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Herein we describe the development of the first reductive cross-electrophile coupling between alkyl sulfones and aryl bromides. The use of alkyl sulfones as coupling partners offers strategic advantages over other alkyl electrophiles used in reductive coupling reactions, as the sulfone moiety can be incorporated into molecules in unique ways and permits α -functionalization prior to coupling. The conditions developed here can be applied to incorporate a wide array of aromatic rings onto (fluoro)alkyl scaffolds with broad functional group tolerance and generality, making this a practical method for late-stage diversification.

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Desulfonylative Arylation of Redox-Active Alkyl Sulfones with Aryl Bromides

Jonathan M. E. Hughes* and Patrick S. Fier*

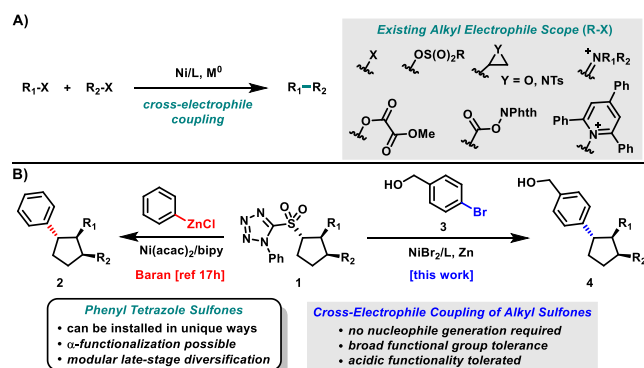
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Supporting Information Placeholder

ABSTRACT: Herein we describe the development of the first reductive cross-electrophile coupling between alkyl sulfones and aryl bromides. The use of alkyl sulfones as coupling partners offers strategic advantages over other alkyl electrophiles used in reductive coupling reactions, as the sulfone moiety can be incorporated into molecules in unique ways and permits α -functionalization prior to coupling. The conditions developed here can be applied to incorporate a wide array of aromatic rings onto (fluoro)alkyl scaffolds with broad functional group tolerance and generality, making this a practical method for late-stage diversification.

In drug discovery and development, the percentage of sp^3 -hybridized carbons in drug candidates is positively correlated to success in the clinic.¹ This has been attributed to factors such as improved biological and physicochemical properties, as well as reduced promiscuity relative to less saturated analogs.¹⁻² Consequently, numerous synthetic methods have been developed that enable the cross-coupling of aliphatic motifs to facilitate access to sp^3 -rich molecules.³ Ni-catalyzed reductive cross-electrophile couplings have been particularly useful in this regard and have undergone extensive development in recent years (Figure 1A).⁴⁻⁵ One attractive feature of these transformations is that they circumvent the need to pre-form nucleophilic reaction partners, resulting in simple reaction setups and broad functional group tolerance. As a result, cross-electrophile couplings have seen rapid uptake by synthetic chemists in recent years.

Figure 1. (A) General scheme for reductive cross-electrophile coupling. (B) Negishi-coupling of alkyl sulfone **1** with phenyl zinc chloride and cross-electrophile coupling of **1** with aryl bromide **3**.



While seminal methods for cross-electrophile coupling employed alkyl halides as sp^3 coupling partners,^{4,6} the scope has since expanded to include alkyl acetates,⁷ carbonates,⁸ sulfonates,⁹ epoxides,¹⁰ aziridines,¹¹ activated esters,¹² oxalates,¹³ pyridinium salts,¹⁴ iminiums,¹⁵ and others (Figure 1A).^{4,16} Such flexibility is valuable during synthetic planning, and further expansion to include alternative alkyl electrophiles is desirable. In this regard,

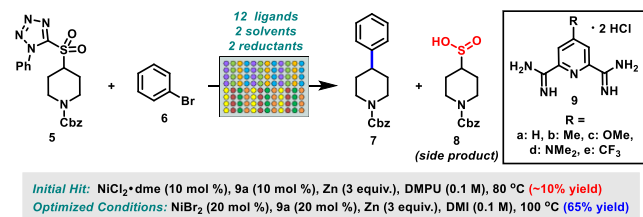
we aimed to develop reductive coupling chemistry with alkyl sulfones due to their unique strategic advantages over other alkyl electrophiles.¹⁷ In particular, alkyl sulfones can be deprotonated and functionalized at the α -position and can be prepared *via* cycloaddition or conjugate addition reactions. These diversifying bond formations can enable rapid exploration of chemical space, which is a vital aspect of drug discovery.

Our proposal to use alkyl sulfones as electrophiles in reductive cross-coupling was inspired by a recent report from the Baran laboratory describing Ni-catalyzed Negishi-type cross-coupling (Figure 1B, left);^{17h} a method that we recently applied towards structure activity relationship (SAR) exploration on scaffold **1**. Notably, the use of an alkyl sulfone electrophile was advantageous here for several reasons, including the ability to perform α -functionalization prior to coupling and its greater stability compared to other alkyl electrophiles. While this method was enabling, the use of pre-formed organometallic reagents prevented direct incorporation of aryl groups with acidic hydrogens (e.g. **3**) and required several additional synthetic operations. To avoid protecting group manipulations and be able to use readily available aryl halides, we hypothesized that direct cross-electrophile coupling between sulfone **1** and aryl bromide **3** could be possible under reducing conditions. Although sulfones have not been previously used as electrophiles in reductive cross-coupling, phenyl tetrazole sulfones (e.g. **1**) are known to be redox active and capable of engaging in single electron transfer reactions.^{17h} We herein describe the discovery and development of the first reductive cross-electrophile coupling reaction between alkyl sulfones and aryl bromides.

To assess the feasibility of using alkyl sulfones as substrates in cross-electrophile couplings, we studied the reaction between sulfone **5** and bromobenzene (**6**) (Scheme 1). A preliminary screen of 48 different reaction conditions (12 ligands, 2 solvents, and 2 reductants) using microscale high-throughput experimentation revealed that arylated product **7** could be formed in *ca.* 10% yield at 80 °C in DMPU in the presence of $NiCl_2 \cdot dme$ /**9a** (10 mol %) and Zn (3 equiv.) (see Supporting Information for details). From this initial hit, further development led to the identification of DMI as being a particularly effective solvent for the reaction. Finally, a thorough screening of Ni sources and electronically differentiated

ligands **9a-e** (R = H, Me, OMe, NMe₂, CF₃) revealed that the combination of NiBr₂ and **9a** enabled the formation of arylated product **7** in 65% yield (Scheme 1).

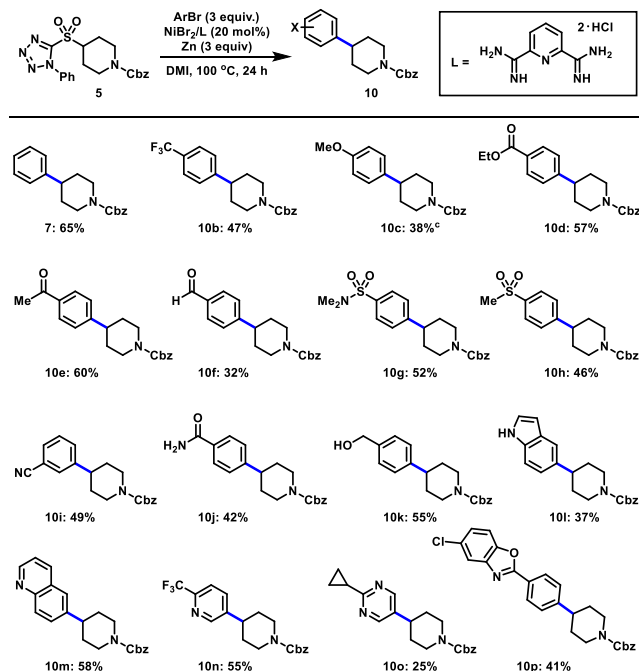
Scheme 1. Initial hit from high throughput screening and final reaction conditions for the cross-coupling of alkyl sulfone **5** and bromobenzene (**6**).



During reaction development, we identified sulfinate **8** as the major side product, which accounts for nearly all of the mass balance of **5**.¹⁸ In attempts to reduce the formation of **8** during the reaction, we investigated the effects of several additives (bases, metal salts, TMSCl, etc.) on product distribution. However, none of these additives resulted in increased yields of cross-coupled product **7**. Control experiments revealed that the reaction does not proceed in the absence of Ni, **9a**, or Zn. Finally, the reaction was found to be largely insensitive towards both water and air, which simplifies material handling and reaction setup (see Supporting Information for details).

With reaction conditions in place, we explored the scope of this reductive cross-coupling reaction and found that a variety of electronically-differentiated aryl bromides were competent coupling partners with sulfone **5** (Table 1). Several common functional groups were tolerated in the reaction, including esters (**10d**), ketones (**10e**), aldehydes (**10f**), sulfonamides (**10g**), sulfones (**10h**), nitriles (**10i**), and amides (**10j**). The synthesis of compound **10h** highlights the method's ability to chemoselectively differentiate between redox-active phenyl tetrazole sulfones and standard aryl sulfones. Moreover, aryl chlorides remain intact under the reaction conditions, thereby offering the potential to deliver products with a synthetic handle for further derivatization (**10p**). The cross-coupling of several pharmaceutically-relevant heteroaryl bromides also proceeded smoothly to form pyridine-, pyrimidine-, indole-, quinoline-, and benzoxazole-containing products in synthetically useful yields (**10l-p**). Of particular significance, functional groups with acidic hydrogens such as primary amides (**10j**), unprotected indoles (**10l**), and alcohols (**10k**) were well-tolerated in the reaction.

Table 1. Aryl bromide scope.^{a,b}

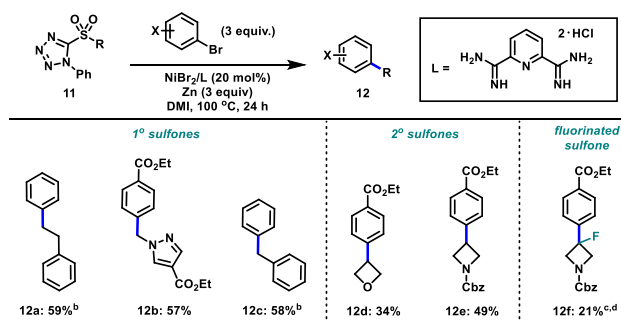


^aIsolated yields shown for reactions conducted with 0.5 mmol of **5**.

^bIn every reaction, the mass balance of limiting reagent **5** is sulfinate **8** (Scheme 1). ^c10 equiv. of 4-bromoanisole used.

In addition to compound **5**, several other sulfones reacted under the standard conditions with similar levels of efficiency (Table 2). For example, primary (**12a-c**), secondary (**12d-e**), benzylic (**12c**), and α -heteroatom-containing (**12b**) sulfones all underwent cross-coupling to give arylated products in moderate to good yields. Notably, a fluorinated sulfone could also be employed in the reaction to deliver **12f** in 21% yield. This example highlights the unique ability of alkyl sulfones to serve as handles for two-point diversification when employed as electrophiles for cross-coupling reactions. However, at this time, the scope of α -fluorosulfones is limited due to the instability of the C-F bonds towards elimination under the reaction conditions.

Table 2. Alkyl sulfone scope.^a

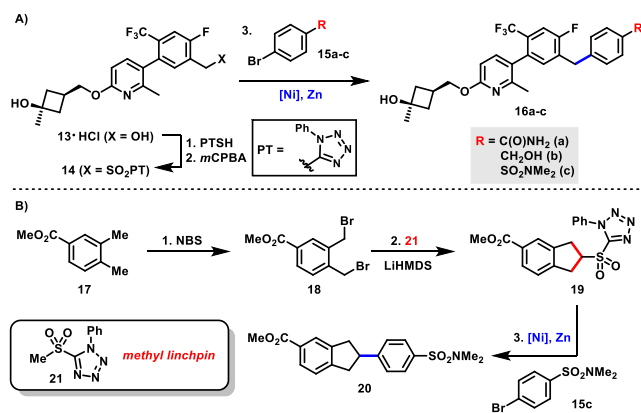


^aIsolated yields shown for reactions conducted with 0.5 mmol of **11**, unless otherwise stated. ^bAssay yield determined by HPLC analysis versus an authentic standard. ^c5 equiv. of ethyl 4-bromobenzoate used. ^dDMPU used in place of DMI.

To highlight the utility of this method for late-stage diversification of complex molecules, we prepared several analogs from benzyl alcohol **13** (Scheme 2A). Common intermediate sulfone **14** was prepared in two steps from **13** in 80% overall yield. Subsequent reductive coupling with aryl bromides **15a-c** proceeded smoothly to deliver diaryl methanes **16a-c** in 34-66% isolated yield. Importantly, each of these cross-couplings proceeded

effectively in the presence of acidic functional groups (benzylic/tertiary alcohols and/or primary amide) without the need for protecting groups. Furthermore, the synthesis of 2-aryl indane **20** was accomplished *via* sequential annulation of dibromide **18** with methyl sulfone **21** followed by reductive coupling of the resulting sulfone **19** (Scheme 2B). This example highlights the ability of sulfone **21** to serve as a methyl linchpin and offers new opportunities for the installation of this versatile functional handle. Notably, this strategy is unique to the use of alkyl sulfones and has not been demonstrated with other alkyl electrophiles within the context of reductive cross-electrophile coupling.

Scheme 2. (A) Modular synthesis of diarylmethanes **16a-c** and (B) synthesis of aryl indane **20** using a methyl linchpin/reductive cross-coupling strategy.^{a,b}

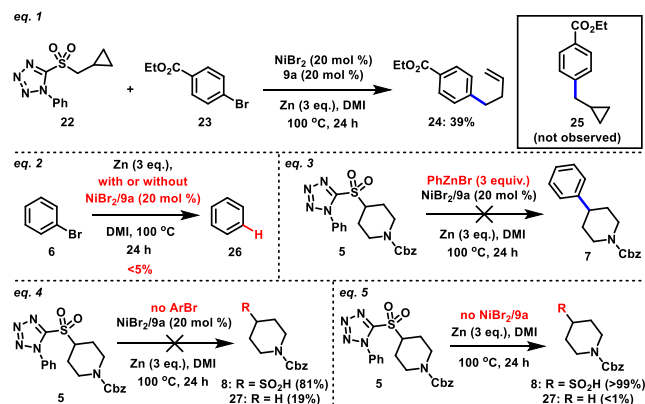


^aConditions and reagents for Scheme 2A: 1. Ph₃P (1.5 equiv.), DIAD (1.5 equiv.), PTSH (1.5 equiv.), THF, 0 °C → rt (88%); 2. i) mCPBA (6 equiv.), 0 °C → rt; ii) B₂Pin₂ (4 equiv.), 0 °C → rt (91%); 3. optimized conditions from Scheme 1 with 5 equiv. of **15a-c**. ^bConditions and reagents for Scheme 2B: 1. NBS (2.2 equiv.), (PhCO₂)₂ (7 mol %), CCl₄, 80 °C (90%); 2. NaH (2.2 equiv.), **21** (1.1 equiv.), rt (36% AY); 3. optimized conditions from Scheme 1 with 3 equiv. of **15c** (20%).

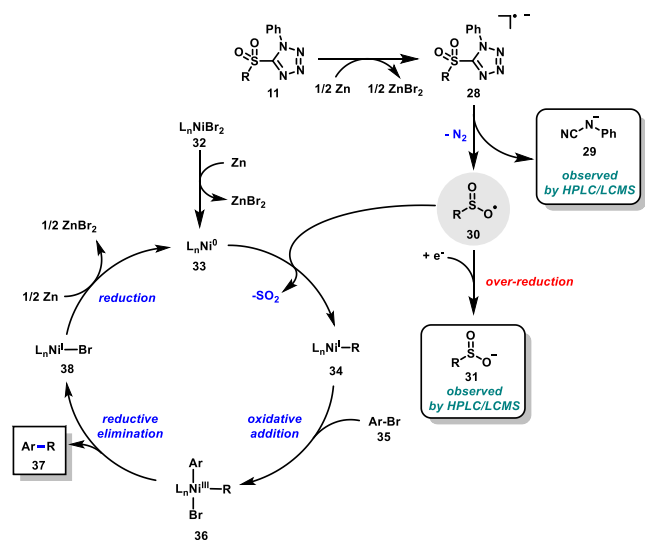
Several experiments and observations provided insight into the mechanism of this reaction (Scheme 3). First, conversion of (cyclopropyl)methyl sulfone **22** into ethyl 4-(3-butenyl)benzoate (**24**) under the reaction conditions is consistent with the formation of a radical-like intermediate (eq. 1). Moreover, control experiments confirmed that arylzinc halides are not generated under the reaction conditions (eq. 2), and pre-formed arylzinc halides do not engage in cross-coupling under the standard conditions (eq. 3).¹⁹ The lack of conversion of bromobenzene (**6**) in eq. 2 suggests a reaction between Ni and the alkyl component precedes oxidative addition into the aryl bromide bond. Furthermore, alkane **27** was formed in 19% yield when sulfone **5** was submit to the standard reaction conditions in the absence of an aryl bromide coupling partner, providing further evidence in support of an initially-generated alkyl-Ni species (eq. 4). Notably, negligible amounts of alkane **27** are generated in the absence of Ni, which further supported this hypothesis (eq. 5). Based on these experiments and literature precedent,²⁰ we propose a possible mechanism that involves an initial single electron reduction of sulfone **11** with Zn to generate radical anion **28** (Scheme 4).²¹ Radical anion **28** can then undergo fragmentation to generate sulfinyl radical **30** and cyanamide **29** (consistently observed in crude reaction mixtures by HPLC/LCMS analysis). Reaction of **30** with Ni(0) might then generate alkyl-Ni(I) species **34** *via* loss of SO₂.²² Finally, reaction of **34** with aryl bromide **35** would lead to the formation of cross-coupled product **37** and Ni(I) species **38** *via*

the intermediacy of Ni(III) species **36**. Reduction of **38** to Ni(0) would complete the catalytic cycle.^{23,24}

Scheme 3. Selected control experiments.



Scheme 4. Possible mechanism for the reductive cross-coupling of alkyl sulfones and aryl bromides.



In conclusion, we have developed the first reductive cross-electrophile coupling reaction between alkyl sulfones and aryl bromides. This new method serves as a convenient approach to forge C(sp³)-aryl bonds without the need for pre-functionalization of the aryl halide coupling partner. Moreover, in combination with well-established chemistry to functionalize alkyl sulfones, this method serves as a platform from which rapid diversification can be accomplished. As such, we anticipate that this method will have meaningful impacts within drug discovery and synthetic chemistry.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for new compounds. The Supporting Information is available free of charge on the ACS Publications website.

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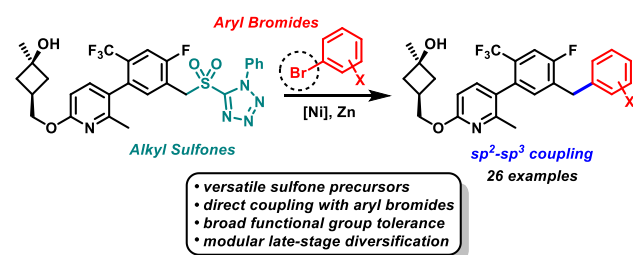
(21) Control experiments showed that sulfone **5** is cleanly reduced to sulfinate **8** in the presence of Zn. However, in the absence of Zn, no reduction of **5** occurs with $NiBr_2$ or $Ni(COD)_2$.

(22) Loss of SO_2 to generate alkyl radicals has been studied computationally and determined to be endergonic in many cases. Thus, while further mechanistic study is required in order to confirm this hypothesis, a Ni species (i.e. **33**) might assist in facilitating SO_2 extrusion from **30**: dos Passos Gomes, G.; Wimmer, A.; Smith, J. M.; König, B.; Alabugin, I. V. CO_2 or SO_2 : Should It Stay, or Should It Go? *J. Org. Chem.* **2019**, DOI: 10.1021/acs.joc.9b00503.

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TOC Graphic



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¹⁸ Assigned based on LCMS analysis of the crude reaction mixture.

¹⁹ Under the conditions shown in eq. 3, sulfone **5** is completely converted to sulfinate **8**.

²⁰ For mechanistic studies of cross-electrophile couplings, see ref. 15 and: (a) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146-6159. (b) Biswas, S.; Weix, D. J.; Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 16192-16197.

²¹ Control experiments showed that sulfone **5** is cleanly reduced to sulfinate **8** in the presence of Zn. However, in the absence of Zn, no reduction of **5** occurs with $NiBr_2$ or $Ni(COD)_2$.

²² Loss of SO_2 to generate alkyl radicals has been studied computationally and determined to be endergonic in many cases. Thus, while further mechanistic study is required in order to confirm this hypothesis, a Ni species (i.e. **33**) might assist in facilitating SO_2 extrusion from **30**: dos Passos Gomes, G.; Wimmer, A.; Smith, J. M.; König, B.; Alabugin, I. V. CO_2 or SO_2 : Should It Stay, or Should It Go? *J. Org. Chem.* **2019**, DOI: 10.1021/acs.joc.9b00503.

²³ Based on our observation that alkyl sulfonates (e.g. **31**) are generated as side products in the reaction, competing reduction of sulfinyl radical **30** is proposed.

²⁴ A catalytic cycle involving oxidative addition of an initially-generated alkyl-Ni(I) species into an aryl bromide bond has been proposed for a Ni-catalyzed cross-coupling of aryl bromides and photoredox-generated radicals: Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015**, *137*, 4896-4899.

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**Desulfonylative Arylation of Redox-Active Alkyl Sulfones
with Aryl Bromides**

Jonathan M. E. Hughes and Patrick S. Fier

Supporting Information

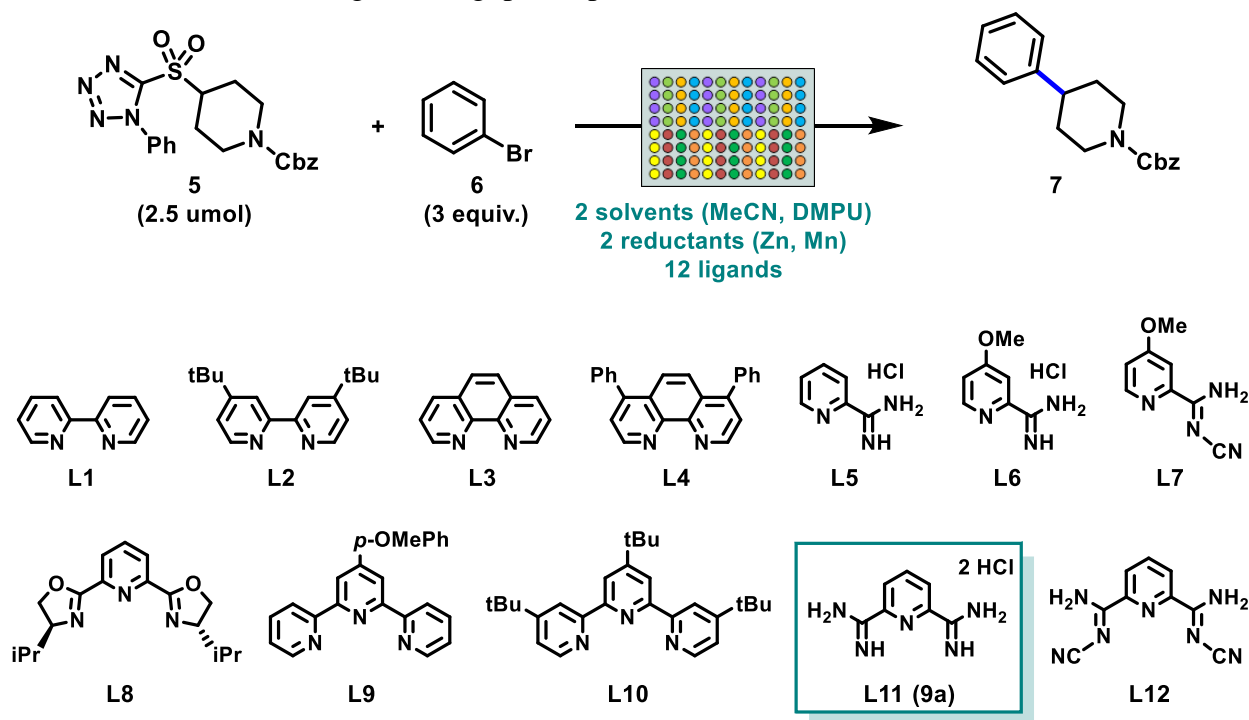
General Experimental. All reactions were performed under an inert N₂ atmosphere in round bottom flasks fitted with rubber septa or in screw-cap vials using magnetic stirring, unless otherwise stated. Reagents and solvents were purchased from commercial suppliers and used as received, unless otherwise stated. Non-commercially available substrates were procured from Merck's building block collection and used as received. Zn dust (<10 µm) was activated according to a literature procedure and stored in a nitrogen filled-glove box.¹ Reaction mixtures were analyzed by high-performance liquid chromatography (HPLC) using a MeCN/0.1 % aq. H₃PO₄ mobile phase and/or thin-layer chromatography (TLC). TLC was carried out on TLC Silica gel 60 F₂₅₄ glass plates and visualized using ultraviolet light and/or by exposure to an acidic solution of cerium (IV) ammonium molybdate followed by heating or a basic solution of potassium permanganate followed by heating. Flash column chromatography was carried out on RediSep Rf Gold[®] Normal-Phase silica using reagent grade solvents. Room temperature (rt) indicates a temperature of 22 °C. NMR spectra were recorded on 400 or 500 MHz Bruker spectrometers. Chemical shifts (δ) were internally referenced to the residual proton resonance of the deuterated solvent used. The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet (quintet), m = multiplet. Coupling constants (J) are reported in Hertz (Hz).

Optimization and Control Experiments:

Initial Microscale High-Throughput Experimentation:

48 reaction conditions were investigated in a high-throughput fashion on 2.5 μmol scale in microvials (Scheme S1). The 48 reactions consisted of an array of 12 ligands (10 mol % each), 2 solvents (MeCN and DMPU, 0.1 M), and 2 reductants (Zn and Mn, 3 equiv. each). Bromobenzene (3 equiv.) was employed as the aryl bromide coupling partner and $\text{NiCl}_2\cdot\text{dme}$ (10 mol %) was employed as the Ni source. The reactions were conducted at 80 $^\circ\text{C}$ for 24 h. Of these 48 initial reactions, only one [L11 (9a in the main text) as the ligand, Zn as the reductant in DMPU] produced appreciable amounts of the desired product ($\sim 10\%$ assay yield).

Scheme S1. Microscale High-Throughput Experimentation.



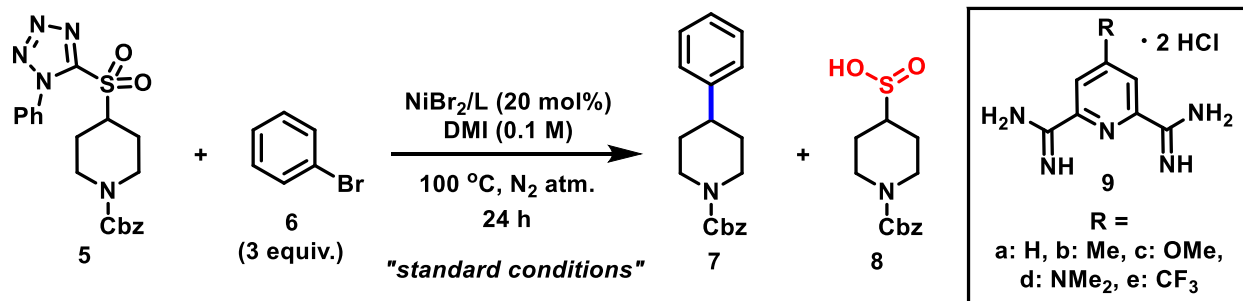
General Procedure for Optimization and Control Experiments:

A 4 mL screw-cap vial was charged with a stir bar, the nickel source, and ligand and then transferred into a nitrogen-filled glove box.² The reaction solvent was added and then the resulting solution was sonicated and/or heat slightly until a fully homogenous catalyst solution was obtained.

A separate 4 mL screw-cap vial was charged with a stir bar and sulfone **5** (43 mg, 0.1 mmol, 1 equiv.) and then was transferred into the glove box. The aryl halide was added followed by the catalyst solution (*vide supra*). Any additive(s) used (if any) were added followed by activated¹ Zn and then the vial was sealed and removed from the glove box. The reaction mixture was stirred at

the indicated temperature for 24 h and then was cooled to rt. The crude mixture was then diluted in 3:1 MeCN:H₂O and then analyzed by HPLC to determine the ratio of **7**:**8** by comparison to authentic material.

Table S1. Optimization of Reductive Cross-Coupling Between Sulfone **5** and Bromobenzene (**6**).



Entry	Changes from “standard conditions” above	Conversion (%) ^a	Ratio of 7:8 (Assay Yield of 7) ^b
1	None	94	5.29:1 (65%)
2	DMPU instead of DMI ^{c,d}	40	1.02:1 (~10%)
3	DMF instead of DMI ^c	59	0.39:1
4	DMAc instead of DMI ^c	81	0.49:1
5	NMP instead of DMI ^c	75	0.52:1
6	MgBr ₂ (1 equiv.) as additive	100	0.71:1
7	LiCl (1 equiv.) as additive	100	0.17:1
8	MgBr ₂ (1 equiv.) and LiCl (1 equiv.) as additives	100	0.61:1
9	ZnBr ₂ (1 equiv.) as additive	100	2.13:1
10	Hunig’s Base (2 equiv.) ^e	39	1.19:1
11	H ₂ O (2 equiv.) as additive	86	3.15:1
12	Conducted under air atm.	83	1.09:1
13	60 °C ^e	16	1.85:1
14	70 °C ^e	46	1.70:1
15	80 °C	88	2.13:1
16	90 °C ^e	86	1.74:1
17	120 °C	100	0.54:1
18	10 mol % NiBr ₂ / 9a	95	1.67:1
19	10 mol % NiBr ₂ / 9a in DMPU ^d	22	1.76:1
20	10 mol % NiI ₂ / 9a in DMPU ^d	20	1.26:1
21	10 mol % Ni(acac) ₂ / 9a in DMPU ^d	14	0:1
22	10 mol % Ni(COD) ₂ / 9a in DMPU ^d	32	0.89:1
23	20% Ni(COD) ₂ / 9a	99	2.13:1 (54%)
24	1.5 equiv. of PhBr (6)	100	0.95:1

25	PhCl ^f	64	0:1
26	PhI ^f	ND ^g	4.9:1 (32%)
27	PhOTf ^f	100	0:1
28	0.05 M; 10 mol % NiBr ₂ /9a	64	1.76:1
29	0.2 M; 10 mol % NiBr ₂ /9a	82	1.52:1
30	0.4 M; 10 mol % NiBr ₂ /9a	86	0.89:1
31	Ligand 9b instead of 9a	95	1.31:1 (56%)
32	Ligand 9c instead of 9a	95	0.81:1 (44%)
33	Ligand 9d instead of 9a	97	1.21:1 (43%)
34	Ligand 9e instead of 9a	100	0.52:1 (22%)
35	20 mol % NiBr ₂ /30 mol % 9a	100	1.62:1
36	20 mol % NiBr ₂ /40 mol % 9a	100	1.29:1
37	40 mol % NiBr ₂ /20 mol % 9a	100	2.34:1
38	1.5 equiv. Zn in DMPU ^c	22	1.34:1
39	5 equiv. Zn	100	2.69:1
40	TDAE (3 equiv.) instead of Zn	100	0:1

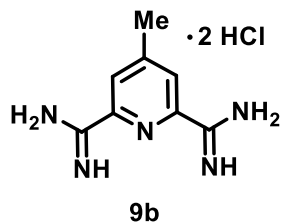
^aConversions determined by HPLC analysis of the crude reaction mixture. ^bAssay yields determined by HPLC analysis versus an authentic standard of 7. ^c10 mol % NiCl₂•dme employed as the Ni source. ^dreaction temperature = 60 °C. ^e10 mol % NiBr₂/9a. ^freaction temperature = 90 °C. ^gND = not determined; sulfone 5 overlaps with PhI under standard HPLC conditions so an accurate conversion was not obtained.

General Procedure A - Reductive Cross-Coupling of Alkyl Sulfones and Aryl Bromides:

A 20 mL screw-cap vial was charged with NiBr₂ (22 mg, 0.1 mmol, 20 mol %), ligand 9a (24 mg, 0.1 mmol, 20 mol %)³ and then transferred into a nitrogen-filled glove box. DMI (5 mL) was added and then the resulting solution was sonicated and/or heat slightly until a fully homogenous catalyst solution was obtained.

A separate 20 mL screw-cap vial was charged with a stir bar, alkyl sulfone (0.5 mmol, 1 equiv.) and the aryl bromide (1.5 mmol, 3 equiv.).⁴ This vial was transferred into the glove box and then the catalyst solution (*vide supra*) was added followed by activated¹ Zn (98 mg, 1.5 mmol, 3 equiv.). The vial was sealed, removed from the glove box and then the reaction mixture was stirred at 100 °C for 24 h. The reaction mixture was cooled to rt and then quenched with sat'd aq. NaHCO₃ (20 mL) and then diluted with EtOAc (20 mL). The resulting mixture was filtered under vacuum and the resulting biphasic filtrate was separated. The organic layer was washed with H₂O (2 x 20 mL) and then dried (Mg₂SO₄) before concentrating *in vacuo*. Purification by flash chromatography using EtOAc:hexanes afforded the desired product.

Synthesis of bis-amidine pyridine ligands:

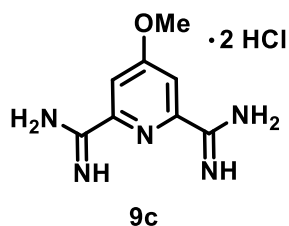


A 40 mL screw-cap vial was charged with a stir bar, 4-methylpyridine-2,6-dicarbonitrile (234 mg, 1.635 mmol, 1 equiv.), MeOH (23 mL) and NaOMe (8.8 mg, 0.16 mmol, 0.1 equiv.). The vial was sealed and the mixture was stirred at rt for 16 h. NH_4Cl (184 mg, 3.43 mmol, 2.1 equiv.) was added, the vial was sealed and the reaction was stirred at 65 °C for 5 h. The mixture was then concentrated *in vacuo* and EtOH (16 mL) was added to the resulting crude product. The suspension was stirred at 80 °C for 2 h and then vacuum filtered to deliver **9b** (186 mg, 0.74 mmol, 46%) as a white solid.

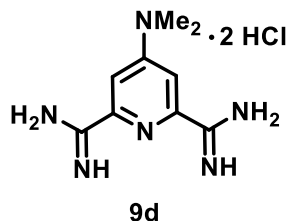
^1H NMR (500 MHz, D_2O) δ 8.22 (s, 2H), 2.57 (s, 3H).

^{13}C NMR (126 MHz, D_2O) δ 161.45, 154.04, 143.91, 127.68, 20.65.

ESI MS calculated for $\text{C}_8\text{H}_{12}\text{N}_5$: 178.11 $[(\text{M}+\text{H}^+)]$, measured 178.11.



Prepared following a literature procedure.⁵



A 50 mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of N_2 , was charged with 4-chloropyridine-2,6-dicarbonitrile (3.5 g, 21.5 mmol, 1.0 equiv.), Me_2NH (1.93 g, 42.9 mmol, 2.0 equiv.) and DMF (35 mL). While stirring at rt, Et_3N (4.6 g, 45.1 mmol, 2.1 equiv.)

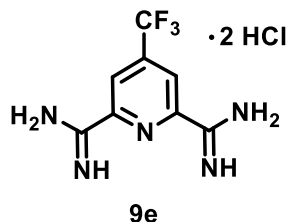
was added and the resulting solution was stirred at 80 °C for 16 h. The reaction was then quenched by the addition of water/ice. A solid precipitated from the solution and was filtered to deliver 4-(dimethylamino)pyridine-2,6-dicarbonitrile (2.1 g, 12.26 mmol, 57%) as a white solid.

Under a N₂ atmosphere, a 40 mL glass tube was charged with a solution of 4-(dimethylamino)pyridine-2,6-dicarbonitrile (500 mg, 2.9 mmol, 1.0 equiv.) in MeOH (5 mL) NaOMe (0.29 mL, 0.29 mmol, 0.1 equiv.). The reaction mixture was stirred at rt for 16 h and then NH₄Cl (465 mg, 8.7 mmol, 3.0 equiv.) was added to the solution. The reaction was stirred at 80 °C for 16 h and then the solids were filtered and taken up into EtOH (3 mL). This suspension was stirred at 70 °C for 30 min and, after cooling to room temperature, filtration yielded **9c** (250 mg, 0.812 mmol, 42%) as a light-yellow solid.

¹H NMR (500 MHz, D₂O) δ 7.33 (s, 2H), 3.07 (s, 6H).

¹³C NMR (126 MHz, D₂O) δ 161.93, 156.36, 143.44, 107.96, 39.17.

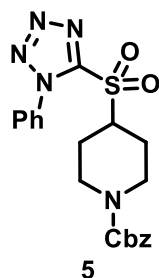
ESI MS calculated for C₉H₁₅N₆: 207.14 [(M+H⁺)], measured 207.16.



Under N₂ atmosphere, a 40 mL glass tube was charged with a solution of 4-(trifluoromethyl)pyridine-2,6-dicarbonitrile (350 mg, 1.78 mmol, 1.0 equiv.)⁶ in i-PrOH (2 mL) and NaOMe (1 M in MeOH, 0.17 mL, 0.17 mmol, 0.1 equiv.). The reaction was stirred at rt for 16 h and then NH₄Cl (280 mg, 5.2 mmol, 3.0 equiv.) was added to the solution. The reaction was stirred at 80 °C for 16 h and then cooled to rt. The crude product was purified by preparatory SFC under the following conditions: (R,R)-WHELK-O1-Kromasil(02) column, 5cm*25cm(5um); mobile phase, DCM & IPA (0.2% DEA); 210 nm detector to afford **9e** (110 mg, 0.360 mmol, 20%) as a light green solid. Ligand **9e** was found to be unstable and was used immediately following its preparation. As a result, NMR analysis was not conducted.

ESI MS calculated for C₈H₉F₃N₅: 232.08 [(M+H⁺)], measured 232.10.

Synthesis of Alkyl Sulfones:

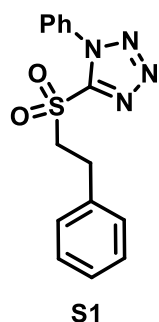


A mixture of benzyl 4-bromopiperidine-1-carboxylate (7.28 ml, 32.2 mmol, 1.0 equiv.), 1-phenyl-1H-tetrazole-5-thiol (6.31 g, 35.4 mmol, 1.1 equiv.), and K_2CO_3 (8.90 g, 64.4 mmol, 2.0 equiv.) in acetone (100 ml) was stirred at 70 °C for 2 days. The reaction mixture was cooled to rt and filtered over a pad of Celite. The thioether intermediate was purified by flash chromatography (0% \rightarrow 70% EtOAc:hexanes) and then taken up into DCM (100 mL). The solution was cooled to 0 °C and mCPBA (15.87 g, 70.8 mmol, 2.2 equiv.) was added portionwise. The reaction mixture was allowed to slowly warm to rt and stirred for a total of 22 h. The reaction was quenched carefully with saturated aq. NaHCO_3 and 10% $\text{Na}_2\text{S}_2\text{O}_3$. Stirred for 4 h, separated the layers and then the aqueous layer was extracted with DCM. The combined organic layers were dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0 \rightarrow 70% EtOAc:hexanes) produced **5** (11.8 g, 27.6 mmol, 86 % yield) as a white solid.

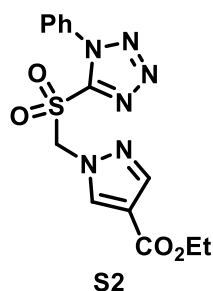
^1H NMR (500 MHz, CDCl_3) δ 7.75 – 7.54 (m, 5H), 7.47 – 7.31 (m, 5H), 5.16 (s, 2H), 4.41 (s, 2H), 4.07 (tt, J = 11.8, 3.6 Hz, 1H), 2.97 (s, 2H), 2.39 – 2.20 (m, 2H), 1.91 (qd, J = 12.4, 4.4 Hz, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ 154.87, 152.52, 136.32, 132.99, 131.58, 129.72, 128.59, 128.24, 128.04, 125.21, 67.58, 62.14, 42.50, 24.24.

ESI MS calculated for $\text{C}_{20}\text{H}_{22}\text{N}_5\text{O}_4\text{S}$: 428.14 $[(\text{M}+\text{H}^+)]$, measured 428.30.



Prepared following a literature procedure.⁷



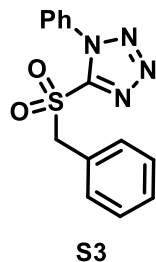
A flask was charged with a stir bar, ethyl 1-(hydroxymethyl)-1H-pyrazole-4-carboxylate (1.5 g, 8.81 mmol, 1.0 equiv.),⁸ Ph_3P (3.47 g, 13.22 mmol, 1.5 equiv.), 1-phenyl-1H-tetrazole-5-thiol (2.36 g, 13.22 mmol, 1.5 equiv.) and THF (30 mL) and then cooled to 0 °C. DIAD (2.01 mL, 10.15 mmol, 1.5 equiv.) was added dropwise and the reaction was allowed to slowly warm to rt and was stirred for a total of 24 h. The crude mixture was concentrated *in vacuo* and purified by flash chromatography (0-50% EtOAc:hexanes) to give the thioether intermediate (1.7 g, 5.15 mmol, 58%) as a white solid, which was immediately used in the next step.

The thioether intermediate (1.0 g, 3.03 mmol, 1.0 equiv.) was suspended in EtOH (20 mL), and ammonium molybdate tetrahydrate (374 mg, 0.303 mmol, 0.1 equiv.) was added followed by the dropwise addition of an aqueous solution of H_2O_2 (30 wt %, 1.24 mL, 12.11 mmol, 4.0 equiv.). The reaction mixture was stirred at rt for 1 h and then at 60 °C for 18 h. The reaction was cooled to 0 °C and diluted with H_2O (40 mL) before quenching with saturated aq. $\text{Na}_2\text{S}_2\text{O}_3$. The mixture was extracted with DCM (x2) and then the combined organic layers were dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0-70% EtOAc:hexanes) afforded **S2** (658 mg, 1.82 mmol, 60%) as a white solid.

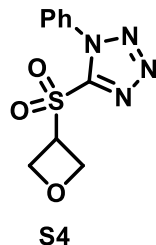
^1H NMR (500 MHz, CDCl_3) δ 8.22 (s, 1H), 7.93 (s, 1H), 7.69 – 7.49 (m, 5H), 5.96 (s, 2H), 4.31 (q, $J = 7.1$ Hz, 2H), 1.36 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 161.83, 151.96, 143.48, 135.30, 132.50, 131.80, 129.71, 125.38, 118.10, 70.99, 60.75, 14.31.

ESI MS calculated for $\text{C}_{14}\text{H}_{15}\text{N}_6\text{O}_4\text{S}$: 363.09 $[(\text{M}+\text{H}^+)]$, measured 363.18.



Prepared following a literature procedure.⁹



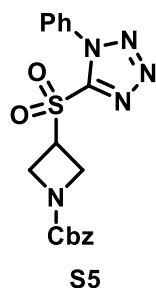
A flask was charged with 1-phenyl-1H-tetrazole-5-thiol (15 g, 84 mmol, 1.0 equiv.), oxetan-3-yl trifluoromethanesulfonate (26 g, 126 mmol, 1.5 equiv.), Cs₂CO₃ (54.8 g, 168 mmol, 2.0 equiv.) and DMF (300 mL) and the reaction mixture was stirred at rt for 16 h. The reaction was quenched with water (1 L) and then EtOAc (500 mL) was added. The combined organic layers were washed with brine, dried (MgSO₄), and then concentrated *in vacuo* to provide the crude thioether intermediate (15 g, 76%) as a yellow oil, which was immediately used in the next step.

The thioether intermediate (20 g, 85 mmol, 1.0 equiv.) was dissolved in EtOH (400 mL) and the resulting solution was cooled to 0 °C. Ammonium molybdate tetrahydrate (10 g, 8.5 mmol, 0.1 equiv.) was added followed by the dropwise addition of an aqueous solution of H₂O₂ (35 wt %, 50 mL, 240 mmol). The resulting solution was warmed to rt and stirred for 16 h. Water (1.2 L) was added and the solids were collected by filtration. Hexane (200 mL) was added to the collected solids, the suspension was stirred at rt for 30 min, and then filtration afforded **S4** (17 g, 63.8 mmol, 75%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.80 – 7.71 (m, 2H), 7.71 – 7.59 (m, 3H), 5.32 – 5.23 (m, 1H), 5.16 – 5.03 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 152.54, 132.77, 131.67, 129.96, 124.70, 69.23, 57.80.

ESI MS calculated for C₁₀H₁₁N₄O₃S: 267.06 [(M+H⁺)], measured 267.08.

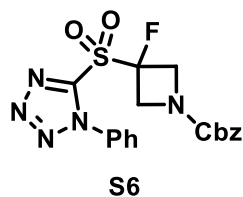


A 4-necked round bottom flask was charged with 1-phenyl-1H-tetrazole-5-thiol (15 g, 84 mmol, 1.0 equiv.), benzyl 3-hydroxyazetidine-1-carboxylate (19.19 g, 93 mmol, 1.1 equiv.), PPh₃ (24.28 g, 93 mmol, 1.1 equiv.) and THF (300 mL). The solution was cooled to 0 °C and DIAD (16 g, 93 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was allowed to warm to rt and was stirred for a total of 16 h. The reaction was quenched with water (1 L) and then EtOAc (500 mL) was added. The two layers were separated and then the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and then concentrated *in vacuo* to provide the crude thioether intermediate (30 g) as a yellow oil. This intermediate was dissolved in EtOH (600 mL) and the resulting solution was cooled to 0 °C. Ammonium molybdate tetrahydrate (5 g, 4.06 mmol, 0.05 equiv.) was added followed by the dropwise addition of an aqueous solution of H₂O₂ (35 wt %, 25 mL 120 mmol, 1.4 equiv.). The reaction mixture was warmed to rt and stirred for 16 h. Water (800 mL) was added and then the solids were collected by filtration. The crude product was purified by Flash-Prep-HPLC with the following conditions (IntelFlash-1): Column, C18; mobile phase, ACN:H₂O=1:3 increasing to ACN:H₂O=3:1 within 20 min; Detector, UV 210 nm, to afford **S5** (17 g, 42.8 mmol, 51%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.78 – 7.70 (m, 2H), 7.70 – 7.59 (m, 3H), 7.42 – 7.31 (m, 5H), 5.14 (s, 2H), 4.84 (p, *J* = 7.0 Hz, 1H), 4.50 (d, *J* = 6.9 Hz, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 155.78, 152.36, 135.89, 132.74, 131.71, 129.96, 128.60, 128.36, 128.14, 124.72, 67.40, 52.27, 49.53.

ESI MS calculated for C₁₈H₁₈N₅O₄S: 400.11 [(M+H⁺)], measured 400.20.



To a solution of LiHMDS in THF (1 M, 13.77 mL, 13.77 mmol, 1.1 equiv.), stirring at -78 °C, was added a solution of benzyl 3-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)azetidine-1-carboxylate (**S5**) (5

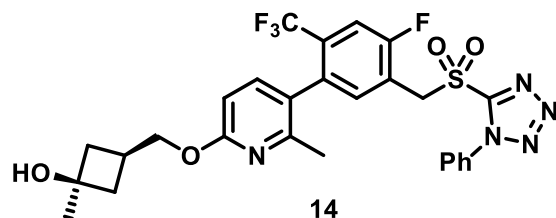
g, 12.52 mmol, 1.0 equiv.) in THF (50 mL) dropwise. Stirred at -78 °C for 30 min and then added a solution of NFSI (4.34 g, 13.77 mmol, 1.1 equiv.) in THF (12.5 mL). The reaction mixture was stirred at -78 °C for 1.5 h and then warmed to rt, where it was stirred for an additional 45 min. The reaction was quenched with saturated aq. NH₄Cl and diluted with H₂O to dissolve the salts. The mixture was extracted with EtOAc (x2) and then the combined organic layers were washed with brine, dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0-25% EtOAc:hexanes) provided **S6** (2.62 g, 6.28 mmol, 50%) as a white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.77 – 7.57 (m, 5H), 7.47 – 7.31 (m, 5H), 5.18 (s, 2H), 4.95 (dd, *J* = 17.3, 12.5 Hz, 2H), 4.54 (dd, *J* = 20.2, 12.5 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 155.68, 155.66, 150.24, 135.85, 135.61, 132.53, 131.92, 129.85, 129.49, 128.66, 128.50, 128.23, 125.25, 103.06, 100.97, 67.85, 56.65 (analysis of the spectrum is complicated by C-F coupling, not all multiplets were assigned).

¹⁹F NMR (471 MHz, CDCl₃) δ -154.18.

ESI MS calculated for C₁₈H₁₇FN₅O₄S: 418.10 [(M+H⁺)], Measured 418.22.



A 200 mL flask was charged with a stir bar, **13•HCl** (2.95 g, 6.77 mmol, 1.0 equiv.), Ph₃P (2.69 g, 10.15 mmol, 1.5 equiv.), 1-phenyl-1H-tetrazole-5-thiol (1.83 g, 10.15 mmol, 1.5 equiv.) and THF (59 mL) and then cooled to 0 °C. DIAD (2.01 ml, 10.15 mmol, 1.5 equiv.) was added dropwise and the reaction was allowed to slowly warm to rt and was stirred for a total of 24 h. The reaction was quenched with 1 M NaOH (50 mL) and then extracted with EtOAc. Washed org layer with brine and dried (MgSO₄). Purification by flash chromatography (0-75% EtOAc:hexanes) provided the thioether intermediate (3.34 g, 5.97 mmol, 88 % yield) as an oil, which was used in the next step without further characterization.

The thioether intermediate (3.34 g, 5.97 mmol, 1.0 equiv.) was dissolved in DCM (33.4 ml) and cooled to 0 °C. mCPBA (77 wt %, 8.03 g, 35.8 mmol, 6.0 equiv.) was added portionwise and then the reaction mixture was warmed to rt and stirred for 24 h. The mixture was again cooled to 0 °C and B₂pin₂ (6.06 g, 23.88 mmol, 4.0 equiv.) was added portionwise. The reaction mixture was warmed to rt and stirred for an additional 24 h. The reaction was quenched with saturated aq. NaHCO₃ and 10% aq. Na₂S₂O₃ and the resulting mixture was stirred overnight. After diluting with H₂O and EtOAc, the two layers were separated. The organic layer was washed with saturated aq.

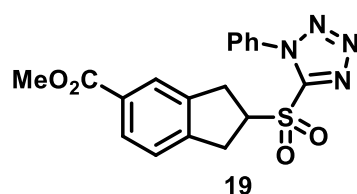
NaHCO₃, brine, and then was dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (0-60% EtOAc:hexanes) provided **14** (3.21 g, 5.43 mmol, 91 % yield) as a gummy white solid.

¹H NMR (500 MHz, CDCl₃) δ 7.72 – 7.54 (m, 6H), 7.46 (d, *J* = 6.8 Hz, 1H), 7.28 (s, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 5.22 – 5.09 (m, 2H), 4.34 (tt, *J* = 10.5, 5.2 Hz, 2H), 2.40 – 2.24 (m, 3H), 2.09 (s, 3H), 2.01 (t, *J* = 9.5 Hz, 2H), 1.94 (s, 1H), 1.26 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 163.31, 161.56, 159.54, 153.90, 153.11, 139.91, 137.27, 137.26, 135.60, 132.75, 131.68, 129.78, 125.03, 124.25, 116.35, 116.24, 114.78, 114.74, 114.70, 114.66, 114.58, 114.54, 114.50, 114.46, 106.92, 69.99, 69.77, 55.13, 41.00, 27.47, 24.87, 24.77, 22.77 (analysis of the spectrum is complicated by C-F coupling, not all multiplets were assigned).

¹⁹F NMR (471 MHz, CDCl₃) δ -60.08, -114.06.

ESI MS calculated for C₂₇H₂₆F₄N₅O₄S: 592.16 [(M+H⁺)], measured 592.46.

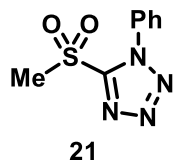


To a solution of methyl 3,4-bis(bromomethyl)benzoate (640 mg, 2.0 mmol, 1.0 equiv.)¹⁰ and sulfone **21** (500 mg, 2.20 mmol, 1.1 equiv.) stirring in DMF (20 mL) was added NaH (60%, 176 mg, 4.40 mmol, 2.2 equiv.). The reaction mixture was stirred at rt for 3 h (assay yield determined to be 36% by HPLC analysis, based on comparison with an authentic standard). The reaction mixture was immediately purified by flash chromatograph (0-100% EtOAc EtOAc:hexanes) to yield **19** (175 mg, 0.46 mmol, 23%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.97 – 7.92 (m, 2H), 7.77 – 7.69 (m, 2H), 7.69 – 7.60 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 1H), 4.93 (p, *J* = 8.2 Hz, 1H), 3.93 (s, 3H), 3.73 – 3.61 (m, 4H).

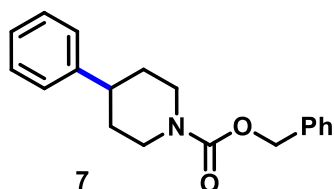
¹³C NMR (126 MHz, CDCl₃) δ 166.73, 153.11, 144.05, 139.16, 133.00, 131.55, 129.89, 129.76, 129.29, 125.78, 125.08, 124.47, 63.48, 52.19, 33.63, 33.15.

ESI MS calculated for C₁₈H₁₇N₄O₄S: 385.10 [(M+H⁺)], measured 385.23.



Prepared following a literature procedure.¹¹

sp²-sp³ Cross-Coupled Products:



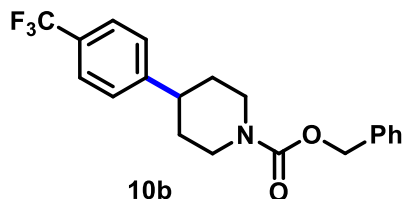
Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-100% EtOAc:hexanes

Yield: 96 mg (65%)

Physical state: colorless oil

Analytical data matched those previously published.¹²



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-40% EtOAc:hexanes

Yield: 85 mg (47%)

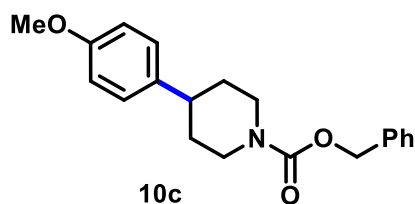
Physical state: colorless oil

¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.47 – 7.28 (m, 7H), 5.20 (s, 2H), 4.39 (s, 2H), 2.93 (t, *J* = 10.7 Hz, 2H), 2.77 (tt, *J* = 12.1, 3.3 Hz, 1H), 1.98 – 1.80 (m, 2H), 1.75 – 1.61 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ 155.20, 149.39, 136.72, 129.06, 128.81, 128.55, 128.43, 128.29, 127.95, 127.84, 127.40, 127.05, 125.46, 125.43, 125.40, 125.37, 125.24, 123.08, 120.92, 67.10, 44.37, 42.42, 32.75 (analysis of the spectrum is complicated by C-F coupling, not all multiplets were assigned).

^{19}F NMR (471 MHz, CDCl_3) δ -62.37.

ESI MS calculated for $\text{C}_{20}\text{H}_{21}\text{F}_3\text{NO}_2$: 364.15 $[(\text{M}+\text{H}^+)]$, measured 364.26.



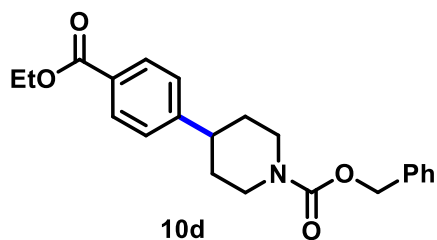
Followed General Procedure A (0.5 mmol scale) with 10 equiv. Ar-Br

Flash chromatography solvent system: 20-40% EtOAc:hexanes

Yield: 62 mg (38%)

Physical State: colorless oil

Analytical data matched those previously published.¹³



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-40% EtOAc:hexanes

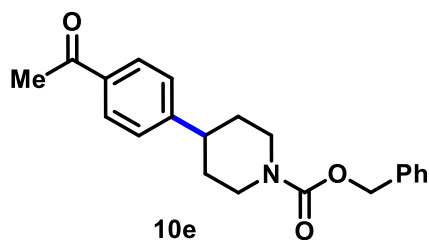
Yield: 104 mg (57%)

Physical State: colorless oil

^1H NMR (500 MHz, CDCl_3) δ 8.01 (d, J = 8.3 Hz, 2H), 7.43 – 7.31 (m, 5H), 7.28 (d, J = 8.3 Hz, 2H), 5.19 (s, 2H), 4.46 – 4.27 (m, 4H), 3.01 – 2.83 (m, 2H), 2.76 (tt, J = 12.1, 3.4 Hz, 1H), 1.93 – 1.80 (m, 2H), 1.75 – 1.59 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 166.52, 155.31, 150.65, 136.82, 129.90, 128.52, 127.93, 126.78, 123.57, 115.30, 67.18, 60.87, 44.50, 42.69, 32.83, 14.36.

ESI MS calculated for $\text{C}_{22}\text{H}_{26}\text{NO}_4$: 368.19 $[(\text{M}+\text{H}^+)]$, measured 368.28.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-50% EtOAc:hexanes

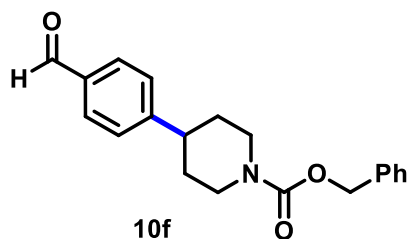
Yield: 101 mg (60%)

Physical State: colorless oil

^1H NMR (500 MHz, CDCl_3) δ 7.93 (d, $J = 8.3$ Hz, 2H), 7.43 – 7.32 (m, 5H), 7.31 (d, $J = 8.3$ Hz, 2H), 5.19 (s, 2H), 4.38 (s, 2H), 3.01 – 2.83 (m, 2H), 2.77 (tt, $J = 12.1, 3.5$ Hz, 1H), 2.61 (s, 3H), 1.88 (d, $J = 12.5$ Hz, 2H), 1.74 – 1.62 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ 197.70, 155.28, 151.03, 136.83, 135.63, 128.76, 128.52, 128.04, 127.95, 127.02, 67.17, 44.47, 42.69, 32.78, 26.57.

ESI MS calculated for $\text{C}_{21}\text{H}_{24}\text{NO}_3$: 338.18 $[(\text{M}+\text{H}^+)]$, measured 338.23.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 15-30% EtOAc:hexanes

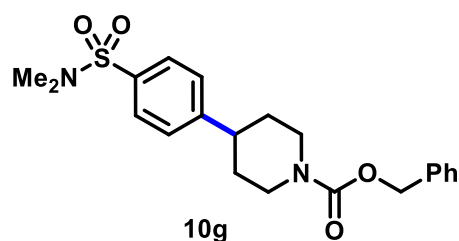
Yield: 51 mg (32%)

Physical State: slightly yellow oil

¹H NMR (500 MHz, CDCl₃) δ 9.98 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.47 – 7.28 (m, 7H), 5.16 (s, 2H), 4.36 (s, 2H), 2.90 (s, 2H), 2.77 (t, *J* = 12.0 Hz, 1H), 1.95 – 1.76 (m, 2H), 1.76 – 1.56 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 191.82, 155.26, 152.58, 136.80, 135.03, 130.13, 128.52, 128.04, 127.94, 127.50, 67.18, 44.43, 42.90, 32.73.

ESI MS calculated for C₂₀H₂₂NO₃: 324.16 [(M+H⁺)], measured 324.23.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-80% EtOAc:hexanes

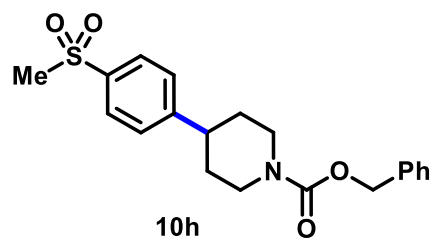
Yield: 102 mg (52%)

Physical State: white solid

¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.31 (m, 7H), 5.18 (s, 2H), 4.38 (s, 2H), 2.99 – 2.85 (m, 2H), 2.79 (tt, *J* = 14.4, 4.0 Hz, 1H), 2.73 (s, 6H), 1.95 – 1.83 (m, 2H), 1.74 – 1.61 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 155.26, 150.60, 136.79, 133.74, 128.53, 128.14, 128.07, 127.96, 127.43, 67.21, 44.41, 42.58, 37.94, 32.78.

ESI MS calculated for C₂₁H₂₇N₂O₄S: 403.17 [(M+H⁺)], measured 403.31.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-60% EtOAc:hexanes

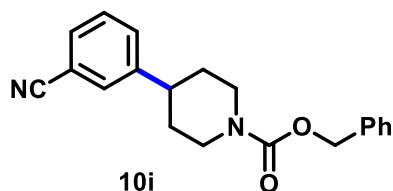
Yield: 86 mg (46%)

Physical State: white solid

¹H NMR (400 MHz, CDCl₃) δ 7.94 – 7.82 (m, 2H), 7.47 – 7.27 (m, 7H), 5.16 (s, 2H), 4.36 (s, 2H), 3.04 (s, 3H), 3.00 – 2.83 (m, 2H), 2.78 (tt, *J* = 12.1, 3.5 Hz, 1H), 1.94 – 1.78 (m, 2H), 1.75 – 1.60 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 155.22, 151.82, 138.70, 136.74, 128.52, 128.06, 127.96, 127.81, 127.75, 67.21, 44.54, 44.36, 42.68, 32.76.

ESI MS calculated for C₂₀H₂₄NO₄S: 374.14 [(M+H⁺)], measured 374.23.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 15-30% EtOAc:hexanes

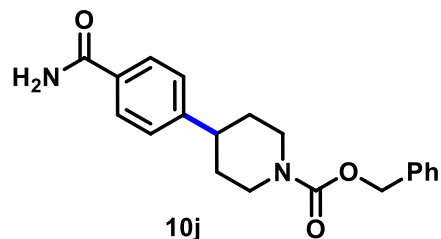
Yield: 78 mg (49%)

Physical State: colorless oil

¹H NMR (500 MHz, CDCl₃) δ 7.67 – 7.31 (m, 9H), 5.18 (s, 2H), 4.38 (s, 2H), 2.91 (s, 2H), 2.74 (tt, *J* = 12.2, 3.3 Hz, 1H), 1.94 – 1.77 (m, 2H), 1.72 – 1.59 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 155.23, 146.82, 136.76, 131.34, 130.51, 130.24, 129.39, 128.52, 128.06, 127.96, 118.86, 112.67, 67.22, 44.37, 42.26, 32.79.

ESI MS calculated for C₂₀H₂₁N₂O₂: 321.16 [(M+H⁺)], measured 321.23.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-80% EtOAc:hexanes

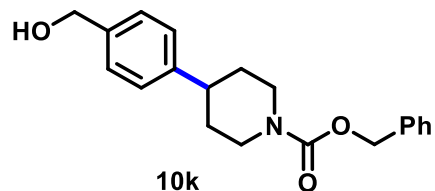
Yield: 71 mg (42%)

Physical State: white solid

¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.45 – 7.29 (m, 7H), 6.02 (s, 1H), 5.52 (s, 1H), 5.18 (s, 2H), 4.38 (s, 2H), 3.00 – 2.82 (m, 2H), 2.76 (tt, *J* = 12.1, 3.5 Hz, 1H), 1.94 – 1.79 (m, 2H), 1.76 – 1.61 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 169.00, 155.27, 149.82, 136.82, 131.51, 128.51, 128.02, 127.93, 127.71, 127.05, 67.16, 44.48, 42.56, 32.88.

ESI MS calculated for C₂₀H₂₃N₂O₃: 339.17 [(M+H⁺)], measured 339.25.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-60% EtOAc:hexanes

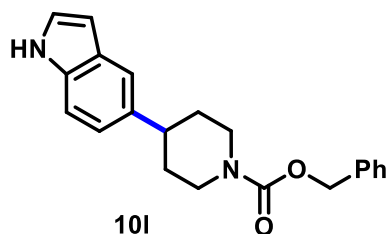
Yield: 89 mg (55%)

Physical State: colorless oil

¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.29 (m, 7H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.18 (s, 2H), 4.69 (s, 2H), 4.35 (d, *J* = 12.0 Hz, 2H), 2.90 (t, *J* = 12.4 Hz, 2H), 2.70 (tt, *J* = 12.1, 3.5 Hz, 1H), 1.85 (d, *J* = 12.9 Hz, 2H), 1.68 (ddd, *J* = 21.3, 14.4, 10.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 155.30, 145.06, 139.07, 136.88, 128.48, 127.97, 127.89, 127.32, 126.96, 67.09, 65.13, 44.61, 42.35, 33.12.

ESI MS calculated for $C_{20}H_{24}NO_3$: 326.18 $[(M+H^+)]$, measured 326.21.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-100% EtOAc:hexanes

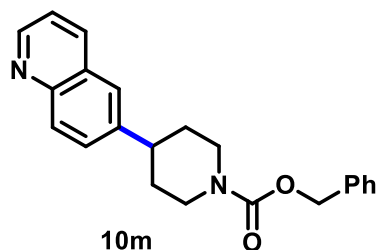
Yield: 62 mg (37%)

Physical State: colorless oil

1H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.49 (s, 1H), 7.45 – 7.30 (m, 6H), 7.22 (t, J = 2.7 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 5.20 (s, 2H), 4.37 (s, 2H), 3.02 – 2.86 (m, 2H), 2.79 (tt, J = 12.1, 3.4 Hz, 1H), 1.99 – 1.83 (m, 2H), 1.84 – 1.65 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.41, 137.22, 136.99, 134.65, 128.51, 128.07, 127.96, 127.89, 124.55, 121.40, 118.16, 110.99, 102.46, 67.07, 44.88, 42.74, 33.84.

ESI MS calculated for $C_{21}H_{23}N_2O_2$: 335.18 $[(M+H^+)]$, measured 335.23.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-100% EtOAc:hexanes

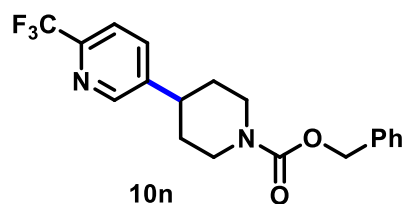
Yield: 101 mg (58%)

Physical State: colorless oil

¹H NMR (500 MHz, CDCl₃) δ 8.89 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.46 – 7.31 (m, 6H), 5.20 (s, 2H), 4.41 (s, 2H), 3.08 – 2.84 (m, 3H), 2.02 – 1.88 (m, 2H), 1.86 – 1.67 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 155.32, 149.96, 147.35, 143.85, 136.87, 135.83, 129.61, 129.40, 128.53, 128.36, 128.03, 127.95, 124.53, 121.24, 67.17, 44.59, 42.51, 33.01.

ESI MS calculated for C₂₂H₂₃N₂O₂: 347.18 [(M+H⁺)], measured 347.25.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-40% EtOAc:hexanes

Yield: 100 mg (55%)

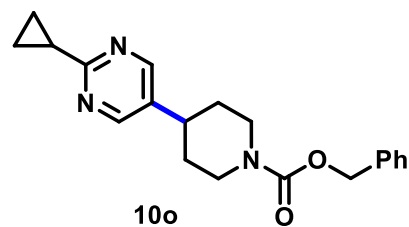
Physical State: colorless oil

¹H NMR (500 MHz, CDCl₃) δ 8.69 – 8.52 (m, 1H), 7.71 – 7.63 (m, 2H), 7.45 – 7.29 (m, 5H), 5.18 (s, 2H), 4.40 (s, 2H), 2.94 (s, 2H), 2.84 (tt, *J* = 12.2, 3.4 Hz, 1H), 1.94 – 1.83 (m, 2H), 1.76 – 1.62 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 155.20, 149.14, 146.61 (q, *J* = 34.7 Hz), 143.86, 136.69, 135.25, 128.53, 128.10, 127.99, 121.59 (q, *J* = 273.85 Hz), 120.39 (q, *J* = 2.7 Hz), 67.28, 44.26, 40.07, 32.56.

¹⁹F NMR (471 MHz, CDCl₃) δ -67.79.

ESI MS calculated for C₁₉H₂₀F₃N₂O₂: 365.15 [(M+H⁺)], measured 365.22.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-90% EtOAc:hexanes

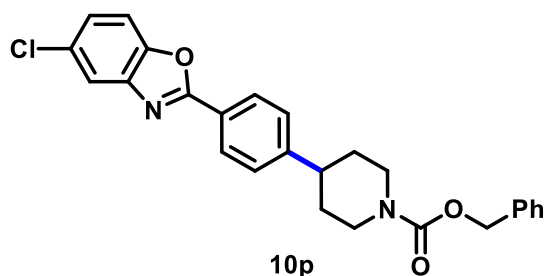
Yield: 42 mg (25%)

Physical State: colorless oil

¹H NMR (500 MHz, CDCl₃) δ 8.42 (s, 2H), 7.49 – 7.30 (m, 5H), 5.18 (s, 2H), 4.38 (s, 2H), 2.91 (s, 2H), 2.67 (tt, *J* = 12.3, 3.5 Hz, 1H), 2.25 (ddd, *J* = 13.0, 8.1, 4.8 Hz, 1H), 1.95 – 1.77 (m, 2H), 1.72 – 1.58 (m, 2H), 1.18 – 0.97 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 170.47, 155.42, 155.22, 136.72, 134.15, 128.53, 128.09, 127.98, 67.26, 44.29, 37.77, 32.50, 17.82, 10.60.

ESI MS calculated for C₂₀H₂₄N₃O₂: 338.19 [(M+H⁺)], measured 338.23.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-60% EtOAc:hexanes

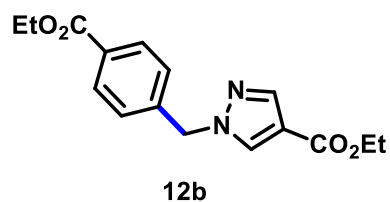
Yield: 86 mg (46%)

Physical State: white solid

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.14 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 2.1 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.43 – 7.30 (m, 5H), 5.11 (s, 2H), 4.17 (d, *J* = 12.5 Hz, 2H), 3.09 – 2.78 (m, 3H), 1.83 (d, *J* = 11.9 Hz, 2H), 1.59 (qd, *J* = 12.6, 4.1 Hz, 2H).

¹³C NMR (126 MHz, DMSO-*d*₆) δ 164.30, 154.89, 150.88, 149.49, 143.34, 137.49, 129.49, 128.90, 128.34, 128.30, 128.14, 128.05, 125.85, 124.47, 119.90, 112.74, 66.66, 44.43, 41.99, 32.77.

ESI MS calculated for C₂₆H₂₄ClN₂O₃: 447.15 [(M+H⁺)], measured 447.30.



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-80% EtOAc:hexanes

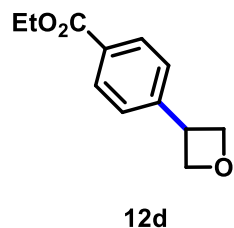
Yield: 86 mg (57%)

Physical State: white solid

¹H NMR (500 MHz, CDCl₃) δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.97 (s, 1H), 7.91 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 5.38 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 166.02, 162.83, 141.51, 140.19, 132.82, 130.67, 130.23, 127.64, 115.89, 61.14, 60.28, 56.02, 14.37, 14.30.

ESI MS calculated for C₁₆H₁₉N₂O₄: 303.13 [(M+H⁺)], measured 303.19.



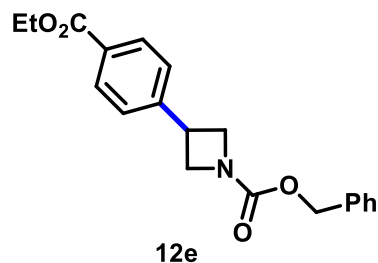
Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-30% EtOAc:hexanes

Yield: 35 mg (34%)

Physical state: colorless oil

Analytical data matched those previously published.¹⁴



Followed General Procedure A (0.5 mmol scale)

Flash chromatography solvent system: 0-50% EtOAc:hexanes

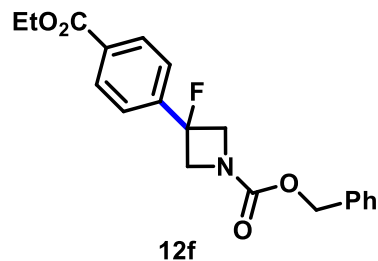
Yield: 83 mg (49%)

Physical State: colorless oil

¹H NMR (500 MHz, CDCl₃) δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.31 (m, 7H), 5.16 (s, 2H), 4.46 (t, *J* = 8.7 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.09 (dd, *J* = 8.5, 6.1 Hz, 2H), 3.90 – 3.81 (m, 1H), 1.41 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 166.15, 156.32, 146.81, 136.51, 129.98, 129.34, 128.42, 128.01, 127.94, 126.64, 66.68, 60.89, 56.38, 33.77, 14.24.

ESI MS calculated for C₂₀H₂₂NO₄: 340.15 [(M+H⁺)], measured 340.22.



Followed General Procedure A (0.5 mmol scale) but with DMPU instead of DMI

Flash chromatography solvent system: 0-50% EtOAc:hexanes

Yield: 38 mg (21%)

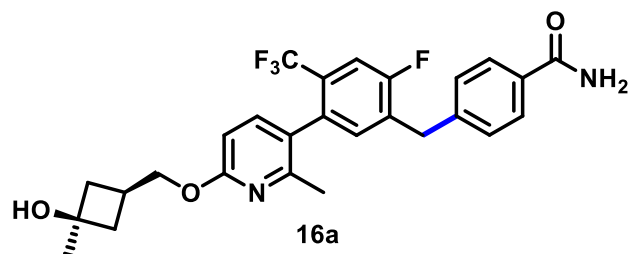
Physical State: colorless oil

¹H NMR (500 MHz, CDCl₃) δ 8.12 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.46 – 7.32 (m, 5H), 5.20 (s, 2H), 4.53 (ddd, *J* = 22.2, 10.3, 1.1 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.40 – 4.31 (m, 2H), 1.43 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 165.92, 156.44, 156.41, 143.53, 143.35, 136.23, 130.90, 130.90, 130.01, 130.00, 129.28, 128.59, 128.31, 128.16, 124.01, 123.94, 118.53, 115.10, 92.10, 90.44, 67.26, 62.98, 62.79, 61.23, 14.32 (analysis of the spectrum is complicated by C-F coupling, not all multiplets were assigned).

¹⁹F NMR (471 MHz, CDCl₃) δ -151.26.

ESI MS calculated for C₂₀H₂₁FNO₄: 358.15 [(M+H⁺)], measured 358.19.



Followed General Procedure A with 5 equiv. of Ar-Br

Flash chromatography solvent system: 0-100% EtOAc:hexanes

Yield: 131 mg (52%)

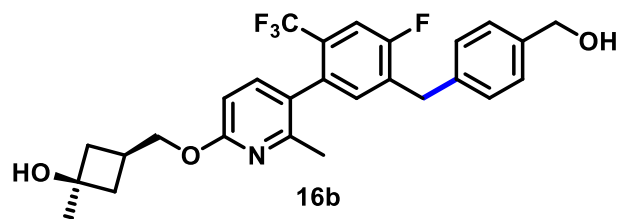
Physical State: colorless oil

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.89 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 10.1 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.30 (s, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 4.88 (s, 1H), 4.24 (dq, *J* = 8.5, 3.6 Hz, 2H), 4.13 (s, 2H), 2.28 – 2.17 (m, 1H), 2.12 – 2.00 (m, 5H), 1.89 – 1.78 (m, 2H), 1.26 (s, 3H).

¹³C NMR (126 MHz, DMSO) δ 168.07, 162.98, 160.64, 158.67, 153.59, 142.58, 140.82, 135.93, 135.89, 134.88, 133.09, 132.71, 132.59, 128.86, 128.33, 125.62, 114.46, 114.43, 114.35, 114.26, 114.22, 114.18, 114.14, 107.26, 70.72, 68.37, 41.42, 41.40, 34.23, 28.16, 24.67, 23.05 (analysis of the spectrum is complicated by C-F coupling, not all multiplets were assigned).

¹⁹F NMR (471 MHz, DMSO-*d*₆) δ -58.04, -116.84.

ESI MS calculated for C₂₇H₂₇F₄N₂O₃: 503.20 [(M+H⁺)], measured 503.48.



Followed General Procedure A (0.25 mmol scale) with 5 equiv. of Ar-Br

Flash chromatography solvent system: 0-75% EtOAc:hexanes

Yield: 42 mg (34%)

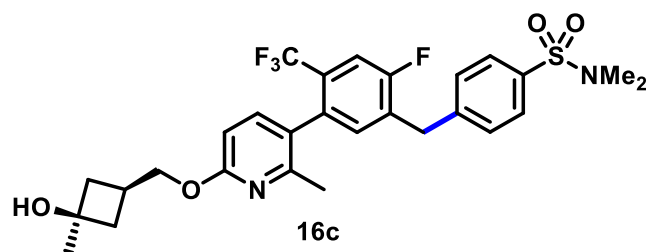
Physical State: colorless oil

¹H NMR (500 MHz, CDCl₃) δ 7.46 (d, *J* = 9.9 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 4.68 (s, 2H), 4.37 – 4.24 (m, 2H), 4.06 (s, 2H), 2.38 – 2.23 (m, 3H), 2.11 (s, 3H), 2.08 – 1.87 (m, 4H), 1.43 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 163.05, 160.57, 158.60, 153.93, 140.15, 139.41, 137.81, 134.78, 134.75, 134.72, 134.70, 132.11, 131.99, 128.97, 127.48, 125.57, 124.18, 124.16, 122.01, 121.99, 113.96, 113.92, 113.88, 113.83, 113.75, 113.71, 113.67, 113.63, 106.52, 69.90, 69.73, 64.95, 40.94, 40.93, 34.34, 34.32, 27.45, 24.78, 22.77 (analysis of the spectrum is complicated by C-F coupling, not all multiplets were assigned).

¹⁹F NMR (471 MHz, CDCl₃) δ -59.49, -117.35.

ESI MS calculated for C₂₇H₂₈F₄NO₃: 490.20 [(M+H⁺)], measured 490.33.



Followed General Procedure A (0.25 mmol scale) with 5 equiv. of Ar-Br

Flash chromatography solvent system: 0-50% EtOAc:hexanes

Yield: 93 mg (66%)

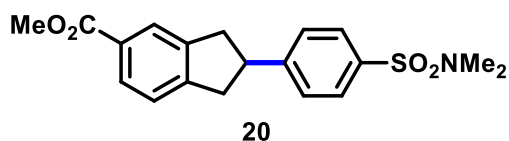
Physical State: thick waxy solid

¹H NMR (500 MHz, CDCl₃) δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.48 (d, *J* = 9.8 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.30 (s, 1H), 7.06 (d, *J* = 6.9 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 4.31 (s, 2H), 4.13 (s, 2H), 2.70 (s, 6H), 2.37 – 2.23 (m, 3H), 2.17 (s, 1H), 2.11 (s, 3H), 2.04 – 1.97 (m, 2H), 1.42 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 163.15, 160.58, 158.61, 153.81, 143.77, 140.05, 135.13, 134.93, 134.90, 134.13, 130.63, 130.50, 129.26, 128.48, 128.25, 127.96, 125.21, 114.25, 114.21, 114.17, 114.13, 114.05, 114.01, 113.97, 113.93, 106.69, 69.98, 69.68, 40.95, 37.90, 34.59, 27.47, 24.78, 22.77 (analysis of the spectrum is complicated by C-F coupling, not all multiplets were assigned).

¹⁹F NMR (471 MHz, CDCl₃) δ -59.59, -116.96.

ESI MS calculated for C₂₈H₃₁F₄N₂O₄S: 567.19 [(M+H⁺)], measured 567.36.



Followed General Procedure A (0.28 mmol scale)

Flash chromatography solvent system: 0-60% EtOAc:hexanes

Yield: 20 mg (20%)

Physical State: white solid

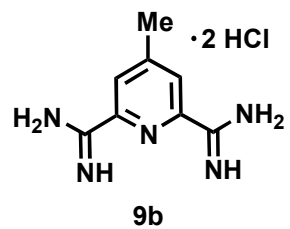
¹H NMR (500 MHz, CDCl₃) δ 7.97 – 7.89 (m, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 1H), 3.94 (s, 3H), 3.83 (p, *J* = 8.2 Hz, 1H), 3.47 (dd, *J* = 16.0, 8.2 Hz, 2H), 3.14 (ddd, *J* = 15.5, 8.2, 3.1 Hz, 2H), 2.74 (s, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 167.28, 150.32, 147.88, 142.66, 133.66, 129.02, 128.61, 128.11, 127.58, 125.56, 124.29, 52.06, 45.09, 40.71, 40.33, 37.95.

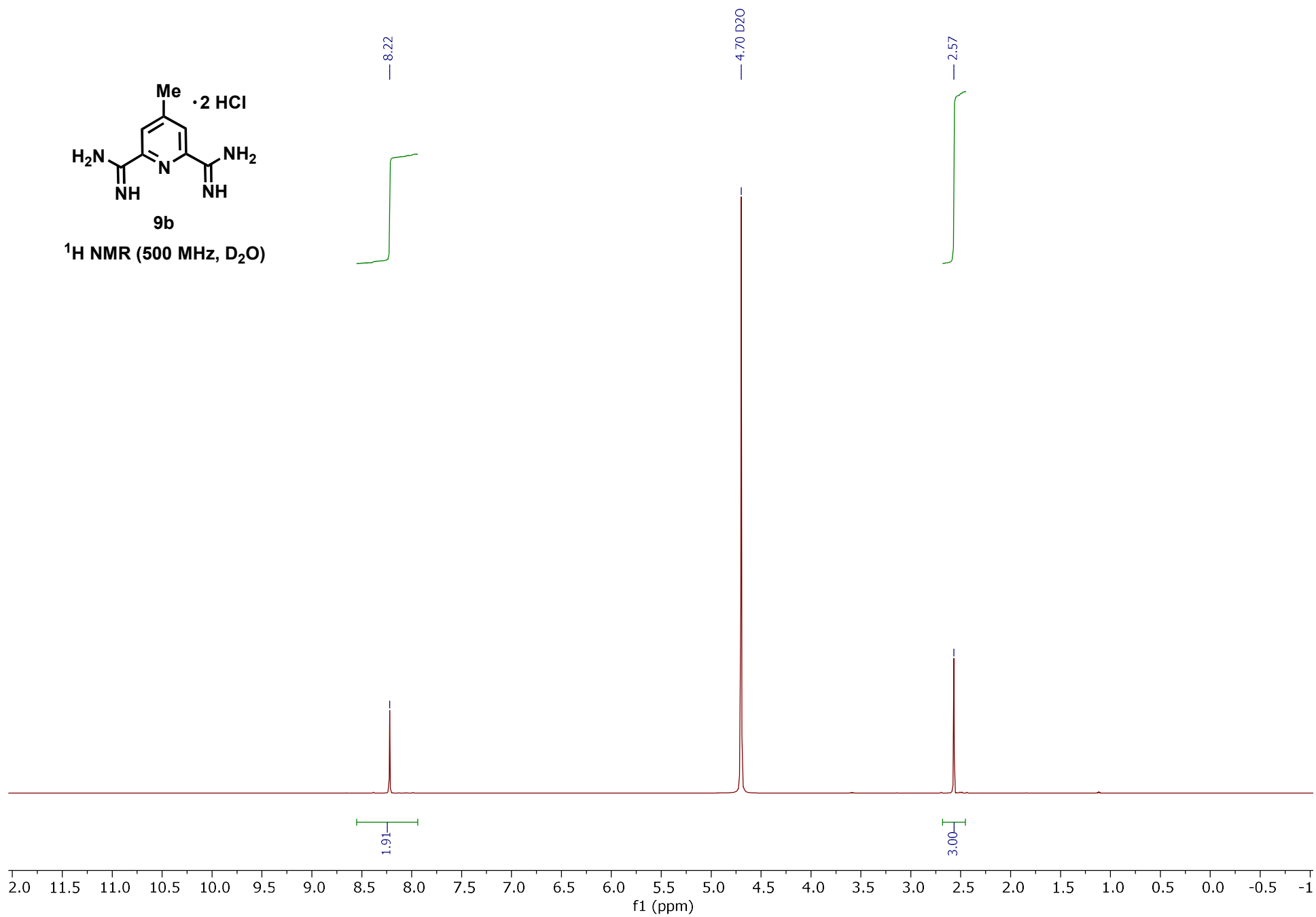
ESI MS calculated for C₁₉H₂₂NO₄S: 360.13 [(M+H⁺)], measured 360.17.

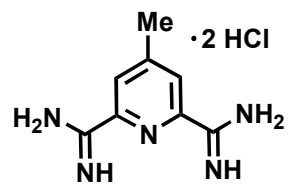
References:

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- (2) Ni(COD)₂ was added in the glovebox under an atmosphere of N₂.
- (3) Ligand **9a** is commercially available from Sigma Aldrich (CAS: 1394382-56-9)
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^1H NMR (500 MHz, D_2O)



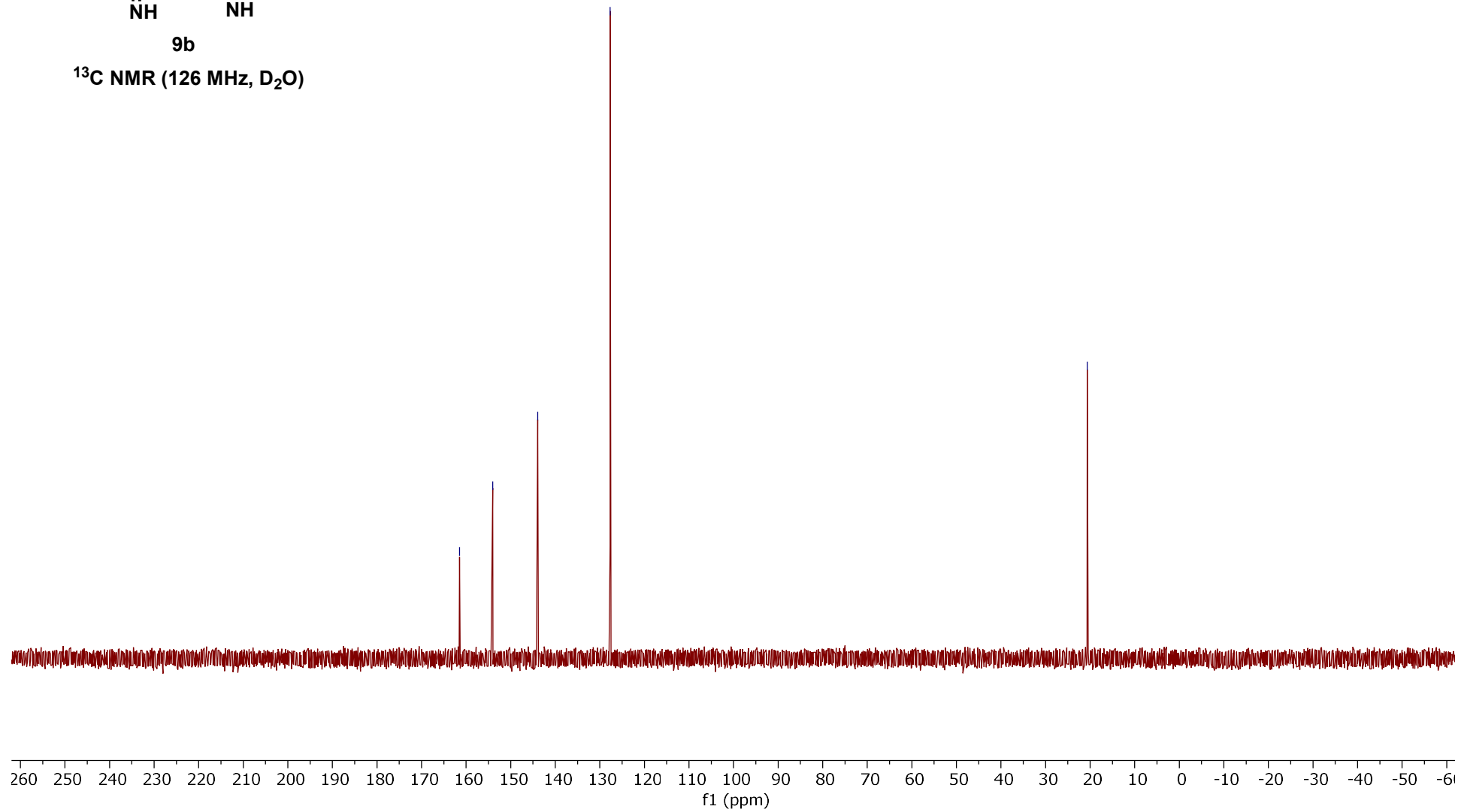


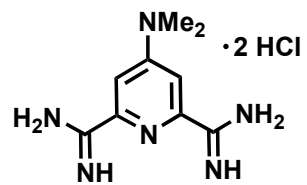
9b

¹³C NMR (126 MHz, D₂O)

— 161.45
— 154.04
— 143.91
— 127.68

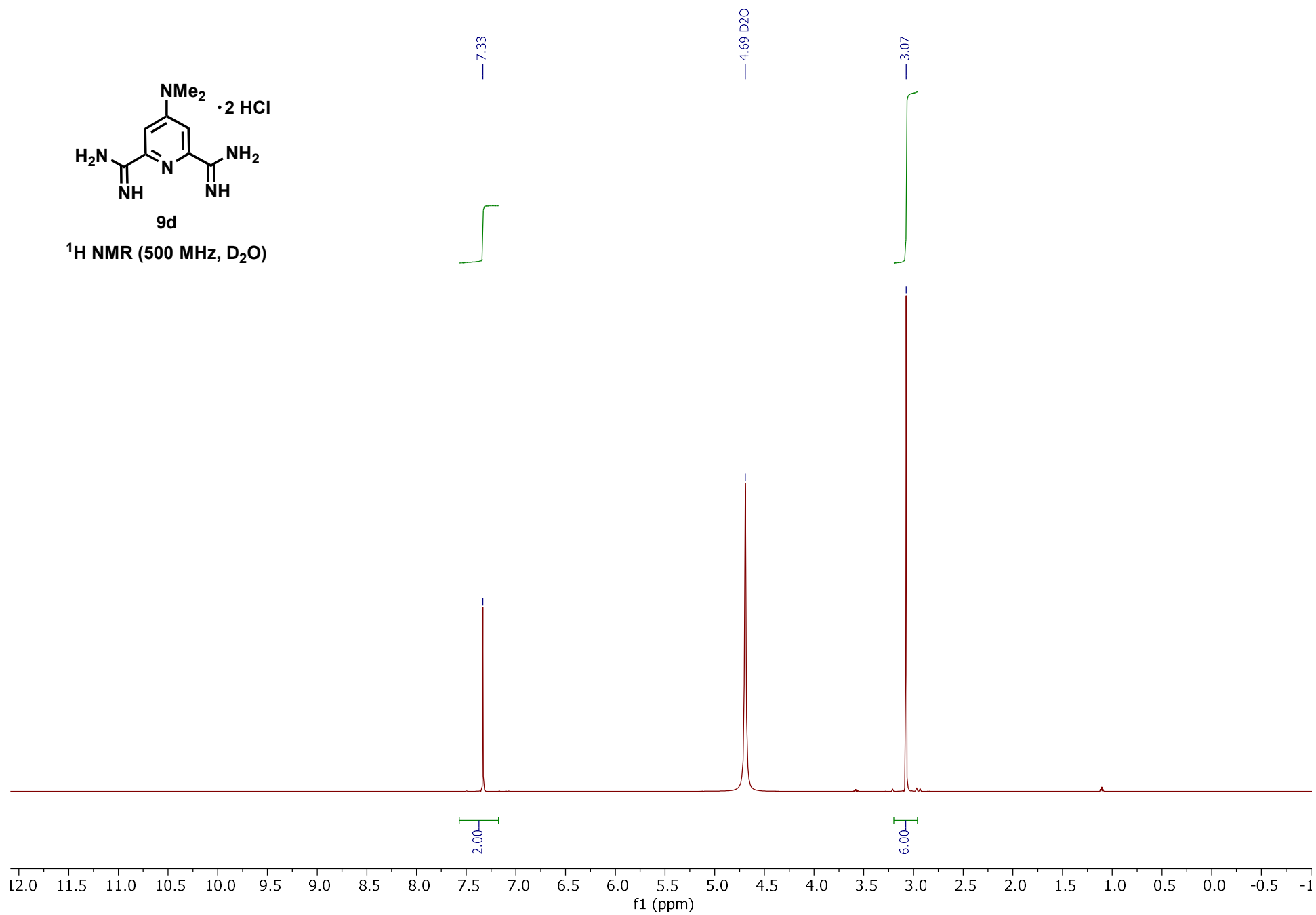
— 20.65

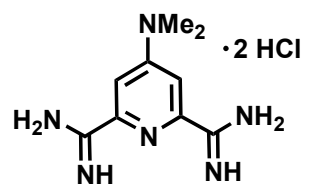




9d

^1H NMR (500 MHz, D_2O)

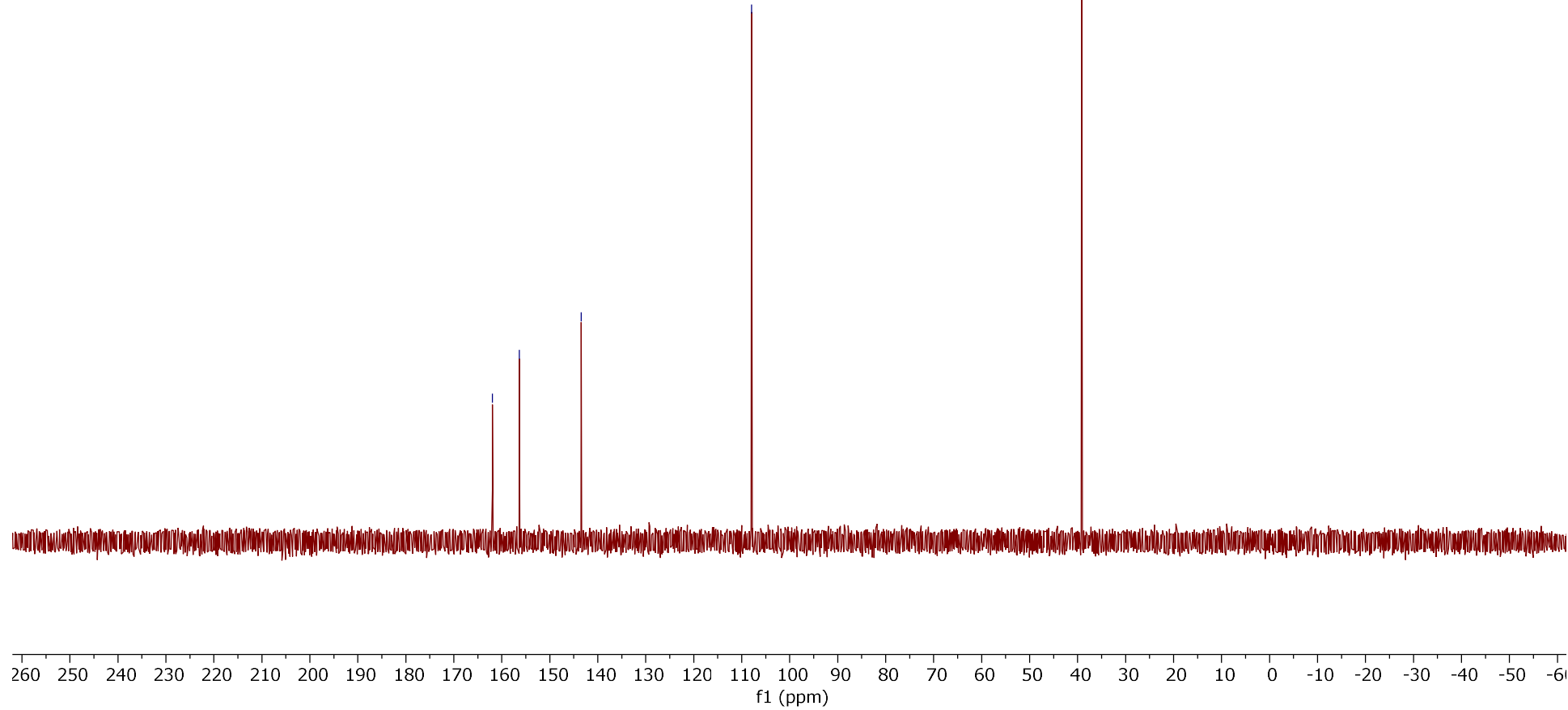


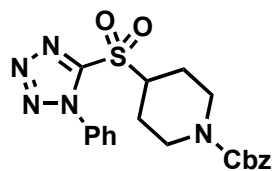


9d

^{13}C NMR (126 MHz, D_2O)

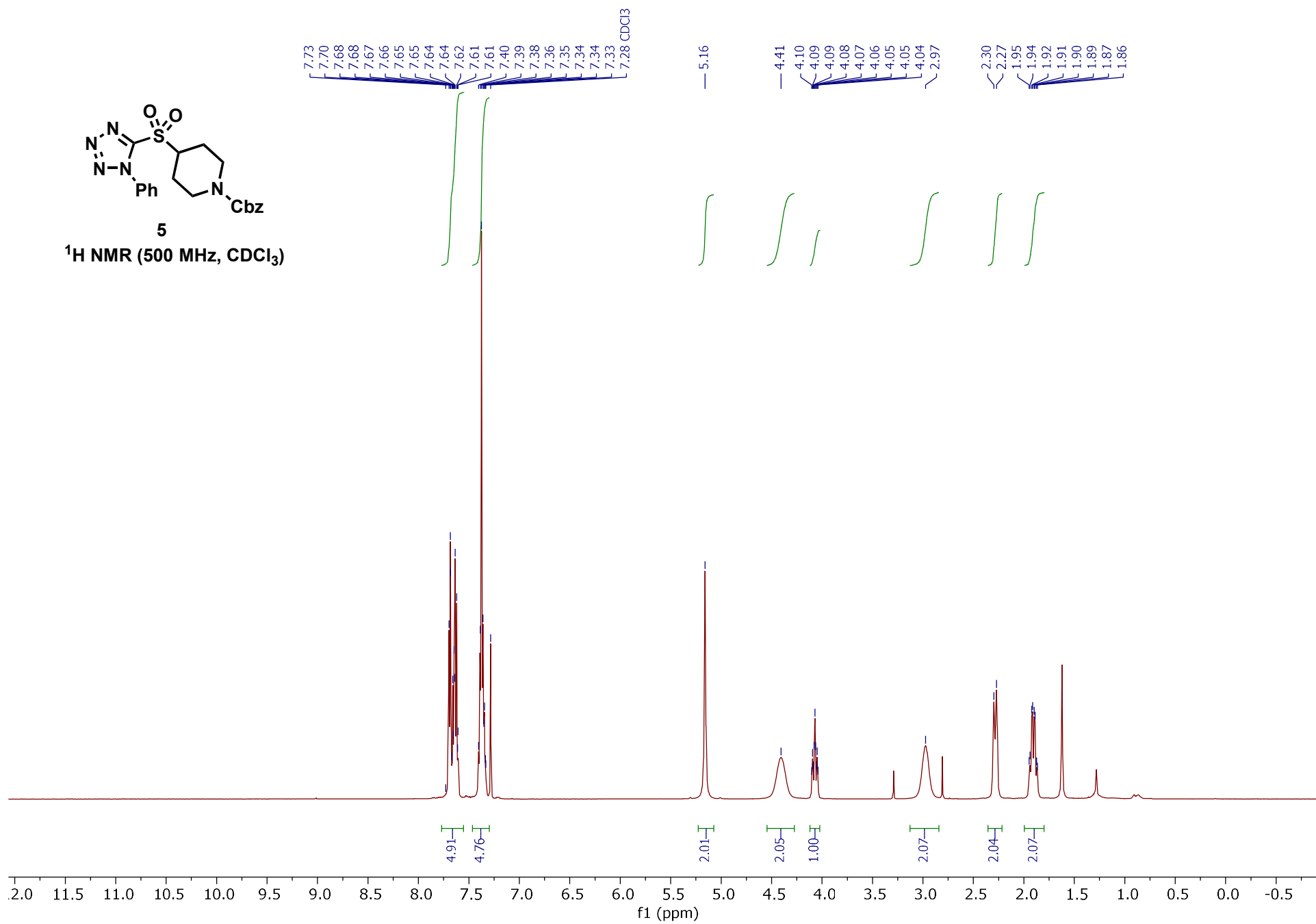
— 161.93
— 156.36
— 143.44
— 107.96
— 39.17

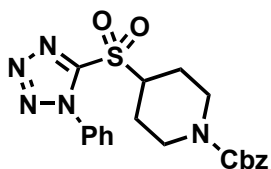




5

^1H NMR (500 MHz, CDCl_3)

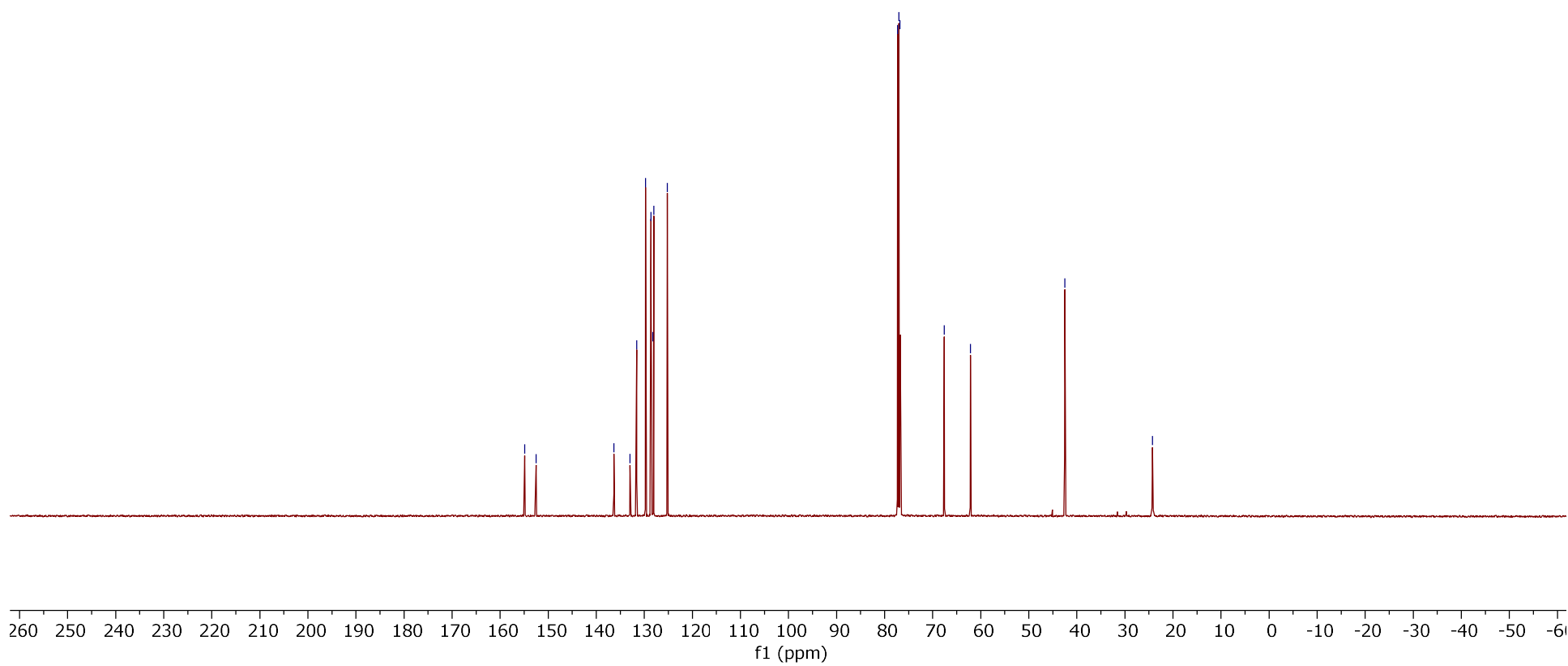


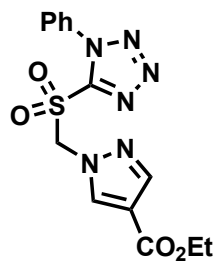


5

¹³C NMR (126 MHz, CDCl₃)

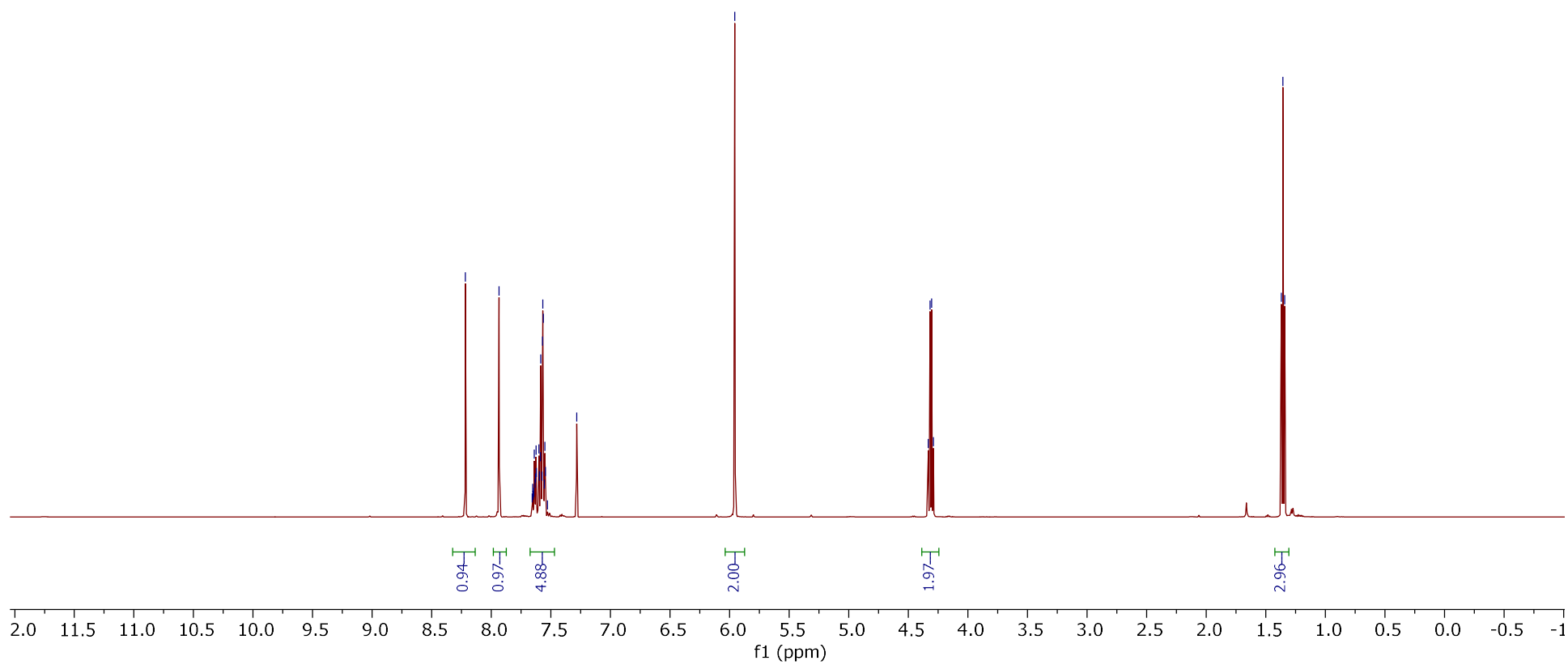
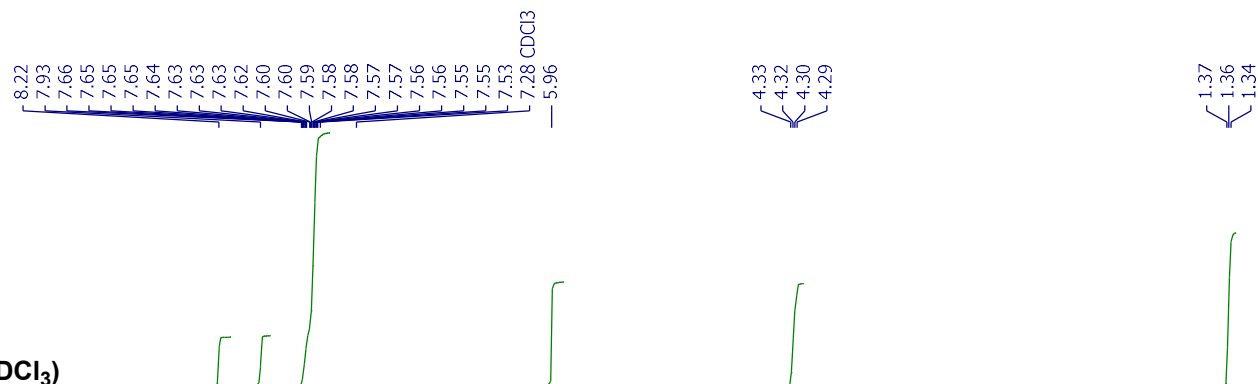
154.87
152.52
136.32
132.99
131.58
129.72
128.59
128.24
128.04
125.21
77.30 CDCl₃
77.04 CDCl₃
76.79 CDCl₃
67.58
62.14
42.50
24.24

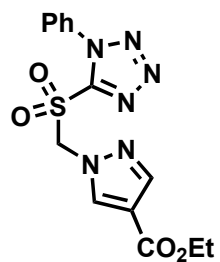




S2

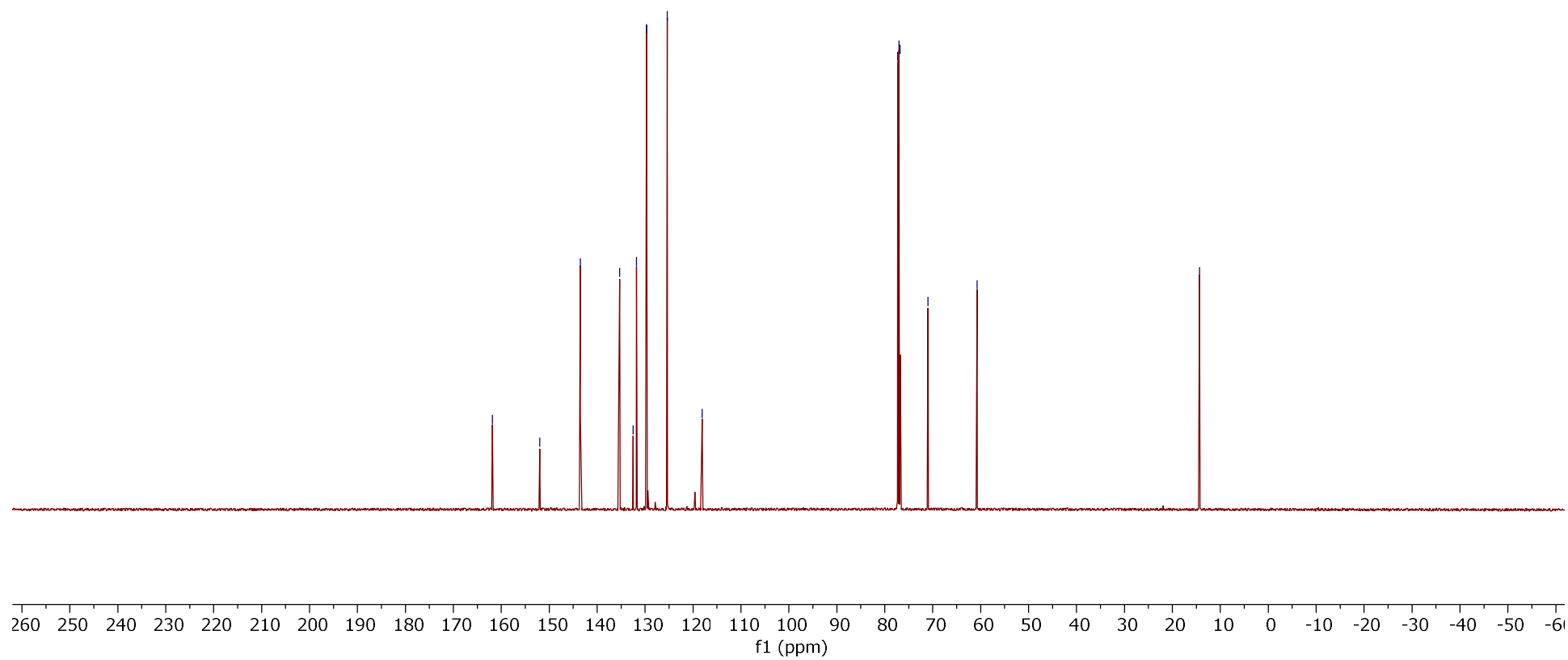
^1H NMR (500 MHz, CDCl_3)

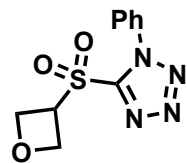




S2

^{13}C NMR (126 MHz, CDCl_3)





S4

^1H NMR (500 MHz, CDCl_3)

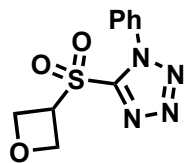
7.77
7.77
7.76
7.76
7.76
7.75
7.75
7.69
7.68
7.68
7.67
7.66
7.65
7.64
7.64
7.63
— 7.28 CDCl_3

5.31
5.29
5.28
5.26
5.25
5.11
5.09
5.08

1.95
2.97

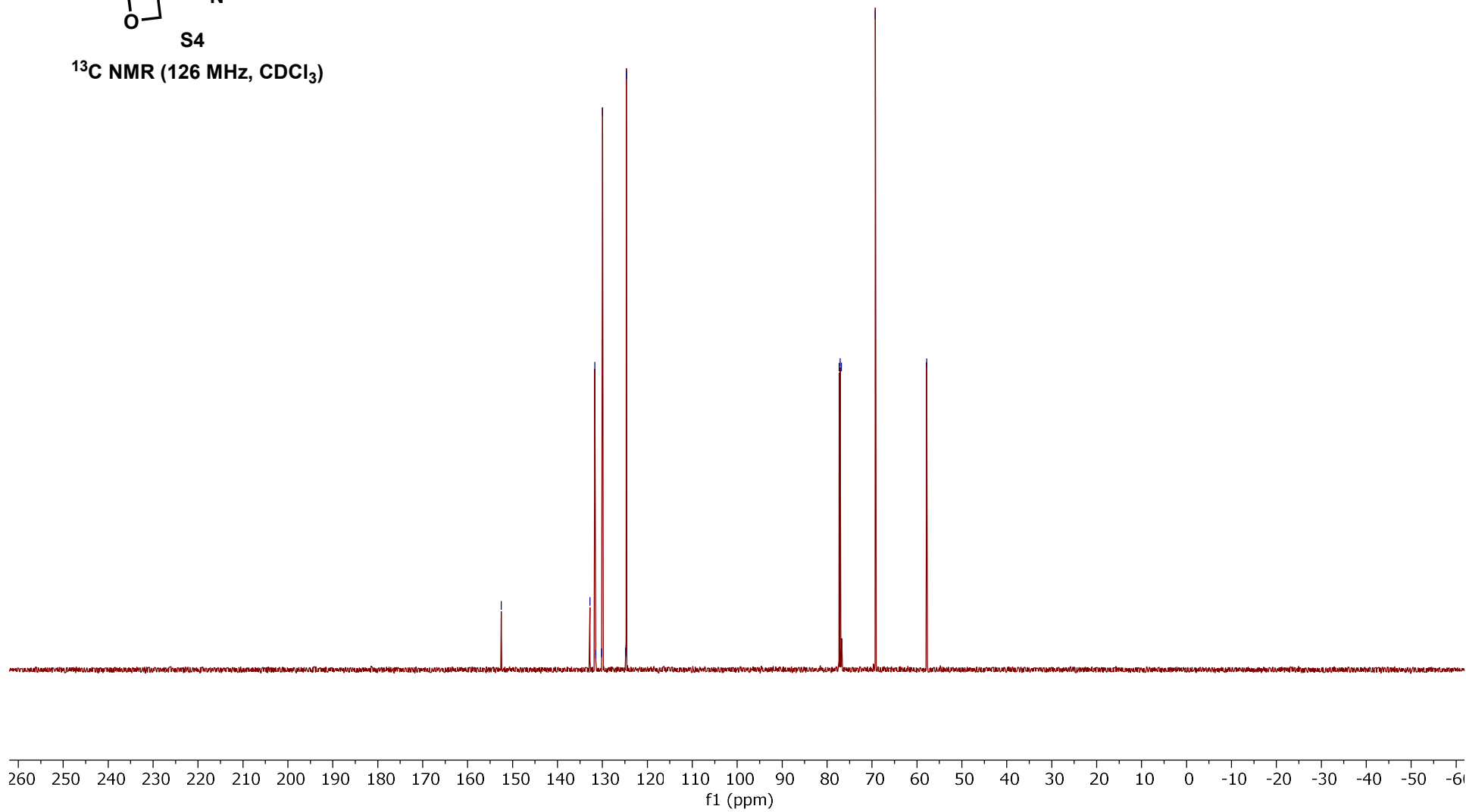
1.01
4.09

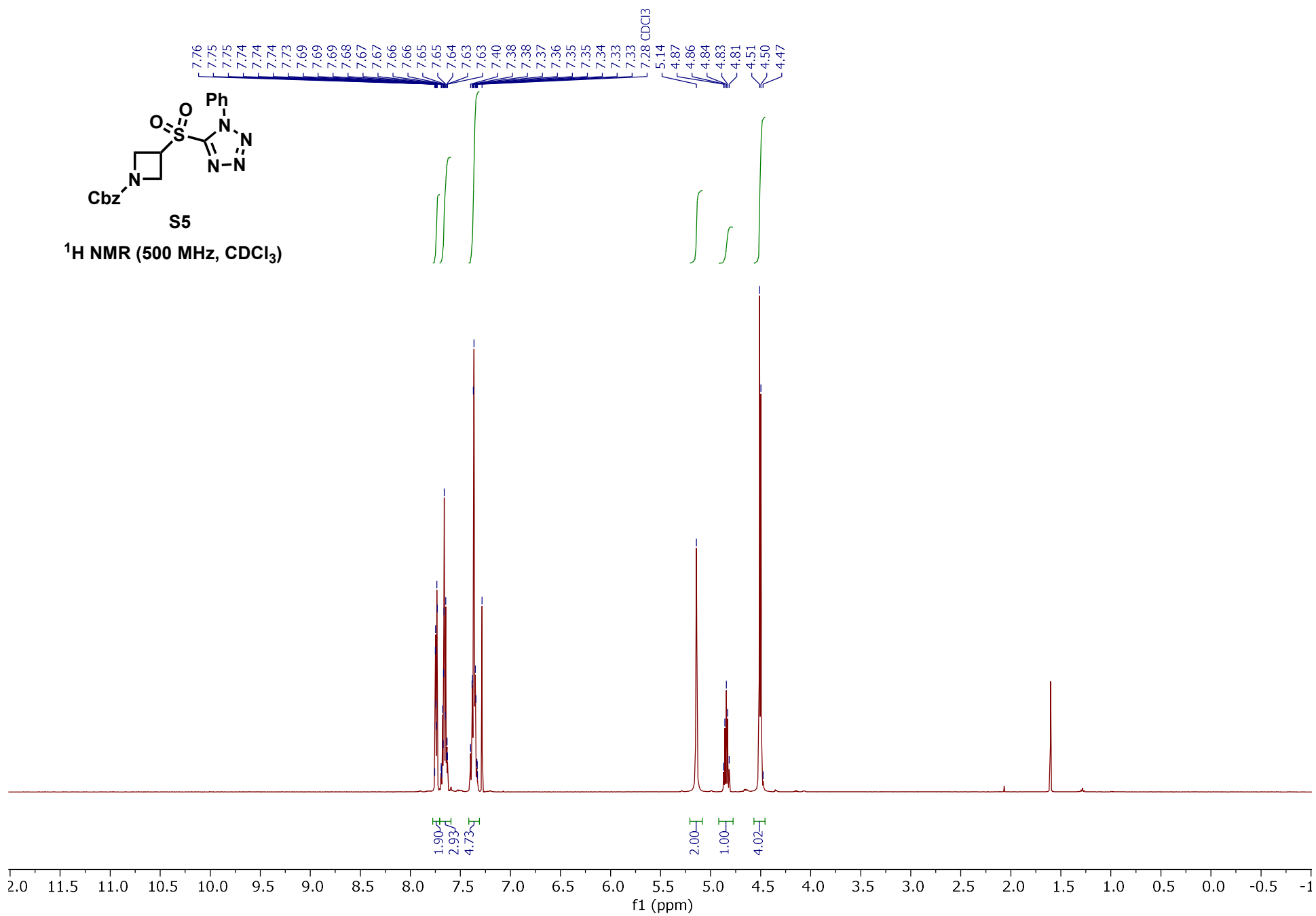
f1 (ppm)

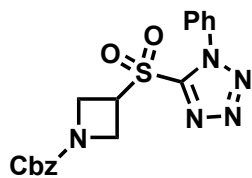


S4

^{13}C NMR (126 MHz, CDCl_3)

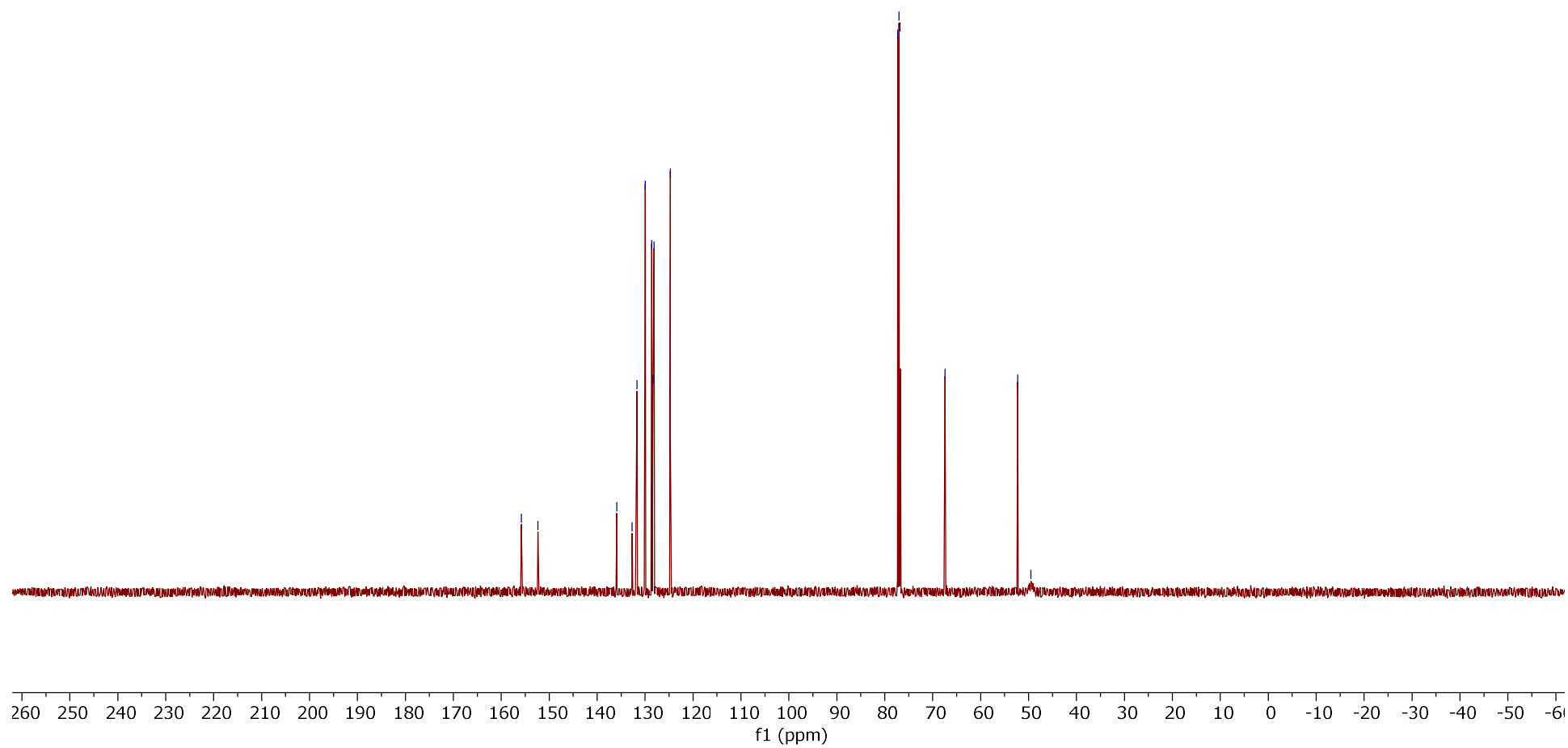




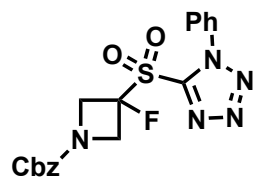


S5

^{13}C NMR (126 MHz, CDCl_3)

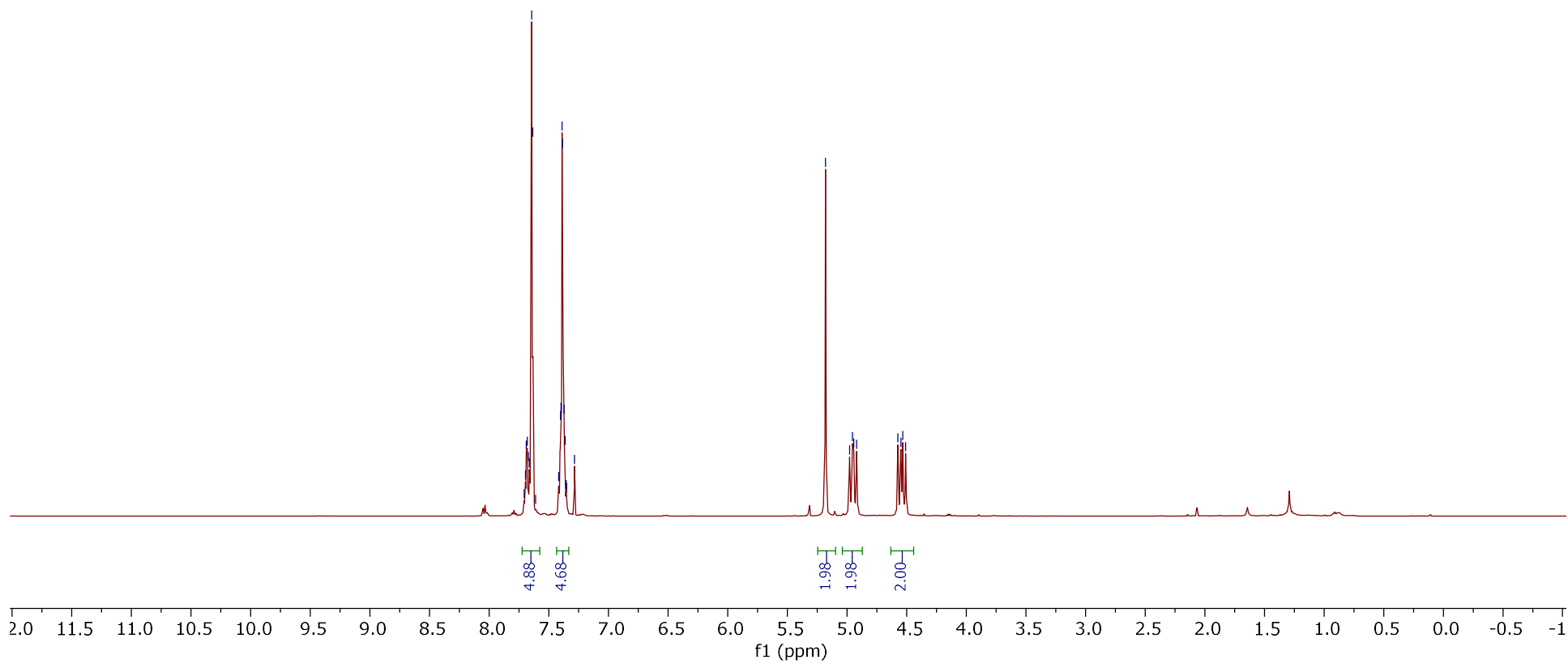
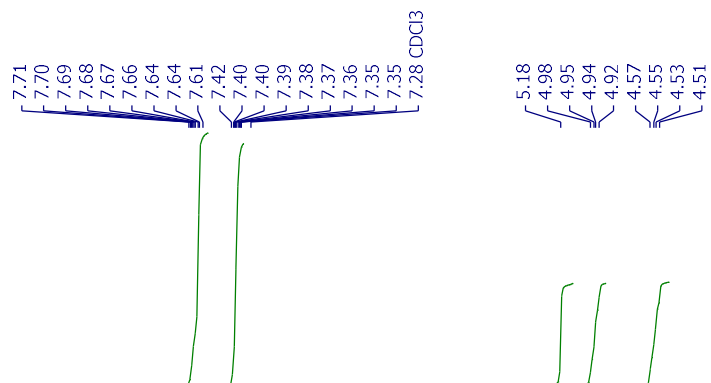


S40

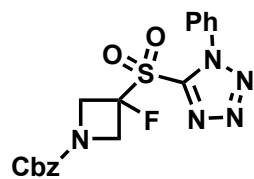


S6

^1H NMR (500 MHz, CDCl_3)



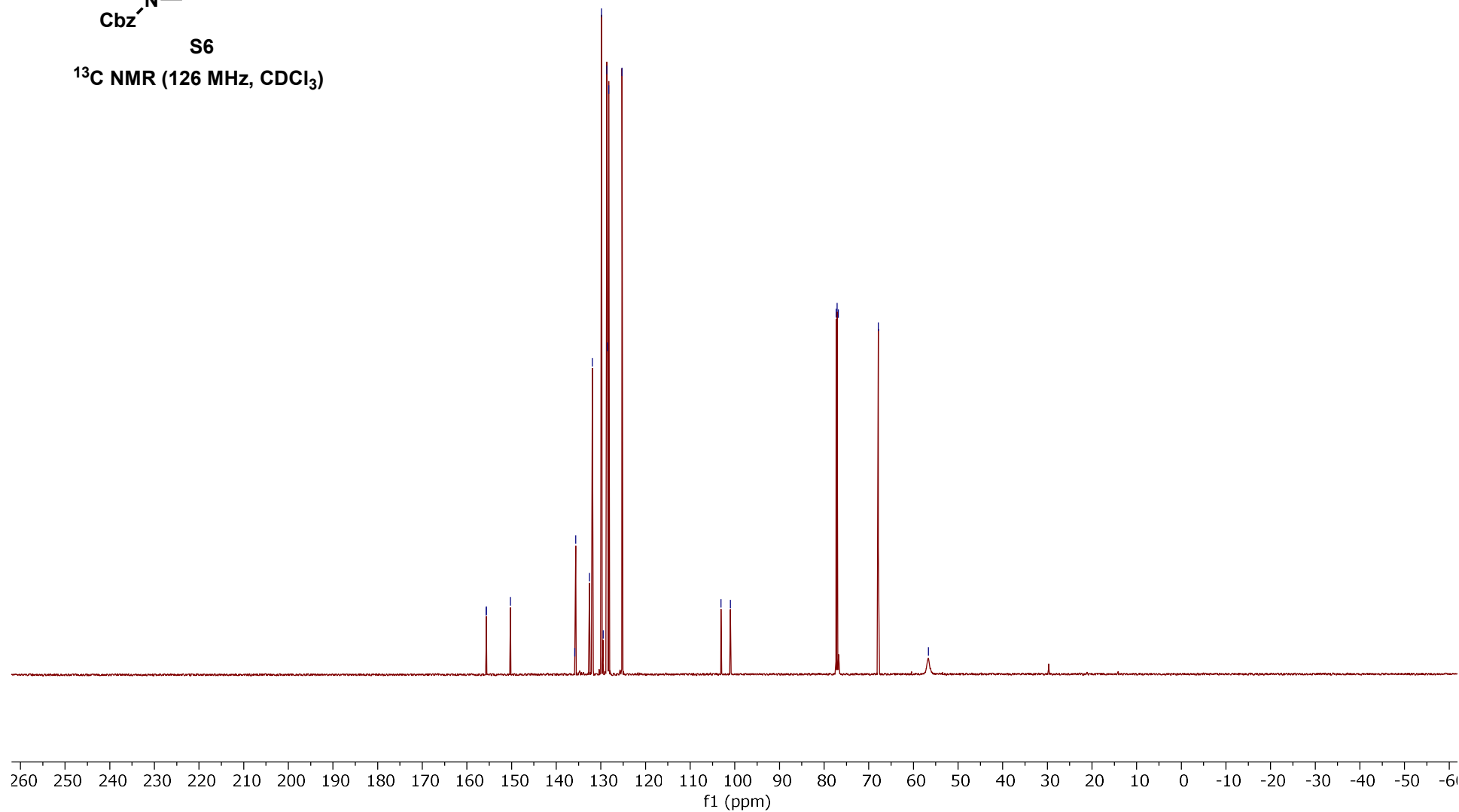
S41

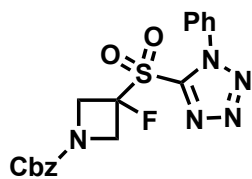


S6

^{13}C NMR (126 MHz, CDCl_3)

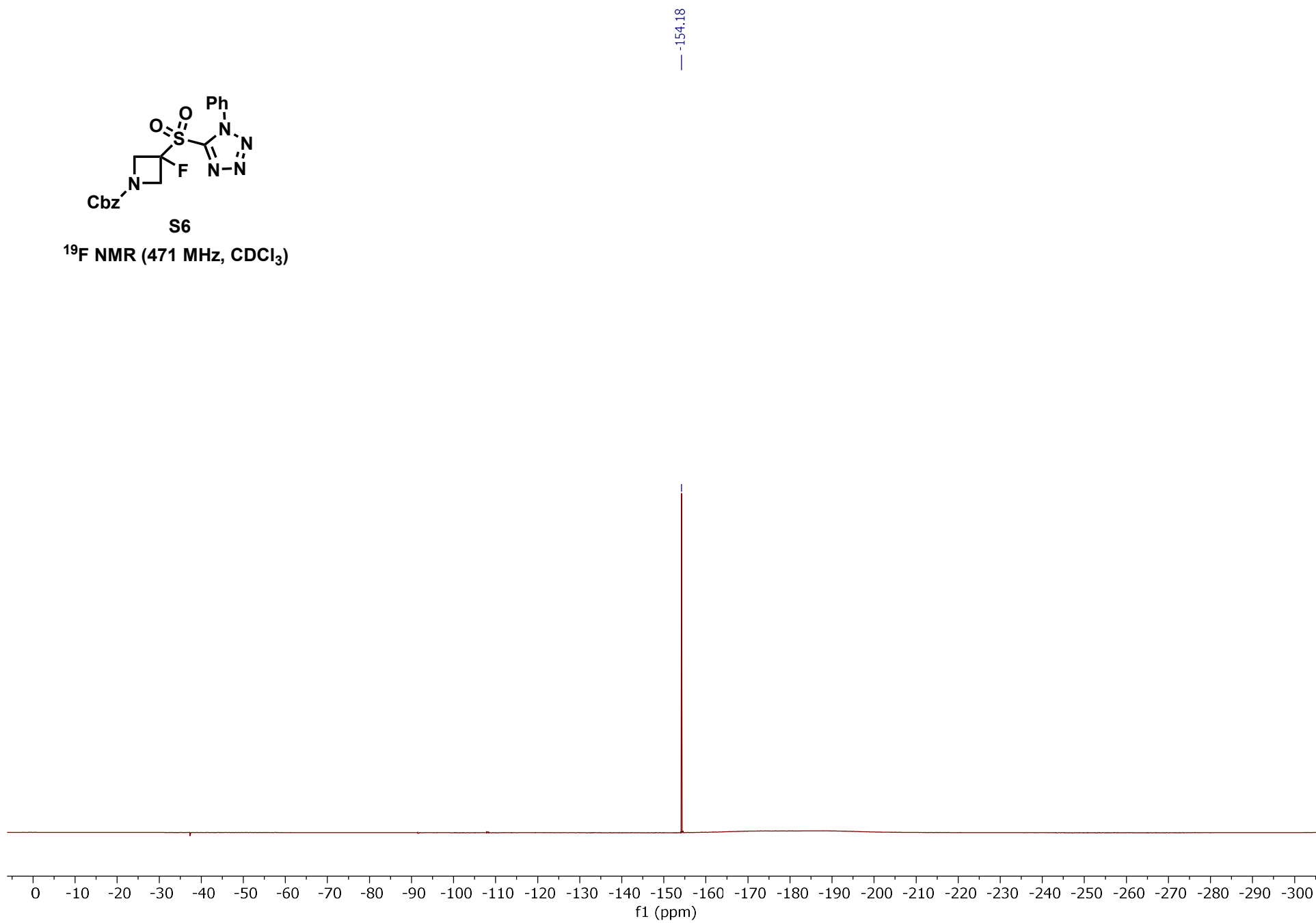
155.68
155.66
150.24
135.85
135.61
132.53
131.92
129.85
129.49
128.66
128.50
128.23
125.25
103.06
100.97
77.32 CDCl_3
77.07 CDCl_3
76.81 CDCl_3
67.85
56.65

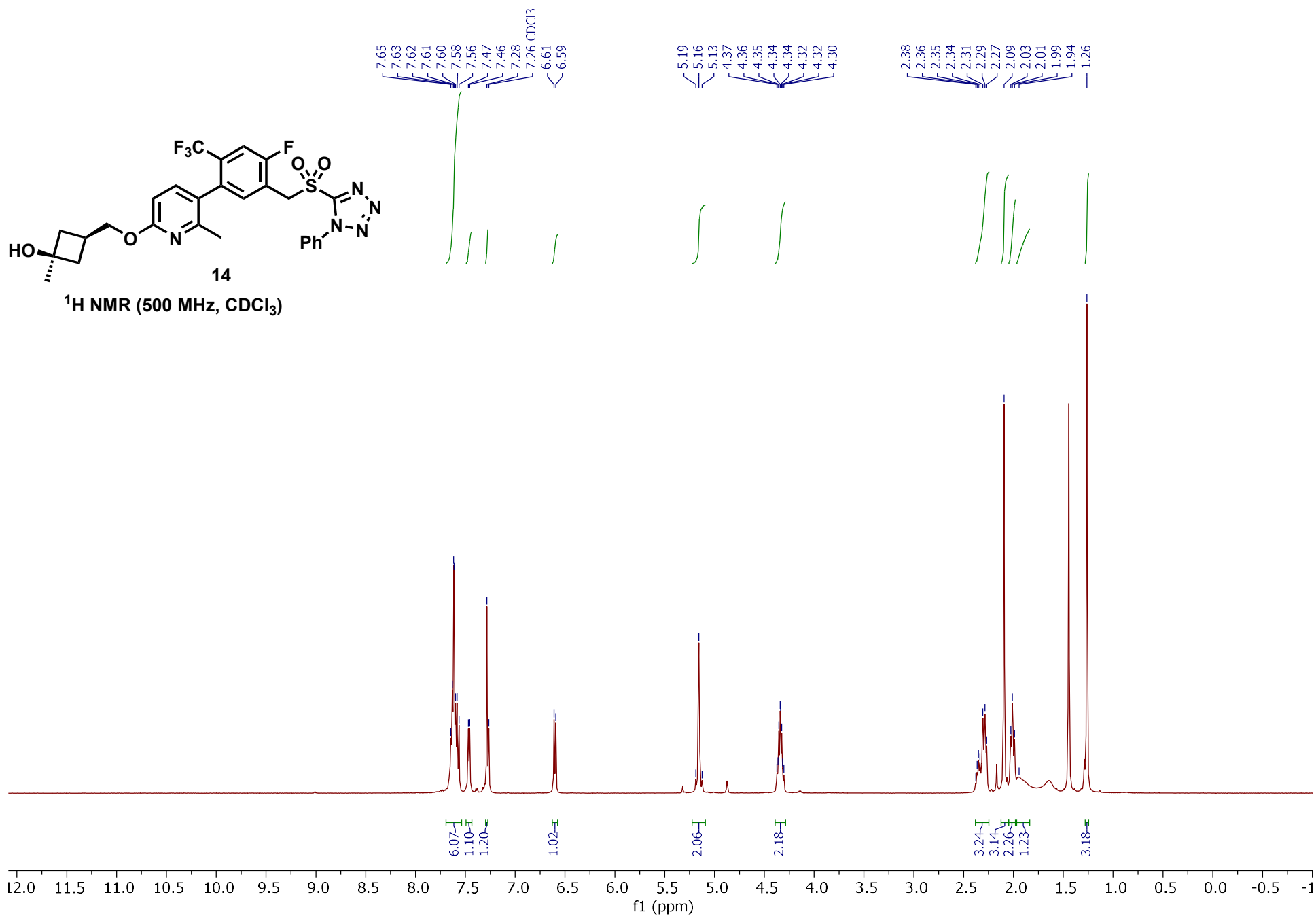


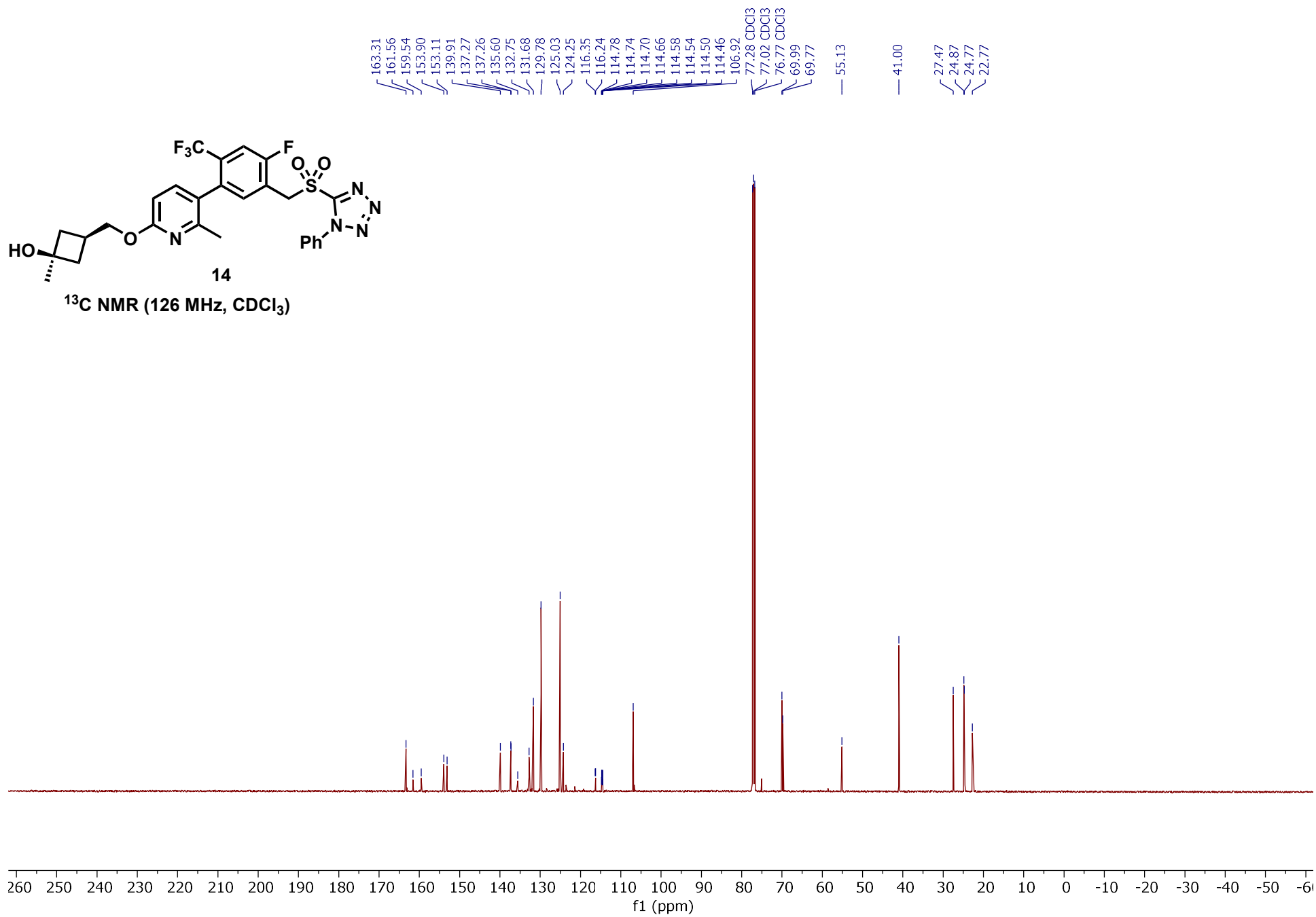


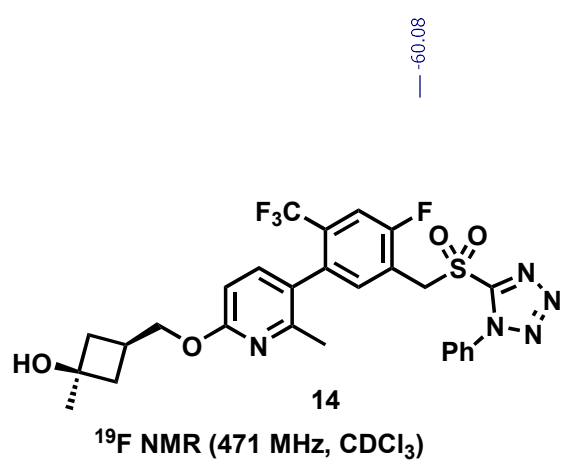
S6

^{19}F NMR (471 MHz, CDCl_3)



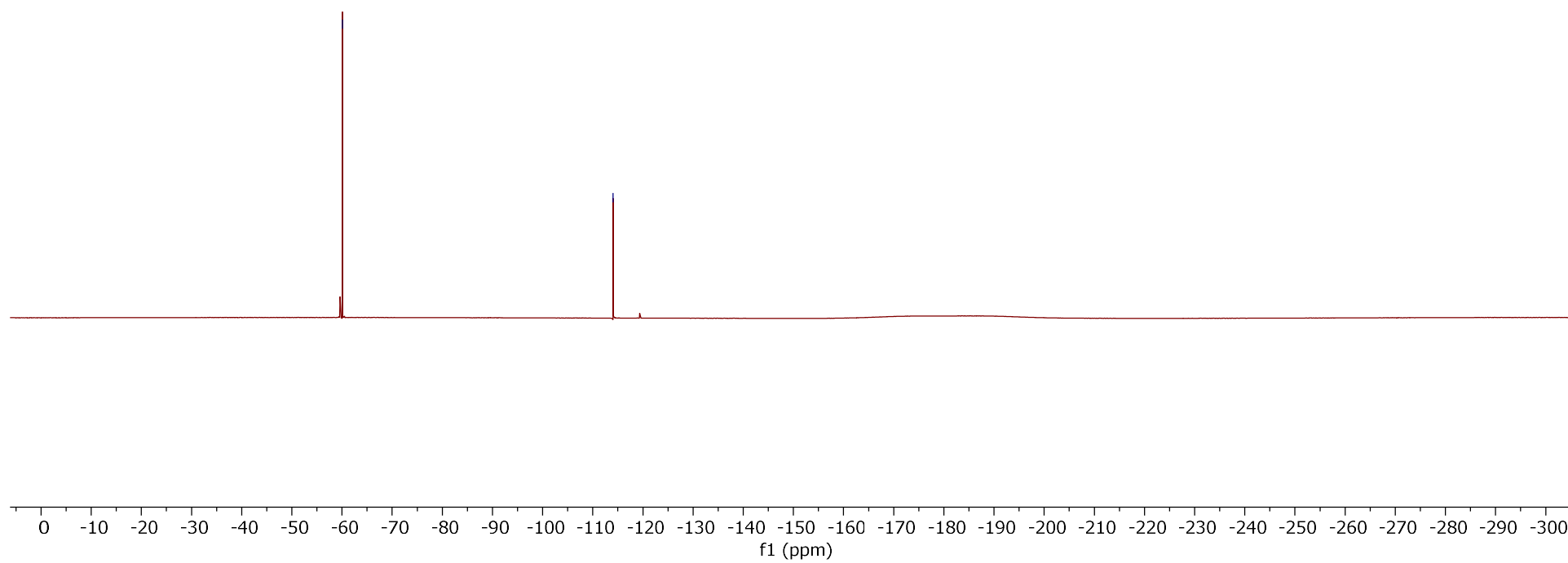


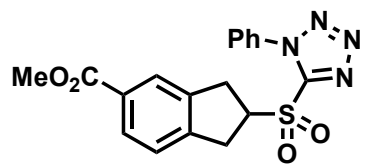




-60.08

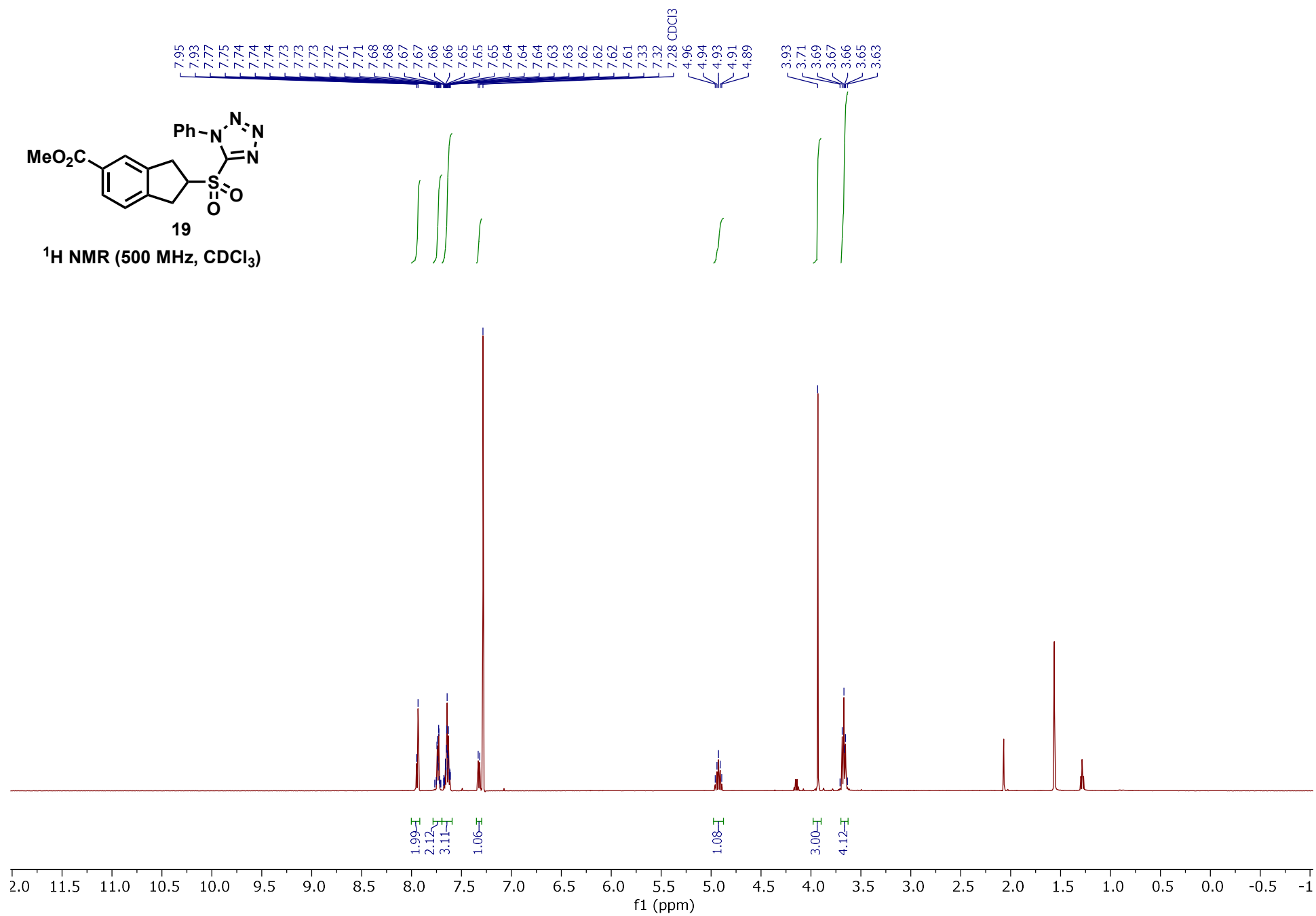
-114.06

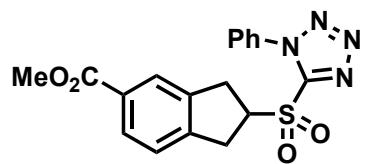




19

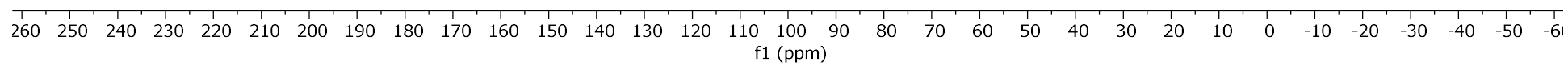
¹H NMR (500 MHz, CDCl₃)

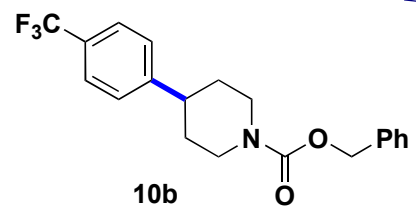




19

^{13}C NMR (126 MHz, CDCl_3)





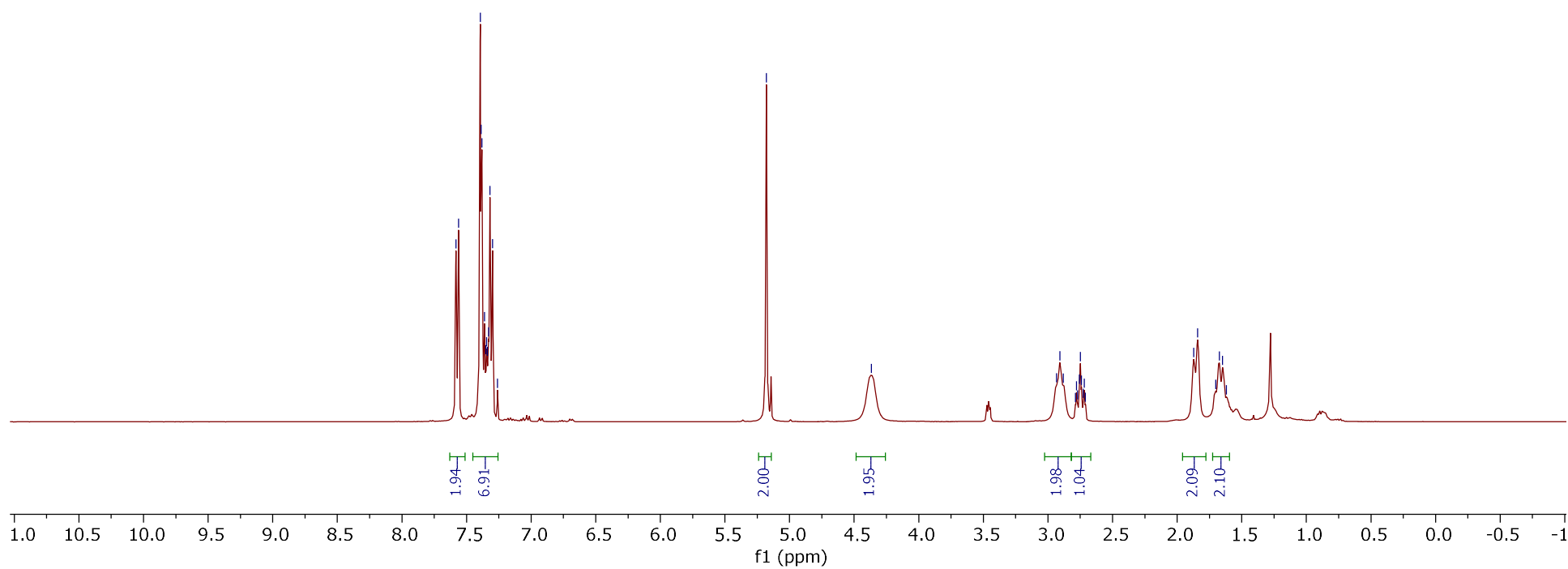
¹H NMR (400 MHz, CDCl₃)

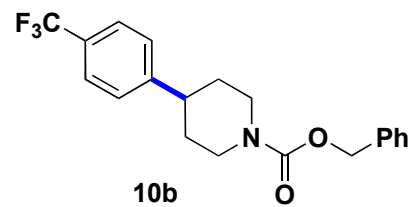
7.58
 7.56
 7.39
 7.39
 7.38
 7.36
 7.35
 7.34
 7.34
 7.33
 7.32
 7.30
 7.26 CDCl₃

5.18

4.37

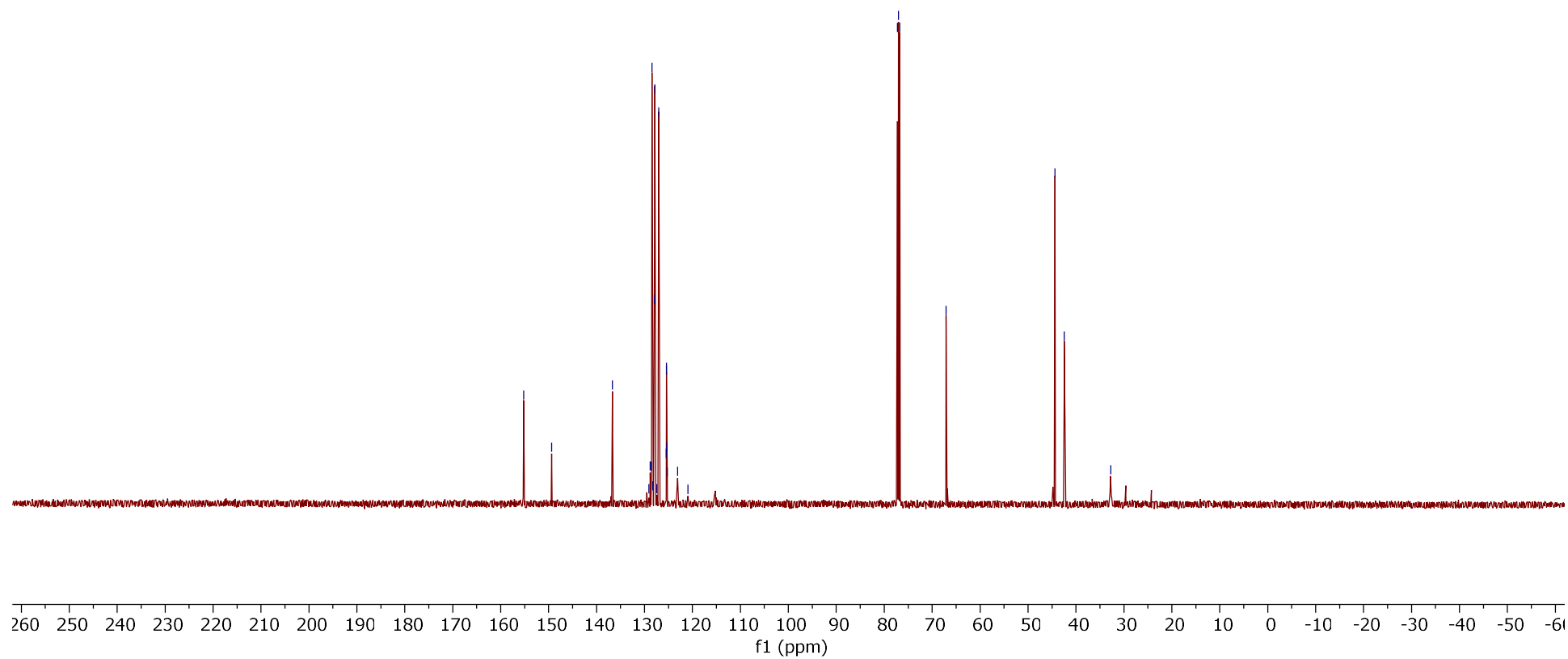
2.93
 2.91
 2.88
 2.79
 2.78
 2.77
 2.76
 2.75
 2.74
 2.73
 2.72
 2.71
 1.87
 1.84
 1.70
 1.67
 1.65
 1.62

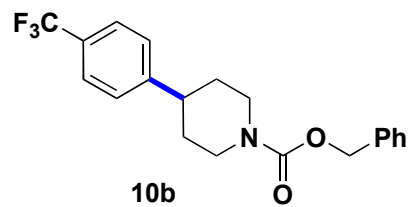




¹³C NMR (126 MHz, CDCl₃)

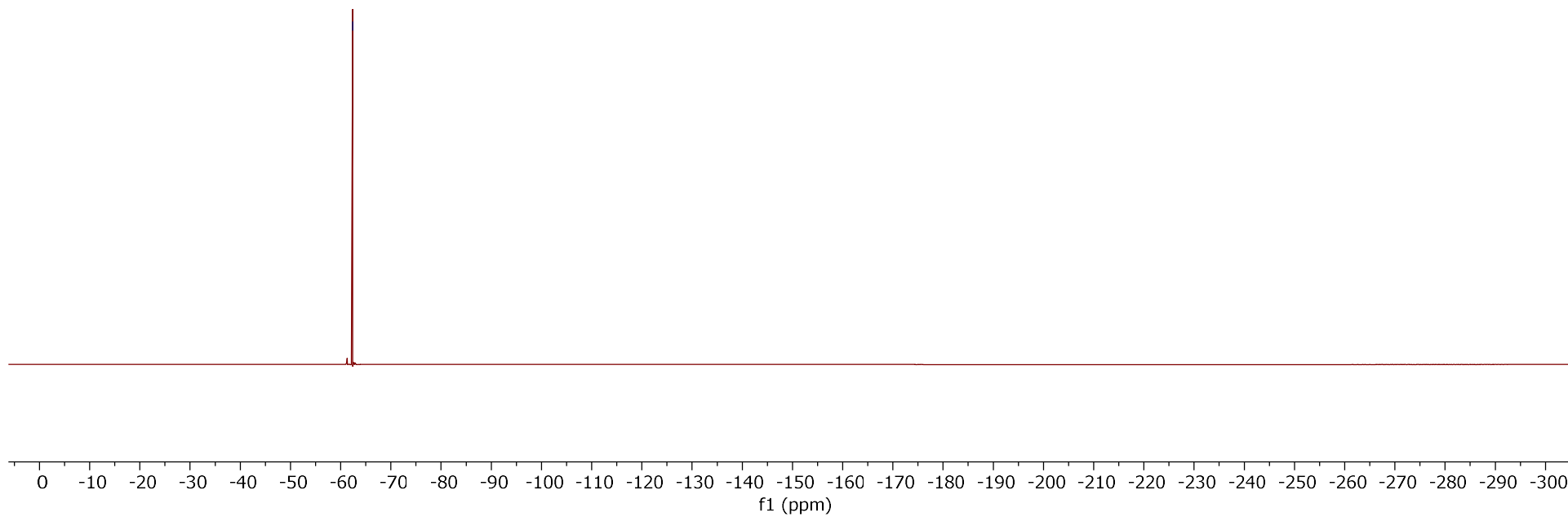
— 155.20 — 149.39
 { 136.72 129.06 128.81 128.55 128.43 128.29 127.95 127.84 127.40 127.05 125.46 125.43 125.40 125.37 125.24 123.08 120.92 }
 { 77.25 CDCl₃ 77.00 CDCl₃ 76.75 CDCl₃ } — 67.10
 { 44.37 42.42 } — 32.75

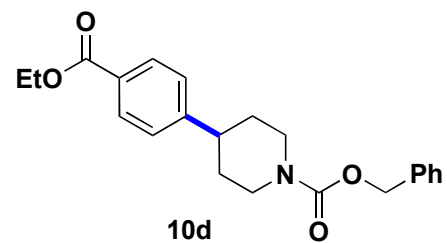




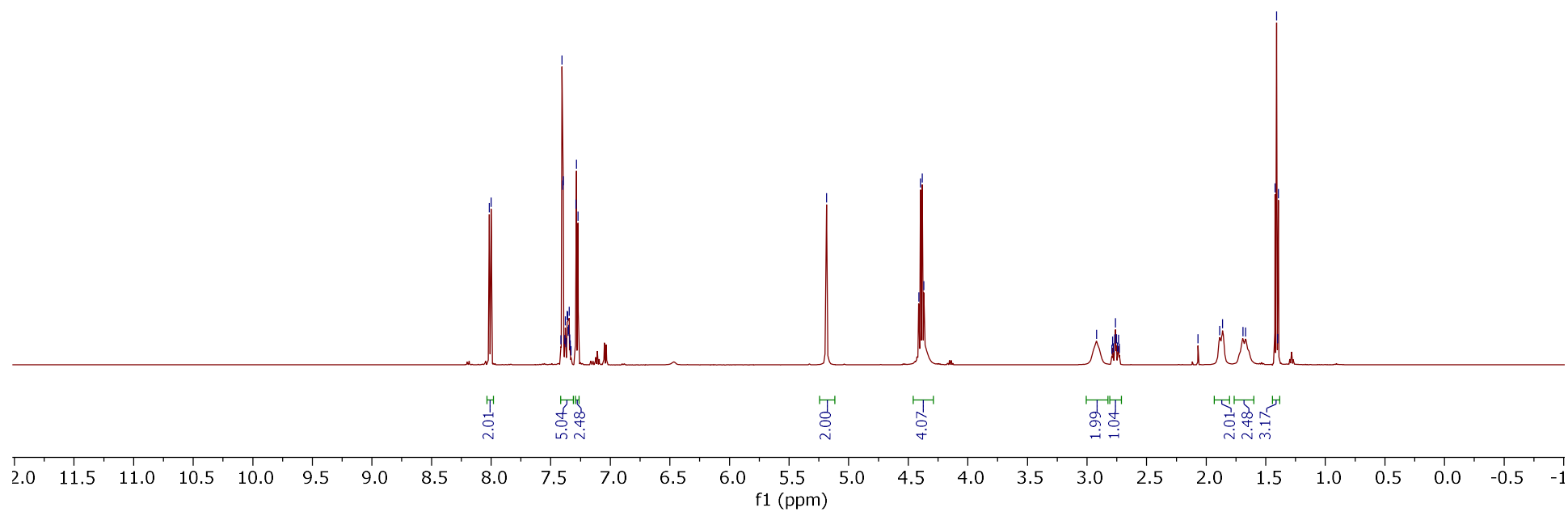
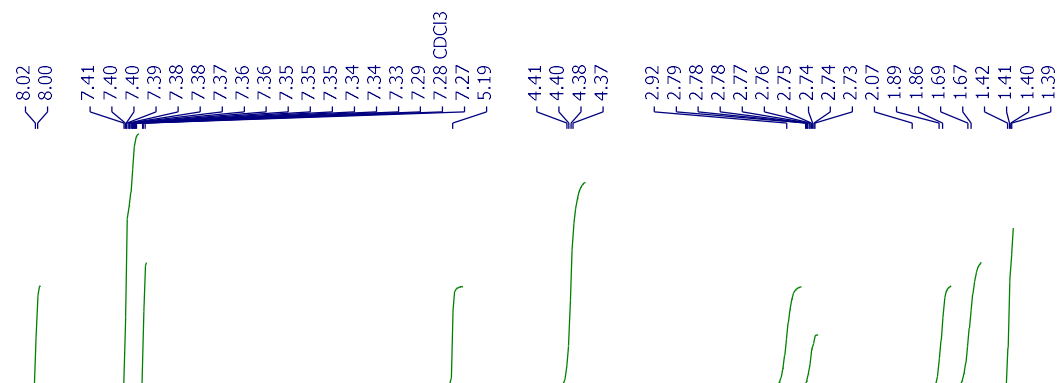
^{19}F NMR (471 MHz, CDCl_3)

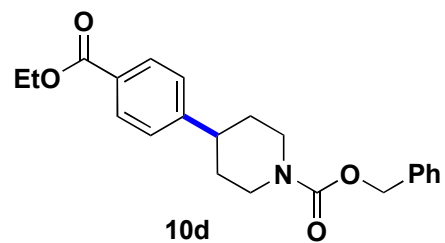
— -62.37





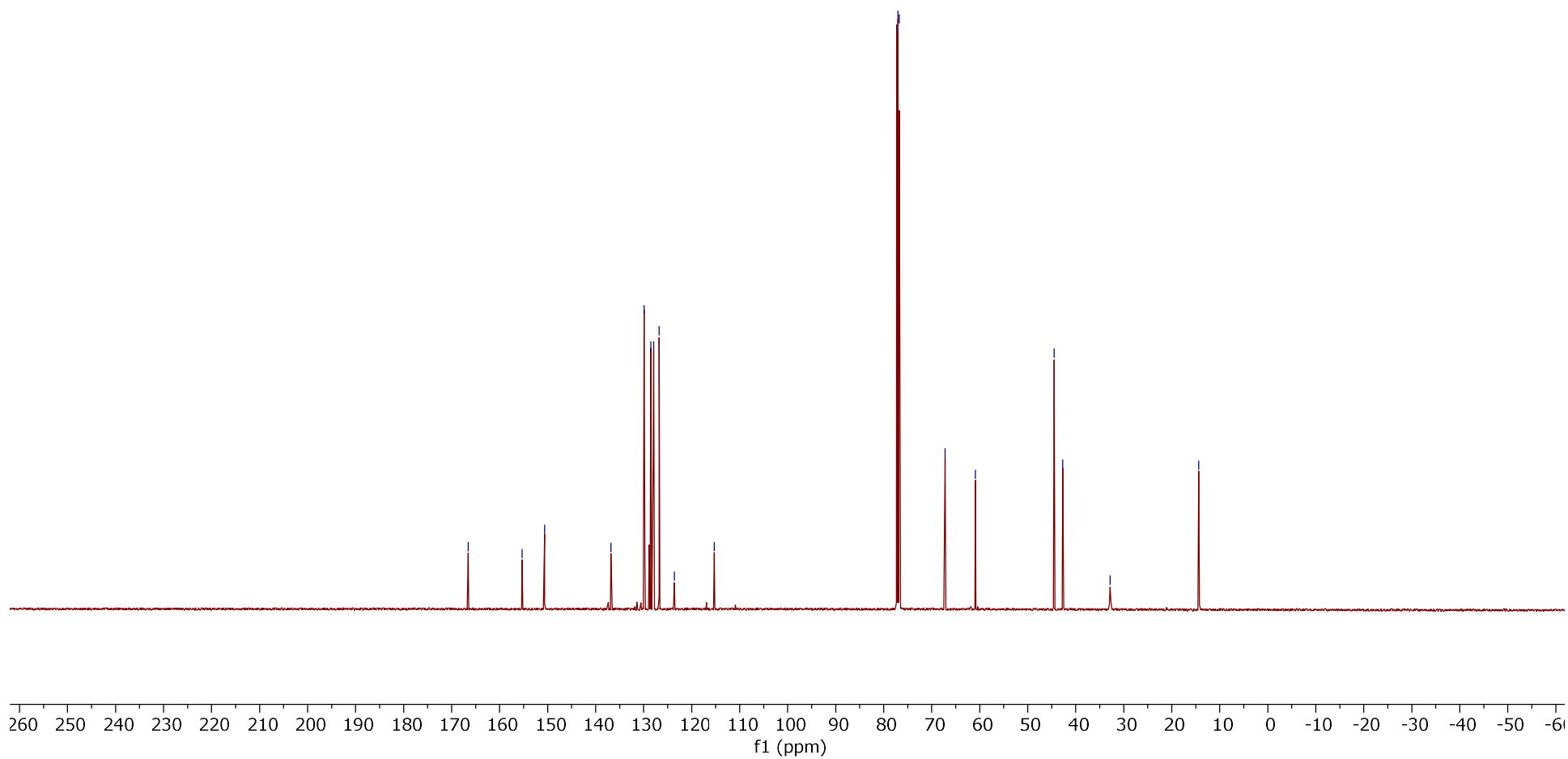
^1H NMR (500 MHz, CDCl_3)

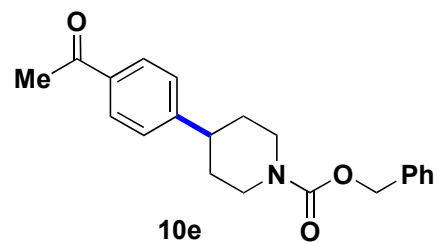




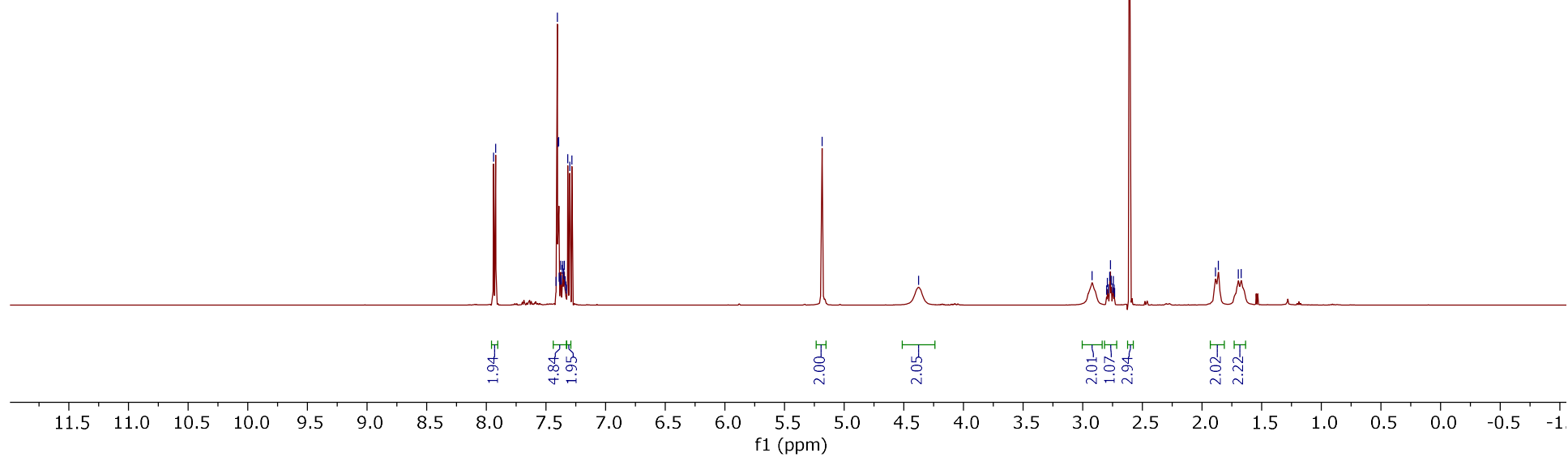
^{13}C NMR (126 MHz, CDCl_3)

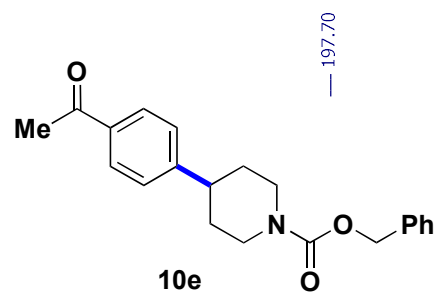
— 166.52
 — 155.31
 — 150.65
 / 136.82
 / 129.90
 / 128.52
 / 127.93
 / 126.78
 / 123.57
 — 115.30
 77.28 CDCl_3
 77.03 CDCl_3
 76.78 CDCl_3
 — 67.18
 — 60.87
 / 44.50
 / 42.69
 — 32.83
 — 14.36



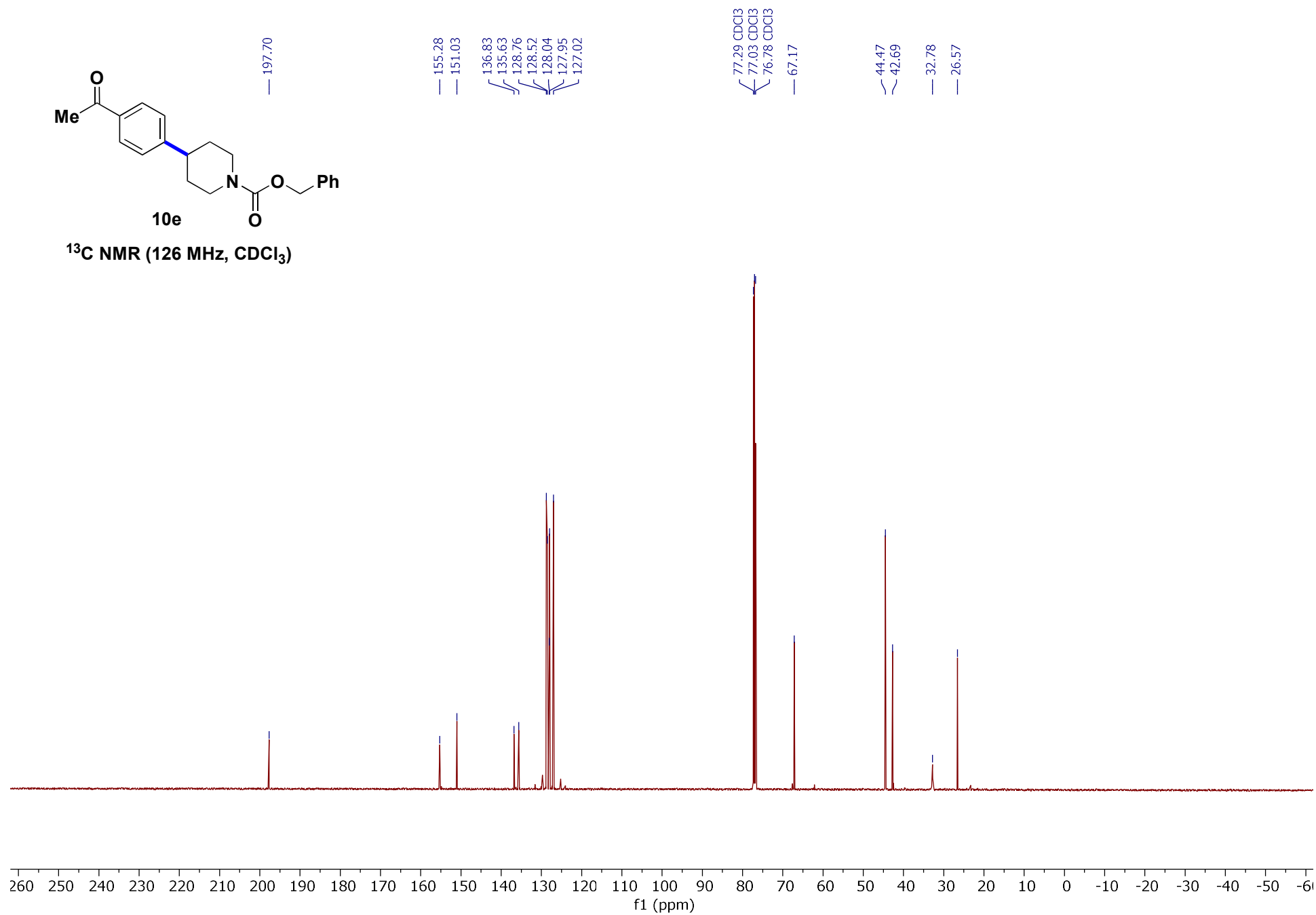


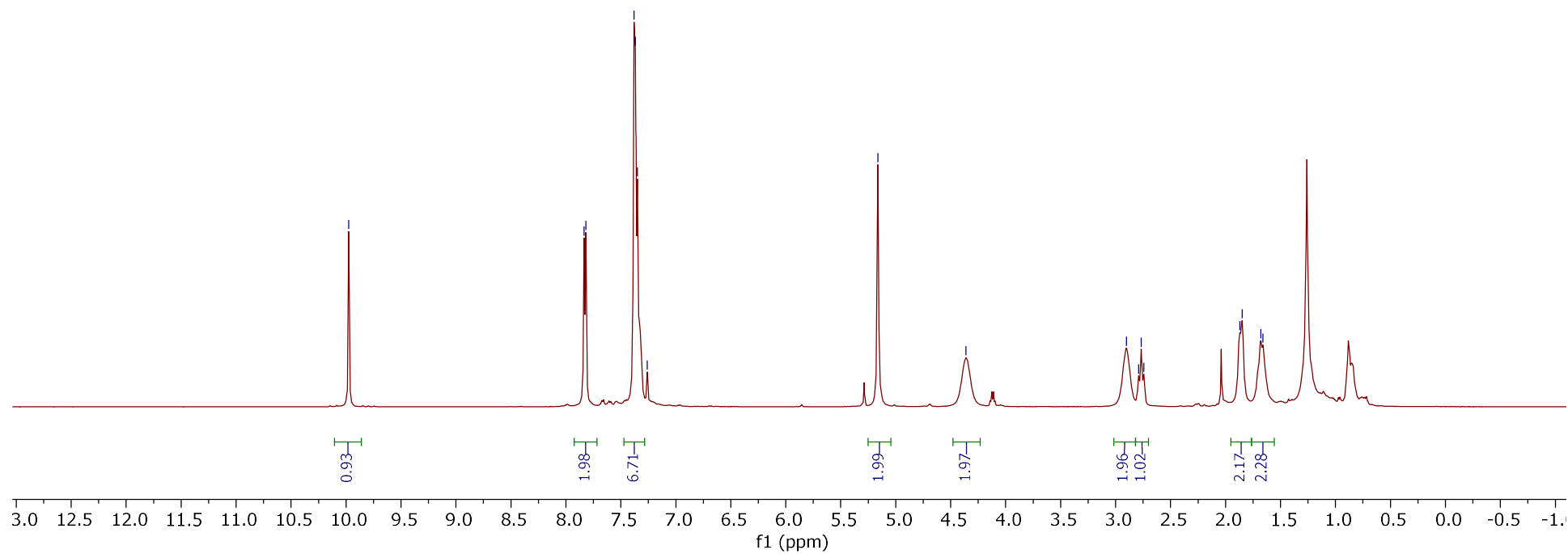
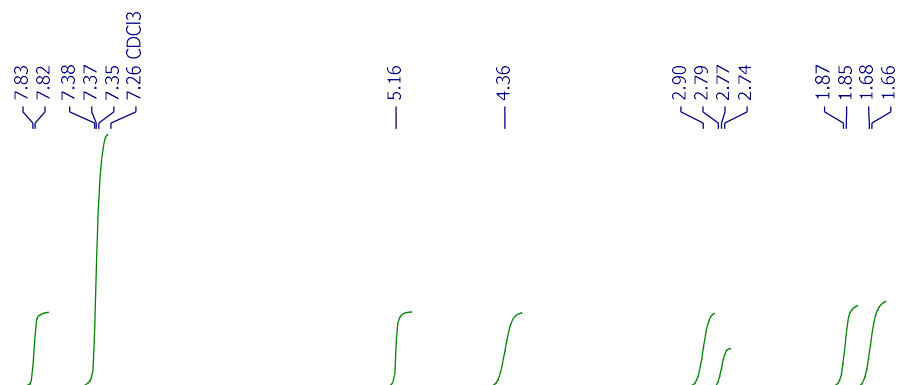
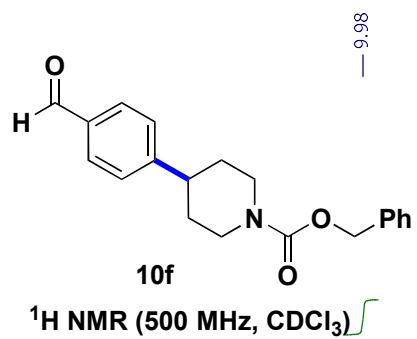
^1H NMR (500 MHz, CDCl_3)

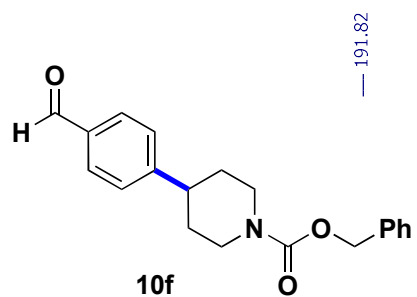




^{13}C NMR (126 MHz, CDCl_3)

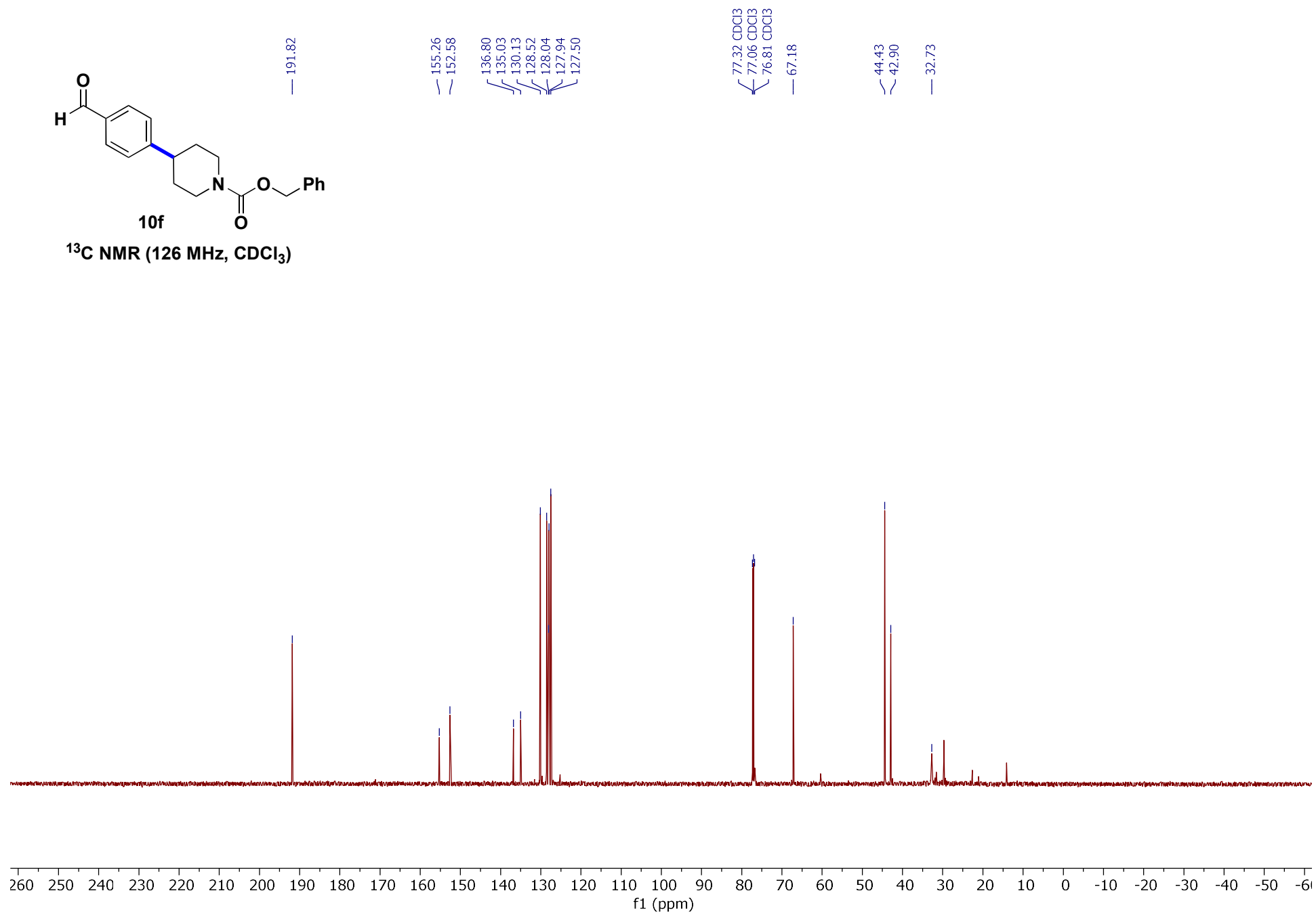


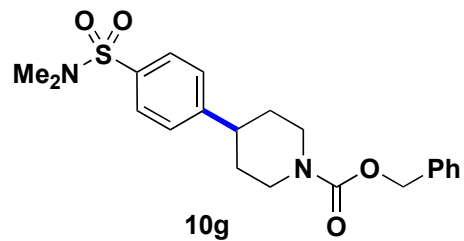




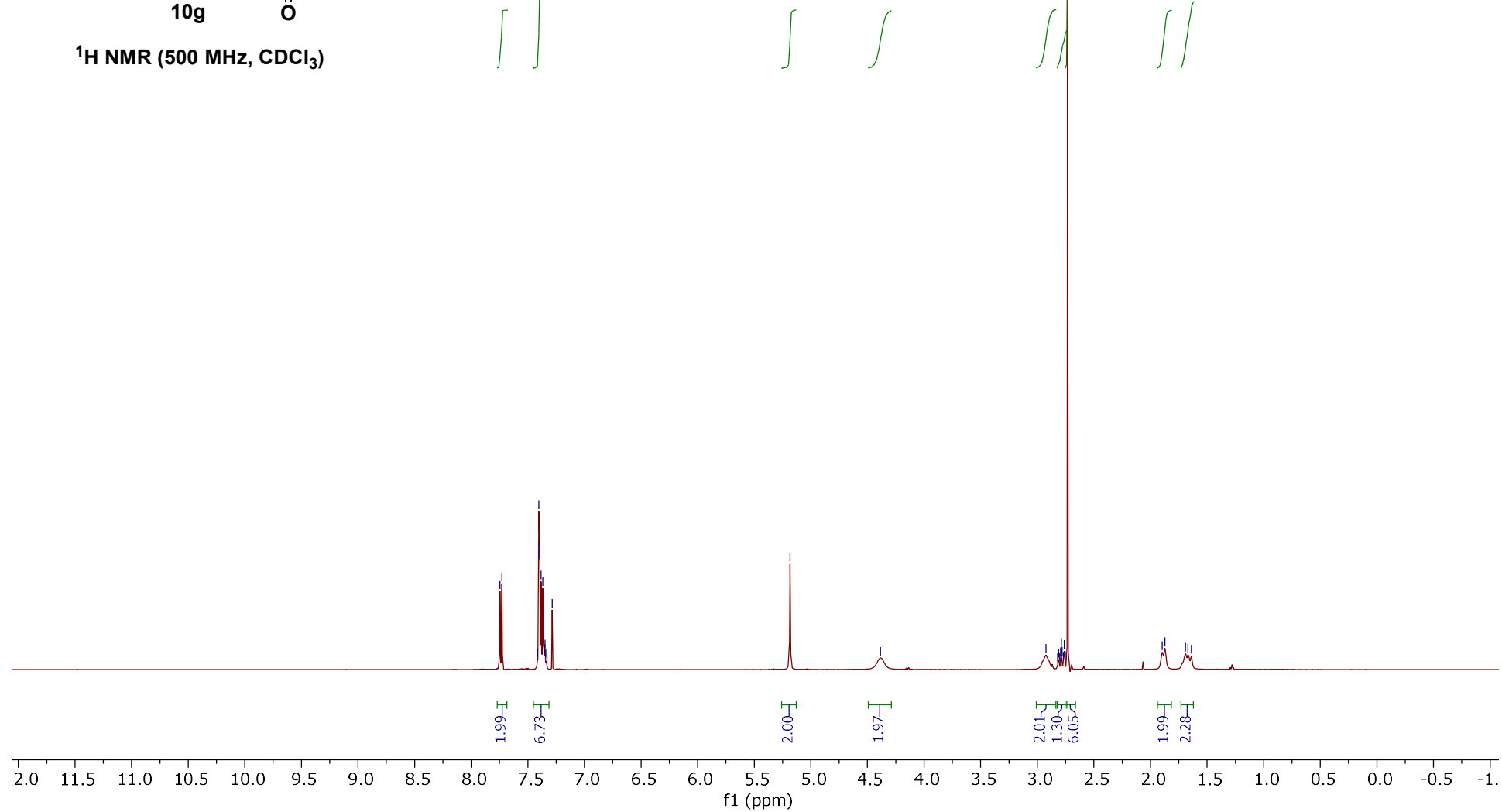
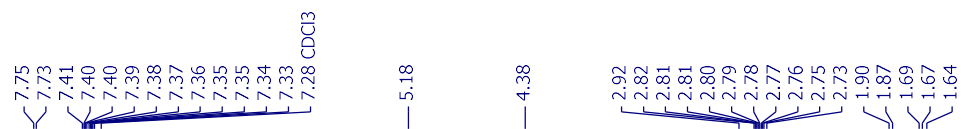
10f

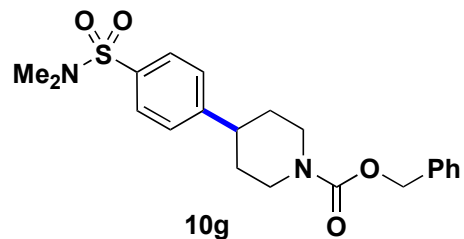
^{13}C NMR (126 MHz, CDCl_3)





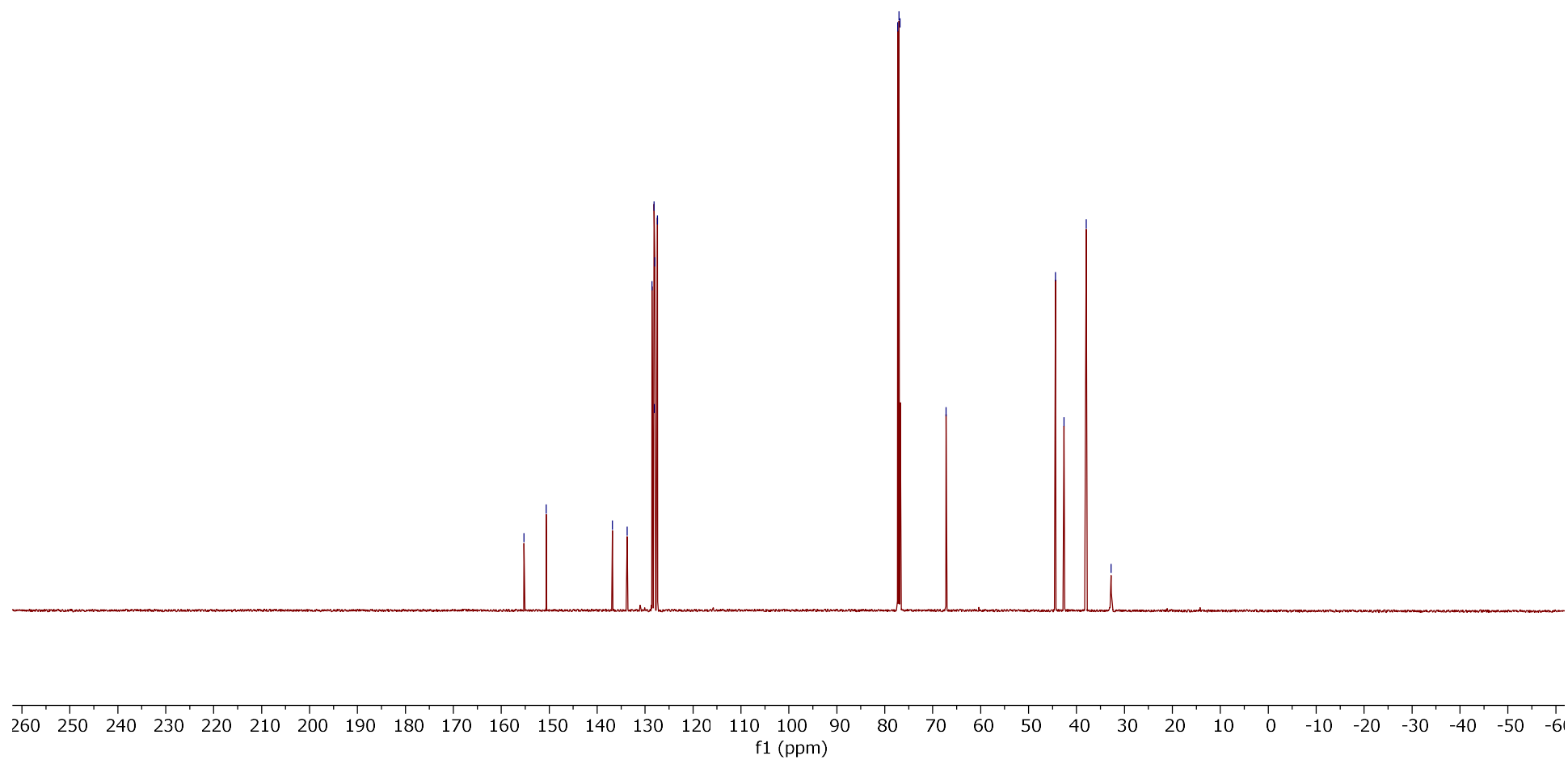
^1H NMR (500 MHz, CDCl_3)

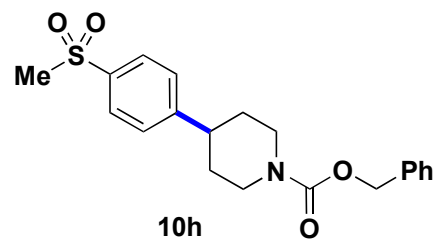




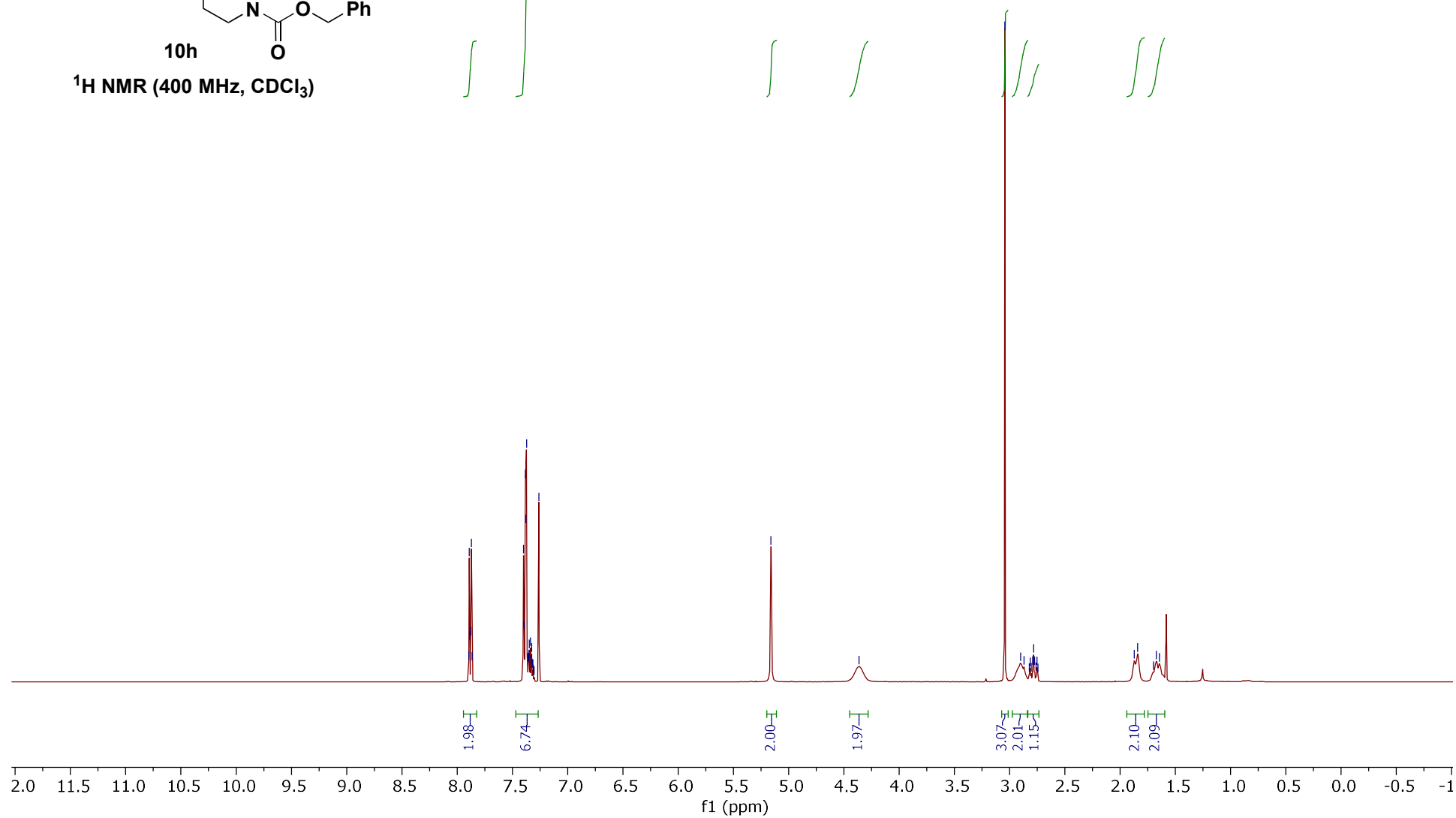
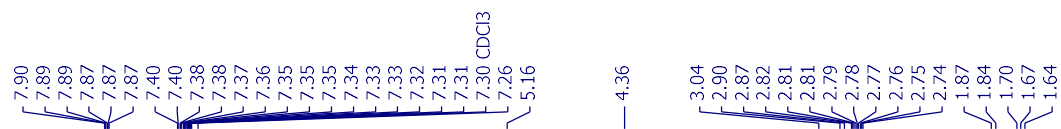
¹³C NMR (126 MHz, CDCl₃)

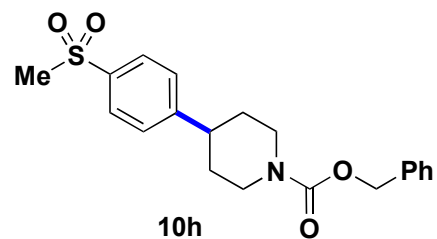
155.26
 150.60
 136.79
 133.74
 128.53
 128.14
 128.07
 127.96
 127.43
 77.29 CDCl₃
 77.04 CDCl₃
 76.79 CDCl₃
 67.21
 44.41
 42.58
 37.94
 32.78



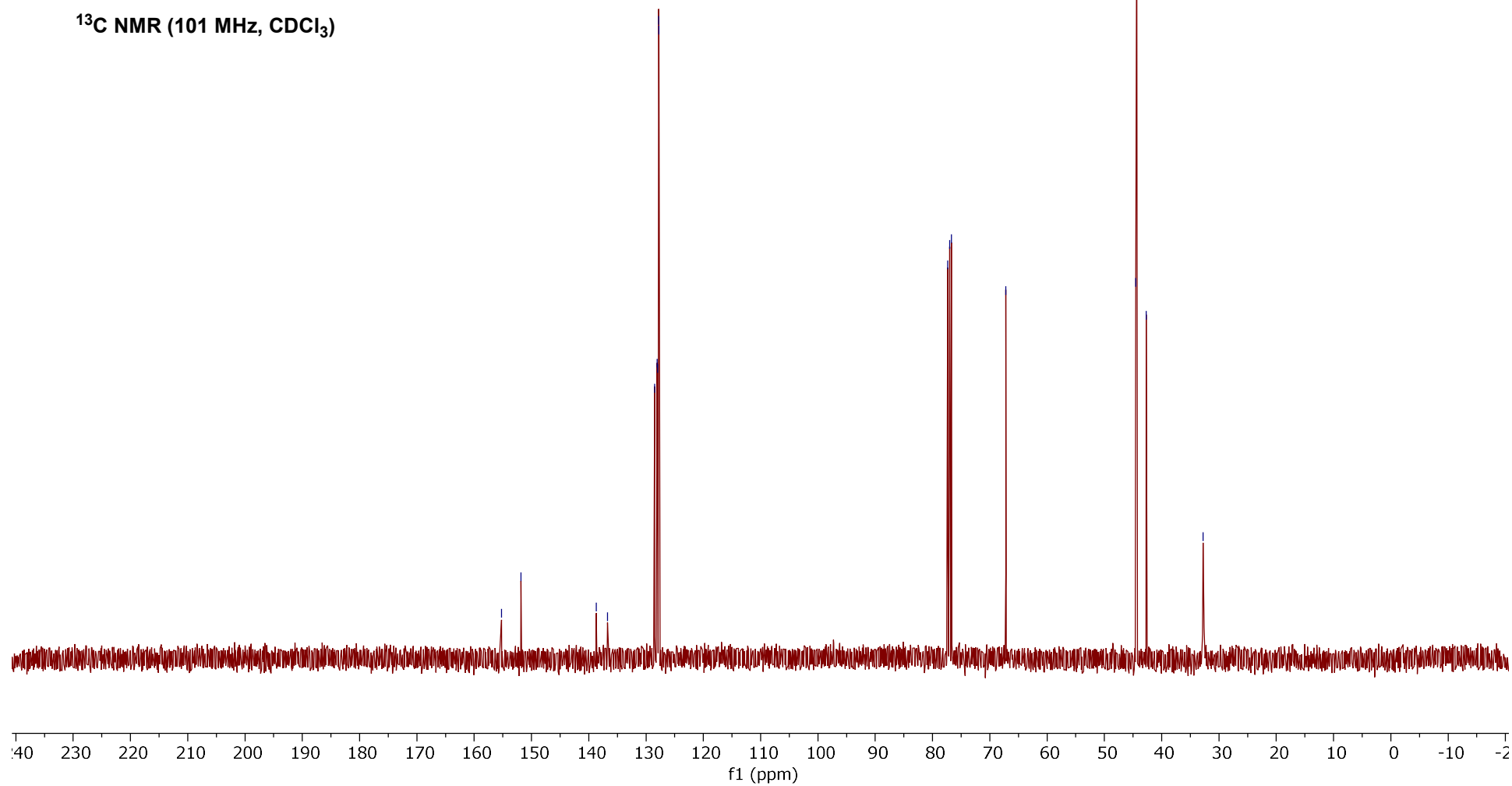


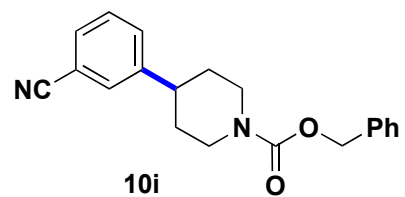
¹H NMR (400 MHz, CDCl₃)





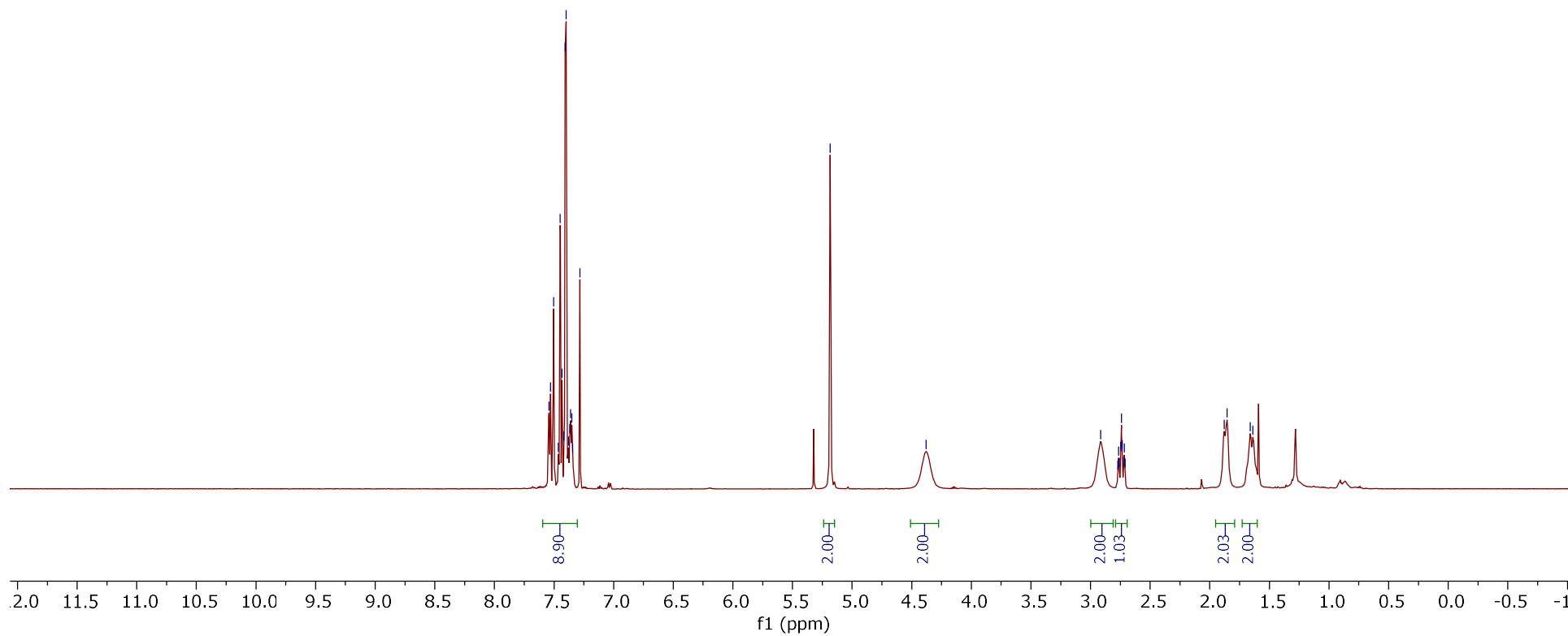
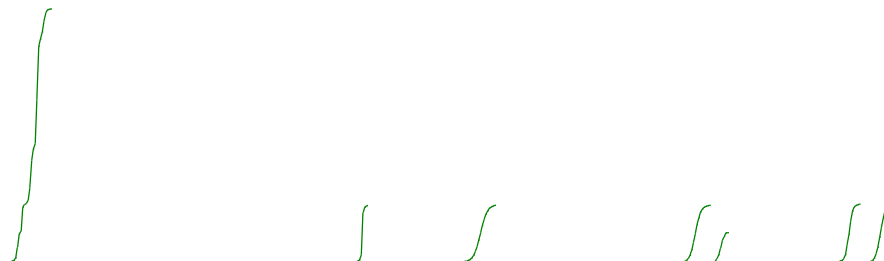
^{13}C NMR (101 MHz, CDCl_3)

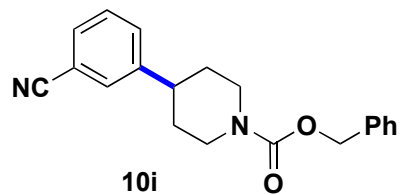




^1H NMR (500 MHz, CDCl_3)

7.54, 7.53, 7.50, 7.46, 7.45, 7.43, 7.42, 7.41, 7.40, 7.38, 7.37, 7.36, 7.35, 7.34, 7.28
 — 5.18 — 4.38
 2.91, 2.77, 2.77, 2.76, 2.75, 2.74, 2.73, 2.72, 2.71, 1.88, 1.86, 1.66, 1.64



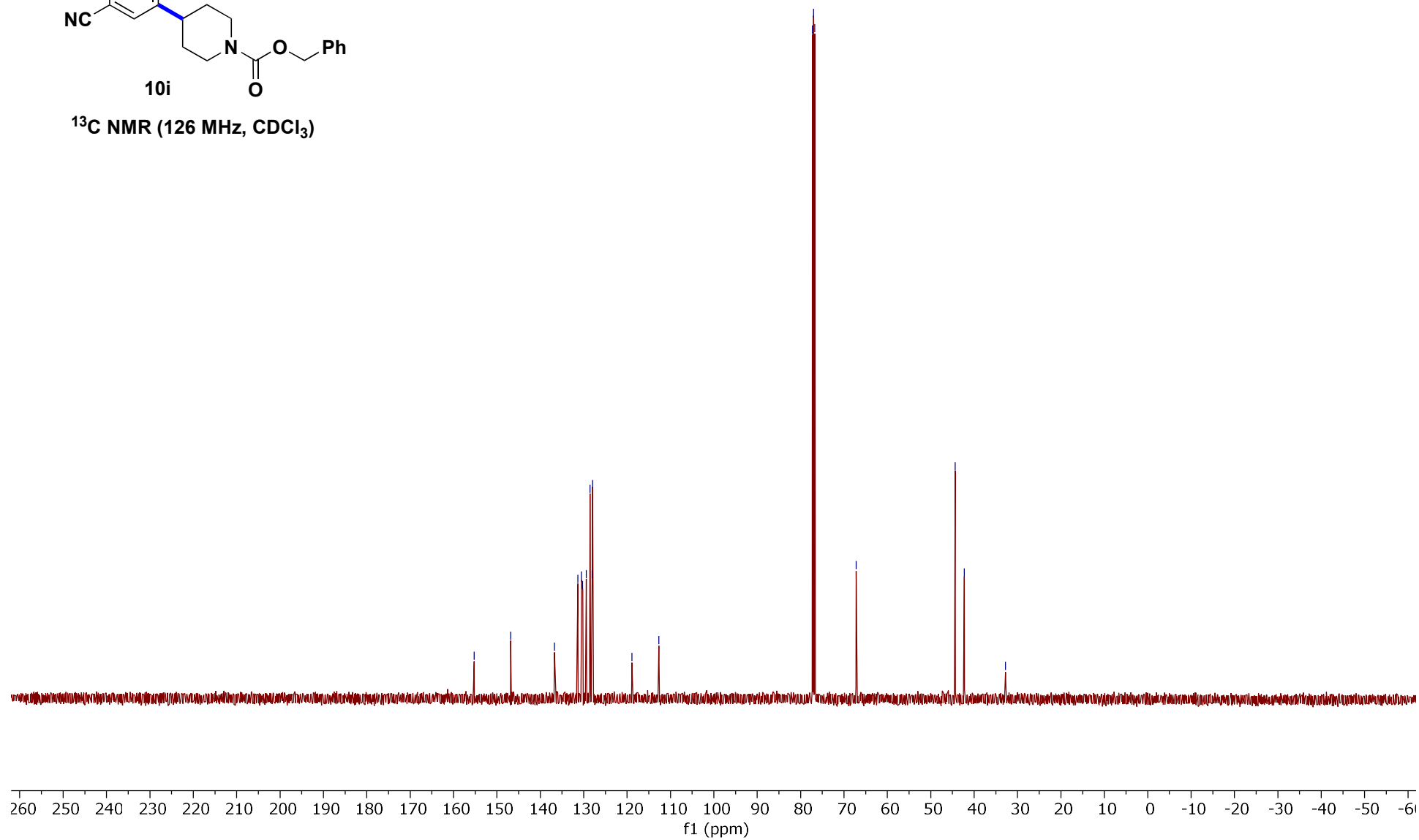


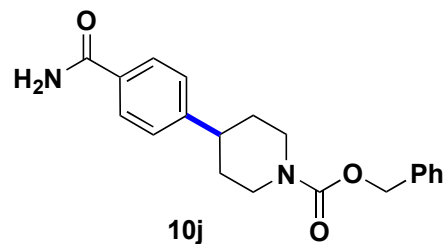
10i

^{13}C NMR (126 MHz, CDCl_3)

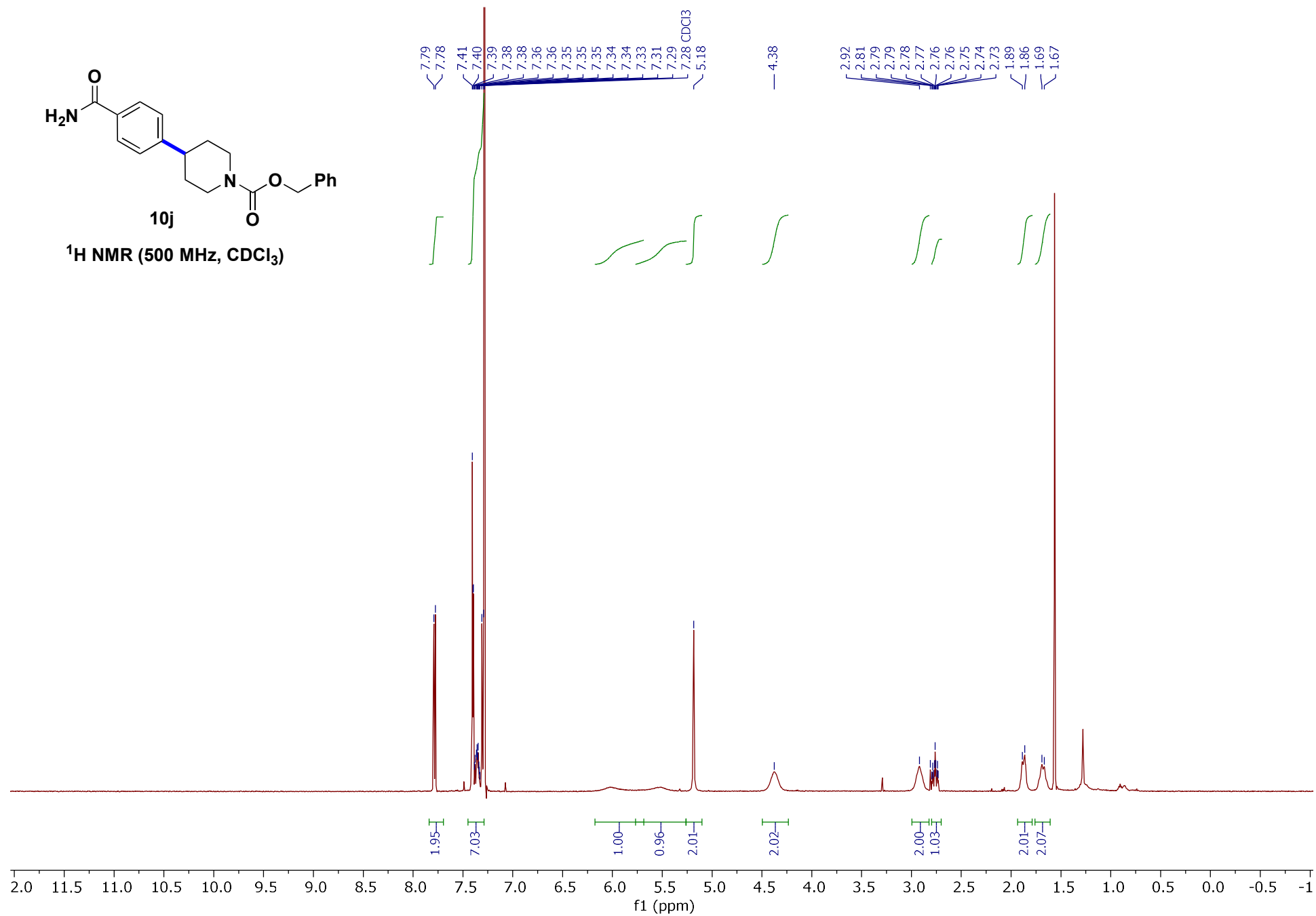
Chemical shift values (ppm):

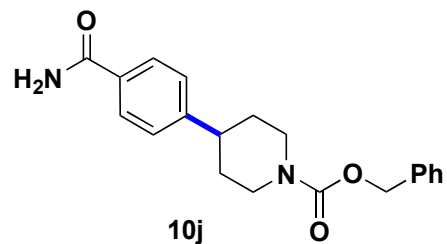
- 155.23
- 146.82
- 136.76
- 131.34
- 130.51
- 130.24
- 129.39
- 128.52
- 128.06
- 127.96
- 118.86
- 112.67
- 77.27 CDCl_3
- 77.02 CDCl_3
- 76.77 CDCl_3
- 67.22
- 44.37
- 42.26
- 32.79



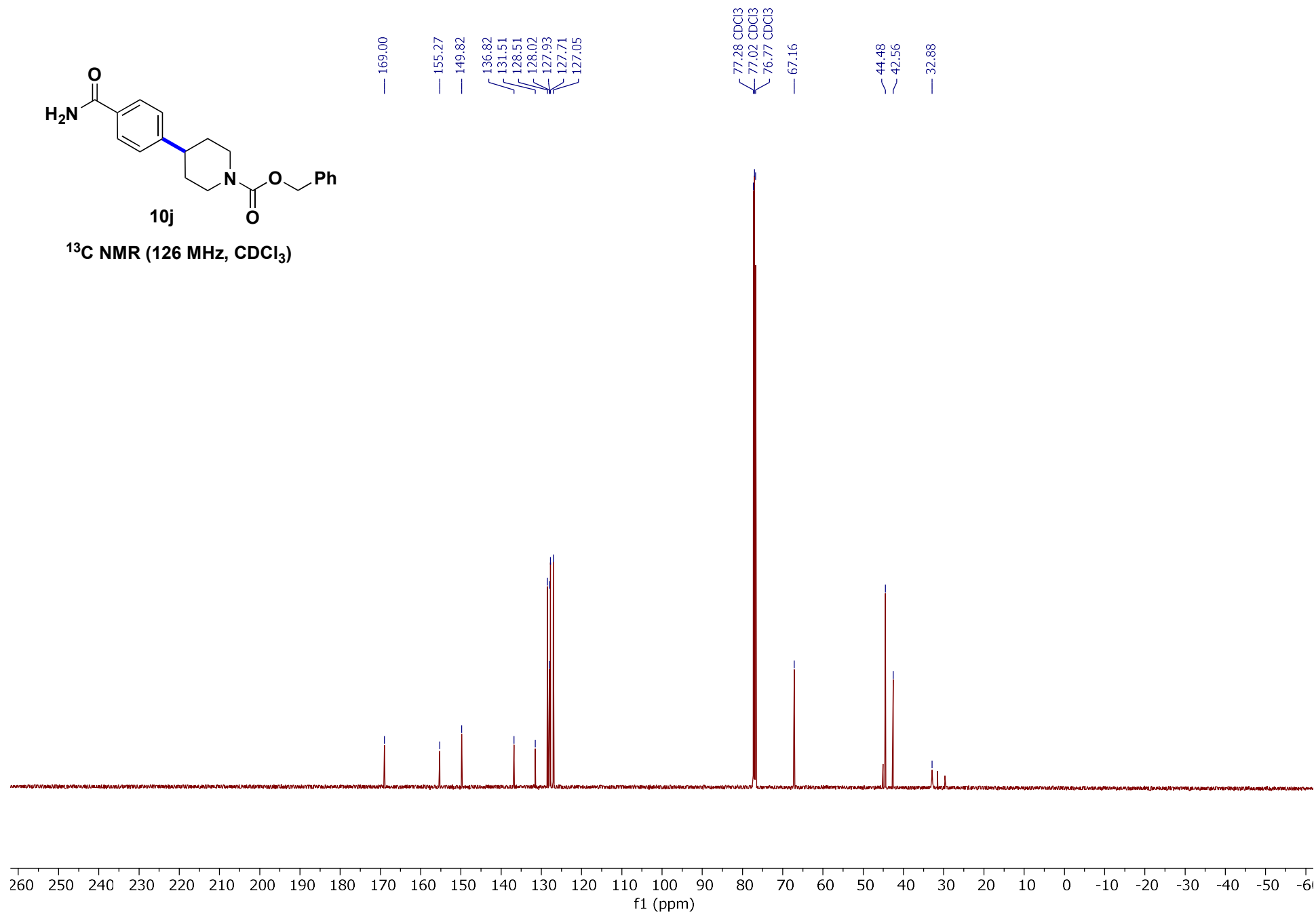


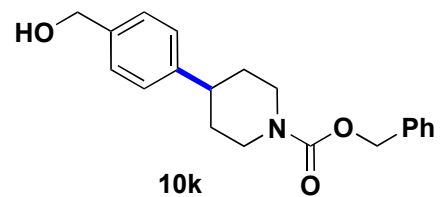
^1H NMR (500 MHz, CDCl_3)



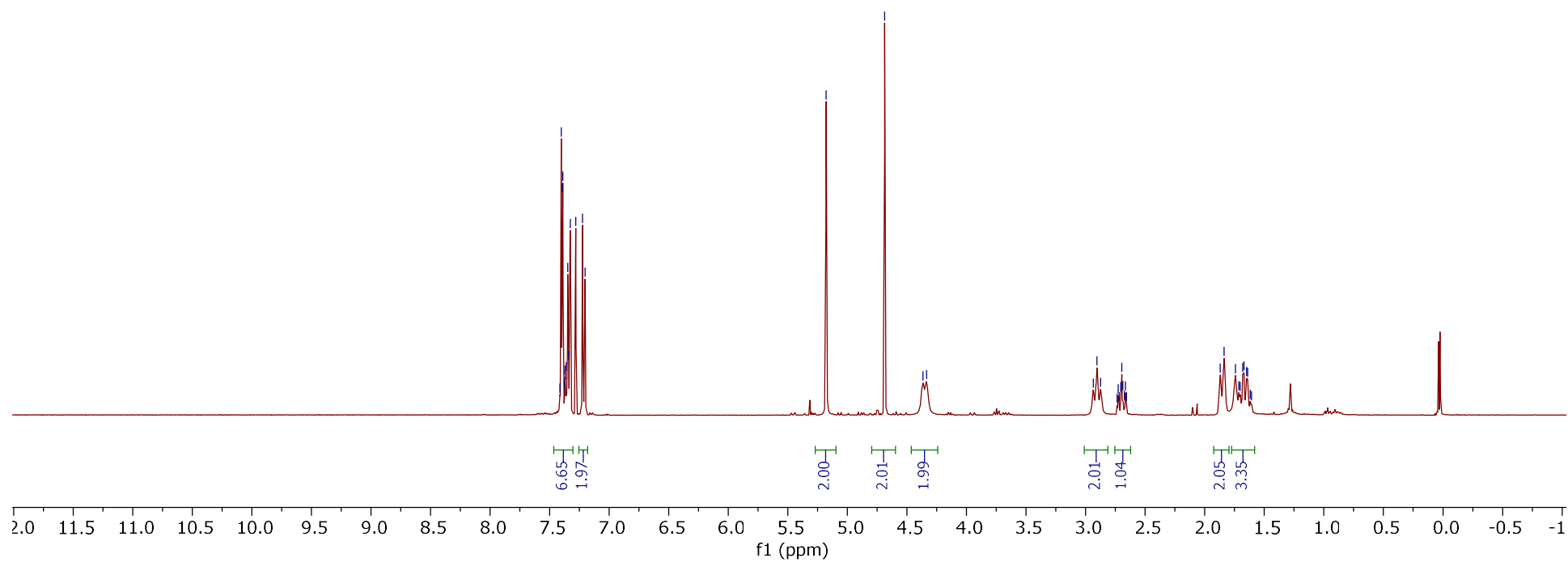
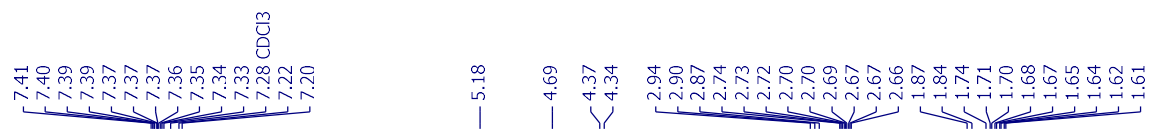


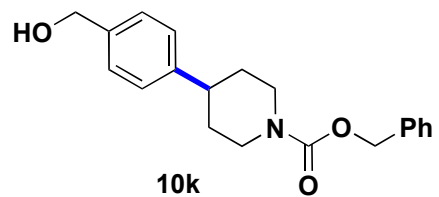
^{13}C NMR (126 MHz, CDCl_3)



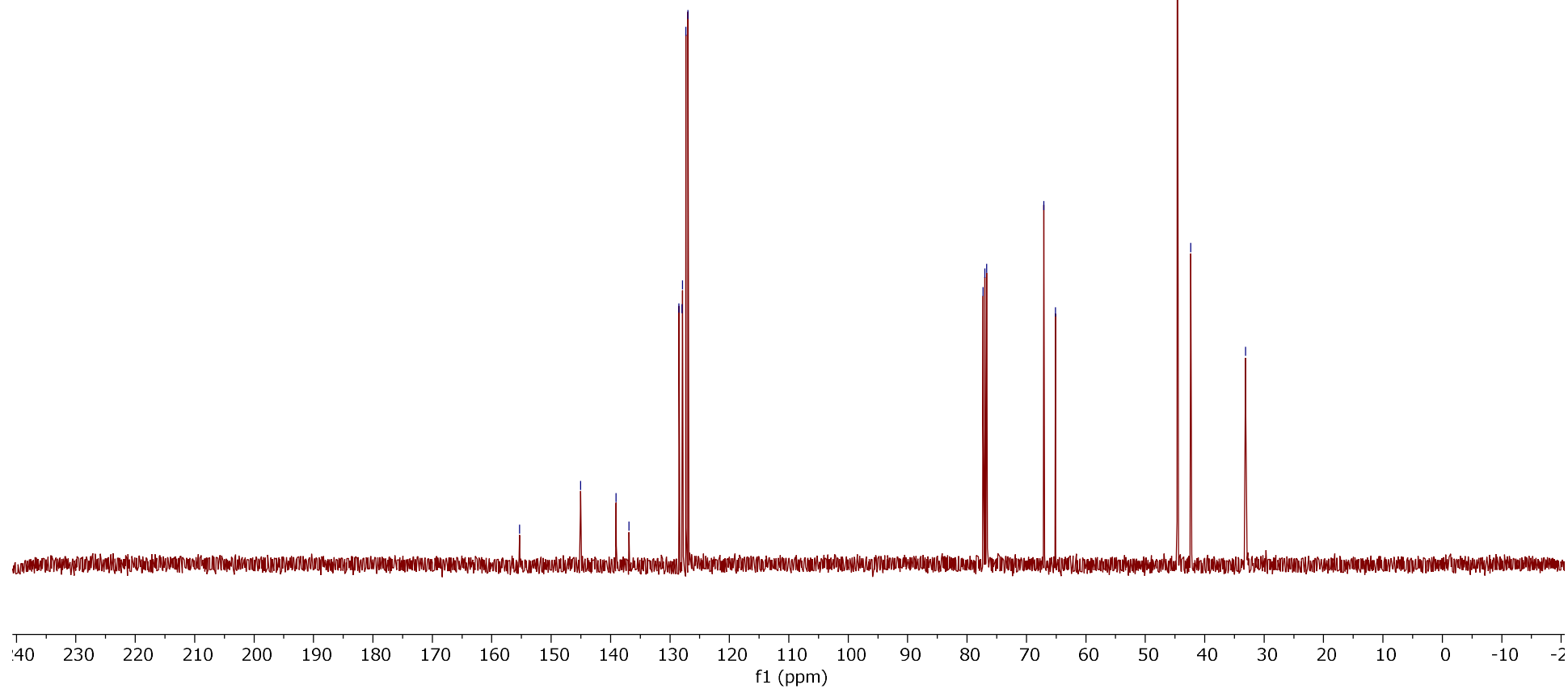


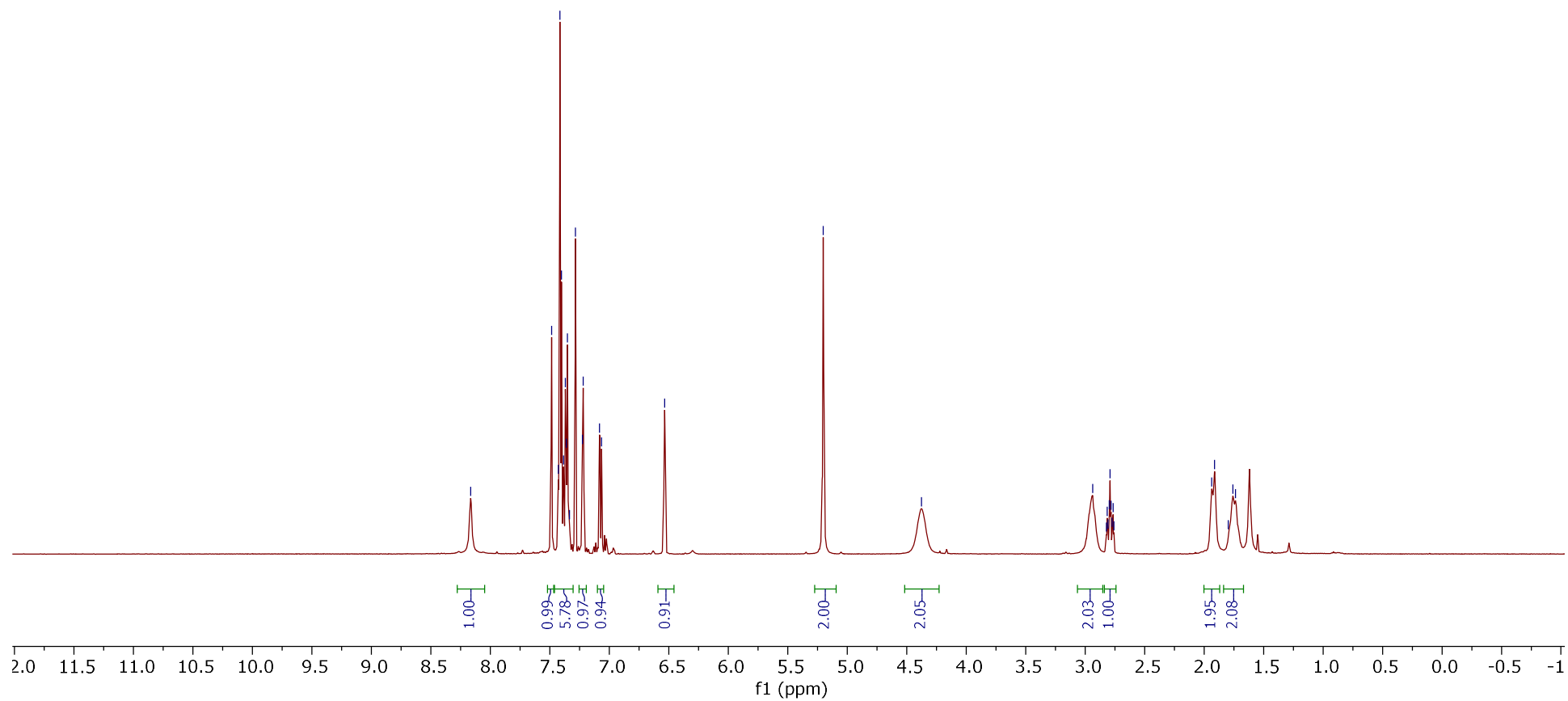
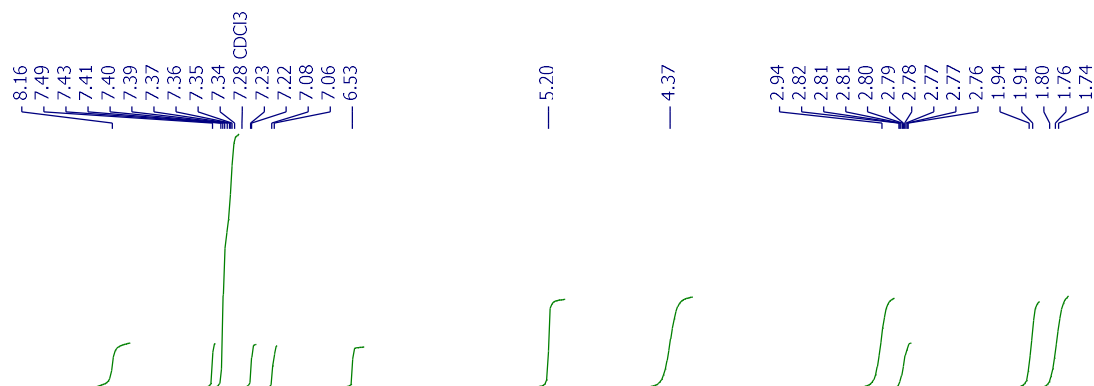
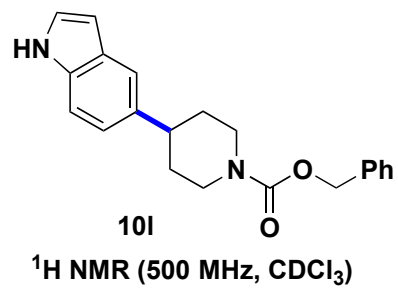
^1H NMR (400 MHz, CDCl_3)

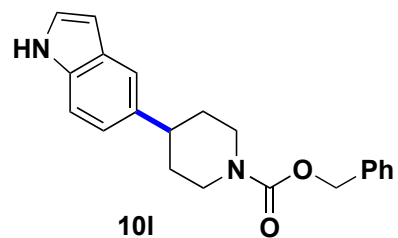




^{13}C NMR (101 MHz, CDCl_3)

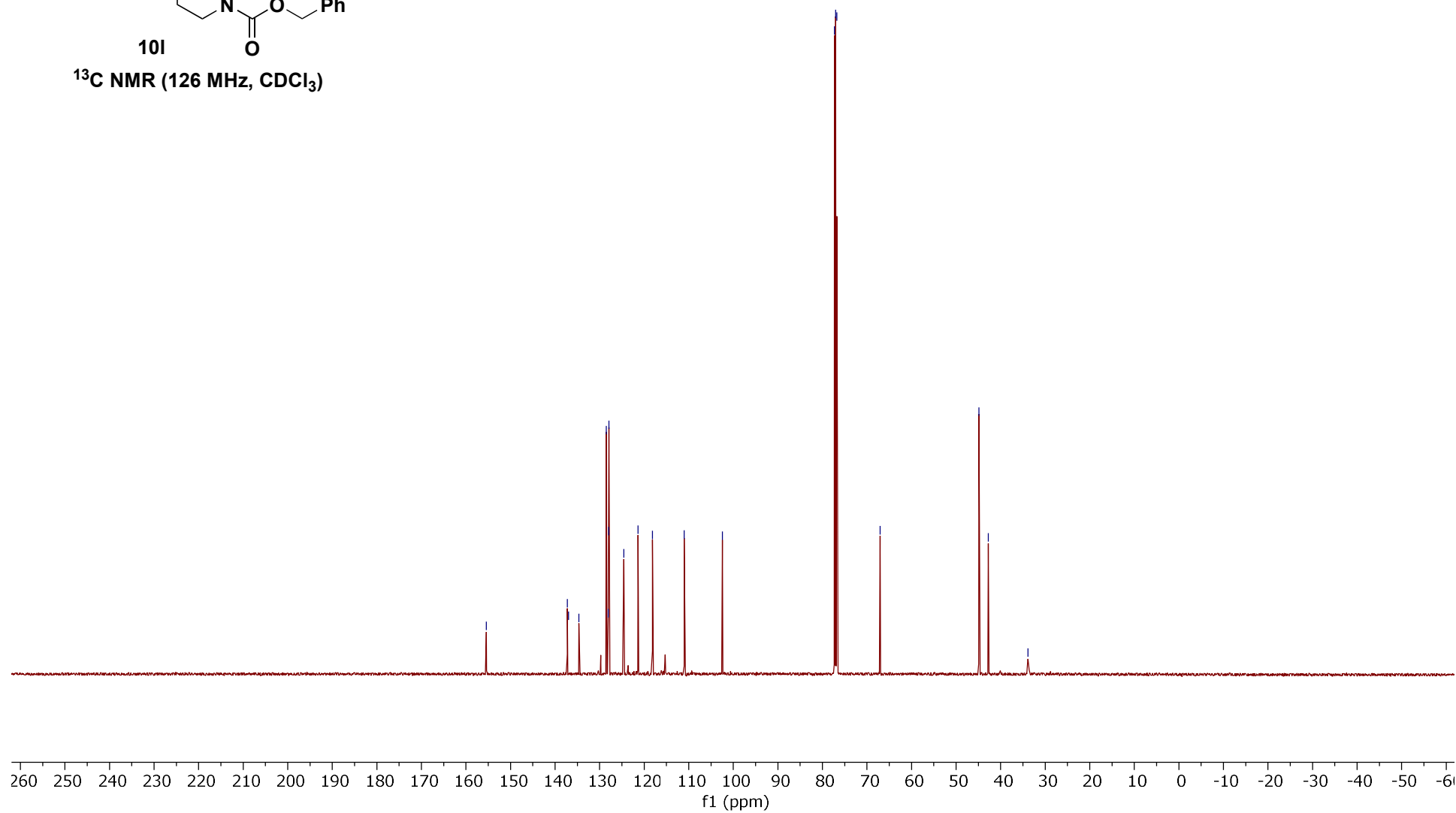


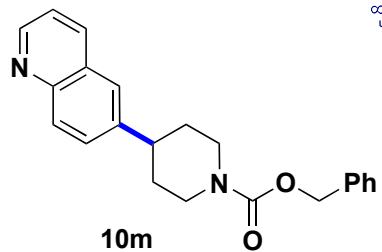




¹³C NMR (126 MHz, CDCl₃)

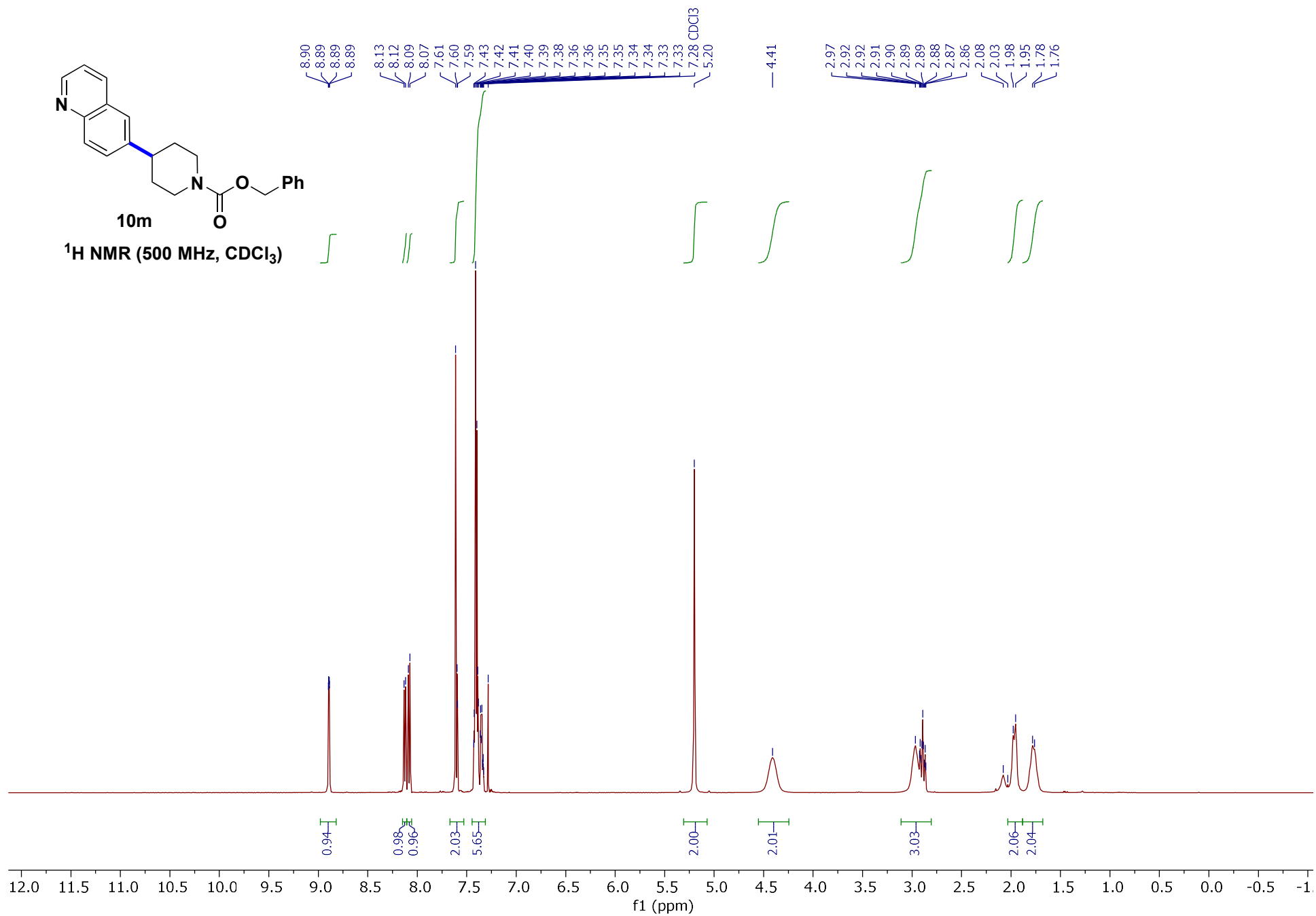
— 155.41
 137.22
 136.99
 134.65
 128.51
 128.07
 127.96
 127.89
 124.55
 121.40
 118.16
 110.99
 102.46
 —
 77.29 CDCl₃
 77.03 CDCl₃
 76.78 CDCl₃
 — 67.07
 —
 44.88
 42.74
 —
 33.84

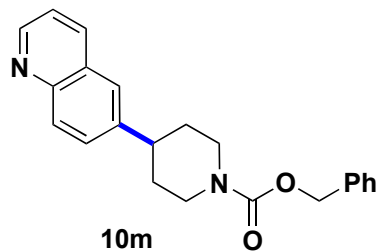




10m

^1H NMR (500 MHz, CDCl_3)



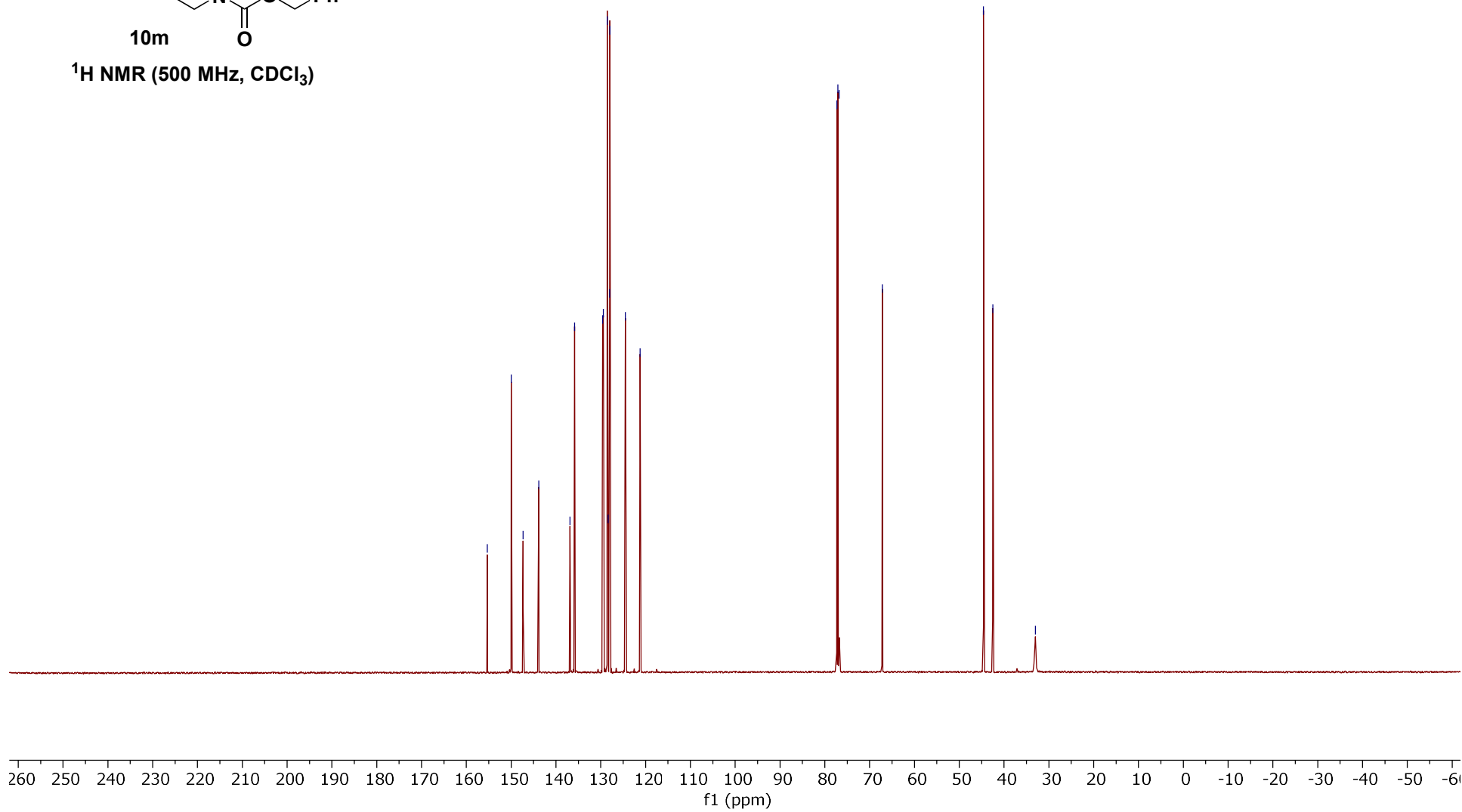


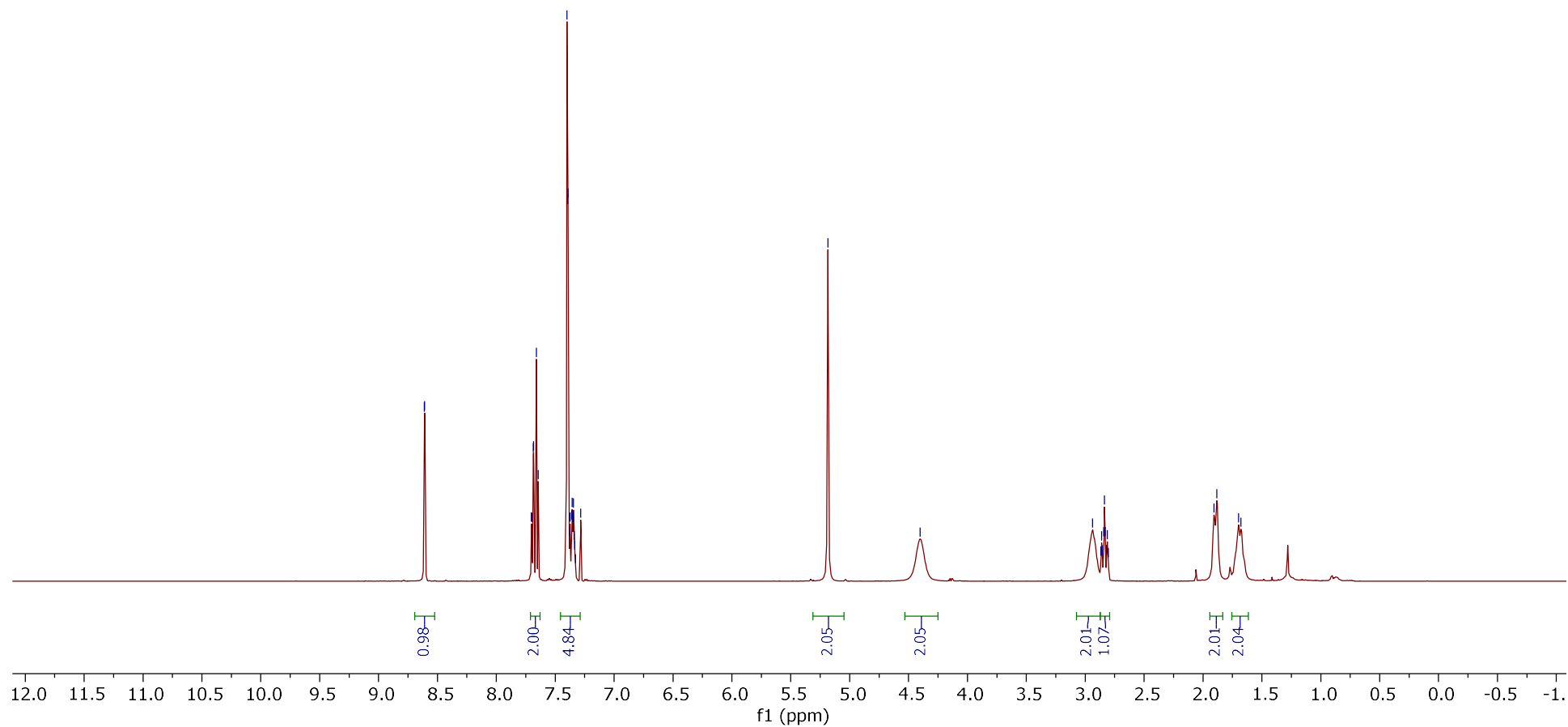
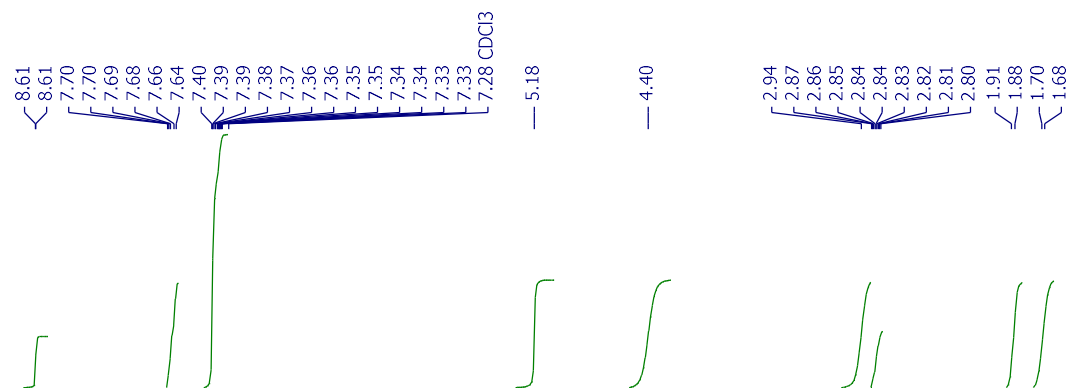
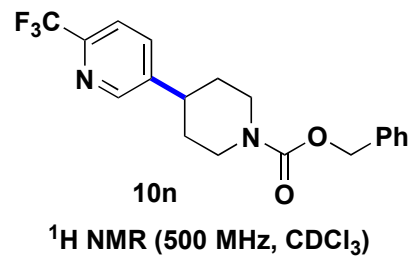
^1H NMR (500 MHz, CDCl_3)

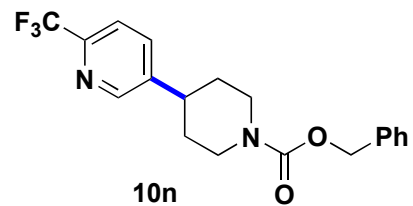
155.32
149.96
147.35
143.85
136.87
135.83
129.61
129.40
128.53
128.36
128.03
127.95
124.53
121.24

77.32 CDCl_3
77.06 CDCl_3
76.81 CDCl_3
67.17

44.59
42.51
33.01

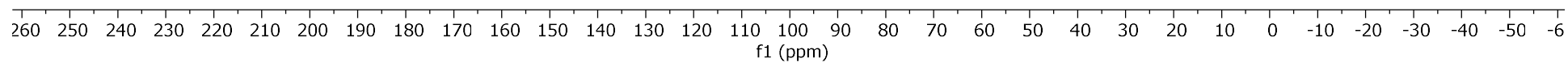


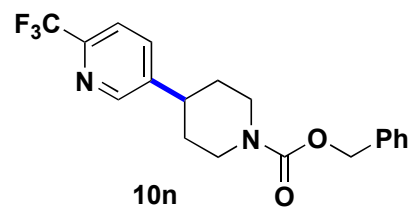




^{13}C NMR (126 MHz, CDCl_3)

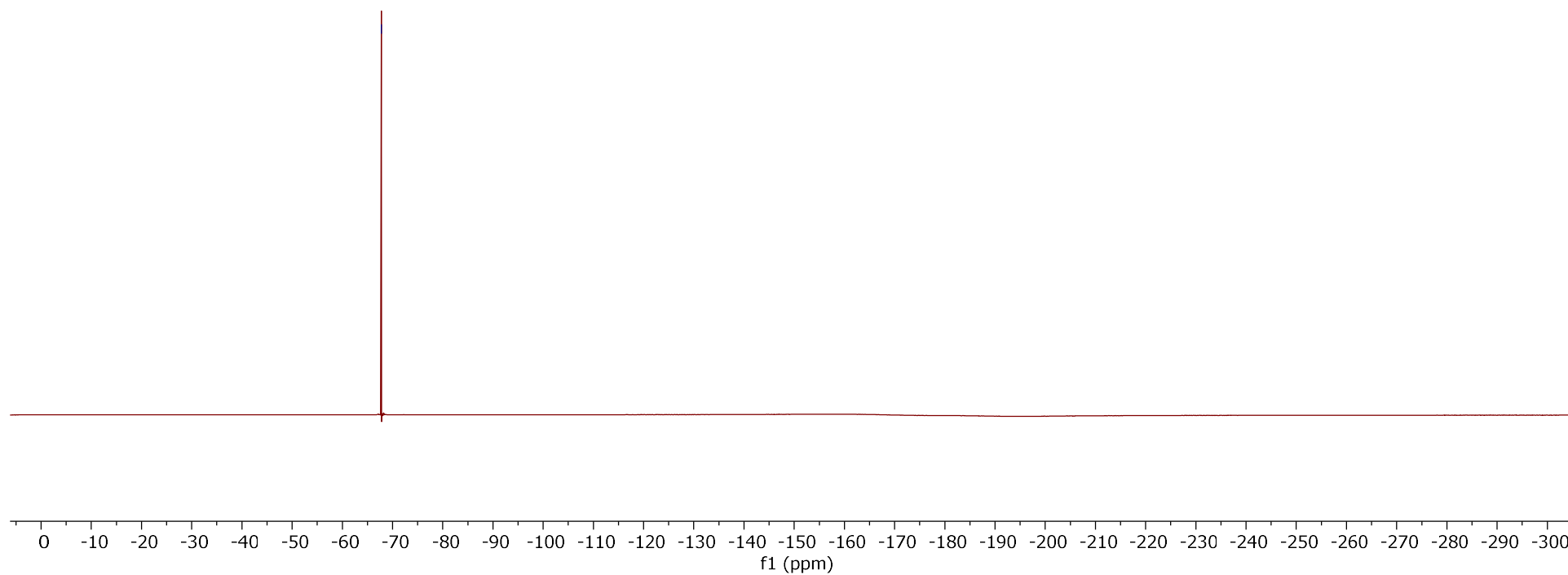
155.20
149.14
147.03
146.75
146.47
146.20
143.86
136.69
135.25
128.53
128.10
127.99
124.84
122.67
120.50
120.42
120.40
120.38
120.36
118.32
77.27 CDCl_3
77.02 CDCl_3
76.76 CDCl_3
67.28
44.26
40.07
32.56

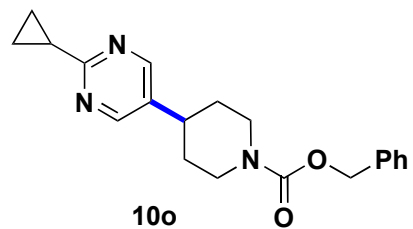




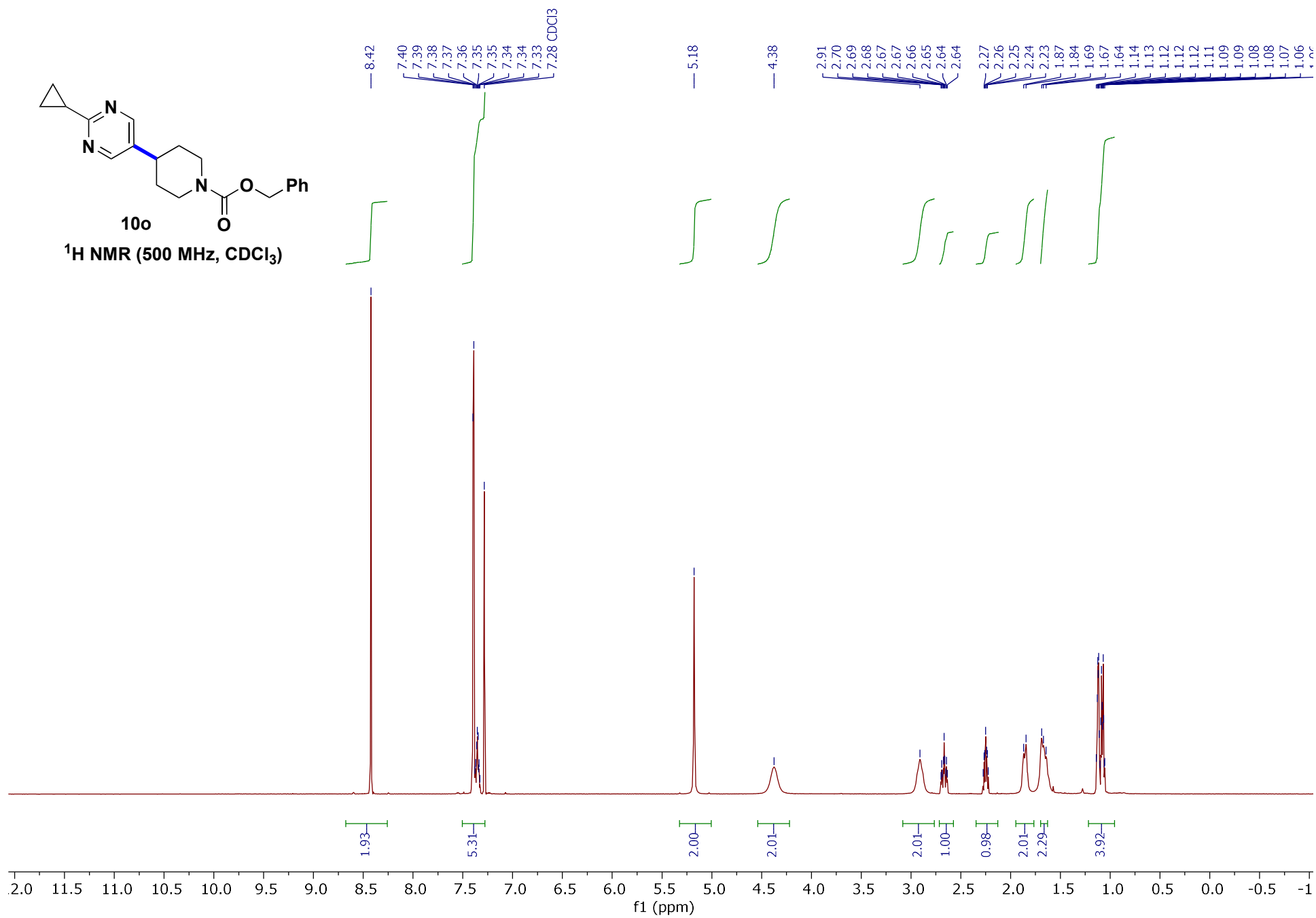
¹⁹F NMR (471 MHz, CDCl₃)

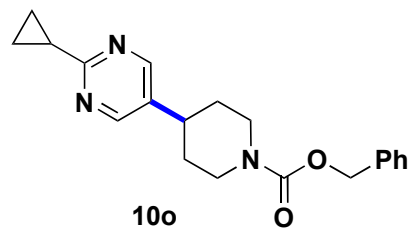
— -67.79



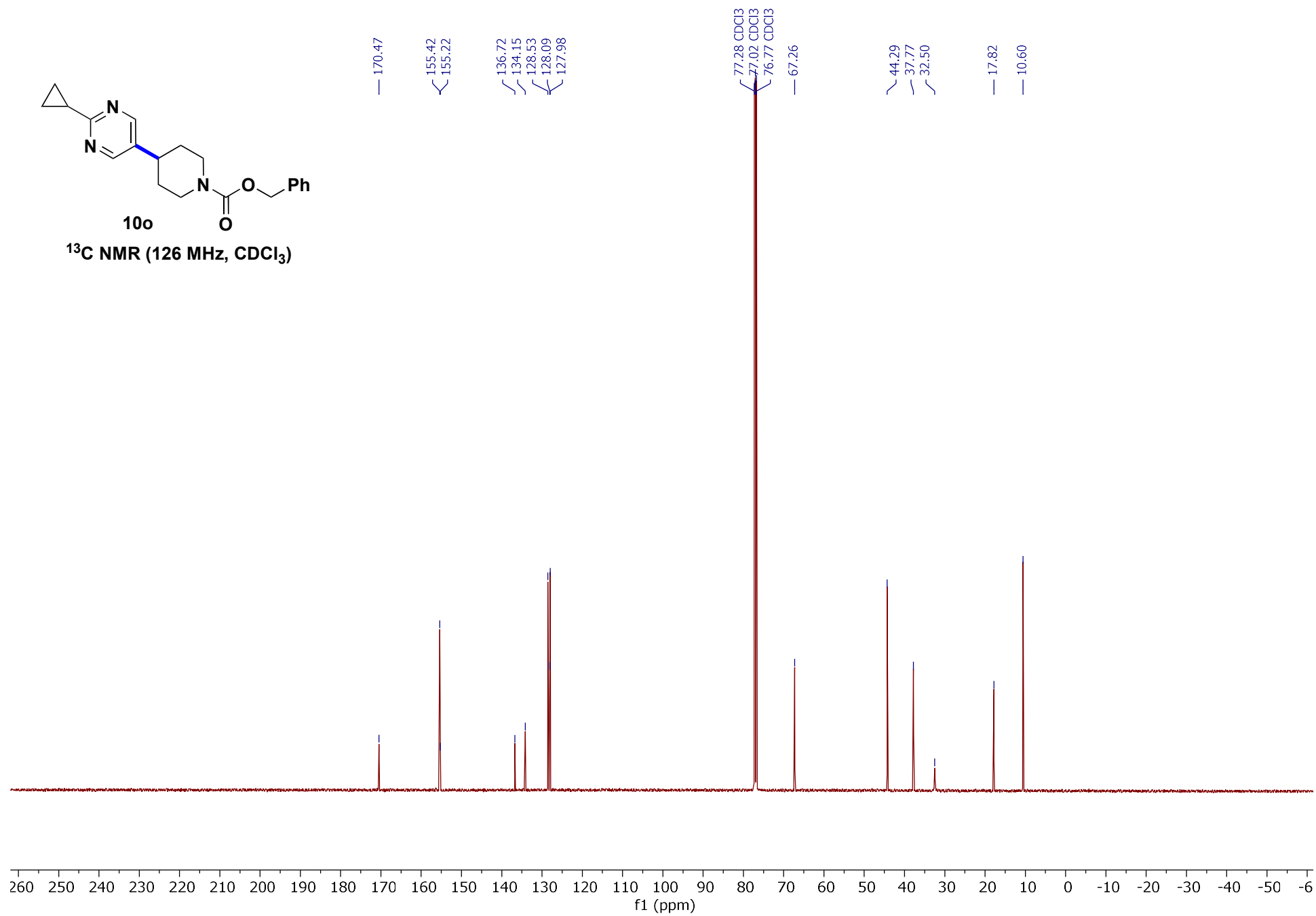


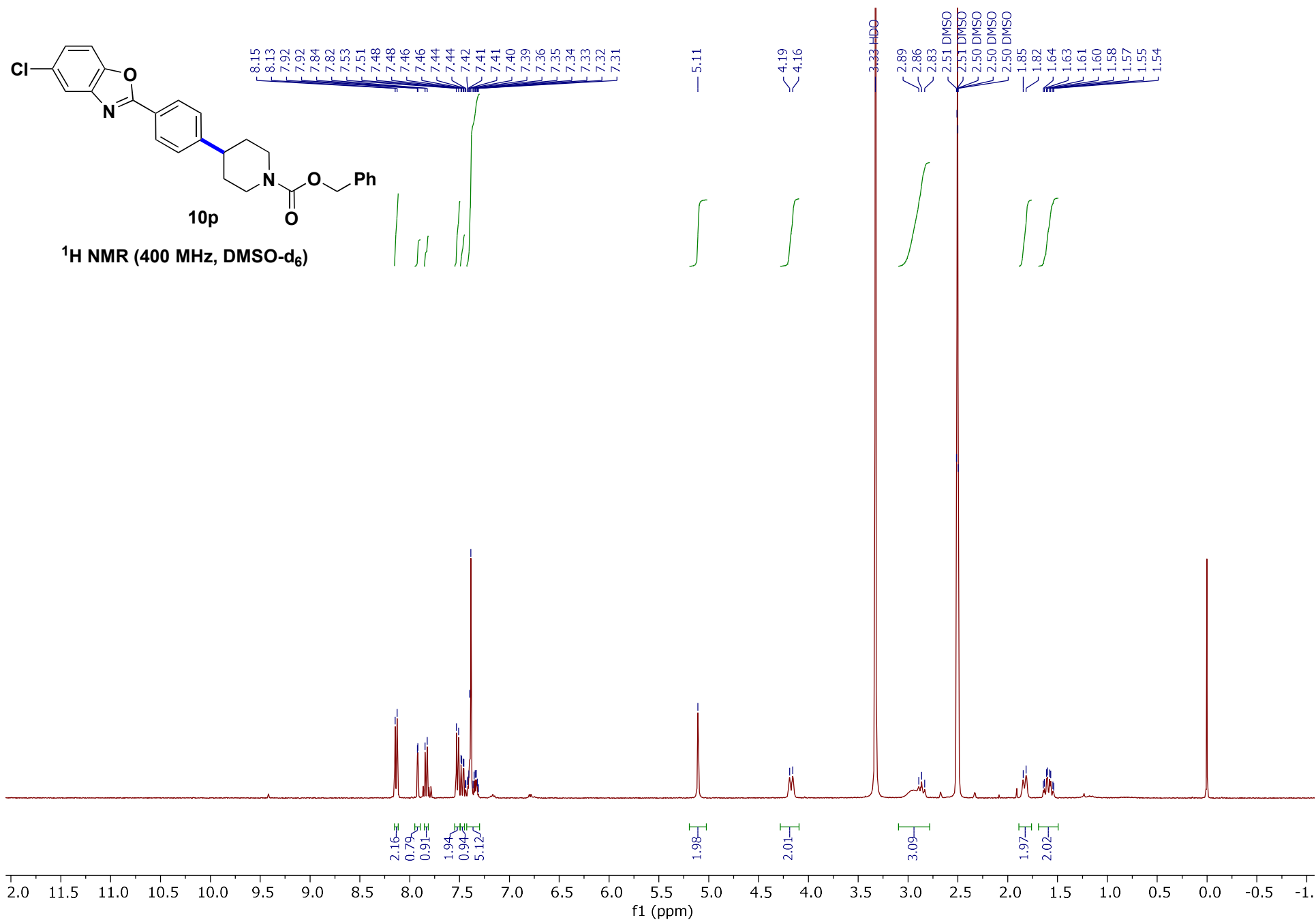
¹H NMR (500 MHz, CDCl₃)

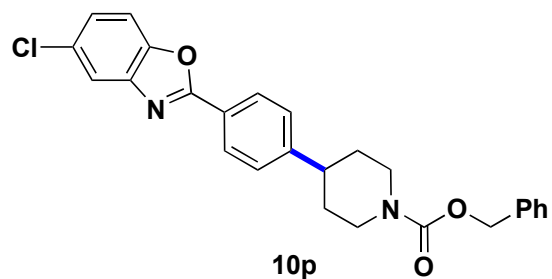




^{13}C NMR (126 MHz, CDCl_3)

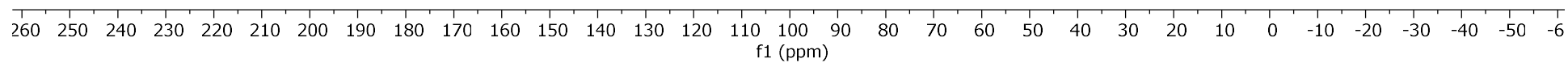


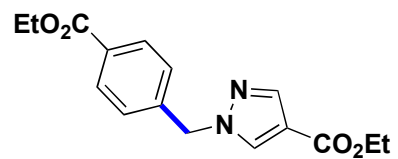




^{13}C NMR (126 MHz, DMSO- d_6)

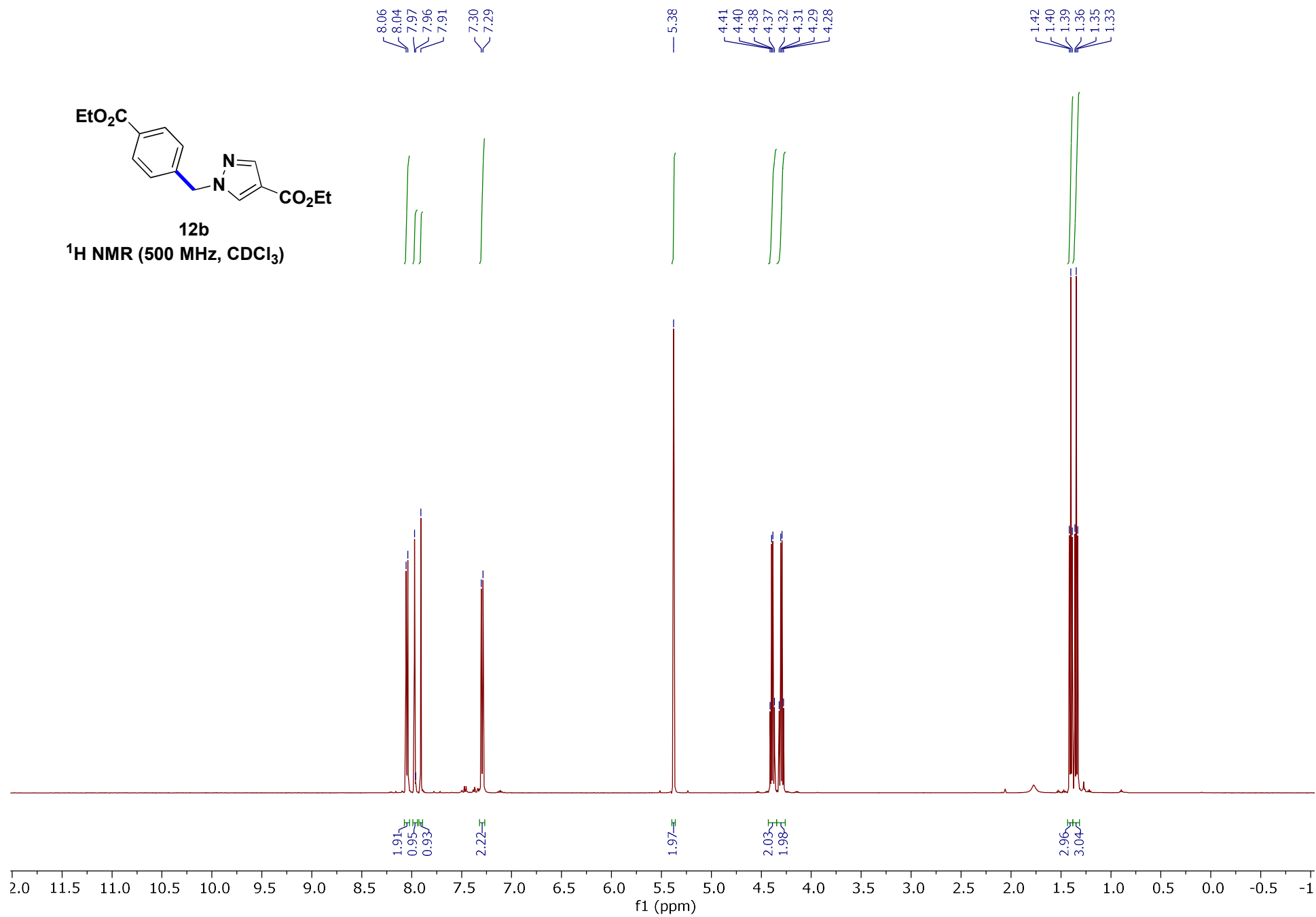
164.30
154.89
150.88
149.49
143.34
137.49
129.49
128.90
128.34
128.30
128.14
128.05
125.85
124.47
119.90
112.74
66.66
44.43
41.99
40.51 DMSO
40.35 DMSO
40.18 DMSO
40.01 DMSO
39.85 DMSO
39.68 DMSO
39.51 DMSO
32.77

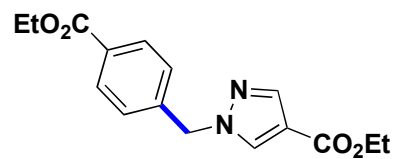




12b

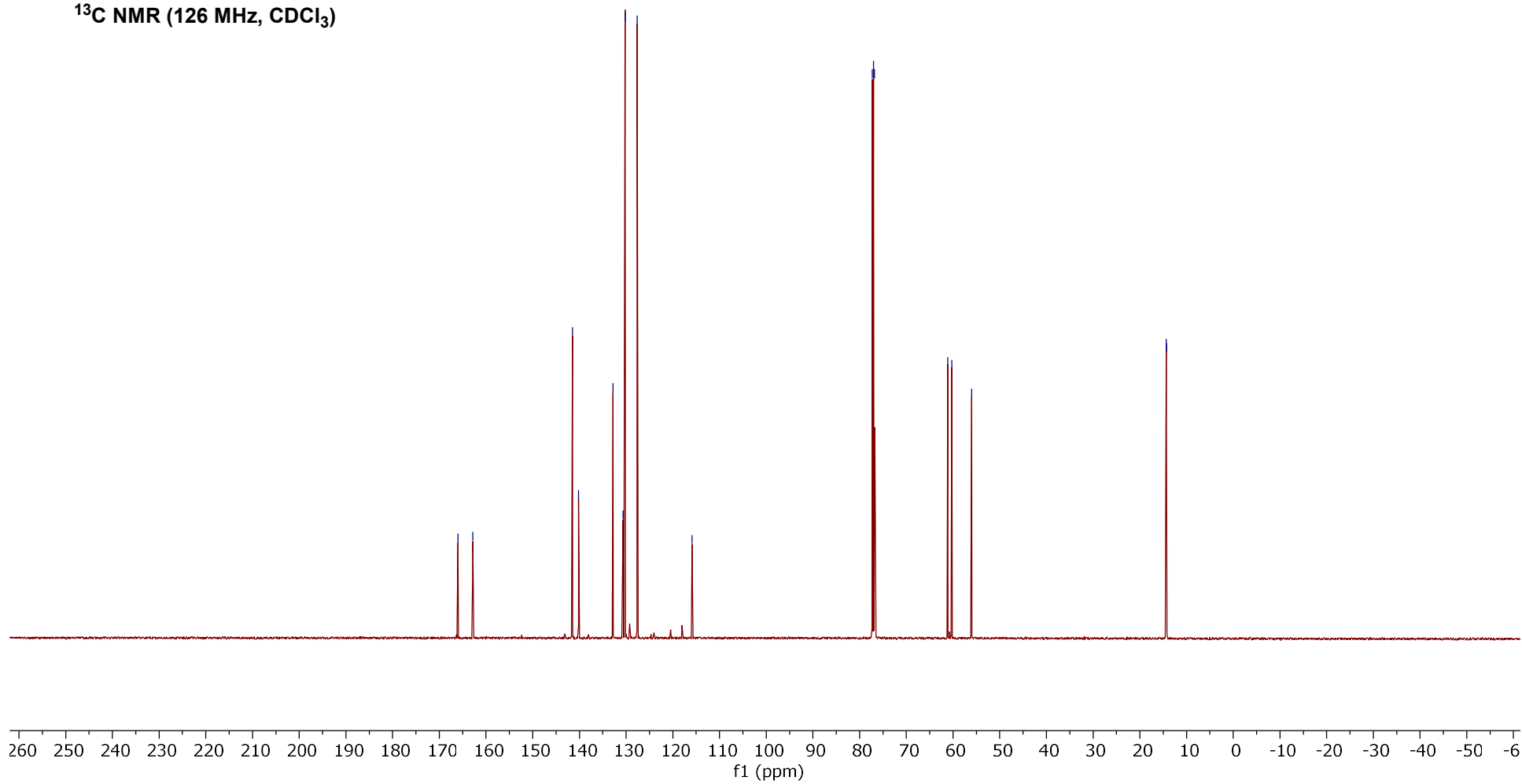
¹H NMR (500 MHz, CDCl₃)

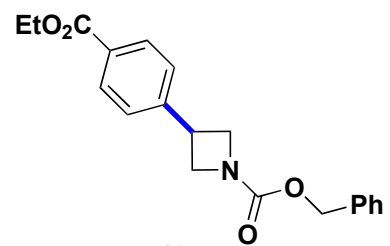




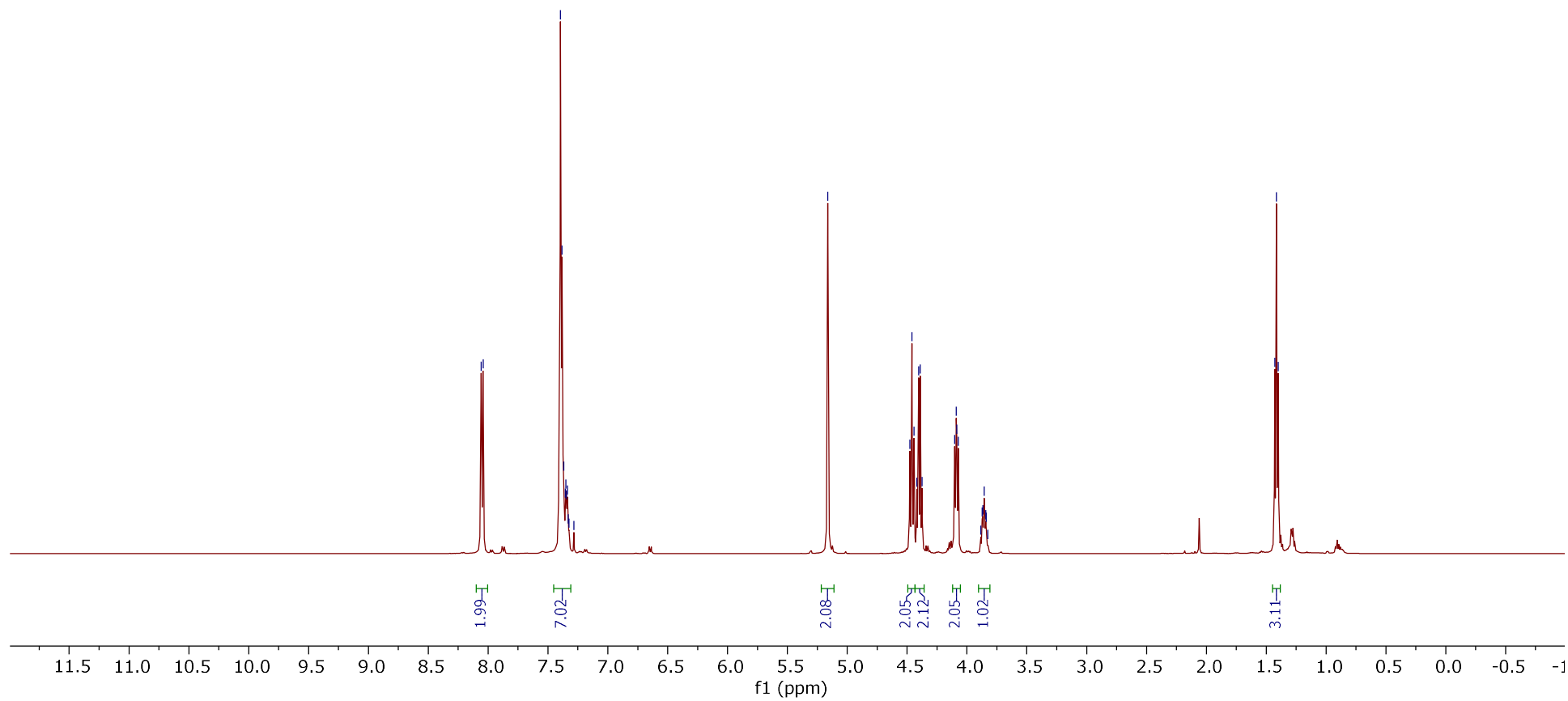
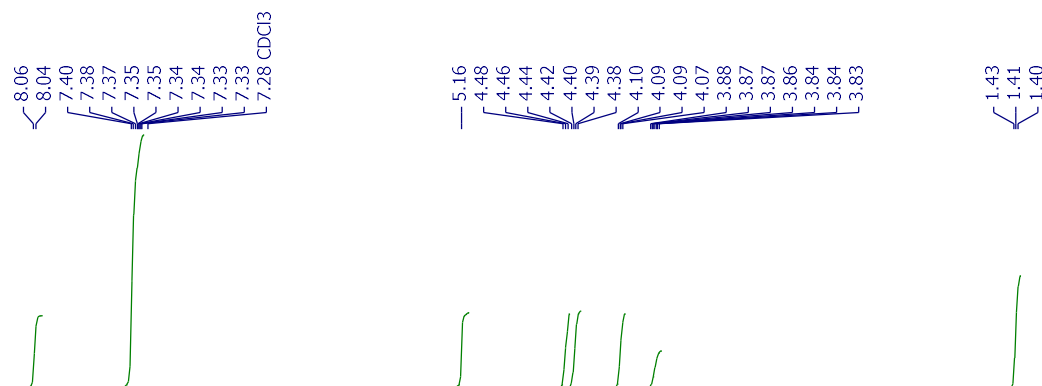
12b

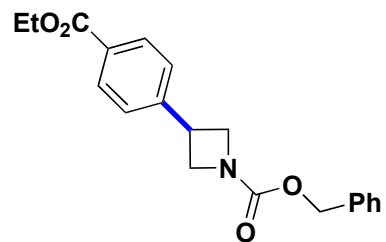
¹³C NMR (126 MHz, CDCl₃)





¹H NMR (500 MHz, CDCl₃)





12e

^{13}C NMR (126 MHz, CDCl_3)

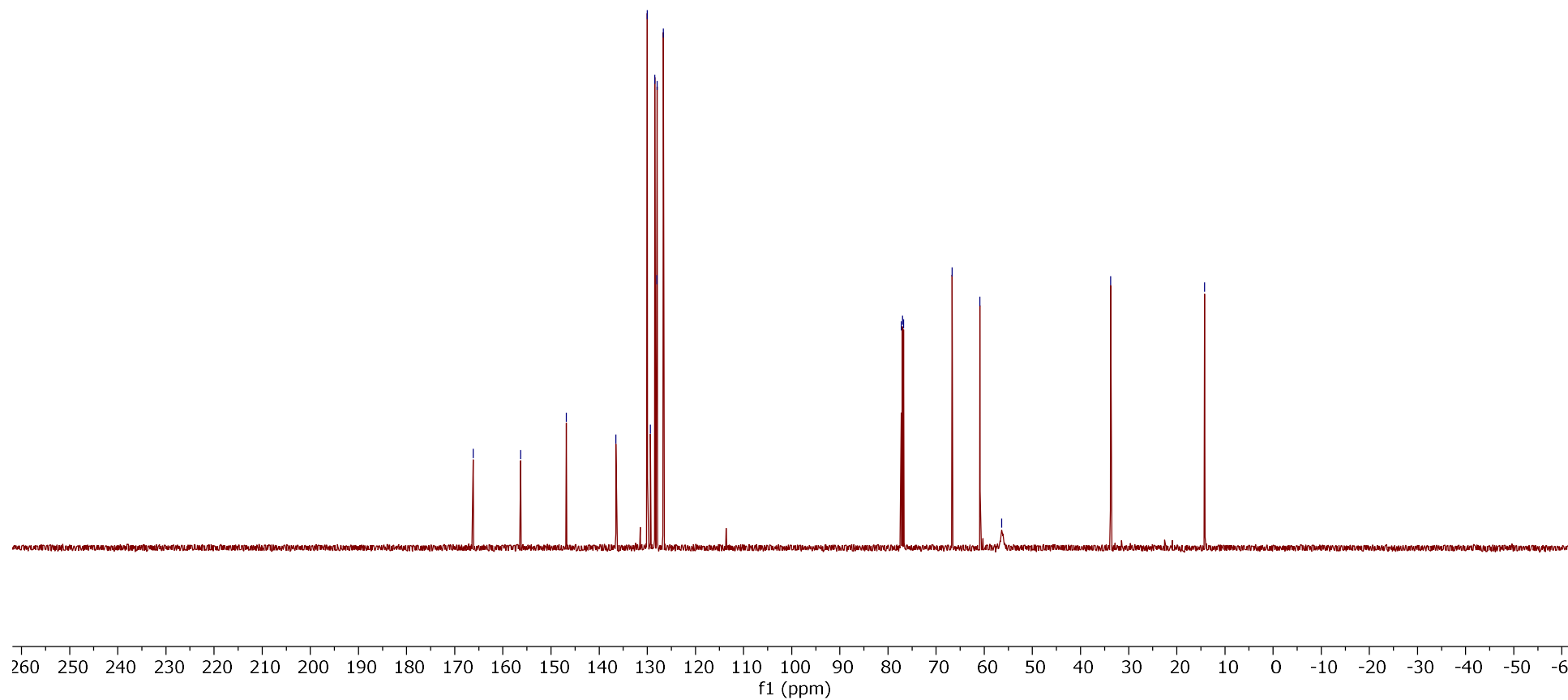
— 166.15
— 156.32
— 146.81
136.51
129.98
129.34
128.42
128.01
127.94
126.64

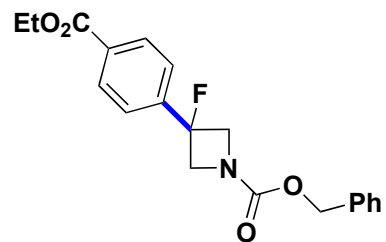
77.25
77.00
76.75

66.68
60.89
56.38

— 33.77

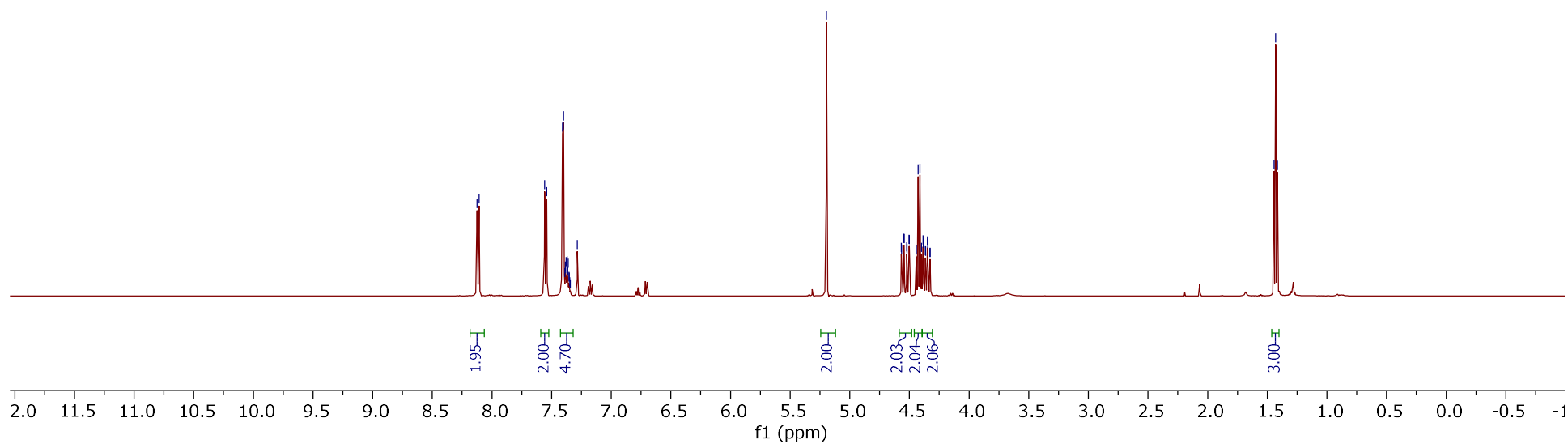
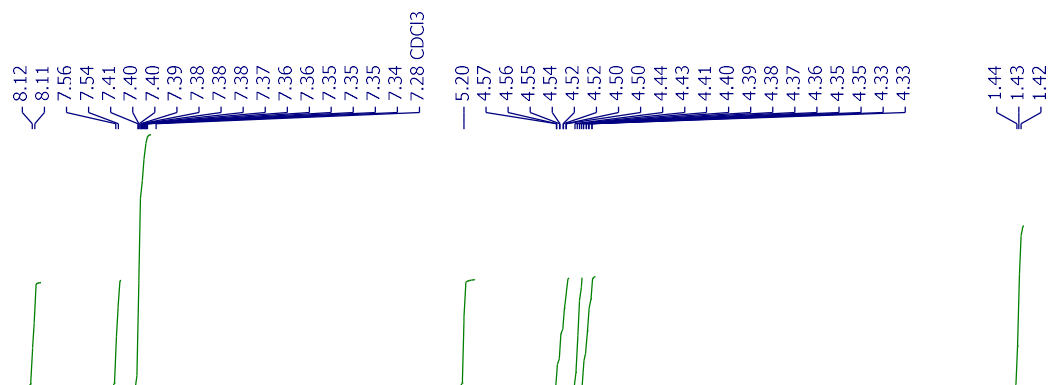
— 14.24

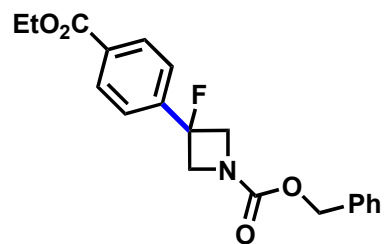




12f

^1H NMR (500 MHz, CDCl_3)

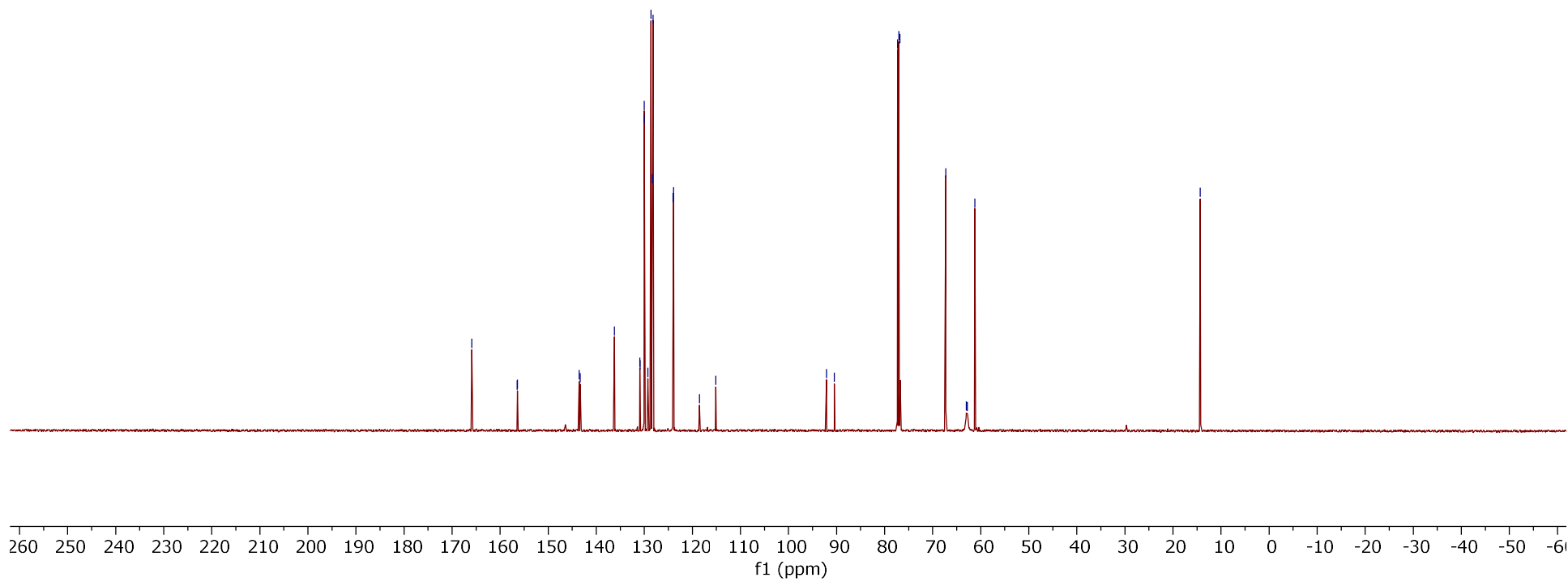


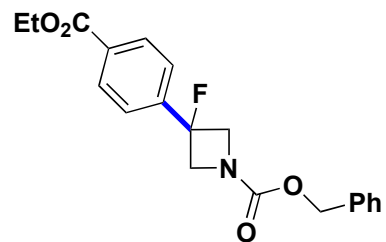


12f

^{13}C NMR (126 MHz, CDCl_3)

165.92, 156.44, 156.41, 143.53, 143.35, 136.23, 130.90, 130.90, 130.01, 130.00, 129.28, 128.59, 128.31, 128.16, 124.01, 123.94, 118.53, 115.10, 92.10, 90.44, 77.31, 77.05, 76.80, 67.26, 62.98, 62.79, 61.23, 14.32

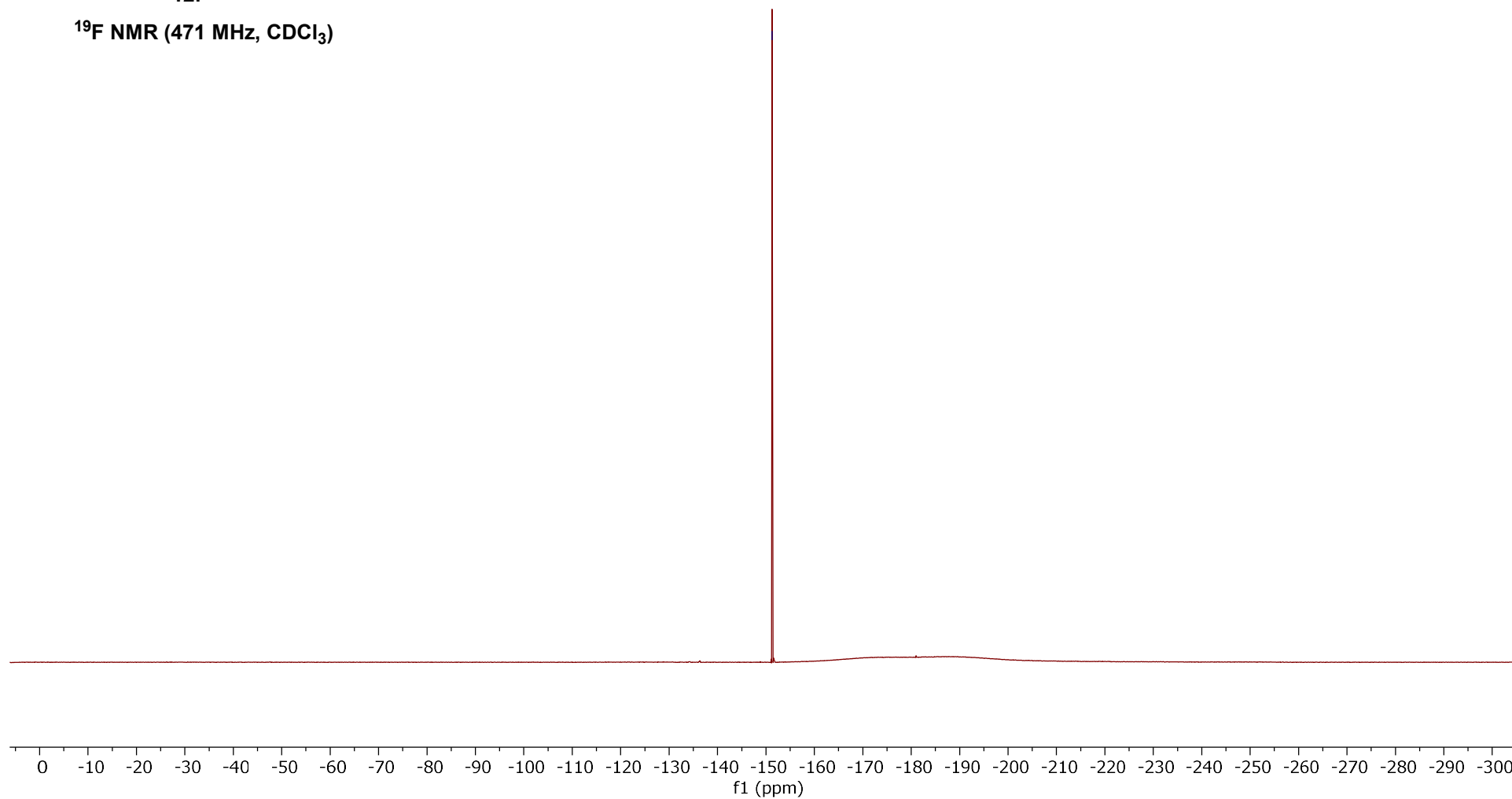


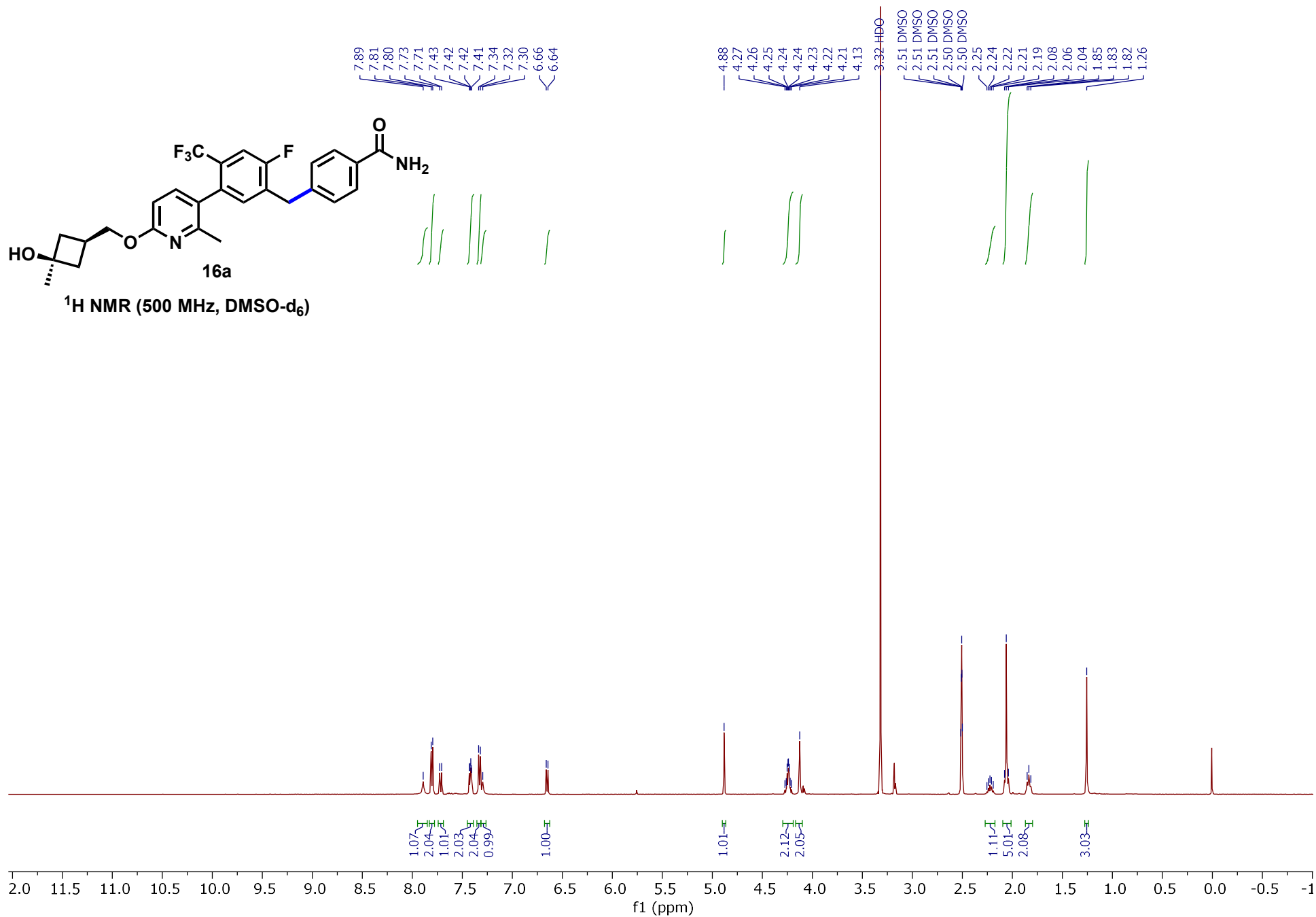
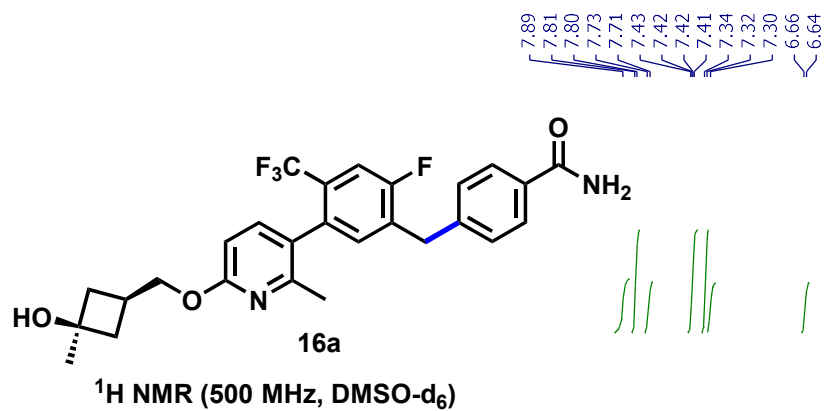


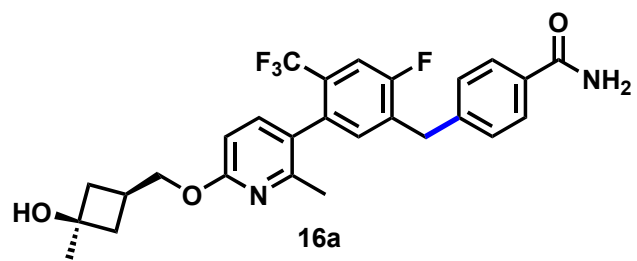
12f

^{19}F NMR (471 MHz, CDCl_3)

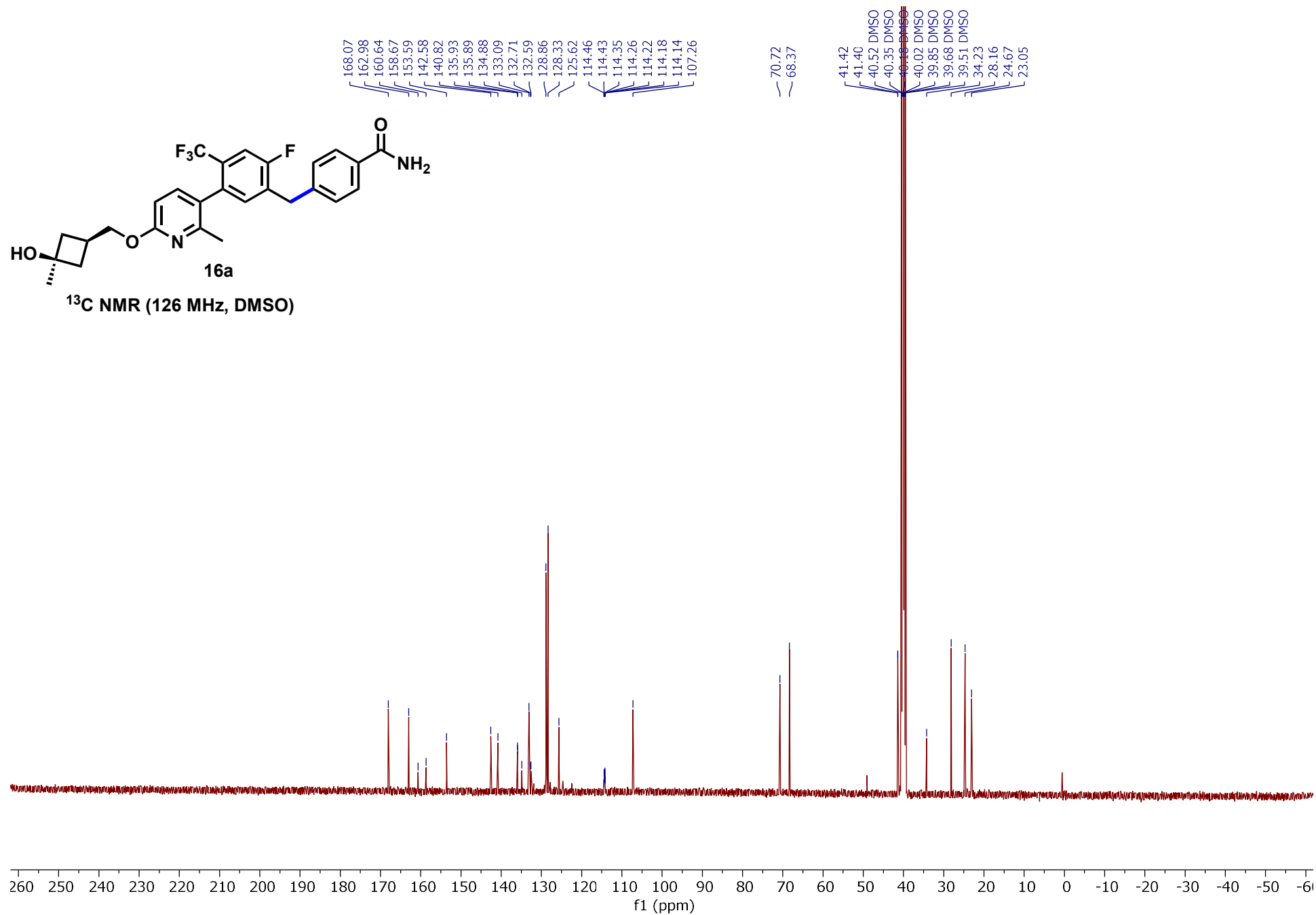
-151.26

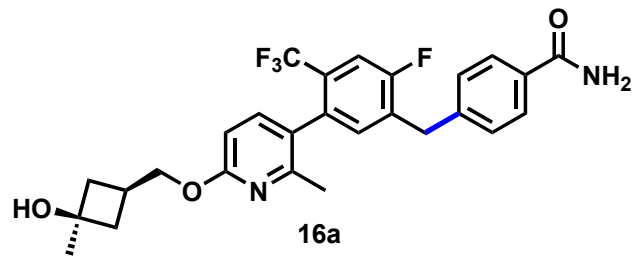






¹³C NMR (126 MHz, DMSO)

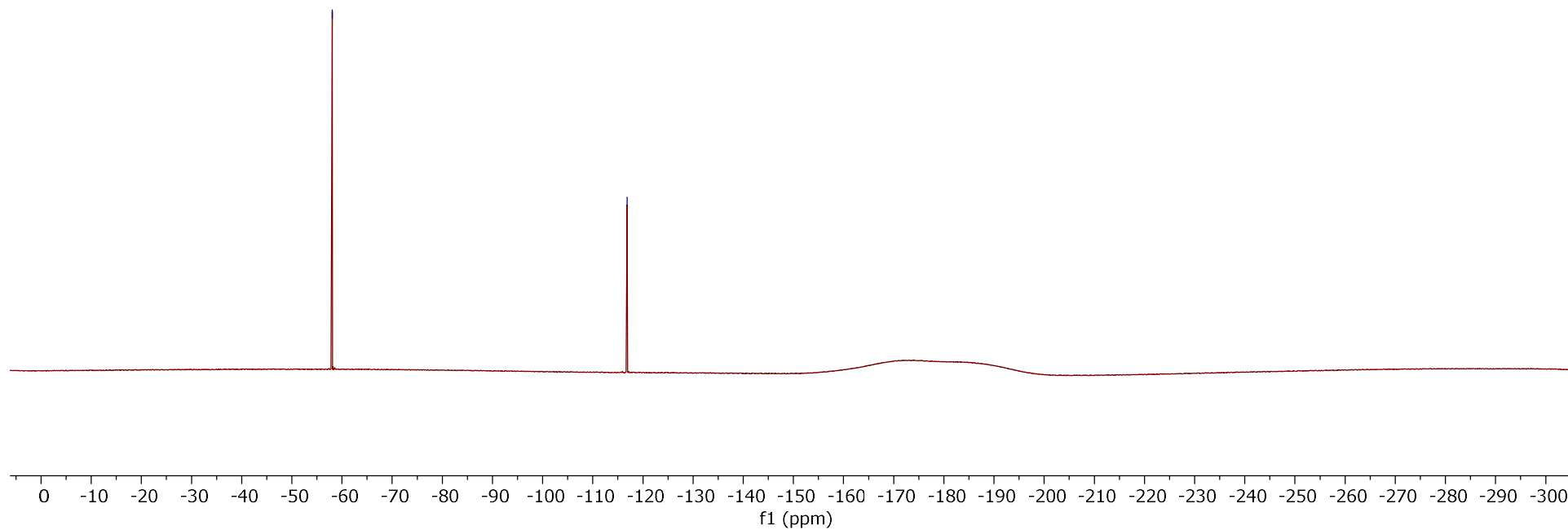


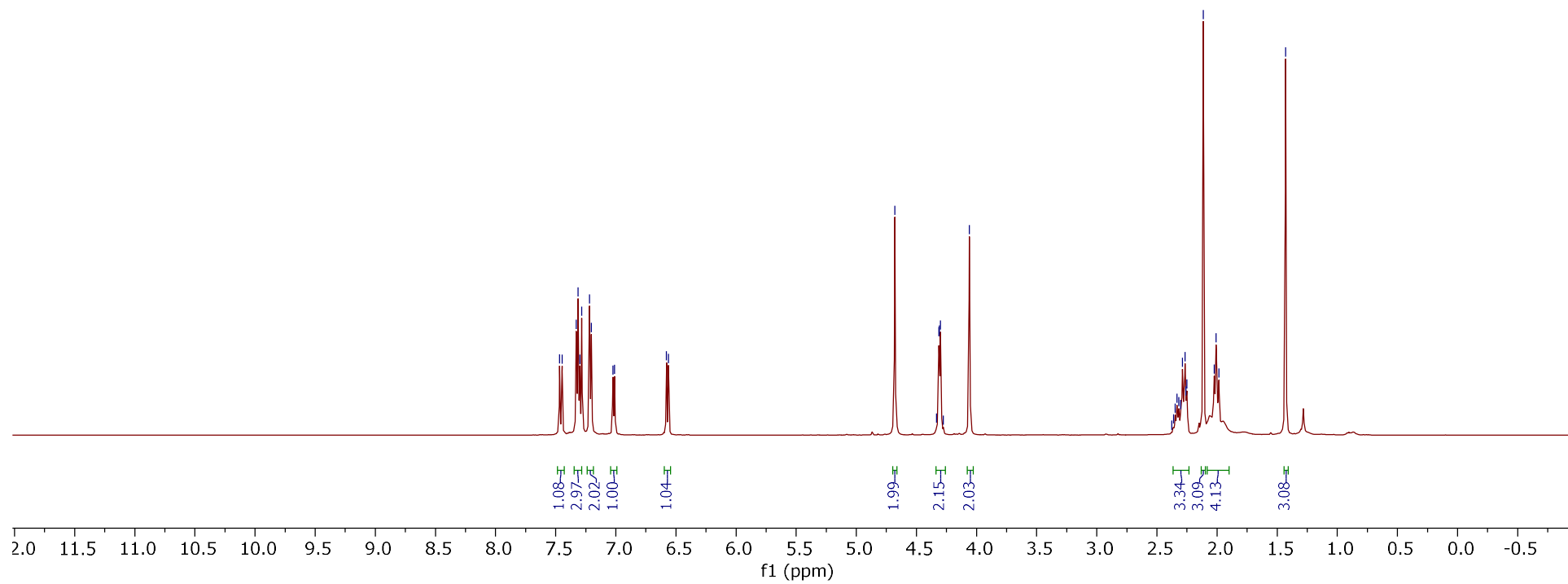
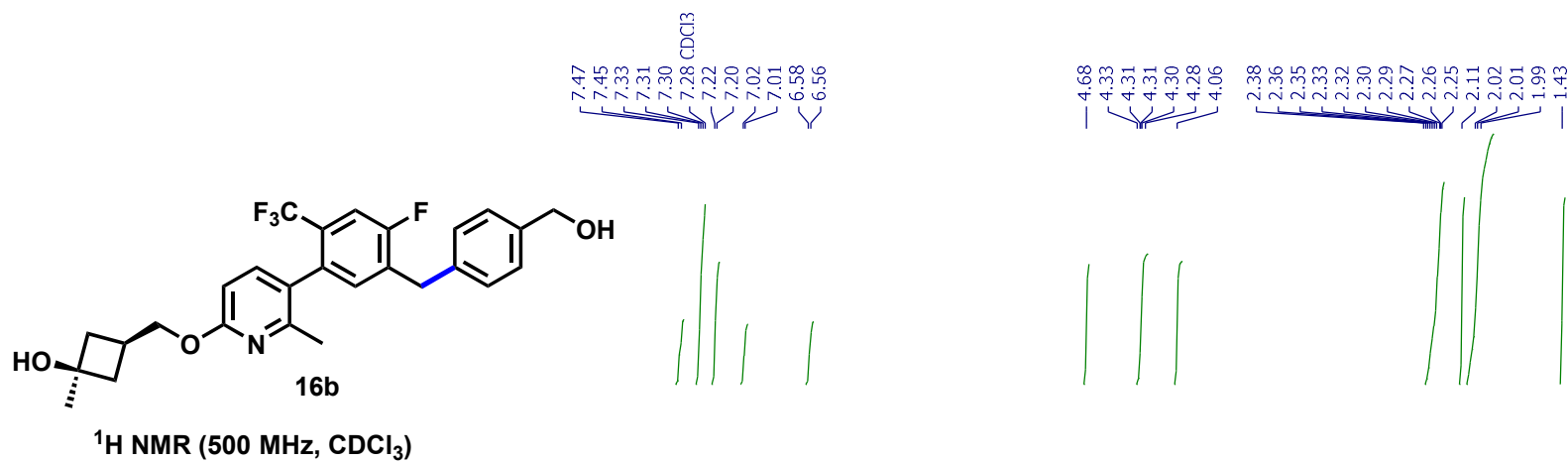


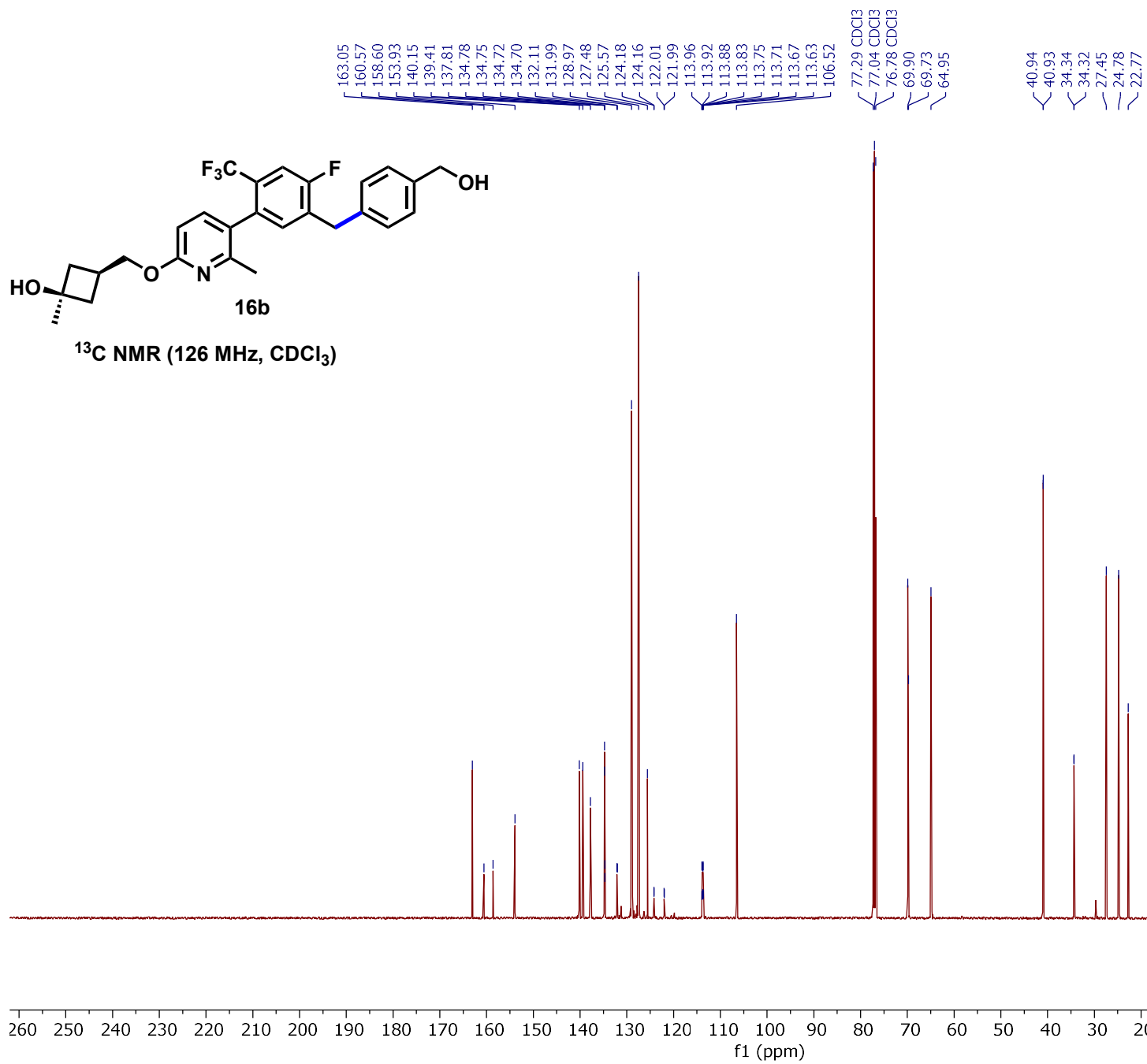
¹⁹F NMR (471 MHz, DMSO-d₆)

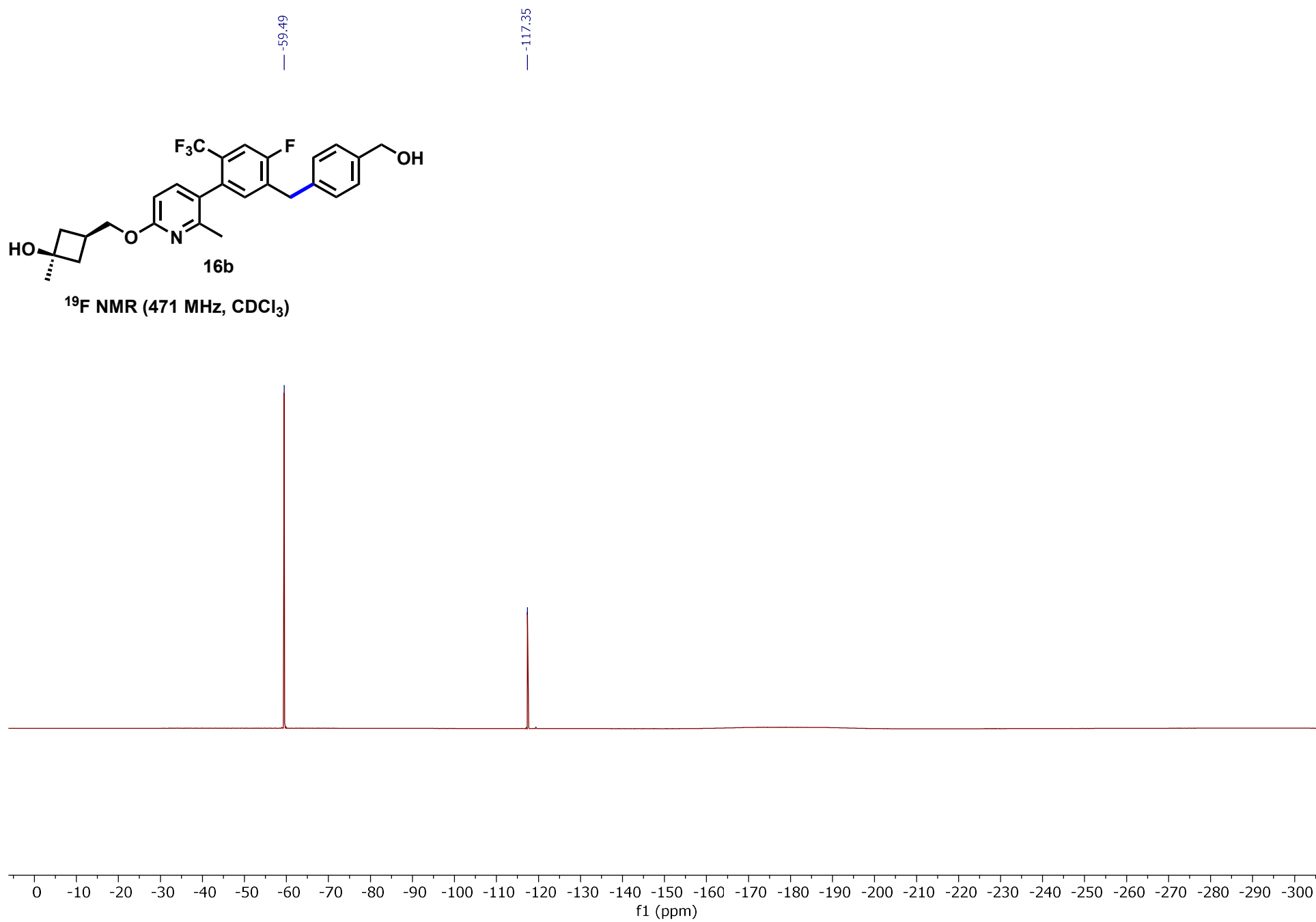
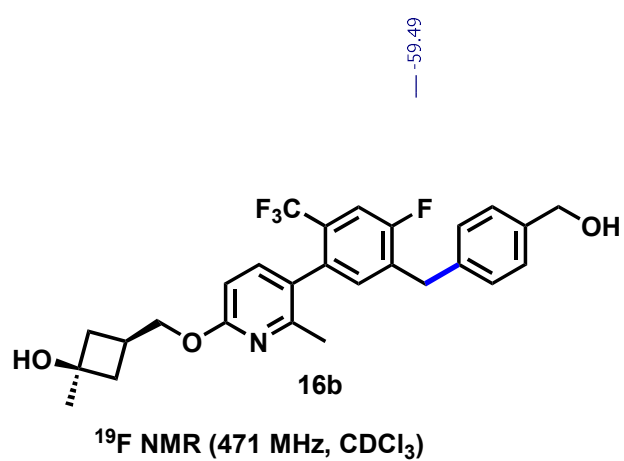
— -58.04

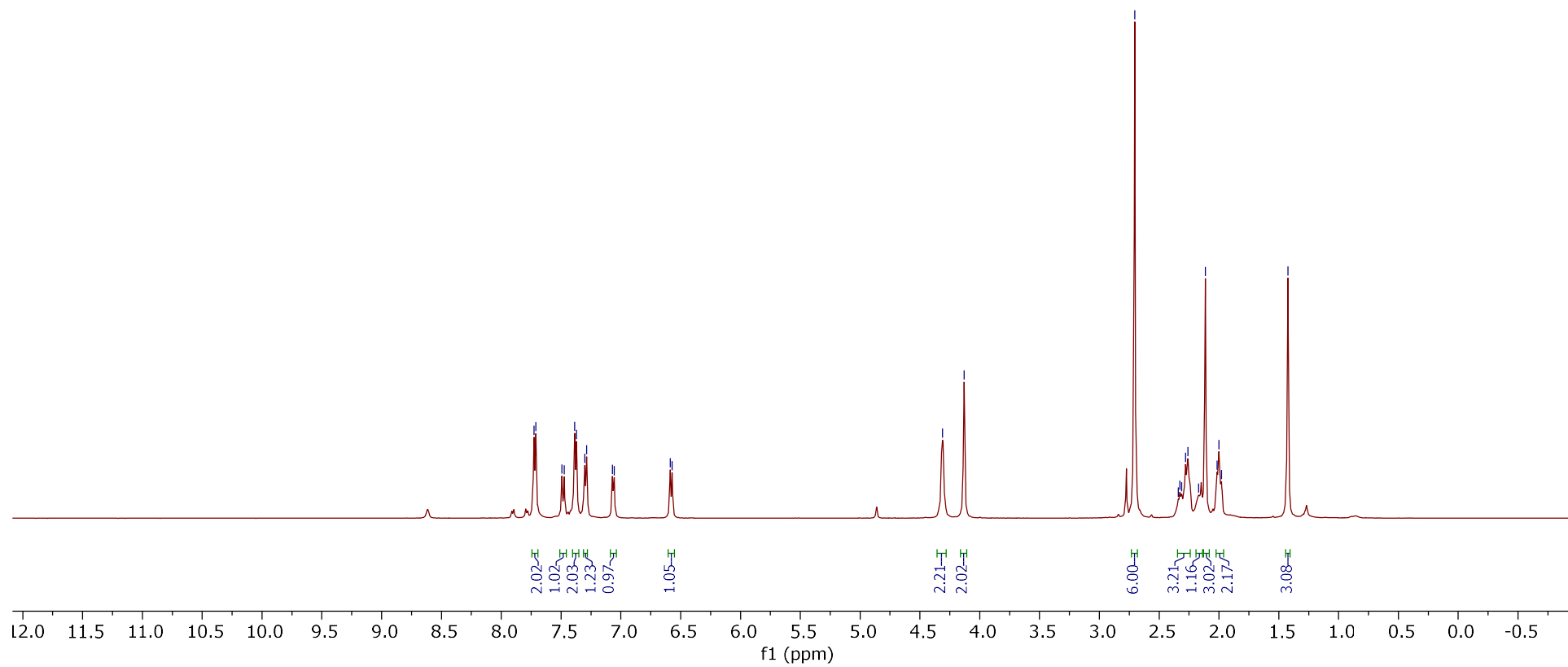
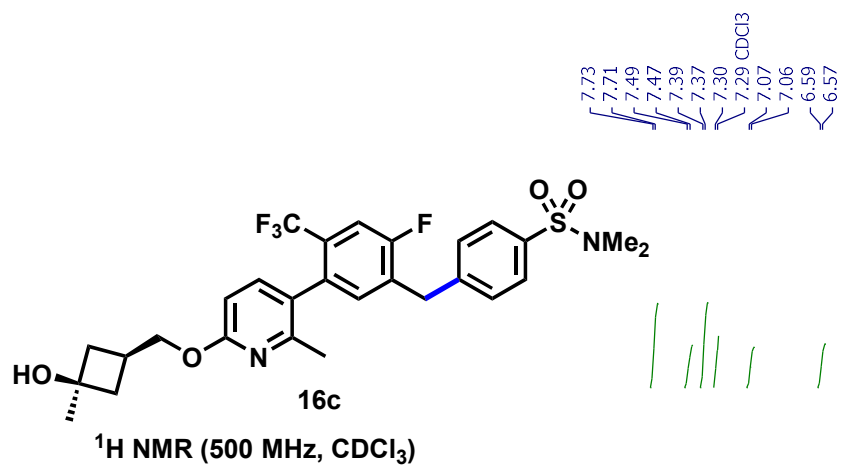
— -116.84

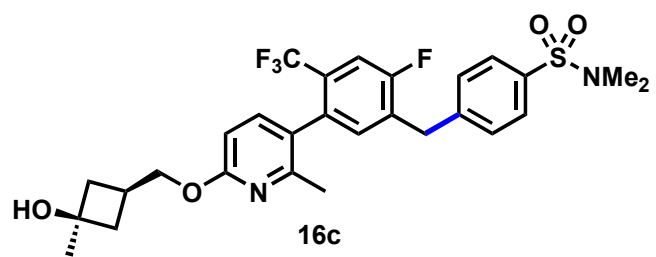
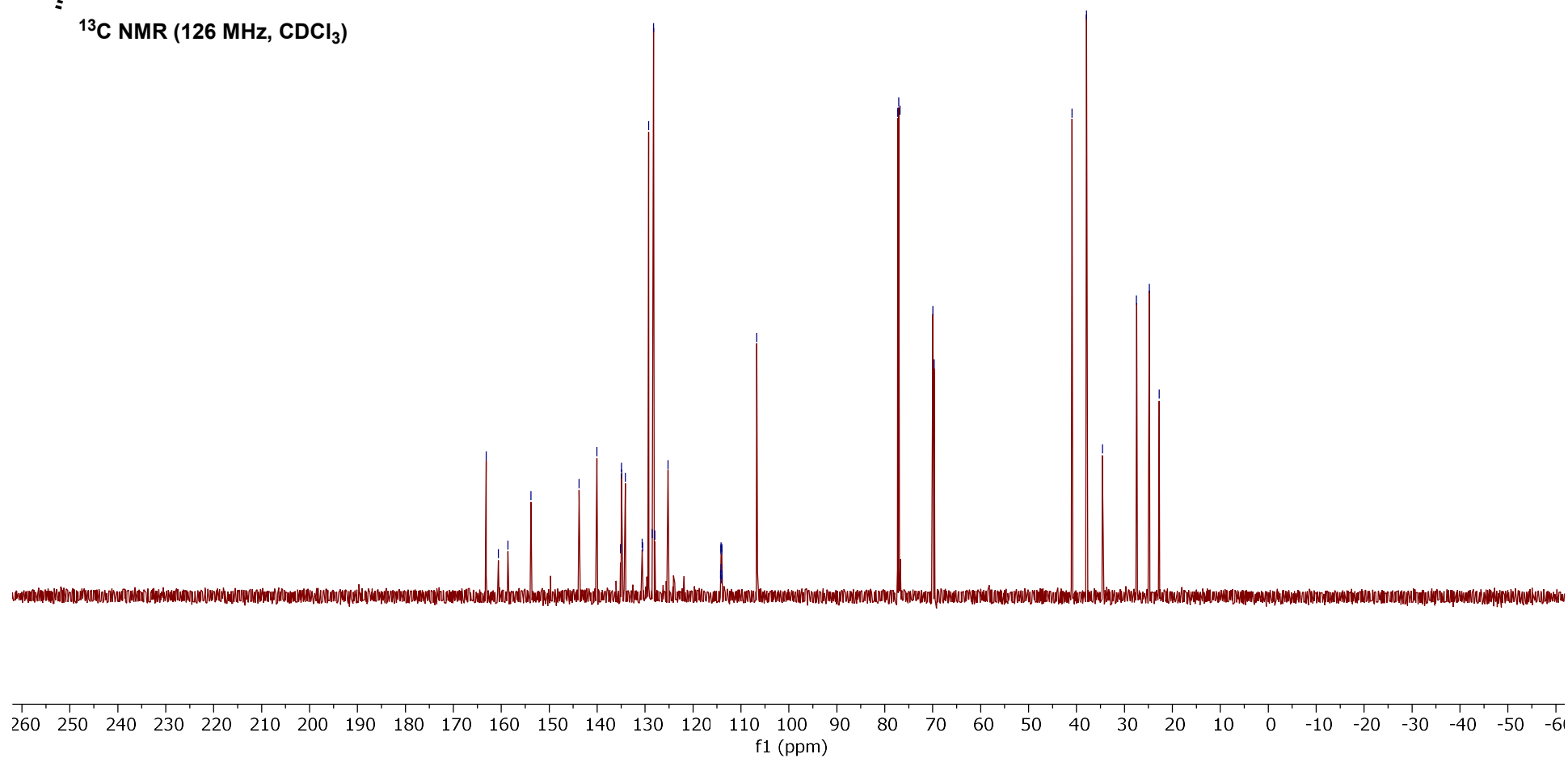


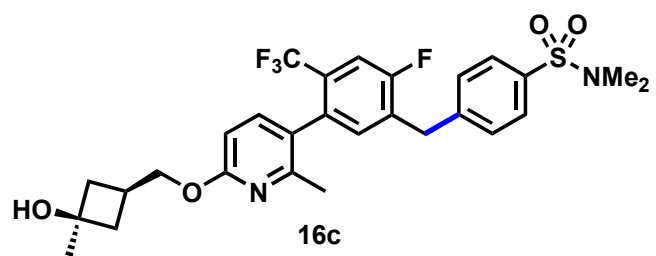








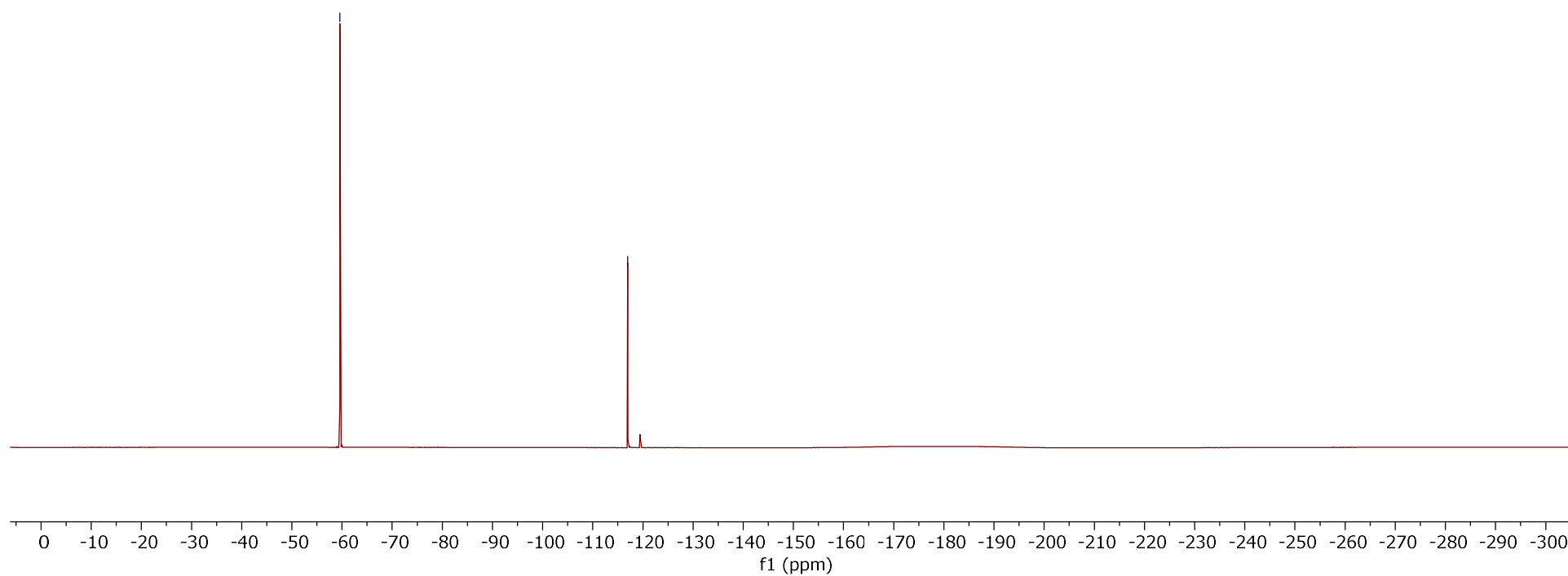
 ^{13}C NMR (126 MHz, CDCl_3)

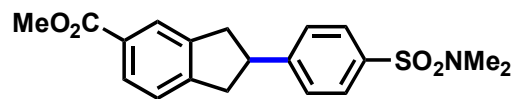


¹⁹F NMR (471 MHz, CDCl₃)

-59.59

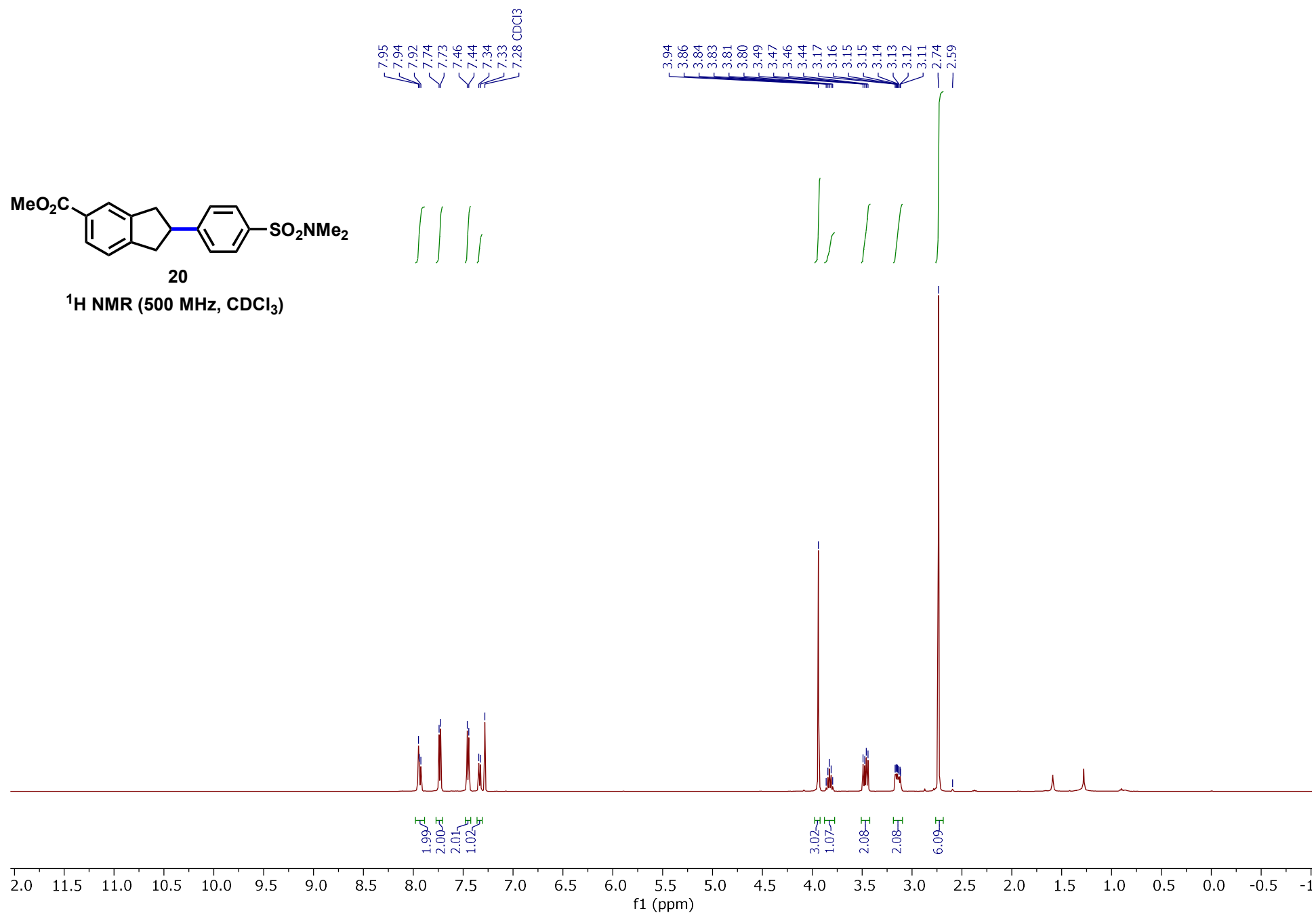
-116.96

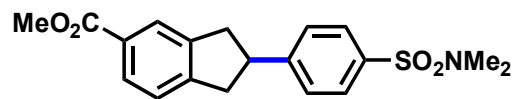




20

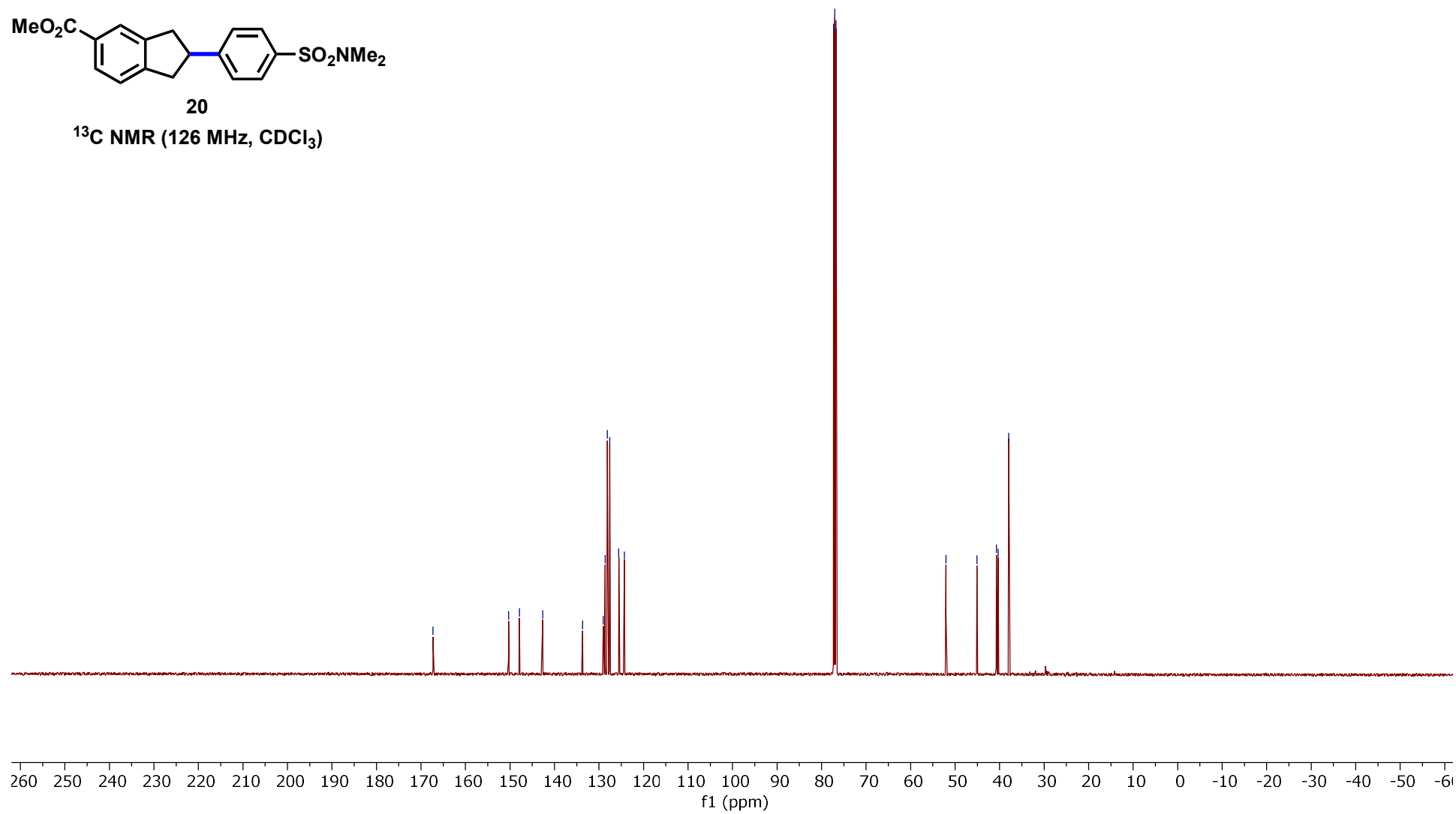
¹H NMR (500 MHz, CDCl₃)





20

^{13}C NMR (126 MHz, CDCl_3)



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