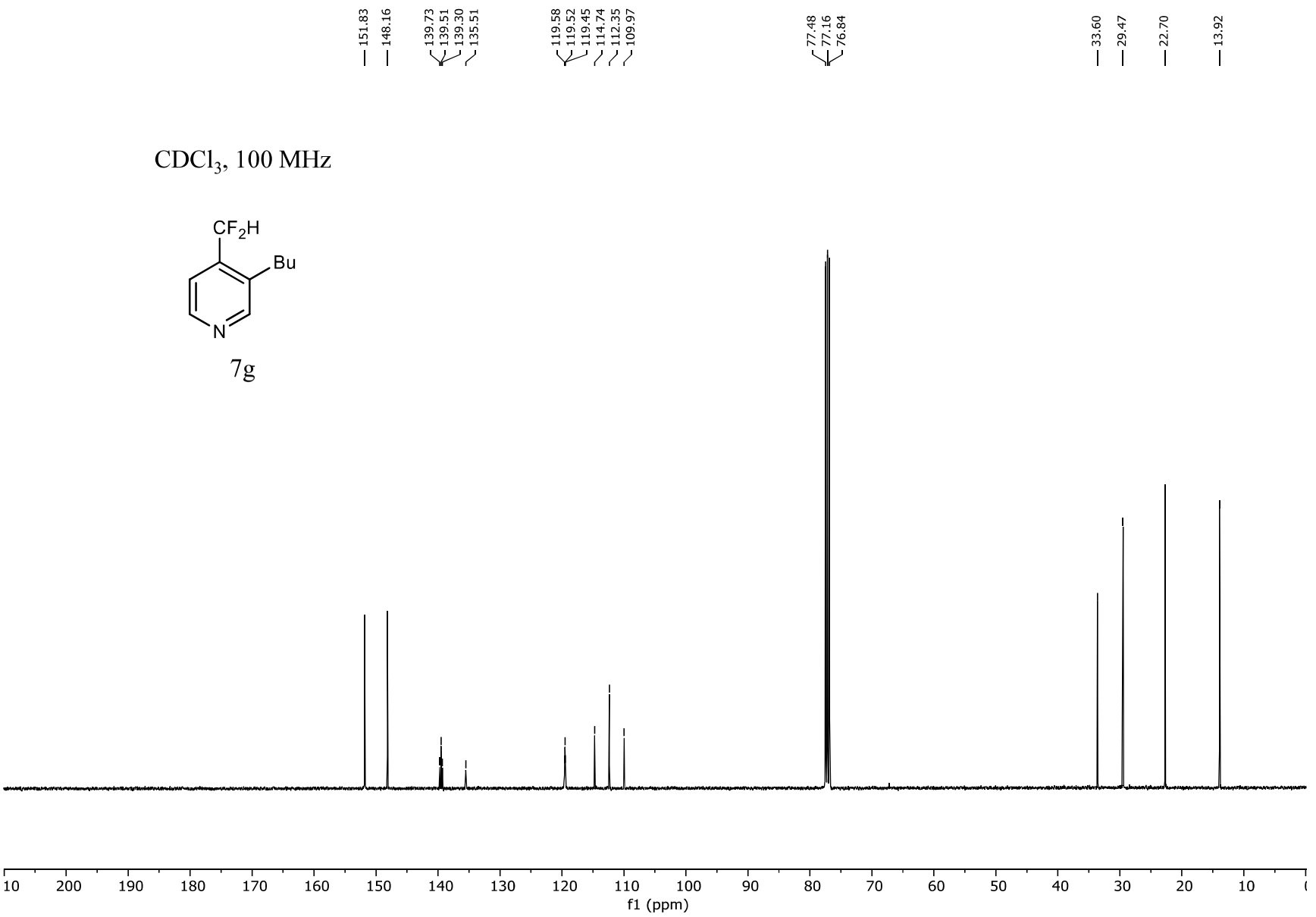
7f

$CDCl_3$, 376 MHz

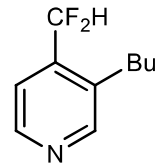


7f

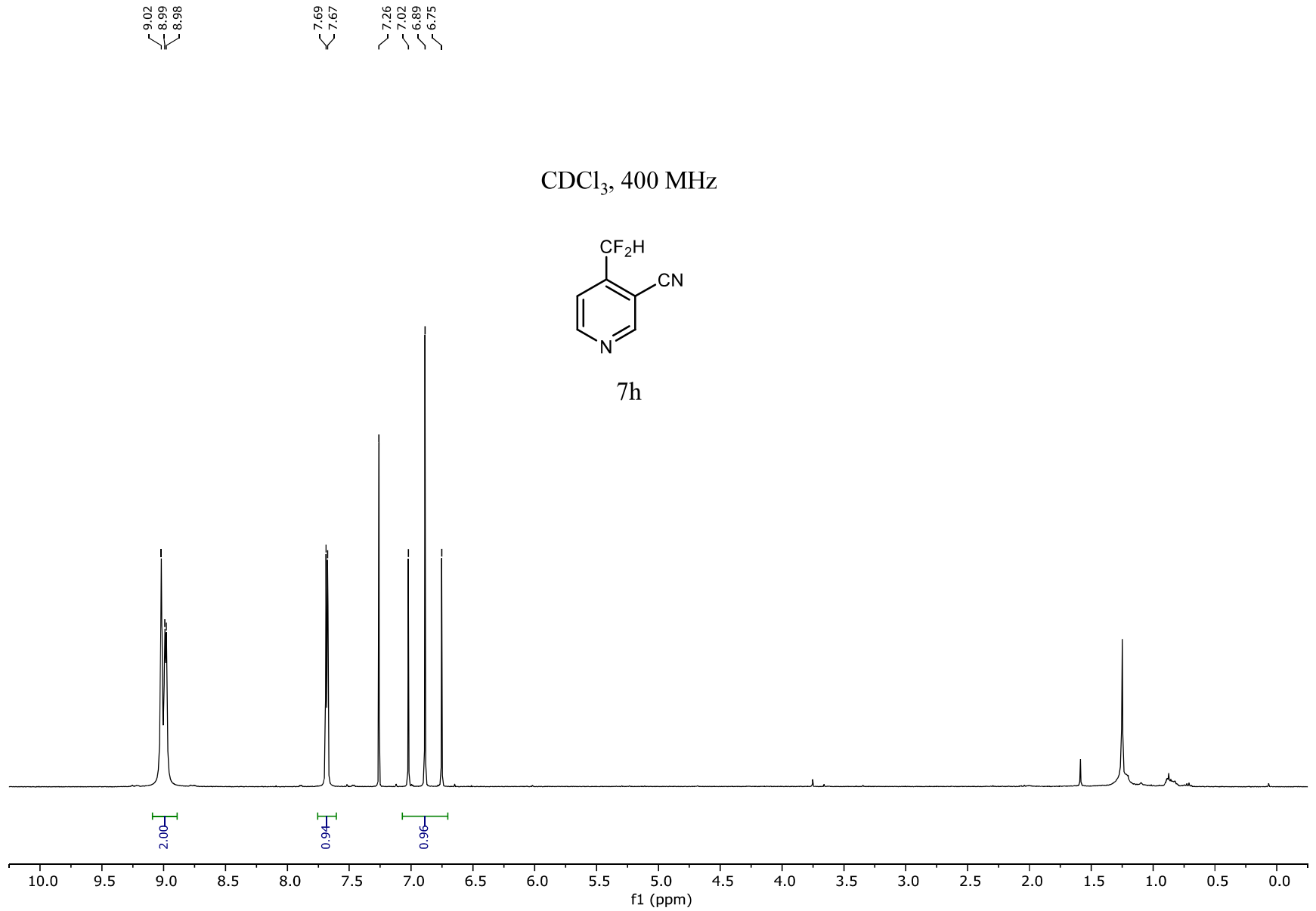

8.57
8.56
8.54
7.42
7.41
7.26
6.91
6.77
6.63
2.73
2.71
2.69
1.64
1.63
1.62
1.62
1.61
1.60
1.59
1.59
1.58
1.58
1.56
1.46
1.44
1.42
1.42
1.41
1.40
1.39
1.38
1.36
0.97
0.95
0.93
CDCl3, 400 MHz
CF2H
Bu
N
7g
2.00
0.91
0.97
1.99
2.05
1.98
2.94
f1 (ppm)


151.83
148.16
139.73
139.51
139.30
135.51
119.58
119.52
119.45
114.74
112.35
109.97
77.48
77.16
76.84
33.60
29.47
22.70
13.92
CDCl3, 100 MHz
CF2H
Bu
N
7g
f1 (ppm)

$CDCl_3$, 376 MHz

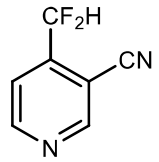


7g

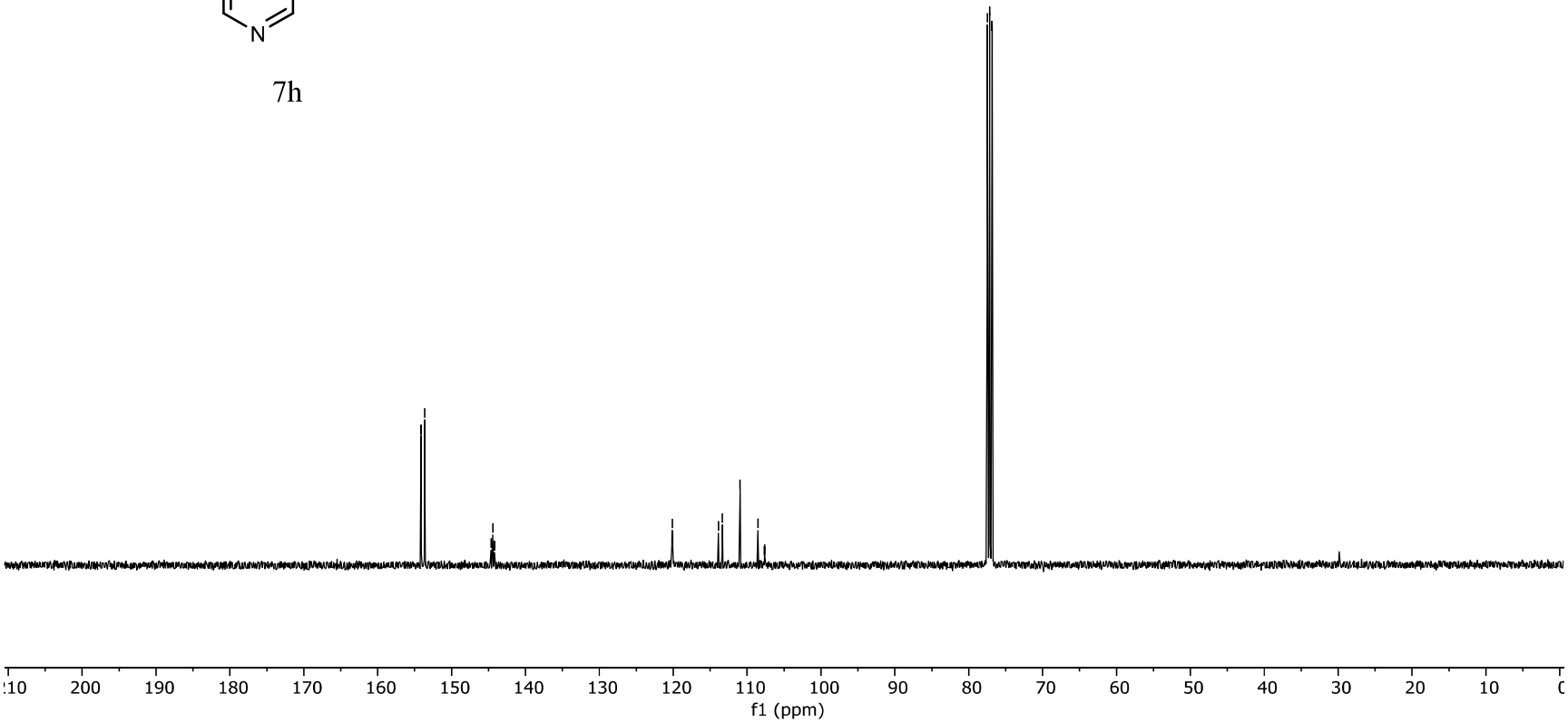

9.02
8.99
8.98
7.69
7.67
7.26
7.02
6.89
6.75
CDCl3, 400 MHz
CF2H
CN
N
7h
2.00
0.94
0.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

154.12
153.64
144.66
144.42
144.17
120.18
120.12
120.07
113.88
113.36
110.94
108.53
107.66
107.64
107.60
77.48
77.16
76.84

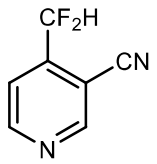
$CDCl_3$, 100 MHz



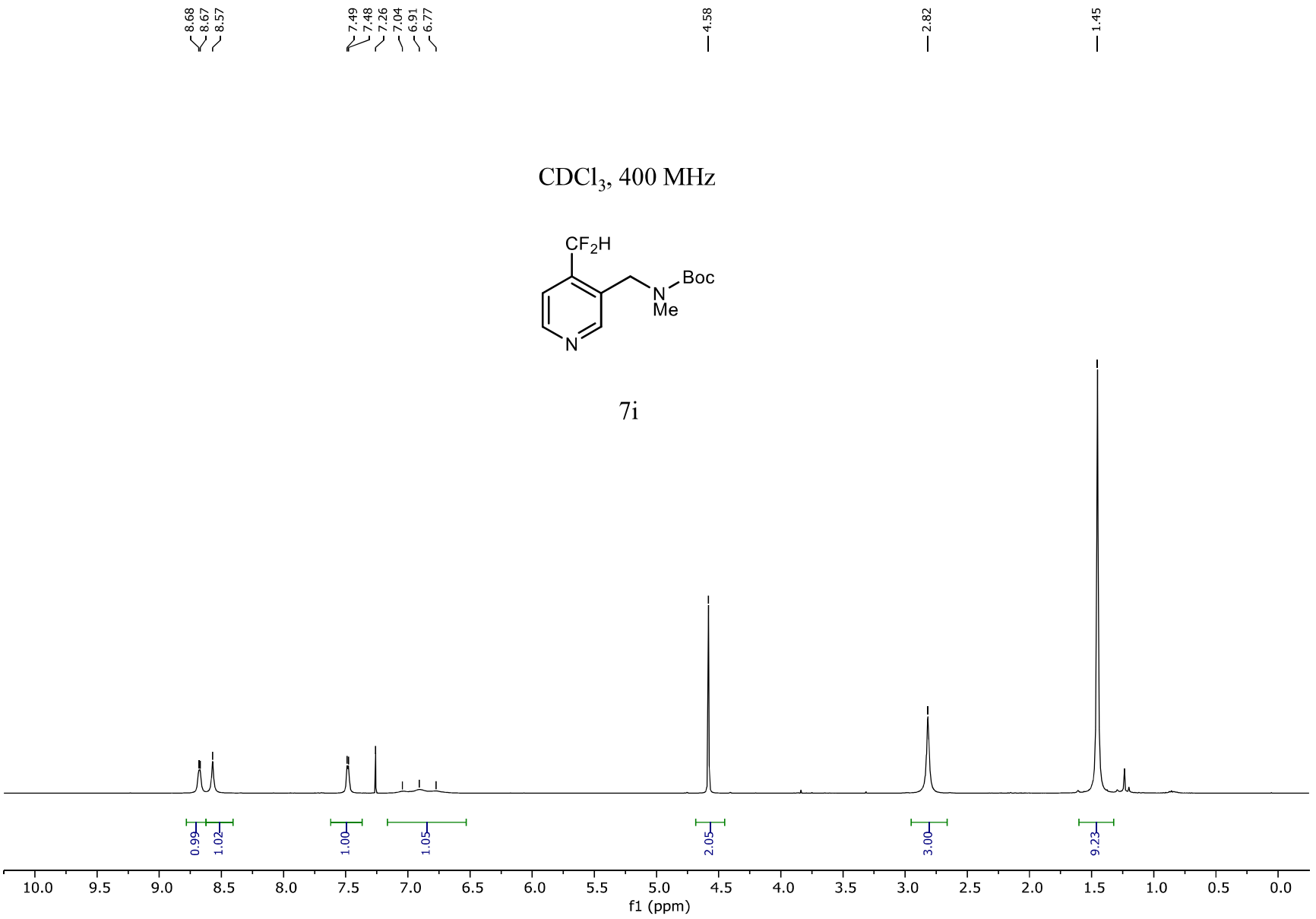
7h



$CDCl_3$, 376 MHz

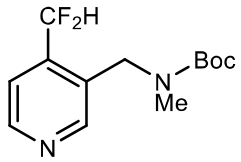


7h

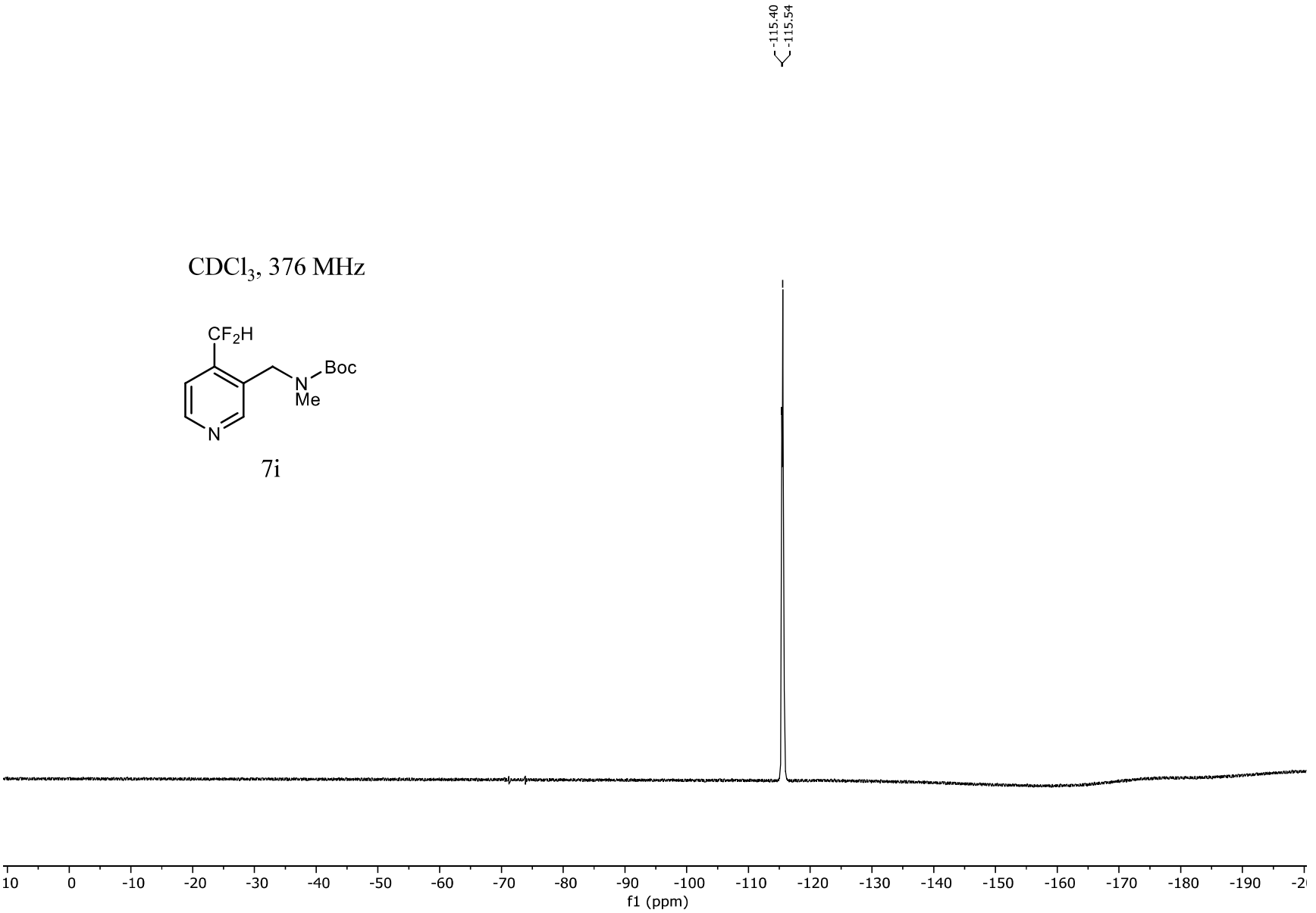

8.68
8.67
8.57
7.49
7.48
7.26
7.04
6.91
6.77
4.58
2.82
1.45
CDCl3, 400 MHz
CF2H
N
Boc
Me
N
7i
0.99
1.02
1.00
1.05
2.05
3.00
9.23
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

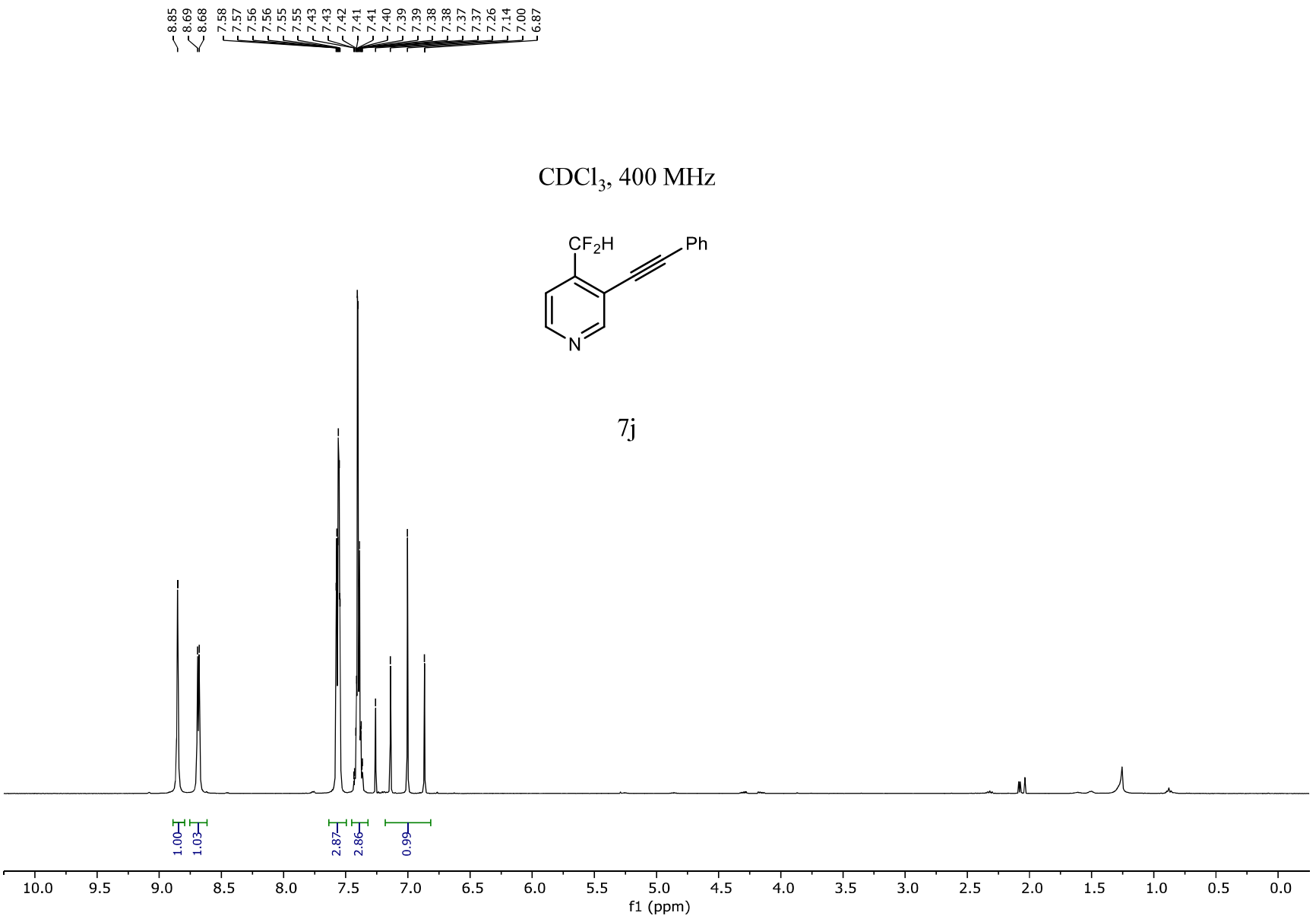
155.69
155.63
150.58
150.47
150.39
149.93
140.63
140.49
139.73
130.85
119.89
114.60
112.22
109.84
80.67
77.48
77.16
76.84
47.22
46.99
46.69
34.13
29.82
28.43

$CDCl_3$, 100 MHz



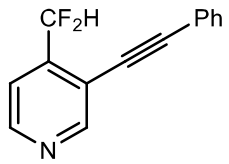
7i


-115.40
-115.54
CDCl3, 376 MHz
CF2H
Boc
N
Me
N
7i
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


8.85
8.69
8.68
7.58
7.57
7.56
7.56
7.55
7.55
7.43
7.43
7.42
7.41
7.41
7.40
7.39
7.39
7.38
7.38
7.37
7.37
7.26
7.14
7.00
6.87
CDCl3, 400 MHz
CF2H
Ph
N
7j
1.00
1.03
2.87
2.86
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)

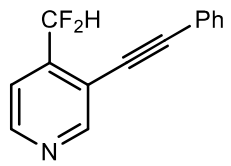
153.21
149.37
142.63
142.40
142.17
131.90
129.57
128.70
121.90
119.07
119.01
118.96
118.50
118.44
118.38
114.36
111.98
109.59
98.26
81.91
77.48
77.16
76.84

$CDCl_3$, 100 MHz

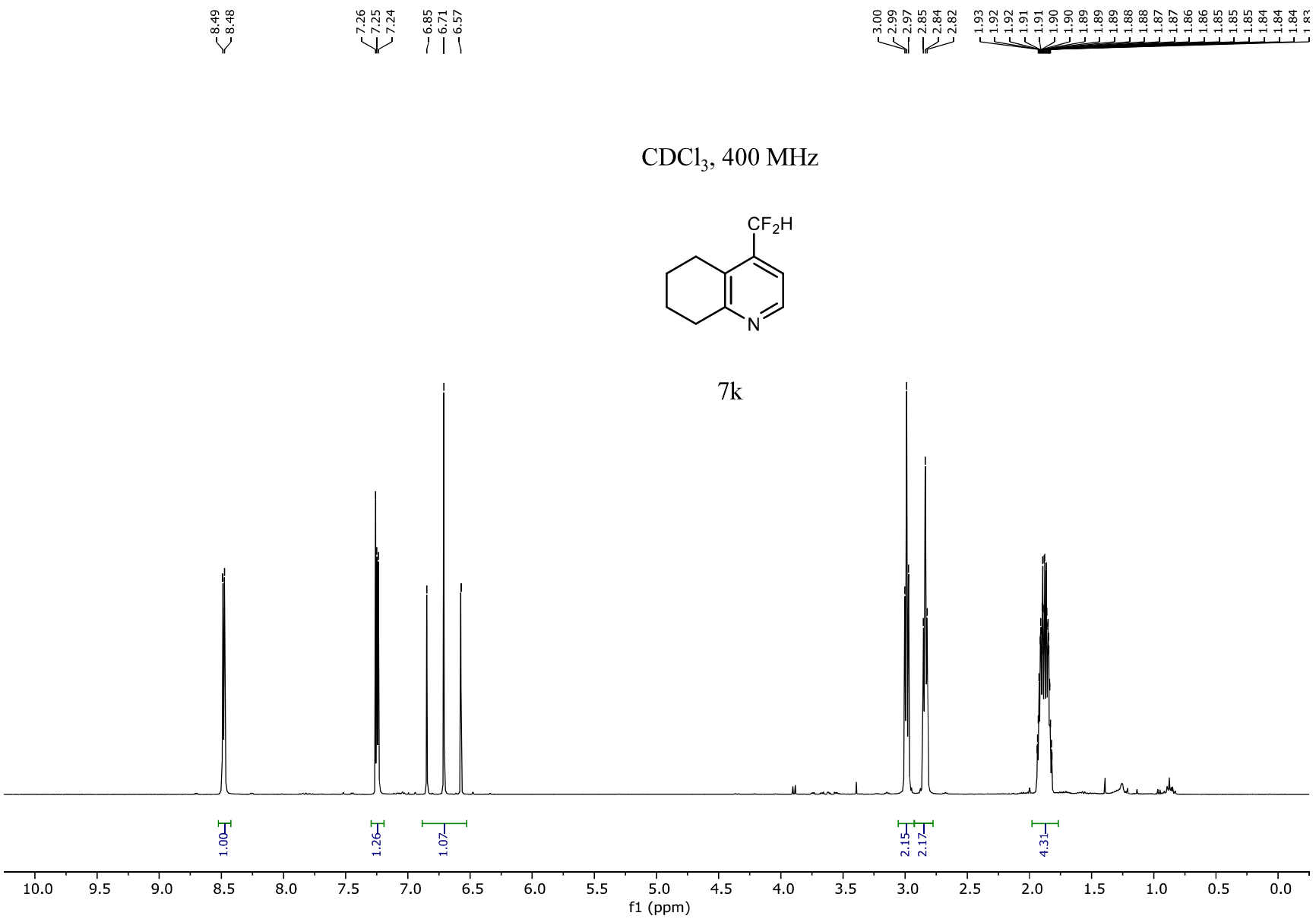


7j

$CDCl_3$, 376 MHz



7j

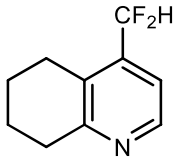


$CDCl_3$, 400 MHz

7k

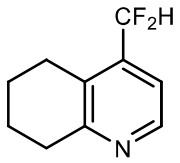
158.72
147.33
140.09
139.88
139.66
129.96
117.24
117.17
117.10
114.99
112.61
110.23
77.48
77.16
76.84
33.05
24.90
22.52
22.32

$CDCl_3$, 100 MHz

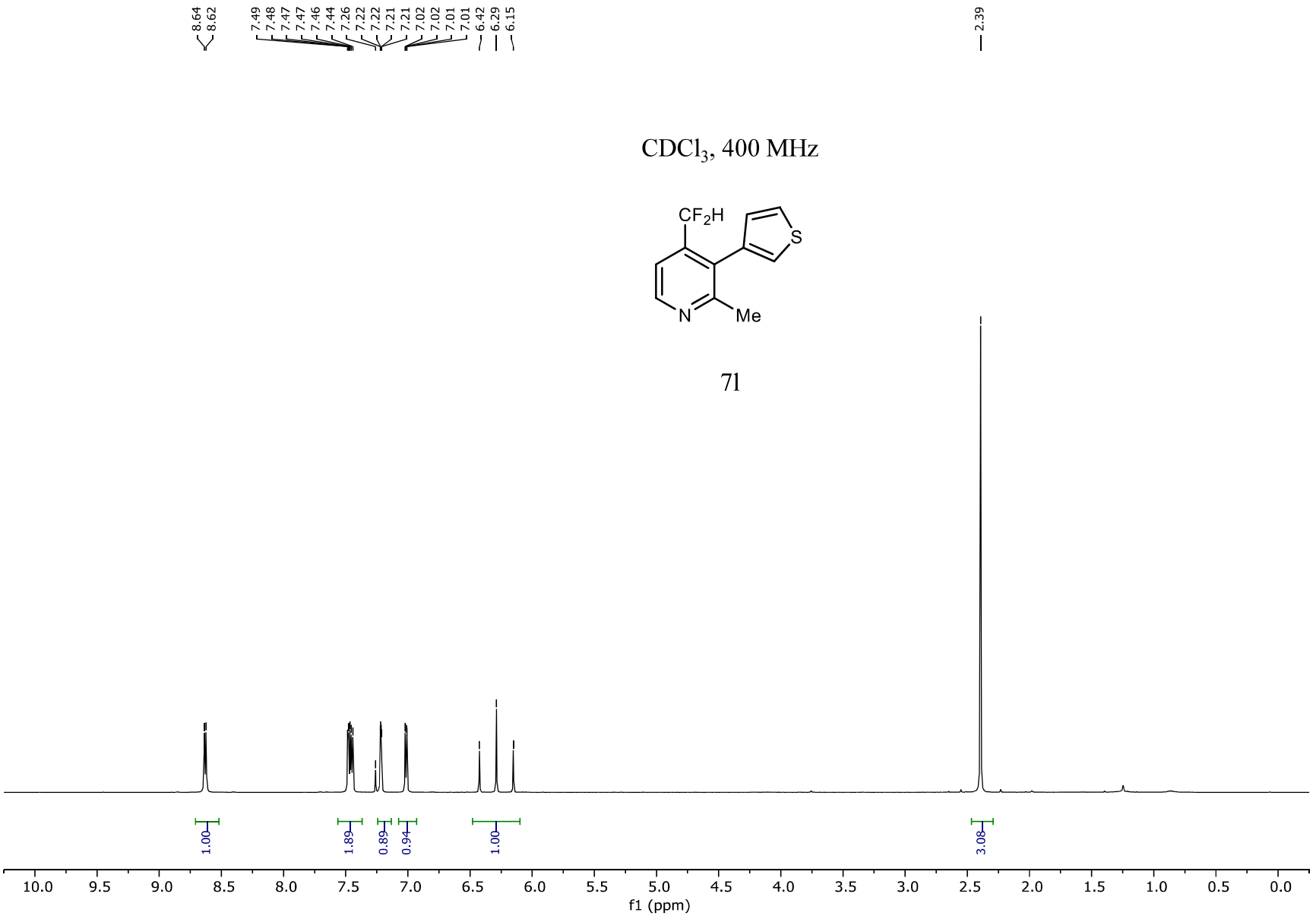


7k

$CDCl_3$, 376 MHz



7k

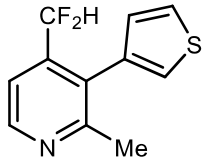


$CDCl_3$, 400 MHz

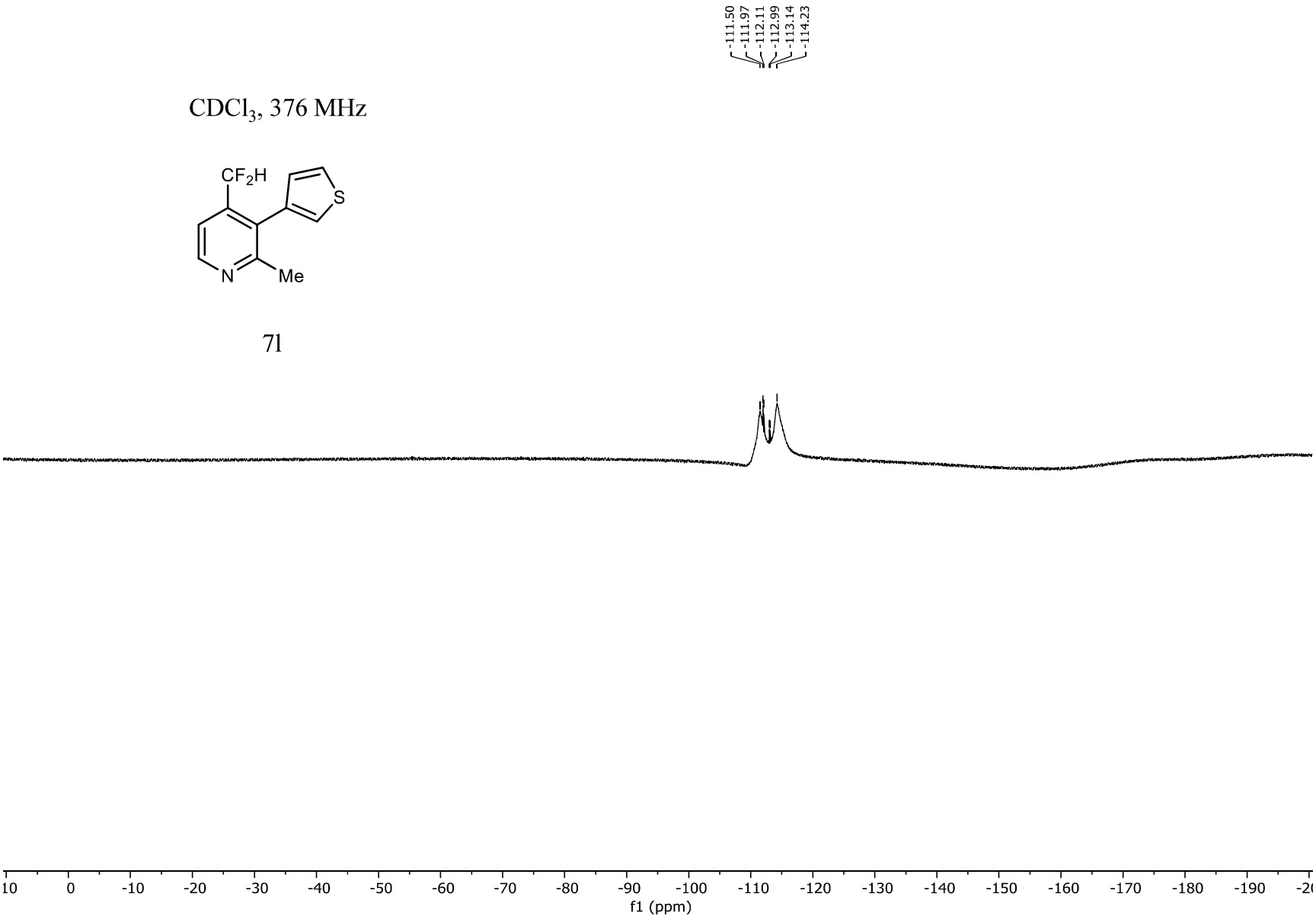
71

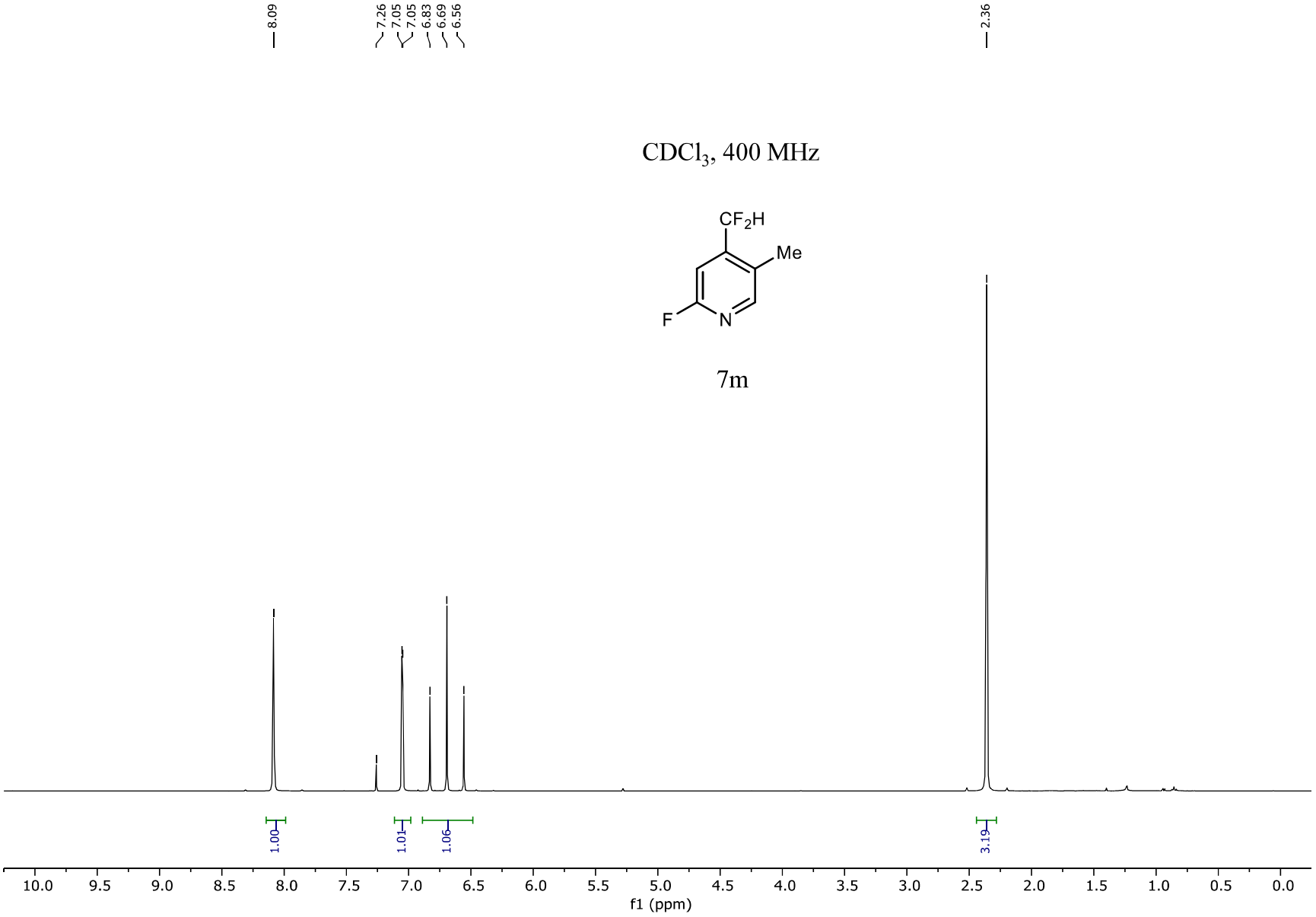
158.60
148.98
140.98
140.76
140.53
134.91
130.29
130.22
130.16
128.80
126.73
125.17
116.74
116.69
116.64
114.35
111.98
109.61
77.48
77.16
76.84
23.52

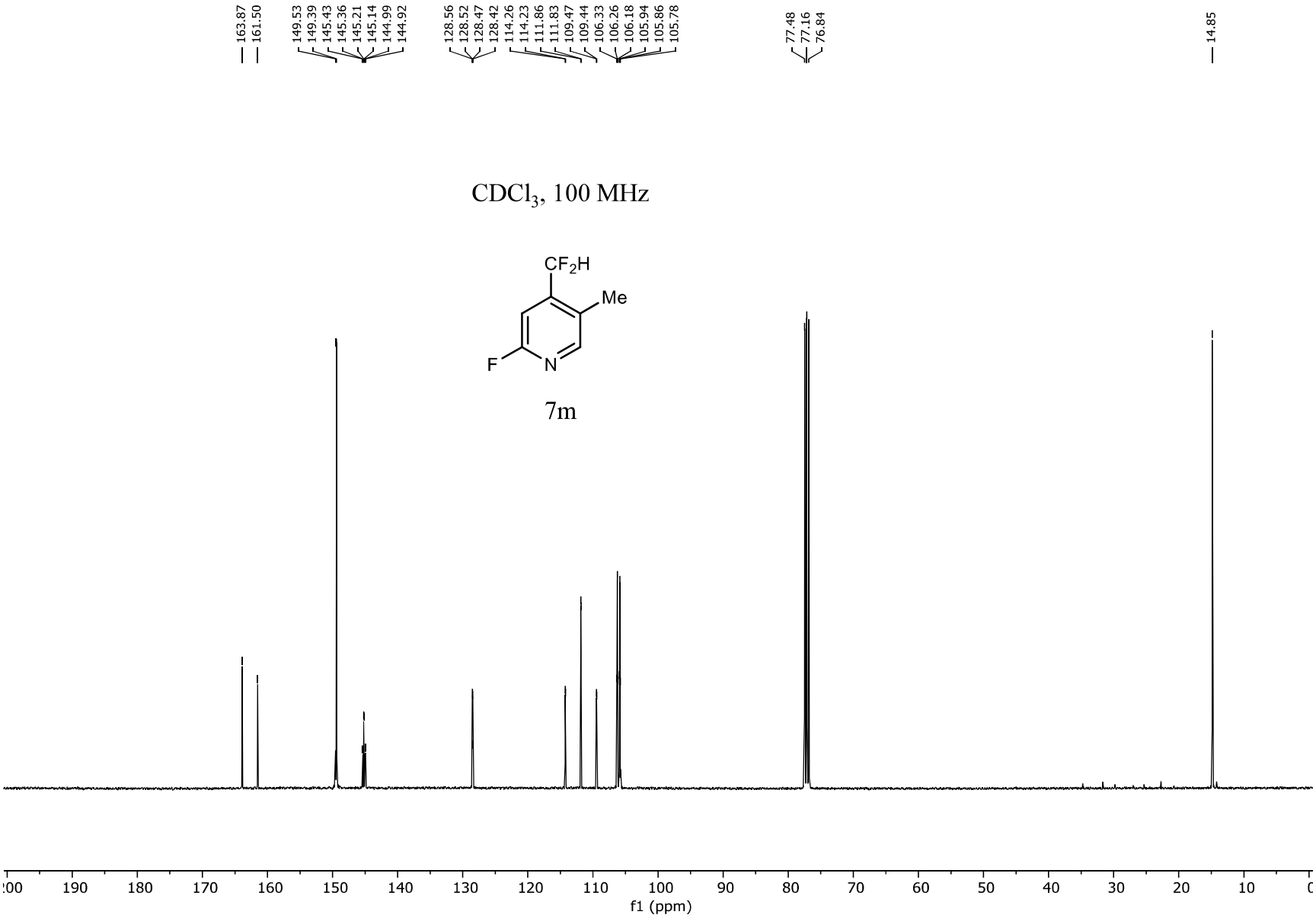
$CDCl_3$, 100 MHz



7l

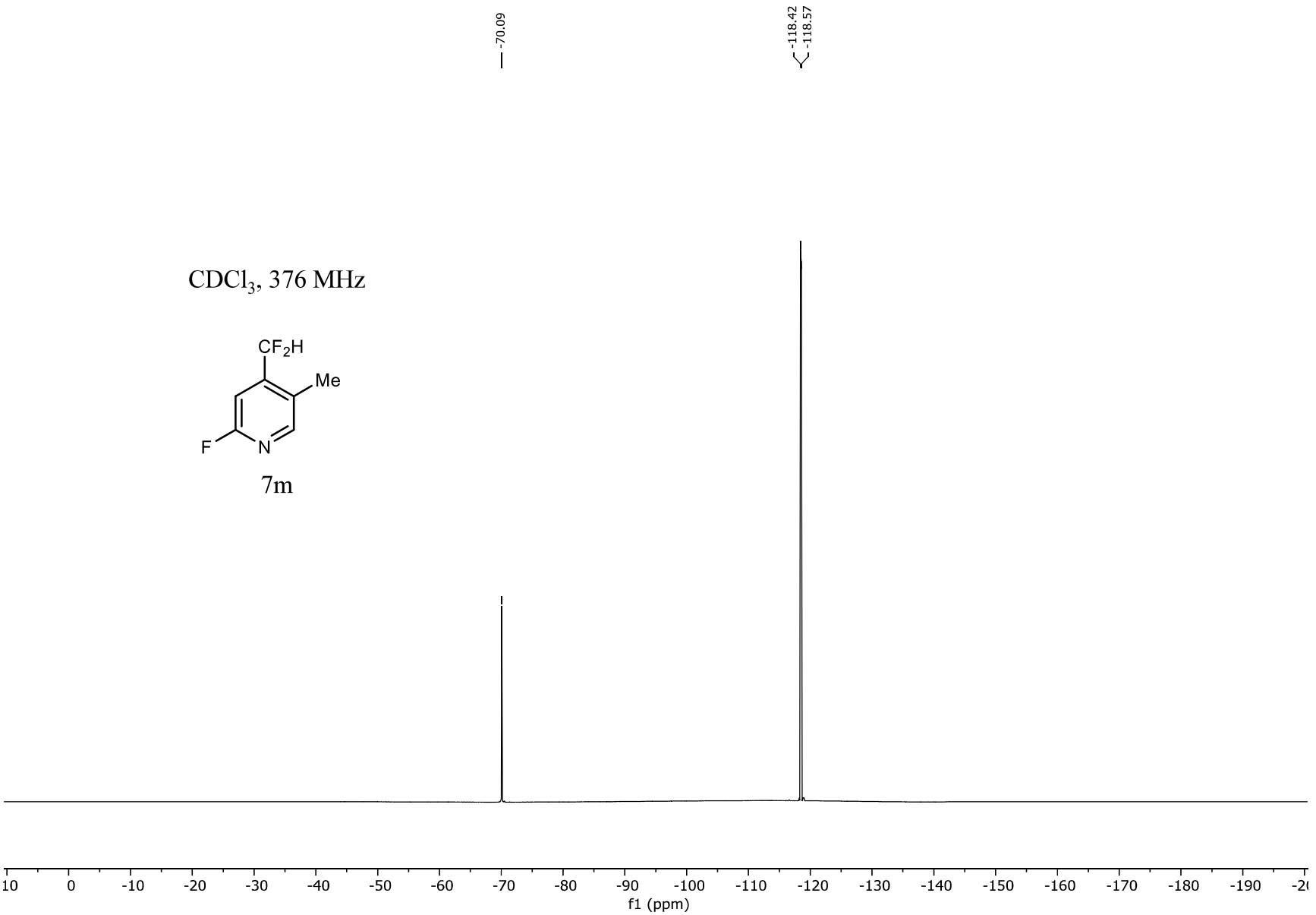

-111.50
-111.97
-112.11
-112.99
-113.14
-114.23
CDCl3, 376 MHz
CF2H
S
N
Me
7l
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

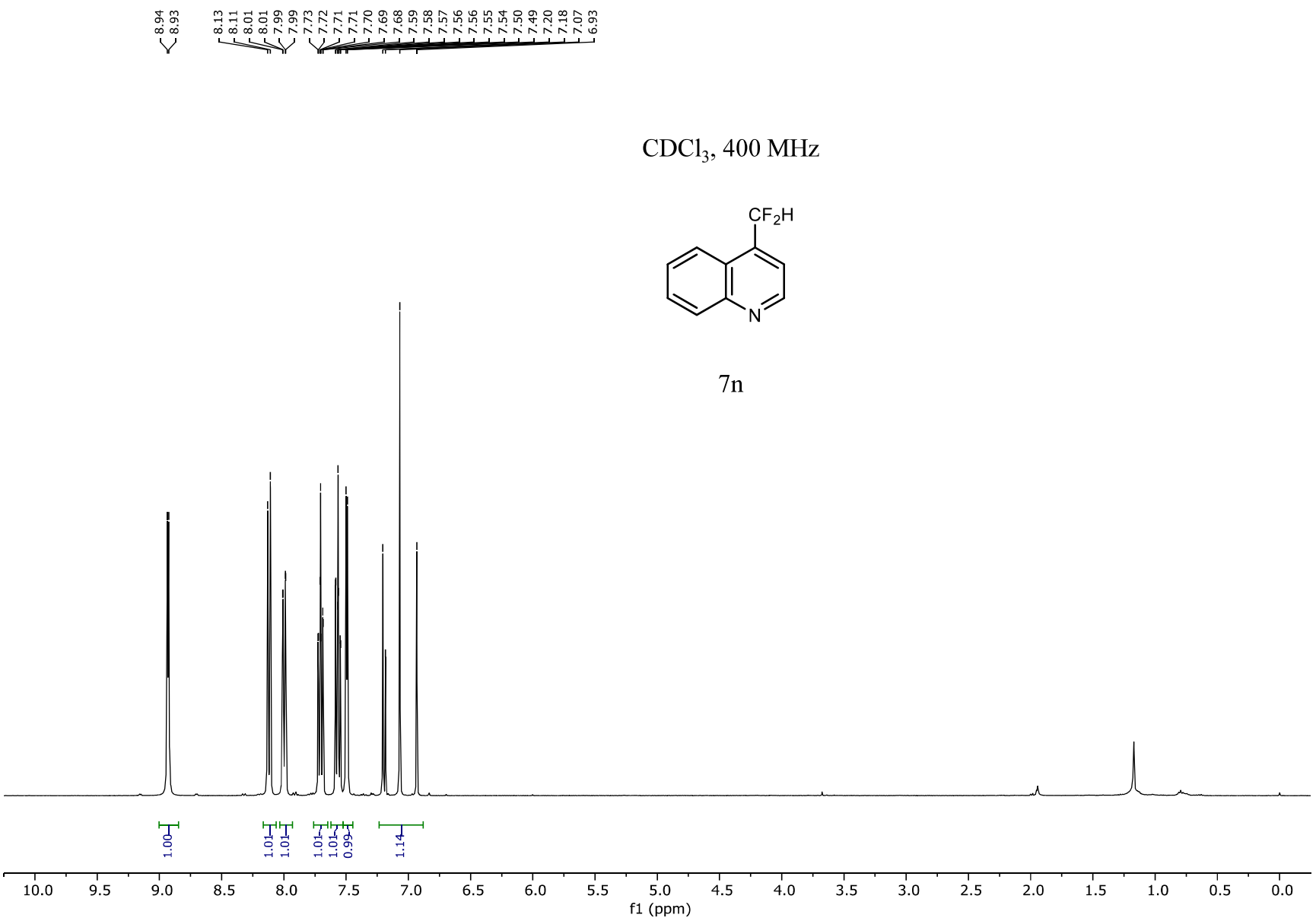

8.09
7.26
7.05
7.05
6.83
6.69
6.56
2.36
CDCl3, 400 MHz
CF2H
Me
F
N
7m
1.00
1.01
1.06
3.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



$CDCl_3$, 100 MHz

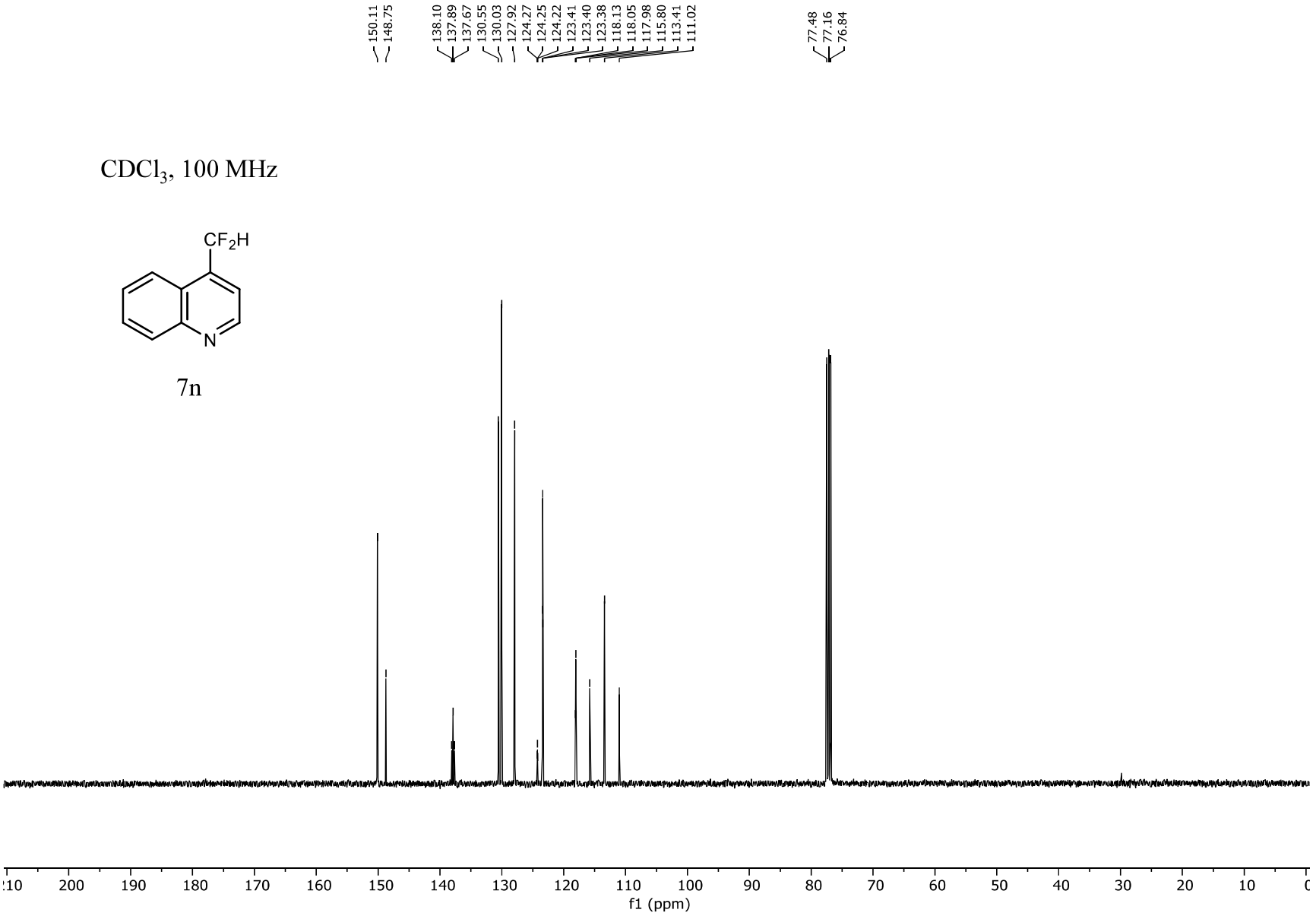
7m


-70.09
-118.42
-118.57
CDCl3, 376 MHz
CF2H
Me
F
N
7m
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

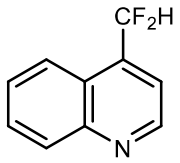


$CDCl_3$, 400 MHz

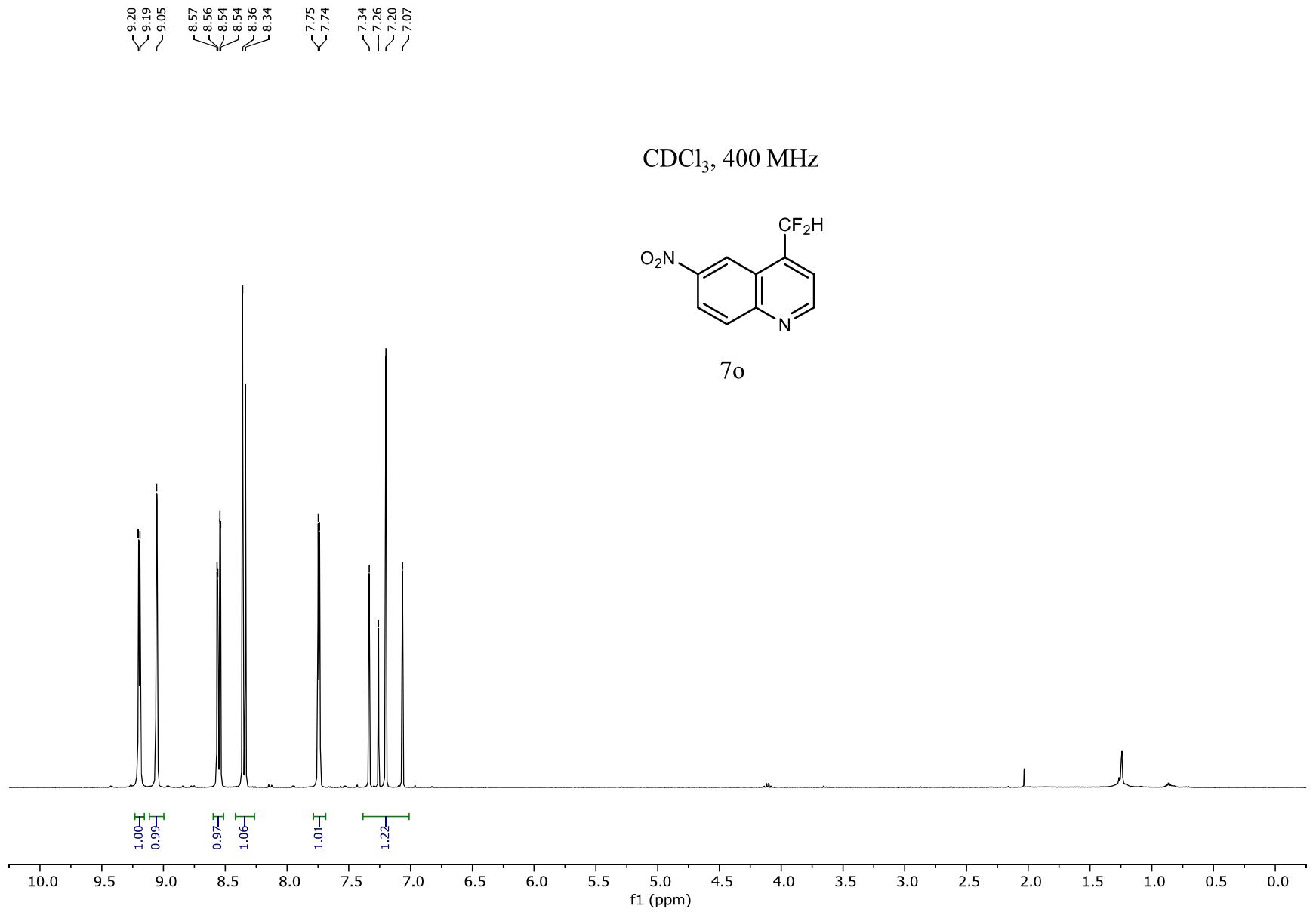
7n


150.11
148.75
138.10
137.89
137.67
130.55
130.03
127.92
124.27
124.25
124.22
123.41
123.40
123.38
118.13
118.05
117.98
115.80
113.41
111.02
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
N
7n
f1 (ppm)

$CDCl_3$, 376 MHz



7n

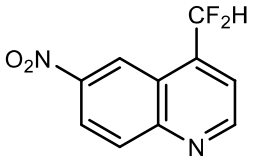


$CDCl_3$, 400 MHz

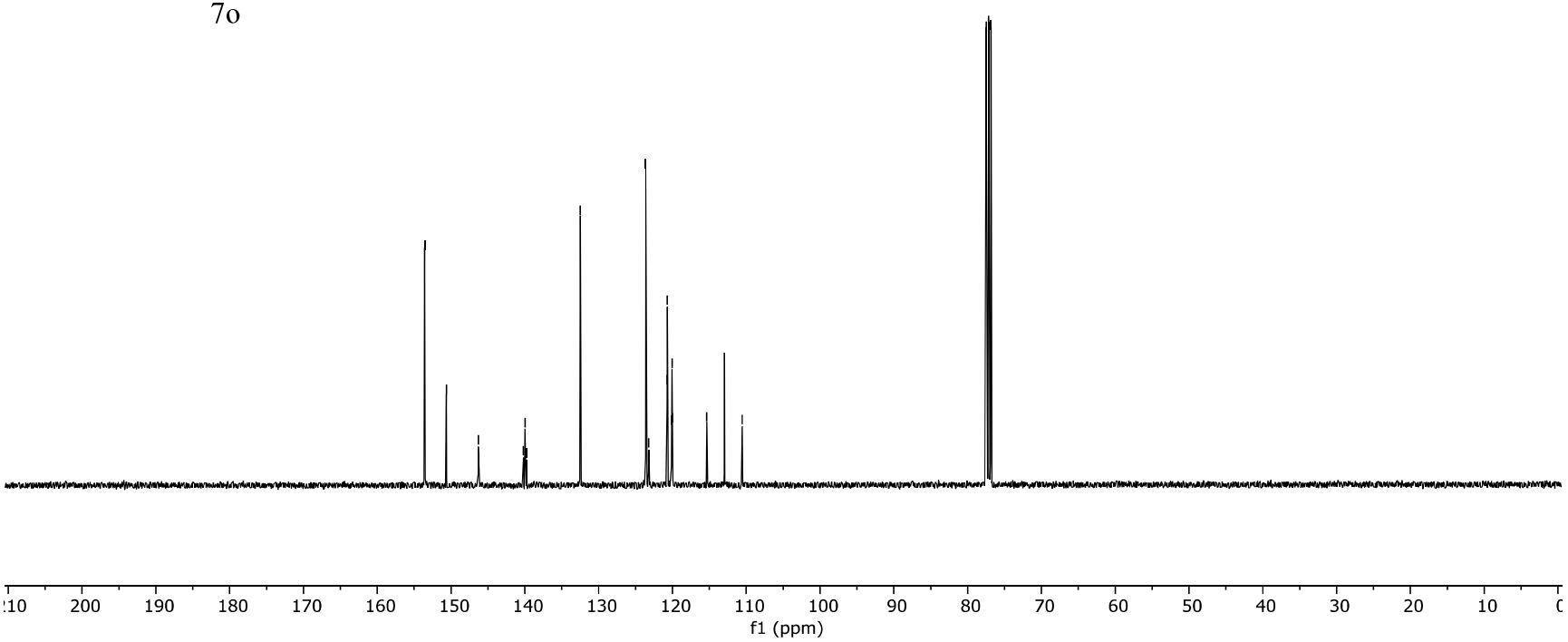
7o

153.58
150.63
146.30
140.20
139.97
139.75
132.49
123.61
123.24
123.21
123.19
120.72
120.71
120.69
120.13
120.06
119.98
115.35
112.95
110.55
77.48
77.16
76.84

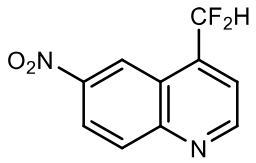
$CDCl_3$, 100 MHz



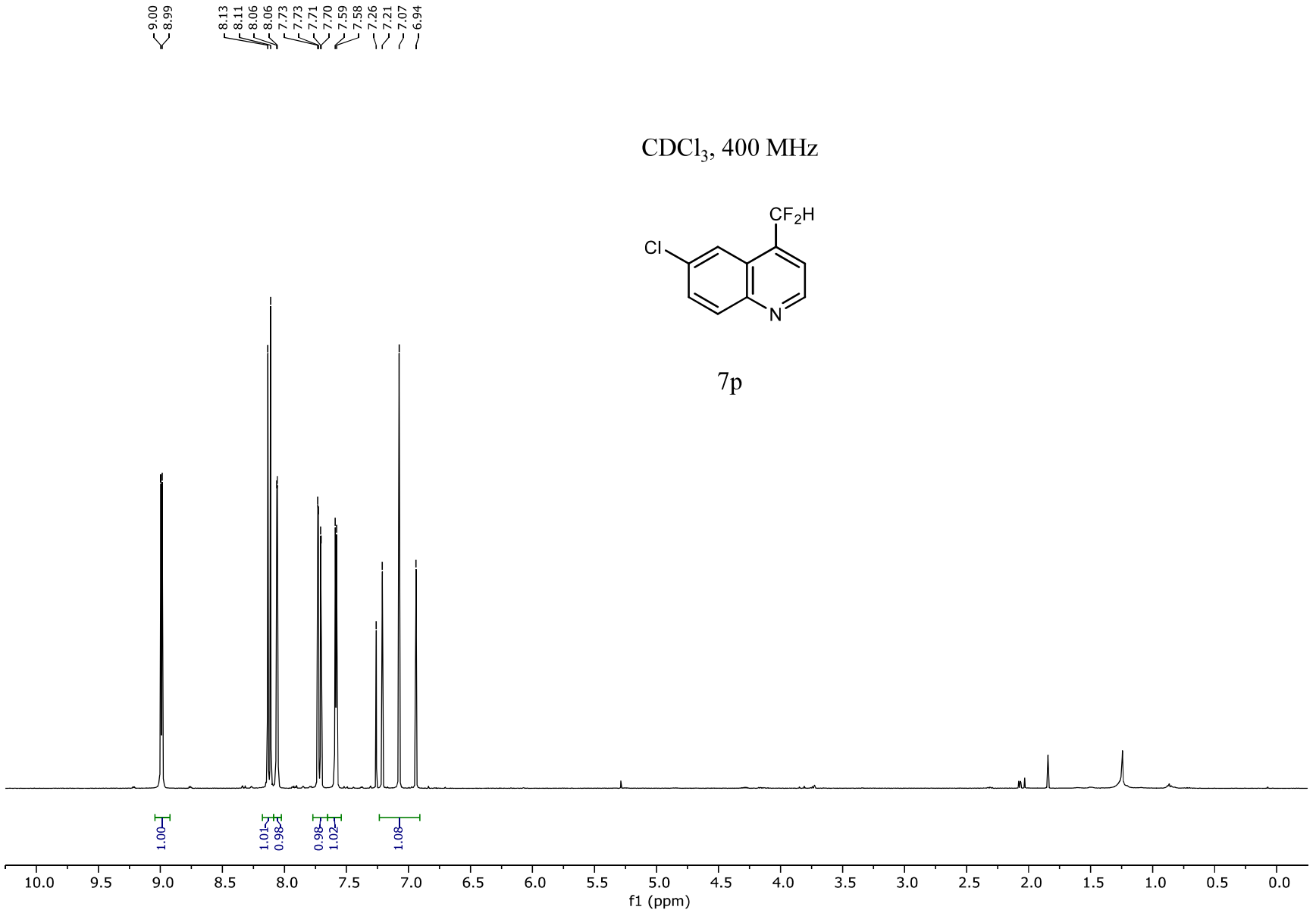
7o



$CDCl_3$, 376 MHz

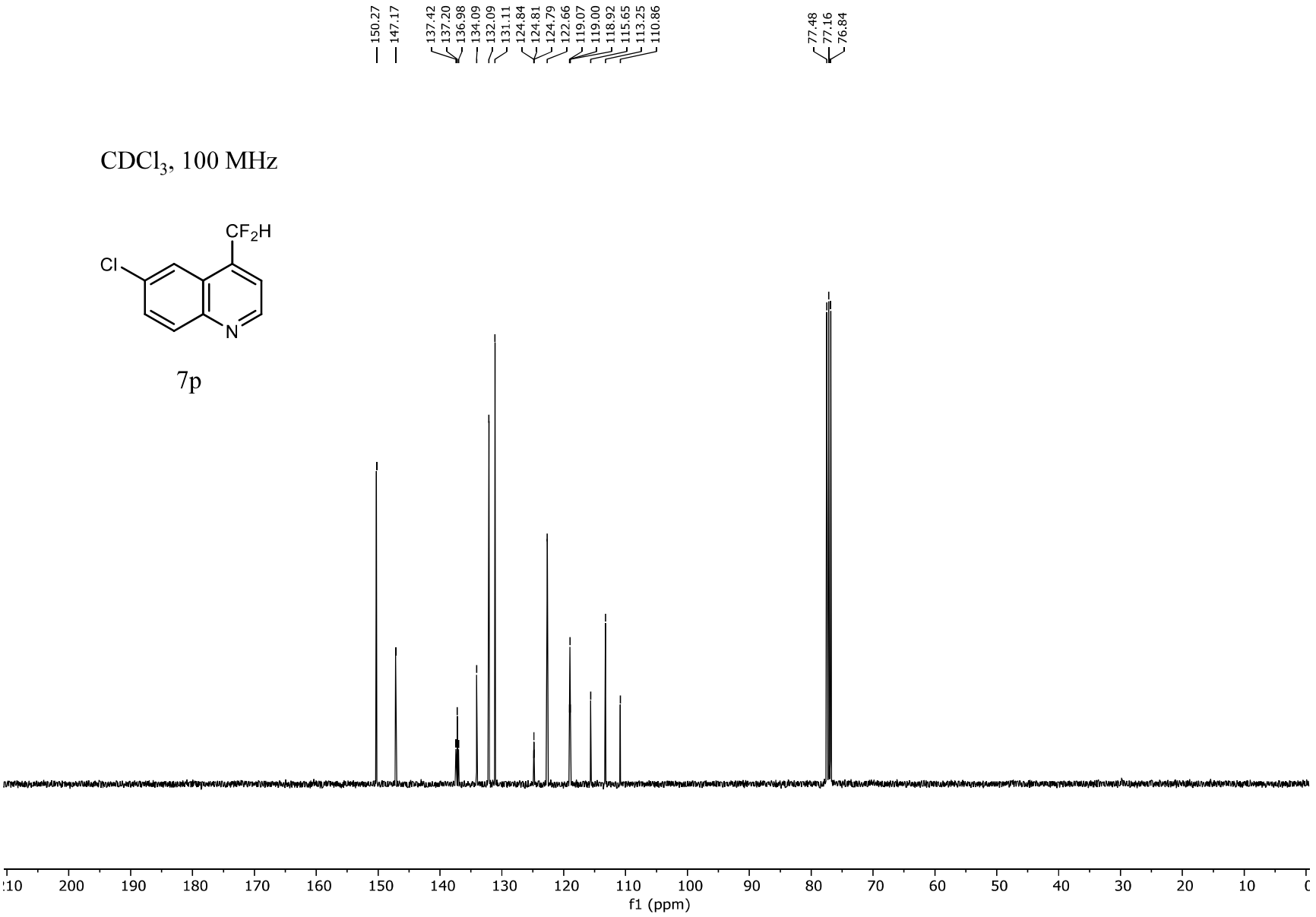


7o

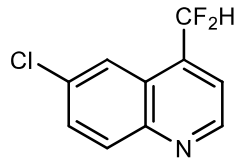


$CDCl_3$, 400 MHz

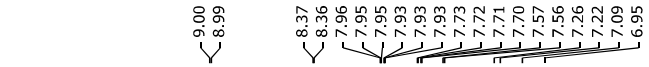
7p


150.27
147.17
137.42
137.20
136.98
134.09
132.09
131.11
124.84
124.81
124.79
122.66
119.07
119.00
118.92
115.65
113.25
110.86
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
Cl
N
7p
f1 (ppm)

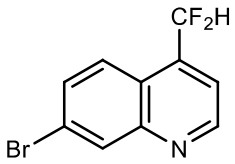
$CDCl_3$, 376 MHz



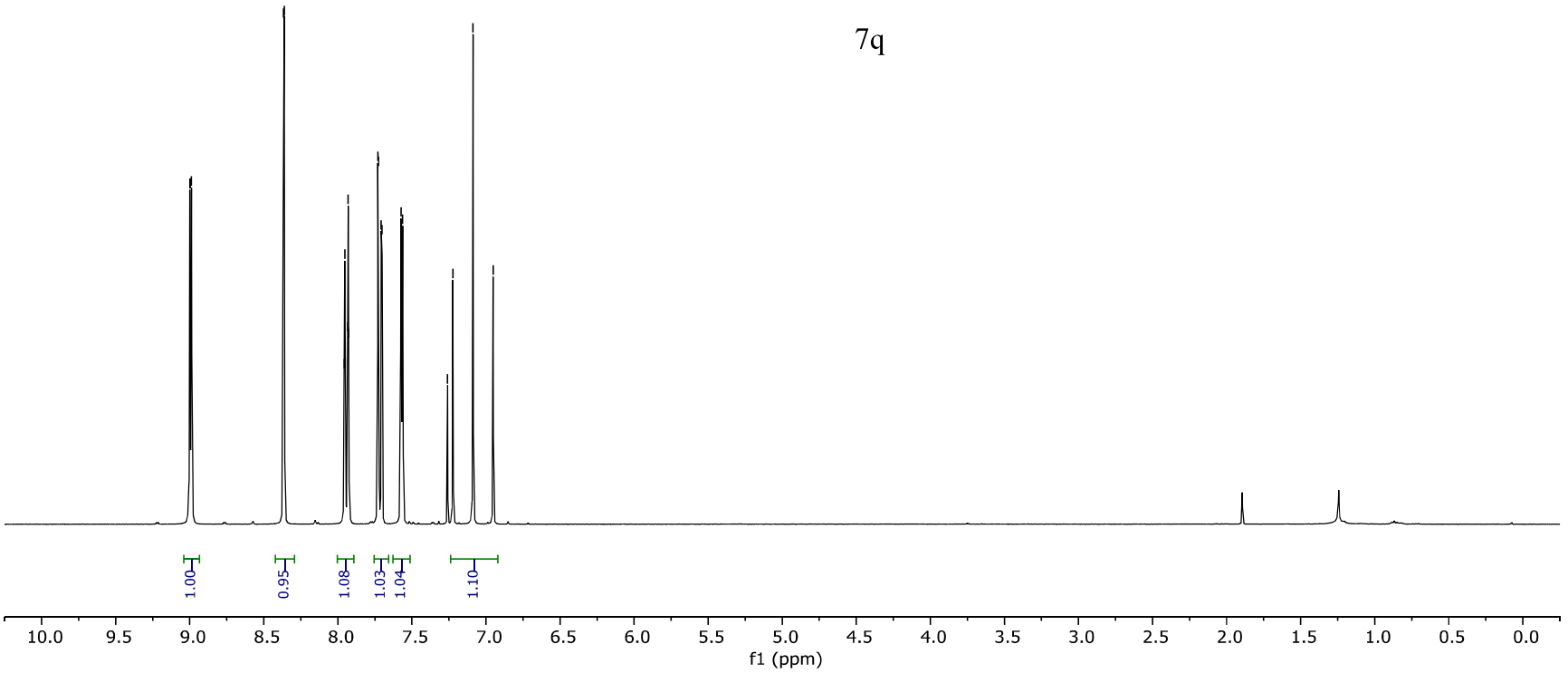
7p

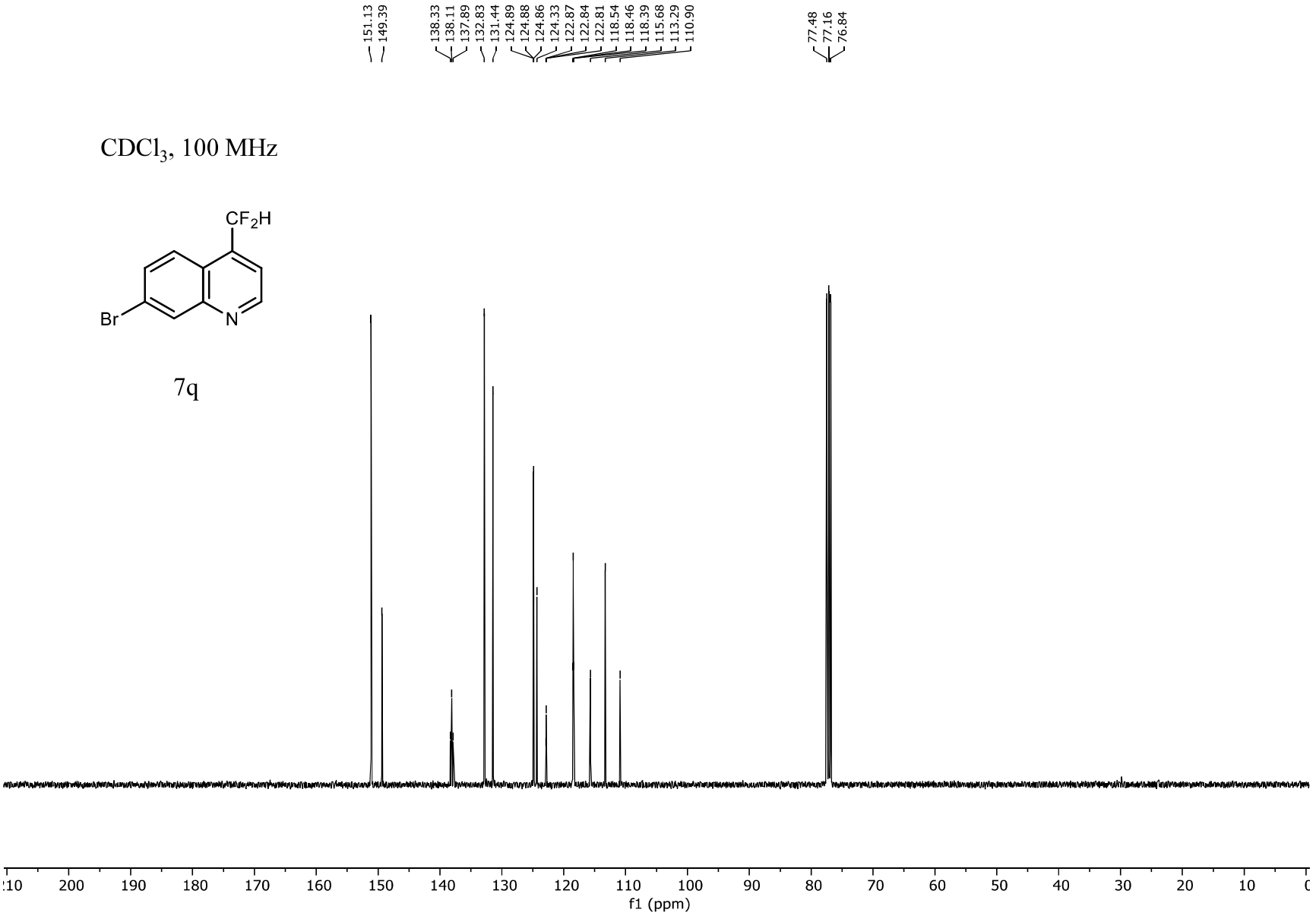


$CDCl_3$, 400 MHz



7q

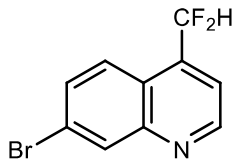




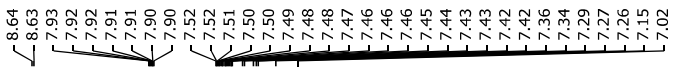
$CDCl_3$, 100 MHz

7q

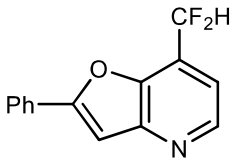
$CDCl_3$, 376 MHz



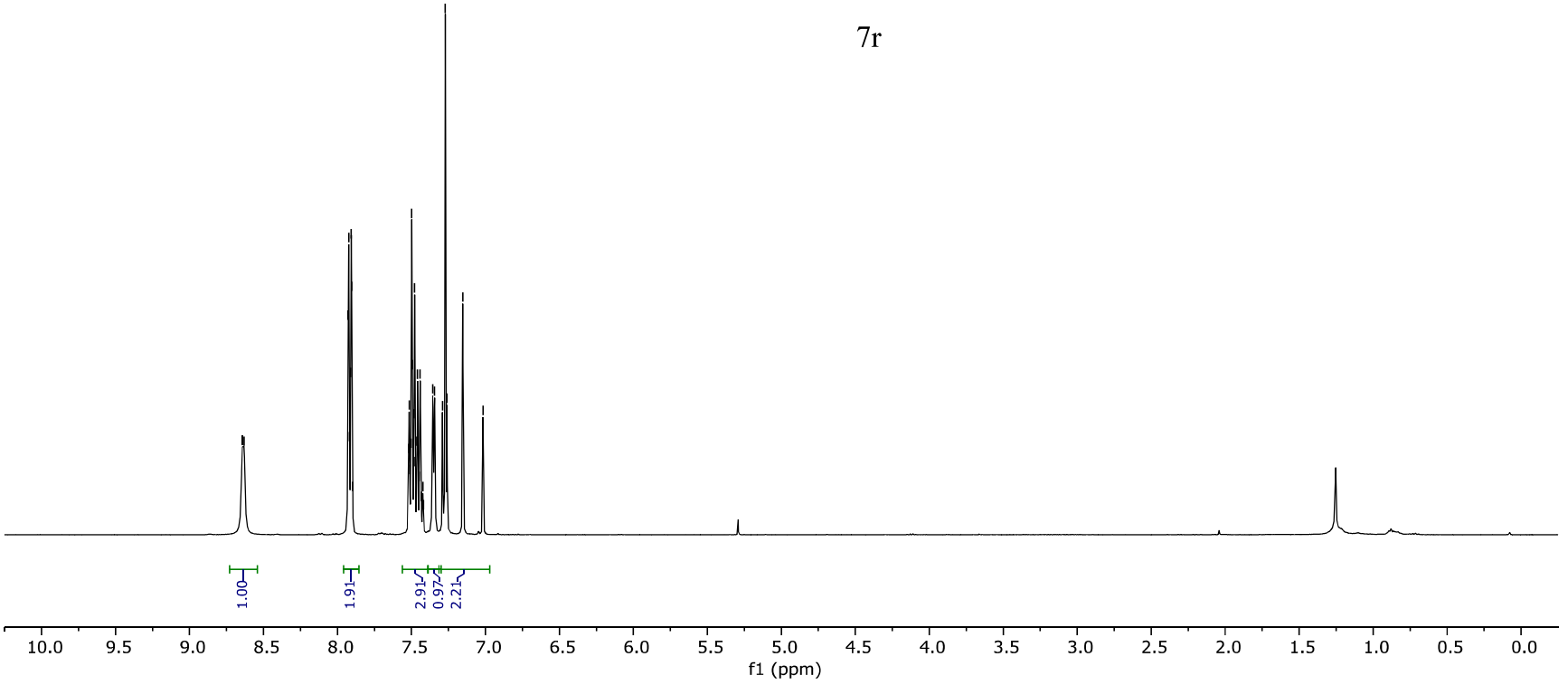
7q

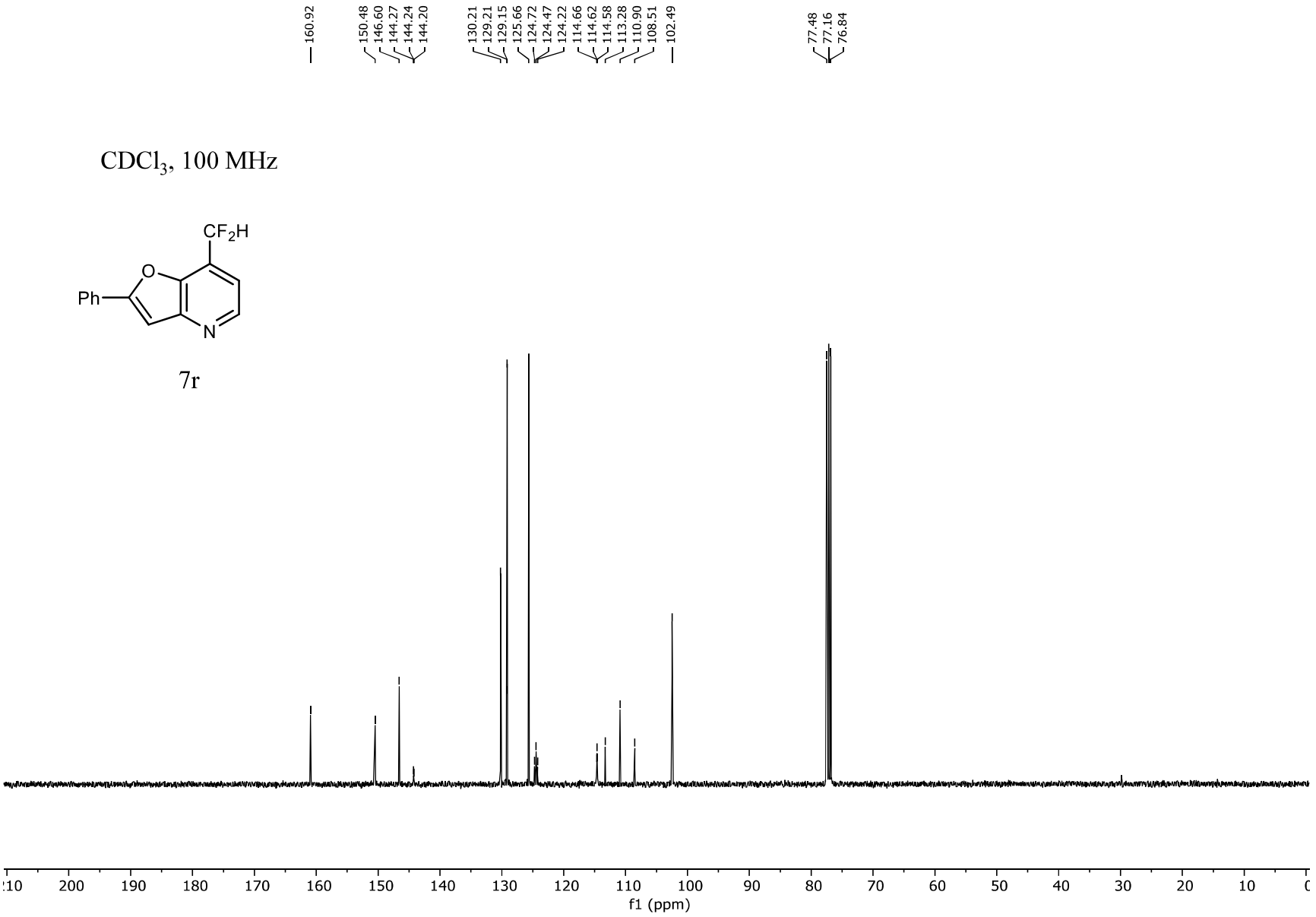


$CDCl_3$, 400 MHz

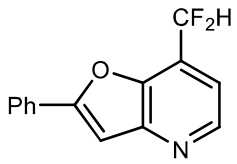


7r

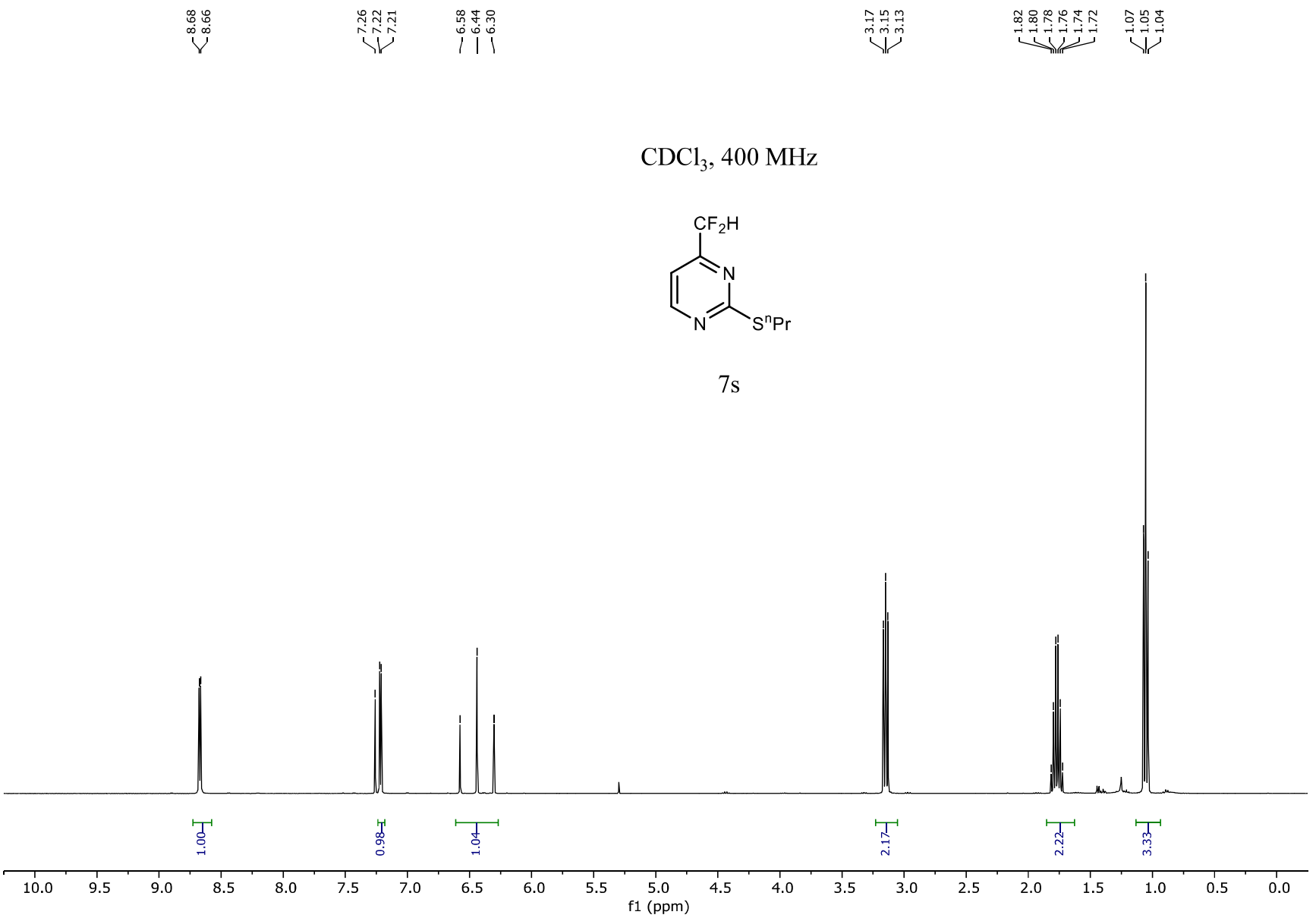



160.92
150.48
146.60
144.27
144.24
144.20
130.21
129.21
129.15
125.66
124.72
124.47
124.22
114.66
114.62
114.58
113.28
110.90
108.51
102.49
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
O
Ph
N
7r
f1 (ppm)

$CDCl_3$, 376 MHz

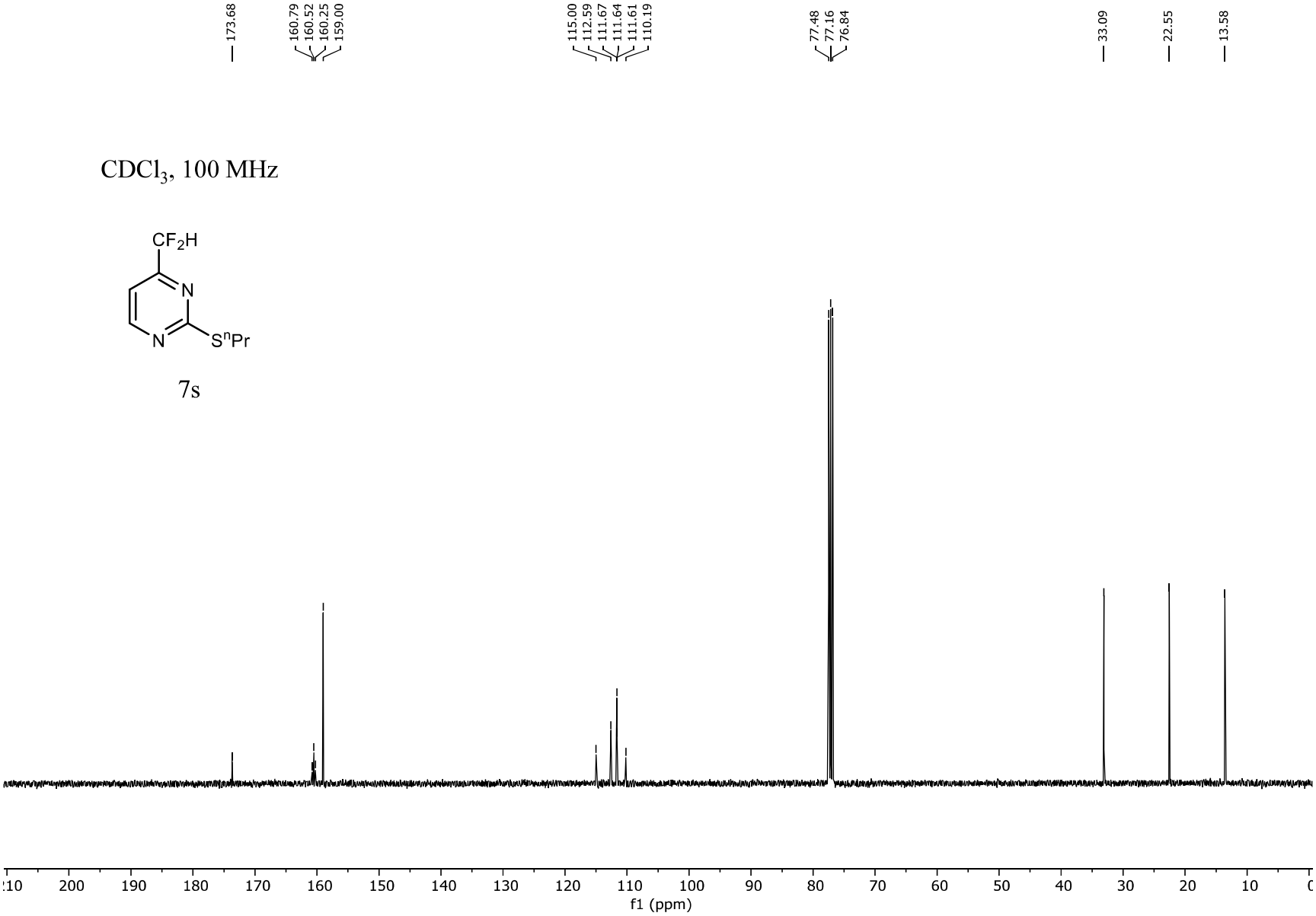


7r



$CDCl_3$, 400 MHz

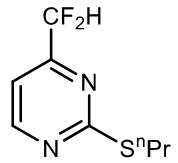
7s



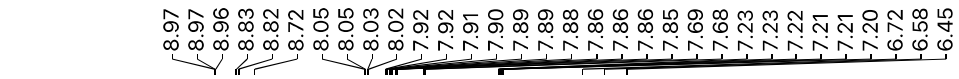
$CDCl_3$, 100 MHz

7s

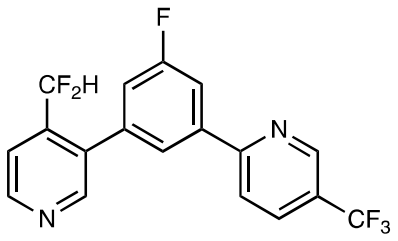
$CDCl_3$, 376 MHz



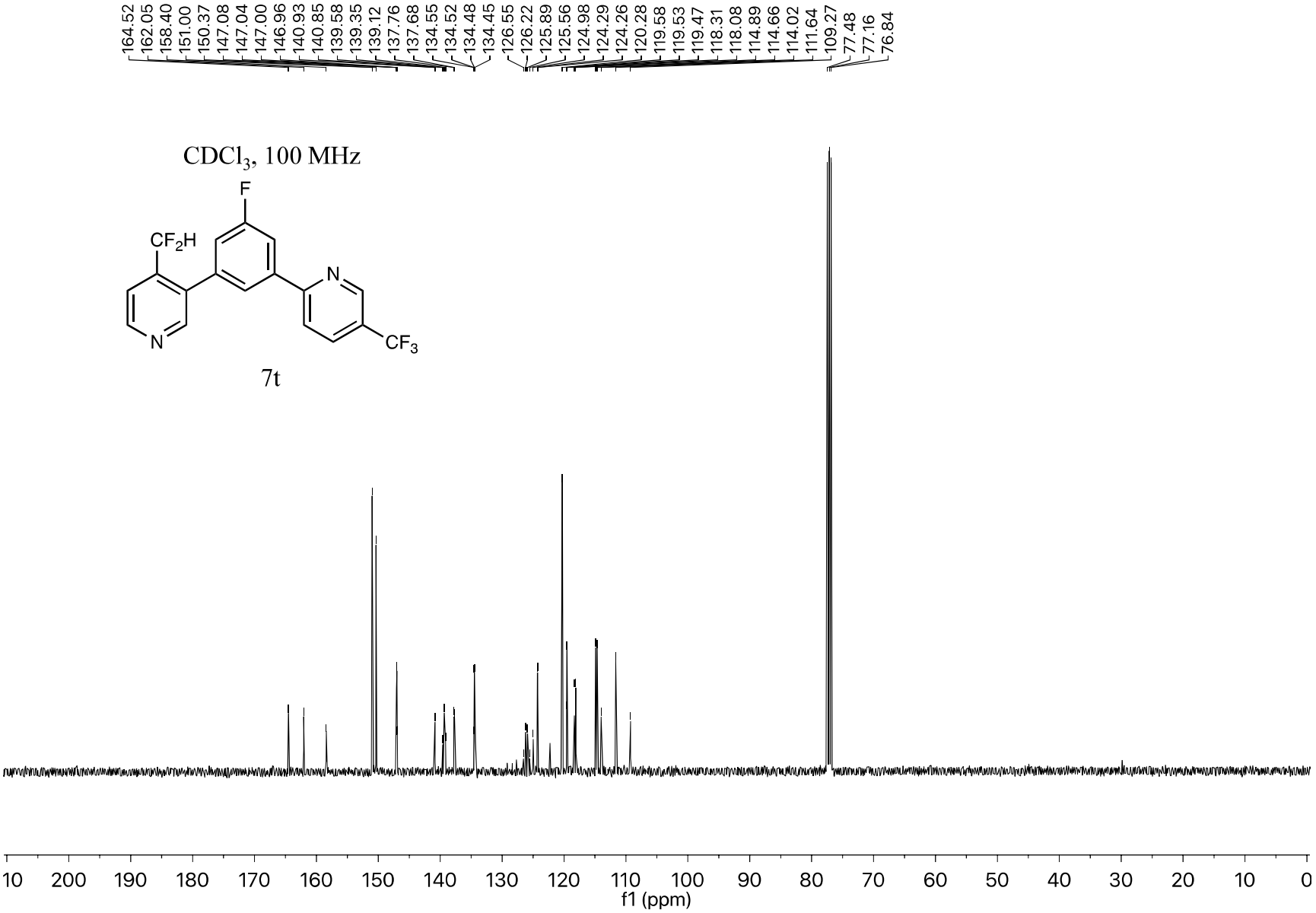
7s

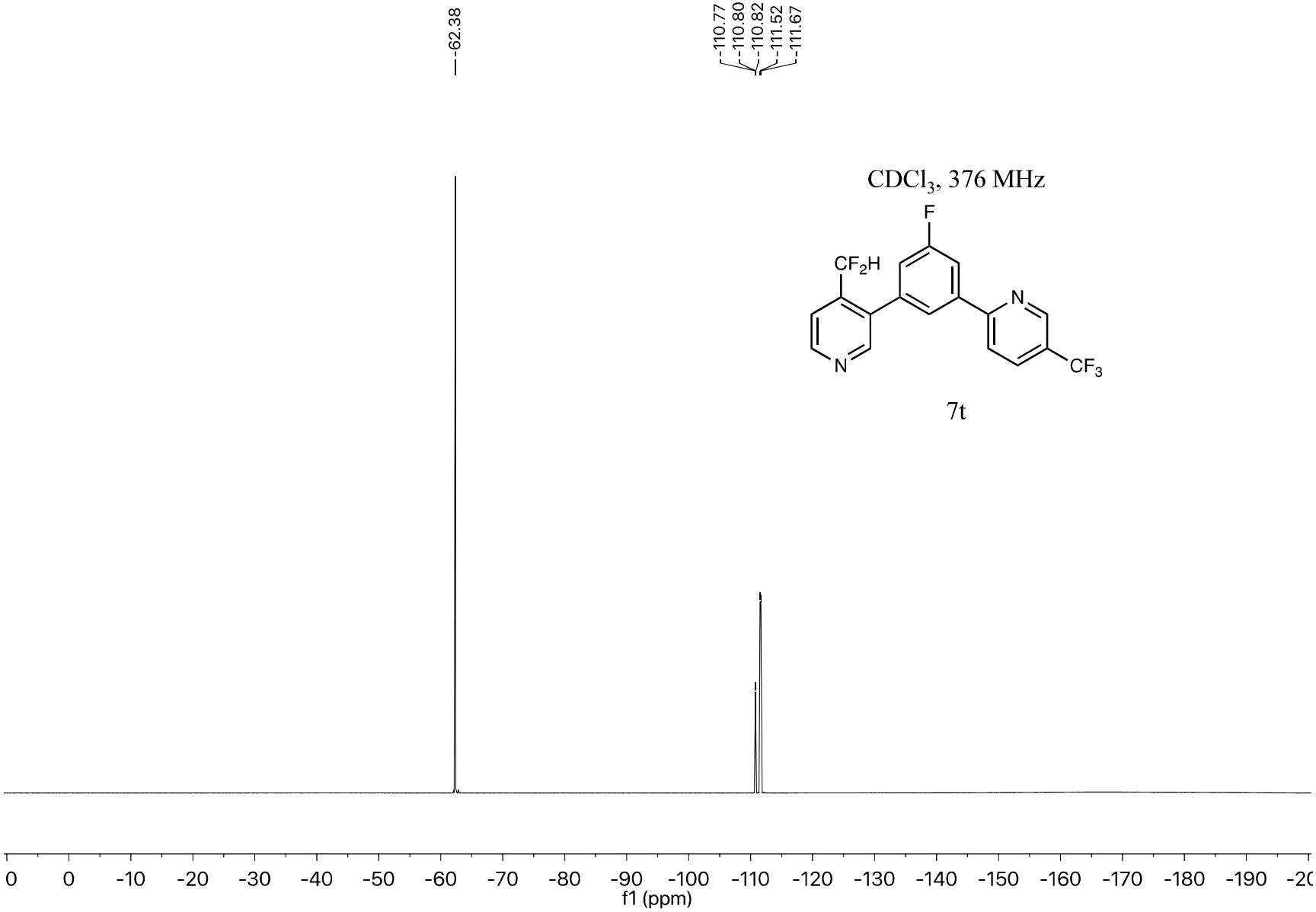


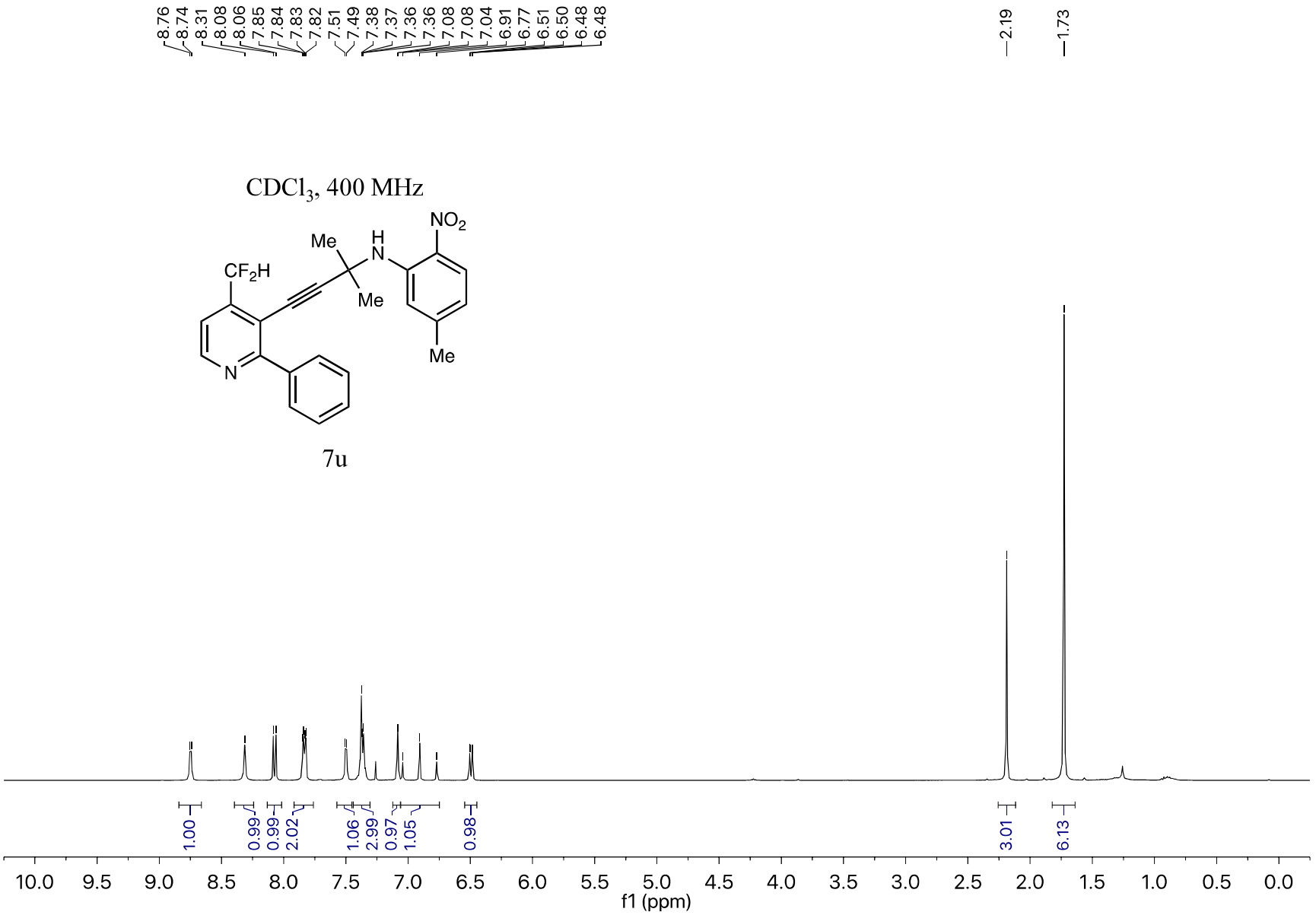
$CDCl_3$, 400 MHz



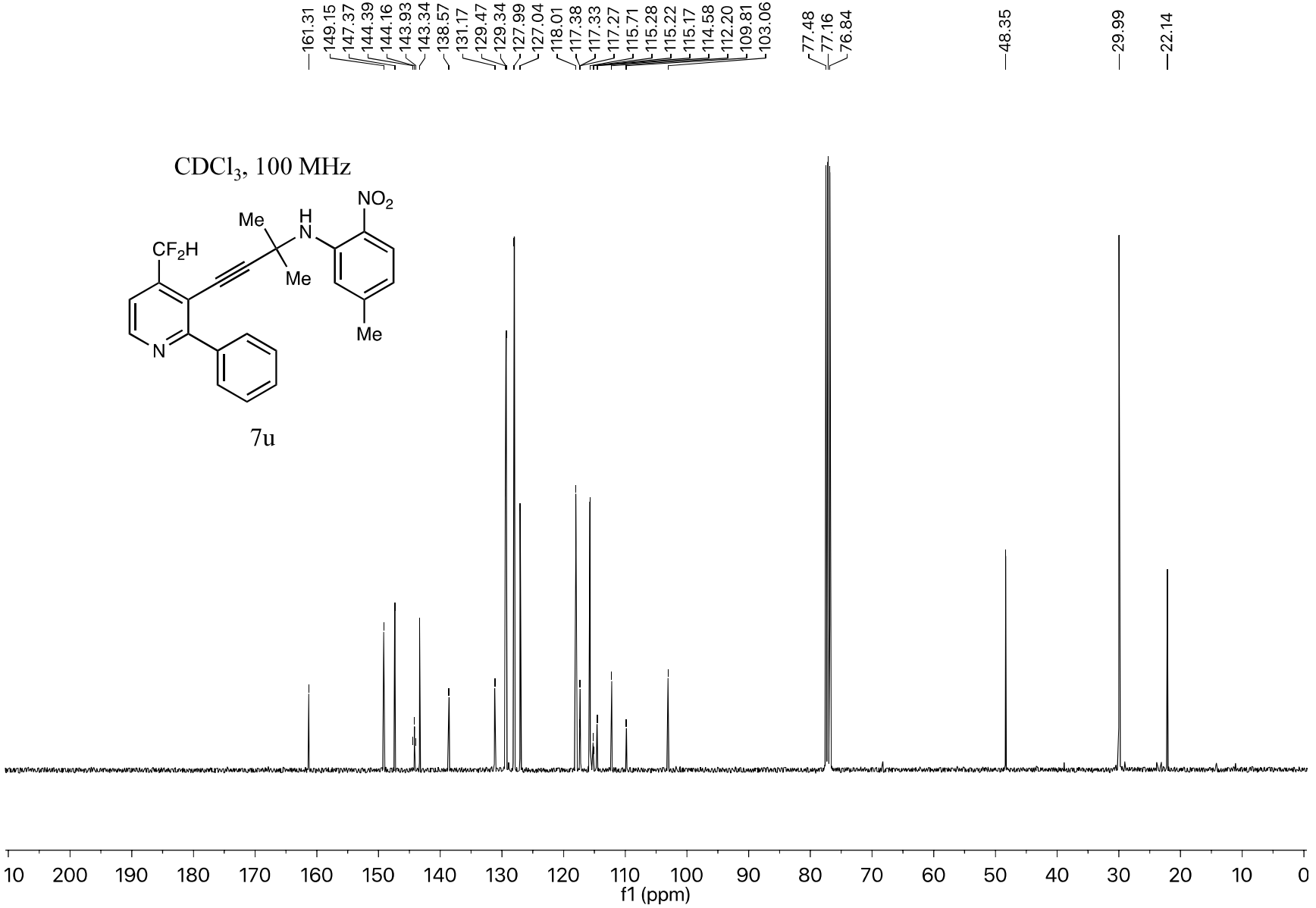
7t


164.52
162.05
158.40
151.00
150.37
147.08
147.04
147.00
146.96
140.93
140.85
139.58
139.35
139.12
137.76
137.68
134.55
134.52
134.48
134.45
126.55
126.22
125.89
125.56
124.98
124.29
124.26
120.28
119.58
119.53
119.47
118.31
118.08
114.89
114.66
114.02
111.64
109.27
77.48
77.16
76.84
CDCl3, 100 MHz
F
CF2H
N
N
CF3
7t
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

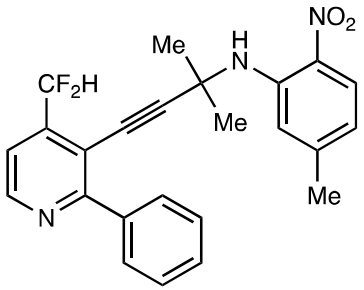

-62.38
-110.77
-110.80
-110.82
-111.52
-111.67
CDCl3, 376 MHz
F
CF2H
N
N
CF3
7t
0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


8.76
8.74
8.31
8.08
8.06
7.85
7.84
7.83
7.82
7.51
7.49
7.38
7.37
7.36
7.36
7.08
7.08
7.04
6.91
6.77
6.51
6.50
6.48
6.48
2.19
1.73
CDCl3, 400 MHz
NO2
H
N
Me
Me
CF2H
N
Me
1.00
0.99
0.99
2.02
1.06
2.99
0.97
1.05
0.98
3.01
6.13
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)

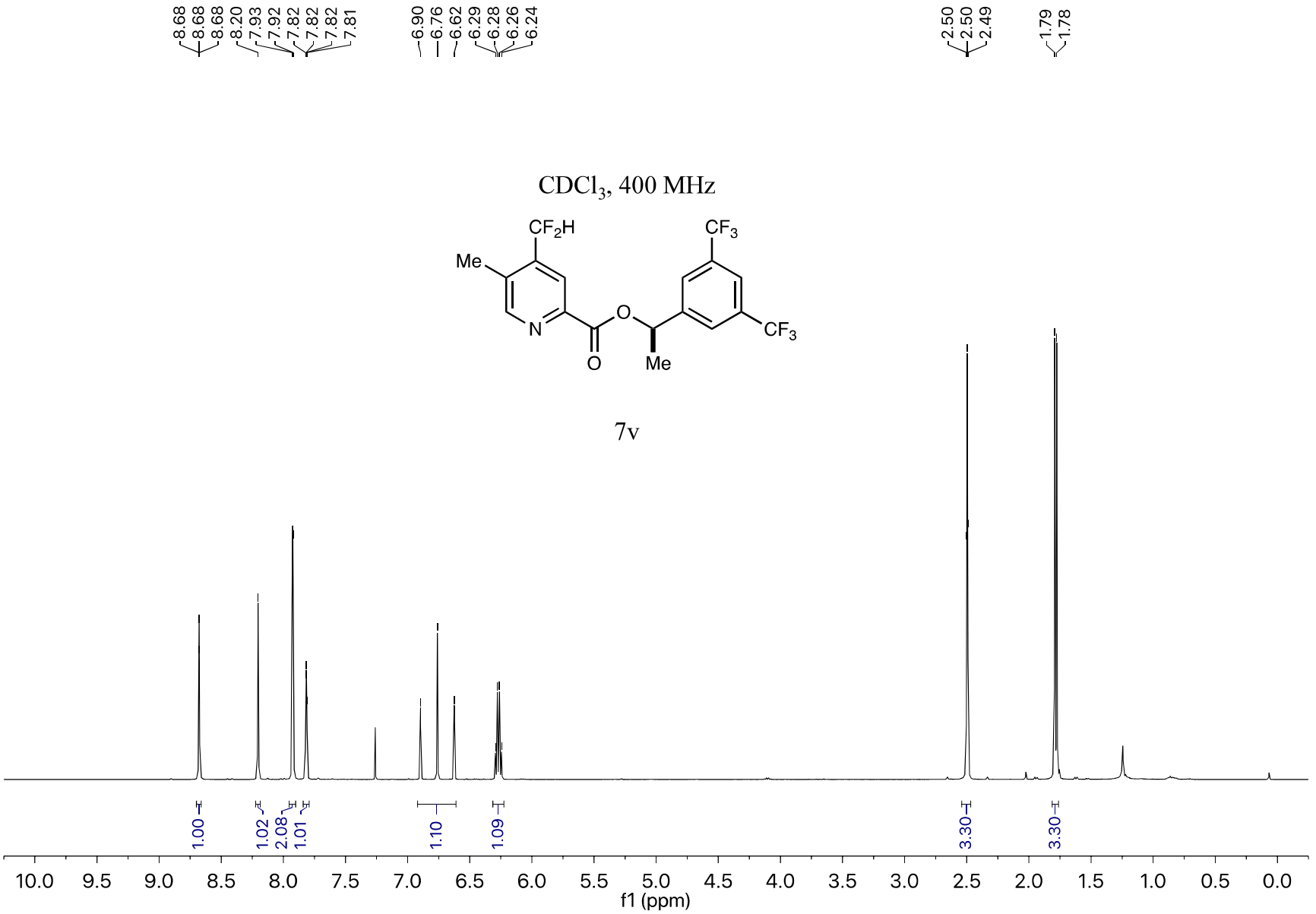
7u

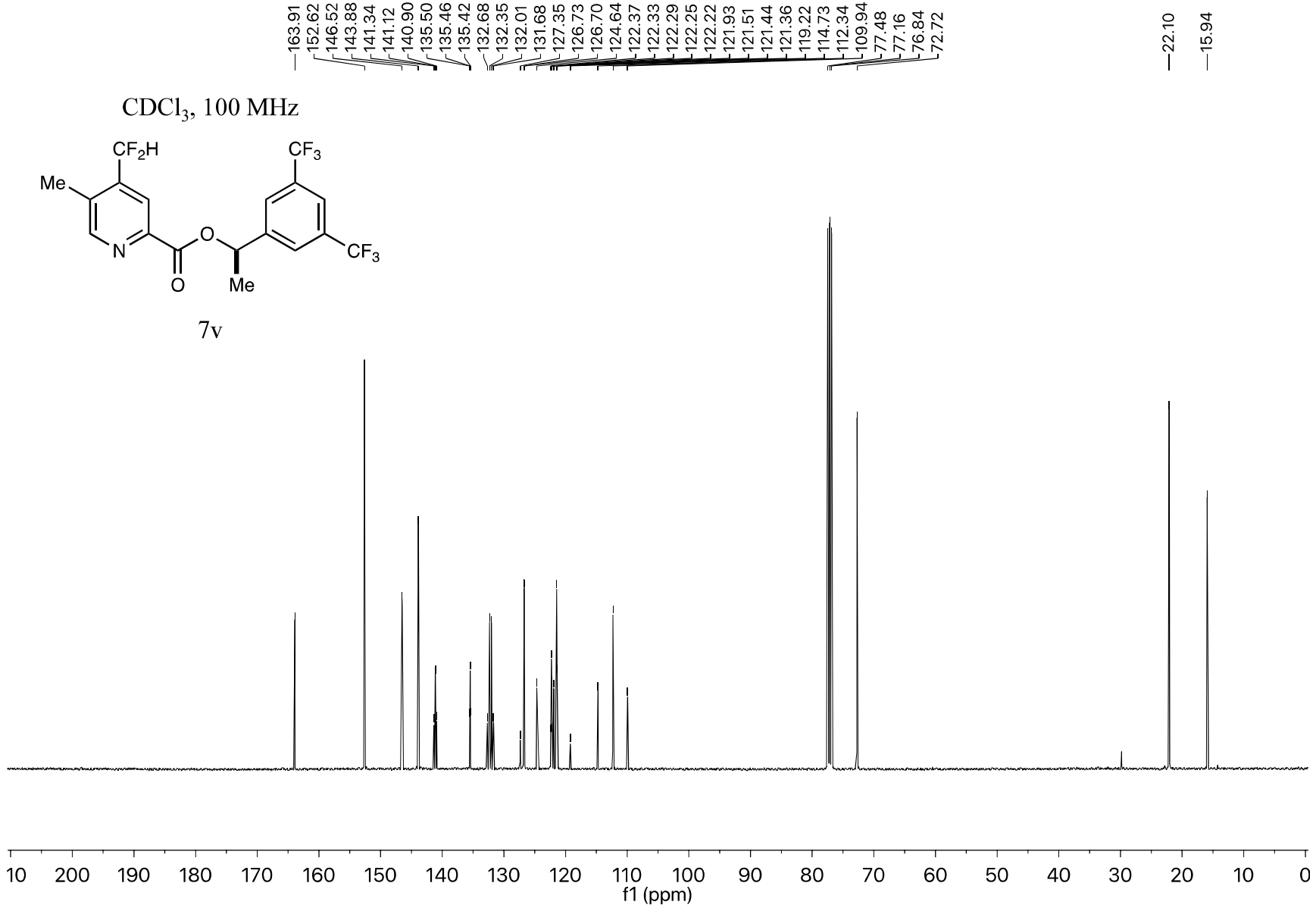

161.31
149.15
147.37
144.39
144.16
143.93
143.34
138.57
131.17
129.47
129.34
127.99
127.04
118.01
117.38
117.33
117.27
115.71
115.28
115.22
115.17
114.58
112.20
109.81
103.06
77.48
77.16
76.84
48.35
29.99
22.14
CDCl3, 100 MHz
NO2
Me
H
N
CF2H
Me
Me
N
7u
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

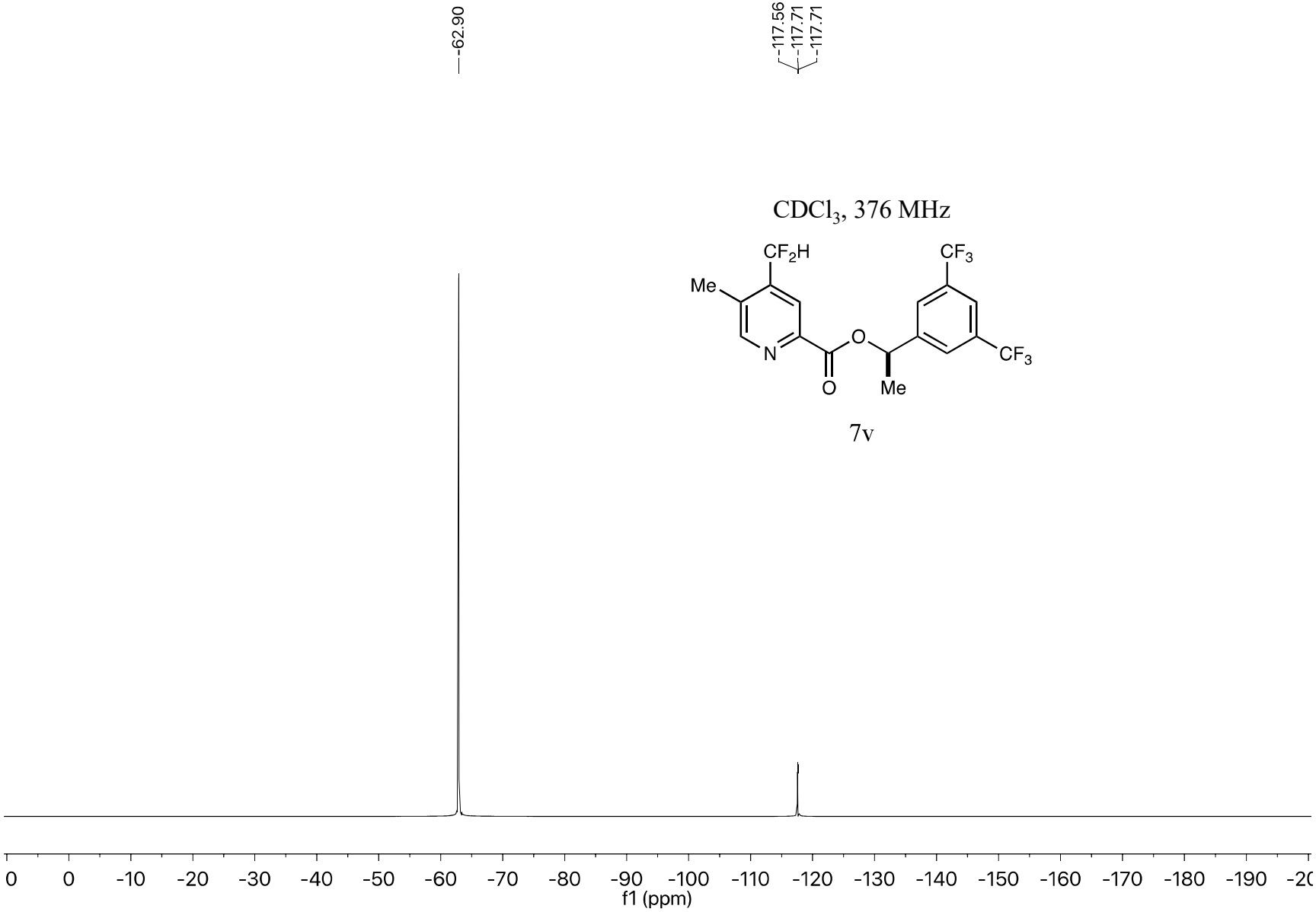
$CDCl_3$, 376 MHz



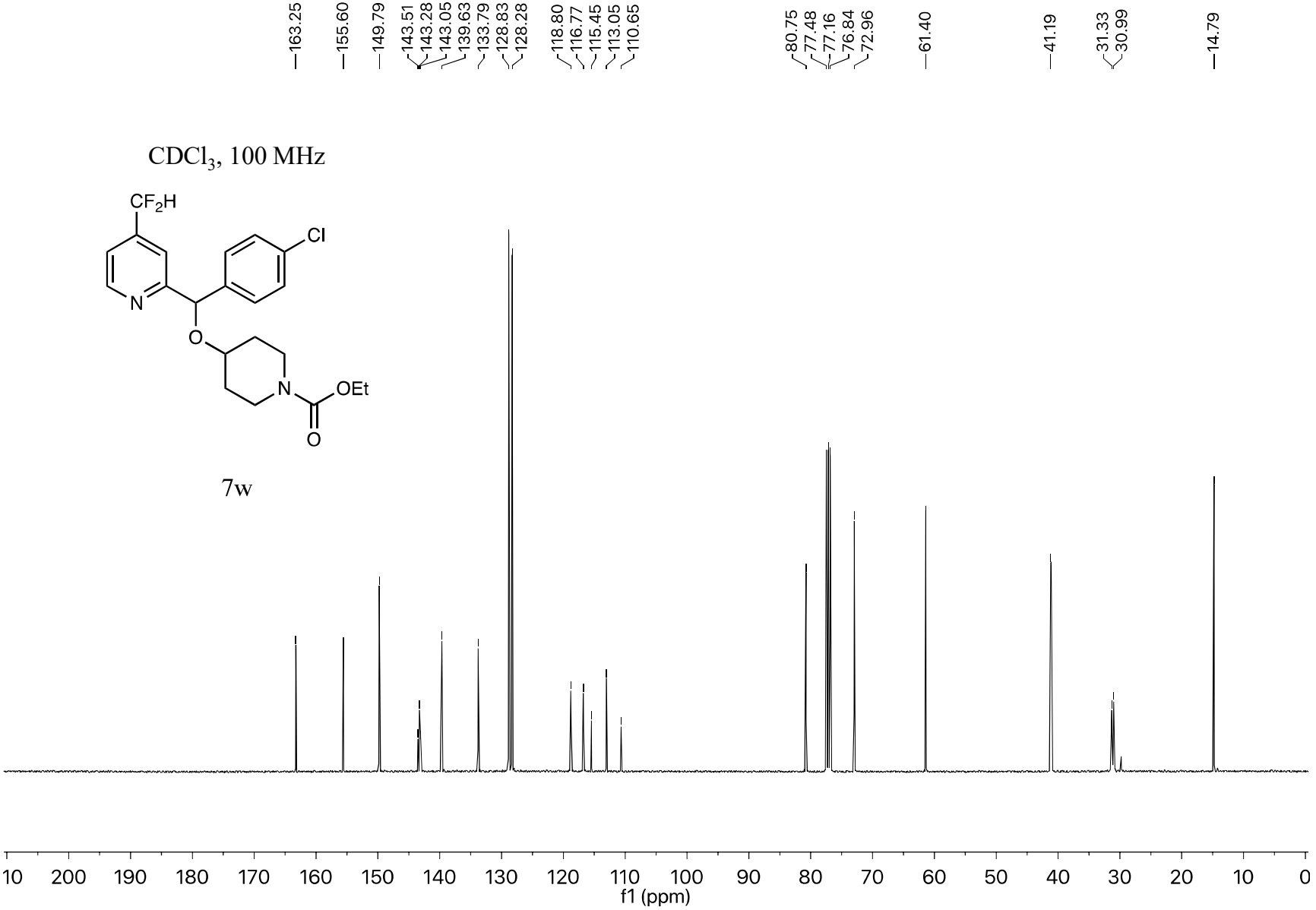
7u

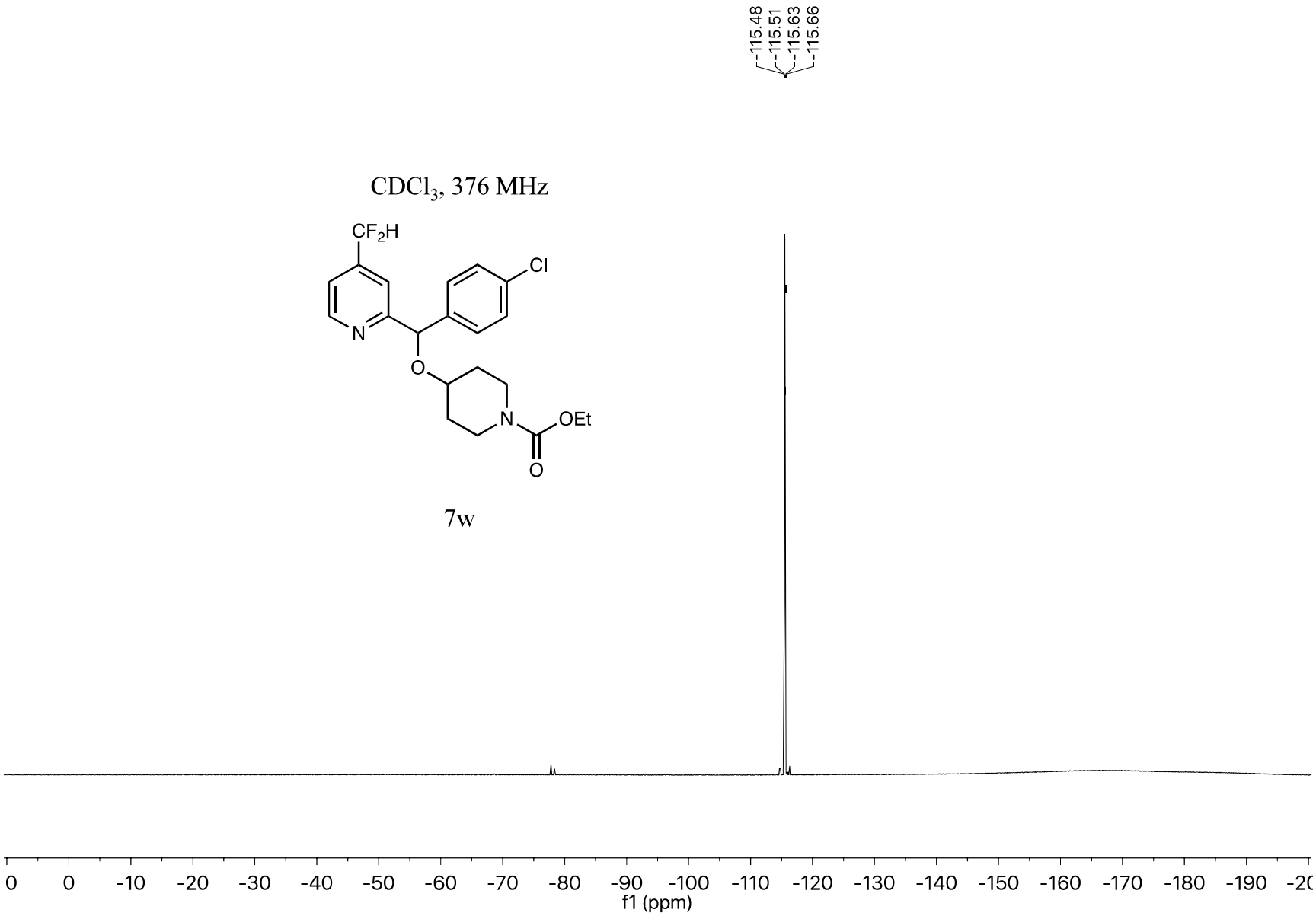

8.68
8.68
8.68
8.20
7.93
7.92
7.82
7.82
7.82
7.81
6.90
6.76
6.62
6.29
6.28
6.26
6.24
2.50
2.50
2.49
1.79
1.78
CDCl3, 400 MHz
CF2H
CF3
Me
N
O
O
Me
CF3
7v
1.00
1.02
2.08
1.01
1.10
1.09
3.30
3.30
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

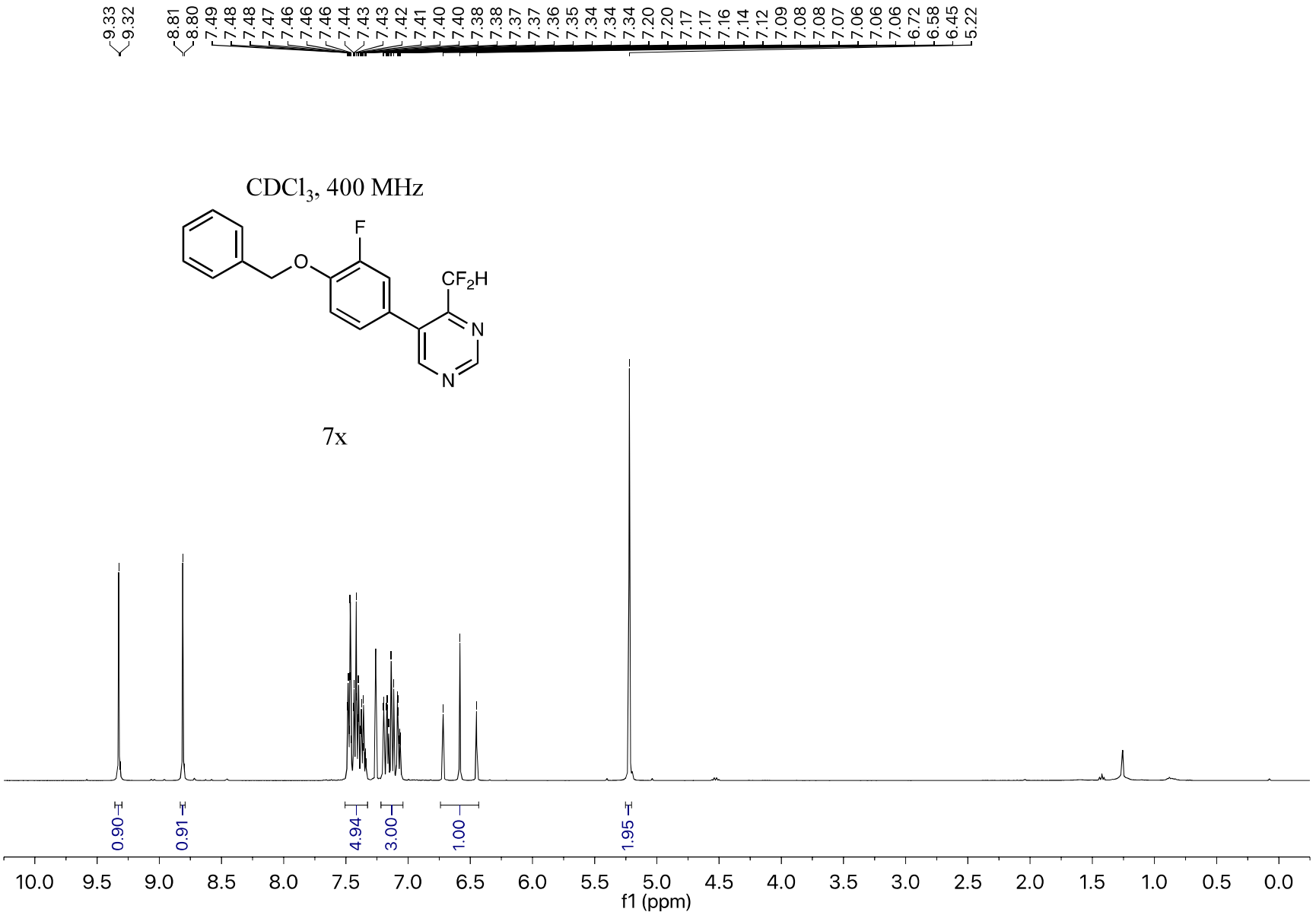

163.91
152.62
146.52
143.88
141.34
141.12
140.90
135.50
135.46
135.42
132.68
132.35
132.01
131.68
127.35
126.73
126.70
124.64
122.37
122.33
122.29
122.25
122.22
121.93
121.51
121.44
121.36
119.22
114.73
112.34
109.94
77.48
77.16
76.84
72.72
22.10
15.94
CDCl3, 100 MHz
CF2H
CF3
Me
N
O
O
Me
CF3
7v
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

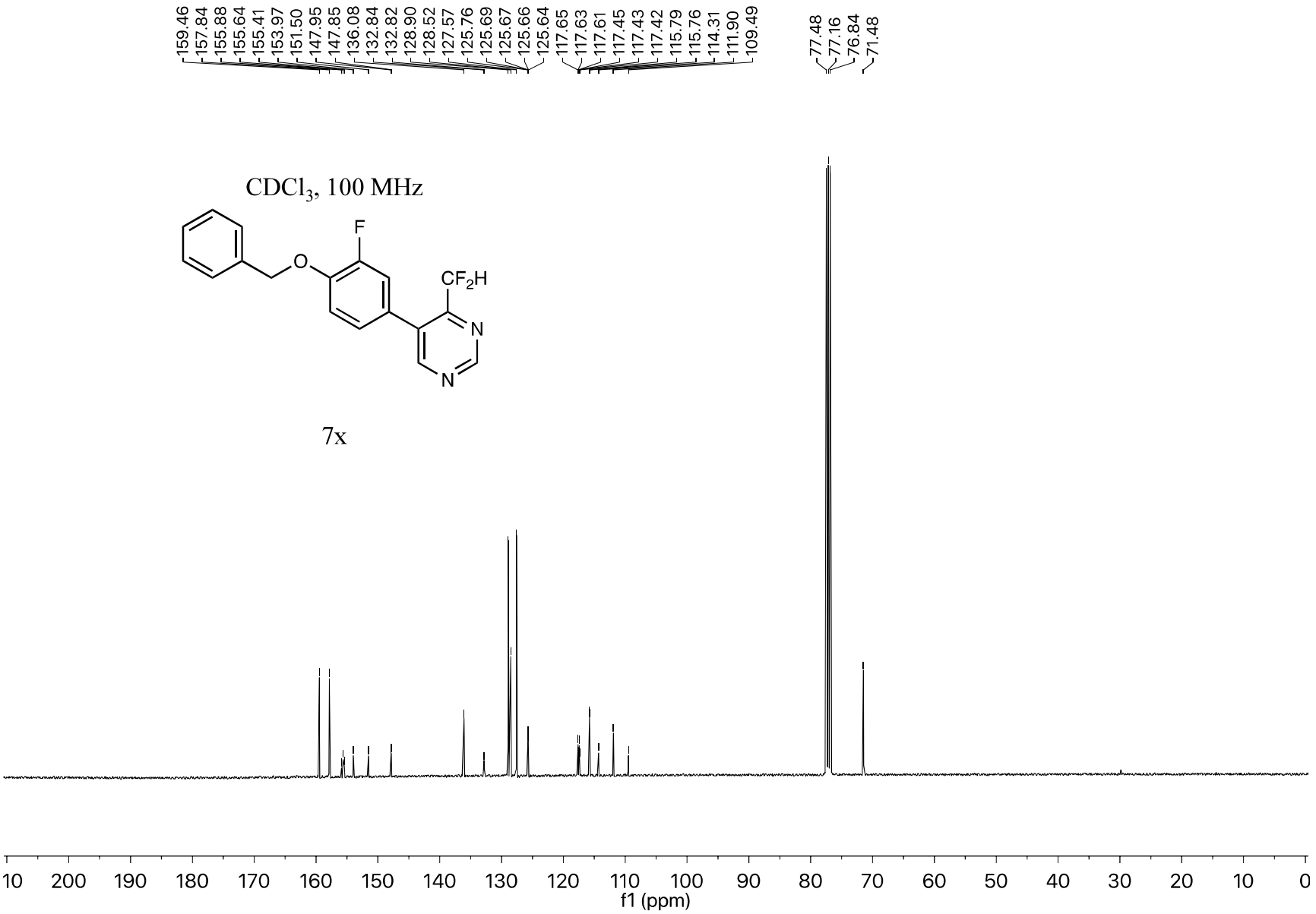

-62.90
-117.56
-117.71
-117.71
CDCl3, 376 MHz
CF2H
CF3
Me
N
O
O
Me
CF3
7v
0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

CDCl3, 400 MHz
7w
f1 (ppm)

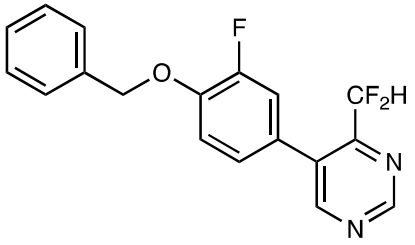

163.25
155.60
149.79
143.51
143.28
143.05
139.63
133.79
128.83
128.28
118.80
116.77
115.45
113.05
110.65
80.75
77.48
77.16
76.84
72.96
61.40
41.19
31.33
30.99
14.79
CDCl3, 100 MHz
CF2H
Cl
N
O
N
OEt
O
7w
f1 (ppm)


-115.48
-115.51
-115.63
-115.66
CDCl3, 376 MHz
CF2H
Cl
N
O
N
OEt
O
7w
0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

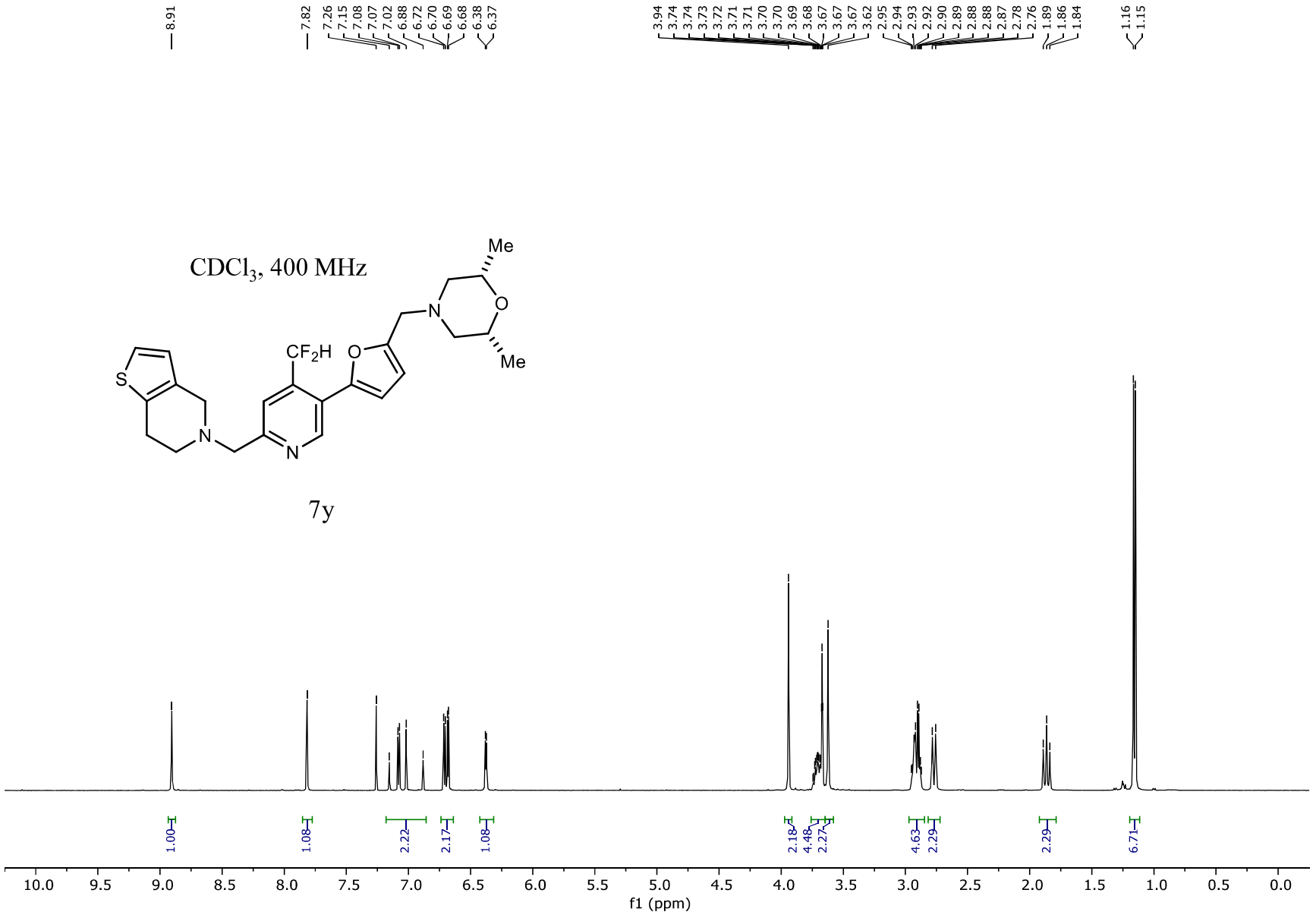

9.33
9.32
8.81
8.80
7.49
7.48
7.48
7.47
7.46
7.46
7.46
7.44
7.43
7.43
7.42
7.41
7.40
7.40
7.38
7.38
7.37
7.37
7.36
7.35
7.34
7.34
7.34
7.20
7.20
7.17
7.17
7.16
7.14
7.12
7.09
7.08
7.08
7.07
7.06
7.06
7.06
6.72
6.58
6.45
5.22
CDCl3, 400 MHz
F
O
CF2H
N
N
7x
0.90
0.91
4.94
3.00
1.00
1.95
10.0
9.5
9.0
8.5
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)

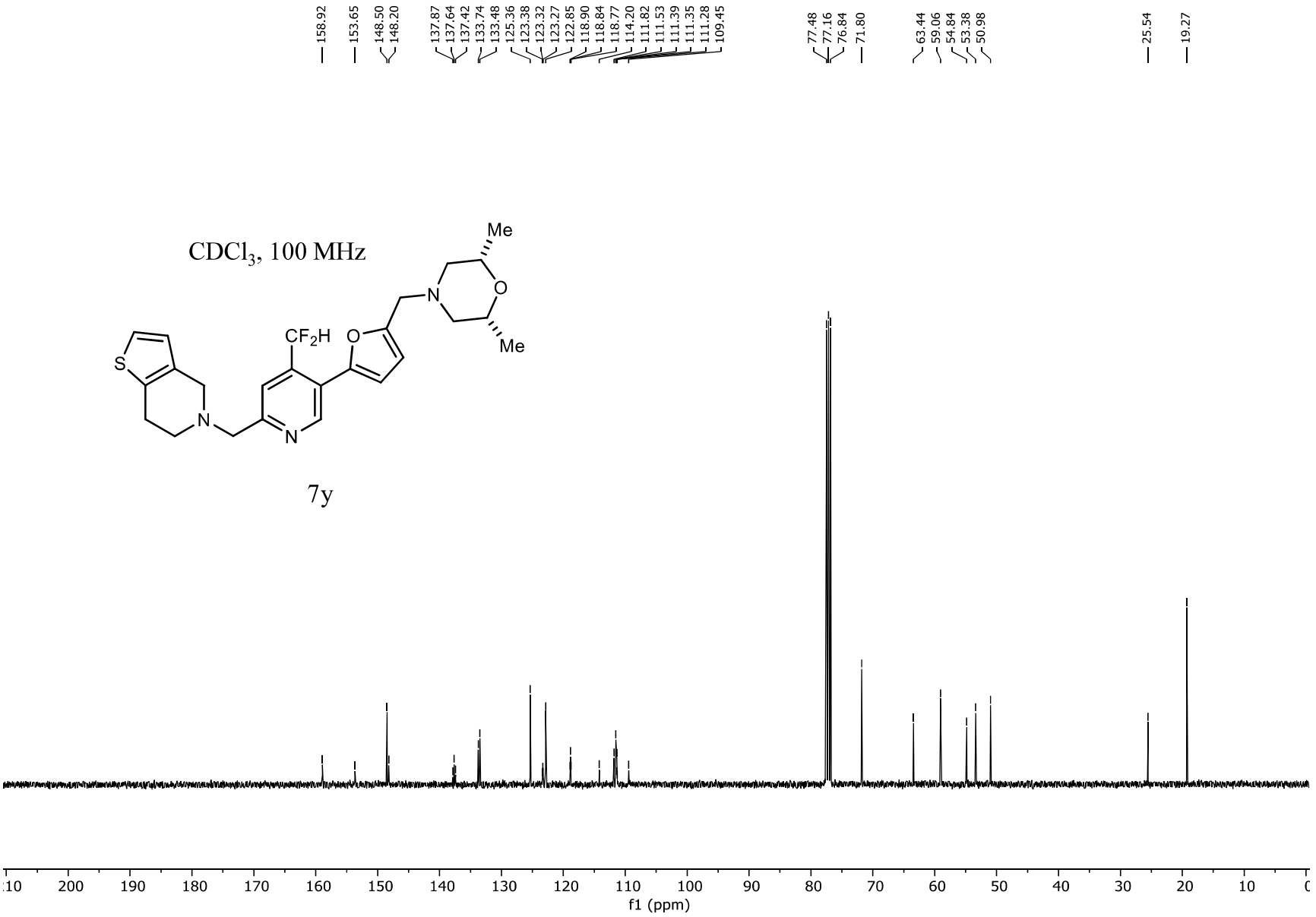

159.46
157.84
155.88
155.64
155.41
153.97
151.50
147.95
147.85
136.08
132.84
132.82
128.90
128.52
127.57
125.76
125.69
125.67
125.66
125.64
117.65
117.63
117.61
117.45
117.43
117.42
115.79
115.76
114.31
111.90
109.49
77.48
77.16
76.84
71.48
CDCl3, 100 MHz
F
O
CF2H
N
N
7x
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

$CDCl_3$, 376 MHz

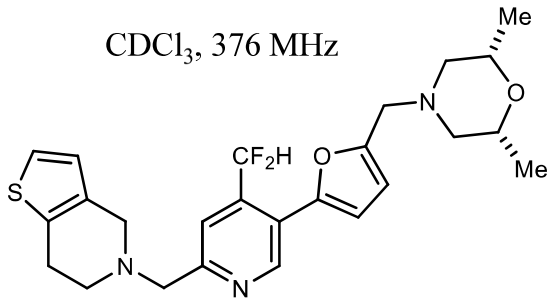


7x

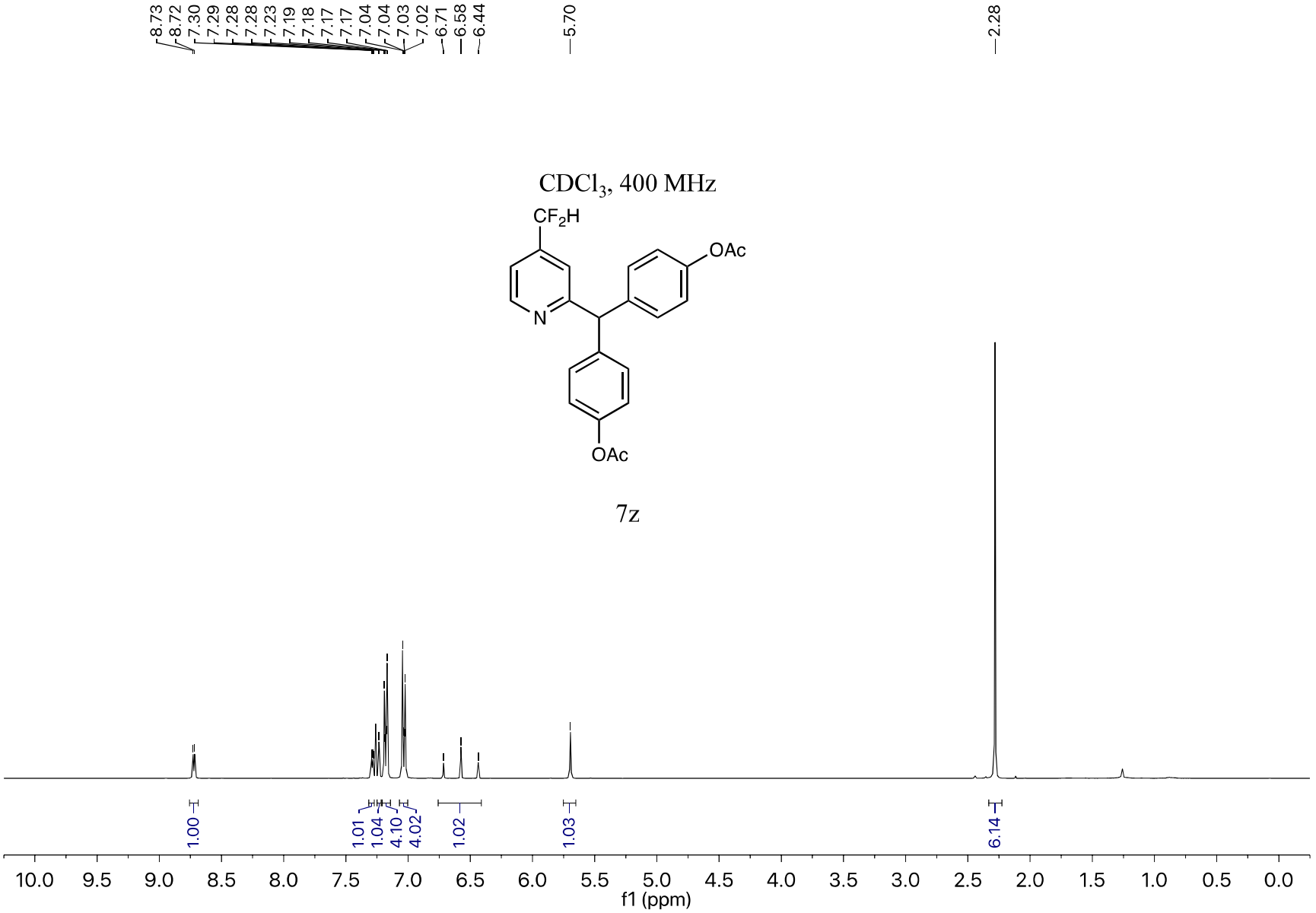

8.91
7.82
7.26
7.15
7.08
7.07
7.02
6.88
6.72
6.70
6.69
6.68
6.38
6.37
3.94
3.74
3.74
3.73
3.72
3.71
3.71
3.70
3.70
3.69
3.68
3.67
3.67
3.67
3.62
2.95
2.94
2.93
2.92
2.90
2.89
2.88
2.88
2.87
2.78
2.76
1.89
1.86
1.84
1.16
1.15
CDCl3, 400 MHz
Me
O
N
Me
CF2H
O
S
N
N
7y
1.00
1.08
2.22
2.17
1.08
2.18
4.48
2.27
4.63
2.29
2.29
6.71
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)


158.92
153.65
148.50
148.20
137.87
137.64
137.42
133.74
133.48
125.36
123.38
123.32
123.27
122.85
118.90
118.84
118.77
114.20
111.82
111.53
111.39
111.35
111.28
109.45
77.48
77.16
76.84
71.80
63.44
59.06
54.84
53.38
50.98
25.54
19.27
CDCl3, 100 MHz
Me
O
N
Me
CF2H
O
S
N
N
7y
f1 (ppm)

$CDCl_3$, 376 MHz

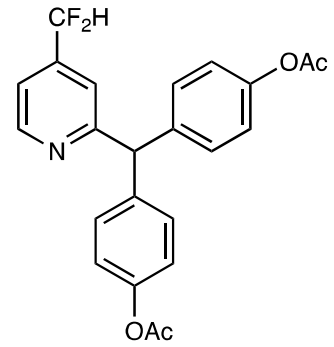


7y

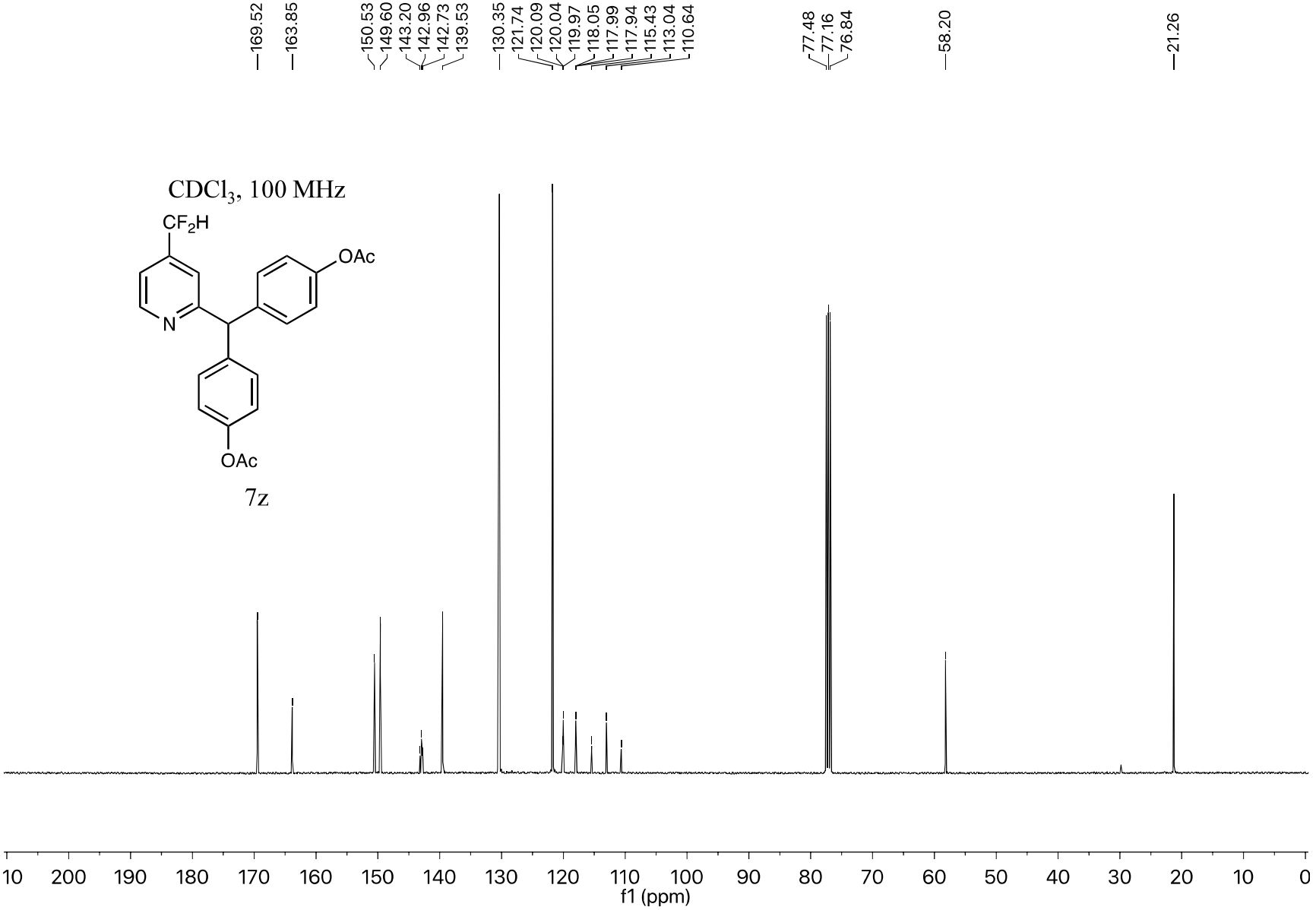

8.73
8.72
7.30
7.29
7.28
7.28
7.23
7.19
7.18
7.17
7.17
7.04
7.04
7.03
7.02
6.71
6.58
6.44
5.70
2.28
CDCl3, 400 MHz
CF2H
OAc
N
OAc
1.00
1.01
1.04
4.10
4.02
1.02
1.03
6.14
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

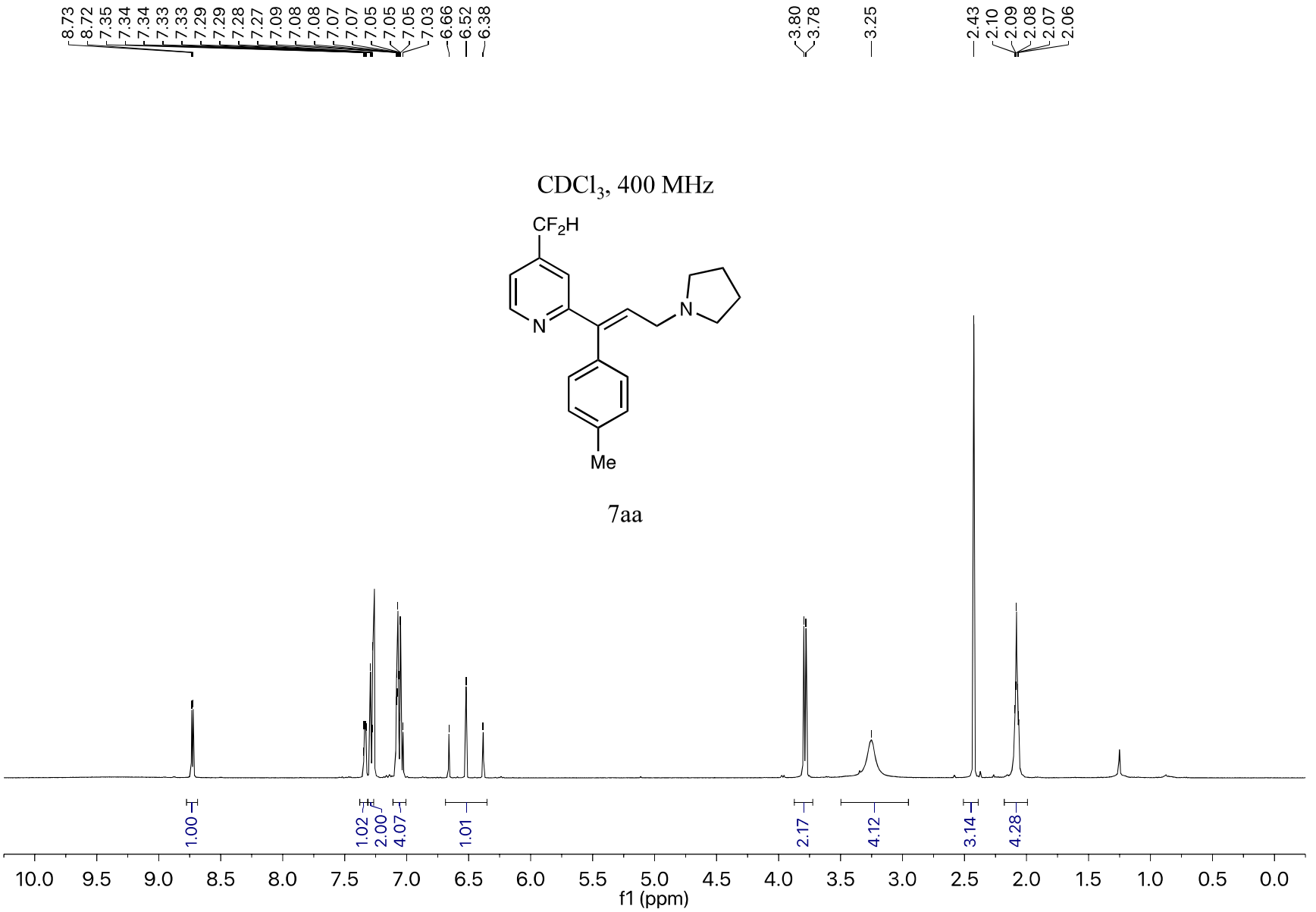
7z

$CDCl_3$, 376 MHz

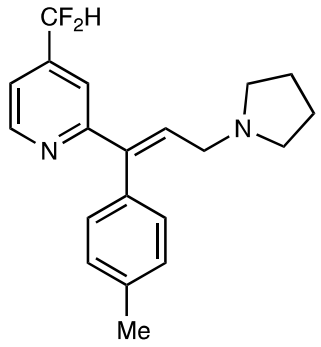


7z

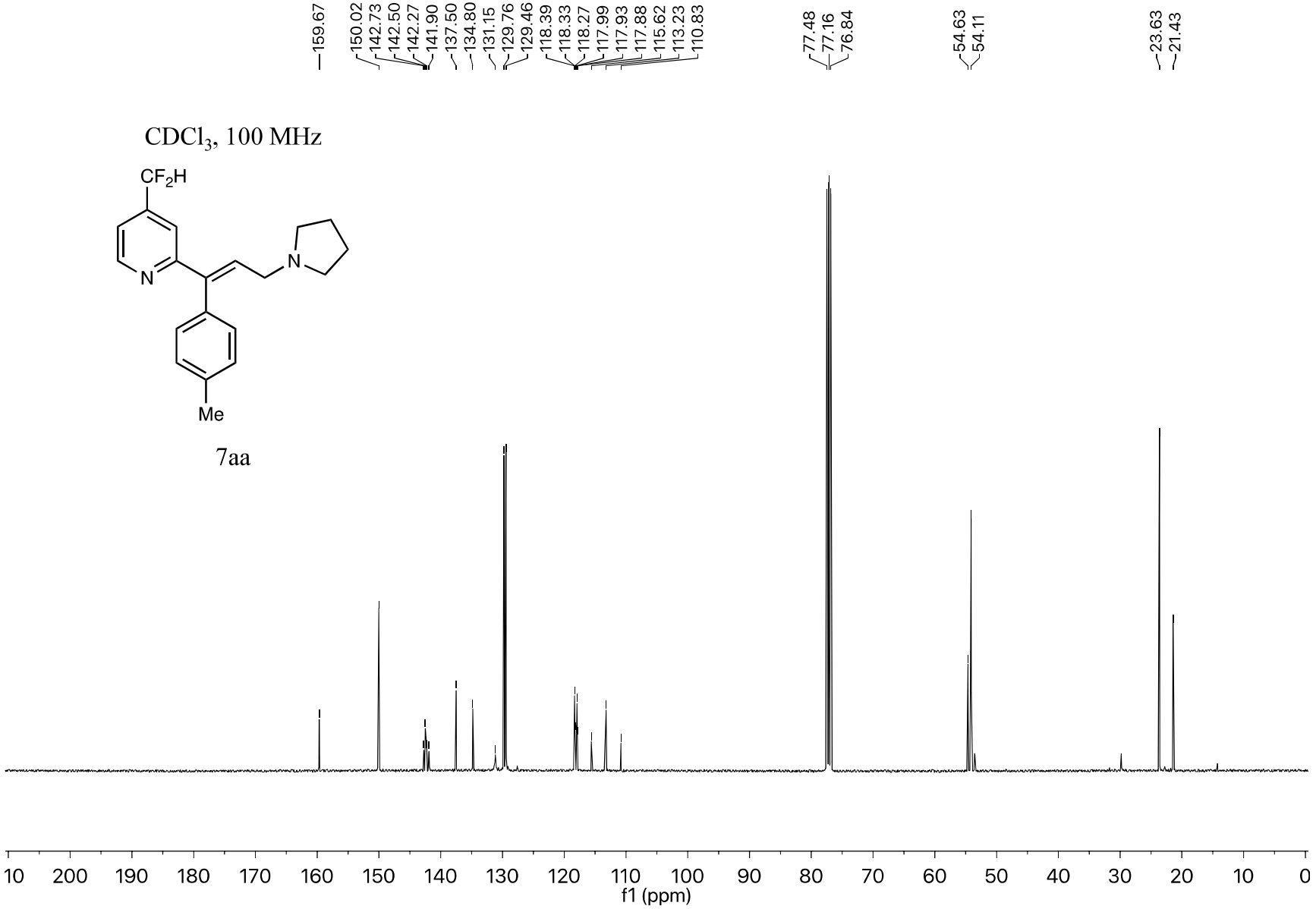

169.52
163.85
150.53
149.60
143.20
142.96
142.73
139.53
130.35
121.74
120.09
120.04
119.97
118.05
117.99
117.94
115.43
113.04
110.64
77.48
77.16
76.84
58.20
21.26
CDCl3, 100 MHz
CF2H
OAc
N
OAc
7z
f1 (ppm)

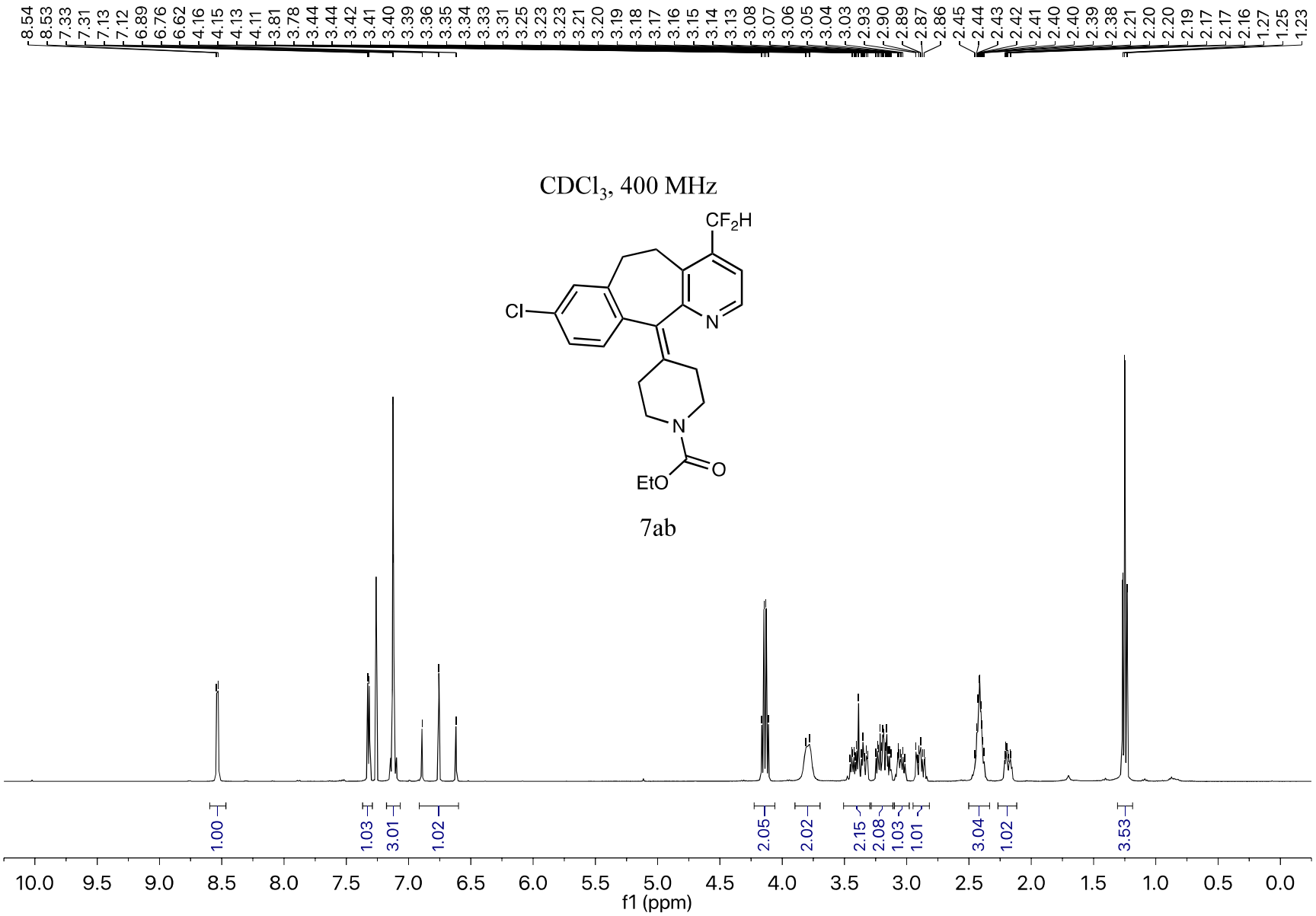

8.73
8.72
7.35
7.34
7.34
7.33
7.33
7.29
7.29
7.28
7.27
7.09
7.08
7.08
7.07
7.07
7.05
7.05
7.05
7.03
6.66
6.52
6.38
3.80
3.78
3.25
2.43
2.10
2.09
2.08
2.07
2.06
CDCl3, 400 MHz
CF2H
N
N
Me
7aa
1.00
1.02
2.00
4.07
1.01
2.17
4.12
3.14
4.28
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

$CDCl_3$, 376 MHz



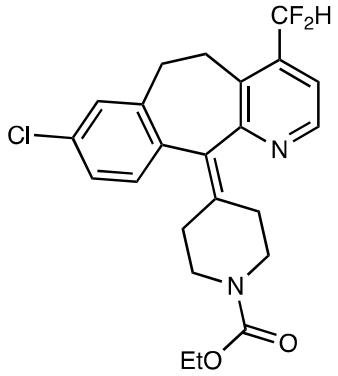
7aa


159.67
150.02
142.73
142.50
142.27
141.90
137.50
134.80
131.15
129.76
129.46
118.39
118.33
118.27
117.99
117.93
117.88
115.62
113.23
110.83
77.48
77.16
76.84
54.63
54.11
23.63
21.43
CDCl3, 100 MHz
CF2H
N
N
Me
7aa
f1 (ppm)

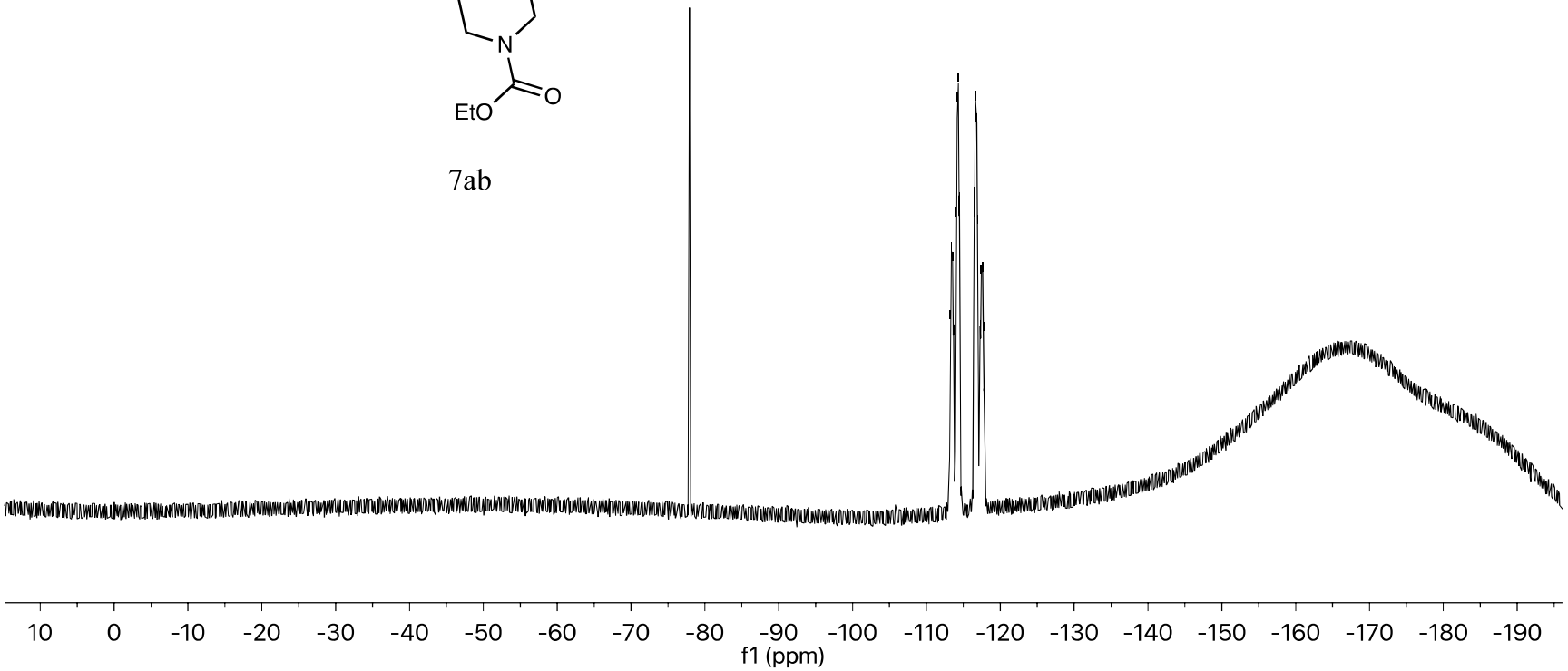

8.54
8.53
7.33
7.31
7.13
7.12
6.89
6.76
6.62
4.16
4.15
4.13
4.11
3.81
3.78
3.44
3.44
3.42
3.41
3.40
3.39
3.36
3.35
3.34
3.33
3.31
3.25
3.23
3.23
3.21
3.20
3.19
3.18
3.17
3.16
3.15
3.14
3.13
3.08
3.07
3.06
3.05
3.04
3.03
2.93
2.90
2.89
2.87
2.86
2.45
2.44
2.43
2.42
2.41
2.40
2.40
2.39
2.38
2.21
2.20
2.20
2.19
2.17
2.17
2.16
1.27
1.25
1.23
CDCl3, 400 MHz
CF2H
Cl
N
N
O
EtO
7ab
1.00
1.03
3.01
1.02
2.05
2.02
2.15
2.08
1.03
1.01
3.04
1.02
3.53
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)

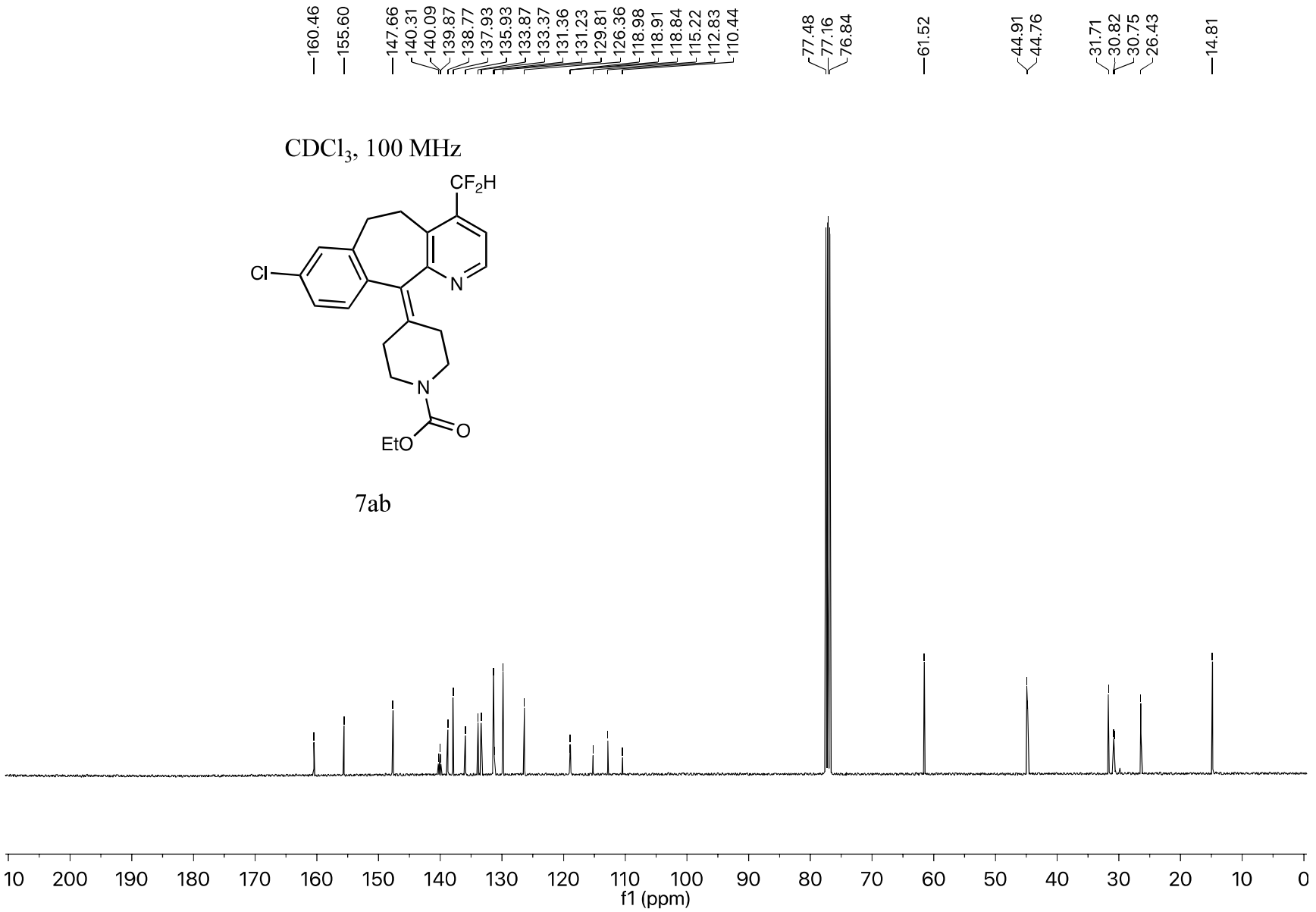
-113.24
-113.39
-113.55
-114.05
-114.19
-114.35
-114.49
-116.47
-116.52
-116.63
-116.81
-116.96
-117.28
-117.42
-117.62
-117.77

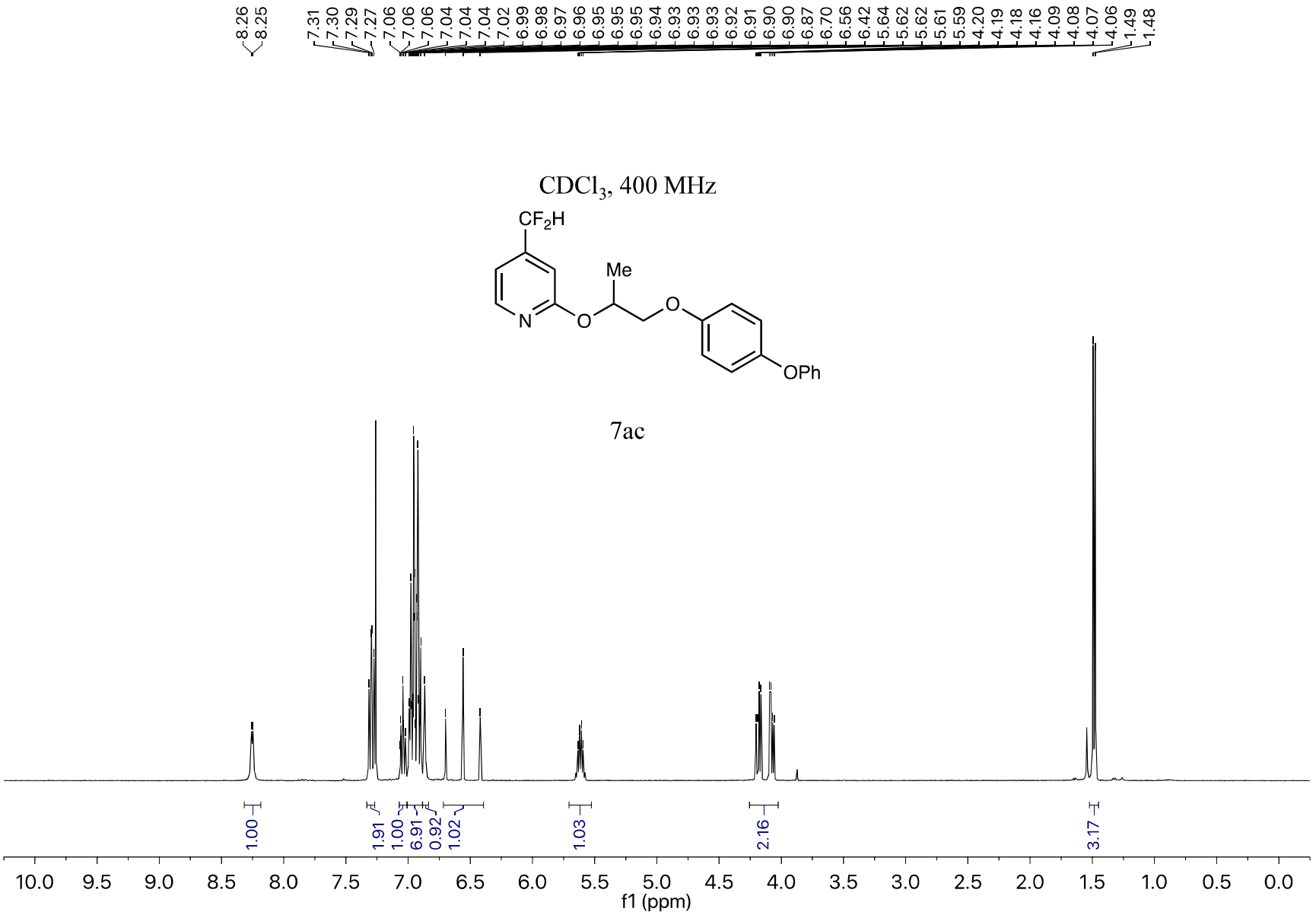
$CDCl_3$, 376 MHz



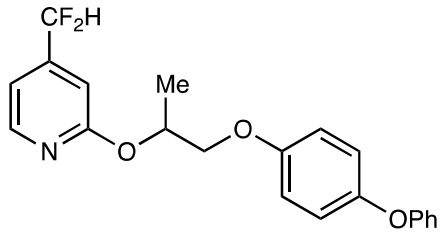
7ab



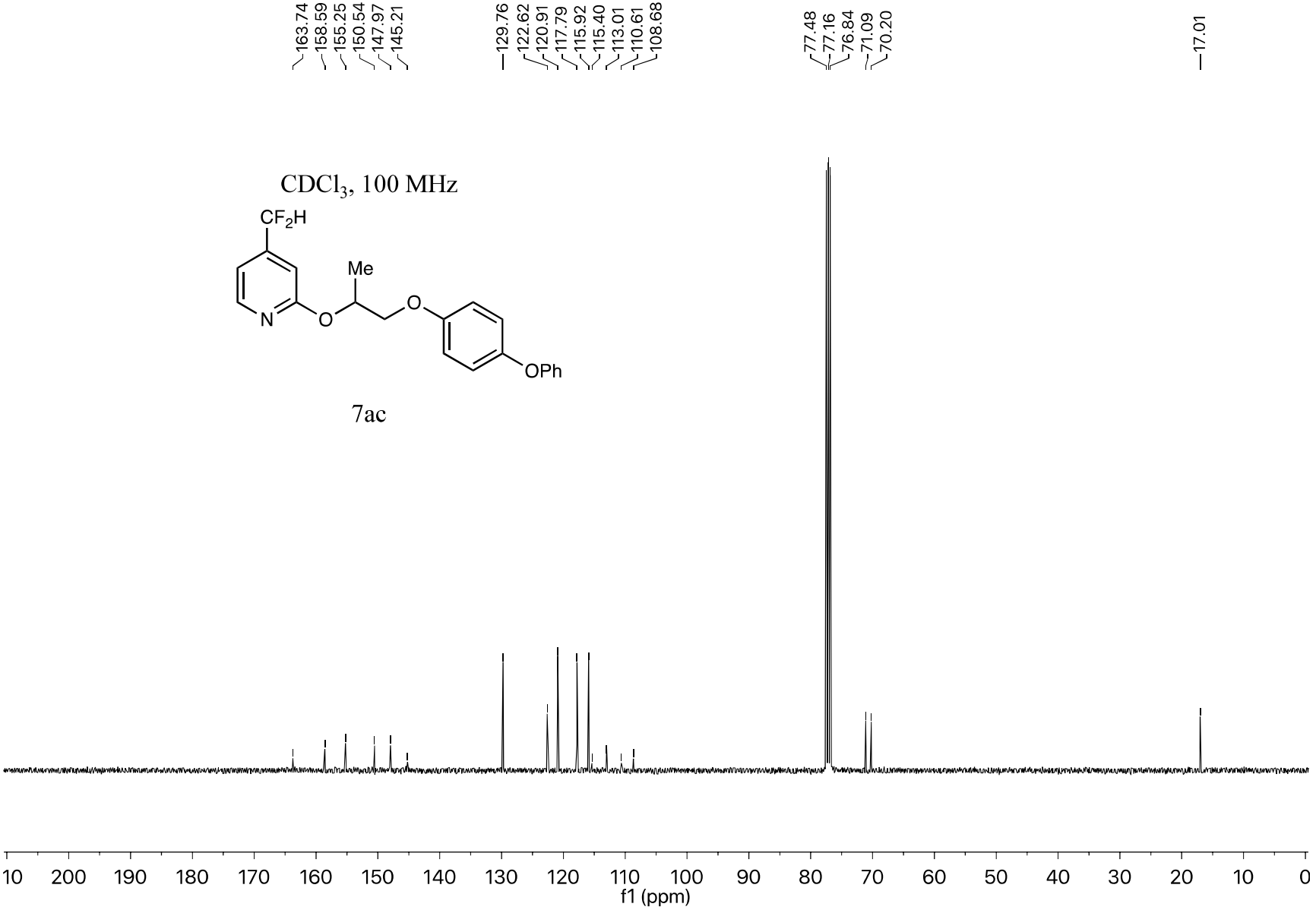

160.46
155.60
147.66
140.31
140.09
139.87
138.77
137.93
135.93
133.87
133.37
131.36
131.23
129.81
126.36
118.98
118.91
118.84
115.22
112.83
110.44
77.48
77.16
76.84
61.52
44.91
44.76
31.71
30.82
30.75
26.43
14.81
CDCl3, 100 MHz
CF2H
Cl
N
N
O
EtO
7ab
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

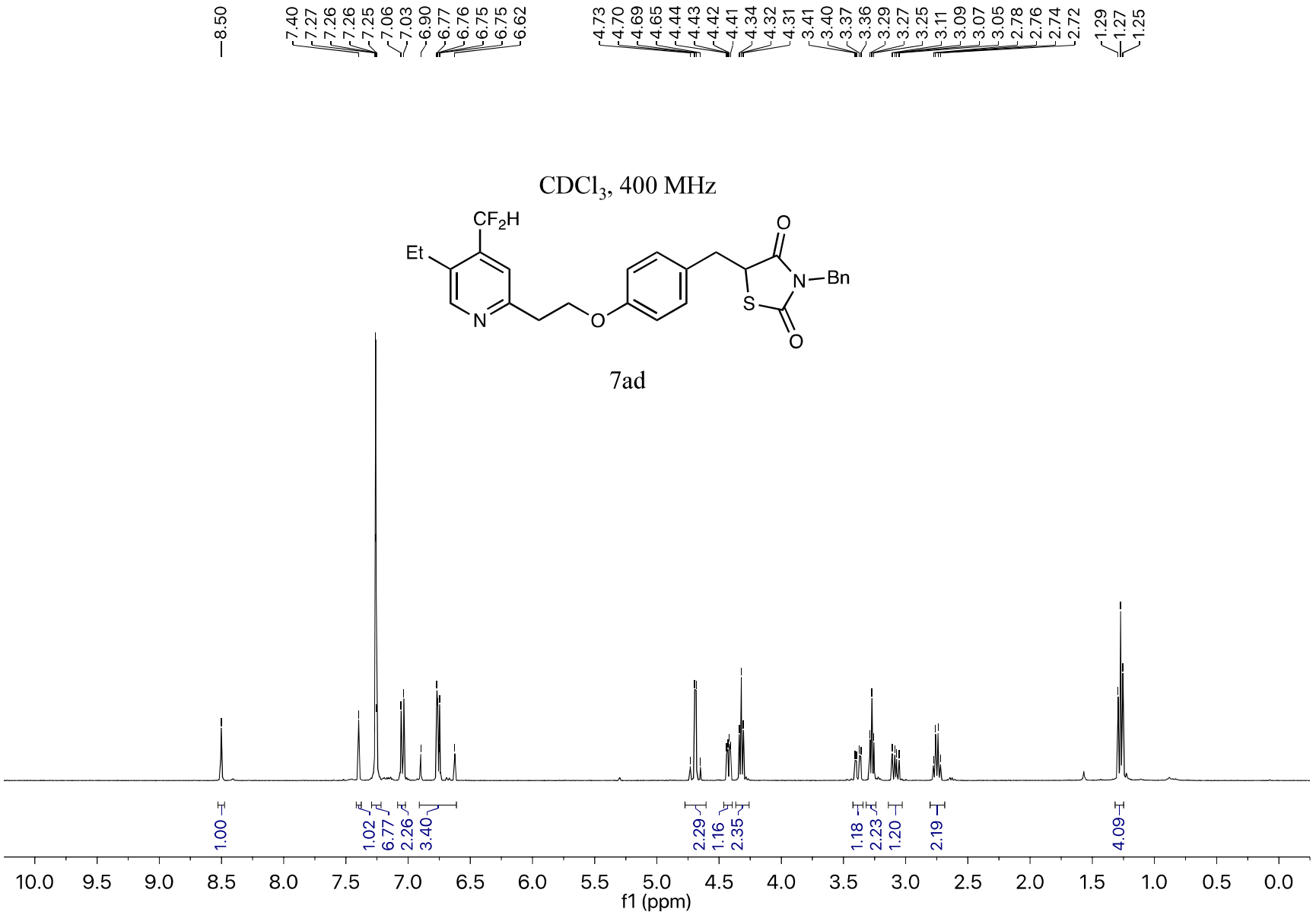

8.26
8.25
7.31
7.30
7.29
7.27
7.06
7.06
7.06
7.04
7.04
7.04
7.02
6.99
6.98
6.97
6.96
6.95
6.95
6.95
6.94
6.93
6.93
6.93
6.92
6.91
6.90
6.90
6.87
6.70
6.56
6.42
5.64
5.62
5.62
5.61
5.59
4.20
4.19
4.18
4.16
4.09
4.08
4.07
4.06
1.49
1.48
CDCl3, 400 MHz
CF2H
Me
N
O
O
O
OPh
7ac
1.00
1.91
1.00
6.91
0.92
1.02
1.03
2.16
3.17
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)

$CDCl_3$, 376 MHz

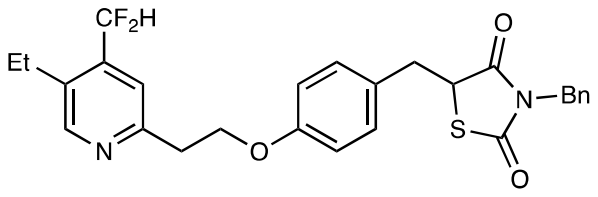


7ac

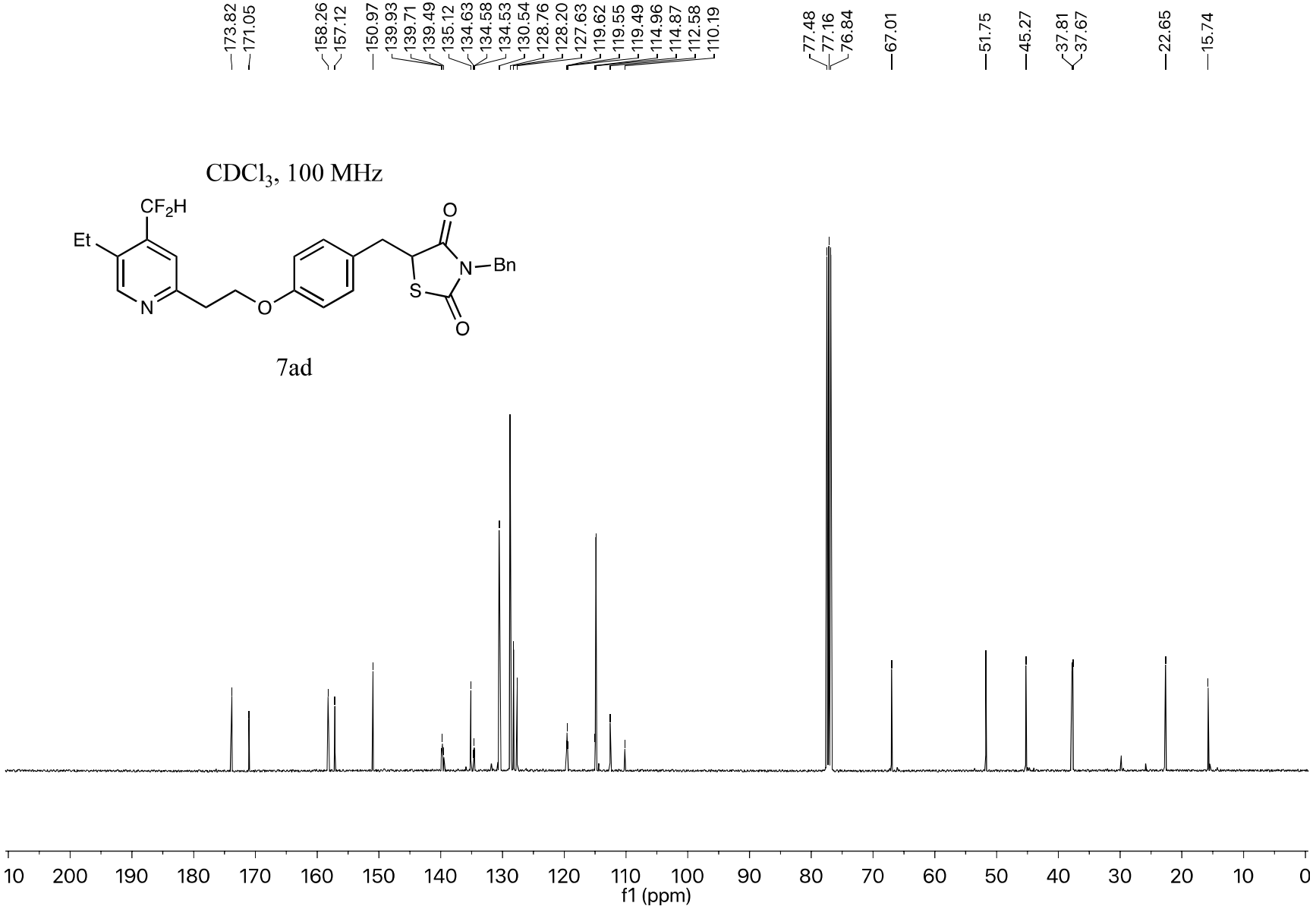

163.74
158.59
155.25
150.54
147.97
145.21
129.76
122.62
120.91
117.79
115.92
115.40
113.01
110.61
108.68
77.48
77.16
76.84
71.09
70.20
17.01
CDCl3, 100 MHz
CF2H
Me
N
O
O
OPh
7ac
f1 (ppm)


8.50
7.40
7.27
7.26
7.26
7.25
7.06
7.03
6.90
6.77
6.76
6.75
6.75
6.62
4.73
4.70
4.69
4.65
4.44
4.43
4.42
4.41
4.34
4.32
4.31
3.41
3.40
3.37
3.36
3.29
3.27
3.25
3.11
3.09
3.07
3.05
2.78
2.76
2.74
2.72
1.29
1.27
1.25
CDCl3, 400 MHz
CF2H
Et
N
O
O
N
Bn
S
O
7ad
1.00
1.02
6.77
2.26
3.40
2.29
1.16
2.35
1.18
2.23
1.20
2.19
4.09
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)

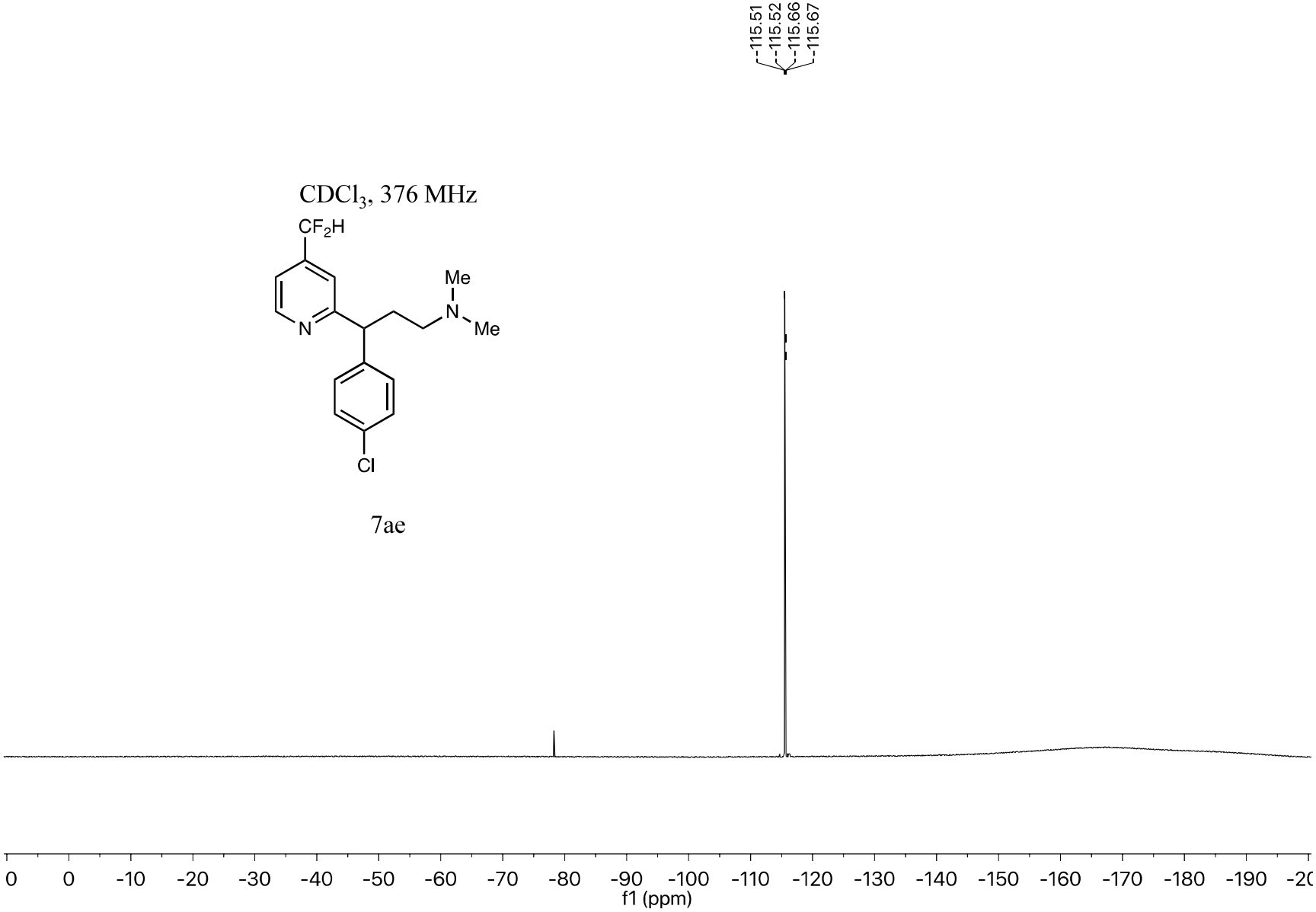
$CDCl_3$, 376 MHz

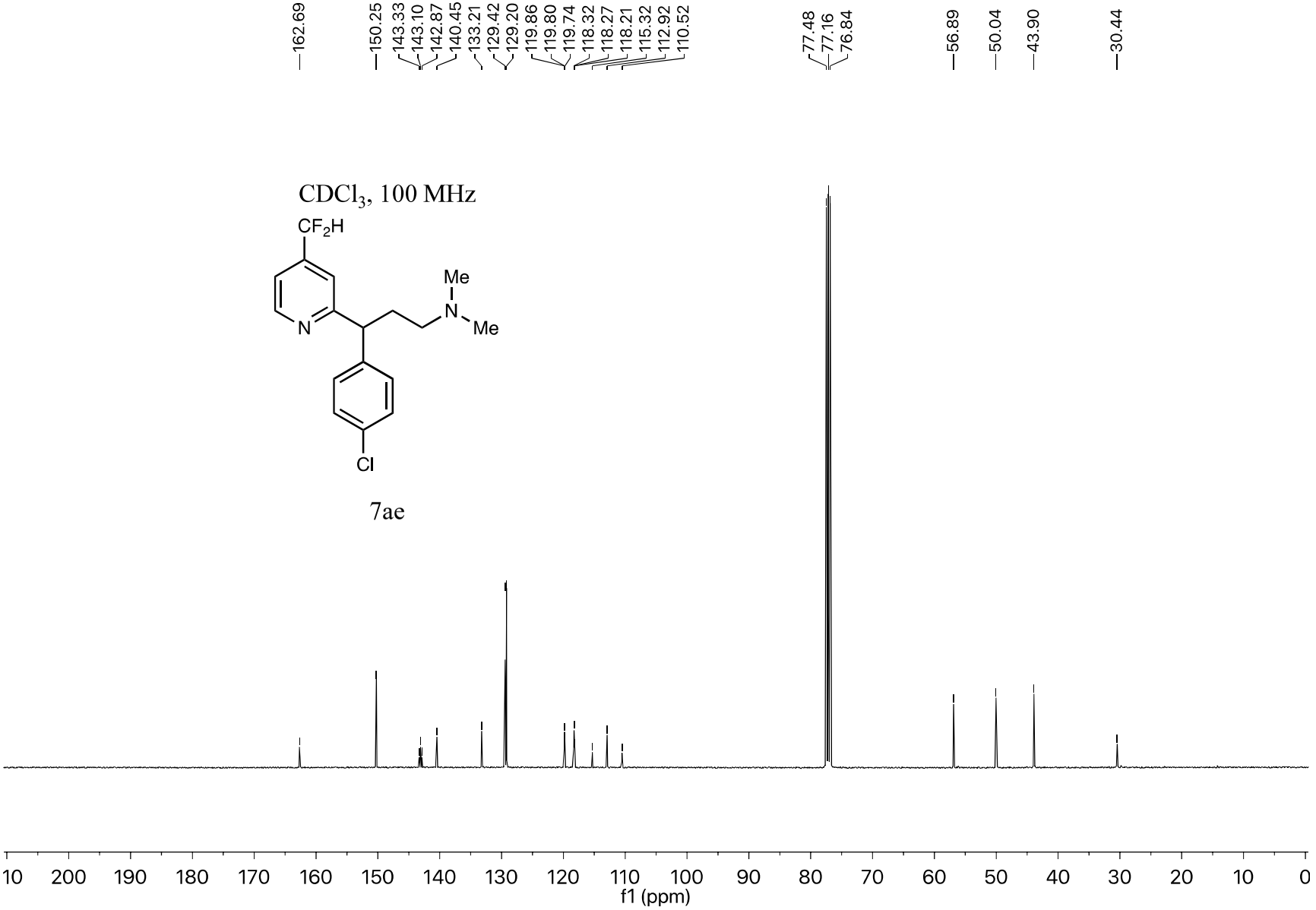


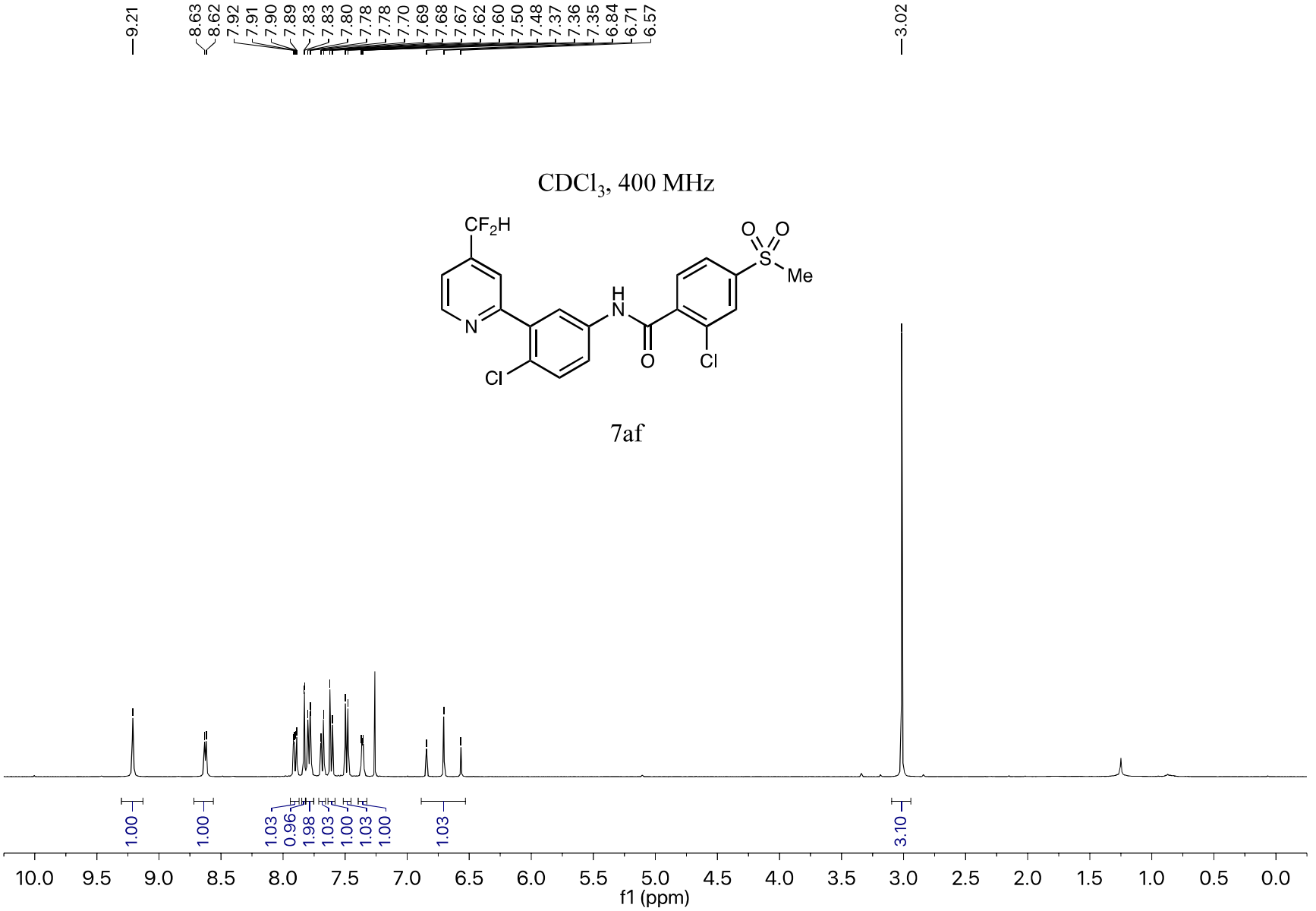
7ad


173.82
171.05
158.26
157.12
150.97
139.93
139.71
139.49
135.12
134.63
134.58
134.53
130.54
128.76
128.20
127.63
119.62
119.55
119.49
114.96
114.87
112.58
110.19
77.48
77.16
76.84
67.01
51.75
45.27
37.81
37.67
22.65
15.74
CDCl3, 100 MHz
CF2H
Et
N
O
O
N
Bn
S
O
7ad
f1 (ppm)

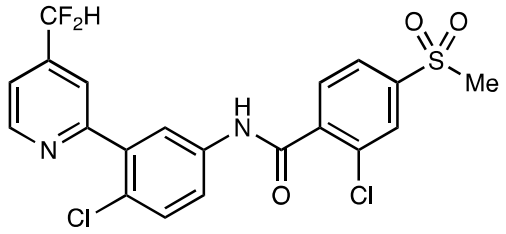
8.68
8.66
7.28
7.27
7.26
7.25
7.24
6.68
6.54
6.41
4.26
4.24
4.22
2.68
2.57
2.45
2.43
2.41
2.40
CDCl3, 400 MHz
CF2H
N
Me
N
Me
Cl
7ae
1.00
6.39
1.10
1.02
2.92
5.83
1.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


-115.51
-115.52
-115.66
-115.67
CDCl3, 376 MHz
CF2H
Me
N
Me
N
Cl
7ae
0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

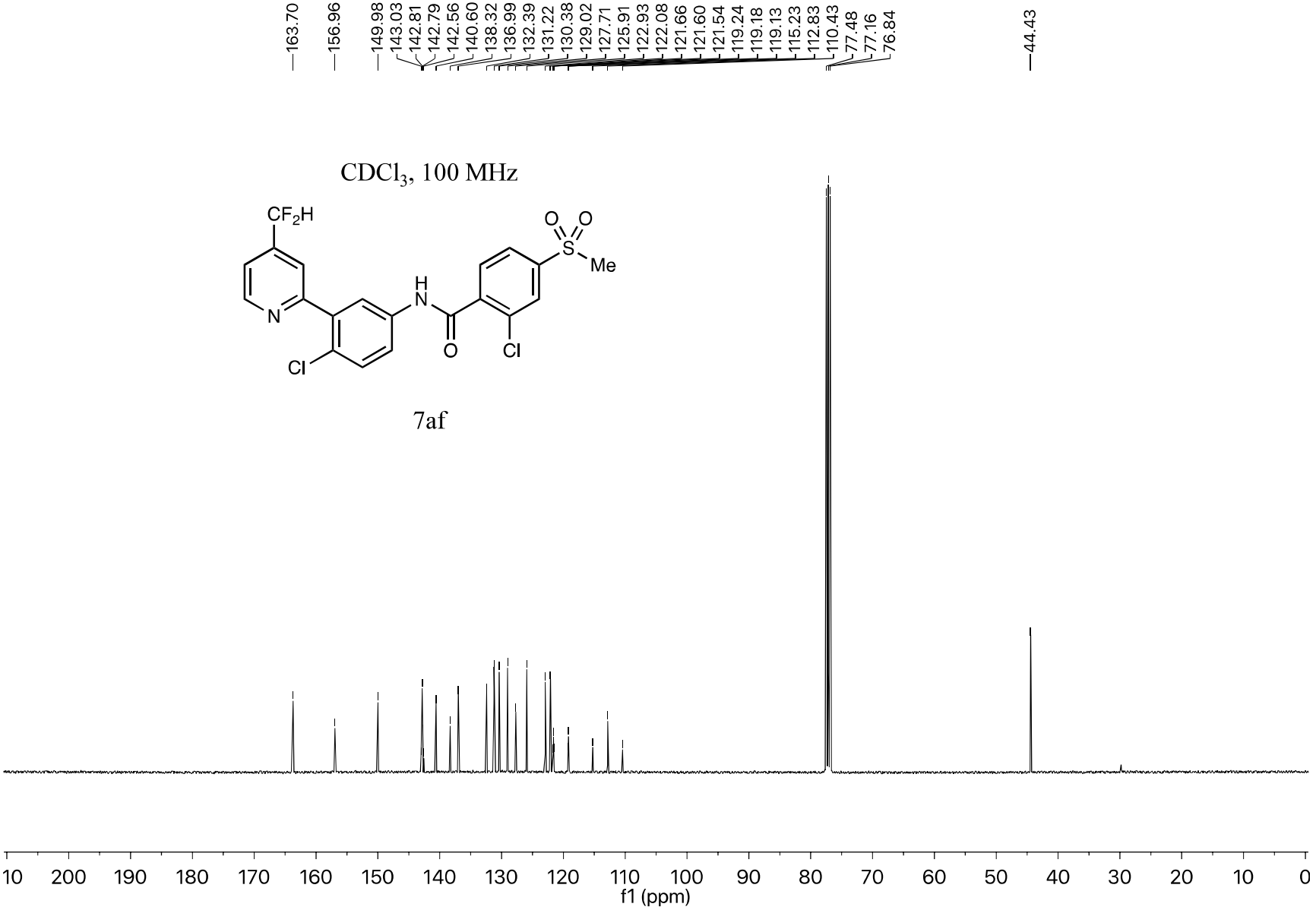

162.69
150.25
143.33
143.10
142.87
140.45
133.21
129.42
129.20
119.86
119.80
119.74
118.32
118.27
118.21
115.32
112.92
110.52
77.48
77.16
76.84
56.89
50.04
43.90
30.44
CDCl3, 100 MHz
CF2H
Me
N
Me
N
Cl
7ae
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

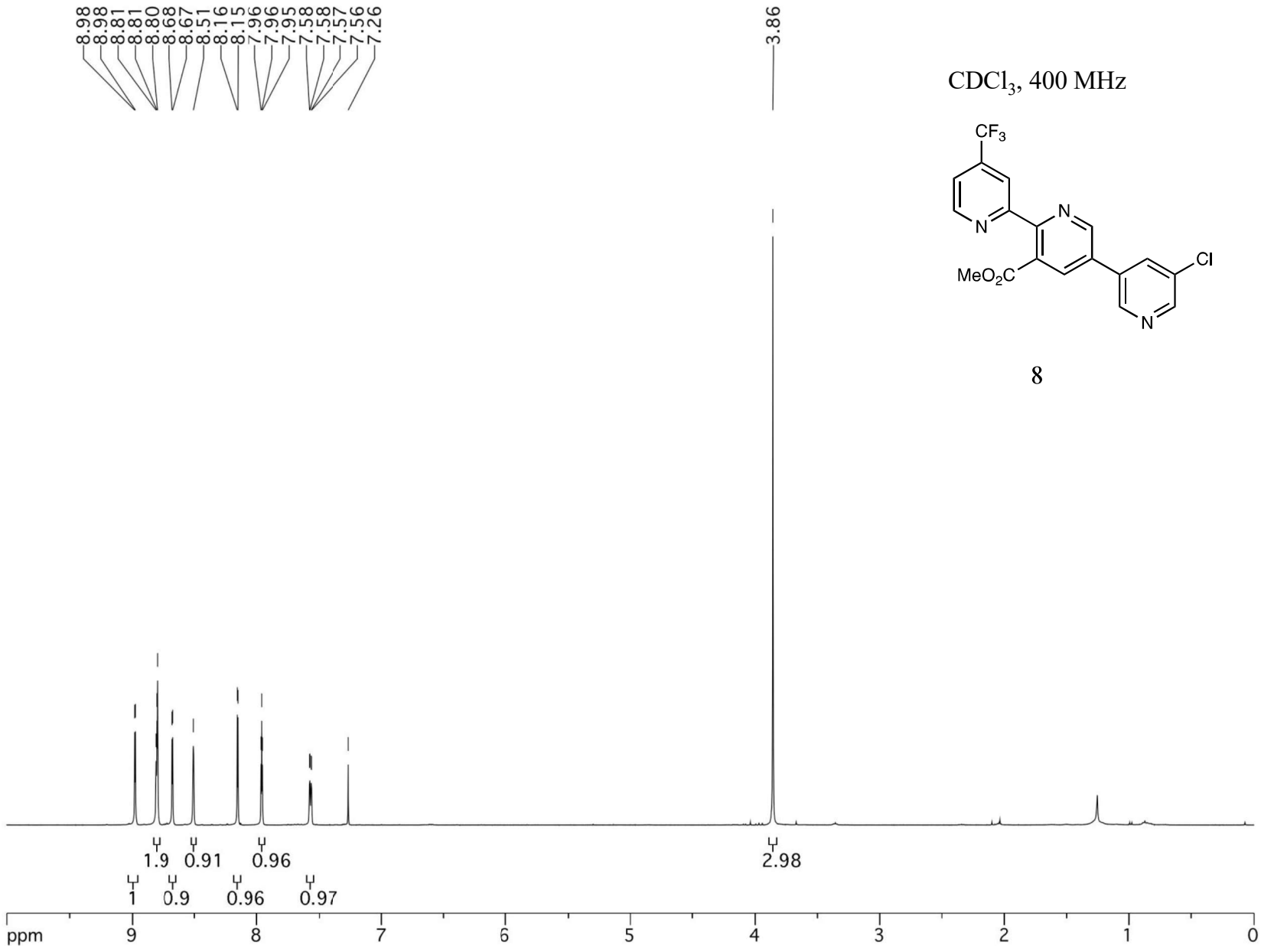

9.21
8.63
8.62
7.92
7.91
7.90
7.89
7.83
7.83
7.80
7.78
7.78
7.70
7.69
7.68
7.67
7.62
7.60
7.50
7.48
7.37
7.36
7.35
6.84
6.71
6.57
3.02
CDCl3, 400 MHz
CF2H
N
H
N
O
O
S
Me
O
Cl
Cl
7af
1.00
1.00
1.03
0.96
1.98
1.03
1.00
1.03
1.00
1.03
3.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

$CDCl_3$, 376 MHz



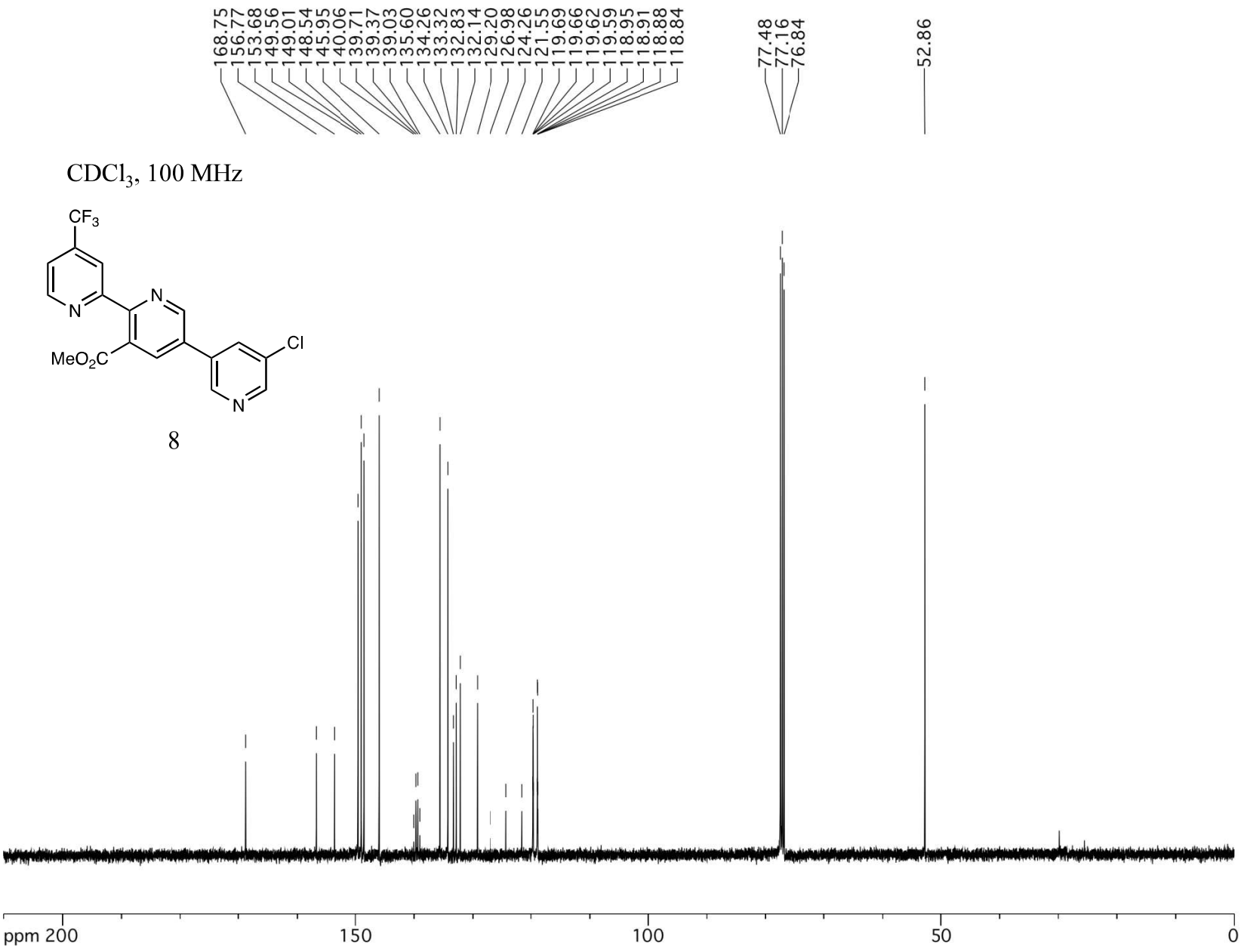
7af


163.70
156.96
149.98
143.03
142.81
142.79
142.56
140.60
138.32
136.99
132.39
131.22
130.38
129.02
127.71
125.91
122.93
122.08
121.66
121.60
121.54
119.24
119.18
119.13
115.23
112.83
110.43
77.48
77.16
76.84
44.43
CDCl3, 100 MHz
CF2H
O
O
S
Me
H
N
N
O
Cl
Cl
7af
10
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

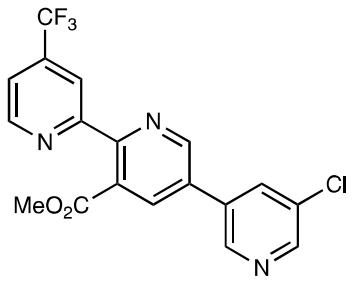
8


168.75
156.77
153.68
149.56
149.01
148.54
145.95
140.06
139.71
139.37
139.03
135.60
134.26
133.32
132.83
132.14
129.20
126.98
124.26
121.55
119.69
119.66
119.62
119.59
118.95
118.91
118.88
118.84
77.48
77.16
76.84
52.86
CDCl3, 100 MHz
CF3
N
N
MeO2C
Cl
N
ppm 200
150
100
50
0

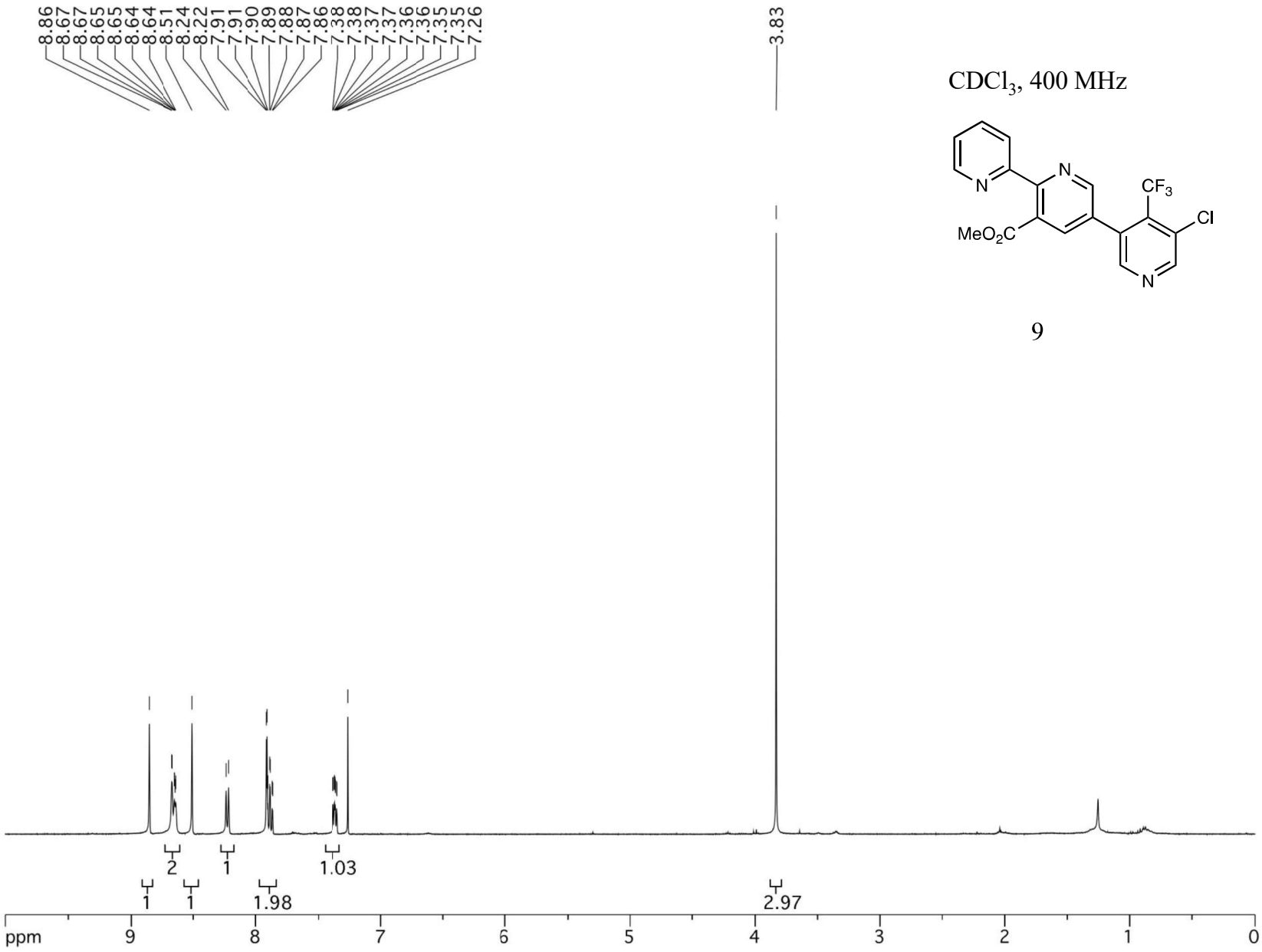
8

-64.76

$CDCl_3$, 376 MHz

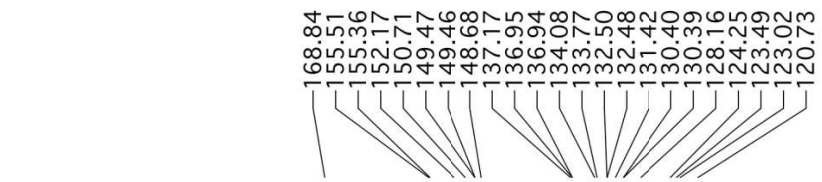


8

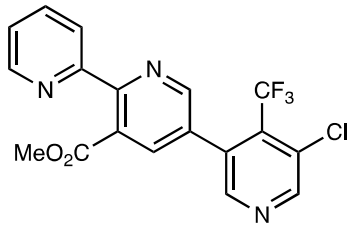


$CDCl_3$, 400 MHz

9



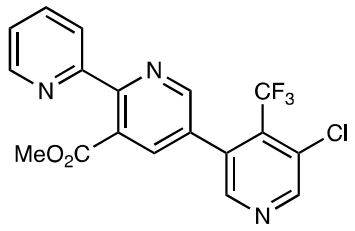
$CDCl_3$, 100 MHz



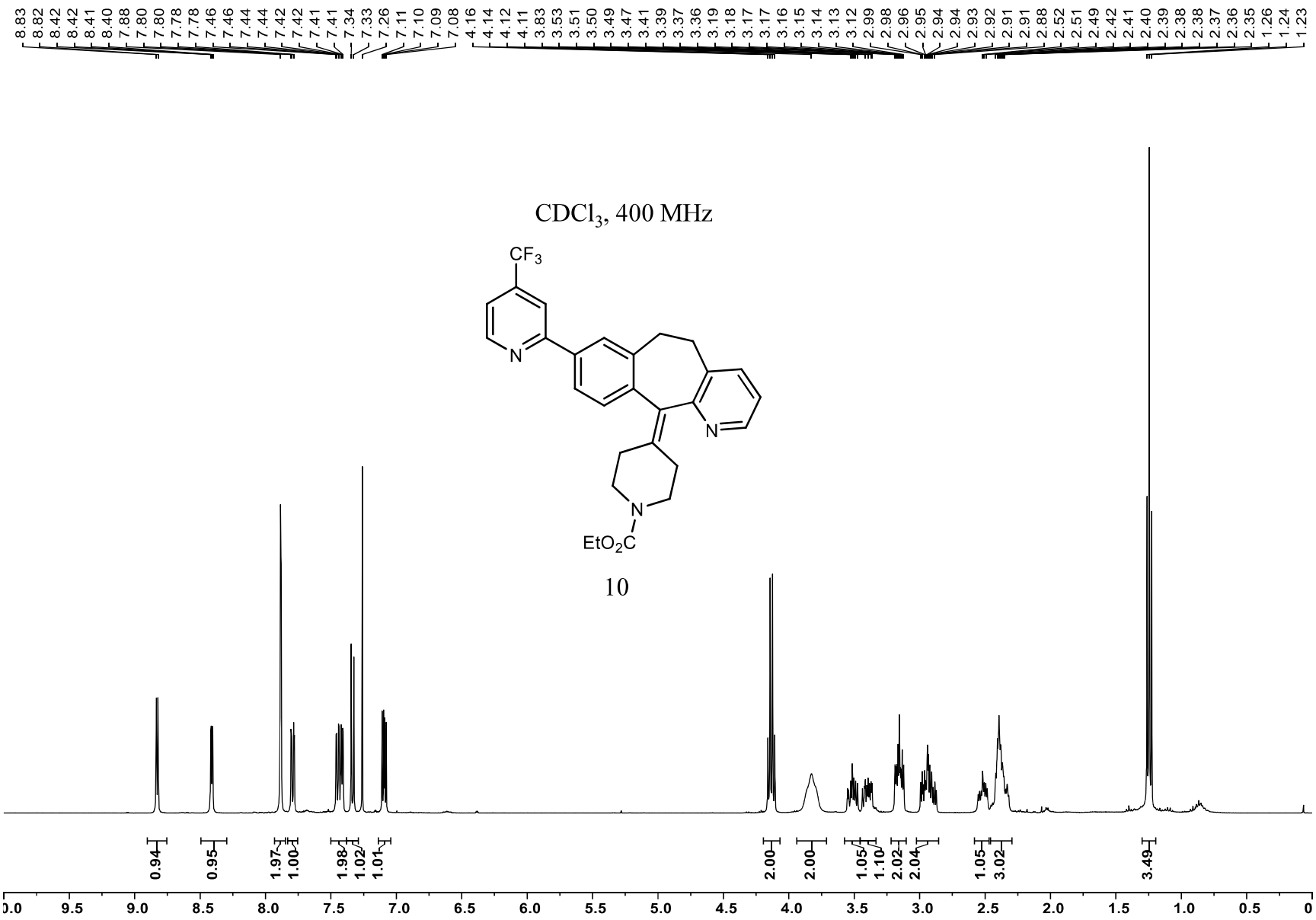
9

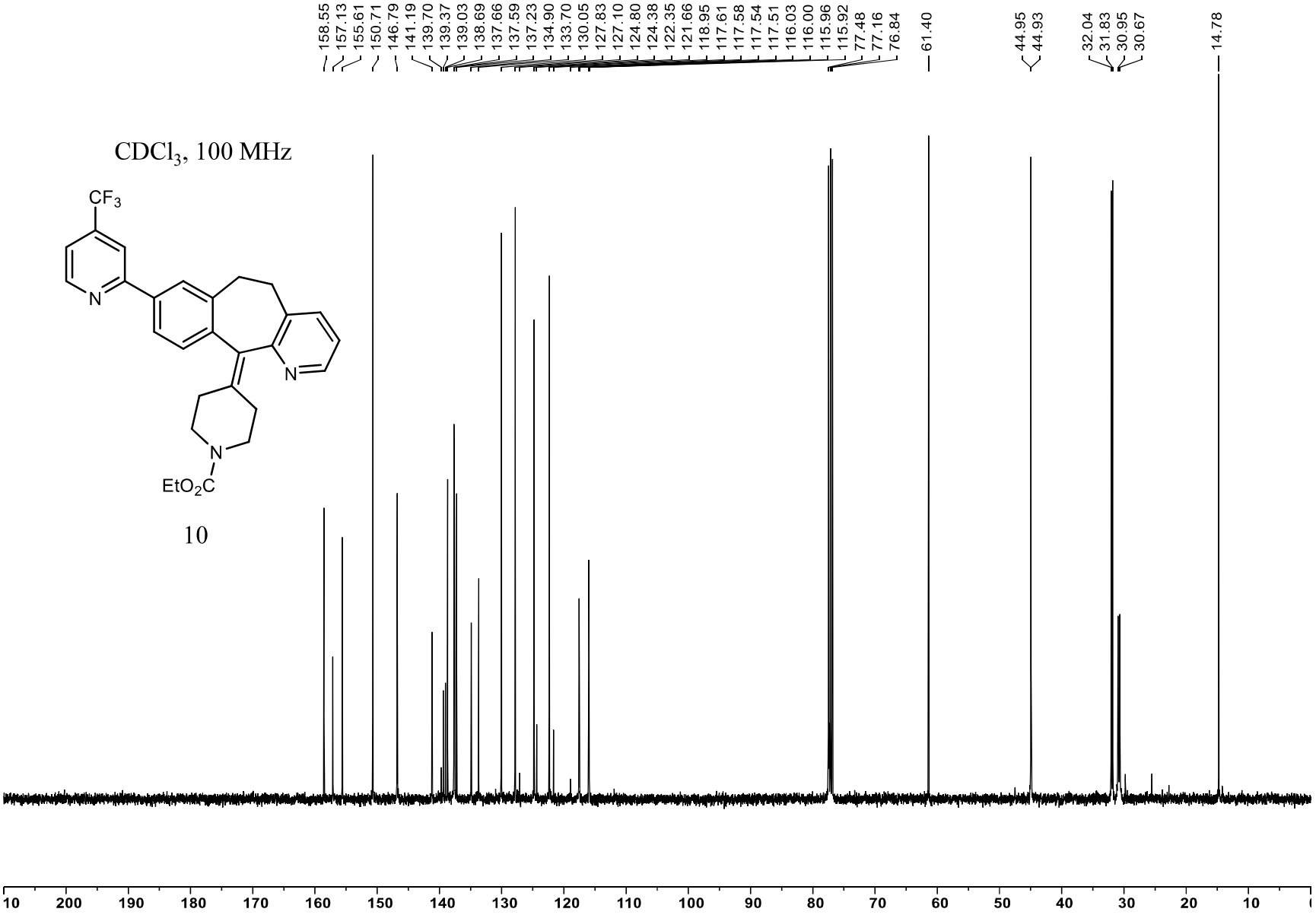
-55.55

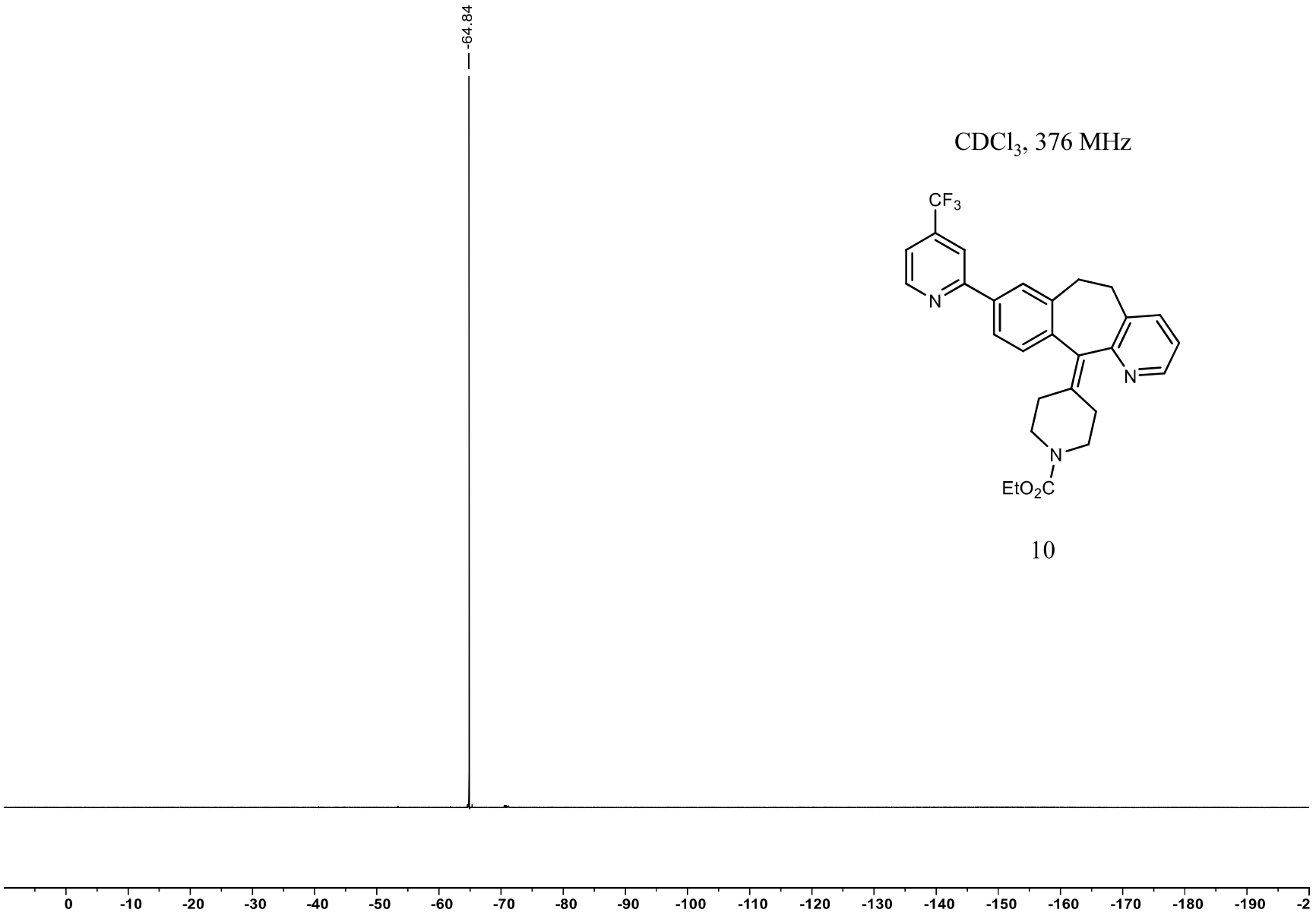
$CDCl_3$, 376 MHz



9

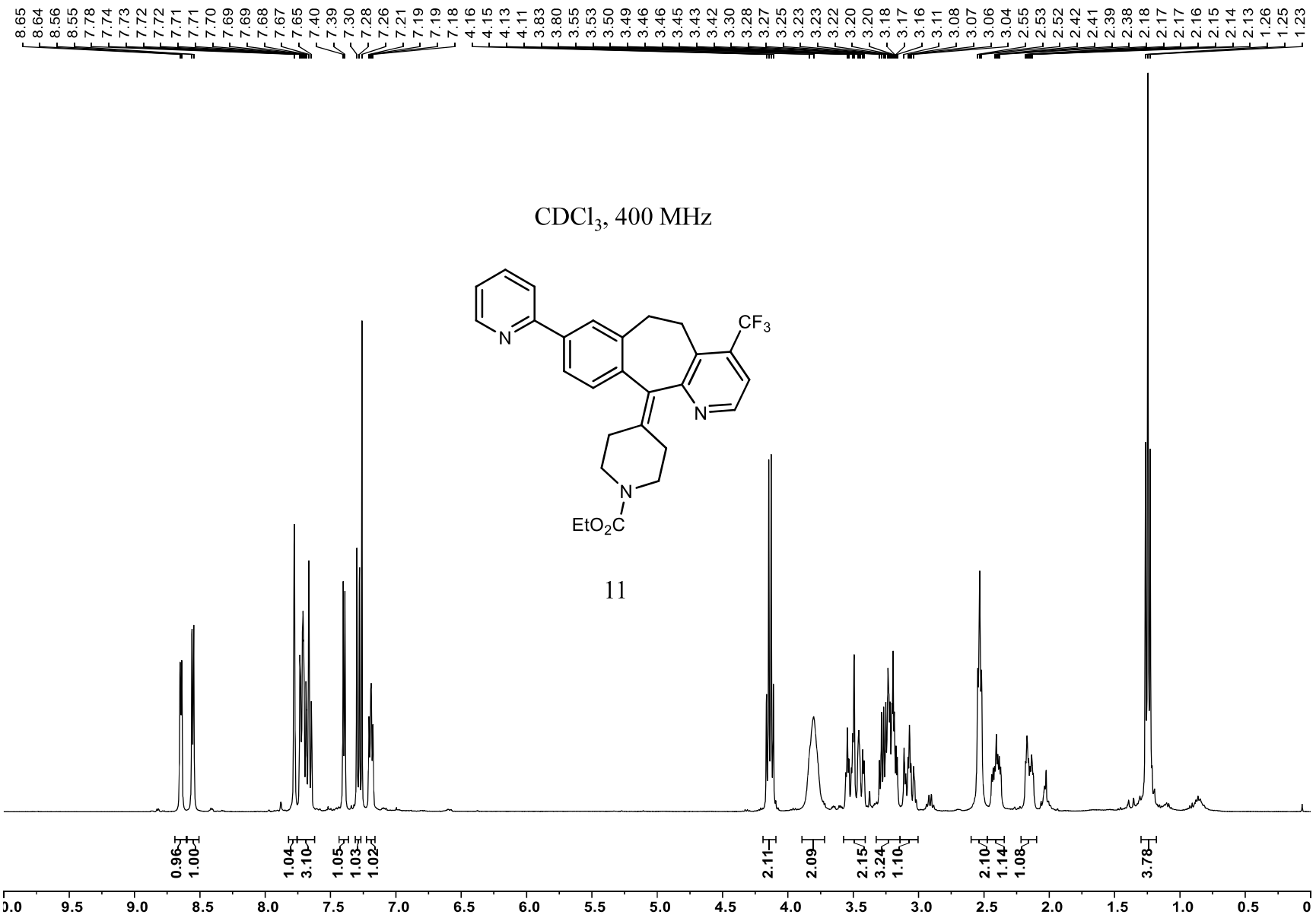

8.83 8.82 8.42 8.42 8.41 8.40 7.88 7.80 7.80 7.78 7.78 7.46 7.46 7.44 7.44 7.42 7.42 7.41 7.41 7.34 7.33 7.26 7.11 7.10 7.09 7.08
4.16 4.14 4.12 4.11 3.83 3.53 3.51 3.50 3.49 3.47 3.41 3.39 3.37 3.36 3.19 3.18 3.17 3.17 3.16 3.15 3.14 3.13 3.12 2.99 2.98 2.96 2.95 2.94 2.94 2.93 2.92 2.91 2.91 2.88 2.52 2.51 2.49 2.42 2.41 2.40 2.39 2.38 2.38 2.37 2.36 2.35 1.26 1.24 1.23
CDCl3, 400 MHz
CF3
N
N
N
EtO2C
10
0.94 0.95 1.97 1.00 1.98 1.02 1.01 2.00 2.00 1.05 1.10 2.02 2.04 1.05 3.02 3.49
0.0 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

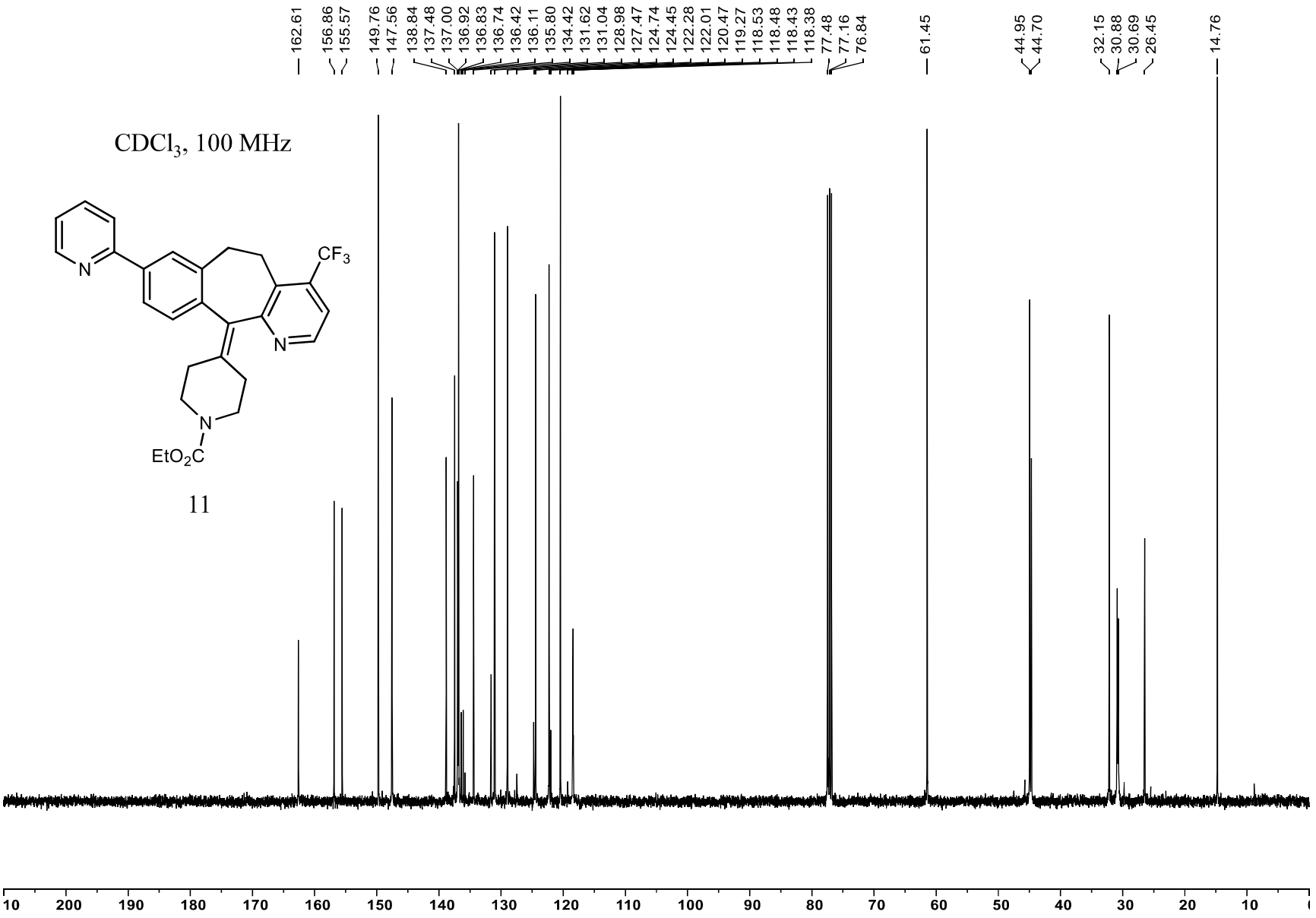

158.55
157.13
155.61
150.71
146.79
141.19
139.70
139.37
139.03
138.69
137.66
137.59
137.23
134.90
133.70
130.05
127.83
127.10
124.80
124.38
122.35
121.66
118.95
117.61
117.58
117.54
117.51
116.03
116.00
115.96
115.92
77.48
77.16
76.84
61.40
44.95
44.93
32.04
31.83
30.95
30.67
14.78
CDCl3, 100 MHz
CF3
N
N
N
EtO2C
10
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

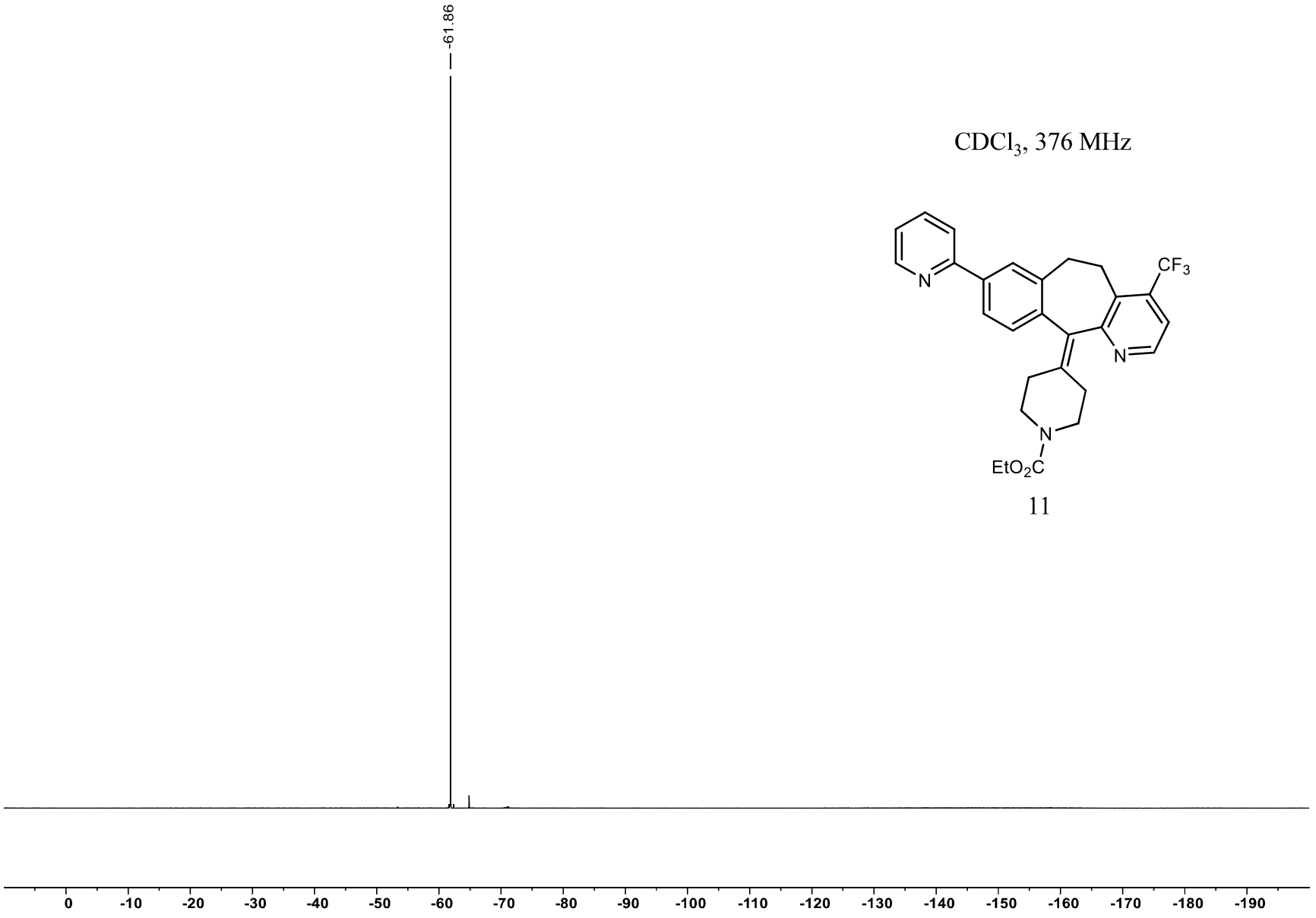


$CDCl_3$, 376 MHz

10


8.65 8.64 8.56 8.55 7.78 7.74 7.73 7.72 7.72 7.71 7.71 7.70 7.69 7.69 7.68 7.67 7.65 7.40 7.39 7.30 7.28 7.26 7.21 7.19 7.19 7.18 4.16 4.15 4.13 4.11 3.83 3.80 3.55 3.53 3.50 3.49 3.46 3.46 3.45 3.43 3.42 3.30 3.28 3.27 3.25 3.23 3.23 3.22 3.20 3.20 3.18 3.17 3.16 3.11 3.08 3.07 3.06 3.04 2.55 2.53 2.52 2.42 2.41 2.39 2.38 2.18 2.17 2.17 2.16 2.15 2.14 2.13 1.26 1.25 1.23
CDCl3, 400 MHz
N
CF3
N
N
EtO2C
11
0.96 1.00 1.04 3.10 1.05 1.03 1.02 2.11 2.09 2.15 3.24 1.10 2.10 1.14 1.08 3.78
0.0 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


162.61
156.86
155.57
149.76
147.56
138.84
137.48
137.00
136.92
136.83
136.74
136.42
136.11
135.80
134.42
131.62
131.04
128.98
127.47
124.74
124.45
122.28
122.01
120.47
119.27
118.53
118.48
118.43
118.38
77.48
77.16
76.84
61.45
44.95
44.70
32.15
30.88
30.69
26.45
14.76
CDCl3, 100 MHz
CF3
N
N
N
EtO2C
11
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



$CDCl_3$, 376 MHz

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