THESIS

SELECTIVE FUNCTIONALIZATION OF PYRIDINES AND DIAZINES VIA NUCLEOPHILIC ADDITION TO HETEROCYCLIC PHOSPHONIUM SALTS

Submitted by

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ABSTRACT

SELECTIVE FUNCTIONALIZATION OF PYRIDINES AND DIAZINES VIA NUCLEOPHILIC ADDITION TO HETEROCYCLIC PHOSPHONIUM SALTS

Nitrogen heterocycles, specifically pyridines and pyrimidines, are common motifs found in pharmaceuticals, agrochemicals and materials. Site-selective functionalization of these azines are highly sought after for medicinal chemistry purposes. It has previously been found in our lab that heterocyclic phosphonium salts can potentially serve as a useful functional handle to selectively functionalize these valuable scaffolds. This work describes the utility of heterocyclic phosphonium salts as electrophiles to selectively form C-O, C-S, C-N and C-Se bonds in a diverse range of pyridines and diazines.

First, the addition of thiolate nucleophiles to heterocyclic phosphonium salts to selectively form heteroaryl thioethers is described. This coupling reaction proceeds through deprotonation of the alkyl thiol followed by addition of the heterocyclic phosphonium salt under mild conditions. The reaction scope was tested for a variety of alkyl thiol nucleophiles as well as different pyridine phosphonium salts. The extent of the method's utility was demonstrated through late-stage functionalization of some complex pharmaceuticals. Additionally, initial results on the reactivity of sulfinate nucleophiles with heterocyclic phosphonium salts is communicated.

Second, aromatic heteronucleophiles were explored for reactivity with heterocyclic phosphonium salts. Aromatic heteronucleophiles can be classified as either exocyclic or endocyclic. Exocyclic aromatic heteronucleophiles, such as phenols, thiophenols and anilines,

were able to be selectively coupled to azines and pharmaceuticals. Endocyclic aromatic heteronucleophiles, such as pyrroles, pyrazoles and imidazoles, also proved to be compatible. All these nucleophiles were able to be coupled to complex drug-like fragments as well as other bioactive molecules via the phosphonium ion. The method also enabled a convergent coupling reaction between two elaborate coupling partners to form a novel tyrosine kinase inhibitor that would be difficult to access using conventional methods.

ACKNOWLEDGEMENTS

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CHAPTER 1: BACKGROUND ON SELECTIVE FUNCTIONALIZATION OF AZINES AND DIAZINES VIA HETEROCYCLIC PHOSPHONIUM SALTS

1.1 Selective Functionalization of Pyridines and Diazines

Nitrogen-containing heteroaromatics are among the most prevalent structural motifs found in FDA approved pharmaceuticals.[1] Pyridine is the second most common nitrogen heterocycle appearing in small-molecule drugs as they are present in 10% of all marketed therapeutics in the US.[1a,e] These 6-membered heterocycles have also shown useful applications in metal catalysis as ligands[2] as well as in functional materials[3] and agrochemicals (Figure 1.1).[4] This widespread popularity warrants a desire for new direct methods to functionalize these valuable azines.

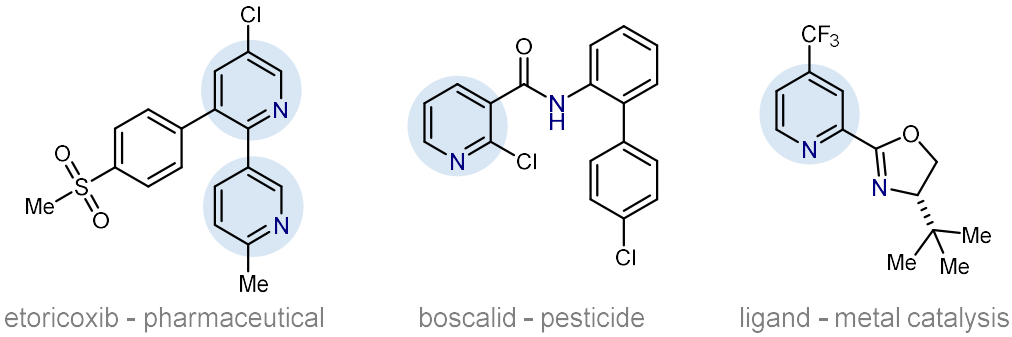

Fig. 1.1: Examples of various applications of pyridine motifs

Furthermore, it is a combined effort from the ring itself along with the substituents that protrude from its scaffold that allow for pyridine's extensive use. For this reason, the development of new reactions that can regioselectively functionalize pyridine and other diazines are in high demand. The majority of pyridine functionalization reactions are either 2- or 3-postion selective processes. There are much fewer methods available to selectively transform the 4-position of the scaffold, leaving a large amount of chemical space that has yet to be explored by medicinal chemists.[5] $SOCl_2$-mediated reactions enable pyridine dimerizations[6] and synergistic

Al/Ni catalysis enables C-C bond formations[7]. Additionally, a 4-selective perfluoroalkylation reaction has been demonstrated using a bulky borane Lewis acid activation strategy.[8] All of these methods are examples of strategies where the targeted functional group is installed in a single step. While this approach is efficient in getting the desired functionality quickly, each type of desired bond construction requires its own chemical method to be developed. A more versatile approach to pyridine functionalization is to selectively install a functional handle that aids in various subsequent bond constructions (Figure 1.2). A functional handle approach is particularly appealing for drug discovery programs that seek access to a wide variety of pyridine analogues.

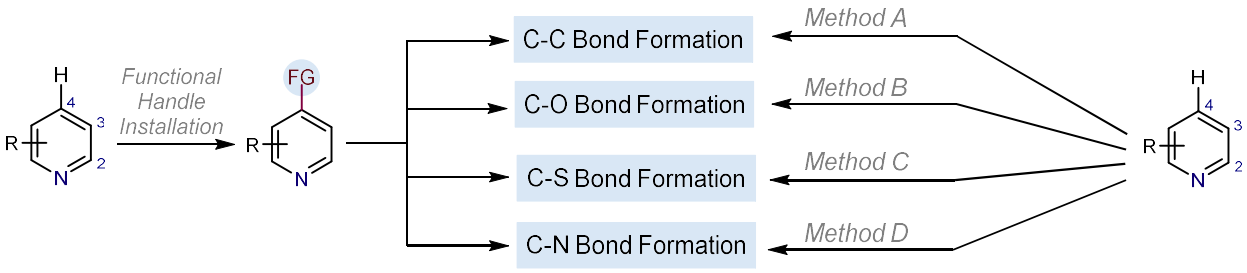

Fig. 1.2: Pyridine functionalization via a versatile functional handle vs. specific bond constructions

1.2 Heterocyclic Phosphonium Salts

Our laboratory has been developing a research program around heterocyclic phosphonium salts to serve as a generic functional handle for 4-selective functionalization of pyridines and diazines.[9] The C-PPh_3^+ group is formed by subjecting the azaarene to sequential addition of Tf_2O, PPh_3 and an organic base at low temperatures (Figure 1.3).[10]

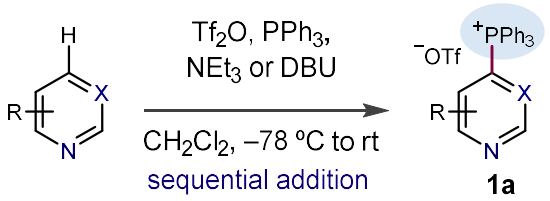

Fig. 1.3: Heterocyclic phosphonium salt formation protocol

Nucleophilic addition of PPh_3 on the activated triflyl pyridium salt (**I**) is has shown considerable selectivity at the 4-position (Figure 1.4). Computational analysis is ongoing, in collaboration with the Paton group, to probe at this observed selectivity. Currently, we believe that there is a lower activation energy barrier ($\Delta G^{\ddagger}$) as well as a lower overall reaction energy (ΔG^{react}) for *para* attack over *ortho*. In addition, we also believe that attack at the 2-position is reversible but irreversible at the 4-position. Nucleophilic addition of PPh_3 is followed up by base-mediated elimination of **II** allows for re-aromatization of the azine to form the heterocyclic phosphonium salt **1a**. The process is broadly applicable for pyridines, diazines and quinolines that contain a wide range of steric and electronic properties including the late stage applications on complex drug molecules.[9,11]

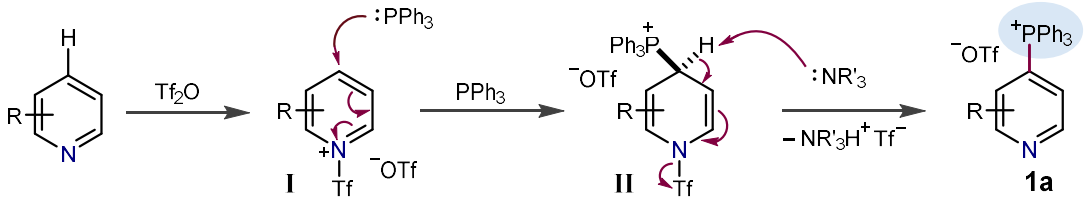

Fig. 1.4: Proposed mechanism for the formation of pyridine phosphonium salts.

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CHAPTER 2: THIOLATE ADDITION TO HETEROCYCLIC PHOSPHONIUM SALTS

2.1 Introduction

The electronic and steric properties of pyridines and diazines can be adjusted by adding heteroatom substituents to their scaffold. Specifically, C-S bond constructions on these electron deficient rings to form heteroaryl thioethers are of great interest to medicinal chemists.[1] Moreover, these thioether moieties are commonly found in biologically active molecules (Figure 2.1).[1,2a-c] Another advantage of the thioether moiety is that it can serve as a precursor to higher oxidation state sulfoxide and sulfone derivatives, which are also commonly found in pharmaceuticals.[2d]

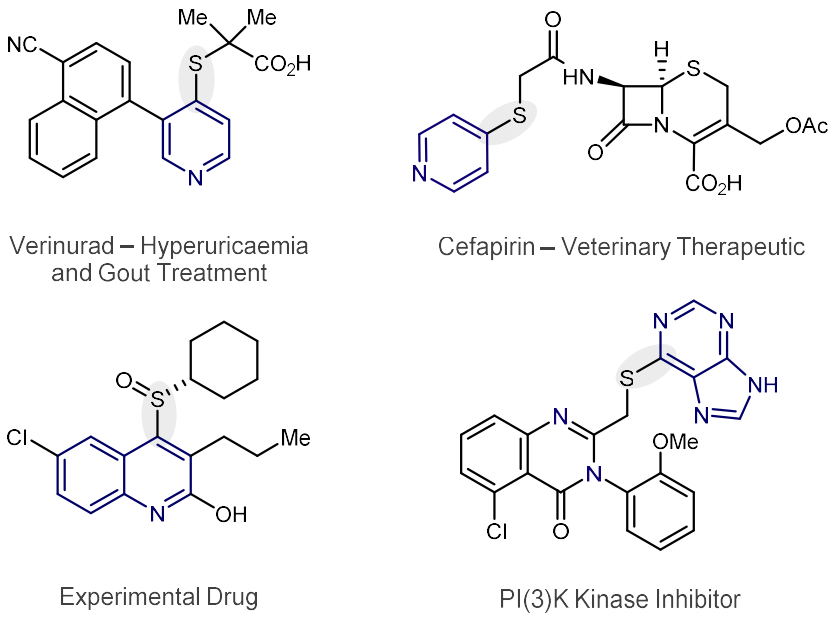


Figure 2.1: Examples of heteroaryl thioethers in biologically active compounds

Existing methods to construct heteroaryl thioethers typically rely on metal-catalyzed cross-couplings or S_NAr reactions, both of which require a halogenated precursor.[3] Due to the need for this functional antecedent, thioether formation on heterocycles is limited by the lack of selective halogenation methods. This, in turn, leads to the inaccessibility of potentially valuable compounds for medicinal chemists.

As previously mentioned in chapter 1, members of the McNally group had shown that heterocyclic phosphonium salts could be used as a more general approach for etherification of pyridines and diazines.[4] They were also able to show a preliminary example of C-S bond formation using this method. With this in mind, it made sense to begin working on a more detailed account of this simple protocol to test its feasibility.[5] Figure 2.2. demonstrates the general transformation for this two-step procedure. The 4-position C-H bond is transformed into the bench stable phosphonium salt via the protocol described in chapter 1. The phosphonium ion can then serve as an electrophilic handle to facilitate the C-S bond formation with the thiolate nucleophile. The coupling procedure involves deprotonating the thiol at 0 ºC with sodium hydride in THF followed by addition of the phosphonium salt and stirring at room temperature.

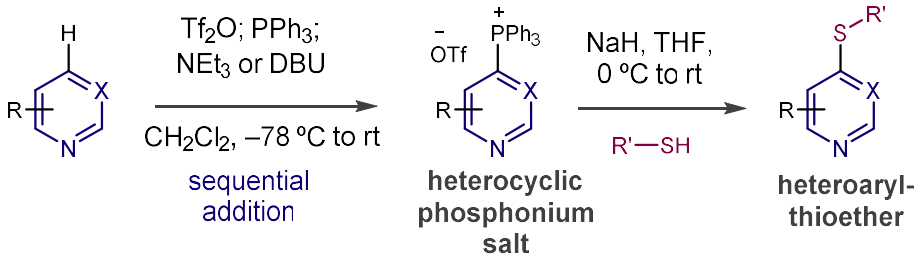


Figure 2.2.: Two step protocol for construction of heteroaryl thioethers

The mechanism for which this transformation proceeds remains unclear, however, there are two distinct pathways that can be imagined (Figure 2.3). Pathway A demonstrates a ligand-coupling mechanism where the thiolate adds to the phosphonium to from a P(V) phosphorane intermediate. This phosphorane would then undergo a ligand coupling process to give off the triphenyl phosphine and form the desired thioether.[6] This proposed mechanistic pathway resembles C-O couplings that are postulated to proceed through alkoxyphosphorane intermediates.[7] We assume that the thiolates would be analogous to this process. S_NAr is another potential route that cannot be ignored (Figure 2.2.3 (B)).[8] In this case, triphenyl phosphine would

be the leaving group which is a by-product that is always observed with the desired C-S bond formation. Mechanistic studies continue to be a topic of focus in the McNally lab.

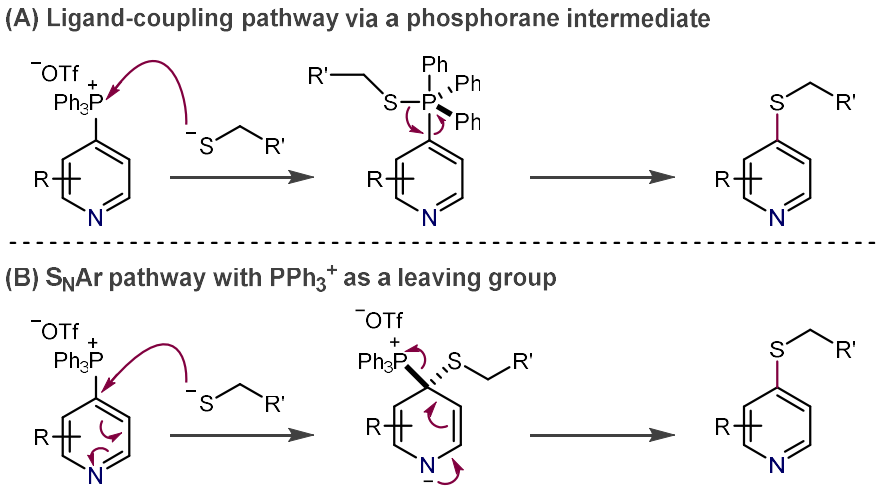
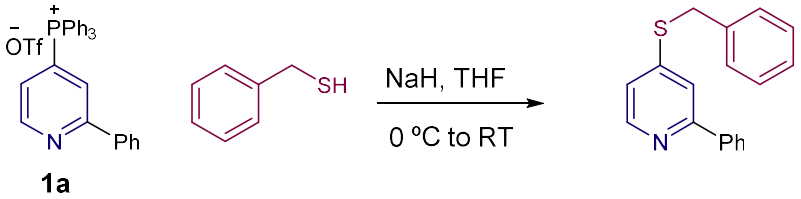


Figure 2.3: Possible mechanistic pathways for the thiolate addition to heterocyclic phosphonium salts

2.2 Results

2.2.1 Optimization

Before analyzing reactivity with variable substitution patterns, we wanted to try to optimize the reaction conditions to improve them and attempt to increase the yield. The initially reported C-S coupling reaction[4] was ran at in THF (0.25 M) at room temperature for 12 hours, using 1.5 equivalents of the alcohol and sodium hydride. Table 2.2.1 depicts the results of the optimization screen that was conducted on triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethane sulfonate (**1a**) and benzyl thiol (figure 2.4). All reactions were ran at 0.25 mmol scale using 1,3,5 trimethoxy benzene as an internal standard. The crude mixtures were concentrated on a rotavap and analyzed using ^{1}H NMR spectroscopy.



1a

Figure 2.4: The test reaction used for optimization. All reactions were ran at 0.25 mmol scale

Table 2.1: Optimization results for the reaction depicted in scheme 2.2.1

Entry	Concentration (M)	Rxn. Time	Equivs. of thiol	% Yield ^{1}H NMR
1	0.25	12	1.5	83%
2	0.125	12	1.5	81%
3	0.08	12	1.5	59%
4	0.25	3	1.5	84%
5	0.25	3	1.25	81%
6	0.25	3	1.1	81%
7	0.25	3	1	76%

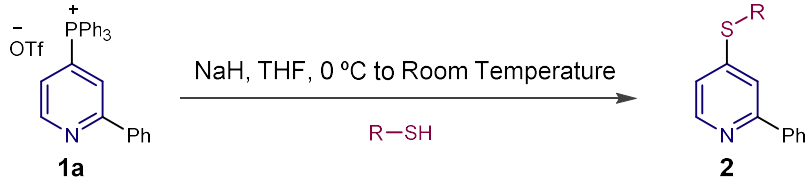
Entries 1-3 of table 2.1 showed how changing the concentration of the reaction effected the yield. We didn't go any more concentrated than 0.25 M due to stirring issues during the deprotonation step. After deciding on 0.25 M as the optimal concentration, a time study was done to see how long the reaction needed to go to completion. An aliquot from the reaction was checked every 30 minutes by LC-MS to see if any of the phosphonium salt remained. At the 3-hour mark there seemed to be no remaining starting material and an ^{1}H NMR was taken (Table 2.1 entry 4). Our attention was then switched to the equivalents of thiol nucleophile needed (Table 2.1 entries 5-6). The yields were all similar at 1.5, 1.25 and 1.1 equivalents, but it was evident that a slight excess was beneficial. Entry 6 shows the optimal conditions that were decided on for further substrate evaluation.

2.2.2 Thiol Nucleophile Scope

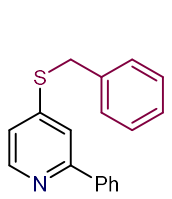
A range of alkyl thiols with various steric and electronic properties were reacted with phosphonium salt **1a** (Table 2.2). Primary benzylic and heterobenzylic thiols formed their respective thioethers in good yields (**2a** & **2b**). Next, steric properties were examined with a

secondary pyranthiol as well as a tertiary tert-butyl thiol (**2c** & **2d**). Both thiols accommodated the reaction well, showing us that the coupling method is not overly sensitive to the steric features of the thiolate. The thiol proved to be relatively chemoselective over an alcohol and a carbamate by forming thioethers **2e** and **2f** in decent yield. Since saturated amine heterocycles are common motifs in pharmaceuticals we decided to see how well a thiol on a boc-protected piperidine as well as a pyrrolidine-thiol withstood the C-S bond construction reaction; both heterocyclic thiols proved to be excellent substrates for this reaction (**2g** & **2h**). Finally, we wanted to see if we could couple an amino acid to 2-phenylpyridine. Unprotected cysteine did not form any of the desired product, likely due to salt decomposition by the free amine and electrophilic competition from the amide group. However, when the amine functionality is protected as a carbamate and the amide group is derivatized to a morpholine amide we were able to isolate a coupled product (**2i**), albeit in lower yield.

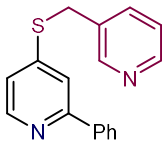
Table 2.2: C-S bond formation: Thiol Scope. Isolated yields are shown. Typical reaction conditions: 1a (0.5 mmol), thiol (0.55 mmol), NaH (0.55 mmol) and THF (2.0 mL).



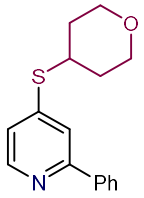
1a 2



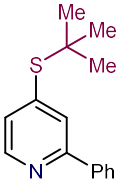
2a, 92%



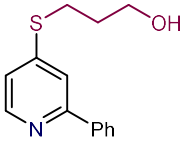
2b, 75%



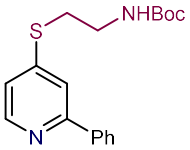
2c, 74%



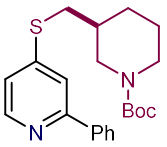
2d, 90%



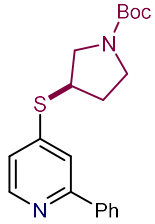
2e, 91%



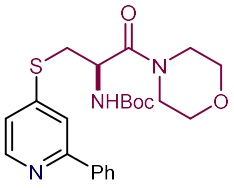
2f, 62%



2g, 87%



2h, 90%



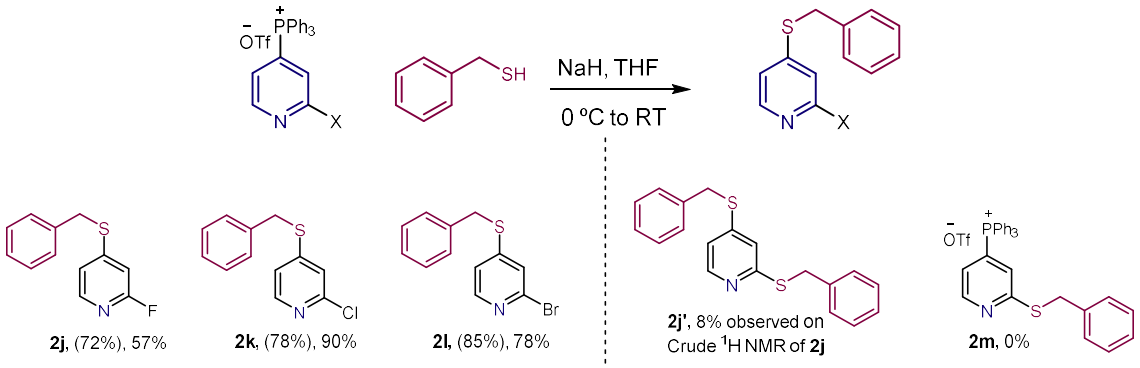
2i, 19%

2.2.3 Azaarene Scope

Next, we looked at various pyridines and diazines to see how different substitution patterns effected their reactivity. First, we looked at pyridines that contained S_NAr active halogens at the 2-position and a triphenyl phosphonium salt at the 4-position (Table 2.3). We wanted to see if the coupling pathway via the phosphonium ion would outcompete the S_NAr pathway via the halide. Each of these 2-halide pyridines were first converted into their respective phosphonium salts and those yields are shown in parenthesis. In each case (2i-2k), the phosphonium ion was able to out compete the S_NAr displacement. Substrate **2j** contains a 2-flouro substituent and gave the lowest yield for 4-position thioether formation. Another

byproduct of this reaction that was observed by crude ^{1}H NMR and LC-MS was the double addition product **2j'** where the thiolate added in at both the 2- and 4-postions. Since fluorine is the most S_NAr active halogen, this makes sense that the excess thiol would add in to the 2-position after fully reacting with the phosphonium ion at the 4-position. The other two substrates (**2k** & **2l**), did not show any of this double addition product and were isolated in good yield. All these 2-halo phosphonium salts did not show any signs of forming product **2m** where the S_NAr pathway would have been more competitive than the intended phosphonium ion coupling pathway. These results were particularly exciting because since the thiolate prefers reacting with the phosphonium ion over the S_NAr active halogen, the halogen can be used for further derivatization in subsequent metal catalyzed cross couplings or S_NAr reactions.

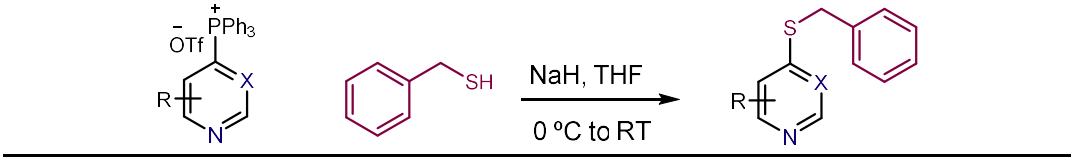
Table 2.3: Competition experiments for S_NAr vs. phosphonium ion coupling. Isolated yields for phosphonium salt formation are shown in parentheses and isolated yields of the coupled product are also shown.

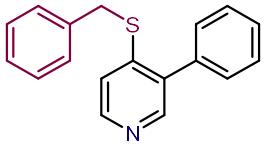


Next, we looked at other substitution patterns on the nitrogen heterocycle to see how different steric and electronic properties effects the transformation (Table 2.4). Entry **2n** shows that sterically bulky groups at the 3-position can be withstood as 3-phenylpyridine formed the thioether in good yield. A 2,3-substitution pattern can also be tolerated since tetrahydroquinoline worked well in the C-S bond forming reaction (**2o**). 2-2-bipyridine underwent the etherification to form **2p** in moderate yield. A 3,4,5-trisubstituted pyridine (**2q**) was forged in excellent yield using this protocol. Diazines also proved to be particularly responsive to this thioetherification

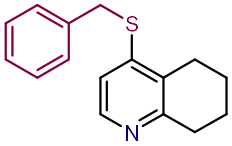
method. The thioether formed quite well on a pyrimidine (2r), however, minor amounts of regioisomer at the 2-position of the pyrimidine were observed during phosphonium salt formation. Quinoxaline, on the other hand, was able to form the thioether **2s** with complete regiocontrol.

Table 2.4: C-S Bond-Formation: Azaarene Scope; Isolated yields of the corresponding phosphonium salt are shown in parentheses and isolated yields of the final product are also shown. Typical reaction conditions: Heterocyclic Phosphonium salt (0.5 mmol), benzyl thiol (0.55 mmol), NaH (0.55 mmol) and THF (2.0 mL).

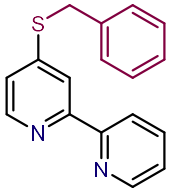




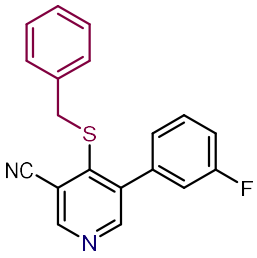
2n, (69%), 87%



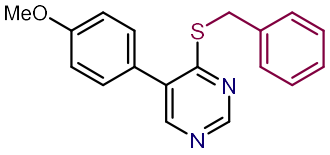
2o, (76%), 75%



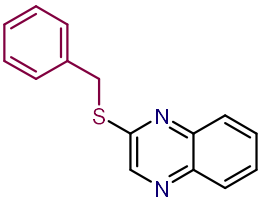
2p, (70%), 61%



2q, (76%), 93%



2r, (50%,(24:1 r.r.)), 88%

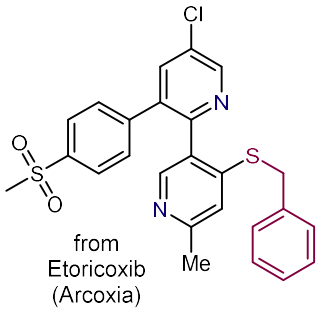


2s, (45%), 91%

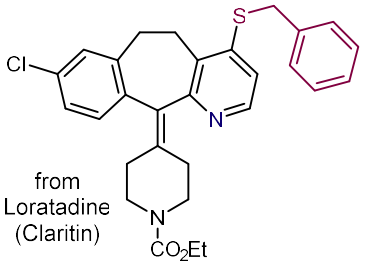
As stated earlier, our goal was to make this heterocyclic functionalization method attractive to medicinal chemists, so we decided to subject the two-step protocol to late-stage derivatization of some complex pharmaceuticals (Table 2.5). Etoricoxib is a pain reliever used to treat Rheumatoid arthritis and can form the C-S bond via the phosphonium salt in reasonable yield (**2t**). The commonly used antihistamine Claritin, also known as Loratadine, can also be form the thioether functionality (**2u**). A thioether moiety was also able to be installed in

moderate yield at the two position of benzyl-protected cinchonidine where the 4-position of the quinoline is blocked (**2v**).

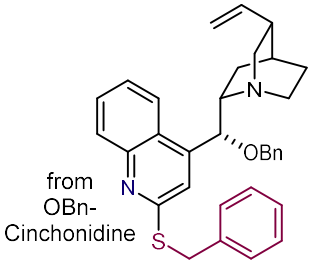
Table 2.5: Late-stage thioetherification of pharmaceuticals. Isolated yields of phosphonium salt formation are shown in parentheses and isolated yields of the final product are also shown.



2t, (73%), 65%



2u, (88%), 51%



2v, (52%), 62%

2.2.4 Initial Studies on Sulfinate and Sulfonamide Addition to Heterocyclic phosphonium salts

Sulfones are another example of heterocyclic functionalities that are commonly found in therapeutics.[9] We were curious to see how sulfinate nucleophiles would react with our heterocyclic phosphonium salts. An initial trial was conducted and showed considerable promise for this reaction going forward. First, the reaction was ran in THF (0.5 M) at 60 ºC for 48 hours using 1.5 equivalents of sodium methane sulfinate and 15-crown-5 (Figure 2.5). There were some solubility issues when there was no crown ether used and no product was formed. It is believed that the crown ether helps with the transformation by active as a phase transfer catalyst as well as making the sulfinate more nucleophilic via sodium trapping. The coupling reaction was then ran in in 1,4-dioxane at a higher temperature of 100 ºC and the yield improved. Although the isolated yield is low right now, we are able to clearly form the intended product. This reaction could certainly be optimized further to improve the yield.

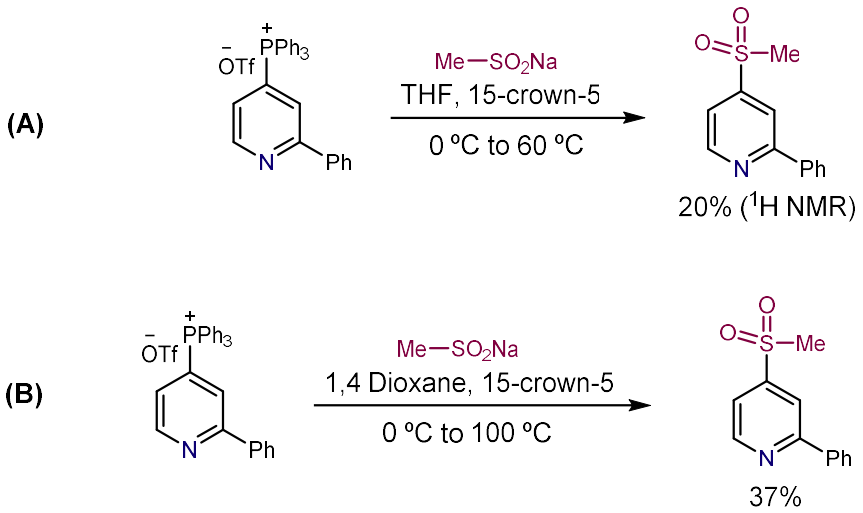


Figure 2.5: Initial trials of sulfinate addition to heterocyclic phosphoniums salts. Yields shown are isolated unless otherwise noted.

2.3 Summary

It has been shown that heteroaryl thioethers can be selectively assembled on pyridines and diazines via nucleophilic attack of heterocyclic phosphonium salts. The reaction showed to withstand a variety of thiolate nucleophiles ranging in steric and electronic properties. A couple of thiols protruding from amine heterocycles and an amino acid derivative were also shown to undergo C-S bond formation in reasonable yields. The heterocyclic portion proved to be more competitive for thioether formation at the 4-position via the phosphonium salt when an S_NAr active halogen was present at the 2-position. The selective formation of thioethers on pyridines with variable substation patterns as well as a couple of diazines were also shown. Bioactive molecules proved responsive to this C-S bond forming strategy, showing that this method is viable for late-stage formation of heteroaryl thioethers on pharmaceuticals. Furthermore, initial results for the selective formation of heteroaryl sulfones via heterocyclic phosphonium salts was communicated. Initial trials for using sulfonamides were also conducted, but no product formation has yet to be observed.

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CHAPTER 3: COUPLING AROMATIC HETERONUCLEOPHILES TO AZINES AND DIAZINES VIA HETEROCYCLIC PHOSPHONIUM SALTS

3.1 Introduction

For the class of nucleophiles described in this chapter we coined the term "aromatic heteronucleophiles" to group them together.[1] Aromatic heteronucleophiles contain an aromatic ring and the nucleophilic portion is a heteroatom. The nucleophilic heteroatom can either be situated within the ring system (endocyclic) or outside of the ring system (exocyclic). As shown in figure 3.1, some examples of endocyclic aromatic heteronucleophiles include pyrroles, imidazoles, pyrazoles and triazoles. Phenols, thiophenols, benzneneselenols and anilines are all examples exocyclic aromatic heteronucleophiles.

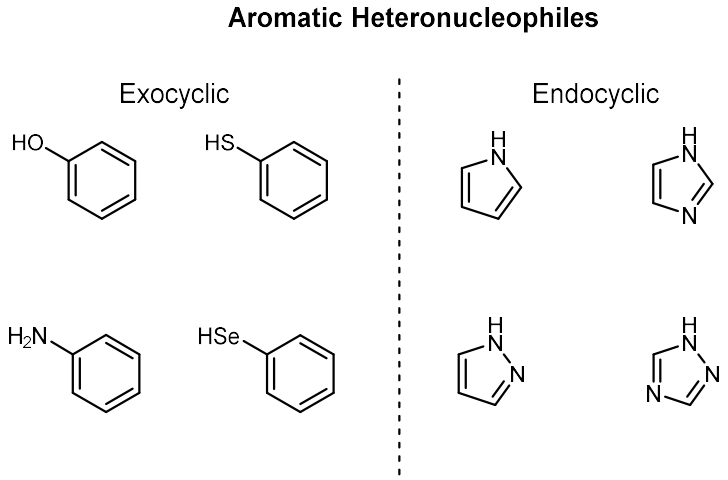


Fig. 3.1: Representative examples of Exocyclic and Endocyclic Aromatic Heteronucleophiles

Aromatic heteronucleophiles are fundamental building blocks commonly found coupled to other heterocycles in drug-like molecules.[2] Figure 3.2 shows these types of linkages present in four different chemotherapy drugs. These motifs are often valuable pharmacophores in drug compounds as they provide possible binding domains with biological targets.

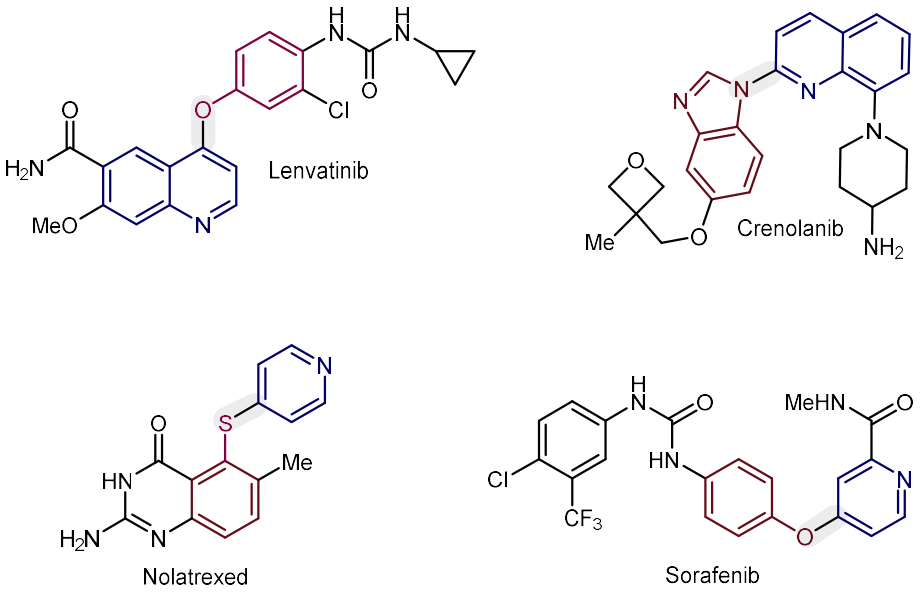


Fig. 3.2: Examples of Aromatic heteronucleophile linkages to pyridines and quinolines in chemotherapy drugs

Traditionally, heteroatom-azine bonds are formed using S_NAr or metal-catalyzed reactions, both of which typically initially require a heteroaryl-halide or -triflate functionality.[3-5] Metal catalyzed reactions are reliant on the oxidative addition of a metal catalyst into the pre-installed halide or triflate group. The oxidative addition complex that is subsequently formed is intercepted by the aromatic heteronucleophile and can undergo reductive elimination to form the new carbon-heteroatom bond. A multitude of metal-oxidative addition complexes consisting of Palladium, Copper and Nickel are used for each different aromatic heteronucleophile. Consequently, these catalytic protocols also vary in their reaction conditions, bases and ligands required for maximum yield. We envisioned that heterocyclic phosphonium salts could serve as a more unified synthetic handle for the formation of these valuable carbon-heteroatom bonds (Figure 3.3). This strategy would allow for a simpler approach to the coupling of aromatic heteronucleophiles to azines and diazines by providing a much narrower set of reaction conditions. Another potential advantage of this method is that heterocyclic phosphonium salts

are bench-stable powders as opposed to reactive intermediates, which could potentially allow for easier access to a wide variety of complex drug derivatives in high-throughput screens.[6]

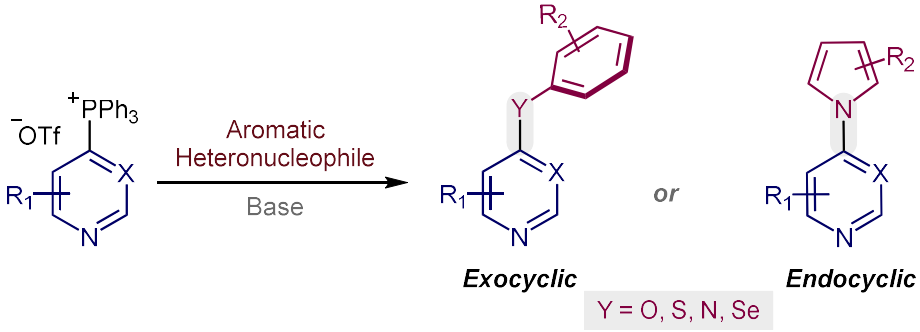


Fig. 3.3: General reaction scheme for addition of aromatic heteronucleophiles to heterocyclic phosphonium salts

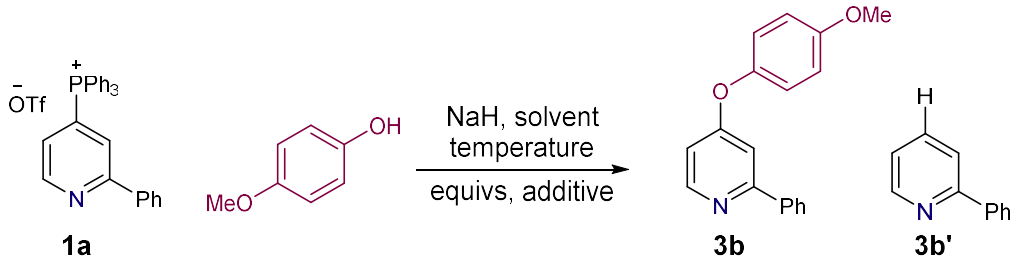
Furthermore, this method is promising for the coupling of heteronucleophiles to complex N-heterocycles where either the halogen precursor can't easily be installed, or the heterocycle contains polar functional groups which are typically problematic for metal-catalyzed strategies.[7] Already knowing that we have the ability to form the phosphonium ion late-stage on complex azines and pharmaceuticals,[8] it made sense to look into coupling this diverse range of heteronucleophiles.

3.2 Results

3.2.1 Optimization of Phenol Coupling

We realized quickly that these aromatic heteronucleophiles were not able to be coupled to azines via the phosphonium salt under the conditions that were reported for the alkyl thiols in chapter 2 (Table 3.1 entry 1).[9] When the reaction fails to undergo the desired coupling, we notice that the salt decomposes to the C-H product **3b'**. The source of this undesired pathway remains elusive, but further mechanistic studies are ongoing in the McNally laboratory.

Table 3.1: Optimization of p-methoxy phenol coupling to phosphonium salts. All reactions ran using 0.2 mmol of **1a** and the equivs of NaH, 15-crown-5 and p-methoxyphenol match. [a]Yields determined by ^{1}H NMR of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard.



1a **3b** **3b'**

Entry	Temp. (°C)	Solvent	*p*-methoxyphenol equivs.	Additive	% Yield[a] 3b	% Yield[a] 3b'
1	rt	THF	1.1	none	0	87
2	rt	THF	1.1	15-crown-5	3	83
3	rt	THF	1.5	none	0	78
4	40	THF	1.5	none	36	62
5	40	THF	1.1	15-crown-5	36	59
6	40	THF	1.5	15-crown-5	49	40
7	60	THF	1.5	15-crown-5	87	6
8	40	DME	1.5	15-crown-5	76	21
9	40	1,4-dioxane	1.5	15-crown-5	14	81
10	40	DMF	1.5	None	1	91

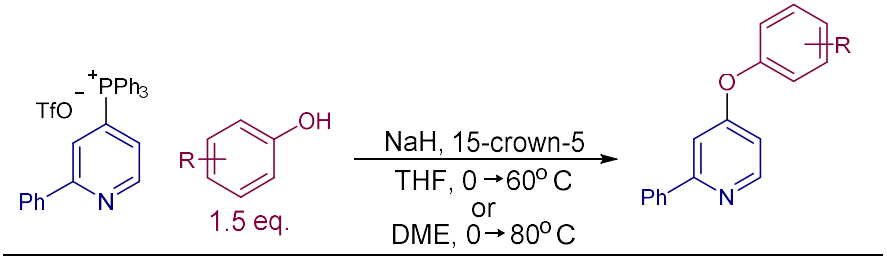
We began to look further into adjusting the reaction conditions of *para*-methoxyphenol with 2-phenyl pyridine phosphonium salt (**1a**) to see if we could get any desired coupling. We looked to see if adding a stoichiometric amount of a crown ether to the reaction could help promote the desired pathway at room temperature (Table 3.1 entry 2), however, this additive only provided a small amount of product formation with the C-H pathway still taking precedent. Increasing the equivalents of phenol from 1.1 to 1.5 in entry 3 also showed no promise. To our delight, elevating the reaction temperature beyond ambient conditions provided enough energy to the system to

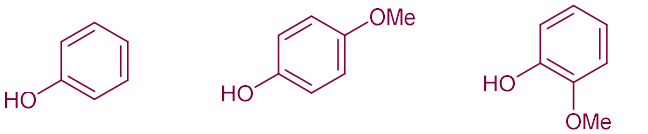
slightly subdue the C-H pathway and afford some of the desired coupled product **3b** (Table 3.1 entry 4). Adding 15-crown-5 in entry 6 improved the yield of the desired diaryl ether further. Increasing the temperature further to 60 ºC showed the most promising result for this coupling reaction (Table 3.1 entry 7). A couple of other common solvents were screened for compatibility with the reaction (Table 3.1 entries 8-10) and only dimethoxyethane (DME) showed reasonable promise at 40 ºC. We decided to continue with the reaction conditions slated out in entry 7 as our most general method, but also kept in mind that DME could also be substituted as the solvent when needed.

3.2.2 Exocyclic Aromatic Heteronucleophile Scopes

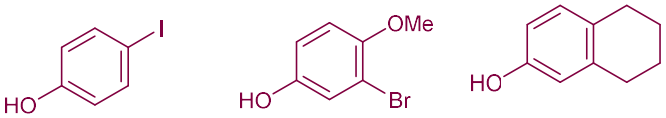
With a generic set of reaction conditions in place, we began to study how varying the functionality on the phenol ring effected the desired coupling pathway (Table 3.4). Phenol was able to be coupled to 2-phenyl pyridine in decent yield (**3a**). Methoxy groups are tolerated at both the *para*- and *ortho*- positions (3b & 3c). Admittedly, electron withdrawing groups tend to decrease the yield of the coupling reaction; however, *para*-iodo phenol was isolated (**3d**) in moderate yield with the halide still intact. A *meta*-bromo-*para*-methoxyphenol (**3e**) was also feasible, showing that another halogen that would prove reactive in metal-catalyzed reactions could be tolerated under our protocol. It is also noted that this phenol showed a higher yield when ran in DME at 80 ºC. Tetrahydro-2-napthol **3f** showed excellent coupling capability with this method. Acetaminophen (Tylenol) reacted through its phenol oxygen with reasonable coupled product being formed (**3g**). The naturally occurring amino acid Tyrosine was coupled to 2-phenyl pyridine in modest yield after boc-protection of its amino group (**3h**). The coupling of benzeneselenol to 2-phenyl pyridine was superlative (**3i**), providing another example of a tolerable endocyclic aromatic heteronucleophile.

Table 3.4: Phenol nucleophile scope. All yields shown are isolated. [a] ran in DME.

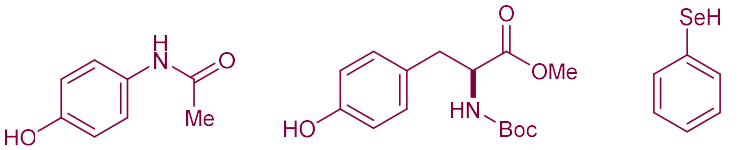




3a, 70% **3b**, 77% **3c**, 57% [a]



3d, 60% **3e**, 52% [a] **3f**, 81%

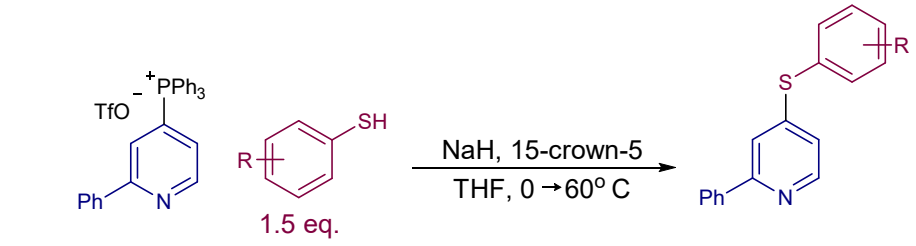


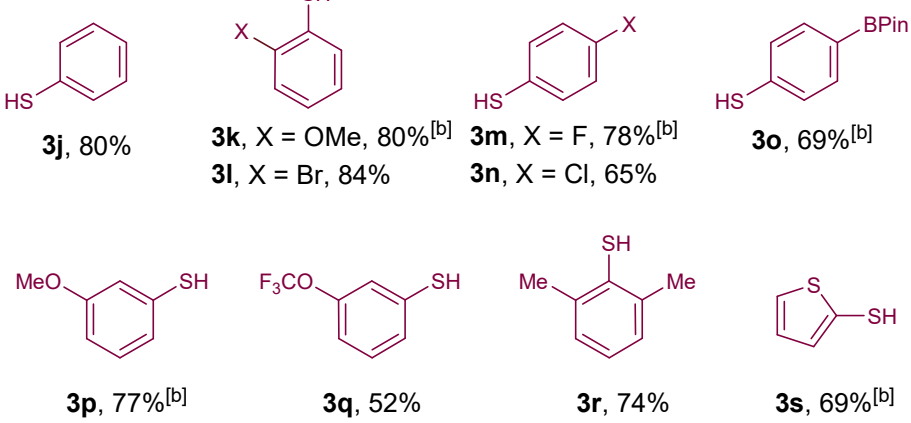
3g, 73% [a] **3h**, 59% **3i**, 91%

Next, our attention turned to the functional alteration on the thiophenol moiety (Table 3.5). Thiophenol (**3j**) proved to be more efficient in this coupling protocol compared to its oxygen equivalent. All of these thiophenols were tested with and without the use of 15-crown-5 and if the ^{1}H NMR yields were within 5% of each other, then the one without the additive was isolated. *Ortho*-methoxythiophenol (**3k**) was one example of a thiophenol that coupled great without the use of the crown ether. A range of halogens at the ortho- and para- positions tolerated the coupling protocol (**3l-n**). A boronic pinnacle ester also withstood this coupling protocol (**3o**), providing another example of a valuable functional handle that remains unscathed in this procedure. **3p** & **3q** show the tolerability of *meta* substituents. Coupling of a sterically hindered

2,6-disubstituted thiophenol **3r** was also cooperative. Substrate **3s** showed us that the exocyclic nucleophile can protrude from a heteroaromatic compound as this thiophene worked well.

Table 3.5: Thiophenol Nucleophile scope. All yields shown are isolated. [b]Substrates showed comparable yield without the use of 15-crown-5.





3j, 80%

3k, X = OMe, 80%[b]
3l, X = Br, 84%

3m, X = F, 78%[b]
3n, X = Cl, 65%

3o, 69%[b]

3p, 77%[b]

3q, 52%

3r, 74%

3s, 69%[b]

The last class of endocyclic aromatic heteronucleophiles in which we modified substitution patterns on the nucleophile were anilines (Table 3.6). These nucleophiles require a modified reaction protocol; the aniline is deprotonated at 0 ºC using n-butyl lithium, after stirring for 30 mins the phosphonium salt is added and the reaction is warmed to room temperature. These reactions occur very quickly and are typically done within 1 hour. One caveat of this class of nucleophiles, however, is that the nitrogen atom must be alkylated for the desired coupling to occur. When aniline is subjected to this coupling protocol, we observe no formation of the desired product (**3t**). Instead we see a mass at 354.2 *m/z* on the LC-MS, which we attribute to iminophosphorane **3t'**. Figure 3.4 demonstrates our hypothesis for the salt decomposition pathway that we believe accounts for this iminophosphorane formation.

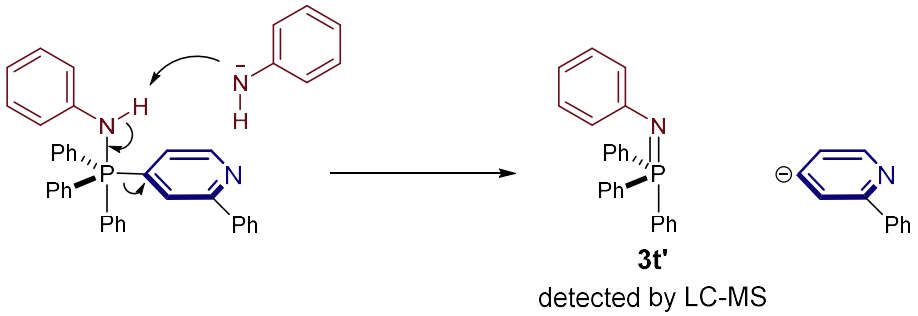
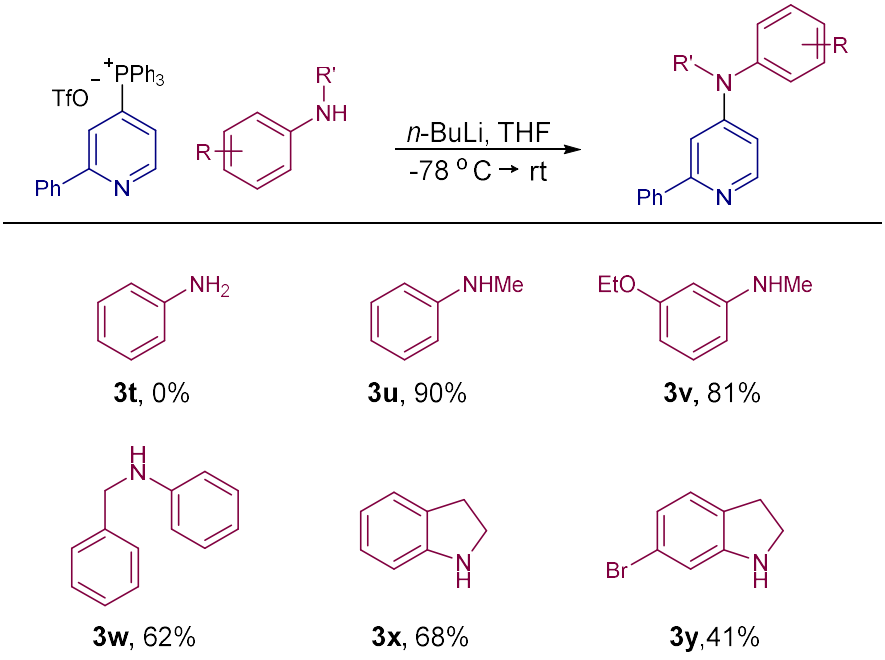


Figure 3.4: Proposed decomposition pathway for aniline as a nucleophile. *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 354.2, $C_{24}H_{21}NP^+$ requires 354.1.

We assumed that we could avoid this undesired reaction if we substituted the aniline nitrogen with an alkyl group, forbidding the deprotonation step and hopefully allowing for ligand coupling to occur. Our hypothesis proved to be correct as we were able to couple *N*-methylaniline to 2-phenyl pyridine in excellent yield (**3u**). An *ortho*-ethoxy substituent was also tolerated on the *N*-methylaniline (**3v**). A benzyl protection strategy was also employed, albeit in lower yield (**3w**). Indolines **3x** & **3w** were also compatible coupling partners under these conditions.

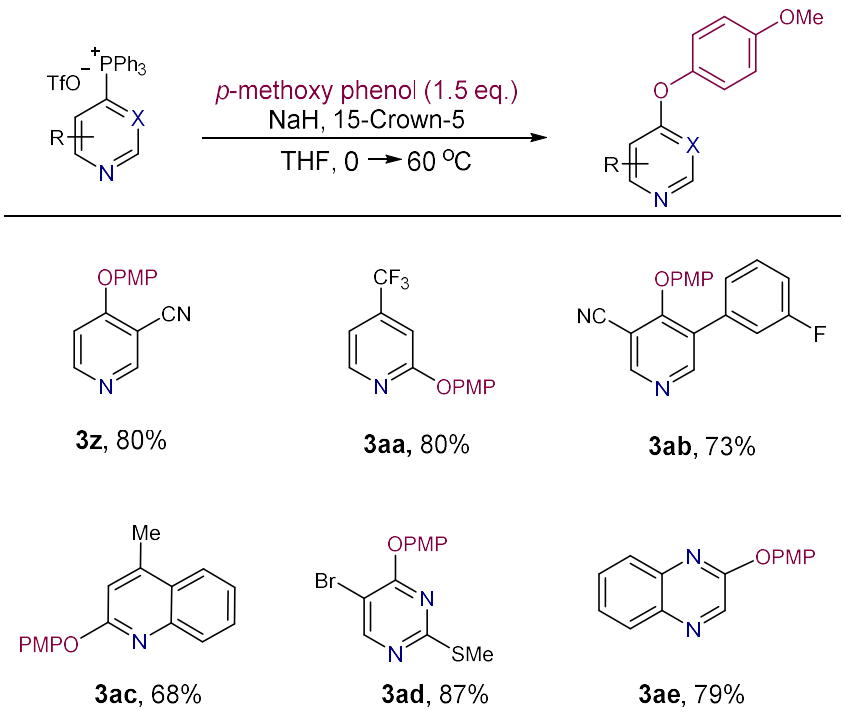
Table 3.6: Aniline nucleophiles scope. All yields shown are isolated.



After proving the validity of the these exocyclic aromatic heteronucleophiles as competent coupling partners to a simple pyridine, we decided to look at the scope of heterocyclic phosphonium salts that could be tolerated. All these phosphonium salts were prepared from their C-H precursors in the protocol described in chapter 1[8a] with complete control of regioselectivity in most cases (refer to appendix 2 for specific reaction details).

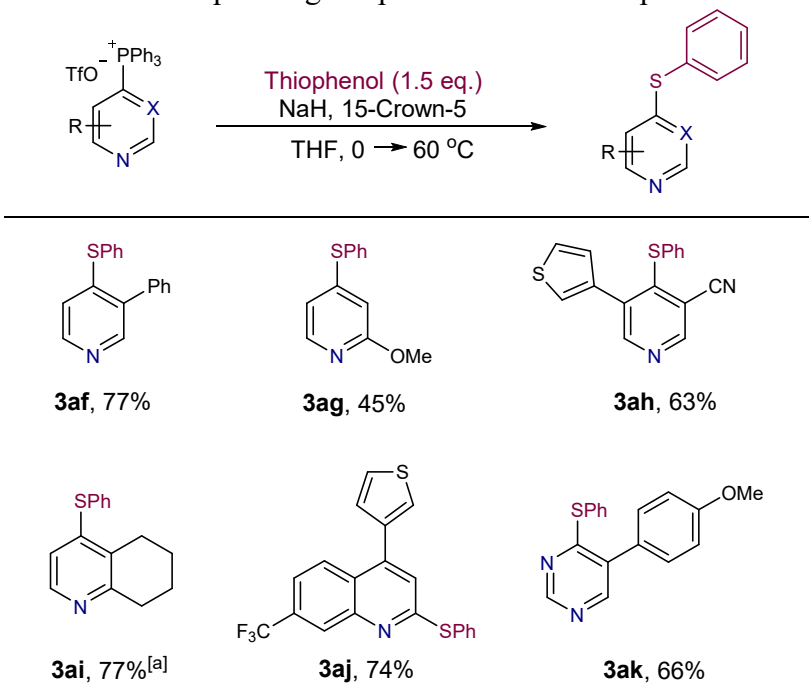
Para-methoxyphenol was kept constant as the coupling partner for a variety of azaarenes in table 3.7. Mono-substituted pyridines at the 3- and 4- positions were tolerated well (**3z** & **3aa**). Steric hindrance on a 3,5-disubstituted pyridine proved to be no issue for phenol coupling to occur (**3ab**). 4-methyl quinoline also proved to be a compatible heterocycle with moderate C-O bond formation at the 2-position (**3ac**). A di-substituted pyrimidine equipped with a methyl thioether at the 2-position and a bromine at the 5- worked great with *para*-methoxy phenol (**3ad**). Quinoxoline **3ae** also proved to be a competent heterocycle for this coupling strategy.

Table 3.7: Azaarene scope using *p*-methoxyphenol as the nucleophile.



Thiophenol was also subjected to a range of heterocyclic phosphonium salts and the results are shown in table 3.8. C-S bond formation occurred on both 3-phenylpyridine (**3af**) as well as 2-methoxypyridine (**3ag**). Sterics were also no trouble for the thiophenol as a 3,5-disubstituted pyridine was capable for coupling (**3ah**). A 2-3-disubstition pattern was also tolerated to form the diaryl-thioether **3ai**. A quinoline equipped with a thiophene and a trifluoromethyl group selectively formed the C-S bond at the 2-position (**3aj**). A monosubstituted pyrimidine phosphonium salt was also compatible with thiophenol (**3ak**).

Table 3.8: Azaarene scope using thiophenol as the nucleophile. [a] ran in DME.

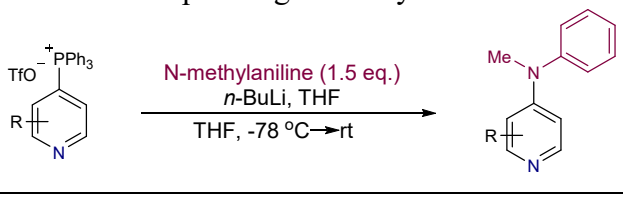


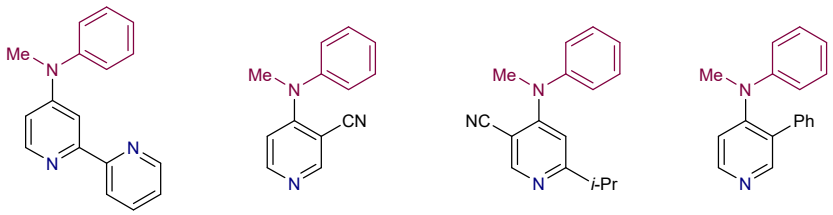
3af, 77% **3ag**, 45% **3ah**, 63%

3ai, 77%[a] **3aj**, 74% **3ak**, 66%

N-methylanilines proved to be difficult to find compatible coupling partners for. 2-position substituents work well for the reaction (**3al**), however substituents at the 3- and 5-positions on the pyridine are troublesome (**3ao**). A cyano group was the only 3-position functionality that allowed for the desired coupling reaction to occur as shown in examples **3am** and **3an**.

Table 3.9: Azaarene scope using N-methylaniline as the nucleophile.



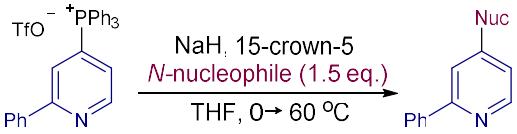


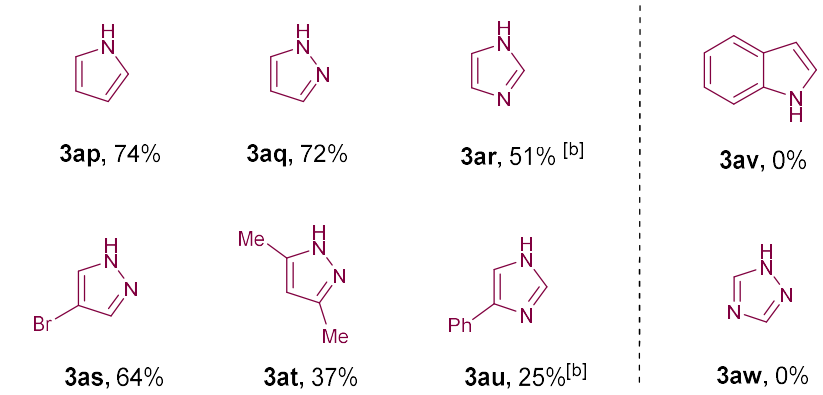
3al, 82% **3am**, 81% **3an**, 69% **3ao**, 0%

3.2.3 Endocyclic Aromatic Heteronucleophile Scopes

After having success in coupling a variety of exocyclic aromatic heteronucleophiles, we wanted to see how successful this strategy was towards nucleophiles where the nucleophilic atom is situated within the aromatic ring system. We used a similar strategy employed in the previous reactions where the nucleophile is first deprotonated at 0 ºC then warmed to 60 ºC after the addition of the phosphonium salt. An array of different azoles was studied for their compatibility with this coupling protocol (Table 3.10).

Table 3.10: Endocyclic aromatic heteronucleophiles scope. All yields shown are isolated. [b] KH and 18-crown-6 used.





3ap, 74% **3aq**, 72% **3ar**, 51% [b] **3av**, 0%

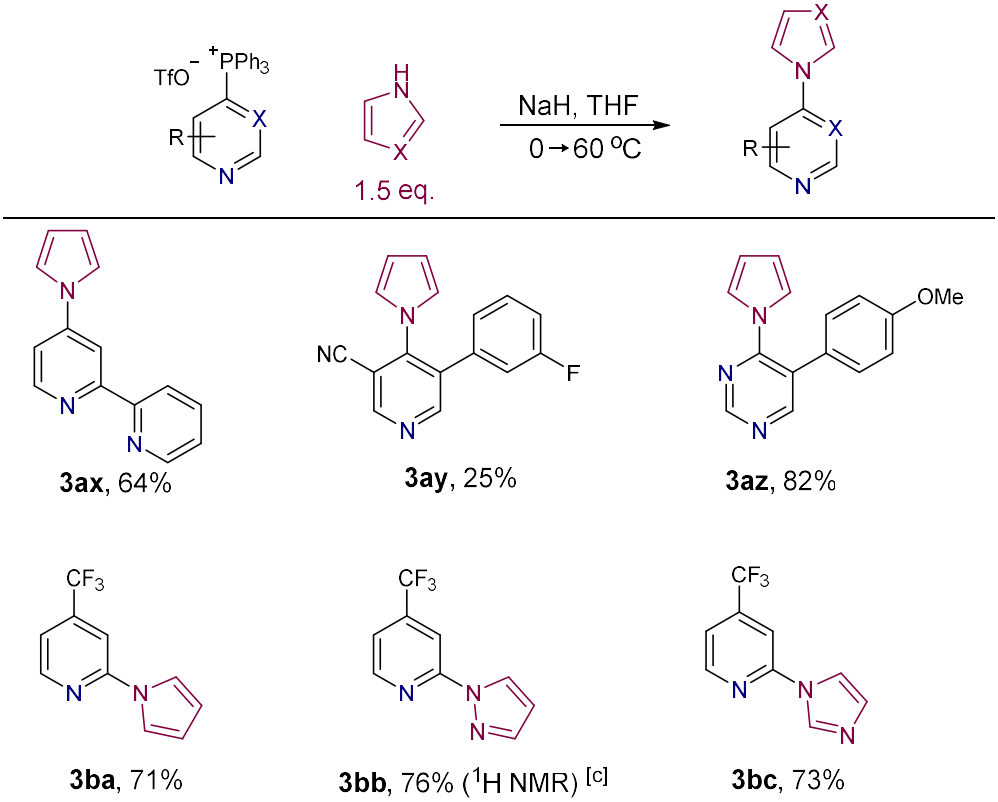
3as, 64% **3at**, 37% **3au**, 25%[b] **3aw**, 0%

We were delighted to find that pyrrole formed a C-N bond at the 4-position of 2-phenylpyridine via the phosphonium salt in excellent yield (**3ap**). This exciting discovery was followed up with pyrazole also showing considerable coupling capability (**3aq**). Imidazole proved to be more precarious under these coupling conditions. However, we were able to improve the coupling of this electron deficient ring by switching to potassium hydride and using 18-crown-6 as the crown ether (**3ar**). We assume that enlarging the anion and trapping it with it's corresponding crown ether allows for a weaker ionic interaction with the nitrogen anion, allowing for increased nucleophilicity and thus better reactivity with the phosphonium. KHMDS was also employed for this strategy, but no product formation was detected and instead it triggered the C-H pathway. 4-bromopyrazole worked well for this reaction (**3as**) and left the halogen in tact for further functionalization. A sterically bulky 3,5-dimethylpyrazole also proved to be compatible (**3at**). A phenylimidazole also formed the C-N bond using the KH conditions (**3au**). We were surprised to see that indole (**3av**) was not suitable as a coupling partner. We currently believe that there might be an unfavorable steric interaction with the 7-position C-H bond that inhibits the desired coupling. Triazoles also proved to be incompatible for C-N bond formation (**3aw**), presumably due to its electron deficient nature.

Having found a few endocyclic aromatic heteronucleophiles that were appropriate for our coupling strategy, we began to look at altering the heterocyclic phosphonium salt (**table 3.11**). Pyrrole was able to be coupled to 2,2-bipyridine in moderate yield (**3ax**). Sterically bulky groups at the 3- and 5-positions of the pyridine proved to hinder the coupling of pyrrole as shown in substrate **3ay**. A phosphonium salt at the 4-position of 5-(4-methoxyphenyl)pyrimidine, on the other hand, worked great in forming the C-N bond (**3az**). By blocking the 4-position of a pyridine with a trifluoromethyl group, we were able to selectively form the phosphonium salt at

the 2-position and subsequently couple pyrrole, pyrazole and imidazole (3ba-3bc). It should be noted, however, that substrate 3bb was volatile so it wasn't able to be isolated. Instead, our evidence for the desired C-N bond formation was based on LC-MS and crude ^{1}H NMR data (refer to appendix 2 for more details).

Table 3.11: Azaarene scope for pyrroles, pyrazole and imidazole. All yields shown are isolated unless otherwise noted. [c]Product was volatile.

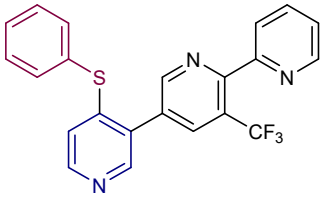


3.2.4 Drug-like Fragments and Bioactive Molecules

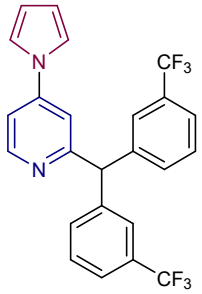
The overarching goal of this project was to be able to couple these nucleophiles in late-stage functionalization applications of bioactive molecules. We began this challenge by subjecting our phosphorous ion-mediated process to a series of complex pyridines and diazines that resemble the structures of bioactive molecules that could potentially be found in drug development programs (table 3.12). First, the C-H precursor of each of these drug-like fragments were constructed then subjected to the formation of a heterocyclic phosphonium salt (refer to

appendix 2). Our goal was to construct intricate fragments that contain functional groups that prove difficult for traditional methods, to further show how our method could be favorable in late-stage applications.

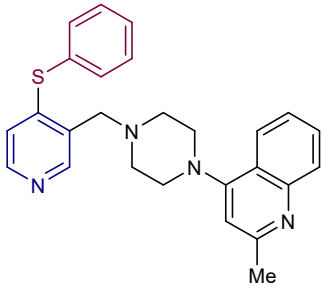
Table 3.12: Scope of aromatic heteronucleophile addition to heterocyclic phosphonium salts on drug-like fragments. All yields shown are isolated from the coupling reaction. Some reactions required modified conditions for higher yields – specific cases are noted in appendix 2.



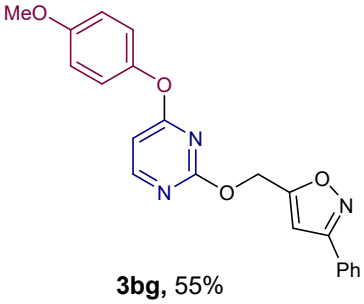
3bd, 65%



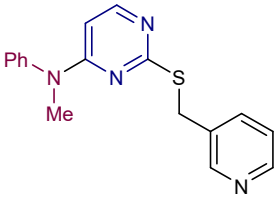
3be, 46%



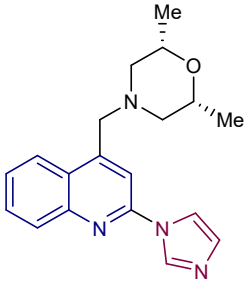
3bf, 34%



3bg, 55%



3bh, 37%



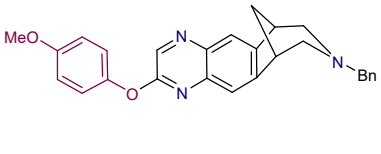
3bi, 64%

A tripyridine system worked great in coupling a thiophenol (**3bd**), and thanks to the 3-substituted pyridine reacting preferentially with triflic anhydride during phosphonium salt formation we were able to accomplish this C-S bond formation with complete site-selectivity. A pyridine containing a benzhydryl center at the 2-position was successful in pyrrole coupling (**2be**). Another polyazine system proved compatible for thioether formation when we were able to couple thiophenol to the 4-position of a pyridine that also contained piperazine and quinoline motifs (**3bf**). *Para*-methoxyphenol was able to be coupled to a pyrimidine fragment containing a 1,2-oxazole moiety (**3bg**). We used our recently disclosed site-selective switching strategy[10] in

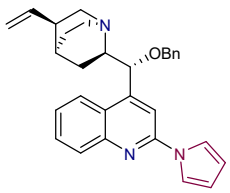
polyazine **3bh** to selectively form the phosphonium on the pyrimidine ring and further couple *N*-methylaniline to it. A quinoline fragment containing a dimethyl morpholine moiety proved worthy in coupling imidazole at the 2-position (**2bi**).

With a representative group of successful coupling examples in place, we decided to turn our attention to employing our site-selective functionalization strategy on complex drugs and other bioactive molecules (table 3.13). A benzyl-protected version of the smoking cessation drug varenicline, also known as Chantix, contains a quinoxoline ring system that reacted well with *para*-methoxyphenol (**3bj**). Pyrrole was able to be coupled to benzyl-protected cinchonidine in moderate yield (3bk). Site-selectivity was further exploited in forming etoricoxib derivative **3bl**. Loratidine, more commonly known as Claritin, forms the phosphonium salt with complete regioselectivity at the 4-position of it's pyridine and proved to be an excellent coupling partner with thiophenol (**3bm**). An analogue of bepotastine was great for further derivatization to a to a selenoether (**3bn**). The prostate cancer drug abiraterone acetate was able to be coupled to a thiophenol to make **3bo** in decent yield. A pesticide also proved competent as para-methoxy phenol reacted well with the phosphonium salt on pyriproxyfen (**3bp**). We were pleased to see that the complex cancer drug imatinib was successful in coupling a thiophenol (**3bq**), however the final product contained 6% of the regioisomer (see appendix 2 for details) of the coupled product.

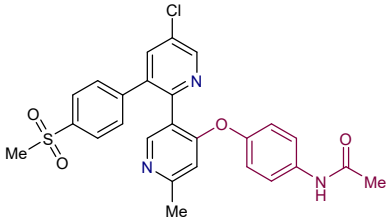
Table 3.13: Scope of aromatic heteronucleophile addition to heterocyclic phosphonium salts on bioactive molecules. All yields shown are isolated. Some reactions required modified conditions for higher yields – specific cases are noted in appendix 2.



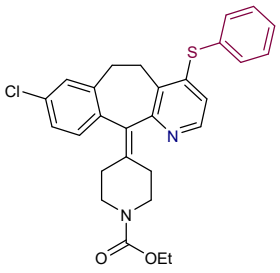
from N-Bn varenicline (Chantix)
3bj, 41%



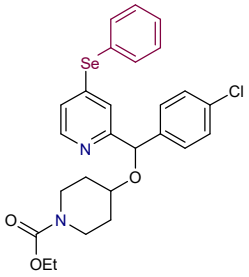
from OBn-cinchonidine
3bk, 54%



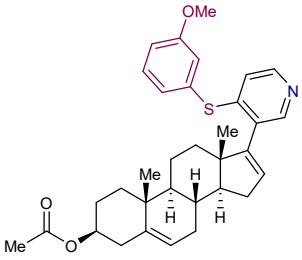
from etoricoxib
3bl, 40%



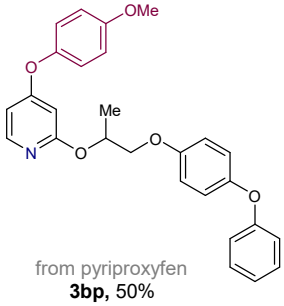
from loratidine (Claritin)
3bm, 83%



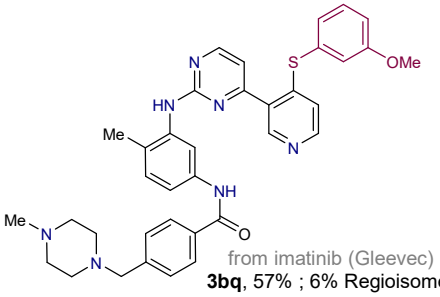
bepotastine derivative
3bn, 70%



from abiraterone acetate (Zytiga)
3bo, 61%



from pyriproxyfen
3bp, 50%



from imatinib (Gleevec)
3bq, 57% ; 6% Regioisomer

3.2.5 Novel Tyrosine Kinase Inhibitor Synthesis

Tyrosine kinase inhibitors (TKIs) are used for treatment of different kinds of cancer, including renal cell, gastrointestinal and hepatocellular cancers.[11] The oldest and most commonly known TKI is imatinib, which is used to treat patients with myeloid leukemia. We were pleased to be able to derivatize imatinib (**3bq**) directly from a C-H bond in the active drug. TKIs can limit cell growth and proliferation by blocking intracellular pathways in malignant tumors and cancer cells. Specifically, they compete with adenosine triphosphate (ATP) at its binding domain which inhibits tyrosine kinases from participating in further cell-growth pathways.[12] Since the

efficacy of these drugs depend on this competitive binding ability, the structure of these pharmaceuticals are intricate and slight derivatizations have the potential to increase its potency considerably. For example, Sorafenib and Regorafenib (**fig. 3.2**) are two FDA approved tyrosine kinase inhibitors and are very similar in structure with only one C-F bond differentiating them. Interestingly, they both serve separate oncogenic purposes as Sorafenib is used to treat kidney cancer and Regorafenib is used for advanced colon cancer. We found it very intriguing that one minor change in the molecular structure of these drugs enables for different therapeutic effects.

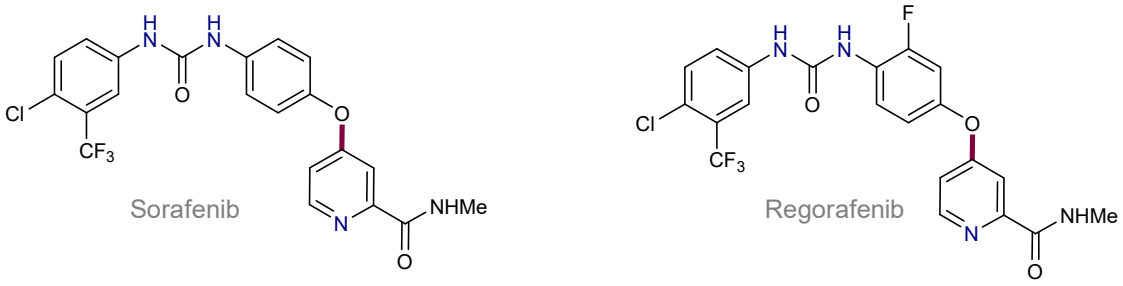


Fig. 3.2: Examples of tyrosine kinase inhibitors containing a possible bond disconnection for our selective heterocycle functionalization strategy.

To further demonstrate the utility of our reaction we wanted to attempt a complex convergent coupling strategy to construct a novel drug derivative that would prove difficult to make via traditional methods. We wanted to use our site-selective coupling strategy to create a unique scaffold that would be challenging to access through the conventional S_NAr and metal-catalyzed approaches. Our eye was caught by the scaffold of sorafenib and regorafenib because the phenolic C-O bond at the 4-position of the pyridine ring (highlighted in red in figure 3.2) was an imaginable bond construction using our coupling protocol.

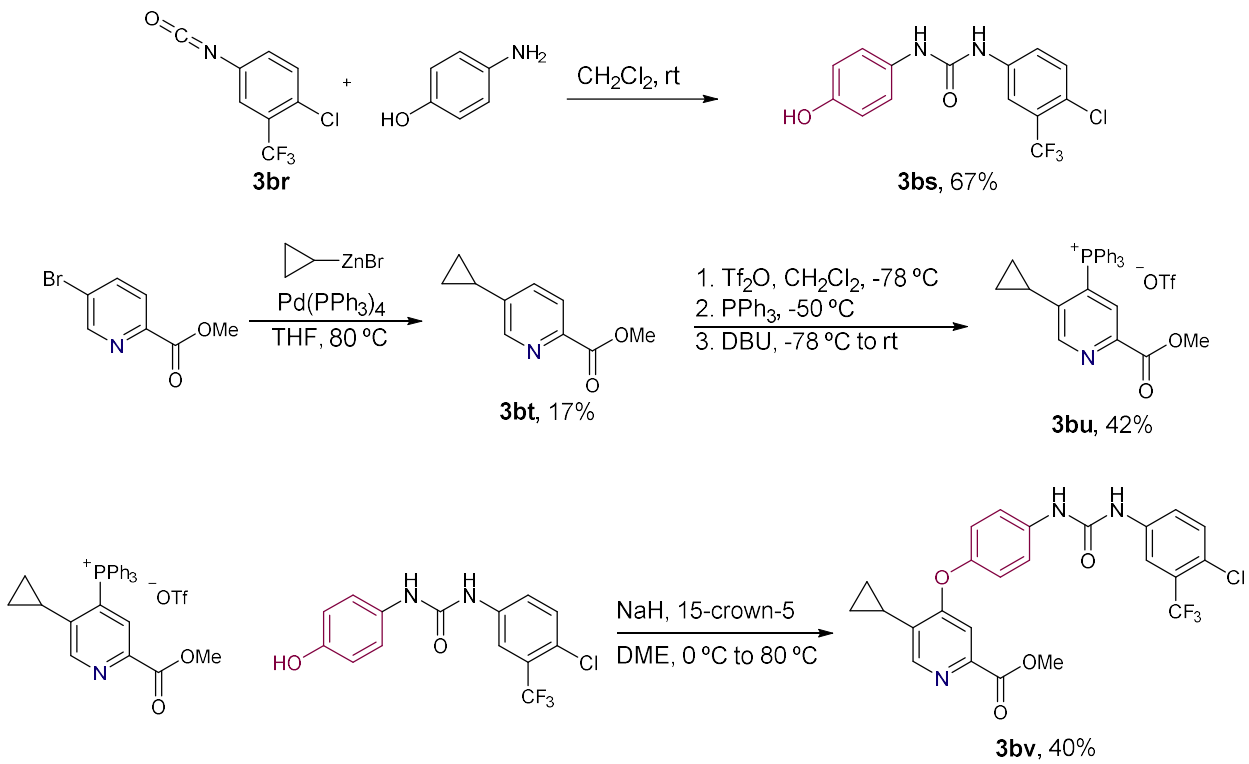


Fig. 3.3: Synthesis of a derivative of Sorafenib via nucleophilic addition to a heterocyclic phosphonium salt. All yields shown are isolated.

We began this convergent coupling strategy (figure 3.3) by first constructing the urea bond off the phenol ring. This was easily achieved by reacting isocyanate **3br** with 4-aminophenol in CH_2Cl_2. Compound **3bs** was isolated and we had a phenol nucleophile that completely resembles the diaryl urea moiety of sorafenib. Next, we needed to induce some novelty into our derivative by introducing some functionality onto the heterocycle that would prove difficult for halide introduction at the 4-position. We believed that a cyclopropyl ring at the 5-position would be an excellent candidate. We employed a Negishi cross coupling reaction to install the cyclopropyl ring (**3bt**). We were able to isolate just enough of this pyridine to carry on to the phosphonium salt reaction, which worked well to selectively form the phosphonium at the 4-position (**3bu**). With our nucleophile and phosphonium handle prepared, we began to look at a variety of coupling conditions to construct the C-O bond. It was found that the reaction

worked best in DME as the diaryl urea suffered some major solubility issues in THF. Nevertheless, we were able to successfully isolate this novel tyrosine kinase inhibitor derivative in 40% yield (**3bv**).

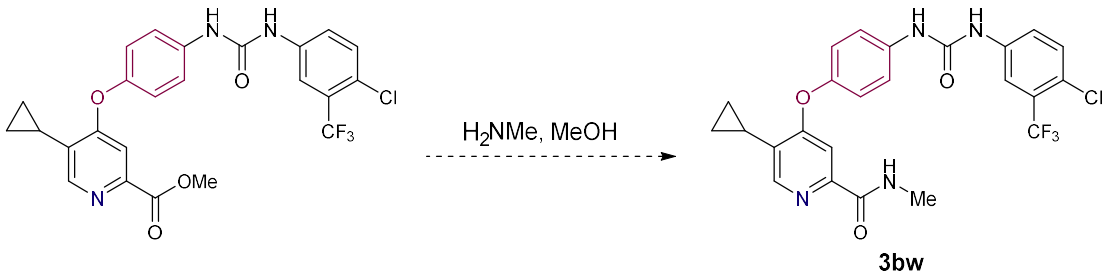


Fig. 3.4: Potential route for amide bond formation on sorafenib derivative.

Notably, we had to use a methyl ester at the 2-position of the pyridine instead of a methyl amide due to amides behaving poorly during the phosphonium salt formation reaction. This amide functionality in sorafenib and regorafenib is actually very important for the inhibition of ATP binding in tyrosine kinases. The pyridine nitrogen and amide N-H bond participate in 'type II binding' where they occupy an allosteric site and the rest of the molecule is perfectly positioned to block the ATP binding site.[13] The amide N-H bond acts as a hydrogen bond donor during this allosteric binding interaction, so we found it important to disclose a possible route for this conversion. The methyl ester should be fairly activated for reactivity with an amine nucleophile because of the electron withdrawing capabilities of the pyridine ring. We imagined that methyl amine could undergo amidation in methanol at high temperatures (figure 3.4). However, due to lack of enough material, we were unable to test this hypothesis.

3.3 Summary

To summarize, we were able to show that seven different classes of aromatic heteronucleophiles can serve as competent coupling partners with heterocyclic phosphonium salts to regioselectivity form C-O, C-S, C-Se and C-N bonds on pyridines and diazines. We believe that our simplified functionalization method, which allows for the use of bench stable

intermediates, is advantageous over traditional metal catalyzed cross couplings and S_NAr reactions. This approach is feasible for late-stage functionalization of complex drug molecules and could allow for quicker access to valuable derivatives without having to worry about the installation of halogen precursors. This approach also allowed for the construction of a novel tyrosine kinase inhibitor via a convergent reaction between two complex coupling partners. This simple procedure should prove valuable to medicinal chemists due to our array of evidence of its applicability to therapeutically-relevant molecules.

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APPENDIX 1: CHAPTER 2 EXPERIMENTAL

General considerations:

Unless stated, all starting materials are either known compounds or were obtained from commercial sources and used without purification. Reactions were carried out under an inert atmosphere of nitrogen unless stated. Reaction progress was monitored by TLC, ^{1}H NMR spectra taken from reaction samples or LCMS analysis. Tetrahydrofuran (THF), toluene, diethyl ether and dichloromethane were degassed and passed through a solvent purification system (alumina columns). 1,2-Dichloroethane (DCE), 1,4-dioxane, chloroform, chlorobenzene and acetone were purchased anhydrous from Sigma Aldrich chemical company. Flash chromatography was performed on Silicycle silica gel (Silaflash P60 (230-400 mesh)) with the indicated solvent system.

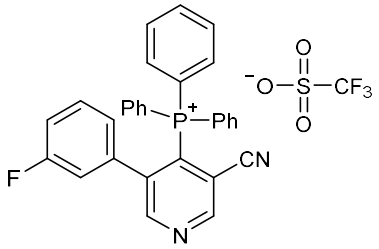
^{1}H NMR spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz) or an Agilent Inova 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). 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. ^{13}C NMR spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz) or an Agilent Inova 400 (100 MHz) spectrometer.

Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the

residual solvent peaks.

Formation of phosphonium salts:

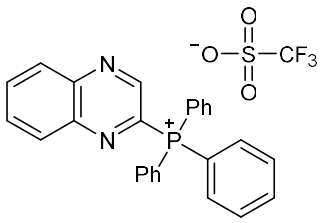
(3-Cyano-5-(3-fluorophenyl)pyridine-4-yl)triphenylphosphonium trfluormethanesulfonate



To a solution of 5-(3- fluorophenyl)nicotinonitrile (1.29 g, 6.51 mmol) in CH_2Cl_2 (65 mL) at –78 ^oC was added Tf_2O (1.09 mL, 6.51 mmol) dropwise over 5 min. The reaction was stirred for 30 min before PPh_3 (1.88 g, 7.16 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and stirred for a further 30 min at 78 ^oC. DBU (0.97 mL, 6.51 mmol) was added dropwise, the cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring (approximately 15 min). The reaction mixture was quenched with H_2O (65 mL) and the mixture transferred to a separatory funnel. The mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated to approximately 10 mL. The concentrated solution was added to an excess of Et_2O (–20 ^oC) and then placed in a –20 ^oC refrigerator for around 1 h. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (– 20 ^oC) and dried *in vacuo* to provide the *title compound* (3.00 g, 4.93 mmol, 76% yield) as a white solid. mp 98-112 ^oC; IR ν_{max}/cm^{-1} (film): 3065, 1585, 1439, 1260, 1150, 1099, 1029, 997, 719, 684, 636, 549; ^1H NMR (400 MHz, $CDCl_3$) d: 9.10 (1H, dd, J = 4.9, 1.2 Hz), 8.83 (1H, dd, J = 5.5, 1.1 Hz), 7.92-7.44 (15H, m),

7.02-6.92 (1H, m), 6.84-6.73 (2H, m), 6.70 (1H, d, J = 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d: 162.59 (d, J = 247.8 Hz), 152.82, 147.29, 140.07, 137.63 (d, J = 7.9 Hz), 135.63, 130.31 (d, J = 8.4 Hz), 128.95, 128.72, 127.93, 125.41 (d, J = 3.1 Hz), 116.68 (d, J = 22.5 Hz), 115.98 (d, J = 21.0 Hz), 115.08; ^{19}F NMR (365 MHz, $CDCl_3$), -78.1; ^{31}P NMR (162 MHz, $CDCl_3$) 21.4; *m/z* HRMS (DART) found $[M\text{-}OTf]^+$ 459.1425, $C_{30}H_{21}FN_2P^+$ requires 459.1421.

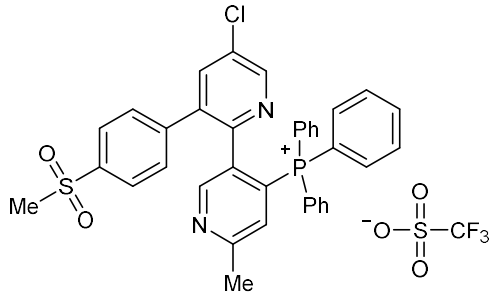
Triphenyl(quinoxalin-2-yl)phosphonium trifluoromethanesulfonate



To a solution of quinoxaline (52 mg, 0.40 mmol) in CH_2Cl_2 (4 mL) at -78 ^{o}C was added Tf_2O (67 μL, 0.40 mmol) dropwise over 5 min. The reaction was stirred for 30 min before PPh_3 (113 mg, 0.44 mmol) and NaOAc (50 mg, 0.60 mmol) were added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and stirred for a further 30 min at -78 ^{o}C before being heated at 40 ^{o}C for 1 h. DBU (60 mL, 0.40 mmol) was added dropwise at room temperature, and the reaction was stirred for a further hour at 40 ^{o}C. The reaction mixture was quenched with H_2O (10 mL) and the mixture transferred to a separatory funnel. The mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated to approximately 10 mL. The concentrated solution was added to an excess of Et_2O (– 20 ^{o}C) and then placed in a –20 ^{o}C refrigerator for around 12 h. The resulting suspension was filtered, dissolved in 10 mL CH_2Cl_2 and the precipitation process was repeated. The resulting solid

was filtered on a frit and dried *in vacuo* to provide the *title compound* (138 mg, 0.26 mmol, 64% yield) as a white solid. mp 130-132 ºC; IR ν_{max}/cm^{-1} (film): 3063, 2360, 1484, 1438, 1262, 1109, 1030, 634; ^{1}H NMR (400 MHz, $CDCl_3$) d: 8.99 (1H, s), 8.27-8.22 (2H, m), 8.09-8.01 (2H, m), 7.93-7.90 (3H, m), 7.79-7.72 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.86 (d, *J* = 25.4 Hz), 143.38 (d, *J* = 2.8 Hz), 142.70 (d, *J* = 17.3 Hz), 140.83 (d, *J* = 111.6 Hz), 136.16 (d, *J* = 3.1 Hz), 134.98, 134.66 (d, *J* = 10.5 Hz), 133.08, 130.86 (d, *J* = 13.0 Hz), 130.19 (d, *J* = 2.0 Hz), 129.85 (d, *J* = 2.3 Hz), 120.76 (q, *J* = 319.5 Hz), 116.03 (d, *J* = 88.1 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 13.54; *m/z* HRMS (DART) found $[M\text{-}OTf]^+$ 391.1355, $C_{26}H_{20}N_2P^+$ requires 391.1359.

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



To a solution of 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (384 mg, 1.07 mmol) in CH_2Cl_2 (11 mL) at -78 ºC was added Tf_2O (180 µL, 1.07 mmol) dropwise over 5 min. The reaction was stirred for 30 min before PPh_3 (309 mg, 1.18 mmol) and NaOAc (88 mg, 1.07 mmol) were added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and stirred for a further 30 min at -78 ºC. DBU (160 µL, 1.07 mmol) was added dropwise, the cooling bath was removed

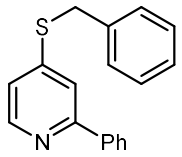
and the reaction was allowed to warm to room temperature while stirring (approximately 15 min). The reaction mixture was quenched with H_2O (30 mL) and the mixture transferred to a separatory funnel. The mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated to approximately 10 mL. The concentrated solution was added to an excess of Et_2O (–20 °C) and then placed in a −20 °C refrigerator 1 h. The resulting solid was filtered on a frit and dried *in vacuo* to provide the *title compound* (603 mg, 0.78 mmol, 73% yield) as a white solid. mp 157-163 °C; IR ν_{max}/cm^{-1} (film): 3062, 1709, 1577, 1542, 1485, 1436, 1311, 1261, 1223, 1150, 1101, 1030, 921, 888, 715, 690, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, d, *J* = 7.1 Hz), 8.10 (2H, d, *J* = 8.2 Hz, H_6), 7.86-7.62 (16H, m), 7.51-7.45 (3H, m), 7.20 (1H, d, *J* = 16.5 Hz), 3.14 (3H, s), 2.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.84 (d, *J* = 11.2 Hz), 152.42 (d, *J* = 7.3 Hz), 147.53 (d, *J* = 2.2 Hz), 146.09, 141.53, 141.02, 138.92, 135.62, 134.84 (d, *J* = 2.9 Hz), 134.17 (d, *J* = 10.0 Hz), 133.29 (d, *J* = 3.6 Hz), 132.10, 130.76 (d, *J* = 10.2 Hz), 130.03 (d, *J* = 13.1 Hz), 129.86, 128.55, 128.19 (d, *J* = 86.2 Hz), 120.77 (q, *J* = 321.1 Hz), 119.34 (d, *J* = 91.8 Hz), 43.96, 24.55; ^{19}F NMR (365 MHz, $CDCl_3$) δ: - 78.14; ^{31}P NMR (162 MHz, $CDCl_3$) δ: (162 MHz, $CDCl_3$) δ: 25.54; *m/z* LRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 619.2, $C_{36}H_{29}N_2O_2PS^+$ requires 619.1.

General procedure for the thiol addition reaction to form heteroaryl thioethers (2a-2v):

An oven dried 8 mL vial with a septa cap was charged with sodium hydride (60% dispersion in mineral oil, 1.1 equiv) and placed under a nitrogen atmosphere. THF (0.25 M) was added, the sus- pension was cooled to 0 °C and the thiol (1.1 equiv) was added dropwise over 5 min

(if the thiol was a solid or viscous liquid, it was added as a 0.5 M solution in THF to an equivalent volume 0.5 M solution of NaH in THF). The resulting thick slurry was stirred for 30 min at 0 ^{o}C before the septa cap was briefly removed and the phosphonium salt (1.0 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen back- fill, the ice bath removed, and the reaction stirred for 3 h while warming to room temperature. The reaction was quenched with H_2O, the aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl thioether product.

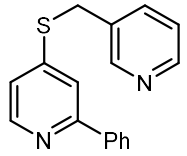
4-(benzylthio)-2-phenylpyridine (2a)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 μL, 0.55 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (1a, 283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 15% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the *title compound* (2a) as a white powder (128 mg, 0.46 mmol, 92% yield). mp 48-52 ^{o}C; IR ν_{max}/ cm^{-1} (film): 3060, 3040, 3027, 2922, 1560, 1533, 1495, 1455, 1377, 770, 709; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (1H, d, *J* 5.3 Hz), 7.90 (2H, d, *J* = 7.7 Hz), 7.54 (1H, m), 7.49-7.27 (8H, m), 7.08 (1H, dd, *J* = 5.2, 1.7 Hz), 4.27 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.27, 149.50, 149.16, 139.07, 135.73, 129.11, 128.82, 128.72, 128.71 (2C),

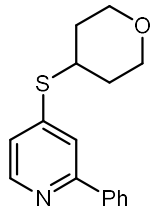
126.96, 119.25, 117.90, 35.92; *m/z* HRMS (DART) found $[M+H]^+$ 278.1001, $C_{18}H_{16}NS^+$ requires 278.0998.

2-Phenyl-4-((pyridine-3-ylmethyl)thio)pyridine (2b)



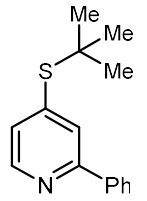
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), pyridine-3-ylmethane thiol (62 μL, 0.55 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (1a, 283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the *title compound (2b)* as a yellow oil (104 mg, 0.38 mmol, 75% yield). IR ν_{max}/cm^{-1} (film): 3049, 2918, 1569, 1534, 1466, 1435, 1381, 772, 730, 693; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, J = 4.7 Hz), 8.45 (1H, d, J = 5.4 Hz) 7.95-7.89 (2H, m), 7.70-7.63 (2H, m), 7.51-7.37 (4H, m), 7.20 (1H, dd, J = 7.2, 4.9 Hz), 7.13 (1H, dd, J = 5.3, 0.7 Hz), 4.41 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.20, 156.64, 149.40, 149.09, 148.93, 138.98, 137.00, 129.10, 128.70, 126.93, 122.86, 122.48, 119.26, 117.84, 37.48; *m/z* HRMS (DART) found $[M+H]^+$ 279.0948, $C_{17}H_{15}N_2S^+$ requires 279.0950.

2-Phenyl-4-((tetrahydro-2H-pyran-4-yl)thio)pyridine (2c)



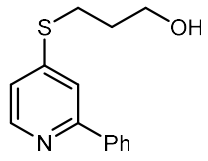
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), tetrahydro-2*H*-pyran-4-thiol (63 μL, 0.55 mmol), triphenyl(2-phenylpyridin-4-yl) phosphonium trifluoromethanesulfonate (1a, 283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel, gradient elution: 40% EtOAc in hexanes) afforded the *title compound (2c)* as a white solid (92 mg, 0.37 mmol, 74% yield). mp 62-64 ^{o}C; IR n_{max}/cm^{-1} (film): 3071, 2956, 2914, 2863, 2839, 1565, 1533, 1461, 1440, 1379, 1126, 1083, 1007, 981, 818, 772, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, d, *J* 5.3 Hz), 7.97-7.91 (2H, m), 7.57 (1H, d, *J* = 1.3 Hz), 7.50-7.38 (3H, m), 7.09 (1H, dd, *J* = 5.3, 1.7 Hz), 4.00 (2H, dt, *J* = 11.9, 3.9 Hz), 3.66-3.49 (3H, m), 2.09-1.99 (2H, m), 1.83-1.70 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.57, 149.39, 147.62, 138.98, 129.19, 128.76, 126.96, 120.65, 119.50, 67.03, 40.54, 32.69; *m/z* HRMS (DART) found $[M+H]^+$ 272.1101, $C_{17}H_{15}N_2S^+$ requires 272.1104.

4-(tert-butylthio)-2-phenylpyridine (2d)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), *tert*-butyl thiol (62 μL, 0.55 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (1a, 283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the *title compound (2d)* as a white crystalline solid (109 mg, 0.45 mmol, 90% yield). mp 56-62 ^{o}C; IR ν_{max}/cm^{-1} (film): 3042, 2976, 2967, 2955, 2921, 2856, 1568, 1533, 1463, 1443, 1375, 1364, 1161, 847, 775, 686, 618; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.6 (1H, d, *J* = 5.1 Hz), 7.99 (2H, d, *J* = 7.6 Hz), 7.83 (1H, m), 7.52-7.40 (3H, m), 7.35 (1H, d, *J* = 5.0, 1.7 Hz), 1.41 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.55, 149.35, 144.77, 138.91, 129.17, 128.78, 128.20, 126.97, 126.90, 47.08, 31.24; *m/z* HRMS (DART) found $[M+H]^+$ 244.1169, $C_{15}H_{18}NS^+$ requires 244.1154.

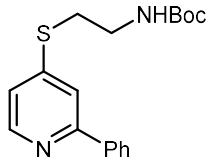
3-((2-Phenylpyridin-4-yl)thio)propan-1-ol (2e)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), 3-mercaptopropan-1-ol (48 μL, 0.55 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (1a, 283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel, dry load: 50% EtOAc in hexanes)

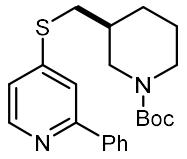
afforded the *title compound (2e)* as a yellow oil (111 mg, 0.45 mmol, 91% yield). IR ν_{max}/cm^{-1} (film): 3285 (br), 2923, 2850, 1571, 1533, 1465, 1444, 1382, 1056, 907, 773, 730, 694; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.48 (1H, d, *J* = 5.3 Hz), 7.95 (2H, d, *J* = 7.7 Hz), 7.57 (1H, m), 7.50-7.38 (3H, m), 7.09 (1H, dd, *J* = 5.2, 1.3 Hz), 3.83 (2H, t, *J* = 6.1 Hz). 3.18 (2H, t, *J* = 7.1 Hz), 2.00 (2H, app t, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.26, 149.97, 148.97, 139.03, 129.15, 128.73, 127.02, 119.02, 117.82, 60.74, 31.28, 27.21; *m/z* HRMS (DART) found $[M+H]^+$ 246.0961, $C_{14}H_{16}NOS^+$ requires 246.0947.

***Tert*-butyl(2-((2-phenylpyridin-4-yl)thio)ethyl)carbamate (2f)**



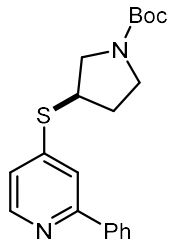
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), *tert*-butyl(2-mercaptoethyl)carbamate (93 mL, 0.75 mmol), triphenyl(2- phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (1a, 283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the *title compound (2f)* as an off-white amorphous solid (102 mg, 0.31 mmol, 62% yield). IR ν_{max}/cm^{-1} (film): 3343, 2976, 2930, 1699, 1571, 1534, 1506, 1365, 1251, 1164, 908, 773, 730, 694; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.47 (1H, d, *J* = 5.3 Hz), 7.98 (2H, d, *J* = 7.5 Hz), 7.64 (1H, m), 7.48e7.34 (3H, m), 7.10 (1H, dd, *J* = 5.3, 1.7 Hz), 3.43 (2H, q, *J* = 6.6 Hz). 3.17 (2H, t, *J* = 6.8 Hz), 2.15 (1H, s). 1.43 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.41, 149.22, 148.73, 138.96, 129.13, 128.67, 127.06, 119.13, 117.69, 79.72, 53.42, 39.69, 30.59, 28.34; *m/z* HRMS (DART) found $[M+H]^+$ 331.1488, $C_{18}H_{23}N_2O_2S^+$ requires 331.1475.

***Tert*-butyl (*S*)-3-(((2-phenylpyridin-4-yl)thio)methyl)piperidine-1-carboxylate (2g)**



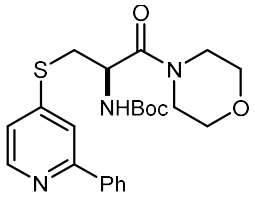
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), *tert*-butyl (*S*)-3-(mercaptomethyl)piperidine-1-carboxylate (127 mg, 0.55 mmol in 1 mL of THF), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (1a, 283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the *title compound (2g)* as a yellow oil (167 mg, 0.44 mmol, 87% yield). IR ν_{max}/cm^{-1} (film): 2975, 2929, 2854, 1681, 1571, 1535, 1424, 1365, 1261, 1241, 1163, 907, 772, 728, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, 1H, dd, *J* 5.3, 0.5 Hz), 7.97-7.92 (2H, m), 7.53 (1H, dd, *J* = 1.8, 0.6 Hz), 7.50-7.39 (3H, m), 7.05 (1H, dd, *J* = 5.3, 1.8 Hz), 4.22-3.73 (2H, m), 3.06-2.64 (4H, m), 2.06-1.94 (1H, m), 1.91-1.79 (1H, m), 1.75-1.63 (1H, m), 1.53-1.40 (10H, m), 1.39-1.27 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.29, 154.74, 149.62, 149.19, 139.07, 129.12, 128.76, 126.96, 119.08, 117.87, 79.56, 48.92 (br), 44.30 (br), 35.18, 34.18 (br), 28.40, 24.24 (br); *m/z* HRMS (DART) found $[M+H]^+$ 385.1913, $C_{22}H_{29}N_2O_2S^+$ requires 385.1944.

***Tert*-butyl (*R*)-3-((2-phenylpyridin-4-yl)thio)pyrrolidine-1-carboxylate (2h)**



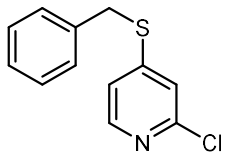
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), *tert*-butyl (*R*)-3-mercaptopyrrolidine-1-carboxylate (112 mg, 0.5 mmol, in 1.0 mL of THF), triphenyl(2-phenylpyridin-4-yl) phosphonium trifluoromethanesulfonate (1a, 283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the *title compound (2h)* as a clear oil (160 mg, 0.45 mmol, 90% yield). IR ν_{max}/cm^{-1} (film): 2976, 2877, 2246, 1685, 1570, 1535, 1400, 1365, 1163, 1115, 908, 772, 728, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, br s), 7.93 (2H, d, J = 7.3 Hz), 7.53 (1H, s), 7.50-7.36 (3H, m), 7.06 (1H, d, J = 5.1 Hz), 4.04-3.76 (2H, m), 3.68-3.25 (3H, m), 2.43-2.28 (1H, m), 2.07-1.91 (1H, m), 1.45 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.67, 154.30, 149.52, 148.39, 139.01, 129.32, 128.85, 127.07, 119.98, 118.76, 79.87, 51.88, $51.62_{(rot)}$, 47.75, $44.53_{(rot)}$, 42.42, $41.71_{(rot)}$, 32.06, $31.41_{(rot)}$, 28.56; *m/z* HRMS (DART) found $[M+H]^+$ 357.1670, $C_{20}H_{35}N_2O_2S^+$ requires 357.1631.

***Tert*-butyl (*R*)-(1-morpholino-1-oxo-3-((2-phenylpyridin-4-yl)thio)propan-2-yl)carbamate (2i)**



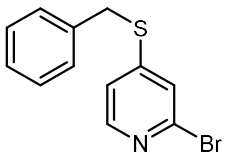
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 11 mg, 0.28 mmol), *tert*-butyl (*R*)-(3-mercapto-1-morpholino-1- oxopropan-2-yl)carbamate (80 mg, 0.28 mmol, in 1.0 mL of THF), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (1a, 142 mg, 0.25 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the *title compound (2i)* as a clear oil (21 mg, 0.05 mmol, 19% yield). IR ν_{max}/cm^{-1} (film): 3062, 2984, 2903, 1784, 1677, 1523, 1161, 1138, 1079, 984, 847, 776, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, d, *J* = 5.1 Hz), 8.08 (2H, d, *J* = 7.4 Hz), 7.76 (1H, m), 7.56-7.37 (3H, m), 7.15 (1H, d, *J* = 5.1 Hz), 4.90 (1H, m), 3.81-3.16 (10H, m), 1.43 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.01, 157.89, 155.04, 149.55, 148.40, 138.91, 129.45, 128.87, 127.28, 119.22, 117.11, 80.71, 66.70, 48.66, 46.69, 33.26, 28.46; *m/z* HRMS (DART) found $[M+H]^+$ 444.1944, $C_{23}H_{30}N_3O_4S^+$ requires 444.1952.

4-(benzylthio)-2-chloropyridine (2k)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (68 μL, 0.58 mmol), (2- chloropyridin-4-yl)triphenylphosphonium trifluormethane sulfonate (262 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the *title compound (2k)* as a white solid (106 mg, 0.45 mmol, 90% yield). mp 58-62 ^{o}C; IR ν_{max}/cm^{-1} (film): 3068, 3028, 3007, 2920, 1568, 1522, 1456, 1370, 1150, 1078, 821, 794, 777, 713, 685; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 815 (1H, d, *J* = 5.3 Hz), 7.42-7.27 (4H, m), 7.15 (1H, d, *J* = 1.5 Hz), 7.02 (1H, dd, *J* = 5.4, 1.7 Hz), 4.21 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.33, 151.65, 148.79, 134.85, 128.90, 128.70, 127.92, 120.24, 119.43, 35.78; *m/z* HRMS (DART) found $[M+H]^+$ 236.0307, $C_{12}H_{11}ClNS^+$ requires 236.0295

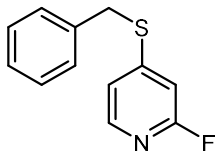
4-(benzylthio)-2-bromopyridine (2l)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (68 μL, 0.58 mmol), (2-bromopyridin-4-yl)triphenylphosphonium trifluormethanesulfonate (284 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel, dry load: 5% EtOAc in hexanes) afforded the *title*

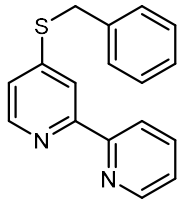
compound (2l) as a white solid (114 mg, 0.41 mmol, 81% yield). mp 59-63 ^{o}C; IR ν_{max}/cm^{-1} (film): 3063, 2918, 1560, 1515, 1453, 1365, 1245, 1069, 981, 821, 765, 712, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (1H, dd, *J* = 5.4, 0.5 Hz), 7.41-7.27 (5H, m), 7.05 (1H, dd, *J* 5.4, 1.7 Hz), 4.21 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.12, 149.15, 142.29, 134.81, 128.90, 128.72, 127.93, 123.90, 119.79, 35.78; *m/z* HRMS (DART) found $[M+H]^+$ 278.9718, $C_{12}H_{11}BrNS^+$ requires 279.9790.

4-(benzylthio)-2-fluoropyridine (2j)



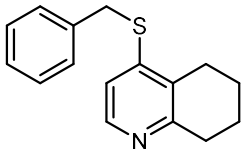
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 μL, 0.55 mmol), (2-fluoropyridin-4-yl)triphenylphosphonium trifluormethanesulfonate (284 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the *title compound (2j)* as a white amorphous solid (62 mg, 0.28 mmol, 57% yield). IR ν_{max}/cm^{-1} (film): 3063, 3027, 2918, 1560, 1515, 1453, 1365, 1244, 1069, 821, 765, 712, 677; ^{1}H NMR (400 MHz, $CDCl_3$) d: 7.99 (1H, d, *J* = 5.4 Hz), 7.42-7.27 (5H, m), 7.05 (1H, dt, *J* = 5.5, 1.7 Hz), 4.23 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d: 163.98 (d, *J* = 237.49 Hz), 154.65, (d, *J* = 8.6 Hz), 146.97, (d, *J* = 16.2 Hz), 135.01, 128.99, 128.77, 127.99, 118.63, (d, *J* = 3.7 Hz), 105.61 (d, *J* = 40.4 Hz), 35.910; ^{19}F NMR (365 MHz, $CDCl_3$), –68.26; *m/z* HRMS (DART) found $[M+H]^+$ 220.0591, $C_{12}H_{11}FNS^+$ requires 220.0591.

4-(benzylthio)-2,2'-bipyridine (2p)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 μL, 0.55 mmol), [2,2'- bipyridin]-4-yltriphenylphosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel, dry load: 10% EtOAc in hexanes) afforded the *title compound (2p)* as a white solid (85 mg, 0.31 mmol, 61% yield). mp 99-103 ^{o}C; IR ν_{max}/cm^{-1} (film): 3064, 2918, 1574, 1561, 1534, 1446, 1378, 987, 789, 716, 705, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, d, *J* = 5.3 Hz), 8.45 (1H, d, *J* = 5.3 Hz), 8.39-8.34 (2H, m), 7.81 (1H, tdd, *J* = 7.7, 1.6, 1.2 Hz), 7.44 (2H, d, *J* = 7.6 Hz), 7.37-7.27 (4H, m), 7.13 (1H, dd, *J* = 5.2, 1.7 Hz), 4.32 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.77, 155.71, 150.13, 149.11, 148.64, 136.90, 135.65, 128.89, 128.74, 127.63, 123.86, 121.26, 120.63, 117.92, 35.77; *m/z* HRMS (DART) found $[M+H]^+$ 279.0958, $C_{15}H_{17}N_2S^+$ requires 279.0.

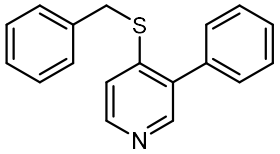
4-(benzylthio)-5,6,7,8-tetrahydroquinoline (2o)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 μL, 0.55 mmol), triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (272 mg, 0.50 mmol)

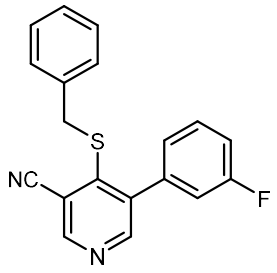
and THF (2.0 mL). Flash column chromatography (basic alumina: 10% EtOAc in hexanes) afforded the *title compound (2o)* as a white solid (96 mg, 0.38 mmol, 75% yield). mp 126-132 ^{o}C; IR ν_{max}/cm^{-1} (film): 3028, 2934, 2861, 1560, 1435, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (1H, d, *J* = 5.3 Hz), 7.44-7.23 (5H, m), 6.92 (1H, d, *J* = 5.3 Hz), 4.17 (2H, s), 2.89 (2H, t, *J* = 6.0 Hz), 2.61 (2H, t, *J* = 6.0 Hz), 1.90-1.77 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.26, 148.38, 146.08, 135.58, 128.84, 128.80, 128.75, 127.63, 116.18, 35.57, 32.91, 25.92, 22.68, 22.54; *m/z* HRMS (DART) found $[M+H]^+$ 256.1161, $C_{16}H_{18}NS^+$ requires 256.1154.

4-(benzylthio)-3-phenylpyridine (2n)



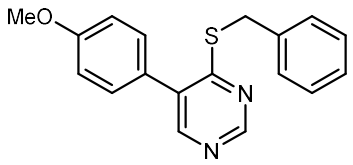
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 mL, 0.55 mmol), triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (basic alumina: 15% EtOAc in hexanes) afforded the *title compound (2n)* as a white powder (120 mg, 0.44 mmol, 87% yield). mp 93-97 ^{o}C; IR ν_{max}/cm^{-1} (film): 3024, 2920, 2645, 1563, 1453, 1390, 764, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (1H, d, *J* = 5.4 Hz), 8.29 (1H, s), 7.49-7.19 (11H, m), 4.10 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.18, 148.29, 147.78, 136.63, 135.42, 135.23, 129.32, 128.85, 128.73, 128.47, 128.29, 127.67, 119.11, 36.21; *m/z* HRMS (DART) found $[M+H]^+$ 278.1000, $C_{18}H_{16}NS^+$ requires 278.0998.

4-(benzylthio)-5-(3-fluorophenyl)nicotinonitrile (2q)



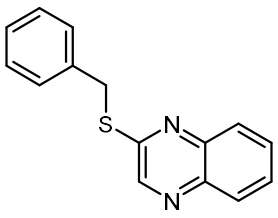
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 μL, 0.55 mmol), (3-cyano-5-(3-fluorophenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (304 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 15% EtOAc in hexanes) afforded the *title compound (2q)* as a yellow oil (149 mg, 0.47 mmol, 93% yield). IR n_{max}/cm^{-1} (film): 3063, 3030, 2230, 1613, 1584, 1545, 1398, 1204, 908, 733, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (1H, s), 8.53, (1H, s), 7.47-7.39 (1H, m), 7.24-7.12 (4H, m), 7.06-6.67 (3H, m), 6.92 (1H, d, J = 9.3 Hz), 4.10 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.45 (d, J = 246.5 Hz), 152.81, 147.28, 140.05, 137.62 (d, J = 7.9 Hz), 135.62, 130.30 (d, J = 8.3 Hz), 128.94, 128.71, 127.92, 125.40 (d, J = 3.0 Hz), 116.67 (d, J = 22.4 Hz), 115.96 (d, J = 20.9 Hz), 115.06, 39.47; *m/z* HRMS (DART) found $[M+H]^+$ 321.0870, $C_{19}H_{14}FN_2S^+$ requires 321.0856.

4-(benzylthio)-5-(4-methoxyphenyl)pyrimidine (2r)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 μL, 0.55 mmol), (5-(4-methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (298 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the *title compound (2r)* as a yellow oil (136 mg, 0.44 mmol, 88% yield). IR ν_{max}/cm^{-1} (film): 3028, 2932, 2835, 1610, 1558, 1522, 1381, 1248, 1118, 1033, 831, 765, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (1H, s), 8.24 (1H, s). 7.38-7.30 (4H, m), 7.29-7.18 (3H, m), 6.97-6.92 (2H, m), 4.41 (2H, s), 3.82 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.97, 160.10, 156.26, 153.64, 137.00, 132.82, 130.25, 129.25, 128.53, 127.31, 126.54, 114.23, 55.29, 34.30; *m/z* HRMS (DART) found $[M+H]^+$ 309.1036, $C_{18}H_{17}N_2OS^+$ requires 309.1056.

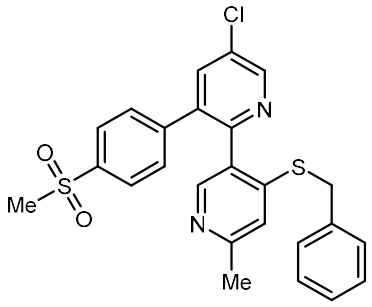
2-(benzylthio)quinoxaline (2s)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 μL, 0.55 mmol), triphenyl(quinoxalin-2-yl)phosphonium

trifluoromethanesulfonate (270 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the *title compound (2s)* as an amorphous tan solid (115 mg, 0.46 mmol, 91% yield). IR ν_{max}/cm^{-1} (film): 3060, 3028, 1539, 1494, 1247, 1150, 1082, 961, 757, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (1H, s), 8.01-7.92 (2H, m), 7.69 (1H, t, *J* = 7.4 Hz), 7.61 (1H, t, *J* = 7.3 Hz), 7.46 (2H, d, *J* = 7.4 Hz), 7.33-7.18 (3H, m), 4.57 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.62, 144.53, 142.63, 139.98, 137.33, 130.19, 129.25, 129.18, 128.57, 128.09, 127.80, 127.39, 33.68; *m/z* HRMS (DART) found $[M+H]^+$ 253.0804, $C_{15}H_{13}N_2S^+$ requires 253.0794.

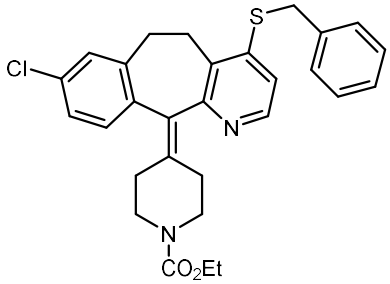
4'-(benzylthio)-5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (2t)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 11 mg, 0.28 mmol), benzyl thiol (33 μL, 0.28 mmol), (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3]bipyridine]-4'-yl)triphenylphosphonium trifluoromethanesulfonate (192 mg, 0.25 mmol) and THF (1.0 mL). Flash column chromatography (basic alumina: 30% EtOAc in hexanes) afforded the *title compound (*2t*)* as a white amorphous solid (78 mg, 0.16 mmol, 65% yield). IR ν_{max}/cm^{-1} (film): 3061, 1708, 1570, 1544, 1481.1301, 1252, 1140, 1028, 911, 882, 690, 640; ^{1}H NMR (400 MHz,

$CDCl_3$) δ: 8.68 (1H, d, J = 2.2 Hz), 7.94, (1H, s), 7.81-7.72 (3H, m), 7.34-7.21 (7H, m), 7.01 (1H, s), 4.08 (2H, s), 3.03 (3H, s), 2.47 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.25, 151.80, 149.17, 148.51, 148.24, 143.14, 140.13, 137.60, 136.84, 135.28, 131.89, 130.11, 129.93, 128.95, 128.89, 127.93, 127.62, 119.12, 44.56, 36.24, 24.57; *m/z* HRMS (DART) found $[M+H]^+$ 481.0792,$C_{25}H_{22}ClN_2O_2S_2^+$ requires 481.0806.

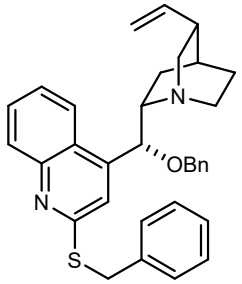
Ethyl-4-(4-benzylthio)-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-ylidene)piperidine-1-carboxylate (2u)



Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 μL, 0.55 mmol), (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphoniun trifluoromethanesulfonate (397 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (basic alumina, dry load, gradient elution: 20% EtOAc in hexanes to 30% EtOAc in hexanes) afforded the *title compound (2u)* as a white solid (129 mg, 0.36 mmol, 51% yield). mp 200-203 ^{o}C; IR ν_{max}/cm^{-1} (film): 2989, 2901, 1694, 1548, 1431, 1216, 1108, 1001, 764, 712, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (1H, d, J = 5.3 Hz), 7.40-7.24 (5H, m), 7.16-7.05 (3H, m), 6.99 (1H, d, J = 5.3 Hz), 4.18-4.08 (4H, m), 3.88-3.68 (2H, m), 3.42-3.31 (1H, m), 3.18-3.04 (3H, m), 2.92-2.71 (2H, m), 2.52-2.39 (1H, m), 2.38-2.23 (3H, m), 1.24 (3H, t, J = 7.1 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.28, 155.61, 149.07, 146.31, 139.75, 137.95, 137.67, 135.37, 134.25, 133.07, 130.35, 129.87, 128.95, 128.94, 128.88, 127.91, 126.33, 117.96, 61.45, 44.88, 36.28, 30.97, 30.75, 28.79, 14.83; *m/z* HRMS (DART) found $[M+H]^+$ 505.1705, $C_{29}H_{30}ClN_2O_2S^+$ requires 505.1711.

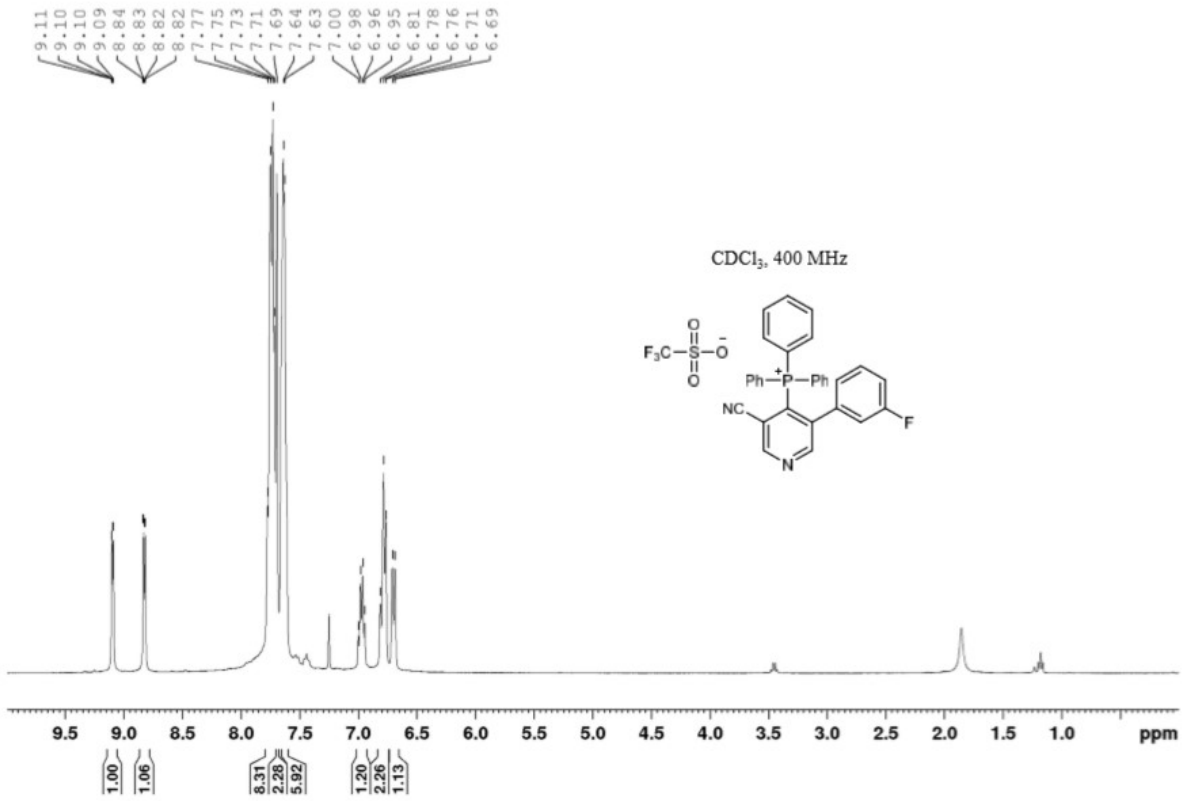
(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-benzyloxy)(2-(benzylthio)quinoline-4-yl)methyl)-5-vinylquinuclidine (2v)

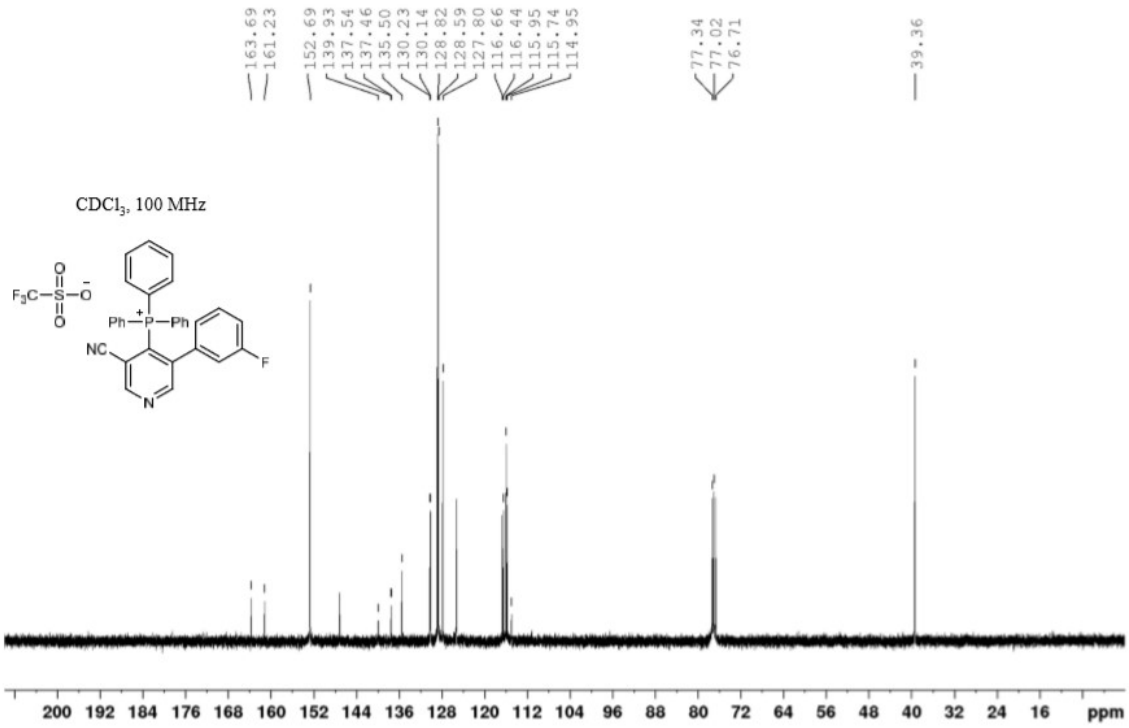


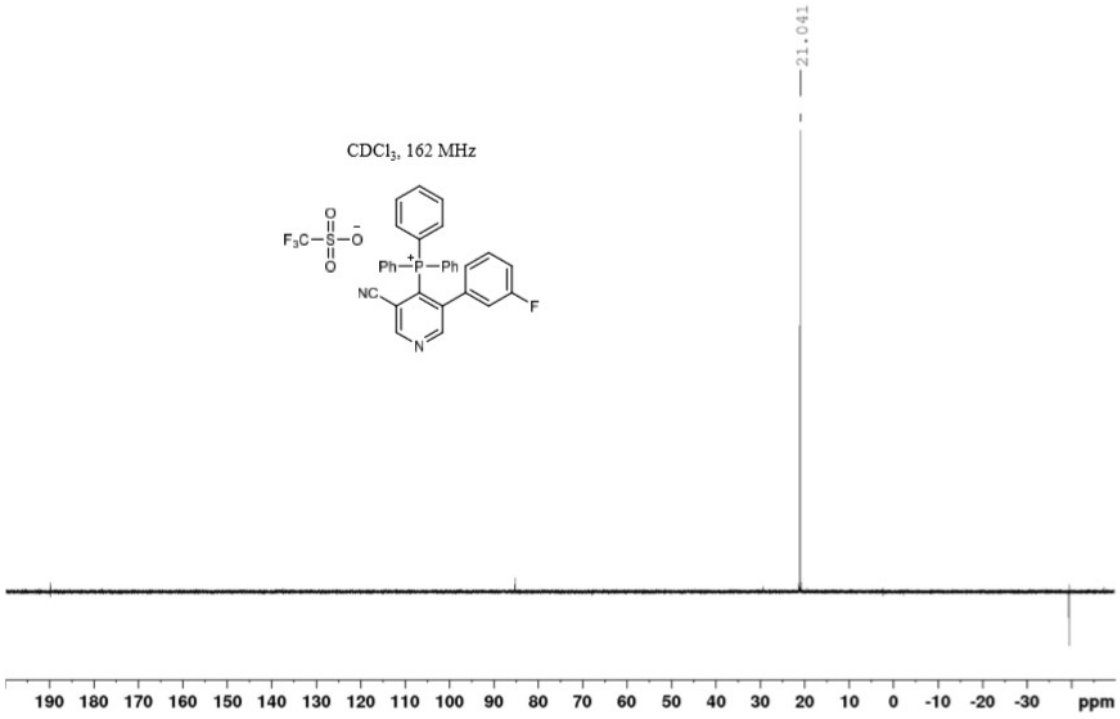
Prepared according to general procedure using sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol), benzyl thiol (65 mL, 0.55 mmol), (4-((*R*)-(benzyloxy)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (397 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (basic alumina: 30% EtOAc in hexanes) afforded the *title compound (2v)* as a yellow amorphous solid (157 mg, 0.31 mmol, 62% yield). IR ν_{max}/ cm^{-1} (film): 3063, 3029, 2928, 2863, 1591, 1549, 1452, 1290, 1094, 907, 758, 729, 697; ^{1}H NMR (400 MHz, $CDCl_3$) d: 8.09-7.95 (2H, m), 7.66 (1H, dd, *J* = 8.2, 7.1 Hz), 7.55-7.42 (3H, m), 7.39-7.18 (9H, m), 5.80-5.66 (1H, m), 5.19 (1H, br s), 4.99-4.85 (2H, m), 4.61 (2H, s), 4.45 (1H, d, *J* = 11.4 Hz), 4.37 (1H, d, *J* = 11.4 Hz), 3.44-3.28 (1H, m), 3.17-3.00 (2H, m), 2.72-2.54 (2H, m), 2.30-2.18 (1H, m), 1.86-1.39 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.90, 148.85, 145.88, 142.07, 138.48, 137.89, 129.48, 129.32,

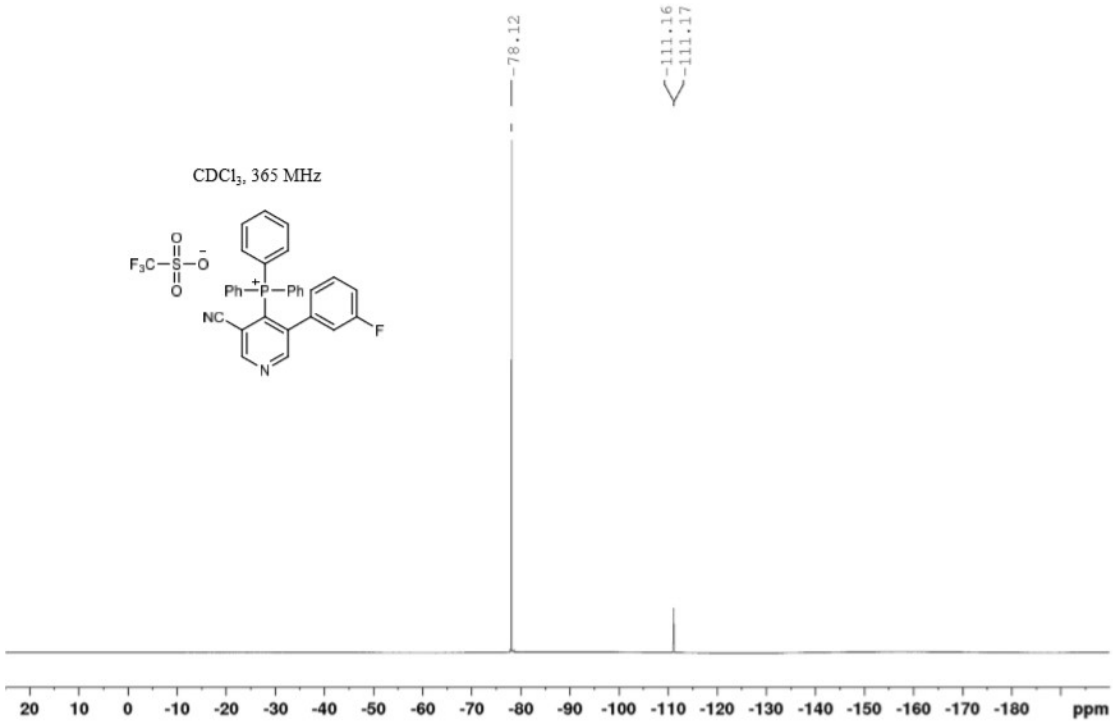
129.13, 128.59, 128.55, 127.88, 127.17, 125.47, 124.57, 123.39 (br), 118.05 (br), 114.31, 81.17 (br), 71.51, 60.67, 57.22, 43.28, 40.18, 34.03, 28.06, 27.85, 22.40 (br); *m/z* HRMS (DART) found $[M+H]^+$ 507.2484, $C_{33}H_{35}N_2OS^+$ requires 507.2465.

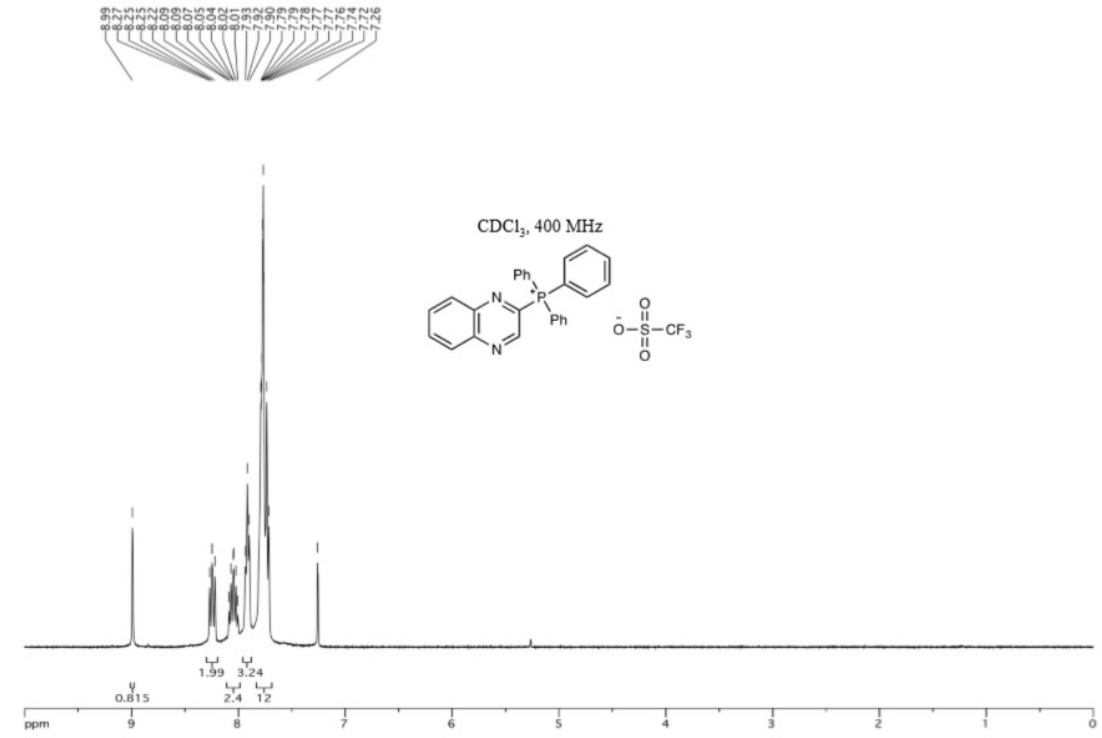
NMR Spectra:

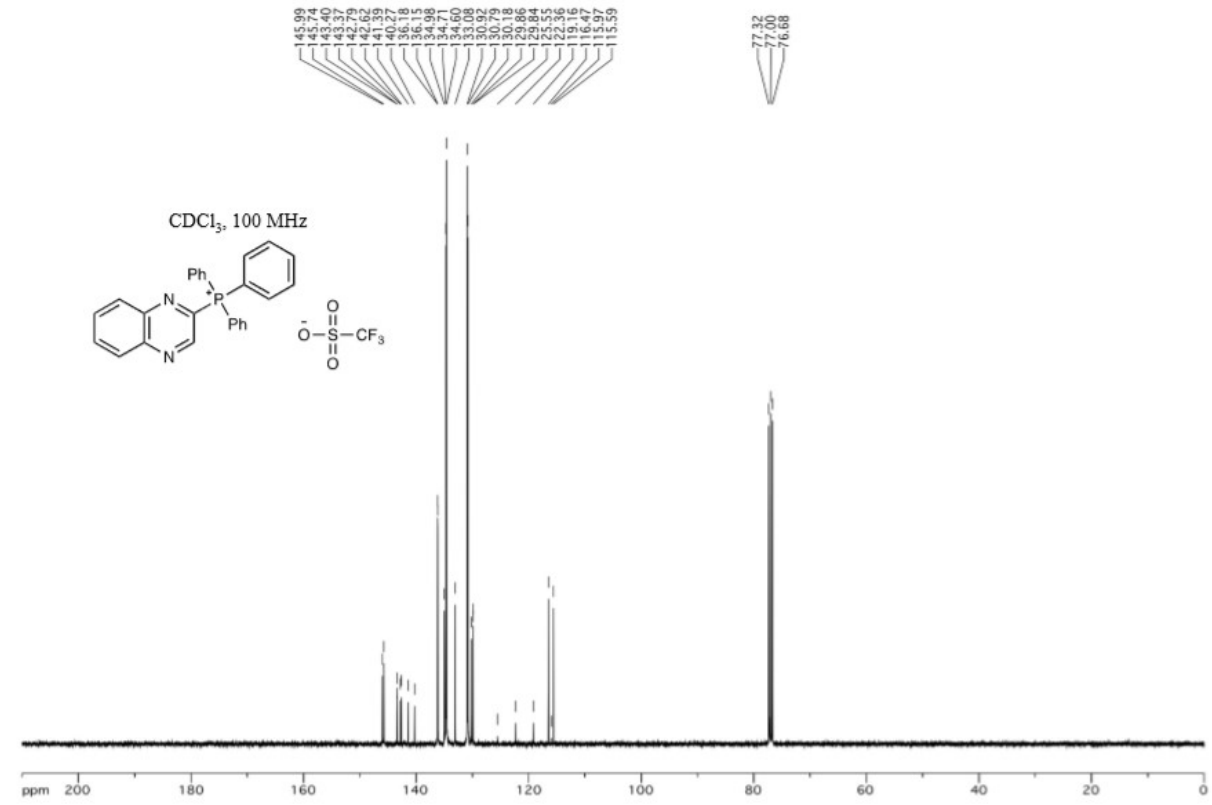



163.69
161.23
152.69
139.93
137.54
137.46
135.50
130.23
130.14
128.82
128.59
127.80
116.66
116.44
115.95
115.74
114.95
77.34
77.02
76.71
39.36
CDCl3, 100 MHz
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


21.041
CDCl3, 162 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 ppm


-78.12
-111.16
-111.17
CDCl3, 365 MHz
F3C—S(=O)(=O)—O⁻
Ph—P⁺—Ph
NC
F
N
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm


8.99
8.27
8.25
8.22
8.09
8.07
8.05
8.04
8.02
7.93
7.92
7.90
7.79
7.78
7.77
7.76
7.74
7.72
7.26
CDCl3, 400 MHz
Ph
P
Ph
N
N
O—S(=O)(=O)—CF3
0.815
1.99
3.24
2.4
12
ppm 9 8 7 6 5 4 3 2 1 0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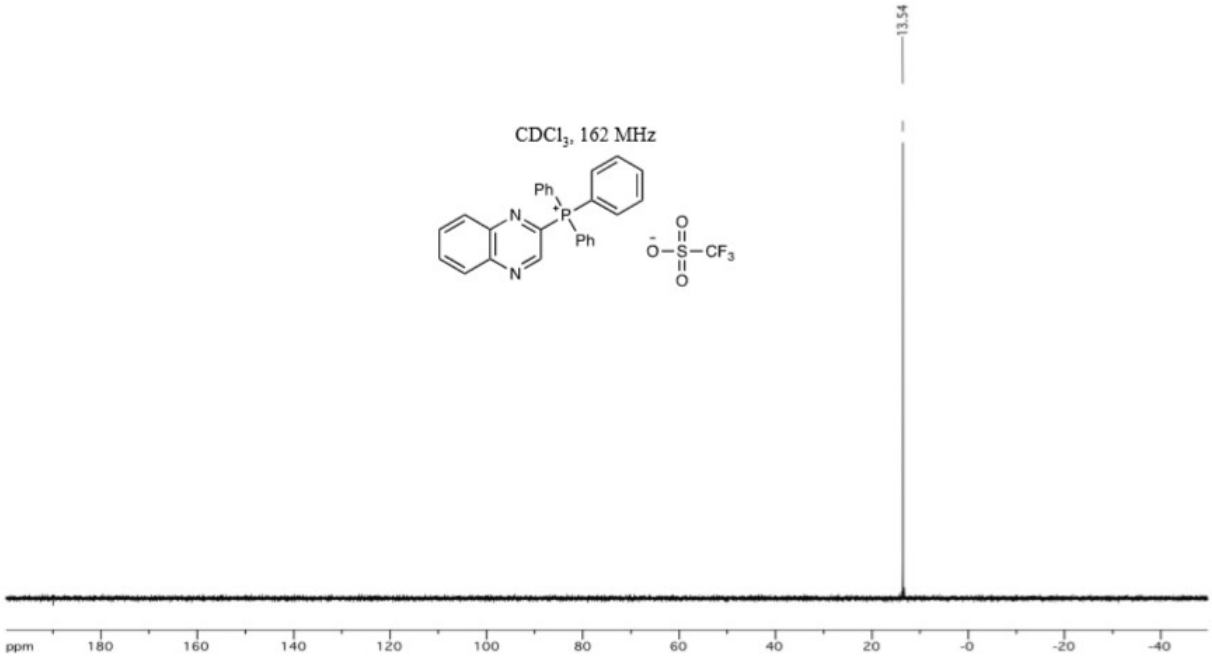
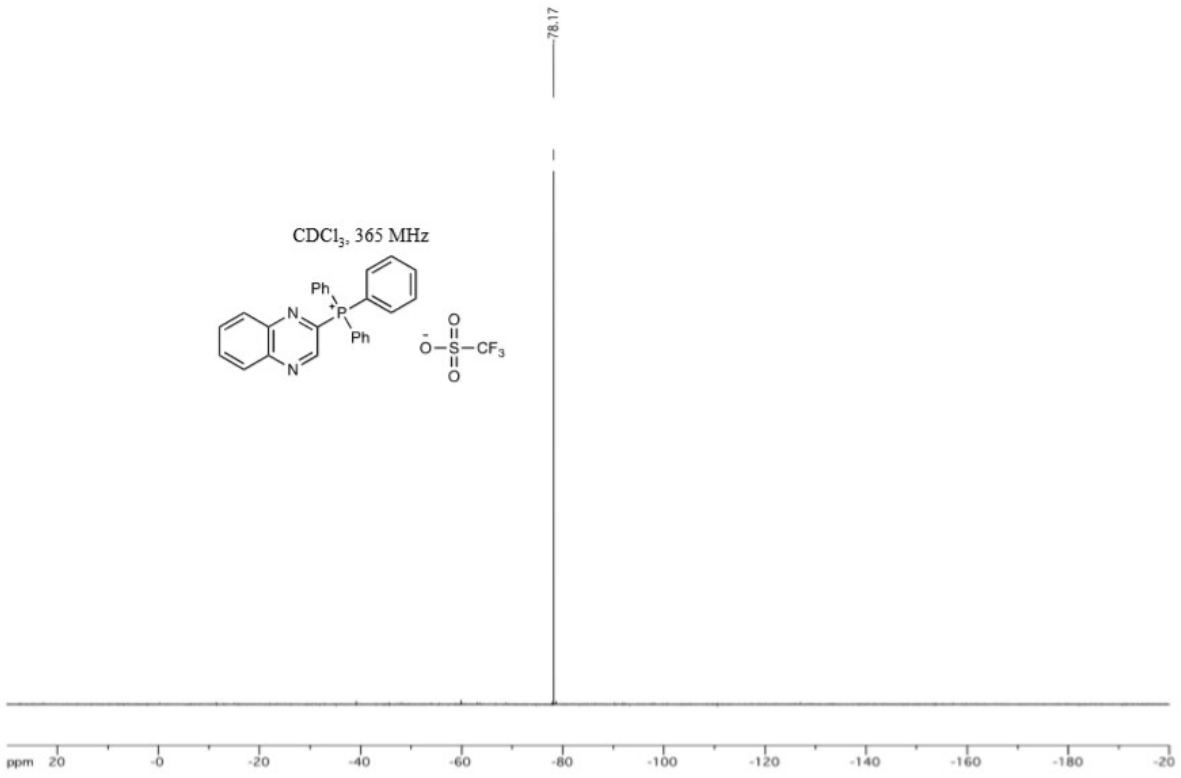
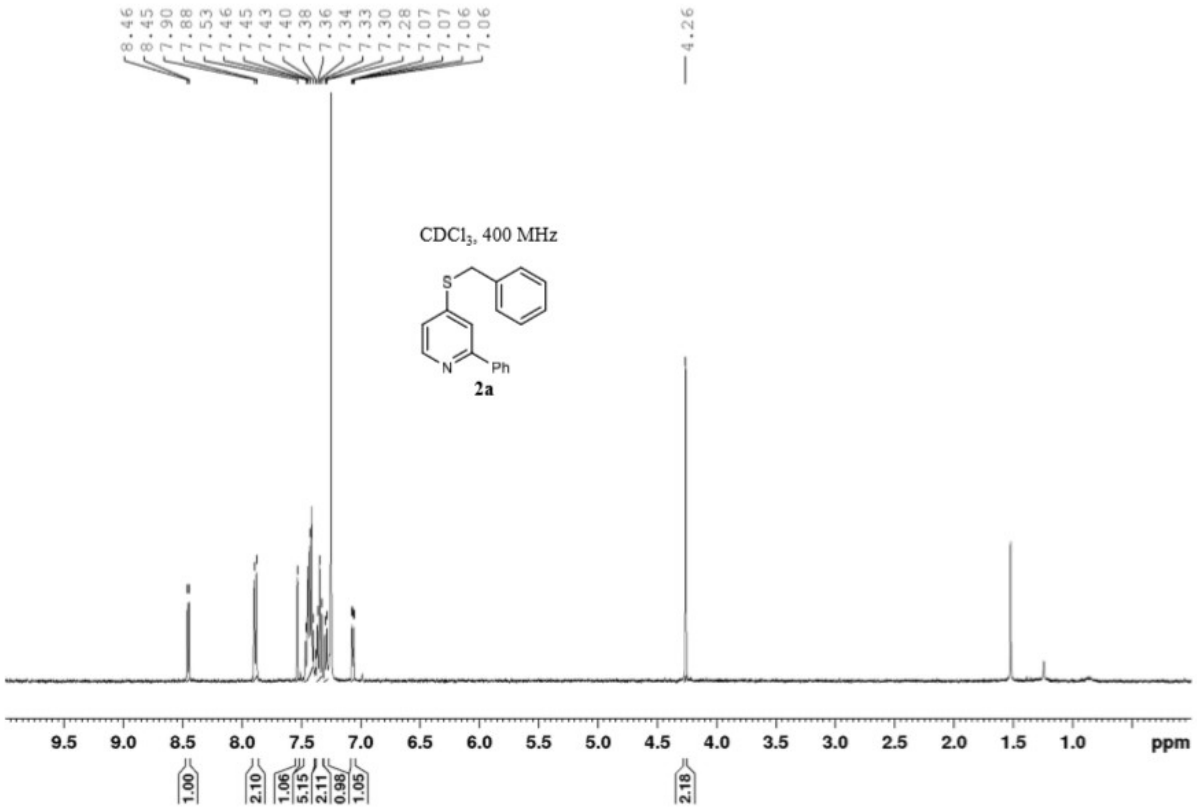
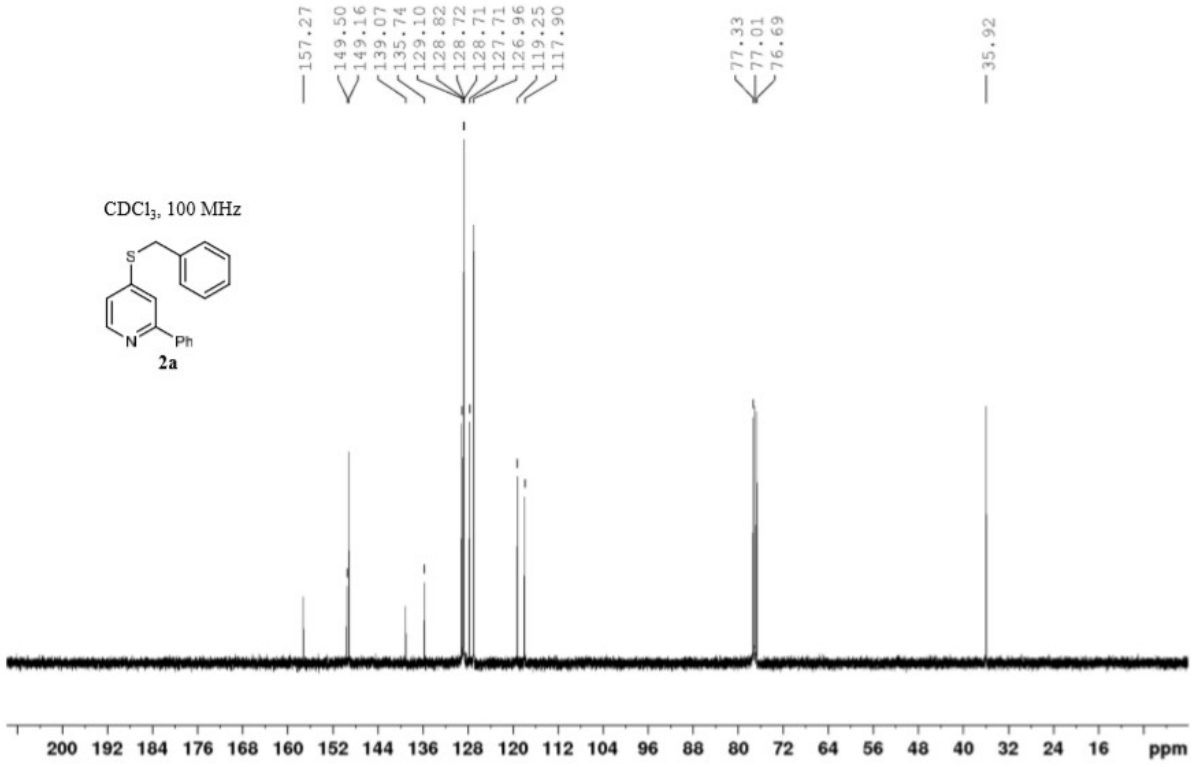
145.74
143.40
143.37
142.79
142.62
141.39
140.27
136.18
136.15
134.98
134.71
134.60
133.08
130.92
130.79
130.18
129.86
129.84
125.55
122.36
119.16
116.47
115.97
115.59
77.32
77.00
76.68
CDCl3, 100 MHz
Ph
P
Ph
N
N
O
O
S
CF3
ppm 200 180 160 140 120 100 80 60 40 20 0


13.54
CDCl3, 162 MHz
Ph
P
Ph
N
N
O
O
S
CF3
ppm 180 160 140 120 100 80 60 40 20 -0 -20 -40


78.17
CDCl3, 365 MHz
Ph
Ph
Ph
N
N
O
O
S
CF3
ppm 20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-20


8.46
8.45
7.90
7.88
7.53
7.46
7.45
7.43
7.40
7.38
7.36
7.34
7.33
7.30
7.28
7.07
7.07
7.06
7.06
4.26
CDCl3, 400 MHz
S
N
Ph
2a
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
2.10
1.06
5.15
2.11
0.98
1.05
2.18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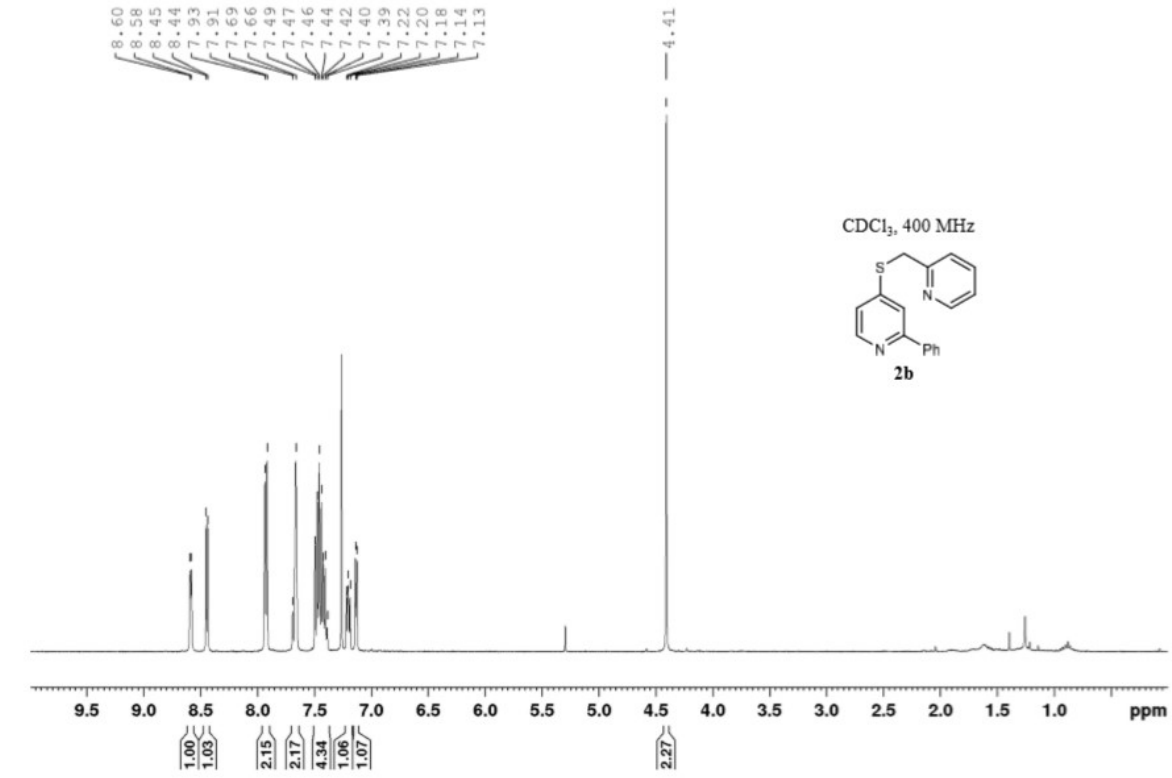
149.50
149.16
139.07
135.74
129.10
128.82
128.72
128.71
127.71
126.96
119.25
117.90
77.33
77.01
76.69
35.92
CDCl3, 100 MHz
S
N
Ph
2a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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8.45
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7.93
7.91
7.69
7.66
7.49
7.47
7.46
7.44
7.42
7.40
7.39
7.22
7.20
7.18
7.14
7.13
4.41
CDCl3, 400 MHz
S
N
N
Ph
2b
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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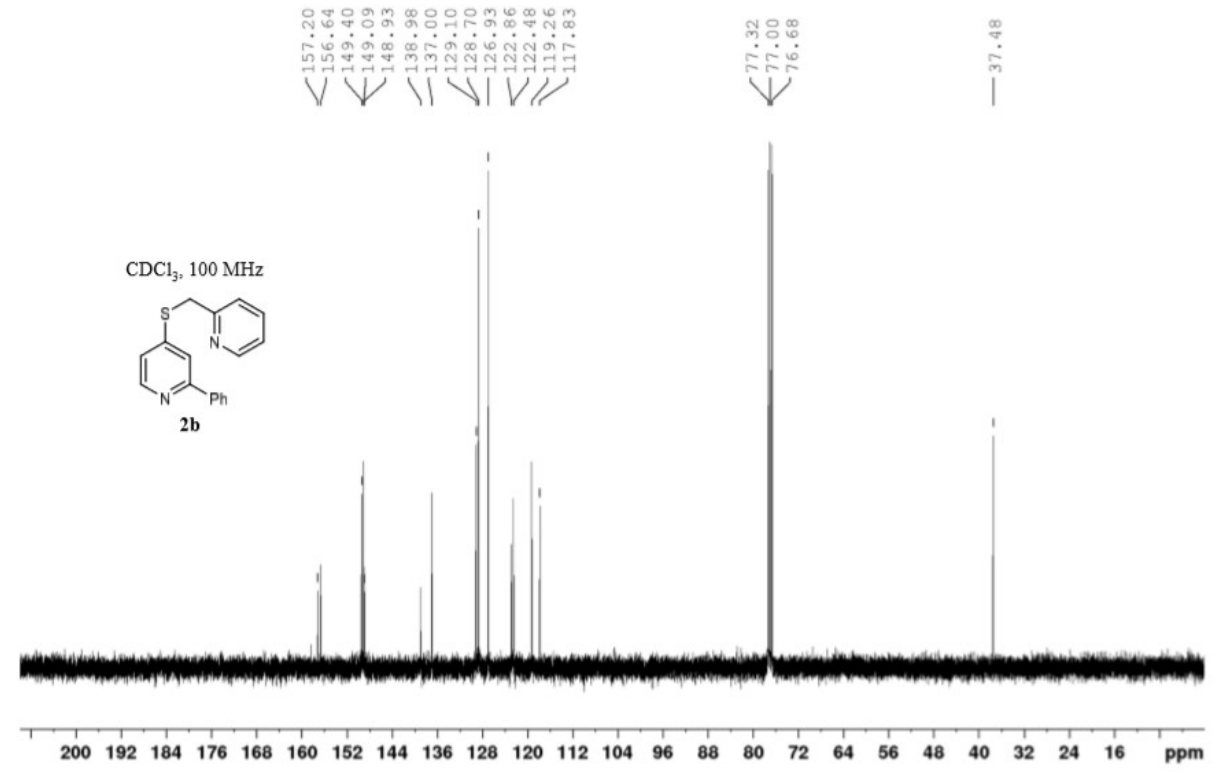
1.03
2.15
2.17
4.34
1.06
1.07
2.27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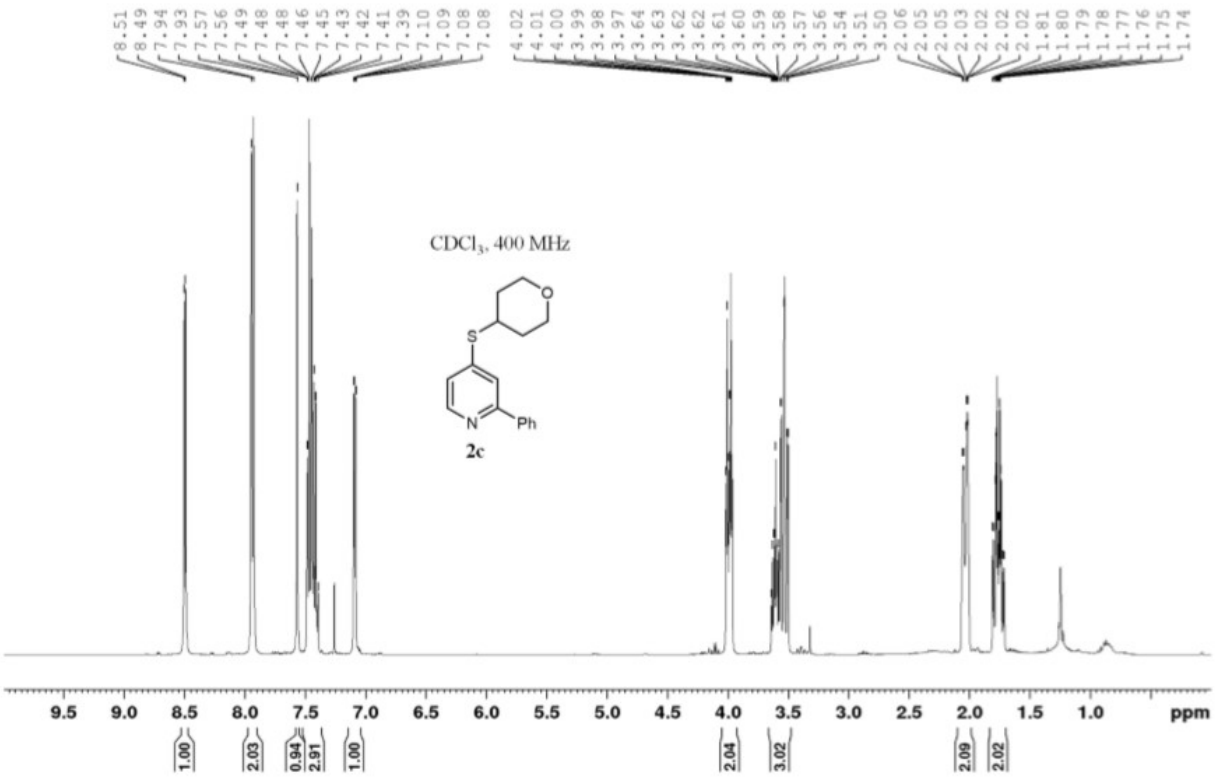
149.09
148.93
138.98
137.00
129.10
128.70
126.93
122.86
122.48
119.26
117.83
77.32
77.00
76.68
37.48
CDCl3, 100 MHz
S
N
N
Ph
2b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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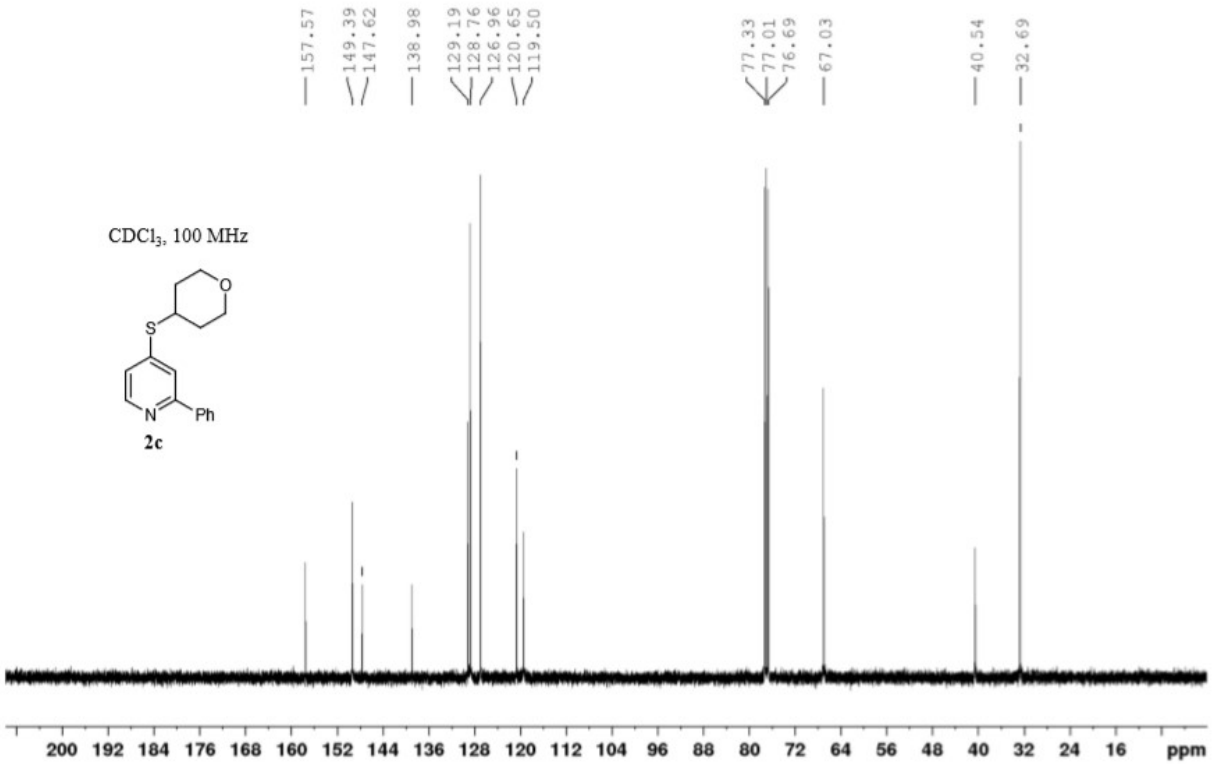
8.49
7.94
7.93
7.57
7.56
7.49
7.48
7.48
7.46
7.45
7.43
7.42
7.41
7.39
7.10
7.09
7.08
7.08
4.02
4.01
4.00
3.99
3.98
3.97
3.64
3.63
3.62
3.62
3.61
3.60
3.59
3.58
3.57
3.56
3.54
3.51
3.50
2.06
2.05
2.05
2.03
2.02
2.02
2.02
1.81
1.80
1.79
1.78
1.77
1.76
1.75
1.74
CDCl3, 400 MHz
S
N
Ph
2c
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.03
0.94
2.91
1.00
2.04
3.02
2.09
2.02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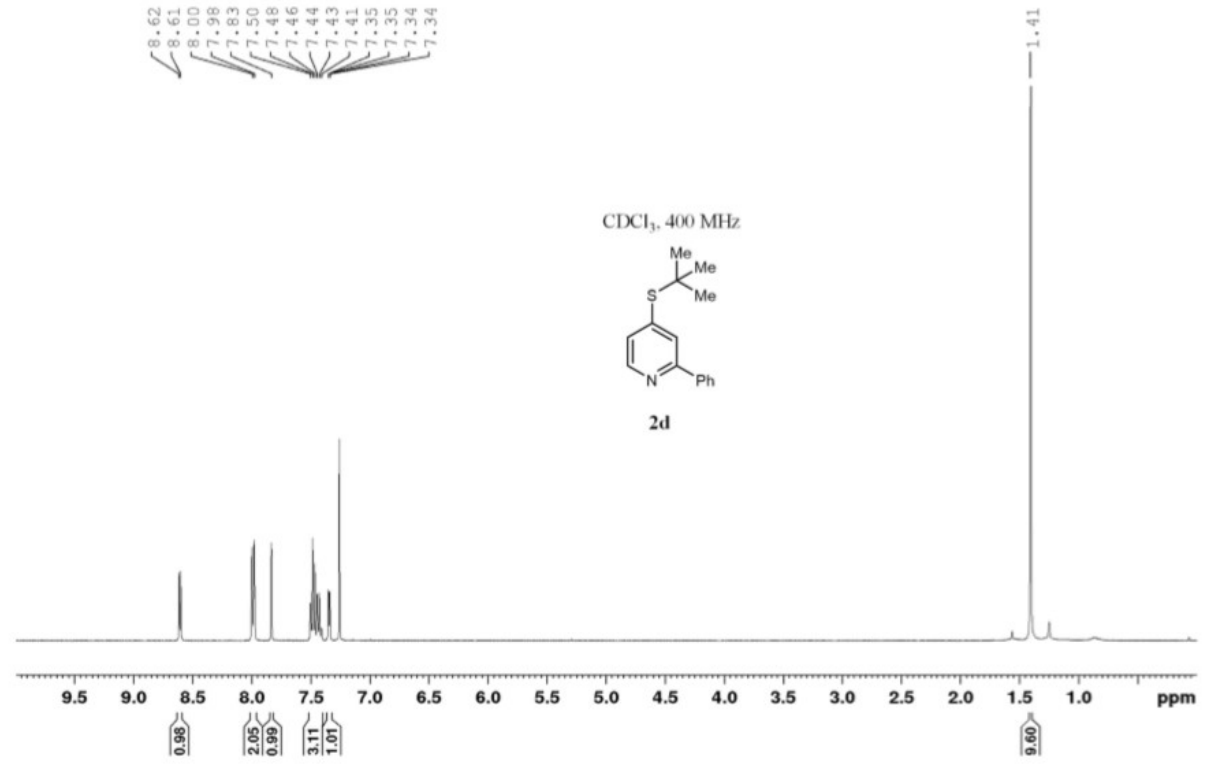
138.98
129.19
128.76
126.96
120.65
119.50
77.33
77.01
76.69
67.03
40.54
32.69
CDCl3, 100 MHz
O
S
N
Ph
2c
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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8.61
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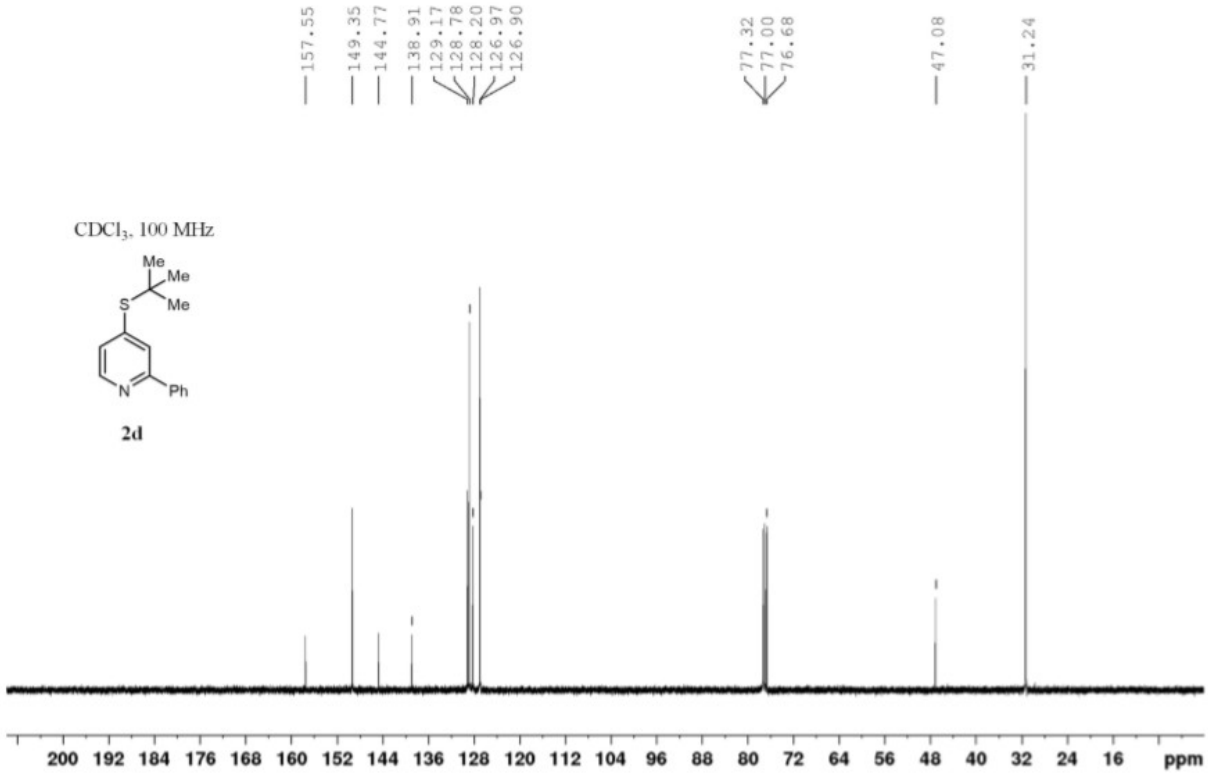
7.83
7.50
7.48
7.46
7.44
7.43
7.41
7.35
7.35
7.34
7.34
1.41
CDCl3, 400 MHz
Me
Me
Me
S
N
Ph
2d
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.98
2.05
0.99
3.11
1.01
9.60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129.17
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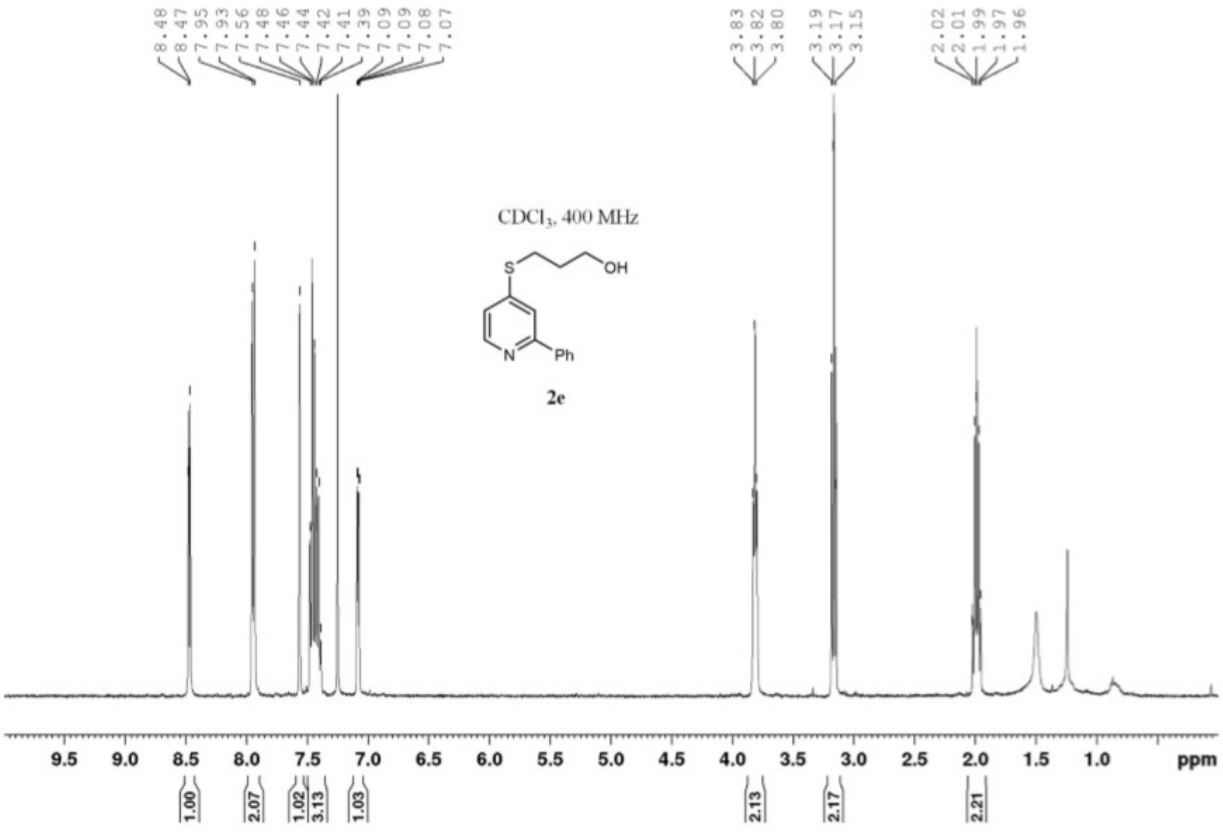
128.20
126.97
126.90
77.32
77.00
76.68
47.08
31.24
CDCl3, 100 MHz
Me
Me
Me
S
N
Ph
2d
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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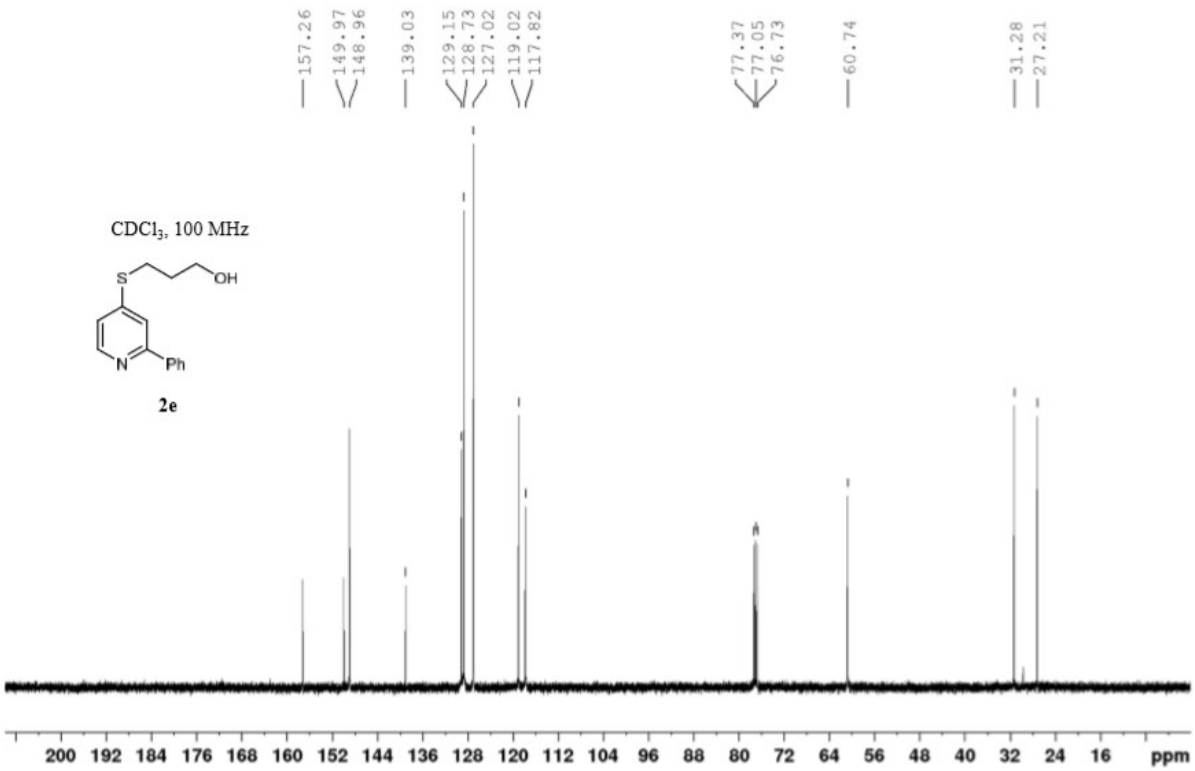
7.48
7.46
7.44
7.42
7.41
7.39
7.09
7.09
7.08
7.07
3.83
3.82
3.80
3.19
3.17
3.15
2.02
2.01
1.99
1.97
1.96
CDCl3, 400 MHz
S
OH
N
Ph
2e
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.07
1.02
3.13
1.03
2.13
2.17
2.21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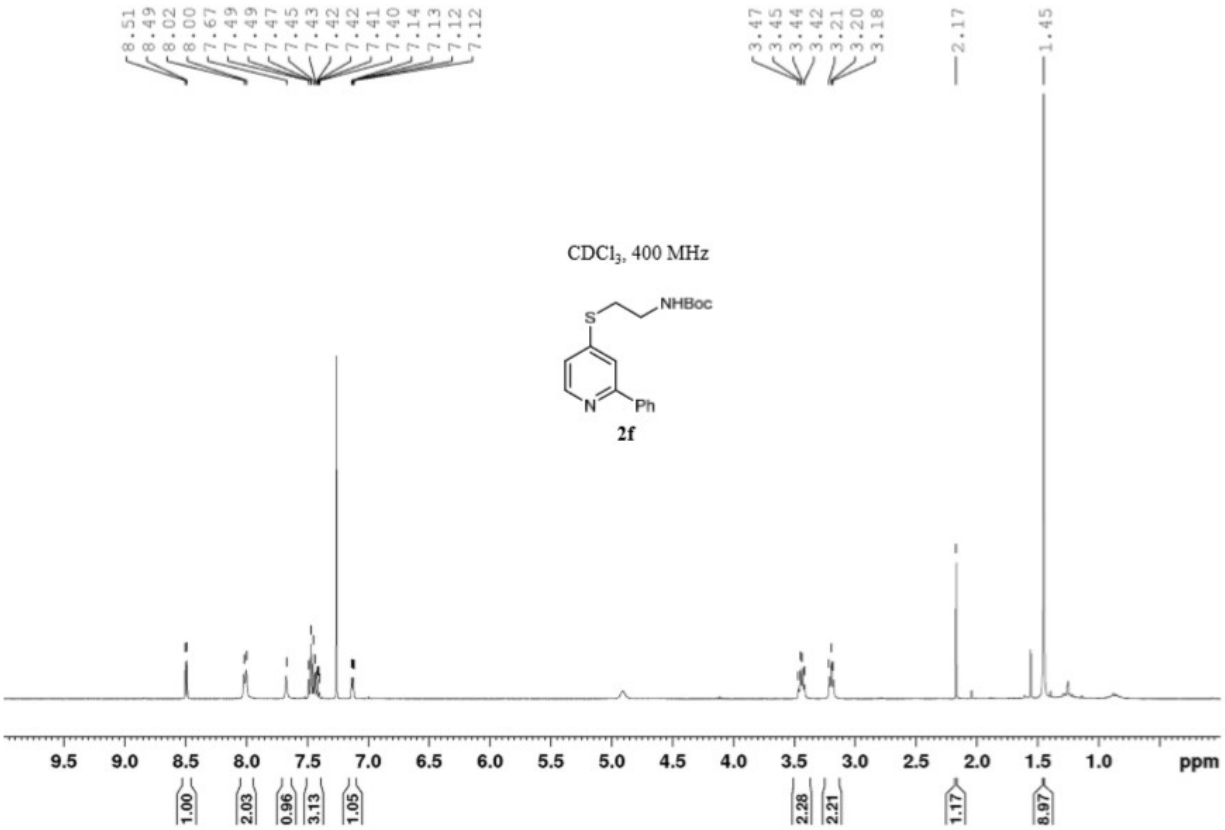
148.96
139.03
129.15
128.73
127.02
119.02
117.82
77.37
77.05
76.73
60.74
31.28
27.21
CDCl3, 100 MHz
S
OH
N
Ph
2e
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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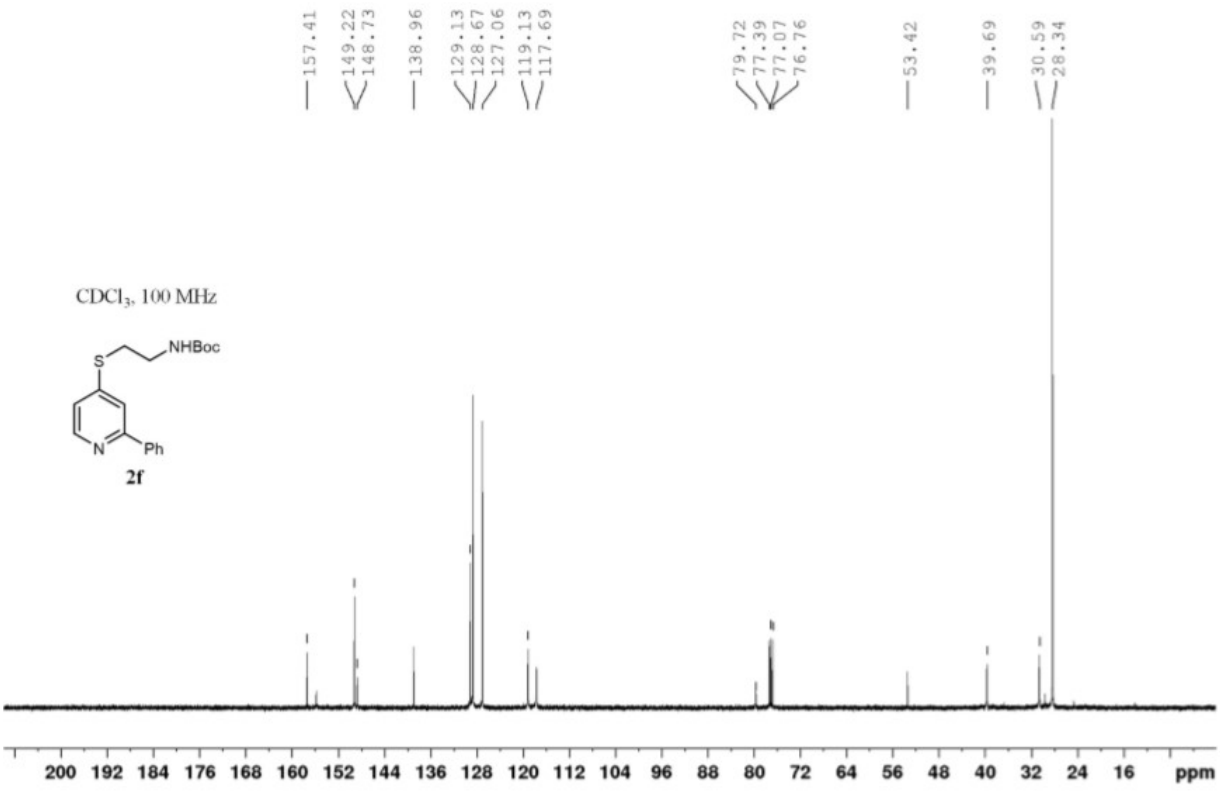
8.00
7.67
7.49
7.49
7.47
7.45
7.43
7.42
7.42
7.41
7.40
7.14
7.13
7.12
7.12
3.47
3.45
3.44
3.42
3.21
3.20
3.18
2.17
1.45
CDCl3, 400 MHz
S
NHBoc
N
Ph
2f
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.03
0.96
3.13
1.05
2.28
2.21
1.17
8.97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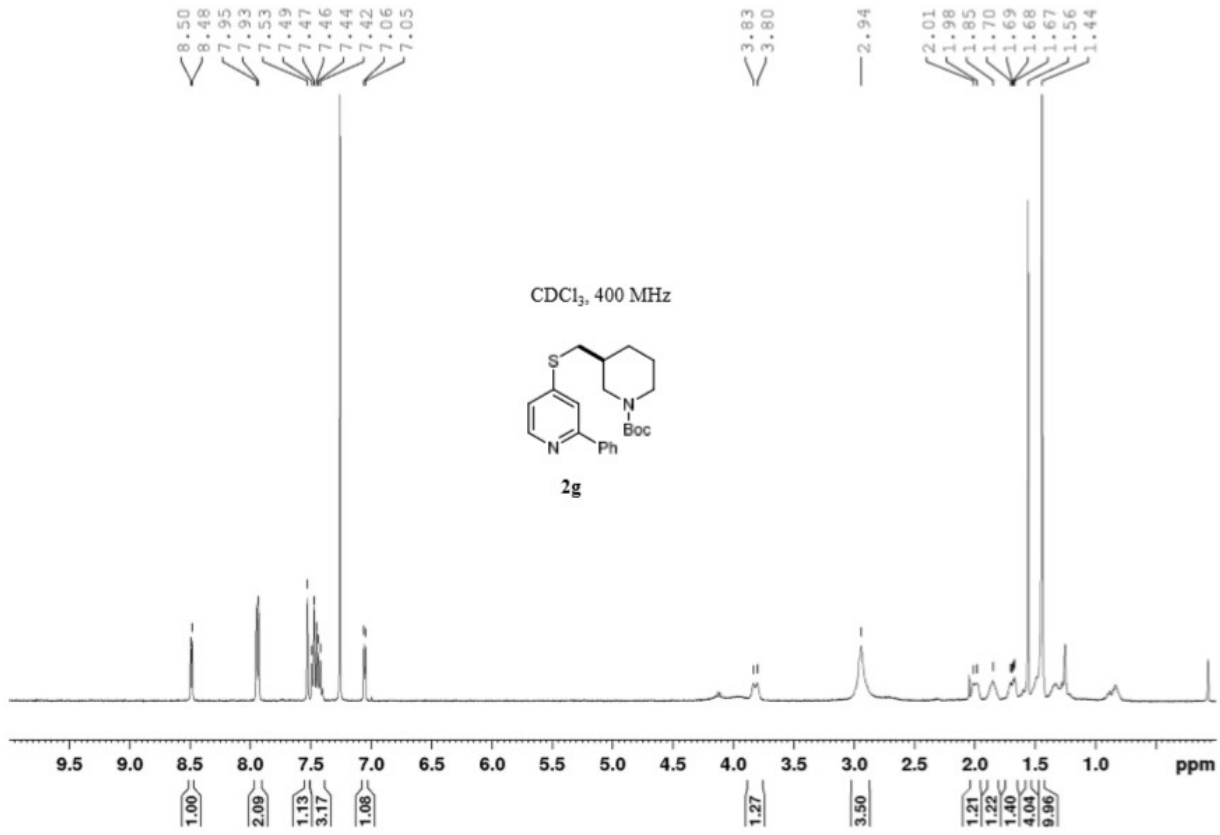
148.73
138.96
129.13
128.67
127.06
119.13
117.69
79.72
77.39
77.07
76.76
53.42
39.69
30.59
28.34
CDCl3, 100 MHz
NHBoc
S
N
Ph
2f
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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7.47
7.46
7.44
7.42
7.06
7.05
3.83
3.80
2.94
2.01
1.98
1.85
1.70
1.69
1.68
1.67
1.56
1.44
CDCl3, 400 MHz
S
N
Boc
N
Ph
2g
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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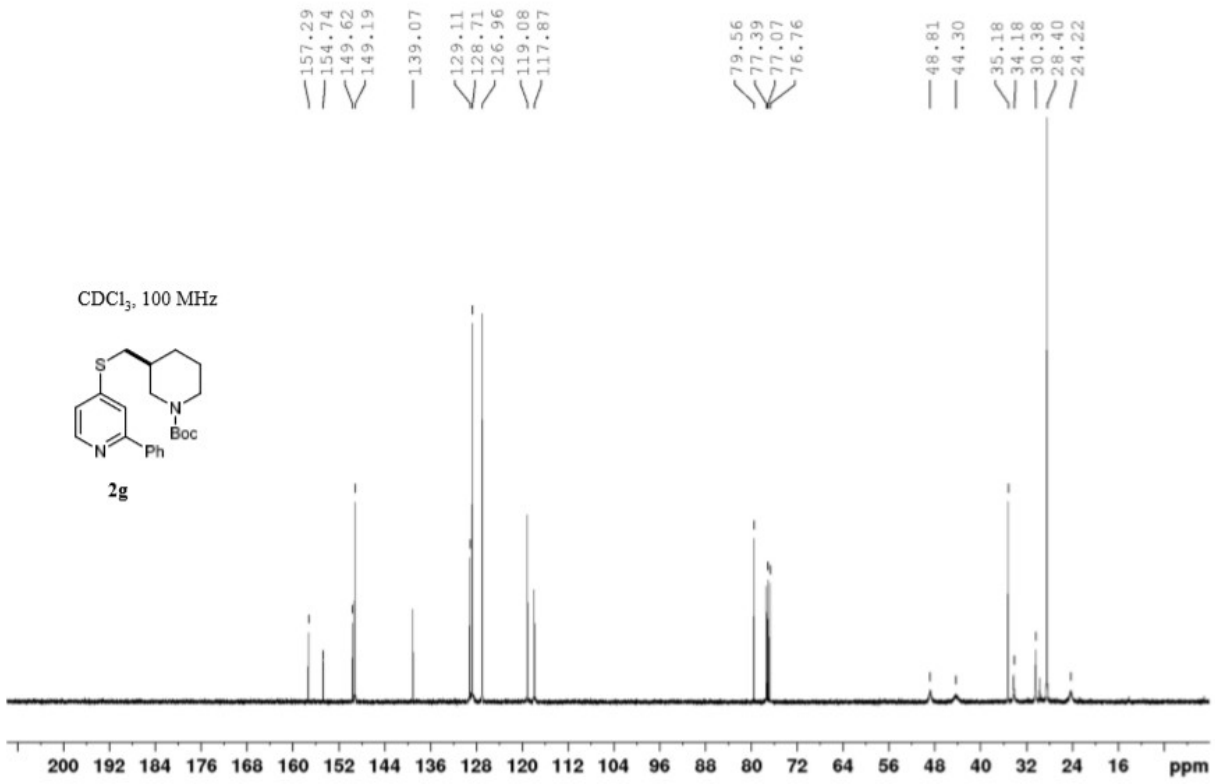
2.09
1.13
3.17
1.08
1.27
3.50
1.21
1.22
1.40
4.04
9.96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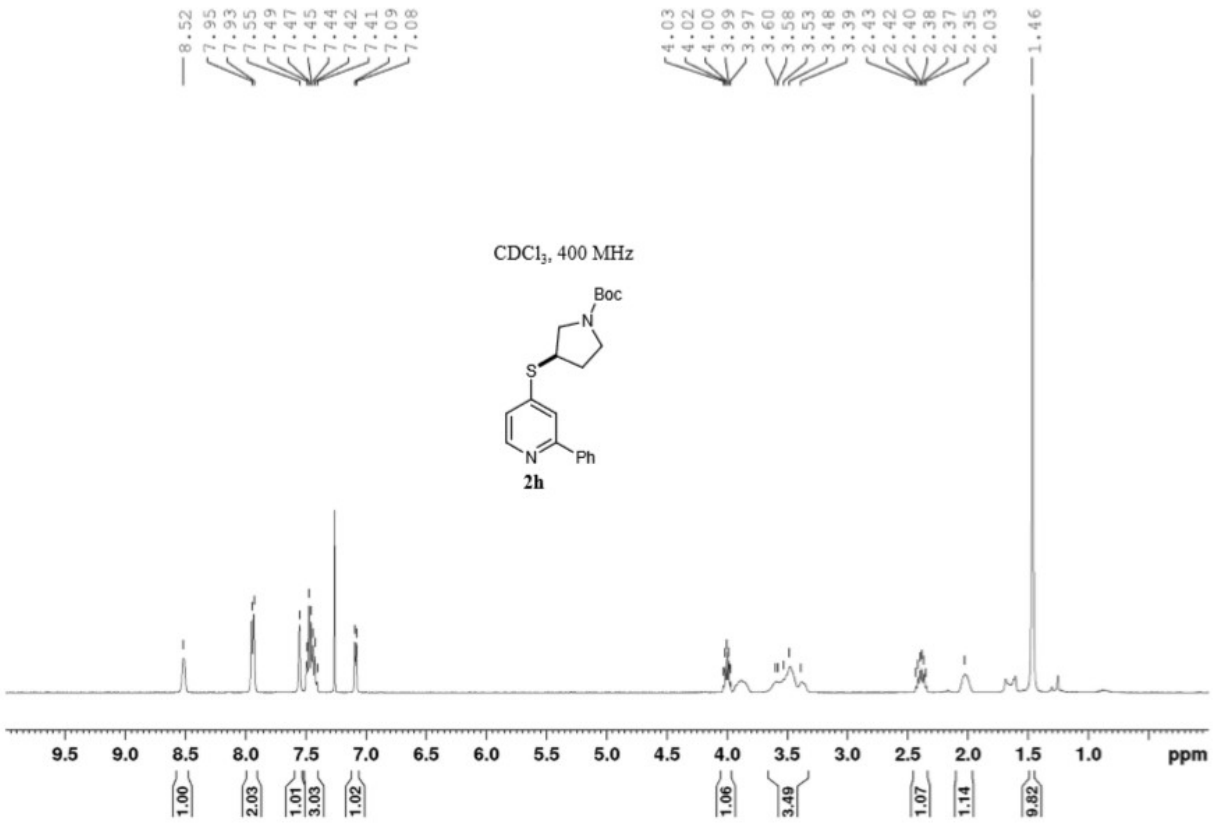
139.07
129.11
128.71
126.96
119.08
117.87
79.56
77.39
77.07
76.76
48.81
44.30
35.18
34.18
30.38
28.40
24.22
CDCl3, 100 MHz
S
N
Boc
N
Ph
2g
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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7.49
7.47
7.45
7.44
7.42
7.41
7.09
7.08
4.03
4.02
4.00
3.99
3.97
3.60
3.58
3.53
3.48
3.39
2.43
2.42
2.40
2.38
2.37
2.35
2.03
1.46
CDCl3, 400 MHz
Boc
N
S
N
Ph
2h
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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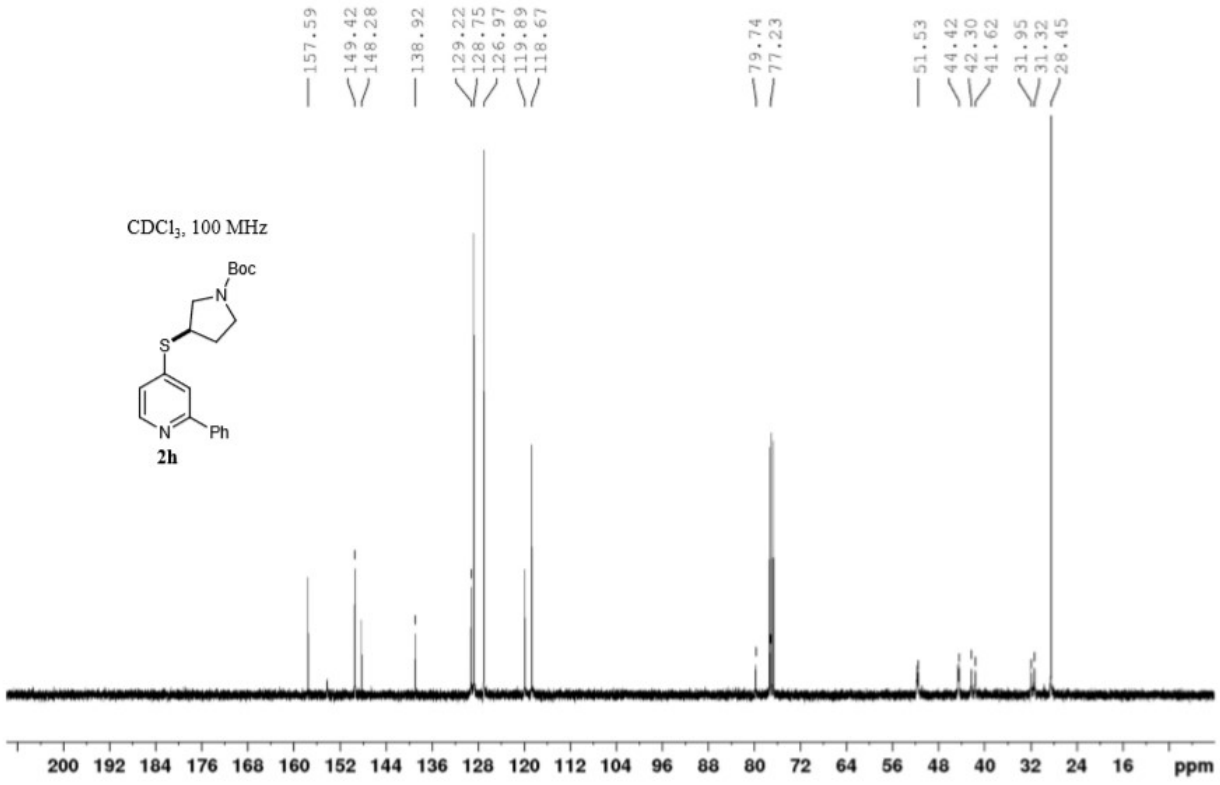
2.03
1.01
3.03
1.02
1.06
3.49
1.07
1.14
9.82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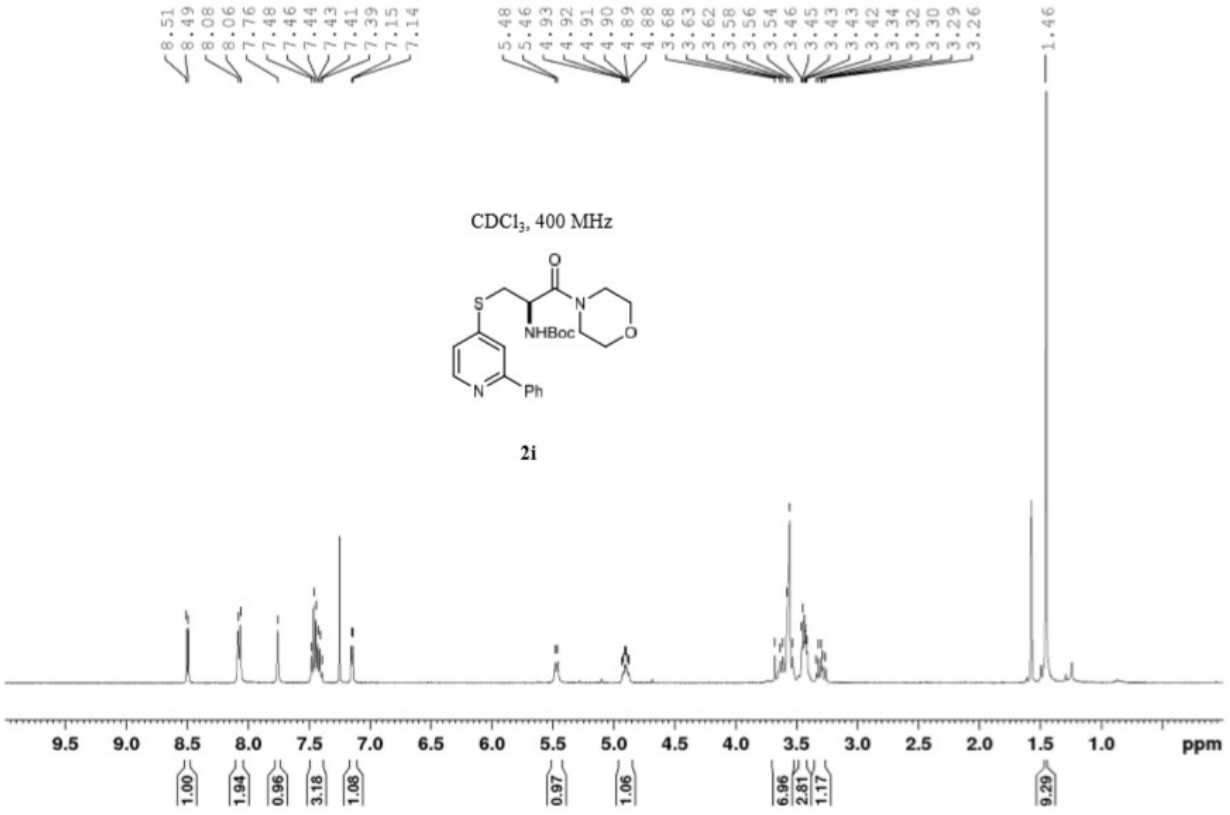
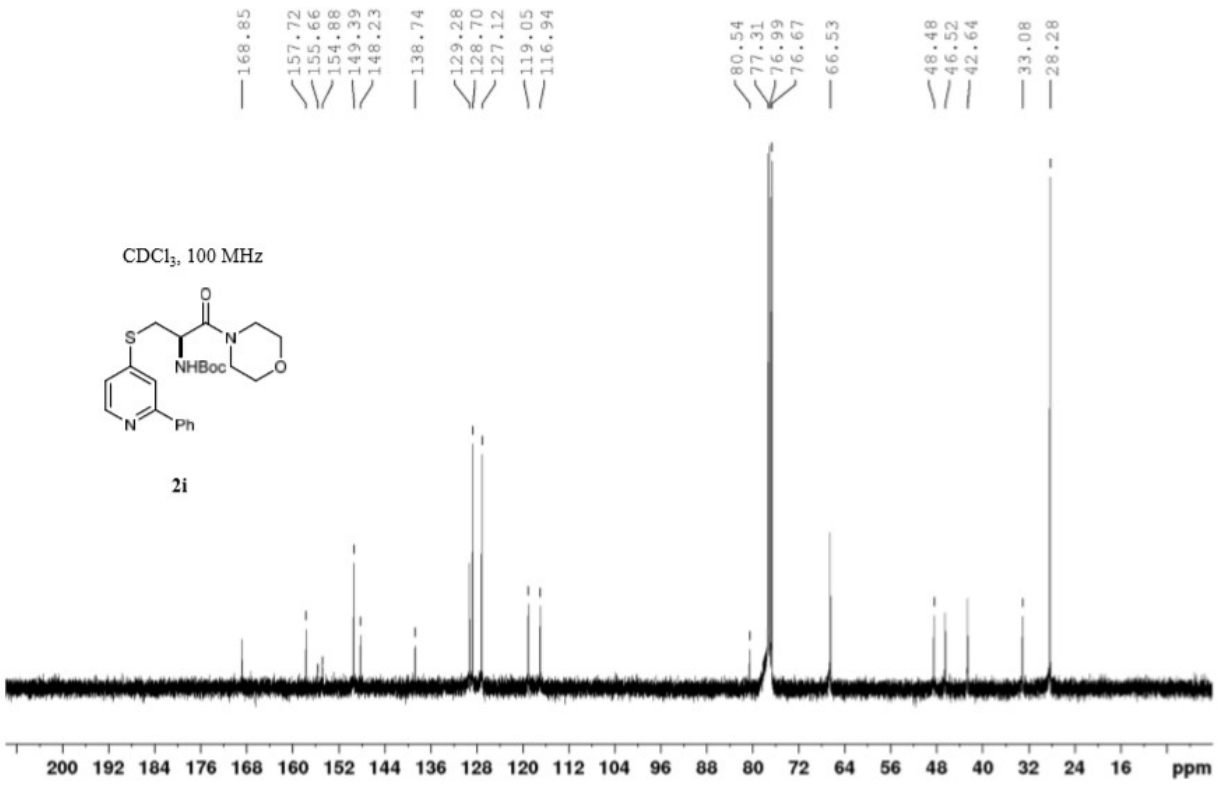
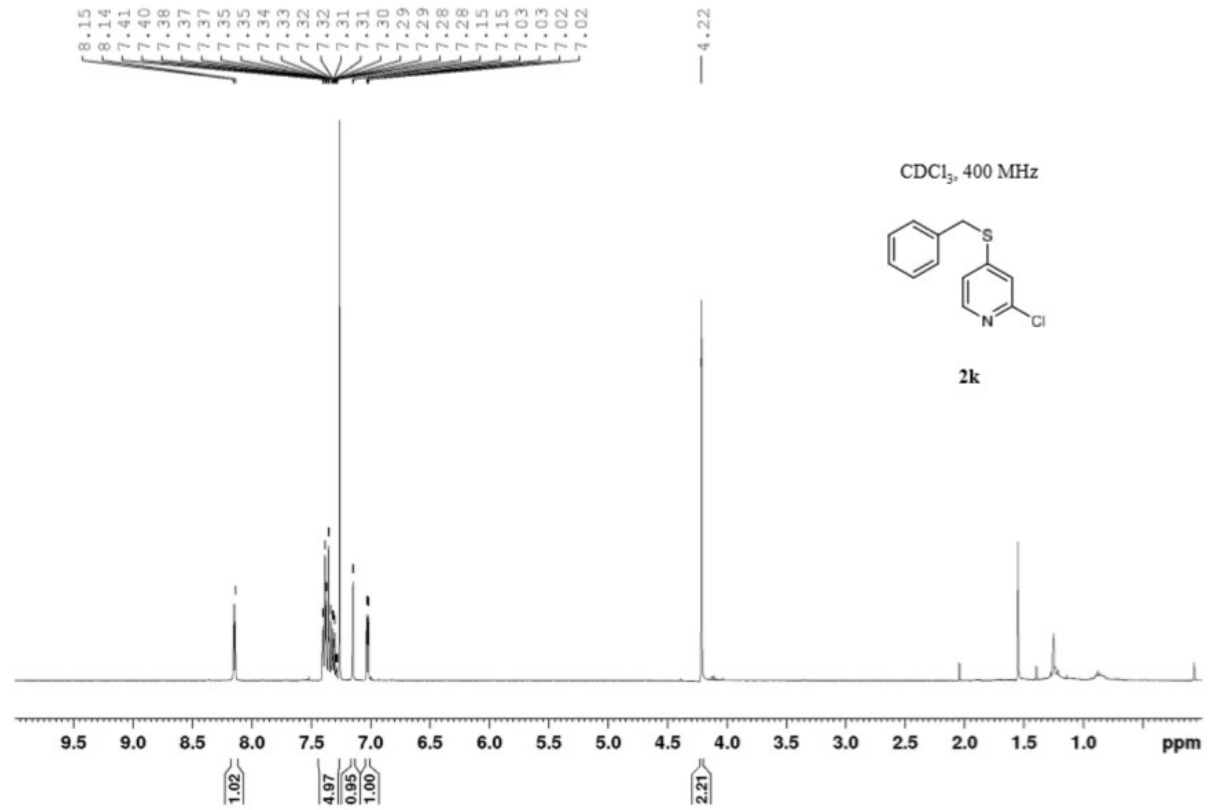
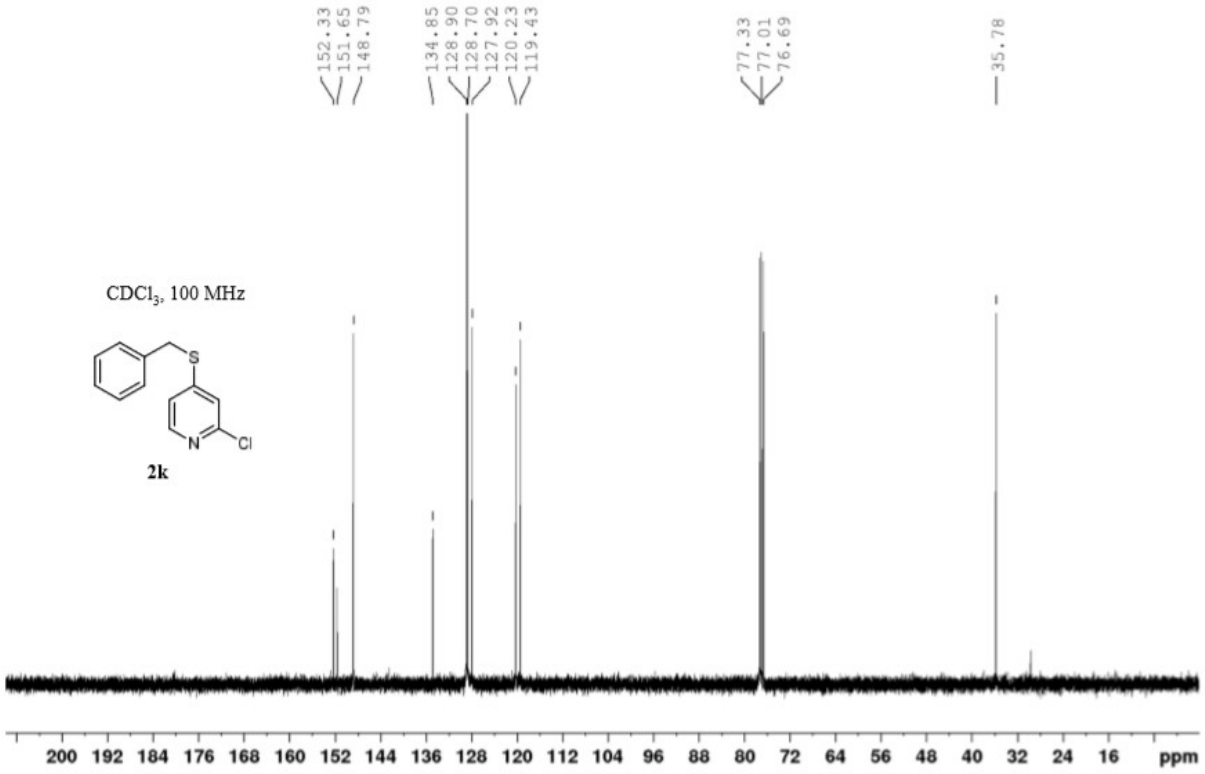
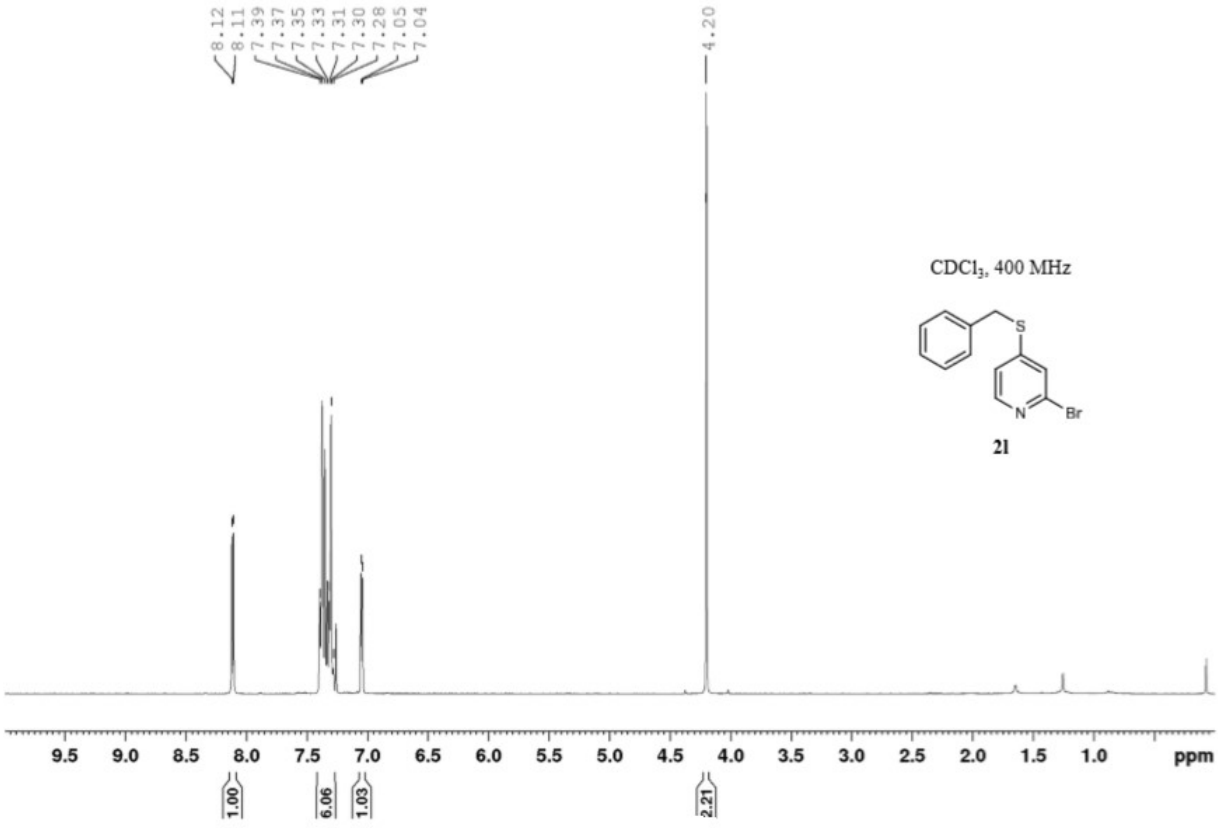
128.75
126.97
119.89
118.67
79.74
77.23
51.53
44.42
42.30
41.62
31.95
31.32
28.45
CDCl3, 100 MHz
Boc
N
S
N
Ph
2h
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

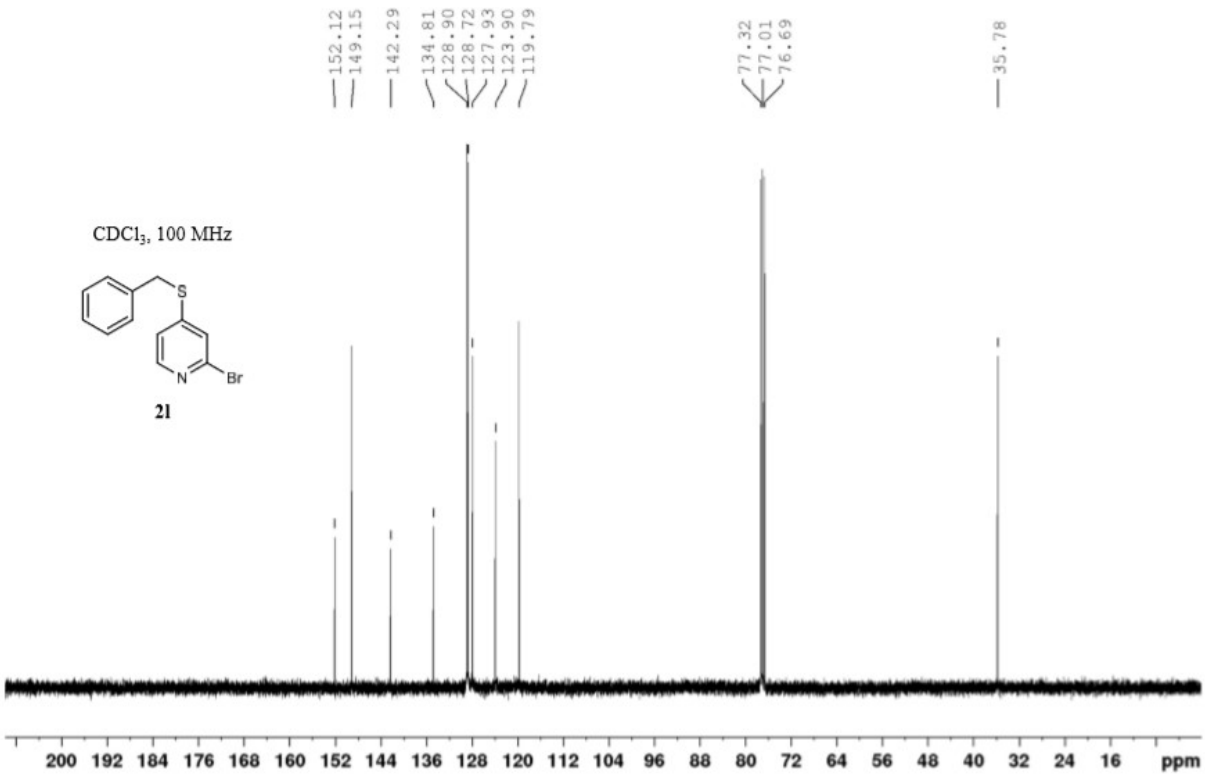

8.51
8.49
8.08
8.06
7.76
7.48
7.46
7.44
7.43
7.41
7.39
7.15
7.14
5.48
5.46
4.93
4.92
4.91
4.90
4.89
4.88
3.68
3.63
3.62
3.58
3.56
3.54
3.46
3.45
3.43
3.43
3.42
3.34
3.32
3.30
3.29
3.26
1.46
CDCl3, 400 MHz
O
S
N
NHBoc
O
N
Ph
2i
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.94
0.96
3.18
1.08
0.97
1.06
6.96
2.81
1.17
9.29


168.85
157.72
155.66
154.88
149.39
148.23
138.74
129.28
128.70
127.12
119.05
116.94
80.54
77.31
76.99
76.67
66.53
48.48
46.52
42.64
33.08
28.28
CDCl3, 100 MHz
O
S
N
NHBoc
O
N
Ph
2i
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

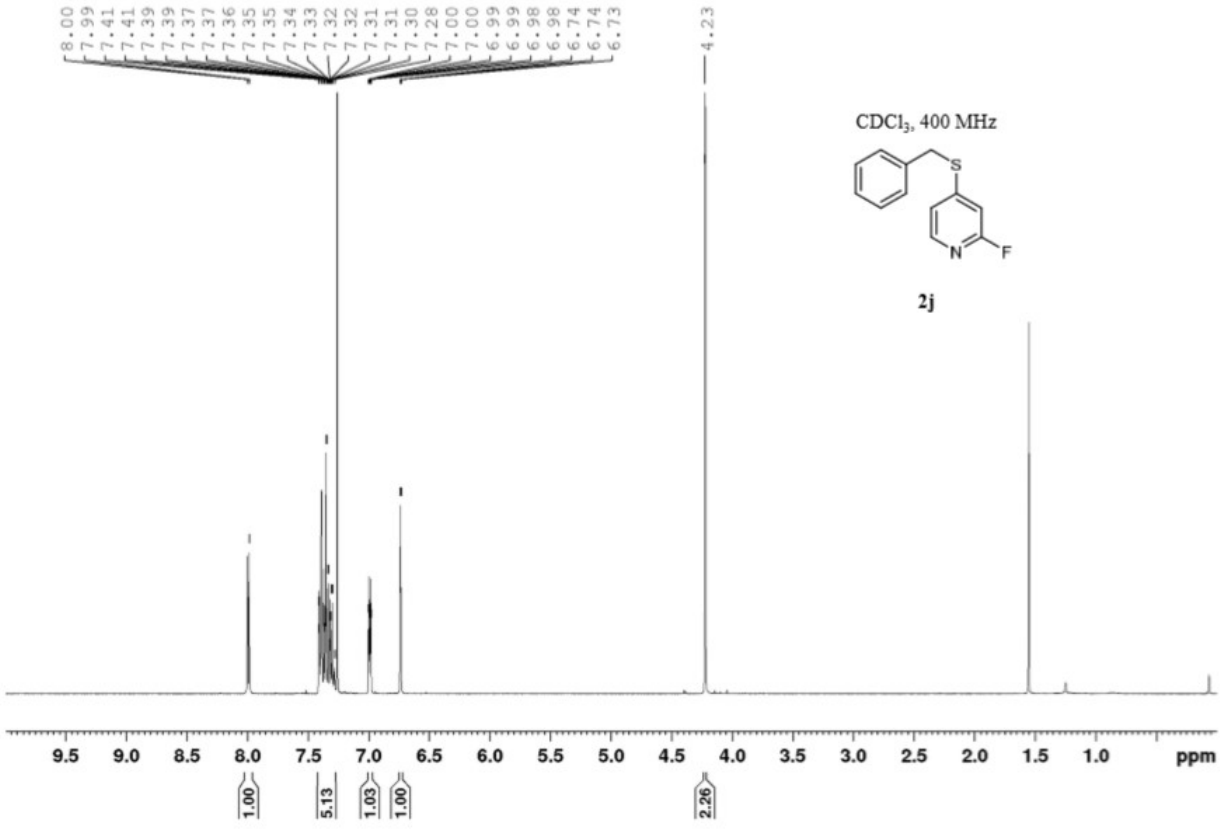

8.15
8.14
7.41
7.40
7.38
7.37
7.37
7.35
7.35
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.28
7.15
7.03
7.03
7.02
7.02
4.22
CDCl3, 400 MHz
S
N
Cl
2k
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.02
4.97
0.95
1.00
2.21


152.33
151.65
148.79
134.85
128.90
128.70
127.92
120.23
119.43
77.33
77.01
76.69
35.78
CDCl3, 100 MHz
S
N
Cl
2k
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

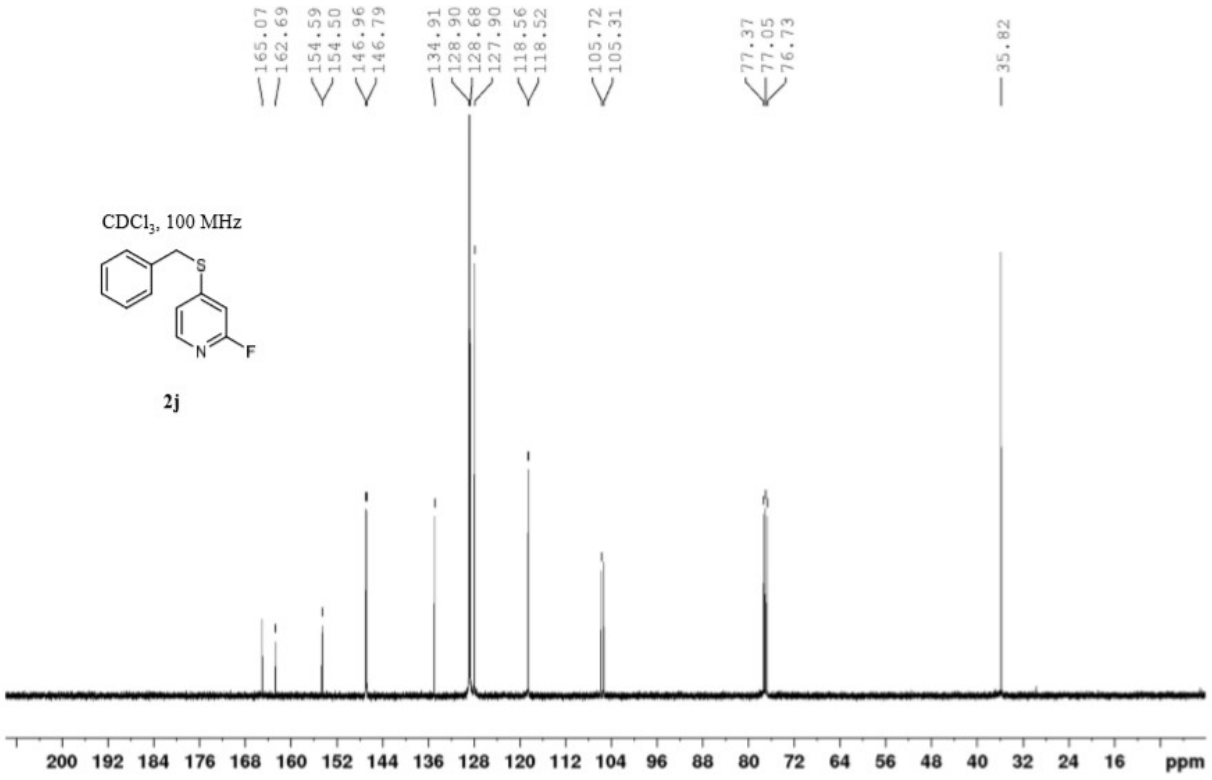

8.12
8.11
7.39
7.37
7.35
7.33
7.31
7.30
7.28
7.05
7.04
4.20
CDCl3, 400 MHz
S
N
Br
21
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
6.06
1.03
2.21

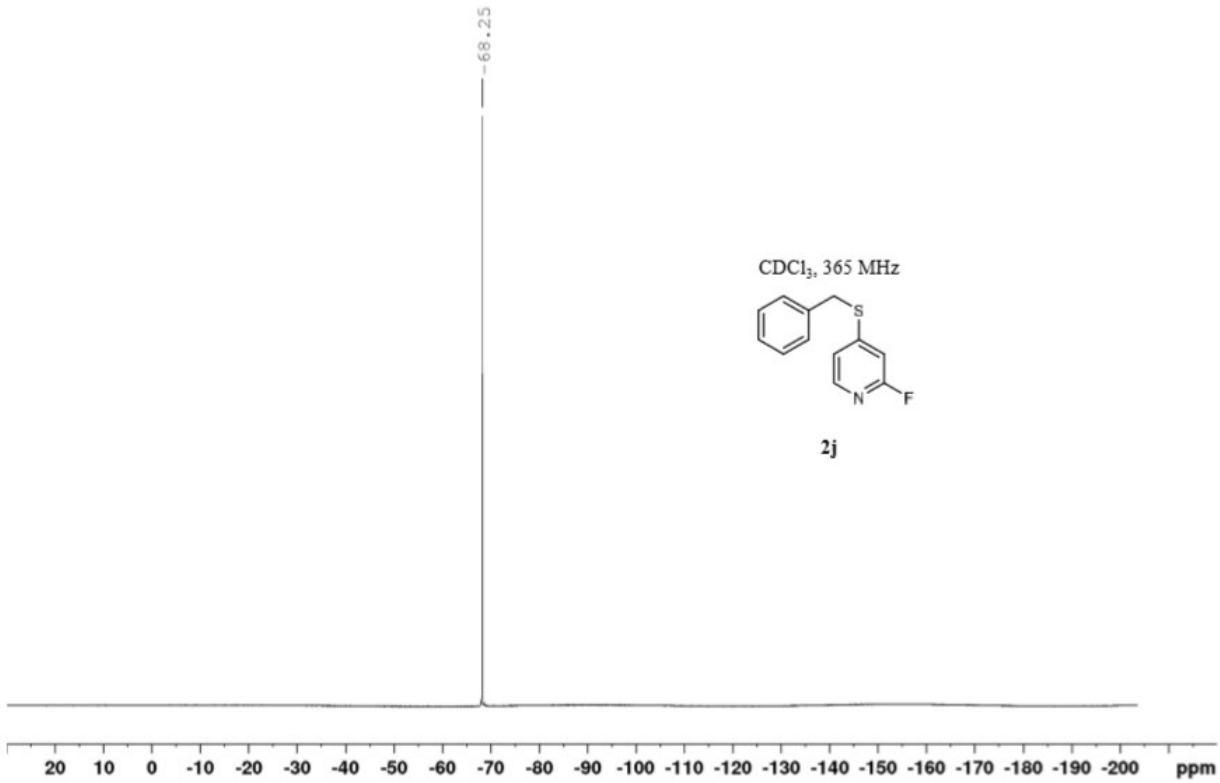

152.12
149.15
142.29
134.81
128.90
128.72
127.93
123.90
119.79
77.32
77.01
76.69
35.78
CDCl3, 100 MHz
S
N
Br
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

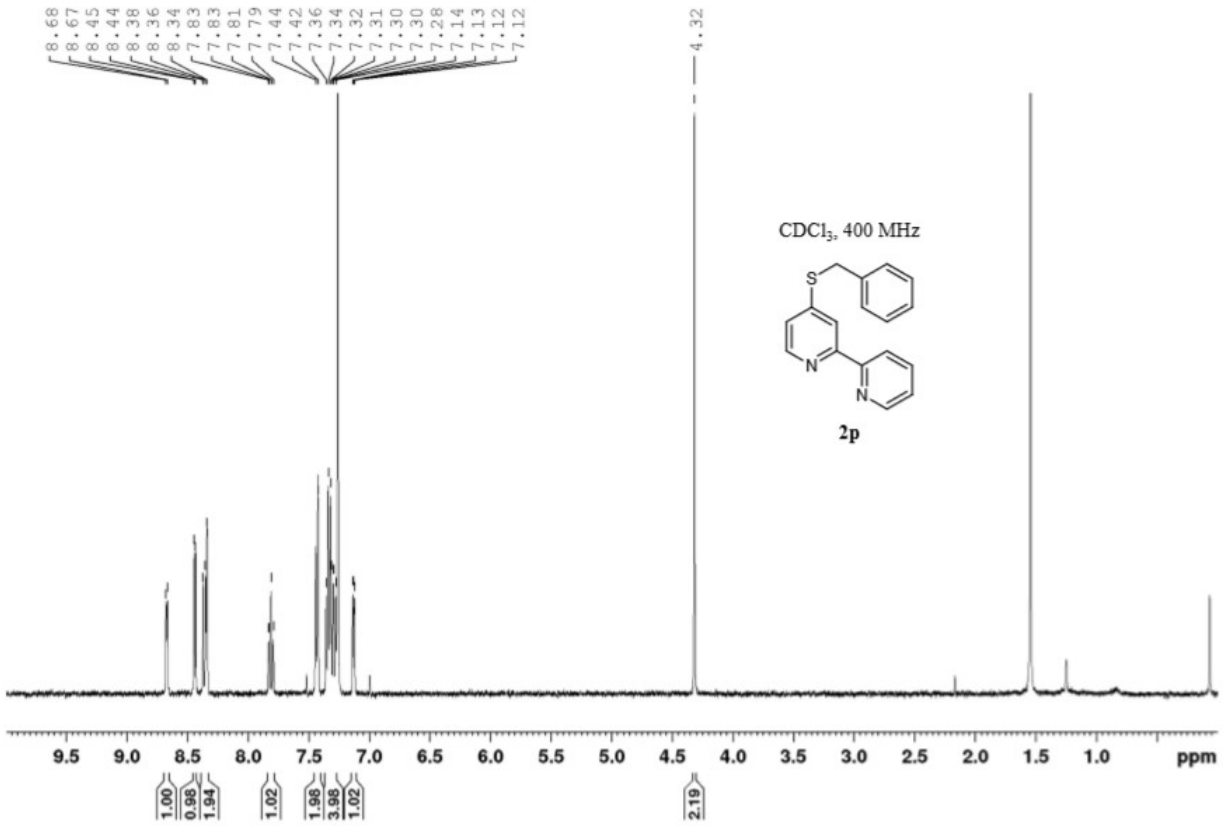
21

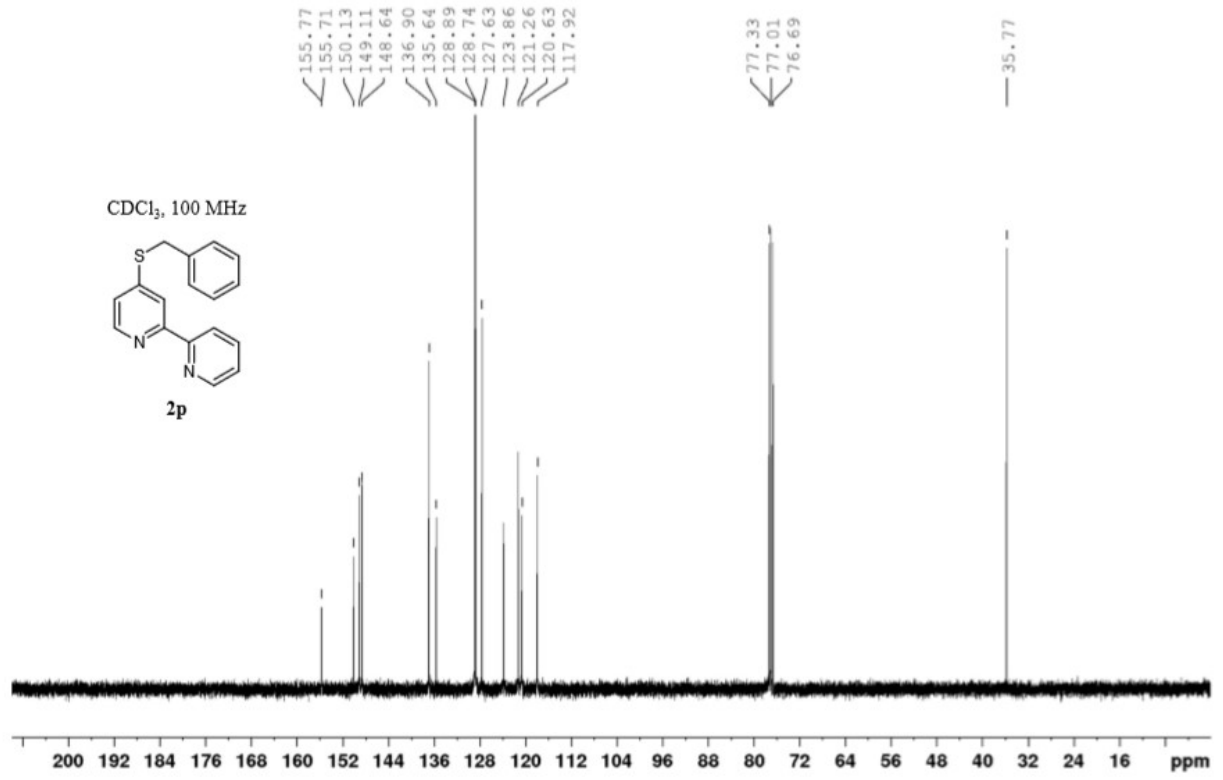

8.00
7.99
7.41
7.41
7.39
7.39
7.37
7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.28
7.00
7.00
6.99
6.99
6.98
6.98
6.74
6.74
6.73
4.23
CDCl3, 400 MHz
S
N
F
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
5.13
1.03
1.00
2.26

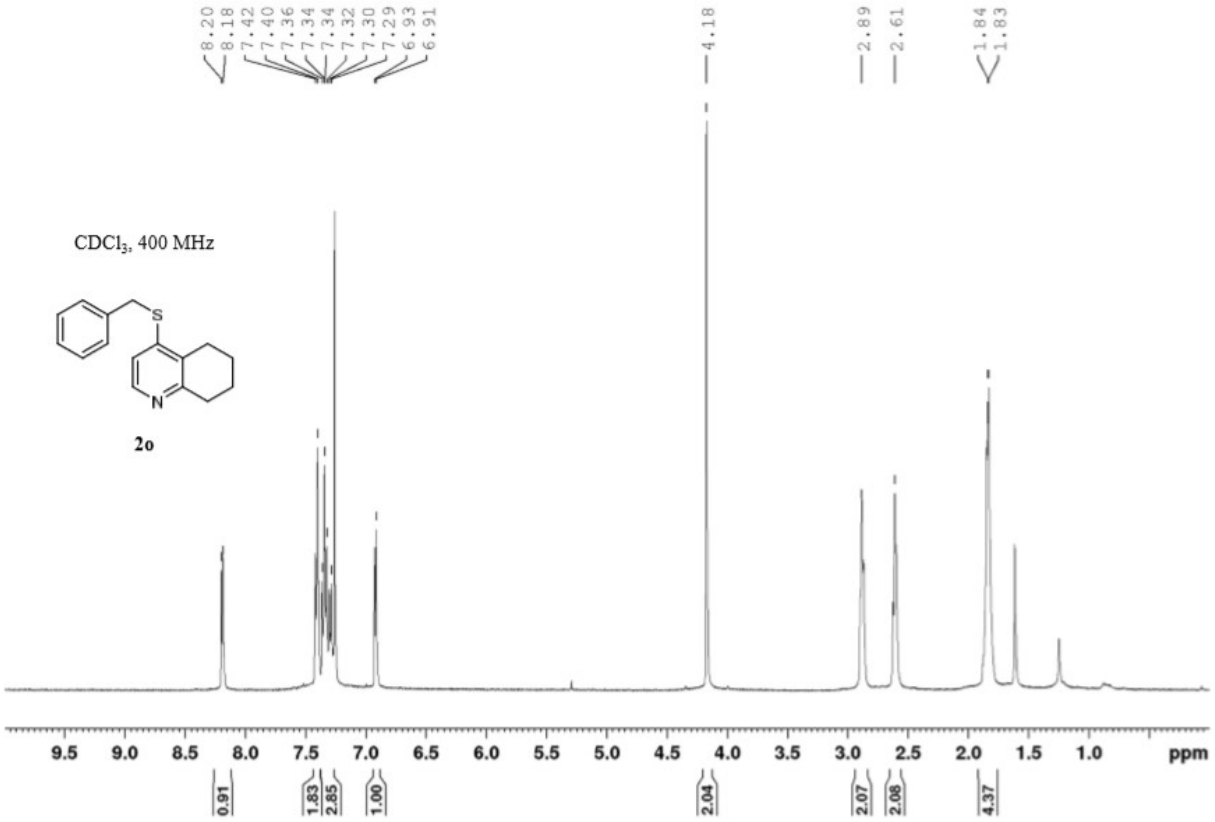
2j

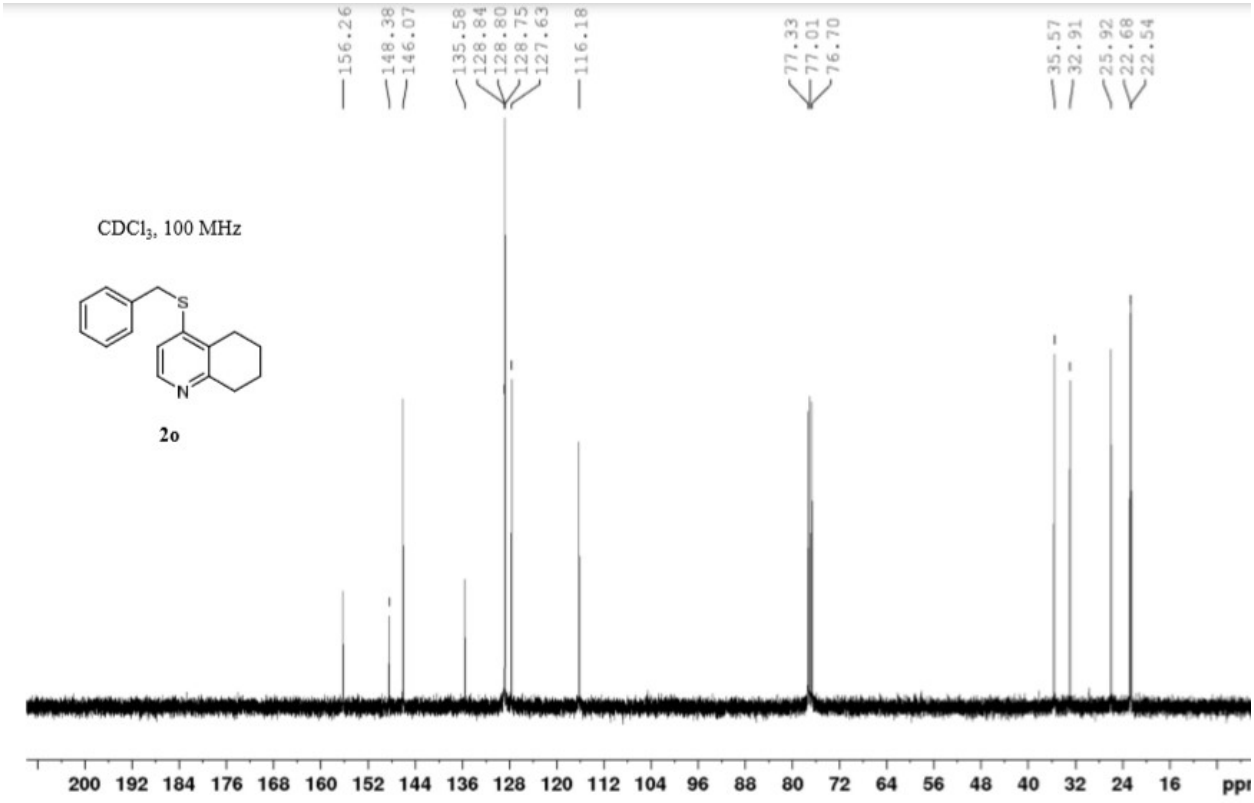

165.07
162.69
154.59
154.50
146.96
146.79
134.91
128.90
128.68
127.90
118.56
118.52
105.72
105.31
77.37
77.05
76.73
35.82
CDCl3, 100 MHz
S
N
F
2j
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

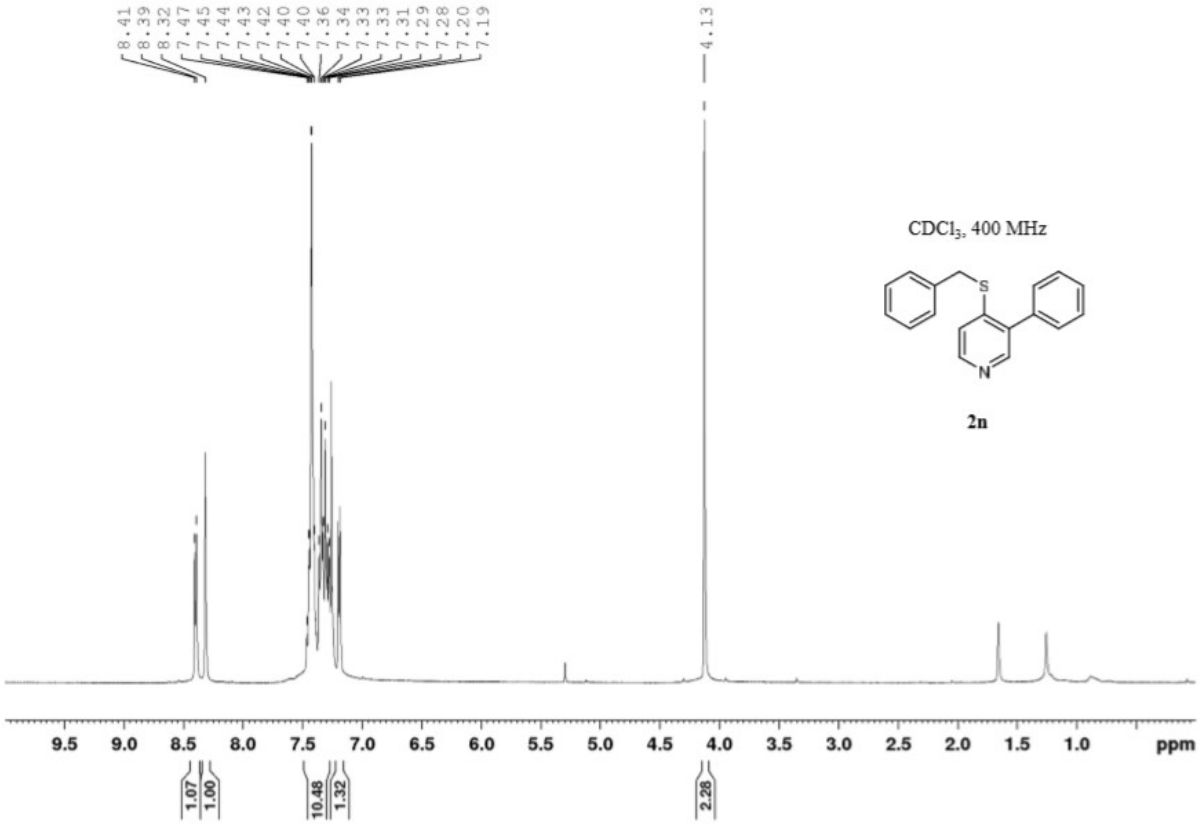

-68.25
CDCl3, 365 MHz
S
N
F
2j
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 ppm

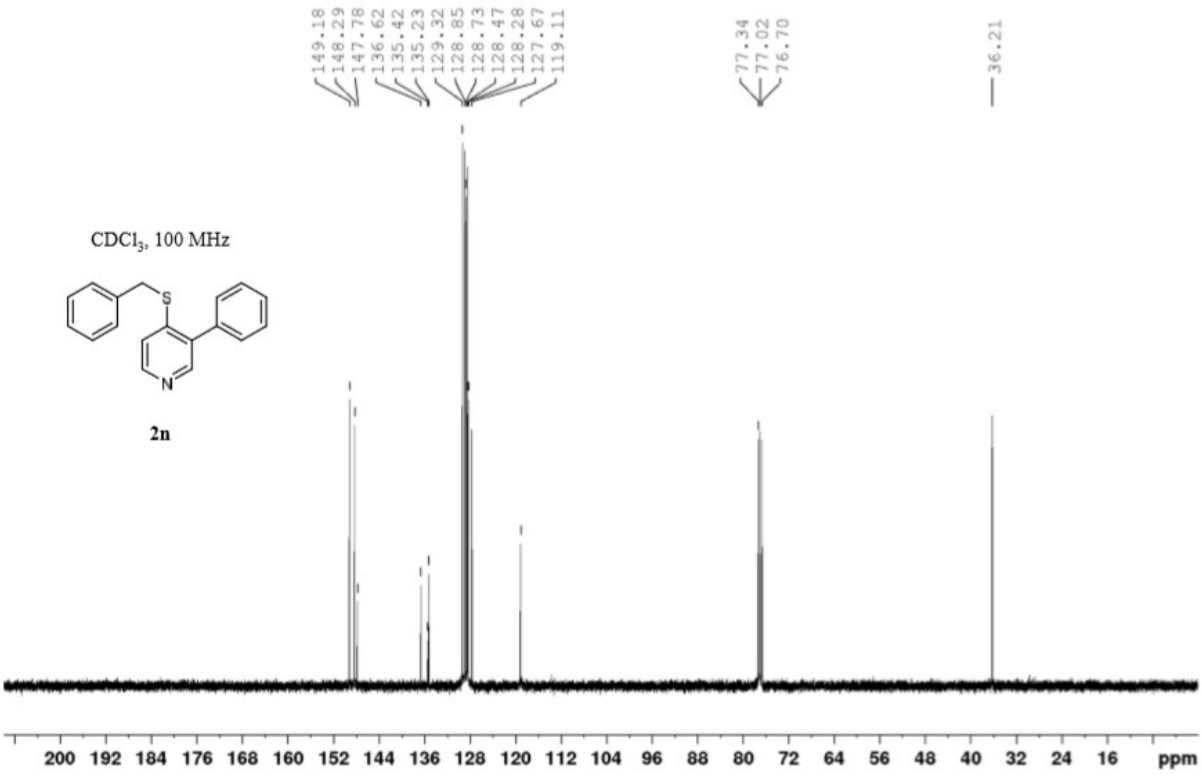

8.68
8.67
8.45
8.44
8.38
8.36
8.34
7.83
7.83
7.81
7.79
7.44
7.42
7.36
7.34
7.32
7.31
7.30
7.30
7.28
7.14
7.13
7.12
7.12
4.32
CDCl3, 400 MHz
2p
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.98
1.94
1.02
1.96
3.96
1.02
2.19

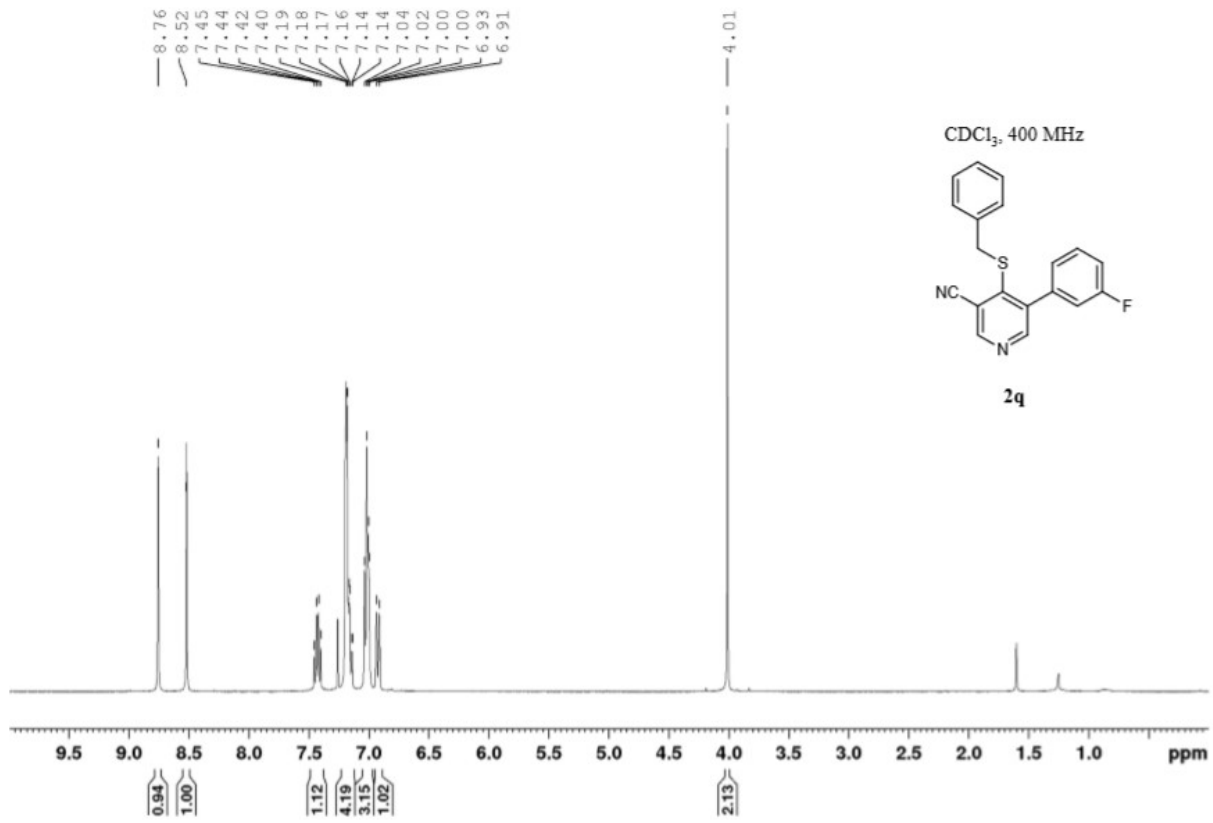

155.77
155.71
150.13
149.11
148.64
136.90
135.64
128.89
128.74
127.63
123.86
121.26
120.63
117.92
77.33
77.01
76.69
35.77
CDCl3, 100 MHz
2p
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

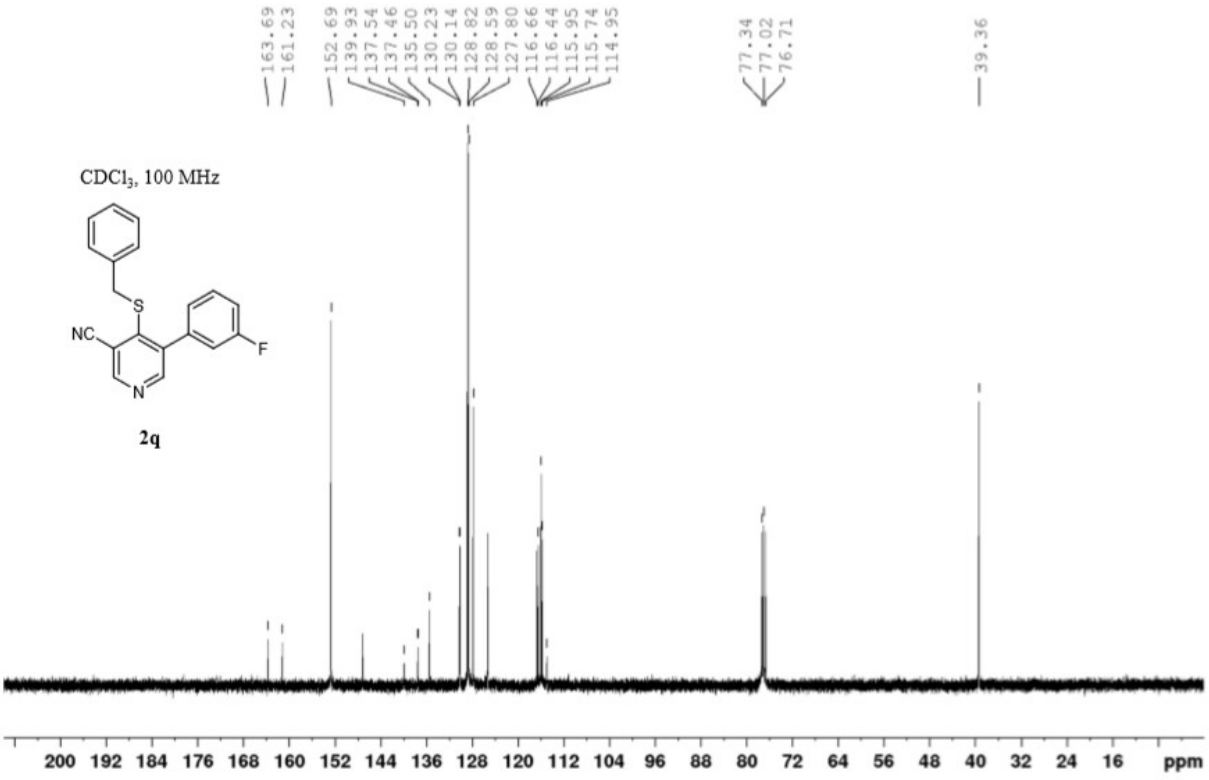

8.20
8.18
7.42
7.40
7.36
7.34
7.34
7.32
7.30
7.29
6.93
6.91
4.18
2.89
2.61
1.84
1.83
CDCl3, 400 MHz
S
N
2o
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.91
1.83
2.85
1.00
2.04
2.07
2.08
4.37

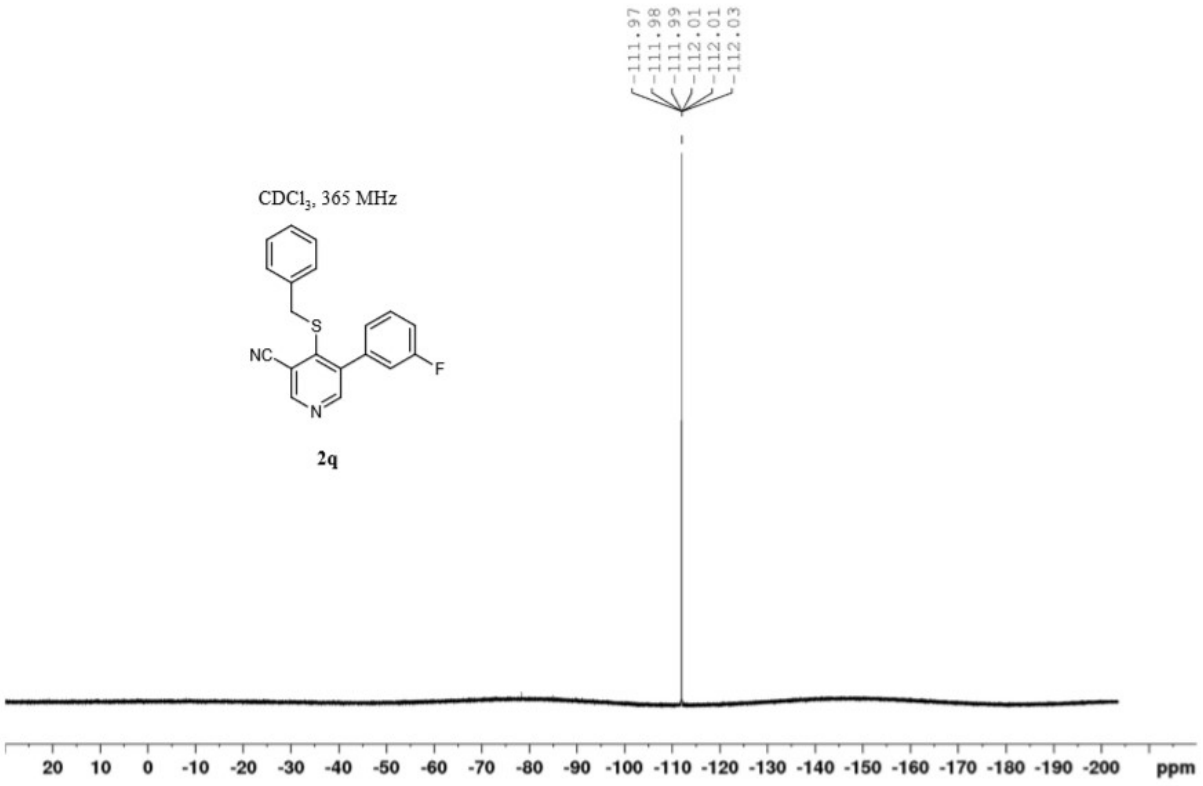

156.26
148.38
146.07
135.58
128.84
128.80
128.75
127.63
116.18
77.33
77.01
76.70
35.57
32.91
25.92
22.68
22.54
CDCl3, 100 MHz
S
N
2o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

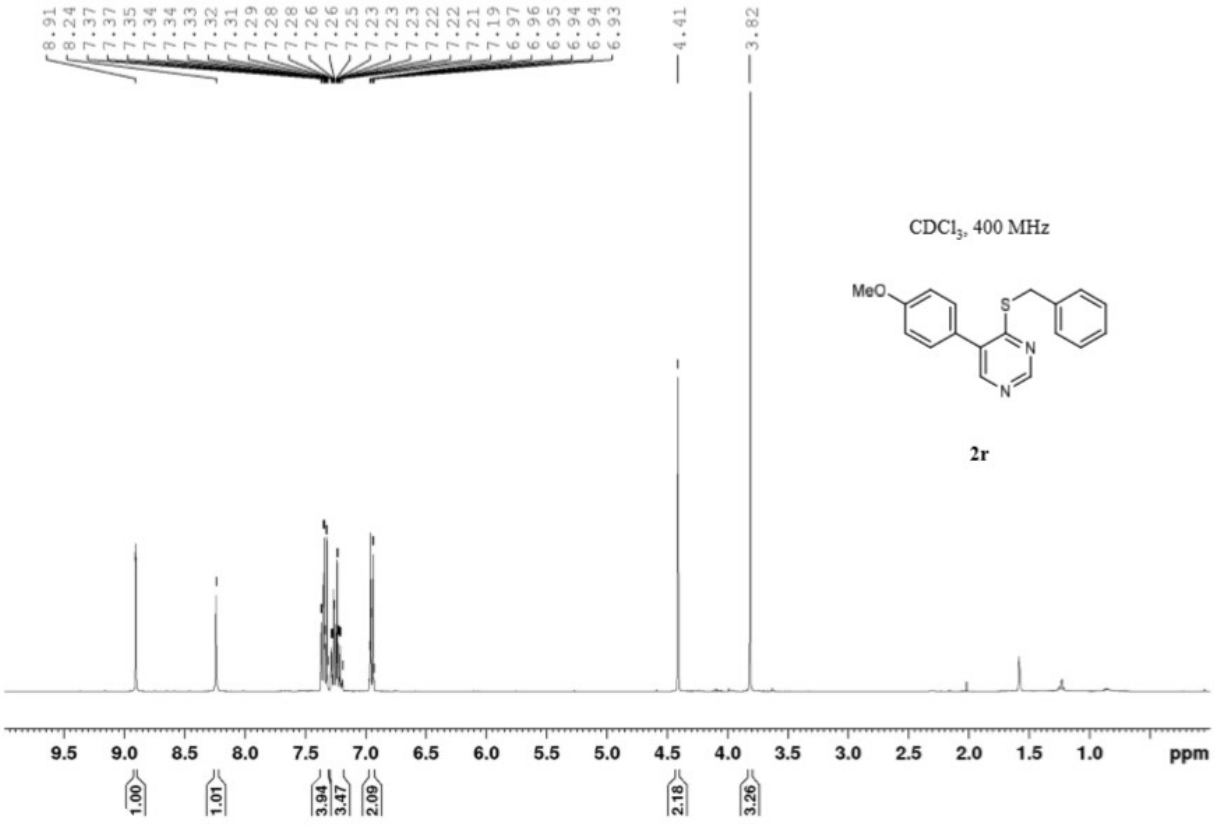

8.41
8.39
8.32
7.47
7.45
7.44
7.43
7.42
7.40
7.40
7.36
7.34
7.33
7.33
7.31
7.29
7.28
7.20
7.19
4.13
CDCl3, 400 MHz
S
N
2n
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.07
1.00
10.48
1.32
2.28

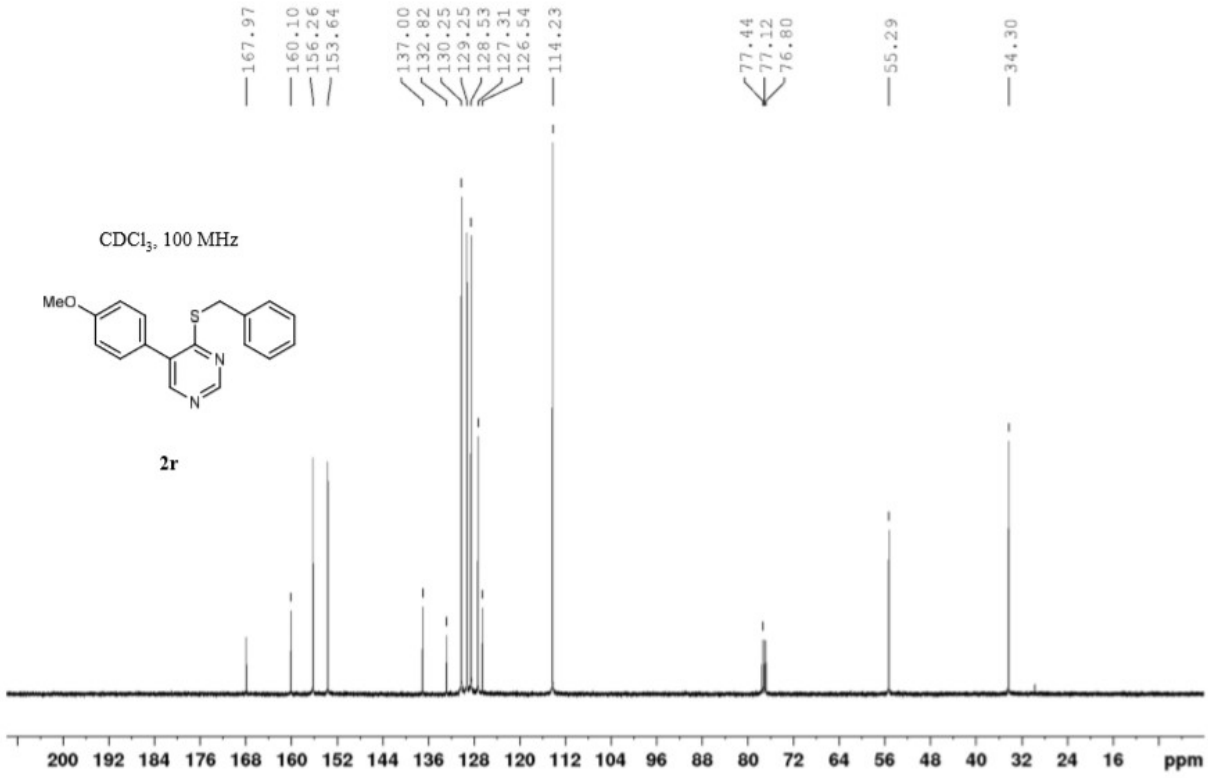

149.18
148.29
147.78
136.62
135.42
135.23
129.32
128.85
128.73
128.47
128.28
127.67
119.11
77.34
77.02
76.70
36.21
CDCl3, 100 MHz
S
N
2n
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

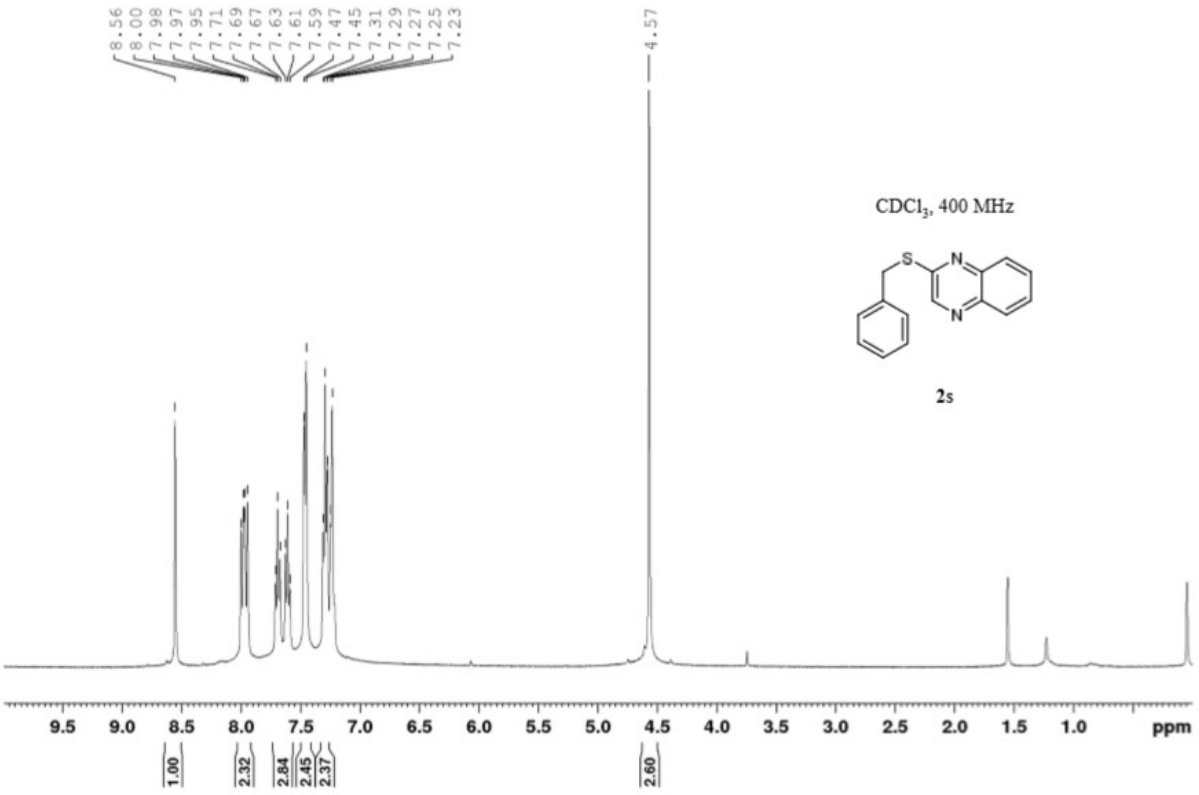

8.76
8.52
7.45
7.44
7.42
7.40
7.19
7.18
7.17
7.16
7.14
7.04
7.02
7.00
7.00
6.93
6.91
4.01
CDCl3, 400 MHz
S
NC
F
N
2q
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.94
1.00
1.12
4.19
3.15
1.02
2.13

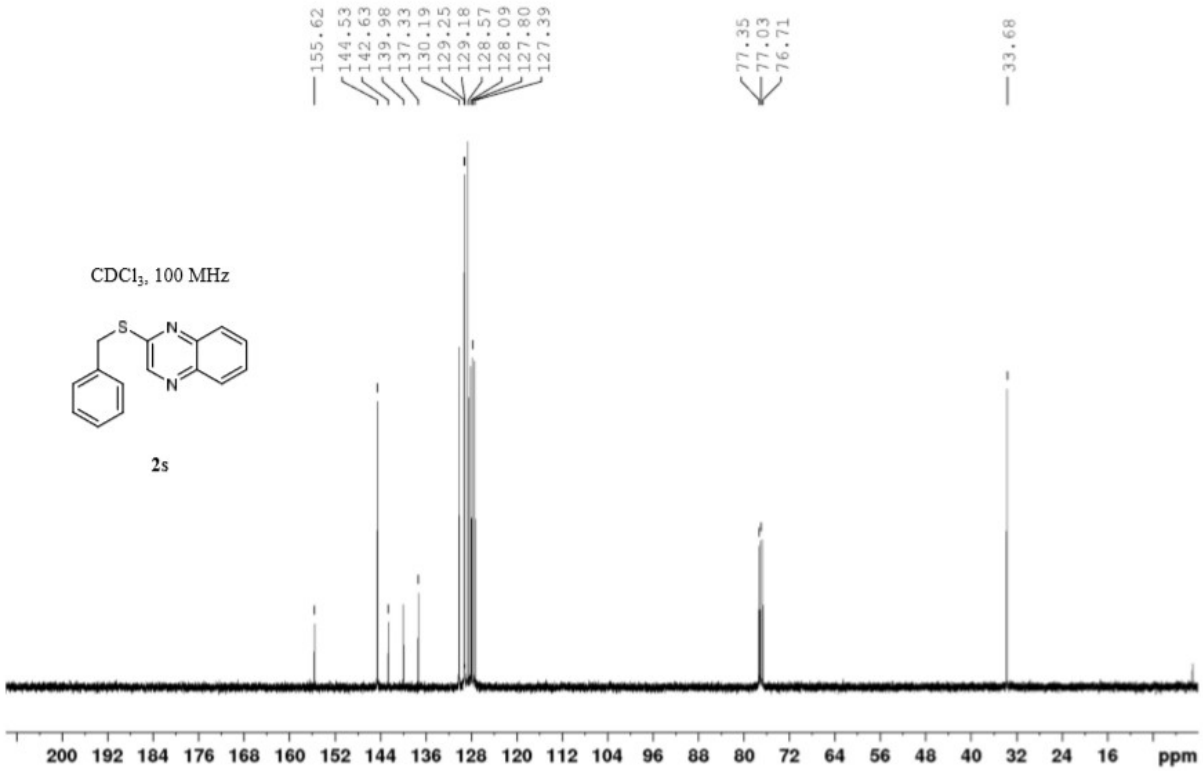

163.69
161.23
152.69
139.93
137.54
137.46
135.50
130.23
130.14
128.82
128.59
127.80
116.66
116.44
115.95
115.74
114.95
77.34
77.02
76.71
39.36
CDCl3, 100 MHz
S
NC
F
N
2q
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

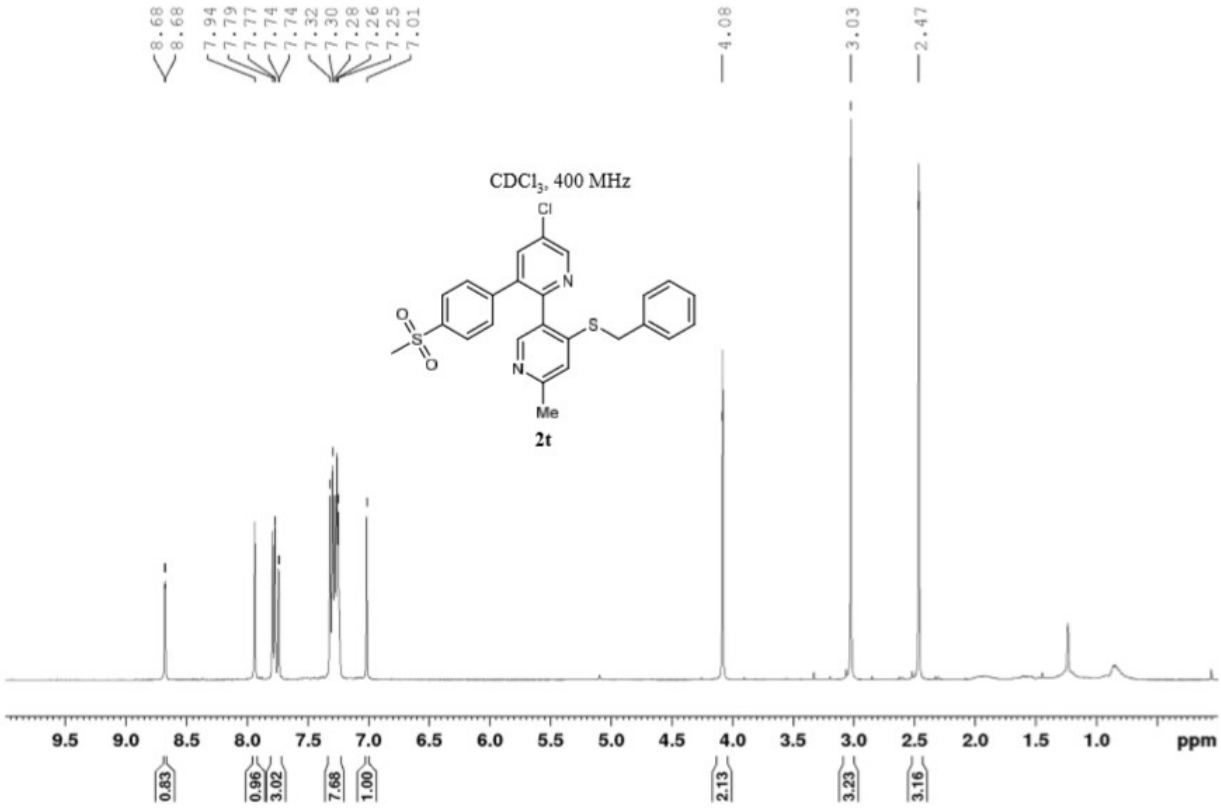

-111.97
-111.98
-111.99
-112.01
-112.03
CDCl3, 365 MHz
S
NC
F
N
2q
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 ppm

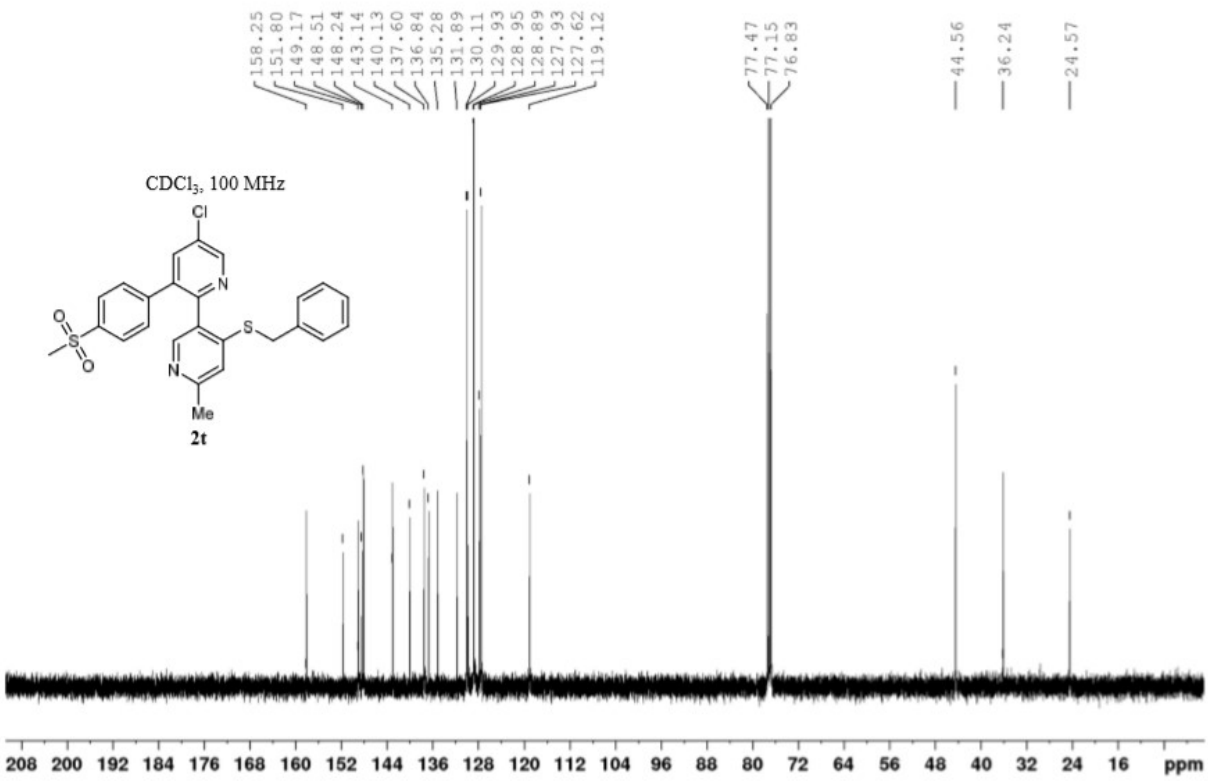

8.91
8.24
7.37
7.37
7.35
7.34
7.34
7.33
7.32
7.31
7.29
7.28
7.28
7.26
7.26
7.25
7.23
7.23
7.23
7.22
7.22
7.21
7.19
6.97
6.96
6.95
6.94
6.94
6.93
4.41
3.82
CDCl3, 400 MHz
MeO
S
N
N
2r
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.01
3.94
3.47
2.09
2.18
3.26

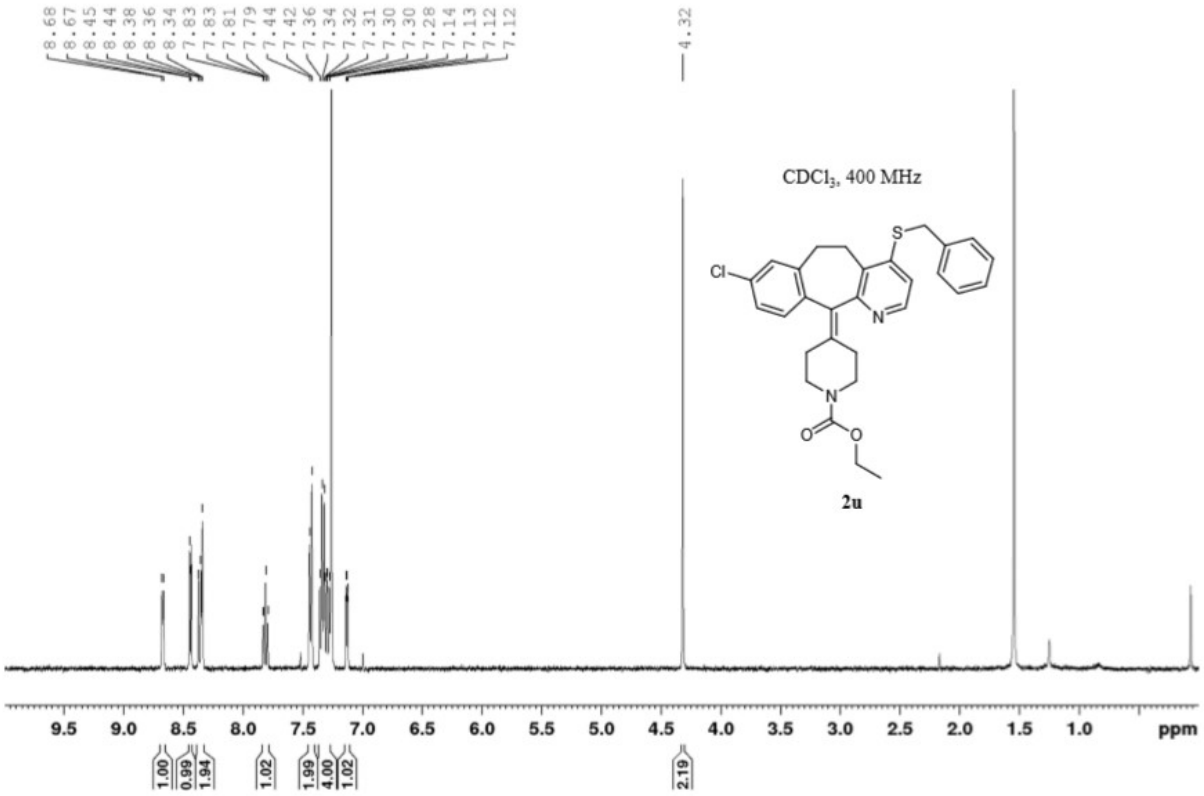

167.97
160.10
156.26
153.64
137.00
132.82
130.25
129.25
128.53
127.31
126.54
114.23
77.44
77.12
76.80
55.29
34.30
CDCl3, 100 MHz
MeO
S
N
N
2r
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

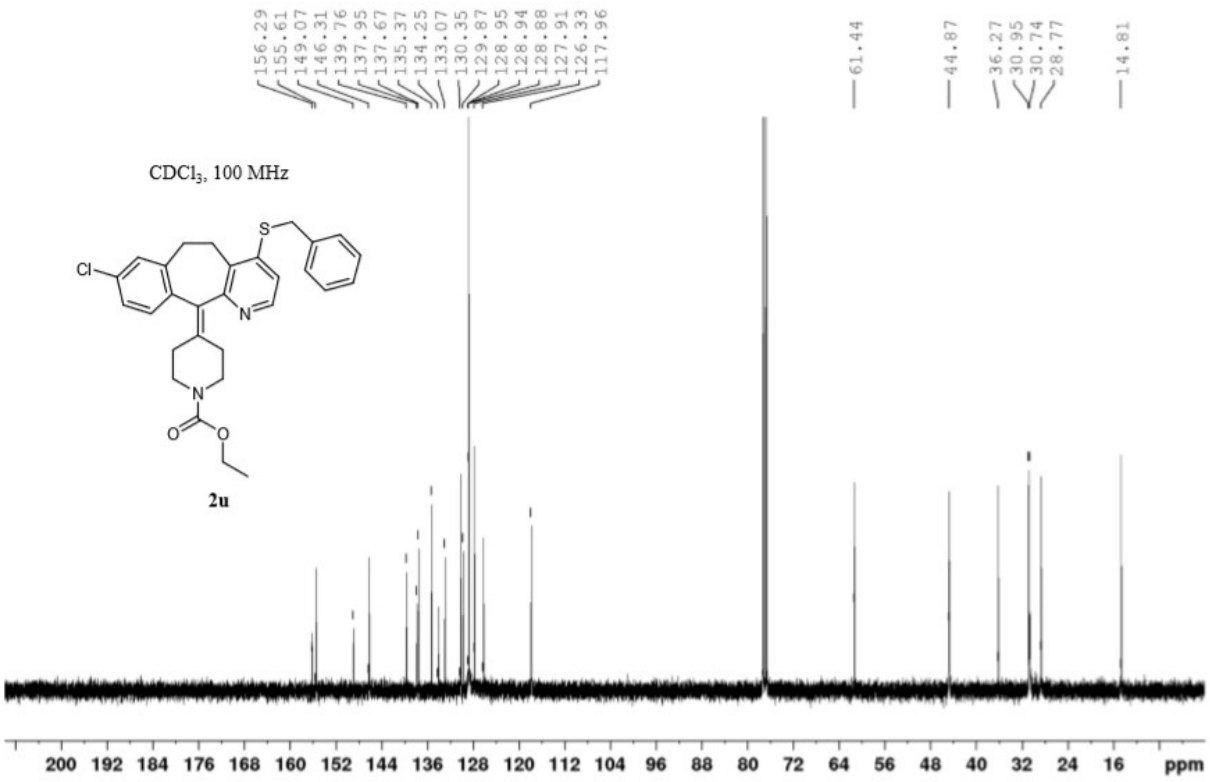

8.56
8.00
7.98
7.97
7.95
7.71
7.69
7.67
7.63
7.61
7.59
7.47
7.45
7.31
7.29
7.27
7.25
7.23
4.57
CDCl3, 400 MHz
S
N
N
2s
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.32
2.84
2.45
2.37
2.60


155.62
144.53
142.63
139.98
137.33
130.19
129.25
129.18
128.57
128.09
127.80
127.39
77.35
77.03
76.71
33.68
CDCl3, 100 MHz
2s
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

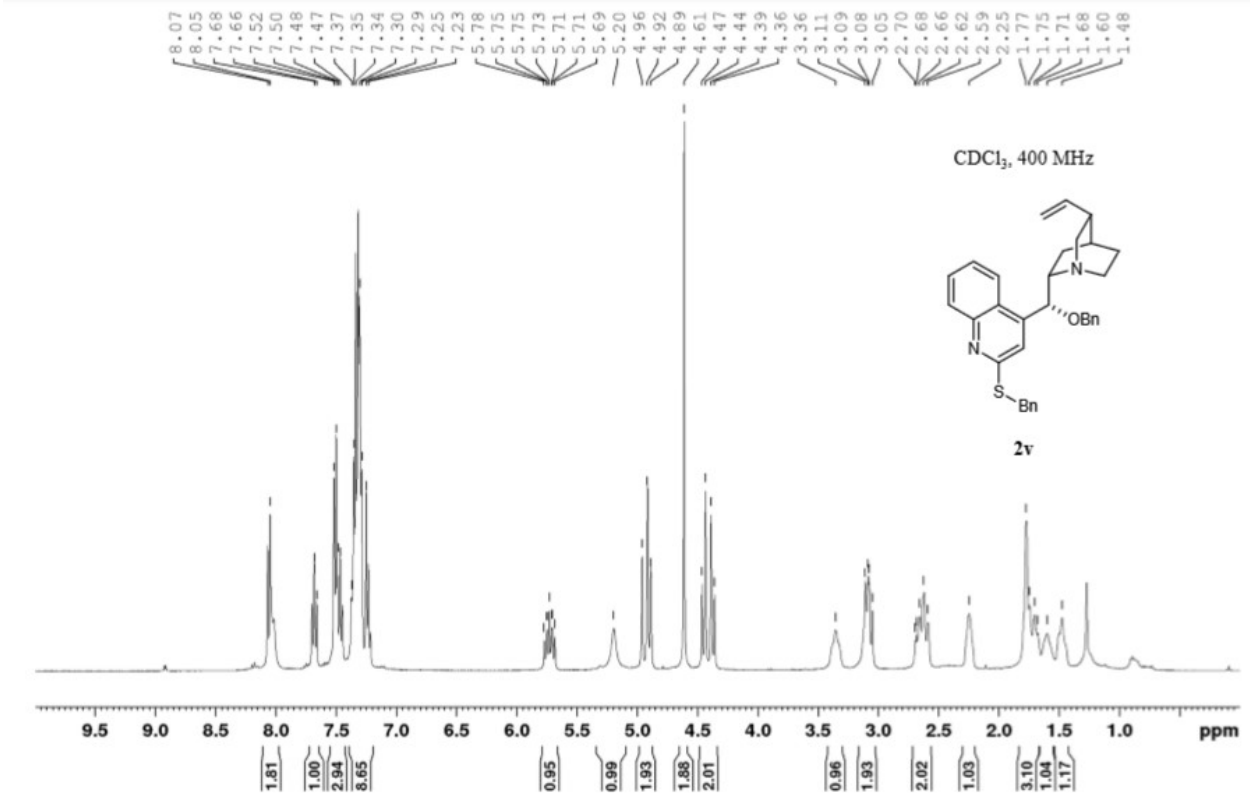

8.68
8.68
7.94
7.79
7.77
7.74
7.74
7.32
7.30
7.28
7.26
7.25
7.01
4.08
3.03
2.47
CDCl3, 400 MHz
2t
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.83
0.96
3.02
7.68
1.00
2.13
3.23
3.16


158.25
151.80
149.17
148.51
148.24
143.14
140.13
137.60
136.84
135.28
131.89
130.11
129.93
128.95
128.89
127.93
127.62
119.12
77.47
77.15
76.83
44.56
36.24
24.57
CDCl3, 100 MHz
Cl
N
S
O
O
N
Me
2t
208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

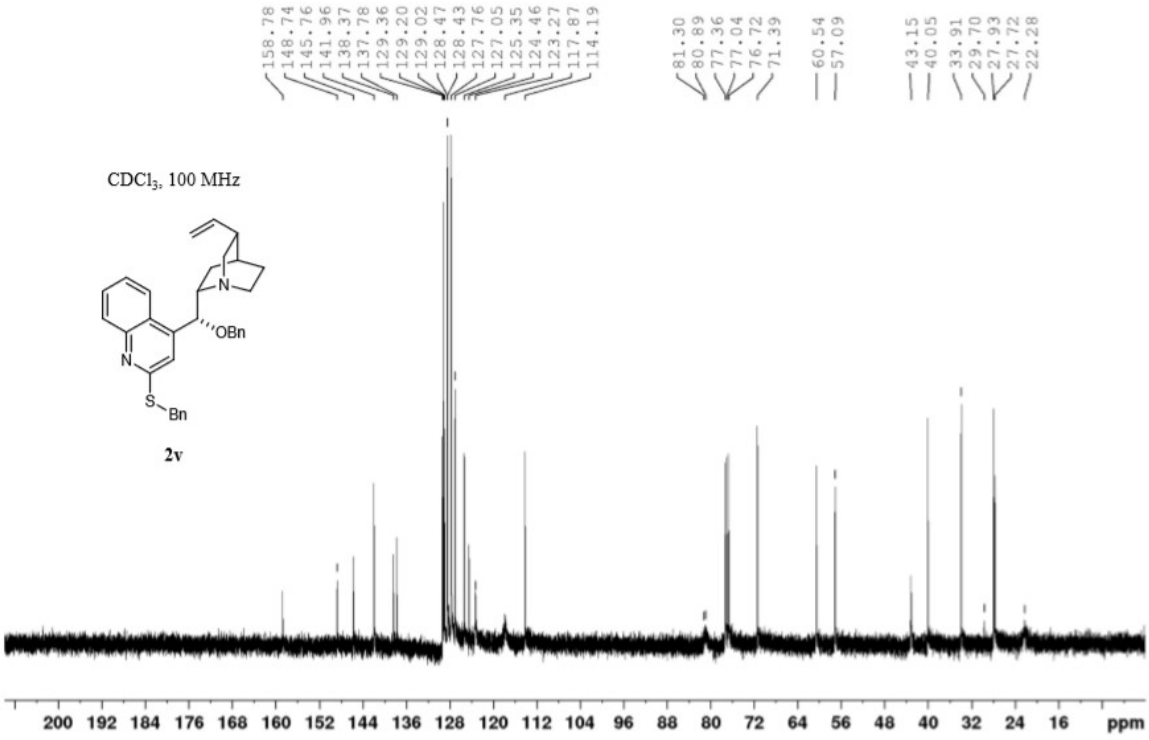

8.68
8.67
8.45
8.44
8.38
8.36
8.34
7.83
7.83
7.81
7.79
7.44
7.42
7.36
7.34
7.32
7.31
7.30
7.30
7.28
7.14
7.13
7.12
7.12
4.32
CDCl3, 400 MHz
S
Cl
N
N
O
O
2u
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.99
1.94
1.02
1.99
4.00
1.02
2.19


156.29
155.61
149.07
146.31
139.76
137.95
137.67
135.37
134.25
133.07
130.35
129.87
128.95
128.94
128.88
127.91
126.33
117.96
61.44
44.87
36.27
30.95
30.74
28.77
14.81
CDCl3, 100 MHz
Cl
S
N
N
O
O
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

2u


8.07
8.05
7.68
7.66
7.52
7.50
7.48
7.47
7.37
7.35
7.34
7.30
7.29
7.25
7.23
5.78
5.75
5.75
5.73
5.71
5.71
5.69
5.20
4.96
4.92
4.89
4.61
4.47
4.44
4.39
4.36
3.36
3.11
3.09
3.08
3.05
2.70
2.68
2.66
2.62
2.59
2.25
1.77
1.75
1.71
1.68
1.60
1.48
CDCl3, 400 MHz
N
OBn
N
S
Bn
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.81
1.00
2.94
8.65
0.95
0.99
1.93
1.88
2.01
0.96
1.93
2.02
1.03
3.10
1.04
1.17

2v


158.78
148.74
145.76
141.96
138.37
137.78
129.36
129.20
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128.47
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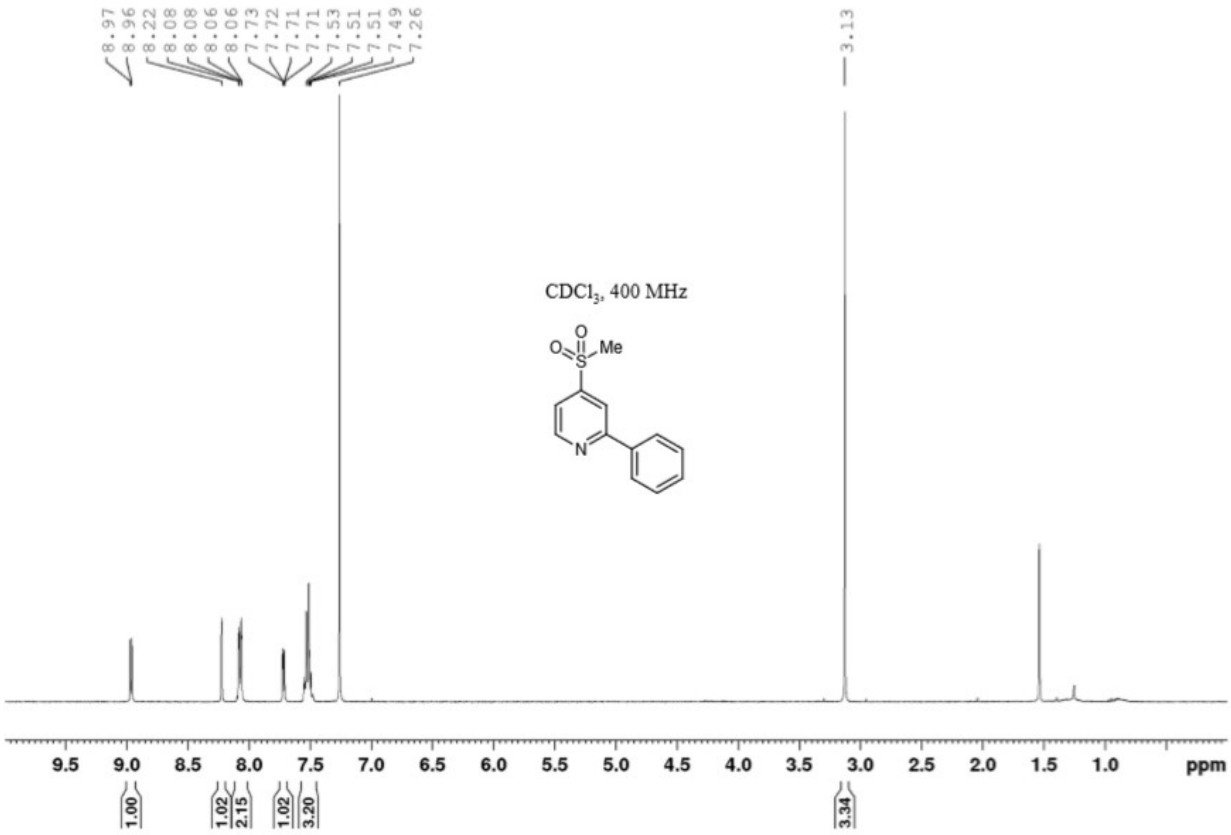
127.05
125.35
124.46
123.27
117.87
114.19
81.30
80.89
77.36
77.04
76.72
71.39
60.54
57.09
43.15
40.05
33.91
29.70
27.93
27.72
22.28
CDCl3, 100 MHz
OBn
N
S
Bn
2v
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.97
8.96
8.22
8.08
8.08
8.06
8.06
7.73
7.72
7.71
7.71
7.53
7.51
7.51
7.49
7.26
3.13
CDCl3, 400 MHz
O
O
S
Me
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.02
2.15
1.02
3.20
3.34

APPENDIX 2: CHAPTER 3 EXPERIMENTAL

General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield-400 (400 MHz) spectrometer, a Varian 400 MR (400 MHz) spectrometer or an Agilent Inova 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). 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 either a Bruker Ultrashield-400 (400 MHz) spectrometer, a Varian 400 MR spectrometer (100 MHz) or an Agilent Inova 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in $CDCl_3$ (77.0 ppm) or $(CD_3)_2SO$ (39.5 ppm). DEPT135, NOE experiments and 2-dimensional experiments (COSY, HMBC and HSQC) were used to support assignments where appropriate.

Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. Infared (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in $CHCl_3$, with absorptions reported in wavenumbers (cm^{-1}).

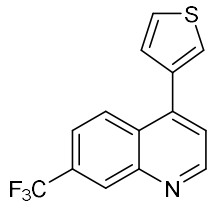
Analytical thin layer chromatography (TLC) was performed using pre-coated Merck glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Fluka or Material Harvest silica gel (230–400 mesh) under a positive pressure of air. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with basic potassium permanganate solution as appropriate.

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

PPh_3 (99%) was purchased from Oakwood Chemical and is most effective when crushed to a powder before use. Tf_2O (99%) was purchased from Oakwood Chemical and used without further purification but was routinely stored in a –20 ºC fridge. NEt_3 and DBU were distilled before use. NaH (60% in mineral oil) was purchased from Sigma Aldrich and was typically distributed into vials and stored in a desiccator. KH (36.3% in Paraffin) was purchased from Sigma Aldrich and was kept in a Glovebox. *n*-BuLi (1.6M in Hexanes) was purchased from Sigma Aldrich and routinely stored in a -20 ºC fridge. 15-Crown-5 was purchased from Oakwood Chemical Company and distilled before use and stored in a -20 ºC fridge. 18-Crown-6 was purchased from Sigma Aldrich and routinely stored in a -20 ºC fridge.

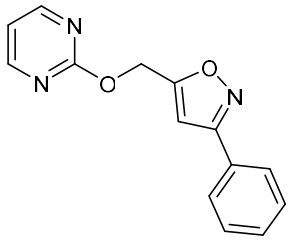
Preparation of Heterocyclic Phosphonium Salt and Aromatic Heteronucleophile Precursors

4-(Thiophen-3-yl)-7-(trifluoromethyl)quinoline



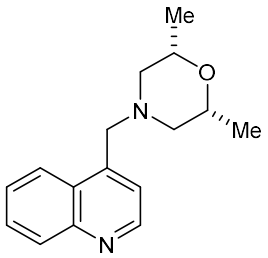
An oven dried 100 mL round bottom flask under N_2 was charged with 4-chloro-7-(trifluoromethyl)quinoline (973 mg, 4.20 mmol), thiophen-3-ylboronic acid (699 mg, 5.46 mmol), $Pd(PPh_3)_4$ (97 mg, 0.08 mmol), K_2CO_3 (1.74 g, 12.6 mmol), 12 mL of H_2O and 36 mL of 1,4-dioxane. After 12 hours of stirring the reaction mixture under reflux was quenched with H_2O (20 mL), organic layer separated, and aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 16% EtOAc in hexanes) to provide the title compound as brown solid (1.147 g, 4.12 mmol, 98% yield). mp 91–93 °C; IR υ_{max}/cm^{-1} (film): 3104, 3064, 1584, 1566, 1506, 1459, 1373, 1325, 1290, 1244, 1219, 1207, 1191, 1156, 1059, 902, 884, 853, 833, 815, 794, 784, 767, 740; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.01 (1H, d, J = 4.4 Hz), 8.47 (1H, s), 8.21 (1H, d, J = 8.8 Hz), 7.70 (1H, dd, J = 1.2, 8.8 Hz), 7.56–7.54 (2H, m), 7.50 (1H, d, J = 4.4 Hz), 7.34 (1H, dd, J = 1.4, 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.3, 147.8, 143.3, 137.6, 131.1 (q, J = 32.6 Hz), 128.6, 128.3, 127.7 (q, J = 4.3 Hz), 127.1, 126.8, 125.4, 123.9 (q, J = 271.1 Hz), 122.6, 122.2 (q, J = 3.1 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -62.76; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 280.1, $C_{14}H_9F_3NS^+$ requires 280.0.

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



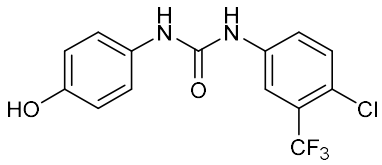
An oven dried 100 mL round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 1.5 equiv.). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of THF (14 mL). The mixture was cooled to 0 °C and a mixture of (3-phenylisoxazol-5-yl)methanol (1.31 g, 7.50 mmol) in THF (7 mL) was added dropwise over 5 minutes, then allowed to stir for 30 mins at 0 °C. A solution of 2-chloropyrimidine (568 mg, 5 mmol) in THF (7 mL) was then added dropwise to the reaction mixture over 5 minutes. The reaction stirred at 0 °C for 5 minutes then was warmed to room temperature and allowed to stir for 14 hours. The mixture was quenched with water (25 mL) and diluted with CH_2Cl_2 (25 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 5% EtOAc in CH_2Cl_2) to provide the title compound as a white solid (993 mg, 3.92 mmol, 78% yield). mp 98-105 ºC; IR ν_{max}/cm^{-1} (film): 3129, 3088, 3052, 2986, 1948, 2249, 2162, 1965, 1815, 1607, 1578, 1567, 1471, 1401, 1375, 1323, 1290, 1044, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (2H, d, *J* = 4.8 Hz), 7.83-7.76 (2H, m), 7.48-7.42 (3H, m), 7.02 (1H, t, *J* = 4.8 Hz), 6.70 (1H, s), 5.59 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.1, 164.3, 162.5, 159.5, 130.0, 128.9, 128.8, 126.8, 115.8, 101.6, 59.9; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 254.2, $C_{14}H_{12}N_3O_2^+$ requires 254.1.

(2R,6S)-2,6-Dimethyl-4-(quinolin-4-ylmethyl)morpholine



An oven-dried 200 mL round bottom flask was charged with 4-quinolinecarboxaldehyde (2.36 g, 15.0 mmol), *cis*-2,6,-dimethylmorpholine (2.03 mL, 16.5 mmol), and sodium triacetoxyhydroborate (6.36 g, 30.0 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill. CH_2Cl_2 (75 mL) was added to the reaction flask along with glacial AcOH (1.73 mL). After 1 hour stirring at room temperature, the reaction was quenched with a saturated aqeuous solution of NH_4Cl (30 mL), diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 50% EtOAc in hexanes) to provide the title compound as a yellow oil (2.98 g, 11.6 mmol, 77% yield). IR ν_{max}/cm^{-1} (film): 3035, 2971, 2868, 2813, 2774, 980, 815, 662, 645, 591; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.84 (1H, d, J = 4.3 Hz), 8.23 (1H, d, J = 8.4 Hz), 8.11 (1H, d, J = 8.4 Hz), 7.70 (1H, m), 7.54 (1H, m), 7.40 (1H, d, J = 4.3 Hz), 3.87 (2H, s), 3.69 (2H, m), 2.72 (2H, d, J = 10.4 Hz), 1.87 (2H, t, J = 10.7 Hz), 1.13 (6H, d, J = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.0, 148.3, 143.6, 129.9, 129.1, 127.6, 126.3, 124.2, 121.4, 71.7 (2C), 59.6, 19.0; *m/z* LRMS (ESI+ APCI) found $[M+H]^+$ 257.2, $C_{16}H_{20}N_2O^+$ requires 257.2.

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)urea (3bs)



An oven dried 200 mL round bottom flask was charged with 4-aminophenol (546 mg, 5.00 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of CH_2Cl_2 (25 mL). A 0.2 M solution of 1-chloro-4-isocyanato-2-(trifluoromethyl)benzene in THF (25 mL) was added dropwise to the reaction flask and stirred at room temperature for 16 hrs. The reaction mixture was then filtered and rinsed with CH_2Cl_2 and H_2O. The material was then further purified by flash chromatography (silica gel: 35% EtOAc in Toluene) to provide the title compound (3bs) as a white solid (1.11 g, 3.36 mmol, 84% yield). mp 185-195 ºC; IR ν_{max}/cm^{-1} (film): 3293, 3109, 2359, 1896, 1672, 1623, 1557, 1480, 1326, 1261, 1180, 1145, 1124, 1031, 831; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ: 9.12 (1H, s), 9.03 (1H, s), 8.48 (1H, s), 8.10 (1H, d, J = 1.6 Hz), 7.64-7.56 (2H, m), 7.23 (2H, d, J = 8.6 Hz), 6.70 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 153.9, 152.6, 139.7, 131.9, 130.5, 126.6 (q, J = 30.7 Hz), 122.9 (q, J = 273.4 Hz), 122.8 (q, J = 4.1 Hz), 121.8, 121.0, 116.5 (q, J = 5.8 Hz), 115.2; ^{19}F NMR (365 MHz, $(CD_3)_2SO$) δ: -61.46; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 331.1, $C_{14}H_{11}ClF_3N_2O_2^+$ requires 331.0.

4. Preparation of Heterocyclic Phosphonium Salts

General Procedure A:

An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before PPh_3 (1.1 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30

minutes at –78 ºC. The stated organic base (NEt_3 or DBU, 1.0 equiv) was added dropwise via syringe, the cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring (approximately 15-30 minutes). The reaction mixture was quenched with H_2O (approximately the same volume as CH_2Cl_2) and the mixture was transferred to a separatory funnel. The mixture was diluted CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to approximately 2-10 mL (depending on the scale of the reaction). An excess of chilled Et_2O (0 ºC) was added to the concentrated solution that was then placed in a –20 ºC refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC) and dried *in vacuo* to provide the pure phosphonium salt.

Notes.

1) PPh_3 was crushed into a powder prior to use.
2) Certain substrates require longer periods for the precipitation step and specific cases are indicated below.
3) In a small number of cases, residual CH_2Cl_2 can become trapped in the phosphonium salt products. In these cases, heating the salts under vacuum (50-100 ºC) removed the solvent.
4) In order to evaluate regioselectivity from the crude reaction mixtures, a duplicate reaction was performed, and aliquots taken after addition of the organic base and warming to room temperature. These aliquots were concentrated *in vacuo* and analyzed by ^{1}H and ^{31}P NMR.

General Procedure B:

In oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and PPh_3 (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was

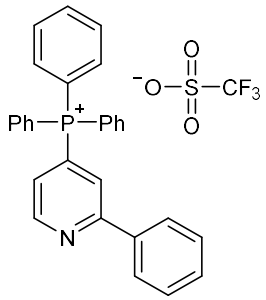
added dropwise over 5 minutes. The reaction was stirred[1] for 1 hour before DBU (1.0 equiv) was added dropwise via syringe, the cooling bath removed, and the reaction warmed to room temperature while stirring (approximately 15-30 minutes). The reaction mixture was quenched with H_2O (approximately the same volume as CH_2Cl_2) and the mixture was transferred to a separatory funnel. The mixture was diluted CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to approximately 2-10 mL (depending on the scale of the reaction). An excess of chilled Et_2O (0 ºC) was added to the concentrated solution that was then placed in a –20 ºC refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC) and dried *in vacuo* to provide the pure phosphonium salt.

Notes.

1) PPh_3 was crushed into a powder prior to use.
2) Certain substrates require longer periods for the precipitation step and specific cases are indicated below.
3) In a small number of cases, residual CH_2Cl_2 can become trapped in the phosphonium salt products. In these cases, heating the salts under vacuum (50-100 ºC) removed the solvent.
4) In order to evaluate regioselectivity from the crude reaction mixtures, a duplicate reaction was performed, and aliquots taken after addition of the organic base and warming to room temperature. These aliquots were concentrated *in vacuo* and analyzed by ^1H and ^{31}P NMR

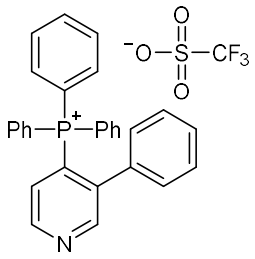
[1] The reaction vessel was placed directly on the middle of the stir plate and the mixture stirred at 1400-2000 rpms for the duration of the reaction.

Triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (1a)



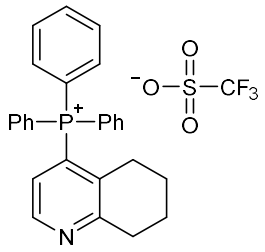
Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (1H, app t, *J* = 5.1 Hz), 7.93-7.54 (18H, m), 7.50 (1H, ddd, *J* = 17.8, 5.1, 1.1 Hz), 7.42-7.36 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ:159.1 (d, *J* = 9.9 Hz), 151.6 (d, *J* = 10.7 Hz), 136.7 (d, *J* = 1.5 Hz), 136.1 (d, J = 3.2 Hz), 134.3 (d, *J* = 9.8 Hz), 130.9 (d, *J* = 13.0 Hz), 130.4, 129.23 (d, *J* = 84.1 Hz), 129.0, 127.0, 125.3 (d, *J* = 7.8 Hz), 123.1, (d, *J* = 8.4 Hz), 120.7 (q, *J* = 321.1 Hz), 115.5 (d, *J* = 89.1 Hz). The spectroscopic data is in agreement with our previous synthesis.[2]

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



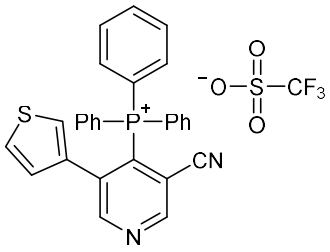
Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, app t, *J* = 4.7 Hz), 8.74 (1H, d, *J* = 6.8 Hz), 7.85-7.73 (3H, m), 7.73-7.40 (13H, m), 7.11 (1H, t, *J* = 7.6 Hz), 6.91 (2H, app t, *J* = 7.6 Hz), 6.71 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.6 (d, *J* = 8.0 Hz), 150.0 (d, *J* = 10.4 Hz), 141.7 (d, *J* = 7.3 Hz), 135.4 (d, *J* = 3.0 Hz), 134.4 (d, *J* = 4.5 Hz), 134.2 (d, *J* = 10.3 Hz), 130.6 (d, *J* = 13.0 Hz), 129.2, 128.9, 128.3, 128.2, 126.4 (d, *J* = 83.4 Hz), 120.8 (q, *J* = 321.2 Hz), 116.9 (d, *J* = 89.2 Hz). The spectroscopic data is in agreement with our previous synthesis.[2]

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



Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.74 (1H, app t, *J* = 5.1 Hz), 8.07-7.93 (3H, m), 7.92-7.71 (12H, m), 6.94 (1H, dd, *J* = 15.3, 5.1 Hz), 3.12-2.97 (2H, m), 2.21-2.04 (2H, m), 1.84-1.71(2H, m), 1.60-1.44 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3 (d, *J* = 8.4 Hz), 148.2 (d, *J* = 11.4 Hz), 135.5 (d, *J* = 7.6 Hz), 135.3 (d, *J* = 3.1 Hz), 134.1 (d, *J* = 10.7 Hz), 130.5 (d, *J* = 13.0 Hz), 126.2 (d, *J* = 9.9 Hz), 125.5 (d, *J* = 82.4 Hz), 120.4 (q, *J* = 322.0 Hz), 116.3 (d, *J* = 87.7 Hz), 32.0 (d, *J* = 2.3 Hz), 29.7 (d, *J* = 5.3 Hz), 21.0, 20.5. The spectroscopic data is in agreement with our previous synthesis.[2]

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



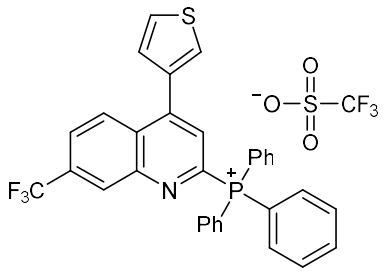
Major

11.4:1 Mixture of Regioisomers

Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.45 (1H, d, *J* = 5.0 Hz), 9.07 (1H, d, *J* = 5.5 Hz), 7.98-7.84 (9H, m), 7.77-7.67 (6H, m), 7.21-7.16 (1H, m), 7.13 (1H, br s), 6.57 (1H, d, *J* = 4.9 Hz); Major isomer, ^{13}C NMR (100 MHz, DMSO-d_6) δ: 157.0 (d, *J* = 6.9 Hz), 154.7 (d, *J* = 5.8 Hz), 140.2 (d, *J* = 5.5 Hz), 135.3 (d, *J* = 3.0 Hz), 134.5 (d, *J* = 10.8 Hz), 130.4 (d, *J* = 13.3 Hz), 128.5,

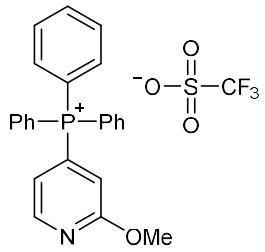
128.3 (d, J = 84.5 Hz), 128.3, 127.8, 120.7 (q, J = 322.4 Hz), 117.0 (d, J = 88.5 Hz), 113.9 (d, J = 6.0 Hz), 113.2 (d, J = 4.4 Hz).

Triphenyl(4-(thiophen-3-yl)-7-(trifluoromethyl)quinolin-2-yl)phosphonium trifluoromethanesulfonate



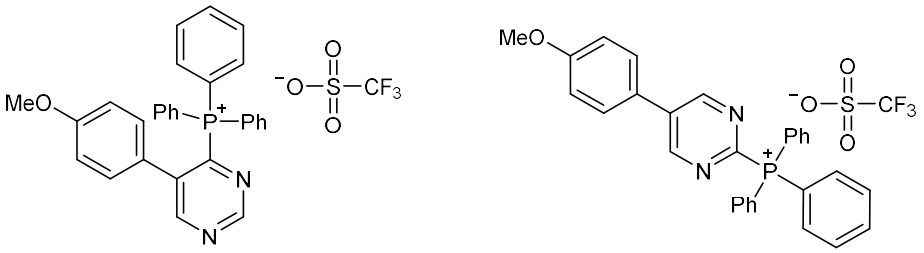
Prepared according to general procedure B (except the reaction was cooled to –50 ºC for the Tf_2O addition, then cooled to –78 ºC for the DBU addition) using 4-(thiophen-3-yl)-7-(trifluoromethyl)quinoline (805 mg, 2.88 mmol), PPh_3 (831 mg, 3.17 mmol), Tf_2O (484 µL, 2.88 mmol) and CH_2Cl_2 (29 mL). After the purification procedure the pure phosphonium salt was isolated as an off-white solid (1.68 g, 2.33 mmol, 81% yield). mp 234-237 °C; IR υ_{max}/cm^{-1} (film): 3064, 1739, 1575, 1540, 1501, 1484, 1439, 1421, 1378, 1335, 1224, 1167, 1140, 1108, 1065, 1030, 997, 918, 835, 797, 785, 748, 728, 701, 689, 663, 631; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (1H, s), 8.40 (1H, d, J = 8.9 Hz), 7.92–7.87 (4H, m), 7.82–7.75 (14H, m), 7.55 (1H, dd, J = 3.0, 4.7 Hz), 7.34 (1H, J = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.6, 148.3, 147.5, 146.5 (d, J = 10.5 Hz), 146.4, 135.9 (d, J = 2.9 Hz), 135.5 (d, J = 1.5 Hz), 134.7 (d, J = 10.1 Hz), 133.2 (q, J = 33.2 Hz), 130.7 (d, J = 12.9 Hz), 128.6 (d, J = 2.4 Hz), 128.3, 128.1, 128.0, 127.8, 125.9–125.6 (m), 123.2 (q, J = 271.7 Hz), 120.7 (q, J = 319.6 Hz), 116.7 (d, J = 88.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –63.08, –78.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.62; m/z LRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 540.2, $C_{32}H_{22}F_3NPS^+$ requires 540.1.

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



Prepared according to general procedure A using 2-methoxypyridine (52.5 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure, the title compound was isolated as a white solid (174 mg, 0.34 mmol, 67% yield). mp 149-154 °C; IR υ_{max}/cm^{-1} (film): 3063, 2956, 2360, 1980, 1583, 1438, 1380, 1264, 1143, 1107, 1031, 722, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (1H, t, *J* = 5.3 Hz), 7.97-7.87 (3H, m), 7.85-7.74 (6H, m), 7.71-7.59 (6H, m), 7.12 (1H, dd, *J* = 11.5 Hz, 5.0 Hz), 6.84 (1H, d, *J* = 15.0 Hz), 4.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5 (d, *J* = 15.7 Hz), 149.8 (d, *J* = 10.5 Hz), 136.1 (d, *J* = 2.9 Hz), 134.2 (d, *J* = 10.5 Hz), 130.9 (d, *J* = 13.5 Hz), 130.5 (d, *J* = 85.2 Hz), 120.7 (q, *J* = 321.2 Hz), 118.8 (d, *J* = 8.3 Hz), 116.2 (d, *J* = 10.0 Hz), 115.6 (d, *J* = 89.6 Hz), 54.3; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.37; *m*/*z* LRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 519.1, $C_{24}H_{21}NOP^+$ requires 519.1.

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

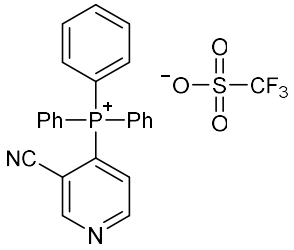


Major Minor

24:1 Mixture of Regioisomers

Prepared according to our previous report.[2] Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.44 (1H, s), 8.98 (1H, d, *J* = 9.0 Hz), 7.80-7.70 (3H, m), 7.67-7.56 (12H, m), 6.91 (2H, d, *J* = 8.7 Hz), 6.55 (2H, d, *J* = 8.7 Hz), 3.72 (3H, s); Minor isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.23 (2H, s), 7.80-7.70 (3H, m), 7.70 (2H, d, *J* = 8.7 Hz), 7.67-7.56 (12H, m), 7.09 (2H, d, *J* = 8.6 Hz), 3.88 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.8 (d, *J* = 5.3 Hz), 160.5, 157.0 (d, *J* = 16.8 Hz), 149.7 (d, *J* = 114.5 Hz), 142.7 (d, *J* = 19.2 Hz), 135.2 (d, *J* = 3.1 Hz), 134.7 (d, *J* = 10.2 Hz), 130.6, 130.3 (d, *J* = 13.1 Hz), 123.6, 120.8 (q, *J* = 321.3 Hz), 117.1 (d, *J* = 88.6 Hz), 114.4, 55.4.

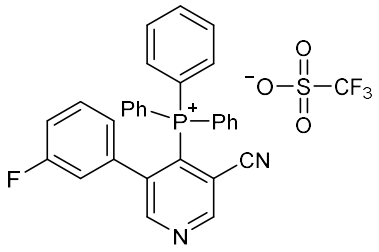
(3-Cyanopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[4] ^{1}H NMR (400 MHz, CDCl3) δ: 9.21 (1H, dd, J = 4.2, 4.1), 9.16 (1H, d, J = 5.5 Hz), 7.95–7.91 (3H, m), 7.83–7.71 (13H, m); ^{13}C NMR (100 MHz, CDCl3) δ: 155.5 (d, J = 9.2 Hz), 154.9 (d, J = 5.5 Hz), 136.4 (d, J = 3.1 Hz), 134.7 (d, J = 10.7 Hz), 131.0 (d, J = 13.3 Hz), 130.9

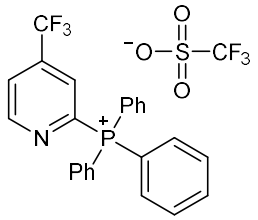
(d, J = 82.7 Hz), 130.2 (d, J = 7.4 Hz), 120.6 (q, J = 319.6 Hz), 114.4 (d, J = 89.5 Hz), 113.6 (d, J = 5.1 Hz), 111.8.

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



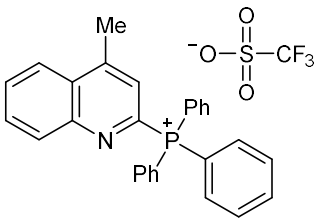
Prepared according to our previous report.[5] ^{1}H NMR (400 MHz, CDCl3) δ: 9.10 (1H, dd, *J* = 4.9, 1.2 Hz), 8.83 (1H, dd, *J* = 5.5, 1.1 Hz), 7.92-7.44 (15H, m), 7.02-6.92 (1H, m), 6.84-6.73 (2H, m), 6.70 (1H, d, *J* = 8.9 Hz); ^{13}C NMR (100 MHz, CDCl3) δ: 162.6 (d, *J* = 247.8 Hz), 152.8, 147.3, 140.1, 137.6 (d, *J* = 7.9 Hz), 135.6, 130.3 (d, *J* = 8.4 Hz), 129.0, 128.7, 127.9, 125.4 (d, *J* = 3.1 Hz), 116.7 (d, *J*, 22.5 Hz), 116.0 (d, *J* = 21.0 Hz), 115.1.

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



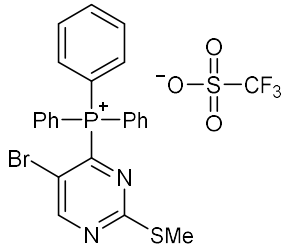
Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, CDCl3) δ: 9.33 (1H, d, *J* = 2.8 Hz), 8.02 (1H, m), 7.92 (3H, m), 7.82–7.69 (13H, m); ^{13}C NMR (100 MHz, CDCl3) δ: 154.2 (d, *J* = 19.9 Hz), 147.0 (d, *J* = 121.0 Hz), 139.9 (qd, *J* = 35.8 Hz, 11.3 Hz), 136.0 (d, *J* = 2.9 Hz), 134.5 (d, *J* = 10.2 Hz), 130.7 (d, *J* = 13.1 Hz), 126.1 (dq, *J* = 25.9, 3.6 Hz), 124.4 (m), 121.5 (qd, *J* = 274.1, 3.0 Hz), 120.7 (q, *J* = 320.5 Hz), 115.9 (d, *J* = 90.0 Hz). The spectroscopic data is in agreement with our reported synthesis.[2]

(4-Methylquinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate



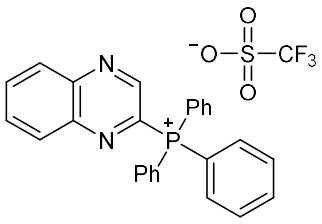
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22-8.12 (2H, m), 7.94-7.65 (17H, m), 7.53, (1H, d, *J* = 4.6 Hz), 2.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.5 (d, *J* = 10.6 Hz), 148.5 (d, *J* = 22.6 Hz), 144.4 (d, *J* = 117.2 Hz), 135.6 (d, *J* = 3.1 Hz), 134.6 (d, *J* = 10.1 Hz), 131.6, 130.6 (d, *J* = 1.2 Hz), 130.5 (d, *J* = 12.9 Hz), 130.4, 128.8, 125.1 (d, *J* = 26.4 Hz), 124.4 (d, *J* = 1.3 Hz), 120.8 (q, *J* = 321.2 Hz), 117.3 (d, *J* = 88.2 Hz), 19.2 (d, *J* = 1.5 Hz).

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



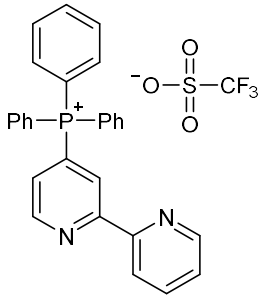
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, d, *J* = 7.9 Hz), 7.97-7.85 (3H, m), 7.83-7.66 (12H, m), 2.15 (3H, s); ^{13}C NMR (100 MHz, CDCl3) δ: 173.9 (d, *J* = 17.2 Hz), 162.0 (d, *J* = 4.1 Hz), 151.4 (d, *J* = 118.7 Hz), 136.1 (d, *J* = 3.1 Hz), 134.8 (d, *J* = 10.4 Hz), 130.7 (d, *J* = 13.3 Hz), 120.9 (q, *J* = 321.2 Hz), 120.9 (d, *J* = 17.1 Hz), 115.0 (d, *J* = 89.9 Hz), 14.4.

Triphenyl(quinoxalin-2-yl)phosphonium trifluoromethanesulfonate



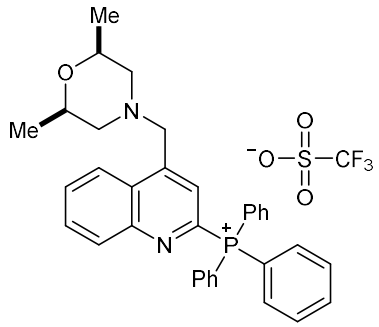
Prepared according to our previous report.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, s), 8.27-8.22 (2H, m), 8.09-8.01 (2H, m), 7.93-7.90 (3H, m), 7.79-7.72 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.9 (d, *J* = 25.4 Hz), 143.4 (d, *J* = 2.8 Hz), 142.7 (d, *J* = 17.3 Hz), 140.8 (d, *J* = 111.6 Hz), 136.2 (d, *J* = 3.1 Hz), 135.0, 134.7 (d, *J* = 10.5 Hz), 133.1, 130.9 (d, *J* = 13.0 Hz), 130.2 (d, *J* = 2.0 Hz), 129.9 (d, *J* = 2.3 Hz), 120.8 (q, *J* = 319.5 Hz), 116.0 (d, *J* = 88.1 Hz).

[2,2'-Bipyridin]-4-yltriphenylphosphonium trifluoromethanesulfonate



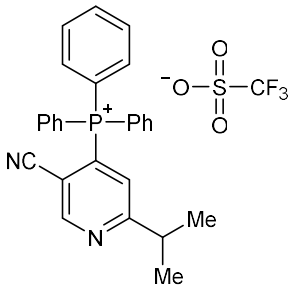
Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.06 (1H, app t, *J* = 5.1 Hz), 8.65 (1H, d, *J* = 13.8 Hz), 8.55 (1H, d, *J* = 4.4 Hz), 8.46 (1H, d, *J* = 7.9 Hz), 7.96-7.88 (3H, m), 7.87-7.74 (7H, m), 7.72-7.55 (7H, m), 7.35 (1H, dd, *J* = 7.7, 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8 (d, *J* = 9.9 Hz), 153.4 (d, *J* = 2.3 Hz), 151.4 (d, *J* = 10.7 Hz), 149.3, 137.3, 136.2 (d, *J* = 3.1 Hz), 134.4 (d, *J* = 9.9 Hz), 131.0 (d, *J* = 13.0 Hz), 129.3 (d, *J* = 83.9 Hz), 126.9 (d, *J* = 8.4 Hz), 125.1, 123.9 (d, *J* = 9.2 Hz), 121.7, 120.8 (q, *J* = 321.2 Hz), 115.8 (d, *J* = 89.3 Hz).

(4-(((2R,6S)-2,6-Dimethylmorpholino)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate



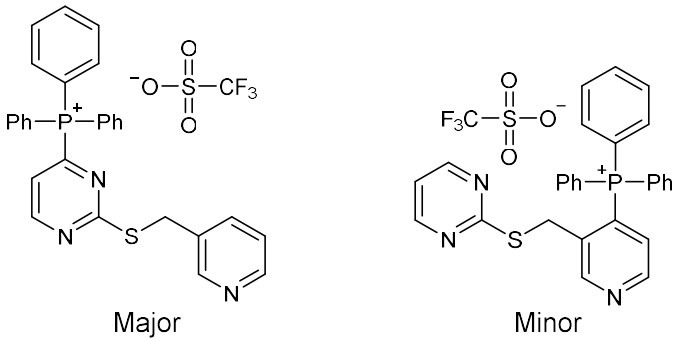
Prepared according to general procedure B (except the reaction was cooled to -50 ºC for the Tf_2O addition, then cooled to -78 ºC for the DBU addition) using (2R,6S)-2,6-dimethyl-4-(quinolin-4-ylmethyl)morpholine (558 mg, 2.18 mmol), PPh_3 (629.3 mg, 2.39 mmol), Tf_2O (340 µL, 2.18 mmol), DBU (325 µL, 2.18 mmol) and CH_2Cl_2 (22 mL). After the purification procedure, the title compound was isolated as a white solid (994 mg, 1.49 mmol, 68% yield). mp 188-195 ºC; IR ν_{max}/cm^{-1} (film): 3072, 2972, 2937, 2825, 1576, 1439, 1267, 1144, 1110, 1027, 727, 633; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.26 (2H, dd, *J* = 8.4, 16.5 Hz), 7.96-7.70 (18H, m), 4.02 (2H, s), 3.50-3.38 (2H, m), 2.60 (2H, d, *J* = 10.7 Hz), 1.92 (2H, t, *J* = 10.5 Hz), 1.10 (6H, d, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.0 (d, *J* = 22.2 Hz), 148.2 (d, *J* = 10.1 Hz), 144.7 (d, *J* = 117.6 Hz), 135.7 (d, *J* = 3.0 Hz), 134.7 (d, *J* = 10.0 Hz), 131.7, 130.9, 130.6, 130.6 (d, *J* = 12.9 Hz), 127.9 (d, *J* = 3.1 Hz), 124.0, 123.6 (d, *J* = 27.4 Hz), 120.9 (q, *J* = 321.1 Hz), 117.4 (d, *J* = 88.2 Hz), 71.6, 59.3, 58.1, 18.9 ; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.09; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 14.47; *m/z* LRMS (ESI + APCI) found 517.3 $[M\text{-}OTf]^+$, $C_{34}H_{34}N_2OP^+$ requires 517.2.

(5-Cyano-2-isopropylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 6-isopropylnicotinonitrile (438.6 mg, 3.0 mmol), Tf_2O (500 µL, 3.0 mmol), PPh_3 (866 mg, 3.3 mmol), DBU (450 µL, 3.0 mmol) and CH_2Cl_2 (30 mL). After the purification procedure, the title compound was isolated as an off-white solid (1.02 g, 1.83 mmol, 61% yield). mp 59-66 °C; IR ν_{max}/cm^{-1} (film): 3063, 2970, 2933, 2873, 2228, 1571, 1481, 1439, 1259, 1147, 1106, 1029; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.10 (1H, d, *J* = 5.8 Hz), 7.96-7.90 (3H, m), 7.86-7.73 (12H, m), 7.34 (1H, d, *J* = 15.3 Hz), 3.20 (1H, sp, *J* = 6.9 Hz), 1.27 (6H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5 (d, *J* = 8.9 Hz), 154.8 (d, *J* = 6.1 Hz), 136.3 (d, *J* = 3.0 Hz), 134.6 (d, *J* = 10.8 Hz), 131.0 (d, *J* = 82.5 Hz), 131.0 (d, *J* = 13.4 Hz), 127.6 (d, *J* = 7.5 Hz), 120.6 (q, *J* = 321.2 Hz), 114.4 (d, *J* = 89.8 Hz), 113.9 (d, *J* = 5.2 Hz), 108.9 (d, *J* = 3.7 Hz), 36.9, 21.5; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.22; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.07; *m/z* LRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 407.2, $C_{27}H_{24}N_2P^+$ requires 407.2.

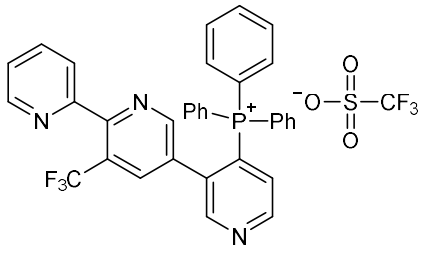
Triphenyl(2-((pyridin-3-ylmethyl)thio)pyrimidin-4-yl)phosphonium trifluoromethanesulfonate



>20:1 Mixture of Regioisomers

Prepared according to our previous report.[7] Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.04 (1H, dd, *J* = 7.6, 5.0 Hz), 8.54-8.35 (2H, m), 8.03-7.57 (17H, m), 7.34-7.11 (1H, m), 4.29 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7 (d, *J* = 17.6 Hz), 160.6 (d, *J* = 7.4 Hz), 154.6 (d, *J* = 111.5 Hz), 149.6, 148.6, 136.2, 136.1 (d, *J* = 2.9 Hz), 134.6 (d, *J* = 10.3 Hz), 132.2, 130.7 (d, *J* = 13.1 Hz), 123.4, 123.1 (d, *J* = 20.3 Hz), 120.7 (q, *J* = 321.1 Hz), 114.9 (d, *J* = 88.9 Hz), 32.5.

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

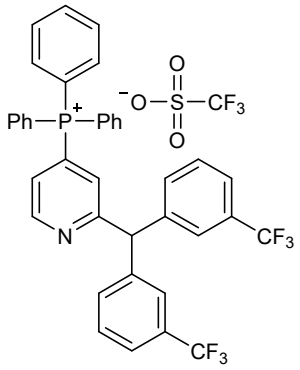


13.4:1:1 Mixture of Regioisomers

Prepared according to our previous report.[3] Major Isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.08 (1H, app t, *J* = 4.7 Hz), 8.79 (1H, d, *J* = 6.8 Hz), 8.70 (1H, d, *J* = 4.7 Hz), 8.27 (1H, d, *J* = 1.7 Hz), 7.87-7.58 (18H, m), 7.55 (1H, d, *J* = 7.8 Hz), 7.39 (1H, dd, *J* = 7.8, 4.7 Hz); Major Isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ:

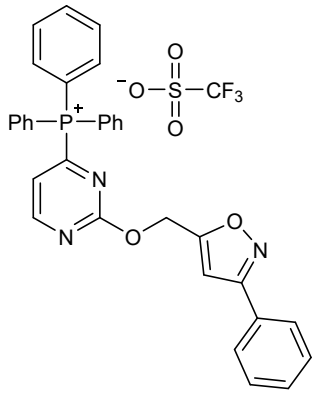
156.1, 155.3, 153.1 (d, J = 7.3 Hz), 151.3 (d, J = 9.9 Hz), 151.0, 150.6, 148.8, 136.4, 136.2-136.1(m), 135.7 (d, J = 6.5 Hz), 135.7 (d, J = 2.8 Hz), 134.2 (d, J = 10.3 Hz), 130.7 (d, J = 13.0 Hz), 128.7 (d, J = 9.0 Hz), 127.5 (d, J = 83.1 Hz), 123.9 (q, J = 33.8 Hz), 123.8, 123.4, 122.2 (q, J = 273.7 Hz), 120.6 (q, J = 321.3 Hz), 116.2 (d, J = 88.6 Hz).

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



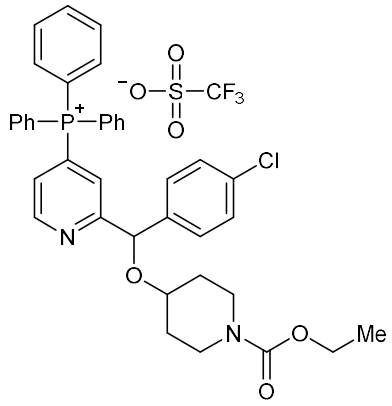
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, app t, J = 5.1 Hz), 7.91-7.80 (3H, m), 7.78-7.66 (6H, m), 7.63-7.37 (15H, m), 7.29 (1H, d, J = 13.8 Hz), 5.97 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0 (d, J = 9.8 Hz), 151.6 (d, J = 10.4 Hz), 141.7, 136.1 (d, J = 3.1 Hz), 134.3 (d, J = 10.5 Hz), 132.9 (d, J = 1.1 Hz), 130.9 (d, J = 13.1 Hz), 130.7 (q, J = 32.2 Hz), 130.0, 129.6 (d, J = 83.7 Hz), 127.0 (d, J = 8.7 Hz), 125.7-125.4 (2C, m), 124.0 (q, J = 3.8 Hz), 123.8 (q, J = 272.5 Hz), 120.8 (q, J = 321.2 Hz), 115.4 (d, J = 89.5 Hz), 57.8.

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



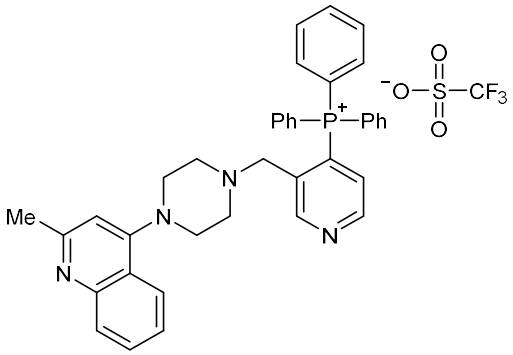
Prepared according to general procedure B (except the reaction was cooled to -50 ºC for the Tf_2O addition, then cooled to -78 ºC for the DBU addition and EtOAc was used instead of CH_2Cl_2) using 3-phenyl-5-((pyrimidin-2-yloxy)methyl)isoxazole (253.3 mg, 3.0 mmol), PPh_3 (865.6 mg, 3.3 mmol), Tf_2O (0.50 mL, 3.0 mmol), DBU (0.45 mL, 3.0 mmol) and EtOAc (15 mL). After the purification procedure, the title compound was isolated as an off-white solid (798.6 mg, 1.20 mmol, 40% yield). mp 49-55 ºC; IR ν_{max}/cm^{-1} (film): 3500, 3064, 2162, 1980, 1613, 1587, 1547, 1439, 1352, 1259, 1223, 1149, 1109, 1029, 688, 635, 529; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.10 (1H, t, *J* = 6.8 Hz), 7.90-7.83 (3H, m), 7.82-7.67 (15H, m), 7.49-7.43 (3H, m), 6.69 (1H, s), 5.58 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.6, 164.4 (d, *J* = 19.5 Hz), 163.8 (d, *J* = 8.4 Hz), 162.5, 156.0 (d, *J* = 112.4 Hz), 136.1 (d, *J* = 3.0 Hz), 134.7 (d, *J* = 10.4 Hz), 130.7 (d, *J* = 13.1 Hz), 130.2, 128.9, 128.4, 126.8, 122.5 (d, *J* = 20.2 Hz), 120.7 (q, *J* = 320.2 Hz), 115.1 (d, *J* = 89.1 Hz), 102.4, 60.6; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.36; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 513.2, $C_{33}H_{26}N_2O_2P^+$ requires 513.2.

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



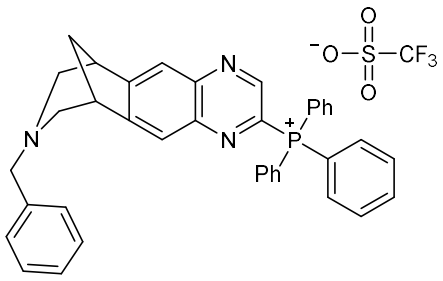
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_{3}$) δ: 8.90 (1H, t, *J* = 5.1 Hz), 7.94-7.86 (3H, m), 7.82-7.73 (6H, m), 7.71-7.59 (7H, m), 7.49 (1H, ddd, *J* = 12.6, 5.0, 1.1 Hz), 7.34-7.25 (4H, m), 5.71 (1H, s), 4.11 (2H, q, *J* = 7.1 Hz), 3.70-3.60 (1H, m), 3.55-3.42 (2H, m), 3.25-3.12 (2H, m), 1.79-1.56 (2H, m), 1.54-1.37 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_{3}$) δ: 164.4 (d, *J* = 9.6 Hz), 155.4, 151.1 (d, *J* =10.5 Hz), 138.7, 136.2 (d, *J* = 3.1 Hz), 134.5 (d, *J* = 10.5 Hz), 134.0, 131.0 (d, *J* = 13.1 Hz), 129.3 (d, *J* = 84.1 Hz), 128.8, 128.5, 125.9 (d, *J* = 8.4 Hz), 123.9 (d, *J* = 9.1 Hz), 120.8 (q, *J* = 321.2 Hz), 115.8 (d, *J* = 89.4 Hz), 79.9, 72.8, 61.3, 40.7 (rot), 40.7, 31.3, 30.4 (rot), 14.7.

(3-((4-(2-Methylquinolin-4-yl)piperazin-1-yl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 (1H, d, *J* = 6.8 Hz), 8.84 (1H, app t, *J* = 4.6 Hz), 7.91-7.70 (17H, m), 7.54 (1H, dd, *J* = 7.4, 7.8 Hz), 7.33 (1H, dd, *J* = 7.6, 7.5 Hz), 7.20 (1H, dd, *J* = 5.0, 15.6 Hz), 6.59 (1H, s), 3.26 (2H, s), 2.81 (4H, s), 2.62 (3H, s), 2.16 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 156.4, 153.5 (d, *J* = 8.3 Hz), 150.8 (d, *J* = 10.6 Hz), 148.4, 137.0 (d, *J* = 5.7 Hz), 135.7 (d, *J* = 2.9 Hz), 134.0 (d, *J* = 10.2 Hz), 131.0 (d, *J* = 13.0 Hz), 129.3, 129.1 (d, *J* = 9.8 Hz), 128.5, 126.7 (d, *J* = 81.7 Hz), 124.6, 123.2, 121.3, 120.8 (q, *J* = 319.4 Hz), 117.0 (d, *J* = 88.9 Hz), 109.2, 59.1 (d, *J* = 3.3 Hz), 52.7, 51.2, 25.1.

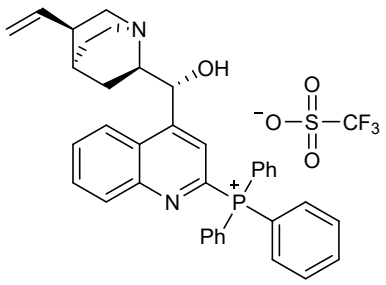
((6R,10S)-8-Benzyl-7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxalin-2-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, s), 8.10-7.72 (17H, m), 7.20-7.05 (3H, m), 6.92-6.80 (2H, m), 3.55-3.27 (4H, m), 3.03-2.87 (2H, m), 2.66-2.42 (2H, m), 2.29-

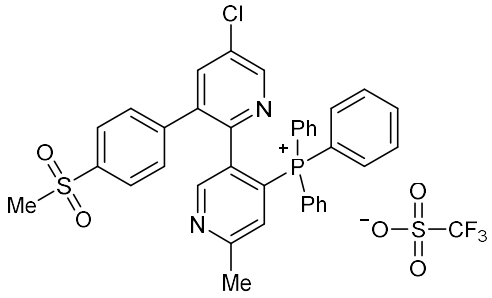
2.15 (1H, m), 1.87 (1H, d, J = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 144.9 (d, J = 23.5 Hz), 144.2, 143.5 (d, J = 16.9 Hz), 137.5 (br s), 136.0 (d, J = 2.9 Hz), 134.6 (d, J = 10.9 Hz), 130.7 (d, J = 13.0 Hz), 129.2-126.2 (3C, m,), 120.7 (br s), 120.7 (q, J = 321.5 Hz), 116.4 (d, J = 88.3 Hz), 61.3, 57.9-56.1 (2C, m), 43.1-40.4 (3C, m).

(4-((R)-(Benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate



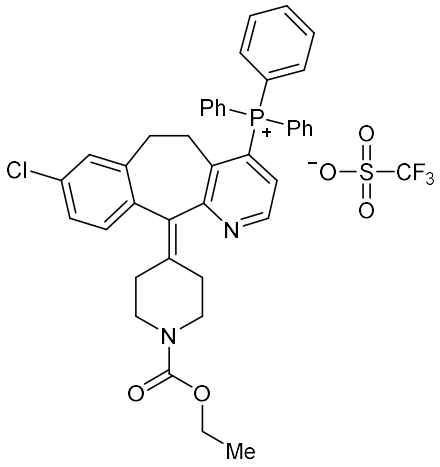
Prepared according to our previous report.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, J = 8.1 Hz), 8.26 (1H, d, J = 8.6 Hz), 7.94 (1H, t, J = 7.2 Hz), 7.91-7.60 (17H, m), 7.29-7.02 (3H, m), 7.14-7.02 (2H, m), 5.83-5.45 (2H, m), 5.07-4.89 (2H, m), 4.60 (1H, d, J = 11.4 Hz), 4.33 (1H, d, J = 11.4 Hz), 3.52-3.06 (3H, m), 2.84-2.62 (2H, m), 2.49-2.33 (1H, br s), 2.06-1.47 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.2 (d, J = 22.1 Hz), 148.5, 145.1, 143.9, 139.5, 136.6, 135.7 (d, J = 3.0 Hz), 134.5 (d, J = 10.0 Hz), 132.0-131.8 (3C, m), 131.2, 130.4 (d, J = 13.2 Hz), 128.4, 127.9, 127.2, 126.7 (d, J = 3.1 Hz), 126.1, 123.8, 120.6 (q, J = 320.3 Hz), 117.0 (d, J = 87.7 Hz), 115.6, 71.8, 60.7, 55.6, 43.0, 38.3, 26.9, 25.8.

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



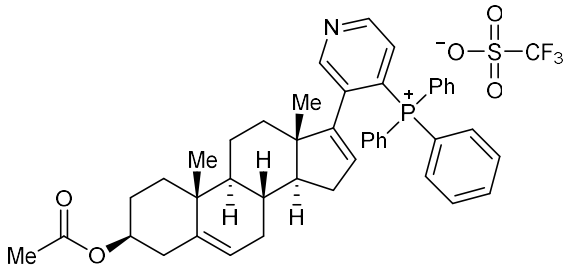
Prepared according to our previous report.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, d, *J* = 7.1 Hz), 8.10 (2H, d, *J* = 8.2 Hz), 7.86-7.62 (16H, m), 7.51-7.45 (3H, m), 7.20 (1H, d, *J* = 16.5 Hz), 3.14 (3H, s), 2.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.8 (d, *J* = 11.2 Hz), 152.4 (d, *J* = 7.3 Hz), 147.5 (d, *J* = 2.2 Hz), 146.1, 141.5, 141.0, 138.9, 135.6, 134.8 (d, *J* = 2.9 Hz), 134.1 (d, *J* = 10.0 Hz), 133.3 (d, *J* = 3.6 Hz), 132.1, 130.8 (d, *J* = 10.2 Hz), 130.0 (d, *J* = 13.1 Hz), 129.8, 128.5, 128.2 (d, *J* = 86.2 Hz), 120.8 (q, *J* = 321.1 Hz), 119.3 (d, *J* = 91.8 Hz), 43.9, 24.6. The spectroscopic data is in agreement with our reported synthesis.[6]

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



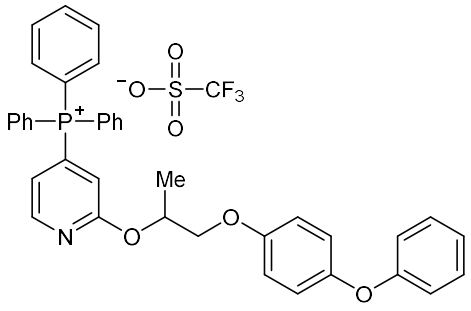
Prepared according to our previous report.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, app t, *J* = 5.0 Hz), 7.97-7.87 (3H, m), 7.86-7.74 (6H, m), 7.73-7.60 (6H, m), 7.16-7.01 (3H, m), 6.71 (1H, s), 4.14 (2H, q, *J* = 7.0 Hz), 3.84-3.61 (2H, m), 3.45- 3.20 (3H, m), 2.75 (1H, dt, *J* = 17.4, 4.7 Hz), 2.58 (1H, dt, *J* = 14.9, 4.7 Hz), 2.53-2.30 (3H, m), 2.26-2.09 (1H, m), 1.60-1.43 (1H, m), 1.25 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6 (d, *J* = 8.3 Hz), 155.4, 149.1 (d, *J* = 11.4 Hz), 139.2, 136.8, 136.7 (d, *J* = 6.8 Hz), 136.0 (d, *J* = 3.1 Hz), 134.2 (d, *J* = 10.7 Hz), 133.9, 133.6, 132.4, 131.6, 131.1 (d, *J* = 13.0 Hz), 129.9, 127.2 (d, *J* = 10.0 Hz), 127.0 (d, *J* = 82.2 Hz), 126.4, 120.8 (q, *J* = 321.3 Hz), 116.4 (d, *J* = 88.5 Hz), 61.4, 44.6, 44.4, 30.7, 30.4, 30.4, 29.4, 14.6. The spectroscopic data is in agreement with our reported synthesis.[2]

(3-((3S,8R,9S,10R,13S,14S)-3-Acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



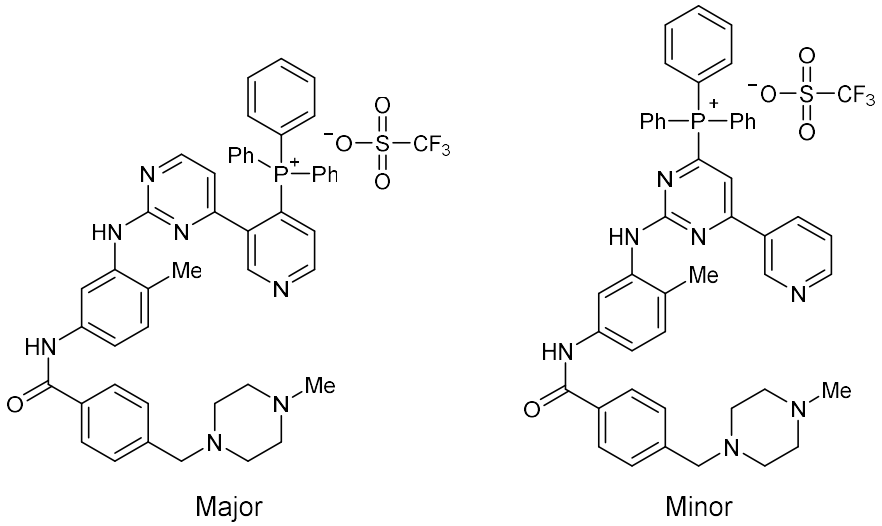
Prepared according to our previous report.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, d, *J* = 7.2 Hz), 8.72 (1H, app t, *J* = 4.1 Hz), 7.88-7.59 (15H, m), 7.27 (1H, dd, *J* = 15.7, 5.2 Hz), 5.55 (1H, s), 5.28 (1H, d, *J* = 3.4 Hz), 4.58 (1H, m), 2.33-2.18 (2H, m), 1.99 (3H, s), 1.87-1.30 (10H, m), 1.24-1.01 (5H, m), 0.94 (3H, s), 0.79 (1H, td, *J* = 12.1, 3.7 Hz), 0.57 (1H, td, *J* = 11.2, 3.9 Hz), –0.22 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.4, 150.6 (d, *J* = 7.5 Hz), 149.0 (d, *J* = 4.2 Hz), 148.7 (d, *J* = 10.8 Hz), 139.9, 139.1, 137.4 (d, *J* = 6.1 Hz), 135.5 (d, *J* = 2.9 Hz), 134.2 (d, *J* = 9.9 Hz), 130.8 (d, *J* = 13.0 Hz), 130.0 (d, *J* = 10.5 Hz), 125.2 (d, *J* = 83.7 Hz), 121.6, 120.7 (q, *J* = 321.2 Hz), 118.0 (d, *J* = 89.6 Hz), 73.5, 55.3, 49.7, 48.7, 37.9, 36.8, 36.4, 33.5, 32.4, 31.0, 29.7, 27.5, 21.3, 20.3, 19.0, 18.6. The spectroscopic data is in agreement with our reported synthesis.[6]

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



Prepared according to our previous report.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, app t, *J* = 5.3 Hz), 7.93-7.87 (3H, m), 7.82-7.74 (6H, m), 7.67-7.59 (6H, m), 7.30-7.23 (2H, m), 7.13 (1H, ddd, *J* = 11.7, 5.3, 1.2 Hz), 7.02 (1H, t, *J* = 7.4 Hz), 6.94-6.77 (7H, m), 5.66 (1H, sext, *J* = 5.3 Hz), 4.18-4.07 (2H, m), 1.48 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7 (d, *J* = 15.9 Hz), 158.1, 154.7, 150.3, 149.8 (d, *J* = 12.1 Hz), 136.1 (d, *J* = 3.0 Hz), 134.3 (d, *J* = 10.6 Hz), 130.9 (d, *J* = 13.0 Hz), 130.8 (d, *J* = 84.2 Hz), 129.5, 122.4, 120.8 (q, *J* = 321.2 Hz), 120.6, 119.1 (d, *J* = 8.1 Hz), 117.5, 116.6 (d, *J* = 10.0 Hz), 115.6 (d, *J* = 89.4 Hz), 115.6, 71.5, 70.5, 16.4.

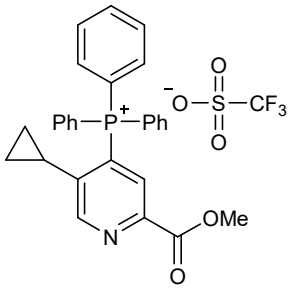
(3-(2-((2-Methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



20:1 Mixture of Regioisomers

Prepared according to our previous report.[6] Major isomer, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.14 (1H, s), 9.55 (1H, d, *J* = 6.7 Hz), 9.09 (1H, app t, *J* = 4.6 Hz), 8.31 (1H, d, *J* = 5.1 Hz), 8.00-7.55 (18H, m), 7.52-7.20 (5H, m), 7.08 (1H, d, *J* = 8.3 Hz), 6.10 (1H, br), 3.55 (2H, s), 2.70-2.13 (11H, m), 1.74 (3H, s); Major isomer, ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.2, 159.8, 159.7 (d, *J* = 2.0 Hz), 158.3, 152.7 (d, *J* = 11.4 Hz), 151.8 (d, *J* = 6.8 Hz), 141.1 (br), 137.3, 136.2, 135.8 (d, *J* = 3.8 Hz), 134.7 (d, *J* = 2.3 Hz), 133.9 (d, *J* = 10.0 Hz), 130.8 (d, *J* = 10.2 Hz), 130.0, 129.9 (d, *J* = 13.4 Hz), 128.7, 127.7, 125.6 (d, *J* = 86.2 Hz), 125.5, 120.7 (q, *J* = 322.8 Hz), 119.5 (d, *J* = 92.3 Hz), 117.0, 117.0, 115.6, 110.3, 60.6, 53.2, 50.1, 43.1, 17.0. The spectroscopic data is in agreement with our reported synthesis.[6]

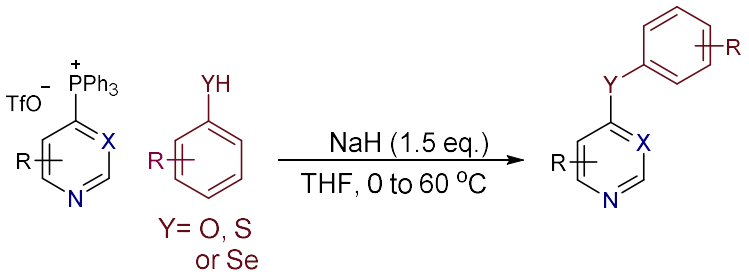
(5-Cyclopropyl-2-(methoxycarbonyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (3bu)



Prepared according to general procedure A (except the reaction was cooled to -50 ºC for the PPh_3 addition) using methyl 5-cyclopropylpicolinate (200 mg, 1.12 mmol), Tf_2O (190 µL, 1.12 mmol), PPh_3 (323 mg, 1.23 mmol), DBU (170 µL, 1.12 mmol) and CH_2Cl_2 (11.2 mL). After the purification procedure, the title compound (3bu) was isolated as a white solid (276 mg, 0.469 mmol, 42% yield). mp: 173-200 °C; IR ν_{max}/cm^{-1} (film): 3069, 2953, 1745, 1577, 1439, 1263, 1133, 1030, 721, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.47 (1H, d, *J* = 6.4 Hz), 7.96-7.88 (3H, m), 7.87-7.78 (6H, m), 7.78-7.68 (7H, m), 3.94 (3H, s), 1.44 (1H, sp, *J* = 4.7 Hz), 1.08-1.00 (2H, m), 0.92-0.84 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.9 (d, *J* = 2.4 Hz), 147.8 (d, *J* = 6.3 Hz), 146.9 (d, *J* = 7.6 Hz), 146.4 (d, *J* = 10.7 Hz), 136.2 (d, *J* = 3.0 Hz), 134.2 (d, *J* = 10.6 Hz), 131.2 (d, *J* = 13.2 Hz), 129.0 (d, *J* = 11.1 Hz), 127.5 (d, *J* = 84.2 Hz), 120.8 (q, *J* = 321.1 Hz), 115.9 (d, *J* = 89.0 Hz), 53.3, 16.4 (d, *J* = 6.5 Hz), 13.9; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.15; *m/z* LRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 438.2, $C_{28}H_{25}NO_2P^+$ requires 438.2.

Preparation of Derivatized Azaarenes:

General Procedure C:



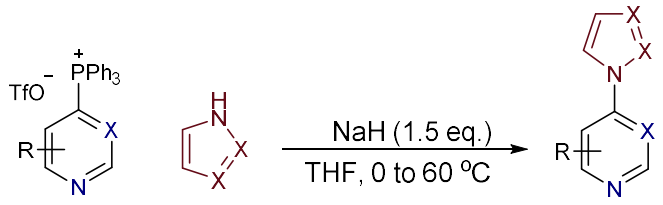
An oven dried 8 mL vial equipped with a septa cap was charged with sodium hydride (60% dispersion in mineral oil, 1.5 equiv) and placed under a nitrogen atmosphere. THF (0.5 M) was added and the suspension was cooled to 0 ºC while stirring. The phenol or thiophenol (1.5 equiv) was added dropwise over 5 min and allowed to stir for 30 min at 0 ºC. The septa cap was briefly removed and the phosphonium salt (1.0 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was warmed to 60 ºC and stirred for 2 h. The reaction was quenched with H_2O, the aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl ether/thioether.

Notes.

1) If the phenol/thiophenol was a solid or viscous liquid, it was added dropwise as a 1.5 M solution to an equivalent volume 1.5 M solution of NaH in THF.
2) Certain substrates required longer reaction times. Specific cases are indicated below.
3) Certain substrates showed improved yields when ran in DME at 80 ºC. Specific cases are indicated below.

4) Certain substrates showed improved yields with the addition of 15-crown-5 right before the salt addition. Specific cases are indicated below (Phenol nucleophiles typically require this addition for tolerable yields).

General Procedure D:



An oven dried 8 mL vial equipped with a septa cap was charged with sodium hydride (60% dispersion in mineral oil, 1.5 equiv) and placed under a nitrogen atmosphere. THF (0.5 M) was added and the suspension was cooled to 0 ºC while stirring. The pyrrole/pyrazole/imidazole (1.5 equiv) was added dropwise over 5 min and allowed to stir for 30 min at 0 ºC. The septa cap was briefly removed and the phosphonium salt (1.0 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was warmed to 60 ºC and stirred for 1 h. The reaction was quenched with H_2O, the aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the coupled azaarene product.

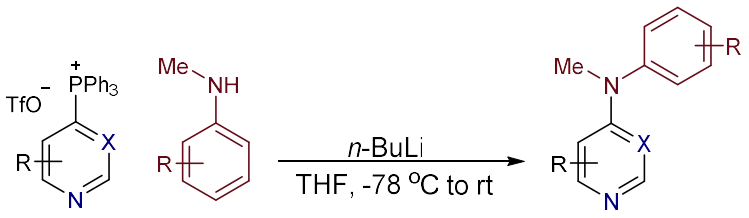
Notes.

1) If the pyrrole/pyrazole/imidazole was a solid or viscous liquid, it was added dropwise as a 1.5 M solution to an equivalent volume 1.5 M solution of NaH in THF.
2) Certain substrates required longer reaction times. Specific cases are indicated below.
3) Certain substrates showed improved yields when ran in DME at 80 ºC. Specific cases are indicated below.

4) Certain substrates showed improved yields with the addition of 15-crown-5 right before the salt addition. Specific cases are indicated below.

5) Certain substrates showed improved yields when KH was used as the base in place of NaH. Specific cases are indicated below.

General Procedure E:

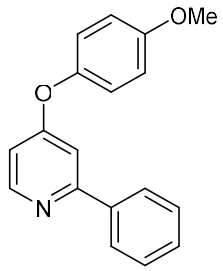


An oven dried 8 mL vial equipped with a septa cap was charged with the aniline (1.5 equiv) and placed under a nitrogen atmosphere. THF (0.25 M) was added and the suspension was cooled to -78 ºC while stirring. *n*-BuLi (1.5 equiv) was added dropwise over 5 min and allowed to stir for 30 min at -78 ºC. The reaction was then allowed to warm to room temp before the septa cap was briefly removed and the phosphonium salt (1.0 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and stirred for 30 min at room temp. The reaction was quenched with H_2O, the aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl ether/thioether.

Notes.

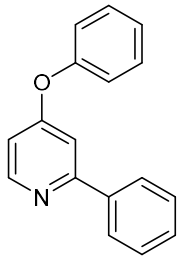
1) Certain substrates required longer reaction times. Specific cases are indicated below.

4-(4-Methoxyphenoxy)-2-phenylpyridine (3b)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-methoxyphenol (93 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.5 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3b) as a clear oil (107 mg, 0.39 mmol, 77% yield). IR ν_{max}/cm^{-1} (film): 3066, 3002, 2947, 2842, 2214, 2042, 1612, 1564, 1499, 1470, 1259, 1208, 1112, 908, 728; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, d, *J* = 5.6 Hz), 7.94-7.88 (2H, m), 7.48-7.37 (3H, m), 7.23 (1H, d, *J* = 2.3 Hz), 7.10-7.04 (2H, m), 6.99-6.93 (2H, m), 6.74 (1H, dd, *J* = 5.7, 2.4 Hz), 3.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3, 159.5, 157.1, 151.1, 147.4, 139.2, 129.1, 128.7, 126.9, 122.0, 115.2, 110.2, 108.5, 55.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 278.1, $C_{18}H_{16}NO_2^+$ requires 278.1.

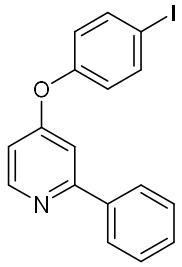
4-Phenoxy-2-phenylpyridine (3a)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), phenol (71 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-

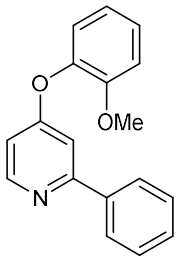
yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 4% EtOAc & 1% AcOH in hexanes) afforded the *title compound* (3a) as a yellow amorphous solid (87 mg, 0.35 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 3062, 2923, 2851, 2215, 1721, 1579, 1562, 1489, 1470, 1305, 1214, 912, 774, 731, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, *J* = 5.6 Hz), 7.95-7.88 (2H, m), 7.49-7.38 (5H, m), 7.30-7.24 (2H, m), 7.17-7.12 (2H, m), 6.78 (1H, dd, *J* = 5.6, 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.6, 159.7, 154.2, 151.2, 139.1, 130.2, 129.1, 128.7, 126.9, 125.3, 120.7, 110.7, 109.1 ; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 248.1, $C_{17}H_{14}NO^+$ requires 248.1.

4-(4-Iodophenoxy)-2-phenylpyridine (3d)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-iodophenol (165 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3d) as a pink solid (112 mg, 0.30 mmol, 60% yield). mp: 50-57 °C; IR ν_{max}/cm^{-1} (film): 3084, 3045, 2925, 2503, 2208, 1879, 1594, 1556, 1477, 1408, 1214, 1023, 844, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.56 (1H, d, *J* = 5.6 Hz), 7.95-7.89 (2H, m), 7.77-7.71 (2H, m), 7.50-7.38 (3H, m), 7.27 (1H, d, *J* = 2.3 Hz), 6.94-6.88 (2H, m), 6.78 (1H, dd, *J* = 5.6, 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.0, 159.8, 154.3, 151.3, 139.2, 138.9, 129.3, 128.7, 126.9, 122.8, 110.8, 109.2, 88.8; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 374.0, $C_{17}H_{13}INO^+$ requires 374.0.

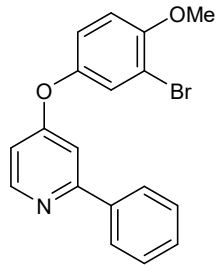
4-(2-Methoxyphenoxy)-2-phenylpyridine (3c)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 2-methoxyphenol (82 μL, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and DME (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3c) as a clear oil (79 mg, 0.28 mmol, 57% yield). IR ν_{max}/cm^{-1} (film): 3066, 3008, 2927, 2839, 2214, 2043, 1580, 1563, 1498, 1470, 1258, 1208, 1112, 907, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, d, *J* = 5.7 Hz), 7.94-7.88 (2H, m), 7.48-7.37 (3H, m), 7.30-7.22 (2H, m), 7.14 (1H, dd, *J* = 7.9, 1.6 Hz), 7.08-6.99 (2H, m), 6.70 (1H, dd, *J* = 5.7, 2.4 Hz), 3.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$)

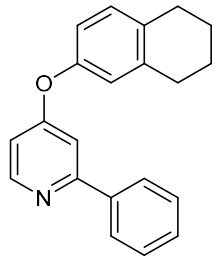
δ: 165.7, 159.4, 151.7, 150.9, 142.2, 139.3, 129.0, 128.6, 126.9, 126.7, 122.7, 121.3, 113.0, 109.6, 108.2, 55.9; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 278.2, $C_{18}H_{16}NO_2^+$ requires 278.1.

4-(3-Bromo-4-methoxyphenoxy)-2-phenylpyridine (3e)



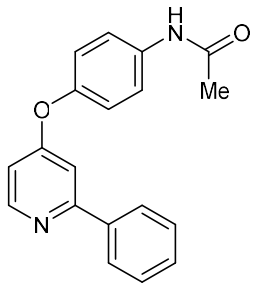
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 3-bromo-4-methoxyphenol (152 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and DME (1.0 mL). Flash column chromatography (basic alumina: 20% EtOAc in hexanes) afforded the *title compound* (3e) as a white solid (92 mg, 0.26 mmol, 52% yield). mp: 88-95 °C; IR ν_{max}/cm^{-1} (film): 3061, 2979, 2947, 2846, 2497, 2161, 2042, 1848, 1584, 1561, 1486, 1468, 1437, 1409, 1257, 1205, 1043, 875, 776, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, *J* = 5.6 Hz), 7.98-7.88 (2H, m), 7.50-7.36 (4H, m), 7.24 (1H, d, *J* = 2.3 Hz), 7.08 (1H, dd, *J* = 8.9, 2.9 Hz), 6.95 (1H, d, *J* = 9.0 Hz), 6.75 (1H, dd, *J* = 5.6, 2.3 Hz), 3.93 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.8, 159.7, 153.7, 151.2, 147.6, 139.0, 129.2, 128.7, 127.0, 126.2, 120.8, 112.5, 112.2, 110.2, 108.6, 56.7 ; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 356.1, $C_{18}H_{15}BrNO_2^+$ requires 356.0.

2-Phenyl-4-((5,6,7,8-tetrahydronaphthalen-2-yl)oxy)pyridine (3f)



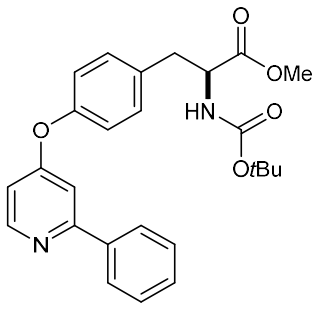
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 5,6,7,8-tetrahydronaphthalen-2-ol (111.2 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (basic alumina: 2% EtOAc in hexanes) afforded the *title compound* (3f) as a white solid (122 mg, 0.41 mmol, 81% yield). mp: 57-61 °C; IR ν_{max}/cm^{-1} (film): 3061, 2925, 2835, 2162, 1579, 1561, 1492, 1469, 1238, 1195, 865, 773, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, d, *J* = 5.7 Hz), 7.94-7.89 (2H, m), 7.49-7.37 (3H, m), 7.27 (1H, d, *J* = 2.3 Hz), 7.11 (1H, d, *J* = 8.2 Hz), 6.88-6.82 (2H, m), 6.77 (1H, dd, *J* = 5.6, 2.4 Hz), 2.82-2.74 (4H, m), 1.88-1.77 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.9, 159.5, 151.7, 151.1, 139.3 (2C), 134.3, 130.6, 129.1, 128.7, 127.0, 120.9, 117.9, 110.5, 109.0, 29.5, 28.9, 23.1, 22.9; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 302.2, $C_{21}H_{20}NO^+$ requires 302.2.

N-(4-((2-Phenylpyridin-4-yl)oxy)phenyl)acetamide (3g)



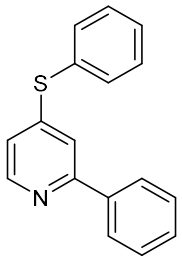
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), N-(4-hydroxyphenyl)acetamide (151.2 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and DME (1.0 mL). Flash column chromatography (silica gel was packed with hexanes and neutralized with NEt_3: 1% MeOH in DCM) afforded the *title compound* (3g) as a white solid (111 mg, 0.36 mmol, 73% yield). mp: 129-139 °C; IR ν_{max}/cm^{-1} (film): 3297, 3206, 3064, 2923, 2852, 1659, 1546, 1501, 1469, 1405, 1302, 1211, 1016, 911, 849, 776, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (1H, d, *J* = 5.6 Hz), 7.93-7.87 (2H, m), 7.60-7.54 (2H, m), 7.48-7.37 (3H, m), 7.32 (1H, br), 7.25 (1H, d, *J* = 2.2 Hz) 7.13-7.07 (2H, m), 6.77 (1H, dd, *J* = 5.7, 2.4 Hz), 2.20 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 165.7, 159.7, 151.2, 150.3, 139.0, 135.3, 129.2, 128.7, 127.0, 121.7, 121.4, 110.5, 108.9, 24.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 305.2, $C_{19}H_{17}N_2O_2^+$ requires 305.1.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-((2-phenylpyridin-4-yl)oxy)phenyl)propanoate (3h)



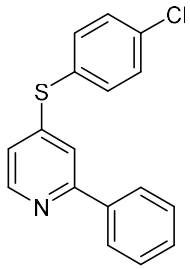
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), methyl (tert-butoxycarbonyl)-L-tyrosinate (222 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel, gradient elution: 30% EtOAc in hexanes to 80% EtOAc in hexanes) afforded the *title compound* (3h) as a white solid (133.1 mg, 0.297 mmol, 59% yield). mp: 29-40 °C; IR ν_{max}/cm^{-1} (film): 3435, 3033, 2979, 2932, 2251, 1979, 1742, 1706, 1586, 1504, 1471, 1219, 1163, 908, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (1H, d, *J* = 5.6 Hz), 7.95-7.90 (2H, m), 7.48-7.37 (3H, m), 7.27 (1H, d, *J* = 2.2 Hz), 7.23-7.18 (2H, m), 7.09-7.04 (2H, m), 6.75 (1H, dd, *J* = 5.6, 2.4 Hz), 5.04 (1H, d, *J* = 7.7 Hz), 4.66-4.56 (1H, m), 3.74 (3H, s), 3.21-3.00 (2H, m), 1.43 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.1, 165.4, 159.6, 155.0, 153.2, 151.1, 139.0, 133.3, 131.0, 129.1, 128.6, 126.9, 120.7, 110.6, 109.1, 79.9, 54.4, 52.2, 37.9, 28.2; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 449.3, $C_{26}H_{29}N_2O_5^+$ requires 449.2.

2-Phenyl-4-(phenylthio)pyridine (3j)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzenethiol (77 μL, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 2.5% EtOAc in hexanes) afforded the *title compound* (3j) as a clear oil (109 mg, 0.42 mmol, 83% yield). IR ν_{max}/cm^{-1} (film): 3689, 3064, 3040, 2997, 2921, 2850, 2612, 2459, 2162, 1977, 1814, 1764, 1699, 1567, 1534, 1462, 1379, 757, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 (1H, d, J = 5.3 Hz), 7.89-7.84 (2H, m), 7.63-7.56 (2H, m), 7.50-7.36 (7H, m), 6.88 (1H, dd, J = 5.3, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4, 150.8, 149.4, 139.0, 135.0, 129.9, 129.7, 129.6, 129.1, 128.7, 126.9, 119.4, 117.8; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 264.1, $C_{17}H_{14}NS^+$ requires 264.1.

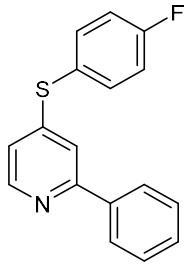
4-((4-Chlorophenyl)thio)-2-phenylpyridine (3n)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-chlorobenzenethiol (109 mg, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium

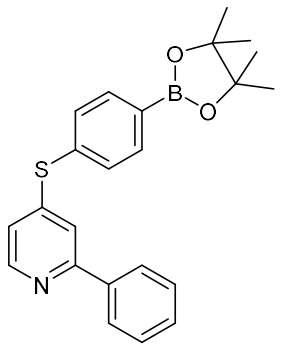
trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 2.5% EtOAc in Toluene) afforded the *title compound* (3n) as a white chrystalline solid (109 mg, 0.37 mmol, 73% yield). mp: 86-90 °C IR ν_{max}/cm^{-1} (film): 3076, 3044, 3012, 2924, 2771, 2464, 1980, 1812, 1585, 1536, 1461, 1378, 1089, 836.8, 797, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (1H, d, *J* = 5.3 Hz), 7.89-7.85 (2H, m), 7.54-7.49 (2H, m), 7.48-7.38 (6H, m), 6.87 (1H, dd, *J* = 5.3, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.6, 150.0, 149.5, 138.9, 136.1, 136.0, 130.2, 129.2, 128.8, 128.4, 126.9, 119.4, 117.9; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 298.1, $C_{17}H_{13}ClNS^+$ requires 298.0.

4-((4-Fluorophenyl)thio)-2-phenylpyridine (3m)



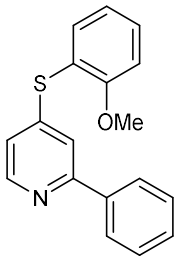
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-fluorobenzenethiol (80 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 2.5% EtOAc in Toluene) afforded the *title compound* (3m) as a white solid (110 mg, 0.39 mmol, 78% yield). mp: 75-79 °C; IR ν_{max}/cm^{-1} (film): 3090, 3067, 3037, 2923, 2853, 2466, 2040, 1813, 1702, 1585, 1570, 1537, 1489, 1223, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (1H, d, *J* = 5.3 Hz), 7.92-7.83 (2H, m), 7.65-7.55 (2H, m), 7.48-7.35 (4H, m), 7.22-7.13 (2H, m), 6.83 (1H, dd, *J* = 5.3, 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7 (d, *J* = 251 Hz), 157.5, 150.9, 149.4, 138.9, 137.5 (d, *J* = 8.5 Hz), 129.2, 128.7, 126.9, 124.8 (d, *J* = 3.5 Hz), 118.96, 117.43, 117.23 (d, *J* = 21.9 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −110.25 ; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 282.1, $C_{17}H_{13}FNS^+$ requires 282.1.

2-Phenyl-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)thio)pyridine (3o)



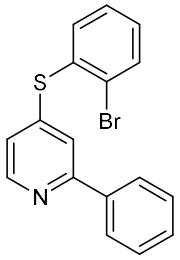
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenethiol (177 mg, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 8% EtOAc in hexanes) afforded the *title compound* (3o) as a yellow oil (119.4 mg, 0.307 mmol, 61% yield). IR ν_{max}/cm^{-1} (film): 2979, 2928, 2247, 2216, 1715, 1569, 1358, 1142, 907, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (1H, d, *J* = 5.3 Hz), 7.90-7.85 (4H, m), 7.60-7.53 (2H, m), 7.50-7.36 (4H, m), 6.90 (1H, dd, *J* = 5.3, 1.7 Hz), 1.37 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.6, 150.1, 149.4, 139.0, 136.0, 133.6, 133.5, 129.1, 128.7, 127.0, 119.9, 118.4, 84.2, 24.9; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 390.2, $C_{23}H_{25}BNO_2S^+$ requires 390.2.

4-((2-Methoxyphenyl)thio)-2-phenylpyridine (3k)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 2-methoxybenzenethiol (91 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the *title compound* (3k) as a clear oil (115 mg, 0.39 mmol, 79% yield). IR ν_{max}/cm^{-1} (film): 3062, 2936, 2835, 2167, 1567, 1476, 1462, 1274, 1247, 1022, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41 (1H, d, J = 5.3 Hz), 7.89-7.84 (2H, m), 7.60-7.54 (1H, m), 7.52-7.36 (5H, m), 7.08-7.00 (2H, m), 6.83 (1H, dd, J = 5.3, 1.8 Hz), 3.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.9, 157.2, 150.1, 149.1, 139.2, 137.2, 131.9, 129.0, 128.7, 126.9, 121.6, 119.1, 117.6, 117.0, 111.7, 56.0; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 294.2, $C_{18}H_{16}NOS^+$ requires 294.1.

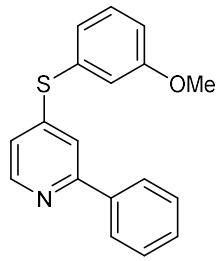
4-((2-Bromophenyl)thio)-2-phenylpyridine (3l)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 2-bromobenzenethiol (90 μL, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash

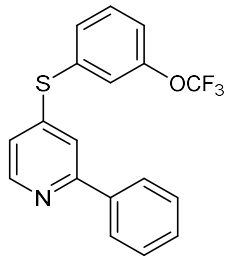
column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 20% EtOAc in hexanes) afforded the *title compound* (3l) as a brown oil (144 mg, 0.42 mmol, 84% yield). IR ν_{max}/cm^{-1} (film): 3056, 2925, 2456, 2162, 1979, 1567, 1536, 1444, 1379, 752, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, d, *J* = 5.3 Hz), 7.91-7.86 (2H, m), 7.77 (1H, dd, *J* = 7.8, 1.2 Hz), 7.64 (1H, dd, *J* = 7.8, 1.7 Hz), 7.50-7.35 (5H, m), 7.35-7.29 (1H, m), 6.88 (1H, dd, *J* = 5.3, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 149.6, 148.4, 138.9, 136.5, 134.1, 131.7, 131.0, 129.6, 129.2, 128.7, 128.6, 127.0, 119.9, 118.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 342.1, $C_{17}H_{13}BrNS^+$ requires 342.0.

4-((3-Methoxyphenyl)thio)-2-phenylpyridine (3p)



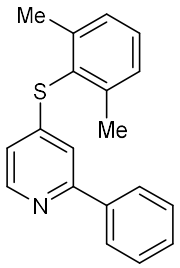
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 3-methoxybenzenethiol (93 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the *title compound* (3p) as a yellow oil (118 mg, 0.40 mmol, 80% yield). IR ν_{max}/cm^{-1} (film): 3001, 2933, 2834, 1566, 1479, 1231, 772, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (1H, d, *J* = 5.3 Hz), 7.90-7.85 (2H, m), 7.47-7.34 (5H, m), 7.17 (1H, d, *J* = 7.6 Hz), 7.13-7.10 (1H, m), 7.00 (1H, dd, *J* = 8.3, 2.6 Hz), 6.90 (1H, dd, *J* = 5.3, 1.7 Hz), 3.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.5, 157.5, 150.6, 149.4, 139.0, 130.8, 130.7, 129.1, 128.7, 127.1, 126.9, 119.8, 119.5, 118.0, 115.7, 55.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 294.1, $C_{18}H_{16}NOS^+$ requires 294.1.

2-Phenyl-4-((3-(trifluoromethoxy)phenyl)thio)pyridine (3q)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 3-(trifluoromethoxy)benzenethiol (146 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.5 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 15% EtOAc in hexanes) afforded the *title compound* (3q) as a clear oil (81.8 mg, 0.235 mmol, 47% yield). IR ν_{max}/cm^{-1} (film): 2925, 2853, 2218, 1568, 1251, 1219, 1205, 1165, 907, 730, 692; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, dd, J = 5.3, 0.5 Hz), 7.90-7.85 (2H, m), 7.52-7.38 (7H, m), 7.34-7.28 (1H, m), 6.93 (1H, dd, J = 5.3, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 149.8, 149.7, 149.0, 138.8, 132.6, 132.5, 131.0, 129.3, 128.8, 126.9, 126.6, 121.8, 120.4 (q, J = 258.2 Hz), 119.9, 118.5; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –57.88; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 348.1, $C_{18}H_{13}F_3NOS^+$ requires 348.1.

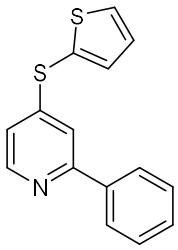
4-((2,6-Dimethylphenyl)thio)-2-phenylpyridine (3r)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 2,6-dimethylbenzenethiol (100 μL, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-

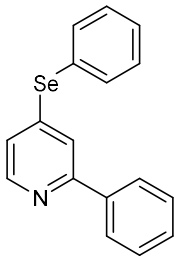
phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 2% EtOAc in toluene) afforded the *title compound* (3r) as a clear oil (108 mg, 0.37 mmol, 74% yield). IR ν_{max}/cm^{-1} (film): 3054, 2958, 2922, 2459, 2161, 1948, 1727, 1567, 1535, 1460, 1375, 1103, 770, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (1H, d, J = 5.3 Hz), 7.84-7.79 (2H, m), 7.44-7.32 (3H, m), 7.30-7.17 (4H, m), 6.63 (1H, dd, J = 5.3, 1.8 Hz), 2.41 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 157.3, 150.3, 149.3, 144.1, 139.1, 130.2, 129.0, 128.8, 128.7, 127.6, 126.9, 118.0, 116.6, 21.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 292.2, $C_{19}H_{18}NS^+$ requires 292.1.

2-Phenyl-4-(thiophen-2-ylthio)pyridine (3s)



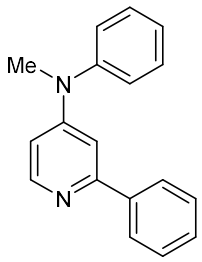
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), thiophene-2-thiol (70 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 2.5% EtOAc in toluene) afforded the *title compound* (3s) as a tan oil (93 mg, 0.35 mmol, 69% yield). IR ν_{max}/cm^{-1} (film): 3062, 3036, 2993, 2923, 2360, 2162, 1952, 1567, 1379, 1072, 771, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (1H, d, J = 5.3 Hz), 7.90-7.85 (2H, m), 7.63 (1H, dd, J = 5.3, 1.2 Hz), 7.48-7.37 (5H, m), 7.19 (1H, dd, J = 5.3, 3.5 Hz), 6.89 (1H, dd, J = 5.3, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5, 151.5, 149.4, 139.0, 137.9, 132.9, 129.1, 128.7, 128.5, 127.0, 126.5, 118.2, 116.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 270.1, $C_{15}H_{12}NS_2^+$ requires 270.0.

2-Phenyl-4-(phenylselanyl)pyridine (3i)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzeneselenol (80 μL, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 5% EtOAc in hexanes) afforded the *title compound* (3i) as a white solid (141 mg, 0.45 mmol, 91% yield). mp: 43-47 °C; IR ν_{max}/cm^{-1} (film): 3064, 3033, 2923, 2452, 2163, 1961, 1891, 1753, 1562, 1534, 1438, 1379, 1019, 825, 774, 738, 698, 679; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (1H, d, *J* = 5.2 Hz), 7.90-7.84 (2H, m), 7.71-7.65 (2H, m), 7.58 (1H, d, *J* = 1.1 Hz), 7.50-7.36 (6H, m), 7.04 (1H, dd, *J* = 5.3, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5, 149.4, 146.2, 138.9, 136.1, 129.9, 129.3, 129.1, 128.7, 126.9, 126.5, 122.4, 120.9; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 312.2, $C_{17}H_{14}NSe^+$ requires 312.0.

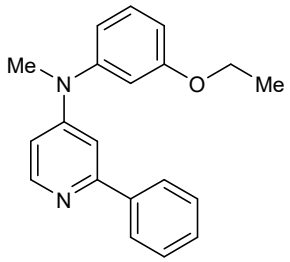
N-Methyl-N,2-diphenylpyridin-4-amine (3u)



Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 470 μL, 0.75 mmol), *N*-methylaniline (81 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium

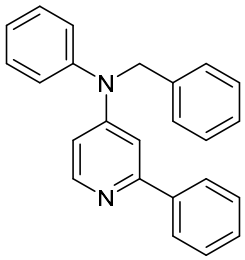
trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3u) as a tan powder (117 mg, 0.45 mmol, 90% yield). mp: 77-82 °C; IR ν_{max}/cm^{-1} (film): 3061, 3045, 3038, 2917, 2852, 2818, 2592, 2501, 2161, 2050, 1953, 1842, 1603, 1597, 1536, 1480, 1445, 1360, 1235, 1135, 983, 825, 760, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (1H, d, *J* = 5.8 Hz), 7.88-7.83 (2H, m), 7.52-7.33 (5H, m), 7.31-7.24 (3H, m), 6.99 (1H, d, *J* = 2.4 Hz), 6.54 (1H, dd, *J* = 8.4, 3.4 Hz), 3.39 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 154.6, 149.8, 146.4, 140.4, 130.0, 128.5, 128.5, 127.0, 126.6, 126.3, 107.2, 105.4, 39.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 261.1, $C_{18}H_{17}N_2^+$ requires 261.1.

N-(3-Ethoxyphenyl)-N-methyl-2-phenylpyridin-4-amine (3v)



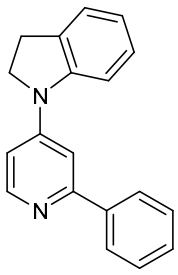
Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 234 μL, 0.38 mmol), 3-ethoxy-*N*-methylaniline (57 mg, 0.38 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (141 mg, 0.25 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the *title compound* (3v) as an orange oil (63 mg, 0.20 mmol, 81% yield). IR ν_{max}/cm^{-1} (film): 2978, 2928, 2162, 1574, 1543, 1478, 1446,. 1245, 1203, 1046, 984, 773, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (1H, d, *J* = 5.8 Hz), 7.90-7.84 (2H, m), 7.46-7.30 (4H, m), 7.01 (1H, d, *J* = 2.4 Hz), 6.86-6.77 (3H, m), 6.56 (1H, dd, *J* = 5.9, 2.5 Hz), 4.04 (2H, q, *J* = 6.9 Hz), 3.37 (3H, s), 1.42 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 158.0, 154.5, 149.8, 147.5, 140.4, 130.6, 128.5, 128.5, 127.0, 118.6, 112.8, 112.4, 107.4, 105.6, 63.6, 39.5, 14.8; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 305.2, $C_{20}H_{21}N_2O^+$ requires 305.2.

N-Benzyl-N,2-diphenylpyridin-4-amine (3w)



Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 234 μL, 0.38 mmol), *N*-benzylaniline (65 μL, 0.38 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (141 mg, 0.25 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3w) as an orange amorphous solid (52 mg, 0.15 mmol, 62% yield). IR ν_{max}/cm^{-1} (film): 3062, 2961, 2930, 2860, 2253, 1715, 1588, 1496, 1385, 1271, 1120, 904, 725, 649; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, d, *J* = 5.9 Hz), 7.79-7.74 (2H, m), 7.46-7.31 (11H, m), 7.30-7.26 (2H, m), 7.01 (1H, d, *J* = 2.4 Hz), 6.55 (1H, dd, *J* = 5.9, 2.5 Hz), 5.03 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 154.1, 149.9, 145.7, 140.3, 137.5, 130.0, 128.8, 128.5, 128.5, 127.3, 126.9, 126.8, 126.5, 126.4, 107.8, 106.0, 56.0; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 337.2, $C_{24}H_{21}N_2^+$ requires 337.2.

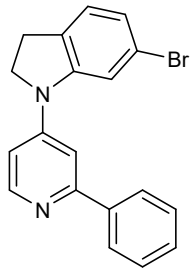
1-(2-Phenylpyridin-4-yl)indoline (3x)



Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 0.47 mL, 0.75 mmol), indoline (84.1 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate

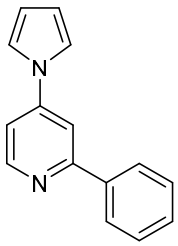
(282.5 mg, 0.5 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3x) as a brown oil (92.3 mg, 0.339 mmol, 68% yield). IR ν_{max}/cm^{-1} (film): 2978, 2928, 2162, 1574, 1543, 1478, 1446, 1245, 1203, 1046, 984, 773, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, d, *J* = 5.8 Hz), 7.99-7.94 (2H, m), 7.51-7.45 (3H, m), 7.45-7.37 (2H, m), 7.26-7.16 (2H, m), 7.02 (1H, dd, *J* = 5.8, 2.3 Hz), 6.94-6.88 (1H, m), 4.07 (2H, t, *J* = 8.3 Hz), 3.21 (2H, t, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 150.3, 150.2, 144.6, 140.1, 132.2, 128.8, 128.6, 127.2, 127.0, 125.5, 121.0, 110.6, 108.9, 107.2, 51.2, 27.9; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 273.1, $C_{19}H_{17}N_2^+$ requires 273.1.

6-Bromo-1-(2-phenylpyridin-4-yl)indoline (3y)



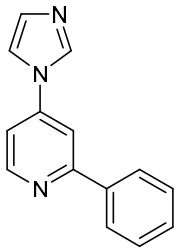
Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 234 μL, 0.375 mmol), 6-bromoindoline (74 mg, 0.38 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (141 mg, 0.25 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the *title compound* (3y) as a white solid (36 mg, 0.10 mmol, 41% yield). mp: 75-80°C; IR ν_{max}/cm^{-1} (film): 3298, 3035, 2956, 2162, 1608, 1574, 1478, 1431, 1270, 988, 769.5, 691.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, *J* = 5.8 Hz), 7.99-7.94 (2H, m), 7.52-7.38 (5H, m), 7.10-7.06 (1H, m), 7.05-6.99 (2H, m), 4.09 (2H, t, *J* = 8.4 Hz), 3.15 (2H, t, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 150.4, 149.8, 146.1, 139.8, 131.2, 129.0, 128.7, 127.0, 126.4, 123.6, 120.8, 113.5, 109.2, 107.5, 51.7, 27.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 351.1, $C_{19}H_{16}BrN_2^+$ requires 351.0.

2-Phenyl-4-(1H-pyrrol-1-yl)pyridine (3ap)



Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), pyrrole (52 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 10% EtOAc in hexanes) afforded the *title compound* (3ap) as a clear oil (81 mg, 0.37 mmol, 74% yield). IR ν_{max}/cm^{-1} (film): 3063, 2925, 2852, 2360, 2340, 2246, 2218, 1718, 1594, 1494, 1351, 1256, 1066, 1176, 905, 723; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (1H, d, *J* = 5.2 Hz), 8.00 (2H, d, *J* = 7.3 Hz), 7.69 (1H, d, *J* = 1.6 Hz), 7.53-7.41(3H, m), 7.29-7.20 (3H, m), 6.42 (2H, t, *J* = 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 151.1, 147.3, 139.0, 129.4, 128.8, 127.0, 118.4, 112.2, 112.1, 110.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 221.1, $C_{15}H_{13}N_2^+$ requires 221.1.

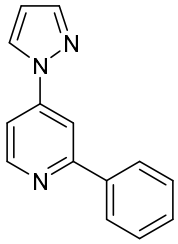
4-(1H-Imidazol-1-yl)-2-phenylpyridine (3ar)



Prepared according to general procedure D using potassium hydride (36.3% dispersion in mineral oil, 41 mg, 0.38 mmol), 18-crown-6 (99 mg, 0.38 mmol) was added at the start with potassium hydride, 1*H*-imidazole (26 mg, 0.38 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate

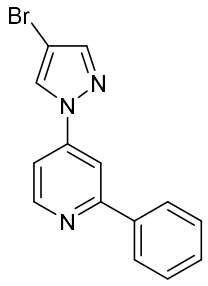
(141 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel was packed with hexanes and neutralized with NEt_3, gradient elution: 60% EtOAc in hexanes to 80% EtOAc in hexanes) afforded the *title compound* (3ar) as a clear oil (28 mg, 0.13 mmol, 51% yield). IR ν_{max}/cm^{-1} (film): 3123, 3062, 2924, 2851, 2222, 1979, 1595, 1568, 1496, 1240, 1054, 905, 725, 693; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.78 (1H, d, *J* = 5.4 Hz); 8.08 (1H, s), 8.05-8.00 (2H, m), 7.73 (1H, d, *J* = 1.9 Hz), 7.55-7.44 (4H, m), 7.31-7.26 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 160.0, 151.5, 144.5, 138.3, 135.0, 131.6, 129.8, 129.0, 127.0, 117.0, 113.1, 111.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 222.1, $C_{14}H_{12}N_3^+$ requires 222.1.

2-Phenyl-4-(1H-pyrazol-1-yl)pyridine (3aq)



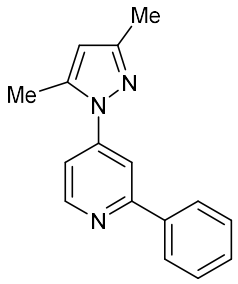
Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 1H-pyrazole (51 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 15% EtOAc in hexanes) afforded the *title compound* (3aq) as a clear oil (80 mg, 0.36 mmol, 72% yield). IR ν_{max}/cm^{-1} (film): 3032, 1591, 1568, 1521, 1482, 1442, 1395, 1381, 1041, 774, 693; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, d, *J* = 5.4 Hz); 8.20-8.00 (4H, m), 7.80 (1H, d, *J* = 1.4 Hz), 7.59-7.40 (4H, m), 6.58-6.53 (1H, dd, *J* = 2.4, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 151.0, 146.8, 142.4, 138.8, 129.4, 128.8, 127.1, 126.7, 110.9, 109.5, 109.0; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 222.1, $C_{14}H_{12}N_3^+$ requires 222.1.

4-(4-Bromo-1H-pyrazol-1-yl)-2-phenylpyridine (3as)



Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-bromo-1H-pyrazole (110 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 10% EtOAc in hexanes) afforded the *title compound* (3as) as a white solid (97 mg, 0.32 mmol, 64% yield). mp: 140-143 °C; IR ν_{max}/cm^{-1} (film): 3142, 3116, 3029, 2921, 1928, 1694, 1593, 1569, 1478, 1447, 1414, 1406, 1339, 1251, 1148, 954, 777, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (1H, d, J = 5.4 Hz); 8.12 (1H, s), 8.10-8.02 (3H, m), 7.76 (1H, s), 7.56-7.43 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.6, 151.1, 146.2, 142.9, 138.6, 129.6, 128.9, 127.0, 126.8, 110.5, 109.1, 97.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 300.1, $C_{14}H_{11}BrN_3^+$ requires 300.0.

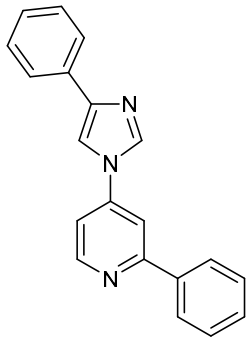
4-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-phenylpyridine (3at)



Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 3,5-dimethyl-1H-pyrazole (72 mg, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium

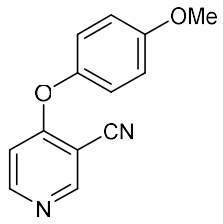
trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 30% EtOAc in hexanes) afforded the *title compound* (3at) as a clear oil (47 mg, 0.19 mmol, 37% yield). IR ν_{max}/cm^{-1} (film): 2925, 2225, 1710, 1593, 1573, 905, 727; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, d, *J* = 5.4 Hz), 8.06-8.01 (2H, m), 7.92 (1H, d, *J* = 1.7 Hz), 7.51-7.40 (3H, m), 7.38 (1H, dd, *J* = 5.4, 2.0 Hz), 6.08 (1H, m), 2.50 (3H, s), 2.32 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 159.0, 150.6, 150.6, 147.5, 139.9, 138.9, 129.3, 128.8, 127.0, 115.4, 114.1, 109.3, 13.6, 13.3; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 250.2, $C_{16}H_{16}N_3^+$ requires 250.1.

2-Phenyl-4-(4-phenyl-1H-imidazol-1-yl)pyridine (3au)



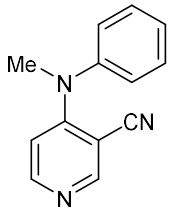
Prepared according to general procedure D using potassium hydride (36.3% dispersion in mineral oil, 83 mg, 0.75 mmol), 4-phenylimidazole (108 mg, 0.75 mmol), 18-Crown-6 (198 mg, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.5 mmol) and THF (1.0 mL). Flash column chromatography (silica gel was packed with hexanes and neutralized with NEt_3: 40% EtOAc in hexanes) afforded the *title compound* (3au) as a yellow oil (38 mg, 0.13 mmol, 25% yield). IR ν_{max}/cm^{-1} (film): 3058, 2924, 2360, 2341, 2217, 1592, 1568, 1493, 1445, 1238, 1056, 726, 692, 906; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.78 (1H, d, J = 5.4 Hz), 8.11 (1H, s), 8.04 (2H, d, J = 6.9 Hz), 7.86 (2H, d, J = 7.3 Hz), 7.76 (1H, d, J = 1.6 Hz), 7.71 (1H, s), 7.56-7.39 (5H, m), 7.35-7.28 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0, 151.5, 144.3 (2C), 138.3, 135.1, 133.0, 129.8, 128.9, 128.7, 127.6, 127.0, 125.1, 112.8, 112.1, 111.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 298.2, $C_{20}H_{16}N_3^+$ requires 298.1.

4-(4-Methoxyphenoxy)nicotinonitrile (3z)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-methoxyphenol (93 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), (3-cyanopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (257 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the *title compound* (3z) as a colorless amorphous solid (90.9 mg, 0.402 mmol, 80% yield). IR ν_{max}/cm^{-1} (film): 3062, 2973, 2936, 2839, 2232, 1585, 1567, 1502, 1481, 1277, 1242, 1195, 1179, 1027, 889, 838; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (1H, s), 8.51 (1H, d, *J* = 5.9 Hz), 7.95-7.10-7.03 (2H, m), 7.00-6.95 (2H, m), 6.64 (1H, d, *J* = 5.9 Hz), 3.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7, 158.0, 154.6, 154.4, 145.9, 122.0, 115.4, 114.0, 109.5, 100.5, 55.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 227.1, $C_{13}H_{11}N_2O_2^+$ requires 227.1.

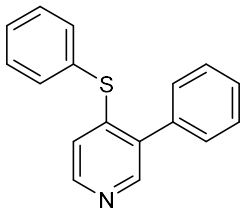
4-(Methyl(phenyl)amino)nicotinonitrile (3am)



Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 470 μL, 0.75 mmol), *N*-methylaniline (81 μL, 0.75 mmol), (3-cyanopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (257 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica

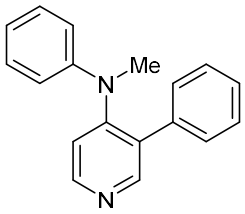
gel: 20% EtOAc in hexanes) afforded the *title compound* (3am) as an orange amorphous solid (86 mg, 0.41 mmol, 82% yield). IR ν_{max}/cm^{-1} (film): 3018, 2920, 2855, 2208, 1600, 1582, 1495, 1405, 1203, 1051, 809, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (1H, s), 8.31 (1H, d, *J* = 6.2 Hz), 7.50-7.42 (2H, m), 7.42-7.33 (1H, m), 7.25-7.20 (2H, m), 6.65 (1H, d, *J* = 6.2 Hz), 3.52 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.3, 155.0, 152.1, 145.9, 130.3, 127.8, 126.6, 116.8, 110.4, 95.9, 41.8; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 210.1, $C_{13}H_{12}N_3^+$ requires 210.1.

3-Phenyl-4-(phenylthio)pyridine (3af)



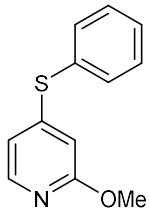
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzenethiol (77 μL, 0.75 mmol), triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 10% EtOAc in toluene) afforded the *title compound* (3af) as a clear oil (101.2 mg, 0.384 mmol, 77% yield). IR ν_{max}/cm^{-1} (film): 3066, 3035, 2997, 2923, 2950, 2612, 1980, 1815, 1763, 1699, 1567, 1462, 1379, 757, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (1H, s), 8.25 (1H, d, *J* = 5.4 Hz), 7.54-7.38 (10H, m), 6.68 (1H, d, *J* = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.3, 149.2, 148.3, 136.7, 135.6, 134.8, 130.0, 129.9, 129.7, 129.4, 128.5, 128.4, 120.0; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 264.1, $C_{17}H_{14}NS^+$ requires 264.1.

N-Methyl-N,3-diphenylpyridin-4-amine (3ao)



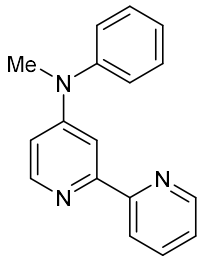
Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 0.468 mL, 0.75 mmol), *N*-methylaniline (81.2 μL, 0.75 mmol), triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (282.6 mg, 0.5 mmol) and THF (2.0 mL).

2-Methoxy-4-(phenylthio)pyridine (3ag)



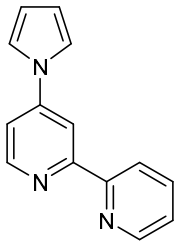
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzenethiol (77 μL, 0.75 mmol), triphenyl(2-methoxypyridin-4-yl)phosphonium trifluoromethanesulfonate (260 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 5% EtOAc in hexanes) followed by filtration through a plug of silica eluting with 100% DCM afforded the *title compound* (3ag) as a clear oil (49 mg, 0.22 mmol, 45% yield). IR ν_{max}/cm^{-1} (film): 3060, 2981, 2947, 2857, 2226, 1588, 1542, 1473, 1385, 1035, 905, 728; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.94 (1H, d, J = 5.5 Hz), 7.57-7.51 (2H, m), 7.46-7.40 (3H, m), 6.60 (1H, dd, J = 5.5, 1.6 Hz) 6.33 (1H, d, J = 1.4 Hz), 3.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5, 152.3, 146.4, 135.2, 129.8, 129.6, 129.5, 114.8, 107.2, 53.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 218.1, $C_{12}H_{12}NOS^+$ requires 218.1.

N-Methyl-N-phenyl-[2,2'-bipyridin]-4-amine (3al)



Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 0.47 mL, 0.75 mmol), *N*-methylaniline (81 μL, 0.75 mmol), [2,2'-bipyridin]-4-yltriphenylphosphoniumtrifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography (silica gel: 20% EtOAc, 2.5% NEt_3 in hexanes) afforded the *title compound* (3al) as a tan solid (107 mg, 0.41 mmol, 82% yield). mp: 107-110 °C; IR ν_{max}/cm^{-1} (film): 3061, 3002, 2907, 2821, 2538, 2162, 1979, 1604, 1578, 1567, 1542, 1490, 1468, 1456, 1370, 953, 786, 774, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (1H, d, J = 4.1 Hz), 8.32 (1H, d, J = 8.0 Hz), 8.22 (1H, d, J = 5.8 Hz), 7.80-7.70 (2H, m), 7.45-7.35 (2H, m), 7.25-7.15 (4H, m), 6.52 (1H, dd, J = 5.8, 2.6 Hz), 3.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8, 156.7, 154.8, 149.2, 148.9, 146.5, 136.7, 129.9, 126.6, 126.2, 123.4, 121.2, 108.9, 105.3, 39.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 262.1, $C_{17}H_{16}N_3^+$ requires 262.1.

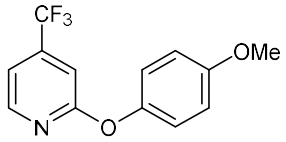
4-(1H-Pyrrol-1-yl)-2,2'-bipyridine (3ax)



Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), 1H-pyrrole (26 μL, 0.38 mmol), [2,2'-bipyridin]-4-yltriphenylphosphonium

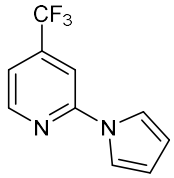
trifluoromethanesulfonate (142 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (basic alumina: 5% EtOAc in hexanes) afforded the *title compound* (3ax) as a tan amorphous solid (36 mg, 0.16 mmol, 64% yield). IR ν_{max}/cm^{-1} (film): 3060, 2922, 2851, 2222, 1723, 1598, 1584, 1563, 1496, 1350, 1062, 907, 723, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72-8.69 (1H, m), 8.66 (1H, d, *J* = 5.4 Hz), 8.50 (1H, d, *J* = 2.2 Hz), 8.47-8.43 (1H, m), 7.85 (1H, td, *J* = 7.8, 1.7 Hz), 7.39-7.30 (4H, m), 6.42 (2H, t, *J* = 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 155.5, 150.6, 149.2, 147.4, 137.0, 124.1, 121.3, 118.5, 113.2, 112.1, 110.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 222.1, $C_{14}H_{12}N_3^+$ requires 222.1.

2-(4-Methoxyphenoxy)-4-(trifluoromethyl)pyridine (3aa)



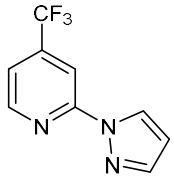
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), 4-methoxyphenol (47 mg, 0.38 mmol), 15-crown-5 (75 μL, 0.38 mmol), triphenyl(4-(trifluoromethyl)pyridin-2-yl)phosphonium trifluoromethanesulfonate (139 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 10% EtOAc in hexanes) afforded the *title compound* (3aa) as a white solid (54 mg, 0.20 mmol, 80% yield). mp: 76-79 °C; IR ν_{max}/cm^{-1} (film): 3073, 3028, 2979, 2921, 2849, 2050, 1758, 1615, 1569, 1503, 1402, 1330, 1294, 1225, 1171, 1137, 1075, 836; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (1H, d, *J* = 5.2 Hz), 7.16 (1H, dd, *J* = 5.2, 0.8 Hz), 7.11 (1H, t, *J* = 1.4 Hz), 7.10-7.05 (2H, m), 6.97-6.92 (2H, m), 3.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.7, 157.0, 149.0, 146.6, 141.6 (q, J = 34.1 Hz), 122.5 (q, J = 273.1 Hz), 122.4, 114.9, 113.7 (q, J = 3.3 Hz), 107.6 (q, J = 4.0 Hz), 55.6; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −64.92; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 270.1, $C_{13}H_{11}F_3NO_2^+$ requires 270.1.

2-(1H-Pyrrol-1-yl)-4-(trifluoromethyl)pyridine (3ba)



Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 1H-pyrrole (52 μL, 0.75 mmol), triphenyl(4-(trifluoromethyl)pyridin-2-yl)phosphonium trifluoromethanesulfonate (279 mg, 0.50 mmol), and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 2% EtOAc in hexanes) afforded the *title compound* (3ba) as a white solid (70 mg, 0.33 mmol, 66% yield). mp: 73-77 °C; IR ν_{max}/cm^{-1} (film): 3160, 3119, 3048, 2922, 1724, 1615, 1575, 1492, 1437, 1352, 1330, 1300, 1276, 1172, 1128, 1059, 935, 839, 735, 675; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 5.1 Hz), 7.55 (2H, t, *J* = 2.3 Hz), 7.48 (1H, s), 7.30 (1H, dd, *J* = 0.7, 5.1 Hz), 6.39 (2H, t, *J* = 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 150.0, 140.8 (q, J = 34.2 Hz), 122.5 (q, J = 273.9 Hz), 118.2, 115.5 (q, J = 3.4 Hz), 112.3, 107.1 (q, J = 3.8 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −64.98 ; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 213.1, $C_{10}H_8F_3N_2^+$ requires 213.1.

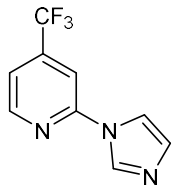
2-(1H-Pyrazol-1-yl)-4-(trifluoromethyl)pyridine (3bb)



Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 1*H*-pyrazole (51 mg, 0.75 mmol), triphenyl(4-(trifluoromethyl)pyridin-2-yl)phosphonium trifluoromethanesulfonate (279 mg, 0.50 mmol), and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 3% EtOAc in hexanes) afforded the *title compound* (3bb), as a volatile clear oil (31 mg, 0.14 mmol, 29% iso. yield, 76% ^1H NMR yield). Note that the product

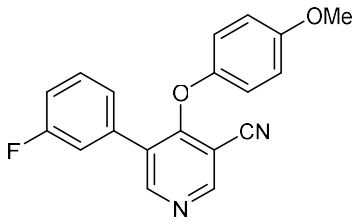
evaporates during solvent evaporation. IR ν_{max}/cm^{-1} (film): 2926, 2253, 1577, 1463, 1398, 1345, 1318, 1179, 1149, 1040, 903, 726, 649; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60-8.55 (2H, m); 8.25 (1H, s), 7.78 (1H, d, *J* = 1.0 Hz), 7.39 (1H, d, *J* = 4.4 Hz), 6.50 (1H, t, *J* = 2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.3, 149.3, 142.8, 141.0 (q, *J* = 34.2 Hz), 127.3, 122.5 (q, *J* = 273.3 Hz), 116.8 (q, *J* = 3.4 Hz), 108.8 (q, *J* = 4.0 Hz), 108.5; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −64.96 ; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 214.1, $C_9H_7F_3N_3^+$ requires 214.1.

2-(1H-Imidazol-1-yl)-4-(trifluoromethyl)pyridine (3bc)



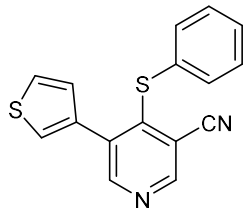
Prepared according to general procedure D using potassium hydride (36.3% dispersion in parafin, 83 mg, 0.75 mmol), 1H-imidazole (51 mg, 0.75 mmol), triphenyl(4-(trifluoromethyl)pyridin-2-yl)phosphonium trifluoromethanesulfonate (279 mg, 0.50 mmol), and THF (1.0 mL). Flash column chromatography (silica gel was packed with hexanes and neutralized with NEt_3: 40% EtOAc in hexanes) afforded the *title compound* (3bc) as a white solid (78 mg, 0.37 mmol, 73% yield). mp: 61-66 °C; IR ν_{max}/cm^{-1} (film): 3119, 3053, 2916, 2848, 2225, 1980, 1673, 1615, 1577, 1481, 1438, 1326, 1176, 1141, 1051, 906, 841, 652; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, d, *J* = 5.1 Hz), 8.42 (1H, s), 7.68 (1H, t, *J* = 1.4 Hz), 7.54 (1H, s), 7.47 (1H, dd, *J* = 0.6, 5.1 Hz), 7.25 (1H, t, *J* = 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.5, 149.9, 141.4 (q, *J* = 34.3 Hz), 135.1, 131.4, 122.3 (q, *J* = 275.2 Hz), 117.5 (q, *J* = 3.4 Hz), 116.0, 108.1 (q, *J* = 3.8 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: −64.90 ; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 214.1, $C_9H_7F_3N_3^+$ requires 214.1.

5-(3-Fluorophenyl)-4-(4-methoxyphenoxy)nicotinonitrile (3ab)



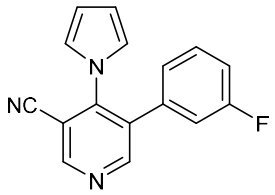
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-methoxyphenol (93 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), (3-cyano-5-(3-fluorophenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (304 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 25% EtOAc in hexanes) afforded the *title compound* (3ab) as a yellow solid (117 mg, 0.37 mmol, 73% yield). mp: 93-97 °C; IR ν_{max}/cm^{-1} (film): 3048, 3011, 2954, 2919, 2847, 2235, 1967, 1871, 1583, 1501, 1446, 1432, 1241, 1183, 1031, 878, 794, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.79 (1H, s), 8.75 (1H, s), 7.40-7.33 (1H, m), 7.24-7.20 (1H, m), 7.19-7.15 (1H, m), 7.10-7.04 (1H, m), 6.84-6.76 (4H, m), 3.76 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6 (d, J = 246.2 Hz), 161.8, 156.7, 155.2, 154.7, 149.6, 134.4 (d, J = 8.1 Hz), 130.3 (d, J = 8.4 Hz), 129.5, 124.9 (d, J = 3.1 Hz), 119.0, 116.3 (d, J = 22.7 Hz), 115.8 (d, J = 21.0 Hz), 114.8, 113.3, 103.5, 55.6; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −112.18; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 321.2, $C_{19}H_{14}FN_2O_2^+$ requires 321.1.

4-(Phenylthio)-5-(thiophen-3-yl)nicotinonitrile (3ah)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzenethiol (77 μL, 0.75 mmol), (3-cyano-5-(thiophen-3-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (298 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3ah) as white solid (121 mg, 0.31 mmol, 63% yield). mp: 129-133 °C; IR ν_{max}/cm^{-1} (film): 3734, 3111, 3054, 2924, 2498, 2232, 1968, 1867, 1725, 1543, 1438, 1077, 842, 787, 736, 656; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (1H, s), 8.67 (1H, s), 7.39-7.34 (1H, m), 7.34-7.29 (1H, m), 7.26-7.18 (4H, m), 7.18-7.12 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.1, 152.9, 148.0, 135.5, 135.4, 132.3, 131.7, 129.4, 128.4, 128.3, 126.1, 125.7, 115.1, 114.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 295.1, $C_{16}H_{11}N_2S_2^+$ requires 295.0.

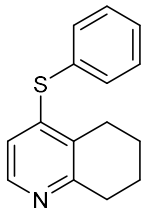
5-(3-Fluorophenyl)-4-(1H-pyrrol-1-yl)nicotinonitrile (3ay)



Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), 1H-pyrrole (26 μL, 0.38 mmol), (3-cyano-5-(3-fluorophenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (152 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 10% EtOAc in hexanes) afforded the *title compound* (3ay) as a brown oil (17 mg, 0.063 mmol, 25% yield). IR ν_{max}/cm^{-1} (film): 3019, 2927, 2236,

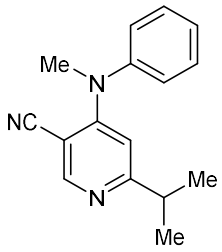
1613, 1587, 1496, 1485, 1324, 1215, 1063, 907, 729, 696, 668; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, s); 8.84 (1H, s), 7.37-7.30 (1H, m), 7.09 (1H, td, *J* = 8.4, 2.6 Hz), 6.85 (1H, d, J = 7.7 Hz), 6.75 (1H, dt, *J* = 9.3, 1.8 Hz), 6.64 (2H, t, *J* = 2.1 Hz), 6.30 (2H, t, *J* = 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.9 (d, *J* = 248.0 Hz), 155.1, 153.8, 147.2, 135.4 (d, *J* = 8.1 Hz), 132.3, 130.7 (d, *J* = 8.4 Hz), 124.0 (d, *J* = 3.1 Hz), 121.5, 116.1 (d, *J* = 21.0 Hz), 115.3 (d, *J* = 22.9 Hz), 114.6, 112.0, 107.3; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −111.30; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 264.1, $C_{16}H_{11}FN_3^+$ requires 264.1.

4-(Phenylthio)-5,6,7,8-tetrahydroquinoline (3ai)



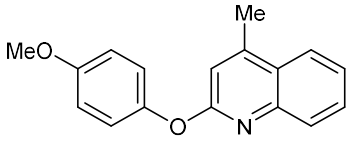
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzenethiol (76.5 μL, 0.75 mmol), triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (272mg, 0.50 mmol) and DME (1.0 mL). Flash column chromatography (silica gel: 30% EtOAc in toluene) afforded the *title compound* (3ai) as a white solid (93 mg, 0.39 mmol, 77% yield). mp: 93-98 °C, IR ν_{max}/cm^{-1} (film): 3034, 2861, 2658, 2535, 2184, 1981, 1880, 1724, 1555, 1433, 1402, 1064, 815, 755, 704, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (1H, d, *J* = 5.3 Hz), 7.55-7.42 (5H, m), 6.41 (1H, d, *J* = 5.3 Hz), 2.91 (2H, t, *J* = 8.0 Hz), 2.73 (2H, t, *J* = 8.0 Hz), 1.94-1.84 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 149.1, 146.1, 135.4, 130.0, 129.9, 129.4, 128.6, 117.7, 32.9, 26.1, 22.8, 22.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 242.1, $C_{15}H_{16}NS^+$ requires 242.1.

6-Isopropyl-4-(methyl(phenyl)amino)nicotinonitrile (3an)



Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 468 μL, 0.75 mmol), *N*-methylaniline (81 μL, 0.75 mmol), (5-cyano-2-isopropylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (278 mg, 0.50 mmol) and THF (2.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3an) as an off-white powder (87 mg, 0.35 mmol, 69% yield). mp: 108-114 °C; IR ν_{max}/cm^{-1} (film): 3060, 3007, 2963, 2921, 2868, 2214, 1863, 1752, 1581, 1534, 1492, 1410, 1310, 1051, 877, 698; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.43 (1H, s), 7.48-7.42 (2H, m), 7.37-7.31 (1H, m), 7.24-7.19 (2H, m), 6.54 (1H, s), 3.49 (3H, s), 2.93 (1H, sp, *J* = 6.8 Hz), 1.26 (6H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.1, 155.8, 155.6, 146.2, 130.1, 127.3, 126.4, 117.1, 107.2, 94.2, 41.7, 36.7, 22.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 252.2, $C_{16}H_{18}N_3^+$ requires 252.1.

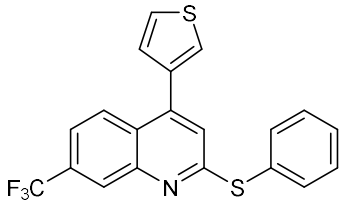
2-(4-Methoxyphenoxy)-4-methylquinoline (3ac)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-methoxyphenol (93 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), (4-methylquinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (277 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (basic alumina: 5% EtOAc in hexanes)

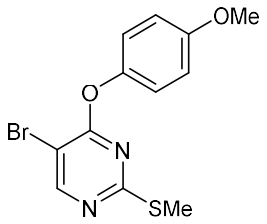
afforded the *title compound* (3ac) as a white solid (90 mg, 0.34 mmol, 68% yield). mp: 96-100 °C; IR ν_{max}/cm^{-1} (film): 3067, 2952, 2920, 2835, 2163, 1615, 1575, 1503, 1463, 1442, 1384, 1336, 1201, 1177, 1022, 828, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (1H, dd, *J* = 8.3, 1.2 Hz), 7.79 (1H, dd, *J* = 8.4, 0.7 Hz), 7.62-7.57 (1H, m), 7.45-7.40 (1H, m), 7.19-7.14 (2H, m), 6.97-6.92 (2H, m), 6.89 (1H, d, J = 0.8 Hz), 3.84 (3H, s), 2.66 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.9, 156.5, 148.0, 147.3, 146.5, 129.5, 128.4, 125.8, 124.4, 123.6, 122.4, 114.6, 112.4, 55.6, 18.9; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 266.1, $C_{17}H_{16}NO_2^+$ requires 266.1.

2-(Phenylthio)-4-(thiophen-3-yl)-7-(trifluoromethyl)quinoline (3aj)



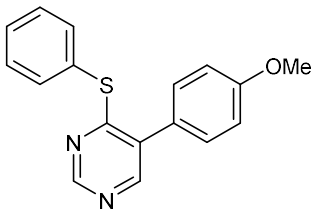
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), benzenethiol (38 μL, 0.38 mmol), triphenyl(4-(thiophen-3-yl)-7-(trifluoromethyl)quinolin-2-yl)phosphonium trifluoromethanesulfonate (172 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel: 40% DCM in hexanes) afforded the *title compound* (3aj) as a white powder (71 mg, 0.18 mmol, 74% yield). mp: 89-93 °C; IR ν_{max}/cm^{-1} (film): 3103, 2923, 2852, 2161, 1792, 1586, 1334, 1288, 1156, 1116, 1097, 1062, 829, 769; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (1H, s), 8.05 (1H, d, *J* = 8.7 Hz), 7.71-7.66 (2H, m), 7.58 (1H, dd, *J* = 8.8, 1.8 Hz), 7.51-7.45 (4H, m), 7.42 (1H, dd, *J* = 2.9, 1.2 Hz), 7.21 (1H, dd, *J* = 5.0, 1.2 Hz), 7.12 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.9, 147.8, 143.4, 137.4, 135.2, 131.6 (q, *J* = 33.1 Hz), 129.9, 129.7, 129.5, 128.5, 126.9, 126.7, 126.5 (q, *J* = 4.4 Hz), 126.4, 125.5, 123.9(q, *J* = 272.1 Hz), 121.3 (q, *J* = 3.2 Hz), 120.8; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −62.79; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 388.1, $C_{20}H_{13}F_3NS_2^+$ requires 388.0.

5-bromo-4-(4-methoxyphenoxy)-2-(methylthio)pyrimidine (3ad)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-methoxyphenol (93 mg, 0.75 mmol), (5-bromo-2-(methylthio)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (307 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the *title compound* (3ad) as a white solid (142 mg, 0.44 mmol, 87% yield). mp: 86-88 °C; IR ν_{max}/cm^{-1} (film): 3024, 3006, 2926, 2836, 1554, 1537, 1501, 1407, 1332, 1288, 1256, 1221, 1176, 1031, 957, 822, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45 (1H, s), 7.11-7.06 (2H, m), 6.94-6.89 (2H, m), 3.83 (3H, s), 2.26 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 164.6, 159.4, 157.3, 145.5, 122.5, 114.3, 100.8, 55.6, 14.3; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 327.0, $C_{12}H_{12}BrN_2O_2S^+$ requires 327.0.

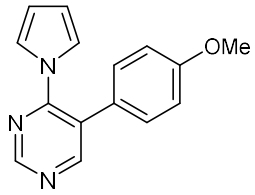
5-(4-Methoxyphenyl)-4-(phenylthio)pyrimidine (3ak)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzenethiol (77 μL, 0.75 mmol), (5-(4-methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (298 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3ak) as a white powder

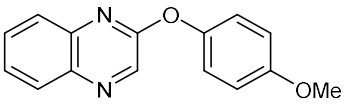
(98 mg, 0.33 mmol, 66% yield). mp: 98-101 °C; IR ν_{max}/cm^{-1} (film): 3074, 3009, 2936, 2835, 2545, 2162, 2061, 1575, 1522, 1509, 1379, 1293, 1252, 1176, 747; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (1H, s); 8.31 (1H, s), 7.56-7.50 (2H, m), 7.49-7.41 (5H, m), 7.09-7.03 (2H, m), 3.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 160.2, 156.7, 154.2, 135.6, 132.5, 130.4, 129.5, 129.2, 128.3, 126.6, 114.3, 55.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 295.1, $C_{17}H_{15}N_2OS^+$ requires 295.1.

5-(4-Methoxyphenyl)-4-(1H-pyrrol-1-yl)pyrimidine (3az)



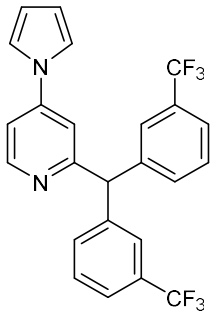
Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), 1H-pyrrole (26 μL, 0.38 mmol), (5-(4-methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (149 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the *title compound* (3az) as a white powder (52 mg, 0.21 mmol, 82% yield). mp: 100-105 °C; IR ν_{max}/cm^{-1} (film): 3158, 3121, 3058, 2924, 2840, 1610, 1578, 1551, 1442, 1393, 1349, 1248, 1178, 1059, 931, 835, 731; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98 (1H, d, s), 8.60 (1H, s), 7.24-7.19 (2H, m), 7.04(2H, t, J = 2.3 Hz), 7.00-6.95 (2H, m), 6.18 (2H, t, J = 2.3 Hz), 3.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.0 (2C), 157.1, 154.6, 130.0, 126.8, 124.4, 120.7, 114.7, 111.4, 55.3; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 252.1, $C_{15}H_{14}N_3O^+$ requires 252.1.

2-(4-Methoxyphenoxy)quinoxaline (3ae)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 4-methoxyphenol (93 mg, 0.75 mmol), 15-crown-5 (150 μL, 0.75 mmol), triphenyl(quinoxalin-2-yl)phosphonium trifluoromethanesulfonate (270 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 10% EtOAc in hexanes) afforded the *title compound* (3ae) as a white amorphous solid (100 mg, 0.40 mmol, 79% yield). IR ν_{max}/cm^{-1} (film): 3060, 3022, 2953, 2931, 2836, 2599, 2042, 1887, 1830, 1641, 1574, 1499, 1401, 1306, 1251, 1205, 1182, 993, 917, 829, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, s), 8.05 (1H, dd, J = 8.0, 1.7 Hz), 7.78-7.74 (1H, m), 7.68-7.57 (2H, m), 7.23-7.18 (2H, m), 7.00-6.95 (2H, m), 3.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 157.2, 156.9, 146.1, 140.0, 139.5, 139.1, 130.2, 128.8, 127.7, 127.2, 122.3, 114.6, 55.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 253.2, $C_{15}H_{13}N_2O_2^+$ requires 253.1.

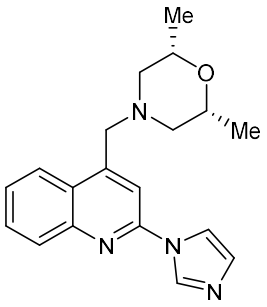
2-(Bis(3-(trifluoromethyl)phenyl)methyl)-4-(1H-pyrrol-1-yl)pyridine (3be)



Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.375 mmol), 1*H*-pyrrole (26 μL, 0.38 mmol), (2-(bis(3-(trifluoromethyl)phenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (198 mg, 0.25 mmol) and THF (0.5 mL). Flash column

chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 20% EtOAc in hexanes) afforded the *title compound* (3be) as a yellow oil (52 mg, 0.12 mmol, 46% yield). IR ν_{max}/cm^{-1} (film): 2927, 2251, 1980, 1722, 1595, 1497, 1328, 1165, 1127, 1075, 904, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, d, *J* = 5.5 Hz), 7.60-7.35 (8H, m), 7.21 (1H, dd, *J* = 5.5, 2.2 Hz), 7.16-7.08 (3H, m), 6.38 (2H, t, *J* = 2.1 Hz), 5.75 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.0, 151.4, 147.3, 142.5, 132.6, 131.0 (q, *J* = 32.2 Hz), 129.2, 125.9 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.8 Hz), 118.3, 113.5, 112.4, 111.9, 58.7; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −62.57 ; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 447.1, $C_{24}H_{17}F_6N_2^+$ requires 447.1.

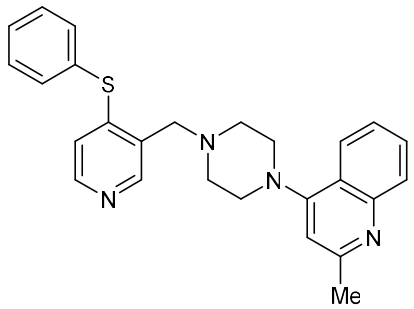
(2R,6S)-4-((2-(1H-Imidazol-1-yl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (3bi)



Prepared according to general procedure D using potassium hydride (36.3% dispersion in mineral oil, 41 mg, 0.38 mmol), 1*H*-imidazole (26 mg, 0.38 mmol), (4-(((2R,6S)-2,6-dimethylmorpholino)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (167 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel: 4% MeOH in DCM) afforded the *title compound* (3bi) as a white amorphous solid (52 mg, 0.16 mmol, 64% yield). IR ν_{max}/cm^{-1} (film): 3150, 3127, 2974, 2931, 2877, 2811, 2773, 2205, 1660, 1599, 1432, 1325, 1084, 1058, 931, 721, 651; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, s), 8.19 (1H, dd, *J* = 8.4, 0.7 Hz), 8.04 (1H, dd, *J* = 8.4 Hz, 0.5 Hz), 7.86 (1H, m), 7.77-7.71 (1H, m), 7.61 (1H, s), 7.57-7.51 (1H, m), 7.25 (1H, m), 3.94 (2H, s), 3.78-3.69 (2H, m), 2.75 (2H, d, *J* = 10.3 Hz), 1.94 (2H, t, *J* = 10.5 Hz), 1.16 (6H, d, *J* = 6.3 Hz); ^{13}C NMR (100

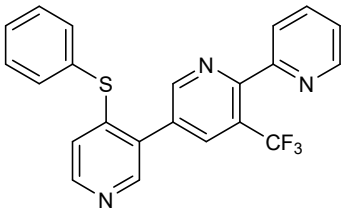
MHz,$CDCl_3$)δ: 148.1, 147.4, 147.3, 135.3, 130.7, 130.5, 129.3, 126.3, 126.2, 124.0, 116.5, 111.5, 71.7, 5 9.7, 59.4, 19.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 323.2, $C_{19}H_{23}N_4O^+$ requires 323.2.

2-Methyl-4-(4-((4-(phenylthio)pyridin-3-yl)methyl)piperazin-1-yl)quinoline (3bf)



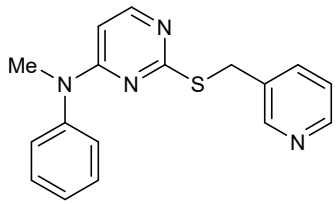
Prepared according to general procedure C sodium hydride (60% dispersion in mineral oil, 6 mg, 0.15 mmol), benzenethiol (16 μL, 0.15 mmol), (3-((4-(2-methylquinolin-4-yl)piperazin-1-yl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (73 mg, 0.10 mmol) and DME (0.4 mL). Flash column chromatography (silica gel, gradient elution: 100% EtOAc to 1% NEt_3 in EtOAc) afforded the *title compound* (3bf) as an orange oil (15 mg, 0.034 mmol, 34% yield). IR ν_{max}/cm^{-1} (film): 3061, 2933, 2825, 2361, 2340, 2205, 1589, 1574, 1416, 1283, 1192, 1136, 1006, 905, 726; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.44 (1H, s), 8.22 (1H, d, *J* = 5.4 Hz), 7.98 (2H, t, *J* = 7.7 Hz), 7.65-7.58 (1H, m), 7.56-7.51 (2H, m), 7.48-7.39 (4H, m), 6.75 (1H, s), 6.71 (1H, d, *J* = 5.4 Hz), 3.75 (2H, s), 3.33-3.17 (4H, m), 3.87-3.78 (4H, m), 2.68 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 157.0, 151.0, 149.6, 149.2, 148.6, 135.1, 131.2, 130.5, 129.9, 129.4, 129.2, 129.0, 124.5, 123.5, 121.9, 121.4, 109.5, 58.4, 52.7, 52.1, 25.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 427.4, $C_{26}H_{27}N_4S^+$ requires 427.2.

4''-(Phenylthio)-3'-(trifluoromethyl)-2,2':5',3''-terpyridine (3bd)



Prepared according to general procedure C sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzenethiol (77 μL, 0.75 mmol), triphenyl(3'-(trifluoromethyl)-[2,2':5',3''-terpyridin]-4''-yl)phosphonium trifluoromethanesulfonate (356 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 100% EtOAc) followed by a second flash column (20% EtOAc, 10% NEt_3 in hexanes) afforded the *title compound* (3bd) as a yellow amorphous solid (132 mg, 0.32 mmol, 65% yield). IR ν_{max}/cm^{-1} (film): 3060, 2925, 2227, 1569, 1448, 1429, 1331, 1285, 1162, 1138, 1019, 906, 727, 689; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.98 (1H, d, *J* = 1.9 Hz), 8.76 (1H, d, *J* = 4.8 Hz), 8.40 (1H, s), 8.37 (1H, d, *J* = 5.5 Hz), 8.28 (1H, d, *J* = 2.0 Hz), 7.88 (1H, td, *J* = 7.8, 1.8 Hz), 7.80-7.76 (1H, m), 7.55-7.39 (6H, m), 6.80 (1H, d, *J* = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.5, 156.1, 151.8, 149.8, 149.8, 149.4, 149.1, 136.5, 136.2 (q, J = 5.0 Hz), 135.4, 132.0, 130.2, 130.0, 129.8, 128.9, 125.0 (q, J = 33.0 Hz), 123.4 (q, J = 273.1 Hz), 123.8, 123.7, 120.7; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −57.64 ; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 410.2, $C_{22}H_{15}F_3N_3S^+$ requires 410.1.

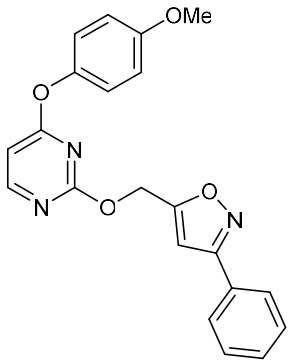
N-Methyl-N-phenyl-2-((pyridin-3-ylmethyl)thio)pyrimidin-4-amine (3bh)



Prepared according to general procedure E using n-butyl lithium (1.6 M in hexanes, 234 μL, 0.38 mmol), *N*-methylaniline (40.6 μL, 0.38 mmol), triphenyl(2-((pyridin-3-ylmethyl)thio)pyrimidin-4-

yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol) and THF (1.0 mL). Flash column chromatography (silica gel was packed with hexanes and neutralized with NEt_3: 15% EtOAc in toluene) afforded the *title compound* (3bh) as a yellow oil (29 mg, 0.093 mmol, 37% yield). IR ν_{max}/cm^{-1} (film): 3035, 2927, 2224, 1710, 1600, 1568, 1498, 1348, 1200, 975, 904, 726, 647; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.64 (1H, d, *J* = 1.8 Hz), 8.47 (1H, dd, *J* = 1.5, 4.9 Hz), 7.87 (1H, d, *J* = 6.1 Hz), 7.77-7.72 (1H, m), 7.48-7.41 (2H, m), 7.35-7.30 (1H, m), 7.25-7.19 (3H, m), 5.99 (1H, d, *J* = 6.0 Hz), 4.36 (2H, s), 3.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7, 161.7, 154.9, 150.2, 148.3, 144.1, 136.3, 134.5, 130.0, 127.3, 126.9, 123.3, 100.9, 37.9, 32.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 309.2, $C_{17}H_{17}N_4S^+$ requires 309.1.

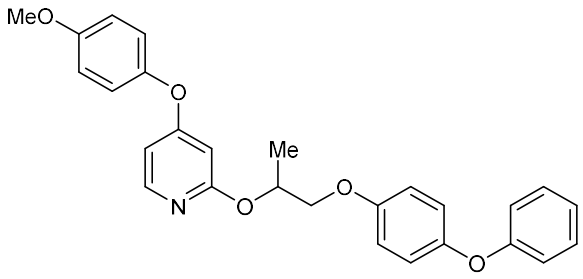
5-(((4-(4-Methoxyphenoxy)pyrimidin-2-yl)oxy)methyl)-3-phenylisoxazole (3bg)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.375 mmol), 4-methoxyphenol (47 mg, 0.38 mmol), 15-crown-5 (74 μL, 0.38 mmol), triphenyl(2-((3-phenylisoxazol-5-yl)methoxy)pyrimidin-4-yl)phosphonium trifluoromethanesulfonate (166 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel, gradient elution: 4% EtOAc in toluene to 8% EtOAc in toluene) afforded the *title compound* (3bg) as a clear oil (52 mg, 0.14 mmol, 55% yield). IR ν_{max}/cm^{-1} (film): 3053, 2917, 2848, 2247, 1610, 1574, 1504, 1441, 1272, 1244, 1193, 1080, 905, 726, 693; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.36 (1H, d, *J* = 5.6 Hz), 7.80-7.74 (2H, m), 7.47-7.42 (3H, m), 7.10-7.04 (2H, m), 6.96-6.90 (2H, m), 6.53 (1H, d, *J* = 5.6 Hz), 6.51 (1H, s), 5.42 (2H, s), 3.82 (3H, s); ^{13}C NMR

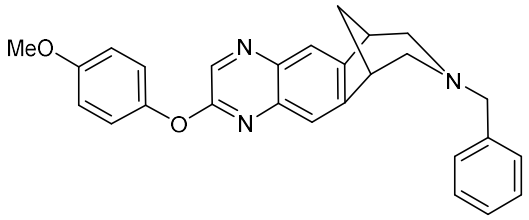
(100 MHz, $CDCl_3$) δ: 171.6, 167.9, 164.2, 162.4, 160.3, 157.4, 145.5, 130.0, 128.9, 126.8, 122.4, 114.8, 102.3, 102.2, 101.8, 59.7, 55.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 376.2, $C_{21}H_{18}N_3O_4^+$ requires 376.1.

4-(4-Methoxyphenoxy)-2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (3bp)



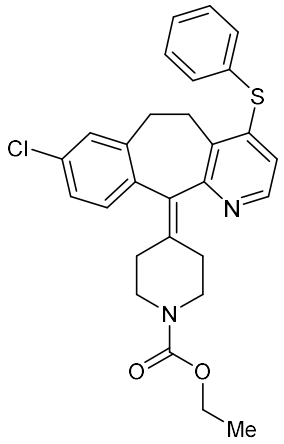
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.375 mmol), 4-methoxyphenol (47 mg, 0.38 mmol), 15-crown-5 (74 μL, 0.38 mmol), (2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (183 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the *title compound* (3bp) as a clear oil (56 mg, 0.13 mmol, 50% yield). IR ν_{max}/cm^{-1} (film): 3042, 2932, 2836, 2578, 2250, 2050, 1594, 1502, 1488, 1472, 1218, 1203, 1147, 906, 839, 728; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.99 (1H, d, J = 5.9 Hz), 7.34-7.27 (2H, m), 7.08-6.99 (3H, m), 6.99-6.88 (8H, m), 6.52 (1H, dd, J = 5.9, 2.2 Hz), 6.12 (1H, d, J = 2.2 Hz), 5.56 (1H, m), 4.18-4.10 (1H, m), 4.08-4.01 (1H, m), 3.82 (3H, m), 1.45 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 165.0, 158.5, 157.1, 155.2, 150.3, 147.8, 147.3, 129.6, 122.4, 122.1, 120.7, 117.6, 115.8, 115.1, 107.0, 97.4, 71.0, 69.6, 55.6, 17.0; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 444.2, $C_{27}H_{26}NO_5^+$ requires 444.2.

(6R,10S)-8-Benzyl-2-(4-methoxyphenoxy)-7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxaline (3bj)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 6 mg, 0.15 mmol), 4-methoxyphenol (19 mg, 0.15 mmol), 15-crown-5 (30 μL, 0.15 mmol), ((6R,10S)-8-benzyl-7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxalin-2-yl)triphenylphosphonium trifluoromethanesulfonate (71 mg, 0.10 mmol) and THF (0.2 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the *title compound* (3bj) as a yellow oil (24 mg, 0.057 mmol, 57% yield). IR ν_{max}/cm^{-1} (film): 3016, 2950, 1836, 2791, 2162, 2049, 1568, 1503, 1347, 1290, 1202, 907, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, s), 7.73 (1H, s), 7.50 (1H, s), 7.24-7.19 (2H, m), 7.14-7.09 (3H, m), 7.00-6.94 (2H, m), 6.88-6.81 (2H, m), 3.85 (3H, s), 3.46 (2H, s), 3.33-3.21 (2H, m), 2.98-2.87 (2H, m), 2.52 (2H, t, *J* = 8.3 Hz), 2.34-2.25 (1H, m), 1.81 (1H, d, *J* = 10.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.9, 156.8, 151.1, 147.8, 146.6, 140.1, 139.6, 138.3, 136.6, 128.3, 128.0, 126.6, 122.3, 120.2, 119.3, 114.6, 61.6, 57.3, 57.2, 55.6, 43.4, 41.4, 41.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 424.2, $C_{27}H_{26}N_3O_2^+$ requires 424.2.

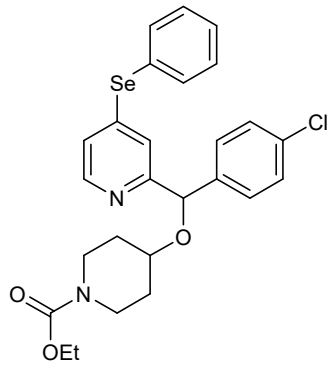
Ethyl 4-(8-chloro-4-(phenylthio)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (3bm)



Prepared according to general procedure C sodium hydride (60% dispersion in mineral oil, 12 mg, 0.30 mmol), benzenethiol (31 μL, 0.30 mmol), (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (159 mg, 0.20 mmol) and THF (0.40 mL). Flash column chromatography (silica gel was packed with hexanes and neutralized with NEt_3, gradient elution: 60% CH_2Cl_2 in hexanes to 70% CH_2Cl_2 in hexanes to 10 % MeOH in CH_2Cl_2) followed by a second flash column (silica gel was packed with hexanes and neutralized with NEt_3, gradient elution: 9.5% CH_2Cl_2, 0.5% NEt_3 in toluene to 8% CH_2Cl_2, 2% NEt_3 in toluene) afforded the *title compound* (3bm) as a white solid (82 mg, 0.17 mmol, 83% yield). 198-201 °C; IR ν_{max}/cm^{-1} (film): 3055, 2977, 2918, 2862, 2360, 2339, 2049, 1693, 1546, 1430, 1222, 1109, 748; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.08 (1H, d, J = 5.4 Hz), 7.54-7.42 (5H, m), 7.21 (1H, d, J = 1.9 Hz), 7.18-7.09 (2H, m), 6.44 (1H, d, J = 5.4 Hz), 4.14 (2H, q, J = 7.2 Hz), 3.90-3.70 (2H, br), 3.50-3.40 (1H, m), 3.28-3.10 (3H, m), 3.04-2.83 (2H, m), 2.54-2.43 (1H, m), 2.40-2.27 (3H, m), 1.25 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 159.2, 155.5, 150.4, 146.1, 139.7, 137.9, 137.7, 135.6, 134.1, 133.0, 130.2, 130.0, 129.8, 129.5,

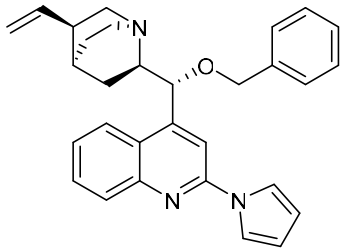
129.1, 128.7, 126.2, 118.8, 61.3, 44.7, 30.9, 30.6, 28.9, 14.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 491.2, $C_{28}H_{28}ClN_2O_2S^+$ requires 491.2.

Ethyl 4-((4-chlorophenyl)(4-(phenylselanyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (3bn)



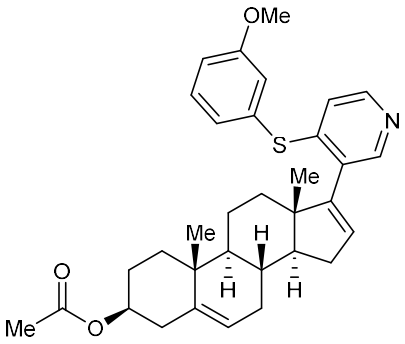
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), benzeneselenol (40 μL, 0.38 mmol), (2-((4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (196 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel: 30% EtOAc in toluene) afforded the *title compound* (3bn) as a clear oil (93 mg, 0.18 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 3289, 3049, 2927, 2667, 2349, 2245, 1690, 1567, 1226, 1085, 1014; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (1H, d, *J* = 5.2 Hz), 7.65-7.60 (2H, m), 7.48-7.36 (3H, m), 7.32 (1H, d, *J* = 1.5 Hz), 7.30-7.23 (4H, m), 6.96 (1H, dd, *J* = 5.3, 1.7 Hz), 5.47 (1H, s), 4.13 (2H, q, *J* = 7.2 Hz), 3.65-3.50 (3H, m), 3.25-3.14 (2H, m), 1.80-1.70 (1H, m), 1.70-1.46 (3H, m), 1.26 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.7, 155.5, 148.7, 147.2, 139.8, 136.5, 133.5, 129.9, 129.5, 128.6, 128.2, 126.1, 122.5, 120.3, 80.6, 73.3, 61.3, 40.8 (rot), 31.0 (rot), 30.7, 14.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 531.2, $C_{26}H_{28}ClN_2O_3Se^+$ requires 531.1.

(1S,2R,4S,5R)-2-((R)-(2-(1H-Pyrrol-1-yl)quinolin-4-yl)(benzyloxy)methyl)-5-vinylquinuclidine (3bk)



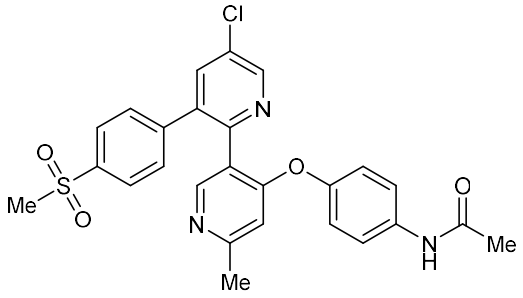
Prepared according to general procedure D using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), 1*H*-pyrrole (26 μL, 0.38 mmol), (4-((R)-(benzyloxy)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (199 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel was packed with hexanes and neutralized with NEt_3: 80% EtOAc in hexanes) followed by another flash column (silica gel, gradient elution: 100% EtOAc to 5% NEt_3 in EtOAc) afforded the *title compound* (3bk) as white solid (61 mg, 0.14 mmol, 54% yield). mp: 70-76 °C; IR ν_{max}/cm^{-1} (film): 3149, 3064, 3030, 2932, 2862, 1635, 1599, 1479, 1357, 1256, 1066, 959, 731, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09-8.02 (2H, m), 7.75-7.63 (4H, m), 7.54-7.47 (1H, m), 7.41-7.30 (5H, m), 6.40 (2H, t, J = 2.2 Hz), 5.80-5.66 (1H, m), 5.32 (1H, br), 4.99-4.85 (2H, m), 4.48 (2H, s), 3.48-3.34 (1H, m), 3.20-3.05 (2H, m), 2.77-2.58 (2H, m), 2.32-2.22 (1H, m), 1.86-1.46 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.8, 149.7, 147.8, 141.9, 137.7, 130.0, 129.5, 128.6, 127.9, 127.8, 127.6, 125.6, 124.6, 123.1 (br), 118.5, 114.3, 111.6, 108.8 (br), 71.6, 60.8, 57.1, 43.3, 40.0, 27.9, 27.8, 22.7 (br); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 450.3, $C_{30}H_{32}N_3O^+$ requires 450.3.

(3S,8R,9S,10R,13S,14S)-17-(4-((3-Methoxyphenyl)thio)pyridin-3-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (3bo)



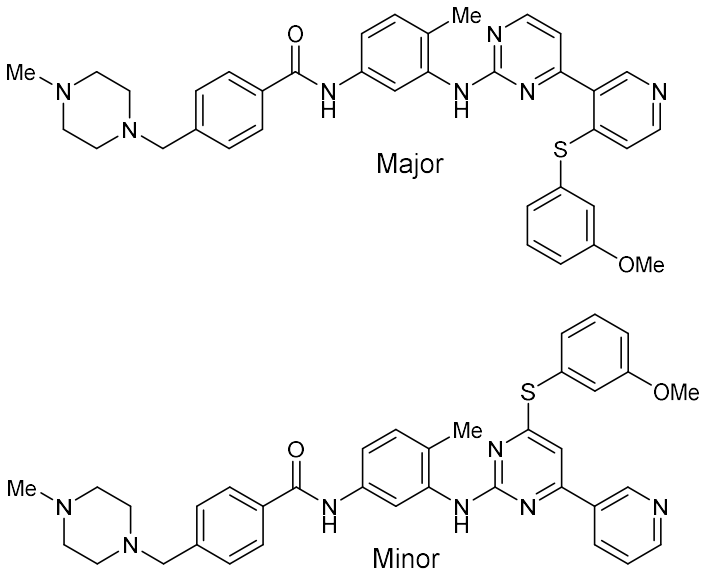
Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 11 mg, 0.28 mmol), 3-methoxybenzenethiol (34 μL, 0.28 mmol), (3-((3S,8R,9S,10R,13S,14S)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (120 mg, 0.15 mmol) and THF (0.3 mL). Flash column chromatography (basic alumina, gradient elution: 20% EtOAc in hexanes to 30% EtOAc in hexanes) afforded the *title compound* (3bo) as a clear oil (49 mg, 0.092 mmol, 61% yield). IR ν_{max}/cm^{-1} (film): 3246, 3032, 2935, 2797, 2361, 2341, 2162, 1655, 1571, 1446, 1402, 1282, 1162, 1010, 814, 726; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (1H, s), 8.14 (1H, d, *J* = 5.0 Hz), 7.35 (1H, t, *J* = 8.0 Hz), 7.11-7.07 (1H, m), 7.05-7.02 (1H, m), 7.00-6.95 (1H, m), 6.65 (1H, d, *J* = 5.3 Hz), 5.97-5.93 (1H, m), 5.43 (1H, d, *J* = 4.9 Hz), 4.68-4.57 (1H, m), 3.82 (3H, s), 2.42-2.31 (3H, m), 2.20-2.00 (6H, m), 1.92-1.81 (2H, m), 1.77-1.52 (7H, m), 1.15-1.00 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 160.4, 157.5, 155.0, 150.3, 149.6, 148.2, 147.7, 140.0, 132.9, 131.8, 130.7, 127.5, 122.3, 120.3, 115.4, 73.9, 56.9, 55.4, 50.4, 49.7, 38.1, 36.9, 36.8, 34.7, 32.3, 31.6, 30.7, 27.7, 21.4, 20.7, 19.3, 16.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 530.3, $C_{33}H_{40}NO_3S^+$ requires 530.3.

N-(4-((5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)oxy)phenyl)acetamide (3bl)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.375 mmol), N-(4-hydroxyphenyl)acetamide (57 mg, 0.38 mmol), 15-crown-5 (74 μL, 0.38 mmol), (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)triphenylphosphonium trifluoromethanesulfonate (192 mg, 0.25 mmol) and DME (0.5 mL). Flash column chromatography (silica gel, gradient elution: 3% MeOH in DCM to 5% MeOH in DCM) afforded the *title compound* (3bl) as a clear oil (49 mg, 0.12 mmol, 48% yield). IR ν_{max}/cm^{-1} (film): 3317, 3062, 2929, 2252, 1980, 1676, 1599, 1504, 1313, 1151, 904, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (1H, d, J = 2.3 Hz), 8.66 (1H, s), 7.84-7.79 (2H, m), 7.72 (1H, d, J = 2.3 Hz), 7.41-7.33 (4H, m), 7.20-7.14 (1H, br), 6.24-6.18 (3H, m), 3.09 (3H, s), 2.43 (3H, s), 2.17 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 162.6, 160.0, 150.0, 148.7, 148.4, 148.0, 144.1, 140.2, 137.3, 136.2, 132.0, 129.6, 127.7, 123.1, 121.6, 120.4, 109.5, 69.1, 44.3, 24.3, 23.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 508.1, $C_{26}H_{23}ClN_3O_4S^+$ requires 508.1.

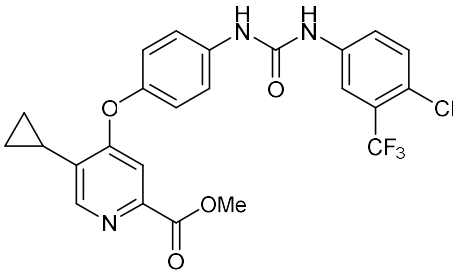
N-(3-((4-(4-((3-Methoxyphenyl)thio)pyridin-3-yl)pyrimidin-2-yl)amino)-4-methylphenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (3bq)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 6 mg, 0.15 mmol), 3-methoxybenzenethiol (19 μL, 0.15 mmol), (3-(2-((2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (90 mg, 0.10 mmol) and THF (0.2 mL). Flash column chromatography (silica gel was packed with hexanes and neutralized with NEt_3: 4% MeOH in DCM) afforded the *title compound* (3bq) as a yellow solid (40 mg, 0.063 mmol, 57% yield, 6% regioisomer) mp: 78-84 °C; IR ν_{max}/cm^{-1} (film): 3246, 3032, 2935, 2797, 2361, 2341, 2162, 1655, 1571, 1446, 1402, 1282, 1162, 1010, 814, 726; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, s), 8.56 (1H, d, *J* = 5.1 Hz), 8.35 (1H, d, *J* = 2.1 Hz), 8.29 (1H, d, *J* = 5.5 Hz), 7.86 (1H, s), 7.77 (2H, d, *J* = 8.2 Hz), 7.58 (1H, dd, *J* = 8.1, 1.6 Hz), 7.41 (2H, d, *J* = 8.2 Hz), 7.31-7.19 (3H, m), 7.09 (1H, d, *J* = 5.1 Hz), 7.07-7.04 (1H, m), 7.02-7.00 (1H, m), 6.95 (1H, dd, *J* = 8.3, 2.4 Hz), 6.78 (1H, d, *J* = 5.5 Hz), 3.75 (3H, s), 3.56 (2H, s), 2.60-2.41 (8H, br), 2.35 (3H, s), 2.30 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.3, 163.6, 160.5, 160.0, 158.8, 150.2, 149.8, 149.5, 142.5, 137.4, 136.6, 133.8, 131.4, 131.0, 130.9,

130.8, 129.2, 127.6, 127.0, 124.5, 121.3, 120.2, 116.0, 115.8, 113.6, 111.4, 62.5, 55.4, 55.1, 53.1, 46.0, 1 7.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 632.4, $C_{36}H_{38}N_7O_2S^+$ requires 632.3.

Methyl 4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)-5-cyclopropylpicolinate (3bv)



Prepared according to general procedure C using sodium hydride (60% dispersion in mineral oil, 11 mg, 0.275 mmol), 1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(4-hydroxyphenyl)urea (67.1 mg, 0.203 mmol), 15-Crown-5 (40.3 μL, 0.203 mmol), (5-cyclopropyl-2-(methoxycarbonyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (79.3 mg, 0.14 mmol) and DME (0.27 mL). Flash column chromatography (silica: 70% EtOAc in hexanes) followed by a second flash column (silica, gradient elution: 85% EtOAc, 5% NEt_3 in hexanes to 100% EtOAc) afforded the *title compound* (3bv) as an off-white amorphous solid (28 mg, 0.055 mmol, 40% yield). IR ν_{max}/cm^{-1} (film): 3350, 3310, 3125, 3082, 2957, 1731, 1710, 1599, 1552, 1504, 1482, 1418, 1301, 1229, 1203, 1173, 1110, 984, 831, 733; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.24 (1H, s), 9.00 (1H, s), 8.28 (1H, s), 8.12 (1H, d, J = 2.2 Hz), 7.69-7.55 (4H, m), 7.20-7.13 (3H, m), 3.78 (3H, s), 2.27-2.18 (1H, m), 1.12-1.05 (2H, m), 1.00-0.94 (2H, m); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 164.8, 163.6, 152.5, 148.4, 147.7, 146.3, 139.3, 136.8, 132.0, 131.8, 126.7 (q, J = 30.2 Hz), 123.1, 122.8 (q, J = 272.2 Hz), 122.3 (q, J = 1.8 Hz), 121.2, 120.6, 116.8 (q, J = 5.4 Hz), 110.0, 52.3, 8.3, 8.0; ^{19}F NMR (365 MHz, $(CD_3)_2SO$) δ: −62.76 ; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 506.1, $C_{24}H_{20}ClF_3N_3O_4^+$ requires 506.1.

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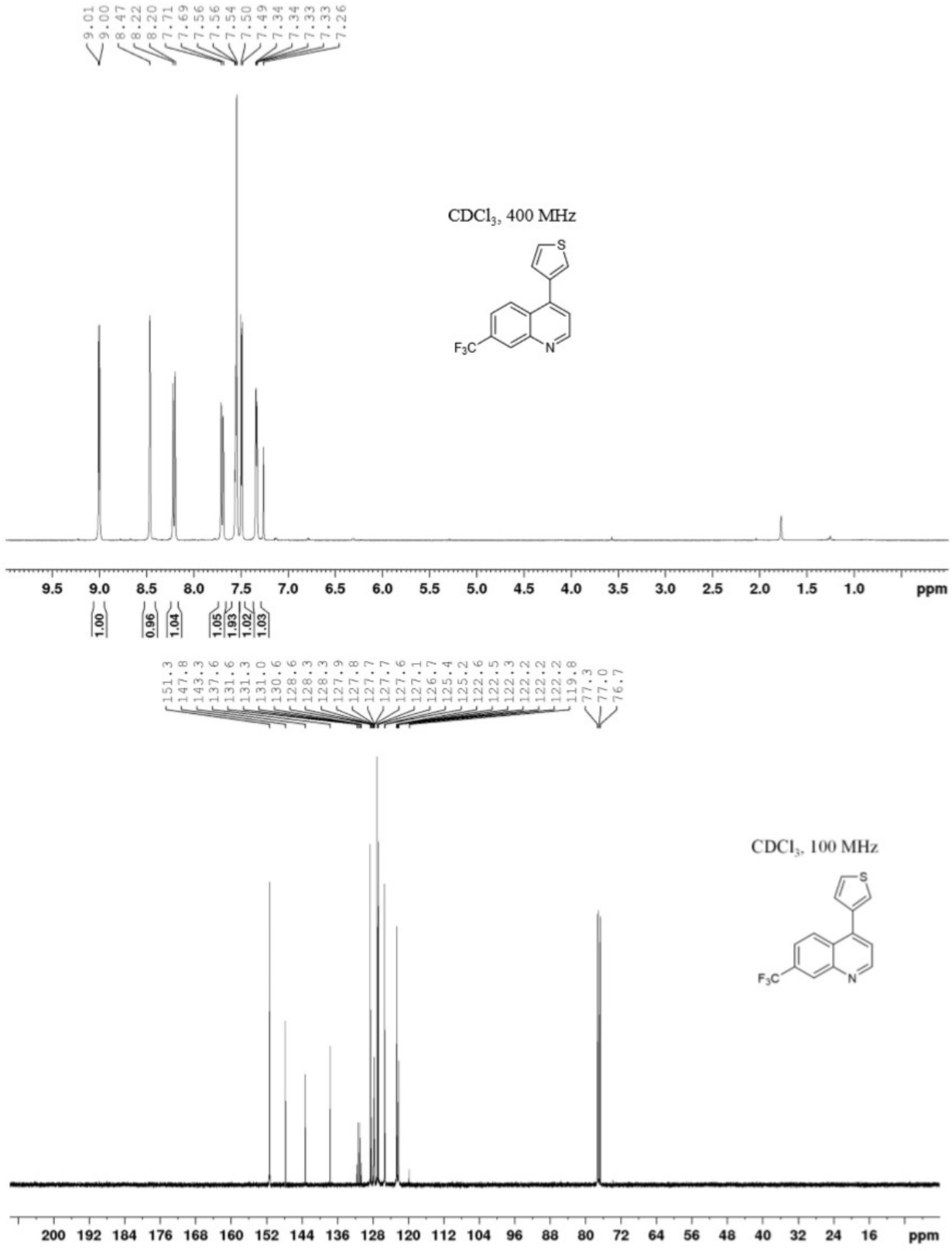
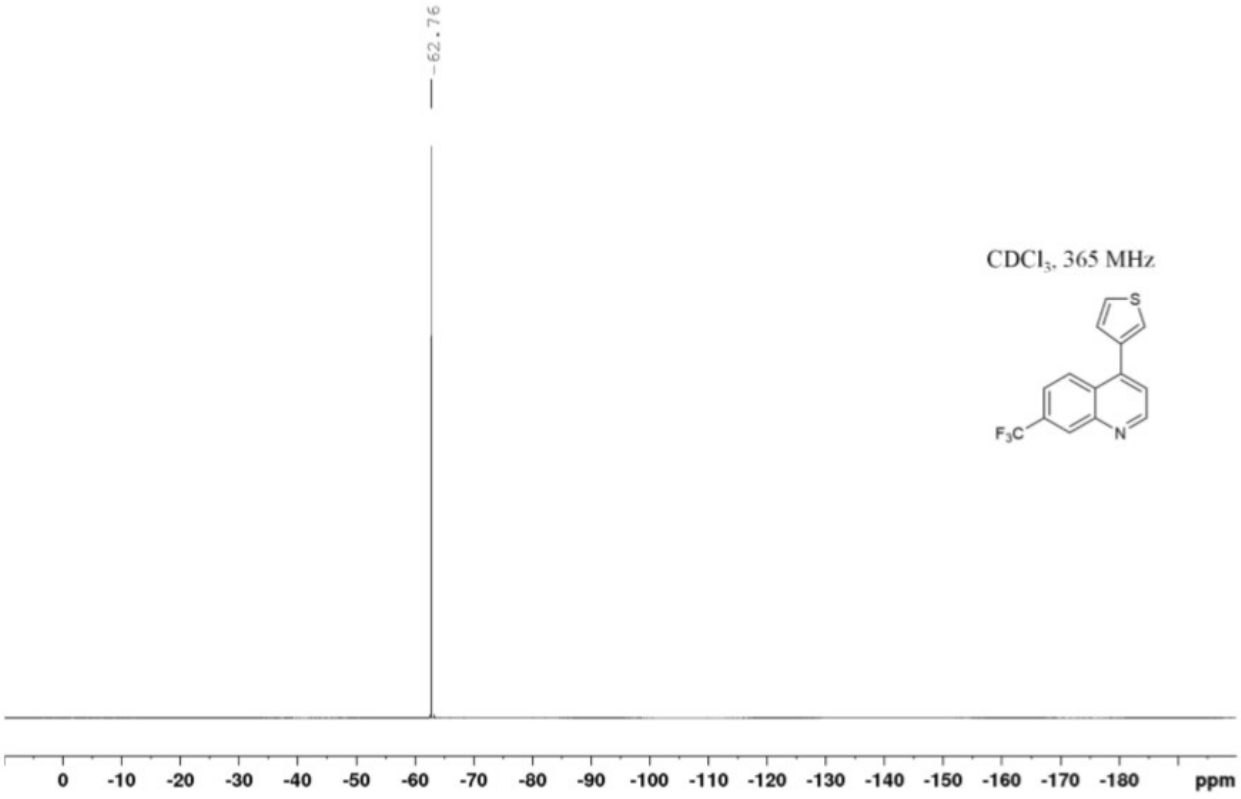
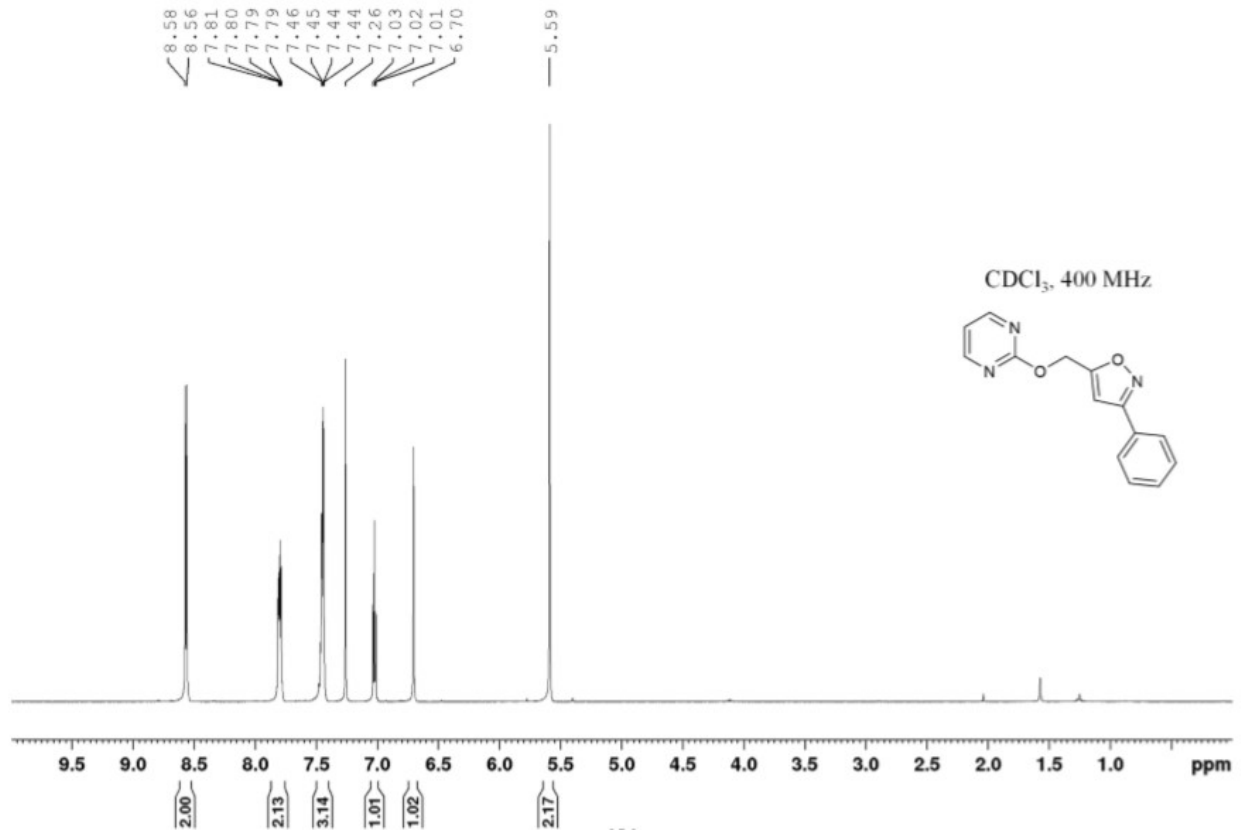
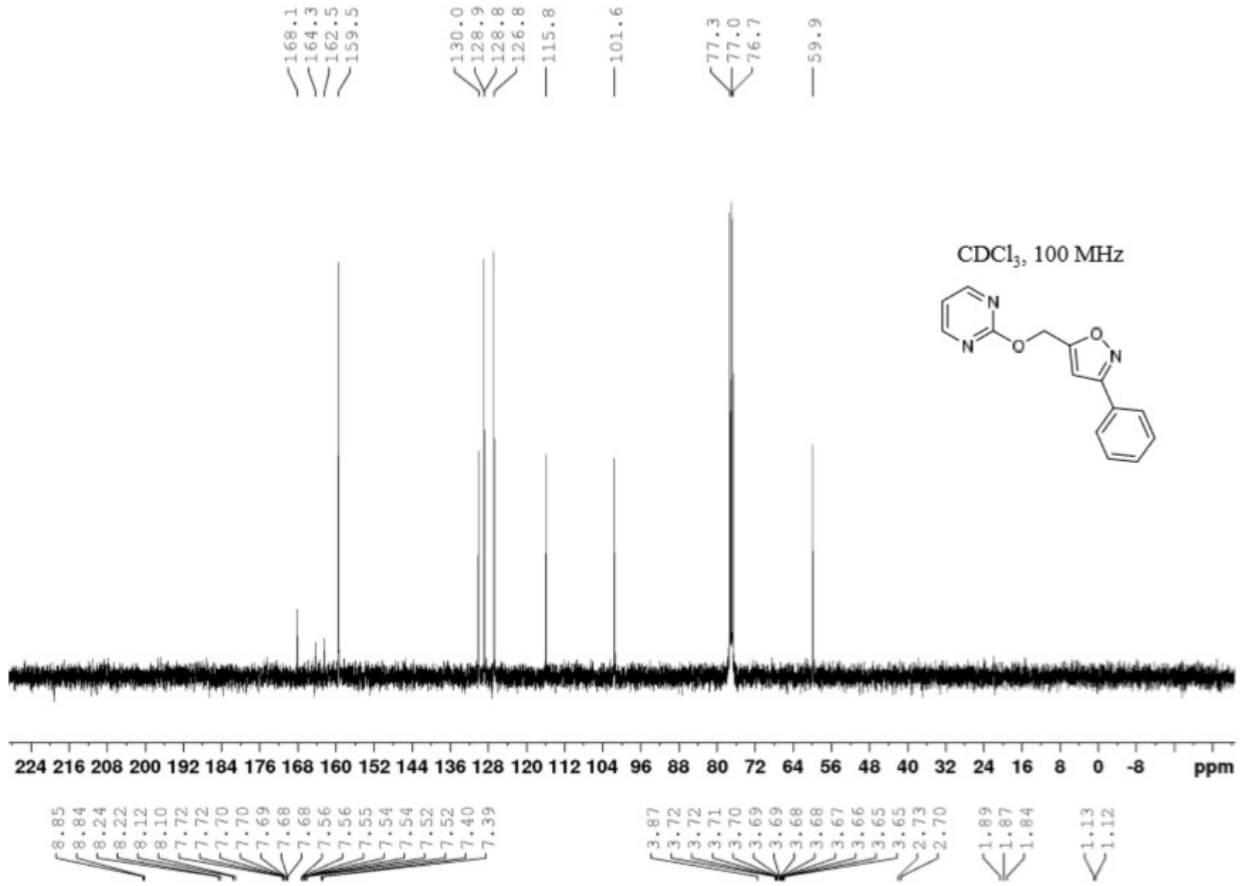
NMR Spectra:


9.01
9.00
8.47
8.22
8.20
7.71
7.69
7.56
7.56
7.54
7.50
7.49
7.34
7.34
7.33
7.33
7.26
CDCl3, 400 MHz
S
F3C
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.96
1.04
1.05
1.93
1.02
1.03
151.3
147.8
143.3
137.6
131.6
131.3
131.0
130.6
128.6
128.3
128.3
127.9
127.8
127.7
127.7
127.6
127.1
126.7
125.4
125.2
122.6
122.5
122.3
122.2
122.2
122.2
119.8
77.3
77.0
76.7
CDCl3, 100 MHz
S
F3C
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


-62.76
CDCl3, 365 MHz
S
F3C
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm


8.58
8.56
7.81
7.80
7.79
7.79
7.46
7.45
7.44
7.44
7.26
7.03
7.02
7.01
6.70
5.59
CDCl3, 400 MHz
N
N
O
O
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.00
2.13
3.14
1.01
1.02
2.17


168.1
164.3
162.5
159.5
130.0
128.9
128.8
126.8
115.8
101.6
77.3
77.0
76.7
59.9
CDCl3, 100 MHz
224 216 208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8 ppm
8.85
8.84
8.24
8.22
8.12
8.10
7.72
7.72
7.70
7.70
7.69
7.68
7.68
7.56
7.56
7.55
7.54
7.54
7.52
7.52
7.40
7.39
3.87
3.72
3.72
3.71
3.70
3.69
3.69
3.68
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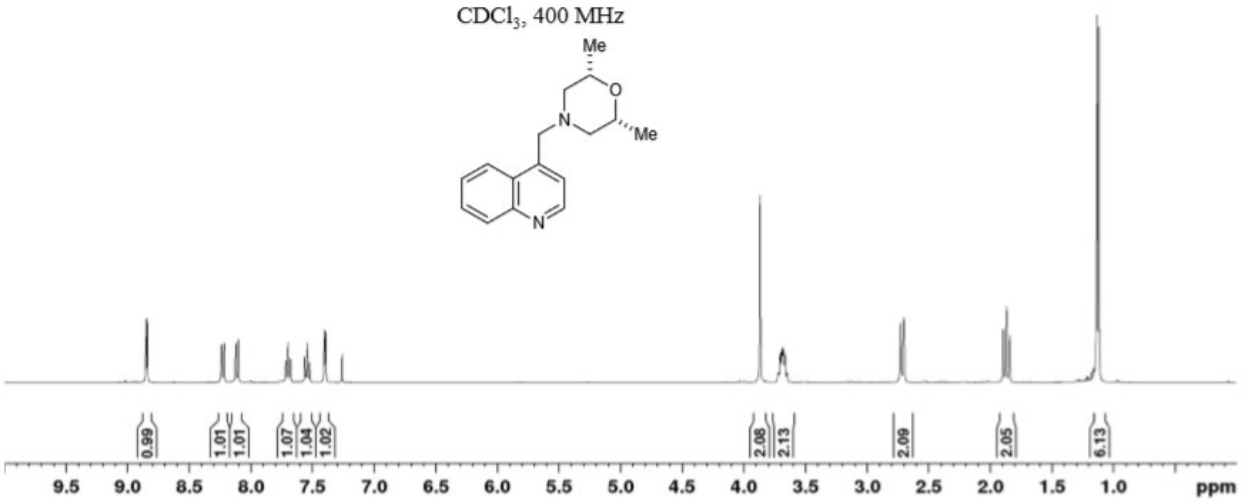
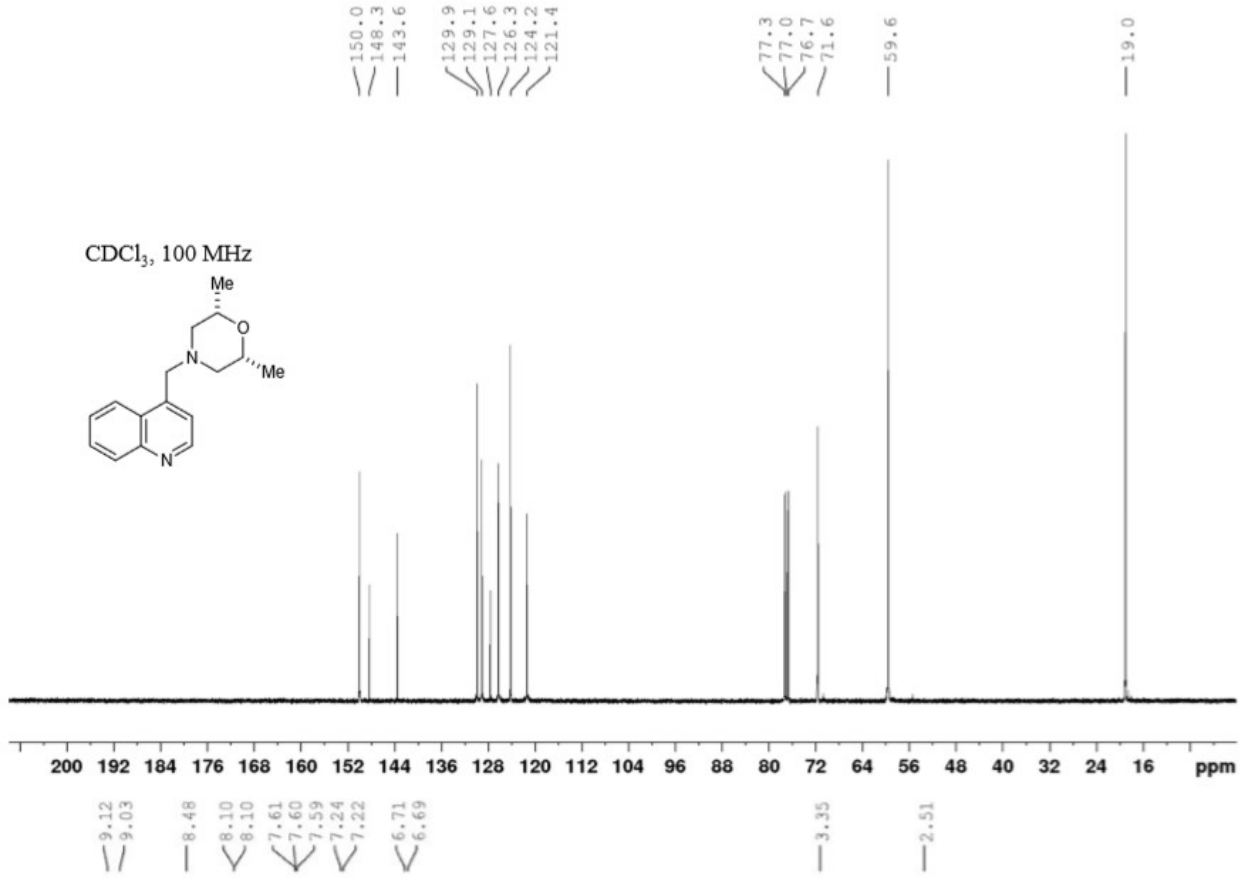
2.70
1.89
1.87
1.84
1.13
1.12


CDCl3, 400 MHz
Me
Me
0.99
1.01
1.01
1.07
1.04
1.02
2.08
2.13
2.09
2.05
6.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


150.0
148.3
143.6
129.9
129.1
127.6
126.3
124.2
121.4
77.3
77.0
76.7
71.6
59.6
19.0
CDCl3, 100 MHz
Me
O
N
Me
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm
9.12
9.03
8.48
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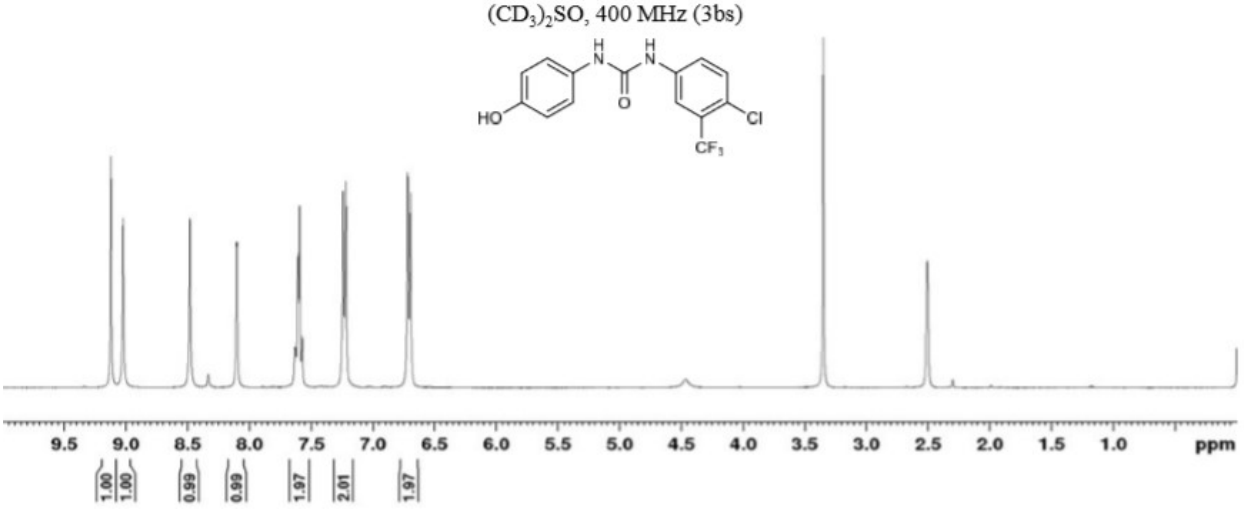
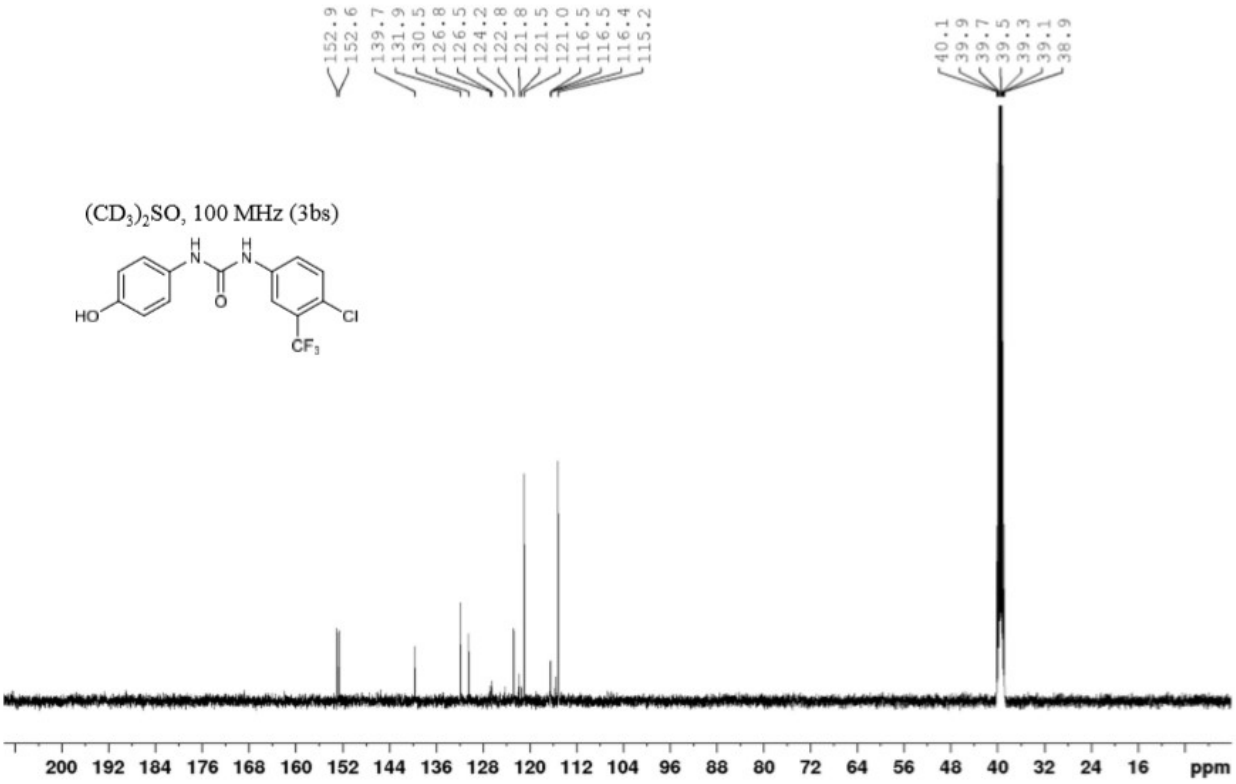
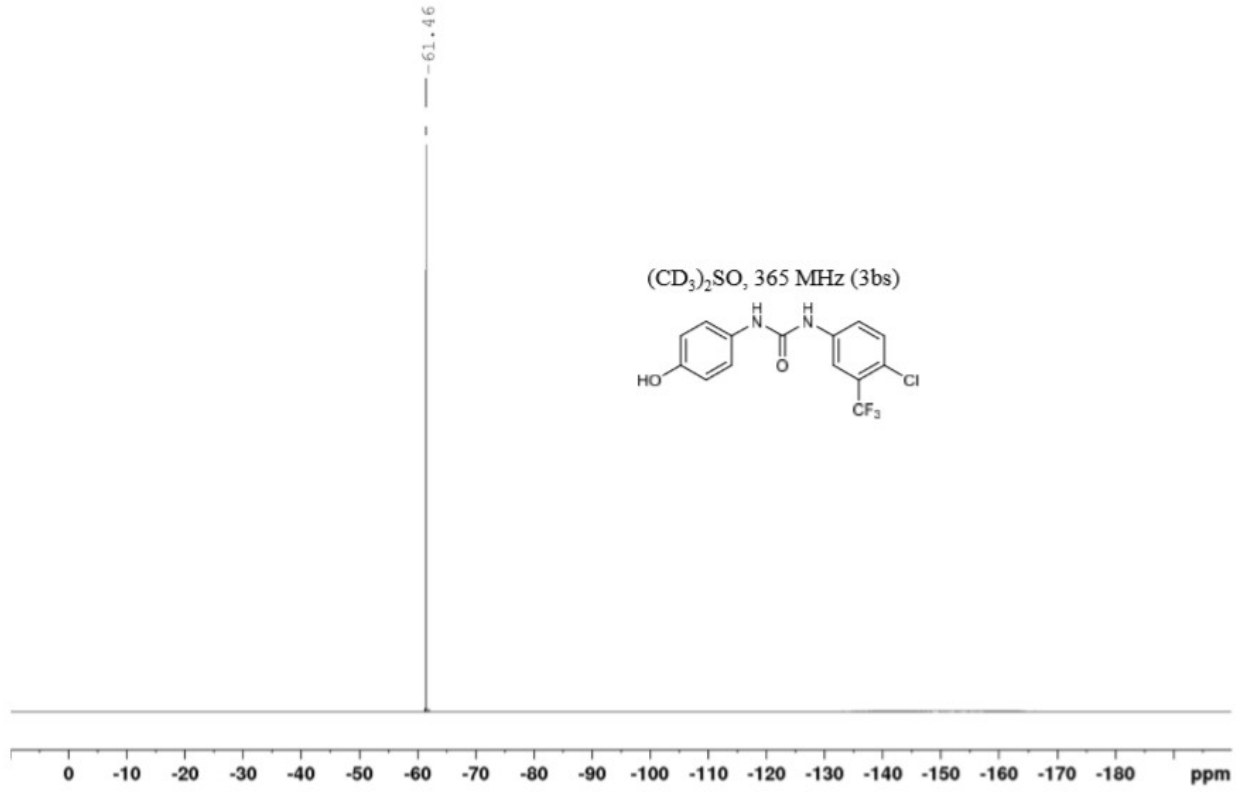
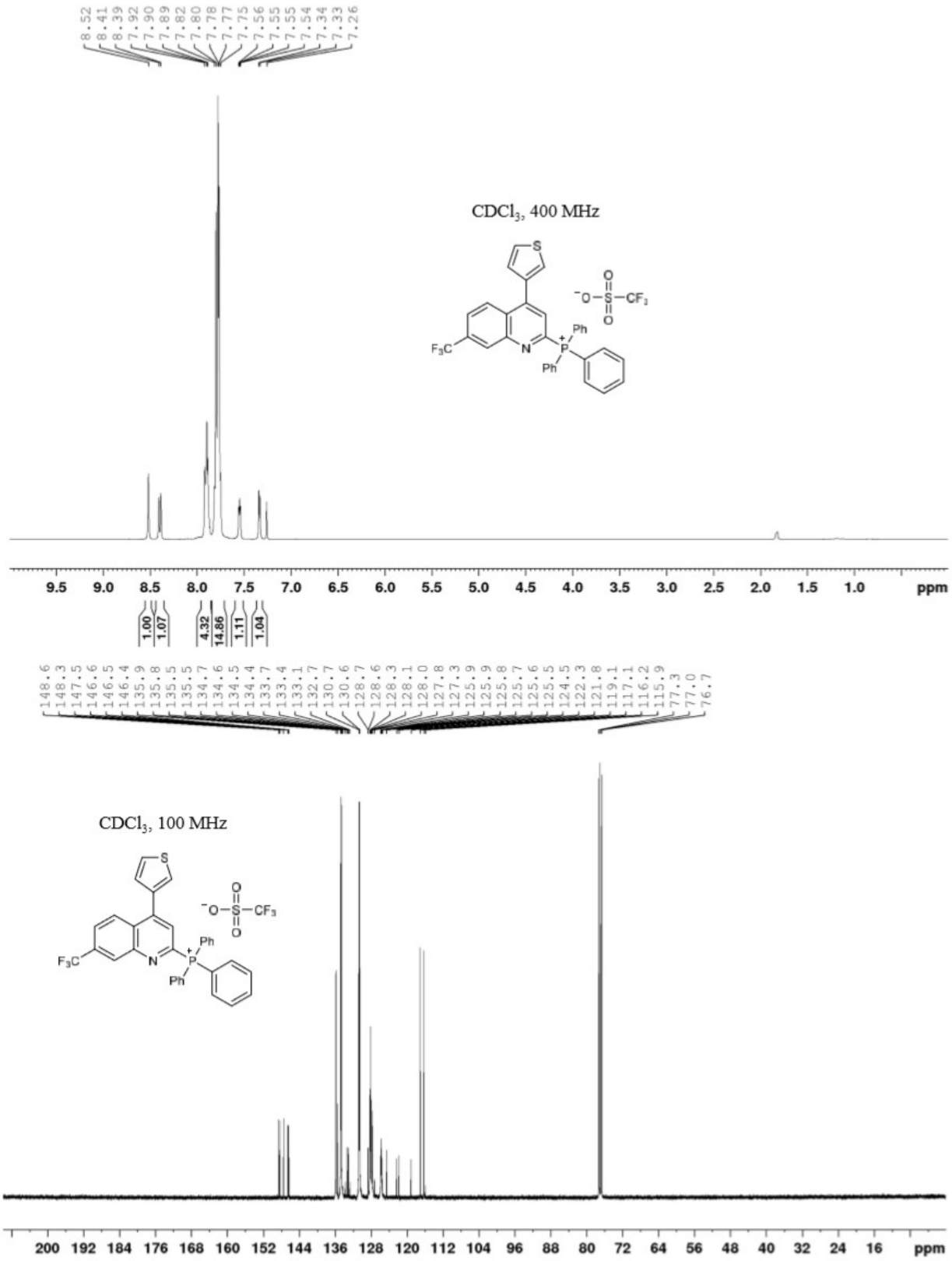
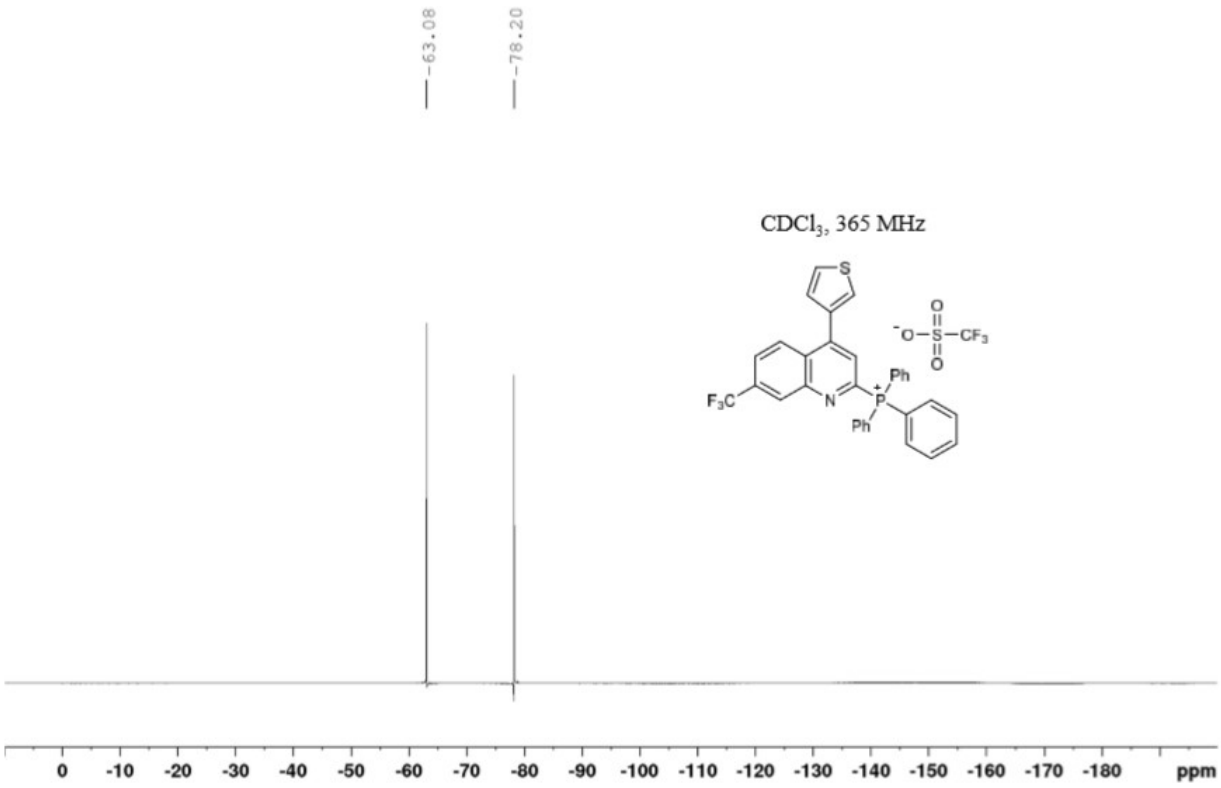
7.24
7.22
6.71
6.69
3.35
2.51

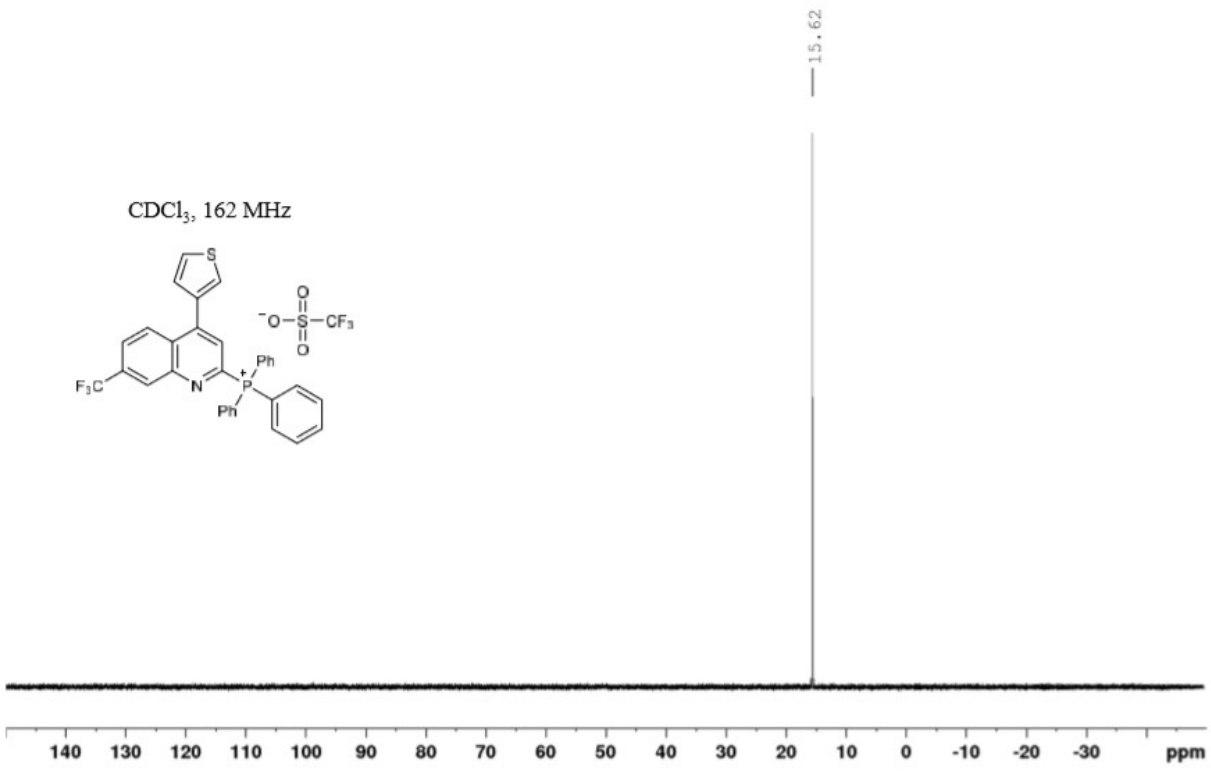

(CD3)2SO, 400 MHz (3bs)
H
N
H
N
O
HO
Cl
CF3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
0.99
0.99
1.97
2.01
1.97

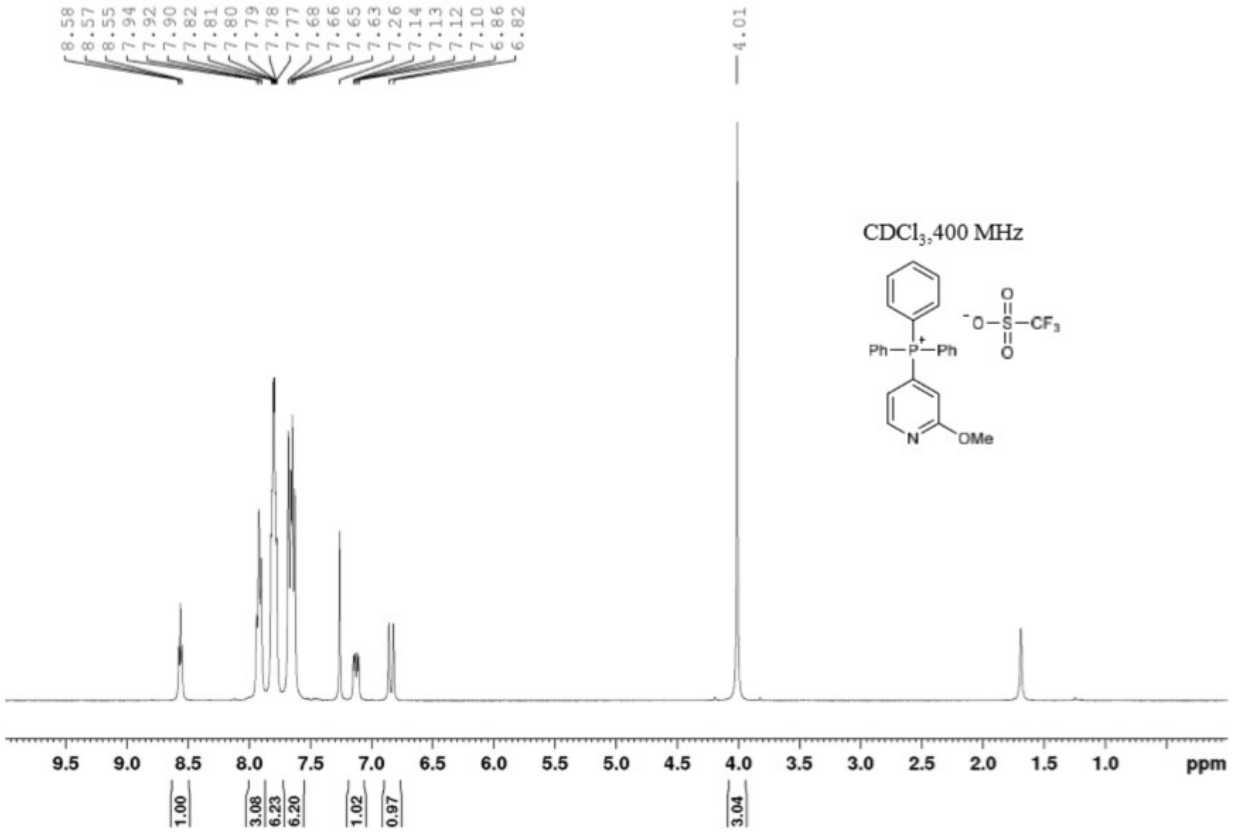

152.9
152.6
139.7
131.9
130.5
126.8
126.5
124.2
122.8
121.8
121.5
121.0
116.5
116.5
116.4
115.2
40.1
39.9
39.7
39.5
39.3
39.1
38.9
(CD3)2SO, 100 MHz (3bs)
HO
Cl
CF3
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

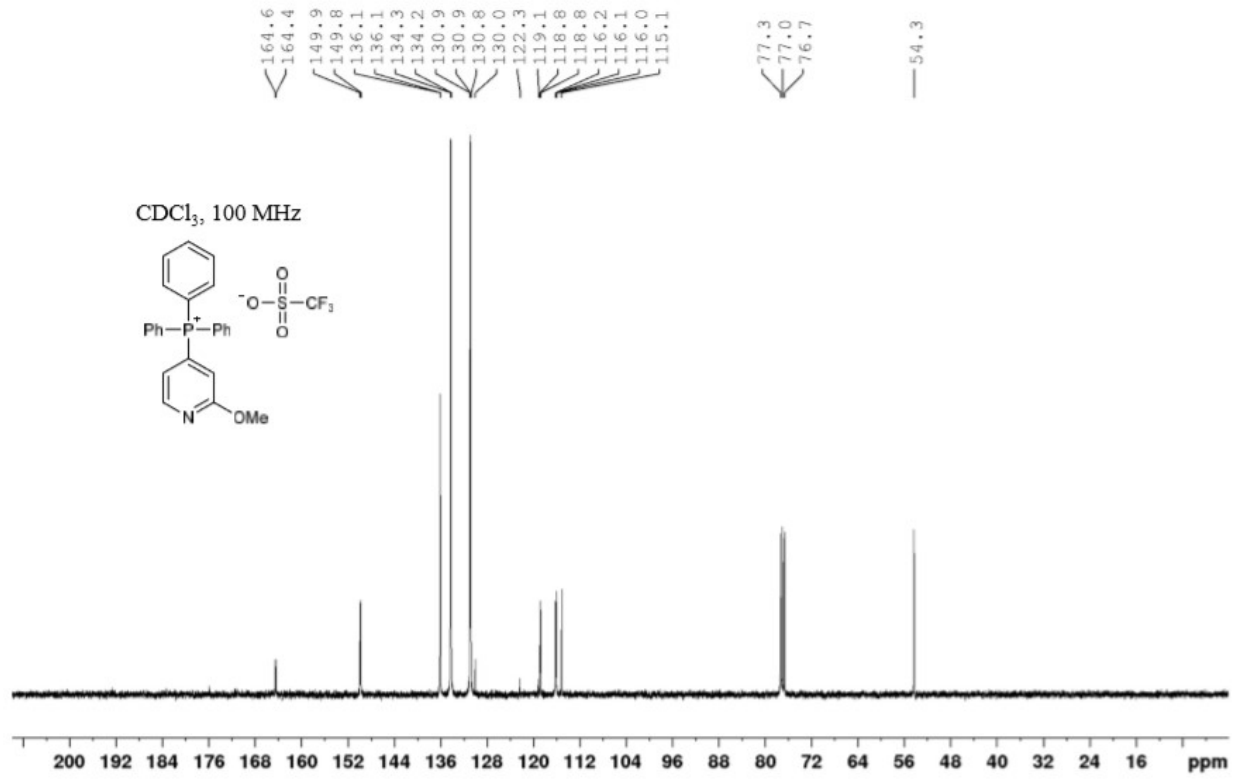

-61.46
(CD3)2SO, 365 MHz (3bs)
HO
Cl
CF3
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

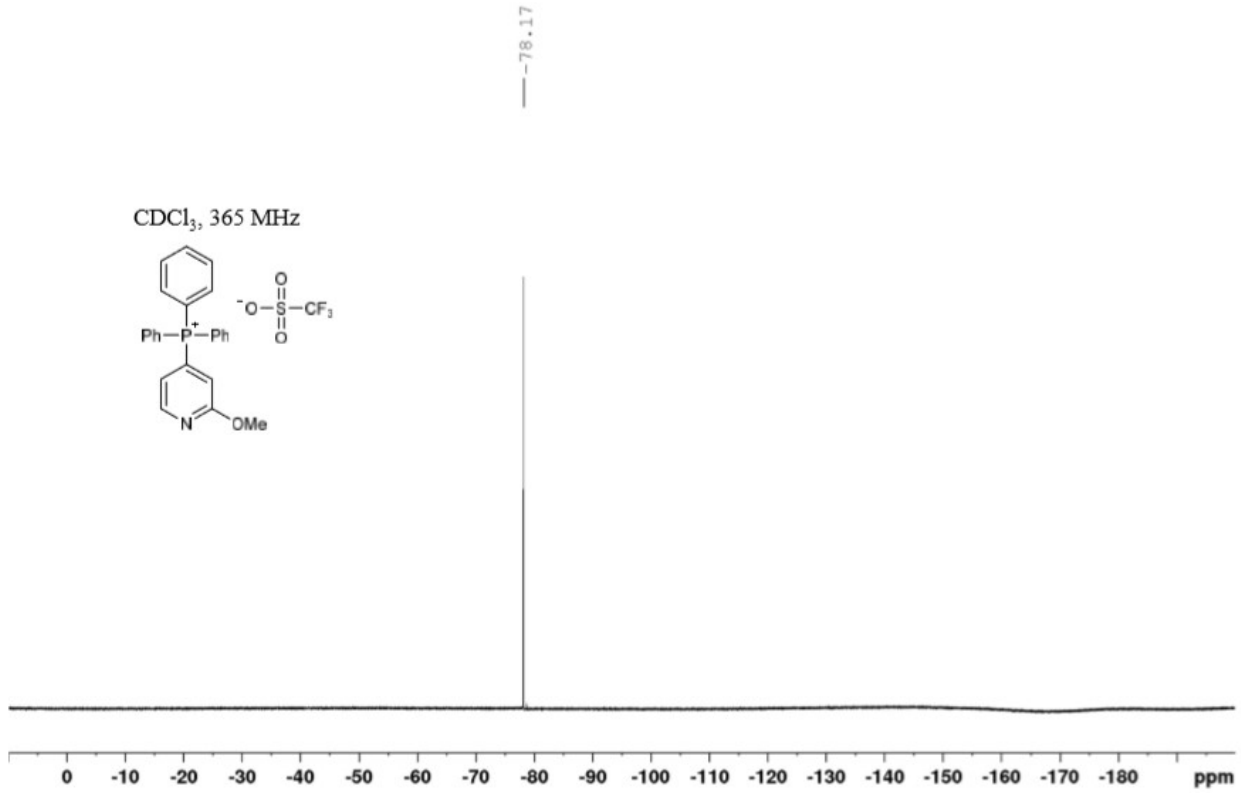

8.52
8.41
8.39
7.92
7.90
7.89
7.82
7.80
7.78
7.77
7.75
7.56
7.55
7.55
7.54
7.34
7.33
7.26
CDCl3, 400 MHz
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 1.07 4.32 14.86 1.11 1.04
148.6
148.3
147.5
146.6
146.5
146.4
135.9
135.8
135.5
135.5
134.7
134.6
134.5
134.4
133.7
133.4
133.1
132.7
130.7
130.6
128.7
128.6
128.3
128.1
128.0
127.8
127.3
125.9
125.9
125.8
125.7
125.6
125.5
124.5
122.3
121.8
119.1
117.1
116.2
115.9
77.3
77.0
76.7
CDCl3, 100 MHz
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

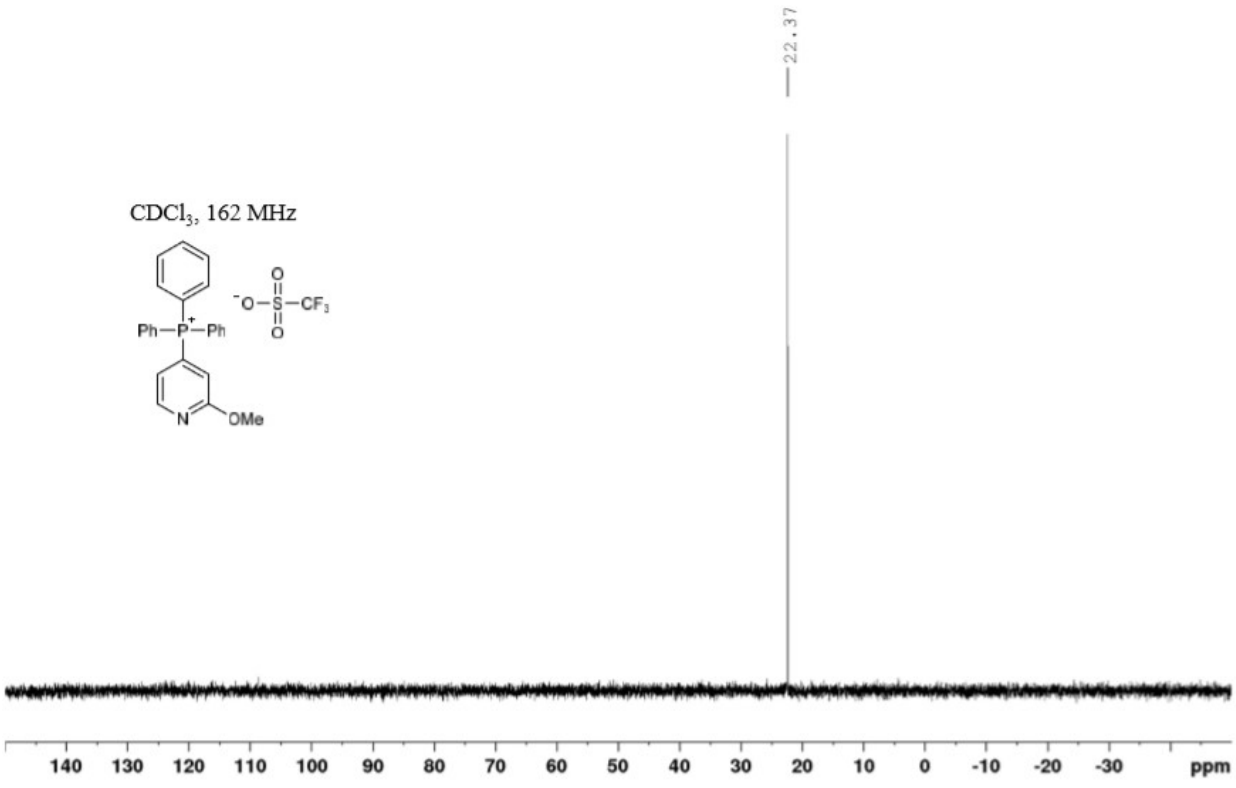

-63.08
-78.20
CDCl3, 365 MHz
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

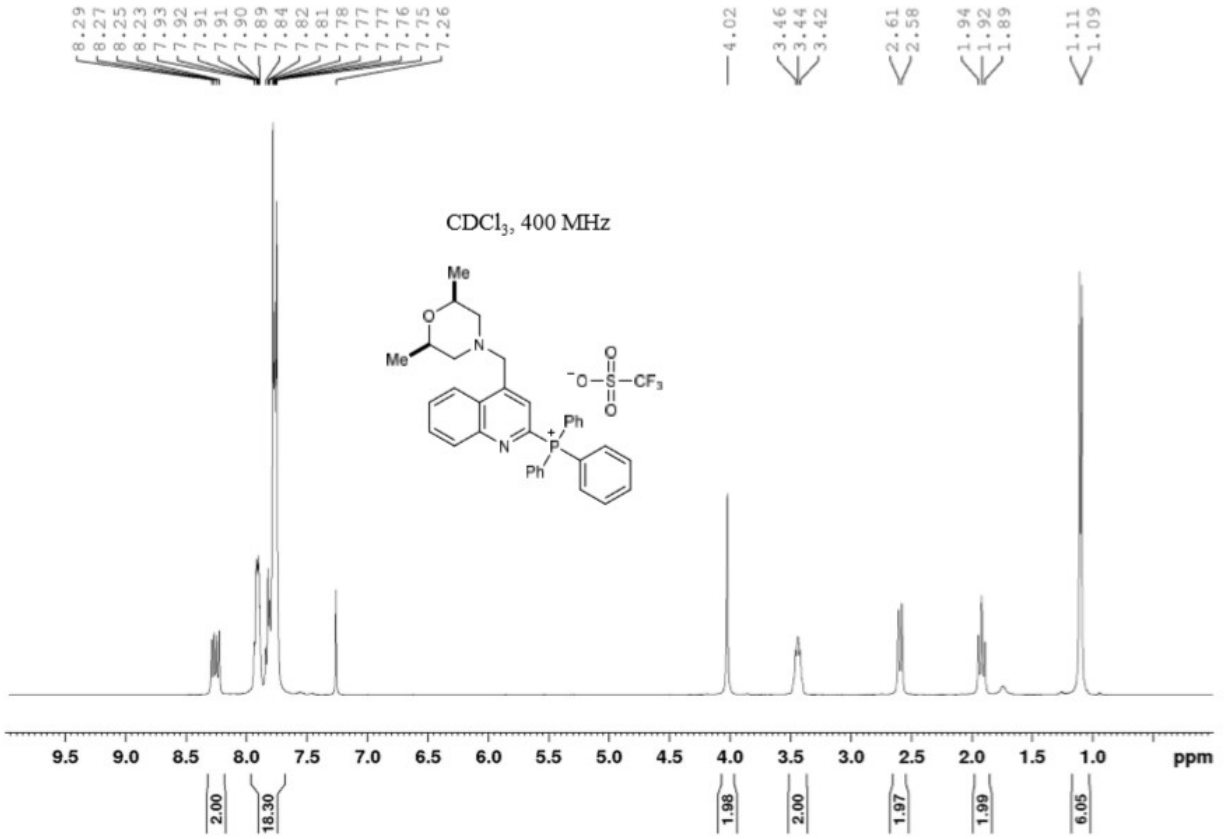

15.62
CDCl3, 162 MHz
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 ppm

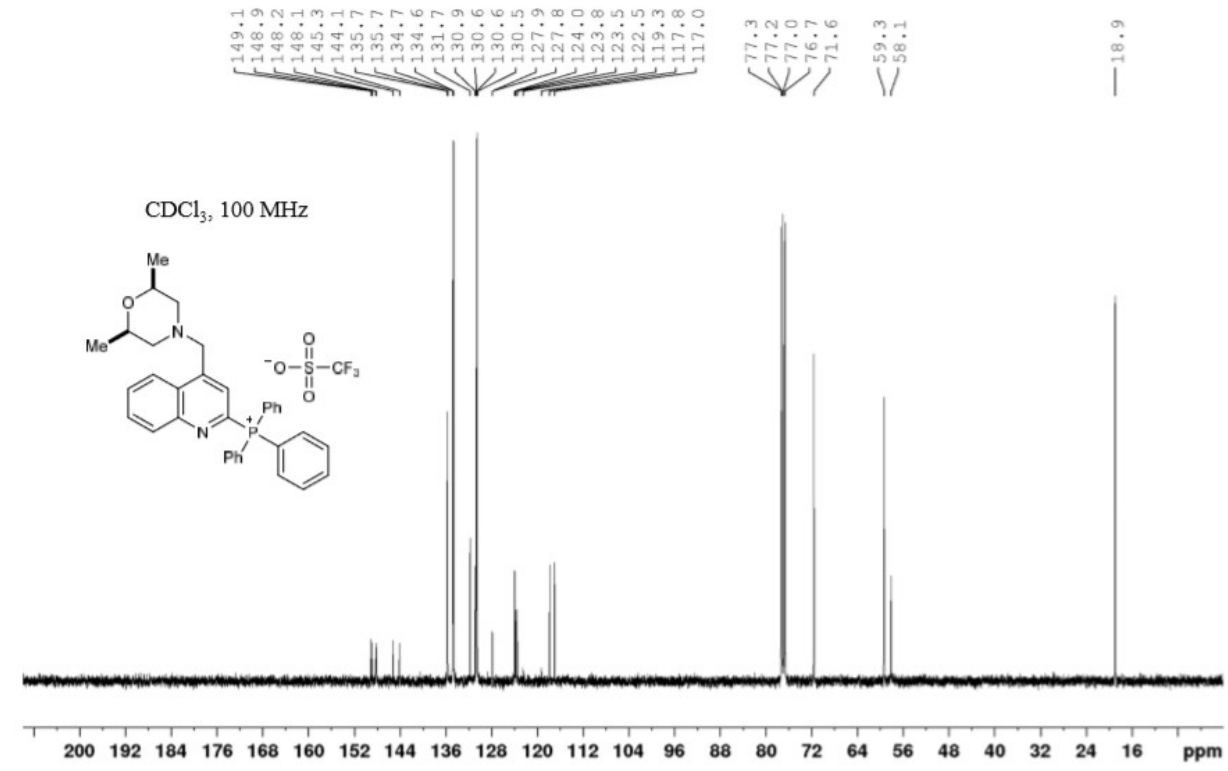

8.58
8.57
8.55
7.94
7.92
7.90
7.82
7.81
7.80
7.79
7.78
7.77
7.68
7.66
7.65
7.63
7.26
7.14
7.13
7.12
7.10
6.86
6.82
4.01
CDCl3,400 MHz
Ph—P—Ph
OMe
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
3.08
6.23
6.20
1.02
0.97
3.04


164.6
164.4
149.9
149.8
136.1
136.1
134.3
134.2
130.9
130.9
130.8
130.0
122.3
119.1
118.8
118.8
116.2
116.1
116.0
115.1
77.3
77.0
76.7
54.3
CDCl3, 100 MHz
Ph—P—Ph
OMe
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

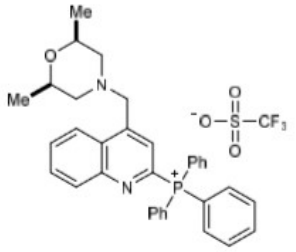

-78.17
CDCl3, 365 MHz
Ph
P
Ph
O
S
CF3
N
OMe
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm


22.37
CDCl3, 162 MHz
Ph
P
Ph
O
S
CF3
N
OMe
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 ppm

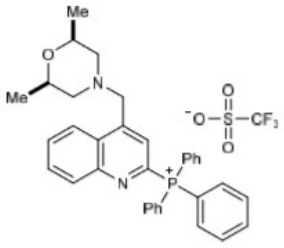

8.29
8.27
8.25
8.23
7.93
7.92
7.91
7.91
7.90
7.89
7.84
7.82
7.81
7.78
7.77
7.77
7.76
7.75
7.26
4.02
3.46
3.44
3.42
2.61
2.58
1.94
1.92
1.89
1.11
1.09
CDCl3, 400 MHz
Me
O
N
Me
O
S
O
CF3
Ph
P
Ph
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.00
18.30
1.98
2.00
1.97
1.99
6.05

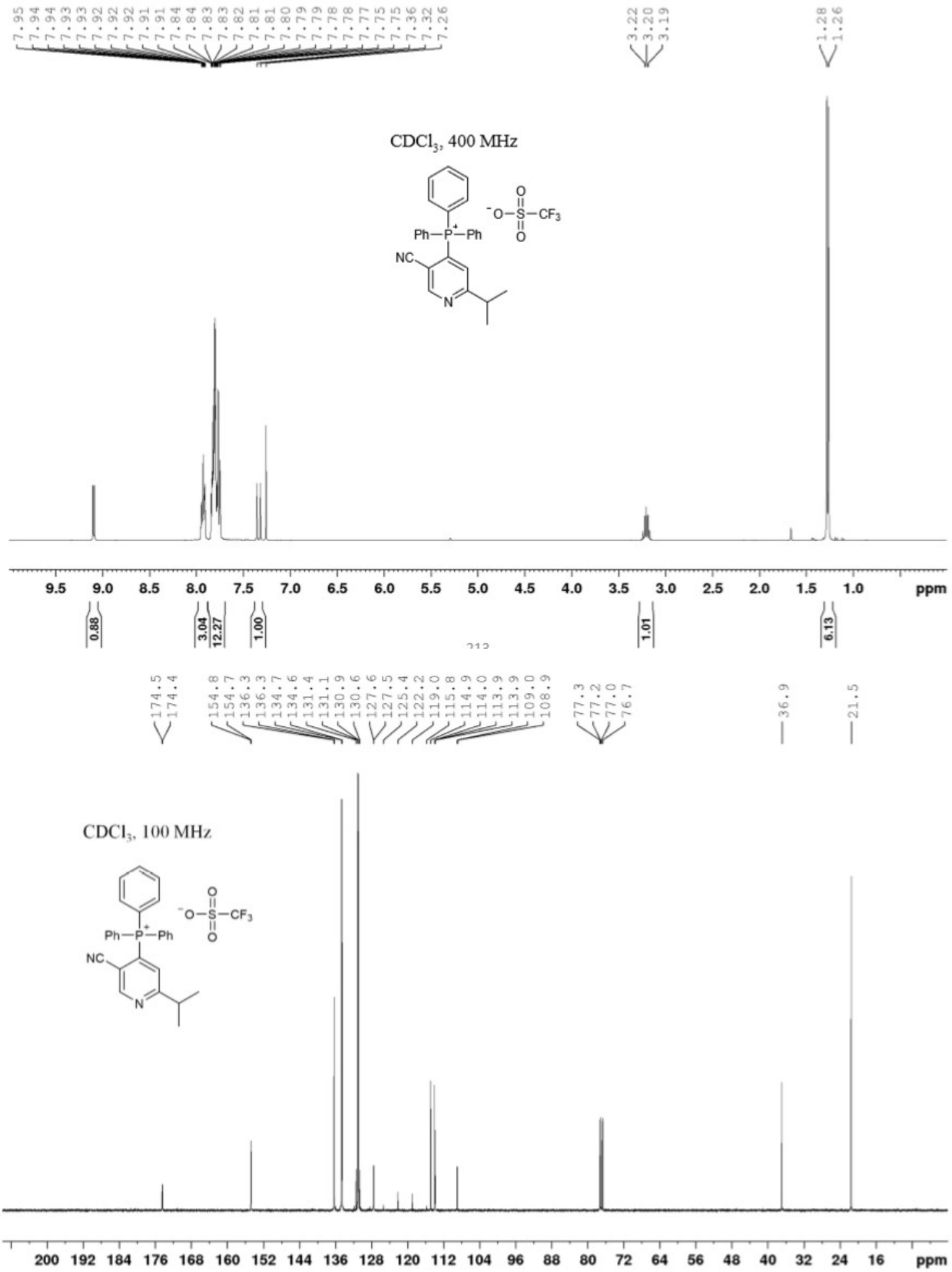

149.1
148.9
148.2
148.1
145.3
144.1
135.7
135.7
134.7
134.6
131.7
130.9
130.6
130.6
130.5
127.9
127.8
124.0
123.8
123.5
122.5
119.3
117.8
117.0
77.3
77.2
77.0
76.7
71.6
59.3
58.1
18.9
CDCl3, 100 MHz
Me
O
N
Me
O
S
O
CF3
Ph
P
Ph
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

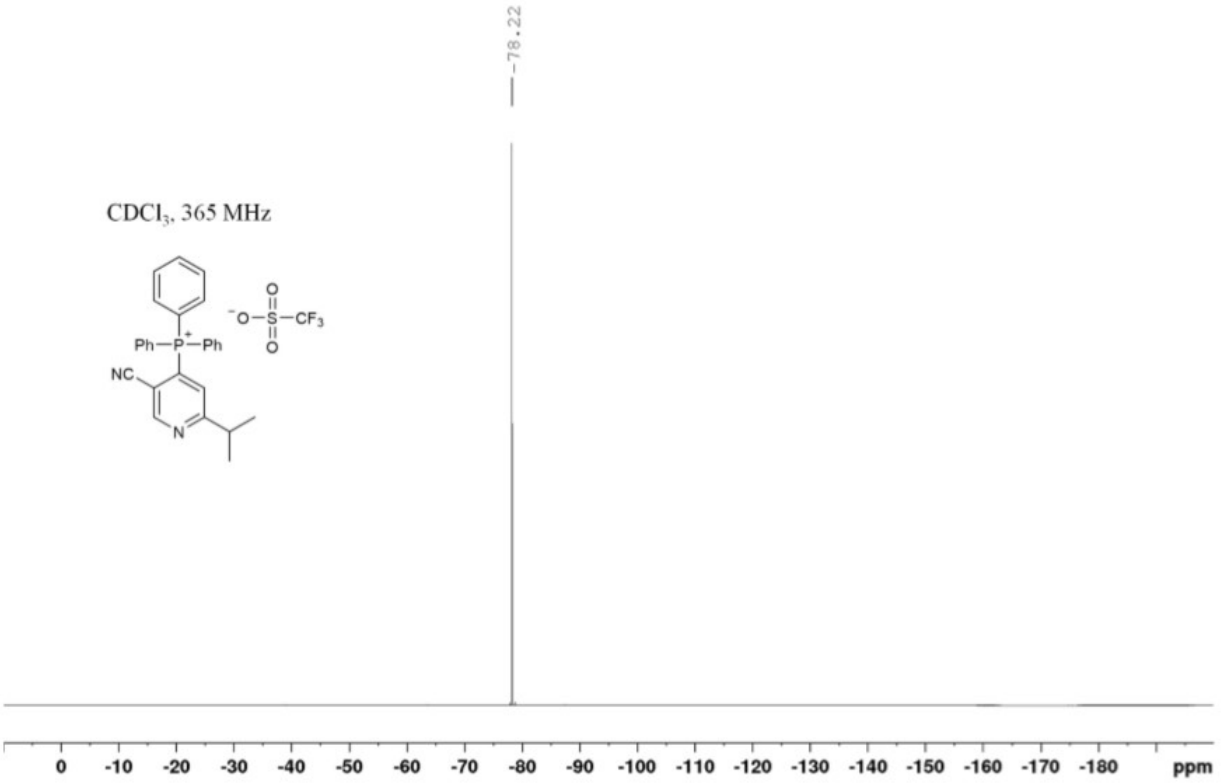
$CDCl_3$, 365 MHz

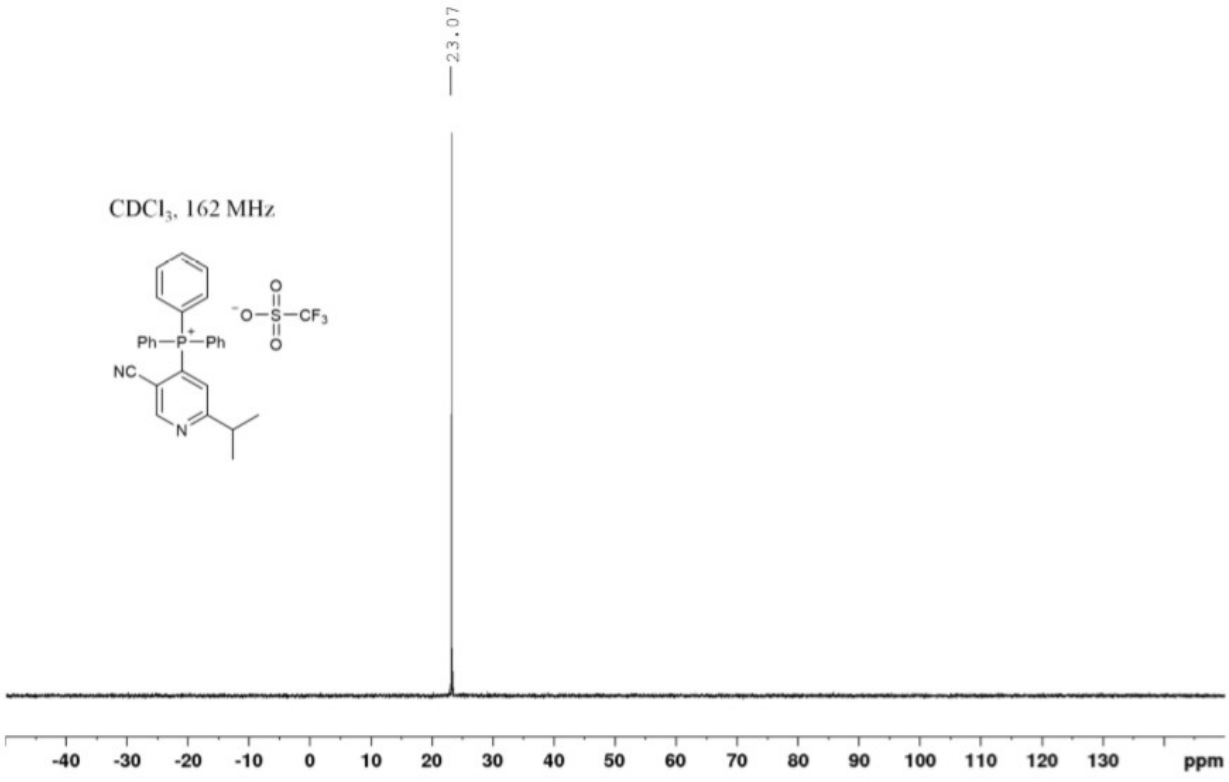


$CDCl_3$, 162 MHz

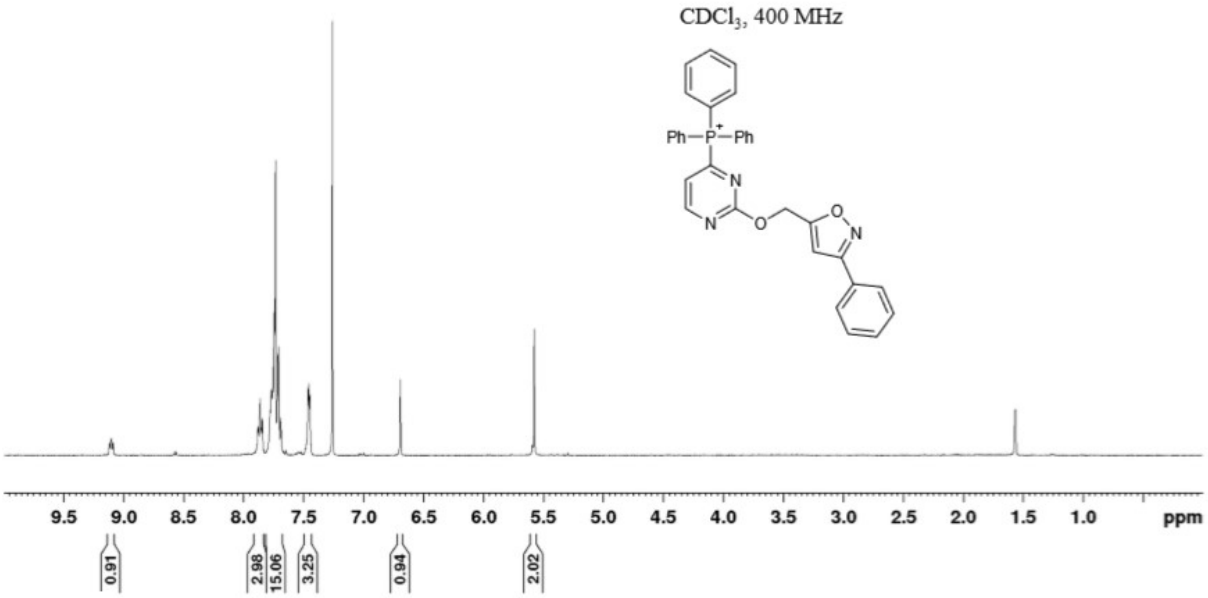


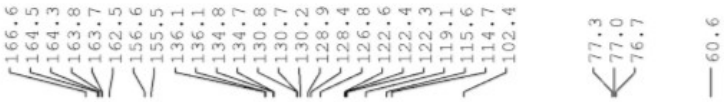

7.95
7.94
7.94
7.93
7.93
7.92
7.92
7.92
7.91
7.91
7.84
7.84
7.83
7.83
7.82
7.81
7.81
7.80
7.79
7.79
7.78
7.78
7.77
7.75
7.75
7.36
7.32
7.26
3.22
3.20
3.19
1.28
1.26
CDCl3, 400 MHz
Ph—P—Ph
NC
N
O—S—CF3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.88
3.04
12.27
1.00
1.01
6.13
174.5
174.4
154.8
154.7
136.3
136.3
134.7
134.6
131.4
131.1
130.9
130.6
127.6
127.5
125.4
122.2
119.0
115.8
114.9
114.0
113.9
113.9
109.0
108.9
77.3
77.2
77.0
76.7
36.9
21.5
CDCl3, 100 MHz
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

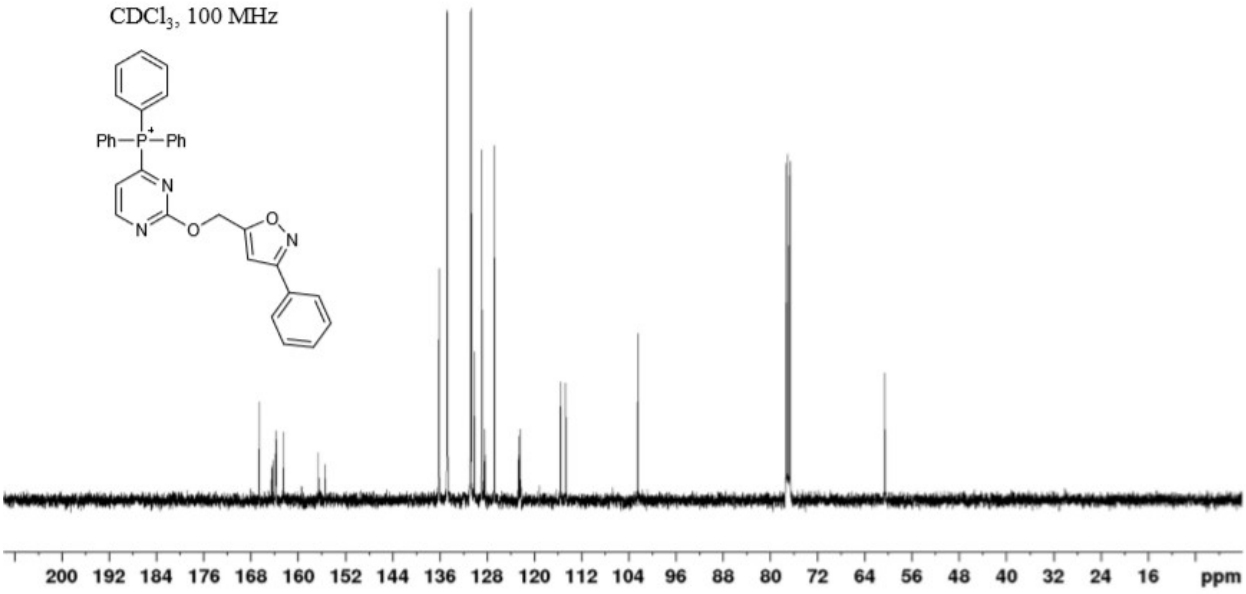

-78.22
CDCl3, 365 MHz
Ph
P
Ph
NC
N
O
S
CF3
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

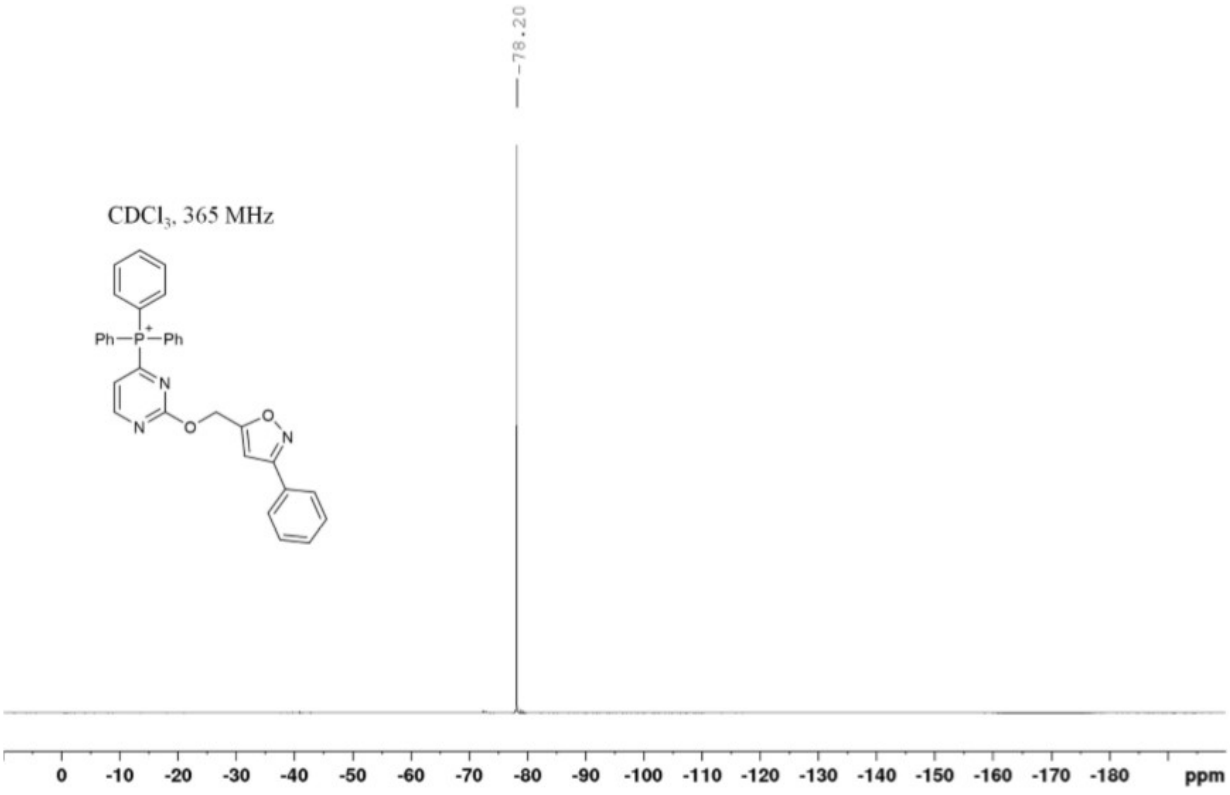

23.07
CDCl3, 162 MHz
Ph
P
Ph
NC
N
O
S
CF3
-40 -30 -20 -10 0 10 20 30 40 50 60 70 80 90 100 110 120 130 ppm

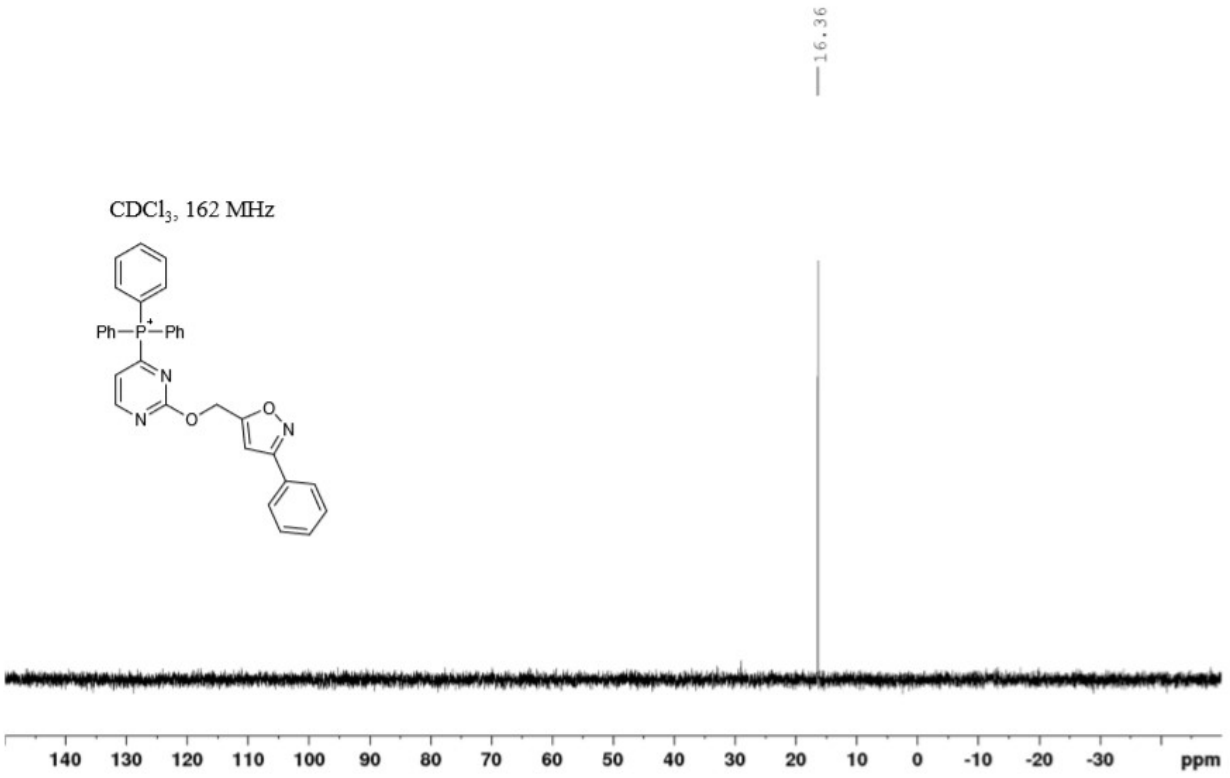

9.12
9.10
9.09
7.88
7.88
7.87
7.86
7.85
7.85
7.78
7.77
7.76
7.76
7.75
7.74
7.73
7.72
7.71
7.69
7.46
7.46
7.45
6.69
5.58

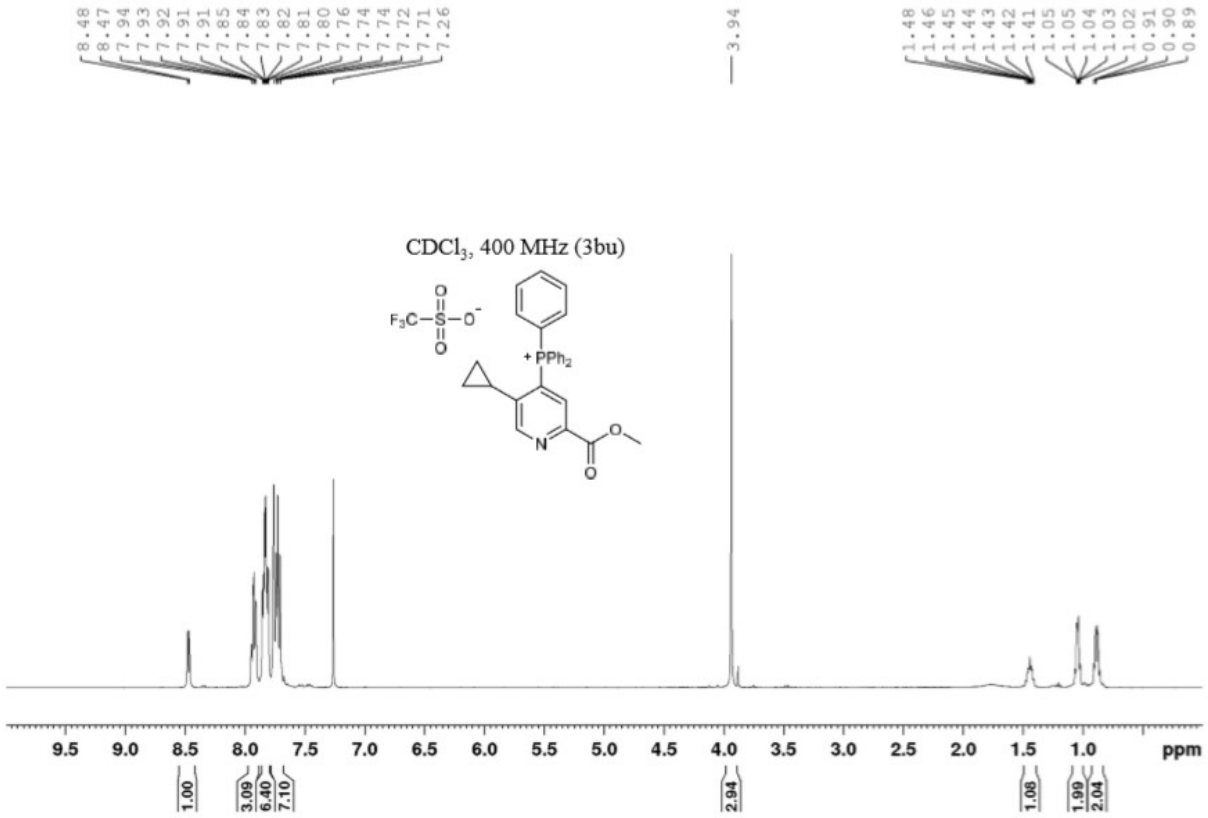

CDCl3, 400 MHz
Ph
P
Ph
N
N
O
O
N
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.91
2.98
15.06
3.25
0.94
2.02

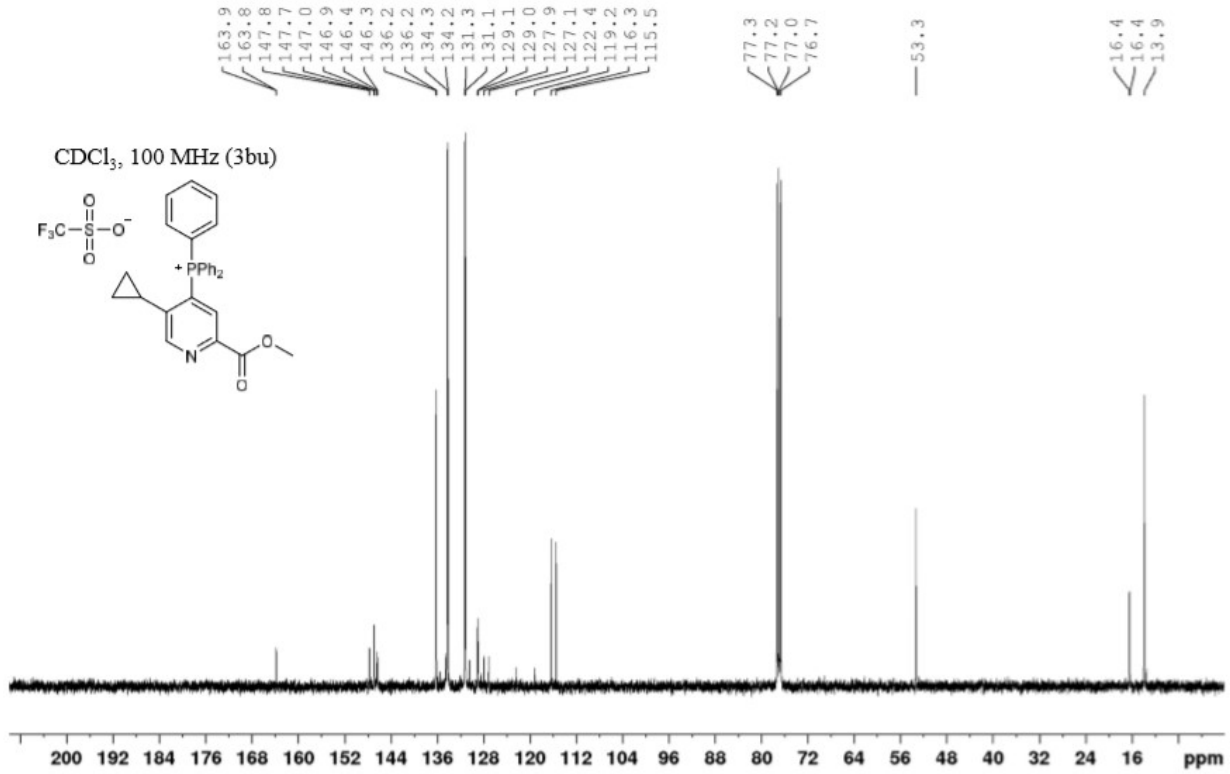

166.6
164.5
164.3
163.8
163.7
162.5
156.6
155.5
136.1
136.1
134.8
134.7
130.8
130.7
130.2
128.9
128.4
126.8
122.6
122.4
122.3
119.1
115.6
114.7
102.4
77.3
77.0
76.7
60.6


CDCl3, 100 MHz
Ph
P
Ph
N
N
O
O
N
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
ppm

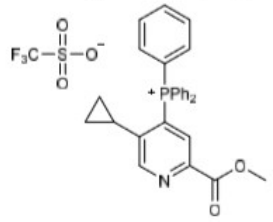

78.20
CDCl3, 365 MHz
Ph
P
Ph
N
N
O
O
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm


16.36
CDCl3, 162 MHz
Ph
P
Ph
N
N
O
O
N
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 ppm

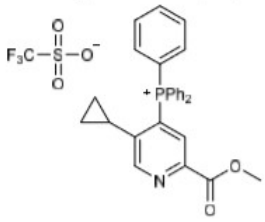

8.48
8.47
7.94
7.93
7.92
7.91
7.91
7.85
7.84
7.83
7.82
7.81
7.80
7.76
7.74
7.74
7.72
7.71
7.26
3.94
1.48
1.46
1.45
1.44
1.43
1.42
1.41
1.05
1.05
1.04
1.03
1.02
0.91
0.90
0.89
CDCl3, 400 MHz (3bu)
F3C−S(=O)(=O)−O-
+PPh2
N
O
O
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
3.09
6.40
7.10
2.94
1.08
1.99
2.04

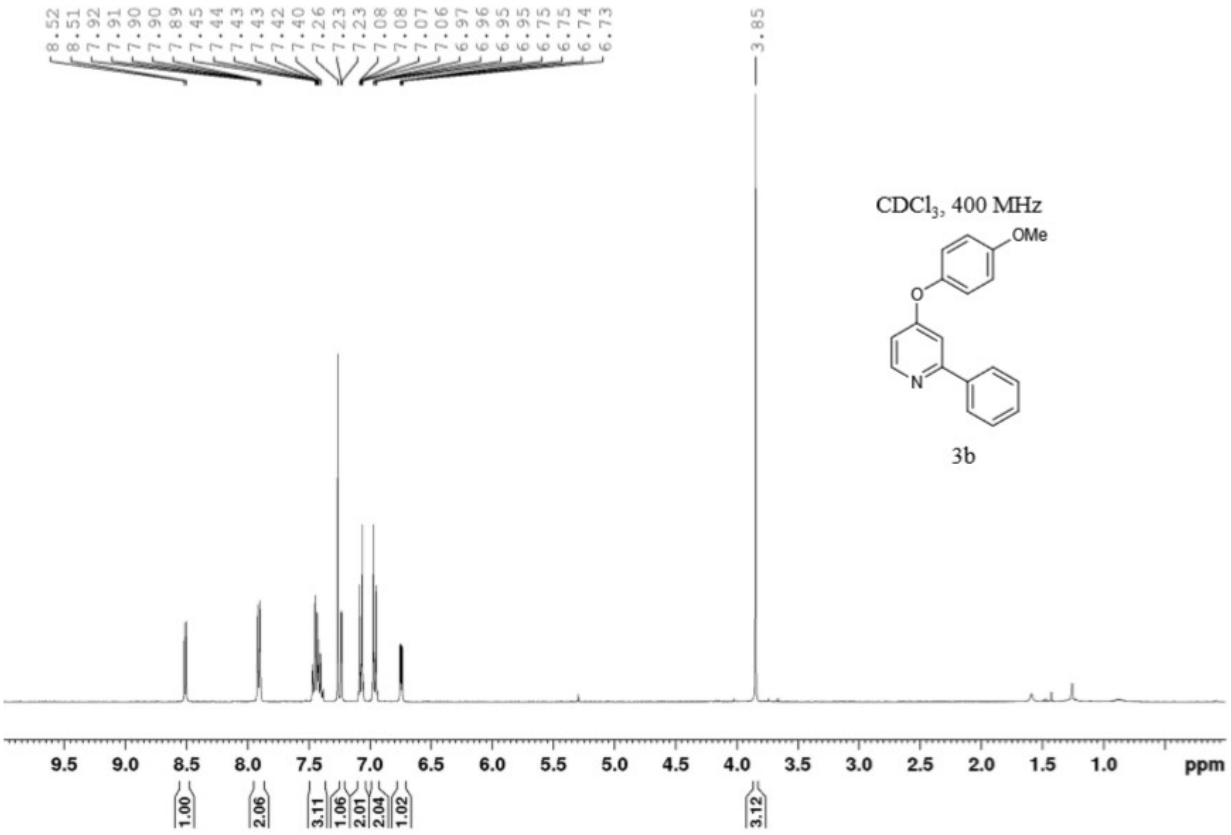

163.9
163.8
147.8
147.7
147.0
146.9
146.4
146.3
136.2
136.2
134.3
134.2
131.3
131.1
129.1
129.0
127.9
127.1
122.4
119.2
116.3
115.5
77.3
77.2
77.0
76.7
53.3
16.4
16.4
13.9
CDCl3, 100 MHz (3bu)
F3C−S(=O)(=O)−O-
+PPh2
N
O
O
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

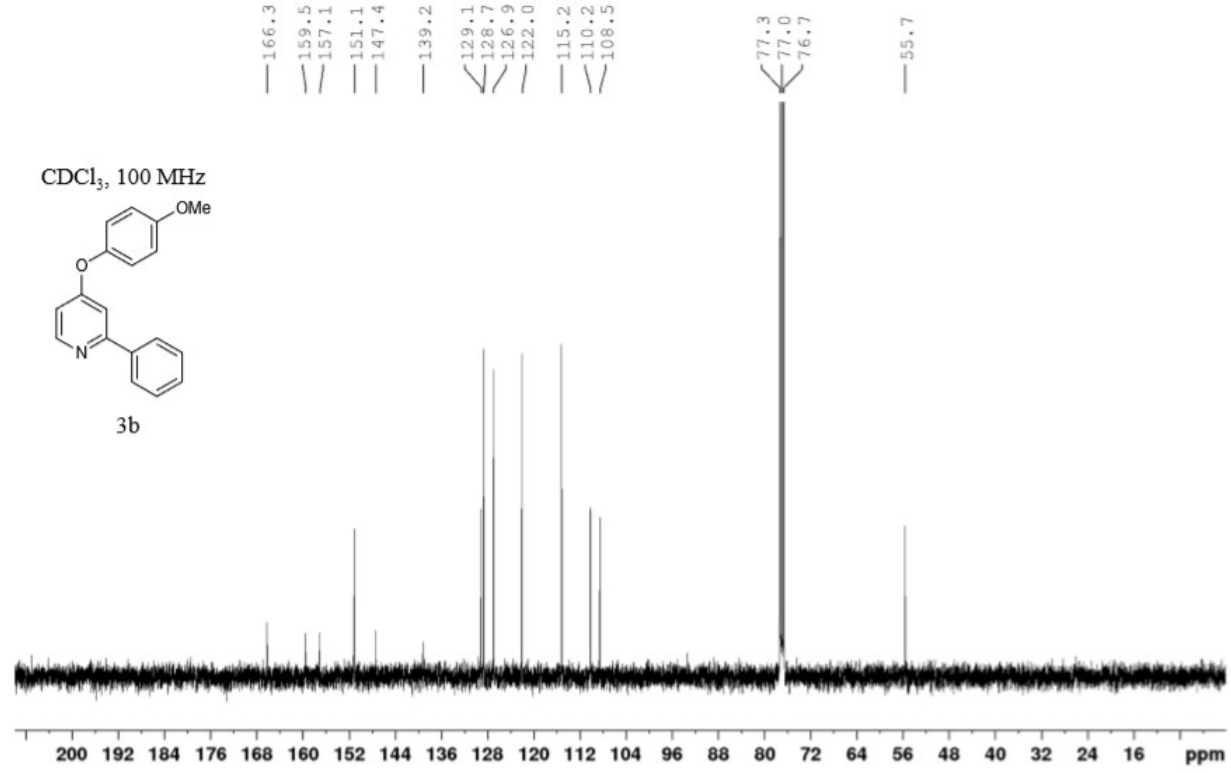
$CDCl_3$, 365MHz (3bu)

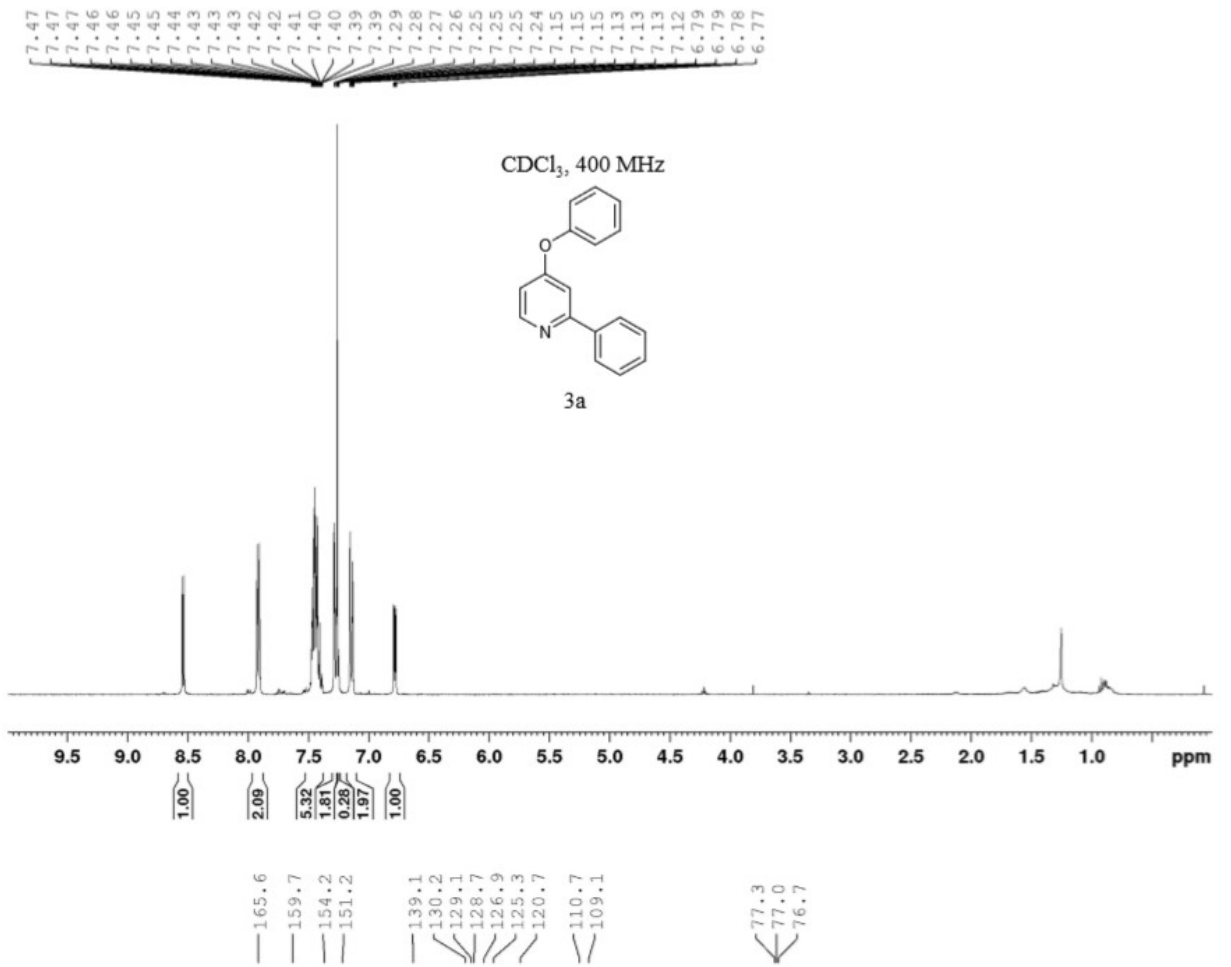


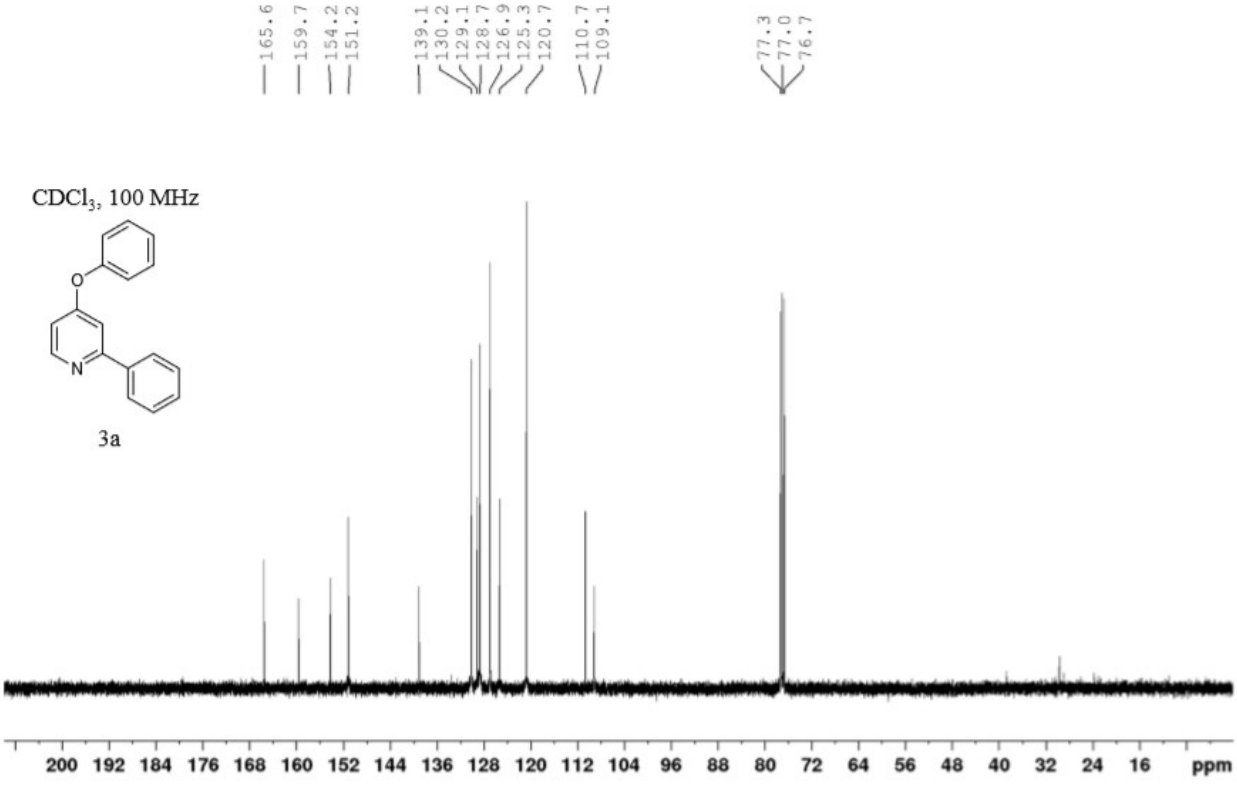
$CDCl_3$, 162 MHz (3bu)

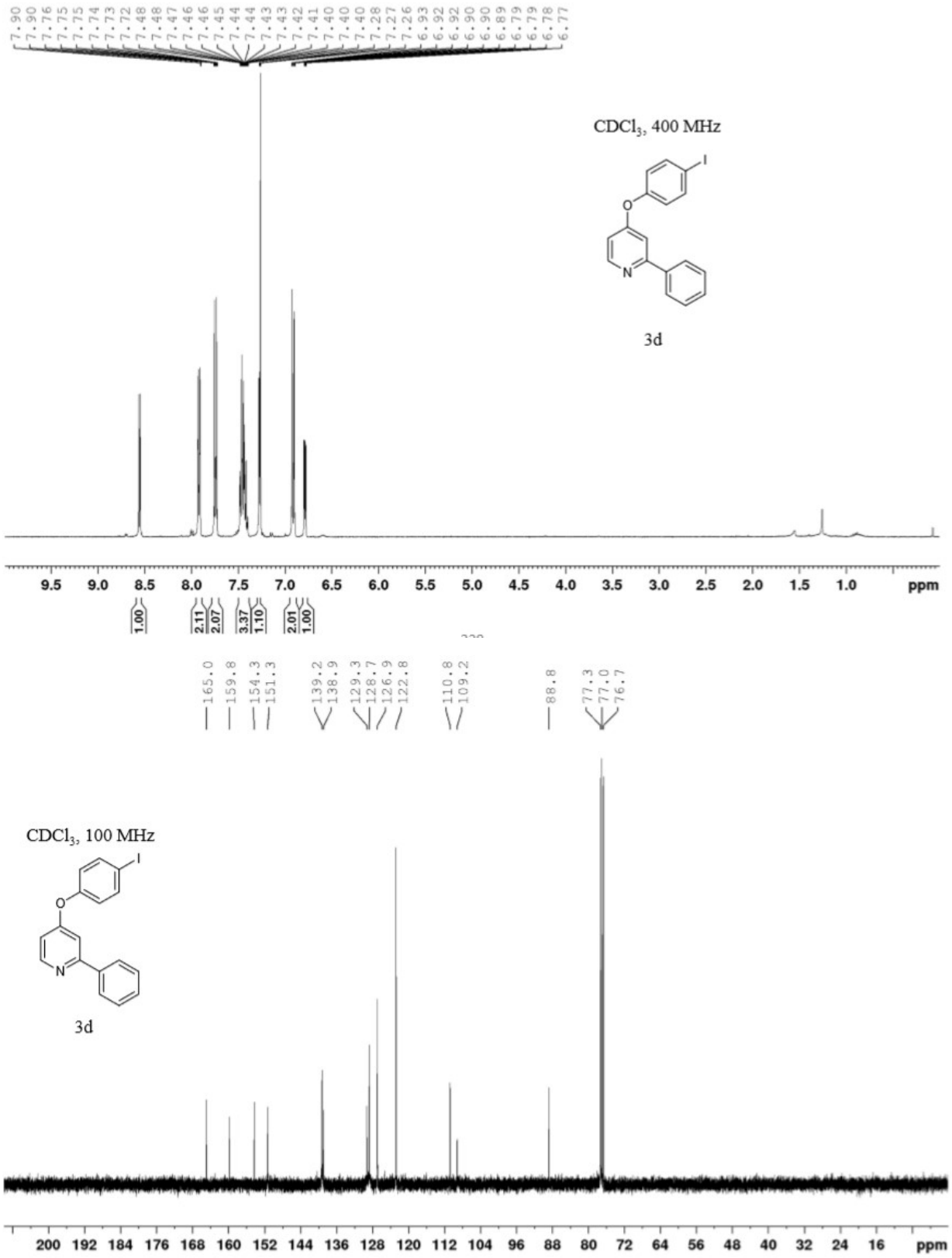


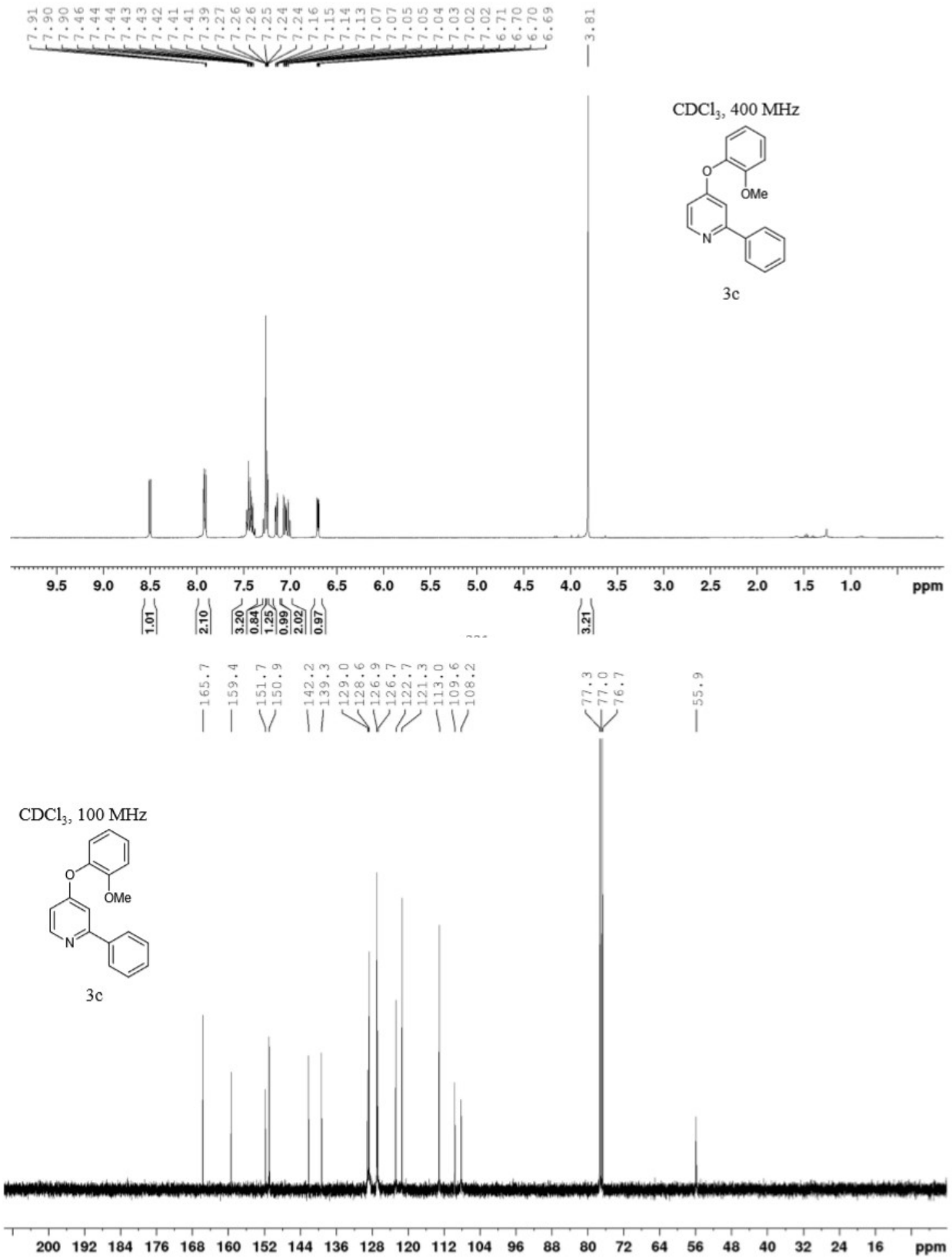

8.52
8.51
7.92
7.91
7.90
7.90
7.89
7.45
7.44
7.43
7.43
7.42
7.40
7.26
7.23
7.23
7.08
7.08
7.07
7.06
6.97
6.96
6.95
6.95
6.75
6.75
6.74
6.73
3.85
CDCl3, 400 MHz
OMe
O
N
3b
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.06
3.11
1.06
2.01
2.04
1.02
3.12


166.3
159.5
157.1
151.1
147.4
139.2
129.1
128.7
126.9
122.0
115.2
110.2
108.5
77.3
77.0
76.7
55.7
CDCl3, 100 MHz
OMe
O
N
3b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


7.47 7.47 7.47 7.46 7.46 7.45 7.45 7.44 7.43 7.43 7.43 7.42 7.42 7.41 7.40 7.40 7.39 7.39 7.29 7.28 7.27 7.26 7.25 7.25 7.24 7.15 7.15 7.15 7.13 7.13 7.13 7.12 6.79 6.79 6.78 6.77
CDCl3, 400 MHz
O
N
3a
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 2.09 5.32 1.81 0.28 1.97 1.00


165.6 159.7 154.2 151.2 139.1 130.2 129.1 128.7 126.9 125.3 120.7 110.7 109.1 77.3 77.0 76.7
CDCl3, 100 MHz
O
N
3a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


7.90
7.90
7.76
7.75
7.75
7.74
7.73
7.72
7.48
7.48
7.47
7.46
7.46
7.45
7.44
7.44
7.43
7.43
7.42
7.41
7.40
7.40
7.40
7.28
7.27
7.26
6.93
6.92
6.90
6.90
6.89
6.79
6.79
6.78
6.77
CDCl3, 400 MHz
I
O
N
3d
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.11
2.07
3.37
1.10
2.01
1.00
165.0
159.8
154.3
151.3
139.2
138.9
129.3
128.7
126.9
122.8
110.8
109.2
88.8
77.3
77.0
76.7
CDCl3, 100 MHz
I
O
N
3d
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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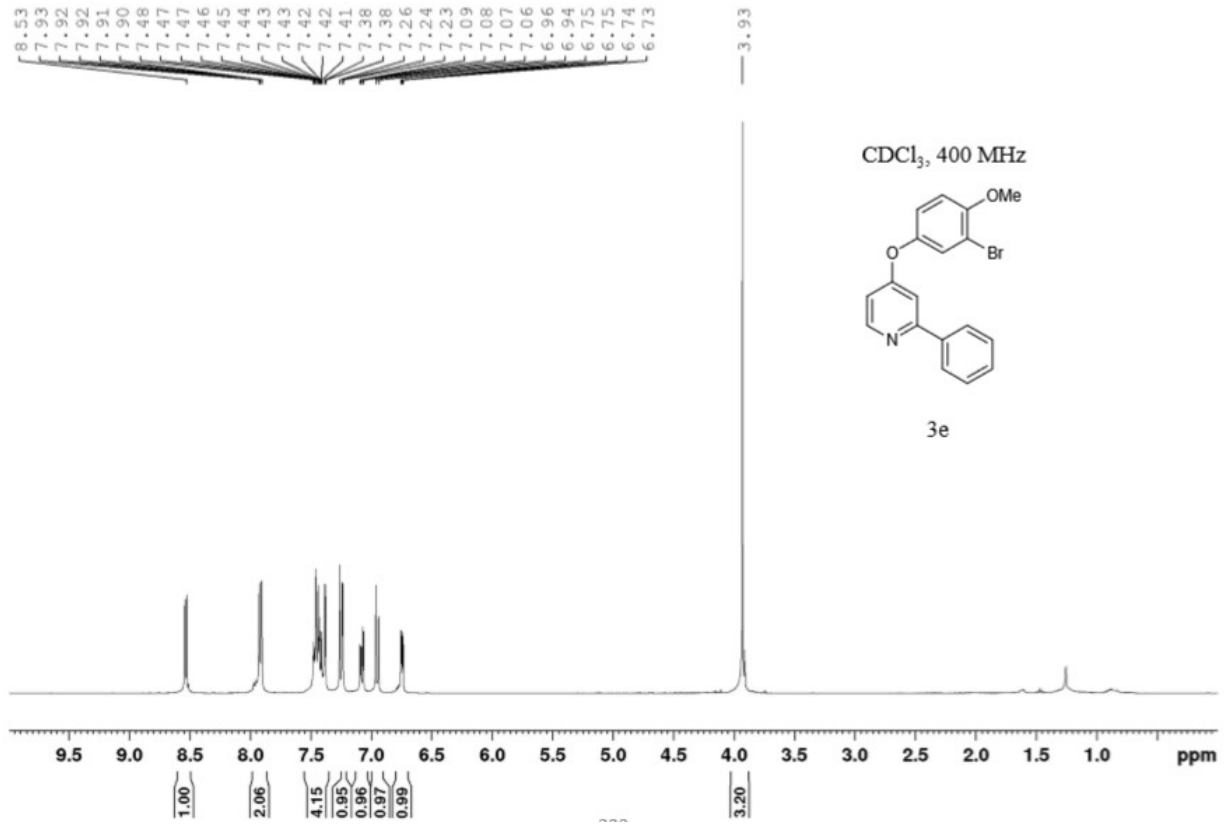
7.90
7.90
7.46
7.44
7.44
7.43
7.43
7.42
7.41
7.41
7.39
7.27
7.26
7.26
7.25
7.24
7.24
7.16
7.15
7.14
7.13
7.07
7.05
7.05
7.04
7.03
7.02
7.02
6.71
6.70
6.70
6.69
3.81
CDCl3, 400 MHz
O
OMe
N
3c
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.01
2.10
3.20
0.84
1.25
0.99
2.02
0.97
3.21
165.7
159.4
151.7
150.9
142.2
139.3
129.0
128.6
126.9
126.7
122.7
121.3
113.0
109.6
108.2
77.3
77.0
76.7
55.9
CDCl3, 100 MHz
O
OMe
N
3c
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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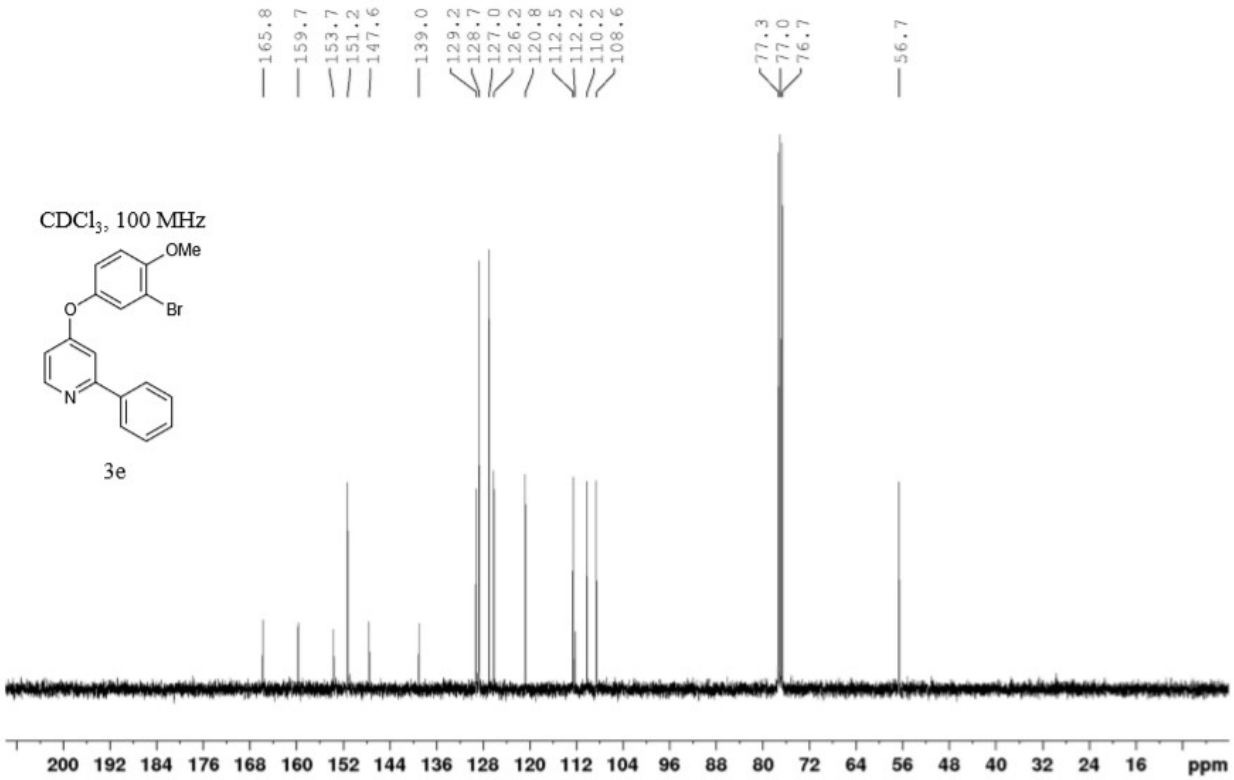
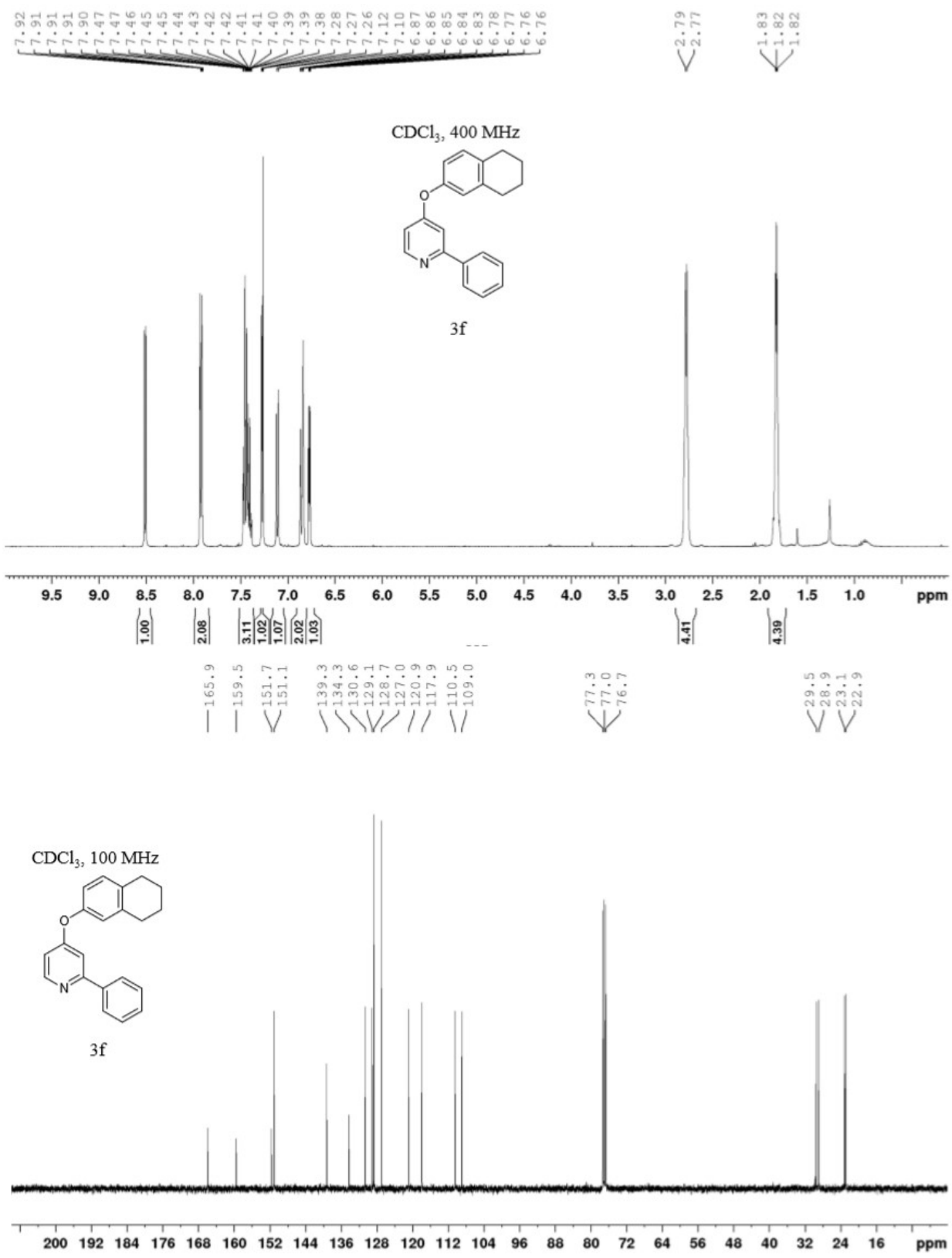
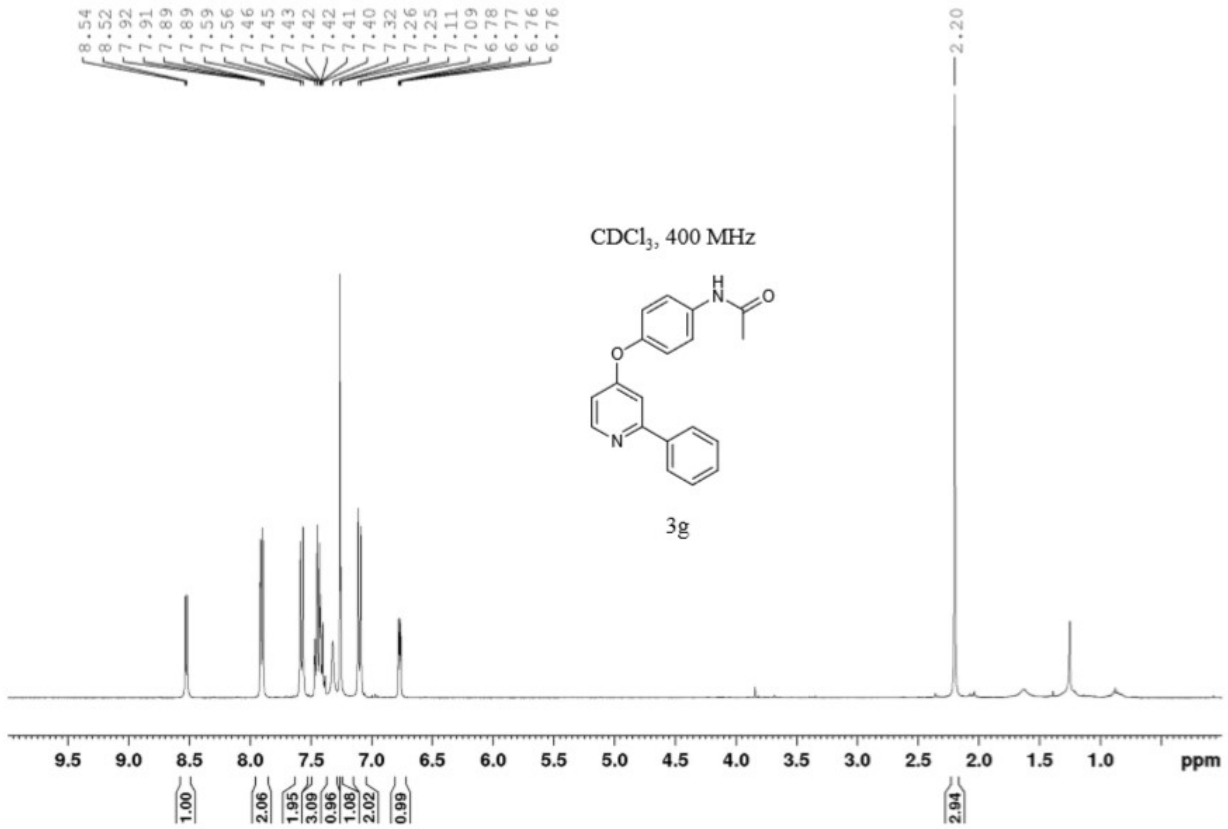
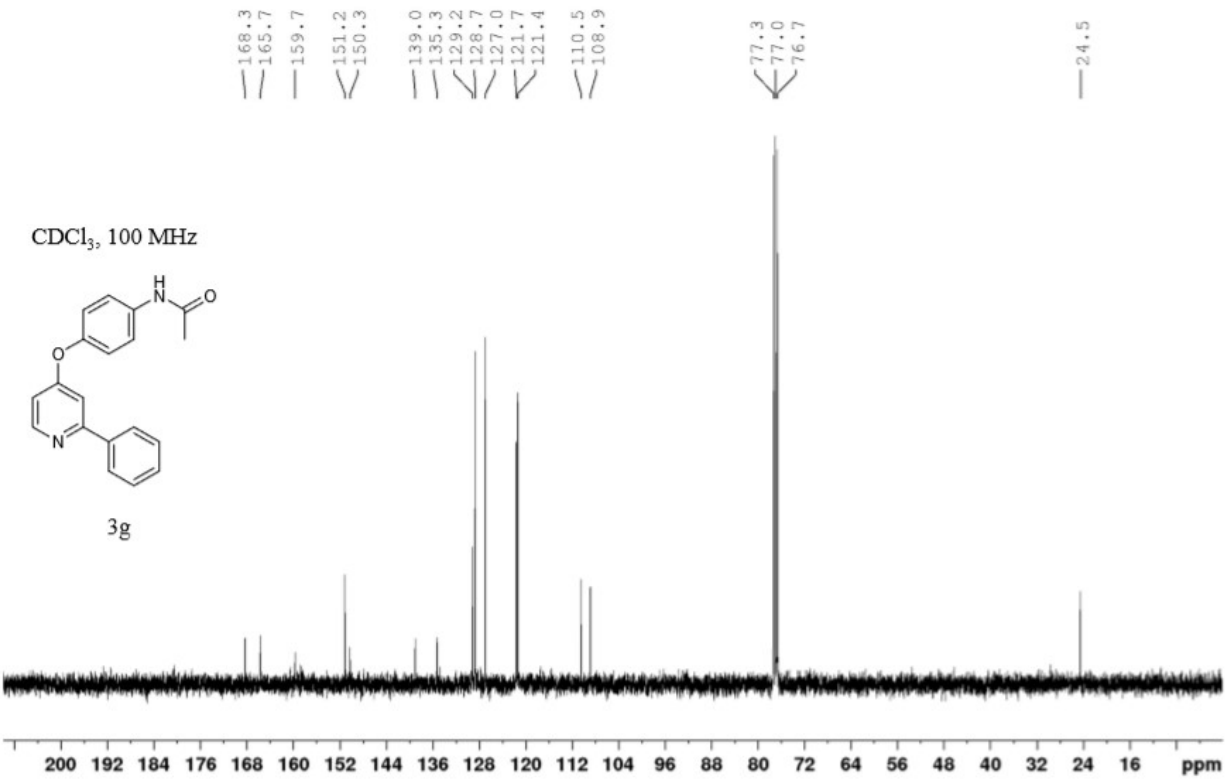
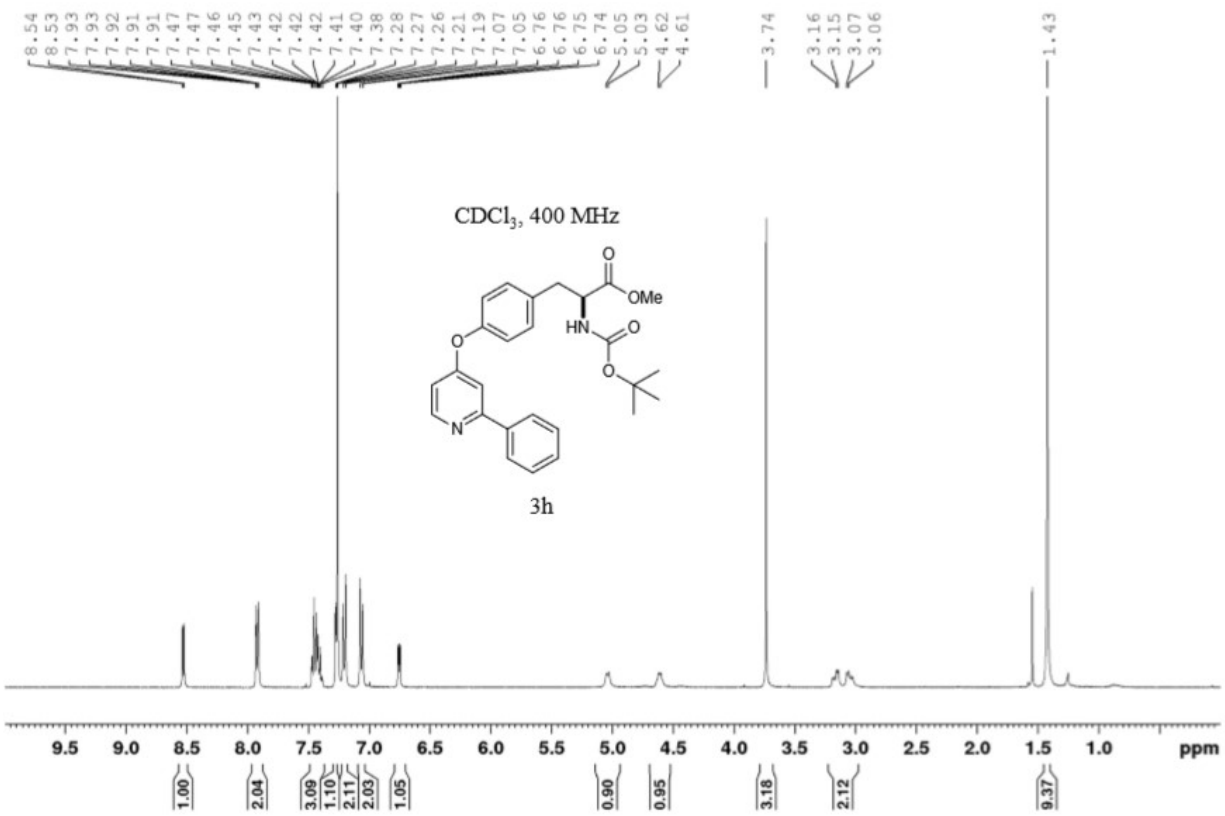
7.93
7.92
7.92
7.91
7.90
7.48
7.47
7.47
7.46
7.45
7.44
7.43
7.43
7.42
7.42
7.41
7.38
7.38
7.26
7.24
7.23
7.09
7.08
7.07
7.06
6.96
6.94
6.75
6.75
6.74
6.73
3.93
CDCl3, 400 MHz
OMe
Br
O
N
3e
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.06
4.15
0.95
0.96
0.97
0.99
3.20

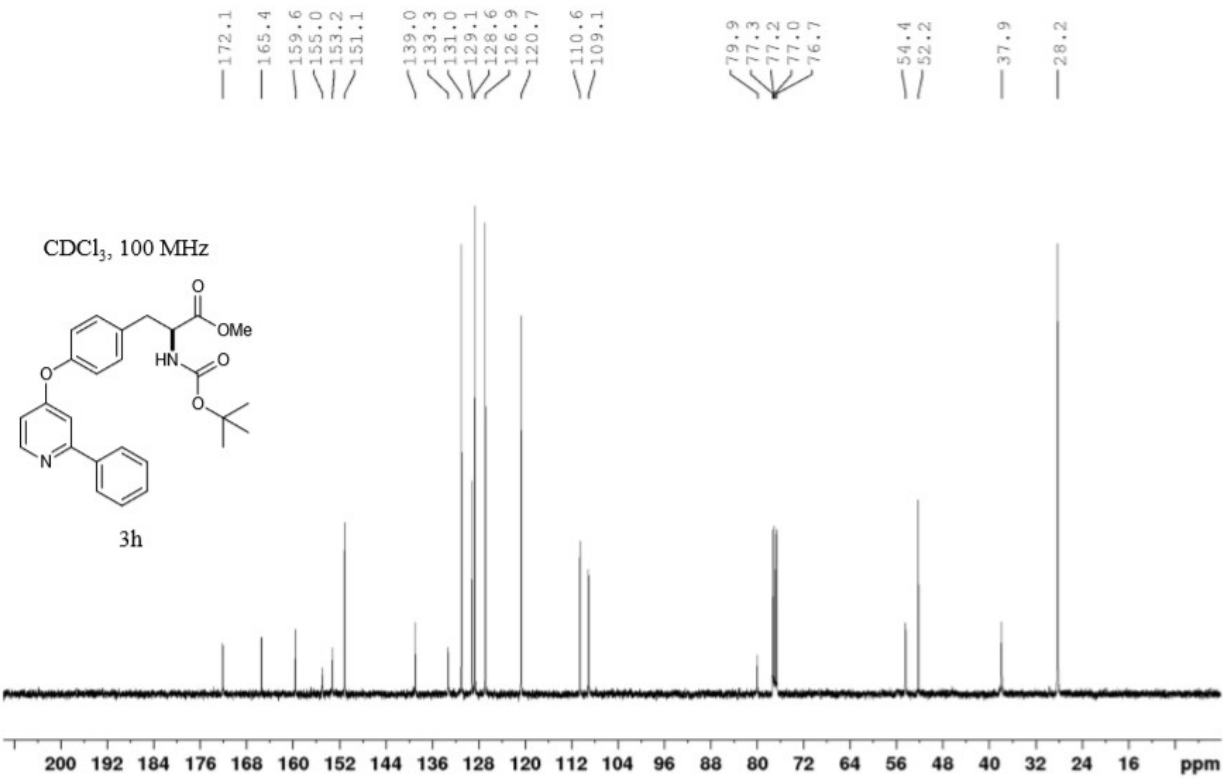

165.8
159.7
153.7
151.2
147.6
139.0
129.2
128.7
127.0
126.2
120.8
112.5
112.2
110.2
108.6
77.3
77.0
76.7
56.7
CDCl3, 100 MHz
OMe
Br
O
N
3e
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

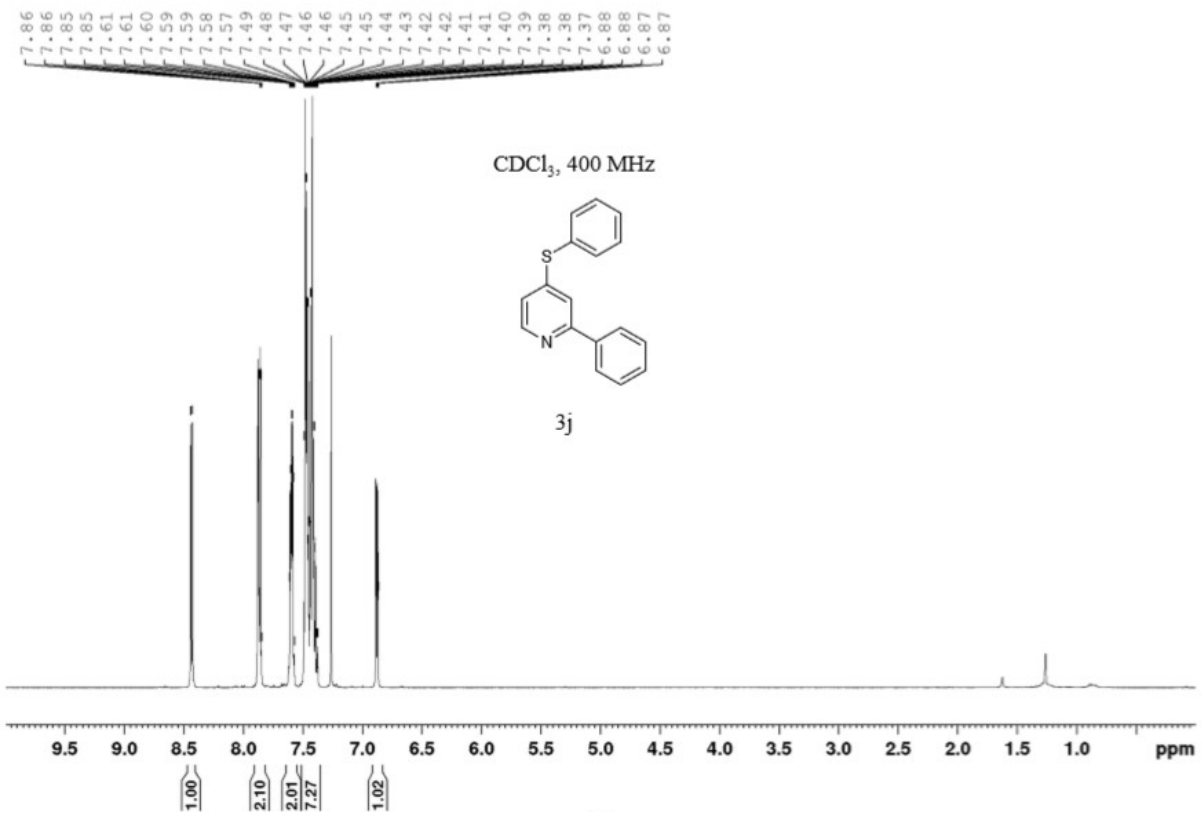

7.92 7.91 7.91 7.91 7.90 7.47 7.47 7.46 7.45 7.45 7.44 7.43 7.42 7.42 7.41 7.41 7.40 7.39 7.39 7.38 7.28 7.27 7.26 7.12 7.10 6.87 6.86 6.85 6.84 6.83 6.78 6.77 6.76 6.76
2.79 2.77
1.83 1.82 1.82
CDCl3, 400 MHz
O
N
3f
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 2.08 3.11 1.02 1.07 2.02 1.03 4.41 4.39
165.9 159.5 151.7 151.1 139.3 134.3 130.6 129.1 128.7 127.0 120.9 117.9 110.5 109.0 77.3 77.0 76.7 29.5 28.9 23.1 22.9
CDCl3, 100 MHz
O
N
3f
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

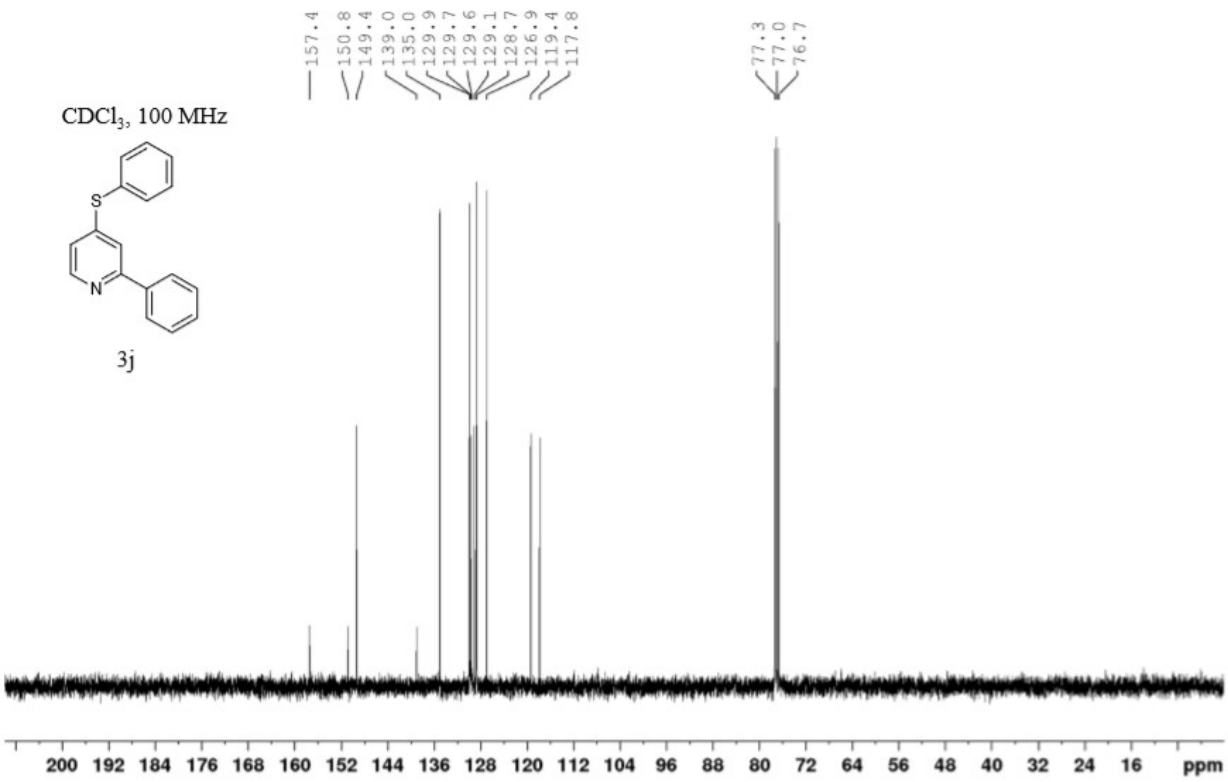

8.54
8.52
7.92
7.91
7.89
7.89
7.59
7.56
7.46
7.45
7.43
7.42
7.42
7.41
7.40
7.32
7.26
7.25
7.11
7.09
6.78
6.77
6.76
6.76
2.20
CDCl3, 400 MHz
3g
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.06
1.95
3.09
0.96
1.08
2.02
0.99
2.94

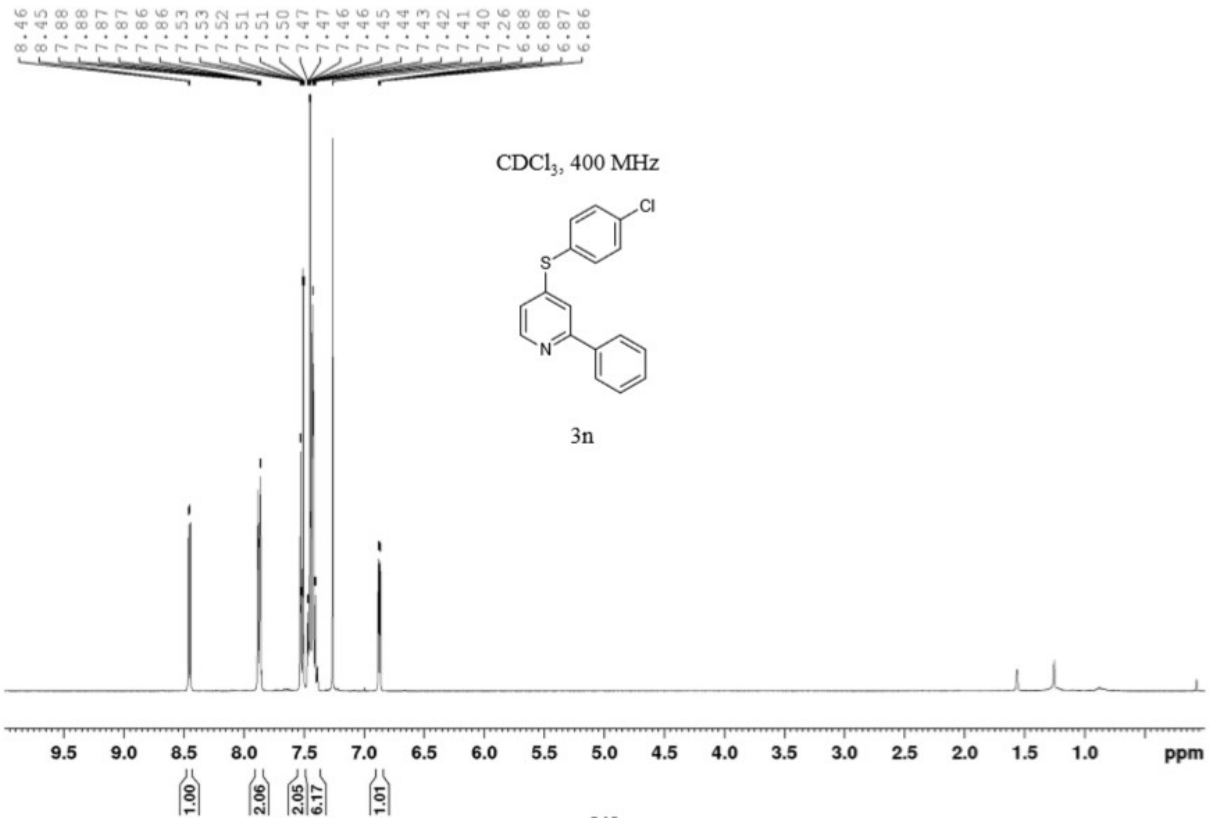

168.3
165.7
159.7
151.2
150.3
139.0
135.3
129.2
128.7
127.0
121.7
121.4
110.5
108.9
77.3
77.0
76.7
24.5
CDCl3, 100 MHz
3g
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

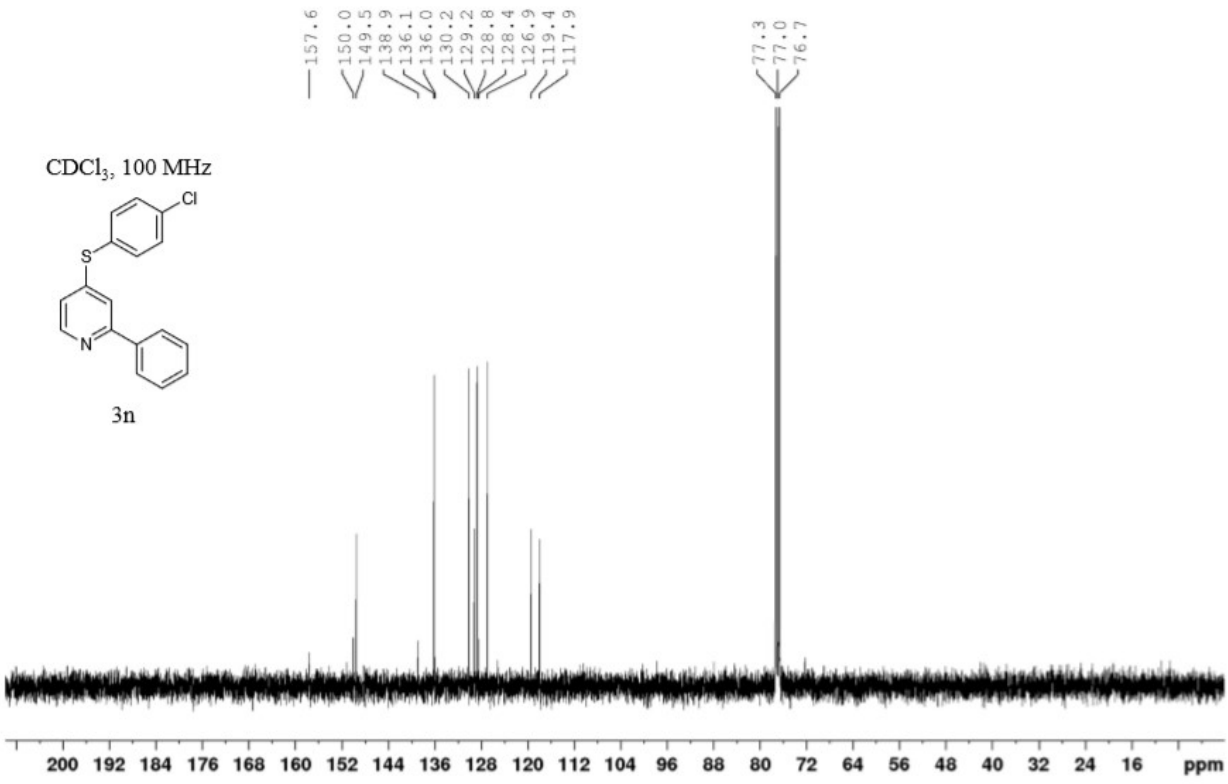

8.54
8.53
7.93
7.93
7.92
7.91
7.91
7.47
7.47
7.46
7.45
7.43
7.42
7.42
7.42
7.41
7.40
7.38
7.28
7.27
7.26
7.21
7.19
7.07
7.05
6.76
6.75
6.74
5.05
5.03
4.62
4.61
3.74
3.16
3.15
3.07
3.06
1.43
CDCl3, 400 MHz
OMe
HN
O
O
O
N
3h
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.04
3.09
1.10
2.11
2.03
1.05
0.90
0.95
3.18
2.12
9.37

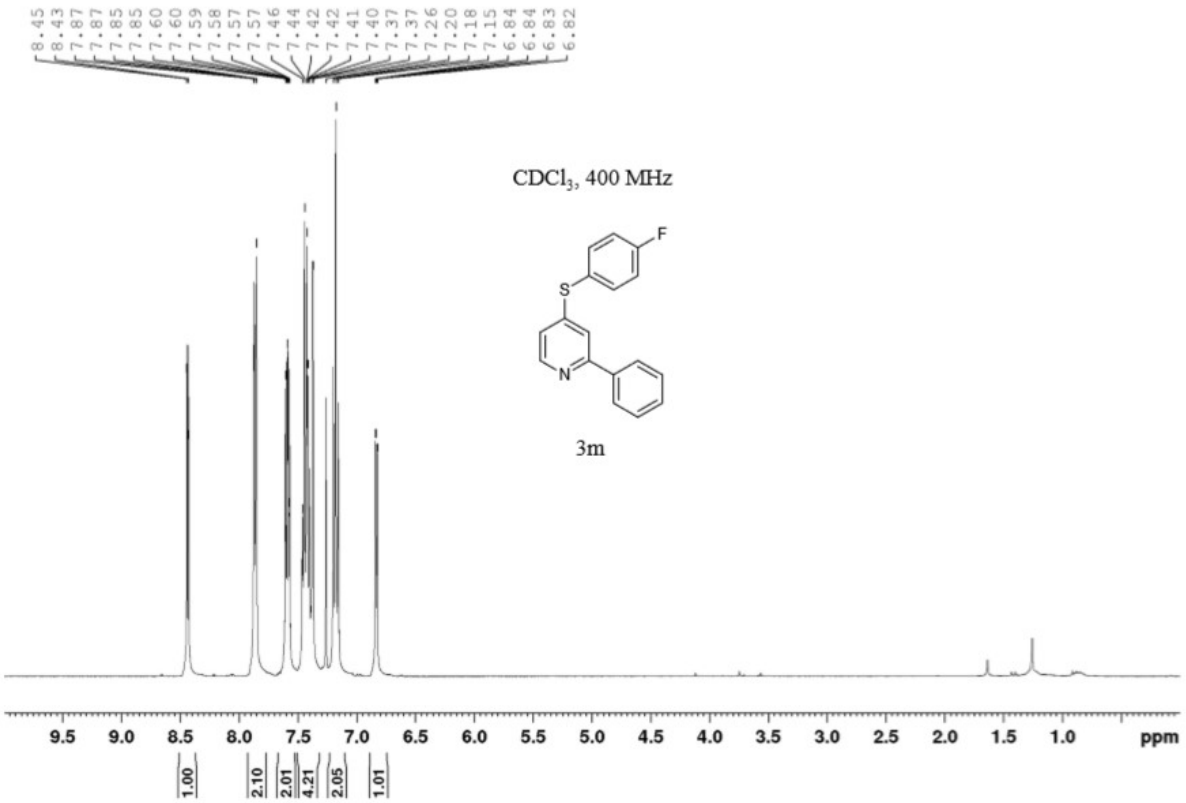

172.1
165.4
159.6
155.0
153.2
151.1
139.0
133.3
131.0
129.1
128.6
126.9
120.7
110.6
109.1
79.9
77.3
77.2
77.0
76.7
54.4
52.2
37.9
28.2
CDCl3, 100 MHz
OMe
HN
O
O
O
N
3h
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

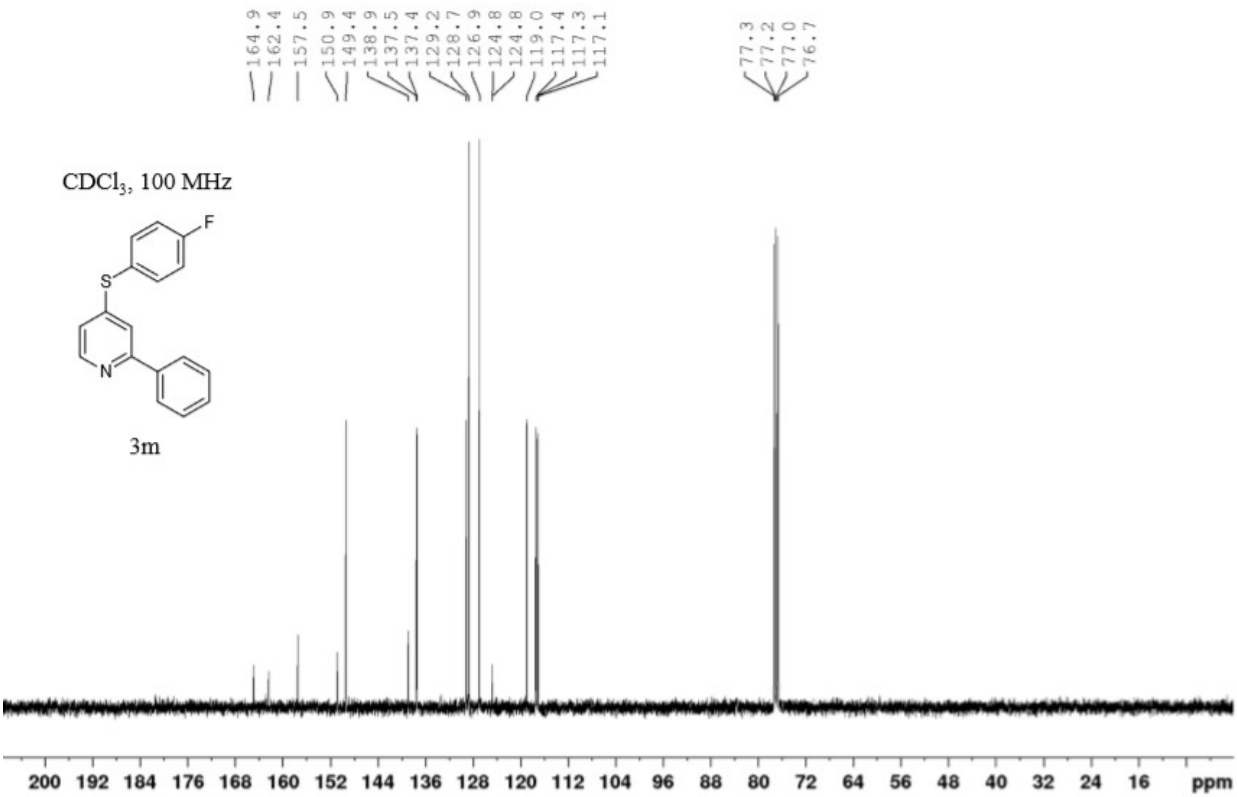

7.86
7.86
7.85
7.85
7.61
7.61
7.60
7.59
7.59
7.58
7.57
7.49
7.48
7.47
7.46
7.46
7.45
7.45
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.39
7.38
7.38
7.37
6.88
6.88
6.87
6.87
CDCl3, 400 MHz
S
N
3j
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.10
2.01
7.27
1.02

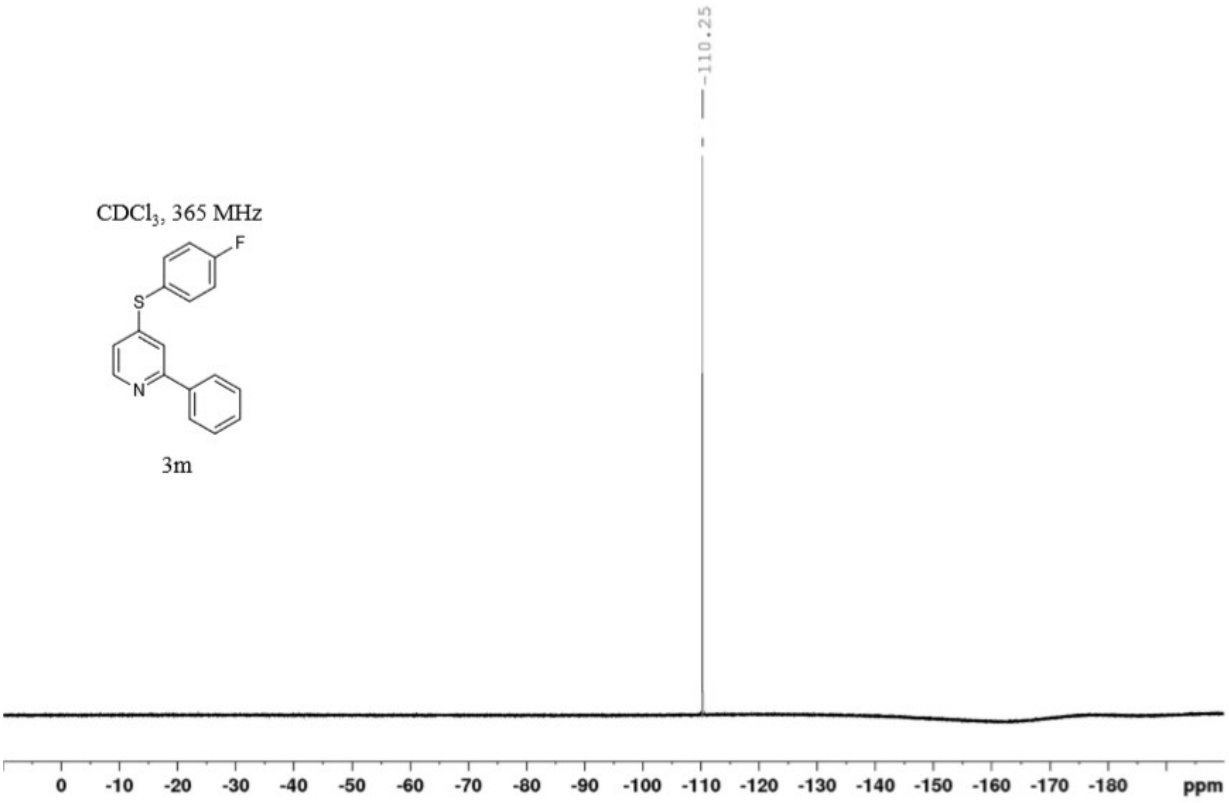

157.4
150.8
149.4
139.0
135.0
129.9
129.7
129.6
129.1
128.7
126.9
119.4
117.8
77.3
77.0
76.7
CDCl3, 100 MHz
S
N
3j
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

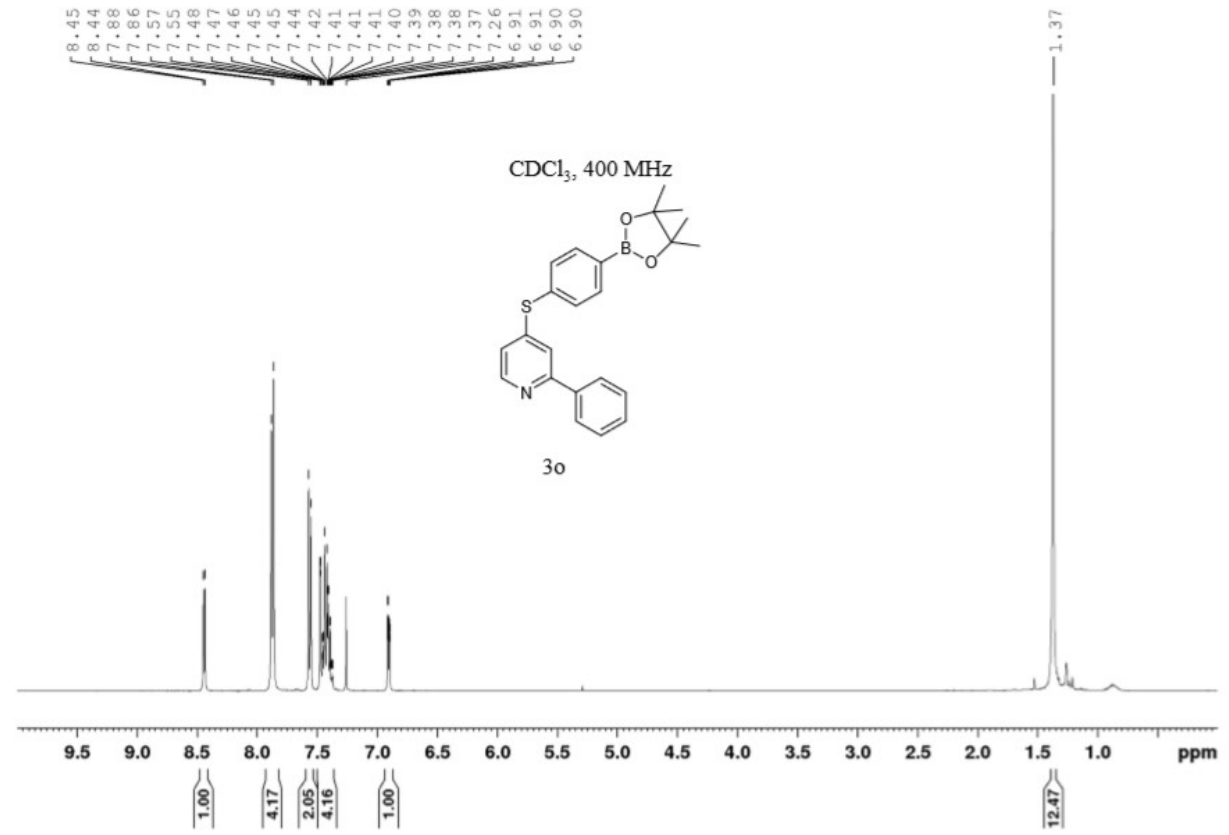

8.46
8.45
7.88
7.88
7.87
7.87
7.86
7.86
7.53
7.52
7.51
7.51
7.50
7.47
7.47
7.46
7.46
7.45
7.44
7.43
7.42
7.41
7.40
7.26
6.88
6.88
6.87
6.86
CDCl3, 400 MHz
Cl
S
N
3n
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.06
2.05
6.17
1.01

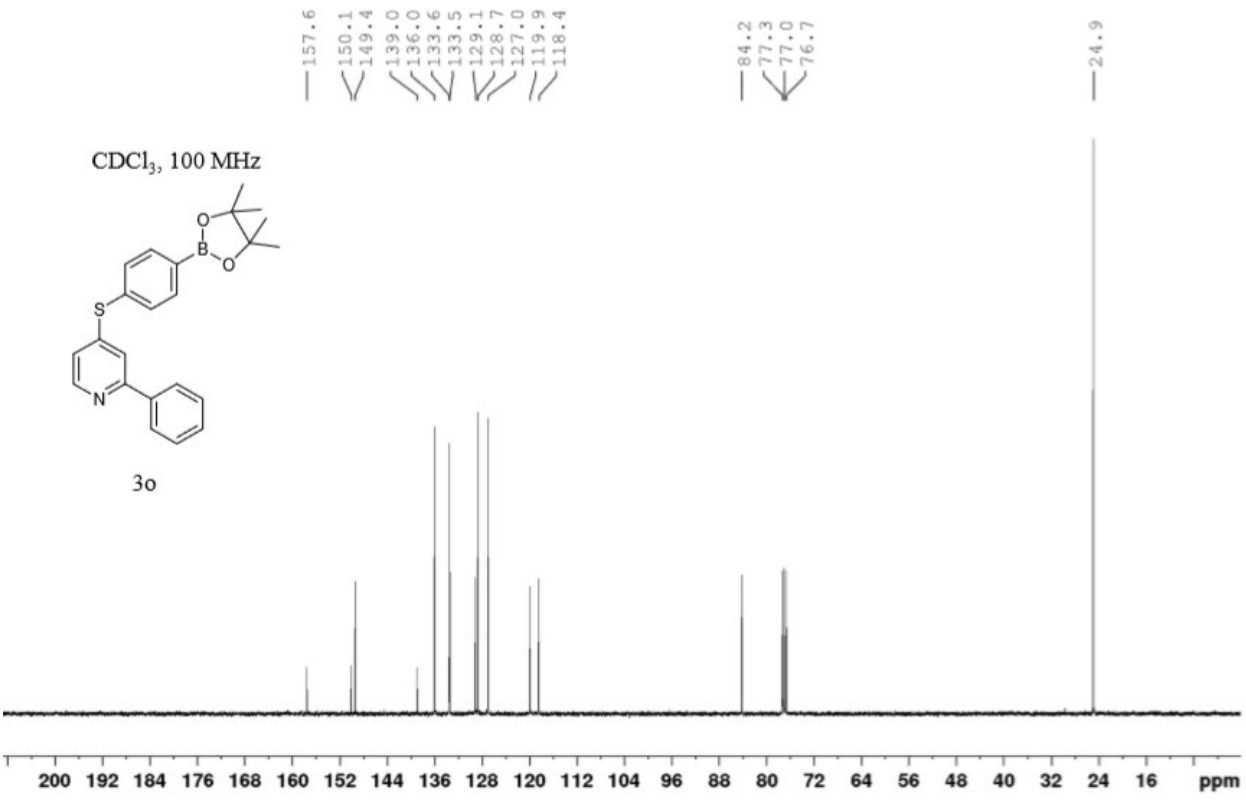

157.6
150.0
149.5
138.9
136.1
136.0
130.2
129.2
128.8
128.4
126.9
119.4
117.9
77.3
77.0
76.7
CDCl3, 100 MHz
Cl
S
N
3n
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

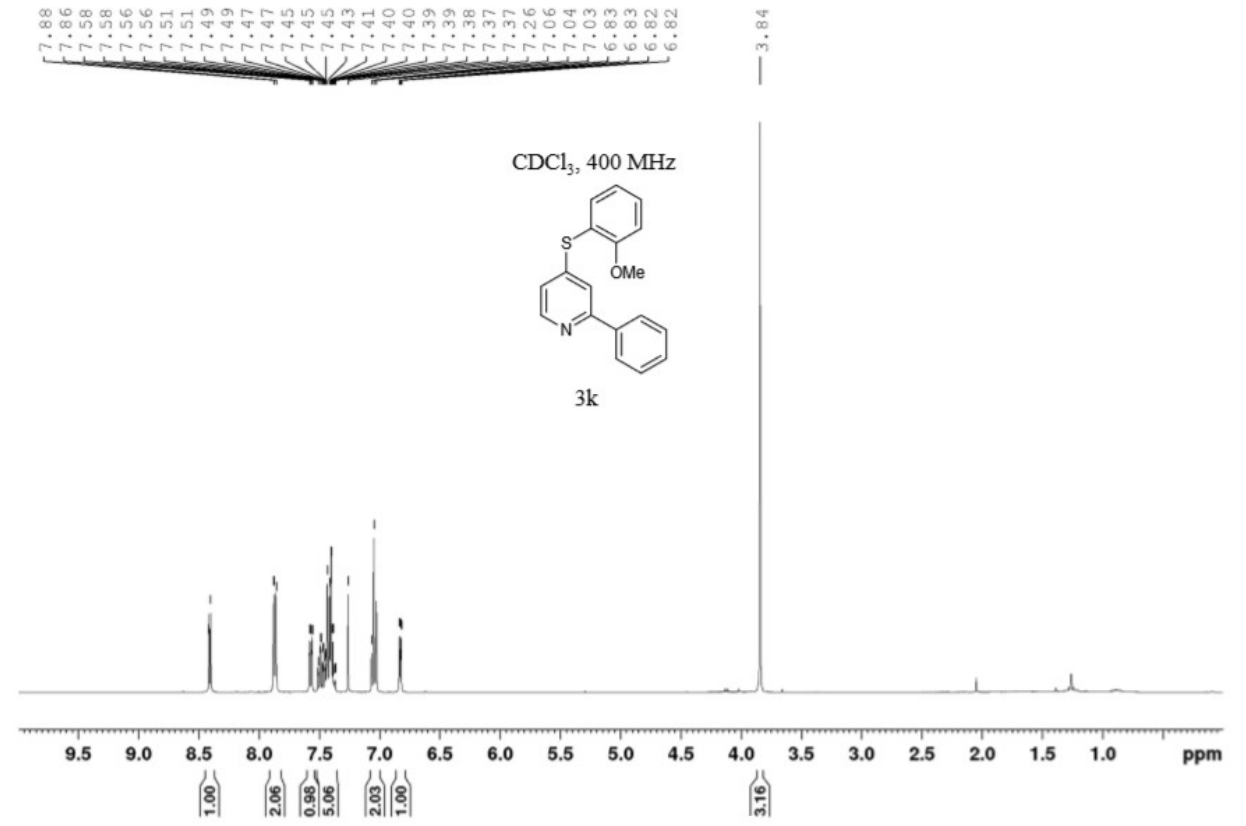

8.45
8.43
7.87
7.87
7.85
7.85
7.60
7.60
7.59
7.58
7.57
7.57
7.46
7.44
7.42
7.42
7.41
7.40
7.37
7.37
7.26
7.20
7.18
7.15
6.84
6.84
6.83
6.82
CDCl3, 400 MHz
F
S
N
3m
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.10
2.01
4.21
2.05
1.01


164.9
162.4
157.5
150.9
149.4
138.9
137.5
137.4
129.2
128.7
126.9
124.8
124.8
119.0
117.4
117.3
117.1
77.3
77.2
77.0
76.7
CDCl3, 100 MHz
F
S
N
3m
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


CDCl3, 365 MHz
F
S
N
3m
-110.25
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm


8.45 8.44 7.88 7.86 7.57 7.55 7.48 7.47 7.46 7.45 7.45 7.44 7.42 7.41 7.41 7.41 7.40 7.39 7.38 7.38 7.37 7.26 6.91 6.90 6.90
1.37
CDCl3, 400 MHz
O
B
O
S
N
3o
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 4.17 2.05 4.16 1.00 12.47


157.6
150.1
149.4
139.0
136.0
133.6
133.5
129.1
128.7
127.0
119.9
118.4
84.2
77.3
77.0
76.7
24.9
CDCl3, 100 MHz
3o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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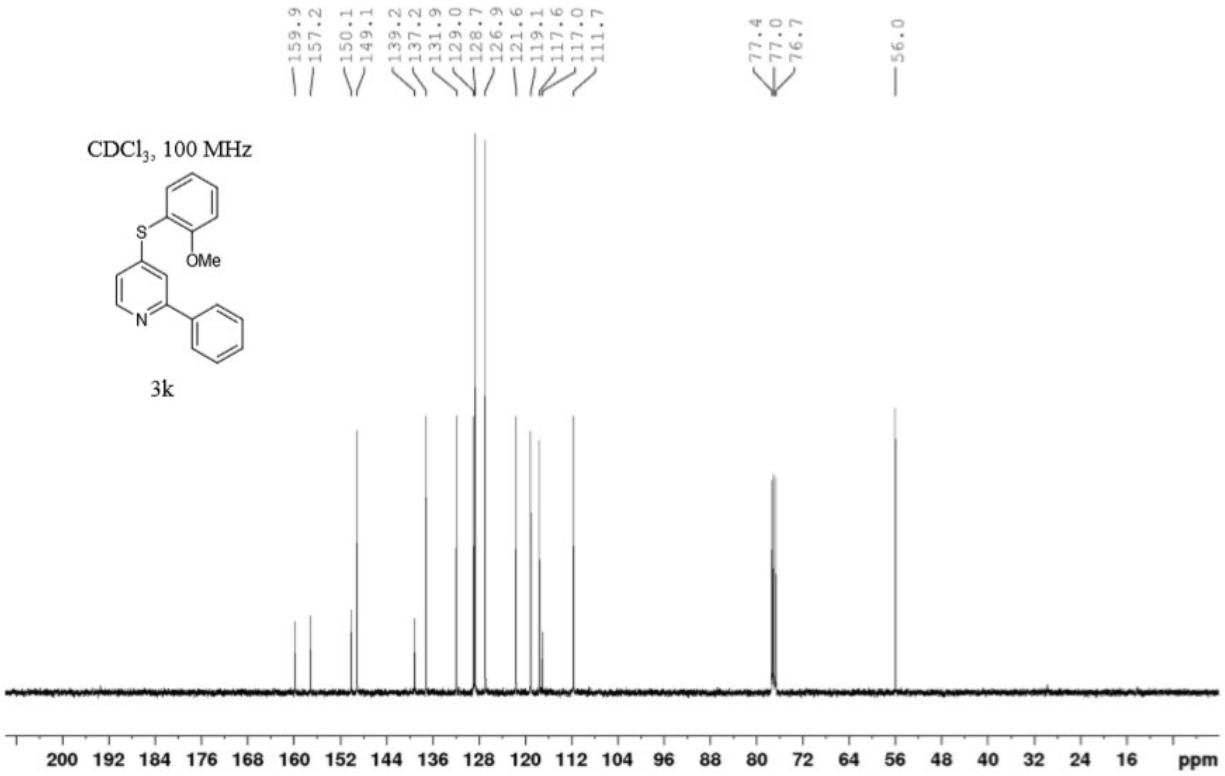
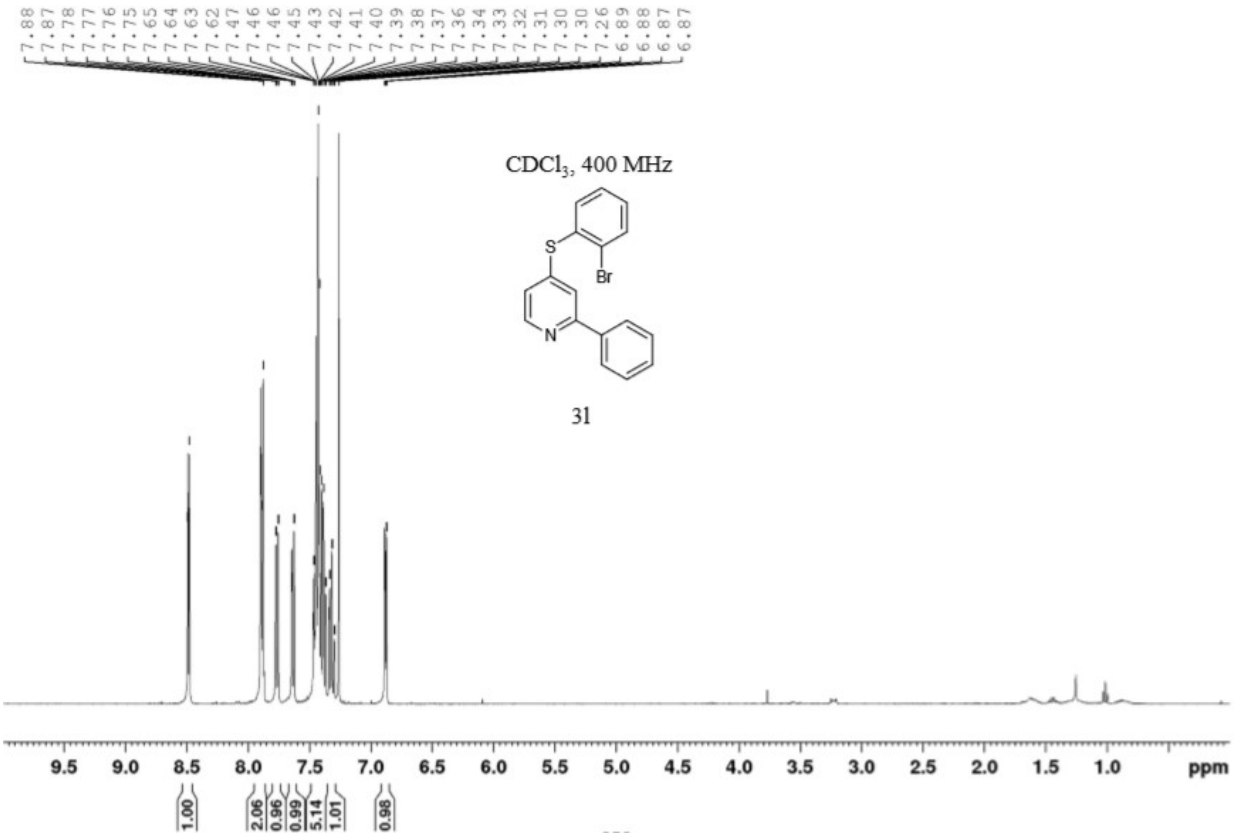
7.86
7.58
7.58
7.56
7.56
7.51
7.51
7.49
7.49
7.47
7.47
7.45
7.45
7.45
7.43
7.41
7.40
7.40
7.39
7.39
7.38
7.37
7.37
7.26
7.06
7.04
7.03
6.83
6.83
6.82
6.82
3.84
CDCl3, 400 MHz
3k
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.06
0.98
5.06
2.03
1.00
3.16


159.9
157.2
150.1
149.1
139.2
137.2
131.9
129.0
128.7
126.9
121.6
119.1
117.6
117.0
111.7
77.4
77.0
76.7
56.0
CDCl3, 100 MHz
S
OMe
N
3k
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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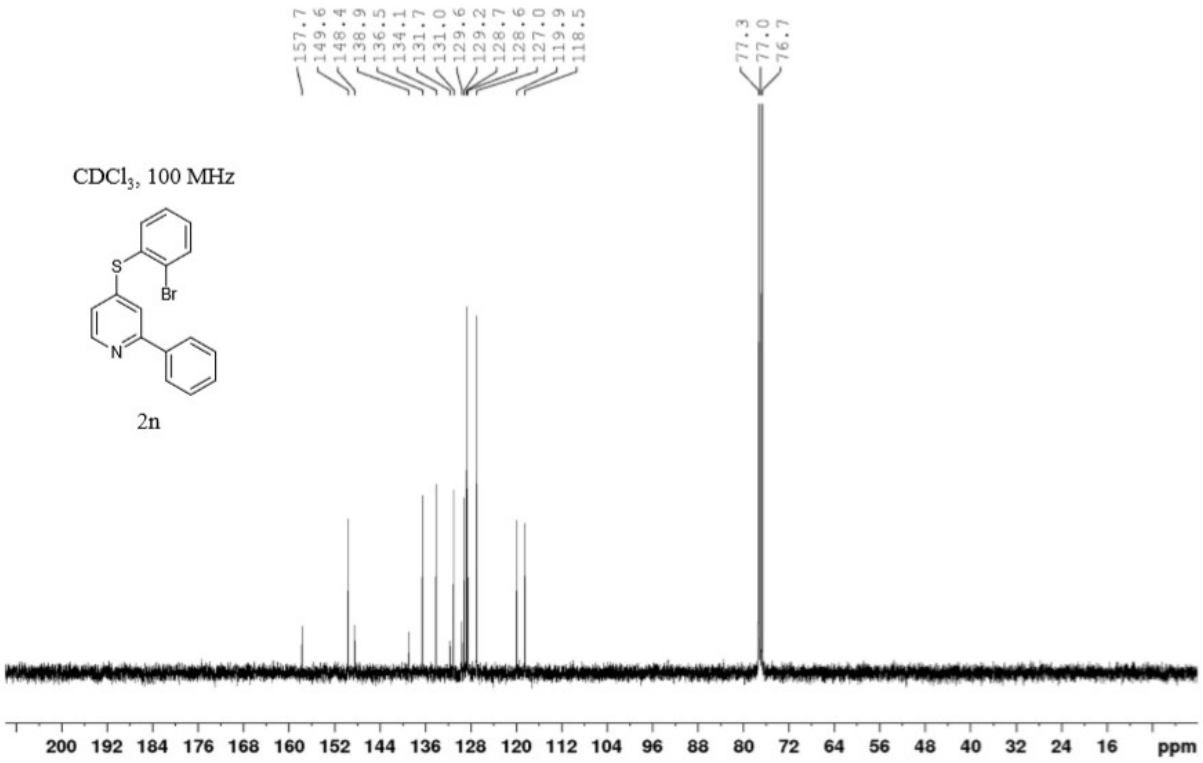
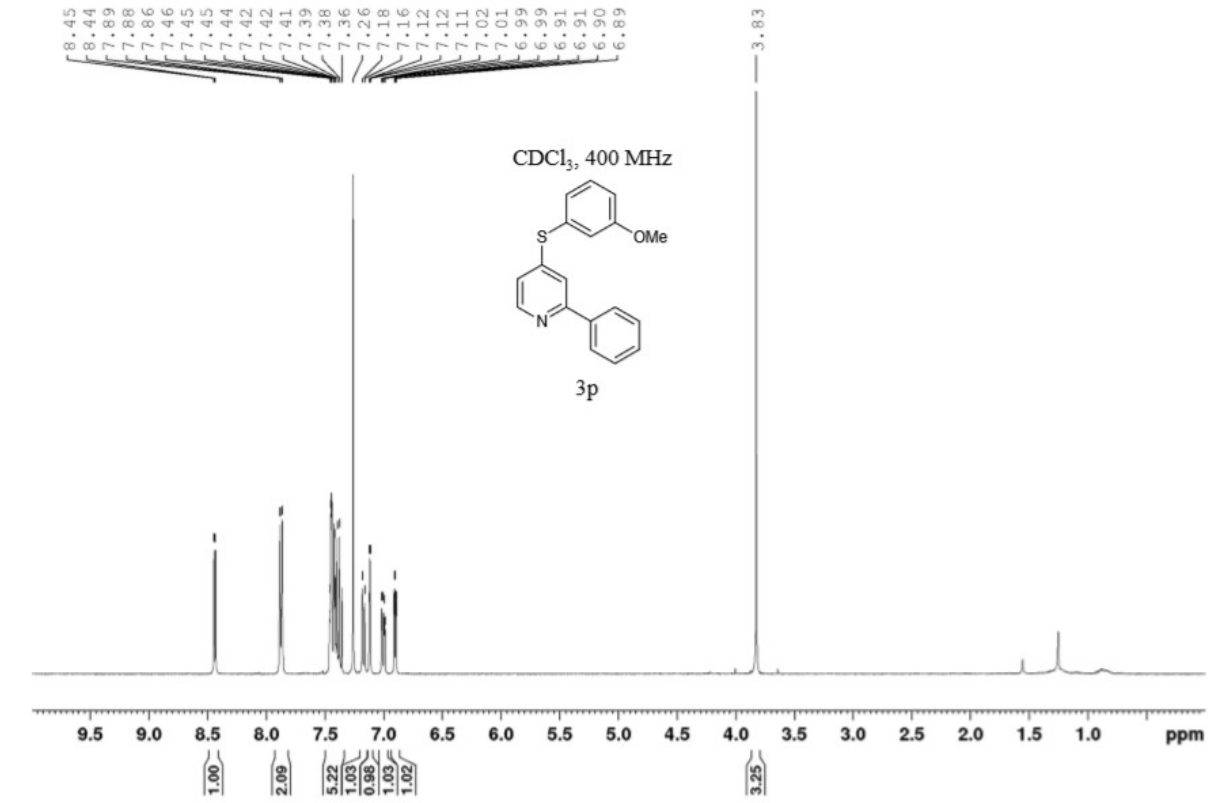
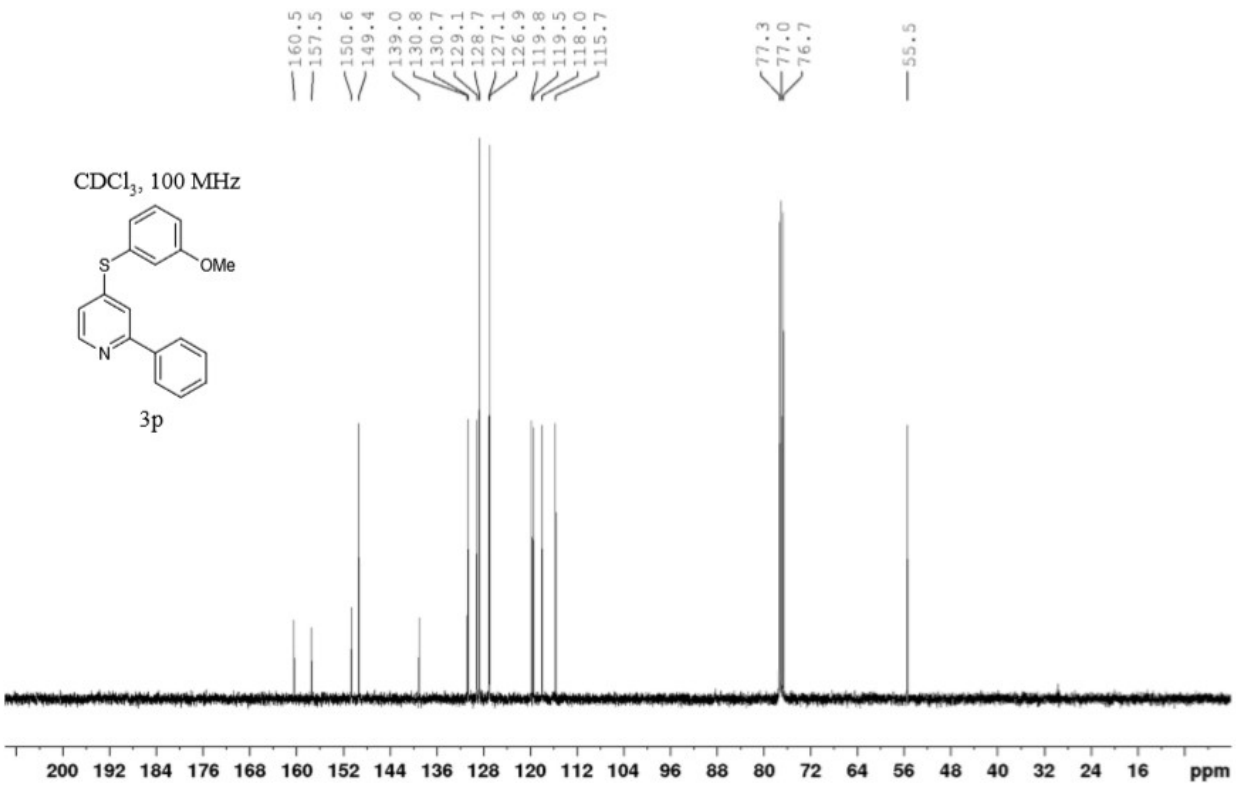
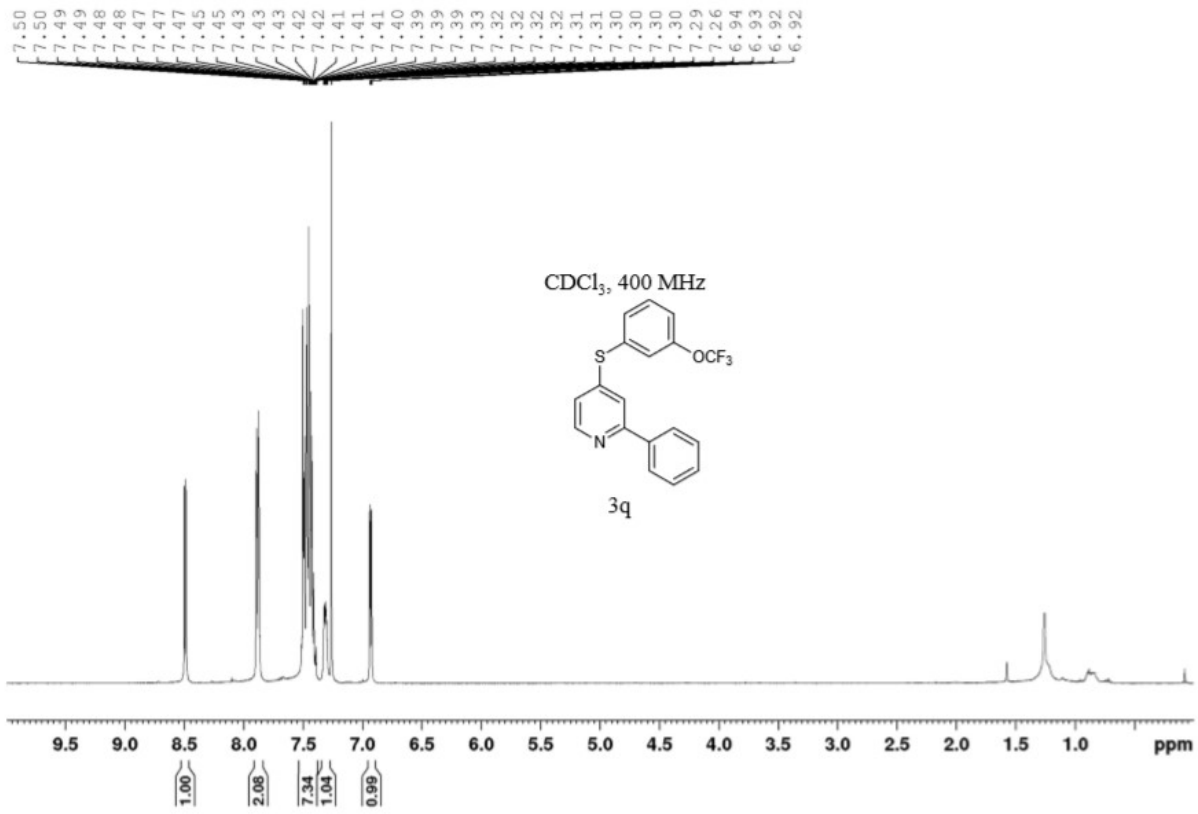
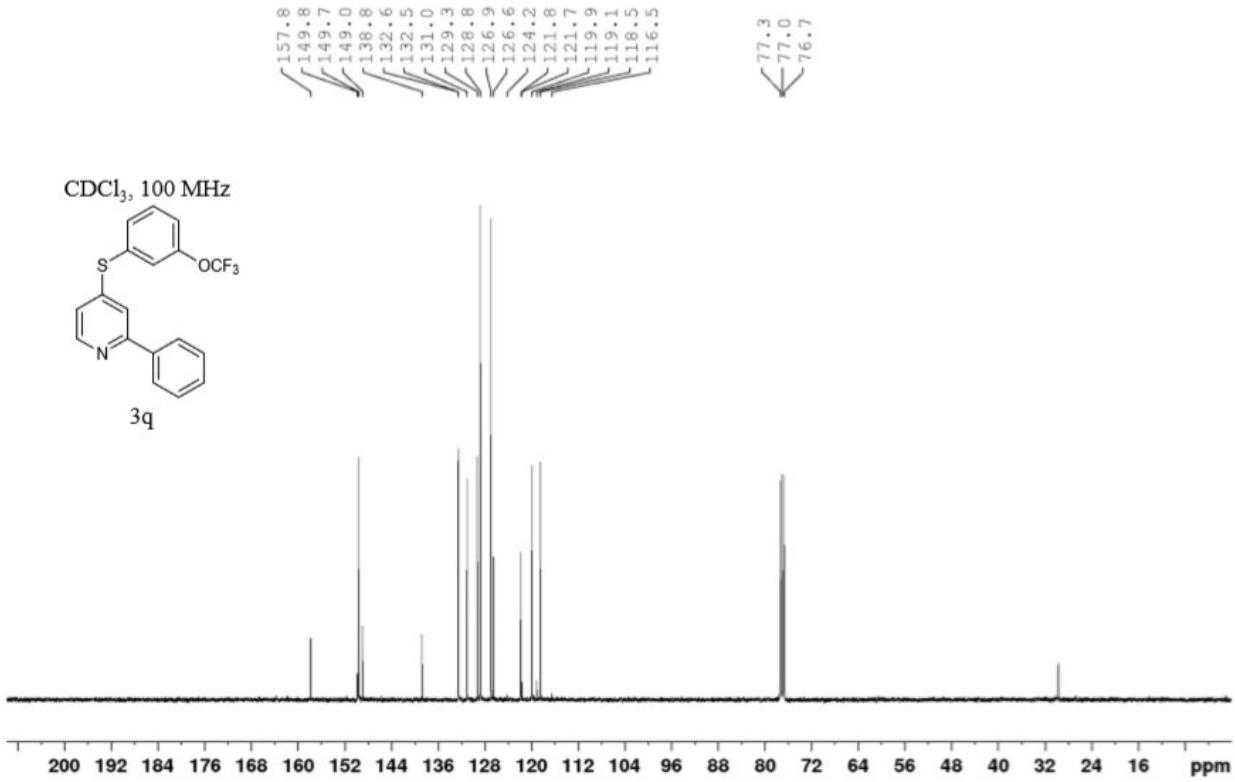
7.87
7.78
7.77
7.76
7.75
7.65
7.64
7.63
7.62
7.47
7.46
7.46
7.45
7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.36
7.34
7.33
7.32
7.31
7.30
7.30
7.26
6.89
6.88
6.87
6.87
CDCl3, 400 MHz
S
Br
N
31
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.06
0.96
0.99
5.14
1.01
0.98


157.7
149.6
148.4
138.9
136.5
134.1
131.7
131.0
129.6
129.2
128.7
128.6
127.0
119.9
118.5
77.3
77.0
76.7
CDCl3, 100 MHz
S
Br
N
2n
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.45
8.44
7.89
7.88
7.86
7.46
7.45
7.45
7.44
7.42
7.42
7.41
7.39
7.38
7.36
7.26
7.18
7.16
7.12
7.12
7.11
7.02
7.01
6.99
6.99
6.91
6.91
6.90
6.89
3.83
CDCl3, 400 MHz
S
OMe
N
3p
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.09
5.22
1.03
0.98
1.03
1.02
3.25


160.5
157.5
150.6
149.4
139.0
130.8
130.7
129.1
128.7
127.1
126.9
119.8
119.5
118.0
115.7
77.3
77.0
76.7
55.5
CDCl3, 100 MHz
S
OMe
N
3p
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.47
7.45
7.45
7.43
7.43
7.43
7.42
7.42
7.41
7.41
7.41
7.40
7.39
7.39
7.39
7.33
7.32
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.30
7.30
7.29
7.26
6.94
6.93
6.92
6.92
CDCl3, 400 MHz
S
OCF3
N
3q
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.08
7.34
1.04
0.99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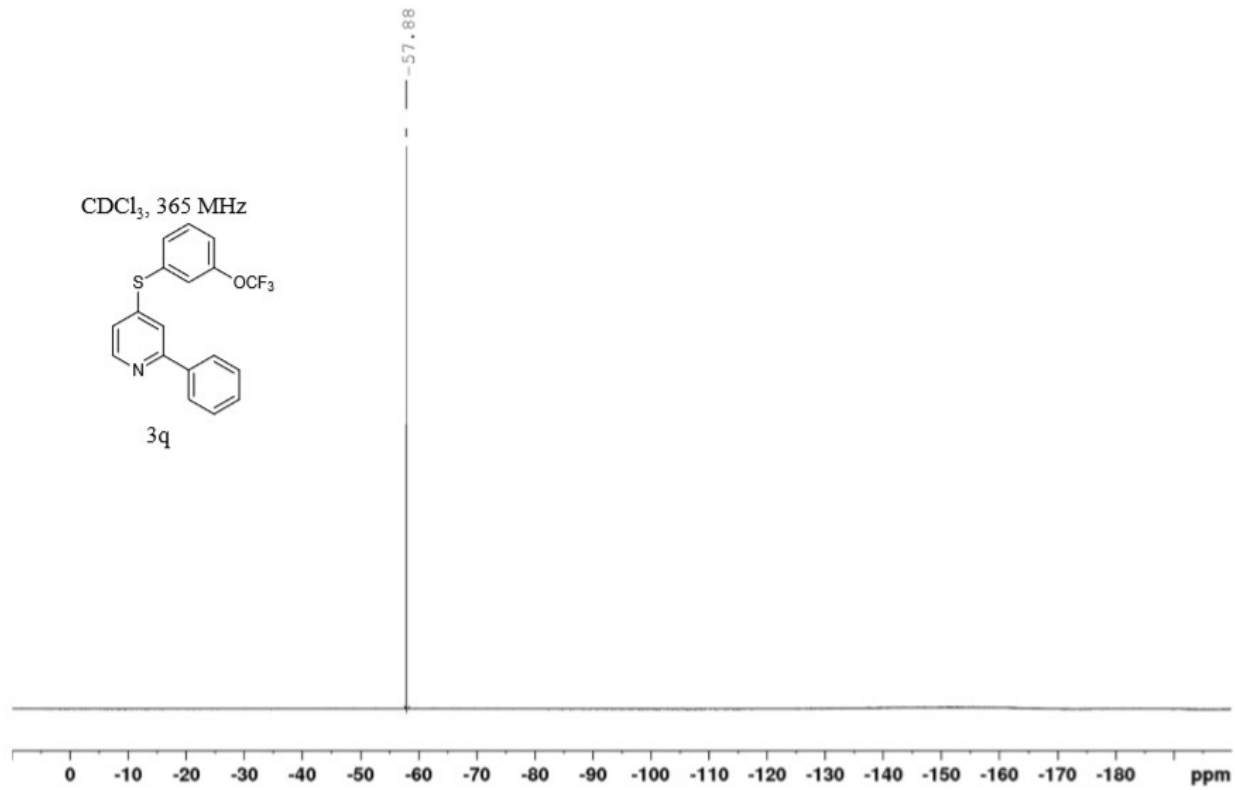
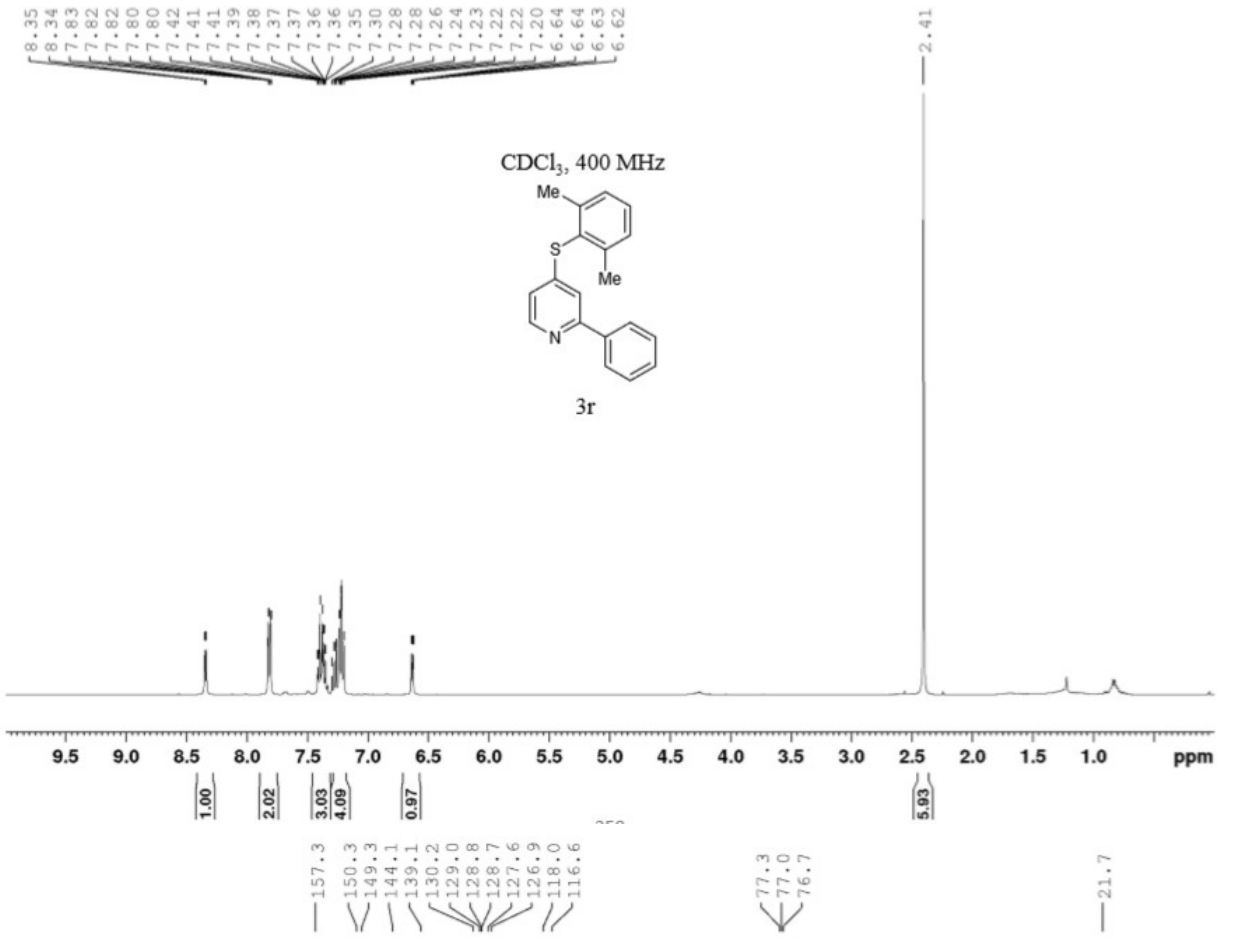
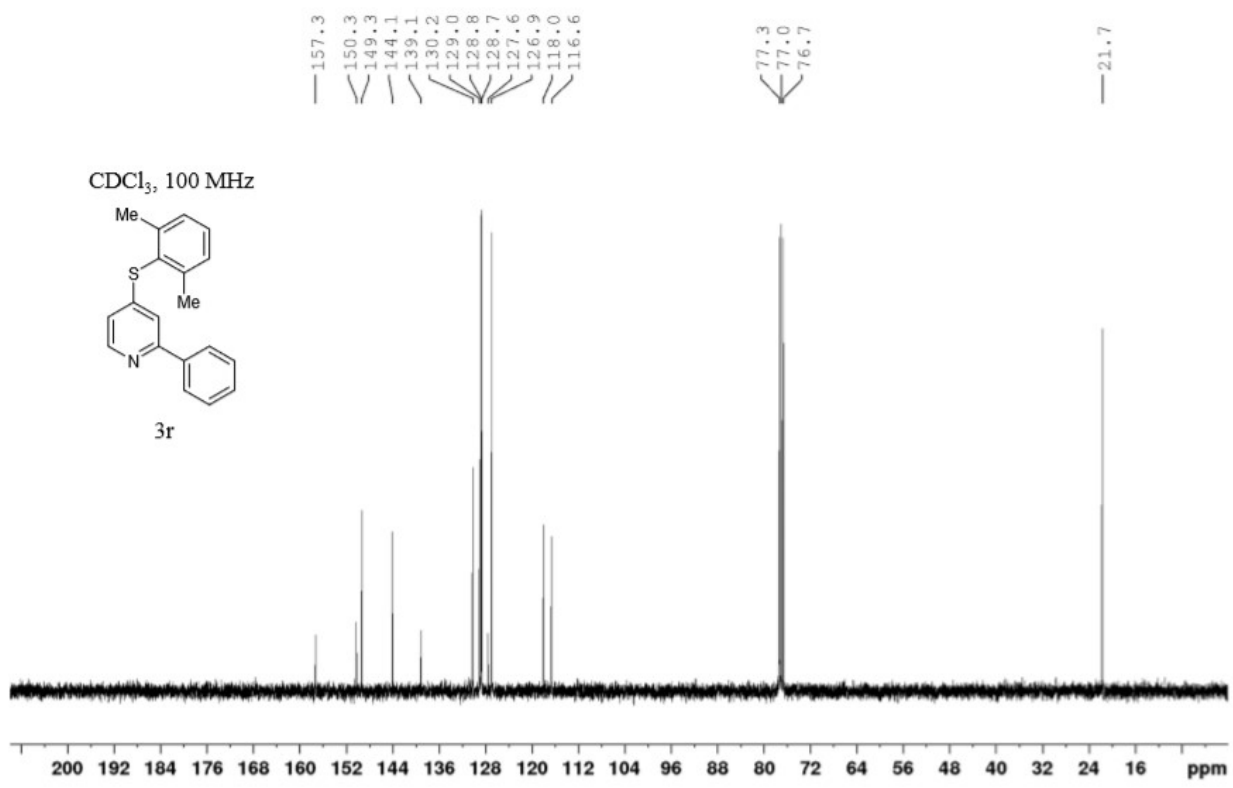
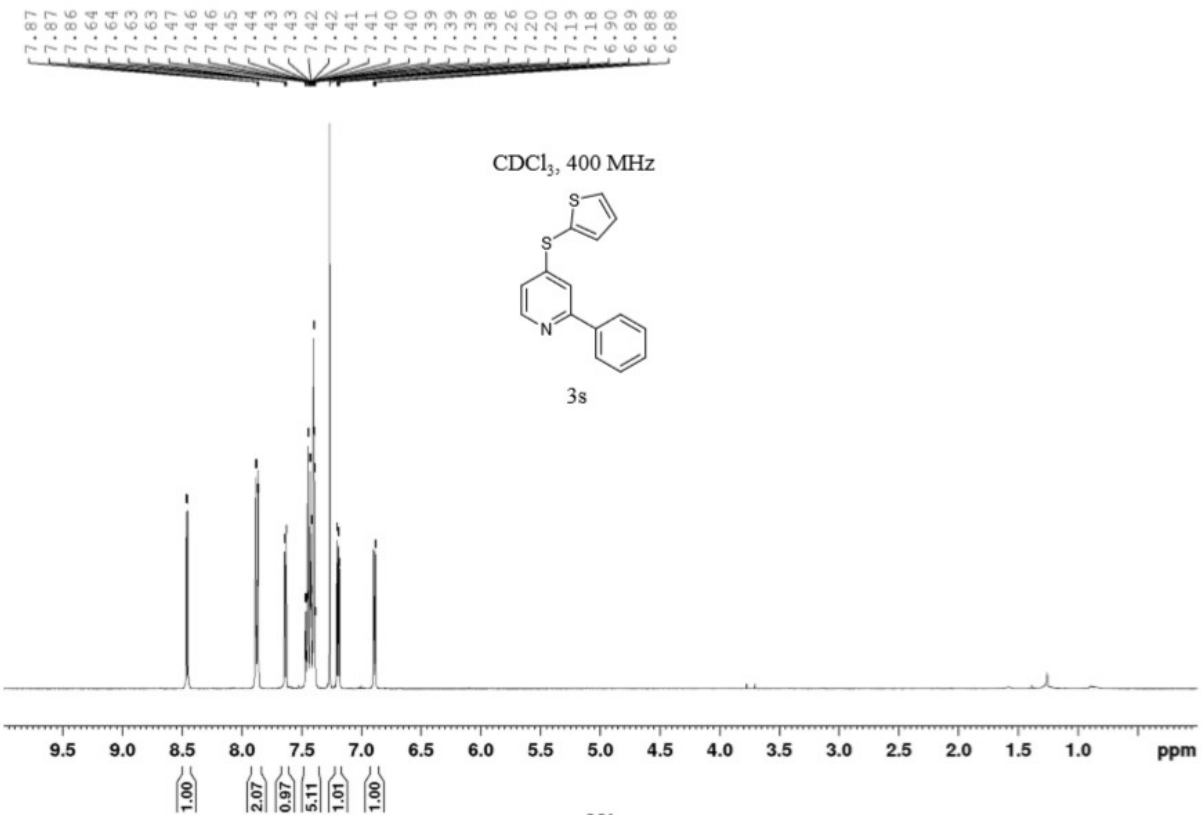
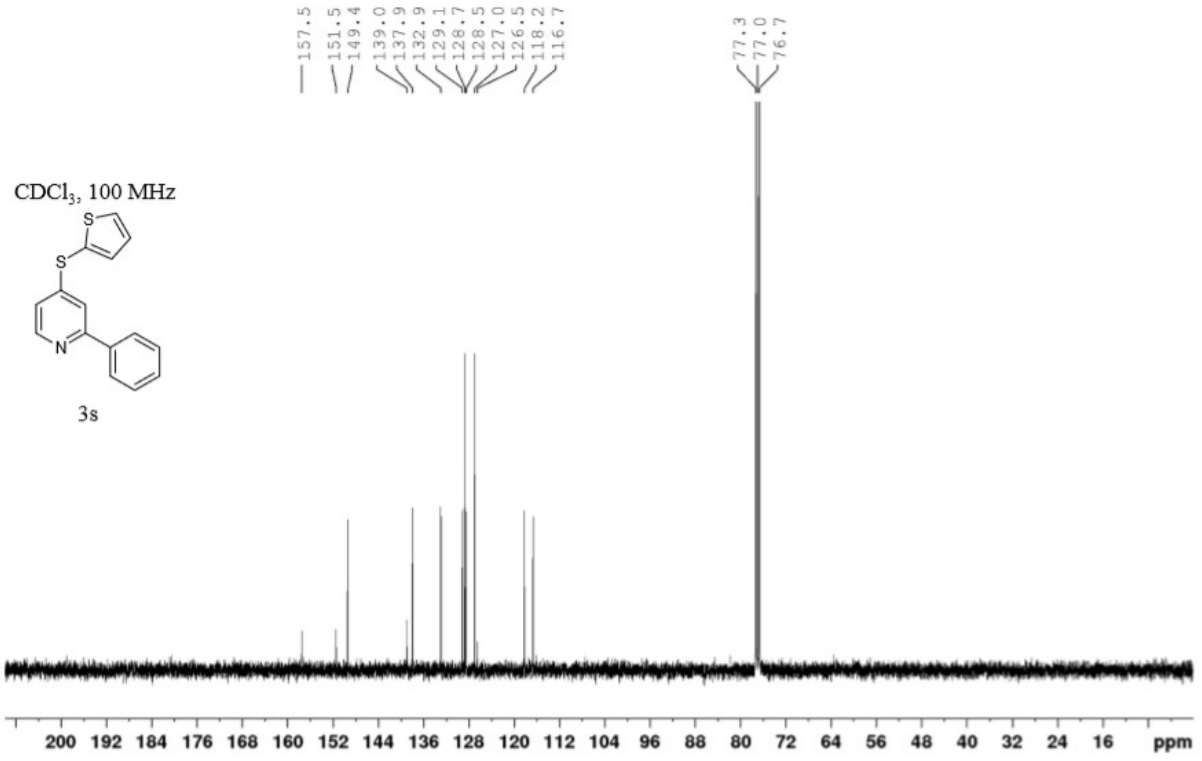
149.8
149.7
149.0
138.8
132.6
132.5
131.0
129.3
128.8
126.9
126.6
124.2
121.8
121.7
119.9
119.1
118.5
116.5
77.3
77.0
76.7
CDCl3, 100 MHz
S
OCF3
N
3q
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

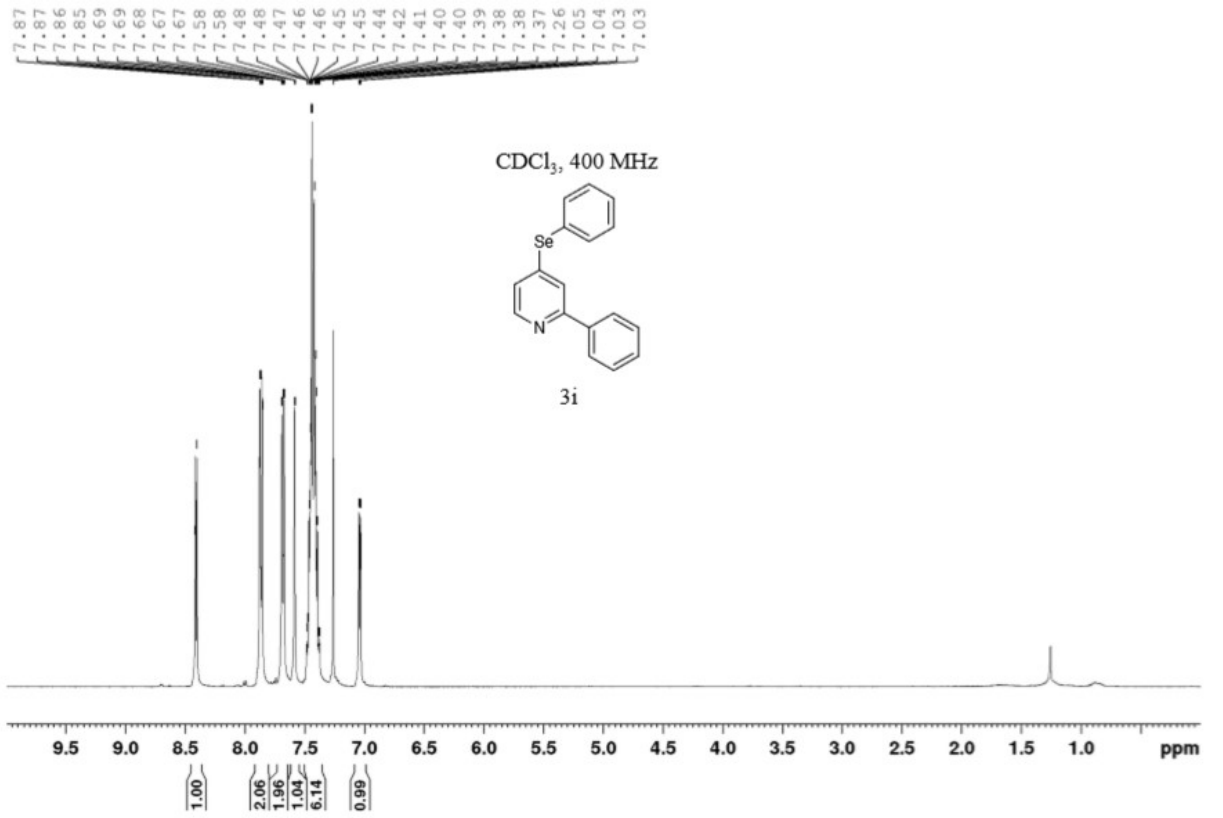

-57.88
CDCl3, 365 MHz
S
OCF3
N
3q
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

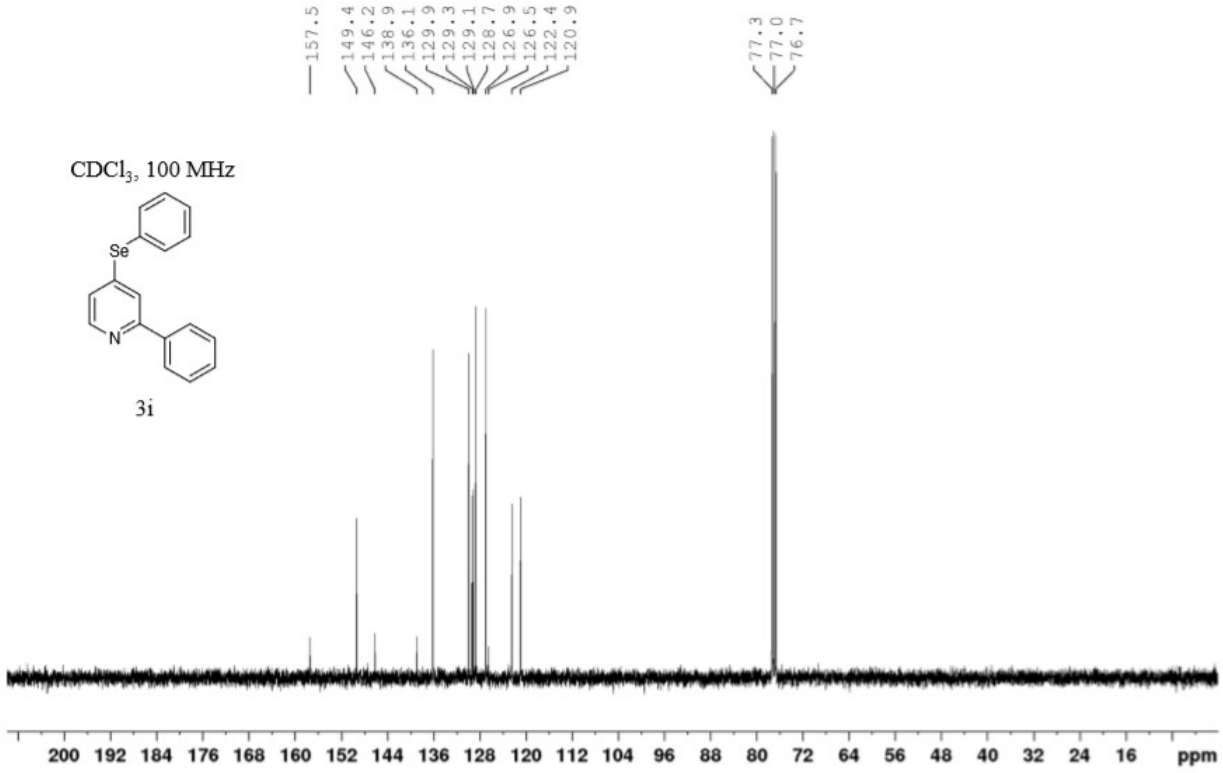

8.35
8.34
7.83
7.82
7.82
7.80
7.80
7.42
7.41
7.41
7.39
7.38
7.37
7.37
7.36
7.36
7.35
7.30
7.28
7.26
7.24
7.23
7.22
7.22
7.20
6.64
6.64
6.63
6.62
2.41
CDCl3, 400 MHz
Me
S
Me
N
3r
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.02
3.03
4.09
0.97
5.93

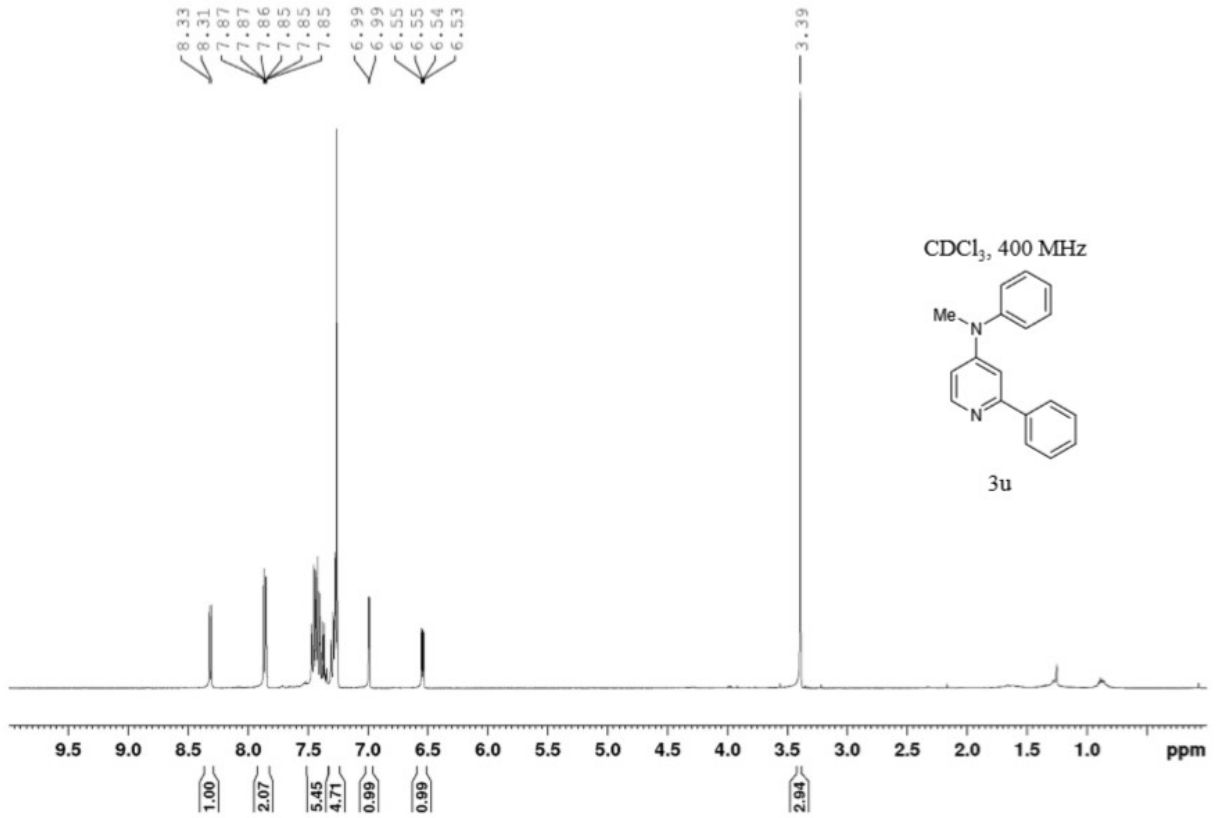

157.3
150.3
149.3
144.1
139.1
130.2
129.0
128.8
128.7
127.6
126.9
118.0
116.6
77.3
77.0
76.7
21.7
CDCl3, 100 MHz
Me
S
Me
N
3r
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

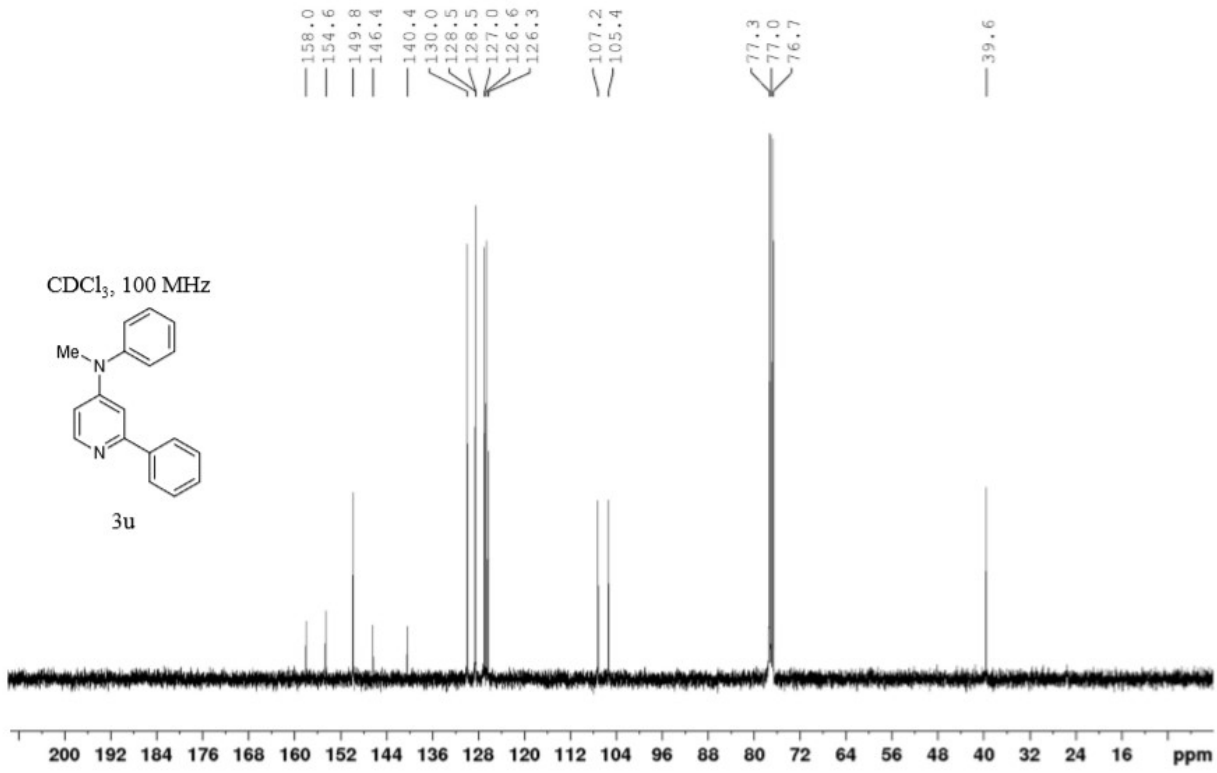

7.87
7.87
7.86
7.64
7.64
7.63
7.63
7.47
7.46
7.46
7.45
7.44
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.39
7.38
7.26
7.20
7.20
7.19
7.18
6.90
6.89
6.88
6.88
CDCl3, 400 MHz
S
S
N
3s
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.07
0.97
5.11
1.01
1.00

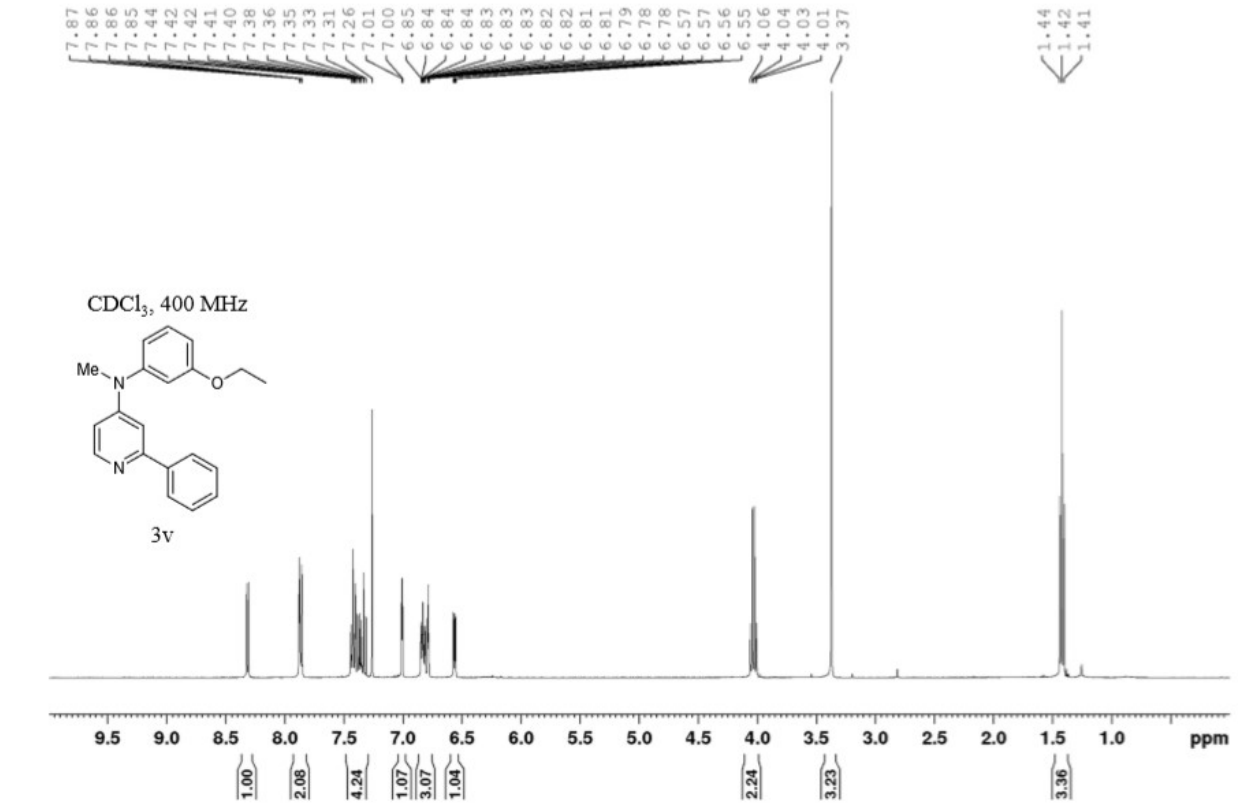

157.5
151.5
149.4
139.0
137.9
132.9
129.1
128.7
128.5
127.0
126.5
118.2
116.7
77.3
77.0
76.7
CDCl3, 100 MHz
S
S
N
3s
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

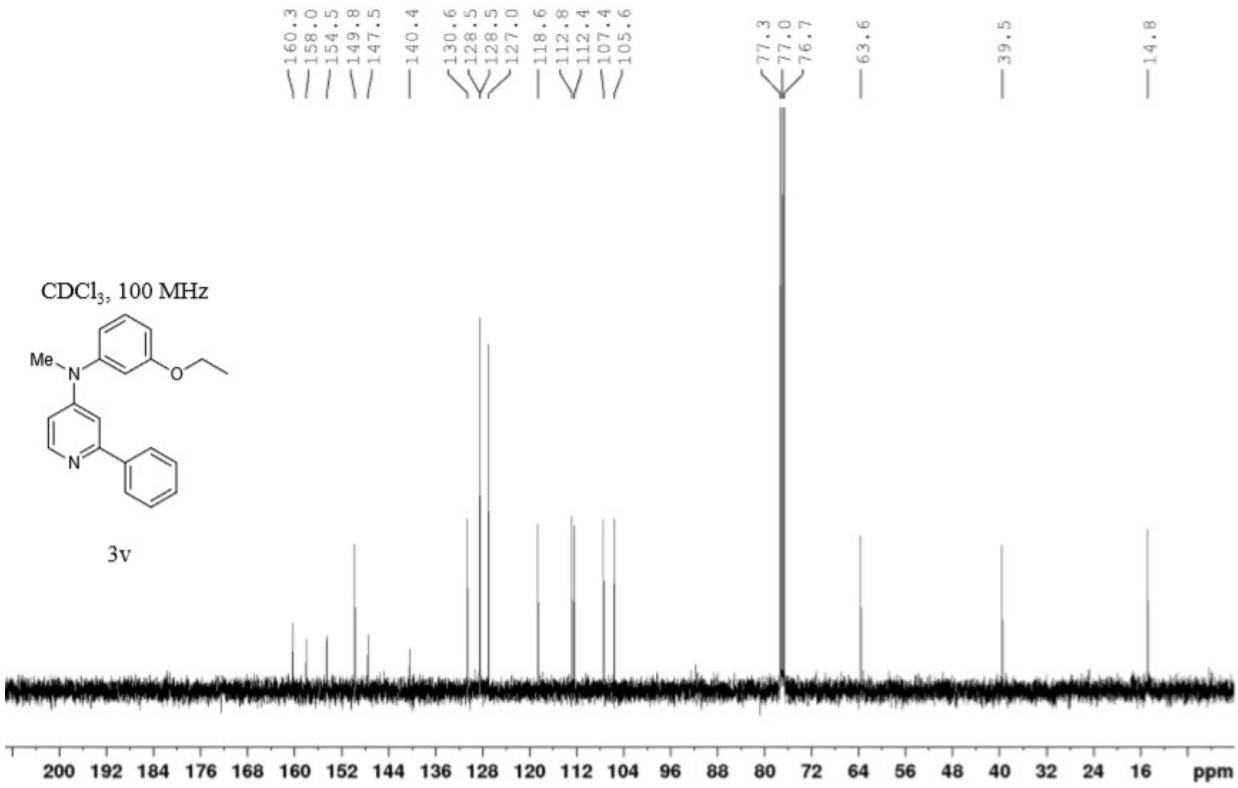

7.87
7.87
7.86
7.85
7.69
7.69
7.68
7.67
7.67
7.58
7.58
7.48
7.48
7.47
7.46
7.46
7.45
7.45
7.44
7.42
7.41
7.40
7.40
7.39
7.38
7.38
7.37
7.26
7.05
7.04
7.03
7.03
CDCl3, 400 MHz
Se
N
3i
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.06
1.96
1.04
6.14
0.99

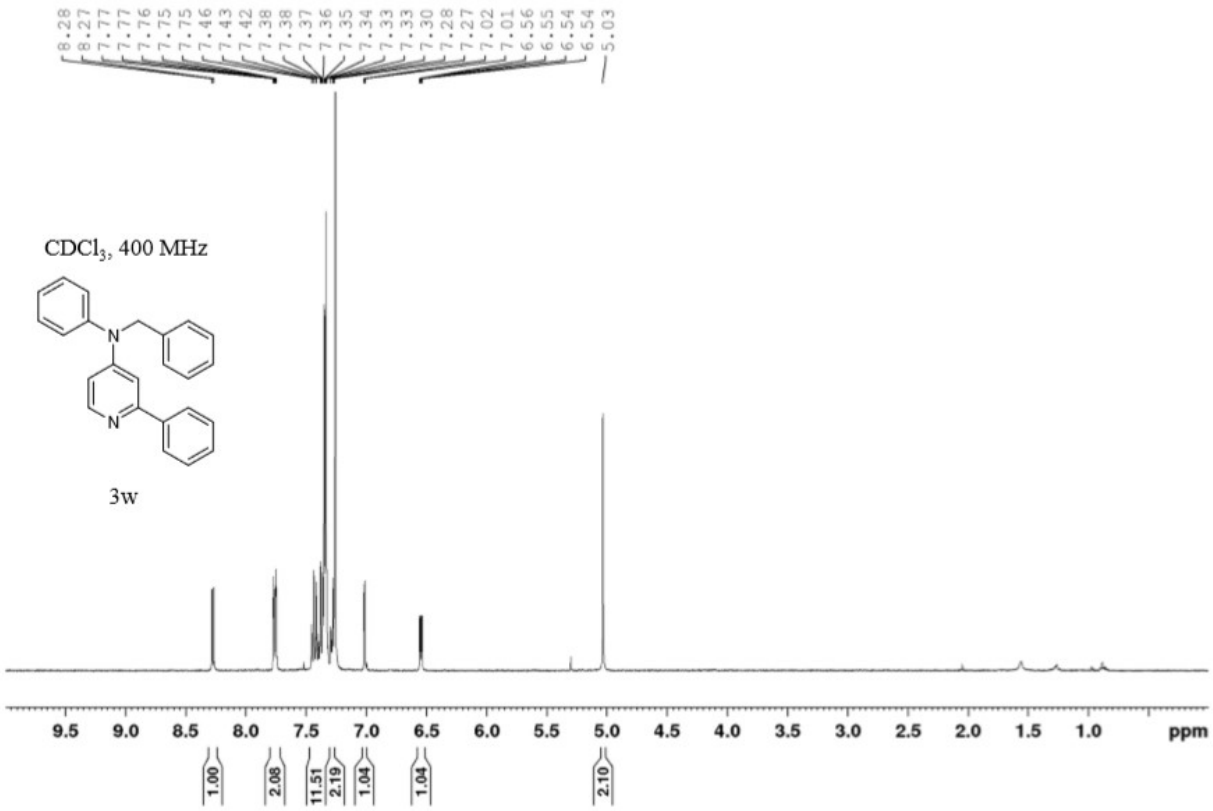

157.5
149.4
146.2
138.9
136.1
129.9
129.3
129.1
128.7
126.9
126.5
122.4
120.9
77.3
77.0
76.7
CDCl3, 100 MHz
Se
N
3i
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.33
8.31
7.87
7.87
7.86
7.85
7.85
7.85
6.99
6.99
6.55
6.55
6.54
6.53
3.39
CDCl3, 400 MHz
Me
N
N
3u
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.07
5.45
4.71
0.99
0.99
2.94


158.0
154.6
149.8
146.4
140.4
130.0
128.5
128.5
127.0
126.6
126.3
107.2
105.4
77.3
77.0
76.7
39.6
CDCl3, 100 MHz
Me
N
N
3u
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


7.87
7.86
7.86
7.85
7.44
7.42
7.42
7.41
7.40
7.38
7.36
7.35
7.33
7.31
7.26
7.01
7.00
6.85
6.84
6.84
6.84
6.83
6.83
6.83
6.82
6.82
6.81
6.81
6.79
6.78
6.78
6.57
6.57
6.56
6.55
4.06
4.04
4.03
4.01
3.37
1.44
1.42
1.41
CDCl3, 400 MHz
Me
N
O
N
3v
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.08
4.24
1.07
3.07
1.04
2.24
3.23
3.36


160.3
158.0
154.5
149.8
147.5
140.4
130.6
128.5
128.5
127.0
118.6
112.8
112.4
107.4
105.6
77.3
77.0
76.7
63.6
39.5
14.8
CDCl3, 100 MHz
Me
N
O
N
3v
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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8.27
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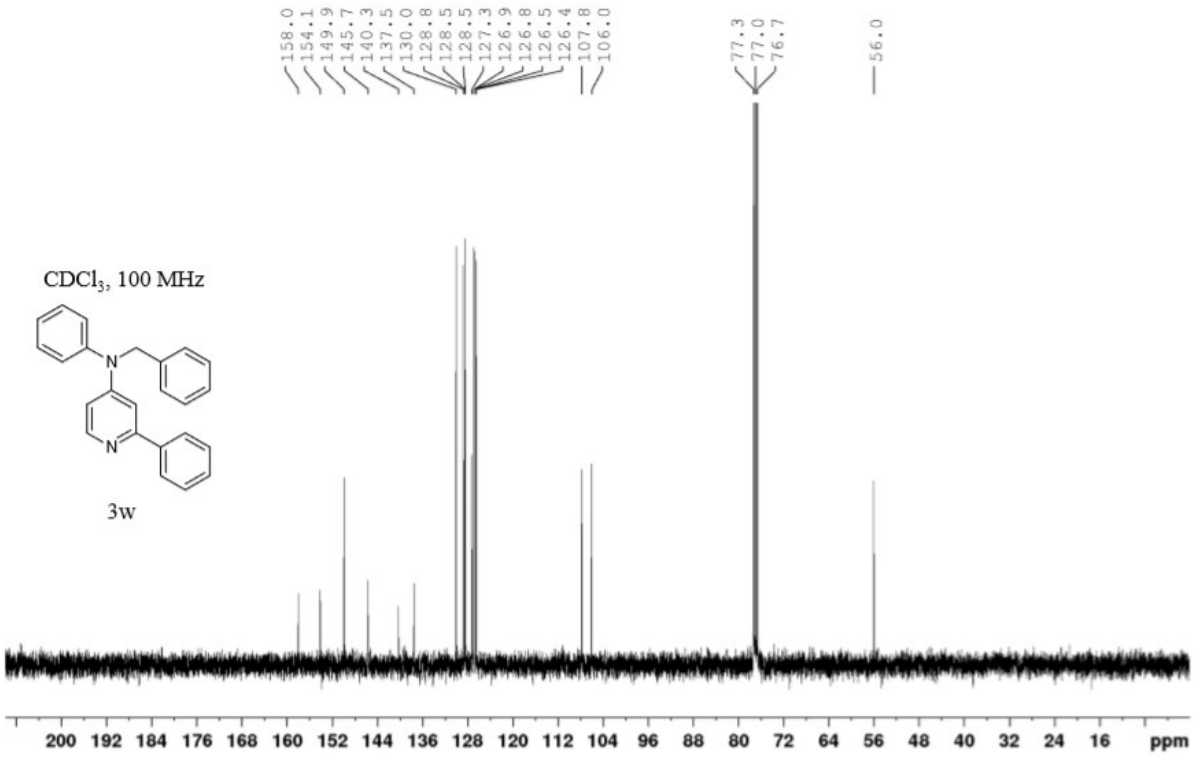
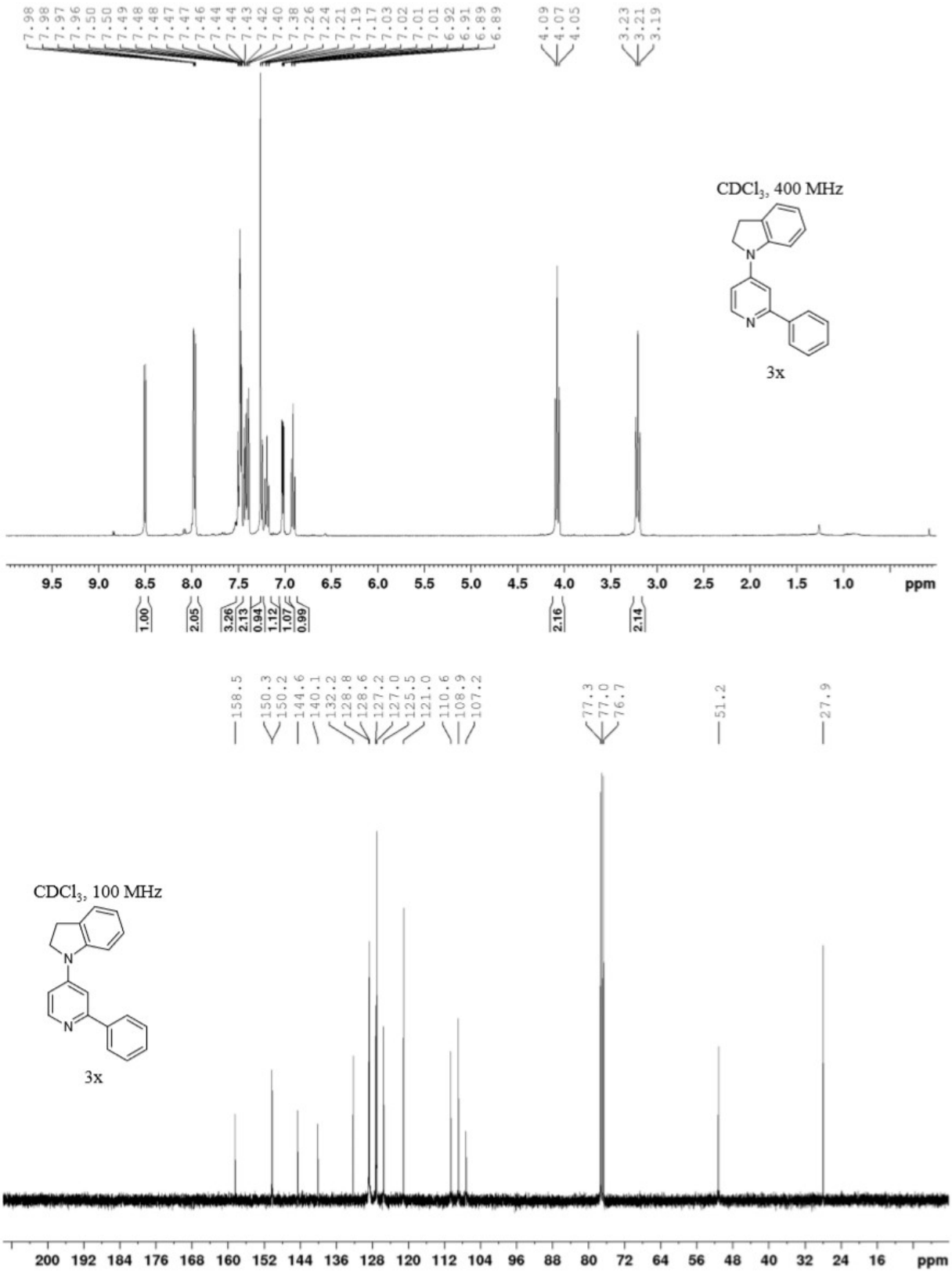
7.77
7.76
7.75
7.75
7.46
7.43
7.42
7.38
7.38
7.37
7.36
7.35
7.34
7.33
7.30
7.28
7.27
7.02
7.01
6.56
6.55
6.54
6.54
5.03
CDCl3, 400 MHz
3w
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.08
11.51
2.19
1.04
1.04
2.10


158.0
154.1
149.9
145.7
140.3
137.5
130.0
128.8
128.5
128.5
127.3
126.9
126.8
126.5
126.4
107.8
106.0
77.3
77.0
76.7
56.0
CDCl3, 100 MHz
3w
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm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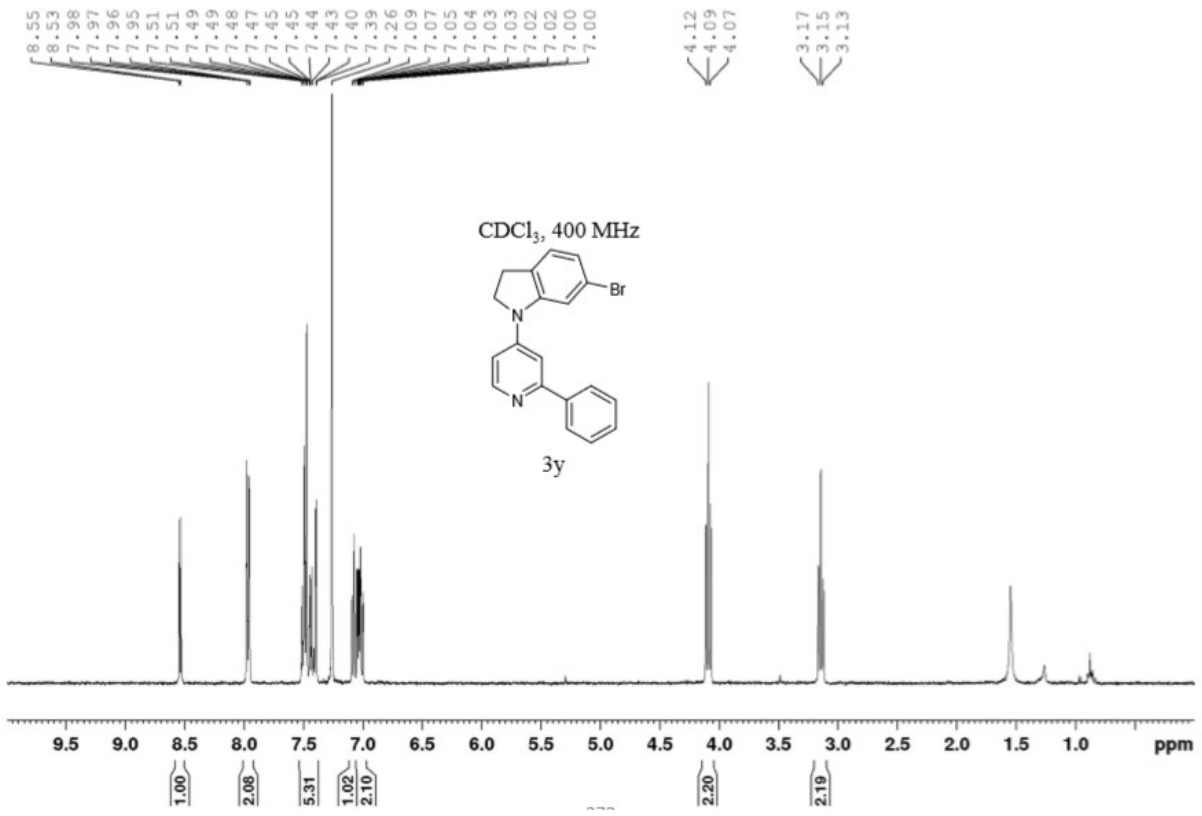
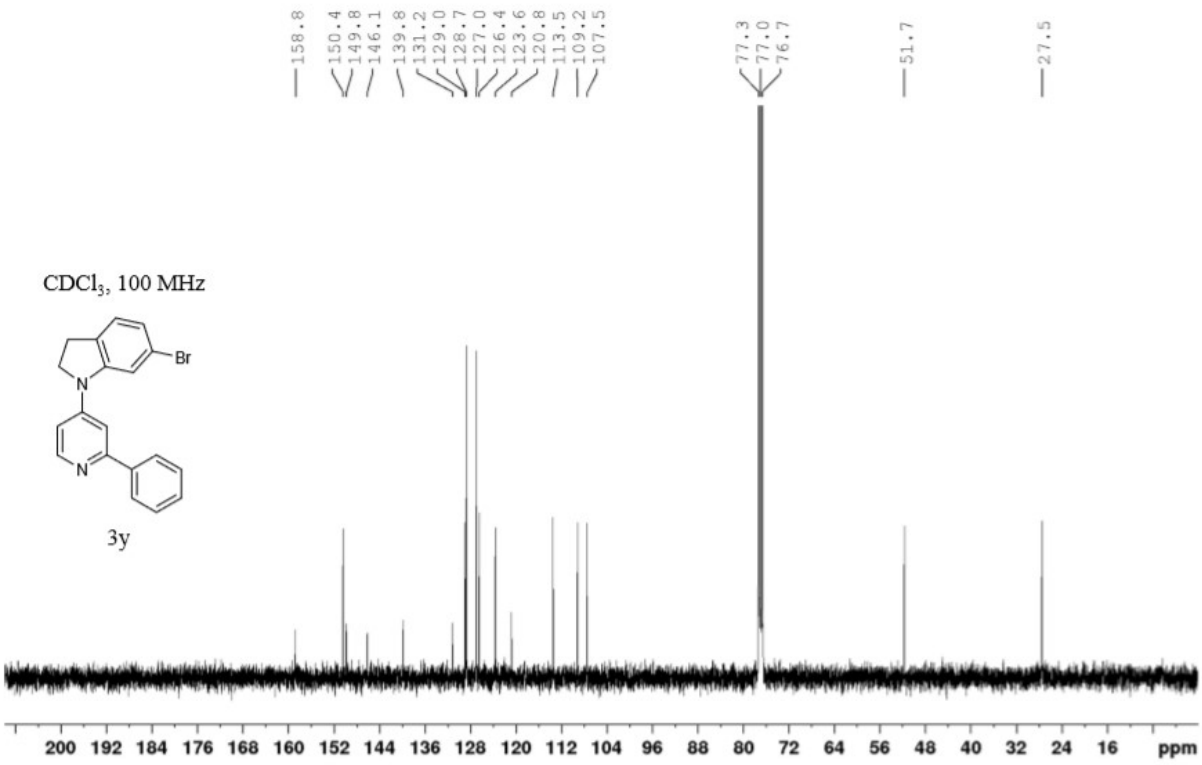
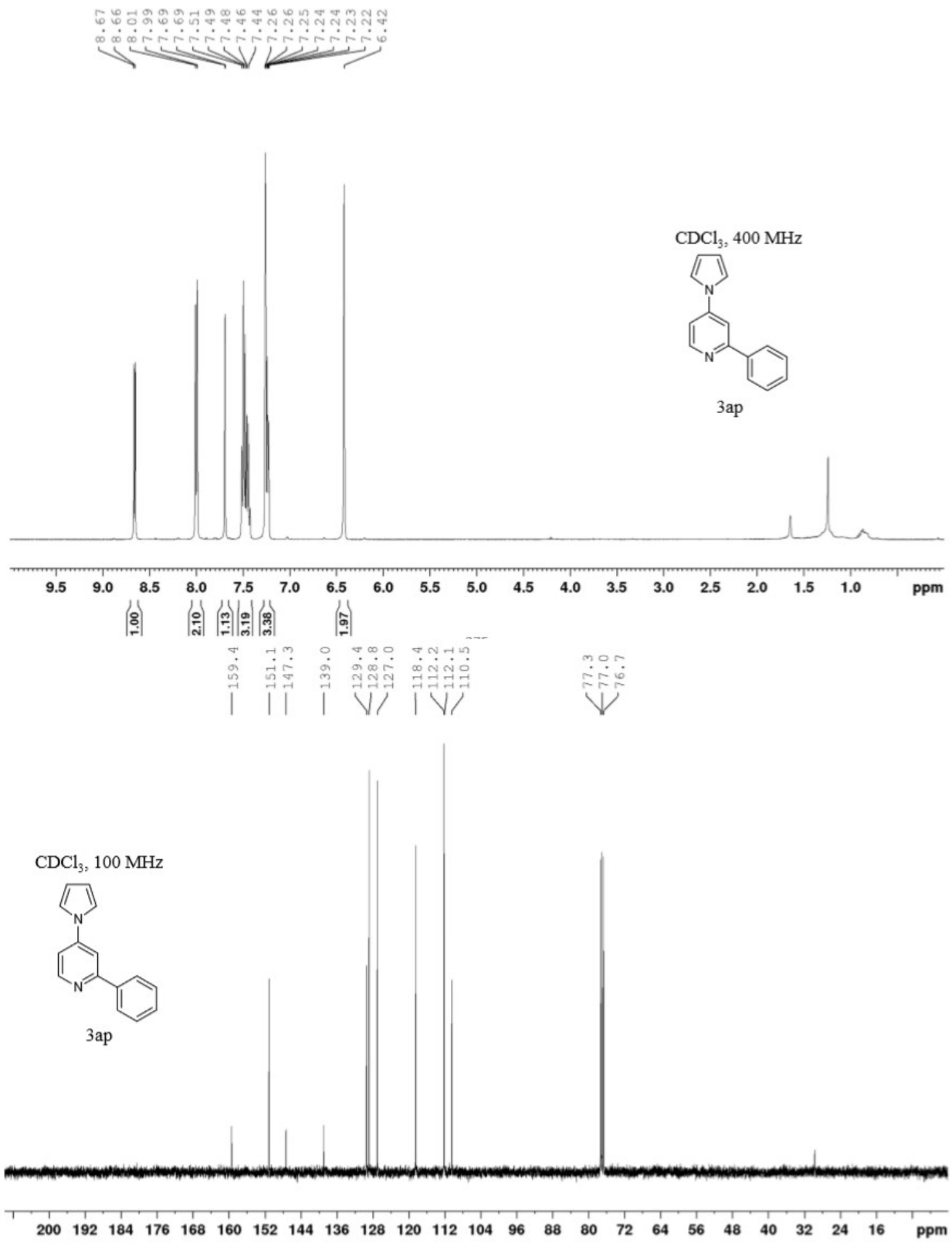
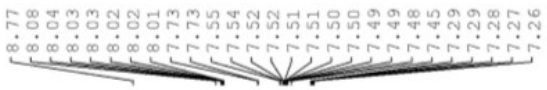
7.98
7.97
7.96
7.50
7.50
7.49
7.48
7.48
7.47
7.47
7.46
7.44
7.44
7.43
7.42
7.40
7.38
7.26
7.24
7.21
7.19
7.17
7.03
7.02
7.01
7.01
6.92
6.91
6.89
6.89
4.09
4.07
4.05
3.23
3.21
3.19
CDCl3, 400 MHz
3x
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.05
3.26
2.13
0.84
1.12
1.07
0.99
2.16
2.14
158.5
150.3
150.2
144.6
140.1
132.2
128.8
128.6
127.2
127.0
125.5
121.0
110.6
108.9
107.2
77.3
77.0
76.7
51.2
27.9
CDCl3, 100 MHz
3x
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.55
8.53
7.98
7.97
7.96
7.95
7.51
7.51
7.49
7.49
7.48
7.47
7.45
7.45
7.44
7.43
7.40
7.39
7.26
7.09
7.07
7.05
7.04
7.03
7.03
7.02
7.02
7.00
7.00
4.12
4.09
4.07
3.17
3.15
3.13
CDCl3, 400 MHz
Br
N
N
3y
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.08
5.31
1.02
2.10
2.20
2.19


158.8
150.4
149.8
146.1
139.8
131.2
129.0
128.7
127.0
126.4
123.6
120.8
113.5
109.2
107.5
77.3
77.0
76.7
51.7
27.5
CDCl3, 100 MHz
Br
N
N
3y
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.67
8.66
8.01
7.99
7.69
7.69
7.51
7.49
7.48
7.46
7.44
7.26
7.26
7.25
7.24
7.24
7.23
7.22
6.42
CDCl3, 400 MHz
3ap
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.10
1.13
3.19
3.38
1.97
159.4
151.1
147.3
139.0
129.4
128.8
127.0
118.4
112.2
112.1
110.5
77.3
77.0
76.7
CDCl3, 100 MHz
3ap
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.77
8.08
8.04
8.03
8.03
8.02
8.02
8.01
7.73
7.73
7.55
7.54
7.52
7.52
7.51
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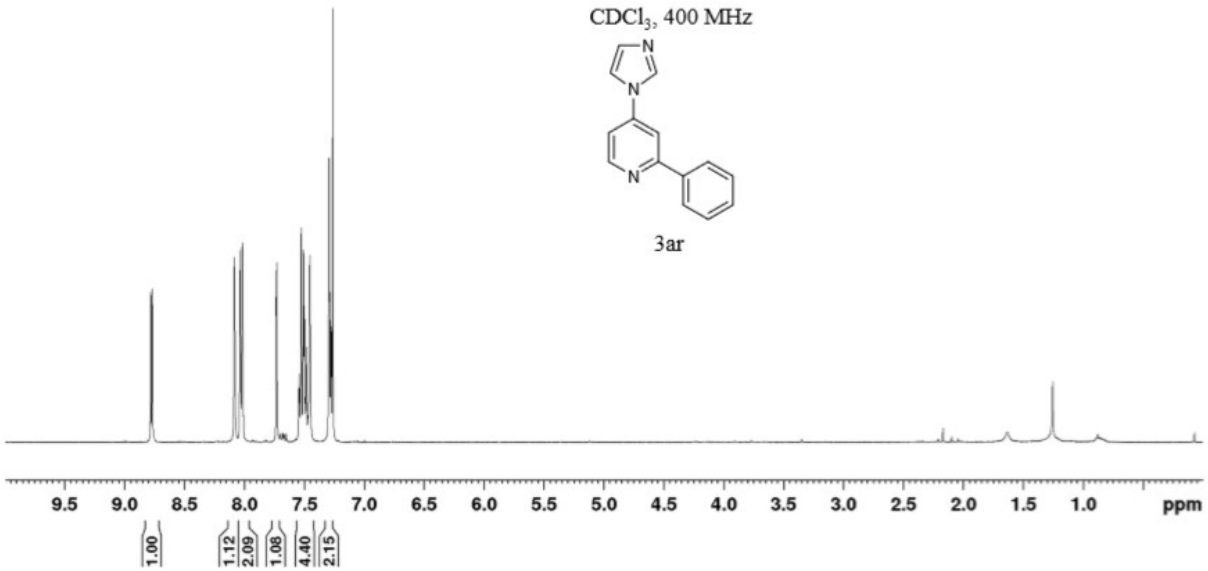
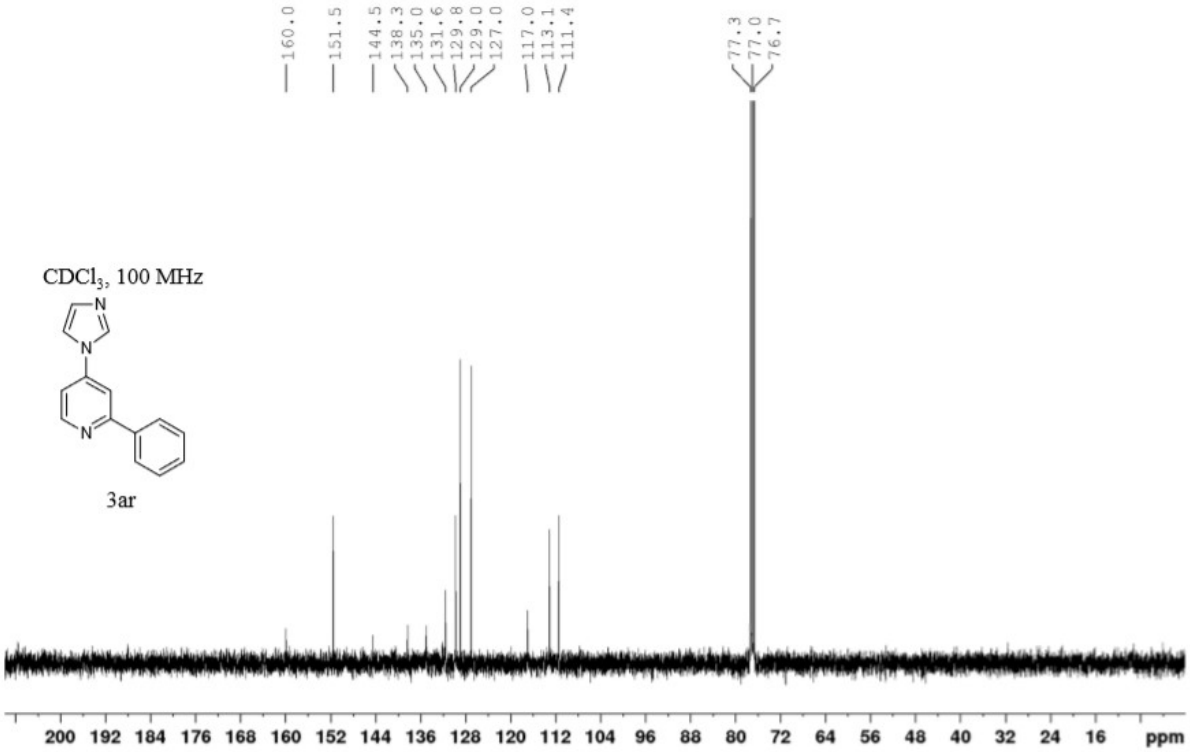
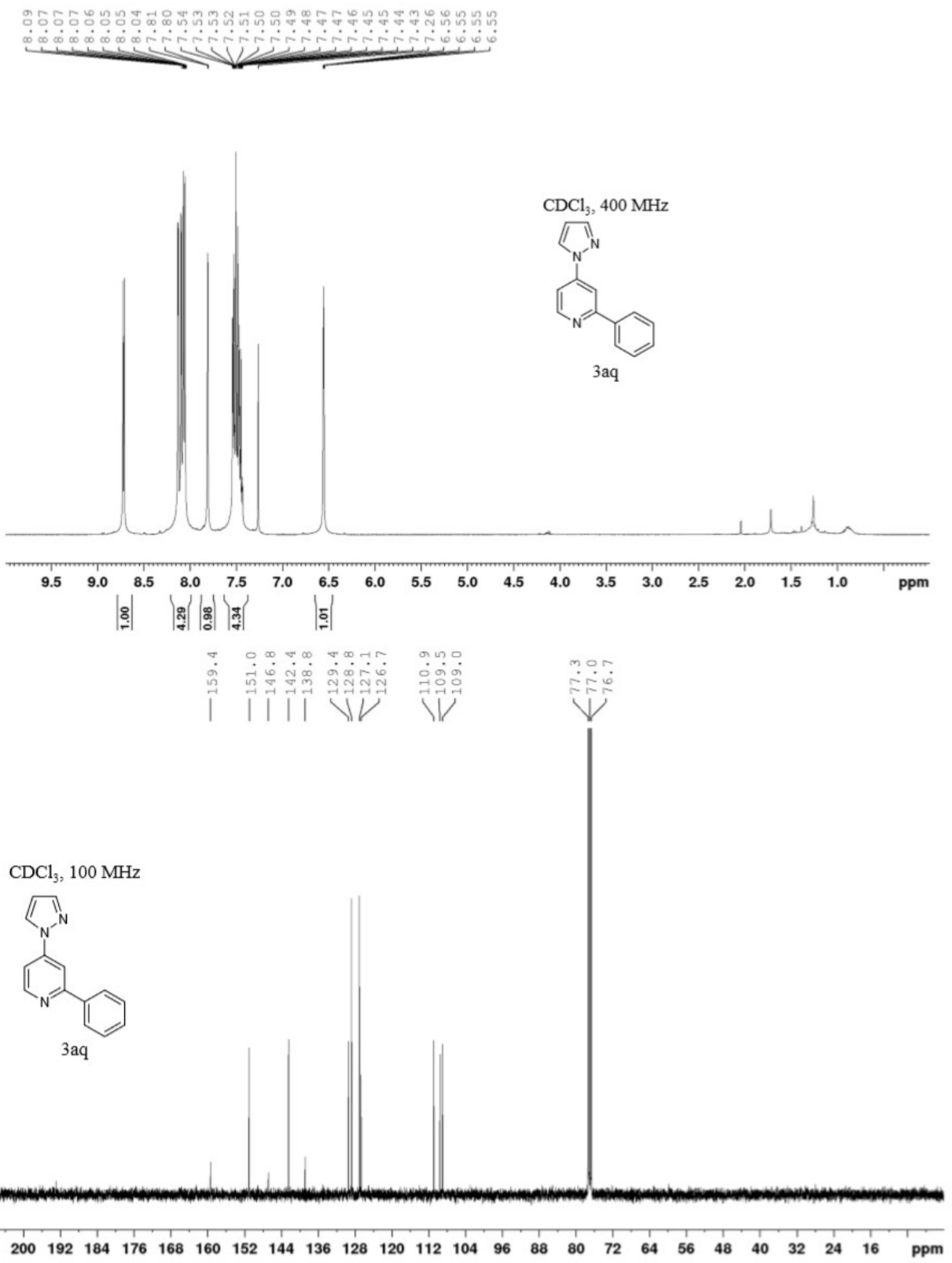
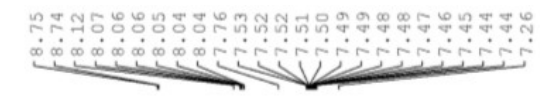
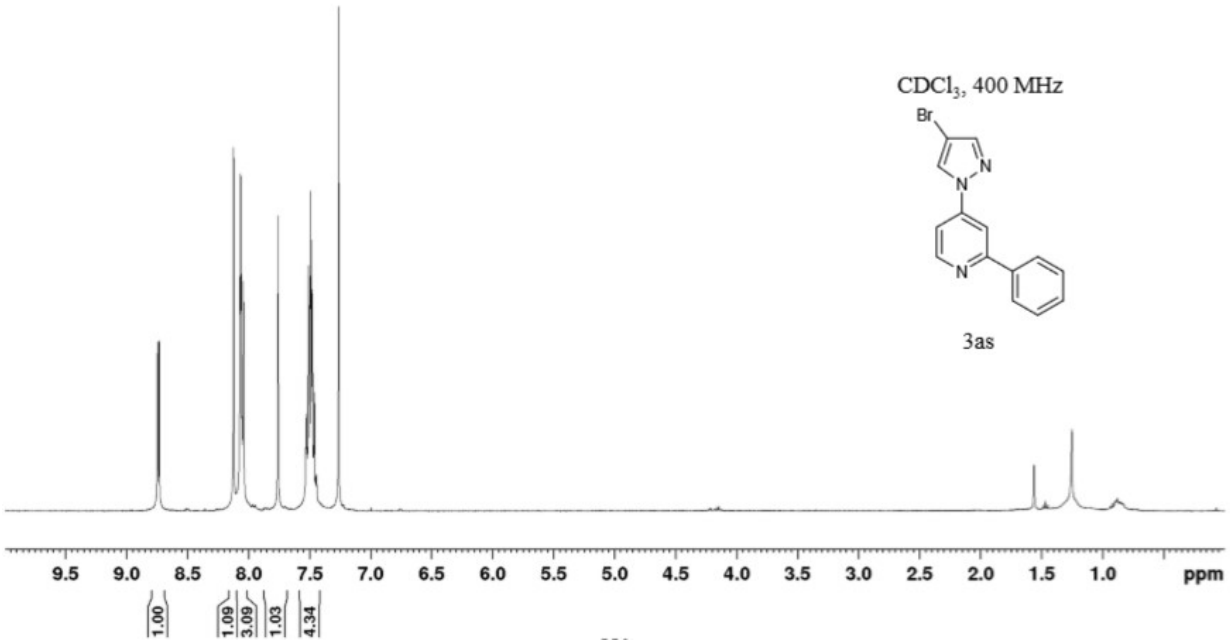
7.45
7.29
7.29
7.28
7.27
7.26

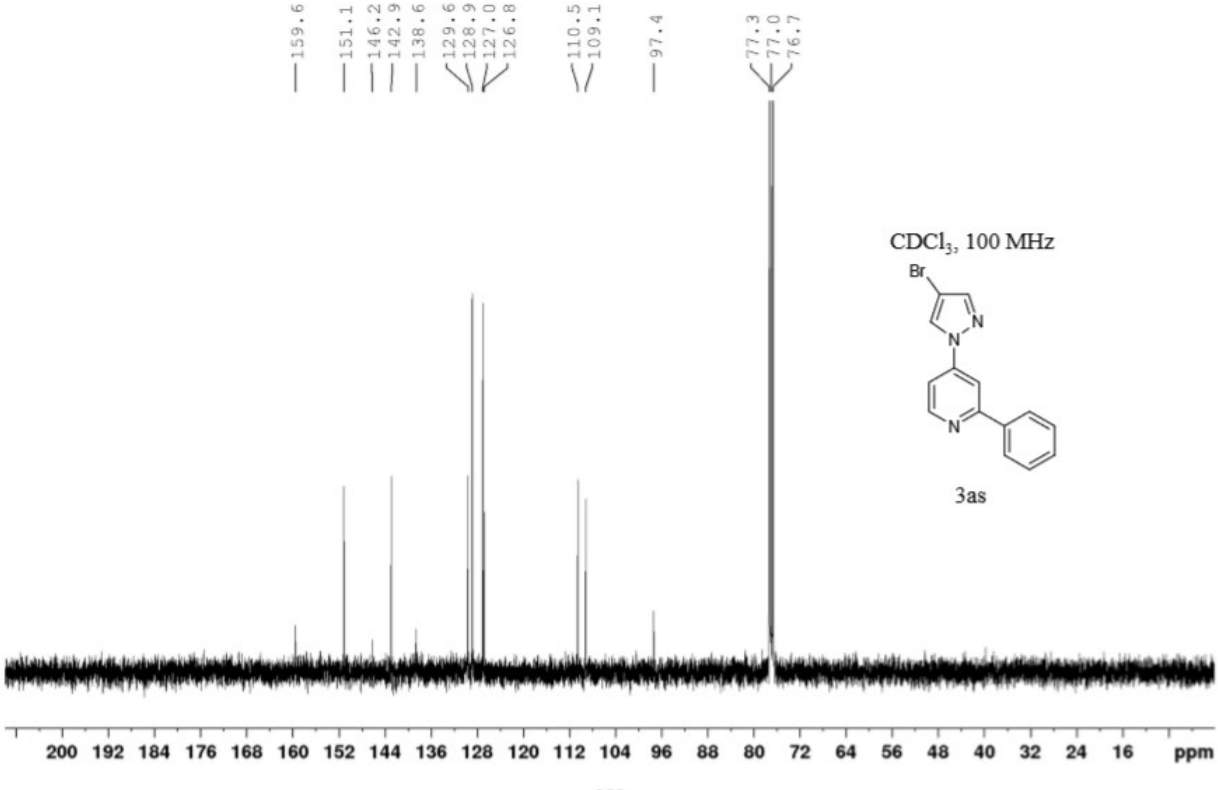

CDCl3, 400 MHz
3ar
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.12
2.09
1.08
4.40
2.15

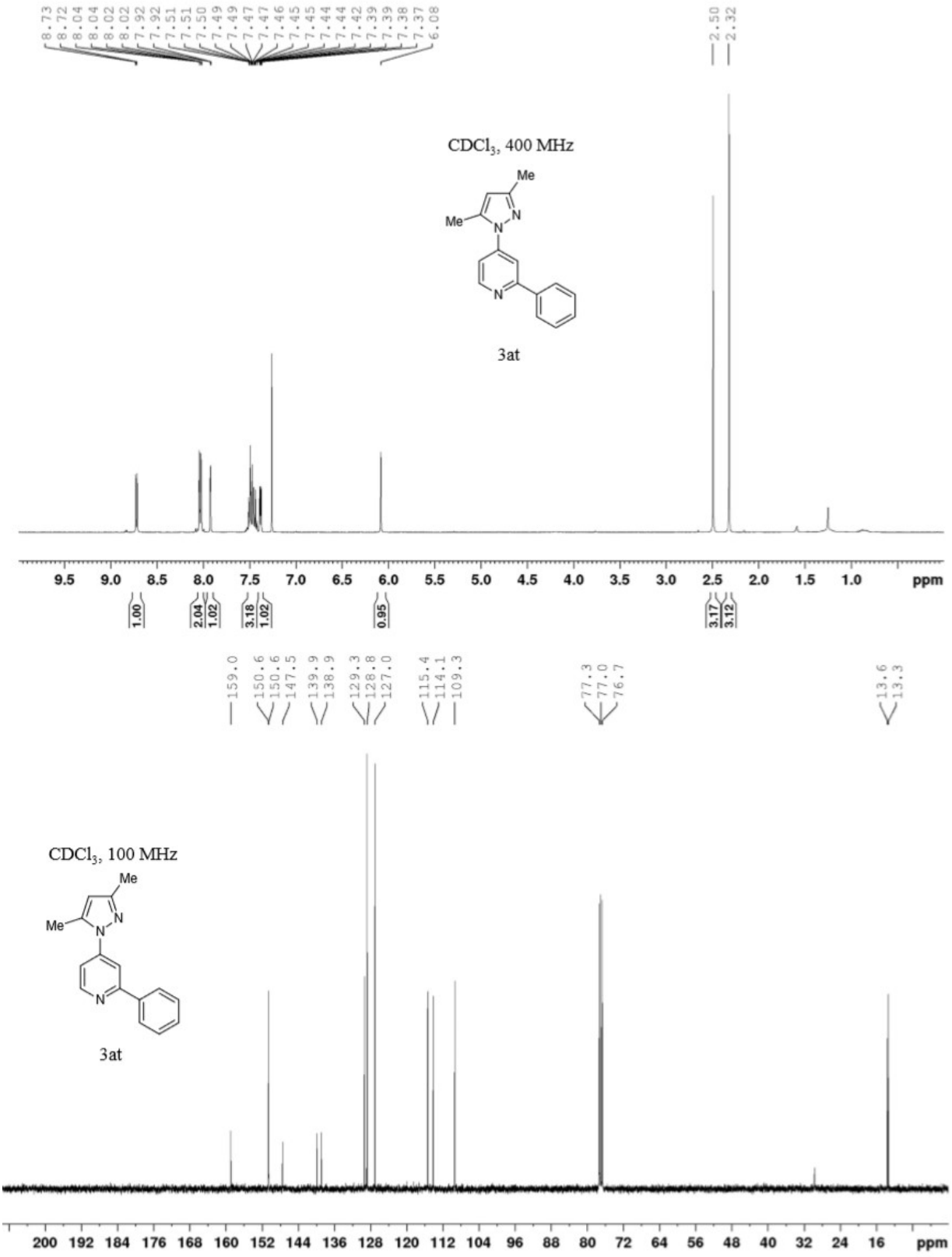

160.0
151.5
144.5
138.3
135.0
131.6
129.8
129.0
127.0
117.0
113.1
111.4
77.3
77.0
76.7
CDCl3, 100 MHz
3ar
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

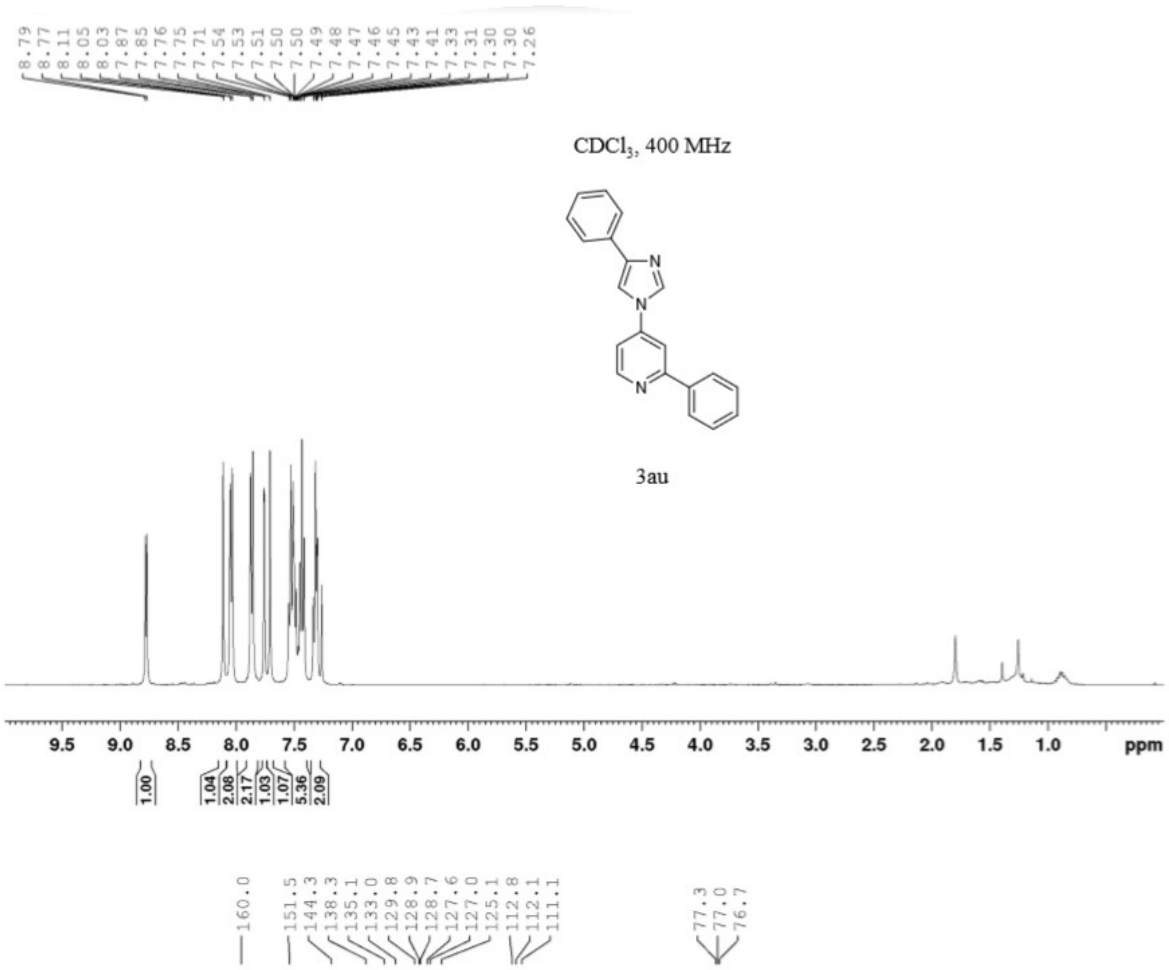

8.09
8.07
8.07
8.07
8.06
8.05
8.05
8.04
7.81
7.80
7.54
7.53
7.53
7.52
7.51
7.50
7.50
7.49
7.48
7.47
7.47
7.46
7.45
7.45
7.44
7.43
7.26
6.56
6.55
6.55
6.55
CDCl3, 400 MHz
3aq
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
4.29
0.98
4.34
1.01
159.4
151.0
146.8
142.4
138.8
129.4
128.8
127.1
126.7
110.9
109.5
109.0
77.3
77.0
76.7
CDCl3, 100 MHz
3aq
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

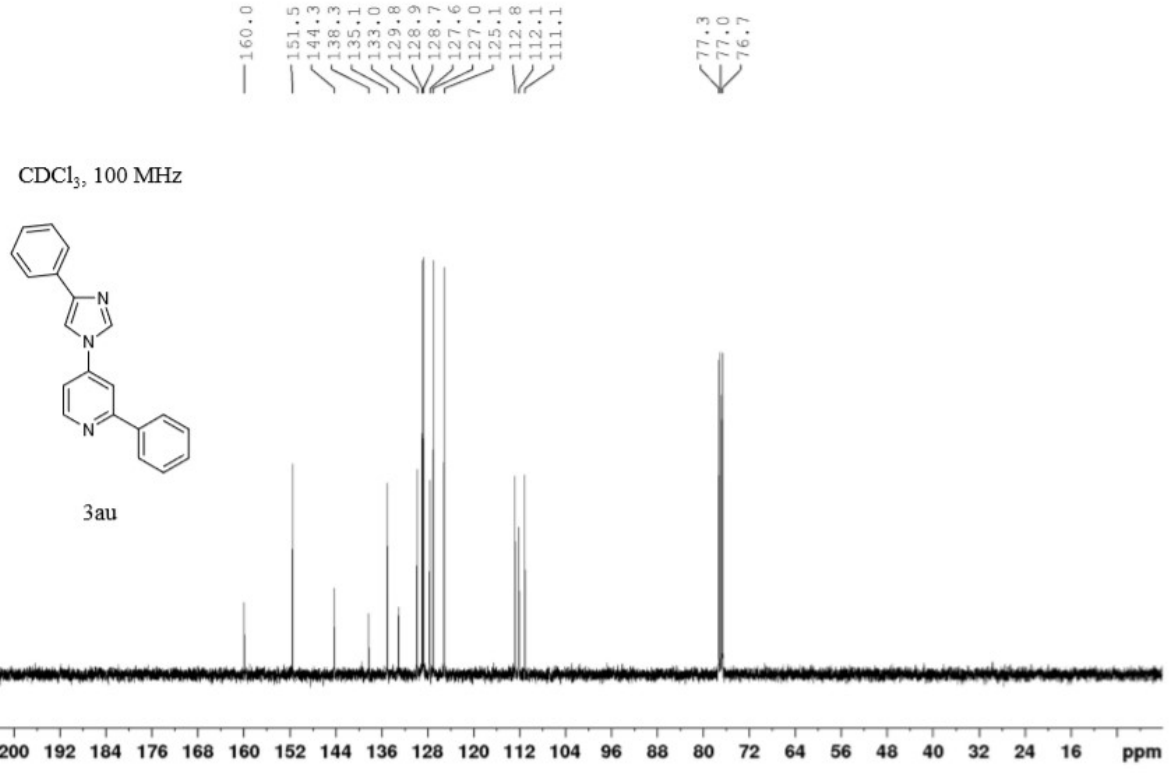

8.75
8.74
8.12
8.07
8.06
8.06
8.05
8.04
8.04
7.76
7.53
7.52
7.51
7.50
7.49
7.49
7.48
7.48
7.47
7.46
7.45
7.44
7.44
7.26

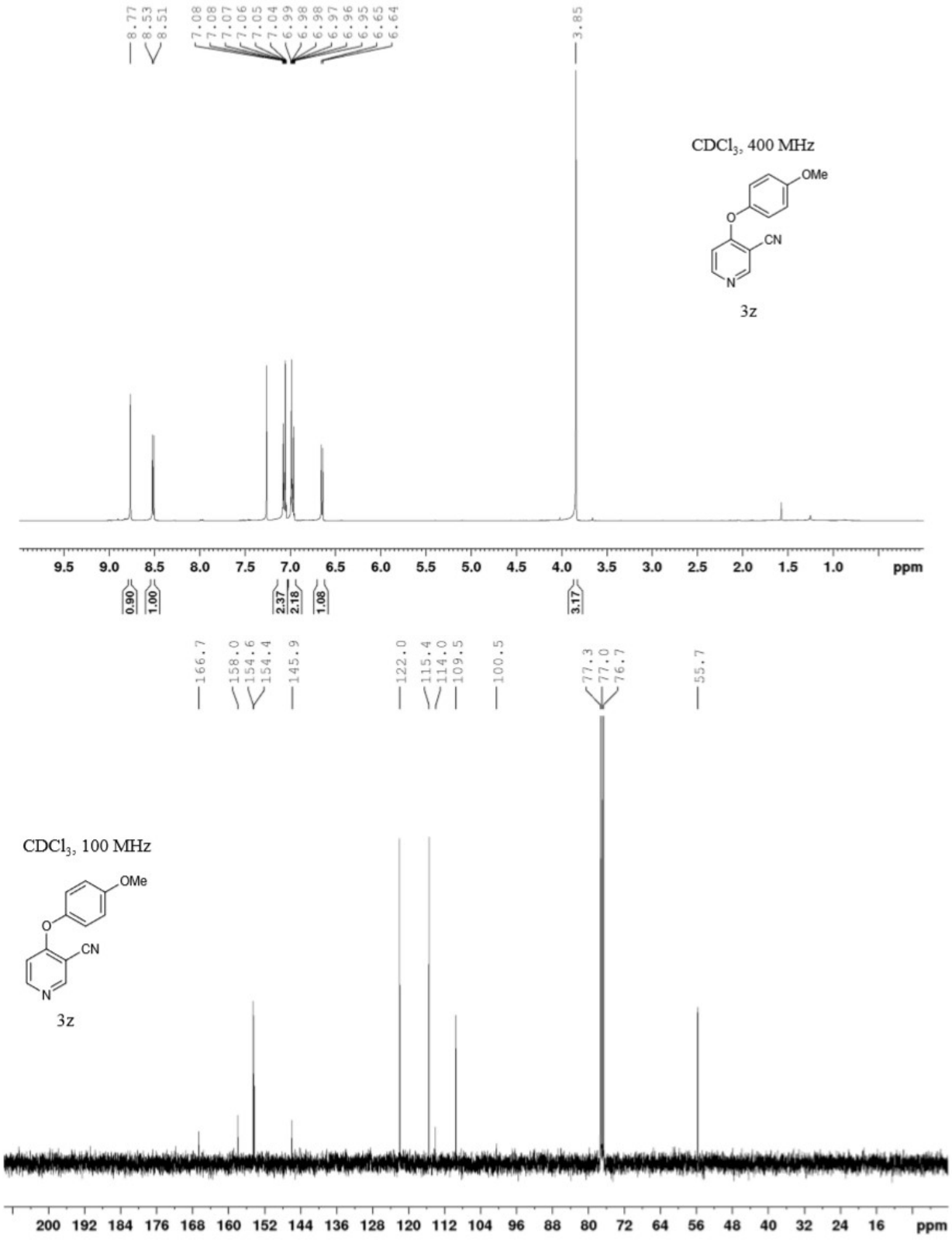

CDCl3, 400 MHz
Br
N
N
N
3as
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.09
3.09
1.03
4.34

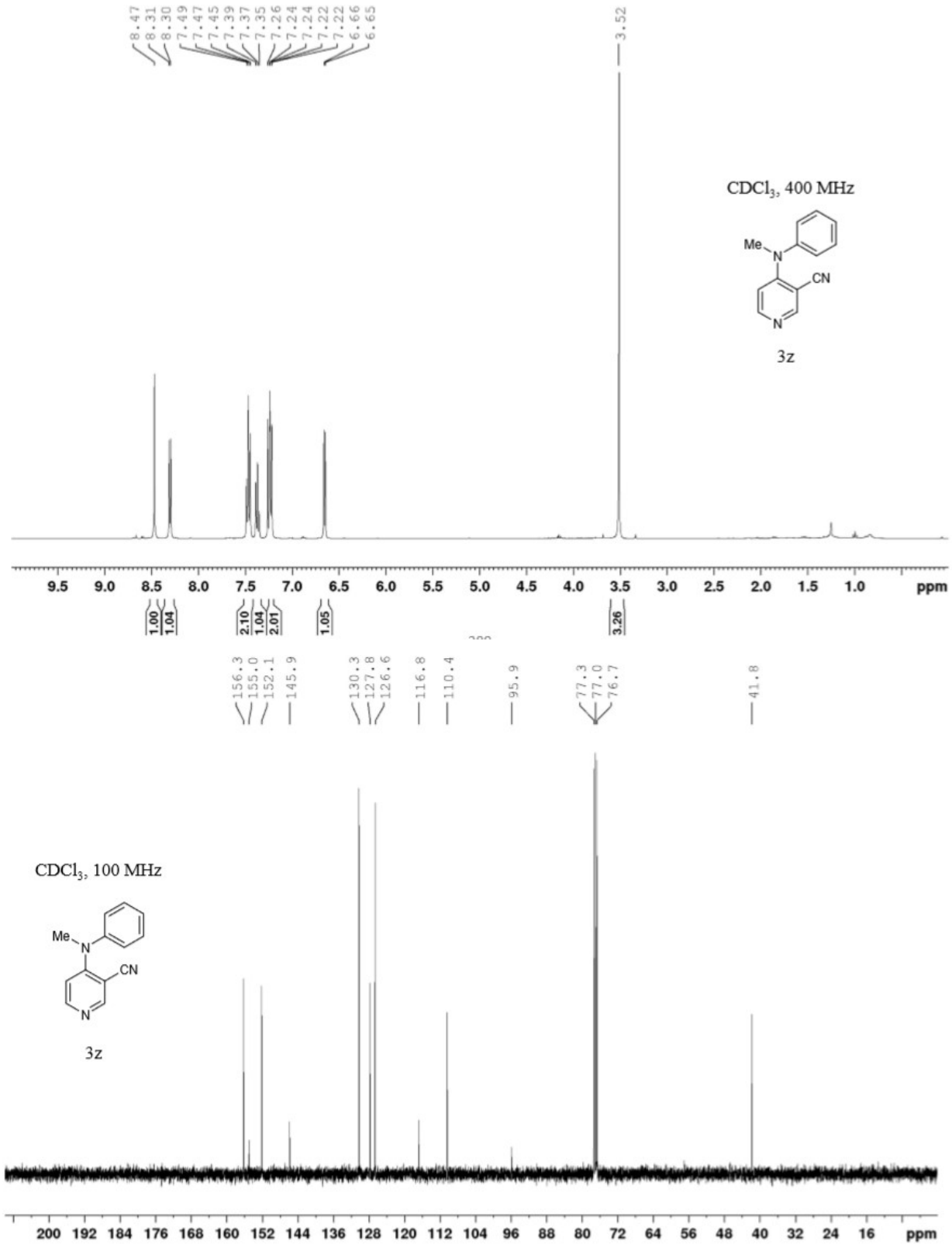

159.6
151.1
146.2
142.9
138.6
129.6
128.9
127.0
126.8
110.5
109.1
97.4
77.3
77.0
76.7
CDCl3, 100 MHz
Br
N
N
N
3as
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

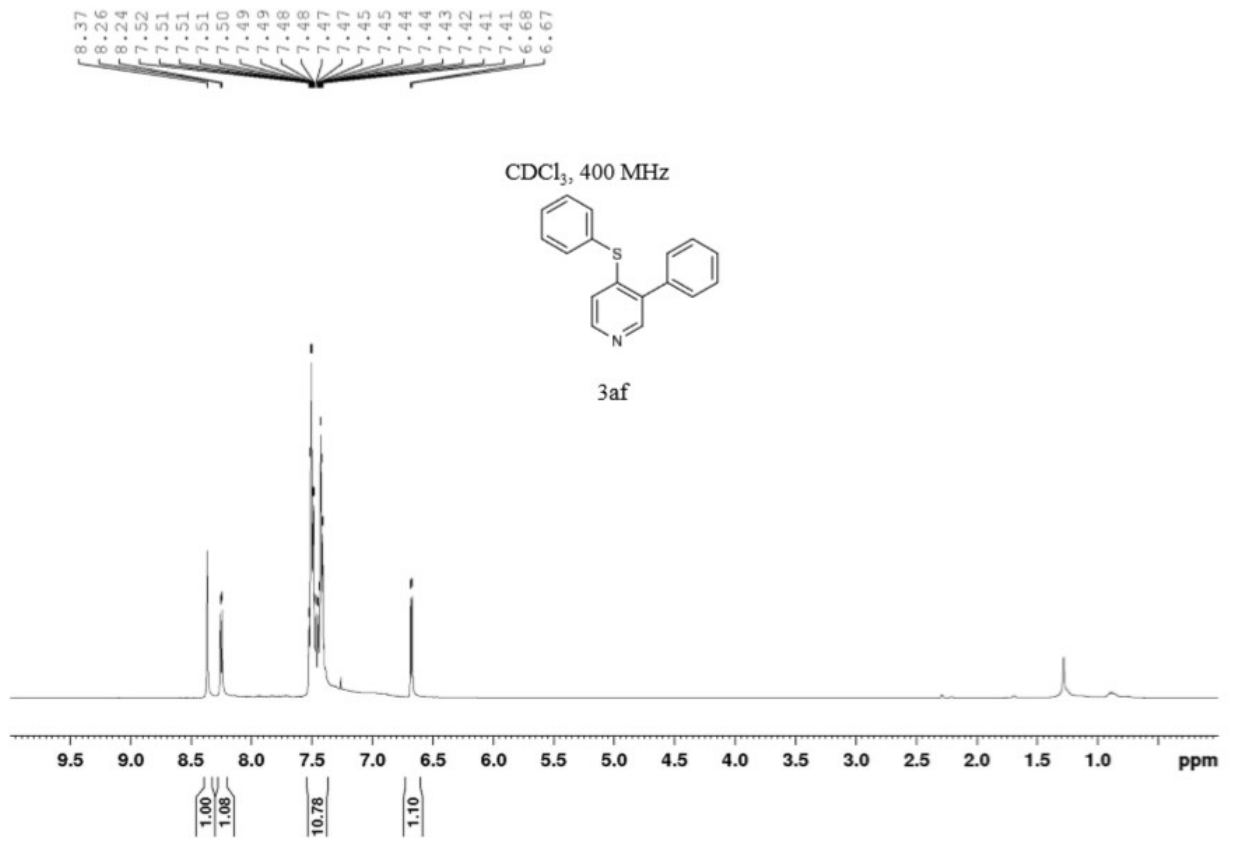

8.73
8.72
8.04
8.04
8.02
8.02
7.92
7.92
7.51
7.51
7.50
7.49
7.49
7.47
7.47
7.46
7.45
7.45
7.44
7.44
7.42
7.39
7.39
7.38
7.37
6.08
2.50
2.32
CDCl3, 400 MHz
Me
Me
N
N
N
3at
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.04
1.02
3.18
1.02
0.95
3.17
3.12
159.0
150.6
150.6
147.5
139.9
138.9
129.3
128.8
127.0
115.4
114.1
109.3
77.3
77.0
76.7
13.6
13.3
CDCl3, 100 MHz
Me
Me
N
N
N
3at
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

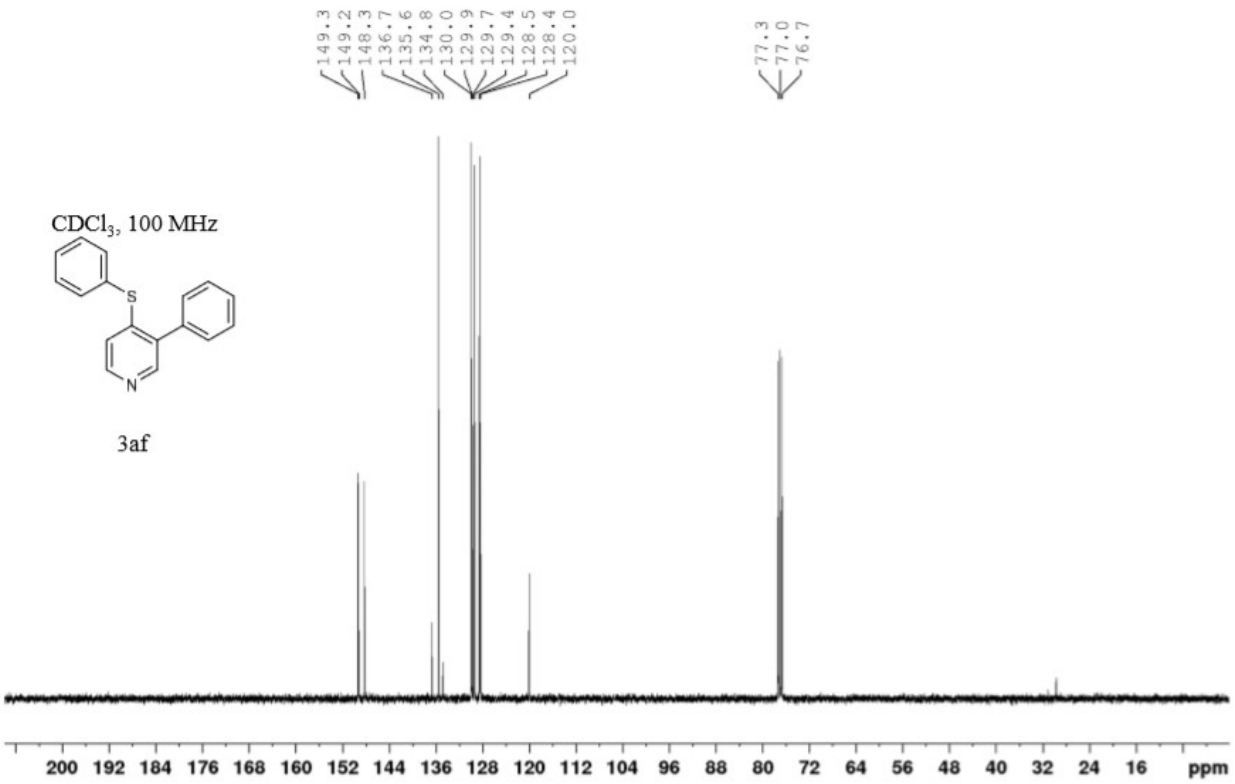

8.79
8.77
8.11
8.05
8.03
7.87
7.85
7.76
7.75
7.71
7.54
7.53
7.51
7.50
7.50
7.49
7.48
7.47
7.46
7.45
7.43
7.41
7.33
7.31
7.30
7.30
7.26
CDCl3, 400 MHz
N
N
N
3au
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.04
2.06
2.17
1.03
1.07
5.36
2.09

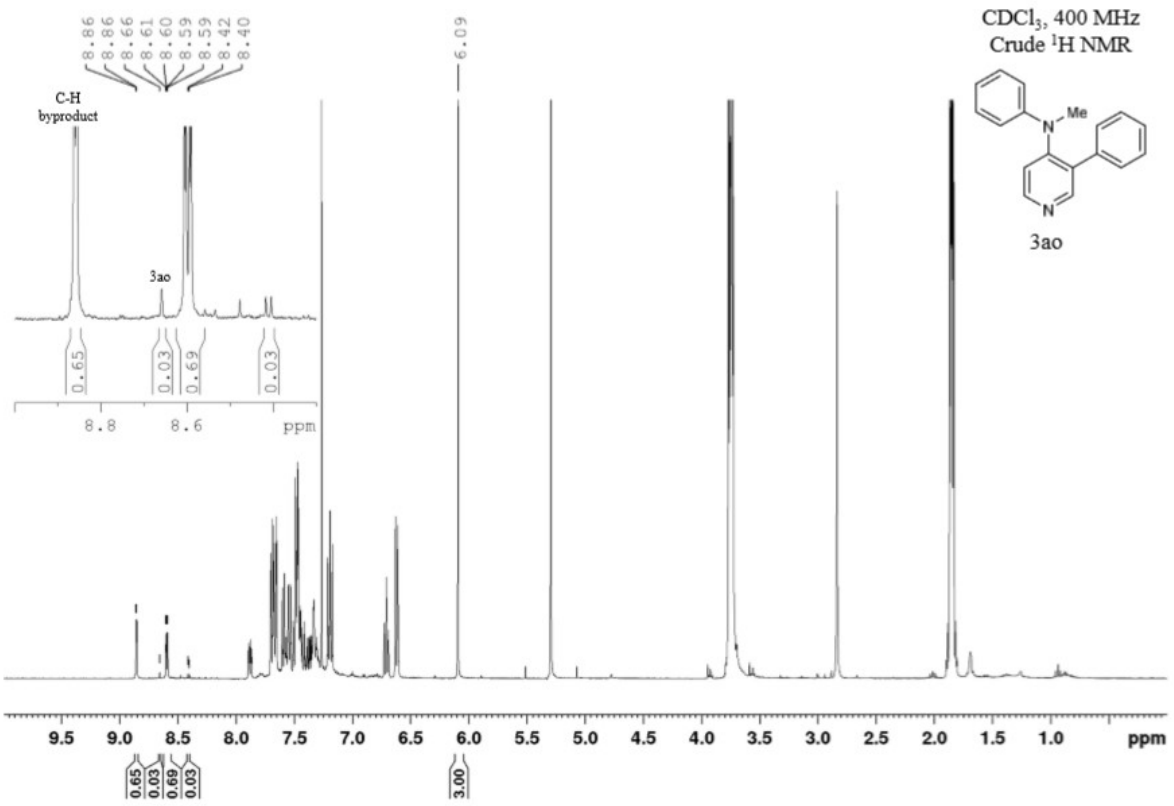

160.0
151.5
144.3
138.3
135.1
133.0
129.8
128.9
128.7
127.6
127.0
125.1
112.8
112.1
111.1
77.3
77.0
76.7
CDCl3, 100 MHz
N
N
N
3au
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

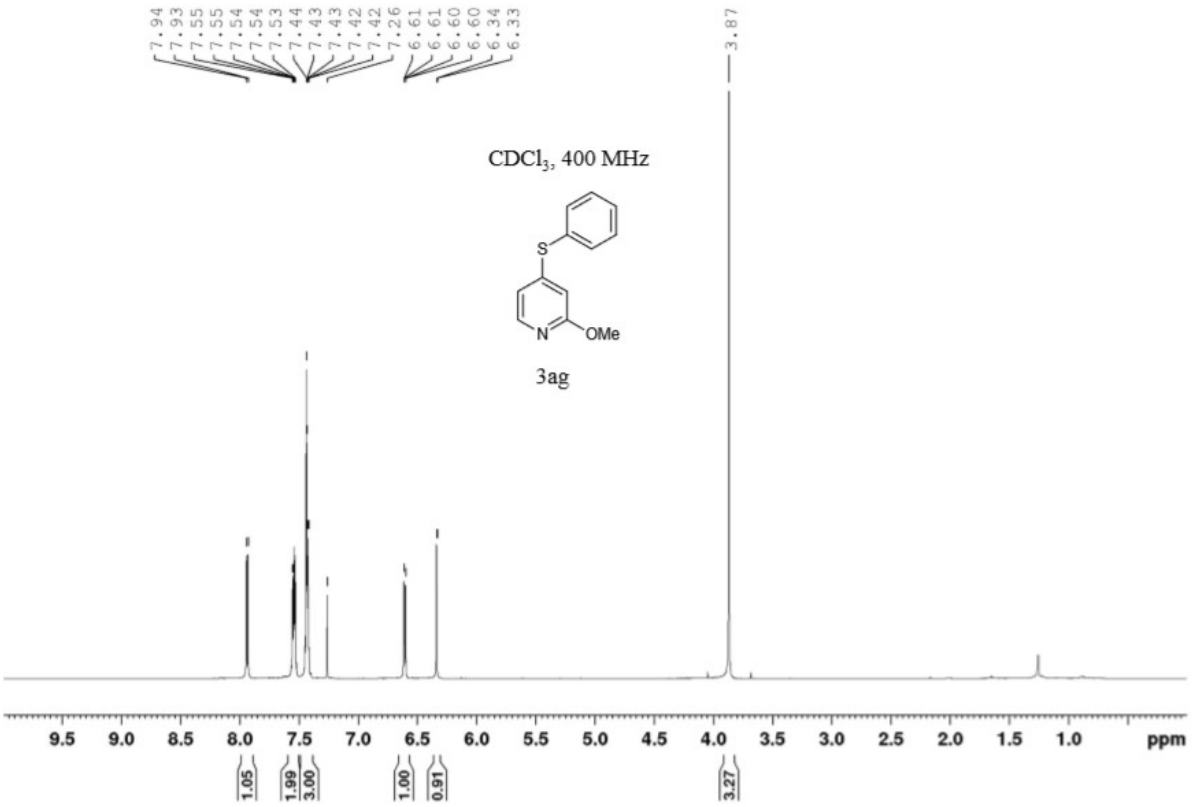

8.77
8.53
8.51
7.08
7.08
7.07
7.06
7.05
7.04
6.99
6.98
6.98
6.97
6.96
6.95
6.65
6.64
3.85
CDCl3, 400 MHz
OMe
O
CN
N
3z
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.90
1.00
2.37
2.18
1.08
3.17
166.7
158.0
154.6
154.4
145.9
122.0
115.4
114.0
109.5
100.5
77.3
77.0
76.7
55.7
CDCl3, 100 MHz
OMe
O
CN
N
3z
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

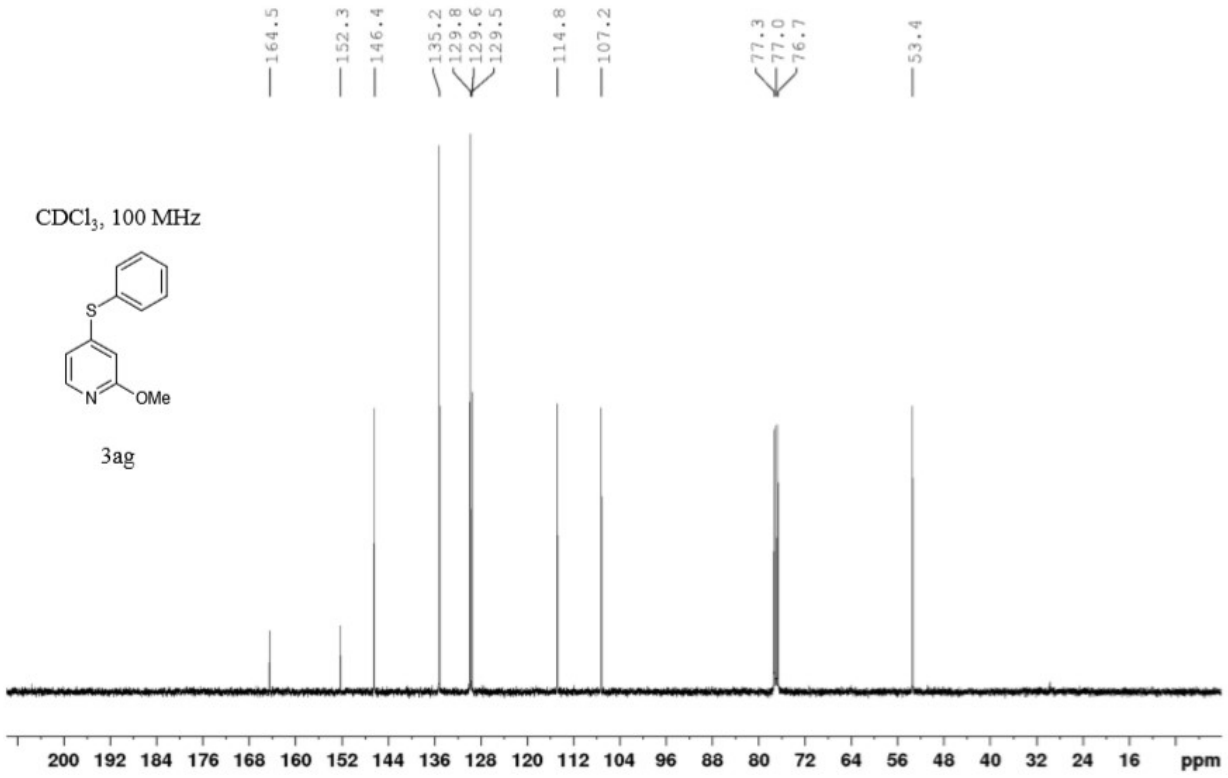

8.47
8.31
8.30
7.49
7.47
7.45
7.39
7.37
7.35
7.26
7.24
7.24
7.22
7.22
6.66
6.65
3.52
CDCl3, 400 MHz
Me
N
CN
N
3z
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.04
2.10
1.04
2.01
1.05
3.26
156.3
155.0
152.1
145.9
130.3
127.8
126.6
116.8
110.4
95.9
77.3
77.0
76.7
41.8
CDCl3, 100 MHz
Me
N
CN
N
3z
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.37
8.26
8.24
7.52
7.51
7.51
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.45
7.45
7.44
7.44
7.43
7.42
7.41
6.68
6.67
CDCl3, 400 MHz
S
N
3af
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.08
10.78
1.10

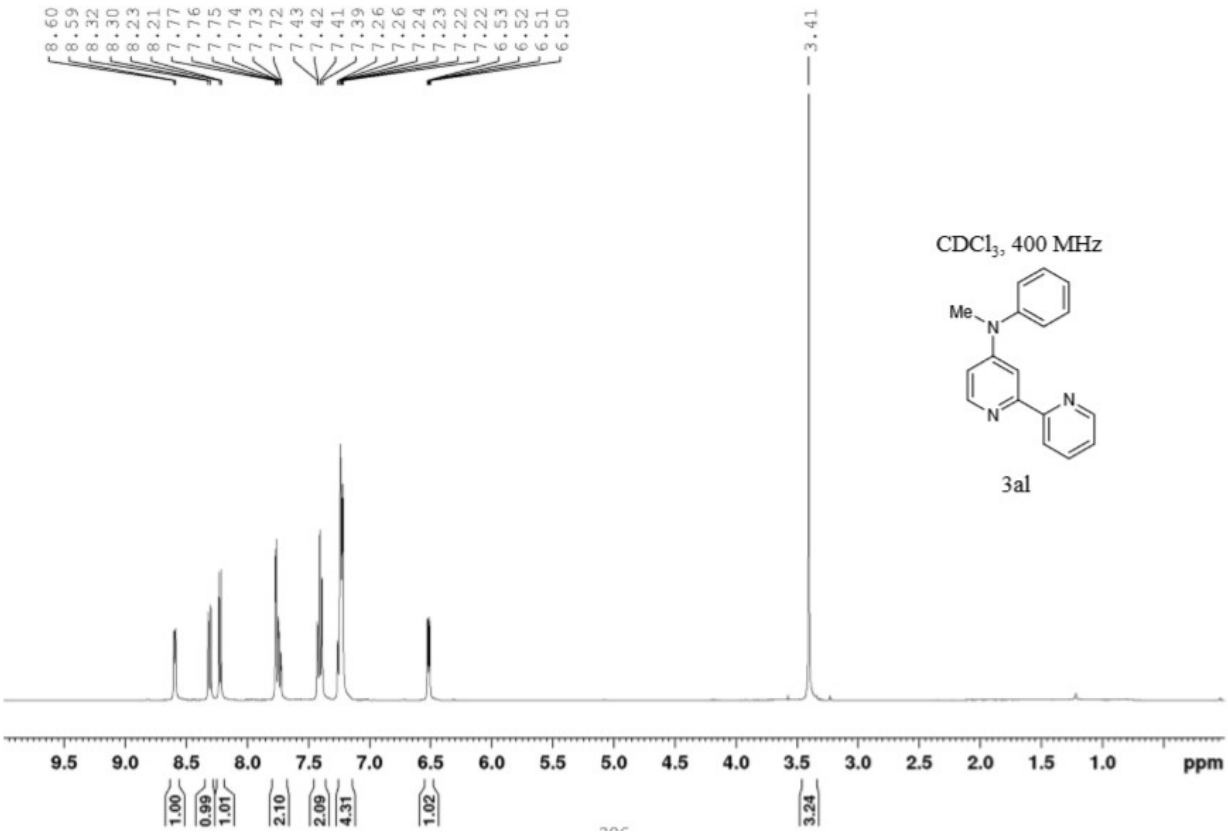

149.3
149.2
148.3
136.7
135.6
134.8
130.0
129.9
129.7
129.4
128.5
128.4
120.0
77.3
77.0
76.7
CDCl3, 100 MHz
S
N
3af
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


CDCl3, 400 MHz
Crude 1H NMR
C-H
byproduct
3ao
ppm

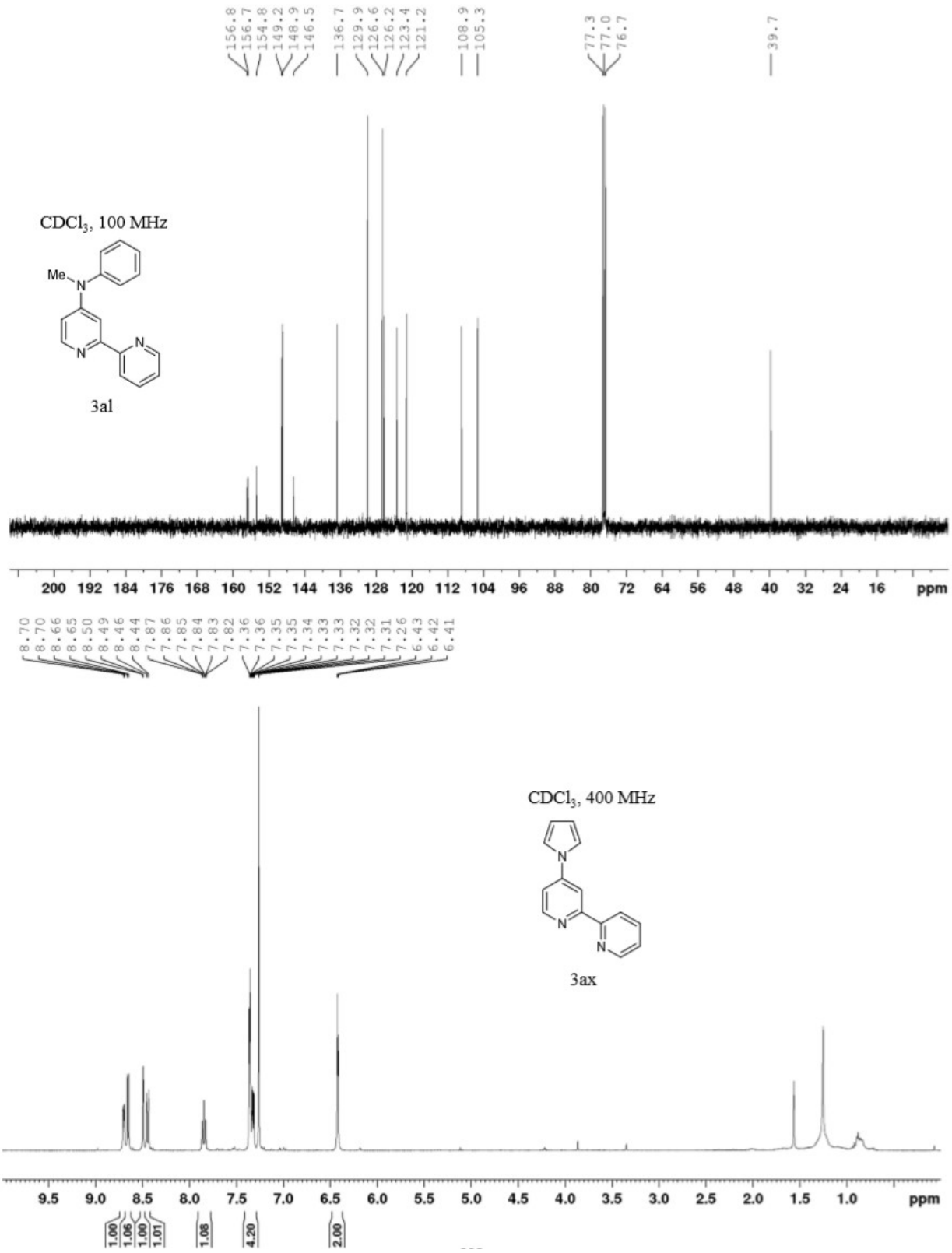

CDCl3, 400 MHz
3ag
ppm

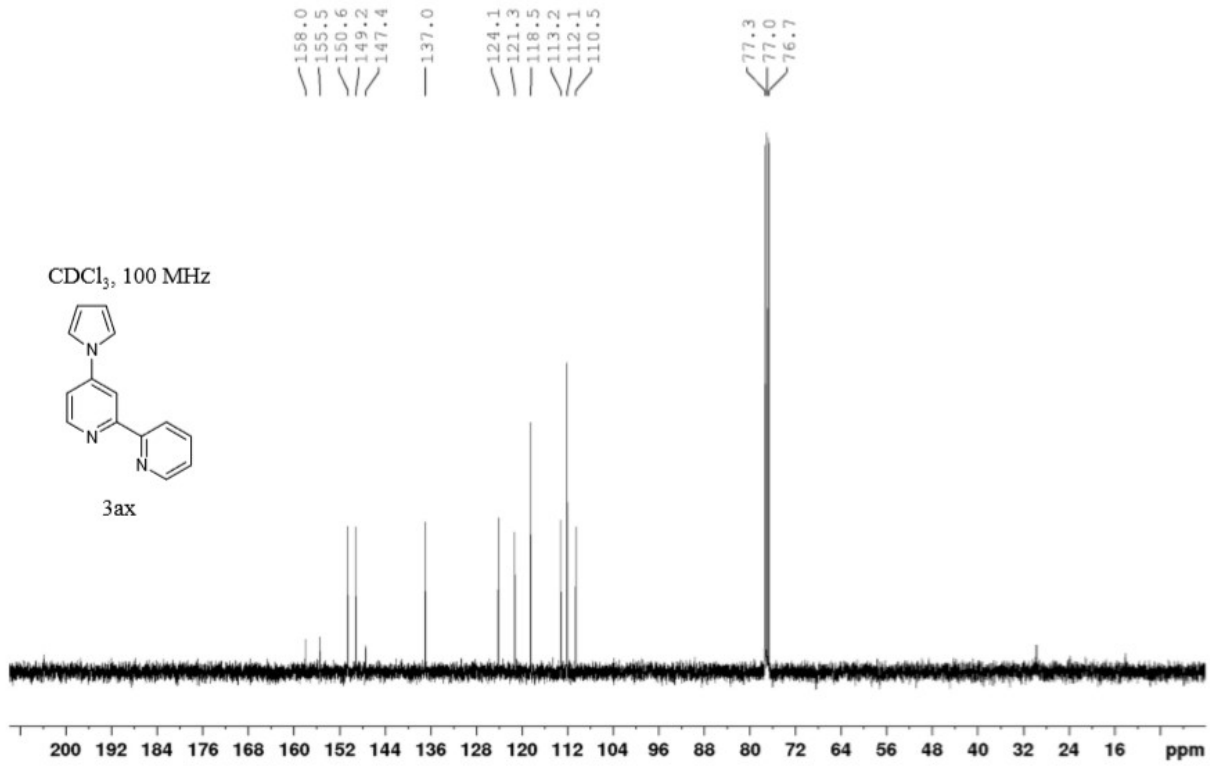

164.5
152.3
146.4
135.2
129.8
129.6
129.5
114.8
107.2
77.3
77.0
76.7
53.4
CDCl3, 100 MHz
S
N
OMe
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

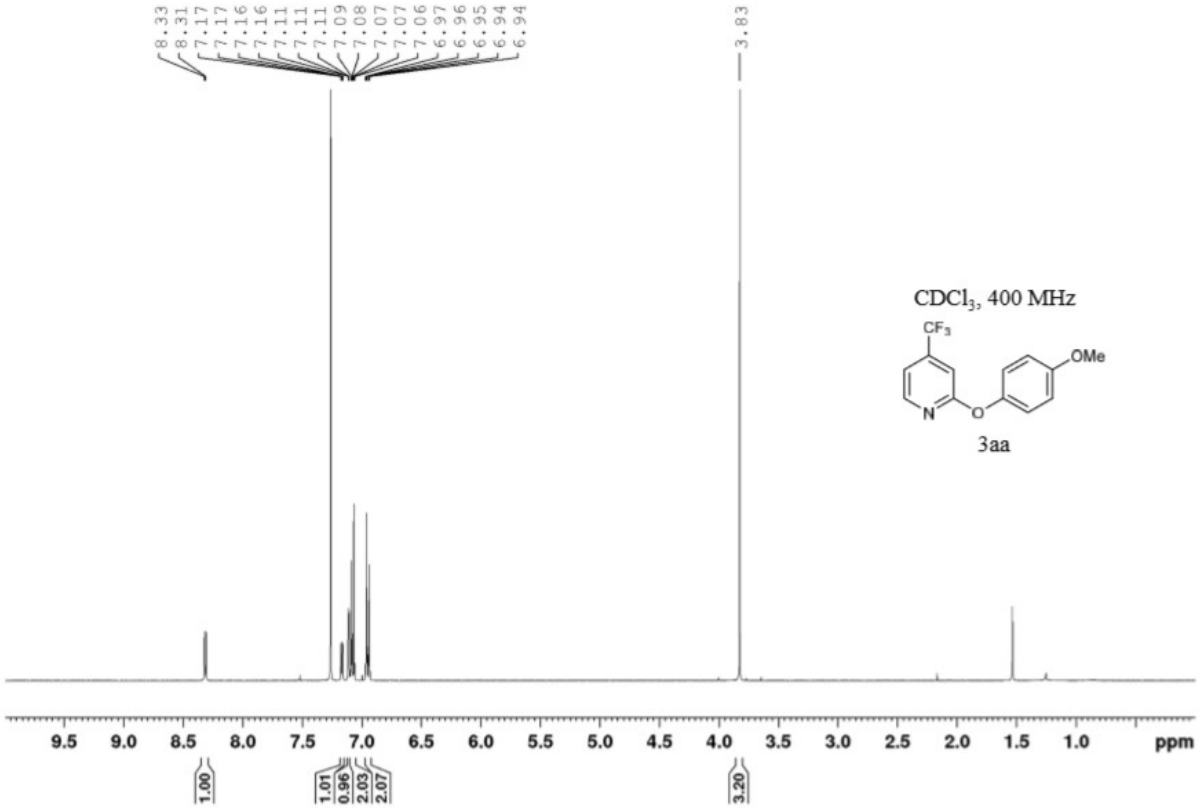
3ag

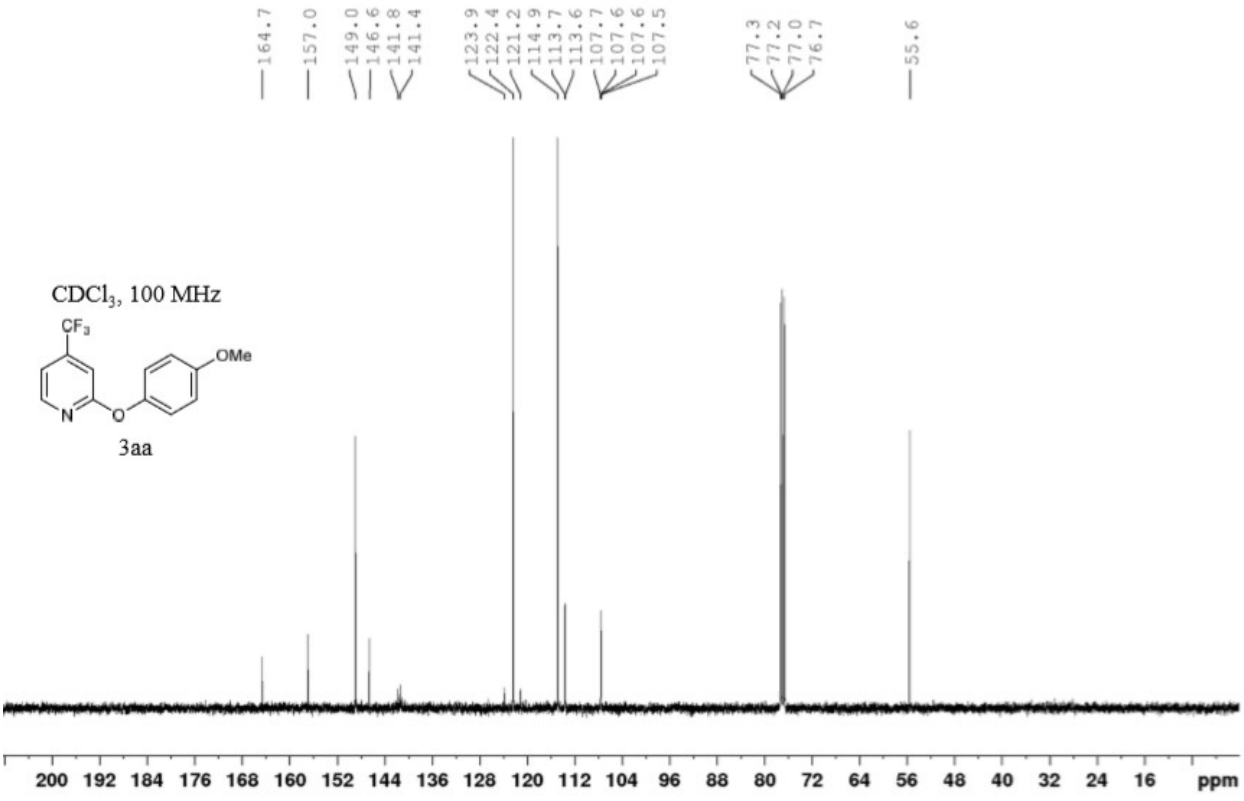

8.60
8.59
8.32
8.30
8.23
8.21
7.77
7.76
7.75
7.74
7.73
7.72
7.43
7.42
7.41
7.39
7.26
7.26
7.24
7.23
7.22
7.22
6.53
6.52
6.51
6.50
3.41
CDCl3, 400 MHz
Me
N
N
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.99
1.01
2.10
2.09
4.31
1.02
3.24

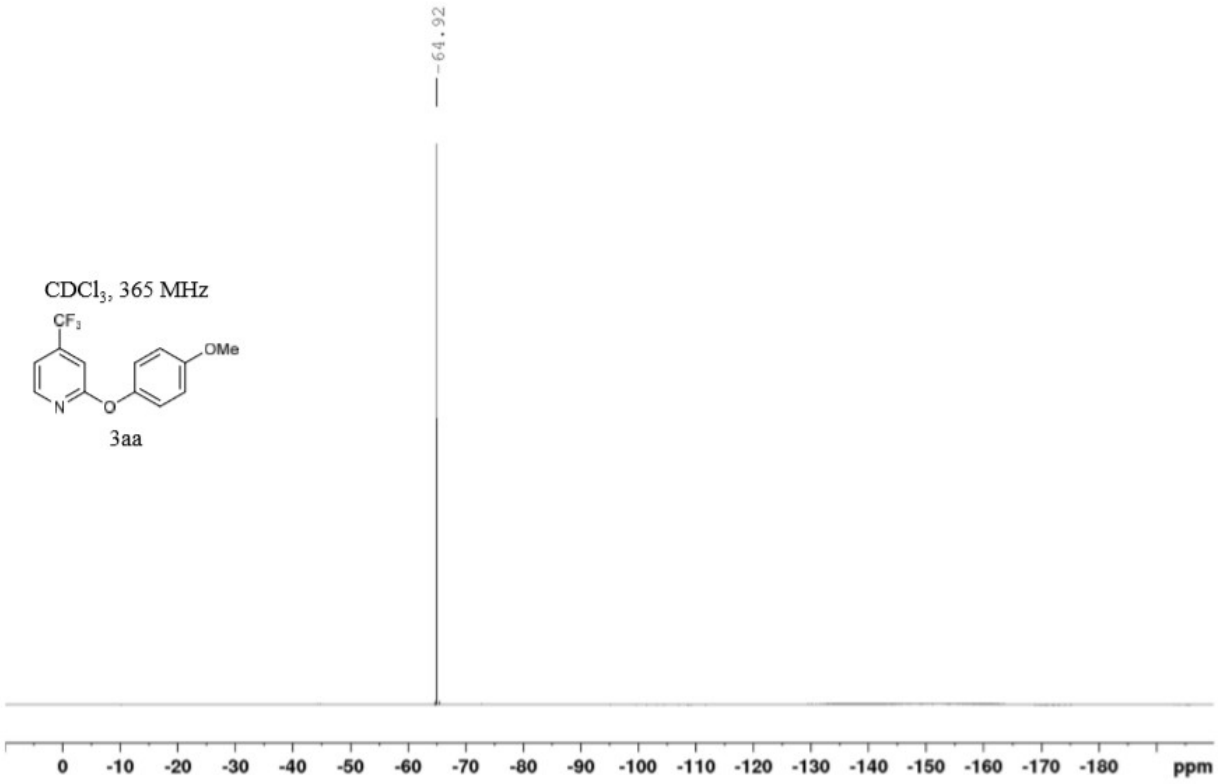
3al

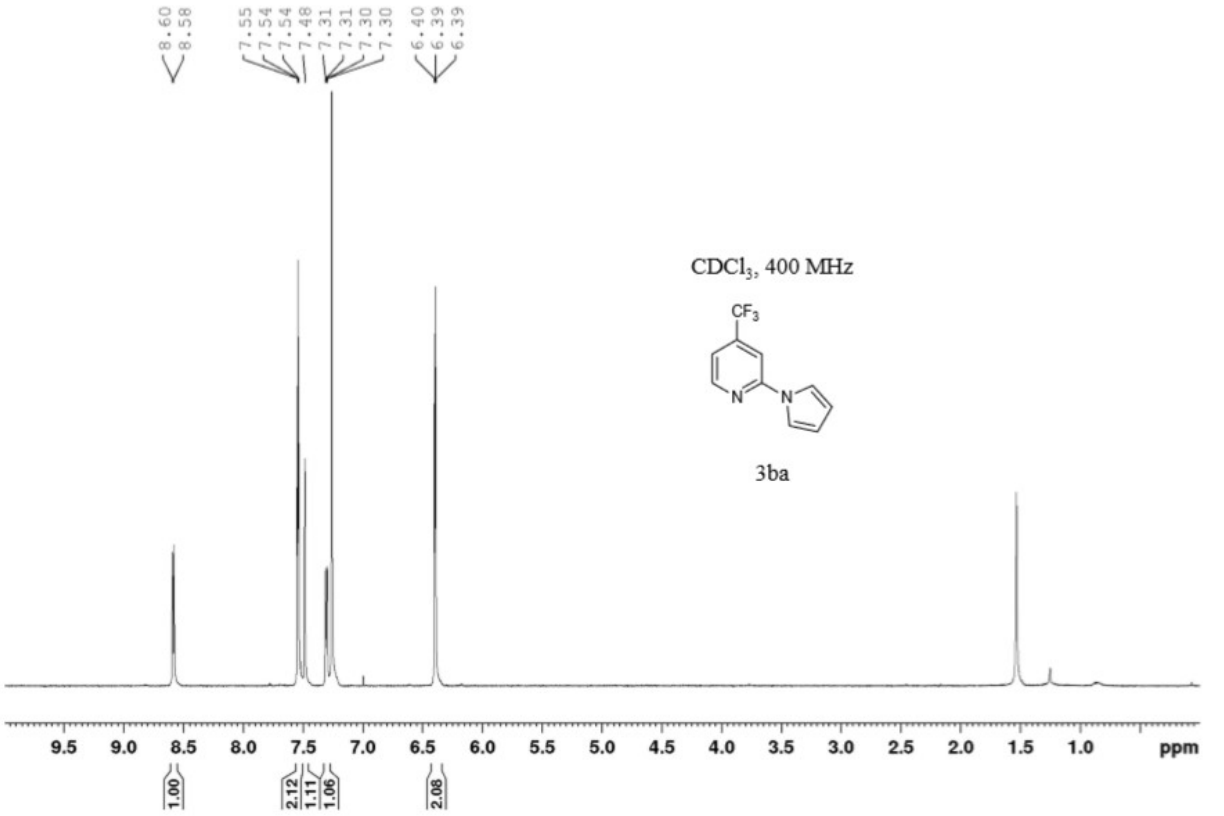

156.8
156.7
154.8
149.2
148.9
146.5
136.7
129.9
126.6
126.2
123.4
121.2
108.9
105.3
77.3
77.0
76.7
39.7
CDCl3, 100 MHz
Me
N
N
N
3al
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm
8.70
8.70
8.66
8.65
8.50
8.49
8.46
8.44
7.87
7.86
7.85
7.84
7.83
7.82
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.26
6.43
6.42
6.41
CDCl3, 400 MHz
N
N
N
3ax
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.06
1.00
1.01
1.06
4.20
2.00

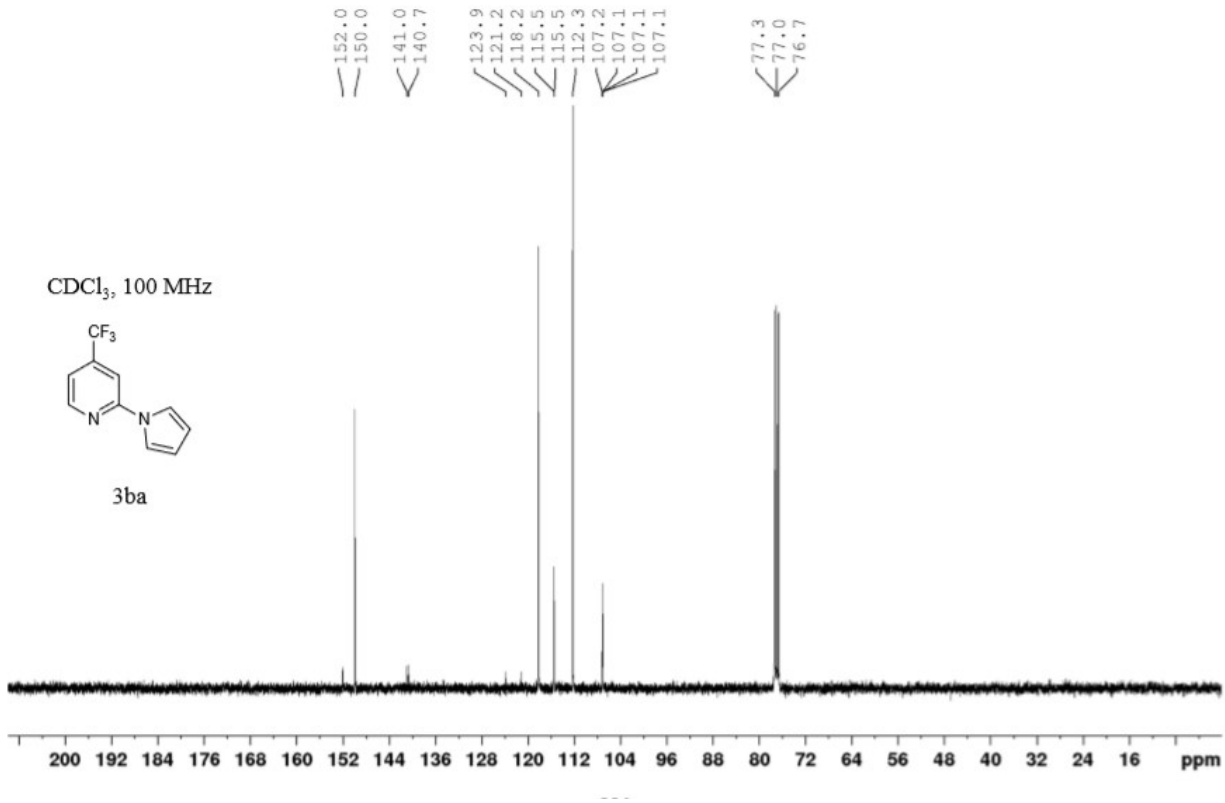

158.0
155.5
150.6
149.2
147.4
137.0
124.1
121.3
118.5
113.2
112.1
110.5
77.3
77.0
76.7
CDCl3, 100 MHz
3ax
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

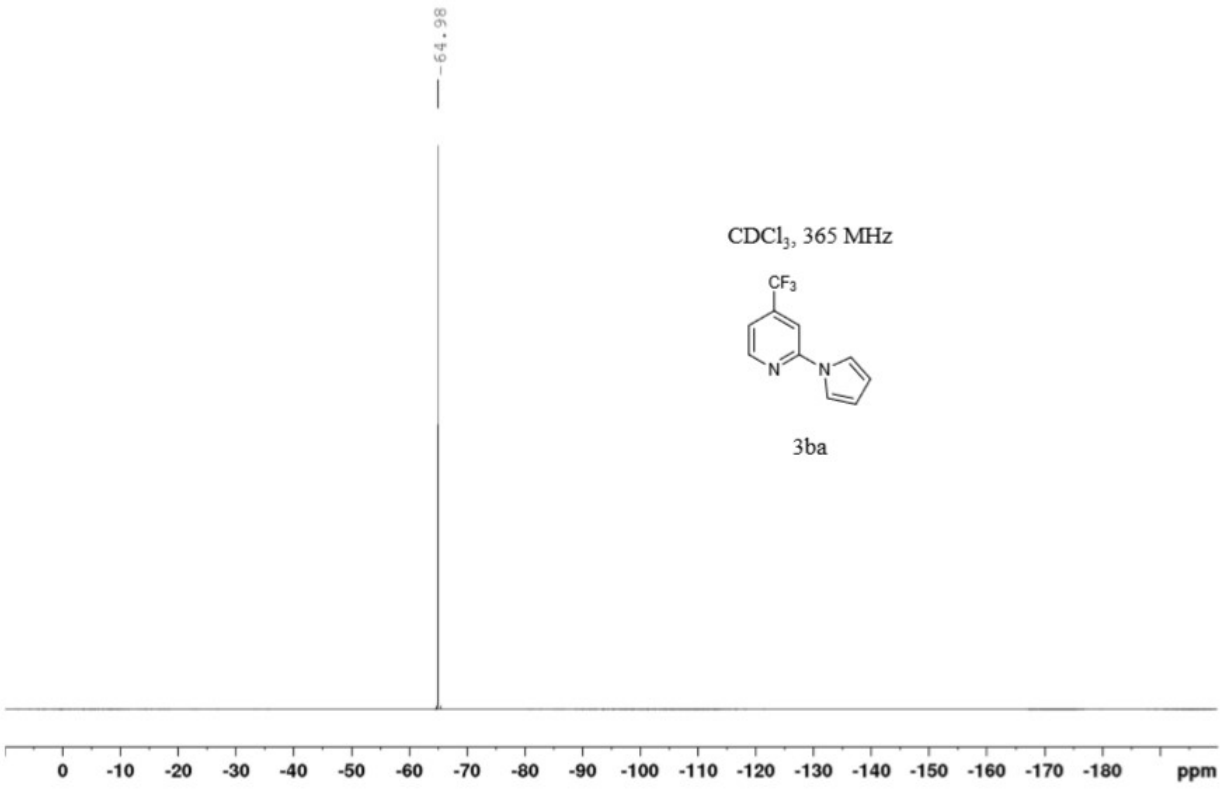

8.33
8.31
7.17
7.17
7.16
7.16
7.11
7.11
7.11
7.09
7.08
7.07
7.07
7.06
6.97
6.96
6.95
6.94
6.94
3.83
CDCl3, 400 MHz
CF3
OMe
N
O
3aa
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.01
0.96
2.03
2.07
3.20

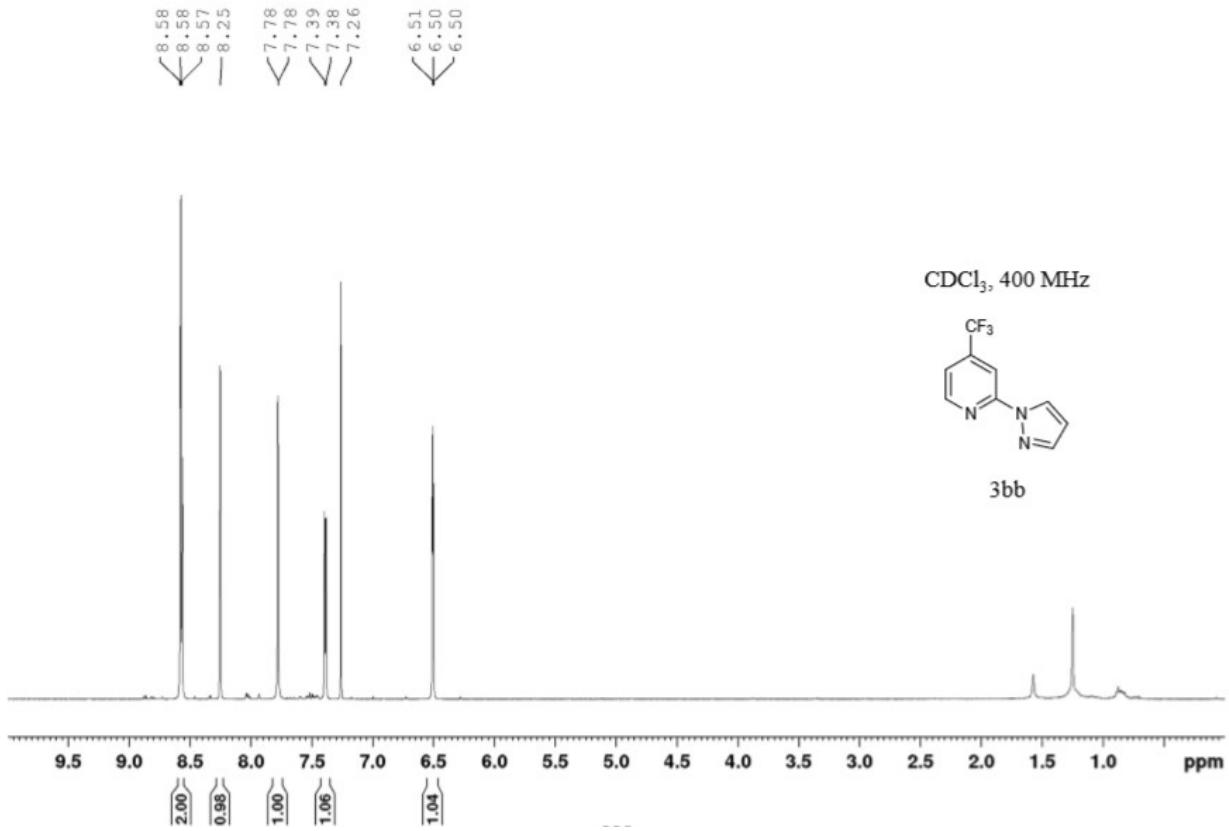

164.7
157.0
149.0
146.6
141.8
141.4
123.9
122.4
121.2
114.9
113.7
113.6
107.7
107.6
107.6
107.5
77.3
77.2
77.0
76.7
55.6
CDCl3, 100 MHz
CF3
OMe
N
O
3aa
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

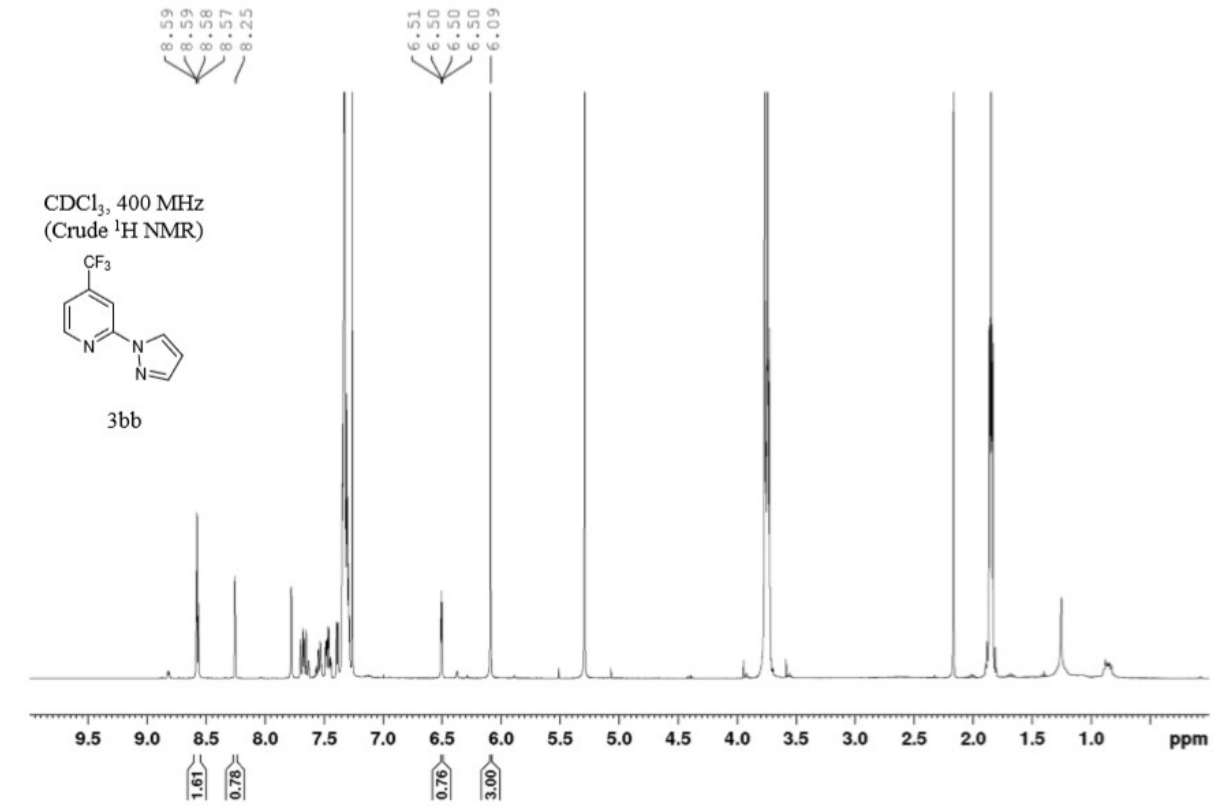

-64.92
CDCl3, 365 MHz
CF3
OMe
N
O
3aa
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

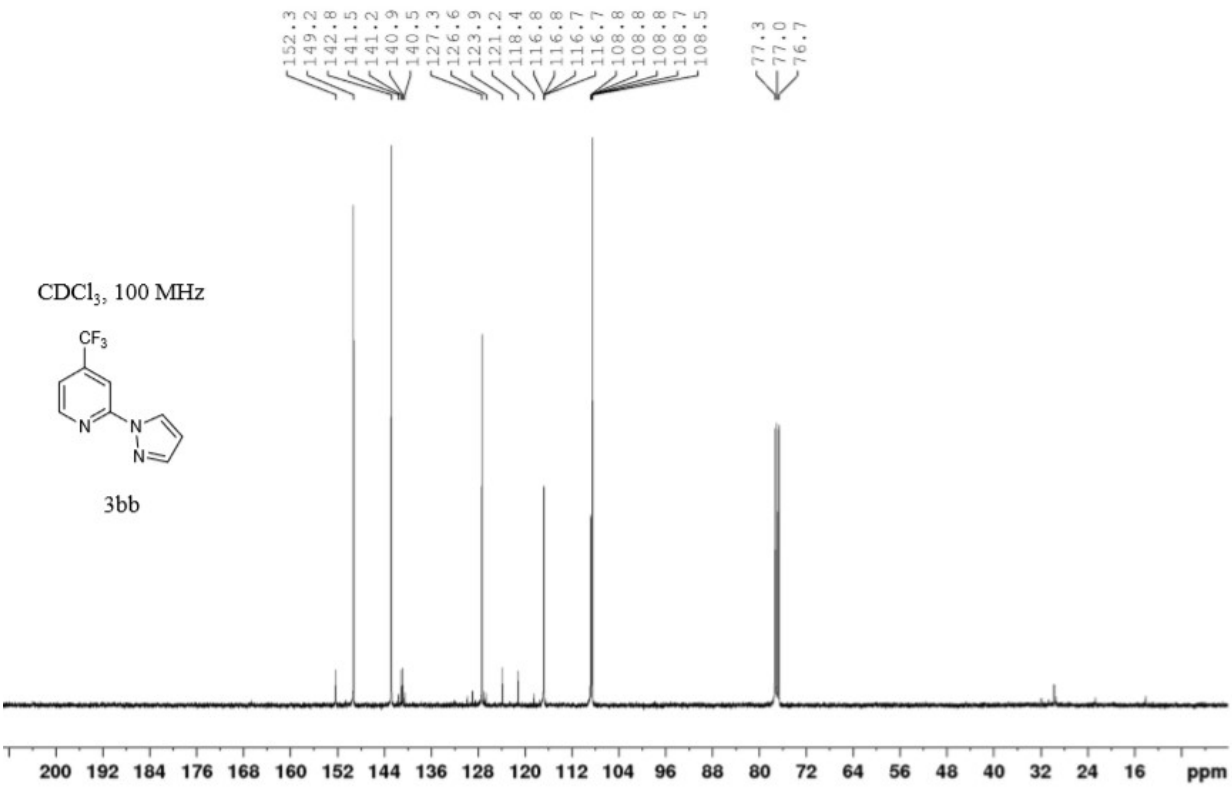

8.60
8.58
7.55
7.54
7.54
7.48
7.31
7.31
7.30
7.30
6.40
6.39
6.39
CDCl3, 400 MHz
CF3
N
N
3ba
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.12
1.11
1.06
2.08

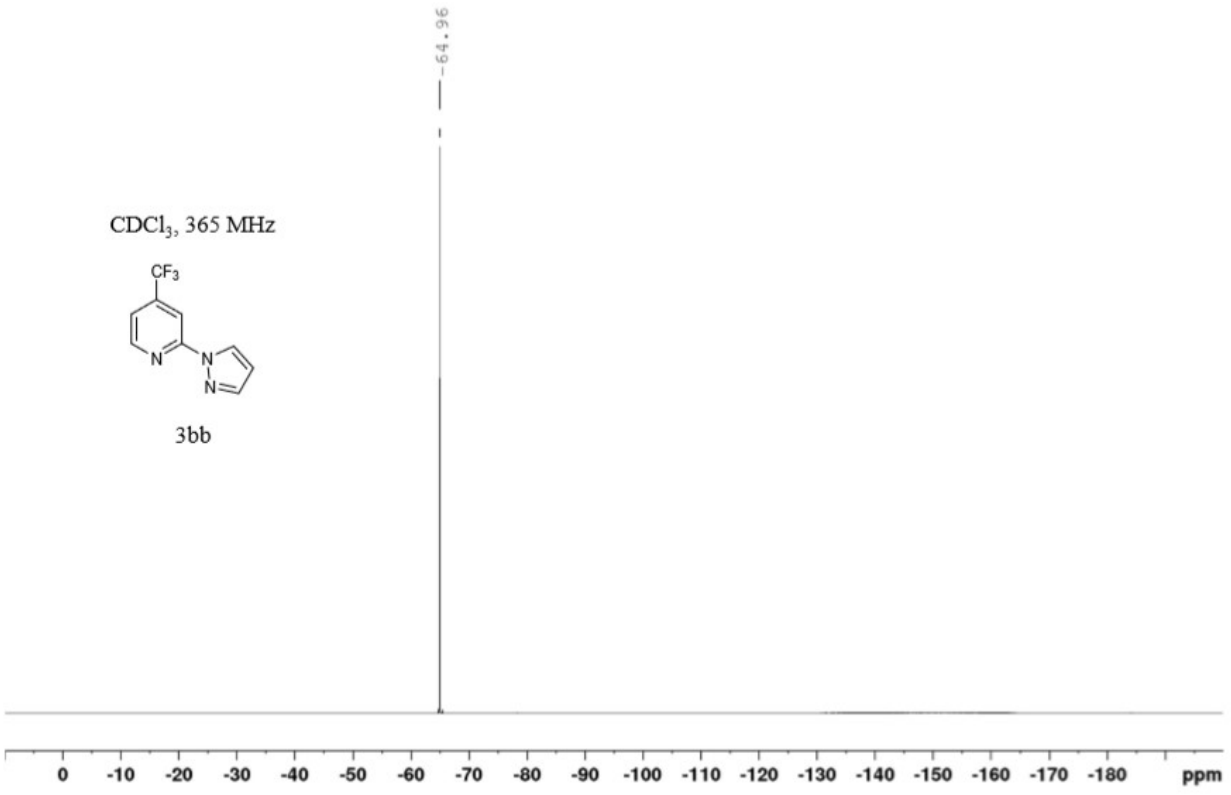

152.0
150.0
141.0
140.7
123.9
121.2
118.2
115.5
115.5
112.3
107.2
107.1
107.1
107.1
77.3
77.0
76.7
CDCl3, 100 MHz
CF3
N
N
3ba
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

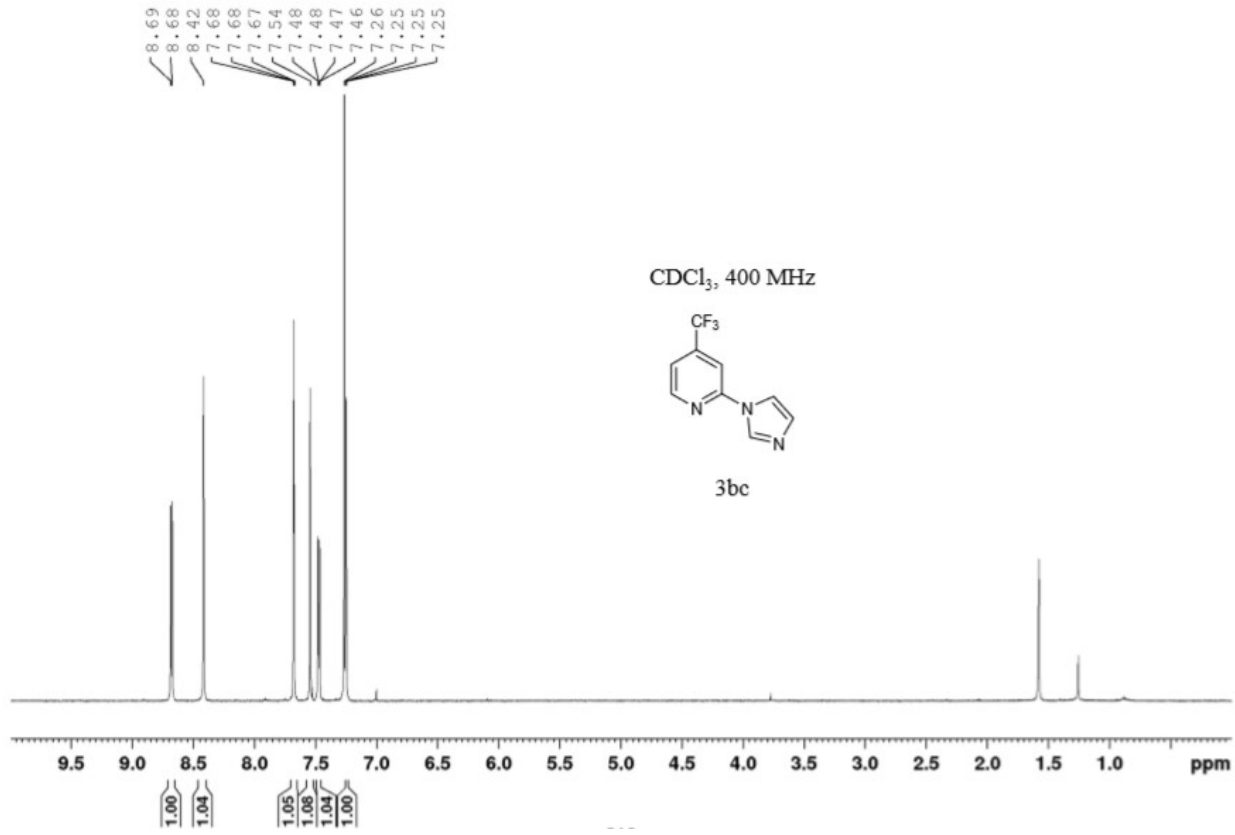

-64.98
CDCl3, 365 MHz
CF3
N
N
3ba
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

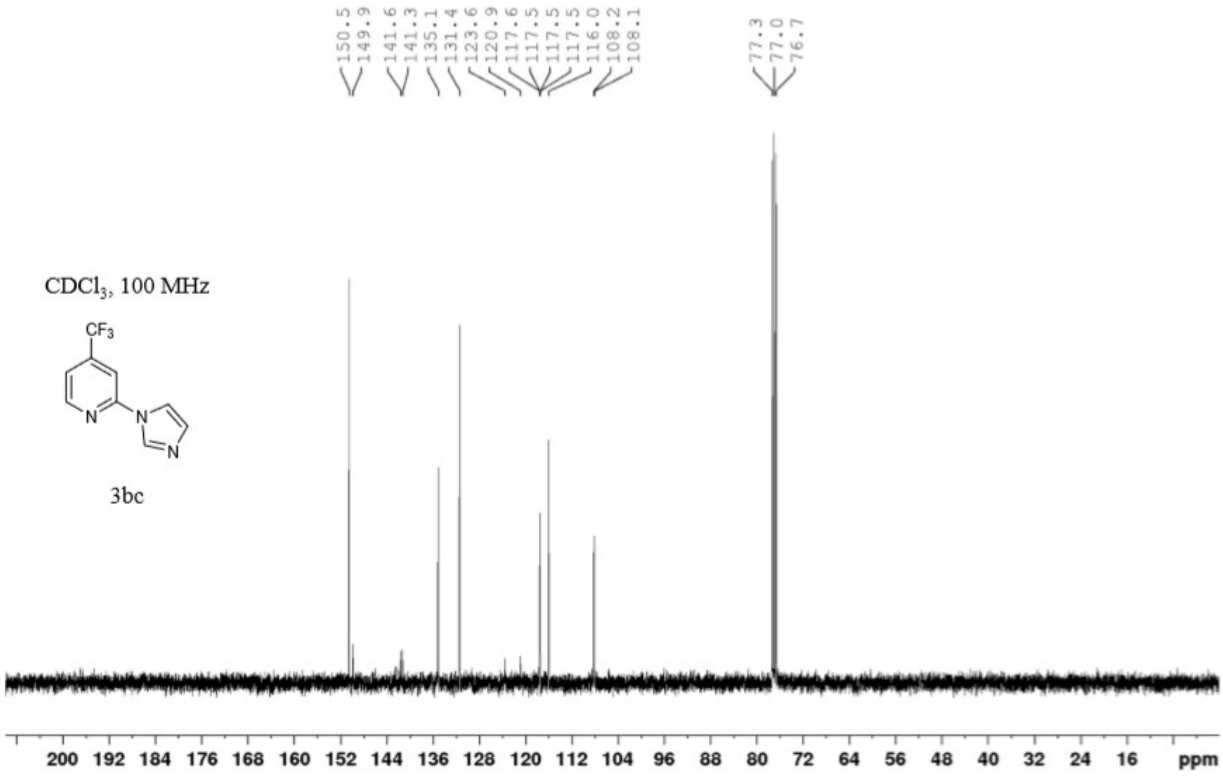

8.58
8.58
8.57
8.25
7.78
7.78
7.39
7.38
7.26
6.51
6.50
6.50
CDCl3, 400 MHz
CF3
N
N
N
3bb
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.00
0.98
1.00
1.06
1.04

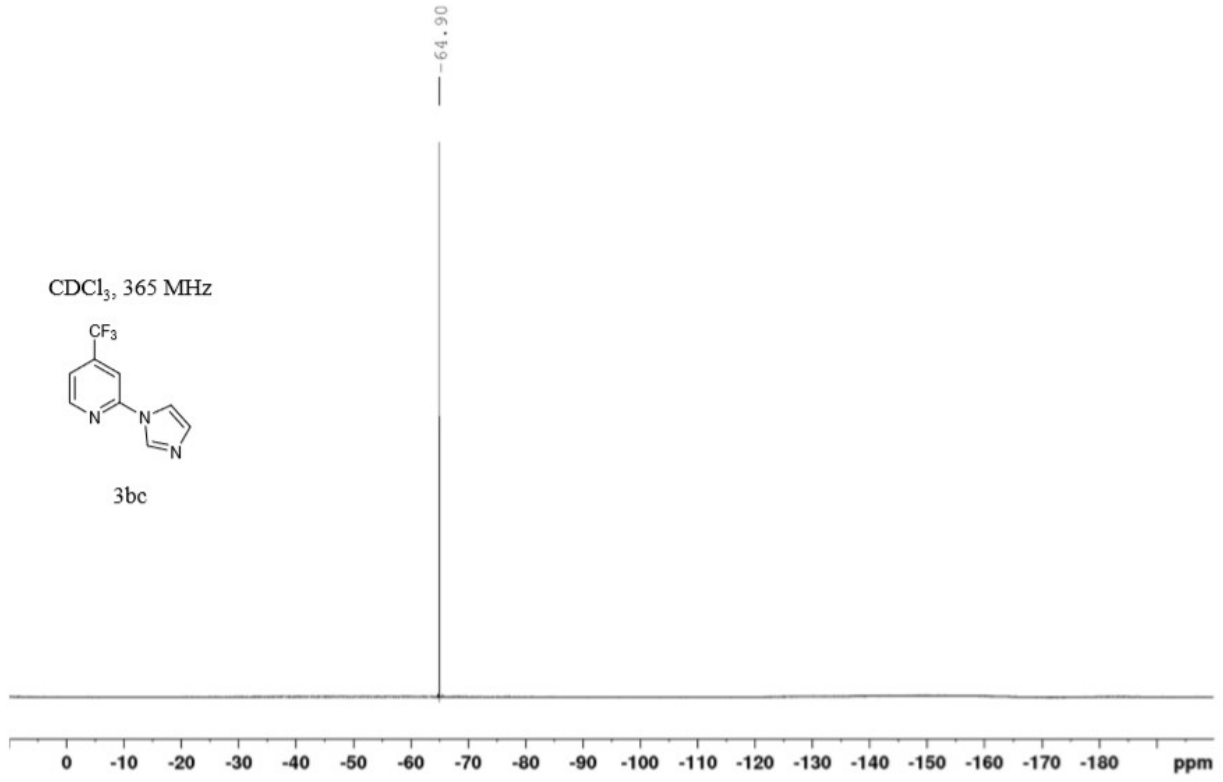

8.59
8.59
8.58
8.57
8.25
6.51
6.50
6.50
6.50
6.09
CDCl3, 400 MHz
(Crude 1H NMR)
CF3
N
N
N
3bb
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.61
0.78
0.76
3.00

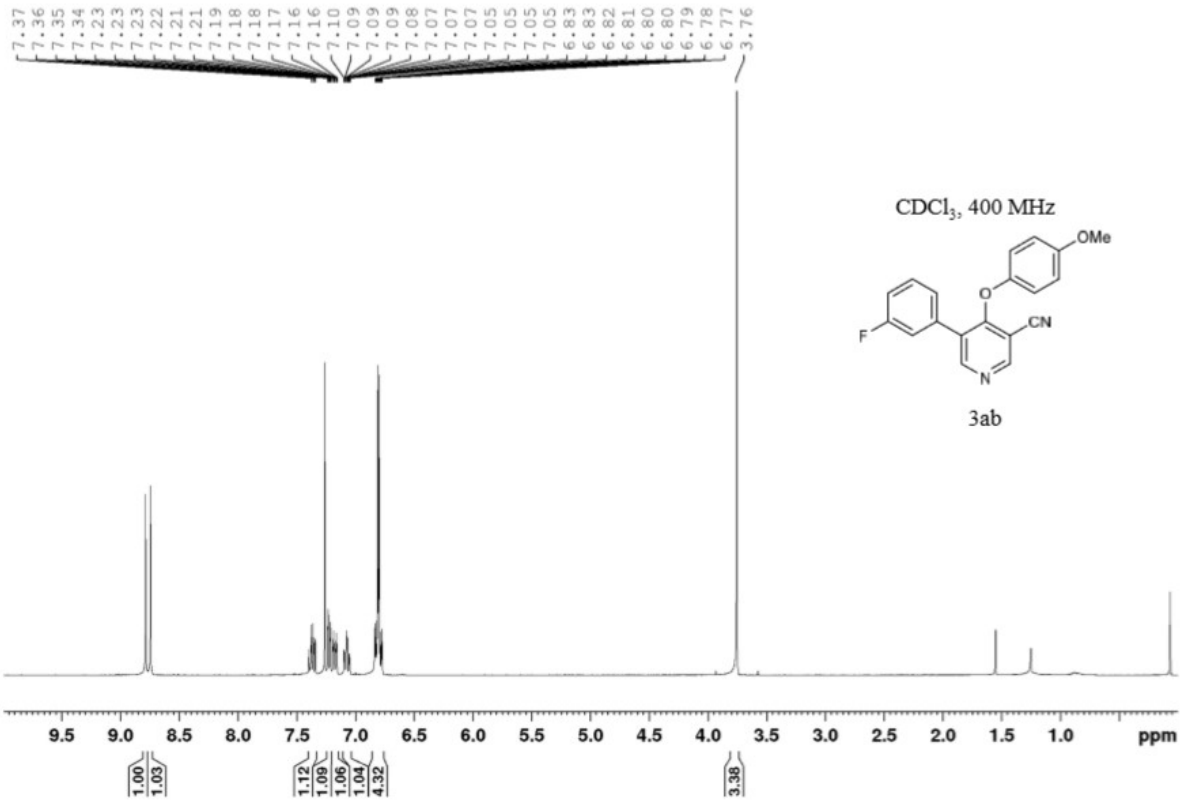

152.3
149.2
142.8
141.5
141.2
140.9
140.5
127.3
126.6
123.9
121.2
118.4
116.8
116.8
116.7
116.7
108.8
108.8
108.8
108.7
108.5
77.3
77.0
76.7
CDCl3, 100 MHz
CF3
N
N
N
3bb
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

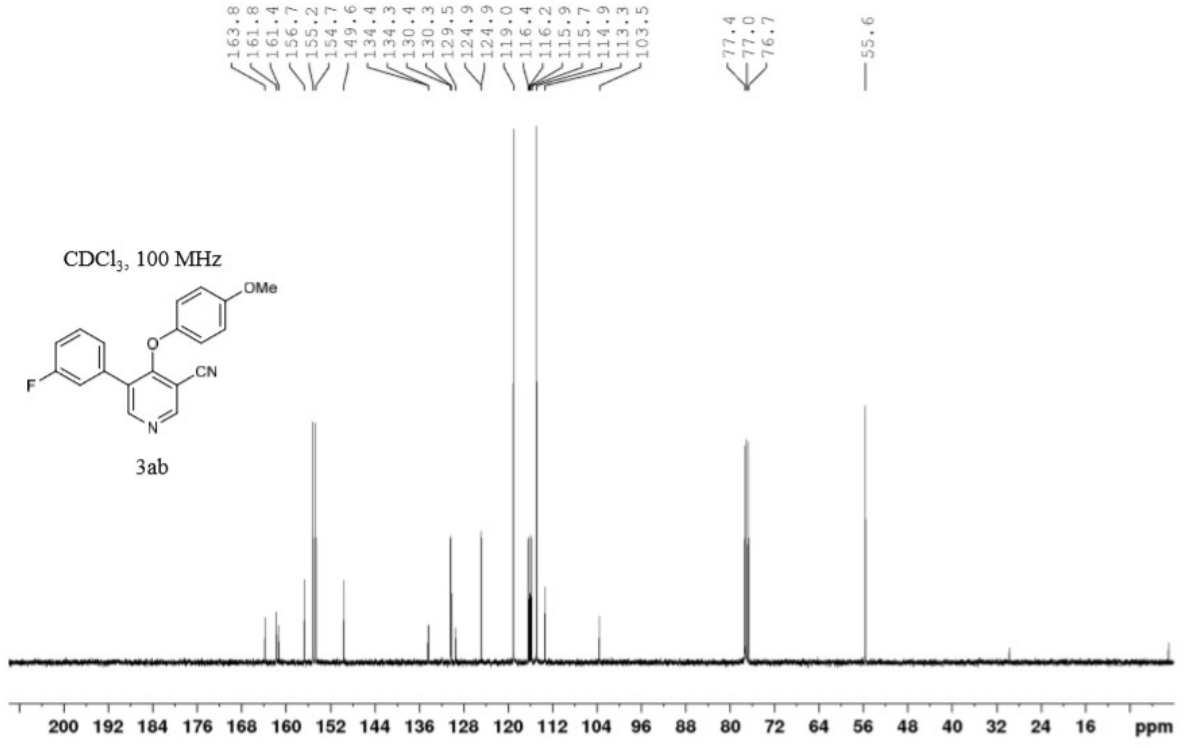

-64.96
CDCl3, 365 MHz
CF3
N
N
N
3bb
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm


8.69
8.68
8.42
7.68
7.68
7.67
7.54
7.48
7.48
7.47
7.46
7.26
7.25
7.25
7.25
CDCl3, 400 MHz
CF3
N
N
N
3bc
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.04
1.05
1.08
1.04
1.00

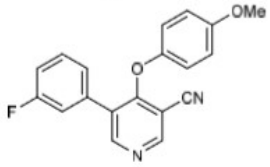

150.5
149.9
141.6
141.3
135.1
131.4
123.6
120.9
117.6
117.5
117.5
117.5
116.0
108.2
108.1
77.3
77.0
76.7
CDCl3, 100 MHz
CF3
N
N
N
3bc
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


-64.90
CDCl3, 365 MHz
CF3
N
N
N
3bc
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm


7.37
7.36
7.35
7.34
7.23
7.23
7.23
7.22
7.21
7.21
7.19
7.18
7.18
7.17
7.16
7.16
7.10
7.09
7.09
7.09
7.08
7.07
7.07
7.07
7.05
7.05
7.05
6.83
6.82
6.81
6.80
6.80
6.79
6.78
6.77
3.76
CDCl3, 400 MHz
OMe
O
CN
F
N
3ab
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.03
1.12
1.09
1.06
1.04
4.32
3.38

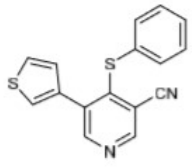

163.8
161.8
161.4
156.7
155.2
154.7
149.6
134.4
134.3
130.4
130.3
129.5
124.9
124.9
119.0
116.4
116.2
115.9
115.7
114.9
113.3
103.5
77.4
77.0
76.7
55.6
CDCl3, 100 MHz
OMe
O
CN
F
N
3ab
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

$CDCl_3$, 365 MHz

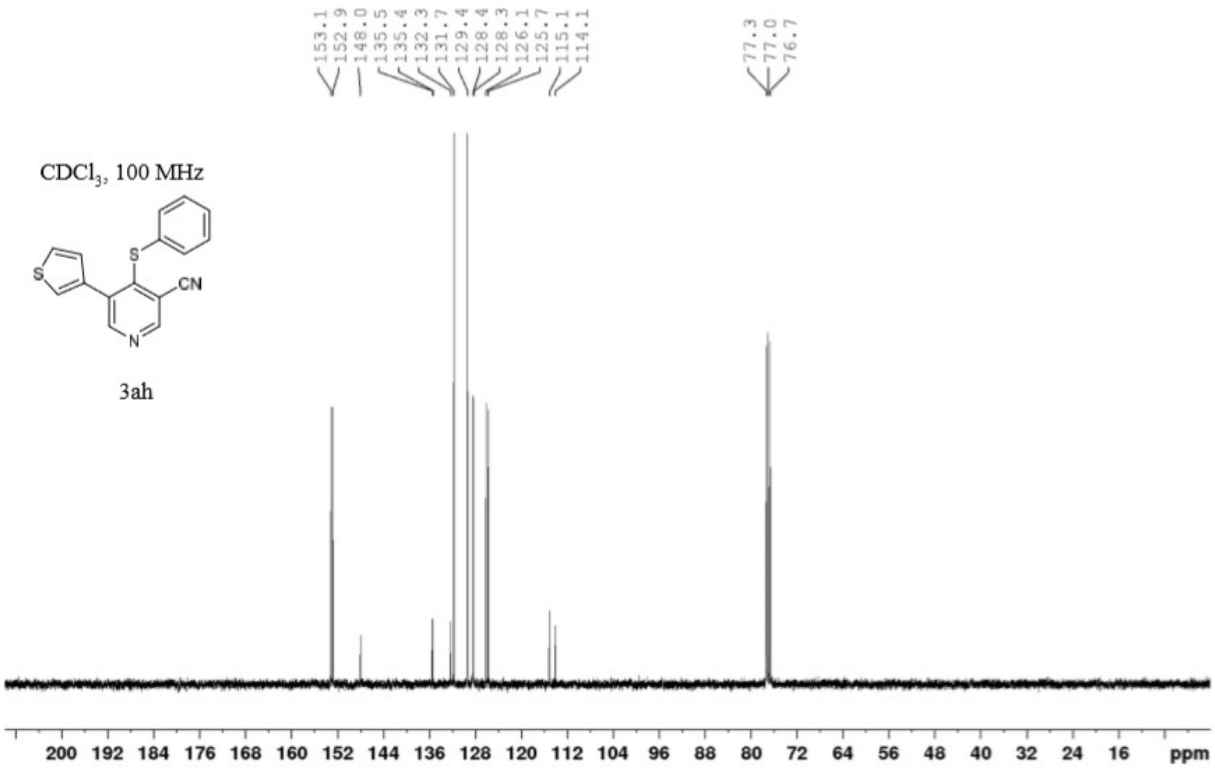


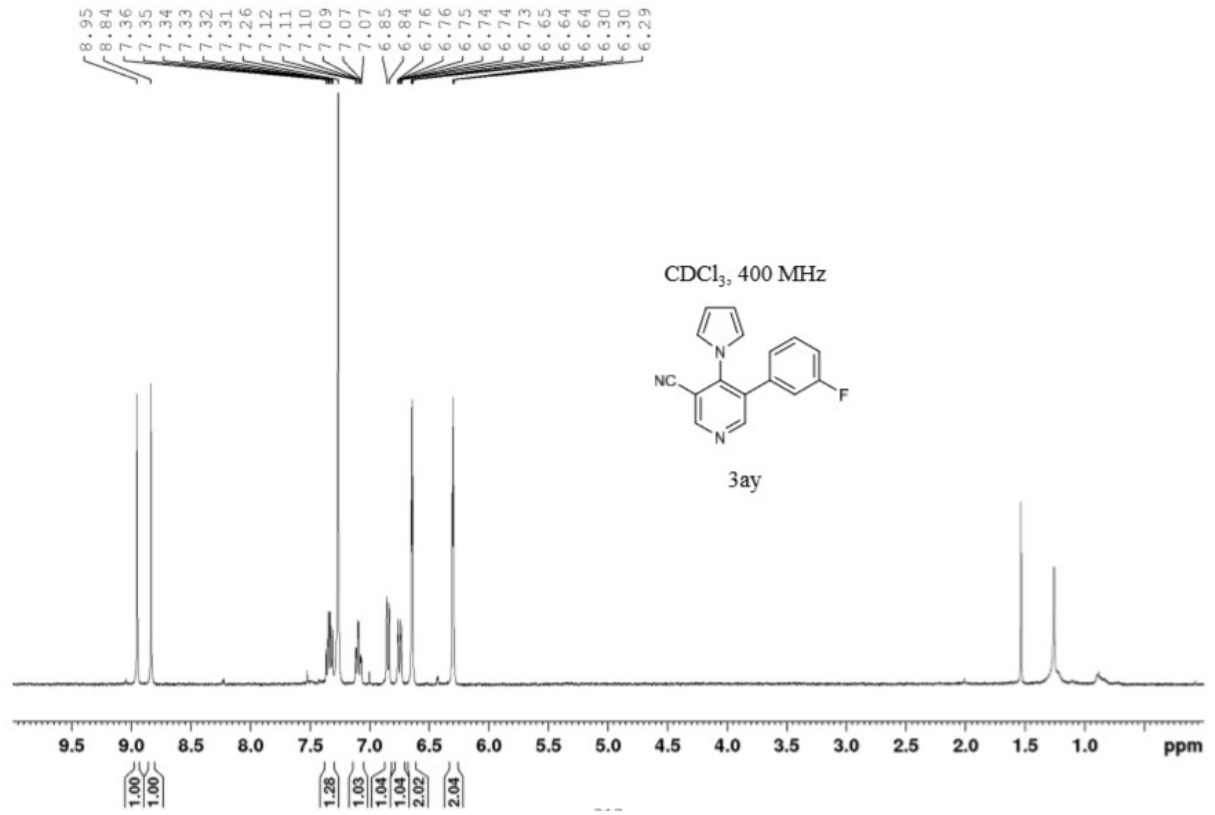
3ab

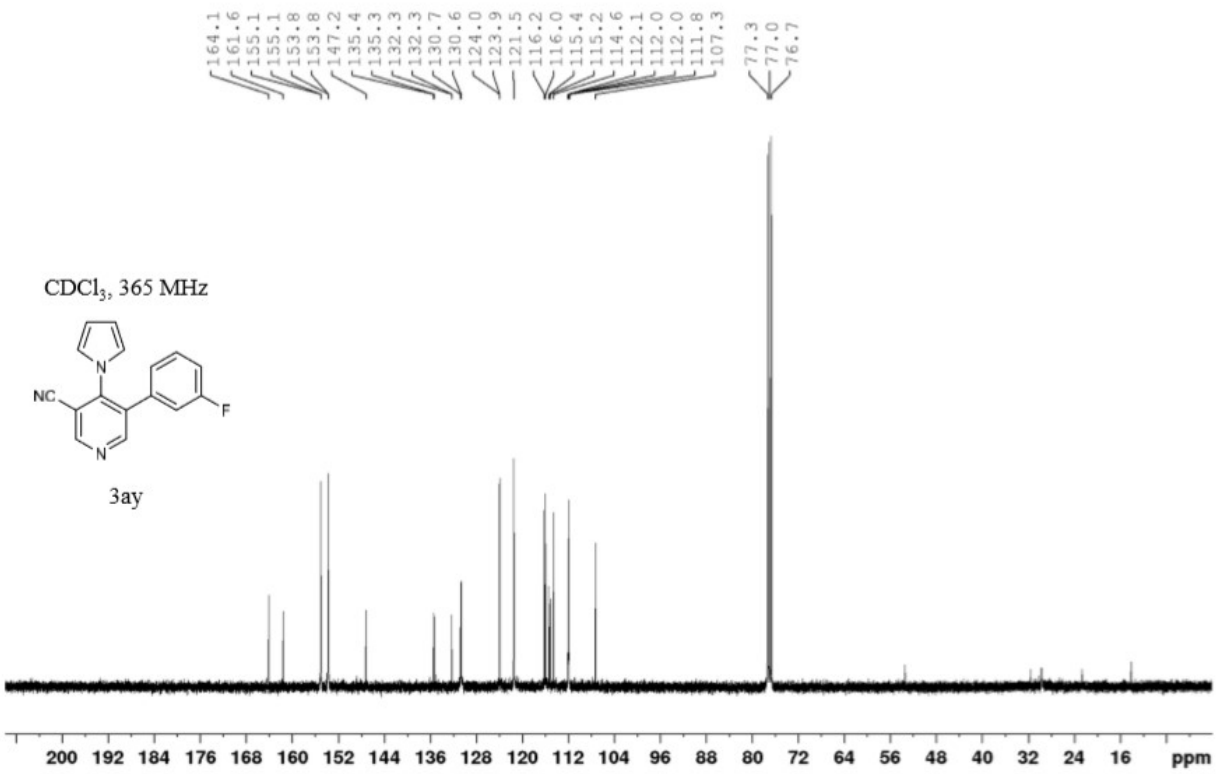
$CDCl_3$, 400 MHz

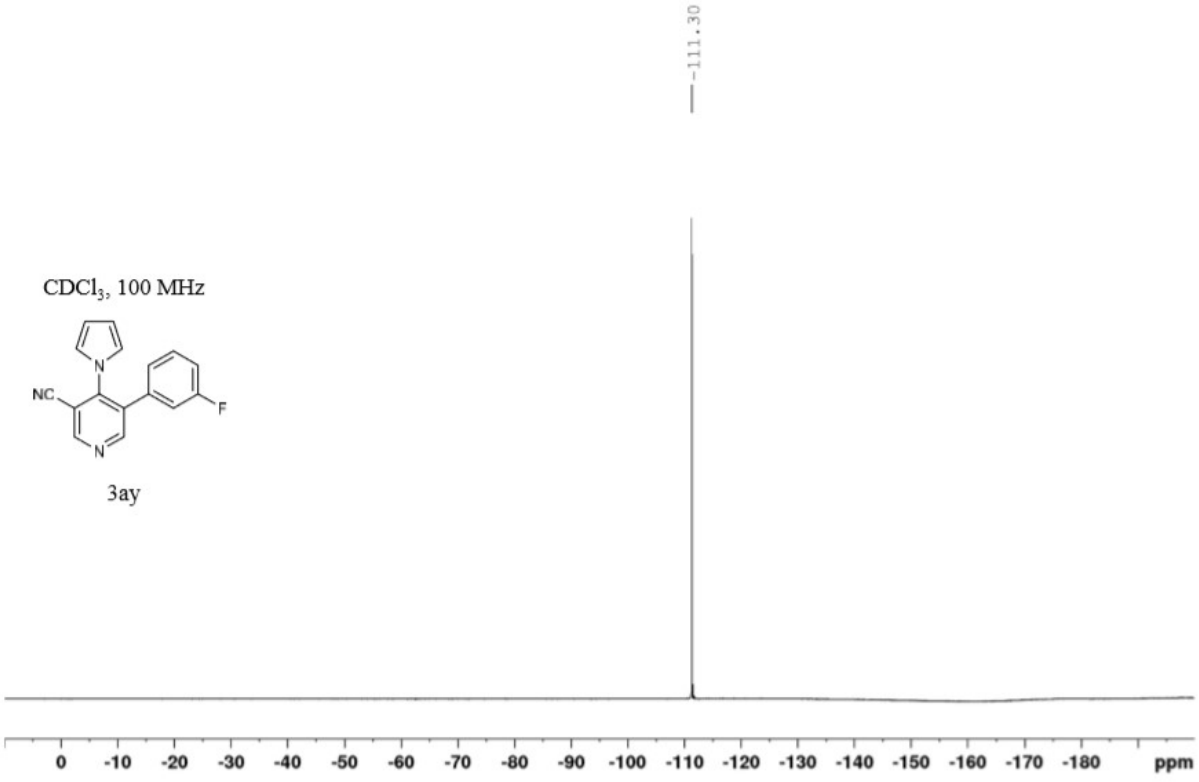


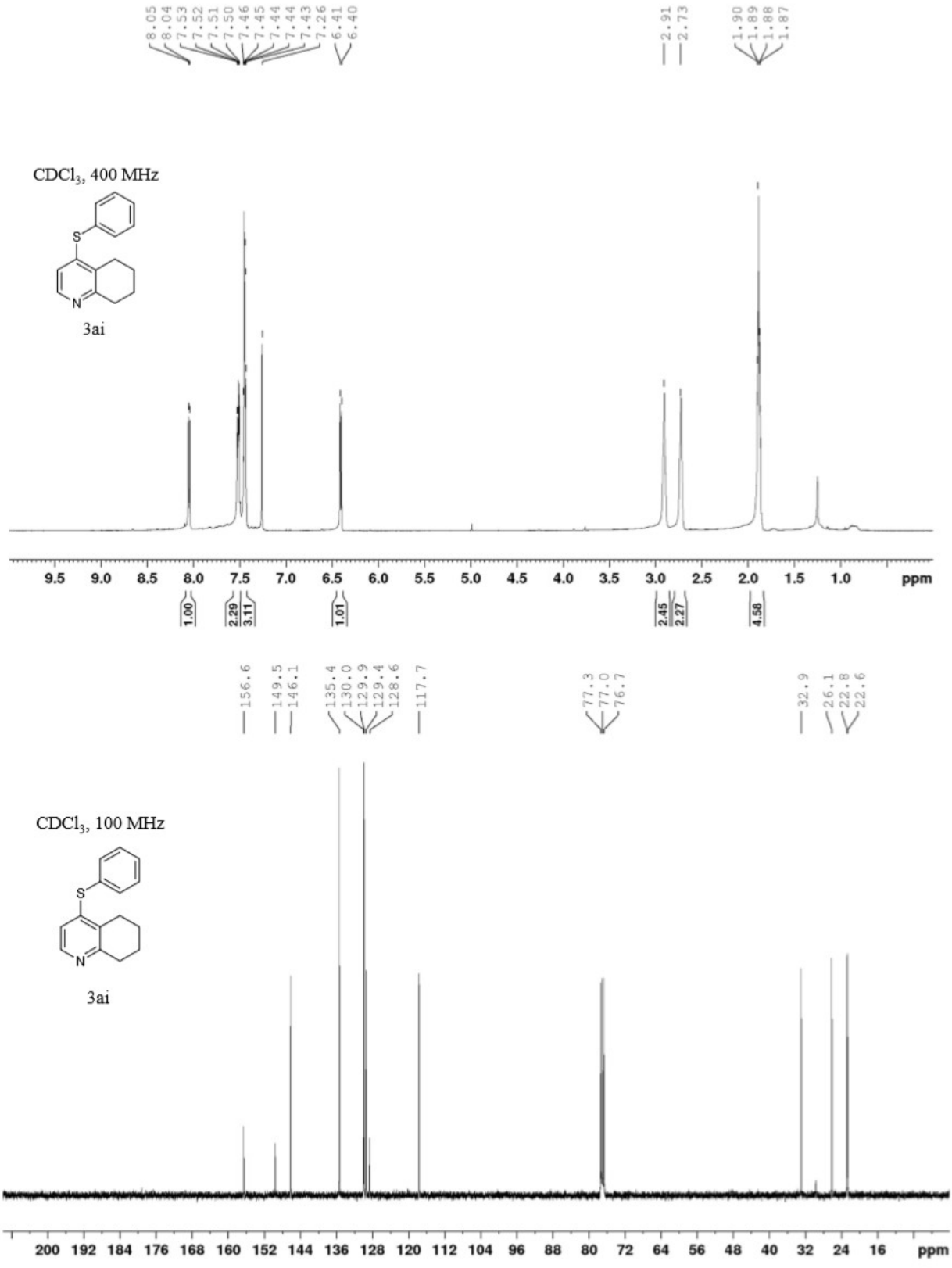
3ah

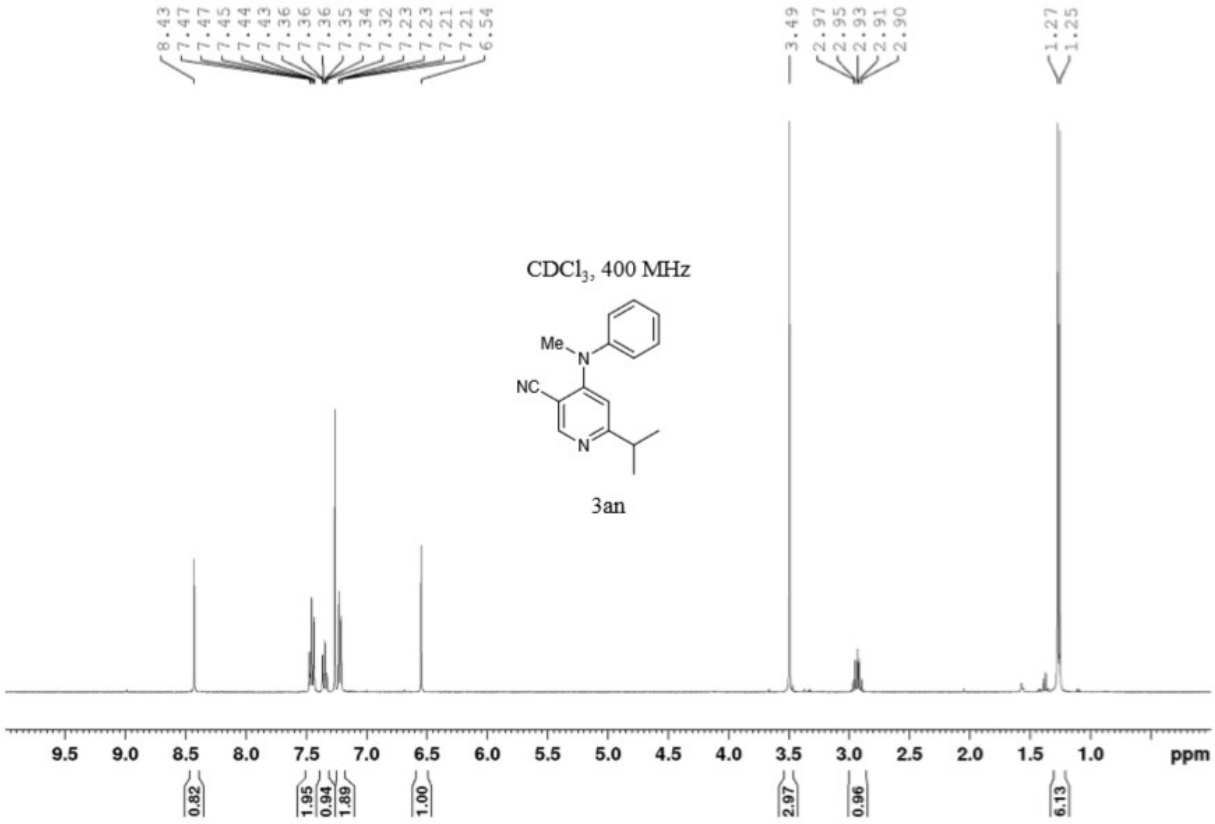

153.1
152.9
148.0
135.5
135.4
132.3
131.7
129.4
128.4
128.3
126.1
125.7
115.1
114.1
77.3
77.0
76.7
CDCl3, 100 MHz
S
CN
N
3ah
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

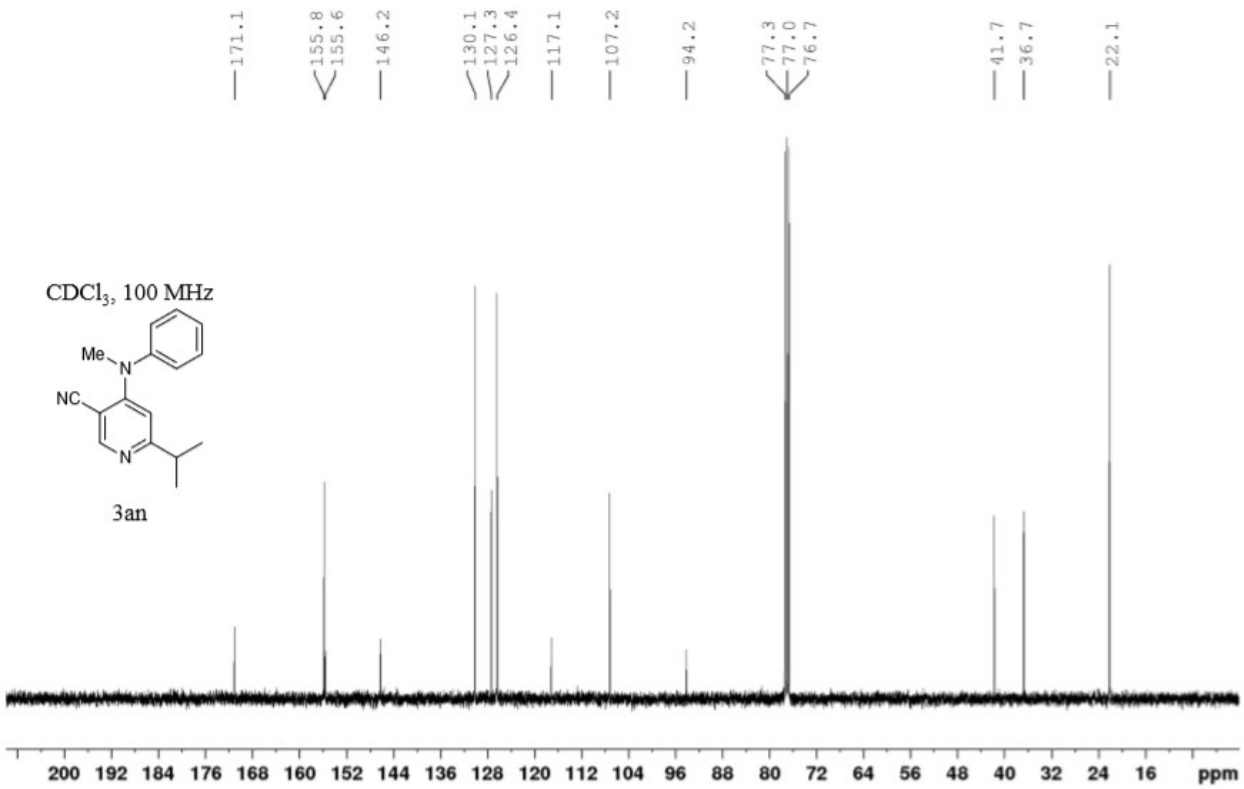

8.95
8.84
7.36
7.35
7.34
7.33
7.32
7.31
7.26
7.12
7.11
7.10
7.09
7.07
7.07
6.85
6.84
6.76
6.76
6.75
6.74
6.74
6.73
6.65
6.64
6.64
6.30
6.29
CDCl3, 400 MHz
N
NC
F
N
3ay
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
1.26
1.03
1.04
1.04
2.02
2.04

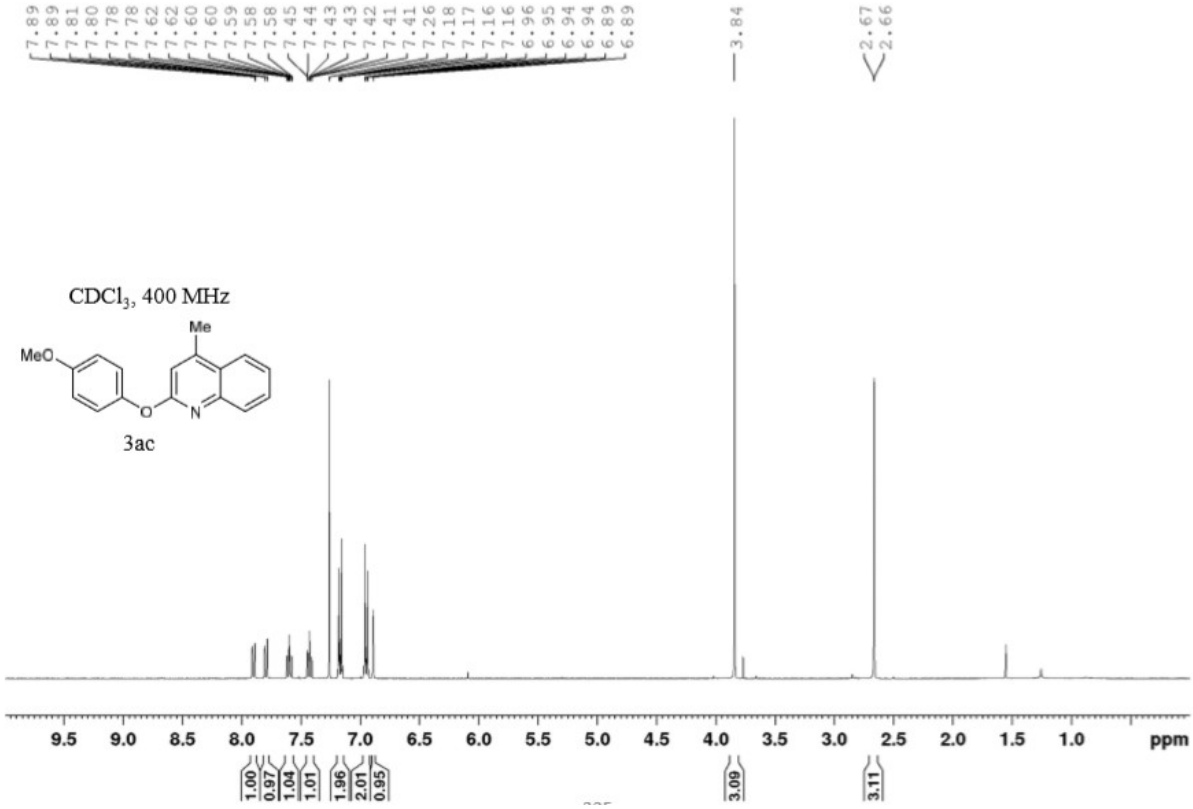

164.1
161.6
155.1
155.1
153.8
153.8
147.2
135.4
135.3
132.3
132.3
130.7
130.6
124.0
123.9
121.5
116.2
116.0
115.4
115.2
114.6
112.1
112.0
112.0
111.8
107.3
77.3
77.0
76.7
CDCl3, 365 MHz
NC
F
N
N
3ay
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

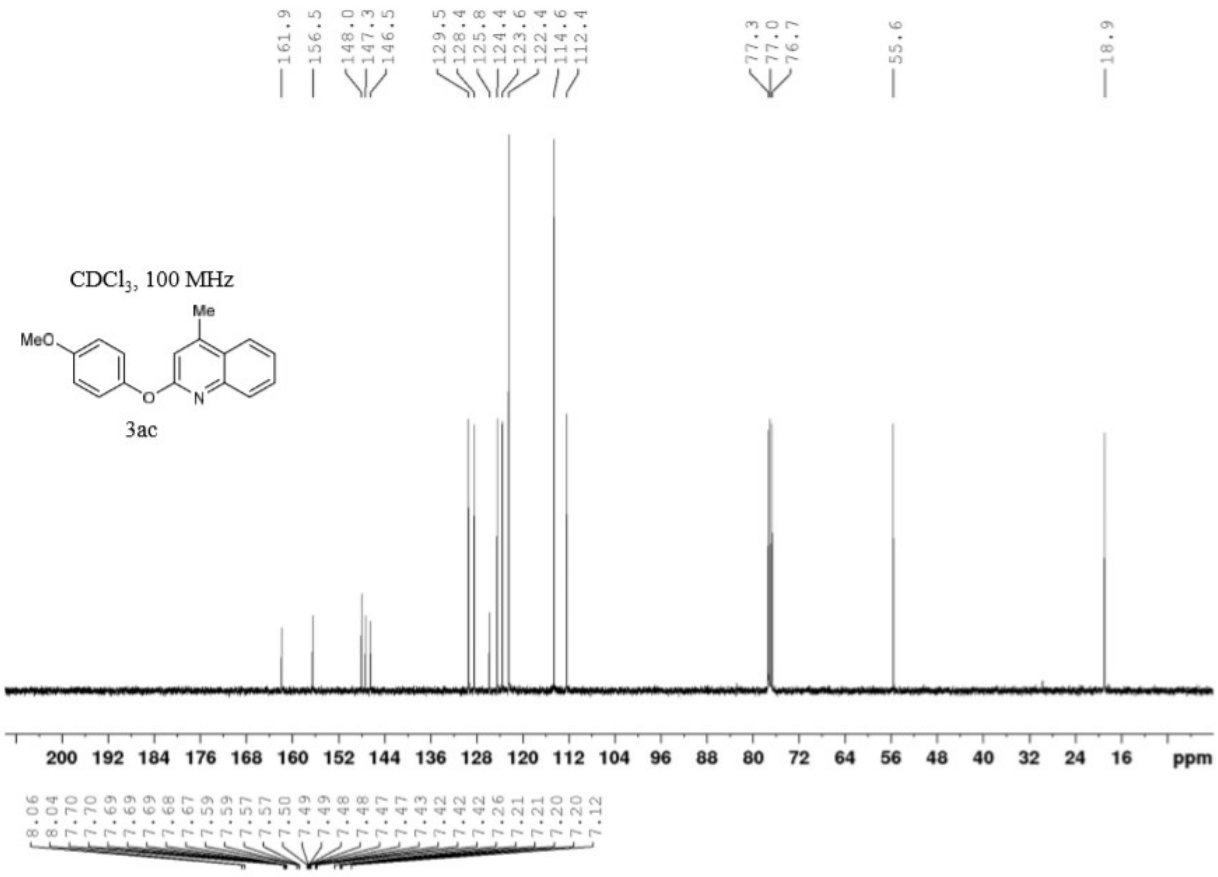

-111.30
CDCl3, 100 MHz
NC
F
N
N
3ay
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

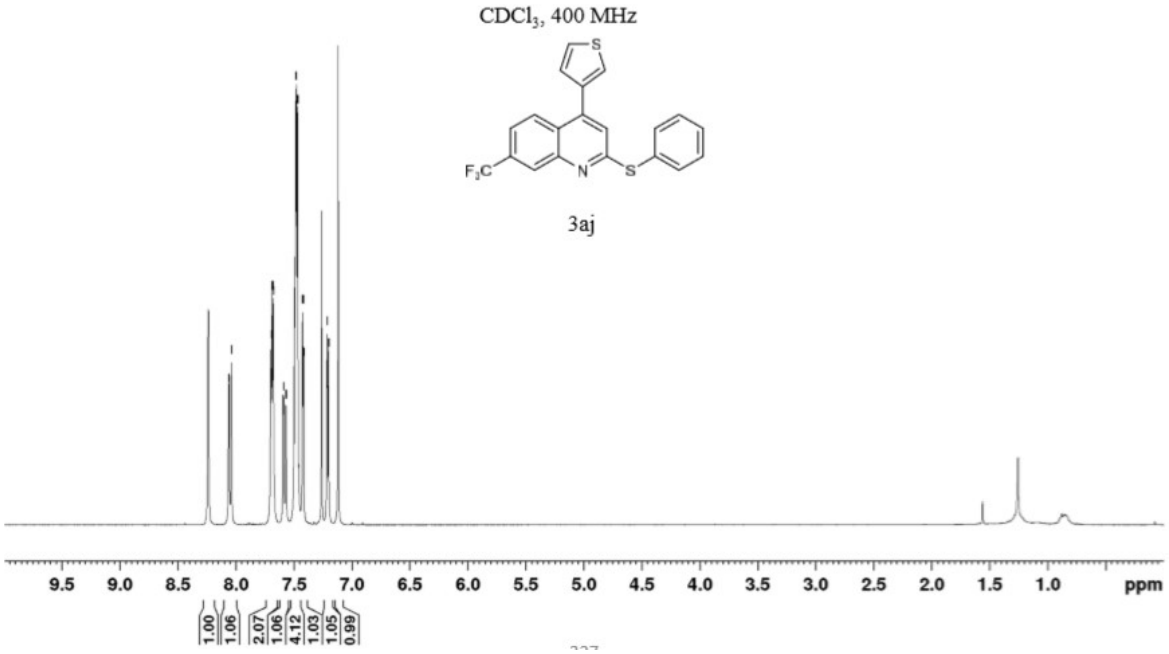

8.05
8.04
7.53
7.52
7.51
7.50
7.46
7.45
7.44
7.44
7.43
7.26
6.41
6.40
2.91
2.73
1.90
1.89
1.88
1.87
CDCl3, 400 MHz
S
N
3ai
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.29
3.11
1.01
2.45
2.27
4.58
156.6
149.5
146.1
135.4
130.0
129.9
129.4
128.6
117.7
77.3
77.0
76.7
32.9
26.1
22.8
22.6
CDCl3, 100 MHz
S
N
3ai
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

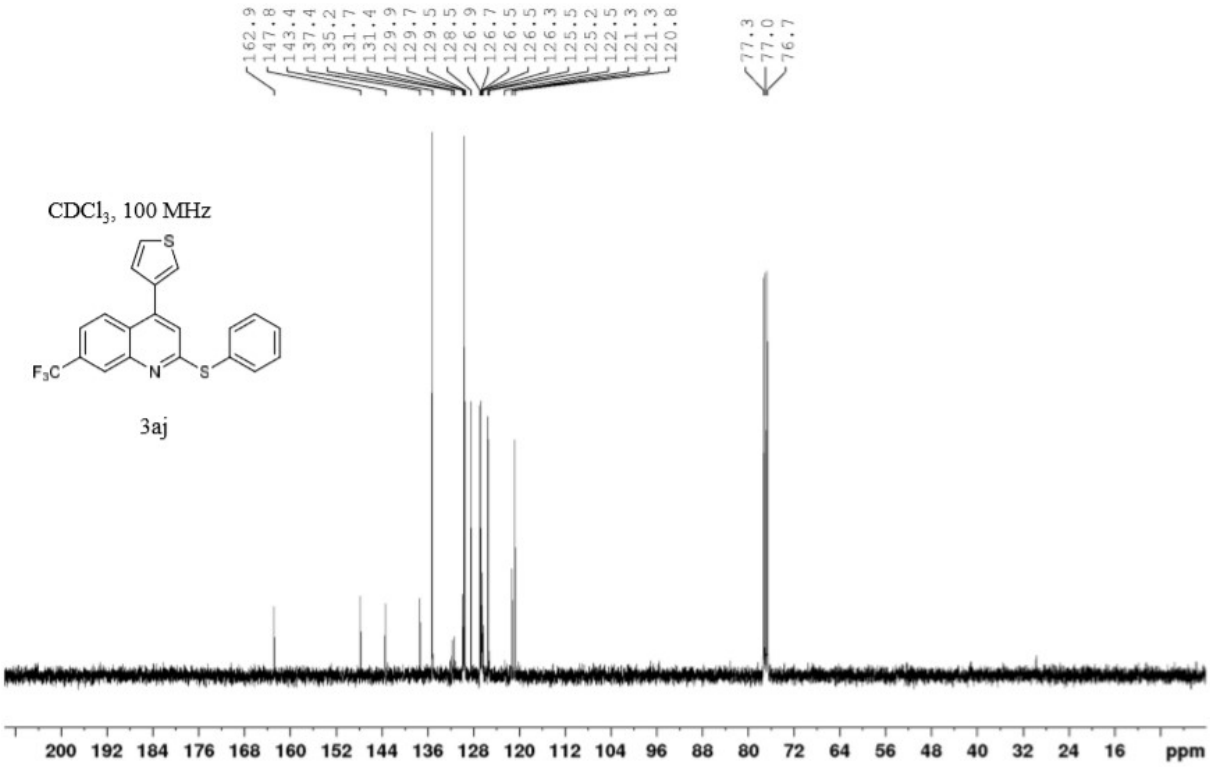

8.43
7.47
7.47
7.45
7.44
7.43
7.36
7.36
7.35
7.34
7.32
7.23
7.21
7.21
6.54
3.49
2.97
2.95
2.93
2.91
2.90
1.27
1.25
CDCl3, 400 MHz
Me
N
NC
N
3an
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.82
1.95
0.94
1.89
1.00
2.97
0.96
6.13

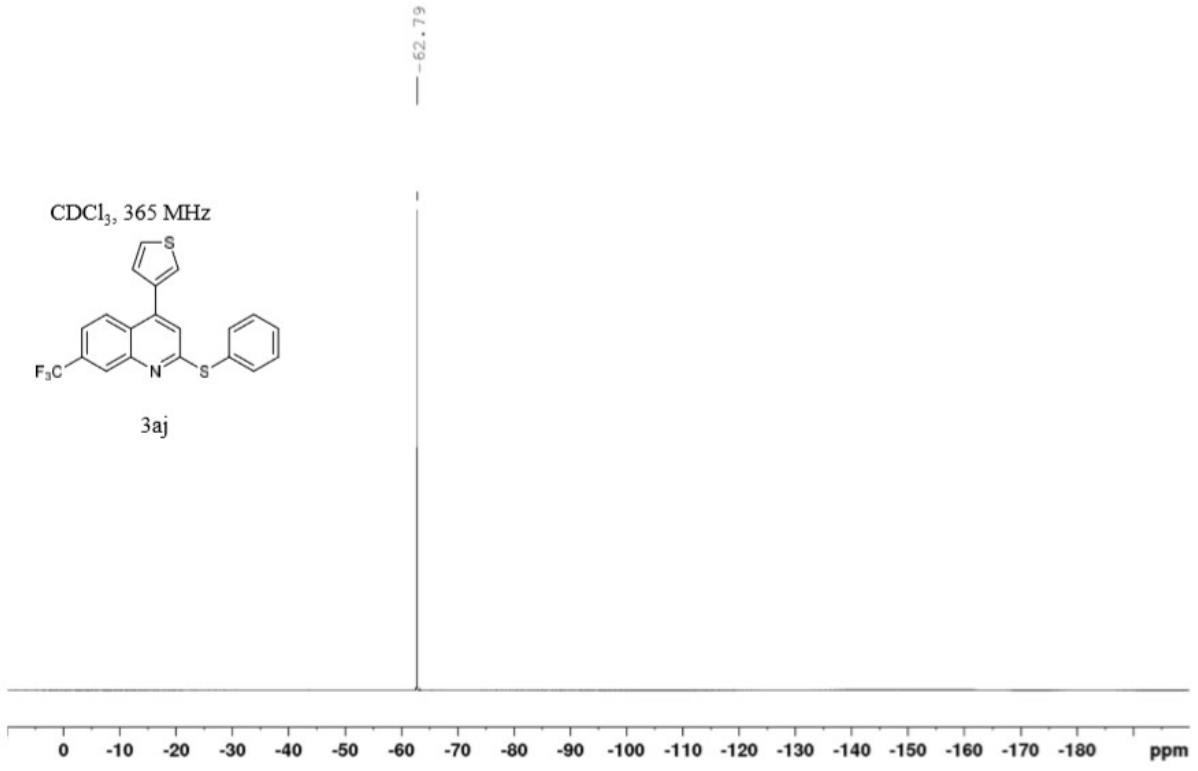

171.1
155.8
155.6
146.2
130.1
127.3
126.4
117.1
107.2
94.2
77.3
77.0
76.7
41.7
36.7
22.1
CDCl3, 100 MHz
Me
N
NC
N
3an
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

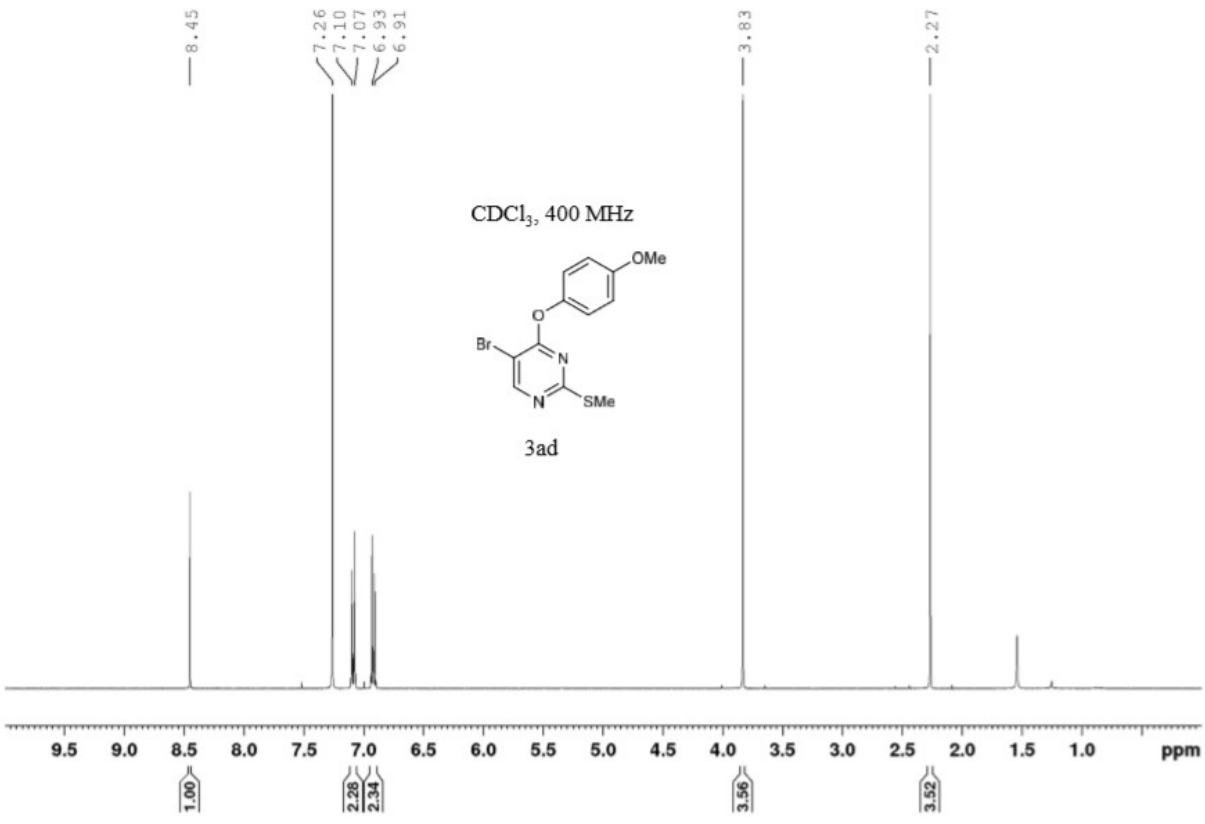

7.89
7.89
7.81
7.80
7.78
7.78
7.62
7.62
7.60
7.60
7.59
7.58
7.58
7.45
7.44
7.43
7.43
7.42
7.41
7.41
7.26
7.18
7.17
7.16
7.16
6.96
6.95
6.94
6.94
6.89
6.89
3.84
2.67
2.66
CDCl3, 400 MHz
Me
MeO
O
N
3ac
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.97
1.04
1.01
1.96
2.01
0.95
3.09
3.11

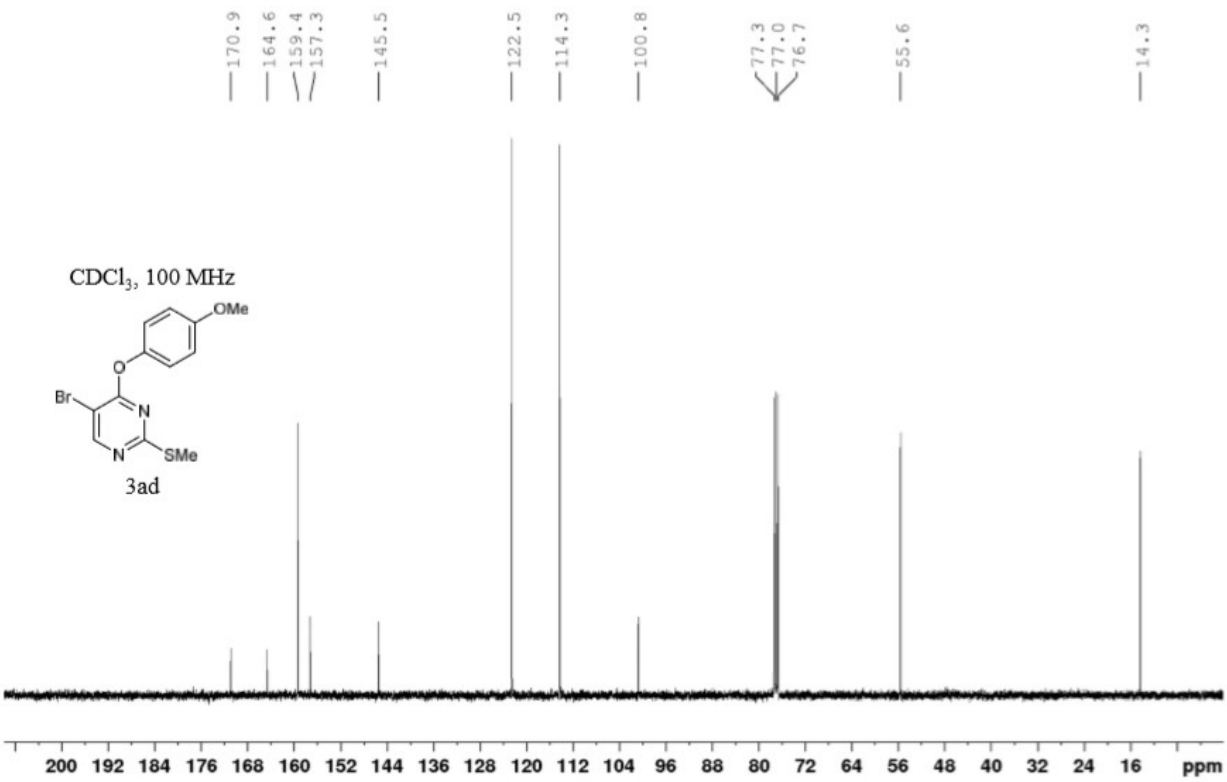

161.9
156.5
148.0
147.3
146.5
129.5
128.4
125.8
124.4
123.6
122.4
114.6
112.4
77.3
77.0
76.7
55.6
18.9
CDCl3, 100 MHz
Me
MeO
O
N
3ac
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm
8.06
8.04
7.70
7.70
7.69
7.69
7.69
7.68
7.67
7.59
7.59
7.57
7.57
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.43
7.42
7.42
7.42
7.26
7.21
7.21
7.20
7.20
7.12

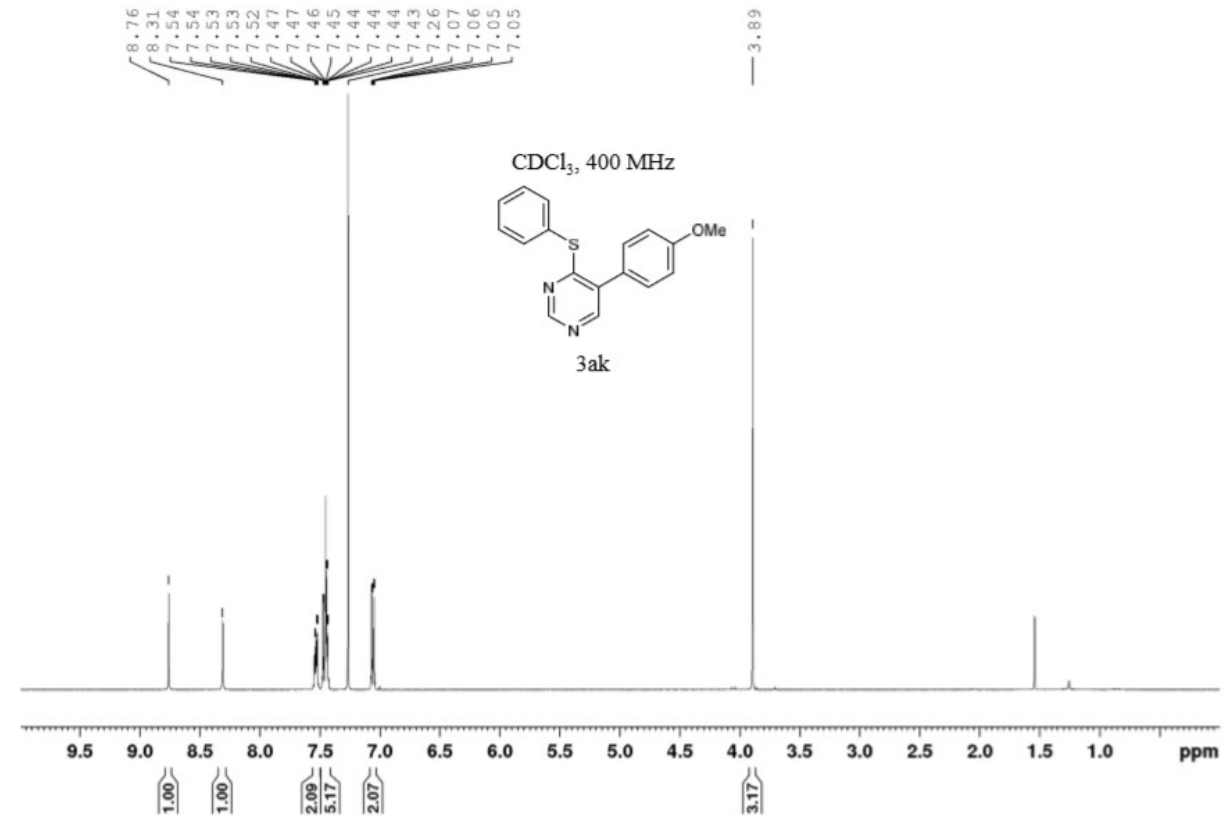

CDCl3, 400 MHz
S
F3C
N
S
3aj
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.06
2.07
1.06
4.12
1.03
1.05
0.99

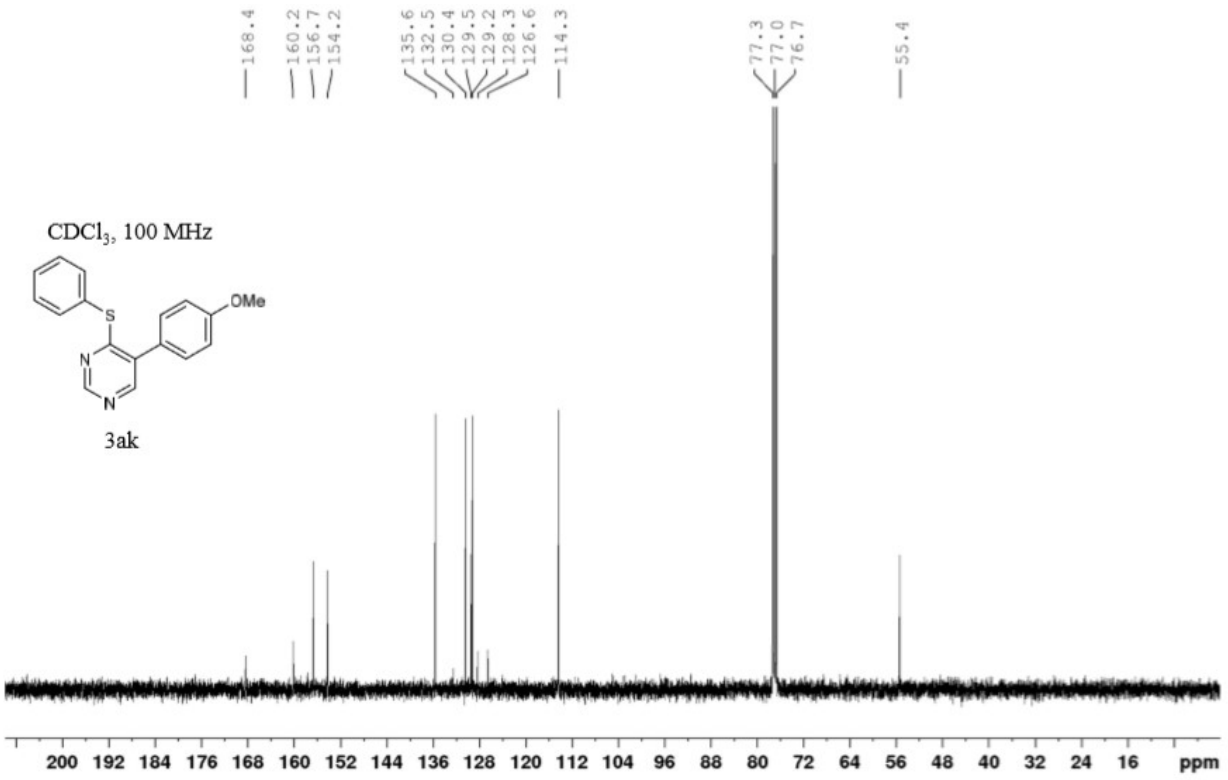

162.9
147.8
143.4
137.4
135.2
131.7
131.4
129.9
129.7
129.5
128.5
126.9
126.7
126.5
126.5
126.3
125.5
125.2
122.5
121.3
121.3
120.8
77.3
77.0
76.7
CDCl3, 100 MHz
S
F3C
N
S
3aj
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

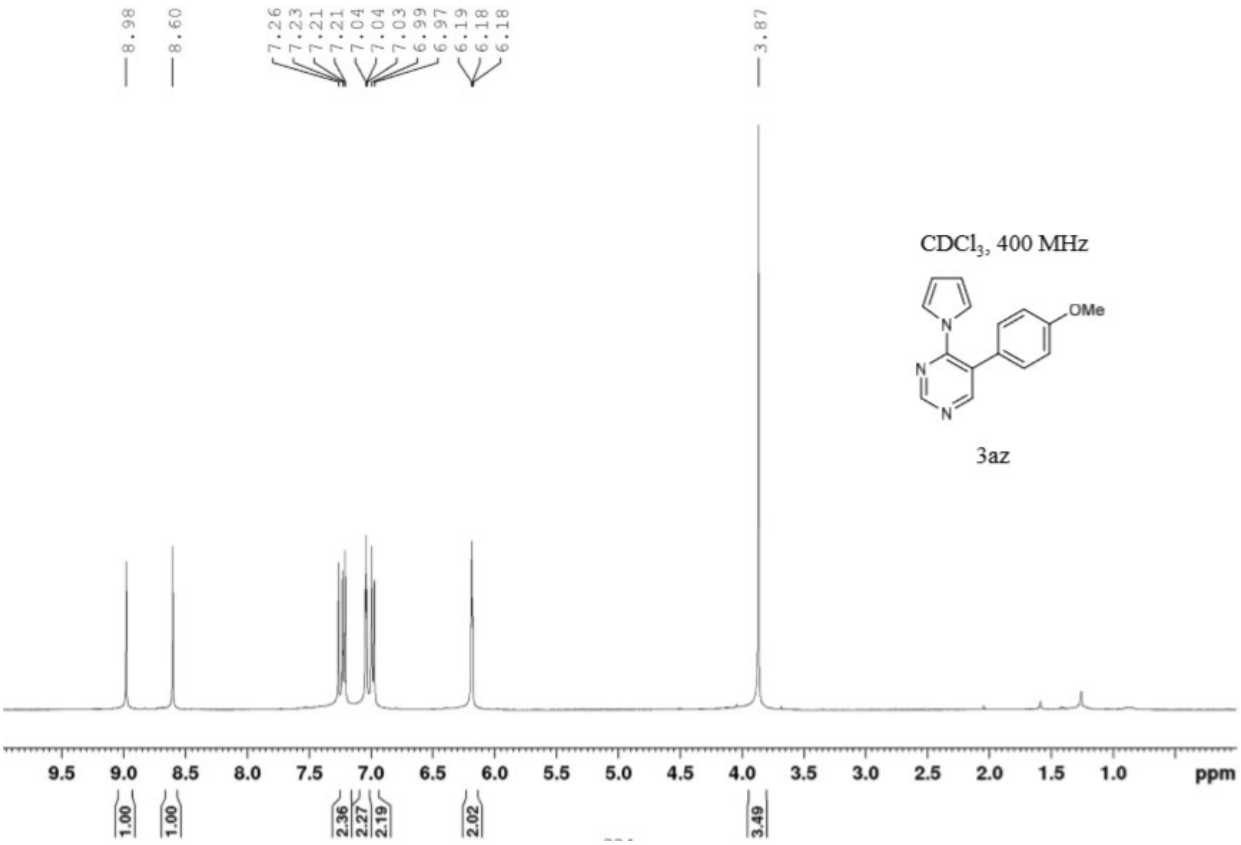

-62.79
CDCl3, 365 MHz
S
F3C
N
S
3aj
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

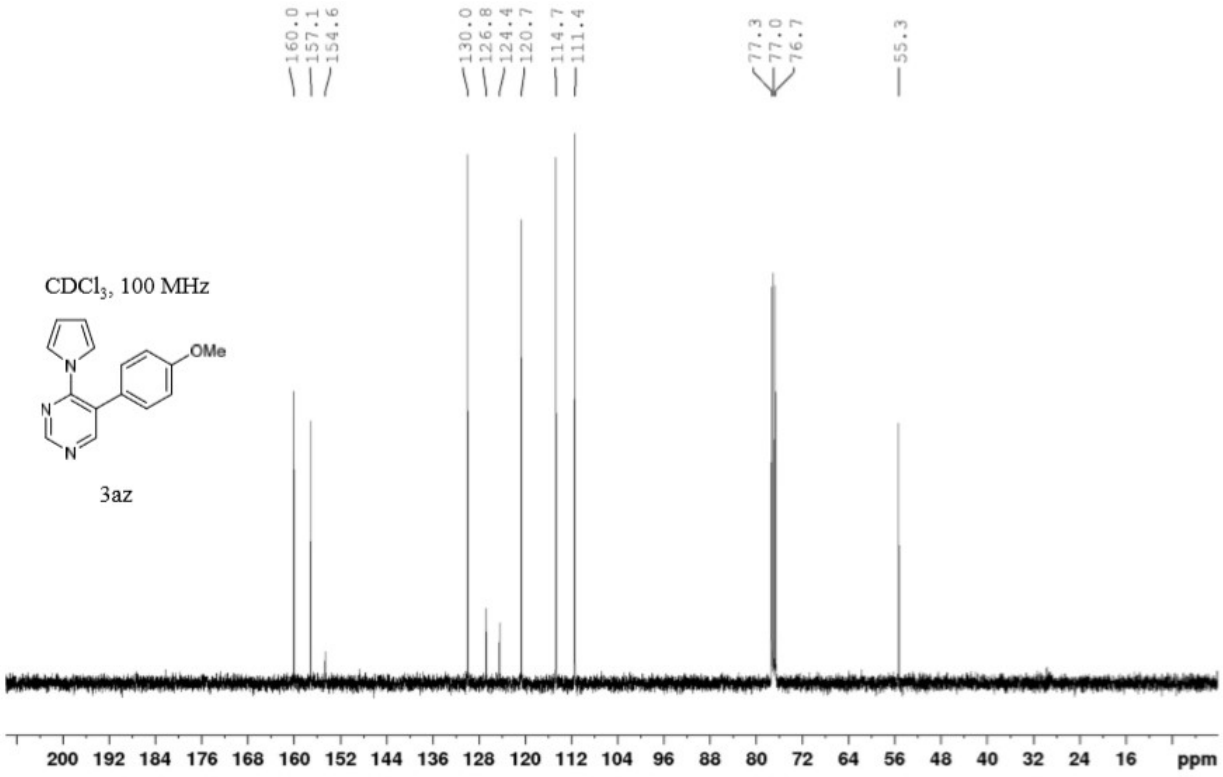

8.45
7.26
7.10
7.07
6.93
6.91
3.83
2.27
CDCl3, 400 MHz
OMe
O
Br
N
N
SMe
3ad
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.28
2.34
3.56
3.52

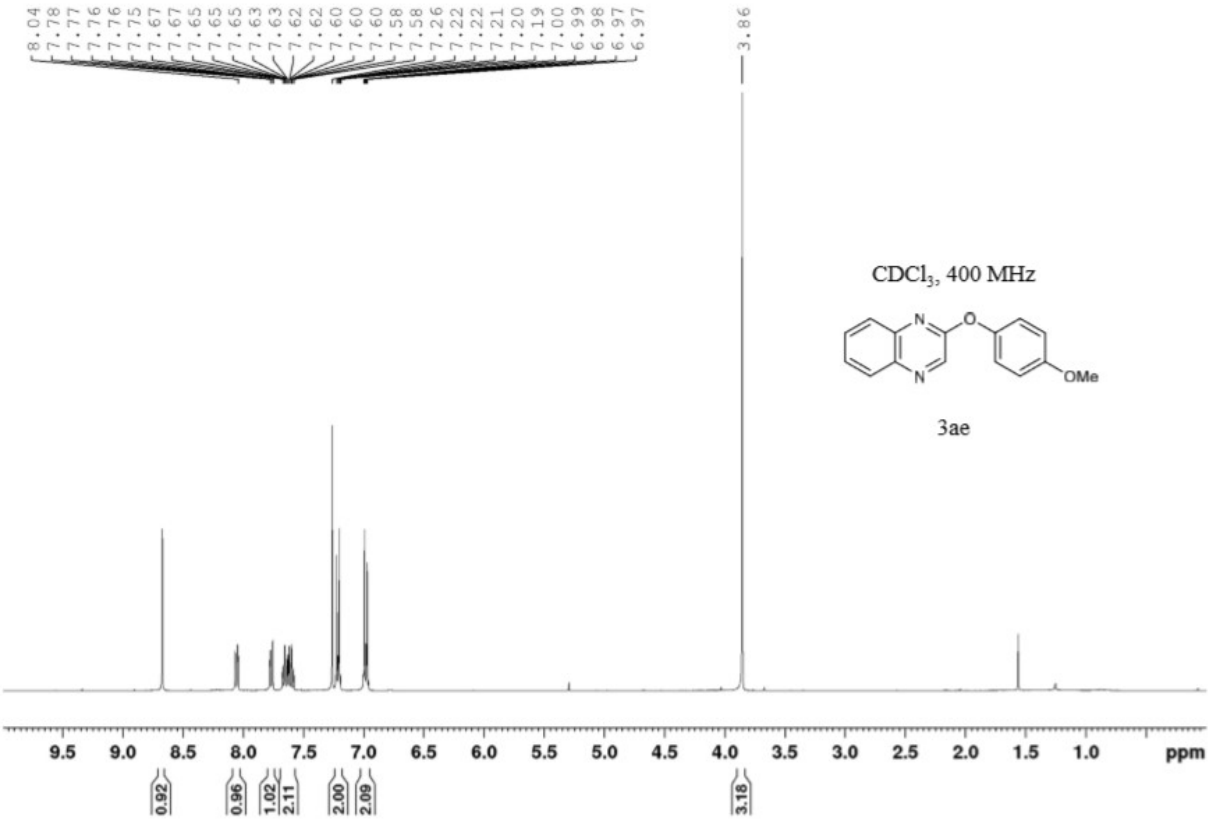

170.9
164.6
159.4
157.3
145.5
122.5
114.3
100.8
77.3
77.0
76.7
55.6
14.3
CDCl3, 100 MHz
OMe
O
Br
N
N
SMe
3ad
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

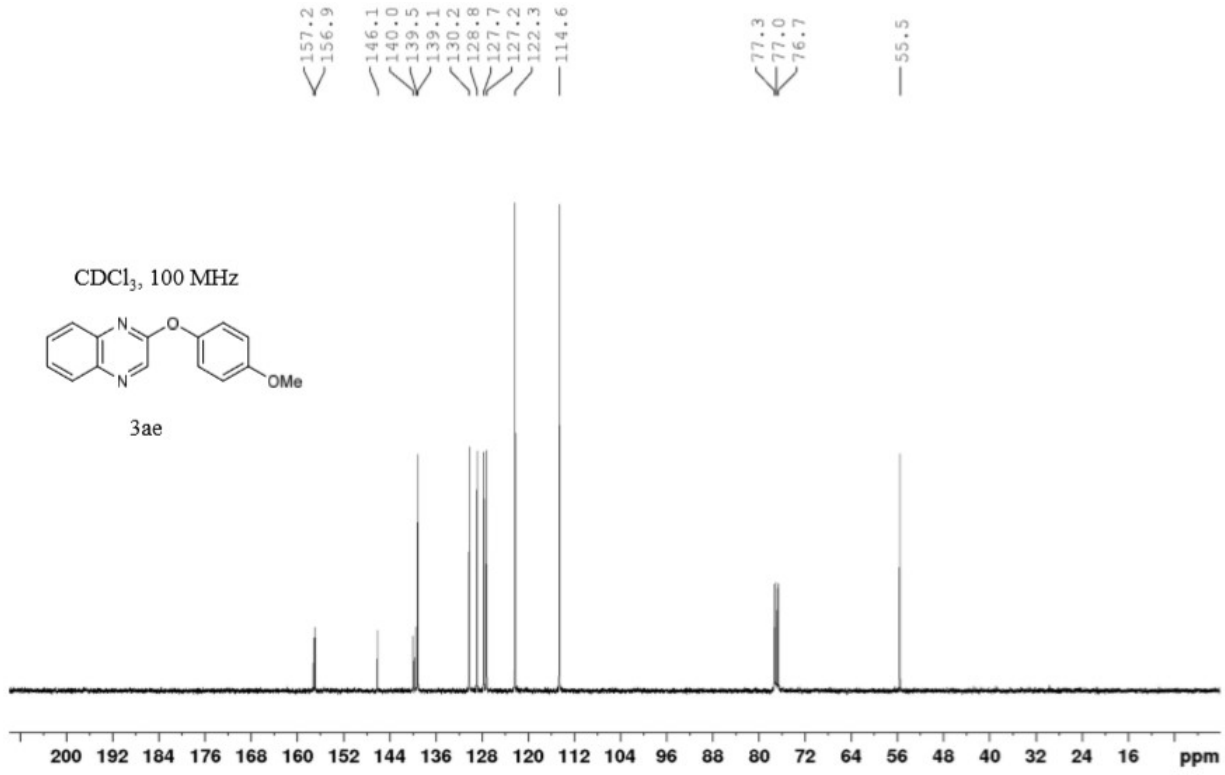

8.76
8.31
7.54
7.54
7.53
7.53
7.52
7.47
7.47
7.46
7.45
7.44
7.44
7.44
7.43
7.26
7.07
7.06
7.05
7.05
3.89
CDCl3, 400 MHz
OMe
S
N
N
3ak
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
2.09
5.17
2.07
3.17

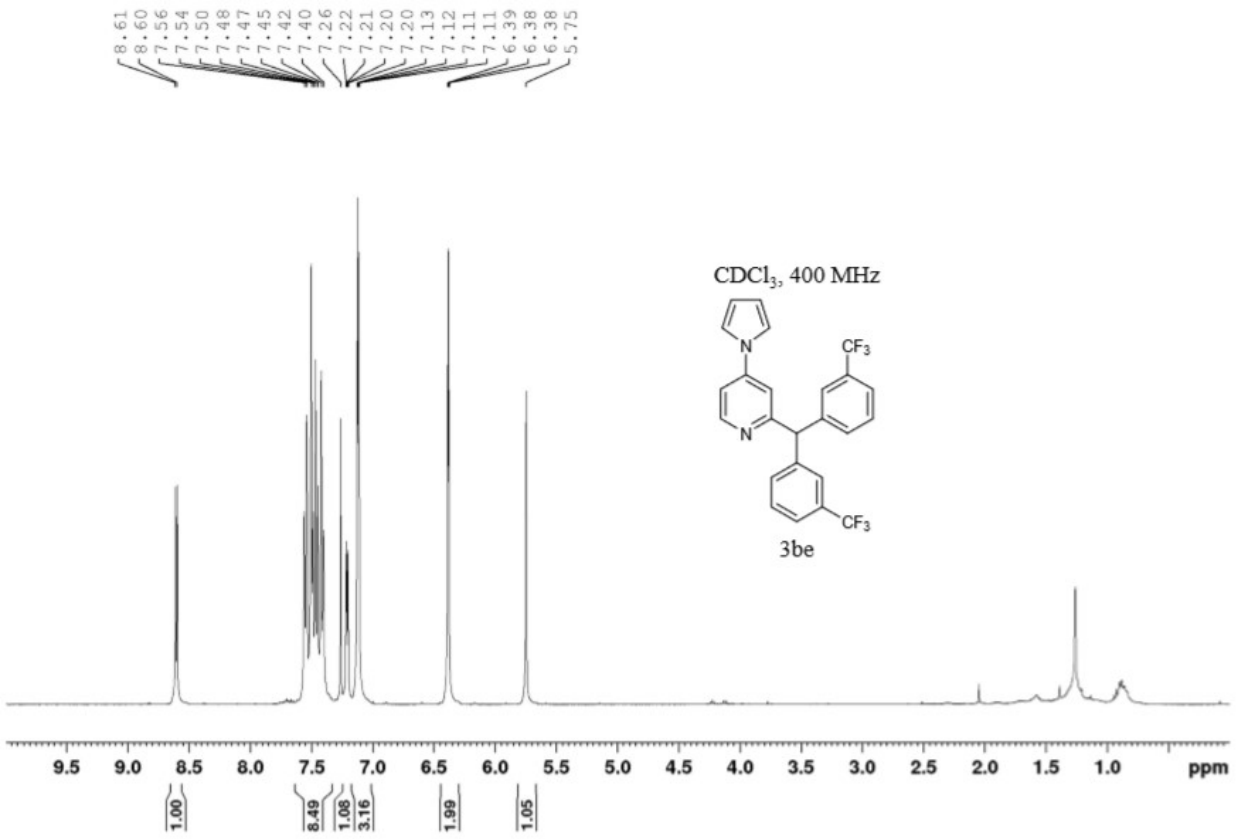

168.4
160.2
156.7
154.2
135.6
132.5
130.4
129.5
129.2
128.3
126.6
114.3
77.3
77.0
76.7
55.4
CDCl3, 100 MHz
OMe
S
N
N
3ak
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

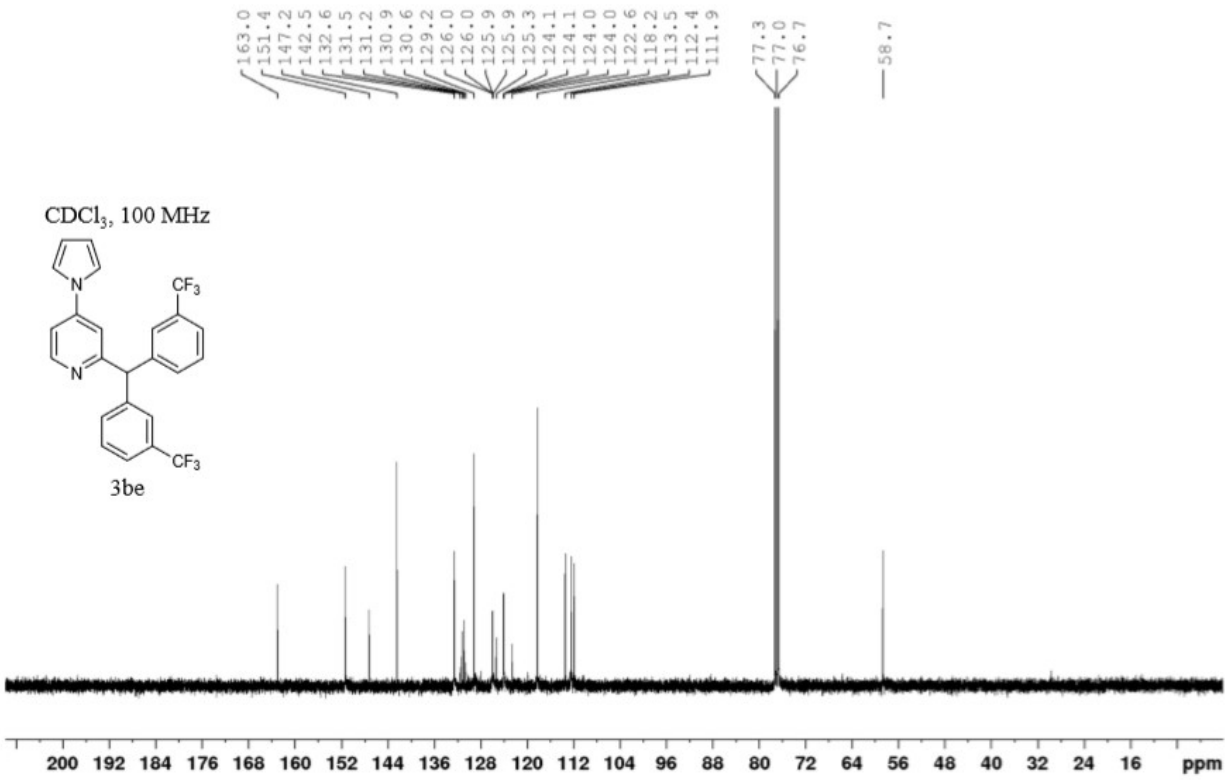

8.98
8.60
7.26
7.23
7.21
7.21
7.04
7.04
7.03
6.99
6.97
6.19
6.18
6.18
3.87
CDCl3, 400 MHz
OMe
N
N
N
3az
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
2.36
2.27
2.19
2.02
3.49

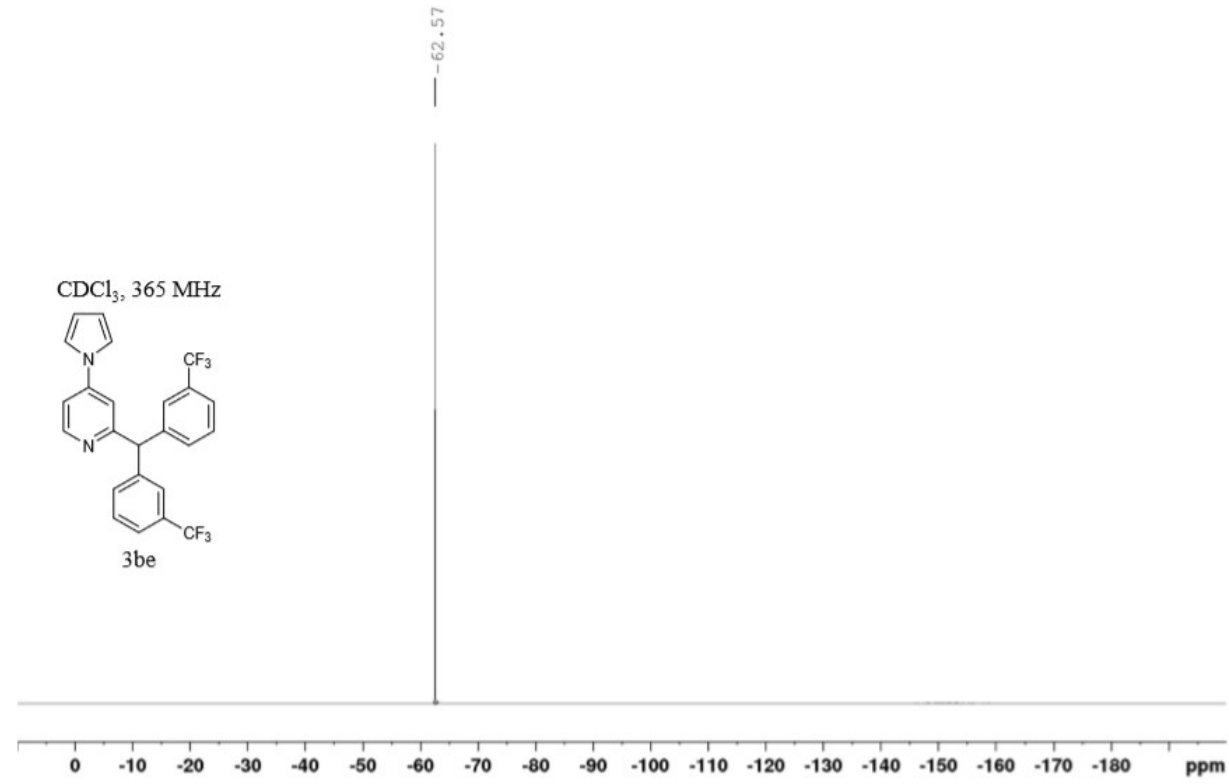

160.0
157.1
154.6
130.0
126.8
124.4
120.7
114.7
111.4
77.3
77.0
76.7
55.3
CDCl3, 100 MHz
OMe
N
N
N
3az
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

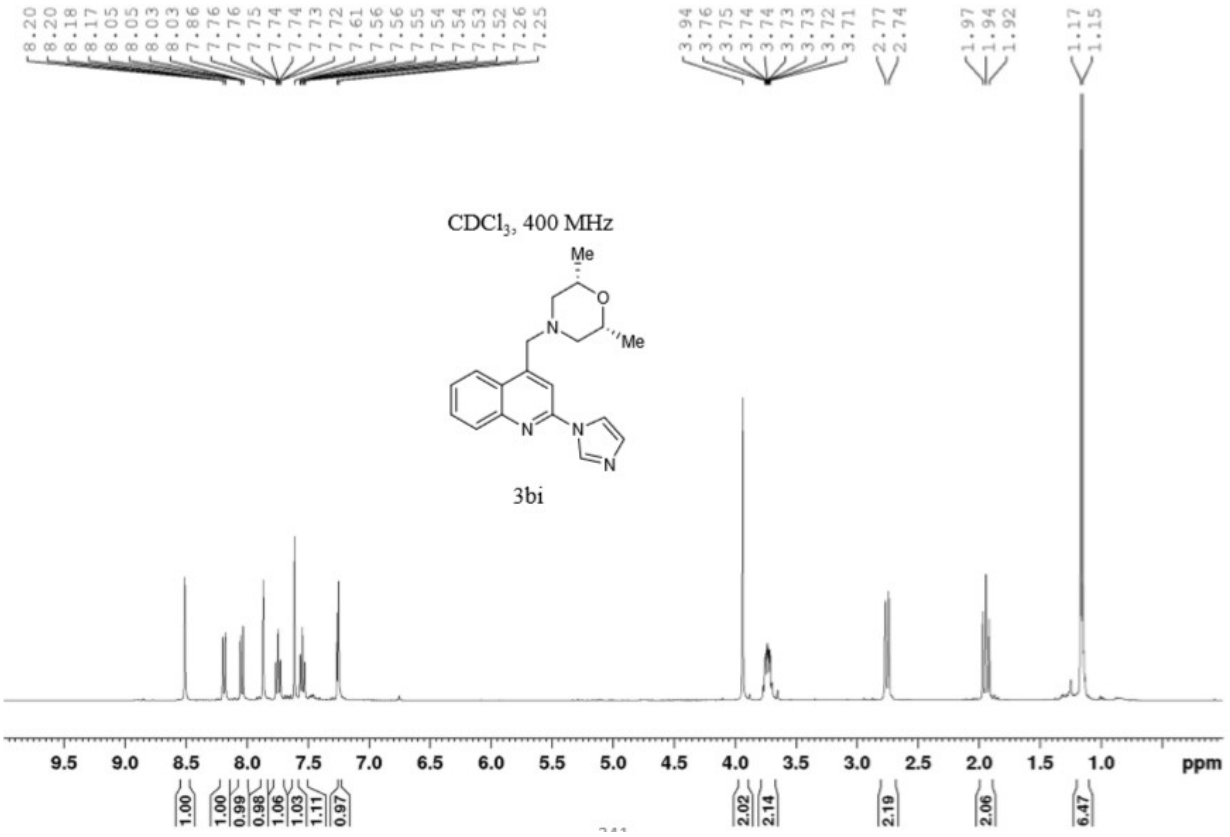

8.04
7.78
7.77
7.76
7.76
7.75
7.67
7.67
7.65
7.65
7.65
7.63
7.63
7.62
7.62
7.60
7.60
7.60
7.58
7.58
7.26
7.22
7.22
7.21
7.20
7.19
7.00
6.99
6.98
6.97
6.97
3.86
CDCl3, 400 MHz
N
O
N
OMe
3ae
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.92
0.96
1.02
2.11
2.00
2.09
3.18

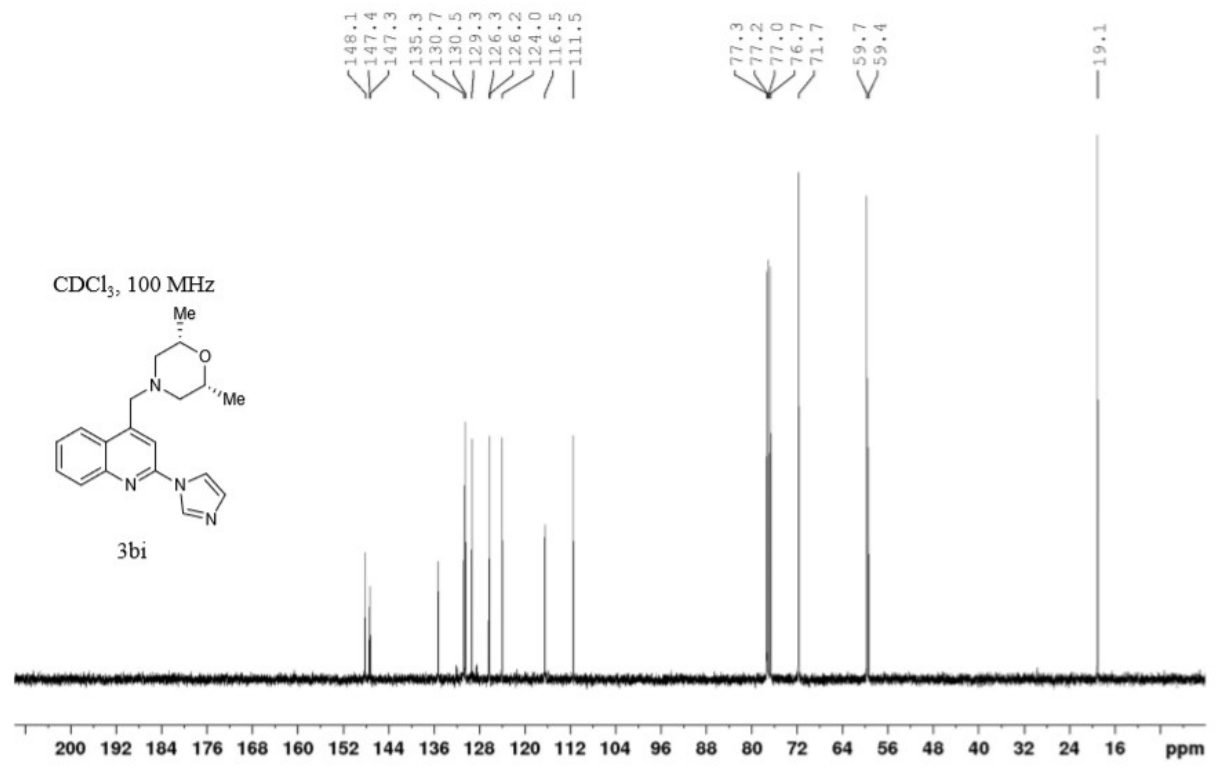

157.2
156.9
146.1
140.0
139.5
139.1
130.2
128.8
127.7
127.2
122.3
114.6
77.3
77.0
76.7
55.5
CDCl3, 100 MHz
OMe
3ae
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

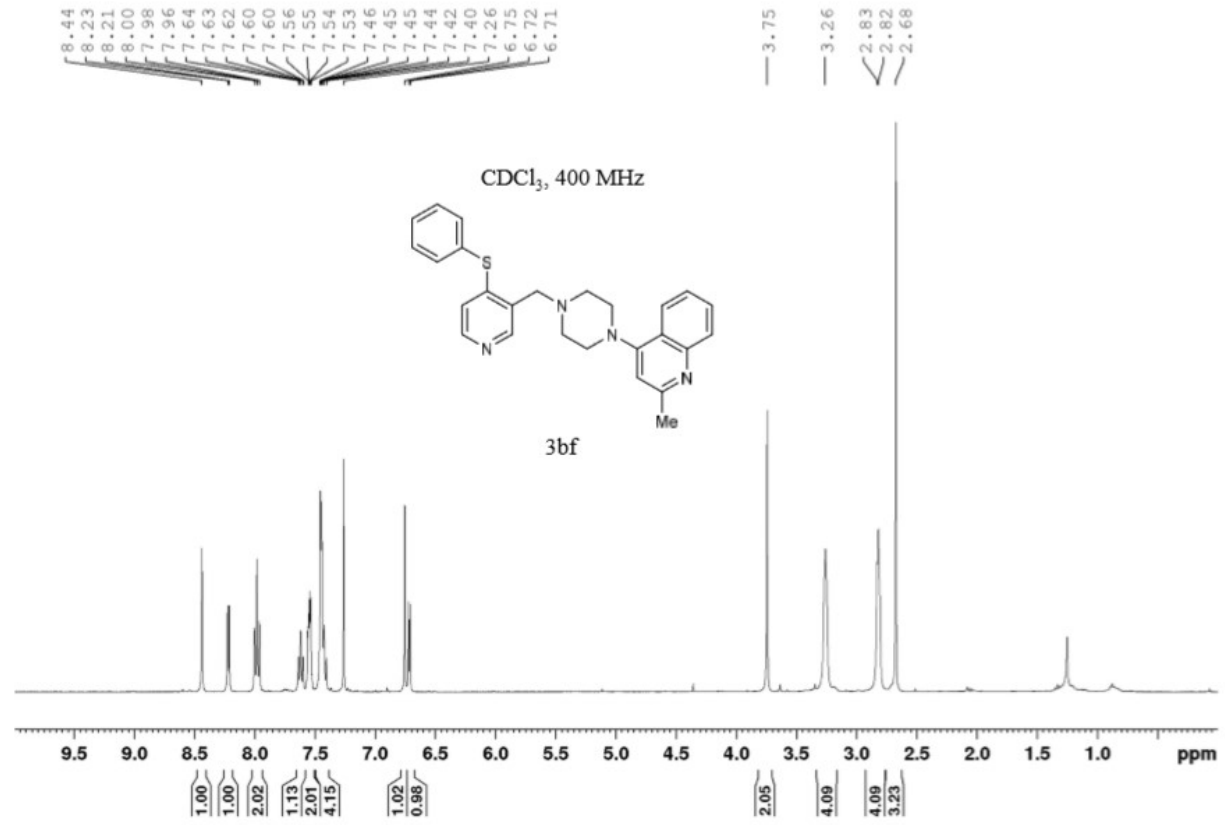

8.61
8.60
7.56
7.54
7.50
7.48
7.47
7.45
7.42
7.40
7.26
7.22
7.21
7.20
7.20
7.13
7.12
7.11
7.11
6.39
6.38
6.38
5.75
CDCl3, 400 MHz
CF3
CF3
3be
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
8.49
1.08
3.16
1.99
1.05

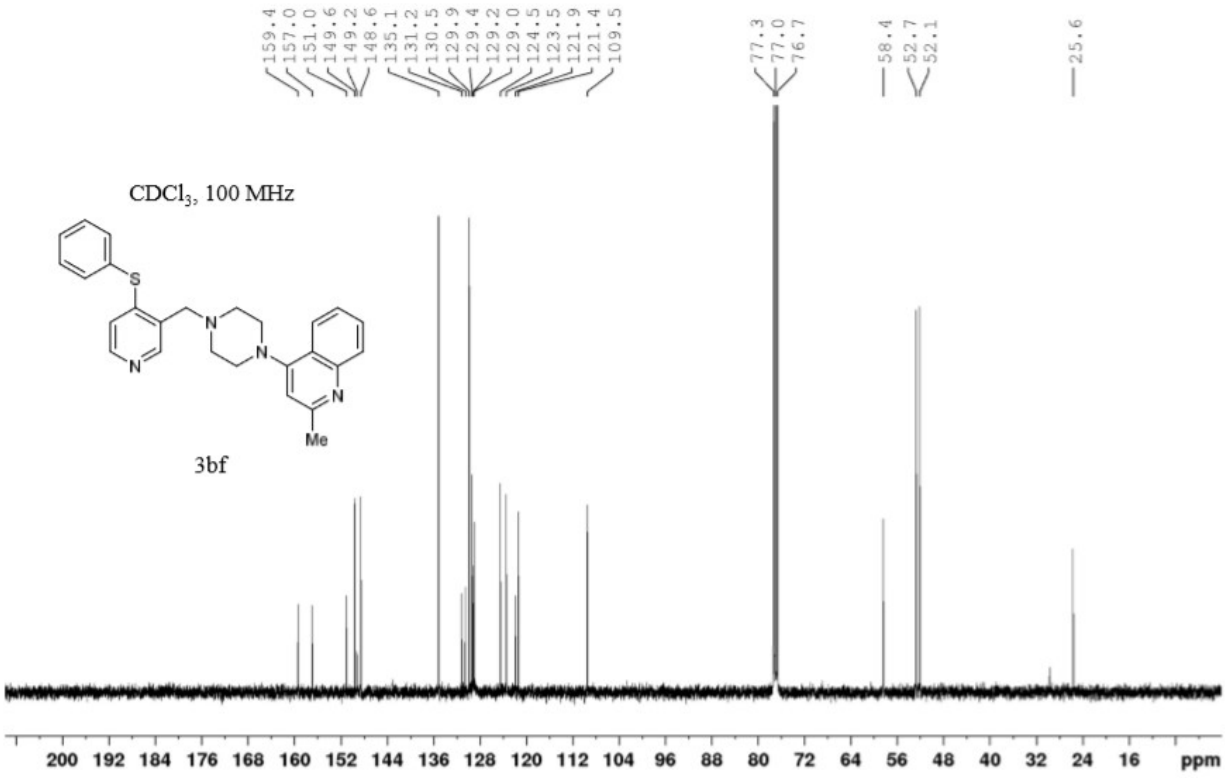

163.0
151.4
147.2
142.5
132.6
131.5
131.2
130.9
130.6
129.2
126.0
126.0
125.9
125.9
125.3
124.1
124.1
124.0
124.0
122.6
118.2
113.5
112.4
111.9
77.3
77.0
76.7
58.7
CDCl3, 100 MHz
CF3
N
N
CF3
3be
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

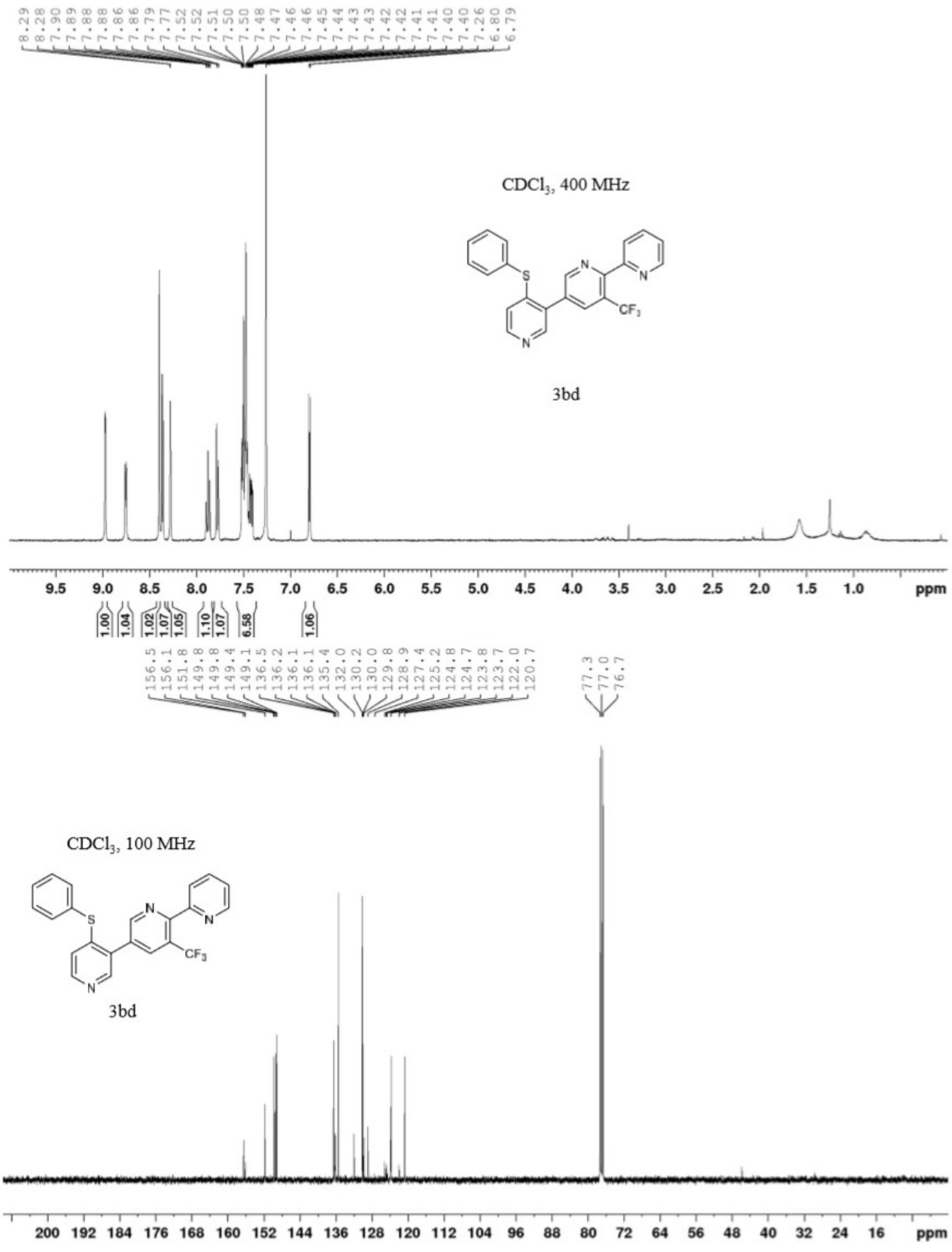

-62.57
CDCl3, 365 MHz
CF3
N
N
CF3
3be
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

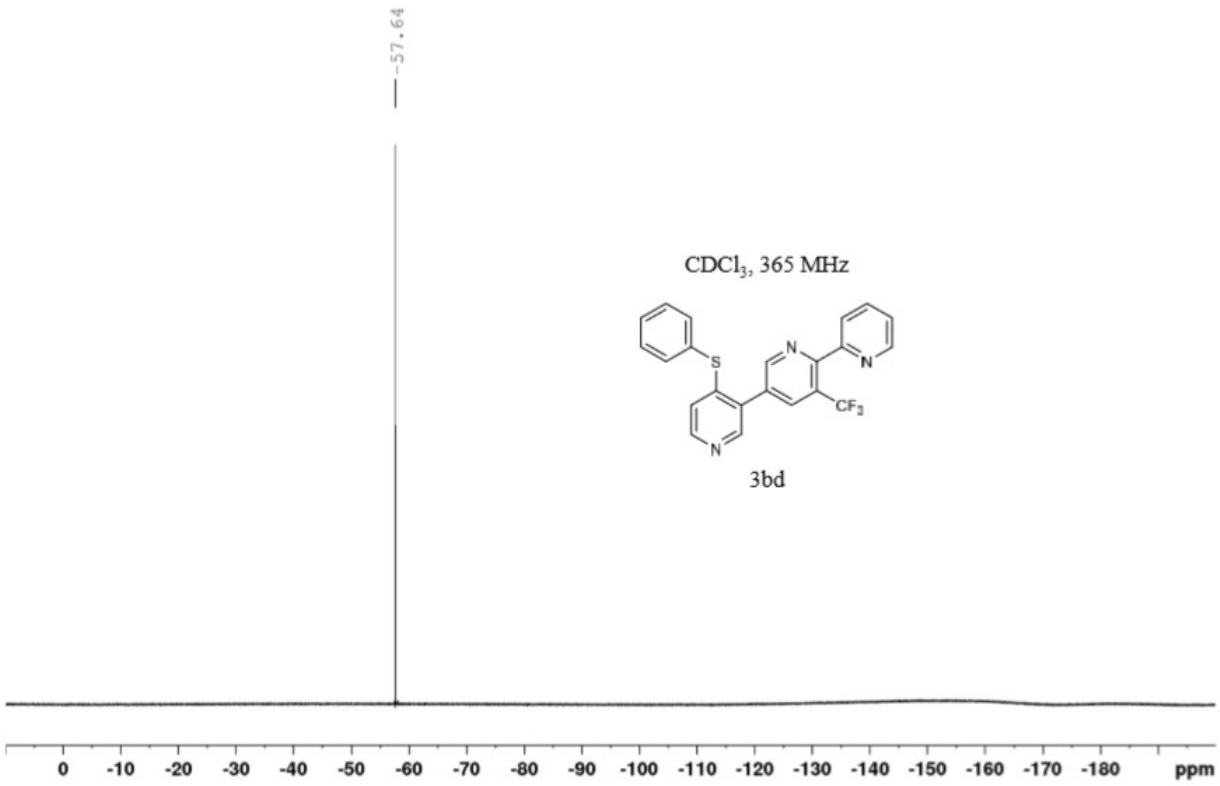

8.20
8.20
8.18
8.17
8.05
8.05
8.03
8.03
7.86
7.76
7.76
7.75
7.74
7.74
7.73
7.72
7.61
7.56
7.56
7.55
7.54
7.54
7.53
7.52
7.26
7.25
3.94
3.76
3.75
3.74
3.74
3.73
3.73
3.72
3.71
2.77
2.74
1.97
1.94
1.92
1.17
1.15
CDCl3, 400 MHz
Me
O
N
Me
N
N
N
3bi
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
0.99
0.98
1.06
1.03
1.11
0.97
2.02
2.14
2.19
2.06
6.47

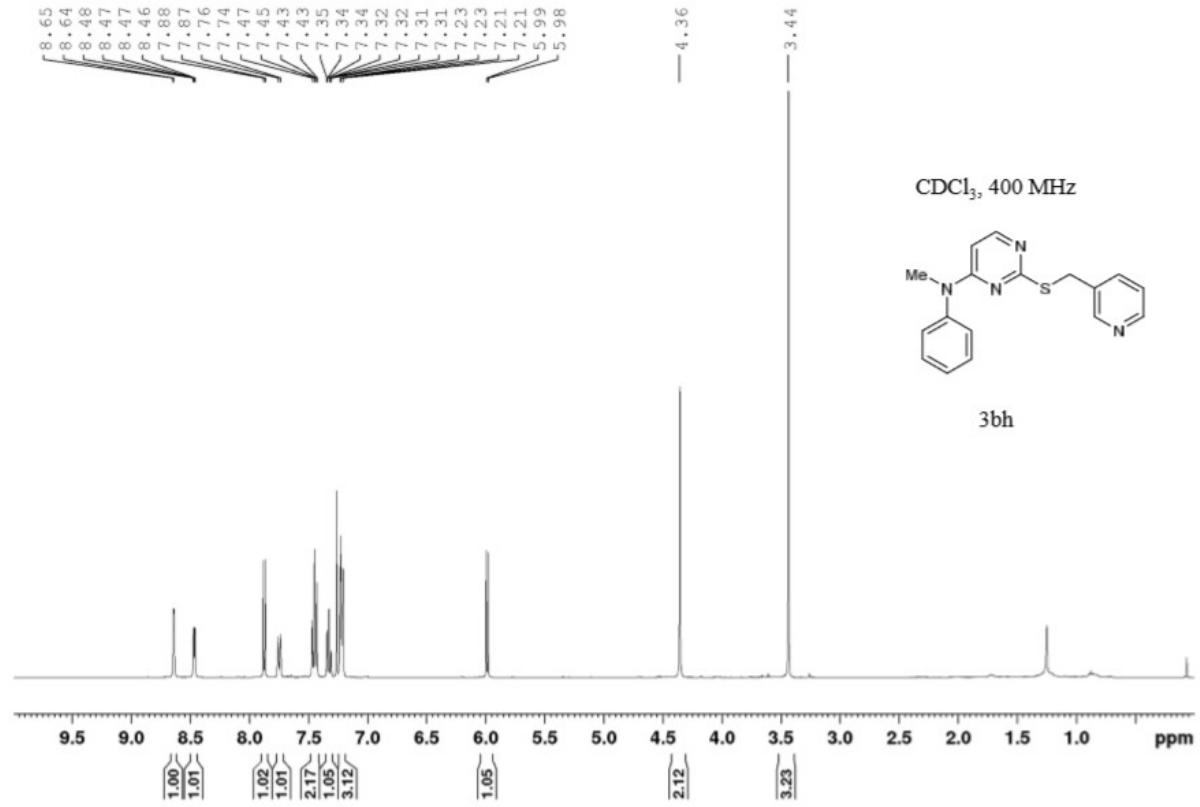

148.1
147.4
147.3
135.3
130.7
130.5
129.3
126.3
126.2
124.0
116.5
111.5
77.3
77.2
77.0
76.7
71.7
59.7
59.4
19.1
CDCl3, 100 MHz
Me
O
N
Me
N
N
N
3bi
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

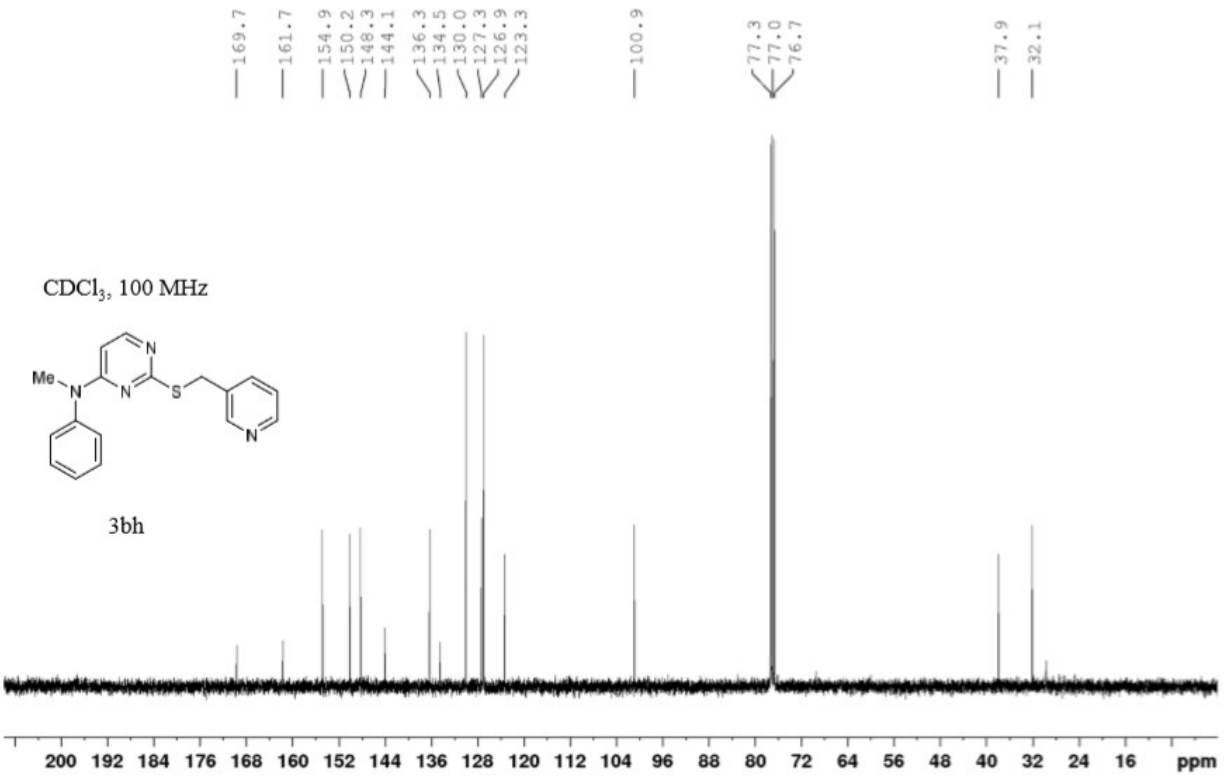

8.44
8.23
8.21
8.00
7.98
7.96
7.64
7.63
7.62
7.60
7.60
7.56
7.55
7.54
7.53
7.46
7.45
7.45
7.44
7.42
7.40
7.26
6.75
6.72
6.71
3.75
3.26
2.83
2.82
2.68
CDCl3, 400 MHz
S
N
N
N
N
Me
3bf
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.00
2.02
1.13
2.01
4.15
1.02
0.98
2.05
4.09
4.09
3.23

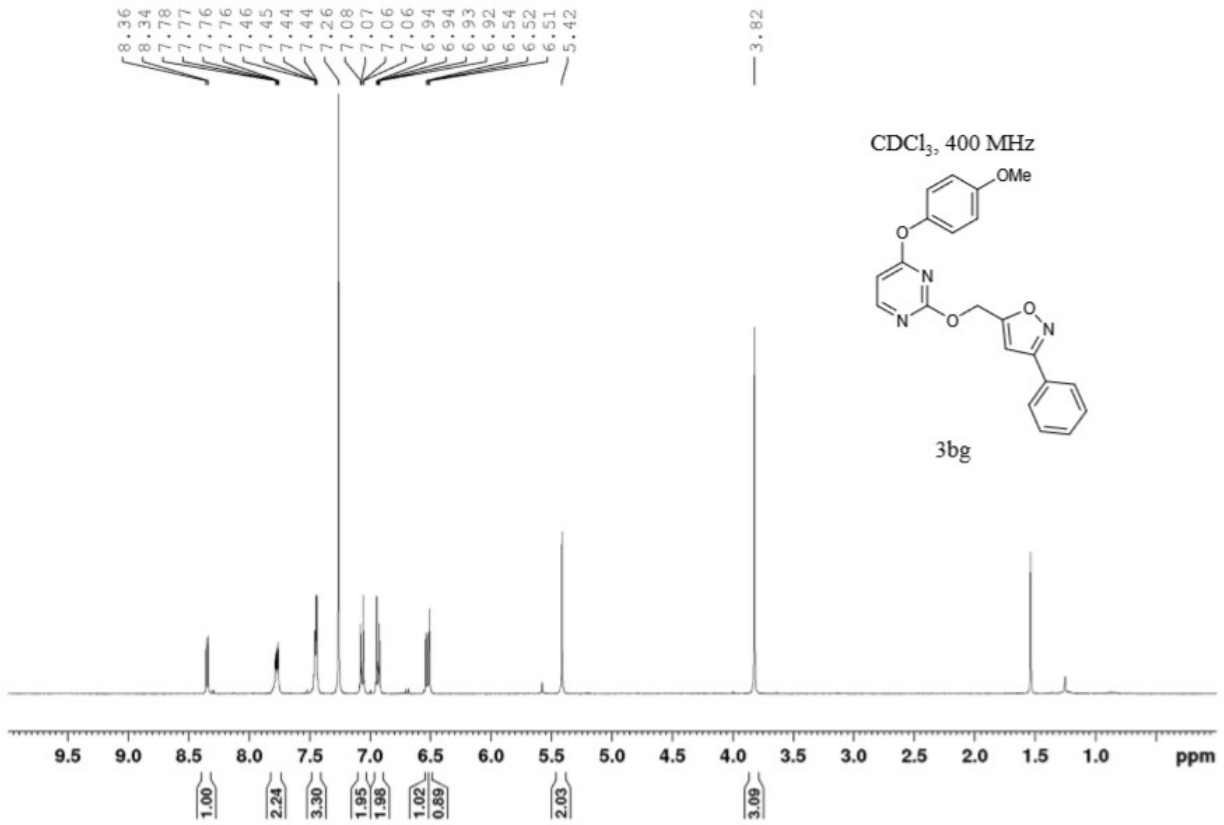

159.4
157.0
151.0
149.6
149.2
148.6
135.1
131.2
130.5
129.9
129.4
129.2
129.0
124.5
123.5
121.9
121.4
109.5
77.3
77.0
76.7
58.4
52.7
52.1
25.6
CDCl3, 100 MHz
S
N
N
N
N
Me
3bf
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

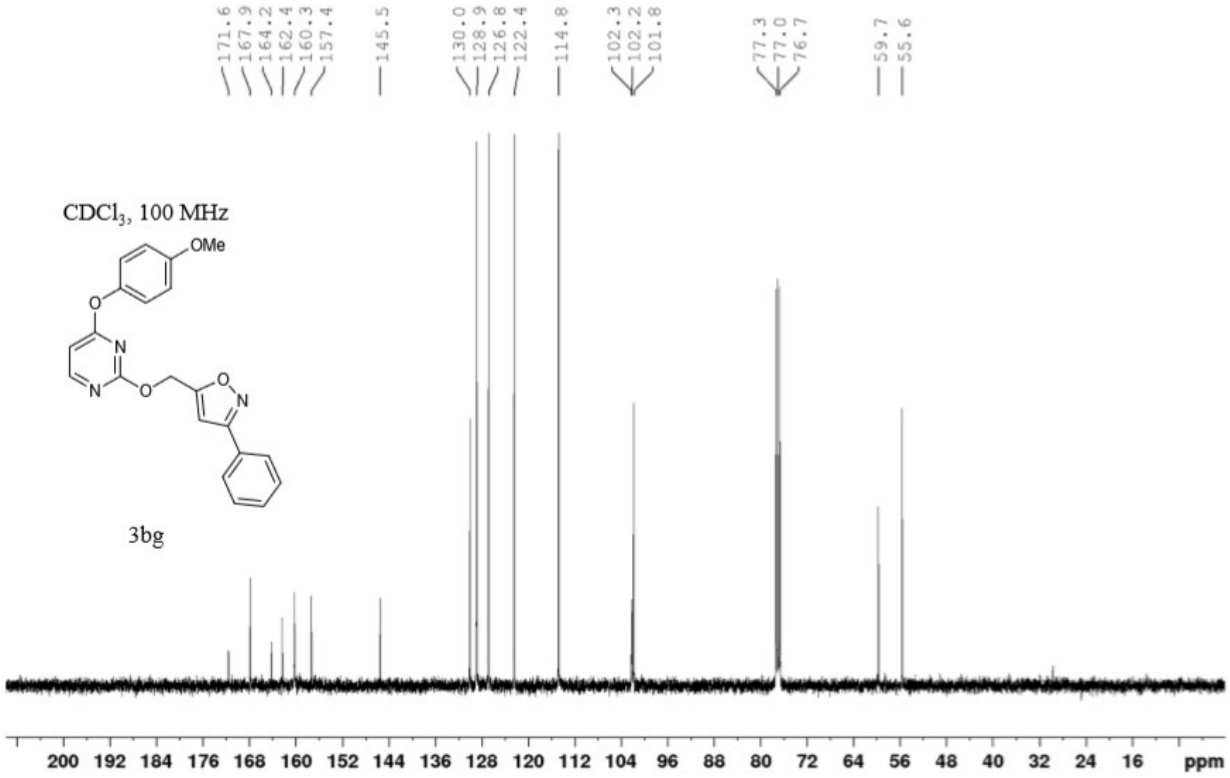

8.29
8.28
7.90
7.89
7.88
7.88
7.86
7.86
7.79
7.77
7.52
7.52
7.51
7.50
7.50
7.48
7.47
7.46
7.46
7.45
7.44
7.43
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.26
6.80
6.79
CDCl3, 400 MHz
S
N
N
N
CF3
3bd
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.04
1.02
1.07
1.05
1.10
1.07
6.58
1.06
156.5
156.1
151.8
149.8
149.8
149.4
149.1
136.5
136.2
136.1
136.1
135.4
132.0
130.2
130.0
129.8
128.9
127.4
125.2
124.8
124.7
123.8
123.7
122.0
120.7
77.3
77.0
76.7
CDCl3, 100 MHz
S
N
N
N
CF3
3bd
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

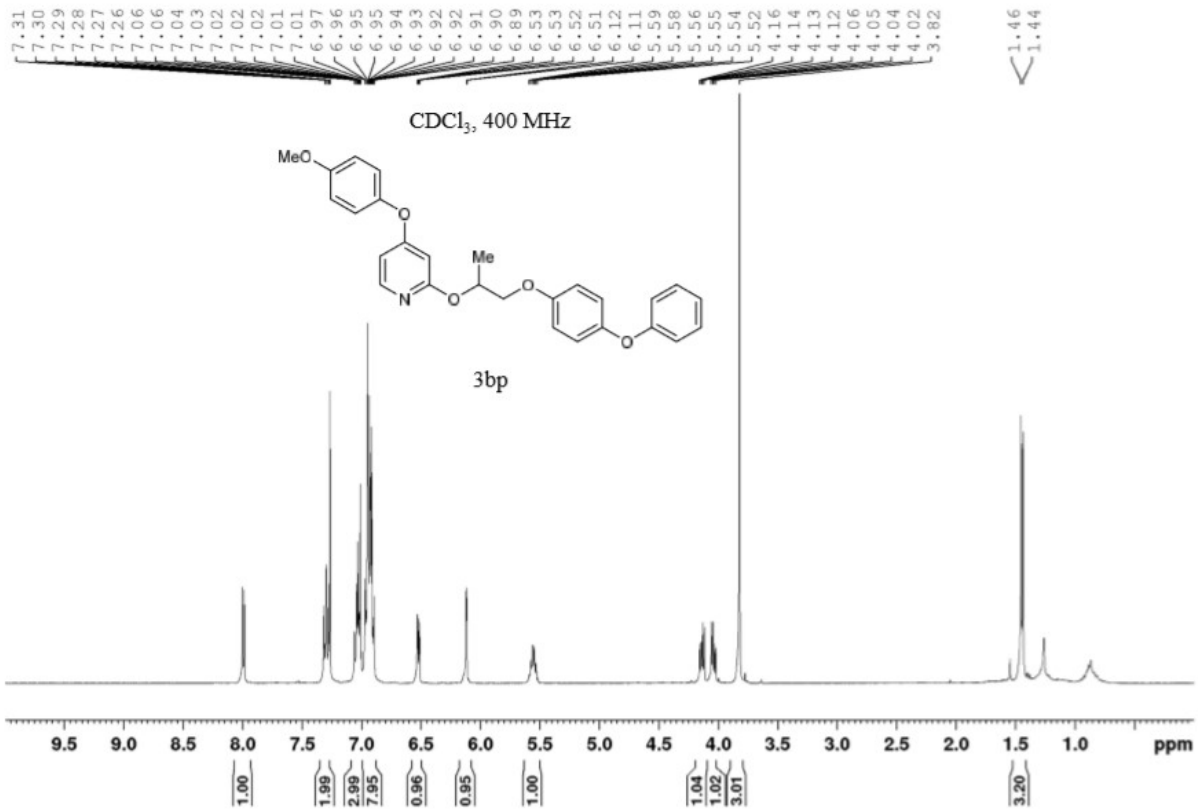

-57.64
CDCl3, 365 MHz
3bd
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm

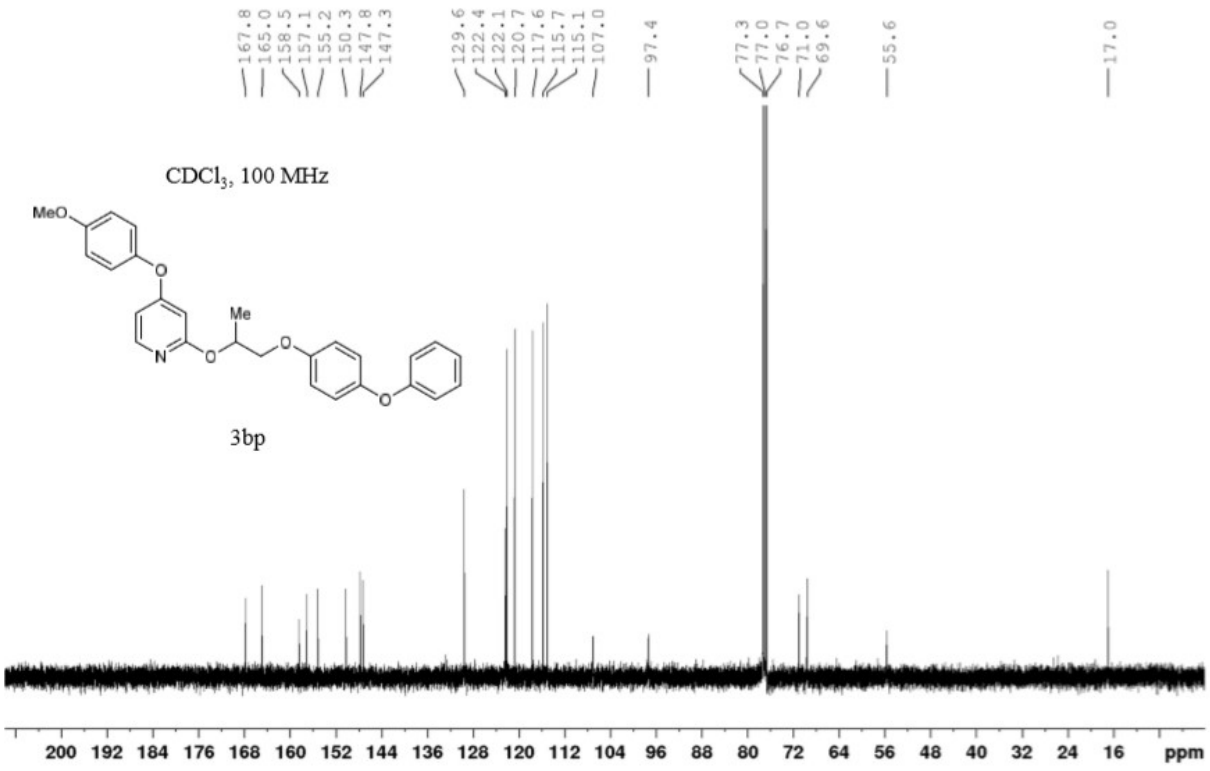

8.65
8.64
8.48
8.47
8.47
8.46
7.88
7.87
7.76
7.74
7.47
7.45
7.43
7.43
7.35
7.34
7.34
7.32
7.32
7.31
7.31
7.23
7.23
7.21
7.21
5.99
5.98
4.36
3.44
CDCl3, 400 MHz
3bh
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.01
1.02
1.01
2.17
1.05
3.12
1.05
2.12
3.23

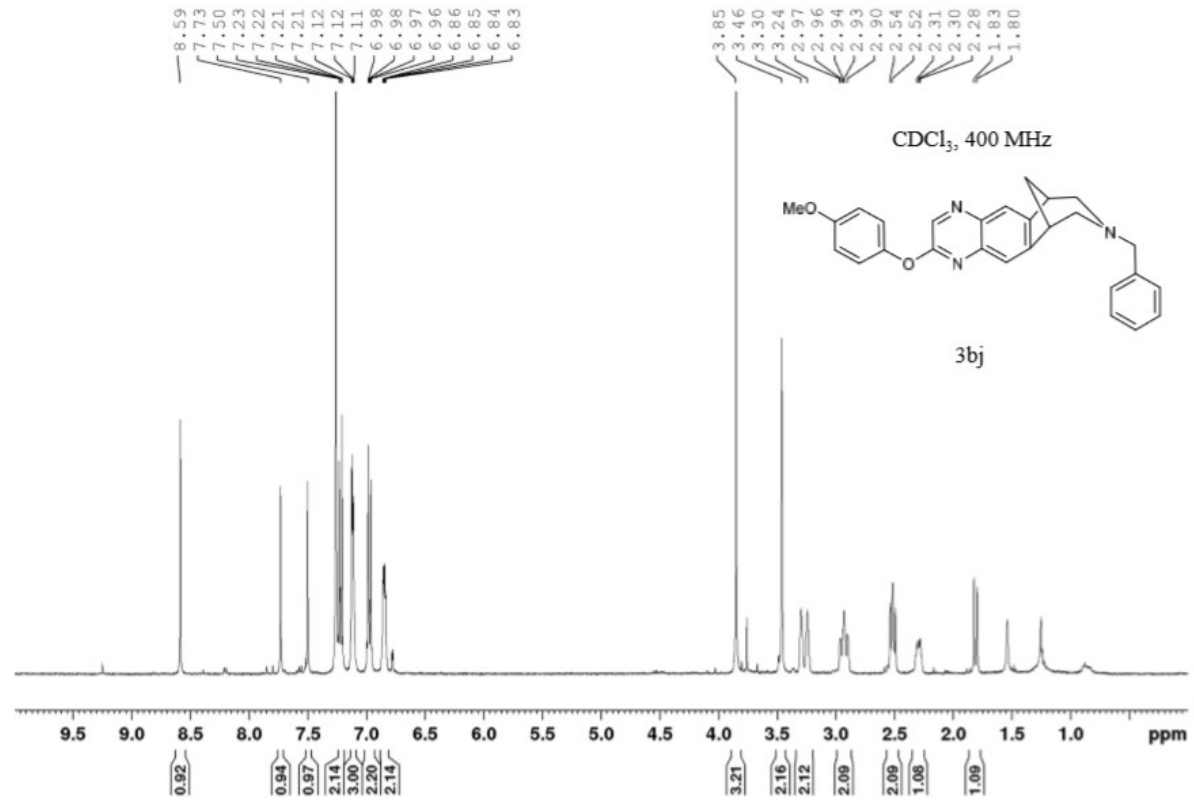

169.7
161.7
154.9
150.2
148.3
144.1
136.3
134.5
130.0
127.3
126.9
123.3
100.9
77.3
77.0
76.7
37.9
32.1
CDCl3, 100 MHz
Me
N
N
N
S
N
3bh
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

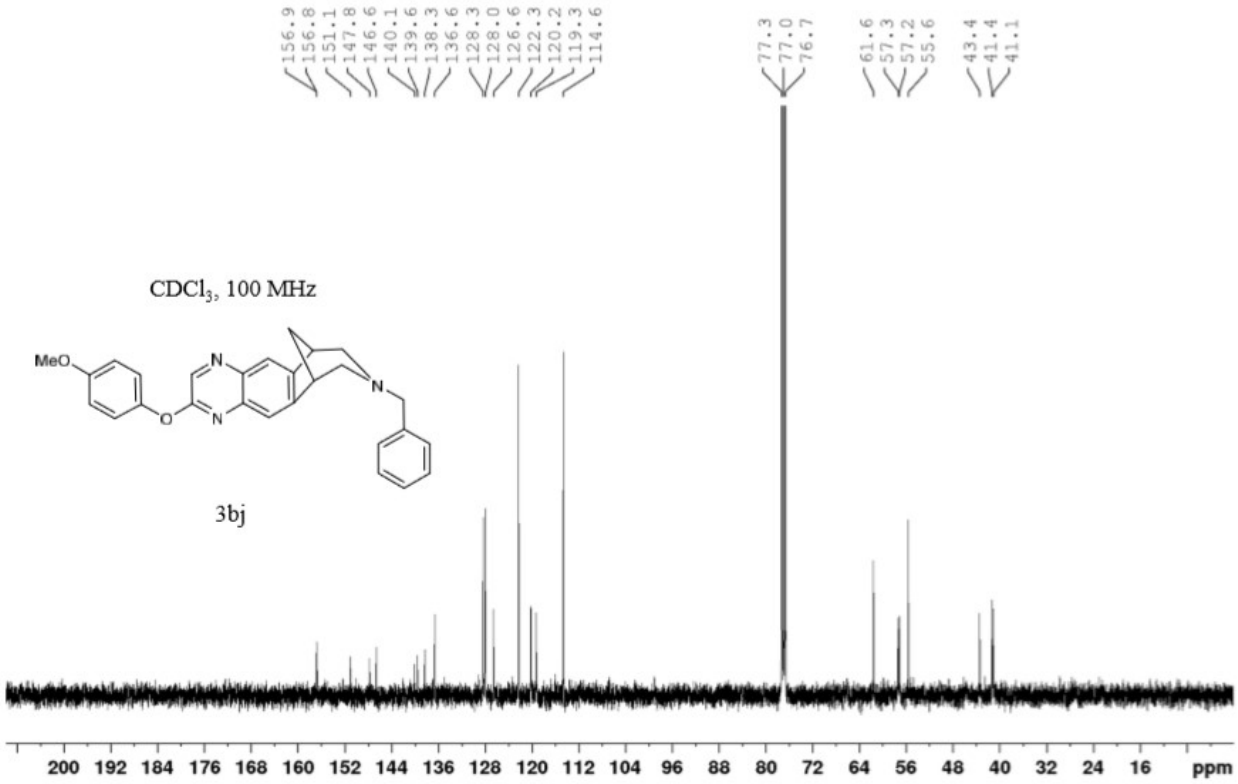

8.36
8.34
7.78
7.77
7.76
7.76
7.46
7.45
7.44
7.44
7.26
7.08
7.07
7.06
7.06
6.94
6.93
6.92
6.54
6.52
6.51
5.42
3.82
CDCl3, 400 MHz
OMe
O
N
N
O
O
N
3bg
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.24
3.30
1.95
1.98
1.02
0.89
2.03
3.09

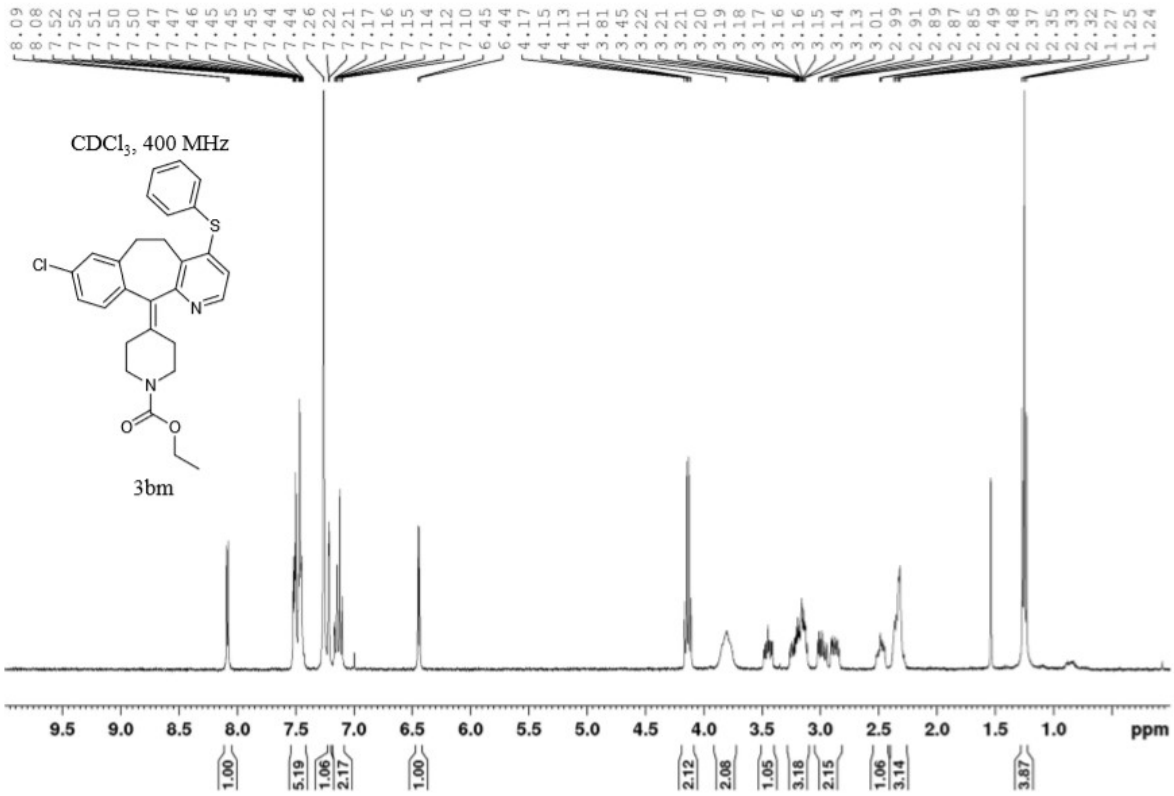

171.6
167.9
164.2
162.4
160.3
157.4
145.5
130.0
128.9
126.8
122.4
114.8
102.3
102.2
101.8
77.3
77.0
76.7
59.7
55.6
CDCl3, 100 MHz
OMe
3bg
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

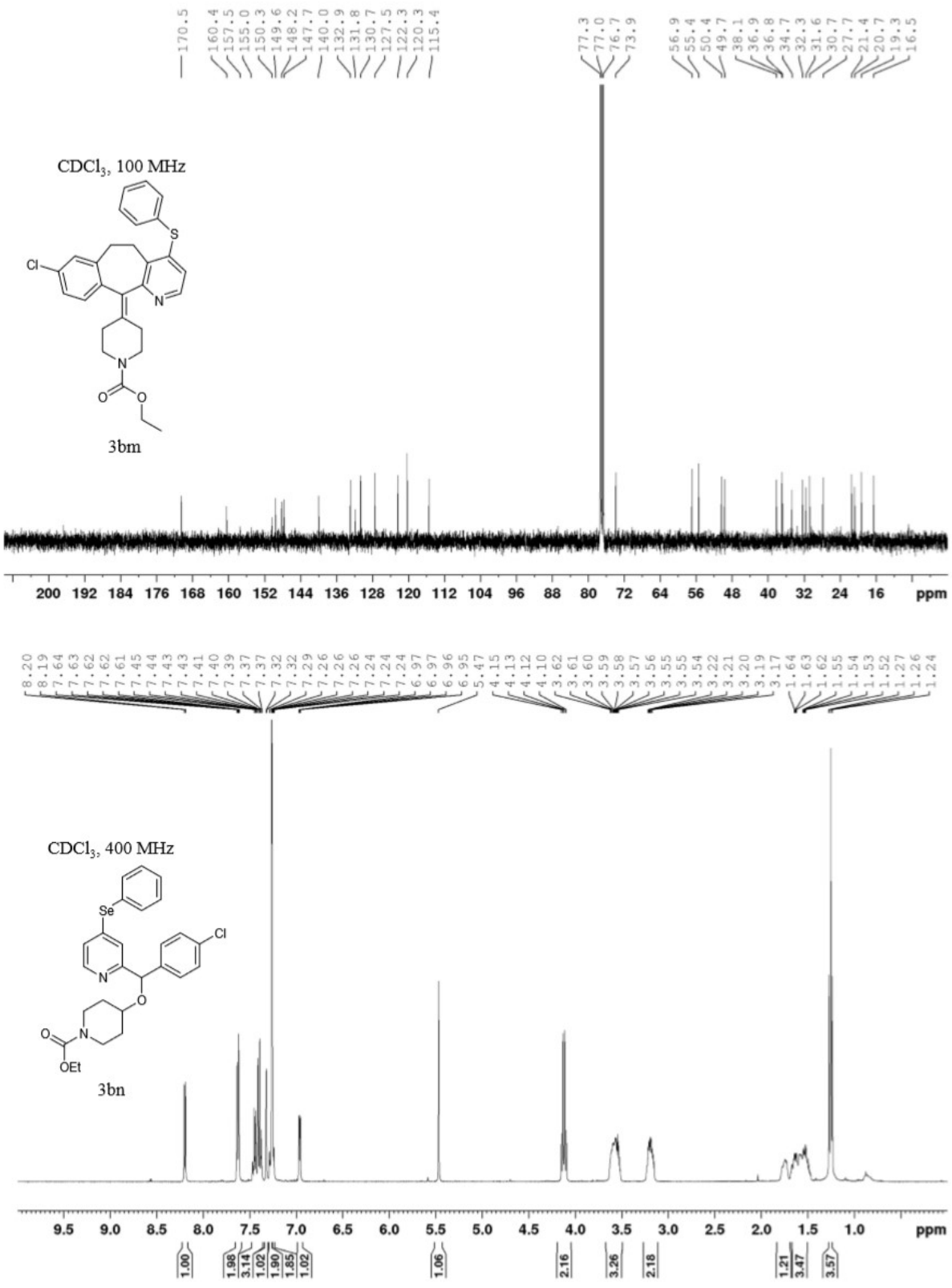

7.31
7.30
7.29
7.28
7.27
7.26
7.06
7.06
7.04
7.03
7.02
7.02
7.02
7.01
7.01
6.97
6.96
6.95
6.95
6.94
6.93
6.92
6.92
6.91
6.90
6.89
6.53
6.53
6.52
6.51
6.12
6.11
5.59
5.58
5.56
5.55
5.54
5.52
4.16
4.14
4.13
4.12
4.06
4.05
4.04
4.02
3.82
1.46
1.44
CDCl3, 400 MHz
MeO
Me
3bp
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.99
2.99
7.95
0.96
0.95
1.00
1.04
1.02
3.01
3.20

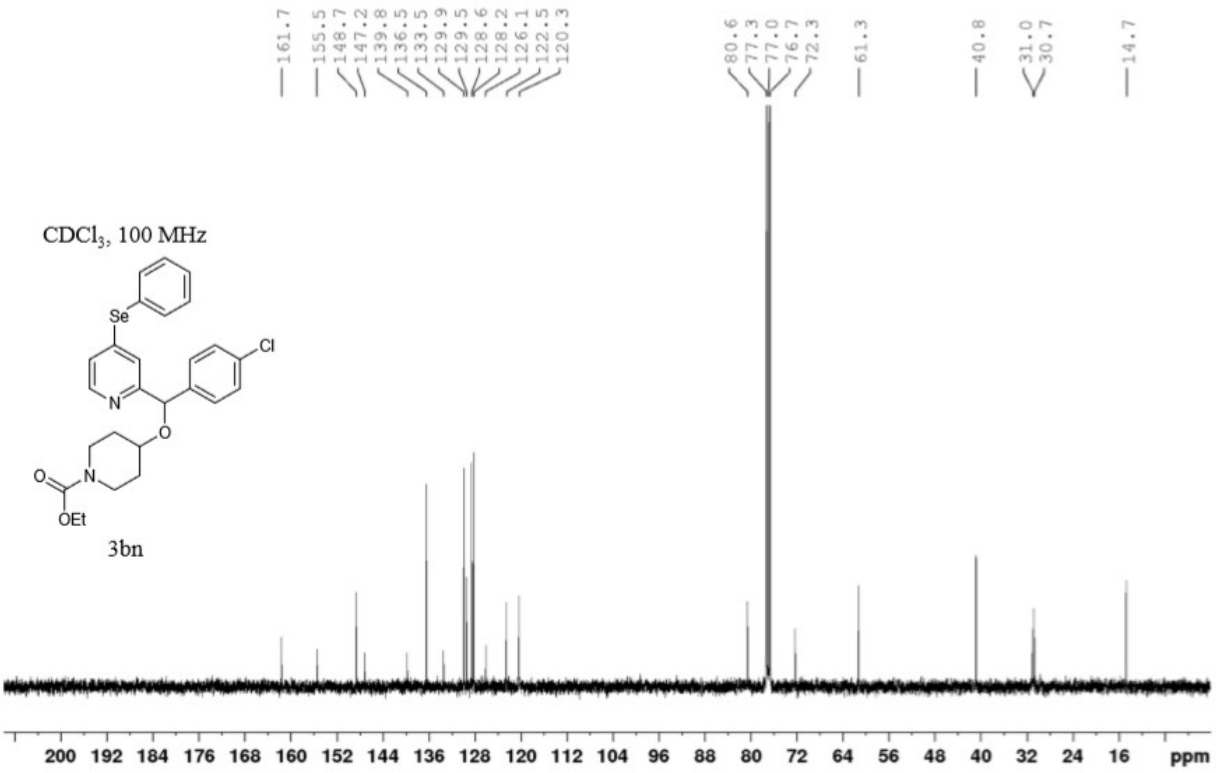

167.8
165.0
158.5
157.1
155.2
150.3
147.8
147.3
129.6
122.4
122.1
120.7
117.6
115.7
115.1
107.0
97.4
77.3
77.0
76.7
71.0
69.6
55.6
17.0
CDCl3, 100 MHz
MeO
Me
3bp
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

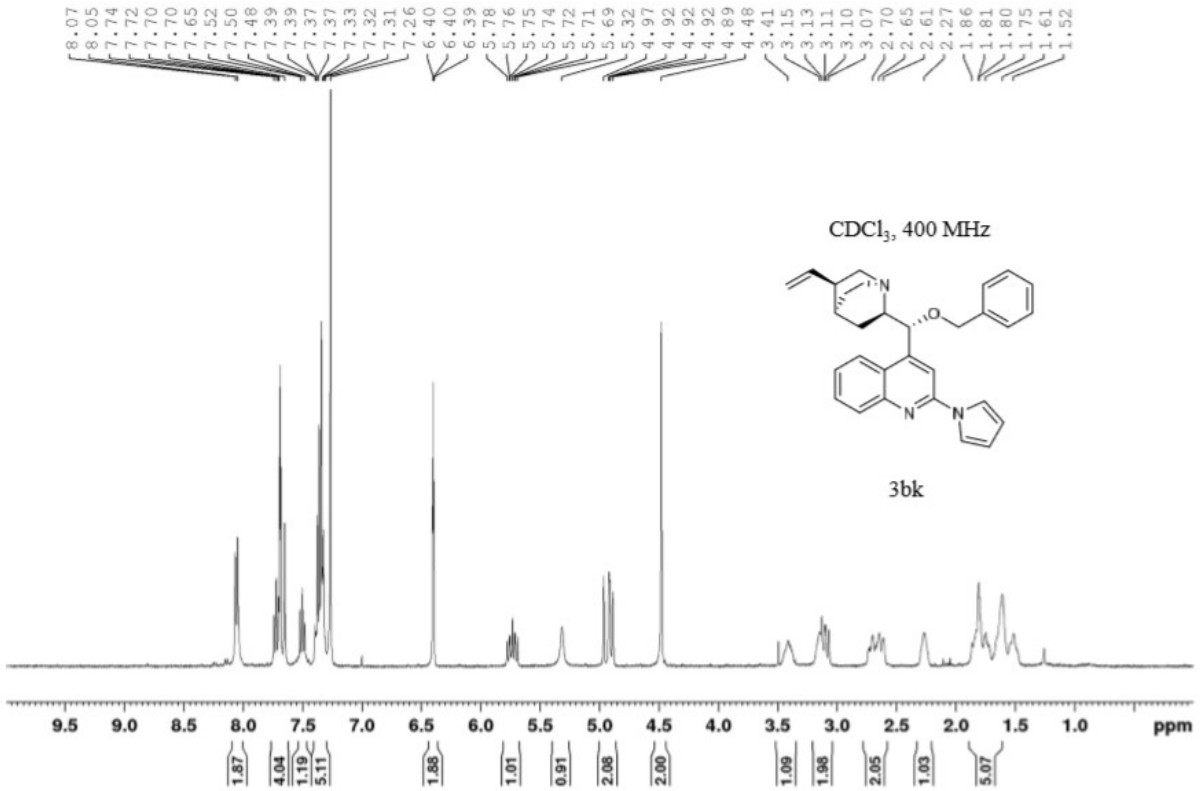

8.59
7.73
7.50
7.23
7.22
7.21
7.21
7.12
7.12
7.11
6.98
6.98
6.97
6.96
6.86
6.85
6.84
6.83
3.85
3.46
3.30
3.24
2.97
2.96
2.94
2.93
2.90
2.54
2.52
2.31
2.30
2.28
1.83
1.80
CDCl3, 400 MHz
MeO
3bj
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.92
0.84
0.97
2.14
3.00
2.20
2.14
3.21
2.16
2.12
2.09
2.09
1.08
1.09

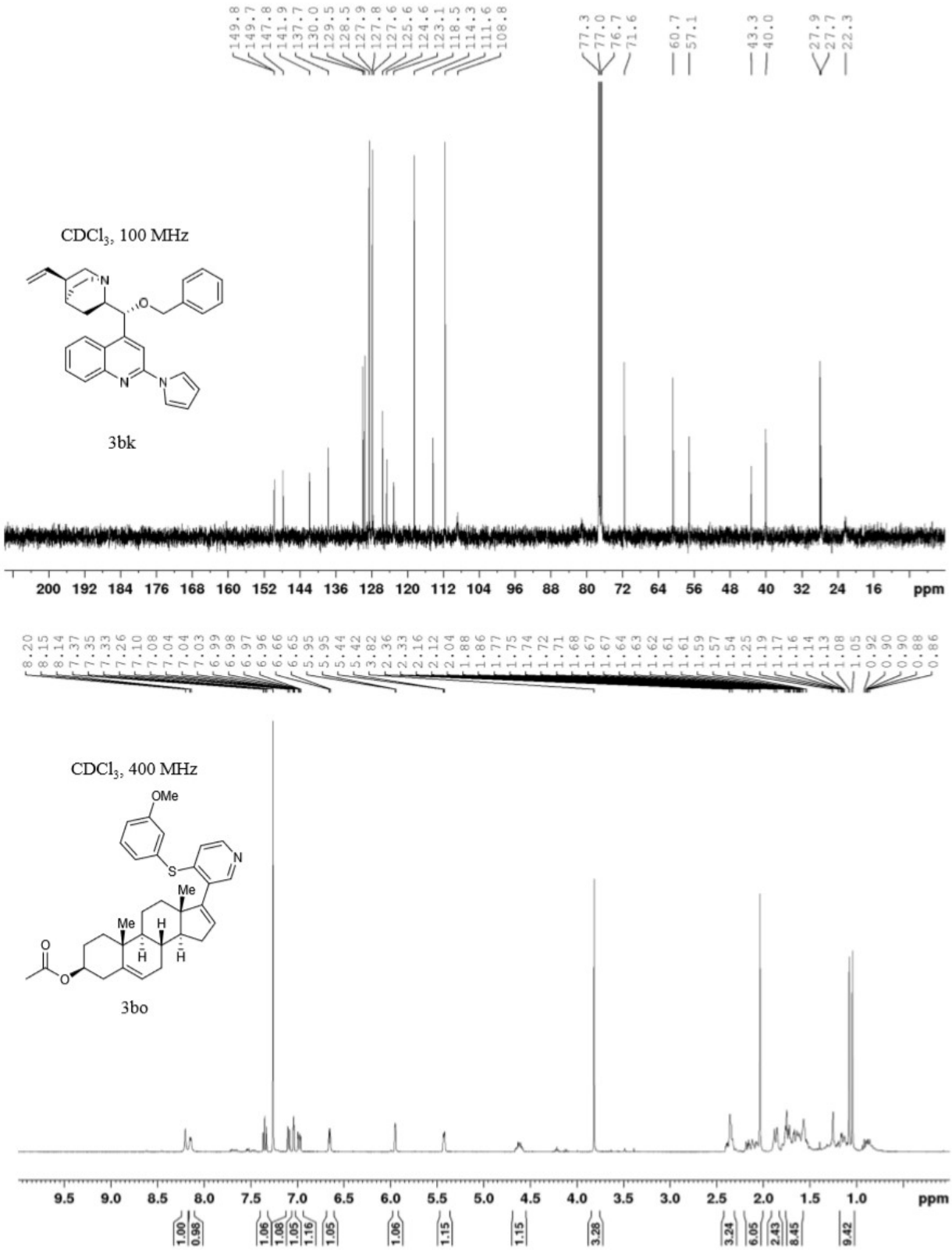

156.9
156.8
151.1
147.8
146.6
140.1
139.6
138.3
136.6
128.3
128.0
126.6
122.3
120.2
119.3
114.6
77.3
77.0
76.7
61.6
57.3
57.2
55.6
43.4
41.4
41.1
CDCl3, 100 MHz
MeO
N
O
N
N
3bj
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

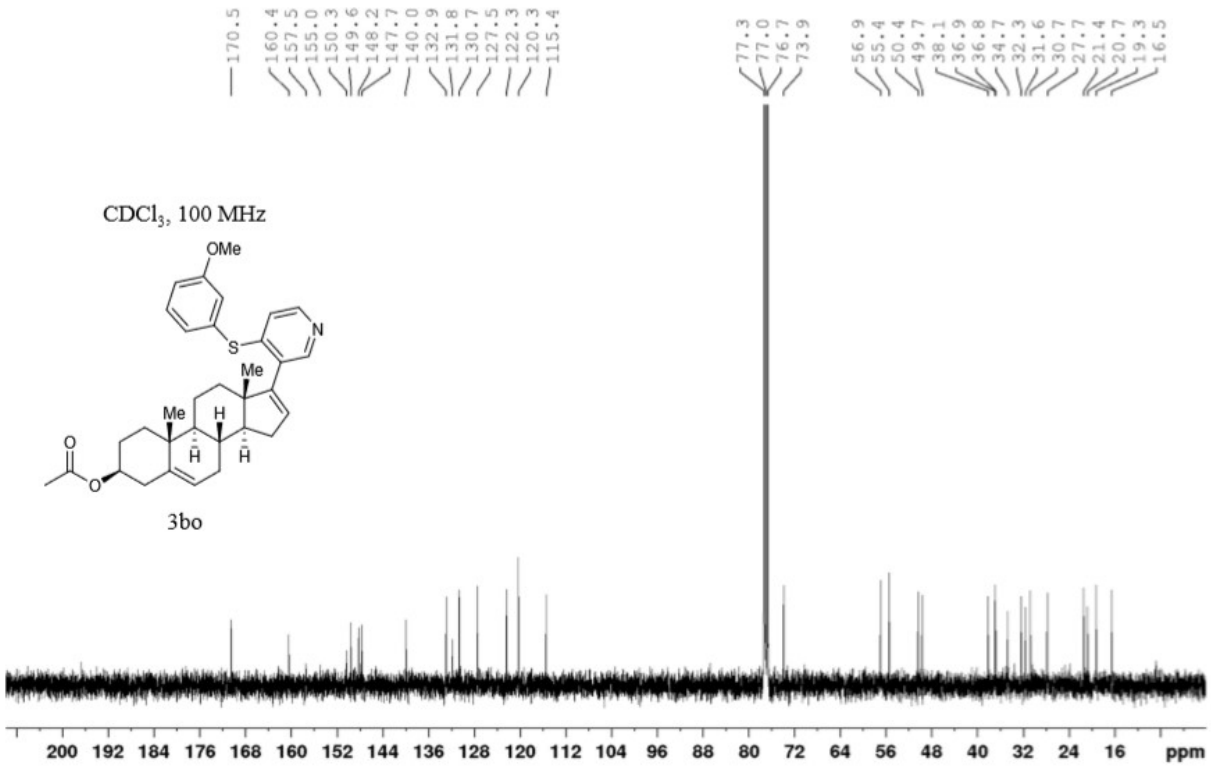

8.09
8.08
7.52
7.52
7.51
7.50
7.50
7.47
7.47
7.46
7.45
7.45
7.45
7.44
7.44
7.26
7.22
7.21
7.17
7.16
7.15
7.14
7.12
7.10
6.45
6.44
4.17
4.15
4.13
4.11
3.81
3.45
3.22
3.21
3.21
3.20
3.19
3.18
3.17
3.16
3.16
3.15
3.14
3.13
3.01
2.99
2.91
2.89
2.87
2.85
2.49
2.48
2.37
2.35
2.33
2.32
1.27
1.25
1.24
CDCl3, 400 MHz
S
Cl
N
N
O
O
3bm
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
5.19
1.06
2.17
1.00
2.12
2.08
1.05
3.18
2.15
1.06
3.14
3.87

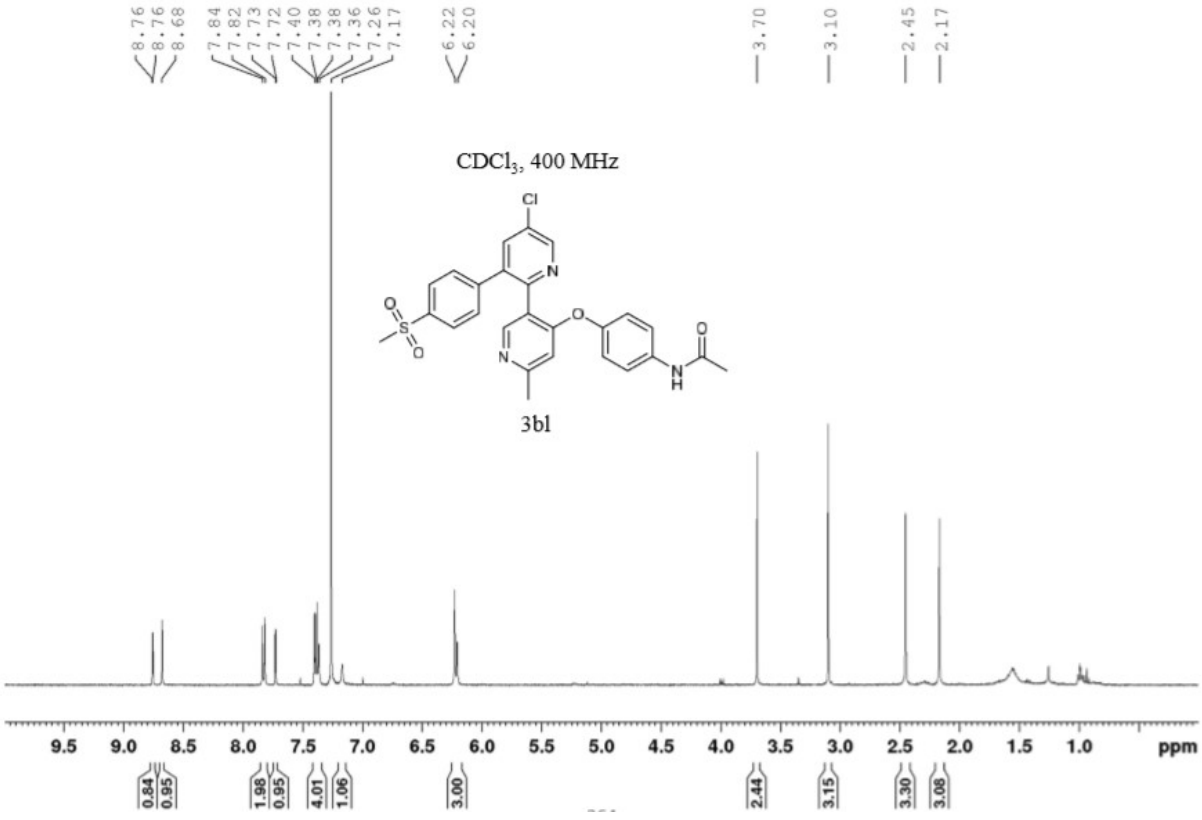

CDCl3, 100 MHz
3bm
CDCl3, 400 MHz
3bn
ppm

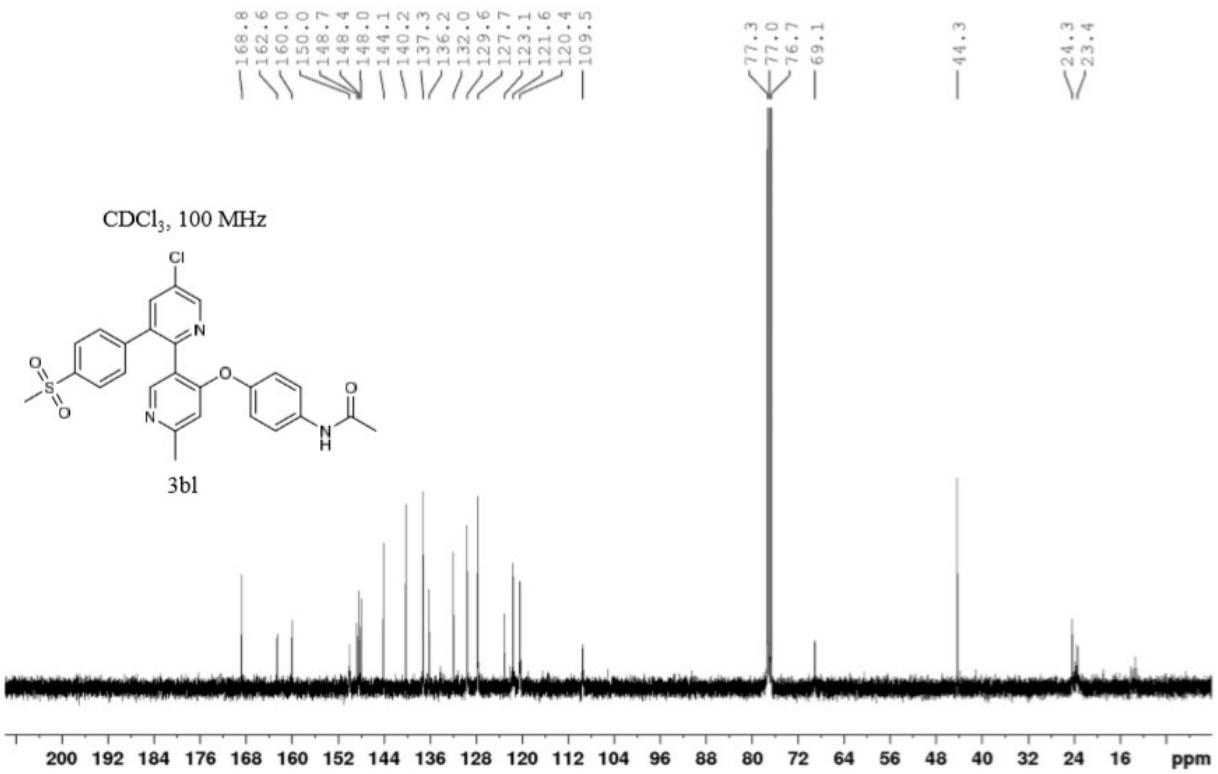

161.7
155.5
148.7
147.2
139.8
136.5
133.5
129.9
129.5
128.6
128.2
126.1
122.5
120.3
80.6
77.3
77.0
76.7
72.3
61.3
40.8
31.0
30.7
14.7
CDCl3, 100 MHz
Se
Cl
N
O
O
N
OEt
3bn
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

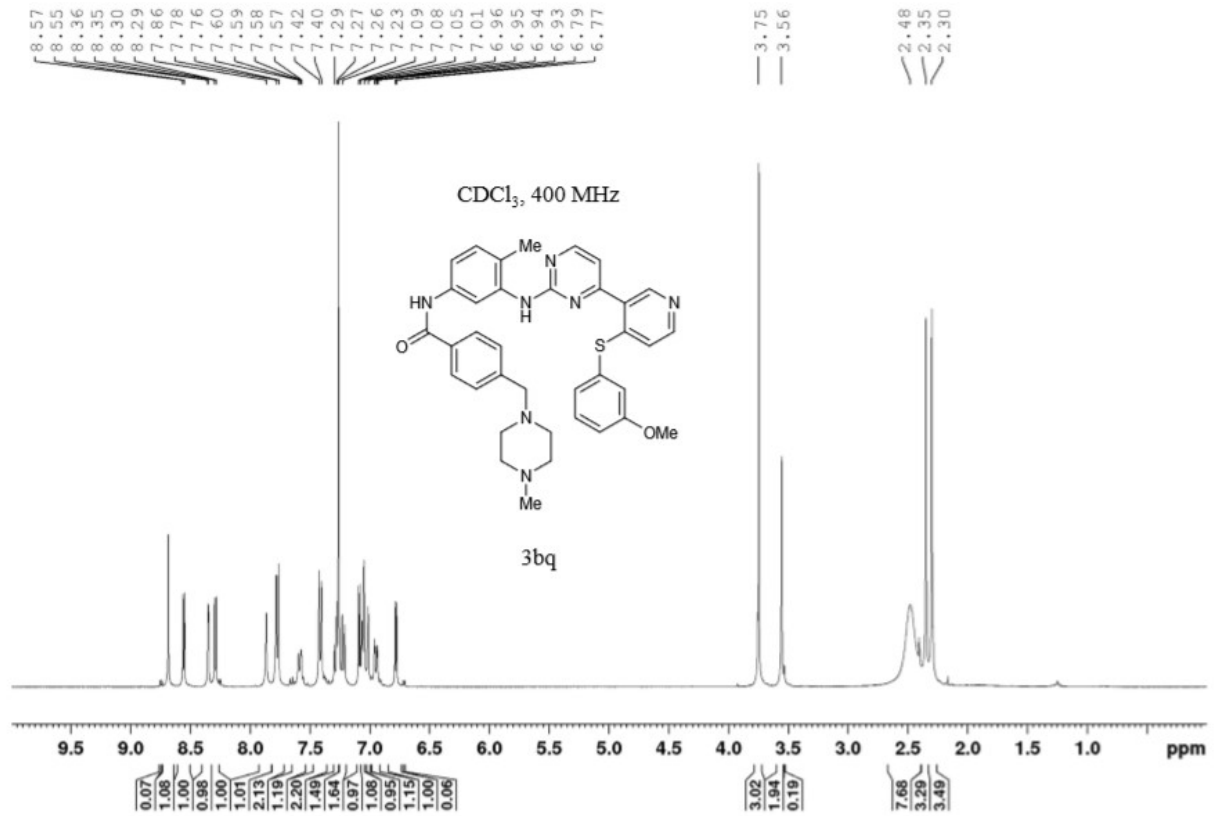

8.07
8.05
7.74
7.72
7.70
7.70
7.65
7.52
7.50
7.48
7.39
7.39
7.37
7.33
7.32
7.31
7.26
6.40
6.40
6.39
5.78
5.76
5.75
5.74
5.72
5.71
5.69
5.32
4.97
4.92
4.92
4.92
4.89
4.48
3.41
3.15
3.13
3.11
3.10
3.07
2.70
2.65
2.61
2.27
1.86
1.81
1.80
1.75
1.61
1.52
CDCl3, 400 MHz
N
O
N
N
3bk
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.87
4.04
1.19
5.11
1.88
1.01
0.91
2.08
2.00
1.09
1.98
2.05
1.03
5.07

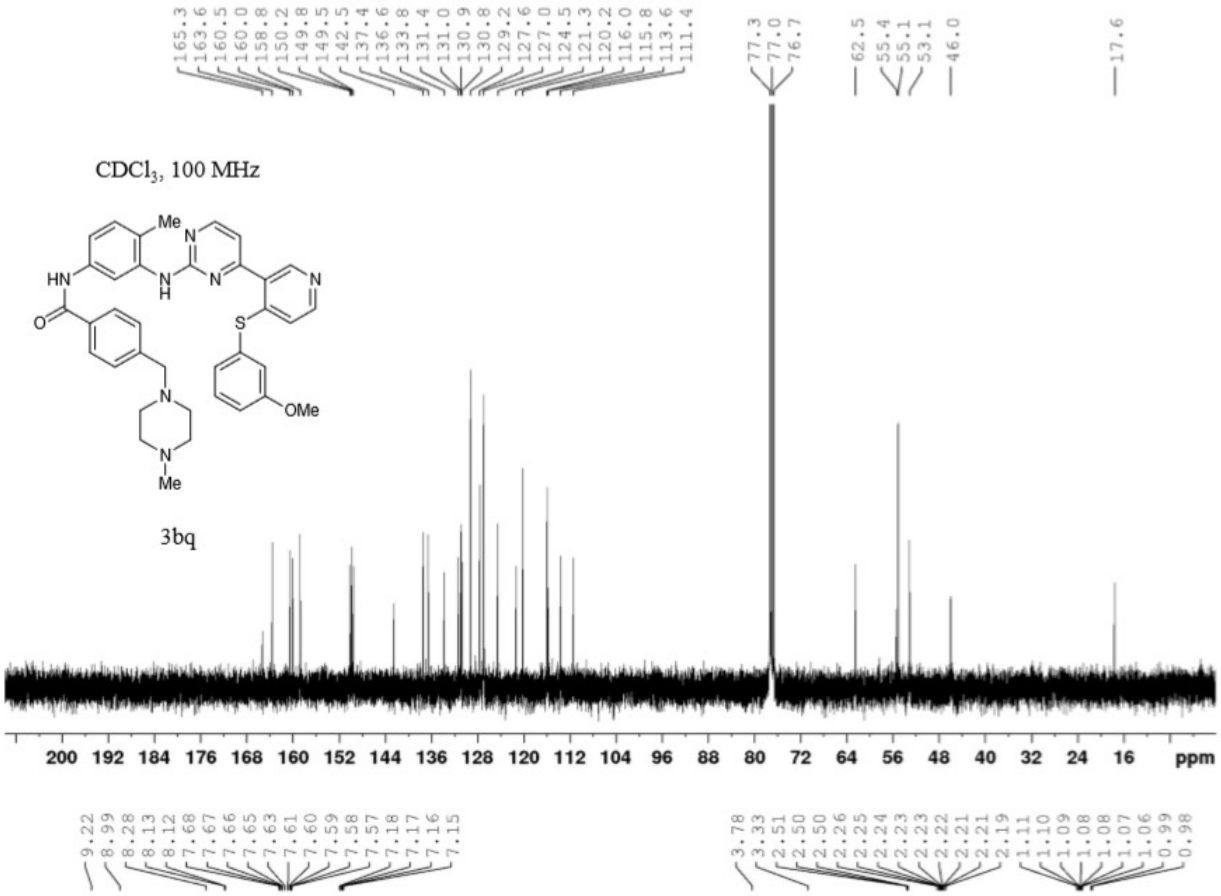

149.8
149.7
147.8
141.9
137.7
130.0
129.5
128.5
127.9
127.8
127.6
125.6
124.6
123.1
118.5
114.3
111.6
108.8
77.3
77.0
76.7
71.6
60.7
57.1
43.3
40.0
27.9
27.7
22.3
CDCl3, 100 MHz
3bk
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm
8.20
8.15
8.14
7.37
7.35
7.33
7.26
7.10
7.08
7.04
7.04
7.03
6.99
6.98
6.97
6.96
6.66
6.65
5.95
5.95
5.44
5.42
3.82
2.36
2.33
2.16
2.12
2.04
1.88
1.86
1.77
1.75
1.74
1.72
1.71
1.68
1.67
1.67
1.64
1.63
1.62
1.61
1.61
1.59
1.57
1.54
1.25
1.19
1.17
1.16
1.14
1.13
1.08
1.05
0.92
0.90
0.90
0.88
0.86
CDCl3, 400 MHz
OMe
S
N
Me
Me
H
H
H
O
O
3bo
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
0.98
1.06
1.08
1.05
1.16
1.05
1.06
1.15
1.15
3.28
3.24
6.05
2.43
8.45
9.42

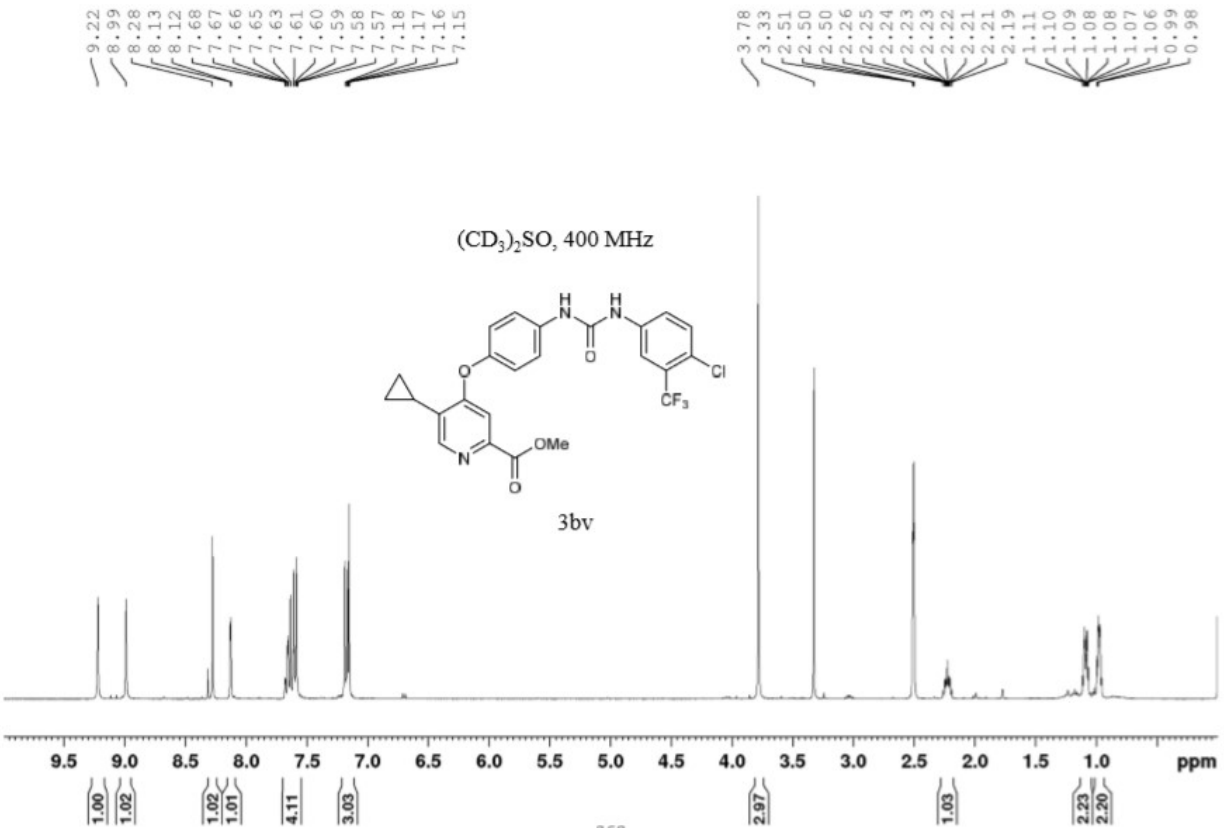

170.5
160.4
157.5
155.0
150.3
149.6
148.2
147.7
140.0
132.9
131.8
130.7
127.5
122.3
120.3
115.4
77.3
77.0
76.7
73.9
56.9
55.4
50.4
49.7
38.1
36.9
36.8
34.7
32.3
31.6
30.7
27.7
21.4
20.7
19.3
16.5
CDCl3, 100 MHz
OMe
S
N
Me
Me
H
H
H
O
O
3bo
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

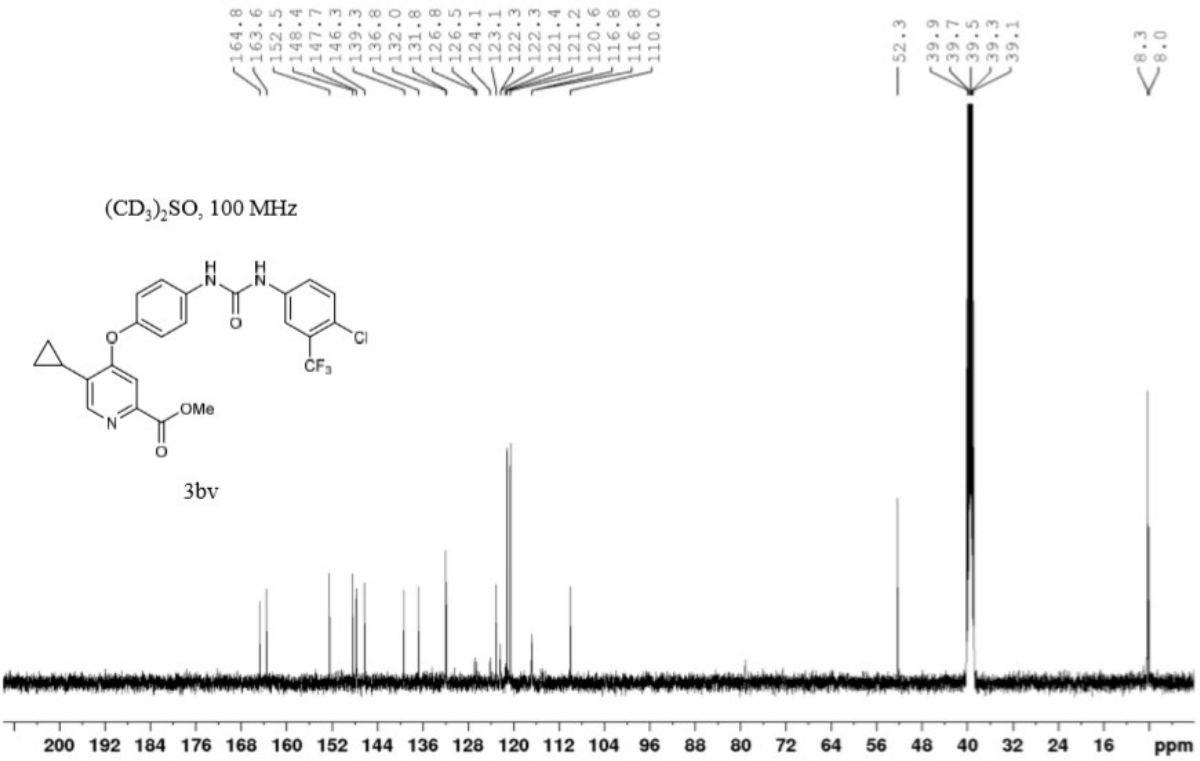

8.76
8.76
8.68
7.84
7.82
7.73
7.72
7.40
7.38
7.38
7.36
7.26
7.17
6.22
6.20
3.70
3.10
2.45
2.17
CDCl3, 400 MHz
Cl
N
O
S
O
O
N
O
NH
3bl
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.84
0.95
1.98
0.95
4.01
1.06
3.00
2.44
3.15
3.30
3.08

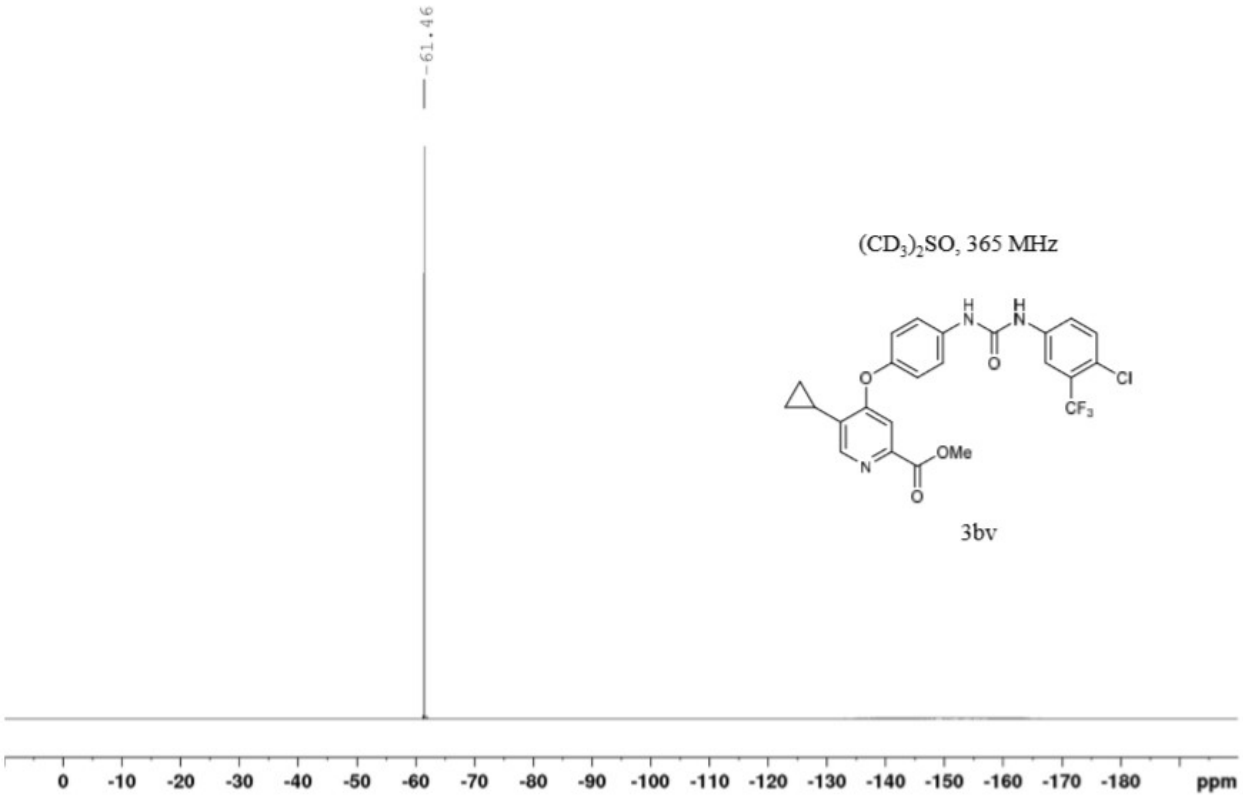

168.8
162.6
160.0
150.0
148.7
148.4
148.0
144.1
140.2
137.3
136.2
132.0
129.6
127.7
123.1
121.6
120.4
109.5
77.3
77.0
76.7
69.1
44.3
24.3
23.4
CDCl3, 100 MHz
Cl
N
O
S
O
O
N
O
N
H
3bl
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.57
8.55
8.36
8.35
8.30
8.29
7.86
7.78
7.76
7.60
7.59
7.58
7.57
7.42
7.40
7.29
7.27
7.26
7.23
7.09
7.08
7.05
7.01
6.96
6.95
6.94
6.93
6.79
6.77
3.75
3.56
2.48
2.35
2.30
CDCl3, 400 MHz
Me
N
HN
N
H
N
N
O
S
N
OMe
N
Me
3bq
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.07
1.08
1.00
0.98
1.00
1.01
2.13
1.19
2.20
1.49
1.64
0.97
1.06
0.95
1.15
1.00
0.06
3.02
1.94
0.19
7.66
3.29
3.49


165.3
163.6
160.5
160.0
158.8
150.2
149.8
149.5
142.5
137.4
136.6
133.8
131.4
131.0
130.9
130.8
129.2
127.6
127.0
124.5
121.3
120.2
116.0
115.8
113.6
111.4
77.3
77.0
76.7
62.5
55.4
55.1
53.1
46.0
17.6
CDCl3, 100 MHz
3bq
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


9.22
8.99
8.28
8.13
8.12
7.68
7.67
7.66
7.65
7.63
7.61
7.60
7.59
7.58
7.57
7.18
7.17
7.16
7.15
3.78
3.33
2.51
2.50
2.50
2.26
2.25
2.24
2.23
2.23
2.22
2.21
2.21
2.19
1.11
1.10
1.09
1.08
1.08
1.07
1.06
0.99
0.98
(CD3)2SO, 400 MHz
3bv
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.02
1.02
1.01
4.11
3.03
2.97
1.03
2.23
2.20


164.8
163.6
152.5
148.4
147.7
146.3
139.3
136.8
132.0
131.8
126.8
126.5
124.1
123.1
122.3
122.3
121.4
121.2
120.6
116.8
116.8
110.0
52.3
39.9
39.7
39.5
39.3
39.1
8.3
8.0
(CD3)2SO, 100 MHz
3bv
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


-61.46
(CD3)2SO, 365 MHz
3bv
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 ppm