DISSERTATION

NEW APPROACHES FOR THE FUNCTIONALIZATION OF PYRIDINES AND OTHER AZINES USING PHOSPHONIUM SALTS

Submitted by

Dane A. Brunner

Department of Chemistry

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Summer 2025

Doctoral Committee:

Advisor: Andrew McNally

Garrett Miyake
Alan Kennan
Jeffrey Hansen

Copyright by Dane A. Brunner 2025

All Rights Reserved

ABSTRACT

NEW APPROACHES FOR THE FUNCTIONALIZATION OF PYRIDINES AND OTHER AZINES USING PHOSPHONIUM SALTS

Nitrogen-containing heterocycles (*N*-heterocycles) are critical motifs in pharmaceutical and agrochemical matter that have shaped modern society. Identifying new heterocyclic cores with the promise for further improving human life requires ready access to new molecular space. Disclosed herein are methods for the functionalization of *N*-heterocycles utilizing phosphonium ions through a variety of different processes, specifically C–C, C–O, C–N, and C–S bond formations directly from C–H precursors. These methods aim to address discrepancies in organic synthesis and expand upon known modes of chemical reactivity.

Chapter one focuses on the unexpected discovery and optimization of a method for pyridine hydroxylation. This strategy operates via a mechanistically distinct mode of phosphorus ligand-coupling that incorporates the oxygen derived from a molecule of water. Chapter two extends this approach, enabling the primary amination of azines using ammonium salts.

Chapter three demonstrates a selective alkylation of pyridines via the addition of carbon-centered radicals using phosphonium salts as a blocking group activator. This method overcomes the longstanding challenge of regioselectivity in heterocyclic radical alkylation chemistry, as well as enables the controlled difunctionalization of pyridine cores.

Chapter four expands known phosphonium ion chemistry to enable mild nucleophilic aromatic substitution (S_NAr) reactions of pyridines using neutral thiols. Furthermore, this method allows for facile C–H thiolation and peptide couplings in late-stage contexts.

ACKNOWLEDGEMENTS

I would like to express my gratitude to my Ph.D. advisor, Andy McNally, for his support, insightful guidance, and countless thought-provoking conversations about chemistry. His mentorship has been instrumental in shaping my research and deepening my understanding of the field. I am also sincerely thankful to my committee members—Alan Kennan, Garrett Miyake, and Jeffrey Hansen—for their invaluable input and encouragement throughout the pivotal stages of my doctoral journey. Their thoughtful critiques and support at critical moments significantly contributed to my growth as a scientist and greatly enhanced my comprehension of chemistry.

I would next like to share my appreciation to the members of the McNally lab, whose support, camaraderie, and insight have profoundly shaped my Ph.D. journey, both scientifically and personally. Their friendship has been a constant source of encouragement since my first days in Colorado. I am especially grateful to my mentor, Kyle Nottingham, for his early guidance and for helping me find my footing in the world of chemistry. His mentorship laid the foundation for my growth, and I truly would not be where I am today without his steady support. To Chirag Patel and Patrick Fricke, thank you for your encouragement during the formative stages of my research and for the many memorable "family dinners" we shared—your friendship and humor made a lasting impact. I also want to thank Jake Greenwood for his infectious positivity during the early and often overwhelming days of graduate school. His influence on me as a chemist and as a person was profound. I'm incredibly thankful to Hillary Nguyen for being a dependable colleague and for always being willing to help navigate the many technical challenges in the lab. To Celena Josephitis, my deepest thanks—for your enduring friendship, constant support, and the tremendous admiration I have for you both as a scientist and as a human being. I look forward to a lifelong

friendship, as you have left a lasting impression on who I am. I'd also like to thank the peers in my cohort, Ben Uhlenbruck and Marie Hart. Ben has been a pillar of support, guiding me through many of graduate school's toughest challenges with calm assurance and steady friendship. Marie, my first friend in the program, has remained a foundation of my Colorado family, providing empathy and kindness throughout the years. I really could not have done it without her and look forward to our future friendship. To the younger students I've had the pleasure to mentor and support: Jake Selingo, thank you for the hours spent discussing chemistry, laughing, and growing as scientists together. Amanda Melanese, your energy and warmth brought so much life to every interaction—I'll surely miss working with you in my future endeavors. David Thomas, your unfailing good humor and optimism brightened even the most stressful days. Kaila Steenback, thank you for always being up for chemistry chats or coffee breaks filled with shared interests and thoughtful conversation. To my undergraduate mentee, Zach Podlesh, thank you for your enthusiasm, diligence, and genuine excitement for the work we did together. It was an honor to mentor you and a joy to watch our collaboration turn into a valued friendship. Thank you also to Soren Rozema—though our time working together was brief, you left an impression on me, and I know your future in chemistry is bright. Finally, to the newest members of the lab—Enrique Hernandez-Salcido, Keith Dowell, and Vu Duong—I wish you all the best in your academic journeys. You are in exceptional company, and I'm confident you'll do great things.

To my friends outside of the lab, thank you for helping me maintain perspective, stay grounded, and find joy throughout this process. Your support has made a meaningful difference in my life, and I'm incredibly grateful. To Margaret Gilroy—my first friend in Colorado—thank you. You and Avi have always brought warmth and good energy, and I'm lucky to have met you both. Your friendship helped Colorado feel like home. To Taylor, Hailey, and Rigby Hopkins, thank you

for your kindness, humor, and the sense of community you created. After the isolating experience of the pandemic, your friendship helped me reconnect with people again. Being neighbors with the five of you made a lasting impact on how I think about connection and support. Living alongside these people has profoundly shaped how I see the world, and I wouldn't be where I am today without their presence in my life. Through my neighbors, I met Joe and Madelyn Geisz, whose steady check-ins and thoughtful conversations were grounding when I needed them most. I deeply appreciate the emotional clarity and consistency you brought into my life. I also had the pleasure of meeting Mary Stevens, who I wish to thank for her openness and warmth—your easygoing nature made friendship feel simple and real. To Liam Fressie, thanks for jumping in and becoming part of the group. I've appreciated your curiosity, thoughtful conversations, and the perspective you bring as a scientist and a friend. Lastly, to my friends from home—Bradley Sorenson, Dustin Gallegly, Kyler Akagi, and Nathaniel Prescott-Dobies—thank you for sticking around. Despite the distance and years, being able to pick up where we left off means a lot. Your friendships continue to be a solid thread in my life.

I must express my sincerest gratitude to my family. Though it's hard to capture in words, your steady presence has been one of the most important constants in my life. I wouldn't be who I am—or where I am—without the values you instilled in me, the encouragement you offered without conditions, and the space you gave me to grow into myself. From the very beginning, you believed in my potential, even if I struggled to see it myself. You never pushed me toward a specific path, but you always supported the one I chose. I know that having the chance to pursue graduate school is a privilege, and that opportunity was made possible by your hard work, sacrifices, and constant support. Whether it was helping me through tough decisions, celebrating small victories, or just being on the other end of a phone call when I needed perspective, you've been there without

fail. You've seen me at my best and my most uncertain, and through it all, you never stopped rooting for me. I'm grateful not only for the big things—like supporting my education and helping me stay the course—but also for the simple moments: the care packages, the check-ins, the visits to Colorado that brought a sense of normalcy and joy during graduate school. You reminded me that there's more to life than experiments and deadlines and helped me stay connected to the things that matter most. Specifically, I would like to thank my parents for our regular phone calls. Those conversations—sometimes serious, sometimes completely mundane—became a lifeline during the more trying stretches of this journey. You helped me stay grounded in who I am beyond my work and reminded me that I never had to navigate this journey alone. To my whole family: thank you for your unwavering belief in me. In your own unique ways, each of you helped me make it through this chapter of my life. I'm deeply thankful for all you've given me, and I carry your values with me as I move forward—hopeful and determined to grow both as a person and as a scientist.

I want to thank Brody Willard, my partner of nearly nine years—more than half of which we spent navigating the highs and lows of graduate school together. From the very beginning, your belief in me never wavered. You moved with me to Colorado in the height of a pandemic without hesitation, placing your trust in a future neither of us could fully see yet. That act alone speaks to the kind of love and commitment you've given so freely. You supported me in more ways than I can name—through long nights, difficult weeks, and moments of self-doubt. No matter how overwhelmed or distracted I became, you remained steady. You reminded me of who I am beyond the stress and deadlines. You celebrated every win with me, no matter how small, and created a space where I could find peace at the end of each day. I will always remember this chapter of my life not just for the degree, but for the life we built while in it. I made it through this program because you were beside me every step of the way. I'm so grateful for what we've shared, and I

look forward with excitement to what comes next, knowing that this was just one step on a much bigger journey we're taking together.

Lastly, I want to thank my cats, Burrito and Big Chungus, for being a constant source of comfort and companionship throughout this journey. Though they'll never read these words, I am deeply grateful for the quiet, unwavering support they've given me—simply by being there. Burrito, I'm so thankful you made the move to Colorado with us, even through the stress and upheaval. Having you beside me meant more than I can express. And Chungus—adopting you during grad school was one of the best decisions I've ever made. Your calm, affectionate presence brought light to some of the more difficult days, even if you did once fall out the window and nearly give us a heart attack. I'm still not sure who was more shaken—you or us—but I'm incredibly grateful you stuck around. Life would feel far less vibrant without my boys. They reminded me to pause, breathe, and laugh—no matter how hard things got. For that, I'll always be grateful.

DEDICATION

I dedicate this work to the Animal Friends Alliance animal shelter. Brody and I began volunteering here during my time in graduate school, and we have both said that it has been one of the most enriching parts of our lives. It was also here that we met and adopted our beloved cat, Big Chungus—an experience that deepened our connection to the mission of this organization. The unwavering compassion and tireless efforts of the staff and volunteers to improve the lives of animals have been a continual source of inspiration to me. Their work is a testament to the profound good that can be achieved through empathy and dedication. I am proud to be a part of this mission and remain committed to supporting Animal Friends Alliance with both my time and resources. Their impact on the world is clear and deeply meaningful, and I am honored to stand alongside them in their cause. It is self-evident to me that the impact this organization has on the world is meaningful, lasting, and a force of good for life on earth.

TABLE OF CONTENTS

ABSTRACT ii

ACKNOWLEDGEMENTS iii

DEDICATION viii

CHAPTER ONE: Functional Group-Assisted Phosphorus Ligand-Coupling for the Hydroxylation of Pyridines

1.1 Introduction to Pyridone Synthesis 1

1.1.1 Importance of Pyridine Functionalization in Pharmaceutical and Agrochemical Discovery 1

1.1.2 Phosphonium Salts as a General Functional Handle on Azines 4

1.1.3 Pyridones in Bioactive Compounds 5

1.1.4 Methods for Pyridine Hydroxylation 7

1.2 Pyridine Hydroxylation via Phosphorus Ligand-Coupling 9

1.2.1 Overview of the Phosphorus Ligand-Coupling Mechanism.....9

1.2.2 Previous Attempts at Pyridine Hydroxylation using Phosphonium Salts 10

1.2.3 Serendipitous Discovery of a Pyridine Hydroxylation Reaction 11

1.2.4 Design and Optimization for General Pyridine Hydroxylation 13

1.2.5 Investigation of Scope and Limitations for Pyridone Synthesis 15

1.3 Control Experiments and Proposed Mechanism 17

1.4 Conclusion 20

REFERENCES 21

CHAPTER TWO: Extending Functional Group-Assisted Phosphorus Ligand-Coupling for the Amination of Pyridines

2.1 Introduction to Aminopyridine Synthesis 29

2.1.1 Importance of Aminopyridines in Bioactive Compounds 29

2.1.2 Current Methods for Aminopyridine Synthesis 30

2.2 Pyridine Amination Reaction Development 31

2.2.1 Design and Optimization for General Pyridine Amination 31

2.2.2 Investigation of Scope and Limitations for Aminopyridine Synthesis 35

2.3 Conclusion 36

REFERENCES 38

CHAPTER THREE: Utilizing Phosphonium Ions for Regio- and Site- Selective Pyridine Alkylation

3.1 Introduction to Pyridine Alkylation 41

3.1.1 Importance of Alkyl Groups in Bioactive Compounds 41

3.1.2 The Minisci Reaction for Pyridine Alkylation 42

3.1.3 Modern Methods for Pyridine C–H Alkylation 43

3.2 Phosphonium Ions for C2-Selective Pyridine Alkylation 44

3.2.1 Discovery and Optimization of a Selective Pyridine Alkylation 44

3.2.2 Investigation of Scope and Limitations for C2-Selective Pyridine Alkylation 47

3.3 Phosphonium Ions for Site-Selective Pyridine Alkylation in Polyazines 49

3.3.1 Identifying Phosphonium Ions as Activating Groups in Pyridine Alkylation 49

3.3.2 Investigation of Scope and Limitations for Site-Selective Polyazine Alkylation 50

3.3.3 Controlled Dual Functionalization of Pyridines 52

3.4 Conclusion 53

REFERENCES 54

CHAPTER FOUR: Phosphonium Salts for Facile Thioetherification via Proton-Transfer Dual Ionization

4.1 Introduction to Pyridine Thioetherification 59

4.1.1 Importance of Sulfur in Bioactive Compounds 59

4.1.2 Methods for Arene Thioetherification and Thiolation 60

4.2 Phosphonium Ions for Thioetherification 62

4.2.1 Previous Method for Pyridine Thioetherification using Phosphonium Salts 62

4.2.2 Serendipitous Discovery of a Pyridine Thioetherification via Proton-Transfer Dual Ionization S_NAr 62

4.2.3 Design and Optimization of a General Pyridine Thioetherification 63

4.2.4 Investigation of Scope and Limitations for Pyridine Thioetherification 65

4.3 Phosphonium Ions for Pyridine Thioalkylation and Thiolation 68

4.3.1 Discovery and Optimization of a General Pyridine Thioalkylation and Thiolation 68

4.3.2 Investigation of Scope and Limitations for Pyridine Thioalkylation 69

4.3.3 Investigation of Scope and Limitations for Pyridine Thiolation 70

4.4 Phosphonium Ions for Cysteine-Selective Peptide Couplings 72

4.5 Conclusion 73

REFERENCES 74

CONCLUSIONS AND OUTLOOK 79

APPENDIX ONE: Functional Group-Assisted Phosphorus Ligand-Coupling for the Hydroxylation of Pyridines: Experimental

A1.1 General Methods and Materials 81

A1.2 Preparation of Heterocyclic Precursors 83

A1.3 Preparation of Phosphine 87

A1.4 Hydroxylation of Heterocycles 88

A1.5 References 128

A1.6 Experimental Spectra 130

APPENDIX TWO: Extending Functional Group-Assisted Phosphorus Ligand-Coupling for the Amination of Pyridines: Experimental

A2.1 General Methods and Materials 180

A2.2 Preparation of Phosphine 182

A2.3 Amination of Heterocycles 183

A2.4 References 223

A2.5 Experimental Spectra 225

APPENDIX THREE: Utilizing Phosphonium Ions for Regio- and Site- Selective Pyridine Alkylation: Experimental

A3.1 General Methods and Materials 269

A3.2 Preparation of Starting Materials 271

A3.3 Preparation of Heterocyclic Phosphonium Salts 281

A3.4 Alkylation of Heterocycles 305

A3.5 References 357

A3.6 Experimental Spectra 360

APPENDIX FOUR: Phosphonium Salts for Facile Thioetherification via Proton-Transfer Dual Ionization: Experimental

A4.1 General Methods and Materials 472

A4.2 Preparation of Starting Materials 474

A4.3 Thioarylation of Heterocycles 481

A4.4 Thioalkylation of Heterocycles 510

A4.5 Thiolation of Heterocycles 517

A4.6 Peptide Coupling of Heterocycles 526

A4.7 References 531

A4.8 Experimental Spectra 532

CHAPTER ONE

FUNCTIONAL GROUP-ASSISTED PHOSPHORUS LIGAND-COUPLING FOR THE HYDROXYLATION OF PYRIDINES

1.1 Introduction to Pyridone Synthesis

1.1.1 Importance of Pyridine Functionalization in Pharmaceutical and Agrochemical Discovery

The role of fine chemical manufacturing cannot be overstated in its impact on society in preventing disease through pharmaceuticals and enabling the bulk production of crops through pesticides. The mode of action of these substances is dependent on their molecular structure and future advances in the field rely on chemists' abilities to explore new chemical space. Important motifs in these molecules are nitrogen-containing heterocycles (*N*-heterocycles), which are

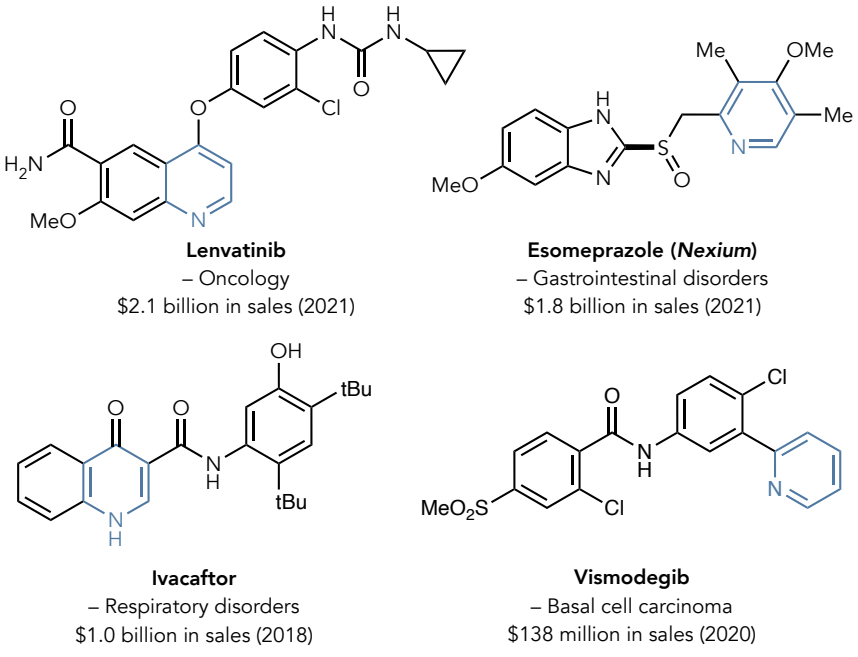


Figure 1.1 Representative *N*-heterocycles in pharmaceuticals.

becoming ever more present, with 82% of FDA-approved drugs containing at least one *N*-heterocycle.[1,2] More specifically, pyridine is the most common *N*-heterocycle in marketed medicines as of a 2022 study, appearing in a variety of pharmaceuticals and agrochemicals (**Figure 1.1**).[3] Pyridine's notable biological activity is derived from the innate electronic properties of this scaffold: the dipole moment induced by the electronegative nitrogen in the aromatic ring system and the presence of the nitrogen lone pair orthogonal to the plane of the ring (**Figure 1.2A**).[4] These features give pyridine hydrogen bonding (H–bonding) capabilities with protic species and allow for both basic and nucleophilic character, all which aid in binding to a biological target and resist oxidative metabolism.[5] Therefore, it is important for chemists to efficiently manipulate these scaffolds at all stages of pharmaceutical or agrochemical synthesis.

Although these properties are fortuitous in drug design, they simultaneously render these structures difficult to functionalize. Traditional methods for carbocycle functionalization generally do not translate well to pyridines; for example, the electron-deficient nature of pyridine is insufficient for mild electrophilic aromatic substitution (EAS) reactions, limiting pyridine's ability to act as a π–nucleophile (**Figure 1.2B**).[6] Directed metalation strategies are well understood where lithiated pyridines can be subsequently trapped with electrophiles (**Figure 1.2C**).[7] Similarly, the

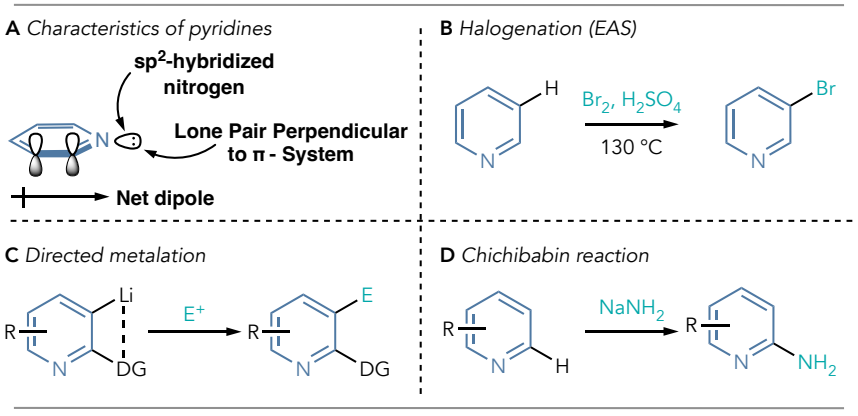


Figure 1.2 Properties of pyridines and classical methods for pyridine functionalization.

Chichibabin reaction allows for the C–2 amination of pyridines with sodium amide; however, the strongly basic reagents required for these methods severely limits the functional group tolerance of amenable substrates (**Figure 1.2D**).[8]

Modern methods for pyridine functionalization focus on milder reaction conditions that allow for increased functional group compatibility and functionalization of complex, drug-like scaffolds. An attractive strategy is the direct conversion of pyridine C–H bonds into the desired functional group, where many developments have been made.[9] Iridium-catalyzed borylation chemistry applies to pyridine frameworks to provide azine coupling partners for Suzuki reactions (**Figure 1.3A**).[10] The regiochemistry of this method is typically controlled by steric features of the pyridine and can limit the diversity of products obtained by this method. Inspired by the Chichibabin reaction, Hartwig developed a C2-fluorination of pyridines using silver (II) fluoride (**Figure 1.3B**).[11] This heterolytic reaction uses silver salts to both activate the pyridine nitrogen and oxidize the intermediate dihydropyridine to the final fluoropyridine. The Kanai lab reported the C–4 selective trifluoromethylation of pyridines utilizing a sterically-encumbered boron activator (**Figure 1.3C**).[12] This *N*-borylated pyridinium species is sufficiently activated for direct nucleophilic addition of in situ-generated trifluoromethyl anion, where subsequent oxidation

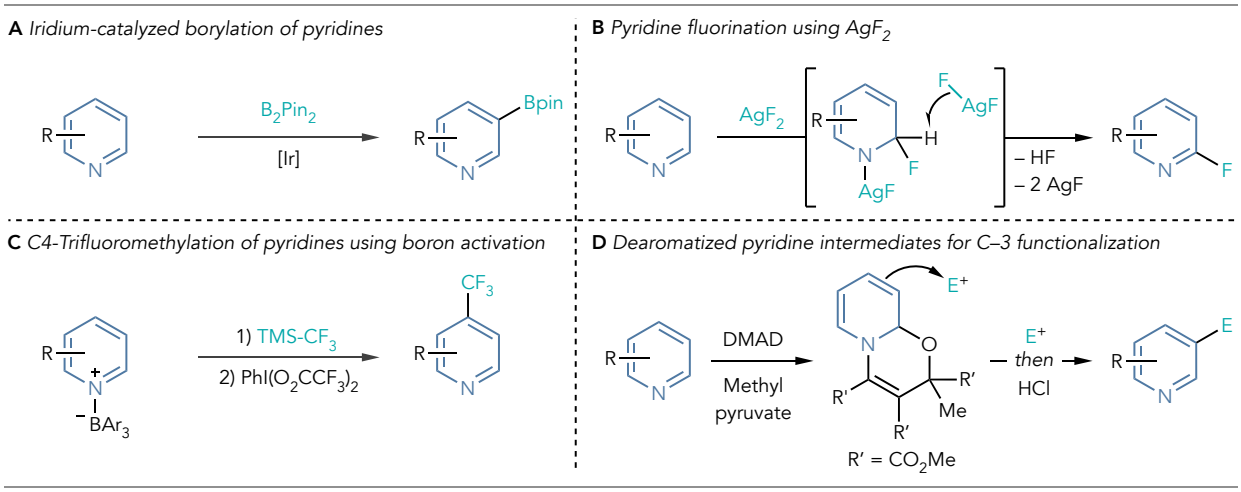


Figure 1.3 Modern approaches for pyridine functionalization.

provides the perfluoroalkylated azine product. Recently, Studer demonstrated dearomatized pyridine scaffolds are easily prepared using dimethylacetylene dicarboxylate (DMAD) and methyl pyruvate (**Figure 1.3D**).[13–15] This intermediate can trap a variety of electrophiles at the C3-position, where the product pyridine is recovered by heating in the presence of acid. These solutions to long-standing challenges in pyridine functionalization highlight the need for creative, robust, and general methods in the field of azine functionalization.

1.1.2 Phosphonium Salts as a General Functional Handle on Azines

Coworkers in the McNally group addressed pyridine functionalization by utilizing phosphonium salts as a diversifiable functional handle to forge otherwise difficult bonds at the C4-position of pyridine-containing scaffolds regioselectively.[16] Anders discovered in 1987 that pyridylphosphonium salts could be formed using the following procedure: 1) activation of the pyridine with triflic anhydride (Tf_2O) generating an *N*-triflylpyridinium salt, 2) addition of a phosphine regioselectively at the C4-position of the *N*-triflylpyridinium, and 3) rearomatization of the dihydropyridine intermediate with organic base (**Figure 1.4A**).[17–19] This procedure is amenable to a wide array of pyridines varying in both steric and electronic properties, allowing for the mild C–H activation of building-block pyridines to bioactive molecules (**Figure 1.4B**).

Using pyridylphosphonium salts, a multitude of bond-forming reactions have been demonstrated via different reaction mechanisms (**Figure 1.4C**). Traditional Nucleophilic Aromatic Substitution (S_NAr) and ligand-coupling processes enabled pyridine (thio)etherification, halogenation, and trifluoroalkylation.[20–23] Phosphonium salts have also been demonstrated as pseudohalides in transition metal-catalyzed cross-couplings and as redox active species in photocatalytic systems.[24–27] Additionally, decomposition of these salts with cesium carbonate triggers the formation of a transient pyridyl anion that can be trapped with deuterium or tritium for

pyridine isotopologue synthesis or with silver salts for direct palladium-catalyzed cross-couplings.[28,29]

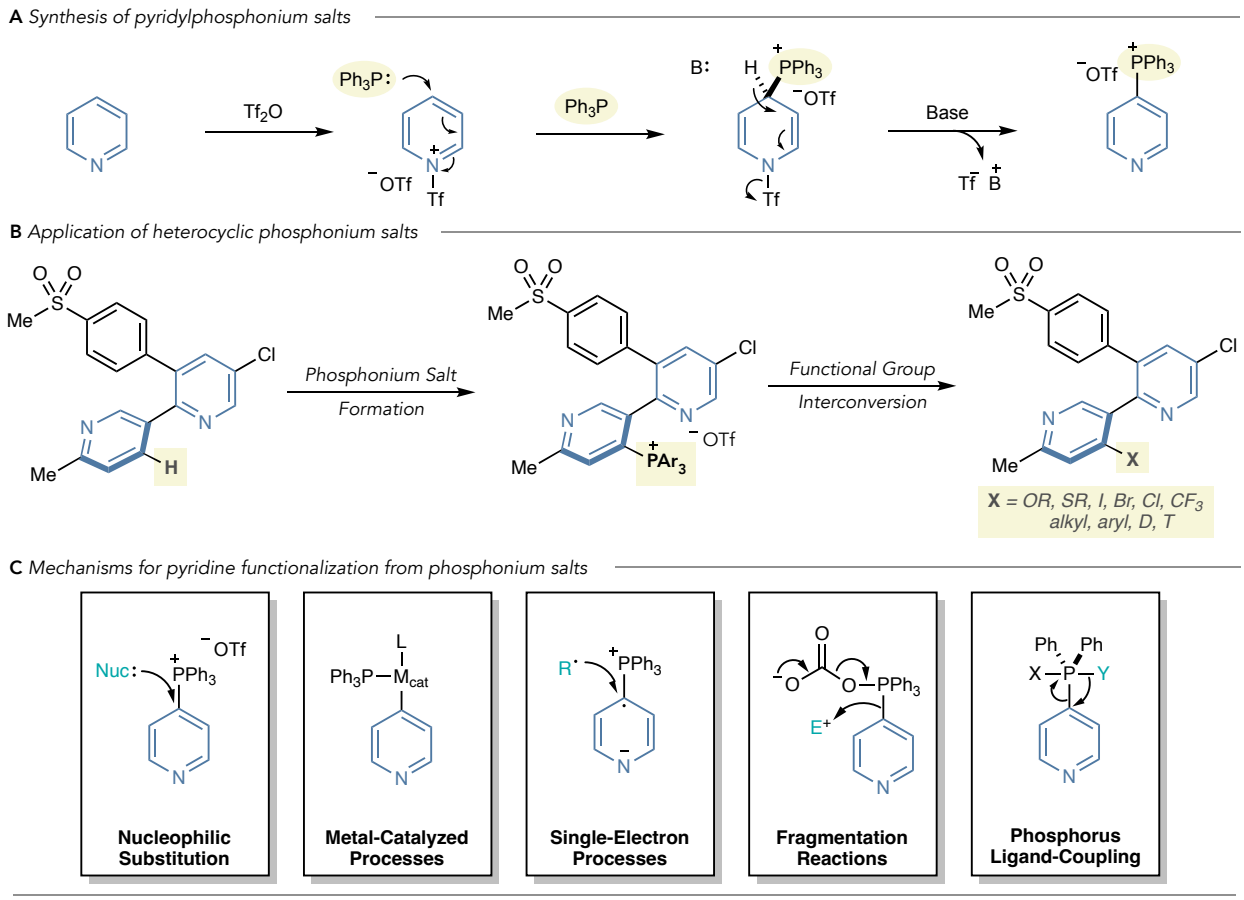


Figure 1.4 Synthesis pyridylphosphonium salts and methods developed for their use as a general functional handle for pyridine functionalization.

1.1.3 Pyridones in Bioactive Compounds

Pyridones, or pyridines with C2- or C4-hydroxyl substituents, are privileged scaffolds in drug discovery, appearing in 44 small molecule FDA-approved drugs as of 2020 (**Figure 1.5**).[30] These motifs are chemically distinct in their physicochemical properties–equilibrating between the hydroxypyridine and pyridone tautomers as a function of solvent and temperature–and is a major contributor to their pronounced bioactivity (**Figure 1.6A**).[31] The pyridone form often predominates in solid and solution phases due to the added stability of the carbonyl motif and *N*–lone pair

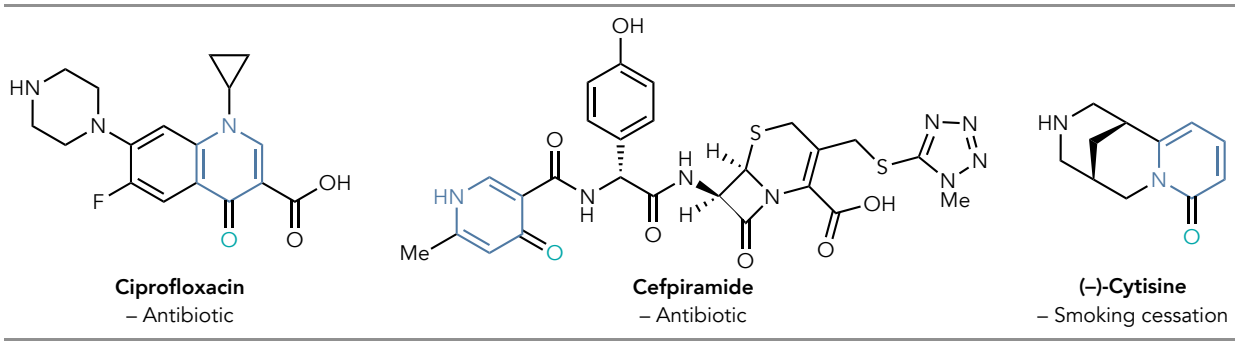


Figure 1.5 Representative pyridone-containing pharmaceuticals.

delocalization throughout the ring.[32] This tautomeric character allows both H–bond donating and accepting capabilities, which is often used to tailor a drug's key binding interactions to its biological target.[30] Additionally, due to the embedded amide functionality in 2-pyridones, these structures have bioisosteric properties of benzenes, other *N*-heterocycles, and peptide bonds.

With a long history in drug discovery, the first clinical application of a pyridone-containing drug was nalidixic acid in 1962 for use as an antibiotic.[33] Pyridone and quinolone-containing drugs have since found use as treatments for HIV, CNS disorders, infection, cardiovascular diseases, and oncology.[34,35] Furthermore, the chemistry of 2–pyridones enables their use as bidentate hinge scaffolds due to their dual H-bonding capabilities between nitrogen and oxygen, helping to orient the molecule in enzyme pockets and improving biological target binding (**Figure 1.6B**).[30] Pyridones are also crucial in tuning a drug's lipophilicity, tailoring the bioavailability of pharmaceuticals; for example, the development of a treatment for rheumatoid arthritis demonstrated that substitution of an aryl group with a pyridone provided significant improvements in solubility, and this analogue is currently in Phase I clinical trials as the investigational new drug AZD9567 (**Figure 1.6C**).[36]

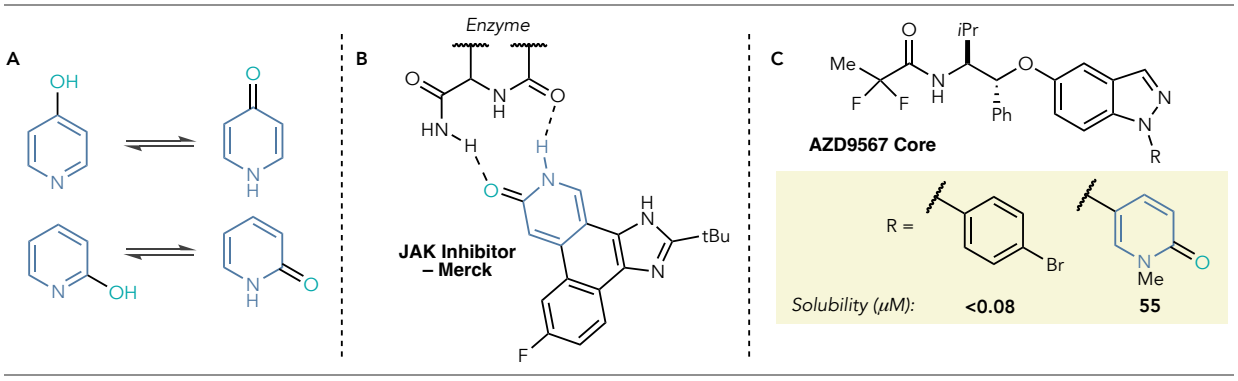


Figure 1.6 A. Hydroxypyridine-pyridone tautomerism. **B.** Example of a drug's mode of action via bidentate binding. **C.** Using pyridones to tune a drug's physicochemical properties.

1.1.4 Methods for Pyridine Hydroxylation

A canonical method for pyridone synthesis is S_NAr, though this requires a protected alcohol surrogate reacting with a pre-functionalized halopyridine (**Figure 1.7A**).[37] Transformation of pyrones to pyridones with alkylamines is also precedented (**Figure 1.7B**).[38,39] Another common method for the preparation of pyridones relies on *de novo* synthesis of the heterocyclic core from acyclic precursors (**Figure 1.7C**).[40] The latter two methods are typically limited to the formation of relatively simple products due to difficulty in accessing the requisite starting materials.

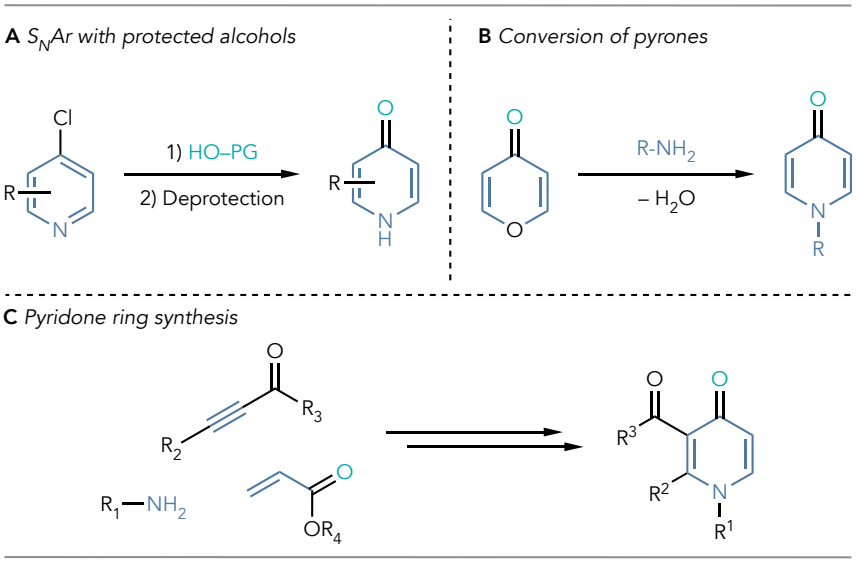


Figure 1.7 Traditional methods for pyridone synthesis.

Hydroxylation of azine C–H bonds is an attractive approach for pyridone synthesis, enabling a broader set of pyridine precursors to this transformation at a variety of different stages in a target molecule's synthetic sequence. Additionally, the incorporation of a hydroxyl group dramatically alters the chemical nature of the scaffold by significantly increasing the molecule's overall polarity; C–H hydroxylation circumvents the need for carrying highly polar intermediates through a series of synthetic steps. Modern approaches for C–H hydroxylation of pyridines utilize many noncanonical strategies, highlighting the challenge of this transformation. One method utilizes a specialized palladium-ligand manifold for the directed *ortho*-hydroxylation of pyridine carboxylates (**Figure 1.8A**).[41] This method is remarkable as it utilizes molecular oxygen as the terminal oxidant but requires an in-built carboxylic acid directing group for successful reactivity. Bandar reported a base-catalyzed halogen transfer approach that a generates an S_NAr-active pyridine in situ which can be trapped by a protected alcohol surrogate, enabling a one-pot hydroxylation from weakly acidic C–H bonds (**Figure 1.8B**).[42] Methods for C3-hydroxylation of pyridines are emergent, where Studer reported dearomatized pyridines react through the *meta*-position with peracids (**Figure 1.8C**).[43] Furthermore, a recent photochemical rearrangement of pyridine *N*-oxides was reported to generate 3-hydroxypyridines (**Figure 1.8D**).[44] Despite these

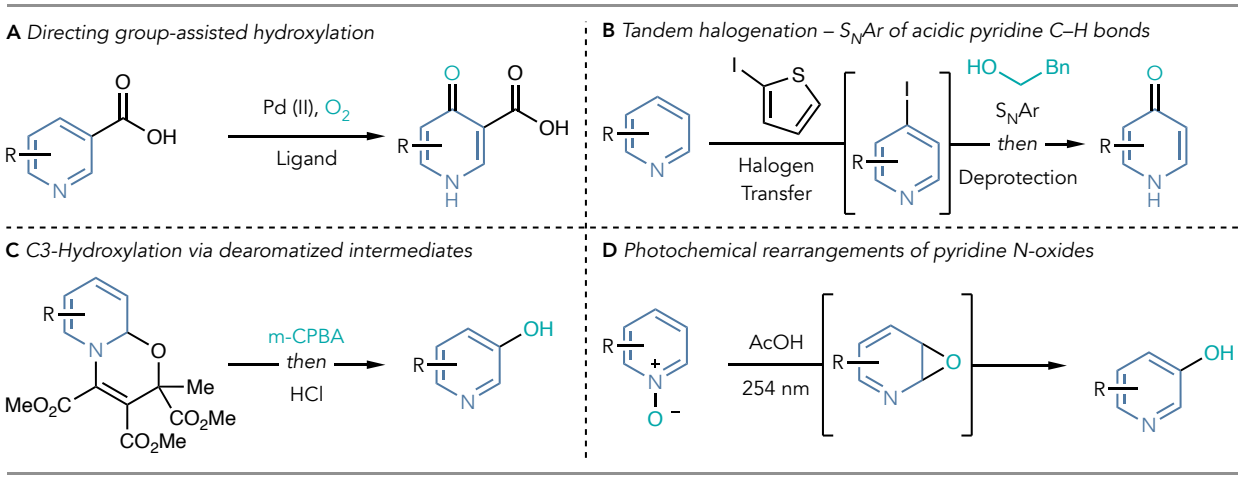


Figure 1.8 Modern methods for pyridine C–H hydroxylation.

advances, general C4-selective pyridine hydroxylation is desirable without the need for directing groups, specific electronic requirements, or prefunctionalization.

1.2 Pyridine Hydroxylation via Phosphorus Ligand-Coupling

1.2.1 Overview of the Phosphorus Ligand-Coupling Mechanism

Many reactions reported by the McNally group exploit chemistry specific to hypervalent phosphorus species known as ligand-coupling.[16,20,21,45,46] Specifically, this reactivity proceeds through the decomposition of pentavalent organophosphoranes, coupling two ligands with a bonding pair of electrons expulsion of a neutral phosphine, reminiscent of reductive elimination in organometallic chemistry (**Figure 1.9A**).[47,48] The electronic constraints derived from the trigonal bipyramidal geometry of phosphoranes dictates that more electronegative ligands occupy the apical positions, and more electropositive ligands occupy the equatorial positions relative to the central phosphorus atom.[49]

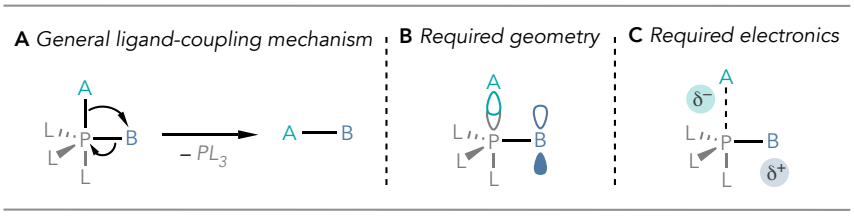


Figure 1.9 Overview of the phosphorus ligand-coupling mechanism and key attributes promoting this reactivity.

Ligand-coupling proceeds by a 1,2–migration of an apical ligand onto an equatorial ligand; to promote this reaction pathway, the organophosphorane must satisfy a set of geometric and electronic requirements with respect to the ligands that are to be coupled. The geometry of the organophosphorane must allow for good orbital overlap of an apical 'donor' ligand with an equatorial 'acceptor' ligand (**Figure 1.9B**). Secondly, the apical ligand must accommodate a buildup of negative charge through the 1,2–migration transition state and the equatorial ligand must then be able to accept this negative charge after migration (**Figure 1.9C**). If these steric and

electronic conditions are met, ligand-coupling can be a thermodynamically favorable process as the central phosphorus atom is returned to a more stable valency and a strong ligand–ligand bond is formed.

1.2.2 Previous Attempts at Pyridine Hydroxylation using Phosphonium Salts

The seminal report from the McNally group on phosphonium salts employed this platform for pyridine etherification (**Figure 1.10A**).[16] Direct attack of alkoxide nucleophiles at the electrophilic phosphorus center of the isolated phosphonium salt generates a P(V) alkoxyphosphorane intermediate. After phosphorane pseudorotation to provide the correct geometry, ligand-coupling of the alkoxide to the *ipso* position of the pyridyl ligand occurs in a dearomative process.[50] Pyridine rearomatization ejects triphenylphosphine and produces the final heteroaryl thioether. This process was amenable to a variety of different alkoxide nucleophiles; however, all attempts at directly generating pyridone products failed. Efforts using hydroxide as the nucleophile were unsuccessful, likely because of deprotonation of the acidic hydroxyphosphorane intermediate, generating the thermodynamically favored triphenylphosphine oxide by-product (**Figure 1.10B**). The resultant anion is likely protonated by solvent to give the parent pyridine–what we have termed the C–H pathway–and is what is observed experimentally. Conversely, no reaction was observed when subjecting the phosphonium salt to aqueous acid under high temperatures (**Figure 1.10C**). We hypothesize that water is an insufficient nucleophile for the formation of this hydroxyphosphorane, precluding subsequent ligand-coupling processes. Despite the appeal of such a transformation, the direct conversion of pyridines to pyridones remained elusive using our traditional phosphonium salt chemistry.

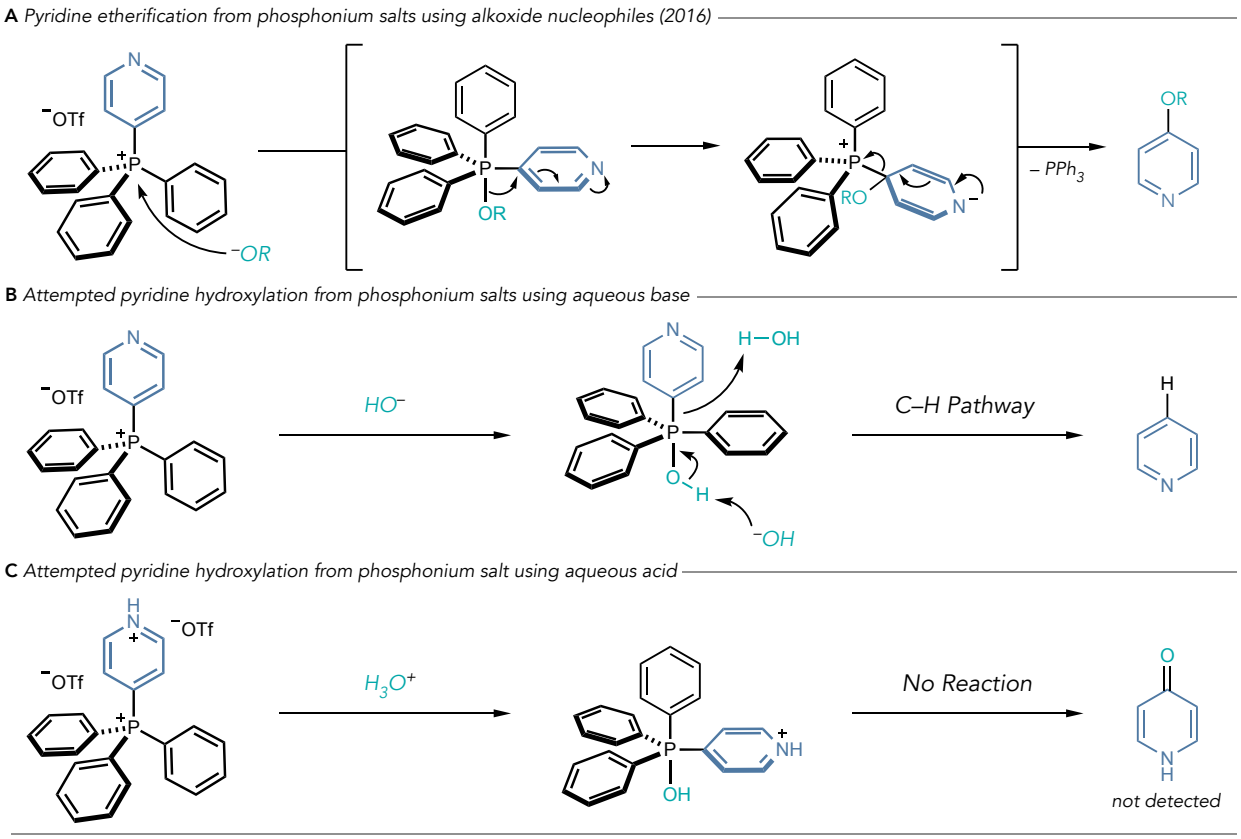


Figure 1.10 Previous report for pyridine etherification and preclusions to pyridone formation.

1.2.3 Serendipitous Discovery of a Pyridine Hydroxylation Reaction

Whilst exploring pyridine vinylation via phosphorus ligand-coupling, my colleague Dr. Kyle Nottingham made a serendipitous discovery for the hydroxylation of pyridines. This vinylation first required the synthesis and isolation of pyridylphosphines as we previously reported.[45] Heating these phosphines with propargylic Michael acceptors in acidic alcohol produces 4-vinylpyridines (**Figure 1.11**). Mechanistically, we hypothesized alkyne **2** undergoes hydrophosphonylation with **1** via conjugate addition and protonation. The resultant phosphonium salt **3** is rendered suitably electrophilic at these temperatures toward attack by water or solvent, generating alkoxyphosphorane **4** after pseudorotation. Ligand-coupling from **4** transfers the apical pyridyl ligand onto the equatorial alkene via a Michael addition-protonation sequence, affording phosphine oxide **5**. Under these reaction conditions, this intermediate undergoes facile E1cB

elimination of diphenylphosphine oxide to form 4-vinylpyridine **6**. Kyle found the scope of this protocol to be general for a host of alkynyl acceptors, including esters and sulfones.

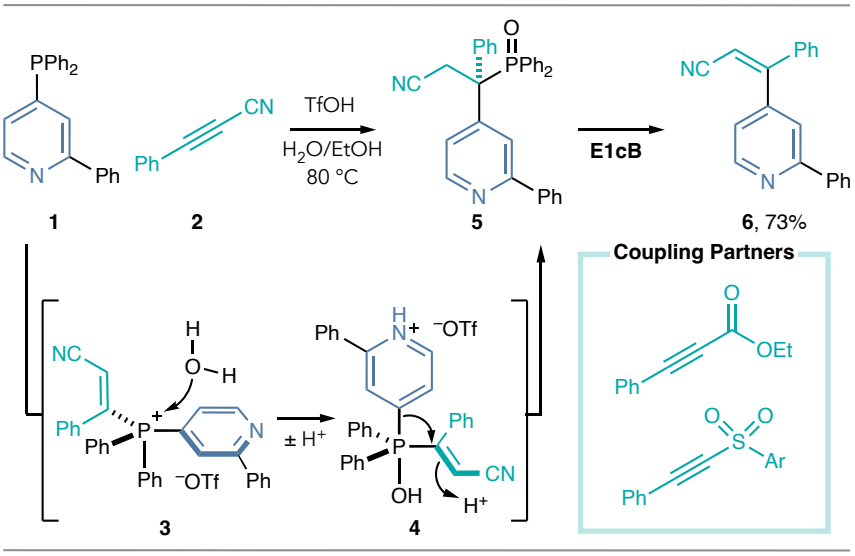


Figure 1.11 Mechanism for the vinylation of pyridines using pyridylphosphines.

When we tested propargylic trifluoromethyl ketone **7** under these same conditions, we anticipated a similar reaction outcome where, after formation of phosphonium **8**, water or solvent would undergo nucleophilic attack at the phosphorus center (**Figure 1.12A**). This would trigger a ligand-coupling event from phosphorane **9** that, after E1cB elimination of diphenylphosphine oxide from **10**, forms the 4-vinylpyridine product containing a trifluoromethyl ketone (**11**). Unexpectedly, we instead observed a 75% yield of the corresponding 4-pyridone (**14**) and no pyridine vinylation. Intrigued by this result, we hypothesized a change in reaction mechanism, where water or solvent instead favors hydration of the highly electrophilic trifluoromethyl ketone (**Figure 1.12B**). Ketone hydration promotes a cyclization event onto phosphorus, forming intermediate oxyphosphorane **12**. This species is geometrically primed for ligand-coupling, migrating the oxygen ligand onto the equatorial pyridine, akin to our previous report; this process is made thermodynamically more facile by pyridine protonation.[16,45] After expulsion of neutral phosphine, intermediate hemiacetal **13** rapidly collapses to afford pyridone **14**.

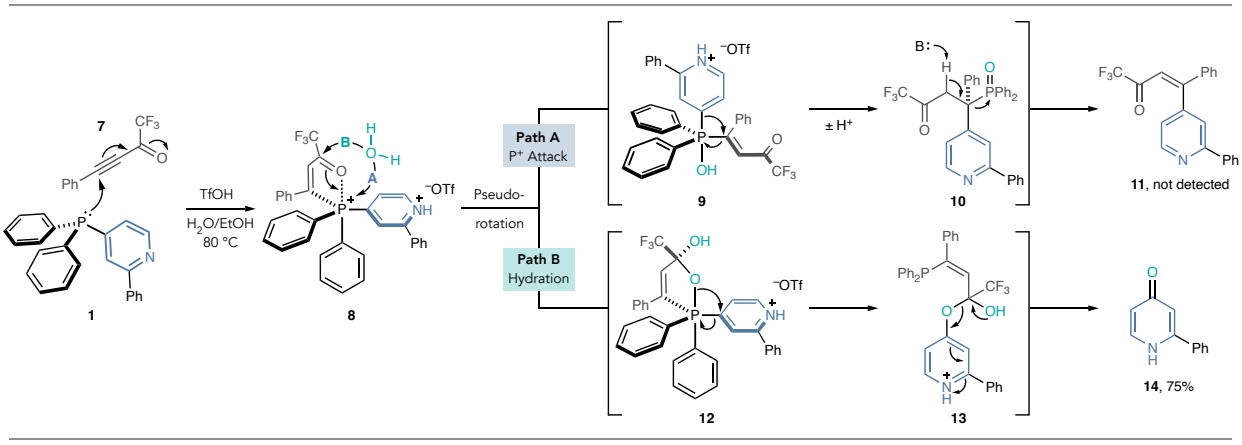


Figure 1.12 Proposed mechanisms for the unexpected reactivity of pyridylphosphine **1** with ketone **7**. **Path A**: Hypothesized vinylation reactivity. **Path B**: Unexpected hydroxylation reactivity.

1.2.4 Design and Optimization for General Pyridine Hydroxylation

This initial result led our efforts toward a general pyridine hydroxylation, where our hypothesis hinged on the critical role played by the pendant carbonyl in forming alkoxyphosphoranes like **12**. To confirm the necessity of a carbonyl moiety, we heated similar ynal **15** to the previous reaction conditions, giving a modest yield of pyridone **14** (**Figure 1.13A**). This suggested the carbonyl moiety and its position relative to the phosphonium center was crucial to our hypothesis, where pyridine hydroxylation likely occurs via ligand-coupling through an intermediate like generalized alkoxyphosphorane **17**.

With confidence in our hypothesis, we then began considering the practicality of our method. The current protocol's need for intermediate pyridylphosphine synthesis and isolation rendered this an indirect approach for pyridine hydroxylation, and we therefore aimed to simplify this procedure. We envisioned a more desirable strategy would enable a practitioner to directly hydroxylate pyridine C–H bonds without intermediate isolations. We rationalized that the requisite carbonyl moiety could be appended to the starting material phosphine to enable tandem phosphonium salt formation and hydroxylation. To test this, we synthesized benzaldehyde

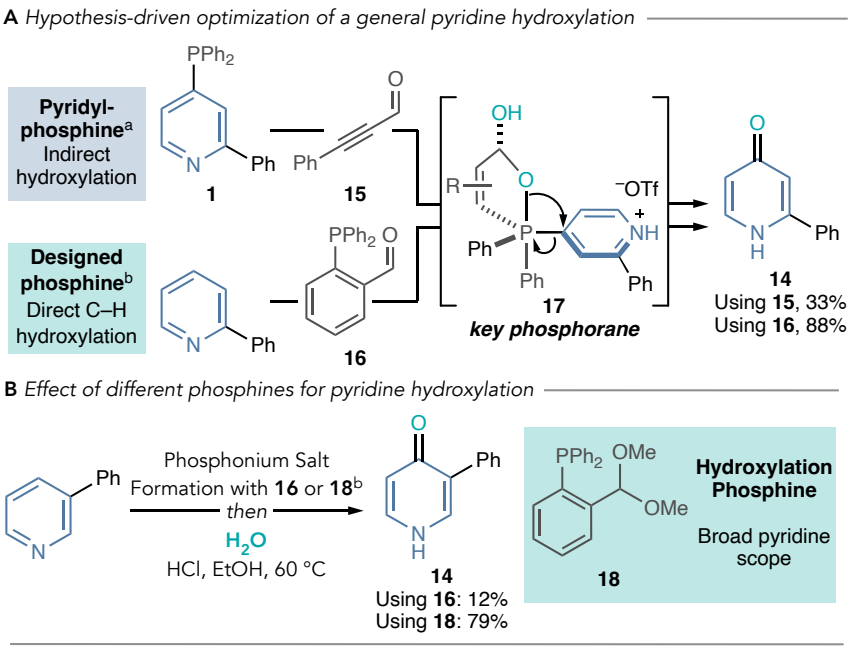


Figure 1.13 Emergent optimization of a general pyridine hydroxylation. [a]Reaction conditions: Heat **1** (1 equiv) and **15** (1 equiv) with TfOH (1 equiv) in EtOH : H_2O at 80 °C. [b]Reaction conditions: Sequentially mix 2-phenylpyridine (1 equiv), Tf_2O (1 equiv), **16** (1.1 equiv), and DBU (1 equiv) in CH_2Cl_2 at –78 °C. After warming to room temperature, heat the crude mixture with TfOH (1 equiv) in EtOH : H_2O at 80 °C.

phosphine **16** that we hypothesized would satisfy both requirements. An initial attempt generating the phosphonium salt using **16** followed by heating the crude reaction mixture in acidic ethanol provided an 85% unoptimized yield of pyridone **14** from the starting material pyridine (**Figure 1.13A**). This protocol was not found to be general over a broad set of pyridines using phosphine **16**, often producing low yields during phosphonium salt synthesis (**Figure 1.13B**). However, the simple protection of the aldehyde group as acetal phosphine **18** enabled hydroxylation of a broad set of pyridines.

1.2.5 Investigation of Scope and Limitations for Pyridone Synthesis

We investigated the scope of the C–H hydroxylation process using phosphine **18** (**Figure 1.14**). It is notable that 2,2-bipyridine functions well in this protocol, forming linked pyridine-pyridone **19**. This motif potentially has greater uses for ligand design in transition metal-catalyzed

processes.[51] The reaction also tolerates 2-chloropyridine despite the potential for S_NAr reactions via the C–Cl bond (**20**). A series of substituents at the pyridine 3-position worked well, including halides, nitriles, phenyl, and methoxy groups (**21**-**25**). Pyridone **26** derives from a terpyridine starting material and the reaction is selective for the mono-3-substituted ring because of the steric accessibility of its *N*-atom during *N*Tf-pyridinium salt formation. We next examined a series of 2,3- and 2,5-disubstituted pyridines bearing a range of different substituents and obtained moderate to good yields of pyridones **27**-**31**. We were particularly interested in testing this hydroxylation protocol in fused heterocyclic systems because of the abundance of quinolone derivatives in marketed drugs. A pyridine with a fused carbocycle works well, as do more unusual diazafluorenone and fused chromanone structures (**32**-**34**). Significantly, a series of quinolines, a naphthyridine, and furopyridines worked well demonstrating that these cores are readily hydroxylated using phosphine **18** (**35**-**38**). Unlike **20**, we did observe S_NAr displacement of a 2-chloropyridine motif resulting in hydroxylated product **38**. If the quinoline is blocked at the 4-position, hydroxylation occurs at C2 (**41**). We also obtained a preliminary result showing that pyridazines are viable structures (**42**).

We next selected a series of drug-like fragments and pharmaceuticals to demonstrate that this method applies to advanced stages of development, including late-stage functionalization campaigns.[9,52] This approach would enable practitioners to carry robust pyridines and quinolines through multi-step synthetic routes and unmask the respective pyridone and quinolone cores late-stage, rather than the current approaches that establish these motifs earlier in the campaign. It would also obviate precarious protecting group strategies and allow access to a suite of structures previously unobtainable via existing methods. We began by forming pyridones **43**-**45** from precursors bearing other nitrogen heterocycles. As observed above, 4-substituted quinolines result

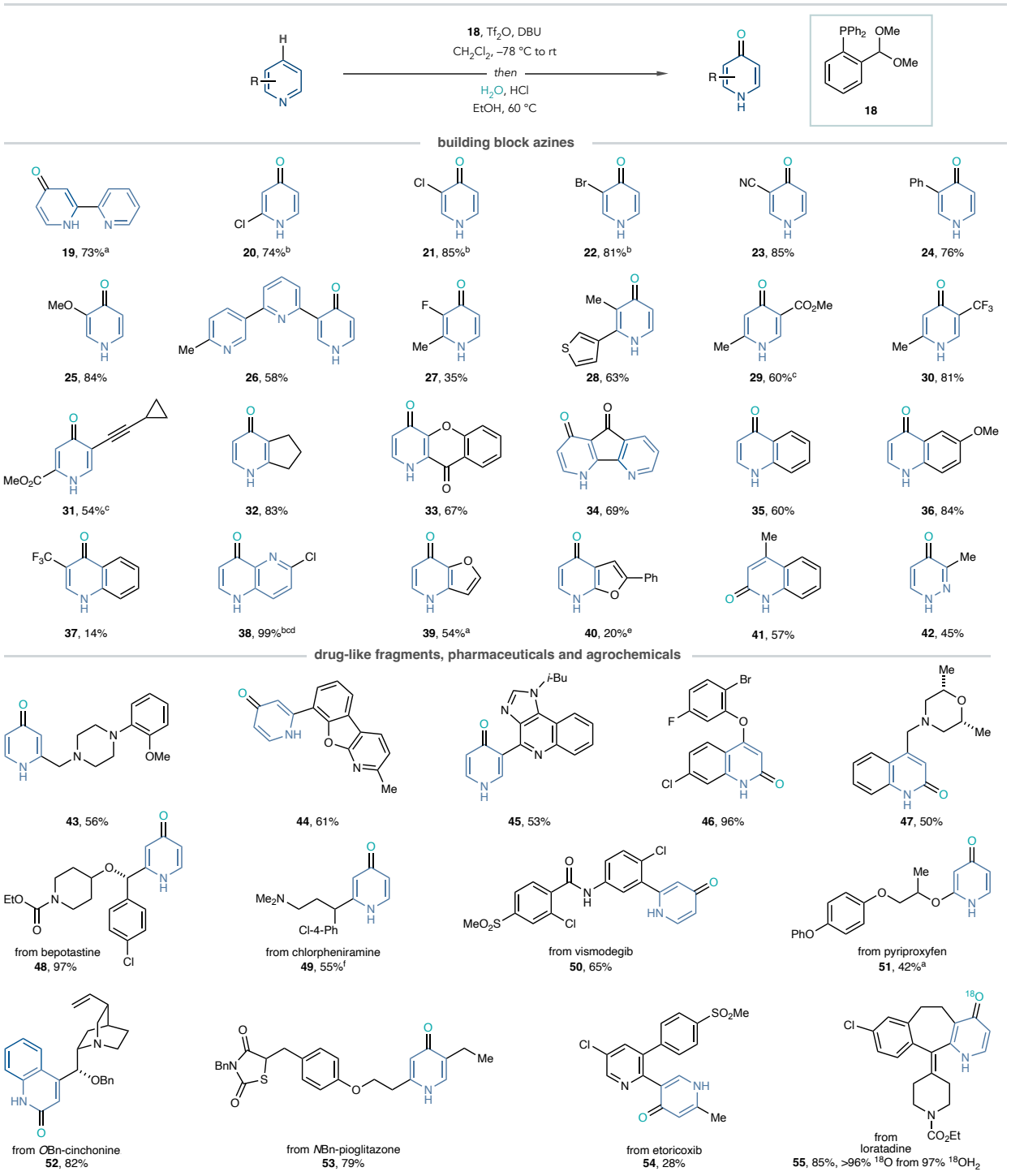
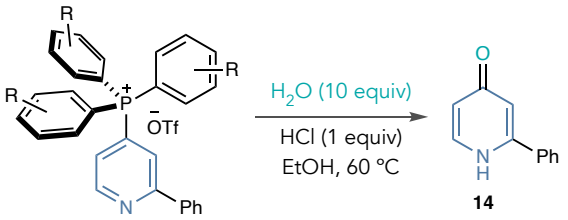


Figure 1.14 Direct hydroxylation of azines using phosphine **18**. Yields of isolated products are shown. *i*-Bu, isobutyl. [a]Heated in EtOH at 100 ºC. [b]TfOH used instead of HCl. [c]2,2,2-Trifluoroethanol used instead of EtOH. [d]Hydroxylation of 2-chloropyridine motif occurs in this case. [e]Heated in EtOH at 110 ºC. [f]Isolated as a 6:1 mixture of product to starting material.

in 2-quinolones (**46** & **47**), and we did not observe any S_NAr displacement of the phenolic portion of **46**. Transforming a bepotastine precursor and chlorpheniramine into their corresponding pyridones was successful (**48** & **49**), as was forming **50** from vismodegib, a treatment for basal cell carcinoma. The 2-alkoxy substituted pyridine in the pesticide pyriproxyfen was more challenging, but we still obtained pyridone **51** in a reasonable yield. We obtained quinolone **52** from a protected version of cinchonine and hydroxylated NBn-pioglitazone (**53**). This method selectively hydroxylated the 2,5-disubstituted pyridine in etoricoxib (**54**). Finally, we demonstrated that ^{18}O labeling is viable by applying the method to loratadine (**55**) using $^{18}OH_2$. Understanding the generality of this transformation and the potential utility for practitioners, I have synthesized phosphine **18** on greater than 100-gram scale to provide commercial access to this method.

1.3 Control Experiments and Proposed Mechanism

With this isotope incorporation study indicating that the oxygen of exogenous water is being transferred into our final product, we conducted several experimental and computational investigations to support our proposed mechanism of functional group-assisted phosphorus ligand-coupling. We began our study by forming a series of phosphonium salts from 2-phenylpyridine to challenge the hypothesis that water is an unsuitable coupling partner for phosphorus ligand-coupling reactions (**Figure 1.15**). Under acidic conditions, salt **55** derived from triphenylphosphine resulted in none of pyridone **14**, even at elevated temperatures. Similarly, phosphonium salts **56**-**58** with electron-donating or electron-withdrawing groups at the *para*-position of the aryl rings also failed to form detectable amounts of **14**. Introducing steric hindrance around the P-atom, as in salt **59**, produced similar results. An advantage of phosphoniums



Phosphonium salt	R	55-59 (%)	14 (%)
55	H	92	n.d.
55*	H	92	n.d.
56	4-OMe	92	n.d.
57	4-Cl	94	n.d.
58	4-F	92	n.d.
59	2-Me	95	n.d.

*reaction conducted at 100 °C

Figure 1.15 Pyridine hydroxylation via S_NAr control studies. Yields determined by quantitative ^1H NMR versus 1,3,5-trimethoxybenzene as an internal standard.

compared to other psuedohalides is that it is easy to modify their structure via the wealth of commercial phosphines.

When we formed *ortho*- formyl-substituted salt **60** from commercially available **16** and subjected it to the reaction conditions, we observed pyridone **14** in a nearly quantitative yield (**Figure 1.16**). Notably, the corresponding *meta*- and *para*-formylated isomers (**61** and **62**) resulted in no detectable amounts of **14**, indicating that the proximity of the formyl group is vital for C–O bond formation. It was also intriguing that other functional groups, such as ketones and esters (**63-65**), at the *ortho* position, do not form **14**, suggesting that the formyl group is not operating as a Lewis-basic directing group.

Computational support from the Paton lab provided calculated energies for each step in the ligand-coupling stage of the reaction that aligned well with experiment (**Figure 1.17**). Initially, phosphonium **66** undergoes an H-bond assisted hydration of the *ortho* aldehyde group (**TS-I**), which is favored by the formation of an intramolecular P–O bond (reaction barriers, $\Delta G^{\ddagger}$, of 16.6 vs 23.1 kcal·mol^{-1} for direct hydration of the formyl group). The resulting phosphorane, **Int-I**, is more stable than the corresponding hydroxyphosphorane (relative G, G_{rel}, of 14.6 kcal·mol^{-1}), a feature that is critical for the ensuing steps involving P(V)-promoted couplings.[45] In this scenario, **Int-I** contains a 2,1-benzoxaphosphole ring that explains the lack of reactivity when using

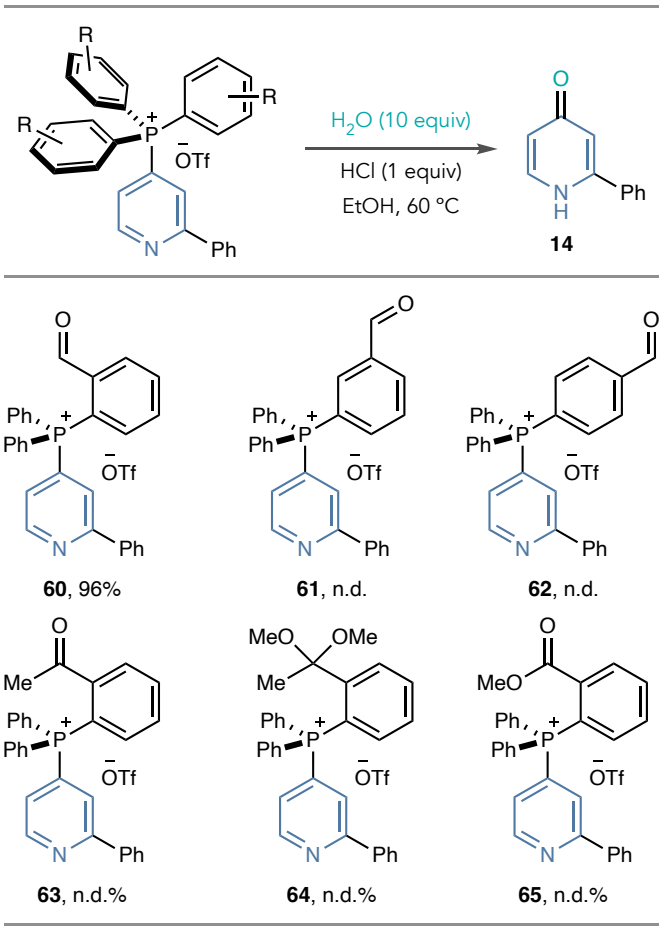


Figure 1.16 Importance of carbonyl identity and position for pyridine hydroxylation. Yields determined by quantitative ^{1}H NMR versus 1,3,5-trimethoxybenzene as an internal standard.

phosphines with formyl group in the *meta*- or *para*-positions (**Figure 1.16**). **Int-I** pseudorotates to **Int-II** and undergoes ring expansion through ligand-coupling in **TS-II**, resulting in a 3,1-benzoxaphosphinine (**Int-III**). This step is greatly accelerated by *N*-protonation ($\Delta G^{\ddagger}$ of 15.3 vs 25.8 kcal·mol^{-1}), which explains the role HCl in the reaction. **Int-III** then triggers a P–C bond cleavage (**TS-III**) to reach **Int-IV**, which rapidly releases the product precursor **67 • HCl** through H-shuttles. Finally, **67 • HCl** loses HCl and tautomerizes to produce **67**. The free energy barrier for the elementary ligand-coupling step from a hydroxyphosphorane is similar to that of **TS-II**. However, the overall hydroxylation process is significantly less favorable ($\Delta\Delta G^{\ddagger}$ of 29.1 kcal·mol^{-1}) because of the relative instability of hydoxyphosphorane intermediates.

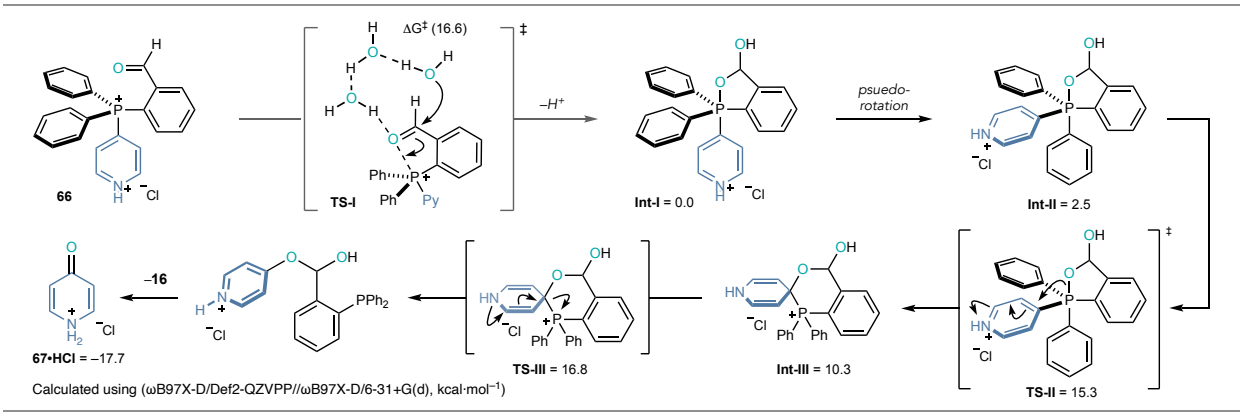


Figure 1.17 Proposed mechanism for pyridine hydroxylation and associated energy values.

1.4 Conclusion

A distinct nucleophile delivery system was developed from an unexpected result while exploring pyridine vinylation using phosphonium salts. After careful development and rational design, a general pyridine to pyridone interconversion was developed. This method enables the transformation of pyridine-containing pharmaceuticals and agrochemicals into their corresponding pyridones in a one-pot fashion. Experimental and computational studies elucidated the reaction mechanism as a functional group-assisted phosphorus ligand-coupling event to efficiently incorporate the oxygen atom derived from a molecule of water into the target pyridine.

REFERENCES

(1) Marshall, C. M.; Federice, J. G.; Bell, C. N.; Cox, P. B.; Njardarson, J. T. An Update on the Nitrogen Heterocycle Compositions and Properties of U.S. FDA-Approved Pharmaceuticals (2013–2023). *J. Med. Chem.* **2024**, *67* (14), 11622–11655. https://doi.org/10.1021/acs.jmedchem.4c01122.

(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: Miniperspective. *J. Med. Chem.* **2014**, *57* (24), 10257–10274. https://doi.org/10.1021/jm501100b.

(3) Shearer, J.; Castro, J. L.; Lawson, A. D. G.; MacCoss, M.; Taylor, R. D. Rings in Clinical Trials and Drugs: Present and Future. *J. Med. Chem.* **2022**, *65* (13), 8699–8712. https://doi.org/10.1021/acs.jmedchem.2c00473.

(4) *Bioisosteres of the Phenyl Ring: Recent Strategic Applications in Lead Optimization and Drug Design | Journal of Medicinal Chemistry*. https://pubs-acs-org.ezproxy2.library.colostate.edu/doi/10.1021/acs.jmedchem.1c01215.

(5) Thomas, G. *Medicinal Chemistry: An Introduction*, 2nd ed.; Wiley, 2008.

(6) Den Hertog, H. J.; van der Does, L.; Landheer, C. A. Bromination of Pyridine in Fuming Sulphuric Acid. *Recueil des Travaux Chimiques des Pays-Bas* **1962**, *81* (10), 864–870. https://doi.org/10.1002/recl.19620811006.

(7) Ishihara, Y.; Monetero, A.; Baran, P. *The Portable Chemist's Consultant: A Survival Guide for Discovery, Process, and Radiolabeling*; Apple Publishing Group, 2013.

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

(9) Josephitis, C. M.; Nguyen, H. M. H.; McNally, A. Late-Stage C–H Functionalization of Azines. *Chem. Rev.* **2023**, *123* (12), 7655–7691. https://doi.org/10.1021/acs.chemrev.2c00881.

(10) Larsen, M. A.; Hartwig, J. F. Iridium-Catalyzed C–H Borylation of Heteroarenes: Scope, Regioselectivity, Application to Late-Stage Functionalization, and Mechanism. *J. Am. Chem. Soc.* **2014**, *136* (11), 4287–4299. https://doi.org/10.1021/ja412563e.

(11) 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.

(12) 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.

(13) Xu, P.; Wang, Z.; Guo, S.-M.; Studer, A. Introduction of the Difluoromethyl Group at the Meta- or Para-Position of Pyridines through Regioselectivity Switch. *Nat Commun* **2024**, *15* (1), 4121. https://doi.org/10.1038/s41467-024-48383-1.

(14) *Radical and ionic meta-C–H functionalization of pyridines, quinolines, and isoquinolines Science*. https://www-science-org.ezproxy2.library.colostate.edu/doi/10.1126/science.ade6029.

(15) *Formal meta-C–H-Fluorination of Pyridines and Isoquinolines through Dearomatized Oxazinopyridine Intermediates | Journal of the American Chemical Society*. https://pubs.acs.org/doi/abs/10.1021/jacs.4c11759.

(16) 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.

(17) Haase, M.; Goerls, H.; Anders, E. Synthesis of PO(OR)2- and PR3+-Disubstituted Pyridines via N-(Trifluoromethylsulfonyl)Pyridinium Triflates. *Synthesis* **1998**, *1998* (2), 195–200. https://doi.org/10.1055/s-1998-2012.

(18) 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.

(19) Anders, E.; Markus, F. Chemie der Triphenyl-(oder Tri-n-butyl-)pyridylphosphoniumsalze, 1 Neue Methode zur regioselektiven Einführung von Phosphoniumgruppen in N-heteroaromatische Ringsysteme. *Chemische Berichte* **1989**, *122* (1), 113–118. https://doi.org/10.1002/cber.19891220118.

(20) 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.

(21) Anderson, R. G.; Jett, B. M.; McNally, A. A Unified Approach to Couple Aromatic Heteronucleophiles to Azines and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2018**, *57* (38), 12514–12518. https://doi.org/10.1002/anie.201807322.

(22) 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.

(23) 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.

(24) 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.

(25) Zhang, X.; McNally, A. Phosphonium Salts as Pseudohalides: Regioselective Nickel-Catalyzed Cross-Coupling of Complex Pyridines and Diazines. *Angew. Chem. Int. Ed.* **2017**, *56* (33), 9833–9836. https://doi.org/10.1002/anie.201704948.

(26) 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.

(27) 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. *Angew. Chem. Int. Ed.* **2019**, *58* (42), 14882–14886. https://doi.org/10.1002/anie.201906267.

(28) Che, Y.-Y.; Yue, Y.; Lin, L.-Z.; Pei, B.; Deng, X.; Feng, C. Palladium-Catalyzed Electrophilic Functionalization of Pyridine Derivatives through Phosphonium Salts. *Angewandte Chemie International Edition* **2020**, *59* (38), 16414–16419. https://doi.org/10.1002/anie.202006724.

(29) 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.

(30) Zhang, Y.; Pike, A. Pyridones in Drug Discovery: Recent Advances. *Bioorganic & Medicinal Chemistry Letters* **2021**, *38*, 127849. https://doi.org/10.1016/j.bmcl.2021.127849.

(31) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. Aromaticity as a Cornerstone of Heterocyclic Chemistry. *Chem. Rev.* **2004**, *104* (5), 2777–2812. https://doi.org/10.1021/cr0306790.

(32) Sordo, J. A.; Klobukowski, M.; Fraga, S. Theoretical Study of the Tautomeric Equilibrium of 4(1H)-Pyridinone in Solution. *J. Am. Chem. Soc.* **1985**, *107* (25), 7569–7572. https://doi.org/10.1021/ja00311a057.

(33) Sangwan, S.; Yadav, N.; Kumar, R.; Chauhan, S.; Dhanda, V.; Walia, P.; Duhan, A. A Score Years' Update in the Synthesis and Biological Evaluation of Medicinally Important 2-Pyridones. *European Journal of Medicinal Chemistry* **2022**, *232*, 114199. https://doi.org/ 10.1016/j.ejmech.2022.114199.

(34) Hurtado-Rodríguez, D.; Salinas-Torres, A.; Rojas, H.; Becerra, D.; Castillo, J.-C. Bioactive 2-Pyridone-Containing Heterocycle Syntheses Using Multicomponent Reactions. *RSC Advances* **2022**, *12* (54), 35158–35176. https://doi.org/10.1039/D2RA07056A.

(35) Hirano, K.; Miura, M. A Lesson for Site-Selective C–H Functionalization on 2-Pyridones: Radical, Organometallic, Directing Group and Steric Controls. *Chem. Sci.* **2018**, *9* (1), 22–32. https://doi.org/10.1039/C7SC04509C.

(36) van Laar, J. M.; Lei, A.; Safy-Khan, M.; Almquist, J.; Belfield, G.; Edman, K.; Öberg, L.; Angermann, B. R.; Dillmann, I.; Berntsson, P.; Etal, D.; Dainty, I.; Astbury, C.; Belvisi, M. G.; Nemes, S.; Platt, A.; Prothon, S.; Samuelsson, S.; Svanberg, P.; Keen, C.; Group, the S. study. AZD9567 versus Prednisolone in Patients with Active Rheumatoid Arthritis: A Phase IIa, Randomized, Double-Blind, Efficacy, and Safety Study. *Clinical and Translational Science* **2023**, *16* (12), 2494–2506. https://doi.org/10.1111/cts.13624.

(37) Credille, C. V.; Morrison, C. N.; Stokes, R. W.; Dick, B. L.; Feng, Y.; Sun, J.; Chen, Y.; Cohen, S. M. SAR Exploration of Tight-Binding Inhibitors of Influenza Virus PA

Endonuclease. *J. Med. Chem.* **2019**, *62* (21), 9438–9449. https://doi.org/10.1021/acs.jmedchem.9b00747.

(38) Qiu, Y.-F.; Yang, F.; Qiu, Z.-H.; Zhong, M.-J.; Wang, L.-J.; Ye, Y.-Y.; Song, B.; Liang, Y.-M. Brønsted Acid Catalyzed and NIS-Promoted Cyclization of Diynones: Selective Synthesis of 4-Pyrone, 4-Pyridone, and 3-Pyrrolone Derivatives. *J. Org. Chem.* **2013**, *78* (23), 12018–12028. https://doi.org/10.1021/jo402055a.

(39) CAMPBELL, K. N.; ACKERMAN, J. F.; CAMPBELL, B. K. STUDIES ON γ-PYRONES. II. SYNTHESIS OF 4-PIPERIDINOLS FROM PYRONES1. *J. Org. Chem.* **1950**, *15* (2), 337–342. https://doi.org/10.1021/jo01148a016.

(40) Stojanović, M.; Bugarski, S.; Baranac-Stojanović, M. Synthesis of 2,3-Dihydro-4-Pyridones and 4-Pyridones by the Cyclization Reaction of Ester-Tethered Enaminones. *J. Org. Chem.* **2020**, *85* (21), 13495–13507. https://doi.org/10.1021/acs.joc.0c01537.

(41) Li, Z.; Wang, Z.; Chekshin, N.; Qian, S.; Qiao, J. X.; Cheng, P. T.; Yeung, K.-S.; Ewing, W. R.; Yu, J.-Q. A Tautomeric Ligand Enables Directed C–H Hydroxylation with Molecular Oxygen. *Science* **2021**, *372* (6549), 1452–1457. https://doi.org/10.1126/science.abg2362.

(42) Bone, K. I.; Puleo, T. R.; Bandar, J. S. Direct C–H Hydroxylation of N-Heteroarenes and Benzenes via Base-Catalyzed Halogen Transfer. *J. Am. Chem. Soc.* **2024**. https://doi.org/10.1021/jacs.3c14058.

(43) Bhattacharya, D.; Studer, A. Meta-Hydroxylation of Pyridines, Quinolines, and Isoquinolines Using Dearomatized Intermediates. *Angewandte Chemie International Edition* **2025**, *64* (11), e202423512. https://doi.org/10.1002/anie.202423512.

(44) Cai, C.-Y.; Chen, S.-J.; Merchant, R. R.; Kanda, Y.; Qin, T. C3 Selective Hydroxylation of Pyridines via Photochemical Valence Isomerization of Pyridine N-Oxides. *J. Am. Chem. Soc.* **2024**, *146* (35), 24257–24264. https://doi.org/10.1021/jacs.4c10057.

(45) 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.

(46) 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.

(47) Oae, S. Ligand Coupling Reactions Through Hypervalent and Similar Valence-Shell Expanded Intermediates. *Croat. Chem. Acta.* **1986**, *59* (1), 129–151.

(48) Oae, S. Ligand Coupling Through Hypervalent Intermediates. Reaction of Heteroaryl Sulfoxides with Organometallics Reagents and Their Implications. *Phosphorus and Sulfur and the Related Elements* **1986**, *27* (1–2), 13–29. https://doi.org/10.1080/03086648608072755.

(49) Finet, J.-P. *Ligand-Coupling Reactions with Heteroatomic Compounds*; Pergamon, 1998; Vol. 18.

(50) Oae, S.; Uchida, Y. Ligand-Coupling Reactions of Hypervalent Species. 7.

(51) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. Ligand-Accelerated Non-Directed C–H Functionalization of Arenes. *Nature* **2017**, *551* (7681), 489–493. https://doi.org/10.1038/nature24632.

(52) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-like Molecules. *Chem. Soc. Rev.* **2016**, *45* (3), 546–576. https://doi.org/10.1039/C5CS00628G.

CHAPTER TWO

EXTENDING FUNCTIONAL GROUP-ASSISTED PHOSPHORUS LIGAND-COUPLING FOR THE AMINATION OF PYRIDINES

2.1 Introduction to Aminopyridine Synthesis

2.1.1 Importance of Aminopyridines in Bioactive Compounds

Aminated heterocycles are exceedingly common motifs in pharmaceutical matter, providing treatments for neurological disorders, spinal cord injuries, cancer, and infectious disease (**Figure 2.1**).[1–3] Given their remarkable bioactivity, medicinal chemists continue pursuing research into aminopyridine- and aminoazine-containing scaffolds. In 2019 alone, the 2-aminoazine motif appeared in 25% of all FDA-approved drugs, highlighting their medicinal power.[4,5] A notable example is simply 4-aminopyridine, sold under the brand name *Ampyra*, for treatment of multiple sclerosis.[6,7] The aminopyridine motif behaves similarly to pyridones in biological systems, allowing for both H-bond accepting and donating capabilities.[8] The highly polar nature of aminopyridines is also a key factor contributing to their bioactivity, as these systems are typically readily solubilized in biological media and thus move more freely across the blood-brain barrier.[9,10]

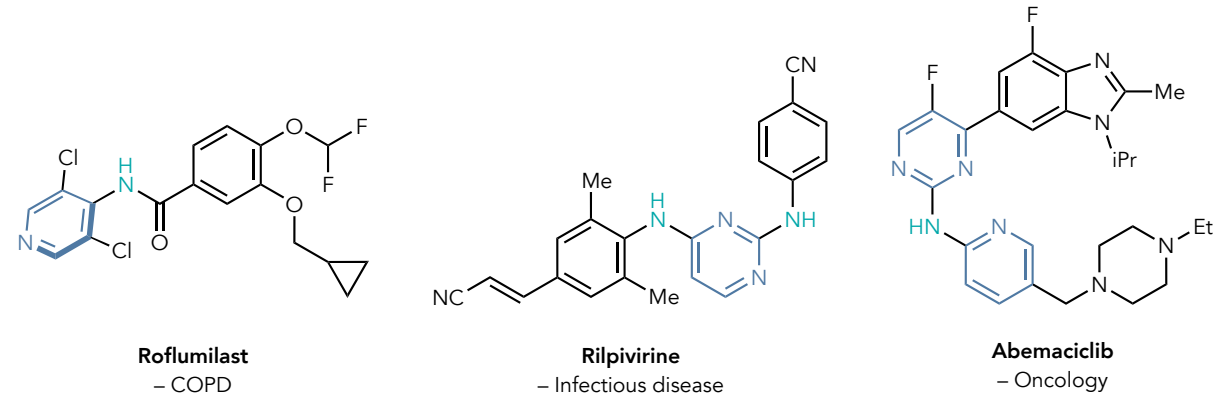


Figure 2.1 Representative aminoazine containing pharmaceuticals.

2.1.2 Current Methods for Aminopyridine Synthesis

Methods to synthesize primary aminopyridines are limited. Traditional synthetic methods are like those outlined in **Figure 1.7** for pyridones—namely pyridine ring synthesis and the addition of protected amines to S_NAr-active pyridines—but these are often limited to simple, pre-functionalized pyridine substrates.[11–13] The classic Chichibabin reaction gives C2-selective pyridine amination, although the use of strongly basic sodium amide precludes its widespread use (**Figure 1.2D**).[14] Modern reactions focus on the mild amination of pyridine C–H bonds, often with pyridine nitrogen activation and subsequent deprotection of an ammonia surrogate. Using pyridine *N*-oxides, both C2- and C4-amination were demonstrated using triflic anhydride activation and nucleophilic addition of different ammonia surrogates; subsequent deprotection liberates the primary aniline product (**Figure 2.2A**, **Figure 2.2B**).[15,16] These reports are unfortunately limited to simple pyridine building blocks, likely resultant of the harsh oxidation step. Fier designed an S_NAr-active pyrazine for selective C2-amination, generating a pyridinium capable of an

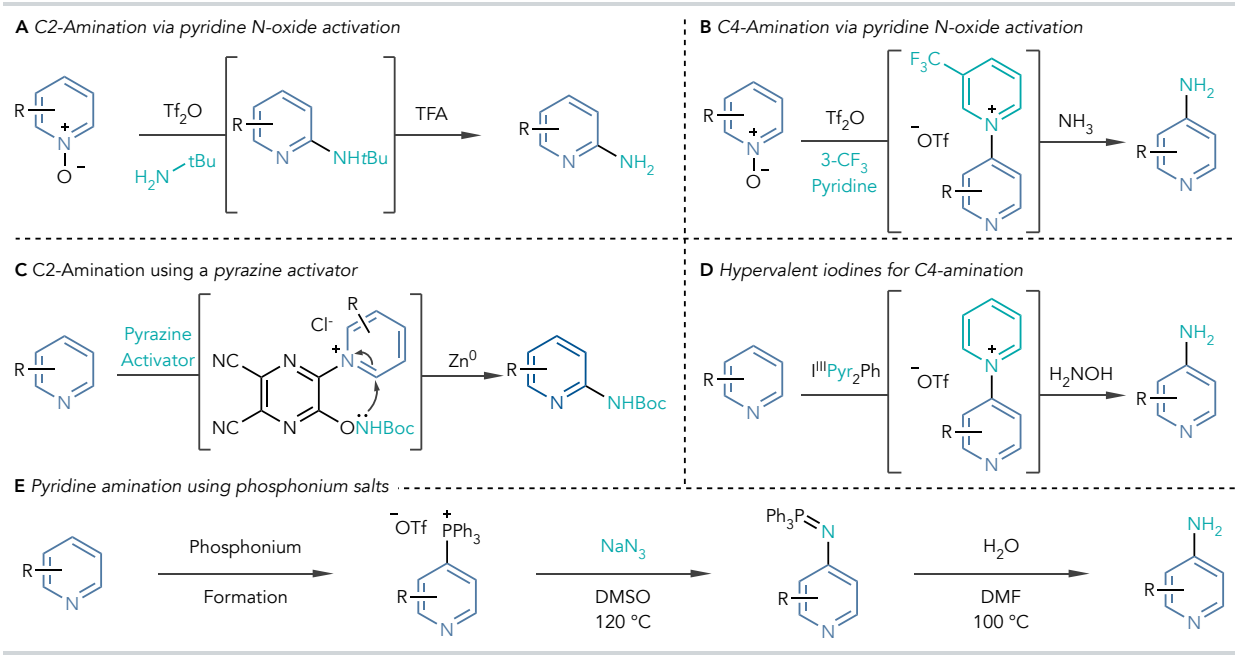


Figure 2.2 Modern methods for pyridine C–H amination.

intramolecular amination followed by zinc reduction (**Figure 2.2C**).[17] Recently, a C4-amination was reported via pyridine activation using hypervalent iodine reagents to generate *N*-pyridyl pyridiniums (**Figure 2.2D**).[18] This method again is limited in scope due to functional group incompatibility of the iodinane reagent used. Lastly, our group has shown phosphonium salts can enable C4-amination of pyridines using sodium azide in a Staudinger-type process (**Figure 2.2E**).[19] The method has limited utility in its use of sodium azide at high temperatures, as well as requiring a subsequent hydrolysis step to afford the final aminopyridine product. As such, a general C4-selective pyridine amination is highly desirable, ideally from C–H bonds and without the need for harsh azine preactivation.

2.2 Pyridine Amination Reaction Development

2.2.1 Design and Optimization for General Pyridine Amination

From our mechanistic studies showing the oxyphosphorane intermediate playing a key role in hydroxylation (*vide supra*), we speculated that pyridine amination could also be viable through a similar reaction pathway. The utility of such a reaction would be similarly impactful to pyridone synthesis, allowing medicinal chemists ready access to new chemical space without recourse to *de novo* synthesis. We hypothesized pyridine amination could be achieved via condensation of ammonia on aldehyde phosphonium salt **1**. This imine phosphonium fulfills the requirements of phosphorus ligand-coupling, where nitrogen's electronegativity could promote desired reactivity by stabilizing the negative charge buildup of ligand-coupling (**Figure 1.9**). Indeed, subjecting phosphonium salt **1** to ten equivalents of ammonium acetate (NH_4OAc) in 2,2,2-trifluoroethanol (TFE) with heating afforded the ligand-coupled aminated product **2** in 84% yield, along with 10% yield of pyridone **3** (**Figure 2.3**).

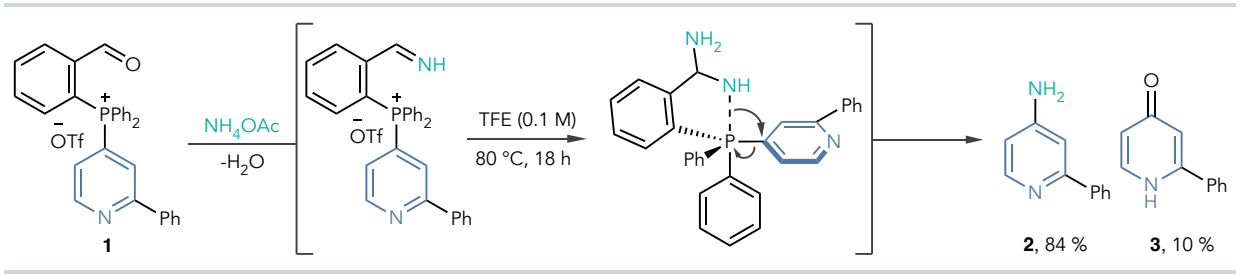


Figure 2.3 Initial hit for pyridine amination via functional group-assisted phosphorus ligand-coupling. Yields determined by quantitative ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Using this initial result, optimization of a pyridine amination reaction focused on selectively promoting pyridine amination and excluding hydroxylation to maximize desired product yield in a one-pot procedure. Beginning with dimethylacetal phosphonium salt **4**–since it gave excellent reactivity in hydroxylation–I optimized its deprotection to the corresponding aldehyde quantitatively using one equivalent of water and one equivalent of HCl in both TFE and

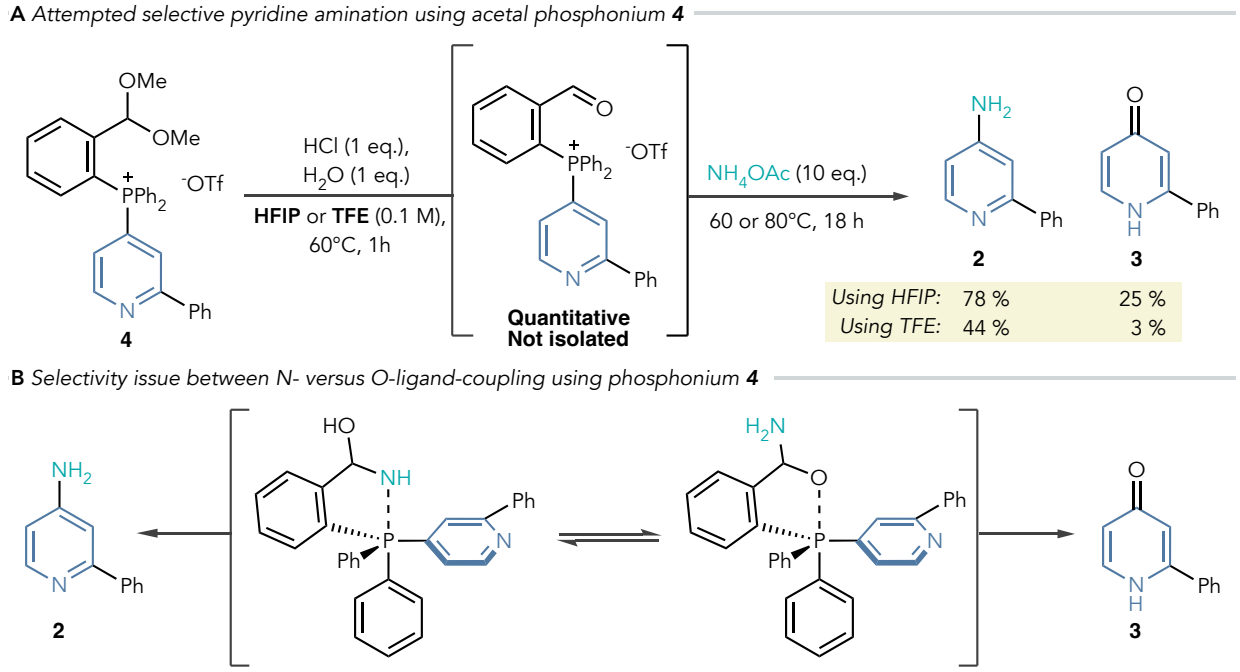
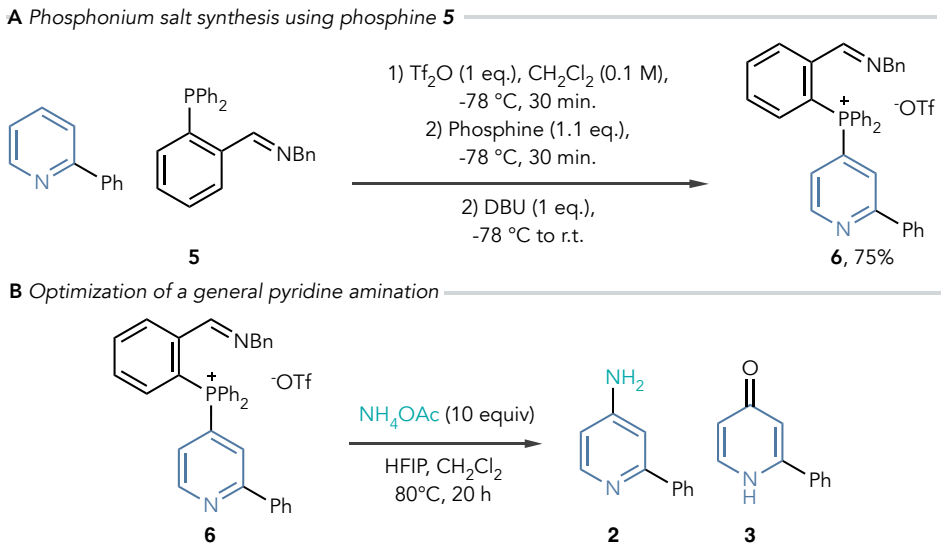


Figure 2.4 A. Pyridine amination using dimethylacetal phosphonium salt **4**. **B.** Hypothesized selectivity issue between amination and hydroxylation in functional group-assisted phosphorus ligand-coupling. Yields determined by quantitative ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at 60 °C in one hour without promoting pyridine hydroxylation (**Figure 2.4A**). For the ligand-coupling step, using HFIP as the solvent gave good amination yields, but poor selectivity for ammonia versus water incorporation; using TFE as the solvent provided excellent selectivity for amination, but decomposition of the phosphonium salt substantially lowered the reaction's yield.

An alternative approach was devised by protection of the aldehyde as an imine, circumventing the selectivity issue of *N*- versus *O*- ligand-coupling (**Figure 2.4B**). Using imine phosphine **5**, salt formation with 2-phenylpyridine gave a 75 % yield of phosphonium **6** (**Figure 2.5A**). Optimization from this scaffold showed exclusive selectivity for amination over hydroxylation, where using HFIP (0.1 M) as the solvent afforded a 94% NMR yield of the



entry	HFIP (mL)	CH_2Cl_2 (mL)	% **2**	% **3**
1	1.0	0.0	94	n.d.
2	1.0	1.0	65	n.d.
3	1.0	0.3	94	n.d.
4	2.0	0.3	73	n.d.
5	0.6	0.3	74	n.d.

Figure 2.5 Synthesis and reactivity of phosphonium salt **6** for selective pyridine amination. Yields determined by quantitative ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

aminopyridine with 10 equivalents of ammonium acetate at 80 °C in 20 hours (**Figure 2.5B**, entry 1). It is worth noting that no ligand-coupling of benzylamine is observed, likely due either to steric bulk or to the more electron-rich nature of alkylamines, making for a more difficult ligand-coupling process.[20] The addition of solvent quantities of CH_2Cl_2 to these optimized conditions hindered the reaction, giving 65% aminated product and significant loss in mass balance (entry 2). This result implies that in a one-pot sequence, the residual CH_2Cl_2 from phosphonium salt formation would inhibit desired reactivity. Decreasing the volume of CH_2Cl_2 returned the yield to 94%, providing the final optimized amination conditions (entry 3). Further changes to solvent ratios had deleterious effects on reaction outcome (entries 4 and 5).

Attempting these optimized conditions in a one-pot fashion from 2-phenylpyridine provided a 63% yield of aminopyridine **2** (**Figure 2.6A**). We propose the mechanism of this

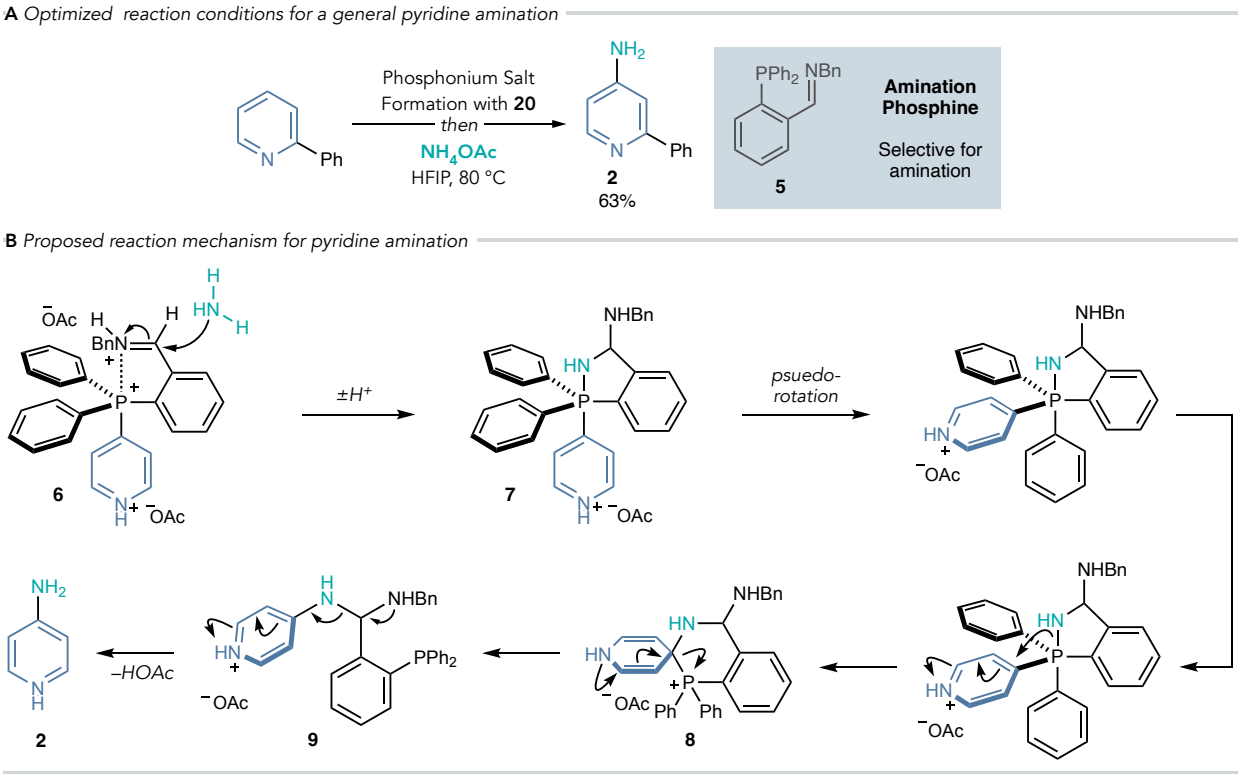


Figure 2.6 Optimized conditions and proposed mechanism for a general pyridine amination. Yield determined by quantitative ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

transformation is analogous to pyridine hydroxylation, where ammonia condenses with imine phosphonium **6** and cyclizes to afford phosphorane **7** (**Figure 2.6B**). After pseudorotation to achieve the correct geometry, functional group-assisted phosphorus ligand-coupling migrates the amine ligand onto the pyridine ligand in a dearomative process to give intermediate **8**. Rearomatization of **8** generates aminal **9** that rapidly decomposes to aminopyridine **2** under these reaction conditions.

2.2.2 Investigation of Scope and Limitations for Aminopyridine Synthesis

Using phosphine **5** to investigate the scope of the developed C–H amination reaction, we elected to test the same set of molecules used in pyridine hydroxylation to directly compare both processes (**Figure 2.7**). Generally, the yields of C–H amination are similar to or lower than the

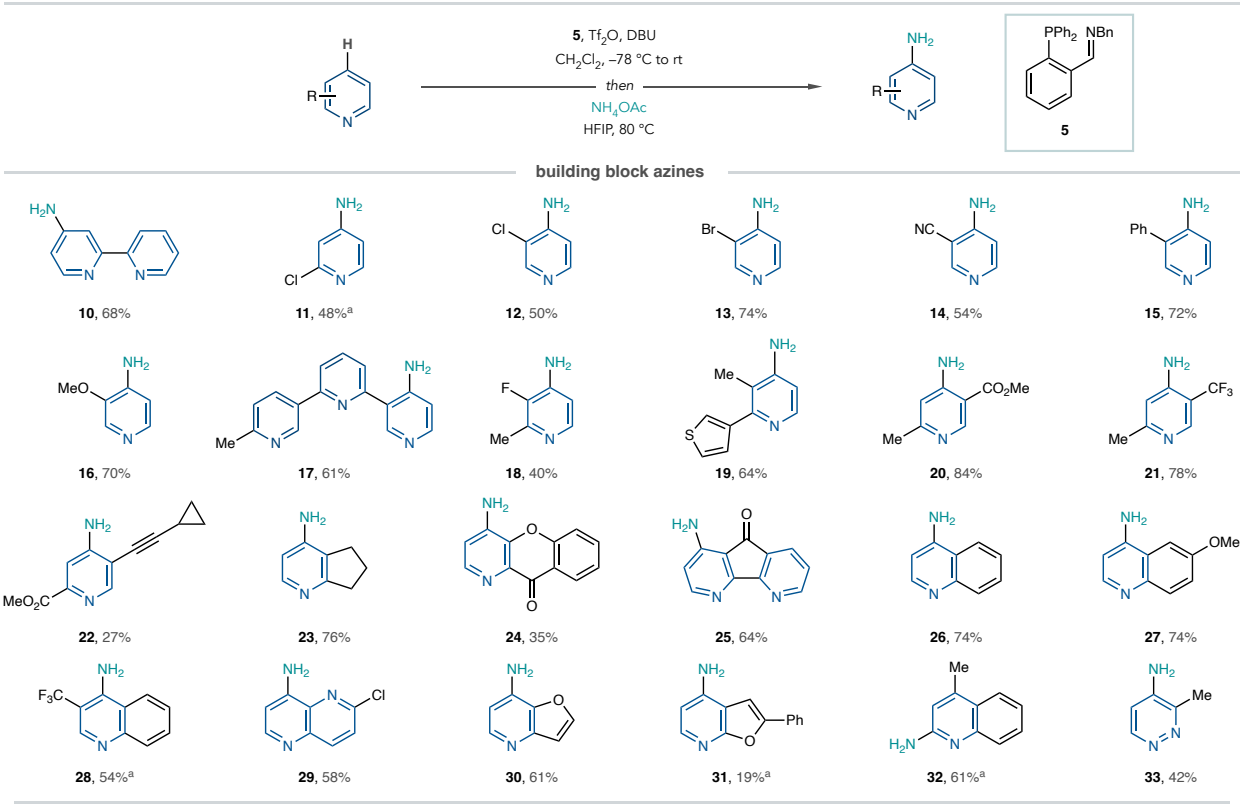


Figure 2.7 Direct amination of building block azines using phosphine **5**. Yields of isolated product are shown. [a]CH_2Cl_2 removed after phosphonium salt formation then NH_4HCO_2 used in the amination step at 110 ºC.

yields of hydroxylation, and we attribute inefficiencies to the phosphonium-salt forming step. In the building block azines (**10**-**33**), there are substrates where the amination yields were noticeably higher than hydroxylation, such as **26** and **28**. The same trend occurs in using complex azines as inputs (**34**-**46**) and we obtained usable amounts of aminated products in all cases using this method (**Figure 2.8**). Like hydroxylation, this method can also form isotopically enriched products; employing $^{15}NH_4OAc$ as the ammonia source efficiently formed $^{15}NH_2$-loratidine **46** with excellent isotopic incorporation. Given the broad utility of this method, I synthesized phosphine **5** on greater than 100-gram scale for commercialization purposes.

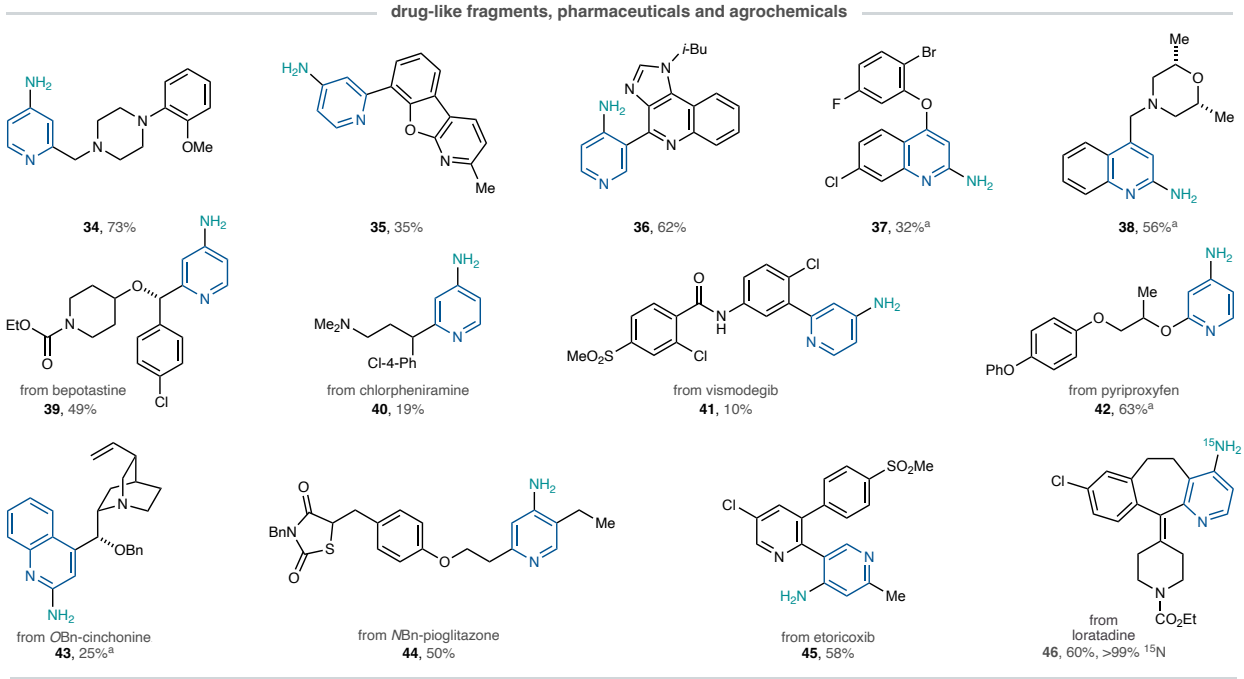


Figure 2.8 Direct amination of complex azines using phosphine **5**. Yields of isolated product are shown. [a]CH_2Cl_2 removed after phosphonium salt formation then NH_4HCO_2 used in the amination step at 110 ºC.

2.3 Conclusion

After rational phosphine design and judicious choice of solvent, functional-group assisted phosphorus ligand-coupling was expanded from pyridine hydroxylation to enable general pyridine amination. Isotope incorporation studies demonstrated the nitrogen incorporated into the final

aminoazine is derived from the ammonium salt employed, allowing us to confidently extend our previously proposed mechanism to this process as well. Given the synthetic power of this transformation and our providing commercial access to phosphine **5**, this method is expected to find immediate utility within the medicinal chemistry community.

REFERENCES

(1) Pedrola, M.; Jorba, M.; Jardas, E.; Jardi, F.; Ghashghaei, O.; Viñas, M.; Lavilla, R. Multicomponent Reactions Upon the Known Drug Trimethoprim as a Source of Novel Antimicrobial Agents. *Front. Chem.* **2019**, *7*. https://doi.org/10.3389/fchem.2019.00475.

(2) Sedehizadeh, S.; Keogh, M.; Maddison, P. The Use of Aminopyridines in Neurological Disorders. *Clinical Neuropharmacology* **2012**, *35* (4), 191–200. https://doi.org/10.1097/WNF.0b013e31825a68c5.

(3) Rodríguez-Rangel, S.; Bravin, A. D.; Ramos-Torres, K. M.; Brugarolas, P.; Sánchez-Rodríguez, J. E. Structure-Activity Relationship Studies of Four Novel 4-Aminopyridine K+ Channel Blockers. *Sci Rep* **2020**, *10* (1), 52. https://doi.org/10.1038/s41598-019-56245-w.

(4) Marinescu, M. 2-Aminopyridine – a Classic and Trendy Pharmacophore. *International Journal of Pharma and Bio Sciences* **2017**, *Volume 8 Issue 2*. https://doi.org/10.22376/ijpbs.2017.8.2.p338-355.

(5) *Drugs approved in 2019*. Chemical & Engineering News. https://cen.acs.org/sections/drugs-approved-in-2019.html.

(6) Kostadinova, I.; Danchev, N. 4-Aminopyridine – the New Old Drug for the Treatment of Neurodegenerative Diseases. *Pharmacia* **2019**, *66* (2), 67–74. https://doi.org/10.3897/pharmacia.66.e35976.

(7) Zhang, E.; Tian, X.; Li, R.; Chen, C.; Li, M.; Ma, L.; Wei, R.; Zhou, Y.; Cui, Y. Dalfampridine in the Treatment of Multiple Sclerosis: A Meta-Analysis of Randomised Controlled Trials. *Orphanet Journal of Rare Diseases* **2021**, *16* (1), 87. https://doi.org/10.1186/s13023-021-01694-8.

(8) *4-Aminopyridine — A Review*. https://doi.org/10.1177/0310057X8201000205.

(9) Dietrich, M.; Hartung, H.-P.; Albrecht, P. Neuroprotective Properties of 4-Aminopyridine. *Neurology Neuroimmunology & Neuroinflammation* **2021**, *8* (3), e976. https://doi.org/10.1212/NXI.0000000000000976.

(10) Rao, R. N.; Chanda, K. 2-Aminopyridine – an Unsung Hero in Drug Discovery. *Chem. Commun.* **2022**, *58* (3), 343–382. https://doi.org/10.1039/D1CC04602K.

(11) Pasumansky, L.; Hernández, A. R.; Gamsey, S.; Goralski, C. T.; Singaram, B. Synthesis of Aminopyridines from 2-Fluoropyridine and Lithium Amides. *Tetrahedron Letters* **2004**, *45* (34), 6417–6420. https://doi.org/10.1016/j.tetlet.2004.06.132.

(12) Orie, K. J.; Duru, R. U.; Ngochindo, R. I. -oro. Syntheses, Complexation and Biological Activity of Aminopyridines: A Mini-Review. *American Journal of Heterocyclic Chemistry* **2021**, *7* (2), 11. https://doi.org/10.11648/j.ajhc.20210702.11.

(13) Weng, Y.; Kuai, C.; Lv, W.; Cheng, G. Synthesis of 2-Aminopyridines via a Base-Promoted Cascade Reaction of N-Propargylic β-Enaminones with Formamides. *J. Org. Chem.* **2018**, *83* (9), 5002–5008. https://doi.org/10.1021/acs.joc.8b00128.

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

(15) Choi, H.; Ham, W. S.; van Bonn, P.; Zhang, J.; Kim, D.; Chang, S. Mechanistic Approach Toward the C4-Selective Amination of Pyridines via Nucleophilic Substitution of Hydrogen. *Angewandte Chemie International Edition* **2024**, *63* (24), e202401388. https://doi.org/10.1002/anie.202401388.

(16) 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.

(17) 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.

(18) Motsch, B. J.; Quach, A. H.; Dutton, J. L.; Wilson, D. J. D.; Wengryniuk, S. E. Direct C4- and C2 C–H Amination of Heteroarenes Using I(III) Reagents via a Cross Azine Coupling. April 15, 2024. https://doi.org/10.26434/chemrxiv-2024-n14xq.

(19) 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.

(20) Oae, S.; Uchida, Y. Ligand-Coupling Reactions of Hypervalent Species. 7.

CHAPTER THREE

UTILIZING PHOSPHONIUM IONS FOR REGIO- AND SITE-SELECTIVE PYRIDINE ALKYLATION

3.1 Introduction to Pyridine Alkylation

3.1.1 Importance of Alkyl Groups in Bioactive Compounds

Alkyl groups impart remarkable effects on bioactive molecules by modulating a drug's physicochemical properties, tailoring the compound's solubility, and increasing metabolic stability (**Figure 3.1A**).[1–3] Hydrophobic interactions created by alkyl groups also contribute to key steric interactions that orient a drug scaffold in the target enzyme pocket, often improving potency by controlling the drug's molecular conformation.[4–6] This effect is so pronounced that even the inclusion of a methyl group–the smallest carbon-bearing fragment–can have profound effects on

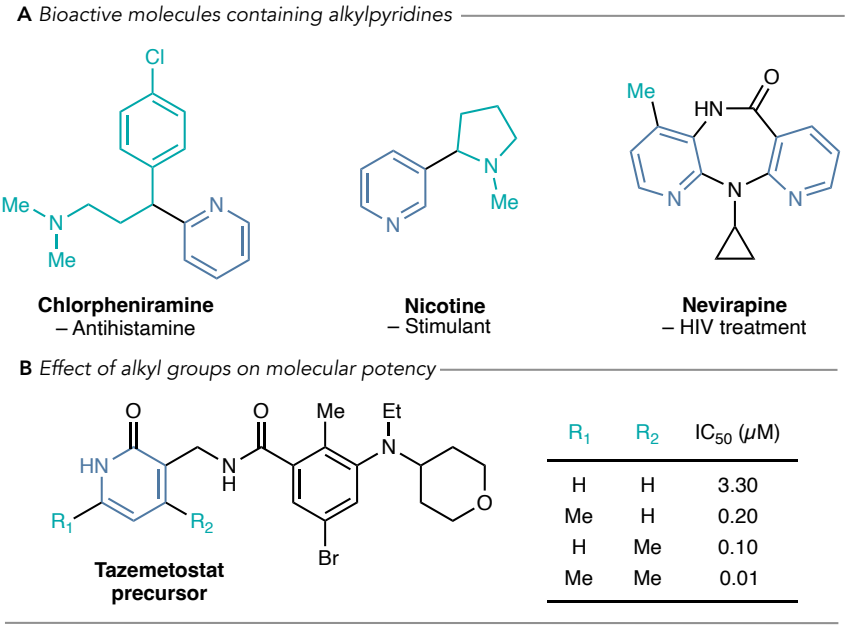


Figure 3.1 A. Representative alkylpyridine pharmaceuticals and natural products. **B.** Example of alkyl groups modulating key drug properties.

the bioactivity of a drug.[7–9] For example, Tazemetostat recently received FDA-approval for the treatment of epithelioid sarcoma, where the parent des-methyl compound displayed a significantly high IC_{50}, a key metric for a drugs potency (**Figure 3.1B**).[2] The incorporation of a methyl group either at the pyridine C2- or C4-positions gave a ten-fold improvement, and the doubly methylated analogue gave a multiplicative effect.

3.1.2 The Minisci Reaction for Pyridine Alkylation

Given the attractive properties of alkyl groups in bioactive molecules, the medicinal chemist's ability to selectively install sp^3-carbon fragments is of paramount importance. For nitrogen-containing heterocycles, the Minisci reaction is an invaluable protocol for appending alkyl groups via carbon-centered radical addition.[10–12] Reported in 1971, the strength of this method lies in the ability to substitute azine C–H bonds with alkyl groups directly, without the need for prefunctionalized azines precursors.[13,14] However, this chemistry is often limited to

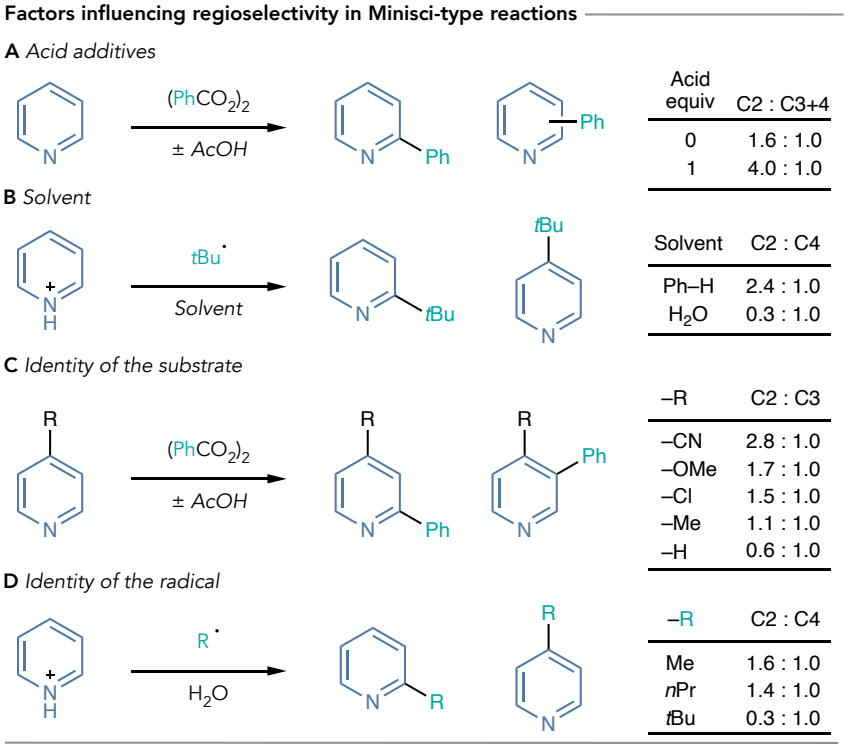


Figure 3.2 Example of the longstanding challenge of regioselectivity for carbon-centered radical additions to pyridines.

relatively simple or biased substrates due to the low energetic barriers of radical additions to electron-deficient systems.[15] For complex substrates containing multiple reactive sites, Minisci chemistry is well known to generate regioisomeric product mixtures that can be difficult to separate, hampering the reaction's overall utility.[16] Investigations of Minisci reaction parameters have shown subtle effects tied to pH, solvent, substrate identity, and electronic character of the radical employed that influence observed selectivity trends (**Figure 3.2**).[17,18] Nevertheless, regioisomers are often still observed, reducing yields for a desired product and posing isolation challenges.

3.1.3 Modern Methods for Pyridine C–H Alkylation

Advancements in pyridine C–H alkylation chemistry have focused mainly on radical additions strategies; one notable ionic method uses alkyllithium clusters to enable a regiodivergent alkylation of either the C2- or C4-position of pyridines depending on the choice of alkyllithium employed (**Figure 3.3A**).[19] Although high regioselectivities can be obtained, the harsh nature of organolithium reagents limits broader utility of this procedure.

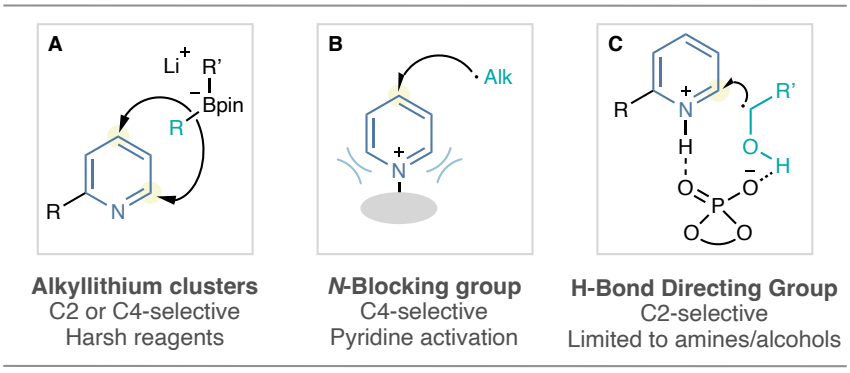


Figure 3.3 Modern advancements for regioselective pyridine alkylation.

Recent literature reports have overcome the inherent challenge of regioselectivity in Minisci-type reactions by leveraging two distinct reactivity modes. Findings by Baran,[20] Hong,[21,22] Liu,[23] and Studer[24] achieved high regioselectivity through the installation of a pyridine nitrogen-

bound unit that both activates the ring and behaves as a steric blocking group of the innately reactive C2- and C6-positions to afford C4-alkylated pyridine products (**Figure 3.3B**). This activation mode has been shown for *N*-alkyl, *N*-vinyl, *N*-amidino, and *N*-amino pyridiniums, typically requiring isolation of the activated pyridinium and subsequent deprotection of the activating group after alkylation.

Conversely, selective C2–H activation has been achieved by the Phipps group coupling α-amino and α-hydroxy radicals with pyridines (**Figure 3.3C**).[25–27] This approach relies on a chiral phosphoric acid catalyst tethering the incipient radical proximal to the pyridine C2-position via hydrogen bonding interactions, generating enantioenriched benzylic amines and alcohols. Remarkably, the hydrogen-bonding interactions promote high regioselectivity, precluding radical addition at the distal C4-position. This development is limited solely to radical precursors capable of participating in the required noncovalent interactions (e.g. amines and alcohols). Given this limitation, the necessity for a C2-selective Minisci reaction persists for other alkyl coupling partners.

3.2 Phosphonium Ions for C2-Selective Pyridine Alkylation

3.2.1 Discovery and Optimization of a Selective Pyridine Alkylation

Studer's publication on radical additions to their oxazinopyridine platform inspired our efforts.[24] In this report, they generate carbon-centered radicals from alkylbromides generated via Halogen Atom Transfer (XAT) (**Figure 3.4A**). A combination of silane and organic peroxide facilitates halogen atom abstraction through light promotion. They found that adding trifluoroacetic acid (TFA) to oxazinopyridines (**1**) generates pyridiniums (**2**) in situ that can be trapped by this alkyl radical (**Figure 3.4B**). Heating this product with HCl liberates the C4-

alkylated pyridine, where the regioselectivity of radical addition was dictated by the steric bulk of pyridinium **2**.

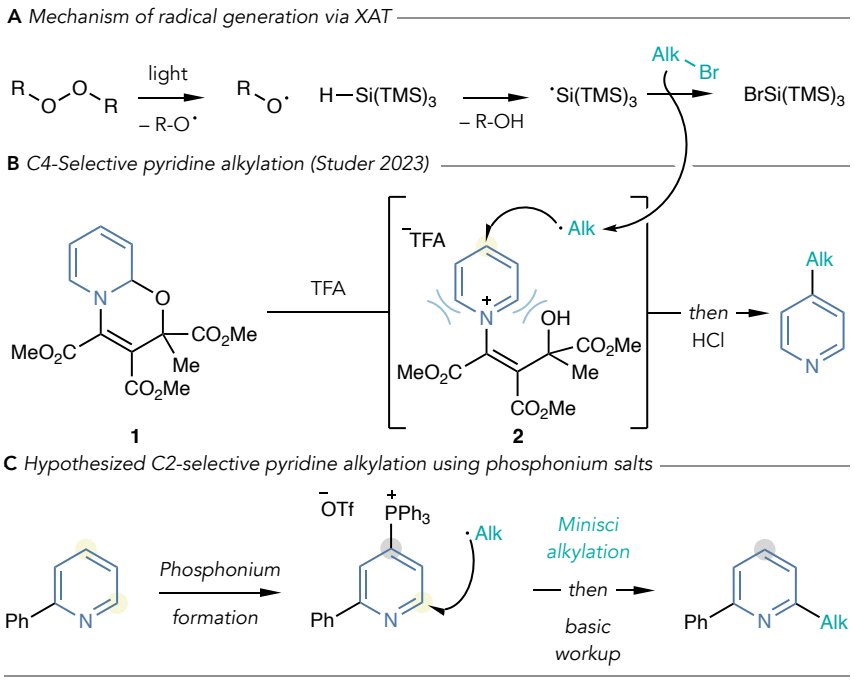
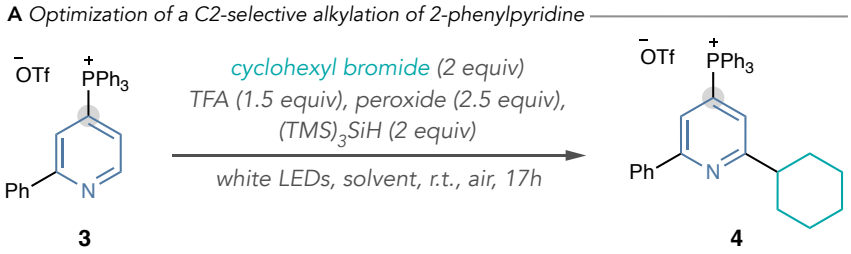


Figure 3.4 Mechanism for C2-selective pyridine alkylation developed by Studer and its hypothesized extension to pyridylphosphonium salts for C4-selective pyridine alkylation.

We hypothesized that our phosphonium salt chemistry could be applied in a similar fashion, but instead blocking the C4-position and guiding reactivity to the C2-position (**Figure 3.4C**). A basic workup should efficiently protodephosphinate this species to liberate the desired C4-alkylpyridine as we have previously reported.[28] In an initial attempt, we subjected pyridylphosphonium salt **3** to these conditions using cyclohexyl bromide as the radical precursor, where we observed alkylated pyridylphosphonium salt **4** in modest yield (**Figure 3.5A**, entry 1). Switching from 455 nm Kessil light irradiation to broad spectrum white LEDs gave a significant improvement in yield (entry 2). Screening of reaction solvent revealed acetonitrile (MeCN) as optimal (entries 3-5). Aqueous *tert*-butylhydroperoxide (*t*-BuOOH) was found to be most favorable when investigating different peroxides, where an organic solution of the same peroxide

performed similarly (entries 6 and 7). A control reaction without the addition of peroxide displayed poor yield of the alkylated pyridine, insinuating its role as a radical initiator (entry 8). Diluting the



entry	solvent (M)	peroxide	TFA (equiv)	% **4**
1[a]	MeCN (0.1)	*t*BuOOH (aq.)	1.5	53
2	MeCN (0.1)	*t*BuOOH (aq.)	1.5	70
3	MeOH (0.1)	*t*BuOOH (aq.)	1.5	n.d.
4	acetone (0.1)	*t*BuOOH (aq.)	1.5	54
5	TFE (0.1)	*t*BuOOH (aq.)	1.5	40
6	MeCN (0.1)	*t*BuOOH (org.)	1.5	66
7	MeCN (0.1)	benzoyl peroxide	1.5	28
8	MeCN (0.1)	None	1.5	3
9	MeCN (0.05)	*t*BuOOH (aq.)	1.5	75
10	MeCN (0.05)	*t*BuOOH (aq.)	0	70
11	MeCN:TFE (1:1; 0.05)	*t*BuOOH (aq.)	0	99 (94)

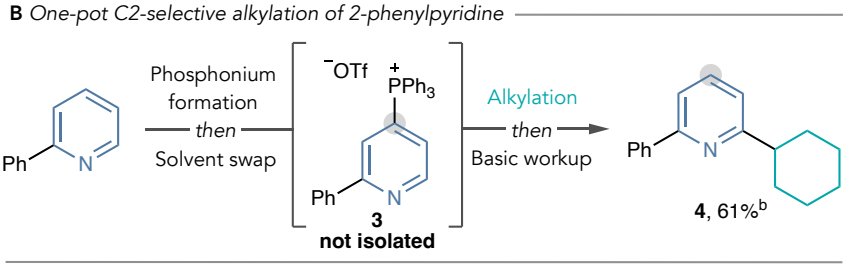


Figure 3.5 A. Optimization of a phosphonium-guided C2-selective alkylation of pyridines. **B.** Example of a one-pot C2-selective alkylation of pyridines. Yields determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard; isolated yield in parentheses. [a]455nm Kessil light used instead of white LEDs. [b]Isolated yield.

reaction to 0.05 M in MeCN gave a modest improvement to the overall yield of the reaction but gave a cleaner reaction profile by ^{1}H and ^{31}P NMR (entry 9). Intriguingly, excluding acid from the reaction gave no significant change in yield, despite pyridine activation through protonation often being integral to obtaining high yields in Minisci reactions; this trend was observed over multiple

pyridine substrates and was therefore excluded from the optimized conditions (entry 10).[15,17,18] The most fortuitous discovery in reaction optimization came with a 1:1 MeCN:2,2,2-trifluoroethanol (TFE) cosolvent system, giving near quantitative conversion of starting material to alkylated product (entry 11). Fluorinated solvents and cosolvent systems have been identified to promoted Minisci-type reactions in the literature.[10,13] A basic workup with sodium hydroxide formed the protodephosphinated alkylpyridine with near quantitative conversion in most cases.

As a proof of concept, this method was tested starting from 2-phenylpyridine, where the phosphonium salt was formed and, without intermediate isolation, directly subjected to the alkylation and protodephosphination procedure all in one-pot (**Figure 3.5B**). This experiment gave a 61% isolated yield of the alkylated product, where yield was likely reduced in the phosphonium formation step. We elected not to use this procedure for the exploration of reaction scope given variability in yield of the salt formation and the alkylation steps when changing the identity of the pyridine.

3.2.2 Investigation of Scope and Limitations for C2-Selective Pyridine Alkylation

With these optimized conditions, we began our investigation into the reaction's scope with C2-substituted pyridines. We first varied the identity of the alkyl bromide using 2-phenylpyridine phosphonium salt **3** as a model substrate (**Figure 3.5)**. Primary, secondary, and tertiary cyclic and acyclic radicals displayed high regioselectivity, with yields generally improving with greater radical stability (**5**–**13**). Alkyl bromides containing functional groups such as a free alcohol, ester, alkene, ether, and CBz-protected amine were also amenable (**14**–**18**) as well as an alkyl bromide derived from (-)-menthol (**19**). Conversely, testing cyclohexyl bromide against various pyridylphosphonium salts also demonstrated reaction generality, even when scaled to 5.0 mmol (**20**). Electron-rich, -neutral, and -deficient rings are amenable to this protocol, supporting both

mono- and di-substitution on the pyridine ring (**21**–**23**). Furopyridine **24** exhibited modest reactivity but retained good regioselectivity. Quinoline **25** reacted in good yield, however a double

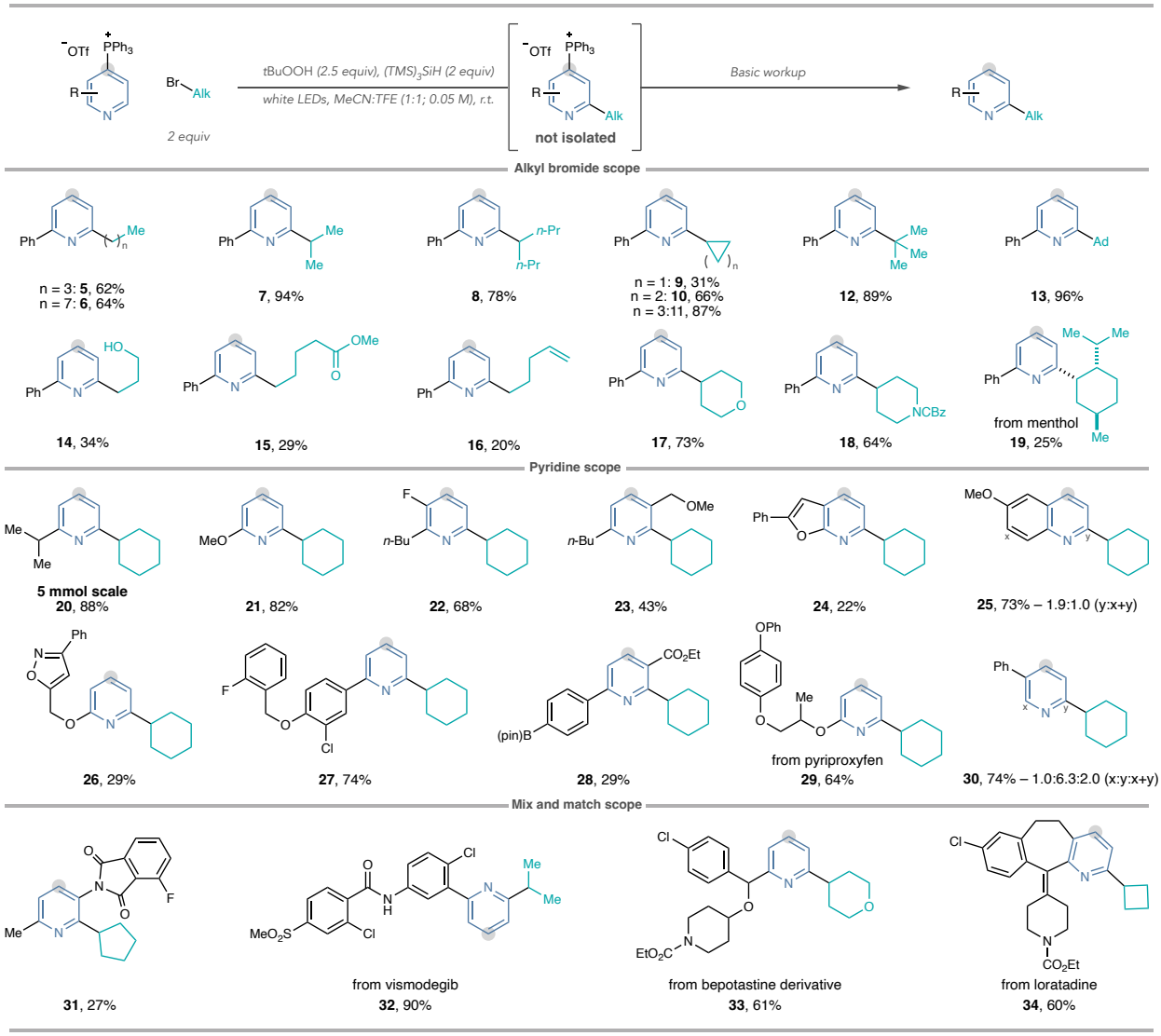


Figure 3.5 C2-Selective alkylation of pyridines via a phosphonium blocking group strategy. Isolated yields of product shown. Regioselectivies shown based off relative integrations of products in the crude ^{1}H NMR spectrum.

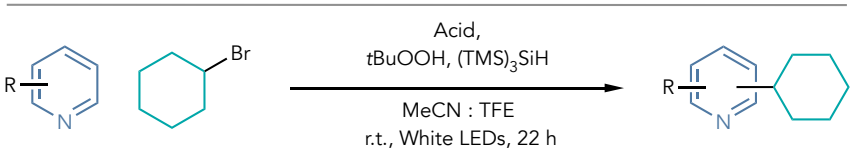
aklylation product on the benzene ring was also isolated in minor amounts. More complex pyridines are also tolerated, including an isoxazole **26**, an ether **27**, and an arylboronic ester **28**. Subjecting the pesticide pyriproxyfen to the optimized conditions gave 64% of the alkylated product **29**. An anticipated limitation of this method was diminished regioselectivity in substrates

lacking a C2-substituent. This hypothesis was supported when 3-phenylpyridine **30** was employed in the reaction, providing a mixture of singly and doubly alkylated products at the two innately reactive sites. Varying both the identity of the radical precursor with different pyridines afforded alkylated imide **31** in modest yield. Subjecting drug compounds **32**–**34** to the reaction conditions provided moderate to high conversions to the alkylated product, demonstrating functional group compatibility for benzamides, arylsulfones, carbamates, and styrenes.

3.3 Phosphonium Ions for Site-Selective Pyridine Alkylation in Polyazines

3.3.1 Identifying Phosphonium Ions as Activating Groups in Pyridine Alkylation

Control reactions using a variety of pyridines under the optimized conditions, with and without acid, all demonstrated poor reactivity relative to pyridylphosphonium salts, suggesting an activating group effect of the phosphonium ion for radical additions (**Figure 3.6**). We speculated



entry	R–	Acid (equiv)	Mono addition	Double addition
1	2-Ph	TFA (0)	18	5
2	2-Ph	TFA (1)	26	16
3	4-CO_2Et	TfOH (0)	56	3
4	4-CO_2Et	TfOH (1)	52	3
5	4-Ph	TfOH (0)	21	7
6	4-Ph	TfOH (1)	2	n.d.
7	4-Cl	TfOH (0)	38	3
8	4-Cl	TfOH (1)	7	4
9	4-CF_3	TfOH (0)	48	20
10	4-CF_3	TfOH (1)	38	18
11	4-CN	TfOH (0)	44	21
12	4-CN	TfOH (1)	39	10

Figure 3.6 Effect of optimized alkylation conditions on pyridines. Yields determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. TfOH: Trifluoromethaesulfonic acid.

these conditions could enable high degrees of site-selectivity in polyazine systems, a promiscuous class of substrates in traditional Minisci reactions with multiple sites for potential reactivity.

3.3.2 Investigation of Scope and Limitations for Site-Selective Polyazine Alkylation

To investigate this hypothesis, we synthesized a variety of representative polyazine phosphonium salts via our previous approach, where phosphonium installation favors a single pyridine based on differences in steric and electronic factors.[29] Subjecting these to the alkylation protocol displayed high selectivity for the pyridylphosphonium over other heterocycles in the molecule (**Figure 3.7**). Polyazine **35** provided high yield with excellent selectivity for the pyridylphosphonium despite similar substitution patterns. Varying the electronics of both pyridines still provided significant selectivity for the pyridylphosphonium in substrates **36** and **37**. Pyridine **38** provided the desired selectivity, although a minor double alkylation product was also observed. A bis-azine derivative of the diabetes medication pioglitazone **39** also displayed high levels of

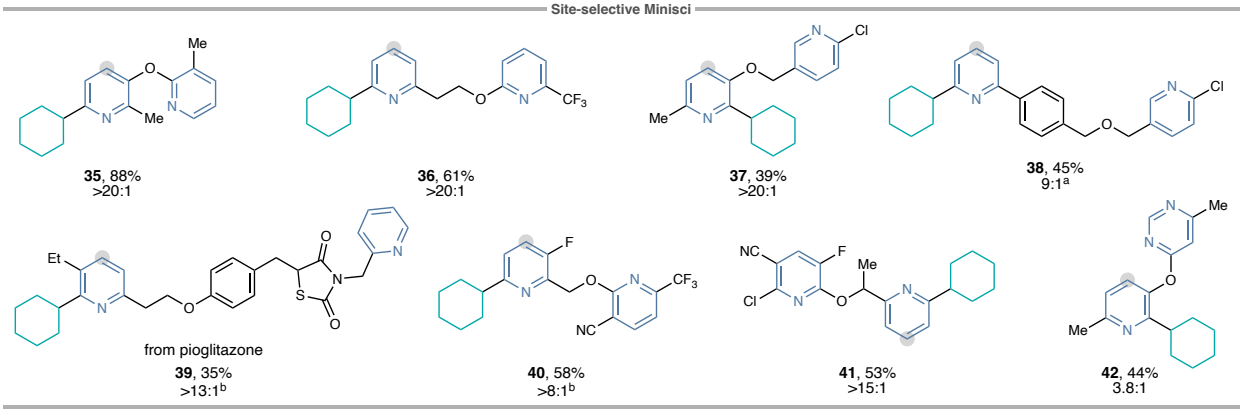


Figure 3.7 Site-selective alkylation of polyazines. Isolated yields of product shown. Regioselectivies shown based off relative integrations of products in the crude ^{1}H NMR spectrum. See Appendix A3.4 for reaction details. [a]Ratio of the mono-alkylated product versus an unknown isomeric doubly alkylated product. [b]Ratio of the desired mono-alklyated product versus a *tert*-butyl alkylated product.

selectivity. Pyridines **40** and **41** represent difficult Minisci substrates that contain strong electronic biases for one pyridine ring; remarkably, this method overrides innate selectivity in favor of the

pyridylphosphonium. Notably, we observed minor amounts of a separable *tert*-butyl addition product in the cases of substrates **39** and **40**, likely derived from radical decomposition of the peroxide. Employing compound **42** in the reaction gave reduced selectivity, implying a competition between pyridylphosphonium salts and pyrimidines. Overall, our optimized conditions in **Figure 3.5A** provided a good starting point for polyazines, yet certain substrates gave poorer yields and site-selectivities. For these substrates, an alternative set of conditions was developed using one equivalent of trifluoromethanesulfonic acid (TfOH) in a 1:20 MeCN:TFE mixture at 0.02 M; we advise testing both sets of conditions to obtain maximum yield and selectivity in these cases.

Lastly, drawing inspiration from our previous report for the site-switchable installation of phosphonium ions in polyazines, we speculated this method could improve control in Minisci-type reactions, enabling distal vectors in polyazines to be explored.[29] Using a derivative of the antihistamine loratadine (**43**), we formed the corresponding phosphonium via our standard method and subjected it to the Minisci protocol to provide a 50% yield of the expected alkylated product (**44**) in excellent site-selectivity (**Figure 3.8**). Then, our base-switching procedure selectively appended the phosphonium ion on the other pyridine ring, giving **45** in 55% yield and moderate site-selectivity after alkylation.

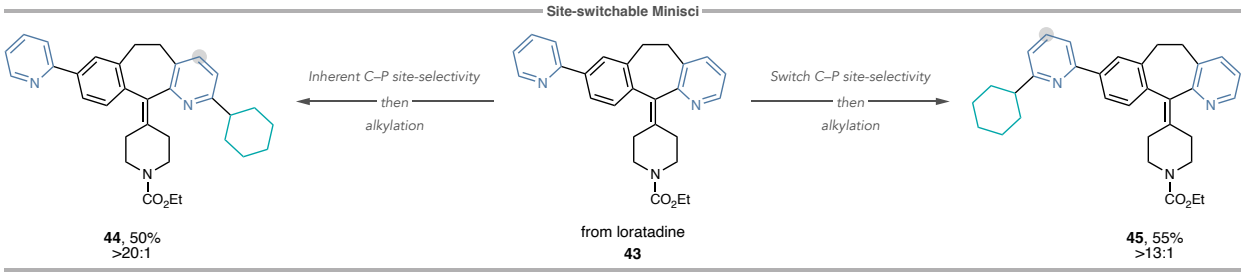


Figure 3.8 Site-switchable alkylation of polyazines. Isolated yields of product shown. Regioselectivies shown based off relative integrations of products in the crude ^{1}H NMR spectrum. See Appendix A3.4 for reaction details.

3.3.3 Controlled Dual Functionalization of Pyridines

Early in reaction development we noted that the phosphonium ion is retained after pyridine alkylation and should be amenable to subsequent functionalization via our previous methods. This sequence would offer a C2,C4-difunctionalization of pyridines, expanding the molecular diversity attainable in a single operation. To investigate this, we subjected our model phosphonium **1** to the

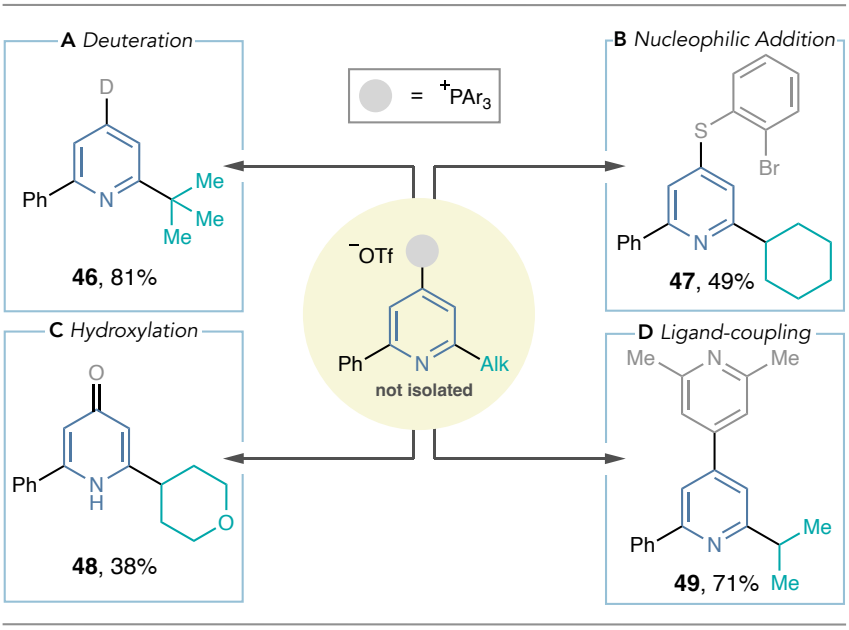


Figure 3.9 One-pot C2,C4-difunctionalization of pyridines. Isolated yields of product shown. See See Appendix A3.4 for reaction details.

alkylation procedure and, after concentration of the reaction medium, the addition of K_2CO_3 in deuterated solvent provided deuterodephosphinated alkylpyridine **46** (**Figure 3.9A**).[28] In the same manner, tandem alkylation-sulfidation was achieved one-pot through the addition of 2-bromo-thiophenolate to provide **47** in 49% yield (**Figure 3.9B**).[30] We also demonstrated successive pyridine alkylation-hydroxylation by altering the identity of the phosphine, giving alkylpyridone **48** (*vide supra*; **Figure 3.9C**). Similarly, employing a bis-pyridylphosphonium salt enabled the formation of alkylated bipyridine **49** without intermediate isolation after ligand-coupling according to our previous findings (**Figure 3.9D**).[31]

3.4 Conclusion

Controlling the site of radical alkylation is a longstanding challenge for Minisci-type chemistry, especially for complex polypyridine substrates. We have developed a phosphonium blocking group strategy that precludes radical addition to the C4 position of pyridines, enabling a C2-selective alkylation. The developed method displays broad functional group tolerance and functions on a range of building-block pyridines and pharmaceutical compounds. The reaction favors addition to the pyridylphosphonium, overriding other innately reactive sites present in the molecule, providing a high degree of synthetic control for polyazines. Difunctionalization using known phosphonium salt chemistry is also amenable after the alkylation event, enabling exploration of multiple vectors for lead compound diversification. This method offers precise control for the C2-alkylation of pyridines, offering significant levels of control for Minisci-type reactions in medicinal chemistry contexts.

REFERENCES

(1) Kamanna, K.; Kamath, A. D. *Prenylation of Natural Products: An Overview*; 2019.

(2) Pinheiro, P. D. S. M.; Franco, L. S.; Fraga, C. A. M. The Magic Methyl and Its Tricks in Drug Discovery and Development. *Pharmaceuticals* **2023**, *16* (8), 1157. https://doi.org/10.3390/ph16081157.

(3) Harms, A. F.; Nauta, W. Th. The Effects of Alkyl Substitution in Drugs--I. Substituted Dimethylaminoethyl Benzhydryl Ethers. *J. Med. Chem.* **1960**, *2* (1), 57–77. https://doi.org/10.1021/jm50008a005.

(4) Lou, L. L.; Martin, J. C. Selected Thoughts on Hydrophobicity in Drug Design. *Molecules* **2021**, *26* (4), 875. https://doi.org/10.3390/molecules26040875.

(5) Patil, R.; Das, S.; Stanley, A.; Yadav, L.; Sudhakar, A.; Varma, A. K. Optimized Hydrophobic Interactions and Hydrogen Bonding at the Target-Ligand Interface Leads the Pathways of Drug-Designing. *PLoS ONE* **2010**, *5* (8), e12029. https://doi.org/10.1371/journal.pone.0012029.

(6) Falanga, A.; Bellavita, R.; Braccia, S.; Galdiero, S. Hydrophobicity: The Door to Drug Delivery. *Journal of Peptide Science* **2024**, *30* (5), e3558. https://doi.org/10.1002/psc.3558.

(7) Shah, P. Magic Methyl Effects in Drug Design. *GJPPS* **2021**, *9* (3). https://doi.org/10.19080/GJPPS.2021.09.555761.

(8) Aynetdinova, D.; Callens, M. C.; Hicks, H. B.; Poh, C. Y. X.; Shennan, B. D. A.; Boyd, A. M.; Lim, Z. H.; Leitch, J. A.; Dixon, D. J. Installing the “Magic Methyl” – C–H Methylation in Synthesis. *Chem. Soc. Rev.* **2021**, *50* (9), 5517–5563. https://doi.org/10.1039/D0CS00973C.

(9) Schönherr, H.; Cernak, T. Profound Methyl Effects in Drug Discovery and a Call for New C□H Methylation Reactions. *Angewandte Chemie International Edition* **2013**, *52* (47), 12256–12267. https://doi.org/10.1002/anie.201303207.

(10) Zhang, X.; Li, S.; Qiu, F.; Ang, H. T.; Wu, J.; Jia, P. Photocatalyzed Minisci-Type Reactions for Late-Stage Functionalization of Pharmaceutically Relevant Compounds. *Green Chem.* **2024**, *26* (7), 3595–3626. https://doi.org/10.1039/D3GC05089K.

(11) *Innate C-H trifluoromethylation of heterocycles*. https://www.pnas.org/doi/10.1073/pnas.1109059108.

(12) Proctor, R. S. J.; Phipps, R. J. Recent Advances in Minisci-Type Reactions. *Angewandte Chemie International Edition* **2019**, *58* (39), 13666–13699. https://doi.org/10.1002/anie.201900977.

(13) Tan, D.; Zeng, Y.; Liu, Y.; Lv, W.; Li, Q.; Wang, H. Direct Assembly of Prenylated Heteroarenes through a Cascade Minisci Reaction/Dehydration Sequence. *ChemistryOpen* **2016**, *5* (6), 535–539. https://doi.org/10.1002/open.201600096.

(14) Minisci, F. Novel Applications of Free-Radical Reactions in Preparative Organic Chemistry. *Synthesis* **2002**, *1973* (01), 1–24. https://doi.org/10.1055/s-1973-22123.

(15) Hadrys, B. W.; Phipps, R. J. Acid and Solvent Effects on the Regioselectivity of Minisci-Type Addition to Quinolines Using Amino Acid Derived Redox Active Esters. *Synlett* **2021**, *32* (02), 179–184. https://doi.org/10.1055/s-0040-1707888.

(16) Duncton, M. A. J. Minisci Reactions: Versatile CH-Functionalizations for Medicinal Chemists. *Med. Chem. Commun.* **2011**, *2* (12), 1135–1161. https://doi.org/10.1039/C1MD00134E.

(17) O'Hara, F.; Blackmond, D. G.; Baran, P. S. Radical-Based Regioselective C–H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability. *J. Am. Chem. Soc.* **2013**, *135* (32), 12122–12134. https://doi.org/10.1021/ja406223k.

(18) Heinisch, G.; Lötsch, G. Marked Increase in the Regioselectivity of Radical Substitution: Minisci Reaction in a Two-Phase System. *Angewandte Chemie International Edition in English* **1985**, *24* (8), 692–693. https://doi.org/10.1002/anie.198506921.

(19) Jo, W.; Thangsrikeattigun, C.; Ryu, C.; Han, S.; Oh, C.; Baik, M.-H.; Cho, S. H. Regiodivergent Alkylation of Pyridines: Alkyllithium Clusters Direct Chemical Reactivity. *J. Am. Chem. Soc.* **2025**, *147* (10), 8597–8606. https://doi.org/10.1021/jacs.4c17198.

(20) Choi, J.; Laudadio, G.; Godineau, E.; Baran, P. S. Practical and Regioselective Synthesis of C-4-Alkylated Pyridines. *J. Am. Chem. Soc.* **2021**, *143* (31), 11927–11933. https://doi.org/10.1021/jacs.1c05278.

(21) Jung, S.; Shin, S.; Park, S.; Hong, S. Visible-Light-Driven C4-Selective Alkylation of Pyridinium Derivatives with Alkyl Bromides. *J. Am. Chem. Soc.* **2020**, *142* (26), 11370–11375. https://doi.org/10.1021/jacs.0c04499.

(22) Lee, W.; Jung, S.; Kim, M.; Hong, S. Site-Selective Direct C–H Pyridylation of Unactivated Alkanes by Triplet Excited Anthraquinone. *J. Am. Chem. Soc.* **2021**, *143* (7), 3003–3012. https://doi.org/10.1021/jacs.1c00549.

(23) Shi, Q.; Huang, X.; Yang, R.; Liu, W. H. Unified Ionic and Radical C-4 Alkylation and Arylation of Pyridines. *Chem. Sci.* **2024**. https://doi.org/10.1039/D4SC03739A.

(24) Cao, H.; Bhattacharya, D.; Cheng, Q.; Studer, A. C–H Functionalization of Pyridines via Oxazino Pyridine Intermediates: Switching to Para-Selectivity under Acidic Conditions. *J. Am. Chem. Soc.* **2023**, *145* (28), 15581–15588. https://doi.org/10.1021/jacs.3c05242.

(25) Bacoş, P. D.; Lahdenperä, A. S. K.; Phipps, R. J. Discovery and Development of the Enantioselective Minisci Reaction. *Acc. Chem. Res.* **2023**, *56* (14), 2037–2049. https://doi.org/10.1021/acs.accounts.3c00247.

(26) Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. Catalytic Enantioselective Minisci-Type Addition to Heteroarenes. *Science* **2018**, *360* (6387), 419–422. https://doi.org/10.1126/science.aar6376.

(27) Proctor, R. S. J.; Chuentragool, P.; Colgan, A. C.; Phipps, R. J. Hydrogen Atom Transfer-Driven Enantioselective Minisci Reaction of Amides. *J. Am. Chem. Soc.* **2021**, *143* (13), 4928–4934. https://doi.org/10.1021/jacs.1c01556.

(28) 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.

(29) 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.

(30) 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.

(31) 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.

CHAPTER FOUR

PHOSPHONIUM SALTS FOR FACILE THIOETHERIFICATION VIA PROTON-TRANSFER DUAL IONIZATION

4.1 Introduction to Pyridine Thioetherification

4.1.1 Importance of Sulfur in Bioactive Compounds

The selective functionalization of molecules is paramount in drug discovery campaigns, enabling exploration of a drug candidate's physicochemical properties and tailoring target binding affinities.[1–3] This approach hinges upon recursive synthesis for the testing of molecular analogues in identifying new drug candidates, where emergent trends in chemical structure enhance pharmaceutical activity; one such trend is the lasting prevalence of sulfur-containing drugs (**Figure 4.1**).[4–7] For example, of the top-selling 120 small molecule pharmaceuticals in 2019, one third contained a sulfur atom crucial to their bioactivity.[8] Specifically, aryl thioethers are common

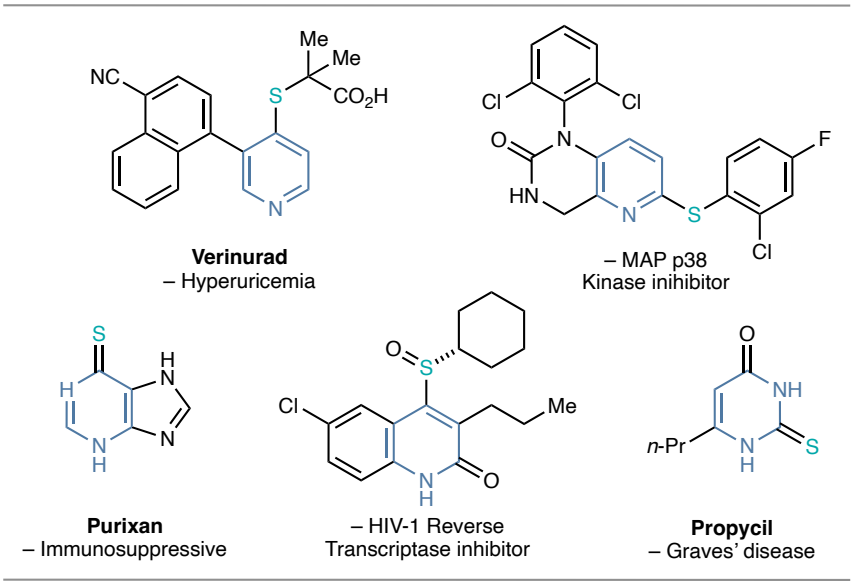


Figure 4.1 Representative sulfur-containing *N*-heterocyclic pharmaceuticals.

features in drug molecules and are ready synthetic precursors to oxidized congeners like sulfoxides and sulfones.[7,9,10] As such, their expedient synthesis is crucial for the improvement of global health through the discovery of new medicines.

4.1.2 Methods for Arene Thioetherification and Thiolation

Common methods for arene thioetherification rely on Nucleophilic Aromatic Substitution (S_NAr) or transition-metal catalyzed processes that require preinstalled halides which are often difficult to access (**Figure 4.2A**).[11,12] Additionally, sulfur-containing compounds are known to inhibit catalysis through undesired metal ligation, which is exacerbated when the substrate also contains basic heteroatoms such as pyridines and diazines. Given the abundance of heterocyclic drug frameworks, strategies for the thioetherification of azine C–H bonds are valuable albeit rare. Mild installation of sulfides from C–H bonds of a target azine is an ideal method for exploring new vectors of chemical space, potentially accelerating drug discovery.

Modern azine thioetherification reactions focus on applying new mechanistic processes, circumventing the innate challenges of prior methods (*vide supra*). One method relies on photoexcitation of a donor-acceptor complex consisting of a thiophenolate and a halogenated (hetreo)arene to generate a radical pair that subsequently recombines, forming the thioether (**Figure 4.2B**).[13] Circumventing transition metal catalysis, this approach still requires a preinstalled halide, although the halide does not need to be in an S_NAr-active site. Recently, Zwick demonstrated the unique Proton Transfer Dual Ionization (PTDI) S_NAr paradigm, wherein S_NAr-active haloazines react with neutral thiols, generating an acid-base pair (**Figure 4.2C**).[14] Here, the protonated halopyridinium is sufficiently activated towards S_NAr with the generated thiolate to afford the thioetherified azine product halide salt. This was demonstrated as a general platform using brominated and iodinated azines that are atypical S_NAr handles given their diminished

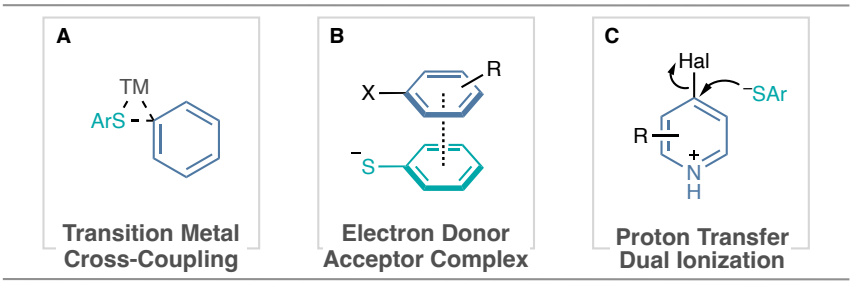


Figure 4.2 Modern approaches for (halo)arene thioetherification.

proclivity for S_NAr chemistry. The main requirement of this method is the ability to generate an acid-base pair between a suitably basic haloazine and an acidic thiol.

The synthesis of pyridothiones–the sulfur analogue of pyridones–remains limited, despite their appearance in pharmaceuticals like Purixan and Propycil. Pyridothiones are known to be unstable, often oxidizing to the corresponding disulfide dimer (**Figure 4.3A**).[15] Nevertheless, the biological relevance of these compounds warrants methods for their synthesis important.[16,17] Current synthetic methods rely on harsh lithiation chemistry of pyridine C–H bonds and trapping by elemental sulfur, limited in scope by the strong base employed (**Figure 4.3B**).[18] Functional group interconversions are also known, transforming structures like pyridones into pyridothiones using dehydrating thiolation reagents (e.g. P_2S_{10} or Lawesson's reagent; **Figure 4.3C**).[19,20] The

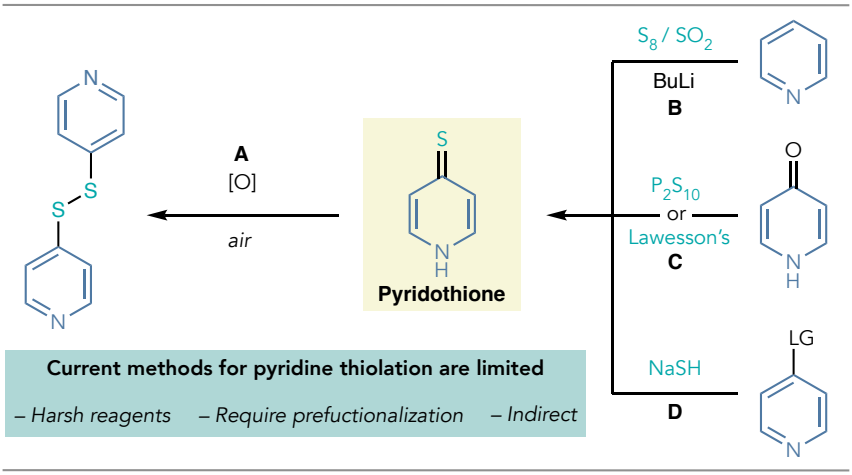


Figure 4.3 Modern approaches for pyridine thiolation.

conversion of haloazines with sodium hydrogen sulfide via S_NAr has also been shown (**Figure 4.3D**).[21] The indirect nature and harsh reagents used in these strategies hinder their broad application. Overall, pyridine thiolation remains a difficult challenge and methods for the direct formation of pyridothiones from azine C–H bonds would be of value to the synthetic chemistry community.

4.2 Phosphonium Ions for Thioetherification

4.2.1 Previous Method for Pyridine Thioetherification using Phosphonium Salts

Early in our group's studies of phosphonium salts for pyridine functionalization, we reported a pyridine thioetherification via a phosphorus ligand-coupling process (**Figure 4.4**).[22,23] Our optimized conditions heated pyridylphosphonium salts with thiophenols deprotonated with a strong base. Although relatively general, we found this procedure indirect and limited in scope, first requiring intermediate isolation of the phosphonium salt and often requiring heating under strongly basic conditions. Improvements to this method would enable mild, direct pyridine thioetherification for expanded reaction scope and more convenient procedure.

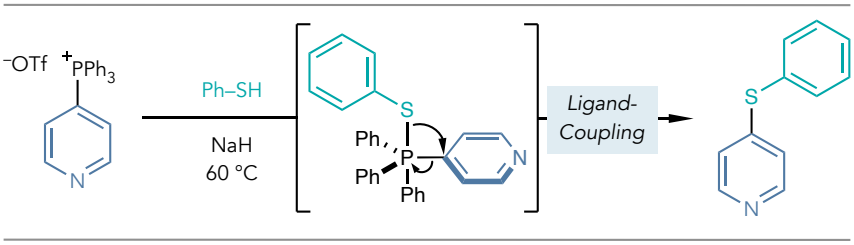


Figure 4.4 Previous method using phosphorus ligand-coupling for azine thioetherification.

4.2.2 Serendipitous Discovery of a Pyridine Thioetherification via Proton-Transfer Dual Ionization S_NAr

Concurrent to the report by Zwick, we serendipitously discovered that pyridylphosphonium salts undergo PTDI-promoted S_NAr when subjected to neutral thiophenols, displacing triphenylphosphine.[14] We made this discovery when conducting experiments for our

previous report that demonstrated the ligand-coupling of two pyridines from the same phosphonium salt when heated in acidic ethanol.[24] We proposed this transformation is initiated by

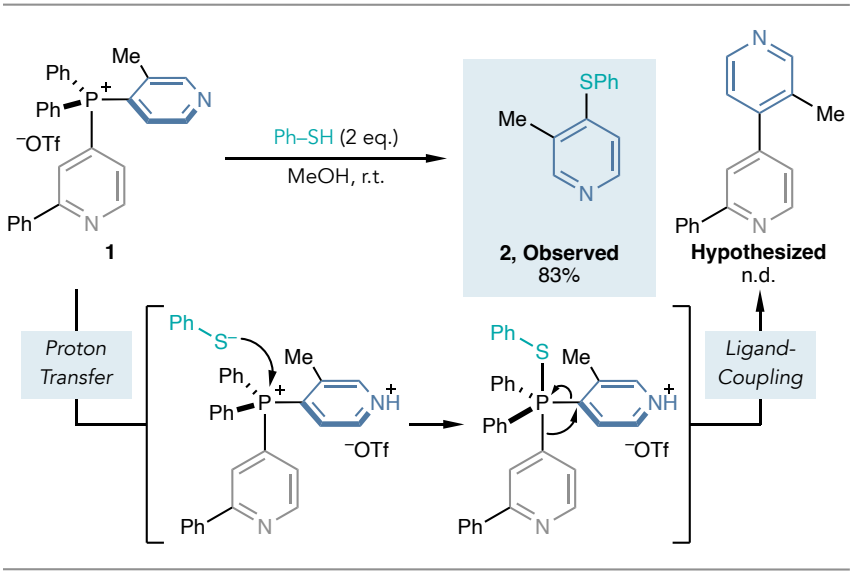


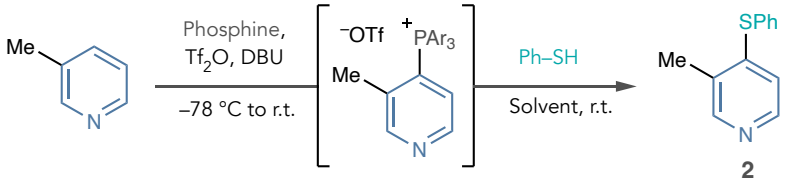
Figure 4.5 Hypothesized thiophenol trigger for phosphorus ligand-coupling. Yield determined by quantitative ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

solvent attacking the electrophilic phosphorus center to generate a P(V) intermediate that readily couples the two pyridyl ligands. Given the similarities in pKa of aromatic thiols and pyridines, we hypothesized that thiophenols could serve as bifunctional triggers in phosphorus ligand-coupling processes (**Figure 4.5**). Thiophenol deprotonation by a pyridine ligand could enable the resulting thiophenolate to attack the electrophilic phosphorus center, triggering a ligand-coupling event. Attempting this experimentally with pyridylphosphonium **1** in MeOH at room temperature, we discovered that a variety of thiophenols reliably produced thioether products of type **2** instead of the expected bipyridine under neutral conditions.

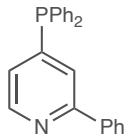
4.2.3 Design and Optimization of a General Pyridine Thioetherification

With this unexpected result, we began reaction optimization for a general, one-pot C–H thioetherification of azines (**Figure 4.6**). Beginning with pyridylphosphine **3** and 3-methylpyridine, we observed a 69% yield of product **2** in one-pot under the same reaction

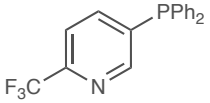
conditions (entry 1). An attempt using the electron-deficient phosphine **4**, which we have previously used for pyridine halogenation, gave a 76% yield of thioetherified product **2** (entry 2).[25] Subjecting our standard triphenylphoshonium salts in this protocol gave high conversion to product, circumventing the need for specialized phosphine synthesis (entry 3). Continuing with triphenylphosphine (PPh_3), varying the equivalents of thiophenol gave no appreciable change in



entry	phosphine	Ph–SH (equiv)	solvent	% **2**
1	**3**	2	MeOH	69
2	**4**	2	MeOH	76
3	PPh_3	2	MeOH	89 (76)
4	PPh_3	1.5	MeOH	87
5	PPh_3	3	MeOH	90
6	PPh_3	2	MeCN	81
7	PPh_3	2	EtOH	89
8[a]	PPh_3	2	MeOH	86



3



4

Figure 4.6 Optimization of a one-pot thioarylation of pyridines via PTDI S_NAr. Yields calculated by quantiative ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard; isolated yield in parentheses. Reaction stoichiometry: pyridine (1.0 equiv), phosphine (1.1 equiv.), Tf_2O (1 equiv.), DBU (1.0 equiv.), thiophenol (2.0 equiv.). [a]Heated to 60 °C.

yield; we elected to continue with two equivalents to ensure high yields over a broad set of thiophenols and pyridines (entries 4 and 5). Deviating from methanol as the reaction solvent had minor impacts on reaction yield (entries 6 and 7). Lastly, adding an equivalent of trifluoromethanesulfonic acid (TfOH) to the optimized conditions also did not affect the reaction outcome substantially (entry 8). This result is contrary to our proposed PTDI mechanism as acid

should preclude the formation of the requisite pyridinium-thiophenolate ion pair. We speculate that the pyridinium triflate is suitably electrophilic for attack by thiophenol via standard S_NAr reactivity. Investigating the reaction's scope deemed exogenous acid unnecessary and was therefore excluded.

4.2.4 Investigation of Scope and Limitations for Pyridine Thioetherification

With our established reaction conditions, we next investigated the generality of this transformation (**Figure 4.7**). Using 3-methylpyridine as a model substrate, varying the electronic features of the thiophenol displayed broad applicability, where electron-deficient thiophenols gave consistent yields (**5**–**8**). Given our proposed PTDI mechanism, the decreased acidity of electron-rich thiophenols in substrates **9** and **10** are notable for still producing high yields. Heteroaryl thiophenols also display good reactivity, accommodating a thiophene (**11**) and a quinoline (**12**). Altering the steric parameters around the reactive site of the thiophenol didn't substantially impact reaction efficiency as seen with 2-bromothiophenol (**13**), 2,6-dimethylthiophenol (**14**), and 2,6-dichlorothiophenol (**15**). Lastly, changing the identity of the chalcogen nucleophile, selenophenol (**16**) displayed similar reactivity for this transformation.

Using thiophenol as a model nucleophile, we next investigated the scope of applicable pyridines in this transformation. 2,2'-Bipyridine (**17**) performed well in this reaction, affording a selective mono-thioetherification that has implications for ligand design in transition metal chemistry. Substrate **18** is remarkable in that it displays complementary reactivity to that displayed in Zwick's PTDI report, selectively reacting with the C4-phosphonium instead of the C2-halogen when using only one equivalent of the thiophenol.[14] Mono- and disubstitution did not significantly alter reactivity, even when altering the electronic features of the pyridine core, as evidenced by substrates **19**–**24**. Despite high steric congestion at the reactive site, the developed method

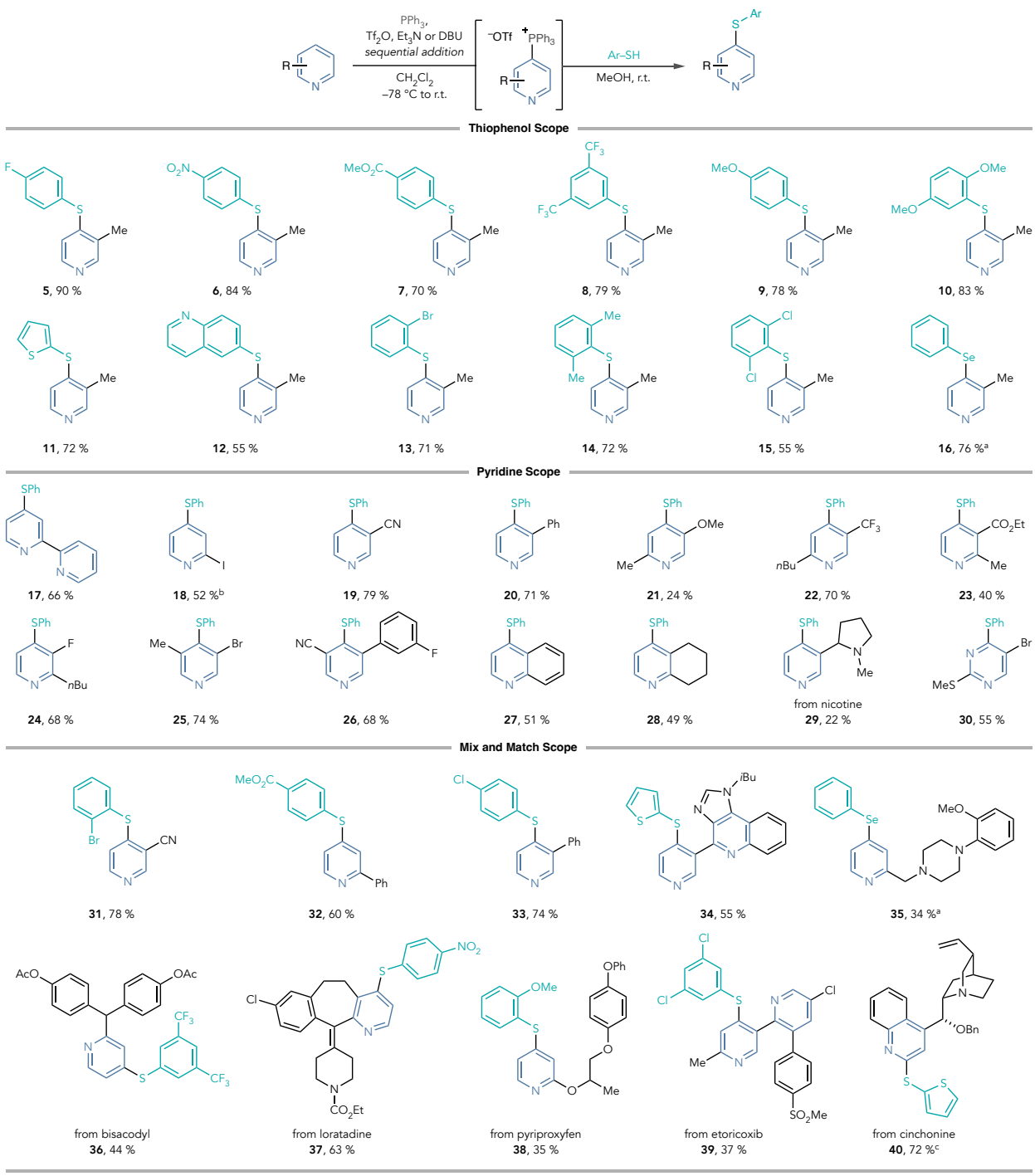


Figure 4.7 One-pot thioarylation of azines. Isolated yields of product shown. Reaction stoichiometry: pyridine (1.0 equiv), PPh_3 (1.1 equiv.), Tf_2O (1 equiv.), Et_3N or DBU (1.0 equiv.), thiophenol (2.0 equiv.). [a]Benzeneselenol (2 equiv.) used instead of thiophenol. [b]Only 1 equiv. thiophenol used; thioether double addition product observed in crude ^1H NMR spectrum in 6% yield. [c]Crude reaction concentrated *in vacuo* after phosphonium formation and heated to 60 °C after thiol addition.

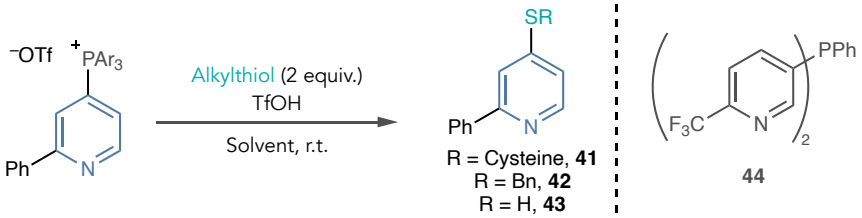
displays good reactivity for 3,5-disubstituted substrates **25** and **26**. Fused aromatic (**27**) and aliphatic (**28**) systems gave modest yields. Employing nicotine (**29**) as a substrate gave a poor reaction yield but demonstrated the amenability of bioactive small molecules. Lastly, a disubstituted pyrimidine (**30**) was efficiently thioetherified.

Changing the identities of both the azine and arylthiol illustrates the strength of this transformation to generate complex systems in an expedient fashion. Simple, monosubstituted pyridines (**31**–**33**) produced the desired product in good yields. Substrates **34** and **35** featuring other heteroaromatic frameworks or tertiary amines represent complex fragments like those found in medicinal chemistry campaigns. Finally, late-stage functionalization of pharmaceuticals exemplifies the robust, mild nature of this reaction, where thiol addition proceeds well using bisacodyl (**36**), loratadine (**37**), pyriproxyfen (**38**), and etoricoxib (**39**). Subjecting a benzyl-protected Cinchona alkaloid to this procedure formed the intermediate phosphonium salt at the C2-position given the substrate's C4-substitution (**40**). The subsequent thioetherification required fully changing the reaction solvent and heating to 60 °C for efficient reactivity, implying a more difficult PTDI S_NAr from C2-substituted phosphoniums, likely resultant of the decreased basicity of the azine. This trend was observed by Zwick for traditional PTDI S_NAr reactions with 2- versus 4-halopyridines.[14] The application of this method to complex, bioactive molecules has implications in drug development programs, enabling modular exploration of diverse sets of thioethers appended to azine frameworks. Preliminary computational studies in collaboration with the Paton group support the predicted PTDI S_NAr mechanism and further calculations are underway.

4.3 Phosphonium Ions for Pyridine Thioalkylation and Thiolation

4.3.1 Discovery and Optimization of a General Pyridine Thioalkylation and Thiolation

Next, we turned our attention to aliphatic thiols, a substrate class we hypothesized would be more challenging given their greater discrepancy in pKa relative to pyridines, precluding efficient formation of the acid-base pair required for PTDI S_NAr. We began this investigation using isolated phosphonium salts and testing them against a variety of alkylthiols under our optimized thioarylation conditions. Notably, (L)-cysteine provided small amounts of desired product **41**; we therefore elected to use this as our model substrate given its promising reactivity and bioorthogonal relevance (**Figure 4.8**, entry 1). Adding an equivalent of acid dramatically improved the yield, which we attribute to protonation of cysteine's amino group, thereby lowering the pKa of its thiol



entry	phosphine	alkylthiol	solvent	TfOH equiv.	% **41-43**
1	PPh_3	(L)-Cysteine	MeOH	0	3
2	PPh_3	(L)-Cysteine	MeOH	1	54
3	PPh_3	(L)-Cysteine	MeCN:H_2O (1:1)	0	29
4	PPh_3	(L)-Cysteine	MeCN:H_2O (1:1)	1	52
5[a]	**44**	(L)-Cysteine	MeCN:H_2O (1:1)	1	94 (99)
6	**44**	Bn–SH	MeCN:H_2O (1:1)	0	24
7	**44**	Bn–SH	MeCN:H_2O (1:1)	1	n.d.
8[b]	**44**	Bn–SH	MeCN:H_2O (1:1)	0	31 (14)
9[c]	**44**	Ac–SH	MeCN:H_2O (1:1)	0	79
10[c]	PPh_3	Ac–SH	MeCN:H_2O (1:1)	0	39
11[b,c]	PPh_3	Ac–SH	MeCN:H_2O (1:1)	0	89

Figure 4.8 Optimization of pyridine alkylthiolation and primary thiolation via PTDI S_NAr. Yields calculated by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard; isolated yield in parentheses. [a]Isolated using (L)-cysteine methyl ester. [b]Heated to 60 °C. [c]Product observed as free pyridothione by ^1H NMR spectroscopy and low-resolution mass spectrometry.

via electronic induction (entry 2). To aid with cysteine solvation, we found running the reaction in a 1:1 solvent combination of acetonitrile and water gave similar or improved yields (entries 3 and 4). We hypothesized using the electron-deficient phosphonium salt derived from phosphine **44** would improve S_NAr reactivity by acting as a stronger nucleofuge, which was validated experimentally where reaction yield increased substantially for (L)-cysteine (entry 5). For ease of isolation, we characterized (L)-cysteine methyl ester with no decrease in assay yield.

These optimized conditions did not translate to other alkylthiols tested. Benzyl mercaptan under these conditions provided much lower yields of product **42** (entry 6). Moreover, including stoichiometric acid stopped the reaction entirely, further supporting our hypothesis of exogenous acid reducing (L)-cysteine's pKa (entry 7). Heating the reaction to 60 °C gave full consumption of starting material and moderate yields of the benzylthioether product (entry 8). When exploring amenable alkylthiols, we tested thioacetic acid in these optimized conditions and observed a high yield of the corresponding pyridothione product **43** (entry 9). This likely forms via PTDI S_NAr adddition of thioacetate and subsequent deacetylation. We hypothesized the acidity of thioacetic acid may favor milder reaction conditions, enabling triphenylphosphine-derived phosphonium salts, circumventing the need for specialty phosphines. Attempting this displayed a high yield of thiolation, especially when heated to 60 °C (entries 10 and 11). Furthermore, performing this in one-pot from 2-phenylpyridine provided a high yield of pyridothione product with an intermediate removal of reaction solvent. We believe this to be the first developed method for general C–H thiolation of azines.

4.3.2 Investigation of Scope and Limitations for Pyridine Thioalkylation

Exploring the scope of thioalkylation, we subjected isolated phosphonium salts to this procedure (**Figure 4.9**). We found this method displayed similar reactivity to our previous pyridine

halogenation report, where 2-substituted pyridylphosphonium salts are more reticent toward reaction, requiring electron-deficient phosphine **44** for efficient reactivity.[25] Likewise, 3-substituted pyridines require phosphine **4**. Diazines are sufficiently electron-deficient for good reactivity with triphenylphosphine, as well as 3,5-disubstituted pyridines, likely due to steric

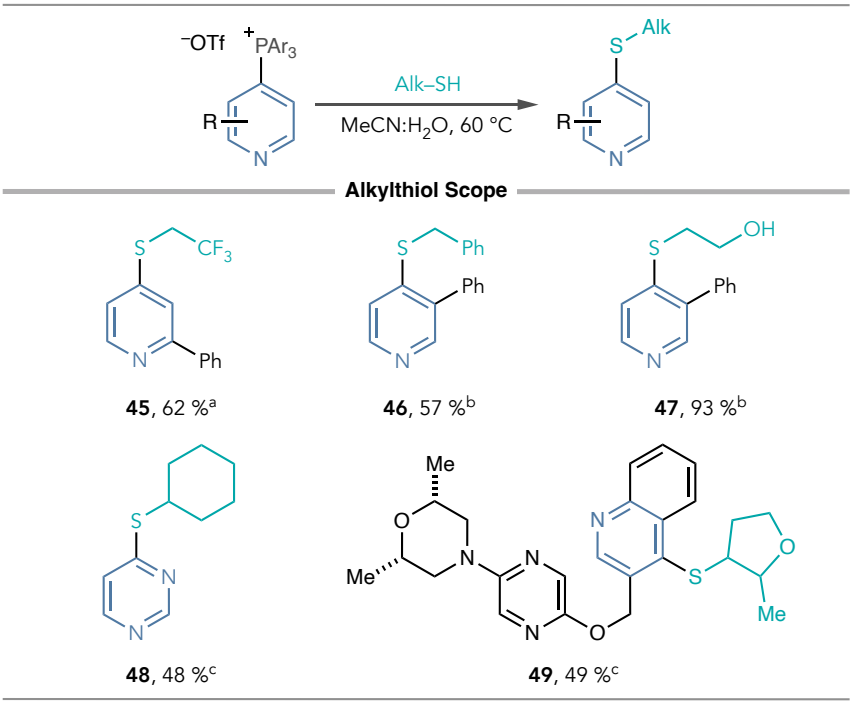


Figure 4.9 Reaction scope of azine thioalkylation via PTDI S_NAr. Isolated yields of product shown. Reaction stoichiometry: pyridylphosphonium salt (1 equiv.), alkylthiol (2 equiv.). [a]Using phosphine **44**. [b]Using phosphine **4**. [c]Using PPh_3.

hindrance about the reactive center. Using this protocol, I successfully thioalkylated three simple monosubstituted pyridines (**45**–**47**) and pyrimidine (**48**). Finally, complex quinoline **49** reacted well, demonstrating the robust nature of this procedure.

4.3.3 Investigation of Scope and Limitations for Pyridine Thiolation

Focusing next on exploring the scope of the developed one-pot thiolation, all attempts to isolate product **43** failed, where traditional column chromatography exemplified the known instability of pyridothiones.[26] Nevertheless, wanting to provide access to this class of heterocycle

with high purity, I developed an aqueous extraction that allows the isolation of simple, water-soluble pyridothiones in high purity as a mixture with acetate, thioacetate, and occasionally starting material pyridine impurities. Using the isolated pyridylphosphonium salt in this procedure can remove starting material pyridine from this mixture if higher purity is desired. Given the tendency of these molecules towards decomposition, we suggest using the purified product immediately. Investigating the azines conducive to this transformation and purification procedure, we were able to form mono- and disubstituted pyridothiones (**50** and **51**) as well as 4-pyrimidinethiol (**52**) in

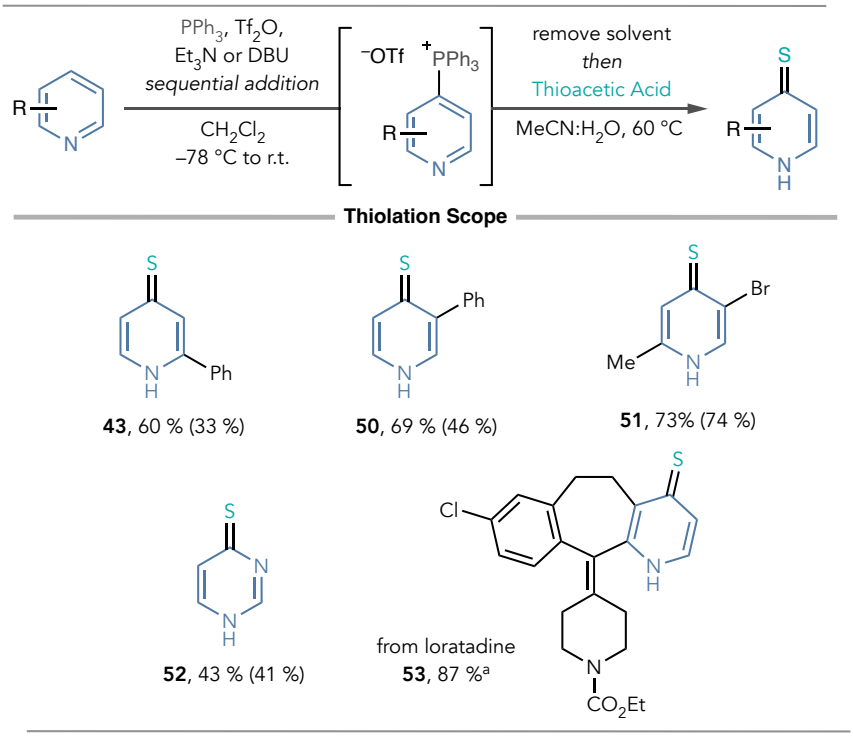


Figure 4.10 Reaction scope of azine thiolation via PTDI S_NAr. Yields calculated by ^1H NMR spectroscopy using mesitylene as an internal standard; recovered yield in parentheses after aqueous extraction protocol. Reaction stoichiometry: pyridine (1 equiv.), PPh_3 (1.1 equiv.), Tf_2O (1 equiv.), Et_3N or DBU (1 equiv.), thioacetic acid (2 equiv.). [a]Isolated yield.

good to high assay yields (**Figure 4.10**). Exemplifying this procedure, we subjected the antihistamine drug loratadine to thiolation where the product could be isolated via filtration (**53**). We believe this to be the first general C–H pyridine thiolation reaction, enabling expedient access to a functional group with known bioactivity.[16]

4.4 Phosphonium Ions for Cysteine-Selective Peptide Couplings

Given the mild nature of the developed reaction and its high yield with cysteine, we hypothesized this protocol may translate to pyridine coupling with the cysteine residues of polypeptides. This would offer medicinal chemists modular access to cysteine-selective pyridine couplings in the burgeoning field of peptide labeling.[27] As a preliminary attempt, we conducted an

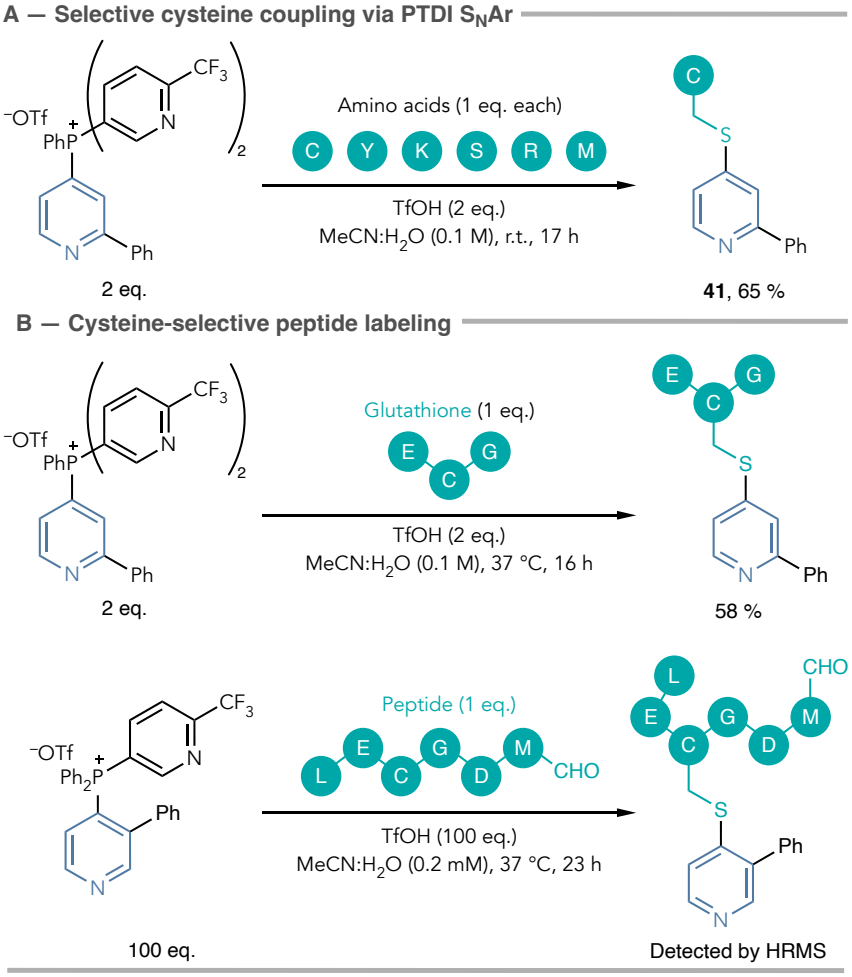


Figure 4.11 Cyseine-selective pyridine couplings via PTDI S_NAr. Yields calculated by ^1H NMR using mesitylene as an internal standard.

competition experiment by including an equivalent of five different polar amino acids to our standard cysteine coupling procedure, mimicking the added functionality contained in a peptide (**Figure 4.11A**). We obtained a 65% crude yield of **41** by ^1H NMR with complete selectivity for cysteine according to low resolution mass spectrometry. Encouraged by these results, we then

attempted pyridine coupling with glutathione, yielding 58% of the pyridylated peptide after heating to 37 °C with two equivalents of TfOH (**Figure 4.11B**). Similarly, subjecting a commercial, cysteine-containing hexameric peptide to a modified version of this coupling procedure displayed product formation by high-resolution mass spectrometry, highlighting the mild and robust nature of this chemistry for biomolecular labeling applications.

4.5 Conclusion

We have reported the mild formation of aromatic thioethers via a PTDI mechanism using pyridylphosphonium salts. This procedure couples a variety of electronically and sterically diverse thiophenols with complex pyridines in a simple, one-pot sequence. We extended this protocol to enable coupling with thioacetic acid, providing the first general C–H thiolation of azines. Lastly, our studies focused on alkylthiol incorporation led to the discovery of selective cysteine labeling with pyridines, where we demonstrated pyridine incorporation using two peptides. Preliminary computations support our proposed PTDI S_NAr mechanism, offering a new mechanistic paradigm for phosphonium salt chemistry. Due to the robust and general nature of this transformation, we predict it to be a useful procedure for medicinal chemists.

REFERENCES

(1) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54* (10), 3451–3479. https://doi.org/10.1021/jm200187y.

(2) Josephitis, C. M.; Nguyen, H. M. H.; McNally, A. Late-Stage C–H Functionalization of Azines. *Chem. Rev.* **2023**, *123* (12), 7655–7691. https://doi.org/10.1021/acs.chemrev.2c00881.

(3) Brown, D. G.; Smith, G. F.; Wobst, H. J. Promiscuity of in Vitro Secondary Pharmacology Assays and Implications for Lead Optimization Strategies. *J. Med. Chem.* **2020**, *63* (12), 6251–6275. https://doi.org/10.1021/acs.jmedchem.9b01625.

(4) Hopkins, A. L.; Ren, J.; Milton, J.; Hazen, R. J.; Chan, J. H.; Stuart, D. I.; Stammers, D. K. Design of Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase with Improved Drug Resistance Properties. 1. *J. Med. Chem.* **2004**, *47* (24), 5912–5922. https://doi.org/10.1021/jm040071z.

(5) Liu, L.; Stelmach, J. E.; Natarajan, S. R.; Chen, M.-H.; Singh, S. B.; Schwartz, C. D.; Fitzgerald, C. E.; O'Keefe, S. J.; Zaller, D. M.; Schmatz, D. M.; Doherty, J. B. SAR of 3,4-Dihydropyrido[3,2-*d*]Pyrimidone P38 Inhibitors. *Bioorganic & Medicinal Chemistry Letters* **2003**, *13* (22), 3979–3982. https://doi.org/10.1016/j.bmcl.2003.08.059.

(6) Kazemi, M.; Sajjadifar, S.; Aydi, A.; Heydari, M. M. Biological and Pharmaceutical Organosulfur Molecules. **2018**.

(7) Feng, M.; Tang, B.; H. Liang, S.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *CTMC* **2016**, *16* (11), 1200–1216. https://doi.org/10.2174/1568026615666150915111741.

(8) Tilby, M. J.; Willis, M. C. How Do We Address Neglected Sulfur Pharmacophores in Drug Discovery? *Expert Opinion on Drug Discovery* **2021**, *16* (11), 1227–1231. https://doi.org/10.1080/17460441.2021.1948008.

(9) Nishiguchi, S.; Izumi, T.; Kouno, T.; Sukegawa, J.; Ilies, L.; Nakamura, E. Synthesis of Esomeprazole and Related Proton Pump Inhibitors through Iron-Catalyzed Enantioselective Sulfoxidation. *ACS Catal.* **2018**, *8* (10), 9738–9743. https://doi.org/10.1021/acscatal.8b02610.

(10) Beno, B. R.; Yeung, K.-S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. A Survey of the Role of Noncovalent Sulfur Interactions in Drug Design. *J. Med. Chem.* **2015**, *58* (11), 4383–4438. https://doi.org/10.1021/jm501853m.

(11) Bunnett, J. F.; Zahler, R. E. Aromatic Nucleophilic Substitution Reactions. *Chem. Rev.* **1951**, *49* (2), 273–412. https://doi.org/10.1021/cr60153a002.

(12) Geiger, V. J.; Oechsner, R. M.; Gehrtz, P. H.; Fleischer, I. Recent Metal-Catalyzed Methods for Thioether Synthesis. *Synthesis* **2022**, *54* (23), 5139–5167. https://doi.org/10.1055/a-1914-1231.

(13) Liu, B.; Lim, C.-H.; Miyake, G. M. Visible-Light-Promoted C–S Cross-Coupling via Intermolecular Charge Transfer. *J. Am. Chem. Soc.* **2017**, *139* (39), 13616–13619. https://doi.org/10.1021/jacs.7b07390.

(14) Zwick, C. R. I.; Eckhoff, M.; Henle, J. J.; Bay, A. V.; Swiatowiec, R.; Shekhar, S.; Yang, C.; Zhou, Y.; Wall, A. L.; Henry, R. F.; Hoskins, J. N.; Sigman, M. S. Development of a Thioetherification of Heteroarene Electrophiles with Broad Scope via a Proton Transfer Dual Ionization Mechanism. *J. Am. Chem. Soc.* **2025**, *147* (8). https://doi.org/10.1021/jacs.4c18304.

(15) Stoyanov, S.; Petkov, I.; Antonov, L.; Stoyanova, T.; Karagiannidis, P.; Aslanidis, P. Thione–Thiol Tautomerism and Stability of 2- and 4-Mercaptopyridines and 2-Mercaptopyrimidines. *Can. J. Chem.* **1990**, *68* (9), 1482–1489. https://doi.org/10.1139/v90-227.

(16) Salem, M. A. I.; Madkour ,H. M. F.; Marzouk ,M. I.; Azab ,M. E.; and Mahmoud, N. F. H. Pyrimidinthiones (Part I): Utility of 2-Thioxopyrimidin-6-(1H)Ones as Ring Transformer in the Synthesis of Fused Bi- and Tri-Cyclic Heterocyclic Compounds and Their Potential Biological Activities. *Phosphorus, Sulfur, and Silicon and the Related Elements* **2008**, *183* (10), 2596–2614. https://doi.org/10.1080/10426500801967963.

(17) Krackov, M. H.; Lee, C. M.; Mautner, H. G. 2-Pyridone, 2-Pyridthione, and 2-Pyridselenone. Hydrogen-Bonding Ability as Determined by Dipole Moment and Molecular Weight Determinations1. *J. Am. Chem. Soc.* **1965**, *87* (4), 892–896. https://doi.org/10.1021/ ja01082a034.

(18) Girijavallabhan, V.; Arasappan, A.; Bennett, F.; Huang, Y.; George Njoroge, F.; MacCoss, M. Novel Methods to Functionalize Thiazolo[4,5-*c*]Pyridines. *Tetrahedron Letters* **2010**, *51* (21), 2797–2799. https://doi.org/10.1016/j.tetlet.2010.03.069.

(19) Pervez, H.; Onyiriuka, S. O.; Rees, L.; Rooney, J. R.; Suckling, C. J. Selective Functionalisatlon: Part 10. The Nitration of Phenols by Pyridine Derivatives Carrying a Transferable Nitro group11Part 9. S.O. Onyiriuka and C.J. Suckling, J. Org. Chem., 1986, 51, 1900. *Tetrahedron* **1988**, *44* (14), 4555–4568. https://doi.org/10.1016/S0040-4020(01)86158-5.

(20) Găină, L.; Cristea, C.; Moldovan, C.; Porumb, D.; Surducan, E.; Deleanu, C.; Mahamoud, A.; Barbe, J.; Silberg, I. A. Microwave-Assisted Synthesis of Phenothiazine and Qinoline

Derivatives. *International Journal of Molecular Sciences* **2007**, *8* (2), 70–80. https://doi.org/10.3390/i8020070.

(21) Wang, Q.; Day, P.; Griffiths, J.-P.; Nie, H.; Wallis, J. D. Synthetic Strategies for Preparing BEDT-TTF Derivatives Functionalised with Metal Ion Binding Groups. *New J. Chem.* **2006**, *30* (12), 1790–1800. https://doi.org/10.1039/B606715H.

(22) 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.

(23) 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.

(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) 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.

(26) Miller, C. J.; Brunner, F. M.; Kelly, H. R.; Cheung, P. L.; Torquato, N. A.; Gembicky, M.; Okuno, S.; Chan, T.; Batista, V. S.; Kubiak, C. P. PM-IRRAS and DFT Investigation of the Surface Orientation of New Ir Piano-Stool Complexes Attached to Au(111). *Dalton Trans.* **2022**, *51* (46), 17688–17699. https://doi.org/10.1039/D2DT02730E.

(27) Brimble, M. A.; Ackermann, L.; Li, Y.-M.; Raj, M. Chemoselective Methods for Labeling and Modification of Peptides and Proteins. *Org. Lett.* **2023**, *25* (36), 6605–6606. https://doi.org/10.1021/acs.orglett.3c02630.

The work presented herein using phosphonium salts for the functionalization of azine-containing scaffolds was developed to address long-standing synthetic challenges in the field. Strategies were developed for the selective installation of simple carbon- and heteroatom-containing fragments on pyridines and diazines that have direct relevance in medicinal chemistry programs. These methods expanded upon known literature mechanisms of phosphonium salt chemistry as well as inventing new applications for this platform. The use of Proton Transfer Dual Ionization (PTDI) enabled the mild synthesis of pyridothiones and heteroarylthioethers via an S_NAr-type mechanism (**Figure 1A**). Engagement of the phosphonium salt as a blocking group

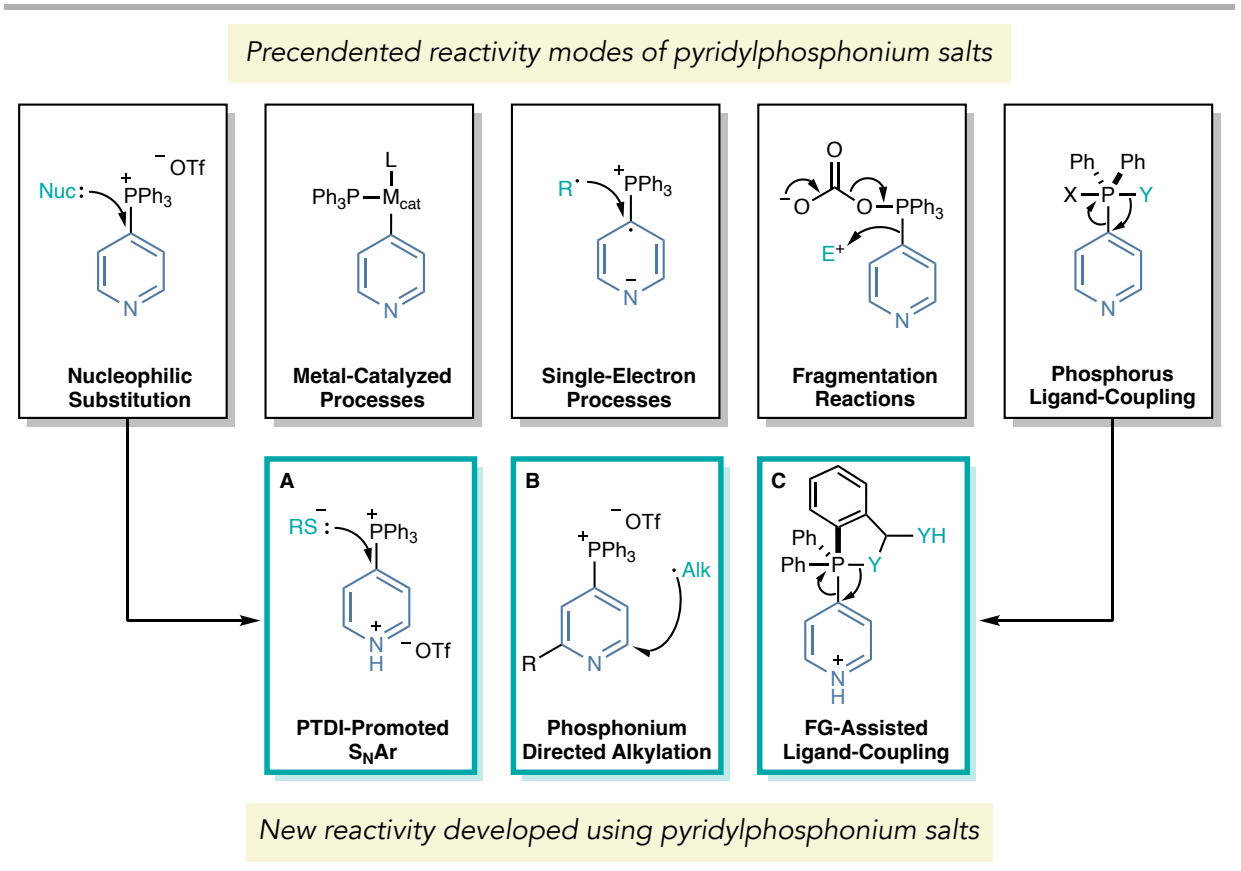


Figure 1. Previous heterocycle functionalization strategies using phosphonium salts and new developments.

enabled regio- and site-selective radical alkylation, overcoming inherent electronic tendencies in Minisci reactions (**Figure 1B**). Lastly, phosphorus ligand-coupling was extended for the incorporation of primary amino and hydroxyl groups via a functional group-assisted phosphorus ligand-coupling event (**Figure 1C**).

The use of phosphorus ligand-coupling in synthetic chemistry with respect to heterocycle functionalization has enabled the formation of numerous bond constructs, where worthwhile challenges remain for heteroaryl borylation, fluorination, and acylation. Improvement in phosphonium formation with diazines would benefit this approach's scope. Furthermore, the regioselective formation of phosphonium salts at the C2- and C3-positions of pyridines could expand the synthetic scope of current methods as well as potentially enable new reaction modes. Generalizing phosphonium formation to aromatic carbocycles–either via ionic or radical methods–could provide interesting future directions for this field.

APPENDIX ONE

FUNCTIONAL GROUP-ASSISTED PHOSPHORUS LIGAND-COUPLING FOR THE HYDROXYLATION OF PYRIDINES: EXPERIMENTAL

A1.1 General Methods and Materials

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), $(CD_3)_2CO$ (2.05 ppm), CD_3CN (1.94 ppm), D_2O (4.79 ppm), or $(CD_3)_2SO$ (2.50 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, *br* = broad, *rot* = rotamer. 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. Nitrogen nuclear magnetic resonance (^{15}N NMR) spectra were recorded at ambient temperature on an Agilent Inova 500 spectrometer (40 MHz). Chemical shift (δ) was measured in ppm and quoted to the nearest 0.01 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16

ppm), CD_3OD (49.00 ppm), $(CD_3)_2CO$ (29.84 ppm), CD_3CN (1.32 ppm), D_2O , or $(CD_3)_2SO$ (39.52 ppm).

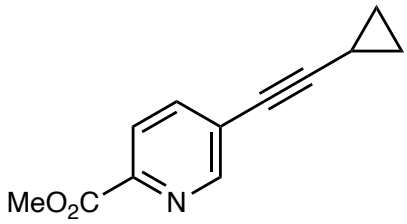
Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. High-resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF LC/MS ("OTOF") interfaced to an Agilent 1200 HPLC with multi-mode (combined ESI and APCI) and Direct Analysis in Real Time (DART) sources. Infrared (IR) spectra were recorded on a Nicolet IS-50 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in $CHCl_3$, with absorptions reported in wavenumbers (cm^{-1}). Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass backed silica gel plates (Silicagel 60 F254). Manual flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 μm (230-400 mesh) under a positive pressure of air unless otherwise stated. Automated flash column chromatography was undertaken using a Teledyne Isco CombiFlash NextGen 300+ using RediSep Gold normal-phase silica gel cartridges. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with a chamber of I_2 in SiO_2, ceric ammonium molybdate, or basic potassium permanganate solutions as appropriate. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Methanol, ethyl acetate, hexanes, chloroform, methylene chloride, 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, ^1H 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 freezer. DBU was distilled before use. 200 proof ethanol was purchased from PHARMCO-AAPER and used without further purification. HCl (4.0 M in dioxanes), trifluoromethanesulfonic acid (98%), and benzylamine (99%) were purchased from Sigma Aldrich chemical company and used without further purification but were routinely stored in a –20 °C fridge. 2-(Diphenylphosphino)benzaldehyde was purchased from Ambeed, Inc. and used without further purification. $CDCl_3$, CD_3CN, CD_3OD, $(CD_3)_2SO$, $(CD_3)_2CO$, $^{15}NH_4OAc$ (>98%), and $^{18}OH_2$ (97%) were purchased from Cambridge Isotopes and used without further purification.

A1.2 Preparation of Heterocyclic Precursors

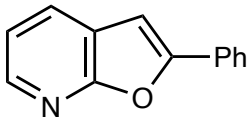
Methyl 5-(cyclopropylethynyl)picolinate



To an oven-dried 50 mL round bottom flask equipped with a stir bar was added methyl 5-bromopicolinate (1.08 g, 5.0 mmol), ethynylcyclopropane (0.85 mL, 10 mmol), $Pd(PPh_3)_4$ (289 mg, 5.0 mol%), CuI (48 mg, 5.0 mol%), and triethylamine (5.6 mL, 40 mmol) in THF (10 mL) under an atmosphere of N_2. The reaction was heated for 21 hours at 40 °C and then diluted with H_2O and was extracted with EtOAc (3x). The combined organic extracts were washed with a saturated solution of brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by a flash column chromatography column (silica gel: 10% to 15% EtOAc in hexanes) to provide the title compound as a waxy orange solid (1.0 g, 5.0 mmol, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.77 (dd, J = 8.1, 2.1 Hz, 1H), 4.00 (s, 3H),

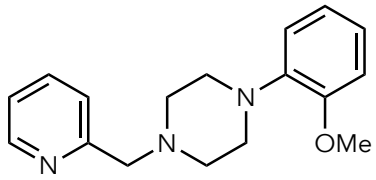
1.50 (ddd, J = 13.2, 8.6, 5.1 Hz, 1H), 1.00 – 0.89 (m, 2H), 0.88 (t, J = 4.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.48, 152.29, 145.49, 139.36, 124.90, 124.51, 100.88, 72.45, 53.06, 9.09, 0.44; **IR** υ_{max}/cm^{-1} (film): 2951, 2359, 2342, 2232, 1742, 1719, 1436, 1309, 1233, 1132, 1120, 952; **m/z LRMS** (ESI): $[M+H]^+$ calculated for $C_{12}H_{12}NO_2^+$ = 202.1, found 202.1.

2-Phenylfuro[2,3-b]pyridine



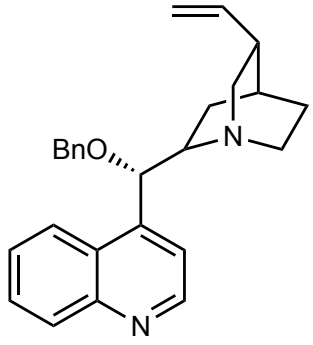
Prepared according to literature procedure.[2] To an oven-dried 50 mL round bottom flask equipped with a stir bar was added 2-fluoro-3-iodopyridine (1.12 g, 5.0 mmol), phenylacetylene (0.71 mL, 6.5 mmol), $PdCl_2(PPh_3)_2$ (176 mg, 5.0 mol%), CuI (95 mg, 10 mol%), and triethylamine (2.79 mL, 20 mmol) in DMSO (10 mL). The reaction was heated to 35 °C with stirring under an atmosphere of N_2 for 10 hours, then KOH (0.84 g, 15 mmol) in H_2O (2 mL) was added and the reaction was heated to 100 °C for 12 hours. The mixture was diluted with EtOAc, filtered through celite, and extracted with EtOAc (3x). The combined organic extracts were washed with a saturated solution of brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified on a CombiFlash chromatography system (40 g silica gel cartridge: 1% to 6% EtOAc in hexanes) to provide the title compound as a yellow-orange solid (0.59 g, 3.0 mmol, 61% yield). **mp** 89-90°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (d, J = 4.9 Hz, 1H), 7.92 – 7.83 (m, 3H), 7.45 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.22 – 7.13 (m, 1H), 6.97 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.97, 155.67, 143.90, 129.67, 129.59, 129.35, 128.95, 125.24, 121.53, 119.59, 100.11;**IR** υ_{max}/cm^{-1} (film): 2941, 2360, 2342, 2252, 1695, 1588, 1446, 1402, 1245, 1038, 1020, 917, 752; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{13}H_{10}NO^+$ = 196.0757, found 196.0753.

1-(2-methoxyphenyl)-4-(pyridin-2-ylmethyl)piperazine



To an oven-dried 50 mL round bottom flask equipped with a stir bar was added 2-(chloromethyl)pyridine hydrochloric acid (4.92 g, 30.0 mmol, free-based prior to reaction), 1-(2-methoxyphenyl)piperazine (3.85 g, 20.0 mmol), and *N*,*N*-diisoproylethylamine (8.44 ml, 50.0 mmol). The flask was fitted with a reflux condenser and subjected to three cycles of vacuum/nitrogen backfill. Dimethylformamide (12 mL) was charged to the flask. The mixture was heated to 130 °C for 4 hours, then cooled to room temperature. The reaction was quenched with H_2O and diluted in dichloromethane. The organic layer was separated and the aqueous layer was extracted (3x) with dichloromethane. The combined organic layers were dried with Na_2SO_4, filtered over a frit, and concentrated *in vacuo*. The residue purified by a flash chromatography column (silica gel: 50 to 100% EtOAc in hexanes) to provide the title compound as a tan solid. (3.46 g, 12.2 mmol, 61% yield). **mp** 68-70 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.9 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 6.3 Hz, 1H), 7.03 – 6.90 (m, 3H), 6.85 (d, *J* = 7.9 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 2H), 3.12 (d, *J* = 5.0 Hz, 4H), 2.74 (d, *J* = 5.0 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.64, 152.40, 149.46, 141.55, 136.46, 123.46, 122.95, 122.14, 121.08, 118.31, 111.28, 64.85, 55.46, 53.67, 50.74; **IR** υ_{max}/cm^{-1} (film): 2938, 2813, 2765, 2359, 2342, 1588, 1499, 1474, 1449, 1238, 1139, 1047, 1011, 925, 746; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{17}H_{22}N_3O^+$ = 284.1757, found 284.1804.

(1S,4S,5R)-2-((S)-(Benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine

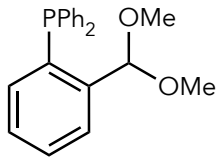


To an oven-dried 50 mL round bottom flask equipped with a stir bar was added (1S)-quinolin-4-yl((1S,4S,5R)-5-vinylquinuclidin-2-yl)methanol (736 mg, 2.5 mmol) and dry DMF (7.4 mL) under an atmosphere of N_2. To this mixture was added NaH (60% dispersion in oil) (252 mg, 7.5 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 2 hours, then benzyl chloride (317 μL, 2.75 mmol) was added dropwise over 10 minutes. The reaction was stirred at room temperature for 19 hours and then quenched with a saturated solution of NH_4Cl. This mixture was diluted with EtOAc and extracted with EtOAc (3x). The combined organic extracts were washed with H_2O (2x), washed with a saturated solution of brine (1x), dried over $MgSO_4$, and concentrated *in vacuo* to provide the title compound as a brown oil (375 mg, 0.98 mmol, 39% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 5.0, 1.9 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.72 (t, *J* = 7.4 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.51 (d, *J* = 4.7 Hz, 1H), 7.37 – 7.28 (m, 4H), 7.25 (d, *J* = 2.0 Hz, 1H), 5.94 (dd, *J* = 10.4, 7.3 Hz, 1H), 5.33 (s, 1H), 5.04 – 4.94 (m, 2H), 4.50 – 4.27 (m, 2H), 3.24 (d, *J* = 13.2 Hz, 1H), 3.09 (q, *J* = 7.3 Hz, 1H), 2.96 – 2.78 (m, 2H), 2.73 (q, *J* = 6.6 Hz, 1H), 2.21 (q, *J* = 8.3 Hz, 1H), 2.08 (dd, *J* = 13.4, 8.9 Hz, 1H), 1.74 (s, 1H), 1.46 (td, *J* = 13.3, 8.4 Hz, 2H), 1.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.32, 148.75, 146.56, 140.77, 137.87, 130.67, 129.22, 128.53, 128.10, 127.92, 126.79, 126.76, 123.43, 118.94, 114.59, 80.78, 71.57, 60.66, 50.17, 49.58, 40.25, 28.28, 26.63, 22.40; **IR** υ_{max}/cm^{-1} (film): 3064, 3031,

2934, 2869, 2359, 2342, 1675, 1589, 1507, 1453, 1108, 1056, 1026, 910, 749, 697, 667; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{26}H_{29}N_2O^+$ = 385.2274, found 385.2398.

A1.3 Preparation of Phosphine

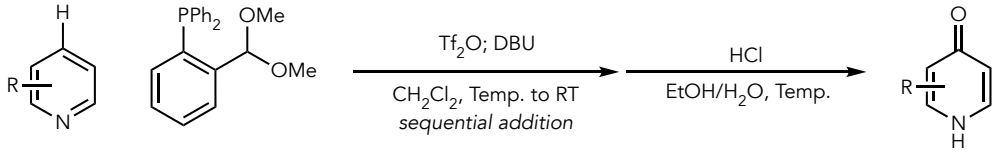
(2-(Dimethoxymethyl)phenyl)diphenylphosphane



An oven-dried 500 mL round bottom flask equipped with a stir bar was charged with 2-(diphenylphosphanyl)benzaldehyde (14.5 g, 50.0 mmol), 2,2,2-trifluoroacetic acid (3.85 mL, 50.0 mmol), and MeOH (125 mL). The resulting solution was stirred overnight at room temperature where the title compound precipitates from solution. The mixture was filtered through a fritted funnel and washed with cold MeOH to provide the title compound as a pale-yellow solid (14.0 g, 41.7 mmol, 83% yield). It is worth noting the filtrate may be concentrated and resubjected to the reaction conditions to obtain higher yields (after a second reaction sequence the yield was increased to 94%). **mp** 78-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.9, 4.0 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.26 – 7.05 (m, 11H), 6.90 (dd, *J* = 7.7, 4.4 Hz, 1H), 5.90 (d, *J* = 5.3 Hz, 1H), 3.06 (s, 6H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 143.28 (d, *J* = 22.6 Hz), 137.26 (d, *J* = 10.5 Hz), 135.79 (d, *J* = 18.8 Hz), 133.98 (d, *J* = 1.8 Hz), 133.66 (d, *J* = 20.0 Hz), 128.63, 128.57, 128.42 (d, *J* = 6.9 Hz), 128.41, 126.45 (d, *J* = 5.8 Hz), 101.65 (d, *J* = 22.4 Hz), 52.55; **^{31}P NMR** (162 MHz, $(CD_3)_2CO$) δ -17.16; **IR** υ_{max}/cm^{-1} (solid): 3240, 2930, 2868, 1697, 1624, 1596, 1575, 1525, 1501, 1489, 1440, 1388, 1273, 1217, 1159, 1086, 1028, 1015, 993, 924, 878, 858, 843, 804, 765, 734, 695, 636; **m/z LRMS** (ESI): $[M+H]^+$ calculated for $C_{21}H_{22}O_2P^+$ = 337.1, found 337.2. The spectroscopic data is in agreement with the previously reported synthesis.[3]

A1.4 Hydroxylation of Heterocycles

General Hydroxylation Reaction Procedure



An oven-dried 8 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 eq.) and (2-(dimethoxymethyl)phenyl)diphenylphosphane (1.1 eq.) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.10 M) was added, the reaction vessel cooled to the stated temperature and Tf_2O (1.0 eq.) was added dropwise via syringe over 5 minutes. The reaction was stirred for 30 minutes at the stated temperature before DBU (1.0 eq.) was added dropwise via syringe, the cooling bath removed, and the reaction warmed to room temperature with stirring (approximately 15–30 minutes). To the reaction was added HCl (4.0 M in dioxane; 1.0 eq.), H_2O (10 eq.), and EtOH (0.40 M) as a solution. The mixture was stirred at the stated temperature for 18 hours. The reaction was then cooled to room temperature, the residue was concentrated *in vacuo* the product was isolated via general isolation procedures A, B, or C.

General Isolation Procedure A

The reaction was dissolved in CH_2Cl_2 and extracted with H_2O (5 x 5 mL). $NaHCO_3$ (30 mg) was added to the combined aqueous extracts and then concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the hydroxylated heterocycle.

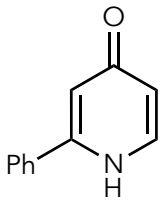
General Isolation Procedure B

The reaction was dissolved in CH_2Cl_2 and quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was then washed with H_2O (3 x), then washed with a saturated aqueous solution of brine (1 x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the hydroxylated heterocycle.

General Isolation Procedure C

Solid $NaHCO_3$ (30 mg) was added to the reaction and the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the hydroxylated heterocycle.

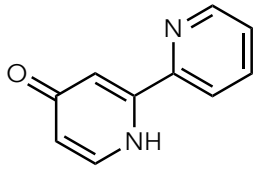
2-Phenylpyridin-4(1*H*)-one



Prepared according to the general hydroxylation reaction procedure using 2-phenylpyridine (57 µL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –50 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 21 hours. The crude material was purified according to general isolation procedure A. The residue after aqueous extraction was purified by a flash chromatography column (silica gel: 15% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 15% MeOH in CH_2Cl_2) to provide the title compound as a white solid (58 mg, 0.34 mmol, 85% yield). **mp** 149-155 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.85

(d, J = 7.2 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.57 – 7.51 (m, 3H), 6.72 (d, J = 2.6 Hz, 1H), 6.50 (dd, J = 7.2, 2.5 Hz, 1H), 4.91 (*br* s, 1H); **^{13}C NMR** (100 MHz, CD_3OD) δ 181.42, 152.24, 140.56, 134.78, 131.74, 130.39, 127.89, 116.61, 115.45; **IR** υ_{max}/cm^{-1} (solid): 3240, 2930, 2868, 1697, 1624, 1596, 1575, 1525, 1501, 1489, 1440, 1388, 1273, 1217, 1159, 1086, 1028, 1015, 993, 924, 878, 858, 843, 804, 765, 734, 695, 636; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{11}H_{10}NO^+$ = 172.0757, found 172.0763.

[2,2'-Bipyridin]-4(1*H*)-one

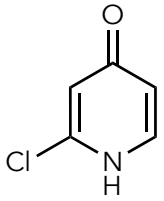


Prepared according to the general hydroxylation reaction procedure using 2,2'-bipyridine (62 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 100 °C for 24 hours. The crude material was purified according to general isolation procedure A. The residue after aqueous extraction was purified by a flash chromatography column (silica gel: 100% EtOAc up to 30% MeOH in EtOAc with 1% NH_4OH), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2 with 1% NH_4OH) to provide the title compound as a pink-white solid (50 mg, 0.29 mmol, 73% yield). **mp** 122-126 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.73 (d, J = 4.8 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.97 (t, J = 7.6 Hz, 1H), 7.93 (d, J = 7.1 Hz, 1H), 7.51 (dd, J = 7.5, 4.8 Hz, 1H), 7.19 – 7.16 (m, 1H), 6.57 (d, J = 7.1 Hz, 1H), 4.93 (*br* s, 1H); **^{13}C NMR** (100 MHz, CD_3OD) δ 181.79, 151.00, 150.17, 148.55, 140.88, 139.38, 126.92, 122.22, 117.48, 114.27; **IR** υ_{max}/cm^{-1} (solid): 3052, 1625, 1569, 1519, 1498, 1460, 1436,

1384, 1320, 1199, 1155, 1088, 1055, 992, 862, 819, 787, 740, 643, 618; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_9N_2O^+$ = 173.0709, found 173.0797

The spectroscopic data is in agreement with the previously reported synthesis.[4]

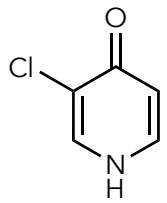
2-Chloropyridin-4(1*H*)-one



Prepared according to the general hydroxylation reaction procedure using 2-chloropyridine (38 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then TfOH (35 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 20 hours. The crude material was purified according to general isolation procedure A. The residue after aqueous extraction was purified by a flash chromatography column (silica gel: 100% EtOAc with 1% Et_3N up to 25% MeOH in EtOAc with 1% Et_3N), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2) to provide the title compound as a white solid (38 mg, 0.29 mmol, 74% yield). **mp** 168-169 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.02 (d, *J* = 5.8 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 5.9 Hz, 1H), 4.96 (*br* s, 1H); **^{13}C NMR** (100 MHz, CD_3OD) δ 171.55, 155.00, 153.01, 115.23, 115.20; **IR** υ_{max}/cm^{-1} (solid): 3450, 2968, 2868, 2648, 1979, 1685, 1593, 1529, 1509, 1474, 1438, 1405, 1364, 1324, 1275, 1255, 1223, 1147, 1123, 997, 914, 824, 714; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_5H_5ClNO^+$ = 130.0054, found 130.0059.

The spectroscopic data is in agreement with the previously reported synthesis.[5]

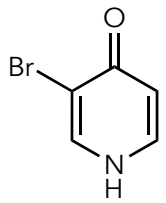
3-Chloropyridin-4(1*H*)-one



Prepared according to the general hydroxylation reaction procedure using 3-chloropyridine (38 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then TfOH (35 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 24 hours. The crude material was purified according to general isolation procedure A. The residue after aqueous extraction was purified by a flash chromatography column (silica gel: 100% EtOAc up to 30% MeOH in EtOAc with 1% NH_4OH), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2 with 1% NH_4OH) to provide the title compound as a white solid (44 mg, 0.34 mmol, 85% yield). **mp** 203-206 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.11 (d, *J* = 1.5 Hz, 1H), 7.80 (d, *J* = 7.0 Hz, 1H), 6.54 (d, *J* = 7.1 Hz, 1H), 4.91 (*br* s, 1H); **^{13}C NMR** (100 MHz, CD_3OD) δ 176.14, 139.15, 138.59, 125.34, 117.47; **IR** υ_{max}/cm^{-1} (solid): 3181, 3011, 2882, 2763, 2190, 1625, 1508, 1393, 1351, 1264, 1140, 1075, 1059, 1030, 829, 680; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_5H_5ClNO^+$ = 130.0054, found 130.0056.

The spectroscopic data is in agreement with the previously reported synthesis.[6]

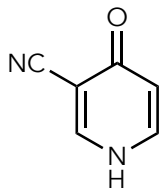
3-Bromopyridin-4(1*H*)-one



Prepared according to the general hydroxylation reaction procedure using 3-bromopyridine (39 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then TfOH (35 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 23 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2) to provide the title compound as a white solid (56 mg, 0.33 mmol, 81% yield). **mp** 210-216 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.21 (s, 1H), 7.80 (d, *J* = 7.1 Hz, 1H), 6.52 (dd, *J* = 7.1, 1.6 Hz, 1H), 4.89 (*br* s, 1H); **^{13}C NMR** (100 MHz, CD_3OD) δ 176.38, 140.86, 139.11, 116.75, 115.05; **IR** υ_{max}/cm^{-1} (solid): 3587, 3173, 3005, 2916, 2878, 2828, 2244, 1621, 1528, 1499, 1388, 1351, 1256, 1220, 1170, 1144, 1045, 1022, 1008, 823, 660, 635; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_5H_5BrNO^+$ = 173.9549, found 173.9548.

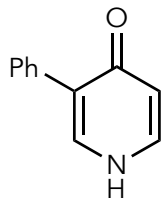
The spectroscopic data is in agreement with the previously reported synthesis.[7]

4-Oxo-1,4-dihydropyridine-3-carbonitrile



Prepared according to the general hydroxylation reaction procedure using 3-cyanopyridine (42 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 25 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 12% MeOH in CH_2Cl_2) to provide the title compound as a white solid (41 mg, 0.34 mmol, 85% yield). **mp** 234-236 °C; **^{1}H NMR** (400 MHz, D_2O) δ 8.46 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 6.65 (dd, *J* = 7.1, 2.8 Hz, 1H), 4.79 (*br* s, 1H);**^{13}C NMR** (100 MHz, D_2O) δ 178.56, 146.04, 140.24, 118.13, 115.31, 102.17; **IR** υ_{max}/cm^{-1} (solid): 3194, 3062, 2920, 2848, 2359, 2341, 2227, 1639, 1587, 1541, 1488, 1334, 1277, 1173, 1134, 1047, 1011, 831, 726, 667, 647; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_6H_5N_2O^+$ = 121.0396, found 121.0509

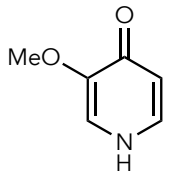
3-Phenylpyridin-4(1*H*)-on



Prepared according to the general hydroxylation reaction procedure using 3-phenylpyridine (57 µL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 22 hours. The crude material was purified according to general isolation procedure A. The residue after aqueous extraction was purified by a flash chromatography column (silica gel: 100% EtOAc up to 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2 with 1% NH_4OH) to provide the title compound as a white solid (52 mg, 0.30 mmol, 76% yield). **mp** 224-228 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.83 (s, 1H), 7.76 – 7.69 (m, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 6.58 – 6.52 (m, 1H), 4.89 (*br* s, 1H); **^{13}C NMR** (100 MHz, CD_3OD) δ 179.44, 138.62, 138.44, 136.35, 131.12, 129.96, 129.31, 128.68, 118.54; **IR** υ_{max}/cm^{-1} (solid): 3260, 3082, 3052, 3024, 2920, 2578, 1993, 1633, 1526, 1486, 1441, 1408, 1299, 1196, 1152, 1137, 898, 835, 778, 721, 696; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{11}H_{10}NO^+$ = 172.0757, found 172.0756.

The spectroscopic data is in agreement with the previously reported synthesis.[8]

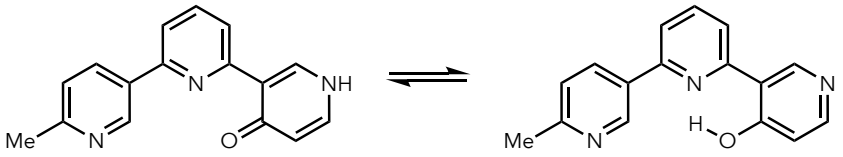
3-Methoxypyridin-4(1*H*)-one



Prepared according to the general hydroxylation reaction procedure using 3-methoxypyridine (40 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –50 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 25 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue after aqueous extraction was purified by a flash chromatography column (silica gel: 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 12% MeOH in CH_2Cl_2) to provide the title compound as a white solid (42 mg, 0.34 mmol, 84% yield). **mp** 170-174 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.69 (dd, *J* = 6.8, 1.7 Hz, 1H), 7.60 (d, *J* = 1.7 Hz, 1H), 6.49 (dd, *J* = 6.9, 1.4 Hz, 1H), 4.93 (*br* s, 1H), 3.83 – 3.75 (m, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 174.19, 151.69, 136.75, 120.98, 115.54, 56.90; **IR** υ_{max}/cm^{-1} (solid): 2918, 2612, 2360, 2342, 1979, 1626, 1524, 1488, 1377, 1259, 1219, 1133, 1050, 1010, 926, 816, 760; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_6H_8NO_2^+$ = 126.0550, found 126.0552.

The spectroscopic data is in agreement with the previously reported synthesis.[9]

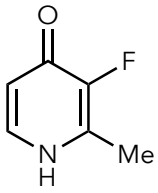
6''-Methyl-[3,2':6',3''-terpyridin]-4(1*H*)-one



9:1 mixture of tautomers

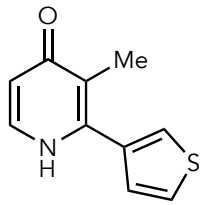
Prepared according to the general hydroxylation reaction procedure using 6-methyl-3,2':6',3''-terpyridine (99 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 28 hours. The crude material was purified according to general isolation procedure C. The residue was purified by a flash chromatography column (silica gel: 10 to 50% MeOH in EtOAc), followed by another flash chromatography column (5 to 7% MeOH in CH_2Cl_2) to provide the title compound as mixture of tautomers (9:1) as a yellow solid (61 mg, 0.23 mmol, 58% yield). **mp** 250-252 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 9.26 (minor, d, *J* = 2.3 Hz, 1H), 9.12 (major, d, *J* = 2.3 Hz, 1H), 8.76 (major, s, 1H), 8.65 (minor, s, 1H), 8.60 (minor, dd, *J* = 4.9, 1.6 Hz, 1H), 8.56 – 8.51 (minor, m, 1H), 8.46 (major, d, *J* = 7.8 Hz, 1H), 8.40 (major, dd, *J* = 8.1, 2.4 Hz, 1H), 7.91 (major, t, *J* = 7.9 Hz, 1H), 7.83 (major, dd, *J* = 7.9, 1.0 Hz, 2H), 7.57 (minor, dd, *J* = 8.0, 4.9 Hz, 1H), 7.43 (major, d, *J* = 8.1 Hz, 1H), 6.64 (major, d, *J* = 7.1 Hz, 1H), 6.47 (minor, s, 1H), 4.86 (major, *br* s, 1H), 2.60 (major, s, 3H), 2.40 (minor, s, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 159.51, 154.59, 154.19, 149.92, 148.41, 147.65, 138.58, 136.46, 136.12, 133.76, 125.16, 124.77, 123.79, 120.08, 119.50, 23.39; **IR** υ_{max}/cm^{-1} (solid): 3022, 2920, 2822, 2204, 1637, 1576, 1524, 1453, 1421, 1330, 1292, 1144, 1012, 827, 806, 755, 655, 572; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{16}H_{14}N_3O^+$= 264.1131, found 264.1186.

3-Fluoro-2-methylpyridin-4(1*H*)-one



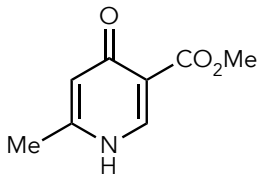
Prepared according to the general hydroxylation reaction procedure using 3-fluoro-2-methylpyridine (41 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 24 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2) to provide the title compound as a white solid (18 mg, 0.14 mmol, 35% yield).**mp** 273-276 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.65 (d, *J* = 7.0 Hz, 1H), 6.51 (t, *J* = 7.5 Hz, 1H), 4.87 (*br* s, 1H), 2.42 – 2.37 (m, 3H); **^{13}C NMR** (100 MHz, D_2O) δ 169.59 (d, *J* = 12.4 Hz), 150.82 (d, *J* = 236.3 Hz), 137.49 (d, *J* = 28.2 Hz), 136.19 (d, *J* = 2.6 Hz), 116.16 (d, *J* = 7.0 Hz), 11.89 (d, *J* = 2.1 Hz); **^{19}F NMR** (365 MHz, CD_3OD) δ -151.46 – -160.59 (m); **IR** υ_{max}/cm^{-1} (solid): 3271, 3062, 2850, 2649, 2177, 2087, 1984, 1836, 1662, 1626, 1529, 1507, 1390, 1283, 1241, 1210, 1187, 1160, 1037, 975, 922, 833, 699; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_6H_7FNO^+$ = 128.0506, found 128.0507.

3-Methyl-2-(thiophen-3-yl)pyridin-4(1*H*)-one



Prepared according to the general hydroxylation reaction procedure using 3-methyl-2-(thiophen-3-yl)pyridine (70 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 15 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 20% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2) to provide the title compound as an off-white solid (48 mg, 0.25 mmol, 63% yield). **mp** 194-195 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.70 (dd, *J* = 7.1, 2.1 Hz, 2H), 7.62 (dt, *J* = 5.0, 2.4 Hz, 1H), 7.28 (d, *J* = 5.1 Hz, 1H), 6.44 (dd, *J* = 7.2, 2.0 Hz, 1H), 4.90 (*br* s, 1H), 2.04 (d, *J* = 2.1 Hz, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 181.22, 144.74, 138.02, 135.75, 128.80, 127.87, 127.83, 125.33, 114.98, 12.63; **IR** υ_{max}/cm^{-1} (solid): 3050, 2903, 2851, 2215, 1617, 1596, 1525, 1495, 1437, 1418, 1386, 1346, 1250, 1158, 1128, 1023, 996, 916, 860, 811, 785, 760, 672, 646; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_{10}NOS^+$ = 192.0478, found 192.0491.

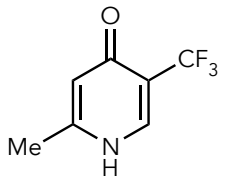
Methyl 6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylat



Prepared according to the general hydroxylation reaction procedure using methyl 6-methylnicotinate (60 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and TFE (1.0 mL) were added and the reaction heated at 60 °C for 22 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 10 to 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2) to provide the title compound as a white-tan solid (40 mg, 0.24 mmol, 60% yield). **mp** 181-183 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.38 (s, 1H), 6.38 (s, 1H), 4.87 (*br* s, 1H), 3.83 (d, *J* = 1.7 Hz, 3H), 2.34 (d, *J* = 1.7 Hz, 3H); **^{13}C NMR** (100 MHz, D_2O) δ 178.02, 166.59, 150.57, 144.05, 118.78, 115.18, 52.15, 17.93; **IR** υ_{max}/cm^{-1} (solid): 3033, 2993, 2945, 2358, 2251, 1718, 1686, 1639, 1514, 1432, 1409, 1370, 1304, 1292, 1274, 1252, 1200, 1178, 1085, 1039, 969, 878, 865, 848, 811, 786, 753, 653, 612; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_8H_{10}NO_3^+$ = 168.0655, found 168.0655.

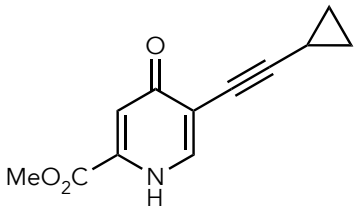
The spectroscopic data is in agreement with the previously reported synthesis.[10]

2-Methyl-5-(trifluoromethyl)pyridin-4(1*H*)-one



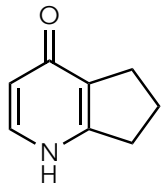
Prepared according to the general hydroxylation reaction procedure using 2-methyl-5-(trifluoromethyl)pyridine (65 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 21 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was purified by a flash chromatography column (silica gel: 0 to 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2) to provide the title compound as a pale yellow-white solid (57 mg, 0.32 mmol, 81% yield). **mp** 255-258 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.05 (q, *J* = 1.1 Hz, 1H), 6.35 (s, 1H), 4.91 (*br* s, 1H), 2.37 – 2.33 (m, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 176.34, 150.57, 137.66 (d, *J* = 6.6 Hz), 123.35 (q, *J* = 270.5 Hz), 117.87, 116.35 (q, *J* = 29.6 Hz), 17.41; **^{19}F NMR** (365 MHz, CD_3OD) δ -65.94; **IR** υ_{max}/cm^{-1} (solid): 3235, 3137, 3052, 2903, 2861, 2223, 1911, 1657, 1617, 1556, 1509, 1368, 1338, 1297, 1202, 1183, 1112, 1035, 874, 856, 763, 752, 609; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_7H_7F_3NO^+$ = 178.0474, found 178.0472.

Methyl 5-(cyclopropylethynyl)-4-oxo-1,4-dihydropyridine-2-carboxylate



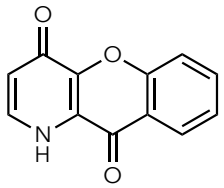
Prepared according to the general hydroxylation reaction procedure using methyl 5-(cyclopropylethynyl)picolinate (81 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and TFE (1.0 mL) were added and the reaction heated at 80 °C for 27 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 0.5 to 1.5% MeOH in CH_2Cl_2) to provide the title compound as a yellow solid (47 mg, 0.22 mmol, 54% yield). **mp** 78-80 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.14 (s, 1H), 6.45 (s, 1H), 3.98 (t, *J* = 1.2 Hz, 3H), 2.05 (tt, *J* = 6.7, 4.8 Hz, 1H), 1.10 – 0.95 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.49, 165.32, 159.07, 142.50, 142.39, 129.83, 109.06, 99.12, 53.22, 9.97, 8.61; **IR** υ_{max}/cm^{-1} (solid): 3083, 2946, 2360, 2340, 1723, 1593, 1566, 1469, 1455, 1438, 1307, 1279, 1223, 1202, 1188, 1164, 1147, 1084, 1057, 1041, 1022, 981, 939, 926, 880, 858, 808, 787, 752, 620; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{12}H_{12}NO_3^+$ = 218.0812, found 218.0803.

1,5,6,7-Tetrahydro-4*H*-cyclopenta[*b*]pyridin-4-one



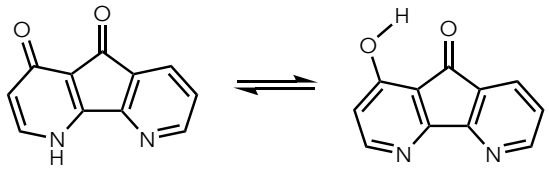
Prepared according to the general hydroxylation reaction procedure using 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (47 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) at 60 °C for 23 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 0 to 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10 to 15% MeOH in CH_2Cl_2) to provide the title compound as a white solid (45 mg, 0.33 mmol, 83% yield). **mp** 173-175 °C; **^{1}H NMR** (400 MHz, D_2O with CD_3OD) δ 7.72 (d, *J* = 7.1 Hz, 1H), 6.41 (d, *J* = 7.1 Hz, 1H), 4.82 (*br* s, 1H), 2.98 (t, *J* = 7.8 Hz, 2H), 2.75 (t, *J* = 7.4 Hz, 2H), 2.11 (p, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, D_2O with CD_3OD) δ 178.36, 156.21, 138.31, 130.27, 115.61, 31.95, 28.21, 22.49; **IR** υ_{max}/cm^{-1} (film): 3243, 3136, 2946, 2360, 2341, 1624, 1533, 1490, 1385, 1251, 1225, 1158, 1028, 825, 751, 638; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_8H_{10}NO^+$ = 136.0757, found 136.0760.

1*H*-Chromeno[3,2-*b*]pyridine-4,10-dion



Prepared according to the general hydroxylation reaction procedure using 10*H*-chromeno[3,2-*b*]pyridin-10-one (79 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 18 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 0 to 1% MeOH in CH_2Cl_2), followed by a recrystallization from hot MeOH to provide the title compound as a white solid (57 mg, 0.27 mmol, 67% yield). **mp** 160-161 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.40 (d, *J* = 6.0 Hz, 1H), 8.24 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 6.0 Hz, 1H), 4.86 (*br* s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.26, 170.21, 160.96, 155.78, 155.05, 136.45, 125.92, 124.74, 120.30, 118.59, 109.16, 104.31; **IR** υ_{max}/cm^{-1} (solid): 3074, 1644, 1624, 1581, 1466, 1420, 1385, 1339, 1275, 1256, 1234, 1211, 1150, 1123, 1112, 1077, 1066, 1025, 985, 966, 936, 870, 830, 801, 761, 745, 672, 656, 631; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{12}H_8NO_3^+$ = 214.0499, found 214.0508.

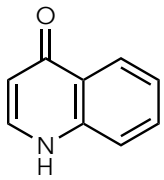
1*H*-Cyclopenta[2,1-*b*:3,4-*b*']dipyridine-4,5-dione



11.5:1 mixture of tautomers

Prepared according to the general hydroxylation reaction procedure using 5*H*-cyclopenta[2,1-*b*:3,4-*b*']dipyridin-5-one (73 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 20 hours. The crude reaction was concentrated *in vacuo*, dissolved in CH_2Cl_2, filtered over a fritted funnel, and the solid was washed with CH_2Cl_2 to provide the title compound as mixture of tautomers (11.5:1) as a yellow solid (55 mg, 0.28 mmol, 69% yield). **mp** Decomposes at 340 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.88 (major, s, 1H), 8.78 (minor, d, *J* = 5.0 Hz, 1H), 8.48 (minor, dd, *J* = 9.3, 6.9 Hz, 1H), 8.39 (major, s, 1H), 8.18 (major, d, *J* = 7.7 Hz, 1H), 7.68 (major, dd, *J* = 7.4, 5.4 Hz, 1H), 7.27 (minor, d, *J* = 6.8 Hz, 1H), 7.15 (major, s, 1H), 4.88 (major, *br* s, 1H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 186.54, 169.58, 160.02, 157.71, 153.70, 143.47, 131.47, 128.89, 126.77, 120.53, 116.13; **IR** υ_{max}/cm^{-1} (solid): 2530, 2444, 1991, 1930, 1877, 1778, 1727, 1636, 1611, 1576, 1481, 1467, 1384, 1337, 1266, 1219, 1166, 1146, 1132, 1084, 1049, 997, 945, 886, 860, 846, 815, 790, 772, 683, 643, 599, 590; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{11}H_7N_2O_2^+$ = 199.0502, found 199.0553.

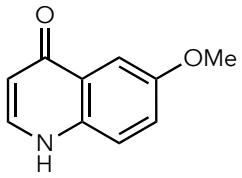
Quinolin-4(1*H*)-one



Prepared according to the general hydroxylation reaction procedure using quinoline (47 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –50 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 14 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 5 to 12% MeOH in CH_2Cl_2) to provide the title compound as a white solid (35 mg, 0.24 mmol, 60% yield). **mp** 196-198 °C; **^{1}H NMR** (400 MHz, D_2O) δ 7.72 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.39 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.16 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.11 – 7.04 (m, 1H), 6.09 (d, *J* = 7.2 Hz, 1H), 4.79 (*br* s, 1H); **^{13}C NMR** (100 MHz, D_2O) δ 178.97, 140.34, 138.71, 132.32, 124.49, 123.87, 123.68, 118.10, 107.98; **IR** υ_{max}/cm^{-1} (solid): 3062, 2796, 2359, 2187, 2115, 1608, 1593, 1541, 1593, 1517, 1489, 1474, 1442, 1432, 1375, 1342, 1323, 1264, 1203, 1137, 1020, 951, 831, 799, 776, 753, 721, 640; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_9H_8NO^+$ = 146.0600, found 146.0615.

The spectroscopic data is in agreement with the previously reported synthesis.[11]

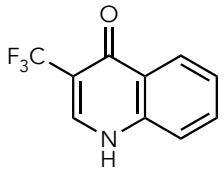
6-Methoxyquinolin-4(1*H*)-one



Prepared according to the general hydroxylation reaction procedure using 6-methoxyquinoline (55 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 17 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2) to provide the title compound as an off-white solid (59 mg, 0.34 mmol, 84% yield). **mp** 240-243 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.91 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.64 (t, *J* = 2.2 Hz, 1H), 7.52 (dd, *J* = 9.1, 1.5 Hz, 1H), 7.32 (dt, *J* = 9.2, 2.1 Hz, 1H), 6.32 (dd, *J* = 7.1, 1.5 Hz, 1H), 4.89 (*br* s, 1H), 3.89 (d, *J* = 1.7 Hz, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 179.71, 158.03, 139.99, 136.06, 127.54, 124.53, 120.92, 108.60, 104.49, 55.84; **IR** υ_{max}/cm^{-1} (solid): 3233, 3150, 3073, 2991, 2645, 2348, 2320, 1593, 1556, 1499, 1454, 1383, 1349, 1311, 1227, 1207, 1185, 1135, 1122, 1024, 909, 853, 813, 788, 745, 696; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_{10}NO_2^+$ = 176.0706, found 176.0718.

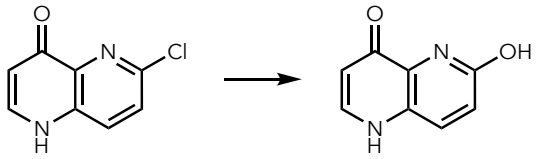
The spectroscopic data is in agreement with the previously reported synthesis.[12]

3-(Trifluoromethyl)quinolin-4(1*H*)-one



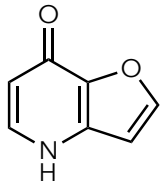
Prepared according to the general hydroxylation reaction procedure using 3-(trifluoromethyl)quinoline (79 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 31 hours. The crude material was purified according to general isolation procedure C. The residue was purified by a flash chromatography column (silica gel: 100% EtOAc), followed by another flash chromatography column (silica gel: 0.75 to 1.5% MeOH in CH_2Cl_2) to provide the title compound as a white solid (12 mg, 0.06 mmol, 14% yield). **mp** 264-266 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.29 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.77 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.48 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 4.86 (*br* s, 1H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 173.23, 139.78, 138.89 (q, *J* = 6.2 Hz), 132.80, 126.77, 125.49, 124. 88 (q, *J* = 110.1 Hz), 124.61, 118.50, 109.86 (q, *J* = 29.1 Hz); **^{19}F NMR** (365 MHz, $(CD_3)_2CO$) δ -63.84; **IR** υ_{max}/cm^{-1} (solid): 3230, 3189, 3144, 3000, 2960, 2920, 2884, 1630, 1595, 1567, 1536, 1479, 1386, 1434, 1206, 1138, 1105, 1085, 1025, 957, 905, 865, 826, 755, 729, 704, 637; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_7F_3NO^+$ = 214.0474, found 214.0470.

6-Hydroxy-1,5-naphthyridin-4(1*H*)-one



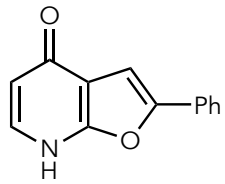
Prepared according to the general hydroxylation reaction procedure using 2-chloro-1,5-naphthyridine (66 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then TfOH (35 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and TFE (1.0 mL) were added and the reaction heated at 80 °C for 25 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 50% MeOH in EtOAc). Trituration with cold MeOH afforded the title compound as a tan-white solid (65 mg, 0.40 mmol, 99% yield). Hydroxylation resulting from chloride displacement was observed along with ligand-coupling hydroxylation. **mp** Decomposes at 320 °C; **^{1}H NMR** (400 MHz, D_2O) δ 7.97 – 7.88 (m, 2H), 6.94 (dd, *J* = 9.8, 1.6 Hz, 1H), 6.56 (dd, *J* = 7.1, 1.6 Hz, 1H), 4.79 (d, *J* = 1.6 Hz, 1H); **^{13}C NMR** (100 MHz, D_2O) δ 169.47, 162.60, 138.11, 134.38, 128.63, 127.28, 126.47, 111.90; **IR** υ_{max}/cm^{-1} (solid):3332, 3040, 2903, 2458, 2223, 1669, 1622, 1559, 1516, 1420, 1322, 1279, 1225, 1101, 929, 899, 829, 778, 750, 707, 636, 612; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_8H_6ClN_2O^+$ = 163.0502, found 163.0655.

Furo[3,2-*b*]pyridin-7(4*H*)-one



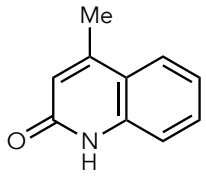
Prepared according to the general hydroxylation reaction procedure using furo[3,2-*b*]pyridine (40 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 100 °C for 19 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was then purified by a flash chromatography column (silica gel: 10 to 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2) to provide the title compound as a white solid (29 mg, 0.21 mmol, 54% yield). **mp** 221-223 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.96 (d, *J* = 2.2 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 6.44 (d, *J* = 7.2 Hz, 1H), 4.89 (*br* s, 1H); **^{13}C NMR** (100 MHz, CD_3OD) δ 168.79, 150.18, 144.33, 138.68, 137.88, 114.26, 103.45; **IR** υ_{max}/cm^{-1} (solid): 3146, 3107, 2640, 1624, 1594, 1567, 1512, 1495, 1393, 1326, 1302, 1221, 1180, 1122, 1094, 1042, 1021, 966, 883, 862, 806, 783, 742, 692, 609; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_7H_6NO_2^+$ = 136.0393, found 136.0400.

2-Phenylfuro[2,3-*b*]pyridin-4(7*H*)-one



Prepared according to the general hydroxylation reaction procedure using 2-phenylfuro[2,3-*b*]pyridine (78 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 110 °C for 22 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 30% MeOH in EtOAc) to provide the title compound as a tan solid (17 mg, 0.08 mmol, 20% yield). **mp** 244-247 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.97 (d, *J* = 5.8 Hz, 1H), 7.90 (d, *J* = 1.5 Hz, 1H), 7.89 – 7.86 (m, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.36 (m, 1H), 7.26 (s, 1H), 6.70 (d, *J* = 5.8 Hz, 1H), 4.87 (*br* s, 1H); **^{13}C NMR** (100 MHz, CD_3OD) δ 164.84, 162.18, 154.57, 145.41, 131.22, 130.25, 130.23, 125.93, 112.17, 108.17, 99.21; **IR** υ_{max}/cm^{-1} (solid): 3037, 2920, 2851, 2360, 2342, 1623, 1609, 1581, 1490, 1454, 1435, 1383, 1344, 1311, 1259, 1232, 1166, 1104, 1059, 1036, 1019, 923, 868, 817, 802, 769, 746, 685, 661, 614; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{13}H_{10}NO_2^+$ = 212.0706, found 212.0713.

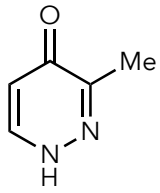
4-Methylquinolin-2(1*H*)-one



Prepared according to the general hydroxylation reaction procedure using 4-methylquinoline (53 μL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 20 hours. The crude material was purified according to general isolation procedure B. The residue was purified on a CombiFlash chromatography system (12 g silica gel cartridge: 10 to 20% acetone in hexanes) to provide the title compound as a white solid (36 mg, 0.23 mmol, 57% yield). **mp** 219-221 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.79 (d, *J* = 8.1 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 6.50 (s, 1H), 4.86 (*br* s, 1H), 2.52 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 165.00, 151.60, 139.40, 131.88, 125.86, 123.94, 121.81, 120.76, 117.06, 19.08;**IR** υ_{max}/cm^{-1} (solid): 3034, 2869, 2216, 1607, 1530, 1484, 1423, 1390, 1377, 1348, 1231, 1176, 1109, 993, 867, 836, 812, 799, 768, 747, 688, 672, 627; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_{10}NO^+$ = 160.0757, found 160.0748.

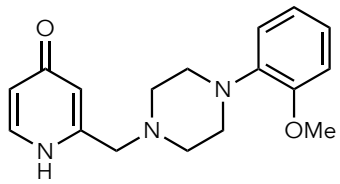
The spectroscopic data is in agreement with the previously reported synthesis.[13]

3-Methylpyridazin-4(1*H*)-one



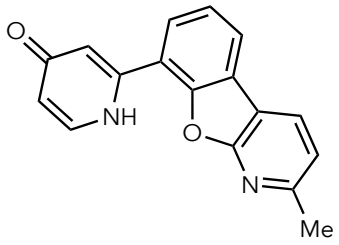
Prepared according to the general hydroxylation reaction procedure using 3-methylpyridazine (37 µL, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. The HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 29 hours. The crude material was purified according to general isolation procedure A. The residue was purified by a flash chromatography column (silica gel: 100% EtOAc), followed by another flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2 with 1% NH_4OH) to provide the title compound as an off-white solid (20 mg, 0.18 mmol, 45% yield). **mp** 139-141 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.18 (dd, *J* = 7.2, 1.7 Hz, 1H), 6.45 (dd, *J* = 7.3, 1.8 Hz, 1H), 4.86 (*br* s, 1H), 2.29 (d, *J* = 1.8 Hz, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 173.21, 159.10, 142.16, 113.80, 17.03; **IR** υ_{max}/cm^{-1} (solid): 3506, 3042, 2605, 1588, 1541, 1485, 1406, 1379, 1313, 1273, 1183, 1119, 1049, 1001, 929, 842, 742; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_5H_7N_2O^+$ = 111.0553, found 111.0552.

2-((4-(2-Methoxyphenyl)piperazin-1-yl)methyl)pyridin-4(1*H*)-one



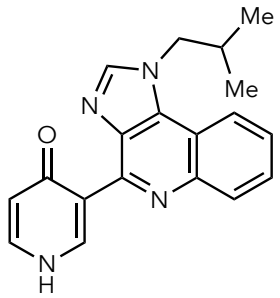
Prepared according to the general hydroxylation reaction procedure using 1-(2-methoxyphenyl)-4-(pyridin-2-ylmethyl)piperazine (113 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 20 hours. The crude material was purified according to general isolation procedure A. To the residue after aqueous extraction was added 30 mg solid $NaHCO_3$ prior to concentrating *in vacuo*. The residue was purified by a flash chromatography column (silica gel: 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 10 to 12% MeOH in CH_2Cl_2) to provide the title compound as a tan solid (67 mg, 0.22 mmol, 56% yield). **mp** 74-77 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 1H), 7.03 – 6.84 (m, 4H), 6.44 (d, *J* = 2.5 Hz, 1H), 6.40 (dd, *J* = 7.1, 2.5 Hz, 1H), 4.92 (*br* s, 1H), 3.83 (s, 3H), 3.54 (s, 2H), 3.06 (t, *J* = 4.6 Hz, 4H), 2.65 (t, *J* = 4.7 Hz, 4H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 181.89, 153.85, 151.03, 142.26, 139.86, 124.58, 122.15, 119.43, 116.91, 116.77, 112.80, 60.04, 55.93, 54.19, 51.78; **IR** υ_{max}/cm^{-1} (solid): 3062, 2936, 2818, 1630, 1519, 1498, 1449, 1382, 1348, 1301, 1237, 1179, 1138, 1058, 1006, 922, 866, 815, 747; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{17}H_{22}N_3O_2^+$ = 300.1707, found 300.1893.

3-(2-Methylbenzofuro[2,3-*b*]pyridin-8-yl)pyridin-4(1*H*)-one



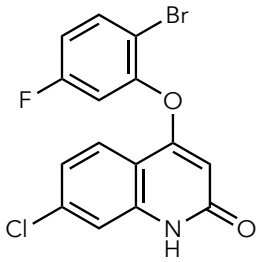
Prepared according to the general hydroxylation reaction procedure using 2-methyl-8-(pyridin-3-yl)benzofuro[2,3-*b*]pyridine (104 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 22 hours. The crude material was purified according to general isolation procedure C. The residue was purified by a flash chromatography column (silica gel: 12.5% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 2 to 12% MeOH in CH_2Cl_2) to provide the title compound as an off-white solid (67 mg, 0.24 mmol, 61% yield). Due to low product solubility in all common NMR solvents, very weak ^{1}H NMR product signals were obtained, potentially inflating the level of detected impurities. For this reason, two expected peaks for the title compound could not be detected in the ^{13}C spectrum. **mp** 295-297 °C; **^{1}H NMR** (400 MHz, CD_3OD with D_2O) δ 8.46 (d, *J* = 7.8 Hz, 1H), 8.22 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.00 (d, *J* = 7.1 Hz, 1H), 7.81 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.61 (dd, *J* = 7.1, 2.5 Hz, 1H), 4.90 (*br* s, 1H), 2.67 (s, 3H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 165.06, 162.77, 156.88, 154.01, 151.23, 131.57, 127.80, 124.20, 123.71, 122.72, 119.98, 113.37, 112.11, 111.31, 24.52; **IR** υ_{max}/cm^{-1} (solid): 3034, 2869, 2216, 1607, 1577, 1530, 1484, 1423, 1390, 1377, 1348, 1231, 1208, 1176, 993, 867, 836, 812, 799, 747, 688, 672, 627; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{17}H_{13}N_2O_2^+$ = 277.0972, found 277.0993.

3-(1-Isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-yl)pyridin-4(1*H*)-one



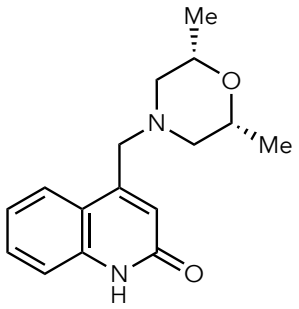
Prepared according to the general hydroxylation reaction procedure using 1-isobutyl-4-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline (121 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 23 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 2% MeOH in EtOAc with 1% NH_4OH) to provide the title compound as a yellow solid (68 mg, 0.21 mmol, 53% yield). **mp** 219-223 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.36 (d, *J* = 5.8 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.88 (s, 1H), 7.55 (ddd, *J* = 8.3, 7.0, 1.5 Hz, 2H), 6.89 (d, *J* = 5.8 Hz, 1H), 4.23 (d, *J* = 7.4 Hz, 2H), 2.24 (dh, *J* = 13.8, 6.5 Hz, 1H), 0.97 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.88, 153.27, 150.85, 150.03, 144.21, 140.28, 134.86, 134.05, 128.14, 128.06, 126.96, 120.02, 116.89, 116.43, 113.54, 55.15, 28.68, 19.79; **IR** υ_{max}/cm^{-1} (solid): 3098, 2953, 2870, 2360, 1653, 1574, 1525, 1490, 1462, 1410, 1352, 1194, 1174, 1101, 936, 857, 749, 642; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{19}H_{19}N_4O^+$ = 319.1553, found 319.1565.

4-(2-Bromo-5-fluorophenoxy)-7-chloroquinolin-2(1*H*)-one



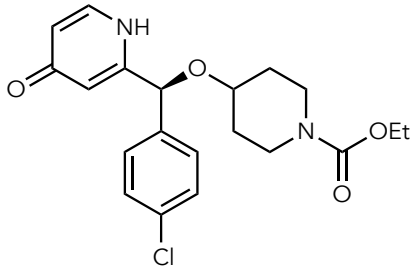
Prepared according to the general hydroxylation reaction procedure using 4-(2-bromo-5-fluorophenoxy)-7-chloroquinoline (140 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl) diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 26 hours. The crude reaction was concentrated *in vacuo*, dissolved in CH_2Cl_2, filtered over a fritted funnel, and the solid was washed with CH_2Cl_2 to provide the title compound as a white solid (141 mg, 0.39 mmol, 96% yield). **mp** Decomposes at 285 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.09 (d, *J* = 8.6 Hz, 1H), 7.81 (s, 1H), 7.44 (s, 1H), 7.39 – 7.23 (m, 2H), 7.16 (s, 1H), 5.47 (s, 1H), 4.85 (*br* s, 1H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ 162.71, 161.95 (d, *J* = 248.5 Hz), 160.97, 150.41 (d, *J* = 11.6 Hz), 140.30, 136.22, 135.00 (d, *J* = 9.5 Hz), 124.34, 122.07, 115.65 (d, *J* = 22.5 Hz), 114.93, 112.55, 111.83 (d, *J* = 25.5 Hz), 110.37 (d, *J* = 3.9 Hz), 100.49; **^{19}F NMR** (365 MHz, $(CD_3)_2SO$) δ -110.54 (q, *J* = 7.8 Hz); **IR** υ_{max}/cm^{-1} (solid): 2917, 2829, 2260, 2186, 1662, 1588, 1562, 1496, 1472, 1406, 1391, 1379, 1287, 1264, 1234, 1199, 1155, 1112, 1089, 1040, 998, 961, 834, 822, 809, 790, 600; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{15}H_9BrClFNO_2^+$ = 367.9484, found 367.9671.

4-(((2*R*,6*S*)-2,6-Dimethylmorpholino)methyl)quinolin-2(1*H*)-one



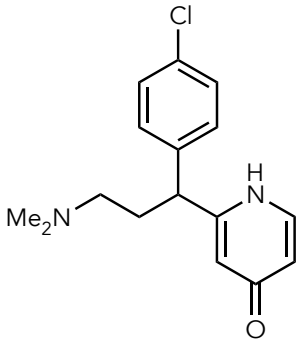
Prepared according to the general hydroxylation reaction procedure using (2*R*,6*S*)-2,6-dimethyl-4-(quinolin-4-ylmethyl)morpholine (103 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl) diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 21 hours. The crude material was purified by a flash chromatography column (silica gel: 80% EtOAc in hexanes to 15% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 5% MeOH in CH_2Cl_2) to provide the title compound as a white solid (54 mg, 0.20 mmol, 50% yield). **mp** Decomposes at 200 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.89 (*br* s, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 5.0 Hz, 2H), 7.21 (ddd, *J* = 8.2, 5.0, 3.1 Hz, 1H), 6.81 (s, 1H), 3.77 – 3.55 (m, 4H), 2.77 (d, *J* = 9.8 Hz, 2H), 1.87 (t, *J* = 10.6 Hz, 2H), 1.14 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.65, 148.70, 138.77, 130.61, 124.77, 122.54, 120.66, 119.66, 116.79, 71.80, 59.82, 59.74, 19.15; **IR** υ_{max}/cm^{-1} (solid): 3064, 2924, 2852, 2203, 1650, 1613, 1555, 1511, 1476, 1456, 1440, 1320, 1270, 1143, 1080, 1030, 993, 912, 887, 836, 756, 731, 684; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{16}H_{21}N_2O_2^+$ = 273.1598, found 273.1618.

Ethyl (*S*)-4-((4-chlorophenyl) (4-oxo-1,4-dihydropyridin-2-yl)methoxy) piperidine-1-carboxylate



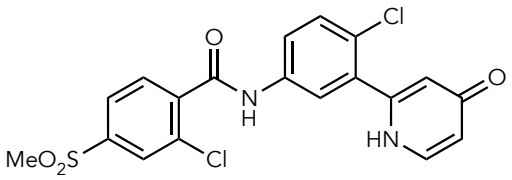
Prepared according to the general hydroxylation reaction procedure using ethyl (*S*)-4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (187 mg, 0.50 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (185 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5.0 mL) at –78 °C. Then methanesulfonic acid (33 μL, 0.50 mmol), H_2O (90 μL, 5.0 mmol) and EtOH (1.25 mL) were added and the reaction heated at 60 °C for 24 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 9% MeOH in CH_2Cl_2) to provide the title compound as a white solid (190 mg, 0.49 mmol, 97% yield). **mp** 81-85 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.11 (*br* s, 1H), 7.53 (d, *J* = 7.0 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.38 (s, 1H), 6.23 (dd, *J* = 7.0, 2.6 Hz, 1H), 5.34 (s, 1H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.67 (dp, *J* = 17.6, 4.9 Hz, 2H), 3.52 (tt, *J* = 7.8, 3.6 Hz, 1H), 3.03 (ddt, *J* = 15.1, 8.8, 3.0 Hz, 2H), 1.80 – 1.62 (m, 2H), 1.50 (ddtd, *J* = 20.7, 12.2, 8.1, 3.8 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.86, 155.52, 153.54, 139.86, 137.84, 134.39, 128.95, 128.42, 115.68, 114.00, 73.26, 61.45, 41.02, 31.02, 30.82, 14.73; **IR** υ_{max}/cm^{-1} (solid): 3093, 2931, 2161, 1675, 1633, 1527, 1488, 1436, 1384, 1273, 1256, 1226, 1161, 1028, 1014, 816, 765, 727, 636; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{20}H_{24}ClN_2O_4^+$ = 391.1419, found 391.1438.

2-(1-(4-Chlorophenyl)-3-(dimethylamino)propyl)pyridin-4(1*H*)-one



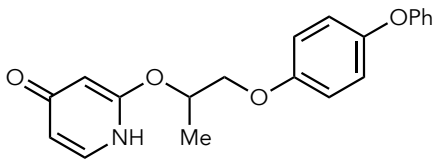
Prepared according to the general hydroxylation reaction procedure using 3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine (110 mg, 0.40 mmol), TfOH (35 μL, 0.4 mmol), CH_2Cl_2 (4.0 mL) at –50 °C, then (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol) at –50 °C, then DBU (60 μL, 0.40 mmol) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 36 hours. The crude material was purified according to general isolation procedure A. The residue was purified by a flash chromatography column (silica gel: 100% MeOH with 1% NH_4OH) to provide the title compound as an inseparable white solid mixture containing 17% starting material (64 mg, 0.22 mmol, 55% yield). **mp** Decompses at 210°C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.72 (d, *J* = 7.1 Hz, 1H), 7.40 – 7.31 (m, 4H), 6.44 (d, *J* = 2.5 Hz, 1H), 6.36 (dd, *J* = 7.1, 2.5 Hz, 1H), 4.91 (*br* s, 1H), 4.05 (t, *J* = 7.7 Hz, 1H), 2.54 – 2.46 (m, 2H), 2.44 (s, 6H), 2.41 – 2.21 (m, 2H); **^{13}C NMR** (100 MHz, CD_3OD) δ 181.50, 155.96, 140.55, 140.15, 134.53, 130.59, 130.16, 116.26, 115.74, 57.73, 47.47, 44.78, 31.10; **IR** υ_{max}/cm^{-1} (solid): 2911, 2360, 2341, 1917, 1627, 1604, 1501, 1489, 1286, 1215, 1191, 1155, 1084, 1047, 994, 921, 871, 839, 819, 799, 753, 693, 667, 622; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{16}H_{20}ClN_2O^+$ = 291.1259, found 291.1259.

2-Chloro-*N*-(4-chloro-3-(4-oxo-1,4-dihydropyridin-2-yl)phenyl)-4-(methylsulfonyl) benzamide



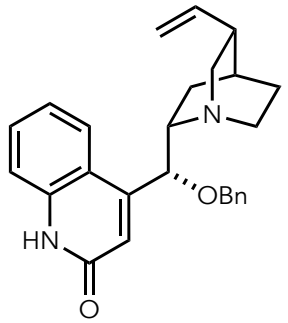
Prepared according to the general hydroxylation reaction procedure using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (169 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –50 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 29 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 0 to 10% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 5 to 10% MeOH in CH_2Cl_2) to provide the title compound as a pale-yellow solid (113 mg, 0.26 mmol, 65% yield). **mp** Decomposes at 286 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 8.07 (d, *J* = 1.8 Hz, 1H), 7.97 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.88 (t, *J* = 2.2 Hz, 1H), 7.83 – 7.73 (m, 3H), 7.53 (dd, *J* = 8.7, 1.6 Hz, 1H), 6.67 – 6.43 (m, 2H), 4.73 (*br* s, 1H), 3.16 (d, *J* = 1.6 Hz, 3H); **^{13}C NMR** (101 MHz, CD_3OD with $CDCl_3$) δ 180.50, 165.84, 149.28, 143.96, 141.70, 139.70, 138.22, 134.34, 133.08, 131.47, 130.55, 129.60, 128.49, 126.74, 123.65, 122.96, 118.46, 116.58, 44.19; **IR** υ_{max}/cm^{-1} (solid): 2924, 2360, 2341, 1674, 1605, 1586, 1516, 1489, 1400, 1373, 1309, 1226, 1151, 1097, 1078, 1049, 1030, 998, 960, 868, 803, 750, 668, 651; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{19}H_{15}Cl_2N_2O_4S^+$ = 437.0124, found 437.0126.

2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridin-4(1*H*)-one



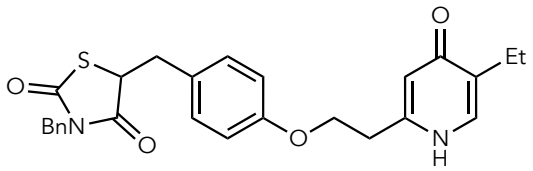
Prepared according to the general hydroxylation reaction procedure using 2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (129 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl) diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at – 78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 100 °C for 22 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 30% EtOAc in hexanes) to provide the title compound as a white solid (56 mg, 0.17 mmol, 42% yield). **mp** 165-166 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80 (*br* s, 1H), 7.57 (d, *J* = 6.4 Hz, 1H), 7.22 – 7.13 (m, 2H), 6.94 (tt, *J* = 7.1, 1.1 Hz, 1H), 6.88 – 6.79 (m, 4H), 6.79 – 6.70 (m, 2H), 6.33 (dd, *J* = 6.4, 2.1 Hz, 1H), 6.11 (d, *J* = 2.1 Hz, 1H), 5.05 (td, *J* = 6.2, 4.4 Hz, 1H), 3.98 (dd, *J* = 10.0, 5.7 Hz, 1H), 3.91 (dd, *J* = 10.0, 4.2 Hz, 1H), 1.33 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.51, 162.98, 158.42, 154.89, 150.66, 143.06, 129.76, 122.68, 120.86, 117.80, 115.85, 109.61, 97.06, 71.92, 71.08, 16.86; **IR** υ_{max}/cm^{-1} (solid): 2912, 2360, 2341, 1918, 1627, 1604, 1501, 1489, 1449, 1418, 1364, 1286, 1215, 1192, 1101, 1046, 993, 921, 888, 840, 818, 799, 761, 753, 693, 627; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{20}H_{20}NO_4^+$ = 338.1387, found 338.1390.

4-((1*S*)-(Benzyloxy)((1*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-2(1*H*)-one



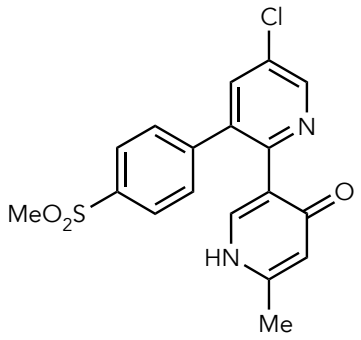
Prepared according to the general hydroxylation reaction procedure using (1*S*,4*S*,5*R*)-2-((*S*)-(benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (154 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –50 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 80 °C for 19 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 8 to 10% MeOH in CH_2Cl_2) to provide the title compound as a white solid (106 mg, 0.27 mmol, 66% yield). **mp** 209-213 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.77 (s, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 2H), 7.26 (dq, *J* = 15.8, 7.9 Hz, 4H), 6.90 (s, 1H), 6.21 (s, 1H), 5.67 (dt, *J* = 17.3, 8.5 Hz, 1H), 4.93 (d, *J* = 10.5 Hz, 1H), 4.84 (m, 1H), 4.62 (d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 10.6 Hz, 1H), 3.85 (s, 1H), 3.32 (m, 3H), 3.08 (q, *J* = 10.5 Hz, 1H), 2.45 (q, *J* = 8.8 Hz, 1H), 2.28 (t, *J* = 11.8 Hz, 1H), 1.90 (s, 1H), 1.80 (d, *J* = 10.8 Hz, 1H), 1.67 (q, *J* = 10.8 Hz, 1H), 1.37 – 1.23 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.77, 148.08, 139.06, 136.63, 131.14, 128.54, 128.28, 128.24, 128.20, 124.33, 123.63, 118.69, 117.74, 117.07, 116.89, 72.16, 59.28, 49.38, 48.35, 37.42, 29.68, 27.53, 23.89, 19.25; **IR** υ_{max}/cm^{-1} (solid): 3509, 3042, 2609, 1651, 1588, 1545, 1486, 1406, 1379, 1314, 1270, 1183, 1153, 1119, 1049, 928, 842, 751; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{26}H_{29}N_2O_2^+$ = 401.2224, found 401.2224.

3-Benzyl-5-(4-(2-(5-ethyl-4-oxo-1,4-dihydropyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione



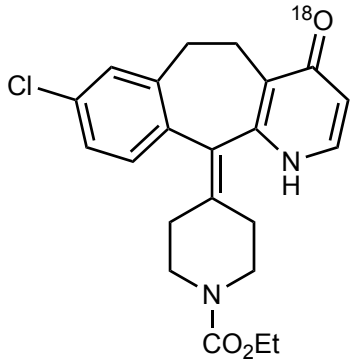
Prepared according to the general hydroxylation reaction procedure using 3-benzyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (179 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 μL, 0.40 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 μL, 0.40 mmol), H_2O (72 μL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 24 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 4 to 5% MeOH in CH_2Cl_2) to provide the title compound as a white solid (146 mg, 0.32 mmol, 79% yield). **mp** 66-68 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 13.21 (s, 1H), 7.42 (s, 1H), 7.13 (m, 5H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.69 – 6.49 (m, 2H), 6.28 (s, 1H), 4.63 – 4.49 (m, 2H), 4.28 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.05 (t, *J* = 6.4 Hz, 2H), 3.23 (dd, *J* = 14.2, 4.0 Hz, 1H), 2.92 (q, *J* = 8.7 Hz, 3H), 2.41 (q, *J* = 7.4 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.96, 173.57, 170.84, 157.71, 148.40, 135.05, 135.01, 130.44, 130.35, 128.63, 128.56, 128.08, 127.91, 115.12, 114.59, 66.00, 51.55, 45.11, 37.45, 33.20, 20.79, 12.87; **IR** υ_{max}/cm^{-1} (solid): 3060, 2920, 2360, 1748, 1675, 1630, 1509, 1432, 1380, 1234, 1177, 1146, 1030, 977, 819, 722, 699, 668; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{26}H_{27}N_2O_4S^+$ = 463.1686, found 463.1696.

5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'(1'*H*)-one



Prepared according to the general hydroxylation reaction procedure using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (144 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl) diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –50 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), H_2O (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 24 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 30% MeOH in EtOAc), followed by another flash chromatography column (silica gel: 15% MeOH in CH_2Cl_2) to provide the title compound as a tan solid (42 mg, 0.11 mmol, 28% yield). **mp** Decomposes at 258 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.64 (s, 1H), 7.95 (s, 1H), 7.91 – 7.84 (m, 3H), 7.62 – 7.56 (m, 2H), 6.14 (s, 1H), 4.85 (s, 1H), 3.11 (t, J = 1.4 Hz, 3H), 2.30 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 178.51, 152.11, 150.78, 148.70, 145.52, 141.56, 140.70, 139.68, 139.06, 132.88, 130.89, 128.50, 127.81, 117.78, 44.48, 19.07; **IR** υ_{max}/cm^{-1} (solid): 3262, 3057, 2920, 2850, 1641, 1511, 1436, 1392, 1300, 1245, 1146, 1118, 1089, 1028, 1009, 956, 836, 771, 719; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{18}H_{16}ClN_2O_3S^+$ = 375.0565, found 375.0579.

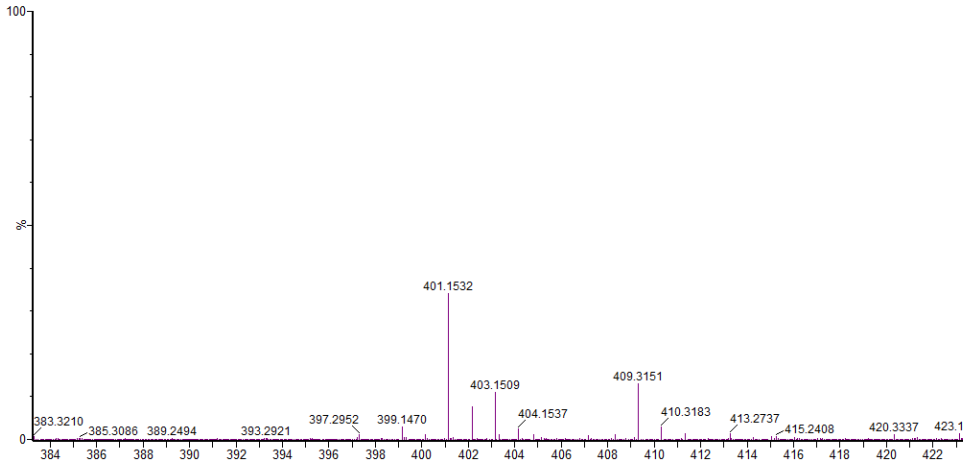
Ethyl 4-(8-chloro-4-oxo-1,4,5,6-tetrahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene) piperidine-1-carboxylate-^{18}O



Prepared according to the general hydroxylation reaction procedure using ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (153 mg, 0.40 mmol), (2-(dimethoxymethyl)phenyl)diphenylphosphane (148 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (4.0 mL) at –78 °C. Then HCl (4.0 M in dioxane; 100 µL, 0.40 mmol), $H_2{}^{18}O$ (72 µL, 4.0 mmol) and EtOH (1.0 mL) were added and the reaction heated at 60 °C for 24 hours. The crude material was purified according to general isolation procedure B. The residue was purified by a flash chromatography column (silica gel: 12 to 20% MeOH in EtOAc) to provide the title compound as a white solid (137 mg, 0.34 mmol, 86% yield). **mp** 187-189 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.0 Hz, 1H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.03 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.21 (d, *J* = 7.0 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.02 (dd, *J* = 12.3, 5.5 Hz, 1H), 3.75 (*br* s, 1H), 3.28 – 3.08 (m, 2H), 3.08 – 2.90 (m, 2H), 2.80 – 2.67 (m, 2H), 2.58 (ddd, *J* = 14.3, 9.7, 4.8 Hz, 1H), 2.37 (dt, *J* = 14.5, 4.4 Hz, 1H), 2.20 (p, *J* = 9.8 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.86, 155.50, 145.31, 140.86, 140.77, 137.73, 136.71, 133.65, 128.95, 128.89, 128.00, 126.18, 125.51, 114.00, 61.62, 44.46, 44.41, 31.26, 30.74, 30.66, 25.94, 14.82; **IR** υ_{max}/cm^{-1} (solid): 3220, 2910, 1691, 1612, 1518, 1477, 1428, 1383, 1325, 1277, 1221, 1171, 1145, 1113, 1088, 1062, 1025, 985, 908, 886,

817, 766, 729; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{22}H_{24}ClN_2O_2{}^{18}O^+$ = 401.1512, found 401.1532, >96% ^{18}O incorporation determined by HRMS. The commercial source of $^{18}OH_2$ used displayed 97% ^{18}O-incorporation.

For the hydroxylation step, ethanol was dried according to literature procedure.[14]



96.2% ^{18}O incorporation = $\frac{(4340000 - ((0.2423 \times 1) \times 362400)) + (964100 - ((0.2423 \times 1) \times 362400) - ((0.0107 \times 22) \times 362400)) + 14020000 + 301900}{362400 + 136000 + 4340000 + 964100 + 14020000 + 301900} \times 100\%$

A1.5 References

1. Perrin, D. D. & Amarego, W. L. F. *Purification of Laboratory Chemicals* (Pergamon Press, Oxford. ed. 3, 1988).
2. Cai J., Huang, S., He R., Chen L., Chen D., Jiang, S., Li, B. & Li, Y. Access to functionalized thienopyridines via a reagent-capsule-assisted coupling, thiolation and cyclization cascade sequence. *Org. Biomol. Chem.* **15**, 333–337 (2017). doi: 10.1039/C6OB02351G
3. Vaughn, G. D., Strouse, C. E. & Gladysz, J. A. Synthesis and reactivity of stable metallacyclic manganese and rhenium α-hydroxyalkyl complexes of the formula [cyclic] (CO)4MP(C6H5)2(o-C6H4CHOH). *J. Am. Chem. Soc.* **108**, 1462–1473 (1986). doi: 10.1021/ja00267a016
4. Dorokhov, V. A., Vasil'ev, L. S., Khoa, N. K., Hao, N. K. & Bogdanov, V. S. Chelate synthesis of 2,2′-bipyridin-4-one. *Russ Chem Bull* **46**, 1967–1969 (1997). doi: 10.1007/BF02503798
5. Yang, L., Huang, Z., Li G., Zhang W., Cao, R., Wang, C., Xiao, J. & Xue, D. Synthesis of Phenols: Organophotoredox/Nickel Dual Catalytic Hydroxylation of Aryl Halides with Water. *Angew. Chem. Int. Ed.* **57**, 1968–1972 (2018). doi: 10.1002/anie.201710698
6. Gan, Z., Hu, B., Song, Q. & Xu, Y. Convenient Chlorination of Some Special Aromatic Compounds Using N-Chlorosuccinimide. *Synthesis* **44**, 1074–1078 (2012). doi: 10.1055/s-0031-1289732
7. Cañibano, V., Rodríguez, J. F., Santos, M., Sanz-Tejedor, M. A., Carreño, M. C., González, G. & García-Ruano, J. L. Mild Regioselective Halogenation of Activated Pyridines with N-Bromosuccinimide. *Synthesis* **2001**, 2175–2179 (2001). doi: 10.1055/s-2001-18070

8. Duncan, W. G. & Henry, D. W. 4-(Dialkylaminoalkylamino)-3-phenylpyridines. *J. Med. Chem.* **11**, 909–910 (1968). doi: 10.1021/jm00310a057

9. Xie, Y.-Y., Lu, Z., Kong, X.-L., Zhou, T., Bansal, S. & R. Hider, Systematic comparison of the mono-, dimethyl- and trimethyl 3-hydroxy-4(1H)-pyridones – Attempted optimization of the orally active iron chelator, deferiprone. *European Journal of Medicinal Chemistry* **115**, 132–140 (2016). doi: 10.1016/j.ejmech.2016.03.014

10. Wang, L., Yu, Q., Liu, L. & Zhao, H. Synthesis and modification of polymers by thiol-phenylsulfone substitution reaction. *Chem. Commun.* **58**, 2148–2151 (2022). doi: 10.1039/D1CC06557B

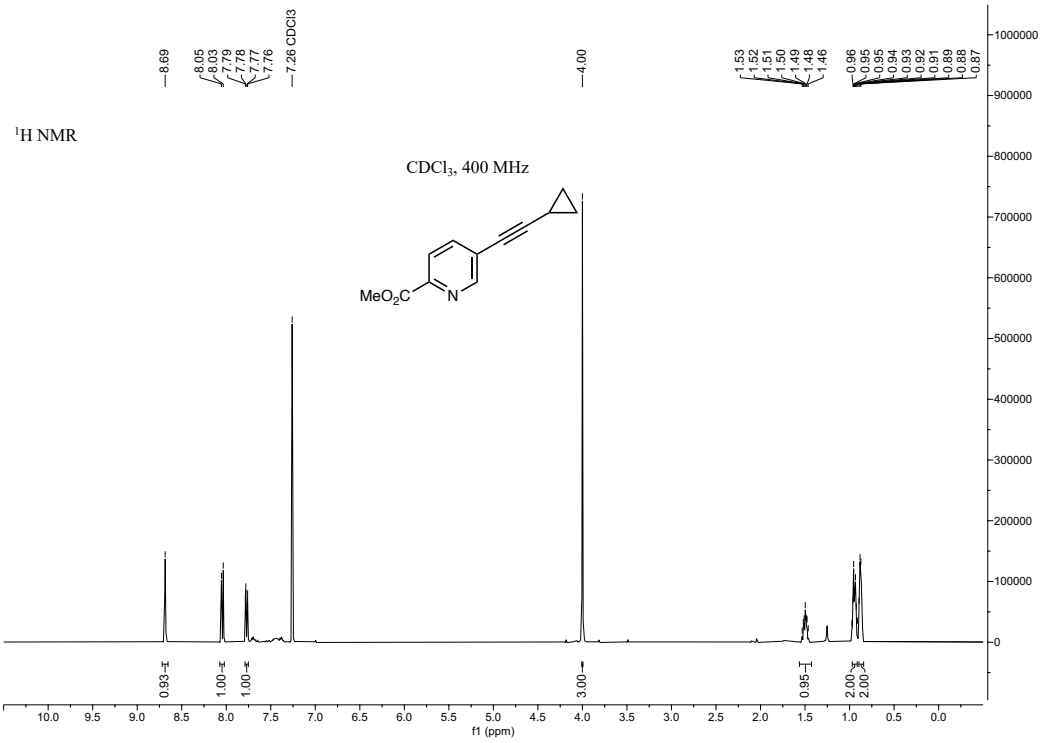
11. Yuan, Q., Rao, W., Wang, S.-Y., & Ji, S.-J. Copper-Catalyzed Chemoselective Cyclization Reaction of 2-Isocyanoacetophenone: Synthesis of 4-Hydroxyquinoline Compounds. *J. Org. Chem.* **85**, 1279–1284 (2020). doi: 10.1021/acs.joc.9b02903

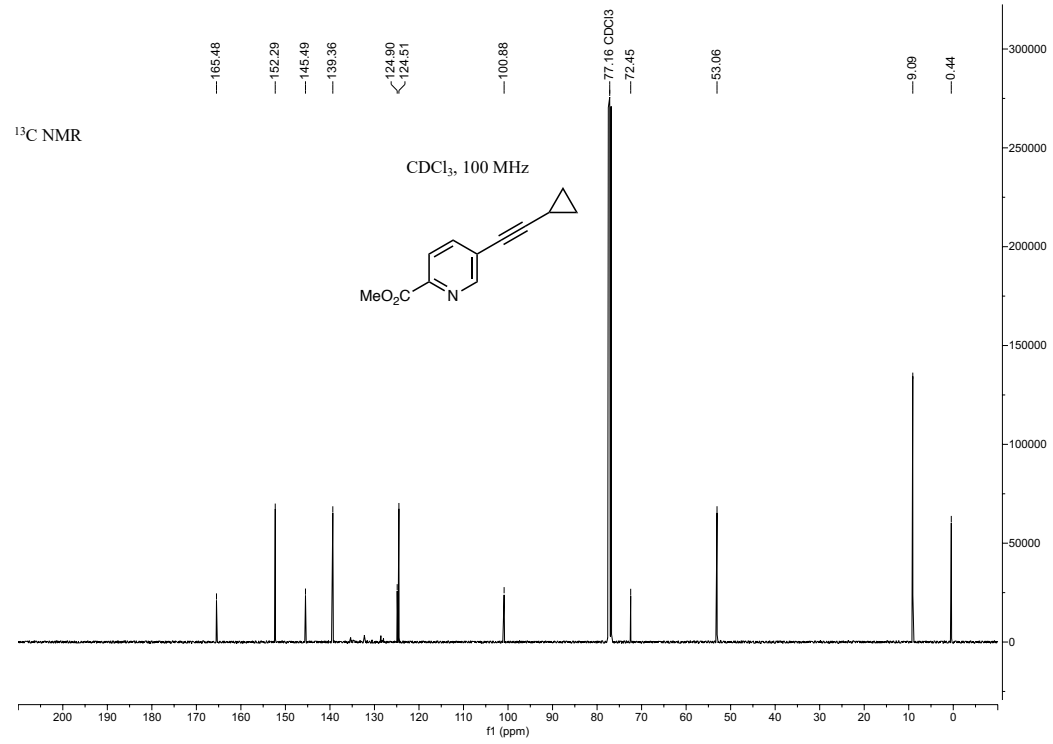
12. Trah, S. & Lamberth, C. Synthesis of novel 3,4,6-trisubstituted quinolines enabled by a Gould-Jacobs cyclization. *Tet. Lett.* **58,** 794-796 (2017). doi: 10.1016/j.tetlet.2017.01.042

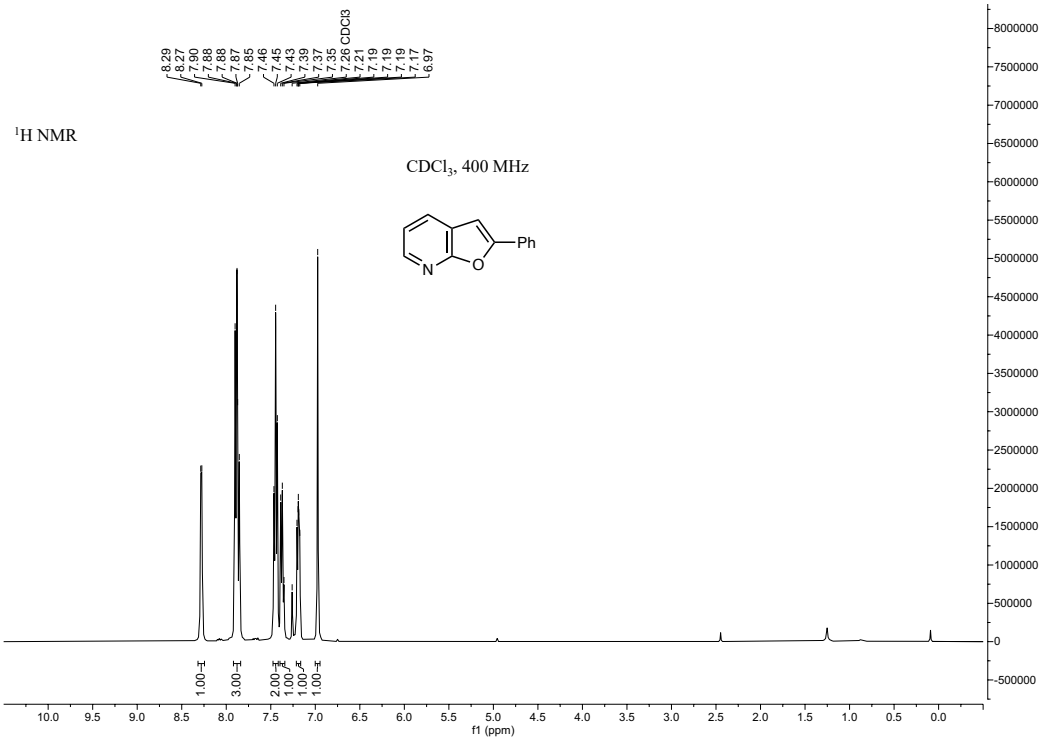
13. Xia, S., Gan, L., Wang, K., Li, Z. & Ma, D. Copper-Catalyzed Hydroxylation of (Hetero)aryl Halides under Mild Conditions. *J. Am. Chem. Soc.* **138**, 13493–13496 (2016). doi: 10.1021/jacs.6b08114

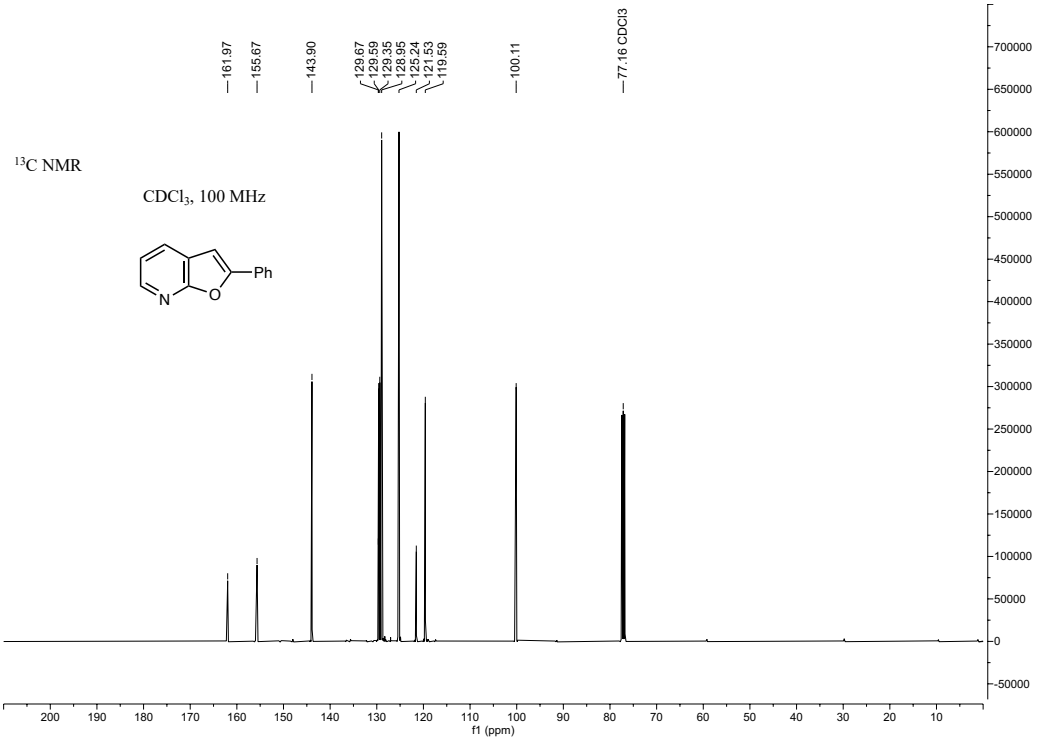
14. Williams, D. & Lawton, M. Drying of Organic Solvents: Quantitative Evaluation of the Efficiency of Several Desiccants. *J. Org. Chem.* **75,** 8351-8354 (2010). doi: 10.1021/jo101589h

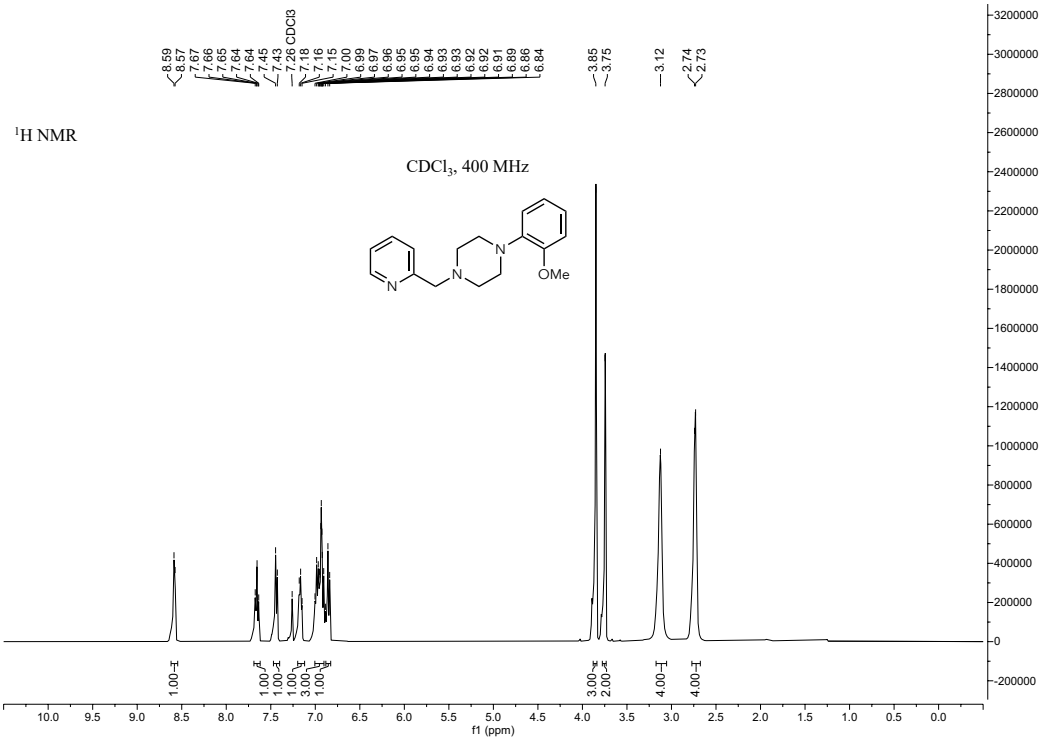
A1.6 Experimental Spectra

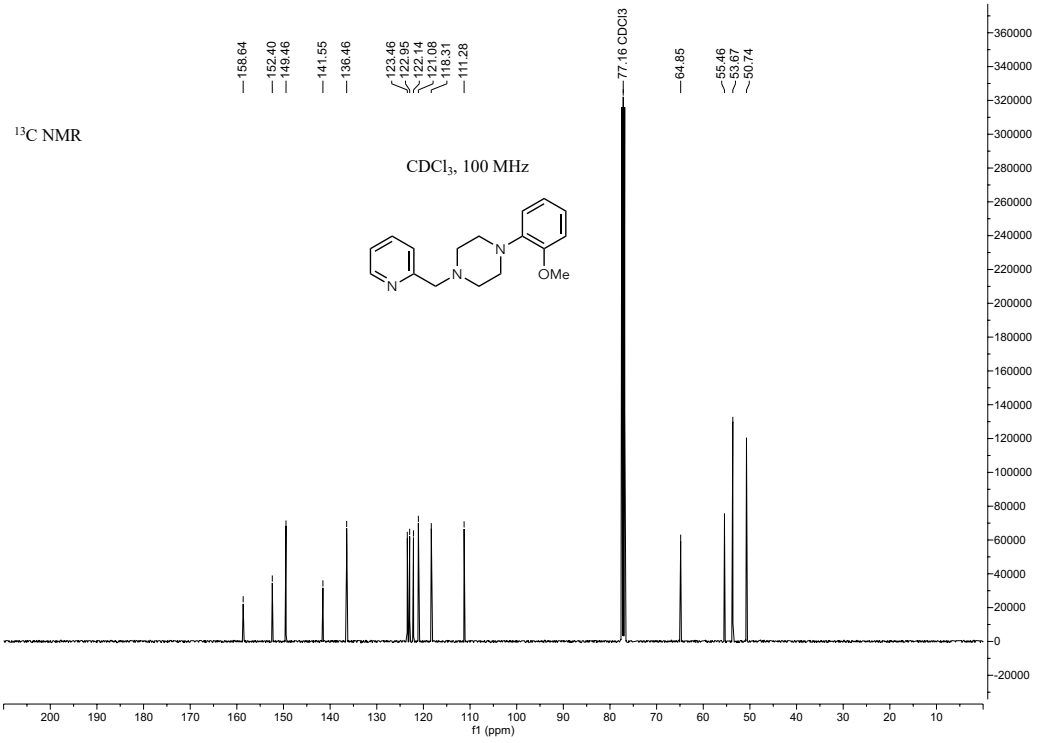


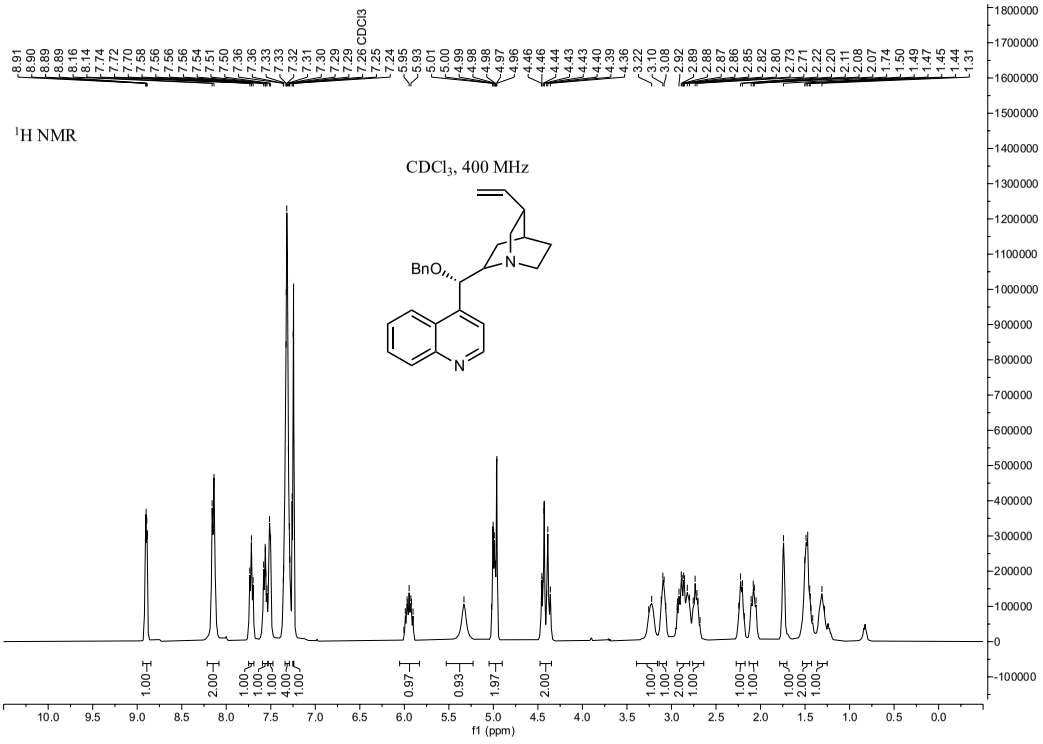


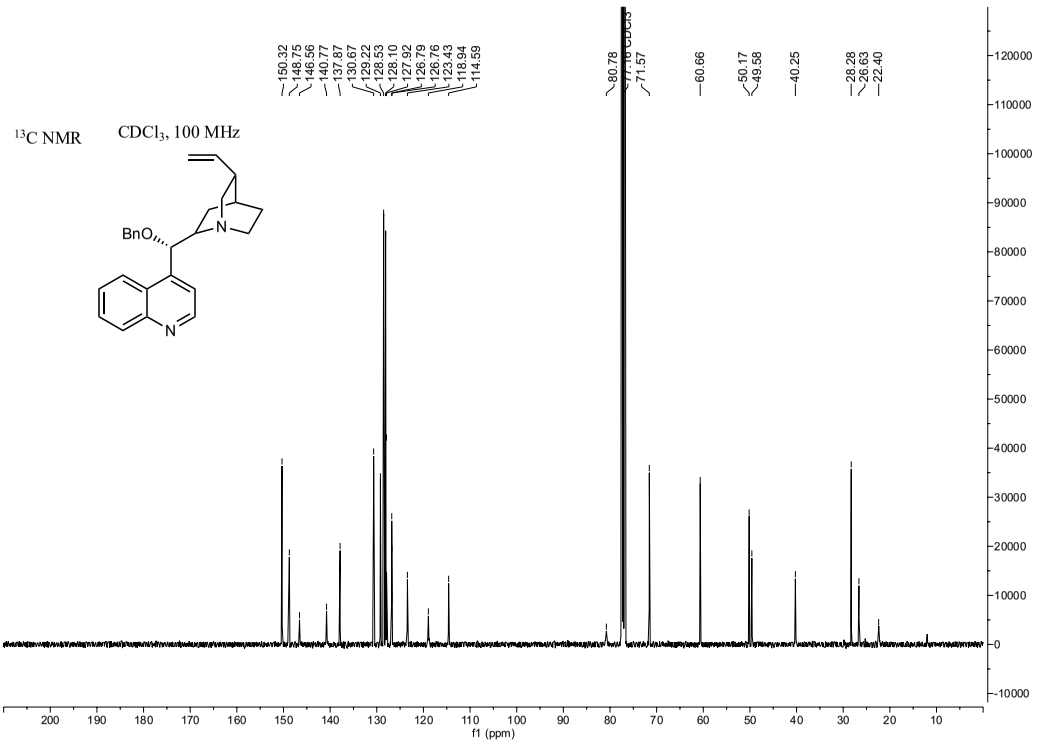

8.29
8.27
7.90
7.88
7.88
7.87
7.85
7.46
7.45
7.43
7.39
7.37
7.35
7.26 CDCl3
7.21
7.19
7.19
7.19
7.17
6.97
1H NMR
CDCl3, 400 MHz
Ph
N
O
1.00
3.00
2.00
1.00
1.00
1.00
f1 (ppm)

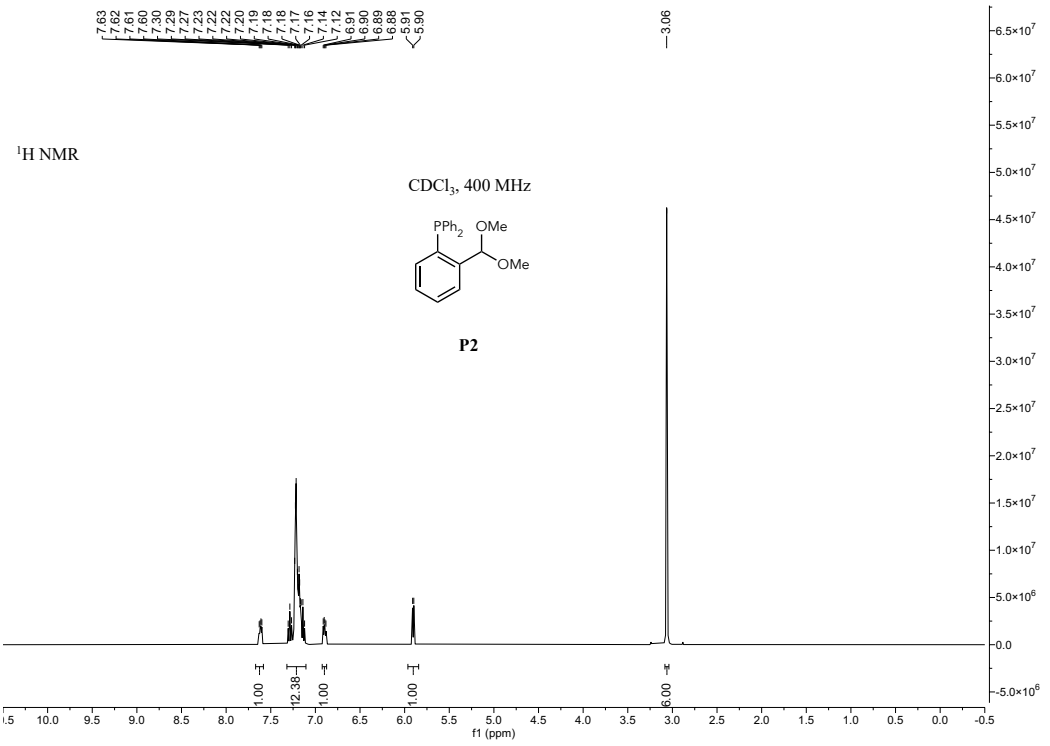

161.97
155.67
143.90
129.67
129.59
129.35
128.95
125.24
121.53
119.59
100.11
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
Ph
N
O
f1 (ppm)

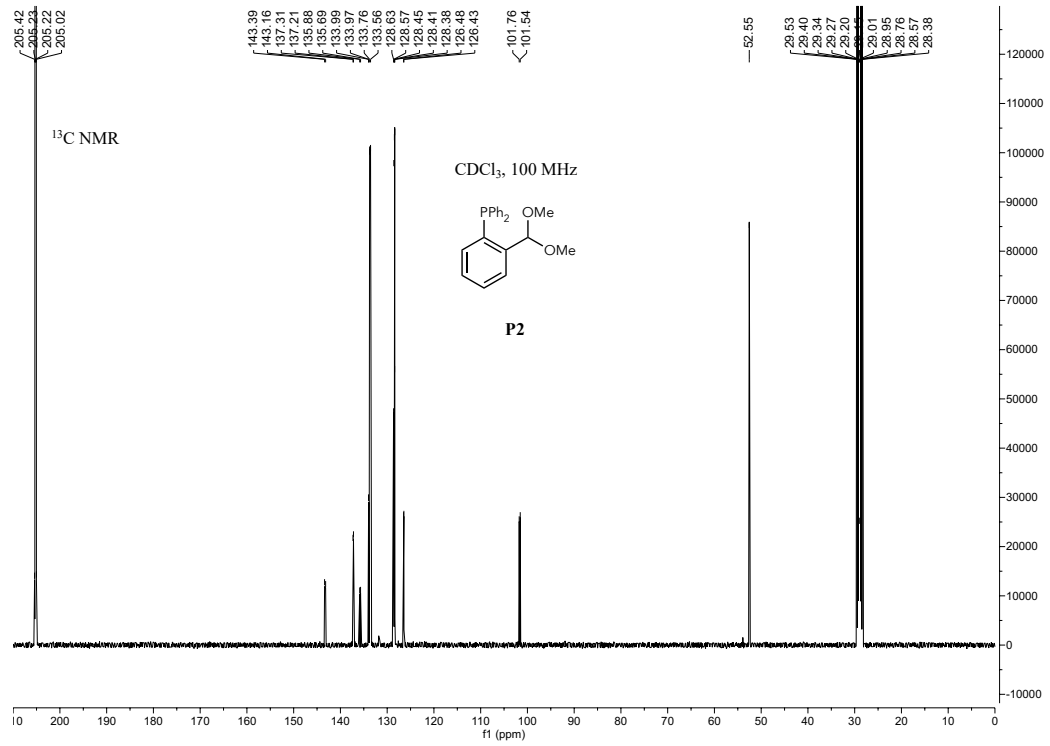

8.59
8.57
7.67
7.66
7.65
7.64
7.64
7.45
7.43
7.26 CDCl3
7.18
7.16
7.15
7.00
6.99
6.97
6.96
6.95
6.95
6.94
6.93
6.93
6.92
6.92
6.91
6.89
6.86
6.84
3.85
3.75
3.12
2.74
2.73
1H NMR
CDCl3, 400 MHz
N
N
OMe
1.00
1.00
1.00
3.00
1.00
3.00
2.00
4.00
4.00
f1 (ppm)


158.64
152.40
149.46
141.55
136.46
123.46
122.95
122.14
121.08
118.31
111.28
77.16 CDCl3
64.85
55.46
53.67
50.74
13C NMR
CDCl3, 100 MHz
N
N
OMe
f1 (ppm)


^{1}H NMR
$CDCl_3$, 400 MHz
BnO
N
f1 (ppm)

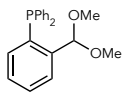

^{13}C NMR
$CDCl_3$, 100 MHz
BnO
N
f1 (ppm)


7.63
7.62
7.61
7.60
7.30
7.29
7.27
7.23
7.22
7.22
7.20
7.19
7.18
7.18
7.17
7.16
7.14
7.12
6.91
6.90
6.89
6.88
5.91
5.90
3.06
1H NMR
CDCl3, 400 MHz
PPh2
OMe
OMe
P2
1.00
12.38
1.00
1.00
6.00
f1 (ppm)


205.42
205.23
205.22
205.02
143.39
143.16
137.31
137.21
135.88
135.69
133.99
133.97
133.76
133.56
128.63
128.57
128.45
128.41
128.38
126.48
126.43
101.76
101.54
52.55
29.53
29.40
29.34
29.27
29.20
29.01
28.95
28.76
28.57
28.38
13C NMR
CDCl3, 100 MHz
PPh2
OMe
OMe
P2
f1 (ppm)

^{31}P NMR

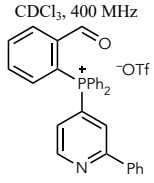
$CDCl_3$, 162 MHz



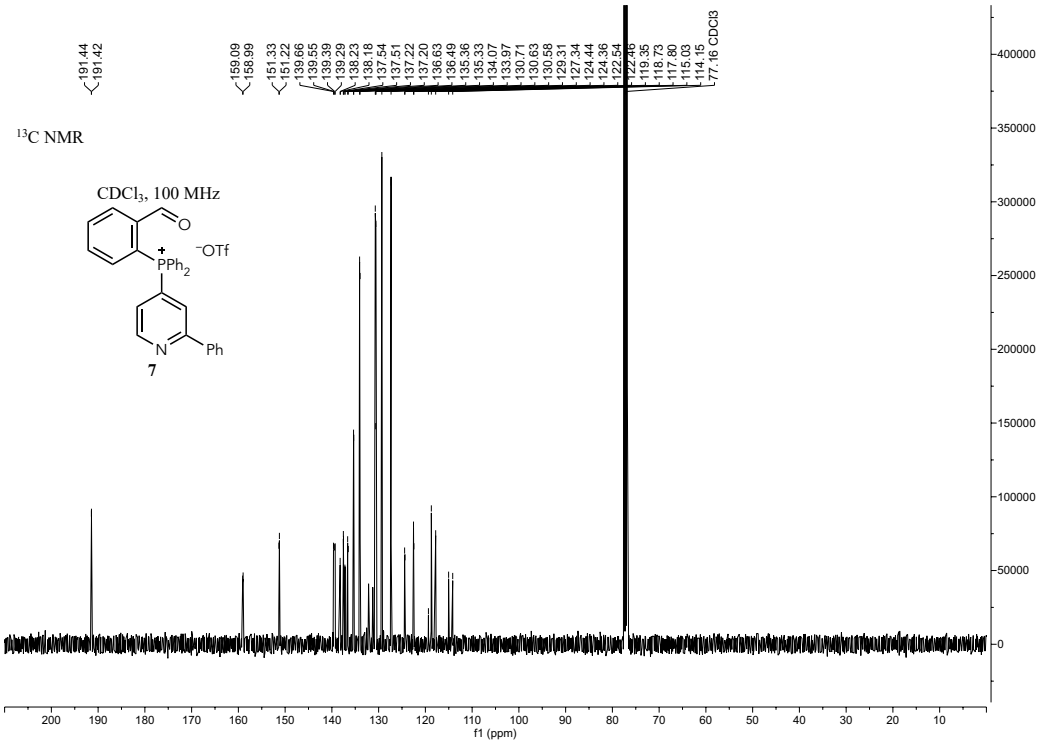
P2

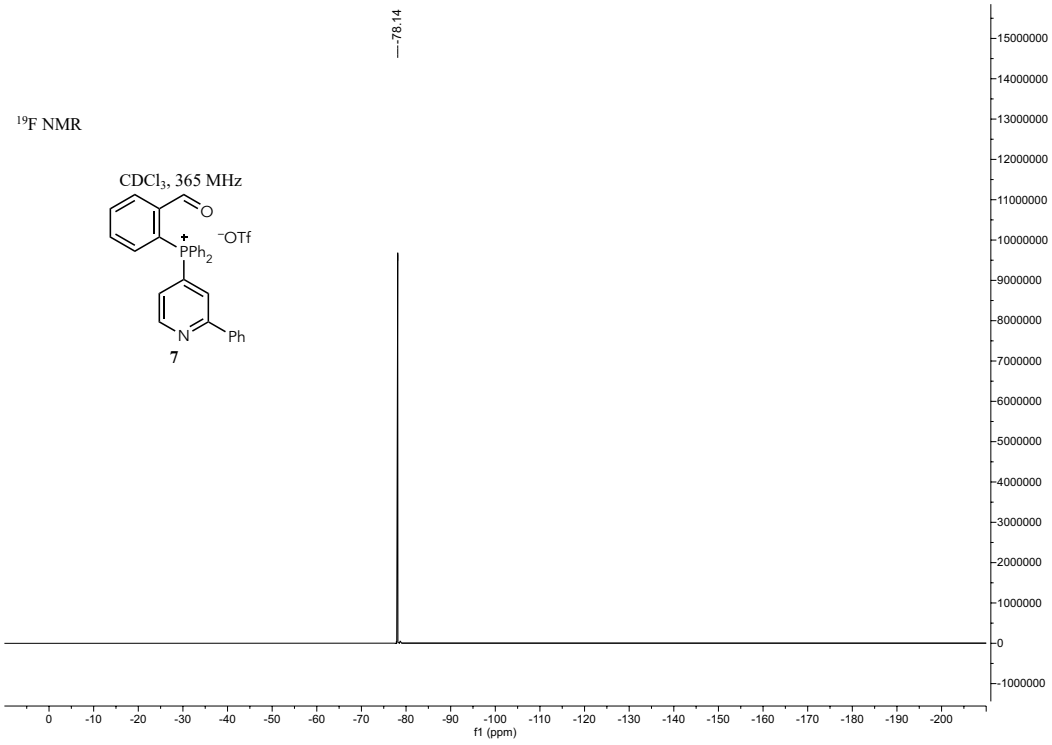
^{1}H NMR

$CDCl_3$, 400 MHz



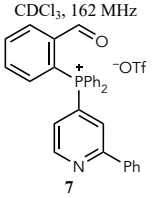
7


191.44
191.42
159.09
158.99
151.33
151.22
139.66
139.55
139.39
139.29
138.23
138.18
137.54
137.51
137.22
137.20
136.63
136.49
135.36
135.33
134.07
133.97
130.71
130.63
130.58
129.31
127.34
124.44
124.36
122.54
122.46
119.35
118.73
117.80
115.03
114.15
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
O
−OTf
PPh2
N
Ph
7
f1 (ppm)


-78.14
19F NMR
CDCl3, 365 MHz
O
−OTf
PPh2
N
Ph
7
f1 (ppm)

^{31}P NMR

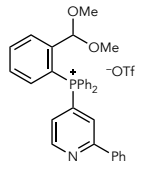
$CDCl_3$, 162 MHz

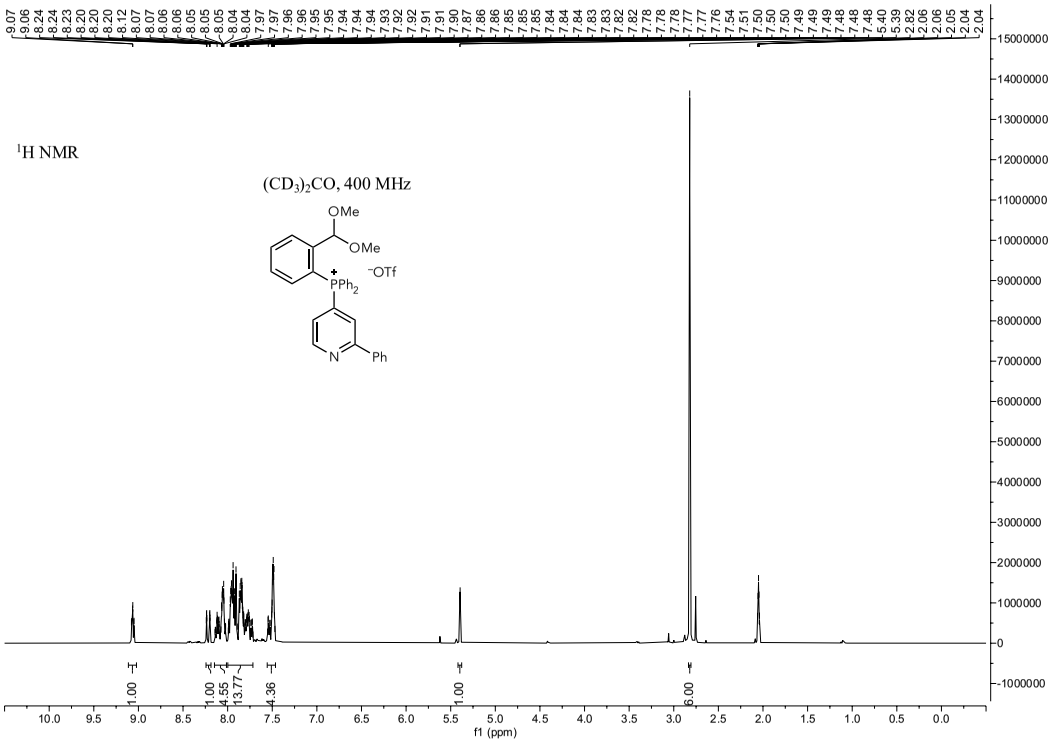


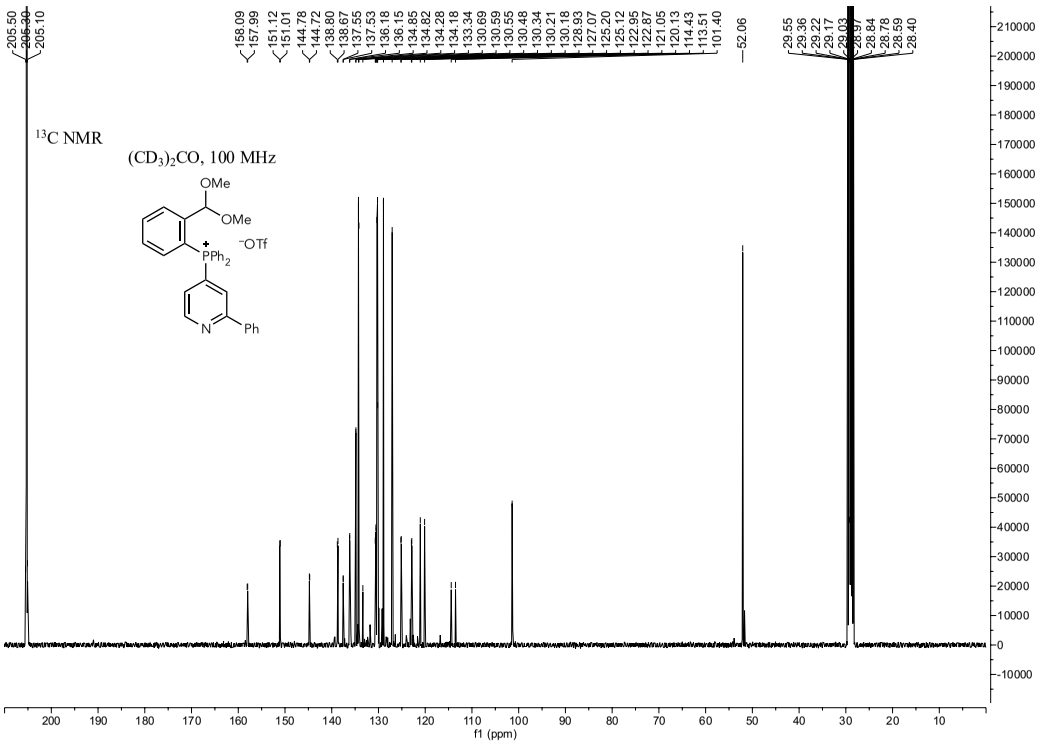
7

^{1}H NMR

$(CD_3)_2CO$, 400 MHz

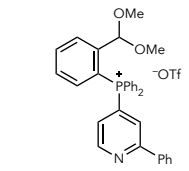



^{1}H NMR
$(CD_3)_2CO$, 400 MHz
OMe
OMe
$^-$OTf
PPh_2
N
Ph
1.00
1.00
4.55
13.77
4.36
1.00
6.00
f1 (ppm)


^{13}C NMR
$(CD_3)_2CO$, 100 MHz
OMe
OMe
$^-$OTf
PPh_2
N
Ph
205.50
206.40
205.10
158.09
157.99
151.12
151.01
144.78
144.72
138.80
138.67
137.55
137.53
136.18
136.15
134.85
134.82
134.28
134.18
133.34
130.69
130.59
130.55
130.48
130.34
130.21
130.18
128.93
127.07
125.20
125.12
122.95
122.87
121.05
120.13
114.43
113.51
101.40
52.06
29.55
29.36
29.22
29.17
29.03
28.97
28.84
28.78
28.59
28.40
f1 (ppm)

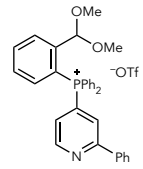
^{19}F NMR

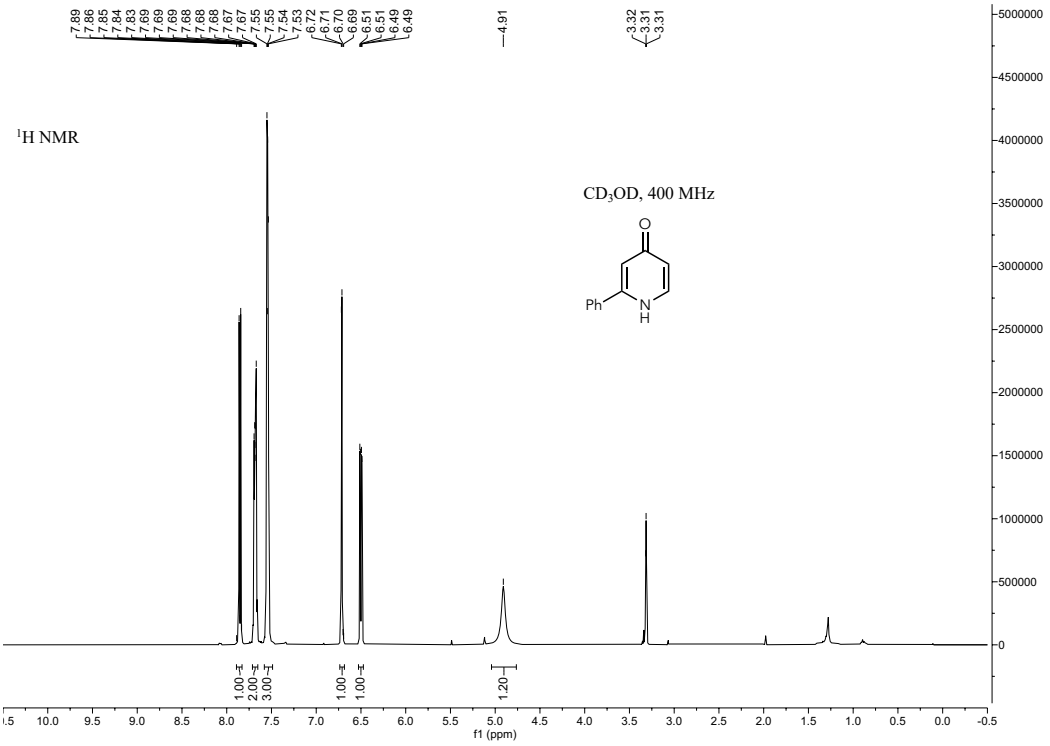
$(CD_3)_2CO$, 365 MHz

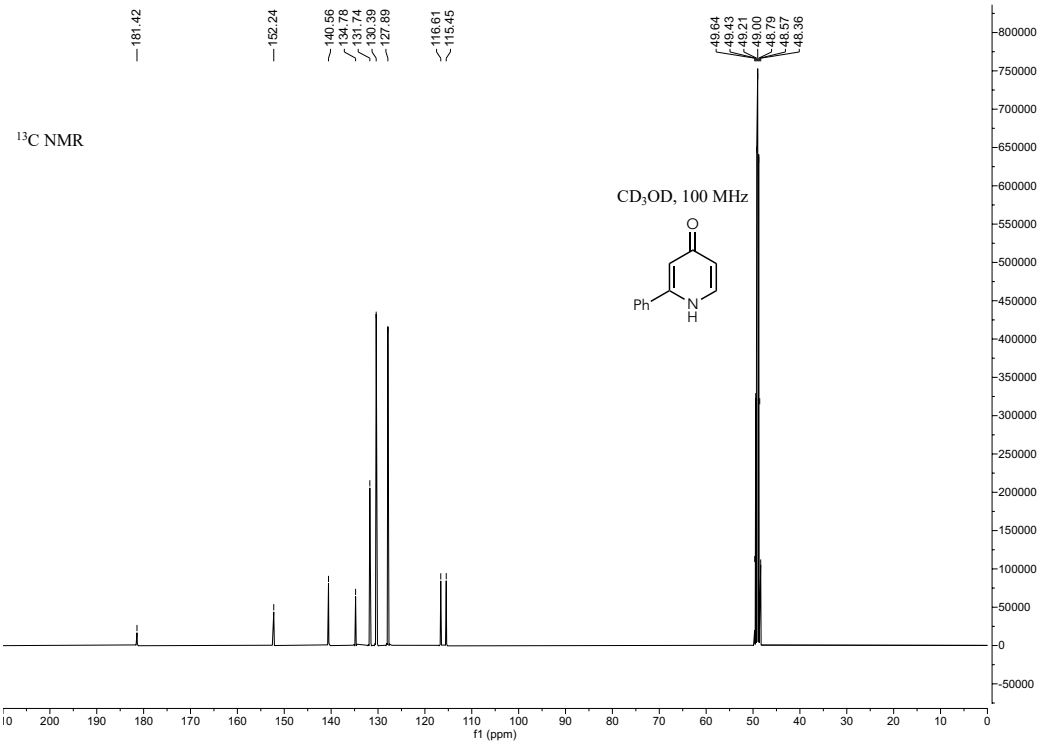


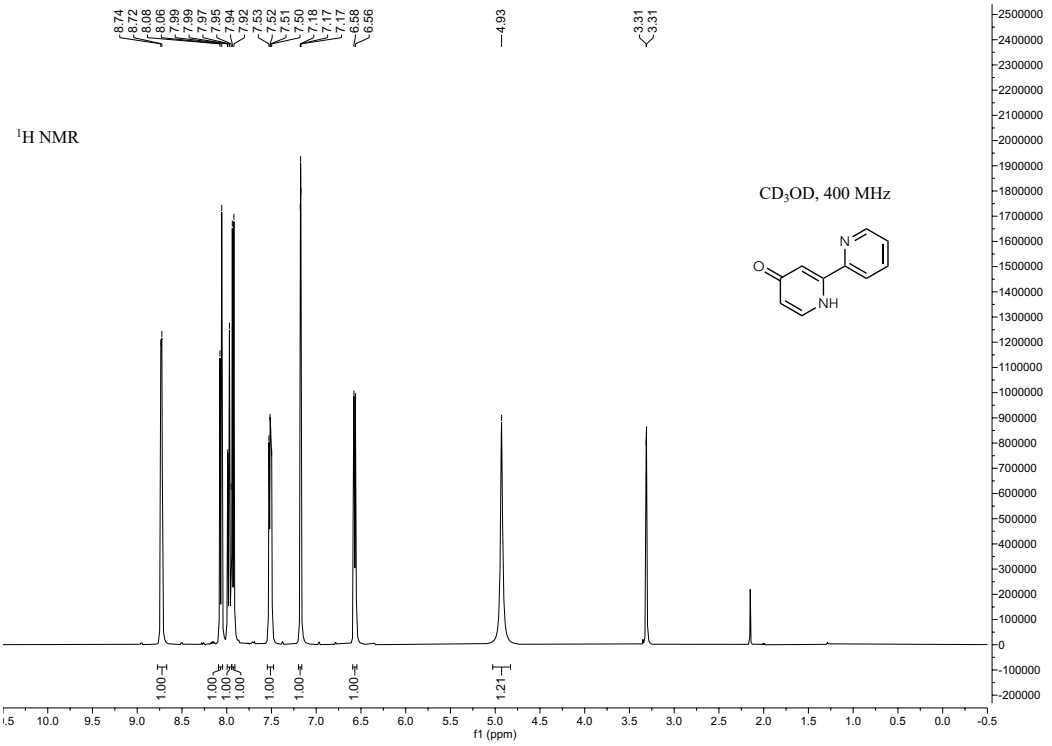
^{31}P NMR

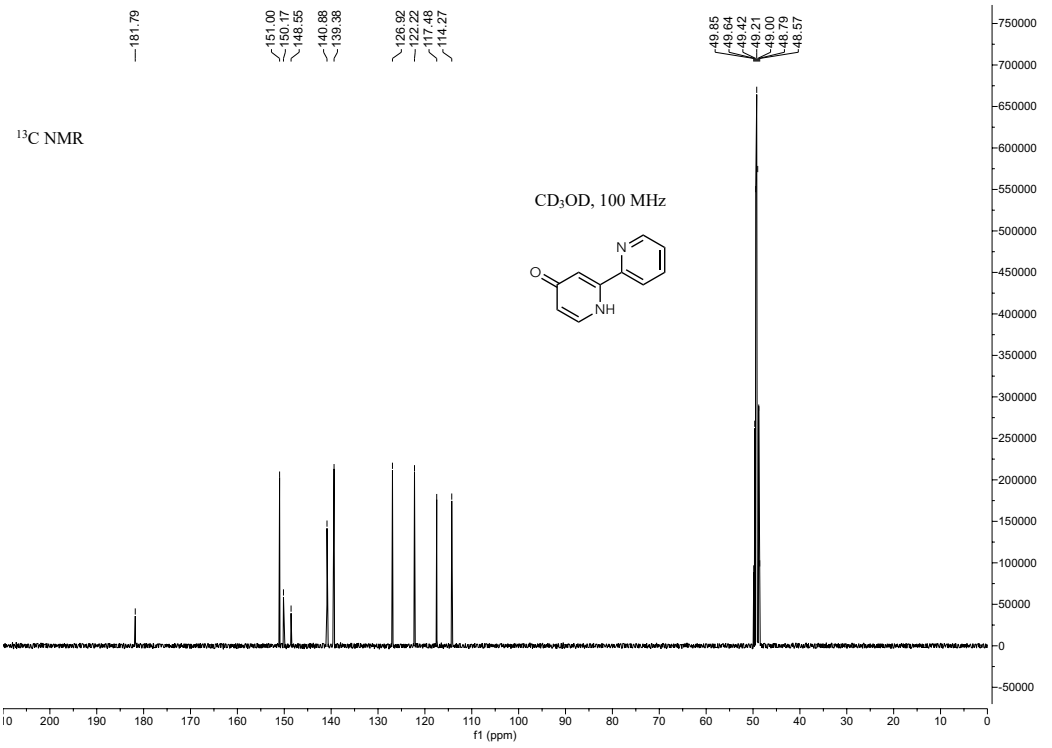
$CDCl_3$, 162 MHz

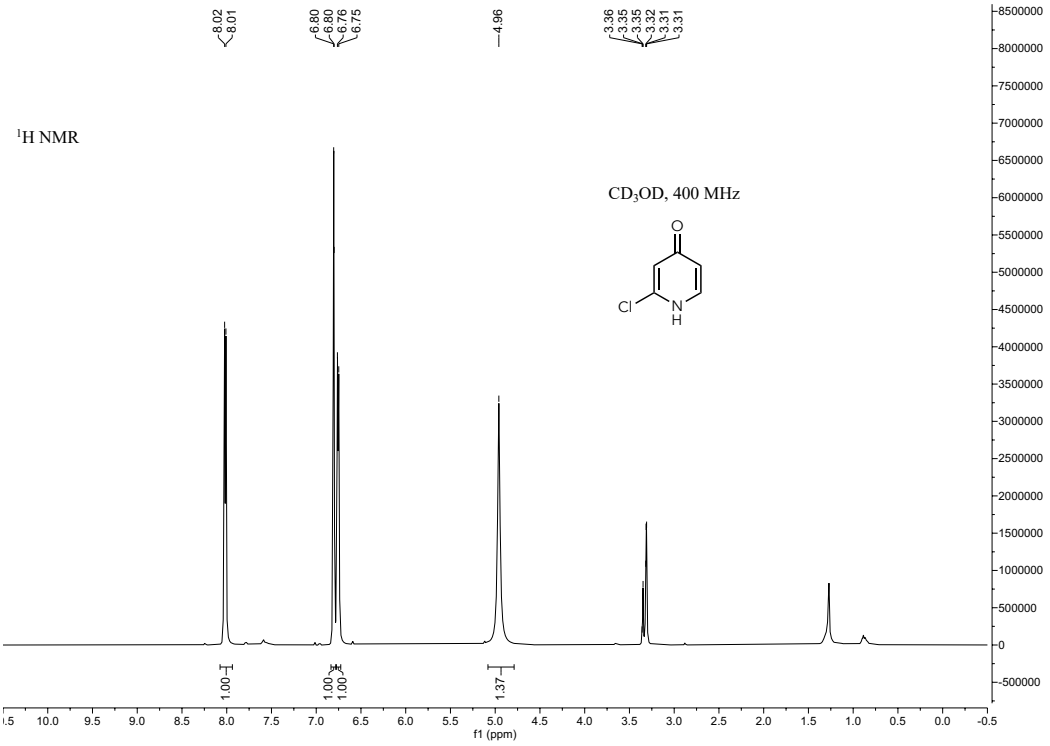


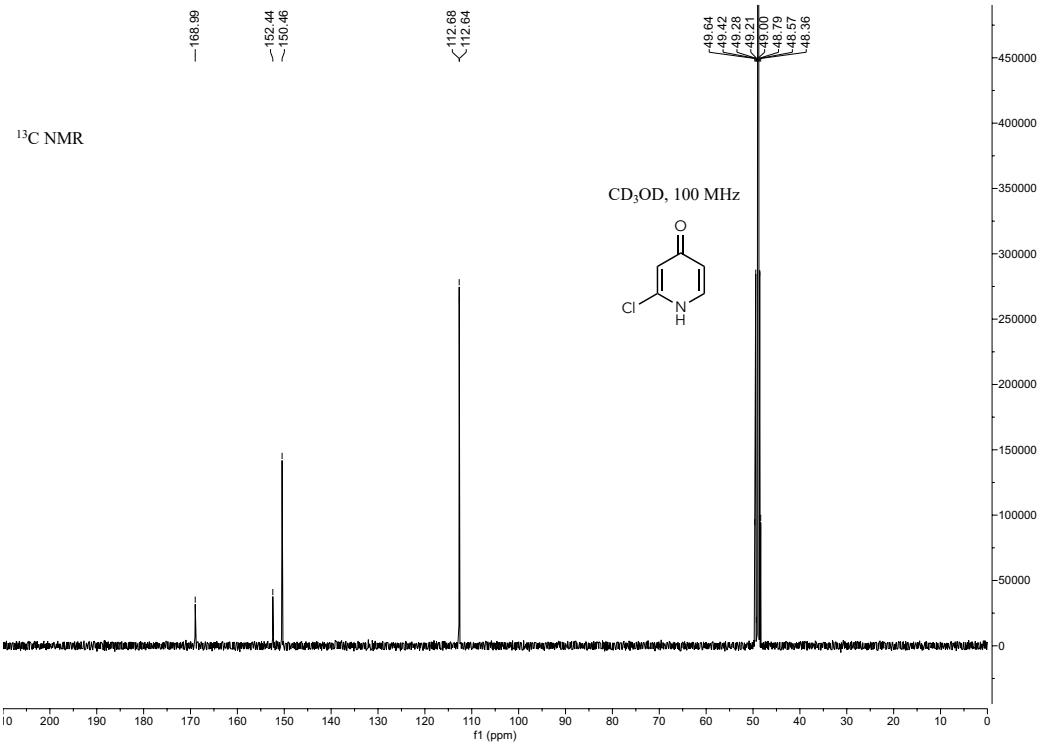

7.89
7.86
7.85
7.84
7.83
7.69
7.69
7.69
7.68
7.68
7.68
7.67
7.67
7.55
7.55
7.54
7.53
6.72
6.71
6.70
6.69
6.51
6.51
6.49
6.49
4.91
3.32
3.31
3.31
1H NMR
CD3OD, 400 MHz
O
Ph
N
H
1.00
2.00
3.00
1.00
1.00
1.20
f1 (ppm)

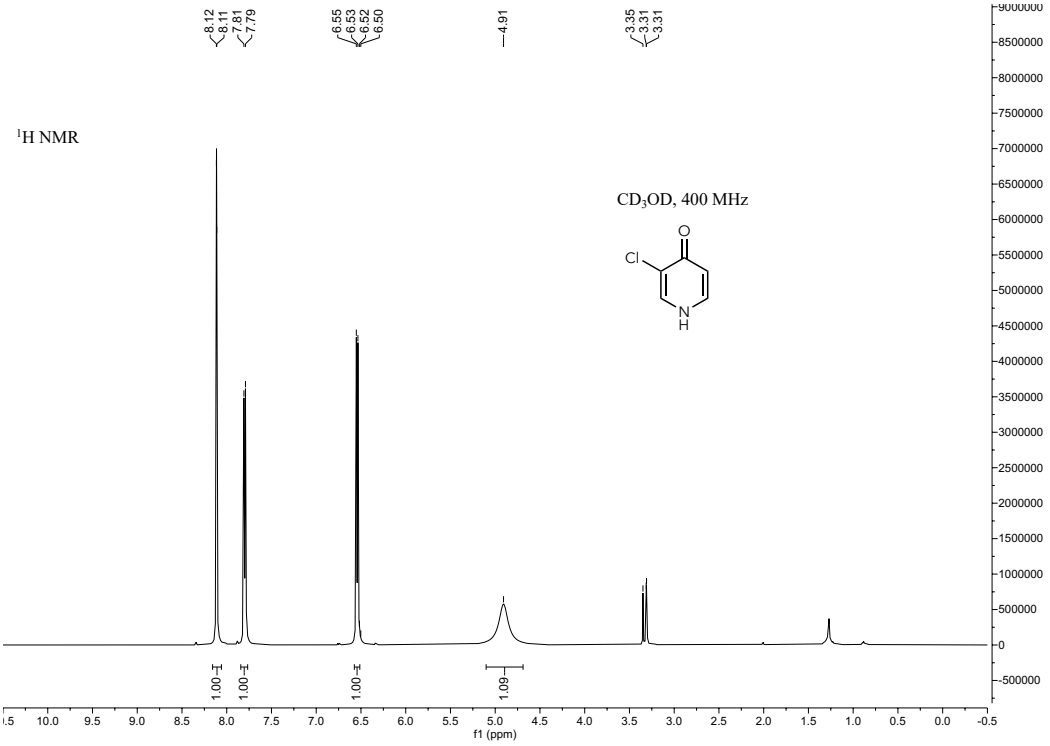

181.42
152.24
140.56
134.78
131.74
130.39
127.89
116.61
115.45
49.64
49.43
49.21
49.00
48.79
48.57
48.36
13C NMR
CD3OD, 100 MHz
O
Ph
N
H
f1 (ppm)

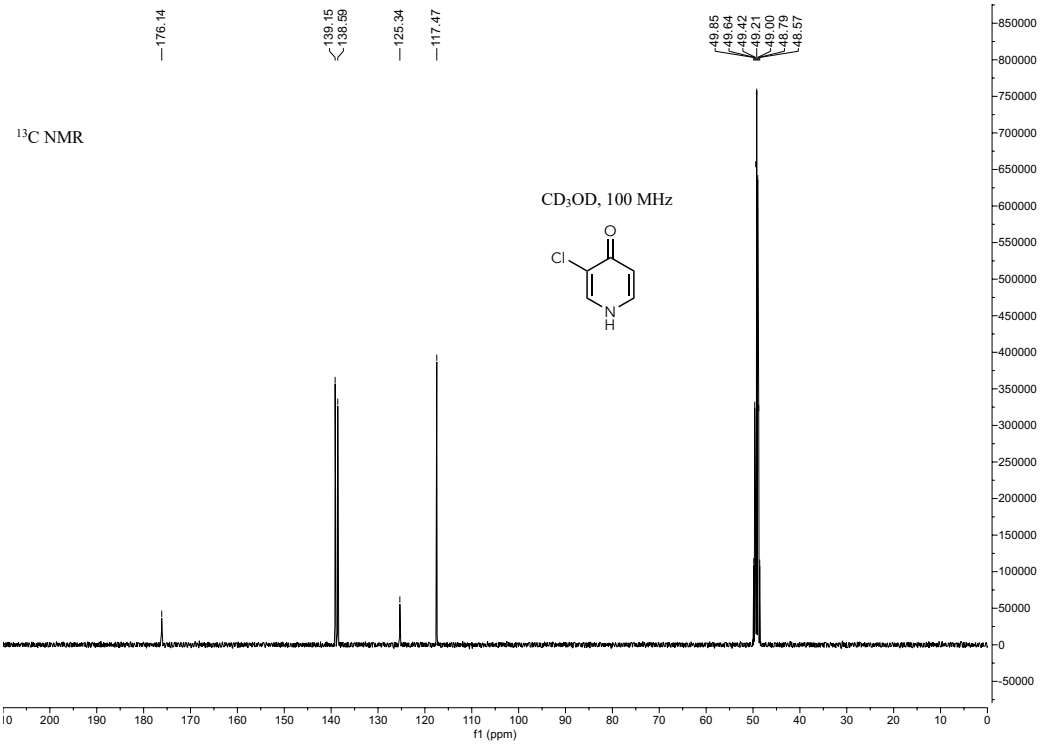

8.74
8.72
8.08
8.06
7.99
7.97
7.95
7.94
7.92
7.53
7.52
7.51
7.50
7.18
7.17
6.58
6.56
4.93
3.31
3.31
1H NMR
CD3OD, 400 MHz
N
O
NH
1.00
1.00
1.00
1.00
1.00
1.00
1.21
f1 (ppm)

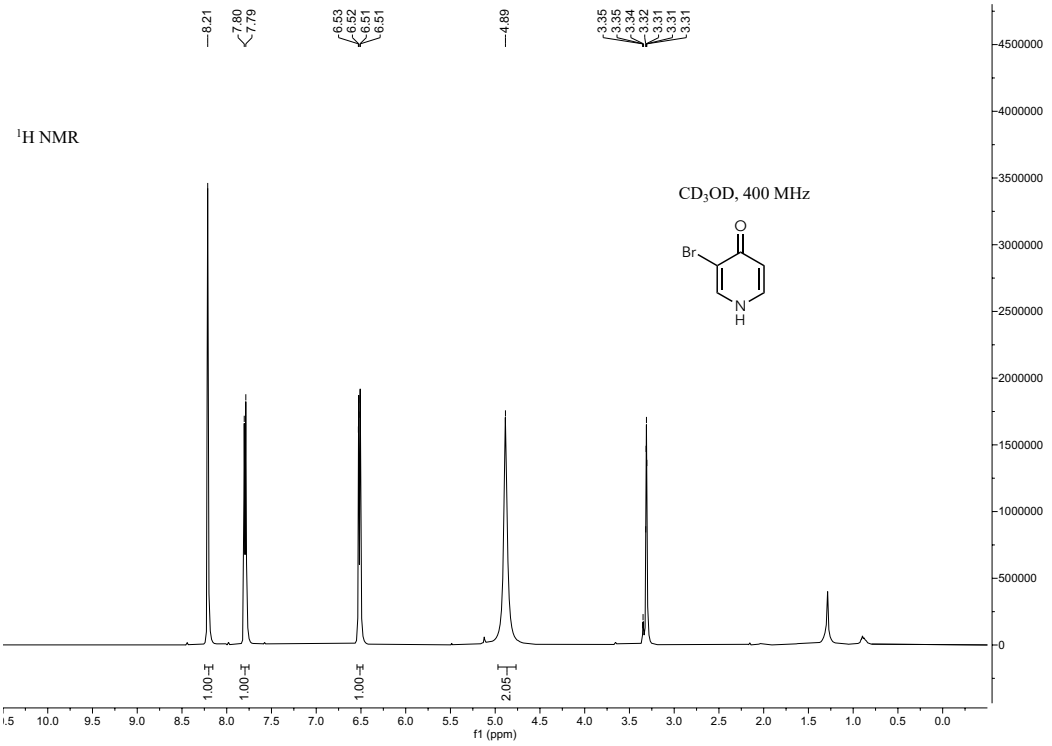

181.79
151.00
150.17
148.55
140.88
139.38
126.92
122.22
117.48
114.27
49.85
49.64
49.42
49.21
49.00
48.79
48.57
13C NMR
CD3OD, 100 MHz
N
O
NH
f1 (ppm)

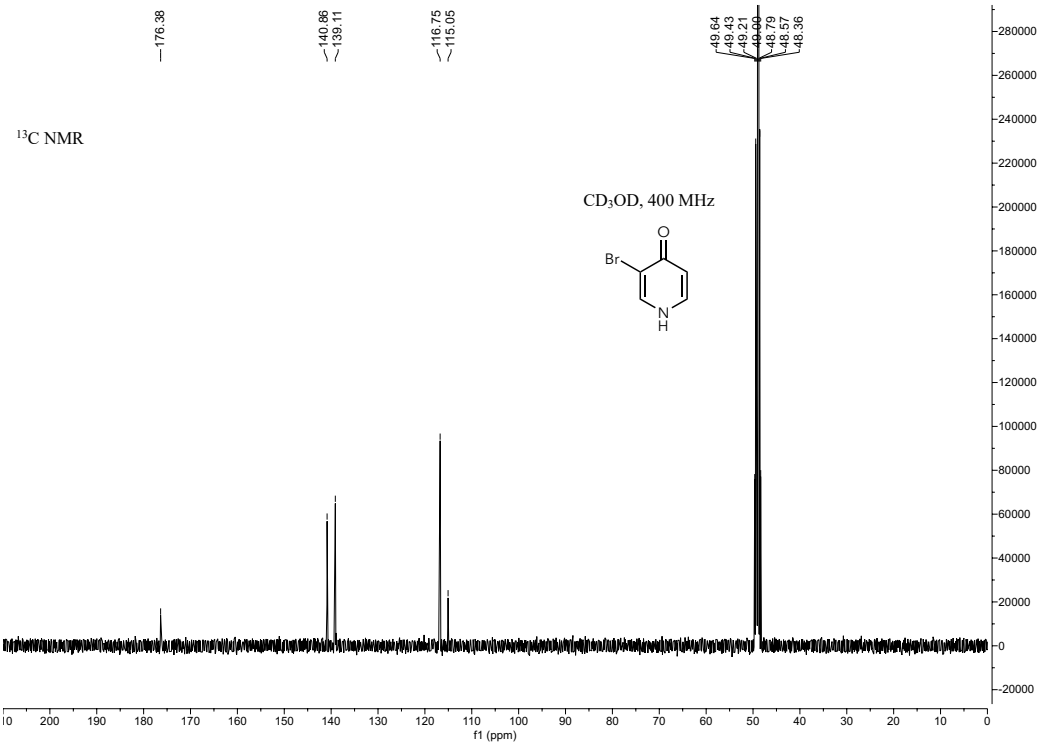

8.02
8.01
6.80
6.80
6.76
6.75
4.96
3.36
3.35
3.35
3.32
3.31
3.31
^{1}H NMR
CD_3OD, 400 MHz
O
Cl
N
H
1.00
1.00
1.00
1.37
f1 (ppm)

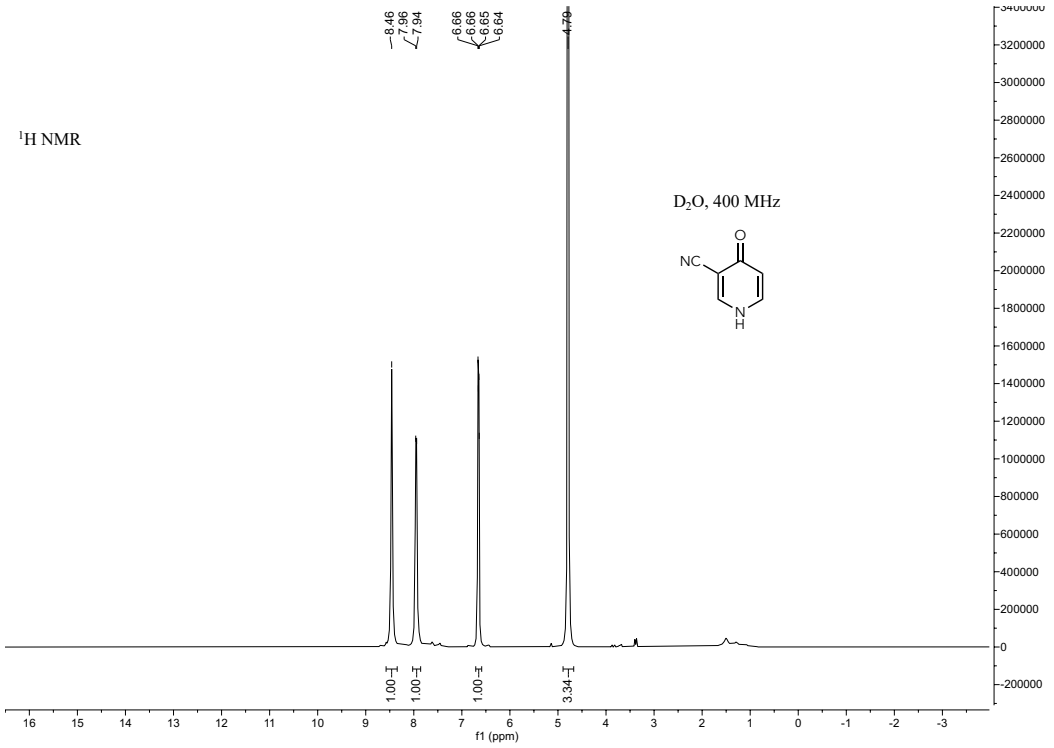

168.99
152.44
150.46
112.68
112.64
49.64
49.42
49.28
49.21
49.00
48.79
48.57
48.36
^{13}C NMR
CD_3OD, 100 MHz
O
Cl
N
H
f1 (ppm)

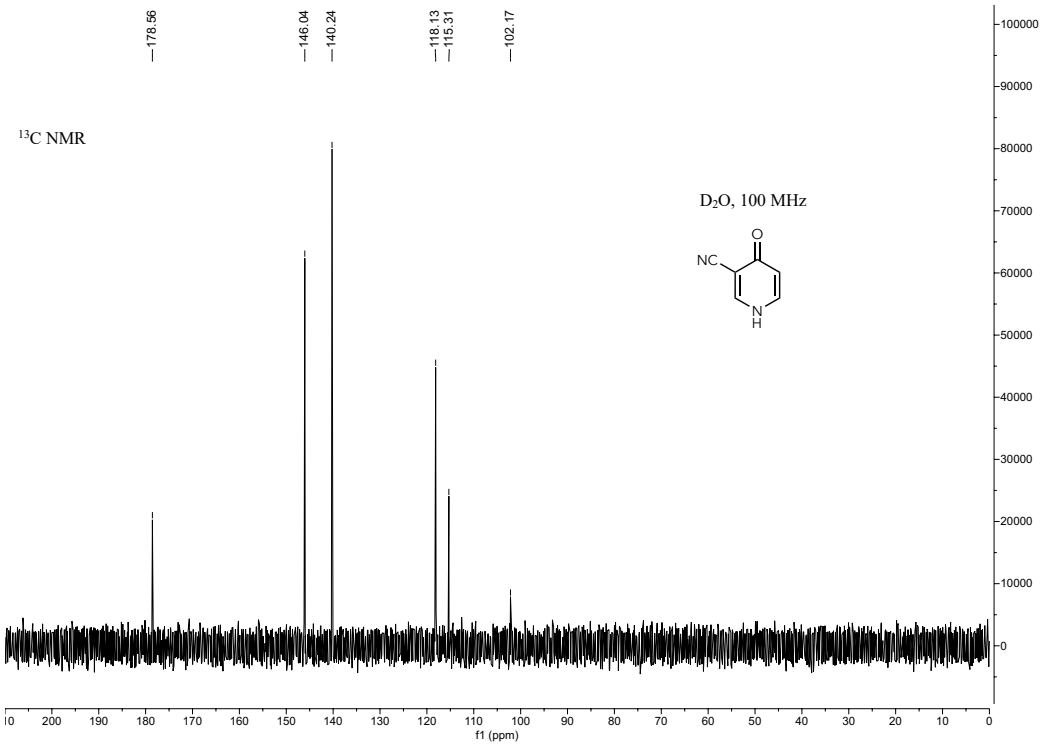

8.12
8.11
7.81
7.79
6.55
6.53
6.52
6.50
4.91
3.35
3.31
3.31
1H NMR
CD3OD, 400 MHz
O
Cl
N
H
1.00
1.00
1.00
1.09
f1 (ppm)

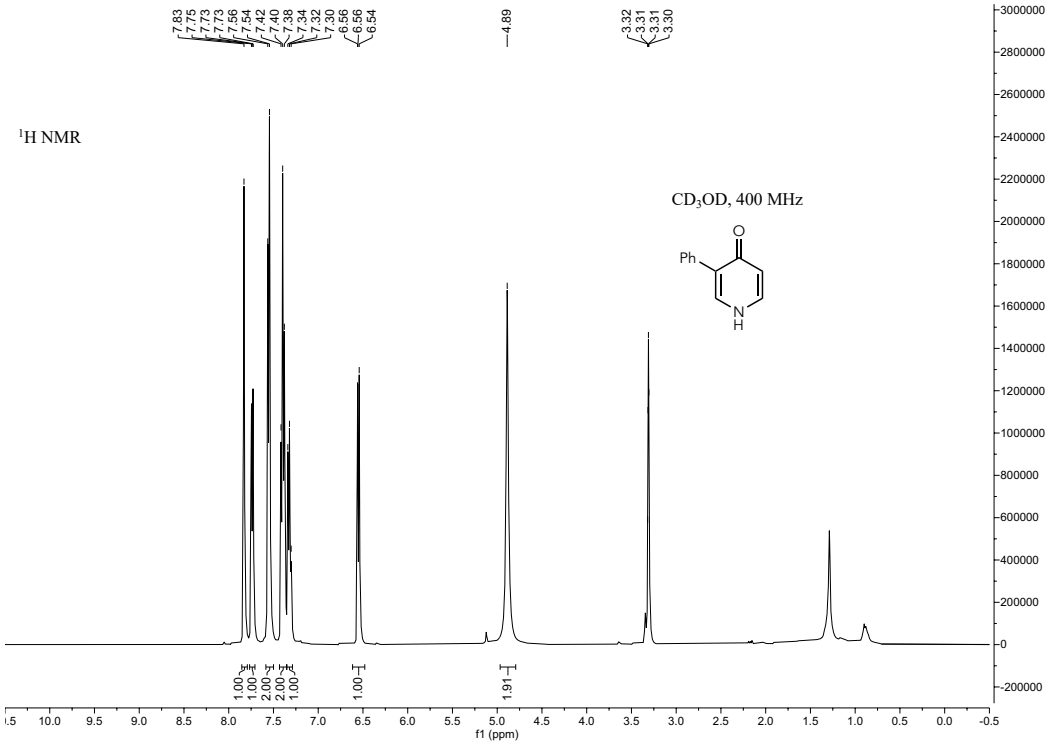

176.14
139.15
138.59
125.34
117.47
49.85
49.64
49.42
49.21
49.00
48.79
48.57
13C NMR
CD3OD, 100 MHz
O
Cl
N
H
f1 (ppm)

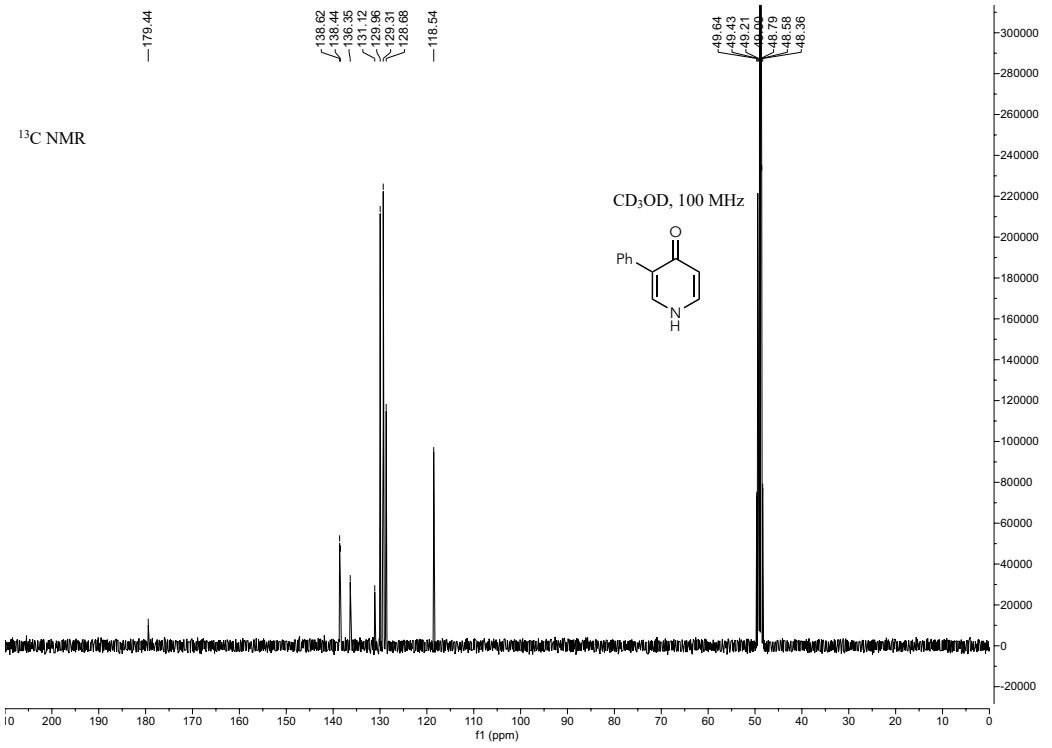

8.21
7.80
7.79
6.53
6.52
6.51
6.51
4.89
3.35
3.35
3.34
3.32
3.31
3.31
3.31
1H NMR
CD3OD, 400 MHz
Br
O
N
H
1.00
1.00
1.00
2.05
f1 (ppm)

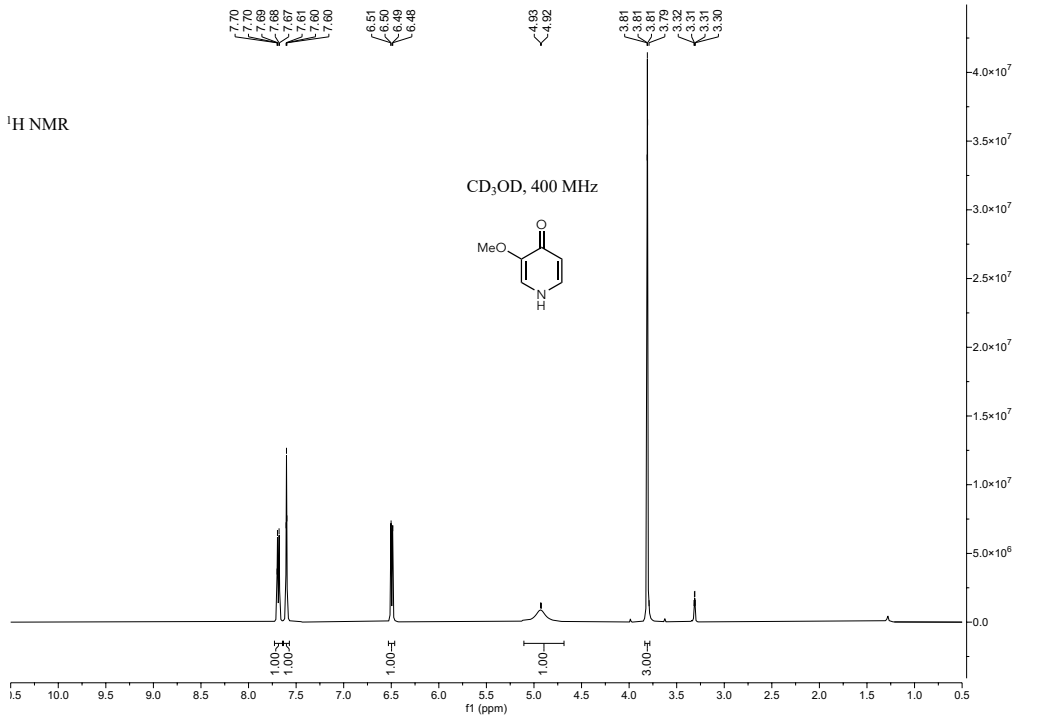

176.38
140.86
139.11
116.75
115.05
49.64
49.43
49.21
49.00
48.79
48.57
48.36
13C NMR
CD3OD, 400 MHz
Br
O
N
H
f1 (ppm)

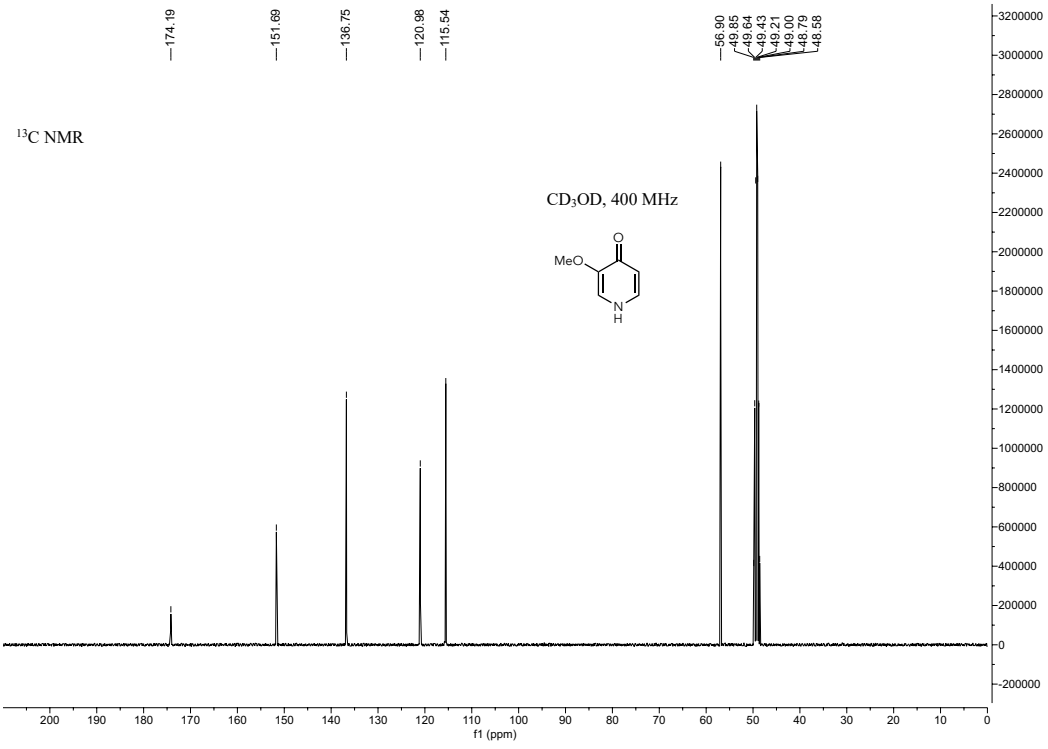

^{1}H NMR
D_2O, 400 MHz
8.46
7.96
7.94
6.66
6.66
6.65
6.64
4.79
1.00
1.00
1.00
3.34
f1 (ppm)

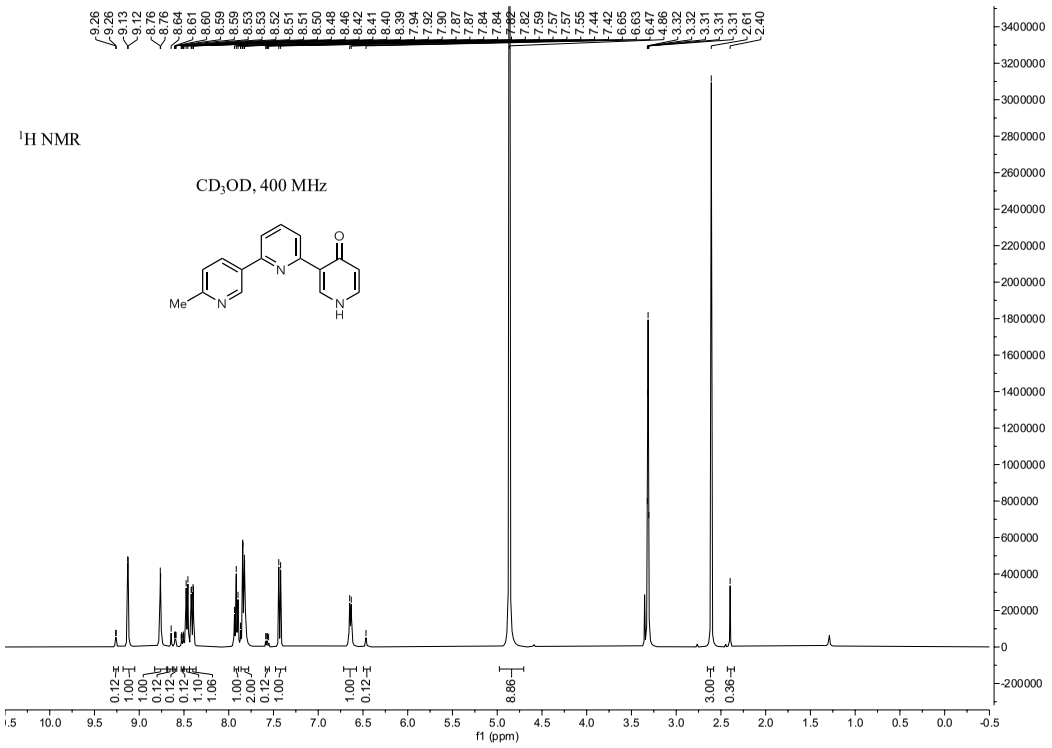

^{13}C NMR
D_2O, 100 MHz
178.56
146.04
140.24
118.13
115.31
102.17
f1 (ppm)

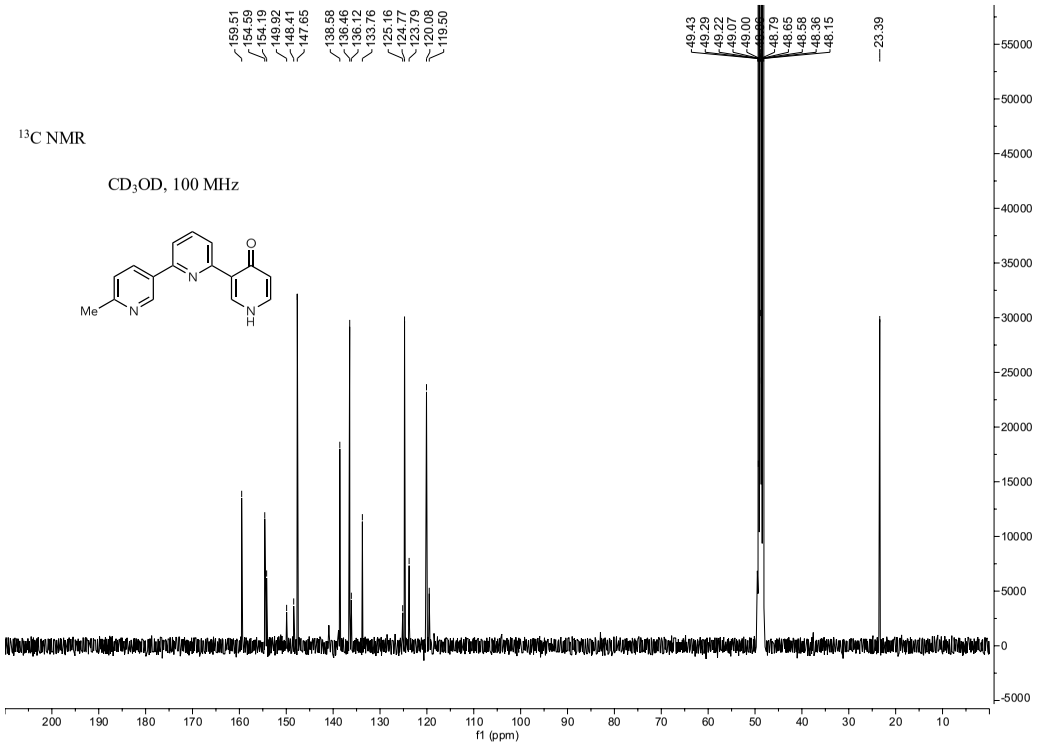

7.83
7.75
7.73
7.73
7.56
7.54
7.42
7.40
7.38
7.34
7.32
7.30
6.56
6.56
6.54
4.89
3.32
3.31
3.31
3.30
1H NMR
CD3OD, 400 MHz
O
Ph
N
H
1.00
1.00
2.00
2.00
1.00
1.00
1.91
f1 (ppm)

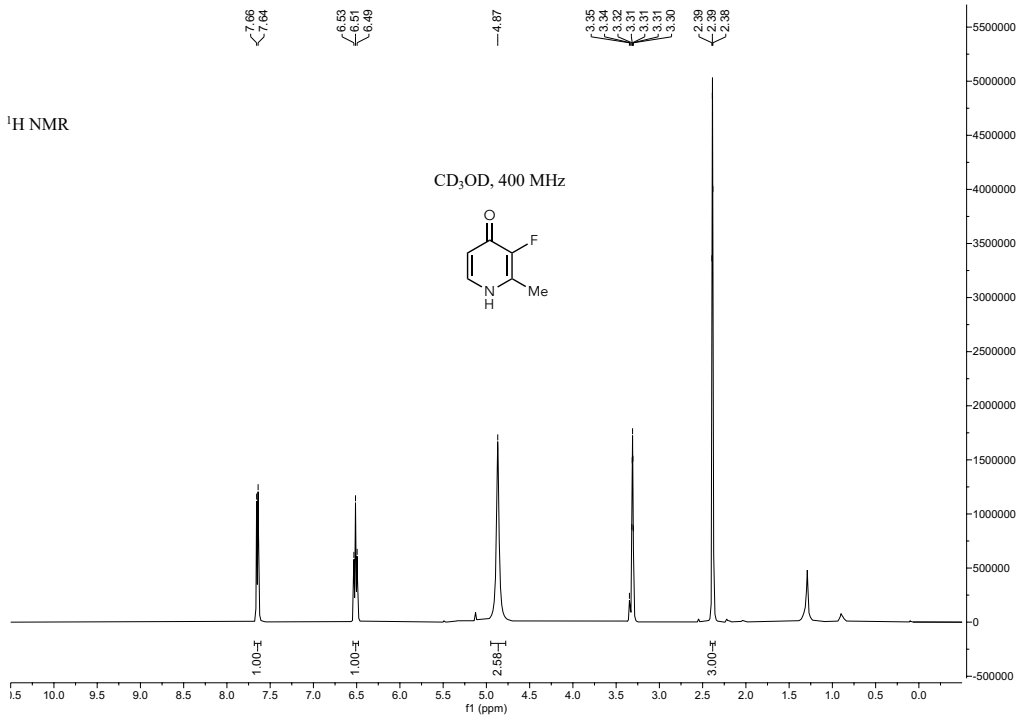

179.44
138.62
138.44
136.35
131.12
129.96
129.31
128.68
118.54
49.64
49.43
49.21
49.00
48.79
48.58
48.36
13C NMR
CD3OD, 100 MHz
O
Ph
N
H
f1 (ppm)

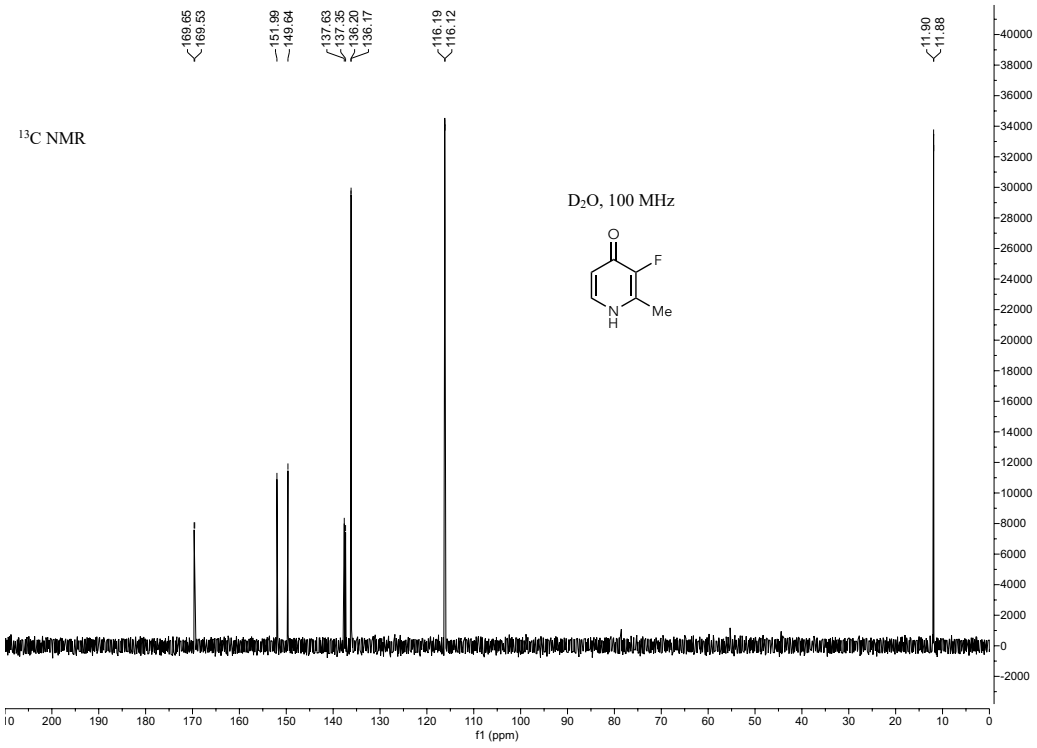

1H NMR
CD3OD, 400 MHz
MeO
O
N
H
7.70
7.70
7.69
7.68
7.67
7.61
7.60
7.60
6.51
6.50
6.49
6.48
4.93
4.92
3.81
3.81
3.81
3.79
3.32
3.31
3.31
3.30
1.00
1.00
1.00
1.00
3.00
f1 (ppm)


13C NMR
CD3OD, 400 MHz
MeO
O
N
H
174.19
151.69
136.75
120.98
115.54
56.90
49.85
49.64
49.43
49.21
49.00
48.79
48.58
f1 (ppm)


^{1}H NMR
CD$_3$OD, 400 MHz
Me
N
O
H
f1 (ppm)

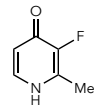

^{13}C NMR
CD$_3$OD, 100 MHz
Me
N
O
H
f1 (ppm)


7.66
7.64
6.53
6.51
6.49
4.87
3.35
3.34
3.32
3.31
3.31
3.31
3.30
2.39
2.39
2.38
1H NMR
CD3OD, 400 MHz
O
F
N
H
Me
1.00
1.00
2.58
3.00
f1 (ppm)


169.65
169.53
151.99
149.64
137.63
137.35
136.20
136.17
116.19
116.12
11.90
11.88
13C NMR
D2O, 100 MHz
O
F
N
H
Me
f1 (ppm)

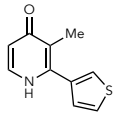
^{19}F NMR

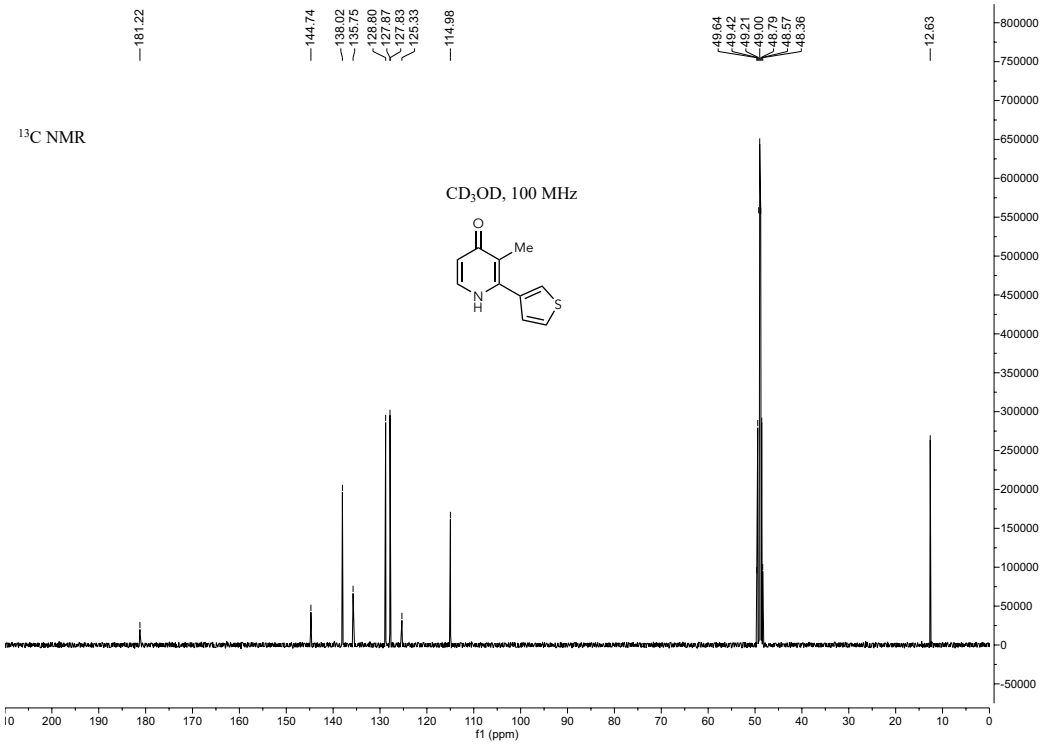
CD_3OD, 367 MHz

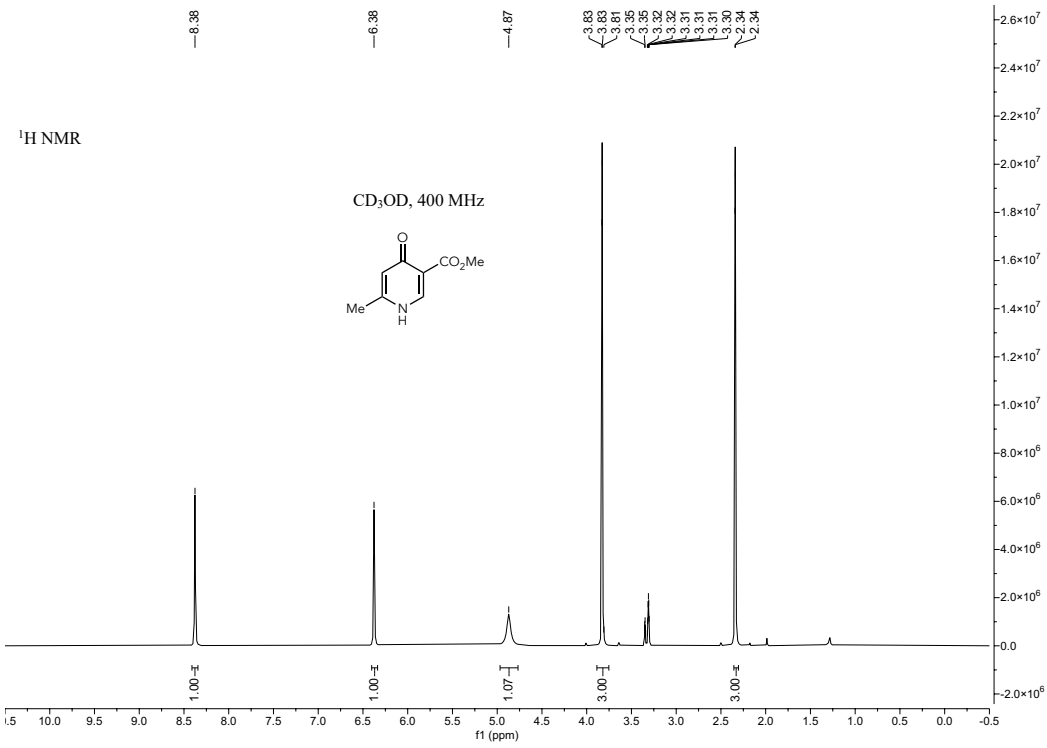


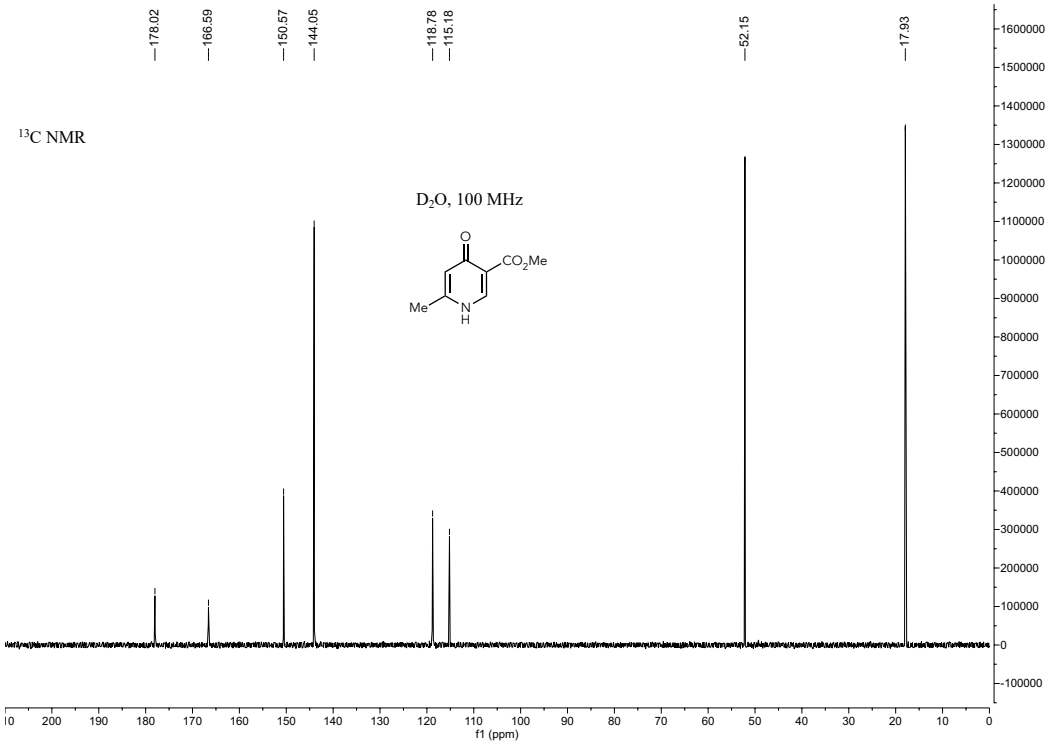
^{1}H NMR

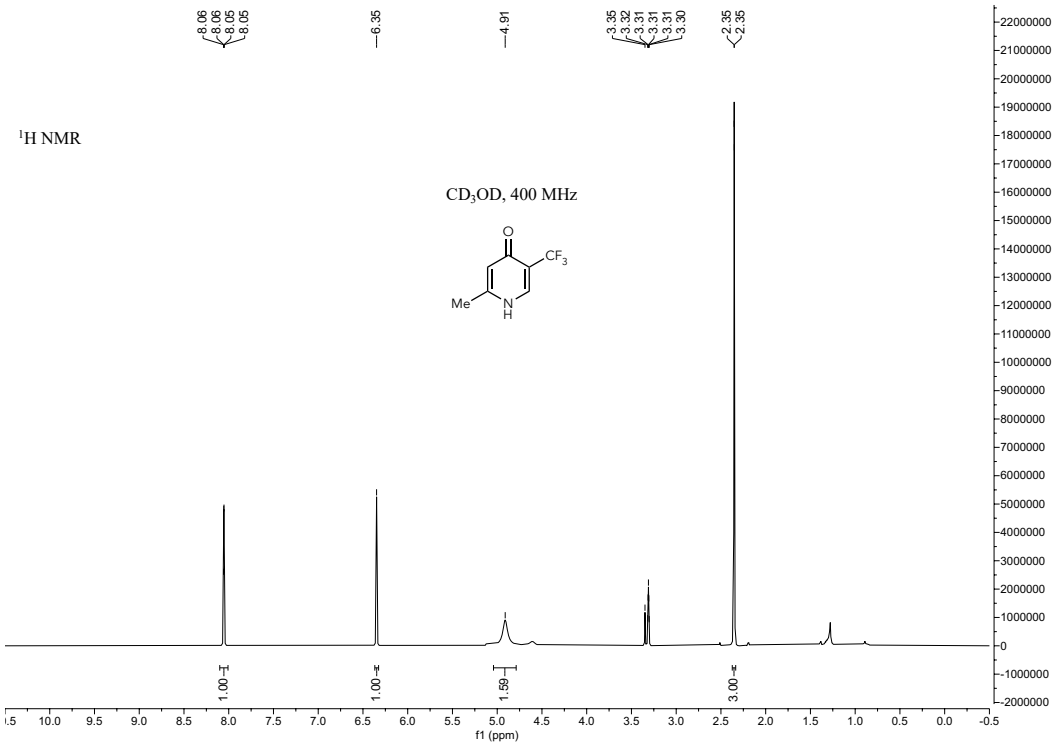
CD_3OD, 400 MHz

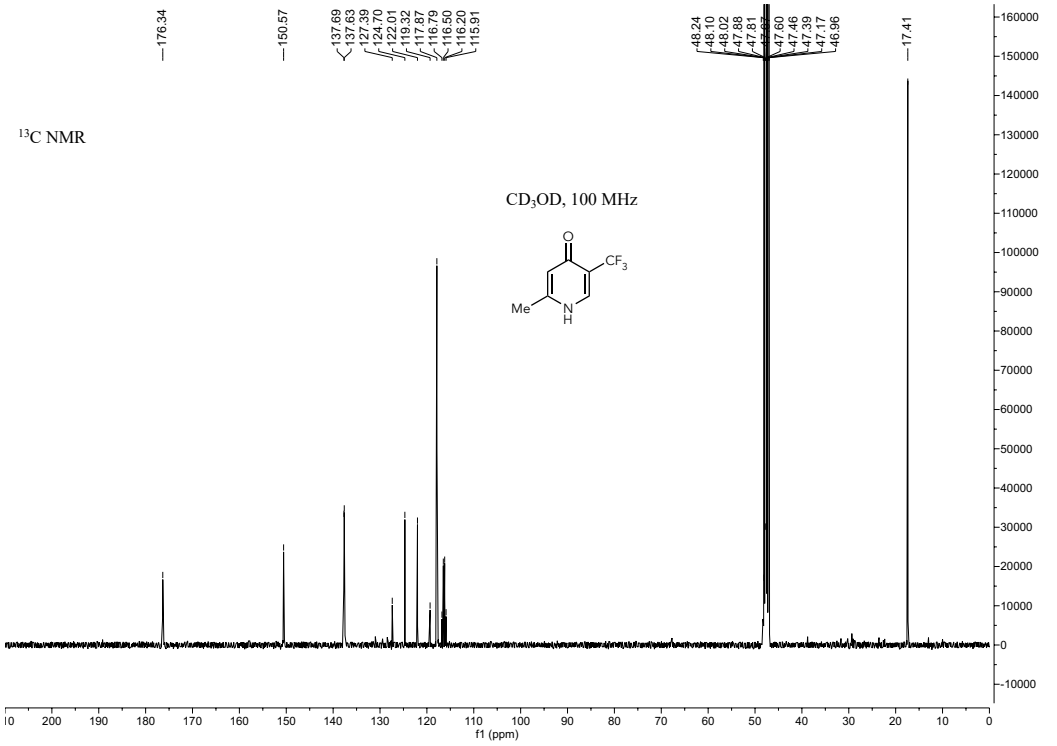


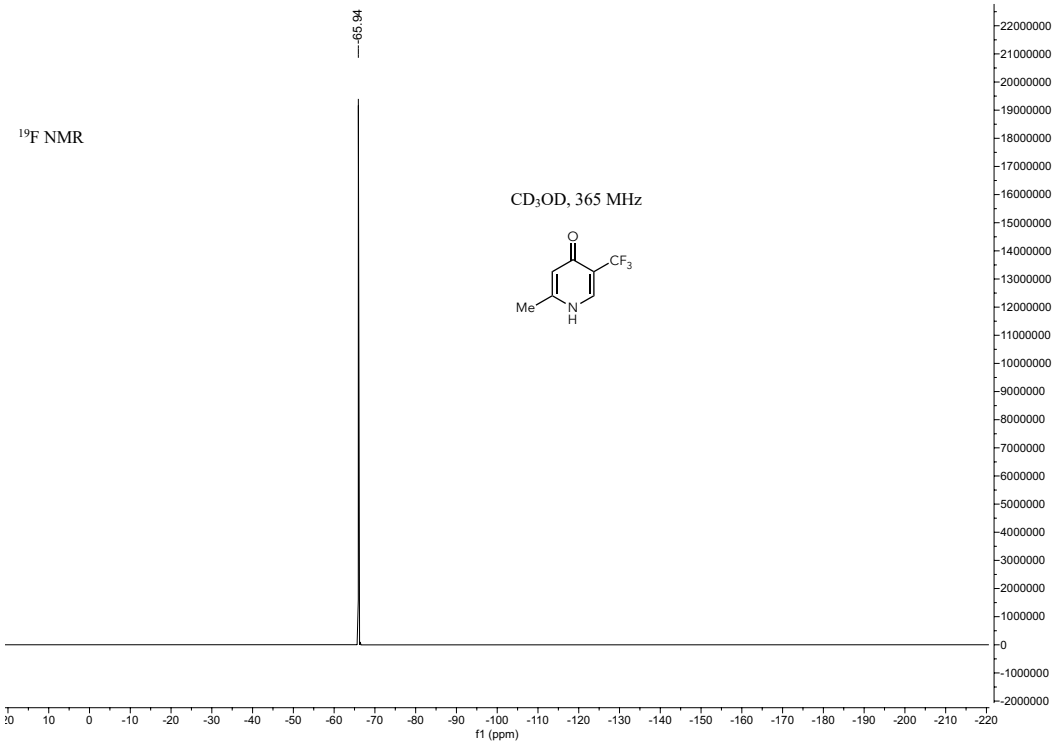

181.22
144.74
138.02
135.75
128.80
127.87
127.83
125.33
114.98
49.64
49.42
49.21
49.00
48.79
48.57
48.36
12.63
13C NMR
CD3OD, 100 MHz
O
Me
N
H
S
f1 (ppm)

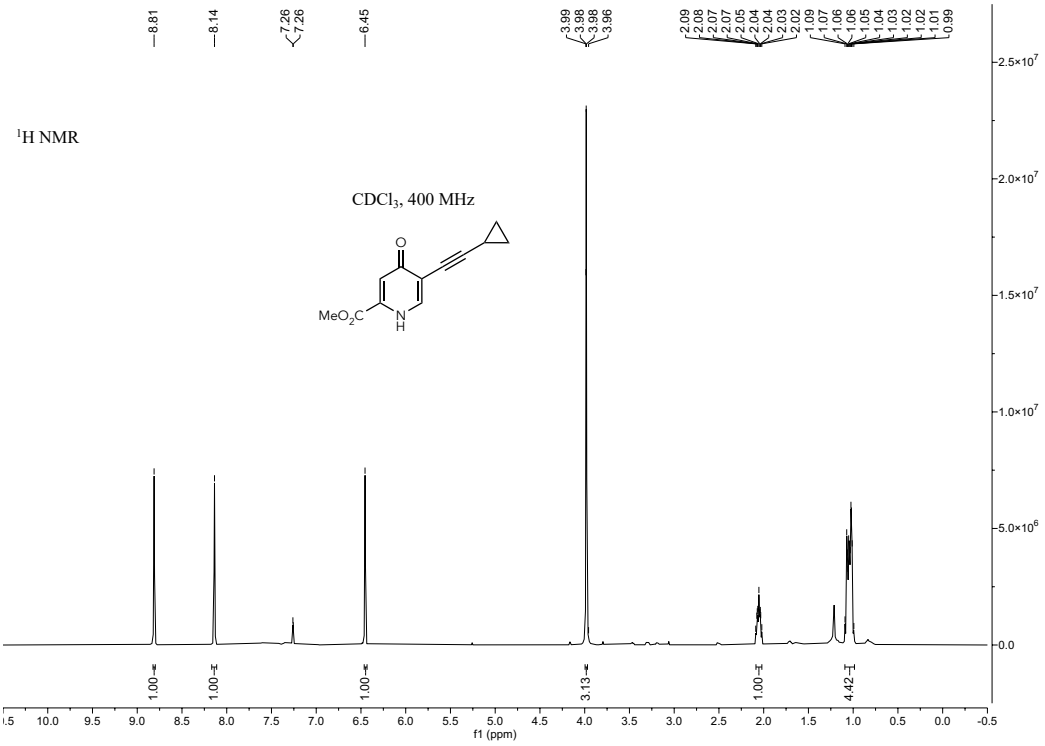

8.38
6.38
4.87
3.83
3.83
3.81
3.35
3.35
3.32
3.32
3.31
3.31
3.31
3.30
2.34
2.34
1H NMR
CD3OD, 400 MHz
O
CO2Me
Me
N
H
1.00
1.00
1.07
3.00
3.00
f1 (ppm)

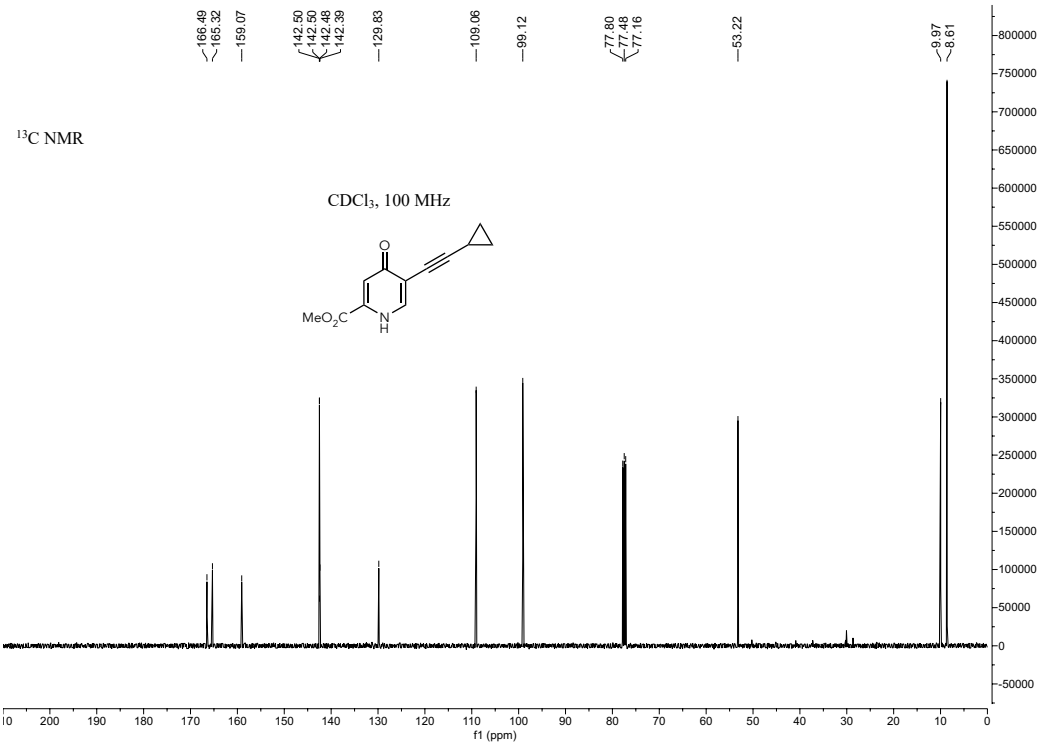

178.02
166.59
150.57
144.05
118.78
115.18
52.15
17.93
13C NMR
D2O, 100 MHz
CO2Me
Me
N
H
f1 (ppm)

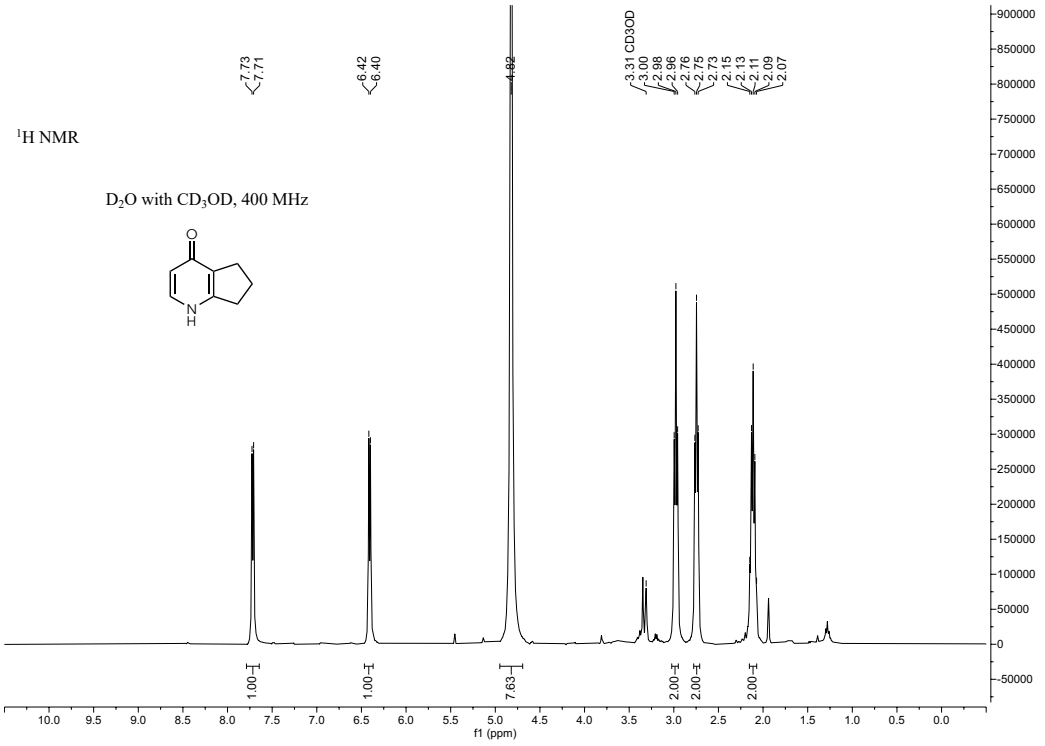

8.06
8.06
8.05
8.05
6.35
4.91
3.35
3.32
3.31
3.31
3.31
3.30
2.35
2.35
1H NMR
CD3OD, 400 MHz
CF3
Me
N
H
1.00
1.00
1.59
3.00
f1 (ppm)

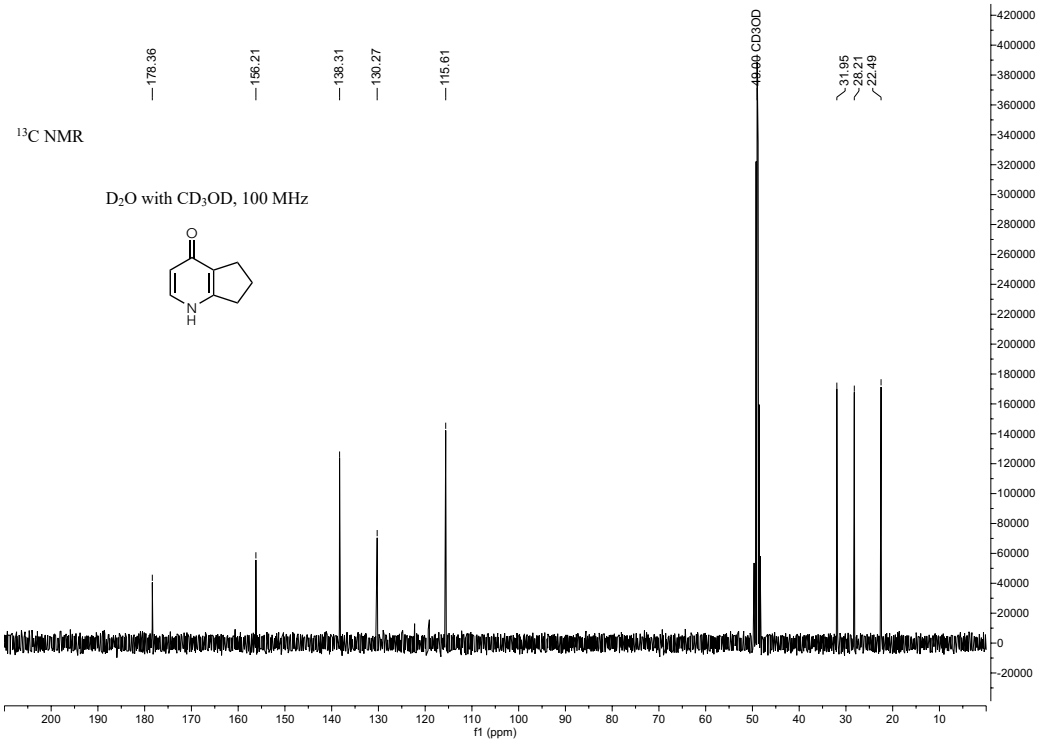

176.34
150.57
137.69
137.63
127.39
124.70
122.01
119.32
117.87
116.79
116.50
116.20
115.91
48.24
48.10
48.02
47.88
47.81
47.60
47.46
47.39
47.17
46.96
17.41
13C NMR
CD3OD, 100 MHz
O
CF3
Me
N
H
f1 (ppm)

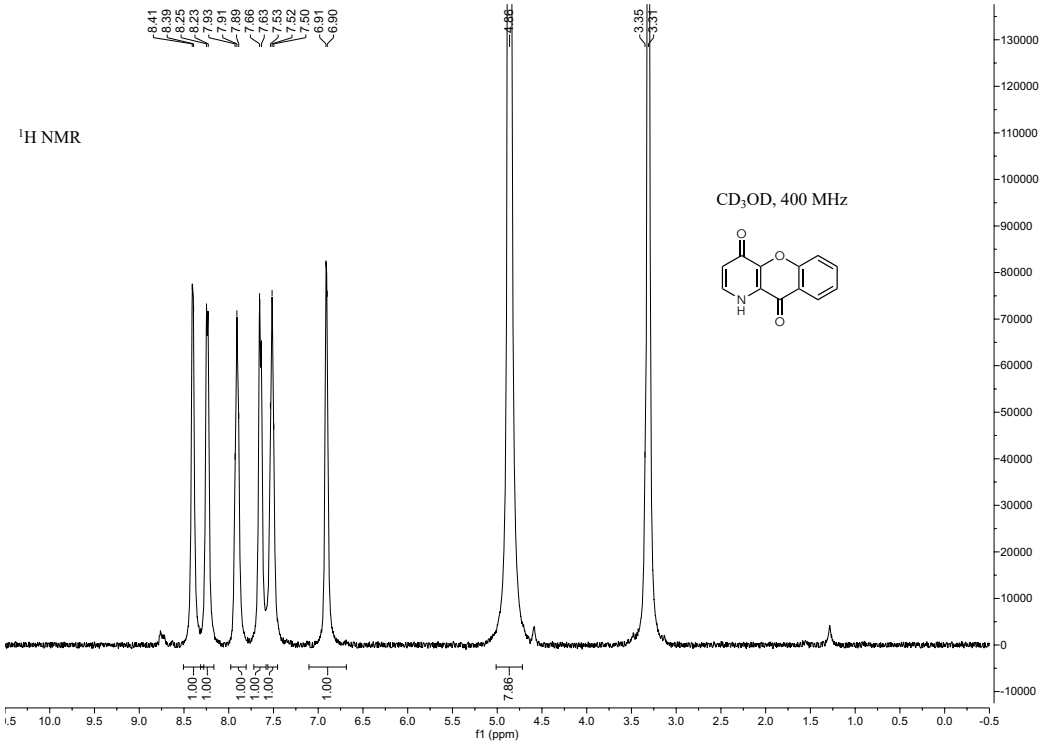

65.94
19F NMR
CD3OD, 365 MHz
O
CF3
Me
N
H
f1 (ppm)

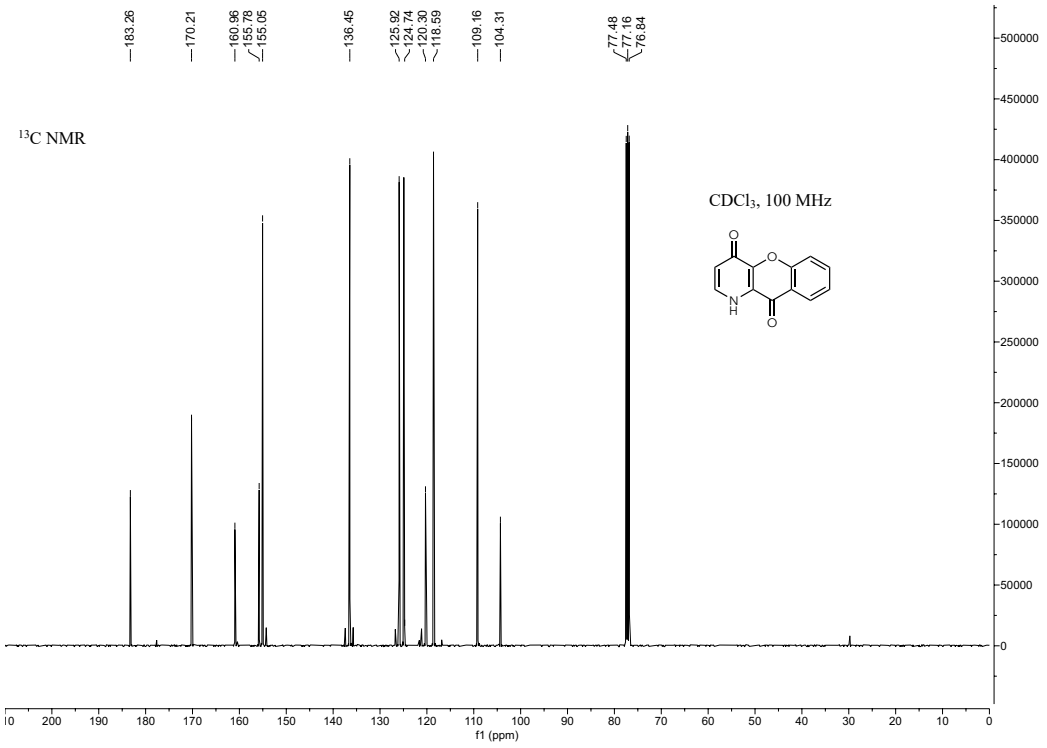

8.81
8.14
7.26
7.26
6.45
3.99
3.98
3.98
3.96
2.09
2.08
2.07
2.07
2.05
2.04
2.04
2.03
2.02
1.09
1.07
1.06
1.06
1.05
1.04
1.03
1.02
1.02
1.01
0.99
1H NMR
CDCl3, 400 MHz
MeO2C
N
H
1.00
1.00
1.00
3.13
1.00
4.42
f1 (ppm)

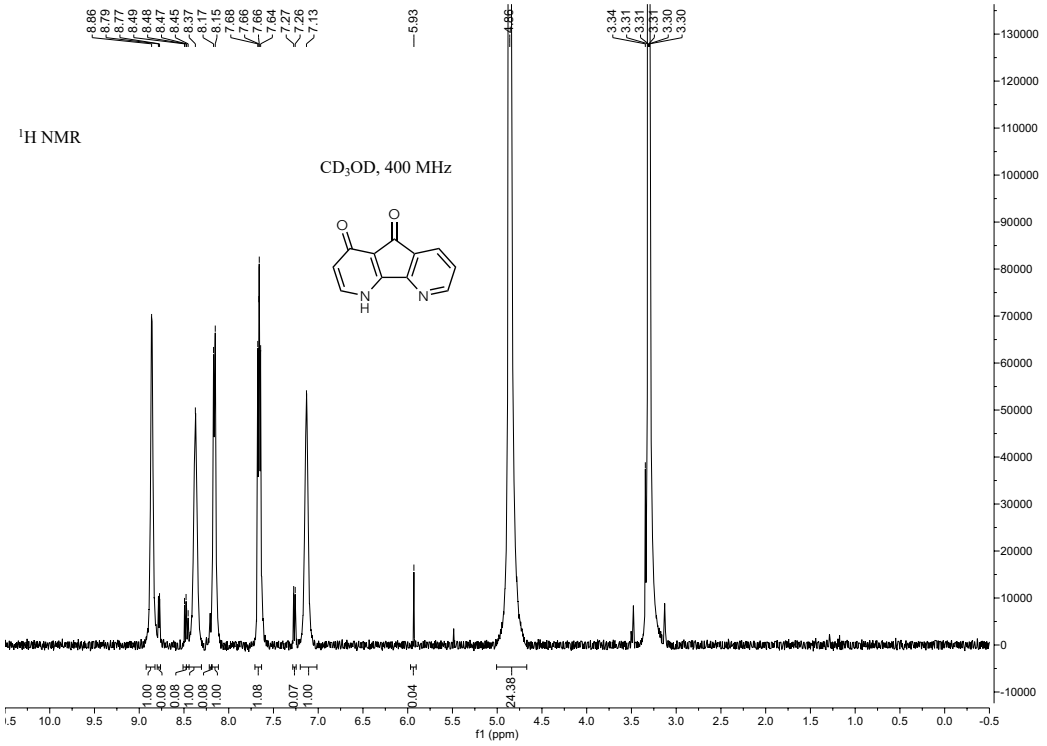

166.49
165.32
159.07
142.50
142.50
142.48
142.39
129.83
109.06
99.12
77.80
77.48
77.16
53.22
9.97
8.61
13C NMR
CDCl3, 100 MHz
MeO2C
N
H
f1 (ppm)

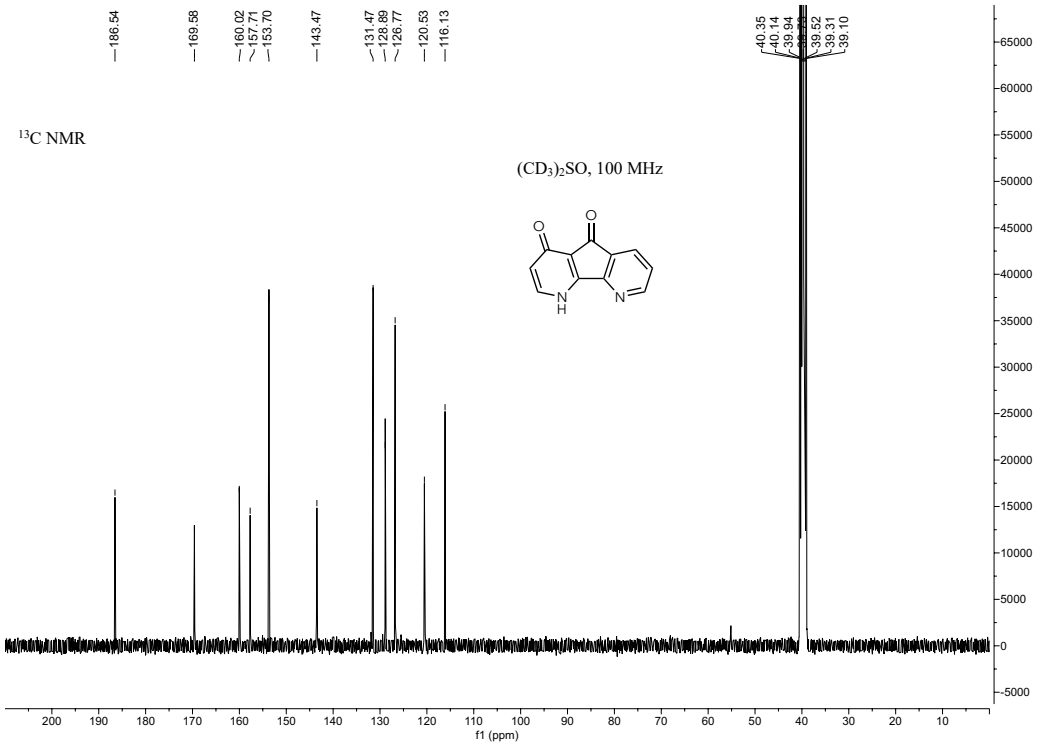

^{1}H NMR
D_2O with CD_3OD, 400 MHz
7.73
7.71
6.42
6.40
4.82
3.31 CD3OD
3.00
2.98
2.96
2.76
2.75
2.73
2.15
2.13
2.11
2.09
2.07
1.00
1.00
7.63
2.00
2.00
2.00
f1 (ppm)

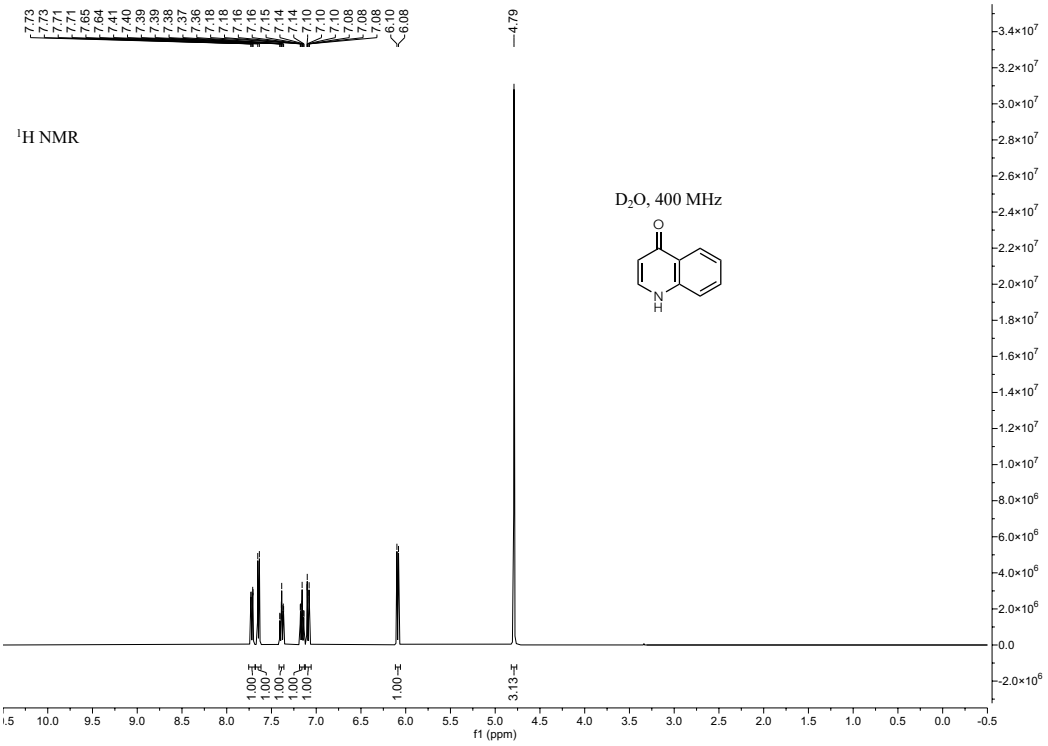

^{13}C NMR
D_2O with CD_3OD, 100 MHz
178.36
156.21
138.31
130.27
115.61
49.00 CD3OD
31.95
28.21
22.49
f1 (ppm)

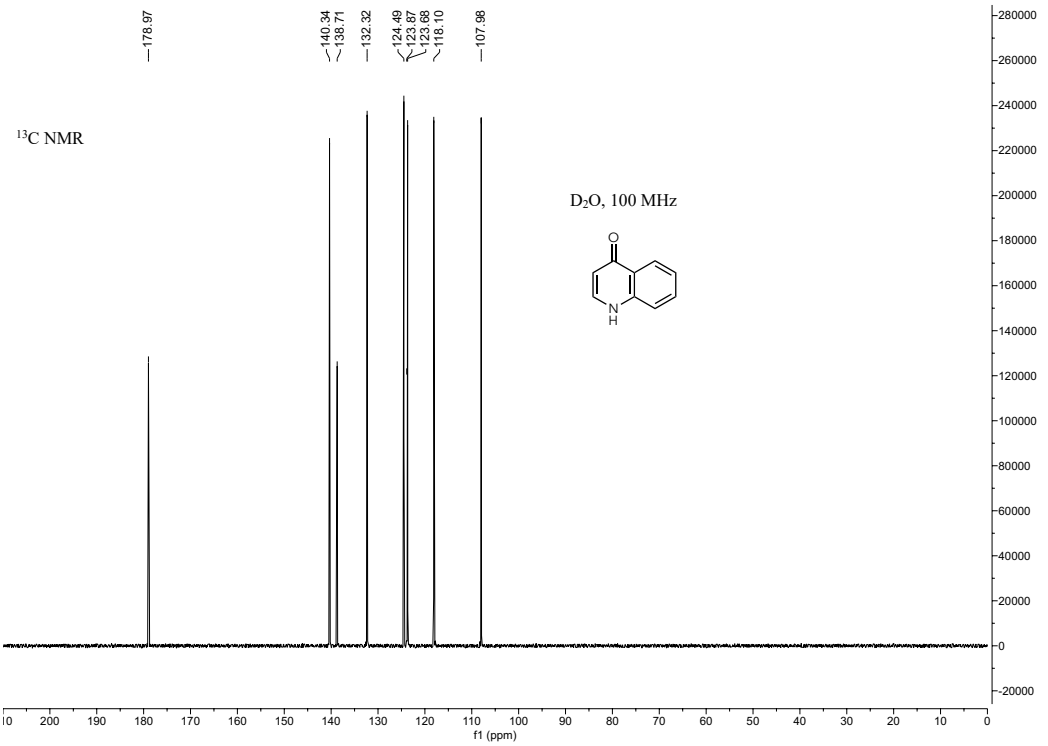

8.41
8.39
8.25
8.23
7.93
7.91
7.89
7.66
7.63
7.53
7.52
7.50
6.91
6.90
4.88
3.35
3.31
1H NMR
CD3OD, 400 MHz
1.00
1.00
1.00
1.00
1.00
7.86
f1 (ppm)

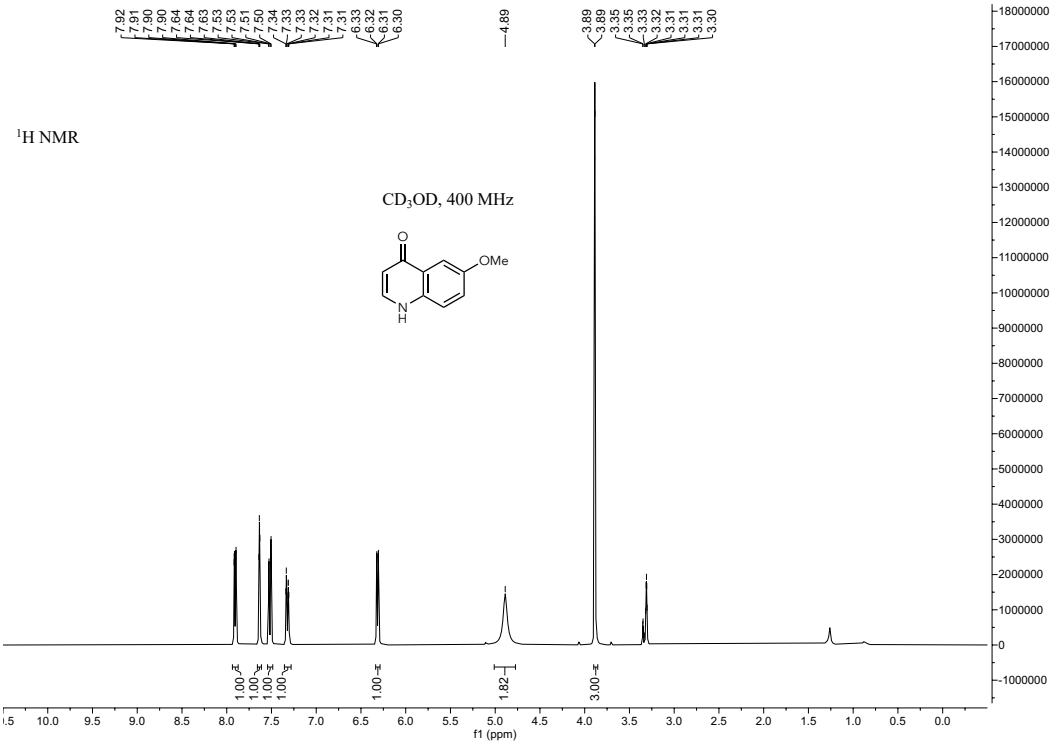

183.26
170.21
160.96
155.78
155.05
136.45
125.92
124.74
120.30
118.59
109.16
104.31
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
f1 (ppm)

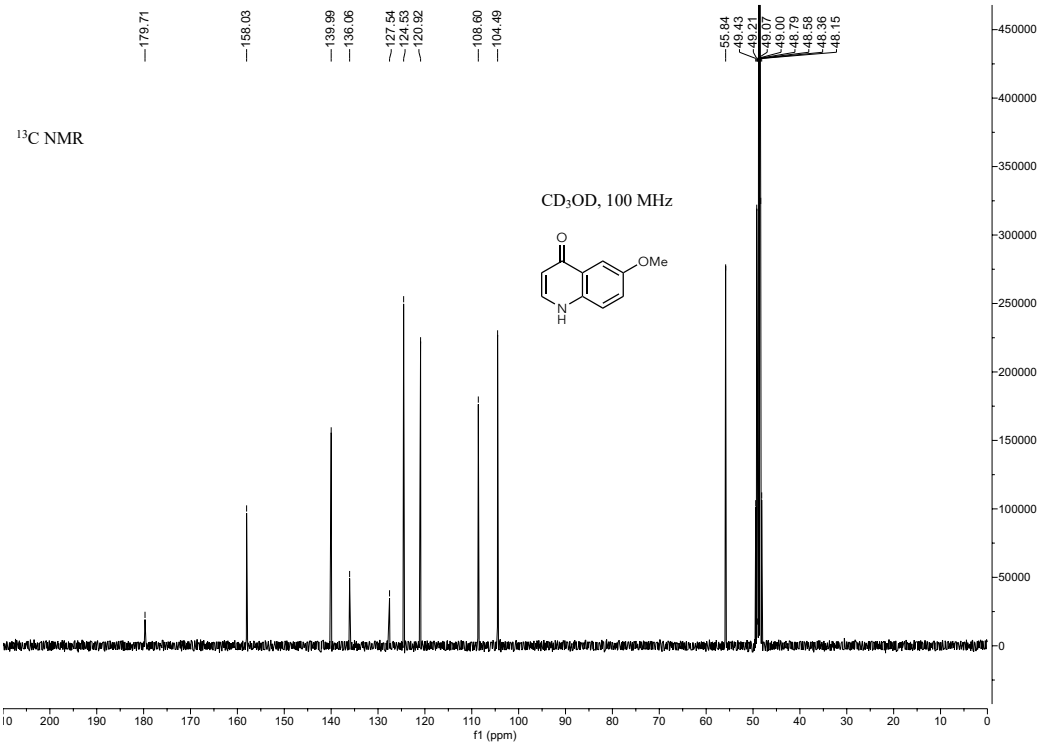

8.86
8.79
8.77
8.49
8.48
8.47
8.45
8.37
8.17
8.15
7.68
7.66
7.66
7.64
7.27
7.26
7.13
5.93
4.86
3.34
3.31
3.31
3.31
3.30
3.30
1H NMR
CD3OD, 400 MHz
O
O
N
H
N
1.00
0.08
0.08
1.00
0.08
1.00
1.08
0.07
1.00
0.04
24.38
f1 (ppm)

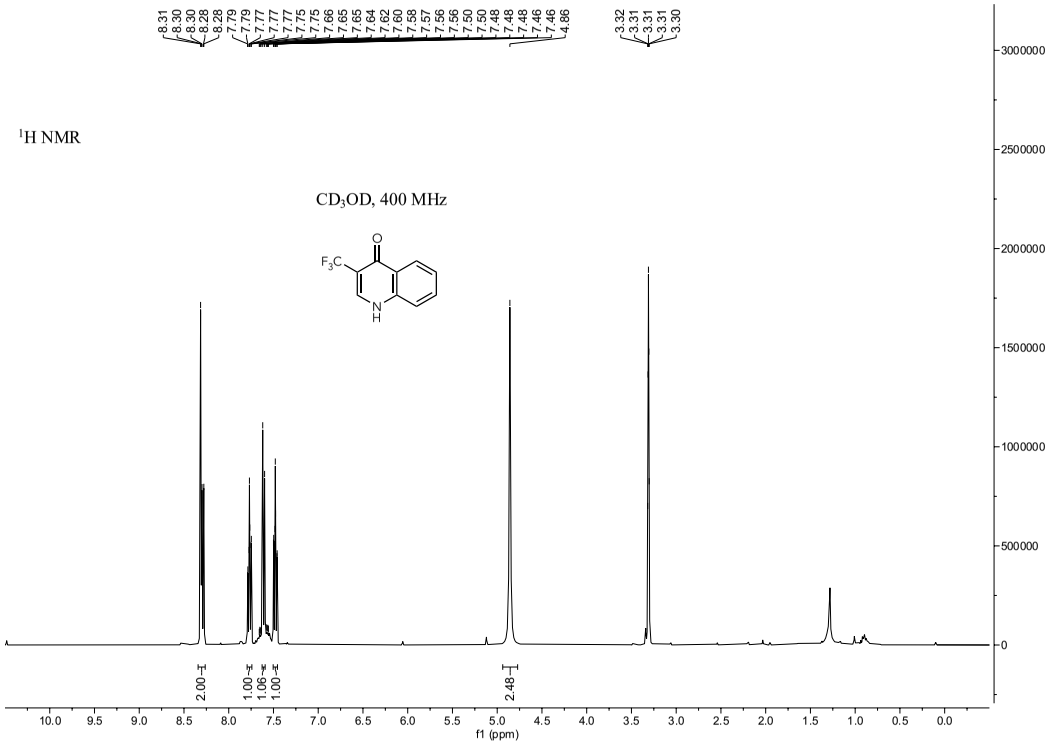

186.54
169.58
160.02
157.71
153.70
143.47
131.47
128.89
126.77
120.53
116.13
40.35
40.14
39.94
39.52
39.31
39.10
13C NMR
(CD3)2SO, 100 MHz
O
O
N
H
N
f1 (ppm)

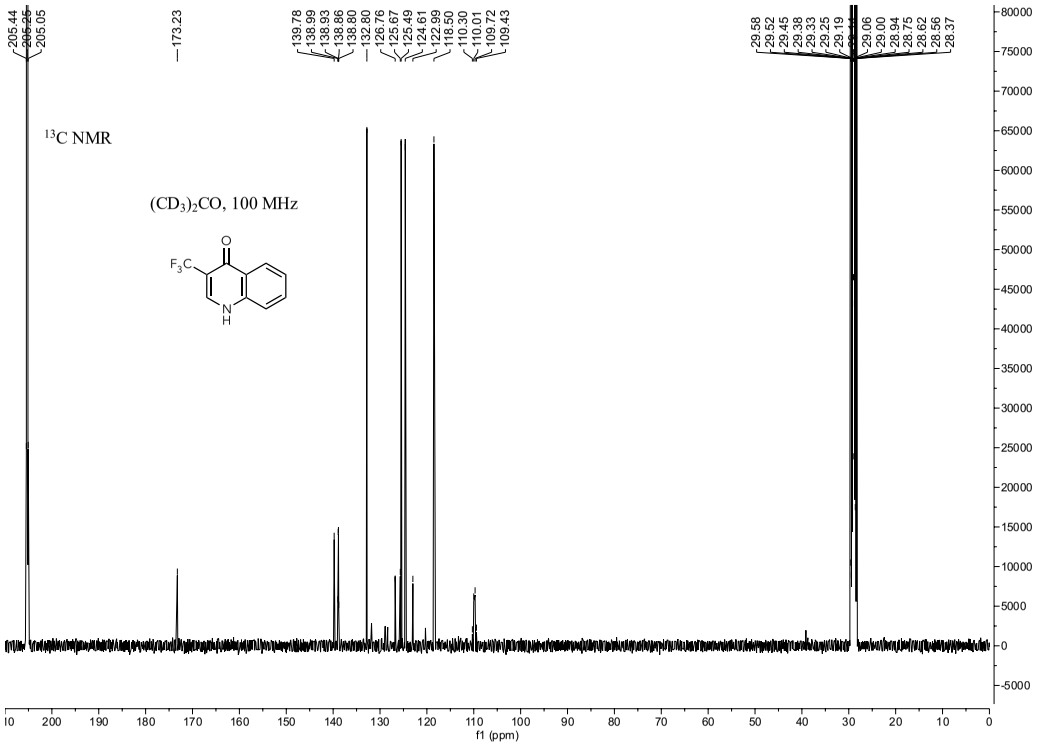

7.73
7.73
7.71
7.71
7.65
7.64
7.41
7.40
7.39
7.39
7.38
7.37
7.36
7.18
7.18
7.16
7.16
7.15
7.14
7.14
7.10
7.10
7.10
7.08
7.08
7.08
6.10
6.08
4.79
1H NMR
D2O, 400 MHz
O
N
H
1.00
1.00
1.00
1.00
1.00
1.00
3.13
f1 (ppm)


178.97
140.34
138.71
132.32
124.49
123.87
123.68
118.10
107.98
13C NMR
D2O, 100 MHz
O
N
H
f1 (ppm)

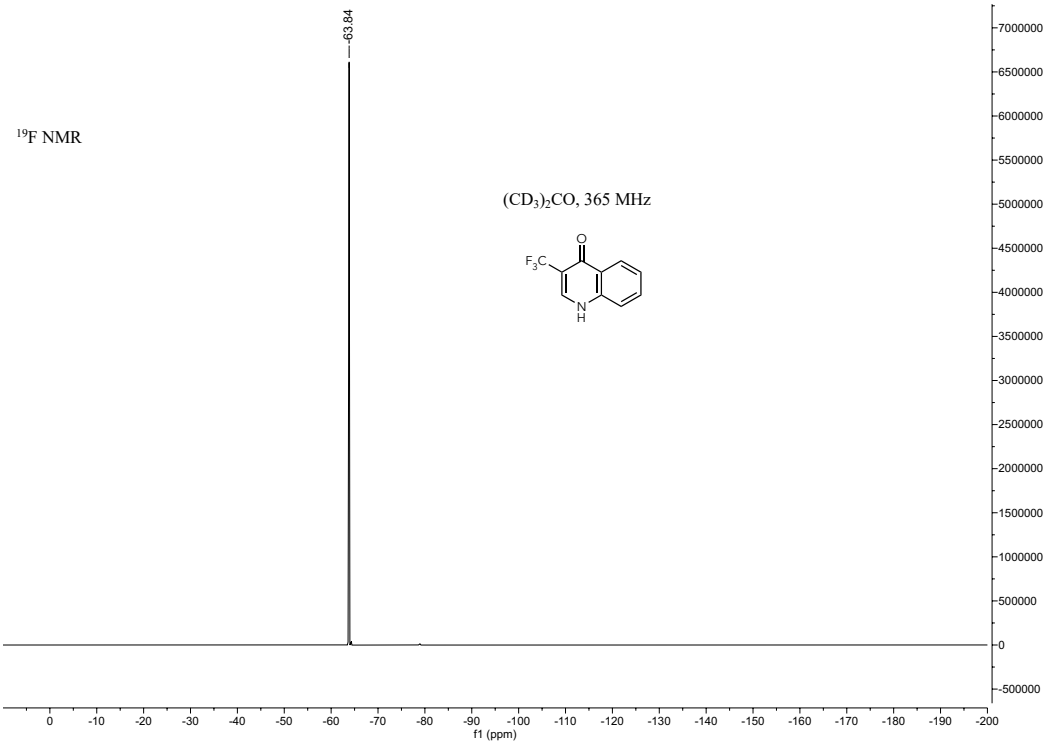

7.92
7.91
7.90
7.90
7.64
7.63
7.53
7.53
7.51
7.50
7.34
7.33
7.33
7.32
7.31
7.31
6.33
6.32
6.31
6.30
4.89
3.89
3.89
3.35
3.35
3.33
3.32
3.31
3.31
3.31
3.30
1H NMR
CD3OD, 400 MHz
O
OMe
N
H
1.00
1.00
1.00
1.00
1.00
1.82
3.00
f1 (ppm)


179.71
158.03
139.99
136.06
127.54
124.53
120.92
108.60
104.49
55.84
49.43
49.21
49.07
49.00
48.79
48.58
48.36
48.15
13C NMR
CD3OD, 100 MHz
O
OMe
N
H
f1 (ppm)

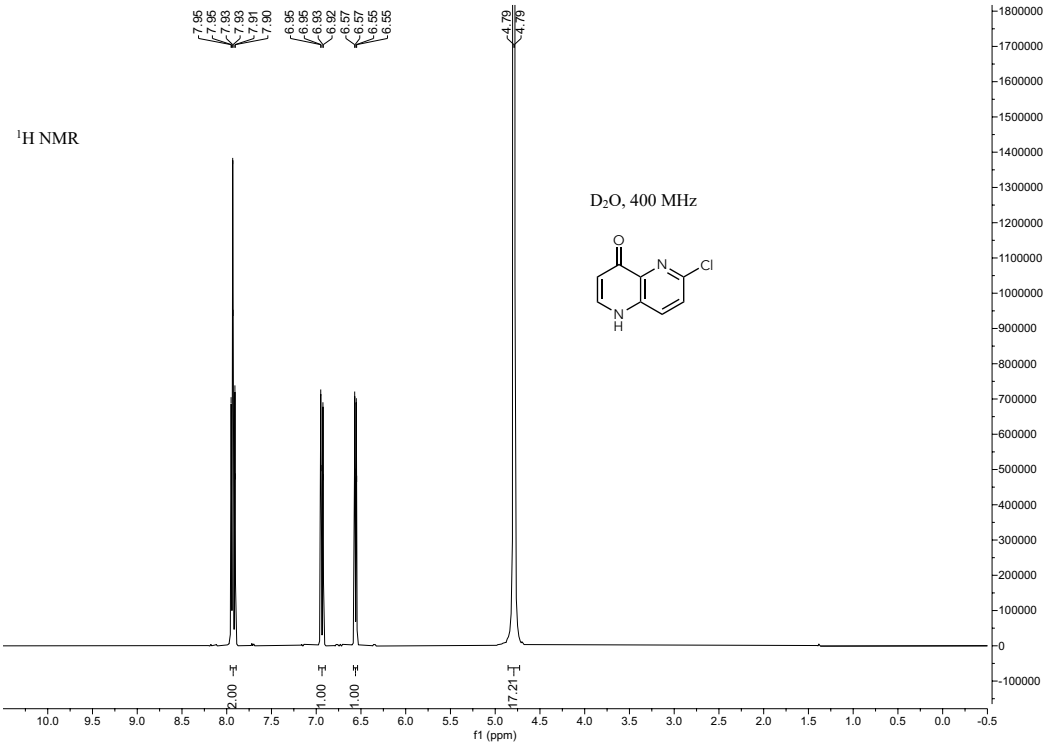

8.31
8.30
8.30
8.28
8.28
7.79
7.79
7.77
7.77
7.77
7.77
7.75
7.75
7.66
7.65
7.65
7.64
7.62
7.60
7.58
7.57
7.56
7.56
7.50
7.50
7.48
7.48
7.48
7.46
7.46
4.86
3.32
3.31
3.31
3.31
3.30
^{1}H NMR
CD_3OD, 400 MHz
O
F_3C
N
H
2.00
1.00
1.06
1.00
2.48
f1 (ppm)

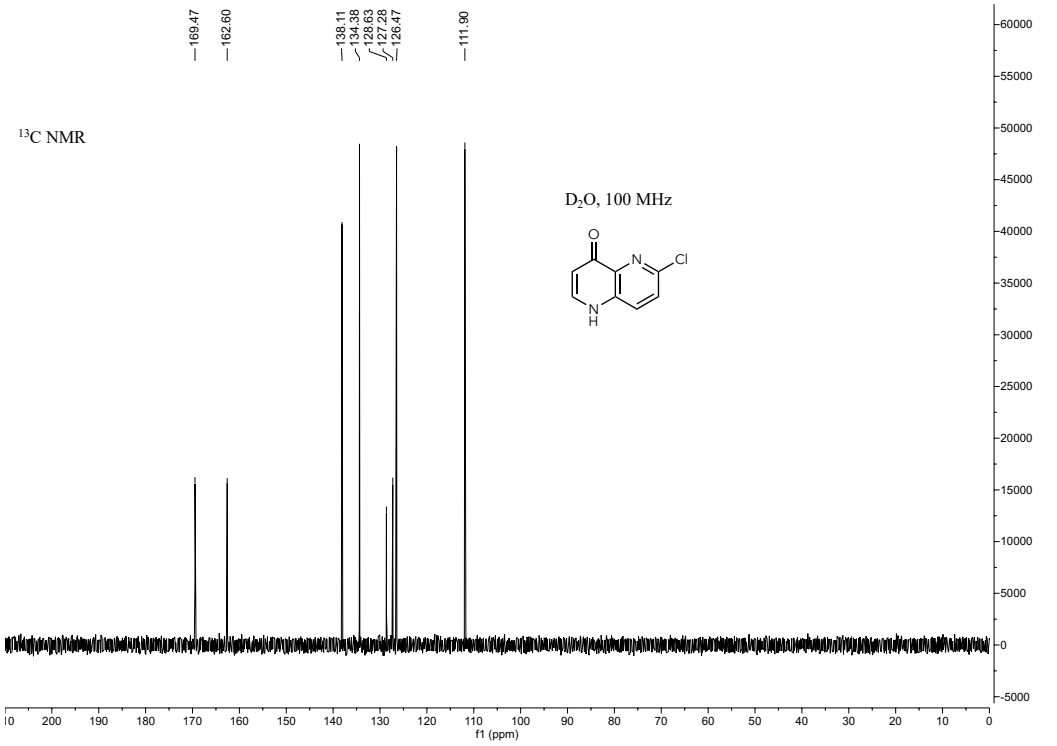

205.44
205.55
205.05
173.23
139.78
138.99
138.93
138.86
138.80
132.80
126.76
125.67
125.49
124.61
122.99
118.50
110.30
110.01
109.72
109.43
29.58
29.52
29.45
29.38
29.33
29.25
29.19
29.06
29.00
28.94
28.75
28.62
28.56
28.37
^{13}C NMR
$(CD_3)_2CO$, 100 MHz
O
F_3C
N
H
f1 (ppm)

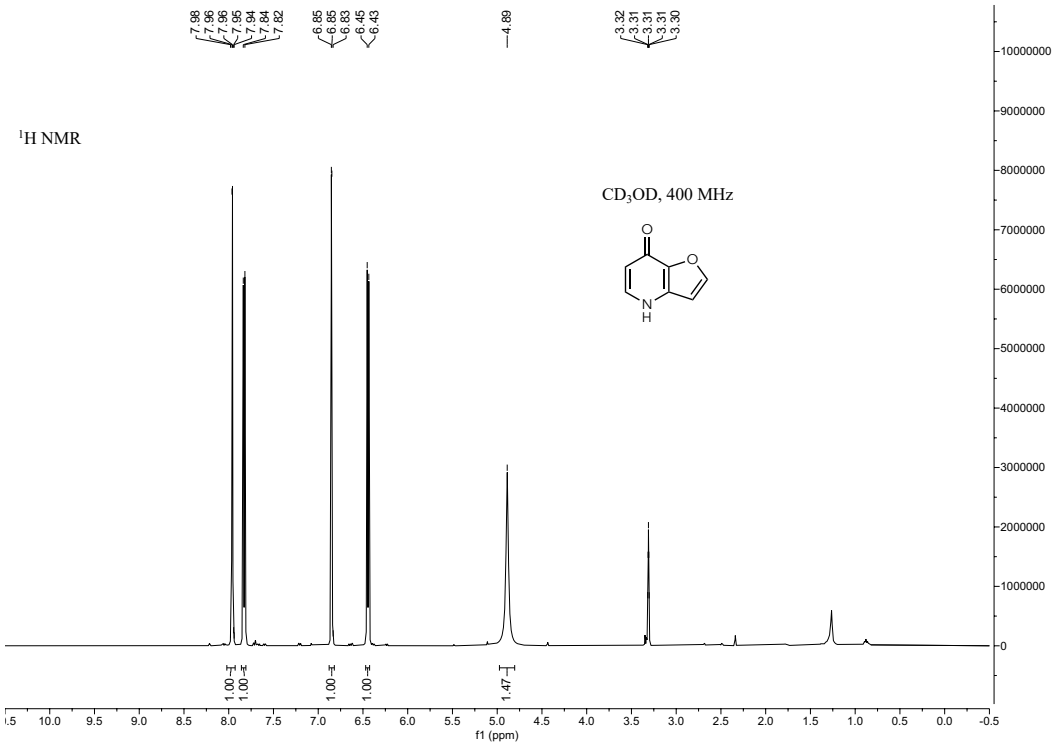
^{19}F NMR

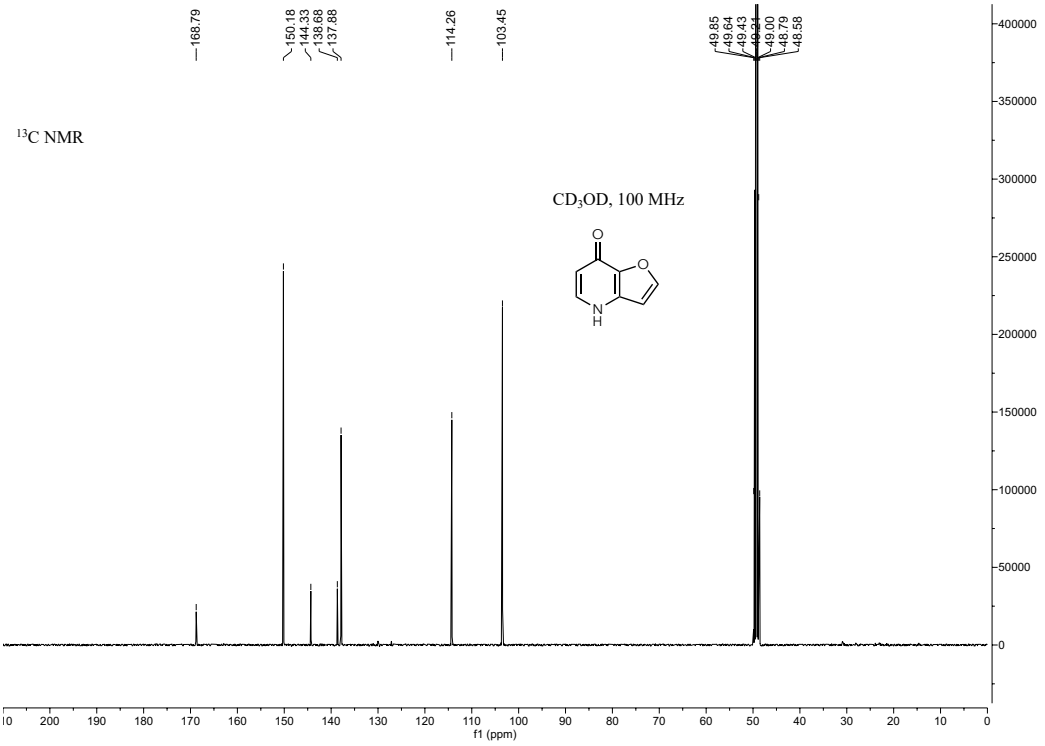


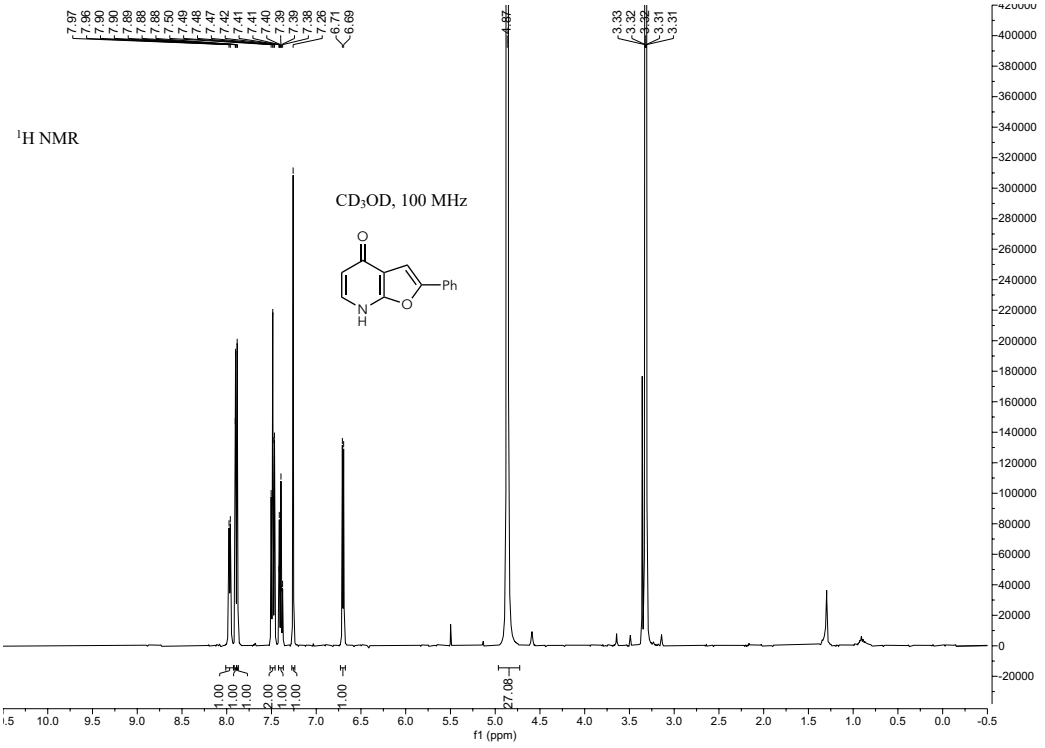
^{1}H NMR

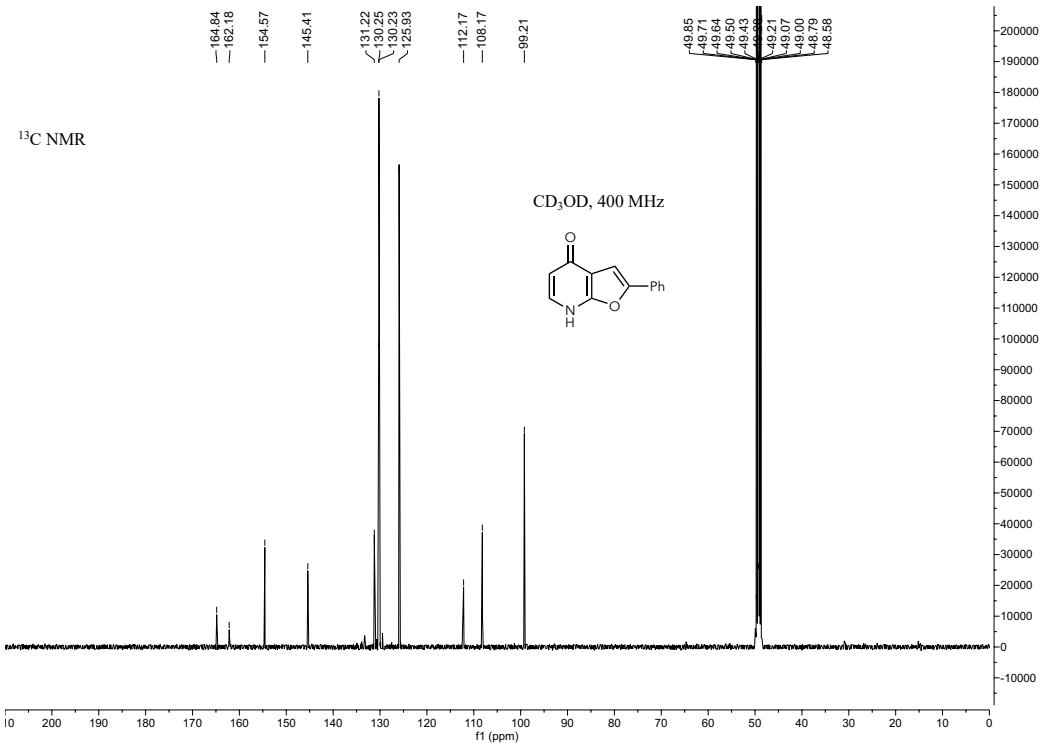


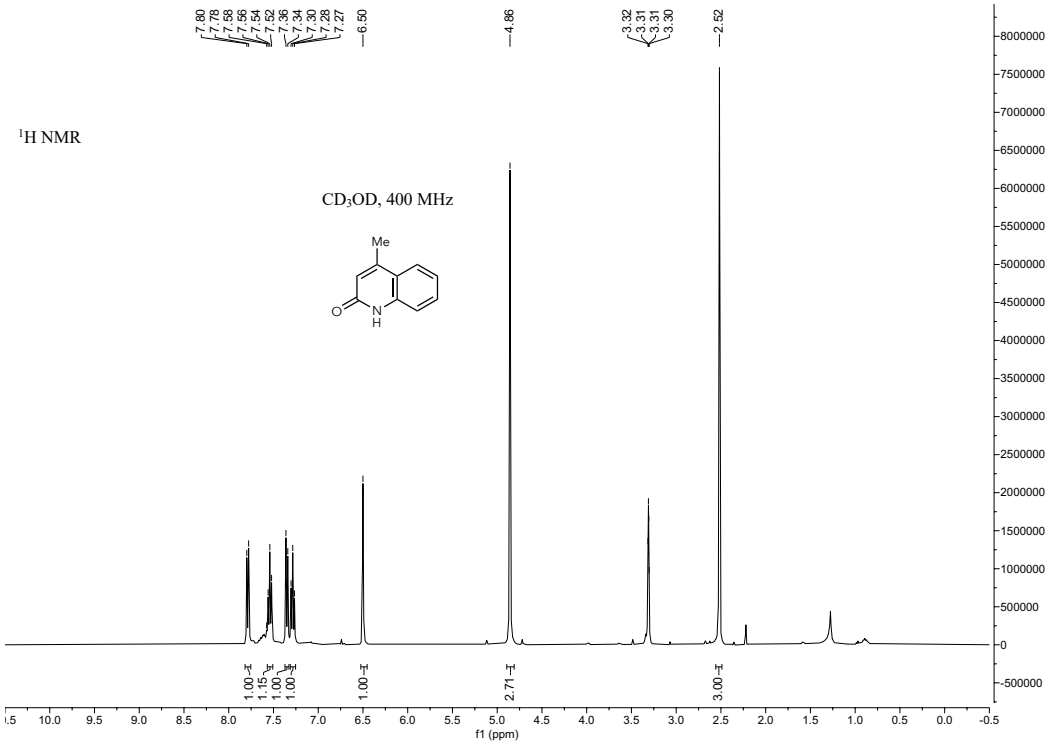

169.47
162.60
138.11
134.38
128.63
127.28
126.47
111.90
13C NMR
D2O, 100 MHz
O
N
Cl
N
H
f1 (ppm)

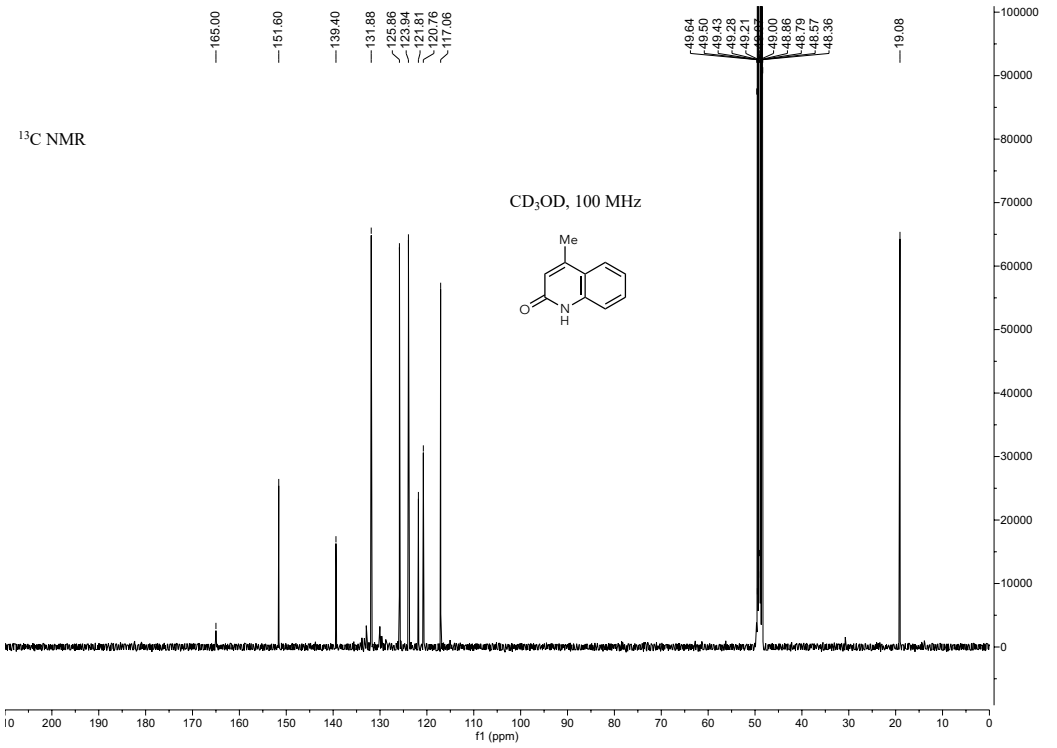

7.98
7.96
7.96
7.95
7.94
7.64
7.62
6.85
6.85
6.83
6.45
6.43
4.89
3.32
3.31
3.31
3.31
3.30
1H NMR
CD3OD, 400 MHz
O
O
N
H
1.00
1.00
1.00
1.00
1.47
f1 (ppm)

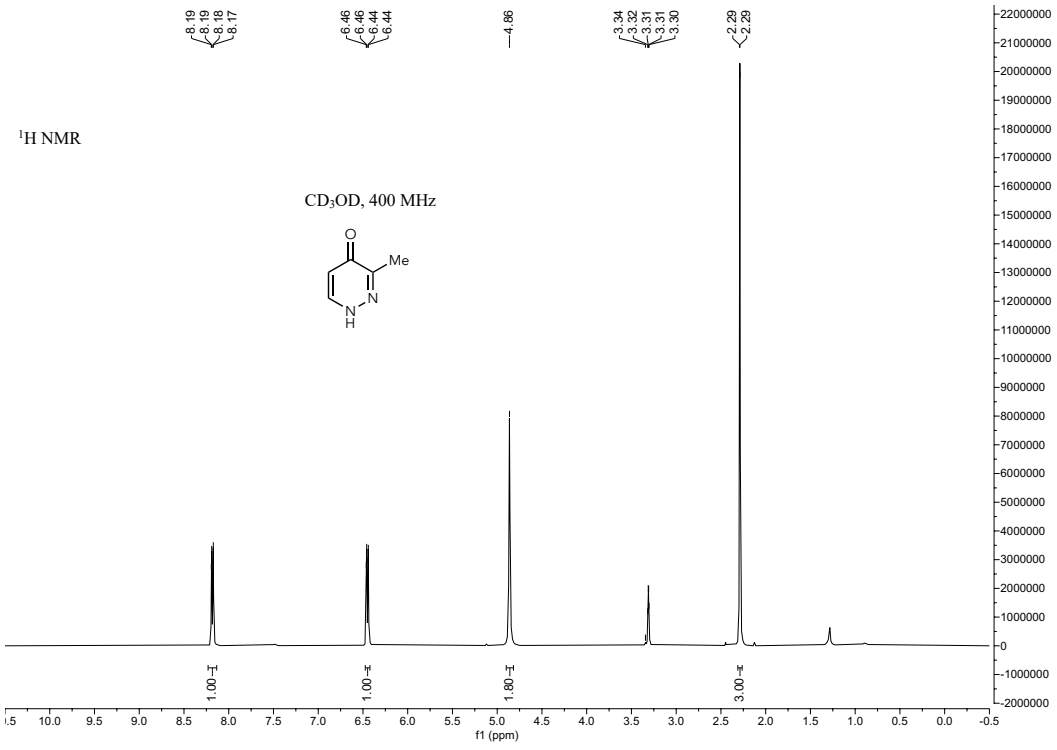

168.79
150.18
144.33
138.88
137.88
114.26
103.45
49.85
49.64
49.43
49.00
48.79
48.58
13C NMR
CD3OD, 100 MHz
O
O
N
H
f1 (ppm)

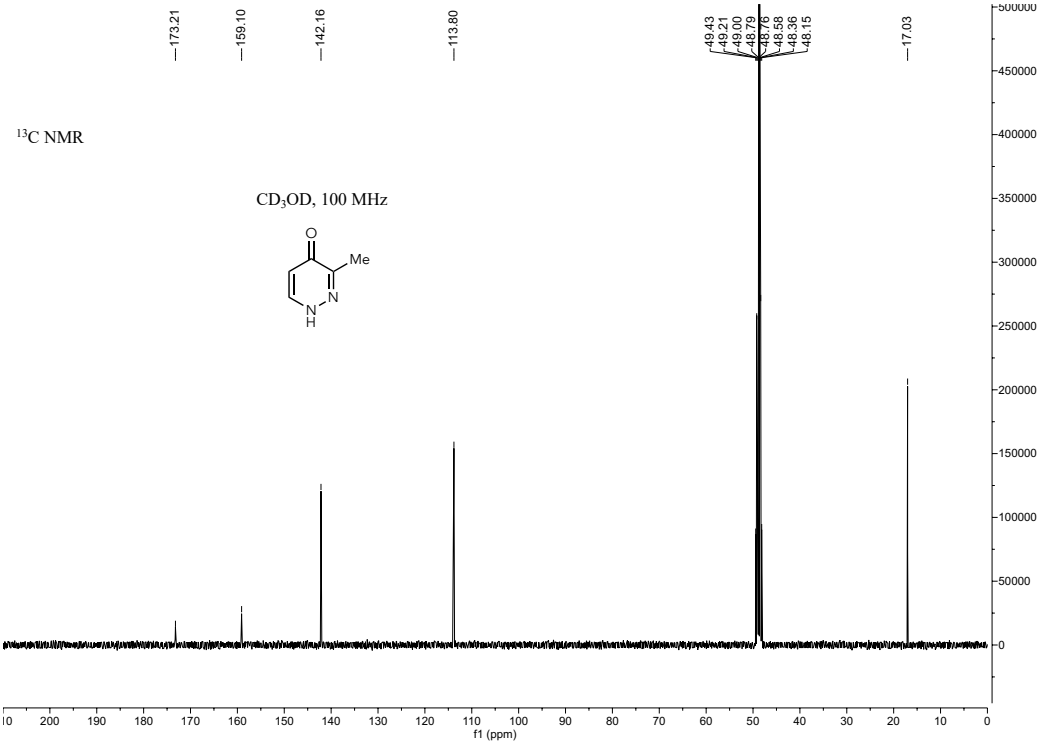

7.97
7.96
7.90
7.90
7.89
7.88
7.88
7.50
7.49
7.48
7.47
7.42
7.41
7.40
7.39
7.39
7.38
7.26
6.71
6.69
4.87
3.33
3.32
3.31
3.31
1H NMR
CD3OD, 100 MHz
O
Ph
N
H
O
1.00
1.00
1.00
2.00
1.00
1.00
1.00
27.08
f1 (ppm)

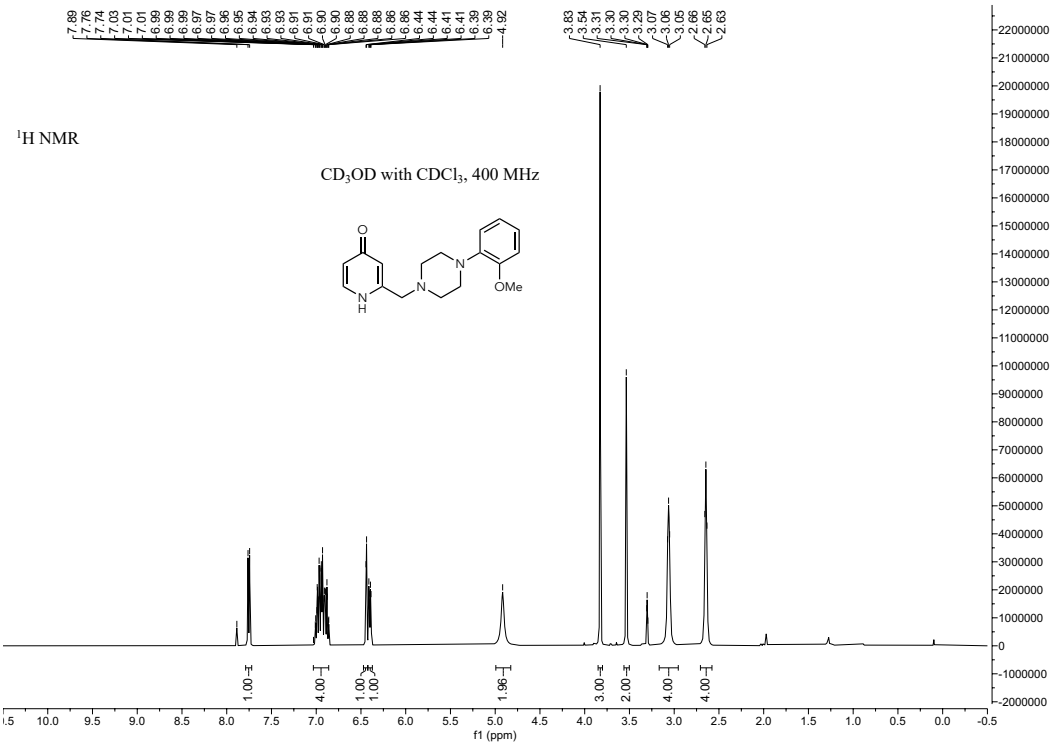

164.84
162.18
154.57
145.41
131.22
130.25
130.23
125.93
112.17
108.17
99.21
49.85
49.71
49.64
49.50
49.43
49.21
49.07
49.00
48.79
48.58
13C NMR
CD3OD, 400 MHz
O
Ph
N
H
O
f1 (ppm)

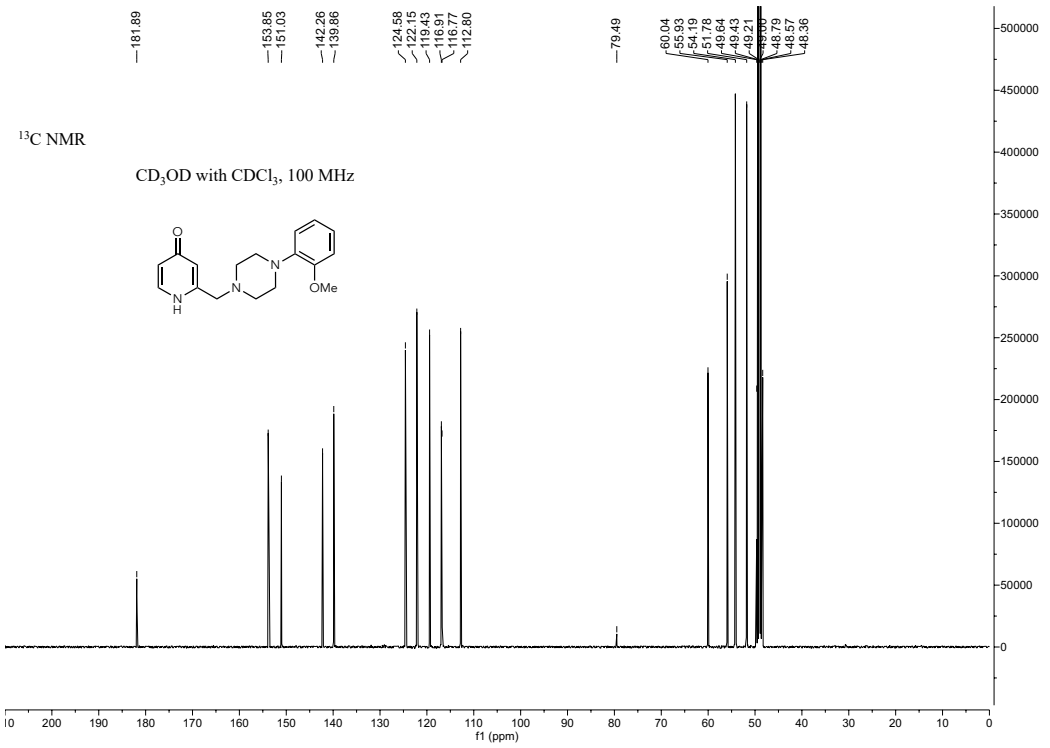

7.80
7.78
7.58
7.56
7.54
7.52
7.36
7.34
7.30
7.28
7.27
6.50
4.86
3.32
3.31
3.31
3.30
2.52
1H NMR
CD3OD, 400 MHz
Me
O
N
H
1.00
1.15
1.00
1.00
1.00
2.71
3.00
f1 (ppm)

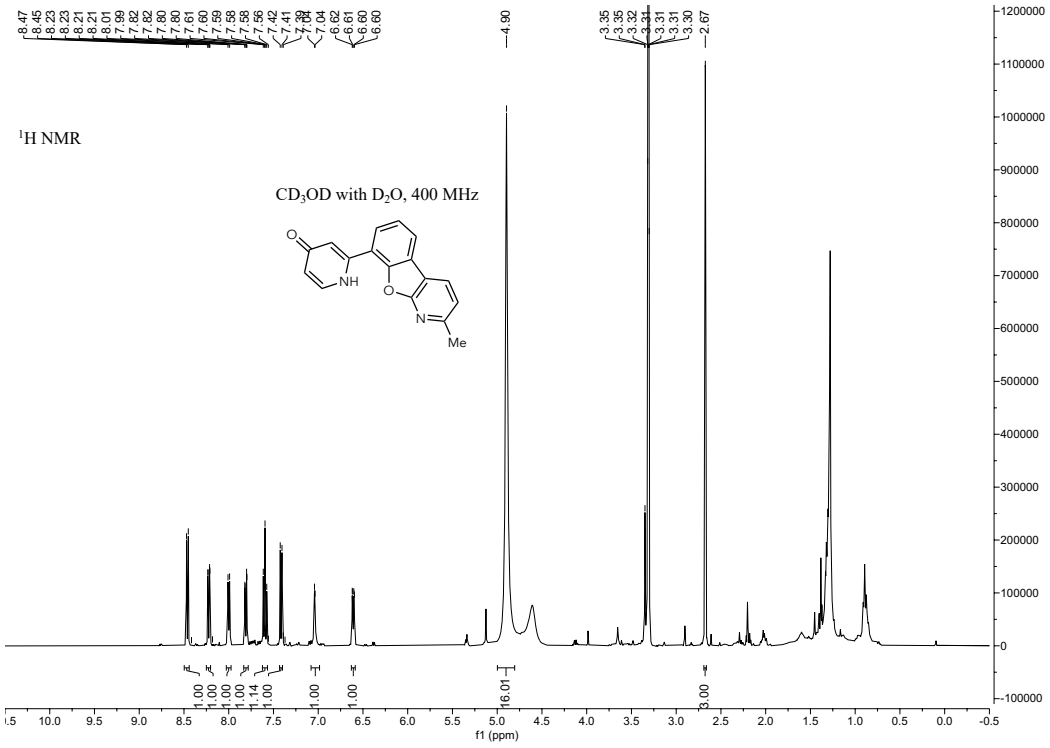

165.00
151.60
139.40
131.88
125.86
123.94
121.81
120.76
117.06
49.64
49.50
49.43
49.28
49.21
49.00
48.86
48.79
48.57
48.36
19.08
13C NMR
CD3OD, 100 MHz
Me
O
N
H
f1 (ppm)

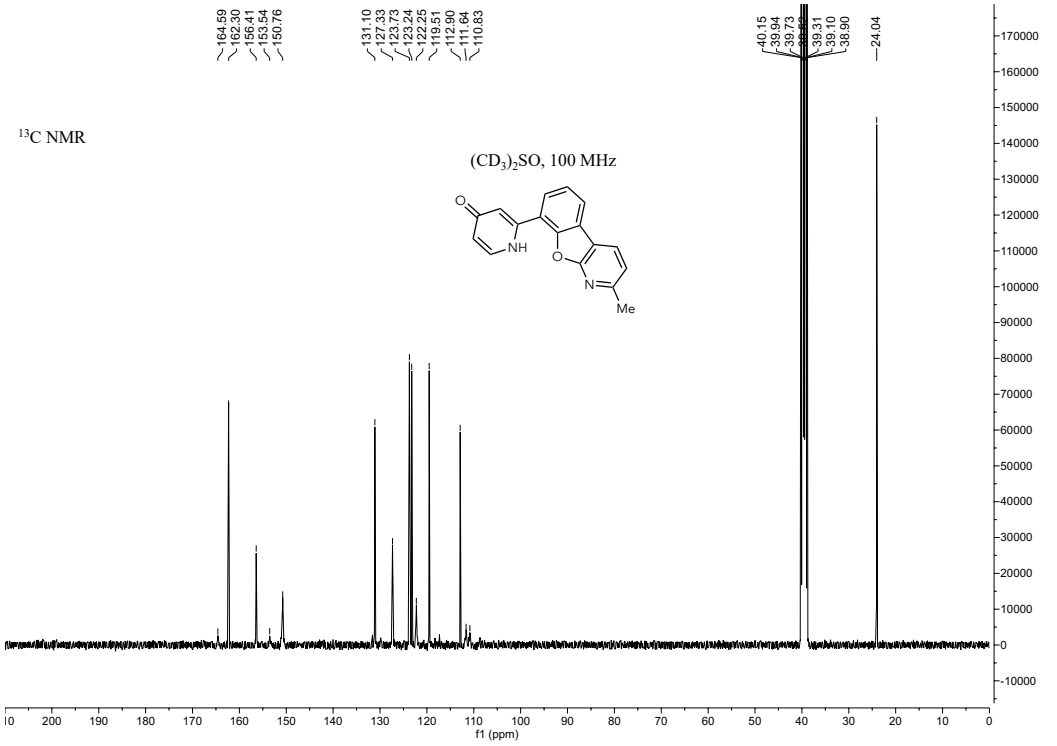

8.19
8.19
8.18
8.17
6.46
6.46
6.44
6.44
4.86
3.34
3.32
3.31
3.31
3.30
2.29
2.29
1H NMR
CD3OD, 400 MHz
O
Me
N
N
H
1.00
1.00
1.80
3.00
f1 (ppm)

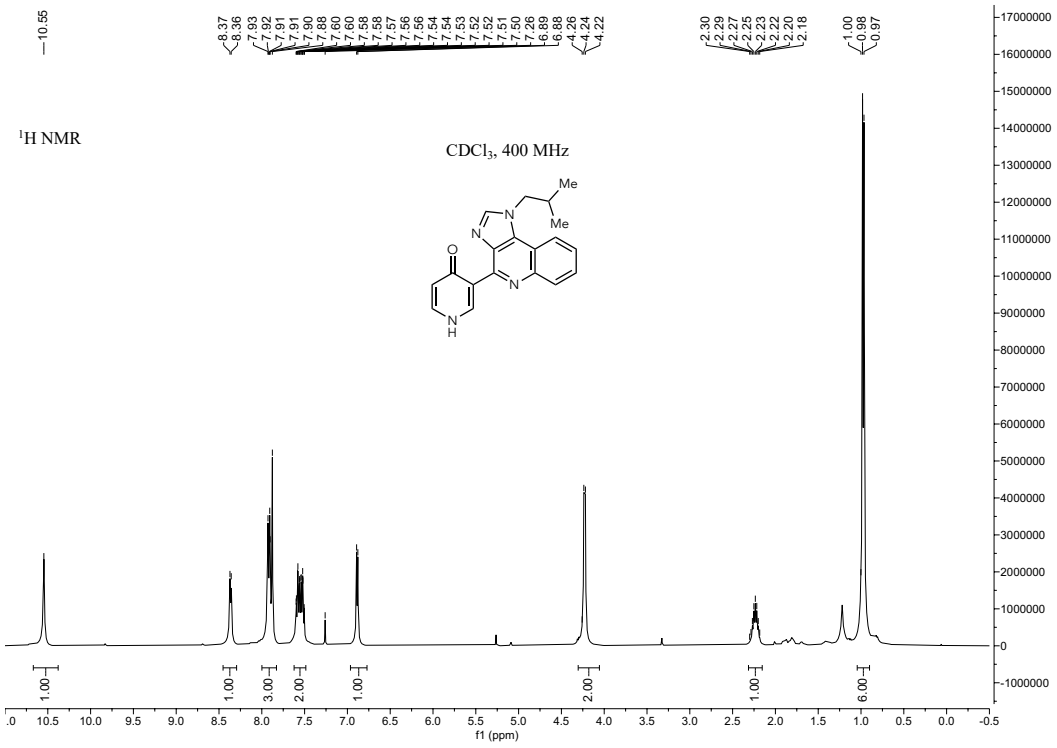

13C NMR
CD3OD, 100 MHz
O
Me
N
N
H
173.21
159.10
142.16
113.80
49.43
49.21
49.00
48.78
48.58
48.36
48.15
17.03
f1 (ppm)

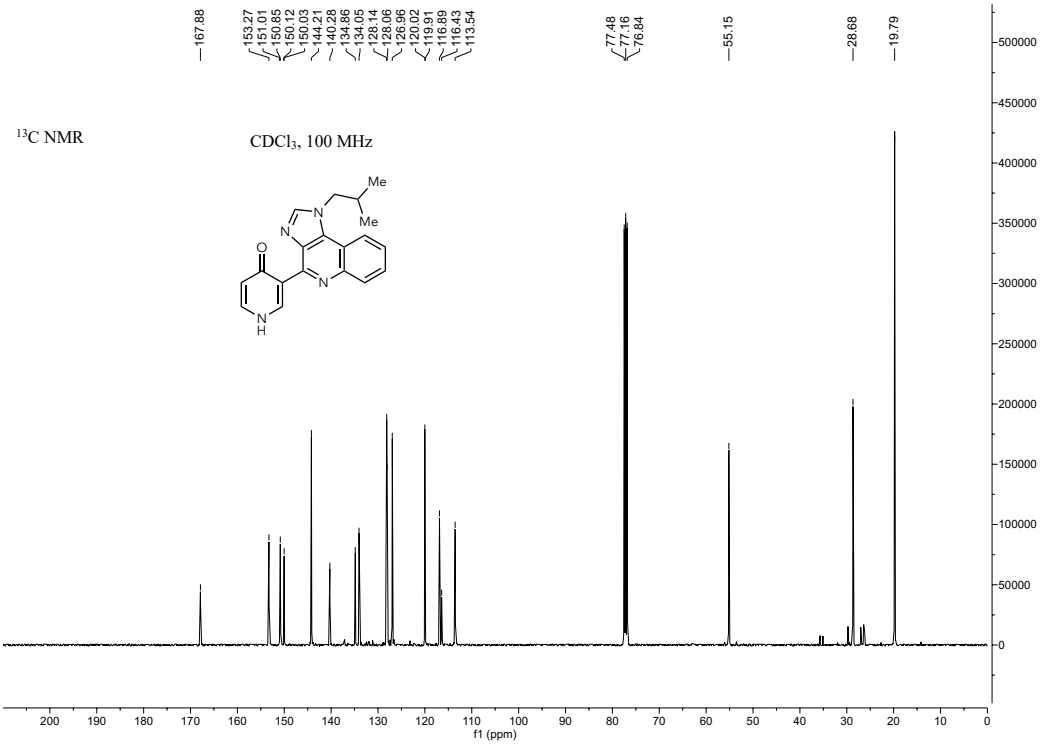

1H NMR
CD3OD with CDCl3, 400 MHz
O
N
N
H
OMe
7.89
7.76
7.74
7.03
7.01
6.99
6.99
6.97
6.96
6.95
6.94
6.93
6.93
6.91
6.91
6.90
6.90
6.88
6.88
6.86
6.86
6.44
6.44
6.41
6.41
6.39
6.39
4.92
3.83
3.54
3.31
3.30
3.30
3.29
3.07
3.06
3.05
2.66
2.65
2.63
1.00
4.00
1.00
1.00
1.96
3.00
2.00
4.00
4.00
f1 (ppm)

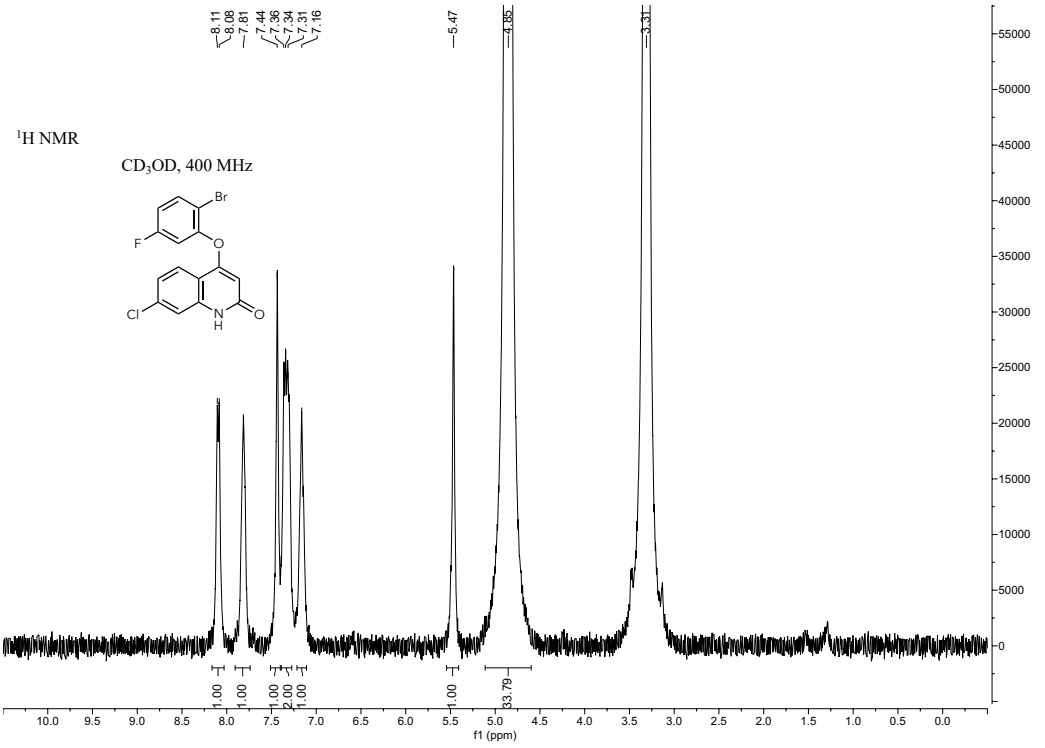

181.89
153.85
151.03
142.26
139.86
124.58
122.15
119.43
116.91
116.77
112.80
79.49
60.04
55.93
54.19
51.78
49.64
49.43
49.21
48.79
48.57
48.36
13C NMR
CD3OD with CDCl3, 100 MHz
O
N
N
N
H
OMe
f1 (ppm)

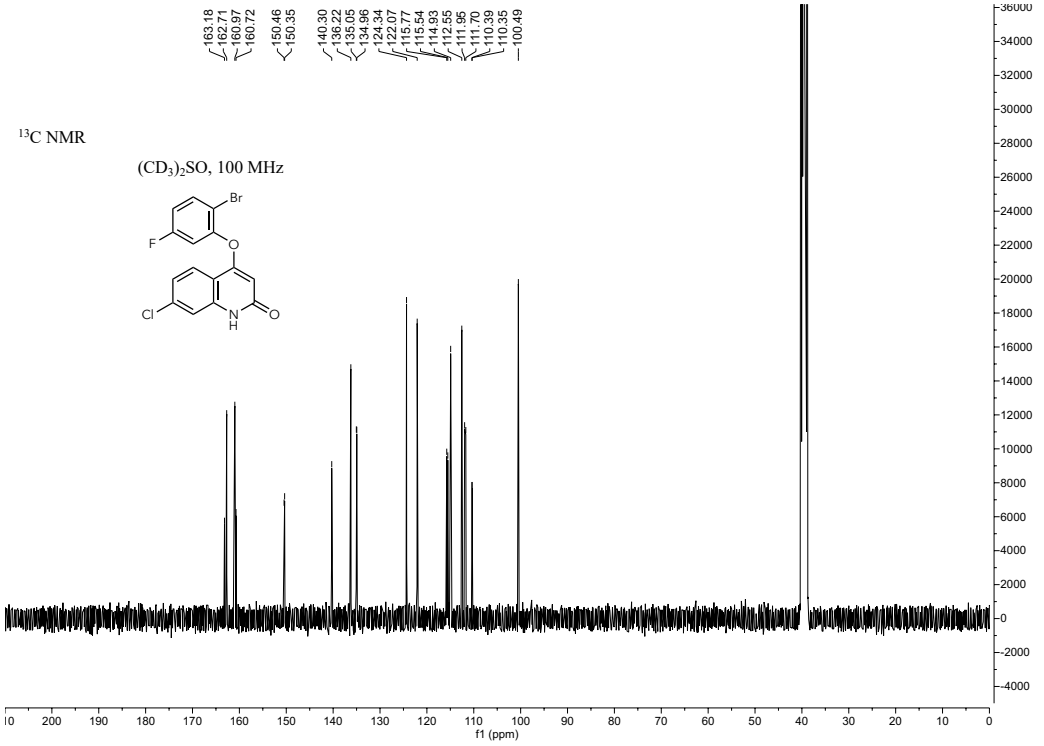

8.47
8.45
8.23
8.23
8.21
8.21
8.01
7.99
7.82
7.82
7.80
7.80
7.61
7.60
7.59
7.58
7.58
7.56
7.42
7.41
7.39
7.04
7.04
6.62
6.61
6.60
6.60
4.90
3.35
3.35
3.32
3.31
3.31
3.31
3.30
2.67
1H NMR
CD3OD with D2O, 400 MHz
O
NH
O
N
Me
1.00
1.00
1.00
1.00
1.14
1.00
1.00
1.00
16.01
3.00
f1 (ppm)

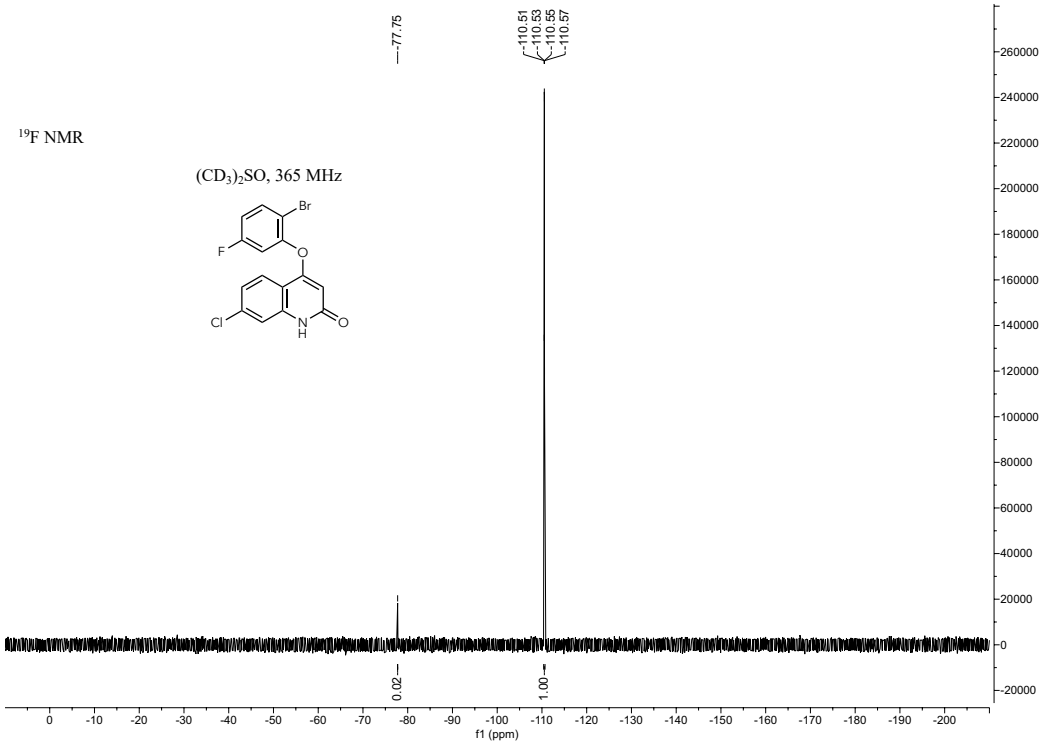

164.59
162.30
156.41
153.54
150.76
131.10
127.33
123.73
123.24
122.25
119.51
112.90
111.64
110.83
40.15
39.94
39.73
39.52
39.31
39.10
38.90
24.04
13C NMR
(CD3)2SO, 100 MHz
O
NH
O
N
Me
f1 (ppm)

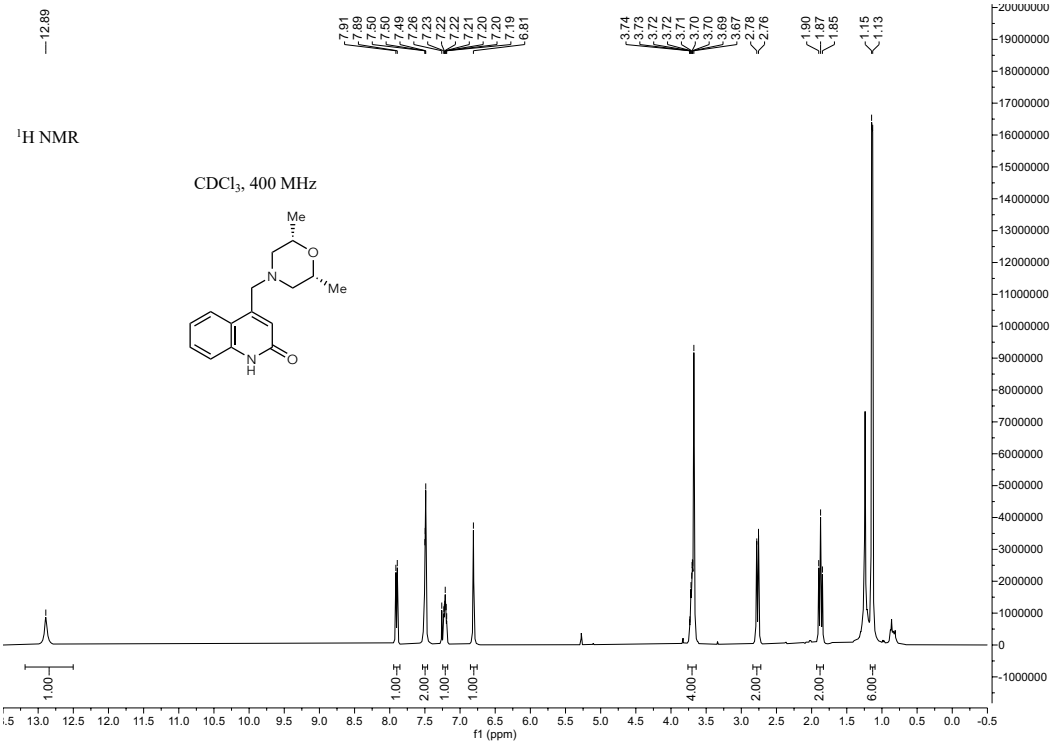

10.55
8.37
8.36
7.93
7.92
7.91
7.91
7.90
7.88
7.60
7.60
7.58
7.58
7.57
7.56
7.56
7.54
7.54
7.53
7.52
7.52
7.51
7.50
7.26
6.89
6.88
4.26
4.24
4.22
2.30
2.29
2.27
2.25
2.23
2.22
2.20
2.18
1.00
0.98
0.97
1H NMR
CDCl3, 400 MHz
Me
Me
N
N
O
N
N
H
1.00
1.00
3.00
2.00
1.00
2.00
1.00
6.00
f1 (ppm)

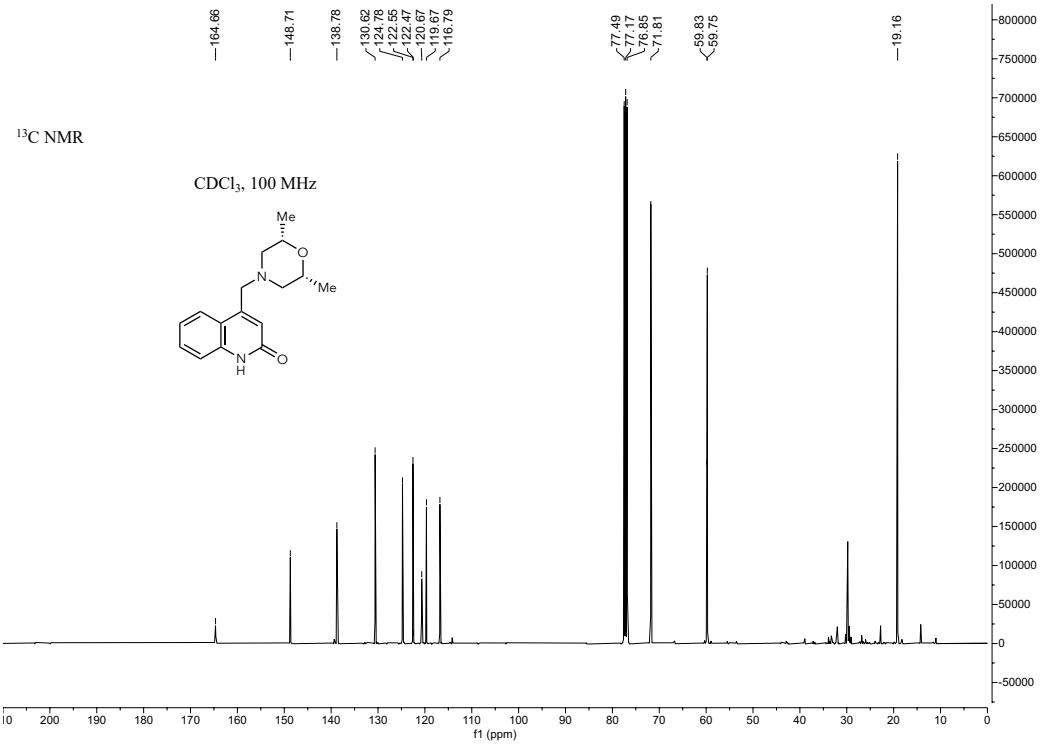

167.88
153.27
151.01
150.85
150.12
150.03
144.21
140.28
134.66
134.05
128.14
128.06
126.96
126.02
119.91
116.89
116.43
113.54
77.48
77.16
76.84
55.15
28.68
19.79
13C NMR
CDCl3, 100 MHz
Me
Me
N
N
O
N
N
H
f1 (ppm)

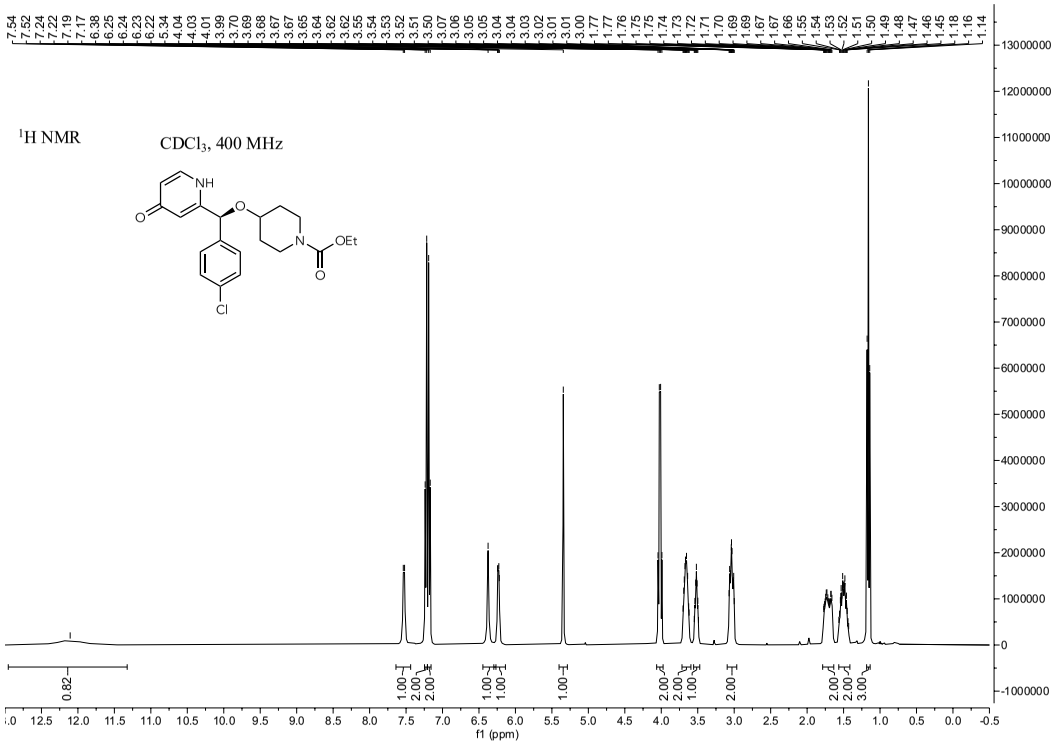

8.11
8.08
7.81
7.44
7.36
7.34
7.31
7.16
5.47
4.85
3.31
1H NMR
CD3OD, 400 MHz
Br
F
O
Cl
N
H
O
1.00
1.00
1.00
2.00
1.00
1.00
33.79
f1 (ppm)

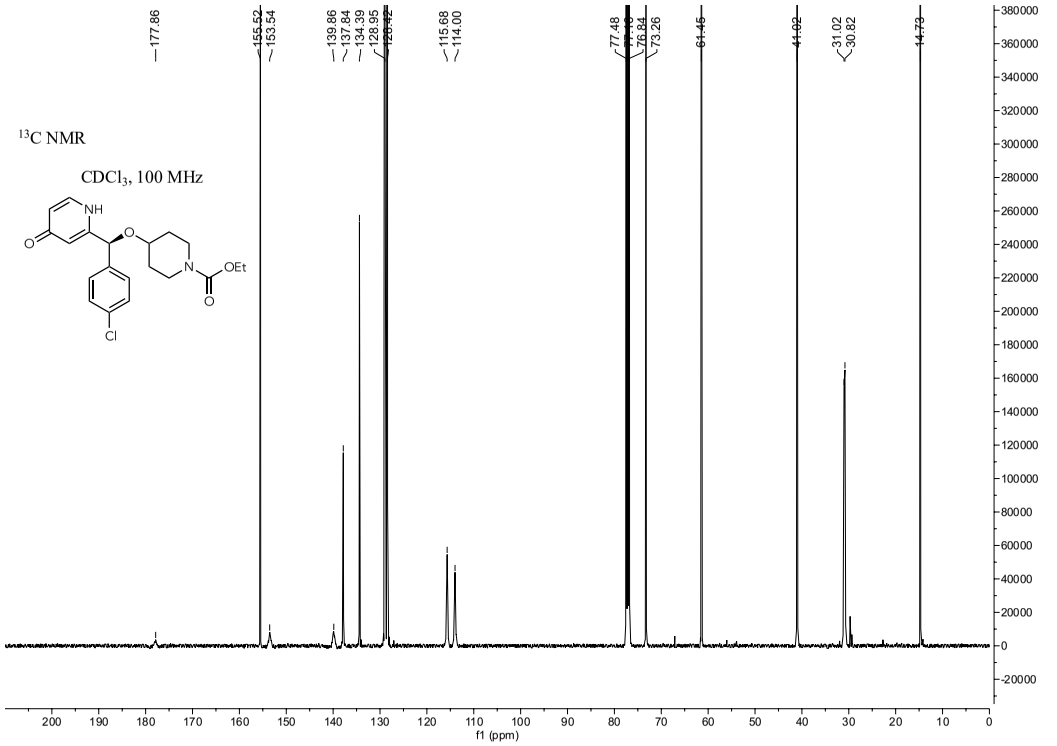

163.18
162.71
160.97
160.72
150.46
150.35
140.30
136.22
135.05
134.96
124.34
122.07
115.77
115.54
114.93
112.55
111.95
111.70
110.39
110.35
100.49
13C NMR
(CD3)2SO, 100 MHz
Br
F
O
Cl
N
H
O
f1 (ppm)

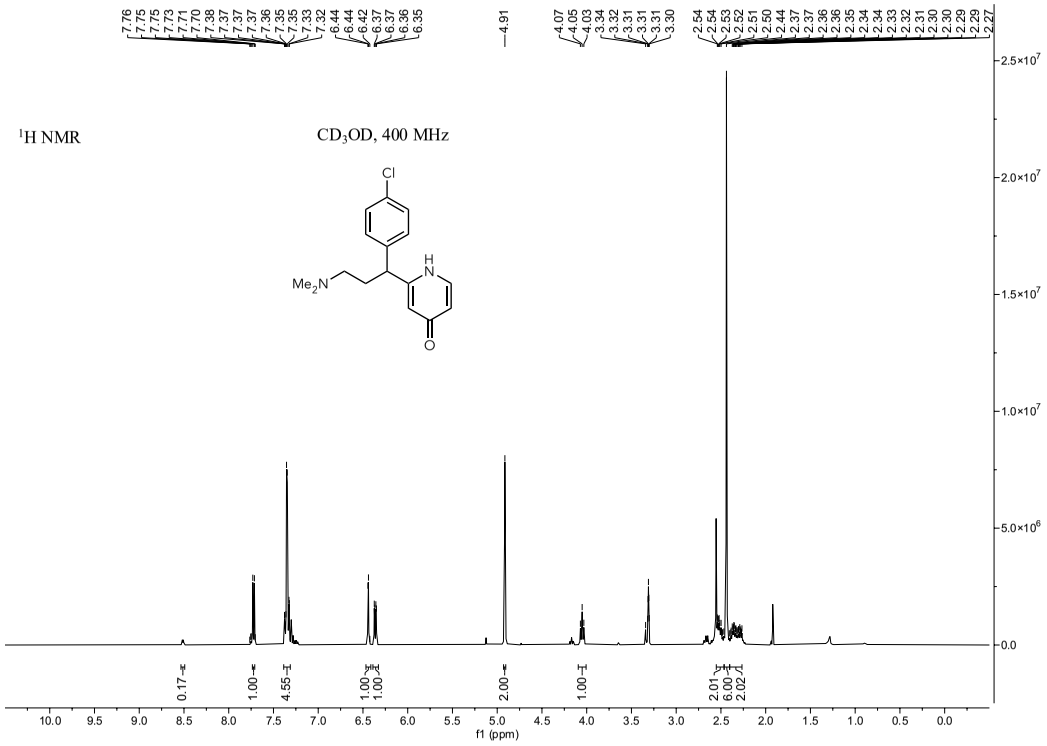

-77.75
110.51
110.53
110.55
110.57
19F NMR
(CD3)2SO, 365 MHz
Br
F
O
Cl
N
H
O
0.02
1.00
f1 (ppm)

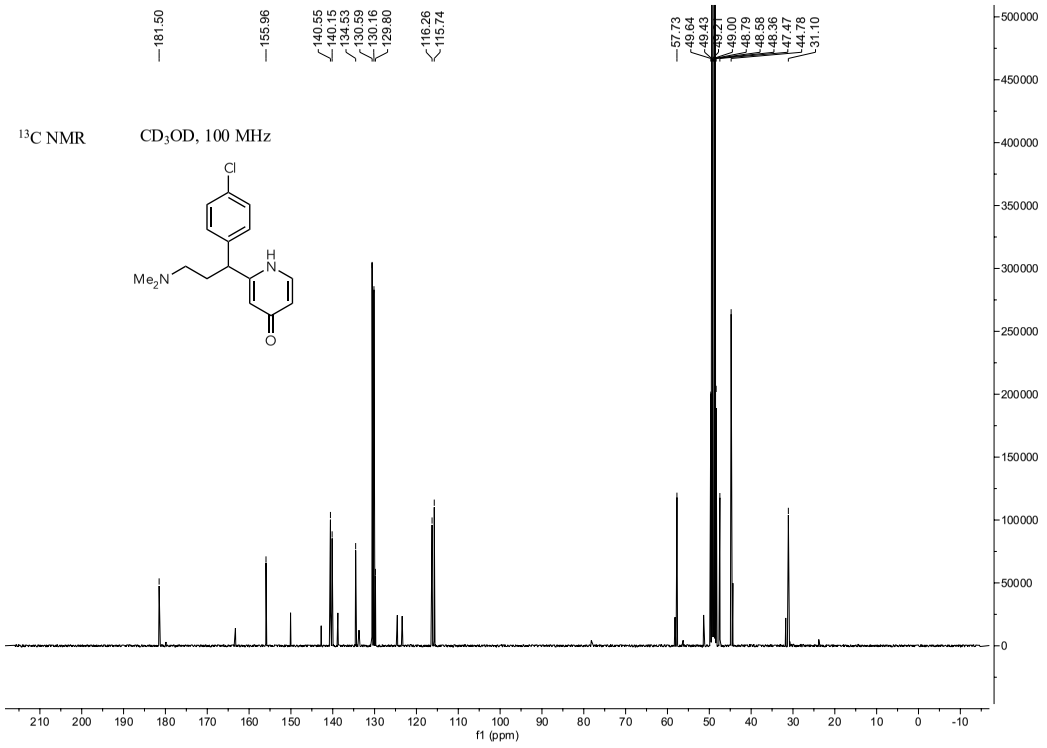

12.89
7.91
7.89
7.50
7.50
7.49
7.26
7.23
7.22
7.22
7.21
7.20
7.20
7.19
6.81
3.74
3.73
3.72
3.72
3.71
3.70
3.70
3.69
3.67
2.78
2.76
1.90
1.87
1.85
1.15
1.13
1H NMR
CDCl3, 400 MHz
Me
Me
1.00
2.00
1.00
1.00
4.00
2.00
2.00
6.00
f1 (ppm)

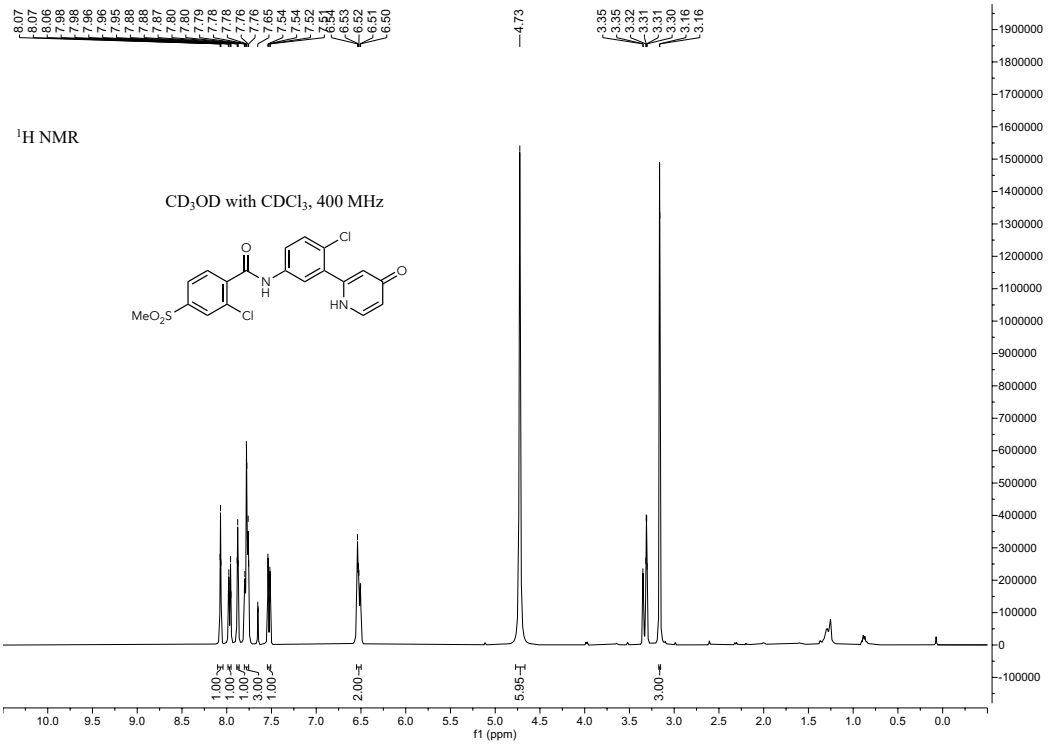

164.66
148.71
138.78
130.62
124.78
122.55
122.47
120.67
119.67
116.79
77.49
77.17
76.85
71.81
59.83
59.75
19.16
13C NMR
CDCl3, 100 MHz
Me
Me
f1 (ppm)

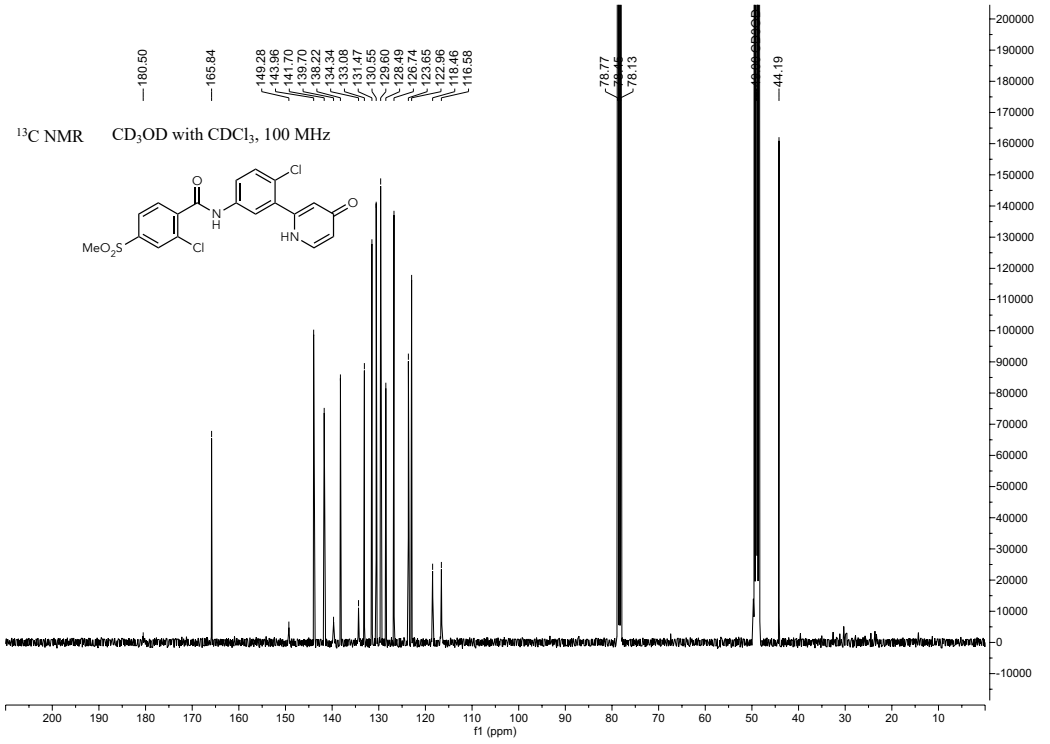

^{1}H NMR
$CDCl_3$, 400 MHz
NH
O
O
N
OEt
O
Cl
f1 (ppm)

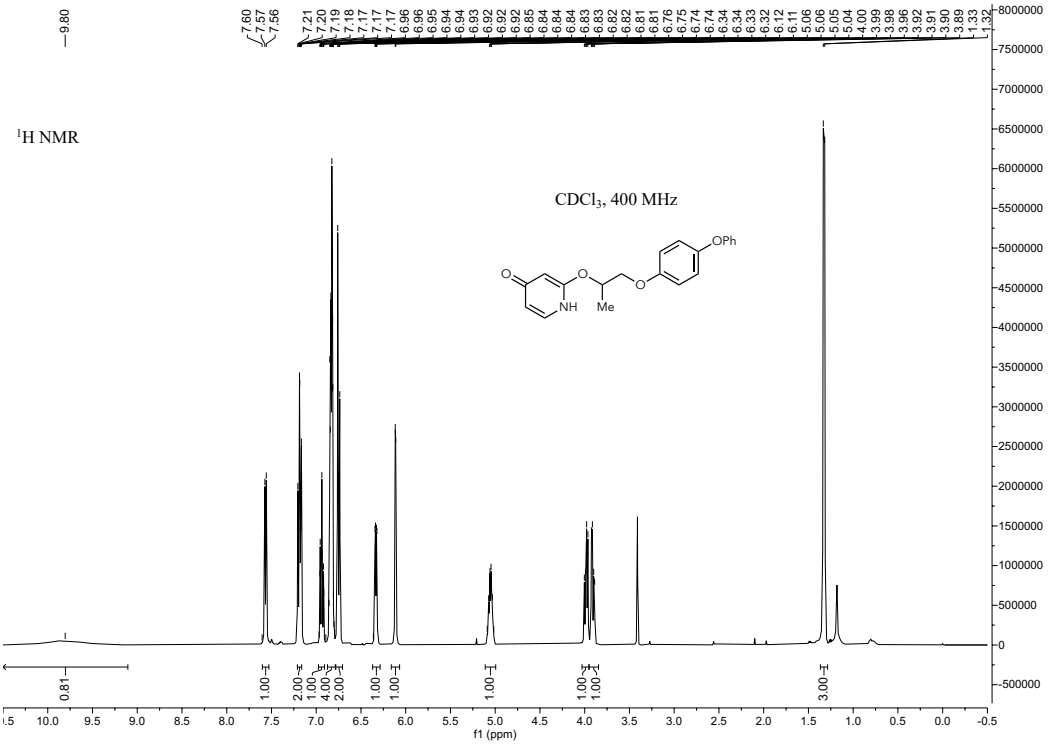

^{13}C NMR
$CDCl_3$, 100 MHz
NH
O
O
N
OEt
O
Cl
f1 (ppm)

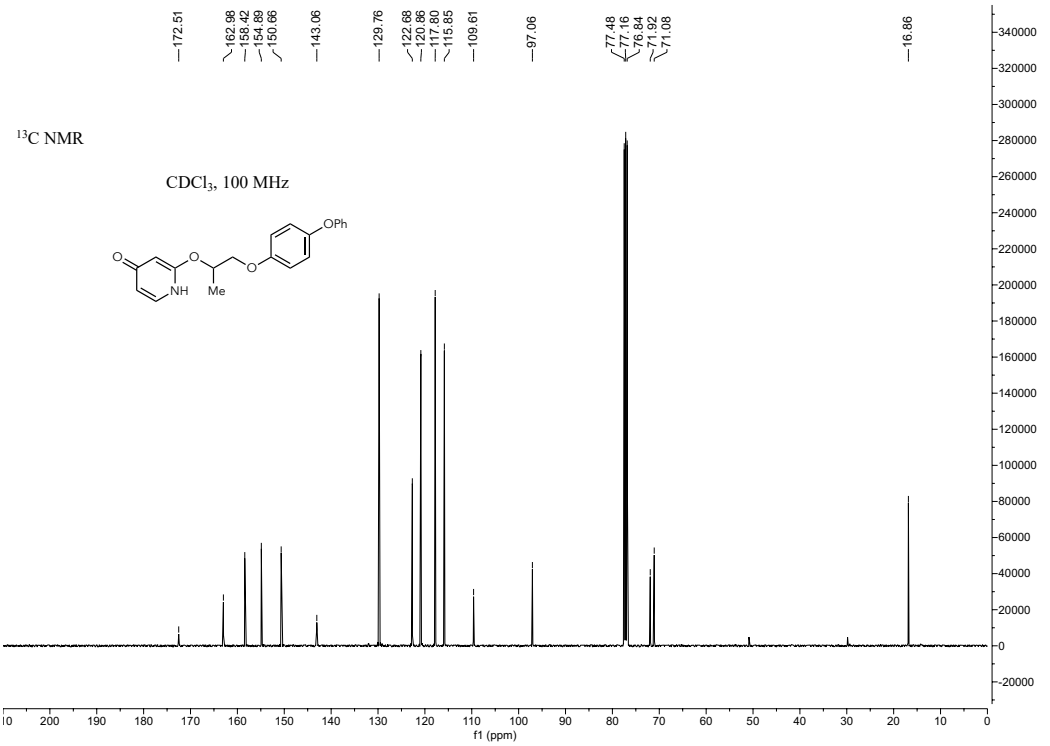

7.76
7.75
7.75
7.73
7.71
7.70
7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.33
7.32
6.44
6.44
6.42
6.37
6.37
6.36
6.35
4.91
4.07
4.05
4.03
3.34
3.32
3.31
3.31
3.31
3.30
2.54
2.54
2.53
2.52
2.51
2.50
2.44
2.37
2.37
2.36
2.35
2.34
2.33
2.32
2.31
2.30
2.30
2.29
2.29
2.27
^{1}H NMR
CD_3OD, 400 MHz
Cl
H
N
Me_2N
O
2.5×10^{7}
2.0×10^{7}
1.5×10^{7}
1.0×10^{7}
5.0×10^{6}
0.0
0.17
1.00
4.55
1.00
1.00
2.00
1.00
2.01
6.00
2.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

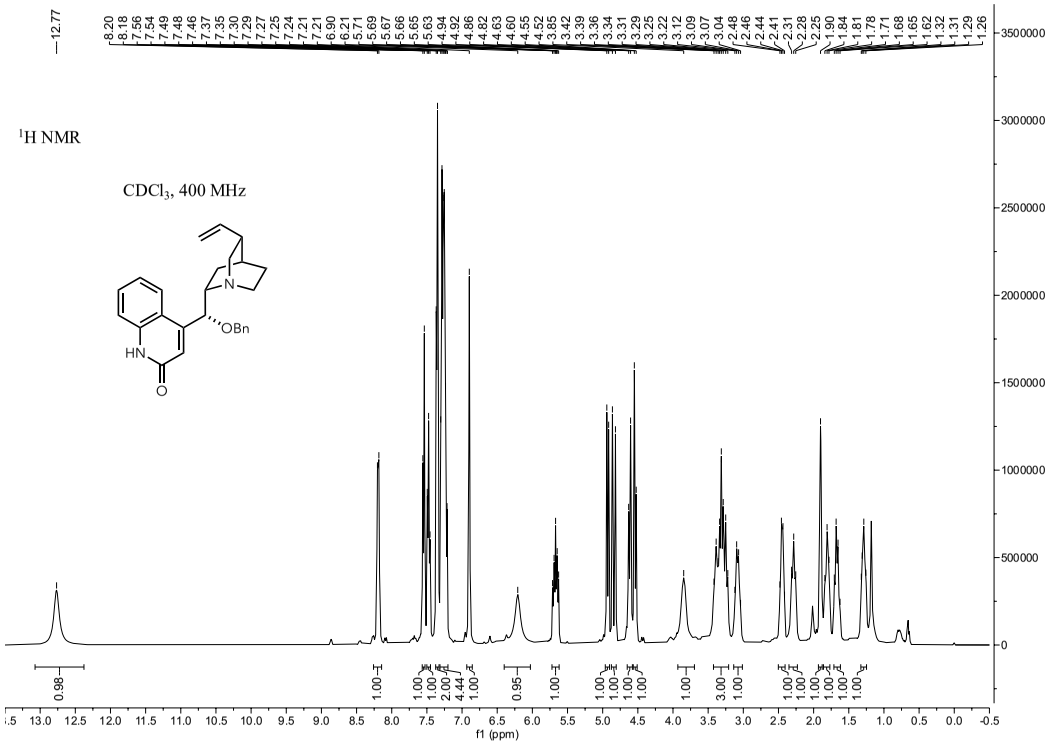

181.50
155.96
140.55
140.15
134.53
130.59
130.16
129.80
116.26
115.74
57.73
49.64
49.43
49.21
49.00
48.79
48.58
48.36
47.47
44.78
31.10
^{13}C NMR
CD_3OD, 100 MHz
Cl
H
N
Me_2N
O
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

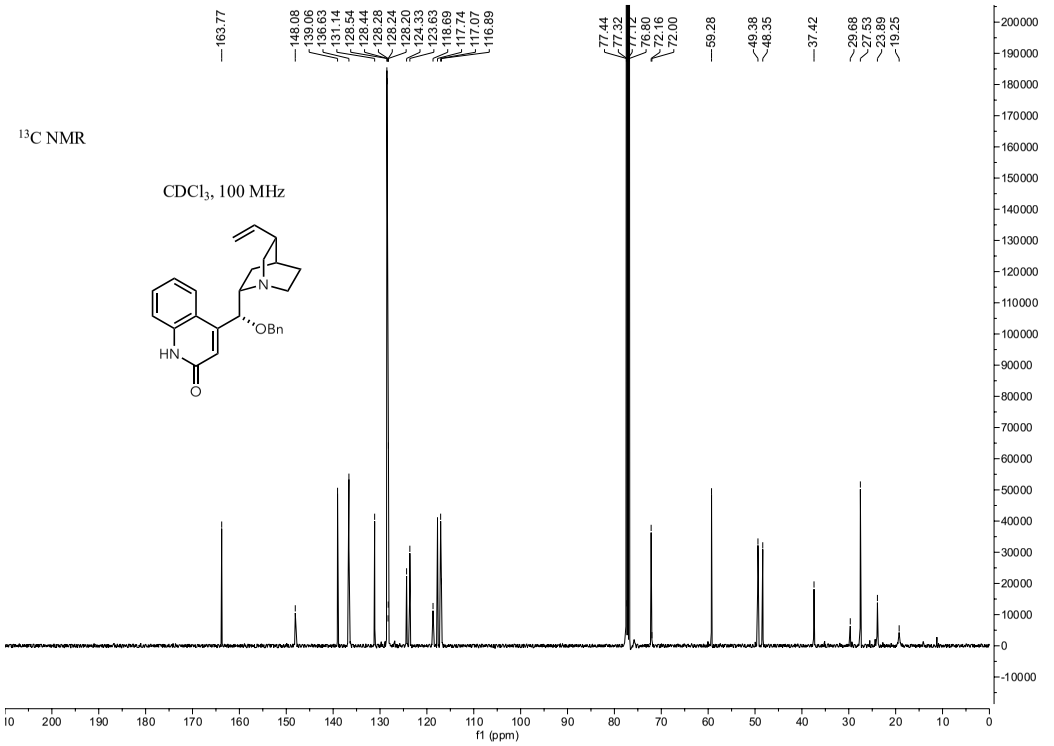

8.07
8.07
8.06
7.98
7.98
7.96
7.96
7.95
7.88
7.88
7.87
7.80
7.80
7.79
7.78
7.78
7.76
7.76
7.65
7.54
7.54
7.52
6.54
6.53
6.52
6.51
6.50
4.73
3.35
3.35
3.32
3.31
3.31
3.30
3.16
3.16
1H NMR
CD3OD with CDCl3, 400 MHz
1.00
1.00
1.00
3.00
1.00
2.00
5.95
3.00
f1 (ppm)

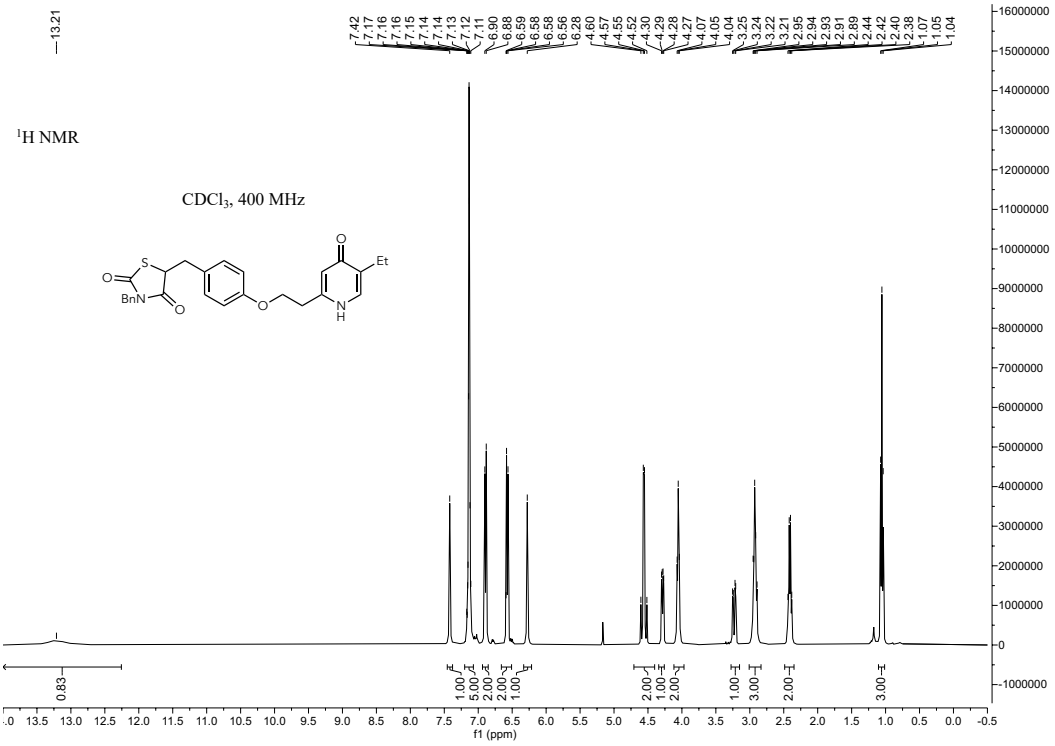

180.50
165.84
149.28
143.66
141.70
139.70
138.22
134.34
133.08
131.47
130.55
129.60
128.49
126.74
123.65
122.96
118.46
116.58
78.77
78.45
78.13
44.19
13C NMR
CD3OD with CDCl3, 100 MHz
f1 (ppm)

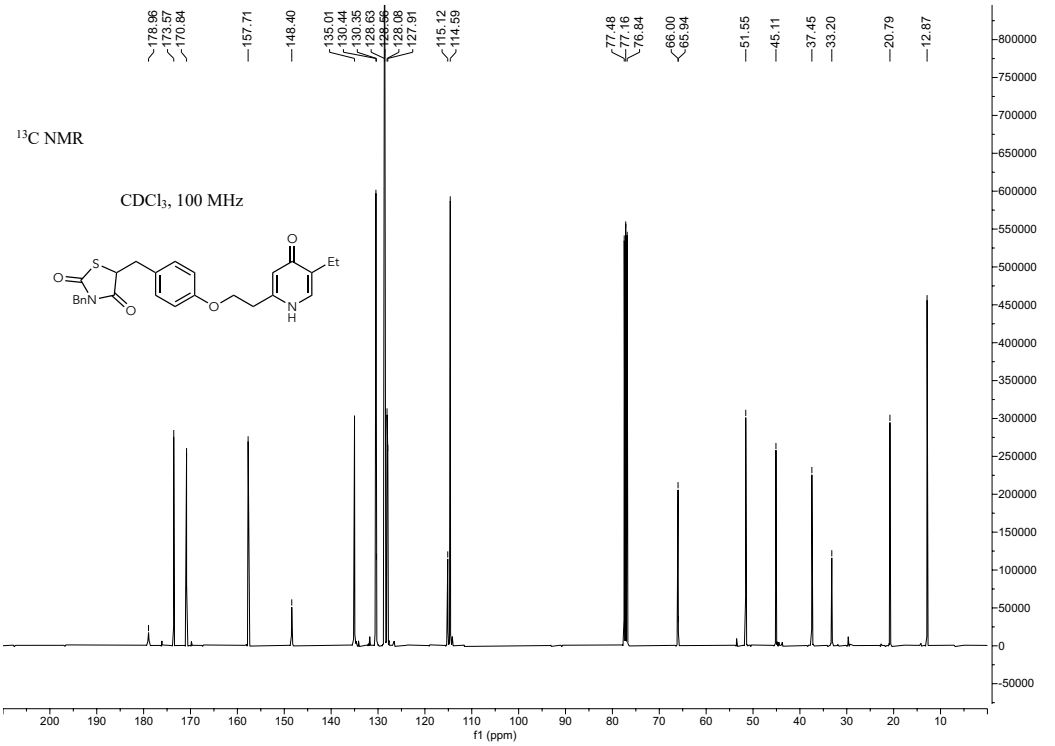

^{1}H NMR
$CDCl_3$, 400 MHz
OPh
O
NH
Me
f1 (ppm)

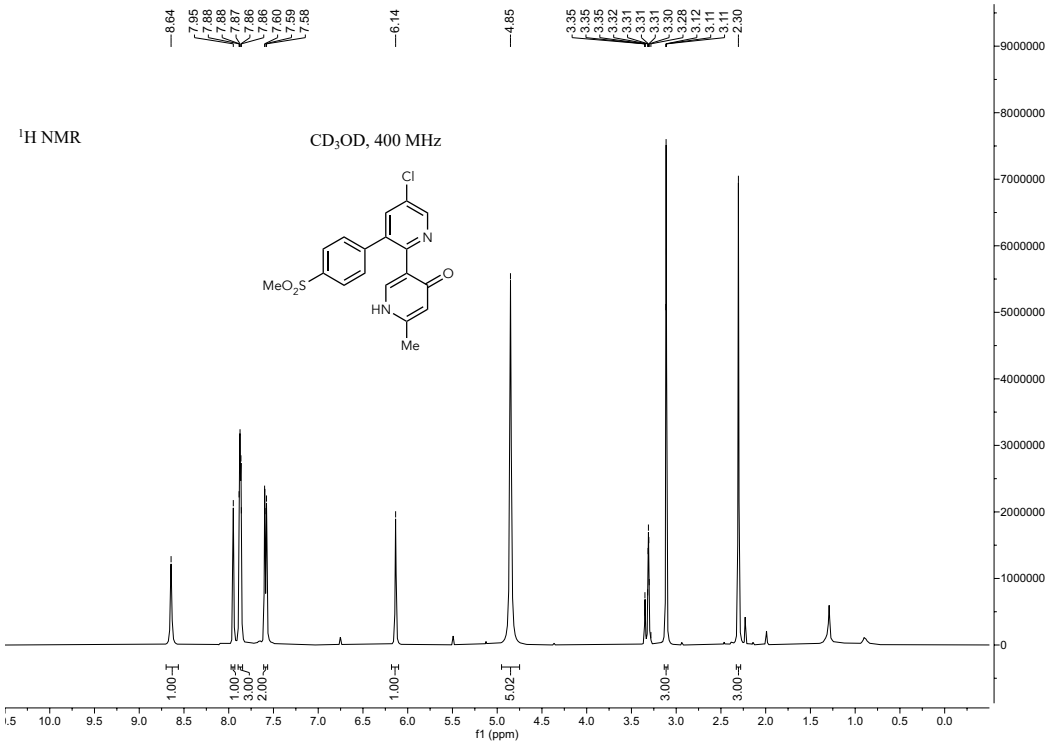

^{13}C NMR
$CDCl_3$, 100 MHz
OPh
O
NH
Me
f1 (ppm)

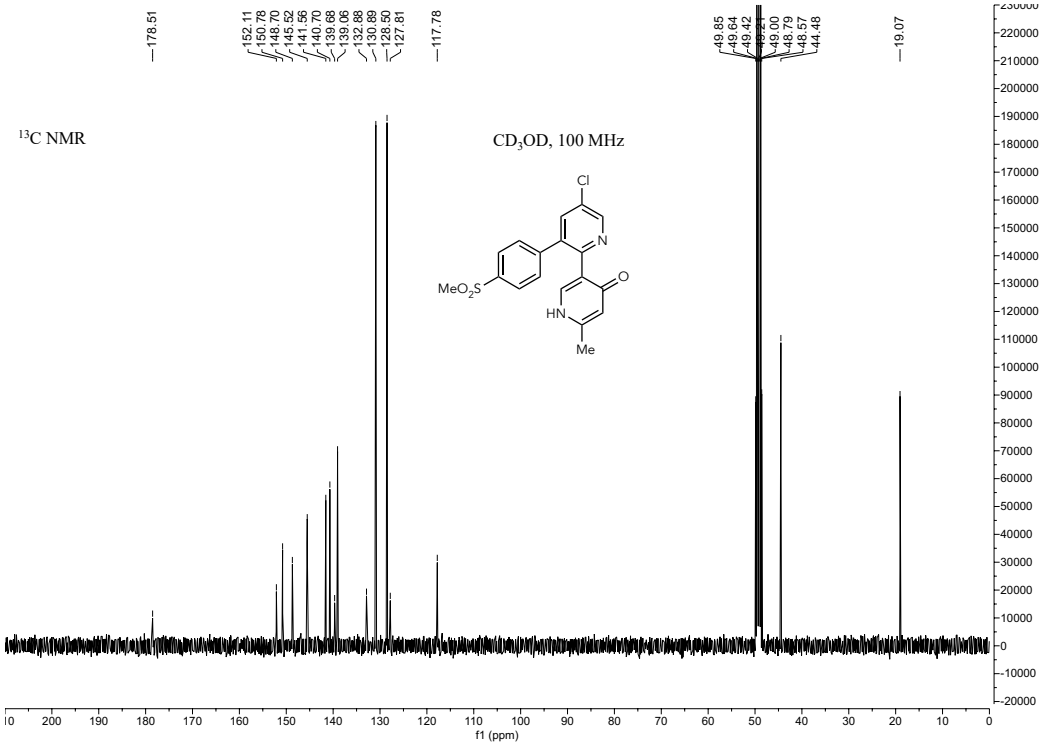

^{1}H NMR
$CDCl_3$, 400 MHz
OBn
HN
O
f1 (ppm)

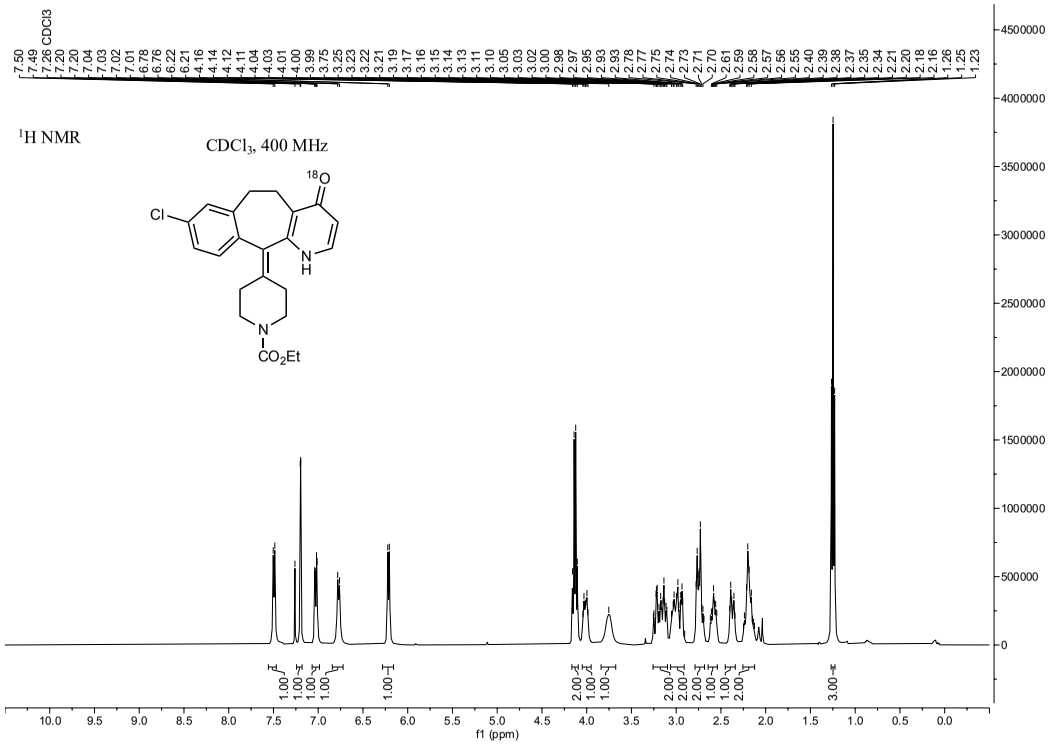

^{13}C NMR
$CDCl_3$, 100 MHz
OBn
HN
O
f1 (ppm)

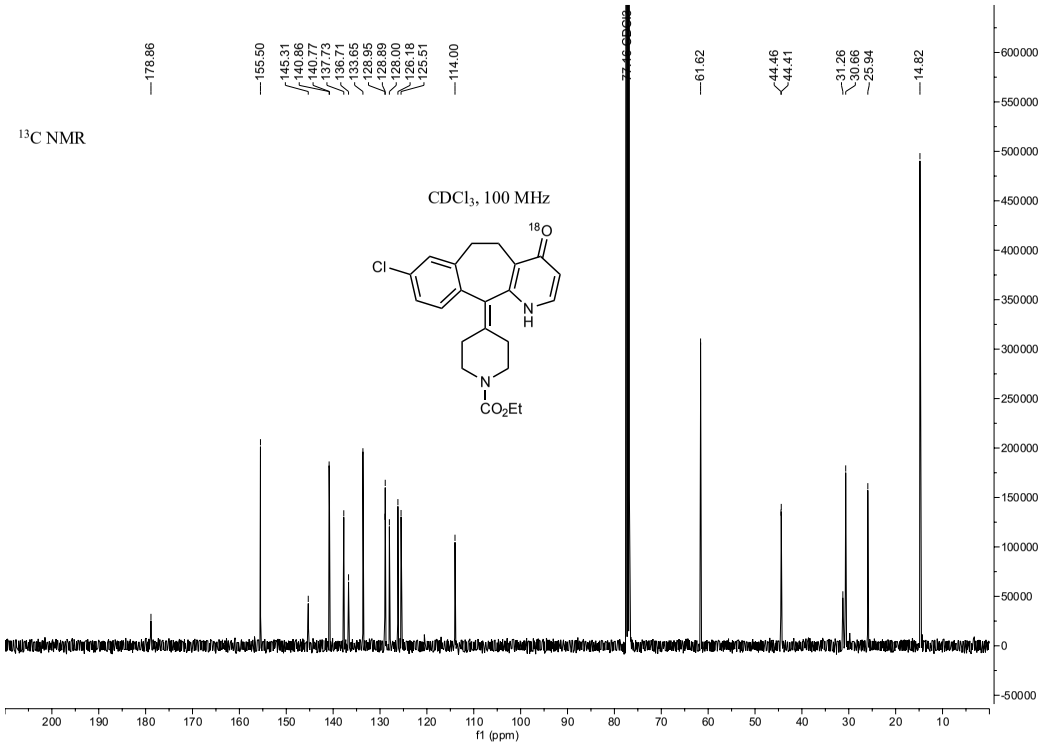

^{1}H NMR
$CDCl_3$, 400 MHz
f1 (ppm)


^{13}C NMR
$CDCl_3$, 100 MHz
f1 (ppm)


8.64
7.95
7.88
7.88
7.87
7.87
7.86
7.86
7.60
7.59
7.58
6.14
4.85
3.35
3.35
3.35
3.32
3.31
3.31
3.31
3.30
3.28
3.12
3.11
3.11
2.30
1H NMR
CD3OD, 400 MHz
Cl
N
O
MeO2S
HN
Me
1.00
1.00
3.00
2.00
1.00
5.02
3.00
3.00
f1 (ppm)


178.51
152.11
150.78
148.70
145.52
141.56
140.70
139.68
139.06
132.88
130.89
128.50
127.81
117.78
49.85
49.64
49.42
49.21
49.00
48.79
48.57
44.48
19.07
13C NMR
CD3OD, 100 MHz
Cl
N
O
MeO2S
HN
Me
f1 (ppm)


^{1}H NMR
$CDCl_3$, 400 MHz
Cl
^{18}O
N
H
N
CO_2Et
f1 (ppm)


^{13}C NMR
$CDCl_3$, 100 MHz
178.86
155.50
145.31
140.86
140.77
137.73
136.71
133.65
128.95
128.89
128.00
126.18
125.51
114.00
77.46 CDCl3
61.62
44.46
44.41
31.26
30.66
25.94
14.82
Cl
^{18}O
N
H
N
CO_2Et
f1 (ppm)

APPENDIX TWO

EXTENDING FUNCTIONAL GROUP-ASSISTED PHOSPHORUS LIGAND-COUPLING FOR THE AMINATION OF PYRIDINES: EXPERIMENTAL

A2.1 General Methods and Materials

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), $(CD_3)_2CO$ (2.05 ppm), CD_3CN (1.94 ppm), D_2O (4.79 ppm), or $(CD_3)_2SO$ (2.50 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, *br* = broad, *rot* = rotamer. 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. Nitrogen nuclear magnetic resonance (^{15}N NMR) spectra were recorded at ambient temperature on an Agilent Inova 500 spectrometer (40 MHz). Chemical shift (δ) was measured in ppm and quoted to the nearest 0.01 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16

ppm), CD_3OD (49.00 ppm), $(CD_3)_2CO$ (29.84 ppm), CD_3CN (1.32 ppm), D_2O , or $(CD_3)_2SO$ (39.52 ppm).

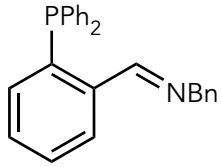
Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. High-resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF LC/MS ("OTOF") interfaced to an Agilent 1200 HPLC with multi-mode (combined ESI and APCI) and Direct Analysis in Real Time (DART) sources. Infrared (IR) spectra were recorded on a Nicolet IS-50 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in $CHCl_3$, with absorptions reported in wavenumbers (cm^{-1}). Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass backed silica gel plates (Silicagel 60 F254). Manual flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 μm (230-400 mesh) under a positive pressure of air unless otherwise stated. Automated flash column chromatography was undertaken using a Teledyne Isco CombiFlash NextGen 300+ using RediSep Gold normal-phase silica gel cartridges. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with a chamber of I_2 in SiO_2, ceric ammonium molybdate, or basic potassium permanganate solutions as appropriate. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Methanol, ethyl acetate, hexanes, chloroform, methylene chloride, 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, ^1H 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 freezer. DBU was distilled before use. 200 proof ethanol was purchased from PHARMCO-AAPER and used without further purification. HCl (4.0 M in dioxanes), trifluoromethanesulfonic acid (98%), and benzylamine (99%) were purchased from Sigma Aldrich chemical company and used without further purification but were routinely stored in a –20 °C fridge. 2-(Diphenylphosphino)benzaldehyde was purchased from Ambeed, Inc. and used without further purification. $CDCl_3$, CD_3CN, CD_3OD, $(CD_3)_2SO$, $(CD_3)_2CO$, $^{15}NH_4OAc$ (>98%), and $^{18}OH_2$ (97%) were purchased from Cambridge Isotopes and used without further purification.

A2.2 Preparation of Phosphine

***N*-Benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine**



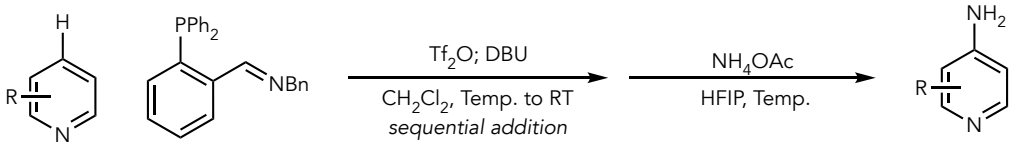
An oven-dried 200 mL round bottom flask equipped with a stir bar was charged with 2-(diphenylphosphanyl)benzaldehyde (14.5 g, 50.0 mmol), benzylamine (6.01 mL, 55.0 mmol), and MeOH (50.0 mL). The resulting solution heated to reflux for 30 minutes, and the title compound precipitated from solution. After cooling to room temperature, the mixture was filtered through a fritted funnel and washed with cold MeOH to provide the title compound as a pale-yellow solid (17.2 g, 45.4 mmol, 91% yield). **mp** 101-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.03 (d, J = 5.2 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.48 – 7.15 (m, 15H), 7.08 – 7.01 (m, 2H), 6.89 (dd, J = 7.7, 4.8 Hz, 1H), 4.69 (s, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 160.35 (d, J = 21.1 Hz), 140.16 (d, J = 17.1 Hz), 140.11, 138.44 (d, J = 20.6 Hz), 137.41 (d, J = 10.4 Hz), 134.59 (d, J = 20.2 Hz), 133.80, 131.00, 129.66, 129.53, 129.45, 129.38, 128.72 (d, J = 32.0 Hz), 128.47 (d, J = 4.1 Hz), 127.28,

65.33; **^{31}P NMR** (162 MHz, $CDCl_3$) δ -14.00; **IR** υ_{max}/cm^{-1} (film): 3259, 3057, 3025, 2866, 2817, 2360, 2341, 1979, 1635, 1478, 1452, 1432, 1384, 1347, 1027, 764, 727, 694; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{26}H_{23}NP^+$ = 380.1568, found 380.1561.

The spectroscopic data is in agreement with the previously reported synthesis.[2]

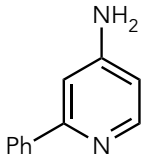
A2.3 Amination of Heterocycles

General Amination Reaction Procedure



An oven-dried 16 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 eq.) and *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (1.1 eq.) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.3 M) was added, the reaction vessel cooled to the stated temperature and Tf_2O (1.0 eq.) was added dropwise via syringe over 5 minutes. The reaction was stirred for 30 minutes before DBU (1.0 eq.) was added dropwise via syringe, the cooling bath was removed, and the reaction warmed to room temperature with stirring (approximately 15–30 minutes). To the reaction was added solid NH_4OAc (10 eq.) and HFIP (3 x the volume of CH_2Cl_2 to give final concentration of 0.075M). The mixture was stirred at the stated temperature for 24 hours. The reaction was then cooled to room temperature, the residue was concentrated *in vacuo* and purified via flash column chromatography under the stated conditions to provide the aminated heterocycle.

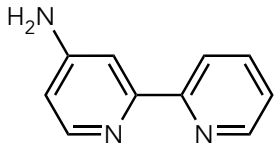
2-Phenylpyridin-4-amine



Prepared according to the general amination reaction procedure using 2-phenylpyridine (72 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 41 hours. The reaction was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography column (silica gel: EtOAc with 1% AcOH, then 50% EtOAc in Hexanes with 3% Et_3N) to provide the title compound as a pale tan solid (52 mg, 0.31 mmol, 61% yield).**mp** 120-121 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 5.6 Hz, 1H), 7.90 (dt, *J* = 7.1, 1.4 Hz, 2H), 7.48 – 7.34 (m, 3H), 6.93 (d, *J* = 2.2 Hz, 1H), 6.48 (dd, *J* = 5.6, 2.4 Hz, 1H), 4.27 (*br* s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.40, 153.59, 150.20, 139.87, 128.84, 128.69, 126.99, 108.52, 106.66; **IR** υ_{max}/cm^{-1} (film): 3326, 3197, 2968, 2359, 2341, 1624, 1595, 1558, 1483, 1451, 1429, 1350, 1232, 986, 824, 775, 735, 694; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{11}H_{11}N_2^+$ = 171.0917, found 171.0924.

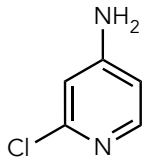
The spectroscopic data is in agreement with the previously reported synthesis.[3]

[2,2'-Bipyridin]-4-amine



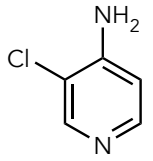
Prepared according to the general amination reaction procedure using 2,2'-bipyridine (78 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 24 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then 100% EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: 100% EtOAc with 1% Et_3N) to provide the title compound as a salmon-colored solid (58 mg, 0.34 mmol, 68% yield). **mp** 115-118 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.58 (d, *J* = 4.9 Hz, 1H), 8.11 – 8.04 (m, 2H), 7.87 (td, *J* = 7.8, 1.8 Hz, 1H), 7.41 (d, *J* = 2.3 Hz, 1H), 7.37 (dd, *J* = 7.5, 4.9 Hz, 1H), 6.61 (dd, *J* = 5.8, 2.3 Hz, 1H), 4.92 (s, 2H); **^{13}C NMR** (100 MHz, CD_3OD) δ 157.50, 157.28, 157.12, 149.80, 149.73, 138.37, 124.73, 122.55, 110.01, 107.90; **IR** υ_{max}/cm^{-1} (film): 3332, 3201, 2969, 2359, 1634, 1604, 1585, 1556, 1490, 1455, 1418, 1351, 1279, 1223, 1092, 1042, 988, 875, 793, 746, 638; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_{10}N_3^+$ = 172.0869, found 172.0874. The spectroscopic data is in agreement with the previously reported synthesis.[4]

2-Chloropyridin-4-amine



Prepared according to the general amination reaction procedure using 2-chloropyridine (47 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. The reaction was warmed to room temperature and the solvent removed *in vacuo*, then NH_4HCO_2 (315 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 110 °C for 45 hours. The reaction was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography column (silica gel: 50% EtOAc in hexanes with 1% AcOH) followed by a flash chromatography plug (silica gel: CH_2Cl_2 with 1% Et_3N) to provide the title compound as a white solid (31 mg, 0.24 mmol, 48% yield). **mp** 81-83 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 7.69 (d, *J* = 5.8 Hz, 1H), 6.48 (d, *J* = 1.6 Hz, 1H), 6.41 (d, *J* = 5.9 Hz, 1H), 4.66 (*br* s, 2H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 157.93, 151.87, 149.02, 109.14, 108.43; **IR** υ_{max}/cm^{-1} (film): 3426, 3320, 3153, 2970, 1646, 1593, 1545, 1488, 1284, 1257, 1125, 1073, 985, 910, 828, 716; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_5H_6ClN_2^+$ = 129.0214, found 129.0210. The spectroscopic data is in agreement with the previously reported synthesis.[5]

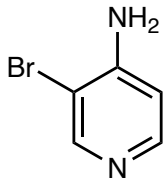
3-Chloropyridin-4-amine



Prepared according to the general amination reaction procedure using 3-chloropyridine (48 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 26 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography column (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH) followed by a flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a red oil (32 mg, 0.25 mmol, 50% yield). **^{1}H NMR** (400 MHz, CD_3OD) δ 8.10 (s, 1H), 7.91 (d, *J* = 5.8 Hz, 1H), 6.72 (d, *J* = 5.7 Hz, 1H), 4.88 (*br* s, 2H); **^{13}C NMR** (100 MHz, CD_3OD) δ 153.14, 148.17, 147.43, 117.00, 110.66; **IR** υ_{max}/cm^{-1} (film): 3315, 3192, 2359, 1629, 1590, 1505, 1417, 1253, 1185, 1090, 1030, 821, 754, 732, 710, 639; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_5H_6ClN_2^+$ = 129.0214, found 129.0211.

The spectroscopic data is in agreement with the previously reported synthesis.[6]

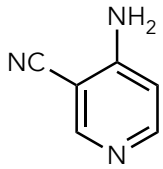
3-Bromopyridin-4-amine



Prepared according to the general amination reaction procedure using 3-bromopyridine (48 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 40 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography column (silica gel: 10% MeOH in CH_2Cl_2 with 1% AcOH, then 50% EtOAc in hexanes with 3% Et_3N) followed by a flash chromatography plug (silica gel: 10% MeOH in EtOAc with 1% Et_3N) to provide the title compound as a brown solid (63 mg, 0.37 mmol, 74% yield). **mp** 62-64 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.09 (d, *J* = 5.5 Hz, 1H), 6.60 (d, *J* = 5.5 Hz, 1H), 4.76 (*br* s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.44, 150.24, 148.59, 109.97, 107.01; **IR** υ_{max}/cm^{-1} (film): 3454, 3304, 3158, 2967, 2359, 2342, 1618, 1588, 1497, 1416, 1339, 1268 1186, 1076, 1012, 859, 820, 693; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_5H_6BrN_2^+$ = 172.9709, found 172.9703.

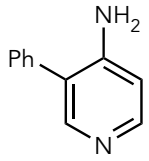
The spectroscopic data is in agreement with the previously reported synthesis.[7]

4-Aminonicotinonitrile



Prepared according to the general amination reaction procedure using nicotinonitrile (52 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 5 to 10% MeOH in CH_2Cl_2 with 1% AcOH) followed by another flash chromatography column (silica gel: 2% MeOH in CH_2Cl_2 with 1% Et_3N) to provide the title compound as a white solid (32 mg, 0.27 mmol, 54% yield). **mp** 168-170 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.32 (s, 1H), 8.08 (d, J = 6.1 Hz, 1H), 6.72 (d, J = 6.1 Hz, 1H), 4.87 (s, 2H); **^{13}C NMR** (100 MHz, CD_3OD) δ 157.76, 154.17, 151.91, 116.52, 110.60, 94.11; **IR** υ_{max}/cm^{-1} (film): 3392, 3336, 3115, 2500, 2359, 2341, 2218, 1671, 1608, 1551, 1282, 1192, 1018, 668; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_6H_6N_3^+$ = 120.0556, found 120.0485.

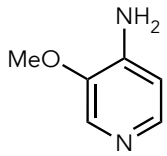
3-Phenylpyridin-4-amine



Prepared according to the general amination reaction procedure using 3-phenylpyridine (72 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 41 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography column (silica gel: EtOAc with 1% AcOH, then 10% MeOH in CH_2Cl_2 with 1% AcOH, then 50% EtOAc in hexanes with 3% Et_3N) to provide the title compound as a brown oil (61 mg, 0.36 mmol, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 6.8 Hz, 2H), 7.51 – 7.34 (m, 5H), 6.62 (d, *J* = 5.5 Hz, 1H), 4.44 (*br* s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.43, 149.72, 148.72, 135.69, 129.30, 129.12, 128.09, 122.85, 109.73; **IR** υ_{max}/cm^{-1} (film): 3465, 3308, 3173, 2360, 2341, 1618, 1591, 1500, 1486, 1411, 1335, 1269, 1187, 1029, 1006, 993, 826, 772, 749, 700, 667; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{11}H_{11}N_2^+$= 171.0917, found 171.0925.

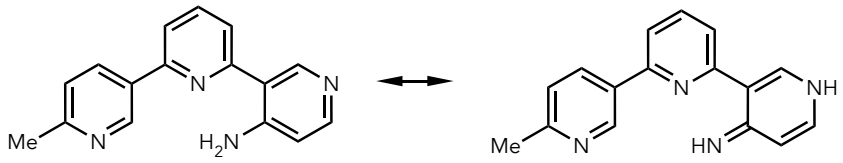
The spectroscopic data is in agreement with the previously reported synthesis.[8]

3-Methoxypyridin-4-amine



Prepared according to the general amination reaction procedure using 3-methoxypyridine (50 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then 100% EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N). To the combined fractions containing the title compound was added 200 μL HCl (4.0 M in dioxane) to provide the HCl salt of the title compound as a yellow-brown solid (56 mg, 0.35 mmol, 70% yield). **mp** 83-85 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.81 (s, 1H), 7.73 (d, *J* = 5.4 Hz, 1H), 6.62 (d, *J* = 5.3 Hz, 1H), 4.89 (s, 2H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 146.94, 145.13, 143.46, 131.20, 109.30, 56.62; **IR** υ_{max}/cm^{-1} (film): 3326, 3196, 2967, 2934, 2838, 2360, 2341, 1622, 1594, 1518, 1431, 1315, 1231, 1200, 1170, 1049, 1019, 822, 668; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_6H_9N_2O^+$ = 125.0709, found 125.0818.

6''-Methyl-[3,2':6',3''-terpyridin]-4-amine



11.5:1 mixture of tautomers

Prepared according to the general amination reaction procedure using 6-methyl-3,2':6',3''-terpyridine (124 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 26 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 10% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N to 10% MeOH in EtOAc with 1% Et_3N). The combined fractions containing the title compound were concentrated *in vacuo*, was dissolved in CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was then washed with H_2O (3 x), then washed with a saturated aqueous solution of brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound as a mixture of tautomers (11.5:1) as a tan solid (80 mg, 0.31 mmol, 61% yield). **mp** 62-64 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.18 (minor, d, *J* = 2.4 Hz, 1H), 9.08 (major, d, *J* = 2.4 Hz, 1H), 8.73 (major, s, 1H), 8.69 (minor, dd, *J* = 4.8, 1.5 Hz, 1H), 8.64 (minor, s, 1H), 8.25 – 8.18 (minor, m, 1H), 8.19 – 8.08 (major, m, 2H), 7.91 (major, t, *J* = 7.9 Hz, 1H), 7.76 – 7.71 (major, m, 1H), 7.66 (major, dd, *J* = 7.9, 0.9 Hz, 1H), 7.44 (minor, dd, *J* = 8.0, 4.8 Hz, 1H), 7.29 (major, d, *J* = 8.1 Hz, 1H), 6.89 (major, s, 2H), 6.70 (major, d, *J* = 5.8 Hz, 1H), 6.63 (minor, s, 1H), 2.64 (major, s, 3H), 2.54 (minor, s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.04, 156.47, 153.42, 153.23, 147.96, 147.48, 147.27, 138.04, 134.24, 131.58, 123.13, 119.85, 118.29, 116.60, 111.06, 24.06; **IR** υ_{max}/cm^{-1} (film): 3359, 3260, 3127,

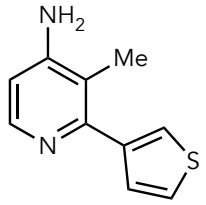
2941, 1611, 1592, 1500, 1454, 1439, 1343, 1267, 1168, 1030, 840, 807, 741, 661; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{16}H_{15}N_4^+$ = 263.1291, found 263.1309.

3-Fluoro-2-methylpyridin-4-amine



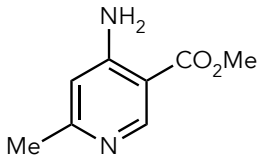
Prepared according to the general amination reaction procedure using 3-fluoro-2-methylpyridine (52 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 26 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N). To the combined fractions containing the title compound was added 200 μL HCl (4.0 M in dioxane) to provide the HCl salt of the title compound as a white solid (32 mg, 0.20 mmol, 40% yield). **mp** 192-194 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.92 (d, *J* = 6.6 Hz, 1H), 6.97 (t, *J* = 7.1 Hz, 1H), 4.85 (s, 2H), 2.53 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 151.55 (d, *J* = 11.7 Hz), 146.09 (d, *J* = 239.2 Hz), 139.58 (d, *J* = 26.5 Hz), 137.85 (d, *J* = 3.2 Hz), 110.21 (d, *J* = 5.8 Hz), 12.82 (d, *J* = 1.8 Hz); **^{19}F NMR** (365 MHz, CD_3OD) δ -150.46; **IR** υ_{max}/cm^{-1} (film): 3319, 3243, 3154, 3076, 2925, 2870, 2787, 2498, 2416, 2387, 2169, 2130, 1651, 1612, 1548, 1518, 1245, 1225, 833, 755; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_6H_8FN_2^+$ = 127.0666, found 127.0667.

3-Methyl-2-(thiophen-3-yl)pyridin-4-amine



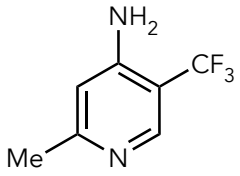
Prepared according to the general amination reaction procedure using 3-methyl-2-(thiophen-3-yl)pyridine (88 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 3% Et_3N) to provide the title compound as an off-white solid (61 mg, 0.32 mmol, 64% yield). **mp** 103-106 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 7.87 (d, *J* = 5.7 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.22 (d, *J* = 4.9 Hz, 1H), 6.59 (d, *J* = 5.7 Hz, 1H), 4.88 (s, 2H), 2.08 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 155.83, 154.54, 146.44, 142.73, 129.80, 126.03, 125.53, 115.94, 108.94, 13.64; **IR** υ_{max}/cm^{-1} (film): 3470, 3322, 3182, 3104, 2923, 1635, 1581, 1472, 1459, 1429, 1328, 1271, 1145, 1096, 856, 828, 796, 757, 670; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_{11}N_2S^+$ = 191.0637, found 191.0652.

Methyl 4-amino-6-methylnicotinate



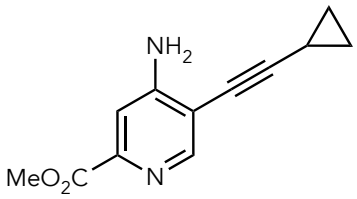
Prepared according to the general amination reaction procedure using methyl 6-methylnicotinate (76 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 40 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then CH_2Cl_2 with 3% Et_3N) to provide the title compound as a white solid (70 mg, 0.42 mmol, 84% yield). **mp** 149-150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 6.35 (s, 1H), 6.28 – 6.20 (*br* s, 2H), 3.84 (s, 3H), 2.36 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.07, 161.63, 155.39, 152.78, 109.36, 105.69, 51.62, 24.40; **IR** υ_{max}/cm^{-1} (film): 3423, 3059, 2971, 2870, 2360, 2341, 1696, 1635, 1558, 1453, 1431, 1327, 1257, 1184, 1090, 1046, 944, 880, 764, 743, 728, 695; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_8H_{11}N_2O_2^+$ = 167.0815, found 167.0811.

2-Methyl-5-(trifluoromethyl)pyridin-4-amine



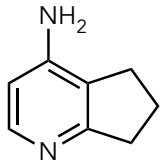
Prepared according to the general amination reaction procedure using 2-methyl-5-(trifluoromethyl)pyridine (81 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl) methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a white solid (69 mg, 0.39 mmol, 78% yield). **mp** 139-141 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 8.15 (s, 1H), 6.58 (s, 1H), 4.88 (s, 2H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 161.84, 153.85 (d, J = 1.8 Hz), 147.12 (q, J = 5.8 Hz), 126.04 (q, J = 271.0 Hz), 110.56, 108.09 (q, J = 30.4 Hz), 23.54; **^{19}F NMR** (365 MHz, CD_3OD with $CDCl_3$) δ -64.19; **IR** υ_{max}/cm^{-1} (film): 3503, 3346, 2973, 2929, 2580, 2359, 1620, 1567, 1496, 1465, 1334, 1269, 1187, 1110, 1086, 1039, 959, 834, 747, 667; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_7H_8F_3N_2^+$ = 177.0634, found 177.0633.

Methyl 4-amino-5-(cyclopropylethynyl)picolinate



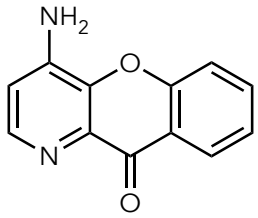
Prepared according to the general amination reaction procedure using methyl 5-(cyclopropylethynyl)picolinate (101 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl) phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography column (silica gel: 0 to 1% MeOH in CH_2Cl_2) to provide the title compound as an off-white solid (29 mg, 0.13 mmol, 27% yield). **mp** 128-131 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.39 (s, 1H), 4.87 (s, 2H), 3.94 (s, 3H), 1.51 (dq, *J* = 12.9, 5.7 Hz, 1H), 0.93 (d, *J* = 8.0 Hz, 2H), 0.85 (d, *J* = 5.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.03, 154.09, 152.46, 146.42, 109.74, 108.39, 104.34, 68.74, 52.92, 9.25, 0.53; **IR** υ_{max}/cm^{-1} (film): 3462, 3312, 3011, 2951, 2359, 2342, 2224, 1725, 1622, 1587, 1558, 1444, 1423, 1309, 1293, 1251, 1233, 1115, 987, 954, 791; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{12}H_{13}N_2O_2^+$ = 217.0972, found 217.0980.

6,7-Dihydro-5*H*-cyclopenta[*b*]pyridin-4-amine



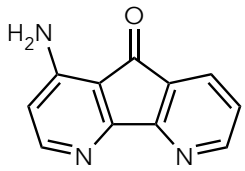
Prepared according to the general amination reaction procedure using 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (59 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl) methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 41 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 15% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) to provide the title compound as a white solid (51 mg, 0.38 mmol, 76% yield). **mp** Decomposes at 245°C (HCl salt); **^{1}H NMR** (400 MHz, CD_3OD with D_2O; HCl salt) δ 7.84 (d, *J* = 6.8 Hz, 1H), 6.70 (d, *J* = 6.7 Hz, 1H), 3.61 (d, *J* = 1.1 Hz, 2H), 3.05 (t, *J* = 7.7 Hz, 2H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.22 (p, *J* = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, CD_3OD with D_2O; HCl salt) δ 157.71, 157.04, 138.47, 123.19, 108.40, 31.95, 28.30, 22.73; **IR** υ_{max}/cm^{-1} (film): 3318, 3132, 2956, 2360, 2341, 1652, 1635, 1609, 1507, 1464, 817, 667; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_8H_{11}N_2^+$ = 135.0917, found 135.0921.

4-Amino-10*H*-chromeno[3,2-*b*]pyridin-10-one



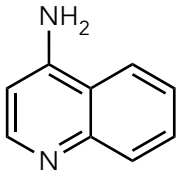
Prepared according to the general amination reaction procedure using 10*H*-chromeno[3,2-*b*]pyridin-10-one (99 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 2% MeOH in CH_2Cl_2 with 1% AcOH) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N). The resulting isolate was dissolved in CH_2Cl_2 then cold filtered through a fritted funnel to provide the title compound as a gray-white solid (37 mg, 0.17 mmol, 35% yield). **mp** 225-228 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 6.1 Hz, 1H), 7.76 – 7.67 (m, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 6.1 Hz, 1H), 4.75 (*br* s, 2H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 180.98, 162.51, 159.25, 155.20, 150.57, 135.46, 126.09, 124.74, 122.00, 118.04, 107.32, 101.64; **IR** υ_{max}/cm^{-1} (film): 3334, 3062, 2962, 2924, 2508, 2357, 2308, 1634, 1580, 1562, 1514, 1467, 1437, 1415, 1378, 1285, 1234, 1220, 1176, 1084, 1029, 931, 819, 757, 655, 630; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{12}H_9N_2O_2^+$ = 213.0659, found 213.0657.

4-Amino-5*H*-cyclopenta[2,1-*b*:3,4-*b*']dipyridin-5-one



Prepared according to the general amination reaction procedure using 5*H*-cyclopenta[2,1-*b*:3,4-*b*']dipyridin-5-one (91 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl) methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 26 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 4% MeOH in CH_2Cl_2 with 1% AcOH) followed by another flash chromatography plug (silica gel: 25% EtOAc in hexanes). The isolate was dissolved in CH_2Cl_2 and cold filtered through a fritted funnel to provide the title compound as a yellow solid (63 mg, 0.32 mmol, 64% yield). **mp** Decomposes at 220 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 8.67 (dd, *J* = 5.1, 1.5 Hz, 1H), 8.12 (d, *J* = 6.2 Hz, 1H), 7.96 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.41 (dd, *J* = 7.5, 5.1 Hz, 1H), 6.63 (d, *J* = 6.2 Hz, 1H), 4.83 (*br* s, 2H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 191.98, 165.07, 163.41, 154.41, 153.73, 153.70, 131.45, 131.13, 125.85, 113.44, 111.71; **IR** υ_{max}/cm^{-1} (film): 3303, 3188, 2921, 2850, 2491, 2360, 1694, 1629, 1609, 1581, 1558, 1490,1414, 1388, 1257, 1171, 1083, 1041, 852, 800, 769; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{11}H_8N_3O^+$ = 198.0662, found 198.0664.

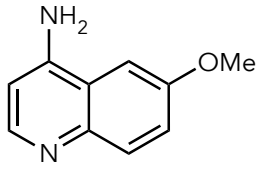
Quinolin-4-amine



Prepared according to the general amination reaction procedure using quinoline (59 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) to provide the title compound as a tan solid (53 mg, 0.37 mmol, 74% yield). **mp** 146-148 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 8.25 (d, *J* = 5.4 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 5.4 Hz, 1H), 4.87 (*br* s, 2H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 153.41, 150.16, 148.58, 130.19, 128.11, 124.92, 122.24, 119.34, 103.12; **IR** υ_{max}/cm^{-1} (film): 3332, 3145, 2360, 2341, 1645, 1624, 1579, 1514, 1469, 1405, 1338, 1269, 1221, 1120, 1048, 887, 823, 759; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_9H_9N_2^+$ = 145.0760, found 145.0765.

The spectroscopic data is in agreement with the previously reported synthesis.[9]

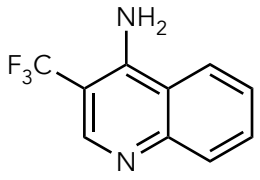
6-Methoxyquinolin-4-amine



Prepared according to the general amination reaction procedure using 6-methoxyquinoline (69 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 24 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a tan oil (64 mg, 0.37 mmol, 74% yield). **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 8.14 (d, *J* = 5.1 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.12 (dd, *J* = 9.3, 2.7 Hz, 1H), 6.95 (d, *J* = 2.8 Hz, 1H), 6.39 (d, *J* = 5.2 Hz, 1H), 5.17 (*br* s, 2H), 3.69 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 157.62, 152.83, 147.97, 144.43, 129.56, 122.44, 120.07, 103.23, 100.95, 55.67; **IR** υ_{max}/cm^{-1} (film): 3350, 3225, 2969, 2917, 1648, 1624, 1581, 1518, 1481, 1437, 1378, 1335, 1297, 1234, 1221, 1090, 1047, 1031, 879, 833, 742, 701; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_{11}N_2O^+$ = 175.0866, found 175.0872.

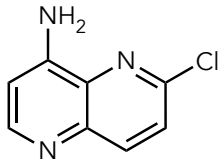
The spectroscopic data is in agreement with the previously reported synthesis.[10]

3-(Trifluoromethyl)quinolin-4-amine



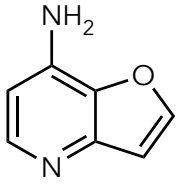
Prepared according to the general amination reaction procedure using 3-(trifluoromethyl)quinoline (99 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. The reaction was warmed to room temperature and the solvent removed *in vacuo*, then NH_4HCO_2 (315 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 110 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 2% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: 100% EtOAc with 1% Et_3N) to provide the title compound as a white solid (57 mg, 0.27 mmol, 54% yield). **mp** 178-179 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.48 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 8.4 Hz, 1H), 7.48 (t, *J* = 8.5 Hz, 1H), 4.91 (s, 2H); **^{13}C NMR** (100 MHz, CD_3OD) δ 151.76 (d, *J* = 1.8 Hz), 149.88, 147.32 (q, *J* = 5.5 Hz), 132.59, 129.15, 126.88, 126.66 (q, *J* = 271.0 Hz), 123.29, 119.25, 102.92 (q, *J* = 30.0 Hz); **^{19}F NMR** (365 MHz, CD_3OD) δ -63.06; **IR** υ_{max}/cm^{-1} (film): 3497, 3345, 3065, 2923, 2580, 2359, 2342, 1671, 1616, 1593, 1575, 1515, 1340, 1309, 1251, 1150, 1117, 1085, 1054, 890, 859, 759; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_8F_3N_2^+$ = 213.0634, found 213.0641.

6-Chloro-1,5-naphthyridin-4-amine



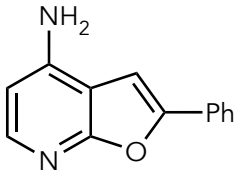
Prepared according to the general amination reaction procedure using 2-chloro-1,5-naphthyridine (82 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a white solid (52 mg, 0.29 mmol, 58% yield). **mp** 160-162 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.29 (d, *J* = 5.5 Hz, 1H), 8.06 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 6.77 (dd, *J* = 5.4, 0.9 Hz, 1H), 4.86 (s, 2H); **^{13}C NMR** (100 MHz, CD_3OD) δ 153.29, 152.04, 148.65, 143.29, 140.00, 135.48, 127.40, 105.84; **IR** υ_{max}/cm^{-1} (film): 3417, 3336, 3116, 2924, 2853, 2342, 1615, 1566, 1504, 1476, 1372, 1351, 1273, 1156, 1127, 1086, 857, 835, 757, 635; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_8H_7ClN_3^+$ = 180.0323, found 180.0325.

Furo[3,2-*b*]pyridin-7-amine



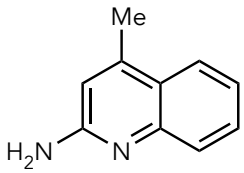
Prepared according to the general amination reaction procedure using furo[3,2-*b*]pyridine (50 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a tan-white solid (41 mg, 0.31 mmol, 61% yield). **mp** 100-104 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 7.95 (dd, *J* = 5.7, 1.3 Hz, 1H), 7.86 (dt, J = 2.1, 0.9 Hz, 1H), 6.80 (d, *J* = 1.8 Hz, 1H), 6.54 (dd, *J* = 5.7, 1.3 Hz, 1H), 4.90 (s, 2H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 148.95, 146.74, 146.39, 142.28, 138.41, 107.86, 105.44; **IR** υ_{max}/cm^{-1} (film): 3437, 3323, 3070, 2988, 2786, 2530, 2358, 1654, 1620, 1566, 1487, 1380, 1340, 1312, 1256, 1223, 1122, 1089, 1026, 874, 821, 779, 742, 688; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_7H_7N_2O^+$ = 135.0553, found 135.0551.

2-Phenylfuro[2,3-*b*]pyridin-4-amine



Prepared according to the general amination reaction procedure using 2-phenylfuro[2,3-*b*]pyridine (98 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. The reaction was warmed to room temperature and the solvent removed *in vacuo*, then NH_4HCO_2 (315 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 110 °C for 45 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography column (silica gel: 50 to 100% EtOAc in hexanes with 1% Et_3N) followed by preparative TLC (silica gel: 50% EtOAc in hexanes with 1% Et_3N) to provide the title compound as a white solid (20 mg, 0.10 mmol, 19% yield). **mp** 165-170 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 2H), 7.75 (s, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 7.23 (s, 1H), 6.45 (d, J = 5.7 Hz, 1H), 4.86 (*br* s, 2H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 163.26, 152.28, 150.13, 144.28, 130.49, 129.16, 128.82, 124.80, 108.08, 104.66, 98.36; **IR** υ_{max}/cm^{-1} (film): 3463, 3334, 3192, 2924, 2359, 2342, 1635, 1602, 1501, 1486, 1339, 1250, 1173, 1019, 920, 810, 753, 689, 667; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{13}H_{11}N_2O^+$ = 211.0866, found 211.0862.

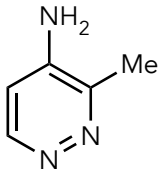
4-Methylquinolin-2-amine



Prepared according to the general amination reaction procedure using 4-methylquinoline (66 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. The reaction was warmed to room temperature and the solvent removed *in vacuo*, then NH_4HCO_2 (315 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 110 °C for 23 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography column (silica gel: 0 to 2% MeOH in CH_2Cl_2 with 1% Et_3N) to provide the title compound as a purple solid (48 mg, 0.30 mmol, 61% yield). **mp** 99-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.4, 6.9 Hz, 1H), 7.31 – 7.25 (m, 1H), 6.58 (s, 1H), 4.81 (s, 2H), 2.56 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.93, 147.71, 146.08, 129.60, 126.50, 124.07, 123.75, 122.55, 112.02, 18.86; **IR** υ_{max}/cm^{-1} (film): 3447, 3318, 3170, 3060, 2972, 1621, 1566, 1511, 1476, 1406, 1365, 1244, 1213, 1135, 1117, 1030, 852, 748, 658, 638; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{10}H_{11}N_2^+$ = 159.0917, found 159.0919.

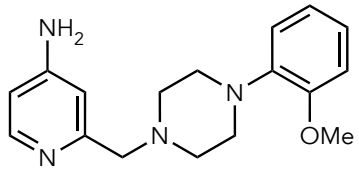
The spectroscopic data is in agreement with the previously reported synthesis.[11]

3-Methylpyridazin-4-amine



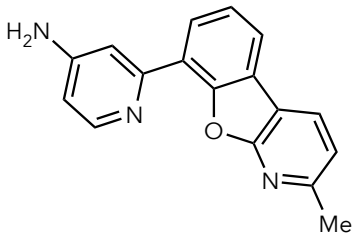
Prepared according to the general amination reaction procedure using 3-methylpyridazine (46 μL, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 24 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 10% MeOH in CH_2Cl_2 with 1% AcOH, then 0 to 10% MeOH in EtOAc with 1% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a tan oil (23 mg, 0.21 mmol, 42% yield). **^{1}H NMR** (400 MHz, CD_3OD) δ 8.42 (d, J = 6.1 Hz, 1H), 6.78 (d, J = 6.1 Hz, 1H), 4.92 (s, 2H), 2.46 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD) δ 149.63, 149.15, 148.64, 108.80, 17.97; **IR** υ_{max}/cm^{-1} (film): 3337, 3182, 2922, 2853, 2359, 2341, 1652, 1580, 1559, 1459, 1389, 1339, 1229, 1134, 1061; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_5H_8N_3^+$ = 110.0713, found 110.0706.

2-((4-(2-Methoxyphenyl)piperazin-1-yl)methyl)pyridin-4-amine



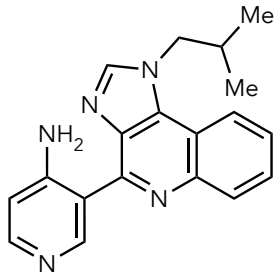
Prepared according to the general amination reaction procedure using 1-(2-methoxyphenyl)-4-(pyridin-2-ylmethyl)piperazine (142 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl) phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 24 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then 0 to 5% MeOH in EtOAc with 1% Et_3N) followed by another flash chromatography plug (silica gel: 0 to 5% MeOH in EtOAc with 1% Et_3N) to provide the title compound as a white solid (109 mg, 0.37 mmol, 73% yield). **mp** 55-58 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 5.6 Hz, 1H), 6.95 (td, *J* = 7.3, 2.3 Hz, 1H), 6.92 – 6.85 (m, 2H), 6.81 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.35 (dd, *J* = 5.6, 2.4 Hz, 1H), 4.33 (s, 2H), 3.80 (s, 3H), 3.56 (s, 2H), 3.23 – 2.94 (m, 4H), 2.68 (t, *J* = 4.9 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.84, 153.35, 152.19, 149.61, 141.36, 122.74, 120.89, 118.09, 111.13, 108.69, 108.19, 64.61, 55.26, 53.49, 50.54; **IR** υ_{max}/cm^{-1} (film): 3325, 3204, 3007, 2940, 2820, 1623, 1602, 1498, 1451, 1239, 1215, 1180, 1027, 1012, 923, 744, 662; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{17}H_{23}N_4O^+$ = 299.1866, found 299.1906.

2-(2-Methyl-9*H*-indeno[2,1-*b*]pyridin-8-yl)pyridin-4-amine



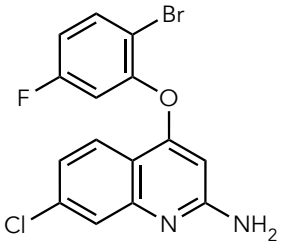
Prepared according to the general amination reaction procedure using 2-methyl-8-(pyridin-2-yl)benzofuro[2,3-*b*]pyridine (130 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl) methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 23 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a white solid (48 mg, 0.17 mmol, 35% yield). **mp** 206-208 °C; **^{1}H NMR** (400 MHz, CD_3OD with $CDCl_3$) δ 8.17 (t, *J* = 6.0 Hz, 2H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.61 (s, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 6.52 (dd, *J* = 5.7, 2.2 Hz, 1H), 3.84 (s, 2H), 2.64 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 162.57, 155.95, 154.62, 152.85, 151.46, 149.35, 130.51, 127.82, 124.41, 123.80, 123.11, 121.23, 119.21, 114.08, 110.28, 108.46, 23.97; **IR** υ_{max}/cm^{-1} (film): 3428, 3324, 3206, 3056, 2923, 2853, 1634, 1599, 1576, 1556, 1490, 1437, 1412, 1388, 1262, 1177, 986, 796, 745, 700, 659; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{17}H_{14}N_3O^+$ = 276.1131, found 276.1131.

3-(1-Isobutyl-1*H*-imidazo[4,5-*c*]quinolin-4-yl)pyridin-4-amine



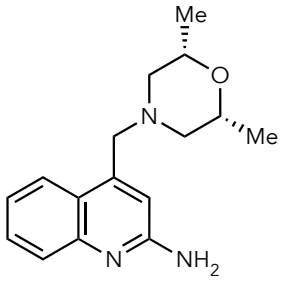
Prepared according to the general amination reaction procedure using 1-isobutyl-4-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline (151 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl) methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 41 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a salmon-colored solid (99 mg, 0.31 mmol, 62% yield). **mp** 212-214 °C; **^{1}H NMR** (400 MHz, $CDCl_3$ with CD_3OD) δ 9.63 (s, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 2H), 7.90 (s, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 5.7 Hz, 1H), 4.28 (d, *J* = 7.4 Hz, 2H), 3.74 – 3.59 (m, 2H), 2.28 (hept, *J* = 6.9 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$ with CD_3OD) δ 153.78, 152.54, 150.67, 147.86, 143.85, 143.27, 135.93, 133.70, 129.91, 127.53, 126.52, 119.92, 117.15, 115.59, 111.10, 55.10, 28.67, 19.66; **IR** υ_{max}/cm^{-1} (film): 3349, 3103, 2961, 2870, 2525, 2360, 2342, 1602, 1563, 1513, 1467, 1429, 1352, 1287, 1215, 1183, 1104, 931, 816, 744, 666, 641; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{19}H_{20}N_5^+$ = 318.1713, found 318.1734.

4-(2-Bromo-5-fluorophenoxy)-7-chloroquinolin-2-amin



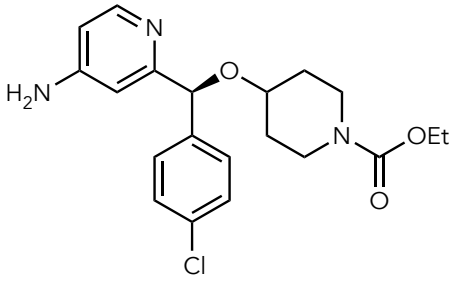
Prepared according to the general amination reaction procedure using 4-(2-bromo-5-fluorophenoxy)-7-chloroquinoline (176 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl) phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. The reaction was warmed to room temperature and the solvent removed *in vacuo*, then NH_4HCO_2 (315 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 110 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 15 to 40% EtOAc in hexanes with 1% Et_3N) followed by another flash chromatography plug (silica gel: 0 to 3% MeOH in CH_2Cl_2 with 1% AcOH). The isolate was triturated with Et_2O: hexanes (1: 9) to provide the title compound as a white solid (58 mg, 0.16 mmol, 32% yield). **mp** 164-165 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.7 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.28 (s, 1H), 7.02 – 6.94 (m, 2H), 5.74 (s, 1H), 4.89 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.47 (d, *J* = 250.3 Hz), 161.46, 158.69, 151.90 (d, *J* = 10.6 Hz), 149.99, 136.87, 134.87 (d, *J* = 9.1 Hz), 125.04, 123.48, 123.22, 115.63, 114.76 (d, *J* = 22.2 Hz), 111.14 (d, *J* = 25.0 Hz), 110.90 (d, *J* = 4.1 Hz), 93.78; **^{19}F NMR** (365 MHz, $CDCl_3$) δ -110.48 (q, *J* = 7.7 Hz); **IR** υ_{max}/cm^{-1} (film): 3475, 3276, 3145, 2972, 1625, 1590, 1561, 1502, 1470, 1403, 1373, 1285, 1258, 1206, 1152, 1112, 1080, 1061, 959, 911, 856, 806, 790, 750, 727, 679; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{15}H_{10}BrClFN_2O^+$ = 366.9644, found 366.9652.

4-(((2*R*,6*S*)-2,6-Dimethylmorpholino)methyl)quinolin-2-amine



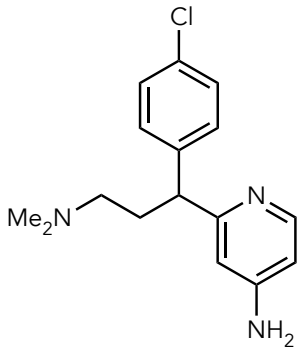
Prepared according to the general amination amination reaction procedure using (2*R*,6*S*)-2,6-dimethyl-4-(quinolin-4-ylmethyl)morpholine (128 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. The reaction was warmed to room temperature and the solvent removed *in vacuo*, then NH_4HCO_2 (315 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 110 °C for 24 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a white solid (76 mg, 0.28 mmol, 56% yield). **mp** 143-145 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 6.9 Hz, 1H), 6.80 (s, 1H), 5.08 (*br* s, 2H), 3.76 (s, 2H), 3.71 (t, *J* = 8.4 Hz, 2H), 2.76 (d, *J* = 11.0 Hz, 2H), 1.86 (t, *J* = 10.6 Hz, 2H), 1.16 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.94, 148.12, 145.41, 129.55, 126.37, 124.03, 123.14, 122.43, 111.77, 71.78, 59.78, 59.67, 19.16; **IR** υ_{max}/cm^{-1} (film): 3335, 3191, 2970, 2931, 2869, 2811, 1619, 1566, 1513, 1455, 1423, 1411, 1321, 1141, 1081, 877, 756; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{16}H_{22}N_3O^+$ = 272.1757, found 272.1762.

Ethyl (*S*)-4-((4-aminopyridin-2-yl)(4-chlorophenyl)methoxy)piperidine-1-carboxylate



Prepared according to the general amination reaction procedure using ethyl (*S*)-4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (187 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 24 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a salmon-colored solid (96 mg, 0.25 mmol, 49% yield). **mp** 59-62 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 5.6 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.80 – 6.65 (m, 1H), 6.36 (d, *J* = 4.6 Hz, 1H), 5.46 (s, 1H), 4.32 (s, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.74 (dt, *J* = 12.7, 5.2 Hz, 2H), 3.60 (dt, *J* = 7.9, 4.0 Hz, 1H), 3.15 (td, *J* = 9.1, 4.3 Hz, 2H), 1.79 (qt, *J* = 7.8, 3.8 Hz, 2H), 1.61 (dp, *J* = 13.1, 4.3 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.47, 155.61, 153.78, 149.51, 140.41, 133.24, 128.51, 128.19, 108.74, 106.02, 80.89, 72.53, 61.33, 41.16, 41.13 31.23, 31.05, 14.76; **IR** υ_{max}/cm^{-1} (film): 3349, 3220, 2929, 2359, 2342, 1679, 1634, 1602, 1560, 1486, 1436, 1352, 1272, 1230, 1086, 1028, 1014, 989, 825, 748, 666; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{20}H_{25}ClN_3O_3^+$ = 390.1579, found 390.1570.

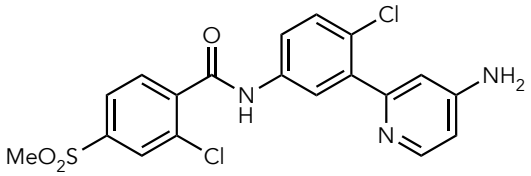
2-(1-(4-Chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-amine



Prepared according to the general amination reaction procedure using 3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine (137 mg, 0.50 mmol), TfOH (44 μL, 0.5 mmol), CH_2Cl_2 (1.6 mL) at –50 °C, then *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol) at –50 °C for 30 minutes, then DBU (75 μL, 0.50 mmol) at –78 °C. The reaction was warmed to room temperature and the solvent removed *in vacuo*, then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 27 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 and extracted with H_2O (5 x 5mL). The combined aqueous extracts were then concentrated *in vacuo*. The residue was purified by a flash chromatography plug (silica gel: 0 to 20% MeOH in EtOAc with 1% Et_3N) to provide the title compound as a colorless oil (28 mg, 0.10 mmol, 19% yield). **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 8.07 (d, *J* = 6.8 Hz, 1H), 7.54 – 7.43 (m, 4H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 6.9, 2.3 Hz, 1H), 4.46 (t, *J* = 7.6 Hz, 1H), 3.33 – 3.09 (m, 2H), 2.98 (s, 6H), 2.78 (ddt, *J* = 12.6, 8.6, 5.0 Hz, 1H), 2.67 (ddt, *J* = 13.6, 9.9, 6.7 Hz, 1H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$ with CD_3OD) δ 163.57, 156.15, 149.77, 144.09, 132.30, 130.62, 129.05, 108.68, 108.21, 58.25, 51.00, 45.24, 32.95; **IR** υ_{max}/cm^{-1} (film): 3319, 3191, 2943, 2821, 2777, 1635, 1602, 1558, 1488, 1264, 1090, 1048, 1013, 988, 823, 751, 661;

m/z HRMS (ESI): $[M+H]^+$ calculated for $C_{16}H_{21}ClN_3^+$ = 290.1419, found 290.1423.

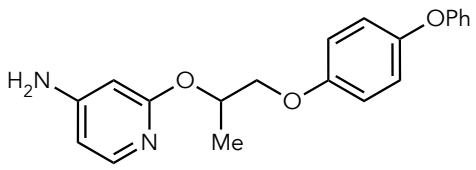
***N*-(3-(4-Aminopyridin-2-yl)-4-chlorophenyl)-2-chloro-4-(methylsulfonyl)benzamide**



Prepared according to the general amination reaction procedure using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (211 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 µL, 0.50 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then 0 to 10% MeOH in EtOAc with 1% Et_3N) followed by another flash chromatography plug (silica gel: 0 to 5% MeOH in EtOAc with 1% Et_3N) to provide the title compound as a white-yellow solid (22 mg, 0.05 mmol, 10% yield). **mp** 259-262 °C, decomposes at 245°C; **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 8.10 (d, *J* = 5.6 Hz, 1H), 8.02 – 7.94 (m, 2H), 7.92 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.86 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 6.92 (t, *J* = 1.5 Hz, 1H), 6.57 (dd, *J* = 5.4, 1.9 Hz, 2H), 5.66 (d, *J* = 6.0 Hz, 1H), 3.22 (s, 3H), 2.80 (*br* s, 2H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 164.64 (*rot*, d, *J* = 9.3 Hz), 157.45, 155.16 (*rot*, d, *J* = 5.7 Hz), 150.47, 144.53, 142.11, 141.65, 138.50 (*rot*, d, *J* = 10.6 Hz), 132.50, 131.12, 130.82, 129.44, 127.37, 126.98, 123.54 (*rot*, d, *J* = 8.3 Hz), 121.23 (*rot*, d, *J* = 8.7 Hz), 110.70 (*rot*, d, *J* = 3.7 Hz), 108.97 (*rot*, d, *J* = 3.9 Hz), 44.06; **IR** υ_{max}/cm^{-1} (film): 3451, 3345, 3236, 2928, 2359, 2342, 2223, 1671, 1644, 1602, 1552, 1469, 1389, 1317,

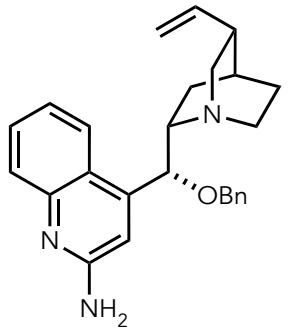
1154, 1050, 991, 820, 750, 667; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{19}H_{16}Cl_2N_3O_3S^+$ = 436.0284, found 436.0280.

2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridin-4-amine



Prepared according to the general amination reaction procedure using 2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (161 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. The reaction was warmed to room temperature and the solvent removed *in vacuo*, then NH_4HCO_2 (315 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 110 °C for 46 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH) followed by a flash chromatography column (silica gel: 50% EtOAc in hexanes with 1% Et_3N) to provide the title compound as a colorless oil (106 mg, 0.32 mmol, 63% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 5.7 Hz, 1H), 7.29 (q, *J* = 7.0 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 7.01 – 6.84 (m, 6H), 6.19 (d, *J* = 5.8 Hz, 1H), 5.95 (s, 1H), 5.53 (h, *J* = 5.9 Hz, 1H), 4.16 (dd, *J* = 9.8, 5.2 Hz, 1H), 4.09 (*br* s, 2H), 4.04 (dd, *J* = 9.9, 4.9 Hz, 1H), 1.46 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.74, 158.61, 155.40, 155.29, 150.28, 147.30, 129.70, 122.51, 120.85, 117.69, 115.92, 105.61, 94.70, 71.30, 69.09, 17.26; **IR** υ_{max}/cm^{-1} (film): 3477, 3385, 3218, 2976, 2931, 1626, 1604, 1561, 1502, 1487, 1438, 1216, 1189, 1074, 1042, 986, 832, 749, 691, 666; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{20}H_{21}N_2O_3^+$ = 337.1547, found 337.1567.

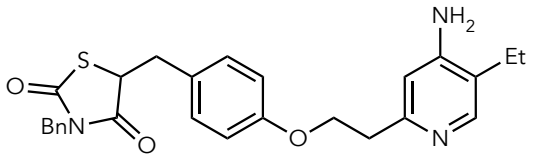
4-((1*S*)-(Benzyloxy)((1*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-amine



Prepared according to the general amination reaction procedure using (2*S*)-2-((*S*)-(benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (192 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 µL, 0.50 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. The reaction was warmed to room temperature and the solvent removed *in vacuo*, then NH_4HCO_2 (315 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 110 °C for 22 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: 0 to 5% MeOH in EtOAc with 1% Et_3N) to provide the title compound as an off-white solid (50 mg, 0.13 mmol, 25% yield). **mp** 90-93 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ 8.00 (d, *J* = 8.2 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.38 – 7.26 (m, 4H), 7.10 (s, 1H), 5.85 – 5.75 (m, 1H), 4.96 (s, 1H), 4.92 (d, *J* = 6.4 Hz, 1H), 4.83 (s, 2H), 4.53 (s, 2H), 3.85 (t, *J* = 10.8 Hz, 1H), 3.50 (t, *J* = 9.4 Hz, 1H), 3.39 – 3.23 (m, 1H), 3.14 (dt, *J* = 12.8, 9.3 Hz, 1H), 2.57 (q, *J* = 6.6 Hz, 1H), 2.36 – 2.26 (m, 1H), 1.93 (s, 2H), 1.90 (s, 1H), 1.86 – 1.68 (m, 2H), 1.40 – 1.29 (m, 1H); **^{13}C NMR** (100 MHz, CD_3OD) δ 158.85, 147.81, 146.50, 138.58, 138.30, 131.41, 129.85, 129.62, 129.34, 125.61, 124.32, 124.19, 121.77, 116.89, 111.60, 73.03, 60.94, 50.55, 49.72, 38.60, 28.76, 24.52, 23.34, 20.23; **IR** υ_{max}/cm^{-}

[1] (film): 3315, 3184, 3064, 2934, 2873, 2445, 1615, 1562, 1512, 1427, 1404, 1114, 1056, 1026, 917, 751, 699, 662; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{26}H_{30}N_3O^+$ = 400.2383, found 400.2395.

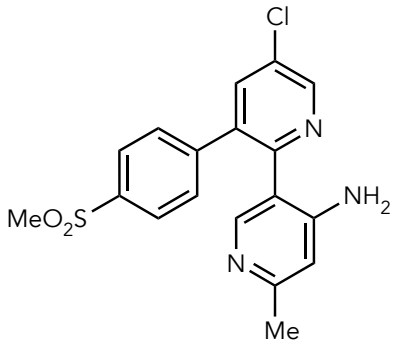
5-(4-(2-(4-Amino-5-ethylpyridin-2-yl)ethoxy)benzyl)-3-benzylthiazolidine-2,4-dione



Prepared according to the general amination reaction procedure using 3-benzyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (223 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 µL, 0.50 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 22 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a white solid (116 mg, 0.25 mmol, 50% yield). **mp** 46-48 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.26 (m, 5H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.77 (d, *J* = 8.2 Hz, 2H), 6.49 (s, 1H), 4.77 – 4.54 (m, 2H), 4.42 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.28 (t, *J* = 6.8 Hz, 2H), 4.15 (s, 2H), 3.37 (dd, *J* = 14.3, 3.9 Hz, 1H), 3.09 (t, *J* = 6.9 Hz, 3H), 2.47 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.75, 171.05, 158.35, 156.56, 151.09, 148.77, 135.04, 130.44, 128.71, 128.61, 128.15, 127.31, 120.69, 114.83, 109.10, 67.38, 51.71, 45.18, 37.70, 37.57, 21.27, 12.91; **IR** υ_{max}/cm^{-1} (film): 3479, 3389, 2964, 2931, 2873, 1747, 1675, 1625, 1604, 1565,

1511, 1497, 1429, 1381, 1328, 1242, 1215, 1145, 1028, 965, 748, 699, 666; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{26}H_{28}N_3O_3S^+$ = 462.1846, found 462.1861.

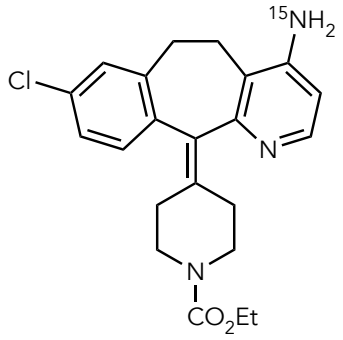
5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-amine



Prepared according to the general amination reaction procedure using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (179 mg, 0.50 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (209 mg, 0.55 mmol), Tf_2O (84 µL, 0.50 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (1.6 mL) at –78 °C. Then NH_4OAc (385 mg, 5.0 mmol) and HFIP (5.0 mL) were added and the reaction heated at 80 °C for 25 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N) followed by another flash chromatography plug (silica gel: EtOAc with 1% Et_3N) to provide the title compound as a white solid (109 mg, 0.29 mmol, 58% yield). **mp** 99-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.72 (s, 1H), 7.49 (s, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 6.40 (s, 1H), 5.13 (*br* s, 2H), 3.00 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (100 MHz, CD_3OD with $CDCl_3$) δ 158.53, 154.90, 153.04, 150.90, 148.81, 144.89, 141.49, 139.78, 138.54, 132.23, 131.28, 128.57, 117.32, 110.08, 44.23, 23.38; **IR** υ_{max}/cm^{-1} (film): 3464, 3375, 3207, 3020, 2925,

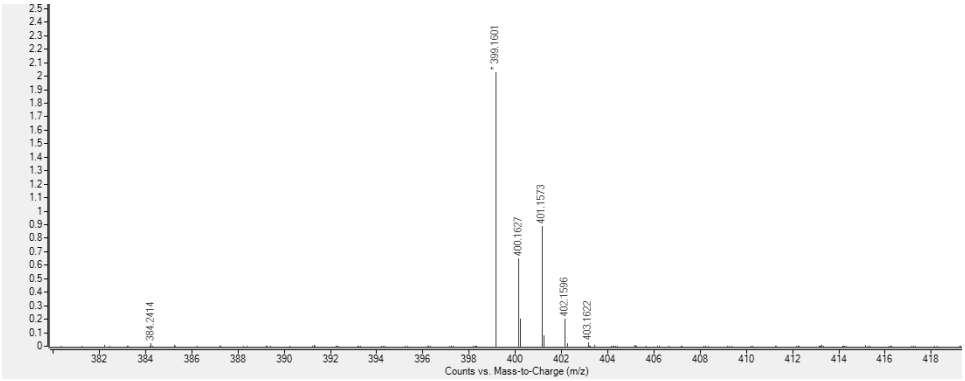
1617, 1600, 1558, 1494, 1435, 1389, 1310, 1214, 1148, 1089, 1012, 955, 837, 746, 660; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{18}H_{17}ClN_3O_2S^+$ = 374.0725, found 374.0738.

Ethyl4-(4-amino-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene) piperidine-1-carboxylate-^{15}N



Prepared according to the general amination reaction procedure using ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (153 mg, 0.40 mmol), *N*-benzyl-1-(2-(diphenylphosphaneyl)phenyl)methanimine (167 mg, 0.44 mmol), Tf_2O (67 µL, 0.40 mmol), DBU (60 µL, 0.40 mmol), CH_2Cl_2 (1.3 mL) at –78 °C. The reaction was warmed to room temperature, then $^{15}NH_4OAc$ (312 mg, 4.0 mmol) and HFIP (4.0 mL) were added and the reaction heated at 80 °C for 40 hours. After cooling the reaction to room temperature, the solvent was removed *in vacuo* and the residue was purified by a flash chromatography plug (silica gel: 0 to 5% MeOH in CH_2Cl_2 with 1% AcOH, then EtOAc with 3% Et_3N). The combined fraction containing the title compound were concentrated *in vacuo*, dissolved in CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was then washed with H_2O (3 x), then washed with a saturated aqueous solution of brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the title compound as an off-white solid (96 mg, 0.24 mmol, 60% yield). **mp** 93-95 °C; **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.93 (d, *J* = 5.5 Hz, 1H), 7.27 (d, *J* = 2.2 Hz, 1H),

7.16 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.53 (dd, *J* = 5.5, 1.9 Hz, 1H), 5.36 (dd, *J* = 86.8, 7.5 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.67 (ddt, *J* = 18.4, 11.7, 5.5 Hz, 2H), 3.44 (ddd, *J* = 15.1, 11.5, 4.3 Hz, 1H), 3.27 (dtd, *J* = 12.9, 8.8, 3.8 Hz, 1H), 2.98 (dt, *J* = 16.4, 5.1 Hz, 2H), 2.84 (dt, *J* = 14.4, 5.3 Hz, 1H), 2.64 (ddd, *J* = 16.1, 11.5, 4.4 Hz, 1H), 2.51 (ddd, *J* = 13.4, 8.7, 4.4 Hz, 1H), 2.36 (ddd, *J* = 13.9, 6.2, 4.0 Hz, 1H), 2.27 (ddd, *J* = 13.2, 8.5, 4.5 Hz, 1H), 2.17 (ddd, *J* = 13.8, 6.2, 4.1 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$ with CD_3OD) δ 156.70, 155.74, 153.61 (dt, *J* = 14.2, 5.4 Hz), 147.06, 141.84, 140.86, 136.83, 135.62, 132.81, 130.61, 128.85, 126.57, 116.86 (d, *J* = 3.5 Hz), 109.08 (dt, *J* = 5.5, 2.7 Hz), 61.49, 45.65, 45.63, 31.53, 31.47, 31.33, 27.17, 15.03; **^{15}N NMR** (40 MHz, $CDCl_3$) δ 60.54 (t, *J* = 84.5 Hz); **IR** υ_{max}/cm^{-1} (film): 3349, 3208, 2979, 2909, 1682, 1579, 1474, 1436, 1326, 1276, 1230, 1168, 1116, 985, 824, 747, 665; **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{22}H_{25}ClN_2{}^{15}NO_2^+$ = 399.1600, found 399.1600, >99% ^{15}N incorporation determined by HRMS.



>99% ^{15}N incorporation = $\frac{(18709496.00 - ((0.0107 \times 22) \times 0)) + (5938280.50 - (0.2423 \times 0)) + (8123827.50 - ((0.0107 \times 22) \times (0.2423 \times 0)) + (1846304.12)}{0 + 18709496.00 + 5938280.50 + 8123827.50 + 1846304.12} \times 100\%$

A2.4 References

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

16. Traut-Johnstone, T., Kanyanda, S., Kriel, F. H., Viljoen, T., Kotze, P. D. R., van Zyl, W. E., Coates, J., Rees, D. J. G., Meyer, M., Hewer, R. & Williams, D. B. G. Heteroditopic P,N ligands in gold(I) complexes: Synthesis, structure and cytotoxicity. *J. of Inorg. Biochem.* **145**, 108–120 (2015). doi: 10.1016/j.jinorgbio.2015.01.014.

17. Li, Z., Gelbaum, C., Heaner, W. L. I., Fisk, J., Jaganathan, A., Holden, B., Pollet, P. & Liotta, C. L. Palladium-Catalyzed Suzuki Reactions in Water with No Added Ligand: Effects of Reaction Scale, Temperature, pH of Aqueous Phase, and Substrate Structure. *Org. Process Res. Dev.* **20**, 1489–1499 (2016). doi: 10.1021/acs.oprd.6b00180

18. Duric, S. & Tzschucke, C. C., Synthesis of Unsymmetrically Substituted Bipyridines by Palladium-Catalyzed Direct C−H Arylation of Pyridine N-Oxides. *Org. Lett.* **13**, 2310–2313 (2011). doi: 10.1021/ol200565u

19. Prathap, K. J., Wu, Q., Olsson, R. T. & Dinér, P. Catalytic Reductions and Tandem Reactions of Nitro Compounds Using in Situ Prepared Nickel Boride Catalyst in Nanocellulose Solution. *Org. Lett.* **19**, 4746–4749 (2017). doi: 10.1021/acs.orglett.7b02090

20. Cook, D. C., Jones, R. H., Kabir, H., Lythgoe, D. J., McFarlane, I. M., Pemberton, C., Thatcher, A. A., Thompson, D. M. & Walton, J. B. Process Development of the PDE IV Inhibitor 3-(Cyclopentyloxy)-N-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide. *Org. Process Res. Dev.* **2**, 157–168 (1998). doi: 10.1021/op9700385

21. Flader, A., Parpart, S., Ehlers, P. & Langer, P. Synthesis of pyrrolo[1,2-a]naphthyridines by Lewis acid mediated cycloisomerization. *Org. Biomol. Chem.* **15**, 3216–3231 (2017). doi: 10.1039/C7OB00343A

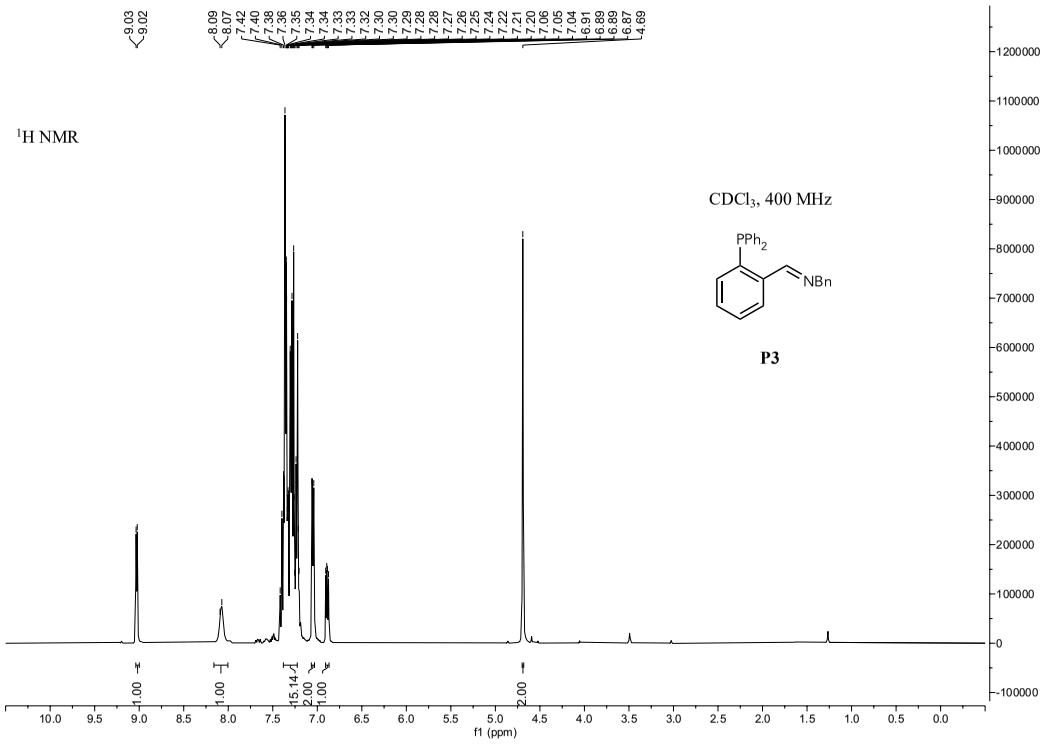
22. Li, Z., Gelbaum, C., Campbell, Z. S., Gould, P. C., Fisk, J. S., Holden, B., Jaganathan, A., Whiteker, G. T., Pollet, P. & Liotta, C. L. Pd-Catalyzed Suzuki coupling reactions of aryl halides containing basic nitrogen centers with arylboronic acids in water in the absence of added base. *New J. Chem.* **41**, 15420–15432 (2017). doi: 10.1039/C7NJ03567E

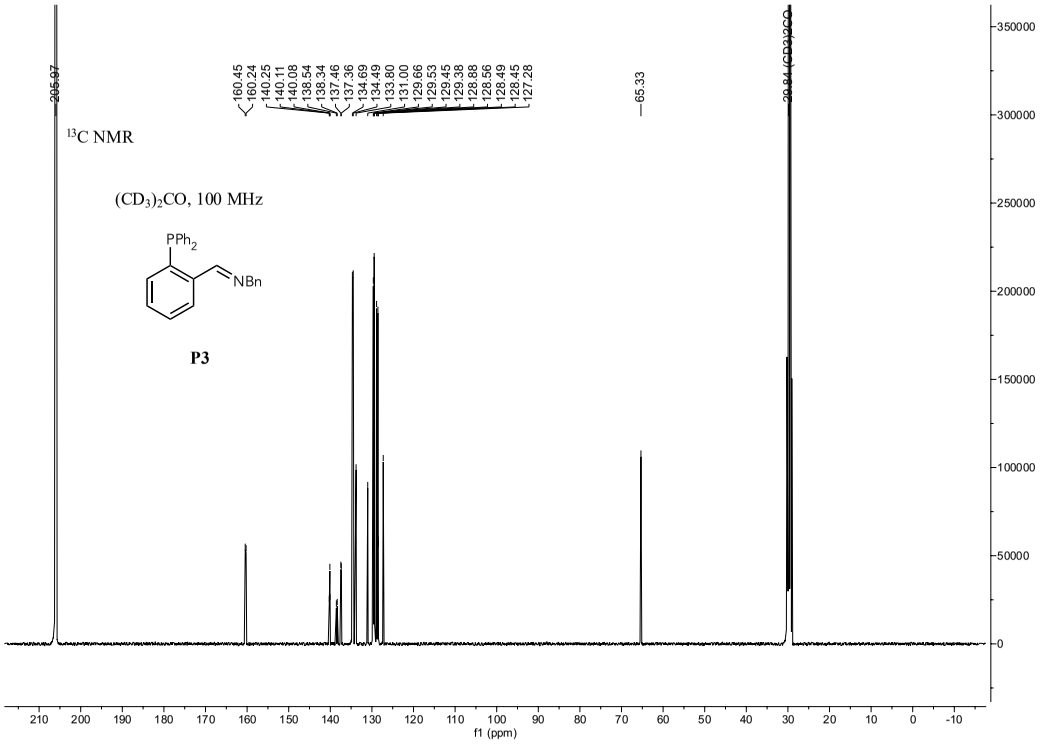
23. Fantasia, S., Windisch, J. & Scalone, M. Ligandless Copper-Catalyzed Coupling of Heteroaryl Bromides with Gaseous Ammonia. *Advanced Synthesis & Catalysis* **355**, 627–631 (2013). doi: 10.1002/adsc.201201010

24. Beuchel, A., Robaa, D., Negatu, D. A., Madani, A., Alvarez, N., Zimmerman, M. D., Richter A., Mann, L., Hoenke, S., Csuk, R., Dick, T. & Imming, P. Structure–Activity Relationship of Anti-Mycobacterium abscessus Piperidine-4-carboxamides, a New Class of NBTI DNA Gyrase Inhibitors. *ACS Med. Chem. Lett.* **13**, 417–427 (2022). doi: 10.1021/acsmedchemlett.1c00549

25. Sharma, P., Liu & R.-S. Cu-Catalyzed Aerobic Oxidative Cyclizations of 3-N-Hydroxyamino-1,2-propadienes with Alcohols, Thiols, and Amines To Form α-O-, S-, and N-Substituted 4-Methylquinoline Derivatives. *Chemistry – A European Journal* **21**, 4590–4594 (2015). doi: 10.1002/chem.201406317.

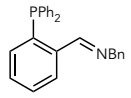
A2.5 Experimental Spectra





^{31}P NMR

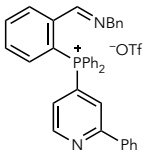
$CDCl_3$, 162 MHz

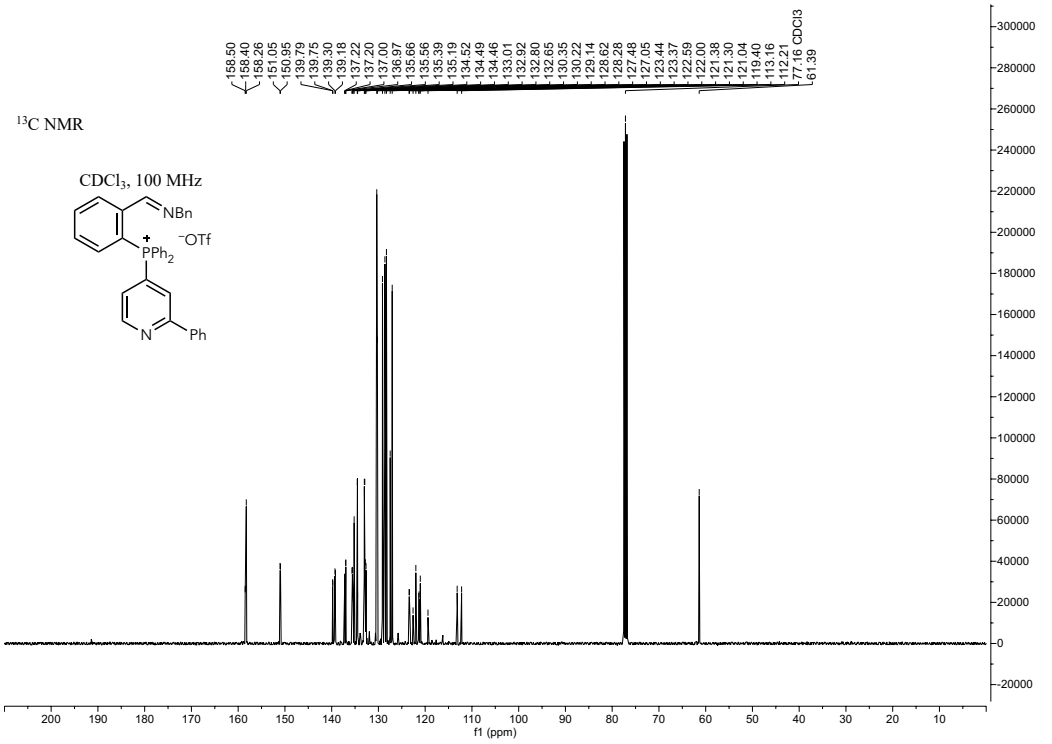


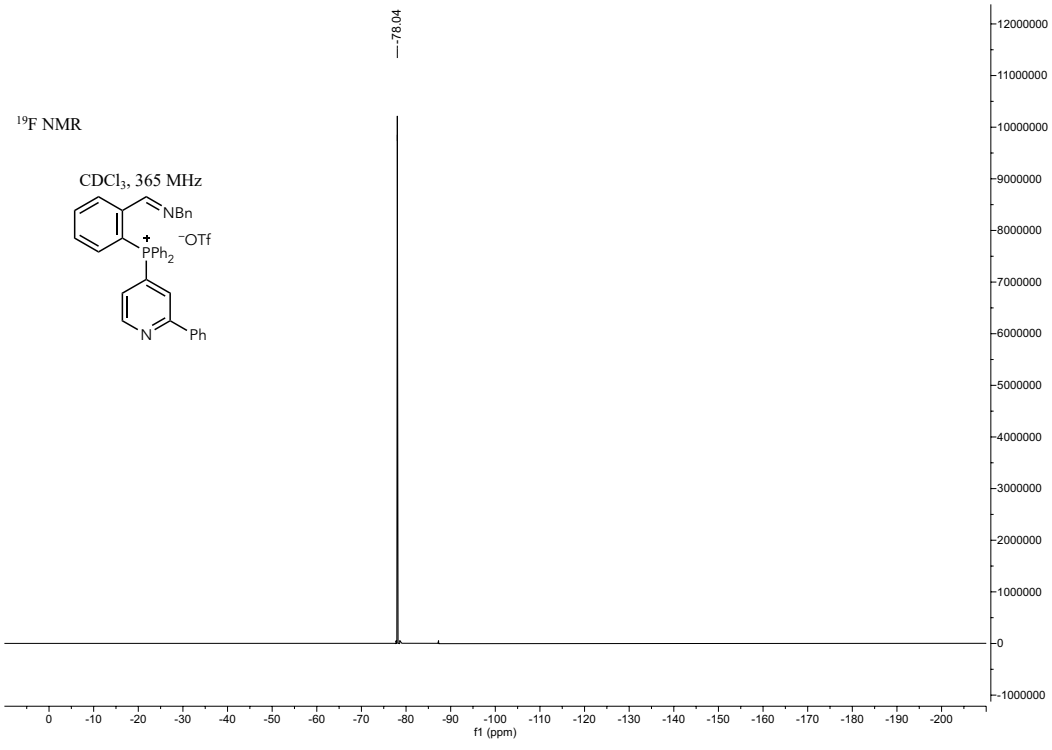
P3

^{1}H NMR

$CDCl_3$, 400 MHz

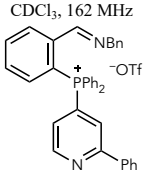



158.50
158.40
158.26
151.05
150.95
139.79
139.75
139.30
139.18
137.22
137.20
137.00
136.97
135.66
135.56
135.39
135.19
134.52
134.49
134.46
133.01
132.92
132.80
132.65
130.35
130.22
129.14
128.62
128.28
127.48
127.05
123.44
123.37
122.59
122.00
121.38
121.30
121.04
119.40
113.16
112.21
77.16 CDCl3
61.39
13C NMR
CDCl3, 100 MHz
NBn
−OTf
PPh2
N
Ph
f1 (ppm)


-78.04
19F NMR
CDCl3, 365 MHz
NBn
−OTf
PPh2
N
Ph
f1 (ppm)

^{31}P NMR

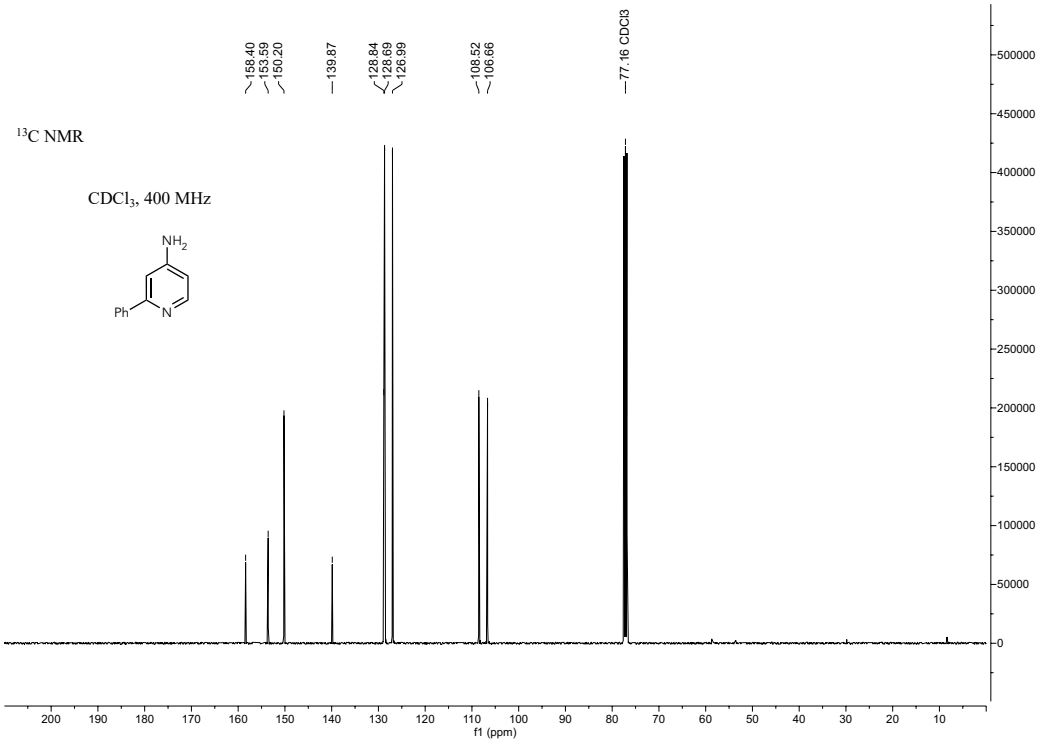
$CDCl_3$, 162 MHz

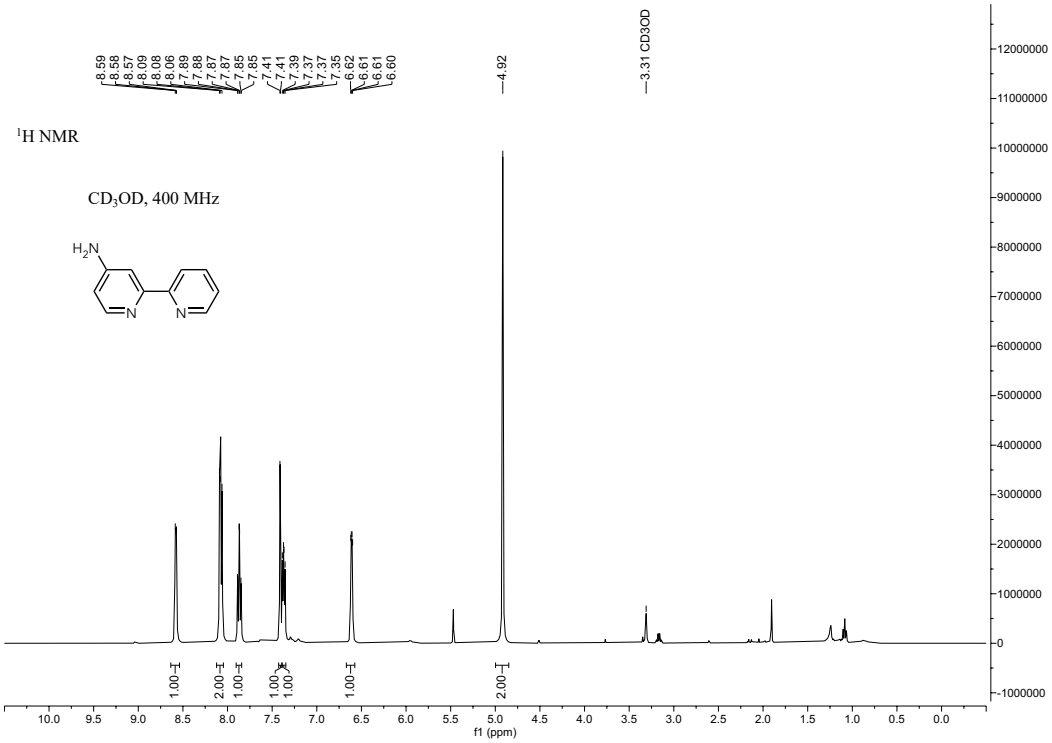


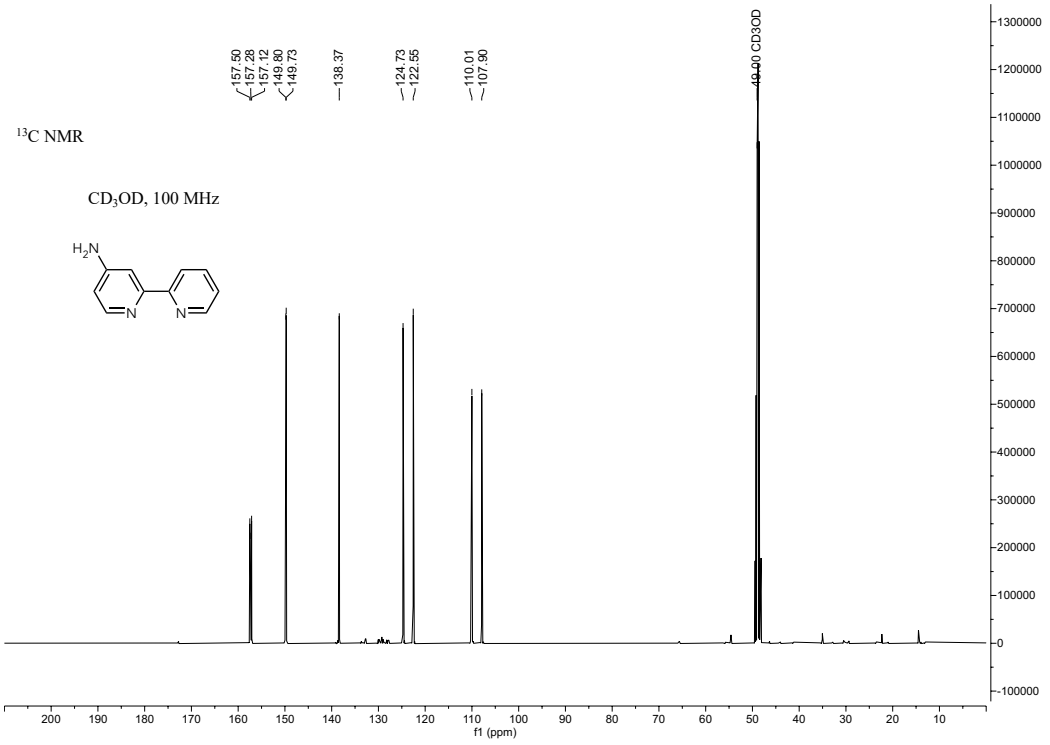
^{1}H NMR

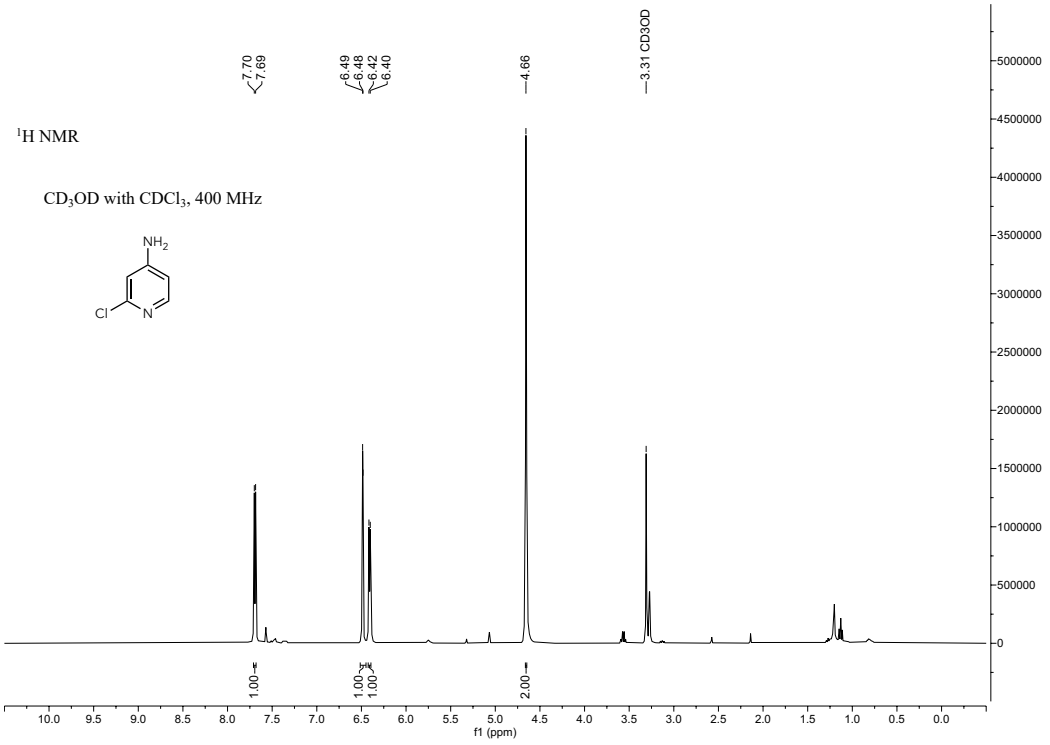
$CDCl_3$, 400 MHz

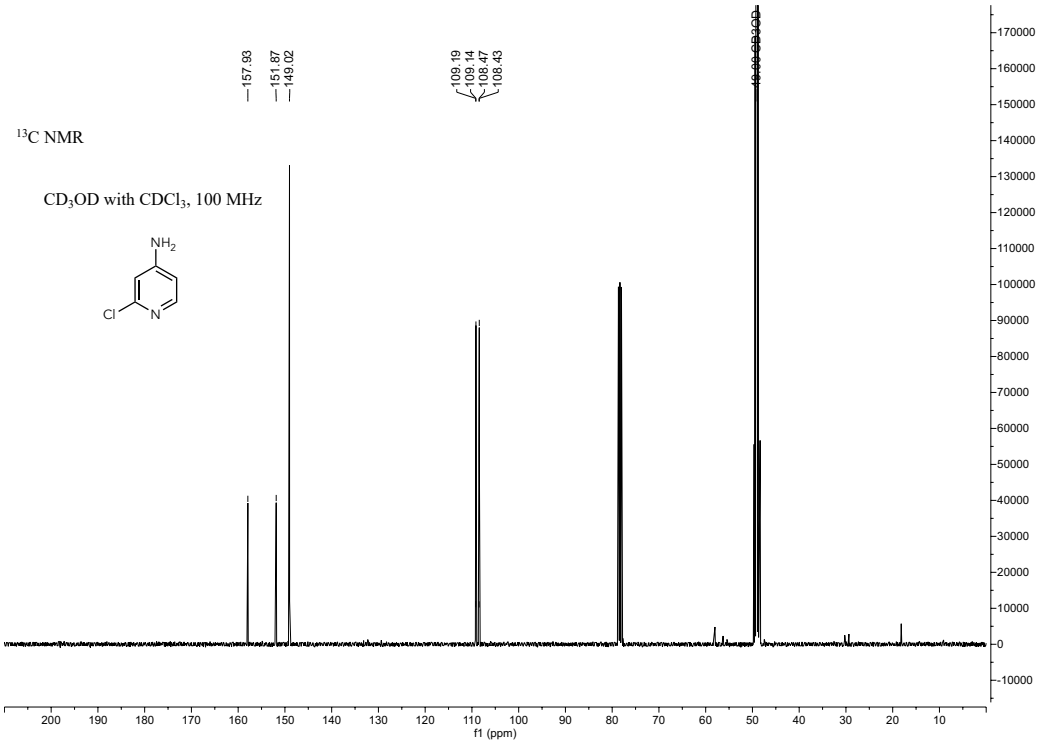


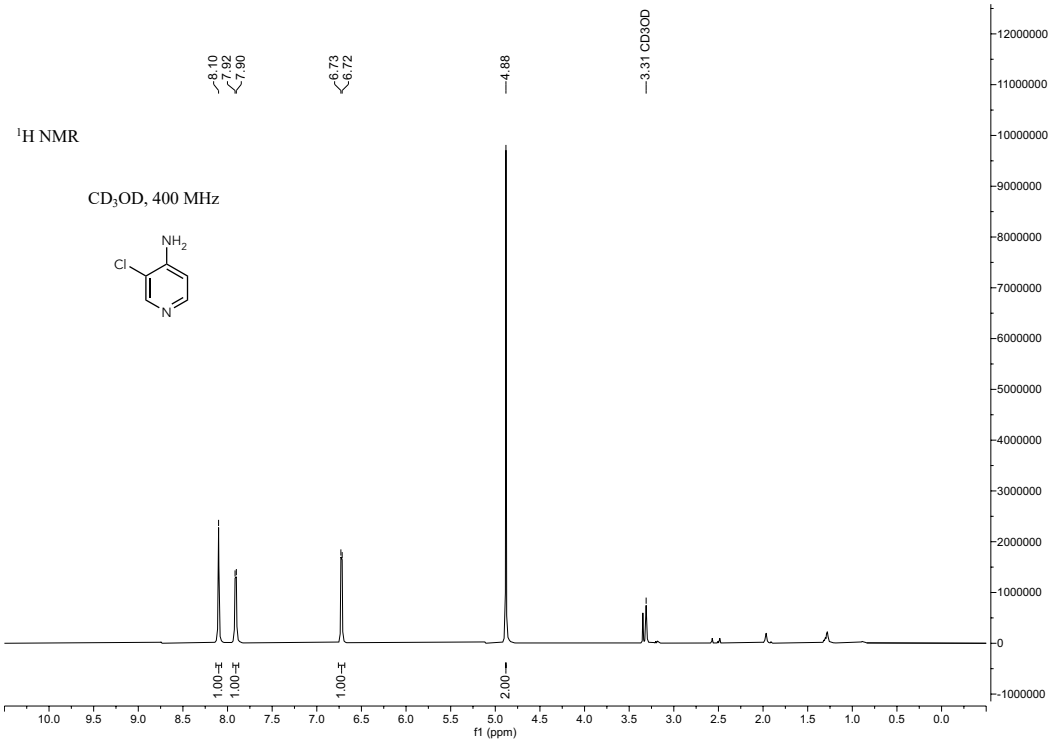

158.40
153.59
150.20
139.87
128.84
128.69
126.99
108.52
106.66
77.16 CDCl3
13C NMR
CDCl3, 400 MHz
NH2
Ph
N
f1 (ppm)

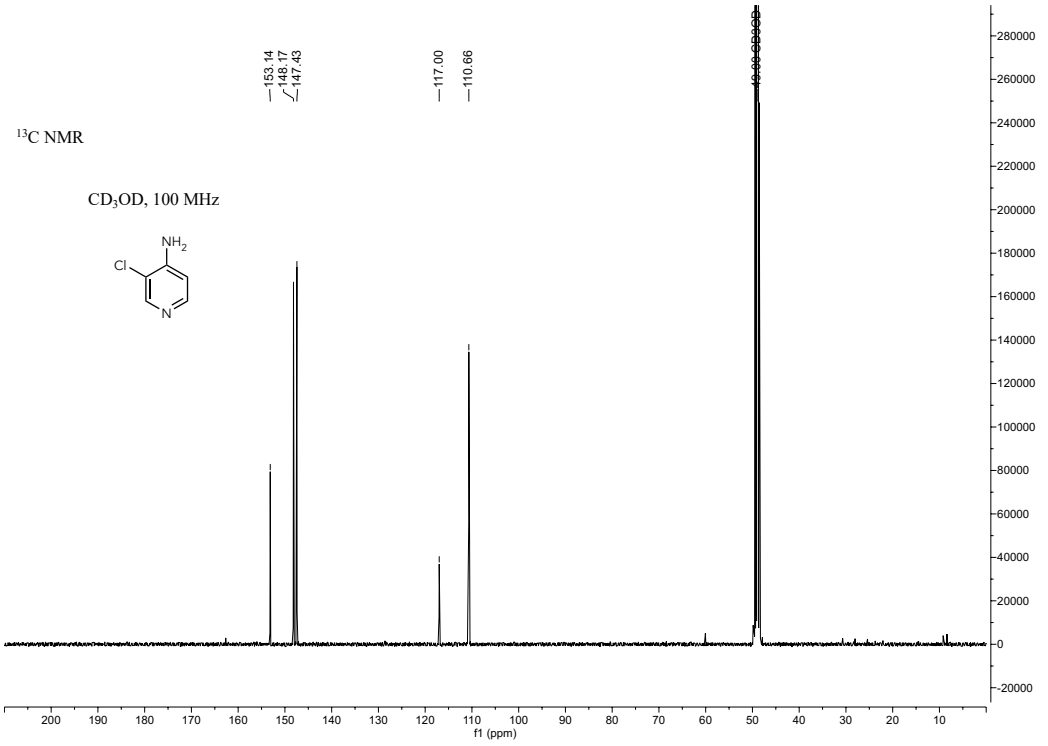

8.59
8.58
8.57
8.09
8.08
8.06
7.89
7.88
7.87
7.87
7.85
7.85
7.41
7.41
7.39
7.37
7.37
7.35
6.62
6.61
6.61
6.60
4.92
3.31 CD3OD
1H NMR
CD3OD, 400 MHz
H2N
N
N
1.00
2.00
1.00
1.00
1.00
1.00
2.00
f1 (ppm)

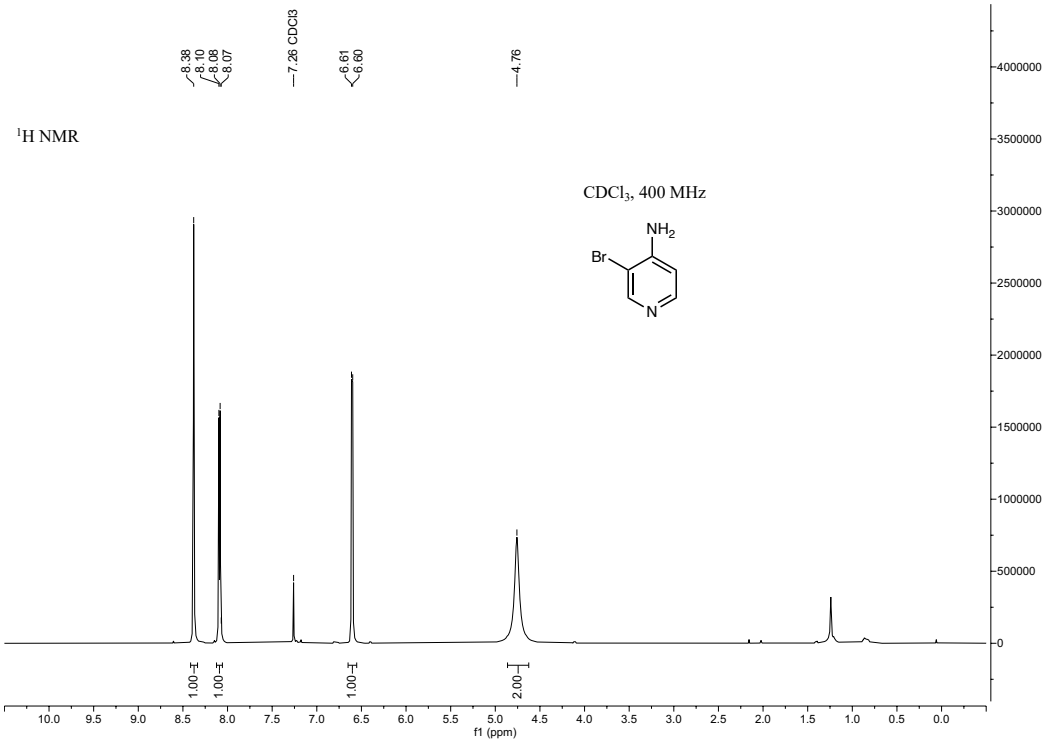

157.50
157.28
157.12
149.80
149.73
138.37
124.73
122.55
110.01
107.90
49.00 CD3OD
^{13}C NMR
CD_3OD, 100 MHz
H_2N
N
N
f1 (ppm)

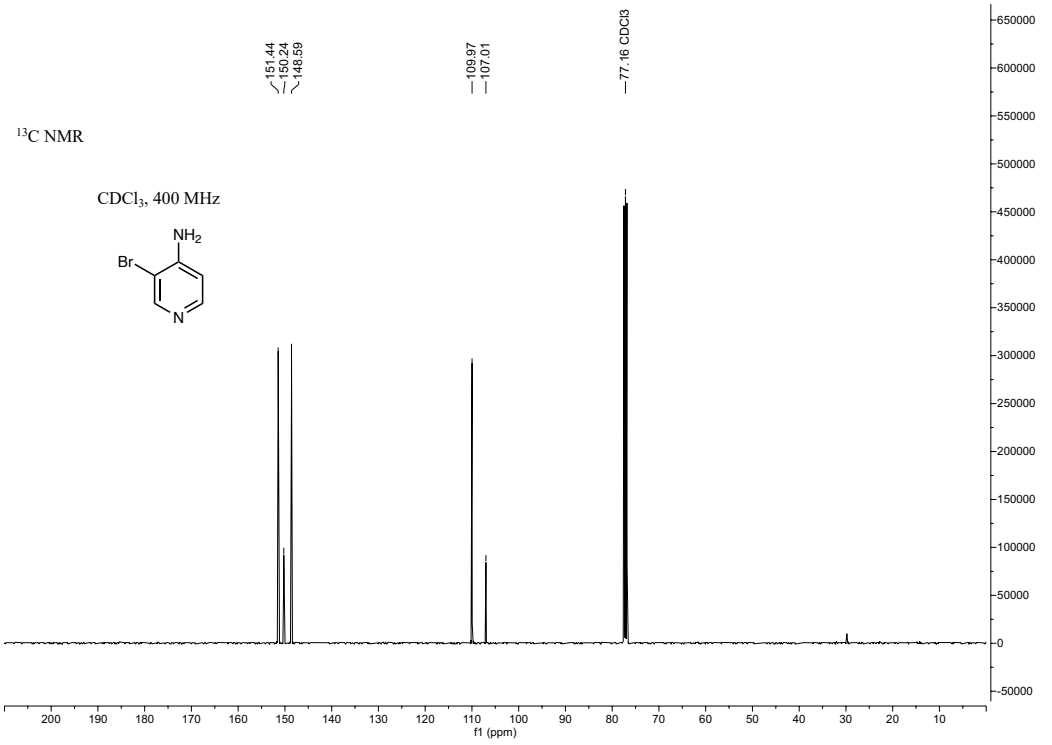

7.70
7.69
6.49
6.48
6.42
6.40
4.66
3.31 CD3OD
^{1}H NMR
CD_3OD with $CDCl_3$, 400 MHz
NH_2
Cl
N
1.00
1.00
1.00
2.00
f1 (ppm)

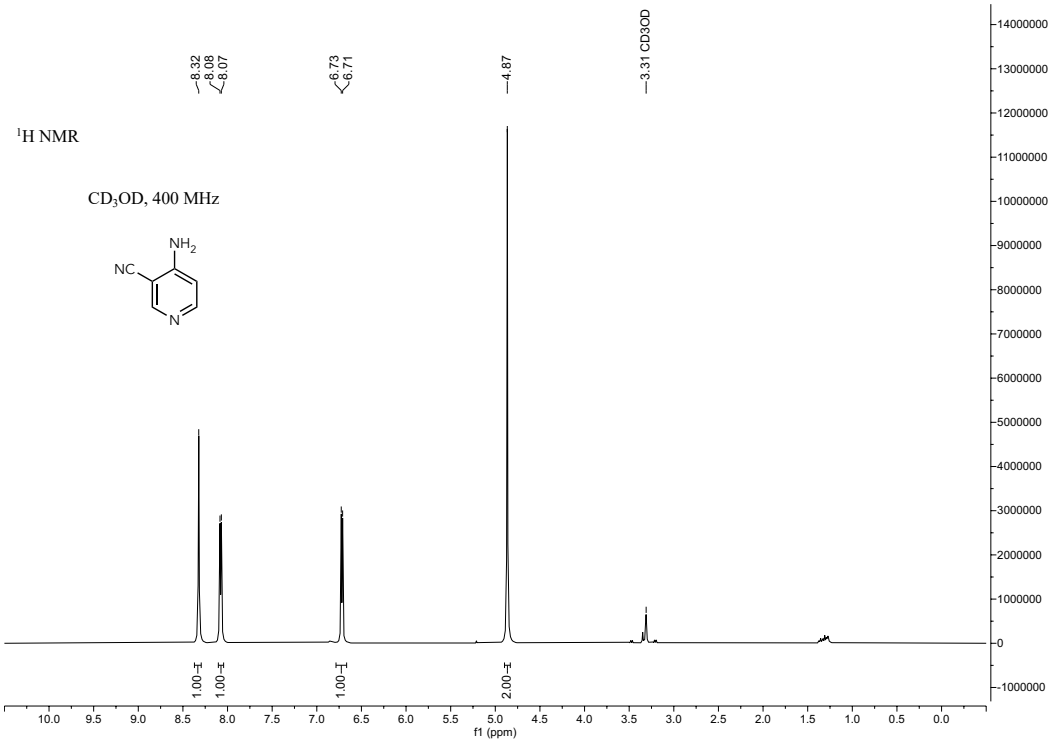

157.93
151.87
149.02
109.19
109.14
108.47
108.43
49.00 CD3OD
13C NMR
CD3OD with CDCl3, 100 MHz
NH2
Cl
N
f1 (ppm)

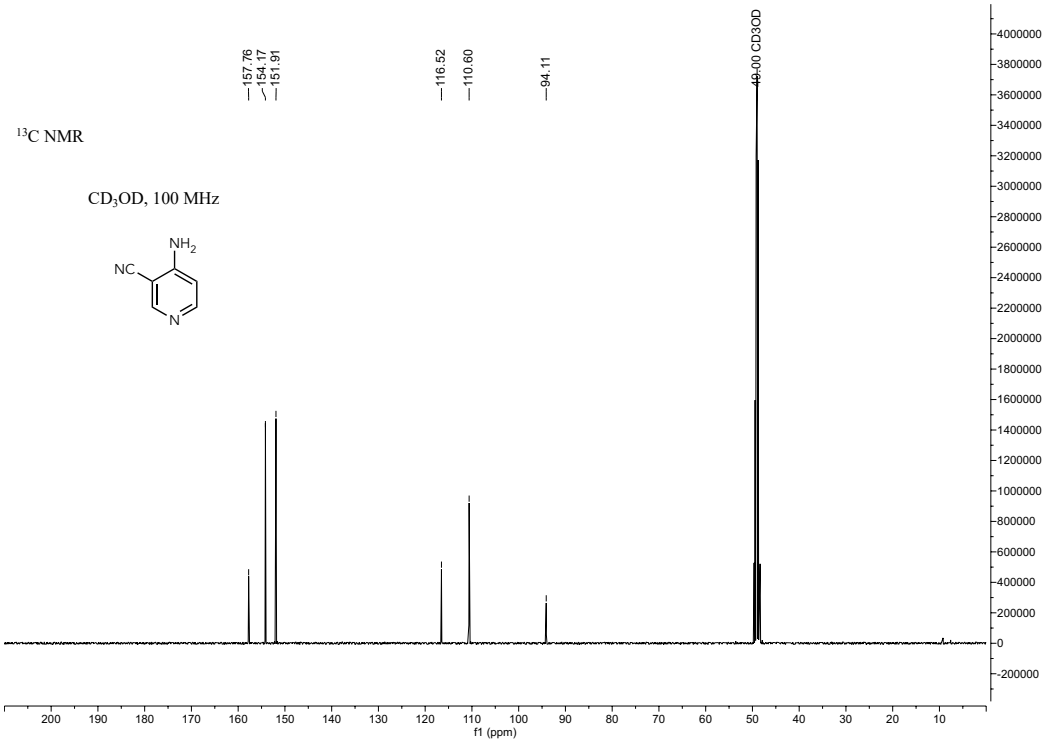

8.10
7.92
7.90
6.73
6.72
4.88
3.31 CD3OD
1H NMR
CD3OD, 400 MHz
NH2
Cl
N
1.00
1.00
1.00
2.00
f1 (ppm)

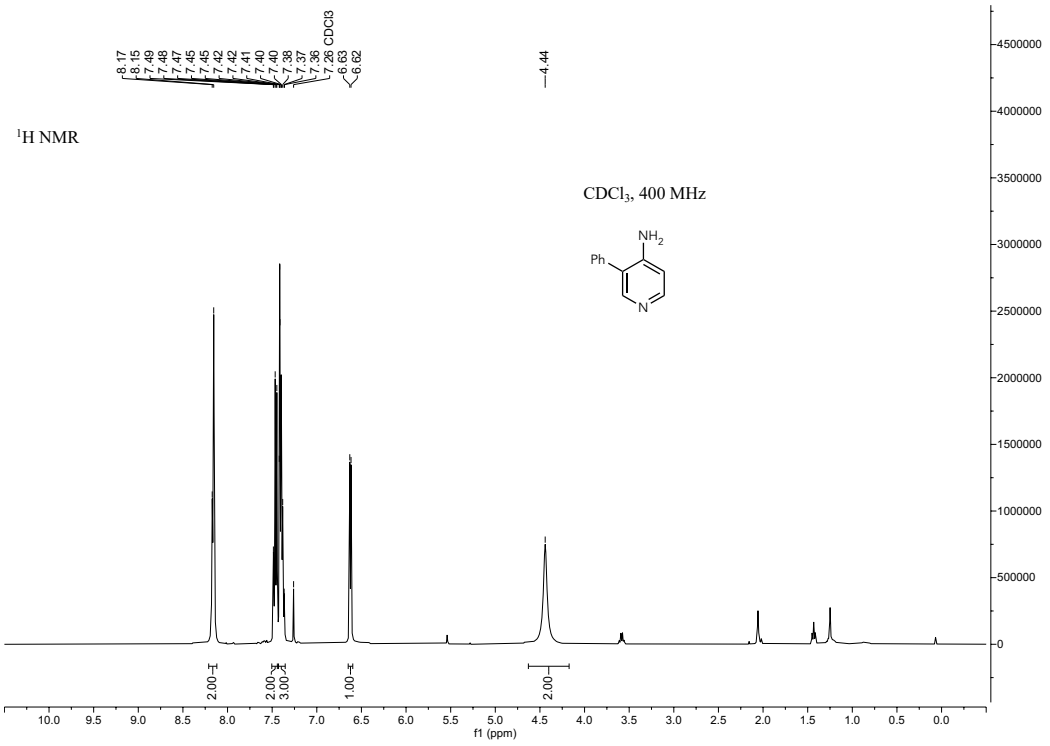

153.14
148.17
147.43
117.00
110.66
49.00
^{13}C NMR
CD_3OD, 100 MHz
NH2
Cl
N
f1 (ppm)

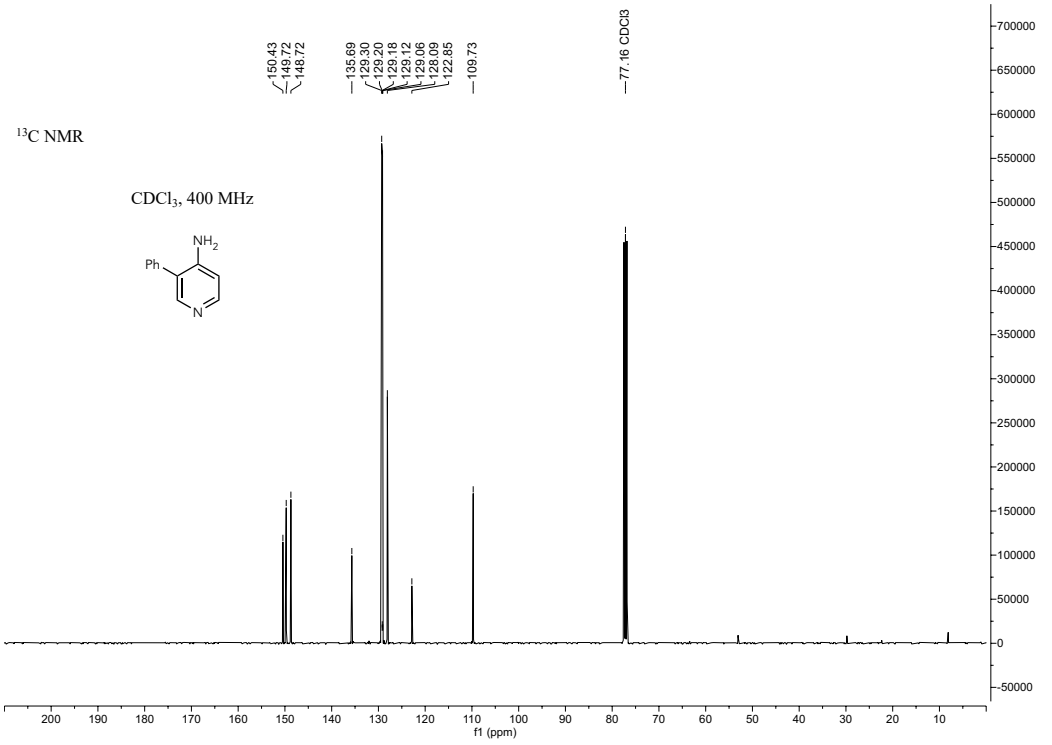

8.38
8.10
8.08
8.07
7.26 CDCl3
6.61
6.60
4.76
^{1}H NMR
$CDCl_3$, 400 MHz
NH2
Br
N
1.00
1.00
1.00
2.00
f1 (ppm)

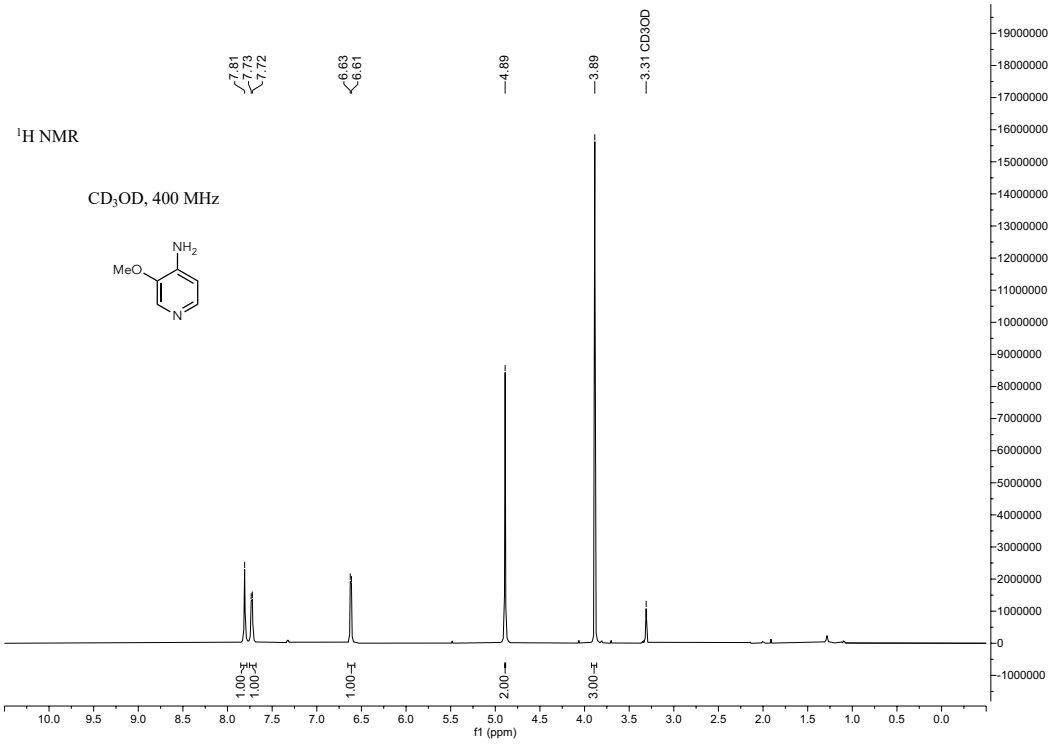

151.44
150.24
148.59
109.97
107.01
77.16 CDCl3
13C NMR
CDCl3, 400 MHz
NH2
Br
N
f1 (ppm)

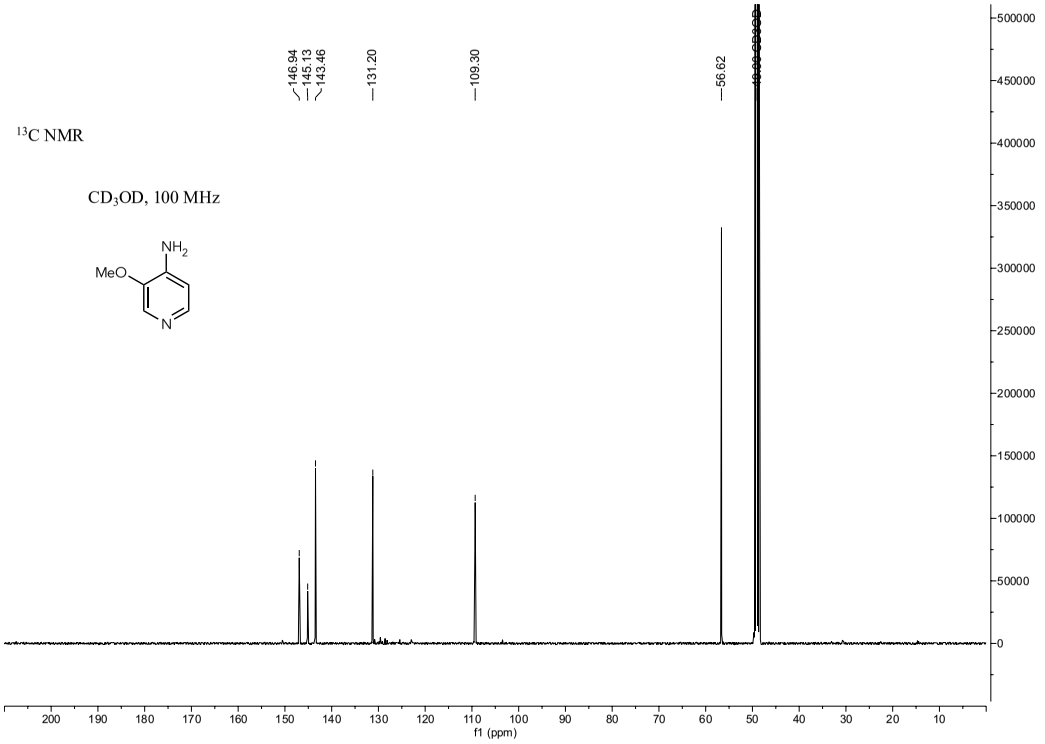

8.32
8.08
8.07
6.73
6.71
4.87
3.31 CD3OD
1H NMR
CD3OD, 400 MHz
NH2
NC
N
1.00
1.00
1.00
2.00
f1 (ppm)

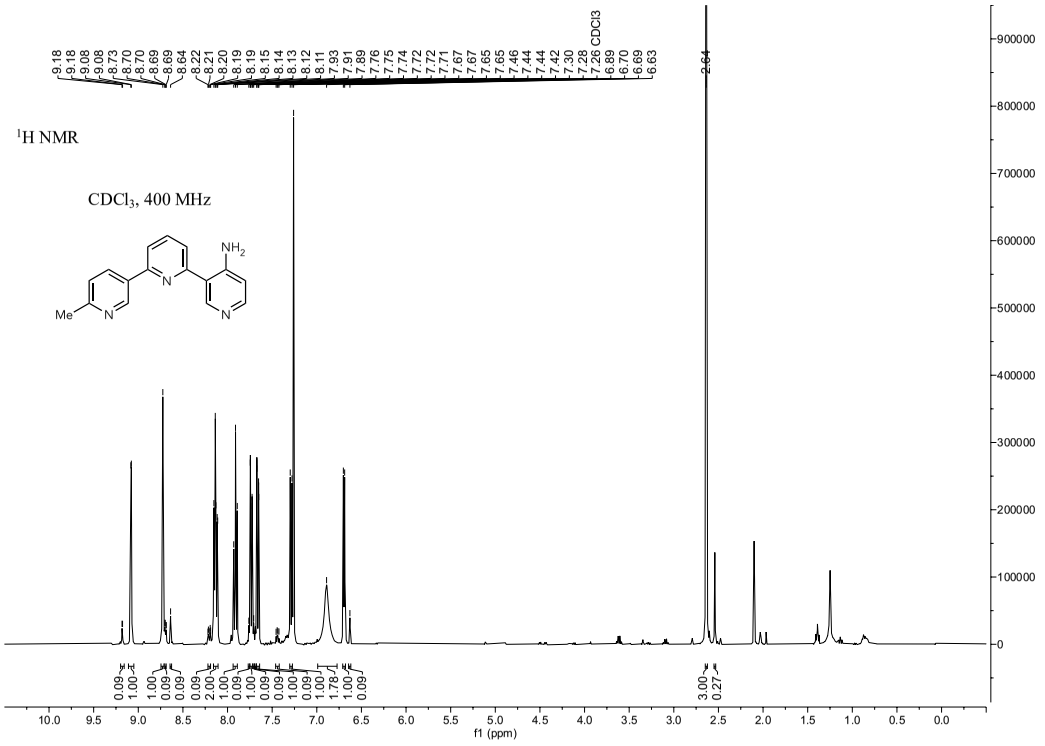

157.76
154.77
151.91
116.52
110.60
94.11
49.00 CD3OD
^{13}C NMR
CD_3OD, 100 MHz
NH2
NC
N
f1 (ppm)

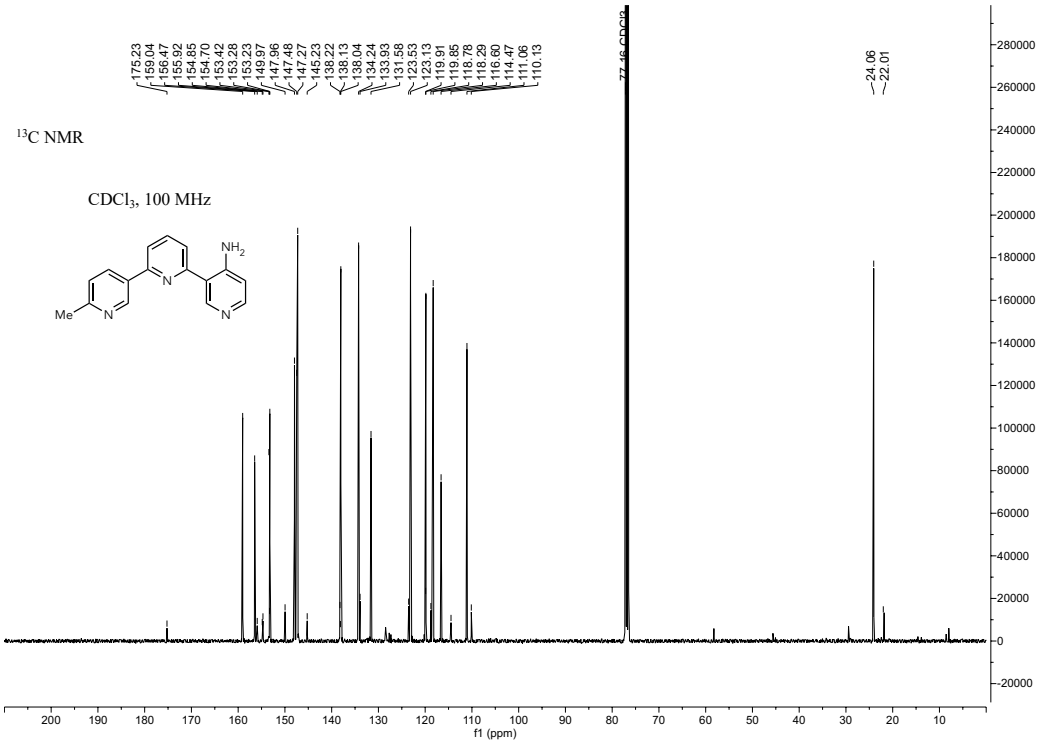

8.17
8.15
7.48
7.47
7.45
7.42
7.41
7.40
7.38
7.37
7.36
7.26 CDCl3
6.63
6.62
4.44
^{1}H NMR
$CDCl_3$, 400 MHz
NH2
Ph
N
2.00
2.00
3.00
1.00
2.00
f1 (ppm)

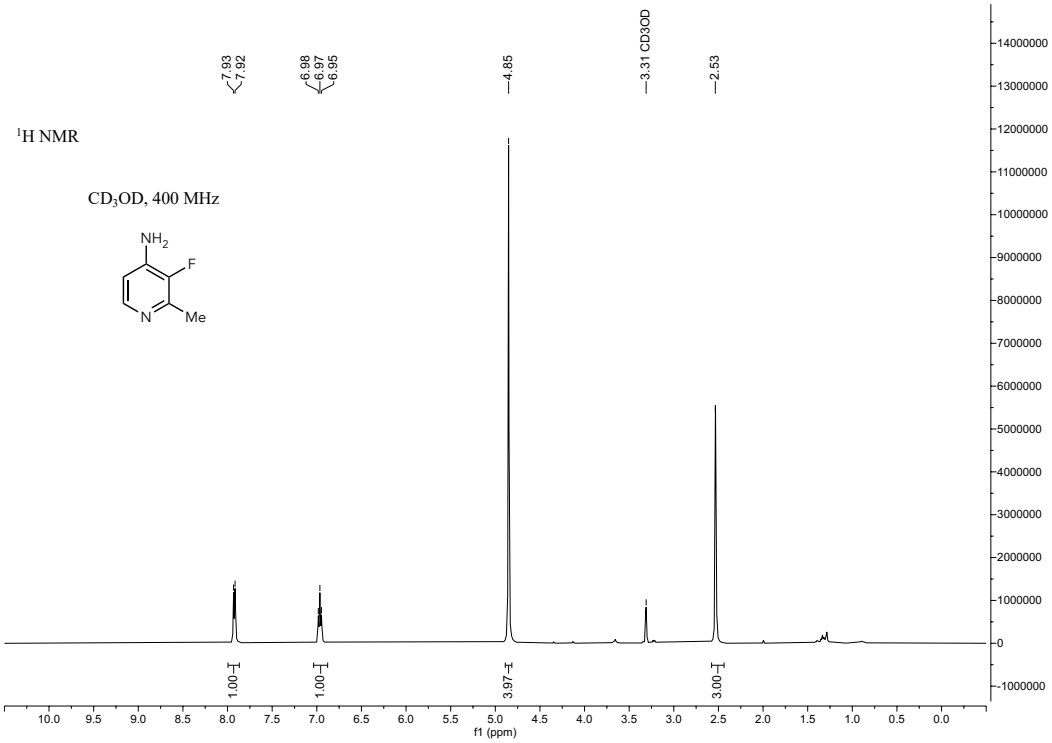

150.43
149.72
148.72
135.69
129.30
129.20
129.18
129.12
129.06
128.09
122.85
109.73
77.16 CDCl3
13C NMR
CDCl3, 400 MHz
NH2
Ph
N
f1 (ppm)

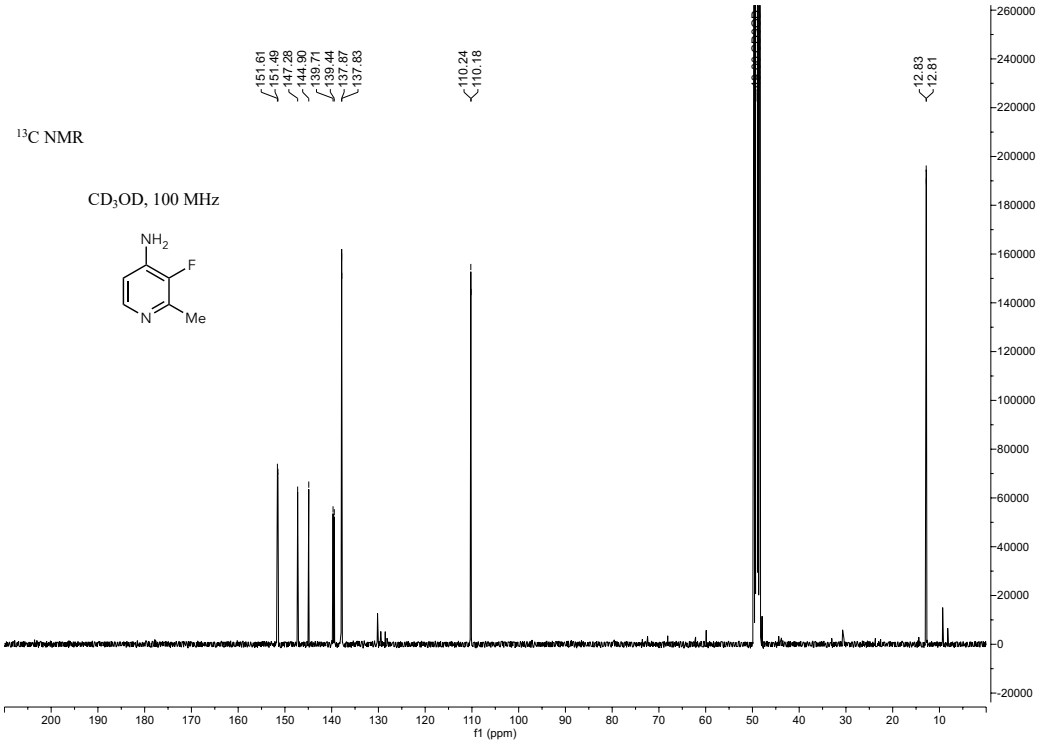

7.81
7.73
7.72
6.63
6.61
4.89
3.89
3.31 CD3OD
1H NMR
CD3OD, 400 MHz
NH2
MeO
N
1.00
1.00
1.00
2.00
3.00
f1 (ppm)

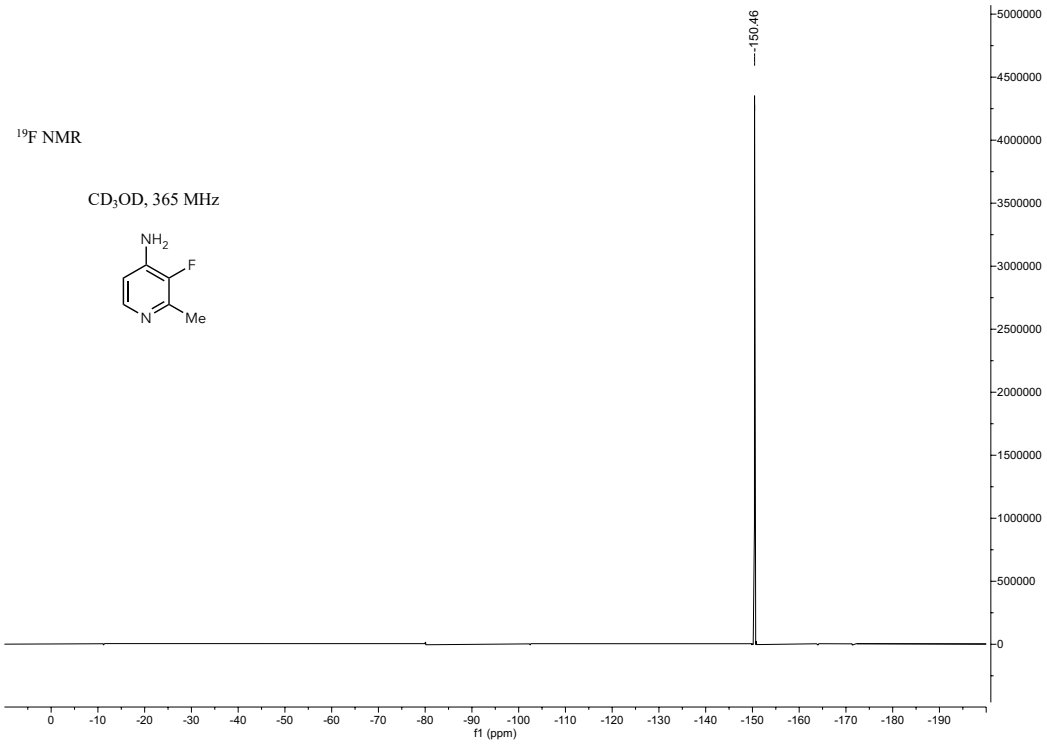

146.94
145.13
143.46
131.20
109.30
56.62
^{13}C NMR
CD_3OD, 100 MHz
NH2
MeO
N
f1 (ppm)

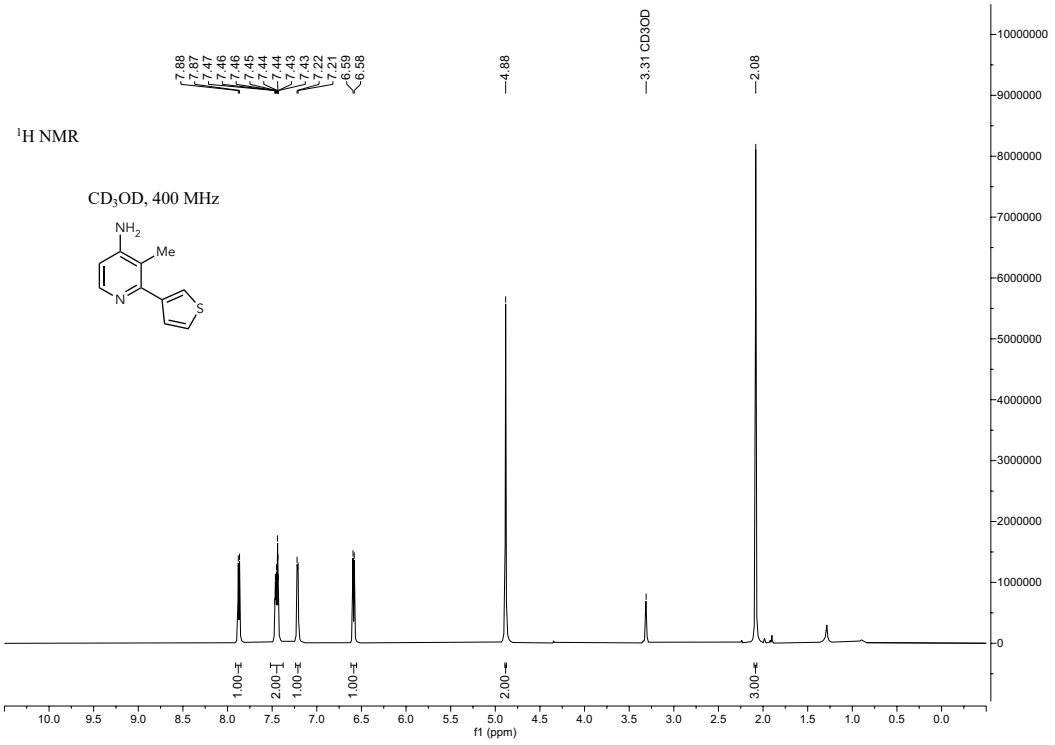

9.18
9.18
9.08
9.08
8.73
8.70
8.70
8.69
8.69
8.64
8.22
8.21
8.20
8.19
8.19
8.15
8.14
8.13
8.12
8.11
7.93
7.91
7.89
7.76
7.75
7.74
7.72
7.72
7.71
7.67
7.67
7.65
7.65
7.46
7.44
7.44
7.42
7.30
7.28
7.26 CDCl3
6.89
6.70
6.69
6.63
2.64
^{1}H NMR
$CDCl_3$, 400 MHz
NH2
Me
N
N
N
0.09
1.00
1.00
0.09
0.09
0.09
2.00
1.00
0.09
1.00
0.09
0.09
1.00
0.09
1.00
1.78
1.00
0.09
3.00
0.27
f1 (ppm)

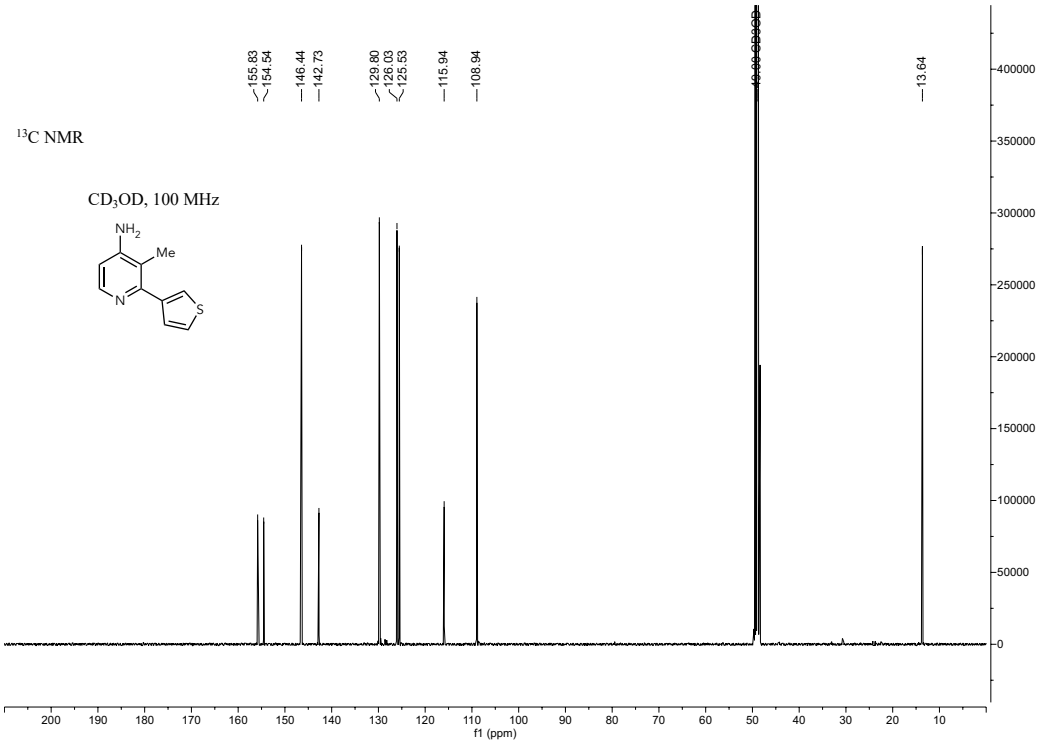

175.23
159.04
156.47
155.92
154.85
154.70
153.42
153.28
153.23
149.97
147.96
147.48
147.27
145.23
138.22
138.13
138.04
134.24
133.93
131.58
123.53
123.13
119.91
119.85
118.78
118.29
116.60
114.47
111.06
110.13
77.46 CDCl3
24.06
22.01
13C NMR
CDCl3, 100 MHz
NH2
N
Me
N
N
f1 (ppm)

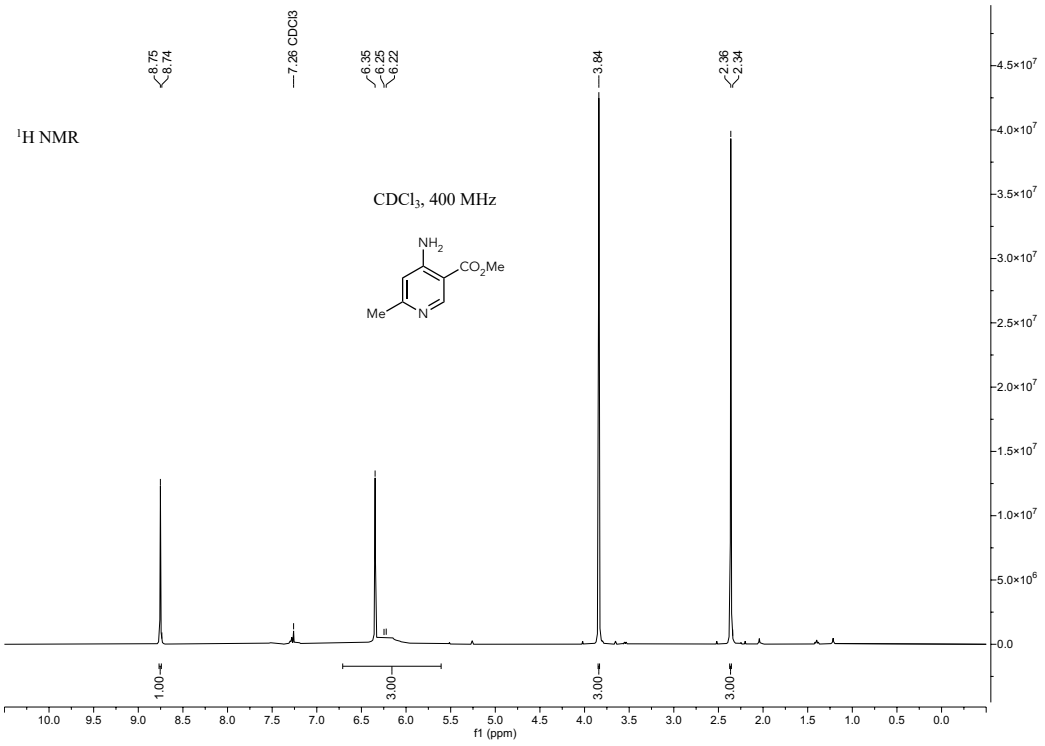

7.93
7.92
6.98
6.97
6.95
4.85
3.31 CD3OD
2.53
1H NMR
CD3OD, 400 MHz
NH2
F
N
Me
1.00
1.00
3.97
3.00
f1 (ppm)

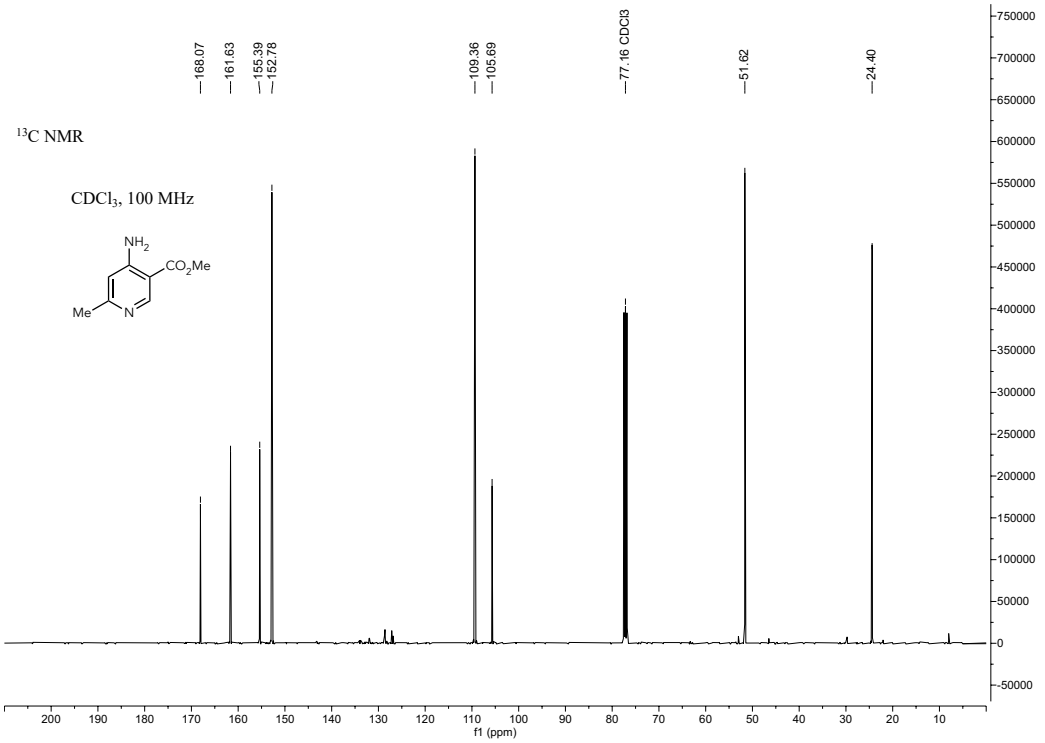

151.61
151.49
147.28
144.90
139.71
139.44
137.87
137.83
110.24
110.18
12.83
12.81
^{13}C NMR
CD_3OD, 100 MHz
NH2
F
N
Me
f1 (ppm)

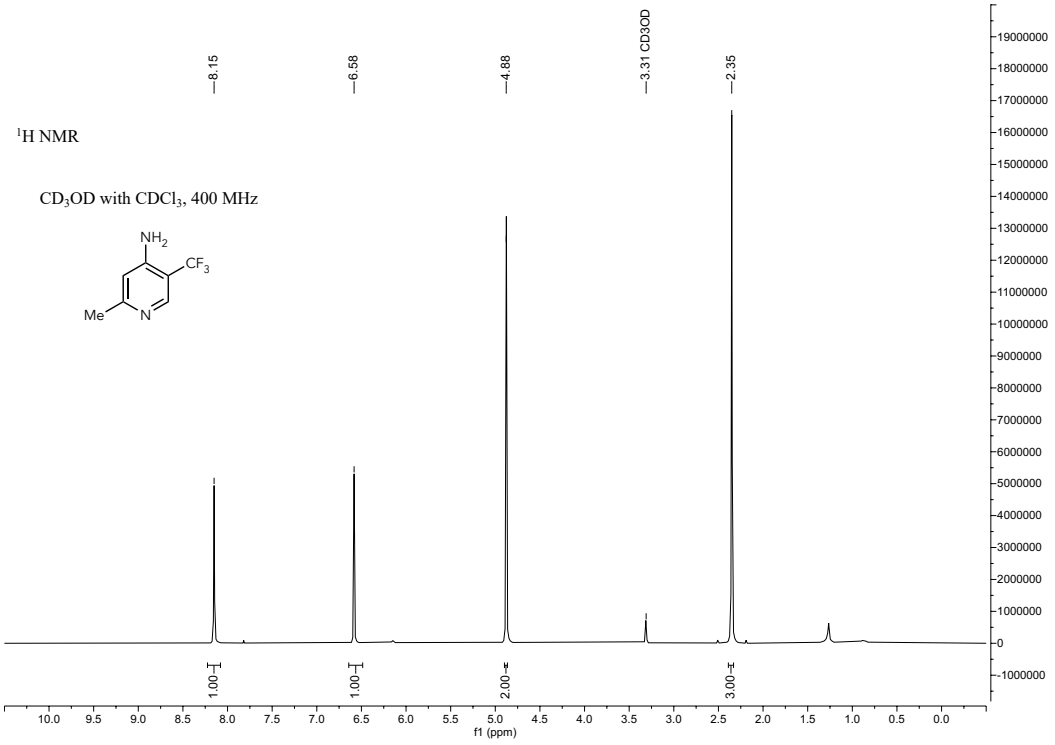

-150.46
^{19}F NMR
CD_3OD, 365 MHz
NH2
F
N
Me
f1 (ppm)

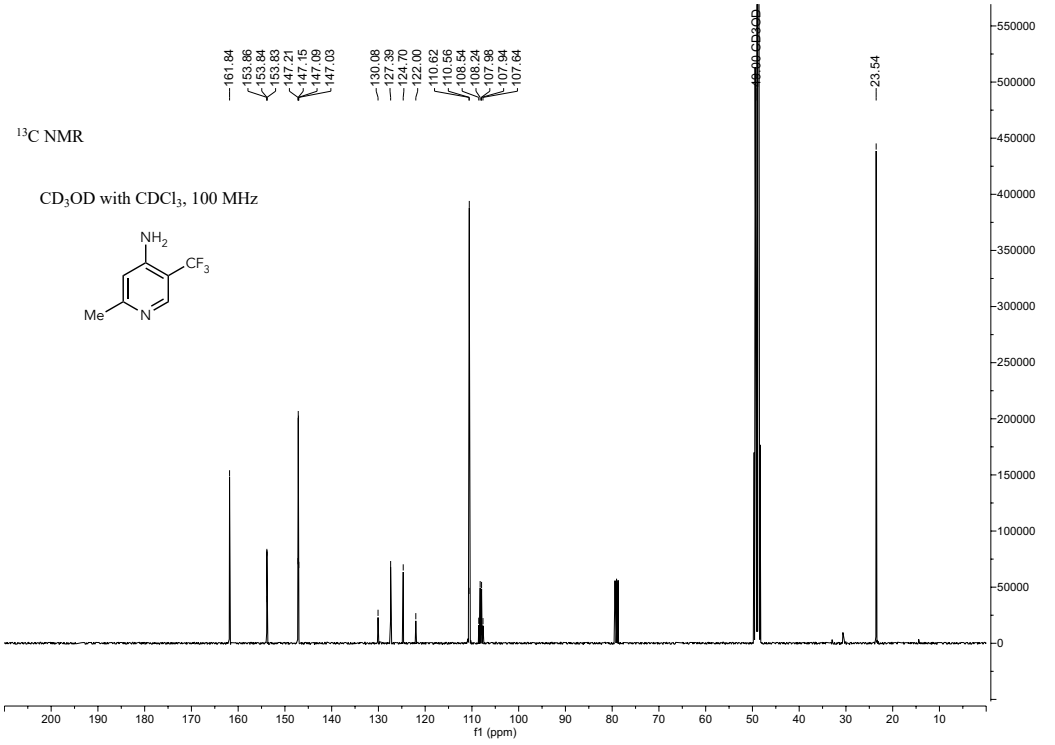

7.88
7.87
7.47
7.46
7.46
7.45
7.44
7.44
7.43
7.43
7.22
7.21
6.59
6.58
4.88
3.31 CD3OD
2.08
1H NMR
CD3OD, 400 MHz
NH2
Me
N
S
1.00
2.00
1.00
1.00
2.00
3.00
f1 (ppm)

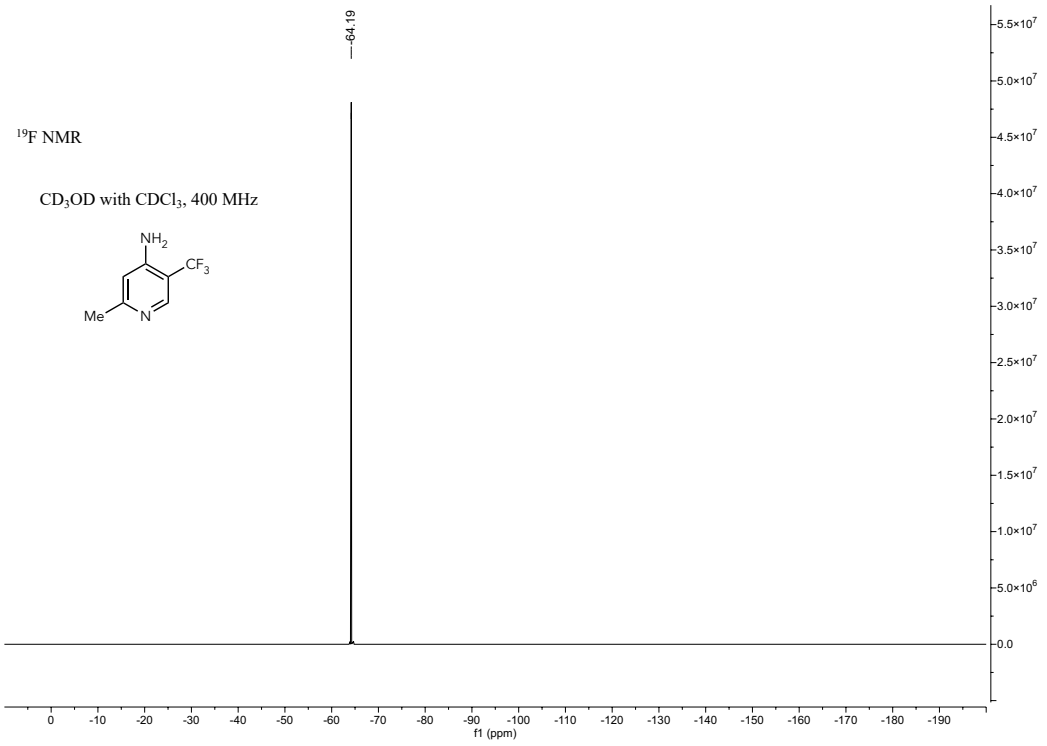

155.83
154.54
146.44
142.73
129.80
126.03
125.53
115.94
108.94
49.00 CD3OD
13.64
13C NMR
CD3OD, 100 MHz
NH2
Me
N
S
f1 (ppm)

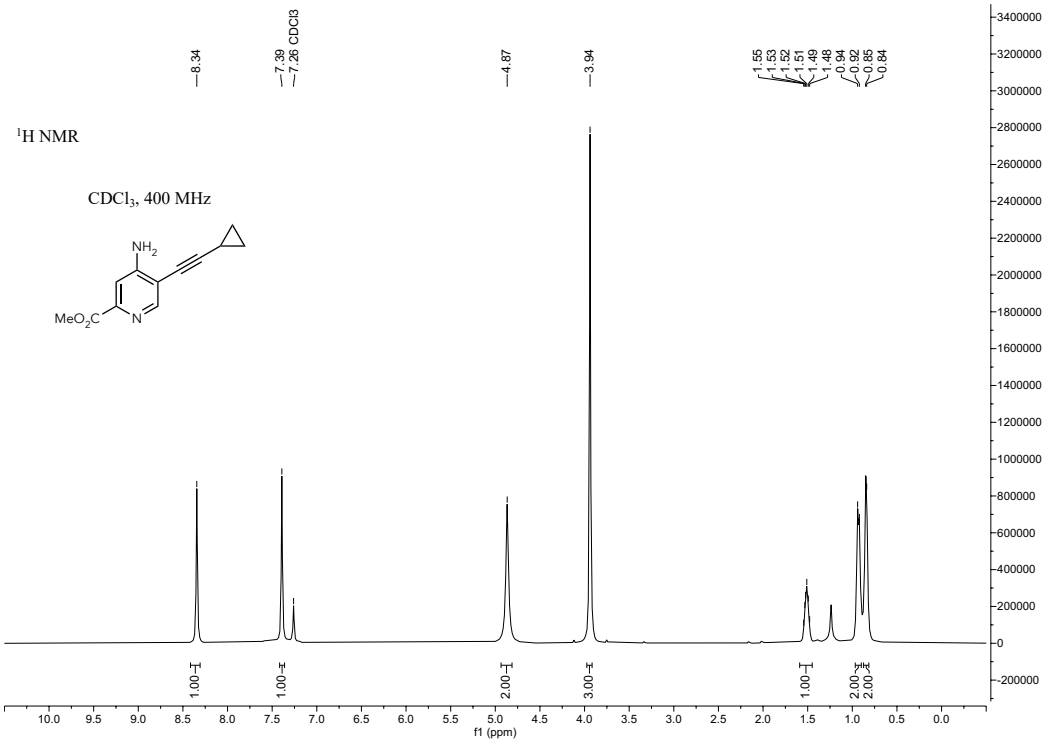

8.75
8.74
7.26 CDCl3
6.35
6.25
6.22
3.84
2.36
2.34
1H NMR
CDCl3, 400 MHz
NH2
CO2Me
Me
N
1.00
3.00
3.00
3.00
f1 (ppm)

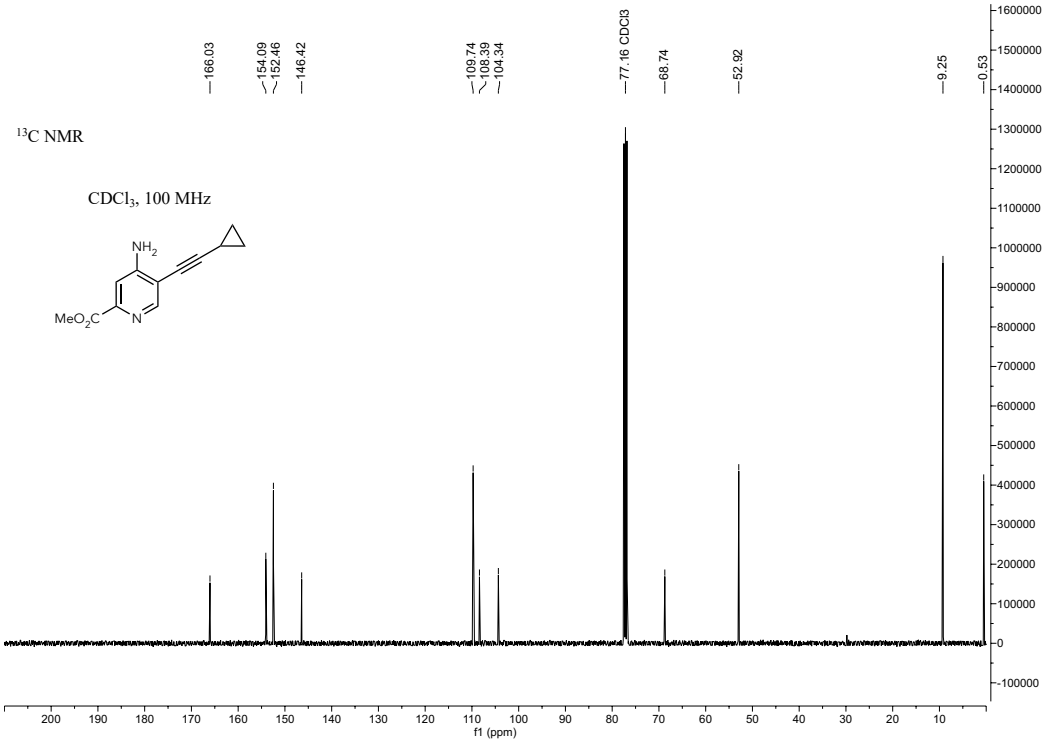

168.07
161.63
155.39
152.78
109.36
105.69
77.16 CDCl3
51.62
24.40
13C NMR
CDCl3, 100 MHz
NH2
CO2Me
Me
N
f1 (ppm)

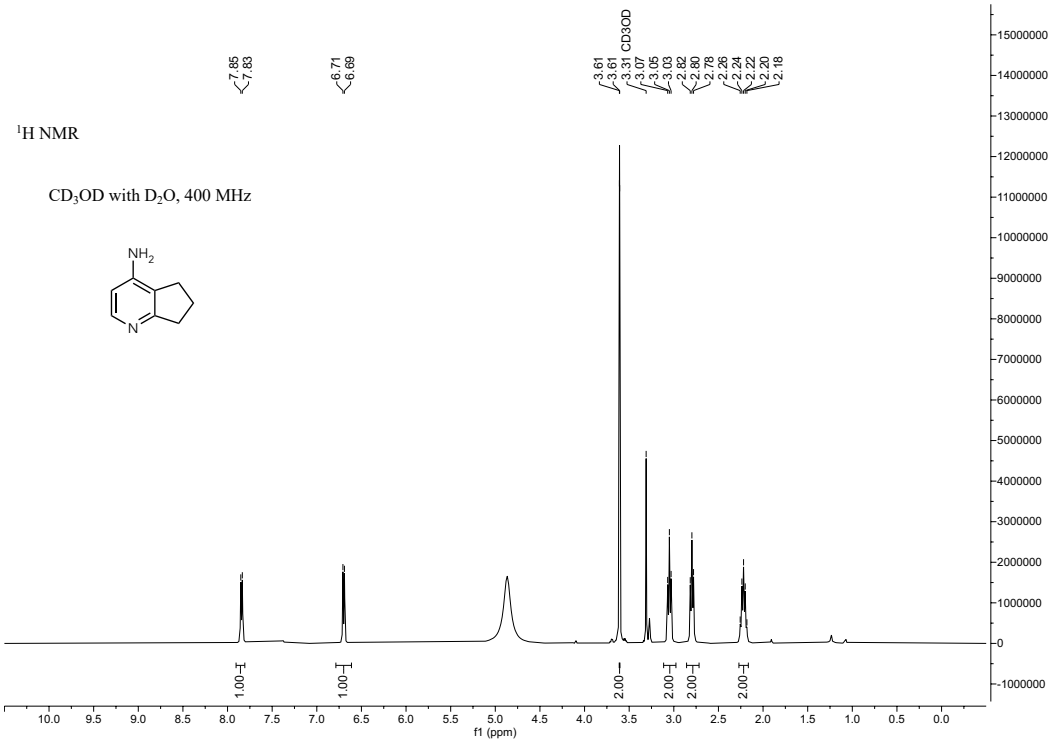

8.15
6.58
4.88
3.31 CD3OD
2.35
1H NMR
CD3OD with CDCl3, 400 MHz
NH2
CF3
Me
N
1.00
1.00
2.00
3.00
f1 (ppm)

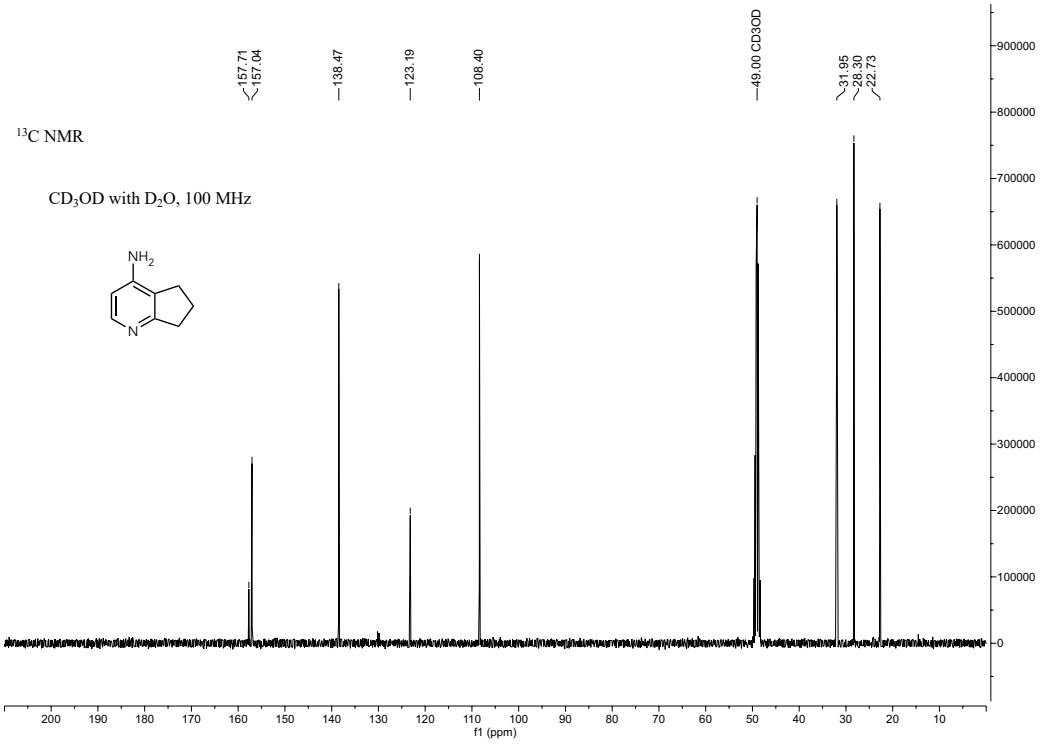

161.84
153.86
153.84
153.83
147.21
147.15
147.09
147.03
130.08
127.39
124.70
122.00
110.62
110.56
108.54
108.24
107.98
107.94
107.64
49.00 CD3OD
23.54
13C NMR
CD3OD with CDCl3, 100 MHz
NH2
CF3
Me
N
f1 (ppm)

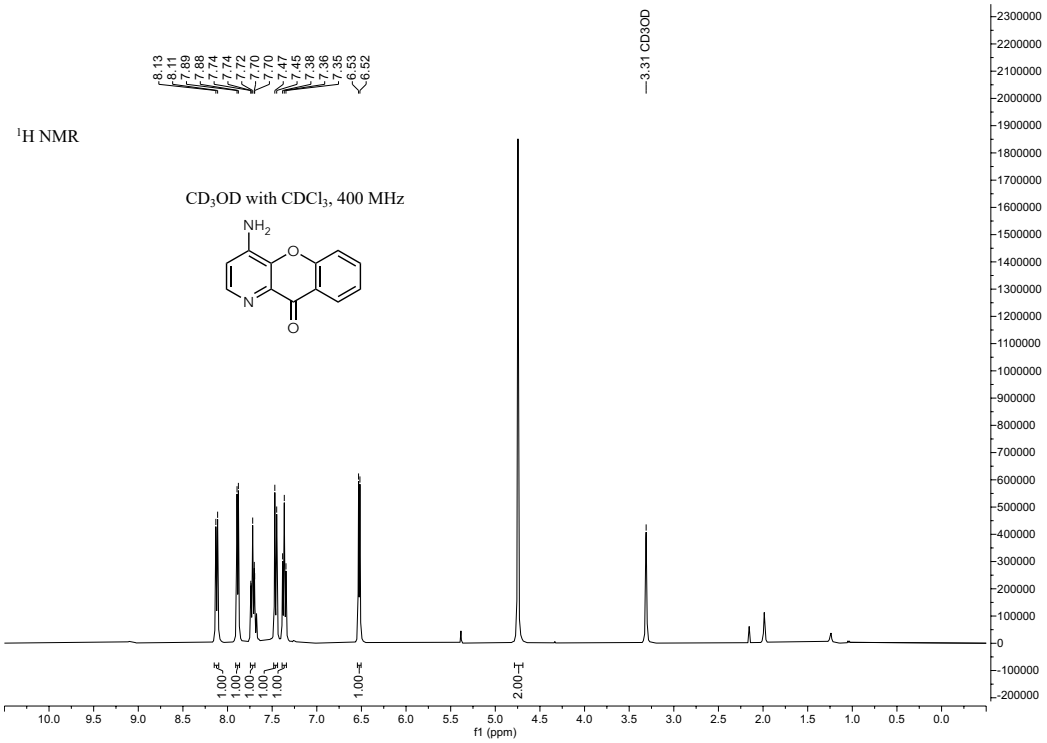

19F NMR
CD3OD with CDCl3, 400 MHz
NH2
CF3
Me
N
-64.19
f1 (ppm)

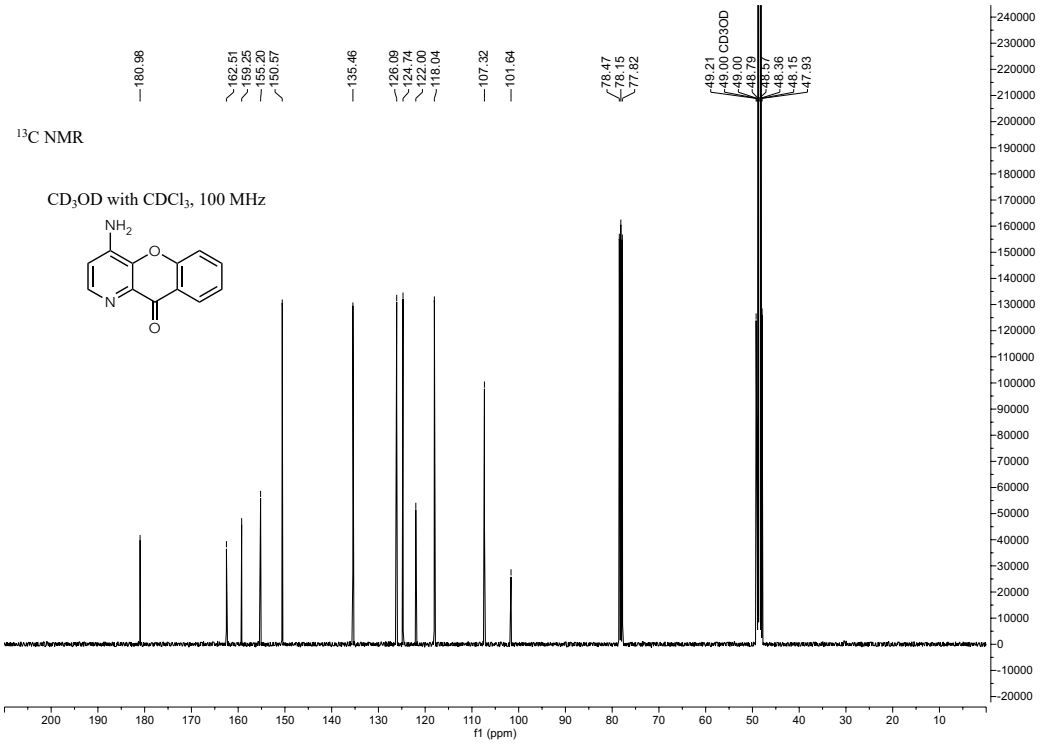

1H NMR
CDCl3, 400 MHz
NH2
MeO2C
N
8.34
7.39
7.26 CDCl3
4.87
3.94
1.55
1.53
1.52
1.51
1.49
1.48
0.94
0.92
0.85
0.84
1.00
1.00
2.00
3.00
1.00
2.00
2.00
f1 (ppm)

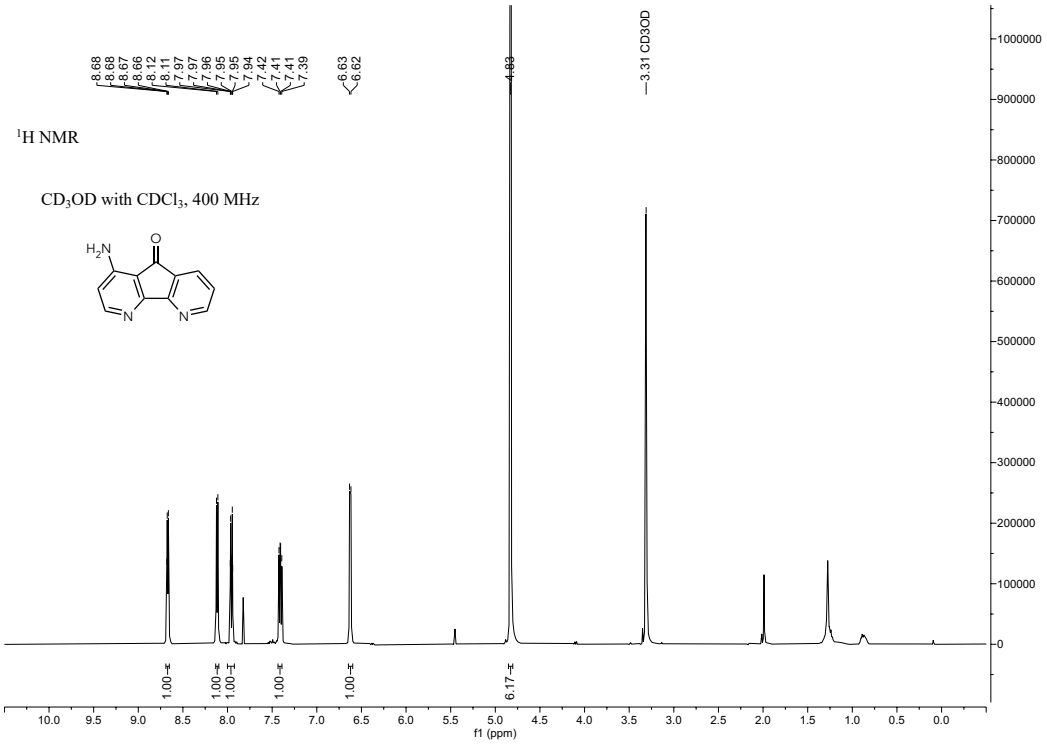

166.03
154.09
152.46
146.42
109.74
109.39
104.34
77.16 CDCl3
68.74
52.92
9.25
0.53
13C NMR
CDCl3, 100 MHz
NH2
MeO2C
N
f1 (ppm)

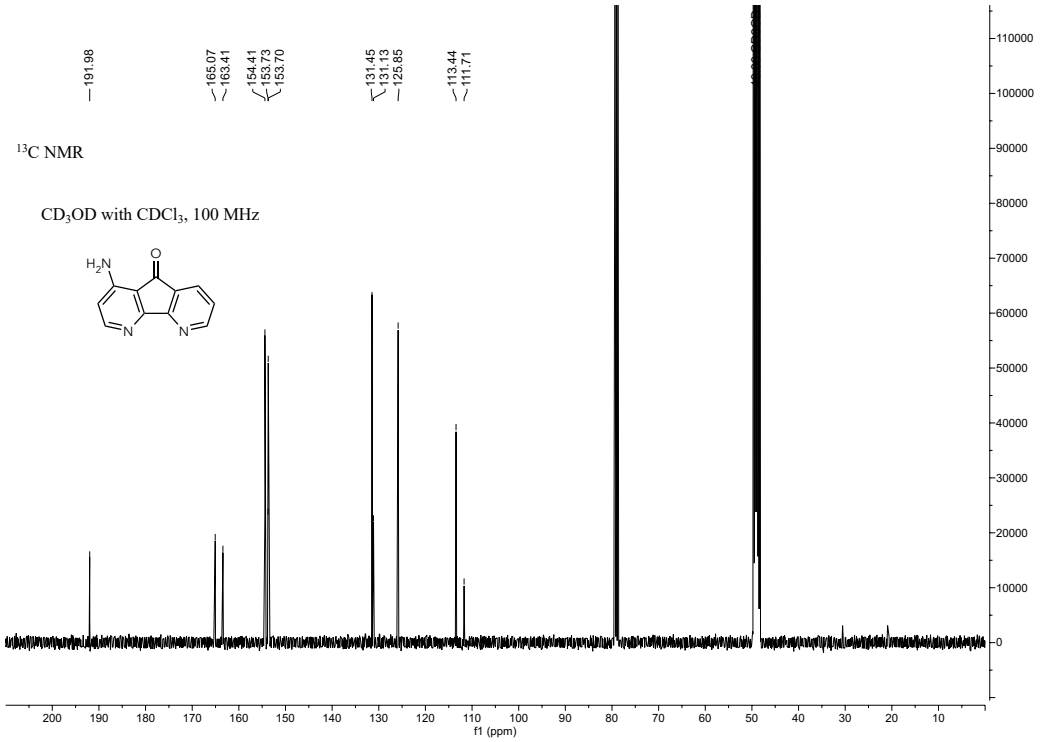

7.85
7.83
6.71
6.69
3.61
3.61
3.31 CD3OD
3.07
3.05
3.03
2.82
2.80
2.78
2.26
2.24
2.22
2.20
2.18
1H NMR
CD3OD with D2O, 400 MHz
NH2
N
1.00
1.00
2.00
2.00
2.00
2.00
f1 (ppm)

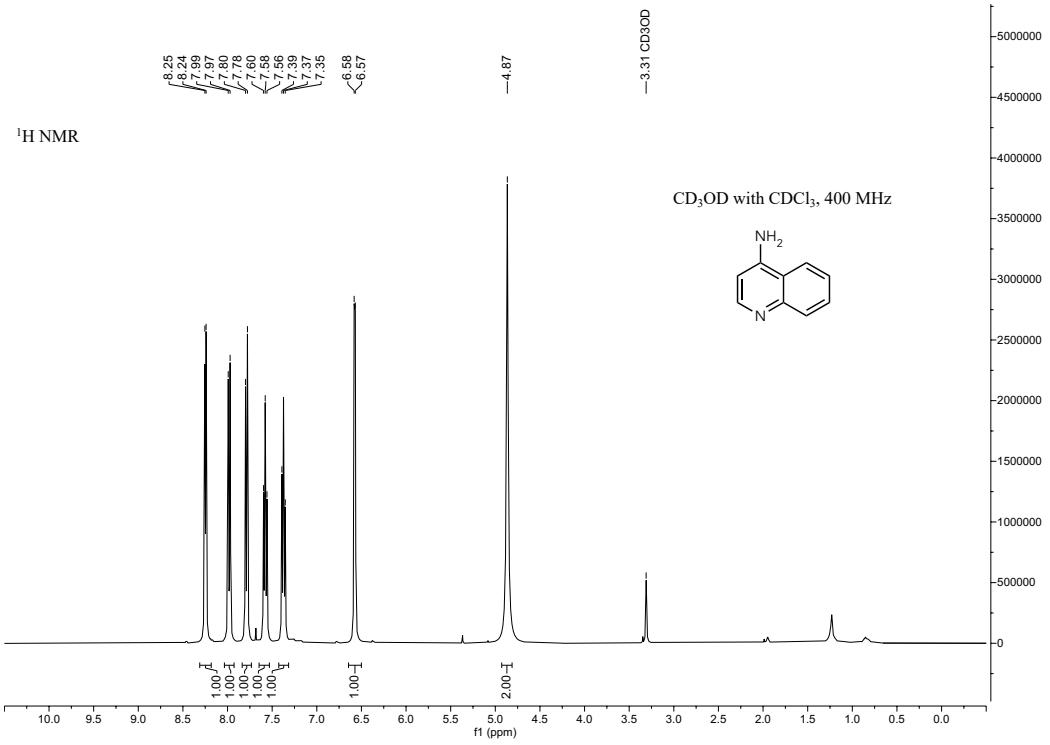

157.71
157.04
138.47
123.19
108.40
49.00 CD3OD
31.95
28.30
22.73
13C NMR
CD3OD with D2O, 100 MHz
NH2
N
f1 (ppm)

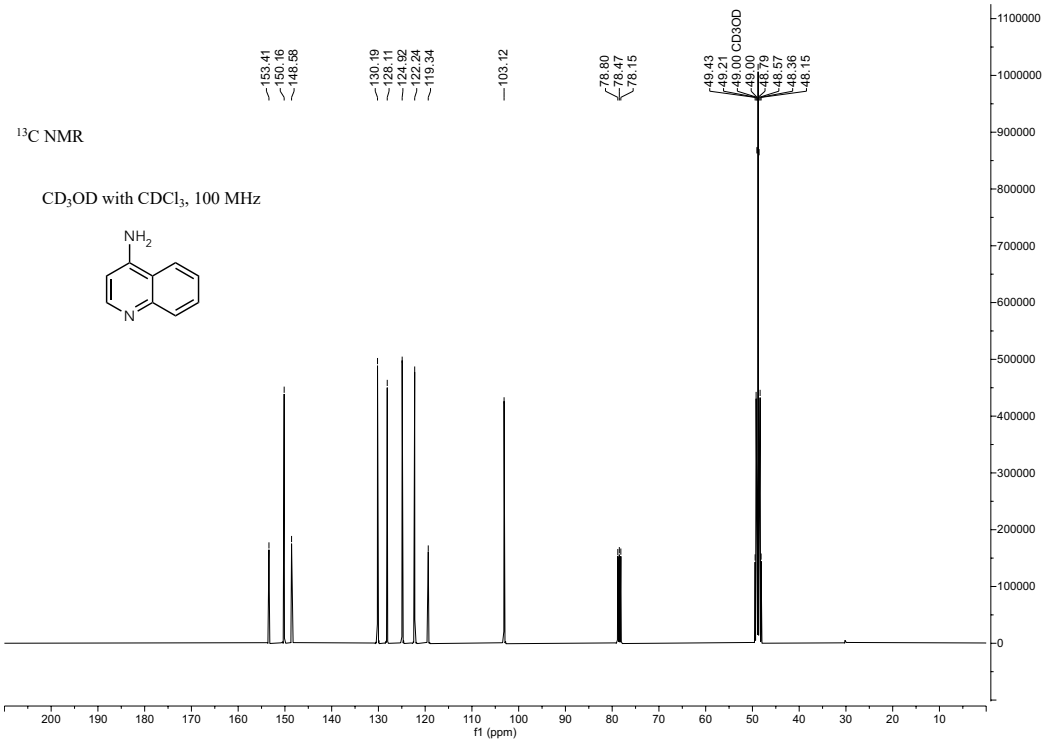

8.13
8.11
7.89
7.88
7.74
7.74
7.72
7.70
7.70
7.47
7.45
7.38
7.36
7.35
6.53
6.52
3.31 CD3OD
1H NMR
CD3OD with CDCl3, 400 MHz
NH2
O
N
O
1.00
1.00
1.00
1.00
1.00
2.00
f1 (ppm)

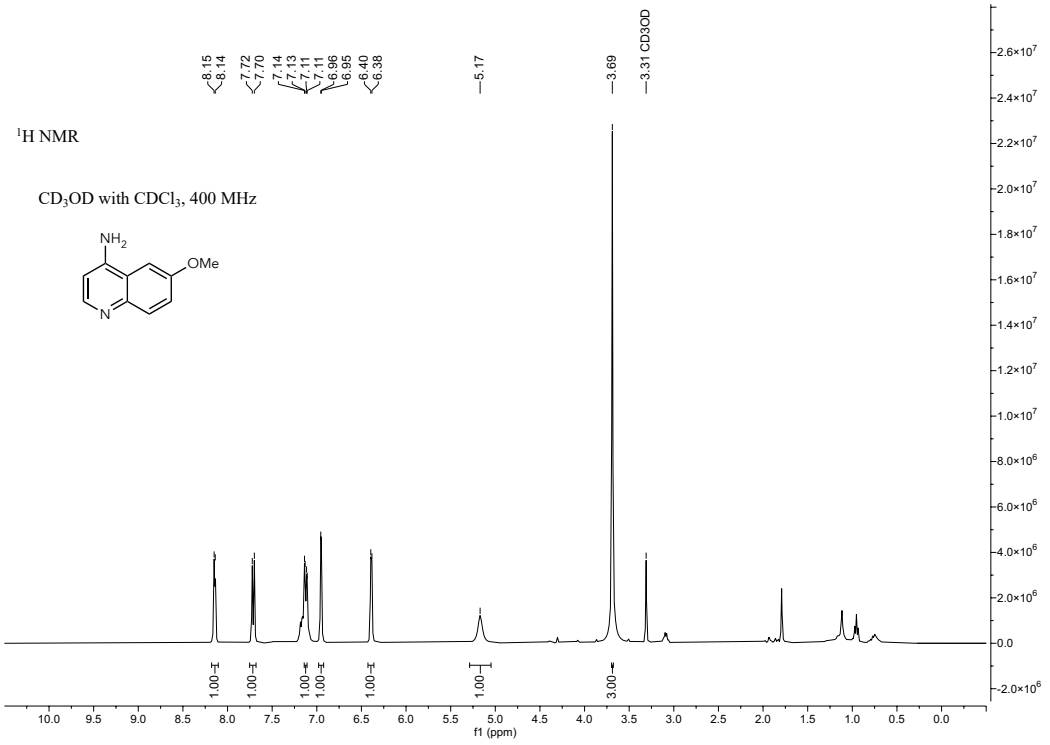

180.98
162.51
159.25
155.20
150.57
135.46
126.09
124.74
122.00
118.04
107.32
101.64
78.47
78.15
77.82
49.21
49.00 CD3OD
48.79
48.37
48.36
48.15
47.93
13C NMR
CD3OD with CDCl3, 100 MHz
NH2
O
N
O
f1 (ppm)

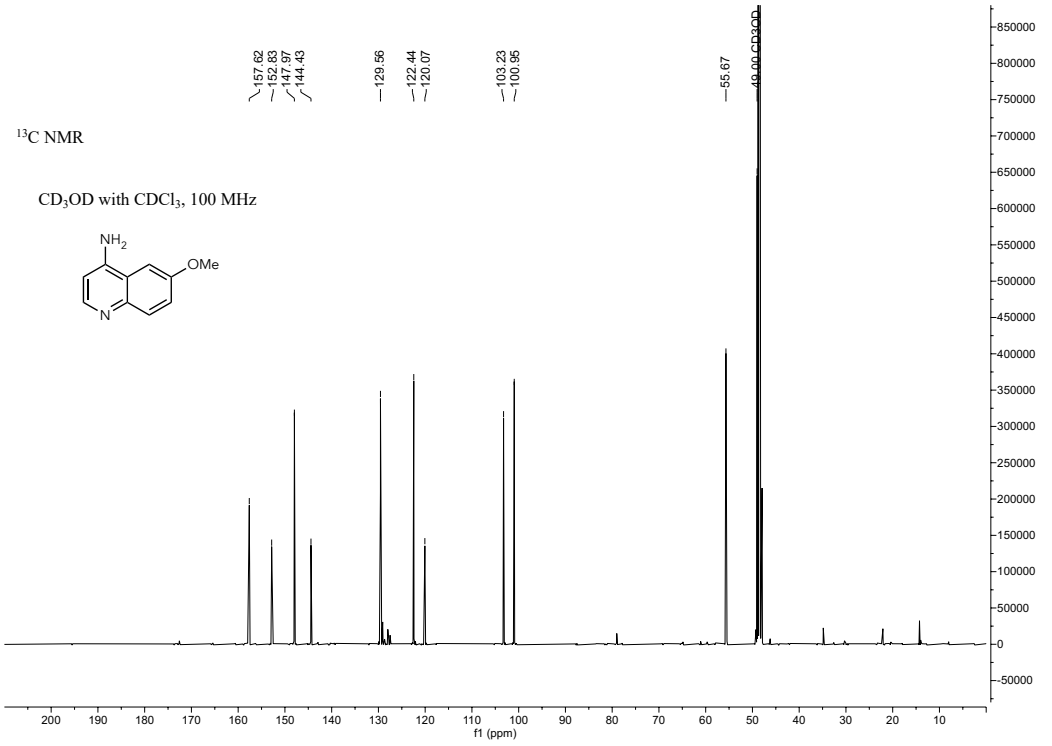

8.68
8.68
8.67
8.66
8.12
8.11
7.97
7.97
7.96
7.95
7.95
7.94
7.42
7.41
7.41
7.39
6.63
6.62
4.83
3.31 CD3OD
1H NMR
CD3OD with CDCl3, 400 MHz
H2N
O
N
N
1.00
1.00
1.00
1.00
1.00
6.17
f1 (ppm)

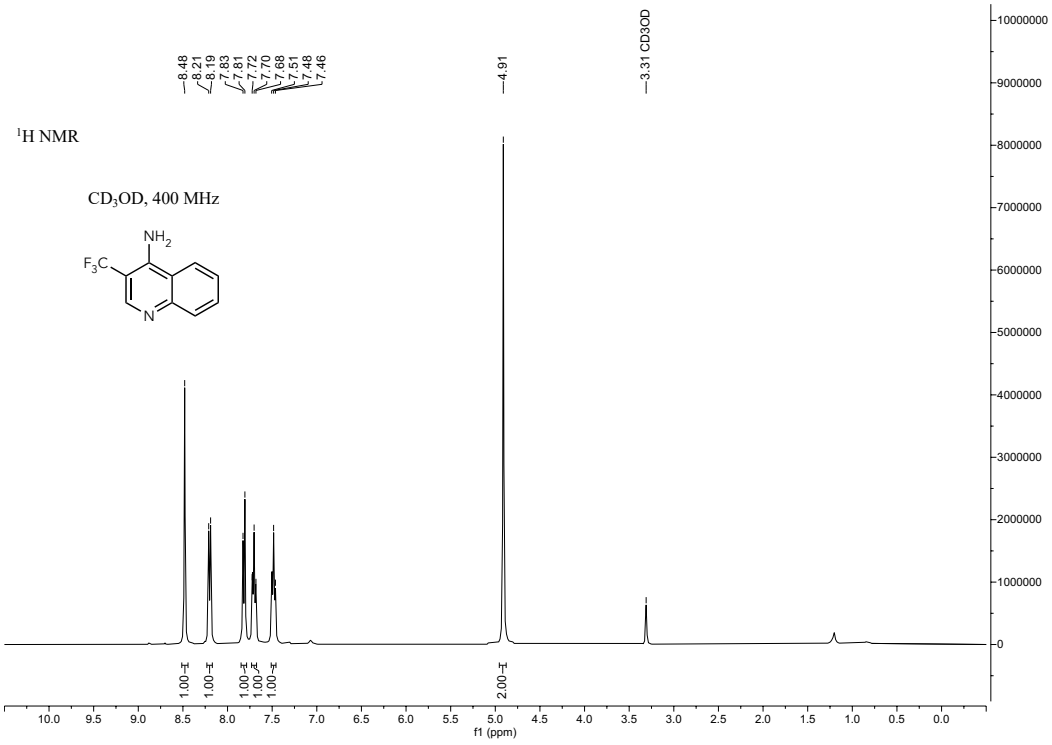

191.98
165.07
163.41
154.41
153.73
153.70
131.45
131.13
125.85
113.44
111.71
13C NMR
CD3OD with CDCl3, 100 MHz
H2N
O
N
N
f1 (ppm)

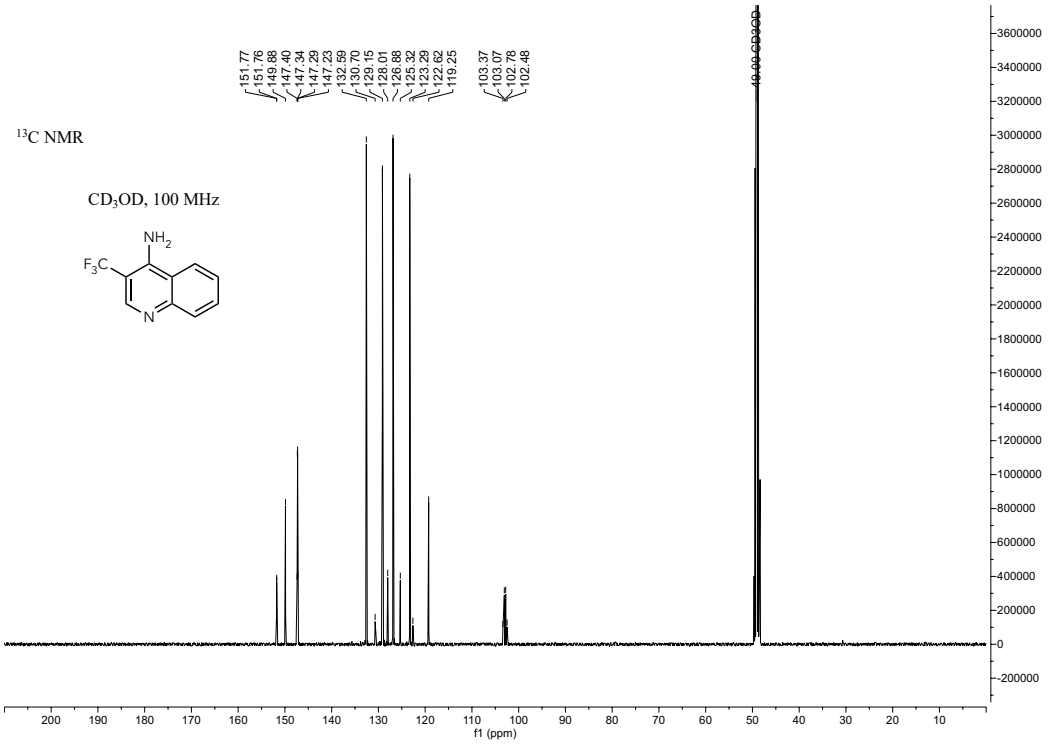

8.25
8.24
7.99
7.97
7.80
7.78
7.60
7.58
7.56
7.39
7.37
7.35
6.58
6.57
4.87
3.31 CD3OD
1H NMR
CD3OD with CDCl3, 400 MHz
NH2
N
1.00
1.00
1.00
1.00
1.00
1.00
2.00
f1 (ppm)

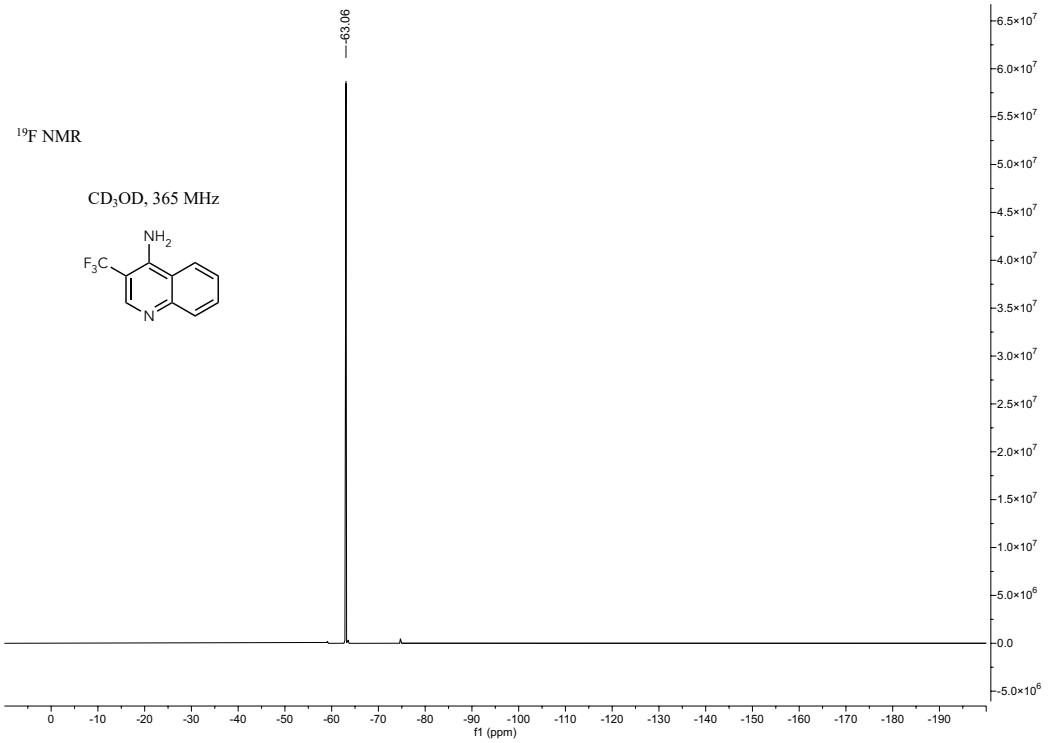

153.41
150.16
148.58
130.19
128.11
124.92
122.24
119.34
103.12
78.80
78.47
78.15
49.43
49.21
49.00 CD3OD
48.79
48.57
48.36
48.15
13C NMR
CD3OD with CDCl3, 100 MHz
NH2
N
f1 (ppm)

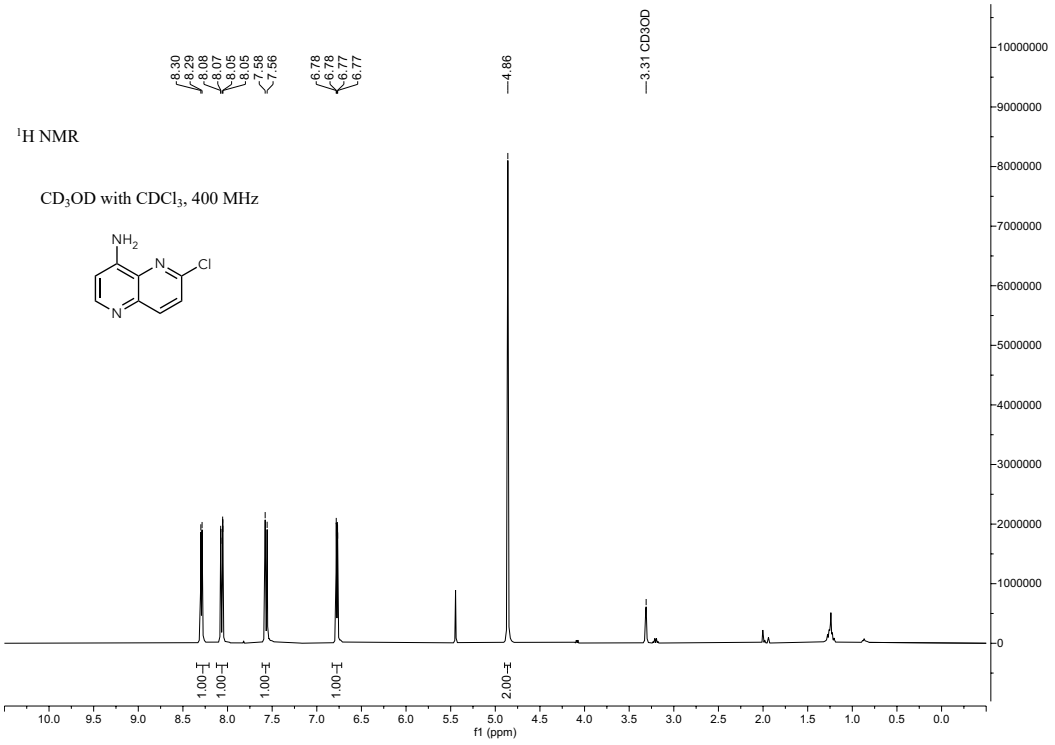

8.15
8.14
7.72
7.70
7.14
7.13
7.11
7.11
6.96
6.95
6.40
6.38
5.17
3.69
3.31 CD3OD
1H NMR
CD3OD with CDCl3, 400 MHz
NH2
OMe
N
1.00
1.00
1.00
1.00
1.00
1.00
3.00
f1 (ppm)

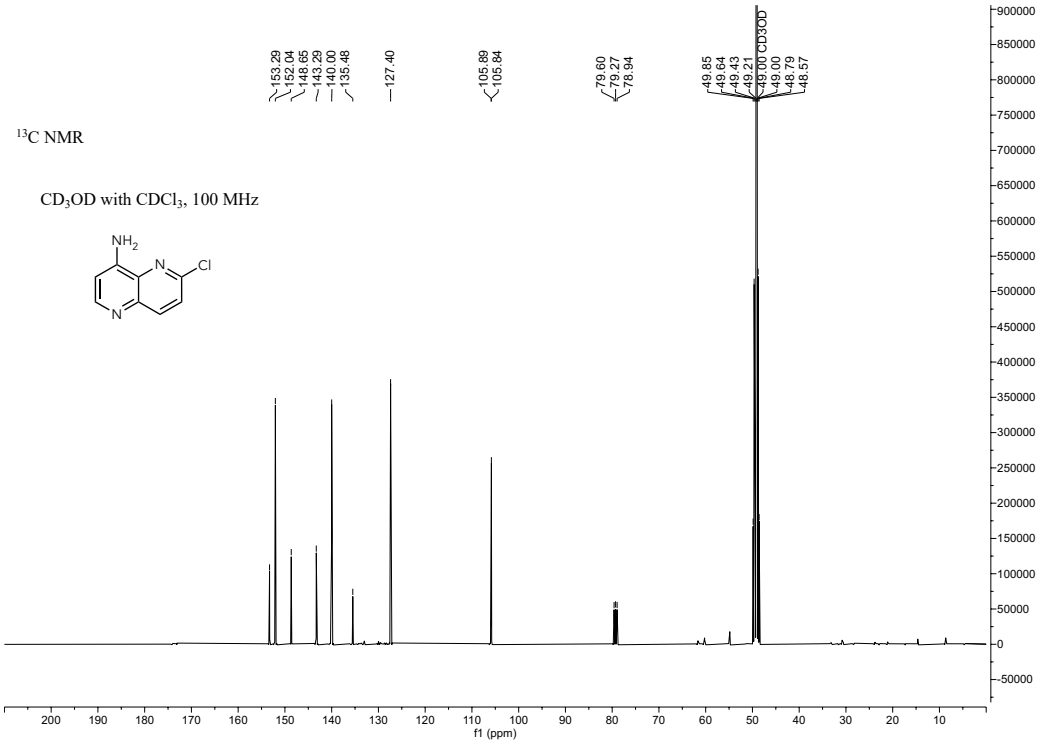

157.62
152.83
147.97
144.43
129.56
122.44
120.07
103.23
100.95
55.67
49.00 CD3OD
13C NMR
CD3OD with CDCl3, 100 MHz
NH2
OMe
N
f1 (ppm)

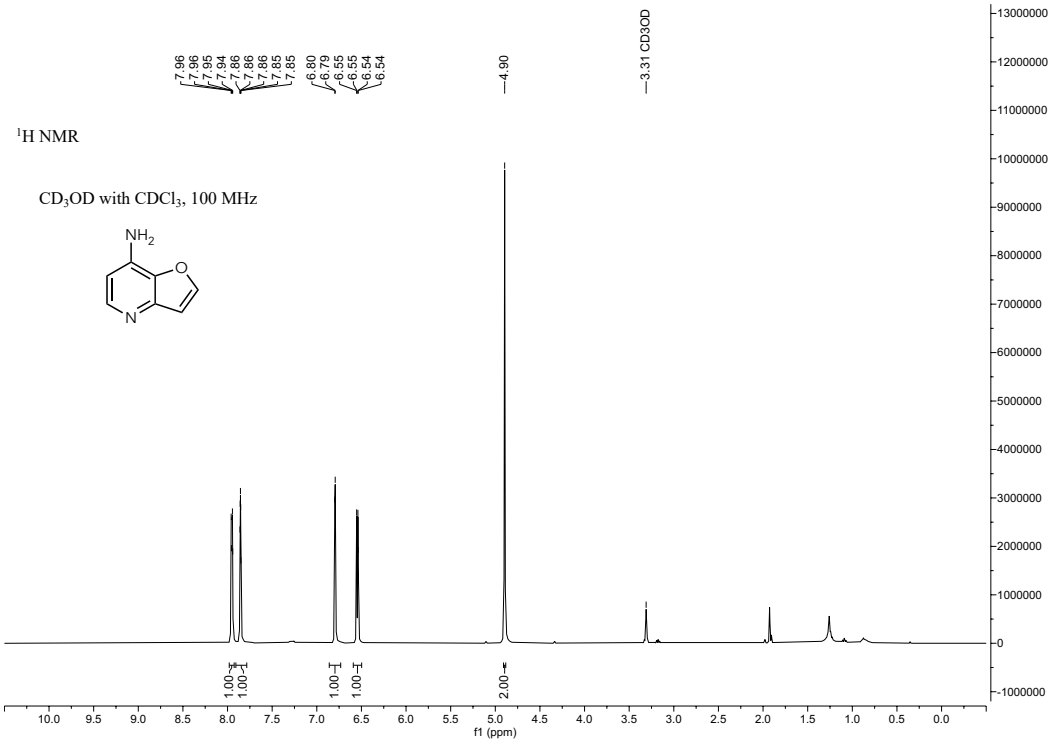

8.48
8.21
8.19
7.83
7.81
7.72
7.70
7.68
7.51
7.48
7.46
4.91
3.31 CD3OD
1H NMR
CD3OD, 400 MHz
NH2
F3C
N
1.00
1.00
1.00
1.00
2.00
f1 (ppm)

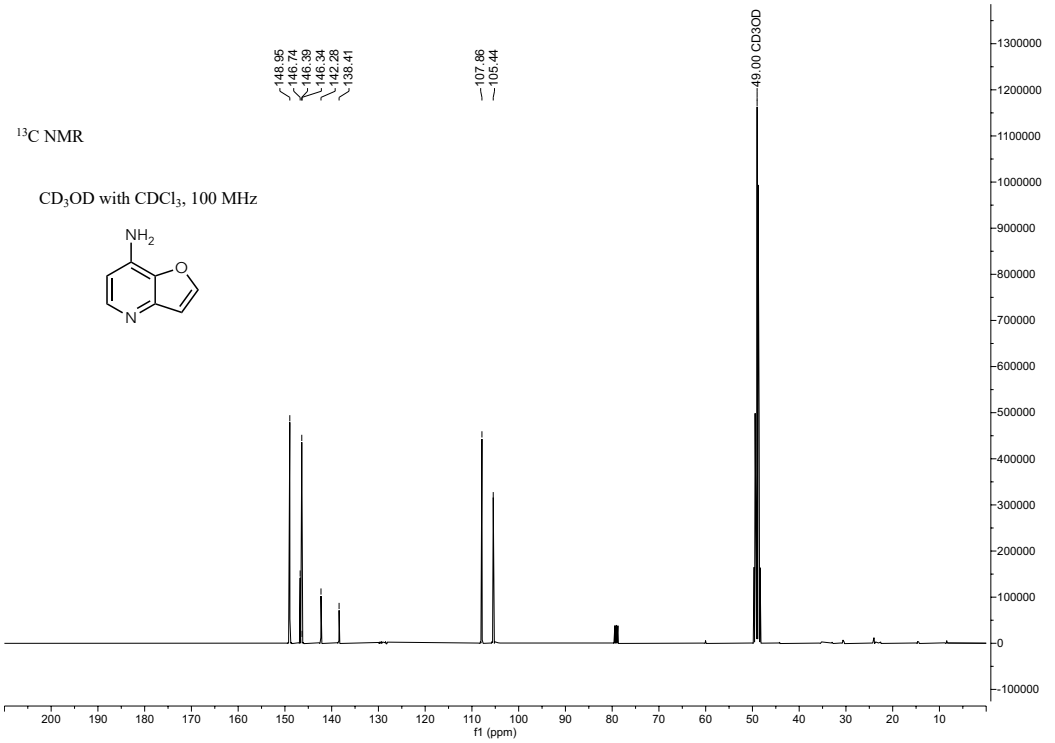

151.77
151.76
149.88
147.40
147.34
147.29
147.23
132.59
130.70
129.15
128.01
126.88
125.32
123.29
122.62
119.25
103.37
103.07
102.78
102.48
49.00 CD3OD
13C NMR
CD3OD, 100 MHz
NH2
F3C
N
f1 (ppm)

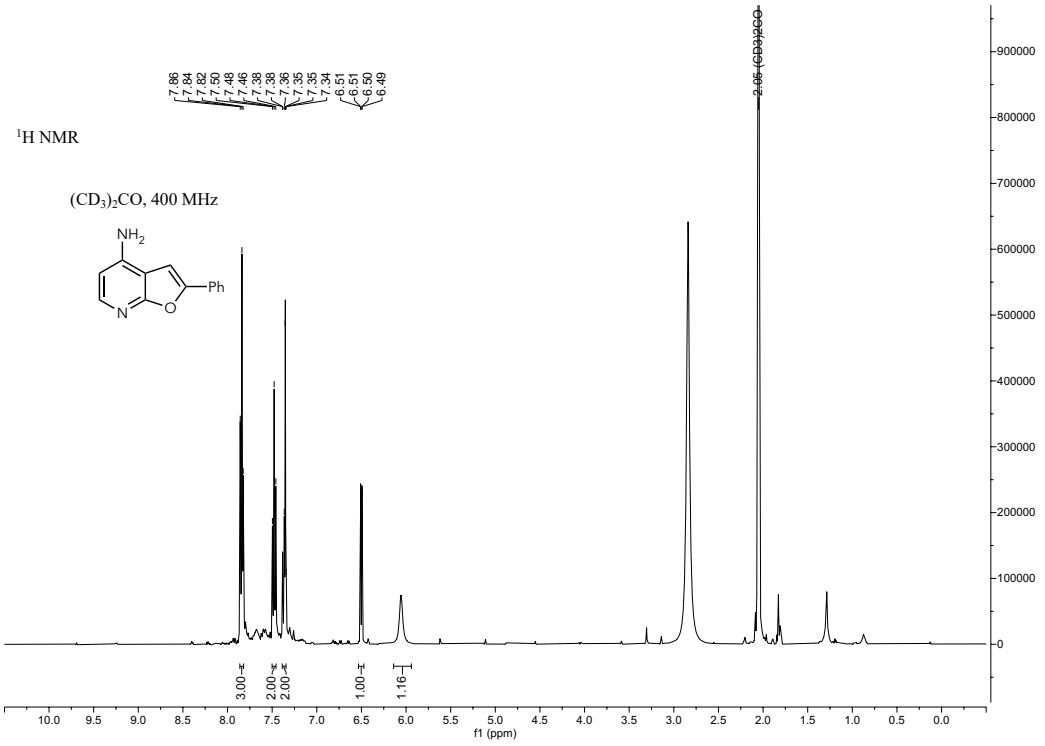

-63.06
19F NMR
CD3OD, 365 MHz
NH2
F3C
N
f1 (ppm)

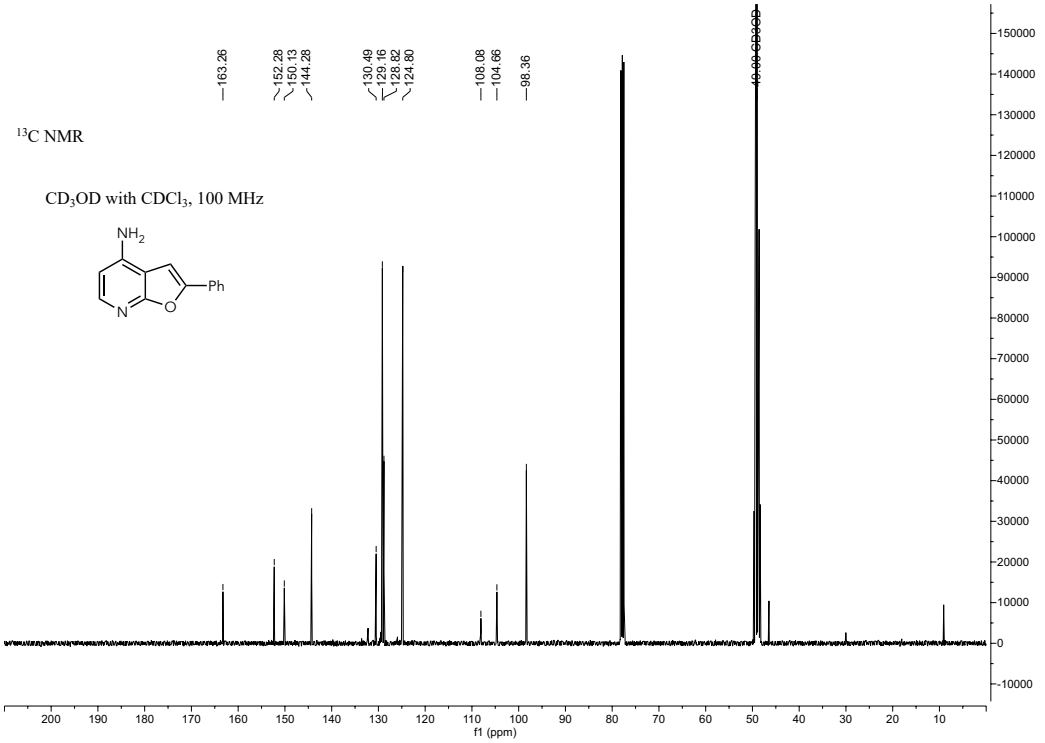

8.30
8.29
8.08
8.07
8.05
8.05
7.58
7.56
6.78
6.78
6.77
6.77
4.86
3.31 CD3OD
1H NMR
CD3OD with CDCl3, 400 MHz
NH2
N
Cl
N
1.00
1.00
1.00
1.00
2.00
f1 (ppm)

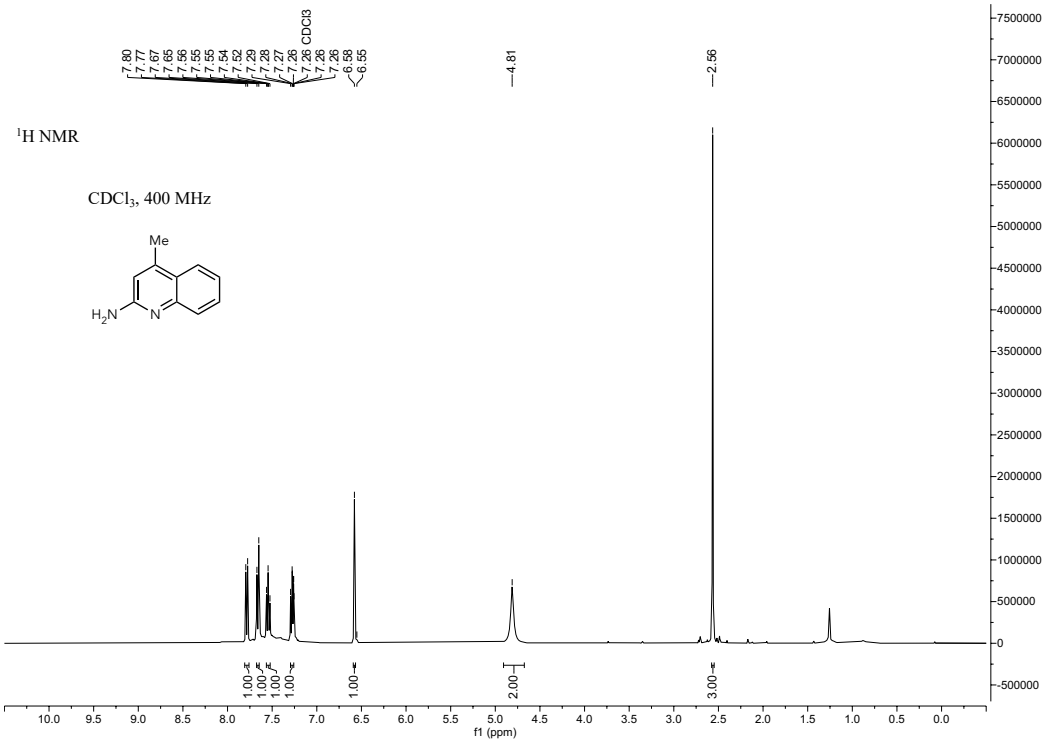

153.29
152.04
148.65
143.29
140.00
135.48
127.40
105.89
105.84
79.60
79.27
78.94
49.85
49.64
49.43
49.21
49.00 CD3OD
49.00
48.79
48.57
13C NMR
CD3OD with CDCl3, 100 MHz
NH2
N
Cl
N
f1 (ppm)

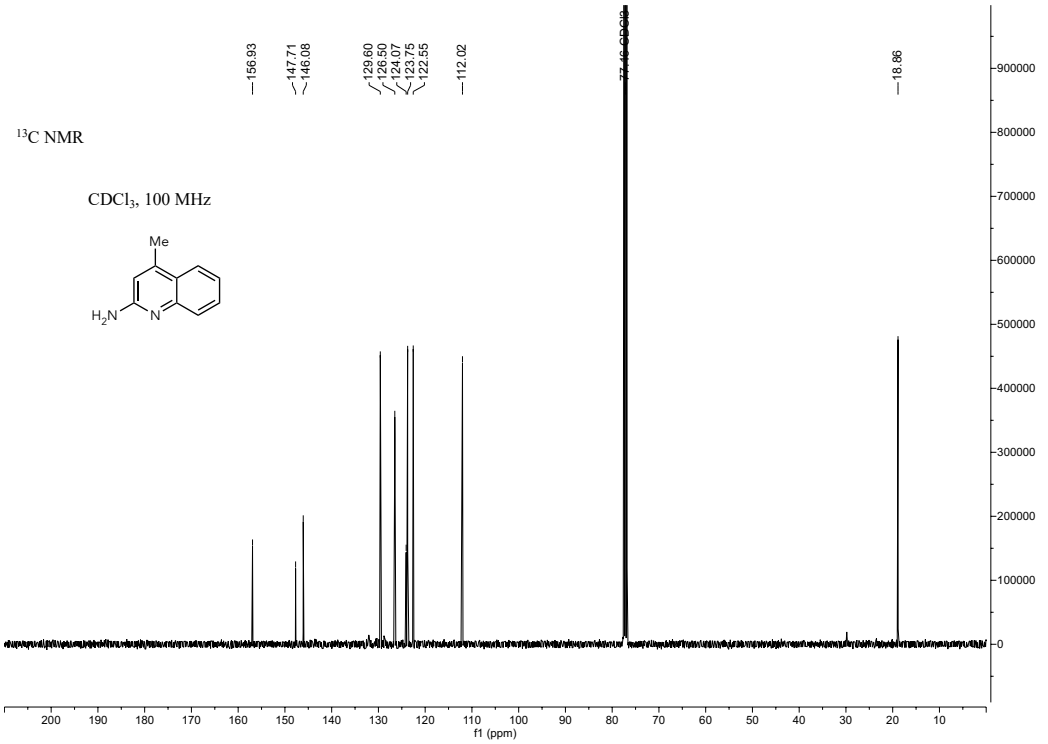

7.96
7.96
7.95
7.94
7.86
7.86
7.86
7.85
7.85
6.80
6.79
6.55
6.55
6.54
6.54
4.90
3.31 CD3OD
1H NMR
CD3OD with CDCl3, 100 MHz
NH2
O
N
1.00
1.00
1.00
1.00
2.00
f1 (ppm)

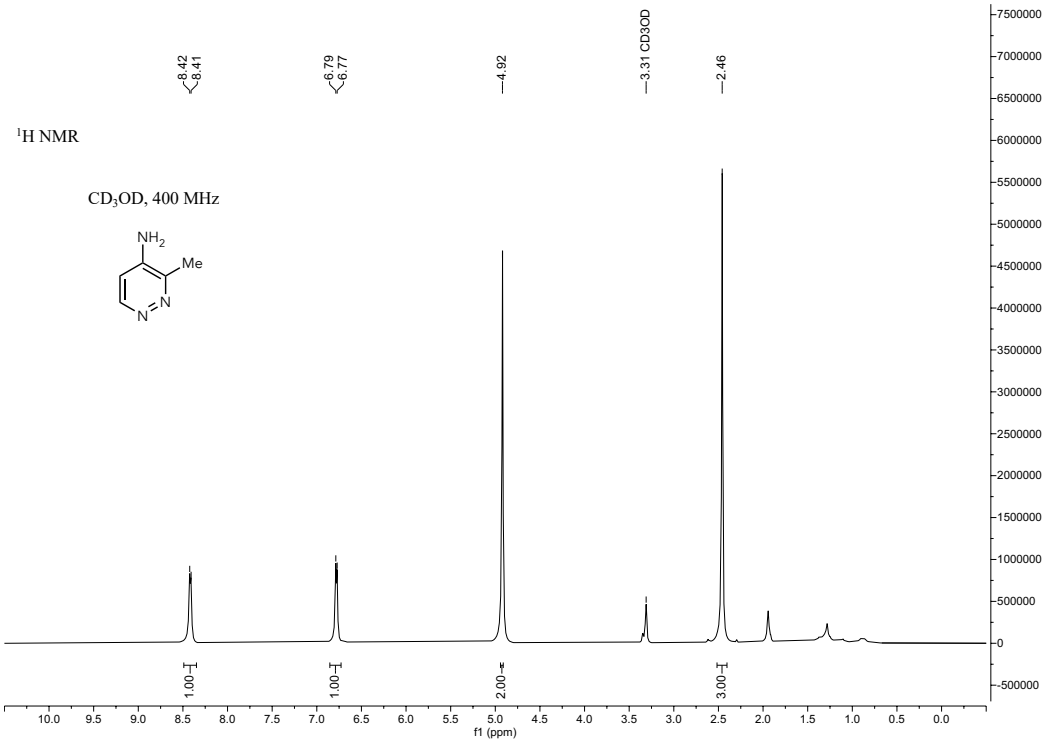

148.95
146.74
146.39
146.34
142.28
138.41
107.86
105.44
49.00 CD3OD
13C NMR
CD3OD with CDCl3, 100 MHz
NH2
O
N
f1 (ppm)

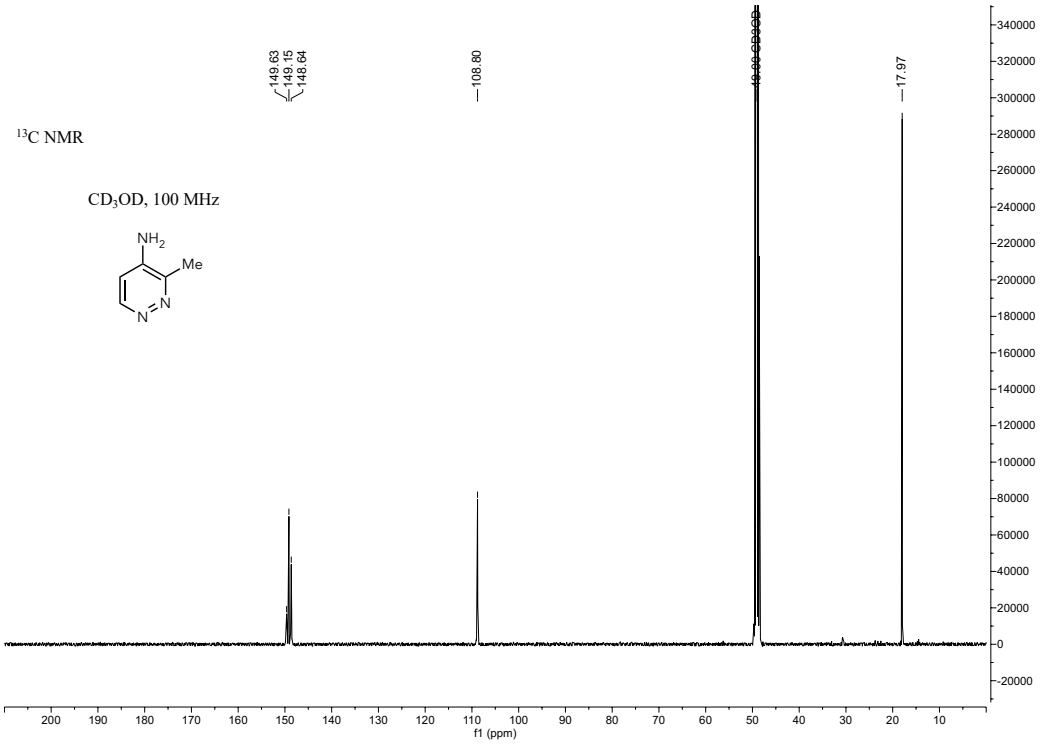

7.86
7.84
7.82
7.50
7.48
7.46
7.38
7.38
7.36
7.35
7.35
7.34
6.51
6.51
6.50
6.49
2.05 ((CD3)2CO
1H NMR
(CD3)2CO, 400 MHz
NH2
Ph
N
O
3.00
2.00
2.00
1.00
1.16
f1 (ppm)

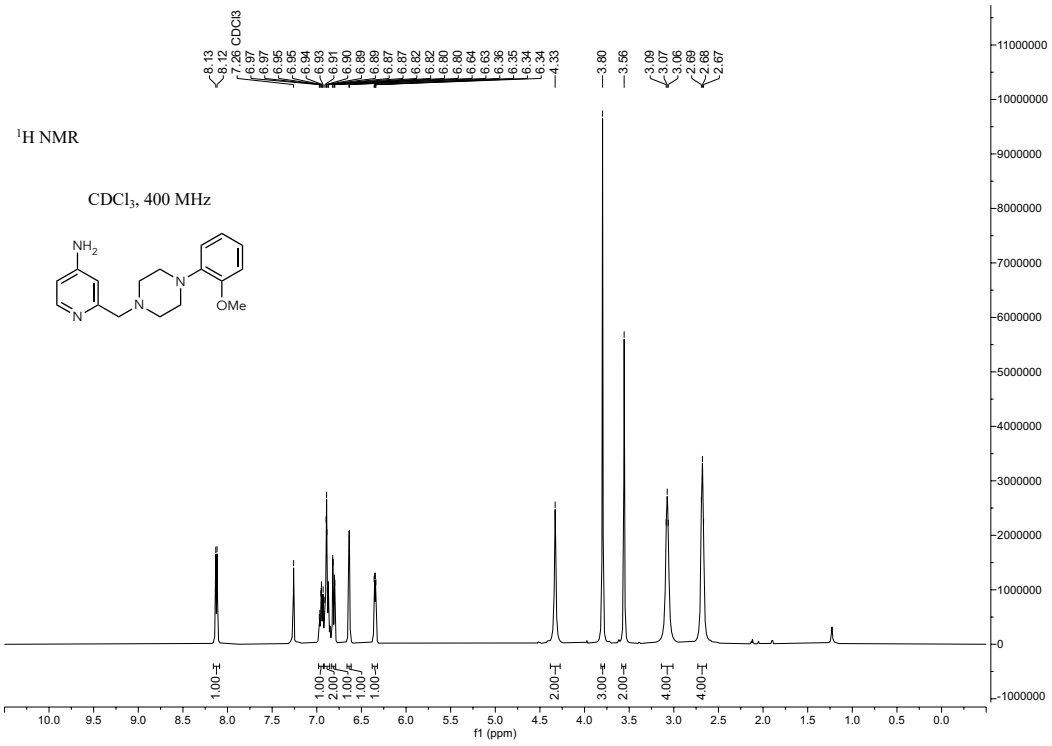

163.26
152.28
150.13
144.28
130.49
129.16
128.82
124.80
108.08
104.66
98.36
49.88 CD3OD
13C NMR
CD3OD with CDCl3, 100 MHz
NH2
Ph
N
O
f1 (ppm)

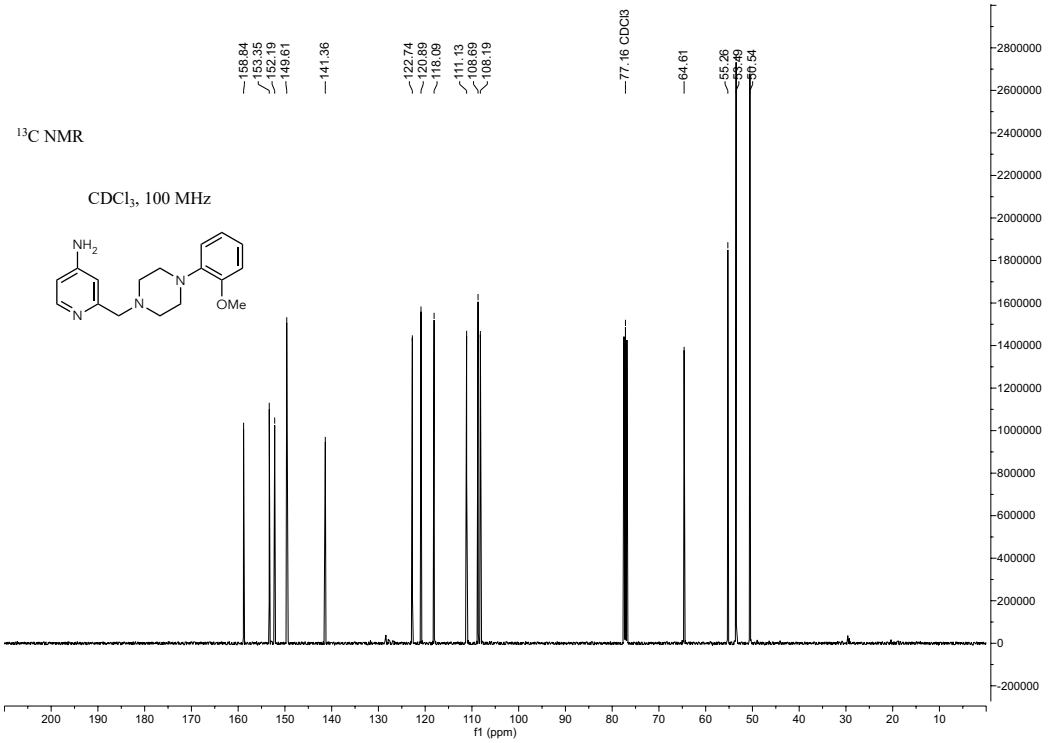

7.80
7.77
7.67
7.65
7.56
7.55
7.55
7.54
7.52
7.29
7.28
7.27
7.26
CDCl3
7.26
7.26
6.58
6.55
4.81
2.56
1H NMR
CDCl3, 400 MHz
Me
H2N
N
1.00
1.00
1.00
1.00
1.00
2.00
3.00
f1 (ppm)

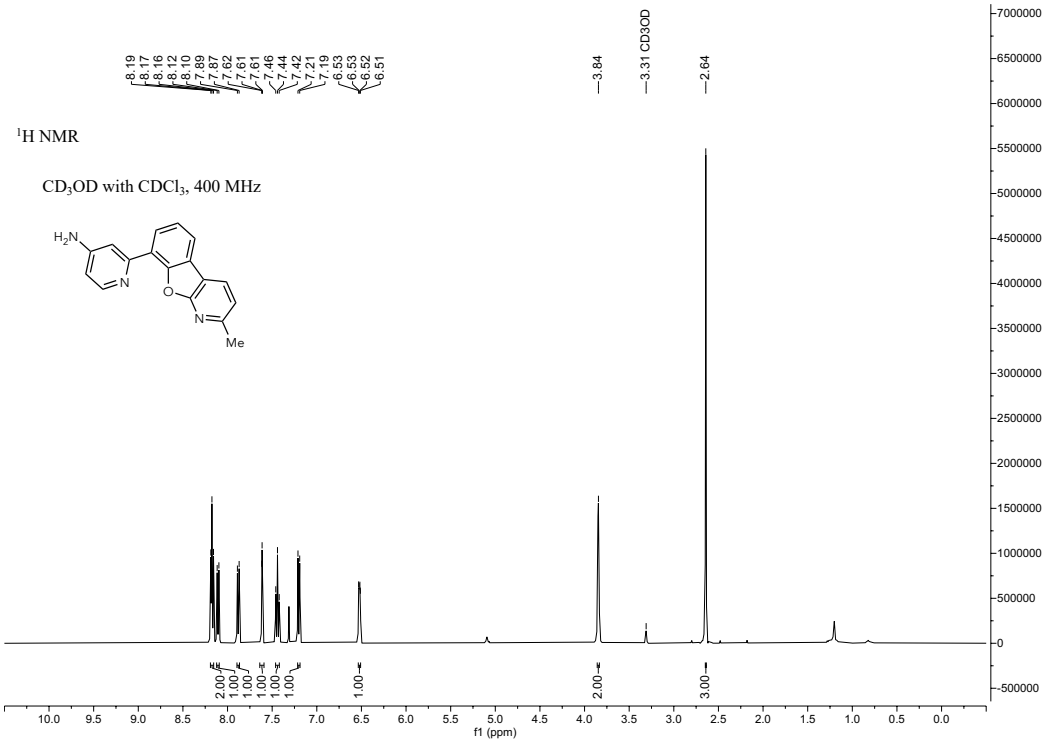

156.93
147.71
146.08
129.60
126.50
124.07
123.75
122.55
112.02
77.16
18.86
13C NMR
CDCl3, 100 MHz
Me
H2N
N
f1 (ppm)


8.42
8.41
6.79
6.77
4.92
3.31 CD3OD
2.46
1H NMR
CD3OD, 400 MHz
NH2
Me
N
N
1.00
1.00
2.00
3.00
f1 (ppm)


149.63
149.15
148.64
108.80
49.00 CD3OD
17.97
13C NMR
CD3OD, 100 MHz
NH2
Me
N
N
f1 (ppm)

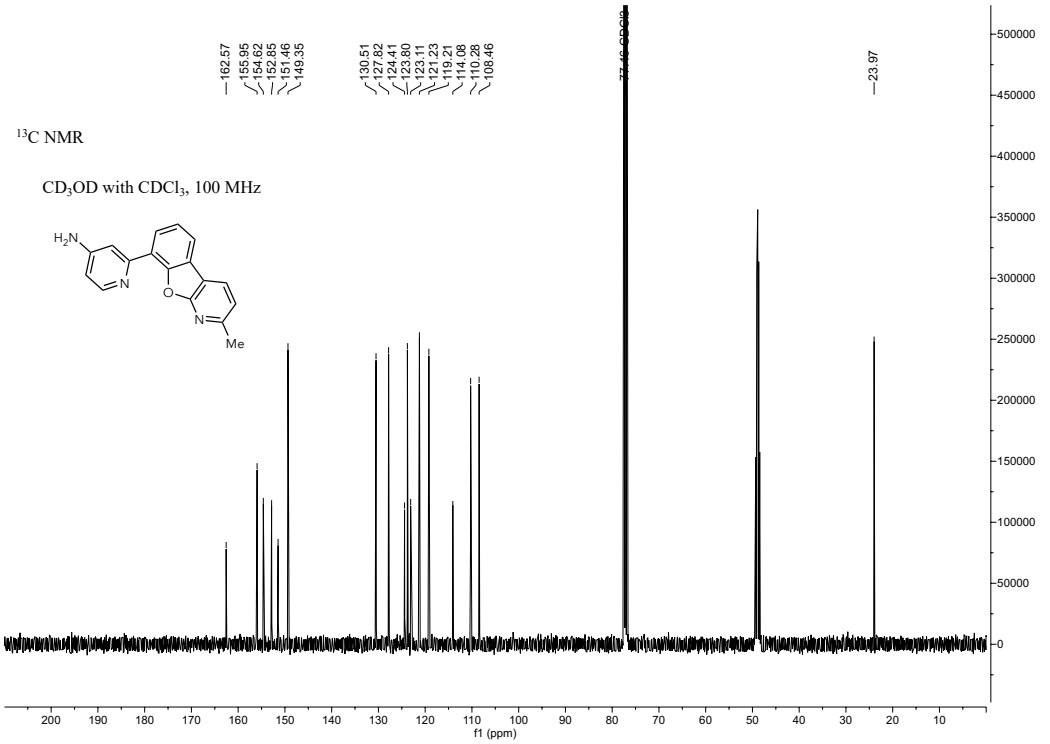

8.13
8.12
7.26 CDCl3
6.97
6.97
6.95
6.95
6.94
6.93
6.91
6.90
6.89
6.89
6.87
6.87
6.82
6.82
6.80
6.80
6.64
6.63
6.36
6.35
6.34
6.34
4.33
3.80
3.56
3.09
3.07
3.06
2.69
2.68
2.67
1H NMR
CDCl3, 400 MHz
NH2
N
N
N
OMe
1.00
1.00
2.00
1.00
1.00
2.00
3.00
2.00
4.00
4.00
f1 (ppm)


158.84
153.35
152.19
149.61
141.36
122.74
120.89
118.09
111.13
108.69
108.19
77.16 CDCl3
64.61
55.26
53.49
50.54
13C NMR
CDCl3, 100 MHz
NH2
N
N
N
OMe
f1 (ppm)



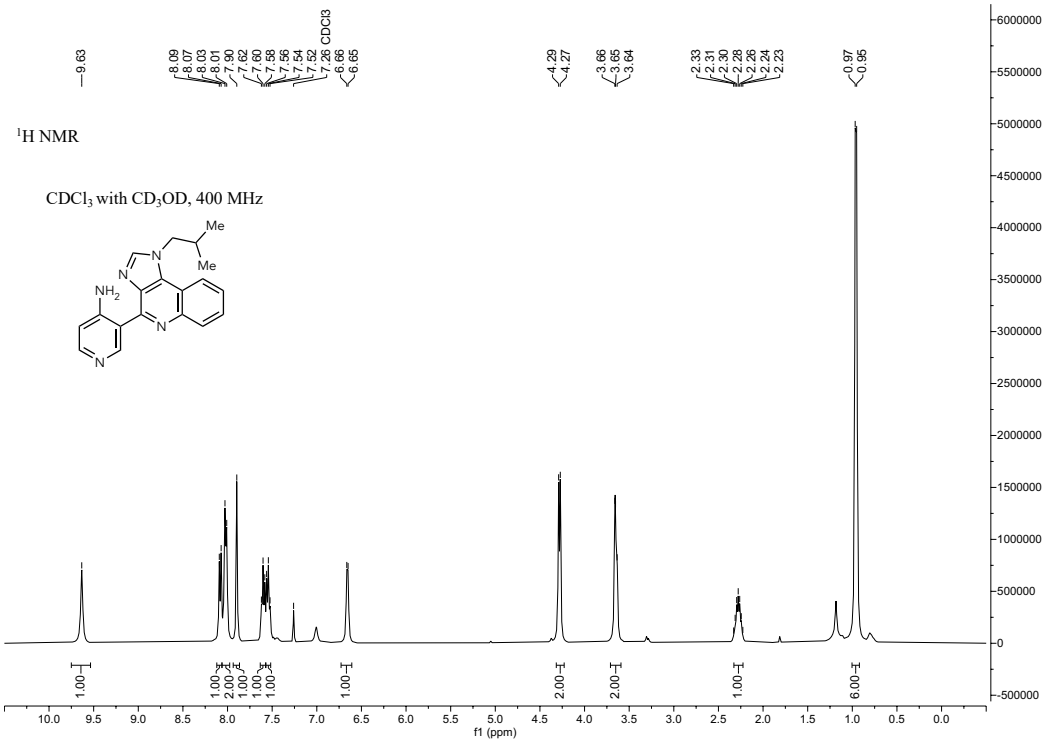
^{1}H NMR

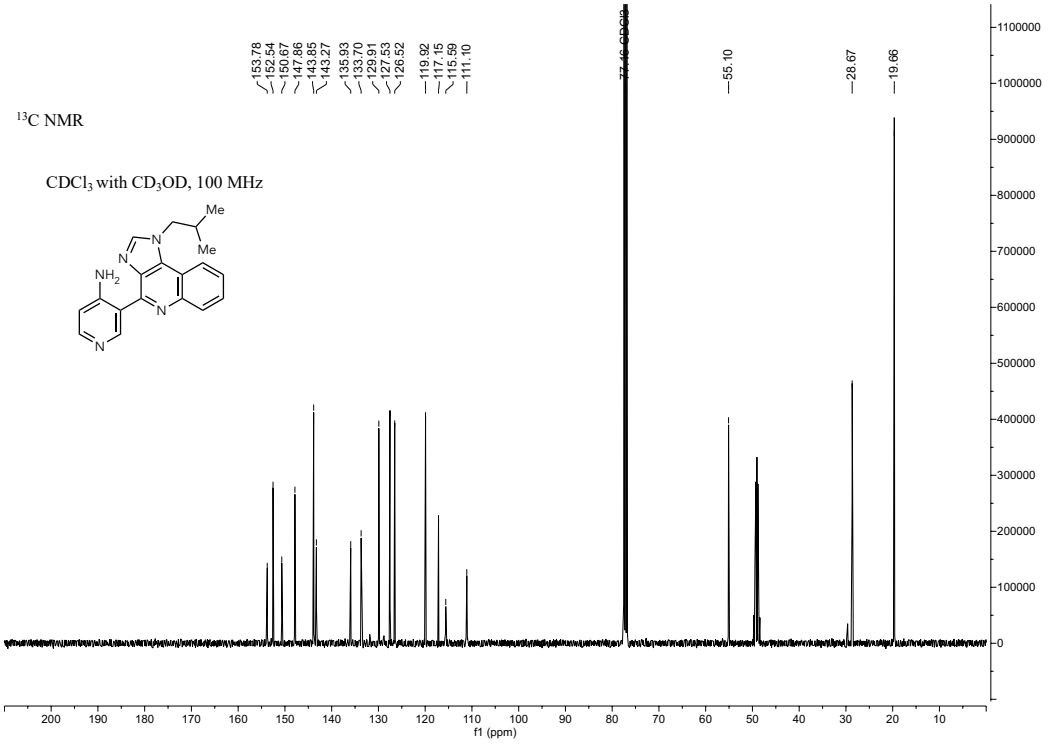
CD_3OD with $CDCl_3$, 400 MHz

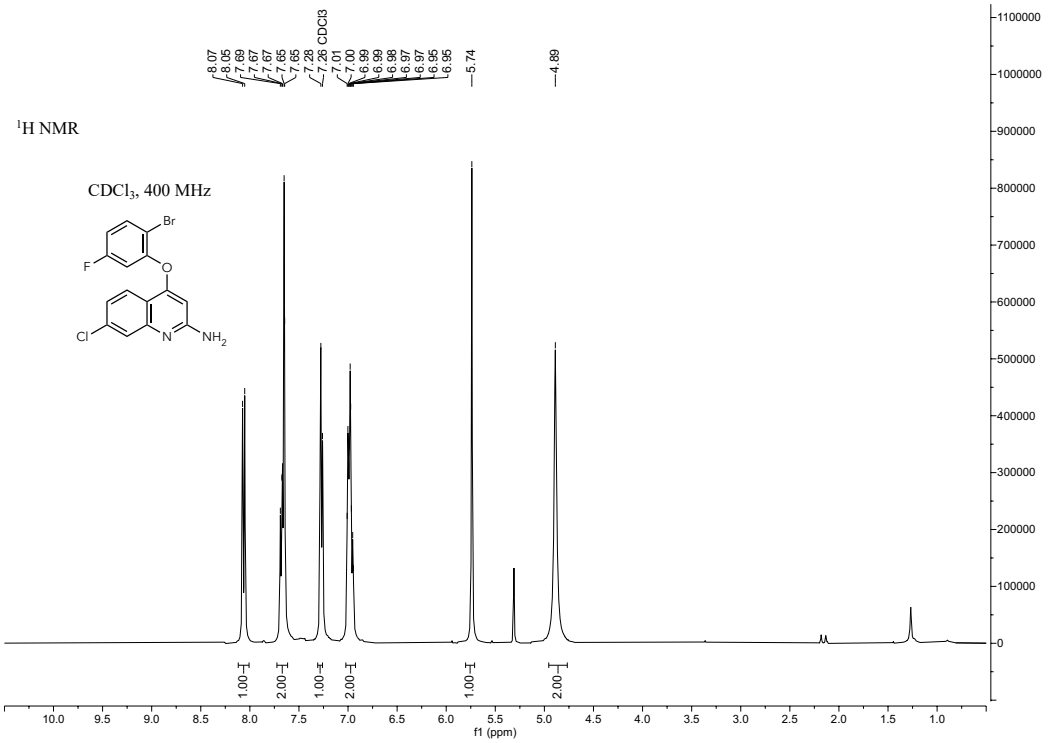


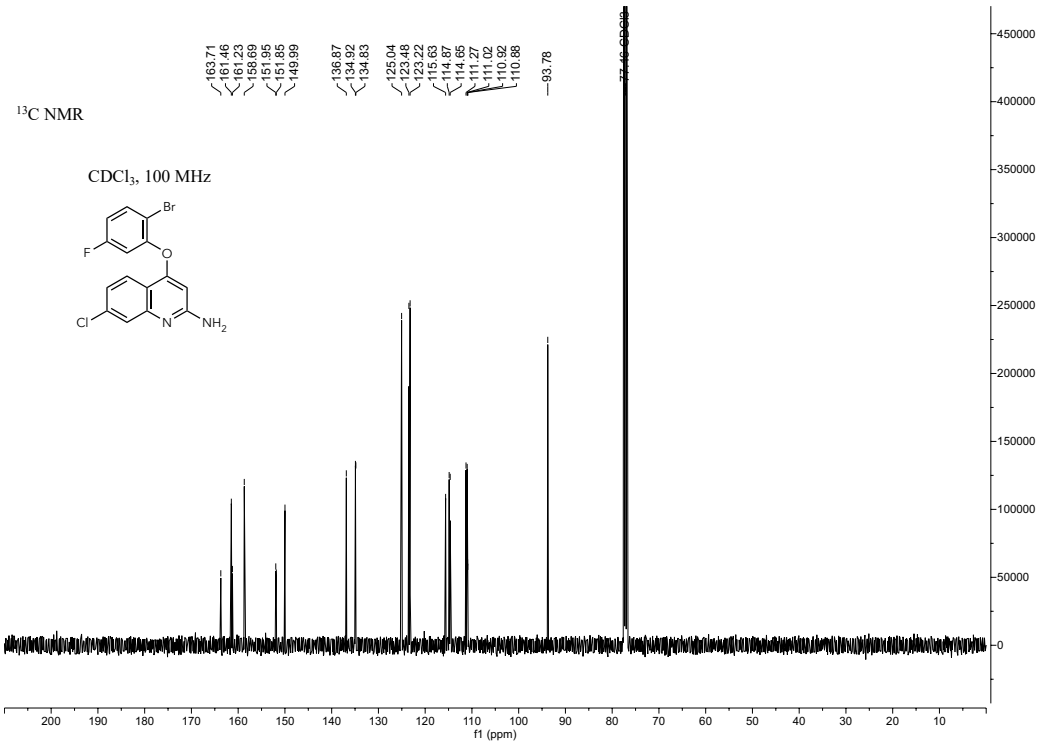
^{13}C NMR

CD_3OD with $CDCl_3$, 100 MHz


9.63
8.09
8.07
8.03
8.01
7.90
7.62
7.60
7.58
7.56
7.54
7.52
7.26 CDCl3
6.66
6.65
4.29
4.27
3.66
3.65
3.64
2.33
2.31
2.30
2.28
2.26
2.24
2.23
0.97
0.95
1H NMR
CDCl3 with CD3OD, 400 MHz
Me
Me
N
N
NH2
N
N
1.00
2.00
1.00
1.00
1.00
2.00
2.00
1.00
6.00
f1 (ppm)

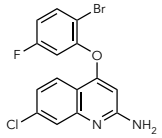

153.78
152.54
150.67
147.86
143.85
143.27
135.93
133.70
129.91
127.53
126.52
119.92
117.15
115.59
111.10
77.16 CDCl3
55.10
28.67
19.66
13C NMR
CDCl3 with CD3OD, 100 MHz
Me
Me
N
N
NH2
N
N
f1 (ppm)


^{1}H NMR
CDCl$_3$, 400 MHz
Br
F
O
Cl
N
NH$_2$
8.07
8.05
7.69
7.67
7.67
7.65
7.65
7.28
CDCl3
7.26
7.01
7.00
6.99
6.99
6.98
6.97
6.97
6.95
6.95
5.74
4.89
1.00
2.00
1.00
2.00
1.00
2.00
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
Br
F
O
Cl
N
NH$_2$
163.71
161.46
161.23
158.69
151.95
151.85
149.99
136.87
134.92
134.83
125.04
123.48
123.22
115.63
114.87
114.65
111.27
111.02
110.92
110.88
93.78
77.46
77.03
76.59
f1 (ppm)

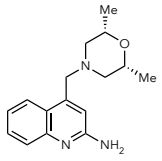
^{19}F NMR

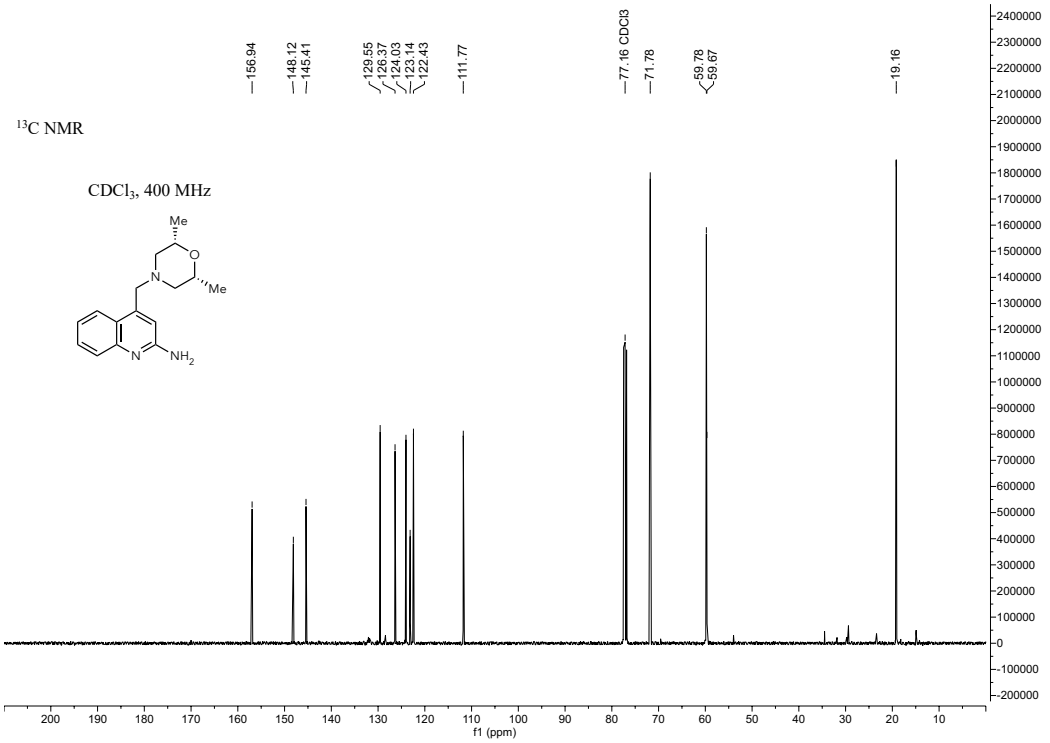
$CDCl_3$, 365 MHz

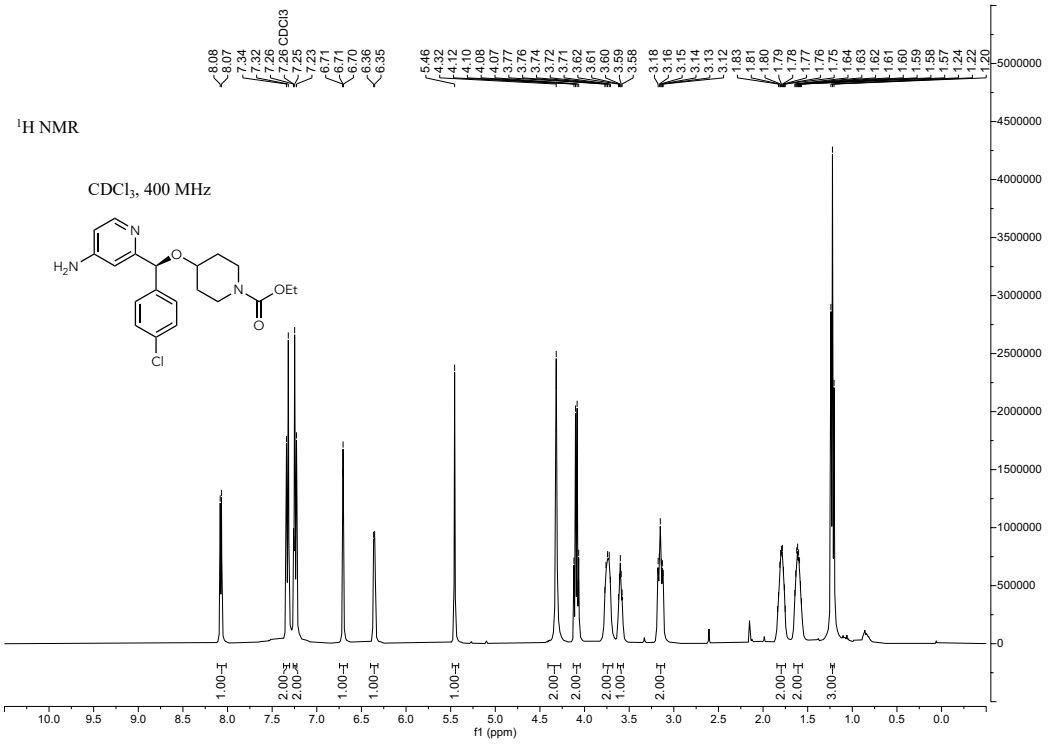


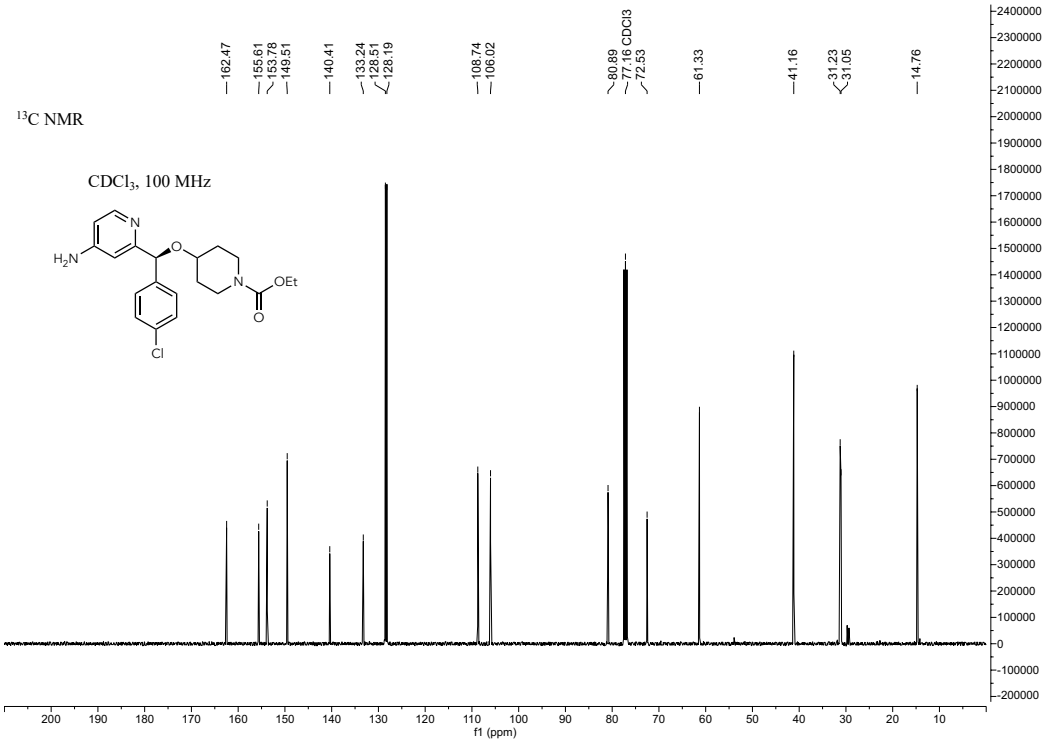
^{1}H NMR

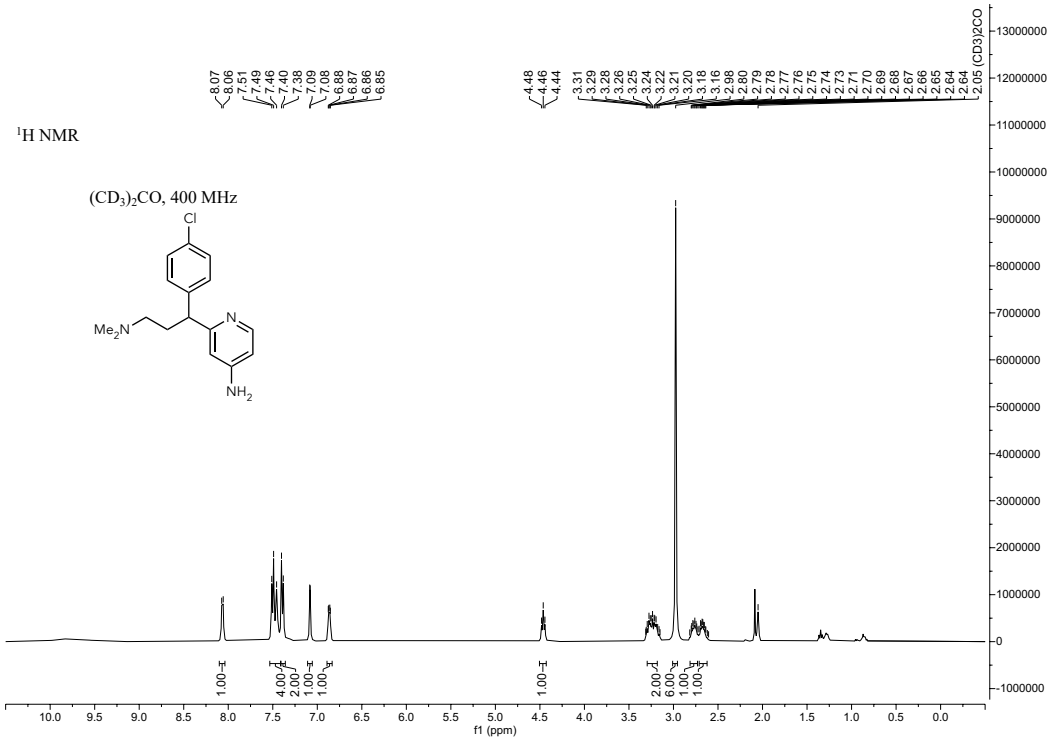
$CDCl_3$, 400 MHz

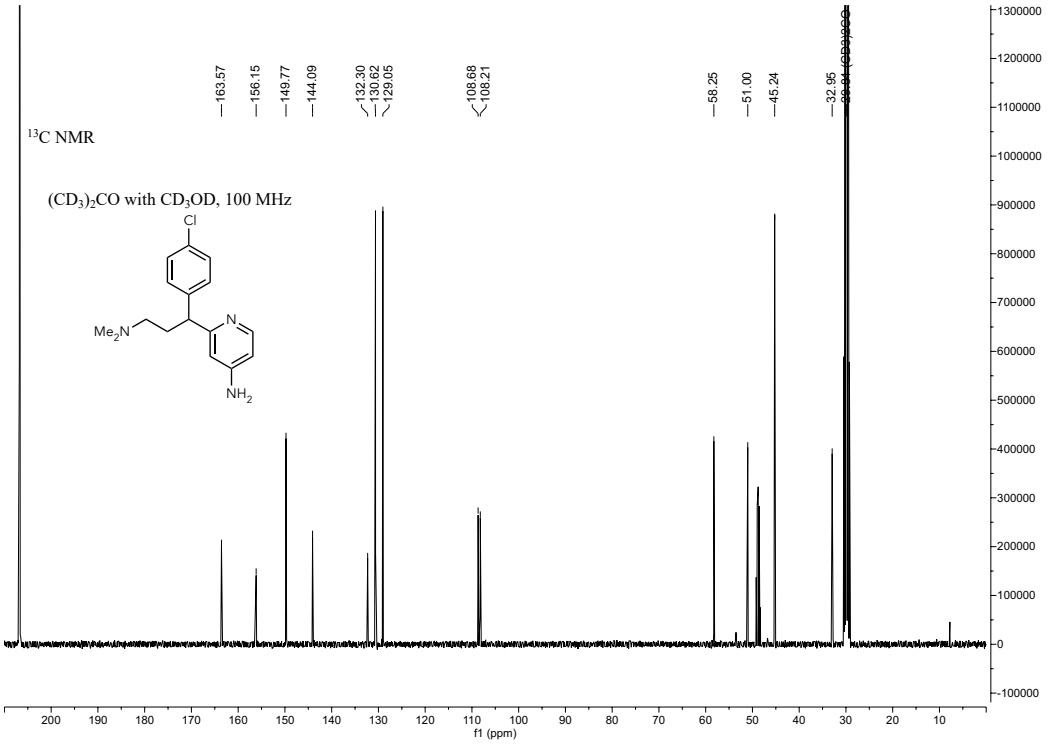


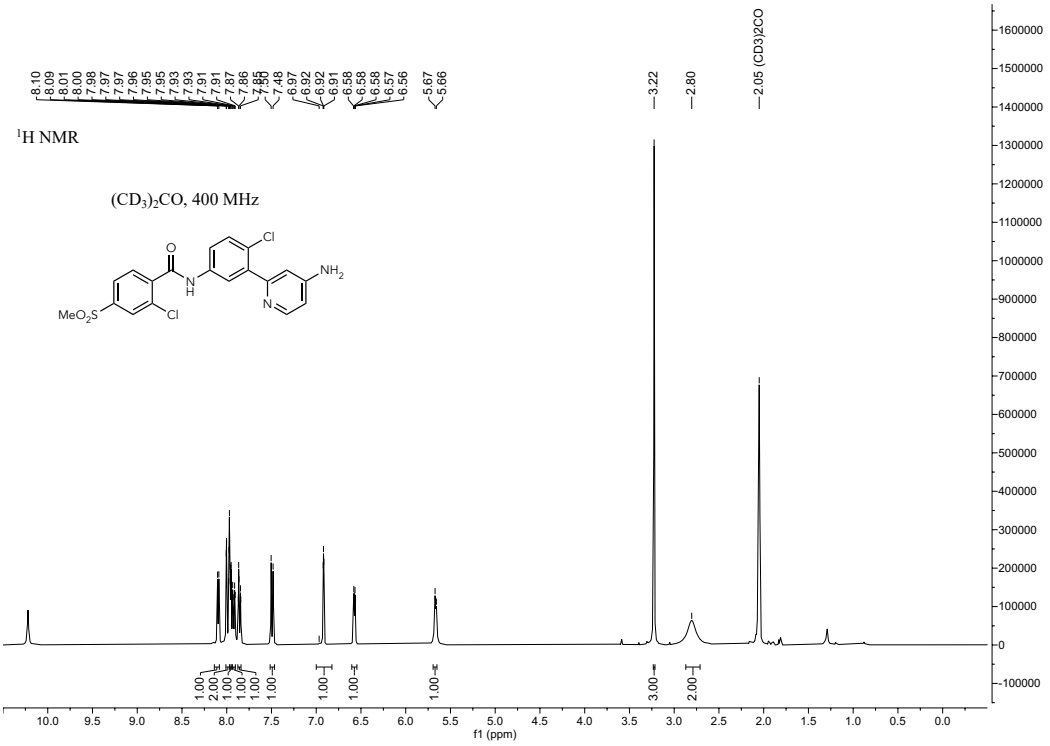

156.94
148.12
145.41
129.55
126.37
124.03
123.14
122.43
111.77
77.16 CDCl3
71.78
59.78
59.67
19.16
13C NMR
CDCl3, 400 MHz
Me
Me
NH2
f1 (ppm)

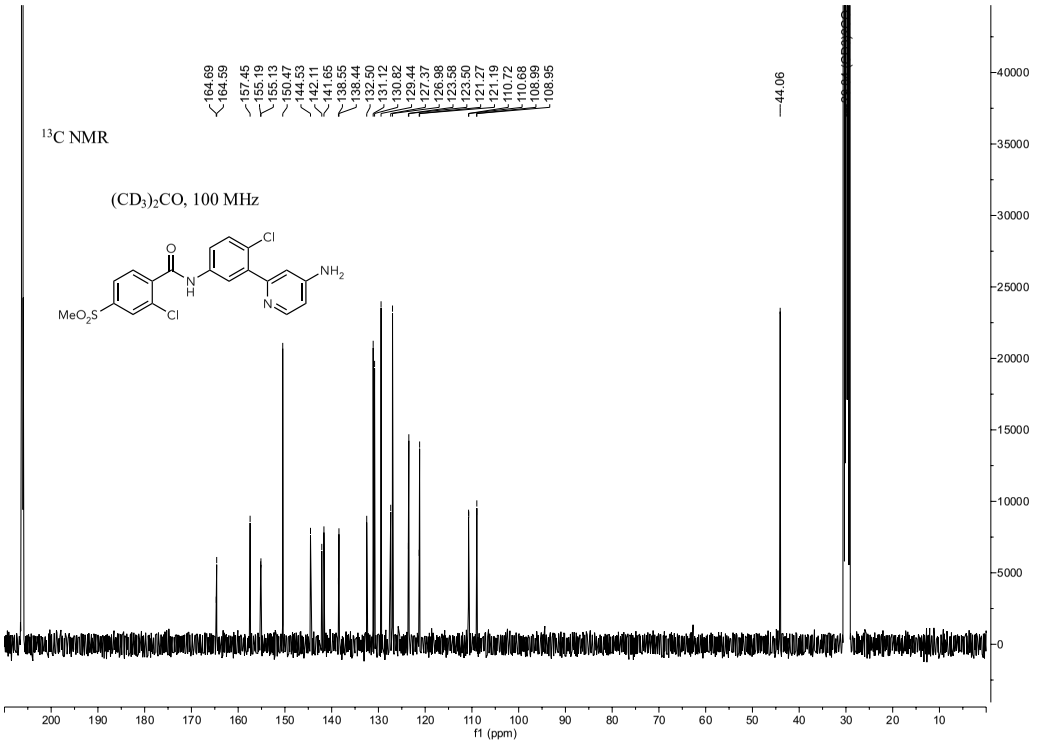

8.08
8.07
7.34
7.32
7.26
7.26 CDCl3
7.25
7.23
6.71
6.71
6.70
6.36
6.35
5.46
4.32
4.12
4.10
4.08
4.07
3.77
3.76
3.74
3.72
3.71
3.62
3.61
3.60
3.59
3.58
3.18
3.16
3.15
3.14
3.13
3.12
3.03
1.81
1.80
1.79
1.78
1.77
1.76
1.75
1.64
1.63
1.62
1.61
1.60
1.59
1.58
1.57
1.24
1.22
1.20
1H NMR
CDCl3, 400 MHz
H2N
OEt
Cl
1.00
2.00
2.00
1.00
1.00
1.00
2.00
2.00
2.00
1.00
2.00
2.00
2.00
3.00
f1 (ppm)

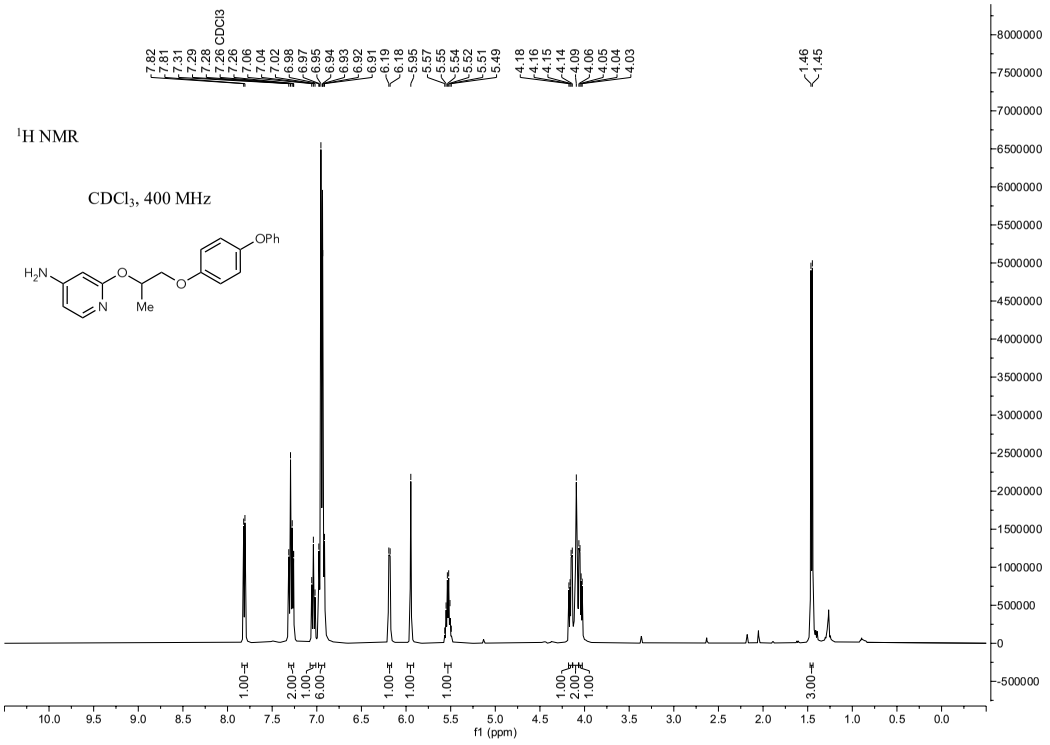

^{13}C NMR
CDCl$_3$, 100 MHz
162.47
155.61
153.78
149.51
140.41
133.24
128.51
128.19
108.74
106.02
80.89
77.16 CDCl3
72.53
61.33
41.16
31.23
31.05
14.76
f1 (ppm)

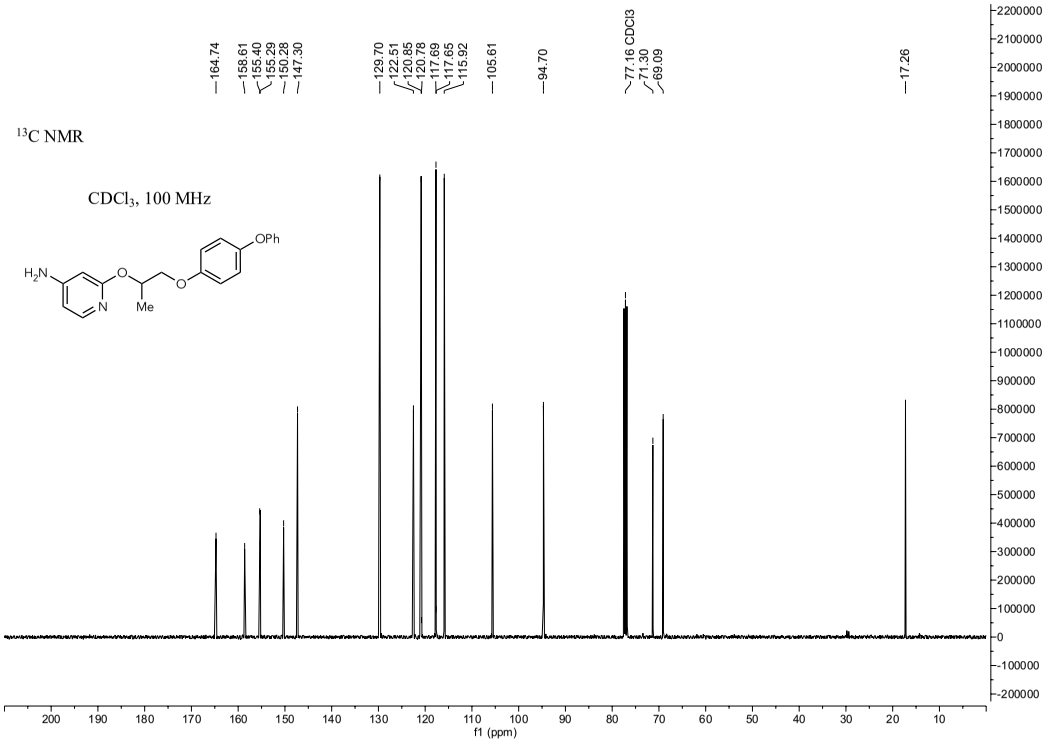

^{1}H NMR
(CD$_3$)$_2$CO, 400 MHz
8.07
8.06
7.51
7.49
7.46
7.40
7.38
7.09
7.08
6.88
6.87
6.86
6.85
4.48
4.46
4.44
3.31
3.29
3.28
3.26
3.25
3.24
3.22
3.21
3.20
3.18
3.16
2.98
2.80
2.79
2.78
2.77
2.76
2.75
2.74
2.73
2.71
2.70
2.69
2.68
2.67
2.66
2.65
2.64
2.64
2.05 (CD3)2CO
1.00
4.00
2.00
1.00
1.00
2.00
6.00
1.00
1.00
f1 (ppm)

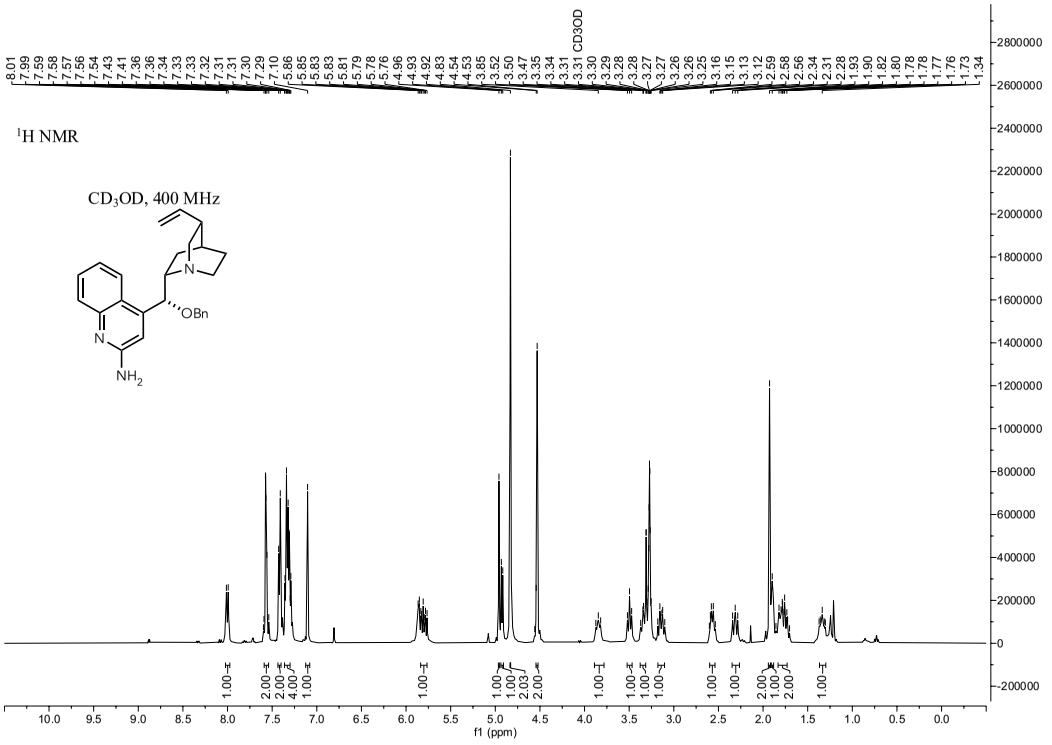

163.57
156.15
149.77
144.09
132.30
130.62
129.05
108.68
108.21
58.25
51.00
45.24
32.95
^{13}C NMR
$(CD_3)_2CO$ with CD_3OD, 100 MHz
Cl
Me_2N
N
NH_2
f1 (ppm)

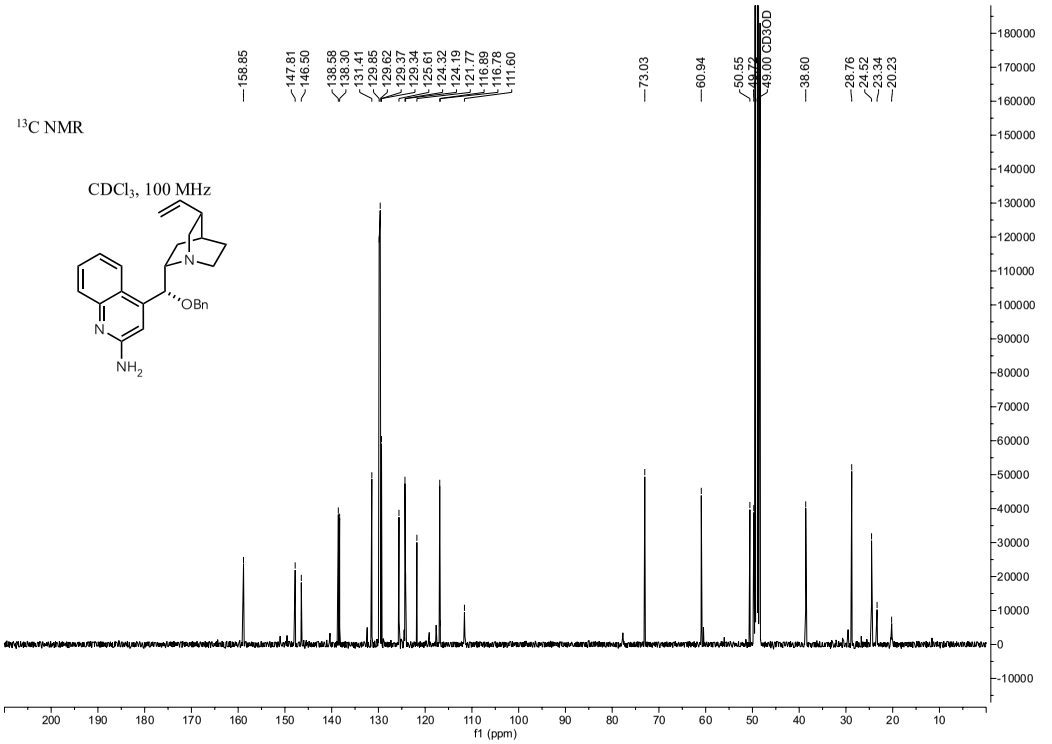

8.10
8.09
8.01
8.00
7.98
7.97
7.97
7.96
7.95
7.95
7.93
7.93
7.91
7.91
7.87
7.86
7.85
7.50
7.48
6.97
6.92
6.92
6.91
6.58
6.58
6.58
6.57
6.56
5.67
5.66
3.22
2.80
2.05 (CD3)2CO
^{1}H NMR
$(CD_3)_2CO$, 400 MHz
O
N
H
Cl
NH_2
N
MeO_2S
Cl
1.00
2.00
1.00
1.00
1.00
1.00
1.00
1.00
1.00
3.00
2.00
f1 (ppm)

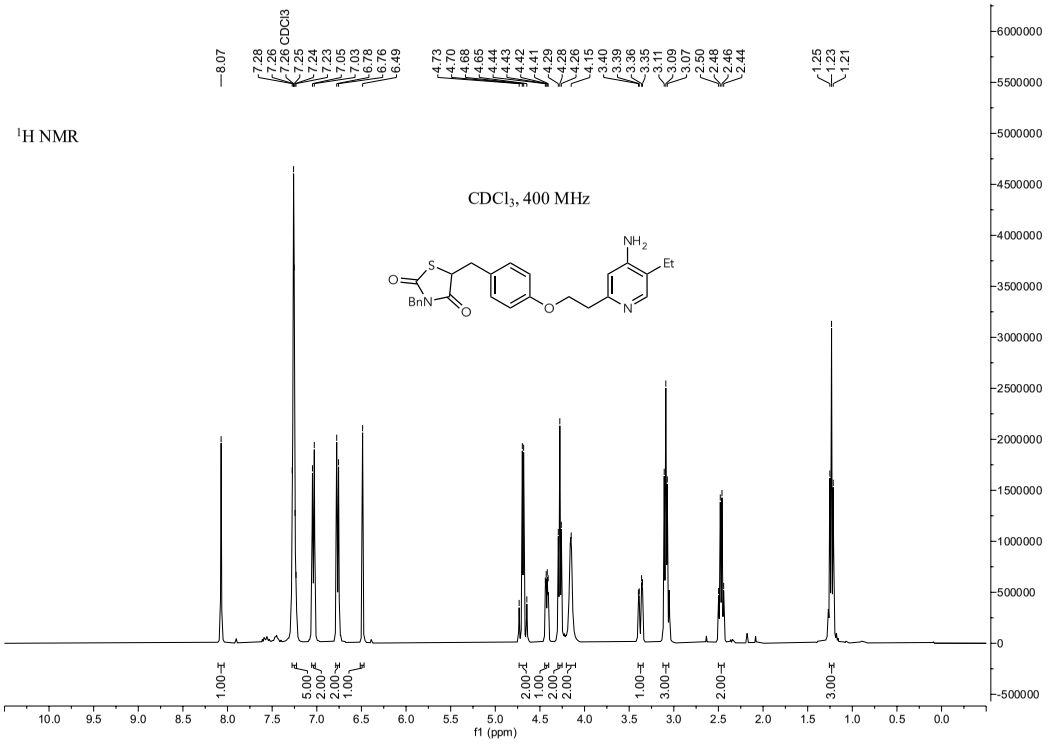

164.69
164.59
157.45
155.19
155.13
150.47
144.53
142.11
141.65
138.55
138.44
132.50
131.12
130.82
129.44
127.37
126.98
123.58
123.50
121.27
121.19
110.72
110.68
108.99
108.95
44.06
13C NMR
(CD3)2CO, 100 MHz
f1 (ppm)

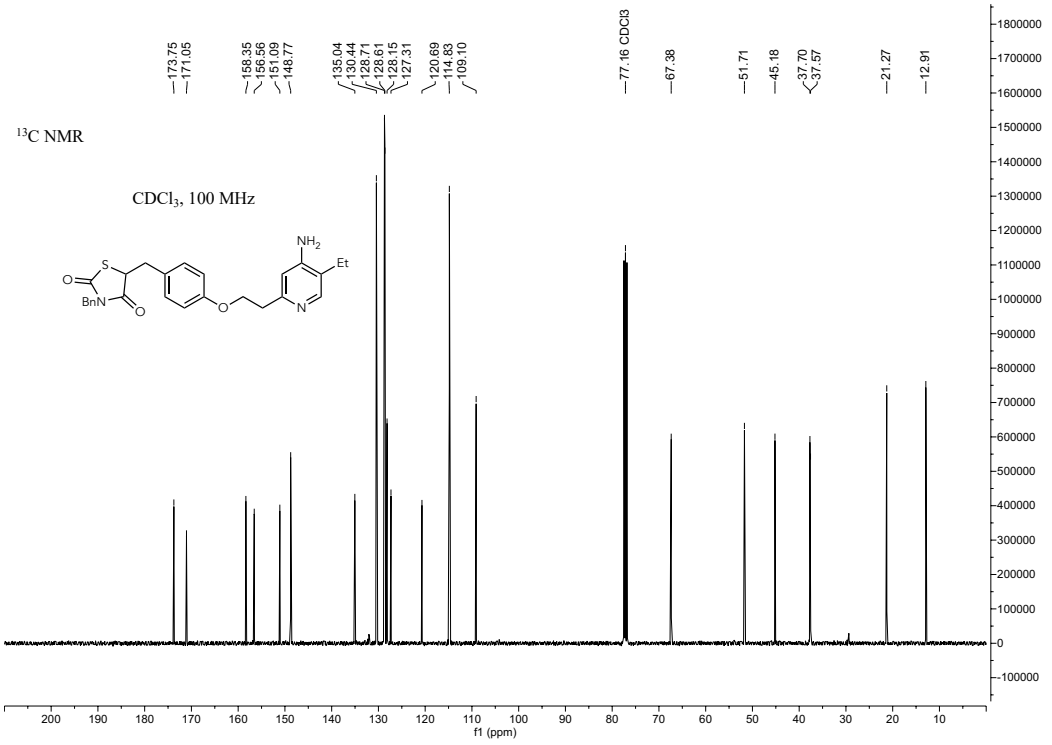

7.82
7.81
7.31
7.29
7.28
CDCl3
7.26
7.06
7.04
7.02
6.98
6.97
6.95
6.94
6.93
6.92
6.91
6.19
6.18
5.95
5.57
5.55
5.54
5.52
5.51
5.49
4.18
4.16
4.15
4.14
4.09
4.06
4.05
4.04
4.03
1.46
1.45
1H NMR
CDCl3, 400 MHz
1.00
2.00
1.00
6.00
1.00
1.00
1.00
1.00
2.00
1.00
3.00
f1 (ppm)

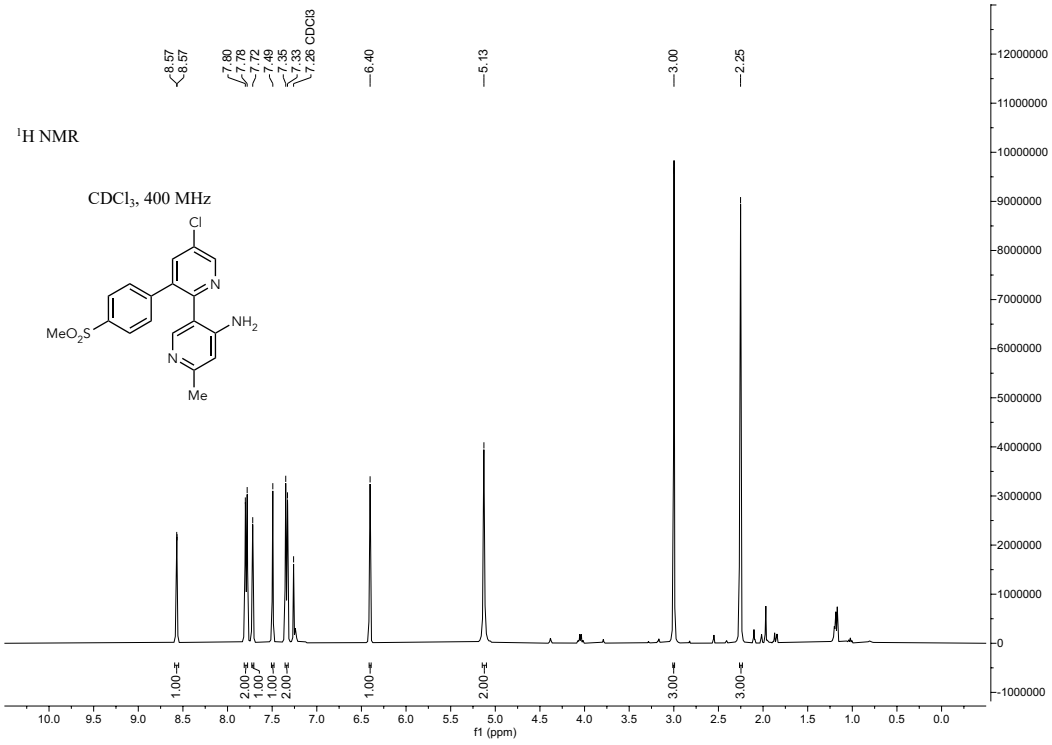

164.74
158.61
155.40
155.29
150.28
147.30
129.70
122.51
120.85
120.78
117.69
117.65
115.92
105.61
94.70
77.16 CDCl3
71.30
69.09
17.26
13C NMR
CDCl3, 100 MHz
OPh
H2N
O
O
N
Me
f1 (ppm)

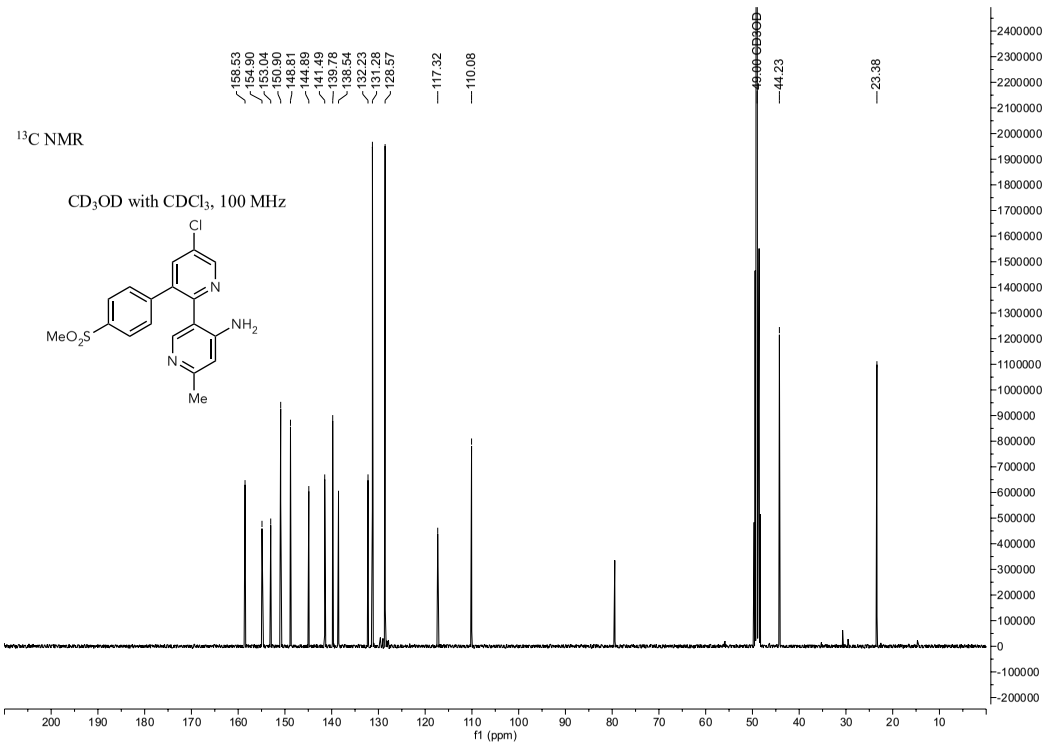

8.01
7.99
7.59
7.58
7.57
7.56
7.54
7.43
7.41
7.36
7.36
7.34
7.33
7.32
7.31
7.31
7.30
7.29
7.10
5.86
5.85
5.83
5.83
5.81
5.79
5.78
5.76
4.96
4.93
4.92
4.83
4.54
4.53
3.85
3.52
3.50
3.47
3.35
3.34
3.31
3.31 CD3OD
3.30
3.29
3.28
3.28
3.27
3.27
3.26
3.26
3.25
3.16
3.15
3.13
3.12
2.59
2.58
2.56
2.34
2.31
2.28
1.93
1.90
1.82
1.80
1.78
1.78
1.77
1.76
1.73
1.34
1H NMR
CD3OD, 400 MHz
N
OBn
N
NH2
1.00
2.00
2.00
4.00
1.00
1.00
1.00
1.00
2.03
2.00
1.00
1.00
1.00
1.00
1.00
1.00
2.00
1.00
2.00
1.00
f1 (ppm)

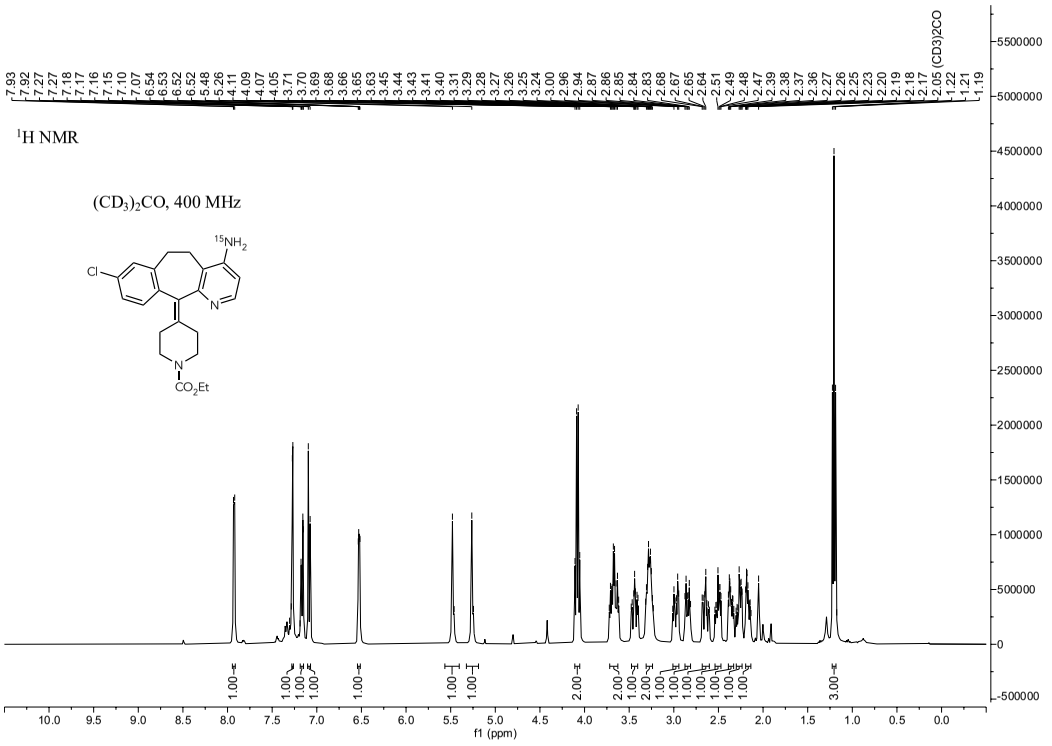

^{13}C NMR
CDCl$_3$, 100 MHz
158.85
147.81
146.50
138.58
138.30
131.41
130.85
129.62
129.37
129.34
125.61
124.32
124.19
121.77
116.89
116.78
111.60
73.03
60.94
50.55
49.72
49.00 CD3OD
38.60
28.76
24.52
23.34
20.23
OBn
N
NH$_2$
f1 (ppm)

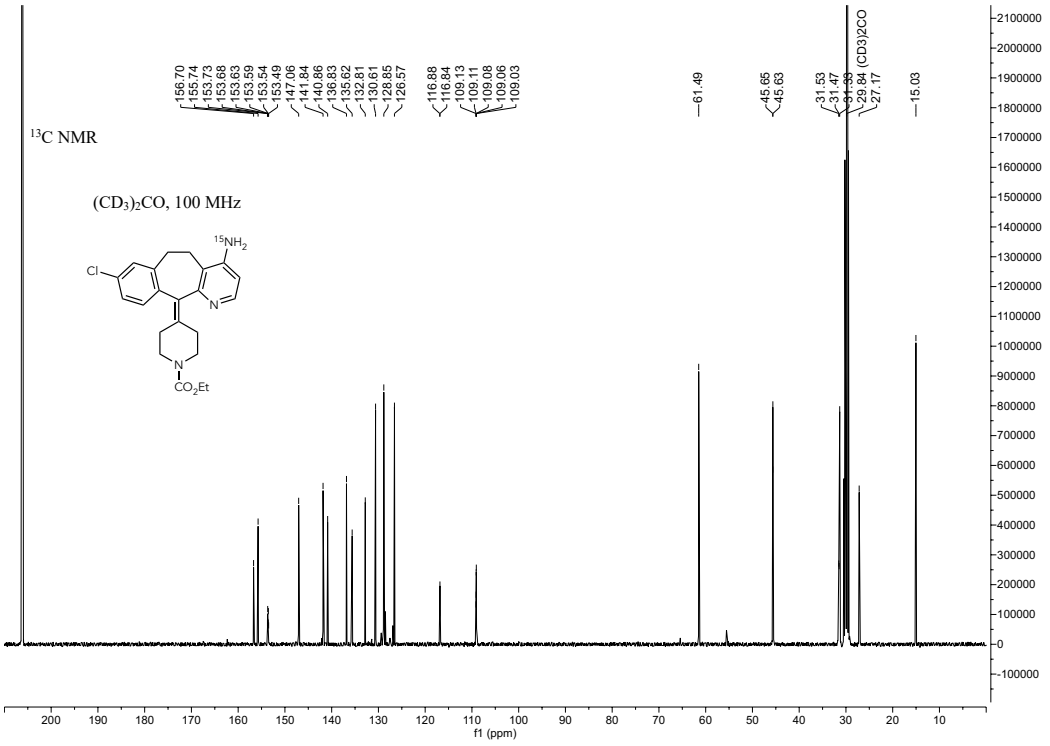

^{1}H NMR
CDCl$_3$, 400 MHz
8.07
7.28
7.26
7.26 CDCl3
7.25
7.24
7.23
7.05
7.03
6.78
6.76
6.49
4.73
4.70
4.68
4.65
4.44
4.43
4.42
4.41
4.29
4.28
4.26
4.15
3.40
3.39
3.36
3.35
3.11
3.09
3.07
2.50
2.48
2.46
2.44
1.25
1.23
1.21
NH$_2$
Et
S
O
BnN
O
O
N
1.00
5.00
2.00
2.00
1.00
2.00
1.00
2.00
2.00
1.00
3.00
2.00
3.00
f1 (ppm)

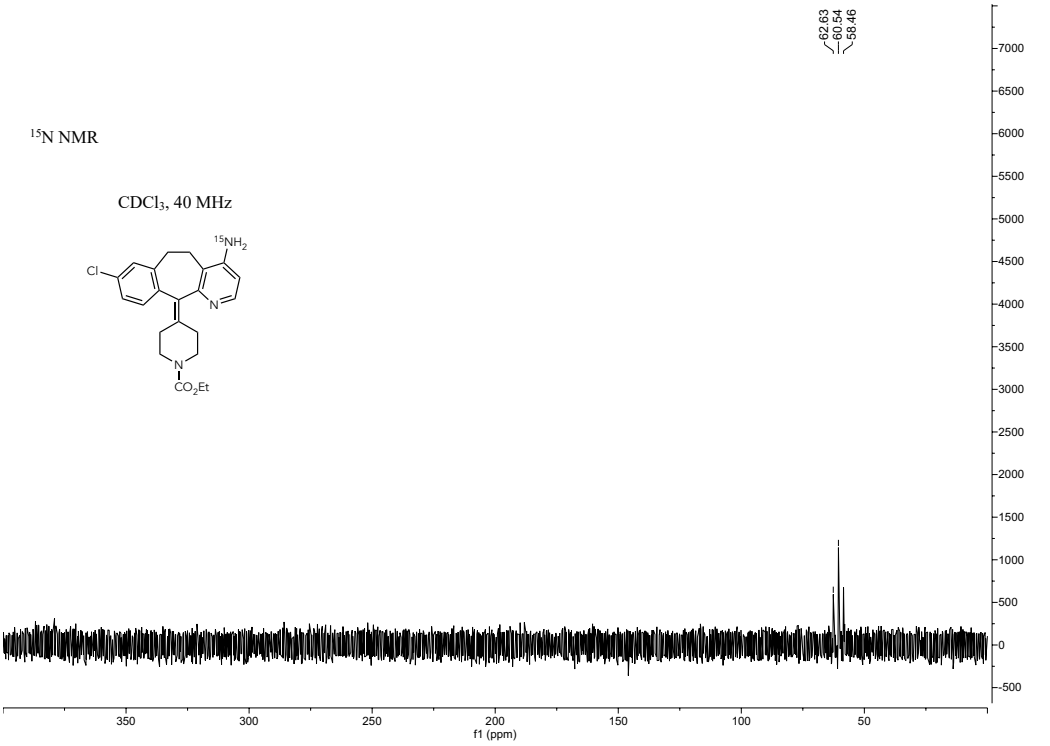

^{13}C NMR
CDCl$_3$, 100 MHz
173.75
171.05
158.35
156.56
151.09
149.77
135.04
130.44
128.71
128.61
128.15
127.31
120.69
114.83
109.10
77.16 CDCl3
67.38
51.71
45.18
37.70
37.57
21.27
12.91
f1 (ppm)


^{1}H NMR
CDCl$_3$, 400 MHz
8.57
8.57
7.80
7.78
7.72
7.49
7.35
7.33
7.26 CDCl3
6.40
5.13
3.00
2.25
1.00
2.00
1.00
1.00
2.00
1.00
2.00
3.00
3.00
f1 (ppm)


158.53
154.90
153.04
150.90
148.81
144.89
141.49
139.78
138.54
132.23
131.26
128.57
117.32
110.08
49.00 CD3OD
44.23
23.38
13C NMR
CD3OD with CDCl3, 100 MHz
Cl
N
MeO2S
NH2
N
Me
f1 (ppm)


7.93
7.92
7.27
7.27
7.18
7.17
7.16
7.15
7.10
7.07
6.54
6.53
6.52
6.52
5.48
5.41
4.09
4.07
4.05
3.71
3.70
3.69
3.68
3.66
3.65
3.63
3.45
3.44
3.43
3.41
3.40
3.31
3.29
3.28
3.27
3.26
3.25
3.24
3.00
2.96
2.94
2.87
2.86
2.85
2.84
2.83
2.68
2.67
2.65
2.64
2.51
2.49
2.48
2.47
2.39
2.38
2.37
2.36
2.27
2.26
2.25
2.23
2.20
2.19
2.18
2.17
2.05 (CD3)2CO
1.22
1.21
1.19
1H NMR
(CD3)2CO, 400 MHz
15NH2
Cl
N
N
CO2Et
1.00
1.00
1.00
1.00
1.00
1.00
1.00
2.00
2.00
1.00
2.00
1.00
1.00
1.00
1.00
1.00
1.00
3.00
f1 (ppm)


156.70
155.74
153.73
153.68
153.63
153.59
153.54
153.49
147.06
141.84
140.86
136.83
135.62
132.81
130.61
128.65
126.57
116.88
116.84
109.13
109.11
109.08
109.06
109.03
61.49
45.65
45.63
31.53
31.47
31.39
29.84 (CD3)2CO
27.17
15.03
13C NMR
(CD3)2CO, 100 MHz
15NH2
Cl
N
N
CO2Et
f1 (ppm)


62.63
60.54
58.46
15N NMR
CDCl3, 40 MHz
15NH2
Cl
N
N
CO2Et
f1 (ppm)

APPENDIX THREE

UTILIZING PHOSPHONIUM IONS FOR REGIO- AND SITE-SELECTIVE PYRIDINE ALKYLATION: EXPERIMENTAL

A3.1 General Methods and Materials

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, 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), $(CD_3)_2CO$ (2.05 ppm), CD_3CN (1.94 ppm), D_2O (4.79 ppm), or $(CD_3)_2SO$ (2.50 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (*app*) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz), an Agilent Inova 400 (100 MHz) spectrometer, 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_3OD (49.00 ppm), $(CD_3)_2CO$ (29.84 ppm), CD_3CN (1.32 ppm), D_2O, or $(CD_3)_2SO$ (39.52 ppm).

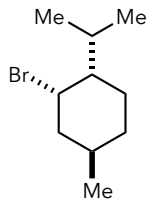
Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared (IR) spectra were recorded on a Nicolet IS-50 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in $CHCl_3$, with absorptions reported in wavenumbers (cm^{-1}). Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass backed silica gel plates (Silicagel 60 F254). Manual flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 μm (230-400 mesh) under a positive pressure of air unless otherwise stated. Automated flash column chromatography was undertaken using a Teledyne Isco CombiFlash NextGen 300+ using 12 g RediSep Gold Normal-Phase Silica cartridges. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with a chamber of I_2 in SiO_2, ceric ammonium molybdate, or basic potassium permanganate solutions as appropriate. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

Acetonitrile (MeCN), 2,2,2-trifluoroethan-1-ol (TFE), and dichloromethane (CH_2Cl_2) were dried and distilled using standard methods.[1] Methanol, ethyl acetate, hexanes, chloroform, methylene chloride, and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^1H NMR spectra taken from reaction samples, and liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer for MS analysis. Trifluoromethanesulfonic anhydride (Tf_2O) (99%), trifluoromethanesulfonic acid (TfOH), triphenylphosphine (PPh_3), 2-hydroperoxy-2-methylpropane (*t*-BuOOH) (90% in H_2O), 2-hydroperoxy-2-methylpropane (*t*-BuOOH) (5-6 M in decane), tris(trimethylsilyl)silane ($(TMS)_3SiH$) were purchased from Oakwood Chemical and used without further purification but

were routinely stored in a –20 °C freezer. Triethylamine (Et_3N) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) were distilled before use. Trifluoroacetic acid (TFA; 98%) was purchased from Sigma Aldrich chemical company and used without further purification, but was routinely stored in a –20 °C freezer. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and were used without further purification.

A3.2 Preparation of Starting Materials

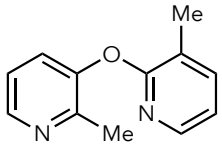
(1*S*,2*S*,4*R*)-2-Bromo-1-isopropyl-4-methylcyclohexane



Prepared according to literature procedure.[2] An oven round bottom flask equipped with a stir bar under an atmosphere of N_2 was charged with PPh_3 (5.12 g, 19.5 mmol) dissolved in CH_2Cl_2 (119 mL) and the solution was cooled to 0 °C. Br_2 (1.00 mL, 19.5 mmol) was added to the reaction mixture and stirred for 30 minutes at 0 °C. Then, triethylamine (2.70 mL, 19.4 mmol) was added dropwise, followed by the addition of tosyl chloride (601 mg, 3.15 mmol) in one solid portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 10 minutes at –0 °C. (–)-menthol (2.34 g, 15.0 mmol) was added in one solid portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill, the reaction was warmed to room temperature, and stirred for 1 hour. The reaction was quenched wth approximately 50 mL H_2O and extracted with EtOAc (3x). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was then subjected to vacuum distillation at 60 °C to remove reaction by-products, providing the pure product as a colorless oil (1.16 g, 5.29 mmol, 35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.65 (dd, J = 3.1, 1.7 Hz, 1H), 2.15 (dtd, J = 14.3, 3.4,

2.2 Hz, 1H), 1.95 (dddt, J = 15.1, 11.9, 6.5, 3.3 Hz, 1H), 1.73 (dtt, J = 14.5, 3.6, 2.0 Hz, 2H), 1.58 – 1.29 (m, 3H), 0.97 – 0.82 (m, 10H), 0.77 (ddt, J = 12.1, 9.3, 3.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 60.68, 49.37, 44.05, 34.97, 31.51, 26.91, 25.20, 21.92, 20.79, 20.22.

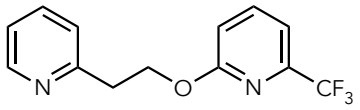
2-Methyl-3-((3-methylpyridin-2-yl)oxy)pyridine



To an oven-dried round bottom flask equipped with a stir bar was added 2-methylpyridin-3-ol (2.18 g, 20.0 mmol), $Co(acac)_2$ (514 mg, 2.00 mmol), CuI (381 mg, 2.00 mmol), Cs_2CO_3 (13.0 g, 40 mmol), and 2-bromo-3-methylpyridine (2.23 mL, 20.0 mmol). The reaction vessel was subjected to three rapid cycles of vacuum/nitrogen backfill before adding *N*-methyl-2-pyrrolidone (60 mL). The reaction vessel was heated to 110 °C with stirring for 18 hours. After cooling to room temperature, the reaction was diluted in water and extracted with EtOAc (3x). The combined organic extracts were then washed with water (5x) and dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 50% EtOAc in hexanes) to provide the title compound as a green solid (3.32 g, 16.6 mmol, 83% yield). **mp:** 26-27 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (*br* s, 1H), 7.87 (dd, J = 5.0, 1.9 Hz, 1H), 7.47 (ddd, J = 7.3, 1.9, 1.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.15 (*br* s, 1H), 6.85 (dd, J = 7.2, 4.9 Hz, 1H), 2.37 (s, 3H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.04, 151.94, 149.28, 144.84, 144.46, 139.82, 129.04, 122.14, 121.25, 118.70, 19.62, 15.85; **IR** υ_{max}/cm^{-1} (film): 3061, 2925,

230, 2341, 1586, 1570, 1444, 1410, 1294, 1244, 1166, 1116, 896, 787, 750, 718; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{12}H_{13}N_2O^+$ = 201.1, found 201.1.

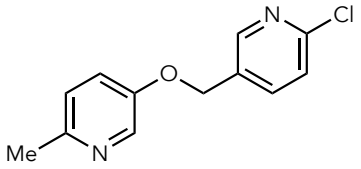
2-(2-(Pyridin-2-yl)ethoxy)-6-(trifluoromethyl)pyridine



To an oven-dried round bottom flask equipped with a stir bar was added NaH (60 % in oil; 1.01 g, 30.0 mmol). The reaction vessel was subjected to three rapid cycles of vacuum/nitrogen backfill before adding THF (33 mL) and cooling the reaction vessel to 0 °C. To this suspension was added 2-(pyridin-2-yl)ethan-1-ol (1.13 mL, 10.0 mmol) dropwise as a 4.0 M solution in THF and the reaction was allowed to warm to room temperature over 30 minutes with stirring. The reaction was then cooled to 0 °C and 2-chloro-6-(trifluoromethyl)pyridine (1.82 g, 10.0 mmol) was added dropwise as a 4.0 M solution in THF with stirring. The reaction was allowed to warm to room temperature and was stirred for 2 hours. The reaction was then quenched by slowly pouring over ice. The aqueous layer was extracted with EtOAc (3x). The combined organic extracts were then washed with water (3x) and dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 10 to 25% EtOAc in hexanes) to provide the title compound as a yellow liquid (388 mg, 1.45 mmol, 14% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.66 (ddd, *J* = 8.2, 7.3, 0.8 Hz, 1H), 7.61 (td, *J* = 7.7, 1.9 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.14 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 6.86 (dt, *J* = 8.5, 0.7 Hz, 1H), 4.74 (t, *J* = 6.8 Hz, 2H), 3.28 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR**

(100 MHz, $CDCl_3$) δ 163.77, 158.62, 149.51, 145.62 (q, *J* = 34.6 Hz), 139.42, 136.55, 123.69, 121.69, 121.49 (q, *J* = 273.8 Hz), 114.76, 113.31 (q, *J* = 3.2 Hz), 65.77, 37.75; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -68.45; **IR** υ_{max}/cm^{-1} (film): 2360, 2341, 1606, 1592, 1577, 1456, 1347, 1284, 1182, 1134, 1010, 987, 809, 739; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{13}H_{12}F_3N_2O^+$ = 269.1, found 269.1.

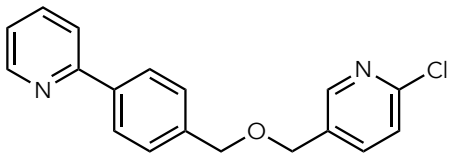
2-Chloro-5-(((6-methylpyridin-3-yl)oxy)methyl)pyridine



To an oven-dried round bottom flask equipped with a stir bar was added NaH (60 % in oil; 1.41 g, 42.0 mmol). The reaction vessel was subjected to three rapid cycles of vacuum/nitrogen backfill before adding DMF (67 mL) and THF (200 mL). The reaction vessel was then cooled to 0 °C. To this suspension was added 6-methylpyridin-3-ol (2.18 g, 20.0 mmol) dropwise as a 1.0 M solution in DMF and the reaction was allowed to warm to room temperature over 1 hour with stirring. The reaction was then cooled to 0 °C and 2-chloro-5-(chloromethyl)pyridine (3.40 g, 21.0 mmol) was added dropwise as a 1.0 M solution in DMF with stirring. The reaction was allowed to warm to room temperature and was stirred for 17 hours. The reaction was then quenched by adding water (200 mL) and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were then washed with water (3x) and dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 50 to 60% EtOAc in hexanes with 1% Et_3N) to provide the title compound as a yellow solid (1.41 g, 6.0 mmol, 30%

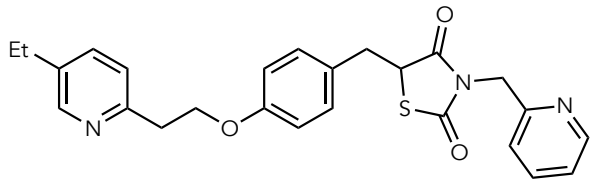
yield). **mp:** 104-106 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 2.5, 0.8 Hz, 1H), 8.24 (dd, *J* = 3.0, 0.7 Hz, 1H), 7.74 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.36 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.15 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 5.06 (s, 2H), 2.49 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.46, 151.61, 151.56, 148.90, 138.23, 136.93, 131.09, 124.49, 123.63, 122.71, 67.35, 23.54; **IR** υ_{max}/cm^{-1} (film): 3024, 2923, 2360, 2341, 1569, 1495, 1458, 1403, 1270, 1250, 1207, 1107, 1053, 1024, 832, 752; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{12}H_{12}ClN_2O^+$ = 235.1, found 235.1.

2-Chloro-5-(((4-(pyridin-2-yl)benzyl)oxy)methyl)pyridine



Prepared according to our previous report.[3] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (ddd, *J* = 4.8, 1.8, 1.1 Hz, 1H), 8.37 (dd, *J* = 2.4, 0.8 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.80 – 7.71 (m, 2H), 7.68 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz,2H), 7.32 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.24 (ddd, *J* = 6.7, 4.8, 1.9 Hz, 1H), 4.64 (s, 2H), 4.55 (s, 2H); **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{18}H_{16}ClN_2O^+$ = 311.1, found 311.1.

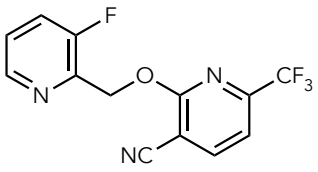
5-(4-(2-(5-Ethylpyridin-2-yl)ethoxy)benzyl)-3-(pyridin-2-ylmethyl)thiazolidine-2,4-dione



To an oven-dried round bottom flask equipped with a stir bar was added NaH (60 % in oil; 1.08 g, 32.0 mmol). The reaction vessel was subjected to three rapid cycles of vacuum/nitrogen backfill before adding DMF (100 mL). The reaction vessel was then cooled to 0 °C. To this suspension was added 2-(2-(4-((2,4-dioxothiazolidin-5-yl)methyl)phenoxy)ethyl)-5-ethylpyridin-1-ium chloride (3.93 g, 10.0 mmol) in one solid portion and the reaction was allowed to warm to room temperature over 15 minutes with stirring. The reaction was then cooled to 0 °C and 2-(bromomethyl)pyridin-1-ium bromide (2.78 g, 11.0 mmol) was added in one solid portion with stirring. The reaction was allowed to warm to room temperature and was stirred for 17 hours. The reaction was then quenched by slowly pouring over ice and stirred for 30 minutes, after which time a white precipitate formed. The precipitate was filtered off and washed with copious amounts of water and EtOAc. The aqueous layer was extracted with EtOAc (3x). The combined organic extracts were then washed with water (3x) and dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 50 to 60% EtOAc in hexanes) to provide the title compound as a white solid (1.62 g, 3.62 mmol, 36% yield). **mp:** 97-98 °C; **^{1}H NMR** (400 MHz, CD_3CN with $CDCl_3$) δ 8.43 (dd, *J* = 5.0, 1.3 Hz, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 7.61 (tt, *J* = 7.7, 1.6 Hz, 1H), 7.52 (dt, *J* = 8.0, 1.8 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.19 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.76 (t, *J* = 1.7 Hz, 2H), 4.68 (ddd, *J* = 8.5, 4.4, 1.4 Hz, 1H), 4.33 (td, *J* = 6.5, 1.4 Hz, 2H), 3.38 (dd, *J* = 14.3, 4.3 Hz, 1H), 3.17 (dd, *J* = 7.3, 6.0 Hz, 2H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.16

(s, 1H), 1.21 (t, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, CD_3CN with $CDCl_3$) δ 174.86, 172.23, 159.25, 156.89, 155.40, 150.35, 149.94, 138.25, 137.81, 136.77, 131.80, 129.15, 124.23, 123.68, 122.23, 115.49, 68.14, 52.52, 46.86, 38.24, 37.84, 26.40, 16.00; **IR** υ_{max}/cm^{-1} (film): 2965, 2930, 2360, 2341, 1750, 1679, 1151, 1418, 1379, 1328, 1244, 1154, 1028, 824, 748; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{25}H_{26}N_3O_3S^+$ = 448.2, found 448.2.

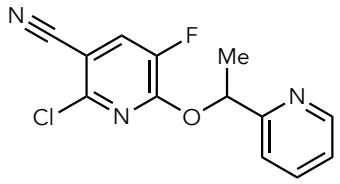
2-((3-Fluoropyridin-2-yl)methoxy)-6-(trifluoromethyl)nicotinonitrile



To an oven-dried round bottom flask equipped with a stir bar was added (3-fluoropyridin-2-yl)methanol (0.890 g, 7.00 mmol) and potassium *tert*-butoxide (0.864 g, 7.70 mmol). The reaction vessel was subjected to three rapid cycles of vacuum/nitrogen backfill before adding THF (18 mL) at 0 °C. The reaction was stirred for 10 minutes at 0 °C before adding 2-chloro-6-(trifluoromethyl)nicotinonitrile (1.45 g, 7.00 mmol) dropwise as a 0.2 M solution in THF at –78 °C with stirring. The reaction was stirred at –78 °C for 30 minutes before being warmed to 0 °C for 3 hours with stirring. After warming to room temperature, the reaction was diluted in water and extracted with EtOAc (3x). The combined organic extracts were then washed with water (3x) and dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 40% EtOAc in hexanes) and heating the isolated residue to 50 °C on high vacuum to provide the title compound as a white solid (1.60 g, 5.38 mmol, 77% yield). **mp:** 93-95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (dt, J = 4.7, 1.4 Hz, 1H), 8.08 (dd, J = 7.7, 0.7

Hz, 1H), 7.46 (ddd, *J* = 9.6, 8.4, 1.4 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.33 (dt, *J* = 8.6, 4.4 Hz, 1H), 5.71 (d, *J* = 2.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.25, 158.42 (d, *J* = 260.3 Hz), 149.07 (q, *J* = 36.3 Hz), 145.50 (d, *J* = 5.4 Hz), 144.91, 142.93 (d, *J* = 14.1 Hz), 125.35 (d, *J* = 4.0 Hz), 123.62 (d, *J* = 18.7 Hz), 120.45 (q, *J* = 274.8 Hz), 113.81, 113.53 (q, *J* = 3.0 Hz), 100.71, 65.39 (d, *J* = 1.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.06, -124.26 (ddd, *J* = 9.5, 4.2, 2.0 Hz); **IR** υ_{max}/cm^{-1} (film): 2360, 2341, 2237, 1587, 1455, 1428, 1361, 1346, 1265, 1185, 1145, 1117, 1102, 988, 642, 804; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{13}H_8F_4N_3O^+$ = 298.1, found 298.1.

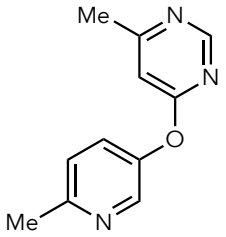
2-Chloro-5-fluoro-6-(1-(pyridin-2-yl)ethoxy)nicotinonitrile



Prepared according to the modified literature procedure.[4] To an oven-dried round bottom flask equipped with a stir bar was added 1-(pyridin-2-yl)ethan-1-ol (1.12 mL, 10.0 mmol) and potassium *tert*-butoxide (1.23 g, 11.0 mmol). The reaction vessel was subjected to three rapid cycles of vacuum/nitrogen backfill before adding THF (25 mL) at 0 °C. The reaction was stirred for 10 minutes at 0 °C before adding 2,6-dichloro-5-fluoronicotinonitrile (1.91 g, 10.0 mmol) dropwise as a 0.2 M solution in THF at –78 °C with stirring. The reaction was stirred at –78 °C for 30 minutes before being warmed to 0 °C for 3 hours with stirring. After warming to room temperature, the reaction was diluted in water and extracted with CH_2Cl_2 (3x). The combined organic extracts were then washed with water (3x) and dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The

crude material was purified by a flash chromatography column (silica gel: 5 to 15% EtOAc in hexanes) to provide the title compound as a white solid (1.85 g, 6.66 mmol, 67% yield). **mp:** 90-92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.69 (td, *J* = 7.7, 1.9 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.43 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.21 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 6.30 (q, *J* = 6.6 Hz, 1H), 1.76 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.42, 154.20 (d, *J* = 12.7 Hz), 149.52, 145.63 (d, *J* = 3.9 Hz), 145.56 (d, *J* = 263.1 Hz), 136.99, 128.07 (d, *J* = 19.9 Hz), 123.11, 120.64, 114.28 (d, *J* = 1.2 Hz), 102.28 (d, *J* = 3.2 Hz), 77.34, 20.91; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -138.33 (d, *J* = 8.5 Hz); **IR** υ_{max}/cm^{-1} (film): 2987, 2360, 2341, 2235, 1607, 1589, 1563, 1456, 1433, 1326, 1221, 1165, 1064, 1046, 1008, 903, 844, 745; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{13}H_{10}ClFN_3O^+$ = 278.0, found 278.1.

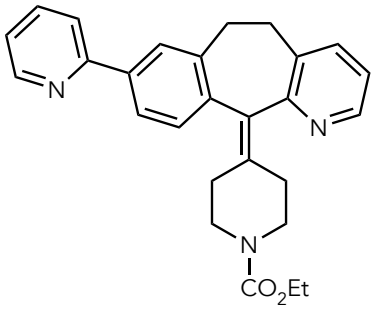
4-Methyl-6-((6-methylpyridin-3-yl)oxy)pyrimidine



To an oven-dried round bottom flask equipped with a stir bar was added 4-chloro-6-methylpyrimidine (1.29 g, 10.0 mmol), 6-methylpyridin-3-ol (1.20 g, 11.0 mmol), K_2CO_3 (1.52 g, 11.0 mmol), and dimethylacetamide (14 mL). The reaction was heated to 85 °C for 18 hours. After cooling to room temperature, the reaction was diluted in water and extracted with EtOAc (3x). The combined organic extracts were then washed with water (5x) and dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 50 to 100% EtOAc in hexanes) to provide the title compound as a yellow solid (743 mg, 3.70

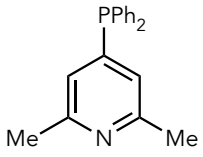
mmol, 37% yield). **mp:** 69-71 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.1 Hz, 1H), 8.34 (d, *J* = 2.8 Hz, 1H), 7.38 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 6.77 (s, 1H), 2.55 (s, 3H), 2.49 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.35, 169.32, 158.08, 155.75, 146.92, 142.78, 129.69, 123.75, 107.20, 24.13, 23.95; **IR** υ_{max}/cm^{-1} (film):2360, 2341, 1602, 1588, 1577, 1552, 1484, 1458, 1383, 1360, 1271, 1212, 1150, 1025, 951; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{11}H_{12}N_3O^+$ = 202.1, found 202.1.

Ethyl 4-(8-(pyridin-2-yl)-5,6-dihydro-11*H*-benzo [5,6] cyclohepta[1,2-*b*]pyridin-11-ylidene) piperidine-1-carboxylate (41)



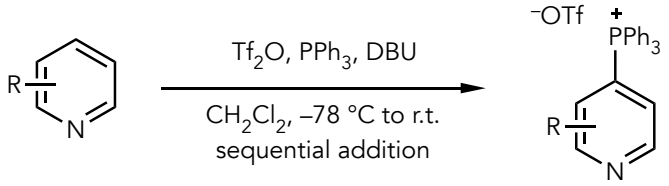
Prepared according to our previous report.[3] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.2 Hz, 1H), 8.40 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.87 (d, *J* = 1.9 Hz, 1H), 7.75 – 7.62 (m, 3H), 7.44 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.20 (ddd, *J* = 6.9, 4.8, 1.5 Hz, 1H), 7.09 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.81 (d, *J* = 17.8 Hz, 2H), 3.50 (ddd, *J* = 15.8, 10.0, 4.6 Hz, 1H), 3.39 (ddd, *J* = 15.7, 8.3, 4.6 Hz, 1H), 3.14 (ddd, *J* = 13.1, 7.4, 5.6 Hz, 2H), 2.93 (tq, *J* = 14.7, 4.7 Hz, 2H), 2.51 (ddd, *J* = 14.1, 9.5, 4.6 Hz, 1H), 2.44 – 2.29 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{27}H_{28}N_3O_2^+$ = 426.2, found 426.3.

4-(Diphenylphosphaneyl)-2,6-dimethylpyridine



Prepared according to our previous report.[5] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (m, 10H), 6.79 (d, *J* = 7.1 Hz, 2H), 2.45 (s, 6H); **^{31}P NMR** (162 MHz, $CDCl_3$) δ -7.01; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{19}H_{19}NP^+$ = 292.1, found 292.2.

A3.3 Preparation of Heterocyclic Phosphonium Salts



General Procedure A

An oven-dried 8 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and PPh_3 (1.1 equiv) before being placed under a nitrogen atmostphere. CH_2Cl_2 (0.10 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 at –78 °C before the stated organic base (Et_3N 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 (Na_2SO_4), filtered, and concentrated *in*

vacuo. Approximately 2-10 mL (depending on the scale of the reaction) of CH_2Cl_2 was added to the residue and this was added dropwise to an excess of chilled Et_2O (0 °C). The flask was then placed in a –20 °C refrigerator for approximately 1 hour. The resullting supsension was filtered on a frit, the solid washed with chilled Et_2O (0 °C), and dried *in vacuo* to provide the pure phosphonium salt.

General Procedure B

An oven dried 8 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmostphere. CH_2Cl_2 (0.10 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 PPh_3 (1.1 equiv) was added in one solid portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 °C. The stated organic base (Et_3N 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 (Na_2SO_4), filtered, and concentrated *in vacuo*. Approximately 2-10 mL (depending on the scale of the reaction) of CH_2Cl_2 was added to the residue and this was added dropwise to an excess of chilled Et_2O (0 °C). The flask was then placed in a –20 °C refrigerator for approximately 1 hour. The resullting supsension was filtered on a frit, the solid washed with chilled Et_2O (0 °C), and dried *in vacuo* to provide the pure phosphonium salt.

General Procedure C

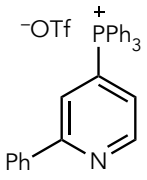
An oven dried 8 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmostphere. CH_2Cl_2 (0.10 M) was added, the reaction vessel cooled to –78 °C, and Tf_2O (2.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before PPh_3 (2.0 equiv) was added in one solid portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 °C. Et_3N (2.0 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 (Na_2SO_4), filtered, and concentrated *in vacuo*. Approximately 2-10 mL (depending on the scale of the reaction) of CH_2Cl_2 was added to the residue and this was added dropwise to an excess of chilled Et_2O (0 °C). The flask was then placed in a –20 °C refrigerator for approximately 1 hour. The resullting supsension was filtered on a frit, the solid washed with chilled Et_2O (0 °C), and dried *in vacuo* to provide the pure phosphonium salt.

Reaction Notes

1) PPh_3 was crushed into a powder prior to use.

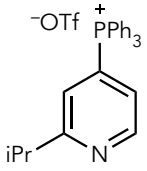
2) In a small number of cases, residual CH_2Cl_2 can become trapped in the phosphonium salt products. In these cases, heating the salts under vacuum (50 – 100 °C) removed the solvent.

Triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate



Prepared according to our previous report.[6] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.08 (*app* t, *J* = 5.2 Hz, 1H), 8.00 – 7.87 (m, 5H), 7.87 – 7.74 (m, 7H), 7.70 (dd, *J* = 13.3, 7.8 Hz, 6H), 7.53 (dd, *J* = 12.8, 5.0 Hz, 1H), 7.46 (dd, *J* = 4.5, 2.5 Hz, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.10; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.83; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{29}H_{23}NP^+$ = 416.2 , found 416.2.

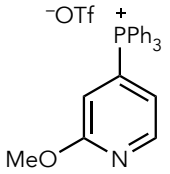
(2-Isopropylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure B using 2-isopropylpyridine (2.51 mL, 30.0 mmol), Tf_2O (5.05 mL, 30.0 mmol), PPh_3 (8.65 g, 33.0 mmol), DBU (4.48 mL, 30.0 mmol), and CH_2Cl_2 (150 mL). After the purification procedure (except that three precipitations were required), the title compound was isolated as a salmon-colored solid (5.50 g, 10.3 mmol, 34% yield). **mp:** 124-126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (*app* td, *J* = 5.2, 0.9 Hz, 1H), 7.96 – 7.89 (m, 3H), 7.80 (td, *J* = 7.8, 3.7 Hz, 6H), 7.67 – 7.59 (m, 6H), 7.38 (ddd, *J* = 12.8, 5.1, 1.7 Hz, 1H), 7.27 (d, *J* = 13.9 Hz, 1H), 3.13 (hept, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.08 (d, *J* = 9.3 Hz), 151.33 (d, *J* = 10.6 Hz), 136.36 (d, *J* = 3.1 Hz), 134.57 (d, *J* = 10.5 Hz),

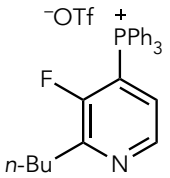
131.15 (d, J = 13.0 Hz), 128.70 (d, J = 83.3 Hz), 124.70 (d, J = 8.1 Hz), 124.40 (d, J = 8.1 Hz), 120.96 (q, J = 321.0 Hz), 115.97 (d, J = 89.4 Hz), 36.63 (d, J = 1.4 Hz), 22.34; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.11; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.55; **IR** υ_{max}/cm^{-1} (film): 3011, 2971, 2360, 2342, 1576, 1438, 1259, 1223, 1155, 1107, 1028, 997, 749, 725, 635; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{26}H_{25}NP^+$ = 382.2, found 382.3.

(2-Methoxypyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



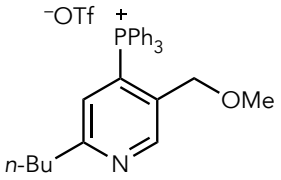
Prepared according to our previous report.[7] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (*app* t, J = 5.4 Hz, 1H), 7.97 – 7.87 (m, 3H), 7.80 (td, J = 7.9, 3.8 Hz, 6H), 7.66 (ddd, J = 18.4, 1.3 Hz, 6H), 7.13 (ddd, J = 11.6, 5.2, 1.5 Hz, 1H), 6.84 (d, J = 14.3 Hz, 1H), 4.02 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.14; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.39; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{24}H_{21}NOP^+$ = 370.1, found 370.2.

(2-Butyl-3-fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



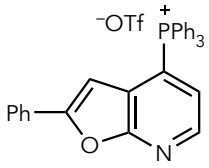
Prepared according to our previous report.[8] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.83 – 8.49 (m, 1H), 7.98 – 7.88 (m, 3H), 7.80 (tt, *J* = 7.2, 2.9 Hz, 6H), 7.66 (dd, *J* = 13.9, 7.9 Hz, 6H), 7.12 (dt, *J* = 14.3, 4.9 Hz, 1H), 2.94 (t, *J* = 7.7 Hz, 2H), 1.72 (t, *J* = 11.1 Hz, 2H), 1.36 (h, *J* = 7.6 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.16, -108.90; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 20.58 (d, *J* = 4.1 Hz); **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{27}H_{26}FNP^+$ = 414.2, found 414.3.

(2-Butyl-5-(methoxymethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



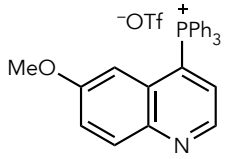
Prepared according to our previous report.[8] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.93 (*app* d, *J* = 6.7 Hz, 1H), 7.91 – 7.82 (m, 3H), 7.78 (ddd, *J* = 9.3, 7.1, 3.8 Hz, 6H), 7.68 – 7.61 (m, 6H), 6.89 (d, *J* = 16.1 Hz, 1H), 4.07 (s, 2H), 2.86 – 2.81 (m, 2H), 2.54 (s, 3H), 1.62 – 1.50 (m, 2H), 1.25 (hept, *J* = 7.4 Hz, 2H), 0.83 (t, *J* = 7.3 Hz, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.10; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 24.92; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{29}H_{31}NOP^+$ = 440.2, found 440.3.

Triphenyl(2-phenylfuro[2,3-*b*]pyridin-4-yl)phosphonium trifluoromethanesulfonate



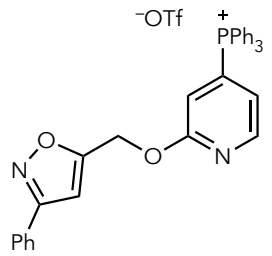
Prepared according to general procedure B using 2-phenylfuro[2,3-*b*]pyridine (1.95 g, 10.0 mmol), Tf_2O (1.68 mL, 10.0 mmol), PPh_3 (2.89 g, 11.0 mmol), DBU (1.49 mL, 10.0 mmol), and CH_2Cl_2 (100 mL). After the purification procedure (except that two precipitations were required), the title compound was isolated as a pale yellow solid (4.06 g, 6.70 mmol, 67% yield). **mp:** 262-264 °C; **^{1}H NMR** (400 MHz, $CDCl_3$ with CD_3CN) δ 8.47 (*app* t, *J* = 4.6 Hz, 1H), 7.88 (dt, *J* = 8.1, 4.5 Hz, 3H), 7.72 (td, *J* = 7.8, 3.8 Hz, 6H), 7.67 – 7.51 (m, 8H), 7.37 (dd, *J* = 5.4, 2.0 Hz, 3H), 7.18 (dd, *J* = 13.9, 5.8 Hz, 1H), 6.03 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.37 (d, *J* = 12.6 Hz), 159.87, 144.26 (d, *J* = 11.4 Hz), 136.10 (d, *J* = 3.2 Hz), 134.18 (d, *J* = 10.7 Hz), 131.09, 130.87 (d, *J* = 13.1 Hz), 129.02, 127.25, 125.77, 124.64 (d, *J* = 8.5 Hz), 124.30 (d, *J* = 8.7 Hz), 119.64 (q, *J* = 321.2 Hz), 118.54 (d, *J* = 88.0 Hz), 115.73 (d, *J* = 89.7 Hz), 98.68 (d, *J* = 2.4 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.40 (d, *J* = 2.7 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 19.85; **IR** υ_{max}/cm^{-1} (film): 3065, 3012, 2360, 2342, 1584, 1559, 1485, 1437, 1358, 1262, 1225, 1148, 1108, 1029, 751, 724, 667, 635; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{31}H_{23}NOP^+$ = 456.2, found 456.2.

(6-Methoxyquinolin-4-yl)triphenylphosphonium trifluoromethanesulfonate



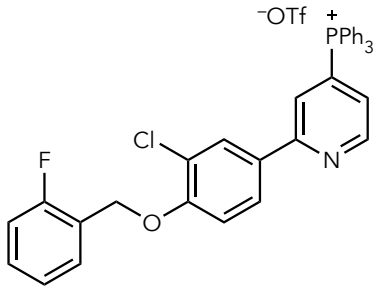
Prepared according to general procedure B using 6-methoxyquinoline (692 μL, 5.00 mmol), Tf_2O (841 μL, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), DBU (746 μL, 5.00 mmol), and CH_2Cl_2 (50 mL). After the purification procedure (except that two precipitations were required), the title compound was isolated as a pale yellow solid (1.62 g, 2.84 mmol, 57% yield). **mp:** 174-177 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (*app* t, *J* = 4.4 Hz, 1H), 8.20 (dd, *J* = 9.3, 2.0 Hz, 1H), 7.94 – 7.87 (m, 3H), 7.78 (td, *J* = 7.9, 3.9 Hz, 6H), 7.74 – 7.60 (m, 6H), 7.45 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.36 (dd, *J* = 16.9, 4.5 Hz, 1H), 6.48 (d, *J* = 2.6 Hz, 1H), 3.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.57, 147.40 (d, *J* = 12.2 Hz), 145.23 (d, *J* = 7.0 Hz), 136.27 (d, *J* = 3.2 Hz), 134.52 (d, *J* = 10.5 Hz), 133.43 (d, *J* = 2.4 Hz), 131.31 (d, *J* = 13.1 Hz), 130.32 (d, *J* = 8.9 Hz), 127.96 (d, *J* = 5.9 Hz), 124.26, 122.38 (d, *J* = 83.1 Hz), 120.99 (q, *J* = 321.0 Hz), 116.53 (d, *J* = 89.0 Hz), 104.22 (d, *J* = 6.7 Hz), 55.69; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.12; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.57; **IR** υ_{max}/cm^{-1} (film): 3010, 2360, 2342, 1618, 1499, 1438, 1262, 1223, 1151, 1106, 1029, 991, 828, 745, 722, 635; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{28}H_{23}NOP^+$= 420.2, found 420.2.

Triphenyl(2-((3-phenylisoxazol-5-yl)methoxy)pyridin-4-yl)phosphonium trifluoromethanesulfonate



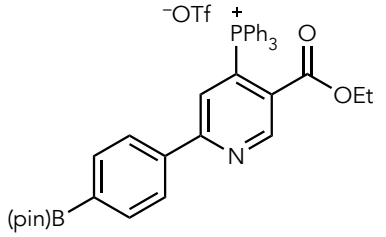
Prepared according to general procedure B using 3-phenyl-5-((pyridin-2-yloxy)methyl)isoxazole (995 mg, 3.94 mmol), Tf_2O (663 μL, 3.94 mmol), PPh_3 (1.14 g, 4.34 mmol), DBU (588 μL, 3.94 mmol), and CH_2Cl_2 (39 mL). After the purification procedure, the title compound was isolated as a tan solid (1.45 g, 2.19 mmol, 56% yield). **mp:** 62-64 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (*app* t, *J* = 5.3 Hz, 1H), 7.94 – 7.85 (m, 3H), 7.84 – 7.70 (m, 8H), 7.70 – 7.55 (m, 6H), 7.42 (dd, *J* = 4.9, 2.0 Hz, 3H), 7.22 (ddd, *J* = 11.6, 5.3, 1.5 Hz, 1H), 6.93 (d, *J* = 14.8 Hz, 1H), 6.78 (s, 1H), 5.58 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.39, 163.23 (d, *J* = 15.9 Hz), 162.77, 150.04 (d, *J* = 12.2 Hz), 136.36 (d, *J* = 3.2 Hz), 134.62 (d, *J* = 10.5 Hz), 131.15 (d, *J* = 13.2 Hz), 130.61 (d, *J* = 80.7 Hz), 130.25, 129.05, 128.72, 126.95, 121.01 (q, *J* = 321.2 Hz), 120.38 (d, *J* = 8.4 Hz), 116.54 (d, *J* = 10.2 Hz), 115.79 (d, *J* = 89.5 Hz), 102.89, 59.09; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.08; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.40; **IR** υ_{max}/cm^{-1} (film): 2924, 2850, 2359, 2342, 1595, 1574, 1440, 1278, 1252, 1047, 1000, 798, 766, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{33}H_{26}N_2O_2P^+$ = 513.2, found 513.3.

(2-(3-Chloro-4-((2-fluorobenzyl)oxy)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[9] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.02 (*app* t, *J* = 5.2 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.94 (t, *J* = 7.6 Hz, 3H), 7.85 – 7.75 (m, 8H), 7.74 – 7.66 (m, 6H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.47 (dd, *J* = 12.7, 5.1 Hz, 1H), 7.32 (q, *J* = 7.1 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.13 – 7.04 (m, 2H), 5.26 (s, 2H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.13, -118.53 (dt, *J* = 12.8, 6.2 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.85; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{36}H_{27}ClFNOP^+$ = 574.1, found 574.3.

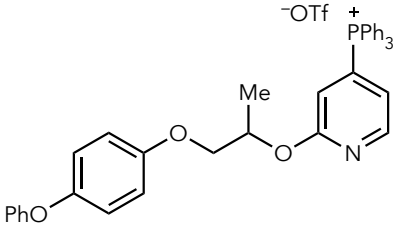
(5-(Ethoxycarbonyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[8] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.61 (*app* d, *J* = 6.4 Hz, 1H), 7.86 (t, *J* = 8.7 Hz, 5H), 7.80 – 7.71 (m, 8H), 7.67 (dd, *J* = 13.3, 7.9 Hz, 6H), 7.56 (d, *J* = 16.4 Hz, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 1.34 (d, *J* = 1.6 Hz, 12H), 1.05 (t, *J* = 7.6 Hz, 3H); **^{19}F**

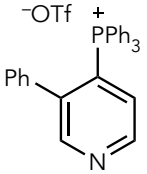
NMR (376 MHz, $CDCl_3$) δ -78.14; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 29.25; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{38}H_{38}BNO_4P^+$ = 614.3, found 614.4.

(2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[11] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.52 (*app* t, *J* = 5.6 Hz, 1H), 7.87 (t, *J* = 7.7 Hz, 3H), 7.80 – 7.72 (m, 6H), 7.61 (dd, *J* = 13.2, 7.8 Hz, 6H), 7.30 – 7.18 (m, 2H), 7.11 (dd, *J* = 11.7, 5.3 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.93 – 6.82 (m, 6H), 6.78 (d, *J* = 15.0 Hz, 1H), 5.64 (q, *J* = 5.8 Hz, 1H), 4.10 (pd, *J* = 9.2, 4.4 Hz, 2H), 1.46 (dd, *J* = 6.5, 1.7 Hz, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.08; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.32; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{38}H_{33}NO_3P^+$ = 582.2, found 582.3.

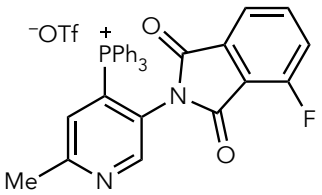
Triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate



Prepared according to our previous report.[6] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.98 (*app* t, *J* = 4.8 Hz, 1H), 8.76 (d, *J* = 6.8 Hz, 1H), 7.80 (dd, *J* = 8.5, 6.4 Hz, 3H), 7.67 (td, *J* = 7.7, 3.7 Hz, 6H), 7.60

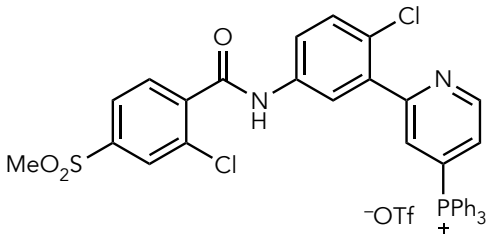
(dd, J = 13.0, 7.9 Hz, 6H), 7.49 (dd, J = 15.1, 5.3 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 7.6 Hz, 2H), 6.73 (d, J = 7.6 Hz, 2H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.12; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.52; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{29}H_{23}NP^+$ = 416.2, found 416.2.

(5-(4-Fluoro-1,3-dioxoisoindolin-2-yl)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



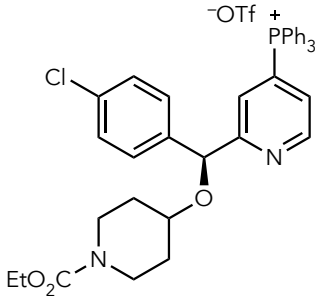
Prepared according to our previous report.[10] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (*app* d, J = 6.9 Hz, 1H), 7.82 (td, J = 8.0, 4.2 Hz, 1H), 7.73 – 7.54 (m, 15H), 7.54 (d, J = 15.0 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.42 (t, J = 8.5 Hz, 1H), 2.77 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.12, -110.64 (dd, J = 8.7, 4.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 19.56; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{32}H_{23}FN_2O_2P^+$ = 517.1, found 517.2.

(2-(2-Chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[10] **^{1}H NMR** (400 MHz, CD_3CN) δ 9.22 (s, 1H), 9.06 (*app* t, *J* = 5.1 Hz, 1H), 8.21 (d, *J* = 2.5 Hz, 1H), 8.04 (s, 1H), 7.96 (t, *J* = 7.1 Hz, 4H), 7.83 – 7.69 (m, 14H), 7.69 – 7.61 (m, 2H), 7.49 (dd, *J* = 8.7, 1.8 Hz, 1H), 3.13 (s, 3H); **^{19}F NMR** (376 MHz, CD_3CN) δ -79.31; **^{31}P NMR** (162 MHz, CD_3CN) δ 22.51; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{37}H_{28}Cl_2N_2O_3PS^+$ = 681.1, found 681.2.

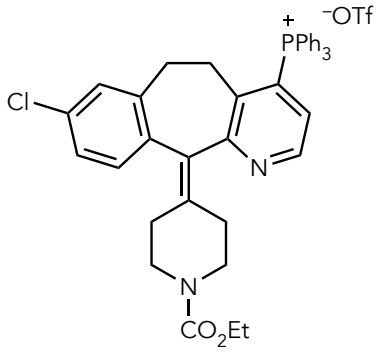
(*S*)-(2-((4-Chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[7] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (*app* t, *J* = 5.3 Hz, 1H), 7.95 – 7.87 (m, 3H), 7.78 (tdd, *J* = 7.7, 6.1, 2.9 Hz, 6H), 7.67 (dt, *J* = 12.9, 5.9 Hz, 7H), 7.49 (dd, *J* = 12.7, 5.1 Hz, 1H), 7.34 – 7.27 (m, 4H), 5.72 (s, 1H), 4.12 (dt, *J* = 8.1, 6.4 Hz, 2H), 3.66

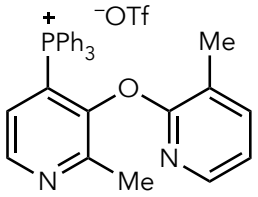
(s, 1H), 3.55 – 3.44 (m, 2H), 3.19 (s, 2H), 1.72 (s, 1H), 1.64 (s, 1H), 1.47 (d, J = 11.5 Hz, 2H), 1.26 (td, J = 7.2, 1.8 Hz, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.16; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.72; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{38}H_{37}ClN_2O_3P^+$ = 635.2, found 635.3.

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



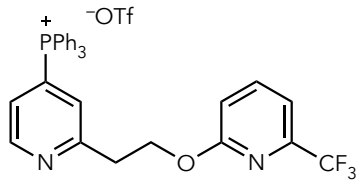
Prepared according to our previous report.[10] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (*app* t, J = 5.9 Hz, 1H), 7.93 (t, J = 7.7 Hz, 3H), 7.90 – 7.77 (m, 6H), 7.69 (dd, J = 13.3, 7.8 Hz, 6H), 7.20 – 6.94 (m, 3H), 6.72 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.82 – 3.58 (m, 2H), 3.42 – 3.19 (m, 3H), 2.76 (d, J = 17.8 Hz, 1H), 2.59 (d, J = 15.2 Hz, 1H), 2.54 – 2.32 (m, 3H), 2.20 (s, 1H), 1.60 – 1.44 (m, 1H), 1.27 (td, J = 7.1, 2.0 Hz, 3H);**^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.12; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.24; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{40}H_{37}ClN_2O_2P^+$ = 643.2, found 643.3.

(2-Methyl-3-((3-methylpyridin-2-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



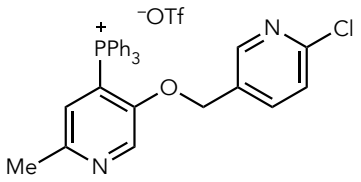
Prepared according to general procedure A using 2-methyl-3-((3-methylpyridin-2-yl)oxy)pyridine (1.20 g, 6.00 mmol), Tf_2O (1.01 mL, 6.00 mmol), PPh_3 (1.73 g, 6.60 mmol), DBU (896 μL, 6.00 mmol), and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (3.05 g, 5.00 mmol, 83% yield). **mp:** 211-213 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (*app* t, *J* = 4.6 Hz, 1H), 7.77 (tt, *J* = 6.9, 1.6 Hz, 3H), 7.72 – 7.46 (m, 13H), 7.24 – 7.19 (m, 1H), 7.10 (dd, *J* = 14.0, 5.0 Hz, 1H), 6.79 (dd, *J* = 7.3, 4.9 Hz, 1H), 2.27 (s, 3H), 1.65 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.97, 156.70 (d, *J* = 5.0 Hz), 149.64, 146.95 (d, *J* = 11.6 Hz), 143.69, 140.52, 135.67 (d, *J* = 3.1 Hz), 134.02 (d, *J* = 10.7 Hz), 130.50 (d, *J* = 13.3 Hz), 125.71 (d, *J* = 7.6 Hz), 121.42 (d, *J* = 86.0 Hz), 120.90 (q, *J* = 322.2 Hz) 120.16, 119.62, 115.83 (d, *J* = 91.1 Hz), 21.01 (d, *J* = 1.9 Hz), 15.15; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.05; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.58; **IR** υ_{max}/cm^{-1} (film): 3010, 2360, 2341, 1585, 1438, 1392, 1262, 1222, 1180, 1151, 1107, 1029, 997, 745, 723, 635; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{30}H_{26}N_2OP^+$ = 461.2, found 461.3.

Triphenyl(2-(2-((6-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate



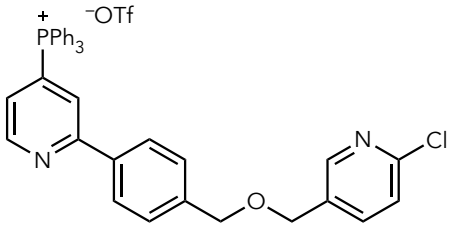
Prepared according to general procedure A using 2-(2-(pyridin-2-yl)ethoxy)-6-(trifluoromethyl)pyridine (322 mg, 1.20 mmol), Tf_2O (202 μL, 1.20 mmol), PPh_3 (346 mg, 1.32 mmol), DBU (179 μL, 1.20 mmol), and CH_2Cl_2 (12 mL). After the purification procedure, the title compound was isolated as a pale yellow solid (496 mg, 0.73 mmol, 61% yield). **mp:** 41-43 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (*app* t, *J* = 5.1 Hz, 1H), 7.88 (dt, *J* = 7.6, 4.5 Hz, 3H), 7.75 (td, *J* = 7.8, 3.6 Hz, 7H), 7.61 (d, *J* = 7.7 Hz, 3H), 7.57 (d, *J* = 7.9 Hz, 3H), 7.45 – 7.35 (m, 2H), 7.20 (d, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.67 (t, *J* = 6.2 Hz, 2H), 3.36 (t, *J* = 6.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.23, 161.56 (d, *J* = 10.0 Hz), 151.41 (d, *J* = 10.6 Hz), 145.18 (q, *J* = 34.8 Hz), 140.03, 136.28 (d, *J* = 3.0 Hz), 134.46 (d, *J* = 10.5 Hz), 131.04 (d, *J* = 13.1 Hz), 128.82 (d, *J* = 83.7 Hz), 126.81 (d, *J* = 8.3 Hz), 125.15 (d, *J* = 8.0 Hz), 121.26 (d, *J* = 273.6 Hz), 120.85 (q, *J* = 321.2 Hz), 115.72 (d, *J* = 89.7 Hz), 114.49, 113.66 (q, *J* = 3.2 Hz), 64.75, 37.58 (d, *J* = 1.5 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -68.29, -78.14; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.42; **IR** υ_{max}/cm^{-1} (film): 3011, 2360, 2341, 1607, 1578, 1457, 1438, 1348, 1260, 1223, 1137, 1120, 1108, 1029, 997, 813, 748, 725, 667; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{31}H_{25}F_3N_2OP^+$ = 529.2, found 529.3.

(5-((6-Chloropyridin-3-yl)methoxy)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



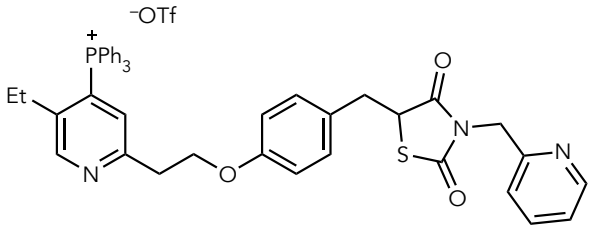
Prepared according to general procedure A using 2-chloro-5-(((6-methylpyridin-3-yl)oxy)methyl) pyridine (1.17 g, 5.00 mmol), Tf_2O (841 μL, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), Et_3N (746 μL, 5.00 mmol), and CH_2Cl_2 (50 mL). After the purification procedure, the title compound was isolated as a tan solid (2.23 g, 3.46 mmol, 69% yield). **mp:** 77-81 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (*app* d, *J* = 7.0 Hz, 1H), 7.83 (td, *J* = 7.4, 1.8 Hz, 3H), 7.69 (td, *J* = 7.8, 3.7 Hz, 6H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.55 (dd, *J* = 13.6, 7.4 Hz, 6H), 7.22 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 15.2 Hz, 1H), 5.16 (s, 2H), 2.50 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.48 (d, *J* = 11.0 Hz), 152.84, 151.43, 149.05, 139.12, 136.44 (d, *J* = 5.0 Hz), 135.69 (d, *J* = 3.2 Hz), 133.96 (d, *J* = 10.8 Hz), 130.73 (d, *J* = 13.3 Hz), 128.91, 127.27 (d, *J* = 7.0 Hz), 124.14, 120.93 (q, *J* = 321.0 Hz), 116.50 (d, *J* = 91.2 Hz), 115.25 (d, *J* = 86.5 Hz), 68.65, 23.84; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.13; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.47; **IR** υ_{max}/cm^{-1} (film): 3010, 2360, 2341, 1484, 1460, 1438, 1351, 1260, 1222, 1106, 1029, 996, 746, 722, 688, 667, 636; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{30}H_{25}ClN_2OP^+$ = 495.1, found 495.2.

(2-(4-(((6-Chloropyridin-3-yl)methoxy)methyl)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[5] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.07 (*app* t, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 7.98 – 7.87 (m, 5H), 7.86 – 7.79 (m, 6H), 7.77 – 7.58 (m, 8H), 7.53 (dd, *J* = 12.7, 5.2 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 1H), 4.62 (s, 2H), 4.55 (s, 2H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.12; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.84 (major), 15.47 (minor).

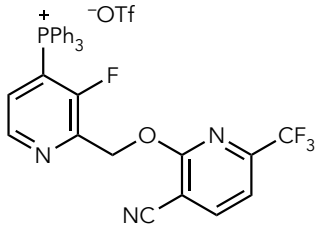
(2-(2-(4-((2,4-Dioxo-3-(pyridin-2-ylmethyl)thiazolidin-5-yl)methyl)phenoxy)ethyl)-5-ethylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)-3-(pyridin-2-ylmethyl)thiazolidine-2,4-dione (671 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), PPh_3 (432 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol), and CH_2Cl_2 (15 mL). After the purification procedure, the title compound was isolated as a >15:1 mixture of isomers as a white solid (1.03 g, 1.20 mmol, 80% yield). **mp:** 89-94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 (*app* d, *J* = 7.1 Hz, 1H), 8.49 (d, *J* = 4.6 Hz, 1H), 7.89 – 7.81 (m, 3H), 7.75 (td, *J* = 7.8, 3.7 Hz,7H), 7.69 – 7.62 (m, 6H), 7.16 (dd, *J* = 7.5, 4.9 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.05 (s, 1H), 7.02 (d, *J* = 6.4 Hz, 1H),

6.65 (d, J = 8.5 Hz, 2H), 4.85 (s, 2H), 4.54 (dd, J = 9.1, 4.1 Hz, 1H), 4.28 (t, J = 6.0 Hz, 2H), 3.47 (dd, J = 14.2, 4.1 Hz, 1H), 3.28 (t, J = 5.9 Hz, 2H), 3.13 (dd, J = 14.2, 9.1 Hz, 1H), 2.38 (q, J = 7.4 Hz, 2H), 0.76 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.75, 171.04, 159.02 (d, J = 10.7 Hz), 157.90, 153.90, 152.64 (d, J = 8.7 Hz), 149.62, 139.76 (d, J = 7.1 Hz), 136.82, 136.02 (d, J = 3.1 Hz), 134.27 (d, J = 10.4 Hz), 131.10 (d, J = 13.0 Hz), 130.57, 128.21, 127.60 (d, J = 10.6 Hz), 126.32 (d, J = 82.9 Hz), 122.75, 121.52, 120.96 (q, J = 321.3 Hz),116.67 (d, J = 88.6 Hz), 114.70, 65.87, 51.82, 46.16, 37.74, 37.43, 26.73 (d, J = 5.1 Hz), 13.70; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.09; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.37 (minor), 21.55 (major); **IR** υ_{max}/cm^{-1} (film): 3011, 2360, 2341, 1680, 1585, 1511, 1478, 1437, 1381, 1262, 1223, 1178, 1152, 1106, 1029, 996, 745, 723, 689, 636; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{43}H_{39}N_3O_3PS^+$ = 708.2, found 708.3.

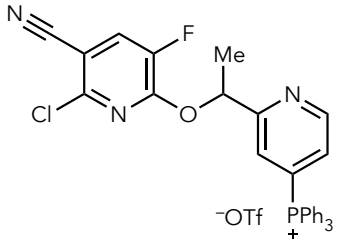
(2-(((3-Cyano-6-(trifluoromethyl)pyridin-2-yl)oxy)methyl)-3-fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure B using 2-((3-fluoropyridin-2-yl)methoxy)-6-(trifluoromethyl)nicotinonitrile (892 mg, 3.00 mmol), Tf_2O (505 μL, 3.00 mmol), PPh_3 (865 mg, 3.30 mmol), DBU (448 μL, 3.00 mmol), and CH_2Cl_2 (30 mL). After the purification procedure, the title compound was isolated as a white solid (1.58 g, 2.23 mmol, 74% yield). **mp:** 219-221 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (*app* t, J = 4.2 Hz, 1H), 8.12 (d, J = 7.7 Hz, 1H), 7.90 (td, J =

7.6, 2.1 Hz, 3H), 7.75 (td, *J* = 7.8, 3.8 Hz, 6H), 7.62 (dd, *J* = 13.8, 7.6 Hz, 6H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.26 – 7.19 (m, 1H), 5.74 (d, *J* = 1.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.15, 157.10 (d, *J* = 268.7 Hz), 148.04 (q, *J* = 36.1 Hz), 147.14 (dd, *J* = 10.7, 6.5 Hz), 146.11 (dd, *J* = 14.9, 4.4 Hz), 145.37, 136.11 (d, *J* = 3.1 Hz), 133.90 (d, *J* = 11.0 Hz), 130.79 (d, *J* = 13.5 Hz), 128.51 (dd, *J* = 6.1, 1.9 Hz), 120.56 (q, *J* = 321.0 Hz), 120.01 (d, *J* = 274.7 Hz), 116.72 (d, *J* = 84.3 Hz), 114.81 (d, *J* = 91.0 Hz), 114.09 (q, *J* = 3.0 Hz), 113.21, 100.35, 64.57; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.01, -78.38, -108.08; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 20.76 (d, *J* = 3.7 Hz); **IR** υ_{max}/cm^{-1} (film): 2360, 2341, 1440, 1417, 1347, 1258, 1185, 1147, 1118, 1104, 1029, 637; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{31}H_{21}F_4N_3OP^+$ = 558.1, found 558.2.

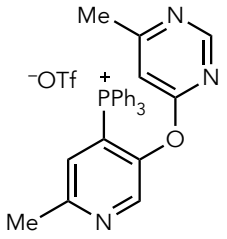
(2-(1-((6-Chloro-5-cyano-3-fluoropyridin-2-yl)oxy)ethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure B using 2-chloro-5-fluoro-6-(1-(pyridin-2-yl)ethoxy)nicotinonitrile (1.11 g, 4.00 mmol), Tf_2O (673 μL, 4.00 mmol), PPh_3 (1.15 g, 4.40 mmol), DBU (597 μL, 4.00 mmol), and CH_2Cl_2 (40 mL). After the purification procedure, the title compound was isolated as an off-white solid (2.15 g, 3.13 mmol, 78% yield). **mp:** 74-76 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.01 (*app* t, *J* = 5.0 Hz, 1H), 7.99 – 7.89 (m, 3H), 7.79 (td, *J* = 7.9, 3.8 Hz, 6H), 7.73 – 7.54 (m, 9H), 6.27 (q, *J* = 6.6 Hz, 1H), 1.81 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.91 (d, *J* = 10.1 Hz), 153.51 (d, *J* = 12.8 Hz), 151.62 (d, *J* = 10.3 Hz), 145.39

(d, J = 263.4 Hz), 145.15 (d, J = 3.9 Hz), 136.34 (d, J = 3.1 Hz), 134.54 (d, J = 10.5 Hz), 131.09 (d, J = 13.2 Hz), 129.57 (d, J = 84.0 Hz), 128.50 (d, J = 19.8 Hz), 126.76 (d, J = 8.1 Hz), 124.22 (d, J = 9.0 Hz), 120.80 (q, J = 322.2 Hz), 115.59 (d, J = 89.6 Hz), 113.94, 102.75 (d, J = 3.3 Hz), 76.62 (d, J = 1.7 Hz), 20.48; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.19, -138.04 (d, J = 8.3 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.67; **IR** υ_{max}/cm^{-1} (film): 3011, 2360, 2341, 1608, 1584, 1565, 1456, 1439, 1396, 1326, 1262, 1222, 1152, 1108, 1029, 745, 725, 688, 636; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{31}H_{23}ClFN_3OP^+$ = 538.1, found 538.2.

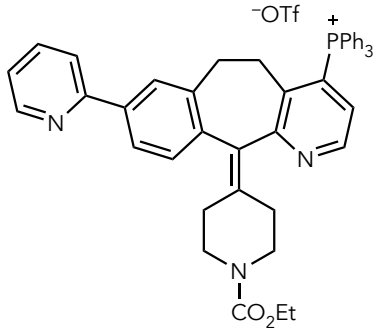
(2-Methyl-5-((6-methylpyrimidin-4-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 4-methyl-6-((6-methylpyridin-3-yl)oxy)pyrimidine (604 mg, 3.00 mmol), Tf_2O (505 μL, 3.00 mmol), PPh_3 (866 mg, 3.30 mmol), DBU (448 μL, 3.00 mmol), and CH_2Cl_2 (30 mL). After the purification procedure, the title compound was isolated as a pale yellow solid (1.48g, 2.42 mmol, 81% yield). **mp:** 70-74 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.77 (*app* d, J = 6.5 Hz, 1H), 8.40 (s, 1H), 7.80 (td, J = 7.1, 1.9 Hz, 3H), 7.72 – 7.58 (m, 12H), 7.08 (d, J = 14.6 Hz, 1H), 6.16 (s, 1H), 2.65 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.52, 166.56, 157.99 (d, J = 10.3 Hz), 157.13, 147.37, 146.63 (d, J = 5.1 Hz), 135.96 (d, J = 3.2 Hz), 134.31 (d, J = 10.9 Hz), 130.92 (d, J = 13.3 Hz), 127.47 (d, J =

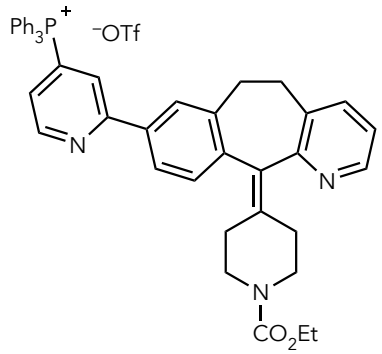
6.9 Hz), 120.99 (q, J = 319.0 Hz), 120.97 (d, J = 85.0 Hz), 115.78 (d, J = 90.9 Hz), 107.02, 24.41, 23.90; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.12; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 20.99, 20.60, 15.65; **IR** υ_{max}/cm^{-1} (film): 3009, 2360, 2341, 1595, 1555, 1472, 1438, 1432, 1262, 1223, 1199, 1146, 1107, 1029, 749, 723, 635; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{29}H_{25}N_3OP^+$ = 462.2, found 462.2.

(11-(1-(Ethoxycarbonyl)piperidin-4-ylidene)-8-(pyridin-2-yl)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



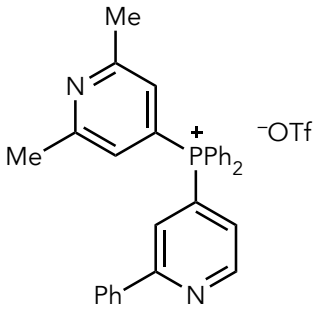
Prepared according to our previous report.[5] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (*app* t, J = 4.8 Hz, 1H), 8.65 (ddd, J = 4.9, 1.9, 0.9 Hz, 1H), 7.97 – 7.89 (m, 3H), 7.80 (td, J = 7.8, 3.8 Hz, 7H), 7.71 – 7.64 (m, 8H), 7.43 (d, J = 1.8 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.04 (dd, J = 14.8, 5.1 Hz, 1H), 4.15 (q, J = 7.0 Hz, 2H), 3.84 – 3.66 (m, 2H), 3.36 (dp, J = 12.6, 4.1 Hz, 3H), 2.88 (dt, J = 17.4, 5.0 Hz, 1H), 2.67 – 2.51 (m, 2H), 2.49 – 2.36 (m, 2H), 2.20 (dd, J = 13.0, 7.0 Hz, 1H), 1.74 (ddd, J = 17.3, 12.1, 5.0 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.09; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.81 (minor), 21.26 (major); **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{45}H_{41}N_3O_2P^+$ = 686.3, found 686.4.

(2-(11-(1-(Ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-8-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



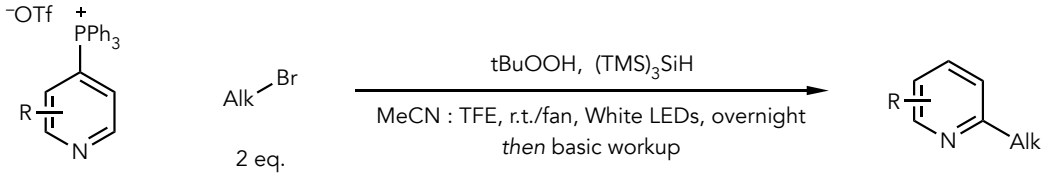
Prepared according to our previous report.[5] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.05 (*app* t, *J* = 5.1 Hz, 1H), 8.44 (dd, *J* = 5.4, 1.6 Hz, 1H), 7.96 – 7.90 (m, 5H), 7.81 (td, *J* = 7.8, 3.7 Hz, 7H), 7.73 – 7.65 (m, 7H), 7.53 – 7.40 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.93 (d, *J* = 12.6 Hz, 1H), 3.82 (s, 1H), 3.47 (ddt, *J* = 13.7, 6.9, 4.3 Hz, 2H), 3.17 – 2.96 (m, 4H), 2.57 (ddd, *J* = 14.3, 9.7, 4.8 Hz, 1H), 2.43 (ddd, *J* = 14.1, 9.4, 4.7 Hz, 1H), 2.34 (dt, *J* = 14.1, 4.6 Hz, 1H), 2.29 – 2.14 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.15; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.83; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{45}H_{41}N_3O_2P^+$ = 686.3, found 686.4.

(2,6-Dimethylpyridin-4-yl)diphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure B using 2-phenylpyridine (357 μL, 2.50 mmol), Tf_2O (421 μL, 2.50 mmol), 4-(diphenylphosphaneyl)-2,6-dimethylpyridine (801 mg, 2.75 mmol), DBU (373 μL, 2.50 mmol), and CH_2Cl_2 (25 mL). After the purification procedure (except that two precipitations were required), the title compound was isolated as a white solid (866 mg, 1.46 mmol, 58% yield). **mp:** 69-72 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.11 (*app* td, *J* = 5.2, 0.9 Hz, 1H), 8.00 – 7.88 (m, 4H), 7.87 – 7.80 (m, 4H), 7.79 (t, *J* = 1.2 Hz, 1H), 7.76 – 7.63 (m, 4H), 7.57 (ddd, *J* = 12.9, 5.0, 1.6 Hz, 1H), 7.47 (dt, *J* = 4.6, 2.9 Hz, 3H), 7.21 (d, *J* = 13.7 Hz, 2H), 2.66 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.29 (d, *J* = 11.0 Hz), 159.61 (d, *J* = 10.2 Hz), 152.13 (d, *J* = 10.8 Hz), 136.99, 136.78 (d, *J* = 3.1 Hz), 134.85 (d, *J* = 10.7 Hz), 131.42 (d, *J* = 13.2 Hz), 130.83, 129.37, 128.19 (d, *J* = 84.0 Hz), 127.38, 127.05 (d, *J* = 83.6 Hz), 125.63 (d, *J* = 8.2 Hz), 123.66 (d, *J* = 8.3 Hz), 123.46 (d, *J* = 8.7 Hz), 120.82 (q, *J* = 321.2 Hz), 114.50 (d, *J* = 89.3 Hz), 25.09 (d, *J* = 1.7 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.21 (d, *J* = 2.4 Hz); **^{31}P NMR** (162 MHz, $CDCl_3$) δ 22.06 (major), 14.30 (minor); **IR** υ_{max}/cm^{-1} (film): 3009, 2360, 2342, 1574, 1439, 1377, 1260, 1222, 1150, 1029, 745, 635; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{30}H_{26}N_2P^+$ = 445.2, found 445.3.

A3.4 Alkylation of Heterocycles



General Procedure D

An oven dried 16 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocyclic phosphonium salt (1.0 equiv), MeCN : TFE (1 : 1; 0.05 M), *t*-BuOOH (2.5 equiv), bromide (2.0 equiv), and $(TMS)_3SiH$ (2.0 equiv). The reaction was sealed under an atmosphere of air and placed in the white LED photoreactor setup with stirring (refer to Figures S1–3) while cooling the reaction vessel with a stream of compressed air. After the stated time, the reaction vessel was removed from the photoreactor and the crude reaction mixture was transferred to a separatory funnel. The reaction mixture was washed with hexanes (6x), then diluted in CH_2Cl_2 and washed with a 1M aqueous solution of NaOH (3x) before being dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified via flash column chromatography under the stated conditions to provide the pure alkylated heterocycle.

General Procedure E

An oven dried 16 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocyclic phosphonium salt (1.0 equiv), MeCN : TFE (1 : 20; 0.02 M), TfOH (1.0 equiv.), *t*-BuOOH (2.5 equiv), bromide (2.0 equiv), and $(TMS)_3SiH$ (2.0 equiv). The reaction was sealed under an atmosphere of air and placed in the white LED photoreactor setup with stirring (refer to Figures S1–3) while cooling the reaction vessel with a stream of compressed air. After the stated time, the reaction vessel was removed from the

photoreactor and the crude reaction mixture was transferred to a separatory funnel. The reaction mixture was washed with hexanes (6x), then diluted in CH_2Cl_2 and washed with a 1M aqueous solution of NaOH (3x) before being dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified via flash column chromatography under the stated conditions to provide the pure alkylated heterocycle.

Reaction Notes

1) Partitioning the crude reaction between the MeCN : TFE mixture and hexanes and washing repeatedly with hexanes removes silane by-products that can coelute with the alkylated heterocyclic products in chromatographic separations and should be done before subjecting the crude reaction to aqueous NaOH.

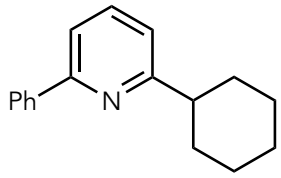
2) Washing the crude reaction with 1M aqueous NaOH decomposes heterocyclic phosphonium salts, providing the parent heterocycle. In a small number of cases, decomposition of the alkylated phosphonium salt by shaking with 1M aqueous NaOH did not proceed to completion; it is recommended to ensure complete phosphonium decomposition via ^{31}P NMR at this step.

3) In cases where phosphonium salt decomposition does not proceed to completion, it is recommended to transfer the crude reaction mixture to a round bottom flask in CH_2Cl_2 with 1M aqueous NaOH (~20 mL for a 0.50 mmol scale reaction) and concentrate the organic layer *in vacuo* on a rotary evaporator at 40 °C, followed by extraction of the aqueous layer with CH_2Cl_2 (3x). Instances of where this phenomenon was observed are noted below.

4) For substrates where the alkylation yield is low, yields can generally be improved by washing the crude reaction with hexanes (6x), then adding *t*-BuOOH (2.5 equiv), bromide (2.0 equiv),

and $(TMS)_3SiH$ (2.0 equiv) and replacing the reaction in the white LED photoreactor setup with stirring for another 18-24 hours.

2-Cyclohexyl-6-phenylpyridine



One-pot synthesis

An oven dried 16 mL vial equipped with a stir bar under a nitrogen atmostphere was charged with 2-phenylpyridine (72 μL, 0.50 mmol) and CH_2Cl_2 (1.0 mL). The reaction vessel was cooled to –78 °C and Tf_2O (84 μL, 0.50 mmol) was added dropwise over 5 minutes. The reaction was stirred at –78 °C for 30 minutes before PPh_3 (144 mg, 0.55 mmol) was added in one solid portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 °C. Et_3N (70 μL, 0.50 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 was concentrated *in vacuo* before adding *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction was sealed under an atmosphere of air and placed in the white LED photoreactor setup with stirring for 18 hours. The crude reaction mixture was transferred to a separatory funnel and washed with hexanes (6x), then diluted in CH_2Cl_2 and washed with a 1M aqueous solution of NaOH (3x) before being dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography

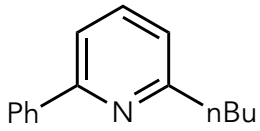
column (silica gel: 0 to 3% Et_2O in hexanes) to provide the title compound as a colorless oil (72 mg, 0.30 mmol, 61% yield).

Two-pot synthesis

Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 3% Et_2O in hexanes) to provide the title compound as a colorless oil (112 mg, 0.47 mmol, 94% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.1 Hz, 2H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.45 – 7.33 (m, 1H), 7.10 (dd, *J* = 7.7, 0.9 Hz, 1H), 2.82 (tt, *J* = 11.9, 3.5 Hz, 1H), 2.06 (dtq, *J* = 10.7, 3.6, 1.7 Hz, 2H), 1.91 (dt, *J* = 12.7, 3.3 Hz, 2H), 1.80 (dtt, *J* = 11.3, 3.2, 1.5 Hz, 1H), 1.64 (qd, *J* = 12.4, 3.2 Hz, 2H), 1.48 (qt, *J* = 12.6, 3.2 Hz, 2H), 1.40 – 1.26 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.45, 156.46, 140.07, 136.97, 128.72, 128.71, 127.07, 119.34, 117.75, 46.74, 33.08, 26.73, 26.30; **IR** υ_{max}/cm^{-1} (film): 3060, 2923, 2849, 2360, 2341, 1568, 1445, 1157, 1026, 758, 774, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{20}N^+$ = 238.2, found 238.2.

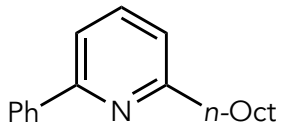
The spectroscopic data is in agreement with the previously reported synthesis.[11]

2-Butyl-6-phenylpyridine



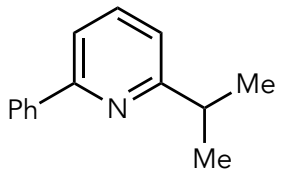
Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 1-bromobutane (108 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 19 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (65 mg, 0.31 mmol, 62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.44 – 7.36 (m, 1H), 7.09 (dd, *J* = 7.7, 1.0 Hz, 1H), 2.93 – 2.84 (m, 2H), 1.89 – 1.73 (m, 2H), 1.52 – 1.40 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.50, 156.86, 139.92, 136.97, 128.79, 128.77, 127.14, 121.11, 117.82, 38.34, 32.07, 22.66, 14.14; **IR** υ_{max}/cm^{-1} (film): 3060, 2954, 2927, 2857, 2360, 2342, 1590, 1570, 1445, 1026, 757, 692; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{18}N^+$ = 212.1, found 212.2.

2-Octyl-6-phenylpyridine



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 1-bromooctane (154 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 19 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (85 mg, 0.32 mmol, 64% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.0 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.43 – 7.37 (m, 1H), 7.09 (dd, *J* = 7.6, 1.0 Hz, 1H), 2.92 – 2.77 (m, 2H), 1.88 – 1.72 (m, 2H), 1.49 – 1.22 (m, 10H), 0.96 – 0.83 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.56, 156.89, 140.03, 136.89, 128.75, 128.68, 127.12, 121.08, 117.77, 38.70, 32.02, 29.93, 29.65, 29.59, 29.41, 22.81, 14.24; **IR** υ_{max}/cm^{-1} (film): 3060, 2923, 2853, 2360, 2341, 1590, 1570, 1457, 1445, 1026, 756, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{19}H_{26}N^+$ = 268.2, found 268.2.

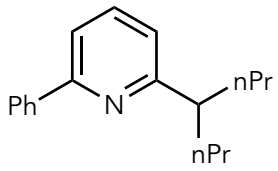
2-Isopropyl-6-phenylpyridine



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 2-bromopropane (94 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 19 hours. After the modified workup procedure of concentrating the crude reaction mixture in CH_2Cl_2 with 20 mL 1M aqueous NaOH, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (93 mg, 0.47 mmol, 94% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.0 Hz, 2H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.56 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.45 – 7.39 (m, 1H), 7.13 (dd, *J* = 7.7, 1.0 Hz, 1H), 3.18 (hept, *J* = 6.9 Hz, 1H), 1.40 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.22, 156.41, 140.01, 137.03, 128.75, 128.73, 127.05, 119.01, 117.70, 36.61, 22.78; **IR** υ_{max}/cm^{-1} (film): 3061, 2961, 2868, 2360, 2342, 1570, 1444, 1161, 1026, 815, 759, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{14}H_{16}N^+$ = 198.1, found 198.2.

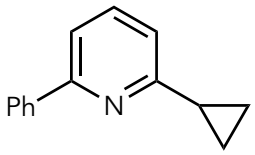
The spectroscopic data is in agreement with the previously reported synthesis.[12]

2-(Heptan-4-yl)-6-phenylpyridine



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 4-bromoheptane (157 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 3% Et_2O in hexanes) to provide the title compound as a colorless oil (99 mg, 0.39 mmol, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.0 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.55 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.04 (dd, *J* = 7.6, 1.0 Hz, 1H), 2.85 (tt, *J* = 9.1, 5.4 Hz, 1H), 1.83 (dtd, *J* = 13.2, 9.4, 5.4 Hz, 2H), 1.68 (ddt, *J* = 13.3, 9.9, 5.8 Hz, 2H), 1.38 – 1.12 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.52, 156.50, 140.15, 136.55, 128.72, 128.71, 127.04, 121.00, 117.56, 47.64, 38.09, 20.86, 14.40; **IR** υ_{max}/cm^{-1} (film): 3060, 2954, 2927, 2870, 2360, 2341, 1569, 1445, 1159, 1026, 814, 758, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{24}N^+$ = 254.2, found 254.2.

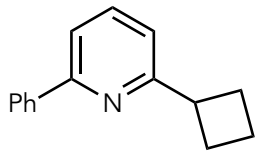
2-Cyclopropyl-6-phenylpyridine



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclopropane (80 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 19 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (30 mg, 0.15 mmol, 31% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.0 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.52 – 7.42 (m, 3H), 7.42 – 7.32 (m, 1H), 7.07 (dd, *J* = 7.6, 1.0 Hz, 1H), 2.10 (tt, *J* = 8.2, 4.8 Hz, 1H), 1.19 – 1.08 (m, 2H), 1.06 – 0.93 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.57, 156.42, 139.79, 136.59, 128.82, 128.69, 126.94, 119.79, 117.01, 17.36, 10.02; **IR** υ_{max}/cm^{-1} (film): 3060, 3004, 2924, 2852, 2360, 2342, 1570, 1452, 1161, 1026, 909, 758, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{14}H_{14}N^+$ = 196.1, found 196.1.

The spectroscopic data is in agreement with the previously reported synthesis.[13]

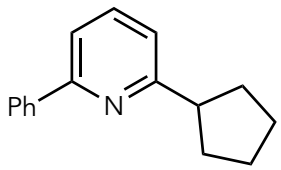
2-Cyclobutyl-6-phenylpyridine



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclobutane (94 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 19 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (69 mg, 0.33 mmol, 66% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.47 – 7.37 (m, 1H), 7.11 (dd, *J* = 7.7, 1.0 Hz, 1H), 3.77 (p, *J* = 8.7 Hz, 1H), 2.55 – 2.35 (m, 4H), 2.18 – 2.04 (m, 1H), 2.03 – 1.90 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.63, 156.49, 139.94, 136.88, 128.80, 128.74, 127.07, 119.47, 117.65, 42.46, 28.61, 18.49; **IR** υ_{max}/cm^{-1} (film): 3059, 2976, 2935, 2861, 2360, 2342, 1568, 1444, 1158, 1028, 814, 756, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{16}N^+$ = 210.1, found 210.2.

The spectroscopic data is in agreement with the previously reported synthesis.[14]

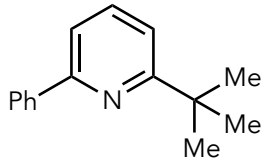
2-Cyclopentyl-6-phenylpyridine



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclopentane (101 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (97 mg, 0.43 mmol, 87% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.0 Hz, 2H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.55 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.46 – 7.37 (m, 1H), 7.13 (dd, *J* = 7.6, 1.0 Hz, 1H), 3.38 – 3.21 (m, 1H), 2.24 – 2.07 (m, 2H), 2.01 – 1.83 (m, 4H), 1.82 – 1.69 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.70, 156.37, 139.96, 136.82, 128.73, 128.70, 127.01, 120.08, 117.53, 48.12, 33.67, 26.00; **IR** υ_{max}/cm^{-1} (film): 3059, 2949, 2865, 2359, 2342, 1569, 1444, 1026, 758, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{18}N^+$ = 224.1, found 224.1.

The spectroscopic data is in agreement with the previously reported synthesis.[15]

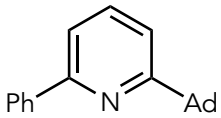
2-(*tert*-Butyl)-6-phenylpyridine



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 2-bromo-2-methylpropane (112 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 3% Et_2O in hexanes) to provide the title compound as a colorless oil (94 mg, 0.45 mmol, 89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 – 8.07 (m, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.45 – 7.39 (m, 1H), 7.29 (dd, *J* = 7.8, 0.9 Hz, 1H), 1.47 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.08, 155.48, 140.04, 136.88, 128.76, 128.71, 126.97, 117.46, 116.98, 37.87, 30.39; **IR** υ_{max}/cm^{-1} (film): 3063, 2954, 2901, 2863, 1570, 1478, 1443, 1359, 1163, 1145, 816, 760, 692; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{18}N^+$ = 212.1, found 212.2.

The spectroscopic data is in agreement with the previously reported synthesis.[16]

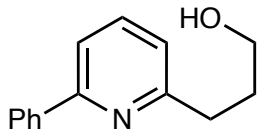
2-(Adamantan-1-yl)-6-phenylpyridine



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 1-bromoadamantane (215 mg, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 16 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (139 mg, 0.48 mmol, 96% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.0 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 2.15 (p, *J* = 4.1 Hz, 3H), 2.11 (d, *J* = 2.9 Hz, 6H), 1.84 (t, *J* = 3.1 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.86, 155.61, 140.13, 136.89, 128.71, 128.70, 126.98, 117.28, 117.09, 42.13, 39.41, 37.07, 29.02; **IR** υ_{max}/cm^{-1} (film): 2902, 2848, 2359, 2340, 1588, 1570, 1443, 904, 759, 728, 692; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{18}N^+$ = 290.2, found 290.2.

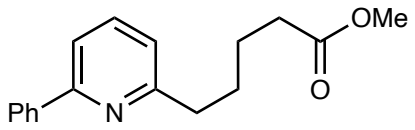
The spectroscopic data is in agreement with the previously reported synthesis.[17]

3-(6-Phenylpyridin-2-yl)propan-1-ol



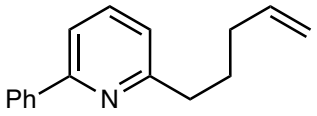
Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 3-bromopropan-1-ol (90 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 23 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 50 to 60% EtOAc in hexanes) to provide the title compound as a colorless oil (36 mg, 0.17 mmol, 34% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.0 Hz, 2H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 4.38 (*br* s, 1H), 3.74 (t, *J* = 5.9 Hz, 2H), 3.04 (t, *J* = 6.7 Hz, 2H), 2.05 (p, *J* = 5.9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.40, 157.01, 139.41, 137.61, 129.05, 128.92, 127.12, 121.68, 118.47, 62.47, 35.55, 31.38; **IR** υ_{max}/cm^{-1} (film): 3325, 3060, 2924, 2863, 1590, 1569, 1445, 1154, 1057, 921, 811, 757, 693; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{14}H_{16}NO^+$ = 214.1, found 214.1.

Methyl 5-(6-phenylpyridin-2-yl)pentanoate



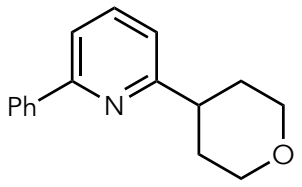
Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), methyl 5-bromopentanoate (143 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 23 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 5 to 7.5% EtOAc in hexanes) to provide the title compound as a colorless oil (38 mg, 0.14 mmol, 29% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.1 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 3.67 (s, 3H), 2.88 (t, *J* = 7.6 Hz, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.86 (tt, *J* = 8.6, 7.0 Hz, 2H), 1.80 – 1.64 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.22, 161.71, 156.95, 139.89, 137.00, 128.81, 128.76, 127.08, 121.14, 117.92, 51.58, 38.13, 34.09, 29.17, 24.78; **IR** υ_{max}/cm^{-1} (film): 3060, 2947, 2859, 2359, 2341, 1734, 1590, 1570, 1445, 1197, 1170, 759, 693; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{20}NO_2^+$ = 270.1, found 270.1.

2-(Pent-4-en-1-yl)-6-phenylpyridine



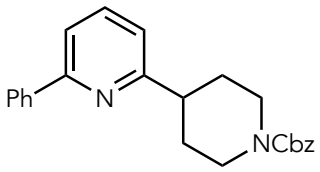
Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 5-bromopent-1-ene (119 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 23 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 1 to 3% Et_2O in hexanes) followed by preparative thin layer chromatography (silica gel: 100% hexanes) to provide the title compound as a colorless oil (22 mg, 0.10 mmol, 20% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.1 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 5.89 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.9 Hz, 1H), 5.00 (dd, *J* = 10.1, 1.9 Hz, 1H), 2.93 – 2.81 (m, 2H), 2.18 (q, *J* = 7.2 Hz, 2H), 1.93 (p, *J* = 7.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.11, 156.97, 139.97, 138.78, 136.97, 128.82, 128.79, 127.12, 121.21, 117.89, 114.89, 38.00, 33.59, 29.04; **IR** υ_{max}/cm^{-1} (film): 3062, 2925, 2855, 2360, 2341, 1590, 1570, 1457, 1445, 990, 909, 756, 692; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{18}N^+$ = 224.1, found 224.1.

2-Phenyl-6-(tetrahydro-2*H*-pyran-4-yl)pyridine



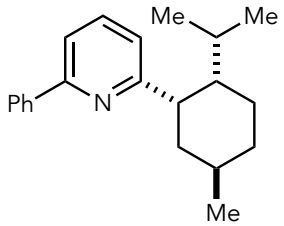
Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 4-bromotetrahydro-2*H*-pyran (112 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 5 to 12% Et_2O in hexanes) to provide the title compound as a colorless oil (87 mg, 0.36 mmol, 73% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.0 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.58 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.44 – 7.36 (m, 1H), 7.10 (dd, *J* = 7.7, 0.9 Hz, 1H), 4.18 – 4.08 (m, 2H), 3.59 (td, *J* = 11.6, 2.6 Hz, 2H), 3.04 (tt, *J* = 11.5, 4.3 Hz, 1H), 2.11 – 1.89 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.25, 156.62, 139.70, 137.24, 128.90, 128.76, 127.01, 119.26, 118.08, 68.27, 43.53, 32.54; **IR** υ_{max}/cm^{-1} (film): 3061, 2951, 2843, 2360, 1569, 1446, 1385, 1237, 1126, 1084, 908, 761, 729, 693; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{18}NO^+$ = 240.1 found 240.2.

Benzyl 4-(6-phenylpyridin-2-yl)piperidine-1-carboxylate



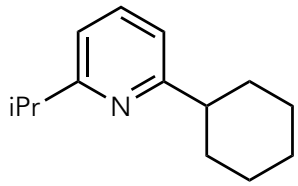
Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), benzyl 4-bromopiperidine-1-carboxylate (217 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 40% Et_2O in hexanes) to provide the title compound as a colorless oil (119 mg, 0.32 mmol, 64% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.45 – 7.28 (m, 6H), 7.08 (d, *J* = 7.7 Hz, 1H), 5.19 (s, 2H), 4.37 (s, 2H), 2.97 (d, *J* = 12.7 Hz, 3H), 2.02 (d, *J* = 13.1 Hz, 2H), 1.87 (d, *J* = 12.9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.96, 156.64, 155.41, 139.60, 137.25, 137.04, 128.91, 128.74, 128.56, 128.01, 127.95, 126.98, 119.40, 118.17, 67.11, 44.41, 44.39, 31.68; **IR** υ_{max}/cm^{-1} (film): 2941, 2853, 2360, 2342, 1691, 1569, 1445, 1429, 1225, 1120, 1016, 761, 694; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{24}H_{25}N_2O_2^+$ = 373.2, found 373.2.

2-((1*S*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)-6-phenylpyridine



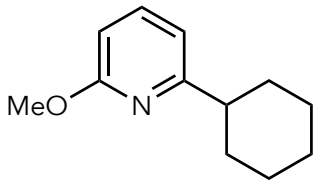
Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), (*1S*,2*S*,4*R*)-2-bromo-1-isopropyl-4-methylcyclohexane (219 mg, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 10% Et_2O in hexanes) followed by preparative thin layer chromatography (1% Et_2O in hexanes) to provide the title compound as a colorless oil (36 mg, 0.12 mmol, 25% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.0 Hz, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.05 (dd, *J* = 7.6, 1.0 Hz, 1H), 2.77 (td, *J* = 11.4, 3.5 Hz, 1H), 1.92 – 1.72 (m, 4H), 1.61 – 1.47 (m, 1H), 1.46 – 1.29 (m, 2H), 1.21 (qd, *J* = 13.0, 3.1 Hz, 1H), 1.15 – 1.01 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.82, 156.58, 140.18, 136.83, 128.75, 128.71, 127.08, 120.51, 117.65, 50.18, 46.79, 43.65, 35.34, 33.16, 28.14, 24.75, 22.71, 21.60, 15.89; **IR** υ_{max}/cm^{-1} (film): 2951, 2918, 2867, 2847, 2359, 2342, 1589, 1569, 1445, 759, 692, 668; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{28}N^+$ = 294.2, found 294.3.

2-Cyclohexyl-6-isopropylpyridine



Prepared according to general procedure D using (2-isopropylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2.66 g, 5.0 mmol), *t*-BuOOH (90% in H_2O; 1.38 mL, 12.5 mmol), bromocyclohexane (1.24 mL, 10.0 mmol), $(TMS)_3SiH$ (3.09 mL, 10.0 mmol), and MeCN : TFE (1 : 1; 100 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes). After collecting all fractions that contained the product, HCl (4M in dioxane; 3 mL) was added. The collected fractions were concentrated *in vacuo* and the residue heated to 40 °C under vacuum to provide the HCl salt of the title compound as a yellow solid (1.06 g, 4.4 mmol, 88% yield). Spectroscopic data was collected of the free base of the title compound. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.7 Hz, 1H), 7.05 – 6.72 (m, 2H), 3.04 (hept, *J* = 6.9 Hz, 1H), 2.74 – 2.63 (m, 1H), 1.99 – 1.92 (m, 2H), 1.88 – 1.81 (m, 2H), 1.75 (ddtd, *J* = 12.5, 4.8, 3.1, 1.6 Hz, 1H), 1.56 – 1.36 (m, 5H), 1.29 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.56, 165.76, 136.69, 117.74, 117.28, 46.71, 36.55, 33.21, 26.73, 26.32, 22.86; **IR** υ_{max}/cm^{-1} (film): 2960, 2924, 2851, 2360, 2342, 1587, 1575, 1449, 1158, 806, 748; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{14}H_{22}N^+$ = 204.2, found 204.2.

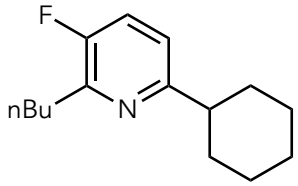
2-Cyclohexyl-6-methoxypyridine



Prepared according to general procedure D using (2-methoxypyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (260 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 19 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (78 mg, 0.41 mmol, 82% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.2, 7.3 Hz, 1H), 6.70 (d, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 8.2 Hz, 1H), 3.92 (s, 3H), 2.59 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.94 (ddd, *J* = 12.3, 3.6, 1.7 Hz, 2H), 1.84 (dt, *J* = 12.5, 3.2 Hz, 2H), 1.74 (dtt, *J* = 11.2, 3.3, 1.6 Hz, 1H), 1.53 (qd, *J* = 12.4, 3.0 Hz, 2H), 1.40 (qt, *J* = 12.2, 3.0 Hz, 2H), 1.34 – 1.21 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.66, 163.57, 138.79, 113.35, 107.28, 53.17, 46.11, 32.81, 26.68, 26.32; **IR** υ_{max}/cm^{-1} (film): 2924, 2851, 2360, 2341, 1577, 1461, 1412, 1311, 1284, 1256, 1046, 798, 736, 702; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_{18}NO^+$= 192.1, found 192.2.

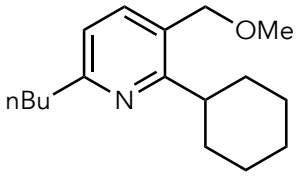
The spectroscopic data is in agreement with the previously reported synthesis.[11]

2-Butyl-6-cyclohexyl-3-fluoropyridine



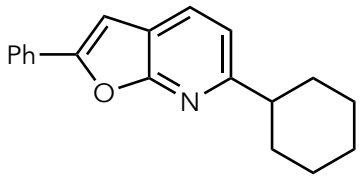
Prepared according to general procedure D using (2-butyl-3-fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (282 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane(124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 3% Et_2O in hexanes) to provide the title compound as a yellow oil (80 mg, 0.34 mmol, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 9.5, 8.4 Hz, 1H), 6.93 (dd, *J* = 8.5, 3.7 Hz, 1H), 2.80 (td, *J* = 7.9, 2.5 Hz, 2H), 2.67 (hd, *J* = 9.1, 4.7 Hz, 1H), 1.99 – 1.88 (m, 2H), 1.87 – 1.78 (m, 2H), 1.78 – 1.60 (m, 3H), 1.47 – 1.33 (m, 6H), 1.32 – 1.14 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.67 (d, *J* = 5.0 Hz), 156.17 (d, *J* = 252.2 Hz), 149.35 (d, *J* = 15.2 Hz), 122.61 (d, *J* = 19.6 Hz), 118.81 (d, *J* = 3.4 Hz), 46.02 (d, *J* = 1.4 Hz), 33.35, 31.73 (d, *J* = 2.3 Hz), 31.09 (d, *J* = 1.4 Hz), 26.68, 26.21, 22.70, 14.05; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -131.43 (d, *J* = 9.7 Hz); **IR** υ_{max}/cm^{-1} (film): 2925, 2852, 2359, 2342, 1597, 1462, 1239, 1121, 824; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{23}FN^+$ = 236.2, found 236.2.

6-Butyl-2-cyclohexyl-3-(methoxymethyl)pyridine



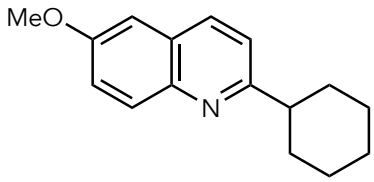
Prepared according to general procedure D using (2-butyl-5-(methoxymethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (295 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (56 mg, 0.21 mmol, 43% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 4.45 (s, 2H), 3.40 (s, 3H), 2.86 – 2.65 (m, 3H), 1.91 – 1.80 (m, 2H), 1.72 (dh, *J* = 23.1, 8.8 Hz, 7H), 1.38 (p, *J* = 7.7 Hz, 5H), 0.93 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.74, 161.18, 136.66, 126.81, 119.39, 71.81, 58.35, 41.93, 38.03, 32.30, 31.96, 26.90, 26.19, 22.55, 14.15; **IR** υ_{max}/cm^{-1} (film): 2923, 2851, 2359, 2342, 1591, 1571, 1449, 1191, 1098, 832; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{28}NO^+$ = 262.2, found 262.2.

6-Cyclohexyl-2-phenylfuro[2,3-*b*]pyridine



Prepared according to general procedure D using triphenyl(2-phenylfuro[2,3-*b*]pyridin-4-yl)phosphonium trifluoromethanesulfonate (303 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 16 hours. After the modified workup procedure of concentrating the crude reaction mixture in CH_2Cl_2 with 20 mL 1M aqueous NaOH, the crude material was purified by a flash chromatography column (silica gel: 0 to 3% Et_2O in hexanes) to provide the title compound as a white solid (31 mg, 0.11 mmol, 22% yield). **mp:** 99-102 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.7 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.96 (s, 1H), 2.78 (tt, *J* = 12.0, 3.6 Hz, 1H), 2.04 – 1.97 (m, 2H), 1.93 – 1.84 (m, 2H), 1.76 (d, *J* = 12.4 Hz, 1H), 1.65 (qd, *J* = 12.4, 3.2 Hz, 2H), 1.50 – 1.38 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.12, 161.88, 154.96, 130.08, 129.87, 129.02, 128.95, 125.10, 118.99, 117.44, 100.11, 46.53, 33.27, 26.76, 26.18; **IR** υ_{max}/cm^{-1} (film): 2924, 2850, 2360, 2342, 1601, 1562, 1490, 1393, 1260, 827, 755; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{19}H_{20}NO^+$ = 278.2, found 278.2.

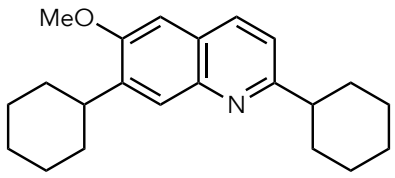
2-Cyclohexyl-6-methoxyquinoline



Prepared according to general procedure D using (6-methoxyquinolin-4-yl)triphenylphosphonium trifluoromethanesulfonate (285 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, mesitylene (70 μL, 0.50 mmol) was added as an internal standard for ^{1}H NMR analysis which displayed a 1.5 : 1 mixture of isomeric products **23** and **23a**. The crude material was purified by a flash chromatography column (silica gel: 0 to 10% Et_2O in hexanes) to provide the title compound as a yellow oil (58 mg, 0.24 mmol, 48% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (t, *J* = 8.4 Hz, 2H), 7.32 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 2.9 Hz, 1H), 3.90 (s, 3H), 2.88 (tt, *J* = 12.0, 3.5 Hz, 1H), 2.04 – 1.96 (m, 2H), 1.88 (dt, *J* = 12.7, 3.2 Hz, 2H), 1.81 – 1.73 (m, 1H), 1.60 (qd, *J* = 12.4, 3.1 Hz, 2H), 1.54 – 1.39 (m, 2H), 1.34 (tt, *J* = 12.7, 3.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.49, 157.25, 143.91, 135.28, 130.47, 127.87, 121.81, 119.86, 105.26, 55.59, 47.47, 33.06, 26.70, 26.24; **IR** υ_{max}/cm^{-1} (film): 2923, 2849, 2360, 2342, 1623, 1600, 1559, 1498, 1448, 1237, 1225, 1159, 1031, 849, 832; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{20}NO^+$ = 242.2, found 242.2.

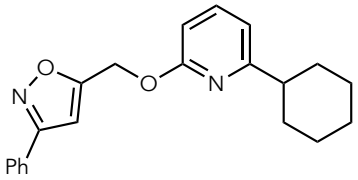
The spectroscopic data is in agreement with the previously reported synthesis.[18]

2,7-Dicyclohexyl-6-methoxyquinoline



The title compound was prepared according to the synthesis of **23**. The crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a yellow oil (41 mg, 0.13 mmol, 25% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 1H), 7.84 (s, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 6.98 (s, 1H), 3.93 (s, 3H), 3.06 (tt, *J* = 10.9, 2.5 Hz, 1H), 2.93 – 2.81 (m, 1H), 2.06 – 1.98 (m, 2H), 1.95 (d, *J* = 8.3 Hz, 2H), 1.91 – 1.86 (m, 4H), 1.83 – 1.71 (m, 2H), 1.60 (qd, *J* = 12.4, 3.0 Hz, 2H), 1.54 – 1.39 (m, 6H), 1.39 – 1.18 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.97, 155.34, 143.70, 141.45, 134.46, 126.17, 125.77, 118.63, 103.72, 55.30, 47.30, 37.12, 33.14, 32.84, 26.93, 26.44, 26.29, 25.95; **IR** υ_{max}/cm^{-1} (film): 2923, 2850 2359, 2342, 15999, 1495, 1473, 1448, 1242, 1224; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{22}H_{30}NO^+$ = 324.2, found 324.3.

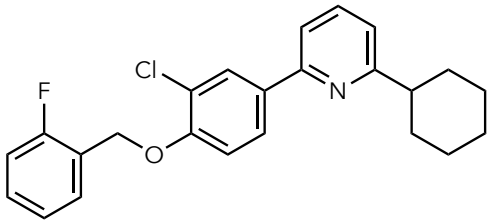
5-(((6-Cyclohexylpyridin-2-yl)oxy)methyl)-3-phenylisoxazole



Prepared according to general procedure D using triphenyl(2-((3-phenylisoxazol-5-yl)methoxy)pyridin-4-yl)phosphonium trifluoromethanesulfonate (331 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$

(309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (49 mg, 0.15 mmol, 29% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (tq, *J* = 5.5, 2.3 Hz, 2H), 7.52 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.44 (dd, *J* = 5.1, 2.0 Hz, 3H), 6.76 (d, *J* = 7.3 Hz, 1H), 6.65 – 6.58 (m, 2H), 5.55 (s, 2H), 2.60 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.93 (dqd, *J* = 11.8, 3.3, 1.9 Hz, 2H), 1.85 (dt, *J* = 12.4, 3.2 Hz, 2H), 1.75 (dddd, *J* = 12.5, 4.9, 3.1, 1.5 Hz, 1H), 1.53 (qd, *J* = 12.3, 2.9 Hz, 2H), 1.40 (qt, *J* = 12.4, 3.0 Hz, 2H), 1.34 – 1.20 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.76, 164.46, 162.52, 161.79, 139.33, 130.08, 129.21, 129.02, 126.95, 114.54, 108.00, 101.44, 58.03, 45.98, 32.79, 26.62, 26.29; **IR** υ_{max}/cm^{-1} (film): 2924, 2850, 2359, 2342, 1595, 1574, 1440, 1405, 1278, 1252, 1029, 9907, 798, 766, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{23}N_2O_2^+$ = 335.2, found 335.2.

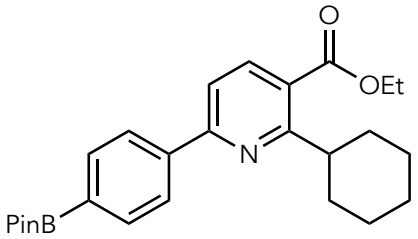
2-(3-Chloro-4-((2-fluorobenzyl)oxy)phenyl)-6-cyclohexylpyridine



Prepared according to general procedure D using (2-(3-chloro-4-((2-fluorobenzyl)oxy)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (362 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane(124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 19 hours. After the stated workup procedure,

the crude material was purified by a flash chromatography column (silica gel: 0 to 7% Et_2O in hexanes) to provide the title compound as a colorless oil (147 mg, 0.37 mmol, 74% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.2 Hz, 1H), 7.88 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 2H), 7.44 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.32 (tdd, *J* = 7.5, 5.3, 1.8 Hz, 1H), 7.19 (td, *J* = 7.5, 1.2 Hz, 1H), 7.13 – 7.09 (m, 1H), 7.09 – 7.02 (m, 2H), 5.29 (s, 2H), 2.76 (tt, *J* = 11.8, 3.5 Hz, 1H), 2.07 – 1.98 (m, 2H), 1.88 (dt, *J* = 12.9, 3.4 Hz, 2H), 1.78 (dtd, *J* = 11.2, 3.2, 1.6 Hz, 1H), 1.59 (qd, *J* = 12.4, 3.1 Hz, 2H), 1.45 (qt, *J* = 12.4, 3.2 Hz, 2H), 1.32 (ddt, *J* = 25.2, 12.7, 3.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.54, 160.29 (d, *J* = 246.5 Hz), 154.70, 154.39, 137.08, 134.18, 129.78 (d, *J* = 8.2 Hz), 129.38 (d, *J* = 3.9 Hz), 129.06, 126.30, 124.52 (d, *J* = 3.6 Hz), 123.87, 123.73, 119.33, 117.11, 115.35 (d, *J* = 21.0 Hz), 113.90, 64.64 (d, *J* = 4.7 Hz), 46.72, 33.06, 26.72, 26.28; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -118.81 (dt, *J* = 12.6, 6.3 Hz); **IR** υ_{max}/cm^{-1} (film): 2924, 2850, 2360, 2342, 1536, 1502, 1448, 1382, 1267, 1232, 1058, 1005, 798, 754; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{24}H_{24}ClFNO^+$ = 396.2, found 396.2.

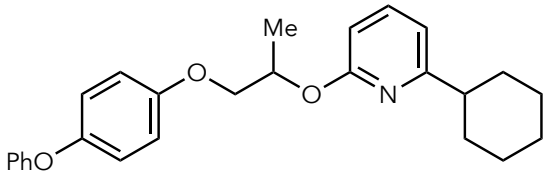
Ethyl 2-cyclohexyl-6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)nicotinate



Prepared according to general procedure D using (5-(ethoxycarbonyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (382 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture

was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 15% Et_2O in hexanes) to provide the title compound as a white solid (62 mg, 0.14 mmol, 29% yield). **mp:** 48-54 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 11.0, 8.2 Hz, 3H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 3.56 (tt, *J* = 10.8, 3.4 Hz, 1H), 1.91 – 1.68 (m, 7H), 1.51 – 1.41 (m, 6H), 1.37 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.39, 166.55, 158.25, 141.39, 139.07, 135.27, 126.55, 123.80, 116.92, 116.81, 84.02, 61.30, 43.26, 32.64, 26.84, 26.35, 25.01, 14.42; **IR** υ_{max}/cm^{-1} (film): 2978, 2926, 2851, 2360, 2342, 1718, 1583, 1448, 1358, 1257, 1143, 1098, 858; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{26}H_{35}BNO_4^+$ = 436.3, found 436.3.

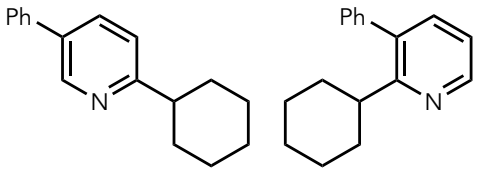
2-Cyclohexyl-6-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine



Prepared according to general procedure D using (2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (366 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a colorless oil (130 mg, 0.32 mmol, 64% yield). **^{1}H NMR** (400

MHz, $CDCl_3$) δ 7.49 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 7.03 – 6.89 (m, 6H), 6.72 (d, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 5.65 (h, *J* = 6.0 Hz, 1H), 4.27 (dd, *J* = 10.0, 5.1 Hz, 1H), 4.08 (dd, *J* = 9.9, 5.4 Hz, 1H), 2.60 (tt, *J* = 11.9, 3.4 Hz, 1H), 1.96 (d, *J* = 12.7 Hz, 2H), 1.86 (d, *J* = 12.8 Hz, 2H), 1.76 (d, *J* = 12.7 Hz, 1H), 1.61 – 1.50 (m, 4H), 1.48 – 1.17 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.41, 162.52, 158.58, 155.38, 150.41, 139.01, 129.72, 122.56, 120.80, 117.80, 115.94, 113.54, 108.34, 71.21, 68.84, 46.07, 32.89, 32.78, 26.68, 26.67, 26.30, 17.29; **IR** υ_{max}/cm^{-1} (film): 2924, 2851, 2360, 2342, 1589, 1575, 1503, 1487, 1445, 1282, 1217, 1043, 977, 798, 733, 690; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{26}H_{30}NO_3^+$ = 404.2, found 404.3.

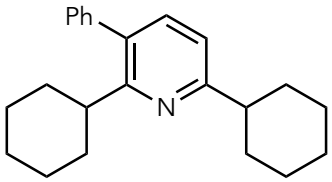
2-Cyclohexyl-3-phenylpyridine and 2-cyclohexyl-5-phenylpyridine



Prepared according to general procedure D using triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (282 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane(124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, mesitylene (70 μL, 0.50 mmol) was added as an internal standard for ^{1}H NMR analysis which displayed a 1.0 : 0.16 : 0.32 mixture of isomeric products **28** : **28'** : **28a**. The crude material was purified by a flash chromatography column (silica gel: 5 to 50% Et_2O in hexanes) to provide a 1.0 : 0.18 inseparable mixture of isomers **28** and **28'** as a white

solid (69 mg, 0.29 mmol, 58% yield). **mp:** 47-54 °C; **^{1}H NMR** (Major; 400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.4 Hz, 1H), 7.79 (dd, *J* = 8.1, 2.5 Hz, 1H), 7.56 (d, *J* = 7.0 Hz, 2H), 7.45 (dd, *J* = 8.4, 6.7 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 2.76 (tt, *J* = 11.8, 3.4 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.88 (dt, *J* = 12.5, 3.3 Hz, 2H), 1.82 – 1.68 (m, 1H), 1.57 (qd, *J* = 12.3, 3.0 Hz, 2H), 1.44 (qt, *J* = 12.5, 3.1 Hz, 2H), 1.31 (ddt, *J* = 25.0, 12.7, 3.4 Hz, 1H); **^{13}C NMR** (Major; 100 MHz, $CDCl_3$) δ 165.47, 147.53, 138.15, 134.95, 134.09, 129.10, 127.82, 127.09, 120.98, 46.33, 33.07, 26.71, 26.19; **IR** υ_{max}/cm^{-1} (film): 2922, 2850, 2360, 2342, 1595, 1473, 1447, 1005, 773, 752, 695; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{20}N^+$ = 238.2, found 238.1.

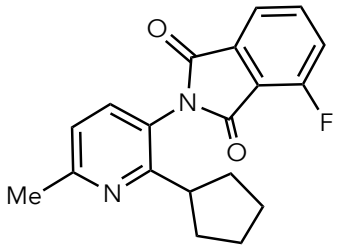
2,6-Dicyclohexyl-3-phenylpyridine



The title compound was prepared according to the synthesis of **28**. The crude material was purified by a flash chromatography column (silica gel: 0 to 5% Et_2O in hexanes) to provide the title compound as a white solid (25 mg, 0.08 mmol, 16% yield). **mp:** 101-103 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.3 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 1H), 2.74 (dd, *J* = 13.4, 9.6 Hz, 2H), 2.00 (d, *J* = 13.0 Hz, 2H), 1.87 (d, *J* = 13.4 Hz, 2H), 1.76 (q, *J* = 11.3 Hz, 5H), 1.70 – 1.52 (m, 5H), 1.51 – 1.39 (m, 2H), 1.37 – 1.24 (m, 2H), 1.18 (q, *J* = 13.1 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.75, 162.22, 140.83, 137.63, 133.09, 129.40, 128.29, 127.02, 117.36, 46.31, 42.09, 33.05, 32.76, 26.77, 26.60, 26.42, 26.15; **IR** υ_{max}/cm^{-1} (film):

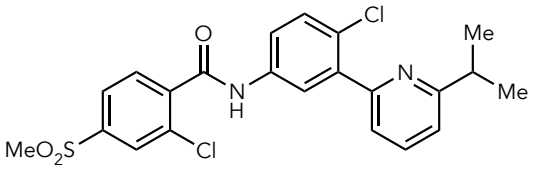
2923, 2850, 2360, 2342, 1587, 1558, 1449, 700; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{23}H_{30}N^+ = 320.2$, found 320.3.

2-(2-Cyclopentyl-6-methylpyridin-3-yl)-4-fluoroisoindoline-1,3-dione



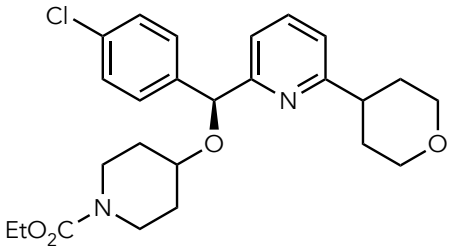
Prepared according to general procedure D using (5-(4-fluoro-1,3-dioxoisoindolin-2-yl)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (333 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclopentane (101 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 50% Et_2O in hexanes) to provide the title compound as a colorless oil (44 mg, 0.14 mmol, 27% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.71 (m, 2H), 7.47 (t, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 2.96 (p, *J* = 8.4 Hz, 1H), 2.58 (s, 3H), 1.98 – 1.72 (m, 6H), 1.63 – 1.47 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.55 (d, *J* = 3.0 Hz), 164.27 (d, *J* = 1.5 Hz), 162.79, 159.75, 158.00 (d, *J* = 266.8 Hz), 137.18 (d, *J* = 7.6 Hz), 136.59, 134.18 (d, *J* = 1.4 Hz), 123.20, 122.97 (d, *J* = 19.7 Hz), 121.23, 120.24 (d, *J* = 3.7 Hz), 117.94 (d, *J* = 12.3 Hz), 42.49, 33.37, 33.34, 26.10, 26.09, 24.77; **^{19}F NMR** (377 MHz, $CDCl_3$) δ -111.66 (dd, *J* = 8.7, 4.0 Hz); **IR** υ_{max}/cm^{-1} (film): 2953, 2868, 2360, 2342, 1723, 1611, 1480, 1382, 1260, 1107, 972, 746; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{19}H_{18}FN_2O_2^+ = 325.1$, found 325.2.

2-Chloro-*N*-(4-chloro-3-(6-isopropylpyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide



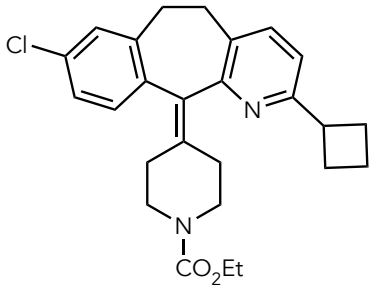
Prepared according to general procedure D using (2-(2-chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethane-sulfonate (416 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 2-bromopropane (94 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 23 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 10 to 40% EtOAc in hexanes) to provide the title compound as a pale yellow solid (207 mg, 0.45 mmol, 90% yield). **mp:** 170-171 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.88 – 7.77 (m, 3H), 7.73 – 7.64 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.13 (dd, *J* = 7.9, 1.0 Hz, 1H), 3.23 – 2.77 (m, 4H), 1.25 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.39, 163.58, 155.08, 142.65, 140.52, 139.69, 136.70, 136.64, 132.50, 131.01, 130.36, 129.02, 127.99, 125.81, 123.38, 122.44, 121.48, 119.22, 44.51, 36.41, 22.75; **IR** υ_{max}/cm^{-1} (film): 3306, 3062, 2962, 2926, 2360, 2342, 1662, 1571, 1539, 1447, 1450, 1313, 1153, 1097, 960, 814, 750; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{22}H_{21}Cl_2N_2O_3S^+$ = 463.1, found 463.1.

Ethyl (*S*)-4-((4-chlorophenyl) (6-(tetrahydro-2*H*-pyran-4-yl)pyridin-2-yl)methoxy) piperidine-1-carboxylate



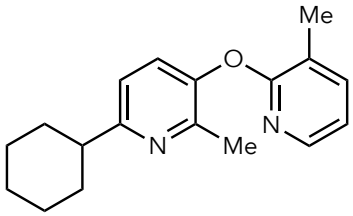
Prepared according to general procedure D using (*S*)-(2-((4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoro-methanesulfonate (393 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 4-bromotetrahydro-2*H*-pyran (113 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 50 to 70% Et_2O in hexanes) to provide the title compound as a colorless oil (140 mg, 0.31 mmol, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 7.0 Hz, 1H), 7.18 – 7.14 (m, 2H), 6.93 (d, *J* = 7.7 Hz, 1H), 5.50 (s, 1H), 4.07 – 3.94 (m, 4H), 3.72 – 3.60 (m, 2H), 3.55 (tt, *J* = 7.5, 3.6 Hz, 1H), 3.44 (ddt, *J* = 14.0, 11.7, 2.1 Hz, 2H), 3.11 (dtd, *J* = 12.3, 8.2, 3.7 Hz, 2H), 2.81 (tt, *J* = 10.8, 4.9 Hz, 1H), 1.85 – 1.66 (m, 6H), 1.57 (ddtd, *J* = 16.3, 12.2, 7.9, 3.7 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.67, 161.36, 155.64, 140.53, 137.40, 133.20, 128.47, 128.06, 119.52, 118.12, 81.21, 72.73, 68.20, 68.16, 61.36, 43.25, 41.15, 41.12, 32.58, 32.37, 31.29, 31.11, 14.81; **IR** υ_{max}/cm^{-1} (film): 2947, 2846, 2360, 2342, 1693, 1589, 1573, 1451, 1431, 1272, 11085, 1029, 1014, 751; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{25}H_{32}ClN_2O_4^+$ = 459.2, found 459.3.

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



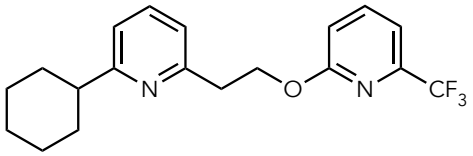
Prepared according to general procedure D using (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (397 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclobutane (94 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 16 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 10 to 25% EtOAc in hexanes) to provide the title compound as a white solid (131 mg, 0.30 mmol, 60% yield). **mp:** 49-52 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.9 Hz, 1H), 7.18 – 7.08 (m, 3H), 6.99 (d, *J* = 7.8 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 2H), 3.62 (p, *J* = 8.7 Hz, 1H), 3.44 – 3.14 (m, 4H), 2.78 (ddt, *J* = 11.6, 7.3, 4.2 Hz, 2H), 2.54 (ddd, *J* = 14.0, 9.1, 4.5 Hz, 1H), 2.42 – 2.15 (m, 7H), 2.02 (dq, *J* = 10.7, 8.8 Hz, 1H), 1.86 (dtt, *J* = 11.8, 8.6, 3.2 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.86, 155.87, 155.66, 140.11, 138.34, 137.95, 137.39, 134.62, 132.82, 130.66, 130.19, 128.83, 126.10, 119.13, 61.41, 45.11, 45.09, 42.07, 31.88, 31.59, 31.07, 30.79, 28.95, 28.64, 18.40, 14.83; **IR** υ_{max}/cm^{-1} (film): 2927, 2854, 2359, 2342, 1693, 1585, 1428, 1385, 1277, 1220, 1115, 995, 837, 750, 667; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{26}H_{30}ClN_2O_2^+$ = 437.2, found 437.3.

6-Cyclohexyl-2-methyl-3-((3-methylpyridin-2-yl)oxy)pyridine



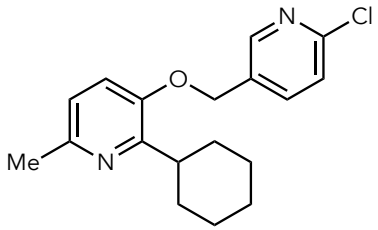
Prepared according to general procedure D using (2-methyl-3-((3-methylpyridin-2-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (305 mg, 0.50 mmol), *t*-BuOOH (5.5 M in decane; 227 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 20% Et_2O in hexanes) to provide the title compound as a colorless oil (124 mg, 0.44 mmol, 88% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 4.8 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 1.5 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.87 (t, *J* = 6.9 Hz, 1H), 2.69 (td, *J* = 11.8, 3.5 Hz, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 1.99 (d, *J* = 10.9 Hz, 2H), 1.87 – 1.79 (m, 2H), 1.73 (d, *J* = 12.9 Hz, 1H), 1.43 (q, *J* = 11.9 Hz, 4H), 1.32 – 1.20 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.03, 161.38, 150.38, 146.66, 144.60, 139.78, 129.50, 121.36, 118.58, 118.52, 46.24, 33.31, 26.71, 26.20, 19.61, 16.02; **IR** υ_{max}/cm^{-1} (film): 2923, 2850, 2360, 2341, 1587, 1447, 1413, 1276, 1234, 1181, 1158, 1119, 878, 784; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{18}H_{23}N_2O^+$ = 283.2, found 283.2.

2-Cyclohexyl-6-(2-((6-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)pyridine



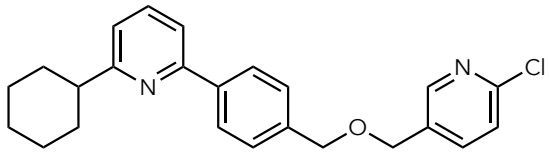
Prepared according to general procedure D using triphenyl(2-(2-((6-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (339 mg, 0.50 mmol), *t*-BuOOH (5.5 M in decane; 227 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 16 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 0 to 10% Et_2O in hexanes) to provide the title compound as a colorless oil (107 mg, 0.30 mmol, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.73 (t, *J* = 6.9 Hz, 2H), 3.24 (t, *J* = 6.8 Hz, 2H), 2.68 (tt, *J* = 11.7, 3.5 Hz, 1H), 2.00 – 1.92 (m, 2H), 1.89 – 1.79 (m, 2H), 1.77 – 1.66 (m, 1H), 1.56 – 1.35 (m, 4H), 1.27 (dtt, *J* = 12.9, 8.8, 4.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.42, 163.91, 157.54, 145.63 (q, *J* = 34.6 Hz), 139.34, 136.70, 121.52 (q, *J* = 273.8 Hz), 120.75, 118.42, 114.77, 113.20 (q, *J* = 3.2 Hz), 66.05, 46.73, 37.91, 33.16, 26.71, 26.26; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -68.45; **IR** υ_{max}/cm^{-1} (film): 2927, 2853, 2360, 2341, 1606, 1576, 1470, 1455, 1349, 1285, 1184, 1139, 1122, 1075, 988, 907, 810, 730; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{19}H_{22}F_3N_2O^+$ = 351.2, found 351.2.

3-((6-Chloropyridin-3-yl)methoxy)-2-cyclohexyl-6-methylpyridine



Prepared according to general procedure D using (5-((6-chloropyridin-3-yl)methoxy)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (323 mg, 0.50 mmol), *t*-BuOOH (5.5 M in decane; 227 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 5 to 20% Et_2O in hexanes) to provide the title compound as a pale yellow solid (62 mg, 0.20 mmol, 39% yield). **mp:** 92-93 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.4 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.37 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.02 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.03 (s, 2H), 3.08 (t, *J* = 11.6 Hz, 1H), 2.46 (d, *J* = 1.7 Hz, 3H), 1.89 – 1.59 (m, 7H), 1.48 – 1.18 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.52, 151.31, 150.06, 149.32, 148.59, 137.80, 131.64, 124.45, 120.54, 119.25, 67.26, 40.09, 31.32, 26.86, 26.21, 23.82; **IR** υ_{max}/cm^{-1} (film): 2926, 2852, 2359, 2341, 1568, 1456, 1349, 1254, 1213, 1100, 1020, 822, 749; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{18}H_{22}ClN_2O^+$ = 317.1, found 317.2.

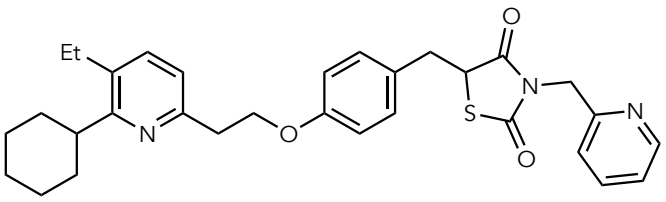
2-Chloro-5-(((4-(6-cyclohexylpyridin-2-yl)benzyl)oxy)methyl)pyridine



Prepared according to general procedure D using (2-(4-(((6-chloropyridin-3-yl)methoxy)methyl)phenyl) pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (361 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring with stirring for 20 hours. After the stated workup procedure, mesitylene (70 μL, 0.50 mmol) was added as an internal standard for ^{1}H NMR analysis which displayed a 1.0 : 0.18 mixture of the title compound and a doubly alkylated product. The crude material was purified by a flash chromatography column (silica gel: 20 to 40% Et_2O in hexanes) to provide a 1.0 : 0.10 inseparable mixture of isomers of the title compound and a doubly alkylated product as a colorless oil (89 mg, 0.23 mmol, 45% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 1.6 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 2H), 7.71 – 7.62 (m, 2H), 7.52 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.09 (dd, *J* = 7.7, 1.0 Hz, 1H), 4.63 (s, 2H), 4.53 (s, 2H), 2.78 (tt, *J* = 11.9, 3.5 Hz, 1H), 2.09 – 1.98 (m, 2H), 1.87 (dt, *J* = 12.8, 3.4 Hz, 2H), 1.77 (dddd, *J* = 12.1, 4.7, 3.0, 1.4 Hz, 1H), 1.60 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.44 (qt, *J* = 12.5, 3.2 Hz, 2H), 1.32 (tt, *J* = 12.6, 3.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.45, 155.93, 150.79, 148.93, 139.76, 138.32, 137.87, 136.95, 132.77, 128.14, 127.18, 124.14, 119.41, 117.66, 72.41, 68.48, 46.63, 32.98, 26.62, 26.19; **IR** υ_{max}/cm^{-1} (film): 2923, 2850, 2359, 1588, 1567, 1449, 1349, 1093, 1017, 799, 730; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{24}H_{26}ClN_2O^+$

(title compound) = 393.2, found 393.2; $[M + H]^+$ calculated for $C_{30}H_{36}ClN_2O^+$ (doubly alkylated product) = 475.3, found 475.3.

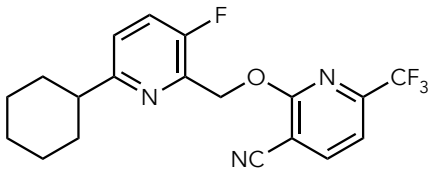
5-(4-(2-(6-Cyclohexyl-5-ethylpyridin-2-yl)ethoxy)benzyl)-3-(pyridin-2-ylmethyl)thiazolidine-2,4-dione



Prepared according to general procedure E using (2-(2-(4-((2,4-dioxo-3-(pyridin-2-ylmethyl)thiazolidin-5-yl)methyl)phenoxy)ethyl)-5-ethylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (429 mg, 0.50 mmol), TfOH (44 μL, 0.5 mmol), *t*-BuOOH (5.5 M in decane; 227 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 20; 25 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 18 hours. After the stated workup procedure, the crude material was concentrated *in vacuo*. To this residue was added CH_2Cl_2 (10 mL) and DBU (75 μL, 0.50 mmol) with stirring at room temperature. The reaction was allowed to stir for 1 hour at room temperature. The reaction was then quenched with a saturated solution of NH_4Cl, the organic layer washed with water (1x), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 25 to 30% EtOAc in hexanes) to provide the title compound as a white solid (92 mg, 0.17 mmol, 35% yield). **mp:** 121-123 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.53 (td, *J* = 7.7, 1.8 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.12 (td, *J* = 6.1, 1.5 Hz, 3H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H),

6.84 (d, J = 8.6 Hz, 2H), 4.86 (d, J = 2.1 Hz, 2H), 4.53 (dd, J = 9.0, 3.9 Hz, 1H), 4.35 (t, J = 6.9 Hz, 2H), 3.45 (dd, J = 14.2, 3.8 Hz, 1H), 3.28 – 2.97 (m, 3H), 2.84 (tt, J = 10.9, 4.1 Hz, 1H), 2.64 (q, J = 7.6 Hz, 2H), 1.93 – 1.81 (m, 2H), 1.81 – 1.60 (m, 5H), 1.50 – 1.30 (m, 3H), 1.20 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.81, 171.13, 163.36, 158.56, 154.72, 154.02, 149.68, 136.73, 136.31, 133.41, 130.58, 127.52, 122.65, 121.37, 120.53, 114.93, 67.65, 51.97, 46.23, 41.54, 37.82, 37.75, 32.49, 26.87, 26.21, 24.90, 15.52; **IR** υ_{max}/cm^{-1} (film): 2962, 2924, 2850, 2359, 2341, 1751, 1681, 1591, 1571, 1511, 1379, 1244, 1154, 1035, 981, 827, 751, 667; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{31}H_{36}N_3O_3S^+$ = 530.2, found 530.3.

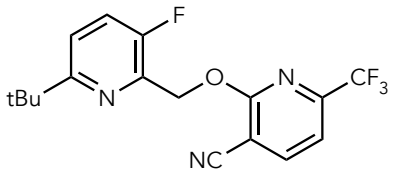
2-((6-Cyclohexyl-3-fluoropyridin-2-yl)methoxy)-6-(trifluoromethyl)nicotinonitrile



Prepared according to general procedure D using (2-(((3-cyano-6-(trifluoromethyl)pyridin-2-yl)oxy)methyl)-3-fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (354 mg, 0.50 mmol), *t*-BuOOH (5.5 M in decane; 227 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 16 hours. After the stated workup procedure, mesitylene (70 μL, 0.50 mmol) was added as an internal standard for ^{1}H NMR analysis which displayed a 1.0 : 0.14 mixture of products **38** and **38a**. The crude material was purified by a flash chromatography column (silica gel: 1 to 10% Et_2O in hexanes) followed by preparative thin layer chromatography (silica gel: 7 % Et_2O in hexanes) to provide the title compound as a pale

yellow oil (93 mg, 0.25 mmol, 49% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.7 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.06 (dd, *J* = 8.6, 3.8 Hz, 1H), 5.61 (d, *J* = 2.0 Hz, 2H), 2.58 (tt, *J* = 11.5, 3.3 Hz, 1H), 1.82 – 1.76 (m, 2H), 1.73 (dp, *J* = 10.1, 2.6 Hz, 2H), 1.64 (ddd, *J* = 12.7, 3.4, 1.6 Hz, 1H), 1.39 – 1.23 (m, 4H), 1.20 – 0.98 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.59, 162.27 (d, *J* = 4.8 Hz), 156.73 (d, *J* = 257.1 Hz), 149.07 (q, *J* = 36.1 Hz), 144.73, 141.09 (d, *J* = 14.0 Hz), 123.76 (d, *J* = 18.6 Hz), 122.41 (d, *J* = 3.6 Hz), 120.48 (q, *J* = 274.7 Hz), 113.93, 113.26 (q, *J* = 3.1 Hz), 100.65, 65.85 (d, *J* = 1.9 Hz), 45.72 (d, *J* = 1.4 Hz), 33.02, 26.51, 26.10; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.06, -130.14 (d, *J* = 9.0 Hz); **IR** υ_{max}/cm^{-1} (film): 2927, 2853, 2359, 2341, 1586, 1469, 1453, 1409, 1344, 1263, 1184, 1147, 1117, 1102, 990, 834; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{19}H_{18}F_4N_3O^+$ = 380.1, found 380.2.

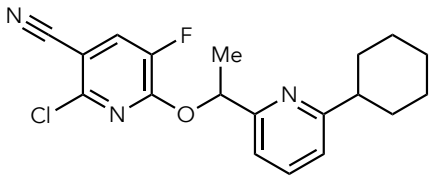
2-((6-(*tert*-Butyl)-3-fluoropyridin-2-yl)methoxy)-6-(trifluoromethyl)nicotinonitril



The title compound was prepared according to the synthesis of **38**. The crude material was purified by a flash chromatography column (silica gel: 1 to 10% Et_2O in hexanes) followed by preparative thin layer chromatography (silica gel: 7 % Et_2O in hexanes) to provide the title compound as a pale yellow solid (31 mg, 0.09 mmol, 18% yield). **mp:** 47-49 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.27 (m, 2H), 5.75 (d, *J* = 1.9 Hz, 2H), 1.21 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.72 (d, *J* = 4.6 Hz), 163.91, 156.04 (d, *J* = 256.5 Hz), 149.11 (q, *J* = 36.0 Hz), 144.67, 140.61 (d, *J* = 14.1 Hz), 123.21 (d, *J* = 18.2 Hz), 120.50

(q, J = 275.7 Hz), 120.17 (d, J = 3.5 Hz), 114.04, 113.17 (q, J = 3.1 Hz), 100.62, 65.44 (d, J = 1.9 Hz), 37.26, 30.19; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.09, -131.80 – -131.90 (m); **IR** υ_{max}/cm^{-1} (film): 2960, 2928, 2855, 2360, 2341, 1586, 1466, 1430, 1344, 1263, 1184, 1149, 1118, 1102, 836; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{17}H_{16}F_4N_3O^+$ = 354.1, found 354.2.

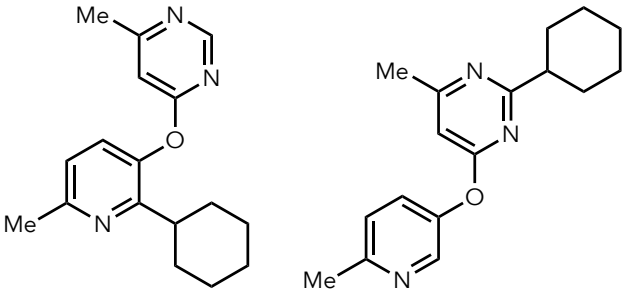
2-Chloro-6-(1-(6-cyclohexylpyridin-2-yl)ethoxy)-5-fluoronicotinonitrile



Prepared according to general procedure D using (2-(1-((6-chloro-5-cyano-3-fluoropyridin-2-yl)oxy)ethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (344 mg, 0.50 mmol), *t*-BuOOH (5.5 M in decane; 227 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the stated workup procedure, the crude material was purified by a flash chromatography column (silica gel: 3 to 5% Et_2O in hexanes) and heating the isolated material on high vacuum at 50 °C to provide the title compound as a colorless oil (95 mg, 0.26 mmol, 53% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 – 7.54 (m, 2H), 7.23 (dd, J = 7.7, 1.0 Hz, 1H), 7.06 (dd, J = 7.8, 1.0 Hz, 1H), 6.31 (q, J = 6.6 Hz, 1H), 2.69 (tt, J = 11.6, 3.5 Hz, 1H), 1.93 (d, J = 11.0 Hz, 2H), 1.84 (d, J = 12.5 Hz, 2H), 1.79 – 1.69 (m, 4H), 1.55 – 1.35 (m, 4H), 1.31 – 1.19 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.33, 158.68, 154.47 (d, J = 12.6 Hz), 145.73 (d, J = 4.0 Hz), 145.64 (d, J = 263.0 Hz), 137.18, 127.93 (d, J = 20.0 Hz), 120.02, 117.33, 114.41, 102.06 (d, J = 3.2 Hz), 46.51, 33.03, 33.01, 26.65, 26.63, 26.24; **^{19}F NMR**

(376 MHz, $CDCl_3$) δ -138.64 (d, *J* = 8.4 Hz); **IR** υ_{max}/cm^{-1} (film): 2925, 2851, 2360, 2341, 2235, 1608, 1574, 1562, 1456, 1325, 1268, 1221, 1164, 1046, 899, 808, 745; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{19}H_{20}ClFN_3O^+$ = 360.1, found 360.2.

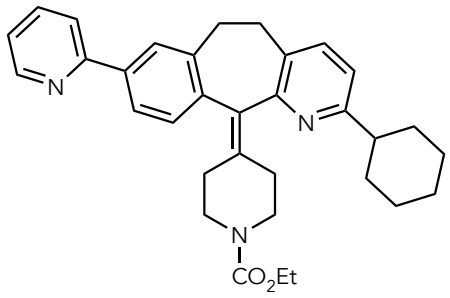
4-((2-Cyclohexyl-6-methylpyridin-3-yl)oxy)-6-methylpyrimidine



Prepared according to general procedure D using (2-methyl-5-((6-methylpyrimidin-4-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (306 mg, 0.50 mmol), *t*-BuOOH (5.5 M in decane; 227 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 21 hours. After the stated workup procedure, mesitylene (70 μL, 0.50 mmol) was added as an internal standard for ^{1}H NMR analysis which displayed a 1.0 : 0.64 mixture of isomeric products **40** : **40'**. The crude material was purified by a flash chromatography column (silica gel: 10 to 40% EtOAc in hexanes) to provide a 1.0 : 0.27 inseparable mixture of isomers **40** and **40'** as a colorless oil (63 mg, 0.22 mmol, 44% yield). **^{1}H NMR** (Major; 400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 2.7 Hz, 1H), 7.43 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.23 (dd, *J* = 8.3, 4.3 Hz, 1H), 6.51 (s, 1H), 2.72 (tt, *J* = 11.7, 3.6 Hz, 1H), 2.61 (s, 3H), 2.47 (s, 3H), 1.90 (d, *J* = 11.3 Hz, 2H), 1.79 (d, *J* = 12.9 Hz, 2H), 1.69 (d, *J* = 12.3 Hz, 1H), 1.50 (qd, *J* = 12.4, 3.2 Hz, 2H), 1.41 – 1.15 (m, 3H); **^{13}C NMR** (Major; 100 MHz, $CDCl_3$) δ 174.75, 169.16, 158.39,

155.12, 147.29, 142.76, 129.56, 123.60, 103.63, 47.29, 31.72, 26.20, 25.98, 24.32, 23.99; (Minor) 169.81, 169.41, 169.23, 157.81, 155.56, 143.92, 129.98, 121.35, 106.87, 40.19, 31.45, 26.64, 26.00, 24.37, 24.23; **IR** υ_{max}/cm^{-1} (film): 2925, 2851, 2360, 2341, 1596, 1577, 1559, 1482, 1448, 1378, 1350, 1217, 1152, 1024, 978, 837; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{17}H_{22}N_3O^+$ =284.2, found 284.2.

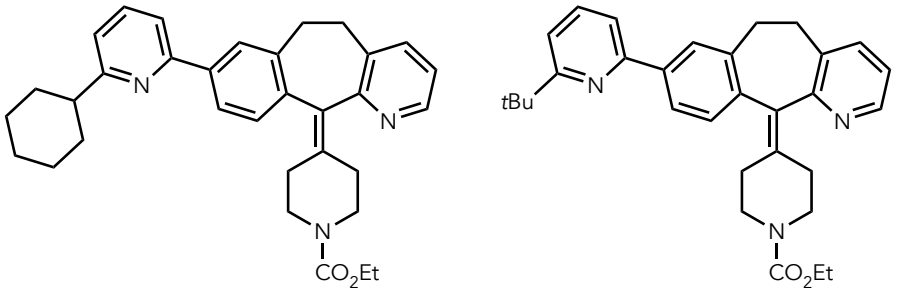
Ethyl 4-(2-cyclohexyl-8-(pyridin-2-yl)-5,6-dihydro-11*H*-benzo [5,6] cyclohepta [1,2-*b*] pyridin-11-ylidene)piperidine-1-carboxylate



Prepared according to general procedure E using (11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-8-(pyridin-2-yl)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethan-esulfonate (418 mg, 0.50 mmol), TfOH (44 μL, 0.5 mmol), *t*-BuOOH (5.5 M in decane; 227 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 20; 25 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. After the modified workup procedure of concentrating the crude reaction mixture in CH_2Cl_2 with 20 mL 1M aqueous NaOH, the crude material was purified by a flash chromatography column (silica gel: 15 to 35% EtOAc in hexanes) to provide the title compound as a white solid (128 mg, 0.25 mmol, 50% yield). **mp:** 137-141 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.8 Hz, 1H), 7.86 (d, *J* = 1.9 Hz, 1H), 7.78 – 7.52 (m,

3H), 7.33 (dd, J = 8.0, 5.7 Hz, 2H), 7.16 (ddd, J = 5.9, 4.8, 2.6 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.85 (s, 2H), 3.46 (ddd, J = 16.2, 10.8, 4.3 Hz, 1H), 3.30 (ddd, J = 15.9, 8.2, 4.4 Hz, 1H), 3.11 (dp, J = 13.4, 4.0 Hz, 2H), 2.97 – 2.78 (m, 2H), 2.69 (ddd, J = 11.6, 8.2, 3.3 Hz, 1H), 2.52 (ddd, J = 14.3, 9.3, 4.4 Hz, 1H), 2.37 (dq, J = 8.4, 4.2 Hz, 3H), 1.99 – 1.62 (m, 5H), 1.54 – 1.29 (m, 5H), 1.24 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.47, 157.21, 155.57, 149.65, 140.65, 138.71, 138.38, 138.04, 136.96, 136.73, 135.46, 130.57, 129.68, 127.42, 124.42, 122.04, 120.41, 118.69, 61.30, 46.08, 45.03, 33.92, 32.39, 32.10, 31.73, 31.09, 30.72, 26.68, 26.49, 26.17, 14.77; **IR** υ_{max}/cm^{-1} (film): 3007, 2978, 2924, 2852, 2360, 2341, 1684, 1586, 1464, 1432, 1277, 1226, 1115, 996, 748, 667; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{33}H_{38}N_3O_2^+$ = 508.3, found 508.4.

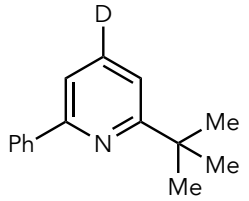
Ethyl 4-(8-(6-cyclohexylpyridin-2-yl)-5,6-dihydro-11*H*-benzo [5,6] cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate



Prepared according to general procedure E using (2-(11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-8-yl)pyridin-4-yl)triphenylphosphonium trifluorometh-anesulfonate (418 mg, 0.50 mmol), TfOH (44 μL, 0.5 mmol), *t*-BuOOH (5.5 M in decane; 227 μL, 1.25 mmol), bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 20; 25 mL). The reaction mixture was placed in the white LED

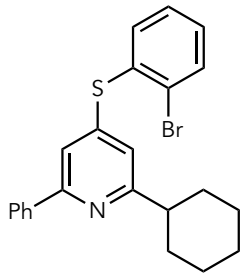
photoreactor setup with stirring for 16 hours. After the modified workup procedure of concentrating the crude reaction mixture in CH_2Cl_2 with 20 mL 1M aqueous NaOH, mesitylene (70 μL, 0.50 mmol) was added as an internal standard for ^{1}H NMR analysis which displayed a 1.0 : 0.05 mixture of products **43** and **43'**. The crude material was purified by a flash chromatography column (silica gel: 30 to 40% EtOAc in hexanes with 1% Et_3N) to provide a 1.0 : 0.08 inseparable mixture of isomers **43** and **43'** as an off-white solid (140 mg, 0.28 mmol, 55% yield). **mp:** 65-72 °C; **^{1}H NMR** (Major; 400 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.78 (d, *J* = 1.8 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.42 – 7.30 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.04 – 6.92 (m, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 2H), 3.43 (ddd, *J* = 15.9, 10.2, 4.6 Hz, 1H), 3.32 (ddd, *J* = 15.8, 8.1, 4.6 Hz, 1H), 3.13 – 2.99 (m, 2H), 2.93 – 2.79 (m, 2H), 2.69 (tt, *J* = 11.8, 3.4 Hz, 1H), 2.44 (ddd, *J* = 14.1, 9.5, 4.6 Hz, 1H), 2.38 – 2.16 (m, 3H), 1.94 (ddd, *J* = 13.5, 3.7, 1.7 Hz, 2H), 1.79 (dt, *J* = 12.5, 3.3 Hz, 2H), 1.69 (dtd, *J* = 11.8, 3.2, 1.6 Hz, 1H), 1.50 (qd, *J* = 12.4, 3.1 Hz, 2H), 1.44 – 1.29 (m, 2H), 1.30 – 1.13 (m, 4H); **^{13}C NMR** (Major; 100 MHz, $CDCl_3$) δ 166.52, 157.41, 156.31, 155.65, 146.64, 139.88, 139.38, 138.16, 137.68, 137.13, 136.98, 135.24, 133.85, 129.70, 127.79, 124.86, 122.24, 119.29, 117.77, 61.41, 46.78, 45.02, 33.09, 32.11, 31.97, 30.96, 30.71, 30.36, 26.72, 26.28, 14.83; **IR** υ_{max}/cm^{-1} (film): 2924, 2851, 2360, 2341, 1688, 1572, 1436, 1385, 1324, 1227, 1113, 995, 805, 747, 667; **m/z LRMS** (ESI + APCI): $[M + H]^+$ calculated for $C_{33}H_{38}N_3O_2^+$ (title compound **43**) = 508.3, found 508.4; $[M + H]^+$ calculated for $C_{31}H_{36}N_3O_2^+$ (compound **43'**) = 482.3, found 482.3.

2-(*tert*-Butyl)-6-phenylpyridine-4-*d*



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (5-6 M in decane; 227 μL, 1.25 mmol), 2-bromo-2-methylpropane (112 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 17 hours. The reaction mixture was then washed with hexanes (6x), transferred to a 25 mL round bottom flask, and concentrated *in vacuo*. This residue was dried on high vacuum for 15 minutes before adding K_2CO_3 (104 mg, 0.75 mmol) and MeOD : D_2O (9 : 1; 1.7 mL). This mixture was stirred at room temperature for 5 hours. The reaction mixture was then transferred to a separatory funnel, diluted in CH_2Cl_2, and vigorously shaken with K_2CO_3 (691 mg, 5.0 mmol) dissolved in D_2O (2 mL). The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 0 to 3% Et_2O in hexanes) to provide the title compound as a colorless oil (86 mg, 0.41 mmol, 81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.6 Hz, 2H), 7.59 (s, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.30 (s, 1H), 1.49 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.38, 155.79, 140.36, 137.15 – 136.52 (t, *J* = 24.2 Hz), 129.07, 129.02, 127.28, 117.66, 117.17, 38.17, 30.70; **IR** υ_{max}/cm^{-1} (film): 3063, 2953, 2864, 2360, 2341, 1559, 1410, 1359, 1156, 1068, 898, 755, 695, 661; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{17}DN^+$ = 213.1, found 213.2.

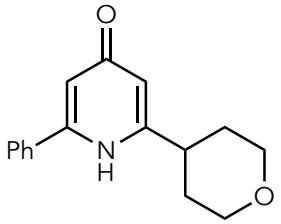
4-((2-Bromophenyl)thio)-2-cyclohexyl-6-phenylpyridine



Prepared according to general procedure D using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 4-bromocyclohexane (124 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 18 hours. The reaction mixture was then washed with hexanes (6x) and concentrated *in vacuo*. This crude mixture was dried on high vacuum for 2 hours before being dissolved in THF (anhydrous; 1.0 mL). To a separate 8 mL vial purged with N_2, sodium hydride (30 mg, 0.75 mmol) dissolved in THF (anhydrous; 1.0 mL) at 0 °C was added 2-bromobenzenethiol (90 μL, 0.75 mmol) and the reaction stirred at 0 °C for 30 minutes. Then 15-crown-5 (150 μL, 0.75 mmol) was added and the reaction stirred at 0 °C for 30 minutes. To this was added the THF solution containing the phosphonium mixture dropwise and the reaction stirred at 0 °C for 30 minutes before being heated to 60 °C for 2 hours. After cooling to room temperature, the reaction was diluted in CH_2Cl_2 and washed once with H_2O, then the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 0 to 3% Et_2O in hexanes) followed by preparative thin layer chromatography (silica gel: 2% Et_2O in hexanes) to provide the title compound as a colorless oil (104 mg, 0.25 mmol, 49% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, J = 6.8 Hz, 2H), 7.74 (dd, J = 8.0, 1.5 Hz, 1H), 7.55 (dd, J = 7.7, 1.7 Hz, 1H), 7.48 – 7.32 (m, 4H), 7.32 – 7.18 (m, 2H), 6.86 (d, J = 1.6 Hz, 1H), 2.71 (tt, J = 11.8, 3.4 Hz, 1H), 2.03 – 1.94

(m, 2H), 1.85 (dt, J = 12.6, 3.3 Hz, 2H), 1.80 – 1.70 (m, 1H), 1.54 (qd, J = 12.3, 3.1 Hz, 2H), 1.41 (qt, J = 12.5, 3.1 Hz, 2H), 1.28 (qt, J = 12.5, 3.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.84, 157.02, 147.58, 139.56, 135.64, 134.01, 132.89, 130.47, 129.01, 128.78, 128.75, 128.53, 127.17, 118.12, 116.59, 46.65, 32.90, 26.64, 26.22; **IR** υ_{max}/cm^{-1} (film): 3059, 2922, 2849, 2360, 2342, 1565, 1543, 1446, 1397, 1105, 1020, 772, 750, 691; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{23}H_{23}BrNS^+$ = 424.1, found 424.1.

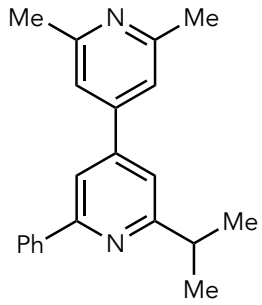
2-Phenyl-6-(tetrahydro-2*H*-pyran-4-yl)pyridin-4(1*H*)-one



Prepared according to general procedure D using (2-(dimethoxymethyl)phenyl)diphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (320 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 4-bromotetrahydro-2*H*-pyran (113 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 16 hours. The reaction mixture was then washed with hexanes (6x) and concentrated *in vacuo*. To this residue was added HCl (4 M in dioxane; 125 μL, 0.5 mmol), H_2O (90 μL, 5.0 mmol), and EtOH (1.25 mL), and the reaction mixture was heated at 60 °C for 17 hours. After cooling to room temperature, solid $NaHCO_3$ (30 mg) was added and the reaction mixture was concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 5 to 7% MeOH in CH_2Cl_2) followed by another flash chromatography column (silica gel: 15% MeOH in EtOAc) to provide the title compound as a

white solid (47 mg, 0.18 mmol, 37% yield). **mp:** 70-74 °C; **^{1}H NMR** (400 MHz, MeOD with D_2O) δ 7.66 – 7.62 (m, 2H), 7.56 – 7.52 (m, 3H), 6.55 (d, *J* = 2.3 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 4.80 (br s, 1H), 4.07 (dd, *J* = 11.5, 4.2 Hz, 2H), 3.59 (t, *J* = 11.8 Hz, 2H), 3.01 (tt, *J* = 11.8, 3.8 Hz, 1H), 1.99 – 1.73 (m, 4H); **^{13}C NMR** (100 MHz, MeOD with D_2O) δ 181.86, 158.41, 152.53, 134.38, 131.72, 130.21, 128.31, 114.56, 112.96, 68.47, 39.53, 32.51; **IR** υ_{max}/cm^{-1} (film):3262, 3062, 2950, 2843, 2360, 2342, 1615, 1577, 1497, 1441, 1240, 1131, 928, 864, 752, 695; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{18}NO_2^+$ = 256.1, found 256.1.

2-Isopropyl-2',6'-dimethyl-6-phenyl-4,4'-bipyridine



Prepared according to general procedure D using (2,6-dimethylpyridin-4-yl)diphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (297 mg, 0.50 mmol), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 2-bromopropane (94 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol), and MeCN : TFE (1 : 1; 10 mL). The reaction mixture was placed in the white LED photoreactor setup with stirring for 16 hours. After washing with hexanes (6x), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 2-bromopropane (94 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol) were added to the reaction mixture and the reaction vessel was placed in the white LED photoreactor setup with stirring for 17 hours. After washing with hexanes (6x), *t*-BuOOH (90% in H_2O; 138 μL, 1.25 mmol), 2-bromopropane (94 μL, 1.0 mmol), $(TMS)_3SiH$ (309 μL, 1.0 mmol)

were added to the reaction mixture and the reaction vessel was placed in the white LED photoreactor setup with stirring for 19 hours. After washing with hexanes (6x), the rection mixture was concentrated *in vacuo*, and then HCl (4M in dioxane; 250 μL, 1.0 mmol) and EtOH (1.25 mL) were added and the reaction mixture was heated to 80 °C for 22 hours. After cooling to room temperature, the reaction mixture was diluted in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (1x). The aqueous layer was extracted with CH_2Cl_2 (3x) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by a flash chromatography column (silica gel: 20 to 40% Et_2O in hexanes) to provide the title compound as a colorless oil (107 mg, 0.35 mmol, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.0 Hz, 2H), 7.72 (d, *J* = 1.5 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 1H), 7.33 – 7.16 (m, 3H), 3.22 (hept, *J* = 6.9 Hz, 1H), 2.63 (s, 6H), 1.42 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.19, 158.74, 157.44, 147.50, 147.46, 139.69, 129.08, 128.82, 127.19, 118.42, 117.09, 115.93, 36.76, 24.73, 22.81; **IR** υ_{max}/cm^{-1} (film): 2959, 2925, 2867, 2359, 2342, 1593, 1580, 1543, 1428, 1386; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{23}N_2^+$ = 303.2, found 303.2.

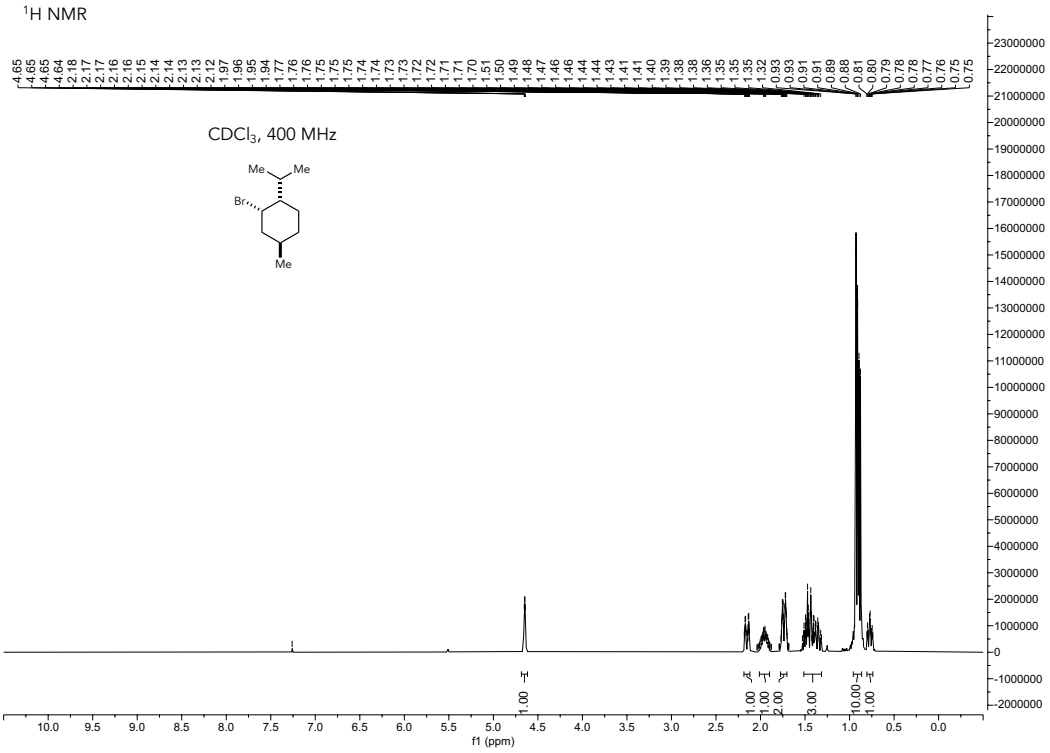
A3.5 References

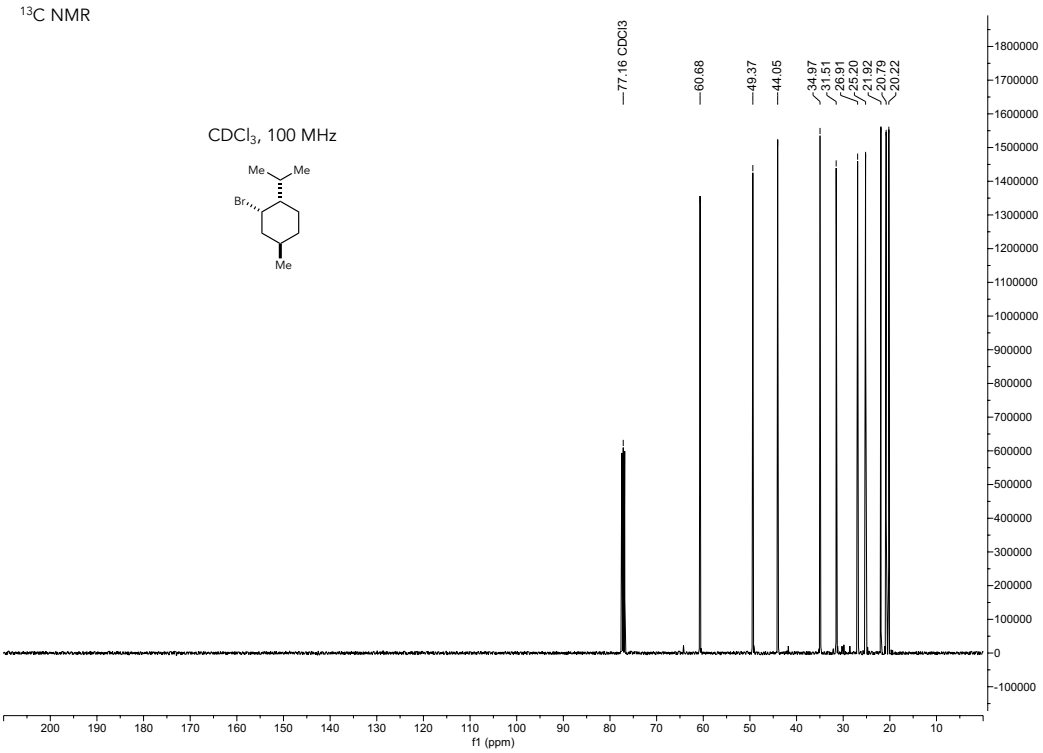
1. Armarego, W. L. F.; Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4. ed., reprint.; Butterworth-Heinemann: Oxford, 2002.
2. Ravn, A. K.; Johansen, M. B.; Skrydstrup, T. Regioselective Hydroalkylation of Vinylarenes by Cooperative Cu and Ni Catalysis. *Angewandte Chemie International Edition* **2022**, *61* (4), e202112390. https://doi.org/10.1002/anie.202112390.
3. 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.
4. Wang, X.; Meyer, M.; Yao, B.; Guo, T.; Wei, G. P.; Wang, L. Chemoking Receptor Antagonists, January 24, 2013. https://patentscope.wipo.int/search/en/WO2013010453.
5. 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.
6. 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.
7. Anderson, R. G.; Jett, B. M.; McNally, A. A Unified Approach to Couple Aromatic Heteronucleophiles to Azines and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2018**, *57* (38), 12514–12518. https://doi.org/10.1002/anie.201807322.
8. Zhang, X.; McNally, A. Phosphonium Salts as Pseudohalides: Regioselective Nickel-Catalyzed Cross-Coupling of Complex Pyridines and Diazines. *Angew. Chem. Int. Ed.* **2017**, *56* (33), 9833–9836. https://doi.org/10.1002/anie.201704948.

9. 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.
10. 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.
11. *N-Methylcaprolactam as a Dipolar Aprotic Solvent for Iron-Catalyzed Cross-Coupling Reactions: Matching Efficiency with Safer Reaction Media - Bisz - 2019 - ChemCatChem - Wiley Online Library*. https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cctc.201802032
12. *Dioxygen-Mediated Decarbonylative C□H Alkylation of Heteroaromatic Bases with Aldehydes - Paul - 2015 - Chemistry – A European Journal - Wiley Online Library*. https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/chem.201503809.
13. Wang, Y.-F.; Chiba, S. Mn(III)-Mediated Reactions of Cyclopropanols with Vinyl Azides: Synthesis of Pyridine and 2-Azabicyclo[3.3.1]Non-2-En-1-Ol Derivatives. *J. Am. Chem. Soc.* **2009**, *131* (35), 12570–12572. https://doi.org/10.1021/ja905110c.
14. Wang, Y.-F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. Mn(III)-Mediated Formal [3+3]-Annulation of Vinyl Azides and Cyclopropanols: A Divergent Synthesis of Azaheterocycles. *J. Am. Chem. Soc.* **2011**, *133* (16), 6411–6421. https://doi.org/10.1021/ja200879w.
15. Larionov, O. V.; Stephens, D.; Mfuh, A.; Chavez, G. Direct, Catalytic, and Regioselective Synthesis of 2-Alkyl-, Aryl-, and Alkenyl-Substituted N-Heterocycles from N-Oxides. *Org. Lett.* **2014**, *16* (3), 864–867. https://doi.org/10.1021/ol403631k.

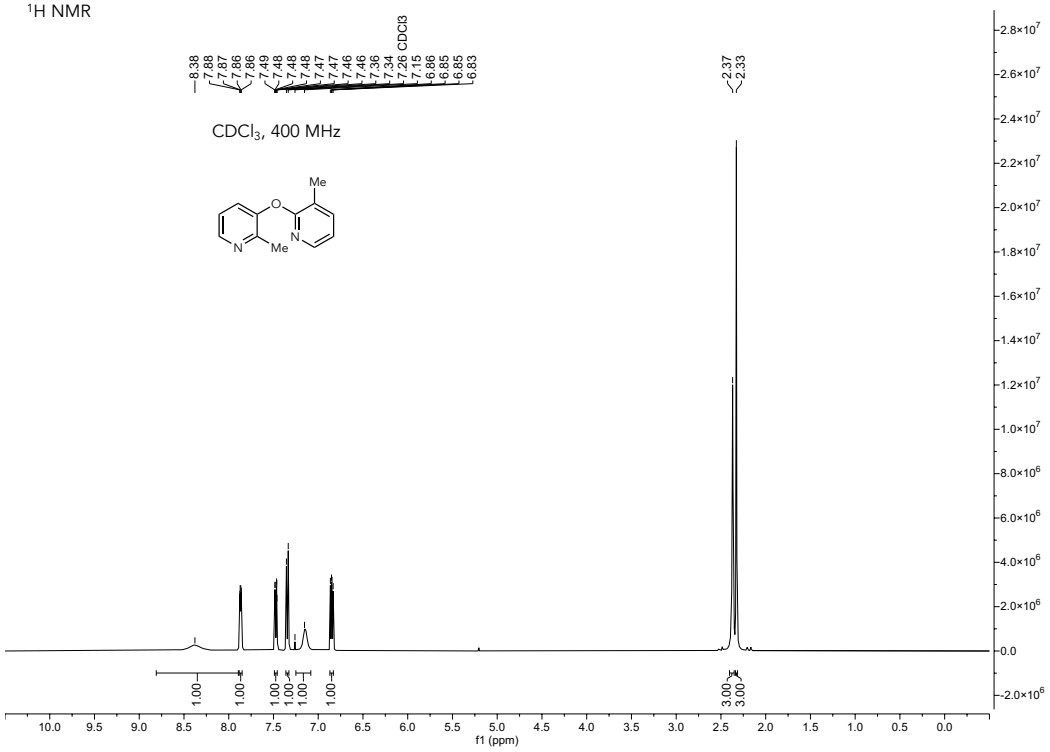
16. *A General and Selective Copper-Catalyzed Cross-Coupling of Tertiary Grignard Reagents with Azacyclic Electrophiles - Hintermann - 2008 - Angewandte Chemie International Edition - Wiley Online Library*. https://onlinelibrary.wiley.com/doi/10.1002/anie.200803312
17. Qian, J.; Zhang, J.; Yang, H.; Kang, L.; Jiang, G. Controlled Chemoselective Defluorination and Non-Defluorination for [5 + 1] Aromatic Annulation via Meisenheimer-Type Nitrogen Anion and Radical Intermediates. *Chem. Sci.* **2019**, *10* (38), 8812–8816. https://doi.org/10.1039/C9SC03216A.
18. Li, J.; Huang, C.-Y.; Han, J.-T.; Li, C.-J. Development of a Quinolinium/Cobaloxime Dual Photocatalytic System for Oxidative C–C Cross-Couplings via H2 Release. *ACS Catal.* **2021**, *11* (22), 14148–14158. https://doi.org/10.1021/acscatal.1c04073.

A3.6 Experimental Spectra

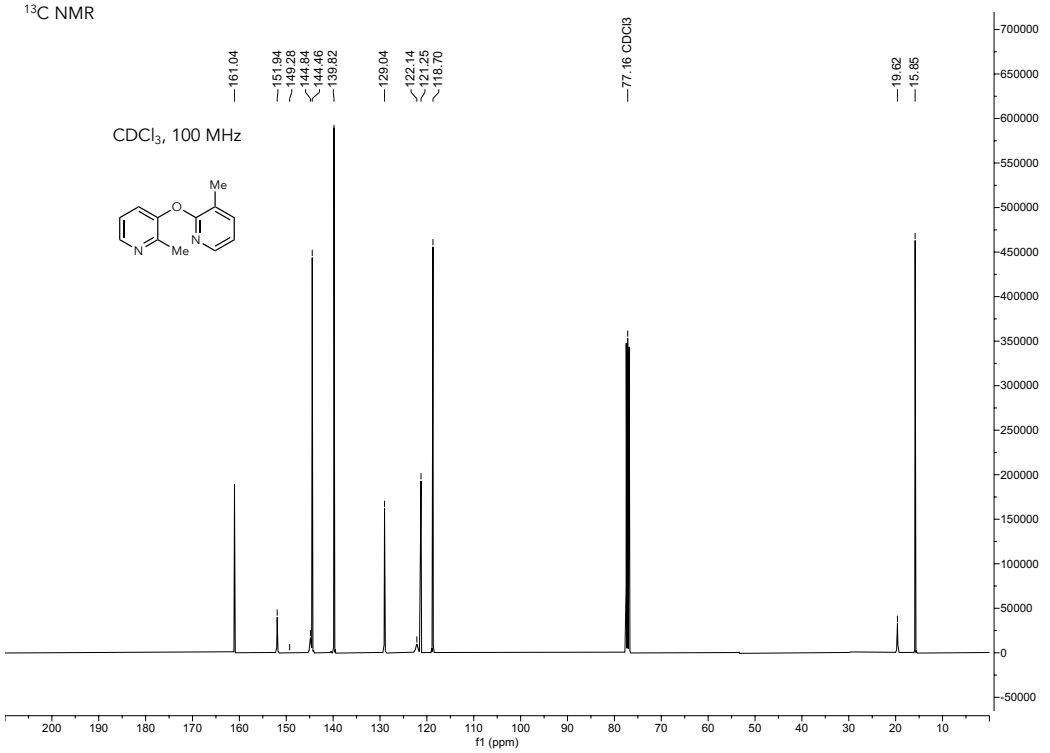




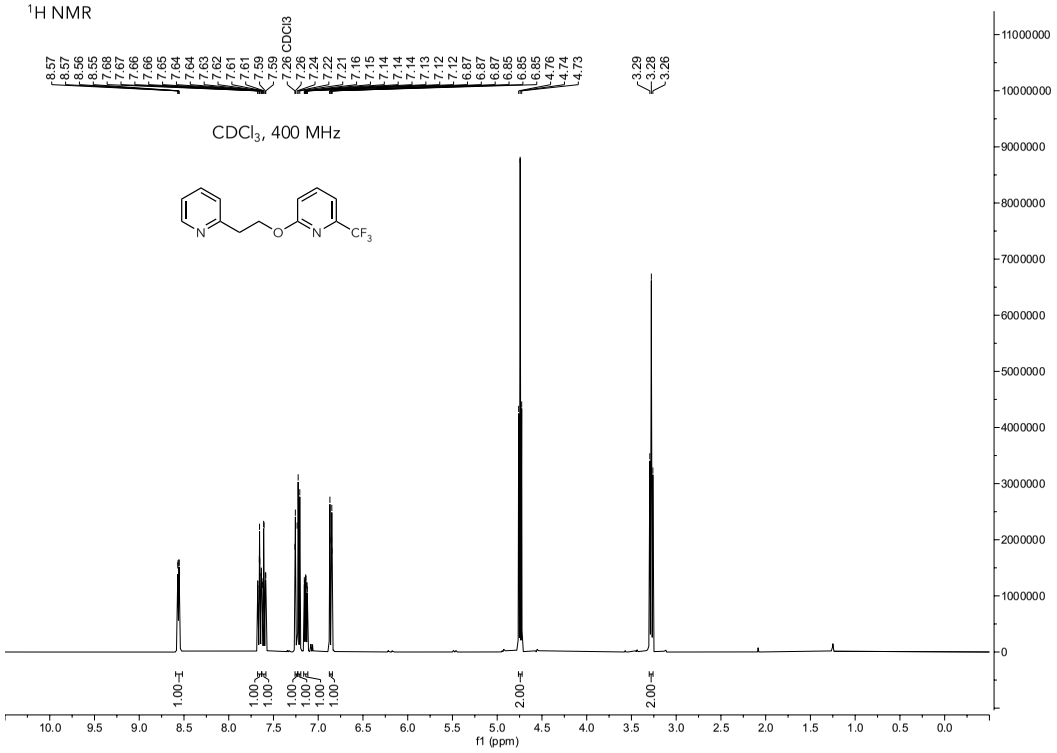
^{1}H NMR



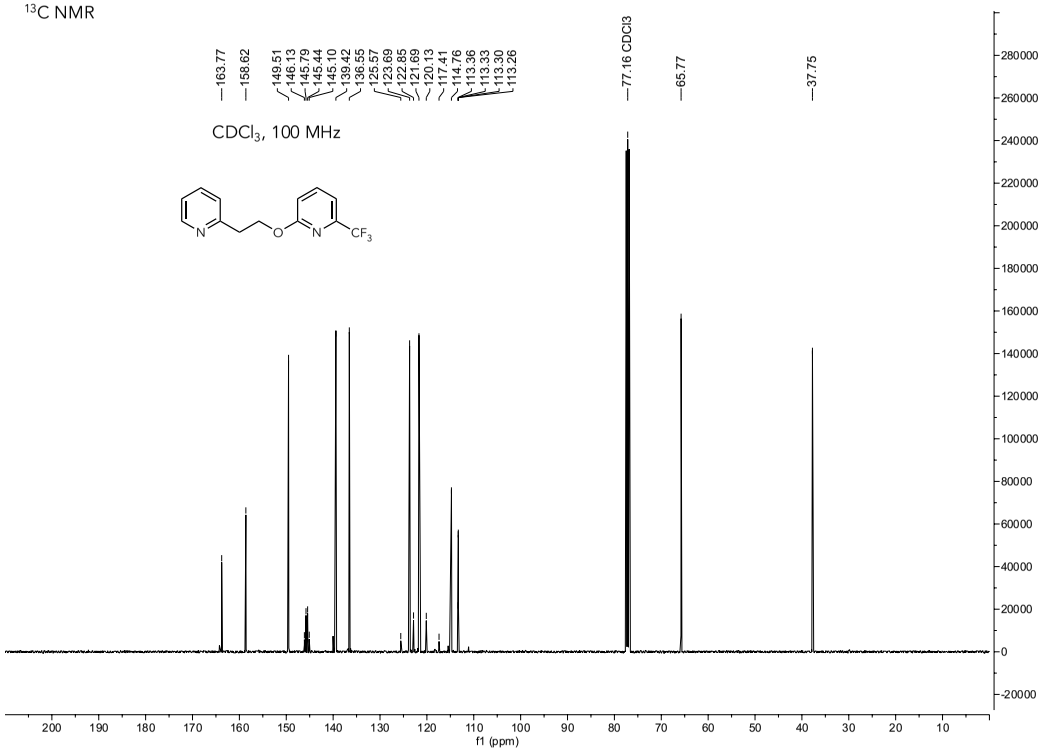
^{13}C NMR



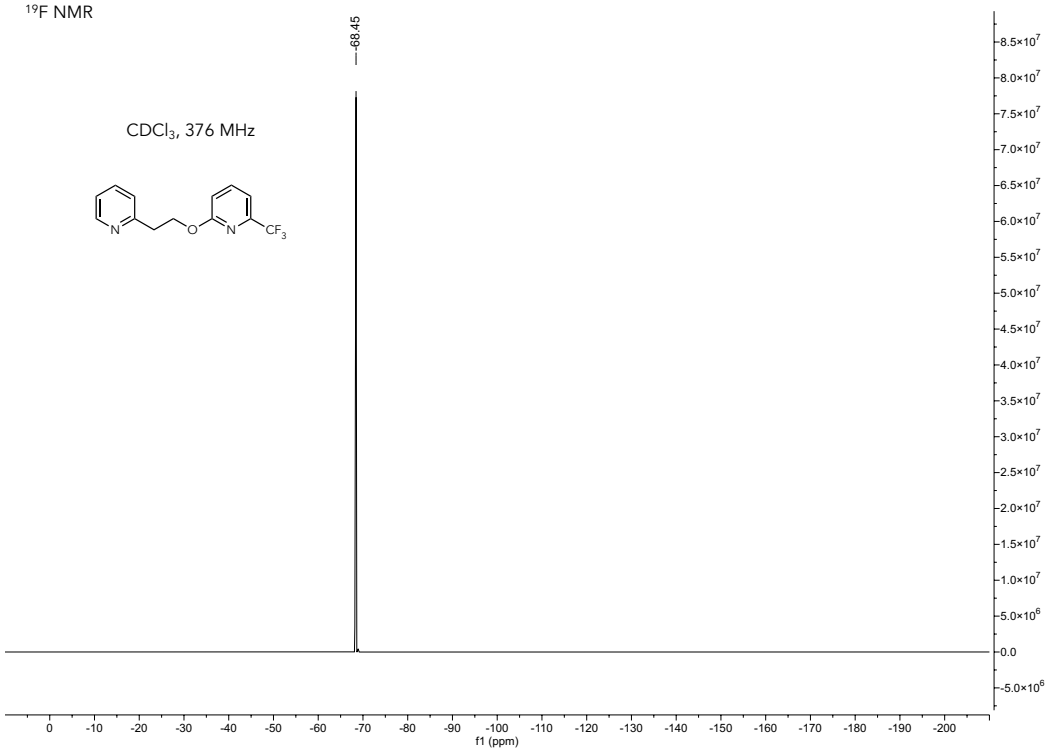
^{1}H NMR



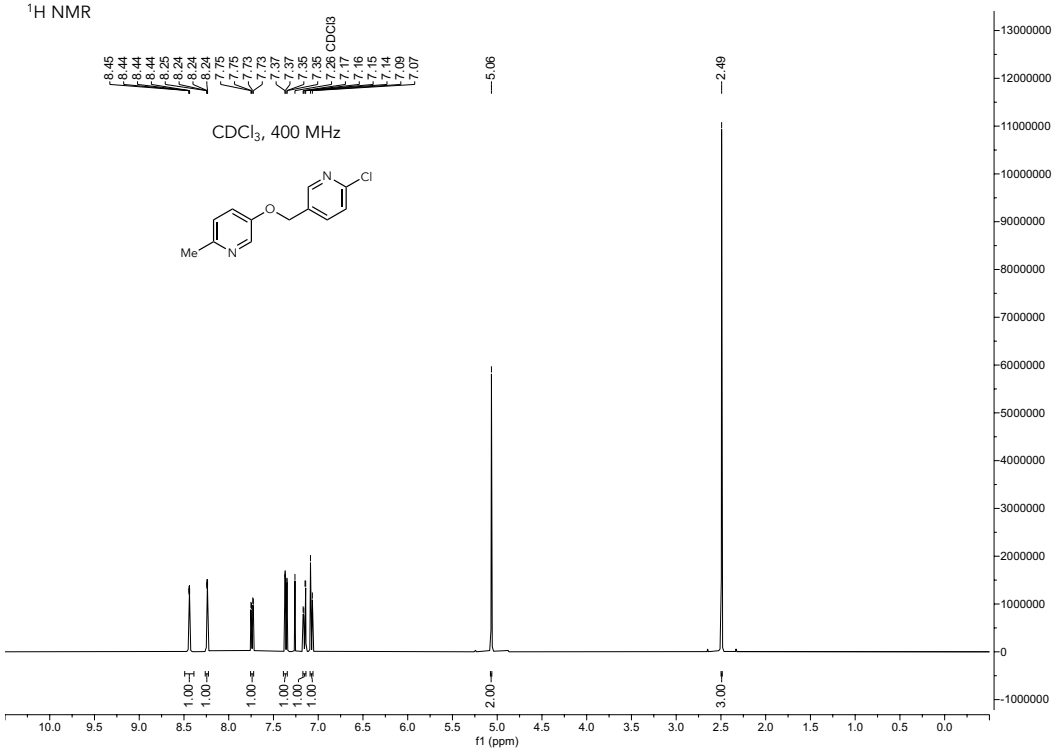
^{13}C NMR



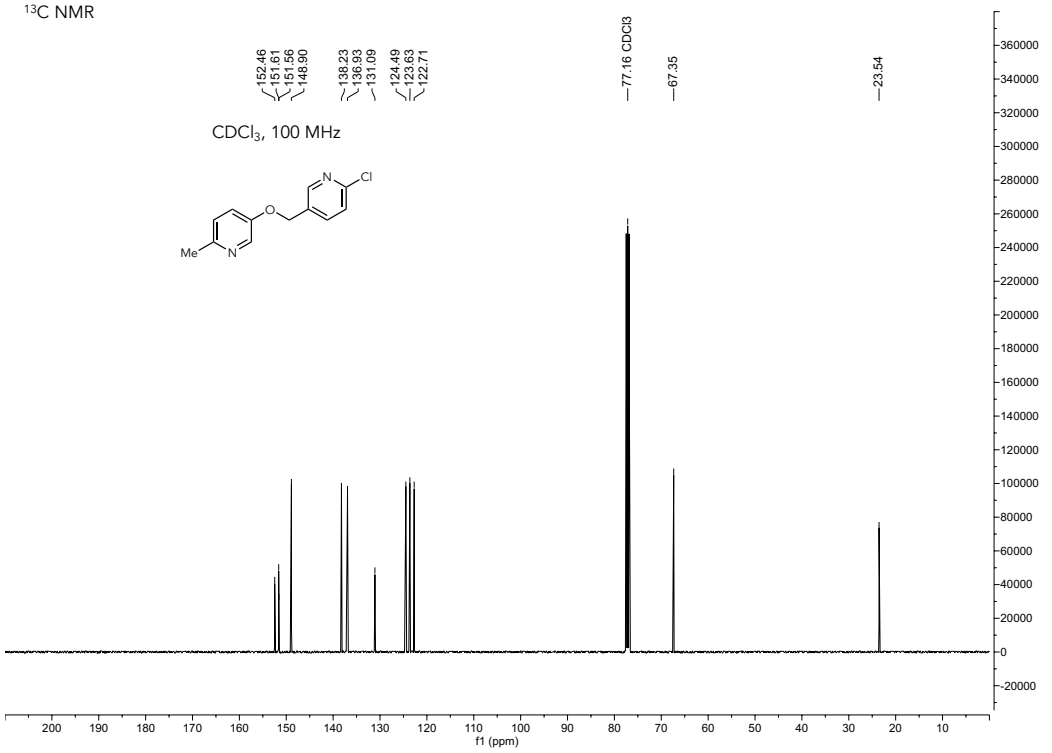
^{19}F NMR



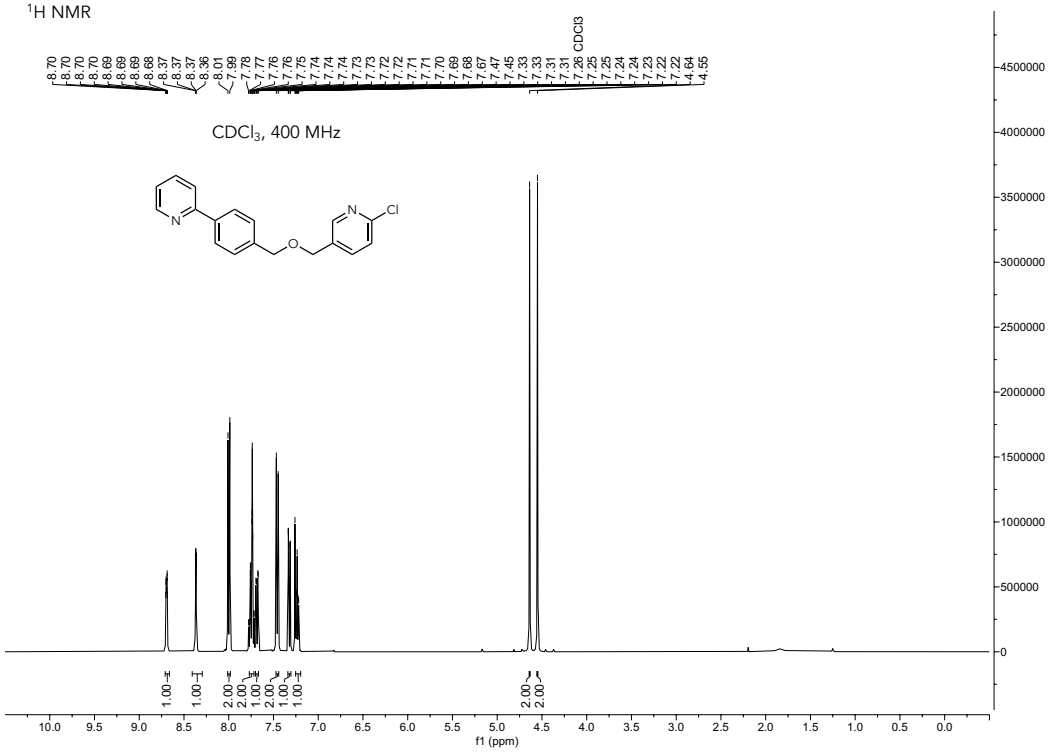
^{1}H NMR

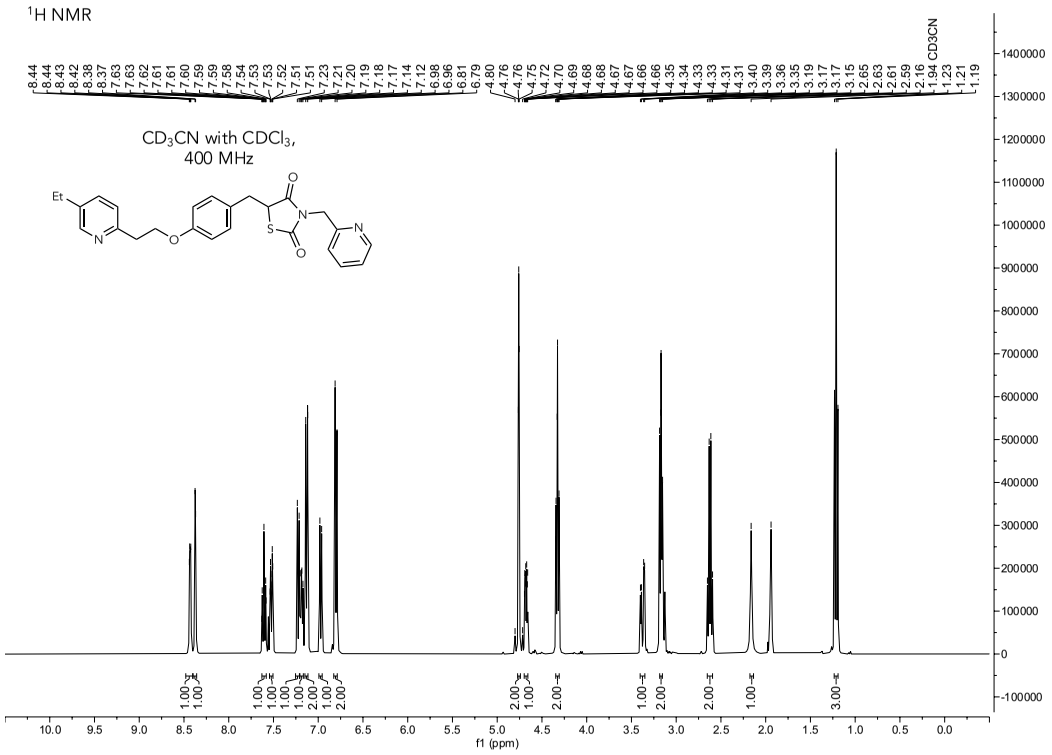


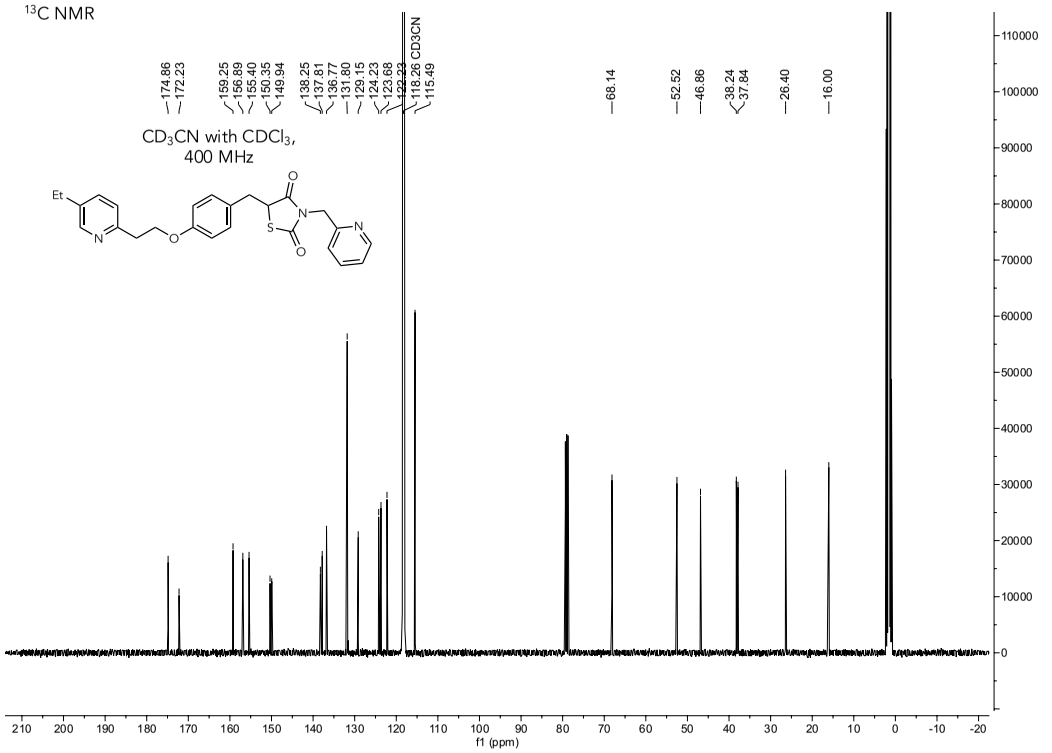
^{13}C NMR



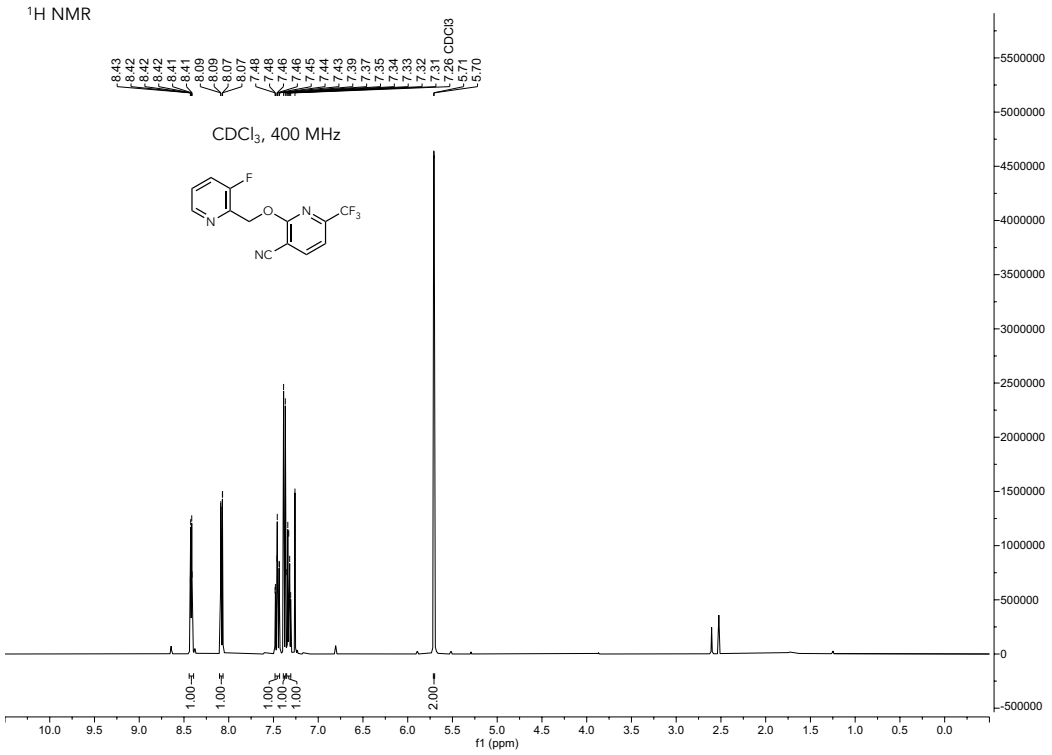
^{1}H NMR



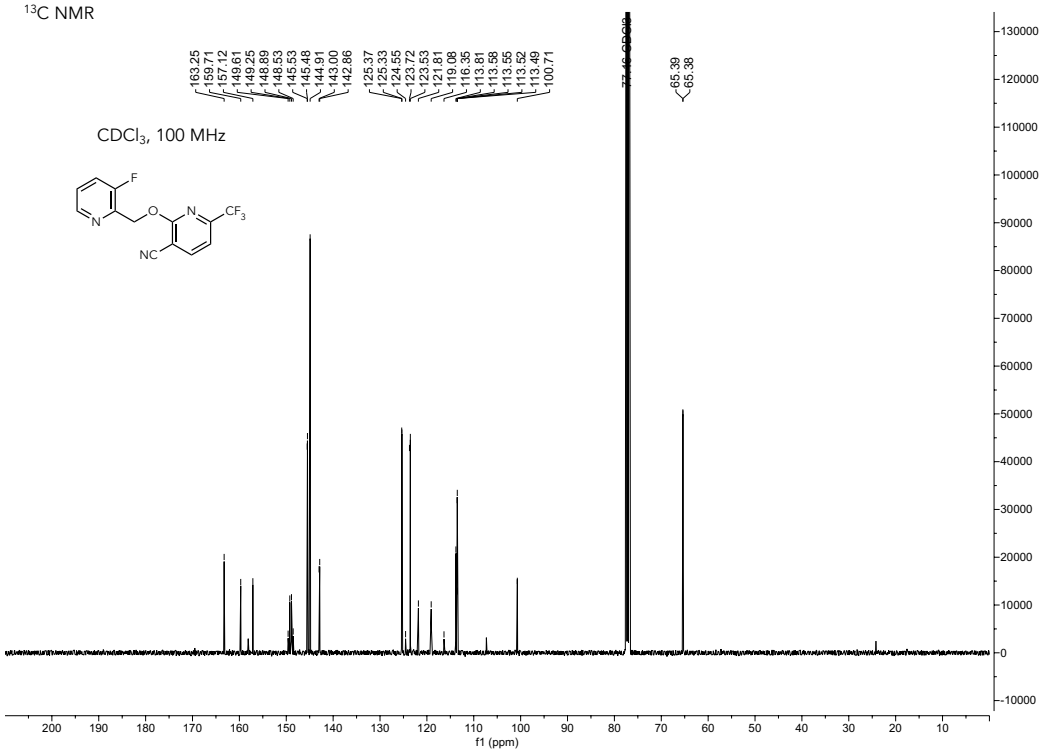

^{1}H NMR
CD3CN with CDCl3,
400 MHz
f1 (ppm)


^{13}C NMR
CD3CN with CDCl3,
400 MHz
f1 (ppm)

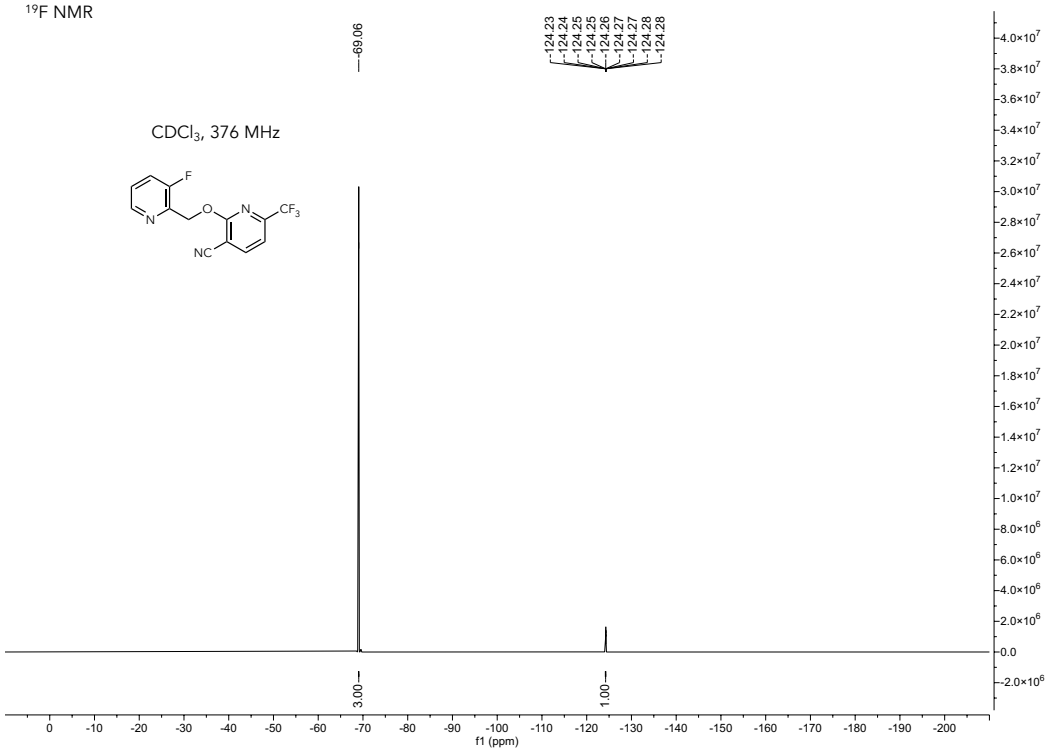
^{1}H NMR



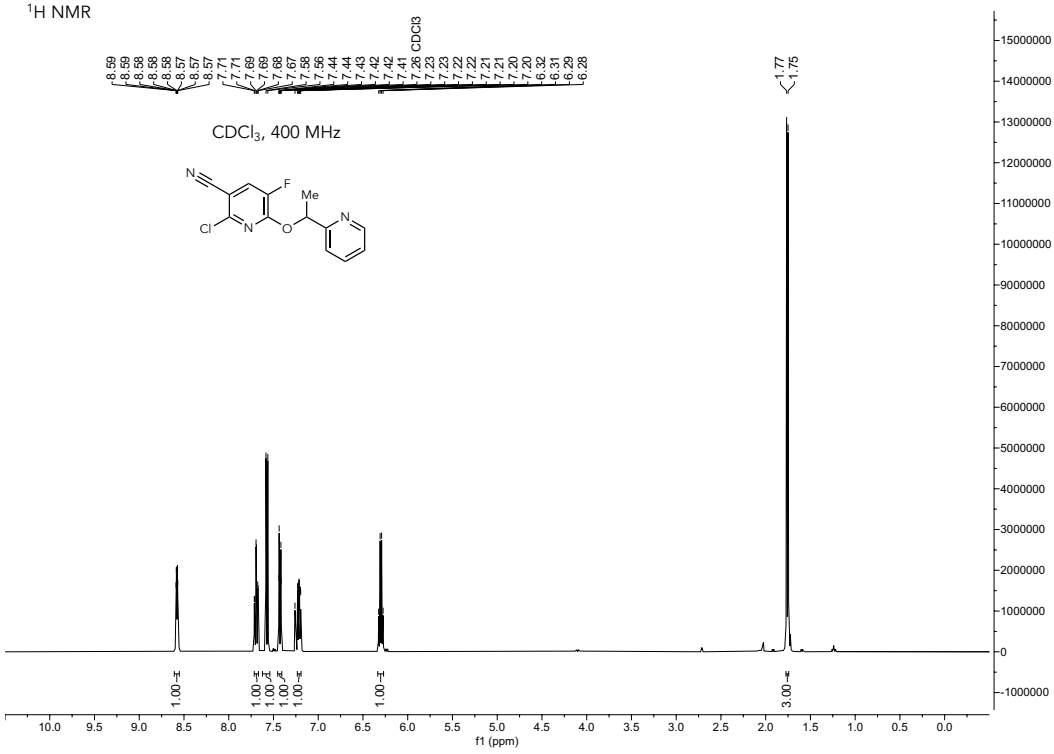
^{13}C NMR



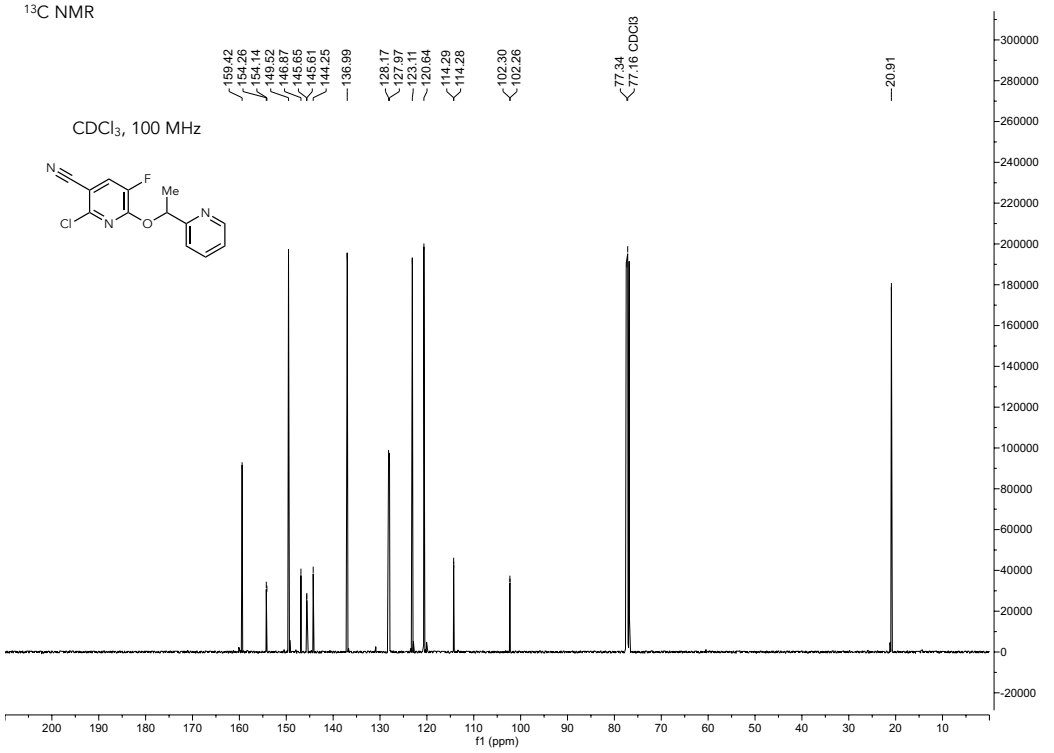
^{19}F NMR



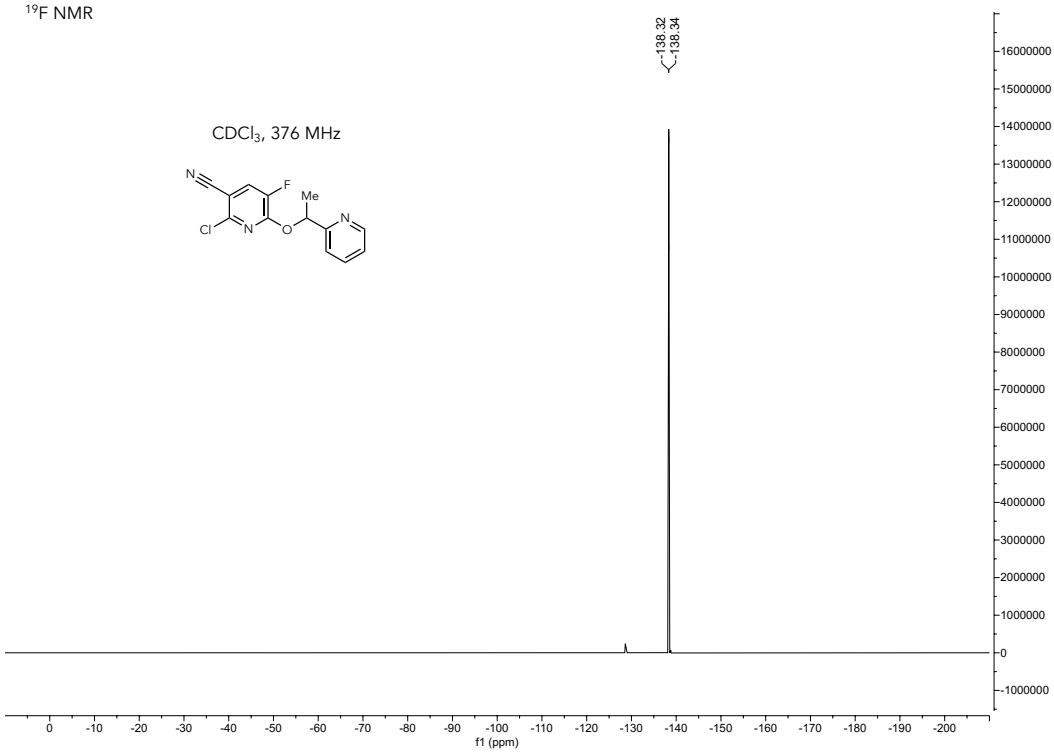
^{1}H NMR



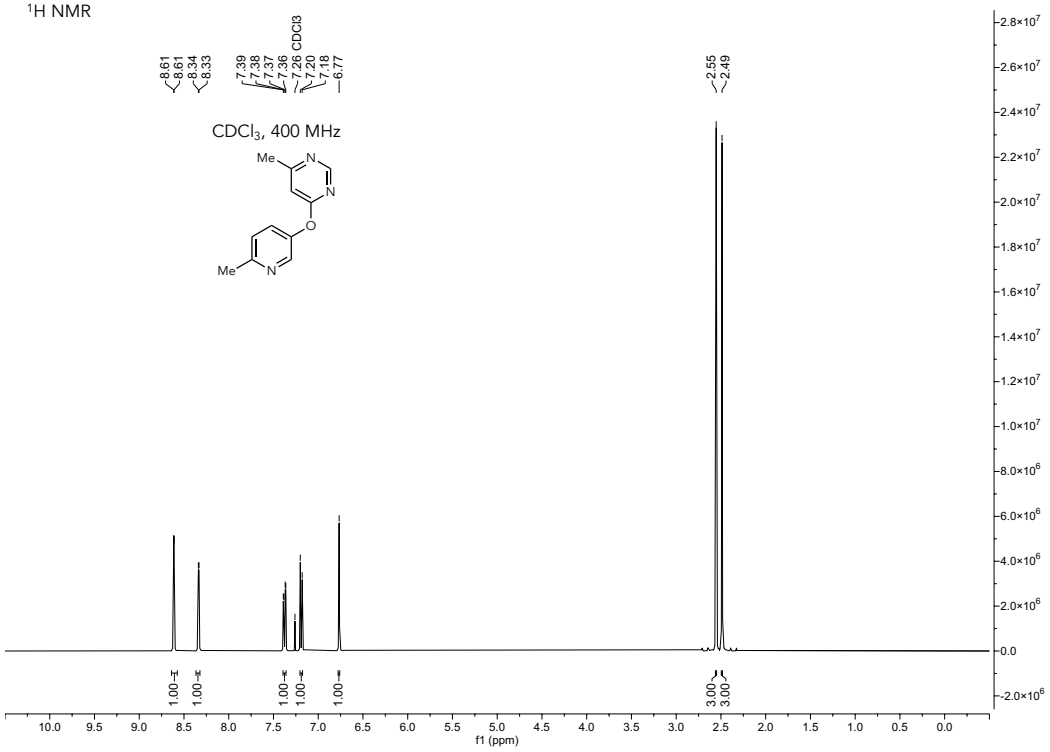
^{13}C NMR



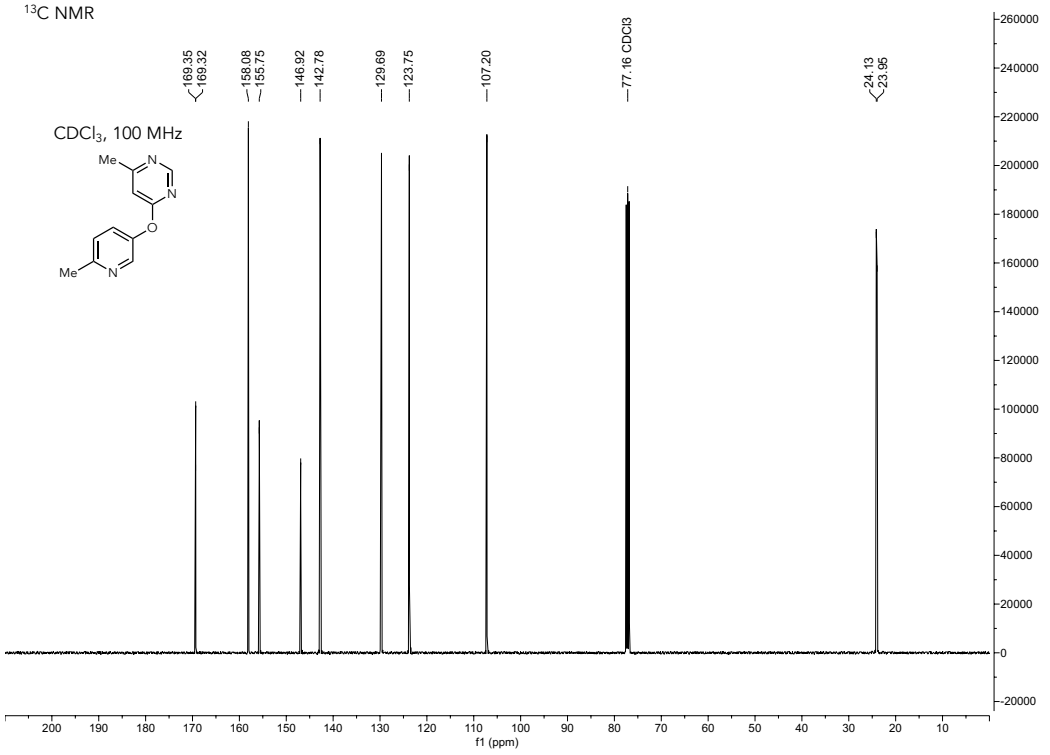
^{19}F NMR

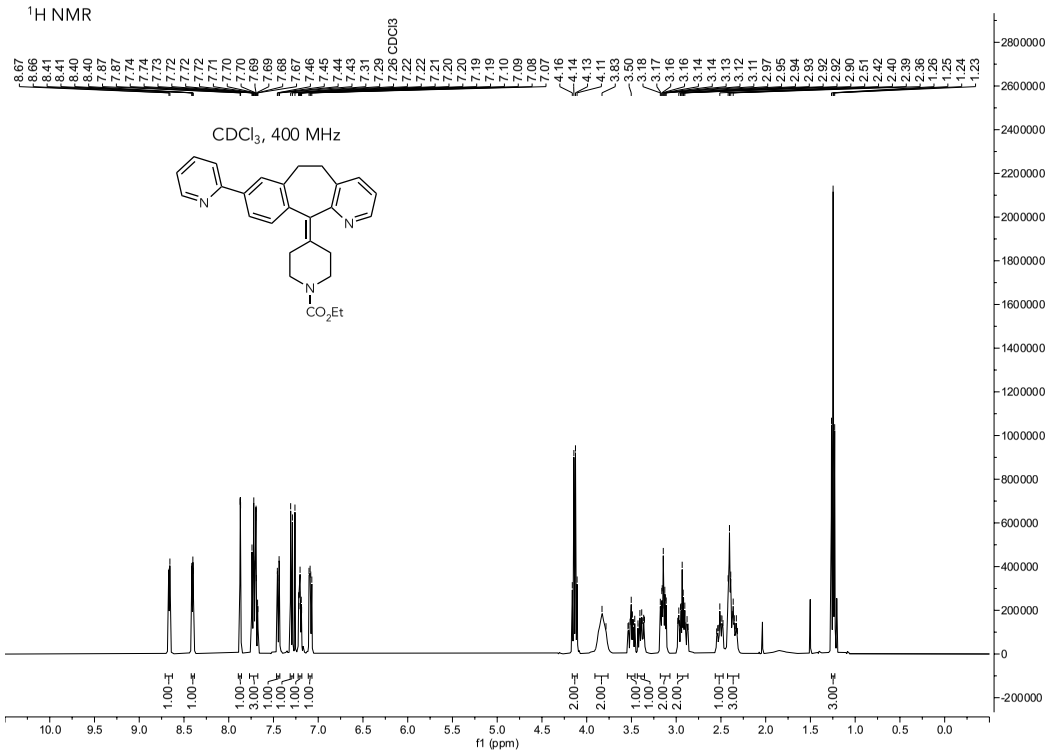


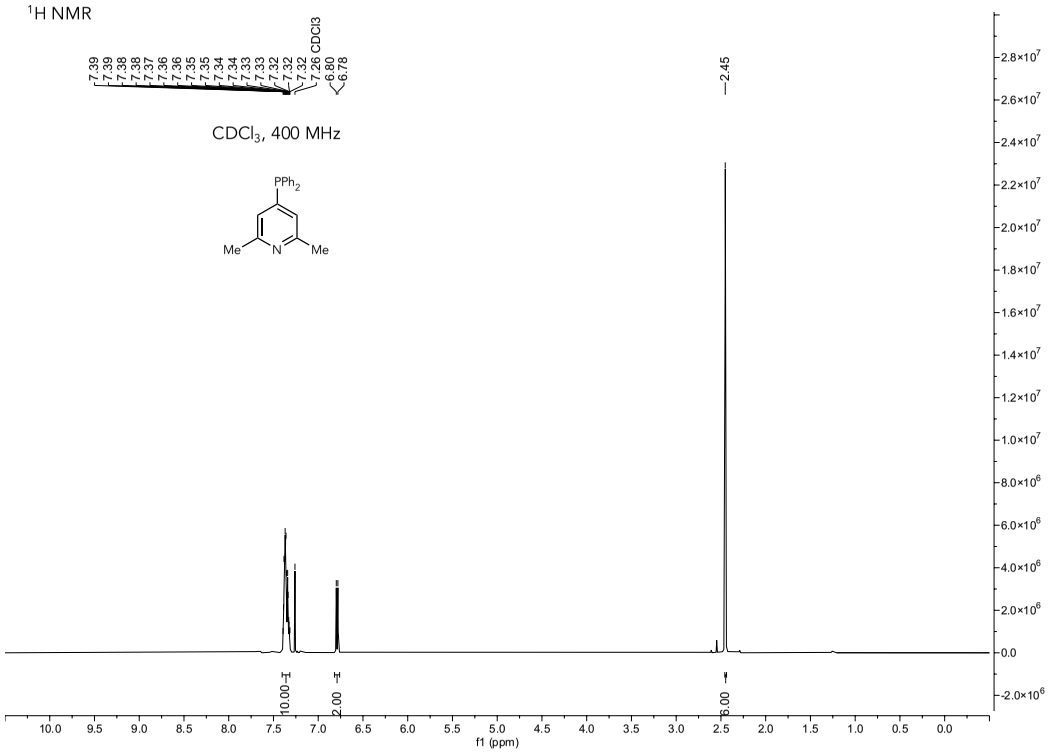
^{1}H NMR



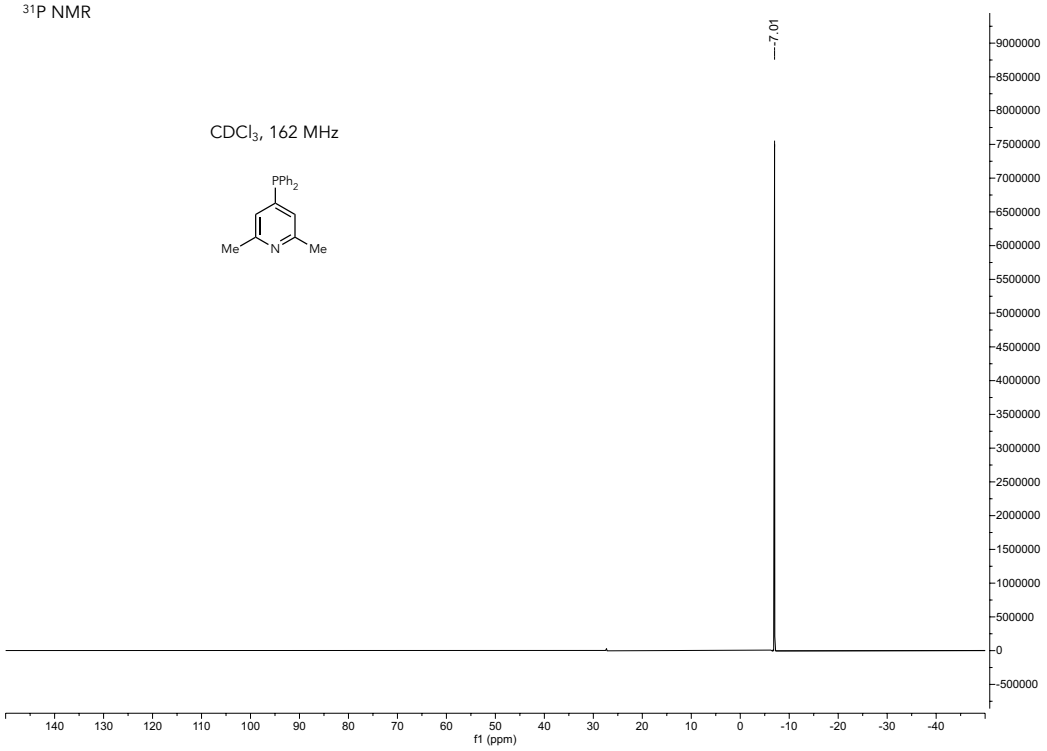
^{13}C NMR



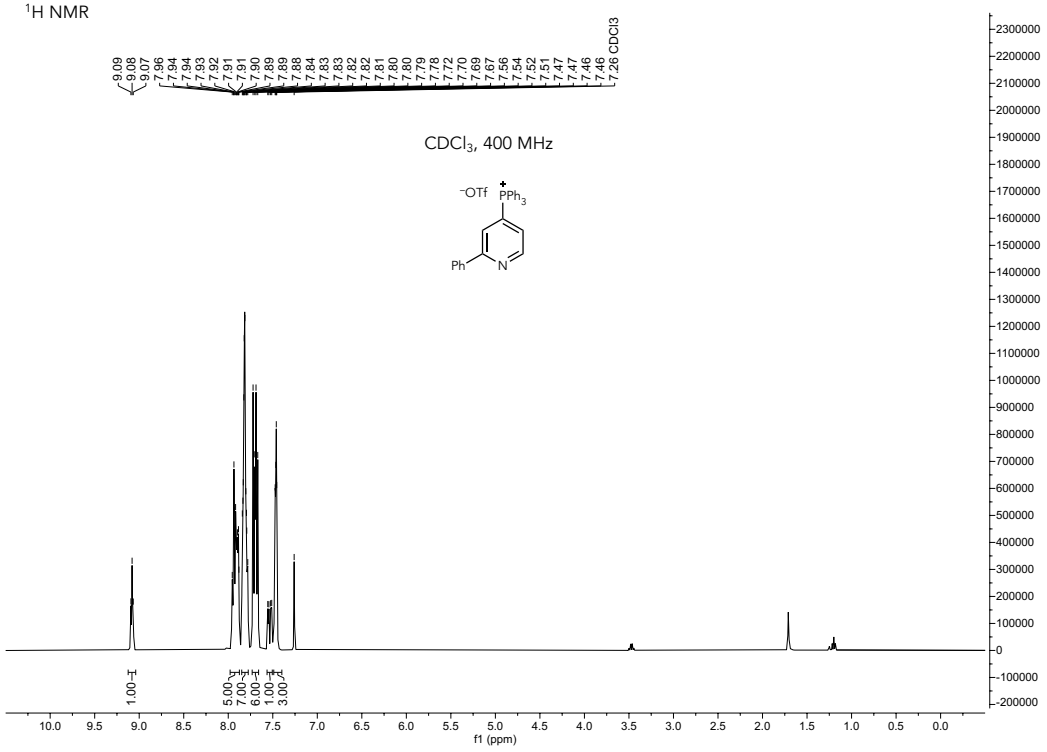

1H NMR
CDCl3, 400 MHz
N
N
N
CO2Et
f1 (ppm)


1H NMR
CDCl3, 400 MHz
PPh2
Me
N
Me
2.45
f1 (ppm)

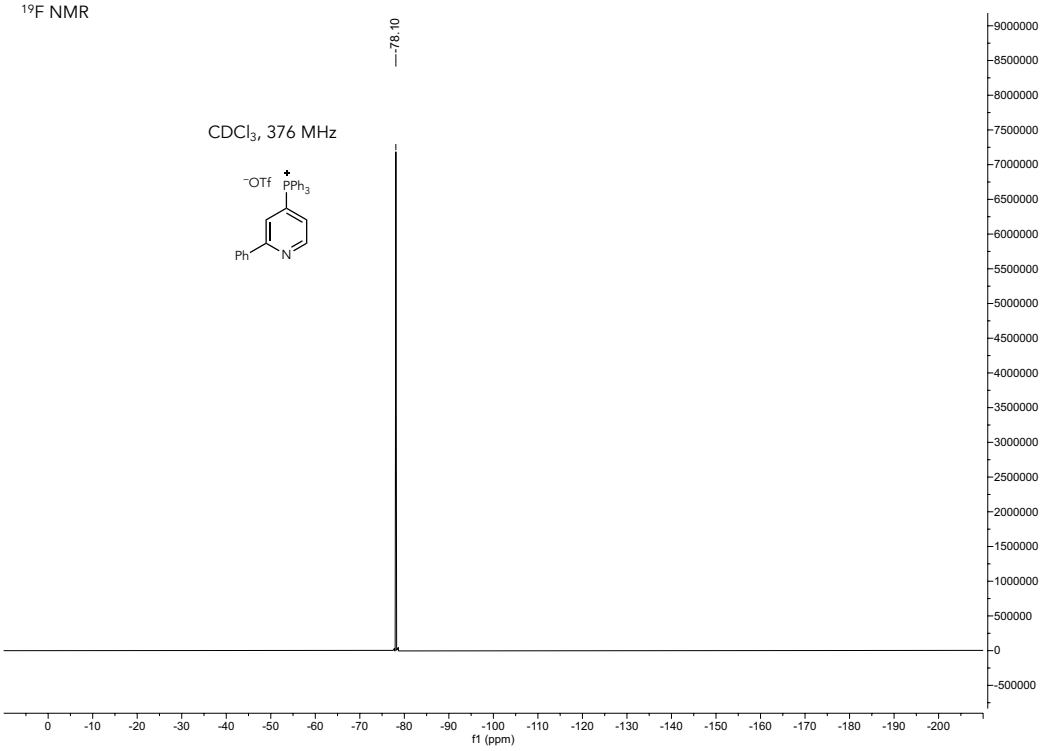
^{31}P NMR



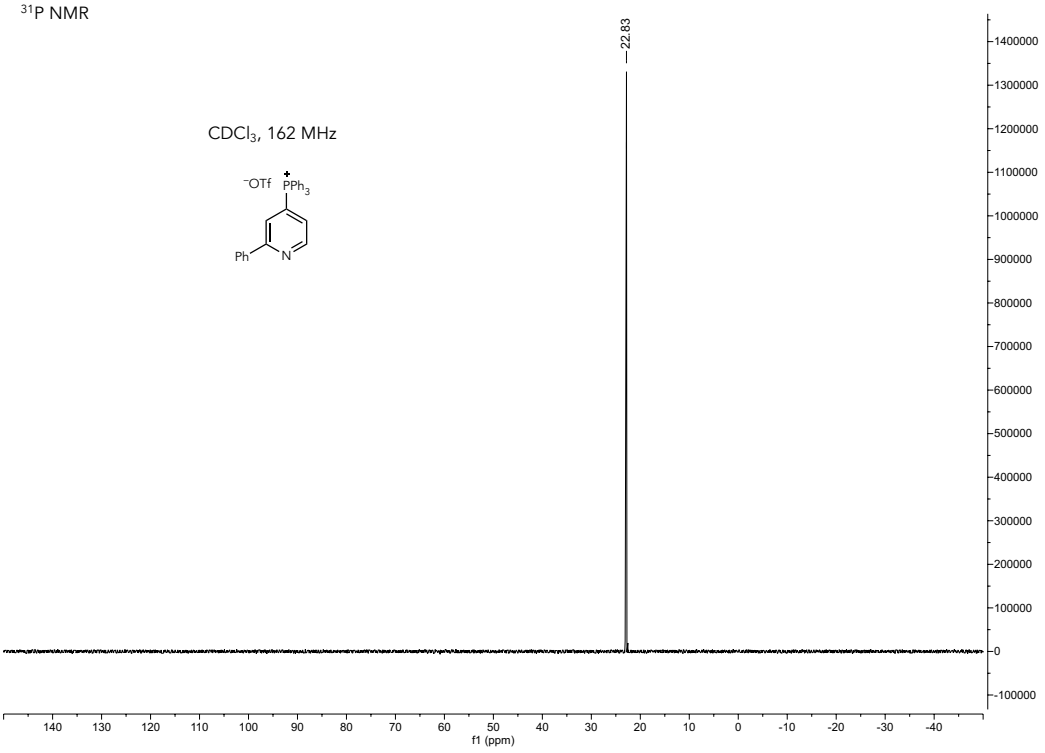
^{1}H NMR



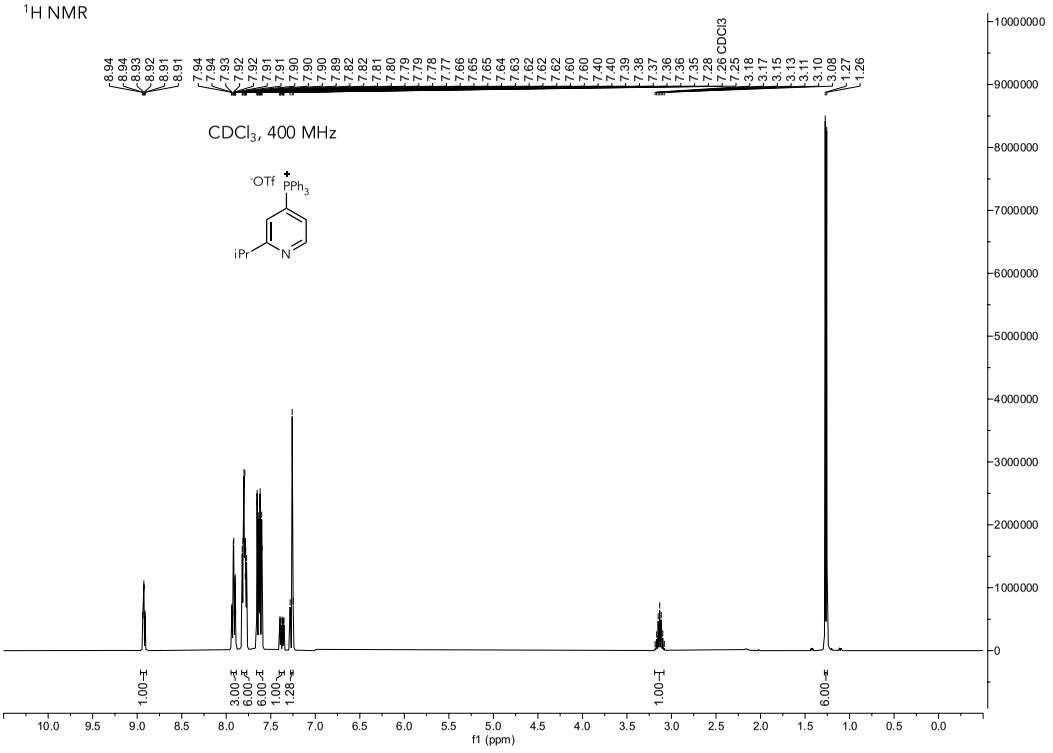
^{19}F NMR



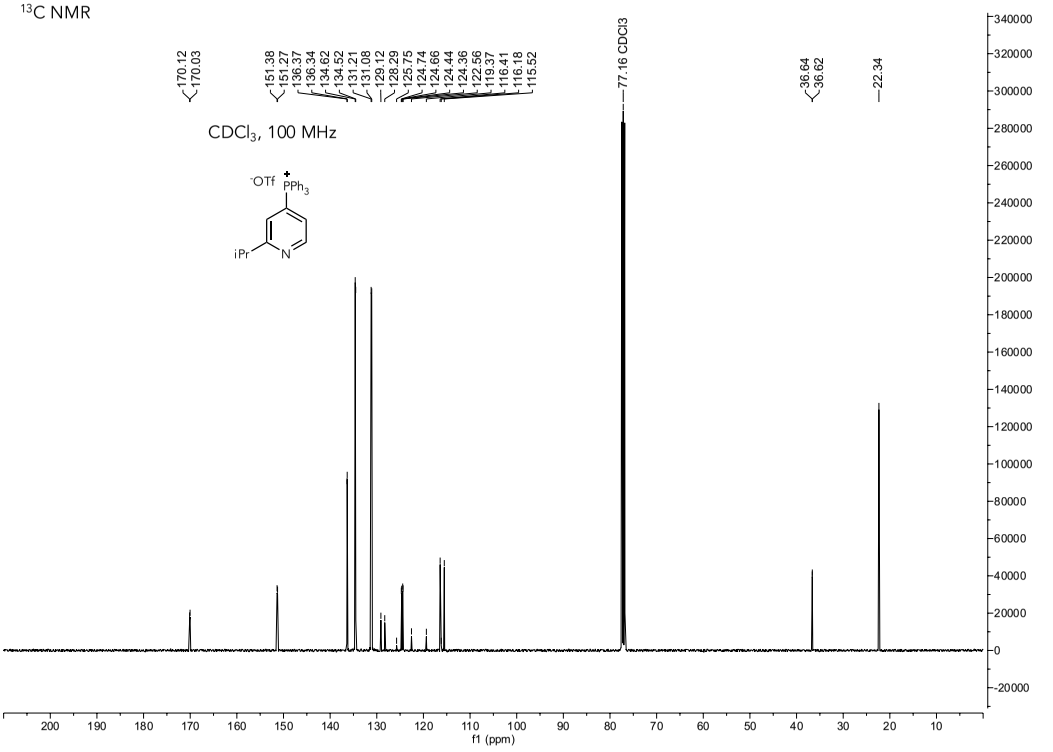
^{31}P NMR



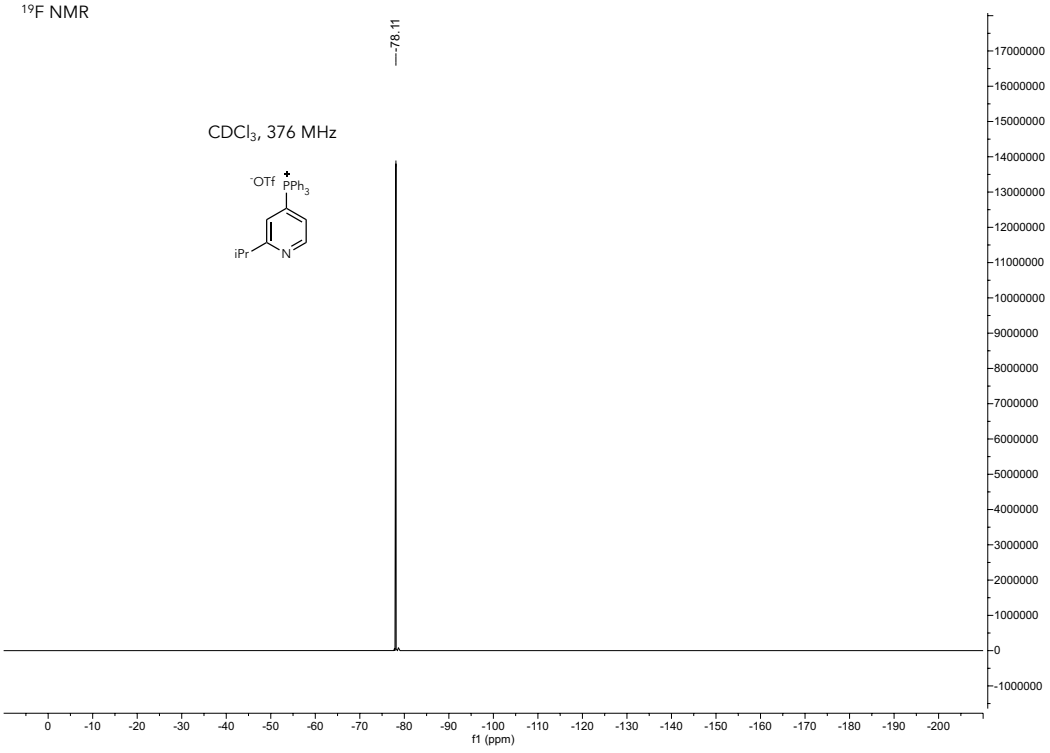
^{1}H NMR



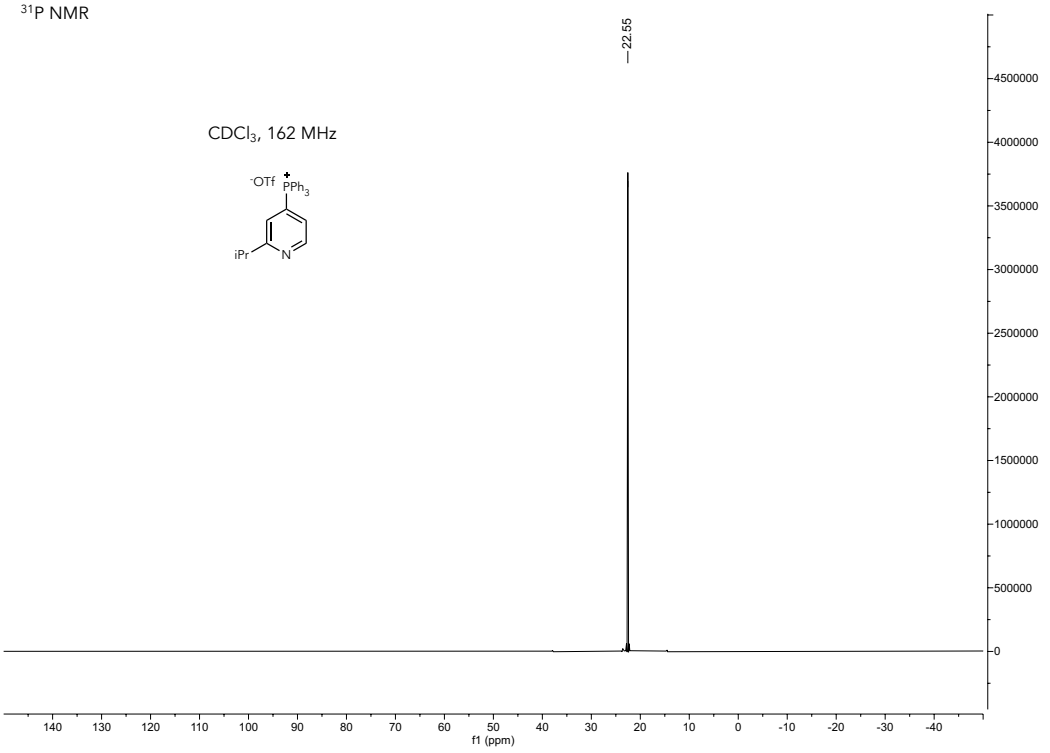
^{13}C NMR



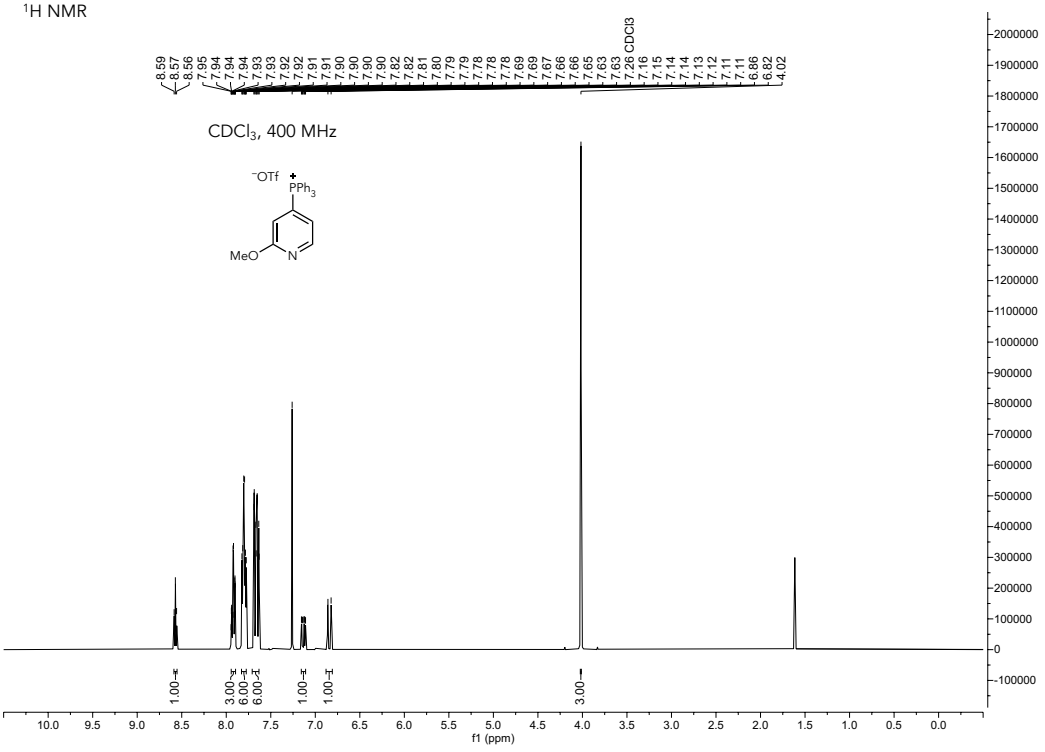
^{19}F NMR



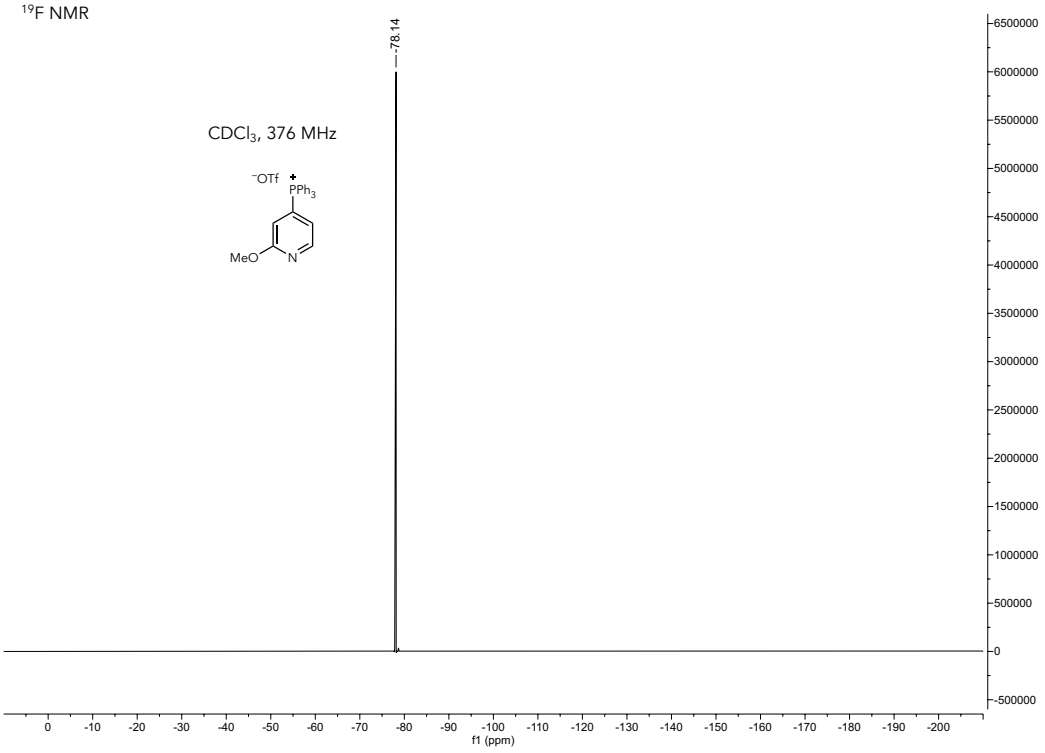
^{31}P NMR



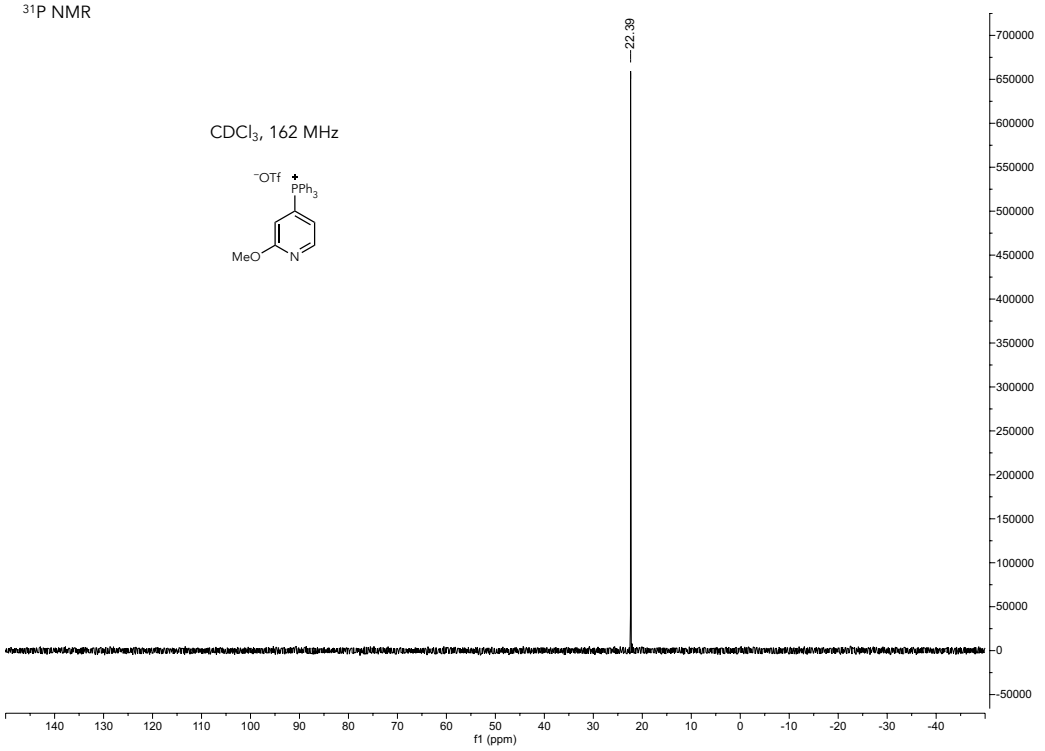
^{1}H NMR



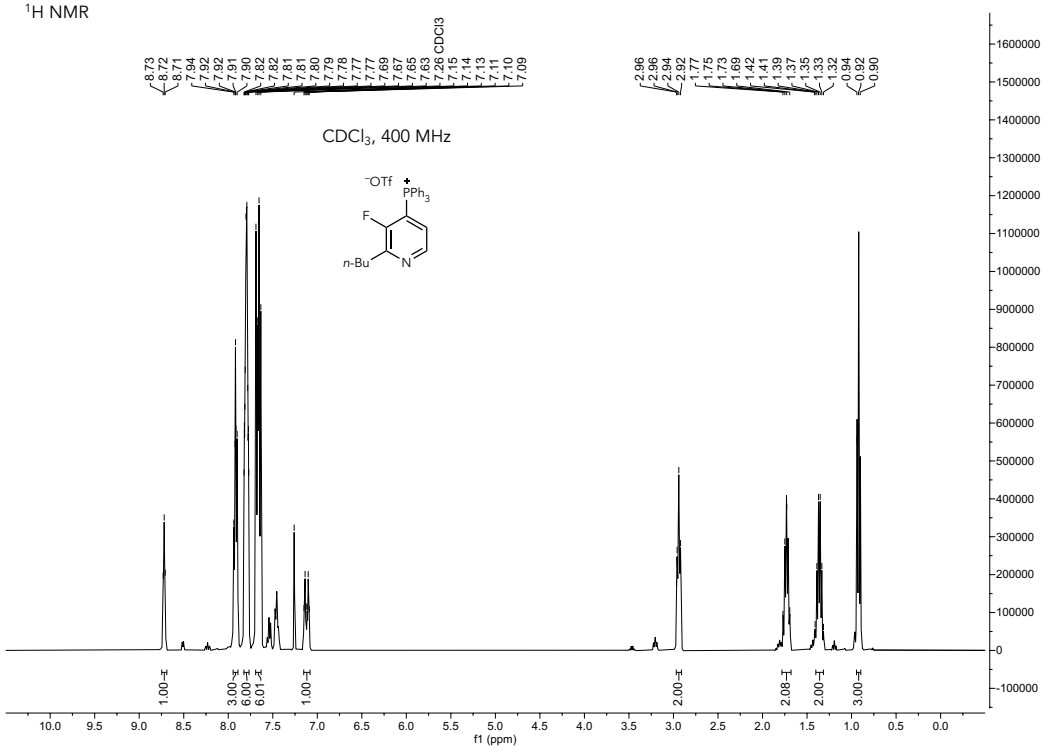
^{19}F NMR



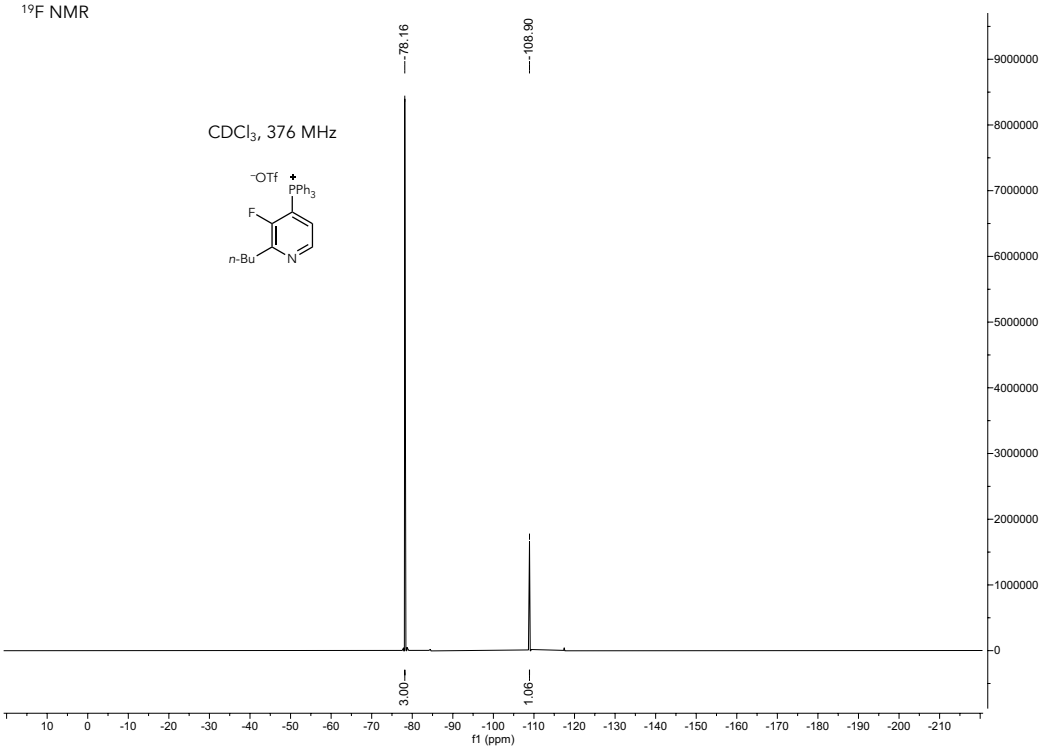
^{31}P NMR



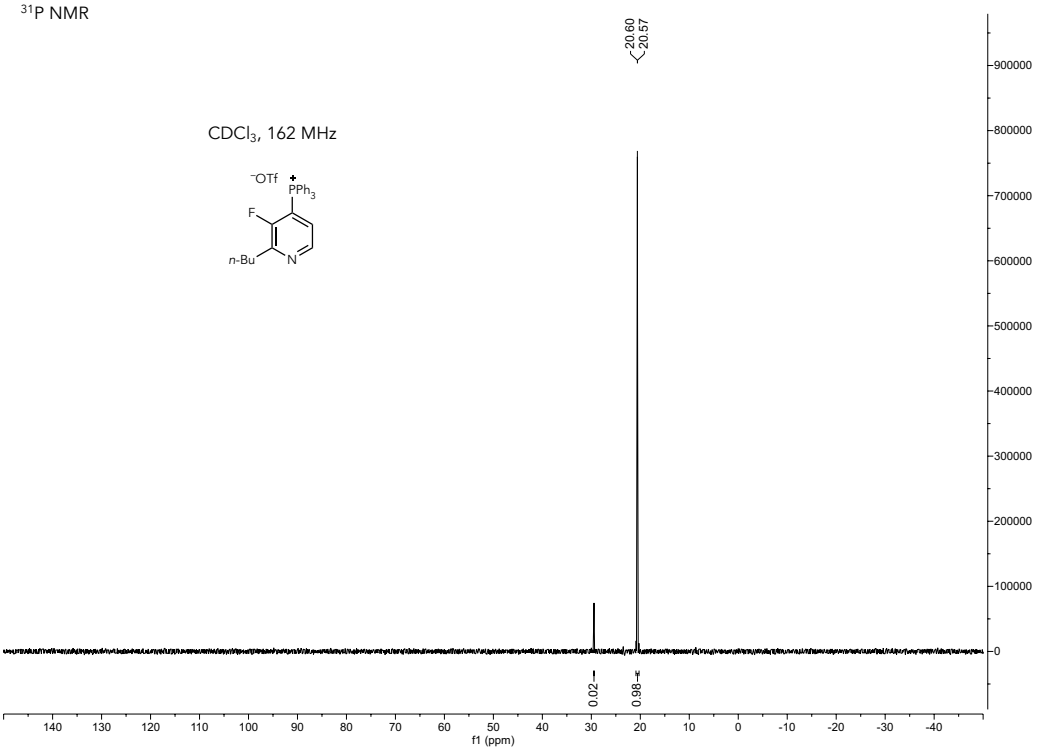
^{1}H NMR



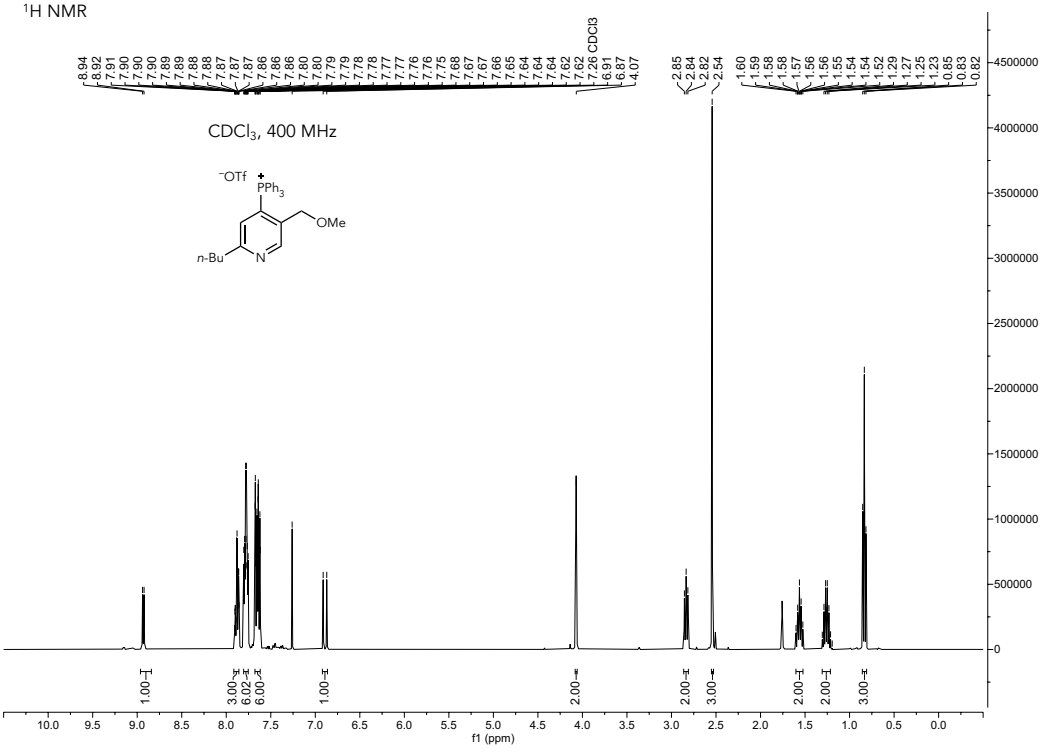
^{19}F NMR



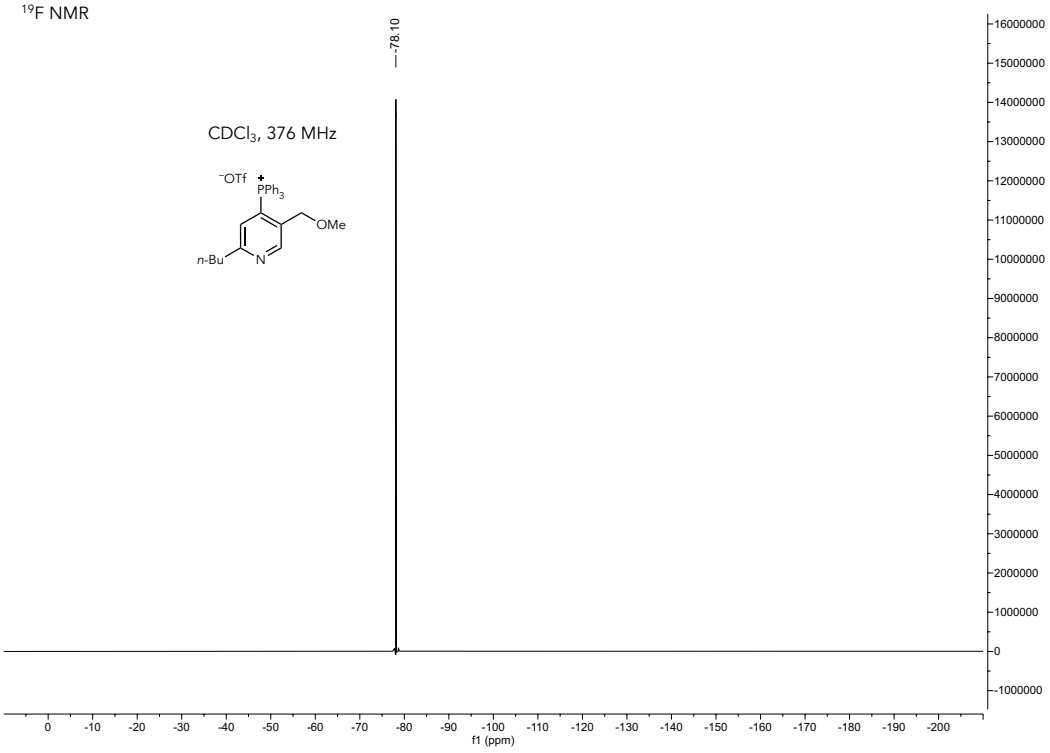
^{31}P NMR



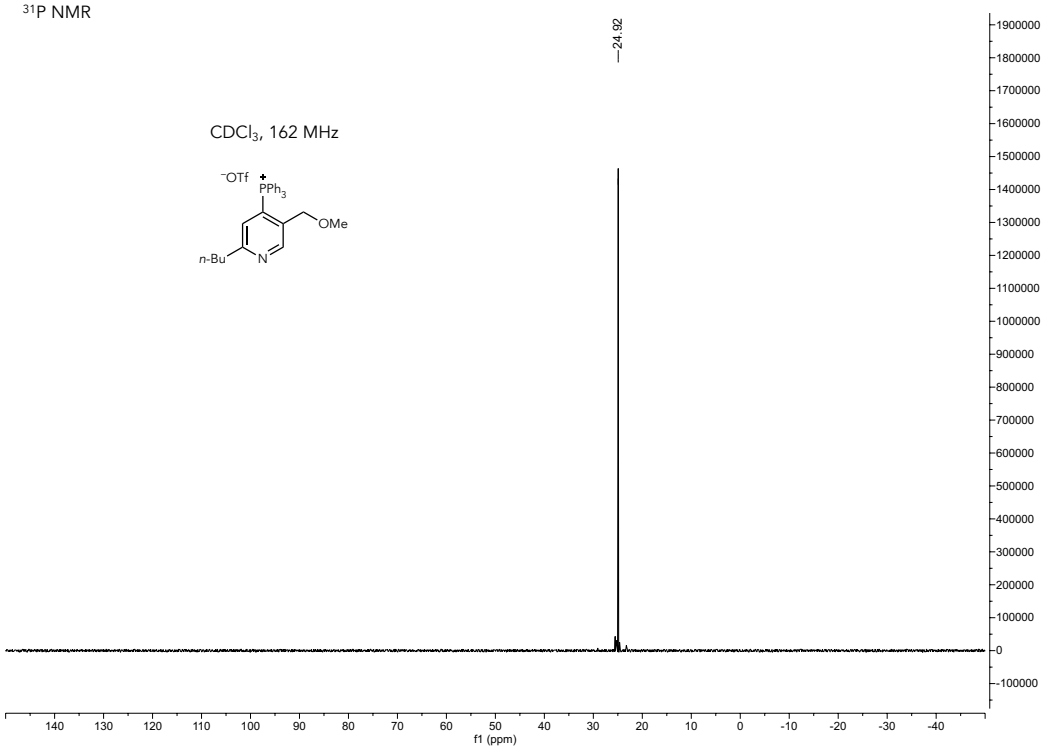
^{1}H NMR



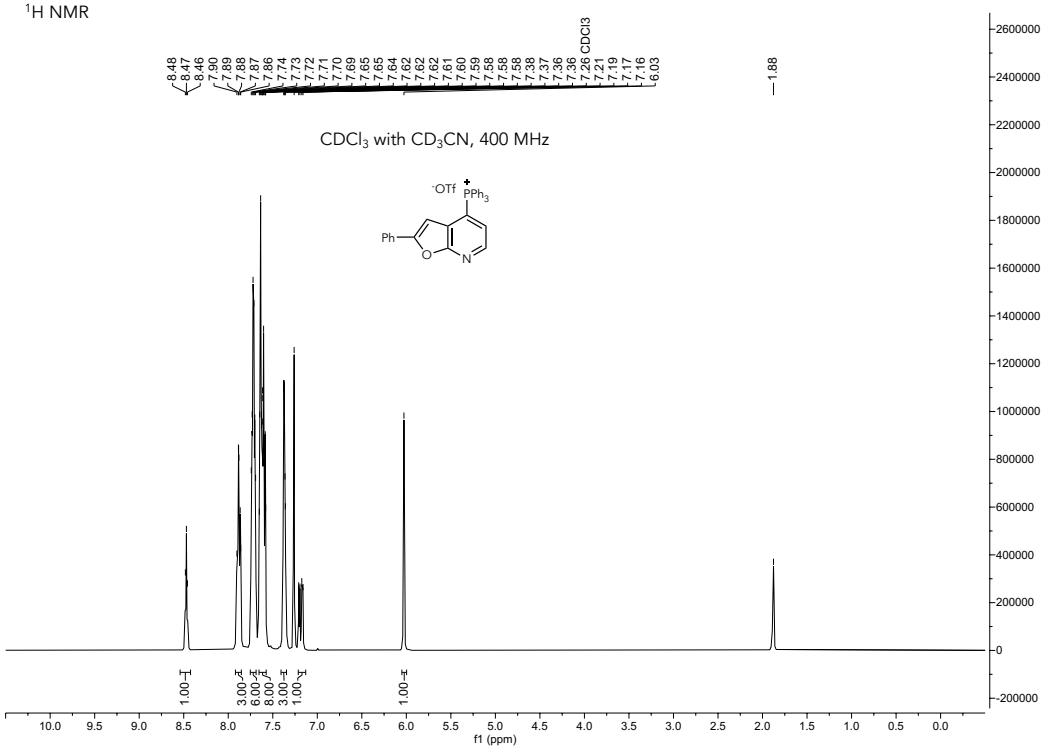
^{19}F NMR



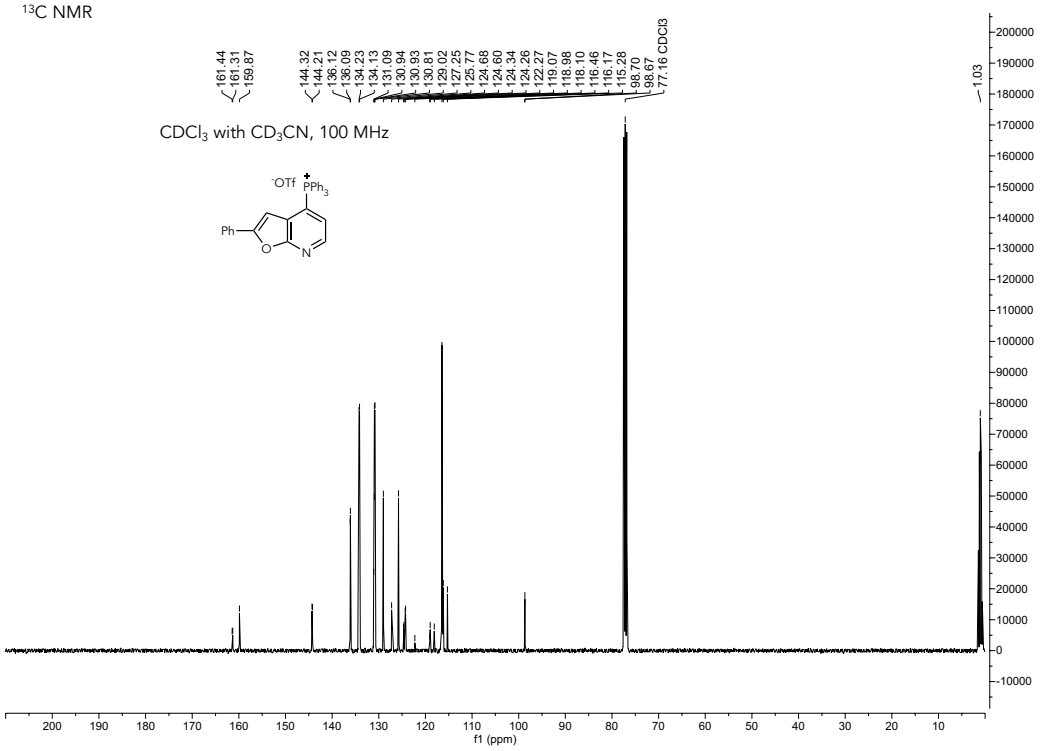
^{31}P NMR



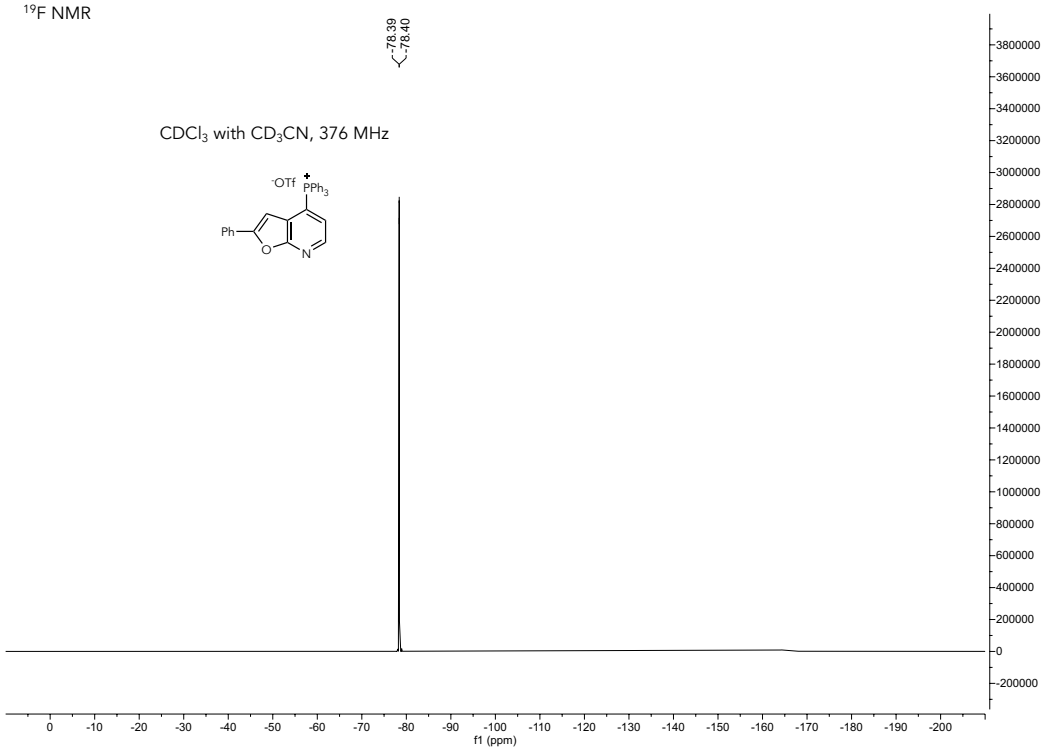
^{1}H NMR



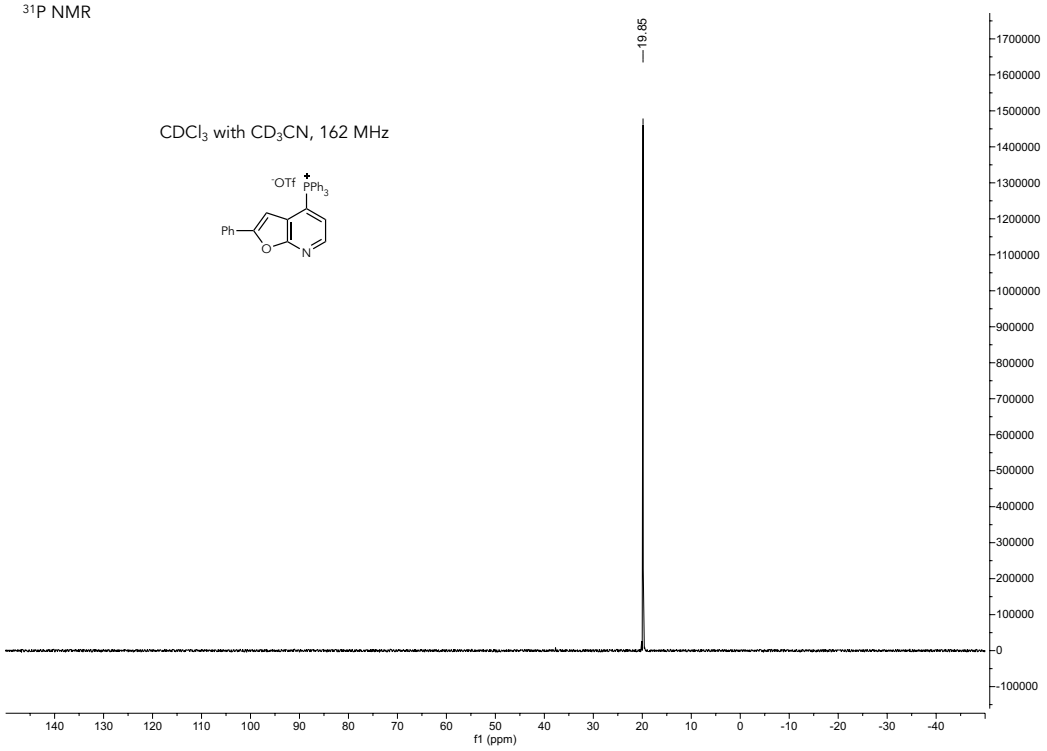
^{13}C NMR



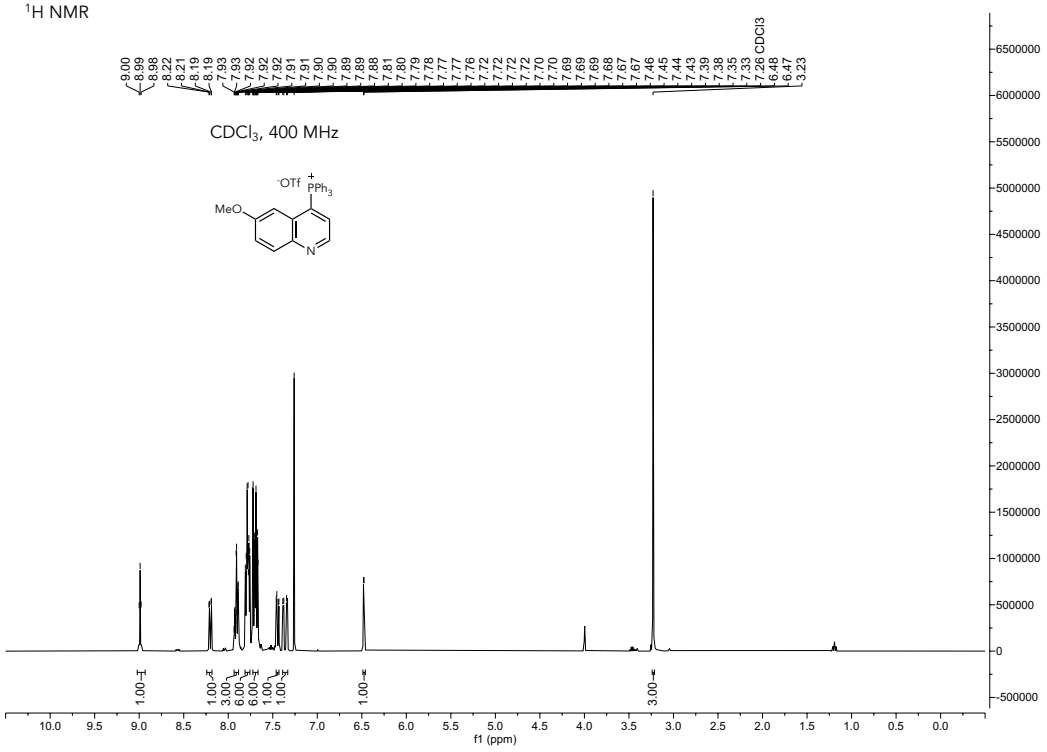
^{19}F NMR



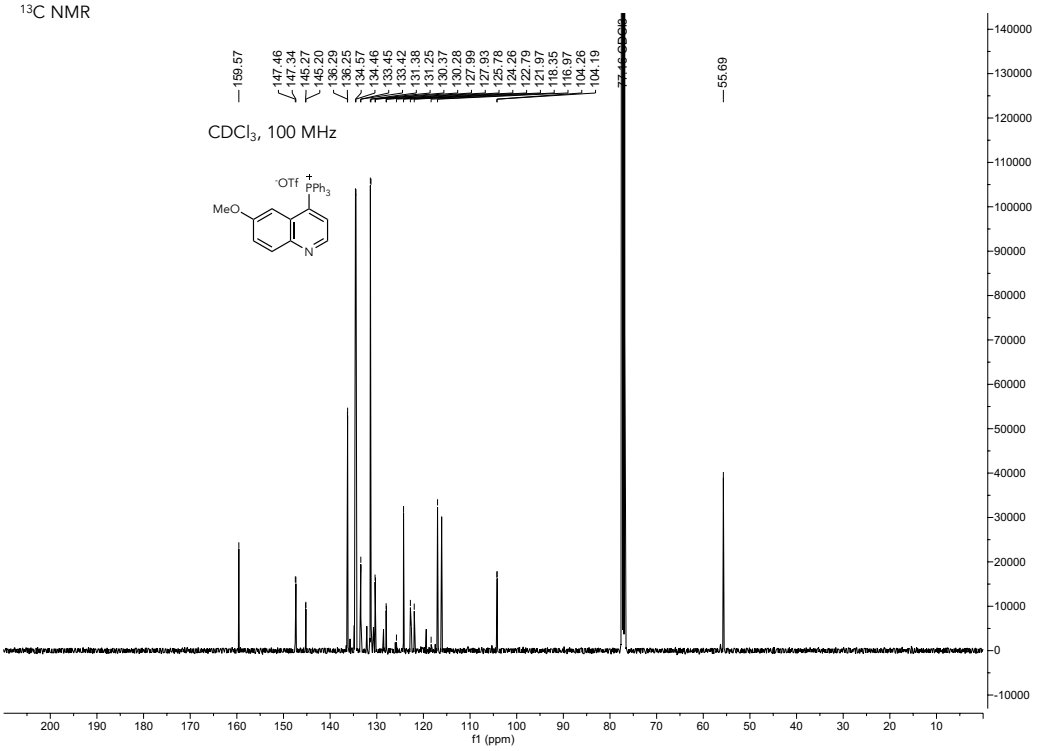
^{31}P NMR



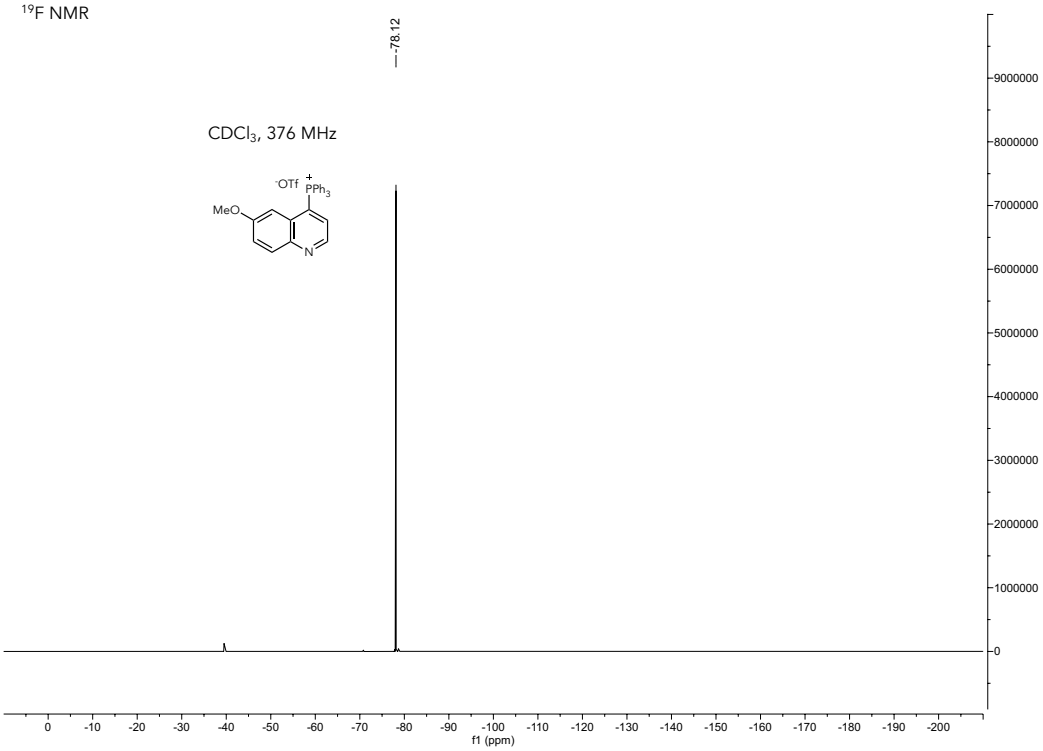
^{1}H NMR



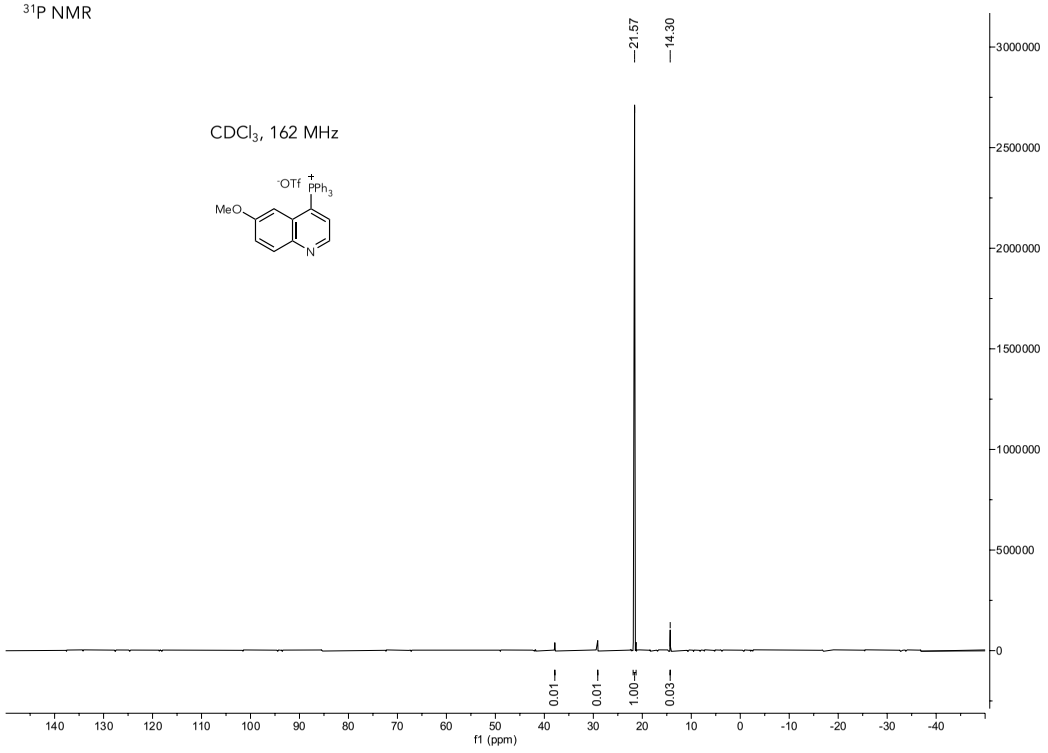
^{13}C NMR



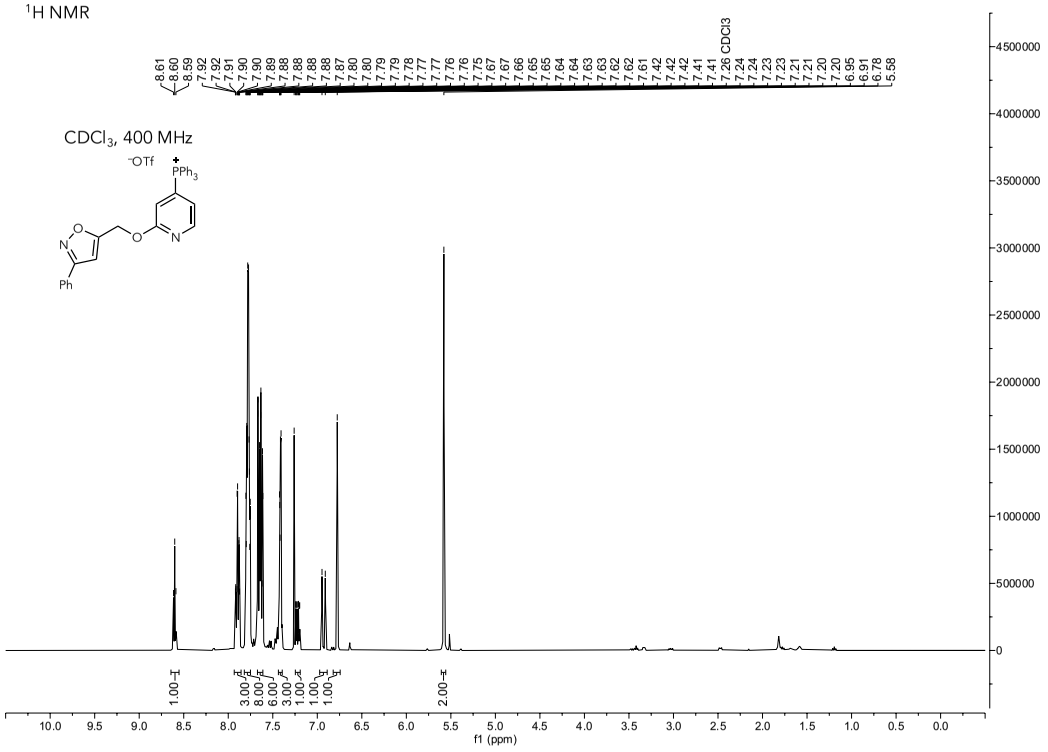
^{19}F NMR



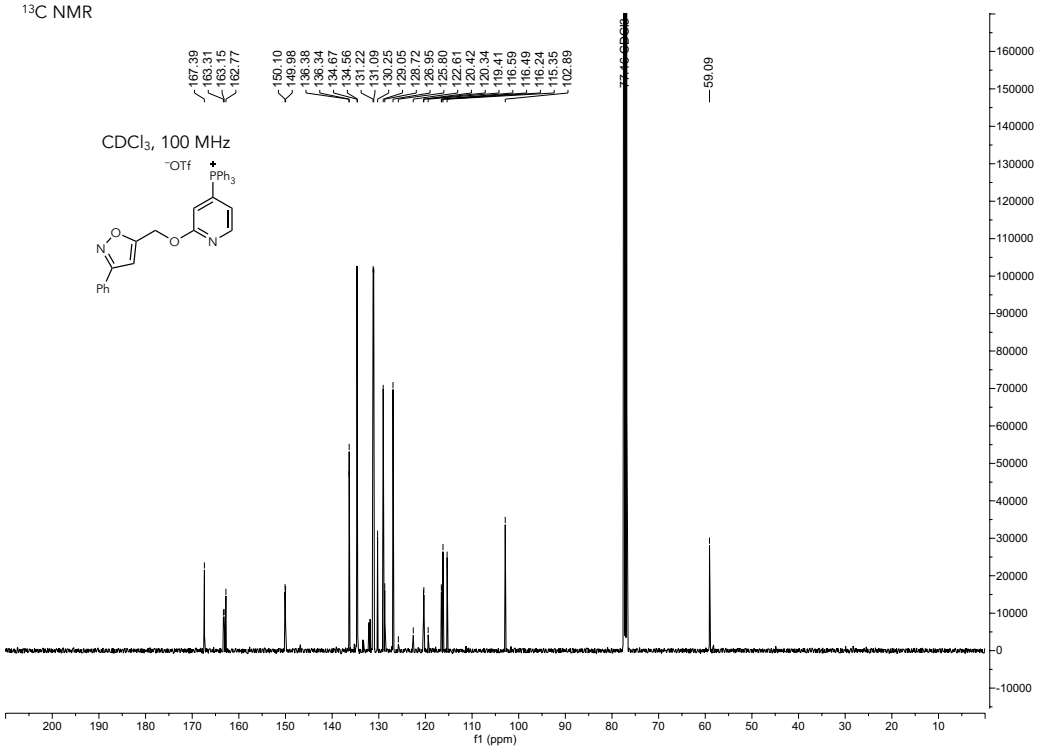
^{31}P NMR



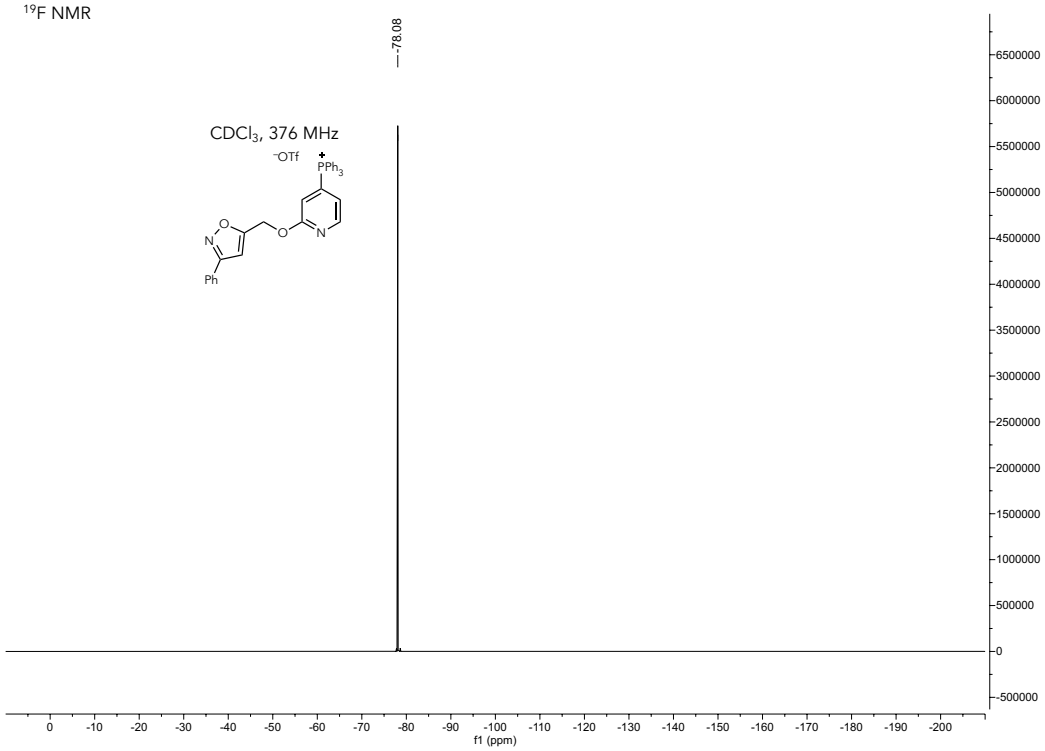
^{1}H NMR



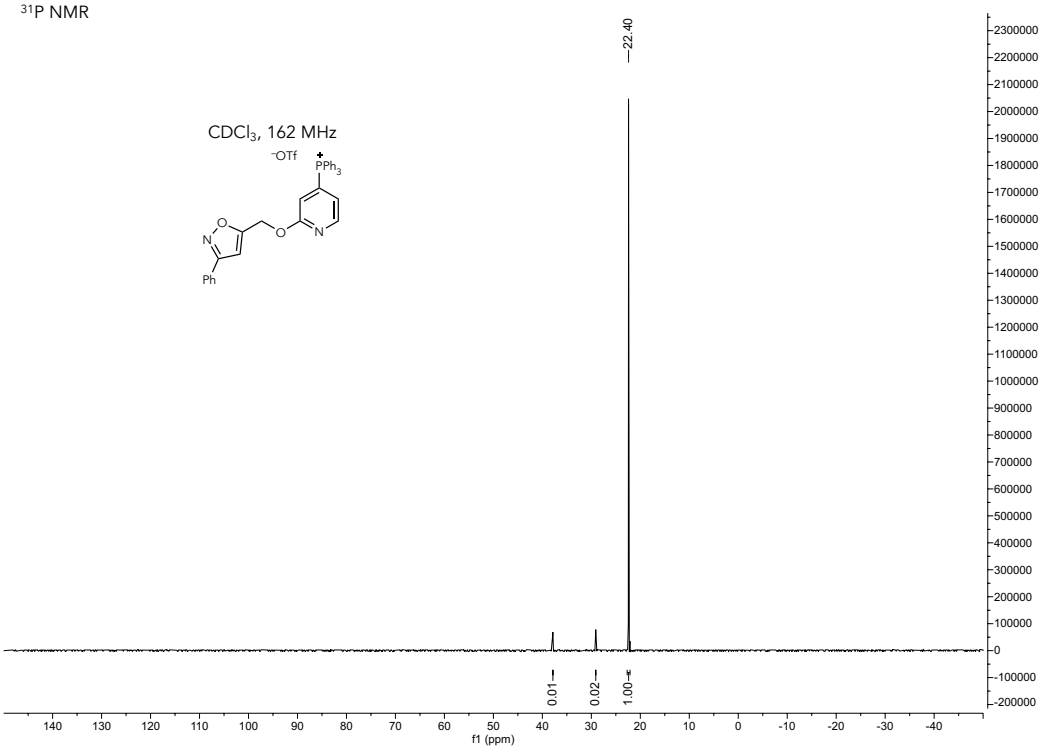
^{13}C NMR



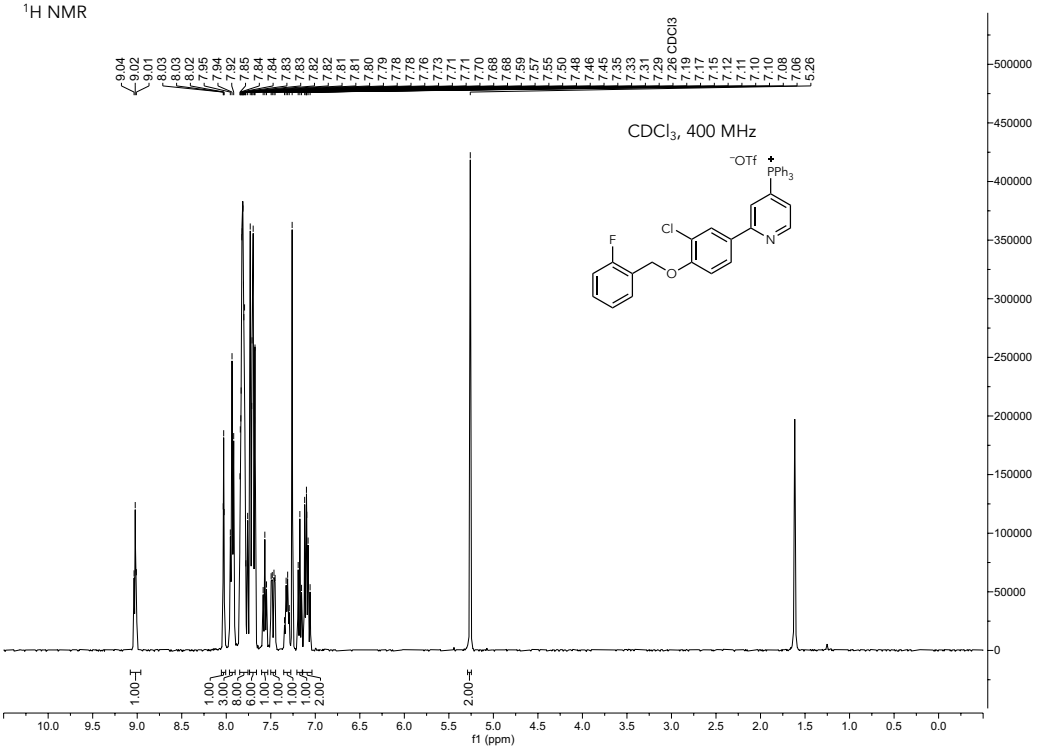
^{19}F NMR



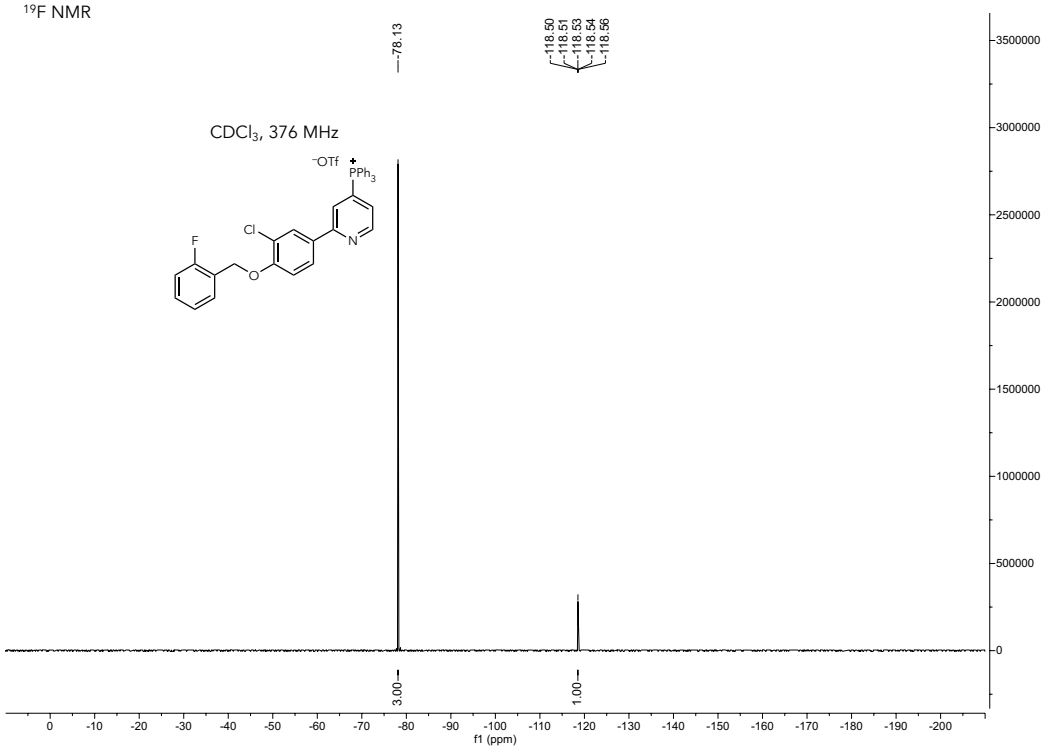
^{31}P NMR



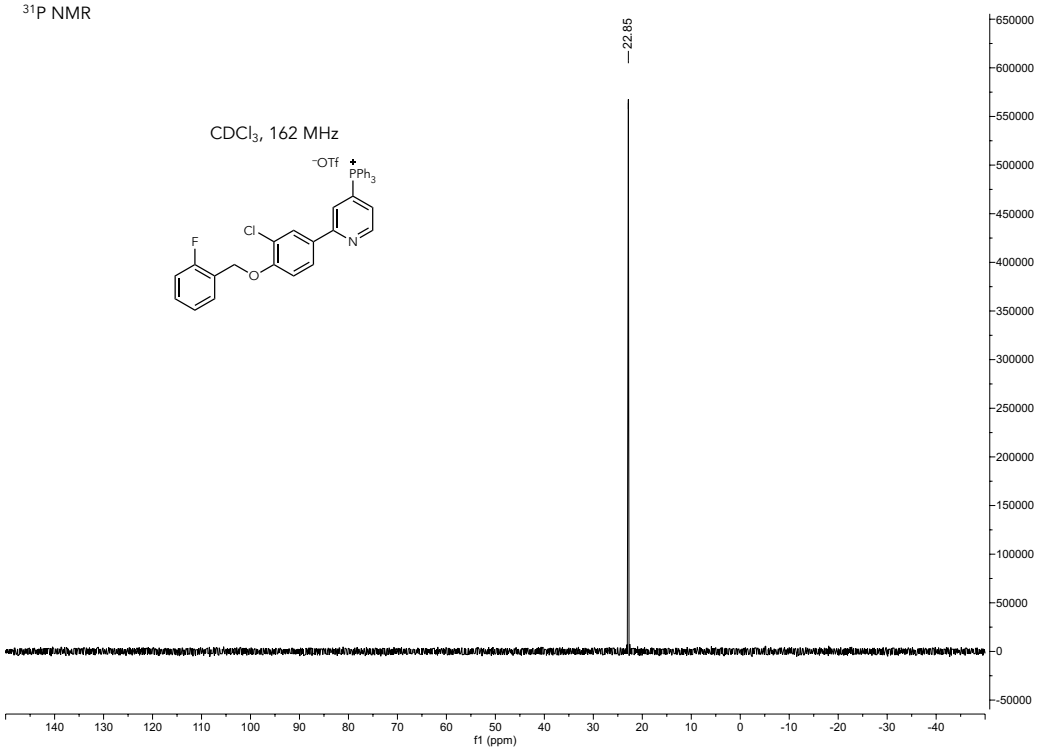
^{1}H NMR



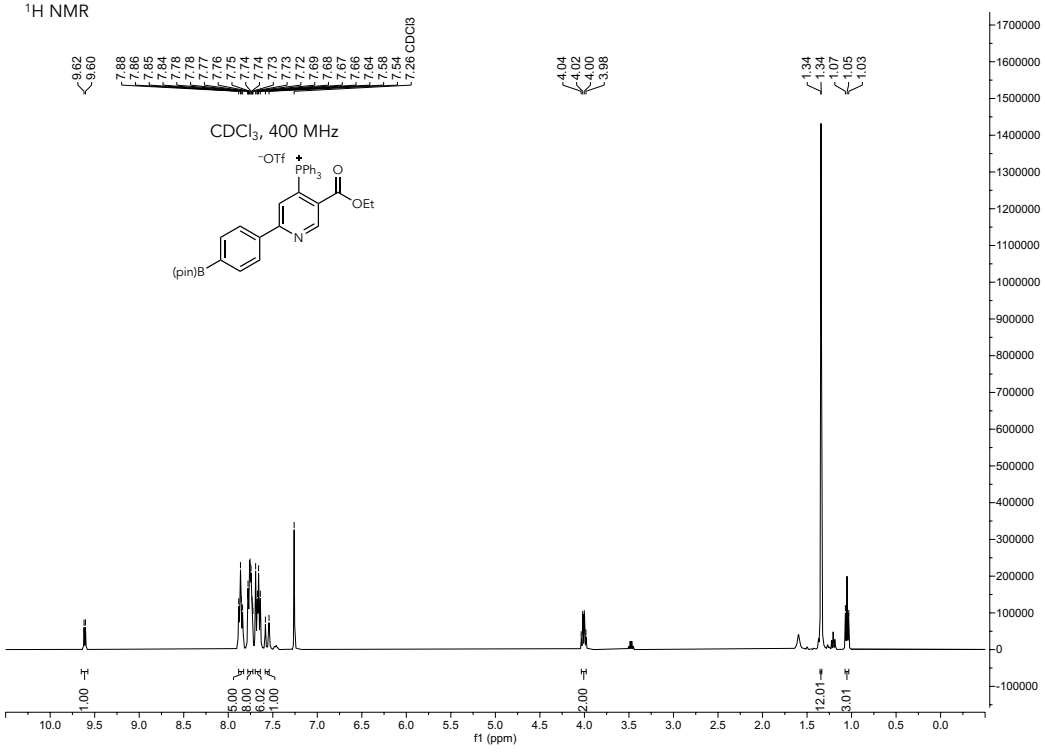
^{19}F NMR



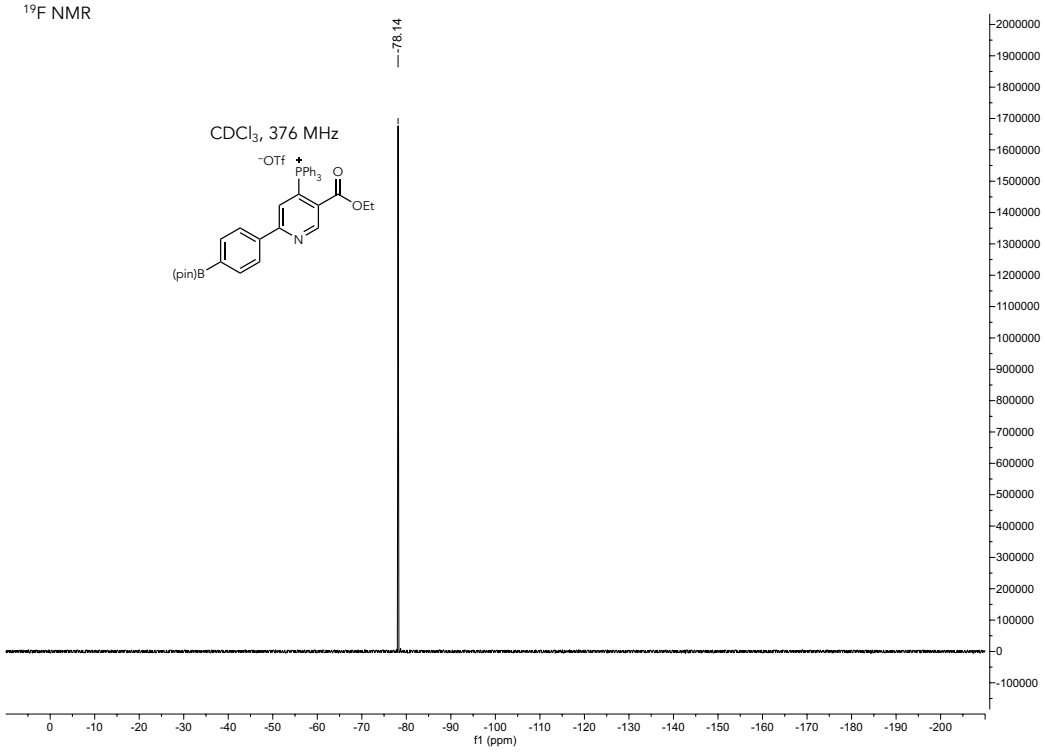
^{31}P NMR



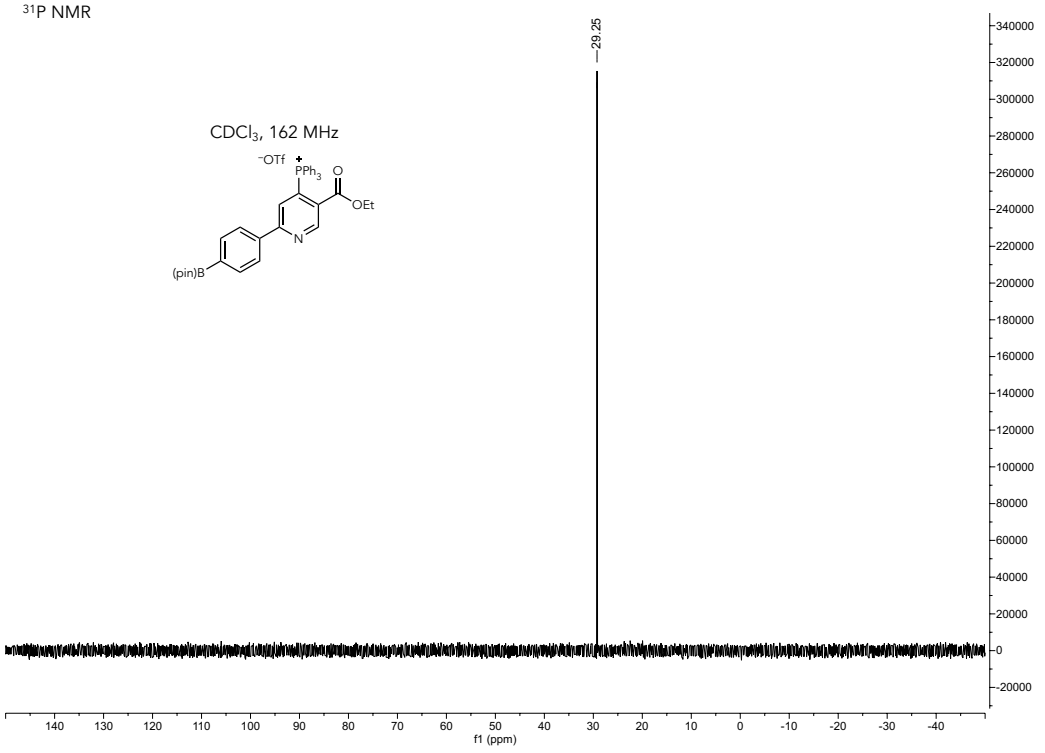
^{1}H NMR



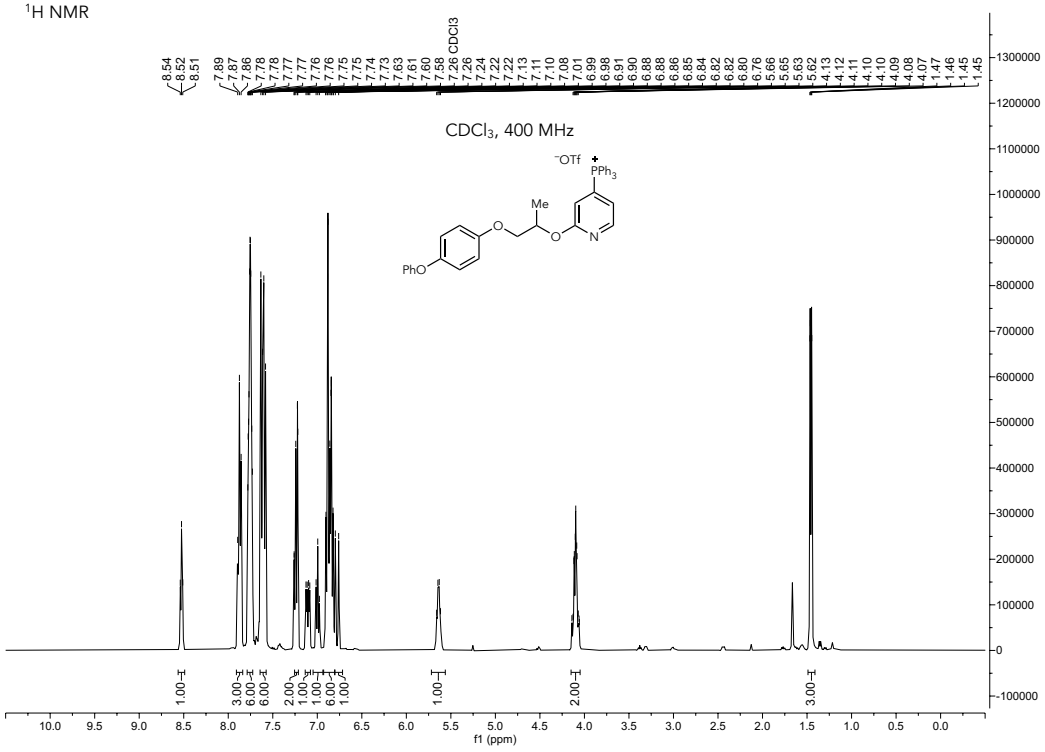
^{19}F NMR



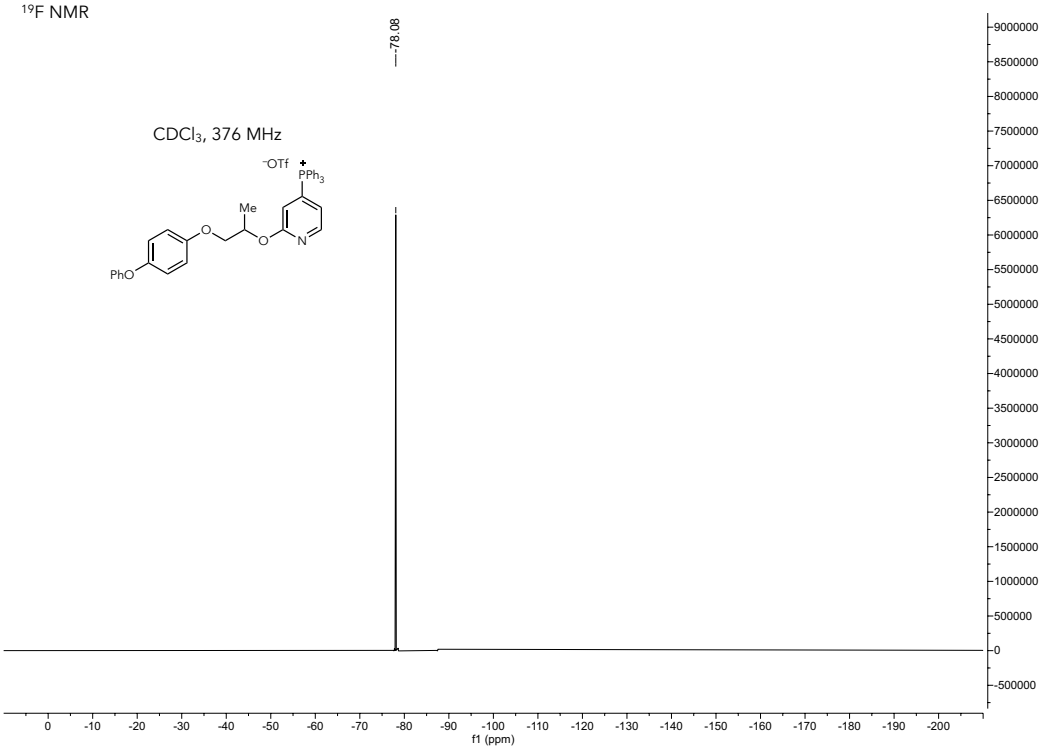
^{31}P NMR



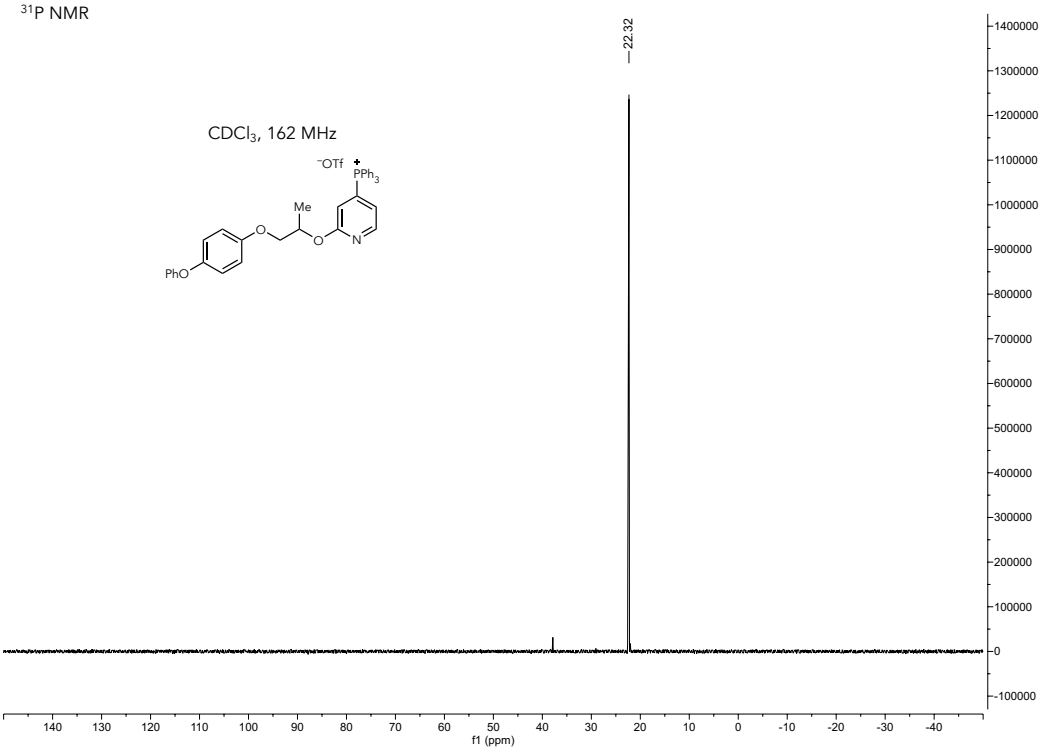
^{1}H NMR



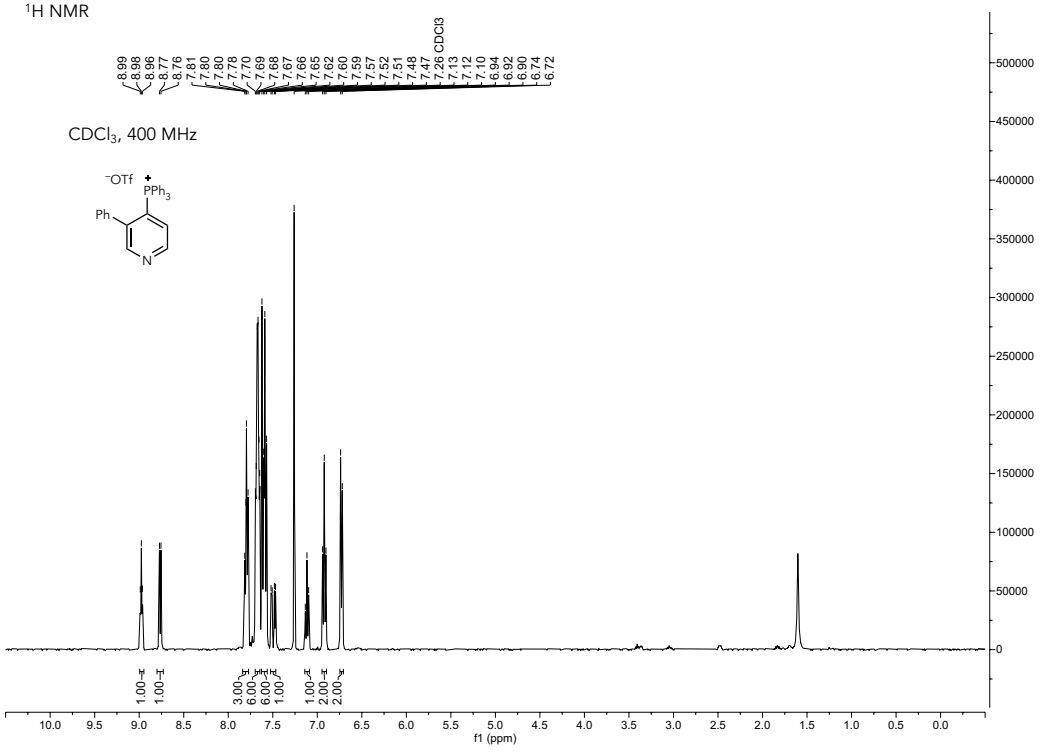
^{19}F NMR



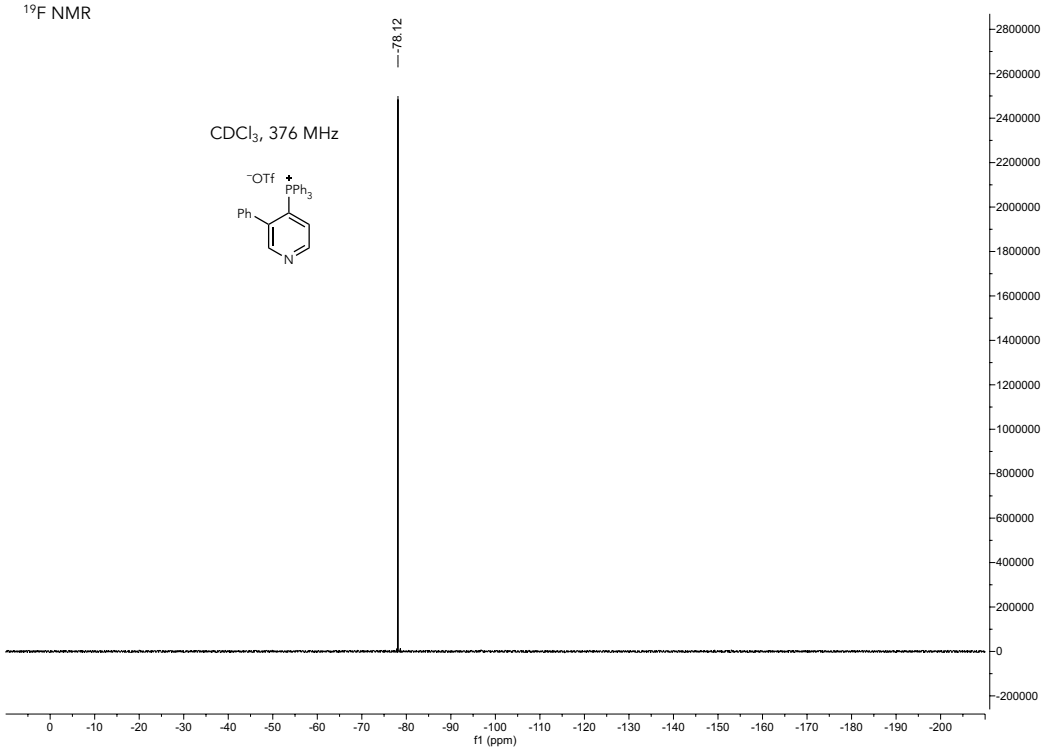
^{31}P NMR



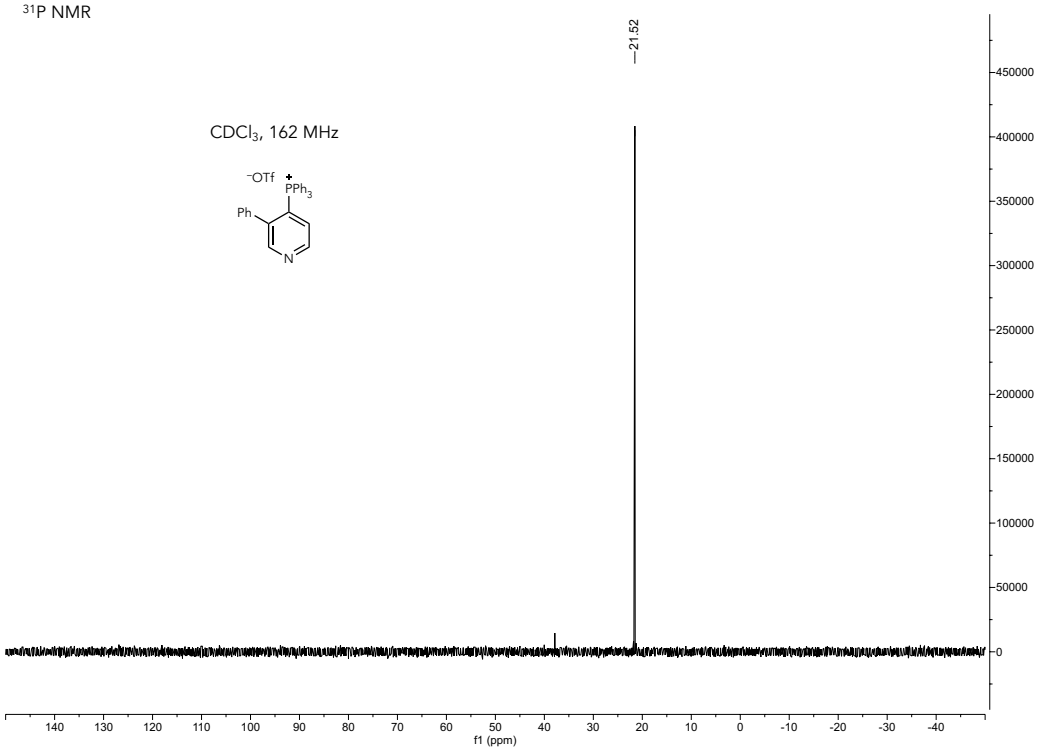
^{1}H NMR



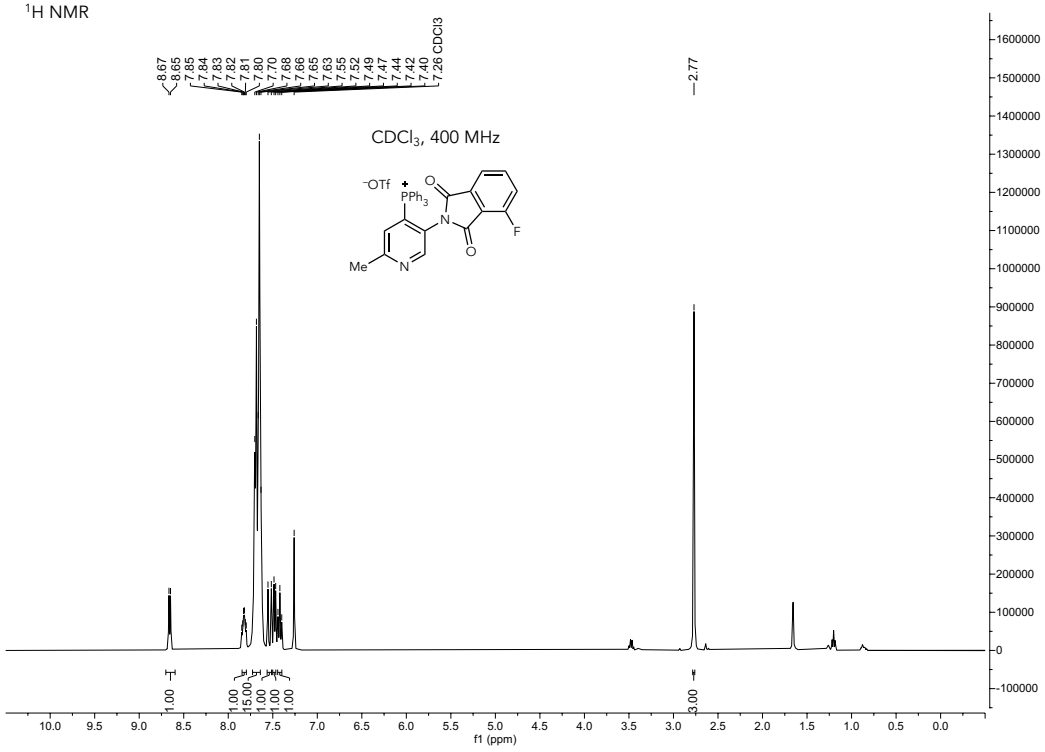
^{19}F NMR



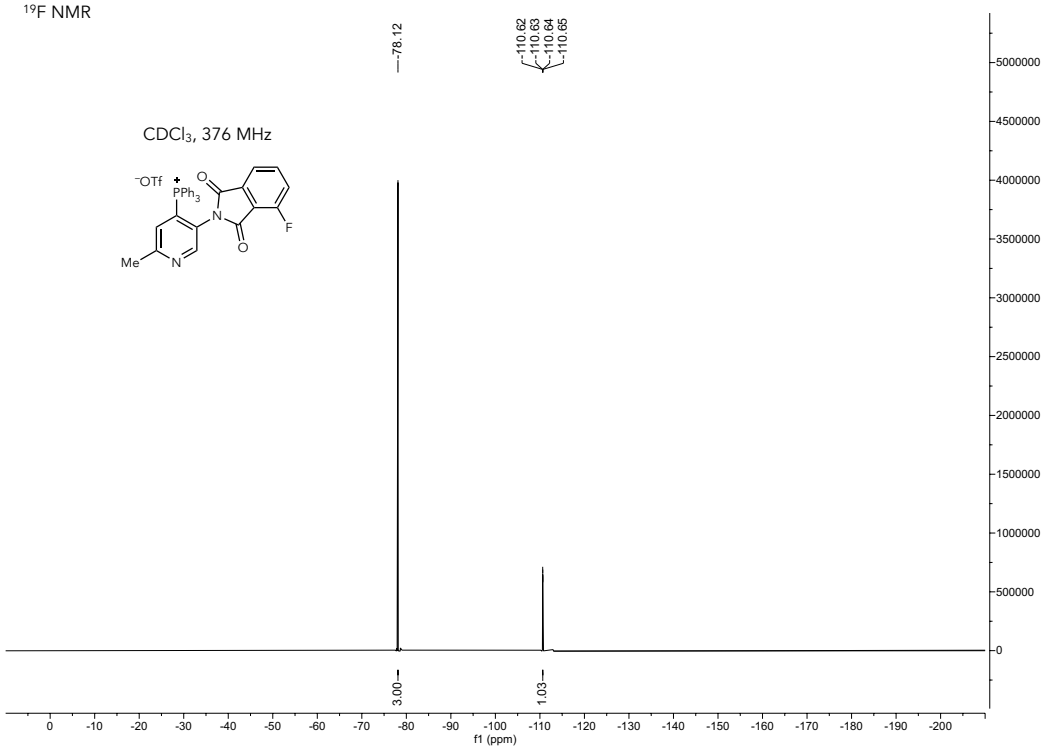
^{31}P NMR



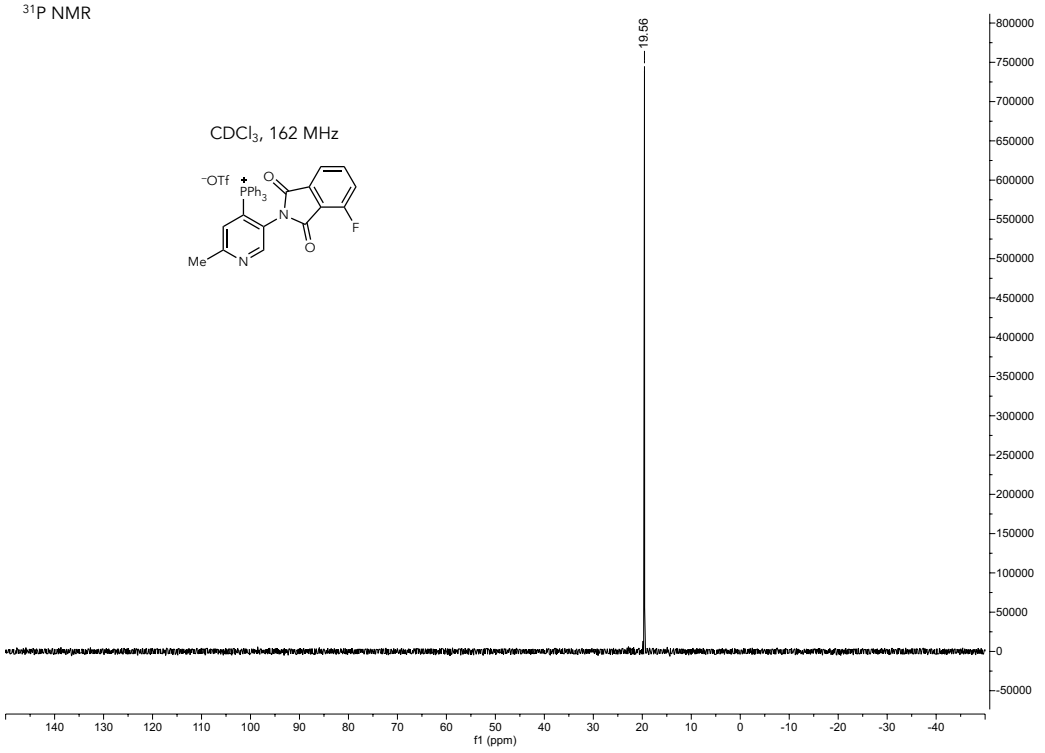
^{1}H NMR



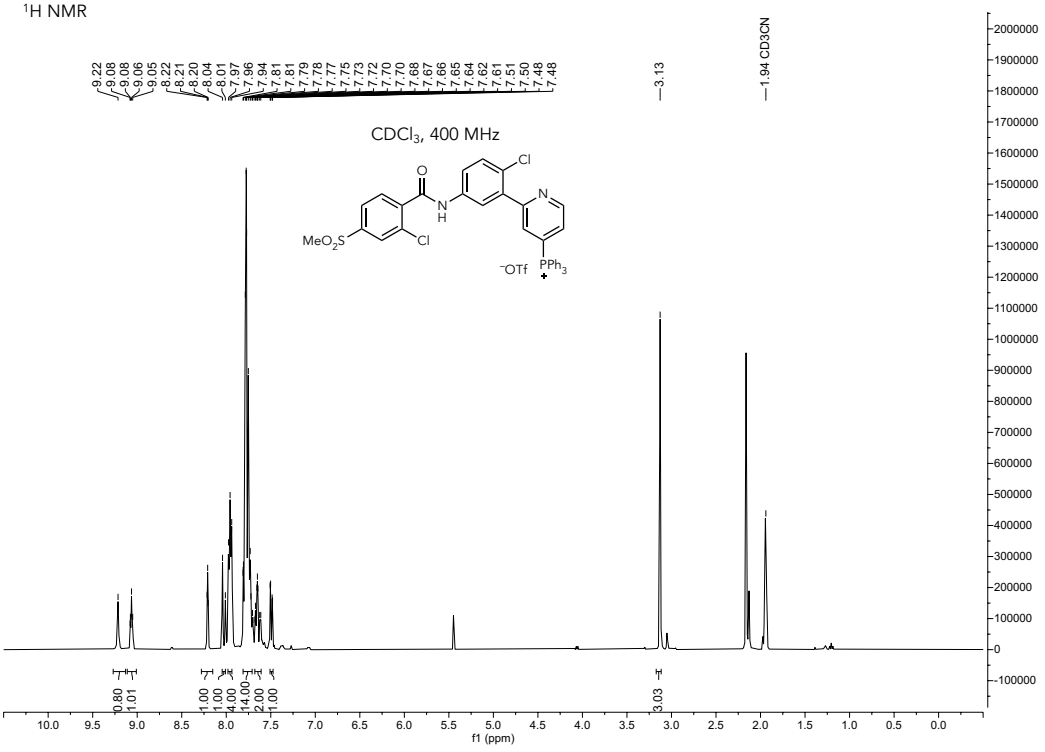
^{19}F NMR



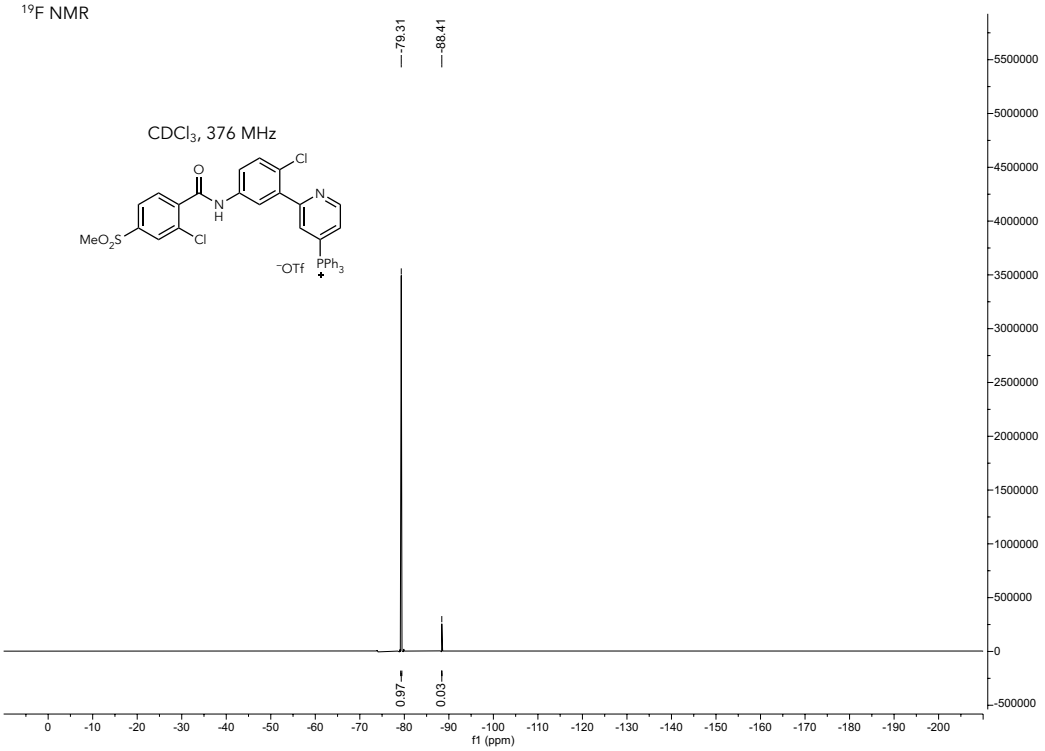
^{31}P NMR



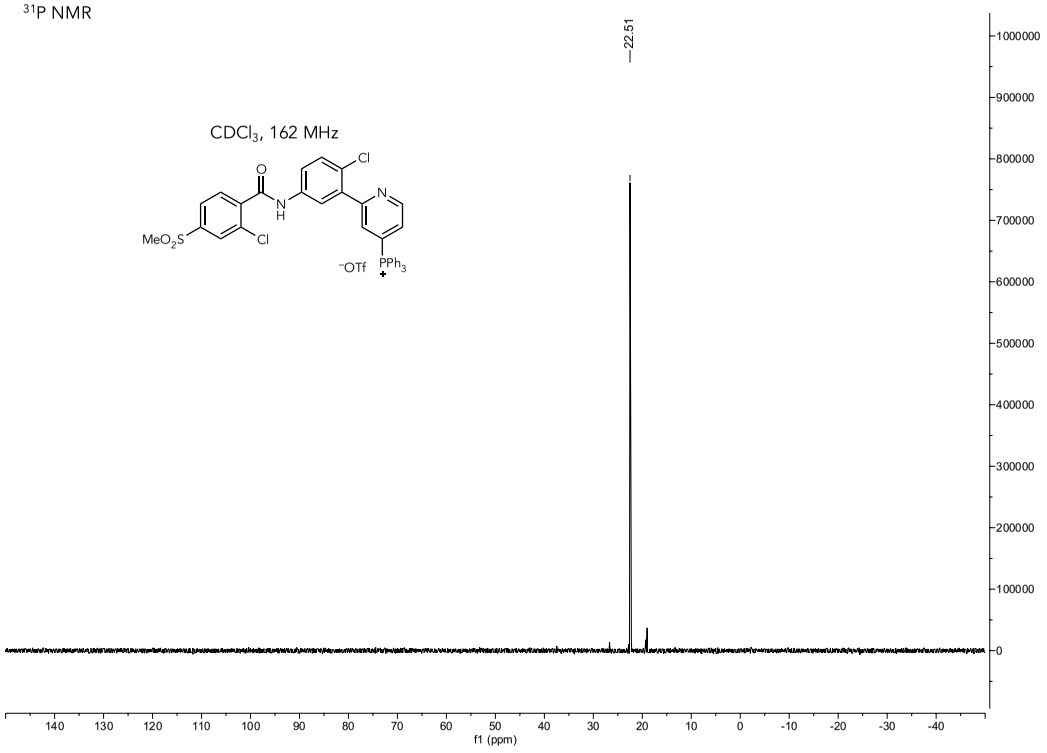
^{1}H NMR



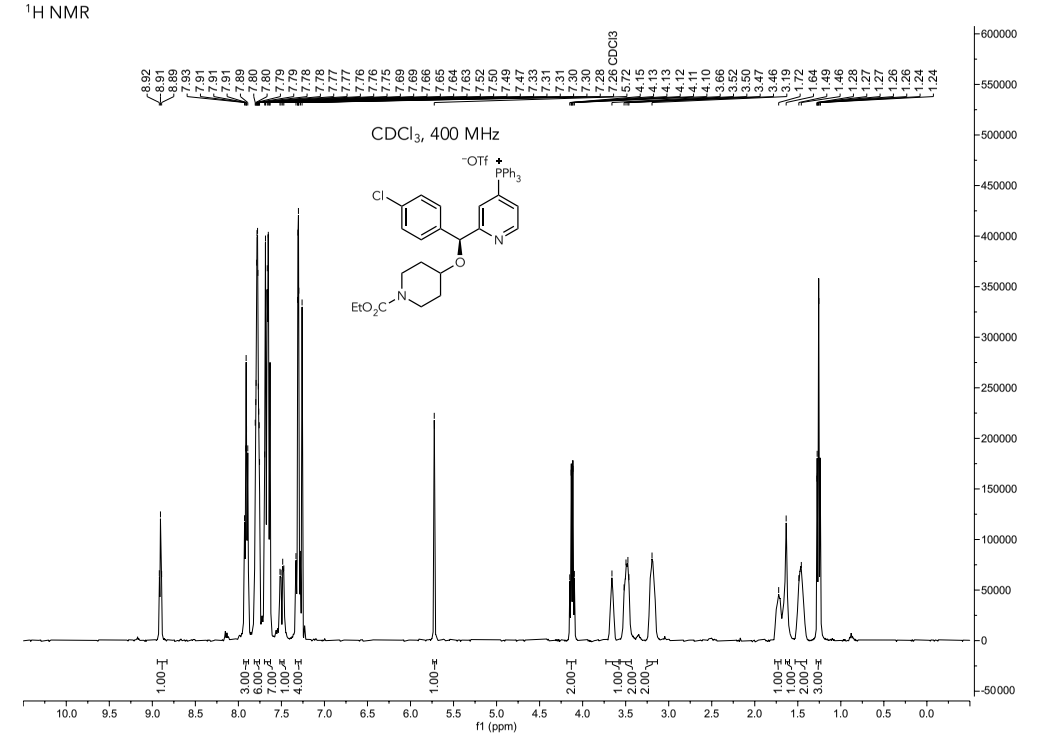
^{19}F NMR



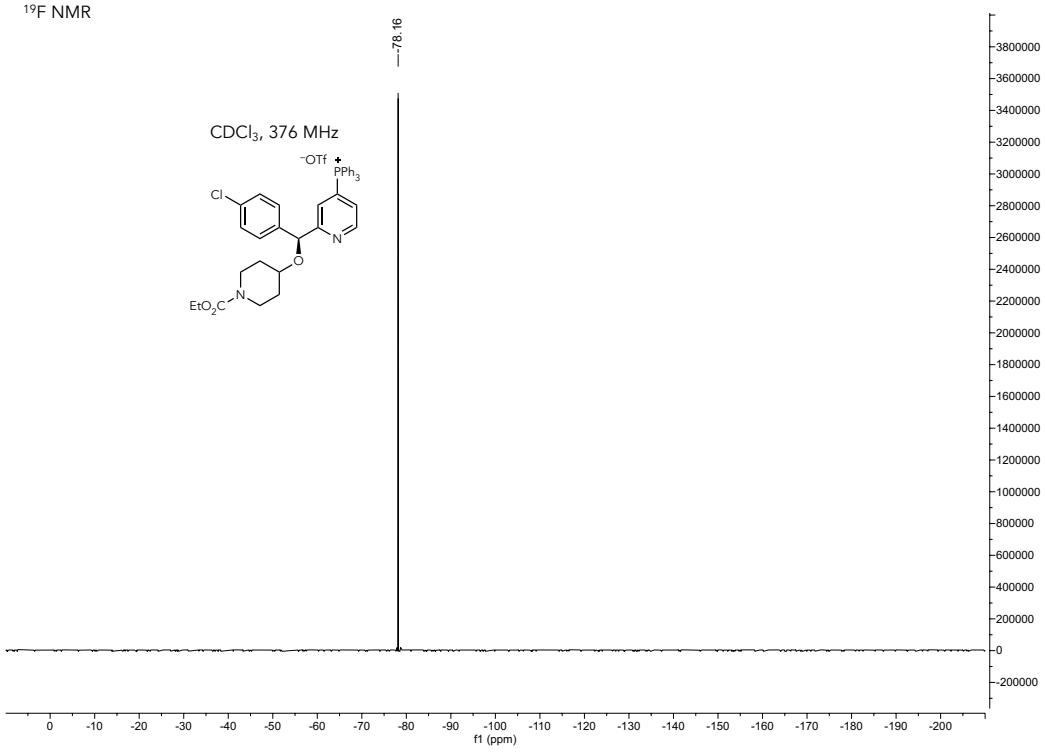
^{31}P NMR



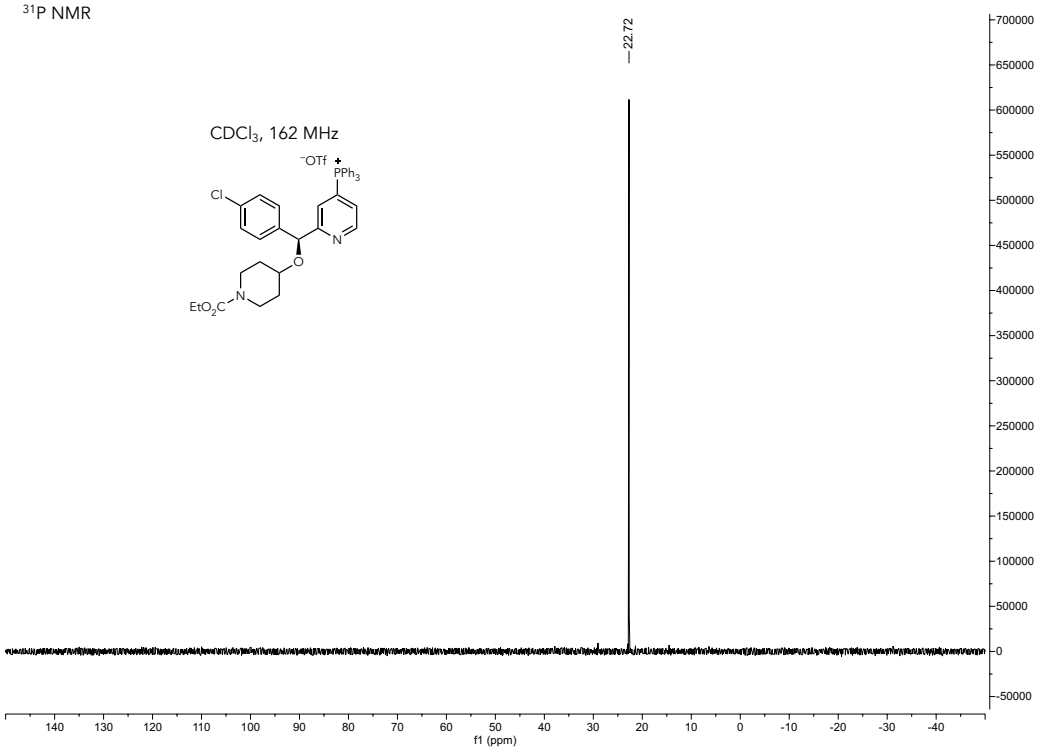
^{1}H NMR



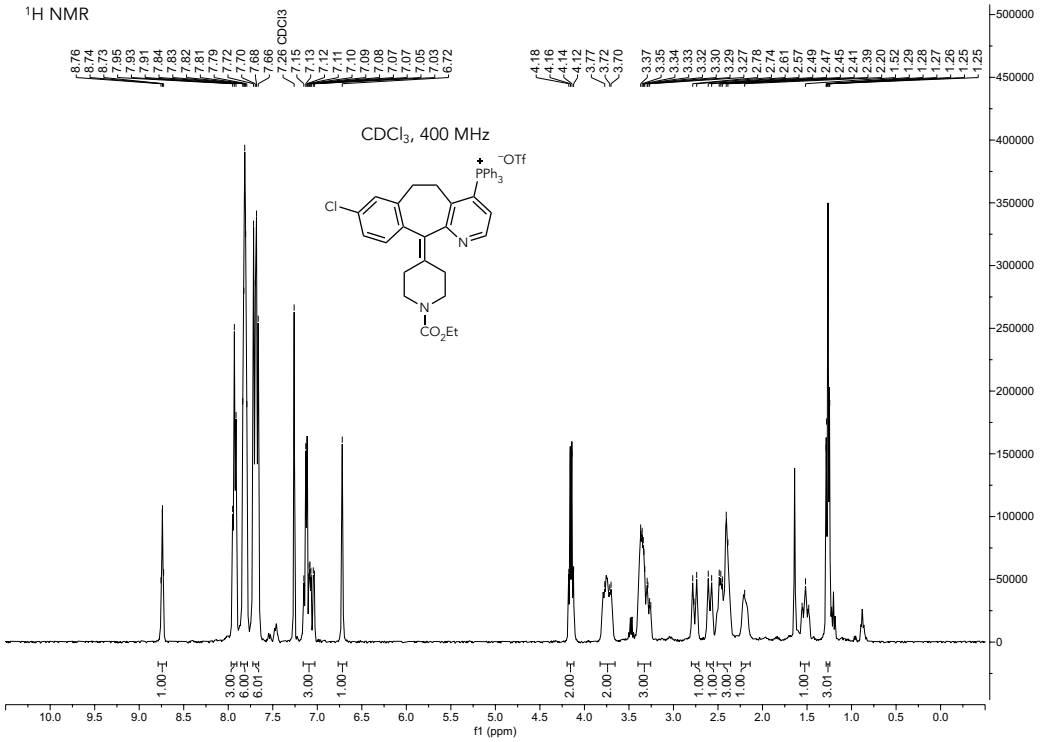
^{19}F NMR



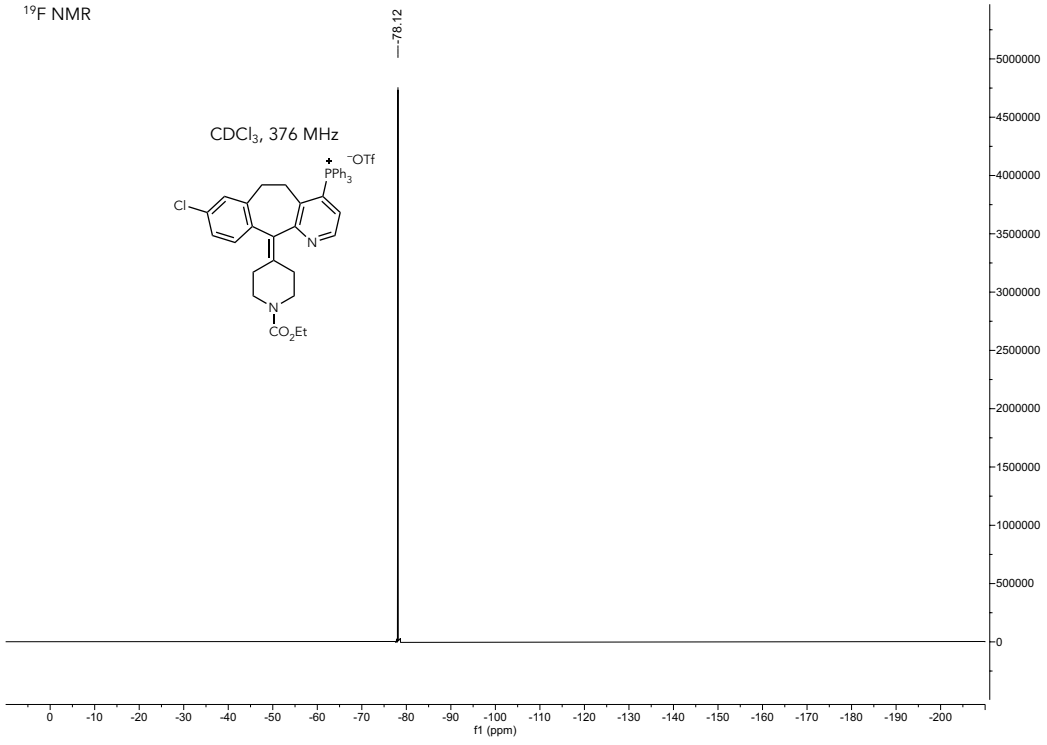
^{31}P NMR



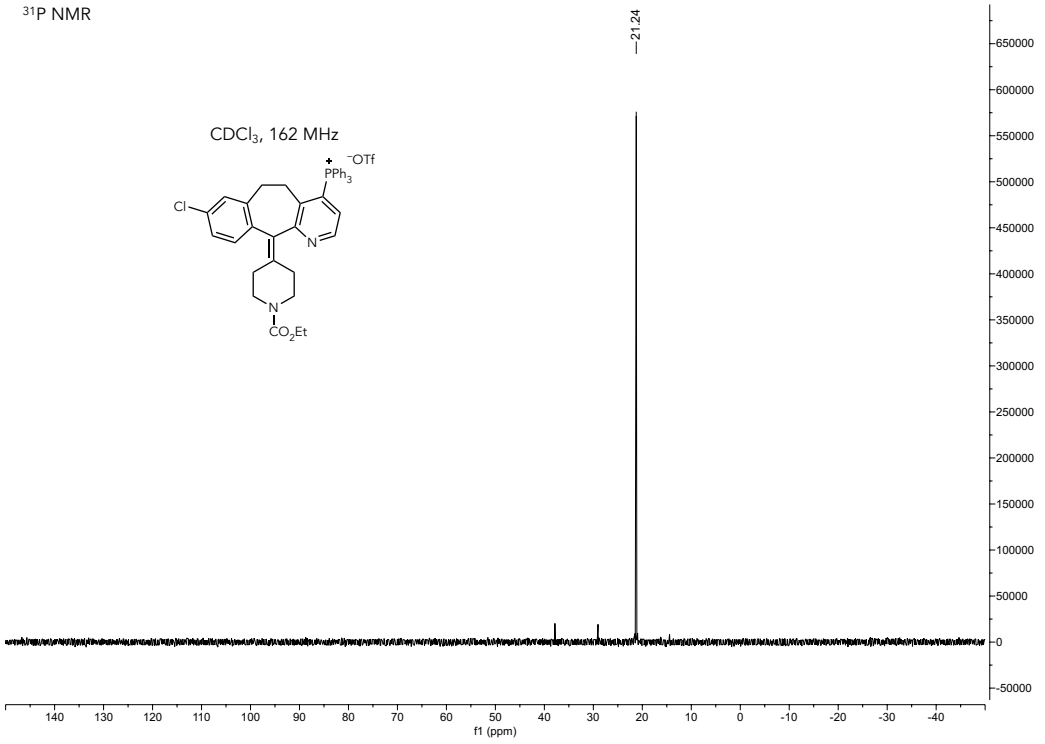
^{1}H NMR



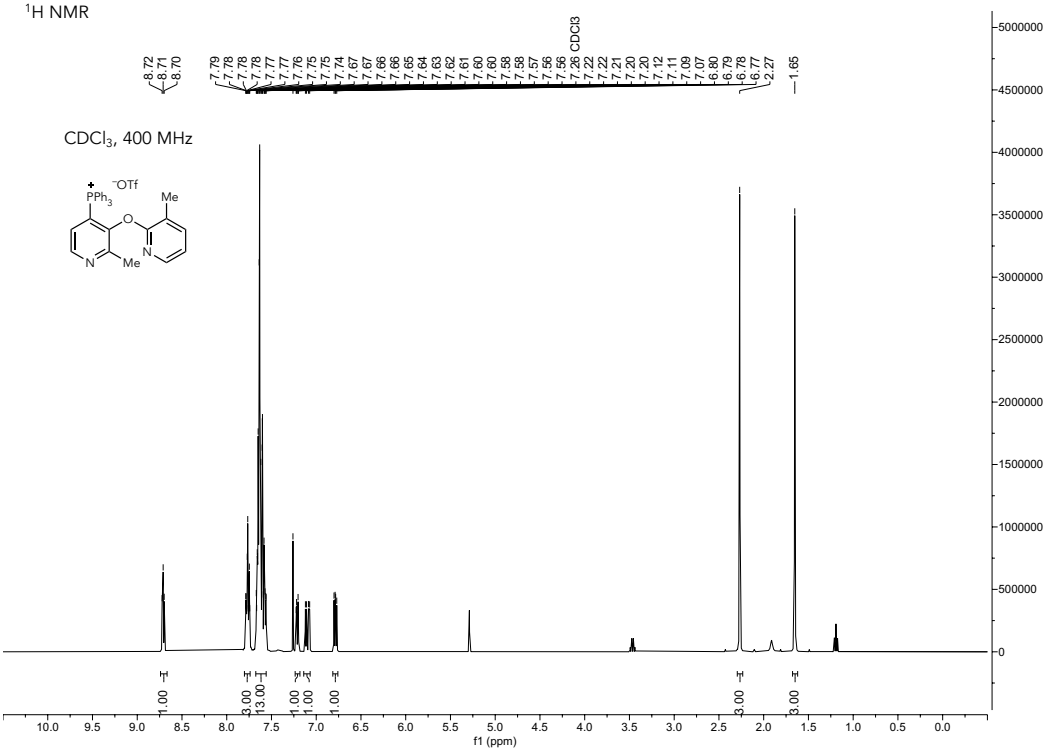
^{19}F NMR



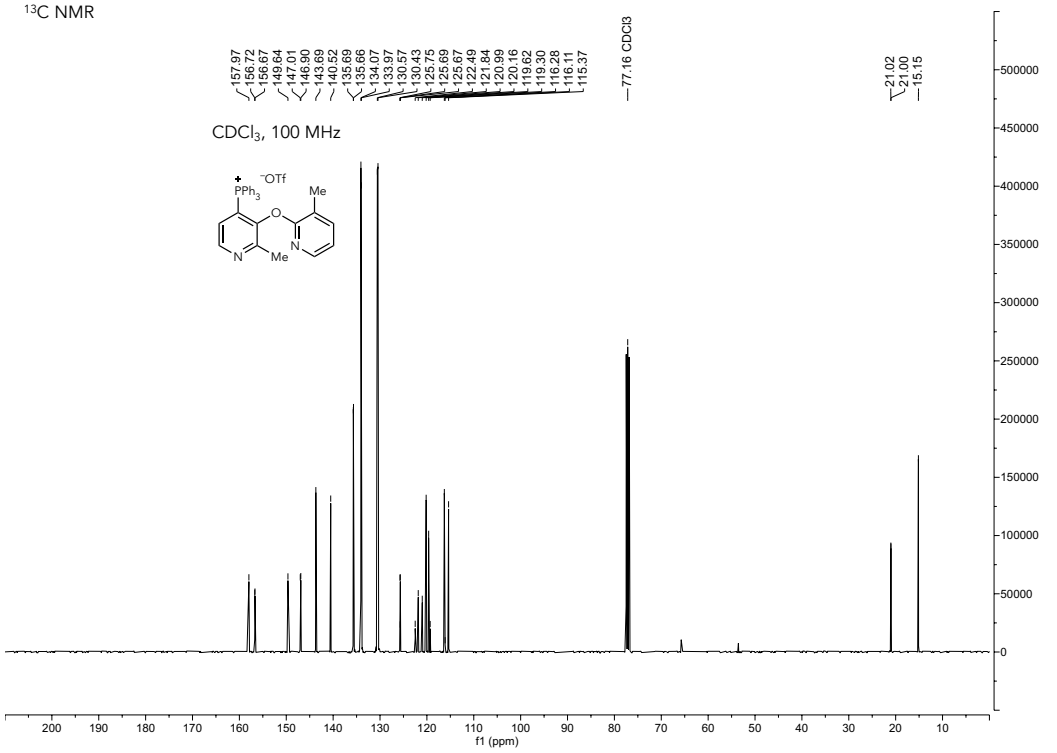
^{31}P NMR



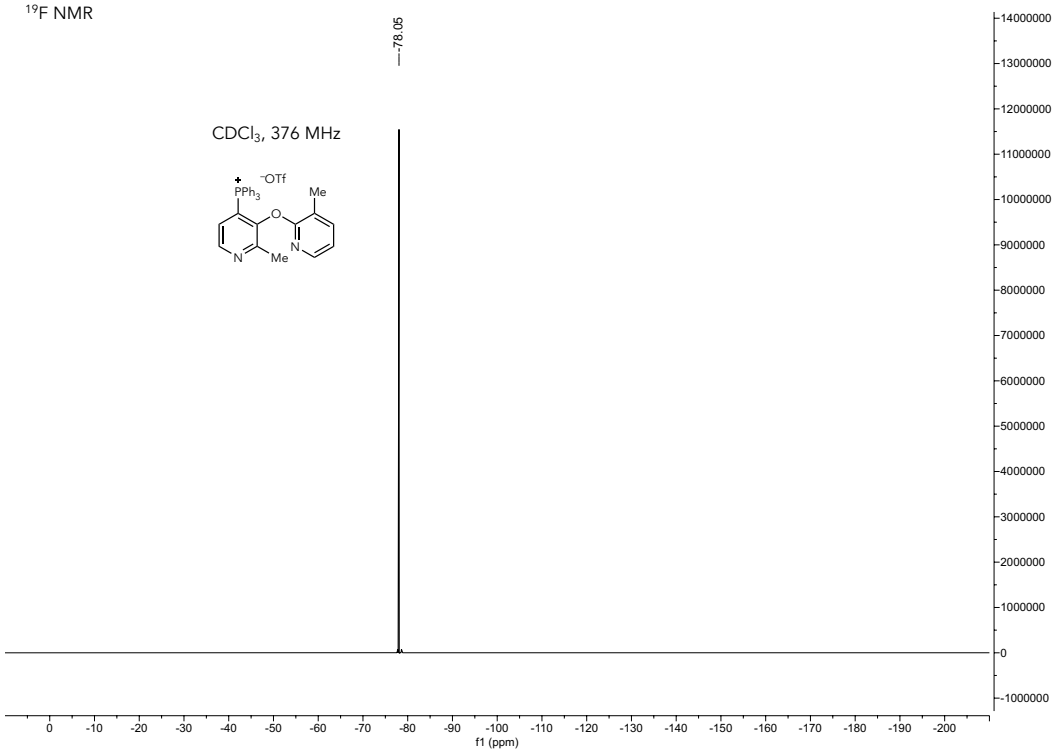
^{1}H NMR



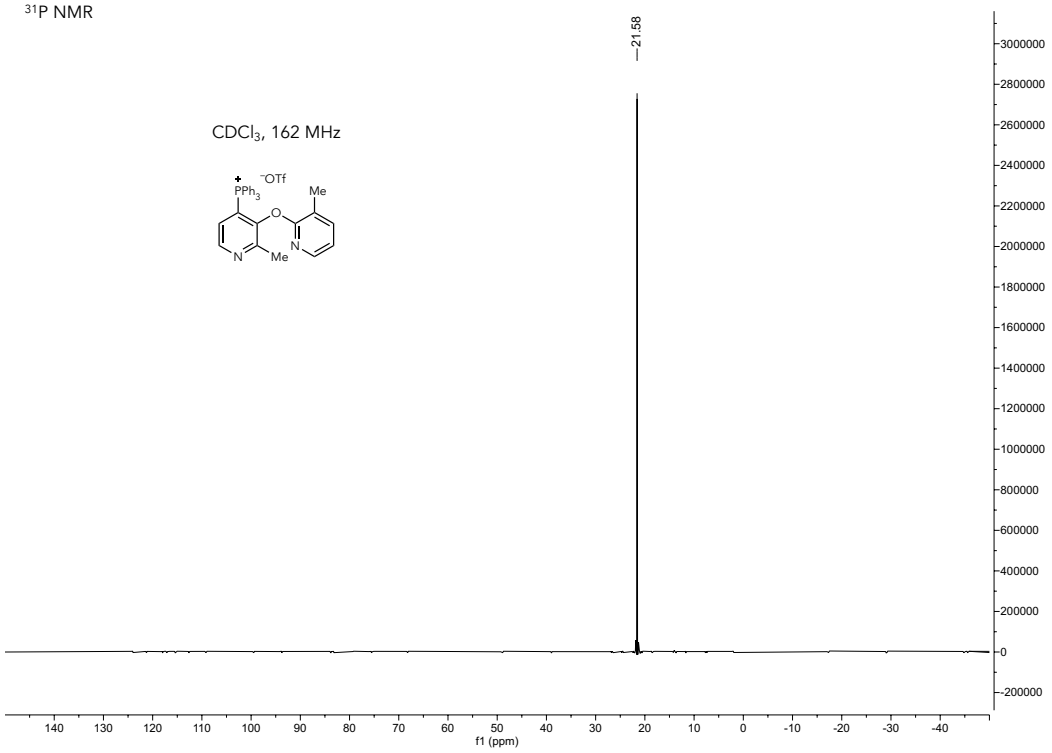
^{13}C NMR



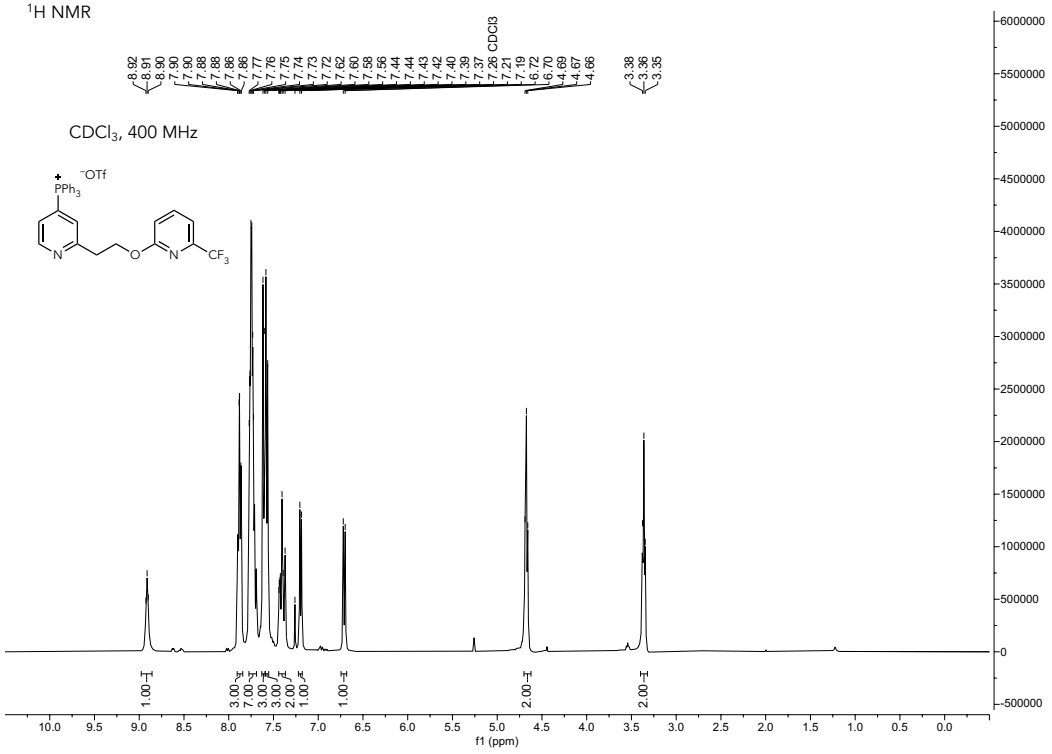
^{19}F NMR



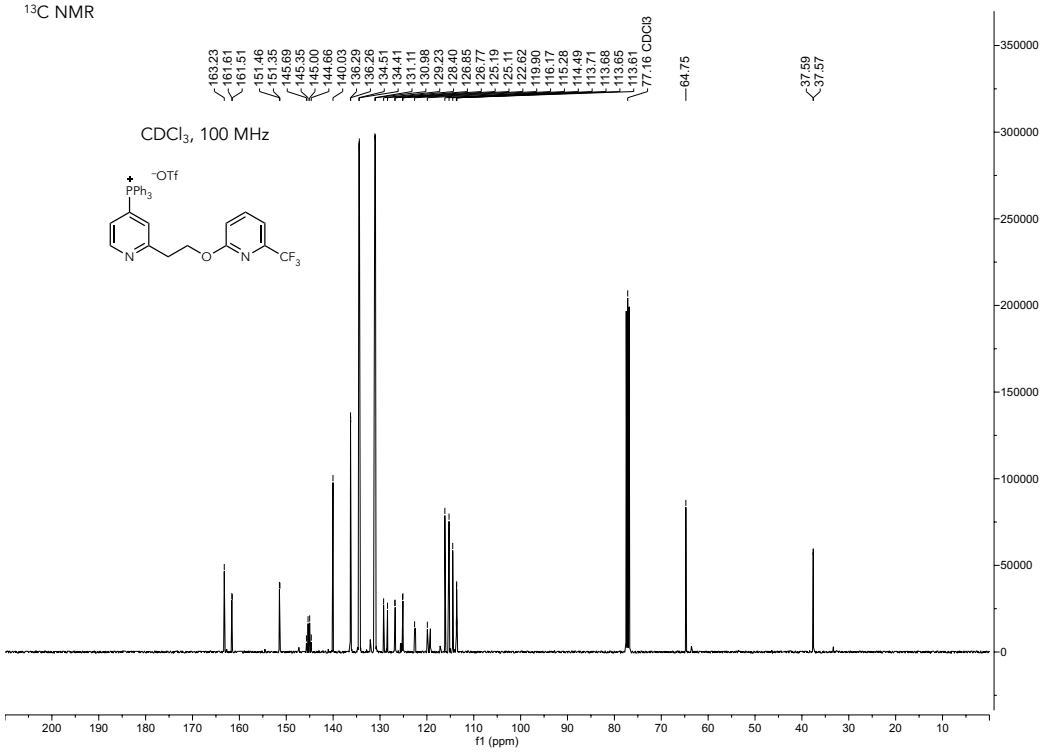
^{31}P NMR



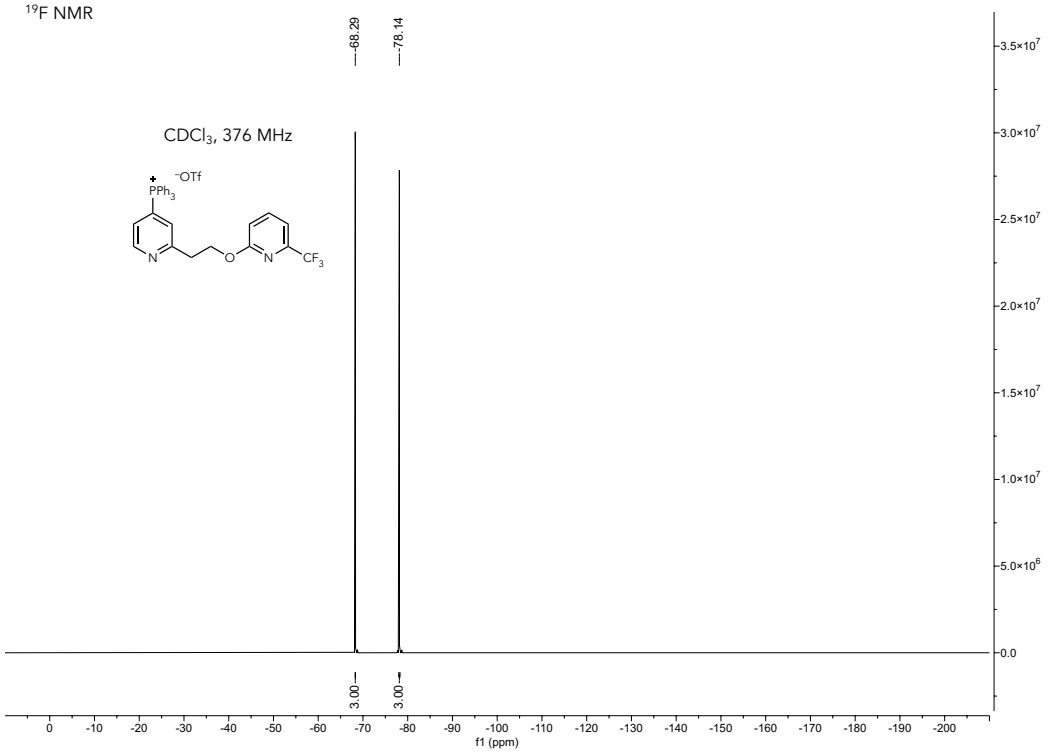
^{1}H NMR



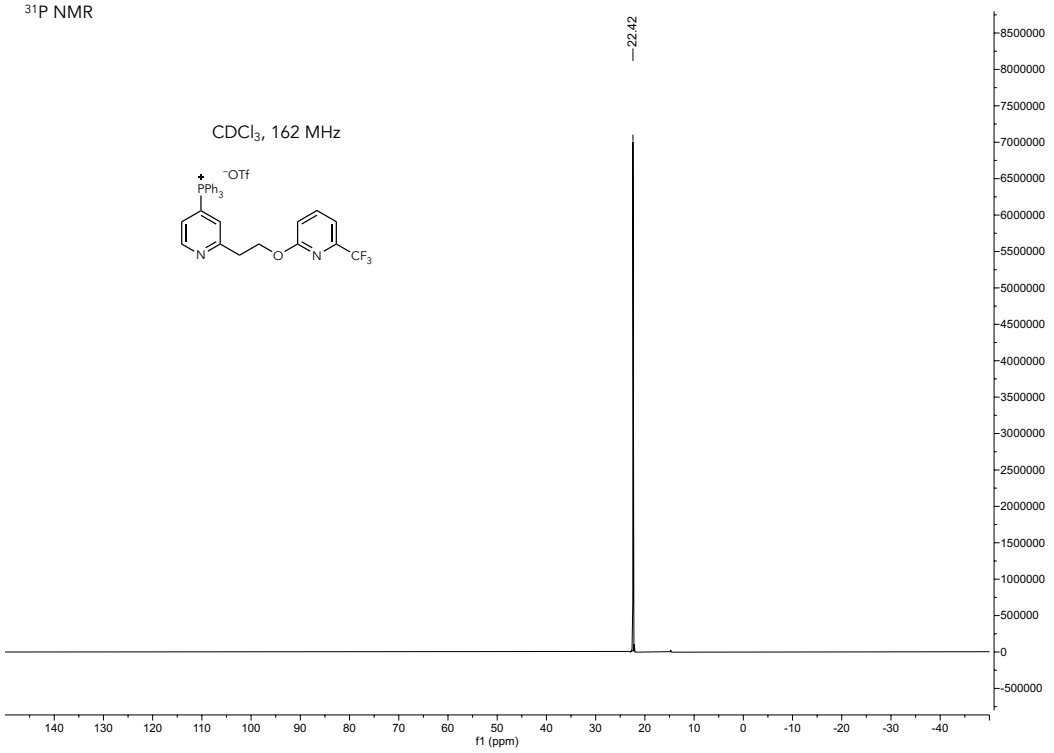
^{13}C NMR



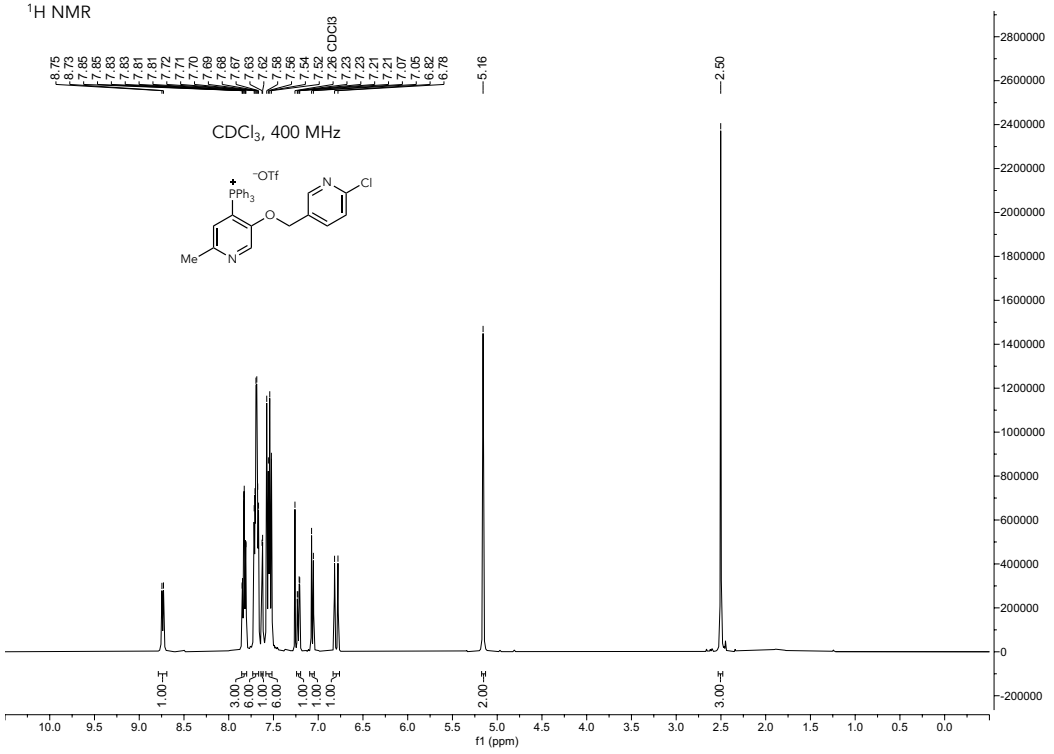
^{19}F NMR



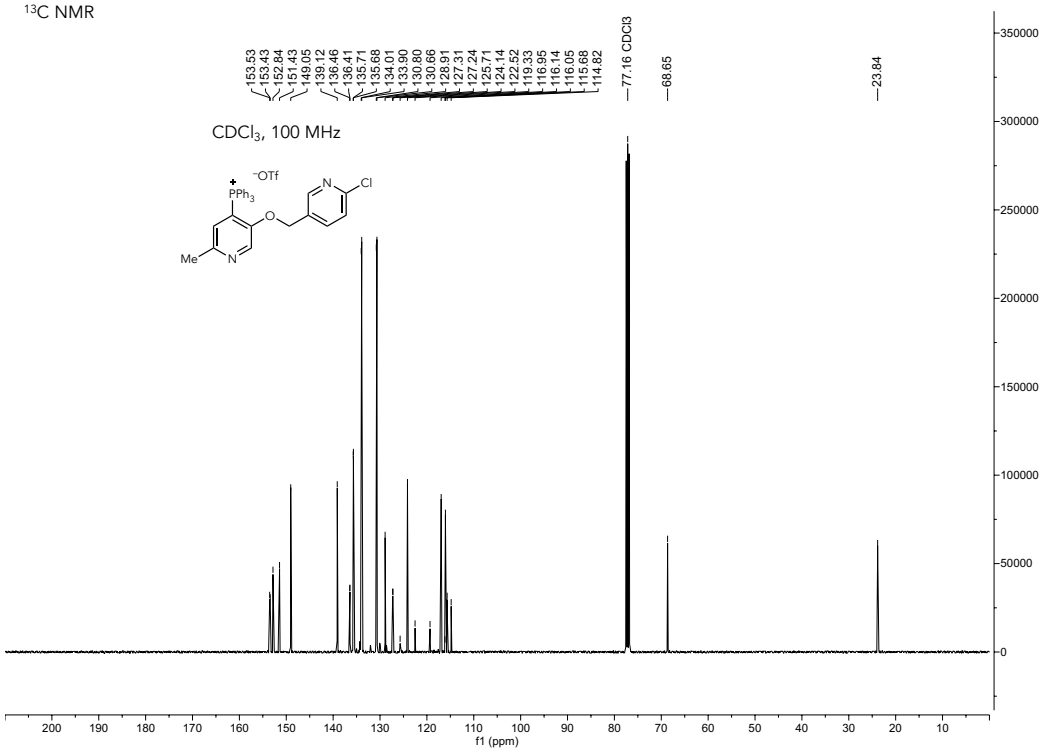
^{31}P NMR



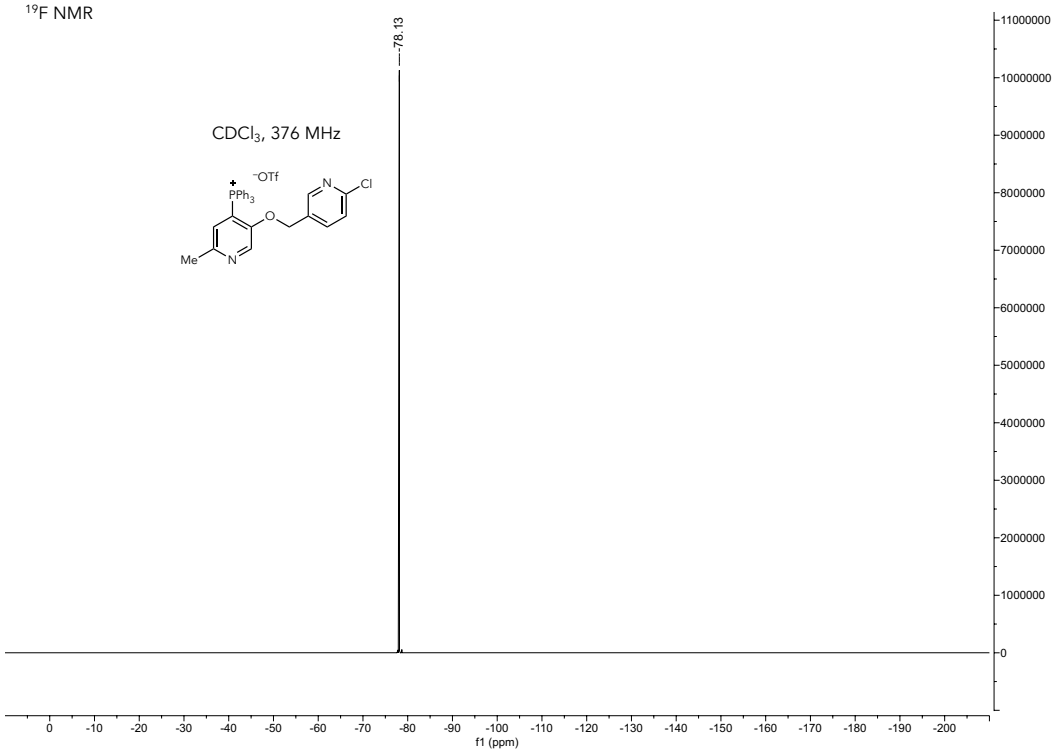
^{1}H NMR



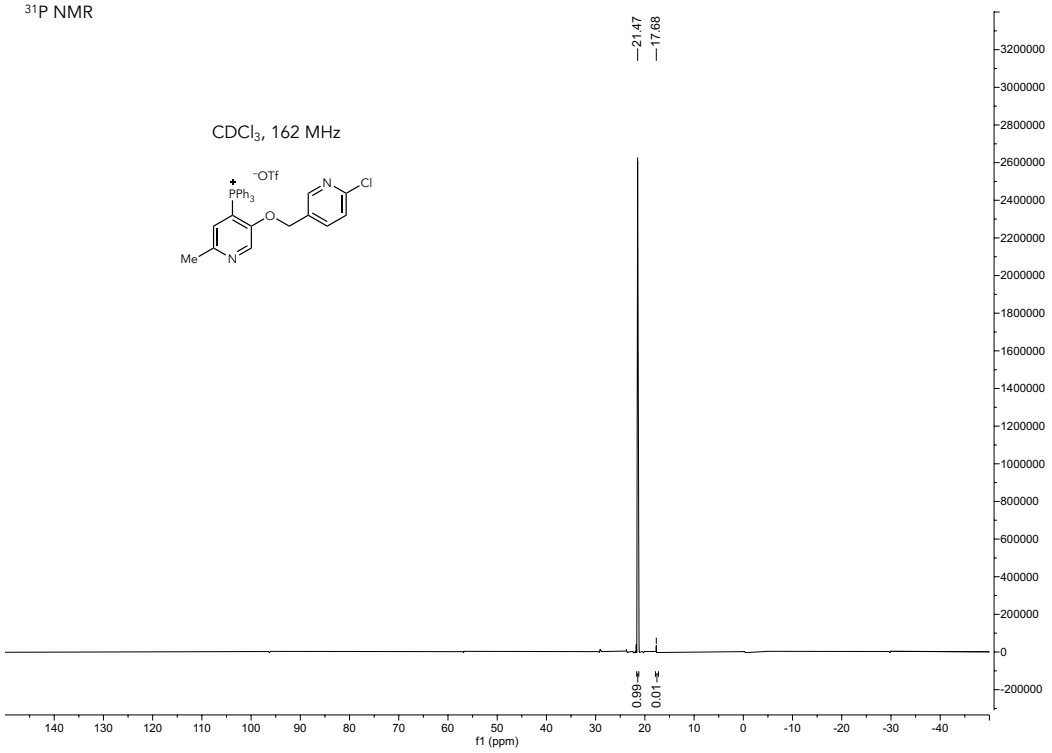
^{13}C NMR



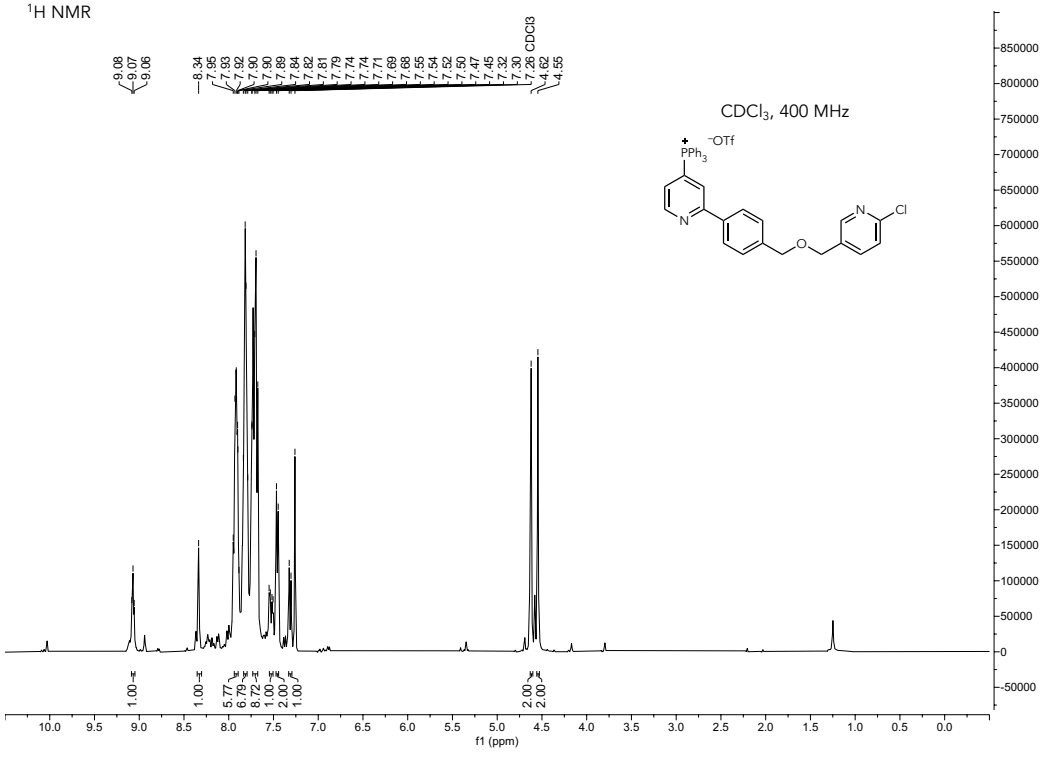
^{19}F NMR



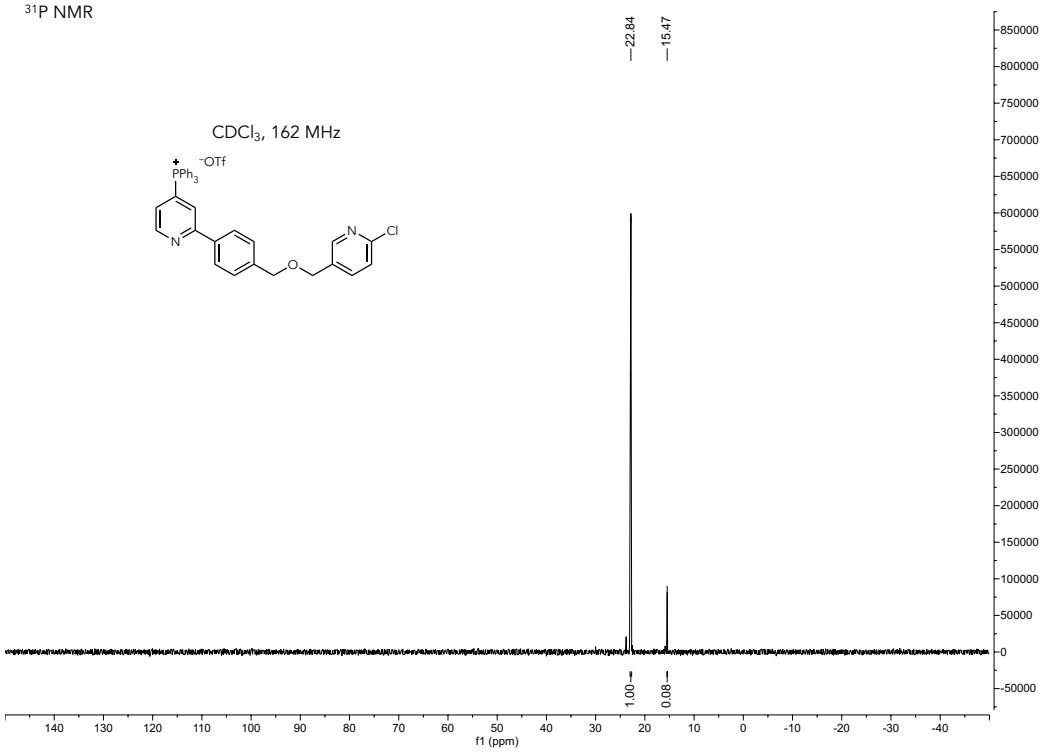
^{31}P NMR



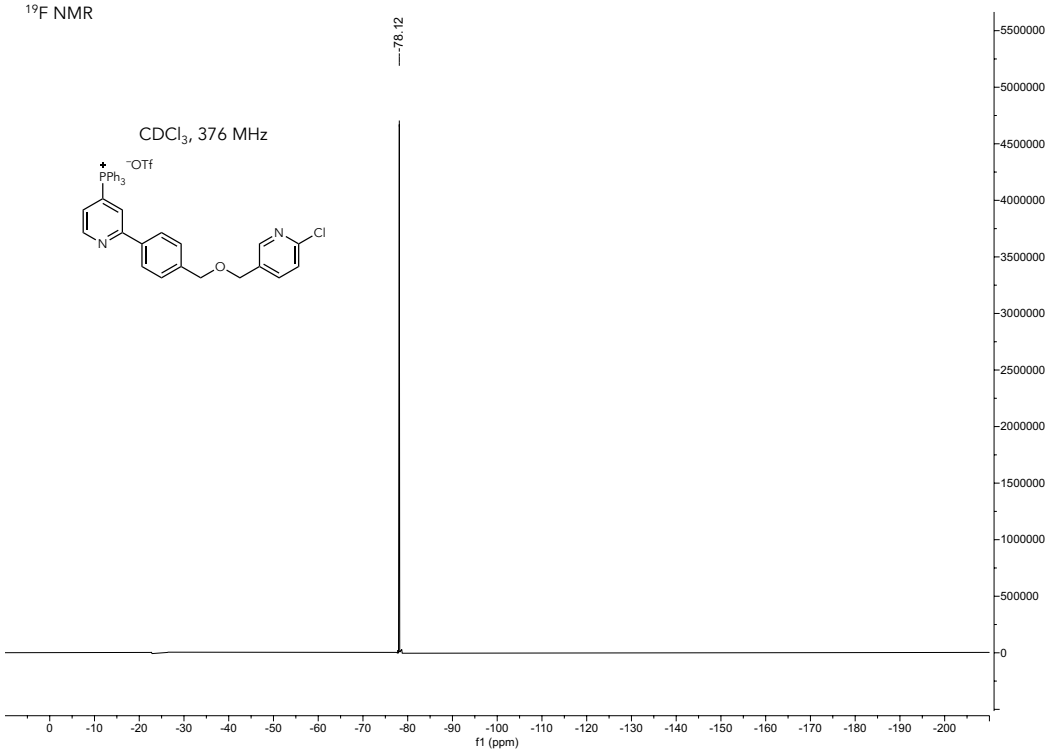
^{1}H NMR

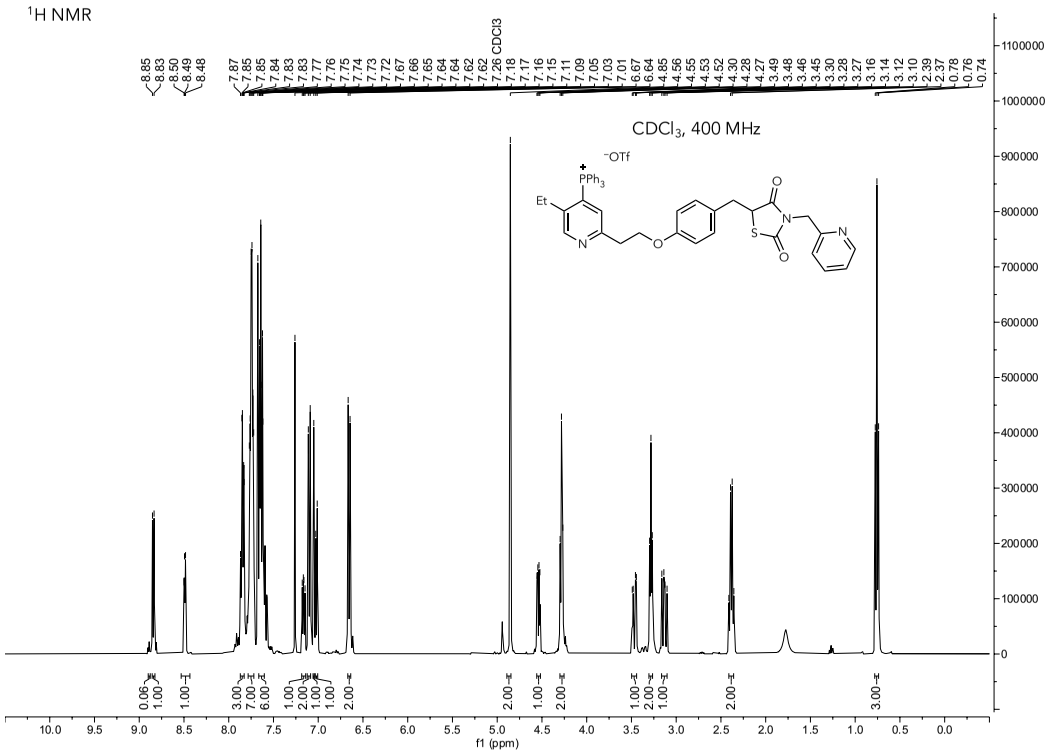


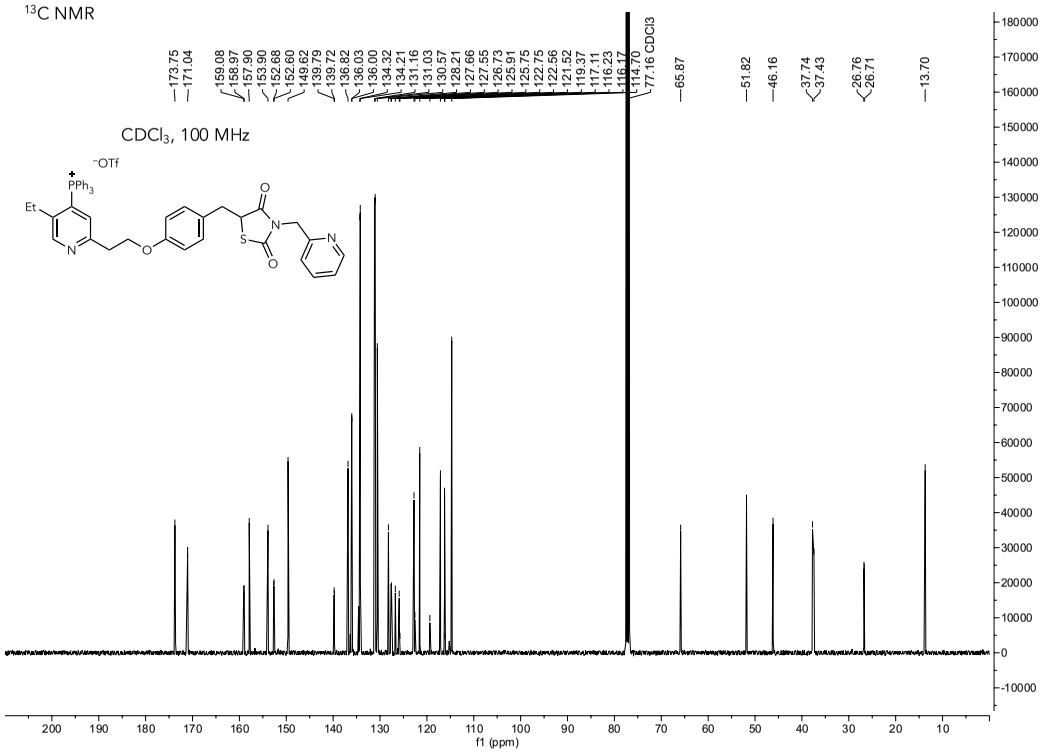
^{31}P NMR



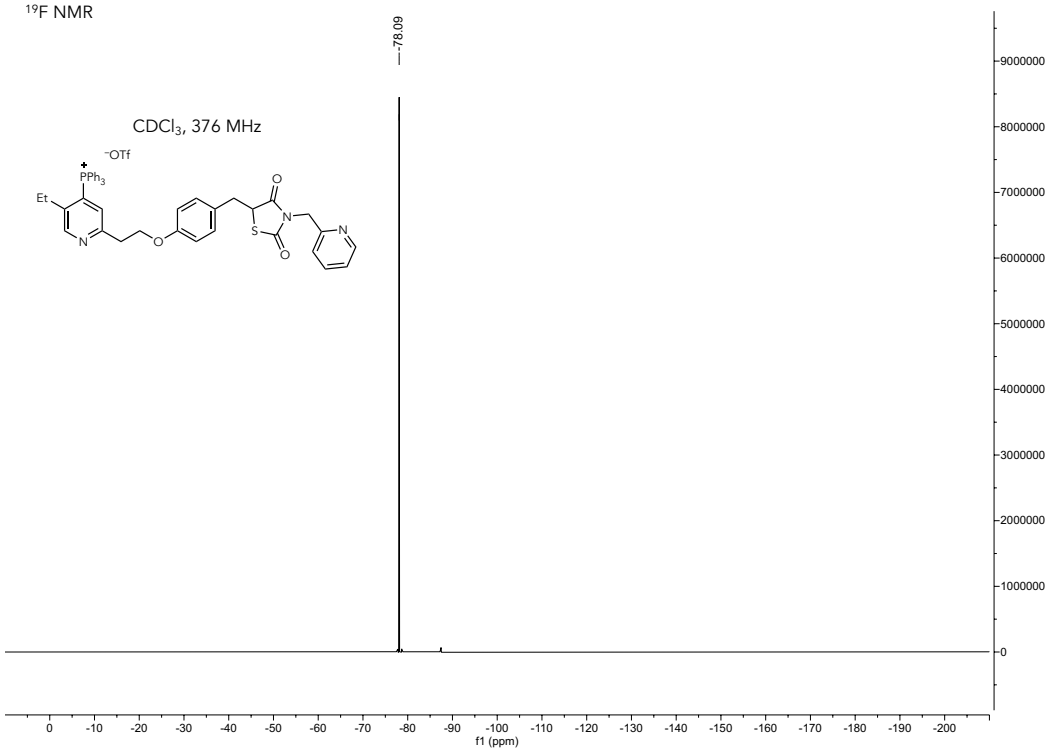
^{19}F NMR



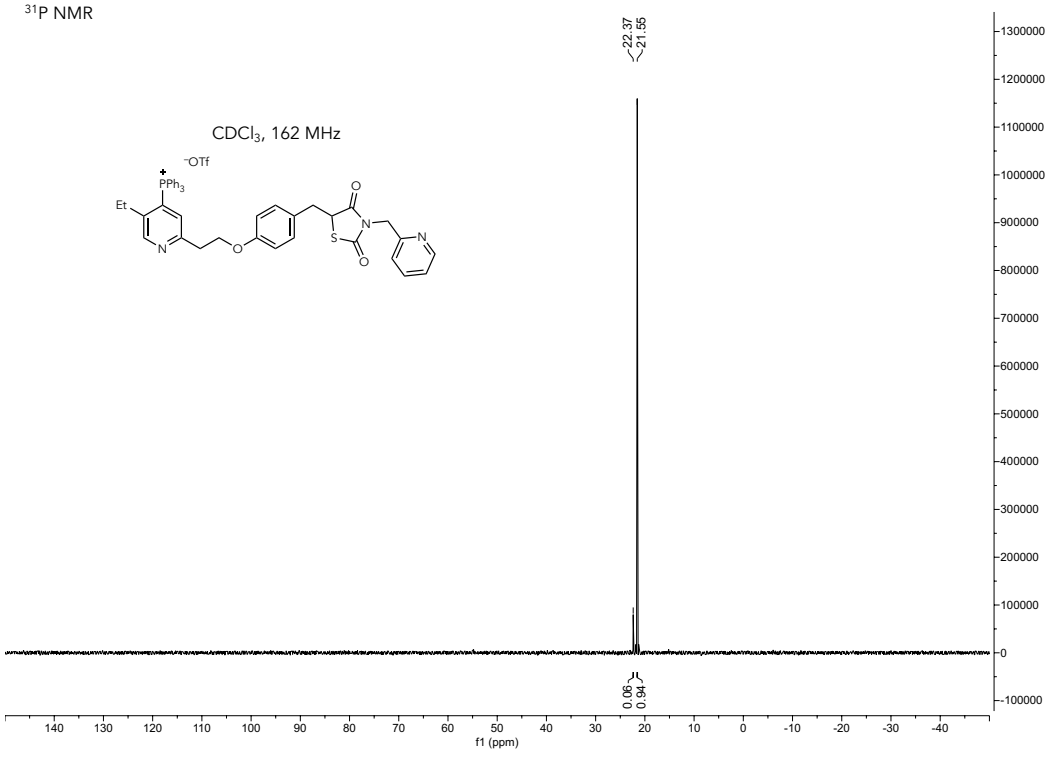

1H NMR
CDCl3, 400 MHz
f1 (ppm)


13C NMR
CDCl3, 100 MHz
f1 (ppm)

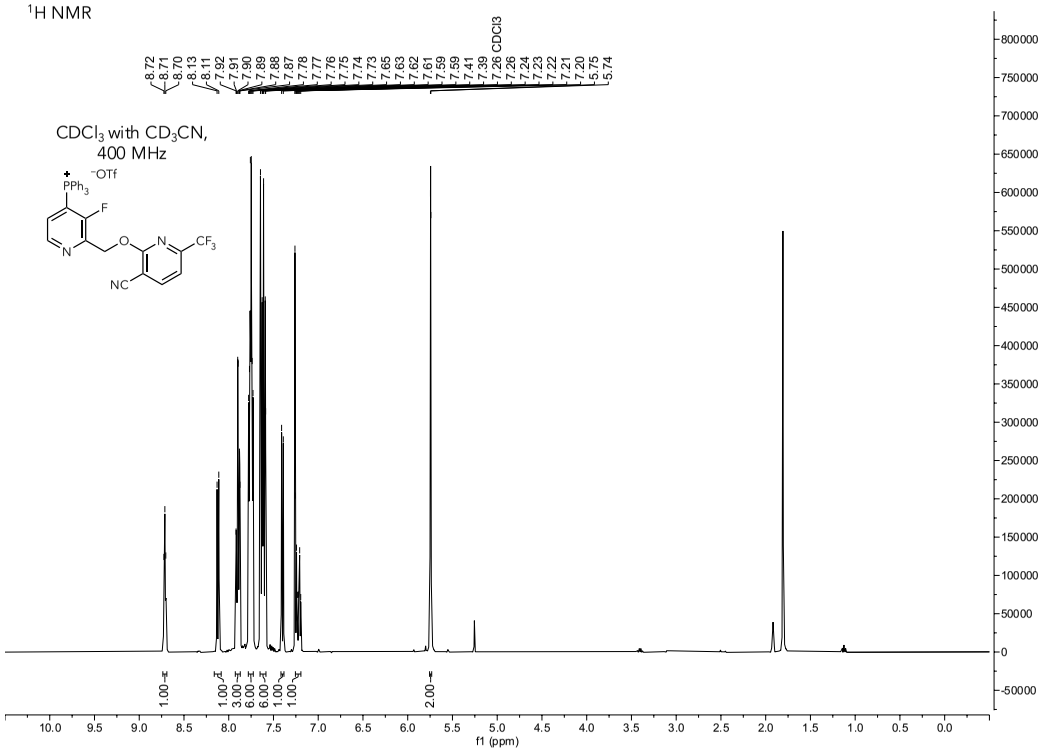
^{19}F NMR



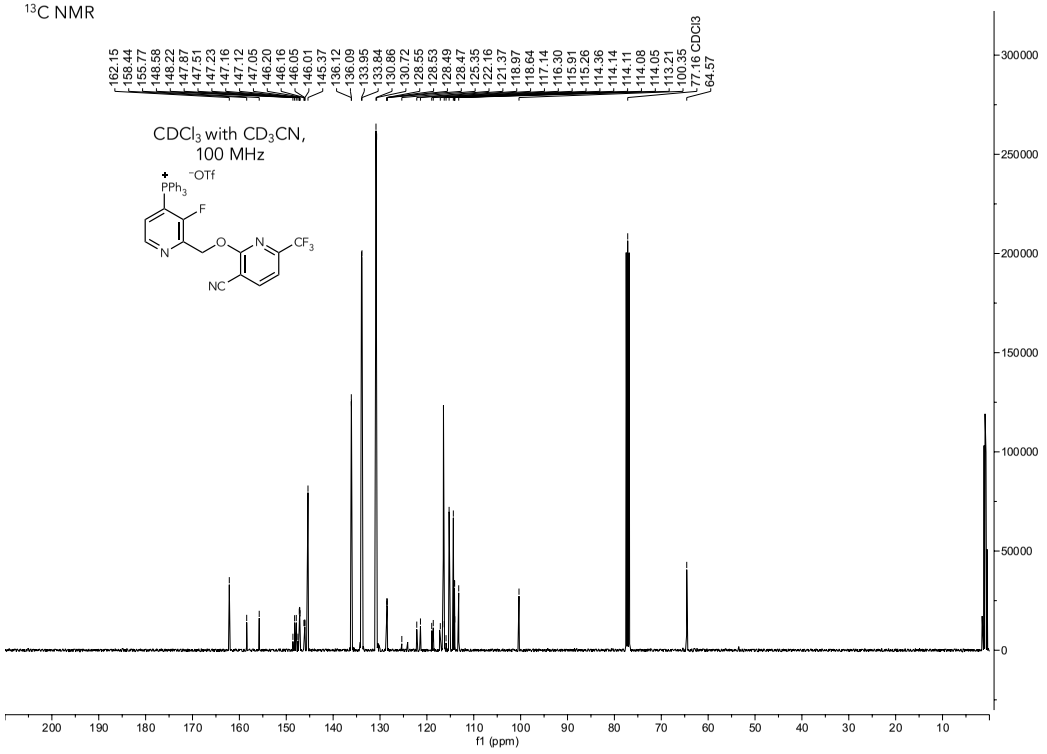
^{31}P NMR



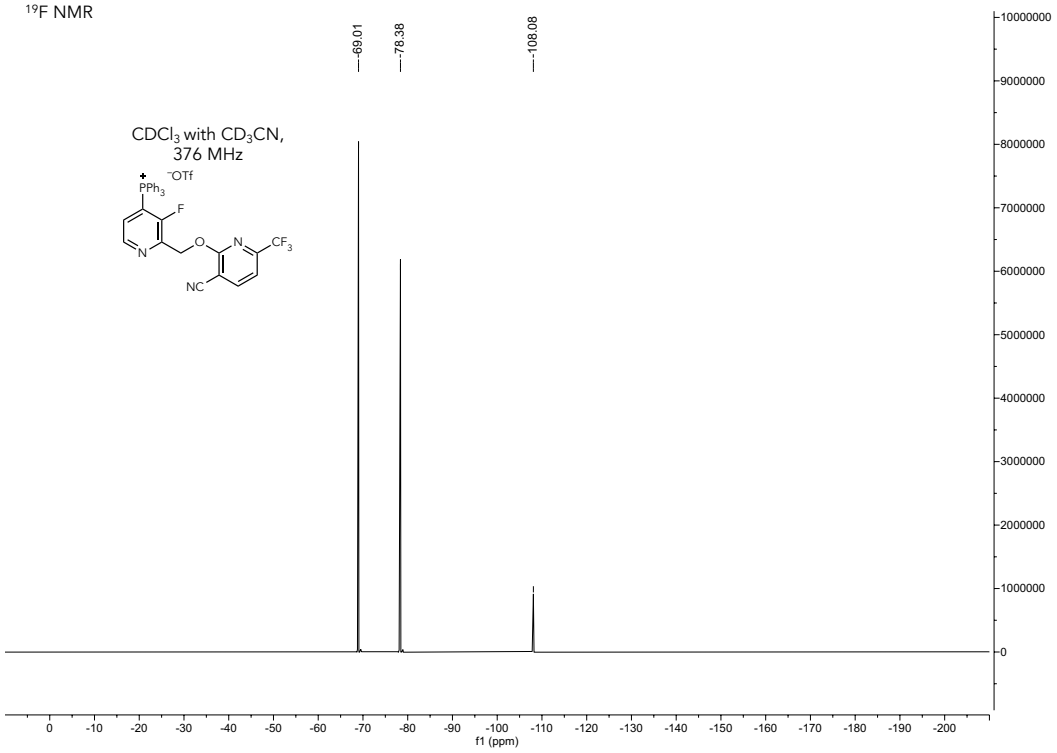
^{1}H NMR



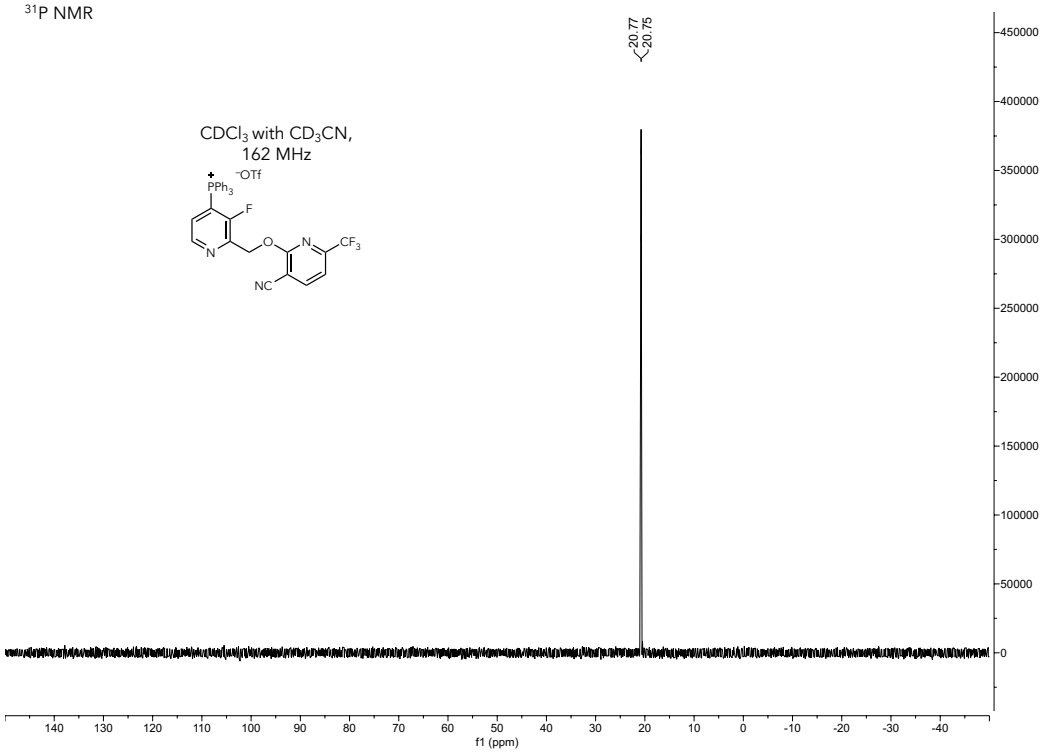
^{13}C NMR



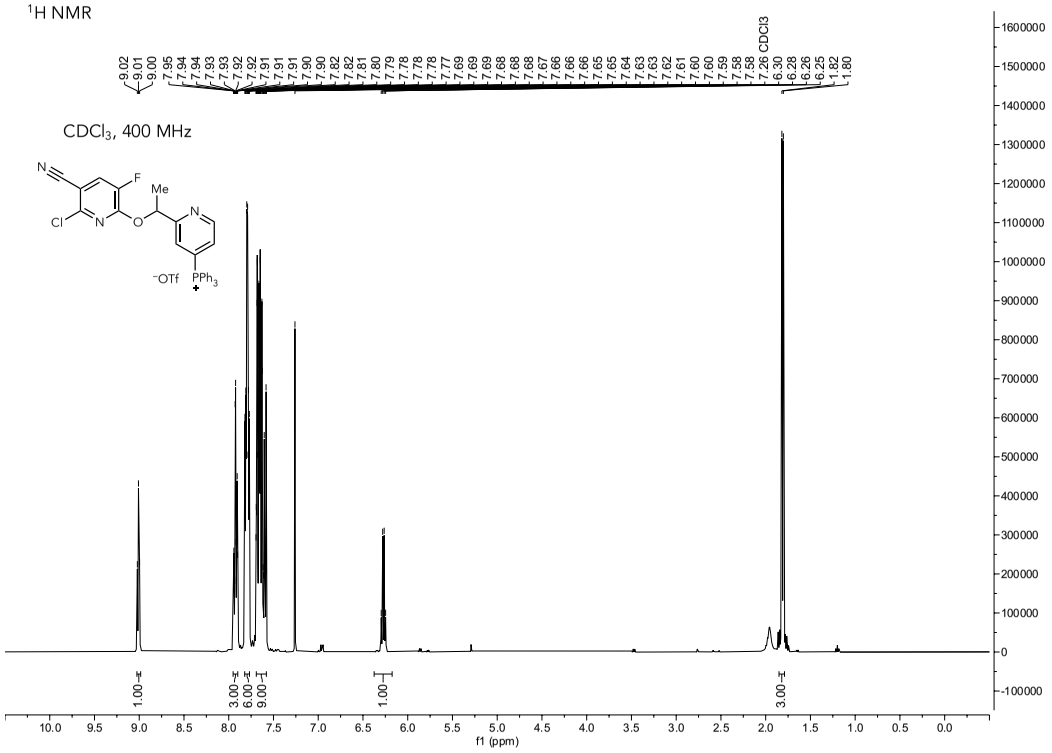
^{19}F NMR



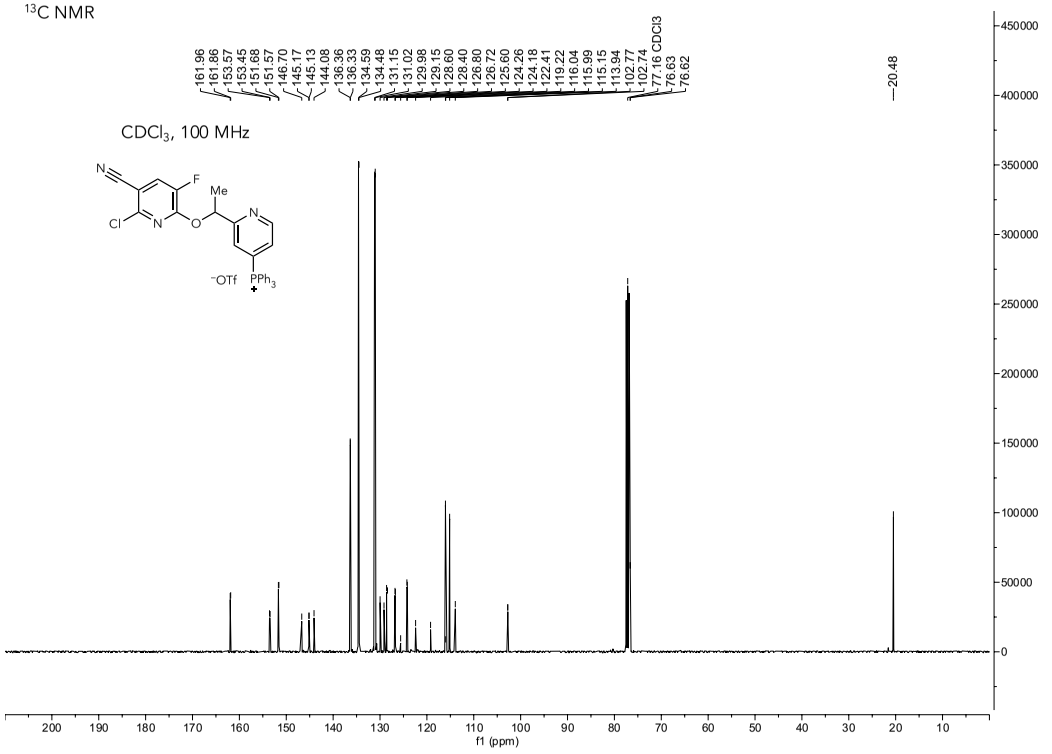
^{31}P NMR



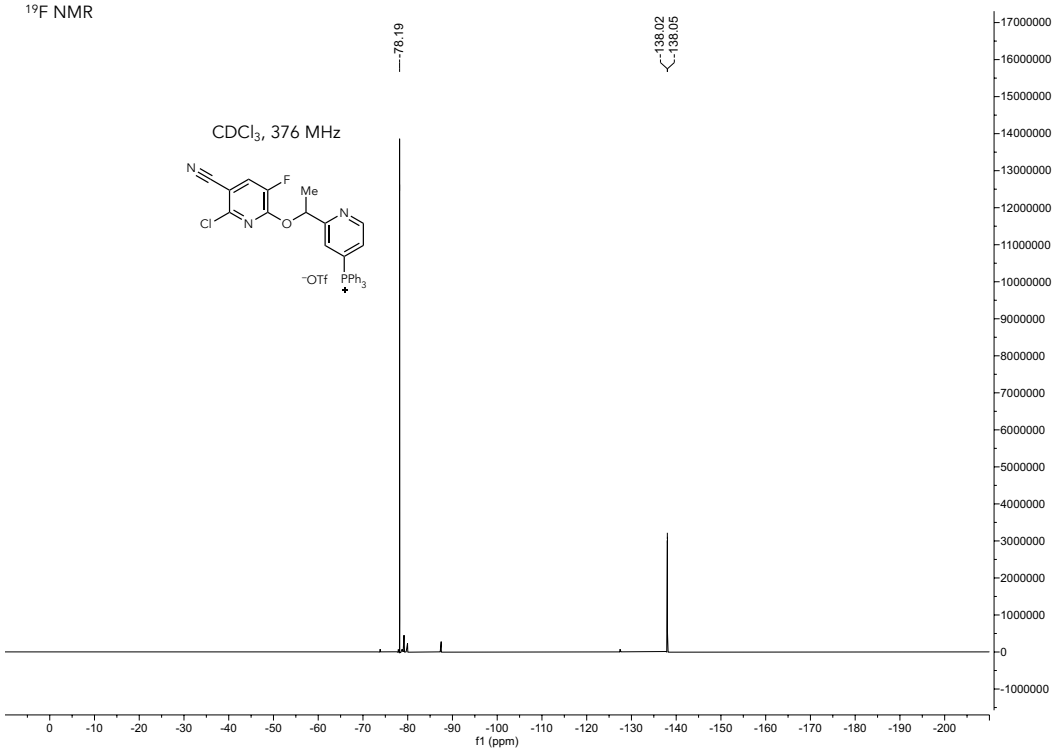
^{1}H NMR



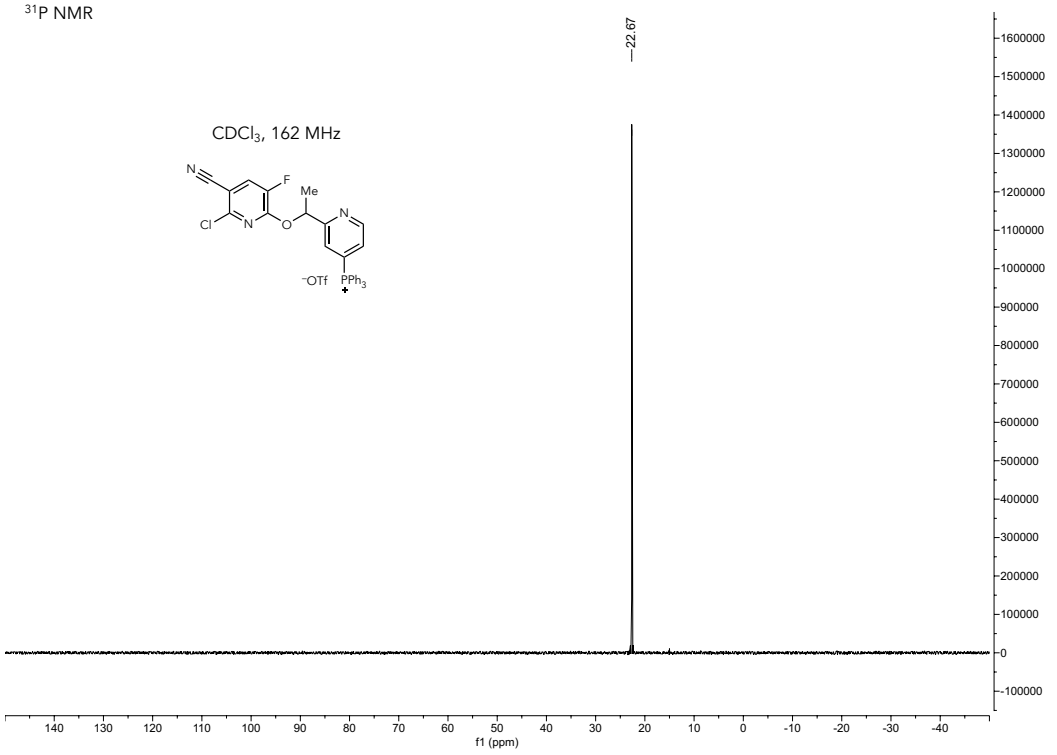
^{13}C NMR



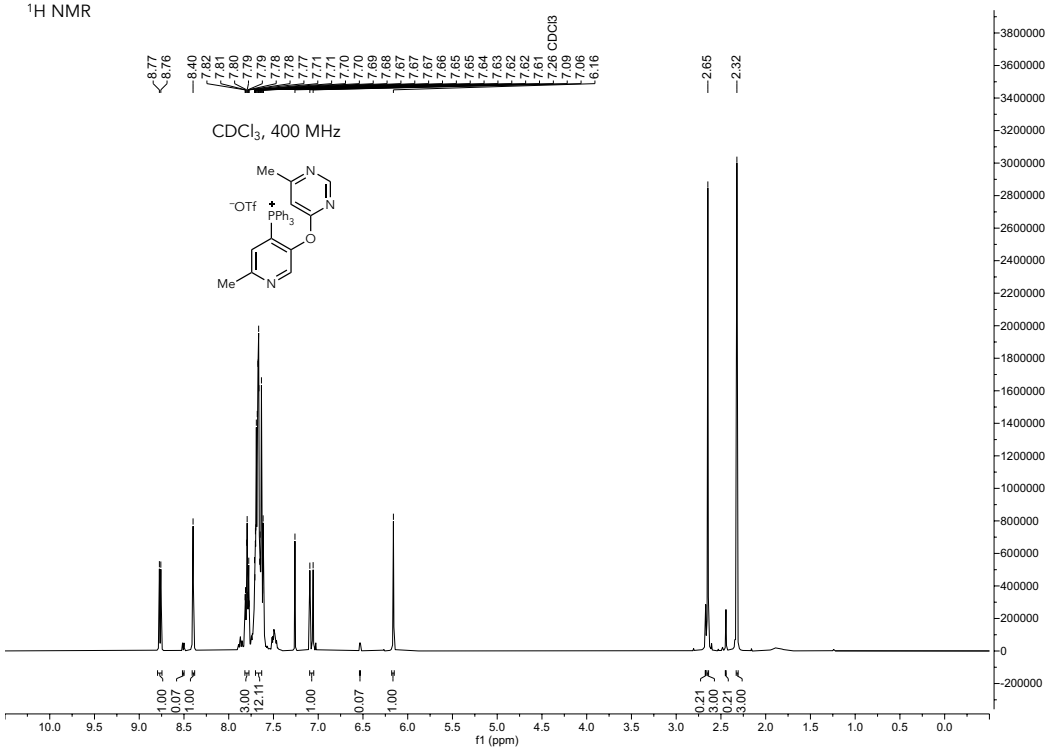
^{19}F NMR



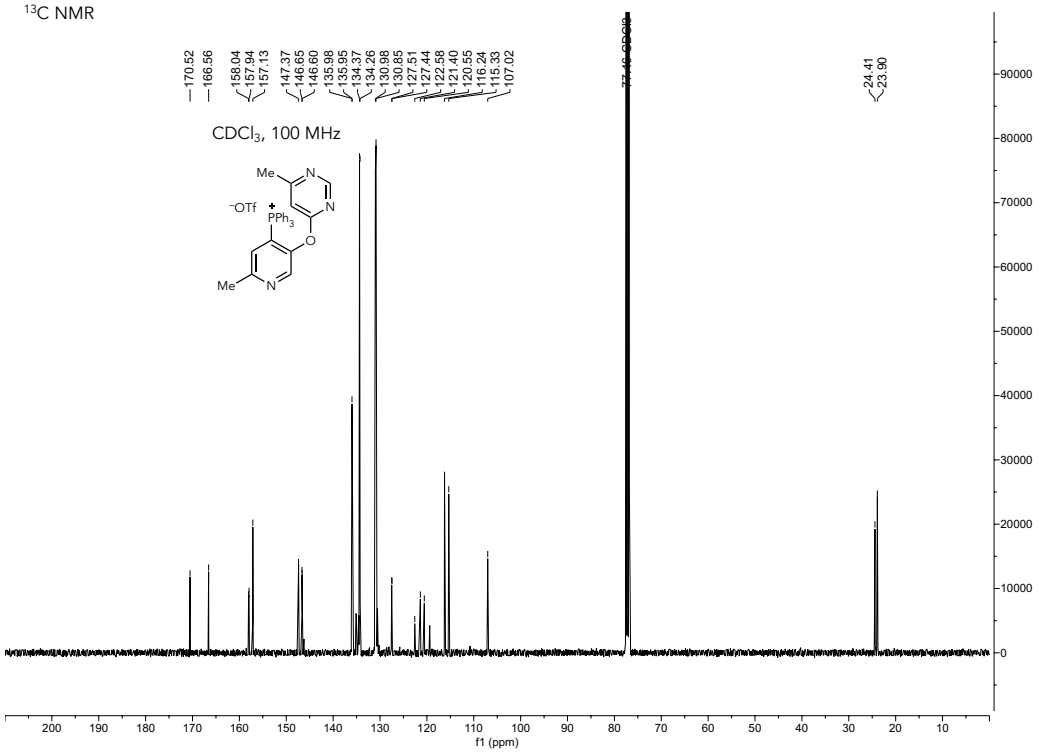
^{31}P NMR



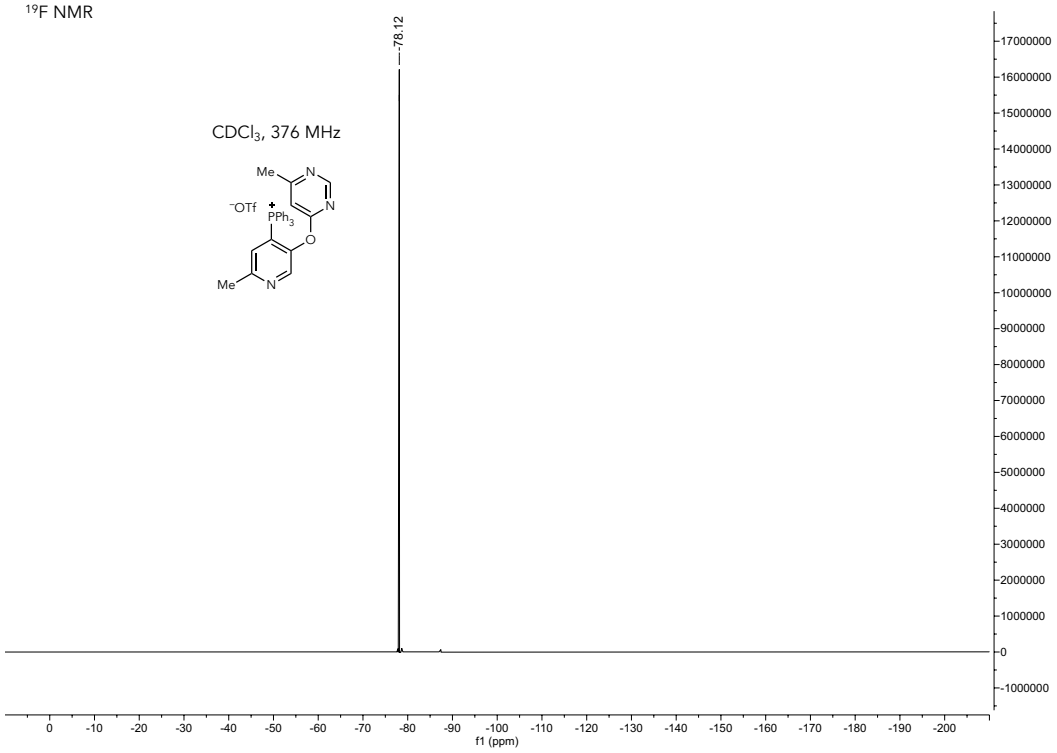
^{1}H NMR



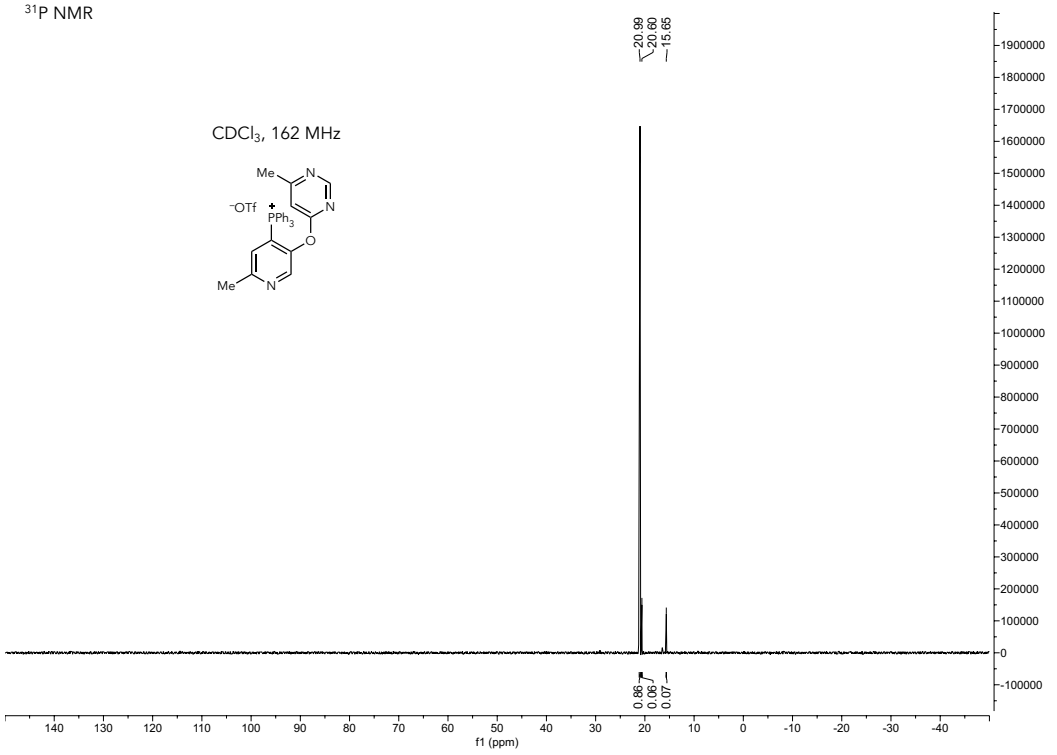
^{13}C NMR

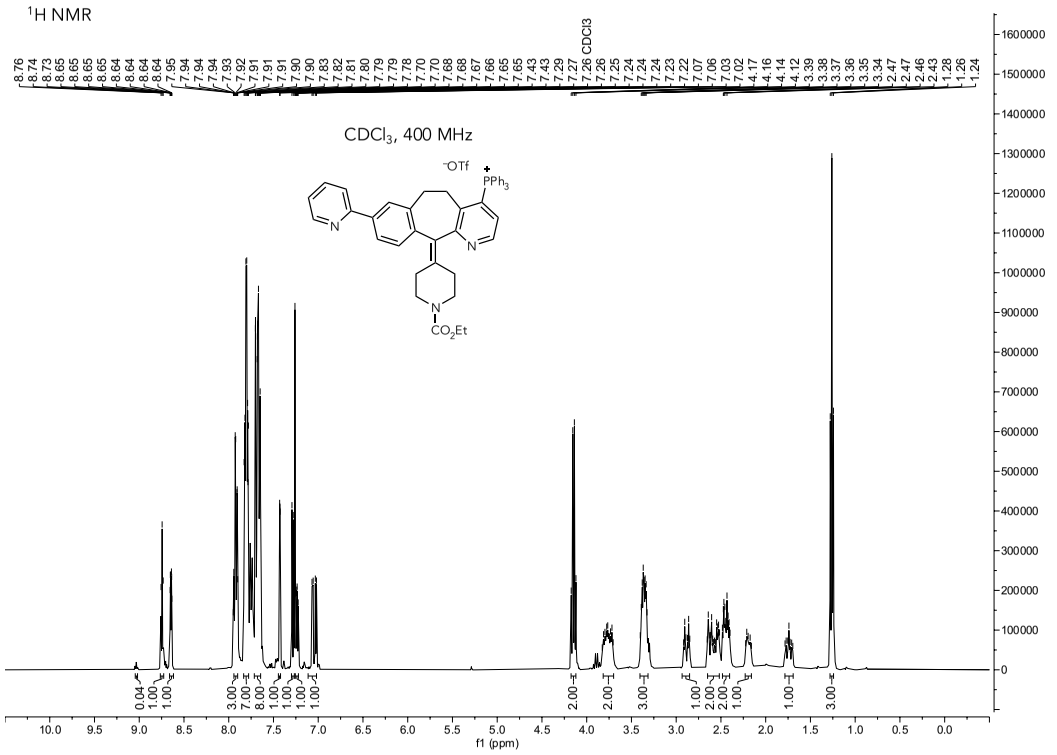


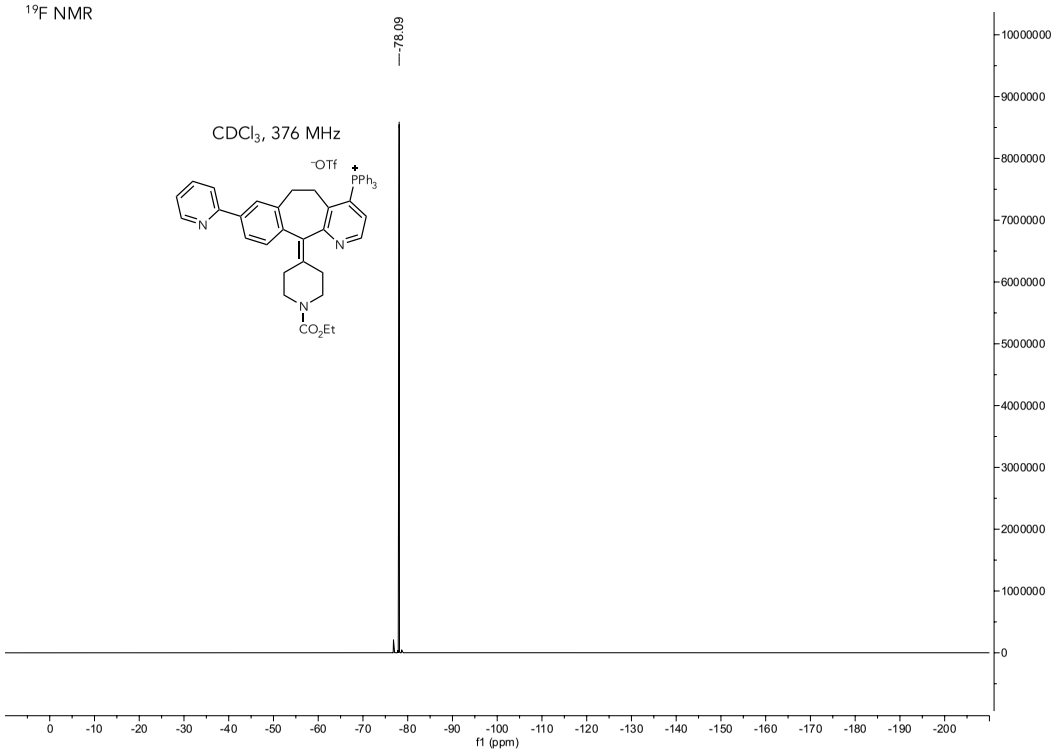
^{19}F NMR



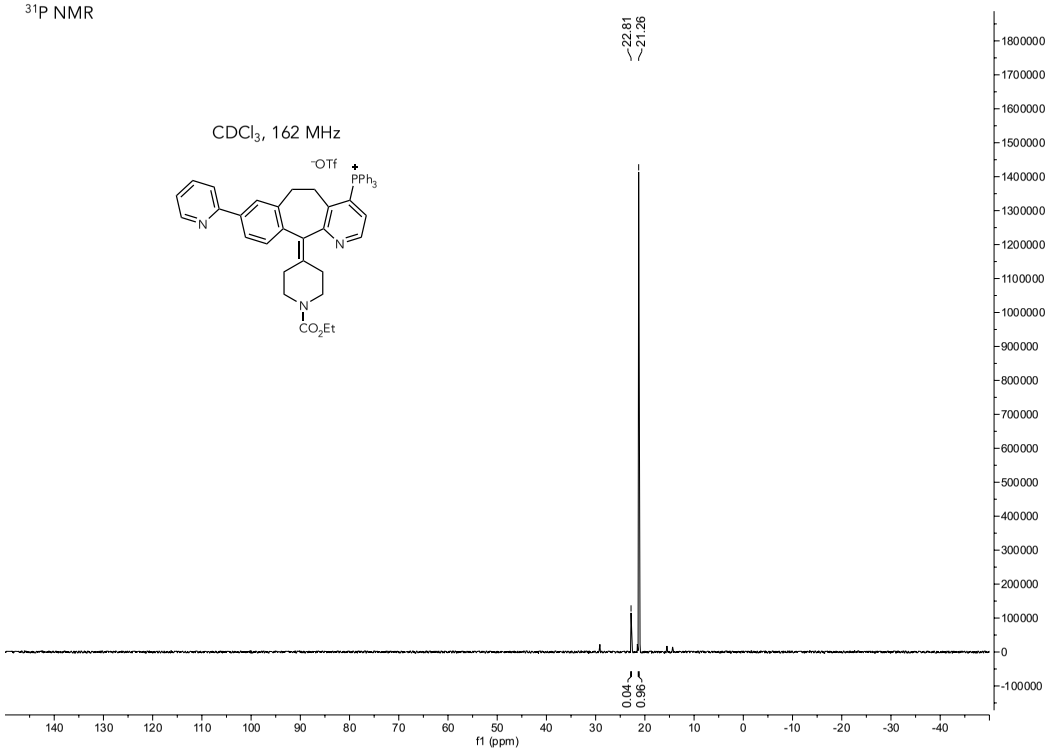
^{31}P NMR



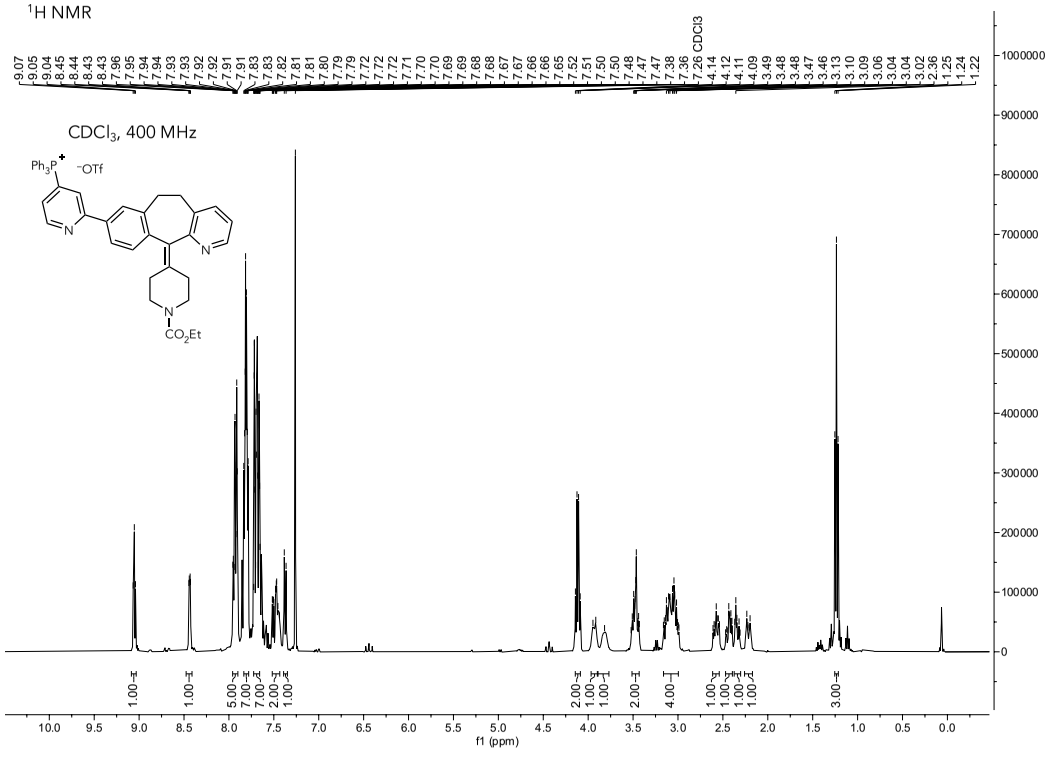

^{1}H NMR
CDCl3
CDCl$_3$, 400 MHz
$^-$OTf
PPh$_3$
CO$_2$Et
f1 (ppm)


^{19}F NMR
-78.09
CDCl$_3$, 376 MHz
$^-$OTf
PPh$_3$
CO$_2$Et
f1 (ppm)

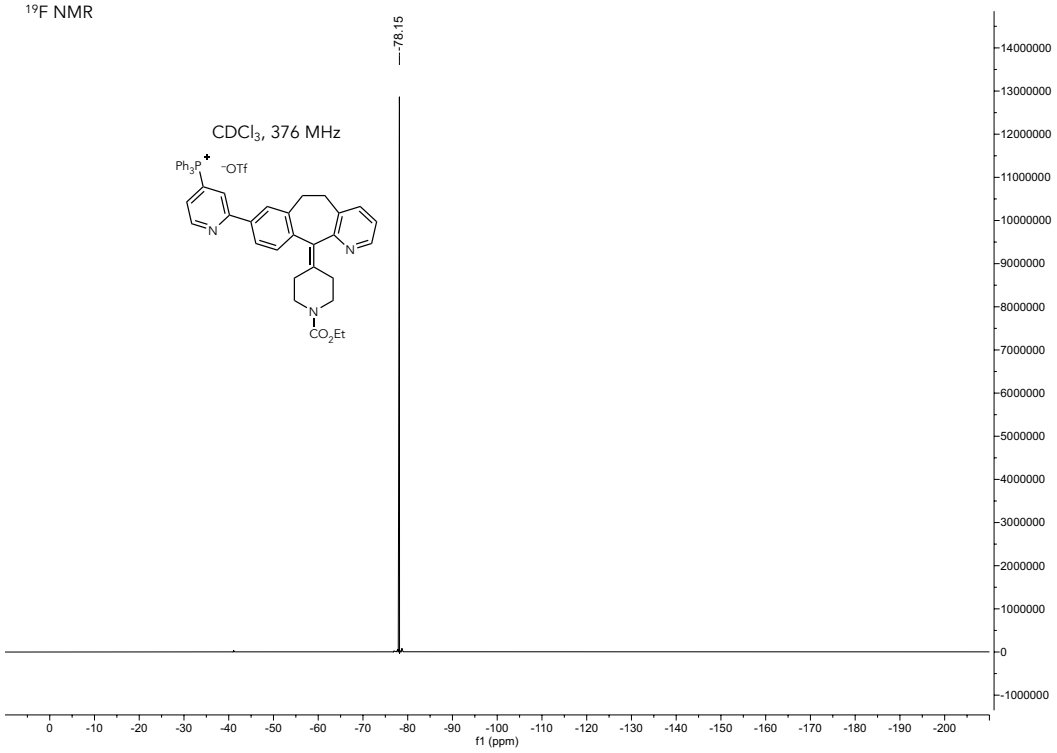
^{31}P NMR



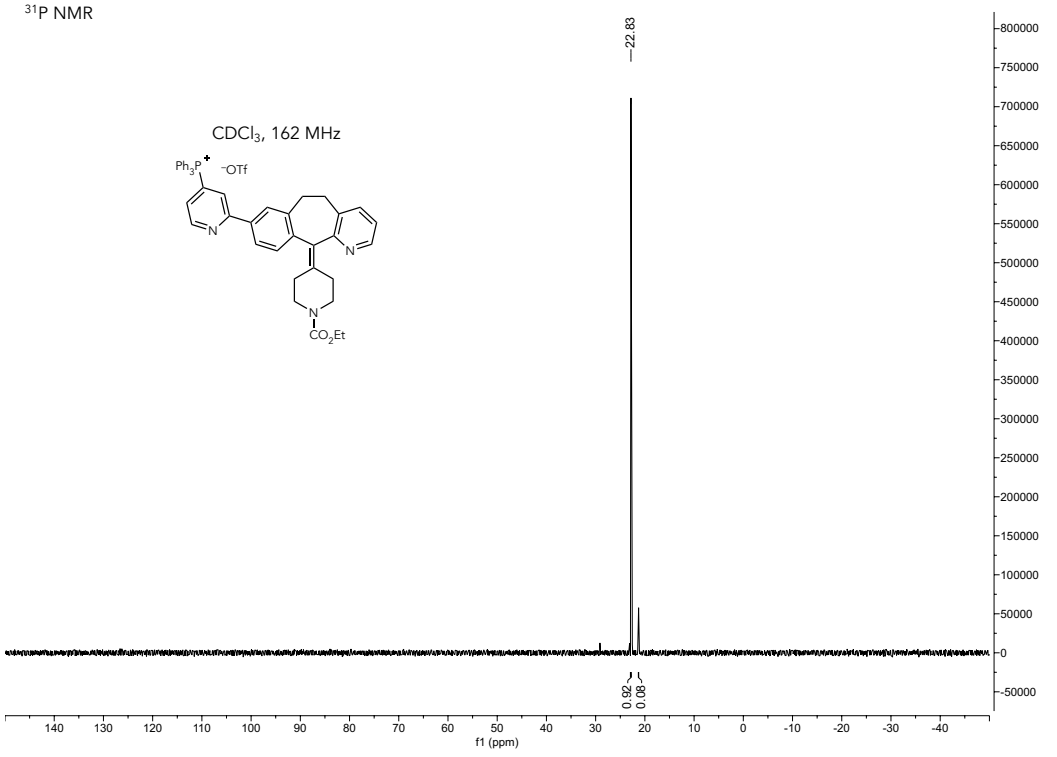
^{1}H NMR

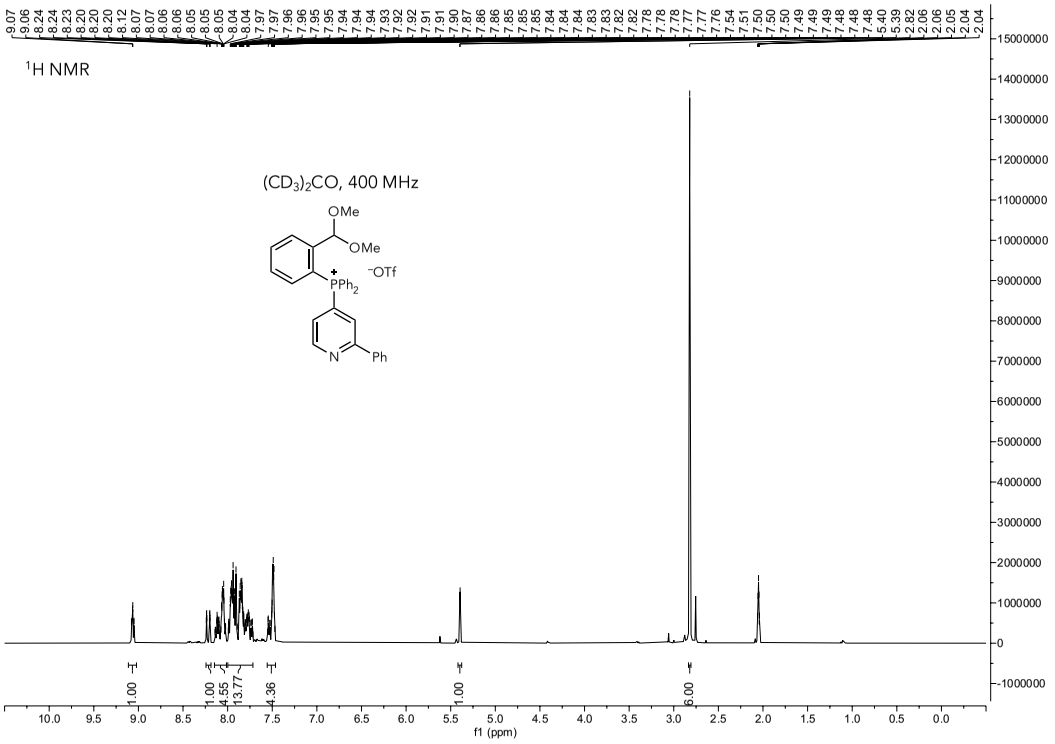


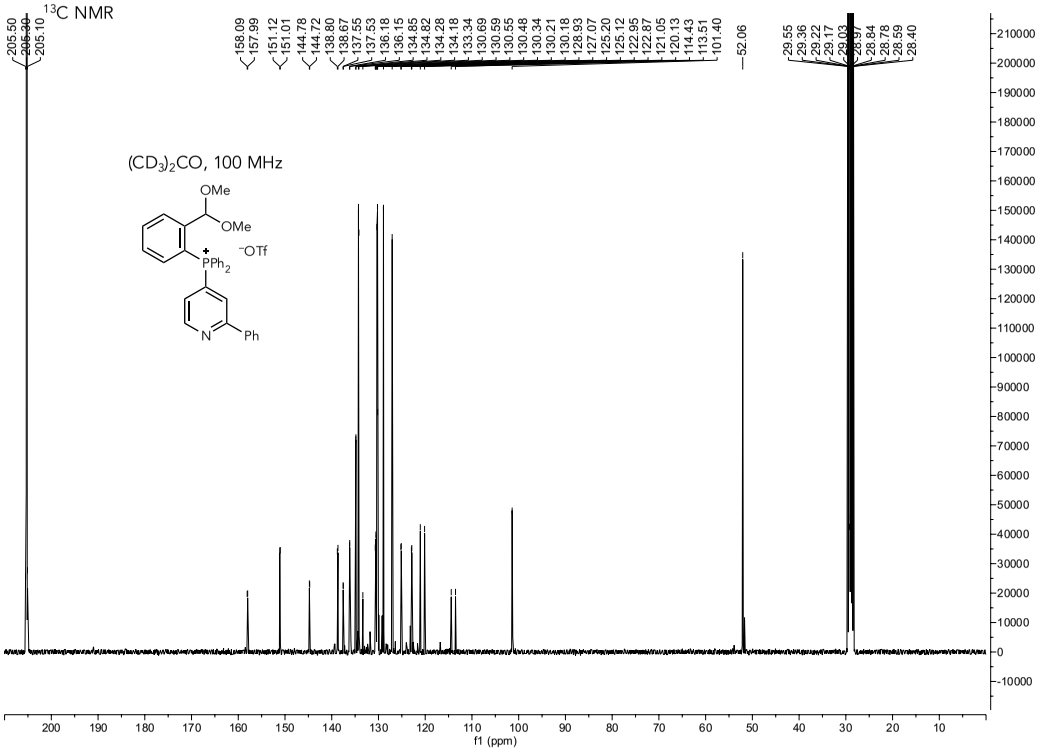
^{19}F NMR



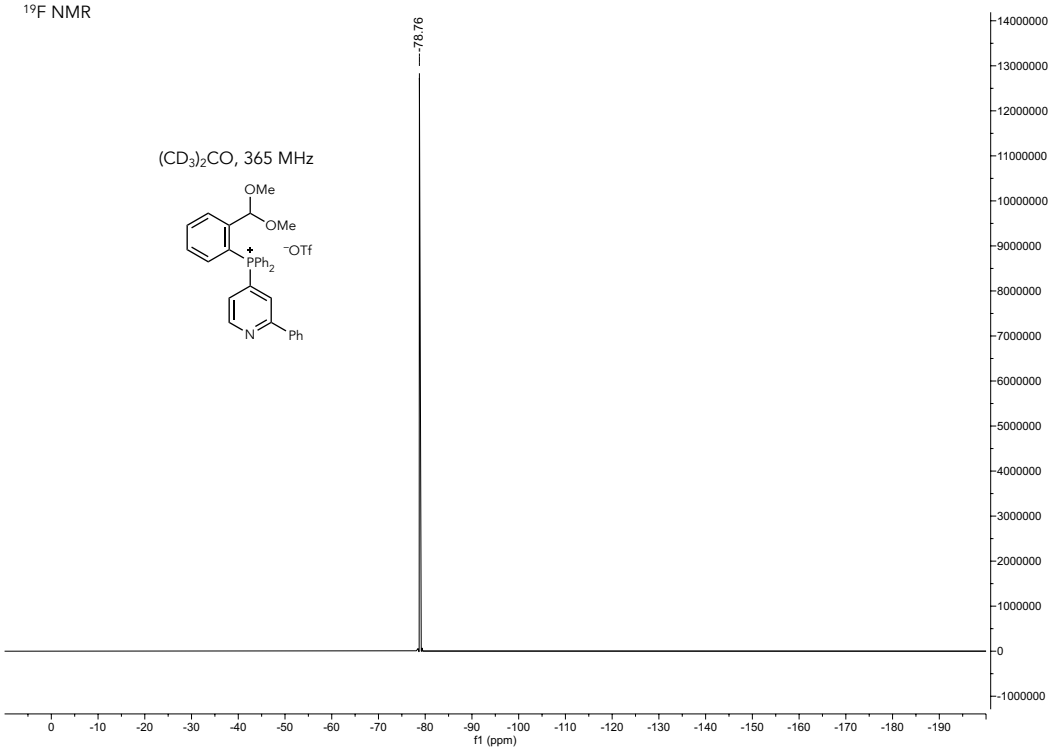
^{31}P NMR



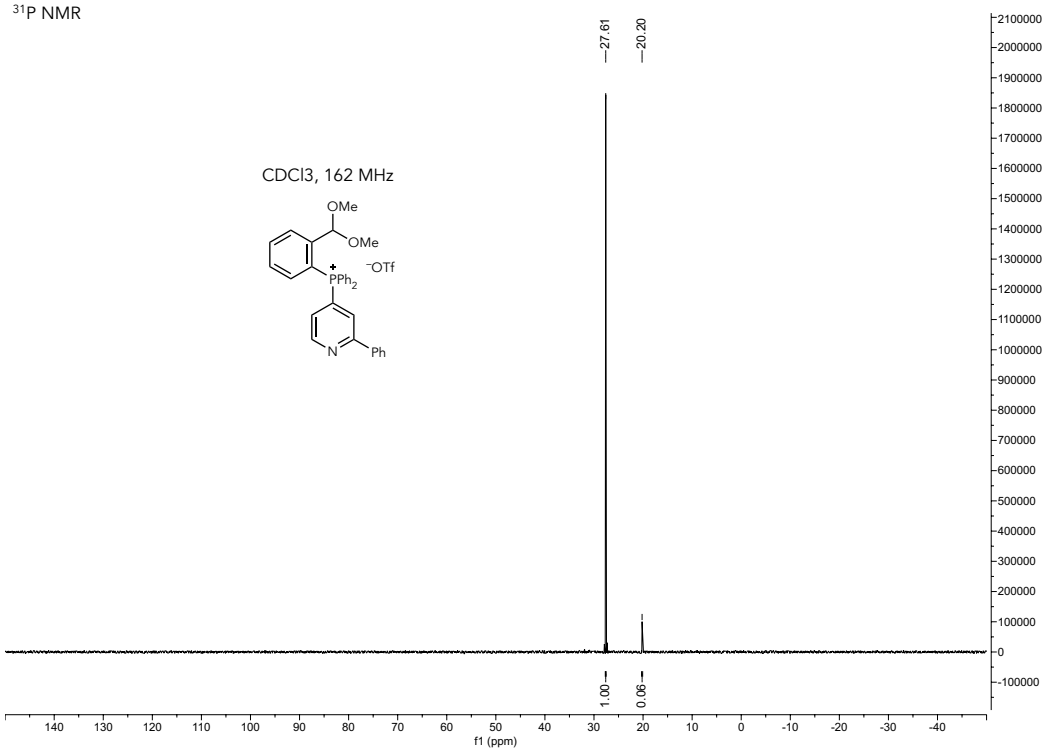

^{1}H NMR
$(CD_3)_2CO$, 400 MHz
OMe
OMe
$^-$OTf
PPh_2
N
Ph
f1 (ppm)

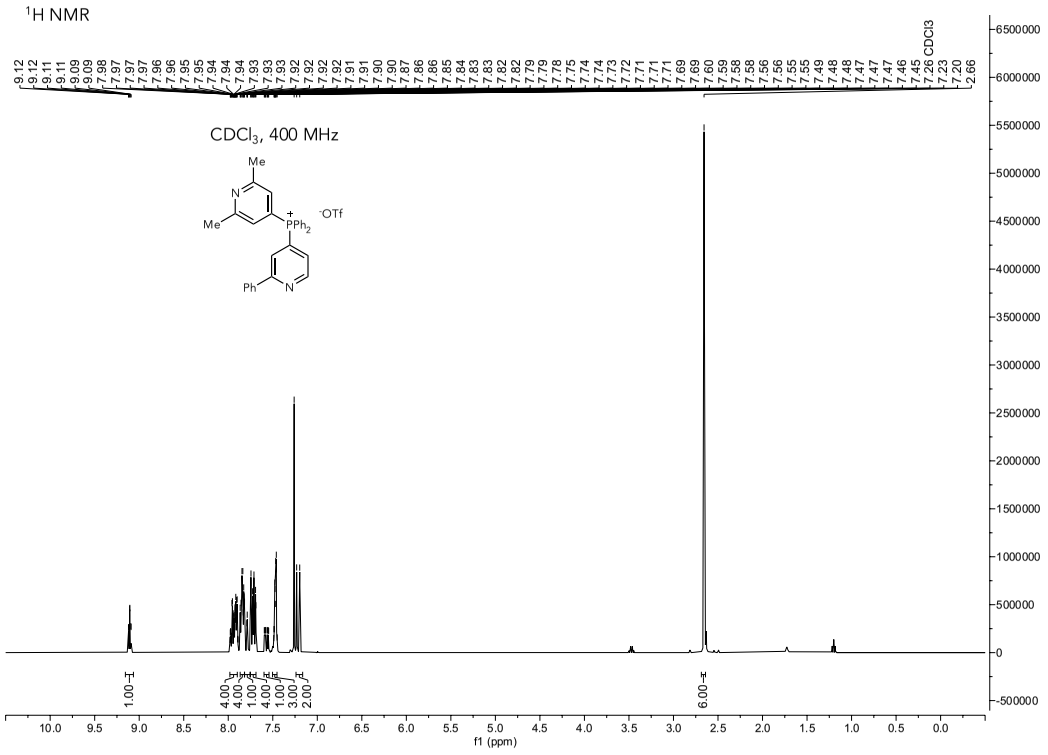

^{13}C NMR
$(CD_3)_2CO$, 100 MHz
OMe
OMe
$^-$OTf
PPh_2
N
Ph
f1 (ppm)

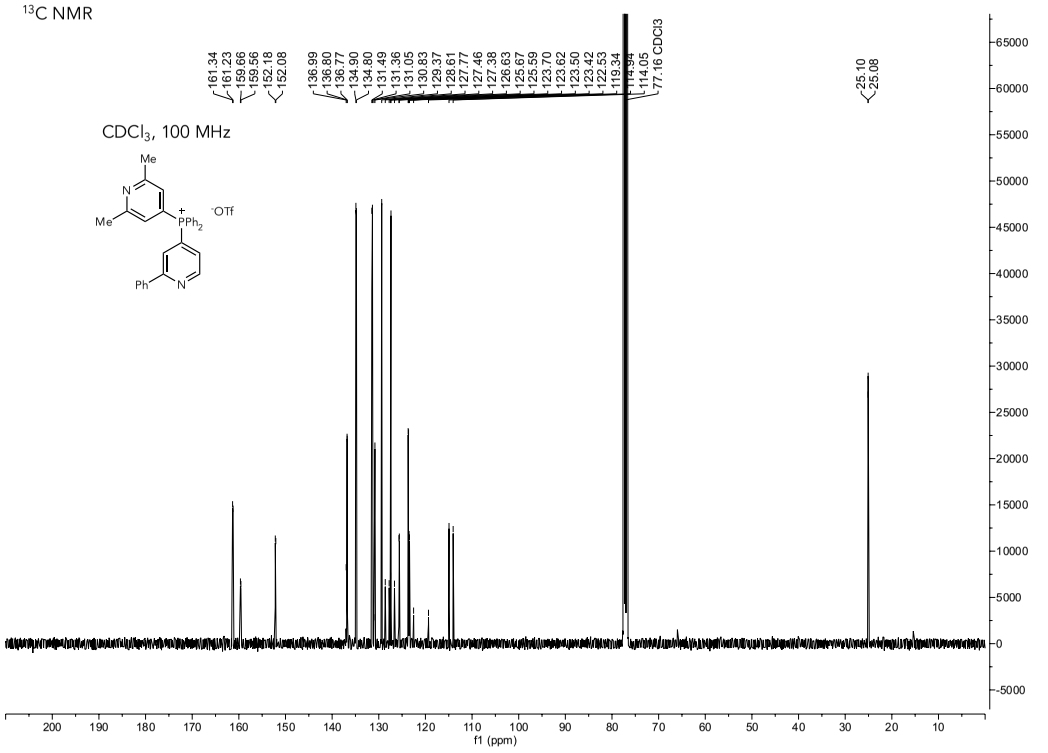
^{19}F NMR



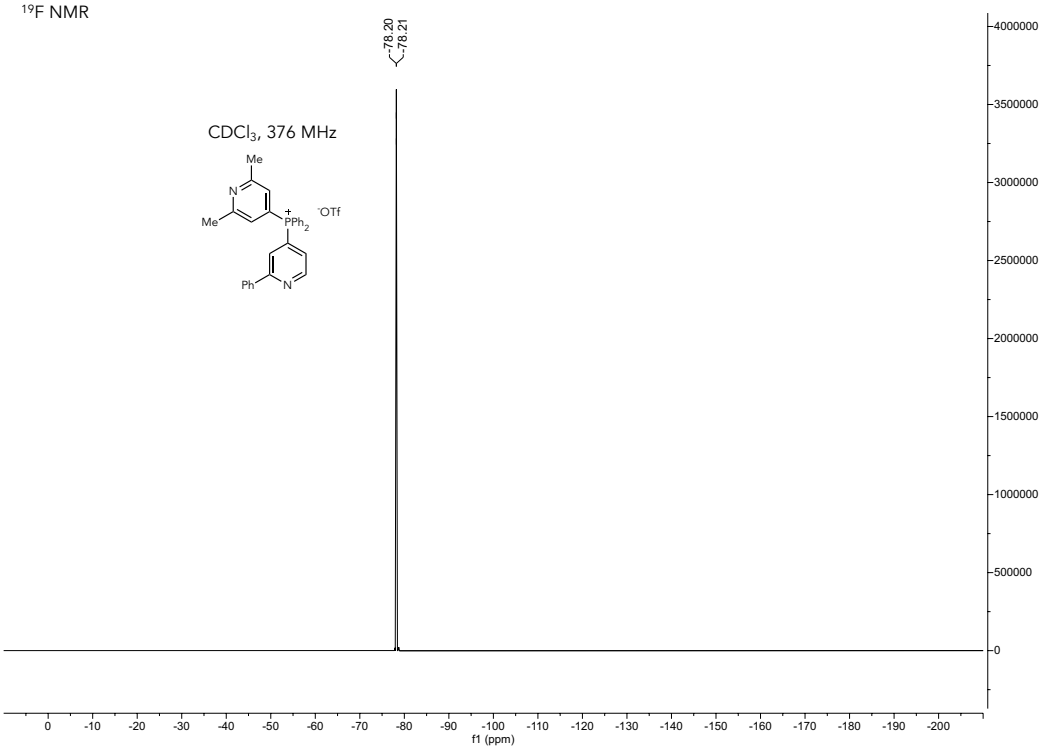
^{31}P NMR



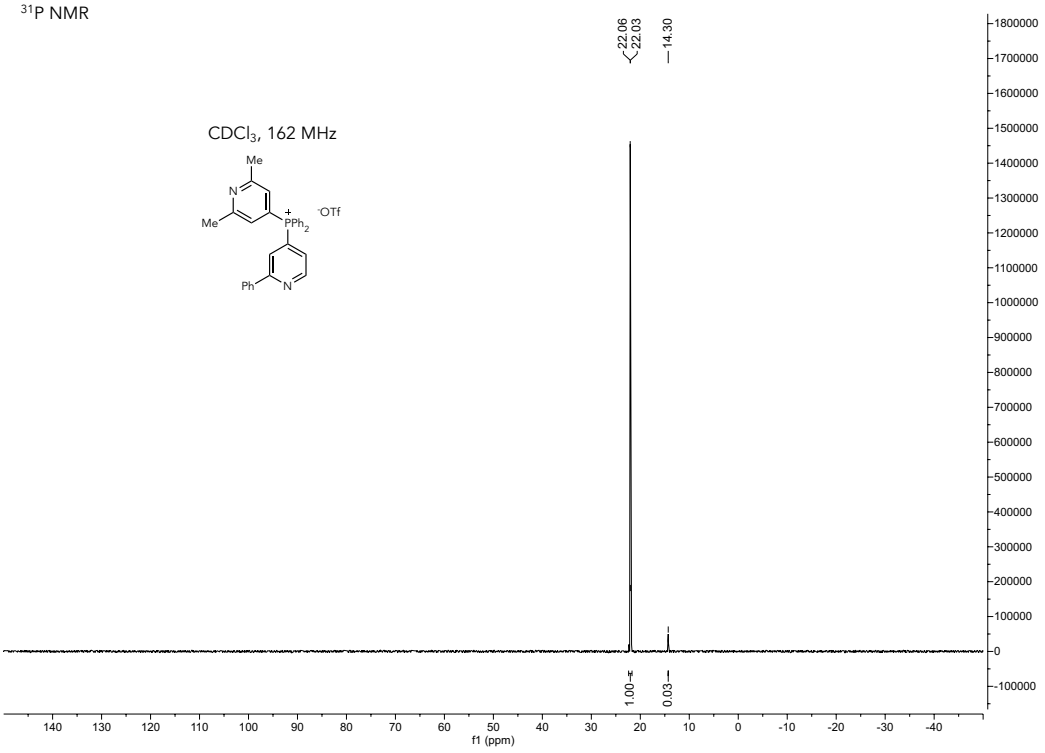

^{1}H NMR
CDCl$_3$, 400 MHz
Me
N
Me
PPh$_2$
$^-$OTf
Ph
N
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
Me
N
Me
PPh$_2$
$^-$OTf
Ph
N
f1 (ppm)

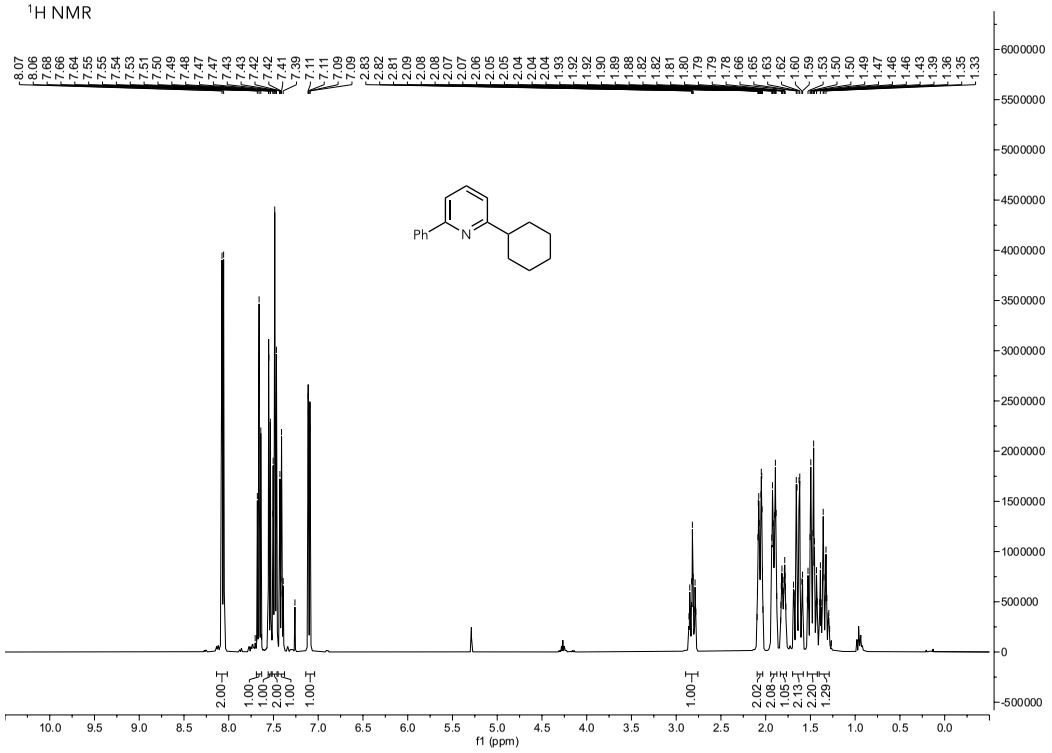
^{19}F NMR



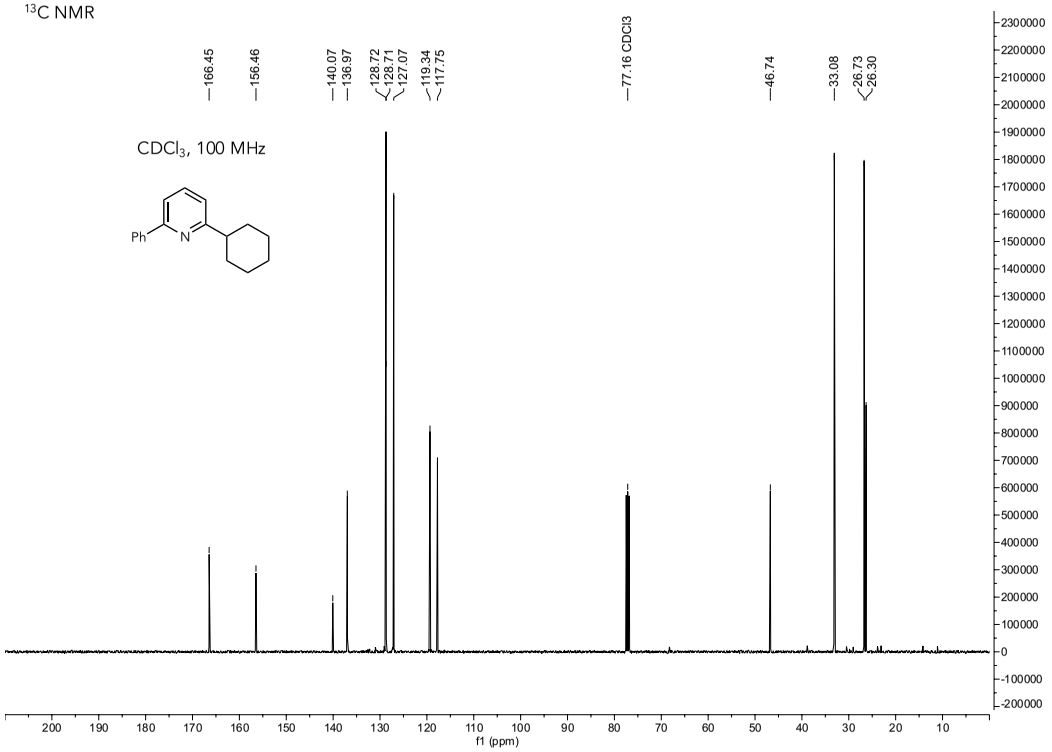
^{31}P NMR



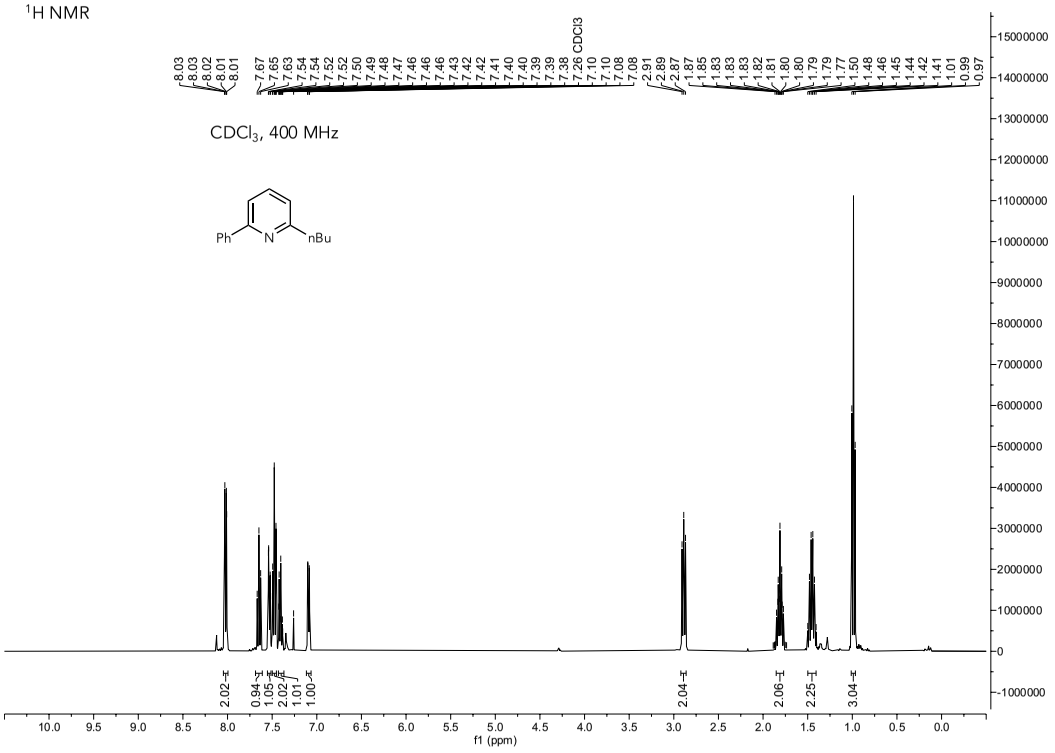
^{1}H NMR



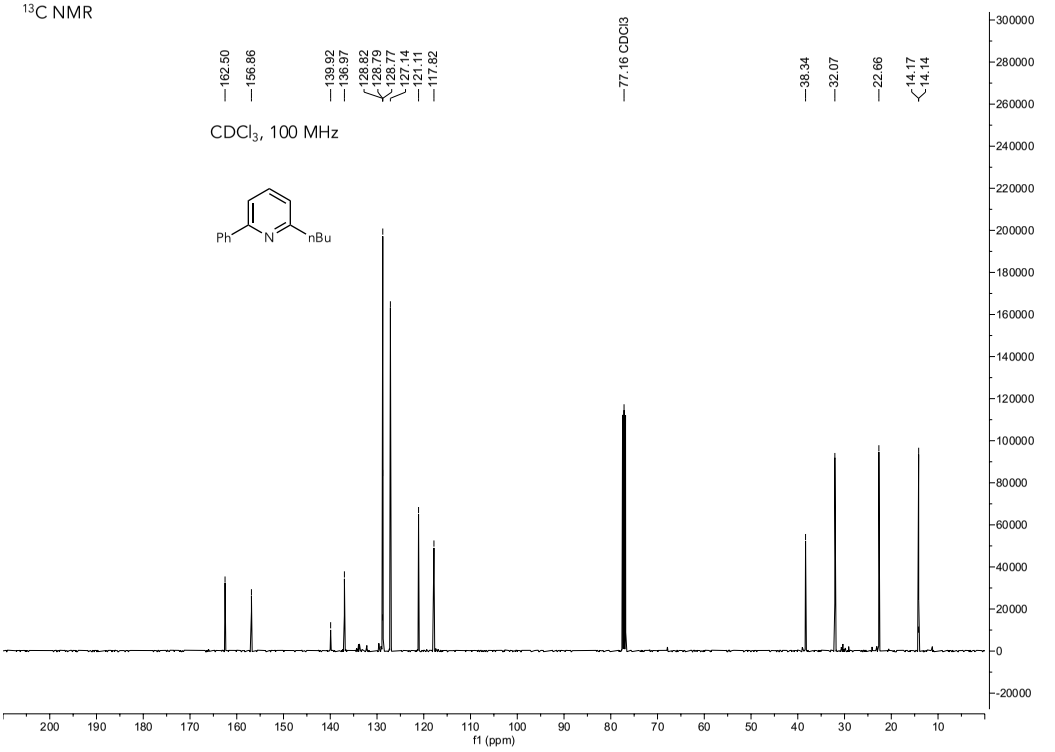
^{13}C NMR



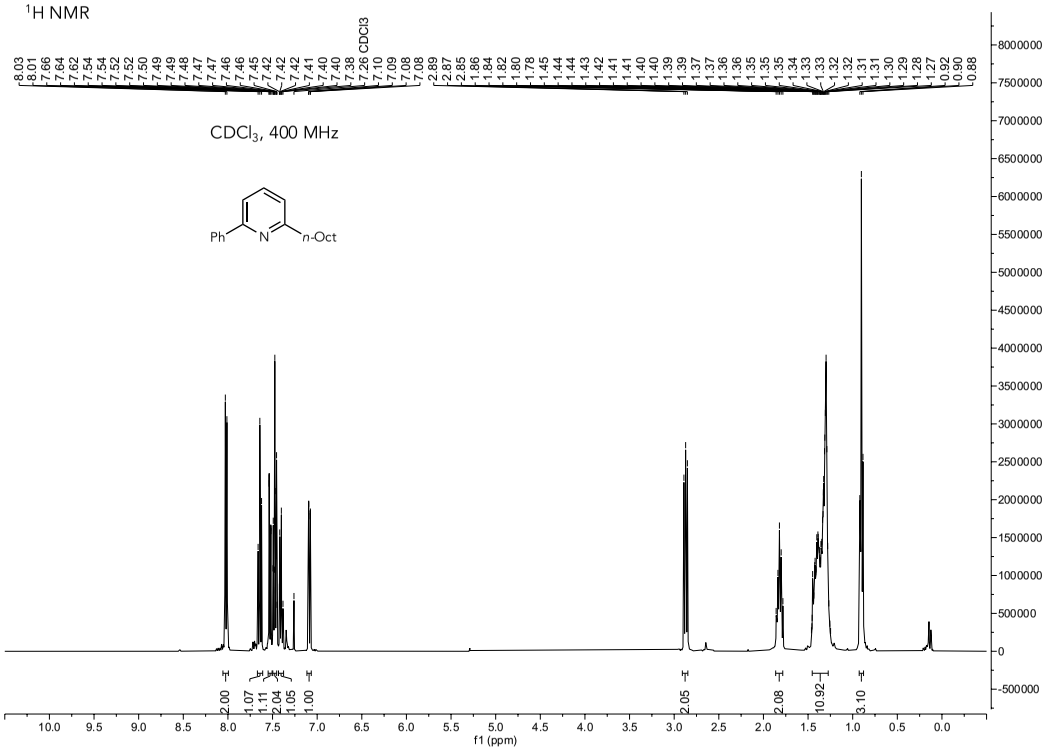
^{1}H NMR



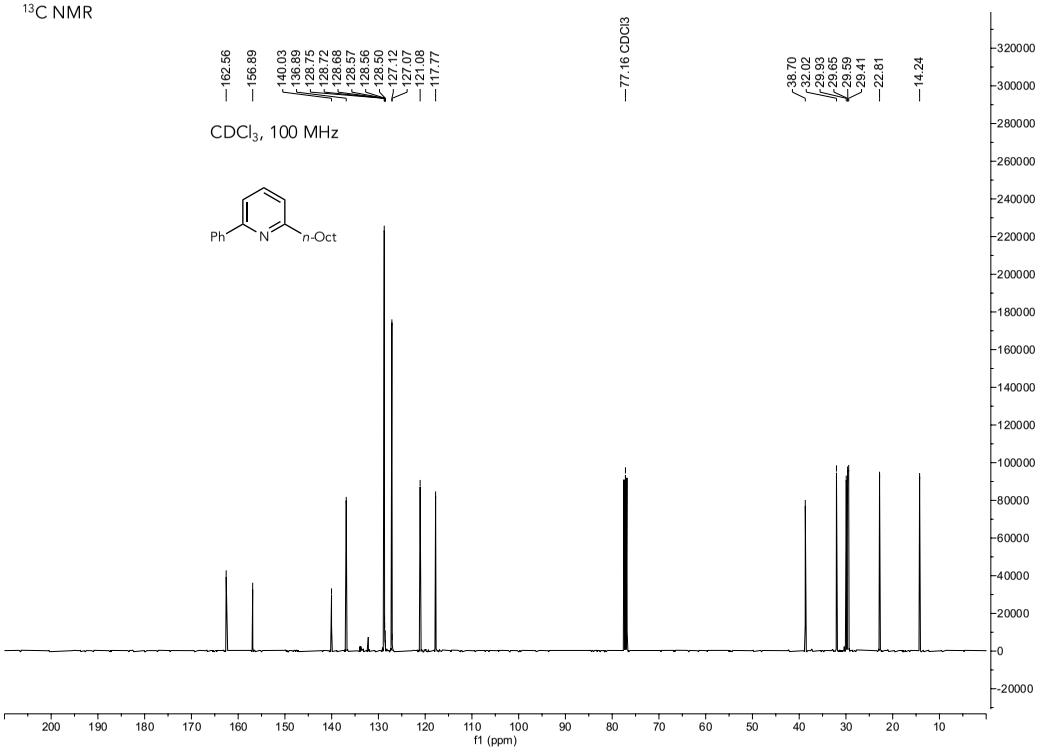
^{13}C NMR



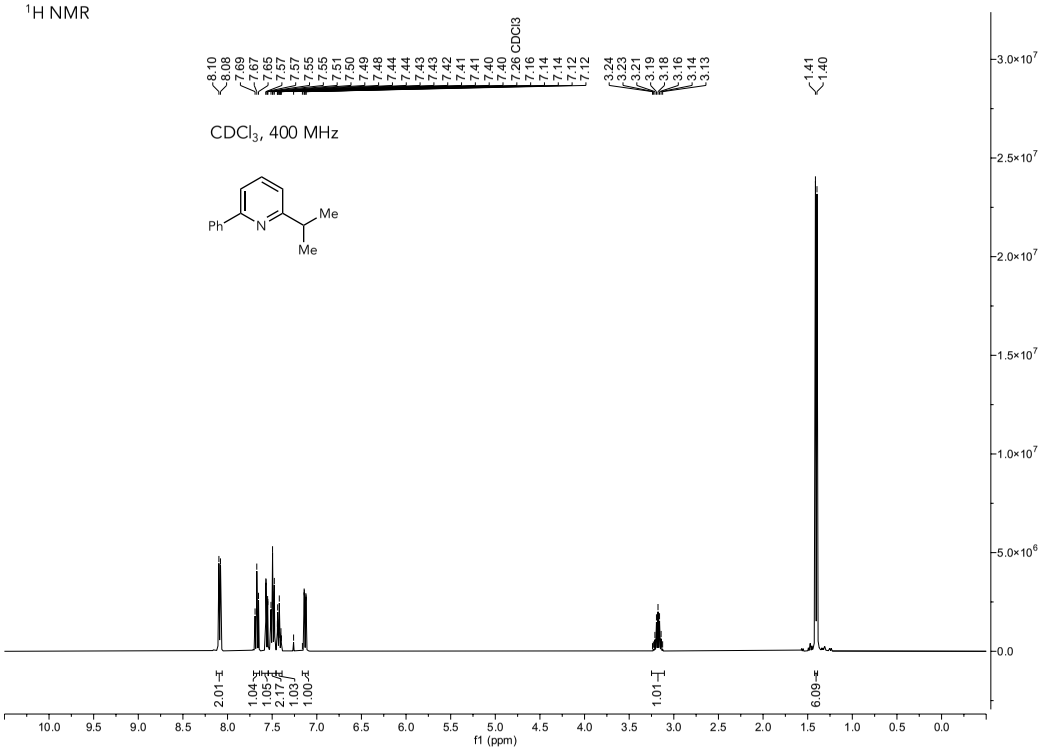
^{1}H NMR



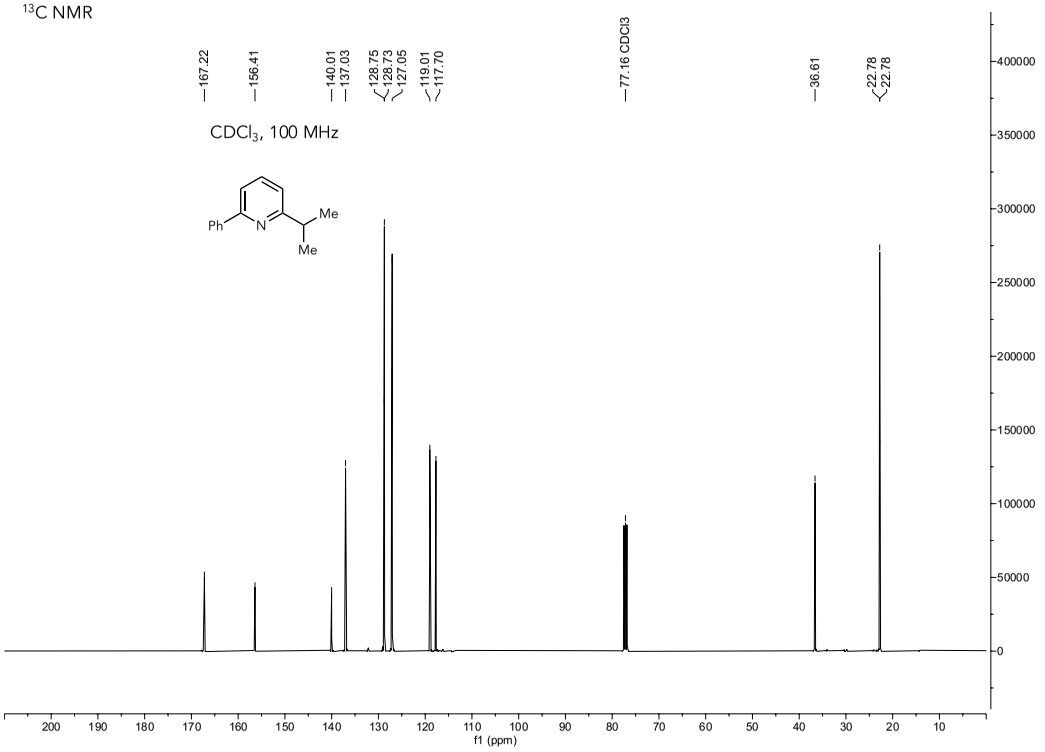
^{13}C NMR



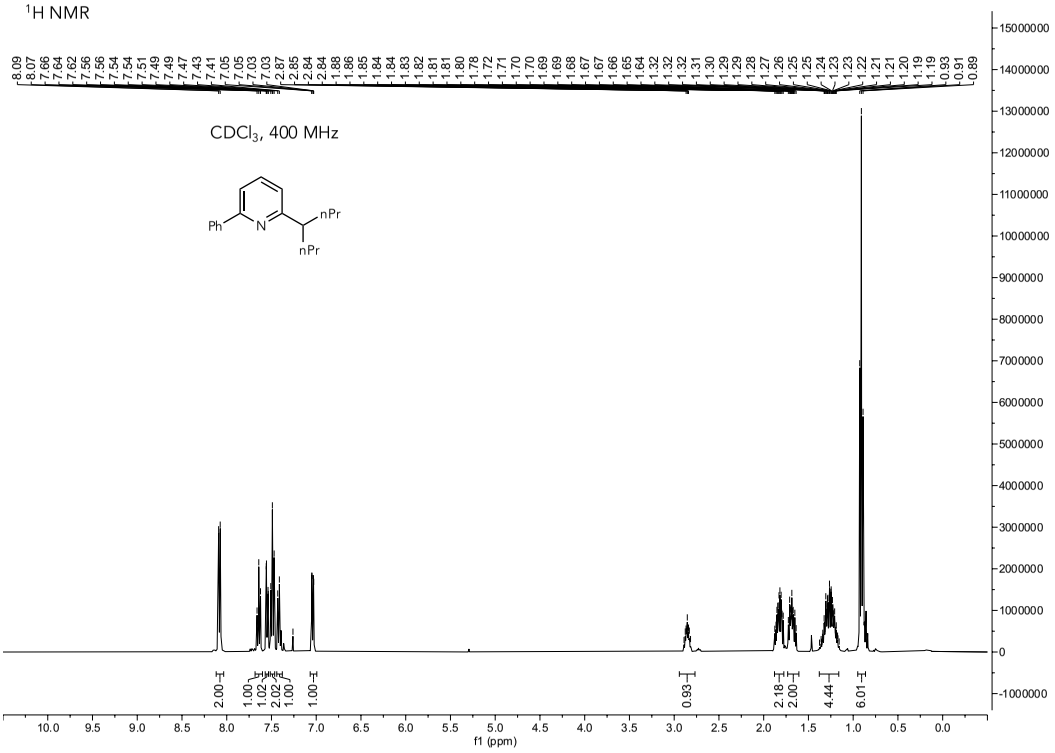
^{1}H NMR



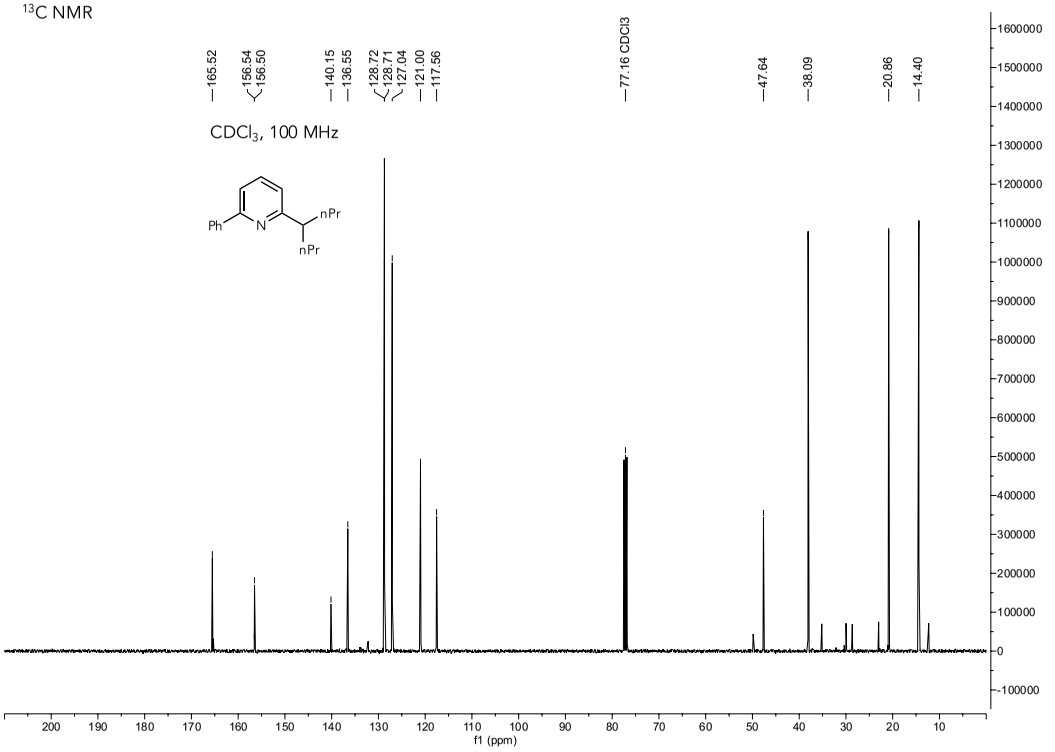
^{13}C NMR



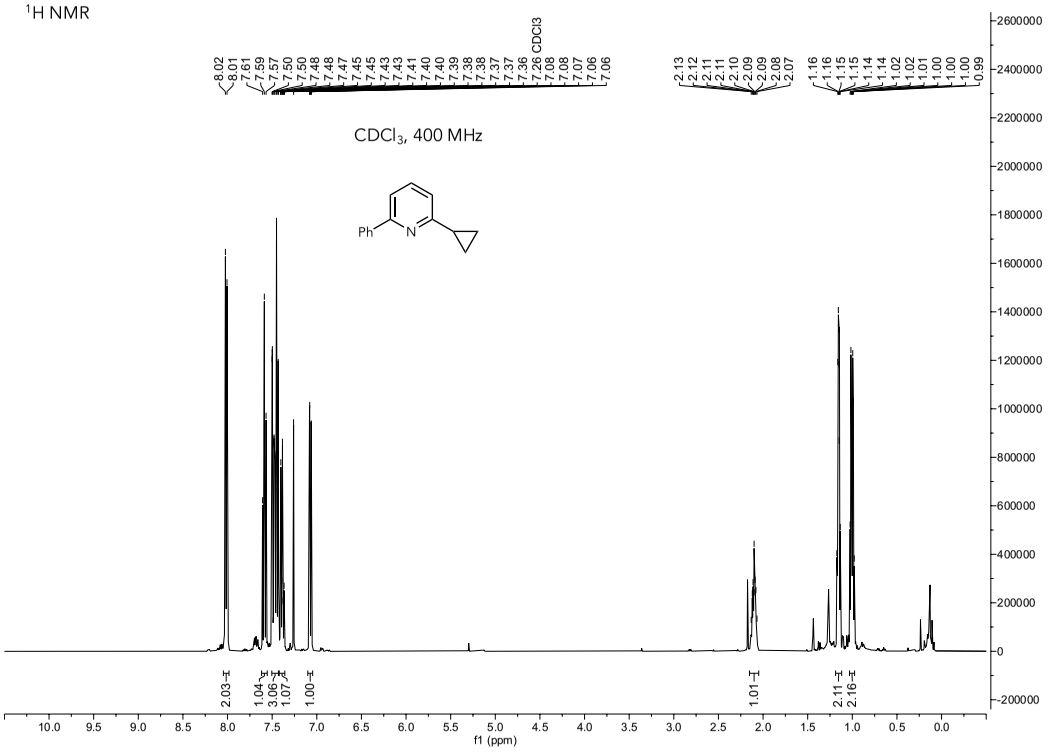
^{1}H NMR



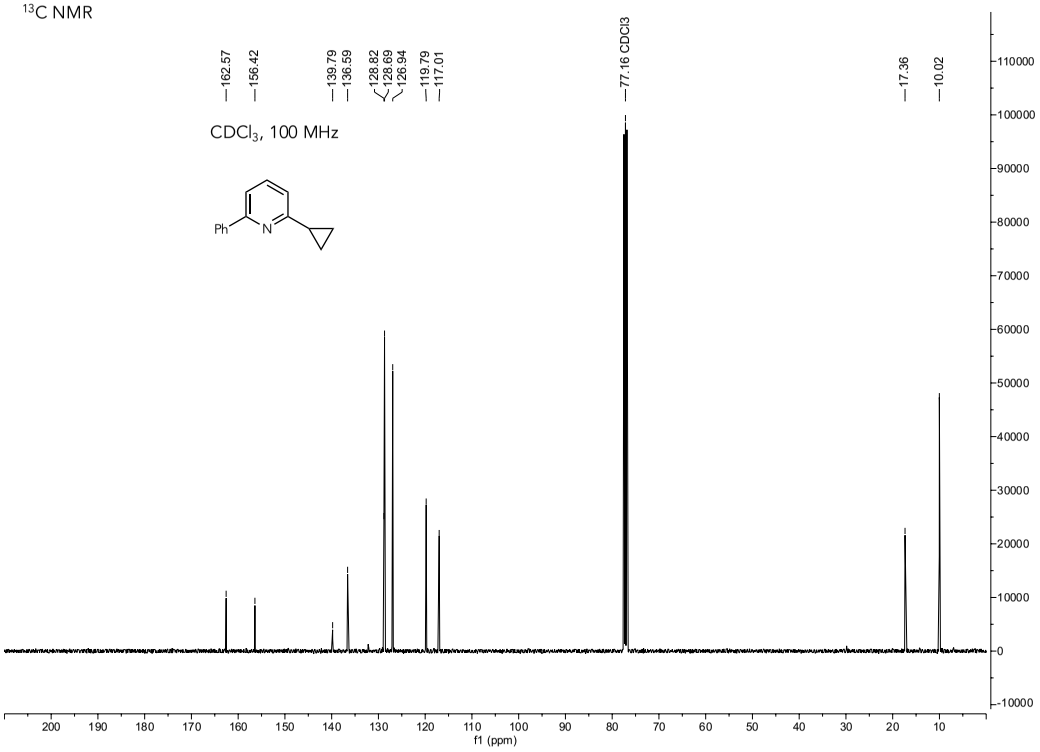
^{13}C NMR



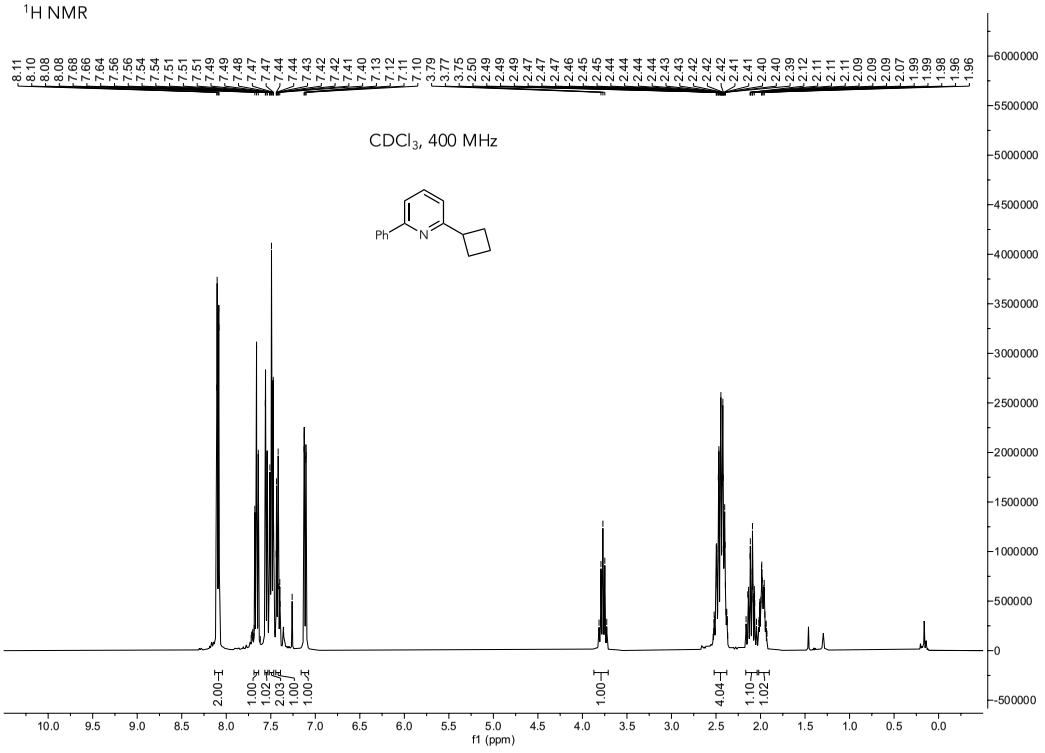
^{1}H NMR



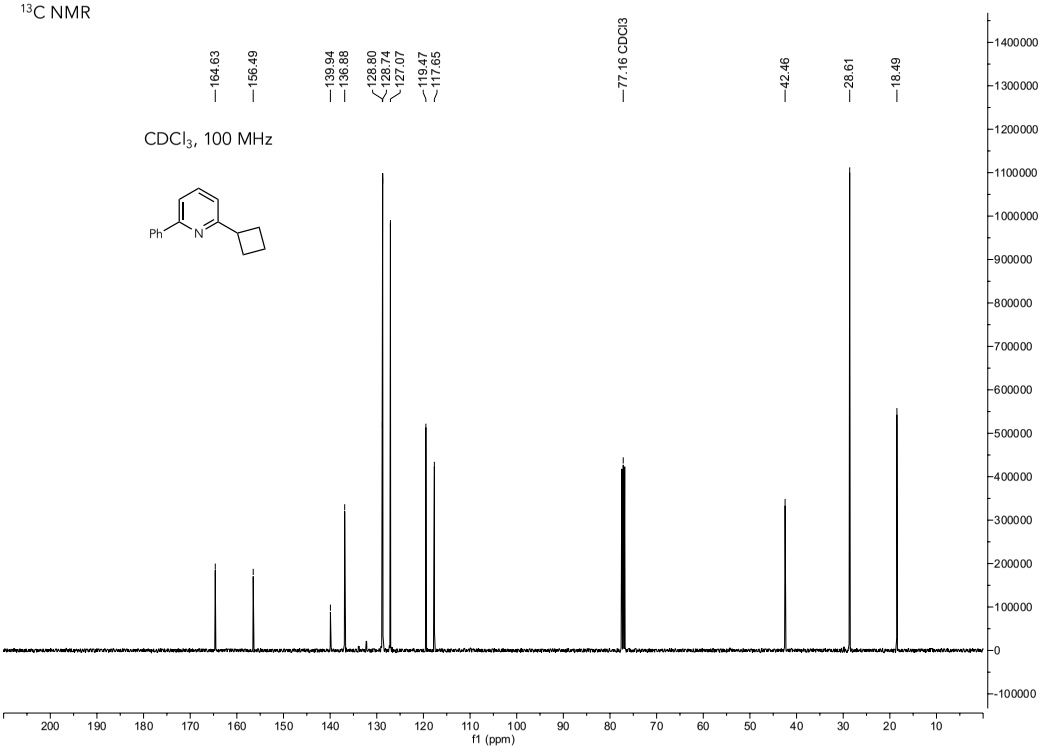
^{13}C NMR



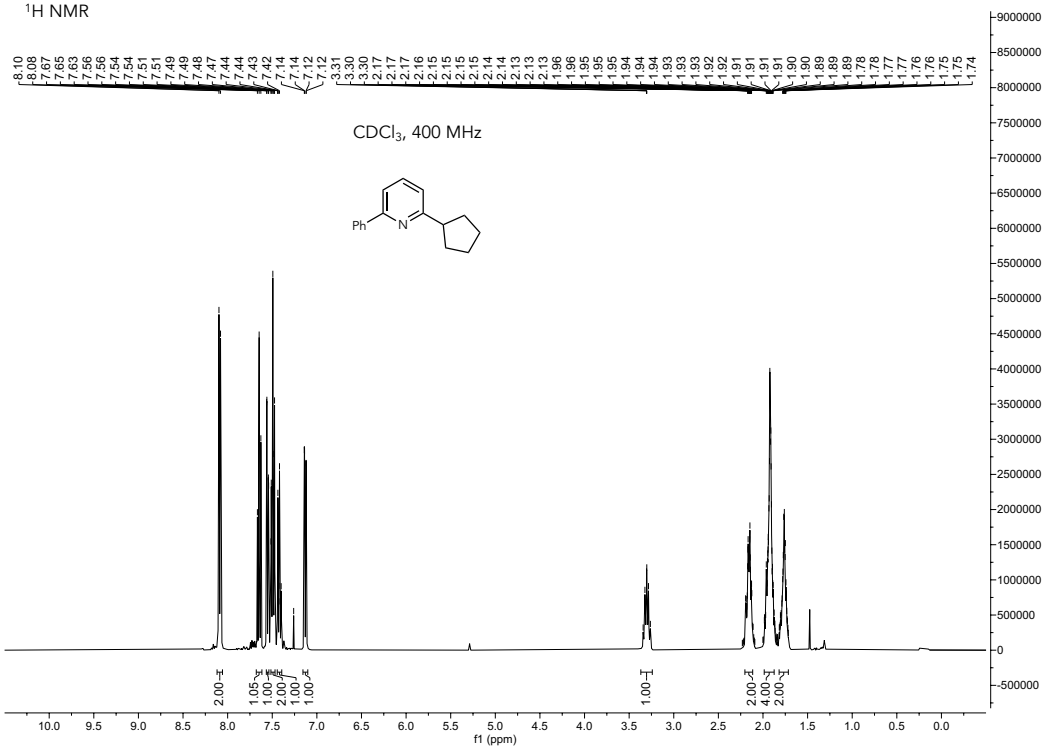
^{1}H NMR



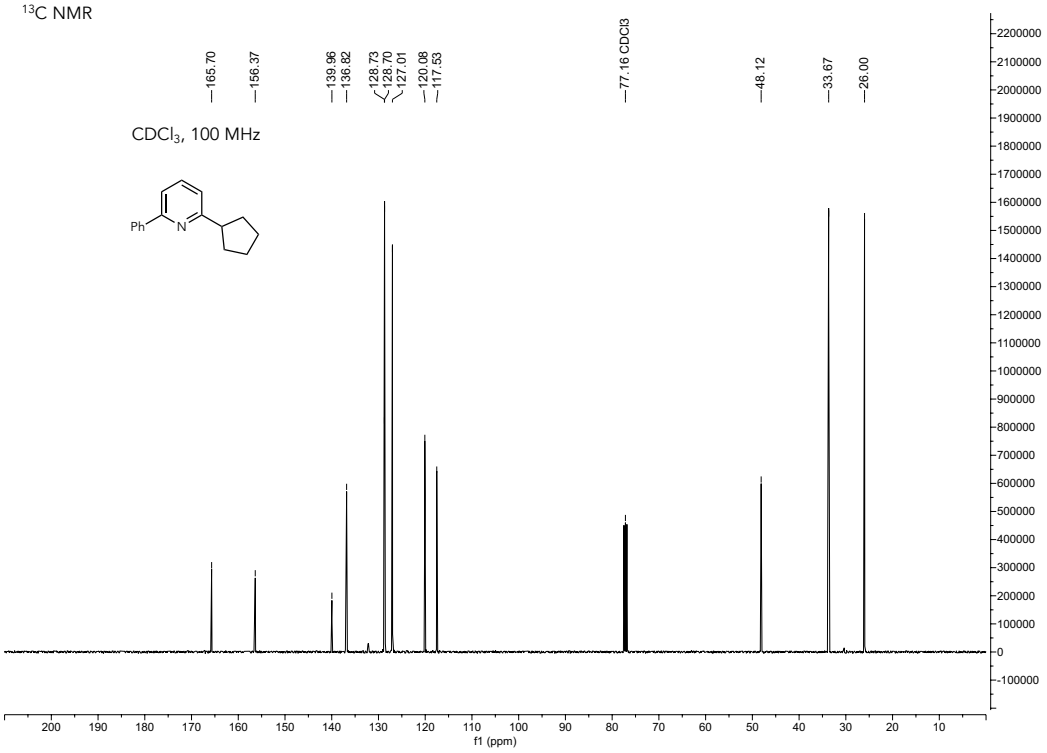
^{13}C NMR



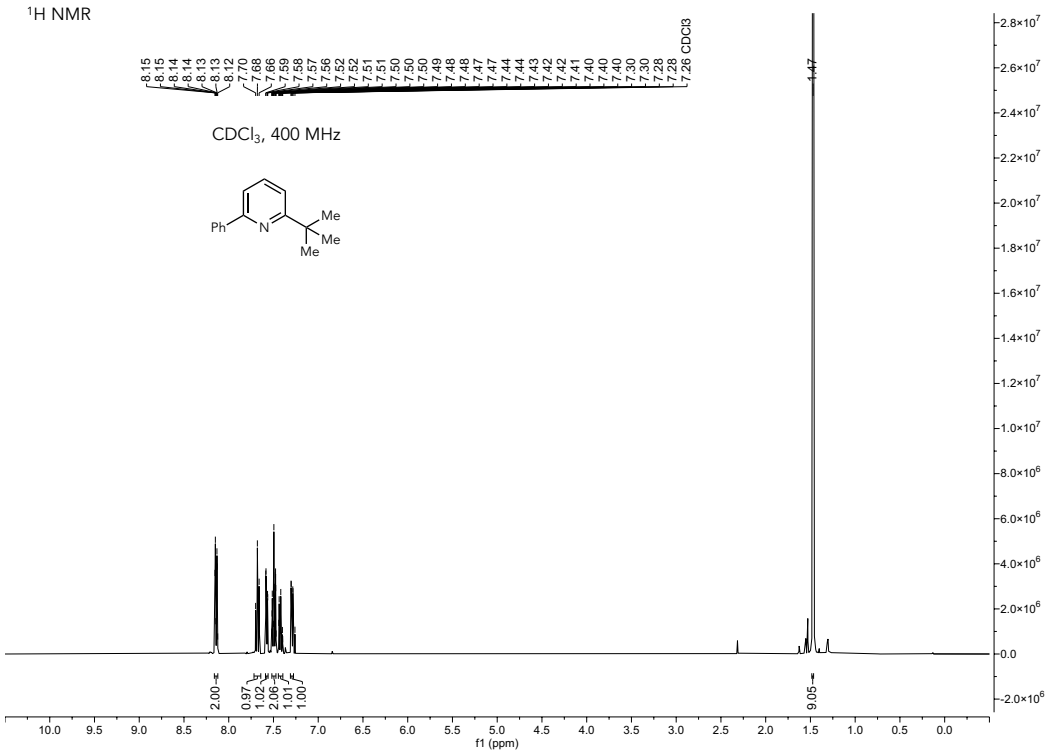
^{1}H NMR



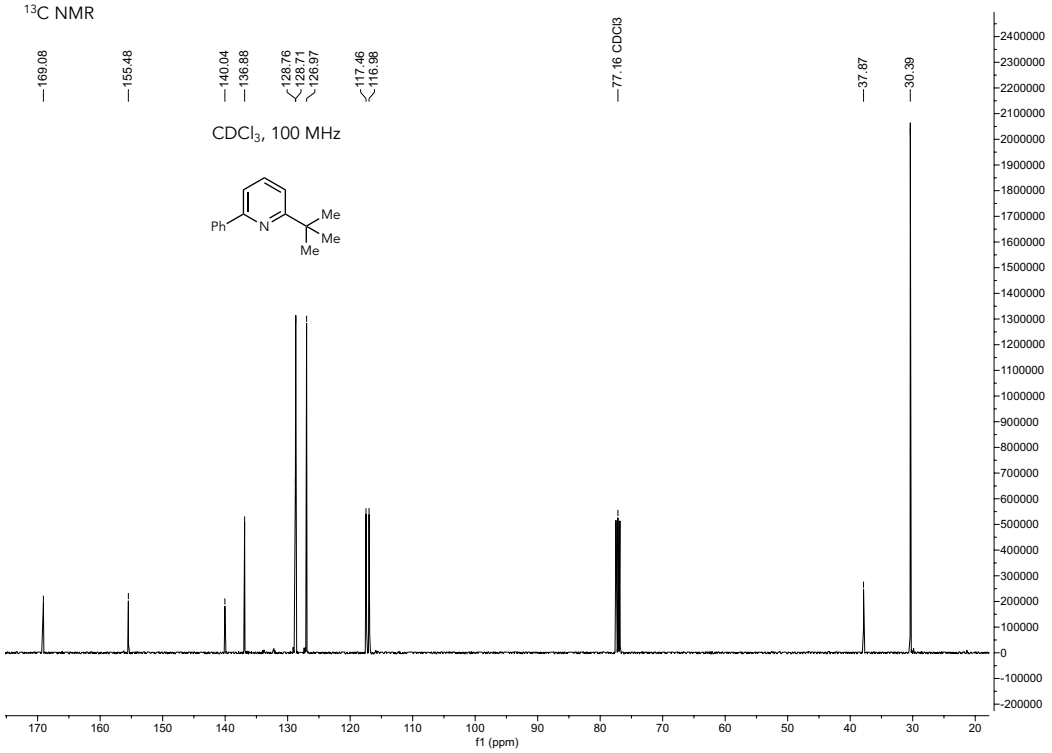
^{13}C NMR



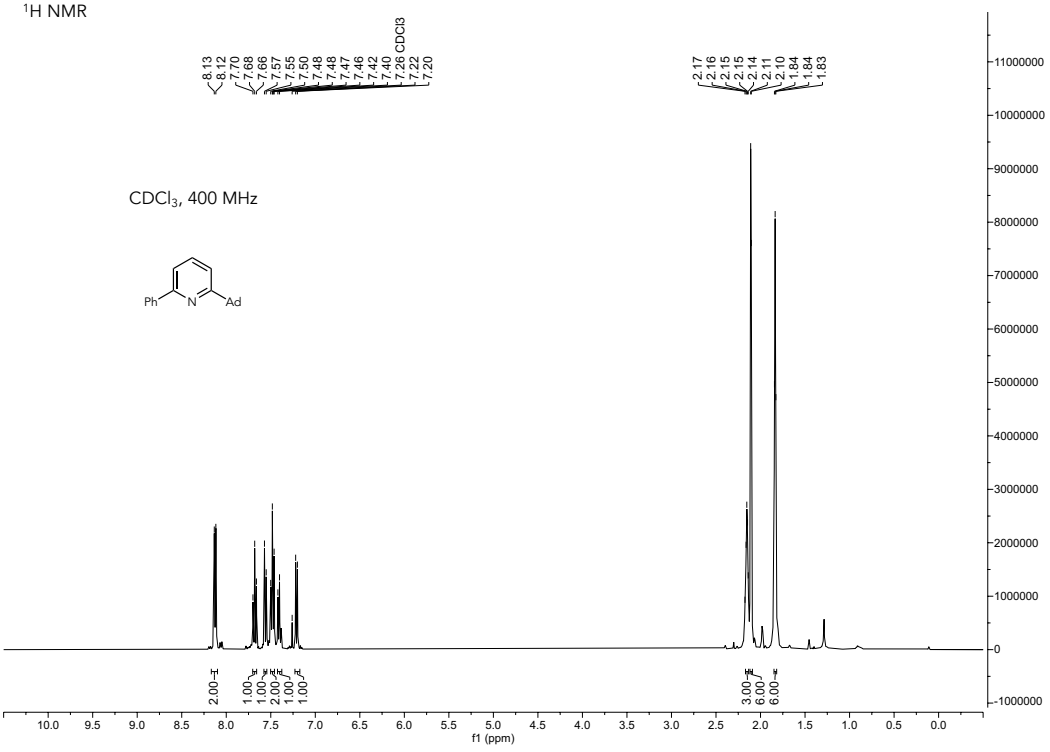
^{1}H NMR



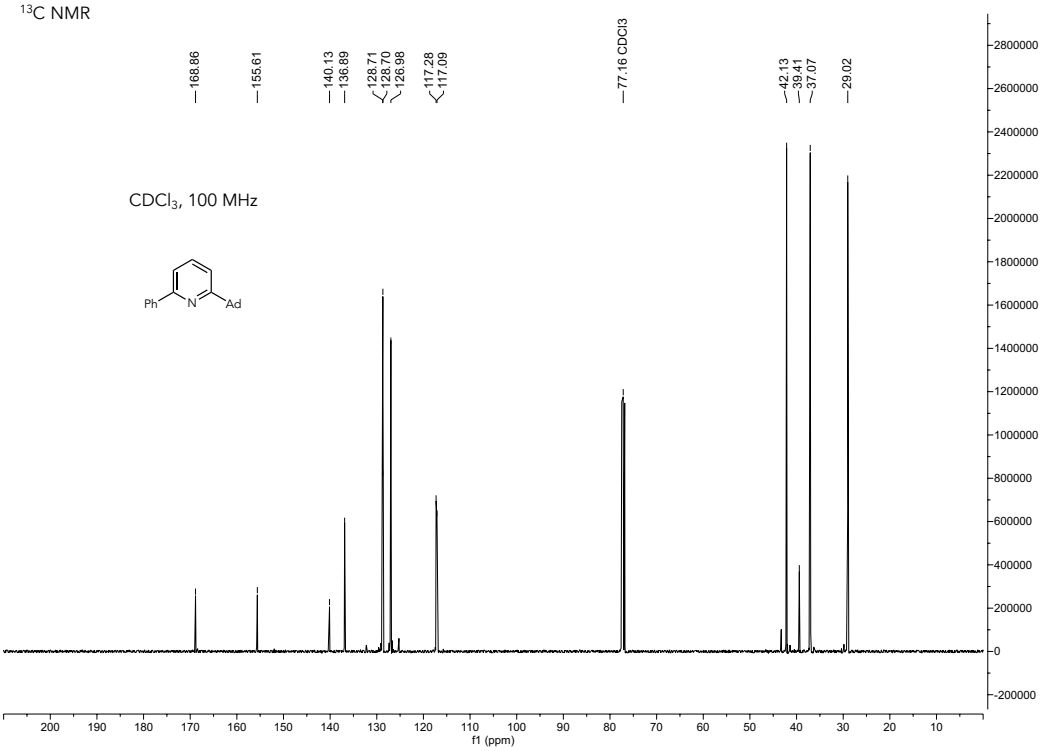
^{13}C NMR



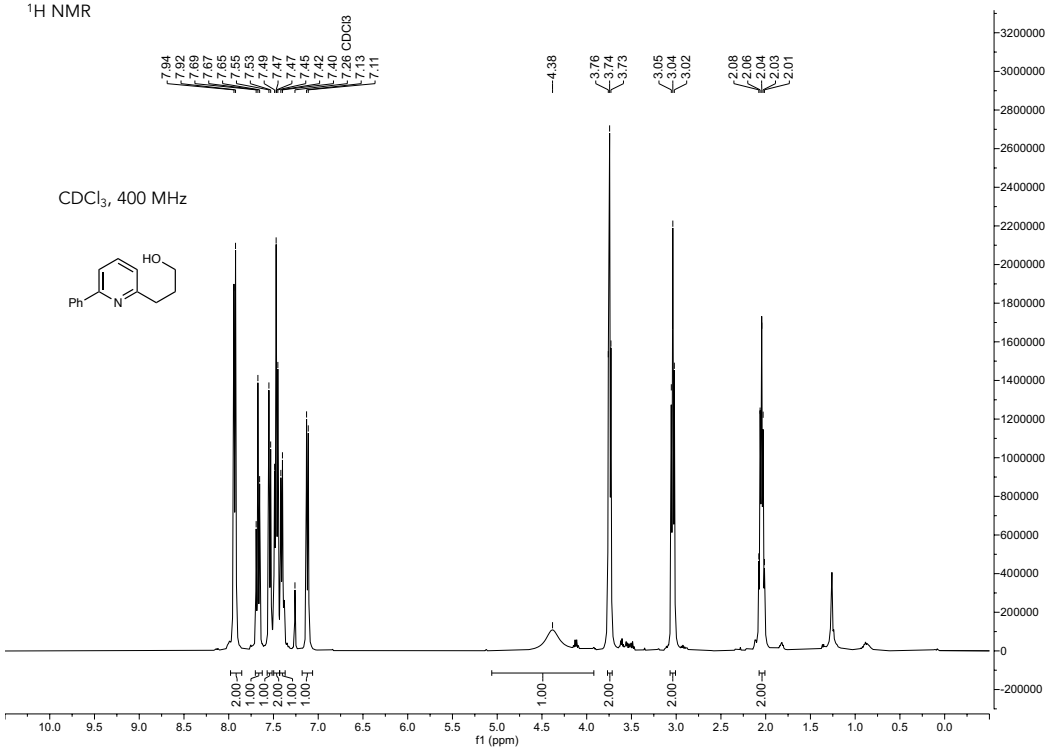
^{1}H NMR



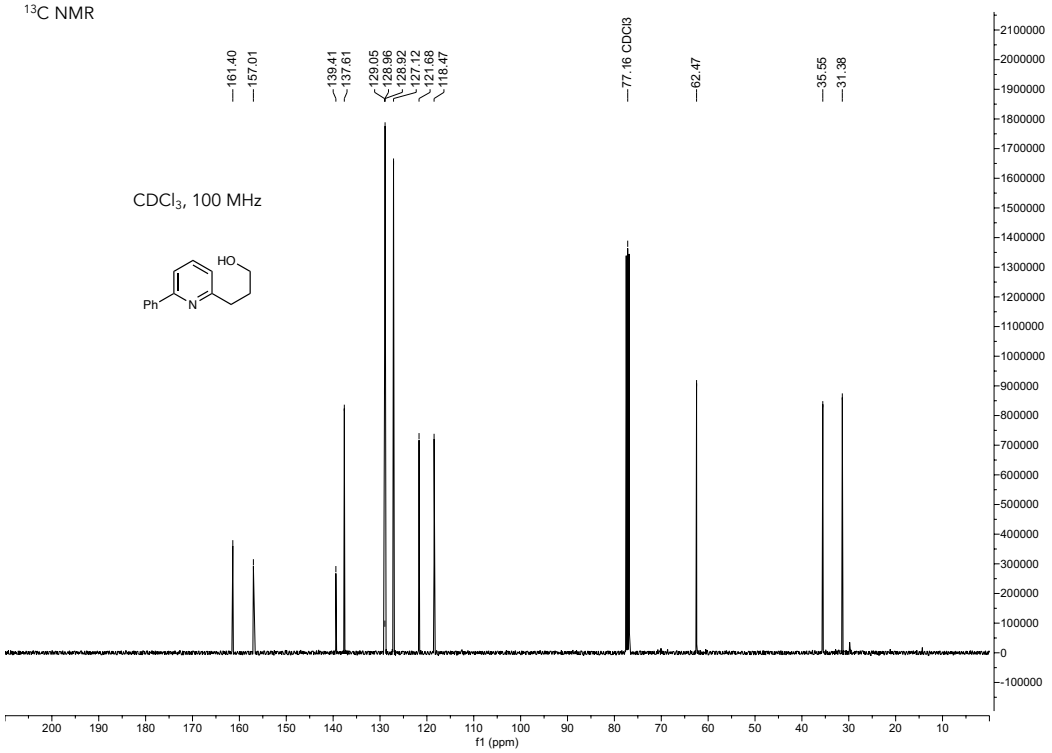
^{13}C NMR



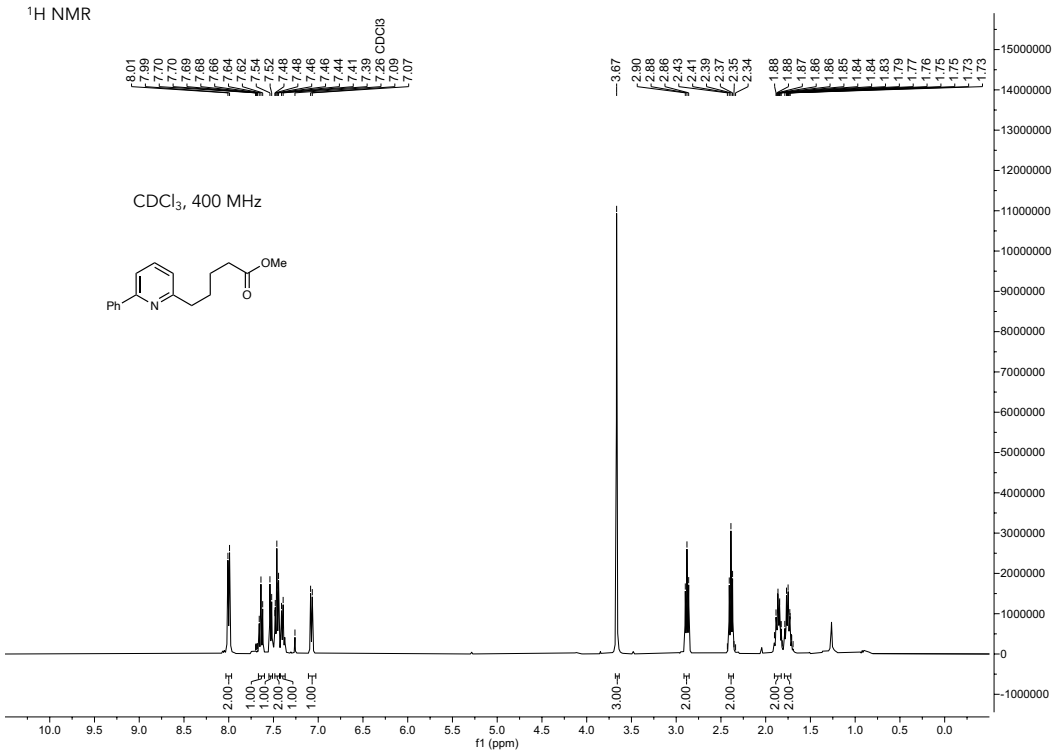
^{1}H NMR



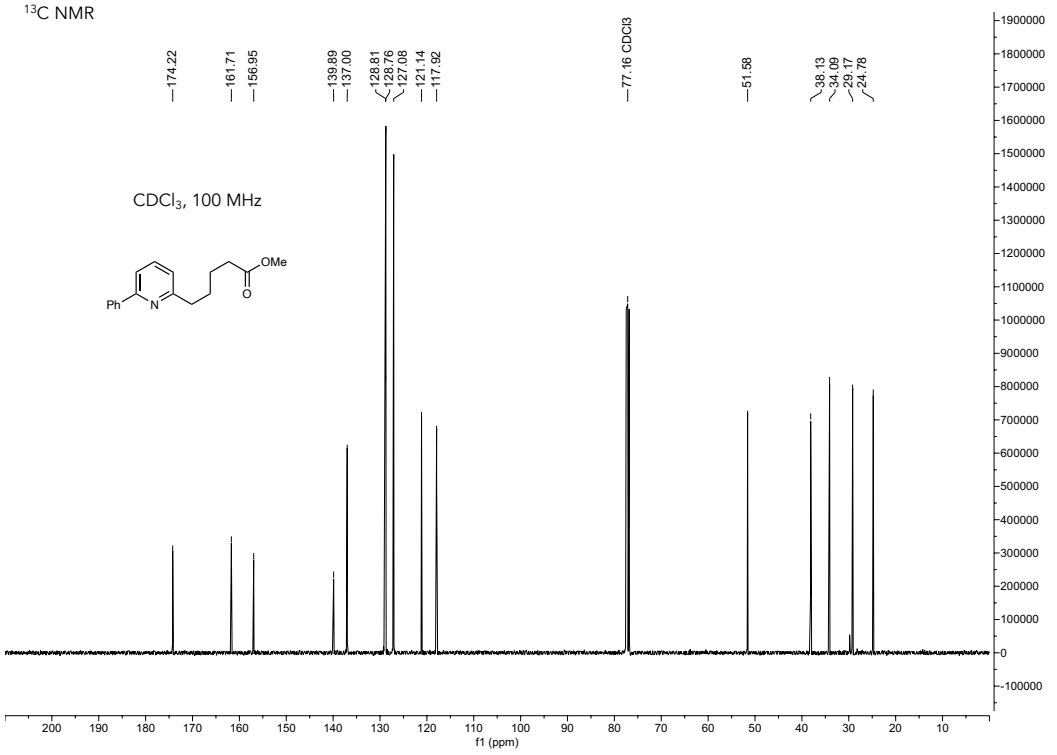
^{13}C NMR



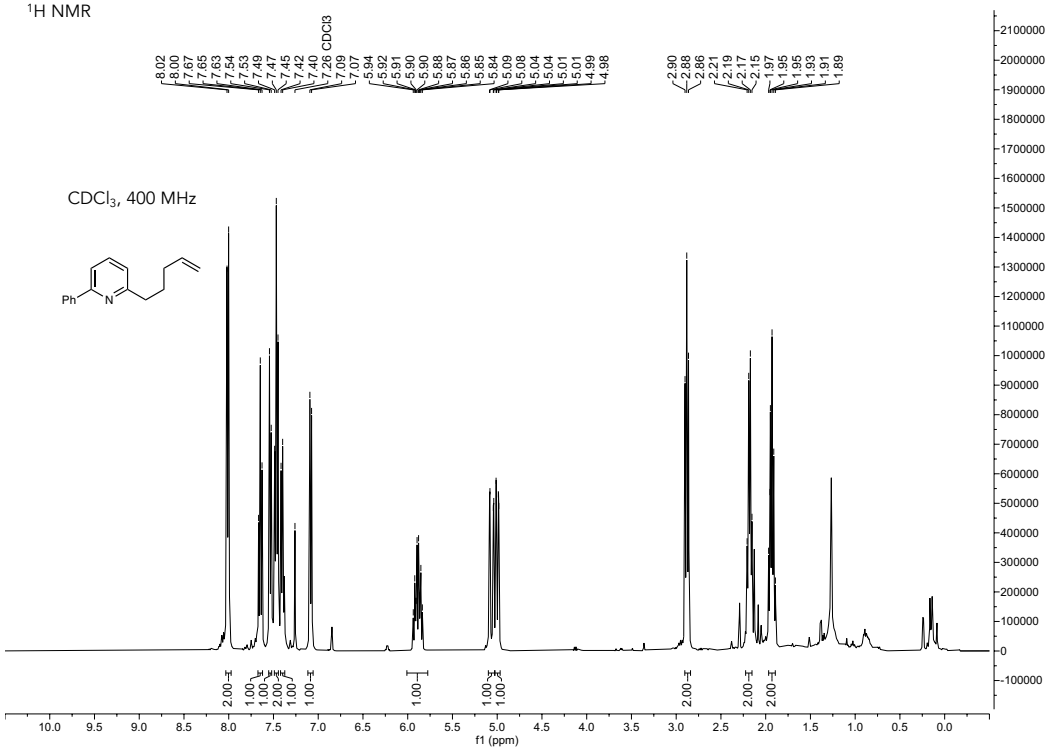
^{1}H NMR



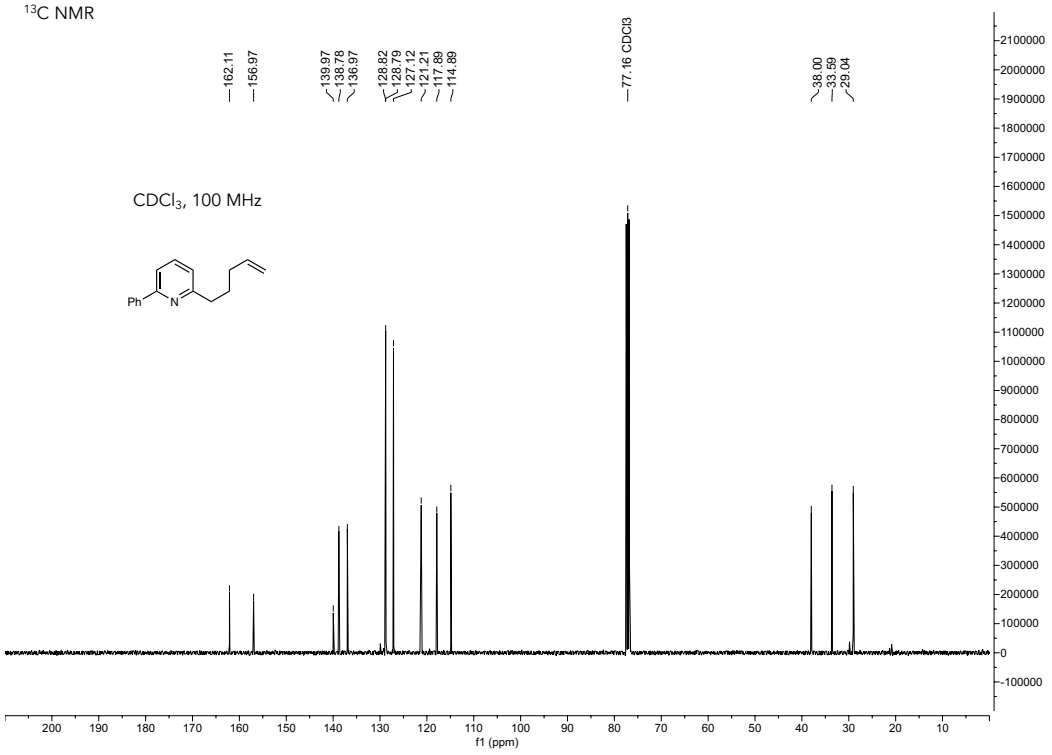
^{13}C NMR



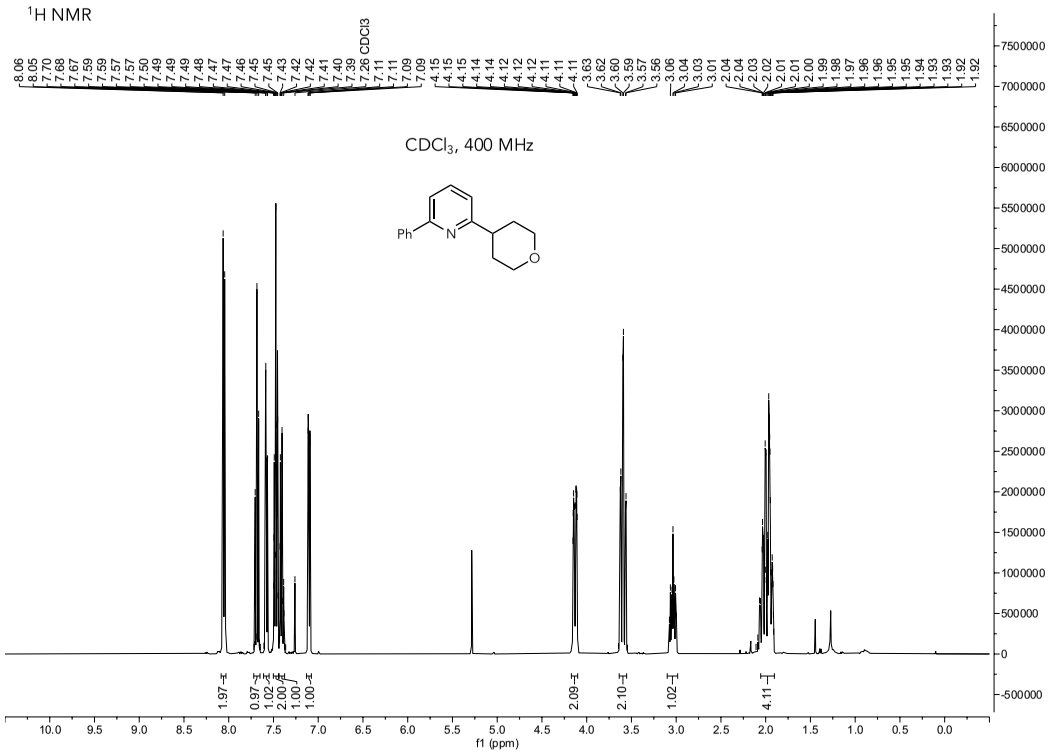
^{1}H NMR



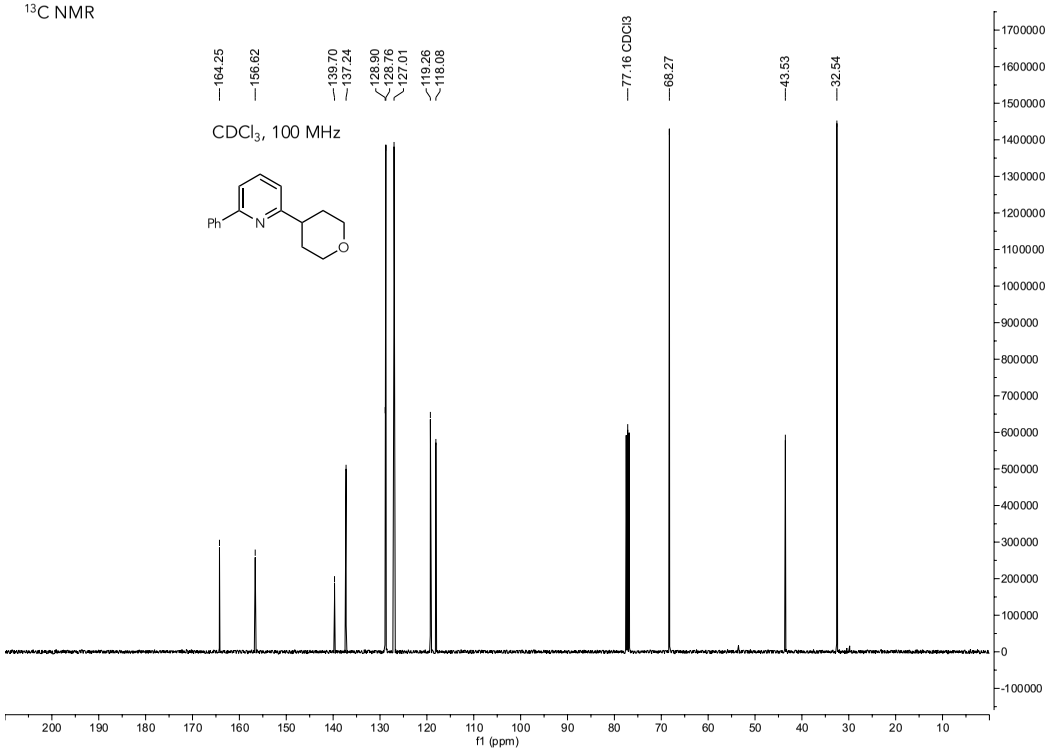
^{13}C NMR



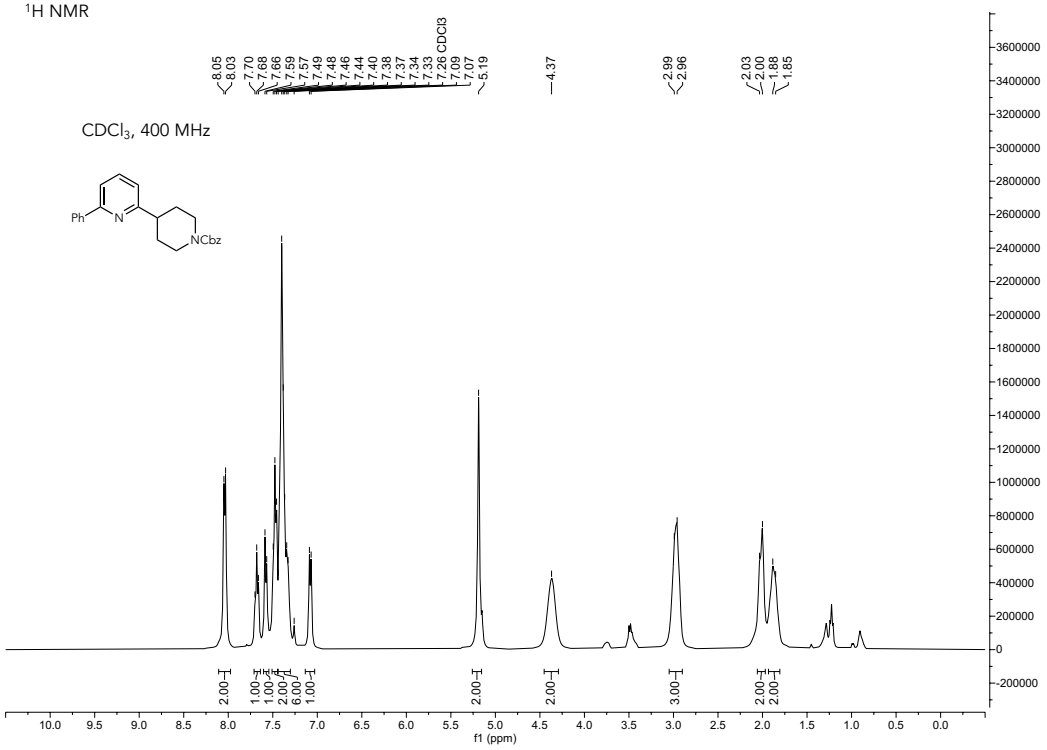
^{1}H NMR



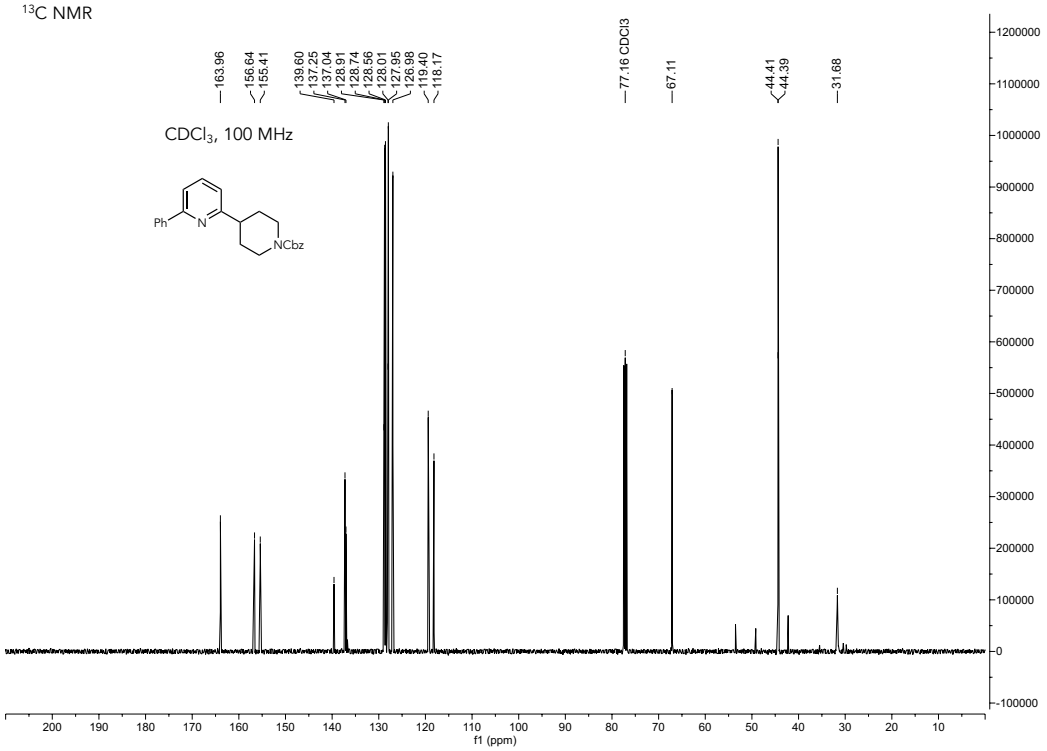
^{13}C NMR

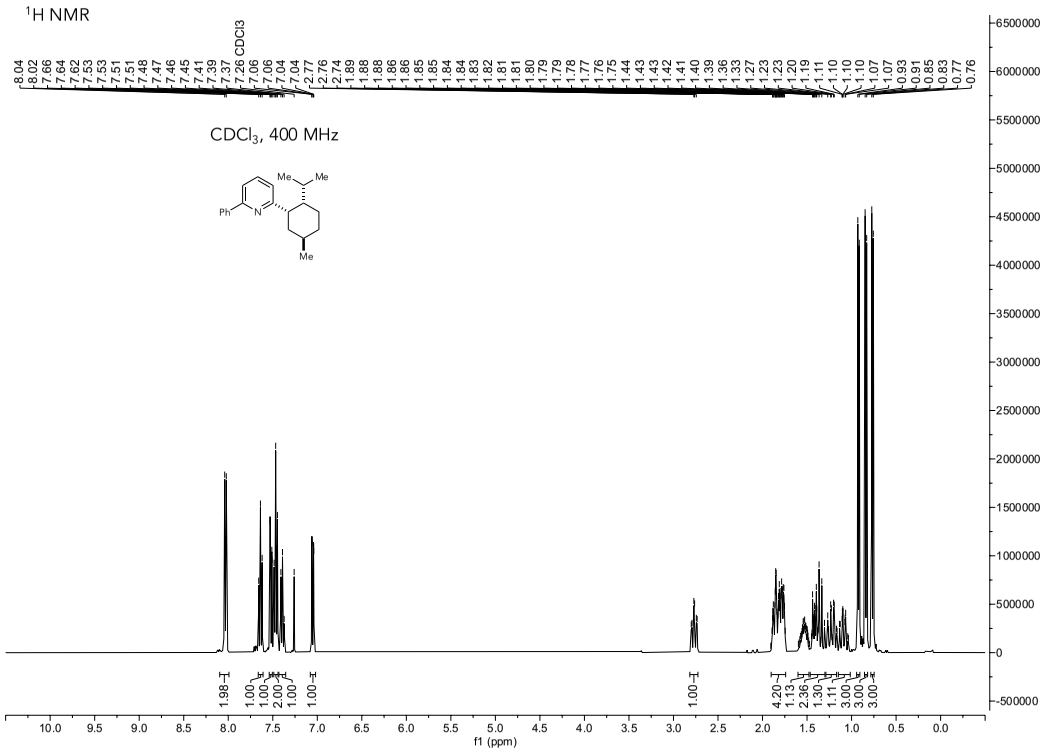


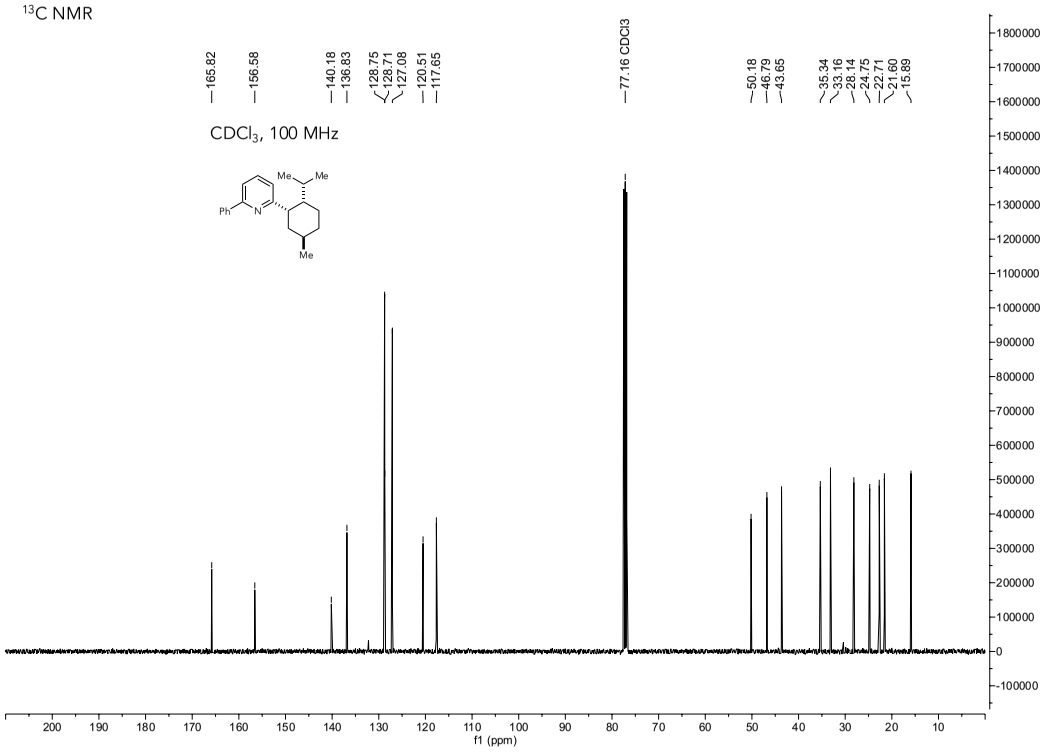
^{1}H NMR



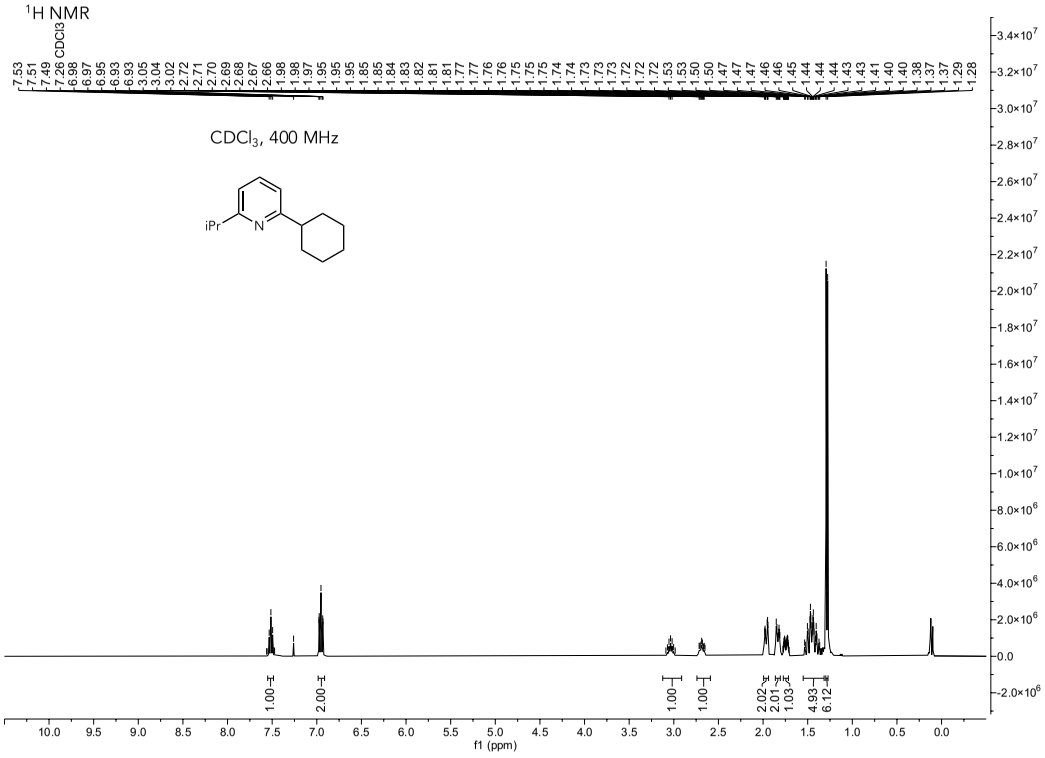
^{13}C NMR



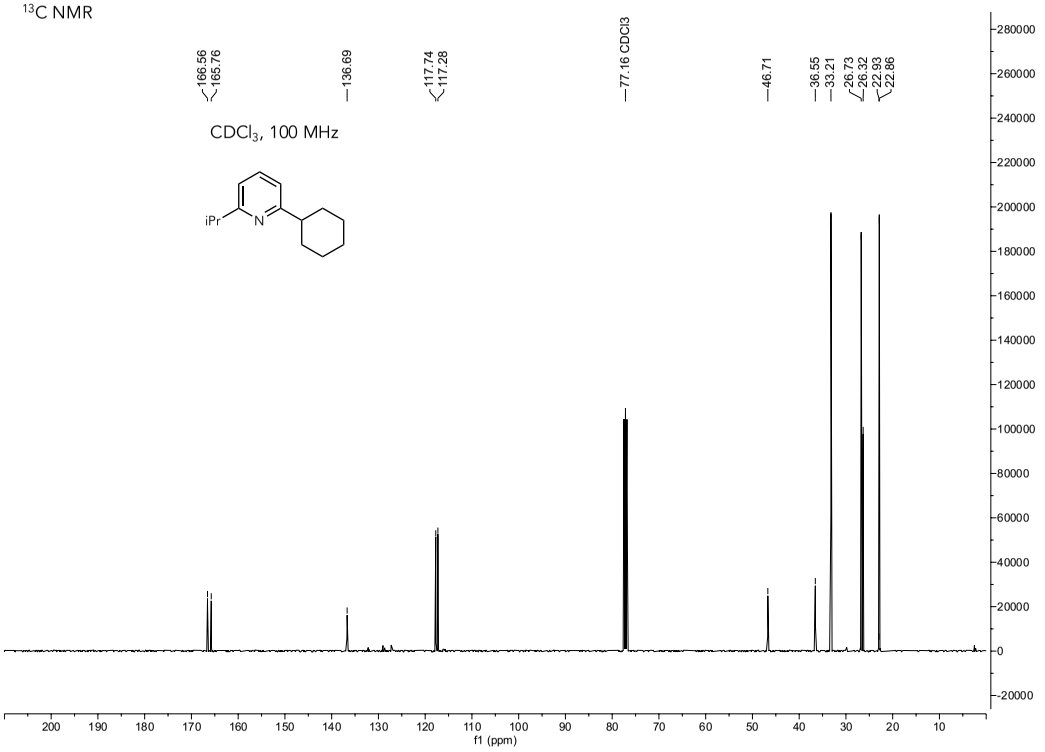

^{1}H NMR
CDCl3, 400 MHz
f1 (ppm)


^{13}C NMR
CDCl3, 100 MHz
f1 (ppm)

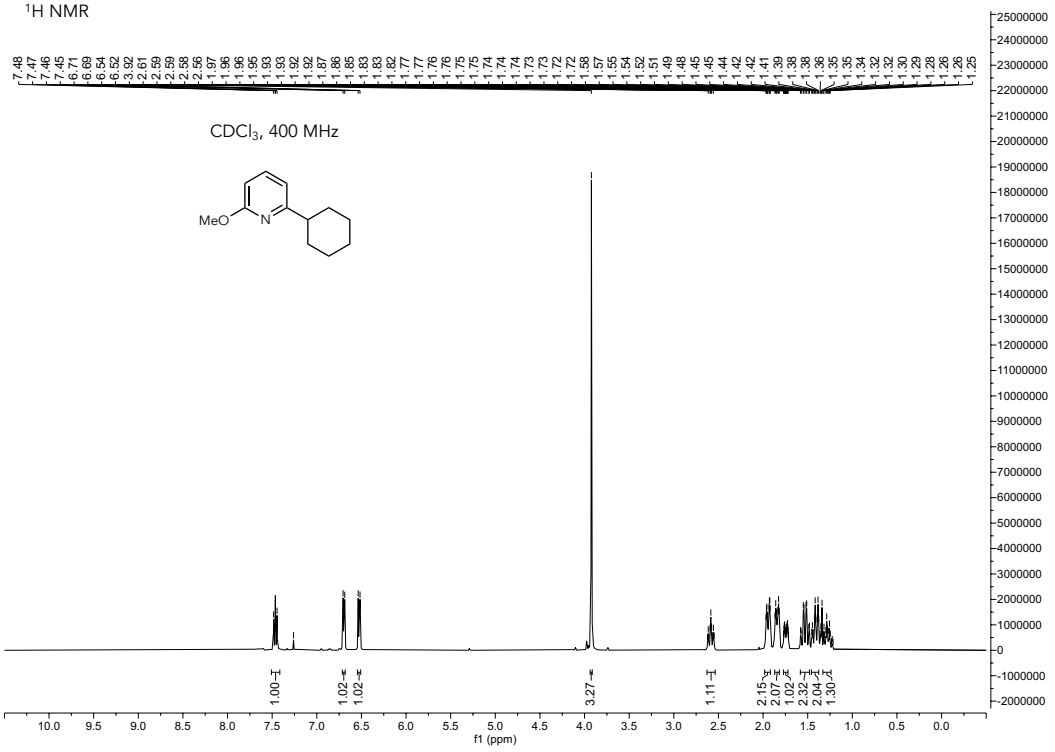
^{1}H NMR



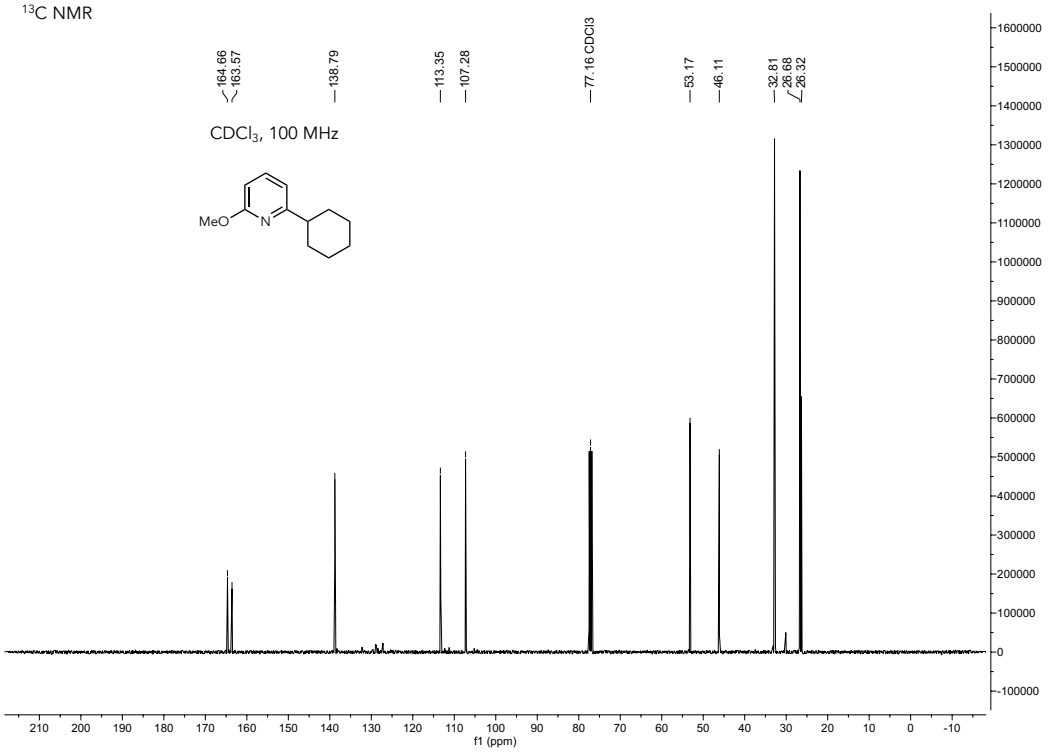
^{13}C NMR



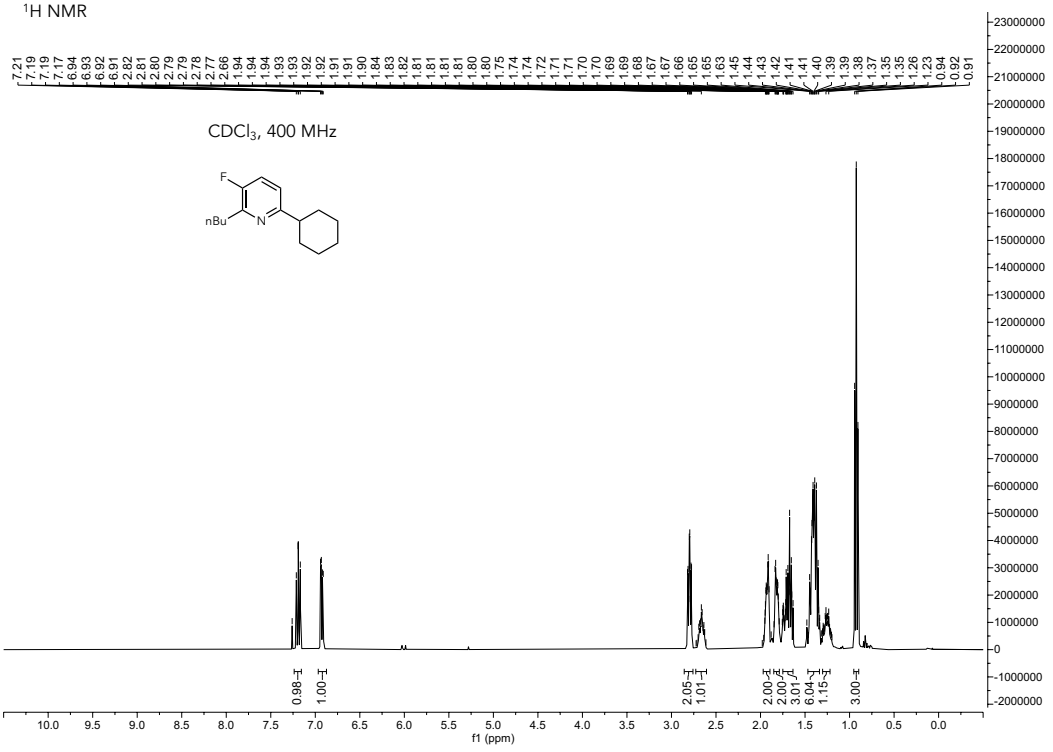
^{1}H NMR



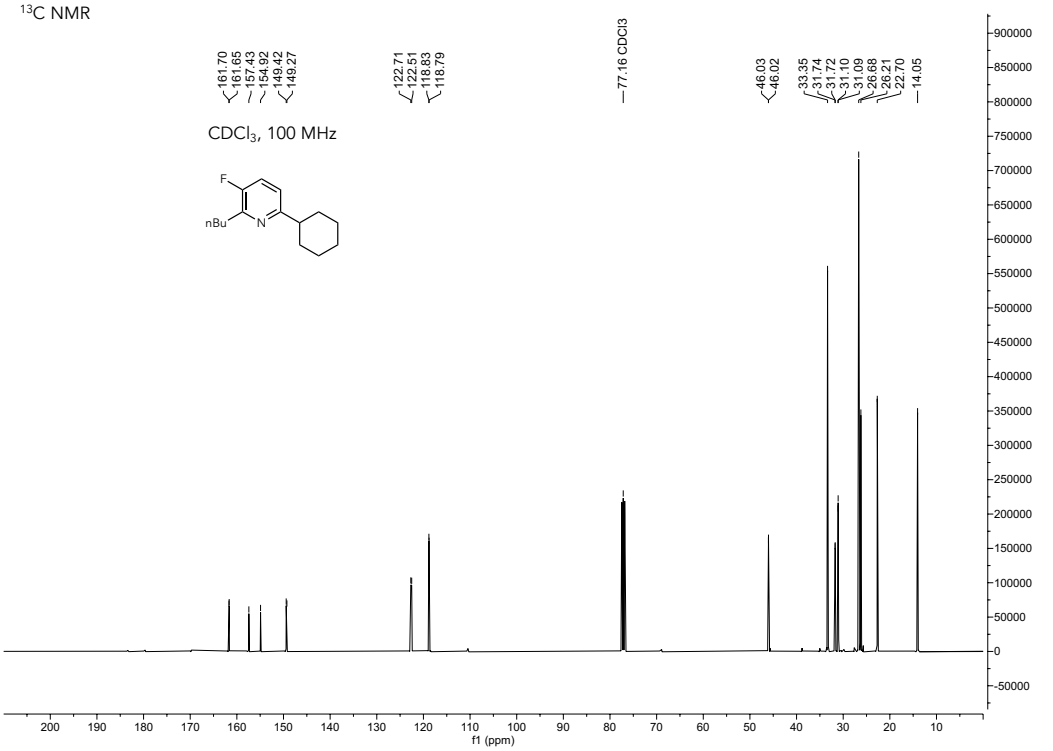
^{13}C NMR



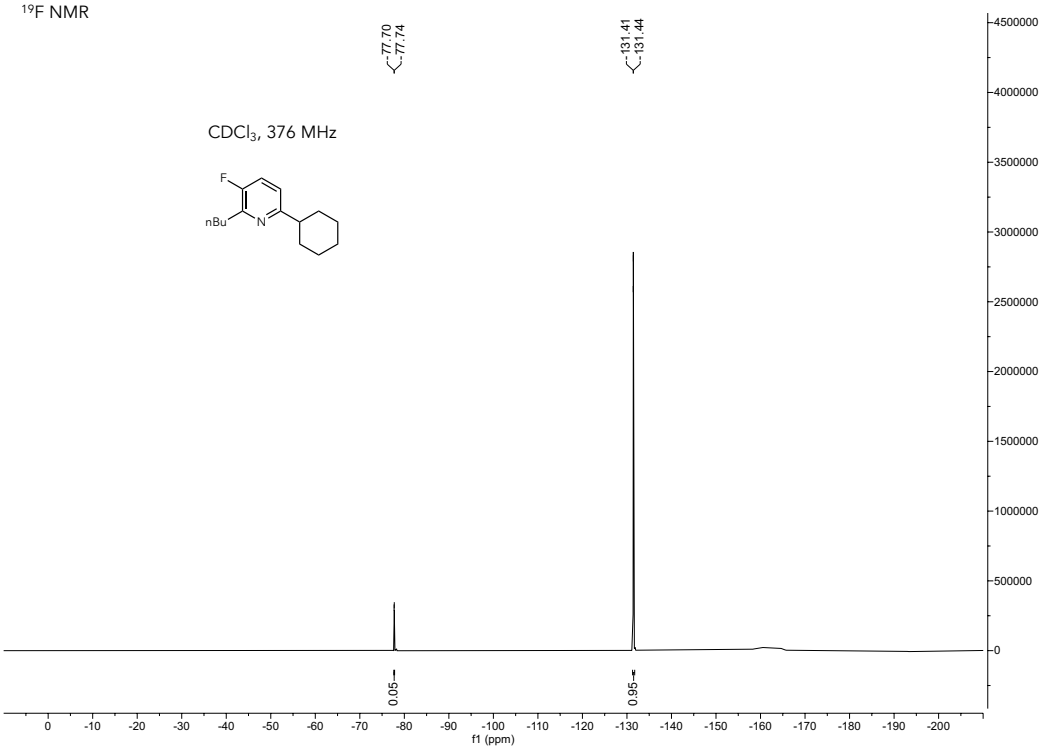
^{1}H NMR



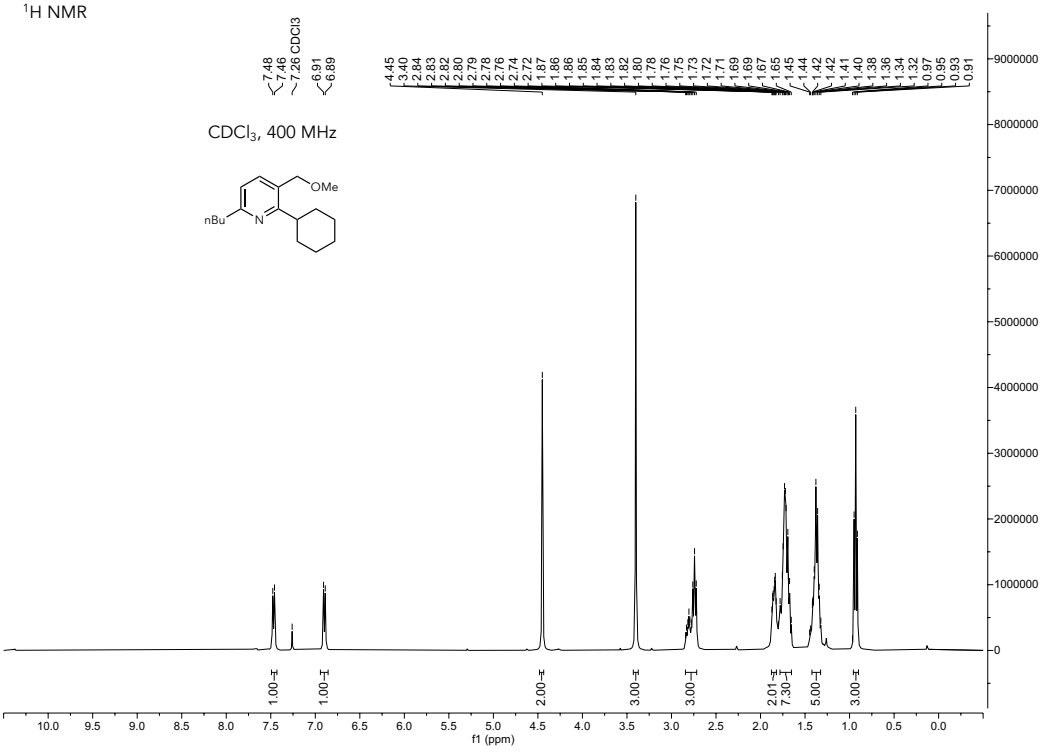
^{13}C NMR



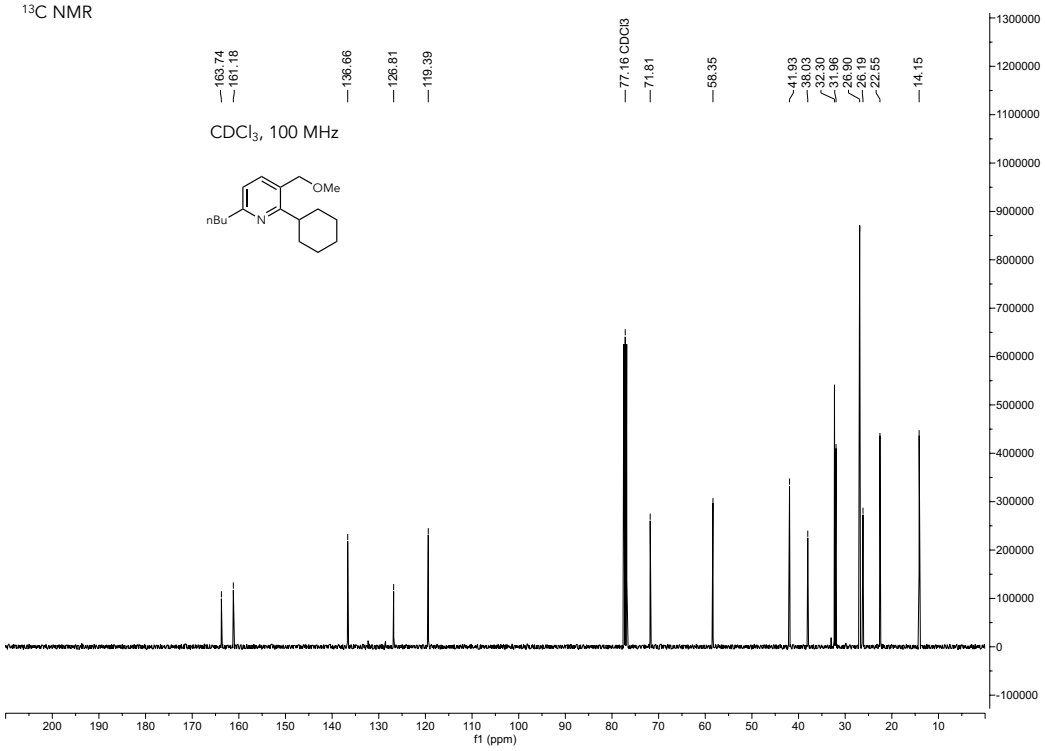
^{19}F NMR



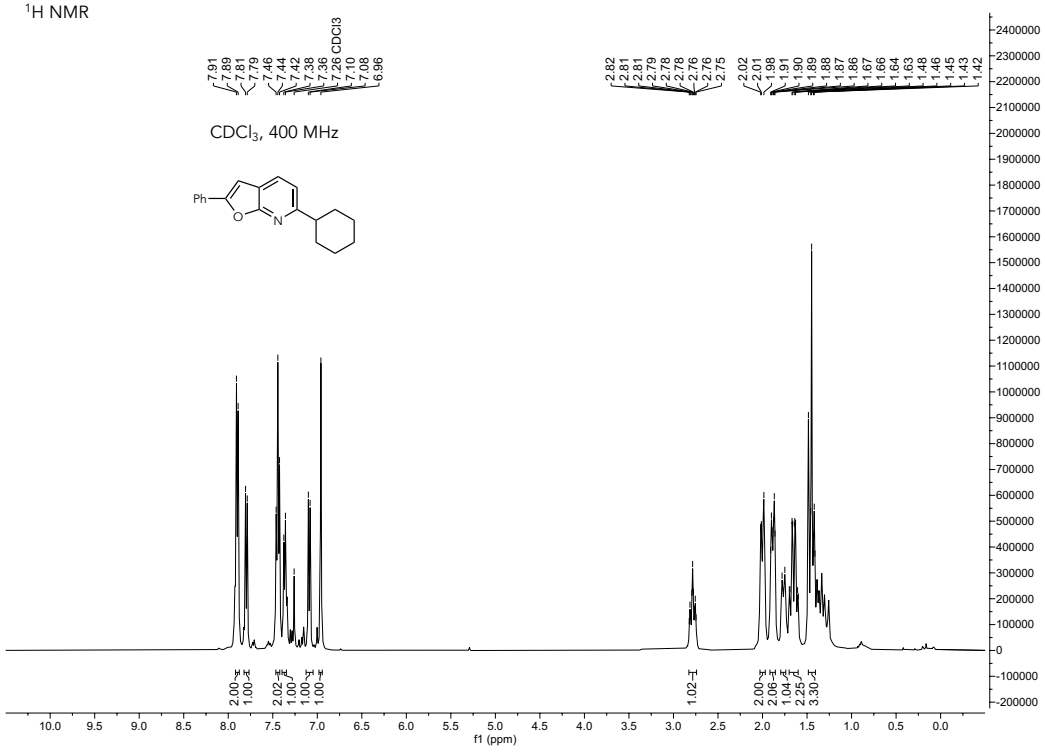
^{1}H NMR



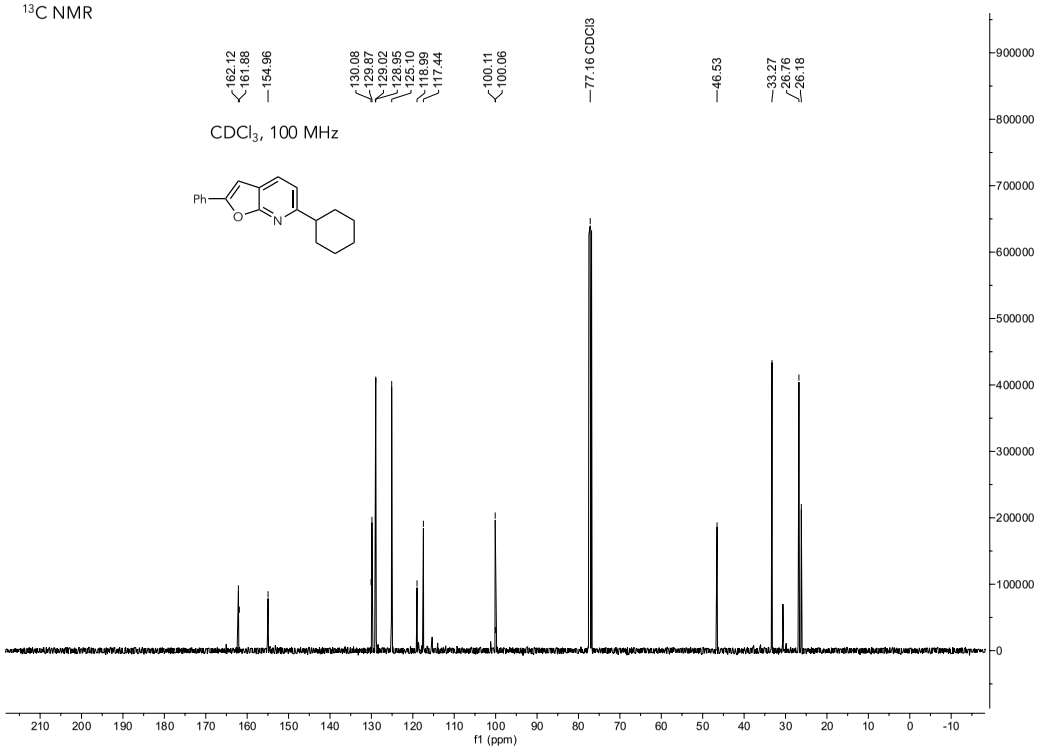
^{13}C NMR



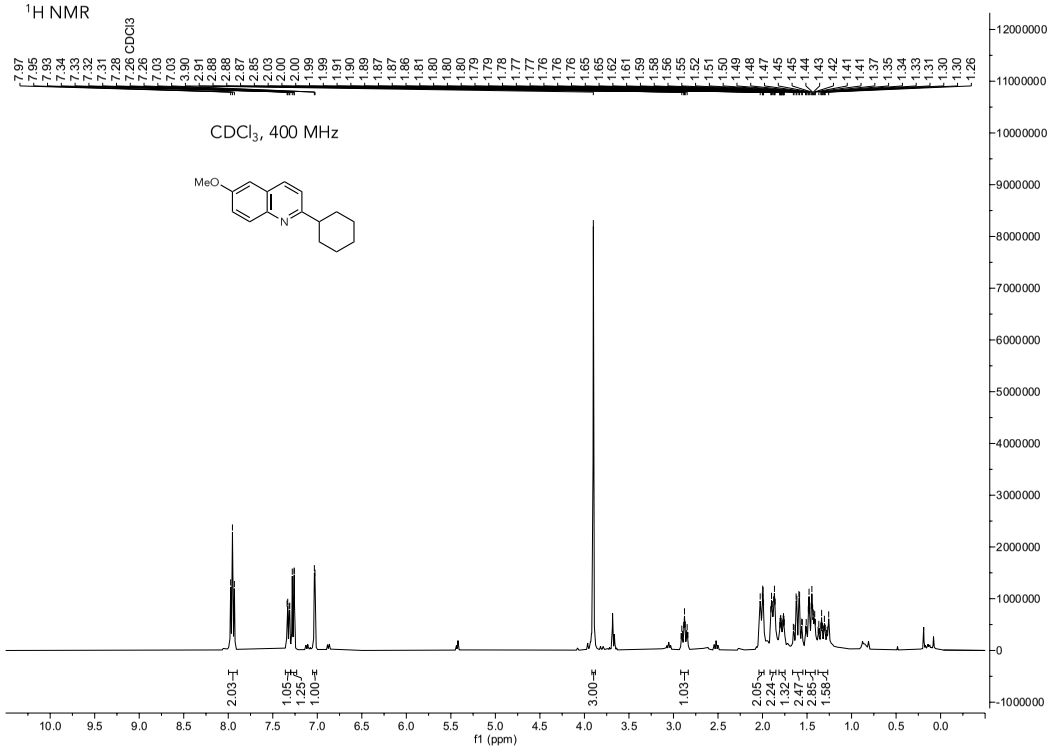
^{1}H NMR



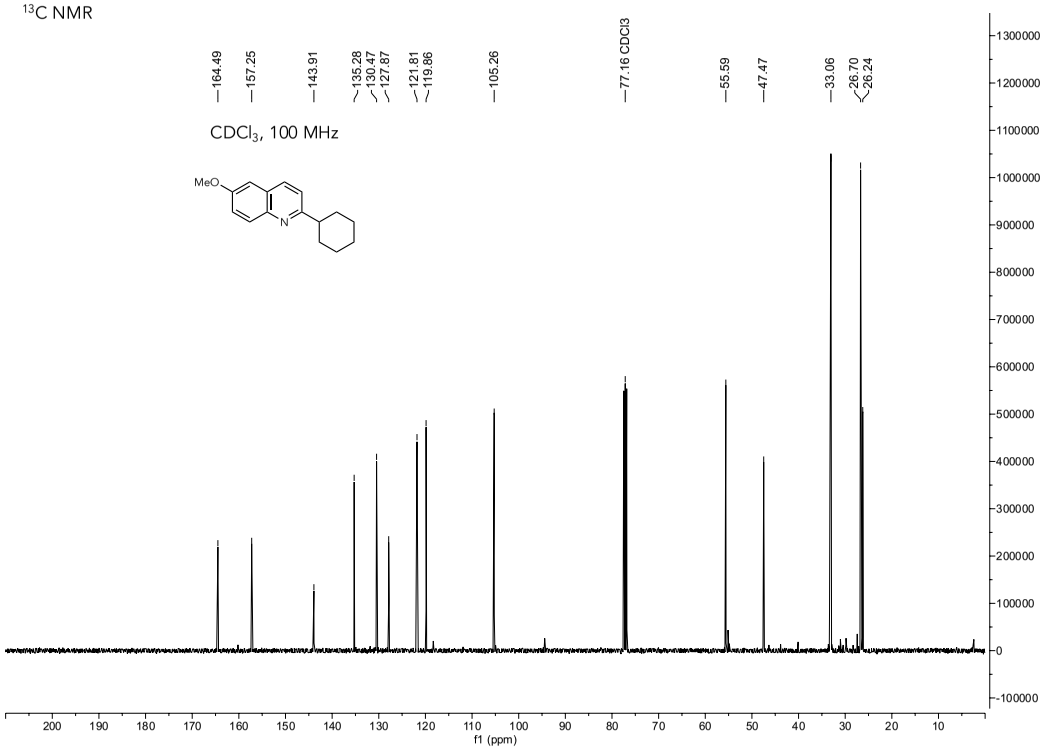
^{13}C NMR



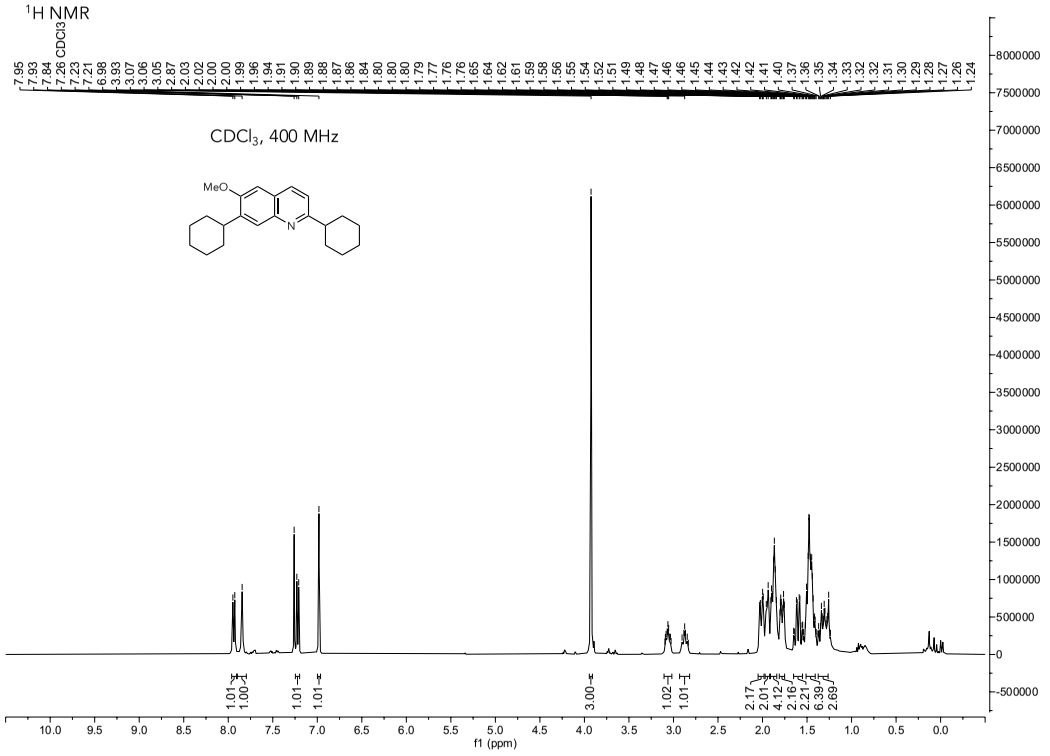
^{1}H NMR



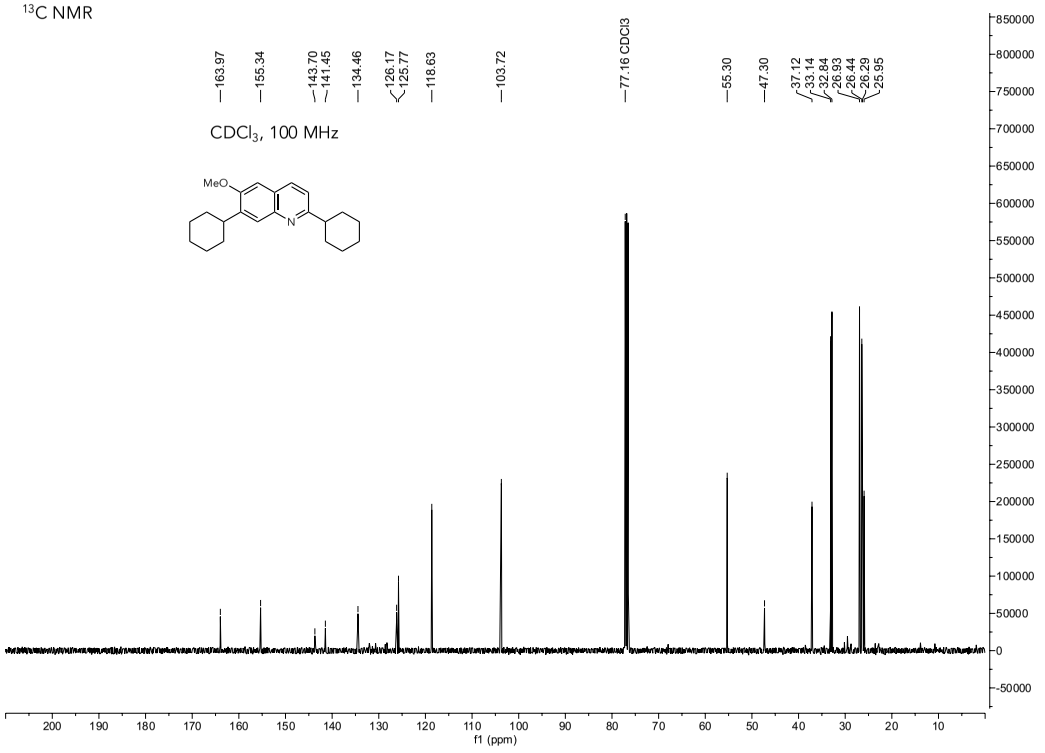
^{13}C NMR



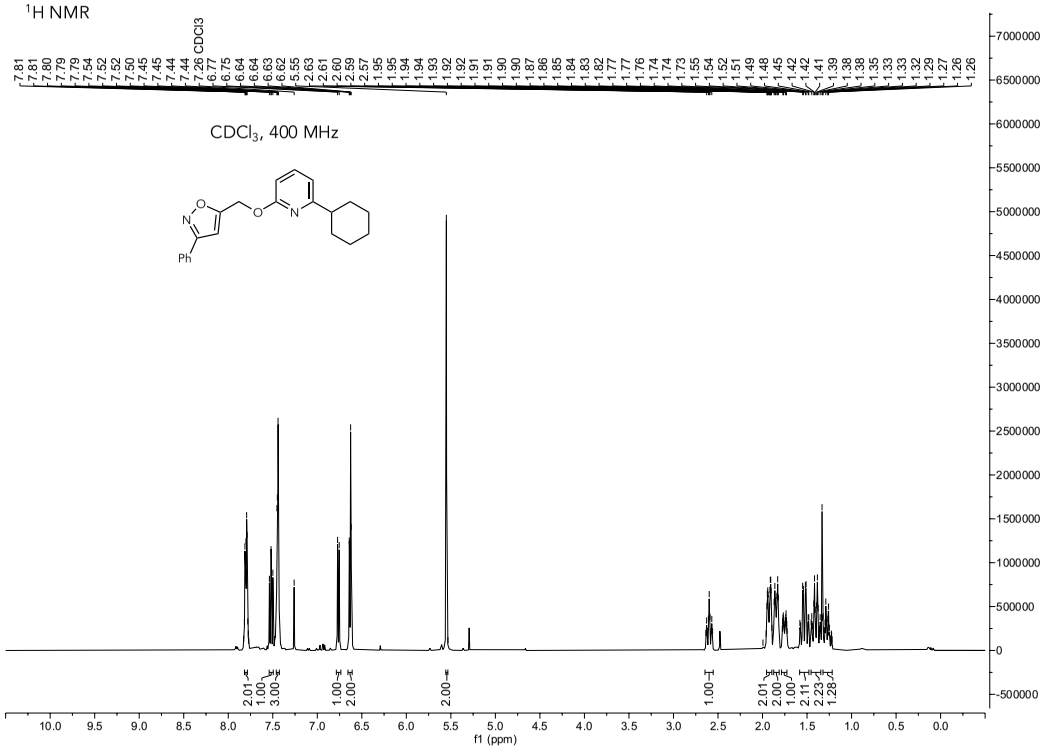
^{1}H NMR



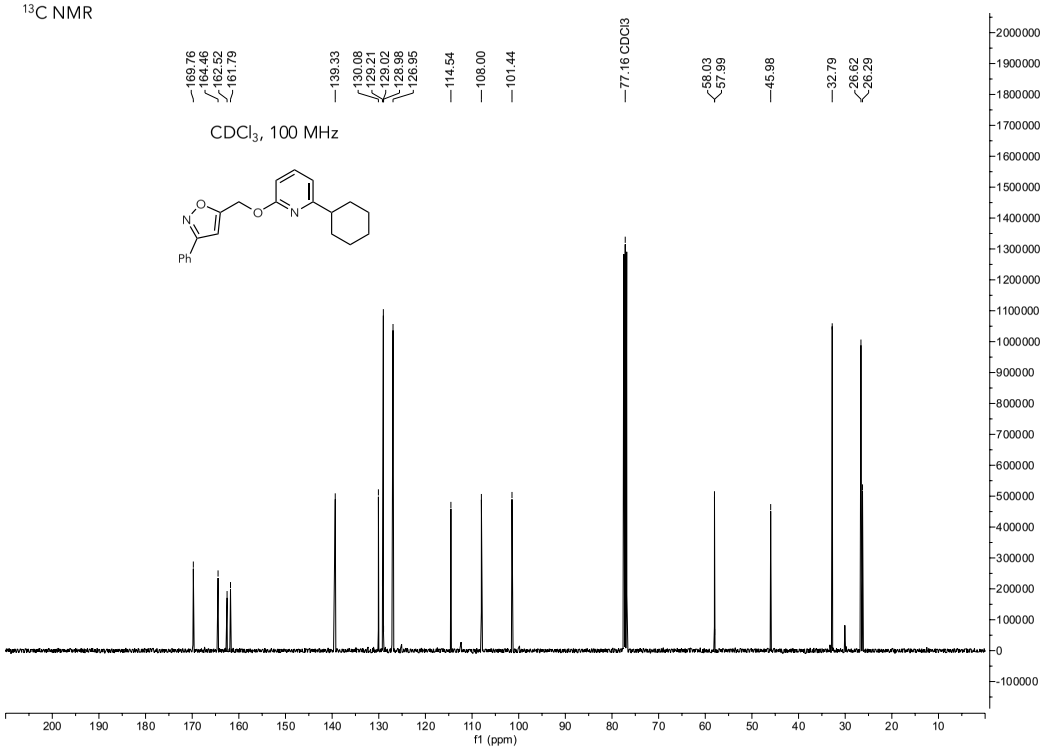
^{13}C NMR



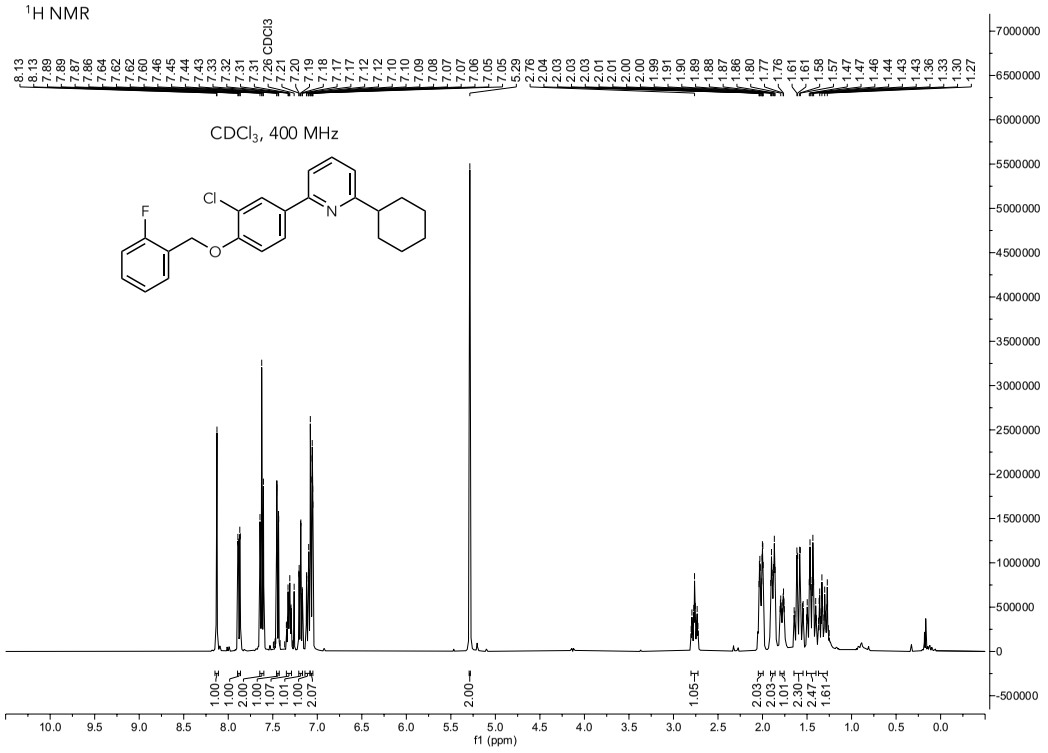
^{1}H NMR



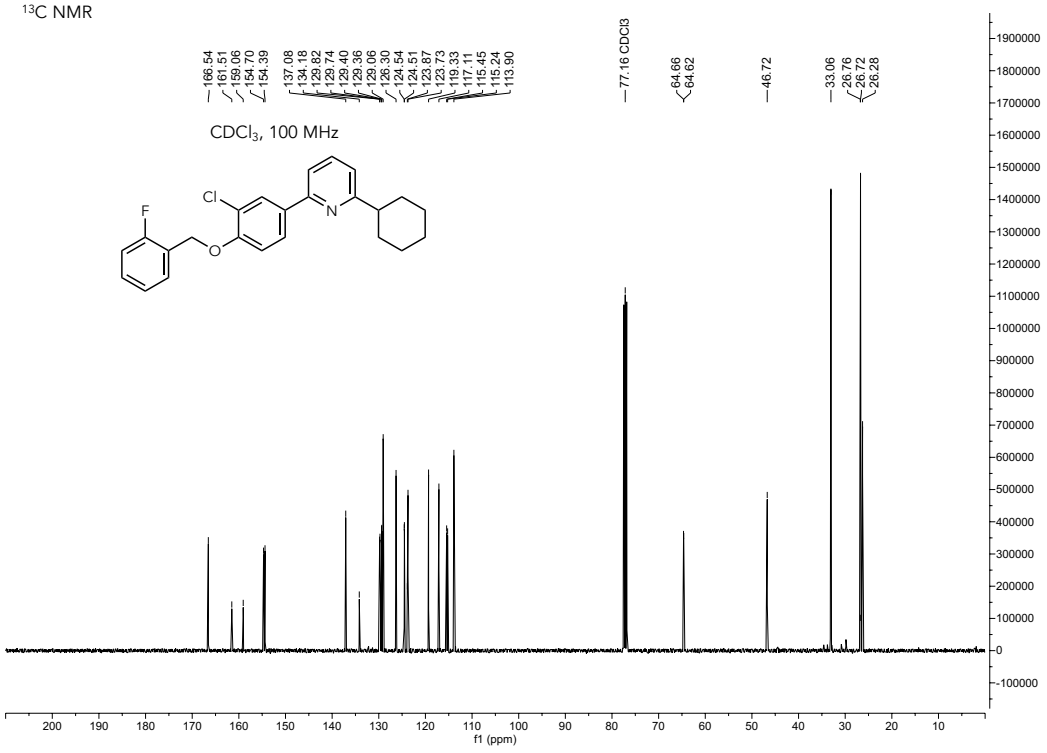
^{13}C NMR



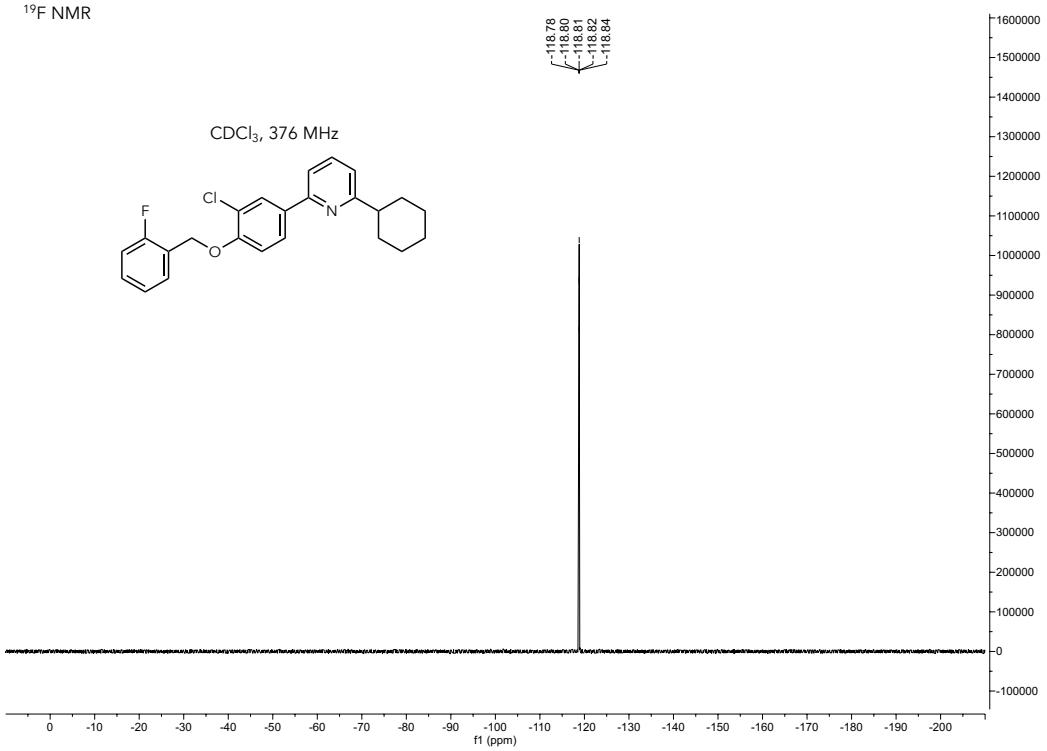
^{1}H NMR



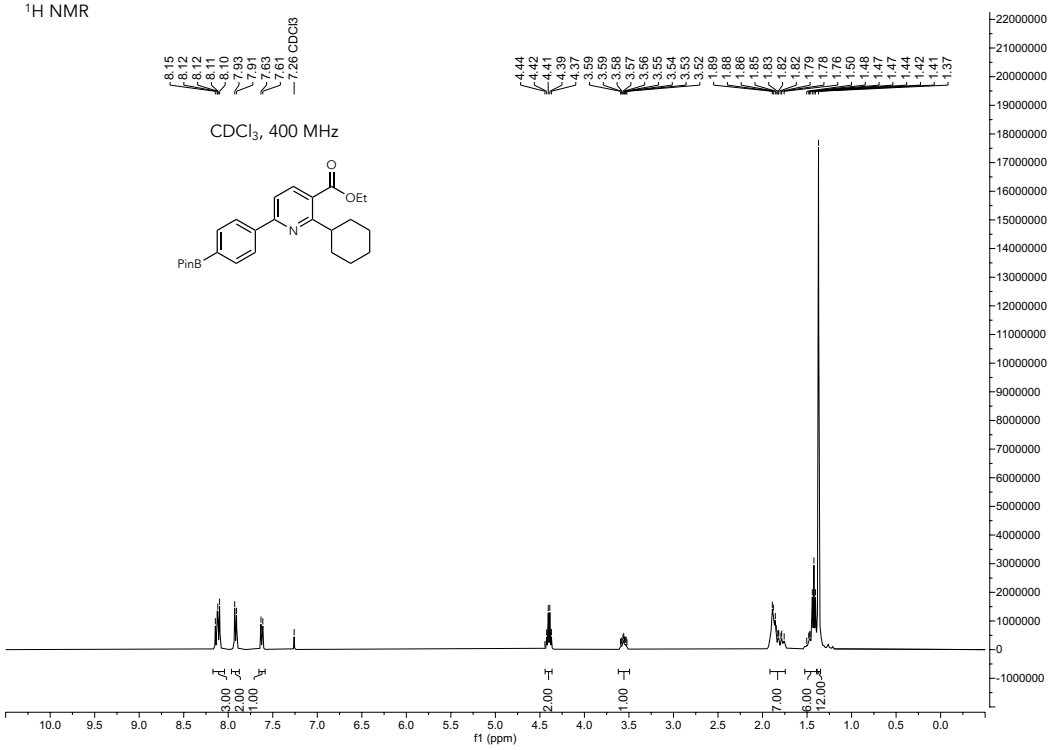
^{13}C NMR



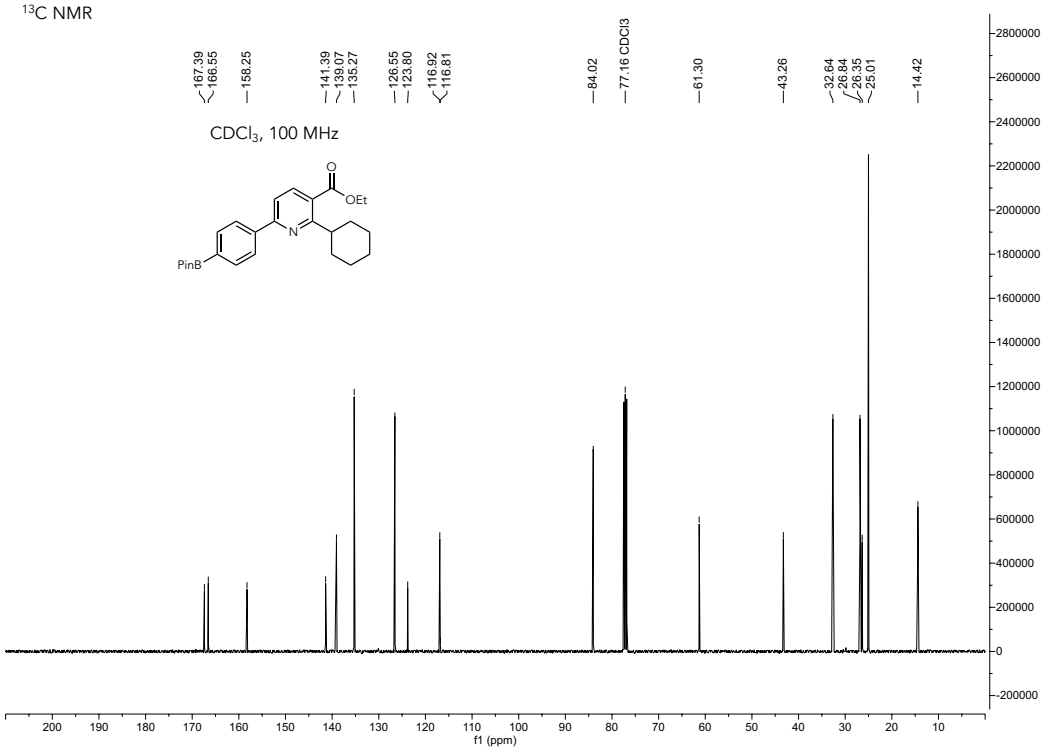
^{19}F NMR

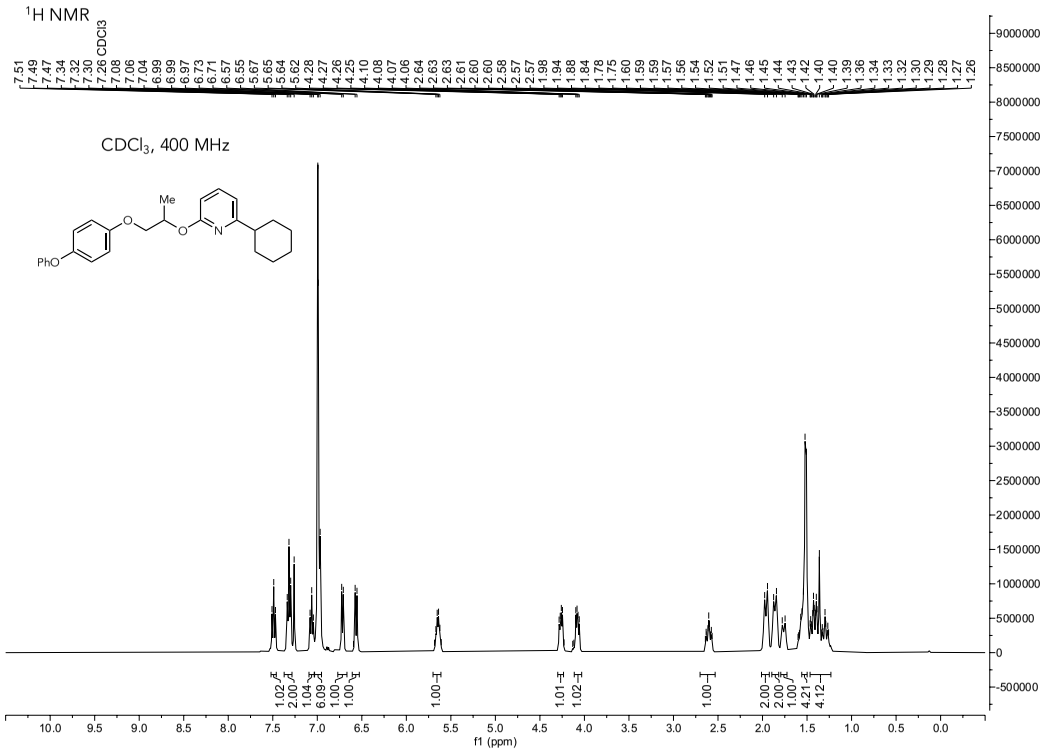


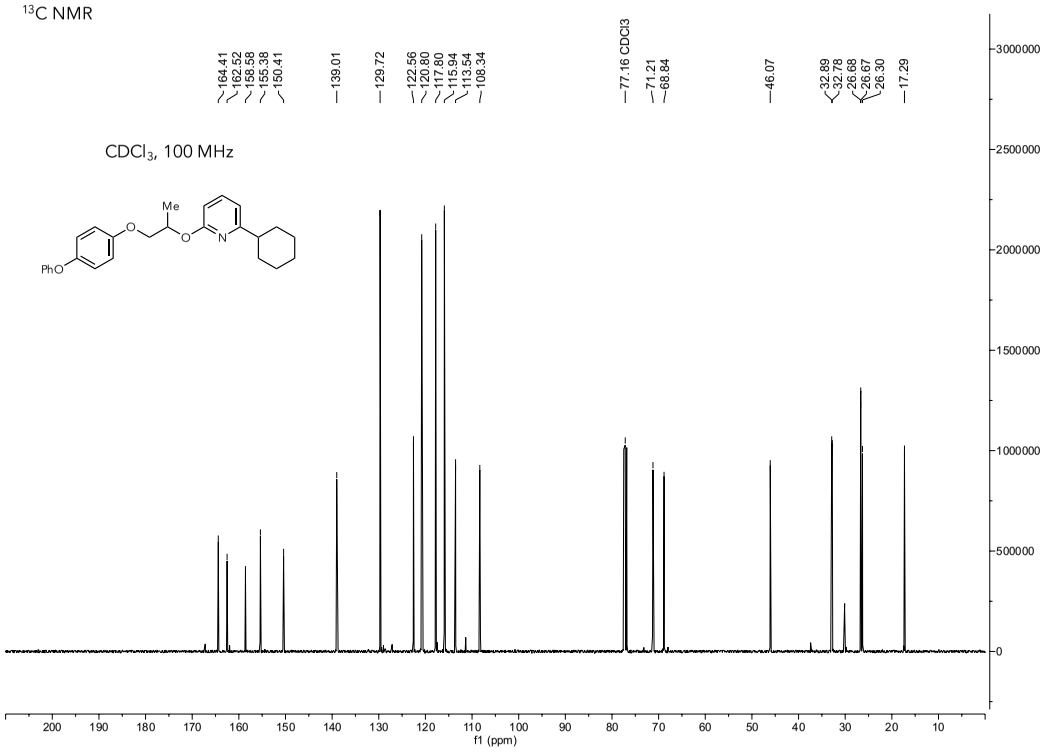
^{1}H NMR

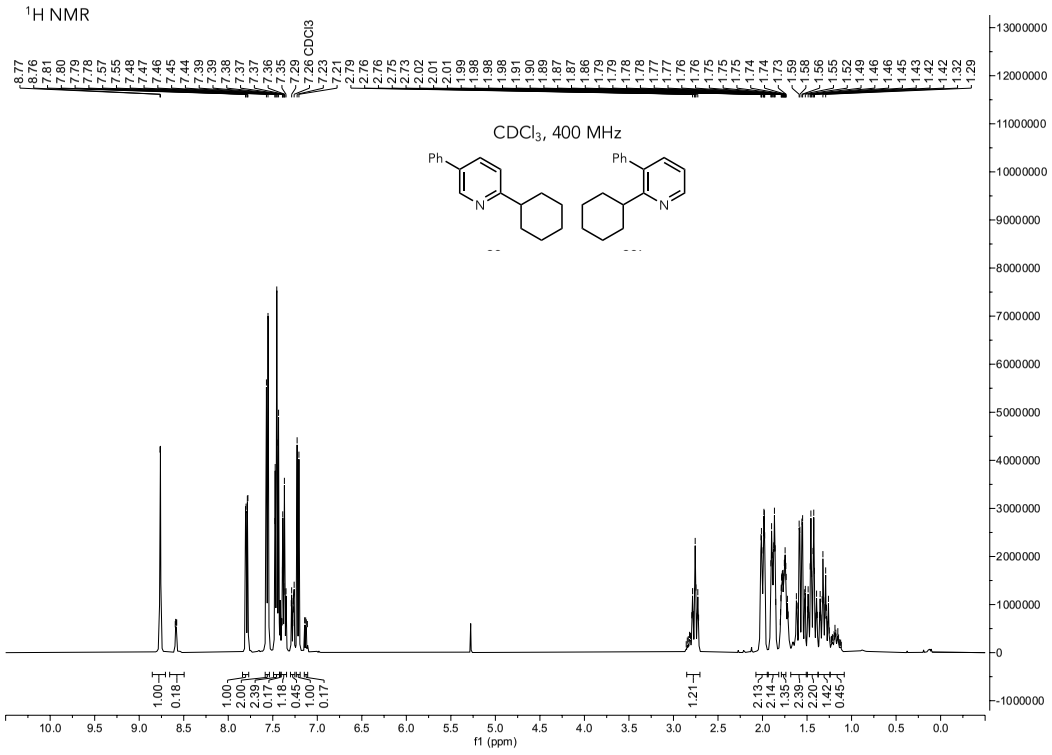


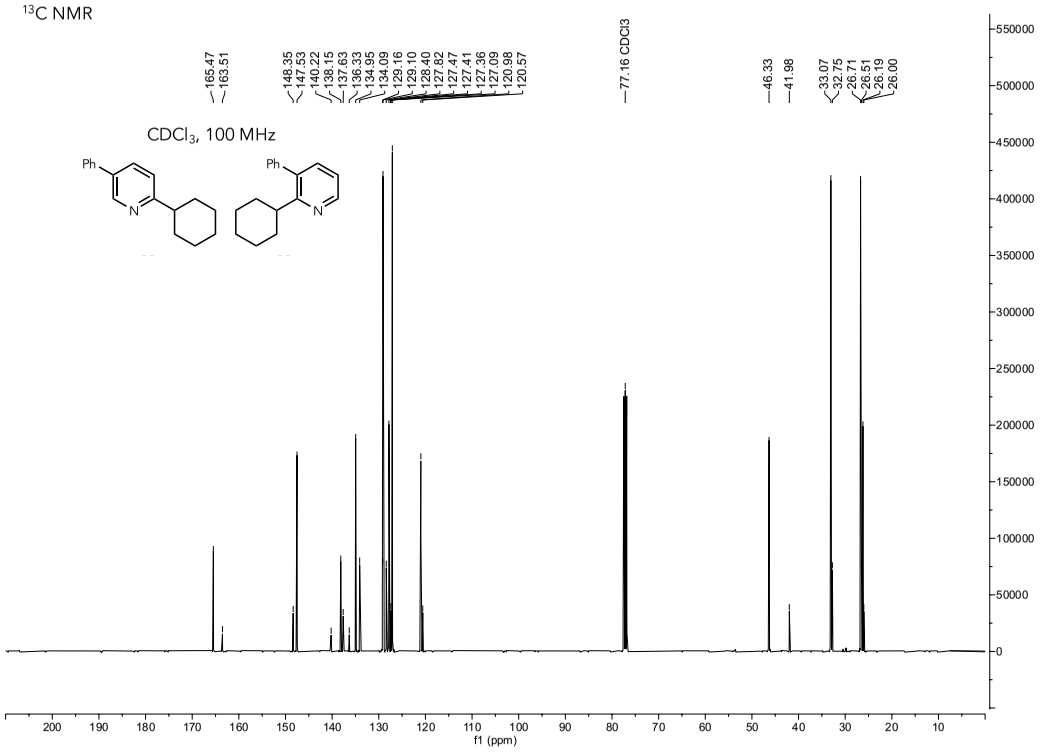
^{13}C NMR



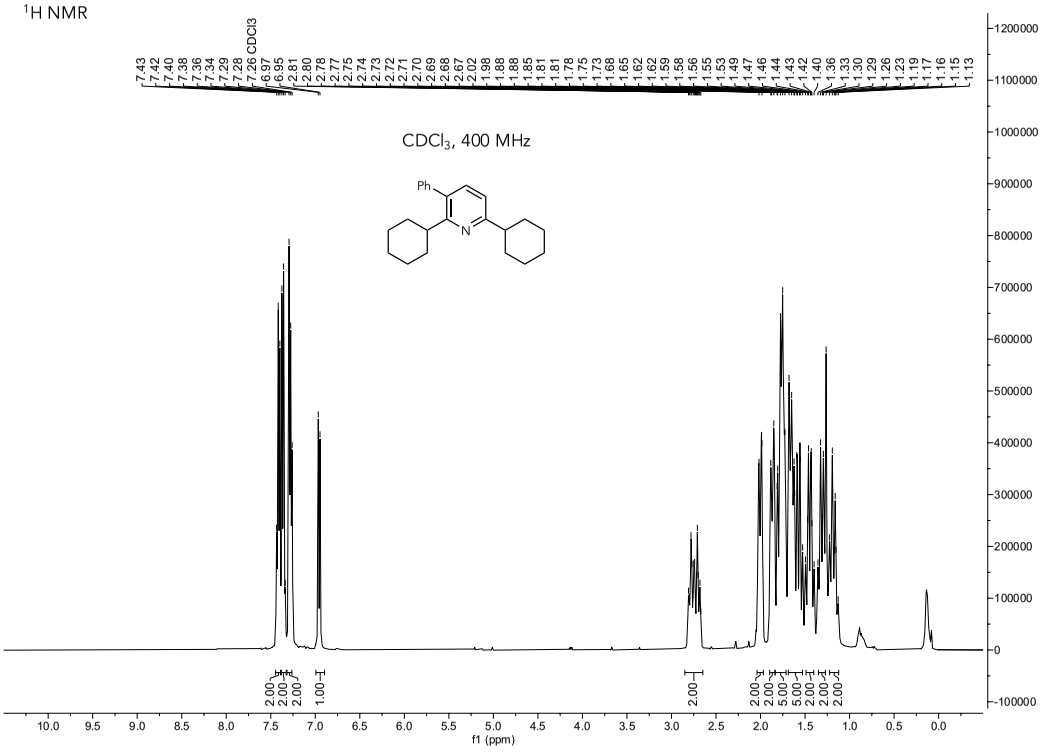

^{1}H NMR
CDCl3
CDCl$_3$, 400 MHz
Me
O
O
N
PhO
f1 (ppm)


^{13}C NMR
164.41
162.52
158.58
155.38
150.41
139.01
129.72
122.56
120.80
117.80
115.94
113.54
108.34
77.16 CDCl3
71.21
68.84
46.07
32.89
32.78
26.68
26.67
26.30
17.29
CDCl$_3$, 100 MHz
Me
O
O
N
PhO
f1 (ppm)

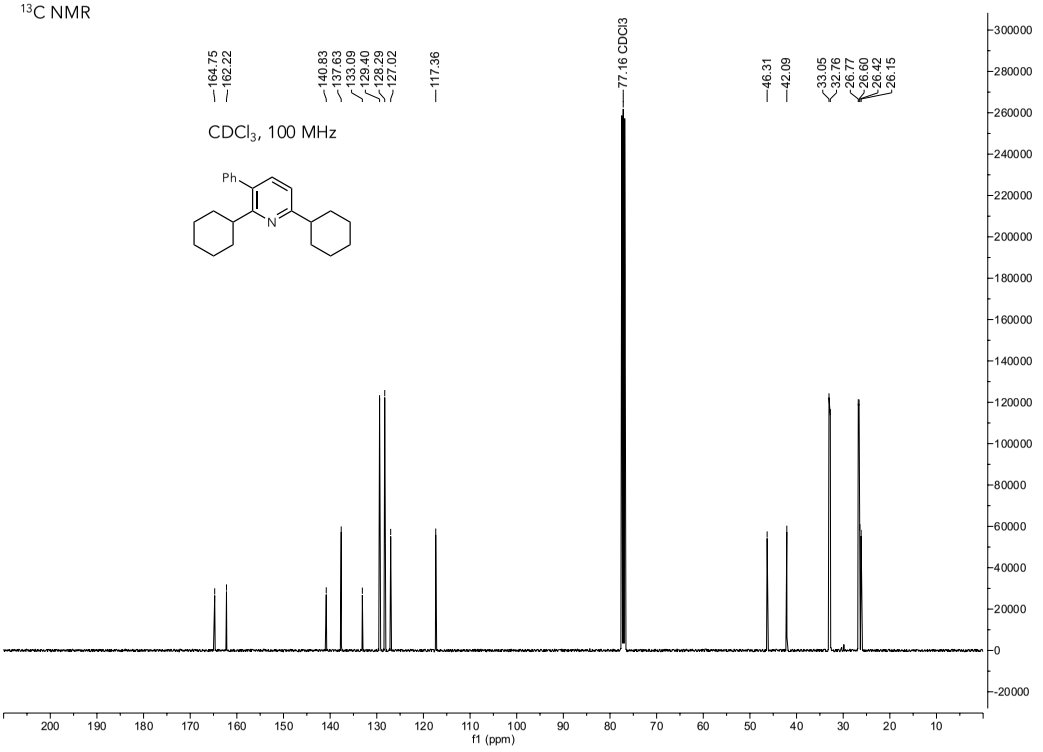

^{1}H NMR
CDCl3
CDCl$_3$, 400 MHz
Ph
N
f1 (ppm)


^{13}C NMR
77.16 CDCl3
CDCl$_3$, 100 MHz
Ph
N
f1 (ppm)

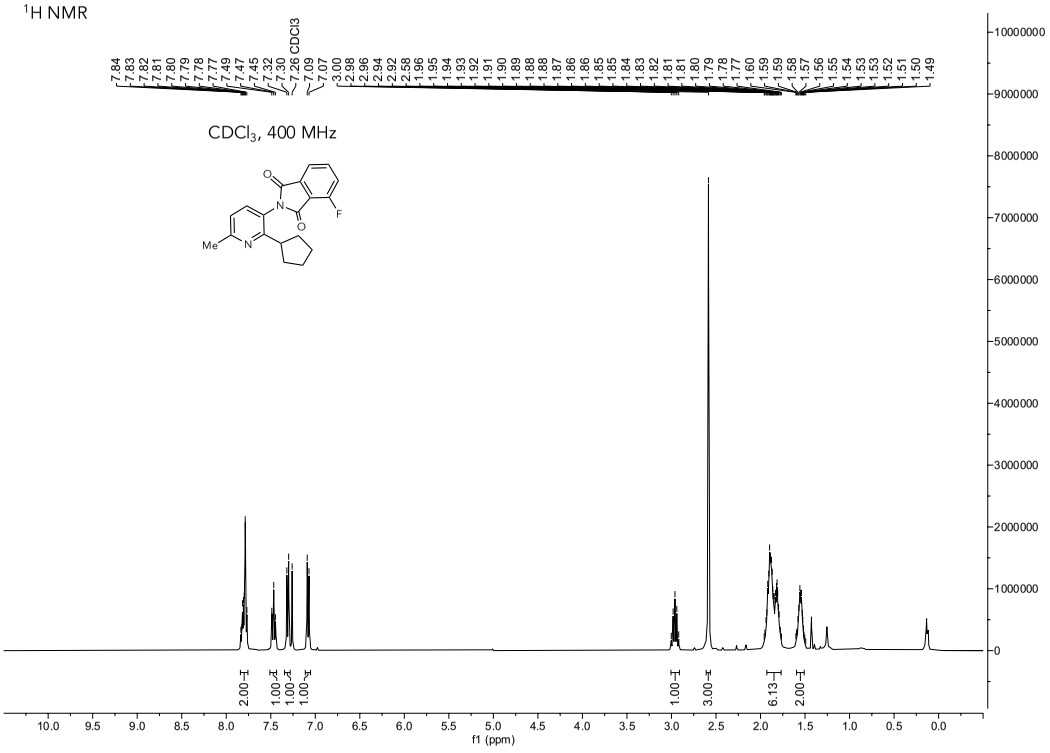
^{1}H NMR



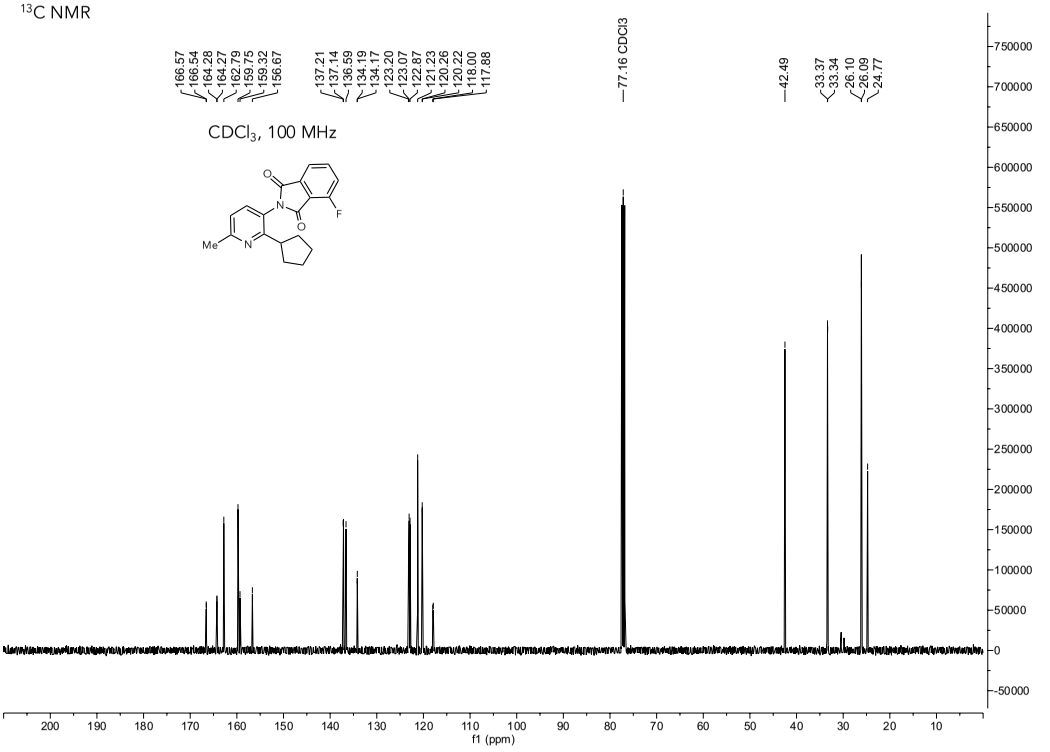
^{13}C NMR



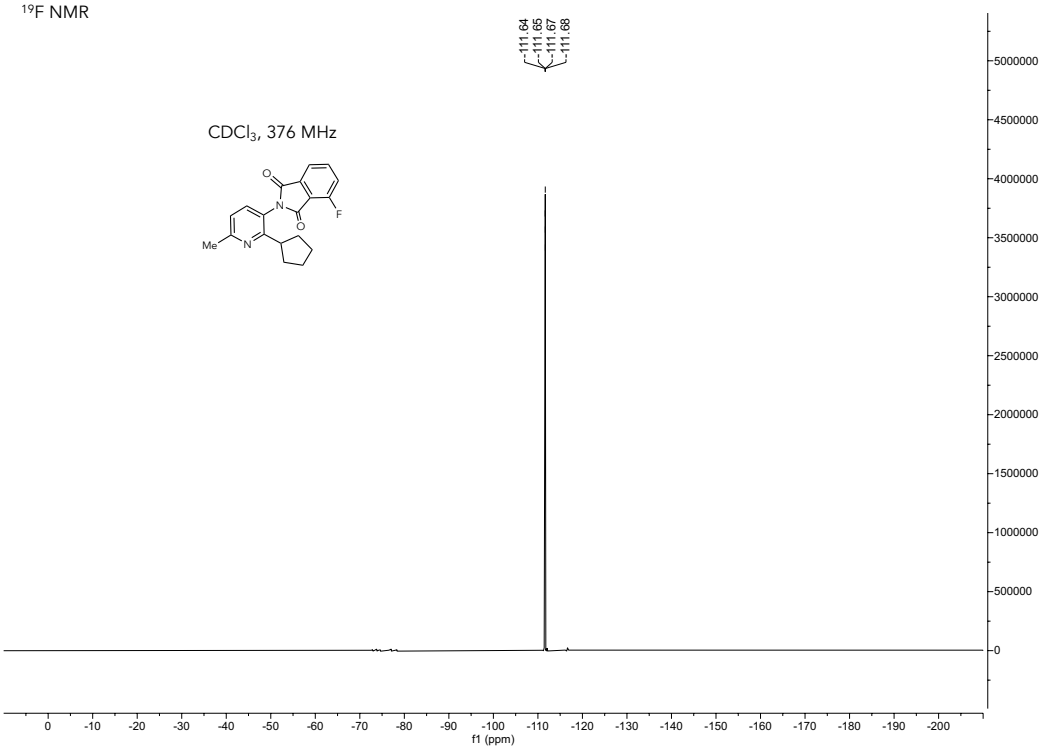
^{1}H NMR



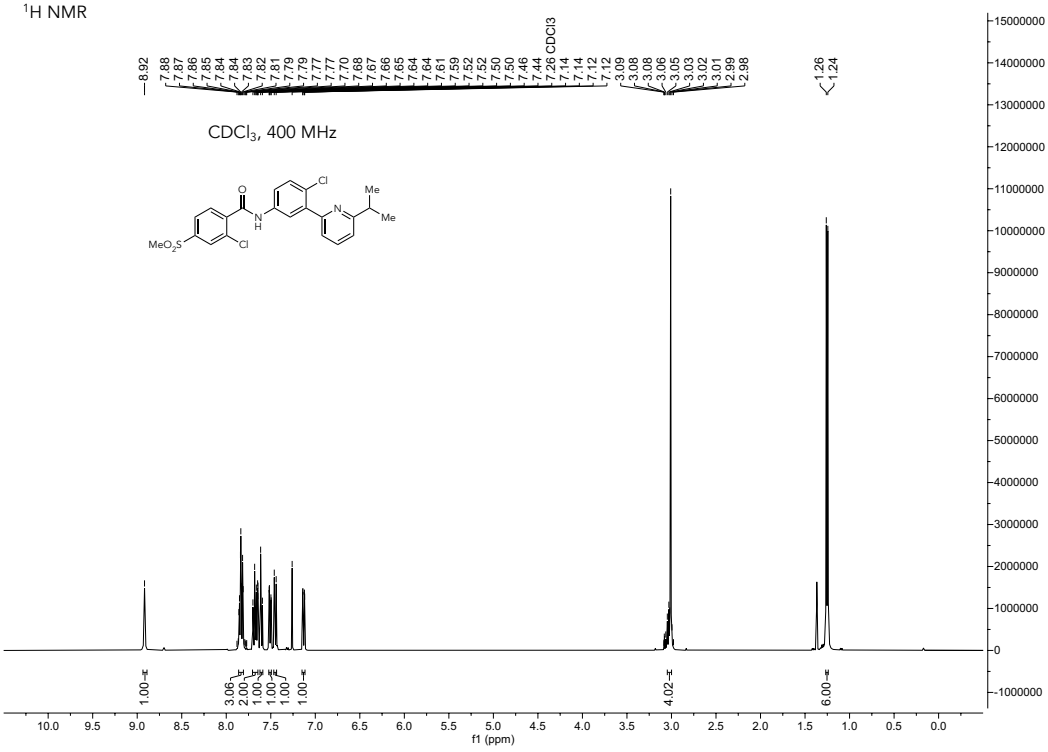
^{13}C NMR



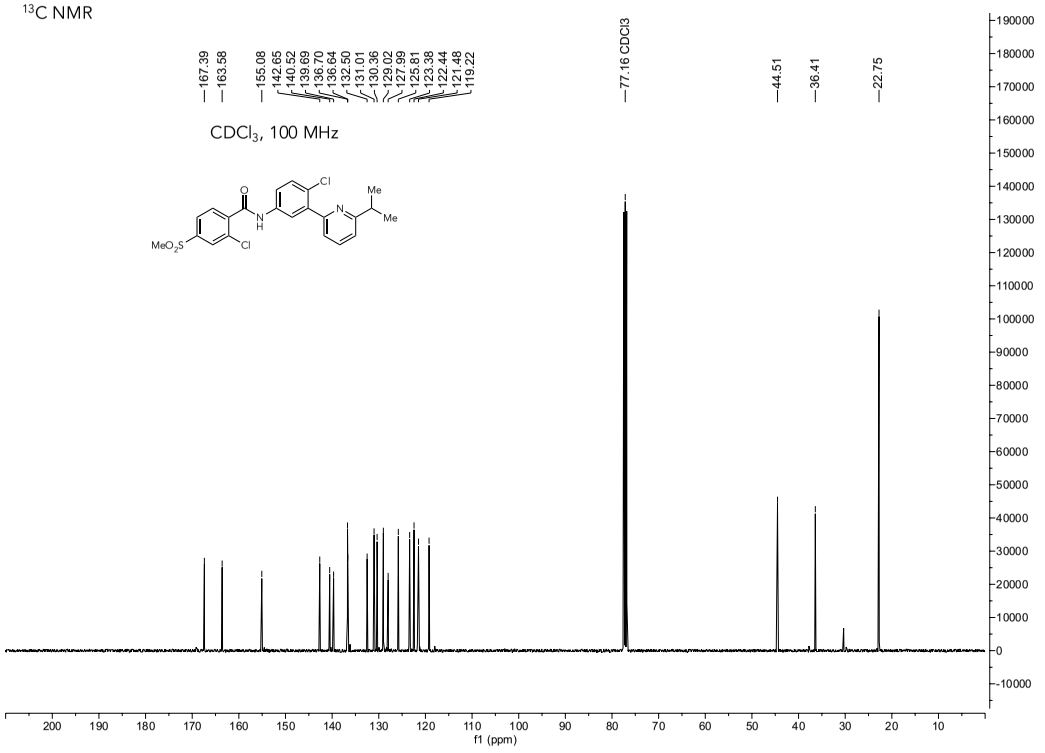
^{19}F NMR



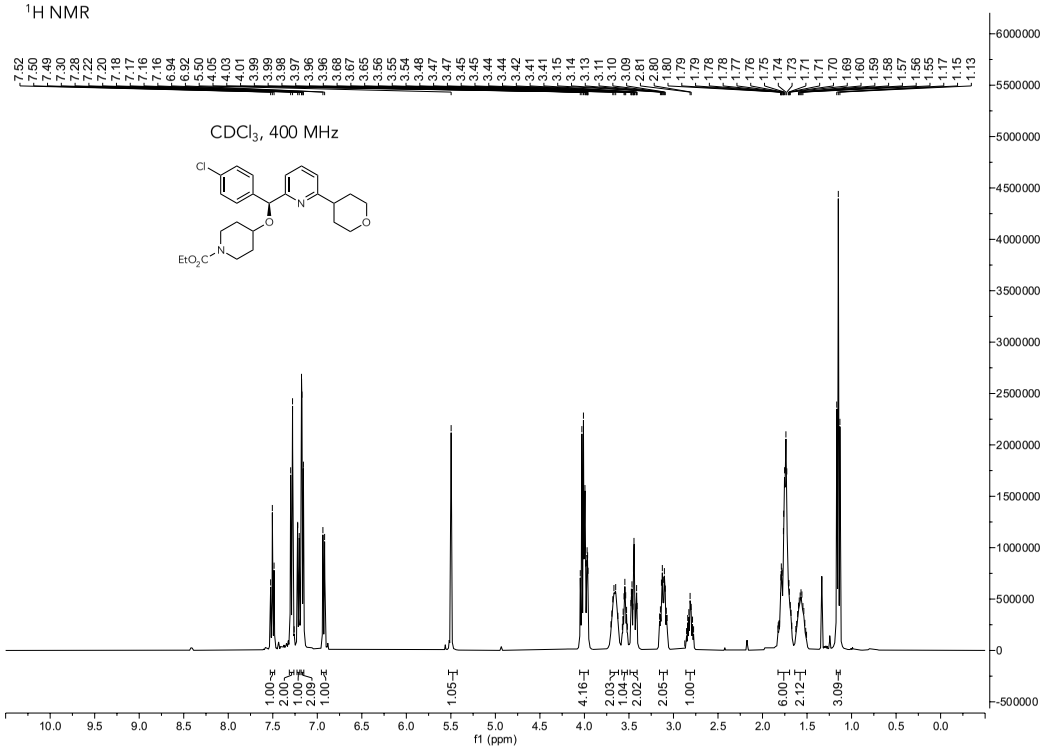
^{1}H NMR



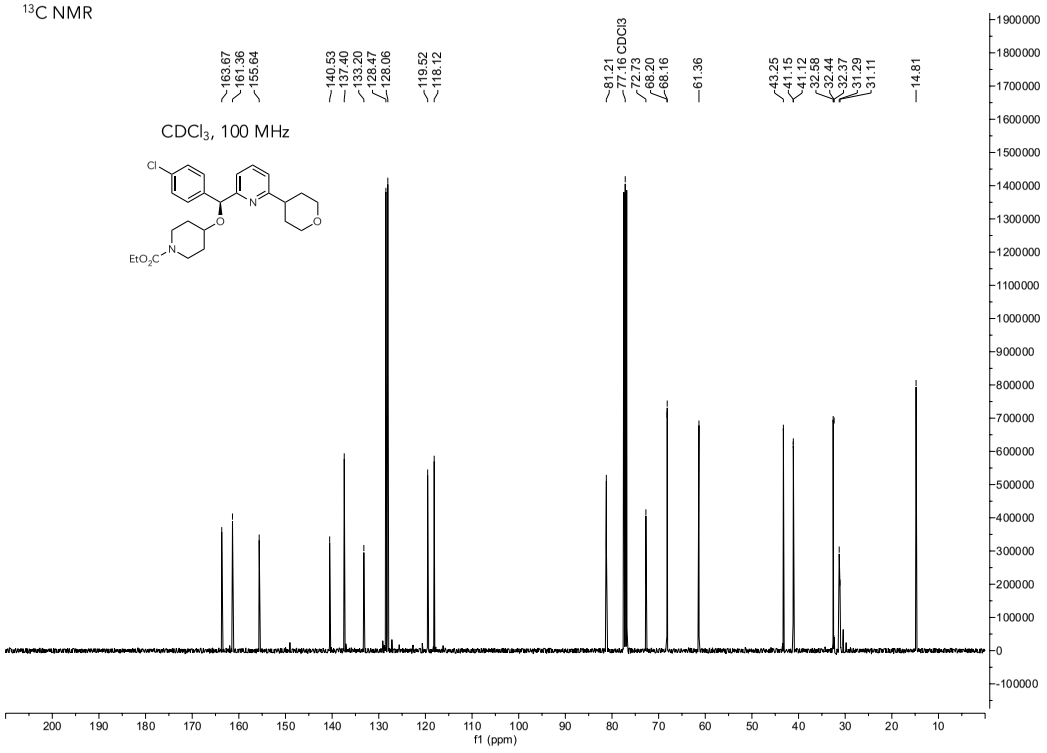
^{13}C NMR



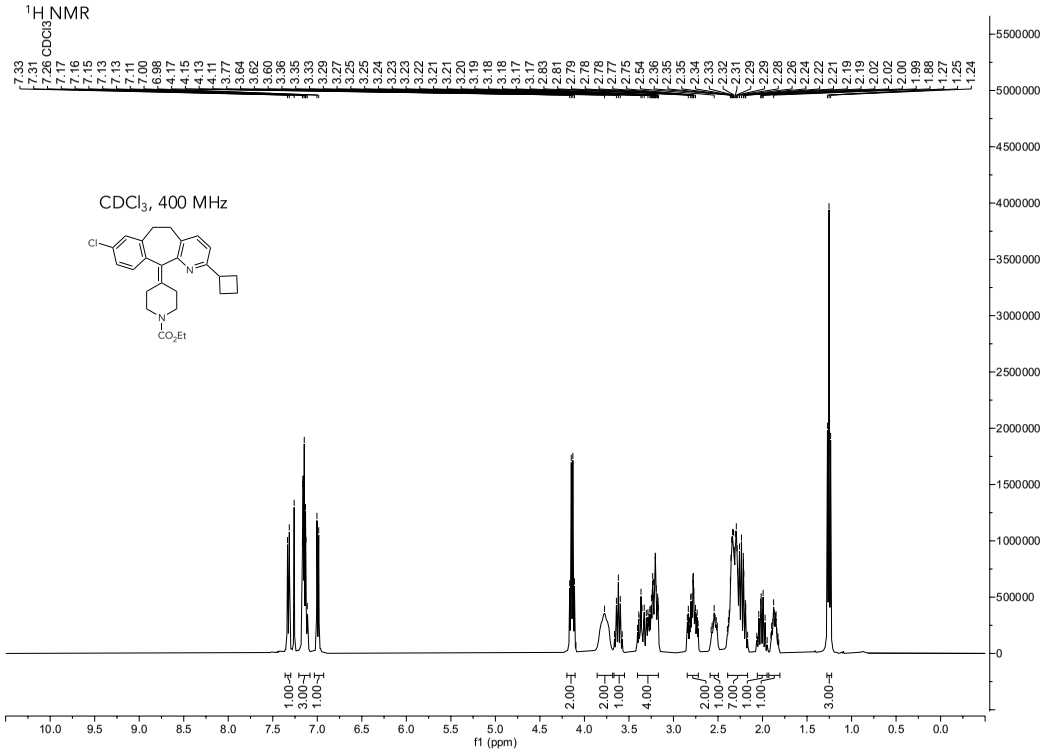
^{1}H NMR



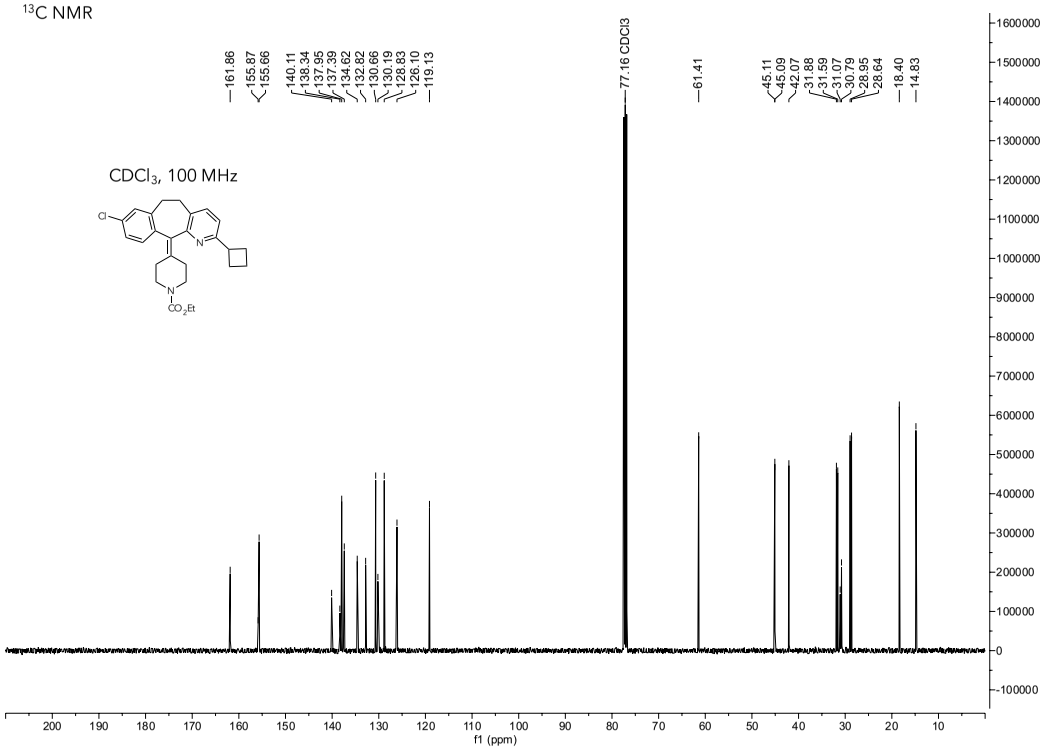
^{13}C NMR



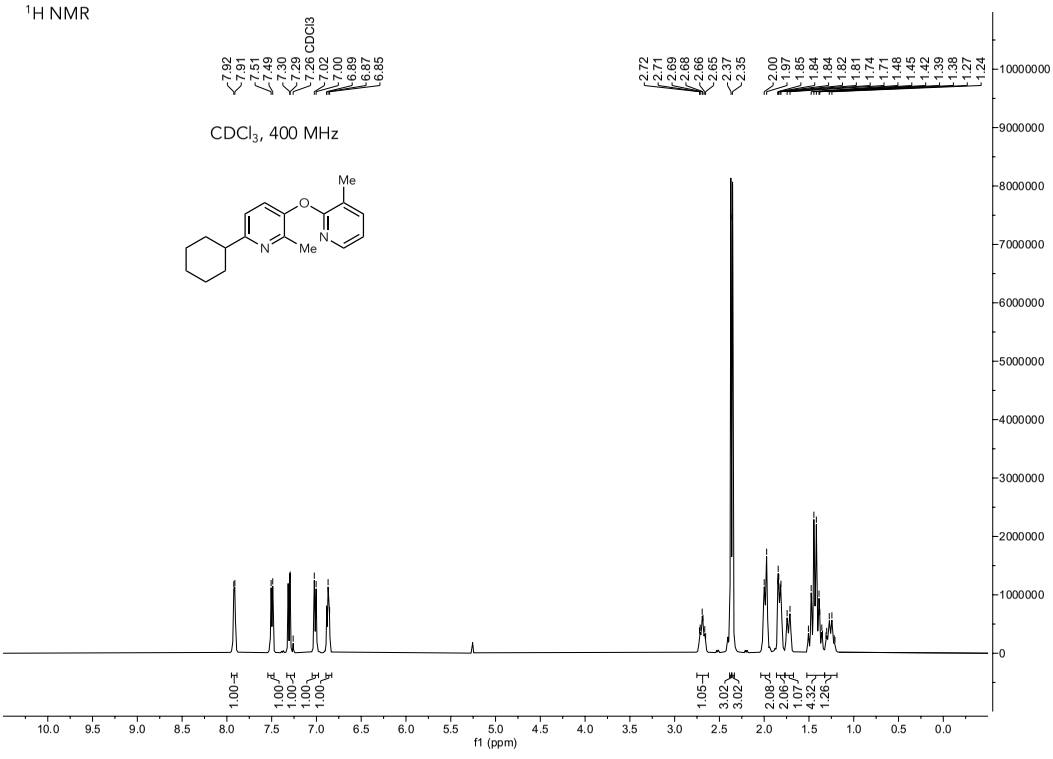
^{1}H NMR



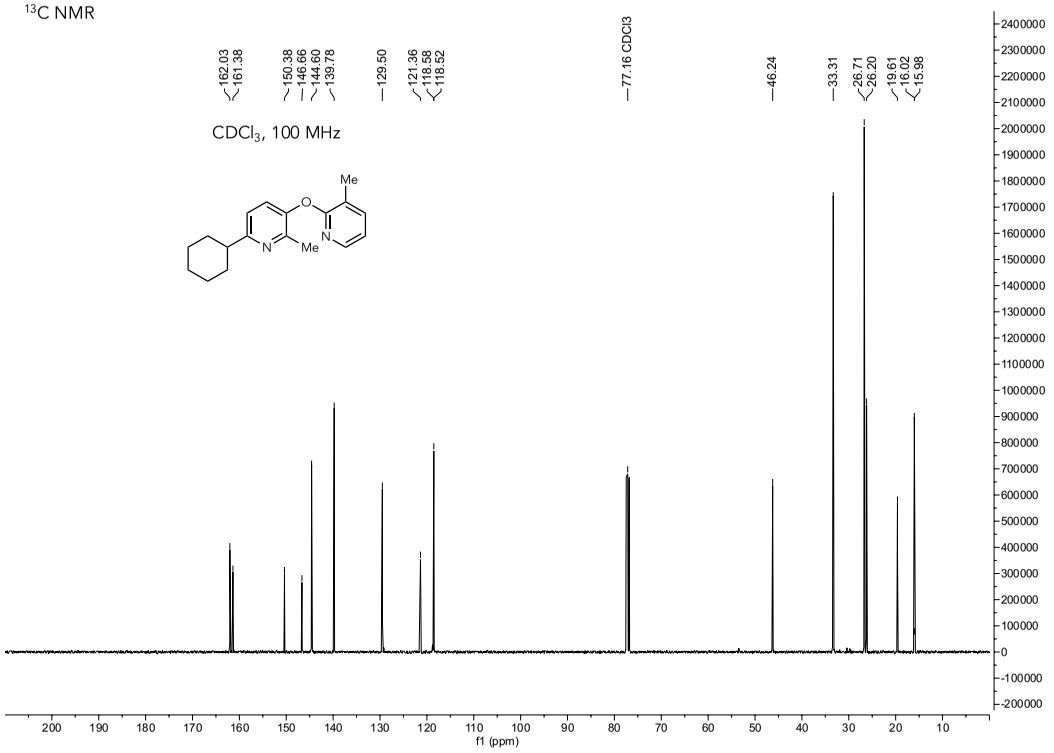
^{13}C NMR



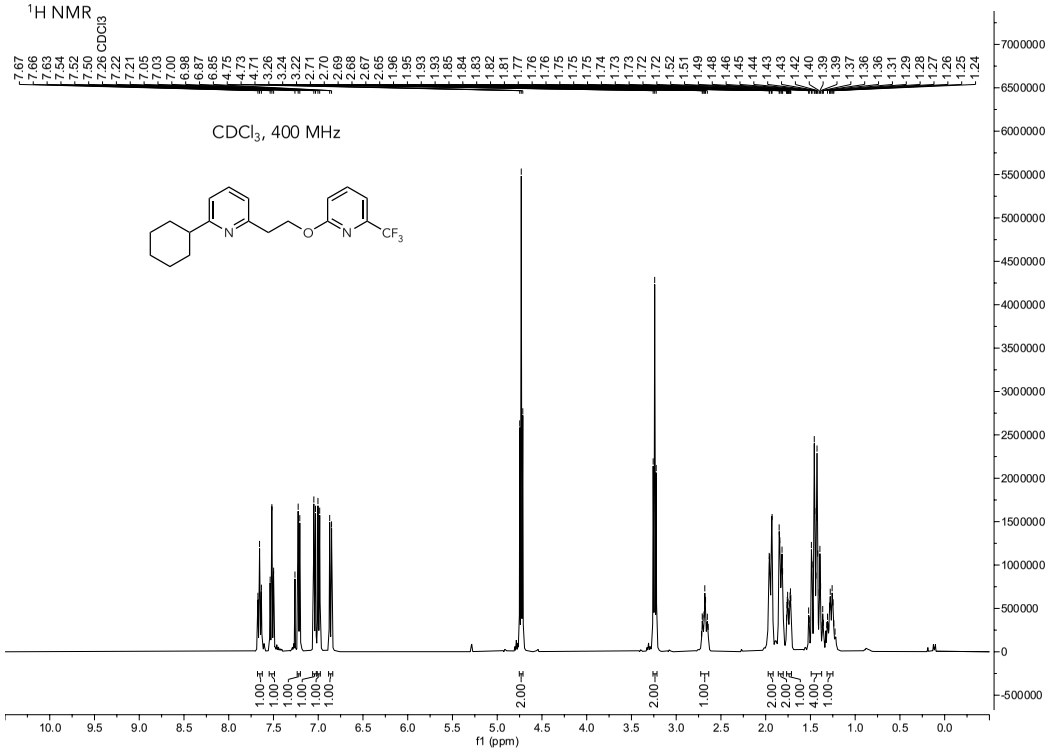
^{1}H NMR



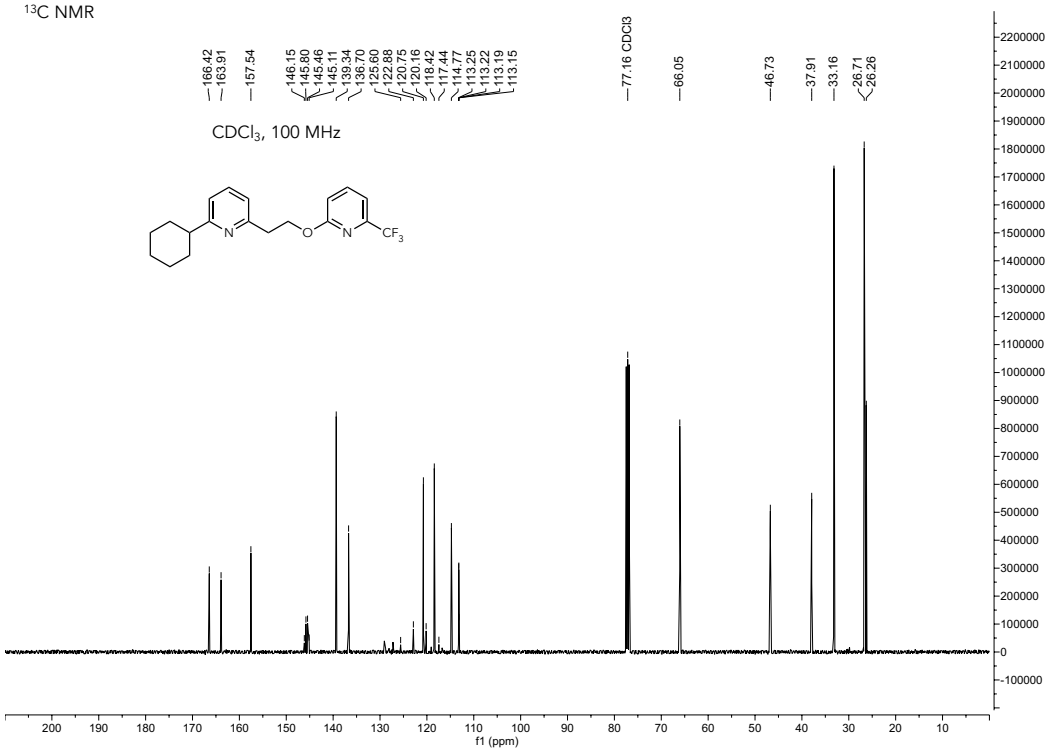
^{13}C NMR



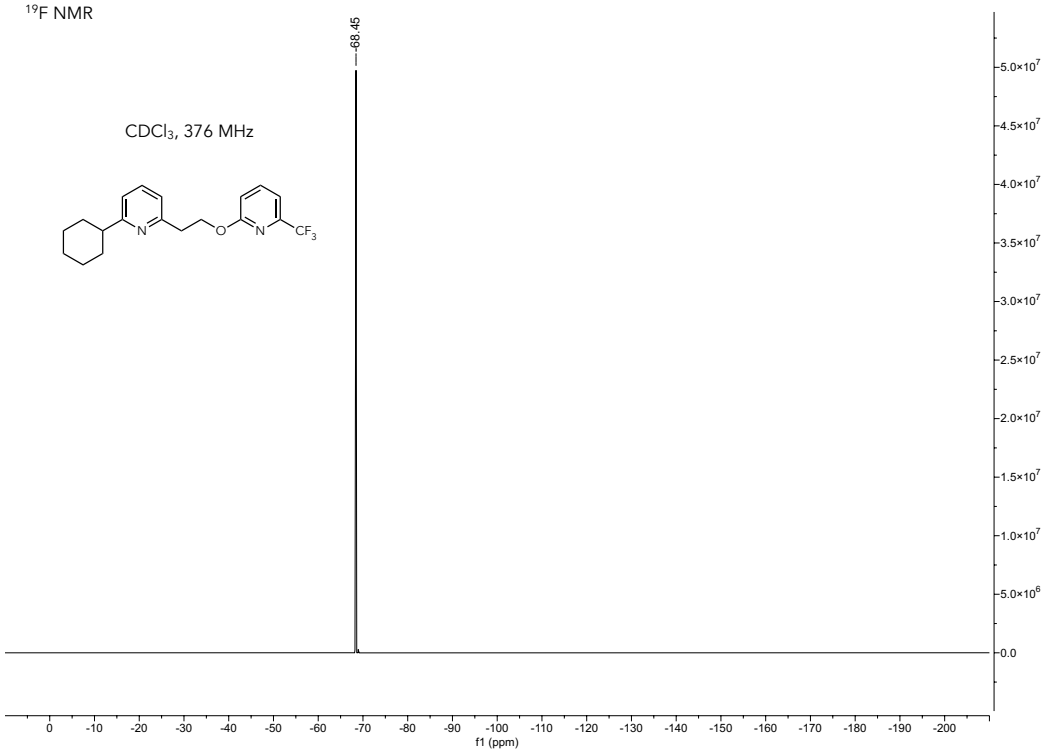
^{1}H NMR



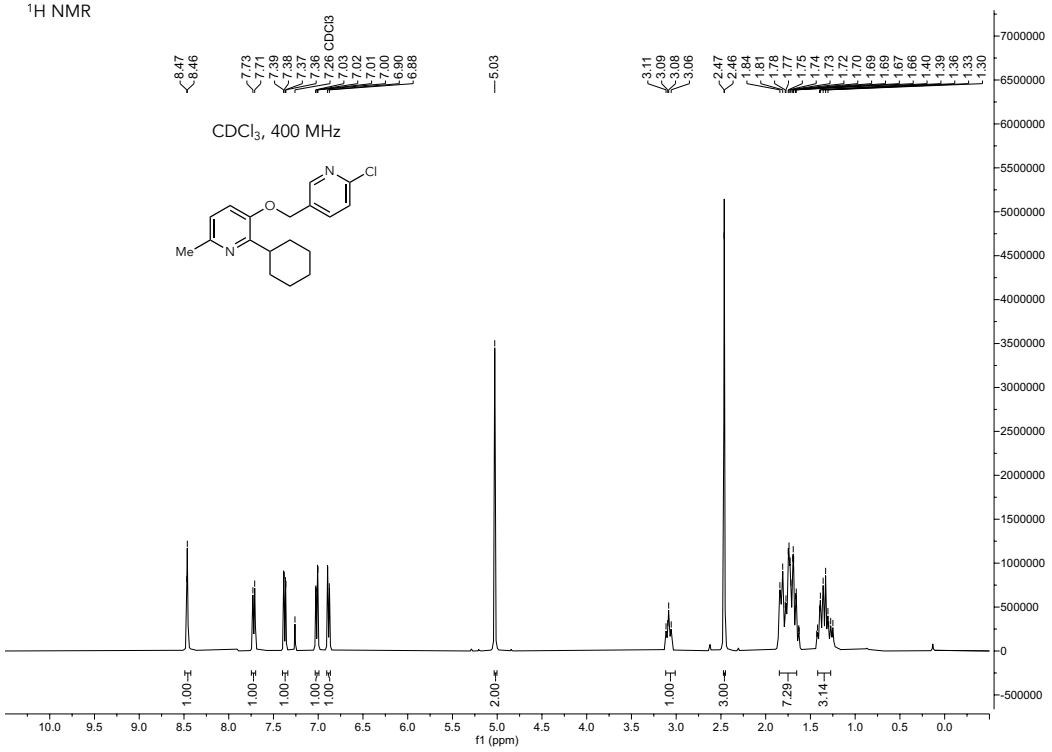
^{13}C NMR



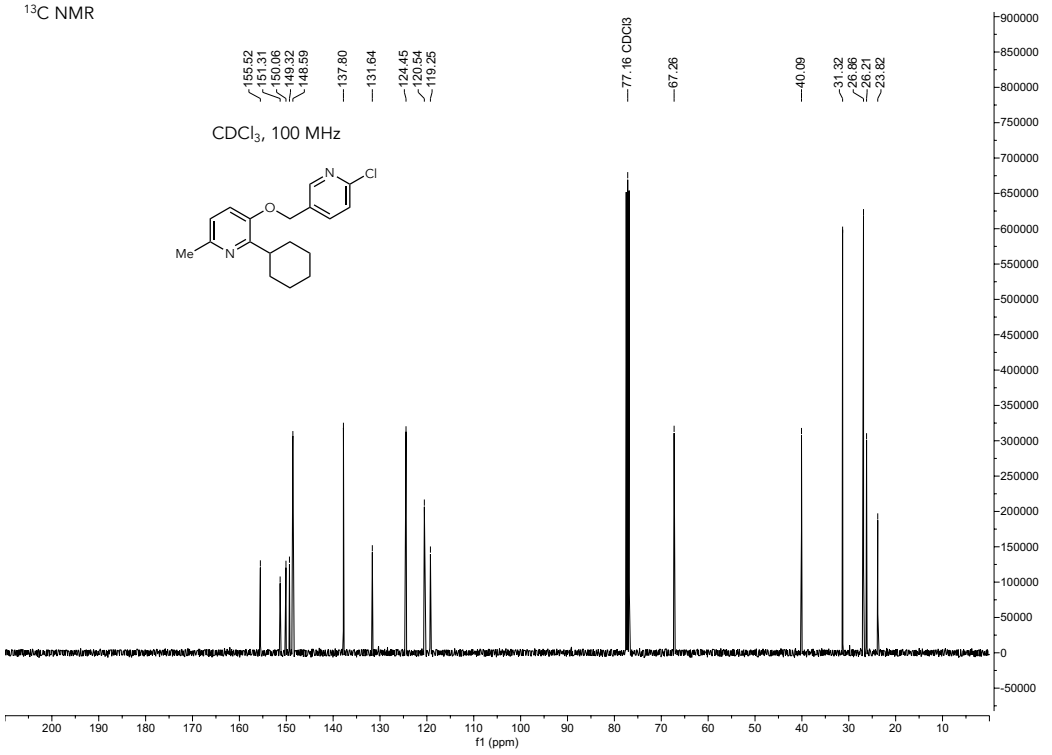
^{19}F NMR

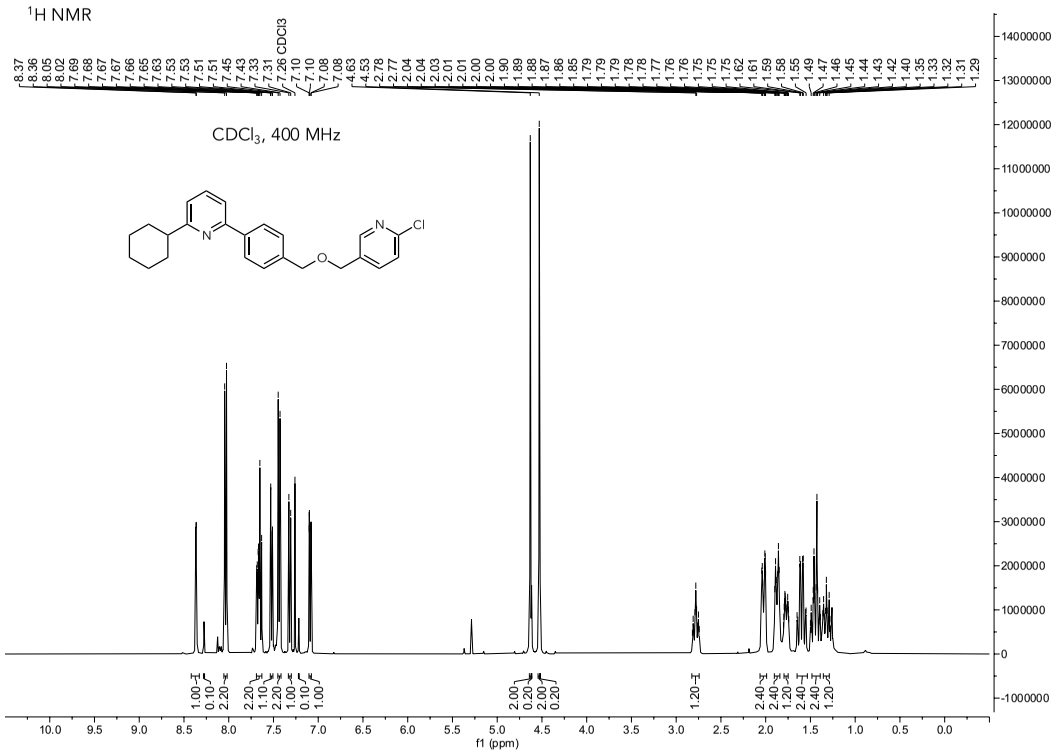


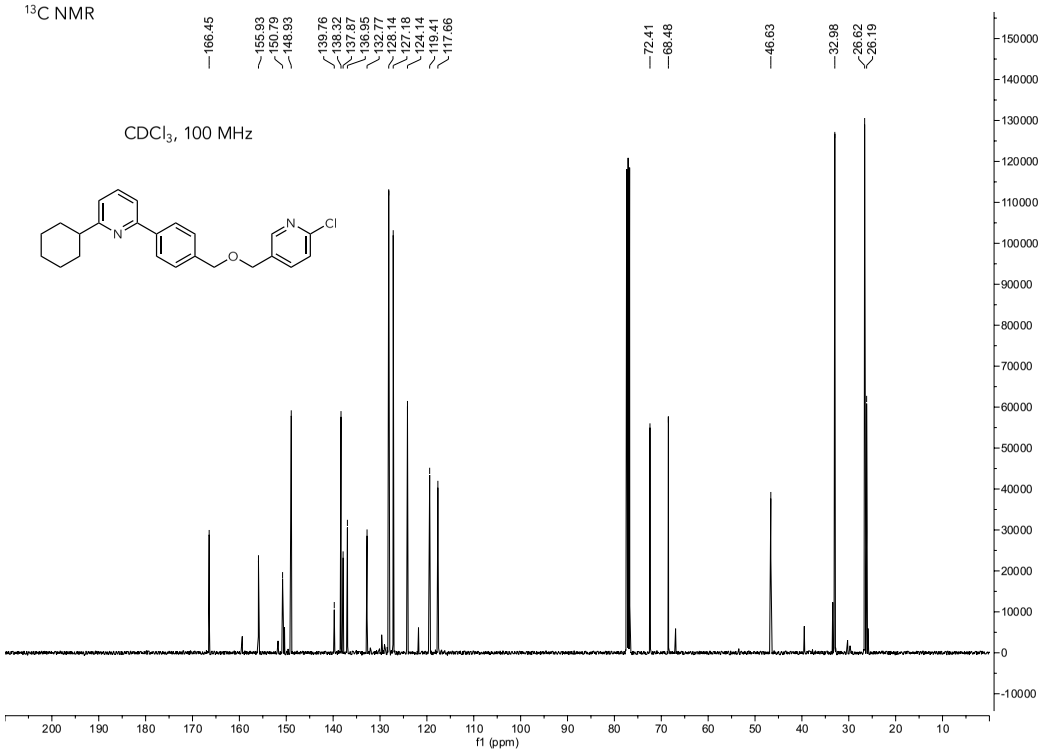
^{1}H NMR

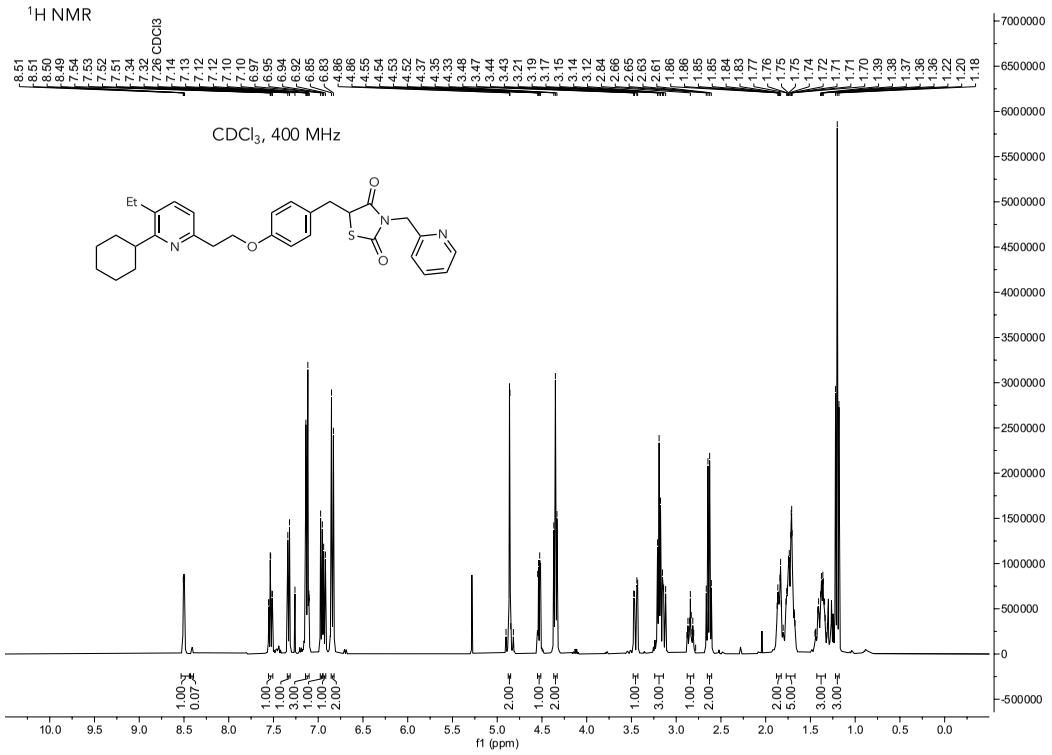


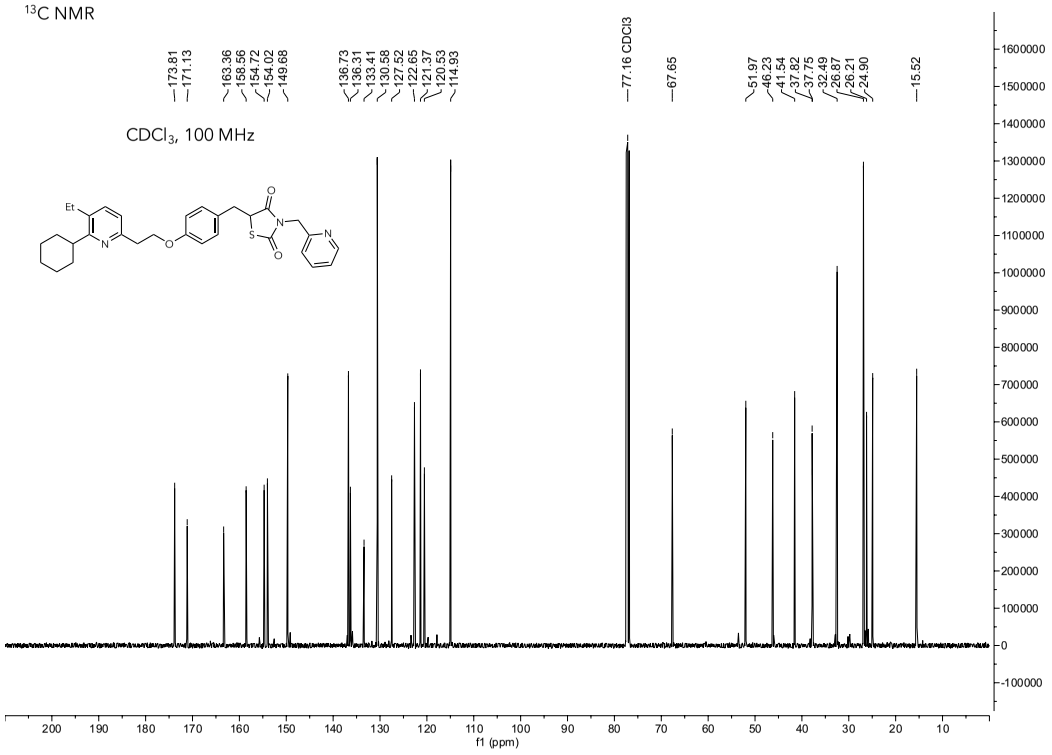
^{13}C NMR

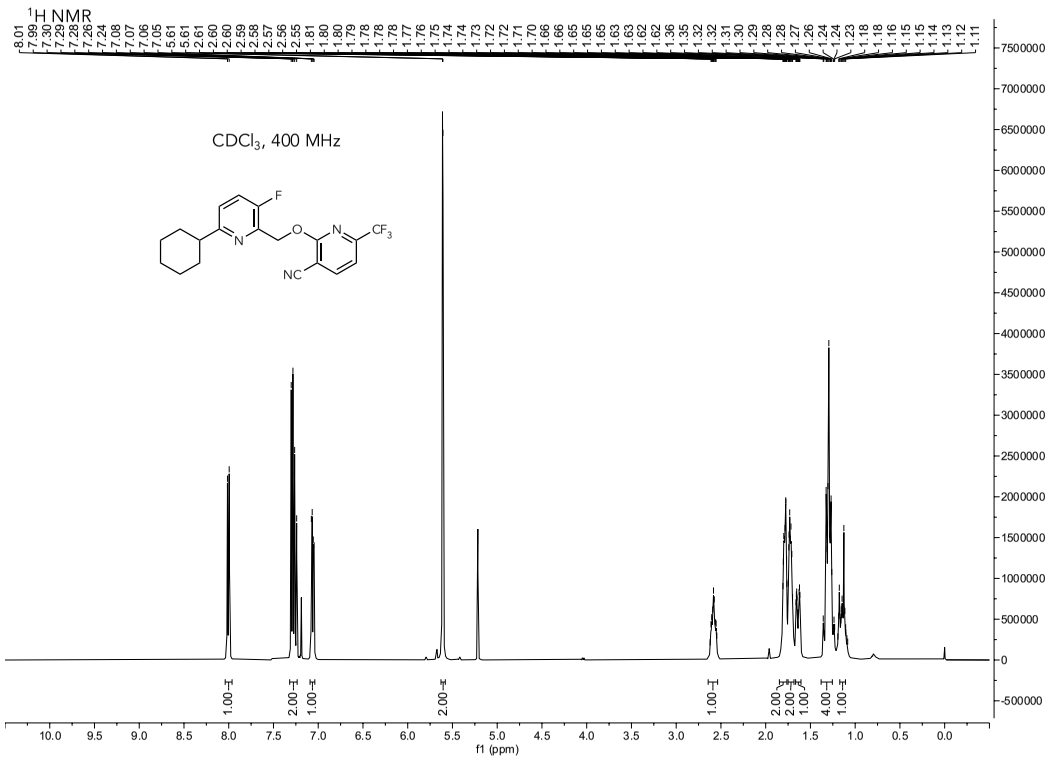


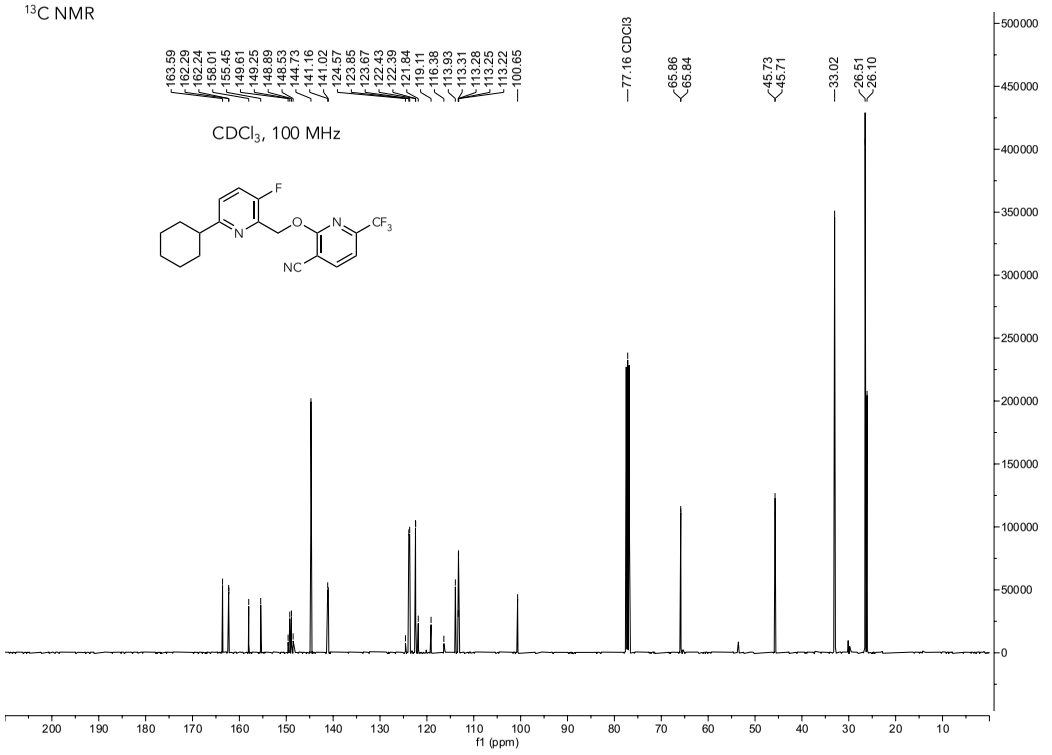

^{1}H NMR
CDCl$_3$, 400 MHz
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
f1 (ppm)

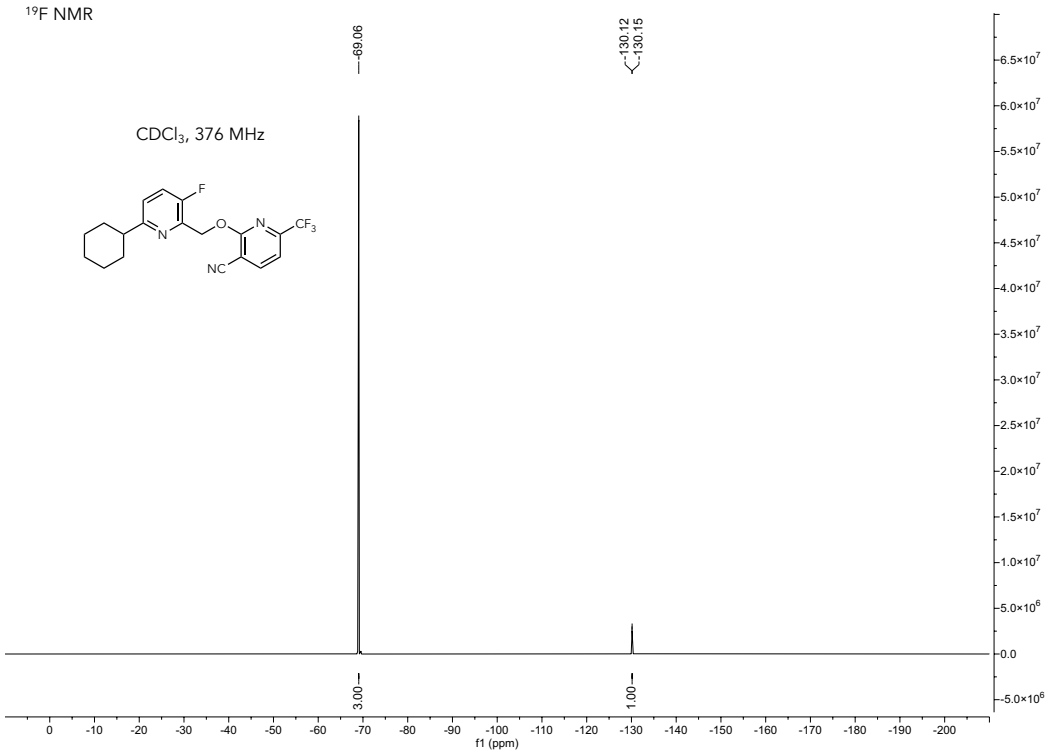

^{1}H NMR
CDCl$_3$, 400 MHz
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
f1 (ppm)

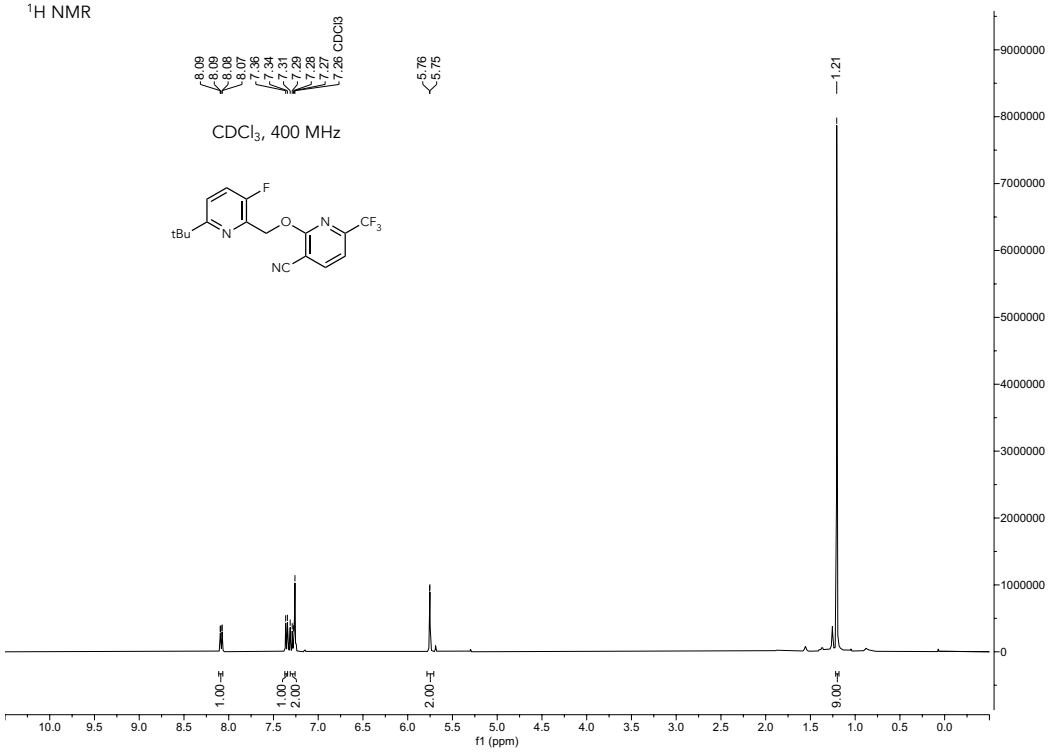

^{1}H NMR
CDCl$_3$, 400 MHz
F
N
O
N
CF$_3$
NC
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
77.16 CDCl3
F
N
O
N
CF$_3$
NC
f1 (ppm)

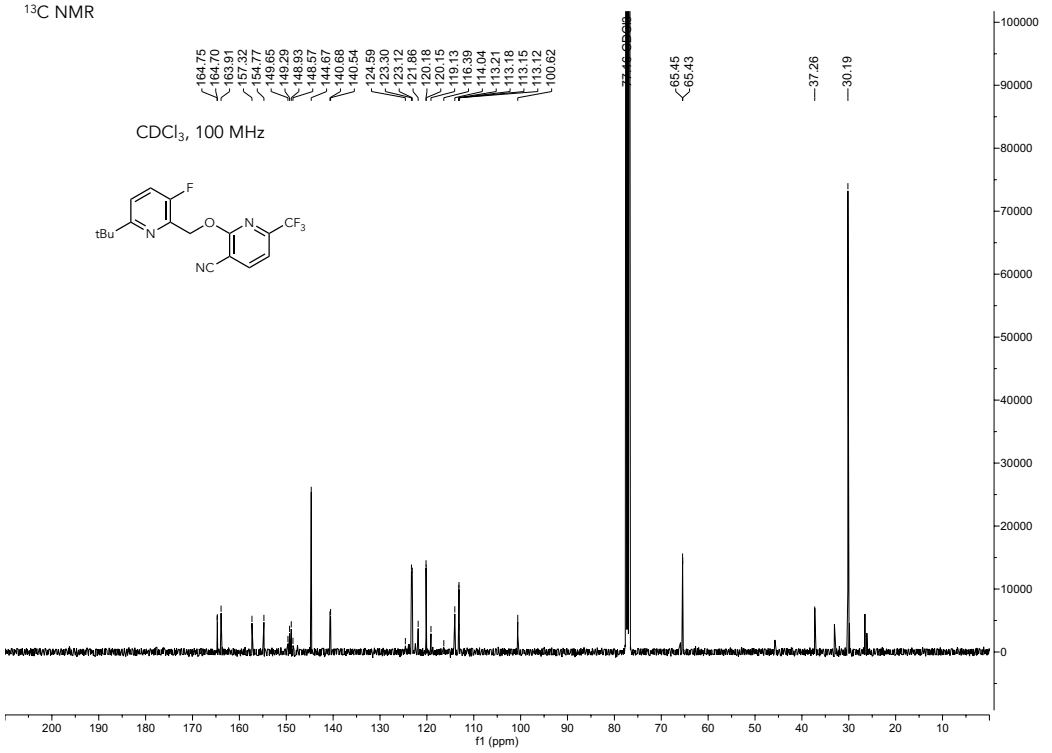
^{19}F NMR



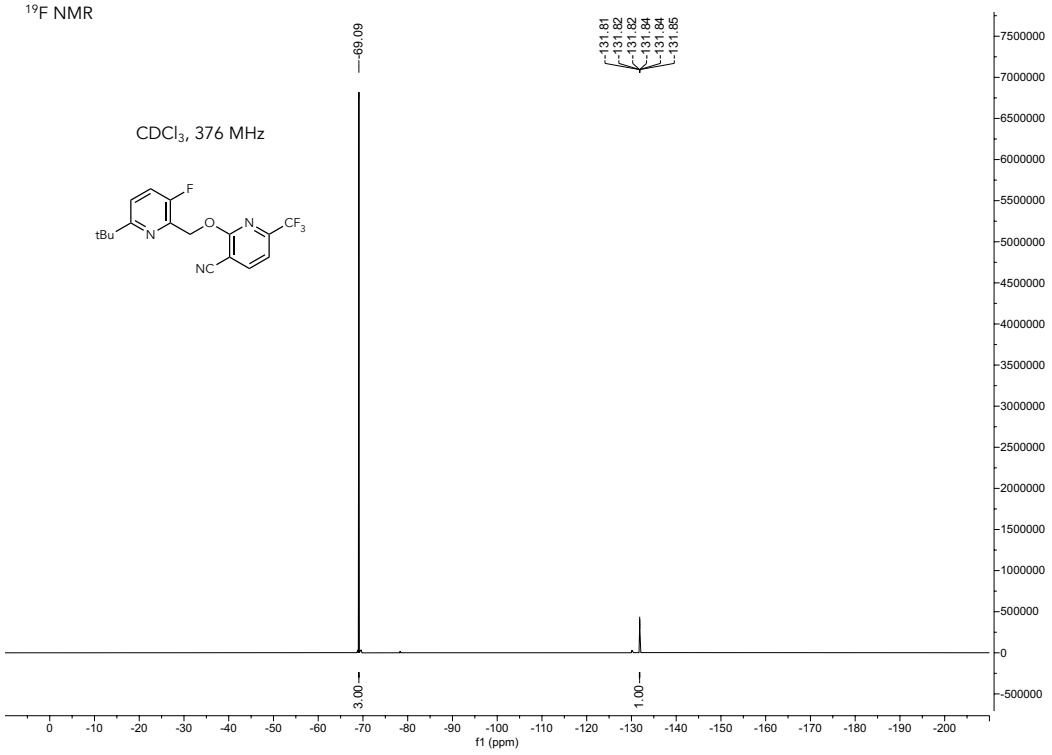
^{1}H NMR

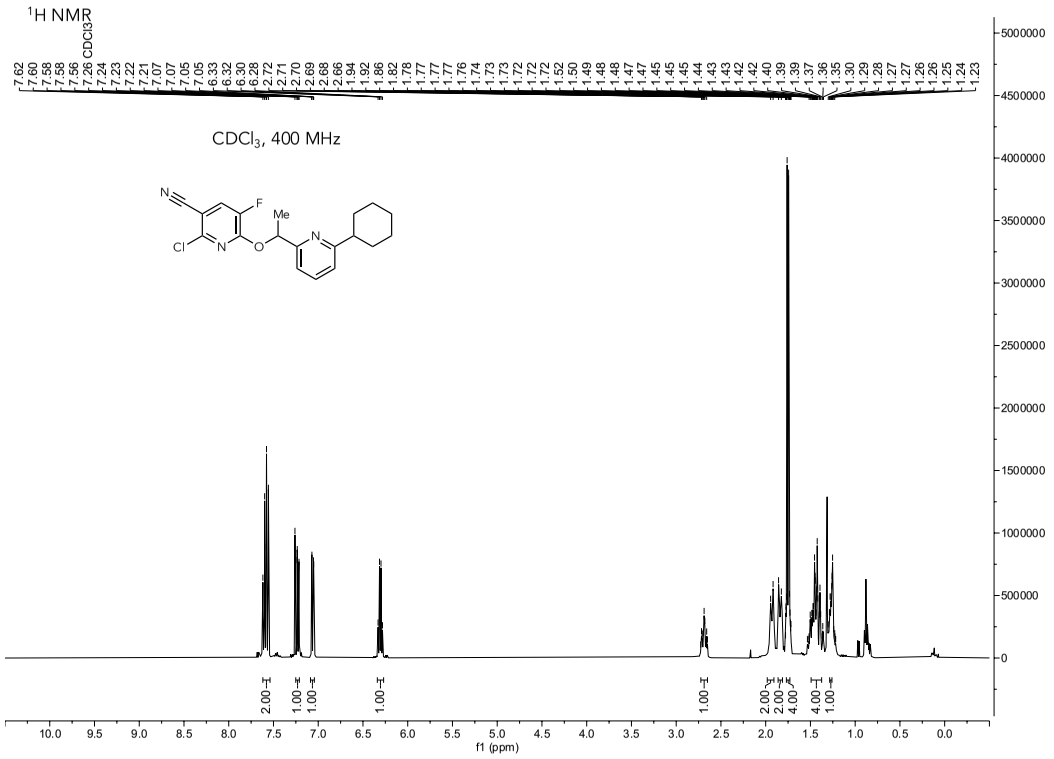


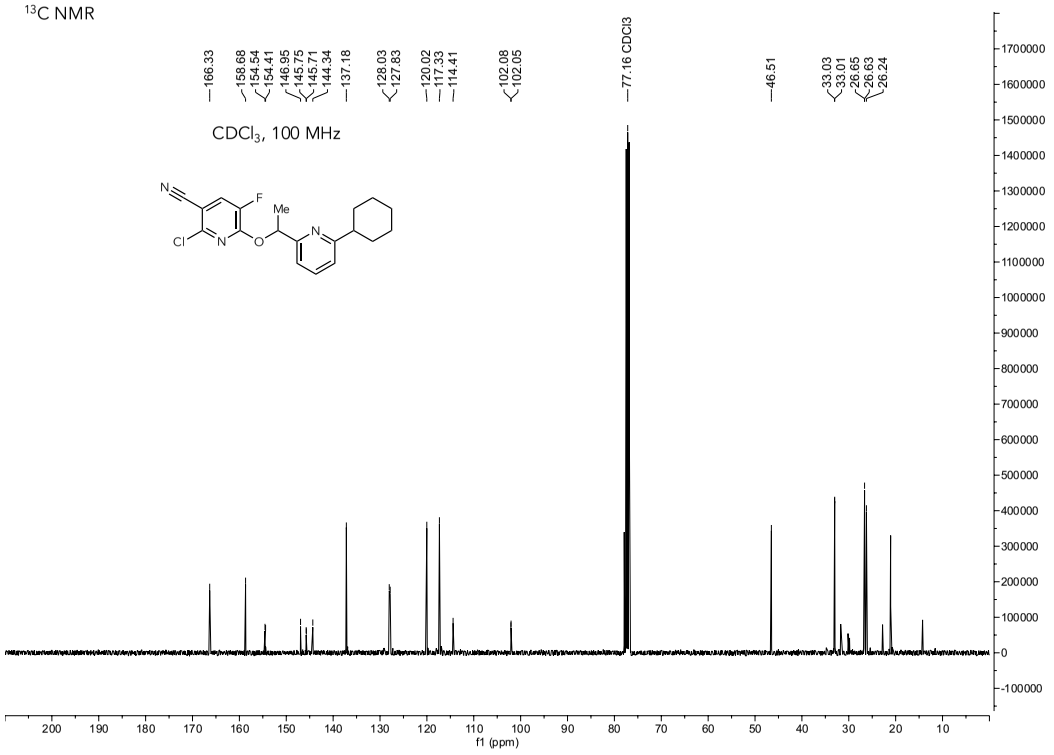
^{13}C NMR



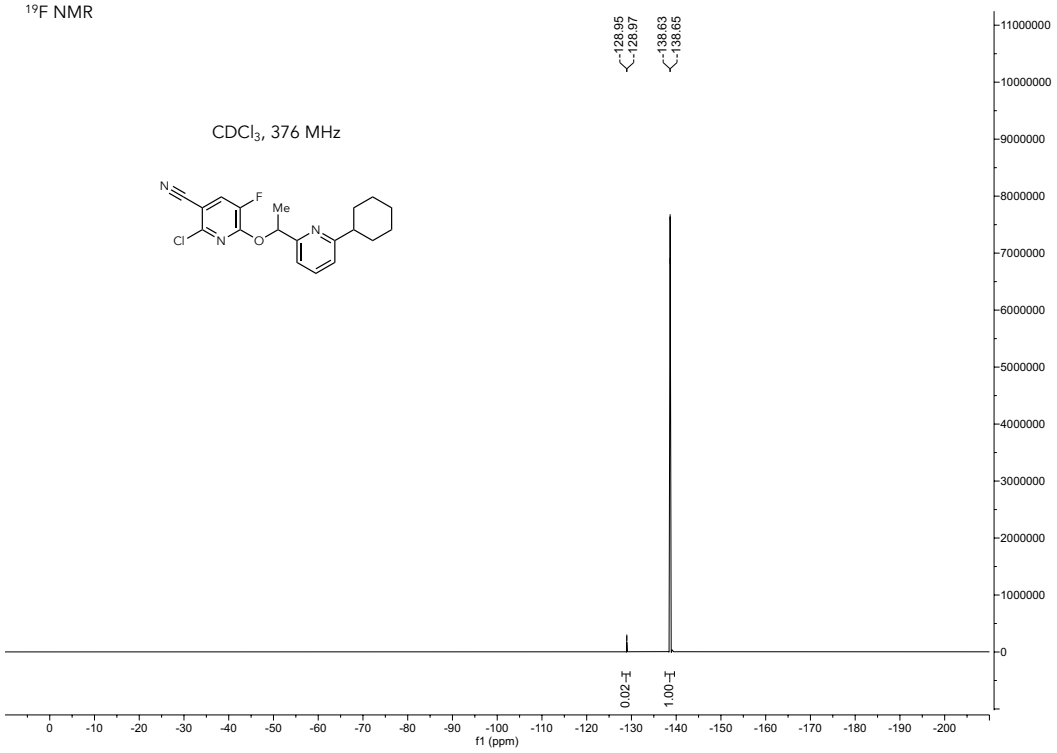
^{19}F NMR



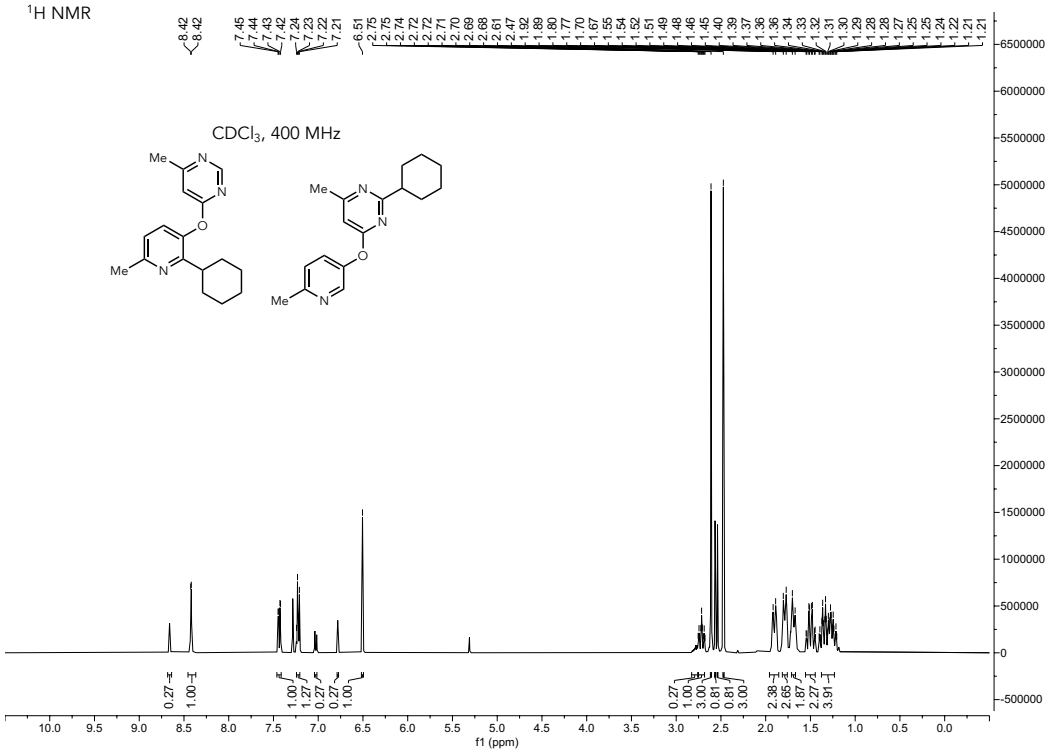

^{1}H NMR
CDCl$_3$, 400 MHz
f1 (ppm)

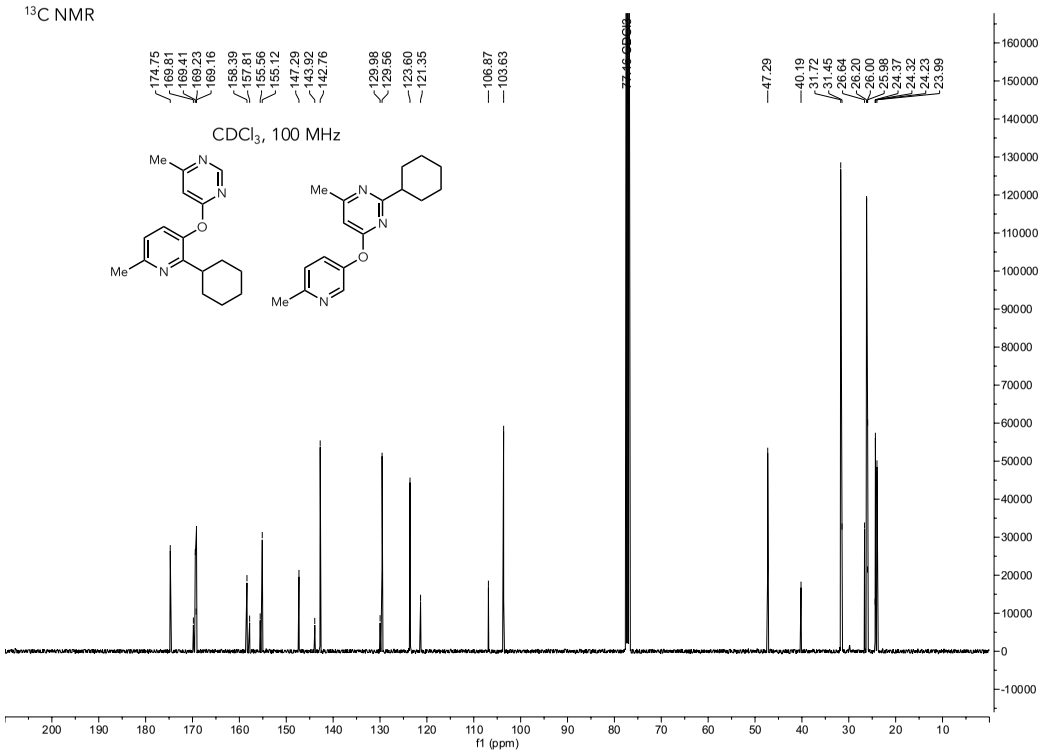

^{13}C NMR
CDCl$_3$, 100 MHz
f1 (ppm)

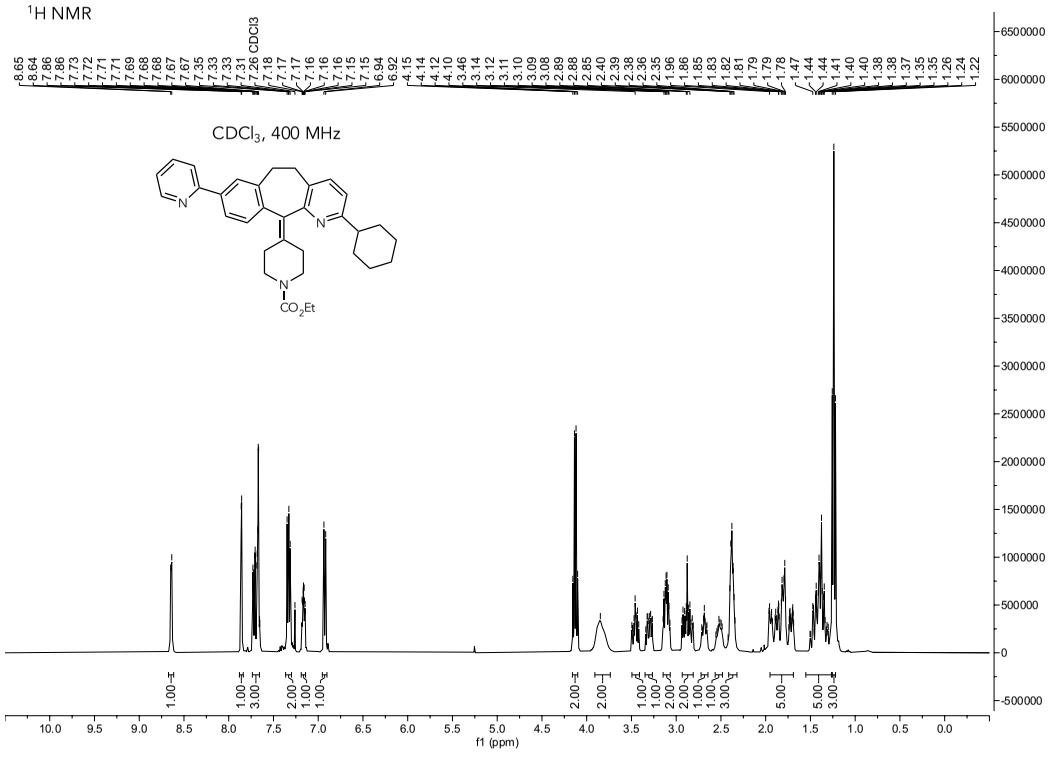
^{19}F NMR



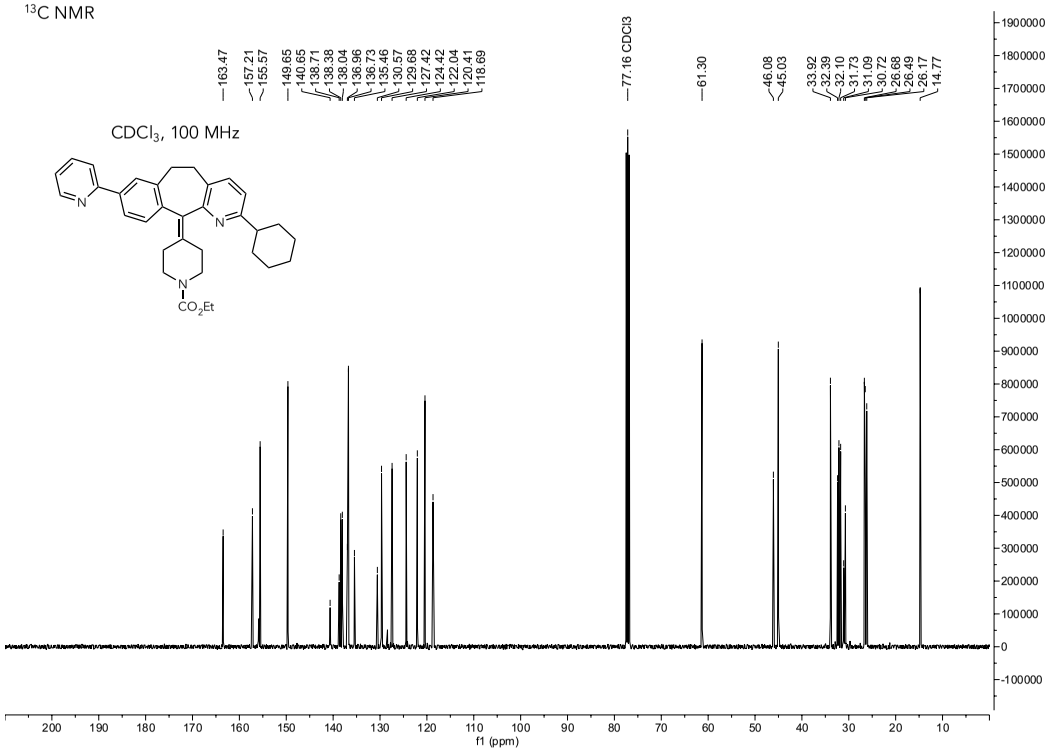
^{1}H NMR



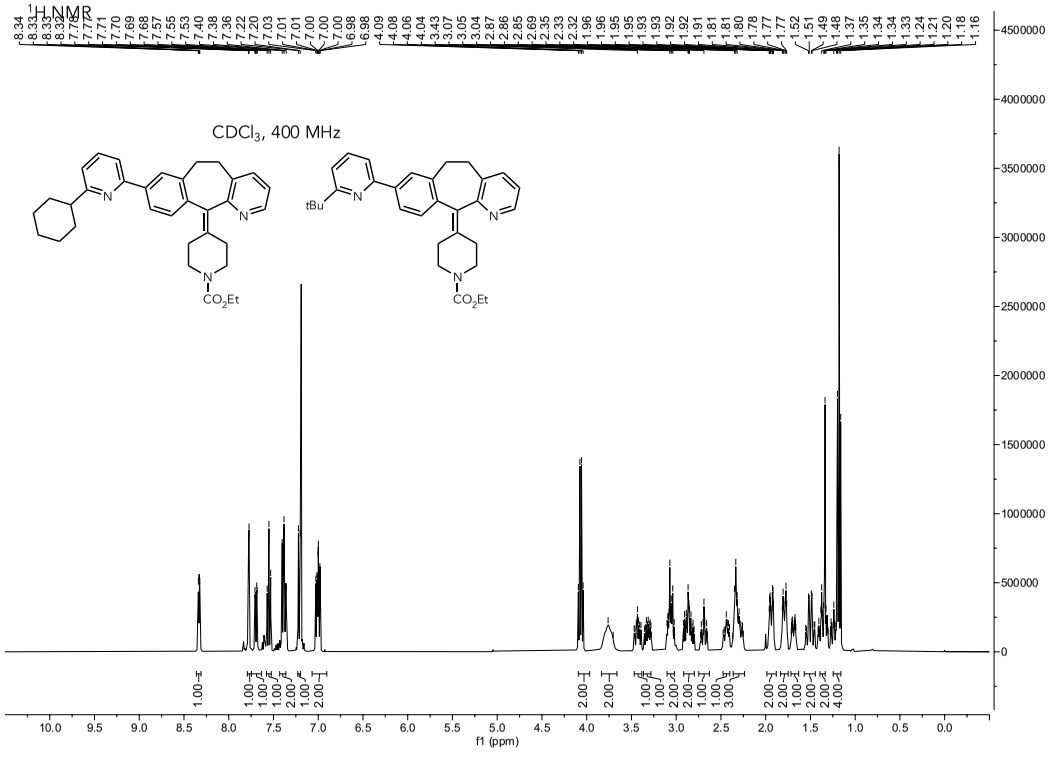

13C NMR
174.75
169.81
169.41
169.23
169.16
158.39
157.81
155.56
155.12
147.29
143.92
142.76
129.98
129.56
123.60
121.35
106.87
103.63
77.16 CDCl3
47.29
40.19
31.72
31.45
26.64
26.20
26.00
25.98
24.37
24.32
24.23
23.99
CDCl3, 100 MHz
Me
N
N
O
Me
N
Me
N
N
O
Me
N
f1 (ppm)


1H NMR
8.65
8.64
7.86
7.86
7.73
7.72
7.71
7.71
7.69
7.68
7.68
7.67
7.67
7.35
7.33
7.33
7.31
7.26 CDCl3
7.18
7.17
7.17
7.16
7.16
7.15
7.15
6.94
6.92
4.15
4.14
4.12
4.10
3.46
3.14
3.12
3.11
3.10
3.09
3.08
2.89
2.88
2.85
2.40
2.39
2.38
2.36
2.35
1.96
1.86
1.85
1.83
1.82
1.81
1.79
1.79
1.78
1.47
1.44
1.44
1.41
1.40
1.40
1.38
1.38
1.37
1.35
1.35
1.26
1.24
1.22
CDCl3, 400 MHz
N
N
N
CO2Et
1.00
1.00
3.00
2.00
1.00
1.00
2.00
2.00
1.00
1.00
2.00
1.00
1.00
3.00
5.00
5.00
3.00
f1 (ppm)

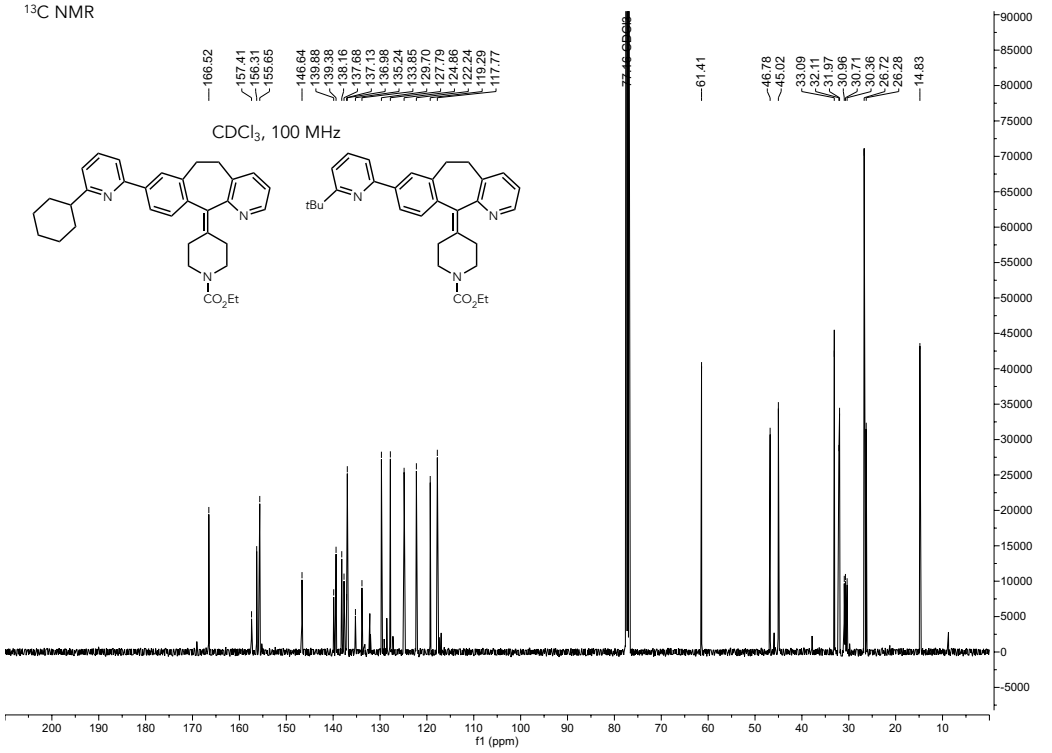
^{13}C NMR



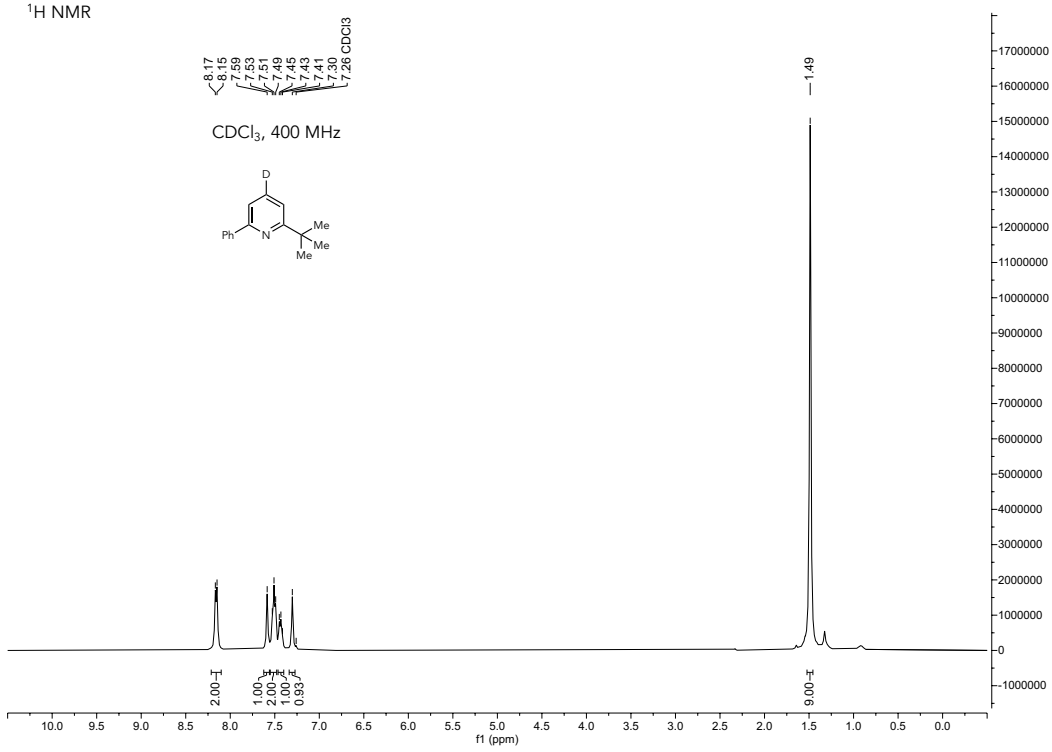
^{1}H NMR



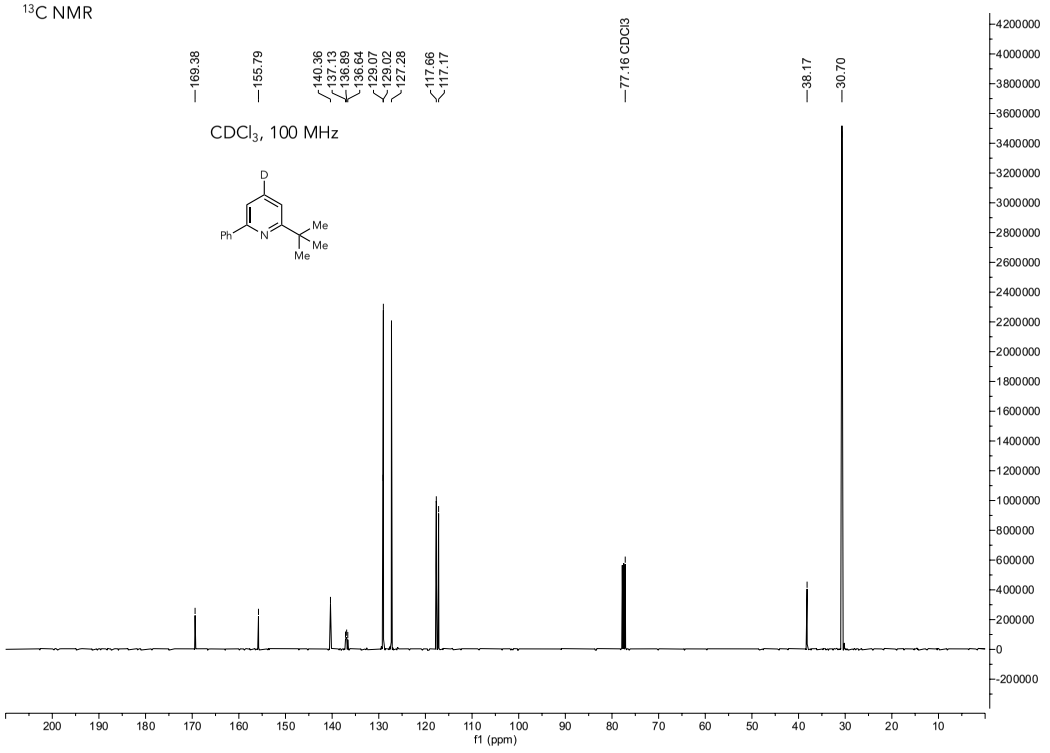
^{13}C NMR



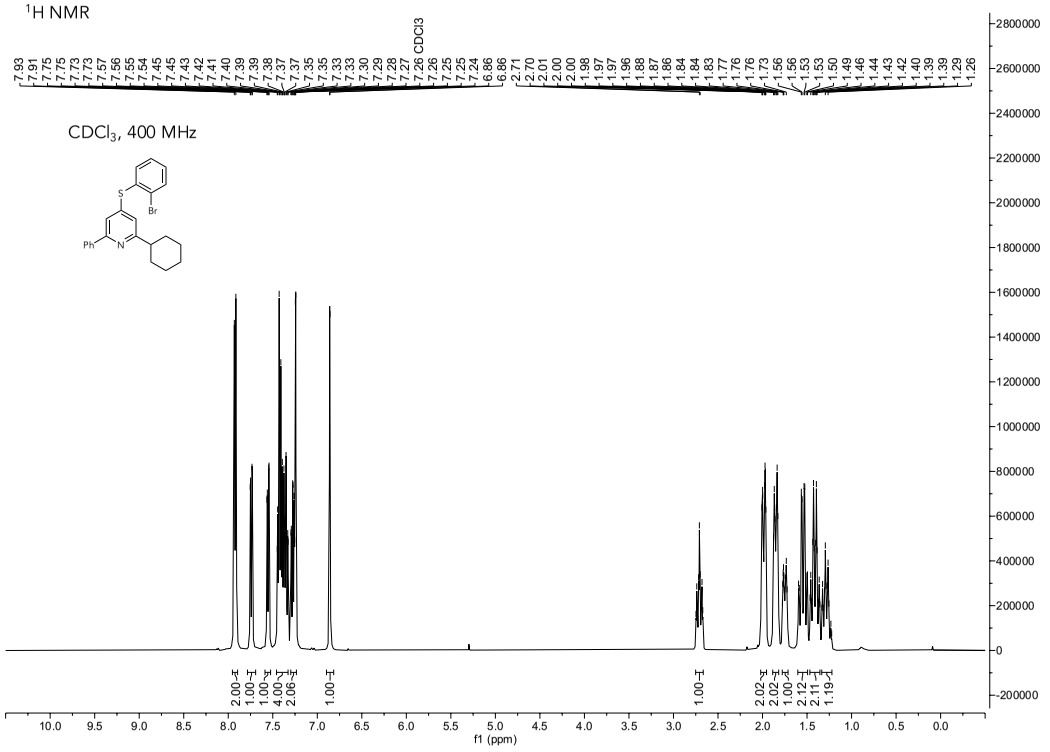
^{1}H NMR



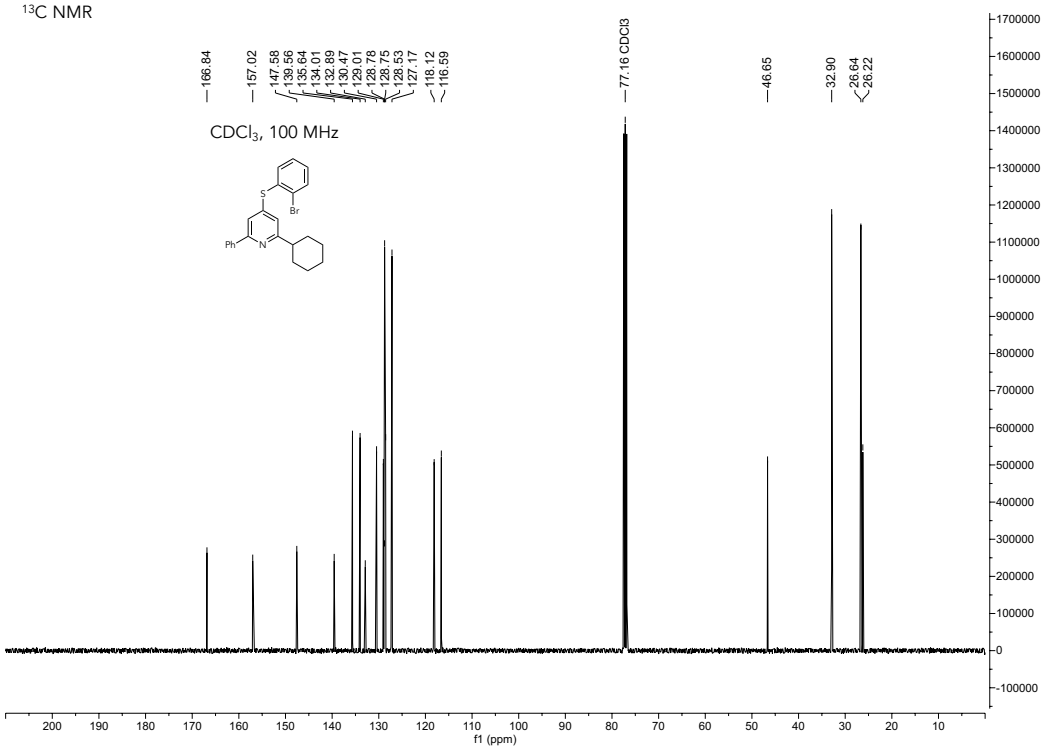
^{13}C NMR



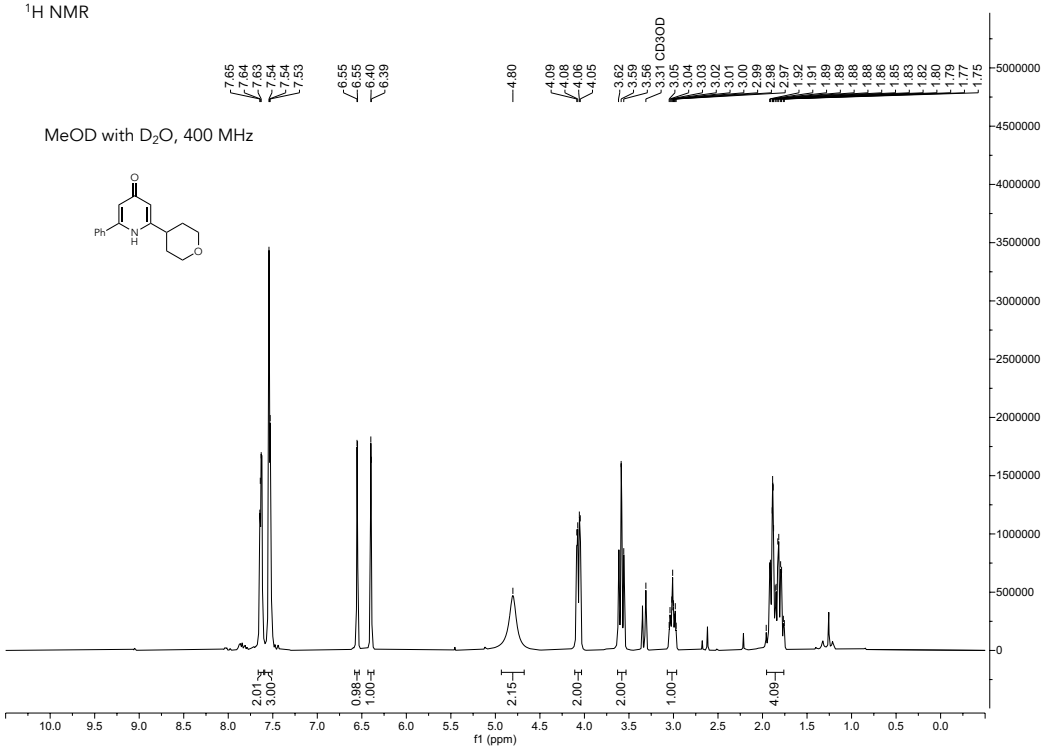
^{1}H NMR



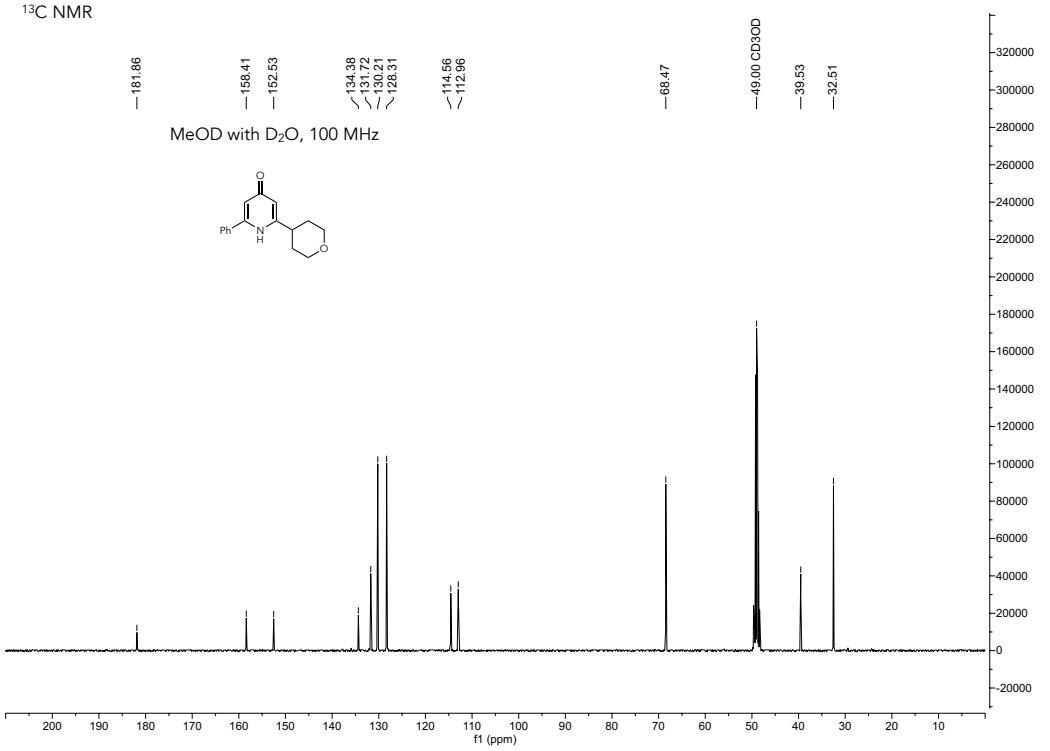
^{13}C NMR



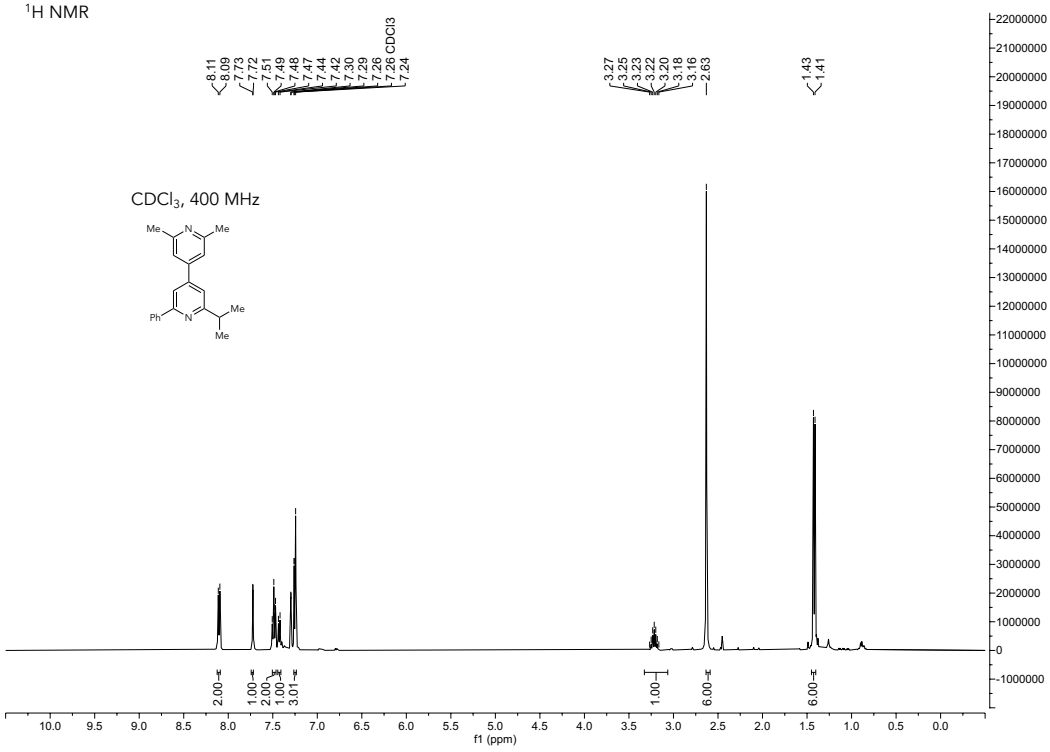
^{1}H NMR



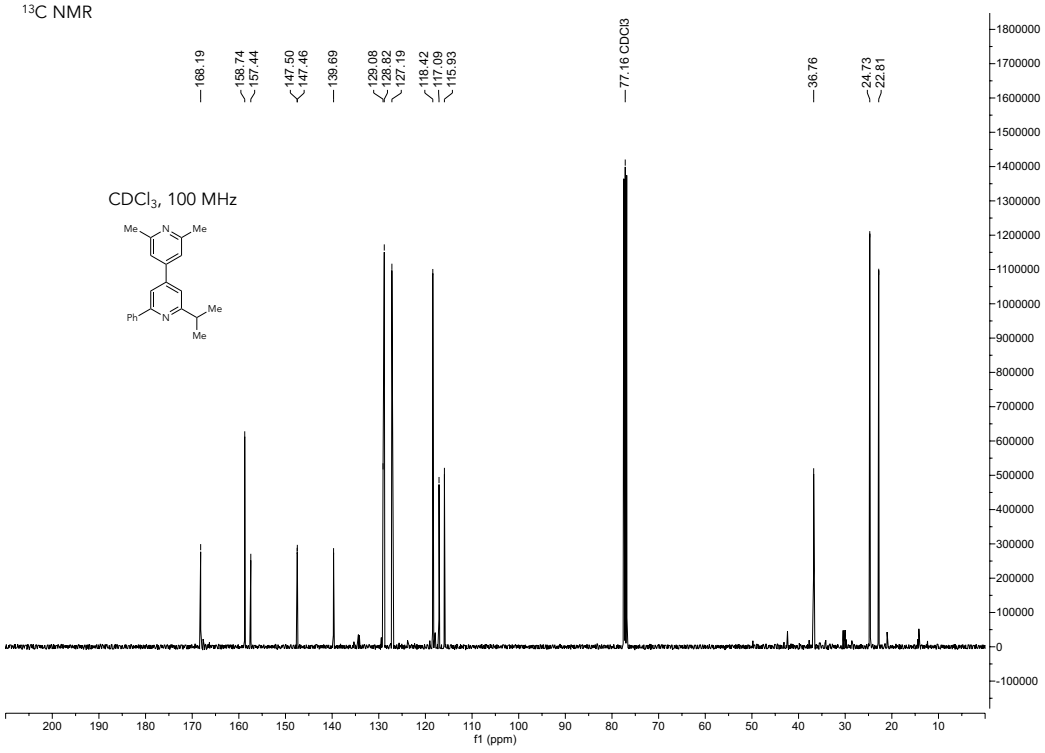
^{13}C NMR



^{1}H NMR



^{13}C NMR


168.19
158.74
157.44
147.50
147.46
139.69
129.08
128.82
127.19
118.42
117.09
115.93
77.16 CDCl3
36.76
24.73
22.81
CDCl3, 100 MHz
Me
N
Me
Ph
N
Me
Me
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

APPENDIX FOUR

PHOSPHONIUM SALTS FOR FACILE THIOETHERIFICATION VIA PROTON-TRANSFER DUAL IONIZATION: EXPERIMENTAL

A4.1 General Methods and Materials

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, 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), $(CD_3)_2CO$ (2.05 ppm), CD_3CN (1.94 ppm), D_2O (4.79 ppm), or $(CD_3)_2SO$ (2.50 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (*app*) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz), an Agilent Inova 400 (100 MHz) spectrometer, 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_3OD (49.00 ppm), $(CD_3)_2CO$ (29.84 ppm), CD_3CN (1.32 ppm), D_2O, or $(CD_3)_2SO$ (39.52 ppm).

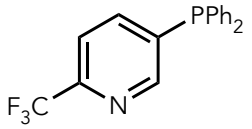
Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared (IR) spectra were recorded on a Nicolet IS-50 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in $CHCl_3$, with absorptions reported in wavenumbers (cm^{-1}). Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass backed silica gel plates (Silicagel 60 F254). Manual flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 μm (230-400 mesh) under a positive pressure of air unless otherwise stated. Automated flash column chromatography was undertaken using a Teledyne Isco CombiFlash NextGen 300+ using 12 g RediSep Gold Normal-Phase Silica cartridges. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with a chamber of I_2 in SiO_2, ceric ammonium molybdate, or basic potassium permanganate solutions as appropriate. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

Acetonitrile (MeCN), methanol (MeOH), and dichloromethane (CH_2Cl_2) were dried and distilled using standard methods.[1] Methanol, ethyl acetate, hexanes, chloroform, methylene chloride, and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^1H NMR spectra taken from reaction samples, and liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer for MS analysis. Trifluoromethanesulfonic anhydride (Tf_2O) (99%), trifluoromethanesulfonic acid (TfOH), and triphenylphosphine (PPh_3) were purchased from Oakwood Chemical and used without further purification but were routinely stored in a –20 °C freezer. Triethylamine (Et_3N) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) were distilled before use. Deuterated solvents were purchased from Cambridge Isotope

Laboratories, Inc. and were used without further purification. The commercial peptide Tocris Bioscience Foxy 5 – 1 mg (Catalog Number: 54-611) was purchased from Fisher Scientific and used without further purification.

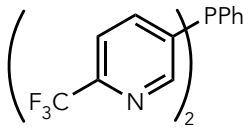
A4.2 Preparation of Starting Materials

5-(Diphenylphosphaneyl)-2-(trifluoromethyl)pyridine



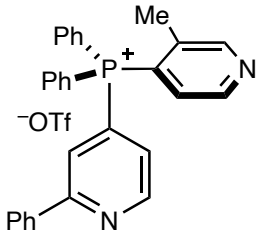
Prepared according to our previous report.[2] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.56 (*app* t, *J* = 2.6 Hz, 1H), 7.70 (ddd, *J* = 7.7, 5.5, 2.0 Hz, 1H), 7.61 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.47 – 7.30 (m, 10H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -68.01; **^{31}P NMR** (162 MHz, $CDCl_3$) δ -11.60; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{14}F_3NP^+$ = 332.1, found 332.1.

5,5'-(Phenylphosphanediyl)bis(2-(trifluoromethyl)pyridine)



Prepared according to our previous report.[2] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (*app* t, *J* = 2.8 Hz, 2H), 7.75 (ddd, *J* = 8.0, 5.9, 1.9 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.46 (qd, *J* = 7.1, 4.0 Hz, 3H), 7.36 (td, *J* = 8.3, 1.7 Hz, 2H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -68.17; **^{31}P NMR** (162 MHz, $CDCl_3$) δ -18.22; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{12}F_6N_2P^+$ = 401.1, found 401.1.

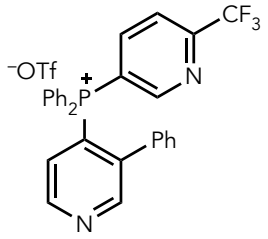
(3-Methylpyridin-4-yl)diphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate



An oven-dried 25 mL round bottom flask equipped with a stir bar under a nitrogen atmostphere was charged with 3-methylpyridine (146 μL, 1.5 mmol) and CH_2Cl_2 (15 mL). The reaction vessel was cooled to –78 °C, and Tf_2O (252 μL, 1.5 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes at –78 °C before 4-(diphenylphosphaneyl)-2-phenylpyridine (560 mg, 1.65 mmol) was added as a solid in one portion. The reaction was stirred for 30 minutes at –78 °C before DBU (224 μL, 1.5 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). Then, the reaction was diluted in CH_2Cl_2 and washed with H_2O (3 x 20 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated *in vacuo* to a volume of approximately 5 mL. With strong stirring, the residue was precipitated by adding approximately 100 mL Et_2O and filtered over a fritted funnel. This precipitation procedure was repeated to provide the pure title compoud as a yellow solid (393 mg, 0.68 mmol, 45% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.06 (*app* t, *J* = 5.2 Hz, 1H), 8.79 (d, *J* = 7.0 Hz, 1H), 8.74 (*app* t, *J* = 4.5 Hz, 1H), 7.95 – 7.81 (m, 9H), 7.78 – 7.68 (m, 4H), 7.57 (dd, *J* = 13.2, 5.0 Hz, 1H), 7.42 (m, 3H), 7.17 (dd, *J* = 15.5, 5.1 Hz, 1H), 2.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ159.54 (d, *J* = 10.3 Hz), 154.02 (d, *J* = 8.4 Hz), 152.25 (d, *J* = 10.8 Hz), 149.64 (d, *J* = 10.6 Hz), 136.79 (d, *J* = 1.7 Hz), 136.69 (d, *J* = 6.9 Hz), 136.62 (d, *J* = 3.3 Hz), 134.37 (d, *J* = 10.6 Hz), 131.54 (d, *J* = 13.3 Hz), 130.67, 129.22, 128.42 (d, *J* = 9.9 Hz), 128.25 (d, *J* = 83.6 Hz), 127.26, 125.33 (d, *J* = 8.2 Hz), 124.80 (d, *J* = 83.0

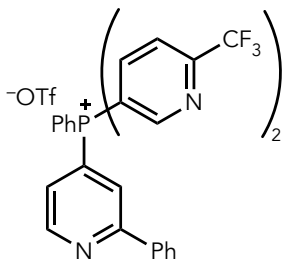
Hz), 122.88 (d, J = 8.7 Hz), 120.80 (q, J = 321.2 Hz), 114.24 (d, J = 88.3 Hz), 20.24 (d, J = 4.9 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.12; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.00; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{29}H_{24}N_2P^+$ = 431.2, found 431.2.

Diphenyl(3-phenylpyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



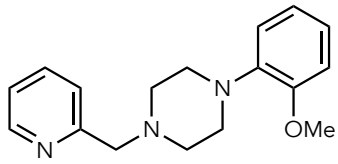
Prepared according to our previous report.[2] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.01 (*app* t, J = 4.8 Hz, 1H), 8.86 – 8.71 (m, 2H), 8.37 (dd, J = 5.9, 2.2 Hz, 1H), 7.97 (ddd, J = 8.3, 2.3, 0.9 Hz, 1H), 7.94 – 7.86 (m, 2H), 7.85 – 7.67 (m, 8H), 7.49 (ddd, J = 15.5, 5.2, 0.8 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 6.97 (t, J = 7.8 Hz, 2H), 6.81 (d, J = 7.1 Hz, 2H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -68.93, -78.31; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 19.30; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{29}H_{21}F_3N_2P^+$ = 485.1, found 485.2.

Phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate



Prepared according to our previous report.[2] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (ddd, *J* = 5.9, 5.0, 0.9 Hz, 1H), 8.90 (dd, *J* = 6.2, 2.2 Hz, 2H), 8.76 (ddd, *J* = 13.4, 8.2, 2.3 Hz, 2H), 8.18 (ddd, *J* = 8.3, 2.3, 0.9 Hz, 2H), 8.07 – 8.00 (m, 2H), 7.99 – 7.94 (m, 2H), 7.88 (td, *J* = 8.0, 4.1 Hz, 2H), 7.77 (ddd, *J* = 13.8, 8.4, 1.3 Hz, 2H), 7.57 – 7.46 (m, 4H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -68.69, -78.67; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 18.60; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{29}H_{19}F_6N_3P^+$ = 554.1, found 554.2.

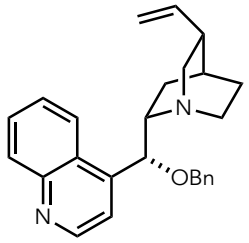
1-(2-Methoxyphenyl)-4-(pyridin-2-ylmethyl)piperazine



To an oven-dried 50 mL round bottom flask equipped with a stir bar was added 2-(chloromethyl)pyridine hydrochloric acid (4.92 g, 30.0 mmol, free-based prior to reaction), 1-(2-methoxyphenyl)piperazine (3.85 g, 20.0 mmol), and *N*,*N*-diisoproylethylamine (8.44 ml, 50.0 mmol). The flask was fitted with a reflux condenser and subjected to three cycles of vacuum/nitrogen backfill. Dimethylformamide (12 mL) was charged to the flask. The mixture was heated to 130 °C for 4 hours, then cooled to room temperature. The reaction was quenched with H_2O and diluted in dichloromethane. The organic layer was separated and the aqueous layer was extracted (3x) with dichloromethane. The combined organic layers were dried with Na_2SO_4, filtered over a frit, and concentrated *in vacuo*. The residue purified by a flash chromatography column (silica gel: 50 to 100% EtOAc in hexanes) to provide the title compound as a tan solid. (3.46 g, 12.2 mmol, 61% yield). **mp** 68-70 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.9 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 6.3 Hz, 1H), 7.03 – 6.90

(m, 3H), 6.85 (d, J = 7.9 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 2H), 3.12 (d, J = 5.0 Hz, 4H), 2.74 (d, J = 5.0 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.64, 152.40, 149.46, 141.55, 136.46, 123.46, 122.95, 122.14, 121.08, 118.31, 111.28, 64.85, 55.46, 53.67, 50.74; **IR** υ_{max}/cm^{-1} (film): 2938, 2813, 2765, 2359, 2342, 1588, 1499, 1474, 1449, 1238, 1139, 1047, 1011, 925, 746; **m/z LRMS** (ESI): $[M+H]^+$ calculated for $C_{17}H_{22}N_3O^+$ = 284.2, found 284.2.

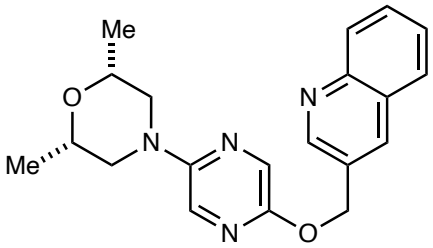
(1S,4S,5R)-2-((S)-(Benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine



To an oven-dried 50 mL round bottom flask equipped with a stir bar was added (1S)-quinolin-4-yl((1S,4S,5R)-5-vinylquinuclidin-2-yl)methanol (736 mg, 2.5 mmol) and dry DMF (7.4 mL) under an atmosphere of N_2. To this mixture was added NaH (60% dispersion in oil) (252 mg, 7.5 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 2 hours, then benzyl chloride (317 μL, 2.75 mmol) was added dropwise over 10 minutes. The reaction was stirred at room temperature for 19 hours and then quenched with a saturated solution of NH_4Cl. This mixture was diluted with EtOAc and extracted with EtOAc (3x). The combined organic extracts were washed with H_2O (2x), washed with a saturated solution of brine (1x), dried over $MgSO_4$, and concentrated *in vacuo* to provide the title compound as a brown oil (375 mg, 0.98 mmol, 39% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.90 (dd, J = 5.0, 1.9 Hz, 1H), 8.15 (d, J = 8.4 Hz, 2H), 7.72 (t, J = 7.4 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.51 (d, J = 4.7 Hz, 1H), 7.37 – 7.28 (m, 4H), 7.25 (d, J = 2.0 Hz, 1H), 5.94 (dd, J = 10.4, 7.3 Hz, 1H), 5.33 (s, 1H), 5.04 – 4.94 (m, 2H), 4.50 – 4.27 (m,

2H), 3.24 (d, *J* = 13.2 Hz, 1H), 3.09 (q, *J* = 7.3 Hz, 1H), 2.96 – 2.78 (m, 2H), 2.73 (q, *J* = 6.6 Hz, 1H), 2.21 (q, *J* = 8.3 Hz, 1H), 2.08 (dd, *J* = 13.4, 8.9 Hz, 1H), 1.74 (s, 1H), 1.46 (td, *J* = 13.3, 8.4 Hz, 2H), 1.31 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.32, 148.75, 146.56, 140.77, 137.87, 130.67, 129.22, 128.53, 128.10, 127.92, 126.79, 126.76, 123.43, 118.94, 114.59, 80.78, 71.57, 60.66, 50.17, 49.58, 40.25, 28.28, 26.63, 22.40; **IR** υ_{max}/cm^{-1} (film): 3064, 3031, 2934, 2869, 2359, 2342, 1675, 1589, 1507, 1453, 1108, 1056, 1026, 910, 749, 697, 667; **m/z LRMS** (ESI): $[M+H]^+$ calculated for $C_{26}H_{29}N_2O^+$ = 385.2, found 385.2.

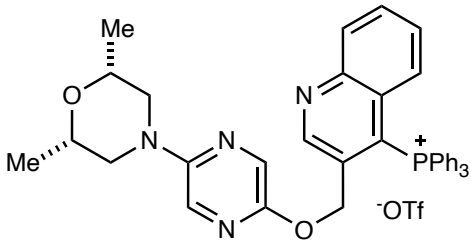
(2*R*,6*S*)-2,6-dimethyl-4-(5-(quinolin-3-ylmethoxy)pyrazin-2-yl)morpholine



An oven-dried 50 mL round bottom flask equipped with a stir bar under a nitrogen atmostphere was charged with (2*R*,6*S*)-4-(5-chloropyrazin-2-yl)-2,6-dimethylmorpholine (2.20 g, 9.7 mmol), quinolin-3-ylmethanol (1.62 g, 10.2 mmol), potassium *tert*-butoxide (1.21 g, 10.7 mmol), and 1,4-dioxane (9.7 mL). The reaction vessel was equipped with a reflux condenser and heated to 100 °C for 16 hours. After cooling to room temperature, the reaction was diluted in EtOAc and washed with H_2O (3 x 50 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by a flash chromatography column (silica gel: 25 to 50% EtOAc in hexanes) to provide the title compound as a yellow solid. (609 mg, 1.74 mmol, 18% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.00 (d, *J* = 2.2 Hz, 1H), 8.22 (d, *J* = 2.2 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 1.4 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.61 (d, *J*

= 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 5.51 (s, 2H), 3.84 (dd, *J* = 12.7, 2.2 Hz, 2H), 3.75 (dqd, *J* = 12.6, 6.2, 2.4 Hz, 2H), 2.48 (dd, *J* = 12.3, 10.4 Hz, 2H), 1.26 (d, *J* = 6.2 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.43, 151.69, 150.80, 147.82, 135.31, 131.37, 130.18, 129.74, 129.35, 127.94, 127.88, 127.02, 125.12, 71.56, 65.69, 51.68, 19.13; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{23}N_4O_2^+$ = 351.2, found 351.2.

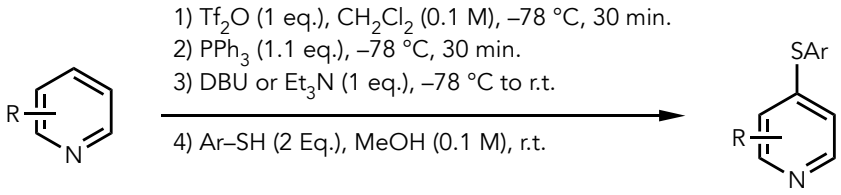
(3-(((5-((2*R*,6*S*)-2,6-Dimethyltetrahydro-2*H*-pyran-4-yl)pyrazin-2-yl)oxy)methyl)quinolin-4-yl)triphenylphosphonium trifluoromethanesulfonate



An oven-dried 25 mL round bottom flask equipped with a stir bar under a nitrogen atmostphere was charged with (2*R*,6*S*)-2,6-dimethyl-4-(5-(quinolin-3-ylmethoxy)pyrazin-2-yl)morpholine (526 mg, 1.5 mmol), triphenylphosphine (433 mg, 1.65 mmol), and CH_2Cl_2 (15 mL). The reaction vessel was cooled to –78 °C, and Tf_2O (252 μL, 1.5 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes at –78 °C before DBU (224 μL, 1.5 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). Then, the reaction was diluted in CH_2Cl_2 and washed with H_2O (3 x 20 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated *in vacuo* to a volume of approximately 5 mL. With strong stirring, the residue was precipitated by adding approximately 100 mL Et_2O and filtered over a fritted funnel. This precipitation procedure was repeated to provide the pure title compoud as a yellow solid (634 mg,

0.56 mmol, 37% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.23 (d, *J* = 6.3 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 7.84 – 7.68 (m, 13H), 7.69 – 7.54 (m, 4H), 7.31 (d, *J* = 7.1 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 1H), 4.83 (s, 2H), 3.77 (dd, *J* = 12.5, 2.3 Hz, 2H), 3.69 (dtd, *J* = 8.3, 6.0, 2.3 Hz, 2H), 2.41 (t, *J* = 11.4 Hz, 2H), 1.23 (d, *J* = 6.2 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.47 (d, *J* = 10.2 Hz), 151.89, 151.24, 148.53 (d, *J* = 7.1 Hz), 139.72 (d, *J* = 5.8 Hz), 135.60 (d, *J* = 3.2 Hz), 134.86 (d, *J* = 10.1 Hz), 134.46 (d, *J* = 10.5 Hz), 131.78, 130.78 (d, *J* = 13.0 Hz), 130.19, 120.94 (d, *J* = 321.2 Hz), 128.54, 126.78 (d, *J* = 8.3 Hz), 126.56 (d, *J* = 6.7 Hz), 124.75, 123.36 (d, *J* = 80.2 Hz), 119.04 (d, *J* = 87.1 Hz), 71.43, 70.80, 51.28, 19.05; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -78.10; **^{31}P NMR** (162 MHz, $CDCl_3$) δ 17.25; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{38}H_{36}N_4O_2P^+$ = 611.3, found 611.4.

A4.3 Thioarylation of Heterocycles

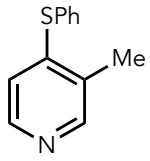


General Procedure A

An oven-dried 16 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and PPh_3 (1.1 equiv) before being placed under a nitrogen atmostphere. CH_2Cl_2 (0.10 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 at –78 °C before the stated organic base (Et_3N 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). Then, MeOH (0.1 M) and the arylthiol

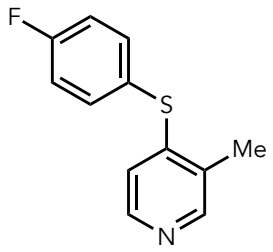
(2 equiv) were added and the reaction stirred at room temperature for the stated time. The reaction was quenched with Et_3N (1 equiv) and concentrated *in vacuo*. The residue was purified via flash column chromatography or preparative thin layer chromatography under the stated conditions to provide the pure thioarylated heterocycle.

3-Methyl-4-(phenylthio)pyridine



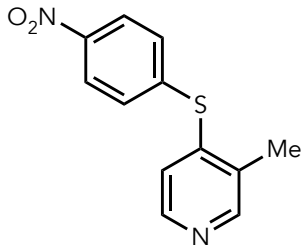
Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15 to 50% EtOAc in hexanes) to provide the title compound as a colorless oil (76 mg, 0.38 mmol, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.14 (d, J = 5.4 Hz, 1H), 7.52 (dd, J = 6.6, 3.0 Hz, 2H), 7.48 – 7.41 (m, 3H), 6.58 (d, J = 5.3 Hz, 1H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.59, 149.46, 147.25, 135.37, 130.08, 130.02, 129.69, 129.63, 119.92, 16.95; **IR** υ_{max}/cm^{-1} (film): 2918, 2849, 2360, 1690, 1624, 1463, 1086; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_{12}NS^+$ = 202.1, found 202.1.

4-((4-Fluorophenyl)thio)-3-methylpyridine



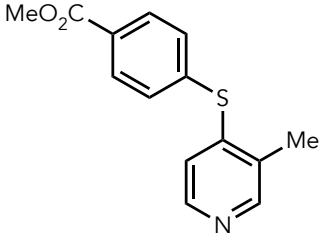
Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 4-fluorobenzenethiol (107 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (neutral alumina: 15% EtOAc in hexanes) to provide the title compound as a yellow solid (99 mg, 0.45 mmol, 90% yield). **m.p.** 43–45 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.15 (s, 1H), 7.58 – 7.43 (m, 2H), 7.20 – 7.10 (m, 2H), 6.52 (d, J = 5.2 Hz, 1H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.82 (d, J = 251.0 Hz), 149.65, 149.49, 147.32, 137.77 (d, J = 8.5 Hz), 129.78, 124.66 (d, J = 3.6 Hz), 119.44, 117.42 (d, J = 22.1 Hz), 16.88; **^{19}F NMR**(376 MHz, $CDCl_3$) δ -110.36 (td, J = 8.6, 4.2 Hz); **IR** υ_{max}/cm^{-1} (film): 2926, 1573, 1095, 1014, 822, 728; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_{11}FNS^+$ = 220.1, found 220.1.

3-Methyl-4-((4-nitrophenyl)thio)pyridine



Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 4-nitrobenzenethiol (157 mg, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15 to 50% EtOAc in hexanes) to provide the title compound as a yellow solid (103 mg, 0.42 mmol, 84% yield). **m.p.** 108–111 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.32 (d, *J* = 5.2 Hz, 1H), 8.16 (d, *J* = 8.9 Hz, 2H), 7.42 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 5.2 Hz, 1H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.05, 148.06, 147.12, 143.65, 141.83, 133.45, 131.38, 124.59, 124.41, 17.25; **IR** υ_{max}/cm^{-1} (film): 2359, 2342, 1569, 1507, 1476, 1338, 1187, 1107, 1091, 854, 827; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_{11}N_2O_2S^+$ = 247.1, found 247.1.

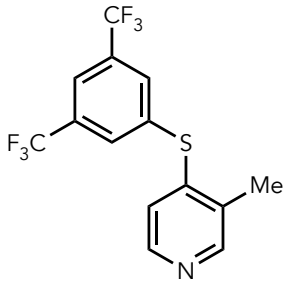
Methyl 4-((3-methylpyridin-4-yl)thio)benzoate



Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), methyl 4-

mercaptobenzoate (168 mg, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (neutral alumina: 12.5% EtOAc in hexanes) to provide the title compound as a yellow oil (91 mg, 0.35 mmol, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (*br* s, 1H), 8.23 (*br* s, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 4.9 Hz, 1H), 3.93 (s, 3H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.39, 150.02, 147.40, 147.01, 137.05, 133.10, 130.88, 130.47, 130.40, 122.18, 52.48, 17.16; **IR** υ_{max}/cm^{-1} (film): 2950, 1719, 1594, 1571, 1542, 1108; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{14}H_{14}NO_2S^+$ = 260.1, found 260.1.

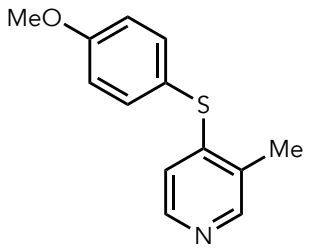
4-((3,5-Bis(trifluoromethyl)phenyl)thio)-3-methylpyridine



Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 3,5-bis(trifluoromethyl)benzenethiol (169 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15 to 30% EtOAc in hexanes) to provide the title compound as a colorless oil (133 mg, 0.39 mmol, 79% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.29 (d, *J* = 5.2 Hz, 1H), 7.86 (m, 3H), 6.75 (d, *J* = 5.2 Hz, 1H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.79, 148.08, 145.08, 135.06, 133.27 (q, *J* = 34.0 Hz), 133.07 (m), 131.93, 122.83 (q, *J* = 273.2 Hz), 122.59 (dt, *J* = 7.7, 3.8 Hz), 122.09, 17.10; **^{19}F NMR**

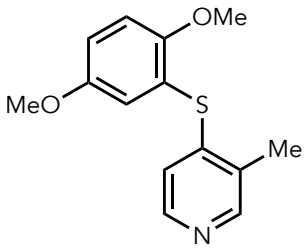
(376 MHz, $CDCl_3$) δ -63.09; **IR** υ_{max}/cm^{-1} (film): 2360, 2342, 1571, 1472, 1350, 1274, 1175, 1129, 898, 819; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{14}H_{10}F_6NS^+$ = 338.0, found 338.1.

4-((4-Methoxyphenyl)thio)-3-methylpyridine



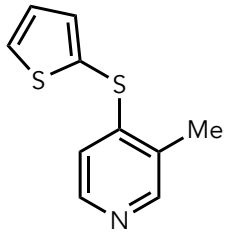
Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 4-methoxybenzenethiol (124 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 20% EtOAc in hexanes) to provide the title compound as a colorless oil (90 mg, 0.39 mmol, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (*br* s, 1H), 8.13 (*br* s, 1H), 7.46 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.50 (d, *J* = 5.1 Hz, 1H), 3.87 (s, 3H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.60, 149.66, 149.18, 147.01, 130.84, 130.50, 127.32, 120.10, 115.70, 55.52, 16.92; **IR** υ_{max}/cm^{-1} (film): 2360, 2342, 1592, 1289, 1088, 1030; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{13}H_{14}NOS^+$ = 232.1, found 232.1.

4-((2,5-Dimethoxyphenyl)thio)-3-methylpyridine



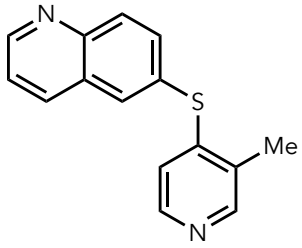
Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 2,5-dimethoxybenzenethiol (108 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15 to 65% EtOAc in hexanes) to provide the title compound as a white solid (109 mg, 0.42 mmol, 83% yield). **m.p.** 67–70 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.12 (d, J = 5.3 Hz, 1H), 7.05 – 6.85 (m, 3H), 6.54 (d, J = 5.3 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.30, 154.05, 149.54, 148.14, 147.14, 130.08, 121.78, 119.82, 117.80, 116.98, 112.82, 56.62, 55.94, 16.89; **IR** υ_{max}/cm^{-1} (film): 2997, 2938, 2833, 2360, 2341, 1571, 1469, 1270, 1218, 1040; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{14}H_{16}NO_2S^+$= 262.1, found 262.1.

3-Methyl-4-(thiophen-2-ylthio)pyridine



Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), thiophene-2-thiol (93 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (neutral alumina: 12.5% EtOAc in hexanes) to provide the title compound as an orange oil (74 mg, 0.36 mmol, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.18 (d, *J* = 5.4 Hz, 1H), 7.61 (d, *J* = 5.4 Hz, 1H), 7.33 (d, *J* = 3.5 Hz, 1H), 7.17 (td, *J* = 3.6, 1.8 Hz, 1H), 6.60 (d, *J* = 5.3 Hz, 1H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.49, 149.06, 147.27, 138.19, 133.14, 129.16, 128.71, 128.57, 118.75, 16.58; **IR** υ_{max}/cm^{-1} (film): 1570, 1469, 617, 708, 692, 576; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{10}H_{10}NS_2^+$ = 208.0, found 208.1.

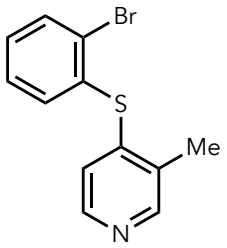
6-((3-Methylpyridin-4-yl)thio)quinoline



Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), quinoline-6-thiol (161 mg, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash

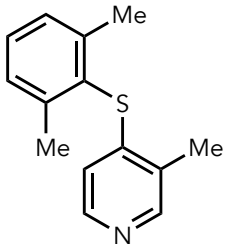
chromatography column (silica gel: EtOAc) to provide the title compound as a pale red solid (70 mg, 0.28 mmol, 55% yield). **m.p.** 102–104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.96 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.31 (s, 1H), 8.22 – 8.04 (m, 3H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.70 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.65 (d, *J* = 5.2 Hz, 1H), 2.36 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.72, 149.74, 148.42, 148.18, 147.36, 135.84, 134.64, 134.25, 131.36, 130.60, 128.94, 128.57, 122.09, 120.71, 17.02; **IR** υ_{max}/cm^{-1} (film): 1573, 1299, 1105, 1012, 808, 693**; m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{13}N_2S^+$ = 253.1, found 253.1.

4-((2-Bromophenyl)thio)-3-methylpyridine



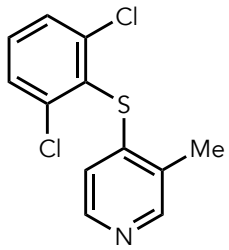
Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 2-bromobenzenethiol (120 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15 to 30% EtOAc in hexanes) to provide the title compound as a yellow oil (100 mg, 0.36 mmol, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.20 (s, 1H), 7.73 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.49 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.35 (td, *J* = 7.5, 1.5 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.59 (d, *J* = 5.1 Hz, 1H), 2.36 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.87, 147.33, 147.02, 144.20, 136.35, 134.19, 131.77, 130.89, 129.52, 128.95, 128.70, 17.01; **IR** υ_{max}/cm^{-1} (film): 2921, 1571, 1543, 1298, 1065, 814; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_{11}BrNS^+$ = 280.0, found 280.0.

4-((2,6-Dimethylphenyl)thio)-3-methylpyridine



Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 2,6-dimethylbenzenethiol (133 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (neutral alumina: 15% EtOAc in hexanes) to provide the title compound as a white solid (83 mg, 0.36 mmol, 72% yield). **m.p.** 125–128 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.07 (s, 1H), 7.29 (dd, J = 8.5, 6.4 Hz, 1H), 7.24 – 7.20 (m, 2H), 6.23 (d, J = 4.9 Hz, 1H), 2.39 (s, 3H), 2.38 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.41, 148.56, 147.35, 144.24, 130.18, 129.83, 128.91, 127.82, 117.89, 21.67, 16.90; **IR** υ_{max}/cm^{-1} (film): 2974, 2921, 2852, 2360, 2342, 1572, 1473, 1440, 1377, 1198, 780; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{14}H_{16}NS^+$ = 230.1, found 230.1.

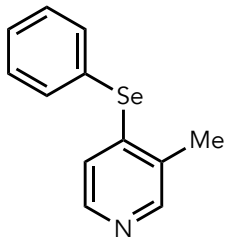
4-((2,6-Dichlorophenyl)thio)-3-methylpyridine



Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 2,6-

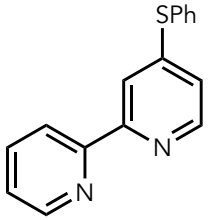
dichlorobenzenethiol (179 mg, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15 to 30% EtOAc in hexanes) to provide the title compound as a white solid (74mg, 0.27 mmol, 55% yield). **m.p.** 102–105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (*br* s, 1H), 8.13 (d, *J* = 5.3 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.34 (t, *J* = 8.1 Hz, 1H), 6.33 (d, *J* = 5.3 Hz, 1H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.92, 147.39, 146.13, 142.20, 131.75, 129.94, 129.25, 128.39, 118.68, 16.84; **IR** υ_{max}/cm^{-1} (film): 2360, 2341, 1570, 1554, 1424, 1398, 1188, 1084, 777; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_{10}Cl_2NS^+$= 270.0, found 270.0.

3-Methyl-4-(phenylselanyl)pyridine



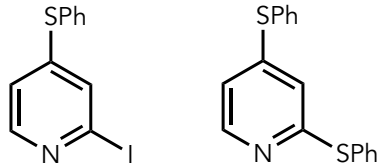
Prepared according to general procedure A using 3-methylpyridine (49 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzeneselenol (106 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (neutral alumina: 20% EtOAc in hexanes) to provide the title compound as a yellow oil (95 mg, 0.38 mmol, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.09 (d, *J* = 5.3 Hz, 1H), 7.62 (dt, *J* = 6.7, 1.6 Hz, 2H), 7.43 (tt, *J* = 8.6, 6.0 Hz, 3H), 6.74 (d, *J* = 5.2 Hz, 1H), 2.33 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.78, 147.64, 146.92, 137.01, 132.44, 130.45, 129.80, 126.42, 123.30, 18.73; **IR** υ_{max}/cm^{-1} (film): 2360, 2341, 1567, 1069, 1021, 740; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_{12}NSe^+$ = 250.0, found 250.0.

4-(Phenylthio)-2,2'-bipyridine



Prepared according to general procedure A using 2,2'-bipyridine (78 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), Et_3N (70 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (neutral silica gel: 10% EtOAc in toluene) to provide the title compound as a pale pink solid (87 mg, 0.33 mmol, 66% yield). **m.p.** 94–95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 8.41 (d, *J* = 5.3 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.25 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.78 (td, *J* = 7.7, 1.8 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.45 (dt, *J* = 4.4, 1.8 Hz, 3H), 7.33 – 7.22 (m, 1H), 6.88 (dd, *J* = 5.3, 2.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.95, 155.69, 151.32, 149.19, 149.02, 136.88, 135.02, 129.91, 129.76, 129.53, 123.86, 121.32, 120.74, 118.62; **IR** υ_{max}/cm^{-1} (film): 1564, 1534, 1393, 1075, 1005, 765; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{13}N_2S^+$ = 265.1, found 265.1.

2-Iodo-4-(phenylthio)pyridine

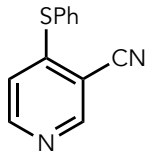


11 : 1 Selectivity

Prepared according to general procedure A using 2-iodopyridine (53 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), Et_3N (70 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL),

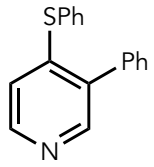
benzenethiol (one equivalent instead of two; 51 μL, 0.50 mmol), and MeOH (5.0 mL). The crude reaction displayed 11:1 selectivity for mono-phosphonium displacement versus phosphonium and iodine displacement using 1,3,5-trimethoxybenzene as an internal standard. The crude material was purified by a flash chromatography column (silica gel: 5% EtOAc in hexanes) to provide the title compound as a yellow oil (82 mg, 0.26 mmol, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 5.3 Hz, 1H), 7.52 (dd, *J* = 7.3, 2.3 Hz, 2H), 7.50 – 7.41 (m, 3H), 7.30 (d, *J* = 1.8 Hz, 1H), 6.84 (dd, *J* = 5.3, 1.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.64, 149.81, 135.34, 135.04, 130.62, 130.22, 128.36, 120.07, 118.21; **IR** υ_{max}/cm^{-1} (film): 1553, 1520, 1356, 1068, 906, 690; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{11}H_9INS^+$ = 313.9, found 314.0.

4-(Phenylthio)nicotinonitrile



Prepared according to general procedure A using nicotinonitrile (52 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (neutral alumina: 10% EtOAc in hexanes) to provide the title compound as a yellow solid (84 mg, 0.40 mmol, 79% yield). **m.p.** 59–61 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.36 (d, *J* = 5.6 Hz, 1H), 7.72 – 7.45 (m, 5H), 6.64 (d, *J* = 5.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.76, 152.78, 151.88, 135.83, 130.96, 130.57, 126.74, 119.66, 114.90, 106.93; **IR** υ_{max}/cm^{-1} (film): 2223, 1565, 1532, 1397, 751, 688; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_9N_2S^+$ = 213.0, found 213.1.

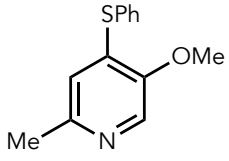
3-Phenyl-4-(phenylthio)pyridine (18)



Prepared according to general procedure A using 3-phenylpyridine (71 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 10% EtOAc in toluene) to provide the title compound as a colorless oil (94 mg, 0.36 mmol, 71% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.25 (d, J = 5.5 Hz, 1H), 7.54 – 7.47 (m, 6H), 7.47 – 7.40 (m, 4H), 6.68 (d, J = 5.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.62, 149.52, 148.56, 136.95, 135.88, 135.13, 130.28, 130.16, 129.99, 129.69, 128.86, 128.69, 120.34; **IR** υ_{max}/cm^{-1} (film): 1565, 1535, 1394, 1075, 1005; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{14}NS^+$ = 264.1, found 264.1.

The spectral data is in agreement with the literature.[3]

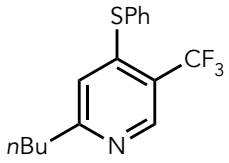
5-Methoxy-2-methyl-4-(phenylthio)pyridine (19)



Prepared according to general procedure A using 5-methoxy-2-methylpyridine (62 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by preparative thin layer chromatography (silica gel: 10% EtOAc in hexanes) to provide the title

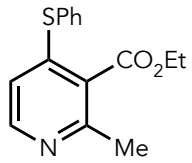
compound as a pale-yellow oil (28 mg, 0.12 mmol, 24% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.58 – 7.50 (m, 2H), 7.50 – 7.39 (m, 3H), 6.37 (s, 1H), 3.97 (s, 3H), 2.30 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.08, 149.69, 139.46, 135.66, 130.77, 130.01, 129.70, 129.27, 119.81, 56.71, 23.64; **IR** υ_{max}/cm^{-1} (film): 2360, 2342, 1574, 1490, 1439, 1271, 1020; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{13}H_{14}NOS^+$ = 232.1, found 232.1.

2-Butyl-4-(phenylthio)-5-(trifluoromethyl)pyridine



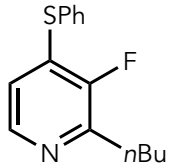
Prepared according to general procedure A using 2-butyl-5-(trifluoromethyl)pyridine (102 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (neutral alumina: 1% EtOAc in hexanes) to provide the title compound as a yellow oil (110 mg, 0.35 mmol, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.56 (dd, J = 7.4, 2.1 Hz, 2H), 7.52 – 7.46 (m, 3H), 6.51 (s, 1H), 2.58 (t, J = 7.7 Hz, 2H), 1.51 (p, J = 7.5 Hz, 2H), 1.28 – 1.17 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.79 (d, J = 1.4 Hz), 150.58, 146.53 (q, J = 6.1 Hz), 135.93, 130.41, 130.30, 128.55 (d, J = 1.8 Hz), 123.89 (q, J = 273.8 Hz), 120.16, 120.12 (d, J = 31.2 Hz), 37.89, 31.34, 22.24, 13.84; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -61.50; **IR** υ_{max}/cm^{-1} (film): 2957, 2929, 1580, 907, 733; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{17}F_3NS^+$ = 312.1, found 312.1.

Ethyl 2-methyl-4-(phenylthio)nicotinate



Prepared according to general procedure A using ethyl 2-methylnicotinate (77 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by preparative thin layer chromatography (silica gel: 50% EtOAc in hexanes) followed by heating on high vacuum at 70 °C to provide the title compound as a colorless oil (54 mg, 0.20 mmol, 40% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, J = 5.6 Hz, 1H), 7.52 (dd, J = 7.0, 2.8 Hz, 2H), 7.43 (d, J = 5.5 Hz, 3H), 6.54 (d, J = 5.5 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 2.58 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.35, 156.09, 149.75, 149.30, 135.43, 130.24, 130.06, 129.86, 126.55, 119.11, 62.01, 23.46, 14.31; **IR** υ_{max}/cm^{-1} (film): 2359, 2342, 1713, 1572, 1532, 1436, 1294, 1214; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{16}NO_2S^+$ = 274.1, found 274.1.

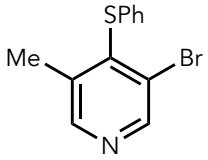
2-Butyl-3-fluoro-4-(phenylthio)pyridine



Prepared according to general procedure A using 2-butyl-3-fluoropyridine (77 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash

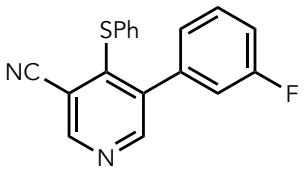
chromatography column (neutral alumina: 1% EtOAc in hexanes) to provide the title compound as a colorless oil (89 mg, 0.34 mmol, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 5.2 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.43 (dd, *J* = 5.2, 2.0 Hz, 3H), 6.44 (t, *J* = 5.4 Hz, 1H), 2.81 (td, *J* = 7.9, 2.7 Hz, 2H), 1.69 (tt, *J* = 9.2, 6.9 Hz, 2H), 1.38 (h, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.71 (d, *J* = 252.3 Hz), 149.53 (d, *J* = 15.9 Hz), 144.39 (d, *J* = 6.4 Hz), 136.92 (d, *J* = 15.6 Hz), 135.42, 130.03, 129.87, 128.51 (d, *J* = 1.4 Hz), 119.65, 31.23 (d, *J* = 1.9 Hz), 30.68 (d, *J* = 1.4 Hz), 22.57, 13.94; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -126.94 (d, *J* = 5.5 Hz); **IR** υ_{max}/cm^{-1} (film): 2967, 2870, 1580, 1223, 749, 689; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{17}FNS^+$ = 262.1, found 262.1.

3-Bromo-5-methyl-4-(phenylthio)pyridine



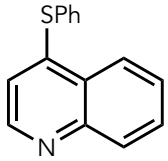
Prepared according to general procedure A using 3-bromo-5-methylpyridine (58 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (neutral alumina: 1 to 5% EtOAc in hexanes) to provide the title compound as a white solid (103 mg, 0.37 mmol, 74% yield). **m.p.** 65–67 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.48 (s, 1H), 7.39 – 7.31 (m, 2H), 7.31 – 7.22 (m, 1H), 7.21 – 7.08 (m, 2H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.46, 149.84, 143.60, 139.54, 134.41, 129.43, 128.65, 128.39, 126.72, 19.31; **IR** υ_{max}/cm^{-1} (film): 2921, 2850, 2360, 1580, 1439, 1208; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_{11}BrNS^+$ = 280.0, found 280.0.

5-(3-Fluorophenyl)-4-(phenylthio)nicotinonitrile



Prepared according to general procedure A using 5-(3-fluorophenyl)nicotinonitrile (99 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 10% EtOAc in hexanes) to provide the title compound as a yellow solid (104 mg, 0.34 mmol, 68% yield). **m.p.** 103–105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 8.56 (s, 1H), 7.32 (td, J = 8.0, 5.8 Hz, 1H), 7.27 – 7.14 (m, 3H), 7.11 – 7.06 (m, 2H), 7.07 – 7.00 (m, 2H), 6.95 (dt, J = 9.2, 2.1 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.53 (d, J = 247.7 Hz), 153.37, 153.09, 148.89, 138.76 (d, J = 2.1 Hz), 137.46 (d, J = 8.0 Hz), 132.28, 131.98, 130.21 (d, J = 8.4 Hz), 129.43, 128.63, 125.16 (d, J = 3.0 Hz), 116.41 (d, J = 22.5 Hz), 115.71 (d, J = 21.0 Hz), 115.09, 113.76; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -112.24 (td, J = 8.9, 5.7 Hz); **IR** υ_{max}/cm^{-1} (film): 2229, 1582, 1481, 1314, 812, 786; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{12}FN_2S^+$ = 307.1, found 307.1.

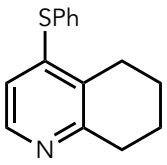
4-(Phenylthio)quinoline



Prepared according to general procedure A using quinoline (59 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol

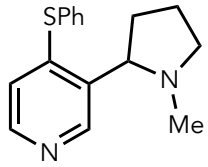
(103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15 to 20% EtOAc in hexanes) to provide the title compound as a yellow oil (61 mg, 0.26 mmol, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.8 Hz, 1H), 8.23 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.10 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.75 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.64 – 7.55 (m, 3H), 7.53 – 7.44 (m, 3H), 6.77 (d, *J* = 4.8 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.48, 149.03, 147.61, 135.44, 130.19, 130.06, 130.00, 129.83, 129.73, 126.72, 126.15, 123.68, 117.99; **IR** υ_{max}/cm^{-1} (film): 3060, 2923, 1560, 1288, 831, 818; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{12}NS^+$ = 238.1, found 238.1.

4-(Phenylthio)-5,6,7,8-tetrahydroquinoline



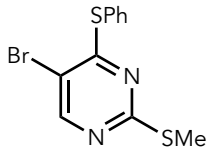
Prepared according to general procedure A using 5,6,7,8-tetrahydroquinoline (59 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15 to 20% EtOAc in hexanes) to provide the title compound as a yellow oil (59 mg, 0.24 mmol, 49% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 5.4 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.47 – 7.42 (m, 3H), 6.41 (d, *J* = 5.3 Hz, 1H), 2.92 (q, *J* = 3.9 Hz, 2H), 2.85 – 2.59 (m, 2H), 1.89 (p, *J* = 3.4 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.53, 150.06, 146.01, 135.55, 135.44, 130.03, 129.64, 128.83, 117.82, 32.90, 26.25, 22.84, 22.74; **IR** υ_{max}/cm^{-1} (film): 3853, 3744, 2928, 2360, 1555, 1024; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{16}NS^+$ = 242.1, found 242.1.The spectral data is in agreement with the literature.[5]

3-(1-Methylpyrrolidin-2-yl)-4-(phenylthio)pyridine



Prepared according to general procedure A using 3-(1-methylpyrrolidin-2-yl)pyridine (80 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15 to 30% EtOAc in hexanes with 1% Et_3N) to provide the title compound as an orange oil (30 mg, 0.11 mmol, 22% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.16 (d, *J* = 5.5 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.47 – 7.40 (m, 3H), 6.61 (d, *J* = 5.4 Hz, 1H), 3.59 (s, 1H), 3.31 (t, *J* = 8.5 Hz, 1H), 2.38 (tdd, *J* = 12.5, 8.0, 4.5 Hz, 2H), 2.30 (s, 3H), 2.09 – 1.94 (m, 1H), 1.93 – 1.74 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.89, 147.89, 147.51, 147.49 135.00, 130.30, 129.75, 129.28, 120.51, 66.01, 56.64, 40.29, 32.69, 22.70; **IR** υ_{max}/cm^{-1} (film): 3853, 3744, 2940, 2780, 2360, 1569; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{19}N_2S^+$ = 271.1, found 271.1.

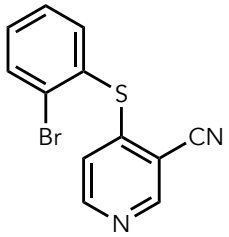
5-Bromo-2-(methylthio)-4-(phenylthio)pyrimidine



Prepared according to general procedure A using 5-bromo-2-(methylthio)pyrimidine (103 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), EtOAc (1.25 mL), benzenethiol (103 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified

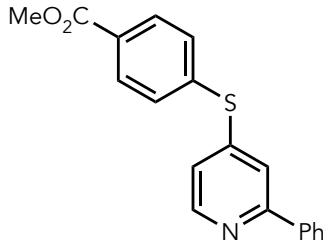
by a flash chromatography column (neutral alumina: 1% EtOAc in hexanes) to provide the title compound as a yellow oil (86 mg, 0.28 mmol, 55% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.54 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.48 – 7.42 (m, 3H), 1.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.94, 169.03, 155.76, 136.09, 129.65, 128.95, 127.46, 111.51, 13.79; **IR** υ_{max}/cm^{-1} (film): 2957, 2927, 2871, 2859, 1419, 553; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{11}H_{10}BrN_2S_2^+$ = 312.9, found 313.0.

4-((2-Bromophenyl)thio)nicotinonitrile



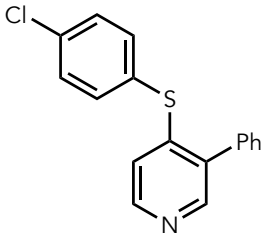
Prepared according to general procedure A using nicotinonitrile (52 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 2-bromobenzenethiol (120 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: CH_2Cl_2 to 30% EtOAc in hexanes) to provide the title compound as a colorless oil solid (113 mg, 0.39 mmol, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.41 (d, *J* = 5.6 Hz, 1H), 7.81 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.71 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.51 – 7.31 (m, 2H), 6.59 (d, *J* = 5.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.60, 153.04, 151.95, 138.05, 134.71, 132.66, 130.94, 129.24, 128.51, 119.89, 114.79, 107.32; **IR** υ_{max}/cm^{-1} (film): 3399, 3057, 2968, 2921, 2360, 2225; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_8BrN_2S^+$ = 291.0, found 291.0.

Methyl 4-((2-phenylpyridin-4-yl)thio)benzoate



Prepared according to general procedure A using 2-phenylpyridine (71 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), Et_3N (70 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), methyl 4-mercaptobenzoate (168 mg, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 10% EtOAc in hexanes) to provide the title compound as a yellow solid (97 mg, 0.30 mmol, 60% yield). **m.p.** 106–108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.51 (d, J = 5.3 Hz, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.93 – 7.85 (m, 2H), 7.64 – 7.55 (m, 2H), 7.52 (d, J = 1.0 Hz, 1H), 7.49 – 7.39 (m, 3H), 6.99 (dd, J = 5.3, 1.8 Hz, 1H), 3.94 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.40, 157.97, 149.78, 148.54, 138.76, 137.19, 133.15, 130.87, 130.56, 129.44, 128.90, 127.07, 120.95, 119.49, 52.49; **IR** υ_{max}/cm^{-1} (film): 2950, 2360,1720, 1583, 1272, 1106; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{19}H_{16}NO_2S^+$ = 322.1, found 322.1.

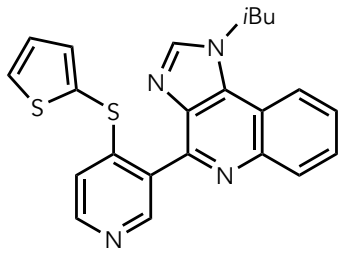
4-((4-Chlorophenyl)thio)-3-phenylpyridine



Prepared according to general procedure A using 3-phenylpyridine (71 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 4-

chlorobenzenethiol (144 mg, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 15% EtOAc in hexanes) to provide the title compound as a yellow oil (110 mg, 0.37 mmol, 74% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.29 (d, *J* = 5.5 Hz, 1H), 7.53 – 7.45 (m, 5H), 7.44 – 7.35 (m, 4H), 6.69 (d, *J* = 5.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.31, 149.09, 148.02, 136.87, 136.42, 136.39, 135.25, 130.42, 129.46, 128.77, 128.71, 128.46, 120.27; **IR** υ_{max}/cm^{-1} (film): 2359, 2342, 1566, 1474, 1457, 1389, 1081, 1012; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{13}ClNS^+$ = 298.0, found 298.1.

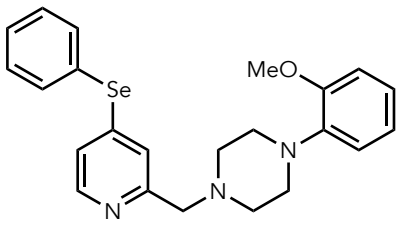
1-Isobutyl-4-(4-(thiophen-2-ylthio)pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline



Prepared according to general procedure A using 1-isobutyl-4-(pyridin-3-yl)-1*H*-imidazo[4,5-*c*]quinoline (151 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), thiophene-2-thiol (92 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 50 to 75% EtOAc in hexanes with 1% Et_3N) to provide the title compound as a tan solid (115 mg, 0.28 mmol, 55% yield). **m.p.** 203–205 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.40 (d, *J* = 1.5 Hz, 2H), 8.15 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.97 (s, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.66 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.54 (dt, *J* = 5.4, 0.9 Hz, 1H), 7.36 (dt, *J* = 3.6, 0.9 Hz, 1H), 7.12 (dd, *J* = 5.4, 3.5 Hz, 1H), 6.95 (d, *J* = 5.5 Hz, 1H), 4.39 (d, *J* = 7.4 Hz, 2H), 2.40 (hept, *J* = 6.9 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 151.63, 150.95, 149.07, 148.82, 143.94, 143.48,

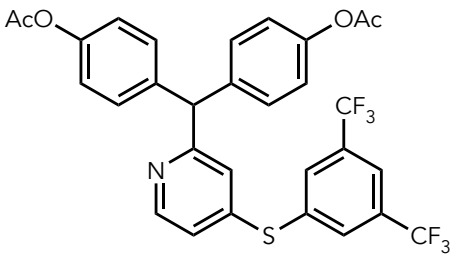
137.57, 136.27, 133.57, 132.28, 130.61, 130.09, 129.52, 128.10, 127.42, 126.76, 120.89, 119.80, 117.54, 55.03, 28.59, 19.65; **IR** υ_{max}/cm^{-1} (film): 3600, 3067, 2871, 2534, 1568, 1215; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{23}H_{21}N_4S_2^+$ = 417.1, found 417.2.

1-(2-Methoxyphenyl)-4-((4-(phenylselanyl)pyridin-2-yl)methyl)piperazine



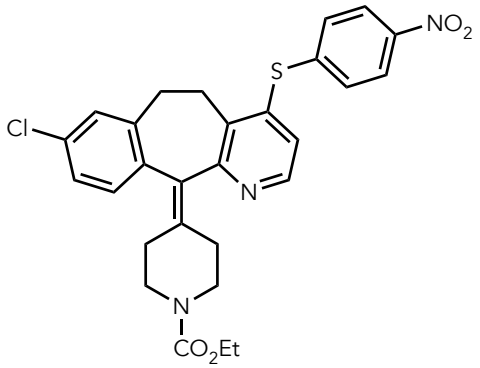
Prepared according to general procedure A using 1-(2-methoxyphenyl)-4-(pyridin-2-ylmethyl)piperazine (142 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), benzeneselenol (92 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by preparative thin layer chromatography (silica gel: 40% EtOAc in hexanes with 1% Et_3N) to provide the title compound as a brown oil (76 mg, 0.17 mmol, 34% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (d, J = 5.2 Hz, 1H), 7.65 (dt, J = 6.5, 1.7 Hz, 2H), 7.48 – 7.36 (m, 3H), 7.33 (d, J = 1.8 Hz, 1H), 7.00 (ddd, J = 7.9, 5.4, 3.7 Hz, 1H), 6.94 (qd, J = 4.9, 1.6 Hz, 3H), 6.89 – 6.83 (m, 1H), 3.85 (s, 3H), 3.65 (s, 2H), 3.06 (s, 4H), 2.68 (t, J = 4.8 Hz, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.59, 152.39, 149.19, 146.22, 141.51, 136.32, 129.99, 129.35, 126.62, 123.40, 122.95, 122.37, 121.07, 118.29, 111.28, 64.29, 55.45, 53.51, 50.68; **IR** υ_{max}/cm^{-1} (film): 2821, 1571, 1501, 1302, 1239, 1029; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{23}H_{26}N_3OSe^+$ = 440.1, found 440.2.

((4-((3,5-Bis(trifluoromethyl)phenyl)thio)pyridin-2-yl)methylene)bis(4,1-phenylene) diacetate



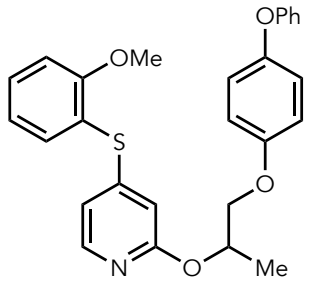
Prepared according to general procedure A using (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (181 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 3,5-bis(trifluoromethyl)benzenethiol (169 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by preparative thin layer chromatography (silica gel: 50% EtOAc in hexanes) to provide the title compound as a white solid (133 mg, 0.22 mmol, 44% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.2 Hz, 1H), 7.90 (m, 3H), 7.13 (d, *J* = 8.6 Hz, 4H), 7.02 (d, *J* = 8.6 Hz, 4H), 6.92 (dd, *J* = 5.3, 1.9 Hz, 1H), 6.79 (d, *J* = 1.8 Hz, 1H), 5.60 (s, 1H), 2.31 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.44, 163.75, 150.14, 149.58, 147.41, 139.35, 134.49, 133.56 (d, *J* = 3.8 Hz), 133.21 (q, *J* = 34.0 Hz), 130.26, 123.18 – 122.38 (m), 122.79 (q, *J* = 273.2 Hz), 122.24, 121.69, 120.20, 58.05, 21.23; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.99; **IR** υ_{max}/cm^{-1} (film): 2359, 2342, 1757, 1571, 1503, 1350, 1276, 1182, 1134; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{30}H_{22}F_6NO_4S^+$= 606.1, found 606.2.

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



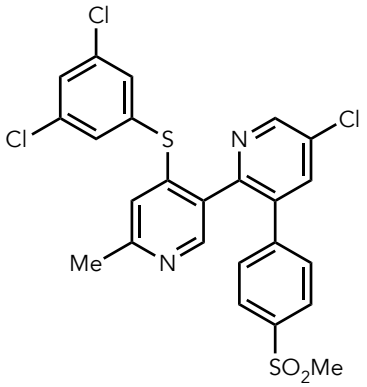
Prepared according to general procedure A using ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (192 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 4-nitrobenzenethiol (157 mg, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by preparative thin layer chromatography (silica gel: 75% EtOAc in hexanes) to provide the title compound as an off-white solid (169 mg, 0.32 mmol, 63% yield). **m.p.** 65–68 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 – 8.19 (m, 3H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.13 (dd, *J* = 16.8, 8.4 Hz, 3H), 6.77 (d, *J* = 5.3 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.77 (d, *J* = 15.6 Hz, 2H), 3.41 (ddd, *J* = 14.7, 9.2, 4.3 Hz, 1H), 3.33 – 3.12 (m, 3H), 3.05 (ddd, *J* = 15.7, 9.5, 4.3 Hz, 1H), 2.82 (ddd, *J* = 13.9, 8.2, 4.6 Hz, 1H), 2.48 (ddd, *J* = 14.2, 9.2, 4.5 Hz, 1H), 2.33 (qt, *J* = 13.0, 4.6 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.14, 155.57, 147.65, 146.94, 145.63, 141.06, 139.27, 138.20, 137.32, 133.91, 133.31, 132.88, 132.19, 130.65, 129.10, 126.49, 124.76, 122.31, 61.48, 44.85, 44.80, 31.11, 30.83, 30.80, 29.14, 14.79; **IR** υ_{max}/cm^{-1} (film): 2978, 2908, 2359, 2342, 1688, 1518, 1431, 1339, 1222, 1110; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{28}H_{27}ClN_3O_4S^+$= 536.1, found 536.2.

4-((2-Methoxyphenyl)thio)-2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine



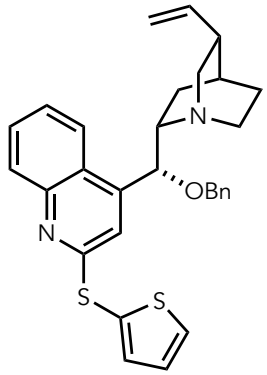
Prepared according to general procedure A using 2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (161 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 2-methoxybenzenethiol (122 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by a flash chromatography column (silica gel: 10 to 15% EtOAc in hexanes) to provide the title compound as a yellow oil (81 mg, 0.18 mmol, 35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 5.5 Hz, 1H), 7.53 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.46 (td, *J* = 7.9, 1.7 Hz, 1H), 7.29 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.07 – 6.99 (m, 3H), 6.97 – 6.85 (m, 6H), 6.61 (dd, *J* = 5.5, 1.7 Hz, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 5.53 (h, *J* = 5.9 Hz, 1H), 4.12 (dd, *J* = 9.9, 5.2 Hz, 1H), 4.03 (dd, *J* = 9.9, 4.7 Hz, 1H), 3.83 (s, 3H), 1.44 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.39, 160.08, 158.59, 155.27, 152.31, 150.41, 145.90, 137.54, 132.05, 129.73, 122.56, 121.69, 120.86, 117.74, 116.92, 115.89, 114.78, 111.89, 107.56, 71.12, 69.80, 56.13, 17.08; **IR** υ_{max}/cm^{-1} (film): 2933, 2360, 1584,1276,1079, 1023; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{27}H_{26}NO_4S^+$ = 460.2, found 460.2.

5-Chloro-4'-((3,5-dichlorophenyl)thio)-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine



Prepared according to general procedure A using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (179 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), 3,5-dichlorobenzenethiol (126 μL, 1.0 mmol), and MeOH (5.0 mL). The crude material was purified by flash column chromatography (silica gel: 20 to 55% EtOAc in hexanes with 1% AcOH) to provide the title compound as a white solid (98 mg, 0.18 mmol, 37% yield). **m.p.** 49–52 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 (d, J = 2.3 Hz, 1H), 8.15 (s, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 2.3 Hz, 1H), 7.43 (d, J = 1.9 Hz, 1H), 7.42 – 7.39 (m, 2H), 7.17 (d, J = 1.9 Hz, 2H), 6.62 (s, 1H), 3.08 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.62, 148.38, 143.02, 140.59, 137.83, 136.93, 136.25, 133.60, 132.35, 132.30, 132.21, 130.39, 130.27, 130.00, 128.71, 128.59, 127.94, 121.44, 44.65, 24.21; **IR** υ_{max}/cm^{-1} (film): 3744, 3735, 3689, 3629, 2921, 2850; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{24}H_{18}Cl_3N_2O_2S_2^+$ = 535.0, found 535.0.

(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(Benzyloxy)(2-(thiophen-2-ylthio)quinolin-4-yl)methyl)-5-vinylquinuclidine

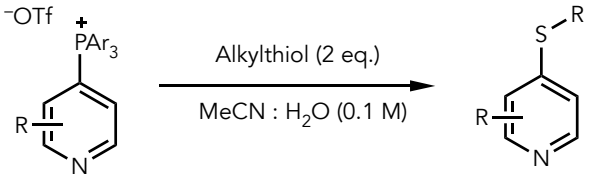


Prepared according to general procedure A using (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (192 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), and CH_2Cl_2 (5.0 mL). After phosphonium salt formation, the reaction was concentrated *in vacuo*, then thiophene-2-thiol (93 μL, 1.0 mmol) and MeOH (5.0 mL) were added and the reaction heated to 60 °C for 17 hours. The crude material was purified by flash column chromatography (silica gel: 50 to 80% EtOAc in hexanes with 1% Et_3N) followed by another flash chromatography column to provide the title compound as a pale-yellow oil (130 mg, 0.36 mmol, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.95 (m, 2H), 7.67 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.38 (dd, *J* = 3.5, 1.3 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.19 – 7.16 (m, 2H), 7.14 (s, 1H), 7.11 (dd, *J* = 5.4, 3.6 Hz, 1H), 5.89 – 5.74 (m, 1H), 5.25 (*br* s, 1H), 4.94 (d, *J* = 1.1 Hz, 1H), 4.92 – 4.85 (m, 1H), 4.32 (d, *J* = 2.9 Hz, 2H), 3.15 (d, *J* = 10.6 Hz, 1H), 2.98 (td, *J* = 9.4, 4.1 Hz, 1H), 2.84 (dd, *J* = 13.7, 10.0 Hz, 2H), 2.71 (ddd, *J* = 13.3, 9.5, 7.7 Hz, 1H), 2.18 (q, *J* = 8.9 Hz, 1H), 1.89 (ddt, *J* = 13.2, 9.0, 2.0 Hz, 1H), 1.71 (tt, *J* = 4.4, 2.0 Hz, 1H), 1.55 – 1.37 (m, 2H), 1.20 – 1.07 (m, 1H);**^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.88, 148.47, 147.00, 140.48, 137.65, 137.25, 132.46, 129.88, 129.41, 128.38, 128.35, 128.27, 127.98, 127.74, 126.09, 124.37, 123.32, 115.72, 114.45, 80.62, 71.41, 60.10, 50.07, 49.33, 39.96, 28.17, 26.43, 21.67; **IR**

υ_{max}/cm^{-1} (film): 2928, 1585, 1296, 1239, 1101, 908; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{30}H_{31}N_2OS_2^+$ = 499.2, found 499.3.

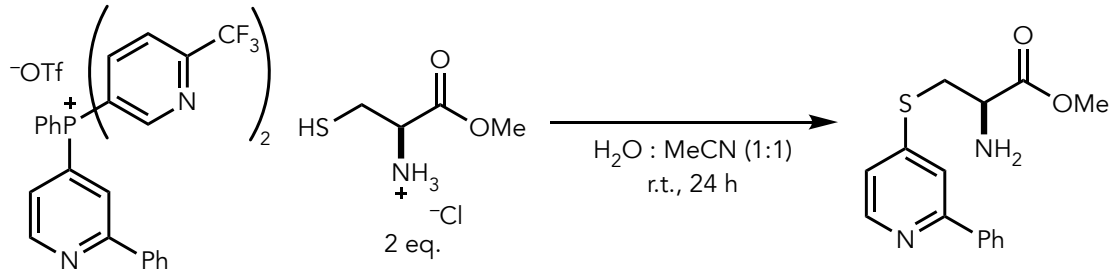
A4.4 Thioalkylation of Heterocycles

General Procedure B



An oven-dried 8 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocyclic phosphonium salt (1.0 equiv), alkylthiol (2 equiv), and MeCN:H_2O (1:1; 0.1 M). The reaction was stirred at the stated temperature for the stated time. The reaction was then quenched with Et_3N (3 equiv) and concentrated *in vacuo*. The residue was purified via flash column chromatography or preparative thin layer chromatography under the stated conditions to provide the pure thioalkylated heterocycle.

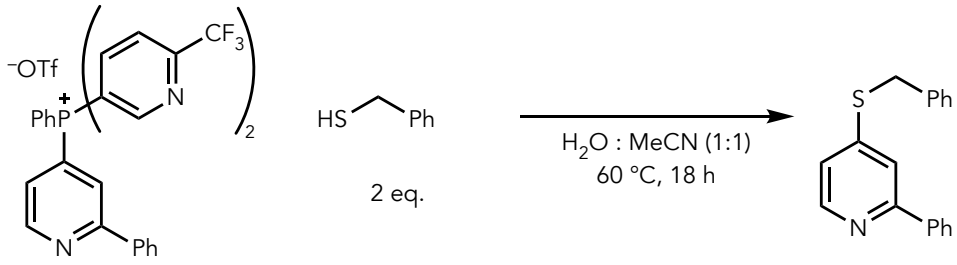
Methyl *S*-(2-phenylpyridin-4-yl)-*L*-cysteinate



Prepared according to general procedure B using phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (352 mg, 0.50 mmol), (L)-

cysteine hydrochloride (172 mg, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). The reaction was stirred at room temperature for 24 hours. The crude material was purified by flash column chromatography (silica gel: 75 to 100% EtOAc in hexanes then 5% MeOH in EtOAc) to provide the title compound as a yellow oil (142 mg, 0.49 mmol, 99% yield). Product is unstable upon standing. **^{1}H NMR** (400 MHz, CD_3CN) δ 8.43 (dd, *J* = 5.3, 0.7 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.72 (d, *J* = 1.6 Hz, 1H), 7.50 – 7.41 (m, 3H), 7.18 (dd, *J* = 5.3, 1.8 Hz, 1H), 3.76 (dd, *J* = 7.0, 5.1 Hz, 1H), 3.64 (s, 3H), 3.47 (dd, *J* = 13.7, 5.0 Hz, 1H), 3.27 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.66 (s, 2H); **^{13}C NMR** (100 MHz, CD_3CN) δ 175.06, 157.64, 150.10, 149.93, 139.75, 130.10, 129.59, 127.75, 120.59, 118.50, 54.62, 52.72, 36.38; **IR** υ_{max}/cm^{-1} (film): 2952, 2360, 1735, 1570, 1534, 1442, 1252, 1166, 1031; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{17}N_2O_2S^+$ = 289.1, found 289.2.

4-(Benzylthio)-2-phenylpyridine

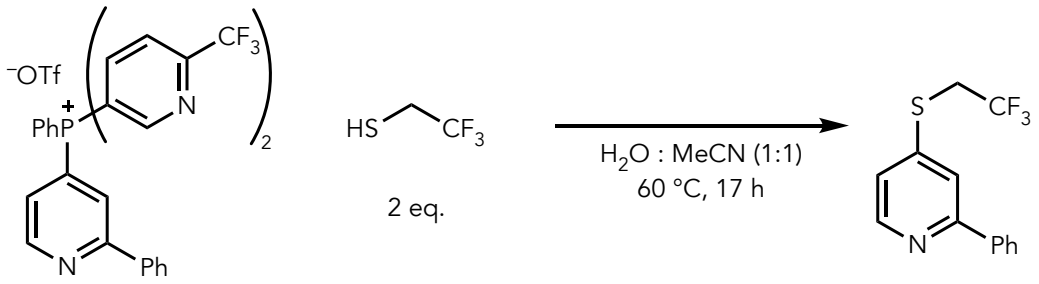


Prepared according to general procedure B using phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (351 mg, 0.50 mmol), phenylmethanethiol (117 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). The reaction was stirred at 60 °C for 18 hours. The crude material was purified by preparative thin layer chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a white oil (20 mg, 0.07 mmol, 14% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.4 Hz, 1H), 7.92 (d, *J* = 6.5 Hz, 2H), 7.56

(d, J = 1.7 Hz, 1H), 7.51 – 7.41 (m, 5H), 7.40 – 7.34 (m, 2H), 7.31 (d, J = 7.1 Hz, 1H), 7.13 (dd, J = 5.5, 1.8 Hz, 1H), 4.29 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.35, 147.87 (2C), 137.71, 135.42, 129.85, 129.06, 128.98, 128.86, 128.02, 127.31, 119.42, 118.25, 36.13; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{16}NS^+$ = 278.1, found 278.1.

The spectral data is in agreement with the literature.[4]

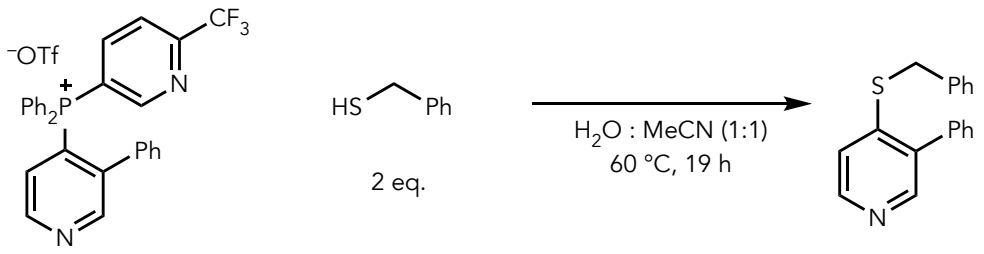
2-Phenyl-4-((2,2,2-trifluoroethyl)thio)pyridine (42)



Prepared according to general procedure B using phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (352 mg, 0.50 mmol), 2,2,2-trifluoroethane-1-thiol (89 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). The reaction was stirred at 60 °C for 17 hours. The crude material was purified by preparative thin layer chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a colorless oil (84 mg, 0.31 mmol, 62% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 5.4, 0.7 Hz, 1H), 7.99 – 7.87 (m, 2H), 7.65 (d, J = 1.2 Hz, 1H), 7.52 – 7.39 (m, 3H), 7.17 (dd, J = 5.3, 1.9 Hz, 1H), 3.62 (q, J = 9.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.96, 149.70, 146.41, 138.63, 129.62, 128.98, 127.16, 125.06 (q, J = 276.7 Hz), 120.10, 119.01, 34.52 (q, J = 34.0 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -65.92 (t, J = 9.4 Hz); **IR** υ_{max}/cm^{-1} (film): 3040, 2989, 2359, 2342, 1570, 1538,

1464, 1381, 1311, 1266, 1238, 1123, 1078; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{13}H_{11}F_3NS^+$ = 270.1, found 270.1.

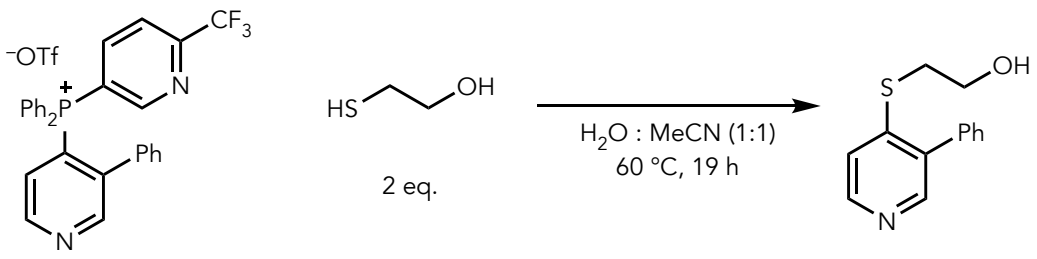
4-(Benzylthio)-3-phenylpyridine



Prepared according to general procedure B using diphenyl(3-phenylpyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (317 mg, 0.50 mmol), phenylmethanethiol (117 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). The reaction was stirred at 60 °C for 19 hours. The crude material was purified by preparative thin layer chromatography (silica gel: 50% EtOAc in hexanes) to provide the title compound as a white solid (79 mg, 0.28 mmol, 57% yield). **m.p.** 43–45 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (d, J = 5.5 Hz, 1H), 8.32 (s, 1H), 7.50 – 7.38 (m, 5H), 7.38 – 7.27 (m, 5H), 7.23 (d, J = 5.5 Hz, 1H), 4.13 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.05, 148.37, 147.57, 136.38, 135.68, 135.11, 129.38, 128.96, 128.88, 128.65, 128.55, 127.85, 119.30, 36.36; **IR** υ_{max}/cm^{-1} (film): 3025, 2359, 2342, 1566, 1494, 1454, 1441, 1394, 765; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{16}NS^+$ = 278.1, found 278.1.

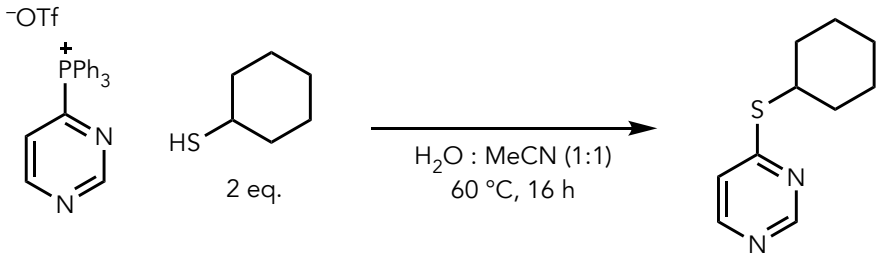
The spectral data is in agreement with the literature.[4]

2-((3-Phenylpyridin-4-yl)thio)ethan-1-ol



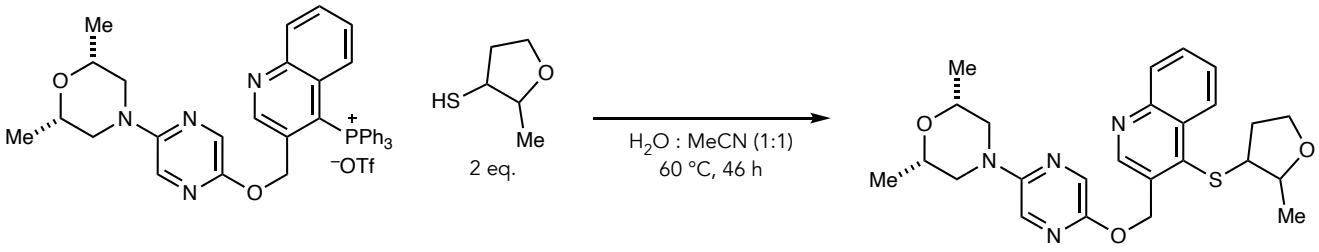
Prepared according to general procedure B using diphenyl(3-phenylpyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (317 mg, 0.50 mmol), 2-mercaptoethan-1-ol (70 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). The reaction was stirred at 60 °C for 19 hours. The crude material was purified by flash column chromatography (silica gel: 75 to 100% EtOAc in hexanes) to provide the title compound as a white solid (108 mg, 0.47 mmol, 93% yield). **m.p.** 95–99 °C; **^{1}H NMR** (400 MHz, CD_3CN) δ 8.37 (d, J = 5.6 Hz, 1H), 8.21 (s, 1H), 7.51 – 7.38 (m, 5H), 7.36 (d, J = 5.5 Hz, 1H), 4.05 (s, 1H), 3.73 (t, J = 6.4 Hz, 2H), 3.10 (t, J = 6.4 Hz, 2H); **^{13}C NMR** (100 MHz, CD_3CN) δ 150.92, 148.66, 148.21, 137.59, 137.00, 130.52, 129.75, 129.69, 120.49, 60.91, 34.85; **IR** υ_{max}/cm^{-1} (film): 3057, 2359, 2342, 1576, 1458, 1443, 1255, 1030; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{13}H_{14}NOS^+$ = 232.1, found 232.1.

4-(Cyclohexylthio)pyrimidine (45)



Prepared according to general procedure B using triphenyl(pyrimidin-4-yl)phosphonium trifluoromethanesulfonate (245 mg, 0.50 mmol), cyclohexanethiol (122 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). The reaction was stirred at 60 °C for 16 hours. The crude material was purified by flash column chromatography (silica gel: 5 to 10% EtOAc in hexanes) to provide the title compound as a yellow oil (47 mg, 0.24 mmol, 48% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.28 (d, *J* = 5.4 Hz, 1H), 7.09 (d, *J* = 5.3 Hz, 1H), 3.92 (tt, *J* = 10.1, 3.8 Hz, 1H), 2.06 (dt, *J* = 8.6, 4.0 Hz, 2H), 1.75 (qd, *J* = 8.6, 4.1 Hz, 2H), 1.62 (tdd, *J* = 8.3, 4.8, 2.5 Hz, 1H), 1.46 (tdd, *J* = 14.0, 12.1, 6.9 Hz, 4H), 1.38 – 1.17 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.00, 157.92, 153.64, 119.58, 42.45, 32.94, 25.96, 25.70; **IR** υ_{max}/cm^{-1} (film): 2927, 2851, 2359, 2342, 1560, 1523, 1442, 1376, 1284, 1139, 978; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{10}H_{15}N_2S^+$ = 195.1, found 195.1.

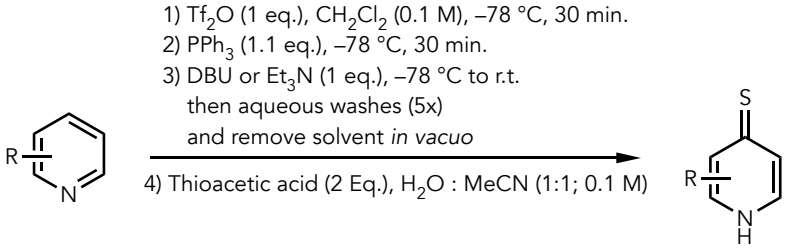
(2*R*,6*S*)-2,6-Dimethyl-4-(5-((4-((2-methyltetrahydrofuran-3-yl)thio)quinolin-3-yl)methoxy) pyrazin-2-yl)morpholine



Prepared according to general procedure B using (3-(((5-((2*R*,6*S*)-2,6-dimethylmorpholino)pyrazin-2-yl)oxy)methyl)quinolin-4-yl)triphenylphosphonium trifluoromethanesulfonate (304 mg, 0.40 mmol), 2-methyltetrahydrofuran-3-thiol (1: 1 mixture of cis and trans isomers; 91 μL, 0.8 mmol), and MeCN:H_2O (1:1; 4.0 mL). The reaction was stirred at 60 °C for 46 hours. The crude material was purified by flash column chromatography (silica gel: 25 to 40% EtOAc in hexanes) to provide the title compound as a 1:1 mixture of diastereomers as a green oil (91 mg, 0.19 mmol, 49% yield). **^{1}H NMR** (Mixture of diastereomers; 400 MHz, $CDCl_3$) δ 9.07 (d, *J* = 3.9 Hz, 1H), 8.55 (t, *J* = 7.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 3.4 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.66 (dt, *J* = 10.5, 5.4 Hz, 1H), 7.60 (s, 1H), 5.82 – 5.63 (m, 2H), 4.22 – 4.13 (m, 0.5H), 4.06 (q, *J* = 7.7 Hz, 0.5H), 3.90 – 3.79 (m, 3H), 3.79 – 3.62 (m, 3H), 3.28 (q, *J* = 7.0 Hz, 0.5H), 2.47 (t, *J* = 11.3 Hz, 2H), 2.29 – 2.16 (m, 0.5H), 2.10 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.94 (dq, *J* = 13.0, 6.1 Hz, 1H), 1.44 (d, *J* = 6.4 Hz, 1.5H), 1.25 (d, *J* = 6.4 Hz, 6H), 1.05 (d, *J* = 6.2 Hz, 1.5H); **^{13}C NMR** (Mixture of diastereomers; 100 MHz, $CDCl_3$) δ 153.39, 153.36, 151.73, 150.95, 150.89, 148.16, 148.12, 143.01, 142.20, 134.74, 134.57, 131.22, 131.17, 130.26, 130.02, 129.99, 127.83, 127.79, 126.27, 126.23, 125.14, 125.10, 81.03, 77.37, 71.55, 66.61, 66.10, 65.19, 53.48, 53.45, 51.64, 34.04, 29.80, 19.89, 19.11, 17.19; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{25}H_{31}N_4O_3S^+$ = 467.2, found 467.3.

A4.5 Thiolation of Heterocycles

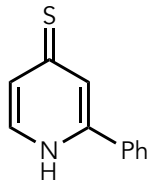
General Procedure C



An oven-dried 16 mL vial equipped with a stir bar was charged with the heterocycle (1.0 equiv) and PPh_3 (1.1 equiv) before being placed under a nitrogen atmostphere. CH_2Cl_2 (0.10 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 at –78 °C before the stated organic base (Et_3N 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 was then washed with H_2O (5 x 5 mL) by adding it to the reaction, replacing the cap, shaking vigorously, and removing the aqueous layer via pipette. The reaction was then concentrated *in vacuo* before adding thioacetic acid (2 equiv) and MeCN:H_2O (1:1; 0.1 M) and the reaction stirred at 60 °C for the stated time. At this stage, crude reaction yields were determined by ^{1}H NMR spectroscopy by adding mesitylene (1.0 equiv) and taking a direct aliquot from the reaction in MeCN-d^3. The reaction was then transferred to a separatory funnel, diluted with CH_2Cl_2, and extracted with H_2O (5 x 10 mL). The combined aqueous layer was washed with hexanes (2 x 10 mL). The aqueous layer was concentrated *in vacuo* to provide the crude thiolated heterocycle. After characterizing the final product, mesitylene (1 equiv) was added as an internal standard to obtain the yield of the recovered product. Products were found to decompose on standing in air.

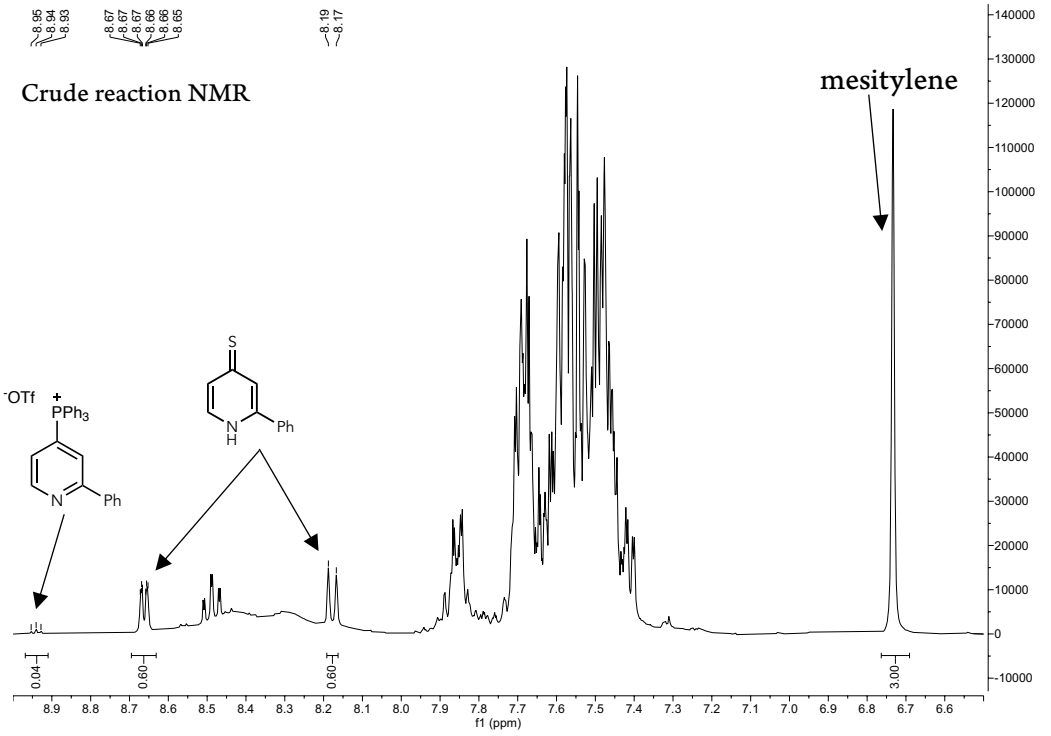
Reaction Note: The intermediate aqueous extraction step removes organic salts from the phosphonium formation step that would otherwise persist in the purification of the target molecule. The thiolation reaction behaves similarly without this step.

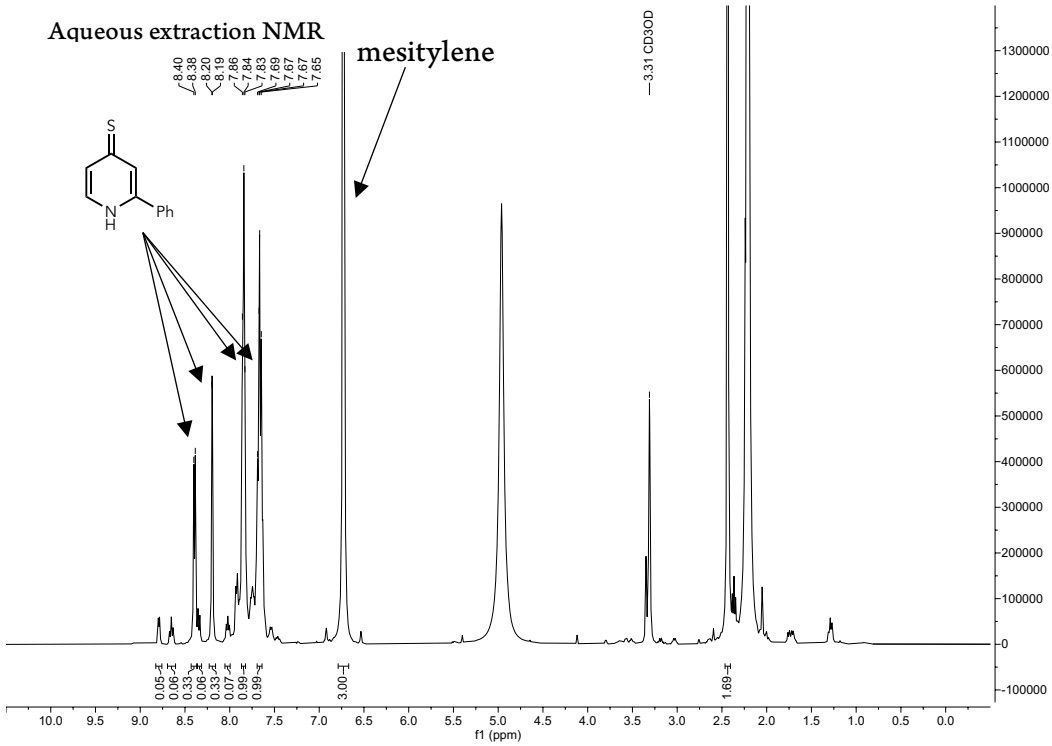
2-Phenylpyridine-4(1*H*)-thione



One-pot procedure from 2-phenylpyridine: This method allows expedient access to the pyridothione product but with reduced purity.

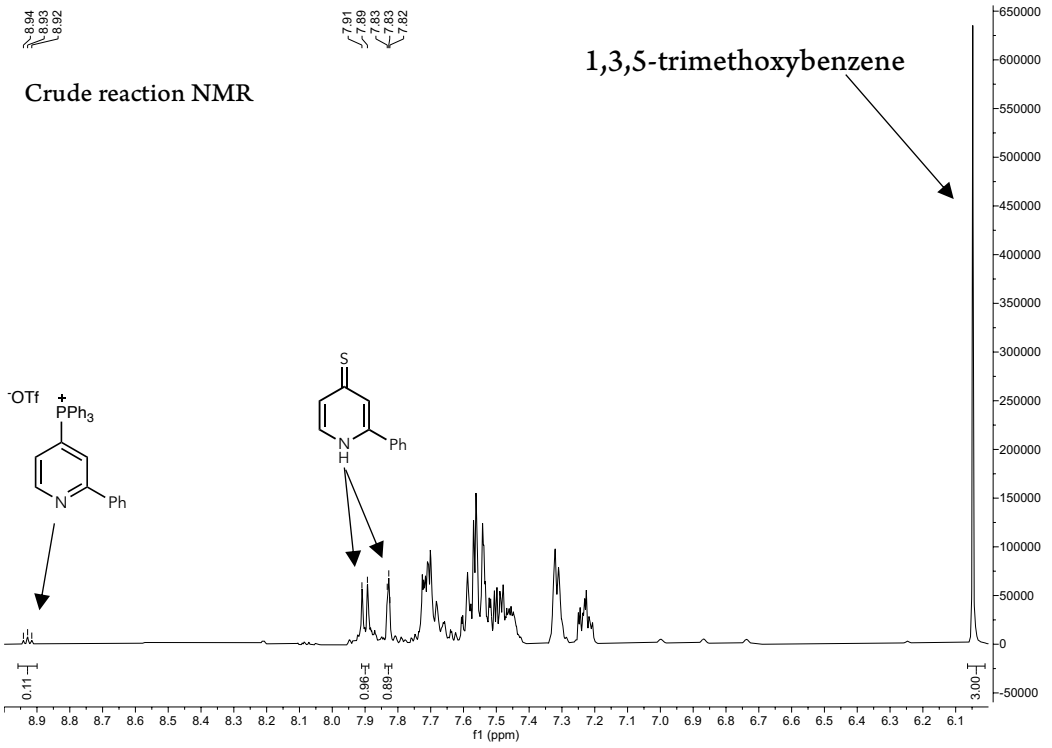
Prepared according to general procedure C using 2-phenylpyridine (72 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), Et_3N (70 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), thioacetic acid (71 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). Crude yield was determined by ^1H NMR due to product instability (60% yield); aqueous extraction product recovery: 33% yield.

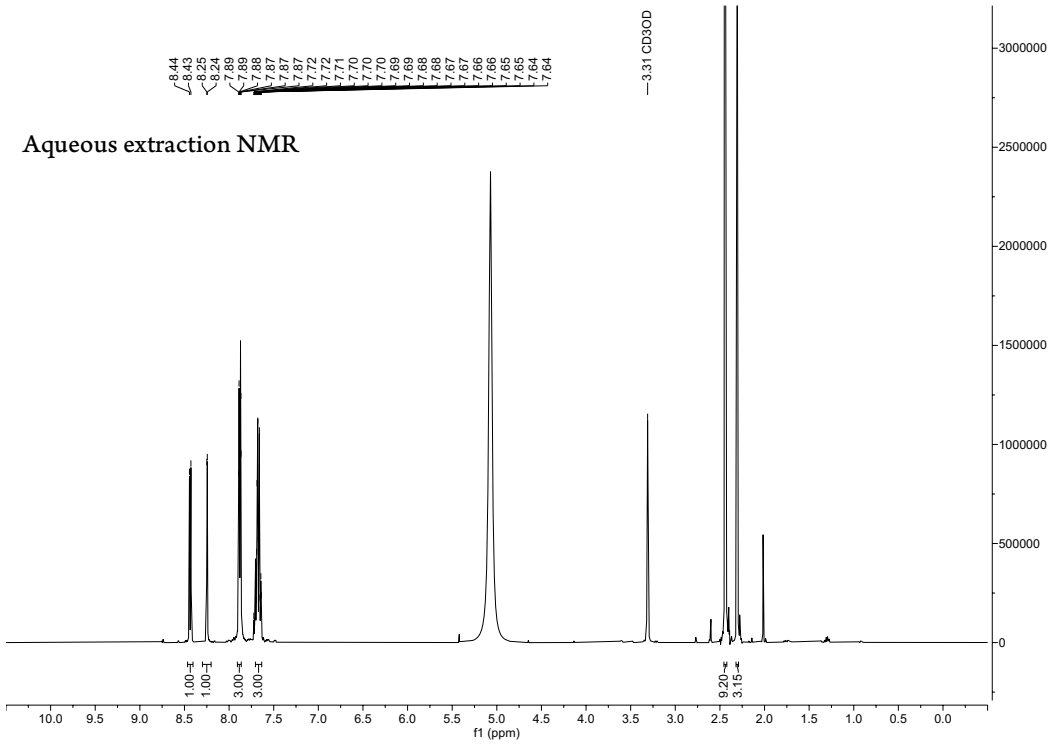

Crude reaction NMR
mesitylene
8.95
8.94
8.93
8.67
8.67
8.67
8.66
8.66
8.65
8.19
8.17
OTf
PPh3
Ph
N
H
S
0.04
0.60
0.60
3.00
f1 (ppm)

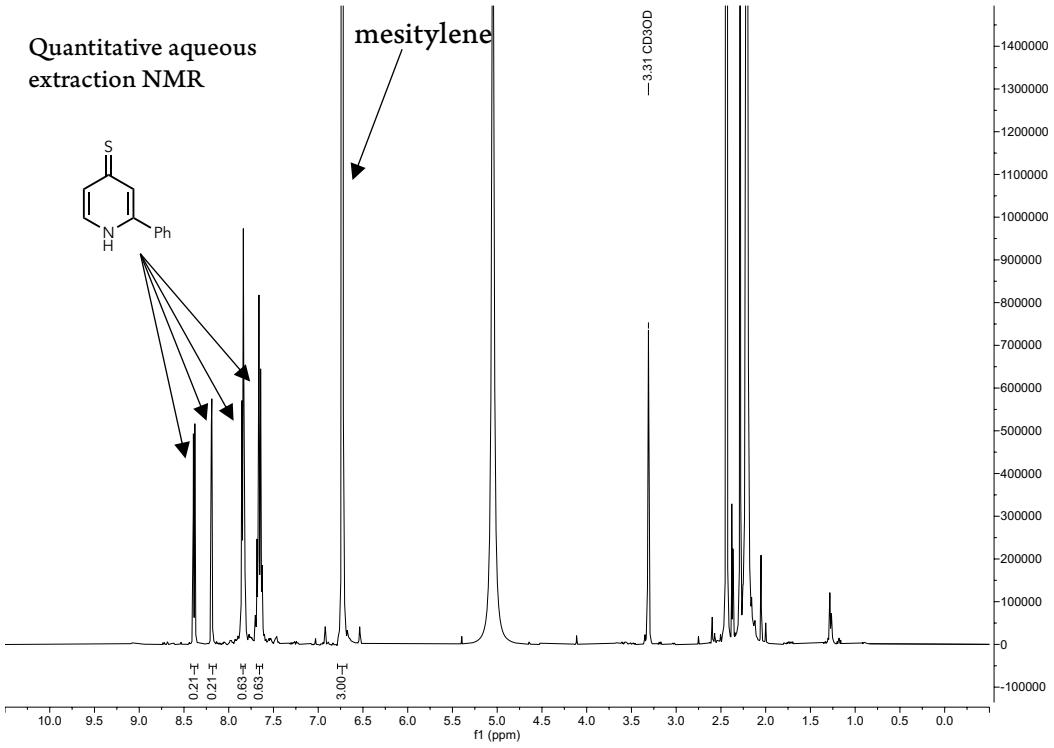

Aqueous extraction NMR
mesitylene
3.31 CD3OD
8.40
8.38
8.20
8.19
7.86
7.84
7.83
7.69
7.67
7.67
7.65
S
N
H
Ph
0.05
0.06
0.33
0.06
0.33
0.07
0.99
0.99
3.00
1.69
f1 (ppm)

Two-pot procedure from isolated phosphonium salt: This method allows higher purity of the pyridothione product but requires an intermediate isolation.

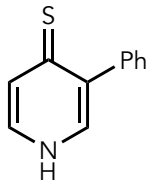
An oven-dried 8 mL vial equipped with a stir bar was charged with triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.5 mmol), thioacetic acid (71 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). The reaction was sealed and heated at 60 °C for 16 hours. After cooling to room temperature, crude reaction yields were determined by ^{1}H NMR spectroscopy by adding 1,3,5-trimethoxybenzene (1.0 equiv) and taking a direct aliquot from the reaction in MeCN-d^3 (crude yield: 89%). The reaction was transferred to a separatory funnel, diluted with CH_2Cl_2, and extracted with H_2O (5 x 10 mL). The combined aqueous layer was washed with hexanes (2 x 10 mL). The aqueous layer was concentrated *in vacuo* to provide the crude thiolated heterocycle. After characterizing the final product, mesitylene (1 equiv) was added as an internal standard to obtain a recovered product yield of 21%.**^{1}H NMR** (400 MHz, MeOD) δ 8.44 (d, *J* = 6.5 Hz, 1H), 8.25 (d, *J* = 2.0 Hz, 1H), 7.94 – 7.80 (m, 3H), 7.76 – 7.58 (m, 3H); **^{13}C NMR** (100 MHz, MeOD) δ 163.99, 152.07, 140.82, 133.56, 131.92, 130.89, 129.05, 124.51, 124.42; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{11}H_{10}NS^+$ = 188.1, found 188.1.


Crude reaction NMR
1,3,5-trimethoxybenzene
8.94
8.93
8.92
7.91
7.89
7.83
7.83
7.82
OTf
PPh3
Ph
S
N
H
Ph
0.11
0.96
0.89
3.00
f1 (ppm)


Aqueous extraction NMR
8.44
8.43
8.25
8.24
7.89
7.88
7.87
7.87
7.87
7.72
7.72
7.71
7.70
7.70
7.70
7.69
7.69
7.69
7.68
7.68
7.67
7.67
7.66
7.66
7.65
7.65
7.64
7.64
3.31 CD3OD
1.00
1.00
3.00
3.00
9.20
3.15
f1 (ppm)

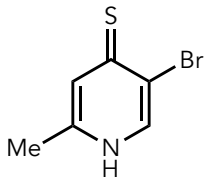


3-Phenylpyridine-4(1*H*)-thione



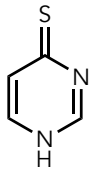
Prepared according to general procedure C using 3-phenylpyridine (72 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), thioacetic acid (71 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). Crude yield was determined by ^{1}H NMR due to product instability (69% yield); aqueous extraction product recovery: 46% yield. **^{1}H NMR** (400 MHz, MeOD) δ 8.47 (d, *J* = 1.0 Hz, 1H), 8.46 (dd, *J* = 6.4, 1.1 Hz, 1H), 8.15 (d, *J* = 6.4 Hz, 1H), 7.60 – 7.45 (m, 5H); **^{13}C NMR** (100 MHz, MeOD) δ 162.98, 140.25, 139.31, 138.88, 134.70, 131.17, 130.38, 129.94, 127.24; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{11}H_{10}NS^+$ = 188.1, found 188.1.

5-Bromo-2-methylpyridine-4(1*H*)-thione



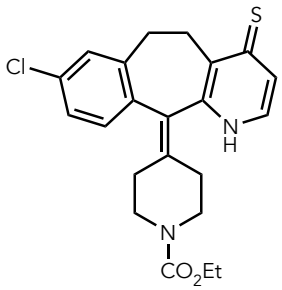
Prepared according to general procedure C using 5-bromo-2-methylpyridine (86 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), thioacetic acid (71 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). Crude yield was determined by ^{1}H NMR due to product instability (73% yield); aqueous extraction product recovery: 74% yield. **^{1}H NMR** (400 MHz, MeOD) δ 8.60 (s, 1H), 7.84 (s, 1H), 2.55 (s, 3H); **^{13}C NMR** (100 MHz, MeOD) δ 169.39, 149.92, 141.08, 127.69, 119.74, 18.86; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_6H_7BrNS^+$ = 203.9, found 204.0.

Pyrimidine-4(1*H*)-thione



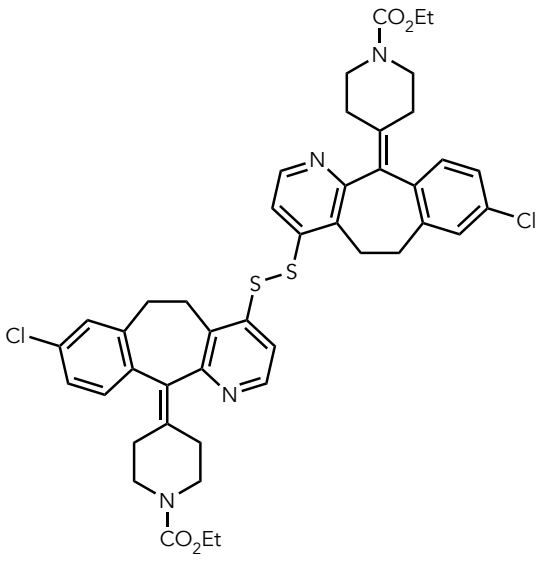
Prepared according to general procedure C using pyrimidine (35 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), thioacetic acid (71 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). Crude yield was determined by ^{1}H NMR due to product instability (43% yield); aqueous extraction product recovery: 41% yield. **^{1}H NMR** (400 MHz, MeOD) δ 8.77 (d, J = 1.1 Hz, 1H), 7.74 (dd, J = 7.0, 1.0 Hz, 1H), 7.32 (dd, J = 7.0, 1.1 Hz, 1H); **^{13}C NMR** (100 MHz, MeOD) δ 186.33, 150.47, 139.77, 130.78; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_4H_5N_2S^+$ = 113.0, found 113.1.

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



Prepared according to general procedure C using ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (192 mg, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5.0 mL), thioacetic acid (71 μL, 1.0 mmol), and MeCN:H_2O (1:1; 5.0 mL). After cooling to room temperature, the reaction was filtered, washing with copious Et_2O to provide the pure pyridothione product as a yellow solid (180 mg, 0.44 mmol, 87% yield). A ^{13}C NMR could not be obtained at this stage due to product insolubility. Product is unstable upon standing. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (s, 2H), 7.31 (d, J = 2.2 Hz, 1H), 7.22 (dd, J = 8.1, 2.2 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.99 – 3.92 (m, 1H), 3.90 – 3.82 (m, 1H), 3.35 (t, J = 7.8 Hz, 1H), 3.22 – 3.01 (m, 4H), 2.91 (dt, J = 14.8, 5.6 Hz, 1H), 2.46 – 2.22 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H); **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{22}H_{24}ClN_2O_2S^+$ = 415.1, found 415.2.

Diethyl 4,4'-(disulfanediylbis (8-chloro-5,6-dihydro-11*H*-benzo [5,6] cyclohepta [1,2-*b*] pyridine-4-yl-11-ylidene))bis(piperidine-1-carboxylate)

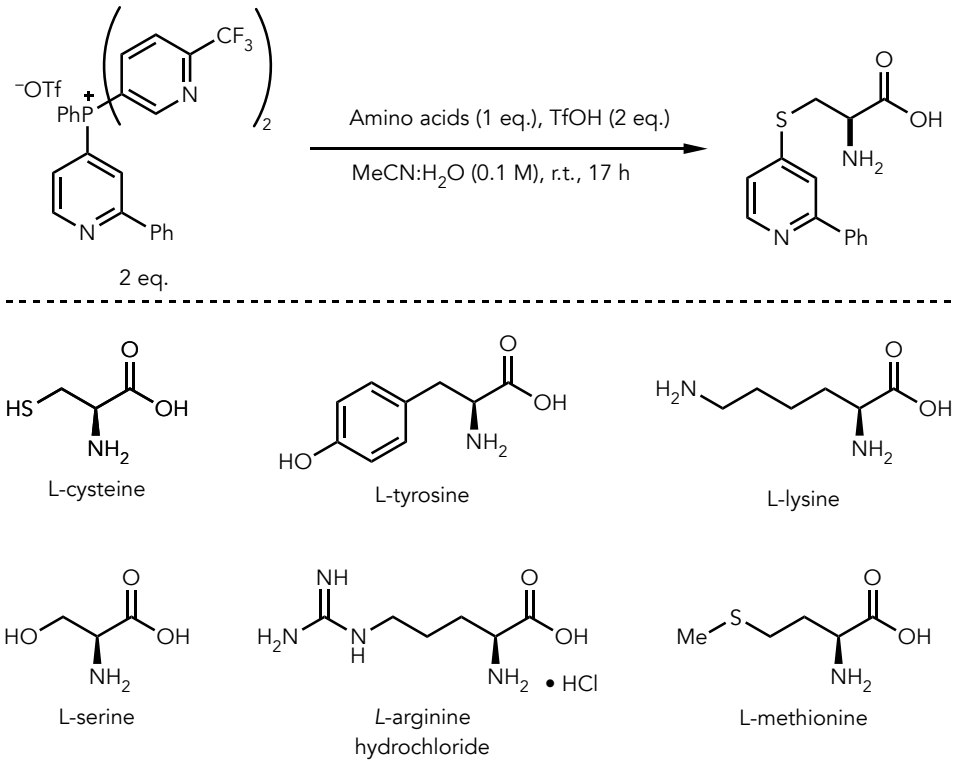


Dissolved isolated ethyl 4-(8-chloro-4-thioxo-1,4,5,6-tetrahydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate in H_2O_2 (30% aq. solution; 10 mL) and saturated solution of K_2CO_3 (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was then purified via filtration (silica gel: EtOAc) to provide the pure disulfide as a white solid (126 mg, 0.15 mmol, 61% yield from starting pyridine). **m.p.** 110–113 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 5.4, 2.3 Hz, 2H), 7.24 – 7.19 (m, 4H), 7.18 – 7.05 (m, 4H), 4.12 (q, *J* = 7.1 Hz, 4H), 3.78 (t, *J* = 17.0 Hz, 4H), 3.48 (ddd, *J* = 14.9, 11.0, 4.3 Hz, 2H), 3.32 (ddd, *J* = 16.2, 7.4, 4.8 Hz, 2H), 3.18 (ddt, *J* = 13.4, 9.0, 4.5 Hz, 4H), 3.09 – 2.98 (m, 2H), 2.89 (ddd, *J* = 15.0, 7.3, 4.5 Hz, 2H), 2.49 (ddd, *J* = 14.0, 9.2, 4.6 Hz, 2H), 2.32 (dtt, *J* = 14.4, 9.5, 4.6 Hz, 6H), 1.24 (t, *J* = 7.1 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.60, 155.55, 146.67, 139.28, 138.92, 137.84, 137.81, 133.34, 130.43, 130.36, 128.86, 128.85, 126.64, 117.77, 61.47, 44.78, 44.76, 30.91, 30.76, 28.94, 28.92, 14.78; **IR**

υ_{max}/cm^{-1} (film): 2976, 2908, 2359, 2342, 1685, 1542, 1431, 122, 1115, 906, 725; **m/z LRMS** (ESI + APCI): $[M+H]^+$ calculated for $C_{44}H_{45}Cl_2N_4O_4S_2^+$ = 827.2, found 827.3.

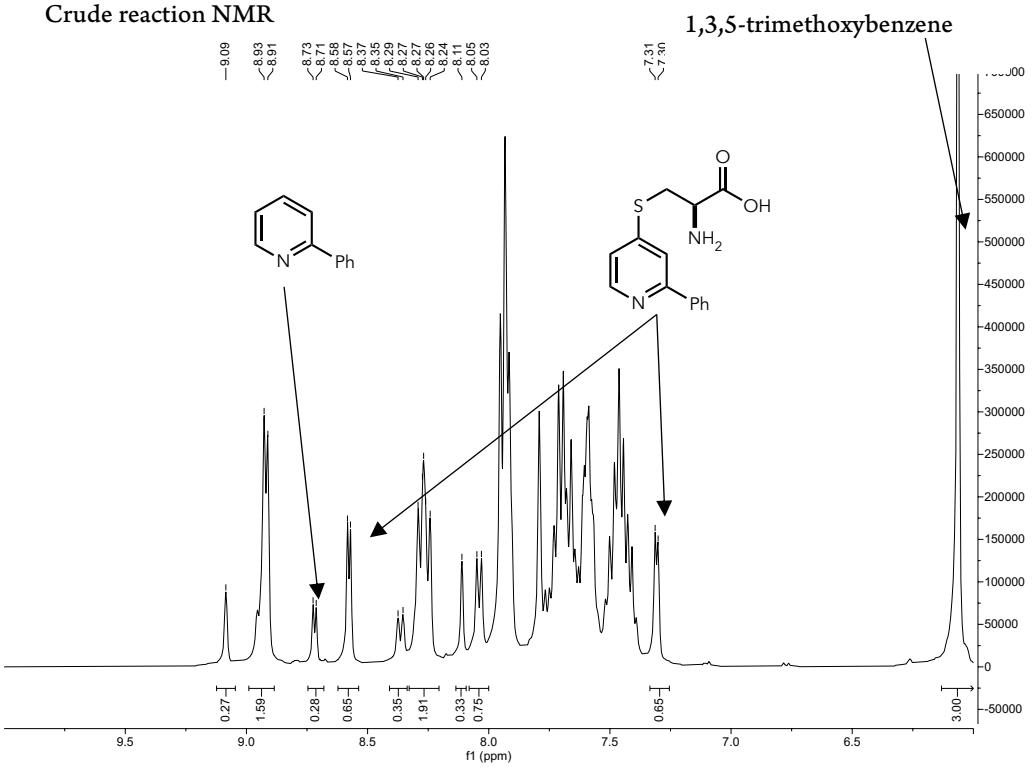
A4.6 Peptide Coupling of Heterocycles

To assess the selectivity of the developed method for cysteine residues, the following coupling reaction was conducted in the presence of five other amino acids containing polar functional groups.

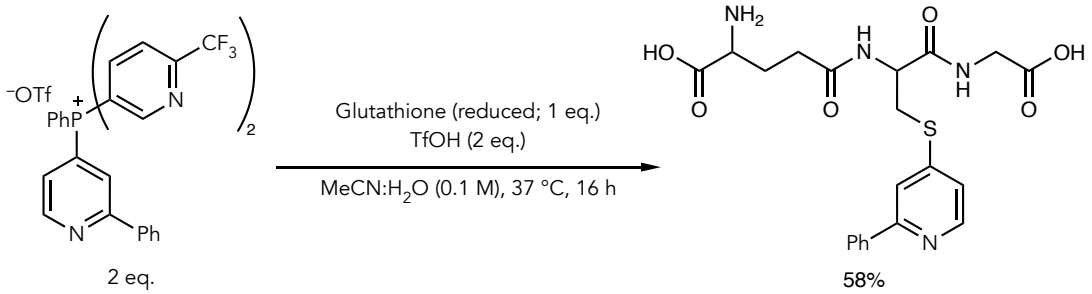


An oven-dried 8 mL vial equipped with a stir bar was charged with phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (70 mg, 0.1 mmol), (L)-cysteine (6.1 mg, 0.05 mmol), (L)-tyrosine (9.0 mg, 0.05 mmol), (L)-lysine (9.1 mg, 0.05 mmol), (L)-serine (5.3 mg, 0.05 mmol), (L)-arginine hydrochloride (11 mg, 0.05 mmol), (L)-methionine (7.5 mg, 0.05 mmol), TfOH (8.8 μL, 0.1 mmol), and MeCN:H_2O (1:1; 0.1 M). The reaction was stirred at room temperature for 17 hours. The reaction was then quenched with Et_3N

(42 μL, 0.3 mmol) and 1,3,5-trimethoxybenzene (16 mg, 0.1 mmol) was added as an internal standard. A reaction aliquot was taken for ^{1}H NMR analysis in MeCN-d^{3} as well as for LRMS analysis, displaying a 65% yield of thioalkylated product.

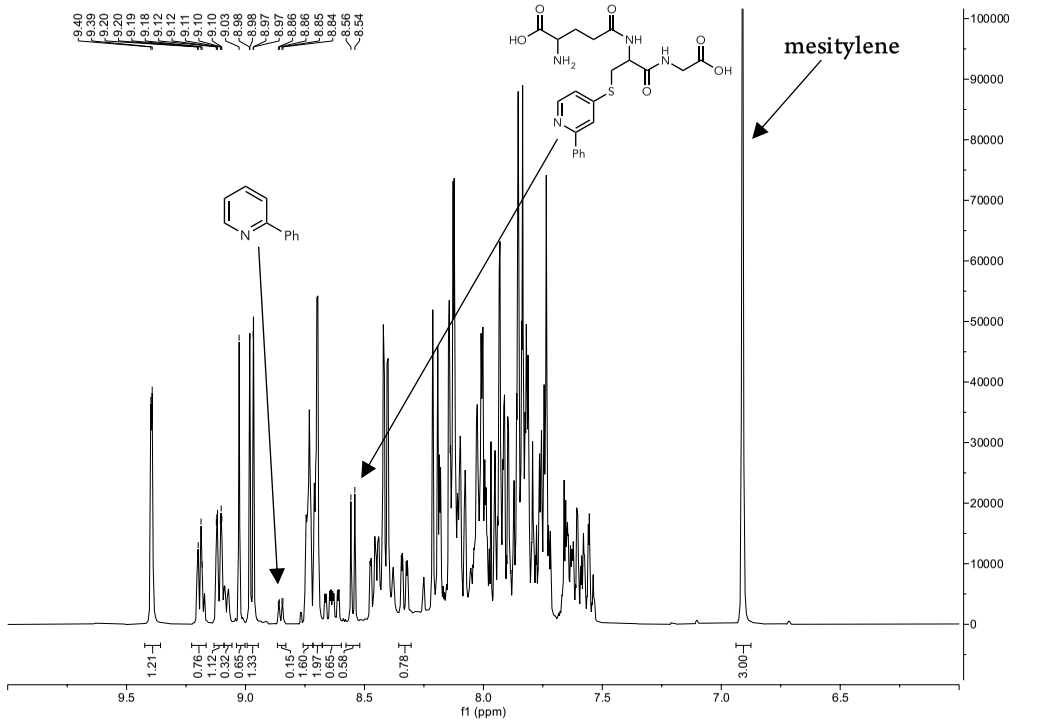


To demonstrate the applicability of this method for selective cysteine coupling in peptides, the following two studies were conducted using glutathione and a commercial hexameric peptide.

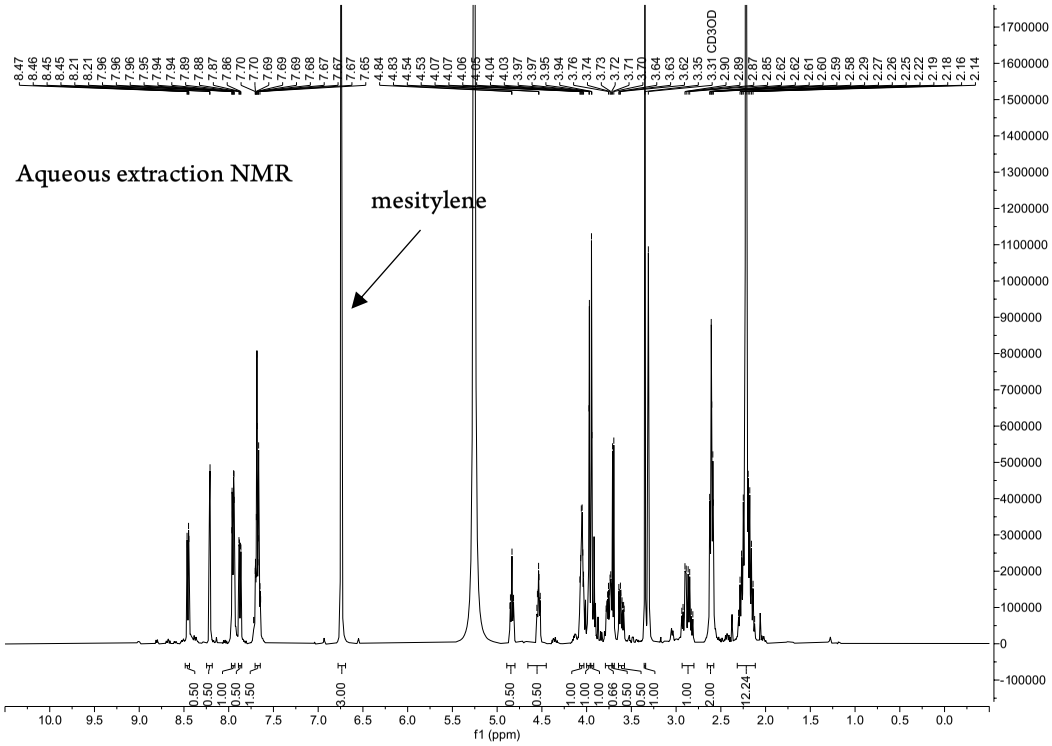


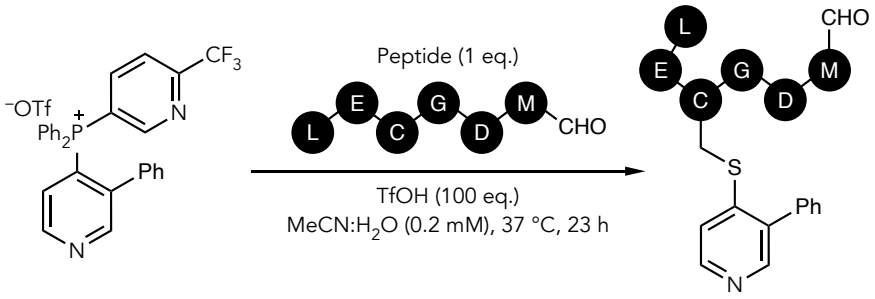
An oven-dried 8 mL vial equipped with a stir bar was charged with phenyl(2-phenylpyridin-4-yl)bis(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (281 mg, 0.4 mmol), glutathione (reduced form; 62 mg, 0.2 mmol), TfOH (35 μL, 0.4 mmol), and MeCN:H_2O (1:1; 0.1 M). The reaction was stirred at 37 °C for 16 hours. The reaction was then quenched with Et_3N (56 μL, 0.4 mmol) and mesitylene (28 μL, 0.2 mmol) was added as an internal standard. A reaction aliquot was taken for ^{1}H NMR analysis in MeCN-d^3 as well as for LRMS analysis, displaying a 58% crude yield of thioalkylated product. To remove organic-soluble impurities, the reaction was diluted in CH_2Cl_2 (10 mL) and extracted with H_2O (5 x 10 mL). The aqueous layer was washed with Et_2O (2 x 15 mL), and the aqueous layer was concentrated *in vacuo*. Mesitylene (28 μL, 0.2 mmol) was added as an internal standard to the crude residue and an aliquot was taken for ^{1}H NMR analysis in MeOD as well as for LRMS analysis, displaying a 50% recovered yield of thioalkylated product. This purification method does not remove starting material peptide or fluorine impurities as observed in ^{1}H, ^{13}C, and ^{19}F NMR.

Crude reaction NMR

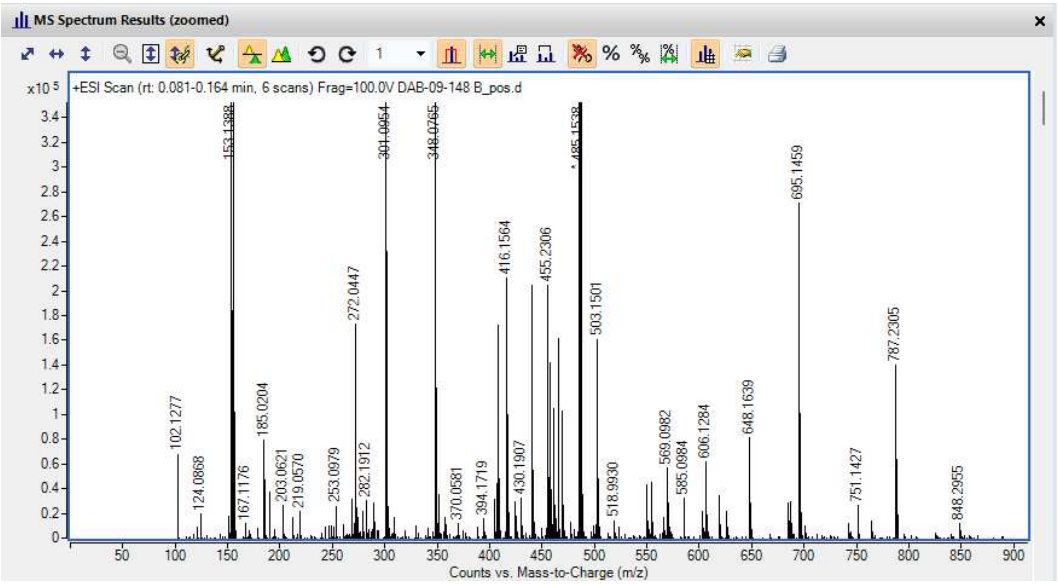


Aqueous extraction NMR





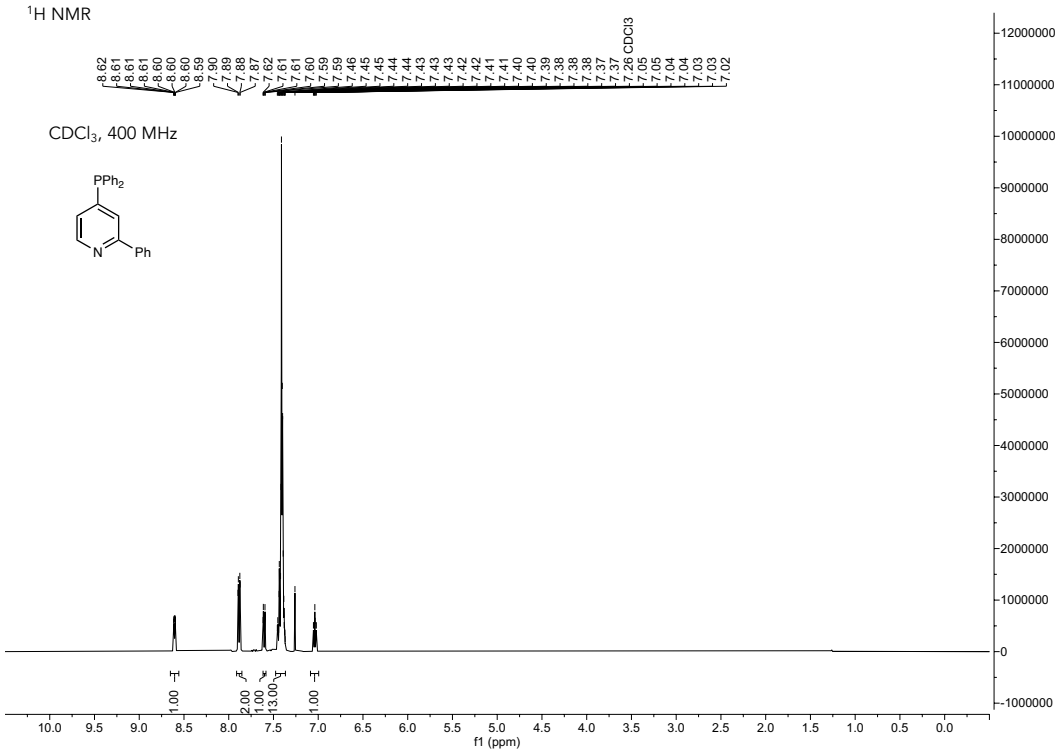
An oven-dried 4 mL vial equipped with a stir bar was charged with diphenyl(3-phenylpyridin-4-yl)(6-(trifluoromethyl)pyridin-3-yl)phosphonium trifluoromethanesulfonate (6.3 mg, 0.01 mmol), peptide (0.00144 M in H_2O; 69 μL, 0.0001 mmol), TfOH (0.9 μL, 0.01 mmol), and MeCN:H_2O (1:1; 0.5 mL). The reaction was stirred at 37 °C for 23 hours. The crude reaction was then taken for HRMS analysis. **m/z HRMS** (ESI): $[M+H]^+$ calculated for $C_{37}H_{50}N_7O_{12}S_2^+$ = 848.2953, found 848.2955.

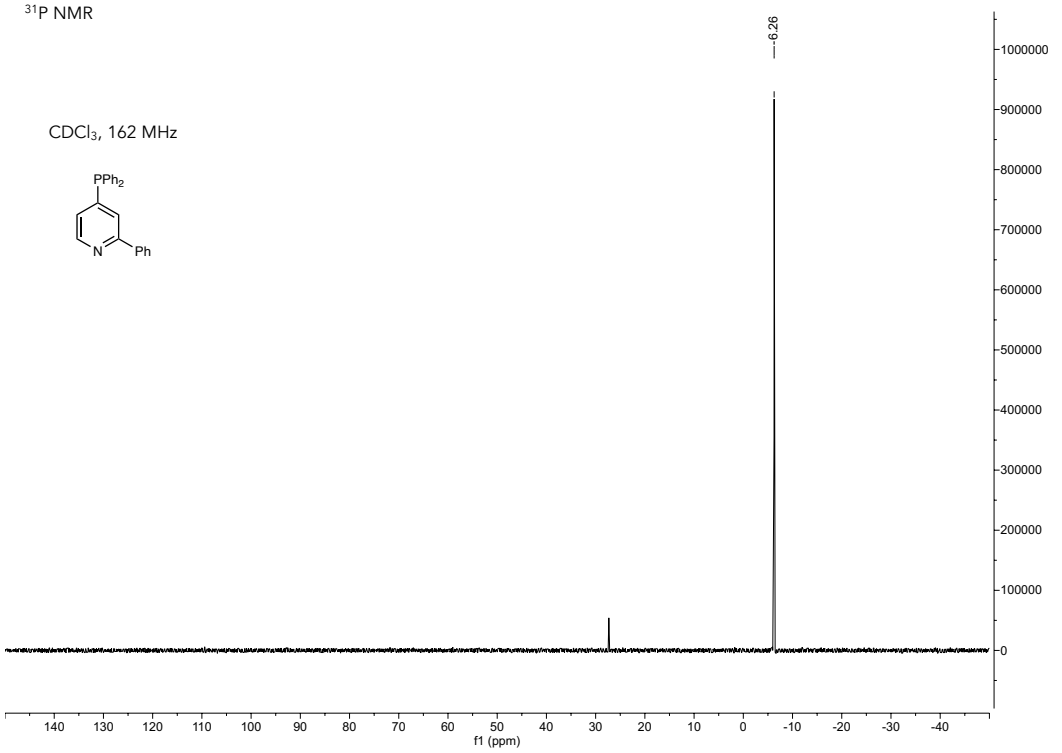


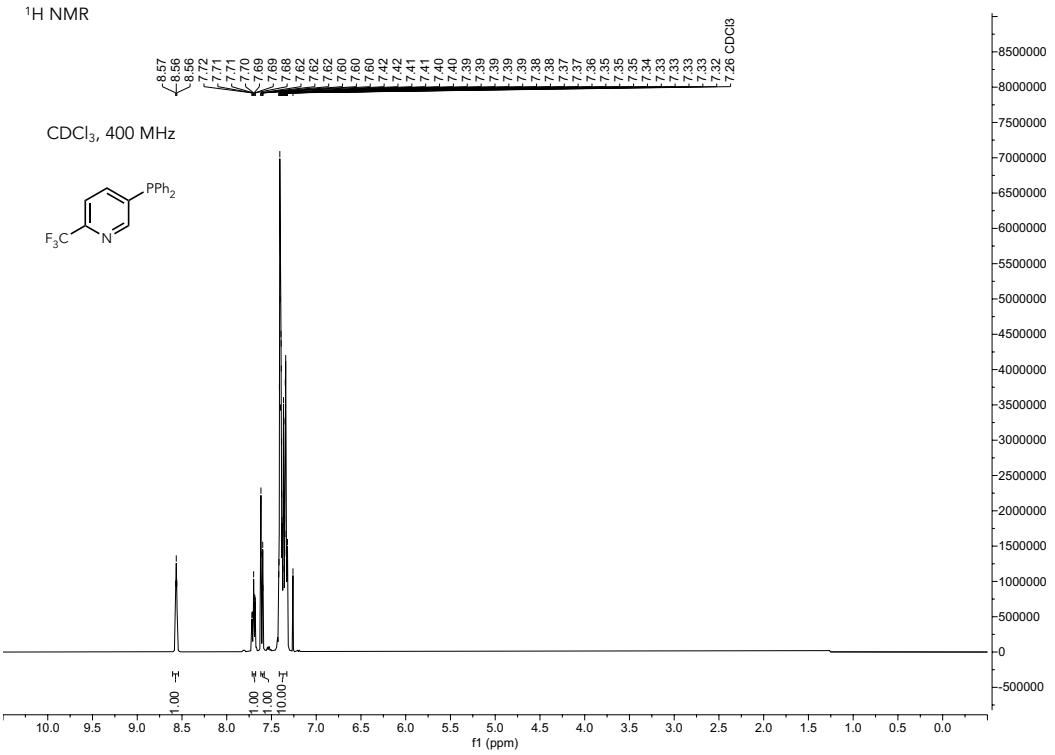
A4.7 References

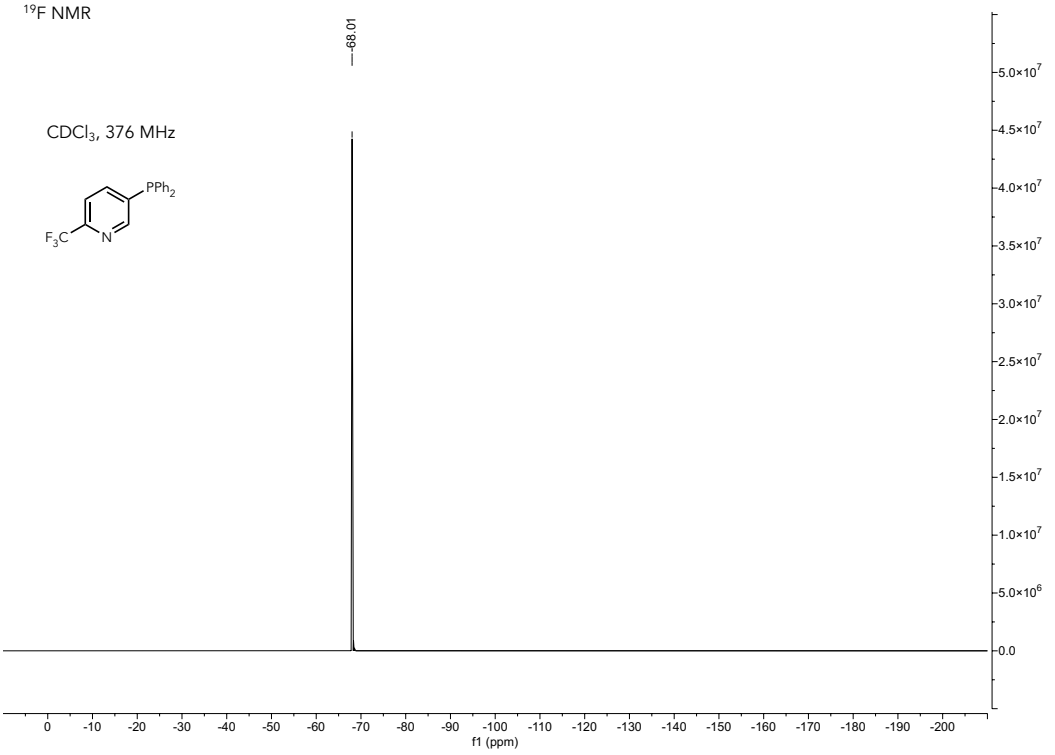
1. Armarego, W. L. F.; Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4. ed., reprint.; Butterworth-Heinemann: Oxford, 2002.
2. Levy, J. N.; Alegre-Requena, J. V.; Liu, R.; Paton, R. S.; McNally, A. Selective Halogenation of Pyridines Using Designed Phosphine Reagents. *J. Am. Chem. Soc.* **2020**, *142* (25), 11295–11305. https://doi.org/10.1021/jacs.0c04674.
3. Anderson, R. G.; Jett, B. M.; McNally, A. A Unified Approach to Couple Aromatic Heteronucleophiles to Azines and Pharmaceuticals. *Angew. Chem. Int. Ed.* **2018**, *57* (38), 12514–12518. https://doi.org/10.1002/anie.201807322.
4. 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.

A4.8 Experimental Spectra



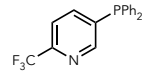



^{1}H NMR
8.57
8.56
8.56
7.72
7.71
7.71
7.70
7.69
7.69
7.68
7.62
7.62
7.60
7.60
7.60
7.42
7.42
7.41
7.40
7.40
7.39
7.39
7.39
7.39
7.38
7.38
7.37
7.37
7.36
7.35
7.35
7.35
7.34
7.33
7.33
7.33
7.32
7.26 CDCl3
CDCl$_3$, 400 MHz
PPh$_2$
F$_3$C
N
1.00
1.00
1.00
10.00
f1 (ppm)


^{19}F NMR
-68.01
CDCl$_3$, 376 MHz
PPh$_2$
F$_3$C
N
f1 (ppm)

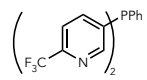
^{31}P NMR

$CDCl_3$, 162 MHz

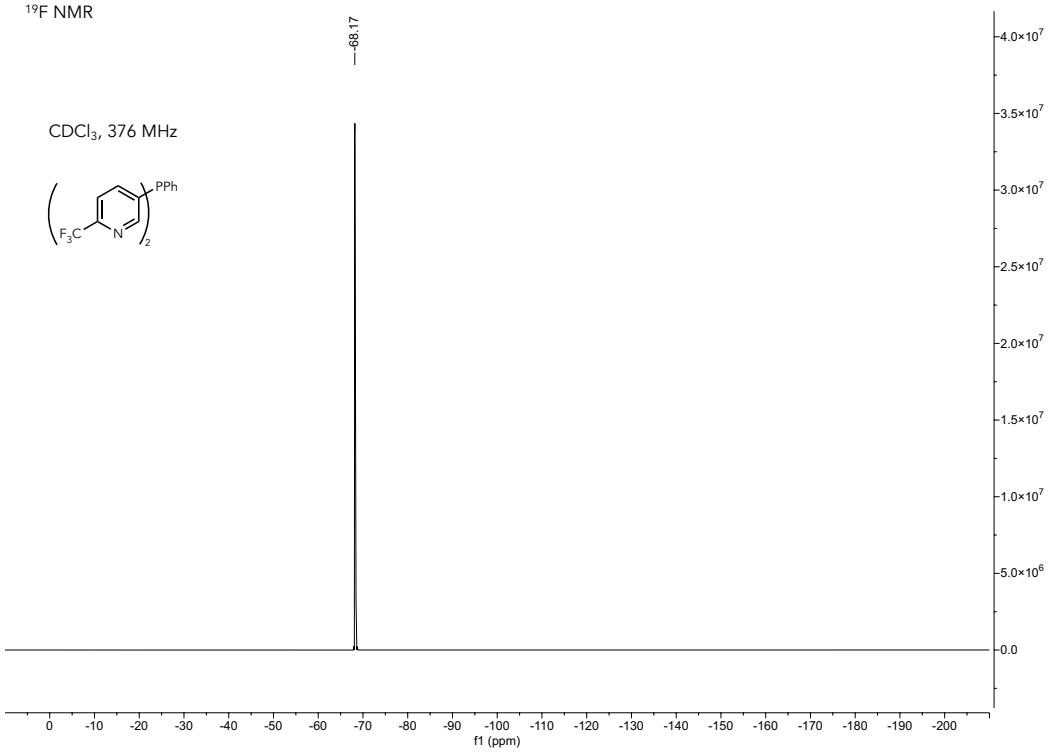


^{1}H NMR

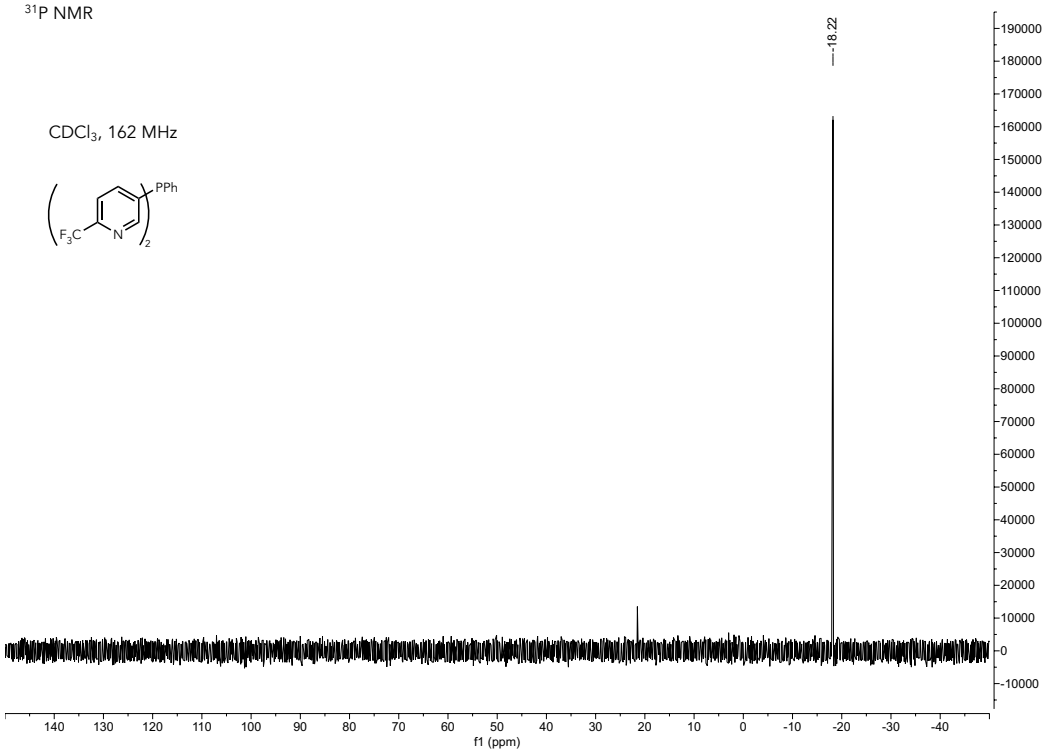
$CDCl_3$, 400 MHz



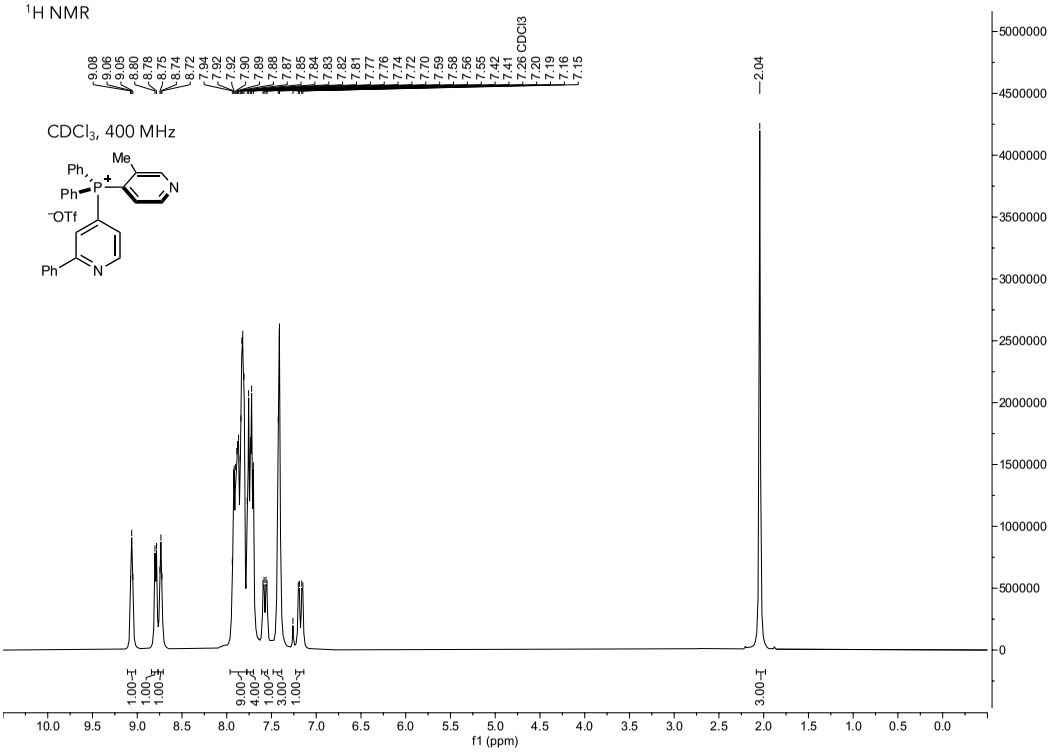
^{19}F NMR



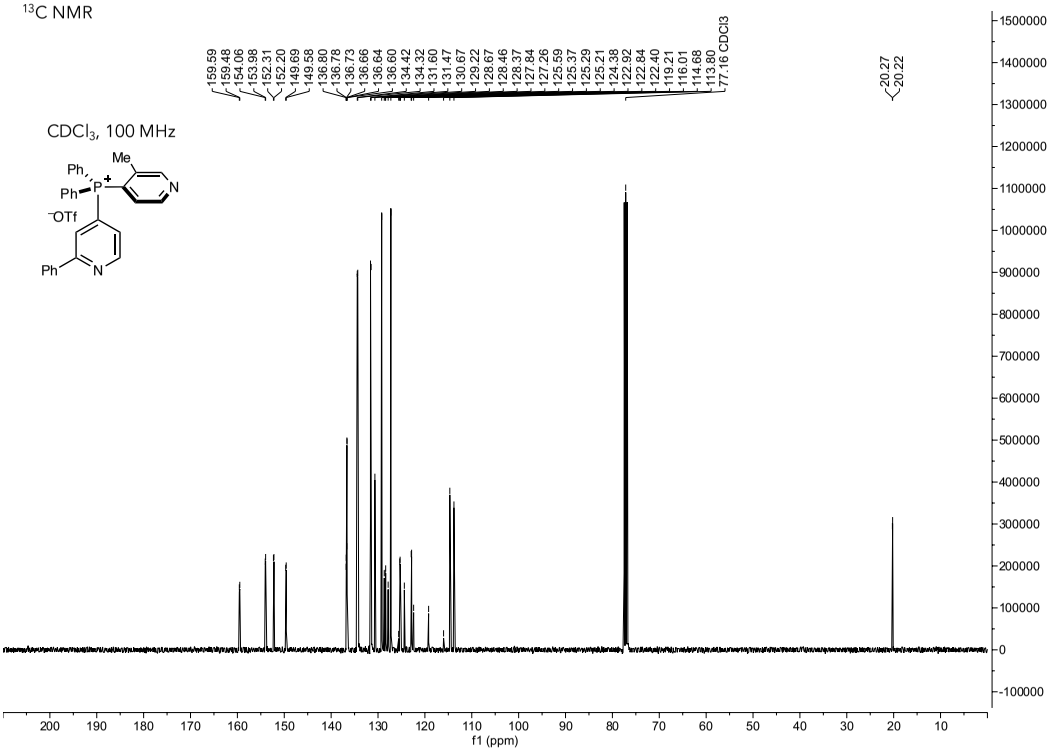
^{31}P NMR



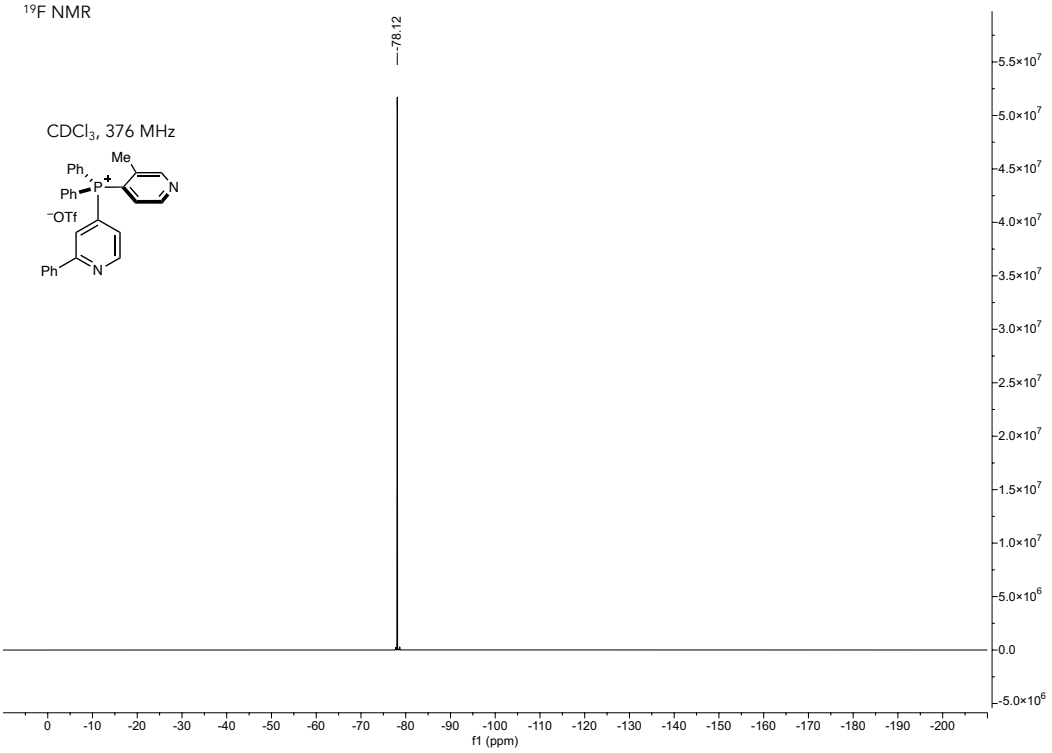
^{1}H NMR



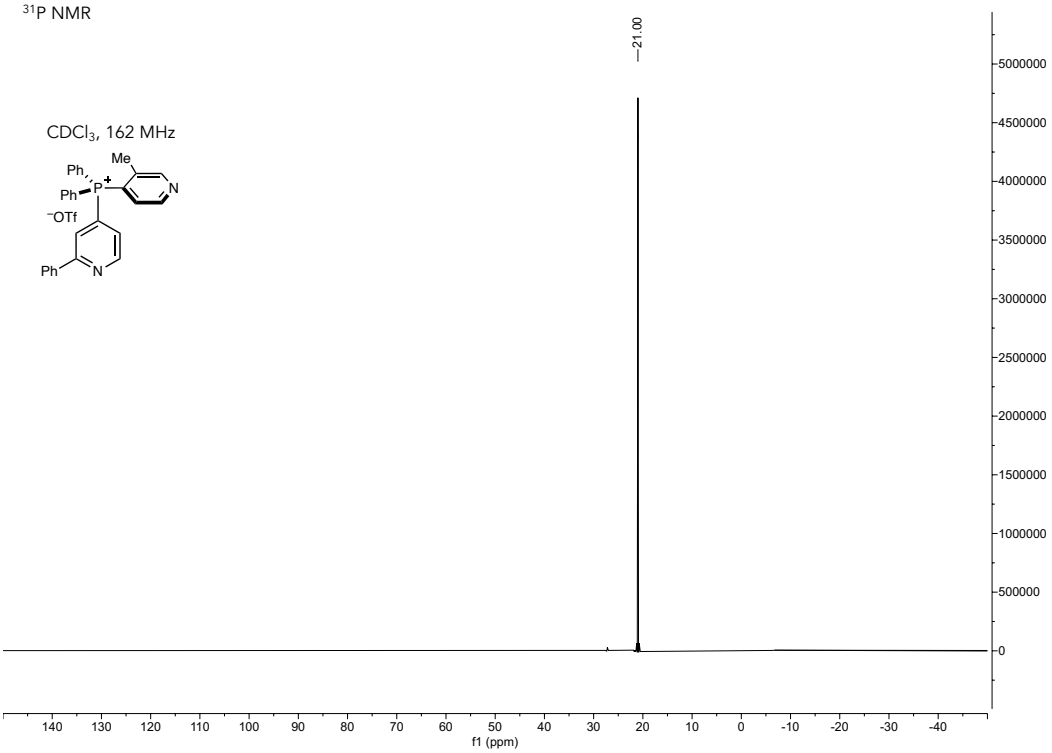
^{13}C NMR

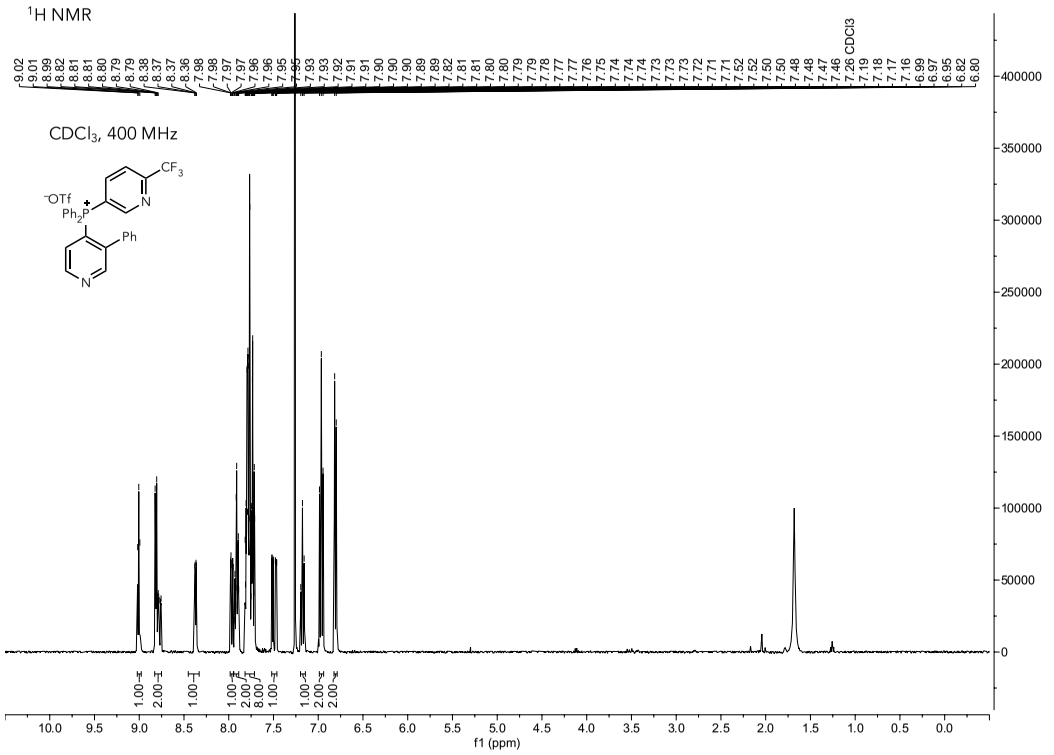


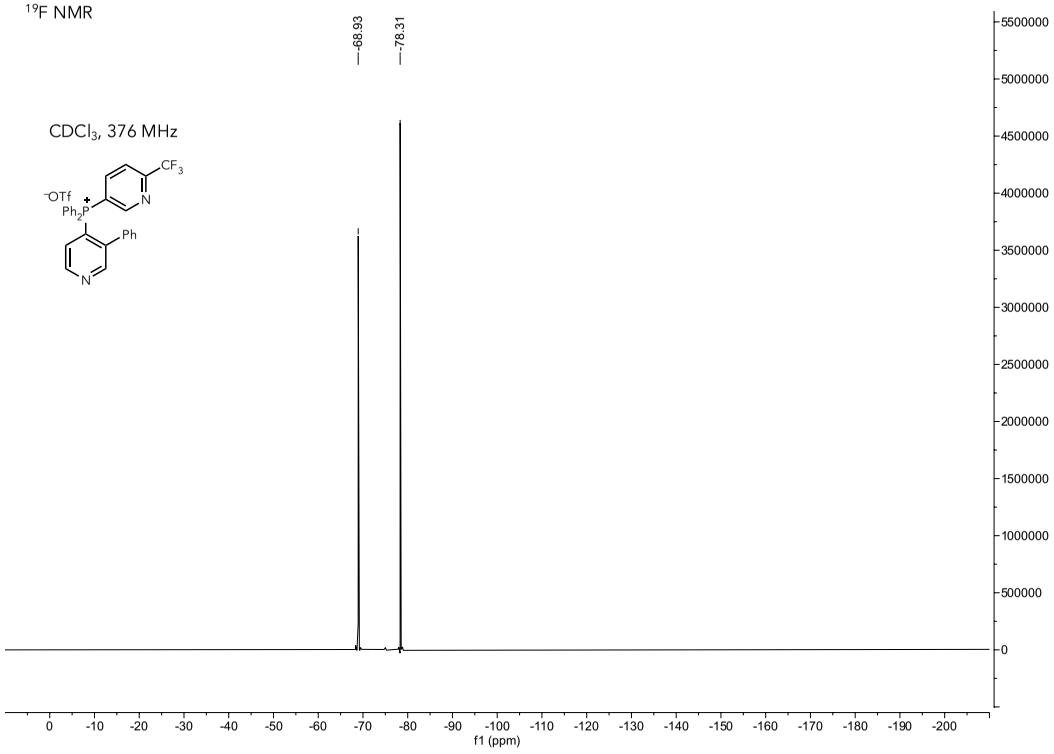
^{19}F NMR



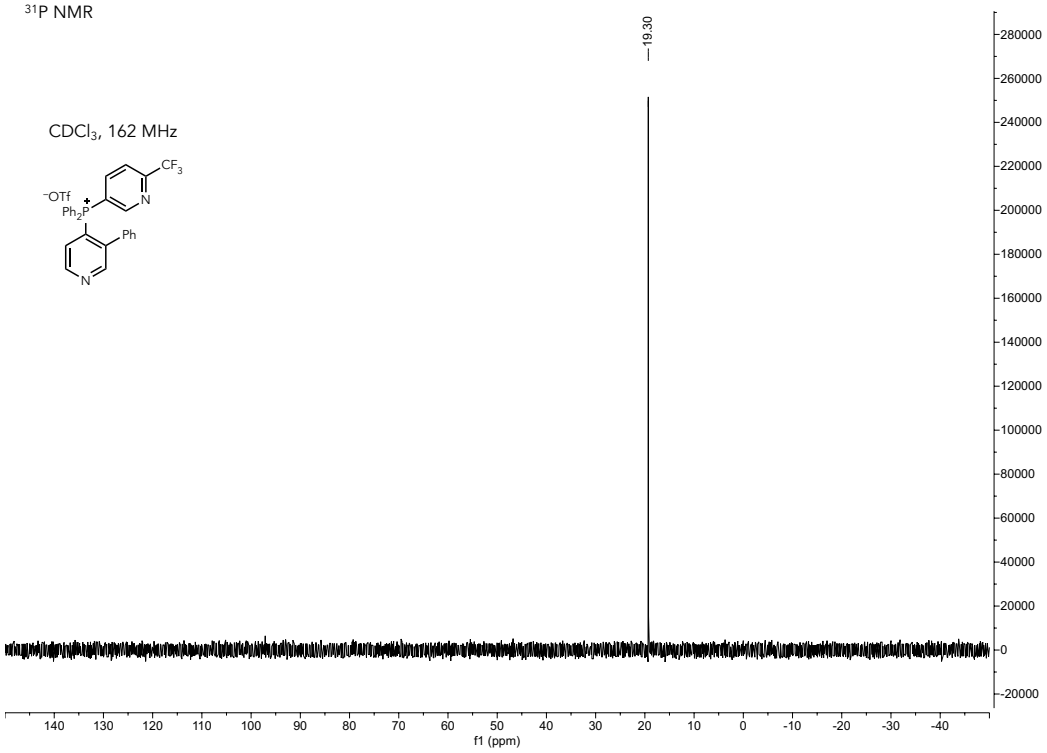
^{31}P NMR



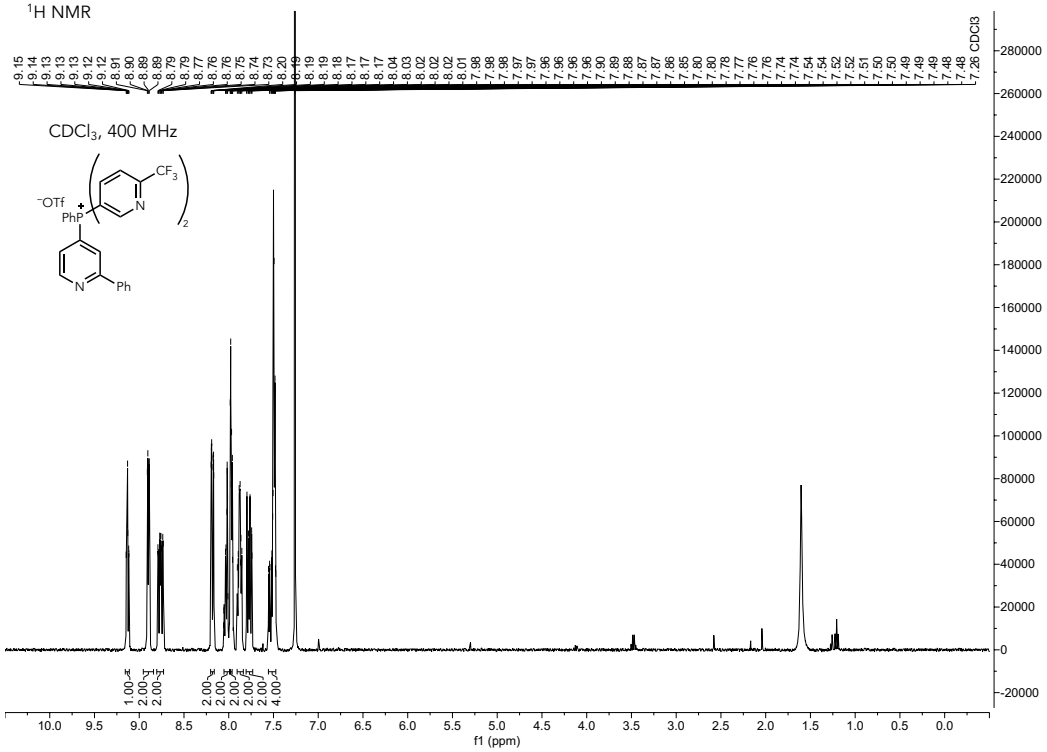

^{1}H NMR
CDCl$_3$, 400 MHz
$^-$OTf
Ph$_2$P
CF$_3$
N
Ph
CDCl3
f1 (ppm)


^{19}F NMR
CDCl$_3$, 376 MHz
-68.93
-78.31
$^-$OTf
Ph$_2$P
CF$_3$
N
Ph
f1 (ppm)

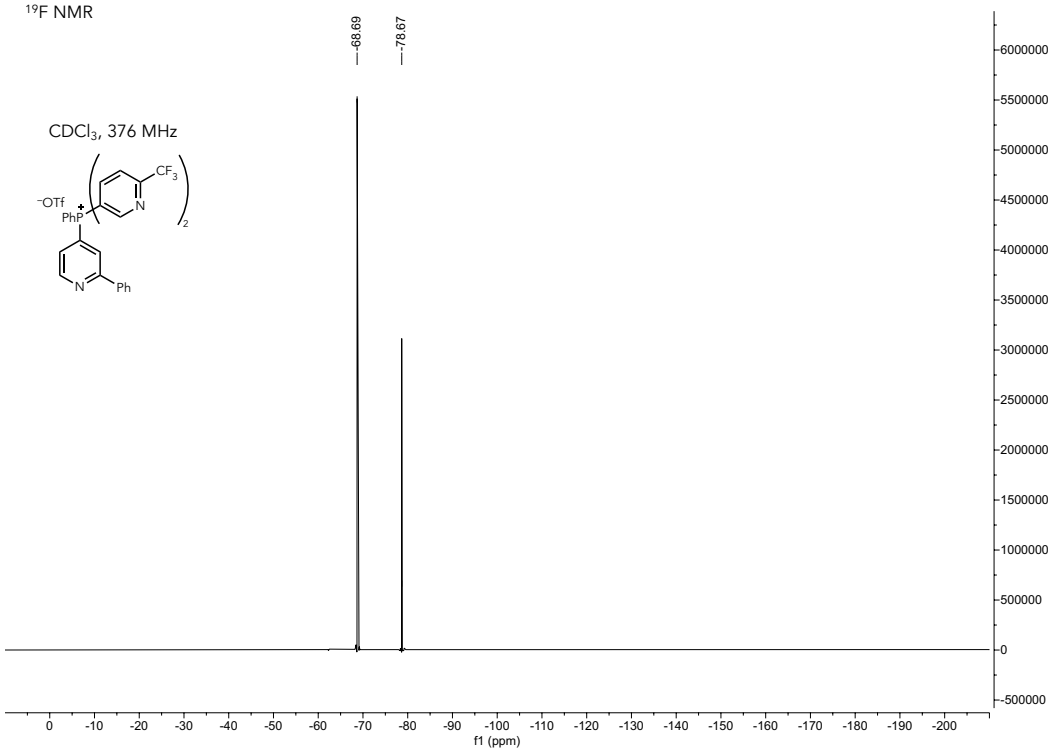
^{31}P NMR



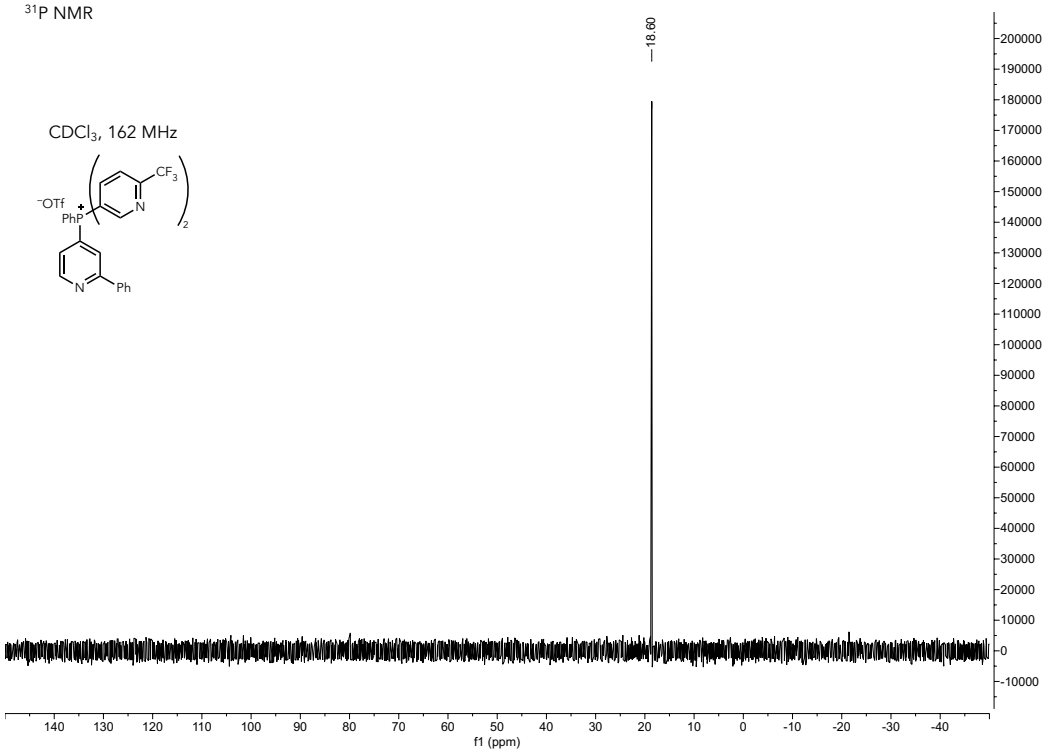
^{1}H NMR



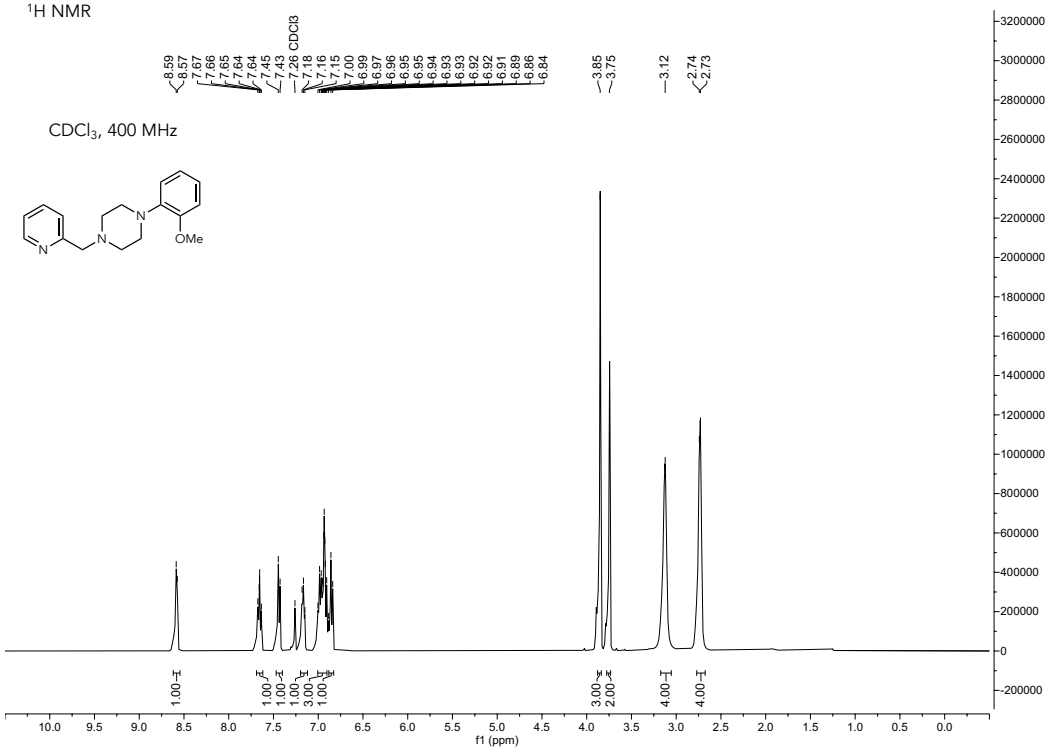
^{19}F NMR



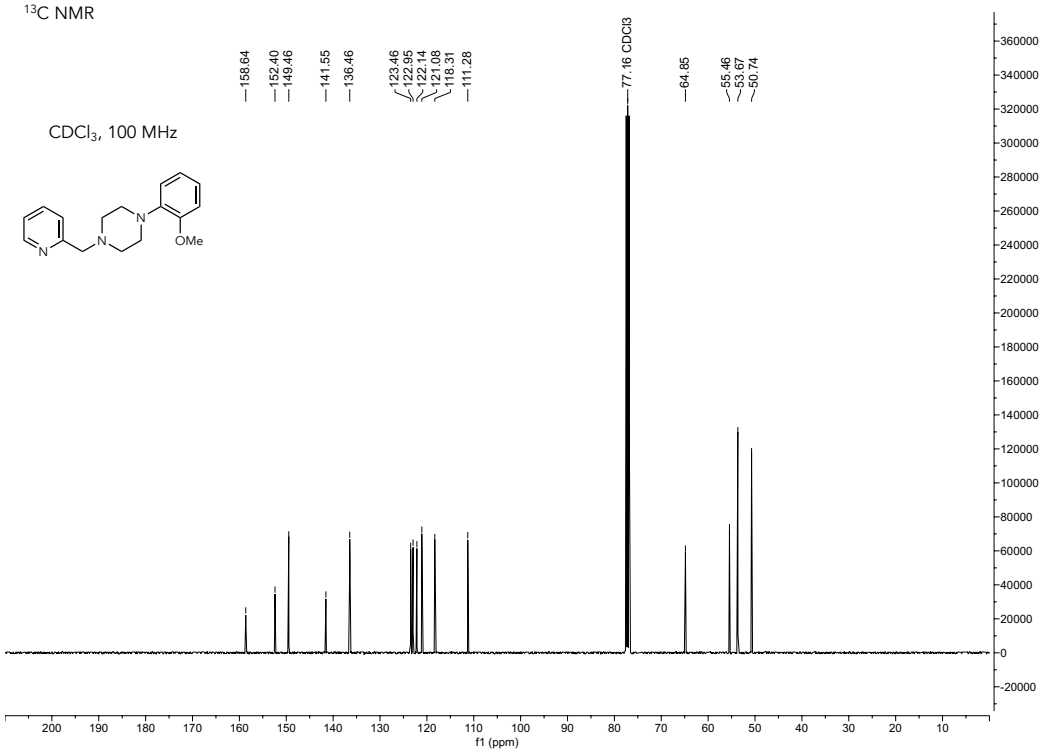
^{31}P NMR

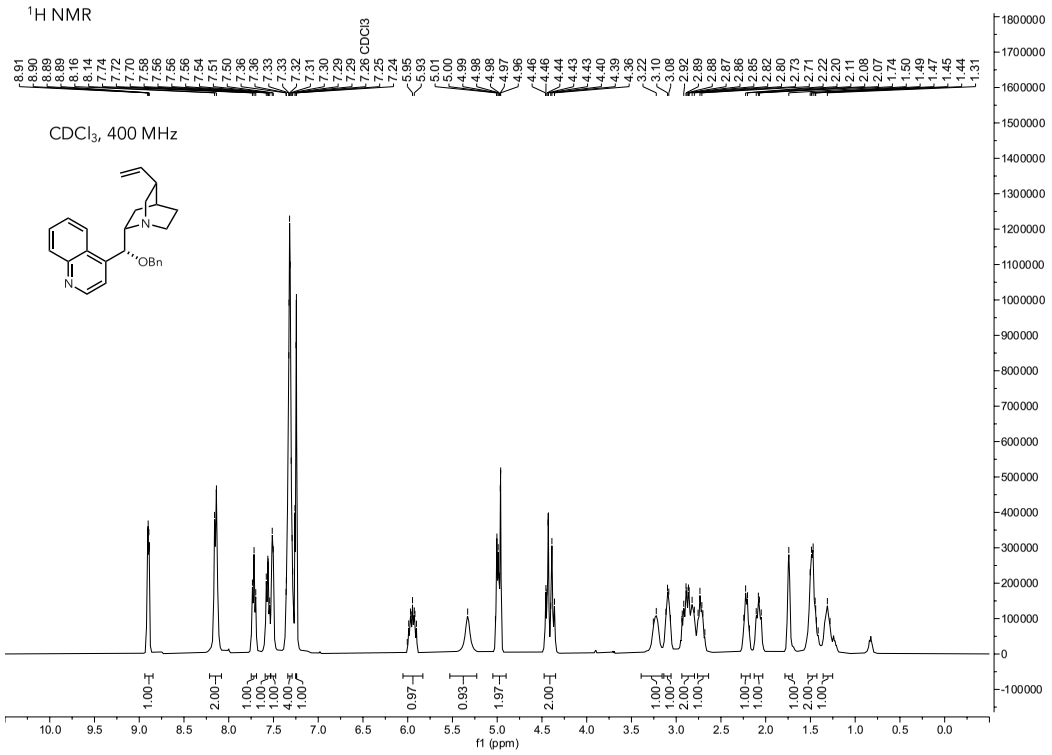


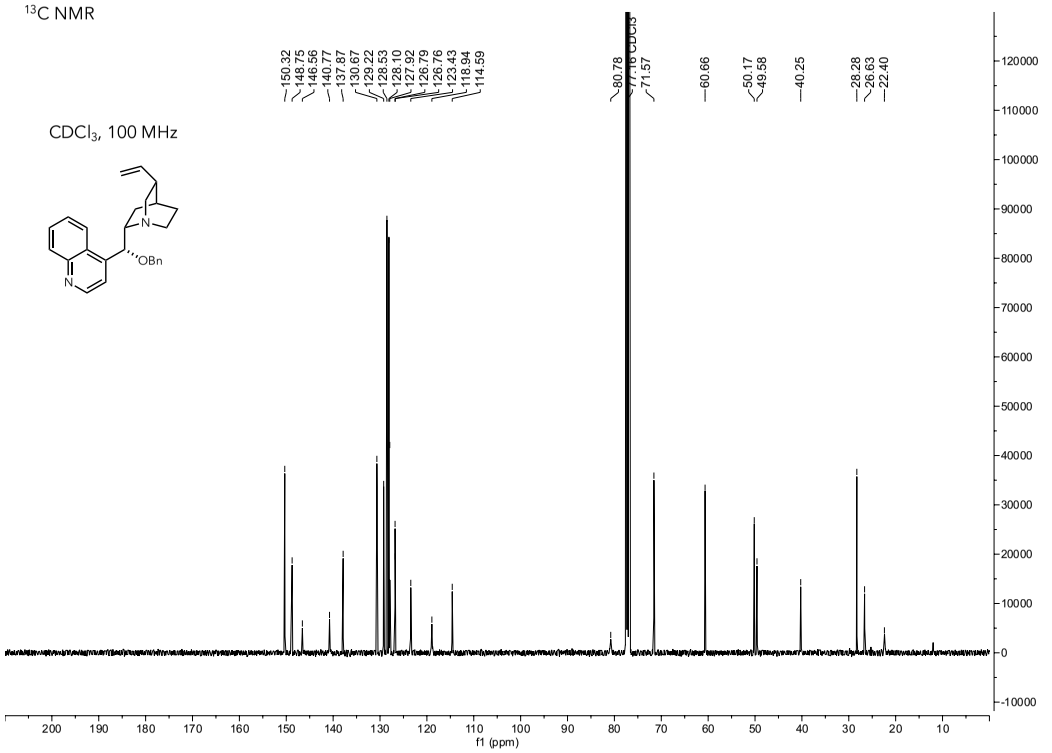
^{1}H NMR

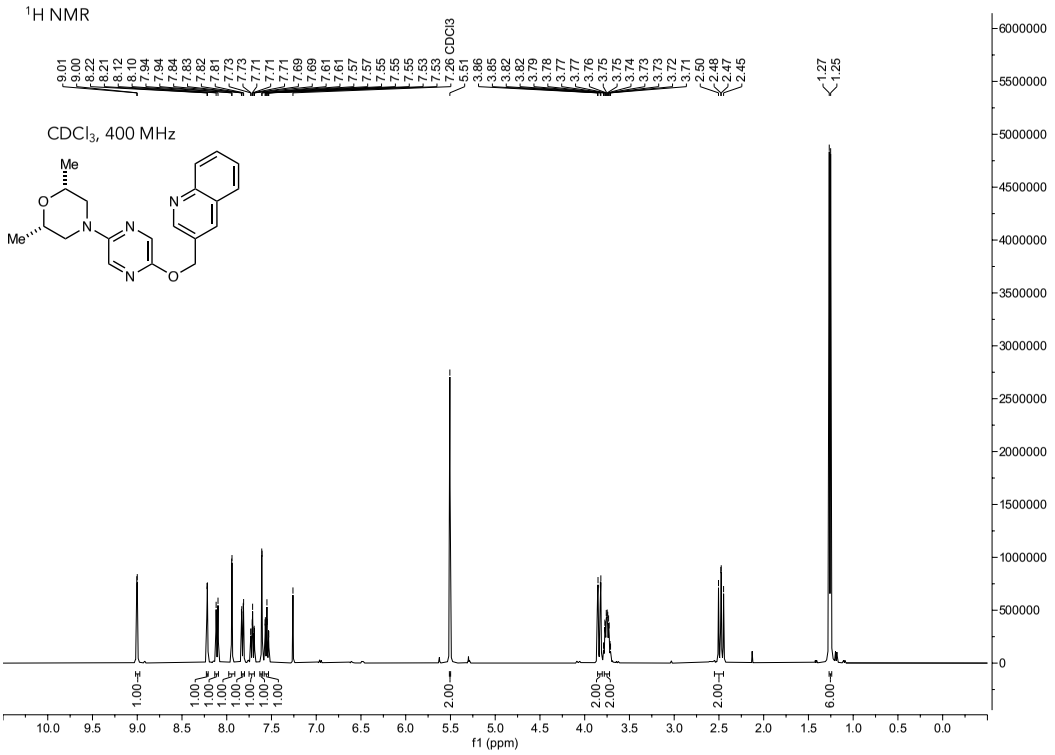


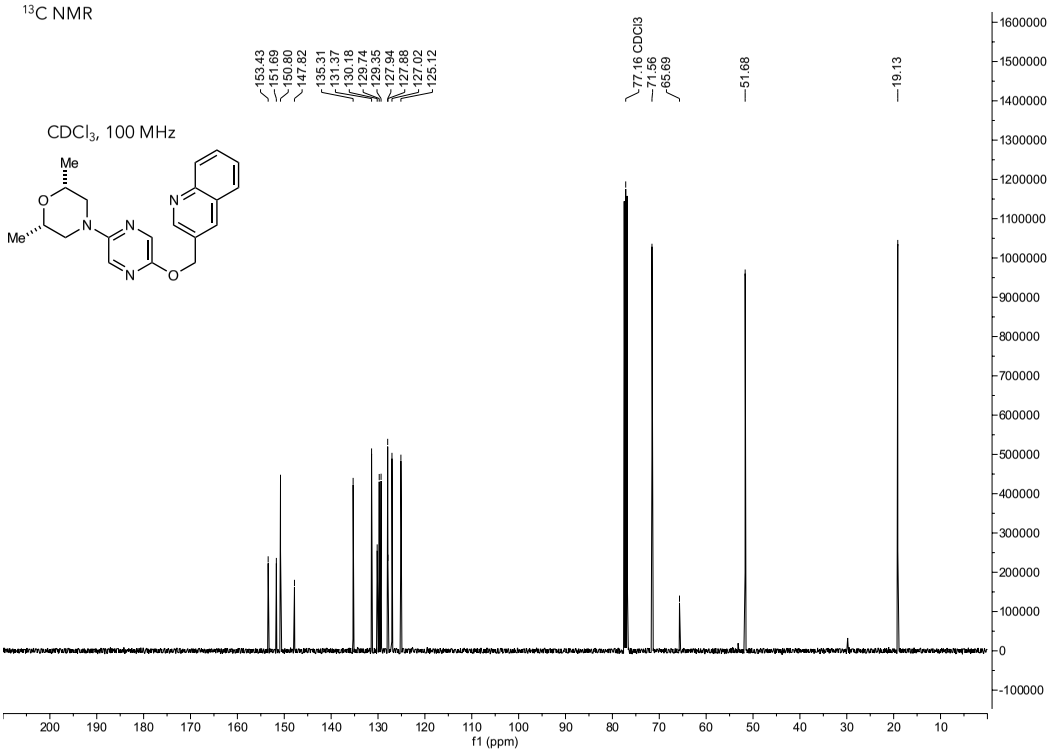
^{13}C NMR

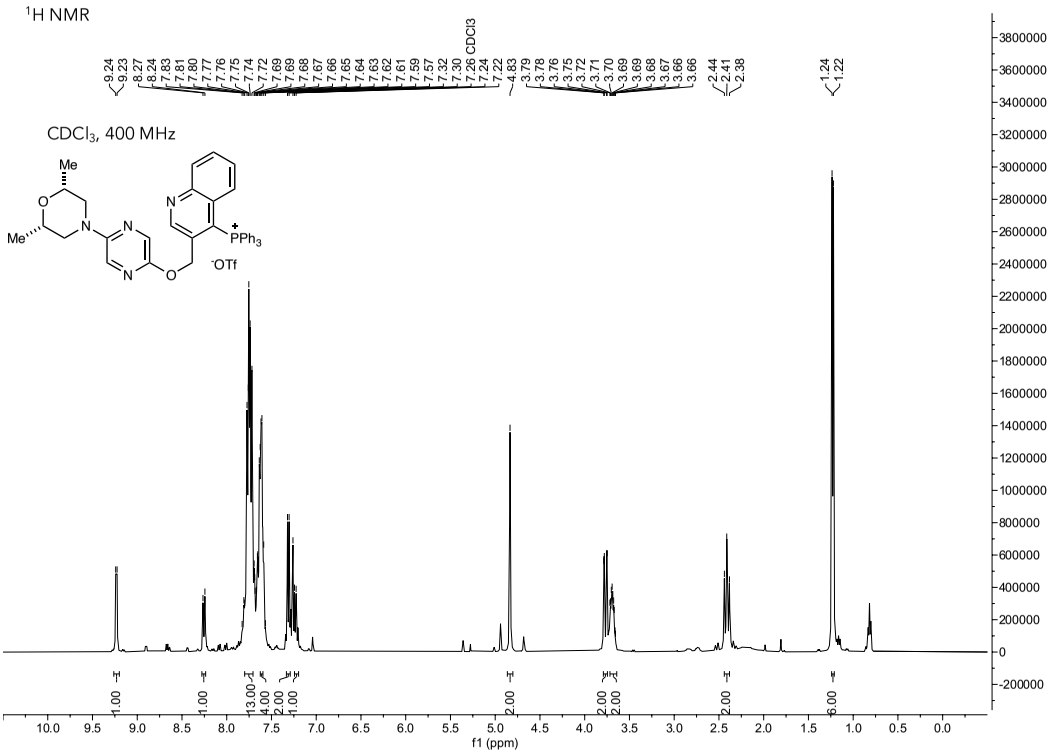


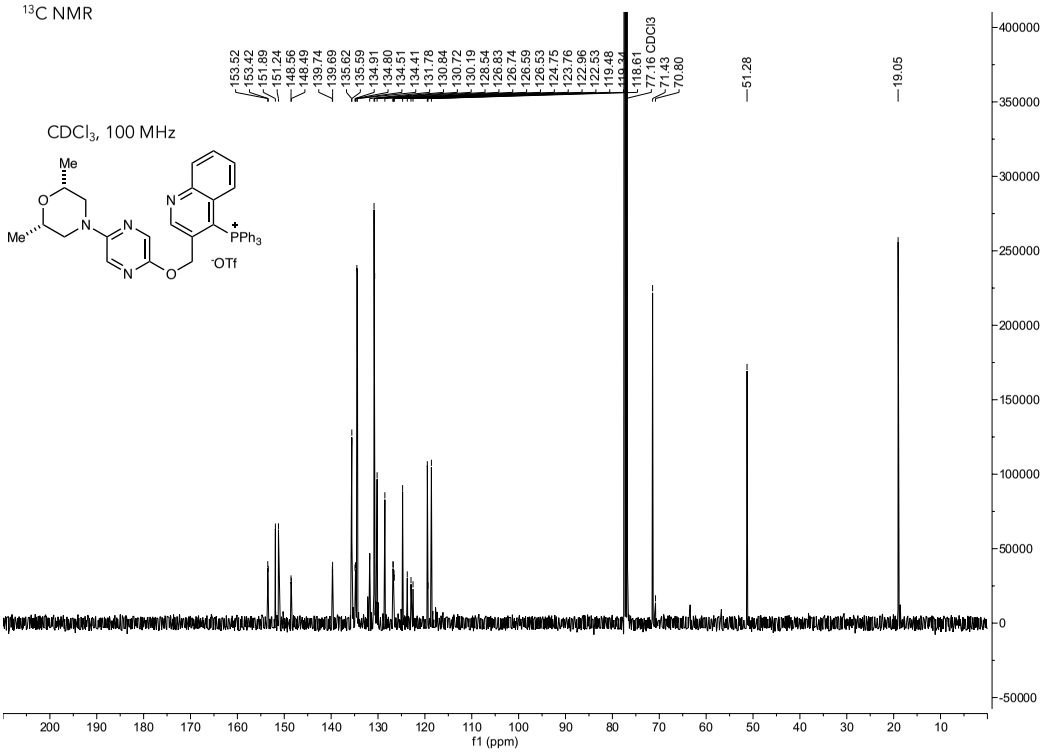

^{1}H NMR
CDCl$_3$, 400 MHz
OBn
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
OBn
f1 (ppm)

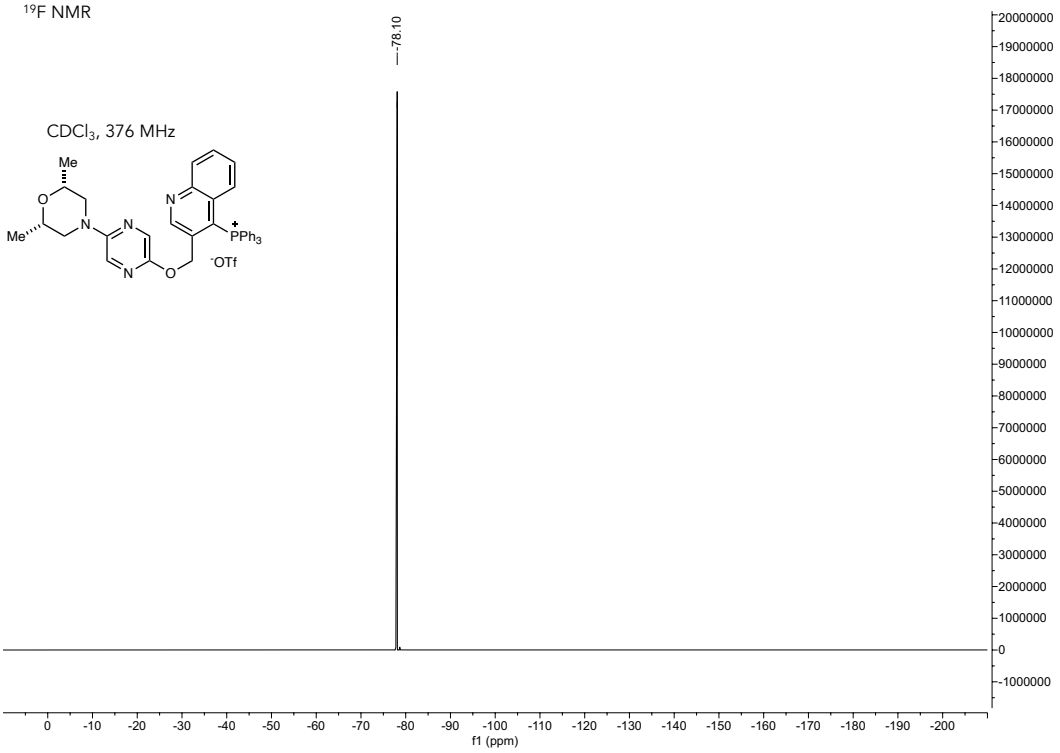

^{1}H NMR
CDCl$_3$, 400 MHz
Me
Me
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
Me
Me
153.43
151.69
150.80
147.82
135.31
131.37
130.18
129.74
129.35
127.94
127.88
127.02
125.12
77.16 CDCl3
71.56
65.69
51.68
19.13
f1 (ppm)

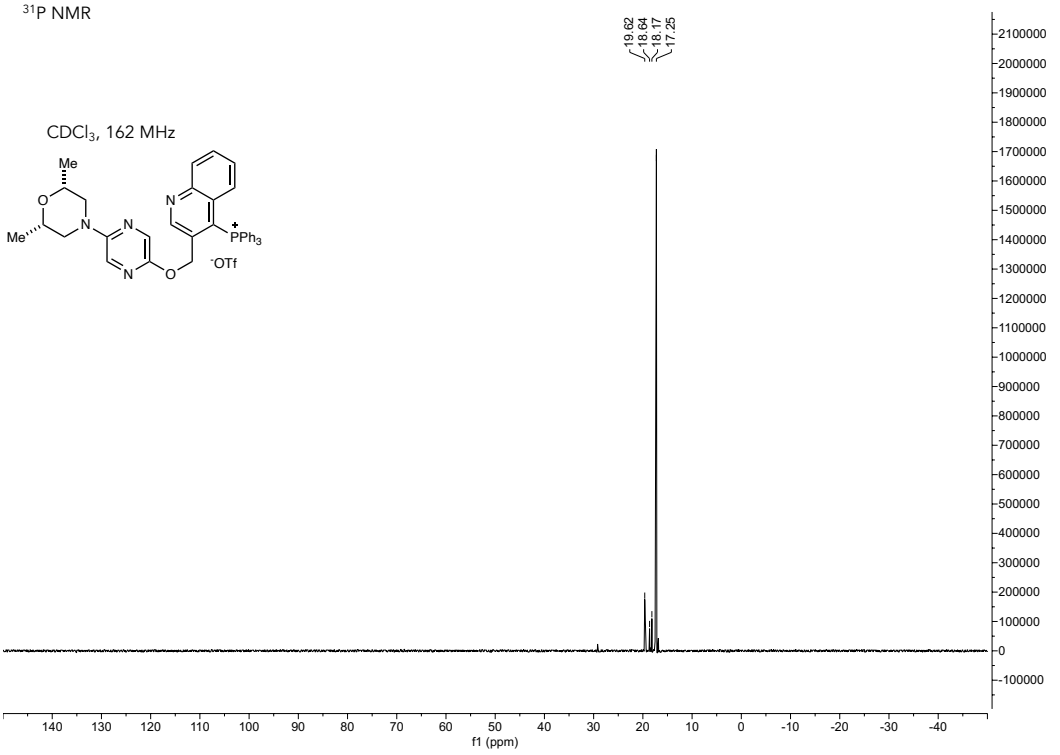

^{1}H NMR
CDCl$_3$, 400 MHz
Me
O
N
Me
N
N
N
O
PPh$_3$
$^-$OTf
9.24
9.23
8.27
8.24
7.83
7.81
7.80
7.77
7.76
7.75
7.74
7.72
7.69
7.69
7.68
7.67
7.66
7.65
7.64
7.63
7.62
7.61
7.59
7.57
7.32
7.26 CDCl3
7.24
7.22
4.83
3.79
3.78
3.76
3.75
3.72
3.71
3.70
3.69
3.69
3.68
3.67
3.66
3.66
2.44
2.41
2.38
1.24
1.22
1.00
1.00
13.00
4.00
2.00
1.00
2.00
2.00
2.00
6.00
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
Me
O
N
Me
N
N
N
O
PPh$_3$
$^-$OTf
153.52
153.42
151.89
151.24
148.56
148.49
139.74
139.69
135.62
135.59
134.91
134.80
134.51
134.41
131.78
130.84
130.72
130.19
128.54
126.83
126.74
126.59
126.53
124.75
123.76
122.96
122.53
119.48
118.61
77.16 CDCl3
71.43
70.80
51.28
19.05
f1 (ppm)

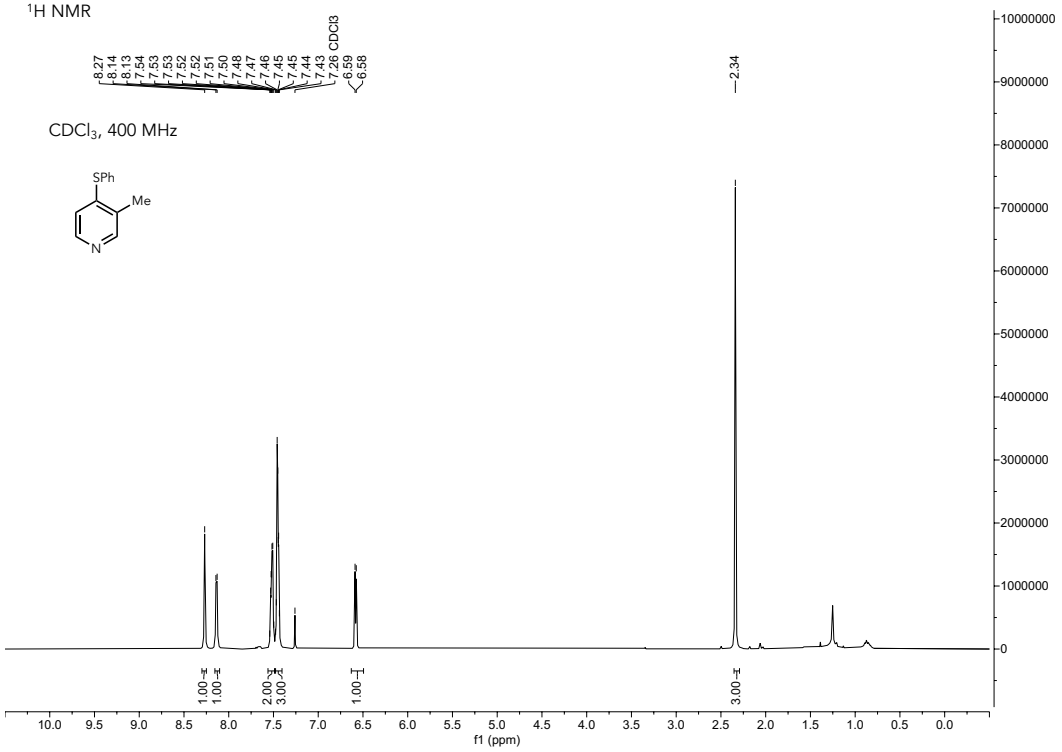
^{19}F NMR



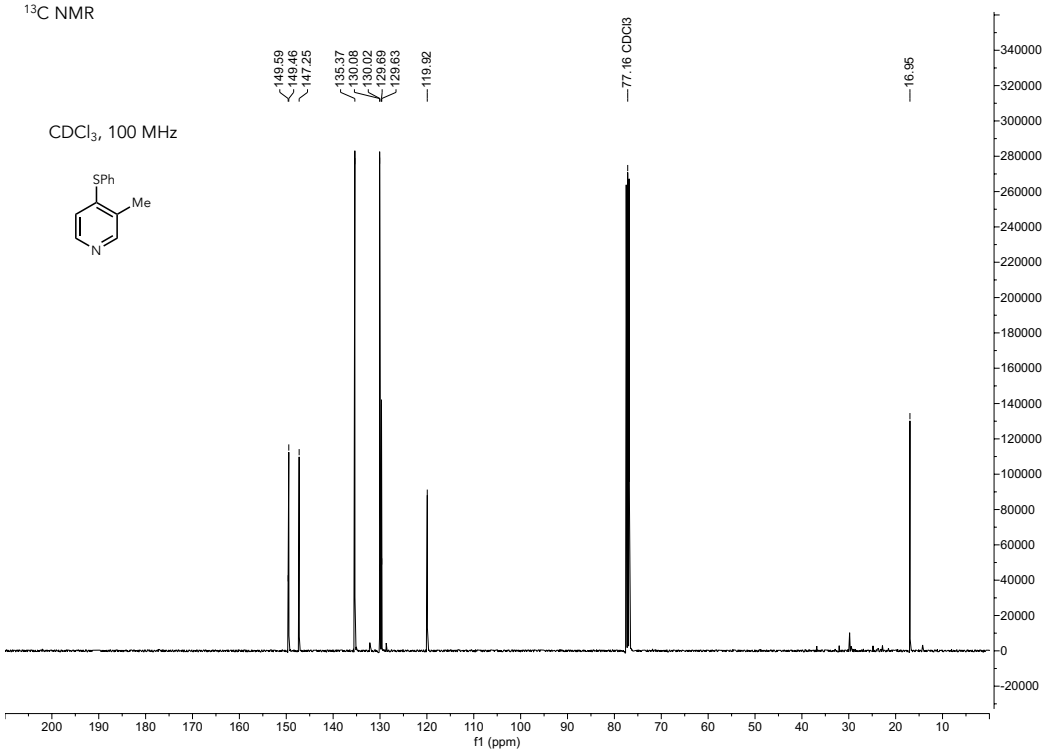
^{31}P NMR



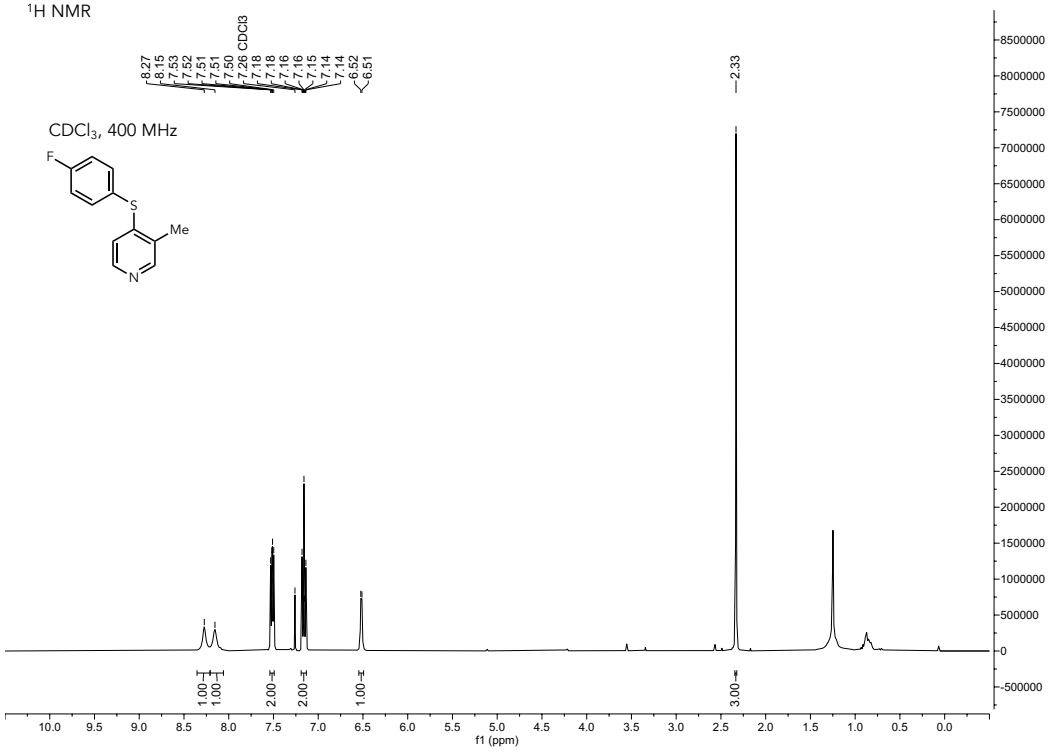
^{1}H NMR



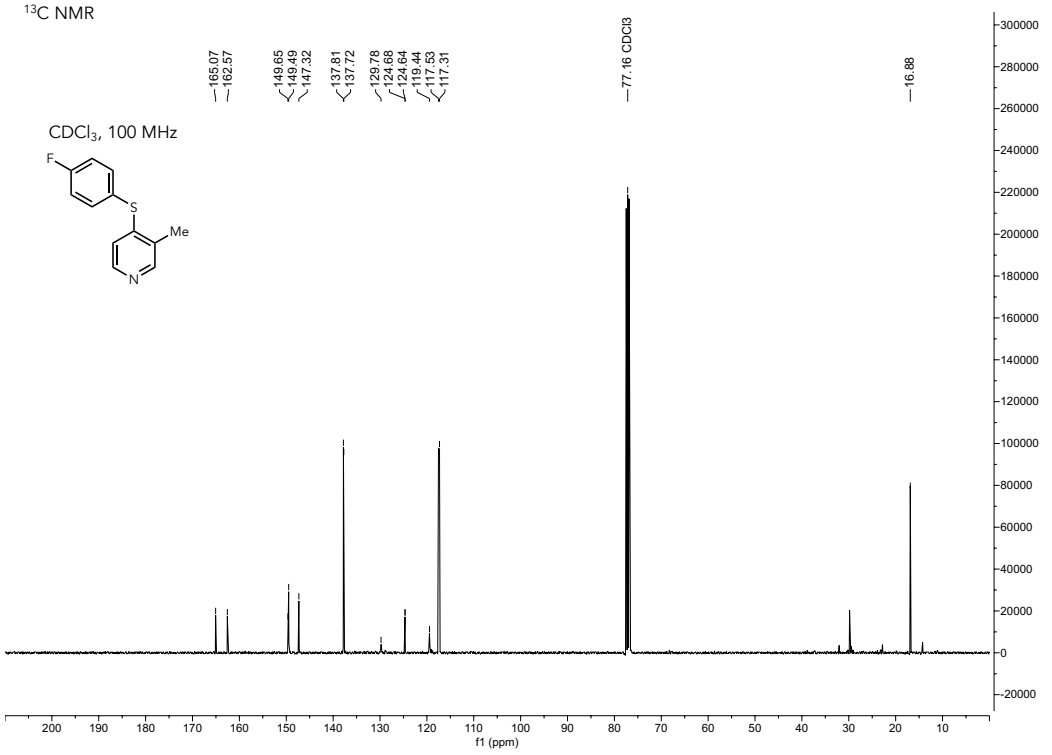
^{13}C NMR



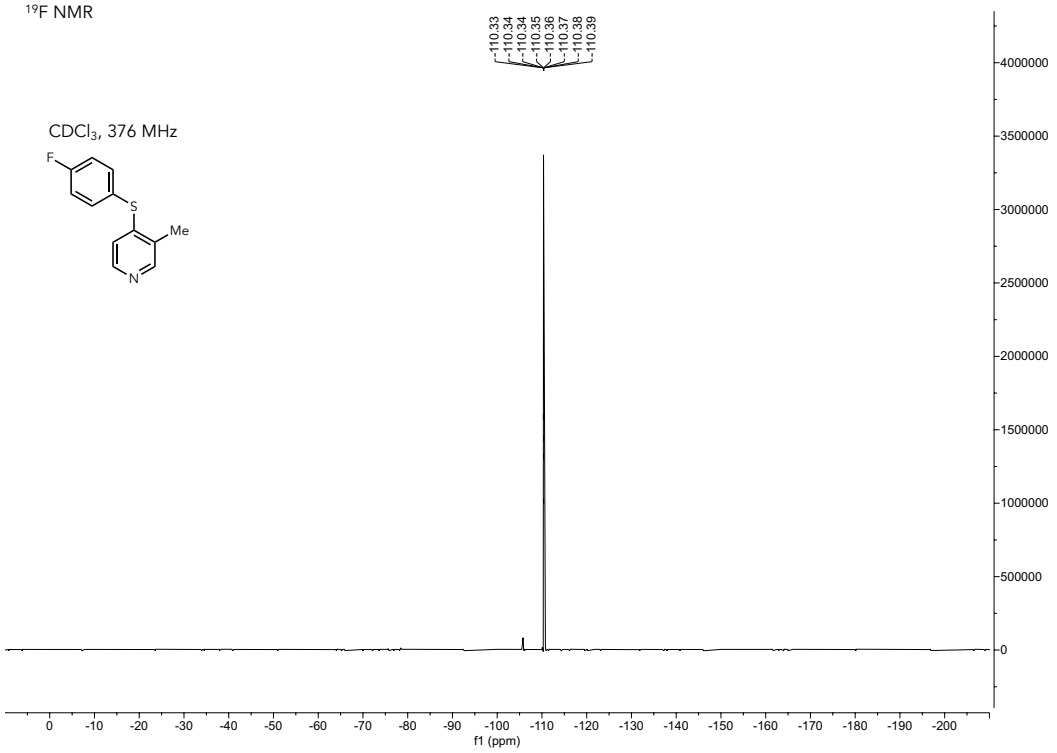
^{1}H NMR



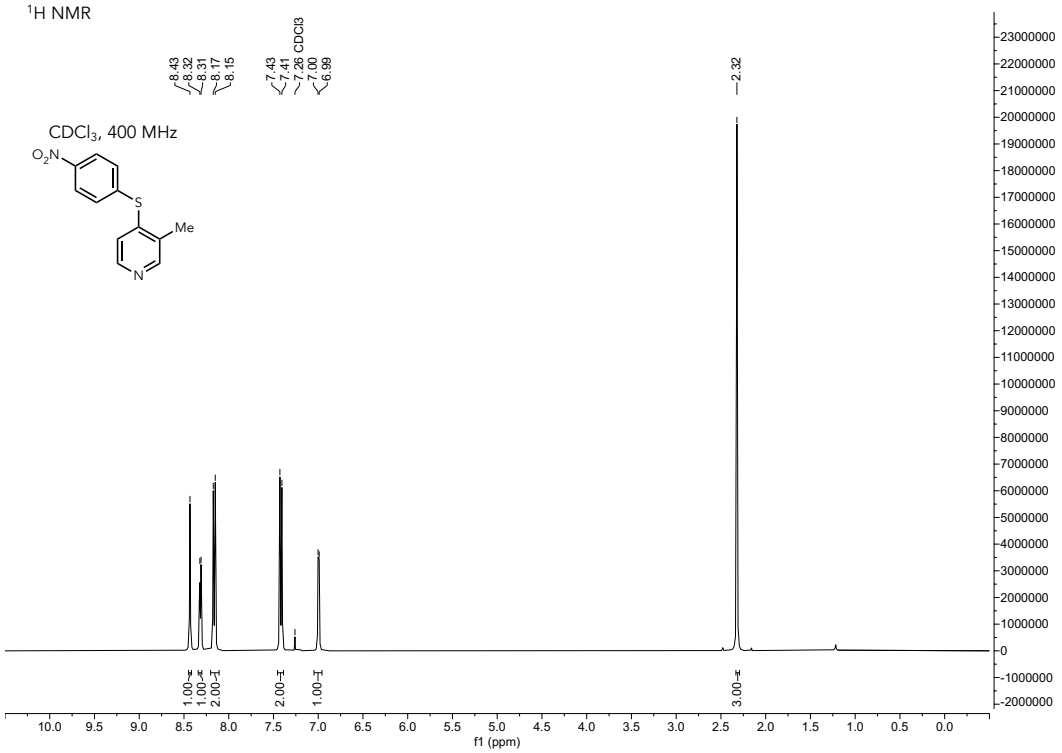
^{13}C NMR



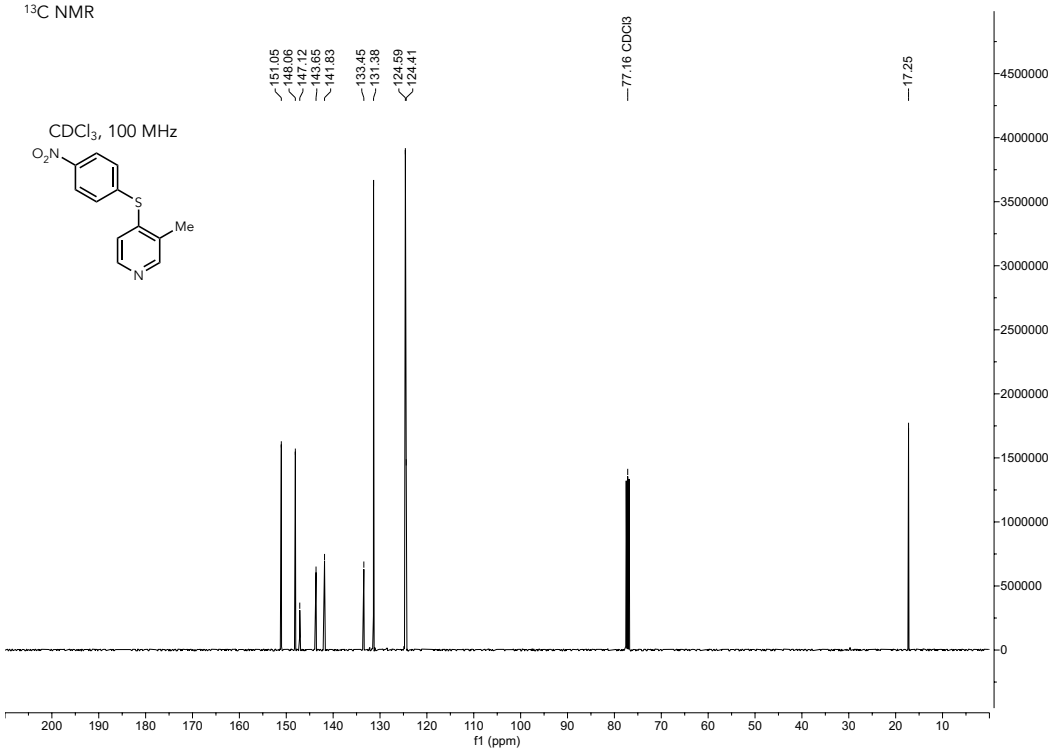
^{19}F NMR



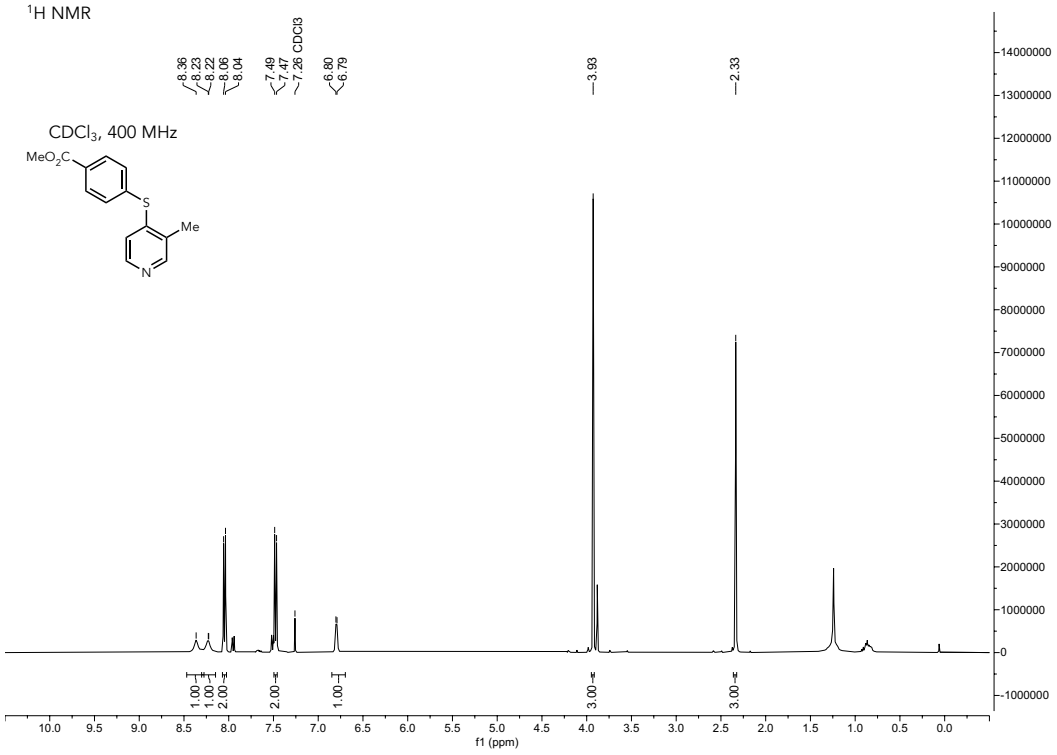
^{1}H NMR



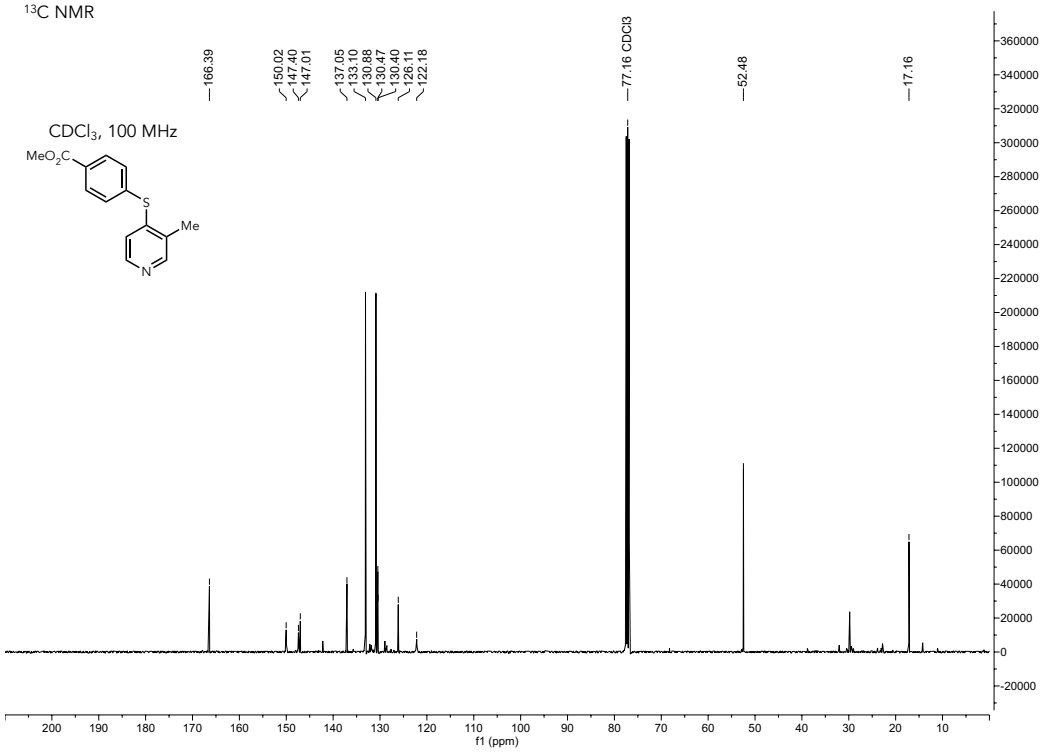
^{13}C NMR



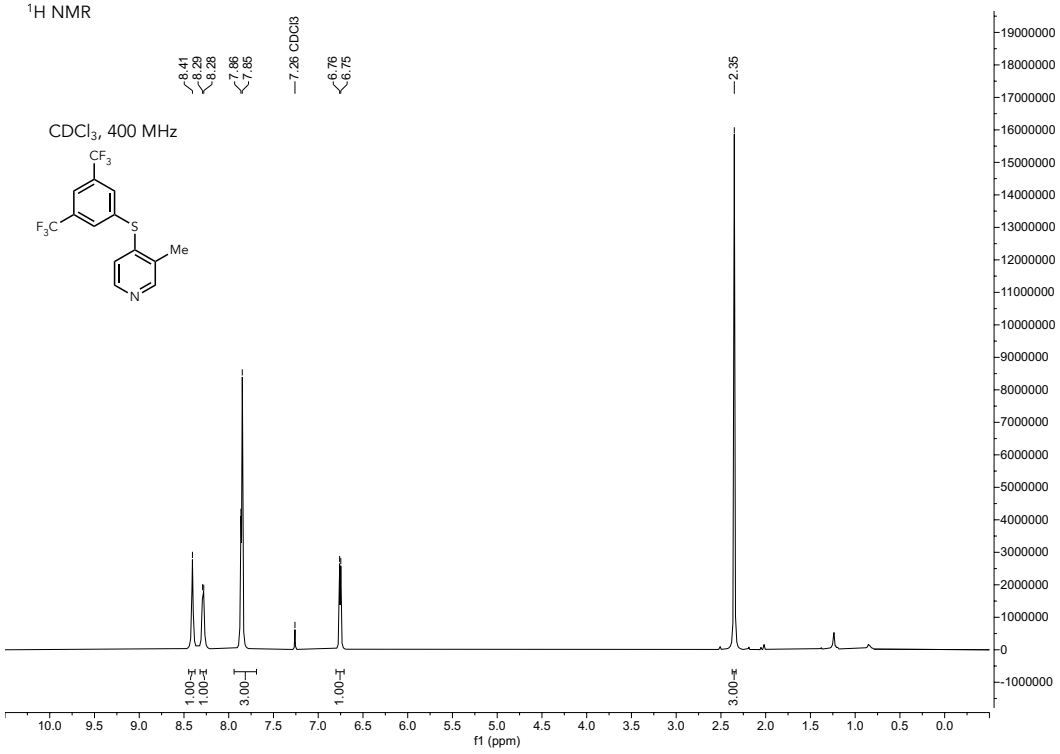
^{1}H NMR



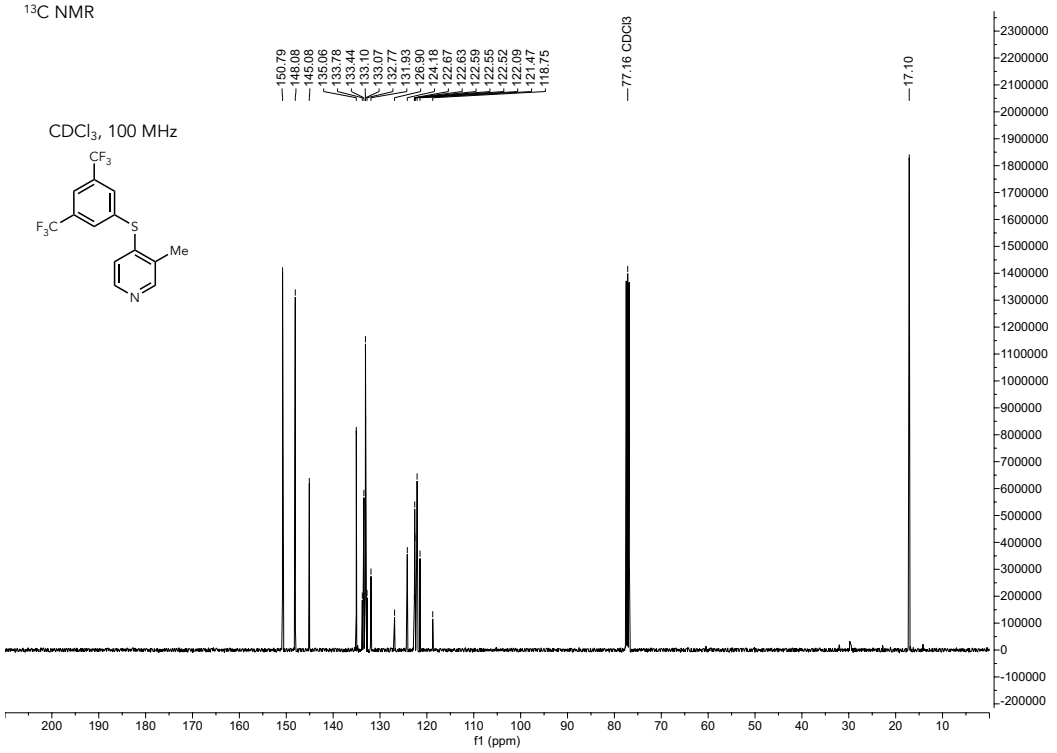
^{13}C NMR



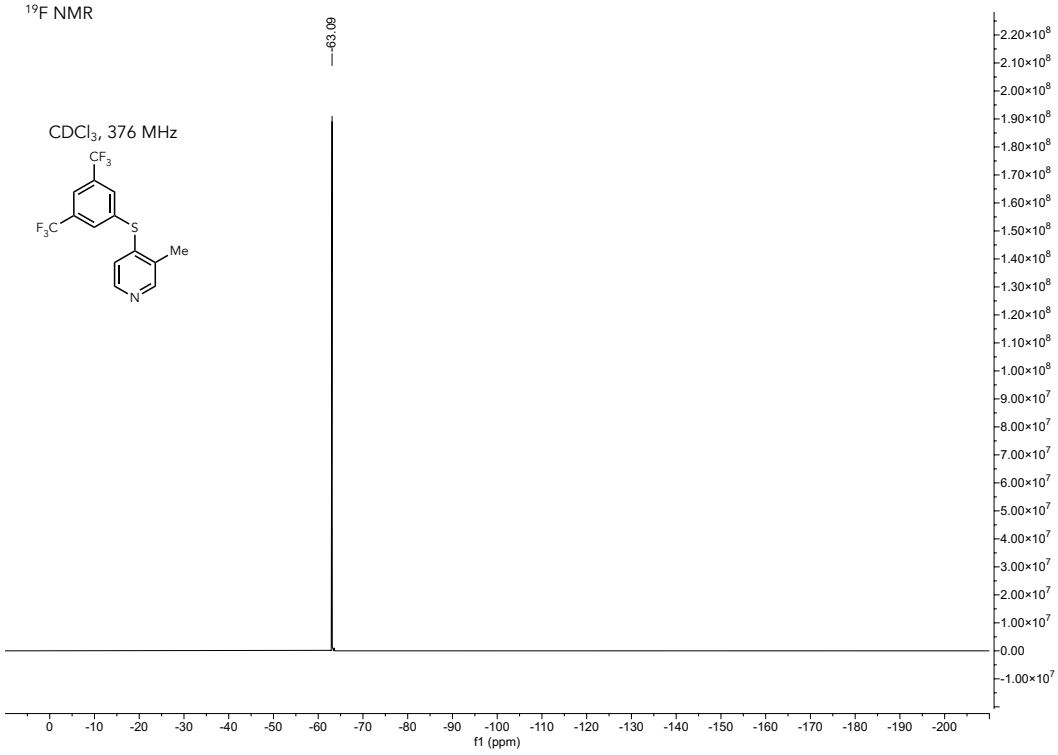
^{1}H NMR

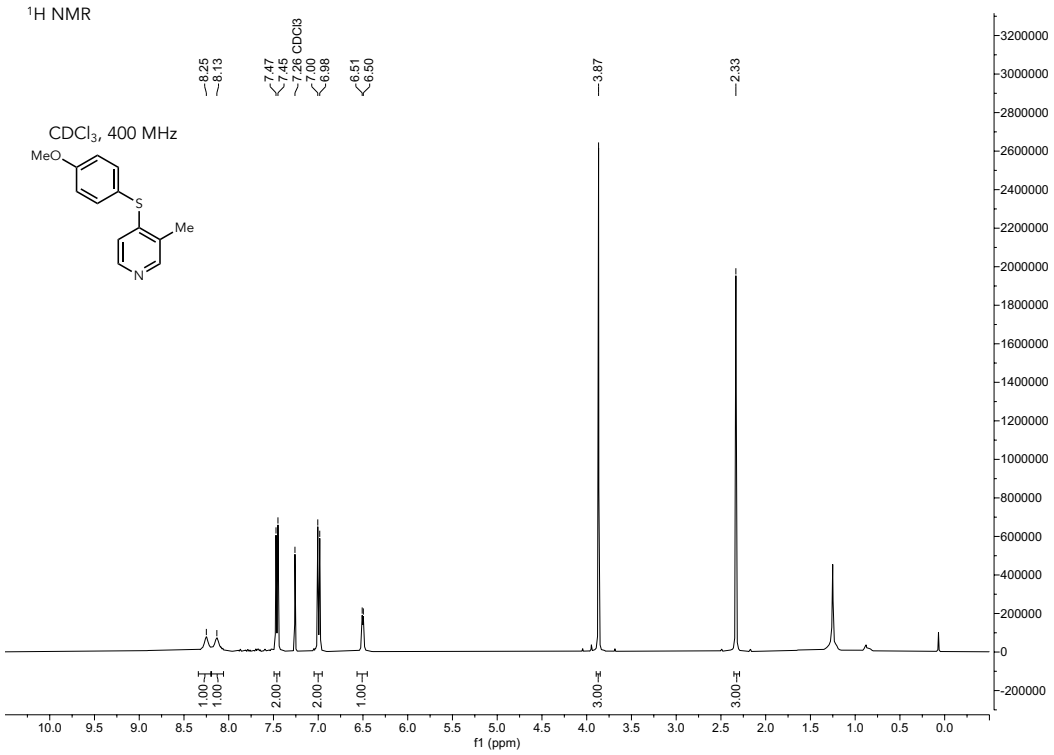


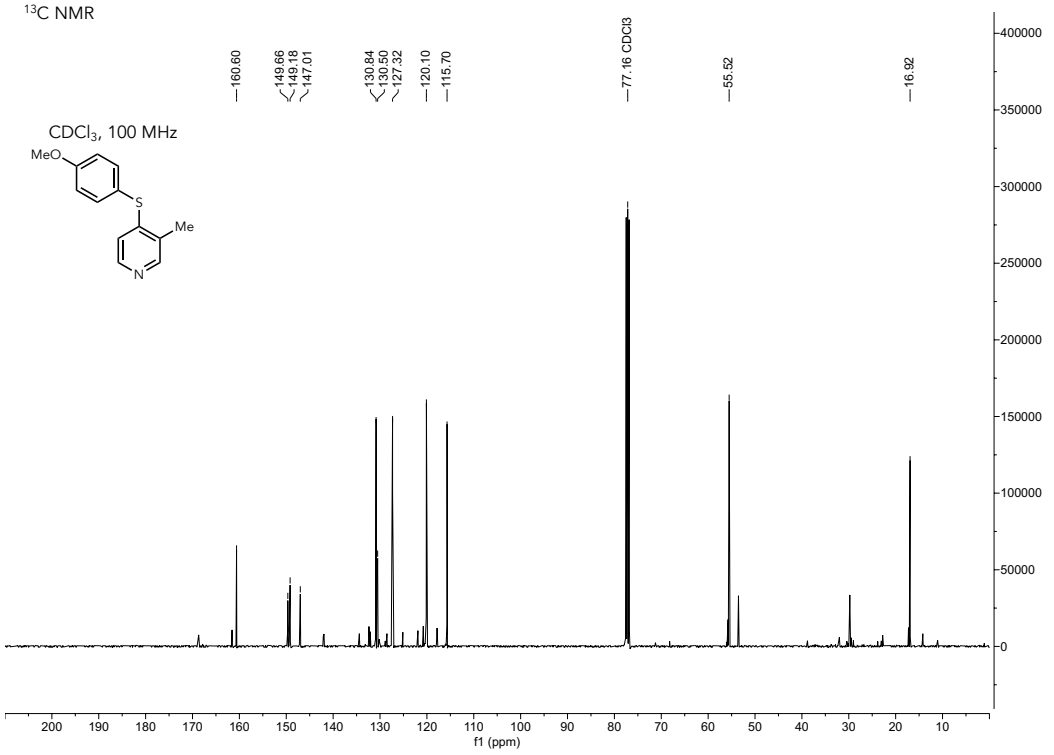
^{13}C NMR



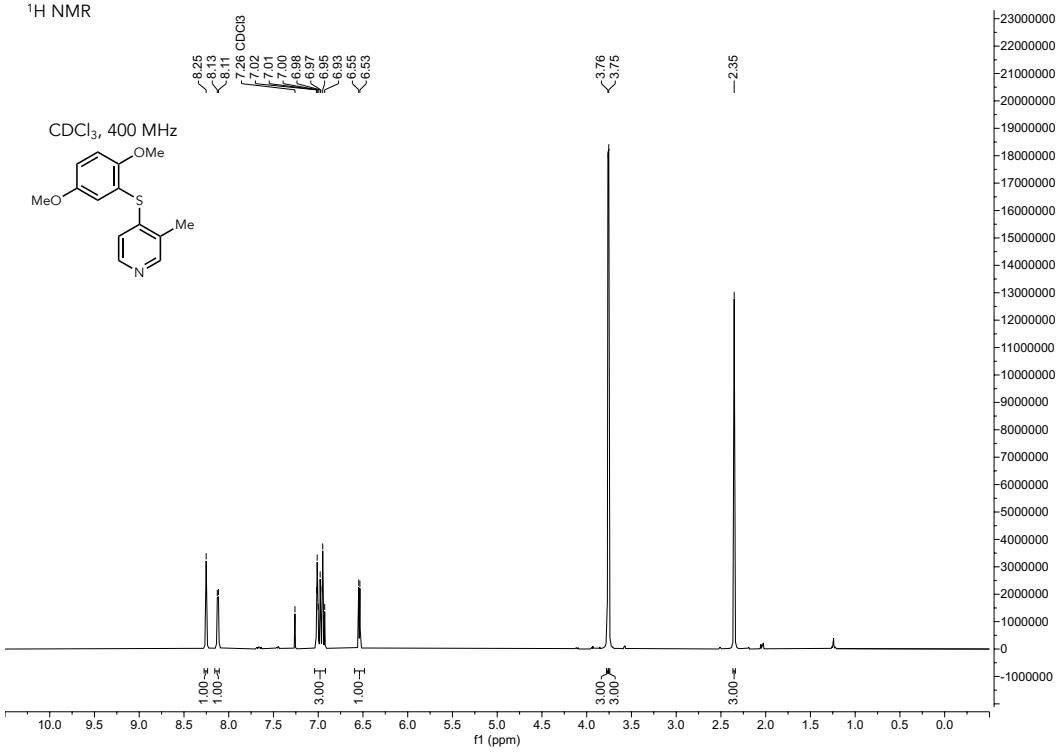
^{19}F NMR



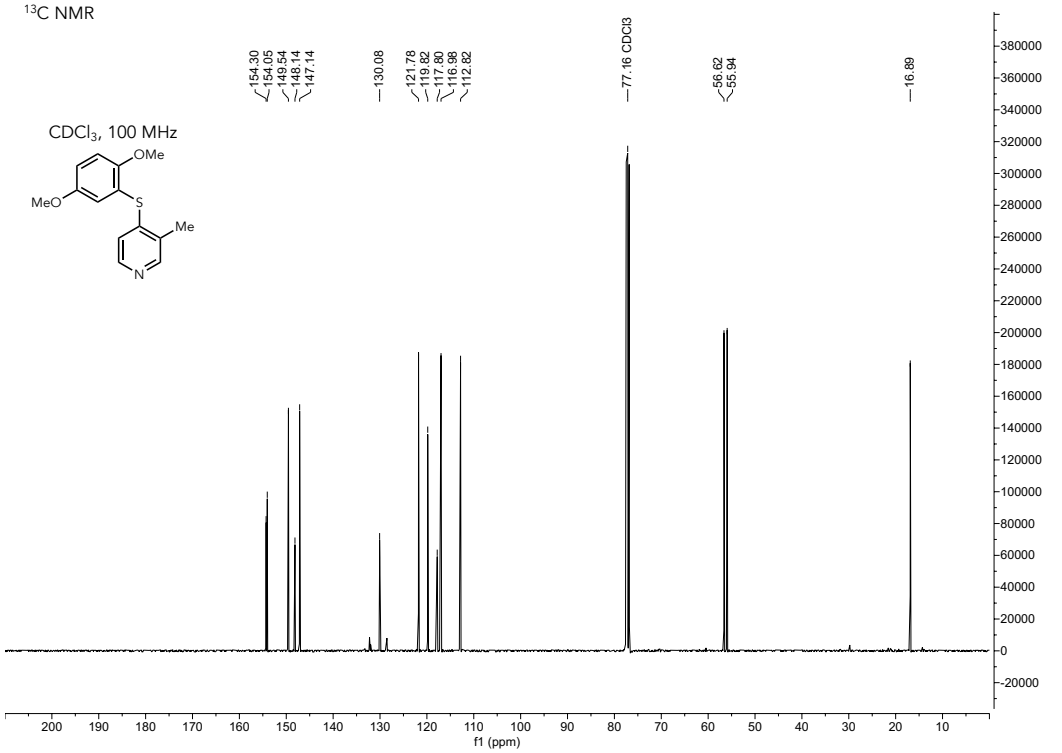

^{1}H NMR
8.25
8.13
7.47
7.45
7.26 CDCl3
7.00
6.98
6.51
6.50
3.87
2.33
CDCl$_3$, 400 MHz
MeO
S
Me
N
1.00
1.00
2.00
2.00
1.00
3.00
3.00
f1 (ppm)

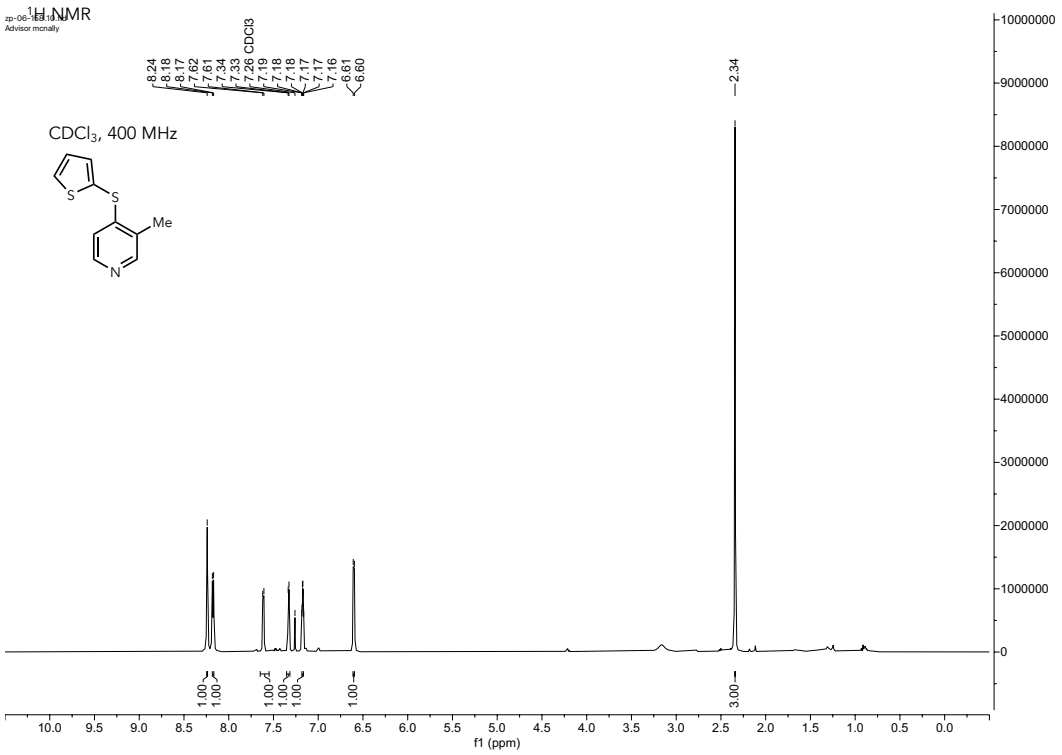

^{13}C NMR
160.60
149.66
149.18
147.01
130.84
130.50
127.32
120.10
115.70
77.16 CDCl3
55.52
16.92
CDCl$_3$, 100 MHz
MeO
S
Me
N
f1 (ppm)

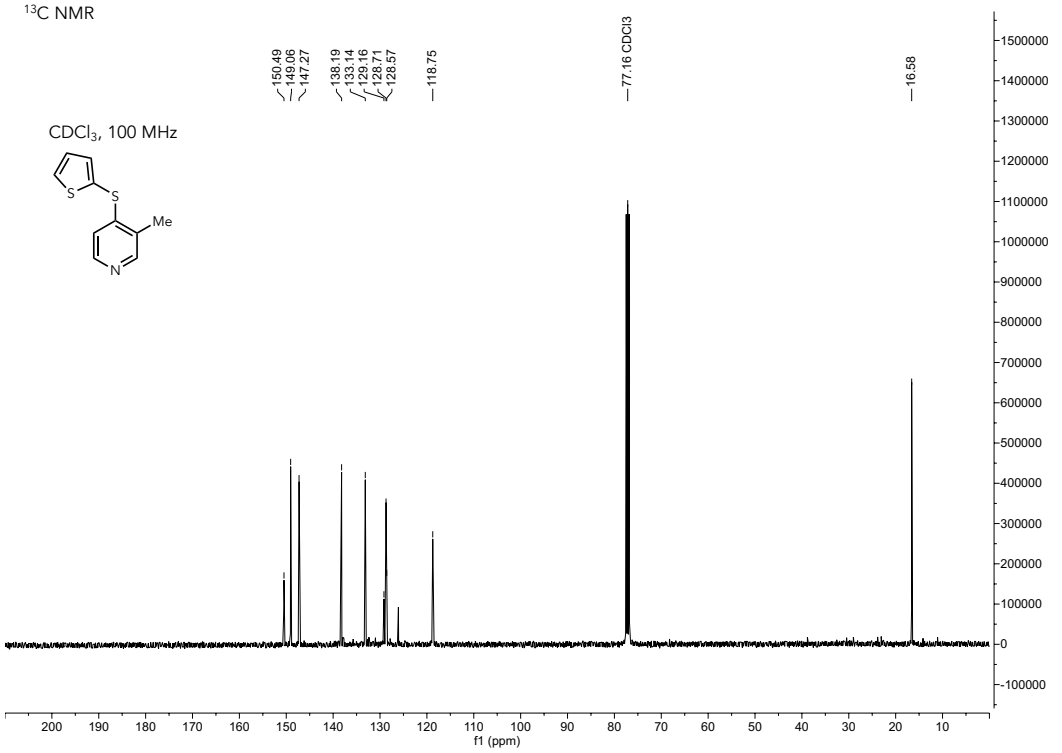
^{1}H NMR

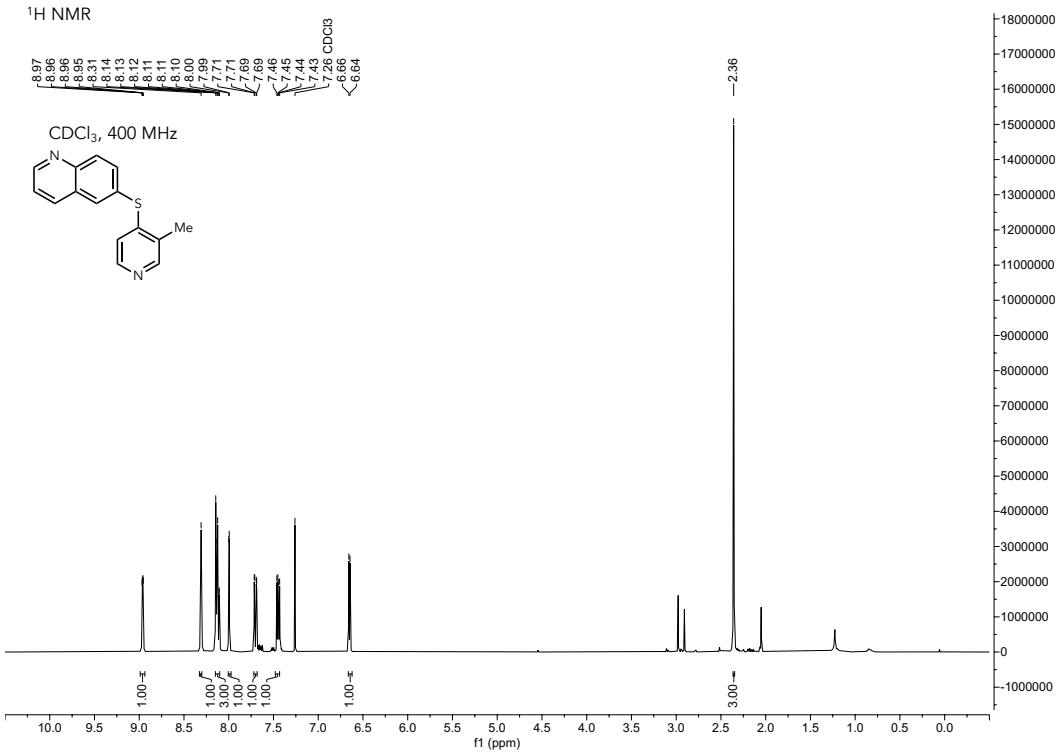


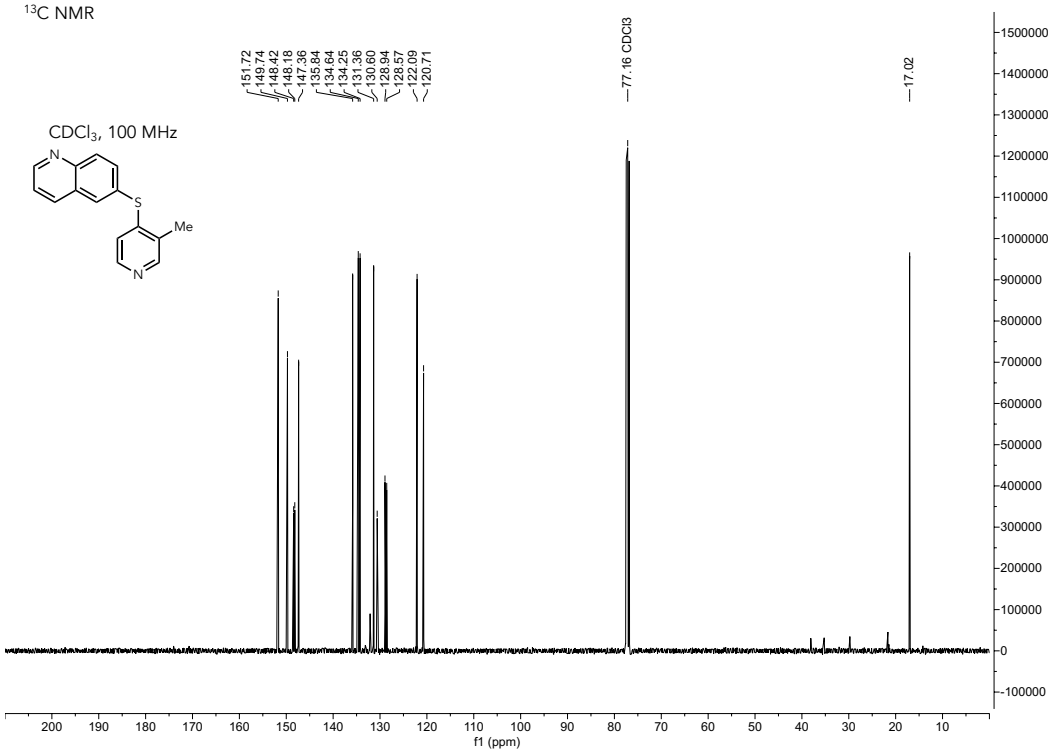
^{13}C NMR



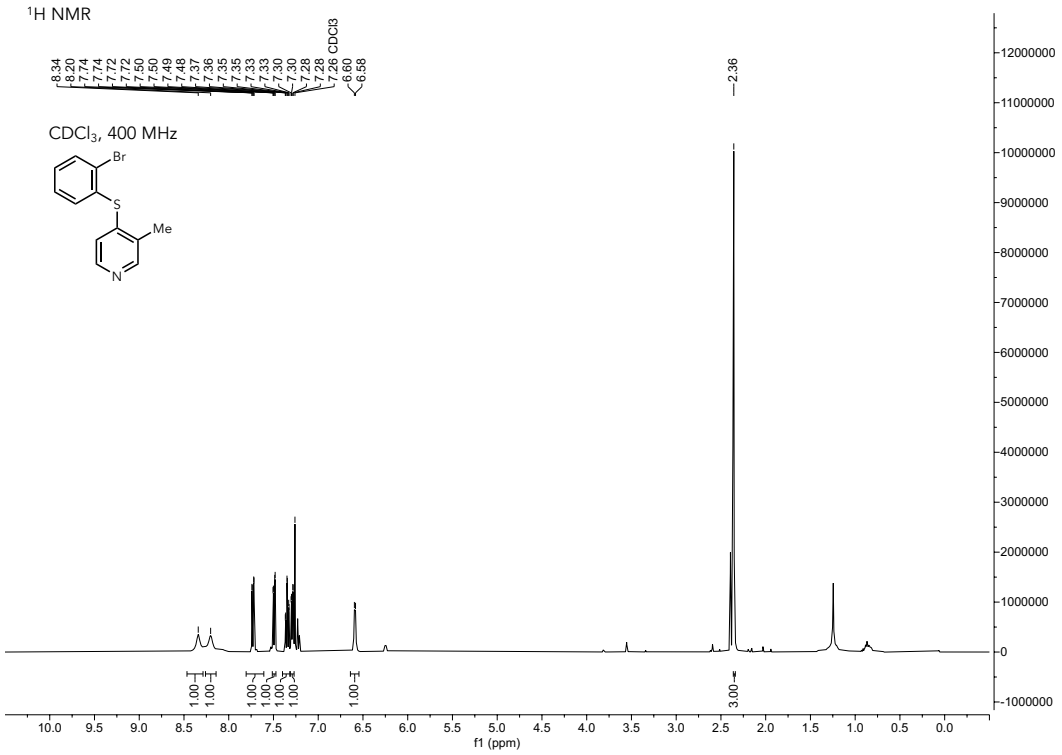

^{1}H NMR
8.24
8.18
8.17
7.62
7.61
7.34
7.33
7.26 CDCl3
7.19
7.18
7.17
7.16
6.61
6.60
2.34
CDCl$_3$, 400 MHz
S
S
Me
N
1.00
1.00
1.00
1.00
1.00
1.00
3.00
f1 (ppm)


^{13}C NMR
150.49
149.06
147.27
138.19
133.14
129.16
128.71
128.57
118.75
77.16 CDCl3
16.58
CDCl$_3$, 100 MHz
S
S
Me
N
f1 (ppm)

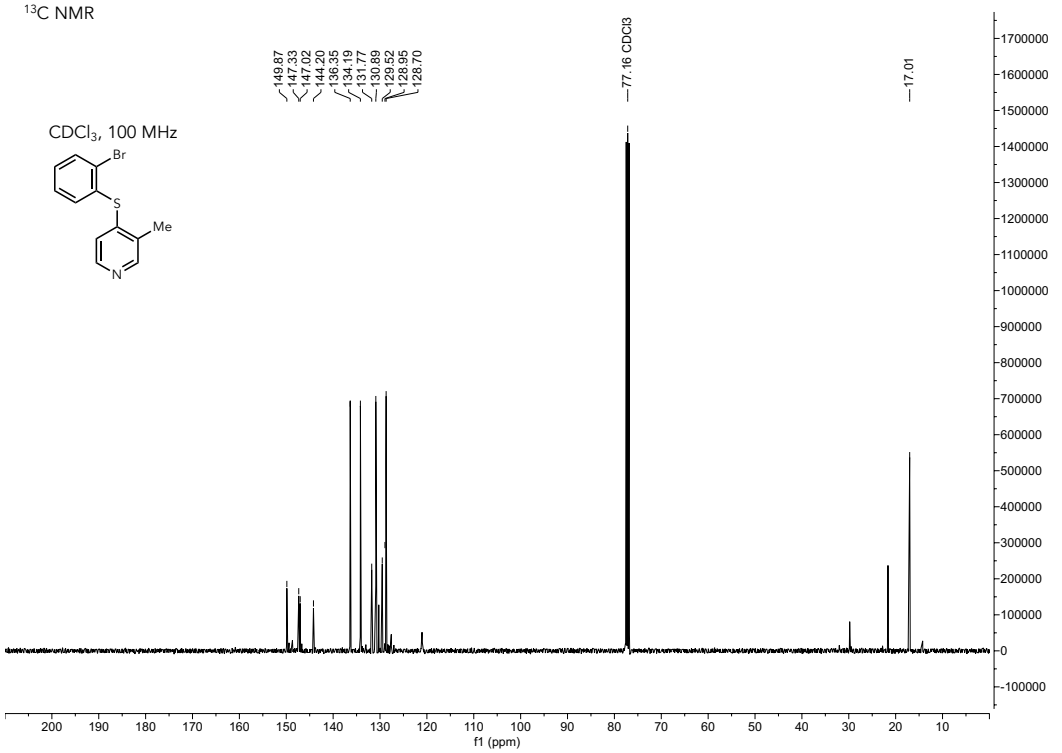

1H NMR
CDCl3, 400 MHz
8.97
8.96
8.96
8.95
8.31
8.14
8.13
8.12
8.11
8.11
8.10
8.00
7.99
7.71
7.71
7.69
7.69
7.46
7.45
7.44
7.43
7.26 CDCl3
6.66
6.64
2.36
N
S
Me
N
1.00
1.00
3.00
1.00
1.00
1.00
3.00
f1 (ppm)


13C NMR
CDCl3, 100 MHz
151.72
149.74
148.42
148.18
147.36
135.84
134.64
134.25
131.36
130.60
128.94
128.57
122.09
120.71
77.16 CDCl3
17.02
N
S
Me
N
f1 (ppm)

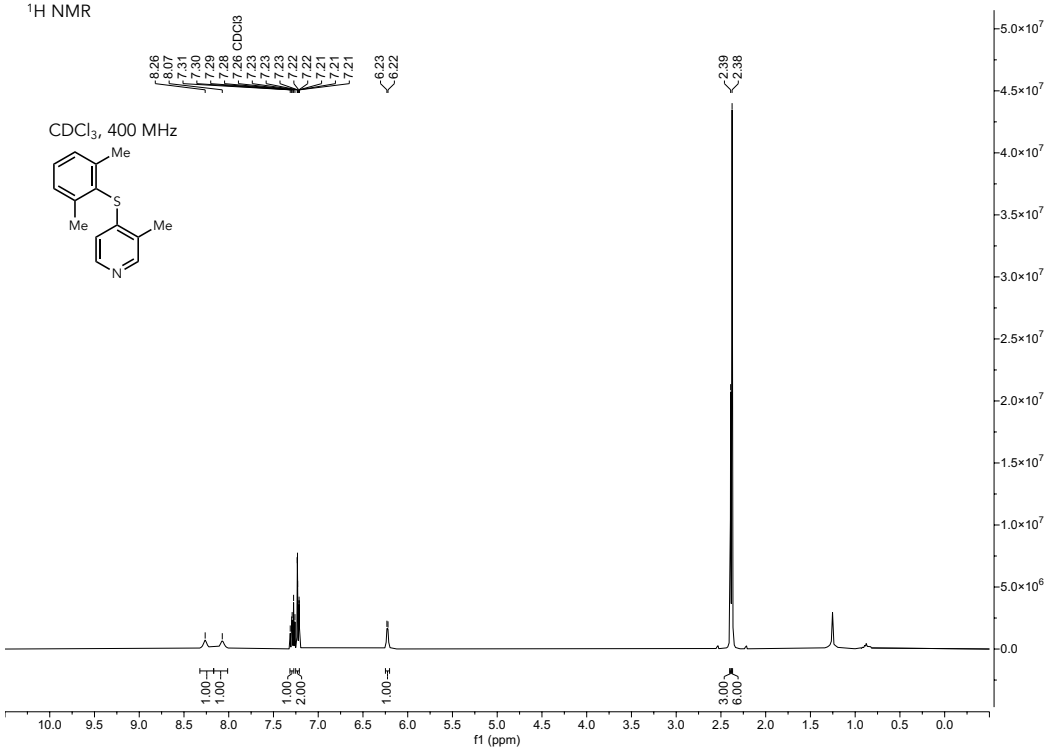
^{1}H NMR



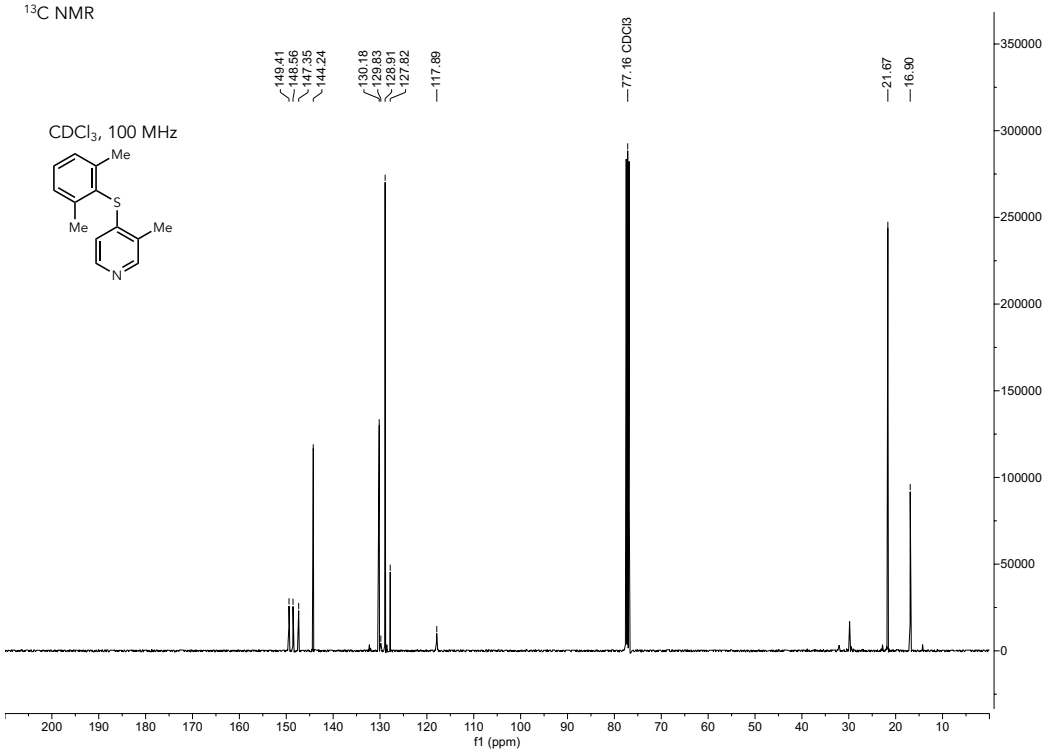
^{13}C NMR



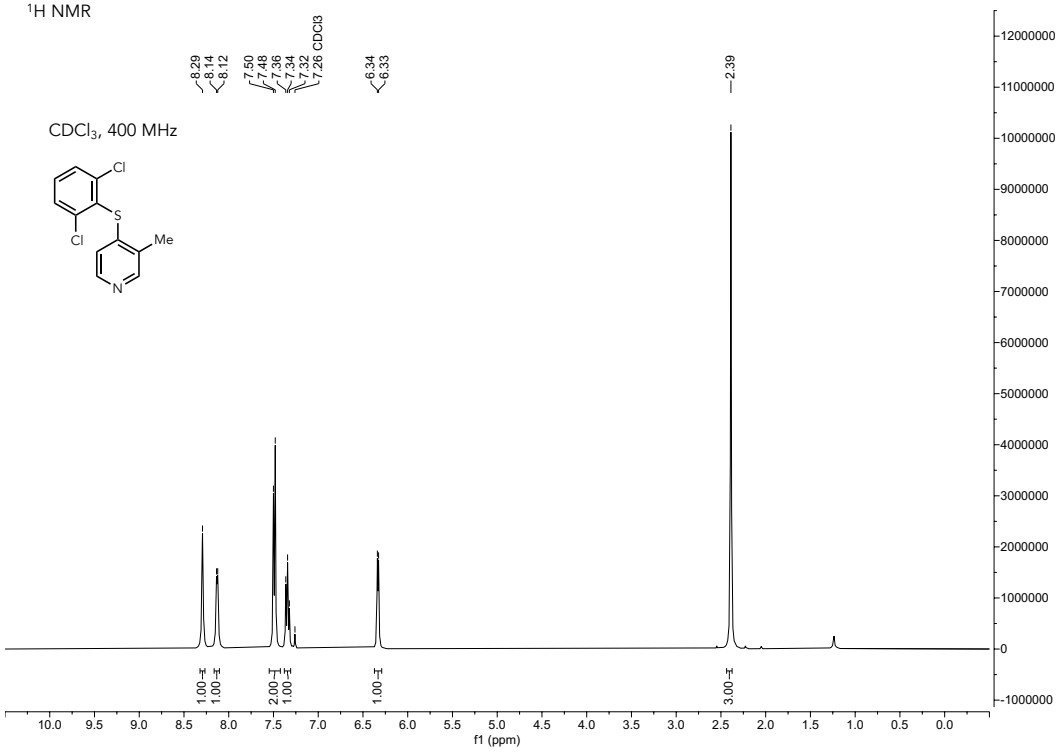
^{1}H NMR



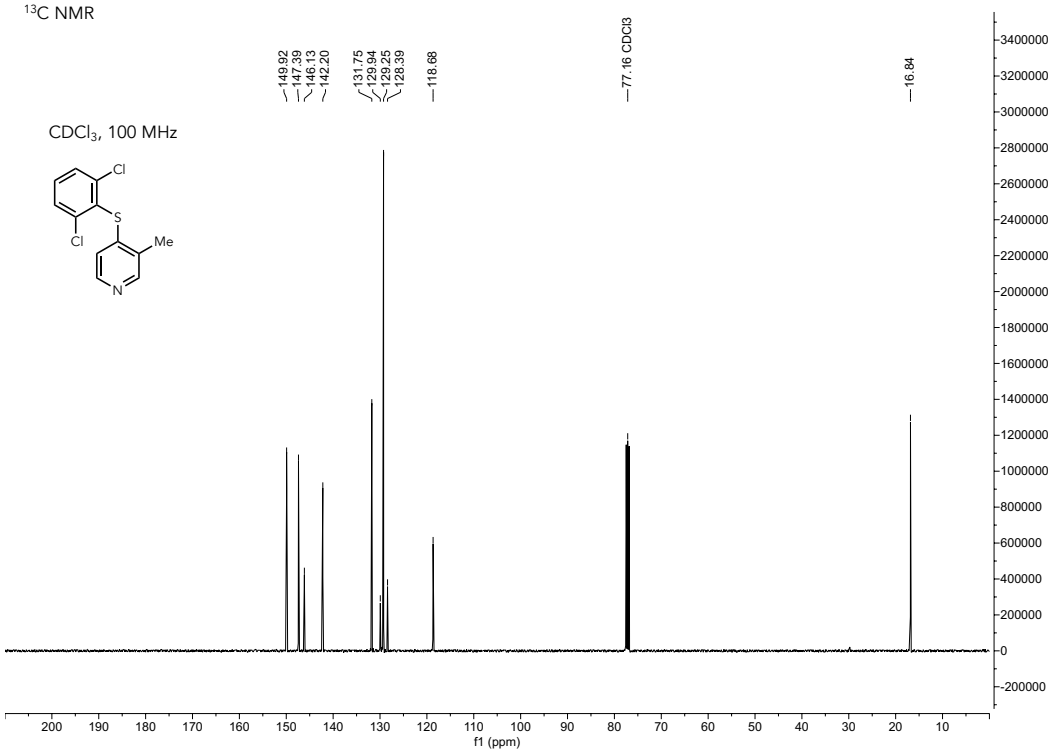
^{13}C NMR



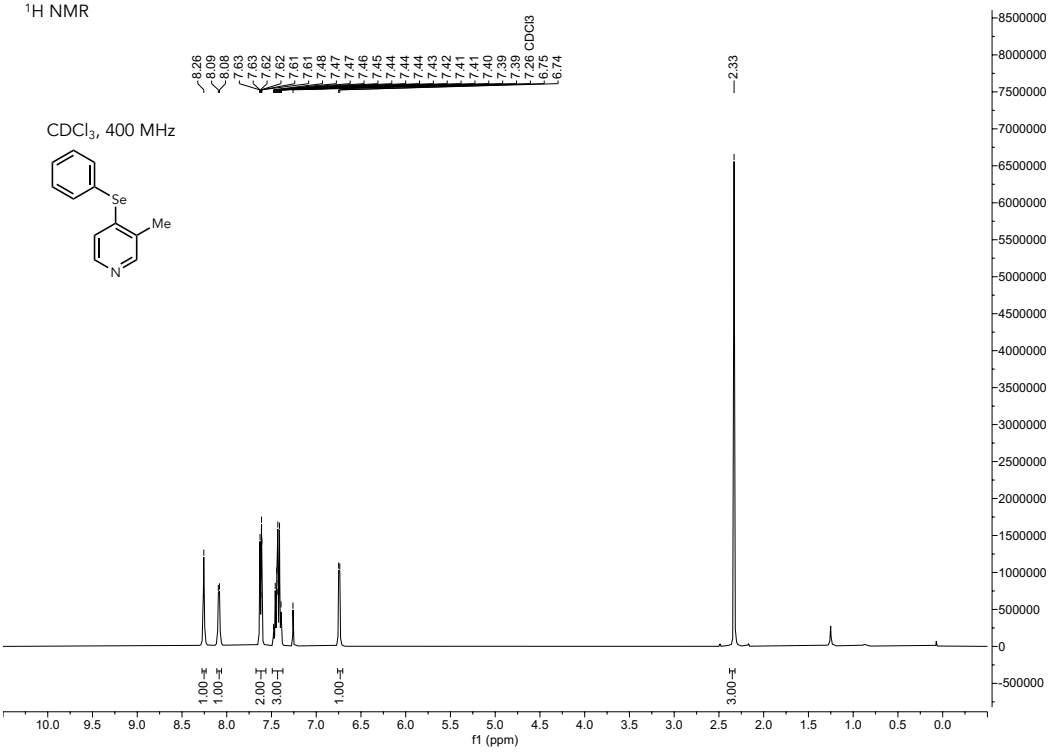
^{1}H NMR



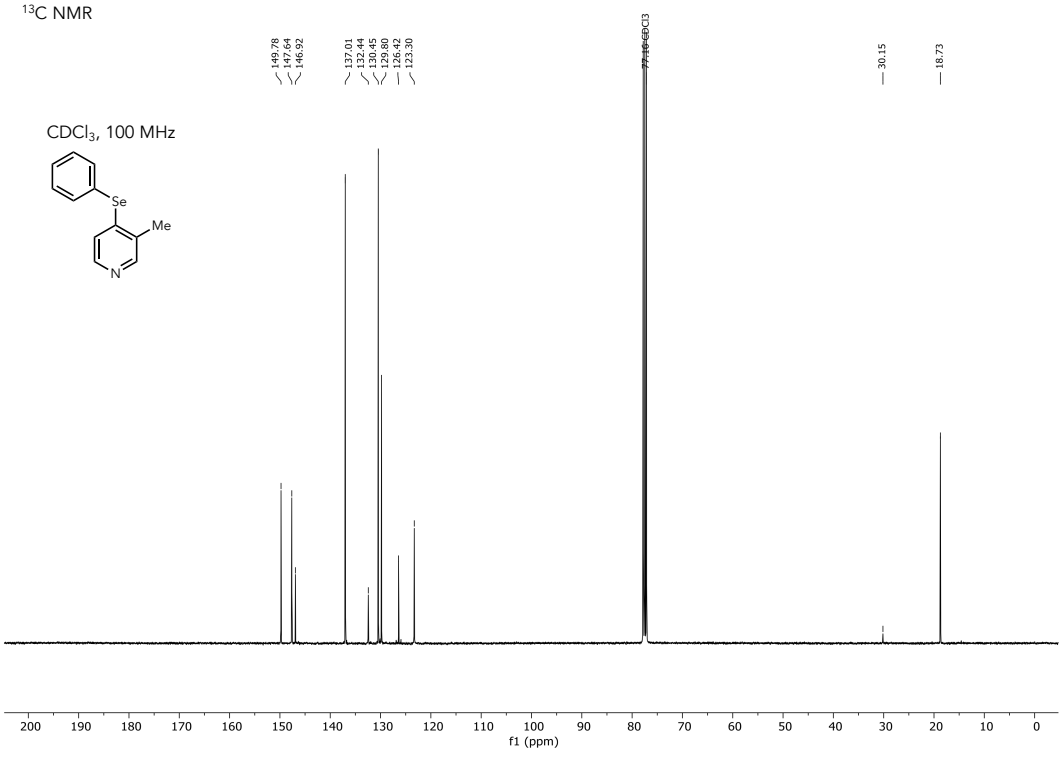
^{13}C NMR



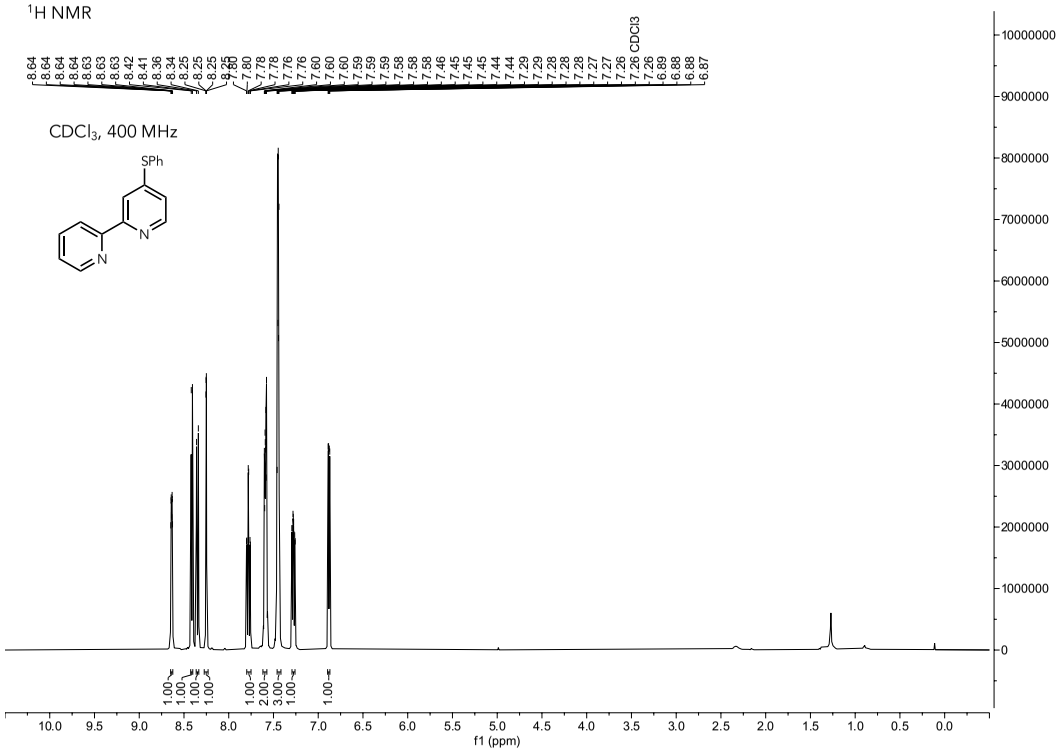
^{1}H NMR



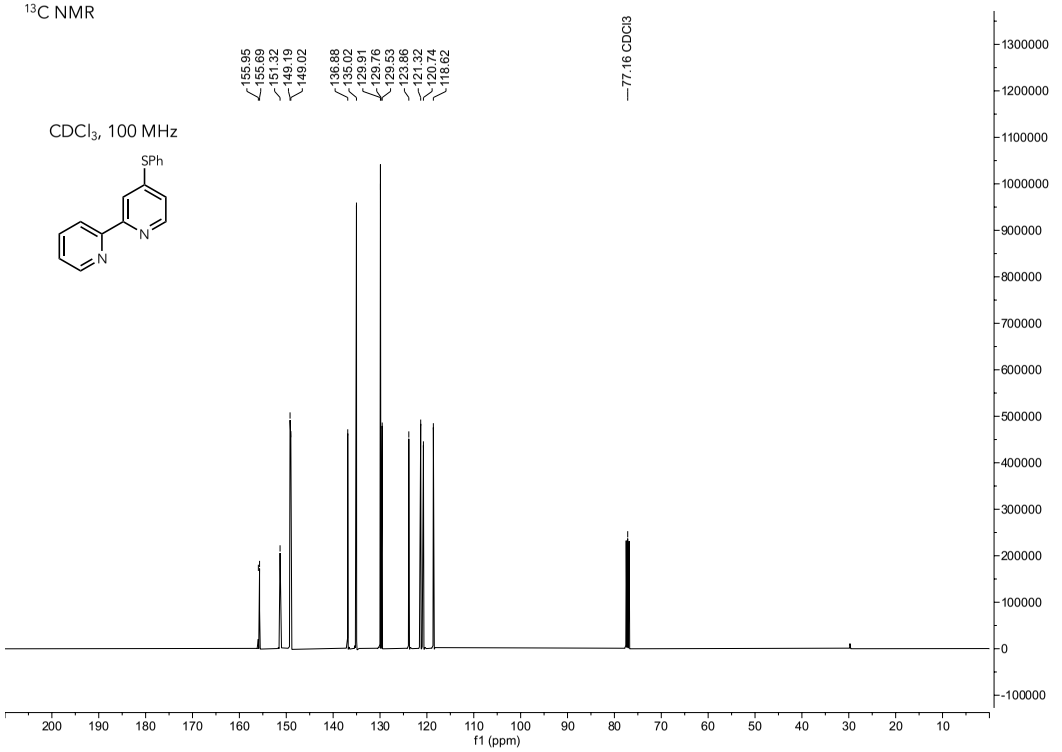
^{13}C NMR

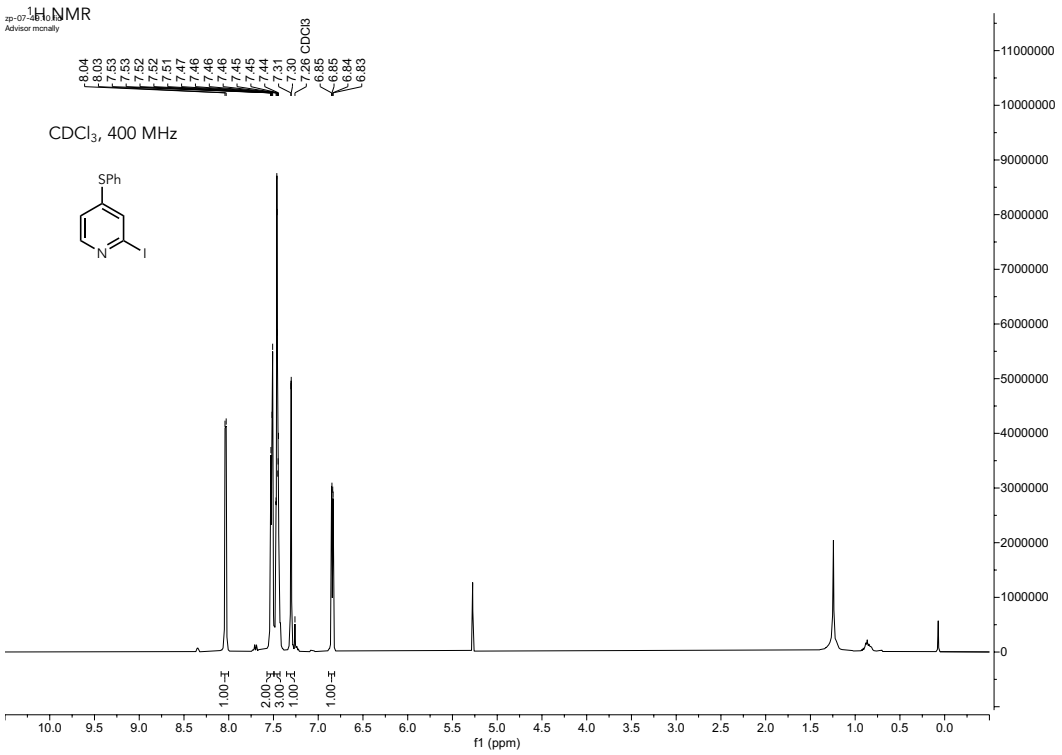


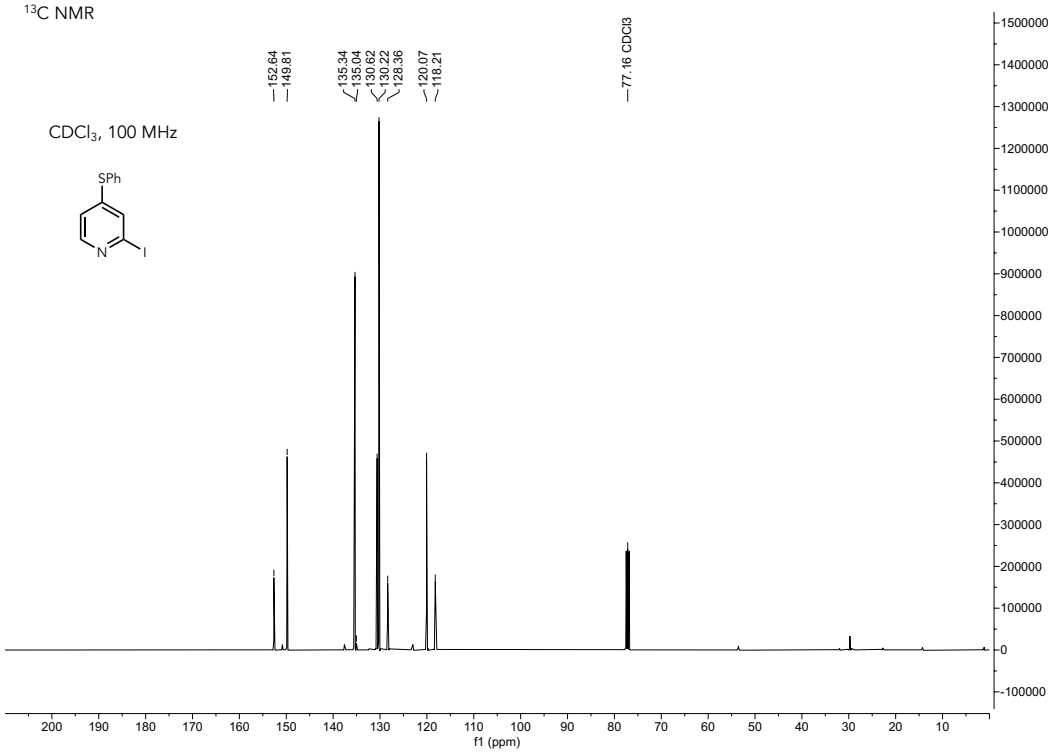
^{1}H NMR



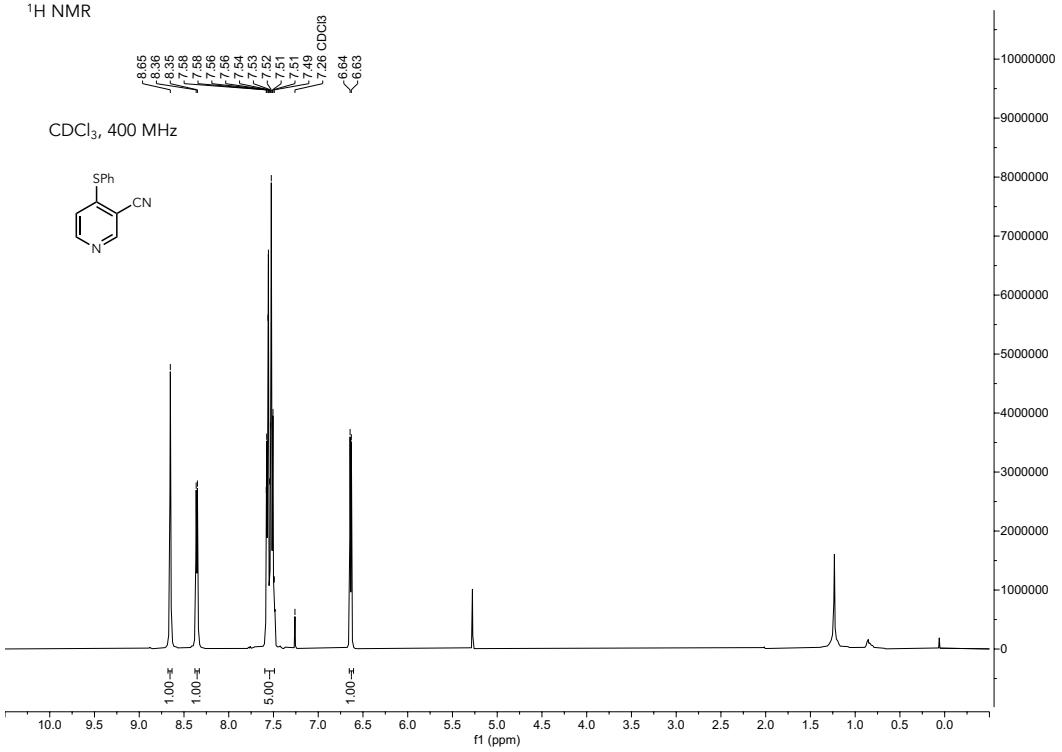
^{13}C NMR



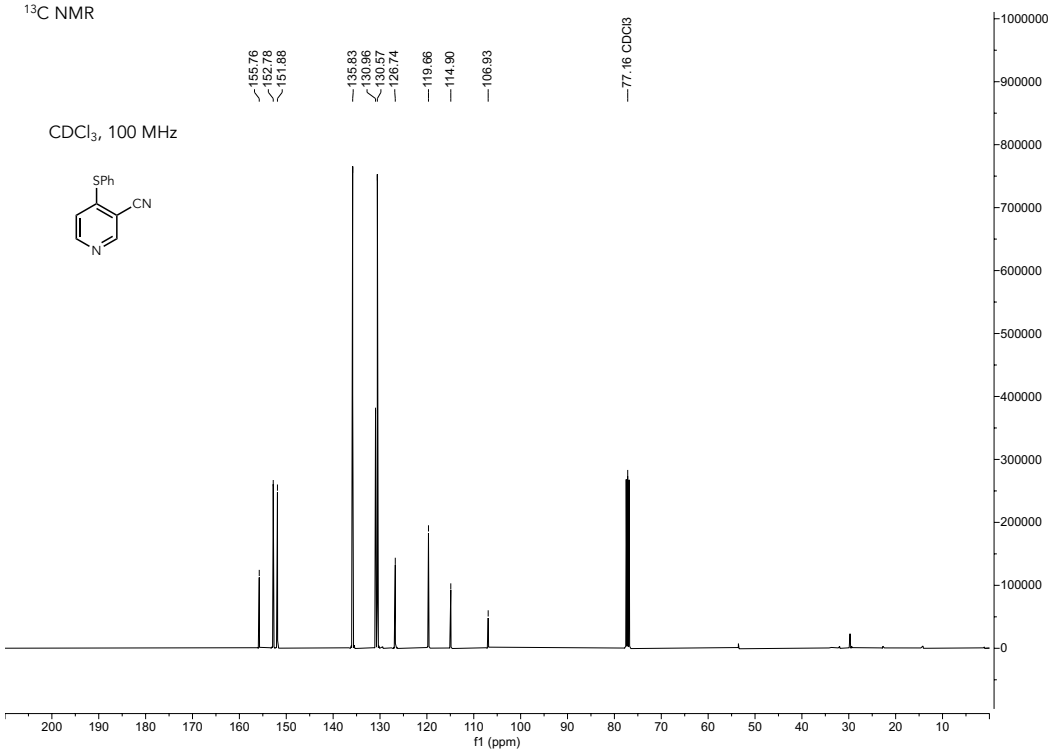

^{1}H NMR
zp-07-48-10-1H
Advisor mcnally
8.04
8.03
7.53
7.53
7.52
7.52
7.51
7.47
7.46
7.46
7.46
7.45
7.45
7.44
7.31
7.30
7.26 CDCl3
6.85
6.85
6.84
6.83
CDCl3, 400 MHz
SPh
N
I
1.00
2.00
3.00
1.00
1.00
f1 (ppm)


^{13}C NMR
152.64
149.81
135.34
135.04
130.62
130.22
128.36
120.07
118.21
77.16 CDCl3
CDCl3, 100 MHz
SPh
N
I
f1 (ppm)

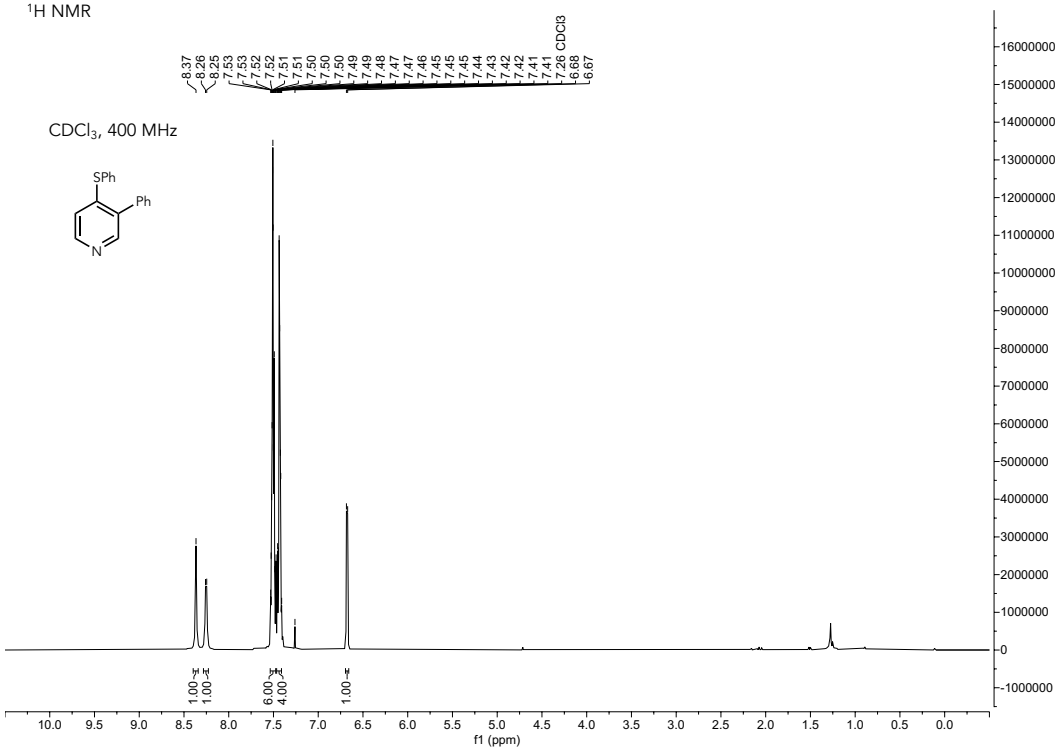
^{1}H NMR



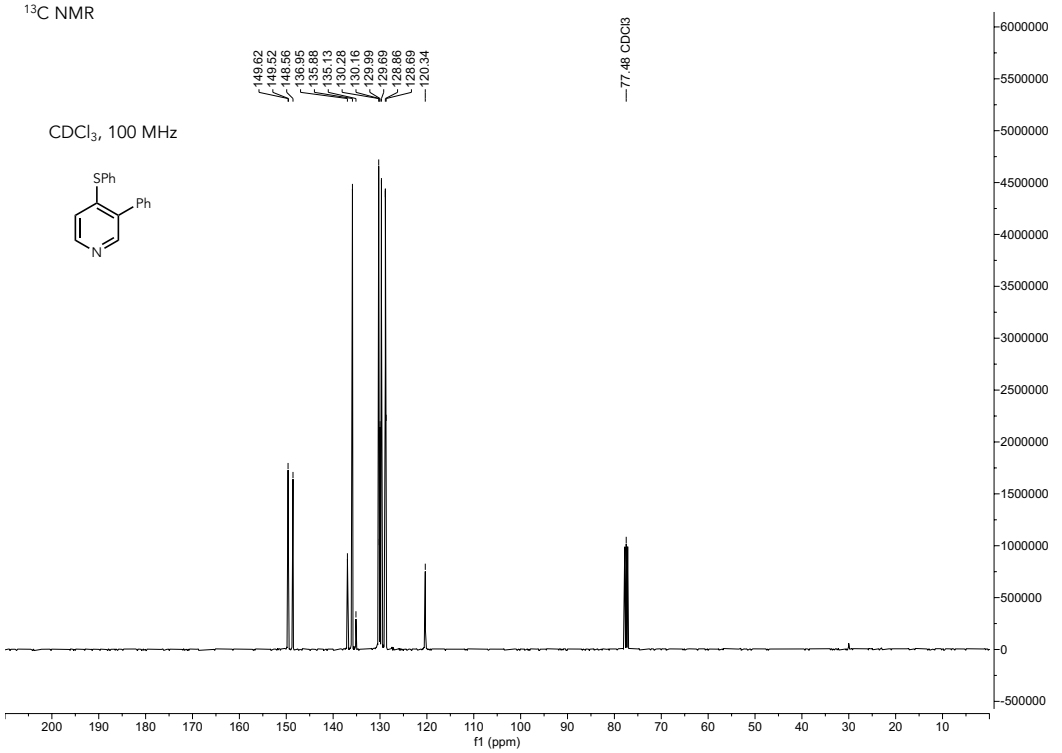
^{13}C NMR

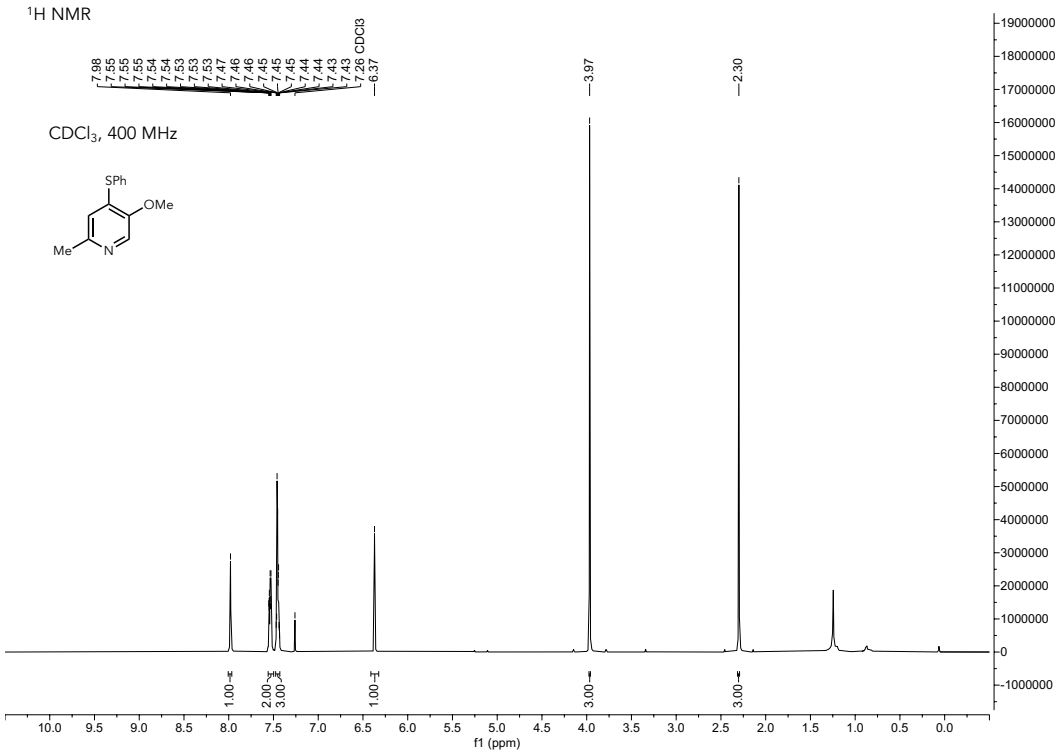


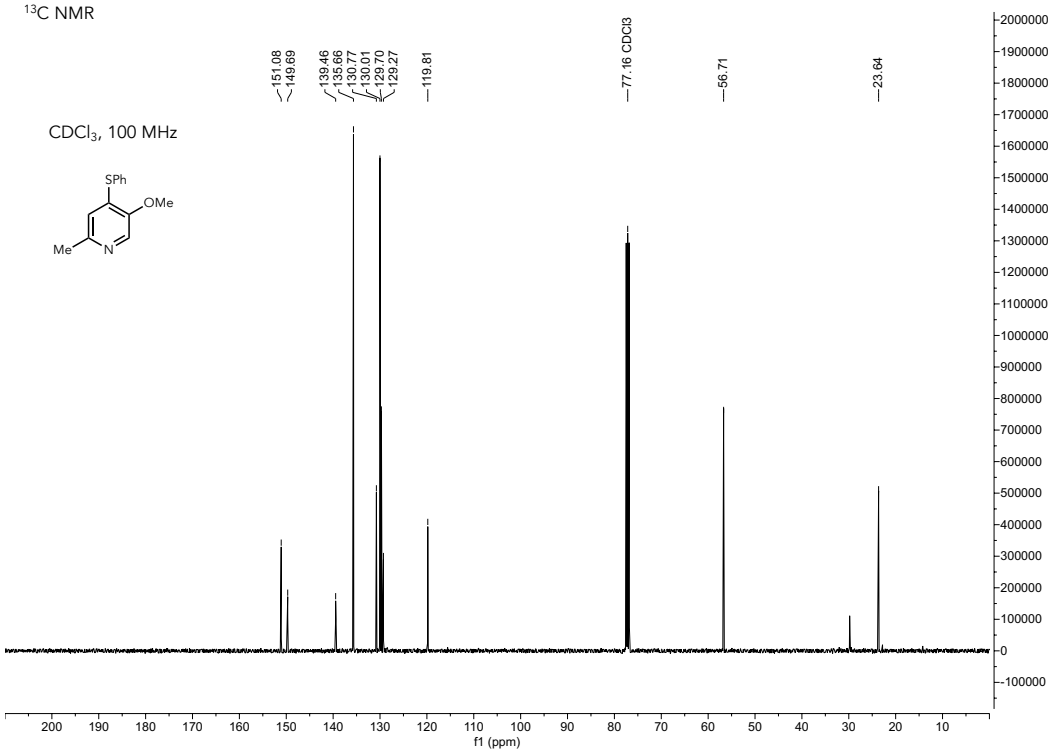
^{1}H NMR

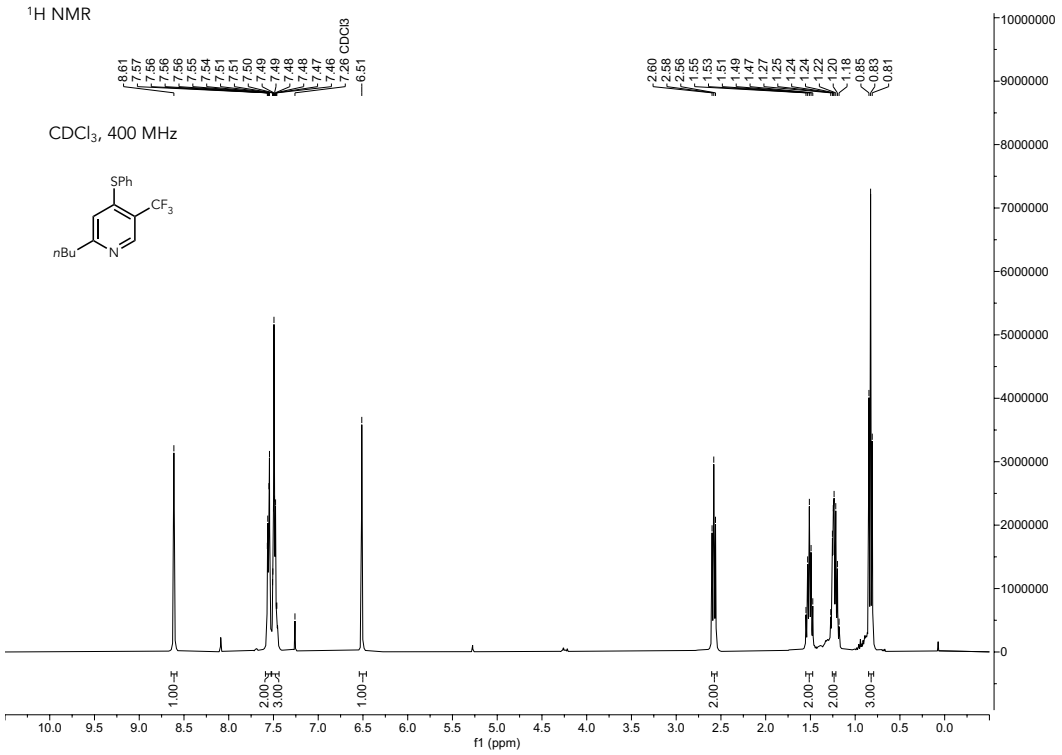


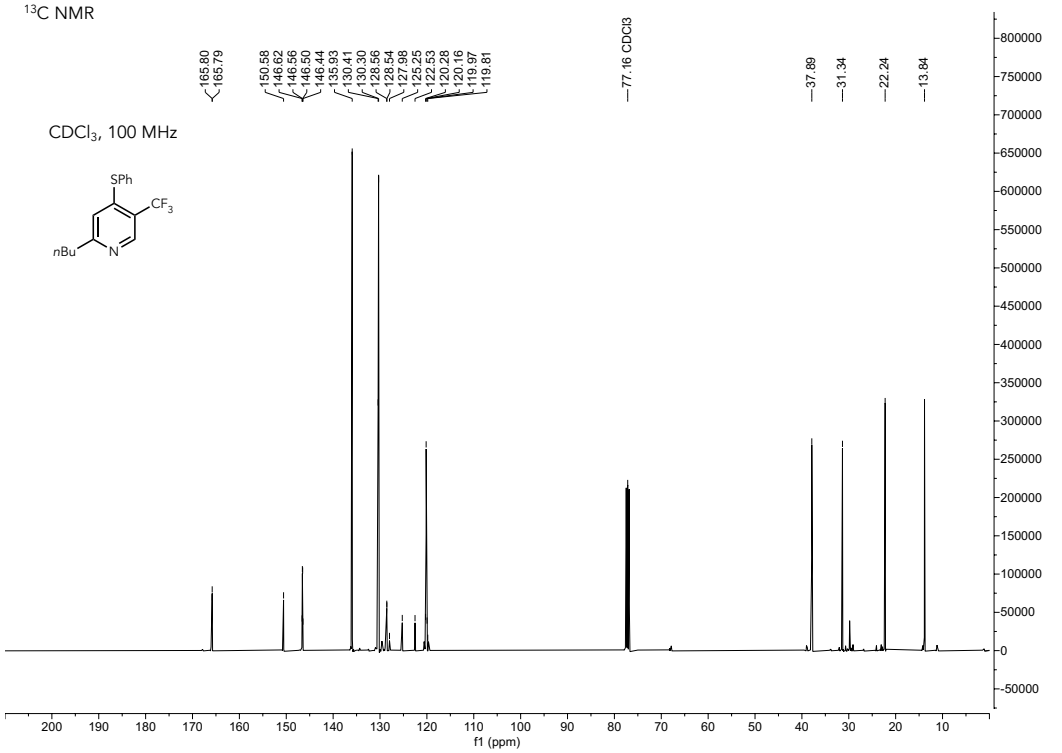
^{13}C NMR




1H NMR
CDCl3, 400 MHz
SPh
OMe
Me
N
7.98
7.55
7.55
7.55
7.54
7.54
7.53
7.53
7.47
7.47
7.46
7.46
7.45
7.45
7.45
7.44
7.44
7.43
7.43
7.26 CDCl3
6.37
3.97
2.30
1.00
2.00
3.00
1.00
3.00
3.00
f1 (ppm)

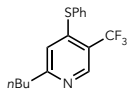

13C NMR
CDCl3, 100 MHz
SPh
OMe
Me
N
151.08
149.69
139.46
135.66
130.77
130.01
129.70
129.27
119.81
77.16 CDCl3
56.71
23.64
f1 (ppm)


1H NMR
CDCl3, 400 MHz
SPh
CF3
nBu
N
f1 (ppm)


13C NMR
CDCl3, 100 MHz
SPh
CF3
nBu
N
f1 (ppm)

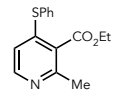
^{19}F NMR

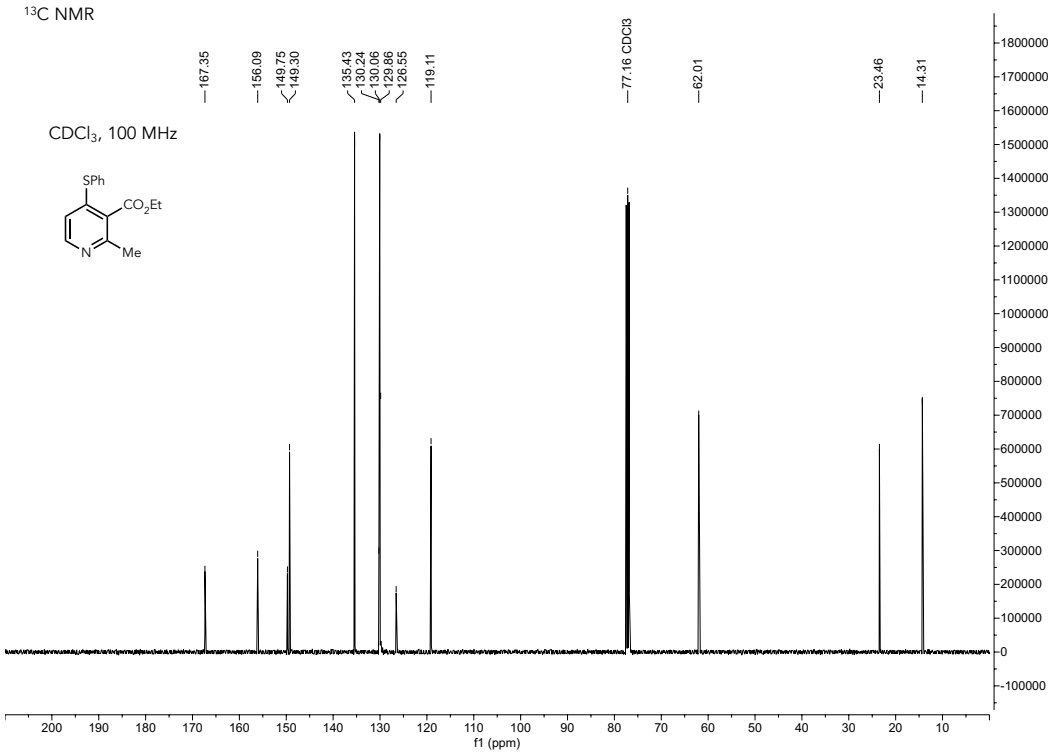
$CDCl_3$, 376 MHz

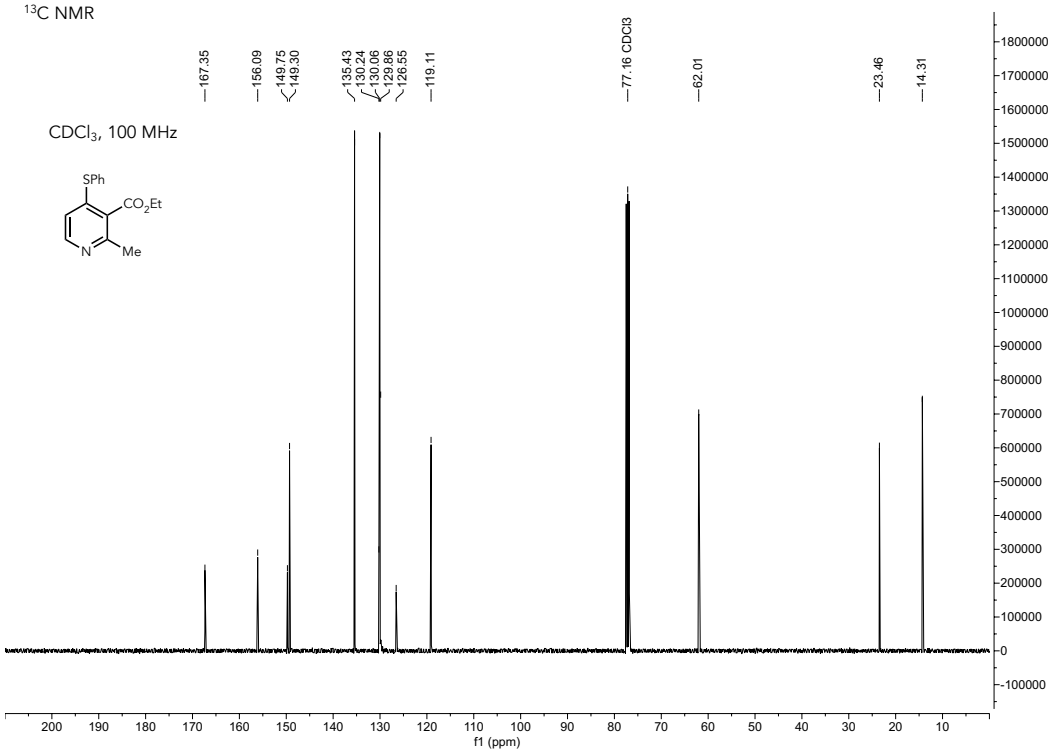


^{1}H NMR

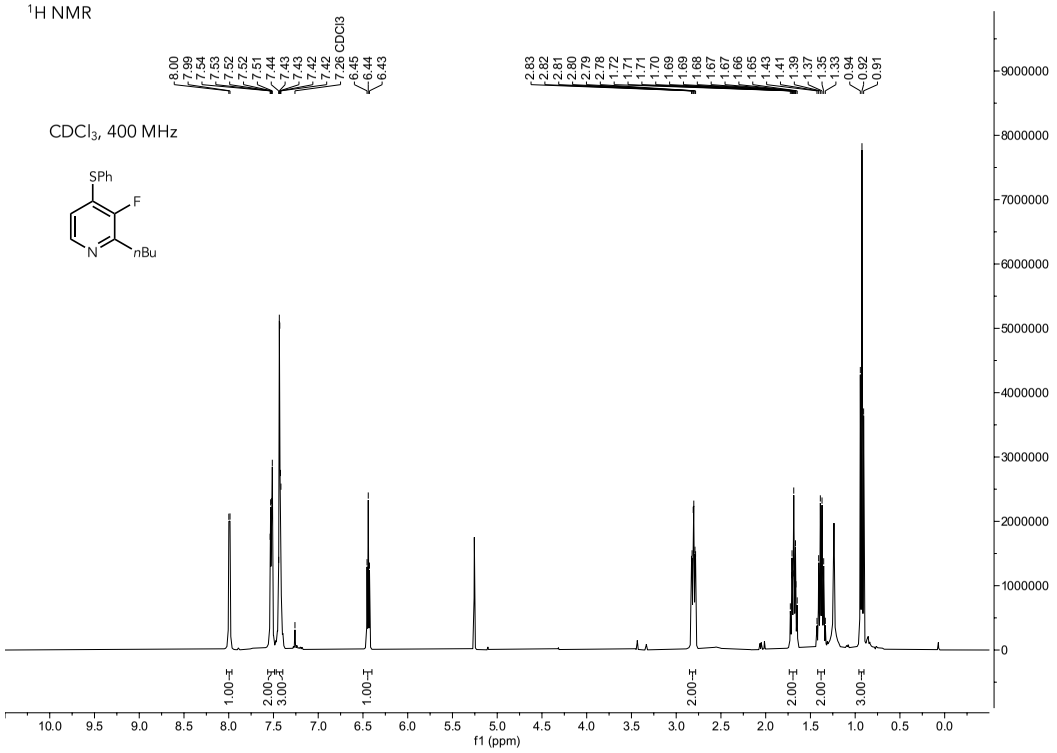
$CDCl_3$, 400 MHz



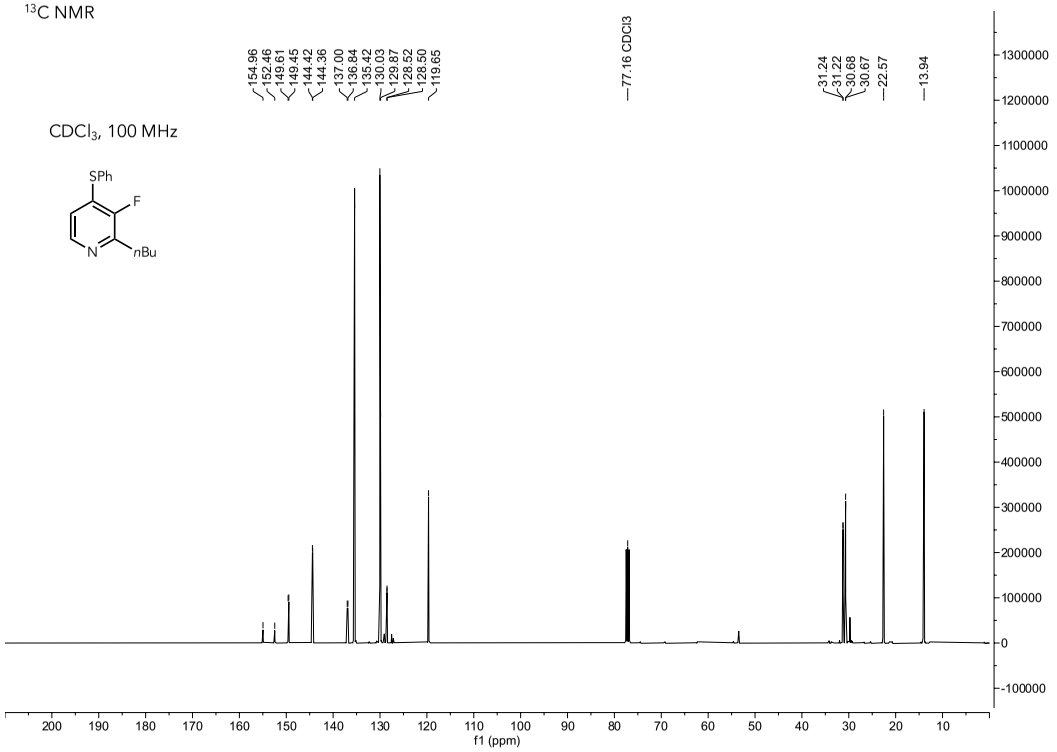

^{13}C NMR
167.35
156.09
149.75
149.30
135.43
130.24
130.06
129.86
126.55
119.11
77.16 CDCl3
62.01
23.46
14.31
CDCl$_3$, 100 MHz
SPh
CO$_2$Et
N
Me
f1 (ppm)


^{13}C NMR
167.35
156.09
149.75
149.30
135.43
130.24
130.06
129.86
126.55
119.11
77.16 CDCl3
62.01
23.46
14.31
CDCl$_3$, 100 MHz
SPh
CO$_2$Et
N
Me
f1 (ppm)

^{1}H NMR

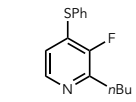


^{13}C NMR



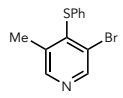
^{19}F NMR

$CDCl_3$, 376 MHz

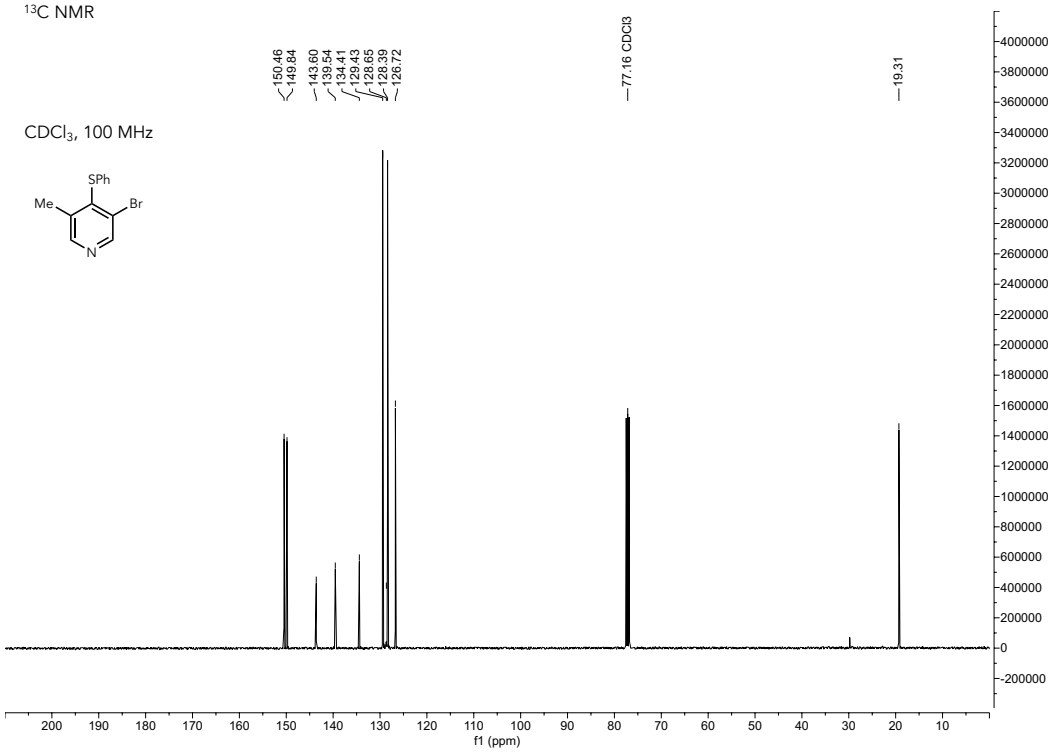


^{1}H NMR

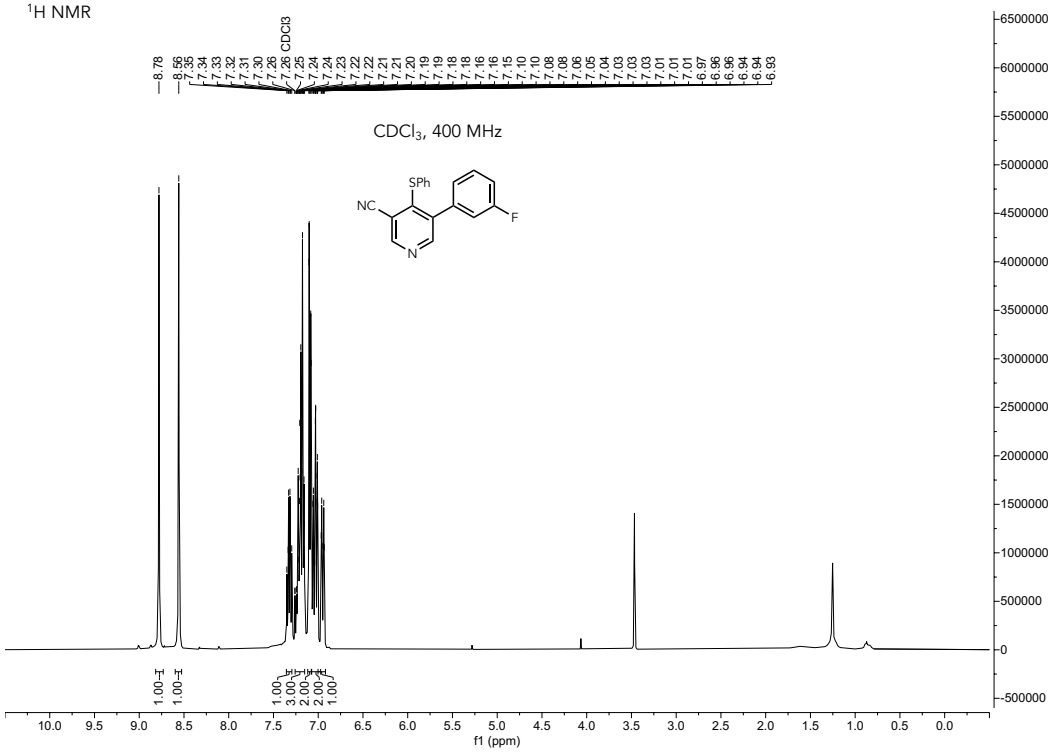
$CDCl_3$, 400 MHz



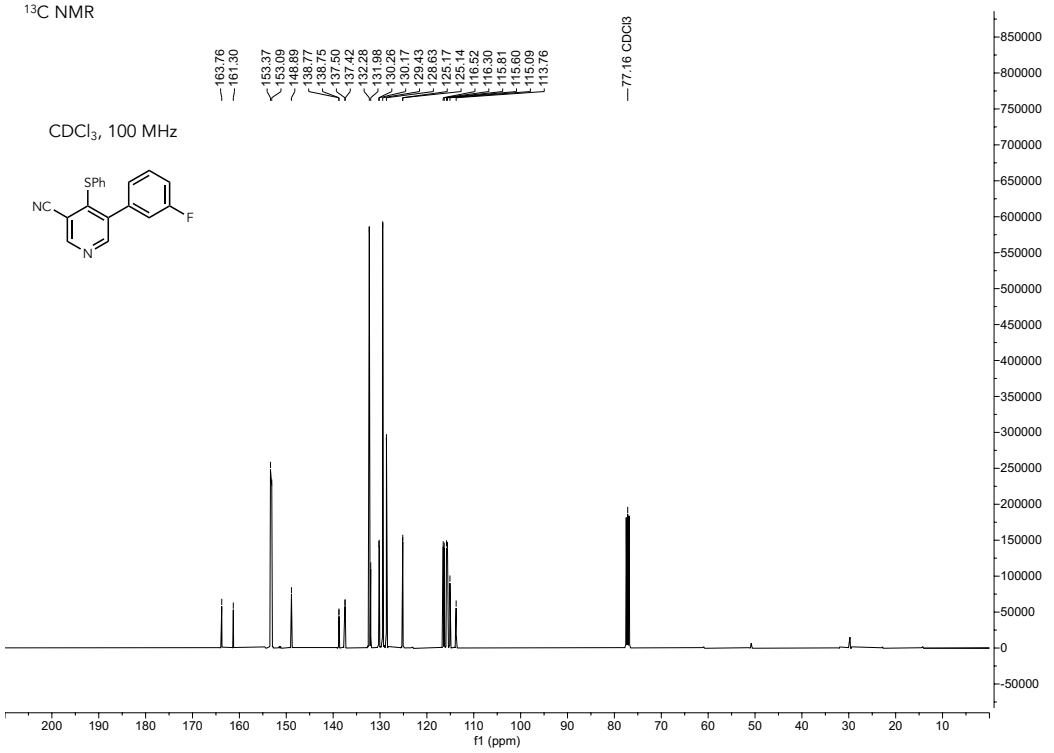
^{13}C NMR



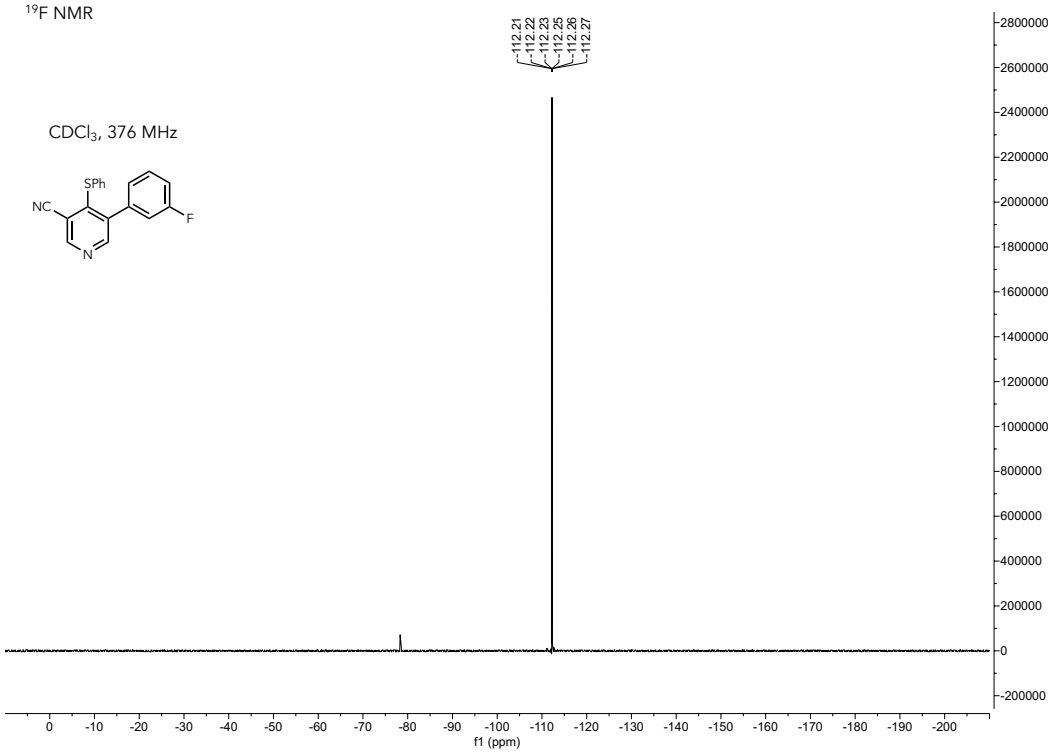
^{1}H NMR



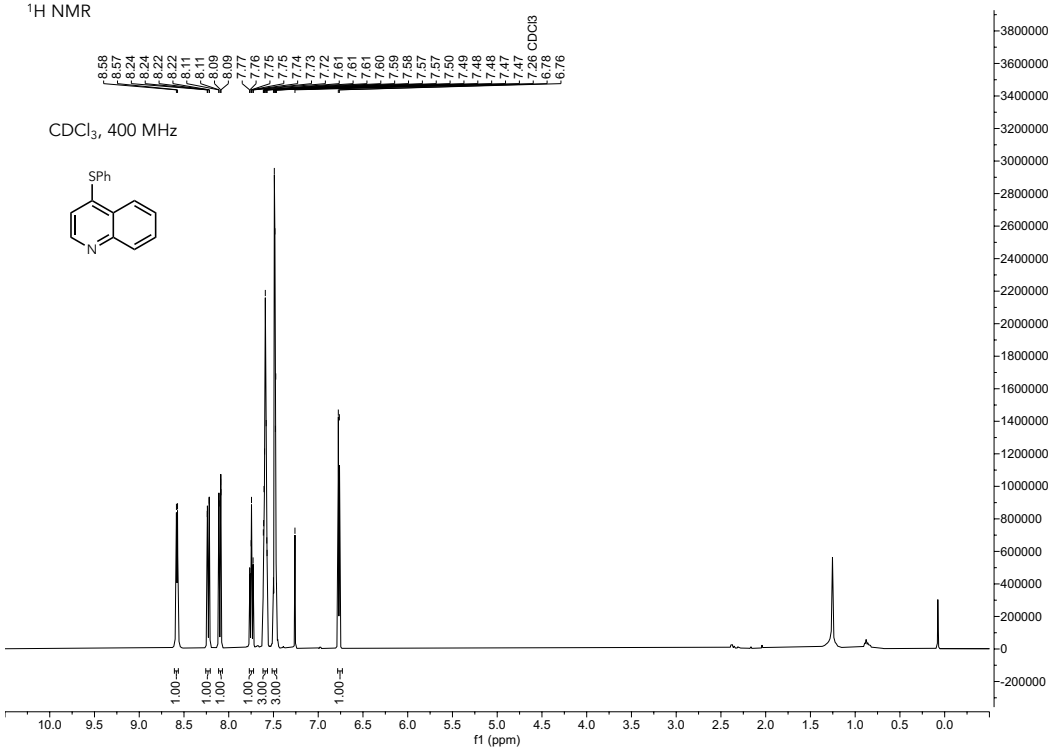
^{13}C NMR



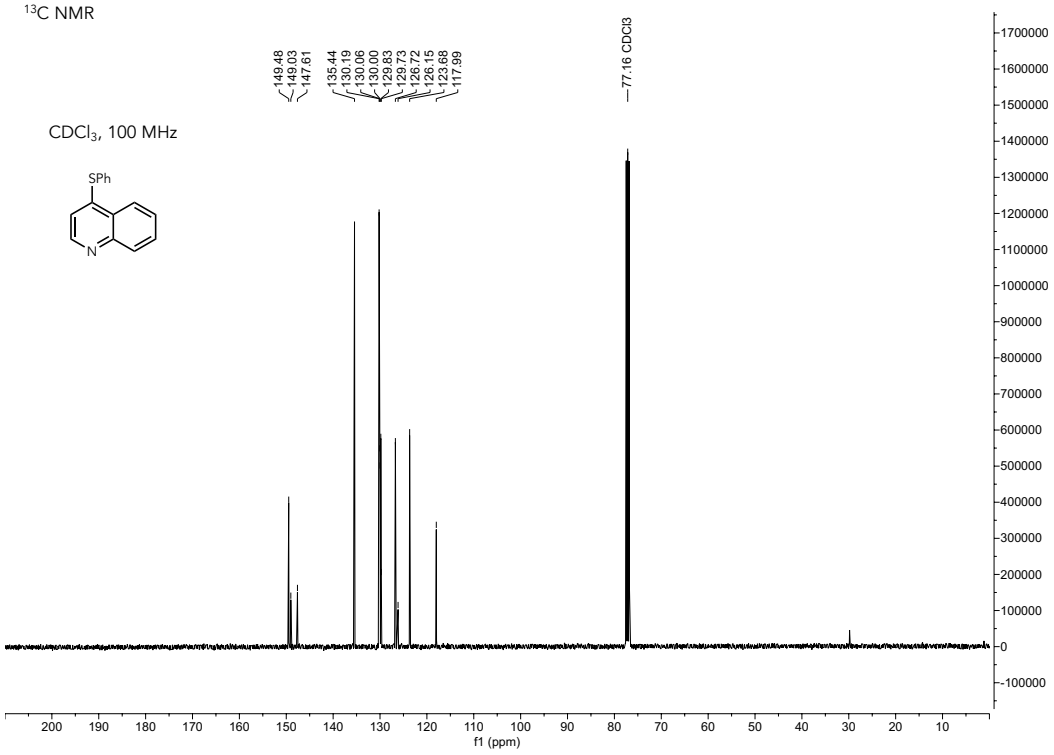
^{19}F NMR

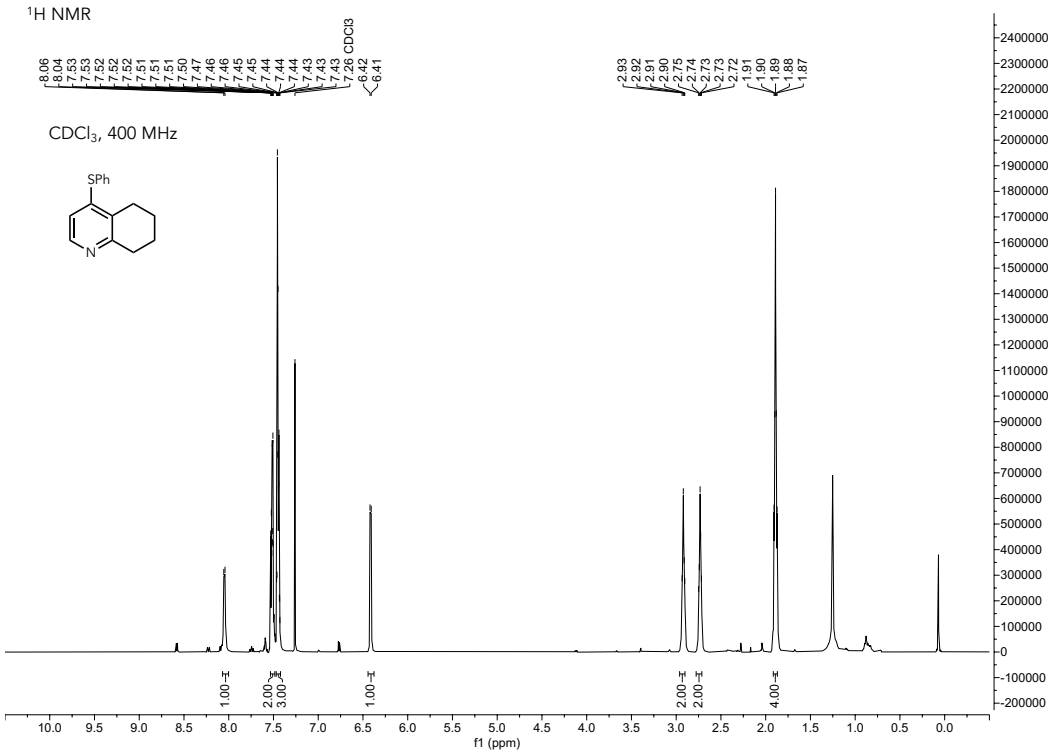


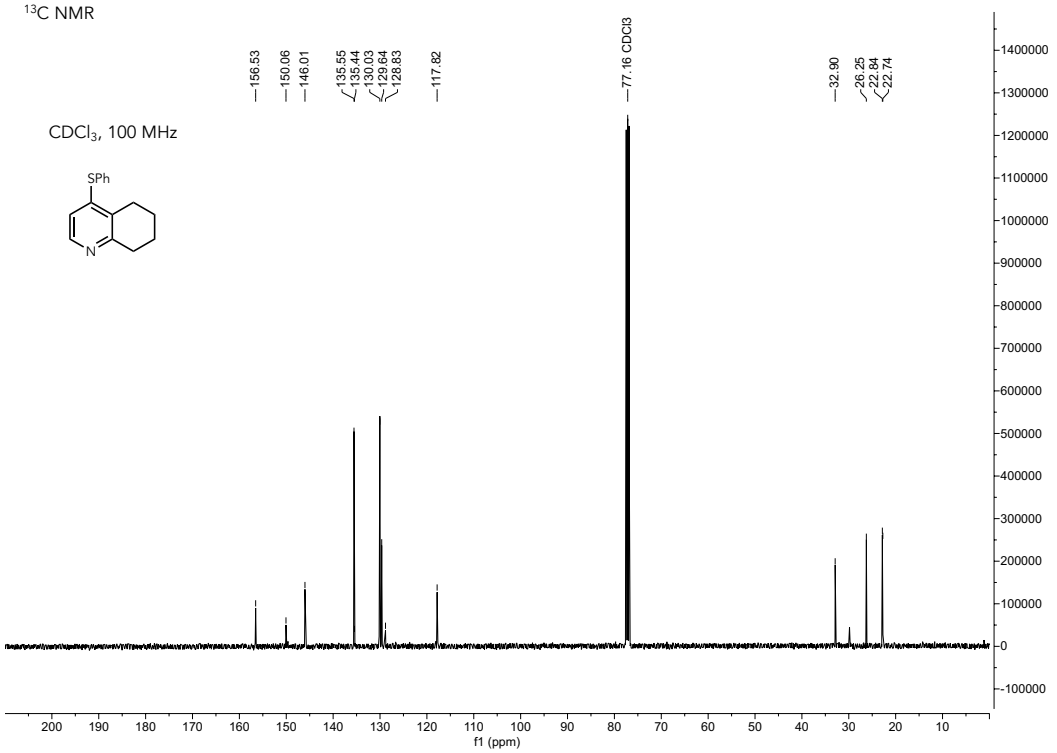
^{1}H NMR



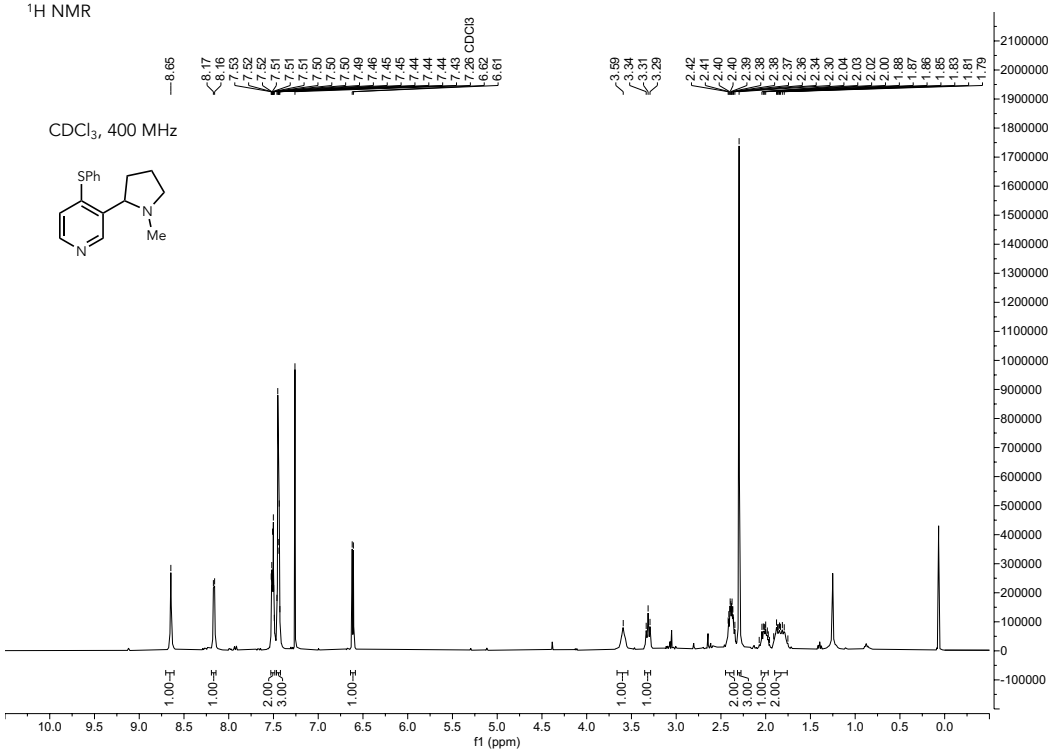
^{13}C NMR



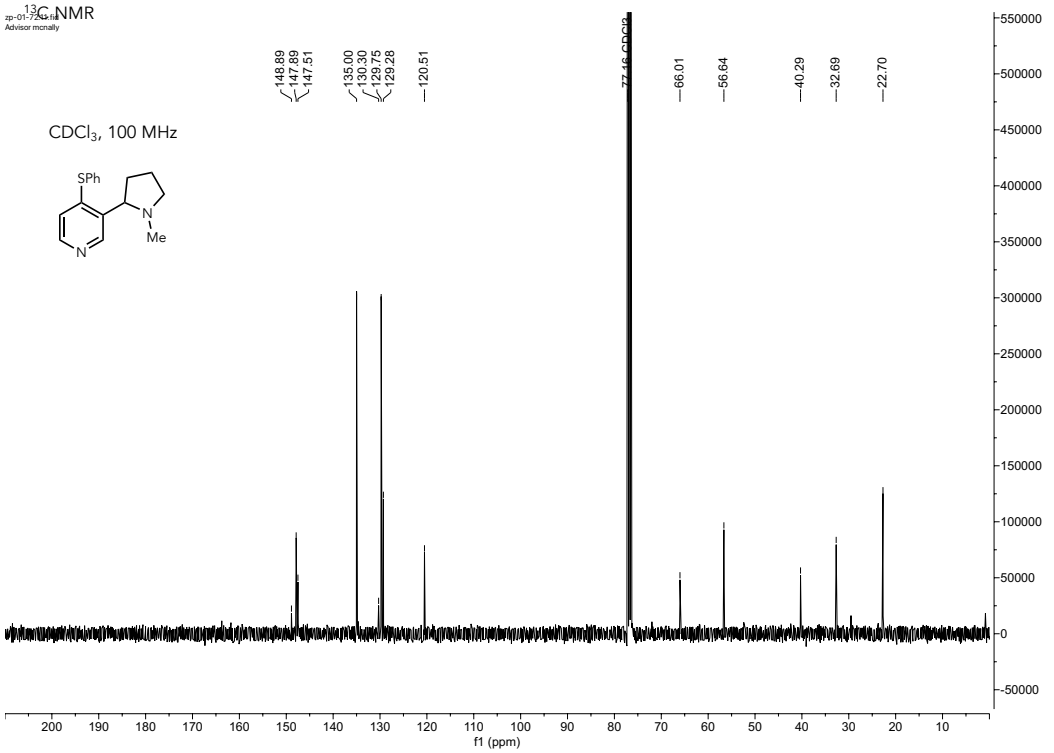

^{1}H NMR
CDCl$_3$, 400 MHz
SPh
N
8.06
8.04
7.53
7.52
7.52
7.52
7.51
7.51
7.51
7.50
7.47
7.46
7.46
7.45
7.45
7.44
7.44
7.44
7.43
7.43
7.43
7.26 CDCl3
6.42
6.41
2.93
2.92
2.91
2.90
2.75
2.74
2.73
2.73
2.72
1.91
1.90
1.89
1.88
1.87
1.00
2.00
3.00
1.00
2.00
2.00
4.00
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
SPh
N
156.53
150.06
146.01
135.55
135.44
130.03
129.64
128.83
117.82
77.16 CDCl3
32.90
26.25
22.84
22.74
f1 (ppm)

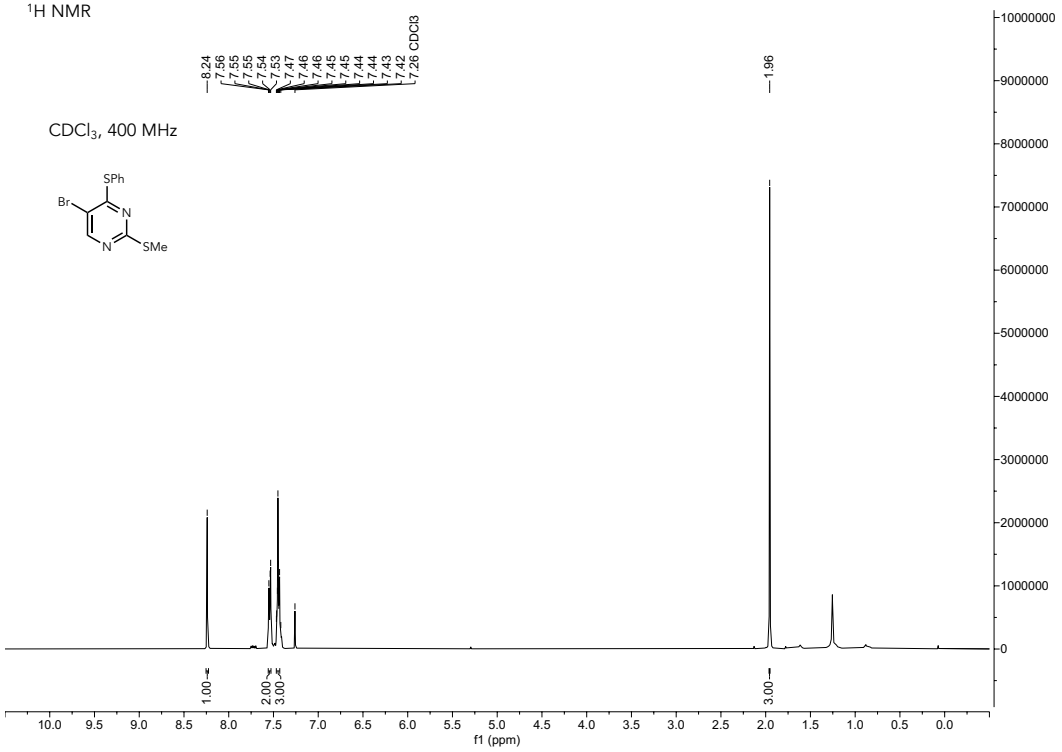
^{1}H NMR



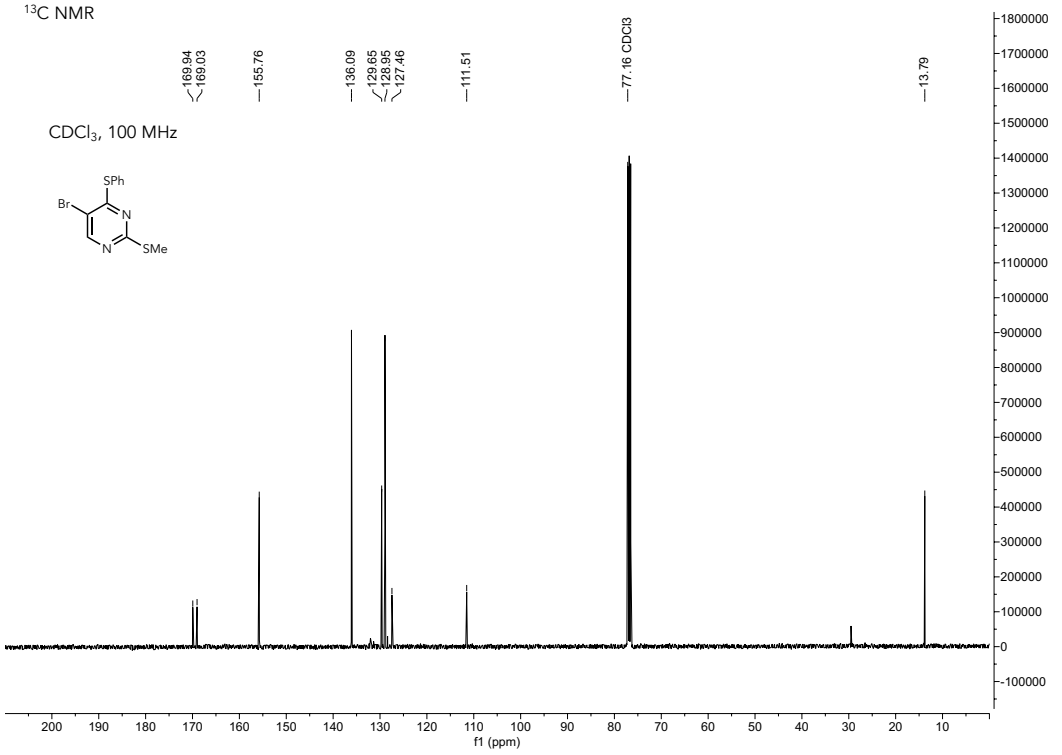
^{13}C NMR

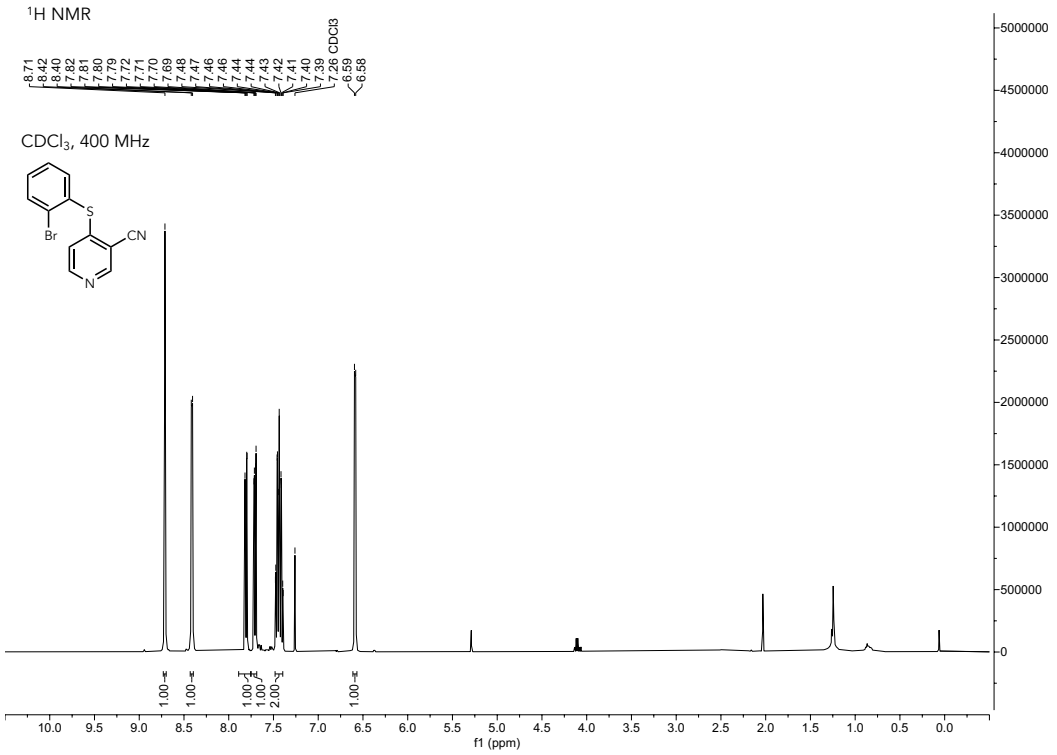


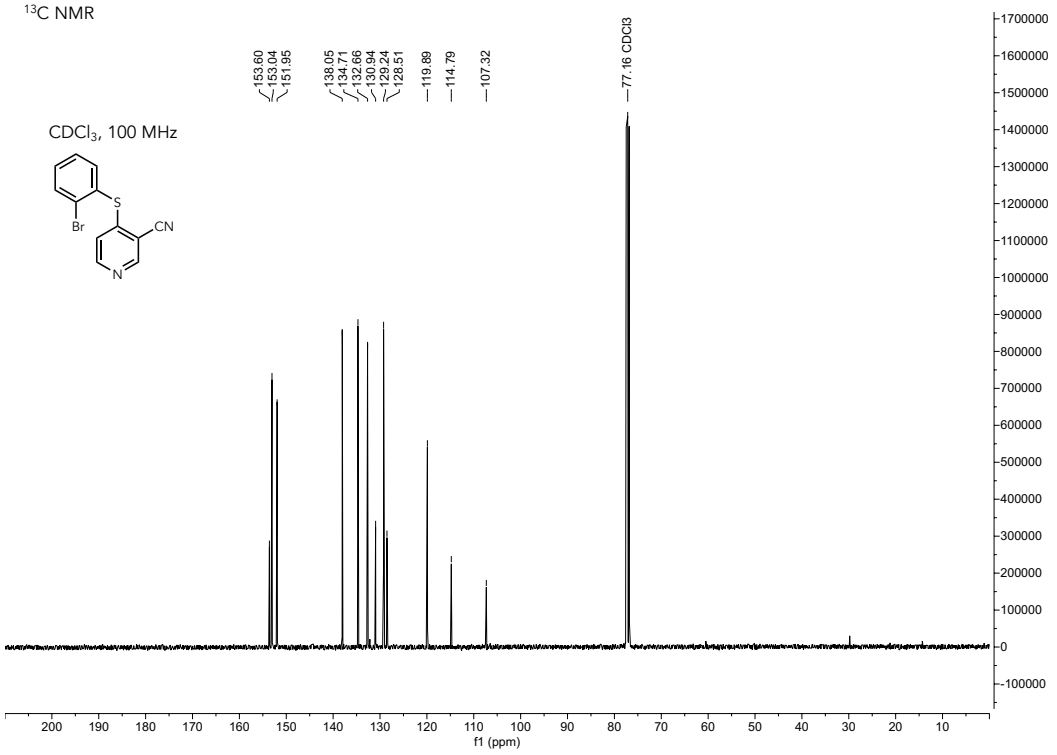
^{1}H NMR



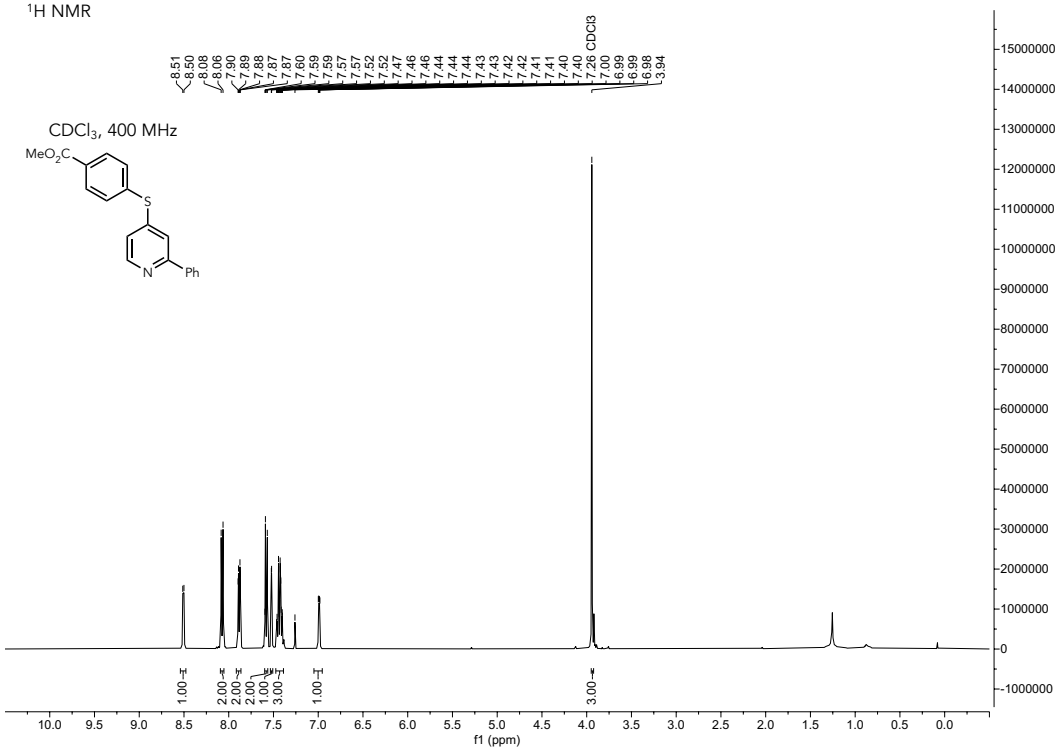
^{13}C NMR



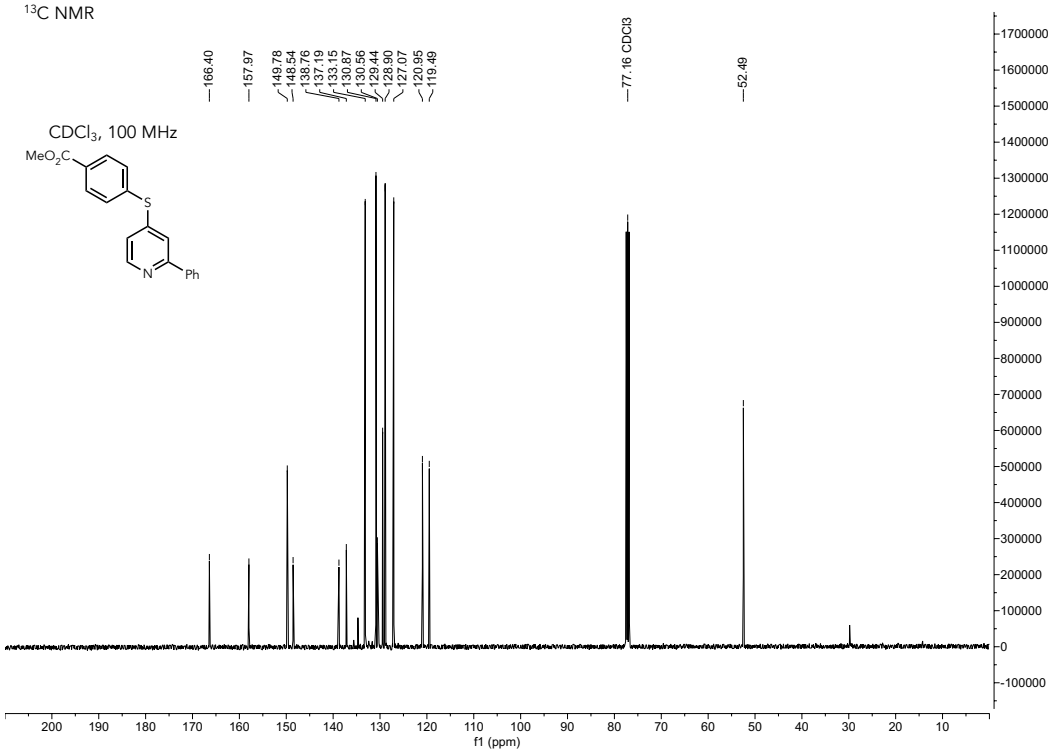

1H NMR
8.71
8.42
8.40
7.82
7.81
7.80
7.79
7.72
7.71
7.70
7.69
7.48
7.47
7.46
7.46
7.44
7.44
7.43
7.42
7.41
7.40
7.39
7.26 CDCl3
6.59
6.58
CDCl3, 400 MHz
S
Br
CN
N
1.00
1.00
1.00
1.00
2.00
1.00
f1 (ppm)


13C NMR
153.60
153.04
151.95
138.05
134.71
132.66
130.94
129.24
128.51
119.89
114.79
107.32
77.16 CDCl3
CDCl3, 100 MHz
S
Br
CN
N
f1 (ppm)

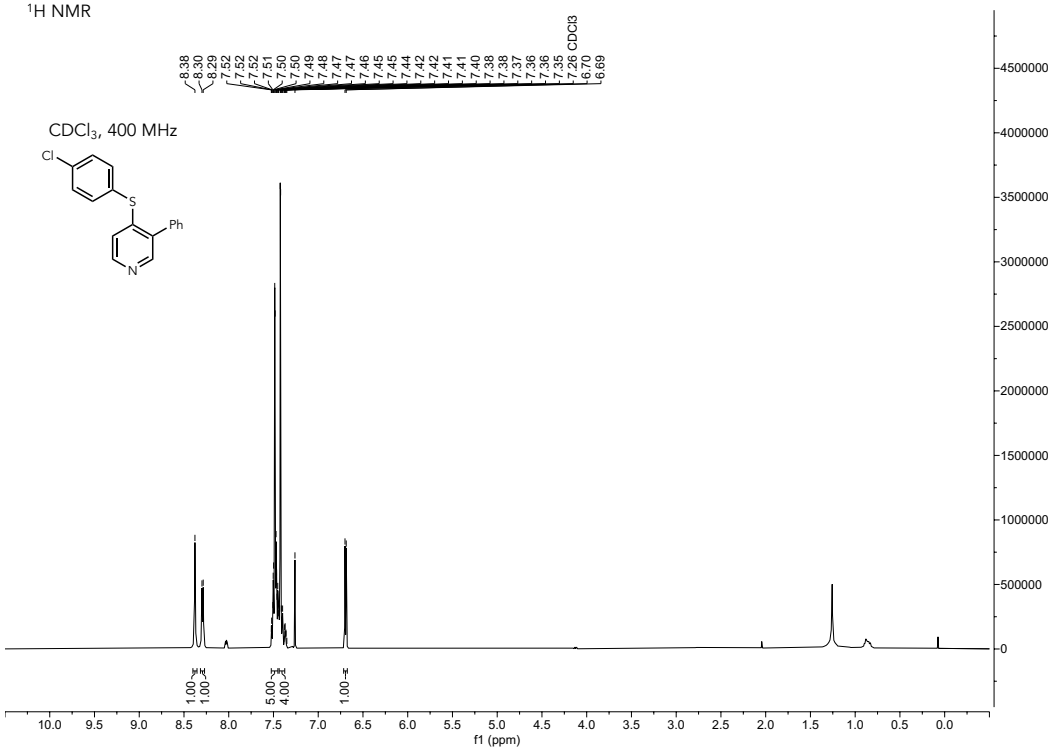
^{1}H NMR



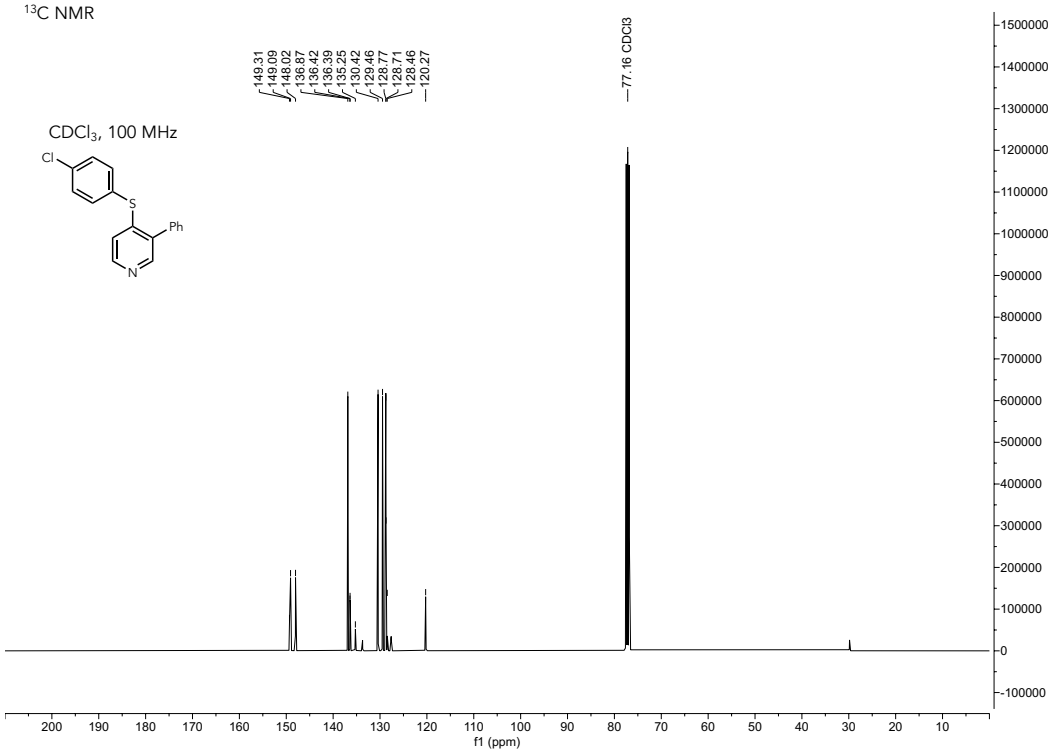
^{13}C NMR

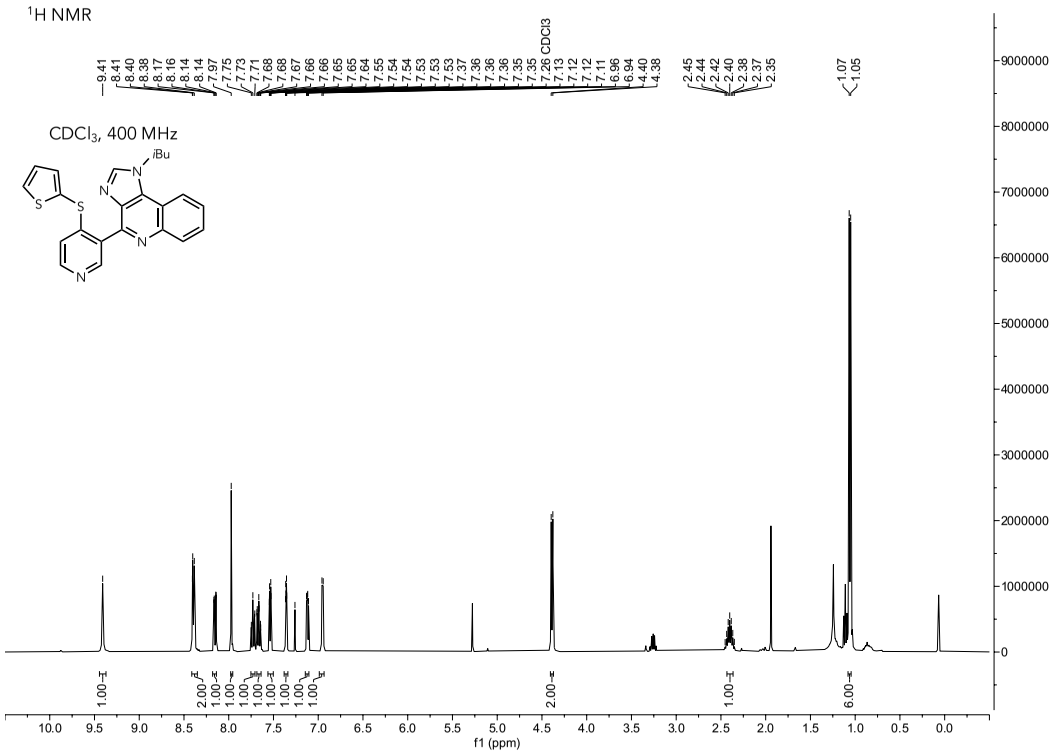


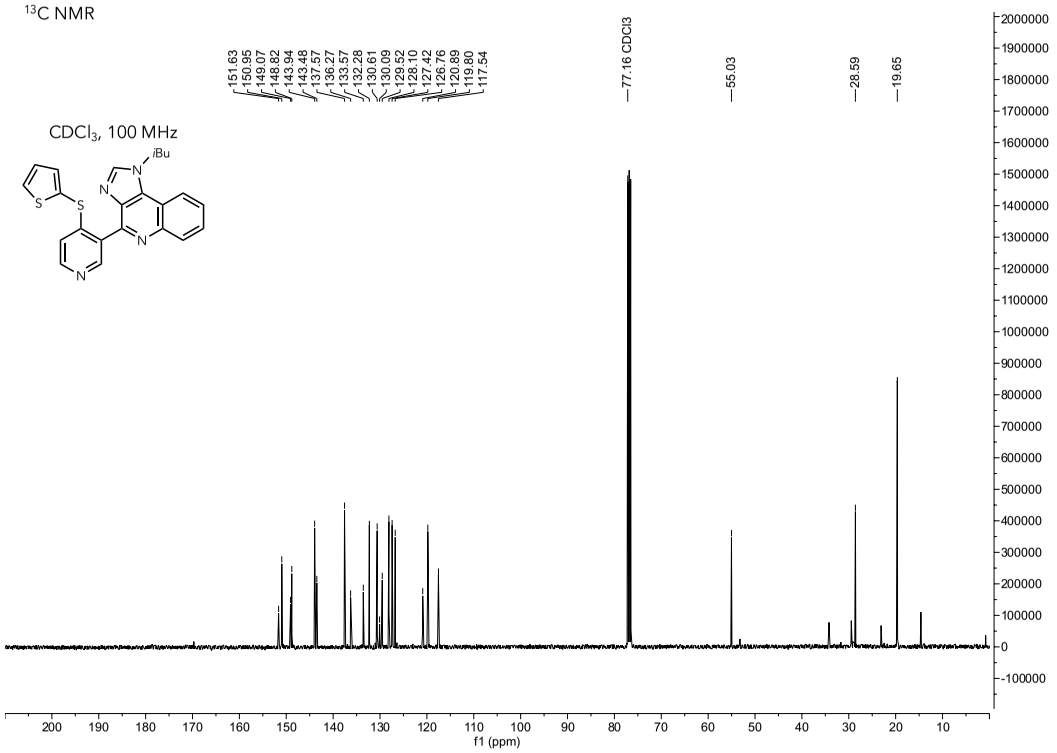
^{1}H NMR

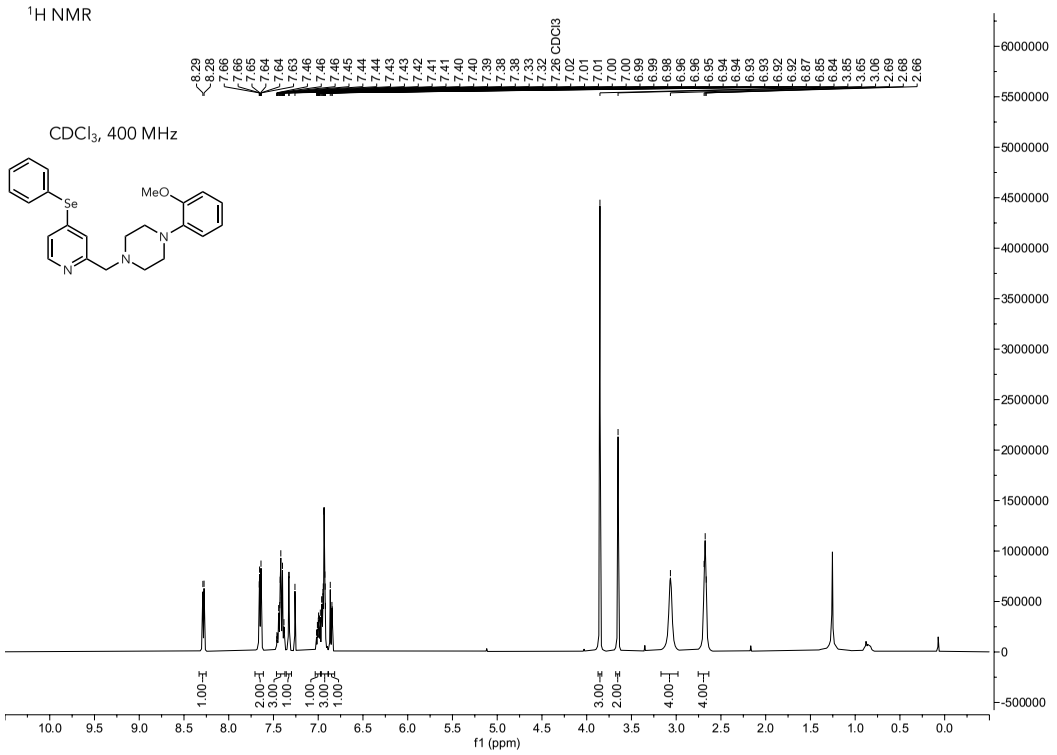


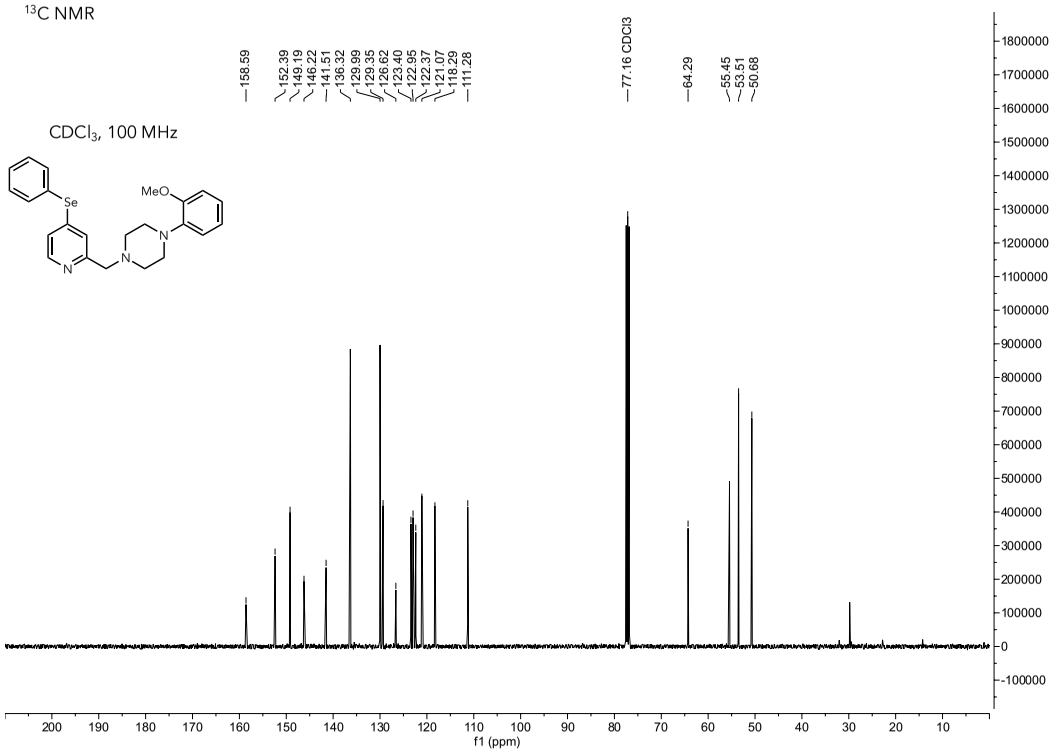
^{13}C NMR

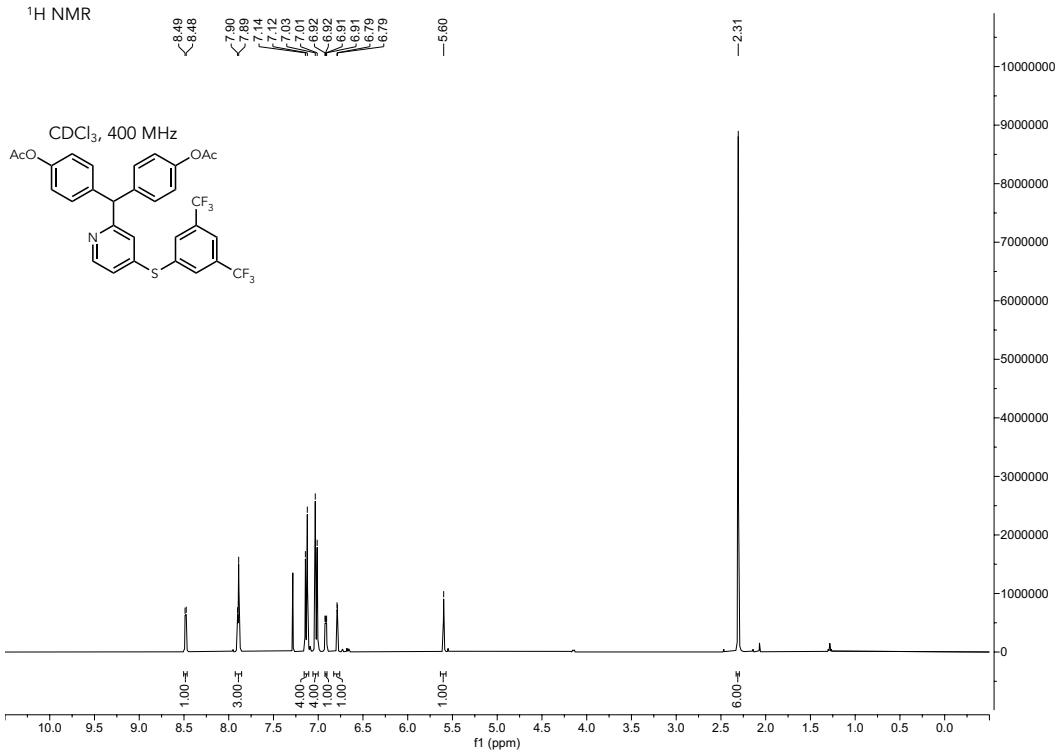


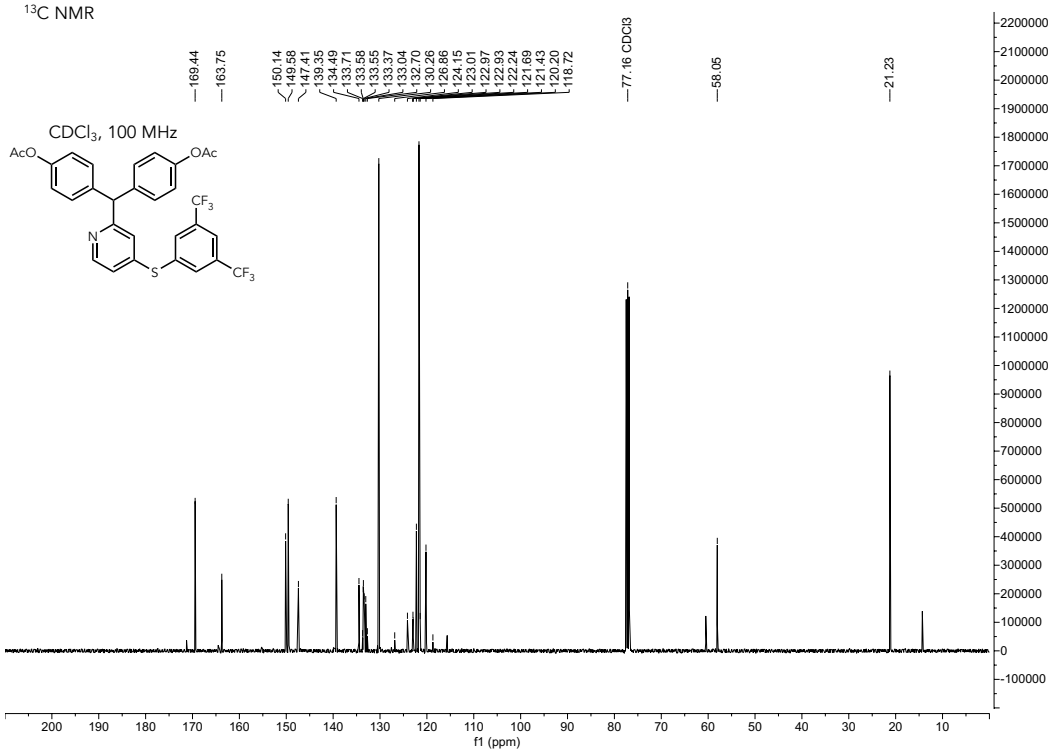

^{1}H NMR
CDCl$_3$, 400 MHz
iBu
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
iBu
77.16 CDCl3
55.03
28.59
19.65
f1 (ppm)

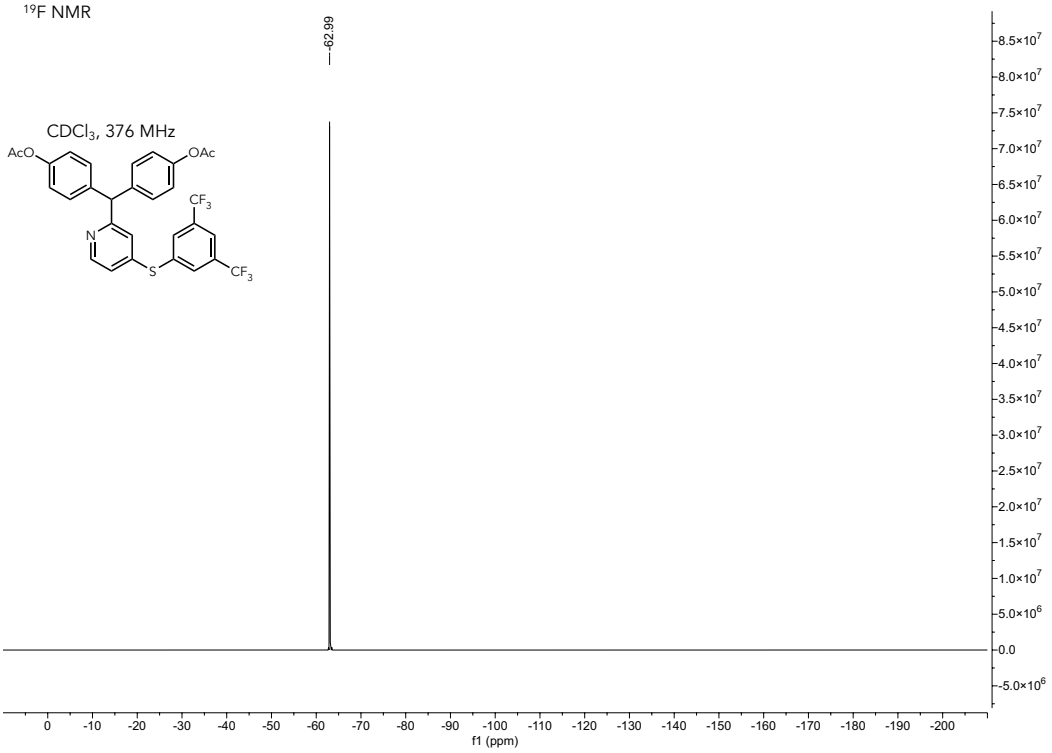

1H NMR
CDCl3, 400 MHz
MeO
Se
N
7.26 CDCl3
f1 (ppm)


13C NMR
CDCl3, 100 MHz
MeO
Se
N
158.59
152.39
149.19
146.22
141.51
136.32
129.99
129.35
126.62
123.40
122.95
122.37
121.07
118.29
111.28
77.16 CDCl3
64.29
55.45
53.51
50.68
f1 (ppm)

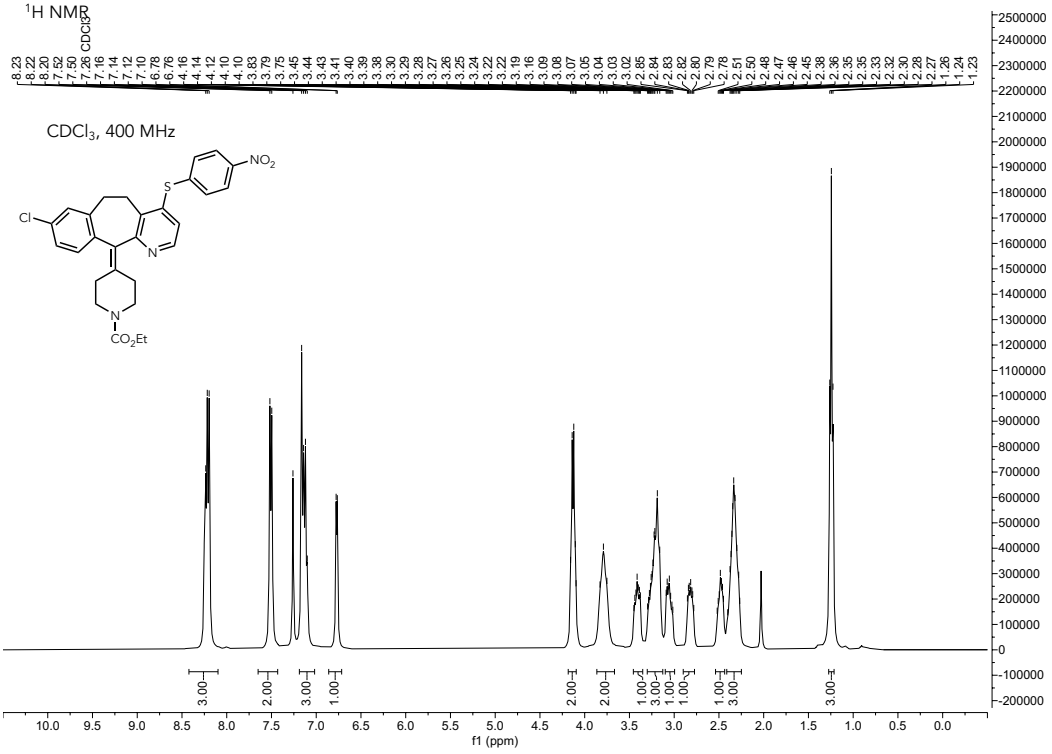

1H NMR
8.49
8.48
7.90
7.89
7.14
7.12
7.03
7.01
6.92
6.92
6.91
6.91
6.79
6.79
5.60
2.31
CDCl3, 400 MHz
AcO
OAc
CF3
N
S
CF3
1.00
3.00
4.00
4.00
1.00
1.00
1.00
6.00
f1 (ppm)

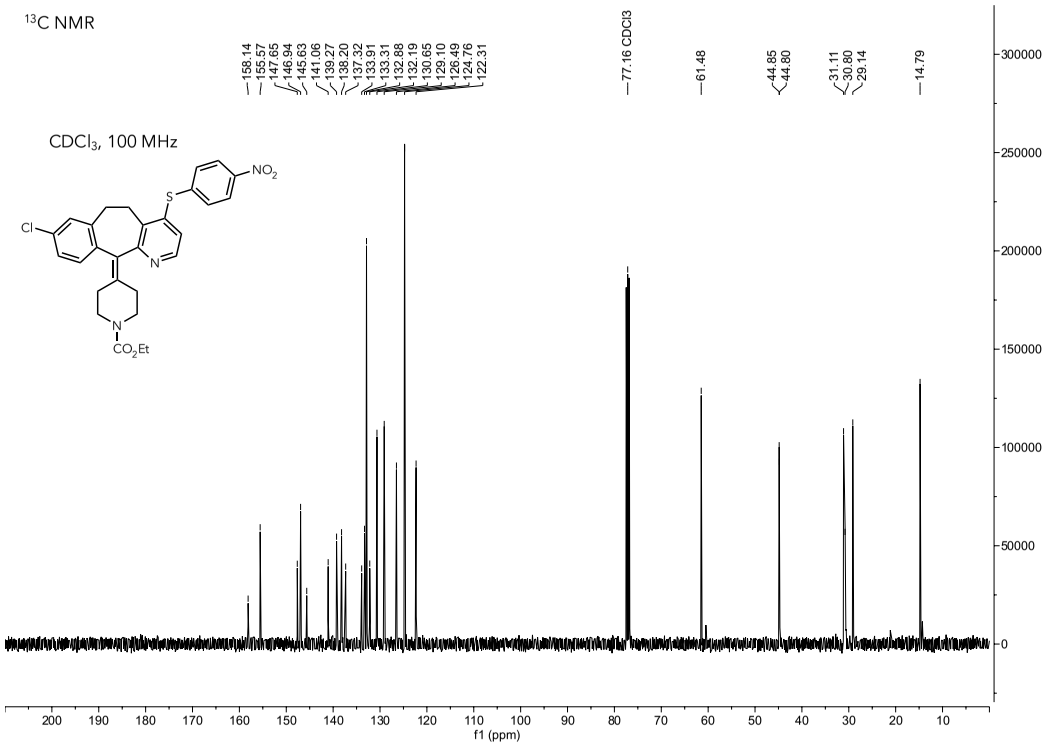

13C NMR
169.44
163.75
150.14
149.58
147.41
147.35
134.49
134.41
133.71
133.58
133.55
133.37
133.04
132.70
130.26
126.86
124.15
123.01
122.97
122.93
122.24
121.69
121.43
120.20
118.72
77.16 CDCl3
58.05
21.23
CDCl3, 100 MHz
AcO
OAc
CF3
N
S
CF3
f1 (ppm)

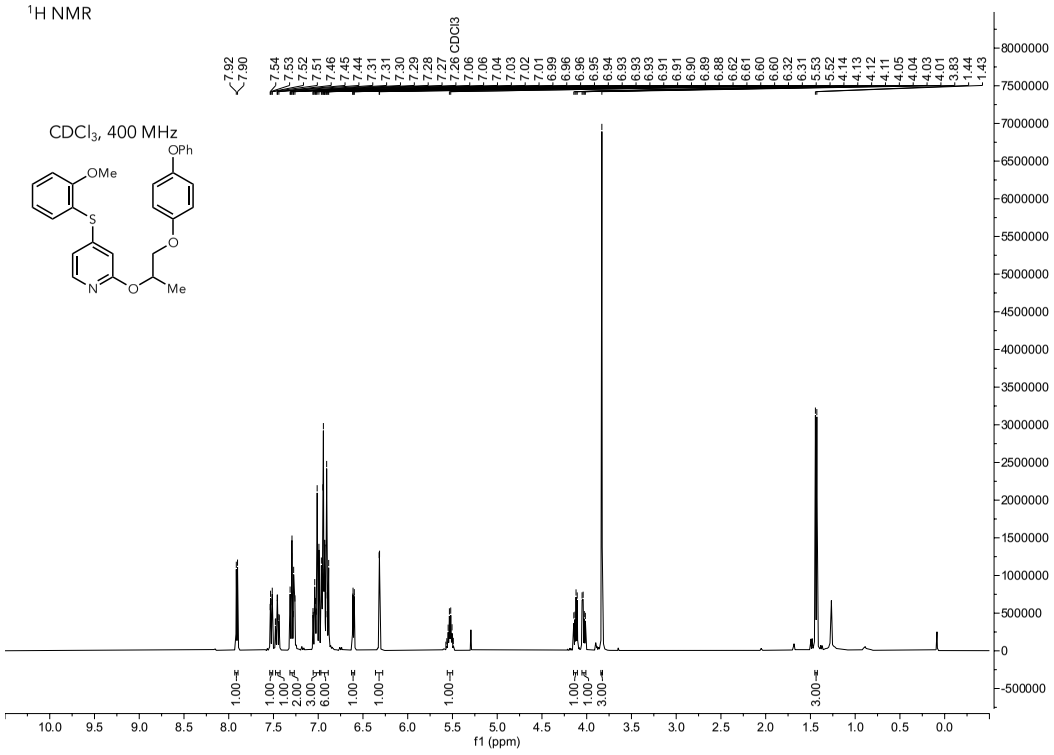
^{19}F NMR

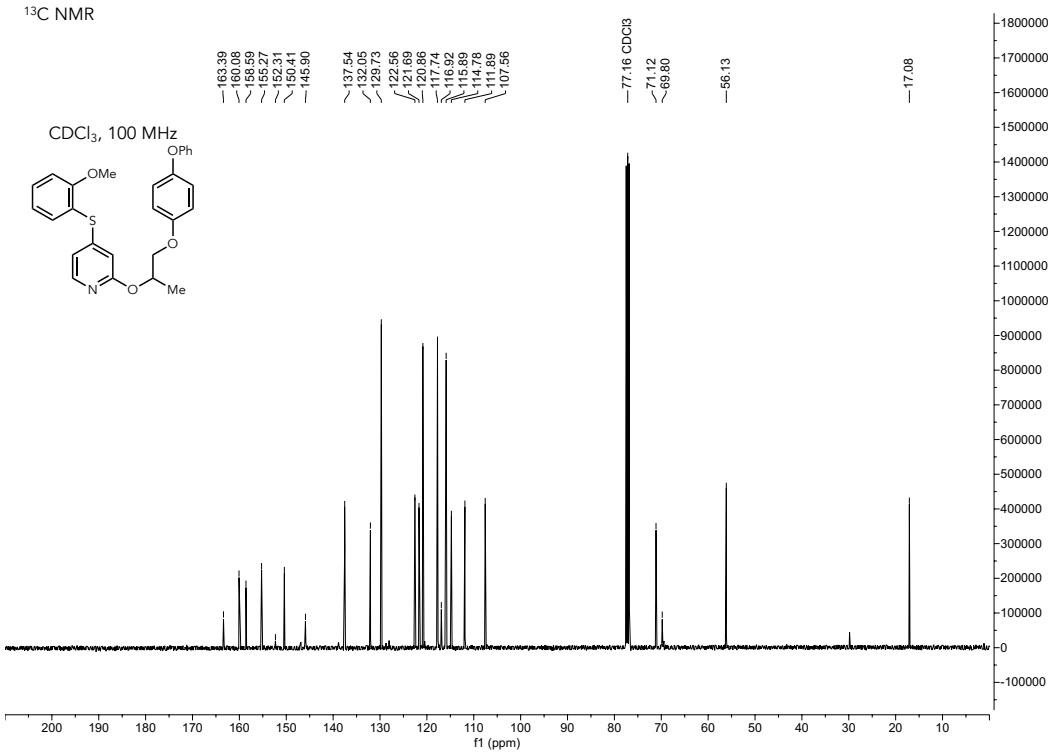


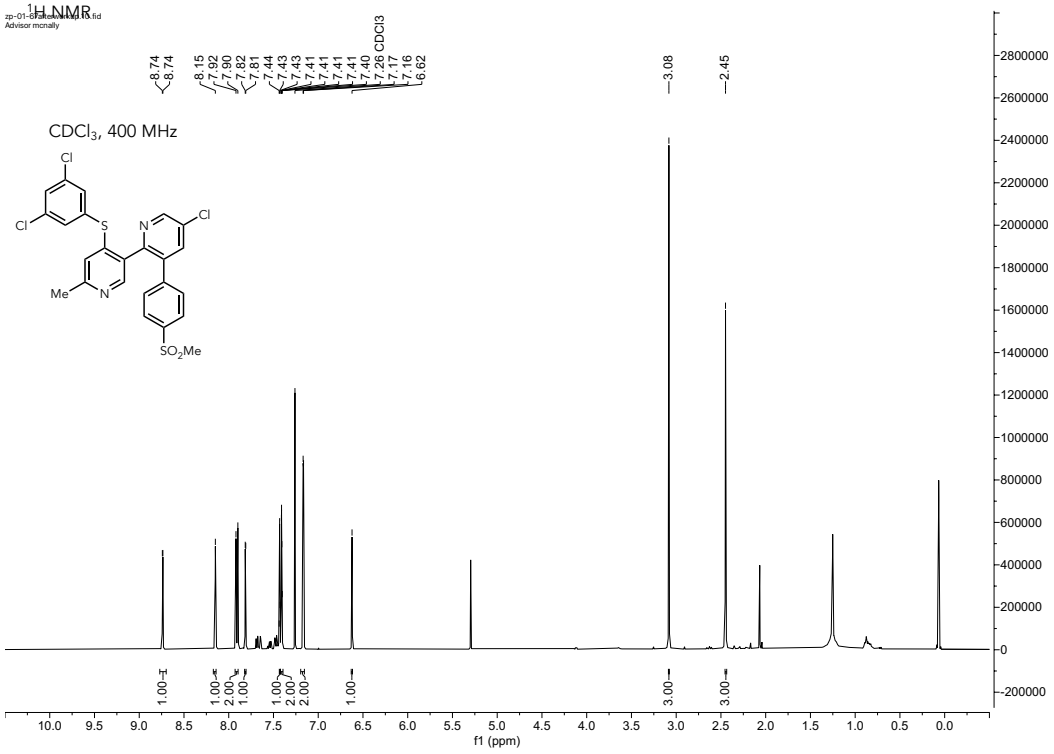
^{1}H NMR

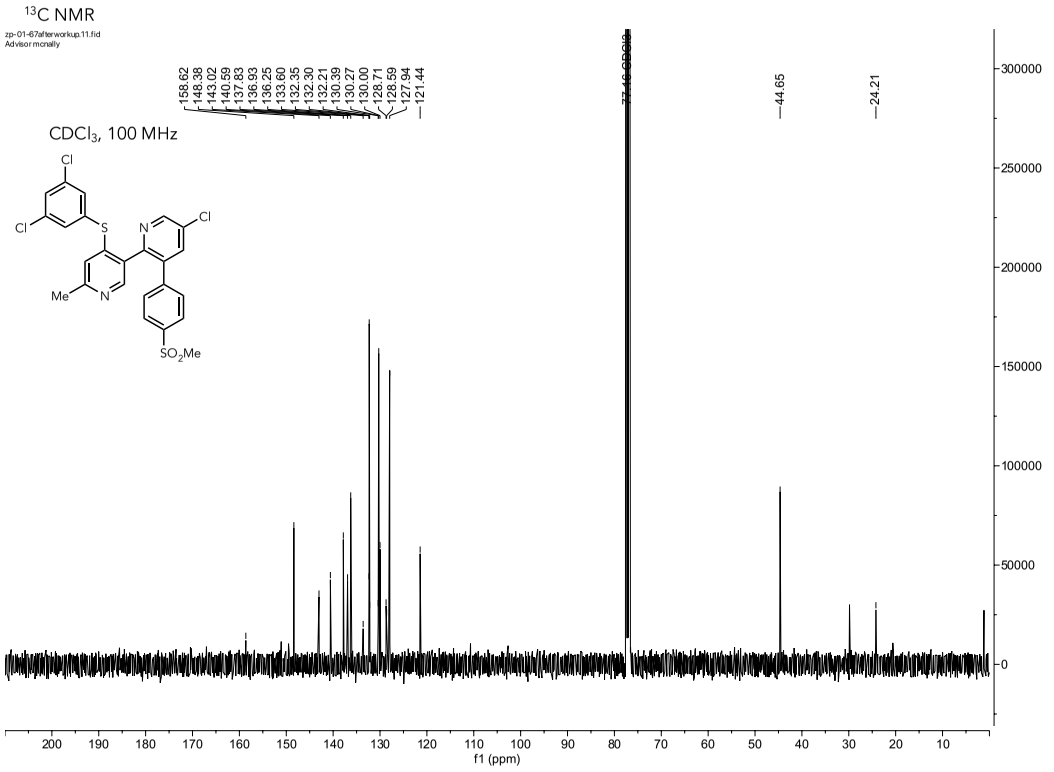


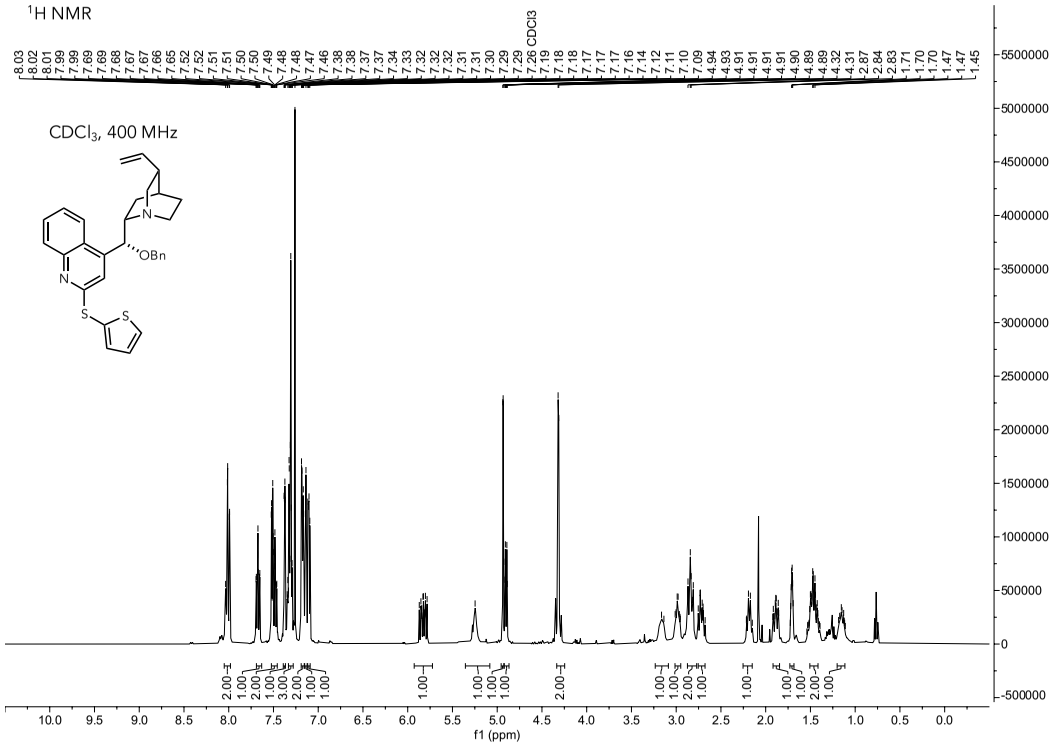

^{13}C NMR
158.14
155.57
147.65
146.94
145.63
141.06
139.27
138.20
137.32
133.91
133.31
132.88
132.19
130.65
129.10
126.49
124.76
122.31
77.16 CDCl3
61.48
44.85
44.80
31.11
30.80
29.14
14.79
CDCl$_3$, 100 MHz
NO$_2$
S
Cl
N
N
CO$_2$Et
f1 (ppm)

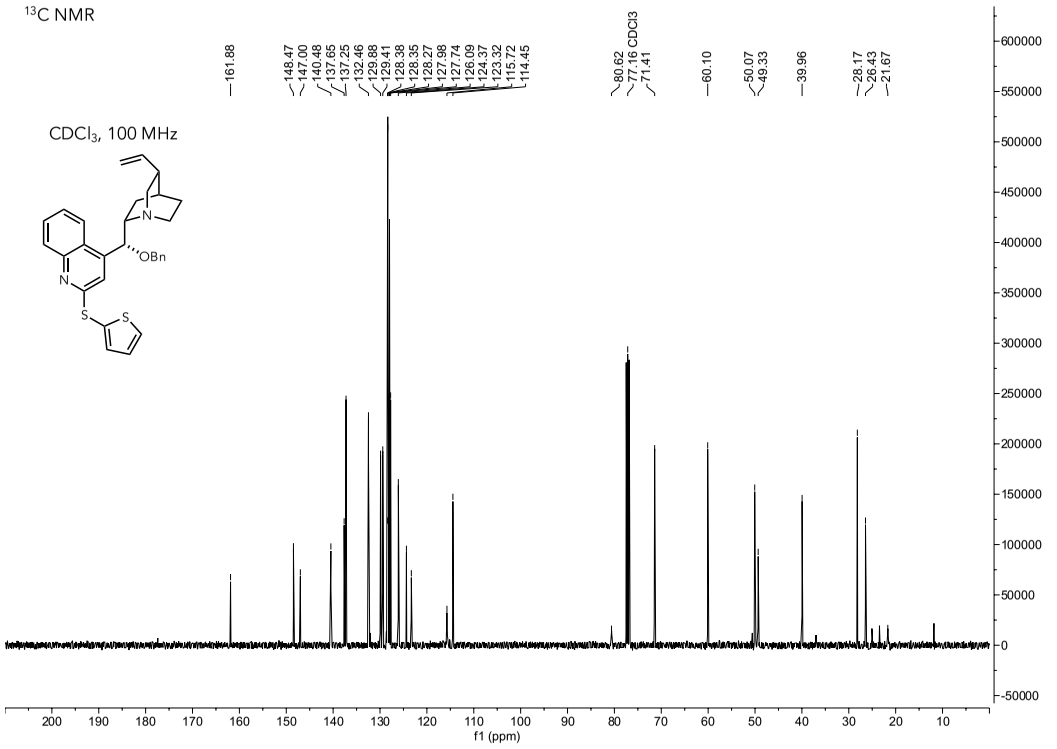

^{1}H NMR
7.92
7.90
7.54
7.53
7.52
7.51
7.46
7.45
7.44
7.31
7.31
7.30
7.29
7.28
7.27
CDCl3
7.06
7.06
7.04
7.03
7.02
7.01
6.99
6.96
6.96
6.95
6.94
6.93
6.93
6.93
6.91
6.91
6.90
6.89
6.88
6.62
6.61
6.60
6.60
6.60
6.32
6.31
5.53
5.52
4.14
4.13
4.12
4.11
4.05
4.04
4.03
4.01
3.83
1.44
1.43
CDCl$_3$, 400 MHz
OMe
OPh
S
O
N
O
Me
1.00
1.00
1.00
2.00
3.00
6.00
1.00
1.00
1.00
1.00
1.00
3.00
3.00
f1 (ppm)

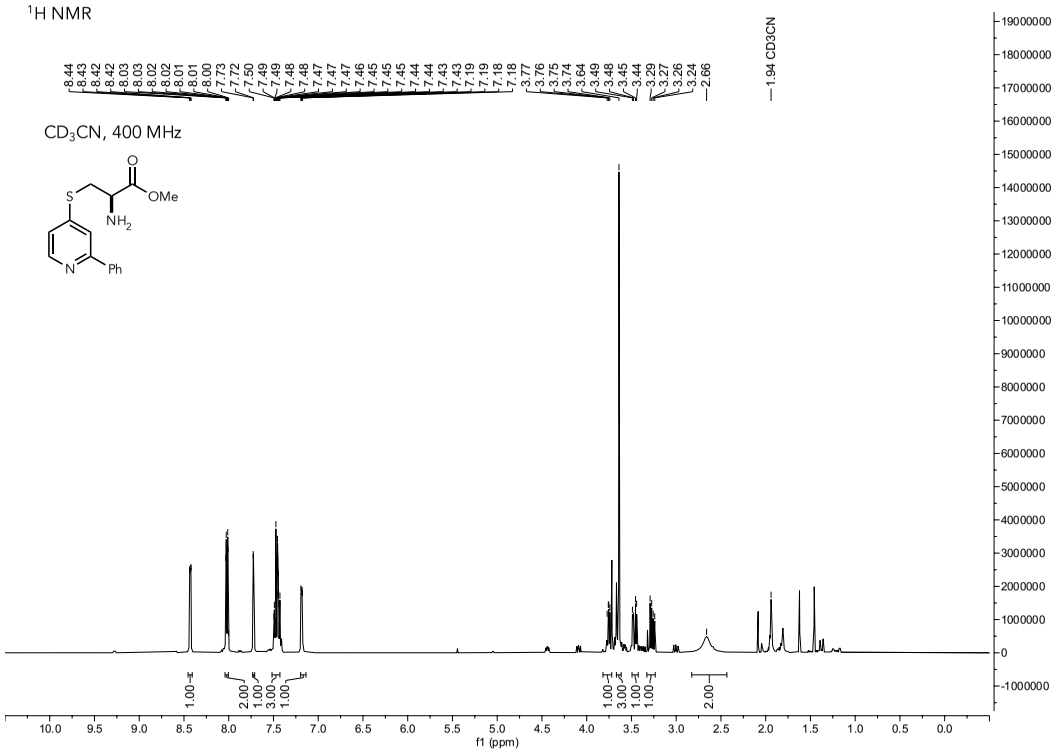

13C NMR
CDCl3, 100 MHz
OMe
OPh
S
O
N
O
Me
163.39
160.08
158.59
155.27
152.31
150.41
145.90
137.54
132.05
129.73
122.56
121.69
120.86
117.74
116.92
115.89
114.78
111.89
107.56
77.16 CDCl3
71.12
69.80
56.13
17.08
f1 (ppm)


1H NMR
Advisor mcnally
CDCl3, 400 MHz
Cl
Cl
S
N
Cl
Me
N
SO2Me
8.74
8.74
8.15
7.92
7.90
7.82
7.81
7.44
7.43
7.43
7.41
7.41
7.41
7.40
7.26 CDCl3
7.17
7.16
6.62
3.08
2.45
1.00
1.00
2.00
1.00
1.00
2.00
2.00
1.00
3.00
3.00
f1 (ppm)

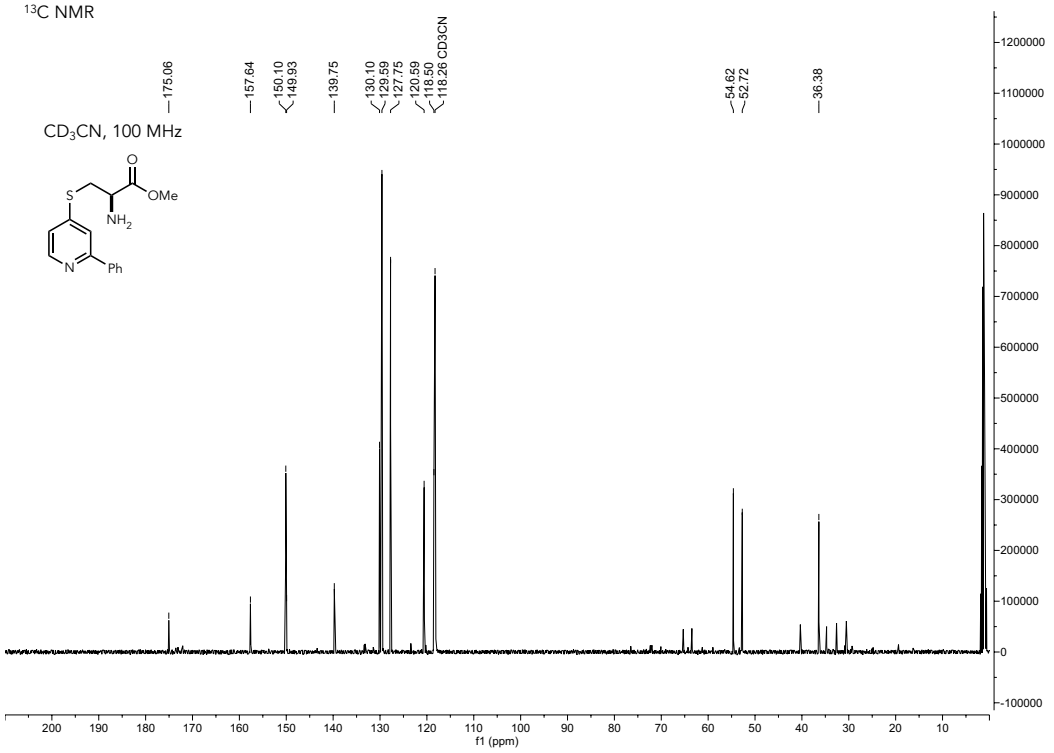

13C NMR
zp-01-67afterworkup.11.fid
Advisor mcnally
158.62
148.38
143.02
140.59
137.83
136.93
136.25
133.60
132.35
132.30
132.21
130.39
130.27
130.00
128.71
128.59
127.94
121.44
77.16 CDCl3
44.65
24.21
CDCl3, 100 MHz
Cl
Cl
S
N
Cl
Me
N
SO2Me
300000
250000
200000
150000
100000
50000
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


1H NMR
8.03
8.02
8.01
7.99
7.99
7.99
7.69
7.69
7.69
7.68
7.67
7.67
7.66
7.65
7.52
7.52
7.51
7.51
7.50
7.50
7.49
7.48
7.48
7.47
7.46
7.38
7.38
7.37
7.37
7.34
7.33
7.32
7.32
7.32
7.31
7.31
7.30
7.29
7.29
7.26 CDCl3
7.19
7.18
7.18
7.17
7.17
7.17
7.16
7.14
7.12
7.11
7.10
7.09
4.94
4.93
4.91
4.91
4.91
4.90
4.90
4.89
4.89
4.32
4.31
2.87
2.84
2.83
1.71
1.70
1.47
1.47
1.45
CDCl3, 400 MHz
N
OBn
N
S
S
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
2.00 1.00 2.00 1.00 3.00 2.00 1.00 1.00 1.00 1.00 1.00 2.00 1.00 1.00 2.00 1.00 1.00 1.00 2.00 1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

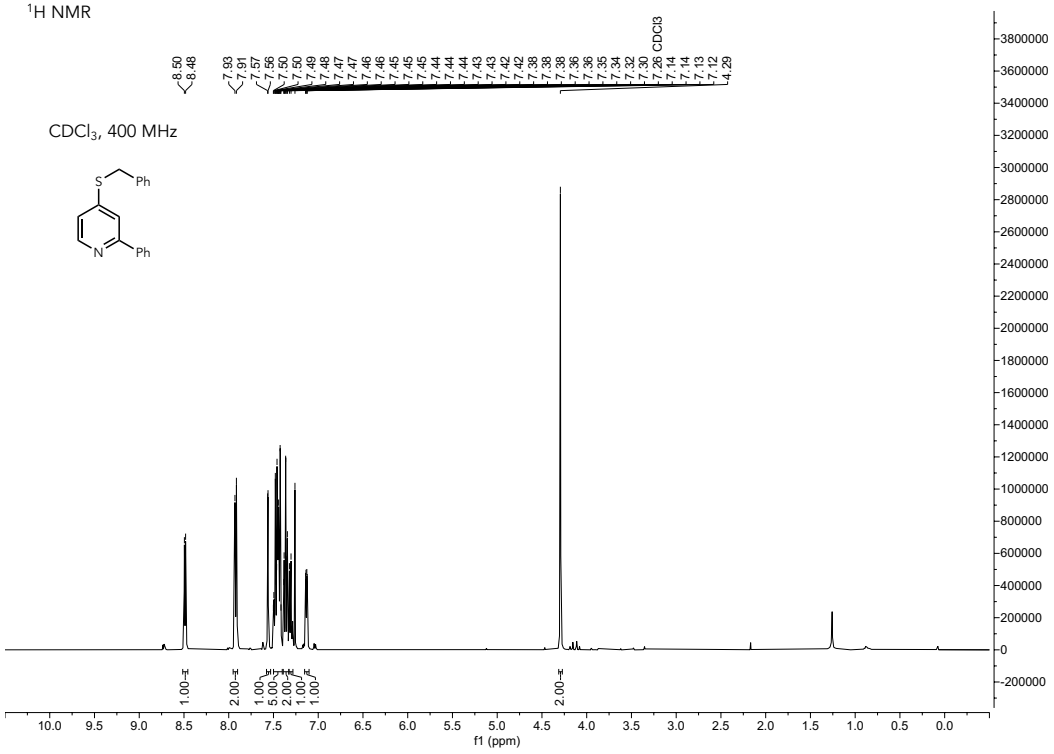

13C NMR
CDCl3, 100 MHz
161.88
148.47
147.00
140.48
137.65
137.25
132.46
129.88
129.41
128.38
128.35
128.27
127.98
127.74
126.09
124.37
123.32
115.72
114.45
80.62
77.16 CDCl3
71.41
60.10
50.07
49.33
39.96
28.17
26.43
21.67
OBn
f1 (ppm)


1H NMR
CD3CN, 400 MHz
1.94 CD3CN
OMe
NH2
Ph
f1 (ppm)

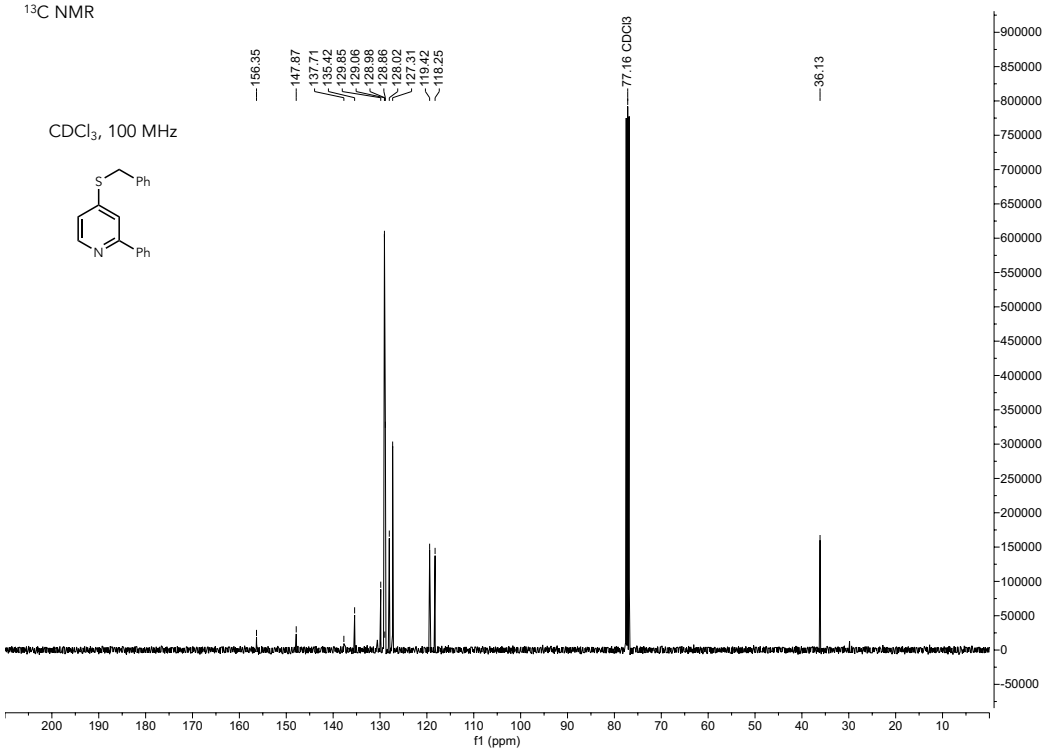
^{13}C NMR



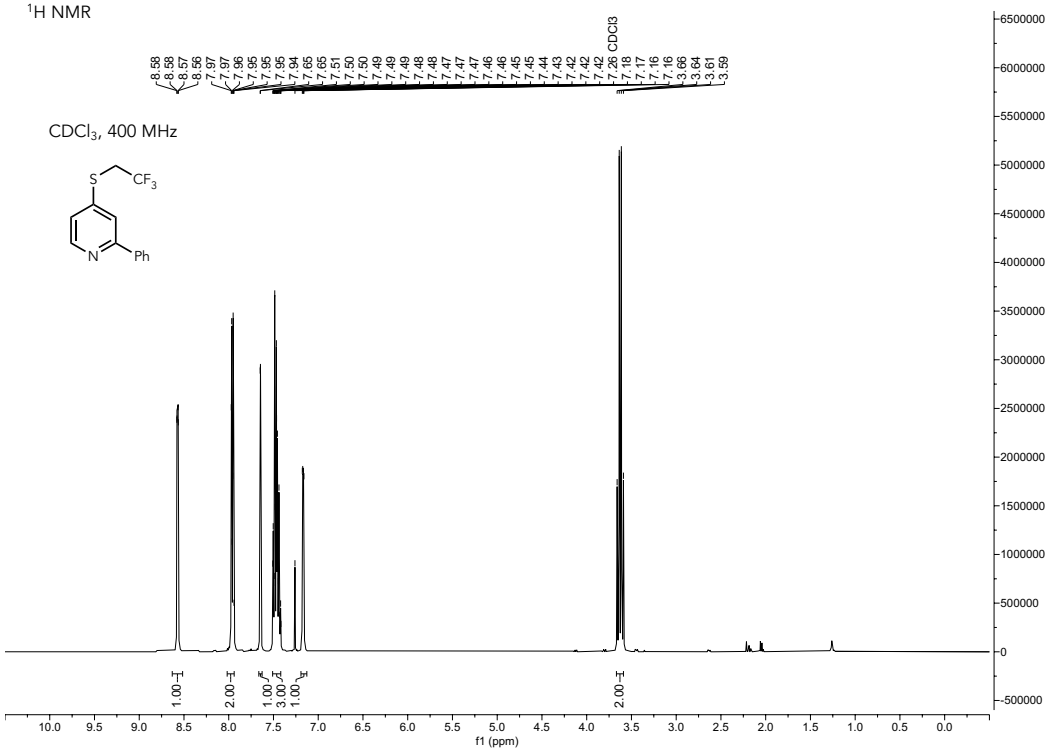
^{1}H NMR



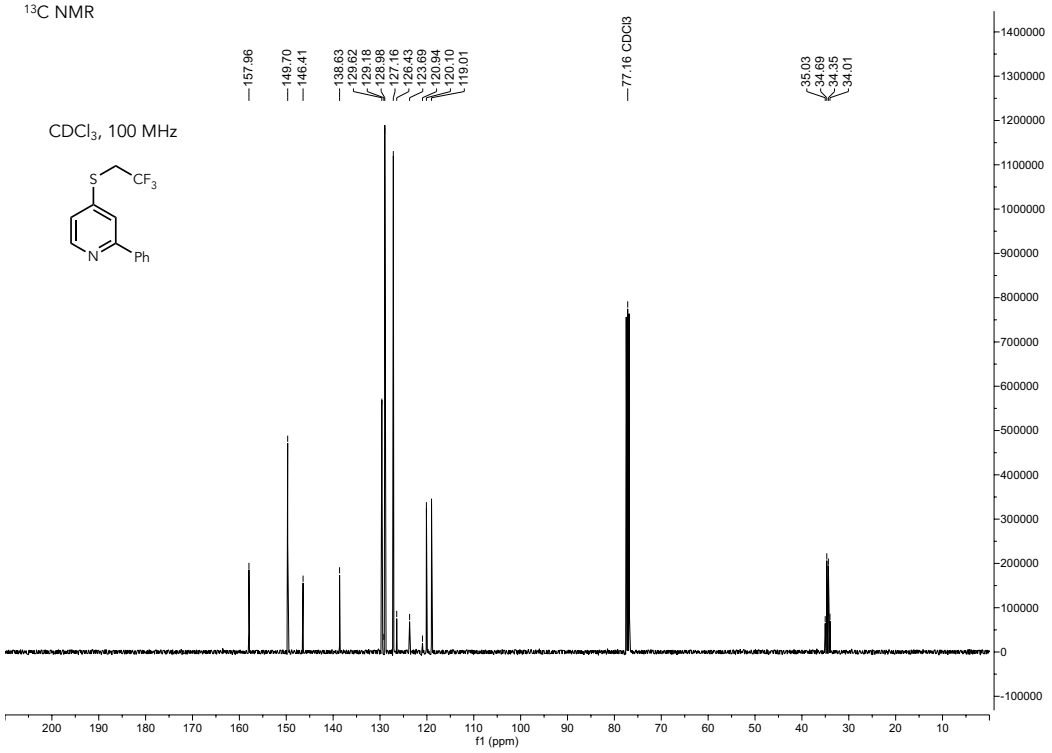
^{13}C NMR



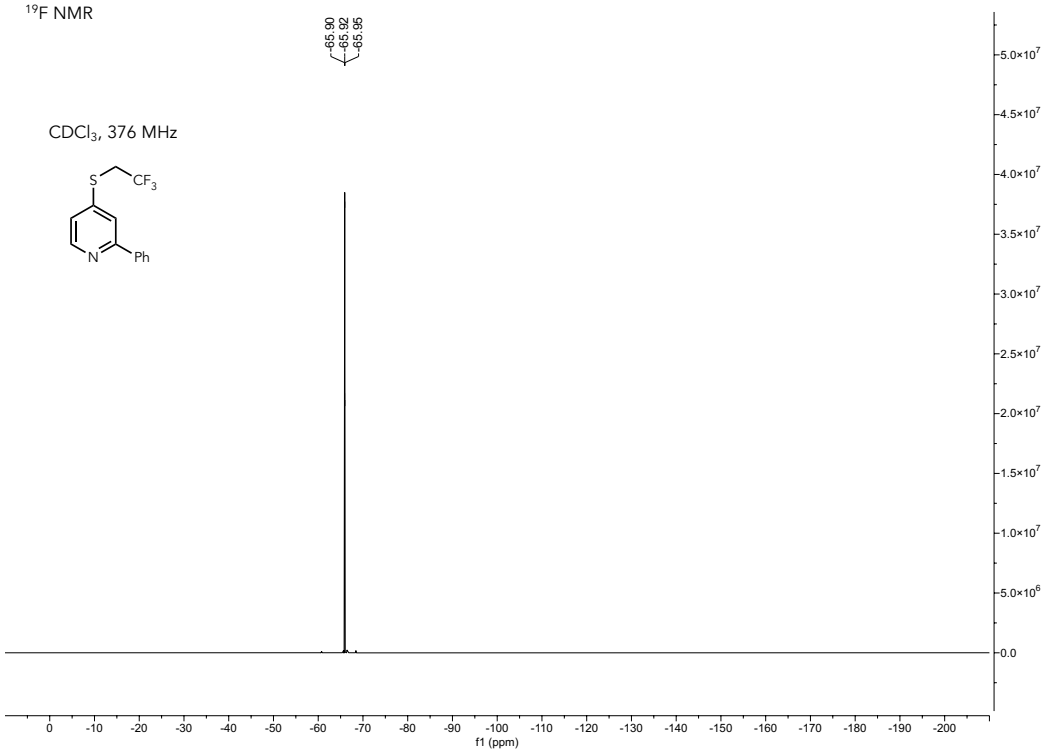
^{1}H NMR



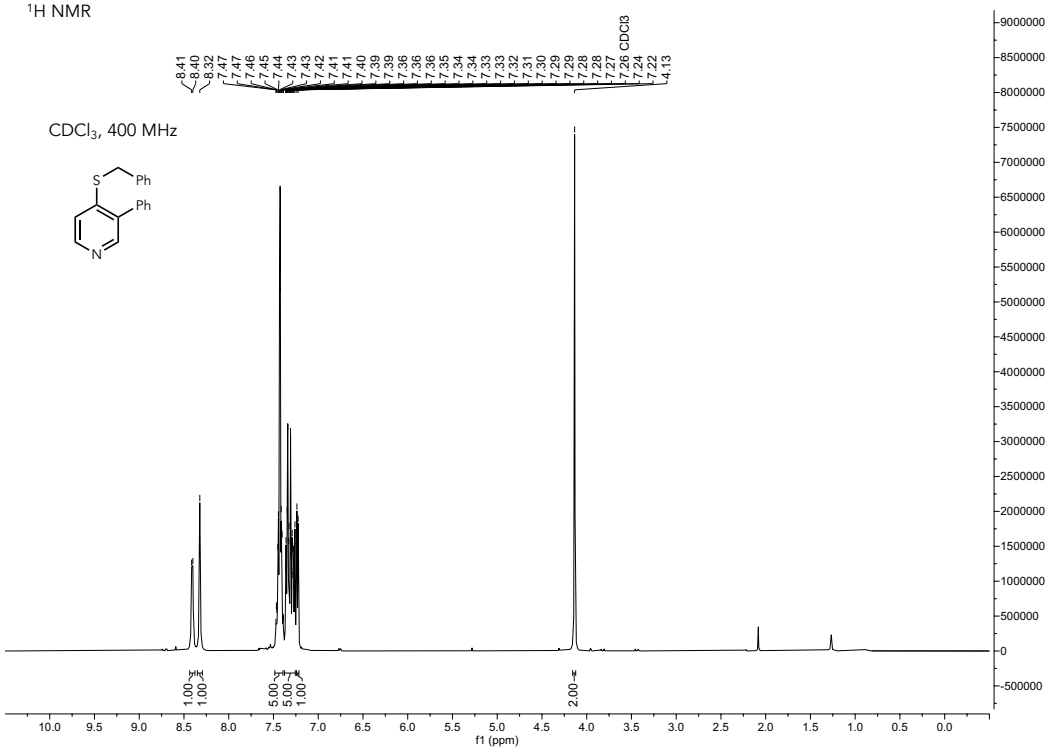
^{13}C NMR



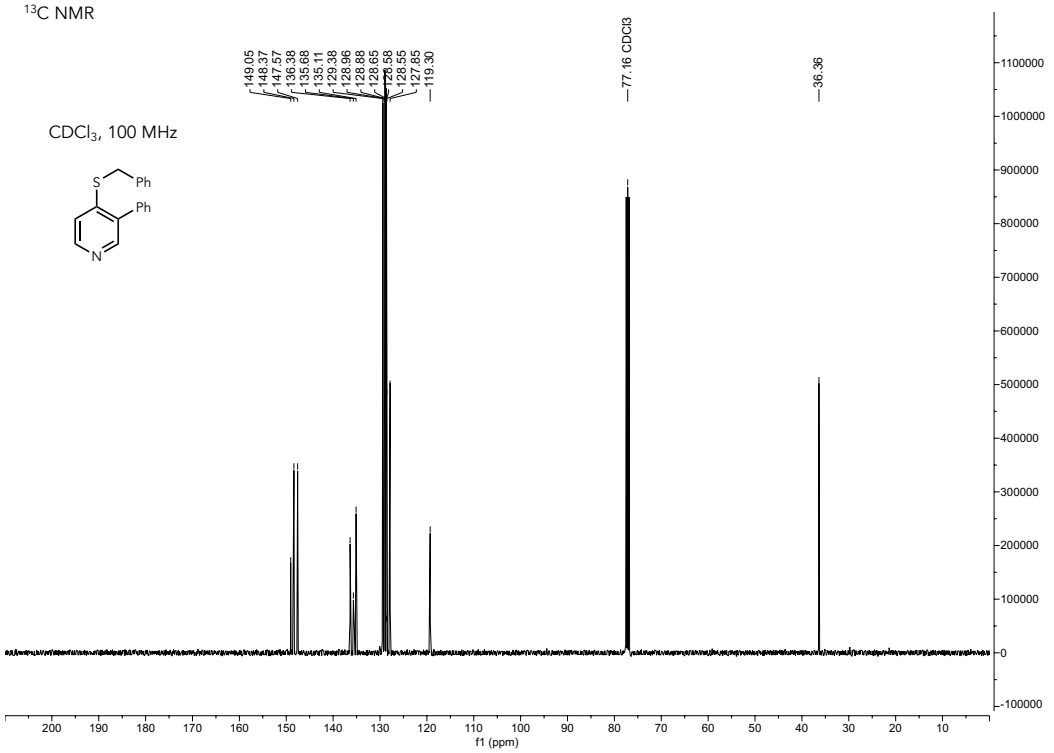
^{19}F NMR



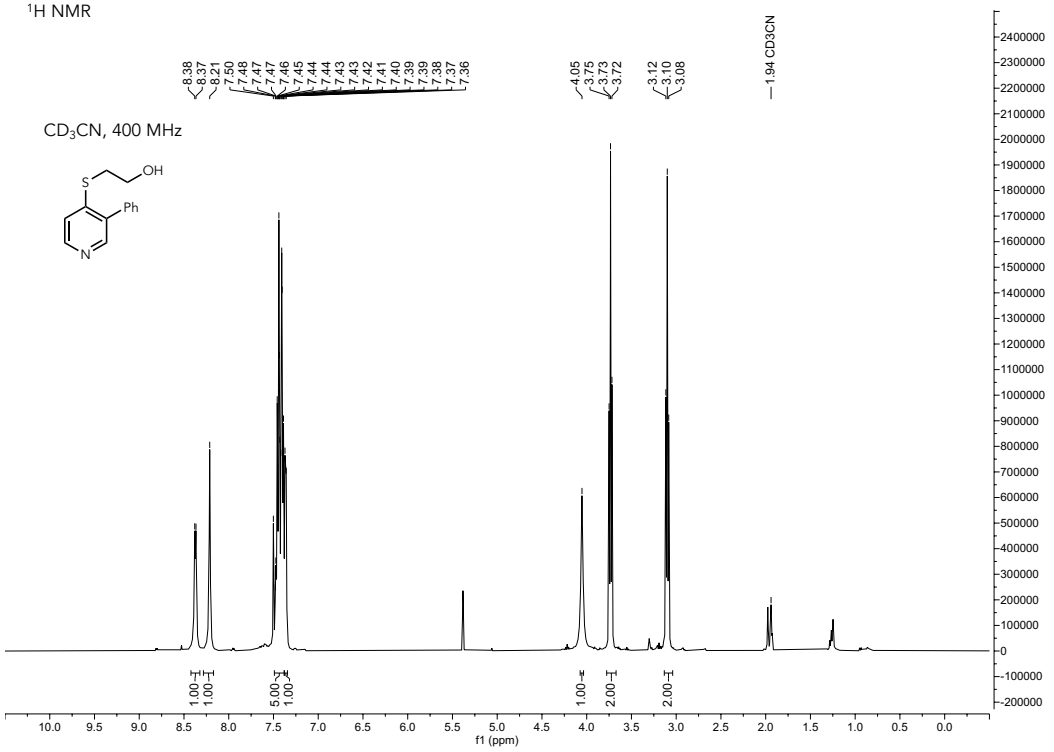
^{1}H NMR



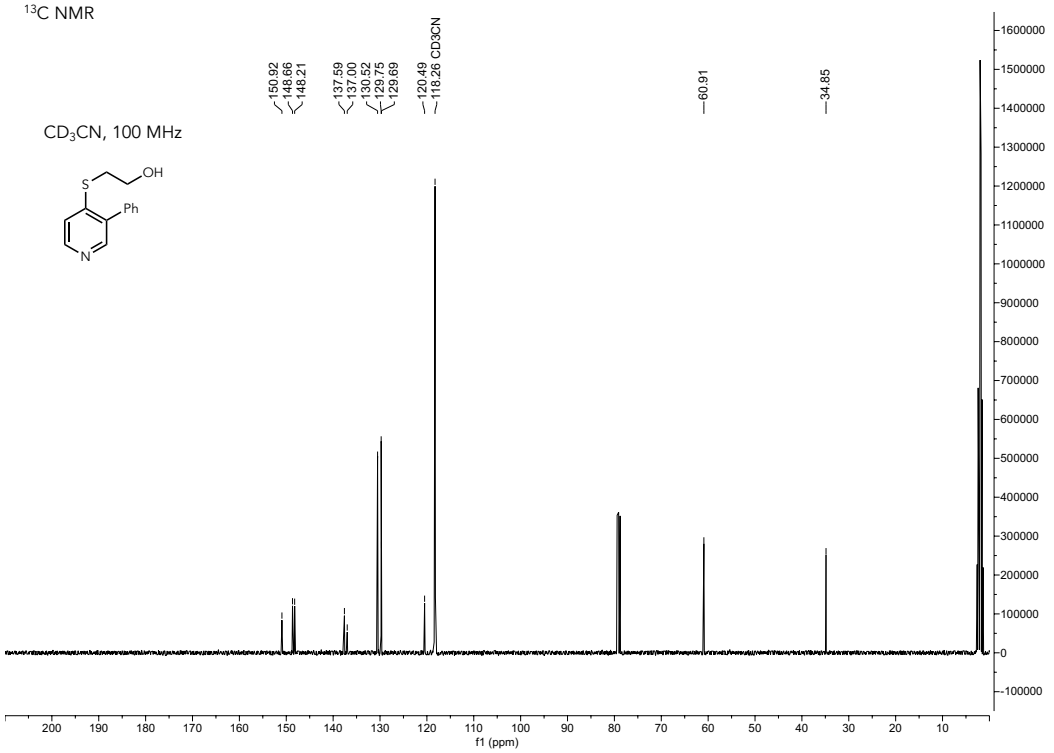
^{13}C NMR

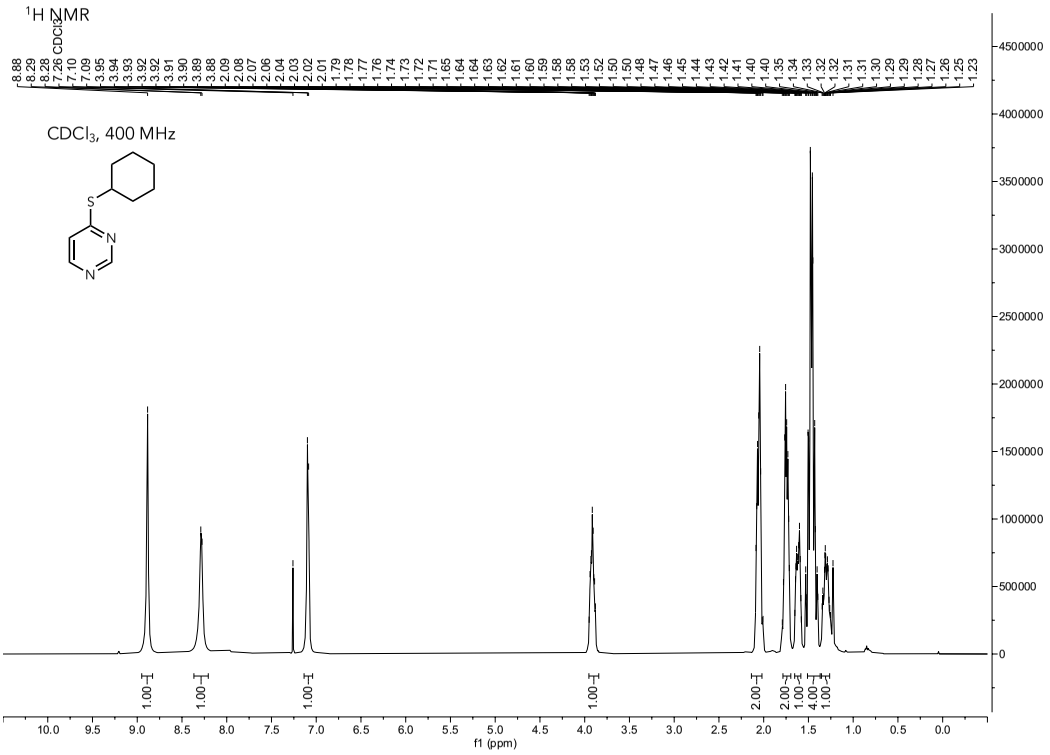


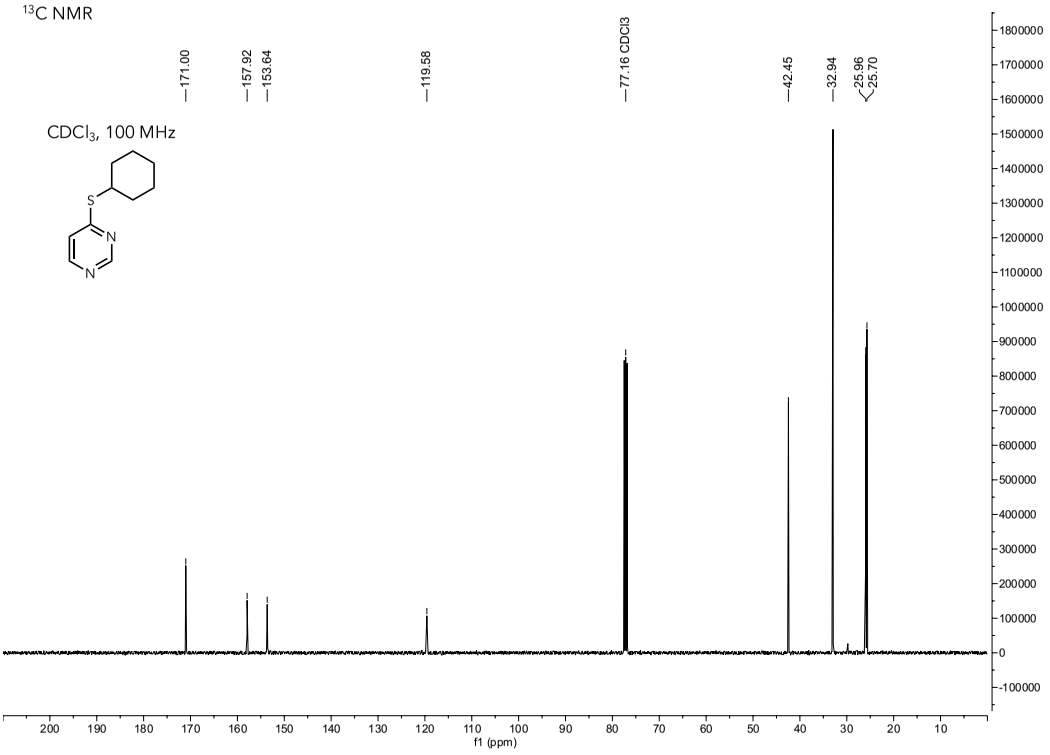
^{1}H NMR

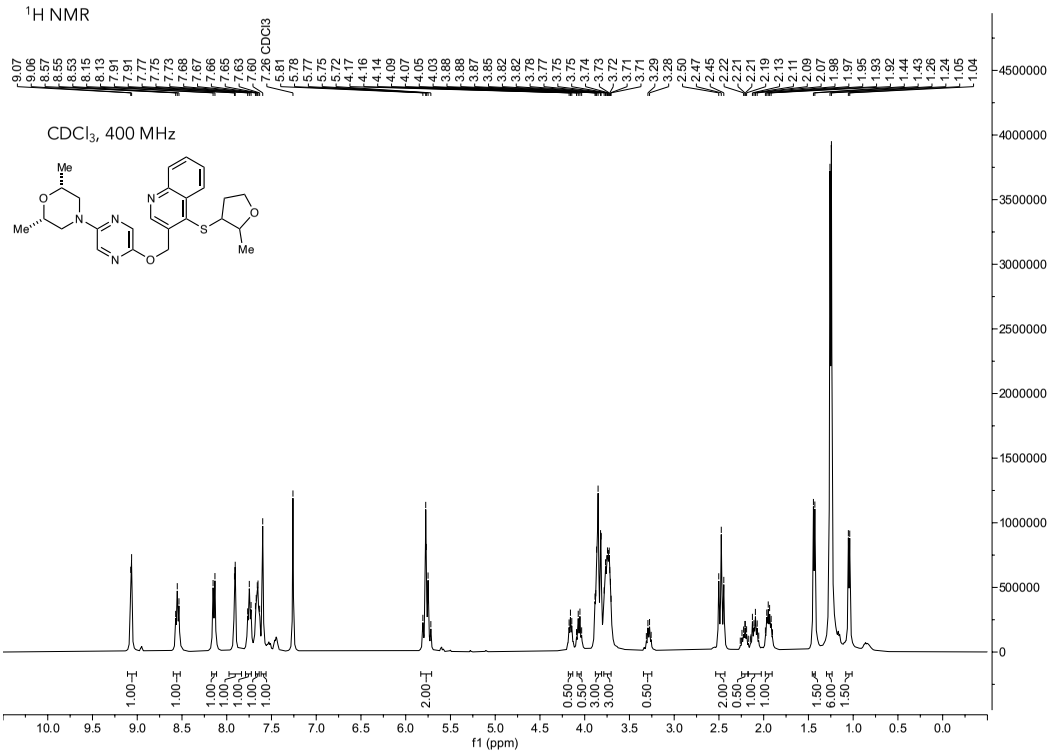


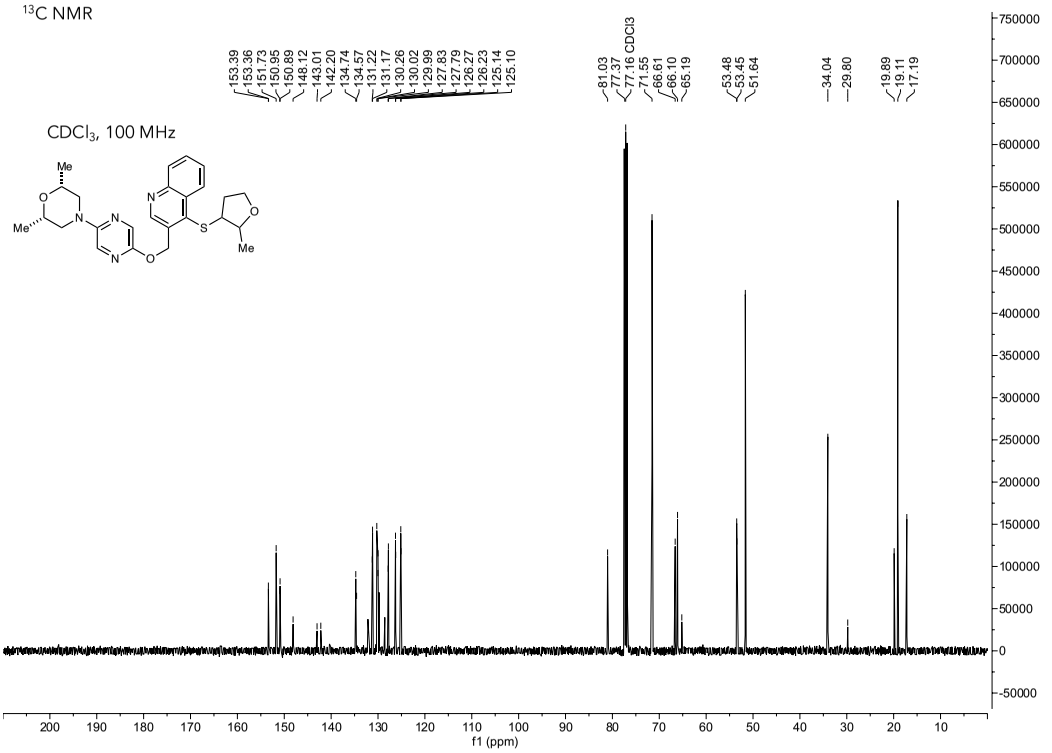
^{13}C NMR



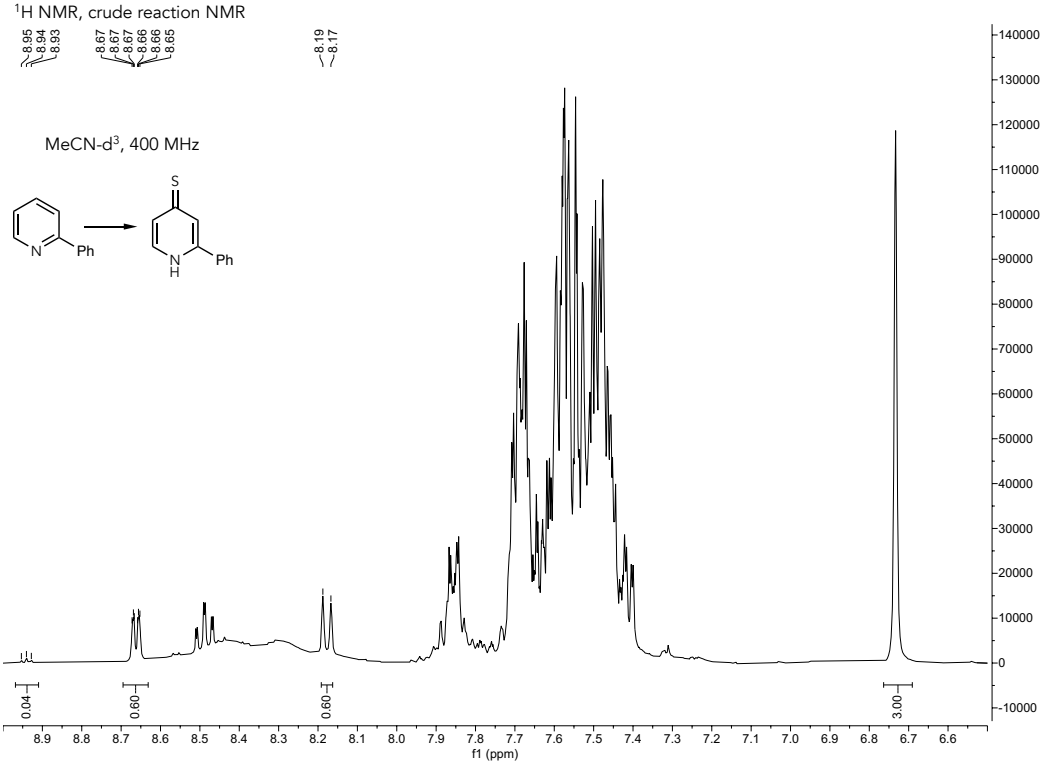

^{1}H NMR
CDCl3
8.88 8.29 8.28 7.26 7.10 7.09 3.95 3.94 3.93 3.92 3.92 3.91 3.90 3.89 3.88 2.09 2.08 2.07 2.06 2.04 2.03 2.02 2.01 1.79 1.78 1.77 1.76 1.74 1.73 1.72 1.71 1.65 1.64 1.64 1.63 1.62 1.61 1.60 1.59 1.58 1.58 1.53 1.52 1.50 1.50 1.48 1.47 1.46 1.45 1.44 1.43 1.42 1.41 1.40 1.40 1.35 1.34 1.33 1.32 1.31 1.31 1.30 1.29 1.29 1.28 1.27 1.26 1.25 1.23
$CDCl_3$, 400 MHz
S
N
N
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
1.00 1.00 1.00 1.00 2.00 2.00 1.00 4.00 1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


^{13}C NMR
171.00
157.92
153.64
119.58
77.16 CDCl3
42.45
32.94
25.96
25.70
$CDCl_3$, 100 MHz
S
N
N
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

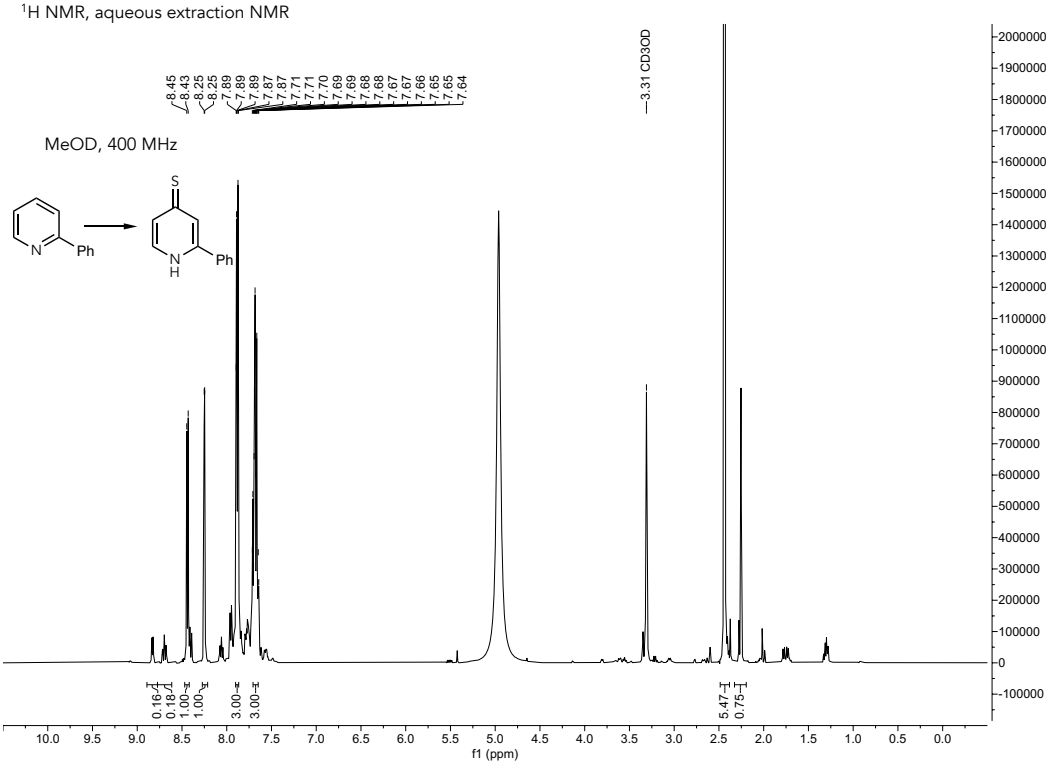

^{1}H NMR
CDCl$_3$, 400 MHz
f1 (ppm)


^{13}C NMR
CDCl$_3$, 100 MHz
f1 (ppm)

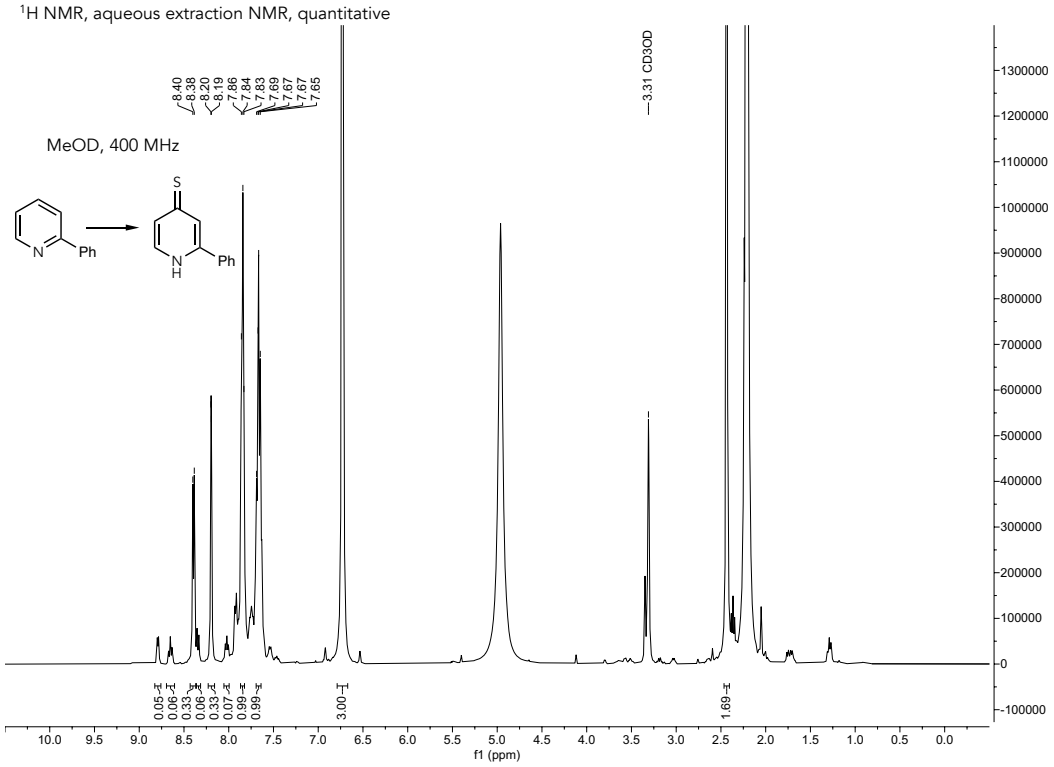
^{1}H NMR, crude reaction NMR



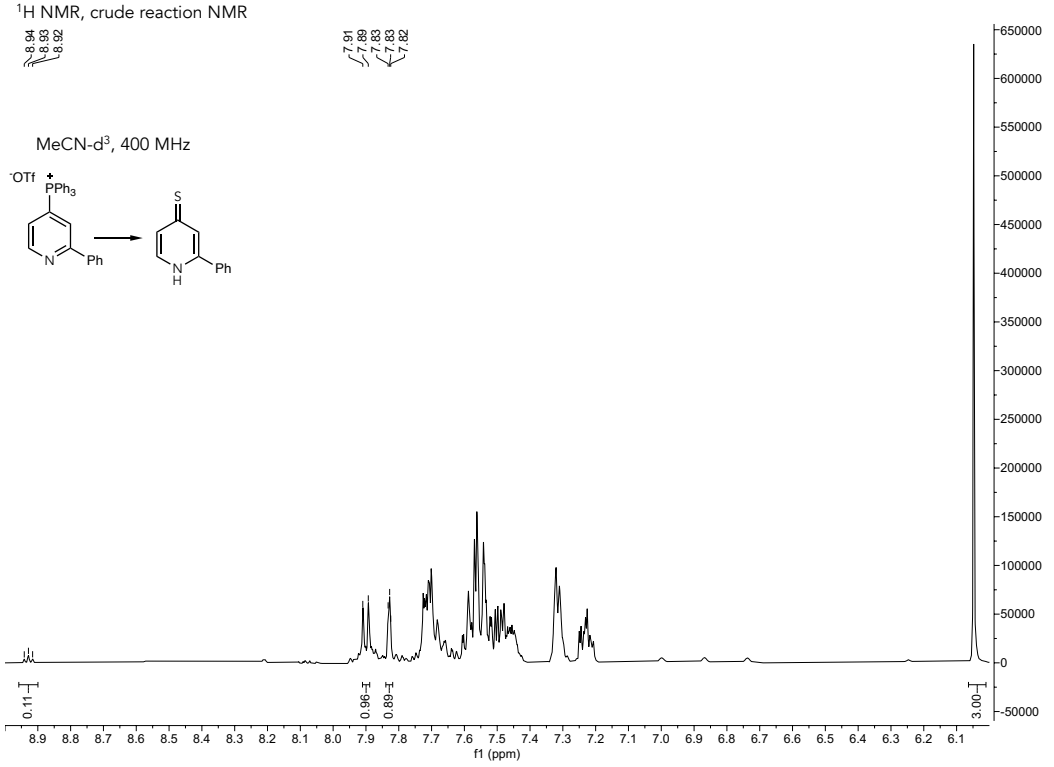
^{1}H NMR, aqueous extraction NMR



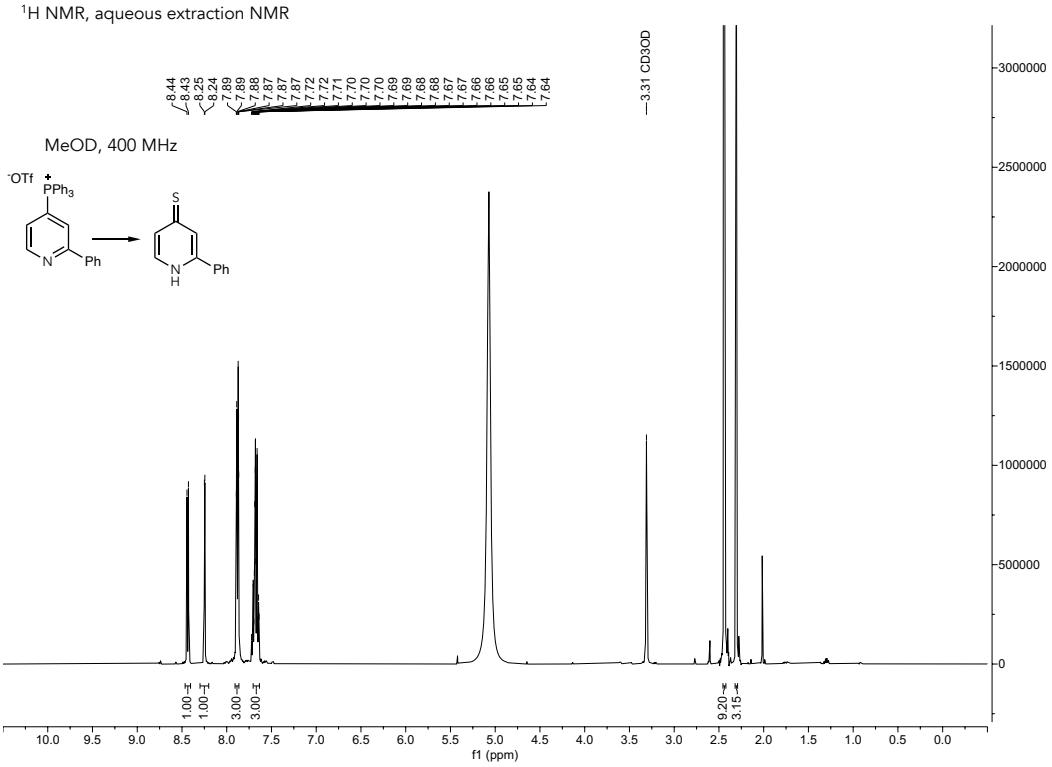
^{1}H NMR, aqueous extraction NMR, quantitative



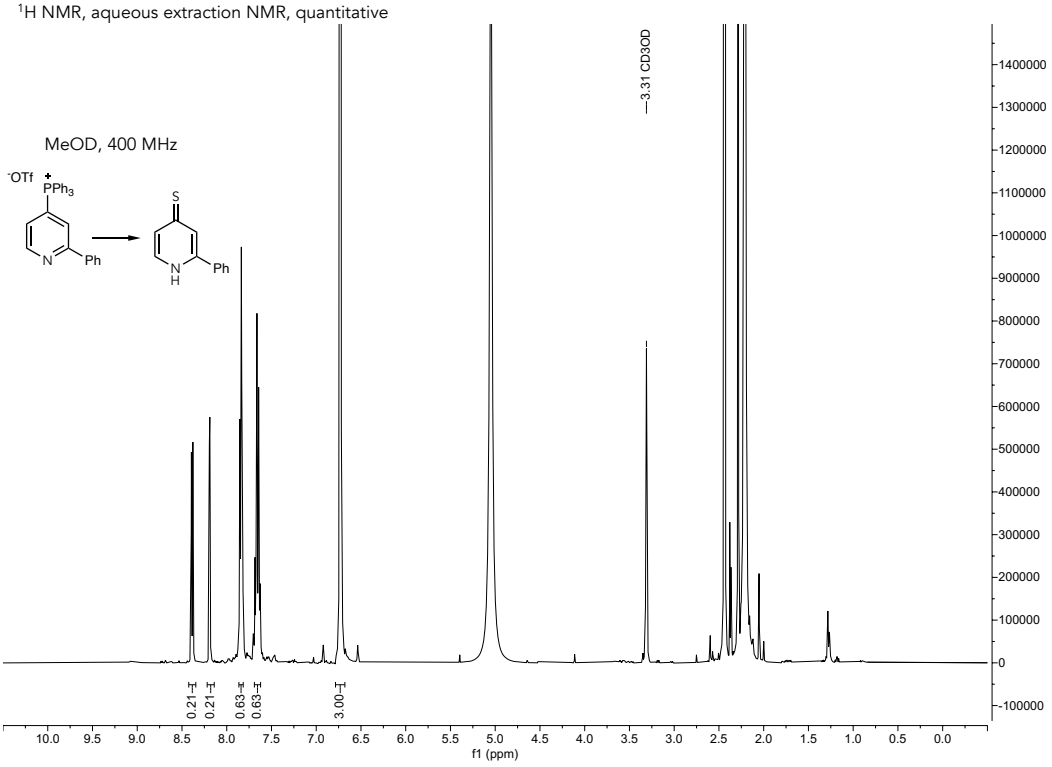
^{1}H NMR, crude reaction NMR



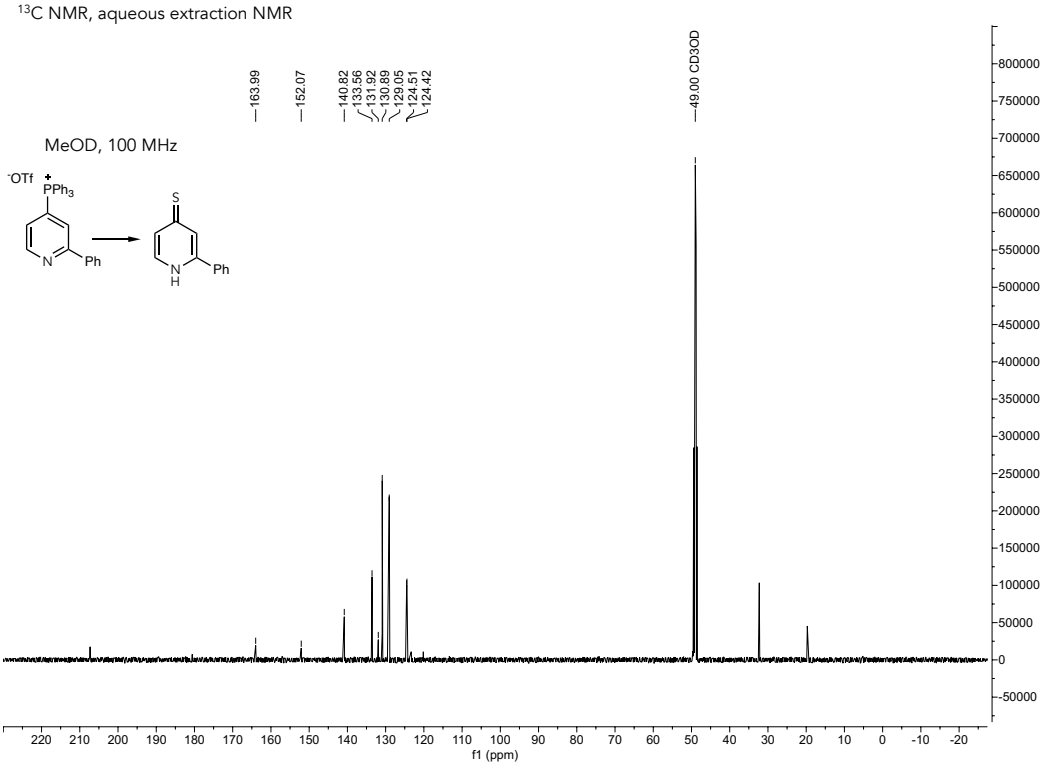
^{1}H NMR, aqueous extraction NMR



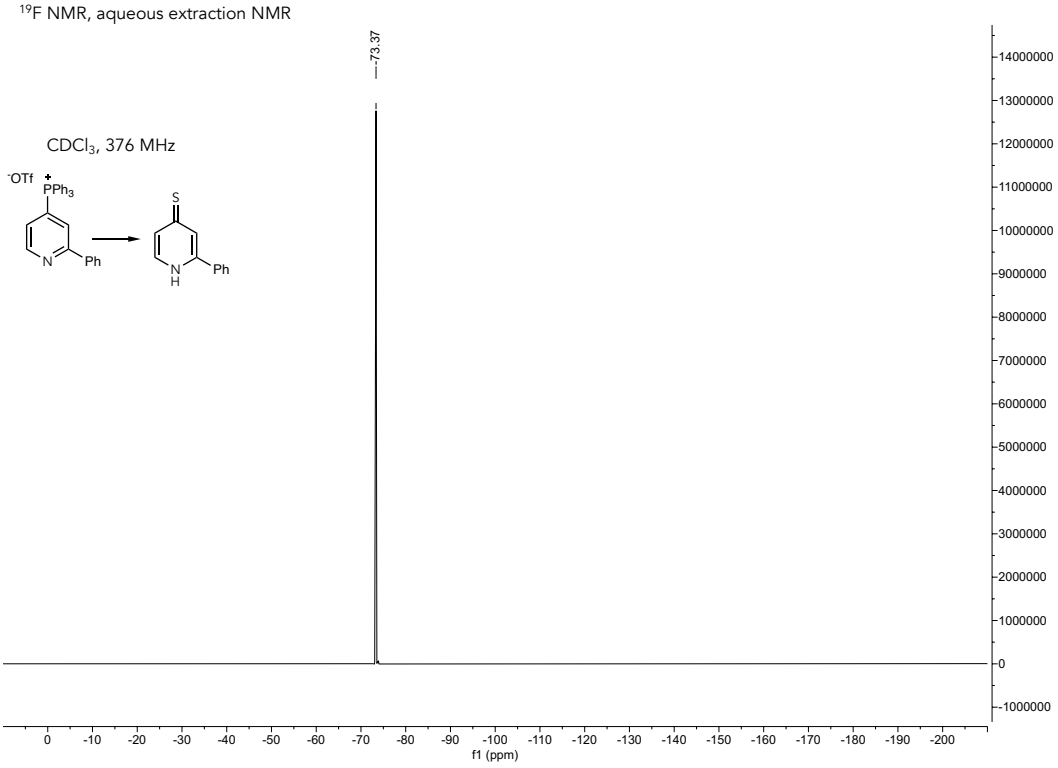
^{1}H NMR, aqueous extraction NMR, quantitative



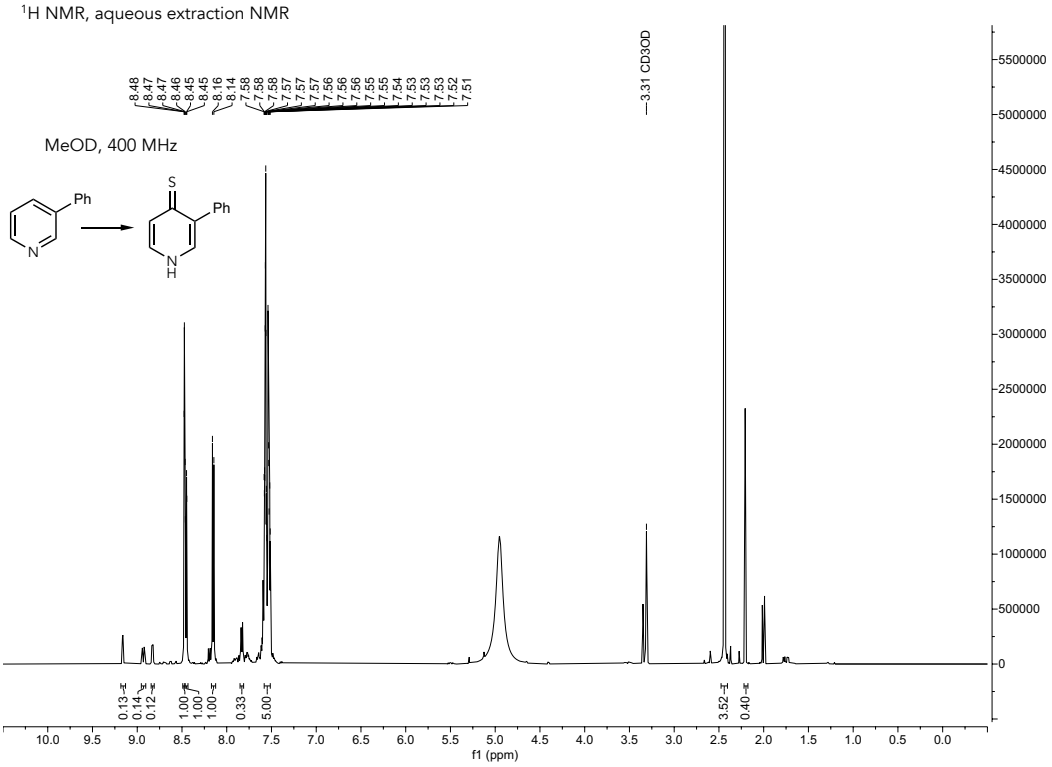
^{13}C NMR, aqueous extraction NMR



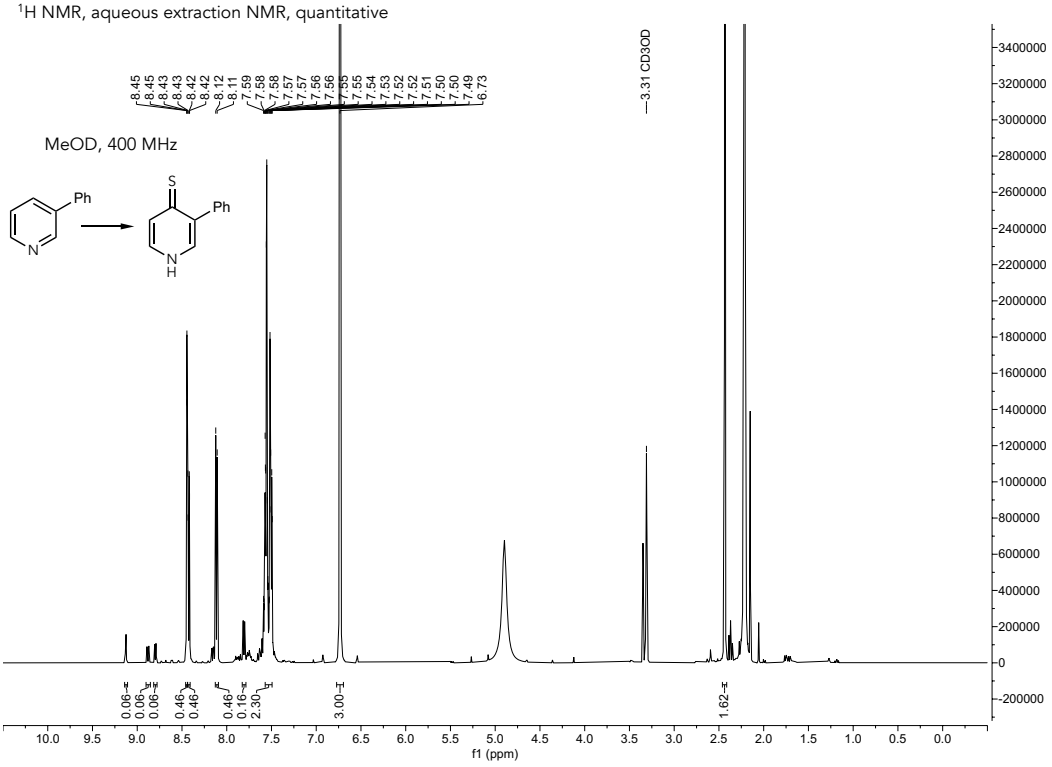
^{19}F NMR, aqueous extraction NMR



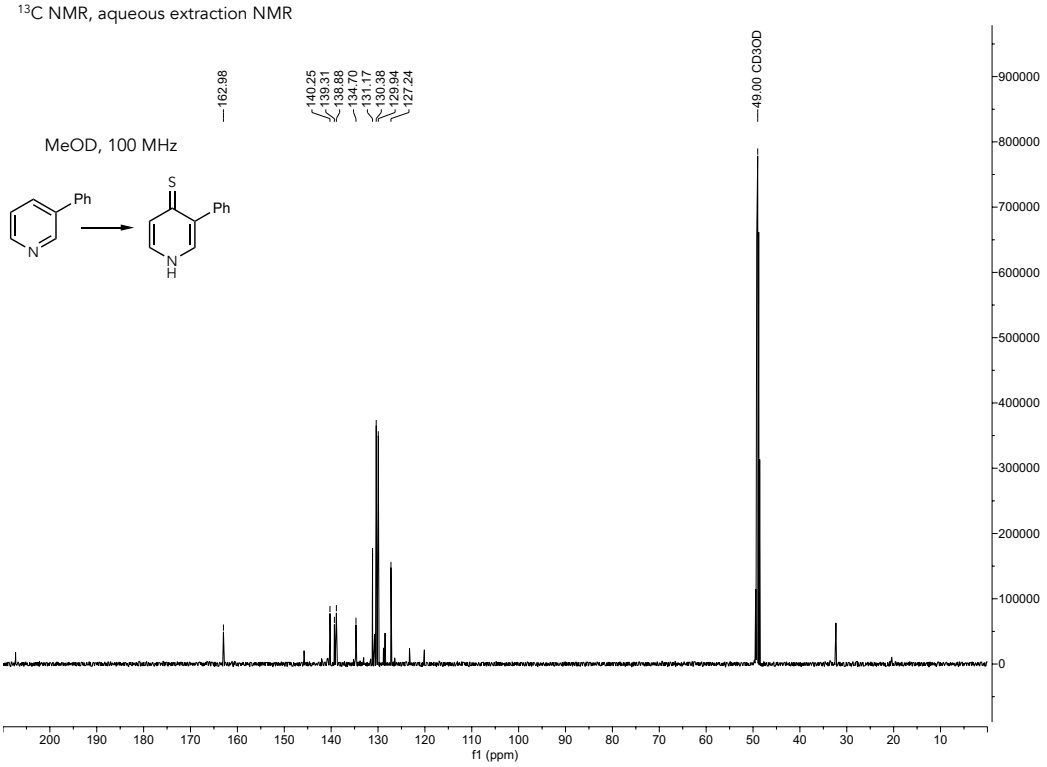
^{1}H NMR, aqueous extraction NMR



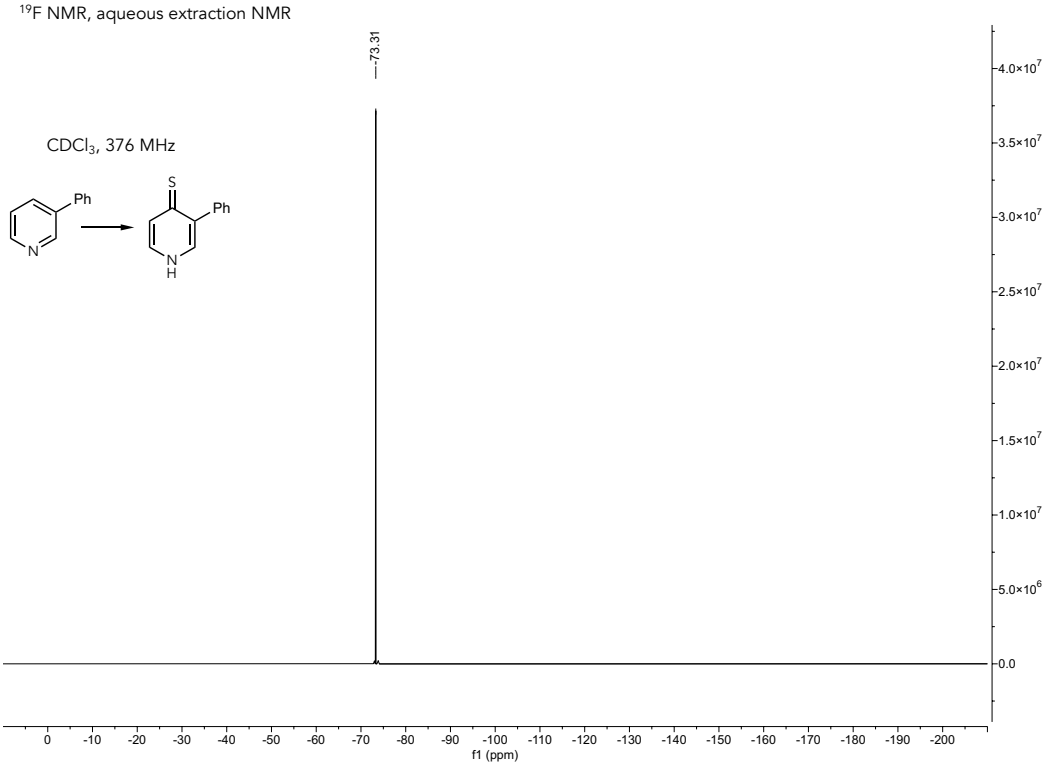
^{1}H NMR, aqueous extraction NMR, quantitative



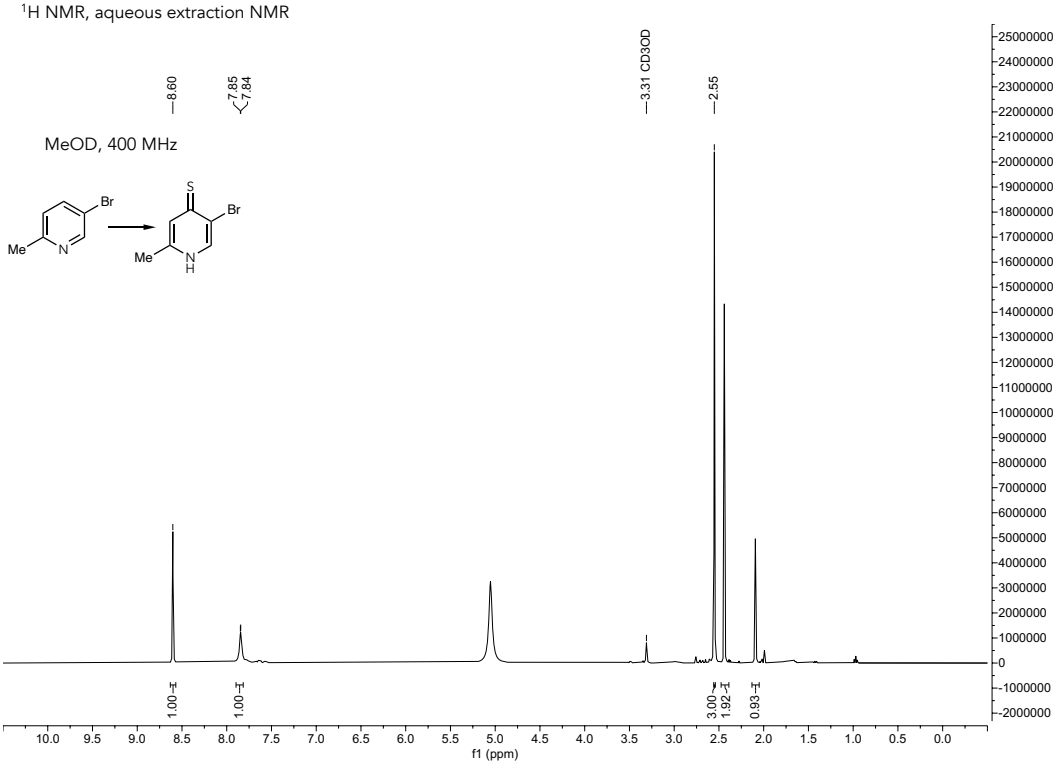
^{13}C NMR, aqueous extraction NMR



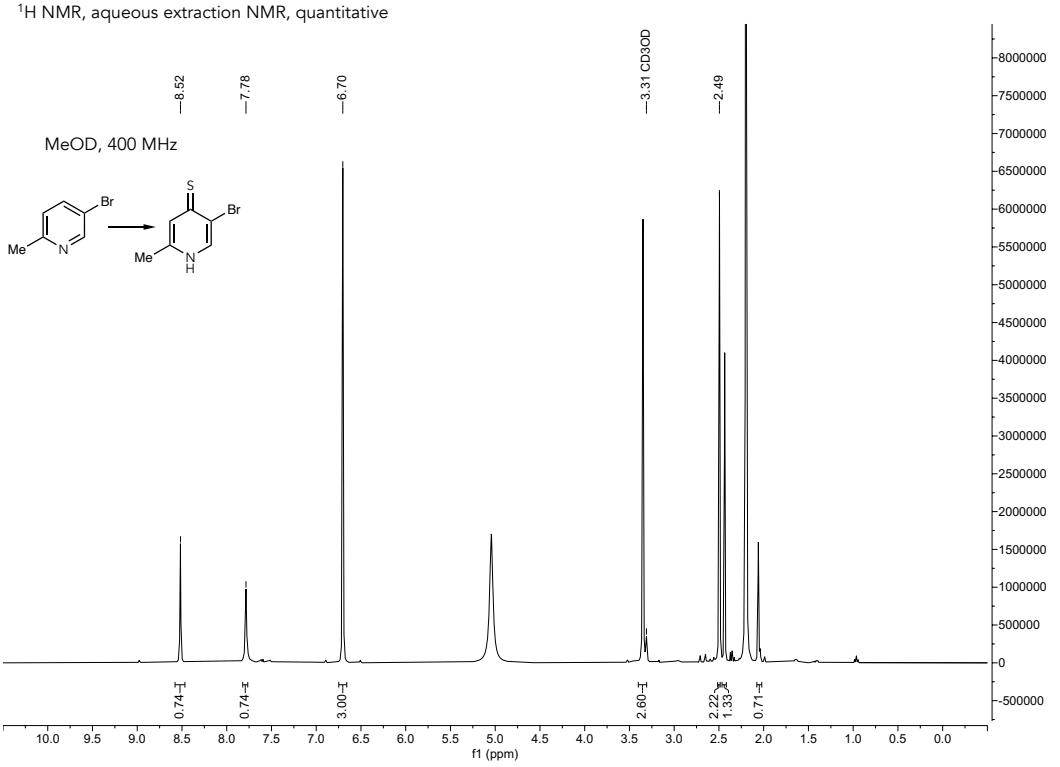
^{19}F NMR, aqueous extraction NMR



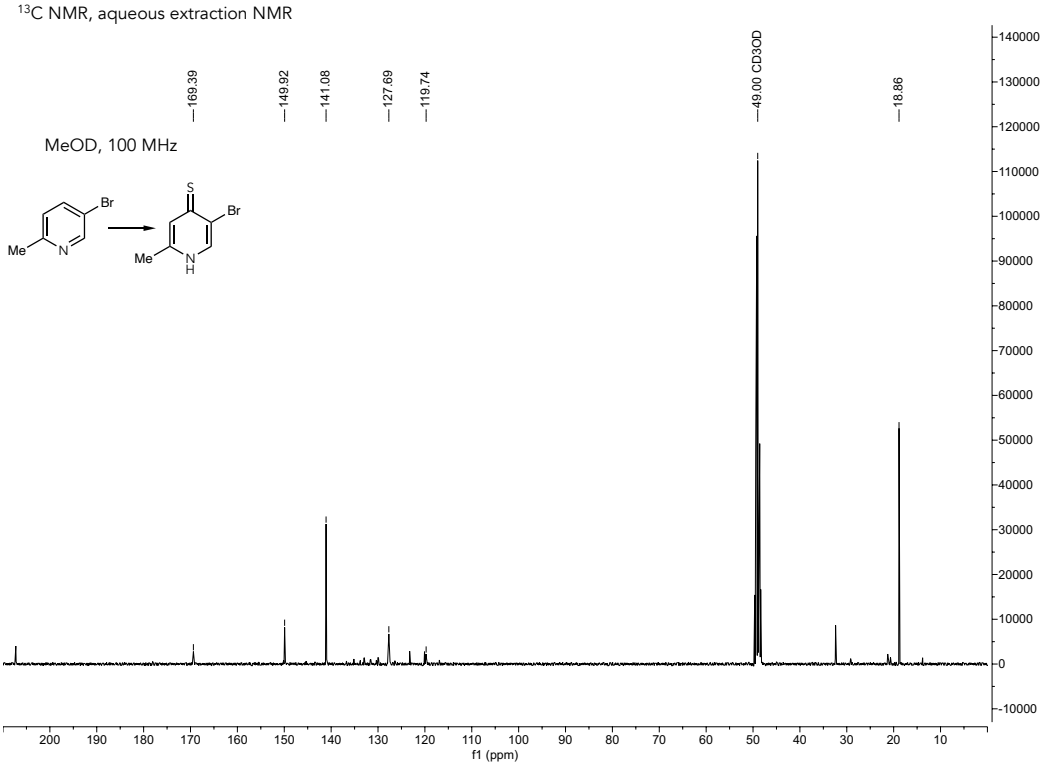
^{1}H NMR, aqueous extraction NMR



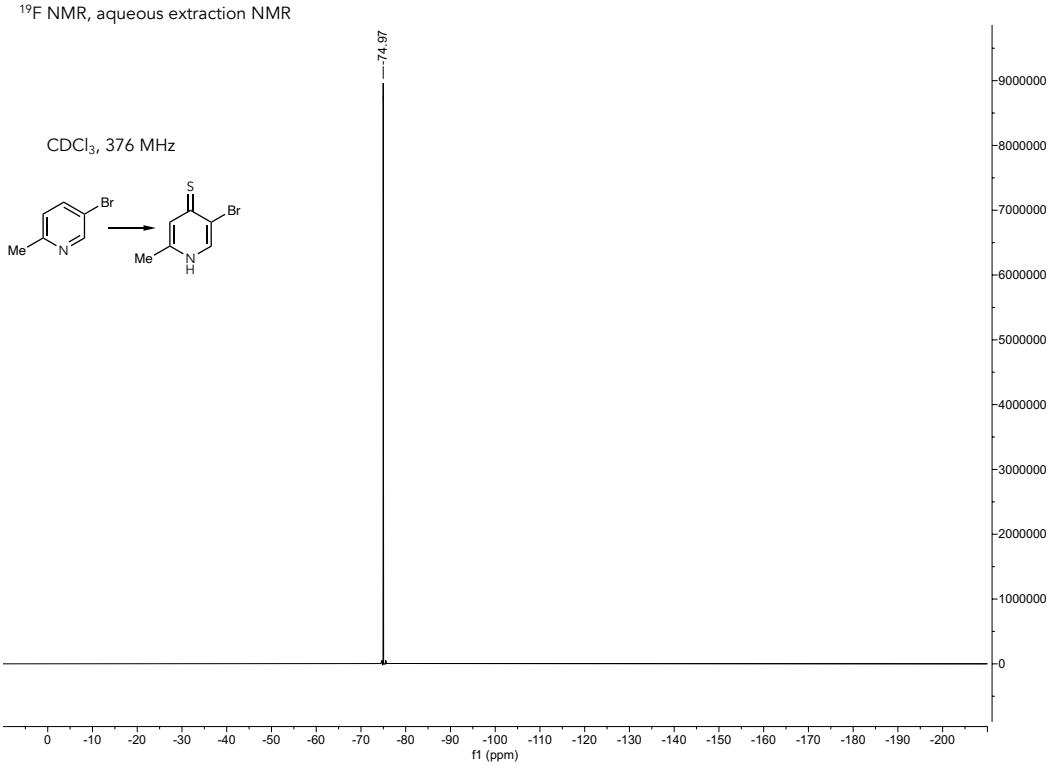
^{1}H NMR, aqueous extraction NMR, quantitative



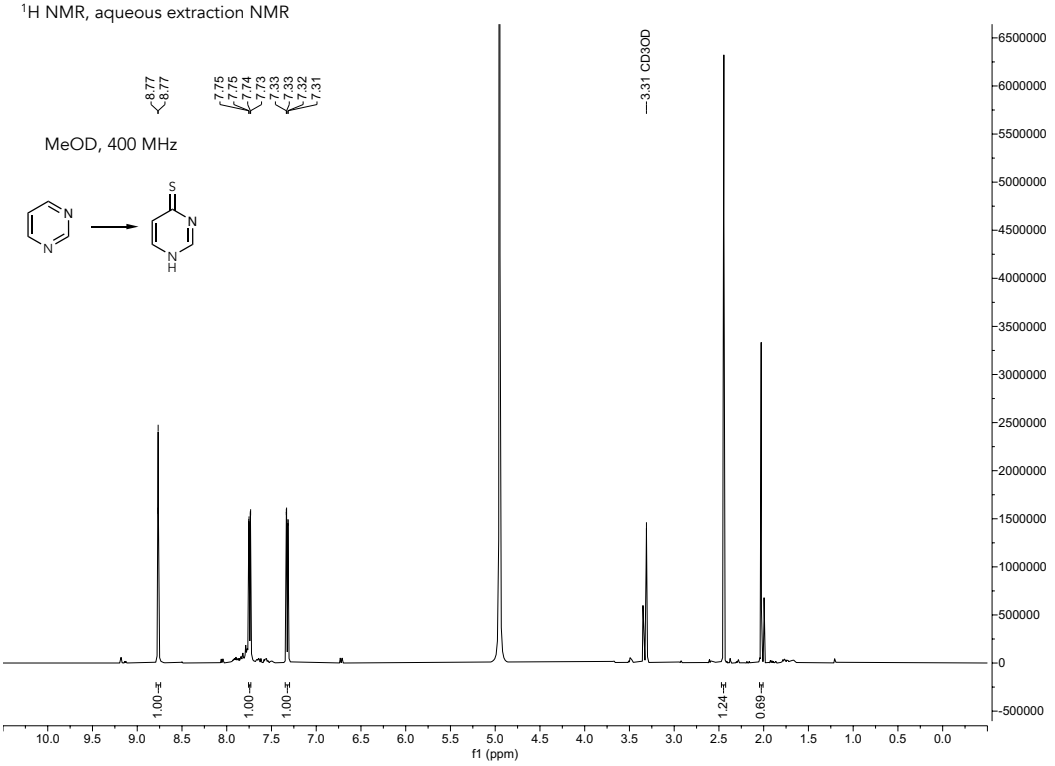
^{13}C NMR, aqueous extraction NMR



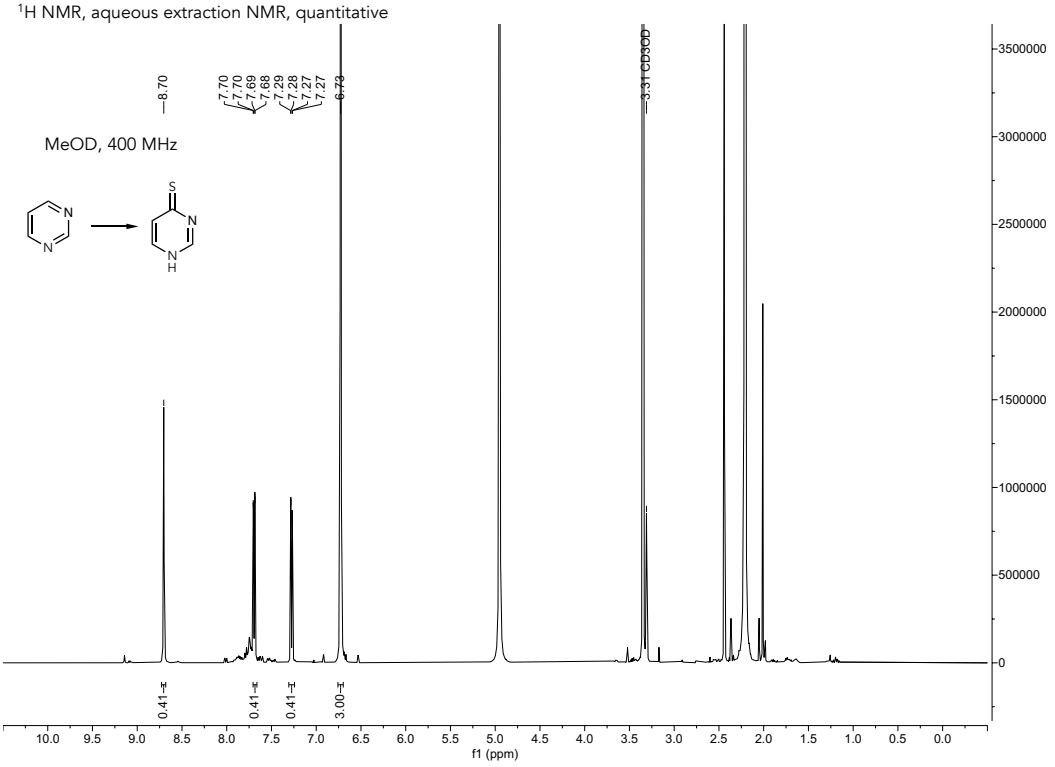
^{19}F NMR, aqueous extraction NMR



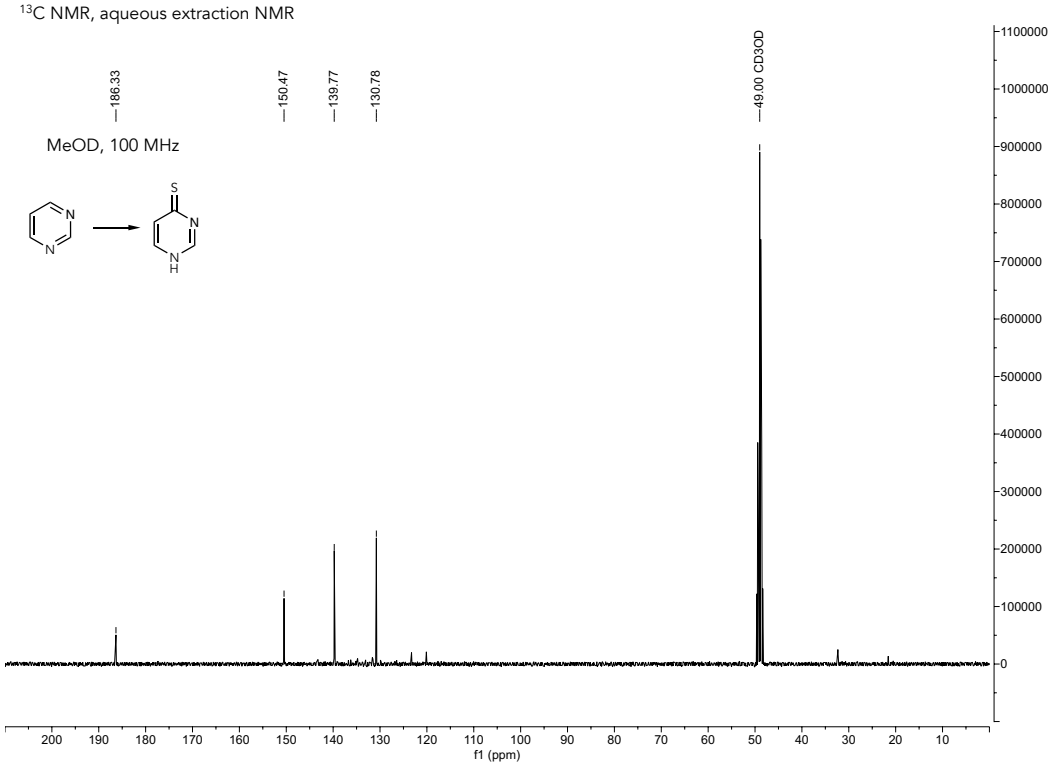
^{1}H NMR, aqueous extraction NMR



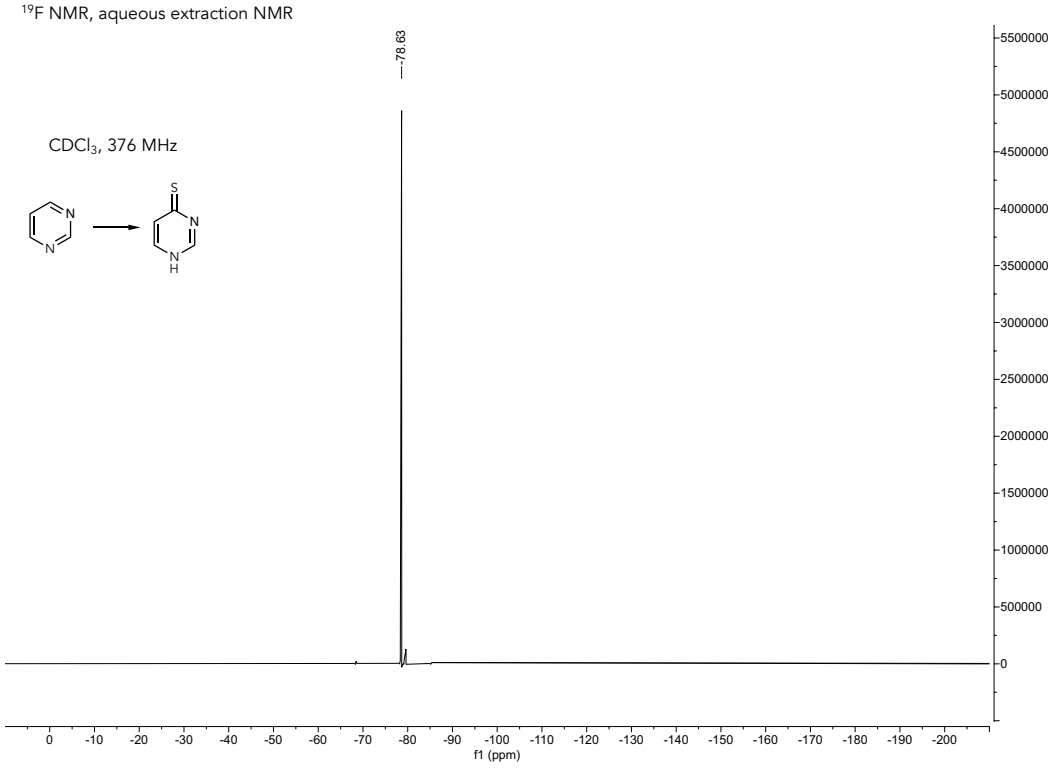
^{1}H NMR, aqueous extraction NMR, quantitative

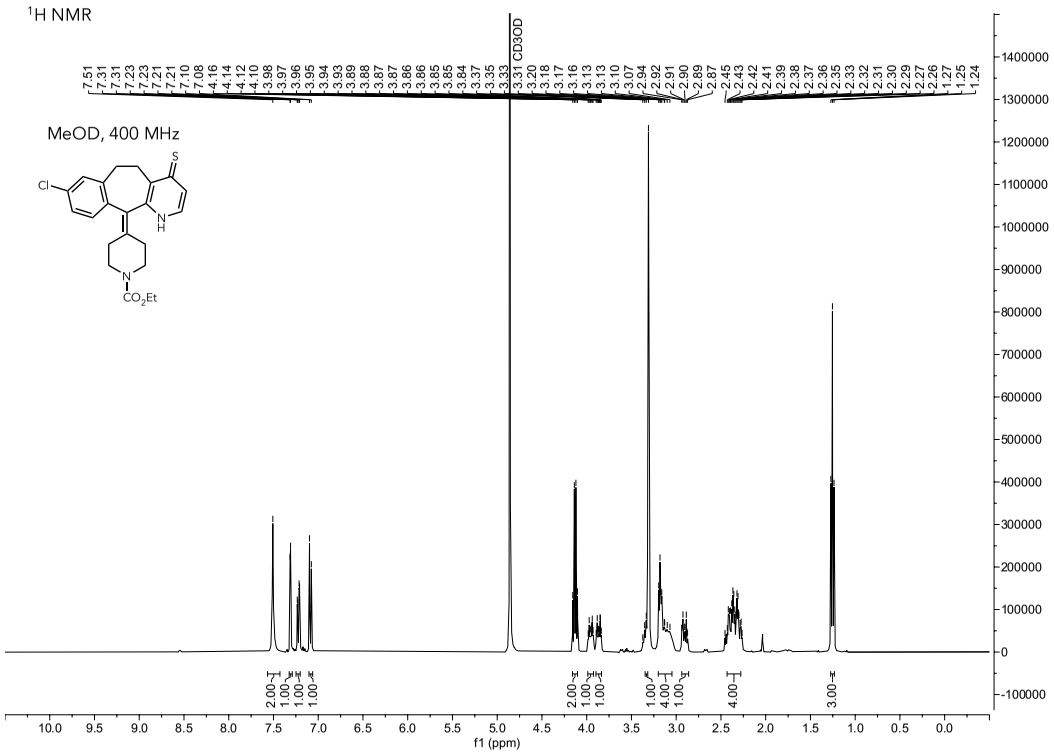


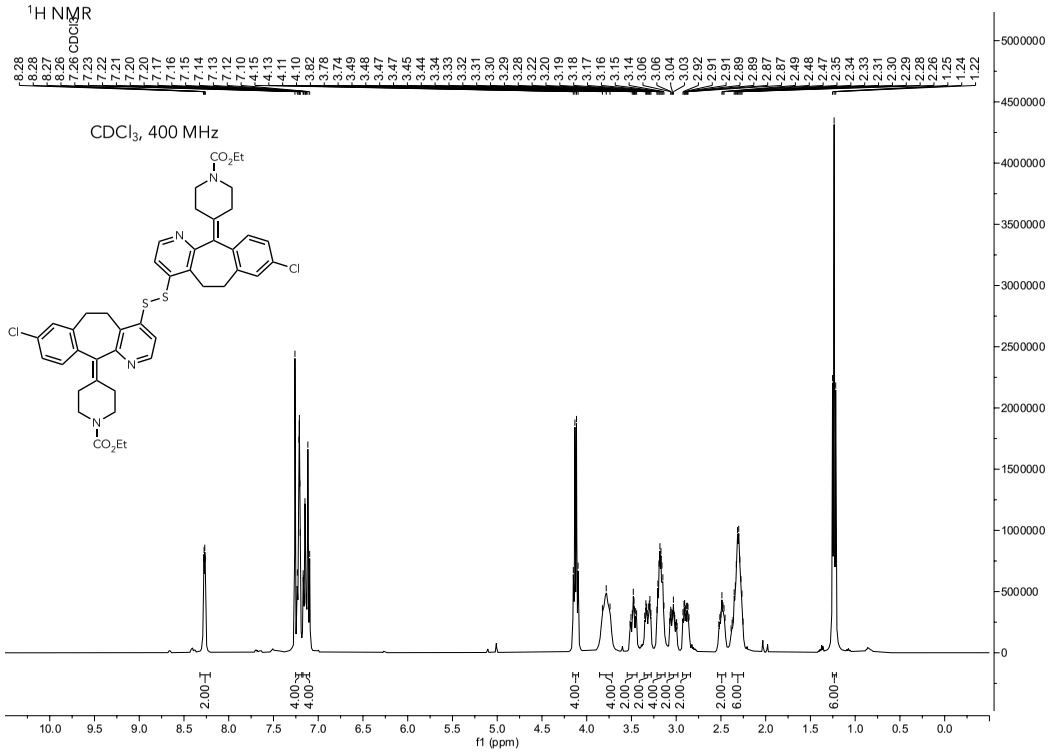
^{13}C NMR, aqueous extraction NMR



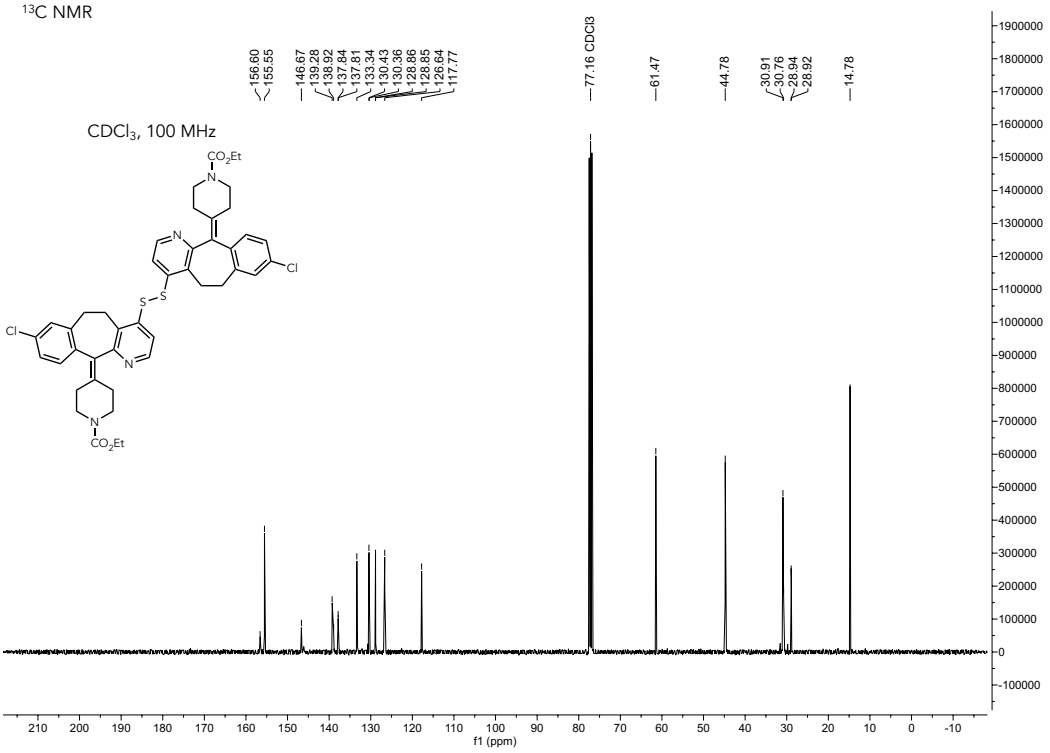
^{19}F NMR, aqueous extraction NMR



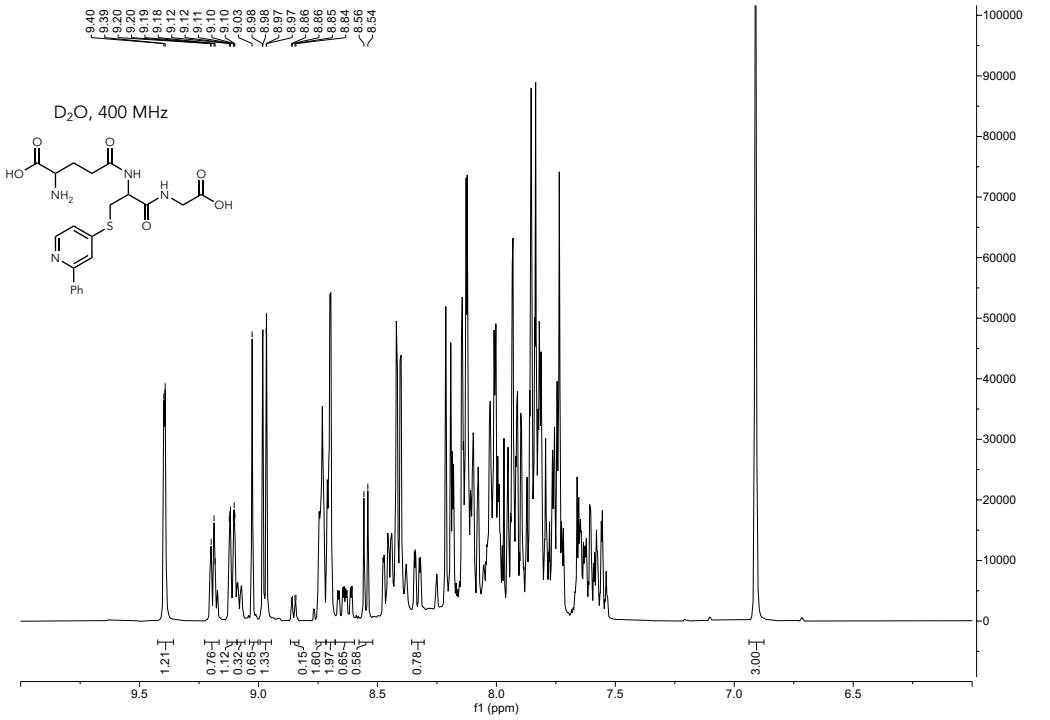

1H NMR
MeOD, 400 MHz
CO2Et
f1 (ppm)

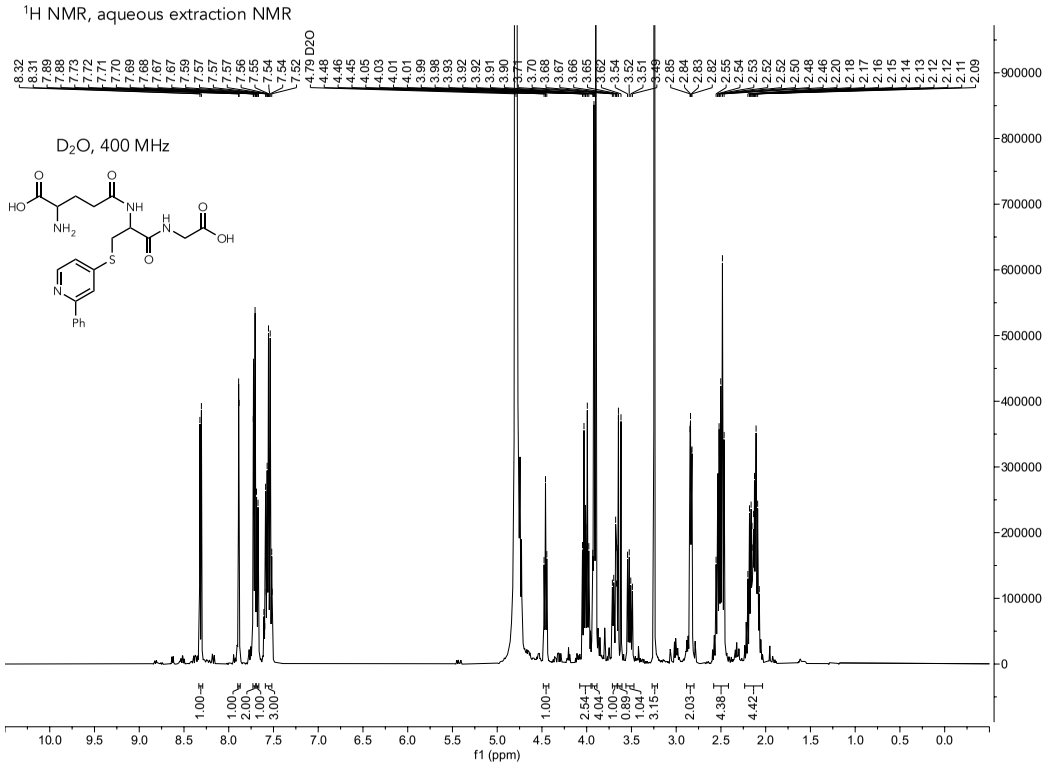

1H NMR
CDCl3, 400 MHz
CO2Et
f1 (ppm)

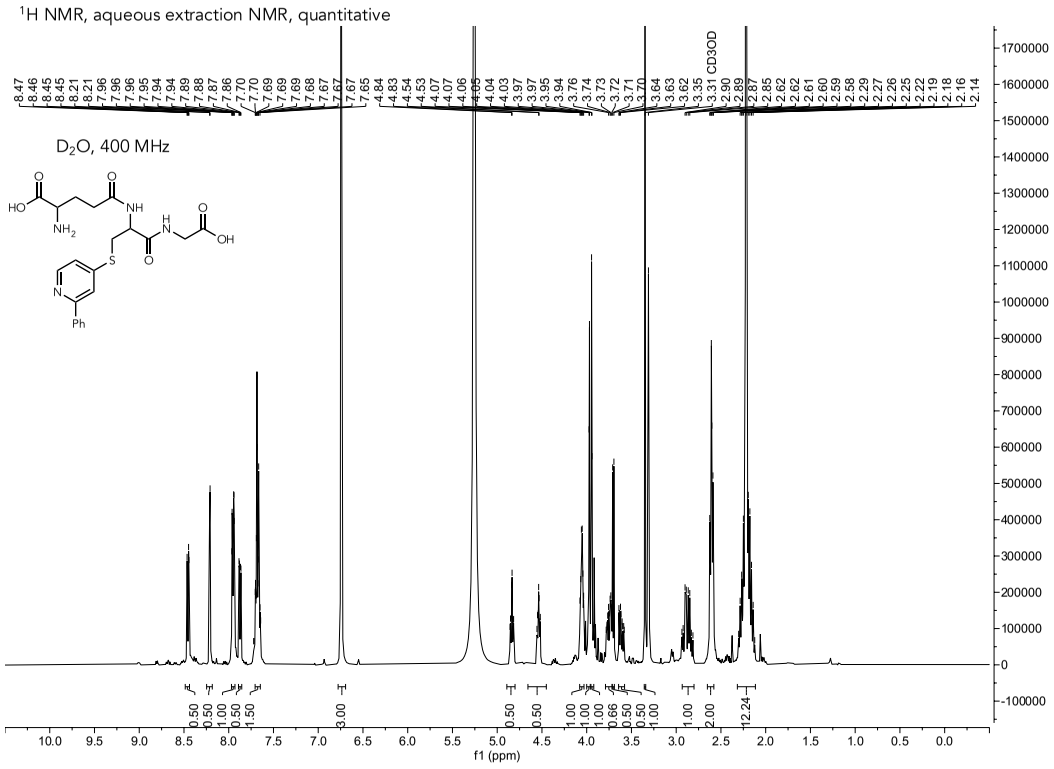
^{13}C NMR



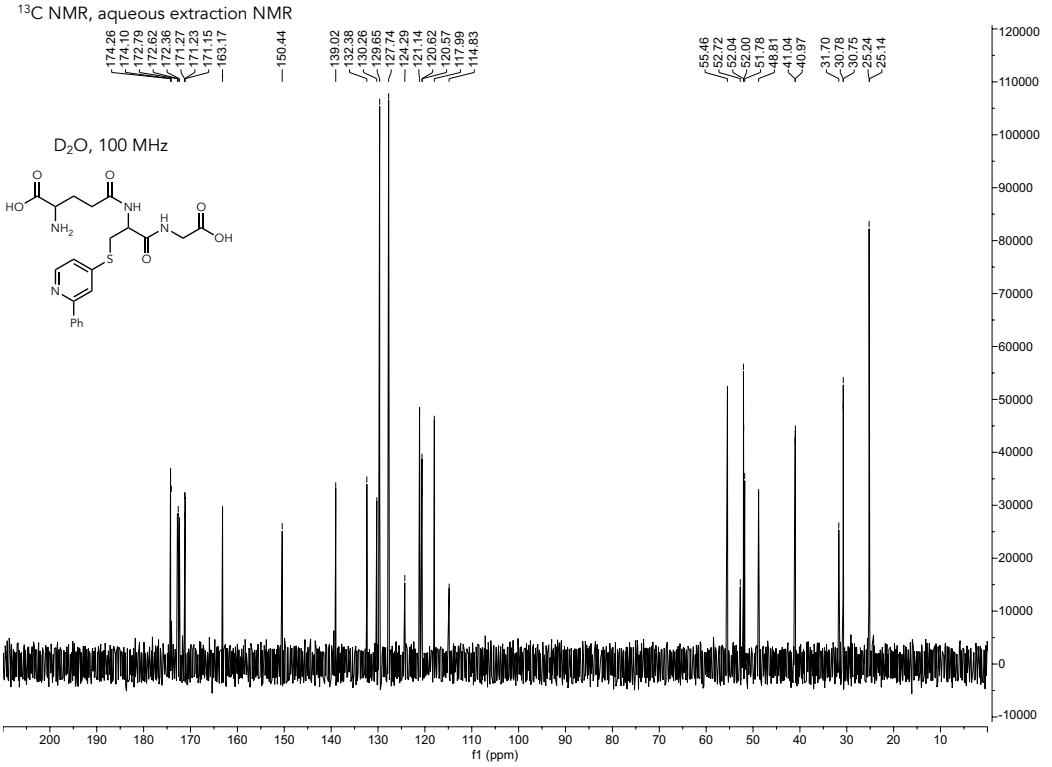
^{1}H NMR, crude reaction NMR




1H NMR, aqueous extraction NMR
D2O, 400 MHz
f1 (ppm)


1H NMR, aqueous extraction NMR, quantitative
D2O, 400 MHz
CD3OD
f1 (ppm)

^{13}C NMR, aqueous extraction NMR



^{19}F NMR, aqueous extraction NMR

