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Supplementary Materials for

Halogenation of the 3-position of pyridines through Zincke imine intermediates

Benjamin T. Boyle *et al.*

Corresponding authors: Robert S. Paton, robert.paton@colostate.edu; Andrew McNally, andy.mcnally@colostate.edu

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The PDF file includes:

Other Supplementary Material for this manuscript includes the following:

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1. General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR (400 MHz) spectrometer or an Agilent Inova 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR spectrometer (100 MHz) or an Agilent Inova 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16 ppm), C_6D_6 (128.06 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32 ppm).

High–resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF LC/MS ("OTOF") interfaced to an Agilent 1200 HPLC with multi-mode (combined ESI and APCI) and Direct Analysis in Real Time (DART) sources. Low–resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 27 FT–IR spectrometer as either solids or neat films, either through direct application or deposited in $CHCl_3$, with absorptions reported in wavenumbers (cm^{-1}).

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

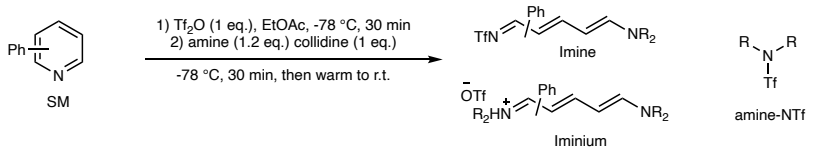
Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods. 1,2–Dichloroethane (DCE), chloroform, and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality and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

N-iodosuccinimide (NIS) was purchased from Combi-Blocks and used without further purification. *N*-bromosuccinimide (NBS) was purchased from Oakwood and recrystallized in water. *N*-chlorosuccinimide (NCS) was purchased from Oakwood and recrystallized in acetic acid. *N*-halosuccinimide reagents were kept in a –20 °C fridge and vials of repurified material were wrapped in aluminum foil. Trifluoroacetic acid (TFA) and HCl (4M in dioxanes) were purchased from Sigma Aldrich and used without further purification, and were routinely stored in a –20 °C fridge. Trifluoromethanesulfonic anhydride (Tf_2O), dibenzylamine ($HNBn_2$), collidine (2,4,6-trimethylpyridine) were purchased from Oakwood and used without further purification, and were routinely stored in a –20 °C fridge. Trimethoxybenzene (TMB) was purchased from Oakwood and used without further purification. Anhydrous Ethyl acetate was purchased from Acros Organics. Ammonium acetate (NH_4OAc) was purchased from Fisher Chemical and used without further purification.

2. Optimization Studies

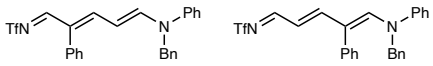
Ring-Opening of Pyridines:

Table S1. Amine screen for ring-opening of 2-phenylpyridine and 3-phenylpyridine.



Entry	Substrate	amine	SM	Imine	Iminium	amine-NTf
1	2-Ph	pyrrolidine	43	40	n.d.	19
2	2-Ph	piperidine	48	44	n.d.	15
3	2-Ph	morpholine	34	62	n.d.	17
4	2-Ph	2-methyl piperidine	23	39	n.d.	<1
5	2-Ph	N-benzylmethylamine	31	47	n.d.	7
6	2-Ph	diisobutylamine	20	51	n.d.	3
7	2-Ph	dibenzylamine	19	84	n.d.	2
8	2-Ph	N-benzylaniline	19	81	n.d	10
9	3-Ph	pyrrolidine	51	34	17	25
10	3-Ph	piperidine	37	41	17	15
11	3-Ph	morpholine	32	40	23	15
12	3-Ph	2-methyl piperidine	24	55	15	<1
13	3-Ph	N-benzylmethylamine	31	32	16	9
14	3-Ph	diisobutylamine	16	67	13	<1
15	3-Ph	dibenzylamine	13	82	n.d.	<1
16	3-Ph	N-benzylaniline	18	57 (2.6:1 r.r)	n.d.	1

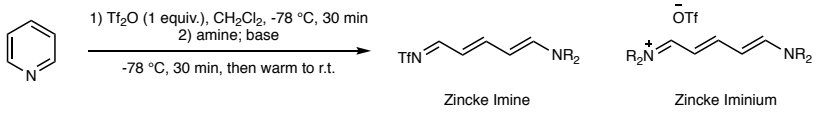
Entry 16: regioisomers



2.6:1 r.r

Yields of SM, imine and iminium determined by ^{1}H NMR using triphenylmethane as an internal standard. Amine-*N*Tf yields determined by ^{19}F NMR using 4,4'-difluorobenzophenone as an internal standard. See below for representative crude NMRs from entry 2.

Table S2. Additional ring-opening results for pyridine.

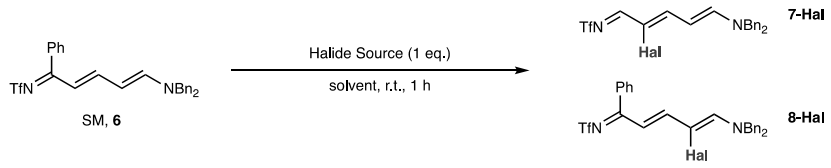


Entry	amine (eq.)	base (eq.)	SM	Imine	Iminium
1	piperidine (2)	none	21	52	20
2	piperidine (1)	Et_3N (2)	15	51	15
3	piperidine (3)	none	0	0	78
4	piperidine (1)	lutidine (1)	19	75	6
5	n-benzylmethylamine (2)	none	27	52	6
6	dibenzylamine (2)	mone	28	88	0
7	dibenzylamine (3)	none	0	98	0
8	dibenzylamine (1.2)	collidine (1)	0	97	0

Yields determined by ^{1}H NMR using triphenylmethane as an internal standard

Halogenation of Imines:

Table S3. Reaction of **6** with electrophilic halogenation reagents.



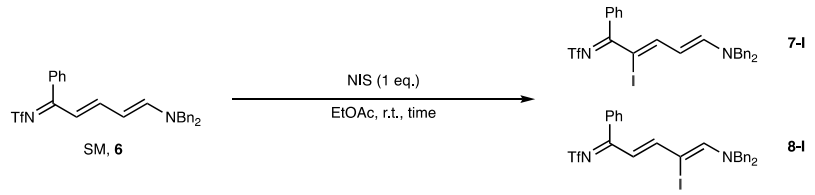
Entry	Solvent	Halide Source	SM, **6**	**7-Hal**	**8-Hal**
1	EtOAc	NIS (5 min) (initial hit)	0	92	0
2	EtOAc	NBS	0	75	17
3	EtOAc	NBS, -78 °C	44	40	6
4	EtOAc	NCS	0	6	21
5	EtOAc	$CuBr_2$	41	58	0
5	EtOAc	$CuCl_2$	33	12	37
6	CH_2Cl_2	NIS	0	98	0
7	CH_2Cl_2	NBS	0	93	2
8	CH_2Cl_2	NBS, -78 °C	0	92	<1
9	CH_2Cl_2	NCS	35	18	29
10	CH_2Cl_2	$CuBr_2$	46	52	0
11	CH_2Cl_2	$CuCl_2$	52	15	25

Yields determined by ^{1}H NMR using triphenylmethane as an internal standard.

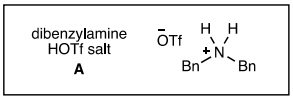
Investigation into effect of imine purity:

It was found that the method of purifying imine **6** affects the reactivity with NIS. The initial iodination result of 92% in 5 minutes (**Table S3, entry 1**) was achieved when using an imine purified via a water workup and hexane precipitation. It was later found that if the imine is purified with basic workup and hexane precipitation, imine **6** undergoes iodination more slowly (**Table S4, entries 2 and 3**). Adding small amounts of the TfOH salt of dibenzylamine (a byproduct from the ring-opening reaction) notably improves the reaction, and trace amounts of this byproduct are observed when the imine is purified via water workup. However, only minor differences are observed when varying the purification of the imine derived from 2-phenethylpyridine (**Table S5**). Even when that imine is purified with a basic workup, the iodination proceeds quantitatively in 5 minutes (**Table S5, entry 3**). This last observation indicates that this effect is not necessarily general. The presence of protonated dibenzylamine doesn't affect the selectivity of the iodination reaction. Other halogenation results presented in Table S3 were gathered using base washed material. Fig. 1 shows representative NMRs of imine **6** purified by basic vs aqueous workups.

Table S4. Effect of purification method on iodination of Zincke imine **6**.



Entry	Purification of SM Imine	time	additive **A**	SM, **6**	**7-I**	**8-I**
1	Water workup	5 min	none	0	92	0
2	Basic workup	60 min	none	7	90	0
3	Basic workup	5 min	none	47	48	0
4	Basic workup	5 min	0.01 eq.	10	90	0
5	Basic workup	5 min	0.1 eq.	0	98	0



Yields determined by ^{1}H NMR using triphenylmethane as an internal standard.

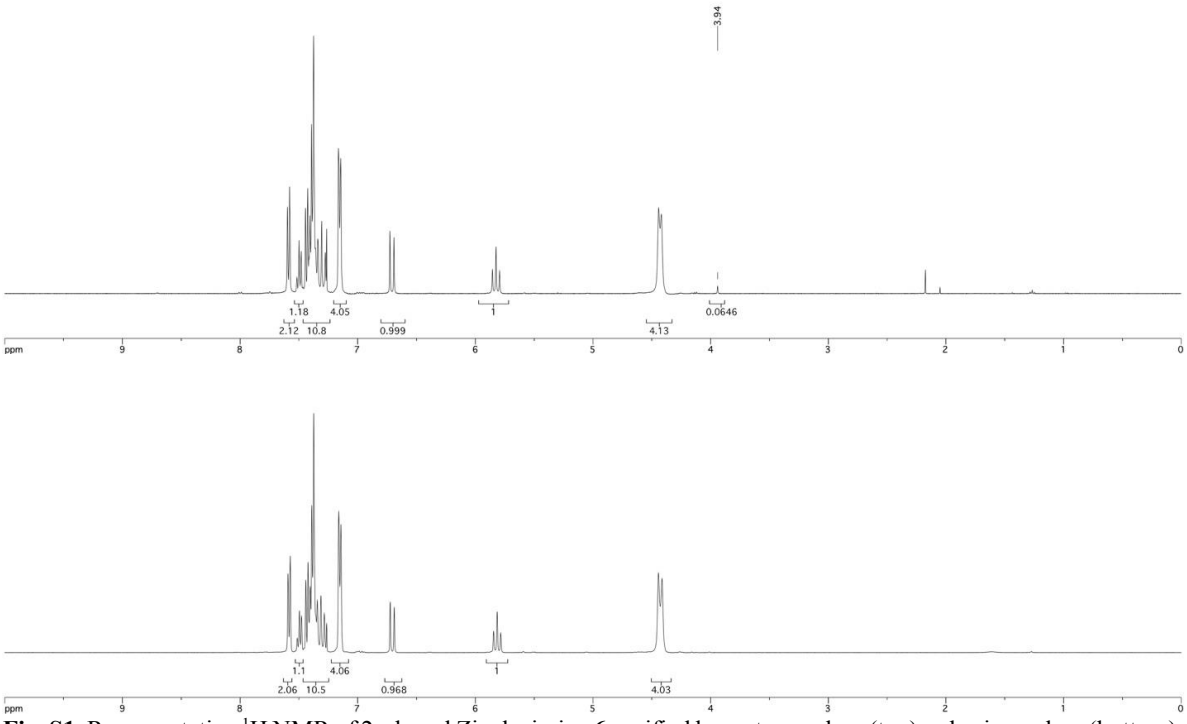
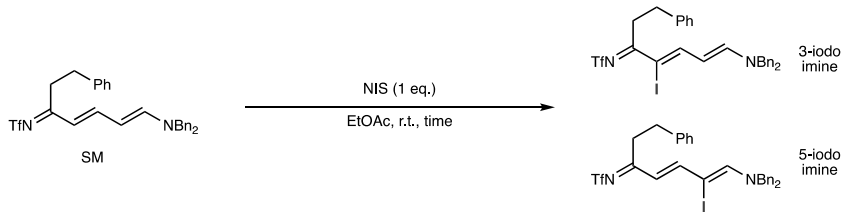


Fig. S1. Representative ^{1}H NMR of 2-phenyl Zincke imine **6** purified by water workup (top) vs basic workup (bottom). Singlet at 3.94 ppm for the top spectrum corresponds to protonated dibenzylamine impurity.

Table S5. Effect of purification method on iodination of 2-phenethyl Zincke imine.



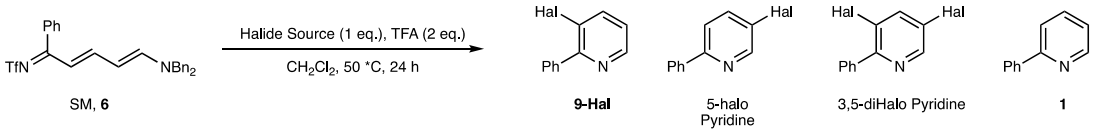
Entry	time	Purification of SM Imine	SM	3-iodo imine	5-iodo imine
1	1 min	Water workup	0	100	0
2	1 min	Basic workup	4	96	0
3	5 min	Basic workup	0	100	0

Yields determined by ^{1}H NMR using triphenylmethane as an internal standard.

Effect of halogenation of **6** *under NXS-TFA conditions:*

It was found that using TFA in the presence of *N*-halosuccinimide reagents led to halogenation at both the 3- and 5-positions, as well as promoting an acid-mediated recyclization to form pyridine products rather than imine products.

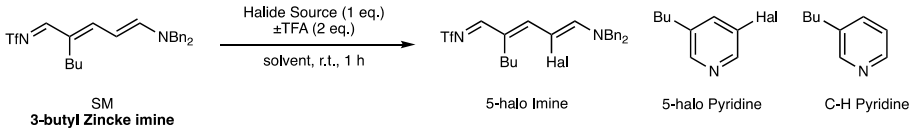
Table S6. Reaction of **6** with *N*-halosuccinimide reagents and TFA.



Entry	Halide Source	SM, **6**	**9-Hal**	5-halo Pyridine	3,5-diHalo Pyridine	**1**
1	NIS	24	8	20	8	24
2	NBS	25	8	24	17	8
3	NCS	21	6	36	10	14

Yields determined by ^{1}H NMR using triphenylmethane as an internal standard.

Table S7. Reactions of 3-butyl imine with electrophilic halogenation reagents.



SM
3-butyl Zincke imine

5-halo Imine

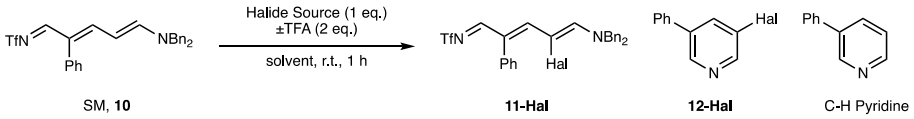
5-halo Pyridine

C-H Pyridine

Entry	Solvent	Halide Source	SM	5-halo Imine	5-halo Pyridine	C-H Pyridine
1	EtOAc	NIS	67	0	0	0
2	EtOAc	NIS-TFA	0	0	95	0
3	EtOAc	NBS	0	76	0	0
4	EtOAc	NBS-TFA	0	0	82	0
5	EtOAc	NCS	67	0	0	0
6	EtOAc	NCS-TFA	19	0	9	6
7	EtOAc	NCS (1.2 eq.), HCl (3 eq.)	10	0	59	5
8	EtOAc	$CuBr_2$	37	0	0	0
9	EtOAc	$CuCl_2$	78	9	0	0
10	CH_2Cl_2	NIS	36	0	0	0
11	CH_2Cl_2	NIS-TFA	0	9	97	2
12	CH_2Cl_2	NBS	28	26	0	0
13	CH_2Cl_2	NBS-TFA	0	0	85	14
14	CH_2Cl_2	NCS	76	0	0	0
15	CH_2Cl_2	NCS-TFA	0	0	13	86
16	CH_2Cl_2	NCS (1.2 eq.), HCl (3 eq.)	0	0	72	4
17	CH_2Cl_2	$CuBr_2$	55	10	0	0
18	CH_2Cl_2	$CuCl_2$	81	2	10	0

Yields determined by ^{1}H NMR using triphenylmethane as an internal standard.

Table S8. Reactions of **10** with electrophilic halogenation reagents.

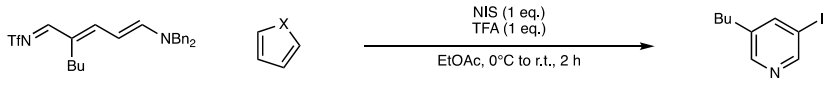


SM, **10** | **11-Hal** | **12-Hal** | C-H Pyridine

Entry	Solvent	Halide Source	SM, **10**	**11-Hal**	**12-Hal**	C-H Pyridine
1	EtOAc	NIS	77	0	0	0
2	EtOAc	NIS-TFA	0	0	90	0
3	EtOAc	NBS-TFA	0	0	76	0
4	EtOAc	NCS-TFA	31	0	3	13
5	EtOAc	NCS (1.2 eq.), HCl (4 eq.)	0	0	71	3
6	CH_2Cl_2	NCS-TFA	0	0	11	92
7	CH_2Cl_2	NCS (1.2 eq.), HCl (4 eq.)	0	9	76	9

Yields determined by ^{1}H NMR using triphenylmethane as an internal standard.

Table S9. Robustness screen for 3-butyl imine halogenation.



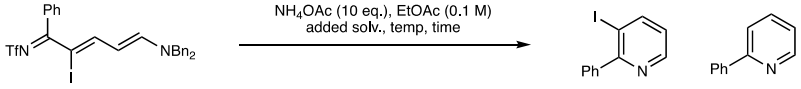
SM **3-butyl Zincke imine** | electron-rich arene additives | 5-iodo Pyridine

Entry	Additive	SM	5-iodo Pyridine
1	none	5	84
2	dimethylaniline	95	2
3	indole	89	1
4	1,4-dimethoxybenzene	6	80
5	thiophene	3	88
6	pyrrole	91	0
7	furan	2	85

Yields determined by ^{1}H NMR using triphenylmethane as an internal standard.

Rearomatization of Imines

Table S10. Rearomatization of Zincke **imine 7-I** under ammonium acetate conditions.

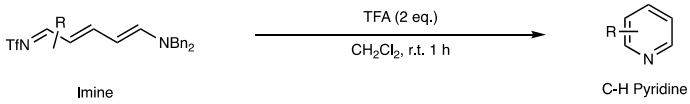


SM, **7-I** | **9-I** | **1**

Entry	added solvent:	temp, time	SM, **7-I**	**9-I**	**1**
1	MeOH (2x vol)	40 °C, 24 h	12	74	3
2	MeOH (2x vol)	50 °C, 4 h	11	73	3
3	MeOH (2x vol)	60 °C, 1 h	3	87	4
4	EtOH (2x vol)	60 °C, 1 h	0	90	5

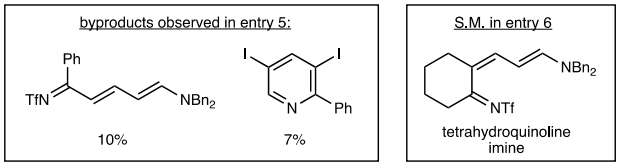
Yields determined by ^{1}H NMR using triphenylmethane as an internal standard.

Table S11. Rearomatization of Zincke imines under TFA conditions.



Imine C-H Pyridine

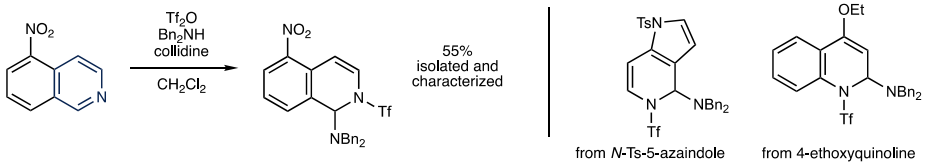
Entry	Imine Substrate	Imine	C-H Pyridine
1	2-Phenyl	98	2
2	2-Methyl	68	36
3	3-Phenyl	0	98
4	3-Butyl	0	98
5	2-Phenyl, 3-Iodo	67	0
6	5,6,7,8 Tetrahydroquinoline	0	89



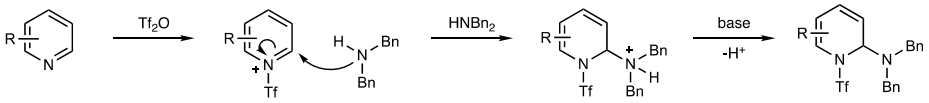
Yields determined by ^{1}H NMR using triphenylmethane as an internal standard.

Presence of ring-closed dihydropyridine intermediates instead of ring-opened imines:

In the cases of quinoline and isoquinolines, "ring-closed" dihydropyridine intermediates were observed. When the ring-opening reaction is successful, the reaction vials become brightly colored yellow/orange solutions (likely due to their similarities to cyanine dyes) and 12 Hz coupling constants are observed in the ^{1}H NMR (consistent with similar structures (*44*)). In comparison, when dihydropyridines form there is no significantly change in color of the reaction, and these 12 Hz coupling constants are not observed. In the case of 5-nitroisoquinoline, the corresponding intermediate was isolated and characterized. The benzyl methylene peaks of the ring-opened imines appear as two singlets, whereas the benzyl methylene peaks (now diastereotopic) of the ring-closed intermediate derived from the 5-nitroisoquinoline are an apparent quartet. In the azaindole case, we observed no color change and no diagnostic 12 Hz coupling constants. In the case of 4-ethoxyquinoline, halogenation of the carbocyclic ring was observed, and the peaks corresponding to the ring-opened intermediate (which can form under alternative conditions) were not observed. These "ring-closed" intermediates react are brominated by reacting with NBS at room temperature, and subsequent addition of 2 equivalents of TFA will convert these intermediates to the halogenated azine product.



Mechanism:



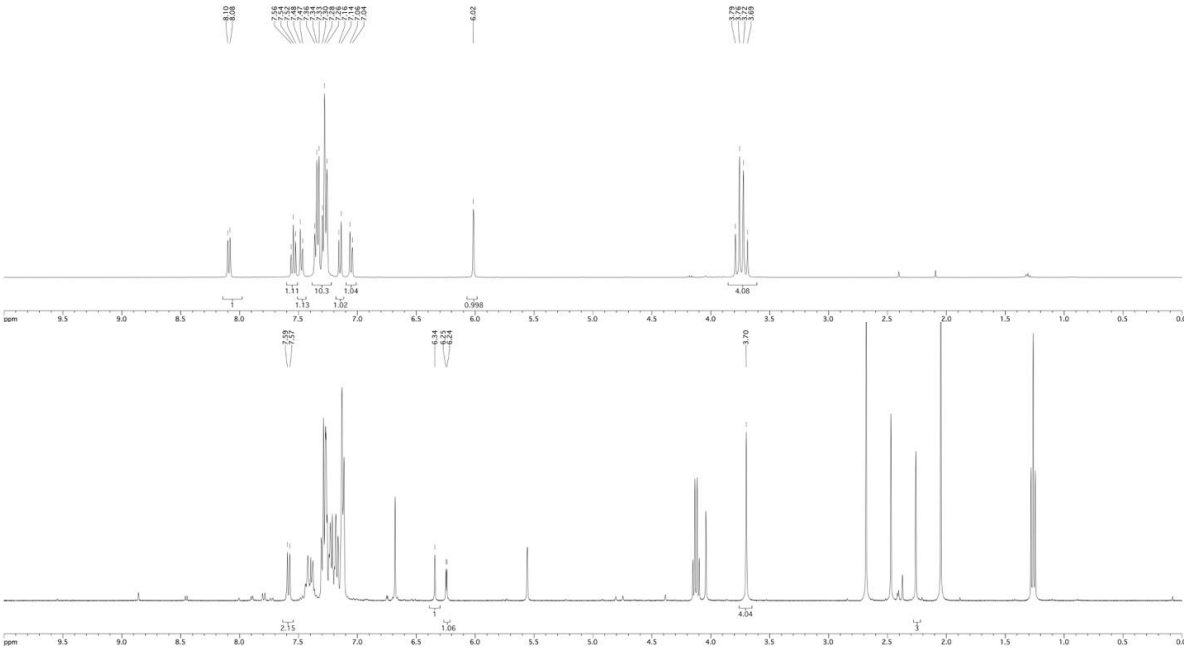


Fig. S2. Proposed ring-closed intermediates for products 41, 42, and 43 and NMR spectra. Top NMR: ^{1}H NMR spectrum of isolated 5-nitroisoquinoline intermediate. Bottom NMR: ^{1}H NMR spectrum of crude azaindole intermediate.

*Representative crude NMRs for **3** from pyridine ring-opening shown in Fig. 1C.*

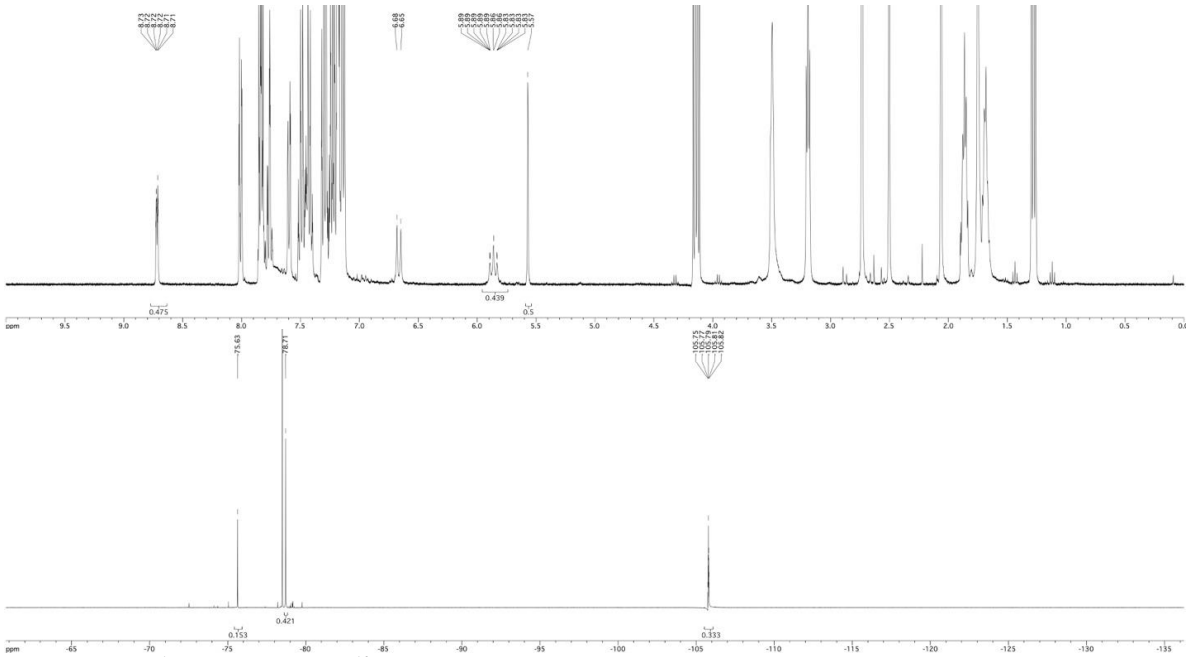


Fig. S3. Crude ^{1}H NMR (top) and ^{19}F NMR (bottom) of ring-opening reaction with piperidine to form product **3** (as shown in Fig. 1C). ^{1}H NMR: 5.86 (t, J = 12 Hz) and 6.67 (d, J = 12 Hz) are ring-opened imine **3**, and 8.72 (dd, J = 4.8, 17 Hz) is 2-phenyl pyridine. Internal standard is triphenylmethane (0.5 equivalents). ^{19}F NMR: -78.71 singlet is imine 2b, -75.63 is *N*-Tf piperidine. Internal standard is 4,4'-difluorobenzophenone (0.5 equivalents).

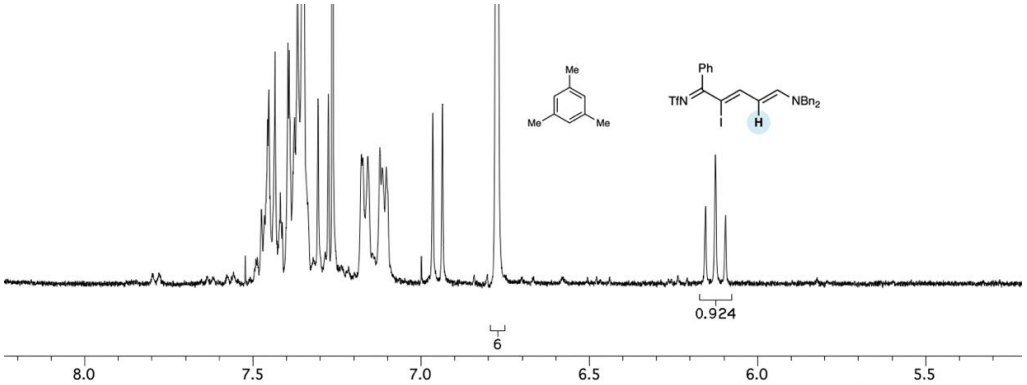


Fig. S4. Representative crude ^{1}H NMR (in $CDCl_3$) of reaction between imine **6** with NIS (1 eq.) in EtOAc.

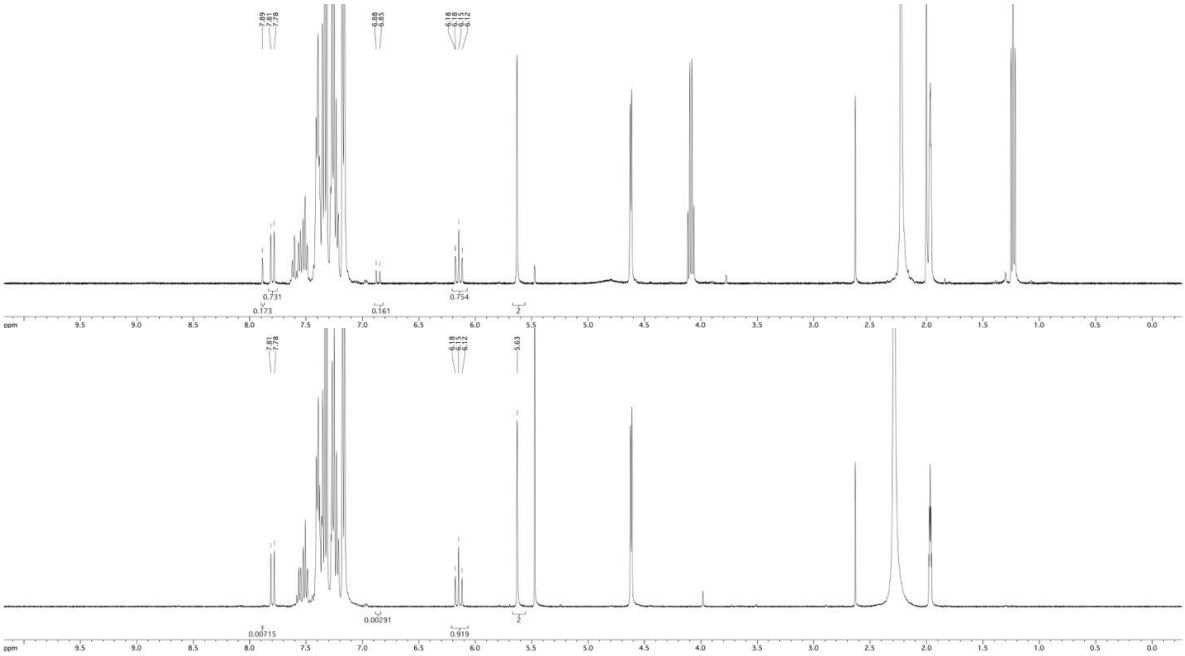


Fig. S5. Representative crude ^{1}H NMR (in CD_3CN) of reaction between imine **6** and NBS (1 eq.). Top NMR: ran at room temperature in EtOAc. Bottom NMR: ran at -78 °C in CH_2Cl_2. Peak at 6.15 (app t, J = 12 Hz) is the 3-brominated imine (3-Br). Peak at 6.87 (d, J = 12 Hz) is the 5-brominated imine. Internal standard is triphenylmethane (2 eq.)

3. Problematic Substrates

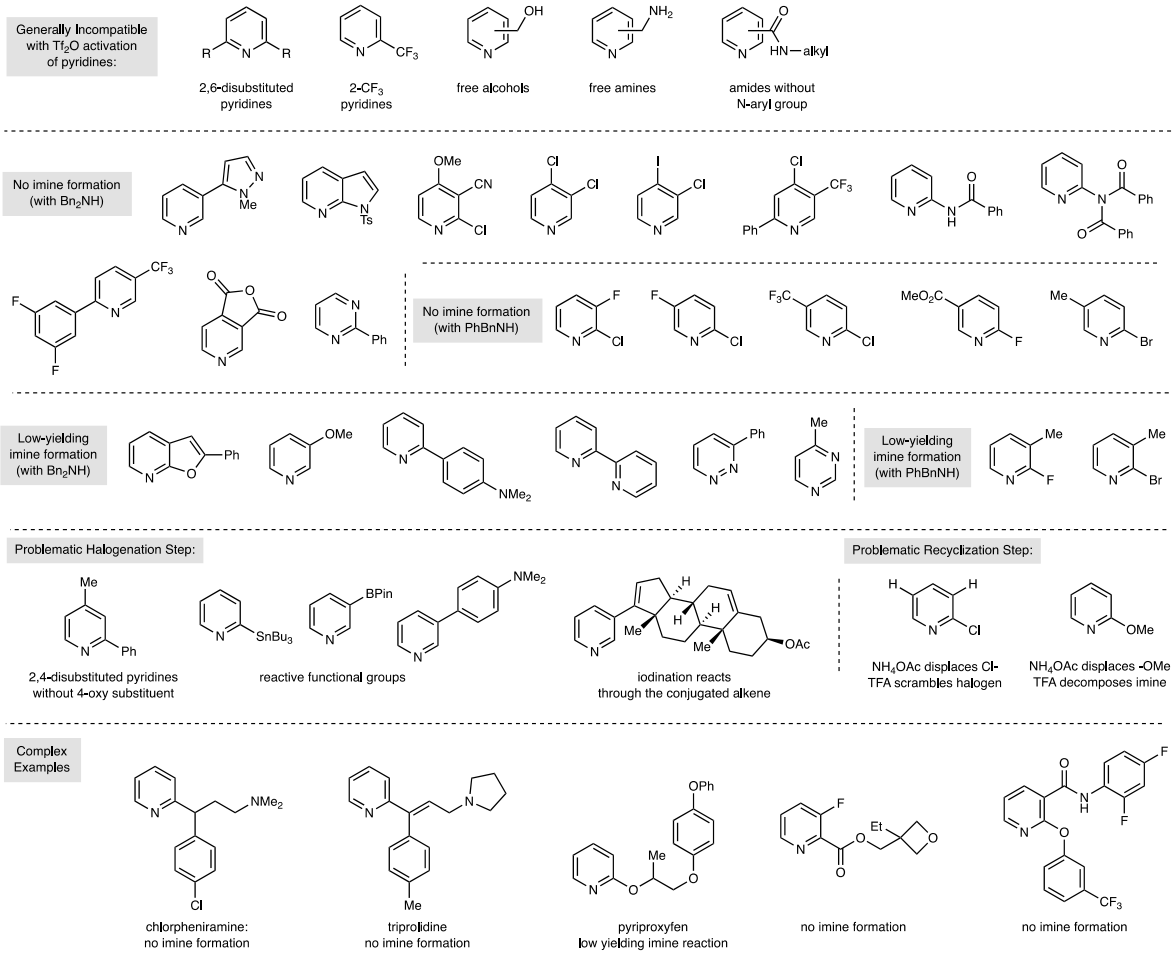


Fig. S6. Problematic Substrates for the halogenation protocol.

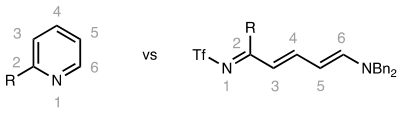
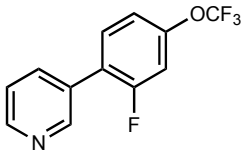


Fig. S7. Origin of the numbering system used here for Zincke imines.

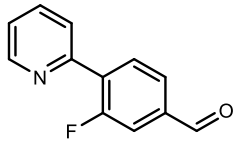
4. Preparation of Heterocycle Precursors

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



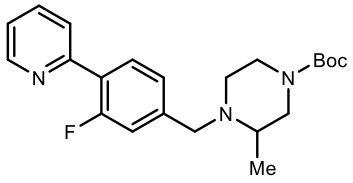
An oven dried 80 mL pressure tube was charged with pyridin-3-ylboronic acid (621 mg, 5.05 mmol), K_2CO_3 (2.073 g, 15.00 mmol), $Pd(OAc)_2$ (56 mg, 0.23 mmol), triphenylphosphine (262 mg, 1.00 mmol), 1-bromo-2-fluoro-4-(trifluoromethoxy)benzene (751 µL, 5.00 mmol) and subjected to three cycles of vacuum/nitrogen backfill. Degassed H_2O (20 mL) and degassed dimethoxyethane (20 mL) were charged to the tube and the mixture was heated at 80 ˚C for 18 hours, then cooled to room temperature and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted 2x with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 35% EtOAc in hexanes) afforded the title compound as a yellow oil (1.01 g, 3.91 mmol, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (1H, s), 8.64 (1H, d, *J* = 4.7 Hz), 7.86 (1H, d, *J* = 7.9 Hz), 7.47 (1H, app t, *J* = 8.5 Hz), 7.40 (1H, dd, *J* = 8.0, 4.9 Hz), 7.18-7.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.86 (d, *J* = 251.9 Hz), 149.81-149.68 (m), 149.59 (d, *J* = 3.1 Hz), 149.32, 136.41 (d, *J* = 3.6 Hz), 131.37 (d, *J* = 4.6 Hz), 130.63 (d, *J* = 1.4 Hz), 124.57 (d, *J* = 14.0 Hz), 123.55, 120.47 (q, *J* = 258.6 Hz), 117.21 (d, *J* = 4.0 Hz), 109.82 (d, *J* = 25.8 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –58.02 (3F), –113.35 (1F); *m/z* HRMS (DART) found $[M+H]^+$ 258.0547, $C_{12}H_8F_4NO^+$ requires 258.0542.

3-Fluoro-4-(pyridin-2-yl)benzaldehyde



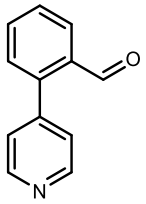
An oven dried 80 mL pressure tube was charged with (2-fluoro-4-formylphenyl)boronic acid (1.85 g, 11.00 mmol), K_2CO_3 (4.42 g, 30.00 mmol), $Pd(OAc)_2$ (112 mg, 0.50 mmol), triphenylphosphine (525 mg, 2.00 mmol), 2-bromopyridine (929 µL, 10.00 mmol) and subjected to three cycles of vacuum/nitrogen backfill. Degassed H_2O (20 mL) and degassed dimethoxyethane (20 mL) were charged to the tube and the mixture was heated at 90 ˚C for 18 hours, then cooled to room temperature and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted 2x with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a white crystalline solid (1.31 g, 6.49 mmol, 65% yield). mp 44 – 45 ˚C; IR ν_{max}/cm^{-1} (film): 3043, 2811, 2727, 1958, 1726, 1690, 1609, 1592, 1541, 1493, 1332, 1303, 1059, 919; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.04 (1H, s), 8.77 (1H, dd, *J* = 4.8, 1.5 Hz), 8.21 (1H, t, *J* = 7.6 Hz), 7.90 – 7.75 (3H, m), 7.68 (1H, dd, *J* = 10.8, 1.5 Hz), 7.33 (1H, ddd, *J* = 7.4, 4.8, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.79 (d, *J* = 2.0 Hz), 160.85 (d, *J* = 252.9 Hz), 152.12 (d, *J* = 2.5 Hz), 150.20, 138.17 (d, *J* = 6.8 Hz), 136.75, 133.24 (d, *J* = 12.2 Hz), 132.11 (d, *J* = 2.9 Hz), 126.20 (d, *J* = 3.3 Hz), 125.07 (d, *J* = 9.8 Hz), 123.48, 116.53 (d, *J* = 24.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –115.5; *m/z* HRMS (DART) found $[M+H]^+$ 202.0670, $C_{12}H_9FNO^+$ requires 202.0668.

Tert-butyl 4-(3-fluoro-4-(pyridin-2-yl)benzyl)-3-methylpiperazine-1-carboxylate



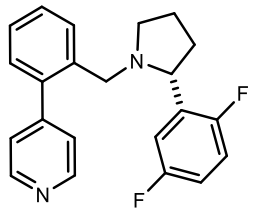
An oven-dried 100 mL round bottom flask was charged with 3-fluoro-4-(pyridin-2-yl)benzaldehyde (1.00 g, 5.00 mmol), tert-butyl 3-methylpiperazine-1-carboxylate (1.21 mL, 6.00 mmol), and sodium triacetoxyhydroborate (2.11 g, 10.0 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill. CH_2Cl_2 (25 mL) was added to the reaction flask and the reaction was cooled to 0 °C. At this temperature, glacial AcOH (583 µL) was added dropwise over a period of 5 minutes, following addition the reaction was allowed to warm to room temperature and stirred for 3.0 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL), diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 40% EtOAc in hexanes) to provide the title compound as a brown oil (1.201 g, 3.15 mmol, 63% yield); IR ν_{max}/cm^{-1} (film): 3026, 1902, 1599, 1577, 1548, 1509, 1475, 1424, 1179, 1010, 888, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, d, J = 5.2 Hz), 7.91 (1H, t, J = 8.0 Hz), 7.82 – 7.70 (2H, m), 7.29 – 7.18 (3H, m), 4.02 (1H, d, J = 13.9 Hz), 3.82 – 3.60 (2H, m), 3.39 – 2.78 (3H, m), 2.74 – 2.60 (1H, br s), 2.49 (1H, br s), 2.25 – 2.06 (1H, br s), 1.46 (9H, s), 1.16 – 1.11 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.12, 160.58 (d, *J* = 249.8 Hz), 154.85, 153.43 (d, *J* = 2.5 Hz), 149.82, 136.53, 130.87 (d, *J* = 3.3 Hz), 126.23 (d, *J* = 11.9 Hz), 125.06 (d, *J* = 3.2 Hz), 124.56 (d, *J* = 9.0 Hz), 122.46, 116.55 (d, *J* = 23.3 Hz), 79.76, 57.39, 55.10, 50.37, 44.22, 43.27, 28.55, 15.23; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –117.8; *m/z* HRMS (DART) found $[M+H]^+$ 386.2266, $C_{22}H_{29}FN_3O_2^+$ requires 386.2244.

2-(Pyridin-4-yl)benzaldehyde



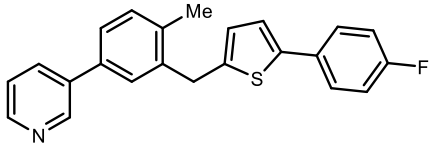
An oven dried 80 mL pressure tube was charged with (2-formylphenyl)boronic acid (1.80 g, 12.00 mmol), K_2CO_3 (5.53 g, 40.00 mmol), $Pd(OAc)_2$ (112 mg, 0.50 mmol), triphenylphosphine (525 mg, 2.00 mmol), 4-bromopyridine hydrochloride (1.95 g, 10.00 mmol) and subjected to three cycles of vacuum/nitrogen backfill. Degassed H_2O (20 mL) and degassed dimethoxyethane (20 mL) were charged to the tube and the mixture was heated at 90 °C for 18 hours, then cooled to room temperature and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted 2x with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a faint brown crystalline solid (1.50 g, 8.19 mmol, 82% yield). mp 65 – 68 °C; IR ν_{max}/cm^{-1} (film): 3043, 2886, 2769, 1956, 1691, 1655, 1609, 1594, 1541, 1450, 1279, 1224, 1175, 1048, 975, 672; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (1H, s), 8.72 (2H, d, *J* = 6.0 Hz), 8.06 (1H, dd, *J* = 7.8, 1.4 Hz), 7.69 (1H, td, *J* = 7.5, 1.4 Hz), 7.58 (1H, td, *J* = 7.6, 1.1 Hz), 7.43 (1H, d, *J* = 1.3 Hz), 7.32 (2H, d, *J* = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.30, 149.99, 145.99, 142.88, 134.04, 133.60, 130.50, 129.18, 128.53, 124.88; *m/z* HRMS (DART) found $[M+H]^+$ 184.0785, $C_{12}H_{10}NO^+$ requires 184.0762.

(R)-4-(2-((2-(2,5-Difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)pyridine



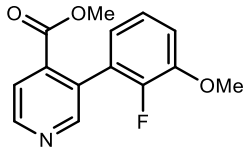
An oven-dried 100 mL round bottom flask was charged with 2-(pyridin-4-yl)benzaldehyde (814 mg, 4.40 mmol), (R)-2-(2,5-difluorophenyl)pyrrolidine hydrochloride (879 mg, 4.00 mmol), and sodium triacetoxyhydroborate (1.69 g, 8.0 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill. CH_2Cl_2 (40 mL) was added to the reaction flask and the reaction was cooled to 0 °C. At this temperature, glacial AcOH (458 µL) was added dropwise over a period of 5 minutes, following addition the reaction was allowed to warm to room temperature and stirred for 3.0 hours. The reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL), diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a yellow oil (1.060 g, 3.03 mmol, 76% yield); IR ν_{max}/cm^{-1} (film): 2965, 2796, 1593, 1540, 1488, 1445, 1426, 1089, 959, 665; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (2H, d, J = 5.6 Hz), 7.64 (1H, d, J = 7.7 Hz), 7.45 – 7.29 (2H, m), 7.22 – 7.18 (2H, m), 7.15 (2H, dd, J = 7.6, 1.4 Hz), 6.94 – 6.78 (2H, m), 3.87 – 3.54 (2H, m), 3.22 (1H, d, J = 13.6 Hz), 3.01 (1H, d, J = 9.4 Hz), 2.21 (1H, ddd, J = 15.0, 11.7, 7.1 Hz), 2.08 (1H, q, J = 8.7 Hz), 1.90 – 1.68 (2H, m), 1.60 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.24 (dd, J = 216.3, 2.4 Hz), 156.84 (dd, J = 215.7, 2.2 Hz), 149.58, 149.41, 139.23, 136.47, 132.98, 130.04, 129.55, 128.51, 127.14, 124.48, 116.20 (d, J = 25.4 Hz), 116.12 (d, J = 25.1 Hz), 114.58 (d, J = 24.8 Hz), 61.60, 55.79, 53.66, 33.66, 22.90; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –118.39, –126.16.; *m/z* HRMS (DART) found $[M+H]^+$ 351.1697, $C_{22}H_{21}F_2N_2^+$ requires 351.1673.

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



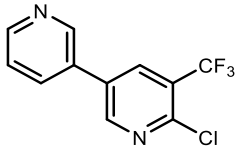
An oven dried 80 mL pressure tube was charged with 2-(5-bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (1.81 g, 5.00 mmol), K_2CO_3 (2.07 g, 15.00 mmol), $Pd(OAc)_2$ (61 mg, 0.25 mmol), triphenylphosphine (262 mg, 1.00 mmol), pyridin-3-ylboronic acid (737 mg, 6.00 mmol) and subjected to three cycles of vacuum/nitrogen backfill. Degassed H_2O (20 mL) and degassed dimethoxyethane (20 mL) were charged to the tube and the mixture was heated at 90 °C for 18 hours, then cooled to room temperature and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted 2x with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as an off-white crystalline solid (1.31 g, 3.64 mmol, 73% yield). mp 55 – 56 °C; IR ν_{max}/cm^{-1} (film): 3026, 1901, 1599, 1577, 1509, 1476, 1424, 1339, 1254, 1128, 1010, 889, 755; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.85 (1H, d, J = 2.3 Hz), 8.57 (1H, d, J = 4.4 Hz), 7.86 (1H, dt, J = 8.2, 2.0 Hz), 7.53 – 7.20 (6H, m), 7.14 – 6.94 (3H, m), 6.80 – 6.66 (1H, m), 4.21 (2H, s), 2.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.25 (d, J = 246.8 Hz), 148.41, 148.37, 143.03, 141.87, 139.17, 136.63, 136.51, 135.94, 134.29, 130.90 (d, J = 3.4 Hz), 129.22, 128.28, 127.27 (d, J = 8.0 Hz), 126.25, 125.72, 123.64, 122.85, 115.85 (d, J = 21.8 Hz), 34.32, 19.37; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –115.1; *m/z* HRMS (DART) found $[M+H]^+$ 360.1245, $C_{23}H_{19}FNS^+$ requires 360.1222.

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



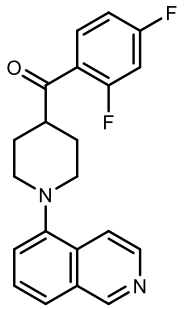
An oven dried 80 mL pressure tube was charged with (2-fluoro-3-methoxyphenyl)boronic acid (935 mg, 5.50 mmol), K_2CO_3 (2.07 g, 15.00 mmol), $Pd(OAc)_2$ (66 mg, 0.25 mmol), triphenylphosphine (263 mg, 1.00 mmol), methyl 3-bromoisonicotinate (675 μL, 5.00 mmol) and subjected to three cycles of vacuum/nitrogen backfill. Degassed H_2O (10 mL) and degassed dimethoxyethane (10 mL) were charged to the tube and the mixture was heated at 80 °C for 18 hours, then cooled to room temperature and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted 2x with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as an orange oil (1.057 g, 8.19 mmol, 82% yield); IR ν_{max}/cm^{-1} (film): 2952, 2841, 2360, 1732, 1674, 1610, 1581, 1482, 1469, 1434, 1397, 1151, 919, 900, 852, 796; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (1H, d, J = 5.1 Hz), 8.67 (1H, s), 7.76 (1H, d, J = 5.0 Hz), 7.17 (1H, t, J = 8.0 Hz), 7.04 (1H, td, J = 8.2, 1.5 Hz), 6.93 – 6.84 (1H, m), 3.92 (3H, s), 3.77 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.37, 152.09, 149.92, 149.73 (d, J = 246.3 Hz), 147.74 (d, J = 10.9 Hz), 137.88, 130.44, 126.03 (d, J = 13.2 Hz), 124.18 (d, J = 4.8 Hz), 122.97, 121.84 (d, J = 2.1 Hz), 113.65 (d, J = 2.1 Hz), 56.47, 52.73; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –138.71 *m/z* HRMS (DART) found $[M+H]^+$ 262.0895, $C_{14}H_{13}FNO_3^+$ requires 262.0879.

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



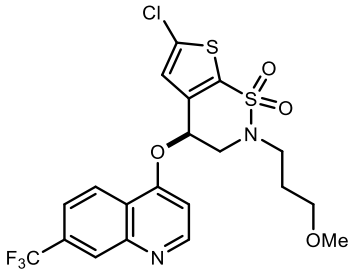
An oven dried 250 mL round bottom flask was charged with 2-chloro-5-iodo-3-(trifluoromethyl)pyridine (4.61 g, 15.00 mmol), pyridin-3-ylboronic acid (2.03 g, 16.50 mmol), $PdCl_2(dppf)$ (1.09 g, 1.50 mmol), Cs_2CO_3 (14.66 g, 45.00 mmol) and subjected to three cycles of vacuum/nitrogen backfill. Degassed H_2O (3 mL) and degassed DMF (60 mL) were charged to the tube and the mixture was stirred at room temperature for 25 hours, then diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted 2x with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a brown crystalline solid (2.06 g, 7.95 mmol, 53% yield). mp 181 – 184 °C; IR ν_{max}/cm^{-1} (film): 3044, 1898, 1691, 1588, 1559, 1509, 1430, 1356, 1221, 1067, 966, 833, 753; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.85 (1H, d, J = 2.4 Hz), 8.82 – 8.69 (2H, m), 8.18 (1H, d, J = 2.4 Hz), 7.89 (1H, dt, J = 8.0, 1.1 Hz), 7.46 (1H, dd, J = 8.0, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.45, 150.37, 148.70, 148.09, 135.12 (q, J = 4.8 Hz), 134.58, 132.82, 131.29, 125.78 (q, J = 33.4 Hz), 124.34, 122.14 (q, J = 273.1 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –63.72; *m/z* HRMS (DART) found $[M+H]^+$ 259.0265, $C_{11}H_7ClF_3N_2^+$ requires 259.0250.

(2,4-Difluorophenyl)(1-(isoquinolin-5-yl)piperidin-4-yl)methanone



An oven dried 80 mL pressure tube was charged with $Pd_2(dba)_3$ (92 mg, 0.1 mmol, 2 mol%), BINAP (187 mg, 0.3 mmol, 6 mol%), and toluene (25 mL) and stirred for 1 hour at room temperature. NaOtBu (1.25 g, 13.00 mmol), 5-bromoisoquinoline (1.04 g, 5.00 mmol), and (2,4-difluorophenyl)(piperidin-4-yl)methanone hydrochloride (1.57 g, 6.00 mmol) were added and the reaction was heated to 100 °C overnight. After cooling to room temperature, the reaction was filtered through celite and concentrated *in vacuo*. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a brown solid (910 g, 2.61 mmol, 52% yield). mp 122 – 125 °C; IR ν_{max}/cm^{-1} (film): 3043, 2998, 2955, 2886, 2810, 1953, 1675, 1609, 1594, 1584, 1541, 1492, 1475, 1442, 1429, 1332, 1303, 1174, 1034, 919, 731, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.23 (1H, d, *J* = 0.9 Hz), 8.53 (1H, d, *J* = 5.8 Hz), 8.02 – 7.79 (2H, m), 7.66 (1H, d, *J* = 8.2 Hz), 7.53 (1H, t, *J* = 7.8 Hz), 7.38 – 7.26 (1H, m), 7.08 – 6.95 (1H, m), 6.92 (1H, ddd, *J* = 11.2, 8.6, 2.5 Hz), 3.61 – 3.27 (3H, m), 2.98 – 2.79 (2H, m), 2.18 – 2.02 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.70 (d, *J* = 4.8 Hz), 165.79 (dd, *J* = 256.8, 12.4 Hz), 162.07 (dd, *J* = 255.8, 12.4 Hz), 152.95 (d, *J* = 2.7 Hz), 149.32, 142.81, 133.15 (dd, *J* = 10.5, 4.6 Hz), 131.96 (d, *J* = 2.0 Hz), 129.98, 127.37, 122.54, 122.51 – 121.51 (m), 118.62 (d, *J* = 2.7 Hz), 116.66 (d, *J* = 2.9 Hz), 112.59 (dd, *J* = 21.4, 3.4 Hz), 104.83 (dd, *J* = 28.0, 25.4 Hz), 53.07, 29.07, 28.76; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –101.97 (dd, *J* = 18.0, 9.0 Hz), –106.56 (q, *J* = 10.8 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 353.1471, $C_{21}H_{19}F_2N_2O^+$ requires 353.1465.

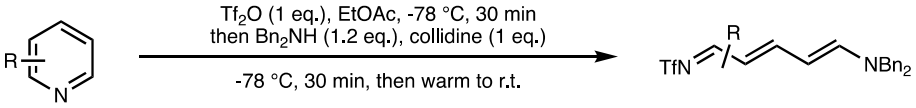
(S)-6-Chloro-2-(3-methoxypropyl)-4-((7-(trifluoromethyl)quinolin-4-yl)oxy)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine 1,1-dioxide



An oven dried 25 mL pressure tube was charged with (S)-6-chloro-4-hydroxy-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine 1,1-dioxide (1.12 g, 3.60 mmol), K_2CO_3 (829 mg, 6.00 mmol), 4-chloro-7-(trifluoromethyl)quinoline (695 mg, 3.00 mmol), and MeCN (10 mL). The reaction was heated to 80 °C for 36 hours and then cooled to room temperature. The mixture was then filtered over a frit and the filtrate was concentrated *in vacuo*. Flash column chromatography (silica gel: 70% EtOAc in hexanes) afforded the title compound as an amorphous white solid (689 mg, 1.35 mmol, 45% yield); IR ν_{max}/cm^{-1} (film): 2928, 2812, 2360, 1675, 1574, 1509, 1460, 1421, 1385, 1237, 1216, 1198, 1068, 1045, 1025, 780, 685, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (1H, d, *J* = 5.2 Hz), 8.37 (1H, d, *J* = 1.9 Hz), 8.21 (1H, d, *J* = 8.7 Hz), 7.68 (1H, dd, *J* = 8.7, 1.8 Hz), 7.01 – 6.90 (2H, m), 5.57 (1H, t, *J* = 3.4 Hz), 4.44 (1H, dd, *J* = 16.0, 4.1 Hz), 4.15 (1H, dd, *J* = 16.0, 2.8 Hz), 3.67 (1H, dt, *J* = 14.0, 7.1 Hz), 3.42 – 3.23 (3H, m), 3.12 (3H, s), 1.79 (2H, p, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.18, 152.51, 148.96, 137.97, 136.84, 134.80, 132.37 (q, *J* = 32.8 Hz), 127.06 (q, *J* = 4.4 Hz), 125.79, 123.85 (d, *J* = 272.6 Hz), 123.31, 123.02, 122.14 (q, *J* = 3.2 Hz), 69.02, 66.42, 58.60, 49.81, 47.80, 29.21; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.83; *m/z* HRMS (DART) found $[M+H]^+$ 507.0452, $C_{20}H_{19}ClF_3N_2O_4S_2^+$ requires 507.0427.

5. Preparation of Zincke Imines

General Procedure A (Zincke Imine Formation)

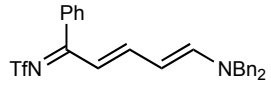


An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before dibenzylamine (1.2 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. The reaction was diluted with EtOAc then washed with H_2O (3x). The organic extract was dried ($MgSO_4$) and filtered. After filtration, the organic extract was added dropwise to excess hexanes (approx. 100 mL per 1.0 mmol) and the resulting oil was allowed to settle overnight in a –20 ºC fridge. After the oil has settled, the hexanes was decanted off and the residual oil was washed with hexanes, then dissolved in CH_2Cl_2 and concentrated *in vacuo* to provide the pure "Zincke imine" product.

Reaction Notes:

- Reaction is sensitive to excess of Tf_2O added (use of 1.2 equiv. results in substantial yield loss).
- Majority of substrates comparably with 1.0 equiv. and 2.0 equiv. collidine, 1.0 equiv. can be used regardless of substrate (Yields in scope table below denote how many equivalents were used for that specific yield, but were within 5% when repeated with the other collidine amount).
- Stirring is critical to achieve consistent yields; recommended stirring 500-750 rpm.
- For 2-halopyridines, *N*-benzylaniline (1.0 equiv) is used instead of dibenzylamine to avoid decomposition of the starting material under the reaction conditions.
- For larger scales, it is recommended to allow the reaction to warm fully to room temperature, the 30 minutes was based on initial smaller scale reactions.
- Substrates with a 4-substituent (and unsubstituted pyridine) are susceptible to "bis-adduct" formation and care should be taken prior to crash out. Concentration *in vacuo* prior to crash out results in significant (>20%) yield loss to bis-addition.
- If "bis-adduct" is observed, a short plug of silica (2-3 inches) and appropriate solvent eluent will remove it.
- Substrates with a 4-substituent (and unsubstituted pyridine) can be run with 1.0 eq Bn_2NH to minimize potential for bis-addition product formation.
- For substrates with a 2-position substituent, the organic extract can be concentrated *in vacuo* then redissolved in 2-10 mL CH_2Cl_2 prior to addition to the hexanes. This will provide higher yields.

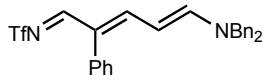
***N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (6)**



Prepared according to general procedure A using 2-phenylpyridine (4.29 mL, 30.0 mmol), EtOAc (300 mL, 0.1 M), Tf_2O (5.04 mL, 30.0 mmol), dibenzylamine (6.35 mL, 33.0 mmol, 1.0 M in EtOAc), and collidine (3.96 mL, 30.0 mmol). Washing 3x with H_2O and crashing out in hexanes afforded the title compound (12.44 g, 25.7 mmol , 86% yield) as a red solid. mp 68 – 70 °C; IR ν_{max}/cm^{-1} (film): 1615, 1558, 1430, 1312, 1154, 1092, 997, 842, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (2H, d, *J* = 7.8 Hz), 7.50 (1H, t, *J* = 7.8 Hz), 7.45 – 7.25 (10H, m), 7.15 (4H, d, *J* = 7.4 Hz), 6.71 (1H, d, *J* = 13.7 Hz), 5.81 (1H, t, *J* = 12.2 Hz), 4.47 – 4.39 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.27,

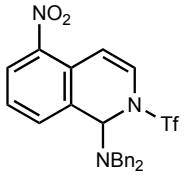
160.32, 157.82, 138.10, 134.39, 133.86, 131.21, 129.79, 129.36, 128.97, 128.55, 128.35, 127.95, 127.34, 119.69 (q, J = 320.1 Hz), 114.59, 102.83, 59.89, 51.53; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –79.10; *m/z* HRMS (DART) found $[M+H]^+$ 485.1506, $C_{26}H_{24}F_3N_2O_2S^+$ requires 485.1511.

***N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-2-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (10)**



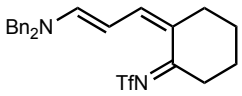
Prepared according to general procedure A using 3-phenylpyridine (1.43 mL, 10.0 mmol), EtOAc (100 mL, 0.1 M), Tf_2O (1.68 mL, 10.0 mmol), dibenzylamine (1.92 mL, 10.0 mmol, 1.0 M in EtOAc), and collidine (1.32 mL, 10.0 mmol). Washing 2x with H_2O and 1x with aqueous sodium bicarbonate, and then crashing out in hexanes afforded the title compound (3.98 g, 8.21 mmol, 82% yield) as a yellow solid. mp 136 – 139 °C; IR ν_{max}/cm^{-1} (film): 3027, 1617, 1485, 1305, 1167, 1100, 843, 734, 687; ^{1}H NMR (400 MHz, CD_3CN) δ: 8.21 (1H, s), 7.91 (1H, d, J = 11.9 Hz), 7.67 (1H, d, J = 13.0 Hz), 7.45 – 7.22 (11H, m), 7.16 – 7.00 (4H, m), 5.73 (1H, d, J = 12.5 Hz), 4.71 (2H, s), 4.40 (2H, s); ^{13}C NMR (100 MHz, CD_3CN) δ: 171.69, 167.27, 163.39, 135.51, 135.46, 135.25, 130.85, 130.04, 129.87, 129.70, 129.48, 129.28, 128.99, 128.30, 128.23, 128.14, 126.55, 121.20 (q, J = 323.1 Hz), 104.89, 62.12, 53.44; ^{19}F NMR (365 MHz, CD_3CN) δ: –79.16; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 485.2, $C_{26}H_{24}F_3N_2O_2S^+$ requires 485.2.

***N*,*N*-Dibenzyl-5-nitro-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinolin-1-amine**



Prepared according to general procedure A using 5-nitroisoquinoline (348 mg, 2.00 mmol), CH_2Cl_2 (20 mL, 0.1 M), Tf_2O (336 µL, 2.00 mmol), dibenzylamine (461 µL, 2.40 mmol, 1.0 M in CH_2Cl_2), and collidine (264 µL, 2.00 mmol). Instead of a precipitation procedure, flash column chromatography (silica gel gradient elution: 20 to 40% Toluene in Hexanes) afforded the title compound (550 mg, 1.10 mmol , 55% yield) as a yellow solid. mp 52 – 56 °C; IR ν_{max}/cm^{-1} (film): 2161, 1528, 1227, 1141, 1027, 923, 737, 654; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (1H, d, J = 7.9 Hz), 7.54 (1H, app t, J = 8.0 Hz), 7.48 (1H, d, J = 7.5 Hz), 7.38 – 7.23 (10H, m), 7.15 (1H, d, J = 8.0 Hz), 7.05 (1H, d, J = 8.0 Hz), 6.02 (1H, s), 3.74 (4H, app q, J = 13.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 114.72, 137.99, 133.46, 132.67, 129.01, 128.50, 128.37, 127.65, 126.90, 125.76, 124.18, 119.84 (q, J = 325.0 Hz), 110.32, 73.43, 51.78; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –74.36; *m/z* HRMS (DART) found $[M+H]^+$ 504.1248, $C_{24}H_{21}F_3N_3O_4S^+$ requires 504.1205.

***N*-((1*E*,2*Z*)-2-((*E*)-3-(Dibenzylamino)allylidene)cyclohexylidene)-1,1,1-trifluoromethanesulfonamide**



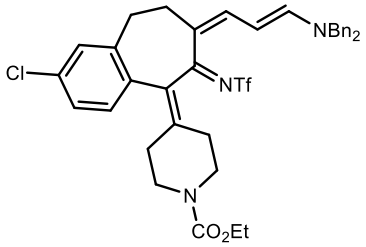
Prepared according to general procedure A using 5,6,7,8-tetrahydroquinoline (647 µL, 5.00 mmol), EtOAc (50 mL, 0.1 M), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), and collidine (640 µL, 5.00 mmol). Washing 3x with H_2O and crashing out in hexanes afforded the title compound (1.86 g, 4.01 mmol , 80% yield) as a yellow solid. mp 160 – 165 °C; IR ν_{max}/cm^{-1} (film): 1611, 1407, 1151, 1099, 852, 813, 667, 605; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 8.52 (1H, d, J = 11.6 Hz), 8.34 (1H, d, J = 13.5 Hz), 7.50 – 7.27 (8H, m), 7.26 – 7.20 (2H, m), 5.98 (1H, t, J = 12.6 Hz), 4.80 (2H, s), 4.72 (2H, s), 2.77 (2H, t, J = 5.9 Hz), 2.19 (2H, t, J = 5.2 Hz), 1.66 – 1.52 (4H, m); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 174.18, 164.80, 156.00, 134.82, 134.35, 129.96, 128.88, 128.76, 128.44, 127.85, 127.36, 119.97 (q, J = 325.8 Hz), 115.20, 103.48, 59.86, 51.60, 32.71, 24.44, 21.84, 21.49; ^{19}F NMR (365 MHz, $(CD_3)_2SO$) δ: –78.11; *m/z* HRMS (DART) found $[M+H]^+$ 463.1642, $C_{24}H_{26}F_3N_2O_2S^+$ requires 463.1667.

N-((1Z,2Z,4E)-5-(Dibenzylamino)-2-fluoropenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide

2.6 1.0

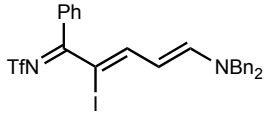
Prepared according to general procedure A using 3-fluoropyridine (172 µL, 2.00 mmol), Tf_2O (340 µL, 2.00 mmol), dibenzylamine (400 µL, 2.00 mmol, 1.0 M in EtOAc), collidine (240 µL, 2.00 mmol), and EtOAc (20 mL, 0.1 M). Purification procedure provided the title compound in a mixture of regioisomers (2.6:1) as a dark green solid (443 mg, 1.04 mmol, 52% yield). ^{1}H NMR (major, 400 MHz, $CDCl_3$) δ: 7.94 – 7.80 (1H, m), 7.60 (1H, d, *J* = 12.2 Hz), 7.44 (6H, dtd, *J* = 7.6, 5.6, 2.8 Hz), 7.28 – 7.16 (4H, m), 6.99 – 6.85 (1H, m), 6.09 (1H, t, *J* = 12.4 Hz), 4.57 (4H, d, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.49, 159.56, 157.31 (d, *J* = 9.1 Hz), 148.38 (d, *J* = 10.7 Hz), 148.14, 145.74, 141.43, 133.17 (d, *J* = 32.8 Hz), 129.68-129.36 (m, 3C), 128.92, 128.71, 128.49, 128.19, 127.61, 127.43, 119.98 (d, *J* = 322.9 Hz), 110.96, 98.67 (d, *J* = 4.5 Hz), 60.33, 52.08; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –77.50 (major), –77.67 (minor), –139.18 (major, dd, *J* = 27.8, 22.1 Hz), –145.65 (minor, t, *J* = 27.4 Hz ; *m/z* HRMS (DART) found $[M+H]^+$ 427.1102, $C_{20}H_{19}F_4N_2O_2S^+$ requires 427.1103.

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



Prepared according to general procedure A using ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta [1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (1.914 g, 5.00 mmol), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (1.149 mL, 6.00 mmol, 1.0 M in EtOAc), collidine (659 µL, 5.00 mmol), and EtOAc (50 mL, 0.1 M). Purification procedure provided the title compound as a bright orange solid (1.85 g, 2.60 mmol, 52% yield). mp 118 – 121 °C; IR ν_{max}/cm^{-1} (film): 3035, 2923, 2032, 1747, 1594, 1563, 1547, 1501, 1457, 1345, 1277, 1100, 1069, 1040, 961, 942, 874, 773, 700, 688; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (1H, d, *J* = 12.7 Hz), 7.55 (1H, d, *J* = 12.0 Hz), 7.49 – 7.33 (6H, m), 7.24 – 6.97 (7H, m), 5.77 (1H, t, *J* = 12.4 Hz), 4.50 (4H, m), 4.12 (2H, q, *J* = 7.1 Hz), 3.89 – 3.64 (2H, m), 3.29 (2H, dddd, *J* = 16.6, 12.7, 8.4, 4.1 Hz), 3.12 (1H, dt, *J* = 16.8, 3.8 Hz), 2.90 – 2.63 (2H, m), 2.58 (2H, dq, *J* = 13.7, 4.2 Hz), 2.45 – 2.05 (3H, m), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 179.46, 158.82, 155.52, 151.39, 138.98, 138.12, 134.35, 133.96, 133.70, 133.46, 133.28, 132.01, 129.89, 129.34, 129.11, 128.99, 128.51, 127.29, 125.94, 120.51, 119.62 (q, *J* = 320.4 Hz), 99.79, 61.40, 60.11, 51.59, 44.27, 44.06, 32.84, 32.00, 30.09, 24.35, 14.7; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –79.03; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 712.3, $C_{37}H_{38}ClF_3N_3O_4S^+$ requires 712.2.

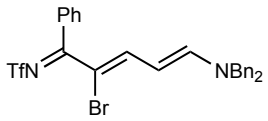
***N*-((1*Z*,2*Z*,4*E*)-5-(Dibenzylamino)-2-iodo-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (7-I)**



A 500 mL round bottom flask was charged with 2-phenylpyridine (715 µL, 5.00 mmol), EtOAc (50 mL), and cooled to -78 °C. Tf_2O (840 µL, 5.00 mmol) was added dropwise, and the reaction was left to stir for 30 mins. Then, dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc) and collidine (661 µL, 5.00 mmol), were added and the reaction

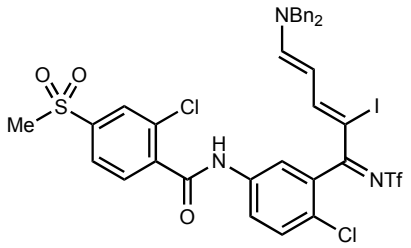
continued to stir at -78 °C. After 30 mins, the -78 °C bath was removed, and the reaction was allowed to warm to room temperature. Then, *N*-iodosuccinimide (1.12 g, 5.00 mmol) was added, the reaction stirred at room temperature for 10 minutes, and then the reaction was quenched with aqueous sodium thiosulfate. The reaction was diluted with EtOAc and H_2O, and the organic layer was washed with H_2O and then aqueous NaCl. The organic layer was collected and the separatory funnel was rinsed with CH_2Cl_2 (this is because the product partially crashes out of EtOAc). The organic extracts were dried ($MgSO_4$), filtered, and concentrated. Approximately 10 mL of CH_2Cl_2 was added to dissolve the solid residue, and the resulting solution was added dropwise to a flask containing 500 mL of hexanes. After sitting in a -20 °C fridge for 16 hours, the hexane was decanted and the solid product was collected on a frit and washed with hexanes to yield the pure compound (2.44 g, 4.00 mmol, 80 % yield) as a red solid. mp 201 – 204 °C; IR ν_{max}/cm^{-1} (film): 1604, 1557, 1312, 1158, 1095, 851, 696, 620; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 8.38 (1H, d, *J* = 11.7 Hz), 7.55 – 7.45 (3H, m), 7.43 – 7.28 (10H, m), 7.26 – 7.18 (2H, d, *J* = 7.4 Hz), 7.10 (1H, d, *J* = 12.0 Hz), 6.06 (1H, t, *J* = 11.9 Hz), 4.76 (2H, s), 4.65 (2H, s); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 175.39, 163.37, 162.37, 136.32, 134.66, 134.16, 130.00, 128.83, 128.43, 128.40 (2C), 128.18, 127.87, 127.25, 119.08 (q, *J* = 320.34 Hz), 110.88, 60.43, 51.94; ^{19}F NMR (365 MHz, $(CD_3)_2SO$) δ: –79.16; *m/z* HRMS (DART) found $[M+H]^+$ 611.0467, $C_{26}H_{23}F_3IN_2O_2S^+$ requires 611.0477

_N_-((1_E_,2_Z_,4_E_)-2-Bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (7-Br)



A 500 mL round bottom flask was charged with 2-phenylpyridine (715 µL, 5.00 mmol), CH_2Cl_2 (50 mL), and cooled to -78 °C. Tf_2O (840 µL, 5.00 mmol) was added dropwise, and the reaction was left to stir for 30 mins. Then, dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in CH_2Cl_2) and collidine (661 µL, 5.00 mmol), were added and the reaction continued to stir at -78 °C. After 30 mins, the -78 °C bath was removed, and the reaction was allowed to warm to room temperature. After reaching room temperature, the reaction flask was then cooled to -78 °C where *N*-bromosuccinimide (890 mg, 5.00 mmol) was added and the reaction was allowed to stir for 15 minutes. Trimethoxybenzene (841 mg, 5.00 mmol) was added and the flask was allowed to warm to room temperature, where it was quenched with aqueous sodium thiosulfate. The reaction was diluted with $CH_2Cl_2$and H_2O, and the organic layer was washed with H_2O and then aqueous NaCl. The organic extracts were dried ($MgSO_4$), filtered, and concentrated. Approximately 10 mL of $CH_2Cl_2$was added to dissolve the oil residue, and the resulting solution was added dropwise to a flask containing 500 mL of hexanes. After sitting in a -20 °C fridge for 16 hours, the hexane was decanted and the solid product was collected on a frit and washed with hexanes to yield the pure compound (2.25 g, 4.00 mmol, 80 % yield) as a yellow solid. mp 179 – 182 °C; IR ν_{max}/cm^{-1} (film): 1607, 1417, 1311, 1165, 1093, 992, 874, 800, 745, 675; ^{1}H NMR (400 MHz, CD_3CN) δ: 7.77 (1H, d, *J* = 11.9 Hz), 7.62 – 7.30 (12H, m), 7.28 – 7.18 (4H, m), 6.12 (1H, t, *J* = 12.0 Hz), 4.61 – 4.58 (4H, m); ^{13}C NMR (100 MHz, CD_3CN) δ: 174.96, 163.31, 159.82, 137.81, 135.34, 135.09, 131.43, 131.13, 129.99, 129.92, 129.82, 129.64, 129.42, 129.13, 129.11, 128.41, 120.48 (q, *J* = 322.1 Hz), 108.41, 106.41, 106.42, 61.71, 53.15; ^{19}F NMR (365 MHz, CD_3CN) δ: –80.71; *m/z* HRMS (DART) found $[M+H]^+$ 611.0467, $C_{26}H_{23}F_3IN_2O_2S^+$ requires 611.0477

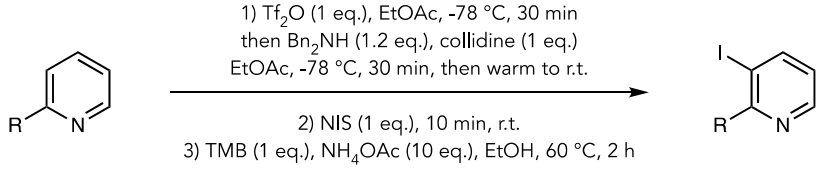
2-Chloro-_N_-(4-chloro-3-((1_E_,2_Z_,4_E_)-5-(dibenzylamino)-2-iodo-1-(((trifluoromethyl)sulfonyl)imino)penta-2,4-dien-1-yl)phenyl)-4-(methylsulfonyl)benzamide



A 100 mL round bottom flask was charged with 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (421 mg, 1.00 mmol) and EtOAc (20 mL). The flask was heated to 60 °C for about 10 minutes to fully dissolve the starting material, and then cooled to -78 °C. Tf_2O (168 µL, 1.00 mmol) was added dropwise, and the reaction was left to stir for 30 mins. Then, dibenzylamine (192 µL, 1.00 mmol, 1.0 M in EtOAc) and collidine (132 µL, 1.00 mmol), were added and the reaction continued to stir at -78 °C. After 30 mins, the -78 °C bath was removed, and the reaction was allowed to warm to room temperature. Then, *N*-iodosuccinimide (225.0 mg, 1.00 mmol) was added, the reaction stirred at room temperature for 10 minutes, and then the reaction was quenched with aqueous sodium thiosulfate. The reaction was diluted with EtOAc and H_2O, and the organic layer was washed 2x with H_2O and 1x with $NaHCO_3$. The organic extracts were dried ($MgSO_4$), filtered, and concentrated. Approximately 10 mL of CH_2Cl_2 was added to dissolve the solid residue, and the resulting solution was added dropwise to a flask containing 500 mL of hexanes. After sitting in a -20 °C fridge for 2 hours, the hexane was decanted and the solid residue was collected on a frit and washed with hexanes. The material was then further purified by flash column chromatography (silica gel: 50% Acetone in Hexanes) to yield the pure compound (443 g, 0.50 mmol, 50 % yield) as a yellow solid (note: column chromatography was used here because the Vismodegib starting material is insoluble in hexanes, and so wasn't removed during the crash-out step). mp 215 – 218 °C; IR ν_{max}/cm^{-1} (film): 3312, 1559, 1417, 1155, 1094, 958, 851, 697, 672; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ: 11.01 (1H, s), 8.53 (1H, d, J = 11.5 Hz), 8.16 (1H, s), 8.03 (1H, d, J = 8.1 Hz), 7.95 – 7.87 (2H, m), 7.62 (1H, s), 7.57 (1H, d, J = 8.8 Hz), 7.44 – 7.28 (8H, m), 7.25 – 7.19 (2H, m), 7.05 (1H, d, J = 12.1 Hz), 6.15 (1H, t, J = 11.9 Hz), 4.81 (2H, s), 4.76 – 4.65 (2H, m), 3.36 (3H, s); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 170.02, 164.36, 163.83, 161.29, 143.19, 140.63, 137.25, 135.49, 134.43, 134.03, 130.96, 130.01, 129.89, 128.89, 128.82, 128.53, 128.42, 128.17, 127.97, 127.31, 125.94, 125.73, 121.69, 120.14, 119.14 (q, J = 326.8 Hz), 112.08, 86.05, 60.76, 52.20, 43.08; ^{19}F NMR (365 MHz, $(CD_3)_2SO$) δ: –78.95; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 876.1, $C_{34}H_{28}Cl_2F_3IN_3O_5S_2^+$ requires 876.0.

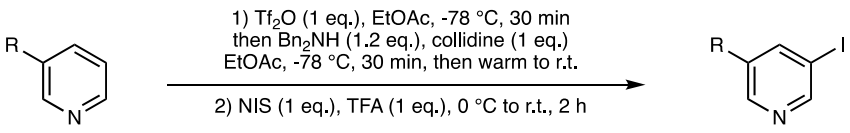
6. General Procedures for Heterocycle Halogenation

General Procedure B (3-Position Iodination)



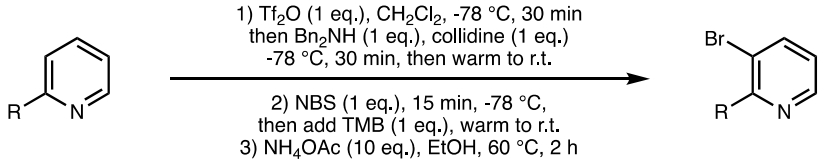
An oven dried 16 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before dibenzylamine (1.2 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. *N*-iodosuccinimide (1 equiv.) was added as a solid, and the reaction was allowed to stir at room temperature for 10 minutes. Trimethoxybenzene (1 equiv.), Ammonium Acetate (10 equiv.) and EtOH (twice the volume of EtOAc used in step 1) was added and the reaction was stirred at 60 °C for 2 hours. After cooling to room temperature, the reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

General Procedure C (5-Position Iodination)



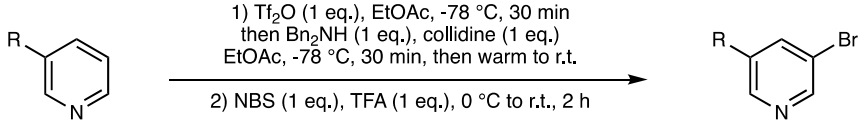
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before dibenzylamine (1 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. The reaction vessel was then placed in a 0 °C ice bath, and *N*-iodosuccinimide (1 equiv.) and trifluoroacetic acid (1 equiv.) were subsequently added. The reaction vessel was removed from the ice bath and allowed to stir at room temperature for 2 hours, before being quenched with aqueous sodium thiosulfate and aqueous sodium bicarbonate. The reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

General Procedure D (3-Position Bromination)



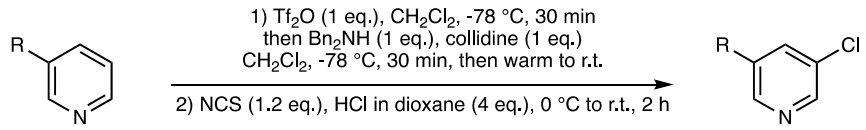
An oven dried 16 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before dibenzylamine (1.0 equiv) was added dropwise as a solution (1.0 M in CH_2Cl_2) followed by collidine (1.0 eq). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. After reaching room temperature, the reaction vessel was cooled to –78 °C again and *N*-bromosuccinimide (1 eq.) was added as a solid. After stirring the reaction at –78 °C for 15 minutes, trimethoxybenzene (1 eq.) was added and the reaction was allowed to warm to room temperature. Ammonium Acetate (10 equiv.) and EtOH (twice the volume of CH_2Cl_2 used in step 1) was added and the reaction was stirred at 60 °C for 20 hours. After cooling to room temperature, the reaction was diluted with CH_2Cl_2 and H_2O, then extracted into CH_2Cl_2 (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

General Procedure E (5-Position Bromination)



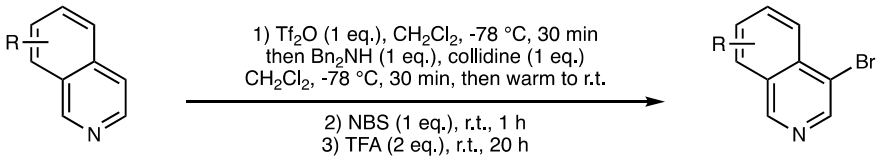
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before dibenzylamine (1 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. The reaction vessel was then placed in a 0 °C ice bath, and *N*-bromosuccinimide (1 equiv.) and trifluoroacetic acid (1 equiv.) were subsequently added. The reaction vessel was removed from the ice bath and allowed to stir at room temperature for 2 hours, before being quenched with aqueous sodium thiosulfate and aqueous sodium bicarbonate. The reaction was diluted with EtOAc and H_2O, then extracted into EtOAc (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

General Procedure F (5-Position Chlorination)



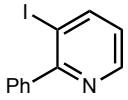
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before dibenzylamine (1 equiv) was added dropwise as a solution (1.0 M in CH_2Cl_2) followed by collidine (1.0 eq). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. The reaction vessel was then placed in a 0 °C ice bath, and *N*-chlorosuccinimide (1.2 equiv.) and HCl (4 M in dioxanes, 4 equiv.) were subsequently added. The reaction vessel was removed from the ice bath and allowed to stir at room temperature for 2 hours, before being quenched with aqueous sodium thiosulfate and aqueous sodium bicarbonate. The reaction was diluted with CH_2Cl_2 and H_2O, then extracted into CH_2Cl_2 (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

General Procedure G (Bromination of Isoquinolines)



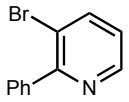
An oven dried 8 mL vial equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise. The reaction was stirred for 30 minutes before dibenzylamine (1 equiv) was added dropwise as a solution (1.0 M in CH_2Cl_2) followed by collidine (1.0 eq). The reaction was stirred for a further 30 minutes at –78 ºC. The cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. *N*-bromosuccinimide (1 equiv) was added and the reaction was allowed to stir at room temperature for 1 hour. Then trifluoroacetic acid (2 equiv) was added and the reaction was left to stir at room temperature overnight. The reaction was quenched with aqueous sodium thiosulfate and aqueous sodium bicarbonate. The reaction was diluted with CH_2Cl_2 and H_2O, then extracted into CH_2Cl_2 (3x). The organic extract was dried ($MgSO_4$), filtered, and concentrated down, and then the crude material was purified with flash column chromatography.

3-Iodo-2-phenylpyridine (9-I)



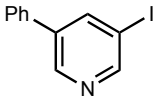
Prepared according to general procedure B using 2-phenylpyridine (1.43 mL, 10.00 mmol), EtOAc (100 mL, 0.1 M), Tf_2O (1.68 mL, 10.00 mmol), dibenzylamine (2.31 µL, 12.00 mmol, 1.0 M in EtOAc), collidine (1.32 mL, 10.00 mmol), *N*-iodosuccinimide (2.25 g, 10.00 mmol), trimethoxybenzene (1.68 g, 10.00 mmol), ammonium acetate (7.71 g, 100.0 mmol), and EtOH (100 mL). The crude material was purified by flash chromatography (silica gel: 2% Acetone in Hexanes, ran twice, then silica gel plug: 0 to 100% CH_2Cl_2 in Hexanes) to afford the title compound as a yellow oil (1.921 g, 6.83 mmol, 68% yield); IR ν_{max}/cm^{-1} (film): 3034, 1561, 1417, 1089, 1004, 915, 781, 740, 696; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.62 (1H, dd, J = 4.7, 1.5 Hz), 8.22 (1H, dd, J = 8.0, 1.5 Hz), 7.63 – 7.56 (2H, m), 7.48 – 7.39 (3H, m), 6.93 (1H, dd, J = 8.0, 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.47, 148.58, 147.55, 141.91, 128.18, 128.63, 127.92, 123.23, 94.26; *m/z* HRMS (DART) found $[M+H]^+$ 281.9790, $C_{11}H_9IN^+$ requires 281.9780.

3-Bromo-2-phenylpyridine (9-Br)



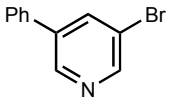
Prepared according to general procedure D (except that the ammonium acetate step was let run for 20 hours) using 2-phenylpyridine (57 µL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL) (Note: the brominated imine crashes out of CH_2Cl_2 at -78 °C, and the reaction vial was physically shaken after adding trimethoxybenzene and while warming to room temperature). The crude material was purified by flash chromatography (silica gel: 0 to 100% CH_2Cl_2 in Hexanes) to provide the title compound as a clear oil (54.7 mg, 0.23 mmol, 58% yield); IR ν_{max}/cm^{-1} (film): 3040, 1616, 1426, 1300, 1179, 1009, 738, 695, 611; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, d, *J* = 4.5 Hz), 7.99 (1H, d, *J* = 8.0 Hz), 7.69 (2H, d, *J* = 7.3 Hz), 7.51 – 7.40 (3H, m), 7.13 (1H, dd, *J* = 7.6, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.28, 148.16, 141.37, 139.66, 129.37, 128.83, 128.06, 123.32, 119.90; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 234.0, $C_{11}H_9BrN^+$ requires 234.0.

3-Iodo-5-phenylpyridine (12-I)



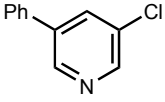
Prepared according to general procedure C using 3-phenylpyridine (1.43 mL, 10.00 mmol), EtOAc (100 mL, 0.1 M), Tf_2O (1.68 mL, 10.00 mmol), dibenzylamine (2.31 µL, 12.00 mmol, 1.0 M in EtOAc), collidine (1.32 mL, 10.00 mmol), *N*-iodosuccinimide (2.25 g, 10.00 mmol), and trifluoroacetic acid (765 µL, 10.00 mmol). The crude material was purified by flash chromatography (silica gel: 10% Et_2O in Hexanes) to provide the title compound as a white solid (2.30 g, 8.19 mmol, 82% yield). mp 79 – 81 °C; IR ν_{max}/cm^{-1} (film): 3014, 1496, 1423, 1103, 1005, 881, 785, 699, 663; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.80 (1H, s), 8.77 (1H, s), 8.21 (1H, d, *J* = 1.4 Hz), 7.57 – 7.53 (2H, m), 7.51 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.35, 146.83, 142.63, 138.68, 136.44, 129.30, 128.77, 127.26, 93.76; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 282.0, $C_{11}H_9IN^+$ requires 282.0.

3-Bromo-5-phenylpyridine (12-Br)



Prepared according to general procedure E using 3-phenylpyridine (57 µL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 10% Ether in Hexanes) to provide the title compound as a clear oil (76 mg, 0.32 mmol, 81% yield); IR ν_{max}/cm^{-1} (film): 3037, 1580, 1428, 1101, 1010, 881, 758, 695; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (1H, d, *J* = 1.4 Hz), 8.65 (1H, d, *J* = 1.8 Hz), 8.00 (1H, app t, *J* = 1.8 Hz), 7.57 – 7.52 (2H, m), 7.50 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.31, 146.16, 137.92, 136.43, 134.12, 132.26, 129.32, 128.80, 127.28; *m/z* HRMS (DART) found $[M+H]^+$ 233.9921, $C_{11}H_9BrN^+$ requires 233.9918.

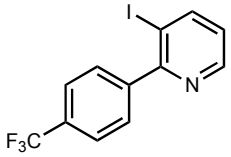
3-Chloro-5-phenylpyridine (12-Cl)



Prepared according to general procedure F using 3-phenylpyridine (57 µL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-chlorosuccinimide (53 mg, 0.40 mmol), and HCl (400 µL, 1.60 mmol, 4 M in dioxane). The crude material was purified by flash chromatography (silica gel: 10% Ether in Hexanes) to provide the title compound as a clear oil (60 mg, 0.32 mmol, 79% yield); IR ν_{max}/cm^{-1} (film): 1674, 1431, 1108, 1016, 906, 727, 697, 640; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, s), 8.55 (1H, s), 7.85 (1H, m), 7.58 – 7.53 (2H, m), 7.52 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.31, 146.16, 137.92, 136.43, 134.12, 132.26, 129.32, 128.80, 127.28; *m/z* HRMS (DART) found $[M+H]^+$ 190.0433, $C_{11}H_9ClN^+$ requires 190.0424

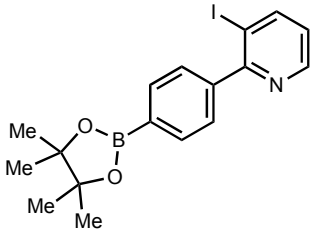
7. Iodination of Building Block Heterocycles

3-Iodo-2-(4-(trifluoromethyl)phenyl)pyridine (13)



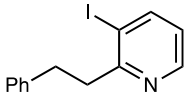
Prepared according to general procedure B using 2-(4-(trifluoromethyl)phenyl)pyridine (80 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 3:1:96 EtOH:MeOH:Hexanes, run twice) to provide the title compound as a white solid (91 mg, 0.26 mmol, 65% yield). mp 34 – 35 °C; IR ν_{max}/cm^{-1} (film): 1564, 1423, 1322, 1161, 1104, 1015, 846, 736; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.65 (1H, dd, J = 4.6, 1.3 Hz), 8.28 (1H, dd, J = 8.0, 1.4 Hz), 7.73 (4H, s), 7.02 (1H, dd, J = 8.0, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.29, 148.93, 147.90, 145.39, 130.76 (q, J = 32.4 Hz), 129.86, 125.12 (q, J = 3.8 Hz), 124.19 (q, J = 272.2 Hz), 123.96, 93.89; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.67; *m/z* HRMS (DART) found $[M+H]^+$ 349.9654, $C_{12}H_8F_3IN^+$ requires 349.9654.

3-Iodo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine (14)



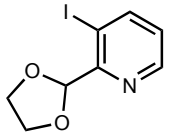
Prepared according to general procedure B using 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine (112 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). Crude NMR showed 68% of the title compound relative to triphenylmethane internal standard. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes, run four times) to provide 20 mg of the title compound as an amorphous solid. IR ν_{max}/cm^{-1} (film): 2977, 1563, 1357, 1267, 1142, 1002, 730, 657; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.64 (1H, d, J = 4.5 Hz), 8.26 (1H, d, J = 8.0 Hz), 7.90 (2H, d, J = 7.5 Hz), 7.60 (2H, d, J = 7.5 Hz), 6.98 (1H, dd, J = 7.9, 4.6 Hz), 1.37 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.58, 148.69, 147.85, 144.51, 134.53, 128.61, 123.50, 94.29, 84.06, 25.07; *m/z* HRMS (DART) found $[M+H]^+$ 408.0680, $C_{17}H_{20}BINO_2^+$ requires 408.0632

3-Iodo-2-phenethylpyridine (15)



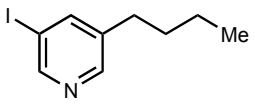
Prepared according to general procedure B using 2-phenethylpyridine (73 µL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). Flash column chromatography (silica gel: 10% EtOAc in Hexanes, second column: 60% to 100% CH_2Cl_2 in Hexanes) afforded the title compound (82 mg, 0.26 mmol, 66% yield) as a yellow oil. IR ν_{max}/cm^{-1} (film): 1566, 1419, 1114, 1007, 908, 755, 697; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, dd, J = 4.6, 1.2 Hz), 8.10 (1H, dd, J = 7.9, 1.3 Hz), 7.36 – 7.32 (4H, m), 7.28 – 7.22 (1H, m), 6.87 (1H, dd, J = 7.9, 4.7 Hz) 3.35 – 3.29 (2H, m), 3.10 – 3.04 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.18, 148.70, 146.92, 141,48, 128.60, 128.52, 126.16, 122.72, 96.42, 43.42, 35.09; *m/z* HRMS (DART) found $[M+H]^+$ 310.0136, $C_{13}H_{13}IN^+$ requires 310.0093.

2-(1,3-Dioxolan-2-yl)-3-iodopyridine (17)



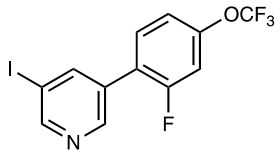
Prepared according to general procedure B using 2-(1,3-dioxolan-2-yl)pyridine (61 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel gradient elution: 35 to 50% EtOAc in Hexanes, run twice) to provide the title compound as a green oil (56 mg, 0.20 mmol, 50% yield); IR ν_{max}/cm^{-1} (film): 2890, 1379, 1028, 1008, 941, 793, 757, 627; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, d, J = 4.6 Hz), 8.16 (1H, dd, J= 8.0, 0.8 Hz), 7.02 (1H, dd, J = 8.0, 4.6 Hz), 6.19 (1H, s), 4.36 – 4.23 (2H, m), 4.17 – 4.02 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.98, 148.74, 147.80, 125.34, 104.79, 93.26, 65.93; *m/z* HRMS (DART) found $[M+H]^+$ 277.9669, $C_8H_9INO_2^+$ requires 277.9678.

3-Butyl-5-iodopyridine (18)



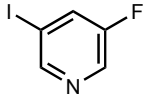
Prepared according to general procedure C using 3-butylpyridinepyridine (59 µL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 5% EtOAc in Hexanes) to provide the title compound as a clear oil (78 mg, 0.30, 74% yield); IR ν_{max}/cm^{-1} (film): 2955, 2927, 2857, 1548, 1419, 1018, 895, 703; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.65 (1H, s), 8.38 (1H, s), 7.84 (1H, s), 2.56 (2H, t, J = 7.8 Hz), 1.64 – 1.55 (2H, m), 1.42 – 1.30 (2H, m), 0.94 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.20, 148.50, 144.09, 140.24, 93.53, 31.11, 32.42, 22.27, 13.90; *m/z* HRMS (DART) found $[M+H]^+$ 262.0098, $C_9H_{13}IN^+$ requires 262.0093.

3-(2-Fluoro-4-(trifluoromethoxy)phenyl)-5-iodopyridine (19)



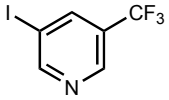
Prepared according to general procedure C using 3-(2-fluoro-4-(trifluoromethoxy)phenyl)pyridine (103 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). Flash column chromatography (silica gel: 10% EtOAc in Hexanes) afforded the title compound (126 mg, 0.33 mmol, 82% yield) as a white solid. mp 68 – 71 °C; IR ν_{max}/cm^{-1} (film): 2924, 1623, 1507, 1401, 1166, 1009, 885, 723, 697; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.83 (1H, s), 8.69 (1H, s), 8.16 (1H, s), 7.44 (1H, app t, *J* = 8.5 Hz), 7.15 – 7.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.73 (d, *J* = 249.7 Hz), 155.21, 150.10 (dq, *J* = 11.0, 2.1 Hz), 147.99 (d, *J* = 3.6 Hz), 144.25 (d, *J* = 3.2 Hz), 132.26, 131.29 (d, *J* = 4.1 Hz), 123.13 (d, *J* = 14.0 Hz), 120.39 (q, *J* = 259.0 Hz), 117.23 (d, *J* = 3.8 Hz), 109.77 (d, *J* = 32.8 Hz), 93.31; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –58.0 (3F, s), –113.05 (1F, app t, *J* = 9.6 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 383.9549, $C_{12}H_7F_4INO^+$ requires 383.9508.

3-Fluoro-5-iodopyridine (20)



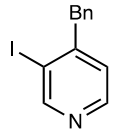
A 2.6:1 mixture of *N*-((1Z,2Z,4E)-5-(Dibenzylamino)-2-fluoropenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethane sulfonamide and *N*-((1Z,2E,4Z)-5-(dibenzylamino)-4-fluoropenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (128 mg, 0.30 mmol) and CH_2Cl_2 (3 mL, 0.1 M) were added to an 8 mL vial which was subsequently cooled to 0 °C. *N*-iodosuccinimide (71 mg, 0.32 mmol) and trifluoroacetic acid (24 µL, 0.32 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir for 2 hours. The reaction was quenched with aqueous sodium thiosulfate and sodium bicarbonate, triphenylmethane (internal standard) was added, and an aliquot was concentrated down. Crude NMR showed 82% of the title compound relative to triphenylmethane internal standard. Flash column chromatography yielded a mixture of the product and other non-pyridine byproducts. Spectra matched an authentic sample purchased from Oakwood Chemical.

3-Iodo-5-(trifluoromethyl)pyridine (21)



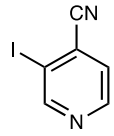
Prepared according to general procedure B (except that 0.9 equivalents of collidine was used and after addition of *N*-iodosuccinimide and TFA, the reaction was heated to 50 °C for 3 hours) using 3-(trifluoromethyl)pyridine (35 µL, 0.30 mmol), EtOAc (3 mL, 0.1 M), Tf_2O (50 µL, 0.30 mmol), dibenzylamine (58 µL, 0.30 mmol, 1.0M in EtOAc), collidine (36 µL, 0.27 mmol), *N*-iodosuccinimide (68 mg, 0.30 mmol), and trifluoroacetic acid (23 µL, 0.30 mmol). Crude NMR showed 65% of the title compound relative to triphenylmethane internal standard. Flash column chromatography yielded a mixture of the product and other non-pyridine byproducts. Spectra matched literature values (*45*).

4-Benzyl-3-iodopyridine (22)



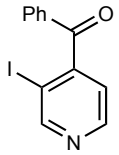
Prepared according to general procedure B using 4-benzylpyridine (64 µL, 0.40 mmol), EtOAc (4 mL), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). Flash column chromatography (silica gel: 15% EtOAc in Hexanes) afforded the title compound (92 mg, 0.26 mmol, 66% yield) as a brown oil. IR ν_{max}/cm^{-1} (film): 3028, 1576, 1394, 1083, 1011, 796, 618; ^1H NMR (400 MHz, CD_3CN) δ: 8.93 (1H, br s), 8.42 (1H, br s), 7.32 (2H, app t, J = 7.6 Hz), 7.27 – 7.19 (3H, m), 7.15 (1H, d, J = 3.0 Hz) 4.06 (2H, s); ^{13}C NMR (100 MHz, CD_3CN) δ: 158.39, 153.45, 150.04, 138.98, 130.03, 129.61, 127.63, 118.24, 101.37, 45.99; *m/z* HRMS (DART) found $[M+H]^+$ 293.9931, $C_{12}H_{11}IN_2^+$ requires 295.9936.

3-Iodoisonicotinonitrile (24)



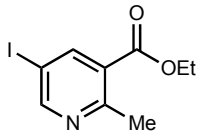
Prepared according to general procedure B (except that the NIS step was ran for 30 minutes instead of 10 minutes) using 4-cyanopyridine (42 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). Flash column chromatography (silica gel gradient elution: 5 to 15% EtOAc in Hexanes) afforded the title compound (33 mg, 0.14 mmol, 36% yield) as a brown solid. mp 115 – 118 °C; IR ν_{max}/cm^{-1} (film): 2922, 2852, 1215, 1082, 1018, 836, 613; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.11 (1H, s), 8.72 (1H, d, J = 4.9 Hz), 7.52 (1H, d, J = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.18, 149.09, 128.12, 127.26, 117.18, 95.07; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 231.0, $C_6H_4IN_2^+$ requires 230.9.

(3-Iodopyridin-4-yl)(phenyl)methanone (25)



Prepared according to a modified version of general procedure B using phenyl(pyridin-4-yl)methanone)pyridine (73 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trimethoxybenzene (67 mg, 0.40 mmol). Instead of adding ammonium acetate, trifluoroacetic acid (92 µL, 1.20 mmol) was added and the reaction was left to stir at room temperature for 2 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in Hexanes) to provide the title compound as a yellow solid (76 mg, 0.25 mmol, 62% yield). mp 79 – 82 °C; IR ν_{max}/cm^{-1} (film): 1670, 1449, 1289, 1174, 979, 702, 638; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, s), 8.67 (1H, d, J = 4.7 Hz), 7.78 (2H, d, J = 7.8 Hz), 7.65 (1H, d, J = 7.4 Hz), 7.50 (2H, d, J = 7.6 Hz), 7.23 (1H, d, J = 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.95, 157.99, 151.62, 148.81, 134.63, 134.26, 130.46, 129.20, 122.47, 91.04; *m/z* HRMS (DART) found $[M+H]^+$ 309.9741, $C_{12}H_9INO^+$ requires 309.9729.

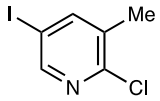
Ethyl 5-iodo-2-methylnicotinate (26)



Prepared according to general procedure C (except that CH_2Cl_2 was the solvent and two equivalents of TFA were used) using ethyl 2-methylnicotinate (62 µL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol),

dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (61 µL, 0.80 mmol). The crude material was purified by flash chromatography (silica gel: 5% EtOAc in Hexanes, run twice) to provide the title compound as a white solid (48 mg, 0.16 mmol, 41% yield). mp 83 – 86 °C; IR ν_{max}/cm^{-1} (film): 2922, 2850, 1724, 1372, 1268, 1247, 1082, 795; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, *J* = 2.2 Hz), 8.48 (1H, d, *J* = 2.2 Hz), 4.39 (2H, q, *J* = 7.1 Hz), 2.78 (3H, s), 1.41 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.35, 158.77, 157.68, 146.16, 127.44, 89.19, 61.80, 24.46, 14.38; *m/z* HRMS (DART) found $[M+H]^+$ 291.9826, $C_9H_{11}INO_2^+$ requires 291.9834.

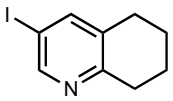
2-Chloro-5-iodo-3-methylpyridine (27)



Prepared according to a modificiation of procedure C (where *N*-benzylaniline was used instead of dibenzylamine and two equivalents of TFA were used) using 2-chloro-3-methylpyridine (44 µL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), *N*-benzylaniline (73 mg, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (180 mg, 0.80 mmol), and trifluoroacetic acid (61 µL, 0.80 mmol) were added, the ice bath was removed, and the reaction was stirred at room temperature for 24 hours. Flash column chromatography (silica gel: 1% Ether in Hexanes; second column: 50% Toluene in Hexanes) afforded the title compound (44 mg, 0.18 mmol, 44% yield) as a clear oil. IR ν_{max}/cm^{-1} (film): 2923, 2237, 1397, 1184, 1076, 906, 724, 646; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 (1H, d, *J* = 1.9 Hz), 7.86 (1H, d, *J* = 1.5 Hz), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.99, 151.34, 147.16, 134.91, 90.89, 19.59; *m/z* HRMS (DART) found $[M+H]^+$ 253.9229, $C_6H_6ClIN^+$ requires 253.9233.

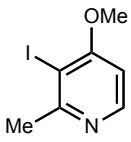
Note: *N*-benzylaniline is required for 2-halopyridines to achieve Zincke imine formation. Dibenzylamine results in near complete decomposition of SM (<10% remaining) and no desired product observed. We believe *N*-benzylaniline is effective due to the attenuated nucleophilicity of the amine mitigating undesired side reactivity, either prior to or after ring-opening.

3-Iodo-5,6,7,8-tetrahydroquinoline (28)



N-((1*E*,2*Z*)-2-((*E*)-3-(dibenzylamino)allylidene)cyclohexylidene)-1,1,1-trifluoromethanesulfonamide (185 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) were added to an 8 mL vial which was subsequently cooled to 0 °C. *N*-iodosuccinimide (94 mg, 0.42 mmol) and trifluoroacetic acid (32 µL, 0.42 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir for 2 hours. After the workup for general procedure C, the crude material was purified by flash chromatography (silica gel: 5% EtOAc in Hexanes) to provide the title compound as a white solid (86 mg, 0.33 mmol, 83% yield). mp 96 – 100 °C; IR ν_{max}/cm^{-1} (film): 2924, 1689, 1433, 1228, 1085, 1014, 799, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, d, *J* = 1.2 Hz), 7.65 (1H, s), 2.83 (2H, t, *J* = 6.5 Hz), 2.70 (2H, t, *J* = 6.2 Hz), 1.90 – 1.80 (2H, m), 1.80 – 1.71 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.44, 152.59, 144.60, 134.80, 89.61, 32.10, 28.63, 22.82, 22.33; *m/z* HRMS (DART) found $[M+H]^+$ 259.9965, $C_9H_{11}IN^+$ requires 259.9936.

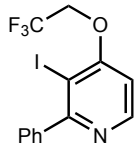
3-Iodo-4-methoxy-2-methylpyridine (30)



Prepared according to a modified version of general procedure B using 4-methoxy-2-methylpyridine (49 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2),

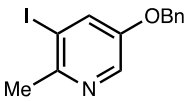
collidine (53 mL, 0.40 mmol), and *N*-iodosuccinimide (90 mg, 0.40 mmol). After stirring with *N*-iodosuccinimide at room temperature for 1 hour, trifluoroacetic acid (61 µL, 0.80 mmol) was added and the reaction was left to stir at room temperature for an additional 2 hours. The crude material was purified by flash chromatography (silica gel: 40% EtOAc in Hexanes) to provide the title compound as a brown solid (47 mg, 0.18 mmol, 44% yield). mp 104 – 106 °C. IR ν_{max}/cm^{-1} (film): 2941, 1574, 1426, 1288, 1074, 981, 822, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (1H, d, *J* = 5.6 Hz), 6.53 (1H, d, *J* = 5.6 Hz), 3.92 (3H, s), 2.75 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.37, 162.20, 149.87, 104.07, 88.09, 56.48, 29.62; *m/z* HRMS (DART) found $[M+H]^+$ 249.9750, $C_7H_9INO^+$ requires 249.9729.

3-Iodo-2-phenyl-4-(2,2,2-trifluoroethoxy)pyridine (31)



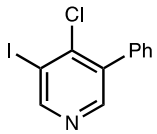
Prepared according to a modified version of general procedure B using 2-phenyl-4-(2,2,2-trifluoroethoxy)pyridine (101 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), and *N*-iodosuccinimide (90 mg, 0.40 mmol). After stirring with *N*-iodosuccinimide at room temperature for 1 hour, trifluoroacetic acid (61 µL, 0.80 mmol) was added and the reaction was left to stir at room temperature for an additional 2 hours. The crude material was purified by flash chromatography (silica gel gradient elution: 20 to 30% EtOAc in Hexanes) to provide the title compound as a white solid (108 mg, 0.28 mmol, 71% yield). mp 152 – 155 °C; IR ν_{max}/cm^{-1} (film): 1568, 1450, 1252, 1073, 978, 892, 856, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (1H, d, *J* = 5.5 Hz), 7.58 – 7.53 (2H, m), 7.49 – 7.40 (3H, m), 6.65 (1H, d, *J* = 5.5 Hz), 4.51 (2H, q, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.87, 162.83, 150.37, 142.21, 129.21, 128.83, 128.04, 122.74 (q, *J* = 278.2 Hz), 105.52, 86.99, 66.21 (q, *J* = 36.7 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –73.43; *m/z* HRMS (DART) found $[M+H]^+$ 379.9764, $C_{13}H_{10}F_3INO^+$ requires 379.9759.

5-(Benzyloxy)-3-iodo-2-methylpyridine (32)



Prepared according to a modified version of general procedure C using 5-(benzyloxy)-2-methylpyridine (80 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), and collidine (53 µL, 0.40 mmol). After *N*-iodosuccinimide (90 mg, 0.40 mmol) and trifluoroacetic acid (31 µL, 0.40 mmol) were added, the reaction was stirred at room temperature for 90 minutes. Then ammonium acetate (308 mg, 4.00 mmol) was added, and the reaction was heated to 50 °C for 22 hours. Flash column chromatography (silica gel 10% EtOAc in Hexanes) afforded the title compound (87 mg, 0.27 mmol, 67% yield) as a brown oil. IR ν_{max}/cm^{-1} (film): 2919, 2218, 1449, 1272, 1221, 1007, 907, 730; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (1H, d, *J* = 2.6 Hz), 7.68 (1H, d, *J* = 2.6 Hz), 7.43 – 7.35 (5H, m), 5.05 (2H, s), 2.68 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.81, 152.36, 136.63, 135.88, 132.29, 128.86, 128.54, 127.68, 95.54, 70.85, 27.71; *m/z* HRMS (DART) found $[M+H]^+$ 326.0094, $C_{13}H_{13}INO^+$ requires 326.0042.

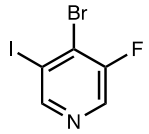
4-Chloro-3-iodo-5-phenylpyridine (35)



Prepared according to general procedure C using 4-chloro-3-phenylpyridine (76 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). Flash column chromatography

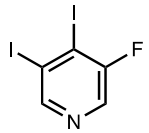
(silica gel: 5% EtOAc in Hexanes) afforded the title compound (72 mg, 0.23 mmol, 57% yield) as a white solid. mp 74 – 77 °C; IR ν_{max}/cm^{-1} (film): 2923, 1534, 1389, 1242, 1076, 892, 765, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, s), 8.42 (1H, s), 7.50 – 7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.12, 150.23, 146.04, 137.98, 135.96, 129.44, 128.86, 128.56, 99.36; *m/z* HRMS (DART) found $[M+H]^+$ 315.9383, $C_{11}H_8ClIN^+$ requires 315.9390.

4-Bromo-3-fluoro-5-iodopyridine (36)



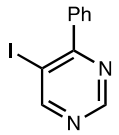
Prepared according to general procedure C using 4-bromo-3-fluoropyridine (70 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). Flash column chromatography (silica gel: 100% Toluene, run twice) afforded the title compound (47 mg, 0.16 mmol, 39% yield) as a white solid. mp 125 – 127 °C; IR ν_{max}/cm^{-1} (film): 1542, 1397, 1268, 1125, 867, 698, 628; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, s), 8.37 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.65 (d, J = 263 Hz), 153.32 (d, J = 4.9 Hz), 137.11 (d, J = 25.3 Hz), 127.36 (d, J = 19.0 Hz), 101.68 (d, J = 4.6 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –112.16; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 301.9, $C_5H_3BrFIN^+$ requires 301.8.

3-Fluoro-4,5-diiodopyridine (37)



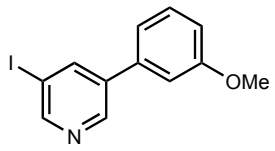
Prepared according to general procedure C using 3-fluoro-4-iodopyridine (89 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). Flash column chromatography (silica gel gradient elution: 2 to 3% EtOAc in Hexanes) afforded the title compound (35 mg, 0.10 mmol, 25% yield) as a white solid. mp 118 – 120 °C; IR ν_{max}/cm^{-1} (film): 1526, 1396, 1266, 1128, 866, 617, 611; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, s), 8.25 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.40 (d, J = 260 Hz), 152.27 (d, J = 4.8 Hz), 135.36 (d, J = 27 Hz), 108.29 (d, J = 3.9 Hz), 107.62 (d, J = 23 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –95.79; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 349.9, $C_5H_3FI_2N^+$ requires 349.8.

5-Iodo-4-phenylpyrimidine (38)



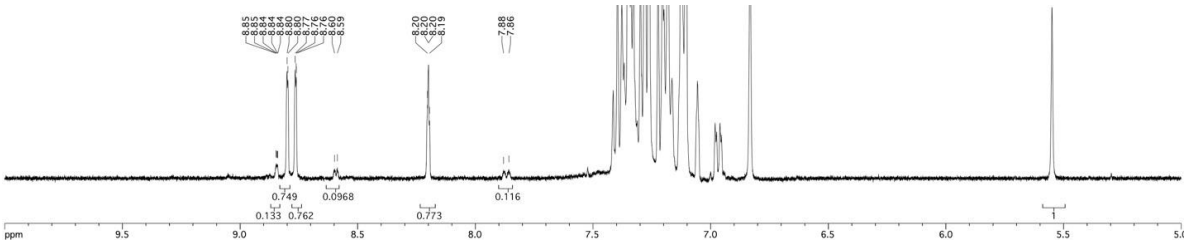
Prepared according to a modified version of general procedure C using 4-phenylpyrimidine (63 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), and collidine (53 µL, 0.40 mmol). After *N*-iodosuccinimide (90 mg, 0.40 mmol) and trifluoroacetic acid (31 µL, 0.40 mmol) were added, the reaction was stirred at room temperature for 1 hour. Then ammonium acetate (308 mg, 4.00 mmol) and EtOH (8 mL) was added, and the reaction was heated to 60 °C for 2 hours. Flash column chromatography (silica gel: 10% EtOAc in Hexanes) afforded the title compound (60 mg, 0.21 mmol, 53% yield) as a white solid. mp 59 – 62 °C; IR ν_{max}/cm^{-1} (film): 1546, 1430, 1303, 1151, 1007, 741, 696, 621; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 – 9.13 (2H, m), 7.72 – 7.69 (2H, m), 7.50 – 7.47 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.80, 165.68, 157.49, 139.12, 130.21, 129.18, 128.36, 94.25; *m/z* HRMS (DART) found $[M+H]^+$ 282.9390, $C_{10}H_8IN_2^+$ requires 282.9732.

3-Iodo-5-(3-methoxyphenyl)pyridine (44)

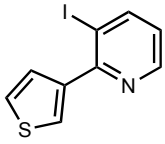


Prepared according to general procedure C using 3-(3-methoxyphenyl)pyridine (74 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 mL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes) to provide the title compound as a white solid (95 mg, 0.30 mmol, 76% yield). mp 66 – 69 °C; IR ν_{max}/cm^{-1} (film): 2927, 1691, 1421, 1294, 1219, 1087, 1011, 710, 664; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, s), 8.77 (1H, s), 8.21 (1H, s), 7.40 (1H, app t, *J* = 8.0 Hz), 7.13 (1H, d, *J* = 7.7 Hz), 7.06 (1H, s), 6.97 (1H, dd, *J* = 8.2, 2.4 Hz), 3.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.23, 154.44, 146.81, 142.59, 138.49, 137.79, 130.32, 119.61, 114.04, 112.99, 93.71, 55.47; *m/z* HRMS (DART) found $[M+H]^+$ 311.9869, $C_{12}H_{11}INO^+$ requires 311.9885.

Crude ^{1}H NMR in $CDCl_3$ (peaks at 7.87, 8.60, and 8.85 are the starting material; peaks at 8.20, 8.76, and 8.80 are the product)

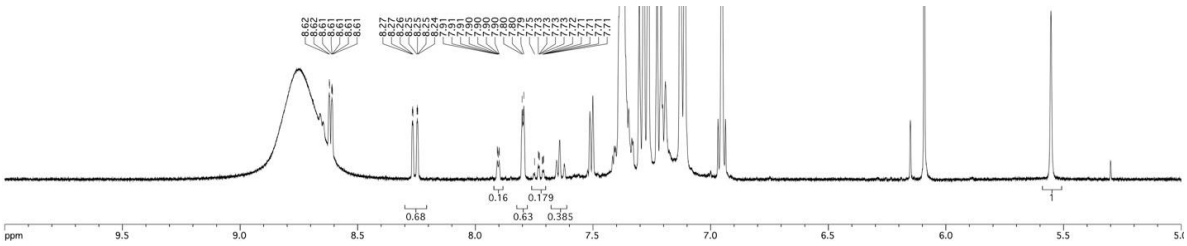


3-Iodo-2-(thiophen-3-yl)pyridine (45)

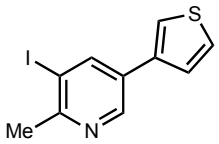


Prepared according to general procedure B using 2-(thiophen-3-yl)pyridine (65 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 90% CH_2Cl_2 in Hexanes) to provide the title compound as a brown oil (79 mg, 0.27 mmol, 68% yield). IR ν_{max}/cm^{-1} (film): 3037, 2220, 1563, 1436, 1186, 1002, 863, 786, 749, 644; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 3.8 Hz), 8.23 (1H, d, *J* = 7.9 Hz), 7.81 (1H, d, *J* = 1.6 Hz), 7.52 (1H, d, *J* = 4.8 Hz), 7.37 (1H, dd, *J* = 4.7, 3.0 Hz), 6.91 (1H, dd, *J* = 7.9, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.79, 148.60, 148.05, 142.51, 128.91, 126.58, 124.99, 123.12, 93.71; *m/z* HRMS (DART) found $[M+H]^+$ 287.9387, $C_9H_7INS^+$ requires 287.9344.

Crude ^{1}H NMR in $CDCl_3$ (peaks at 7.73 and 7.90 are the starting material; peaks at 7.80, 8.25, and 8.61 are the product)

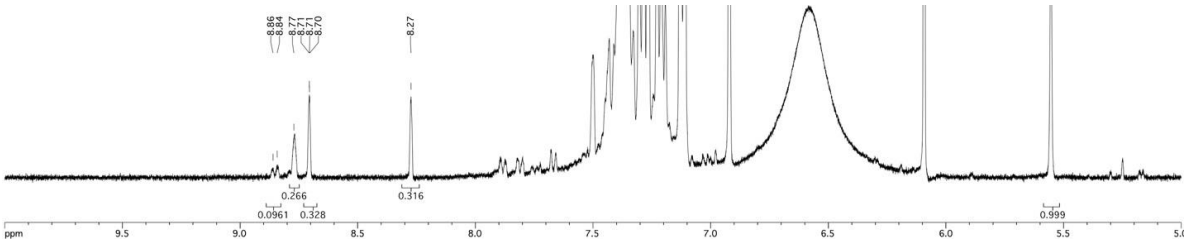


3-Iodo-2-methyl-5-(thiophen-3-yl)pyridine (jnl-vii-p183) (46)

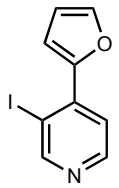


Prepared according to general procedure B using 2-methyl-5-(thiophen-3-yl)pyridine (70 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes) to provide the title compound as a brown solid (48 mg, 0.09 mmol, 23% yield). mp 67 – 70 °C; IR ν_{max}/cm^{-1} (film): 3061, 2921, 2852, 1461, 1029, 816, 778, 640; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (1H, d, *J* = 1.9 Hz), 8.26 (1H, d, *J* = 1.9 Hz), 7.50 (1H, dd, *J* = 2.9, 1.2 Hz), 7.45 (1H, dd, *J* = 5.0, 2.9 Hz), 7.36 (1H, dd, *J* = 5.0, 1.2 Hz), 2.77 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.59, 146.17, 143.85, 137.19, 130.69, 127.25, 125.89, 121.75, 96.67, 28.69; *m/z* HRMS (DART) found $[M+H]^+$ 301.9538, $C_{10}H_9INS^+$ requires 301.9500.

<u>*Crude ^{1}H NMR in $CDCl_3$*</u> (peak at 8.77 is the starting material; peaks at 8.27 and 8.71 are the product)



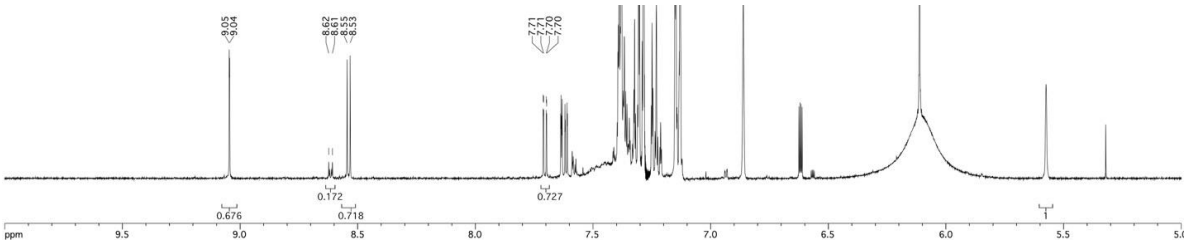
4-(Furan-2-yl)-3-iodopyridine (47)



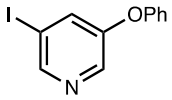
Prepared according to general procedure B using ethyl 4-(furan-2-yl)pyridine (58 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes) to provide the title compound as a brown amorphous solid (68 mg, 0.25 mmol, 62% yield); IR ν_{max}/cm^{-1} (film): 2924, 1581, 1393, 1093, 1003, 839, 742, 663; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, s), 8.52 (1H, d, *J* = 5.1

Hz), 7.66 (1H, d, J = 5.0 Hz), 7.61 (1H, d), 7.57 (1H, d, J = 3.5 Hz), 6.59 (1H, d, J = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.49, 150.61, 148.75, 144.00, 141.00, 122.23, 112.77, 111.82, 91.06; *m/z* HRMS (DART) found $[M+H]^+$ 271.9596, $C_9H_7INO^+$ requires 271.9572.

Crude ^{1}H NMR in $CDCl_3$ (peak at 8.62 is the starting material; peaks at 7.71, 8.54, and 9.04 are the product)

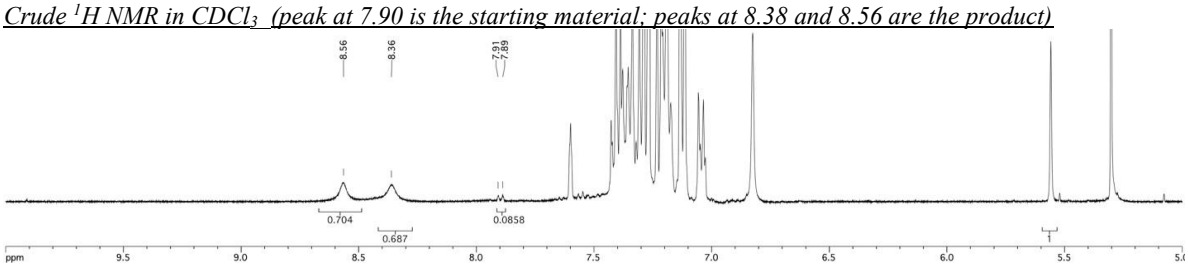


3-Iodo-5-phenoxypyridine (48)

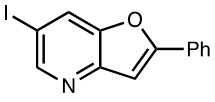


Prepared according to general procedure C (except that the solvent was CH_2Cl_2 and two equivalents of NIS and TFA were used) using 3-phenoxypyridine (69 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), and collidine (53 µL, 0.40 mmol) After *N*-iodosuccinimide (180 mg, 0.80 mmol) and trifluoroacetic acid (61 µL, 0.80 mmol) were added, the reaction was stirred at room temperature for 21 hours. Flash column chromatography (silica gel: 10% EtOAc in Hexanes) afforded the title compound (76 mg, 0.26 mmol, 64% yield) as a light yellow solid. mp 43 – 45 °C; IR ν_{max}/cm^{-1} (film): 2923, 1550, 1417, 1241, 1196, 1009, 881, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, s), 8.35 (1H, s), 7.59 (1H, app t, J = 2.0 Hz), 7.42 – 7.32 (2H, m), 7.20 (1H, t, J = 7.5 Hz), 7.06 – 7.01 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.58, 154.47, 150.08, 139.76, 133.24, 130.34, 124.89, 119.49, 92.81; *m/z* HRMS (DART) found $[M+H]^+$ 297.9718, $C_{11}H_9INO^+$ requires 297.9729.

Crude ^{1}H NMR in $CDCl_3$ (peak at 7.90 is the starting material; peaks at 8.38 and 8.56 are the product)



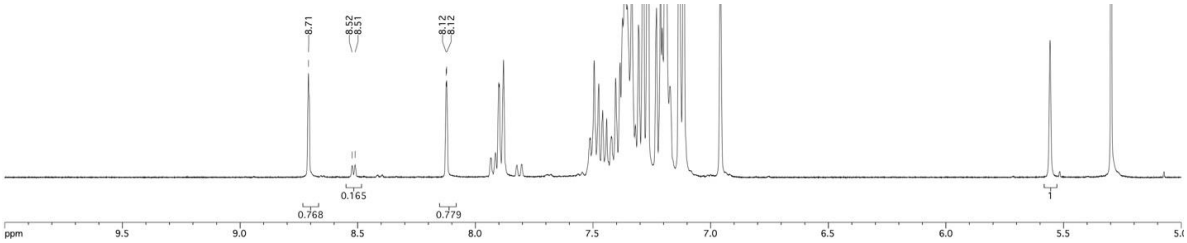
6-Iodo-2-phenylfuro[3,2-*b*]pyridine (49)



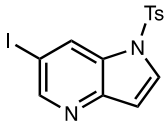
Prepared according to general procedure C (except that CH_2Cl_2 was the solvent) using 2-phenylfuro[3,2-*b*]pyridine (78 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in CH_2Cl_2), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol).. Flash column chromatography (silica gel gradient elution: 5 to 7.5% EtOAc in Hexanes) afforded the title compound (96 mg, 0.34 mmol, 74% yield) as a yellow solid. mp 190 – 194 °C; IR ν_{max}/cm^{-1} (film): 1527, 1402, 1227, 1142, 1028, 753, 698, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, s), 8.10 (1H, s), 7.87 (2H, d, J = 7.1 Hz), 7.50 –

7.41 (3H, m), 7.17 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.17, 151.96, 148.52, 148.06, 139.06, 129.32, 129.14, 126.25, 125.55, 102.39, 85.78; *m/z* HRMS (DART) found $[M+H]^+$ 321.9749, $C_{13}H_9INO^+$ requires 321.9729.

<u>*Crude ^{1}H NMR in $CDCl_3$*</u> (peak at 8.51 is the starting material; peaks at 8.12 and 8.71 are the product)

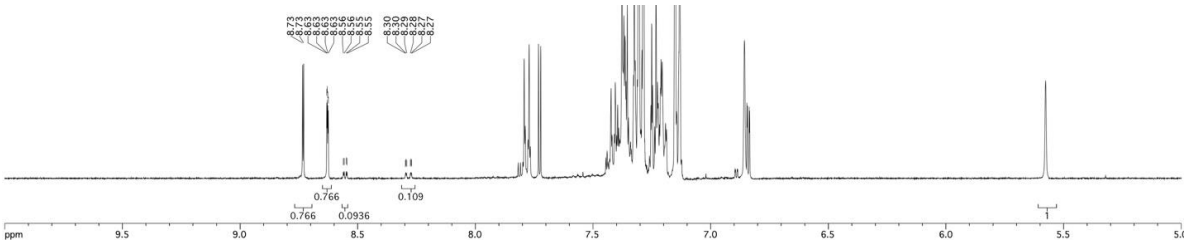


6-Iodo-1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridine (50)

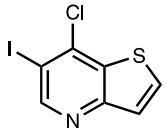


Prepared according to general procedure C using 1-tosyl-1*H*-pyrrolo[3,2-*b*]pyridine (109 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), and collidine (53 µL, 0.40 mmol), After *N*-iodosuccinimide (90 mg, 0.40 mmol) and trifluoroacetic acid (31 µL, 0.40 mmol) were added, the reaction was stirred at room temperature for 24 hours. Flash column chromatography (silica gel gradient elution: 10 to 15% EtOAc in Hexanes) afforded the title compound (118 mg, 0.30 mmol, 74% yield) as a white solid. mp 120 – 122 °C; IR ν_{max}/cm^{-1} (film): 1577, 1377, 1132, 1006, 894, 706, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, s), 8.61 (1H, s), 7.77 (2H, d, J = 8.4 Hz) 8.82 (1H, d, J = 3.8 Hz), 7.29 (2H, d, J = 8.1 Hz), 6.82 (1H, d, J = 3.7 Hz), 2.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.03, 147.36, 145.95, 134.79, 139.35, 129.78, 128.81, 126.91, 110.03, 87.13, 21.73; *m/z* HRMS (DART) found $[M+H]^+$ 398.9683, $C_{14}H_{12}IN_2O_2S^+$ requires 398.9664.

<u>*Crude ^{1}H NMR in $CDCl_3$*</u> (peaks at 8.29 and 8.56 are the starting material; peaks at 8.63 and 8.73 are the product)



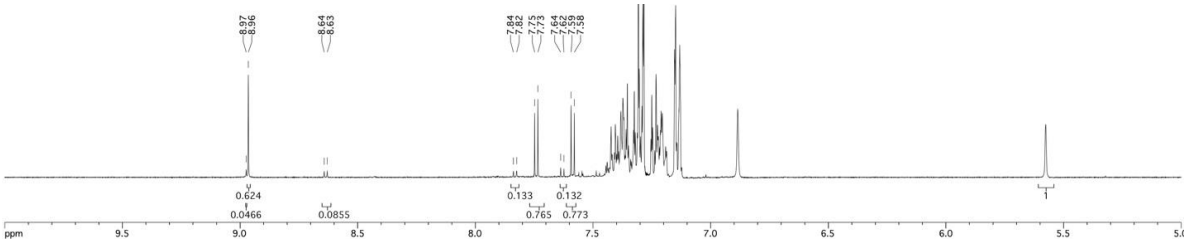
7-Chloro-6-iodothieno[3,2-*b*]pyridine (50)



Prepared according to general procedure C (except that two equivalents of NIS and TFA were used) using 1 7-chlorothieno[3,2-*b*]pyridine (68 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0M in EtOAc), and collidine (53 µL, 0.40 mmol). After *N*-iodosuccinimide (180 mg, 0.80 mmol) and trifluoroacetic acid (61 µL, 0.80 mmol) were added, the reaction was stirred at room temperature for 22 hours. Flash column chromatography (silica gel: 7.5% EtOAc in Hexanes) afforded the title compound (89 mg, 0.29 mmol, 73% yield) as a white solid. mp 104 – 106 °C; IR ν_{max}/cm^{-1} (film): 3065, 1562, 1467, 1241, 1196, 1009, 882, 785, 684;

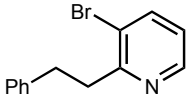
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (1H, s), 7.69 (1H, d, *J* = 5.5 Hz), 7.53 (1H, d, *J* = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.37, 155.29, 141.55, 134.14, 132.02, 125.83, 91.46; *m/z* HRMS (DART) found $[M+H]^+$ 295.8803, $C_7H_4ClINS^+$ requires 295.8798.

<u>*Crude ^{1}H NMR in $CDCl_3$*</u> (peaks at 7.63, 7.83, 8.64, and 8.97 are the starting material; peaks at 7.60, 7.74, and 8.97 are the product)



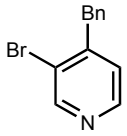
8. Bromination and Chlorination of Building Block Heterocycles

3-Bromo-2-phenethylpyridine (16)



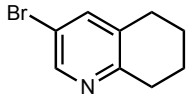
Prepared according to general procedure D using 2-phenethylpyridine (73 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). ^{1}H NMR of the crude material showed >20:1 selectivity for the desired product over the 5-bromo isomer. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes, second column: 100% CH_2Cl_2 in Hexanes) to provide the title compound as a yellow oil (69 mg, 0.26 mmol, 66% yield); IR ν_{max}/cm^{-1} (film): 2928, 1574, 1424, 1118, 1022, 791, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (1H, dd, *J* = 4.7, 1.2 Hz), 7.85 (1H, dd, *J* = 8.0, 1.3 Hz), 7.36 – 7.22 (5H, m), 7.05 (1H, dd, *J* = 8.0, 4.7 Hz), 3.33 – 3.22 (2H, m), 3.12 – 3.05 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.70, 147.95, 141.58, 140.34, 128.59, 128.53, 126.15, 122.72, 121.51, 39.74, 34.64; *m/z* HRMS (DART) found $[M+H]^+$ 262.0239, $C_{13}H_{13}BrN^+$ requires 262.0231.

4-Benzyl-3-bromopyridine (23)



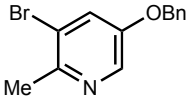
Prepared according to general procedure D using 4-benzylpyridinepyridine (64 µL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel gradient elution: 15 to 20% Ether in Hexanes) to provide the title compound as a brown oil (52 mg, 0.21 mmol, 52% yield); IR ν_{max}/cm^{-1} (film): 1670, 1569, 1254, 1175, 1073, 934, 701, 638; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (1H, s), 8.38 (1H, d, *J* = 4.9 Hz), 7.33 (2H, t, *J* = 7.6 Hz), 7.27 (1H, t, *J* = 7.1 Hz), 7.19 (2H, d, *J* = 7.3 Hz), 7.00 1H, d, *J* = 4.9 Hz), 4.08 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.99, 149.39, 148.42, 137.42, 129.28, 128.90, 127.01, 125.70, 123.45, 41.19; *m/z* HRMS (DART) found $[M+H]^+$ 248.0083, $C_{12}H_{11}BrN^+$ requires 248.0075.

3-Bromo-5,6,7,8-tetrahydroquinoline (29)



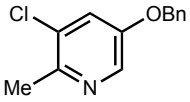
N-((1*E*,2*Z*)-2-((*E*)-3-(dibenzylamino)allylidene)cyclohexylidene)-1,1,1-trifluoromethanesulfonamide (185 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) were added to an 8 mL vial which was subsequently cooled to 0 °C. *N*-bromosuccinimide (75 mg, 0.42 mmol) and trifluoroacetic acid (32 µL, 0.42 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir at room temperature for 2 hours. The crude material was purified by flash chromatography (silica gel: 10% Ether in Hexanes) to provide the title compound as a yellow oil (36 mg, 0.17 mmol, 42% yield); IR ν_{max}/cm^{-1} (film): 2928, 1557, 1436, 1394, 1157, 1017, 744, 695; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.39 (1H, d, *J* = 2.0 Hz), 7.49 (1H, d, *J* = 1.7 Hz), 2.85 (2H, t, *J* = 6.5 Hz), 2.75 (2H, t, *J* = 6.3 Hz), 1.92 – 1.84 (2H, m), 1.82 – 1.75 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.12, 147.74, 139.03, 134.31, 117.35, 32.13, 28.78, 22.95, 22.42; *m/z* HRMS (DART) found $[M+H]^+$ 212.0071, $C_9H_{11}BrN^+$ requires 212.0075.

5-(Benzyloxy)-3-bromo-2-methylpyridine (33)



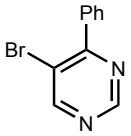
Prepared according to a modified version of general procedure D using 5-(benzyloxy)-2-methylpyridine (80 µL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), and collidine (53 mL, 0.40 mmol). After *N*-bromosuccinimide (71 mg, 0.40 mmol) and trifluoroacetic acid (31 µL, 0.40 mmol) were added, the reaction was stirred at room temperature for 1 hour. Then, ammonium acetate (308 mg, 4.00 mmol) was added and the reaction was heated to 50 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% Ether in Hexanes) to provide the title compound as a yellow oil (79 mg, 0.28 mmol, 69% yield); IR ν_{max}/cm^{-1} (film): 1670, 1569, 1289, 1254, 1174, 1012, 837, 701; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.21 (1H, d, *J* = 2.6 Hz), 7.44 (1H, d, *J* = 2.6 Hz), 7.42 – 7.32 (5H, m), 5.06 (2H, s), 2.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.37, 149.42, 136.00, 135.84, 128.84, 128.52, 127.64, 125.88, 120.86, 70.86, 23.94; *m/z* HRMS (DART) found $[M+H]^+$ 278.0171, $C_{13}H_{13}BrNO^+$ requires 278.0181.

5-(Benzyloxy)-3-chloro-2-methylpyridine (34)



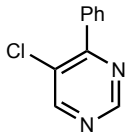
Prepared according to modified version of general procedure F using 5-(benzyloxy)-2-methylpyridine (80 µL, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), and collidine (53 mL, 0.40 mmol). After *N*-chlorosuccinimide (53 mg, 0.40 mmol) and HCl (400 µL, 1.60 mmol, 4.0 M in dioxanes solution) were added, the reaction was stirred at room temperature for 1 hour. Then, ammonium acetate (308 mg, 4.00 mmol) was added and the reaction was heated to 50 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% Ether in Hexanes) to provide the title compound as a yellow oil (54 mg, 0.23 mmol, 58% yield); IR ν_{max}/cm^{-1} (film): 1670, 1149, 1288, 1264, 1174, 1012, 837, 701; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.18 (1H, d, *J* = 2.6 Hz), 7.45 – 7.33 (5H, m), 7.27 (1H, d, *J* = 2.6 Hz), 5.07 (2H, s), 2.55 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.60, 148.16, 135.88, 135.51, 131.01, 128.86, 128.52, 127.64, 122.74, 70.87, 21.79; *m/z* HRMS (DART) found $[M+H]^+$ 234.0693, $C_{13}H_{13}ClNO^+$ requires 234.0686.

5-Bromo-4-phenylpyrimidine (39)



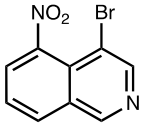
Prepared according to a modified version of general procedure E using 4-phenylpyrimidine (63 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 mL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), and collidine (53 mL, 0.40 mmol). After *N*-bromosuccinimide (71 mg, 0.40 mmol) and trifluoroacetic acid (31 µL, 0.40 mmol) were added, the reaction was stirred at room temperature for 1 hour. Then, ammonium acetate (308 mg, 4.00 mmol) and EtOH (8 mL) were added and the reaction was heated to 60 °C for 2 hours. The crude material was purified by flash chromatography (silica gel: 15% Ether in Hexanes) to provide the title compound as a white solid (41 mg, 0.18 mmol, 44% yield). mp 90 – 92 °C; IR ν_{max}/cm^{-1} (film): 1559, 1437, 1395, 1172, 1017, 787, 743, 694; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.17 (1H, s), 8.93 (1H, s), 7.85 – 7.79 (2H, m), 7.54 – 7.43 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.42, 160.26, 157.02, 136.88, 130.45, 129.39, 128.41, 119.29; *m/z* HRMS (DART) found $[M+H]^+$ 234.9875, $C_{10}H_8BrN_2^+$ requires 234.9871.

5-Chloro-4-phenylpyrimidine (40)



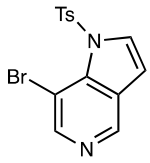
Prepared according to a modified version of general procedure F using 4-phenylpyrimidine (63 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), and collidine (53 mL, 0.40 mmol). After *N*-chlorosuccinimide (53 mg, 0.40 mmol) and trifluoroacetic acid (61 µL, 0.80 mmol) were added, the reaction was stirred at 50 °C for 3 hours. Then, ammonium acetate (308 mg, 4.00 mmol) and EtOH (8 mL) were added and the reaction was heated to 60 °C for 2 hours. The crude material was purified by flash chromatography (silica gel: 15% Ether in Hexanes) to provide the title compound as a white solid (21 mg, 0.11 mmol, 28% yield). mp 84 – 86 °C; IR ν_{max}/cm^{-1} (film): 1558, 1514, 1437, 1395, 1157, 1017, 743, 695; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.14 (1H, s), 8.78 (1H, s), 7.92 – 7.85 (2H, m), 7.55 – 7.49 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.71, 157.77, 156.57, 135.63, 130.63, 129.50, 129.33, 128.50; *m/z* HRMS (DART) found $[M+H]^+$ 191.0368, $C_{10}H_8ClN_2^+$ requires 191.0376.

4-Bromo-5-nitroisoquinoline (41)



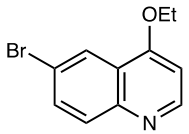
In an 8 mL vial, *N*,*N*-dibenzyl-5-nitro-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinolin-1-amine (201 mg, 0.40 mmol) was dissolved in CH_2Cl_2 (4 mL, 0.1 M). *N*-bromosuccinimide (71 mg, 0.40 mmol) was added, and the reaction was stirred at room temperature for one hour. Then trifluoroacetic acid (61 µL, 0.80 mmol) was added and the reaction was stirred for 24 hours. Flash column chromatography (silica gel: 30% EtOAc in Hexanes) afforded the title compound (86 mg, 0.34 mmol, 85% yield) as an amorphous solid. IR ν_{max}/cm^{-1} (film): 1526, 1401, 1227, 1193, 1141, 1027, 772, 697; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.27 (1H, s), 8.87 (1H, s), 8.21 (1H, d, J = 8.2 Hz), 7.96 (1H, d, J = 7.5 Hz), 7.74 (1H, app t, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.10, 149.62, 147.20, 132.22, 130.54, 127.21, 127.13, 125.54, 113.39; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 253.0, $C_9H_6BrN_2O_2^+$ requires 253.0.

7-Bromo-1-tosyl-1*H*-pyrrolo[3,2-*c*]pyridine (42)



Prepared according to modified version of general procedure E using 1-tosyl-1*H*-pyrrolo[3,2-*c*]pyridine (109 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in CH_2Cl_2), and collidine (53 µL, 0.40 mmol). After warming to room temperature, *N*-bromosuccinimide (71 mg, 0.40 mmol) was added and the reaction was stirred at room temperature for 1 h. Then, trifluoroacetic acid (61 µL, 0.80 mmol) as added and the reaction was stirred at room temperature for 2 hours. Flash column chromatography (silica gel: 30% EtOAc in Hexanes) afforded the title compound (50 mg, 0.14 mmol, 36% yield) as a brown solid. mp 152 – 158 °C; IR ν_{max}/cm^{-1} (film): 1405, 1360, 1170, 1120, 988, 922, 820, 703; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.80 (1H, s), 8.51 (1H, s), 7.94 (1H, d, *J* = 3.8 Hz), 7.71 (2H, d, *J* = 8.4 Hz), 7.29 (2H, d, *J* = 8.1 Hz), 6.80 (1H, d, *J* = 3.8 Hz), 2.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.99, 145.57, 142.98, 137.43, 136.60, 131.19, 130.46, 130.06, 127.46, 105.66, 104.05, 21.82; *m/z* HRMS (DART) found $[M+H]^+$ 350.9850, $C_{14}H_{12}BrN_2O_2S^+$ requires 350.9803.

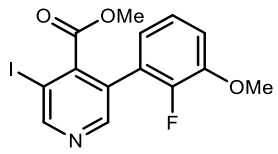
6-Bromo-4-ethoxyquinoline (43)



Prepared according to a modified version of general procedure G using 4-ethoxyquinoline (69 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in CH_2Cl_2), and collidine (53 µL, 0.40 mmol). After warming to room temperature, *N*-bromosuccinimide (71 mg, 0.40 mmol) was added and the reaction was stirred at room temperature for 1 h. Then, trifluoroacetic acid (61 µL, 0.80 mmol) as added and the reaction was stirred at room temperature for 2 hours. Flash column chromatography (silica gel: 50% EtOAc in Hexanes, second column: 2% MeOH in CH_2Cl_2) afforded the title compound (35 mg, 0.14 mmol, 35% yield) as a white solid. mp 83 – 83 °C; IR ν_{max}/cm^{-1} (film): 2921, 2851, 1570, 1350, 1302, 1153, 839, 748; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.70 (1H, br s), 8.36 (1H, d, *J* = 1.7 Hz), 7.88 (1H, d, *J* = 8.9 Hz), 7.74 (1H, dd, *J* = 8.9, 2.1 Hz), 6.71 (1H, d, *J* = 5.0 Hz), 4.24 (2H, q, *J* = 7.0 Hz), 1.57 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.74, 151.83, 148.00, 133.21, 130.85, 124.61, 122.85, 119.55, 101.40, 64.52, 14.58; *m/z* HRMS (DART) found $[M+H]^+$ 252.0077, $C_{11}H_{11}BrNO^+$ requires 252.0024.

9. Halogenation of Complex Heterocycles

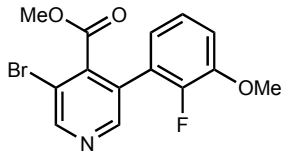
Methyl 3-(2-fluoro-3-methoxyphenyl)-5-iodoisonicotinate (59)



Prepared according to general procedure C using methyl 3-(2-fluoro-3-methoxyphenyl)isonicotinate (105 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 30% Et_2O in hexanes) to provide the title compound as faint yellow amorphous solid (108 mg, 0.28 mmol, 70% yield); IR ν_{max}/cm^{-1} (film): 2950, 2840, 2360, 1735, 1618, 1581, 1527, 1477, 1401, 1325, 1220, 1195, 1176, 877; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.97 (1H, s), 8.57 (1H, d, *J* = 1.5 Hz), 7.11 (1H, td, *J* = 8.0, 1.4 Hz), 7.02 (1H, td, *J* = 8.1, 1.6 Hz), 6.82 (1H, ddd, *J* = 7.9, 6.1, 1.6 Hz), 3.91 (3H, s), 3.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.69, 156.90, 150.14 (d, *J* = 2.4 Hz), 149.50 (d, *J* = 248.4

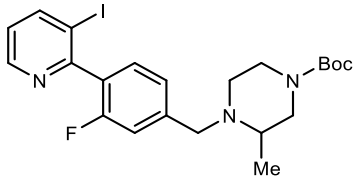
Hz), 148.17, 148.06, 146.22, 130.09, 124.24 (d, J = 4.9 Hz), 122.05 (d, J = 1.4 Hz), 114.15 (d, J = 2.1 Hz), 91.22, 56.44, 52.93; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –137.98; *m/z* HRMS (DART) found $[M+H]^+$ 387.9873, $C_{14}H_{12}FINO_3^+$ requires 387.9846.

Methyl 3-bromo-5-(2-fluoro-3-methoxyphenyl)isonicotinate (60)



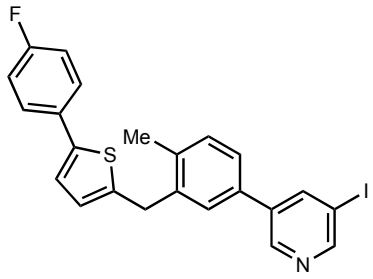
Prepared according to general procedure D using methyl 3-(2-fluoro-3-methoxyphenyl)isonicotinate (105 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The reaction was stirred at 60 °C for 3 hours before quenching. The crude material was purified by flash chromatography (silica gel gradient elution: 0 to 50% EtOAc in Hexanes) to provide the title compound as a clear oil (92 mg, 0.27 mmol, 68% yield); IR ν_{max}/cm^{-1} (film): 2917, 1699, 1430, 1275, 1113, 993, 892, 723, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.79 (1H, s), 8.59 (1H, s), 7.13 (1H, td, J = 8.0, 1.2 Hz), 7.03 (1H, td, J = 7.9, 1.4 Hz), 6.84 (1H, ddd, J = 7.8, 6.4, 1.5 Hz), 3.92 (3H, s), 3.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.65, 151.48, 149.67 (d, J = 2.3 Hz), 149.56 (d, J = 248.7 Hz), 148.16 (d, J = 10.5 Hz), 142.20, 130.13, 124.33, 124.28, 123.83 (d, J = 13.3 Hz), 122.06 (d, J = 1.3 Hz), 117.46, 114.21 (d, J = 2.2 Hz), 56.46, 52.95; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –138.09 (t, J = 7.0 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 339.9994, $C_{14}H_{12}BrFNO_3^+$ requires 339.9985.

Tert-butyl 4-(3-fluoro-4-(3-iodopyridin-2-yl)benzyl)-3-methylpiperazine-1-carboxylate (61)



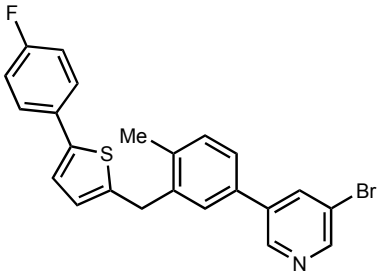
Prepared according to general procedure B using tert-butyl 4-(3-fluoro-4-(pyridin-2-yl)benzyl)-3-methylpiperazine-1-carboxylate (154 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (93 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a faint yellow oil (104 mg, 0.20 mmol, 51% yield); IR ν_{max}/cm^{-1} (film): 2976, 2360, 1679, 1626, 1565, 1426, 1391, 1365, 1080, 1052, 792, 768; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (1H, dd, J = 4.7, 1.5 Hz), 8.24 (1H, dd, J = 8.0, 1.5 Hz), 7.31 (1H, t, J = 7.6 Hz), 7.19 (2H, t, J = 8.4 Hz), 7.03 (1H, dd, J = 8.0, 4.7 Hz), 4.03 (1H, d, J = 13.8 Hz), 3.65 (1H, dd, J = 13.2, 4.2 Hz), 3.25 (1H, d, J = 13.8 Hz), 3.11 (1H, s), 2.89 (1H, s), 2.68 (1H, d, J = 11.6 Hz), 2.47 (1H, ddd, J = 9.1, 6.2, 3.2 Hz), 2.12 (1H, s), 1.46 (9H, s), 1.12 (3H, d, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.34 (d, J = 248.1 Hz), 158.31, 154.89, 148.74, 146.97, 143.00 (d, J = 7.3 Hz), 130.70 (d, J = 3.3 Hz), 129.07 (d, J = 18.6 Hz), 124.43 (d, J = 3.0 Hz), 123.96, 116.07 (d, J = 21.9 Hz), 96.62, 79.71, 57.61, 55.10, 50.62, 44.12, 28.59, 12.26; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –114.18; *m/z* HRMS (DART) found $[M+H]^+$ 512.1207, $C_{22}H_{28}FIN_3O_2^+$ requires 512.1210.

3-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-5-iodopyridine (62)



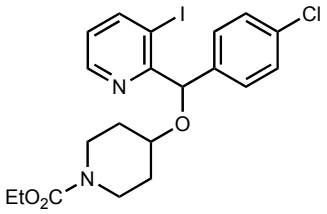
Prepared according to general procedure B using 3-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine (144 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a brown crystalline solid (153 mg, 0.32 mmol, 79% yield). mp 130 – 131 °C; IR ν_{max}/cm^{-1} (film): 3073, 3037, 2916, 1882, 1599, 1566, 1546, 1507, 1466, 1385, 1253, 1052, 952, 903, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83–8.63 (2H, m), 8.15 (1H, t, *J* = 2.0 Hz), 7.49 – 7.30 (4H, m), 7.28 – 7.19 (1H, m), 7.03 – 6.93 (3H, m), 6.67 (1H, d, *J* = 3.5 Hz), 4.15 (2H, s), 2.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.24 (d, *J* = 246.8 Hz), 154.12, 146.71, 142.84, 142.39, 141.91, 139.33, 138.52, 137.34, 134.40, 131.51, 130.85, 130.81, 128.27, 127.26 (d, *J* = 7.9 Hz), 125.98 (d, *J* = 49.0 Hz), 122.83, 115.84 (d, *J* = 21.8 Hz), 93.85, 34.30, 19.4; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –114.93; *m/z* HRMS (DART) found $[M+H]^+$ 486.0199, $C_{23}H_{18}FINS^+$ requires 486.0189.

3-Bromo-5-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine (63)



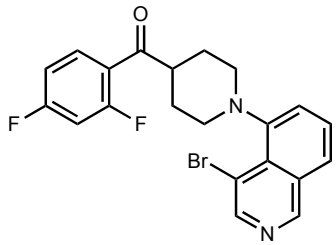
Prepared according to general procedure E using 3-(3-((5-(4-fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)pyridine (144 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes) to provide the title compound as a white solid (120 mg, 0.27 mmol, 68% yield). mp 115 – 117 °C; IR ν_{max}/cm^{-1} (film): 1508, 1422, 1228, 1098, 877, 802, 697, 653; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (1H, d, *J* = 1.8 Hz), 8.63 (1H, d, *J* = 2.1 Hz), 8.00 (1H, app t, *J* = 2.1 Hz), 7.50 – 7.45 (2H, m), 7.43 (1H, d, *J* = 1.6 Hz), 7.39 (1H, dd, *J* = 7.8, 1.9 Hz), 7.30 (1H, d, *J* = 7.8 Hz), 7.06 – 6.98 (3H, m), 6.72 (1H, d, *J* = 3.6 Hz), 4.20 (2H, s), 2.39 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.21 (d, *J* = 246.7 Hz), 149.20, 146.37, 142.78, 141.90, 139.34, 138.13, 137.37, 136.73, 134.33, 131.51, 130.79 (d, *J* = 1.7 Hz), 128.26, 127.23 (d, *J* = 7.9 Hz), 126.22, 125.74, 122.82 (d, *J* = 1.1 Hz), 121.01, 115.82 (d, *J* = 22.0 Hz), 34.28, 19.39; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –114.85 – –114.95 (m); *m/z* HRMS (DART) found $[M+H]^+$ 438.0342, $C_{23}H_{18}BrFNS^+$ requires 438.0327.

Ethyl 4-((4-chlorophenyl)(3-iodopyridin-2-yl)methoxy)piperidine-1-carboxylate (64)



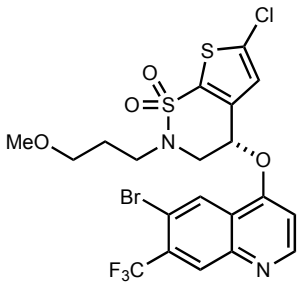
Prepared according to general procedure B using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (150 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 25% EtOAc in Hexanes) to provide the title compound as a brown oil (105 mg, 0.21 mmol, 53% yield); IR ν_{max}/cm^{-1} (film): 2928, 1687, 1433, 1228, 1085, 1006, 908, 794, 727; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 4.5 Hz), 8.10 (1H, d, *J* = 8.0 Hz), 7.44 (2H, d, *J* = 8.4 Hz), 7.27 (2H, d, *J* = 8.4 Hz), 6.91 (1H, dd, *J* = 8.0, 4.6 Hz), 6.06 (1H, s), 7.10 (2H, q, *J* = 7.1 Hz), 3.85 – 3.70 (2H, m), 3.60 – 3.53 (1H, m), 3.20 – 3.05 (2H, m), 1.90 – 1.60 (4H, m), 1.23 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.09, 155.56, 149.36, 147.60, 138.83, 133.55, 128.54, 128.54, 124.20, 95.31, 81.31, 73.33, 61.31, 41.27, 31.50, 31.04, 14.77; *m/z* HRMS (DART) found $[M+H]^+$ 501.0424, $C_{20}H_{23}ClIN_2O_3^+$ requires 501.0442.

3-(3-((5-(4-Fluorophenyl)thiophen-2-yl)methyl)-4-methylphenyl)-5-iodopyridine (65)



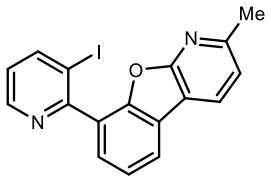
Prepared according to a procedure G using (2,4-difluorophenyl)(1-(isoquinolin-5-yl)piperidin-4-yl)methanone (141 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 µL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (64 µL, 0.80 mmol). The crude material was purified by flash chromatography (silica gel: 5% acetone in hexanes) to provide the title compound as a faint brown oil (62 mg, 0.14 mmol, 36% yield); IR ν_{max}/cm^{-1} (film): 2951, 2803, 2360, 1738, 1680, 1607, 1572, 1557, 1494, 1422, 1298, 1171, 996, 787, 662; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.07 (1H, s), 8.68 (1H, s), 7.96 – 7.81 (1H, m), 7.69 (1H, dd, *J* = 8.1, 1.3 Hz), 7.61 – 7.44 (2H, m), 7.04 – 6.94 (1H, m), 6.89 (1H, ddd, *J* = 11.1, 8.6, 2.4 Hz), 3.40 (2H, d, *J* = 12.2 Hz), 3.31 – 3.20 (1H, m), 2.77 (2H, td, *J* = 12.0, 2.3 Hz), 2.39 – 2.16 (2H, m), 2.00 (2H, dt, *J* = 12.9, 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.88 (d, *J* = 4.9 Hz), 152.48, 149.88, 147.83, 133.23 (dd, *J* = 10.4, 4.6 Hz), 132.27, 129.82, 128.02, 124.02, 122.06, 115.37, 112.87 – 112.36 (m), 105.85 – 104.13 (m); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –102.23 (dq, *J* = 11.9, 7.7 Hz), –106.62 (q, *J* = 10.8 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 431.0550, $C_{21}H_{18}BrF_2N_2O^+$ requires 431.0571.

(*S*)-4-((6-Bromo-7-(trifluoromethyl)quinolin-4-yl)oxy)-6-chloro-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine 1,1-dioxide (66)



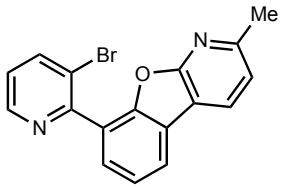
Prepared according to a modified version of general procedure G using (S)-6-chloro-2-(3-methoxypropyl)-4-((7-(trifluoromethyl)quinolin-4-yl)oxy)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine 1,1-dioxide (203 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 µL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel gradient elution: 3% MeOH in CHCl2 to 6% MeOH in CH_2Cl_2 followed silica gel gradient elution: 4% acetone in CH_2Cl_2 to 10% acetone in CH_2Cl_2) to provide the title compound as amorphous white solid (129 mg, 0.21 mmol, 53% yield); IR ν_{max}/cm^{-1} (film): 3022, 2360, 1591, 1565, 1484, 1339, 1238, 1198, 1090, 1068, 1047, 966 932, 907, 816; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, d, *J* = 5.1 Hz), 8.44 (1H, s), 8.38 (1H, s), 7.00 – 6.88 (2H, m), 5.57 (1H, d, *J* = 3.4 Hz), 4.43 (1H, dd, *J* = 16.0, 4.2 Hz), 4.14 (1H, dd, *J* = 16.1, 2.8 Hz), 3.67 (1H, dt, *J* = 13.9, 7.1 Hz), 3.44 – 3.29 (3H, m), 3.14 (3H, s), 1.81 (2H, ddd, *J* = 11.7, 5.8, 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.08, 152.85, 147.67, 137.55, 137.05, 134.87, 131.68 (q, *J* = 31.7 Hz), 130.15 (q, *J* = 5.7 Hz), 128.21, 125.71, 123.79, 122.29 (d, *J* = 203.1 Hz), 115.93, 102.93, 69.05, 66.61, 58.73, 49.73, 47.87, 29.30; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.88; *m/z* HRMS (DART) found $[M+H]^+$ 586.9505, $C_{20}H_{18}BrClF_3N_2O_4S_2^+$ requires 586.9512.

8-(3-Iodopyridin-2-yl)-2-methylbenzofuro[2,3-b]pyridine (67)



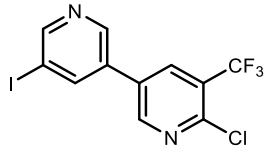
Prepared according to general procedure B using 2-methyl-8-(pyridin-2-yl)benzofuro[2,3-b]pyridine (104 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel gradient elution: 10% EtOAc in hexanes to 25% EtOAc in hexanes) to provide the title compound as an off-white solid (107 mg, 0.29 mmol, 72% yield). mp 198 – 200 °C; IR ν_{max}/cm^{-1} (film): 3053, 2920, 2360, 1942, 1628, 1596, 1578, 1562, 1493, 1360, 1307, 1221, 1145, 1033, 935, 903, 843; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, dd, *J* = 4.7, 1.5 Hz), 8.27 (1H, dd, *J* = 8.0, 1.5 Hz), 8.16 (1H, d, *J* = 7.7 Hz), 7.96 (1H, dd, *J* = 7.7, 1.4 Hz), 7.55 (1H, dd, *J* = 7.6, 1.3 Hz), 7.46 (1H, t, *J* = 7.6 Hz), 7.19 (1H, d, *J* = 7.8 Hz), 7.06 (1H, dd, *J* = 8.0, 4.7 Hz), 2.65 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.14, 158.27, 156.77, 151.26, 148.76, 147.08, 130.08, 128.27, 127.58, 124.08, 123.30, 123.18, 121.53, 119.00, 113.83, 96.55, 24.61; *m/z* HRMS (DART) found $[M+H]^+$ 387.0002, $C_{17}H_{12}IN_2O^+$ requires 386.9994.

8-(3-Bromopyridin-2-yl)-2-methylbenzofuro[2,3-*b*]pyridine (68)



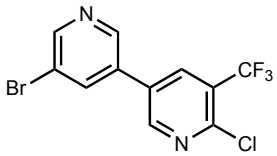
Prepared according to general procedure D using 2-methyl-8-(pyridin-2-yl)benzofuro[2,3-*b*]pyridine (104 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The reaction was stirred at 60 °C for 24 hours before quenching. ^{1}H NMR of the crude material showed >20:1 selectivity for the desired product over the 5-bromo isomer. The crude material was purified by flash chromatography (silica gel gradient elution: 20 to 30% EtOAc in Hexanes) to provide the title compound as an off-white solid (99 mg, 0.29 mmol, 73% yield). mp 175 – 178 °C; IR ν_{max}/cm^{-1} (film): 1572, 1416, 1177, 1013, 934, 761, 745, 643; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (1H, dd, *J* = 4.7, 1.4 Hz), 8.13 (1H, d, *J* = 7.7 Hz), 8.02 (1H, dd, *J* = 8.1, 1.4 Hz), 7.95 (1H, dd, *J* = 7.7, 1.1 Hz), 7.59 (1H, dd, *J* = 7.6, 1.1 Hz), 7.45 (1H, app t, *J* = 7.6 Hz), 7.22 (1H, dd, *J* = 8.1, 4.7 Hz), 7.17 (1H, d, *J* = 7.8 Hz), 2.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.10, 156.70, 154.71, 151.48, 148.13, 140.82, 130.02, 128.39, 125.09, 124.11, 123.25, 123.11, 121.87, 121.57, 118.94, 113.73, 24.57; *m/z* HRMS (DART) found $[M+H]^+$ 339.0121, $C_{17}H_{12}BrN_2O^+$ requires 339.0133.

6-Chloro-5'-iodo-5-(trifluoromethyl)-3,3'-bipyridine (69)



Prepared according to general procedure C using 6-chloro-5-(trifluoromethyl)-3,3'-bipyridine (103 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white solid (109 mg, 0.28 mmol, 71% yield). mp 161 – 162 °C; IR ν_{max}/cm^{-1} (film): 3074, 3038, 1885, 1601, 1565, 1546, 1465, 1378, 1236, 1224, 1052, 869; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, d, *J* = 2.0 Hz), 8.78 – 8.73 (2H, m), 8.22 (1H t, *J* = 2.1 Hz), 8.15 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.44, 150.30, 149.28 (d, *J* = 1.6 Hz), 146.51, 142.67, 135.12 (q, *J* = 4.8 Hz), 132.90, 131.35, 127.91 – 124.83 (m), 122.03 (q, *J* = 273.3 Hz), 93.99; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –63.70; *m/z* HRMS (DART) found $[M+H]^+$ 384.9242, $C_{11}H_6ClF_3IN_2^+$ requires 384.9216.

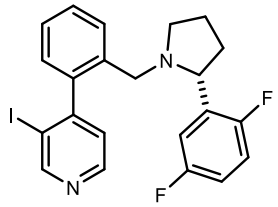
5'-Bromo-6-chloro-5-(trifluoromethyl)-3,3'-bipyridine (70)



Prepared according to general procedure E using 6-chloro-5-(trifluoromethyl)-3,3'-bipyridine (103 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), and trifluoroacetic acid (31 µL, 0.40 mmol). The reaction was stirred at room temperature for 4 hours before quenching. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in Hexanes) to provide the title compound as a white solid (92 mg, 0.27

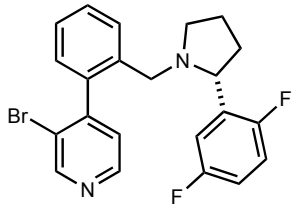
mmol, 68% yield). mp 140 – 143 ˚C; IR ν_{max}/cm^{-1} (film): 3044, 1566, 1431, 1341, 1135, 1054, 893, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 – 8.72 (3H, m), 8.16 (1H, d, *J* = 2.0 Hz), 8.03 (1H, app t, *J* = 2.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.51, 150.31 (q, *J* = 0.9 Hz), 149.29 (q, *J* = 1.3 Hz), 146.14, 137.05, 135.14 (q, *J* = 4.8 Hz), 132.58, 131.30, 125.88 (q, *J* = 33.3 Hz), 121.97 (q, *J* = 269.1 Hz), 121.49; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –63.74; *m/z* HRMS (DART) found $[M+H]^+$ 338.9357, $C_{11}H_6BrClF_3N_2^+$ requires 338.9335.

(R)-4-(2-((2-(2,5-Difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)-3-iodopyridine (71)



Prepared according to general procedure B using (R)-4-(2-((2-(2,5-difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)pyridine (140 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a colorless oil as a 1:1 mixture of diastereomers (143 mg, 0.30 mmol, 75% yield); IR ν_{max}/cm^{-1} (film):, 2360, 1572, 1489, 1461, 1426, 1395, 1025, 840, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, s), 8.97 (1H, s), 8.51 (1H, d, *J* = 4.8 Hz), 8.44 (1H, d, *J* = 4.9 Hz), 7.68 (1H, d, *J* = 7.8 Hz), 7.56 (1H, dd, *J* = 7.7, 1.4 Hz), 7.43 (2H, dtd, *J* = 9.2, 7.6, 1.4 Hz), 7.32 (3H, tdd, *J* = 7.5, 3.0, 1.3 Hz), 7.11 (1H, dd, *J* = 4.8, 0.7 Hz), 7.07 (1H, d, *J* = 4.8 Hz), 7.03 – 6.95 (3H, m), 6.93 – 6.77 (6H, m), 3.71 (1H, d, *J* = 13.1 Hz), 3.65 – 3.51 (4H, m), 3.11 (1H, ddd, *J* = 9.8, 7.4, 2.7 Hz), 2.99 (1H, ddd, *J* = 9.3, 7.4, 2.1 Hz), 2.95 – 2.82 (2H, m), 2.27 – 2.11 (4H, m), 2.02 (1H, td, *J* = 9.3, 7.8 Hz), 1.91 – 1.63 (3H, m), 1.56 (2H, dddd, *J* = 13.1, 10.2, 8.0, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.13 (ddd, *J* = 241.7, 7.2, 2.1 Hz), 157.20 (d, *J* = 6.0 Hz), 157.06 (ddd, *J* = 241.0, 6.5, 2.4 Hz), 154.30 (d, *J* = 15.6 Hz), 148.36, 141.55, 141.06, 132.79 (dd, *J* = 15.3, 6.9 Hz), 129.43, 129.03 (d, *J* = 4.1 Hz), 128.90 (d, *J* = 5.2 Hz), 127.22, 127.05, 125.82, 124.90, 116.33 (dd, *J* = 8.5, 5.9 Hz), 116.08 (dd, *J* = 8.6, 6.0 Hz), 114.97 – 114.01 (m, 2C), 100.49, 99.29, 61.66, 61.56, 56.40, 56.14, 54.02, 53.94, 33.63, 33.57, 23.02, 22.95; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –118.00 (ddtd, *J* = 138.2, 17.3, 8.4, 4.7 Hz), –126.20 (dddt, *J* = 79.9, 18.6, 9.6, 4.9 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 477.0654, $C_{22}H_{20}F_2IN_2^+$ requires 477.0639.

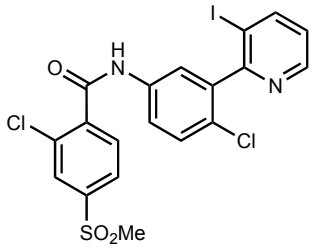
(*R*)-3-Bromo-4-(2-((2-(2,5-difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)pyridine (72)



Prepared according to general procedure D using (*R*)-4-(2-((2-(2,5-difluorophenyl)pyrrolidin-1-yl)methyl)phenyl)pyridine (140 mg, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (71 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and EtOH (8 mL). The reaction was stirred at 60 °C for 24 hours before quenching. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in Hexanes, second plug: 0 to 5% MeOH in CH_2Cl_2) to provide the title compound as a yellow oil as a 1:1 mixture of diastereomers (104 mg, 0.24 mmol, 60% yield); IR ν_{max}/cm^{-1} (film): 2907, 1699, 1431, 1343, 1214, 1135, 892, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H,s), 8.75 (1H, s), 8.51 (1H, d, *J* = 4.8 Hz), 8.46 (1H, d, *J* = 4.8 Hz), 7.66 (1H, d, *J* = 7.7 Hz), 7.57 (1H, d, *J* = 7.7 Hz), 7.42 (2H, qd, *J* = 7.5, 1.1 Hz), 7.31 (2H, app t, *J* = 7.5 Hz), 7.11 (1H d, *J* = 4.8 Hz), 7.08 (1H, d, *J* = 4.8 Hz), 7.04 (2H, app t, *J* = 7.6 Hz), 7.01 – 6.78 (6H, m), 3.75 (1H, d, *J* =

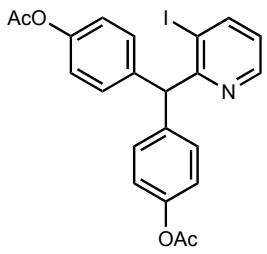
13.1 Hz), 3.65 – 3.55 (3H, m), 3.07 (1H, ddd, *J* = 9.5, 7.1, 2.4 Hz), 2.99 – 2.93 (2H, m), 2.89 (1H, d, *J* = 13.3 Hz), 2.25 – 2.08 (3H, m), 2.01 (1H, q, *J* = 8.2 Hz), 1.87 – 1.63 (4H, m), 1.62 – 1.50 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.05 (qt, *J* = 241.4, 2.3 Hz), 156.94 (qdd, *J* = 241.1, 4.7, 2.3 Hz), 151.97 (q, *J* = 6.6 Hz), 150.03 (d, *J* = 18.9 Hz), 147.88 (d, *J* = 4.6 Hz), 138.07 (d, *J* = 32.5 Hz), 136.87 (d, *J* = 10.0 Hz), 132.76 (ddd, *J* = 15.1, 6.9, 5.7 Hz), 129.88, 129.38, 128.94 (d, *J* = 8.7 Hz), 128.84 (d, *J* = 4.1 Hz), 126.95 (d, *J* = 11.9 Hz), 126.16, 125.33, 123.07, 121.80, 116.09 (ddd, *J* = 25.2, 8.6, 2.3 Hz), 114.44 (dd, *J* = 24.5, 8.7 Hz), 114.32 (ddd, *J* = 24.5, 5.2, 2.1 Hz), 61.65, 61.45, 56.23, 55.92, 53.76, 53.62, 33.95, 33.53, 22.90, 22.85; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –118.00 – –118.35 (m), –126.10 – –126.43 (m); *m/z* HRMS (DART) found $[M+H]^+$ 429.0784, $C_{22}H_{20}BrF_2N_2^+$ requires 429.0778.

2-Chloro-*N*-(4-chloro-3-(3-iodopyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (73)



Prepared according to general procedure B using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (126 mg, 0.30 mmol), EtOAc (6 mL, 0.05 M), Tf_2O (50 µL, 0.30 mmol), dibenzylamine (69 µL, 0.36 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (67 mg, 0.30 mmol), and trimethoxybenzene (51 mg, 0.30 mmol) ammonium acetate (231 mg, 3.00 mmol), and EtOH (6 mL). The crude material was purified by flash chromatography (silica gel: 5% Acetone in CH_2Cl_2) to provide the title compound as a white solid (71 mg, 0.13 mmol, 43% yield). mp 210 – 213 °C; IR ν_{max}/cm^{-1} (film): 2923, 1669, 1444, 1311, 1154, 1017, 804, 678; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 10.95 (1H, s), 8.66 (1H, d, *J* = 4.5 Hz), 8.41 (1H, d, *J* = 7.9 Hz), 8.13 (1H, s), 8.01 (1H, d, *J* = 8.1 Hz), 7.94 (1H, d, *J* = 8.0 Hz), 7.78 – 7.70 (2H, m), 7.58 (1H, d, *J* = 8.4 Hz), 7.24 (1H, dd, *J* = 7.9, 4.7 Hz), 3.35 (3H, s); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 163.86, 159.51, 148.52, 146.55, 143.13, 141.63, 140.80, 137.45, 130.95, 129.97, 129.73, 128.09, 126.35, 125.91, 124.73, 121.04, 120.94, 96.80, 43.08; *m/z* HRMS (DART) found $[M+H]^+$ 546.9145, $C_{19}H_{14}Cl_2IN_2O_3S^+$ requires 546.9147

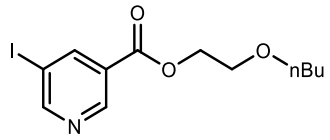
((3-Iodopyridin-2-yl)methylene)bis(4,1-phenylene) diacetate (74)



Prepared according to general procedure B (except after addition of NH_4OAc, the reaction was stirred for 1 hour at room temperature and washed 3x with H_2O (10 mL), the organic layer was then diluted with EtOH and heated to 60 °C for 1 hour) using pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (145 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and ethanol (8 mL). The crude material was purified by flash chromatography (silica gel: 30 to 45% Et_2O in hexanes) followed by a second flash chromatography (silica gel: 2% Et_2O in CH_2Cl_2) to provide the title compound as a faint yellow solid (109 mg, 0.22 mmol, 56% yield). mp 63 – 65 °C; IR ν_{max}/cm^{-1} (film): 3035, 2923, 2852, 2032, 1747, 1672, 1594, 1563, 1547, 1501, 1458, 1406, 1345, 1313, 1100, 1068, 1058, 942, 874, 773, 747, 719, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, dd, *J* = 4.6, 1.5 Hz), 8.11 (1H, dd, *J* = 8.0, 1.6 Hz), 7.26 (4H, d, *J* = 8.4 Hz), 7.06 – 6.97 (4H, m), 6.85 (1H, dd, *J* = 8.0, 4.6 Hz), 6.09 (1H, s), 2.28 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.59,

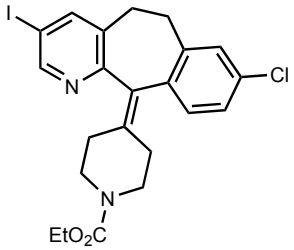
162.81, 149.47, 149.09, 147.42, 139.51, 130.57, 123.10, 121.42, 98.10, 58.74, 21.31; *m/z* HRMS (DART) found $[M+H]^+$ 488.0369, $C_{22}H_{19}INO_4^+$ requires 488.0359.

2-Butoxyethyl 5-iodonicotinate (75)



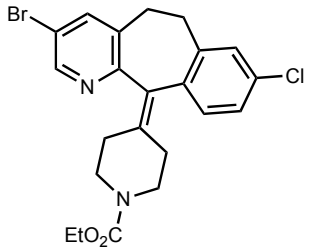
Prepared according to general procedure C (except after addition of *N*-iodosuccinimide and TFA, the reaction was heated to 50 ºC) using 2-butoxyethyl nicotinate (89 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (32 µL, 0.40 mmol). The crude material was purified by flash chromatography (silica gel: 20% Et_2O in hexanes) to provide the title compound as a colorless oil (82 mg, 0.24 mmol, 59% yield); IR ν_{max}/cm^{-1} (film): 3973, 3037, 2956, 2866, 2360, 1882, 1724, 1599, 1565, 1546, 1507, 1466, 1385, 1310, 1035, 952, 932, 783, 665; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.16 (1H, d, J = 1.9 Hz), 8.99 (1H, d, J = 2.2 Hz), 8.62 (1H, t, J = 2.0 Hz), 4.53 – 4.46 (2H, m), 3.79 – 3.72 (2H, m), 3.51 (2H, t, J = 6.6 Hz), 1.58 (2H, dq, J = 8.5, 6.7 Hz), 1.45 – 1.31 (2H, m), 0.92 (3H, t, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.13, 159.54, 149.43, 145.34, 127.74, 92.87, 71.38, 68.46, 65.08, 31.77, 19.39, 14.02; *m/z* HRMS (DART) found $[M+H]^+$ 350.0270, $C_{12}H_{17}INO_3^+$ requires 350.0253.

Ethyl 4-(8-chloro-3-iodo-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (76)



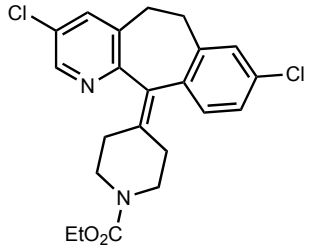
Ethyl 4-((6*Z*,7*Z*)-2-chloro-7-((*E*)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl)sulfonyl)imino)-6,7,8,9-tetra hydro-5*H*-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate (213 mg, 0.30 mmol) and CH_2Cl_2 (3 mL, 0.1 M) were added to an 8 mL vial and subsequently cooled to 0 °C. *N*-iodosuccinimide (74 mg, 0.33 mmol) and trifluoroacetic acid (25 µL, 0.33 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir at room temperature for 2 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in Hexanes, second column: 15% Ether in Hexanes) to provide the title compound as a white solid (96 mg, 0.19 mmol, 63% yield). mp 165 – 167 ˚C; IR ν_{max}/cm^{-1} (film): 2906, 1702, 1431, 1215, 993, 890, 820, 664; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 1.2 Hz), 7.77 (1H, d, *J* = 1.0 Hz), 7.18 – 7.12 (2H, m), 7.08 (1H, d, *J* = 8.0 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.90 – 3.70 (2H, m), 3.41 – 3.23 (2H, m), 3.19 – 3.10 (2H, m), 2.85 – 2.73 (2H, m), 2.47 (1H, ddd, *J* = 14.0, 9.4, 4.6 Hz), 2.39 – 2.25 (3H, m), 1.25 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.83, 155.57, 152.60, 145.66, 139.38, 138.48, 137.47, 135.75, 133.28, 130.60, 129.05, 126.50, 91.47, 61.49, 44.87, 44.85, 31.51, 31.40, 30.92, 30.69, 14.81; *m/z* HRMS (DART) found $[M+H]^+$ 509.0491, $C_{22}H_{23}ClIN_2O_2^+$ requires 509.0493.

Ethyl 4-(3-bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (77)



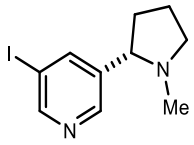
Ethyl 4-((6*Z*,7*Z*)-2-chloro-7-((*E*)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl)sulfonyl)imino)-6,7,8,9-tetra hydro-5*H*-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate (213 mg, 0.30 mmol) and CH_2Cl_2 (3 mL, 0.1 M) were added to an 8 mL vial and subsequently cooled to 0 °C. *N*-bromosuccinimide (59 mg, 0.33 mmol) and trifluoroacetic acid (25 µL, 0.33 mmol) were added, the cooling bath was removed, and the reaction was allowed to stir at room temperature for 2 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in Hexanes, second column: 30% Ether in Hexanes with 1% Et_3N) to provide the title compound as a white solid (85 mg, 0.18 mmol, 61% yield). mp 140 – 144 °C; IR ν_{max}/cm^{-1} (film): 2906, 1701, 1432, 1215, 1109, 993, 891, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (1H, d, *J* = 2.0 Hz), 7.58 (1H, d, *J* = 2.0 Hz), 7.18 – 7.12 (2H, m), 7.08 (1H, d, *J* = 8.1 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.85 – 3.70 (2H, m), 3.42 – 3.24 (2H, m), 3.20 – 3.10 (2H, m), 2.88 – 2.73 (2H, m), 2.47 (1H, ddd, *J* = 13.9, 9.3, 4.5 Hz), 2.39 – 2.23 (3H, m), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.54, 155.48, 147.65, 140.01, 139.35, 138.49, 137.48, 135.32, 133.25, 133.23, 130.57, 129.04, 126.48, 118.93, 61.46, 44.86, 44.83, 31.58, 31.39, 30.90, 30.67, 14.79; *m/z* HRMS (DART) found $[M+H]^+$ 463.0611, $C_{22}H_{23}BrClN_2O_2^+$ requires 463.0611.

Ethyl 4-(3,8-dichloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (78)



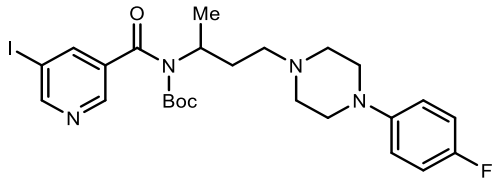
Ethyl 4-((6*Z*,7*Z*)-2-chloro-7-((*E*)-3-(dibenzylamino)allylidene)-6-(((trifluoromethyl)sulfonyl)imino)-6,7,8,9-tetra hydro-5*H*-benzo[7]annulen-5-ylidene)piperidine-1-carboxylate (213 mg, 0.30 mmol) and CH_2Cl_2 (3 mL, 0.1 M) were added to an 8 mL vial and subsequently cooled to 0 °C. *N*-chlorosuccinimide (44 mg, 0.33 mmol) and trifluoroacetic acid (25 µL, 0.33 mmol) were added, the cooling bath was removed, and the reaction was stirred at room temperature for 24 hours before quenching. The crude material was purified by flash chromatography (silica gel gradient elution: 0 to 50% EtOAc in Hexanes) to provide the title compound as a slightly yellow solid (54 mg, 0.13 mmol, 43% yield). mp 134 – 136 °C; IR ν_{max}/cm^{-1} (film): 2907, 1700, 1430, 1215, 1100, 993, 893, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.35 (1H, d, *J* = 2.2 Hz), 7.43 (1H, d, *J* = 2.2 Hz), 7.18 – 7.12 (2H, m), 7.11 (1H, d, *J* = 8.1 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.88 – 3.70 (2H, m), 3.43 – 3.25 (2H, m), 3.20 – 3.10 (2H, m), 2.90 – 2.73 (2H, m), 2.47 (1H, ddd, *J* = 13.9, 9.3, 4.5 Hz), 2.40 – 2.23 (3H, m), 1.25 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.56, 155.12, 145.48, 139.37, 138.53, 137.57, 137.24, 134.84, 134.84, 133.26, 133.22, 130.58, 130.32, 129.05, 126.49, 61.48, 44.88, 44.83, 31.61, 31.40, 30.91, 30.67, 14.80; *m/z* HRMS (DART) found $[M+H]^+$ 417.1141, $C_{22}H_{23}Cl_2N_2O_2^+$ requires 417.1137.

(*S*)-3-Iodo-5-(1-methylpyrrolidin-2-yl)pyridine (79)



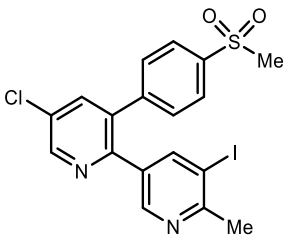
Prepared according to general procedure C (except using CH_2Cl_2 as the solvent and 3 eq TFA instead of 1 eq) using (s)-3-(1-methylpyrrolidin-2-yl)pyridine (64 mL, 0.40 mmol), CH_2Cl_2 (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in CH_2Cl_2), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (96 µL, 1.20 mmol). The crude material was purified by flash chromatography (silica gel: 3% MeOH in CH_2Cl_2) followed by a second flash chromatography (2% Et_3N and 40% EtOAc in hexanes) to provide the title compound as a colorless oil (58 mg, 0.20 mmol, 51% yield); IR ν_{max}/cm^{-1} (film): 2924, 2257, 1720, 1667, 1594, 1566, 1547, 1502, 1455, 1428, 1313, 1266, 1177, 1105, 1072, 961, 918, 874, 774, 666; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.64 (1H, d, *J* = 2.1 Hz), 8.39 (1H, d, *J* = 1.9 Hz), 7.99 (1H, t, *J* = 2.0 Hz), 3.17 (1H, ddd, *J* = 9.6, 7.8, 2.2 Hz), 2.99 (1H, t, *J* = 8.3 Hz), 2.26 (1H, q, *J* = 9.1 Hz), 2.12 (3H, s), 1.99 – 1.56 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.76, 148.12, 143.19, 141.44, 93.98, 68.35, 57.08, 40.57, 35.47, 22.85; *m/z* HRMS (DART) found $[M+H]^+$ 289.0215, $C_{10}H_{14}IN_2^+$ requires 289.0202.

Tert-butyl (4-(4-(4-fluorophenyl)piperazin-1-yl)butan-2-yl)(5-iodonicotinoyl)carbamate (80)



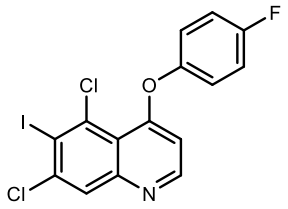
Prepared according to general procedure C (except using 2 eq TFA instead of 1 eq) using tert-butyl (4-(4-(4-fluorophenyl)piperazin-1-yl)butan-2-yl)(nicotinoyl)carbamate (184 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (77 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), and trifluoroacetic acid (64 µL, 0.80 mmol). The crude material was purified by flash chromatography (silica gel: 70% Et_2O in hexanes) to provide the title compound as a white solid (79 mg, 0.14 mmol, 34% yield). mp 63 – 65 °C; IR ν_{max}/cm^{-1} (film): 3037, 2924, 2360, 2257, 2031, 1720, 1667, 1594, 1566, 1547, 1502, 1455, 1369, 1266, 1117, 1057, 1036, 918, 903, 893, 773, 666; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, d, *J* = 2.1 Hz), 8.67 (1H, d, *J* = 2.0 Hz), 8.14 (1H, t, *J* = 2.1 Hz), 7.15 – 6.78 (4H, m), 4.65 (1H, dt, *J* = 8.3, 6.5 Hz), 3.10 (4H, t, *J* = 5.0 Hz), 2.60 (4H, q, *J* = 3.8 Hz), 2.56 – 2.35 (2H, m), 2.24 (1H, ddd, *J* = 17.1, 8.7, 4.4 Hz), 1.92 (1H, dt, *J* = 13.9, 7.5 Hz), 1.43 (3H, d, *J* = 6.8 Hz), 1.22 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.79, 157.86, 157.52, 157.31 (d, *J* = 238.7 Hz), 152.93, 148.07, 146.67, 142.97, 135.75, 117.95 (d, *J* = 7.6 Hz), 115.62 (d, *J* = 22.0 Hz), 92.62, 84.12, 55.86, 53.41, 52.00, 50.20, 31.57, 29.85, 27.74, 19.04; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -124.66; *m/z* HRMS (DART) found $[M+H]^+$ 583.1583, $C_{25}H_{33}FIN_4O_3^+$ requires 583.1581.

5-Chloro-5'-iodo-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (81)



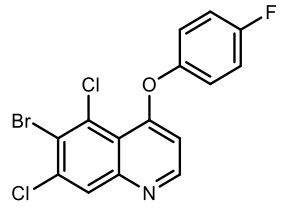
Prepared according to general procedure B (except no trimethoxybenzene was added prior to addition of NH_4OAc and the reaction was heated for 18 hours at 60 °C after the addition) using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (143 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.48 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), ammonium acetate (308 mg, 4.00 mmol), and ethanol (8 mL). The crude material was purified by flash chromatography (silica gel: 3% acetone in CH_2Cl_2) to provide the title compound as an amorphous colorless solid (83 mg, 0.17 mmol, 43% yield); IR ν_{max}/cm^{-1} (film): 2924, 1581, 1423, 1312, 1150, 956, 905, 767, 727, 647; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, d, J = 2.3 Hz), 8.23 (1H, d, J = 1.6 Hz), 8.14 (1H, d, J = 1.8 Hz), 7.95 (2H, d, J = 8.3 Hz), 7.75 (1H, d, J = 2.3 Hz), 7.42 (2H, d, J = 8.3 Hz), 3.10 (3H, s), 2.71 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.26, 150.43, 148.89, 148.74, 147.43, 143.50, 140.69, 138.15, 135.59, 132.99, 131.76, 130.49, 128.26, 95.94, 44.76, 28.83; *m/z* HRMS (DART) found $[M+H]^+$ 484.9538, $C_{18}H_{15}ClIN_2O_2S^+$ requires 484.9587

5,7-Dichloro-4-(4-fluorophenoxy)-6-iodoquinoline (82)



Prepared according to a modified version of general procedure G (except using using trimethoxybenzene to quench the *N*-iodosuccinimide, 3 eq trifluoroacetic acid, and heating to 80 °C overnight for the rearomatization step) using 5,7-dichloro-4-(4-fluorophenoxy)quinoline (123 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 µL, 0.40 mmol), *N*-iodosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), and trifluoroacetic acid (96 µL, 1.20 mmol). The crude material was purified by flash chromatography (silica gel: 10% Et_2O in hexanes) to provide the title compound as white crystalline solid (85 mg, 0.20 mmol, 49% yield). mp 140 – 143 °C; IR ν_{max}/cm^{-1} (film): 3065, 2923, 2029, 1593, 1543, 1496, 1453, 1365, 1230, 1150, 1084, 1036, 780, 692, 657; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, d, J = 5.1 Hz), 8.18 (1H, s), 7.22 – 7.06 (4H, m), 6.66 (1H, d, J = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.30 (d, J = 244.8 Hz), 152.82, 150.87, 150.00, 149.97, 140.52, 129.82, 127.99, 122.56, 122.44 (d, J = 8.5 Hz), 117.34 (d, J = 23.6 Hz), 107.75, 107.43; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –116.60; *m/z* HRMS (DART) found $[M+H]^+$ 433.9029, $C_{15}H_8Cl_2FINO^+$ requires 433.9012.

5,7-Dichloro-4-(4-fluorophenoxy)-6-bromoquinoline (83)

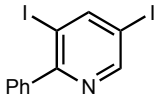


Prepared according to a modified version of general procedure G (except using trimethoxybenzene to quench the *N*-bromosuccinimide, and 3 eq trifluoroacetic acid instead of 2 eq, and heating to 80 °C overnight for the rearomatization step) using 5,7-dichloro-4-(4-fluorophenoxy)quinoline (123 mg, 0.40 mmol), EtOAc (4 mL, 0.1 M), Tf_2O (67 µL, 0.40 mmol), dibenzylamine (92 µL, 0.40 mmol, 1.0 M in EtOAc), collidine (53 mL, 0.40 mmol), *N*-bromosuccinimide (90 mg, 0.40 mmol), trimethoxybenzene (67 mg, 0.40 mmol), and trifluoroacetic acid (96 µL, 1.20 mmol). The crude material was purified by flash chromatography (silica gel: 10% Et_2O in hexanes) to provide the title compound as white crystalline solid (84 mg, 0.22 mmol, 54% yield). mp 128 – 131 °C; IR ν_{max}/cm^{-1} (film): 3039, 2922, 2360, 2031, 1746, 1594, 1547, 1497, 1458, 1370, 1276, 1227, 1036, 952, 904, 893, 782, 666; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, s), 8.18 (1H, s), 7.23 – 7.07 (4H, m), 6.66 (1H, d, J = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.89, 160.32 (d, J = 245.0 Hz), 152.68, 149.97, 149.94, 136.92, 131.14, 129.24, 125.37, 122.56, 122.46 (d, J = 8.4 Hz), 117.35 (d,

J = 23.6 Hz), 107.57; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –116.56; *m/z* HRMS (DART) found $[M+H]^+$ 387.9124, $C_{15}H_8BrCl_2FNO^+$ requires 387.9130.

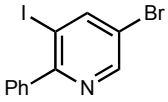
10. Synthesis of Dihalogenated Pyridines

3,5-Diiodo-2-phenylpyridine (52)



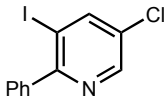
An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-5-(dibenzylamino)-2-iodo-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (244 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-iodosuccinimide (99 mg, 0.44 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was first subjected to flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes). The resulting mixture was then dissolved in Et_2O and 1.0 mmol of TfOH was added to precipitate out the TfOH salt at -78 °C. After filtration, the solid was dissolved in CH_2Cl_2 and washed 3 times with a saturated aqueous Na_2CO_3 solution. Drying with $MgSO_4$ and concentrating in vacuo provided the title compound as a white solid (138 mg, 0.34 mmol, 85% yield). mp 100 – 103 °C; IR ν_{max}/cm^{-1} (film): 3060, 1420, 1354, 1102, 998, 892, 781, 735, 633; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, J = 1.7 Hz), 8.58 (1H, d, J = 1.7 Hz), 7.60 – 7.55 (2H, m) 7.50 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.44, 154.62, 154.45, 140.90, 129.20, 129.11, 128.19, 95.02, 91.48; *m/z* HRMS (DART) found $[M+H]^+$ 407.8746, $C_{11}H_8I_2N^+$ requires 407.8746.

5-Bromo-3-iodo-2-phenylpyridine (53)



An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-5-(dibenzylamino)-2-iodo-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (244 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-bromosuccinimide (71 mg, 0.44 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was purified by flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes) to provide the title compound as a white solid (123 mg, 0.34 mmol, 85% yield). mp 76 – 79 °C; IR ν_{max}/cm^{-1} (film): 1692, 1418, 1104, 1000, 891, 775, 692, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, J = 1.9 Hz), 8.41 (1H, d, J = 2.0 Hz), 7.61 – 7.55 (2H, m) 7.44 – 7.41 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.09, 149.65, 149.13, 140.80, 129.21, 129.05, 128.12, 118.80, 94.18; *m/z* HRMS (DART) found $[M+H]^+$ 359.8897, $C_{11}H_8BrIN^+$ requires 359.8885.

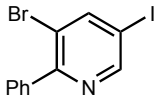
5-Chloro-3-iodo-2-phenylpyridine (54)



An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-5-(dibenzylamino)-2-iodo-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (244 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-chlorosuccinimide (59 mg, 0.44 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was purified by flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes) to provide the title compound as a clear oil (101 mg, 0.32 mmol, 80% yield); IR ν_{max}/cm^{-1} (film): 1508, 1422, 1228, 1161, 1013, 906, 827, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, J = 2.2 Hz), 8.26 (1H, d, J = 2.2 Hz), 7.60 – 7.56 (2H, m) 7.44 – 7.40 (3H,

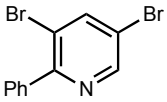
m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.83, 147.53, 146.60, 140.84, 130.30, 129.28, 129.06, 128.14, 93.59; *m/z* HRMS (DART) found $[M+H]^+$ 315.9403, $C_{11}H_8ClIN^+$ requires 315.9390.

3-Bromo-5-iodo-2-phenylpyridine (55)



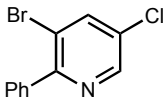
An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-2-bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (225 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-iodosuccinimide (90 mg, 0.40 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was first subjected to flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes). The resulting mixture was then dissolved in Et_2O and 1.0 mmol of TfOH was added to precipitate out the TfOH salt at -78 °C. After filtration, the solid was dissolved in CH_2Cl_2 and washed 3 times with a saturated aqueous Na_2CO_3 solution. Drying with $MgSO_4$ and concentrating in vacuo provided the title compound as a white solid (109 mg, 0.30 mmol, 76% yield). mp 93 – 95 °C; IR ν_{max}/cm^{-1} (film): 3023, 1422, 1103, 1002, 891, 789, 734, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, *J* = 1.7 Hz), 8.33 (1H, d, *J* = 1.8 Hz), 7.70 – 7.64 (2H, m) 7.50 – 7.40 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.79, 153.66, 149.04, 138.00, 129.39, 129.28, 128.24, 120.52, 91.16; *m/z* HRMS (DART) found $[M+H]^+$ 359.8880, $C_{11}H_8BrIN^+$ requires 359.8885.

3,5-Dibromo-2-phenylpyridine (56)



An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-2-bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (225 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-bromosuccinimide (71 mg, 0.40 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was first subjected to flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes). The resulting mixture was then dissolved in Et_2O and 1.0 mmol of TfOH was added to precipitate out the TfOH salt at -78 °C. After filtration, the solid was dissolved in CH_2Cl_2 and washed 3 times with a saturated aqueous Na_2CO_3 solution. Drying with $MgSO_4$ and concentrating in vacuo provided the title compound as a white solid (79 mg, 0.25 mmol, 63% yield). mp 87 – 89 °C; IR ν_{max}/cm^{-1} (film): 3060, 1421, 1362, 1097, 1030, 913, 798, 775, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, *J* = 2.0 Hz), 8.16 (1H, d, *J* = 2.0 Hz), 7.69 – 7.65 (2H, m) 7.50 – 7.42 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.76, 149.18, 143.20, 138.57, 129.31, 129.18, 128.19, 119.92, 118.87; *m/z* HRMS (DART) found $[M+H]^+$ 313.9010, $C_{11}H_8Br_2N^+$ requires 313.9003.

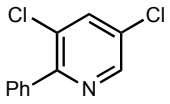
3-Bromo-5-chloro-2-phenylpyridine (57)



An 8 mL vial charged with *N*-((1*Z*,2*Z*,4*E*)-2-bromo-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (225 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-chlorosuccinimide (59 mg, 0.44 mmol) and trifluoroacetic acid (34 µL, 0.44 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 2 hours. The crude material was first subjected to flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes). The resulting mixture was then dissolved in Et_2O and 1.0 mmol of TfOH was added to precipitate out the TfOH salt at -78 °C. After filtration, the solid was dissolved in CH_2Cl_2 and washed 3 times with a saturated aqueous Na_2CO_3 solution. Drying

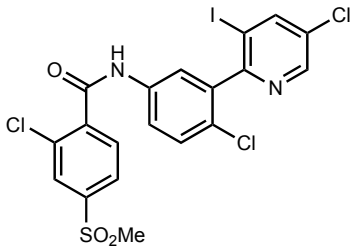
with $MgSO_4$ and concentrating in vacuo provided the title compound as a white solid (76 mg, 0.28 mmol, 71% yield). mp 60 – 62 °C; IR ν_{max}/cm^{-1} (film): 3026, 1424, 1199, 1112, 1009, 889, 814, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (1H, d, *J* = 2.0 Hz), 8.02 (1H, d, *J* = 2.0 Hz), 7.69 – 7.64 (2H, m) 7.50 – 7.42 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.36, 146.91, 140.74, 138.37, 130.60, 129.36, 129.22, 128.19, 119.58; *m/z* HRMS (DART) found $[M+H]^+$ 269.9534, $C_{11}H_8BrClN^+$ requires 269.9508.

3,5-Dichloro-2-phenylpyridine (58)



An 8 mL vial charged with *N*-((1*E*,2*E*,4*E*)-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (194 mg, 0.40 mmol) and CH_2Cl_2 (4 mL, 0.1 M) was cooled to 0 °C. *N*-chlorosuccinimide (110 mg, 0.82 mmol) and HCl (400 µL, 1.60 mmol, 4 M in dioxane) were added and the reaction was warmed to room temperature and allowed to stir for 14 hours. The crude material was subjected to flash chromatography (Combiflash Autocolumn, silica gel gradient elution: 0 to 50% CH_2Cl_2 in Hexanes) to provide the title compound as a clear oil (41 mg, 0.18 mmol, 45% yield); IR ν_{max}/cm^{-1} (film): 3060, 1422, 1353, 1199, 1102, 1001, 889, 776, 733, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (1H, d, *J* = 2.1 Hz), 7.83 (1H, d, *J* = 2.1 Hz), 7.74 – 7.69 (2H, m) 7.53 – 7.43 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.85, 146.62, 137.55, 137.28, 130.57, 130.29, 129.40, 129.25, 128.26; *m/z* HRMS (DART) found $[M+H]^+$ 224.0044, $C_{11}H_8Cl_2N^+$ requires 224.0034.

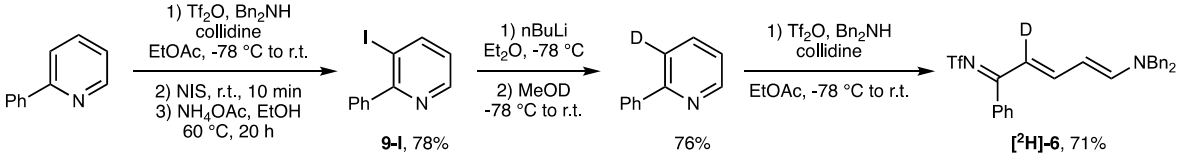
2-Chloro-*N*-(4-chloro-3-(5-chloro-3-iodopyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (84)



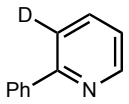
An 8 mL vial charged with 2-chloro-*N*-(4-chloro-3-((1*E*,2*Z*,4*E*)-5-(dibenzylamino)-2-iodo-1-(((trifluoromethyl) sulfonyl)imino)penta-2,4-dien-1-yl)phenyl)-4-(methylsulfonyl)benzamide (1785 mg, 0.20 mmol) and CH_2Cl_2 (12 mL, 0.017 M) was cooled to 0 °C. *N*-chlorosuccinimide (29 mg, 0.22 mmol) and trifluoroacetic acid (17 µL, 0.22 mmol) were added and the reaction was warmed to room temperature and allowed to stir for 15 hours. The crude material was purified by flash chromatography (silica gel: 30% Acetone in Hexanes) to provide the title compound as a white solid (86 mg, 0.15 mmol, 74% yield). mp 256 – 259 °C; IR ν_{max}/cm^{-1} (film): 3263, 2923, 1658, 1538, 1422, 1306, 1094, 961, 890, 734, 692, 639; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 10.98 (1H, s), 8.74 (1H, d, *J* = 2.0 Hz), 8.62 (1h, d, *J* = 2.0 Hz), 8.15 (1H, s), 8.02 (1H, d, *J* = 8.0 Hz), 7.95 (1H, d, *J* = 8.0 Hz), 7.80 – 7.74 (2H, m), 7.61 (1H, d, *J* = 8.5 Hz), 3.36 (3H, s); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 163.88, 158.16, 147.09, 145.34, 143.14, 140.78, 140.53, 137.51, 130.97, 130.42, 129.98, 129.81, 128.10, 126.35, 125.92, 121.33, 120.93, 97.17, 43.09; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 581.0, $C_{19}H_{13}Cl_3IN_2O_3S^+$ requires 580.9.

11. Deuteration Study

Synthesis of Deuterated Imine:

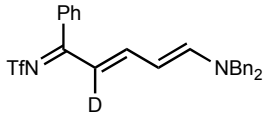


2-Phenylpyridine-3-*d*



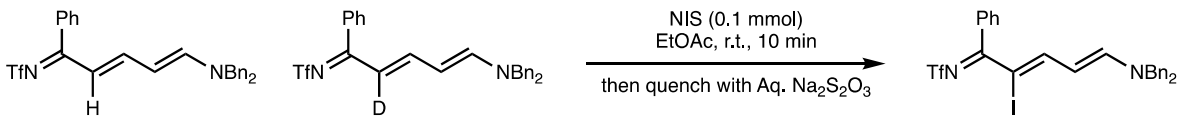
A 500 mL round bottom flask was charged with 3-iodo-2-phenylpyridine (1.97 g, 7.00 mmol) and brought under an N_2 atmosphere. Et_2O (35 mL) was added, and the flask was cooled to -78 °C. *n*-BuLi (4.6 mL, 7.35 mmol, 1.6 M in hexanes) was added dropwise and the reaction was stirred for 15 minutes. CH_3OD (3 mL, 73.5 mmol) was added dropwise over five minutes, and then the reaction was warmed to room temperature. At room temperature, the reaction was quenched with water and transferred to a separatory funnel. The aqueous layer was extracted from into EtOAc (3x). The organic extracts were combined, dried ($MgSO_4$), and concentrated. The resulting material was purified by flash column chromatography (silica gel gradient elution: 2% to 3% Acetone in Hexanes) to yield the pure product (836 mg, 6.59 mmol, 76% yield) as a clear oil. IR ν_{max}/cm^{-1} (film): 3048, 1573, 1556, 1438, 1414, 1021, 861, 737, 693, 632; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, dd, J = 4.8, 1.8 Hz), 8.02 – 7.98 (2H, m), 7.73 (1H, d, J = 7.3 Hz), 7.51 – 7.46 (2H, m), 7.45 – 7.39 (1H, m), 7.22 (1H, dd, J = 7.5, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.49, 149.76, 139.46, 136.71, 129.04, 128.84, 126.99, 122.16, 120.34 (t, J = 24.6 Hz); *m/z* HRMS (DART) found $[M+H]^+$ 157.0875, $C_{11}H_9DN^+$ requires 157.0876.

***N*-((1*Z*,2*E*,4*E*)-5-(Dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene-2-*d*)-1,1,1-trifluoromethanesulfonamide ([^{2}H]-6)**



Prepared according to general procedure A using 2-phenylpyridine-3-*d* (781 mg, 5.00 mmol), EtOAc (50 mL, 0.1 M), Tf_2O (840 µL, 5.00 mmol), dibenzylamine (1.15 mL, 6.00 mmol, 1.0 M in EtOAc), and collidine (661 µL, 5.00 mmol). Washing 1x with H_2O and 2x with aqueous sodium bicarbonate, and then crashing out in hexanes afforded the title compound (1.72 g, 3.53 mmol, 71% yield) as a yellow solid. mp 59 – 62 °C; IR ν_{max}/cm^{-1} (film): 3028, 1617, 1485, 1316, 1167, 1101, 969, 839, 696, 654; ^1H NMR (400 MHz, CD_3CN) δ: 7.76 (1H, d, J = 11.9 Hz), 7.58 – 7.30 (12H, m), 7.30 – 7.15 (4H, m), 6.06 (1H, t, J = 12.2 Hz), 4.60-4.50 (4H, m); ^{13}C NMR (100 MHz, CD_3CN) δ: 176.45, 163.12, 163.01, 139.49, 135.65, 135.31, 131.65, 130.19, 129.97, 129.90, 129.57, 129.35, 129.24, 129.06, 128.39, 120.96 (q, J = 320.3 Hz), 113.21 (t, J = 23.5 Hz), 105.94, 61.11, 52.75; ^{19}F NMR (365 MHz, CD_3CN) δ: –80.16; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 486.2, $C_{26}H_{23}DF_3N_2O_2S^+$ requires 486.2.

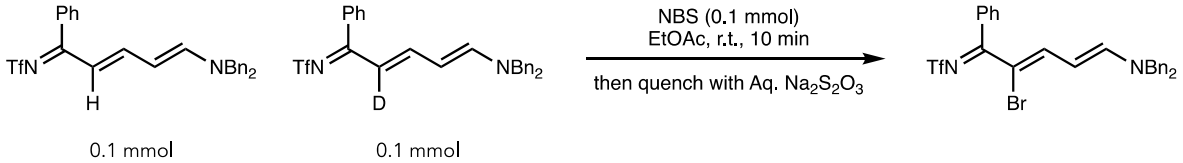
N-Iodosuccinimide Competition:



An 8 mL vial was charged with *N*-((1*E*,2*E*,4*E*)-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-ylidene)-1,1,1-trifluoromethanesulfonamide (49 mg, 0.10 mmol), *N*-((1*E*,2*E*,4*E*)-5-(dibenzylamino)-1-phenylpenta-2,4-dien-1-

ylidene-2-*d*)-1,1,1-trifluoromethanesulfonamide (49 mg, 0.10 mmol), and EtOAc (1 mL). *N*-iodosuccinimide (23 mg, 0.10 mmol) was added and the reaction was allowed to stir at room temperature for 10 minutes. Aqueous sodium thiosulfate was then added to quench the reaction, and triphenylmethane (49 mg, 0.20 mmol) was added as an internal standard. An aliquot of the organic layer was then concentrated, and a crude NMR was taken.

N-Bromosuccinimide Competition:



The above procedure was repeated, except that *N*-bromosuccinimide (18 mg, 0.10 mmol) was used in place of *N*-iodosuccinimide.

NMR Analysis of Deuteration Study:

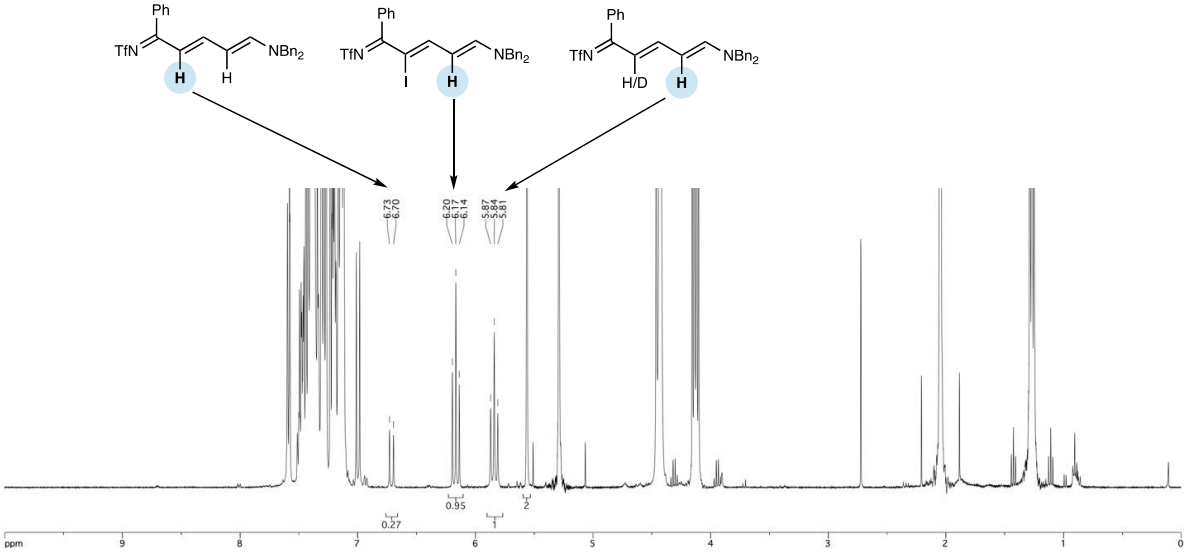


Fig. S8. Crude ^{1}H NMR from NIS competition experiment.

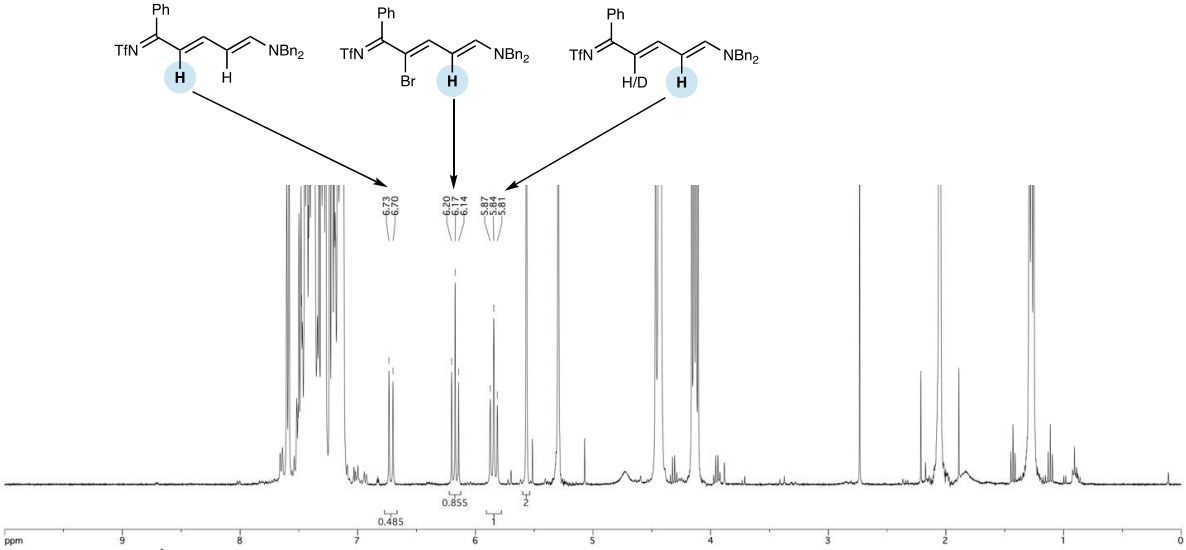


Fig. S9. Crude ^{1}H NMR from NBS competition experiment.

For NIS reaction:
3-Iodinated Product: 95%
SM 3-position proton (SM_H): 27%
SM 5-position proton: 100%
Deuterated Starting Material (SM_D): 100% - 27% = 73%

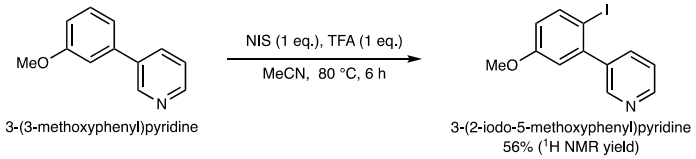
SM_D/SM_H = 73/27 = 2.70

For NBS reaction:
3-Brominated Product: 85.5%
SM 3-position proton (SM_H): 48.5%
SM 5-position proton: 100%
Deuterated Starting Material (SM_D): 100% - 48.5% = 51.5%

SM_D/SM_H = 51.5/48.5 = 1.06

12. Complementary EAS Reaction

Demonstration of Regiodiversity with Conventional Electrophilic Aromatic Halogenation:
As described in the manuscript, general procedure C was applied to 3-(3-methoxyphenyl)pyridine to form iodopyridine **44** in 76% yield. To demonstrate complementary reactivity of the Zincke ring-opening strategy to existing methods, we performed an EAS iodination on this substrate to form an iodoanisole product. Note that the reaction is sluggish until heated to 80 ºC and MeCN outperforms EtOAc and CH_2Cl_2 as solvents. As separation between starting material and product is challenging in this case, we have reported an assay yield based on analysis of the crude ^{1}H NMR spectrum using mesitylene as an internal standard. This crude spectrum also indicates that the iodinated isomer shown below is the major regioisomer.



3-(3-methoxyphenyl)pyridine

3-(2-iodo-5-methoxyphenyl)pyridine
56% (^{1}H NMR yield)

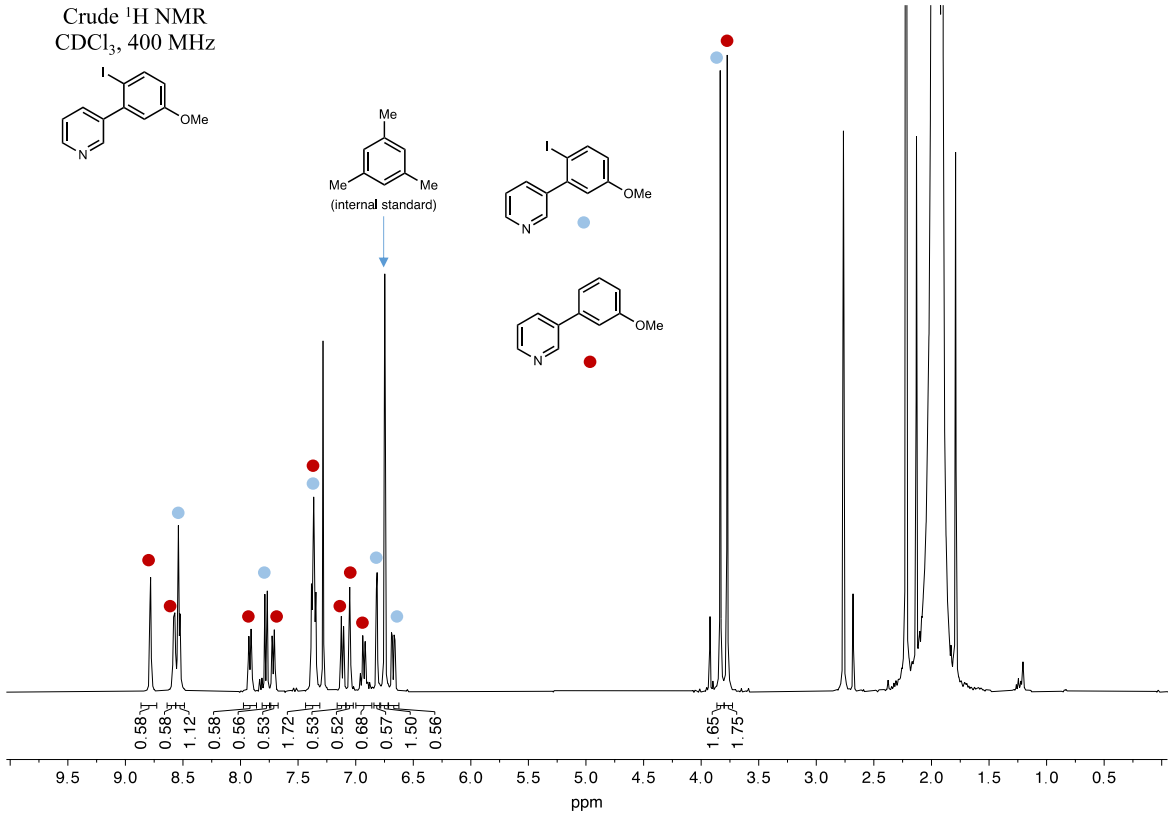


Fig. S10. Iodination of an anisole substituted pyridine and crude ^{1}H NMR spectrum.

Procedure for EAS halogenation: 3-(3-methoxyphenyl)pyridine (37 mg, 0.20 mmol) and MeCN (1 mL) were added to an 8 mL vial. *N*-iodosuccinimide (45 mg, 0.20 mmol) and trifluoroacetic acid (15 µL, 0.20 mmol) were added at room temperature. The reaction was stirred at 80 °C 6 hours. After cooling to room temperature and quenching with saturated aqueous $NaHCO_3$, mesitylene (14 uL, 0.10 mmol) was added and an aliquot was added to an NMR tube with $CDCl_3$. ^{1}H NMR analysis showed 56% of the corresponding iodoaniline product as the major product in the reaction mixture. Trace amounts of other products were seen in the ^{1}H NMR but were not identified. An analytically pure sample of the product, 3-(2-iodo-5-methoxyphenyl)pyridine , was obtained using flash column chromatography (silica gel: 100% CH_2Cl_2 to 10% EtOAc in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75-8.57 (2H, m), 7.82 (1H, d, J = 8.7 Hz), 7.72 (1H, d, J = 7.5 Hz), 7.38 (1H, dd, J = 7.2, 5.0 Hz), 6.87 (1H, d, J = 2.8 Hz), 6.70 (1H, dd, J = 8.8, 2.7 Hz), 3.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.10, 149.64, 148.72, 143.79, 140.44, 139.91, 137.15, 123.00, 116.31, 115.98, 86.95, 55.64; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ xxx, $C_{12}H_{11}INO^+$ requires 312.0, found 312.0.

13. Computational Details

The range separated dispersion-corrected ωB97X-D (*47,* 47) functional and the 6-31+G(d,p) (*48-52*) basis set (def2-SVPD (*53, 54*) basis set for I atoms) was used to optimize all stationary point geometries. The use of 5 Cartesian d functions was requested throughout with Gen/GenECP keywords (*55*). Vibrational frequency calculations were used to confirm stationary points as minima or first-order saddle points on the potential energy surface (PES) and to obtain quasi-harmonic rigid-rotor/harmonic oscillator thermochemistry values with the *GoodVibes* program (*56*). Where possible, Intrinsic reaction coordinate (IRC) calculations were carried out to ensure that the intermediates (**Int**) of the different pathways connected to their corresponding transition structure (**TS**).
Energies were refined with single-point energy calculations at the B3LYP/def2-TZVP level with an empirical D3 dispersion correction and Becke-Johnson damping (GD3BJ). In all cases, the calculations included the integral

equation formalism variant of the polarizable continuum model (IEF-PCM (*57-61*)) with the SMD (*62*) solvation model (solvent=dichloromethane) to account for solvent effects. We found this level of theory to be appropriate for calculation of $\Delta\Delta G^{\ddagger}$ in these halogenations (**Table S12**)
Conformational sampling (due to rotations about single bonds) of ground state (**GS**) and transition states (TSs) structures was performed using a combination of manual sampling and CREST (*63*). To enumerate the different conformers, a letter/combination of letters is appended at the end of each name (*e.g.* _a, _b, _c, _ab, _ac, *etc.*). Representations in the main text and supporting information refer to the most stable rotameric and isomeric conformation found for each step. Gibbs Free Energies (G) values of all the energy profiles correspond to the Boltzmann weighted G of all the conformers found in each step (G_{av}).
Gaussian 16 was employed for all density functional theory (DFT) calculations, using an "ultrafine" pruned (99,590) grid for numerical integration of the exchange-correlation functional and its derivatives. Visualization settings have been made openly accessible (*64*). Atomic charges, Wiberg bond orders (*65*) and Fukui indices were computed using natural population analysis (NPA) with *NBO 7.0* (*66*), interfaced to *Gaussian 16*.

Thermochemical Data Calculation with *GoodVibes*

Quasi-harmonic corrections were introduced to the computed vibrational entropies using a frequency cut-off value of 100.0 cm^{-1} with GoodVibes, following the approach proposed by Grimme (*67*) at 273.15 K. Also, a correction for the change in standard state from gas phase at 1 atm to a 1 M solution was introduced (*68*). A few of the GS calculations showed persistent imaginary frequencies lower than 50 cm^{-1}. These imaginary frequencies were inverted to obtain thermochemical contributions (*69*). After conformational sampling, duplicate structures at the DFT level were automatically excluded. Boltzmann weighted Gibbs energies (G_{av}) are quoted throughout, which include considerations of molecular point group and entropies of mixing (*70-73*).
All the thermochemical data including absolute energies, zero-point energies (ZPE) and T·S, among other parameters, at the ωB97X-D/6-31+G(d,p) level, as well as the absolute energies, corrected final G and relative G obtained after B3LYP-D3(BJ)/def2-TZVP single point energy calculations, are tabulated in separate files of the ESI labeled *Adduct_NXS_PES.dat*.

Level of theory Benchmarks

Computed $\Delta\Delta G^{\ddagger}$ values are broadly consistent across the methods examined, such that regioselectivity predictions for any given elementary step are relatively insensitive (< 1 kcal/mol). However absolute barrier heights do show greater variation, with ωB97X-D or M062X level of theory giving Gibbs energy barriers that are relatively high in relation to the experimental reaction temperatures. Overall, B3LYP-D3(BJ)/def2-TZVP single point calculations yield $\Delta\Delta G^{\ddagger}$ values in good agreement with experiment for all our halogenations while also providing reasonable $\Delta G^{\ddagger}$ values.

Table S12. Gibbs free energies with different single point energy corrections for ωB97X-D/6-31+G(d,p) stationary points.

LoT	TS-I-C3-NCS	TS-I-C5-NCS	$\Delta\Delta G^{\ddagger}$
B3LYP-D3(BJ)/def2-TZVP	22.4	22.9	0.5
M062X/def2-TZVP	29.6	29.6	0
ωB97X-D/def2-TZVP	28.9	28.6	0.3

LoT	TS-I-C3-NBS	TS-I-C5-NBS	$\Delta\Delta G^{\ddagger}$
B3LYP-D3(BJ)/def2-TZVP	19.3	21.9	2.6
M062X/def2-TZVP	25.0	26.8	1.8
ωB97X-D/def2-TZVP	23.7	25.1	1.4

LoT	TS-II-C3-NIS	TS-II-C5-NIS	$\Delta\Delta G^{\ddagger}$
B3LYP-D3(BJ)/def2-TZVP	22.2	25.6	3.4
M062X/def2-TZVP	24.7	27.5	2.8
ωB97X-D/def2-TZVP	21.9	24.9	3.0

Zincke imine electronic descriptors

NBO partial charge, Fukui indices, natural population, natural charge and HOMO coefficient calculated (wb97xd/6-31+g(d,p)) for the most stable conformer of the 2Ph Zincke Imine. The f^- Fukui index is computed as the difference in natural population (from NBO calculation) at a particular atom between the neutral and oxidized molecule. The f^+ Fukui index is computed as the difference in natural population (from NBO calculation) at a particular atom between the neutral and reduced molecule.

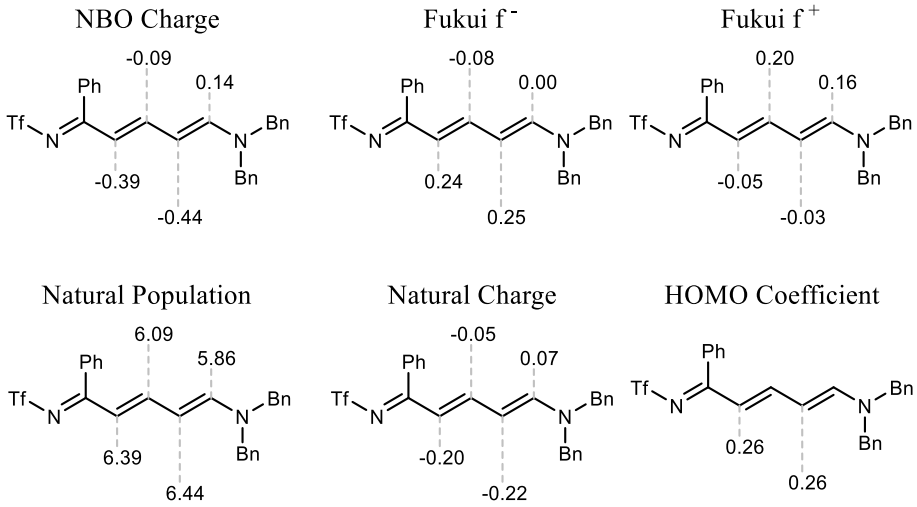


Fig. S11. Natural populations, Fukui *f*-, Fukui *f*+ indices and HOMO coefficient for 2Ph substituted Zincke Imine. Results are tabulated in the file *2PhAdduct_diBnAmine_NBO_Fukui_Charges.csv*

Complete PES and Representations of the Most Stable Conformers

Calculated Gibbs energy profiles for the reaction of NIS (**Fig. S11**), NBS (**Fig. S13**) and NCS (**Fig. S15**) with a 2-phenyl substituted Zincke imine are shown below. In all cases, the *N*-benzyl groups of the enamine were modeled computationally as *N*-methyl groups.

In all cases, the halogenation reaction was found computationally to occur preferentially through a closed-shell pathway rather than outer-sphere electron transfer, with a difference of more than 10 kcal/mol separating the two possibilities (see below). For bromination and chlorination reactions (with NBS and NCS) we found a stepwise process

with distinct electrophilic halogenation and deprotonation elementary steps. In both reactions the halogenation transition structure was found to be rate- and selectivity-limiting. For iodination with NIS, a halogenation transition structure could not be located. Scans along the forming C—I bond reveal a flat PES. Nevertheless, these energies are lower than computed for the deprotonation, and so we propose that reversible iodination is followed by rate- and selectivity-determining deprotonation. In all cases $\Delta\Delta G^{\ddagger}$ are in good agreement with experimental results. In a DFT study of the electrophilic aromatic substitution of anisole, Brinck and coworkers observed the iodination of anisole with ICl under the M02-2X/6-311G(d,p) level of theory does not possess a discreet halogenation TS but observed halogenation TSs for chlorination and bromination (*35*). These results are concordant with our work.

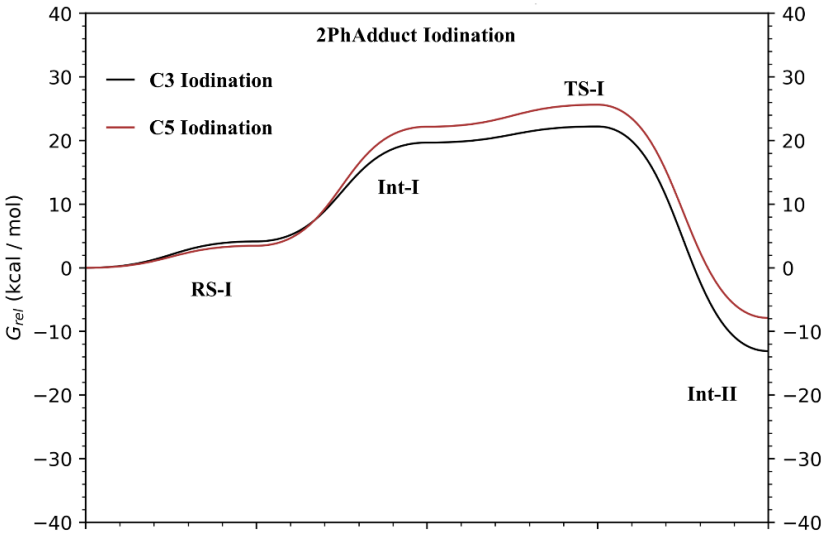


Fig. S12. PES of the reaction between NIS and 2Ph substituted Zincke imine. B3LYP(GD3BJ)/def2-TZVP//ωB97X-D/6-31+G(d,p) (def2-SVPD for Iodine during optimization).

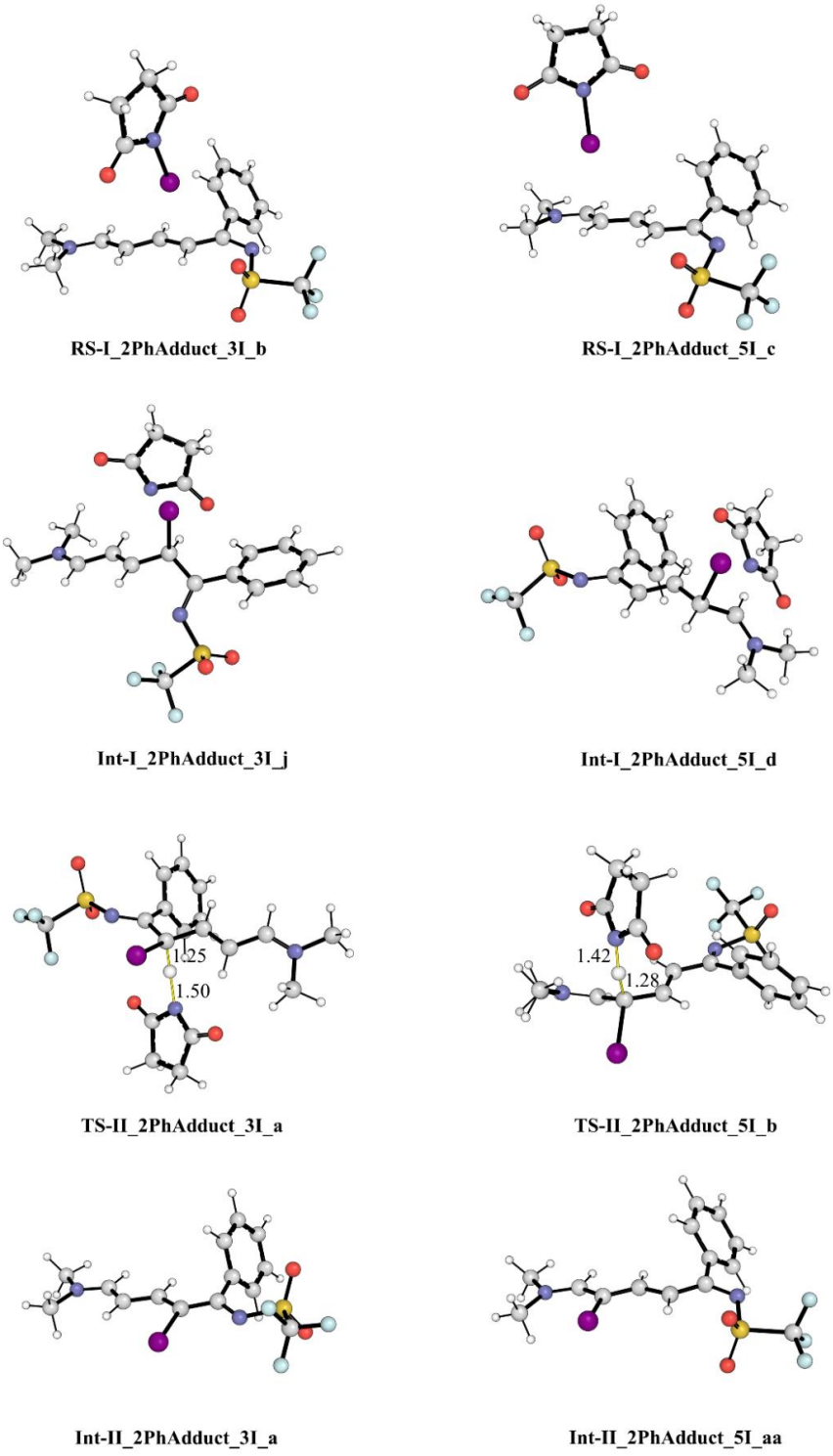


Fig. S13. Representations of the most stable conformer of each reaction step in the NIS reaction. Distance shown in Å.

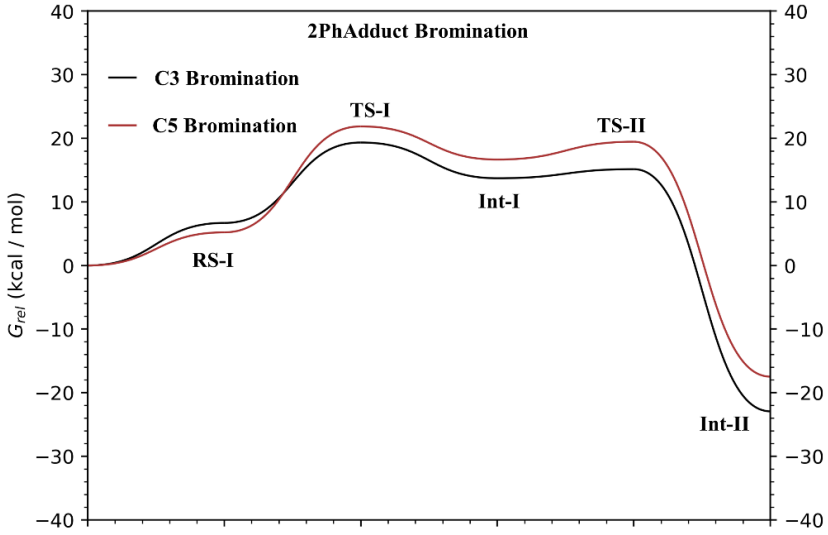


Fig. S14. PES of the reaction between NBS and 2-Ph substituted Zincke imine. B3LYP(GD3BJ)/def2-TZVP//ωB97X-D/6-31+G(d,p).

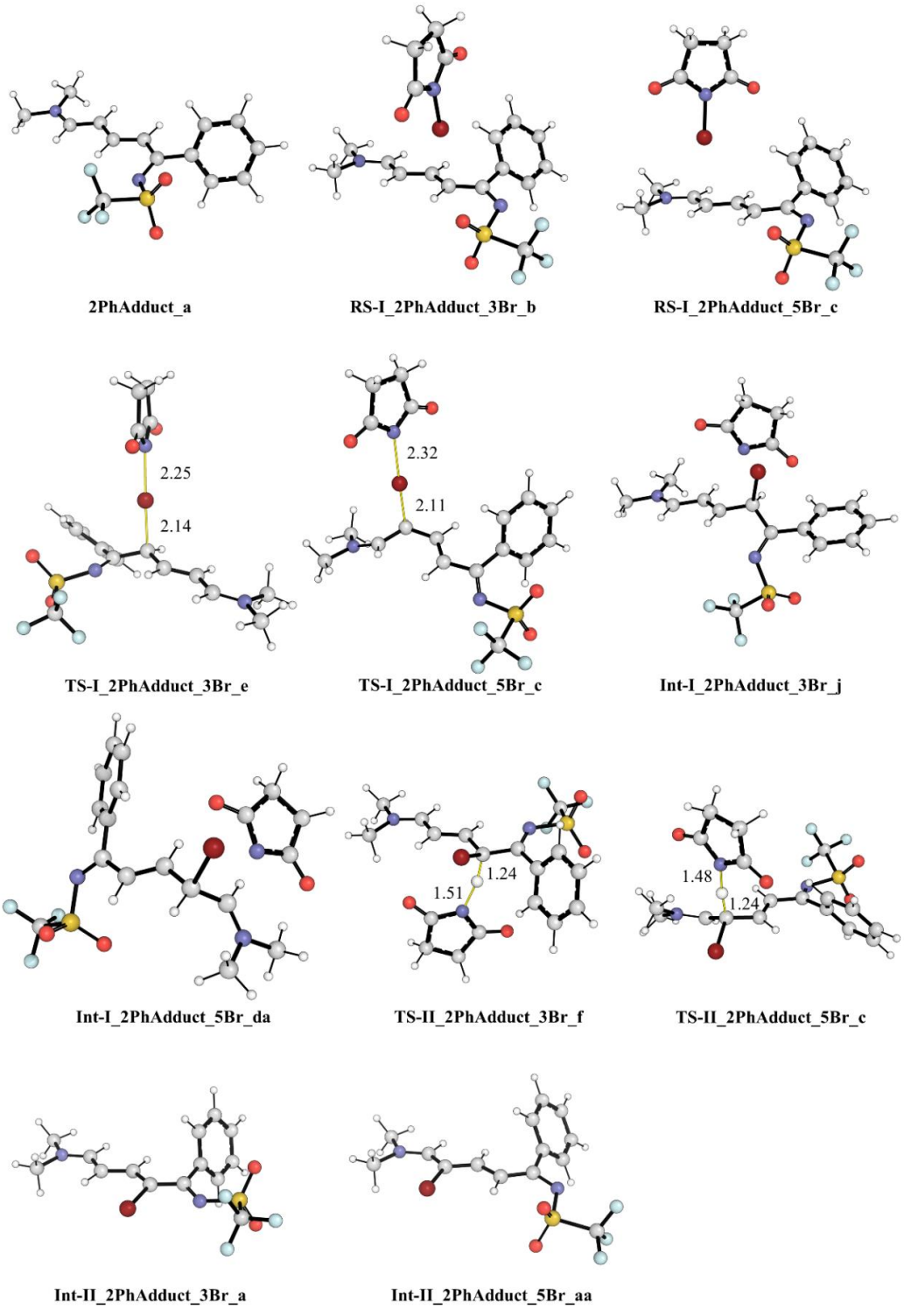


Fig. S15. Representations of the most stable conformer of each reaction step in the NBS reaction. Distances shown in Å.

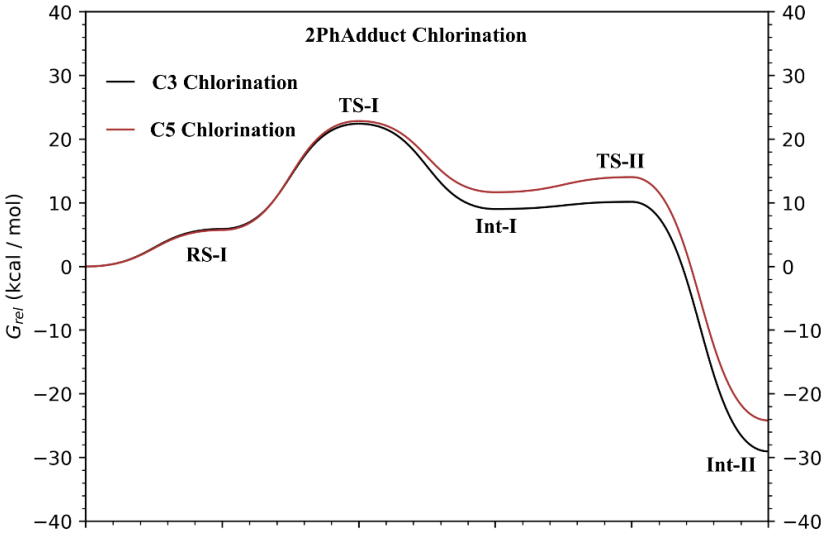


Fig. S16. PES of the reaction between NCS and 2Ph substituted Zincke imine. B3LYP(GD3BJ)/def2-TZVP//ωB97X-D/6-31+G(d,p).

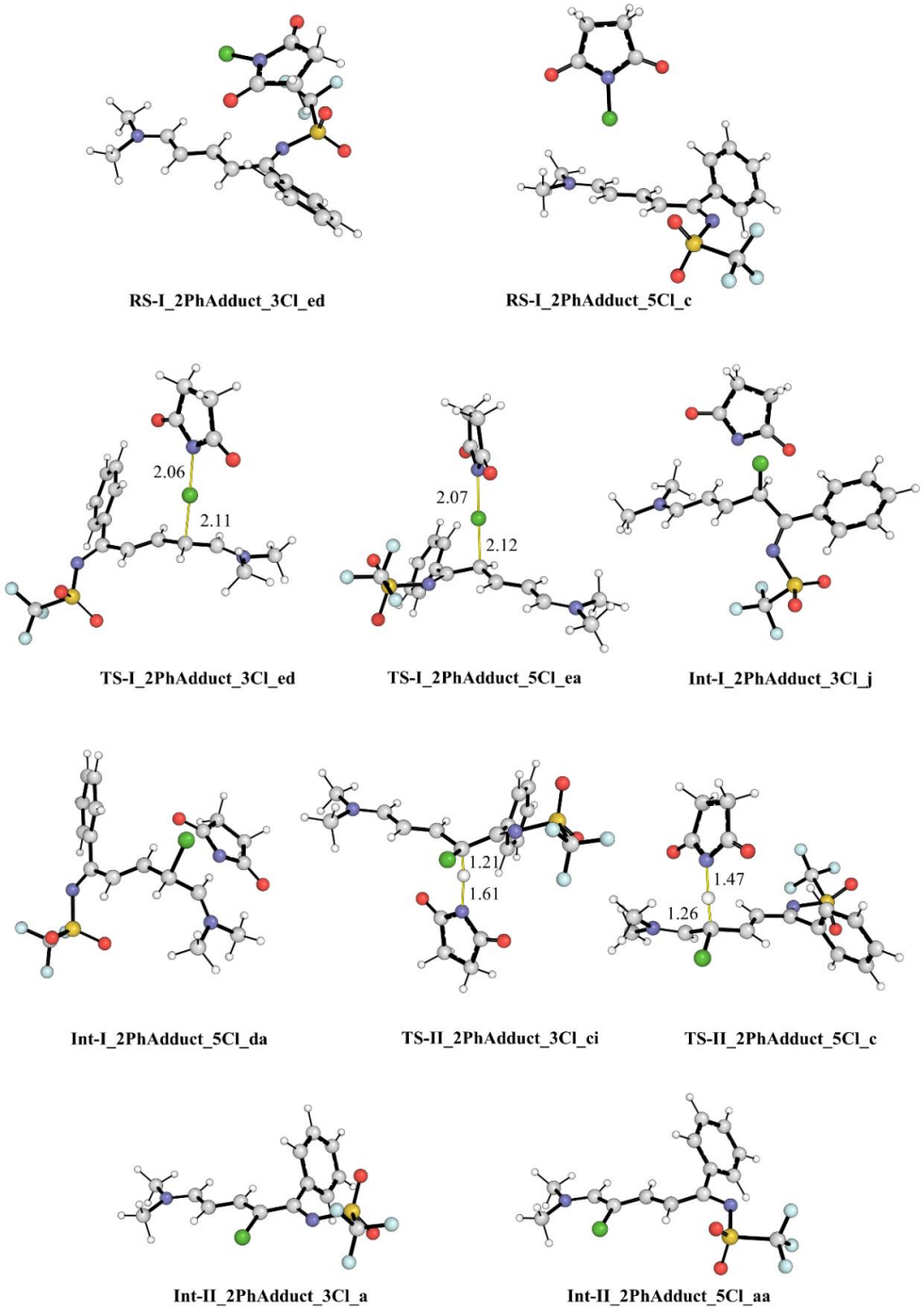


Fig. S17. Representations of the most stable conformer of each reaction step in the NCS reaction. Distances shown in Å.

Potential energy surface for other substrates

A pyridine and 2Me substituted pyridine Zincke imine were also modeled undergoing the different halogenations. The selectivity and trends observed are the same as for the 2-Ph Zincke imine.

Table S13. Tabulated energies for the reaction of *N*-halosuccinimides and different imines (2Me Pyridine and Pyridine derivate).

	TS-I_C3	TS-I_C5	Int-I_C3	Int-I_C5	TS-II_C3	TS-II_C5	Int-II_C3	Int-II_C5
2Me_NIS	N/A	N/A	17.2	20.4	20.1	24.6	-13.6	-6.9
2Me_NBS	17.1	21.3	12.4	17.4	14.9	19.7	-19.9	-16.5
2Me_NCS	22.0	23.4	8.5	12.0	10.2	13.1	-26.8	-23.5
Pyr_NIS	N/A	N/A	23.8	25.3	25.2	27.4	-14.1	-6.4
Pyr_NBS	20.7	N/A	15.9	16.9	17.1	20.1	-21.6	-16.8
Pyr_NCS	25.6	24.9	14.0	15.8	14.6	15.8	-29.8	-23.7

Non-Covalent Interaction Plots of TS-I

To investigate if any non-covalent interaction could be responsible for the observed selectivity, we performed a non-covalent interaction analysis (NCI) using the NCI software (*74*). The NCI plots did not reveal any major selective interaction between the two reaction components during the halogenation.

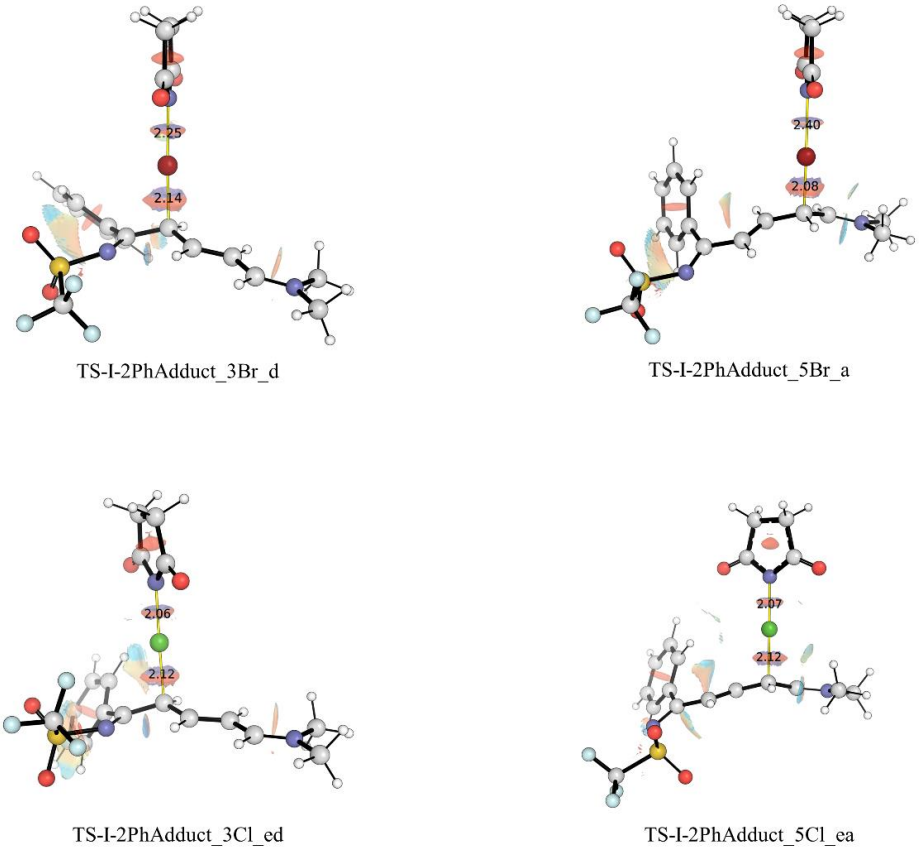
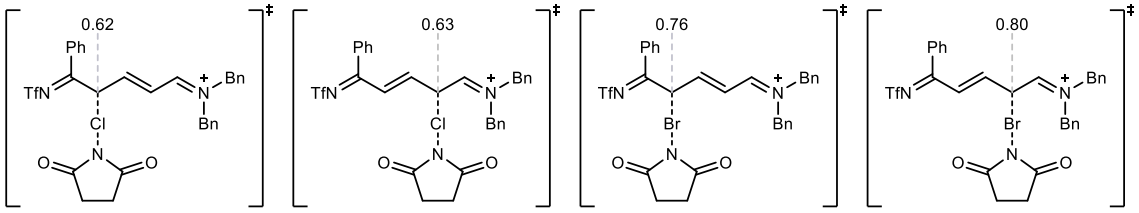


Fig. S18. NCI Plots for the halogenation TS (**TS-I**) of the NCS and NBS reaction with the 2Ph Zincke Imine. Interactions are shown on a red to blue scale with blue representing attractive interaction and red repulsive. Distances in Å.

Pyramidalization in the halogenation (TS-I)

A study of the pyramidalization value of the carbon being functionalized (C3/C5) shows the TS for bromination happens later along the reaction coordinate with pyramidalization values of 0.76 and 0.80 (these are relative to the pyramidalization at the intermediate following the TS) compared to chlorination with pyramidalization values of 0.62 and 0.63



TS-I-C3-NCS TS-I-C5-NCS TS-I-C3-NBS TS-I-C5-NBS

Fig. S19. Pyramidalization values at the reacting carbon in the halogenation (**TS-I**). Value shown are relative to pyramidalization at the intermediate following the TS (**Int-I**)

Steric versus electronic effect in the deprotonation (TS-II)

The TSs for the deprotonation of the 2-phenyl Zincke Imine were calculated. Barriers of 34.7 and 35.7 kcal/mol were found for the C3 and C5 positions, respectively. This example shows a substantial portion of the selectivity during the deprotonation comes from the steric interaction of the C5 substituent and the nearby iminium substituent. The remaining selectivity would come from the stability induced by the larger conjugated iminium in the C3 deprotonation. This steric interaction is very clearly observed in the product geometry (**Int-II**). In the case of the C3 regioisomer, a bond angle (C2-C3-C4) of 122° is observed versus a bond angle (C4-C5-C6) of 115° for the C5 regioisomer. The presence of the iminium methyl group also results in a slight distortion of the planarity of the adduct, which is best reflected in the dihedral angles of the conjugated system; in the C3 regioisomer 180° (C2-C3-C4-C5), and in the C5 regioisomer 176° (C4-C5-C6-N7). Similar $\Delta\Delta G^{\ddagger}$ values for this step are obtained in the reaction with NCS and NBS (3.9 and 4.3 kcal mol^{-1}).

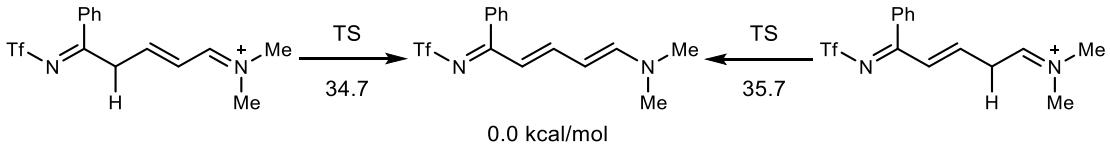


Fig. S20. Gibbs activation barriers (kcal/mol) for intermolecular deprotonation by the succinimide anion.

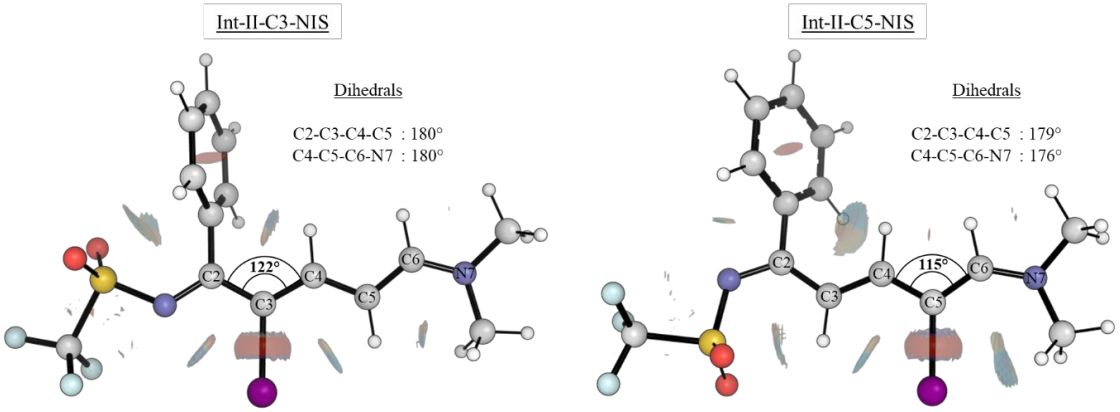


Fig. S21. Geometry of Int-II in the NIS reaction.

Energy Decomposition Analysis during Halogenation (TS-I)

The most stable conformer of **TS-I** in the NBS and NCS reaction with 2Ph Zincke Imine was subjected to an Energy Decomposition Analysis (EDA). In this study **TS-I** is split into its two components (NXS and Zincke Imine) and a single point energy calculation of the distorted component is performed. $E_{DIST\ NXS}$ is defined as the difference in energy between ground state NXS and the energy of the NXS fragment in **TS-I**. $E_{DIST\ Imine}$ is defined as the difference in energy between ground state Zincke Imine and the energy of the Zincke Imine fragment in **TS-I**. E_{Int} is defined as the difference between the Energy of Activation (E_{Act}) and the combined distortion energies of NXS and the Imine ($E_{DIST\ NXS} + E_{DIST\ Imine}$). Our results show the bromination TS feature higher distortion components than the chlorination indicating a latter character.

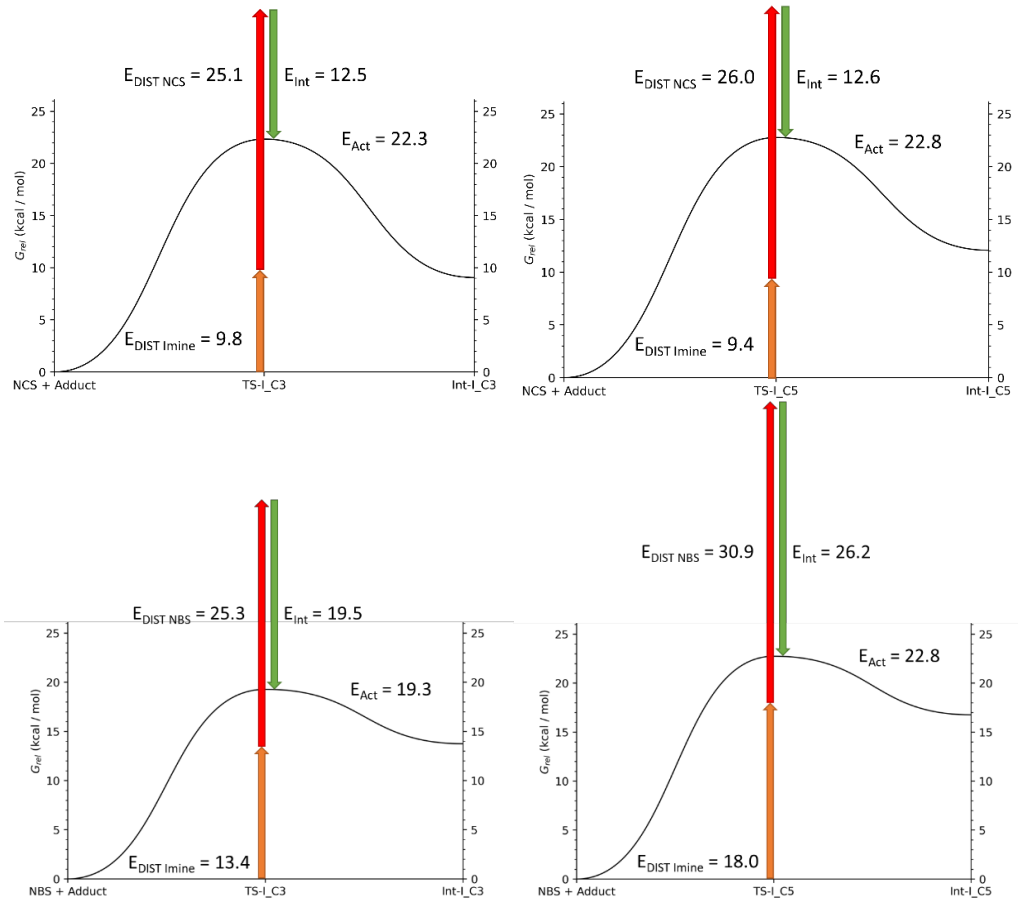


Fig. S22. Energy decomposition diagrams for the halogenation TSs of the reaction of 2Ph Zincke Imine with NBS and NCS.

Single Electron Transfer Initiation

We explored the possibility for the reaction to begin via a single electron transfer pathway from the imine to the N-halosuccinimide. We found this initiation to be too high in energy to be considered as a potential competing pathway. The $\Delta G_{reaction}$ of the SET from 2Ph substituted Imine to NIS, NBS and NCS are, respectively, 34.1, 38.7 and 35.6 kcal/mol. These values are calculated at the ωB97X-D/6-31+G(d,p) level of theory.

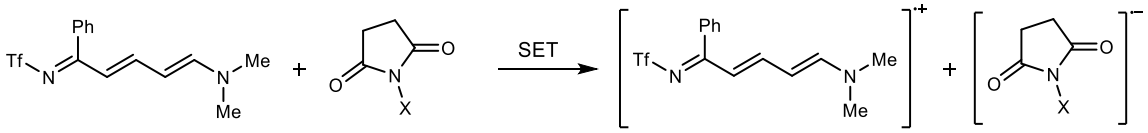
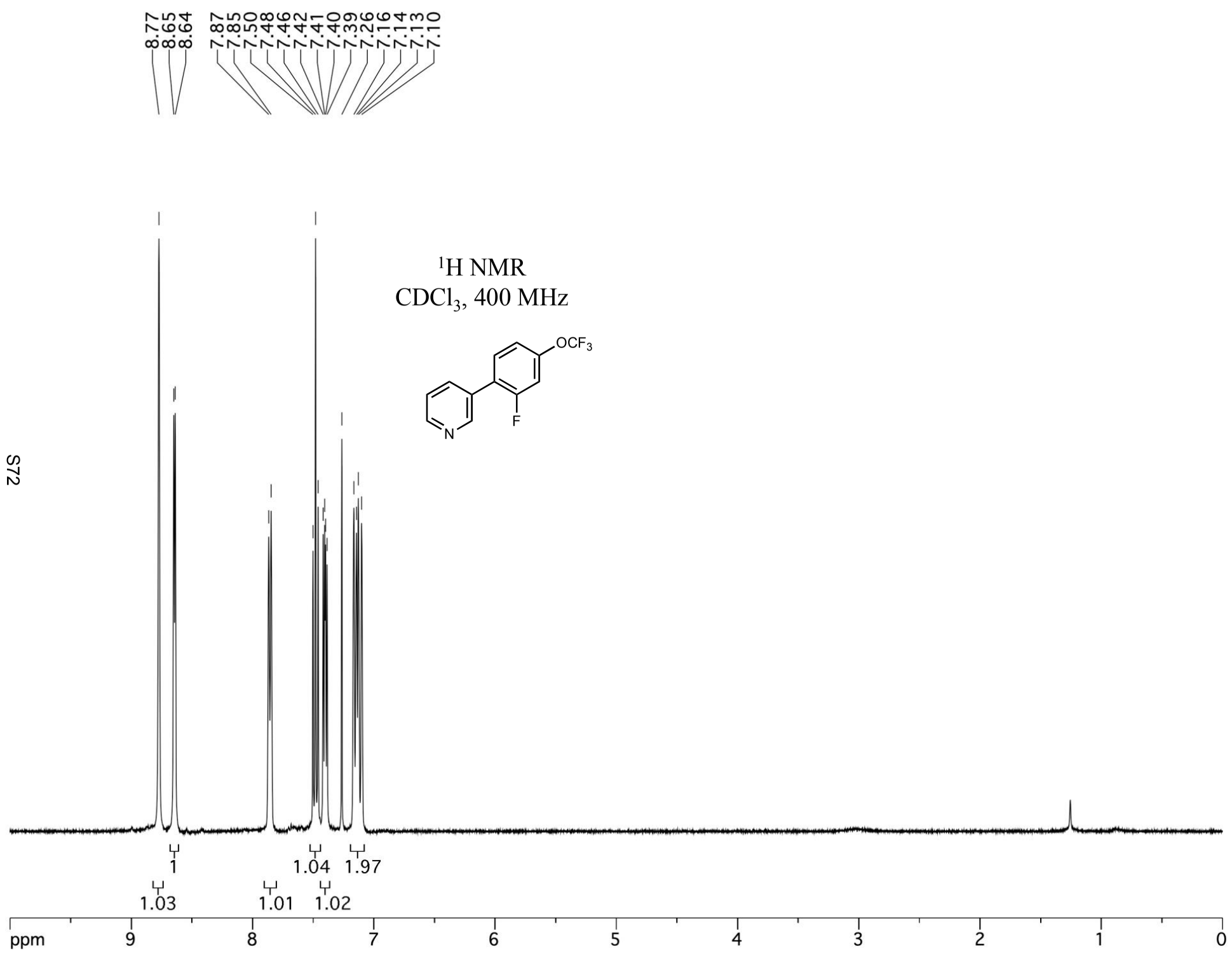


Fig. S23. Single Electron transfer Initiation from Zincke Imine to *N*-Halosuccinimide to generate a radical anion intermediate.

14. NMR Data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7.87
7.85
7.50
7.48
7.46
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7.41
7.40
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7.26
7.16
7.14
7.13
7.10
^{1}H NMR
$CDCl_3$, 400 MHz
OCF_3
F
N
S72
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1.97
1.03
1.01
1.02
ppm
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7
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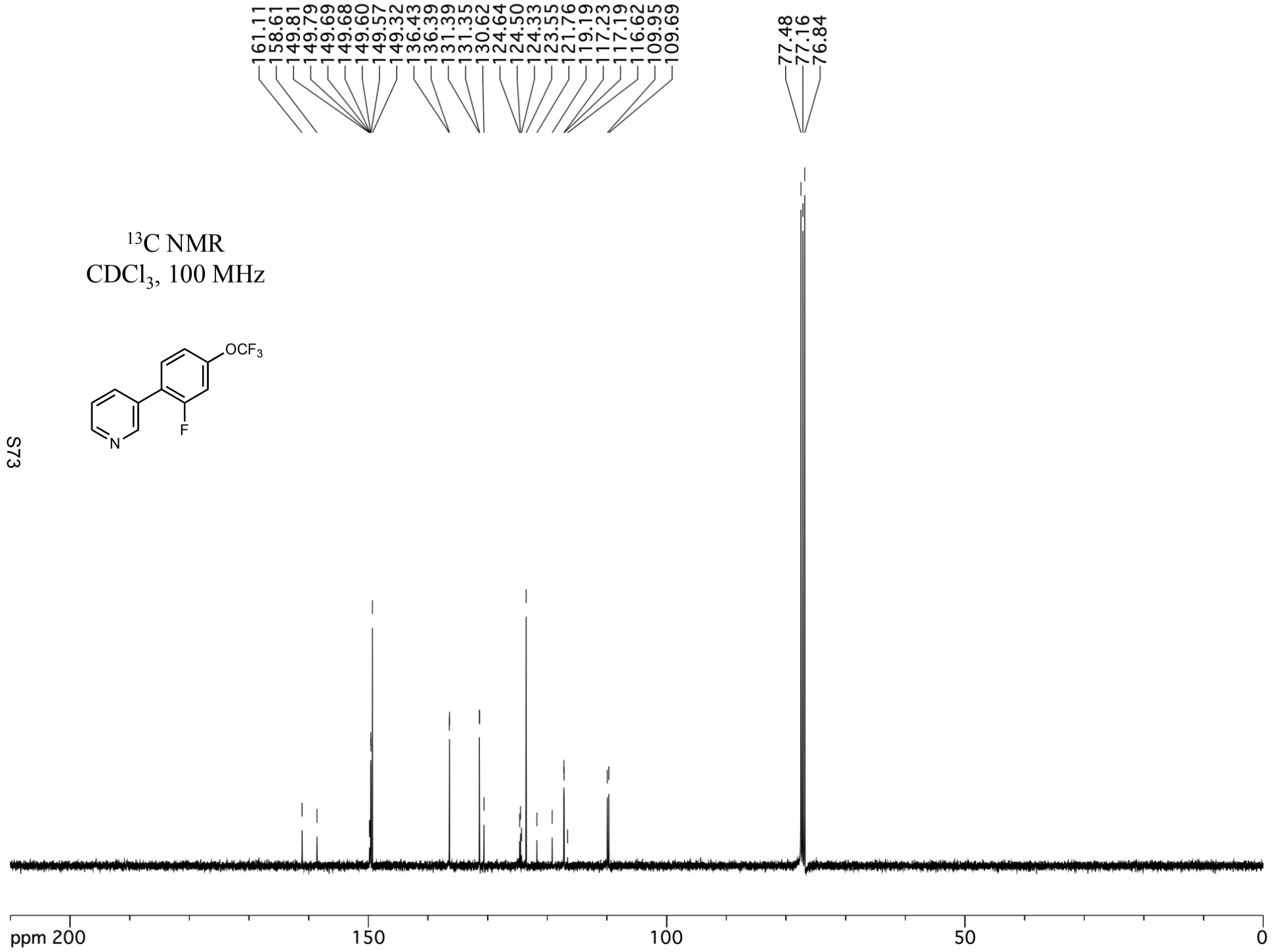
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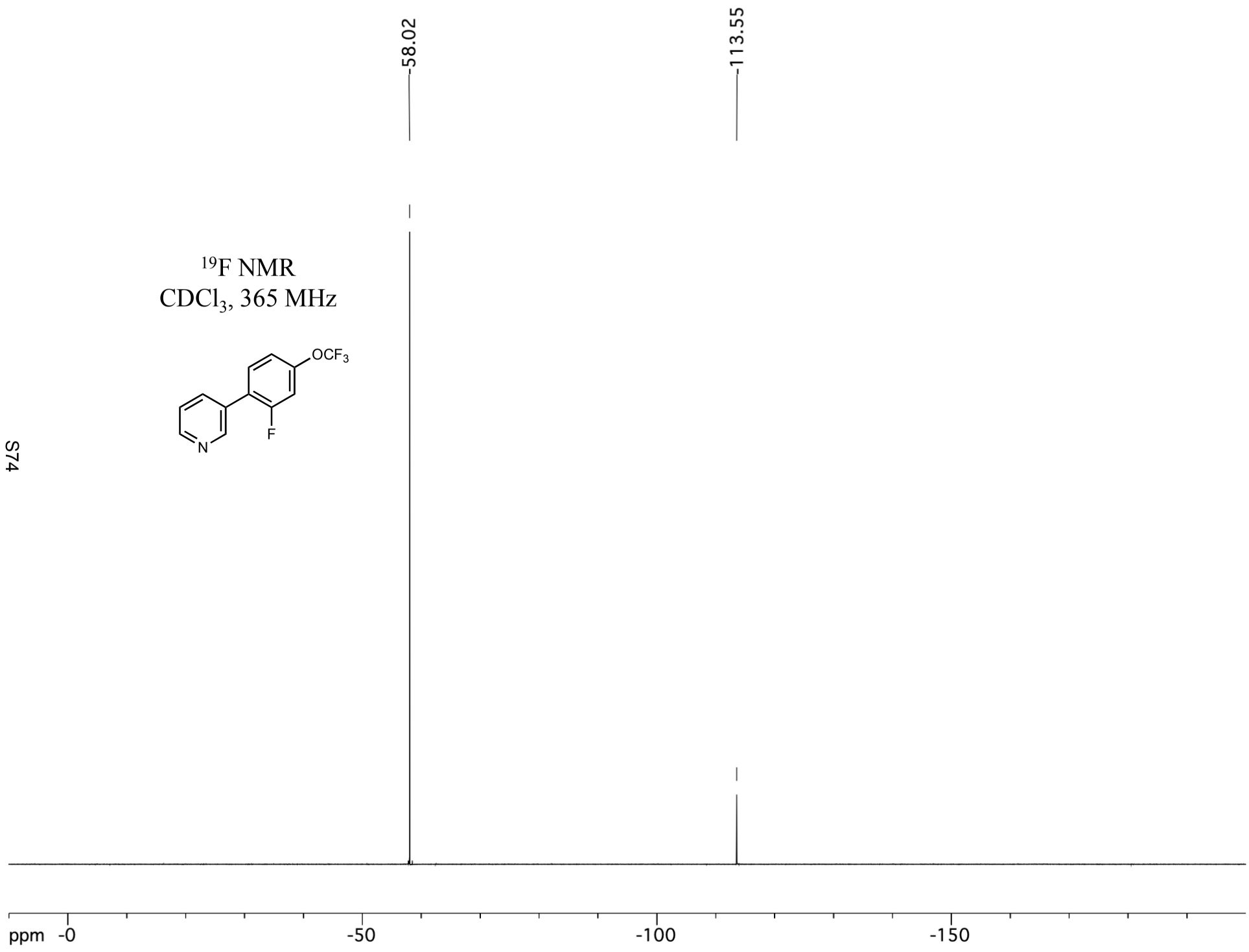
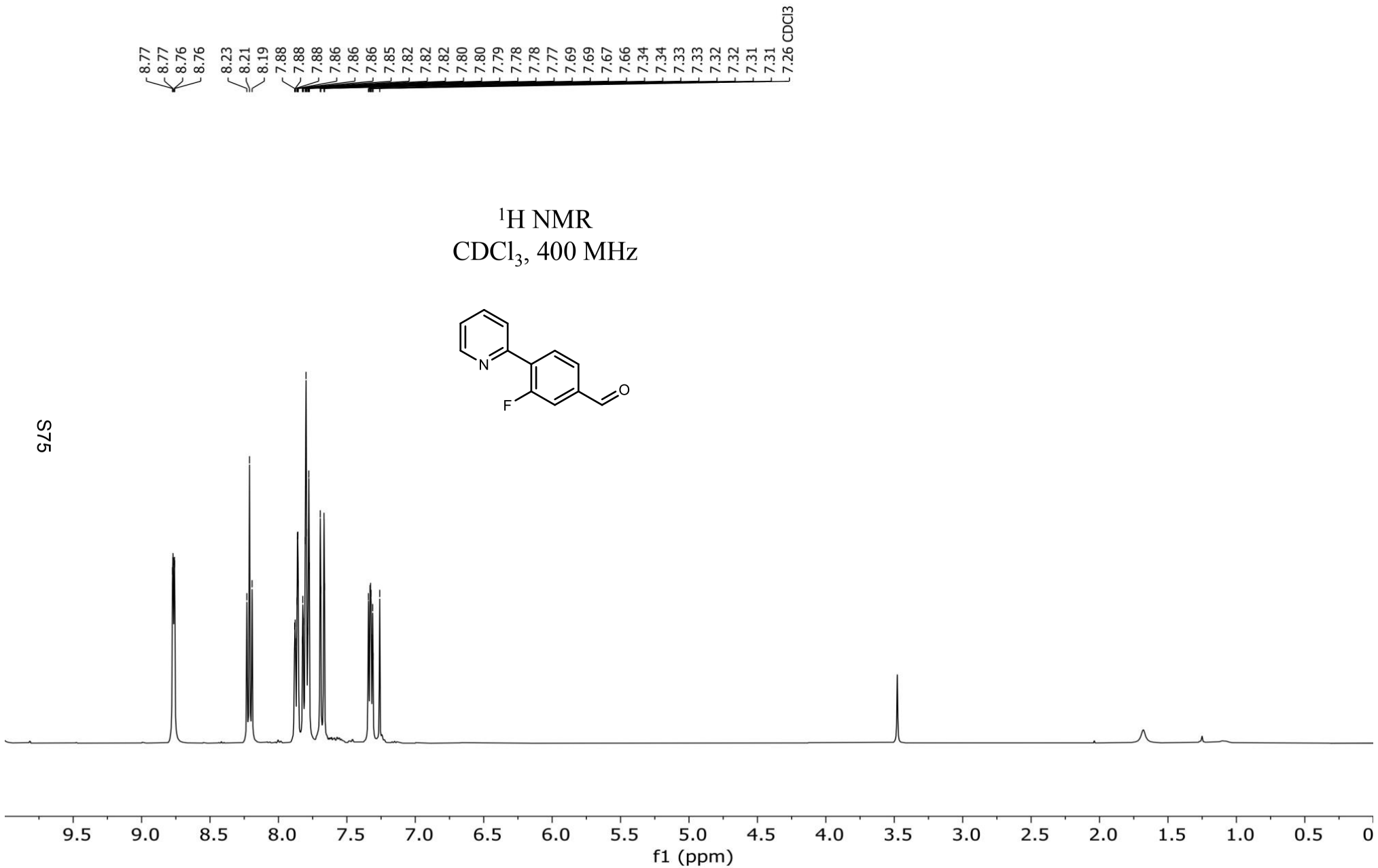
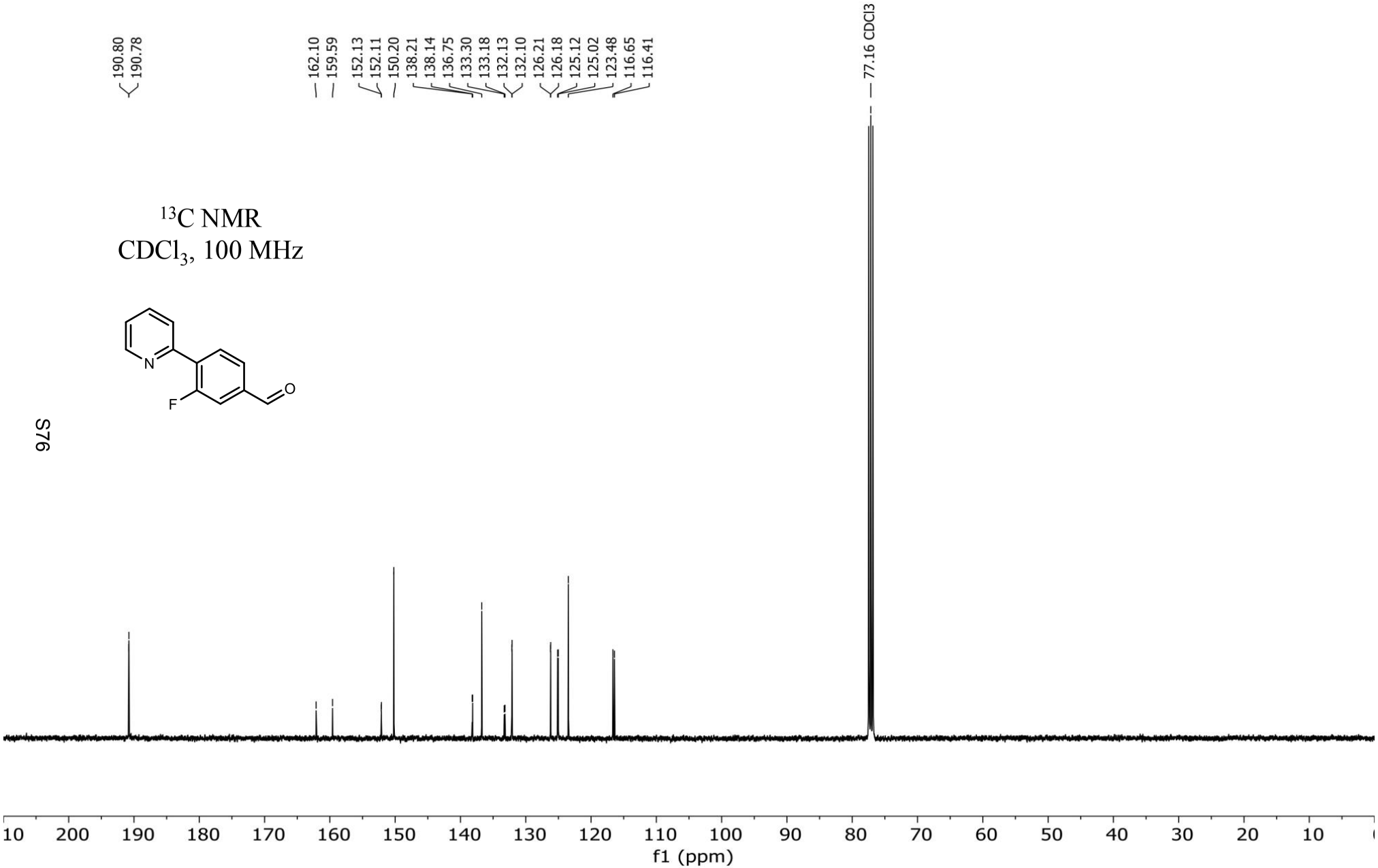
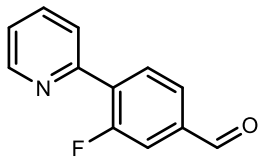
124.33
123.55
121.76
119.19
117.23
117.19
116.62
109.95
109.69
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
OCF3
F
N
ppm 200
150
100
50
0

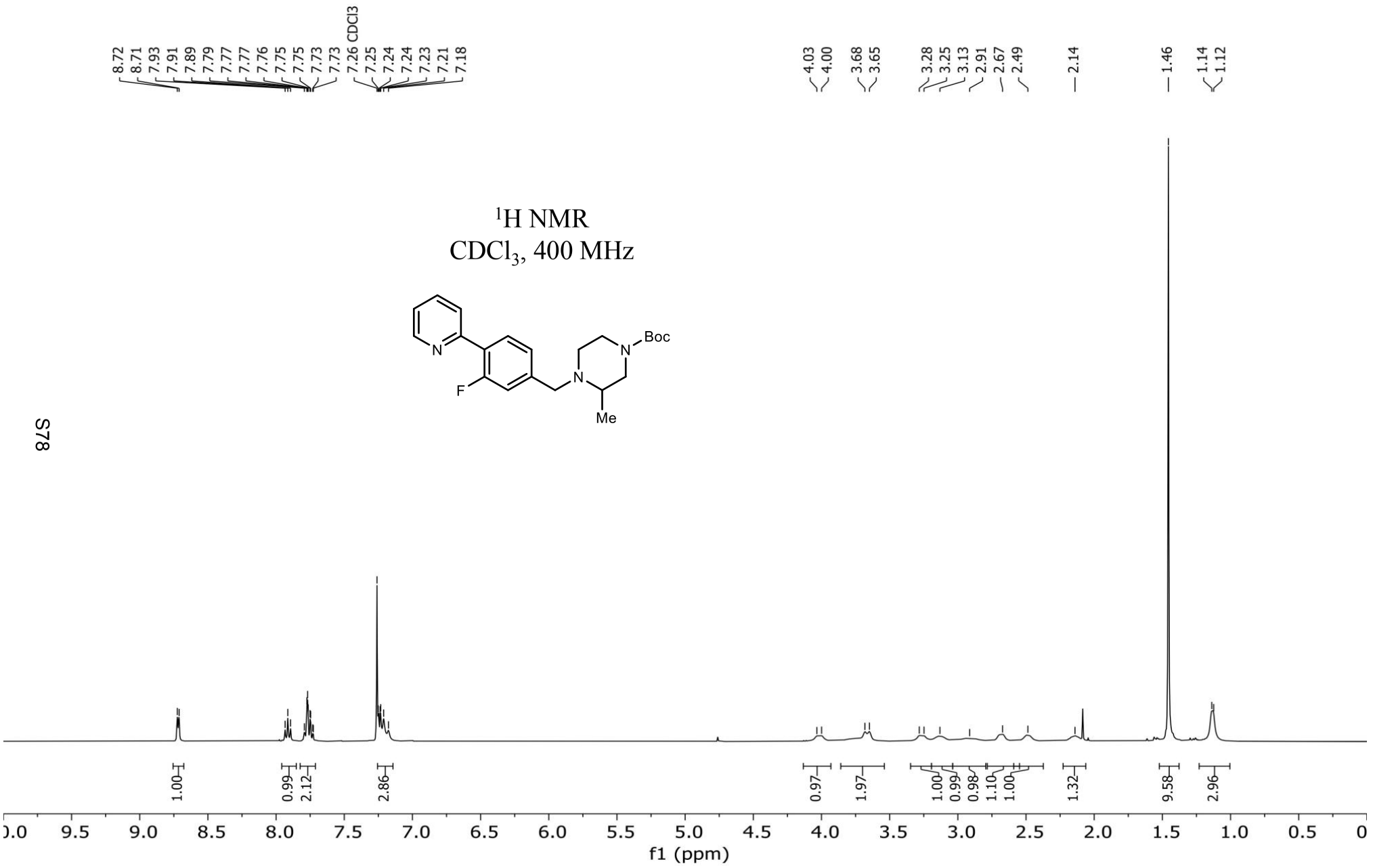

58.02
113.55
^{19}F NMR
$CDCl_3$, 365 MHz
OCF3
F
N
ppm -0
-50
-100
-150


8.77
8.77
8.76
8.76
8.23
8.21
8.19
7.88
7.88
7.88
7.86
7.86
7.86
7.85
7.82
7.82
7.82
7.80
7.80
7.79
7.78
7.78
7.77
7.69
7.69
7.67
7.66
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.26 CDCl3
^{1}H NMR
$CDCl_3$, 400 MHz
N
F
O
S75
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


190.80
190.78
162.10
159.59
152.13
152.11
150.20
138.21
138.14
136.75
133.30
133.18
132.13
132.10
126.21
126.18
125.12
125.02
123.48
116.65
116.41
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
N
F
O
f1 (ppm)

^{19}F NMR
$CDCl_3$, 365 MHz

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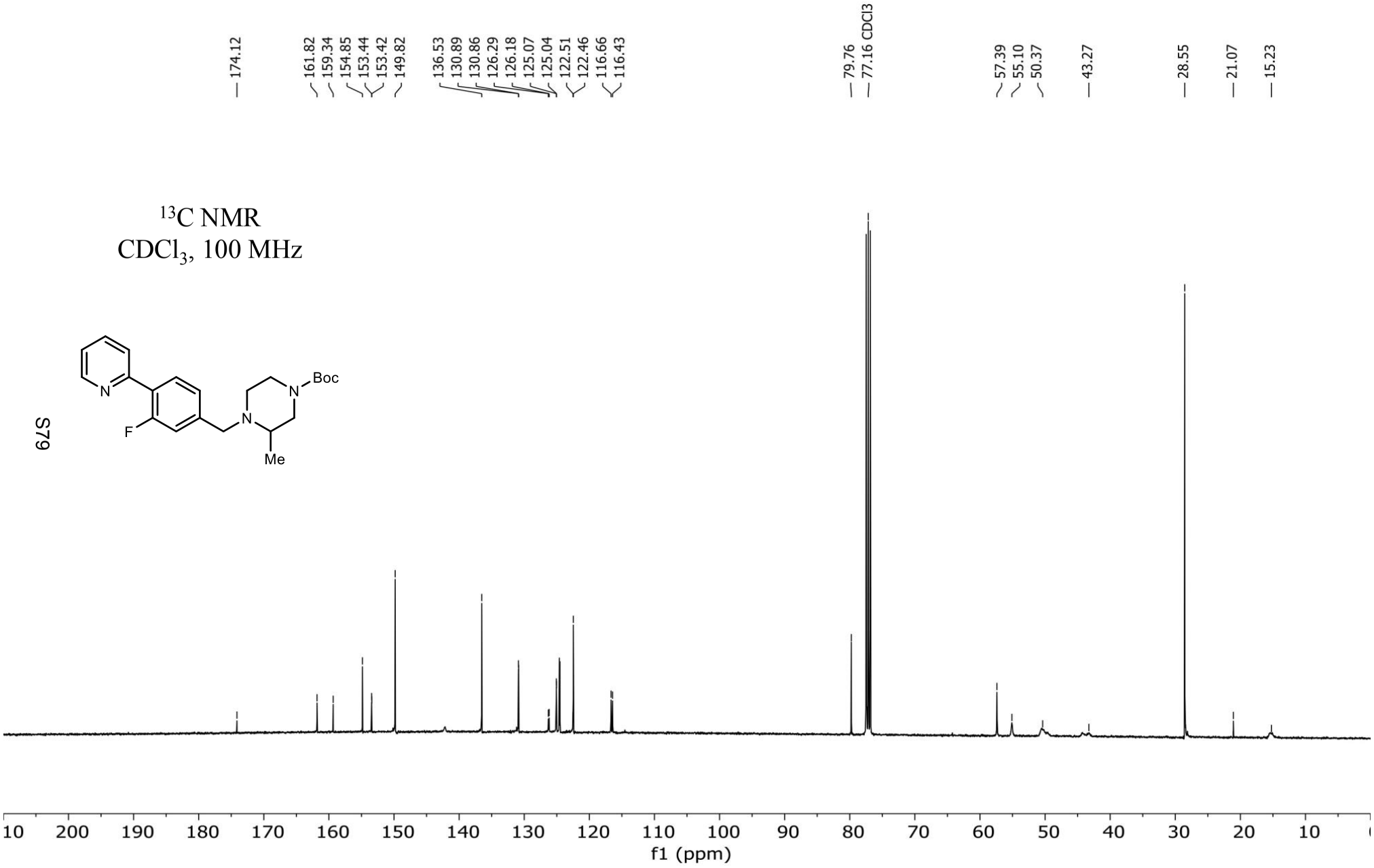
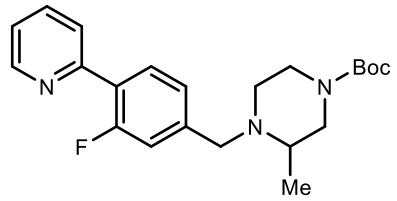
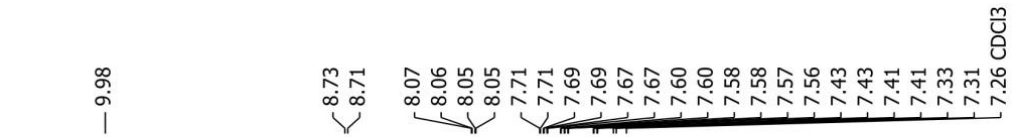
8.71
7.93
7.91
7.89
7.79
7.77
7.77
7.76
7.75
7.75
7.73
7.73
7.26 CDCl3
7.25
7.24
7.24
7.23
7.21
7.18
4.03
4.00
3.68
3.65
3.28
3.25
3.13
2.91
2.67
2.49
2.14
1.46
1.14
1.12
1H NMR
CDCl3, 400 MHz
N
F
N
N
Boc
Me
1.00
0.99
2.12
2.86
0.97
1.97
1.00
0.99
0.98
1.10
1.00
1.32
9.58
2.96
f1 (ppm)

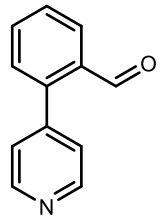

174.12
161.82
159.34
154.85
153.44
153.42
149.82
136.53
130.89
130.86
126.29
126.18
125.07
125.04
122.51
122.46
116.66
116.43
79.76
77.16 CDCl3
57.39
55.10
50.37
43.27
28.55
21.07
15.23
13C NMR
CDCl3, 100 MHz
Boc
N
N
N
F
Me
S79
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

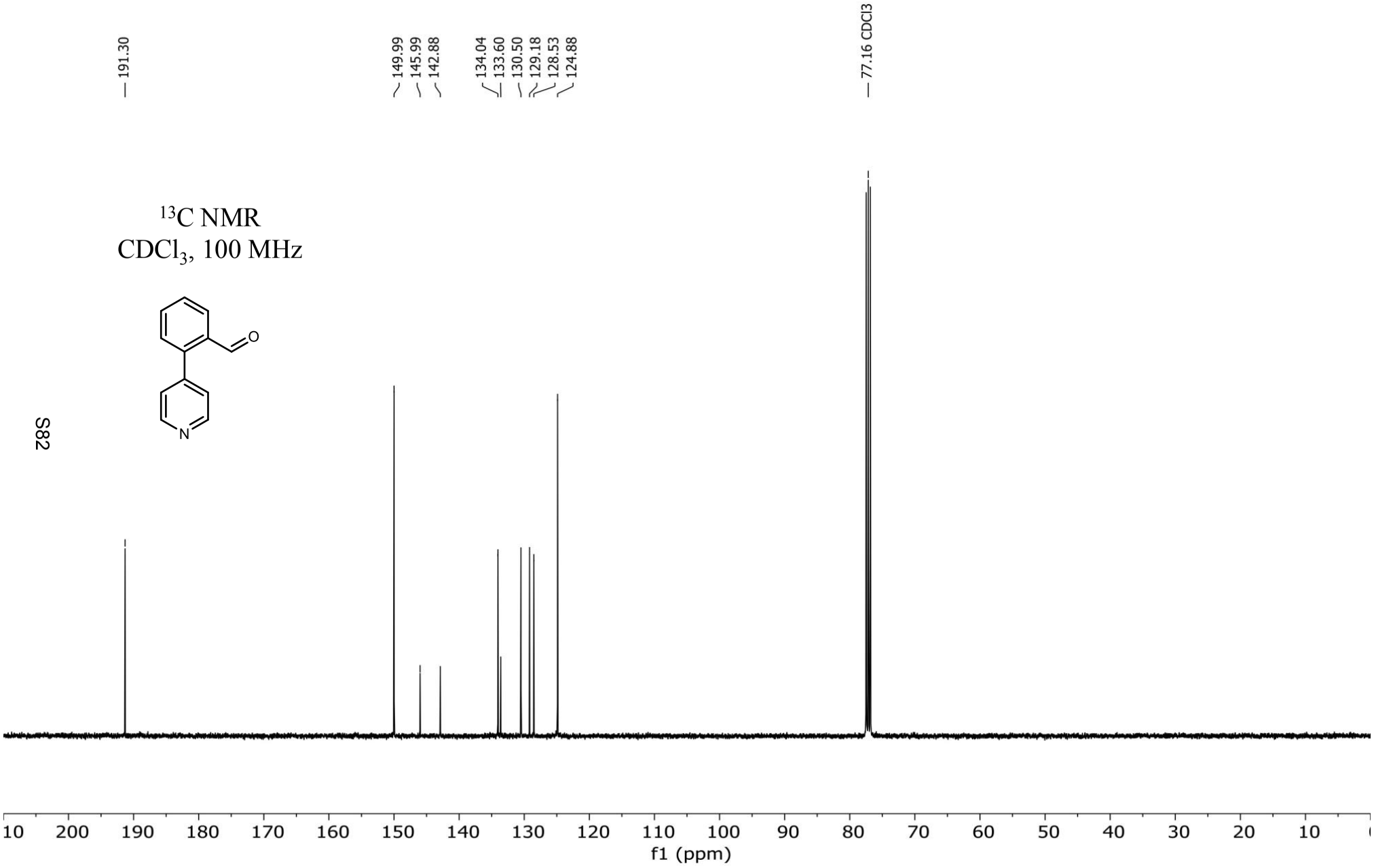
^{19}F NMR
$CDCl_3$, 365 MHz

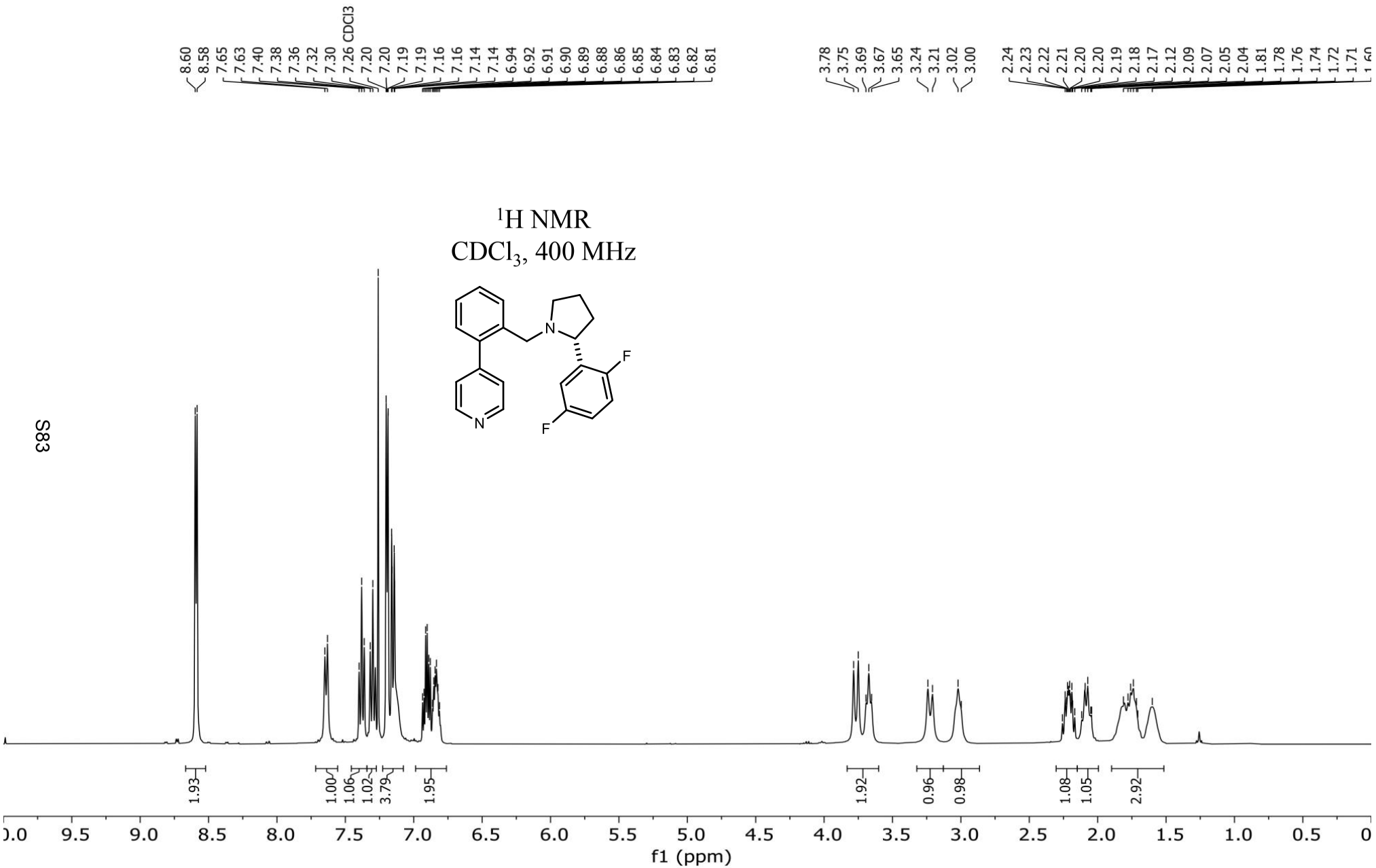




^{1}H NMR
$CDCl_3$, 400 MHz

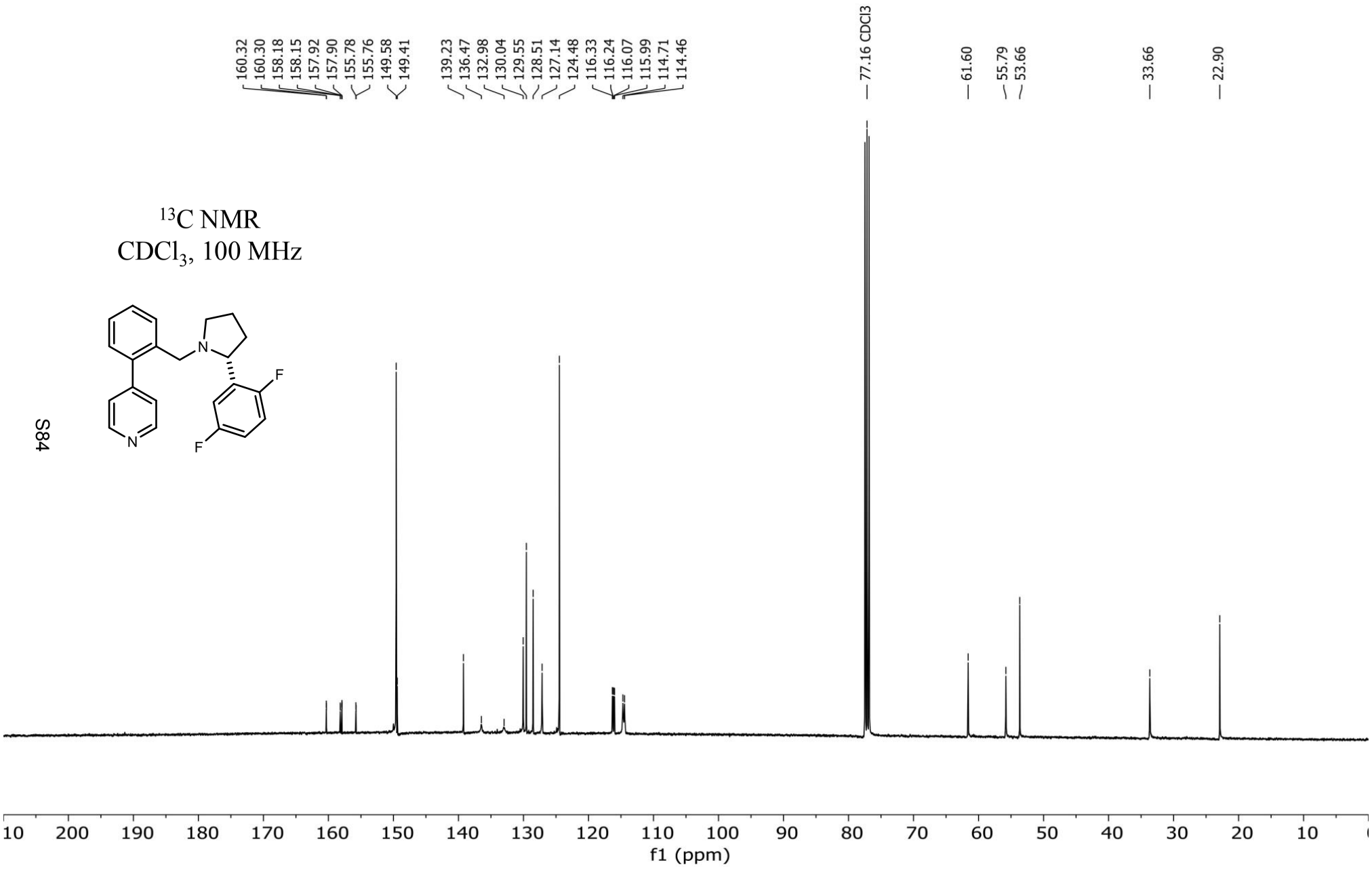



191.30
149.99
145.99
142.88
134.04
133.60
130.50
129.18
128.53
124.88
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
O
N
S82
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

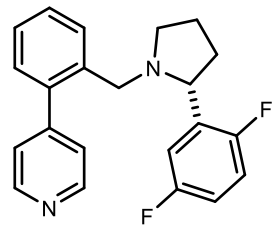


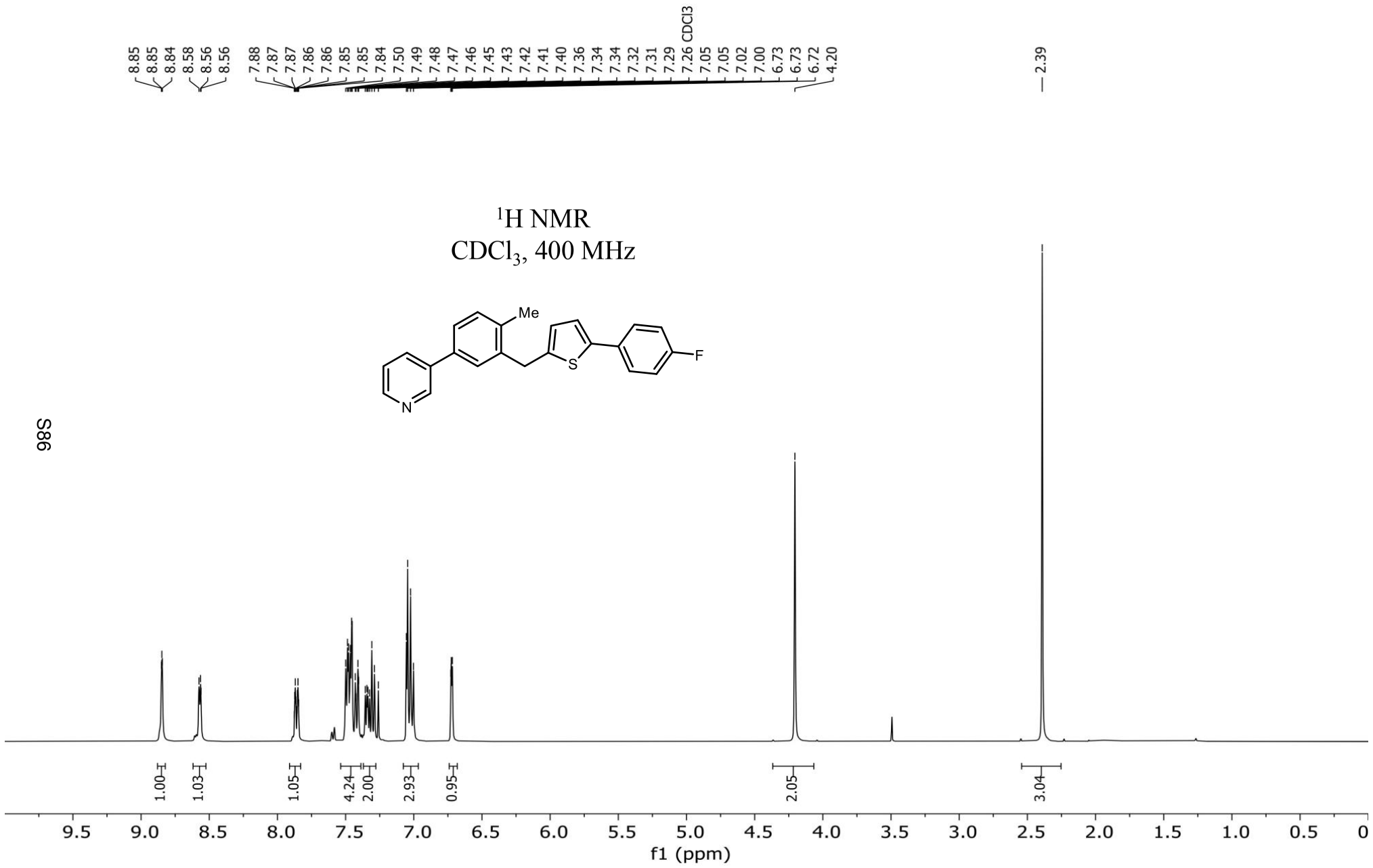
^{1}H NMR

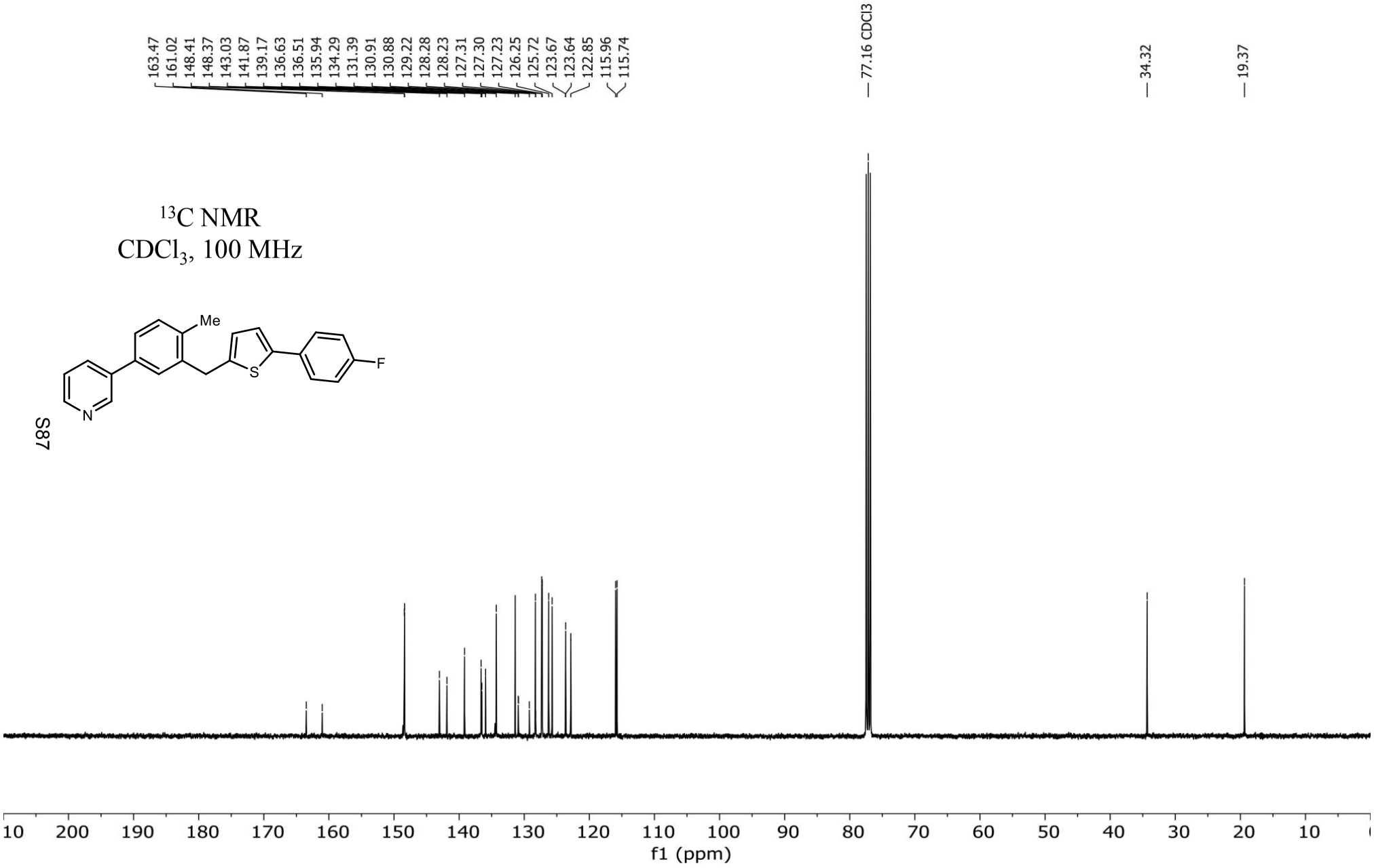
$CDCl_3$, 400 MHz


160.32
160.30
158.18
158.15
157.92
157.90
155.78
155.76
149.58
149.41
139.23
136.47
132.98
130.04
129.55
128.51
127.14
124.48
116.33
116.24
116.07
115.99
114.71
114.46
77.16 CDCl3
61.60
55.79
53.66
33.66
22.90
13C NMR
CDCl3, 100 MHz
N
F
F
N
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

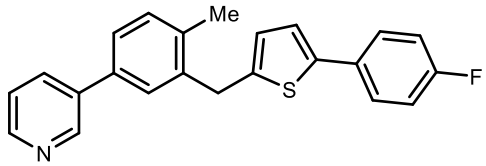
^{19}F NMR
$CDCl_3$, 365 MHz

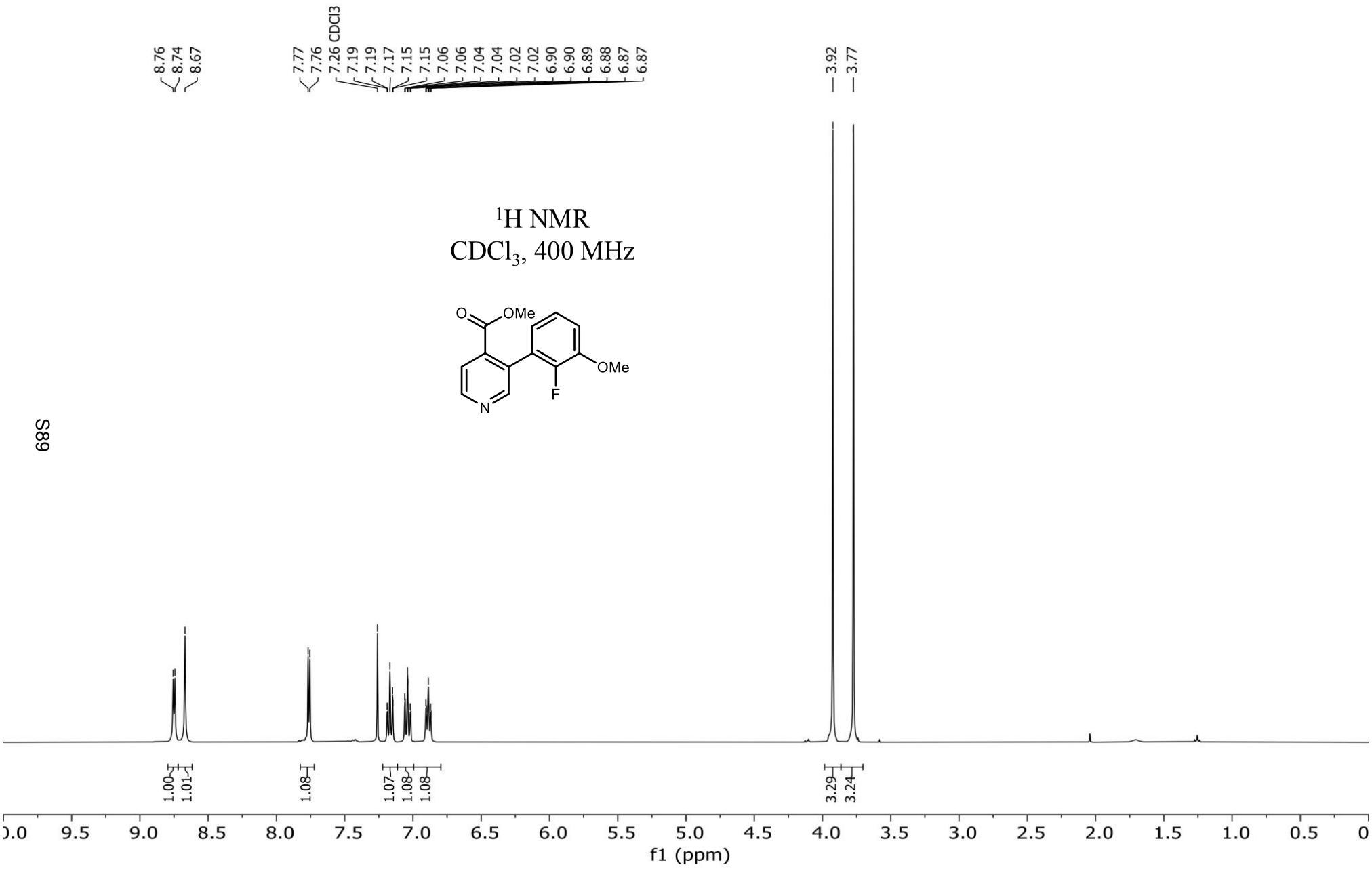


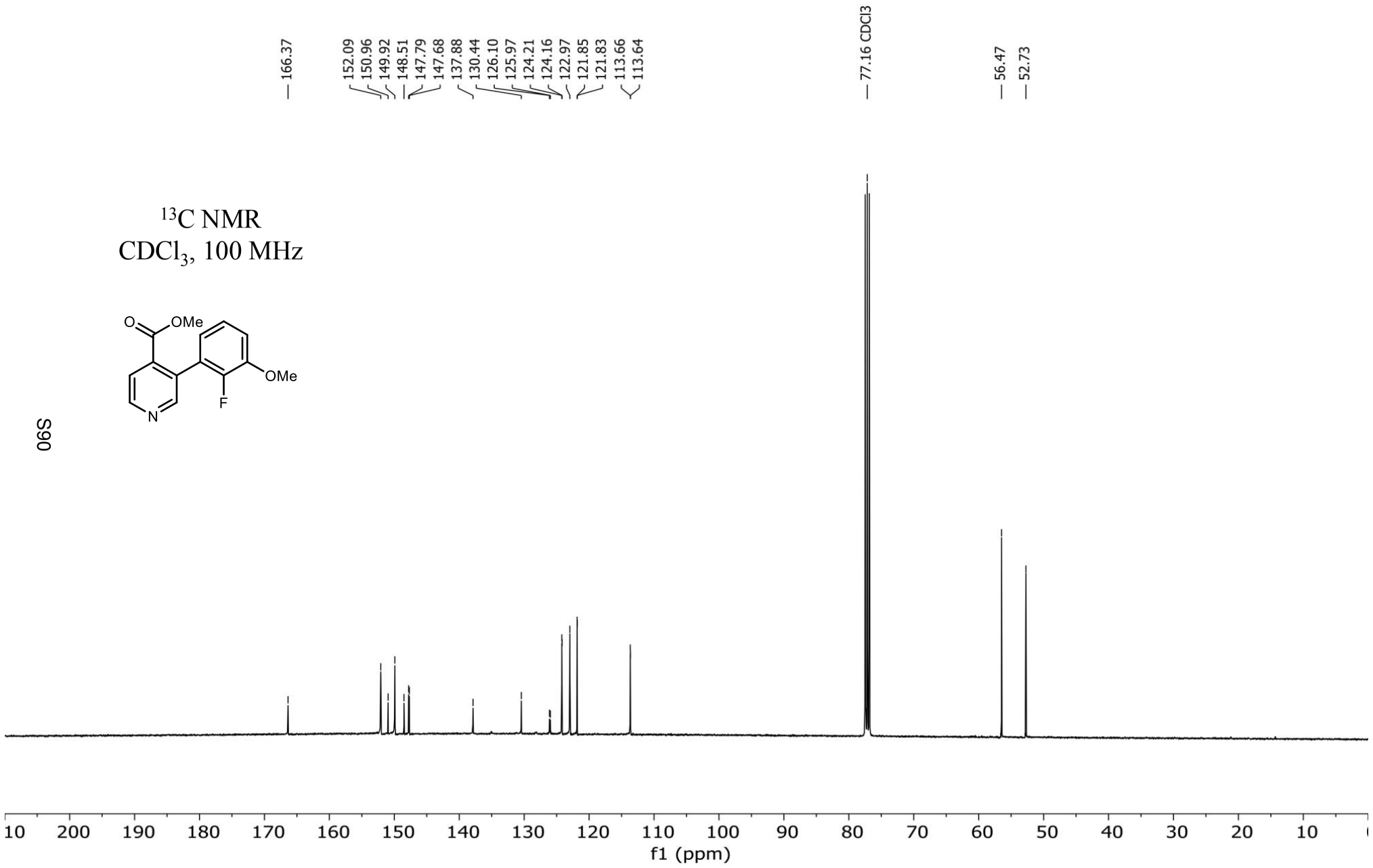

8.85
8.85
8.84
8.58
8.56
8.56
7.88
7.87
7.87
7.86
7.86
7.85
7.85
7.84
7.50
7.49
7.48
7.47
7.46
7.45
7.43
7.42
7.41
7.40
7.36
7.34
7.34
7.32
7.31
7.29
7.26 CDCl3
7.05
7.05
7.02
7.00
6.73
6.73
6.72
4.20
2.39
1H NMR
CDCl3, 400 MHz
Me
S
F
N
S86
1.00
1.03
1.05
4.24
2.00
2.93
0.95
2.05
3.04
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


163.47
161.02
148.41
148.37
143.03
141.87
139.17
136.63
136.51
135.94
134.29
131.39
130.91
130.88
129.22
128.28
128.23
127.31
127.30
127.23
126.25
125.72
123.67
123.64
122.85
115.96
115.74
77.16 CDCl3
34.32
19.37
13C NMR
CDCl3, 100 MHz
Me
F
S
N
f1 (ppm)

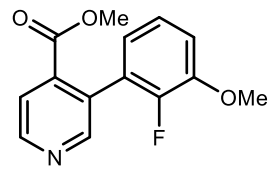
^{19}F NMR
$CDCl_3$, 365 MHz

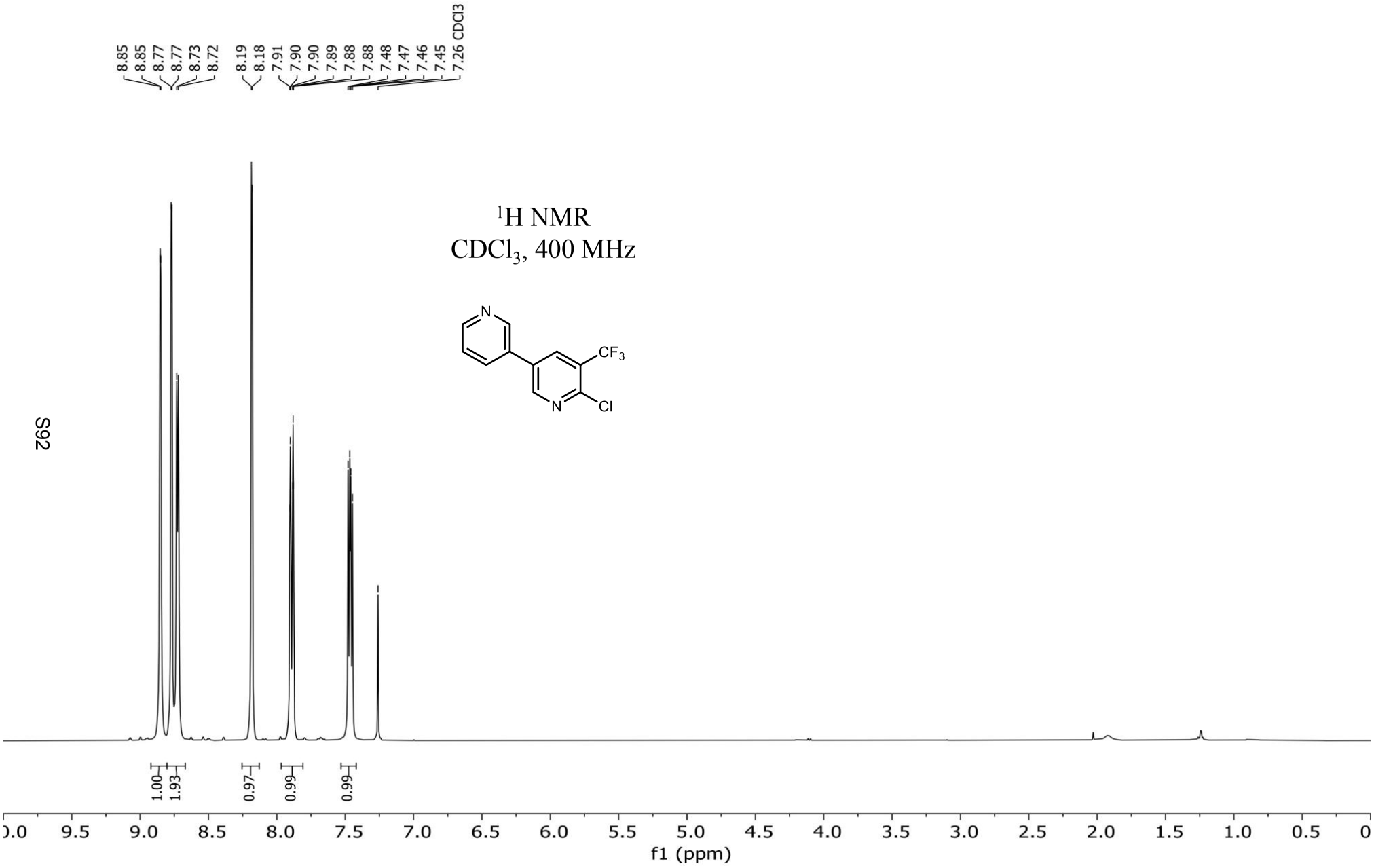


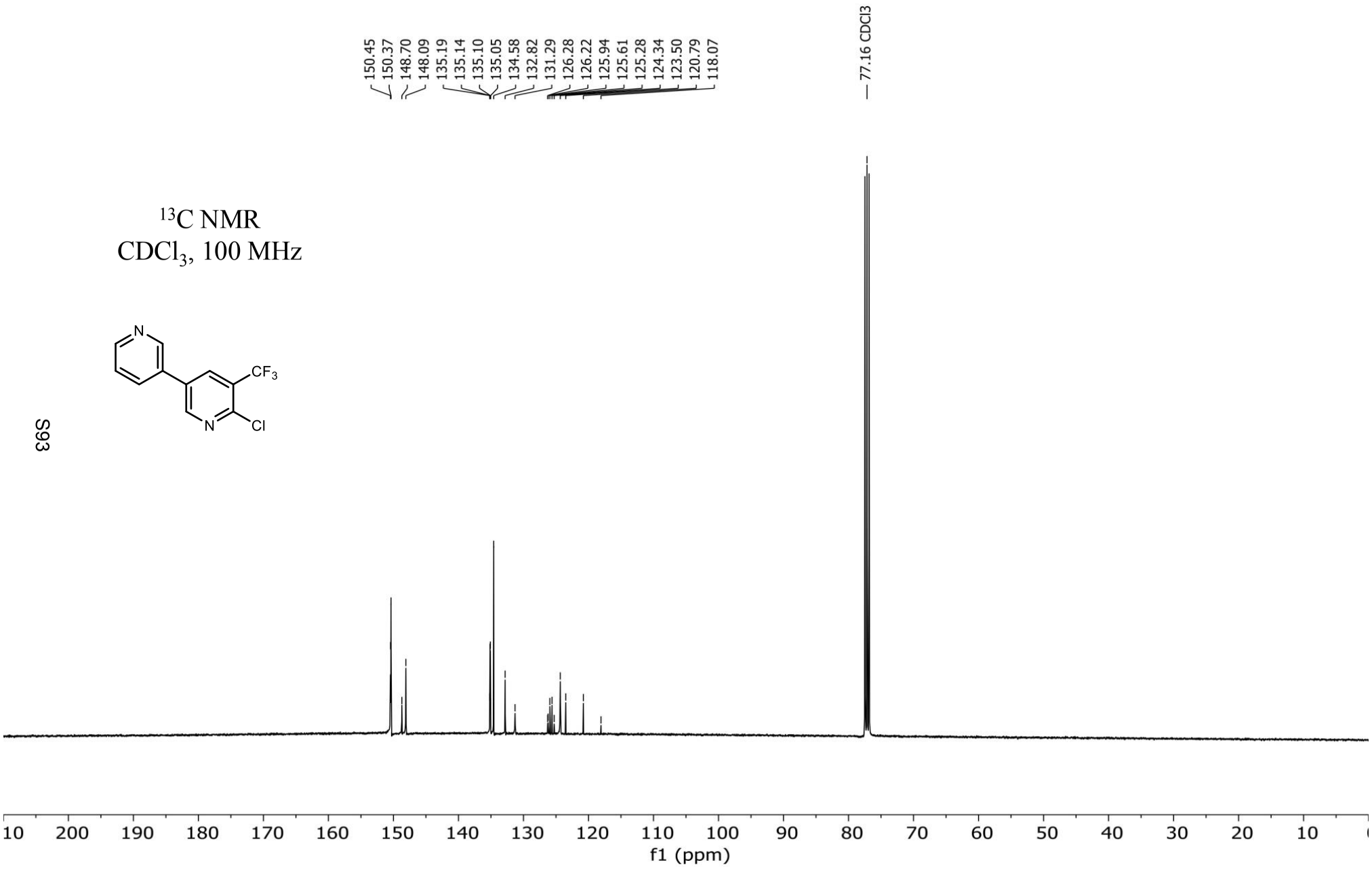

8.76
8.74
8.67
7.77
7.76
7.26 CDCl3
7.19
7.19
7.17
7.15
7.15
7.06
7.06
7.04
7.04
7.02
7.02
6.90
6.90
6.89
6.88
6.87
6.87
3.92
3.77
1H NMR
CDCl3, 400 MHz
O
OMe
OMe
F
N
1.00
1.01
1.08
1.07
1.08
1.08
3.29
3.24
f1 (ppm)

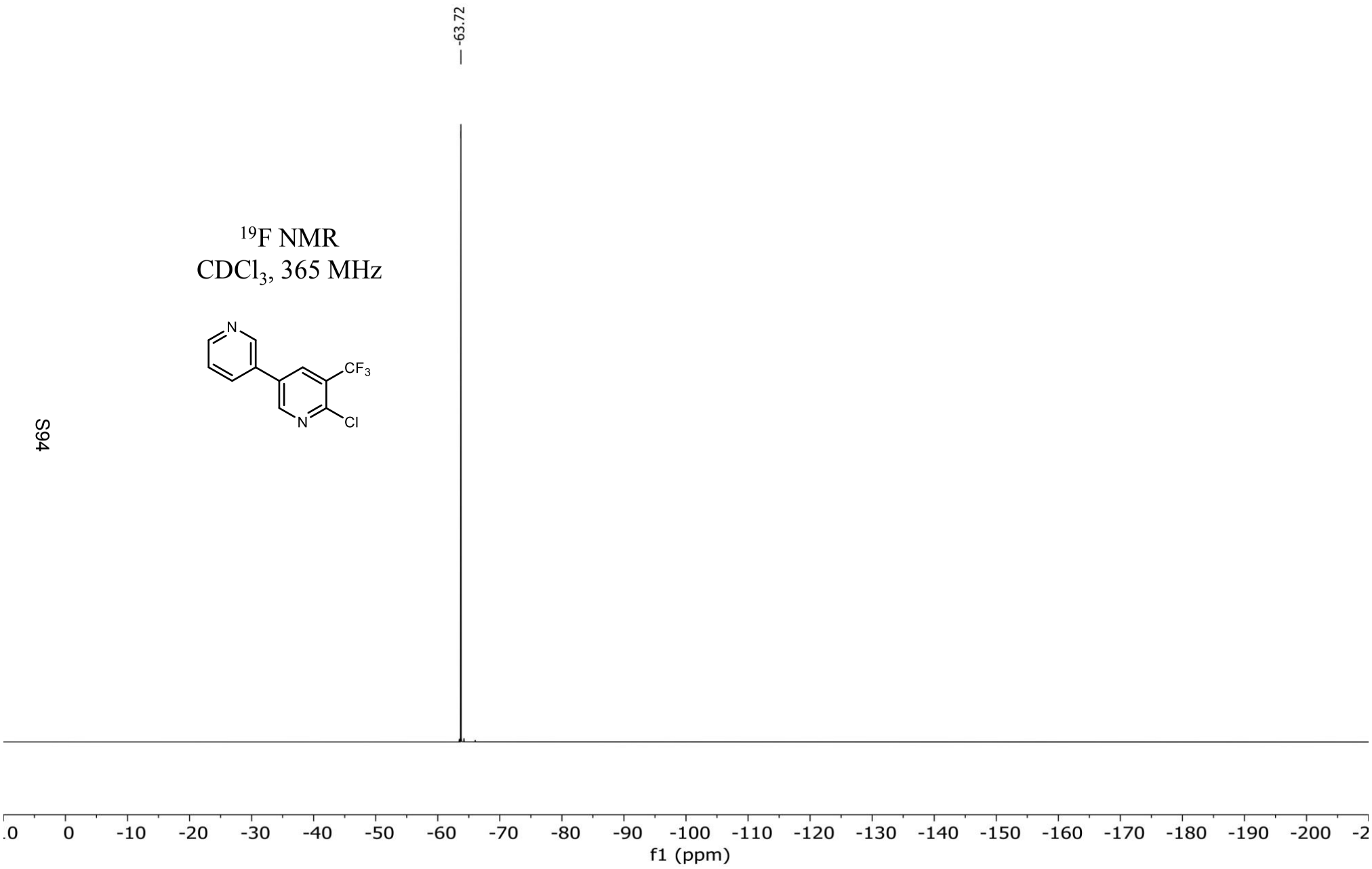

166.37
152.09
150.96
149.92
148.51
147.79
147.68
137.88
130.44
126.10
125.97
124.21
124.16
122.97
121.85
121.83
113.66
113.64
77.16 CDCl3
56.47
52.73
13C NMR
CDCl3, 100 MHz
O
OMe
OMe
F
N
f1 (ppm)

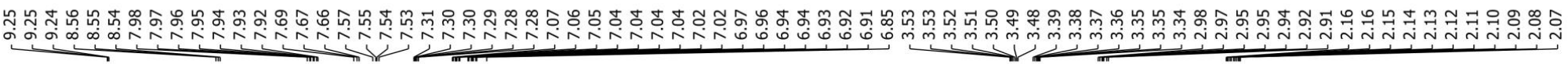
^{19}F NMR
$CDCl_3$, 365 MHz




8.85
8.85
8.77
8.77
8.73
8.72
8.19
8.18
7.91
7.90
7.90
7.89
7.88
7.88
7.48
7.47
7.46
7.45
7.26 CDCl3
1H NMR
CDCl3, 400 MHz
N
CF3
N
Cl
S92
1.00
1.93
0.97
0.99
0.99
f1 (ppm)

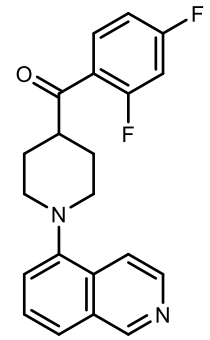

150.45
150.37
148.70
148.09
135.19
135.14
135.10
135.05
134.58
132.82
131.29
126.28
126.22
125.94
125.61
125.28
124.34
123.50
120.79
118.07
77.16 CDCl3
13C NMR
CDCl3, 100 MHz
N
CF3
N
Cl
S93
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


-63.72
^{19}F NMR
$CDCl_3$, 365 MHz
N
CF_3
N
Cl
.0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -2
f1 (ppm)



^{1}H NMR

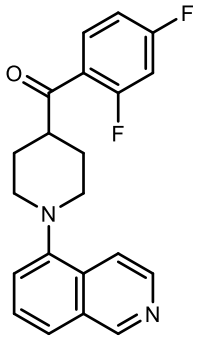
$CDCl_3$, 400 MHz



199.72
199.68
167.13
167.00
164.57
164.45
163.40
163.28
160.86
160.74
153.37
153.29
152.97
152.94
149.44
149.35
149.32
143.13
142.81
142.75
133.26
133.23
133.18
133.16
133.12
133.08
131.97
131.95
131.65
131.54
131.44
131.33
130.68
130.44
129.98
127.73
127.37
127.34
126.58
122.54
122.46
122.41
122.05
122.01
121.91
121.87
120.55
118.63
118.61
118.47
116.70
116.67
116.64
112.80
112.71
112.68
112.50
112.46
109.91
109.80
109.69
109.58
108.90
108.67
106.54
106.31
105.10
104.92
104.89
104.85
104.82
104.57
77.16 CDCl3
53.07
28.76

^{13}C NMR

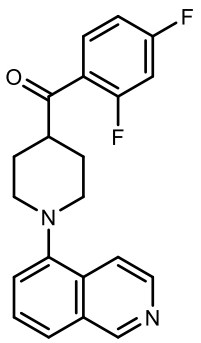
$CDCl_3$, 100 MHz



96S

^{19}F NMR

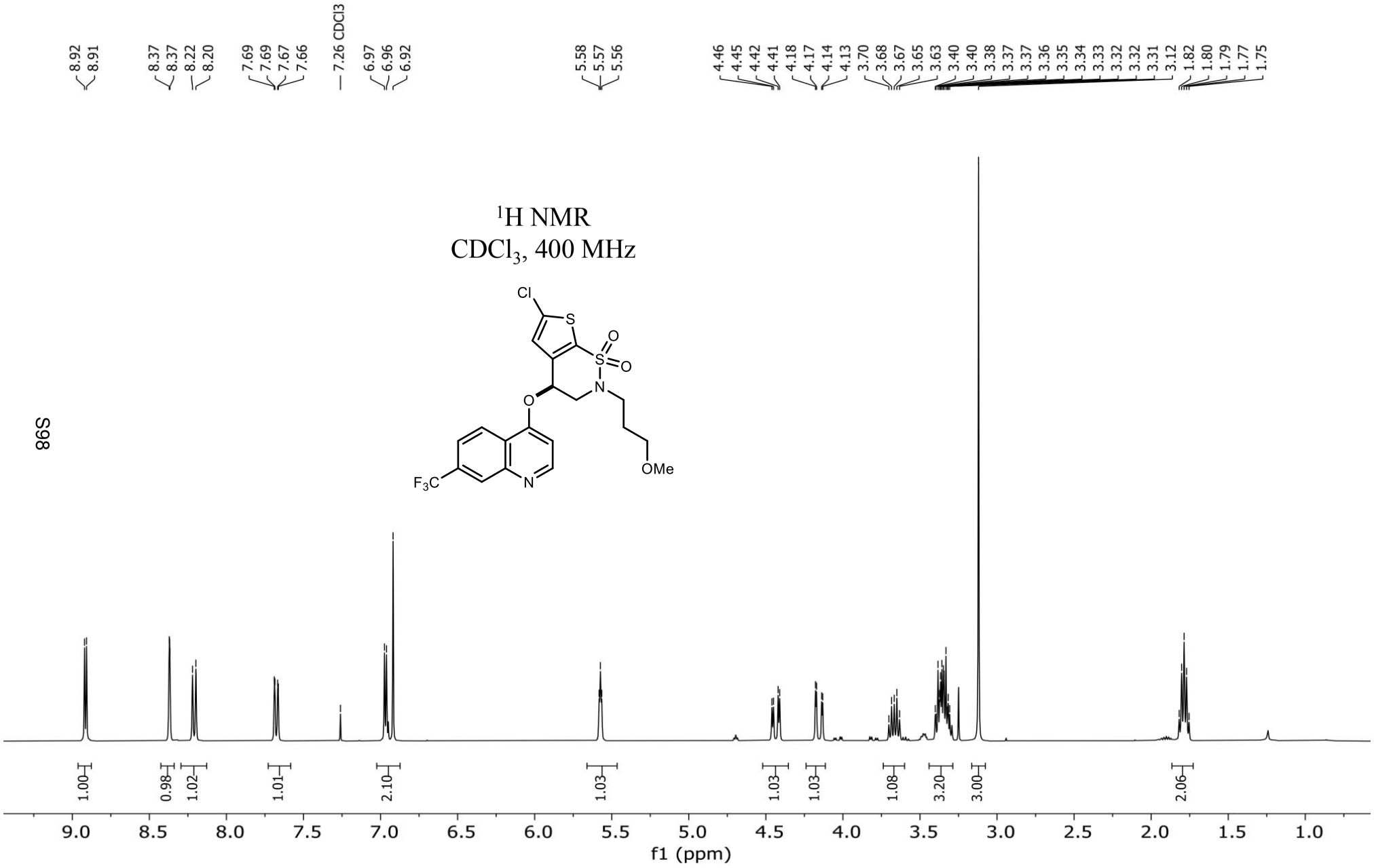
$CDCl_3$, 365 MHz

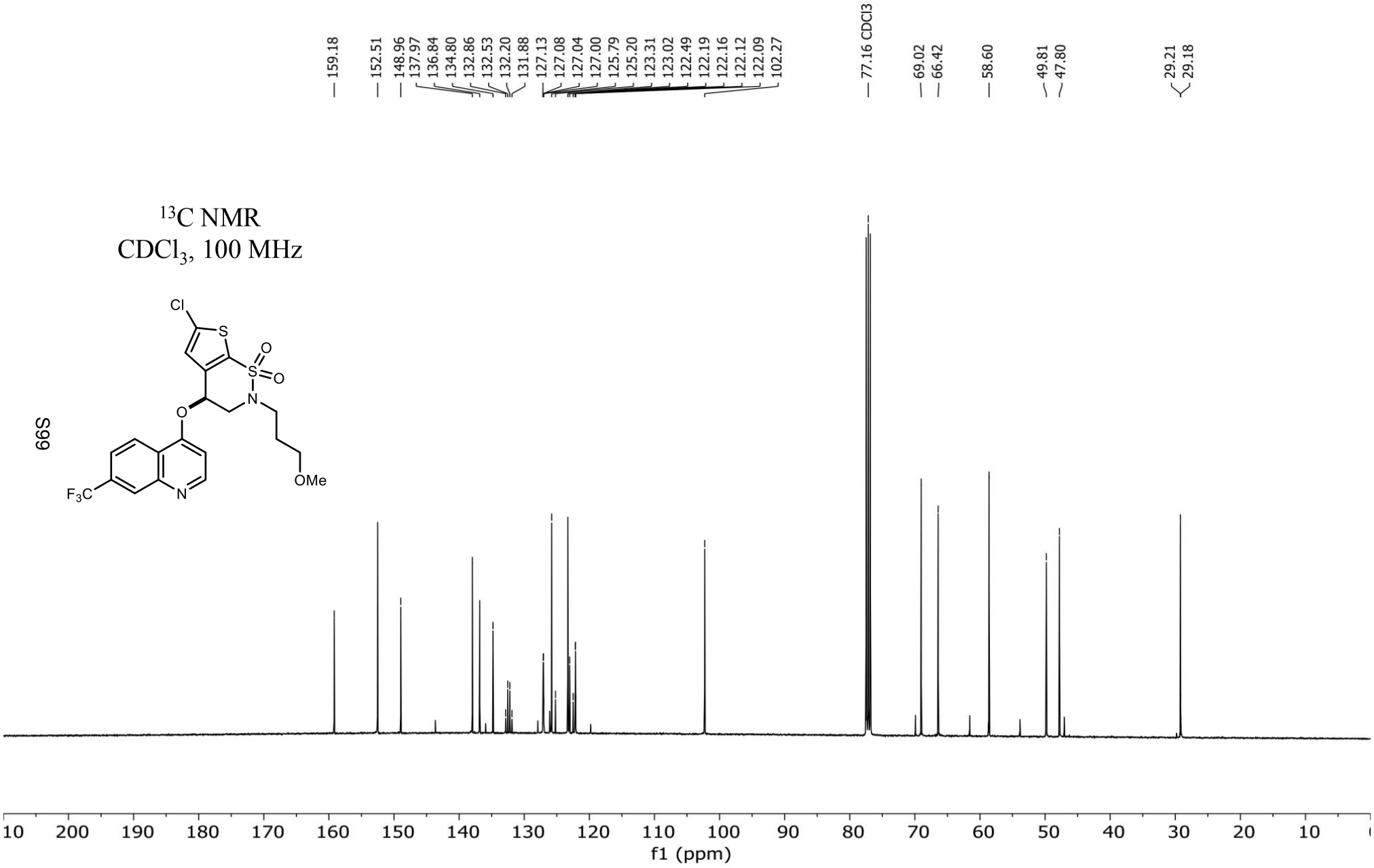


-101.92
-101.95
-101.96
-101.98
-106.54
-106.57

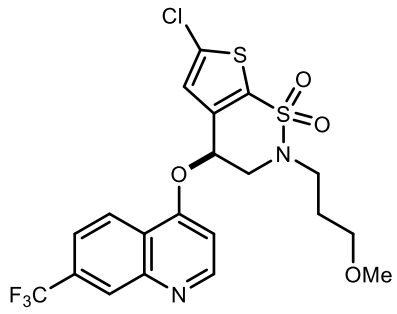
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210

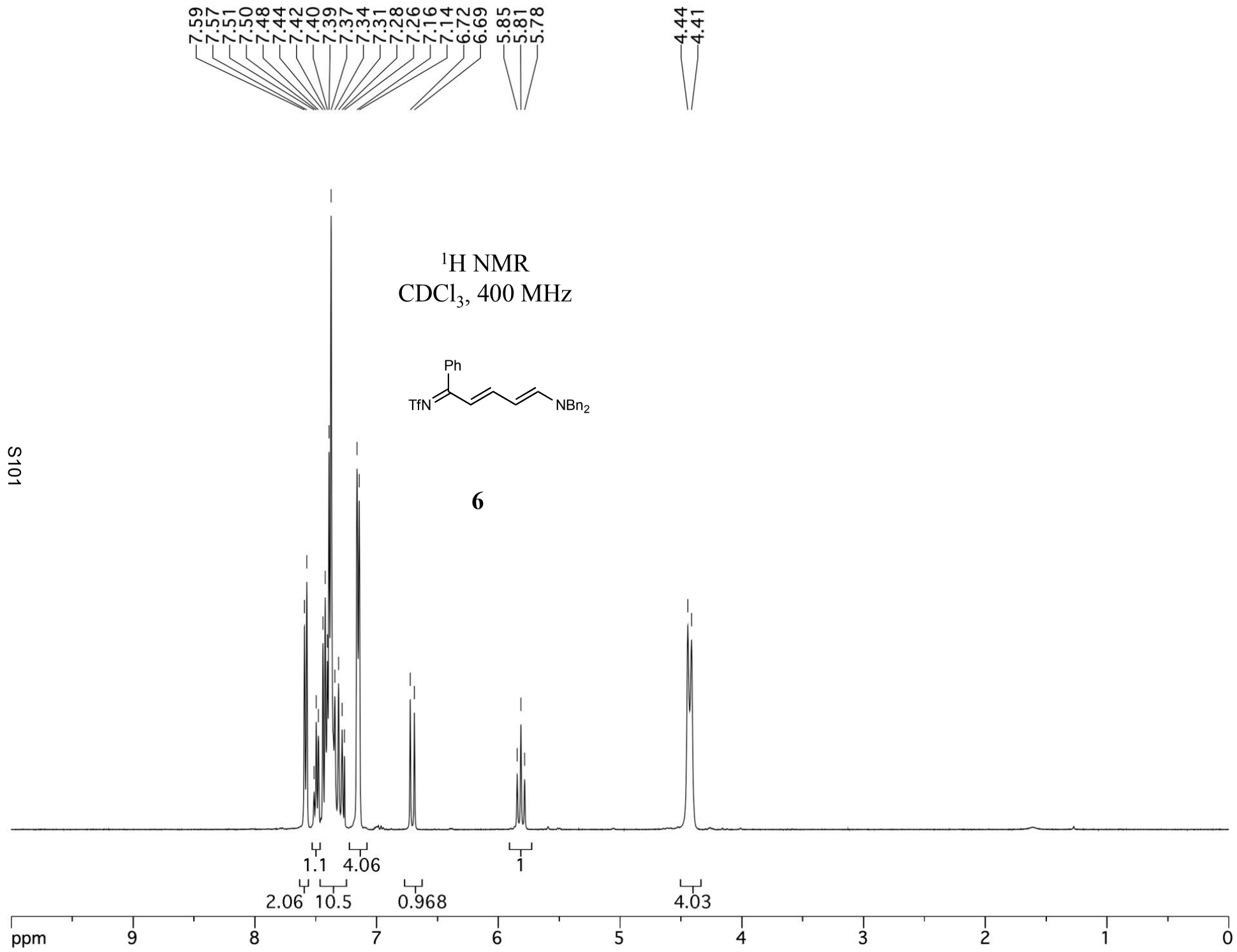
f1 (ppm)


8.92
8.91
8.37
8.37
8.22
8.20
7.69
7.69
7.67
7.66
7.26 CDCl3
6.97
6.96
6.92
5.58
5.57
5.56
4.46
4.45
4.42
4.41
4.18
4.17
4.14
4.13
3.70
3.68
3.67
3.65
3.63
3.40
3.40
3.38
3.37
3.37
3.36
3.35
3.34
3.33
3.32
3.32
3.31
3.12
1.82
1.80
1.79
1.77
1.75
S98
1H NMR
CDCl3, 400 MHz
Cl
S
O
S
O
N
O
OMe
F3C
N
1.00
0.98
1.02
1.01
2.10
1.03
1.03
1.03
1.08
3.20
3.00
2.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


159.18
152.51
148.96
137.97
136.84
134.80
132.86
132.53
132.20
131.88
127.13
127.08
127.04
127.00
125.79
125.20
123.31
123.02
122.49
122.19
122.16
122.12
122.09
102.27
77.16 CDCl3
69.02
66.42
58.60
49.81
47.80
29.21
29.18
13C NMR
CDCl3, 100 MHz
66S
Cl
S
O
S
O
N
O
OMe
F3C
N
f1 (ppm)

^{19}F NMR
$CDCl_3$, 365 MHz

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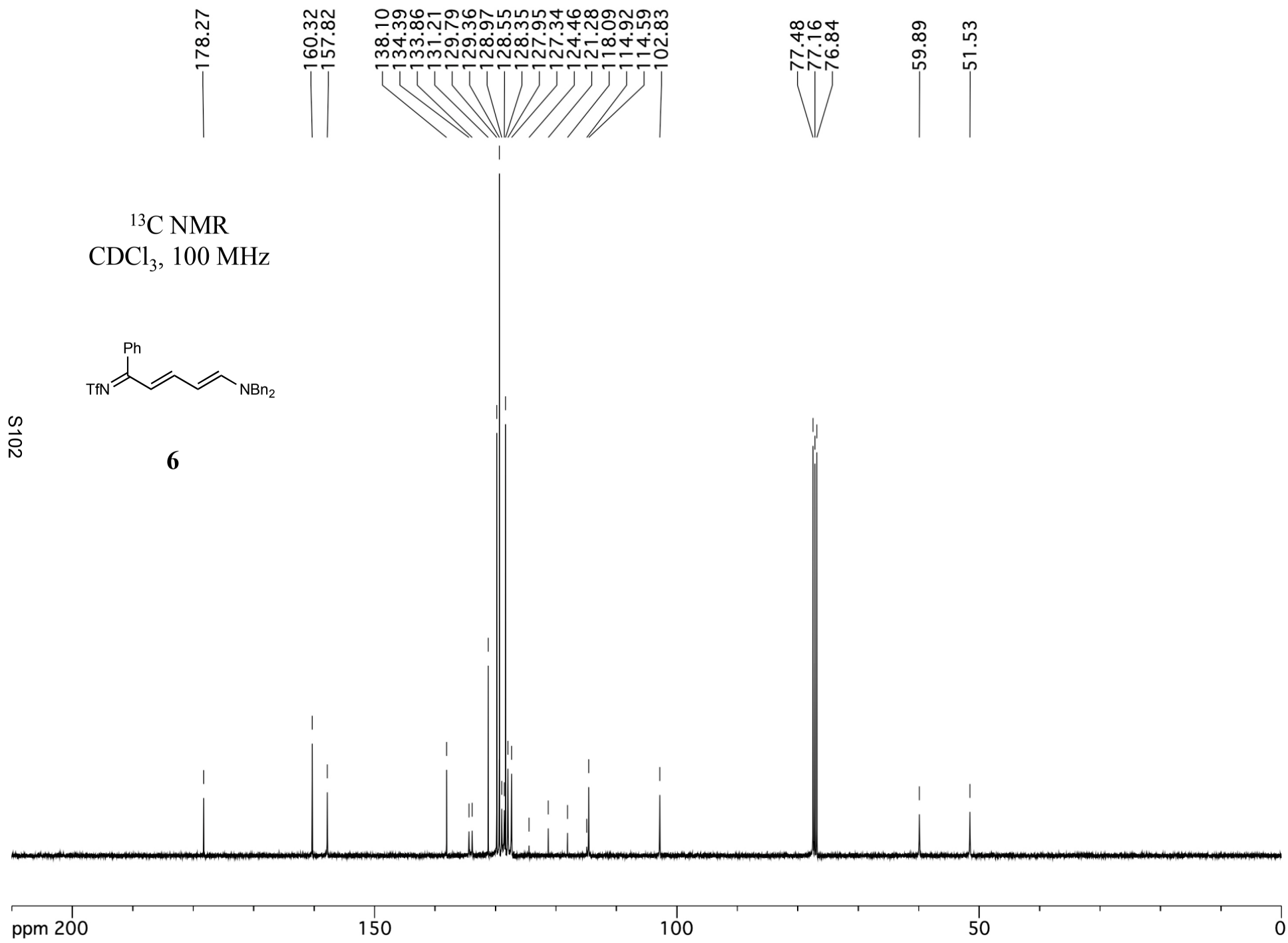
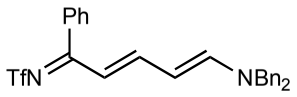
7.57
7.51
7.50
7.48
7.44
7.42
7.40
7.39
7.37
7.34
7.31
7.28
7.26
7.16
7.14
6.72
6.69
5.85
5.81
5.78
4.44
4.41
1H NMR
CDCl3, 400 MHz
Ph
TfN
NBn2
6
S101
1.1
4.06
1
2.06
10.5
0.968
4.03
ppm
9
8
7
6
5
4
3
2
1
0


178.27
160.32
157.82
138.10
134.39
133.86
131.21
129.79
129.36
128.97
128.55
128.35
127.95
127.34
124.46
121.28
118.09
114.92
114.59
102.83
77.48
77.16
76.84
59.89
51.53
^{13}C NMR
$CDCl_3$, 100 MHz
Ph
TfN
NBn$_2$
6
S102
ppm 200
150
100
50
0

^{19}F NMR
$CDCl_3$, 365 MHz



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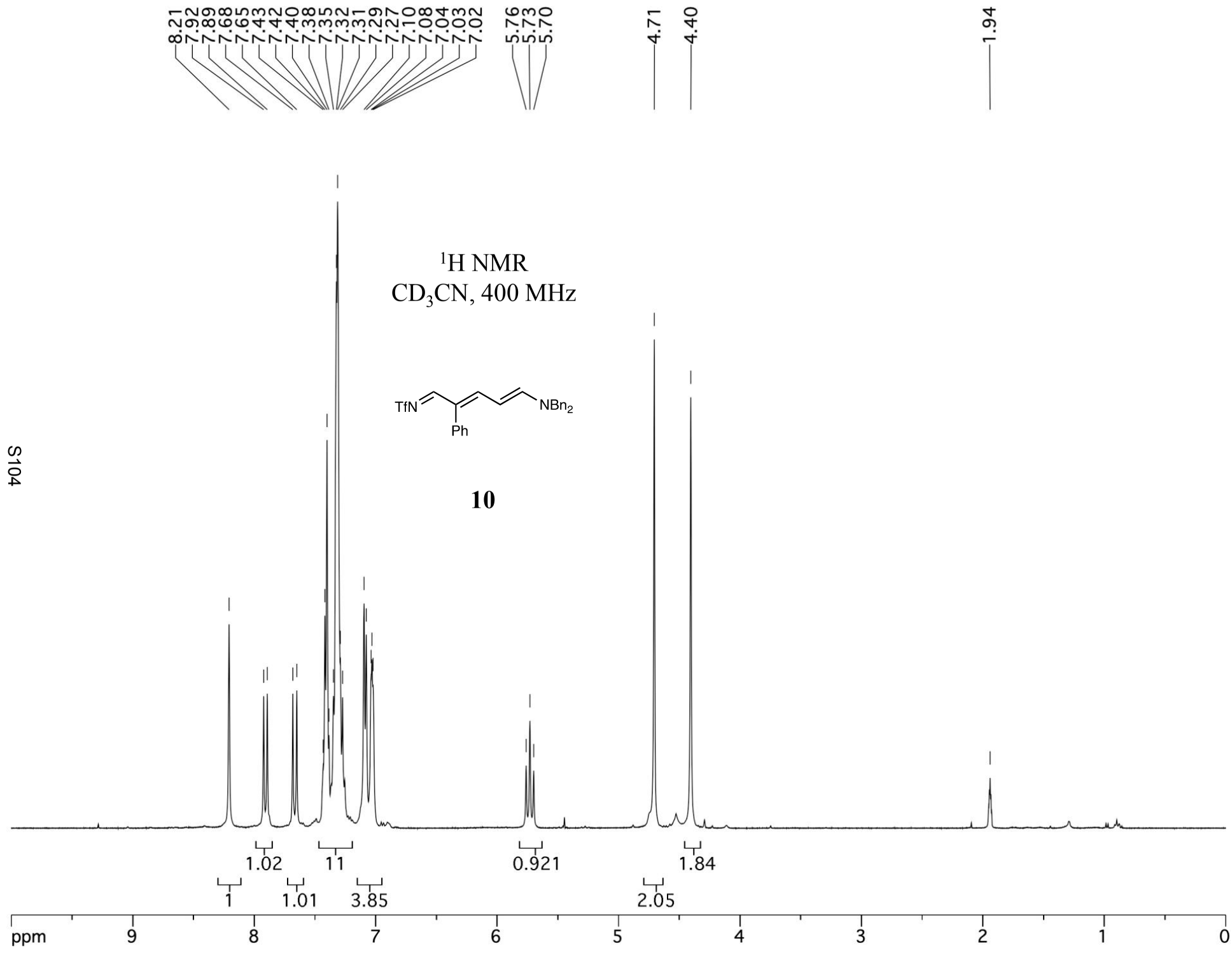
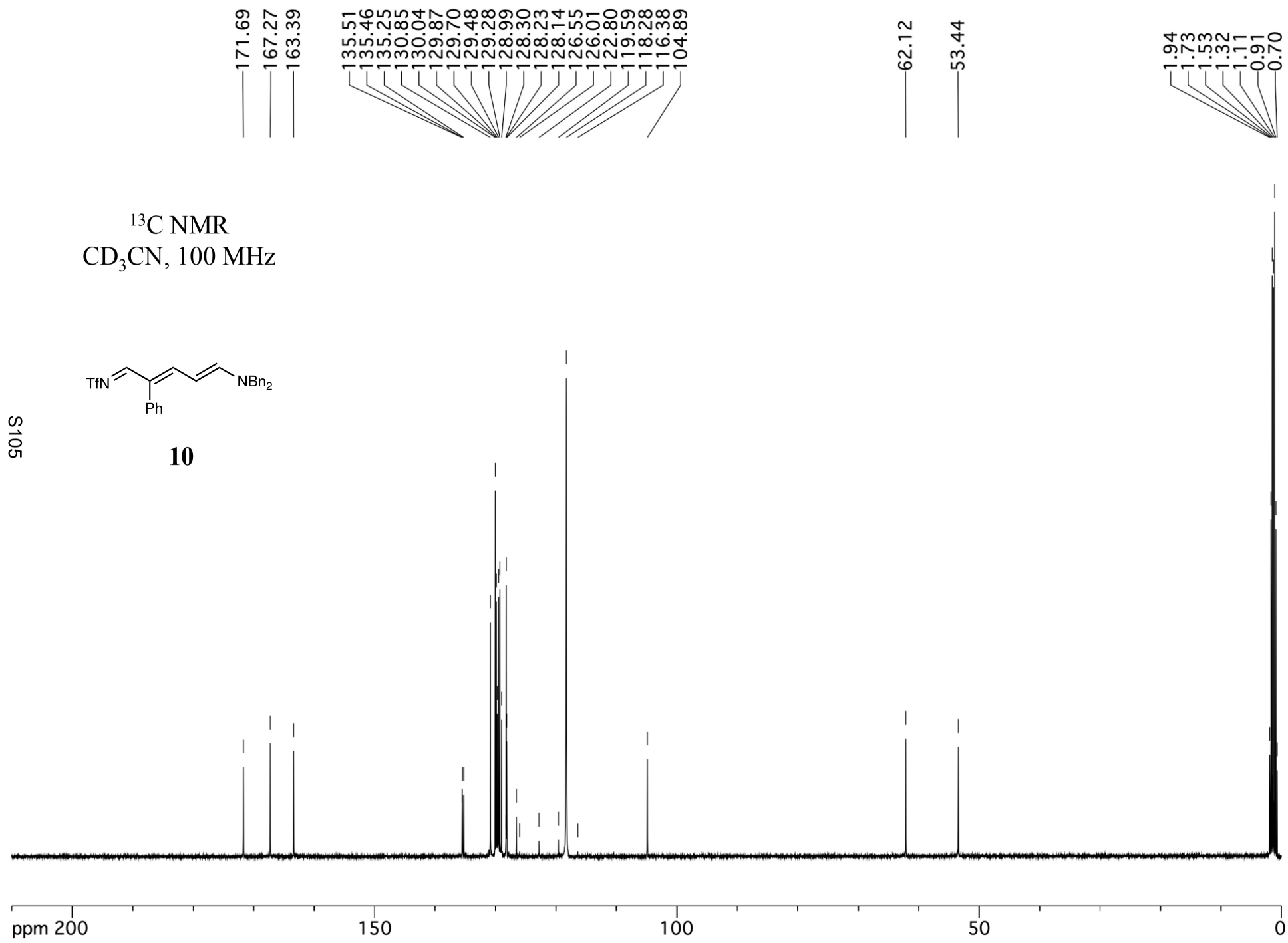
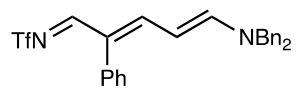

8.21
7.92
7.89
7.68
7.65
7.43
7.42
7.40
7.38
7.35
7.32
7.31
7.29
7.27
7.10
7.08
7.04
7.03
7.02
5.76
5.73
5.70
4.71
4.40
1.94
^{1}H NMR
CD_3CN, 400 MHz
TfN
NBn$_2$
Ph
10
1.02
11
0.921
1.84
1
1.01
3.85
2.05
ppm
9
8
7
6
5
4
3
2
1
0


171.69
167.27
163.39
135.51
135.46
135.25
130.85
130.04
129.87
129.70
129.48
129.28
128.99
128.30
128.23
128.14
126.55
126.01
122.80
119.59
118.28
116.38
104.89
62.12
53.44
1.94
1.73
1.53
1.32
1.11
0.91
0.70
^{13}C NMR
CD_3CN, 100 MHz
TfN
NBn$_2$
Ph
10
S105
ppm 200
150
100
50
0

^{19}F NMR
CD_3CN, 365 MHz



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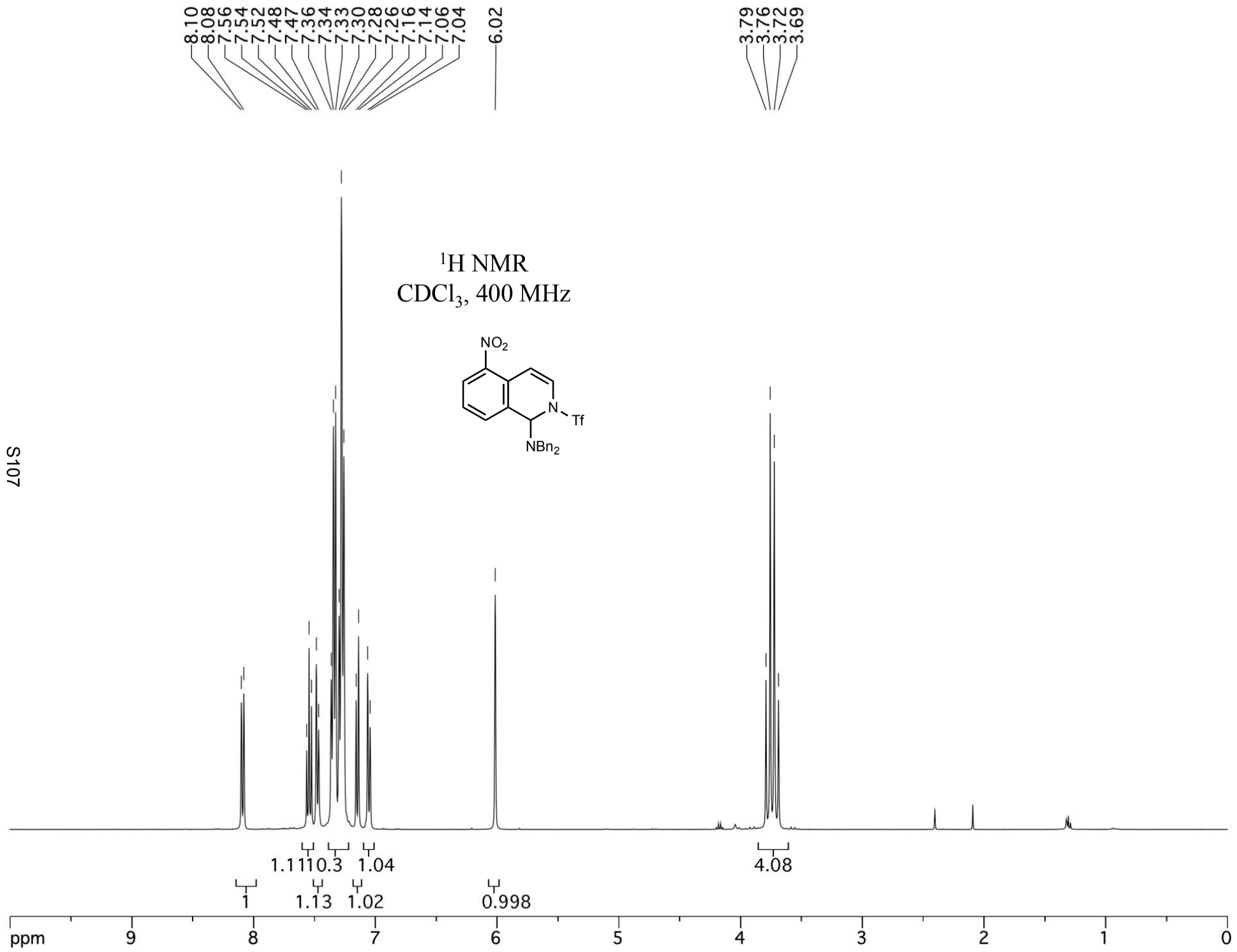
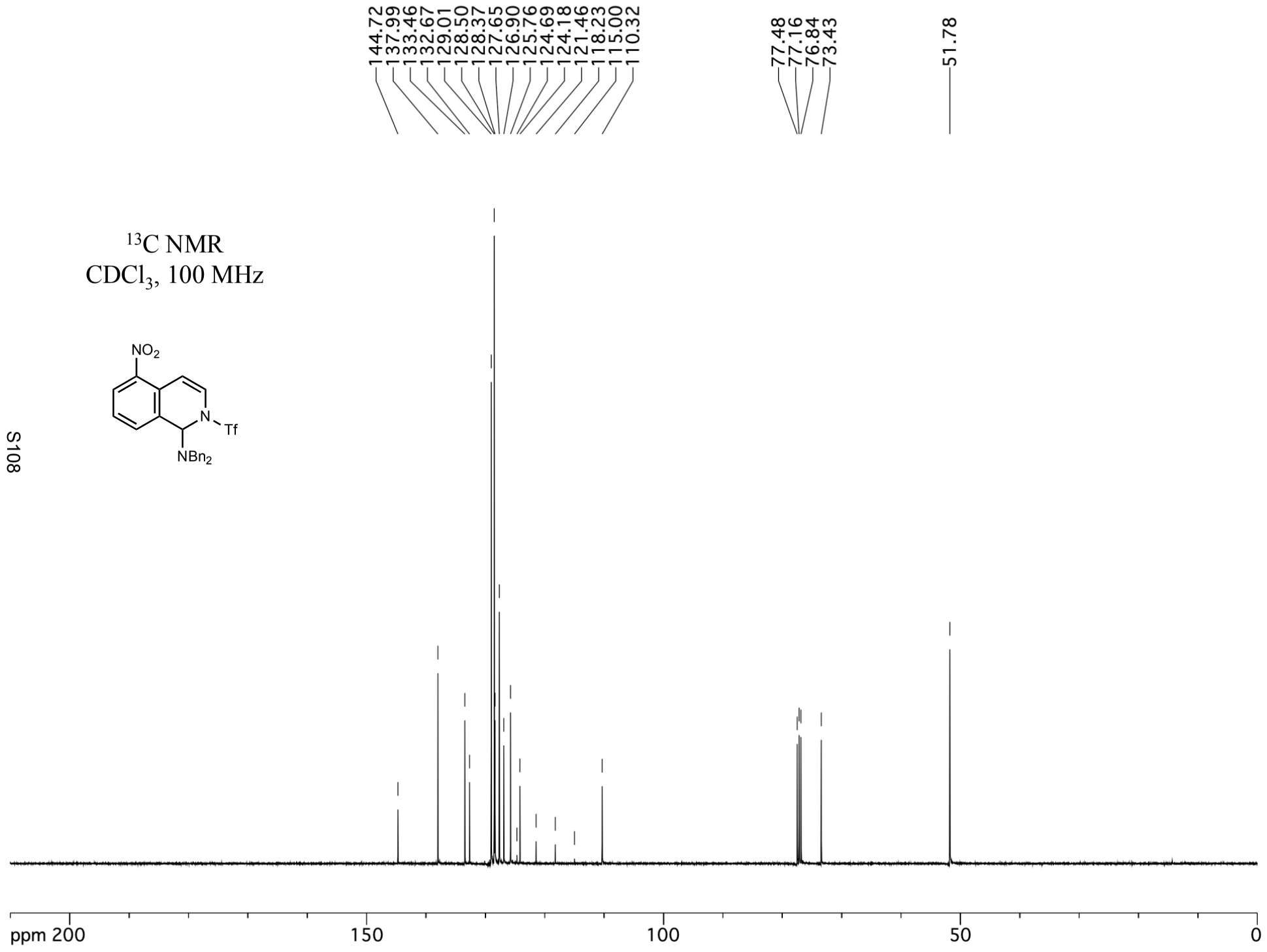
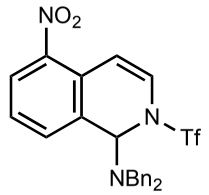
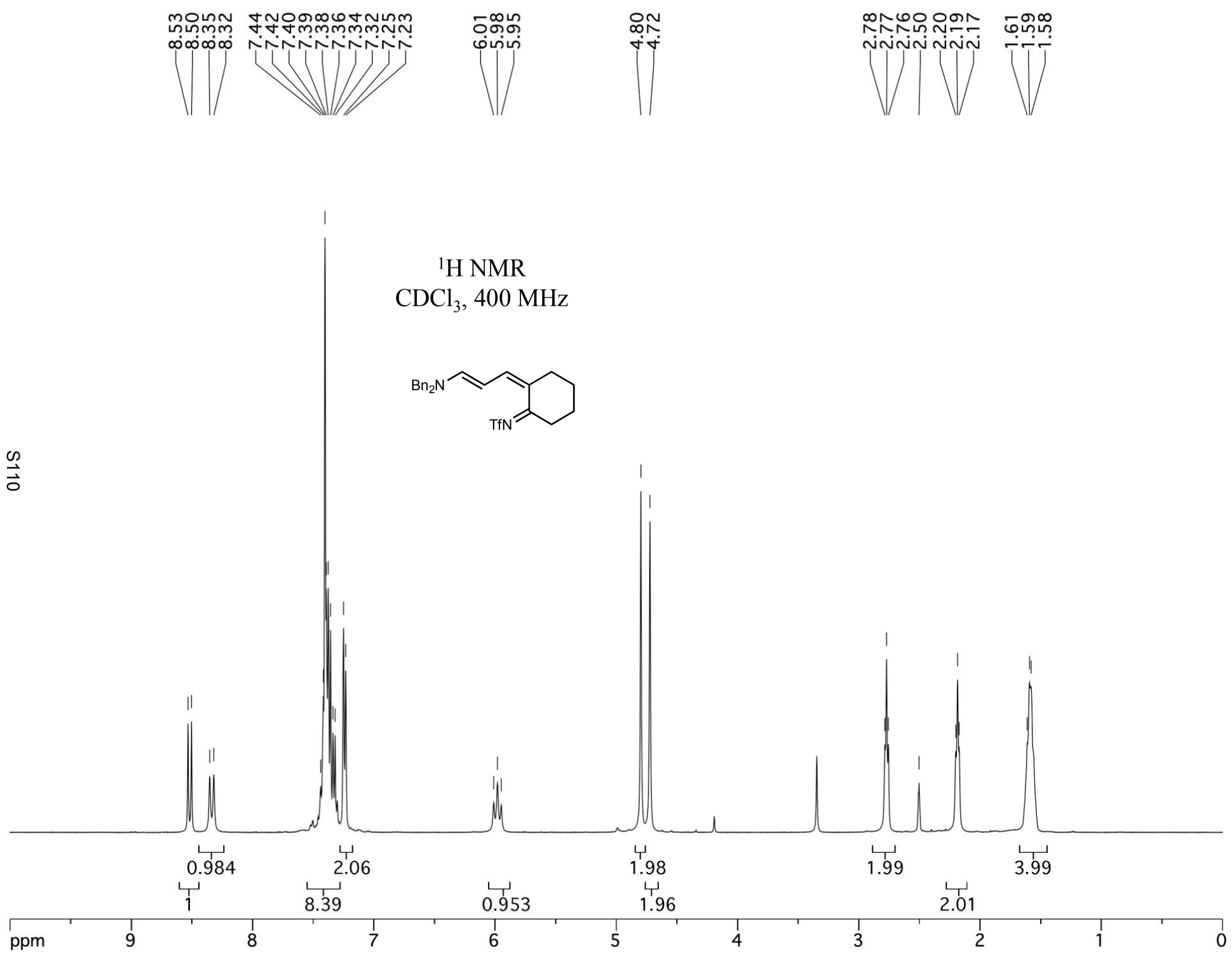
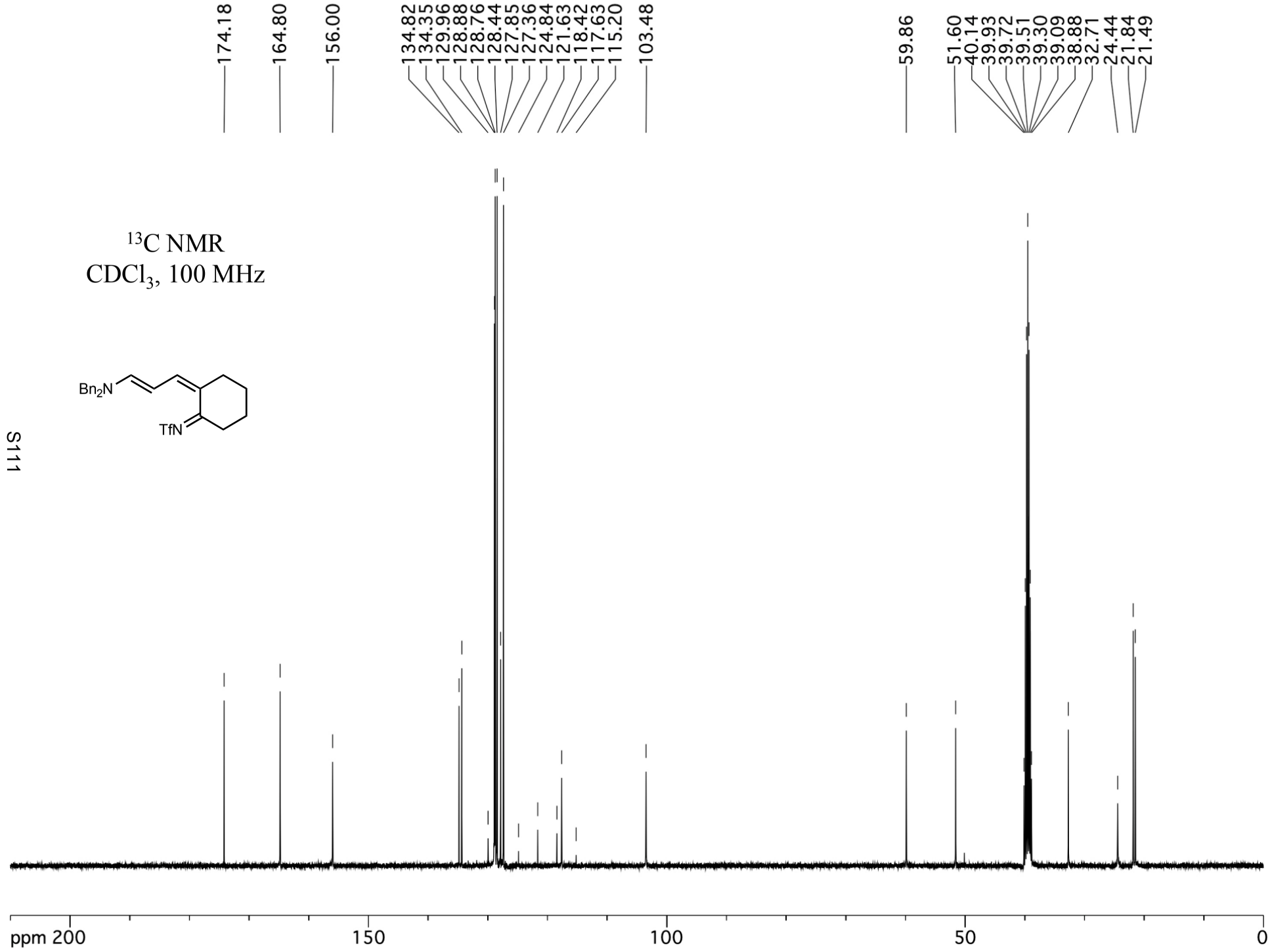

8.10
8.08
7.56
7.54
7.52
7.48
7.47
7.36
7.34
7.33
7.30
7.28
7.26
7.16
7.14
7.06
7.04
6.02
3.79
3.76
3.72
3.69
1H NMR
CDCl3, 400 MHz
NO2
N
Tf
NBn2
1.11
1
0.3
1.04
4.08
1
1.13
1.02
0.998
ppm
9
8
7
6
5
4
3
2
1
0

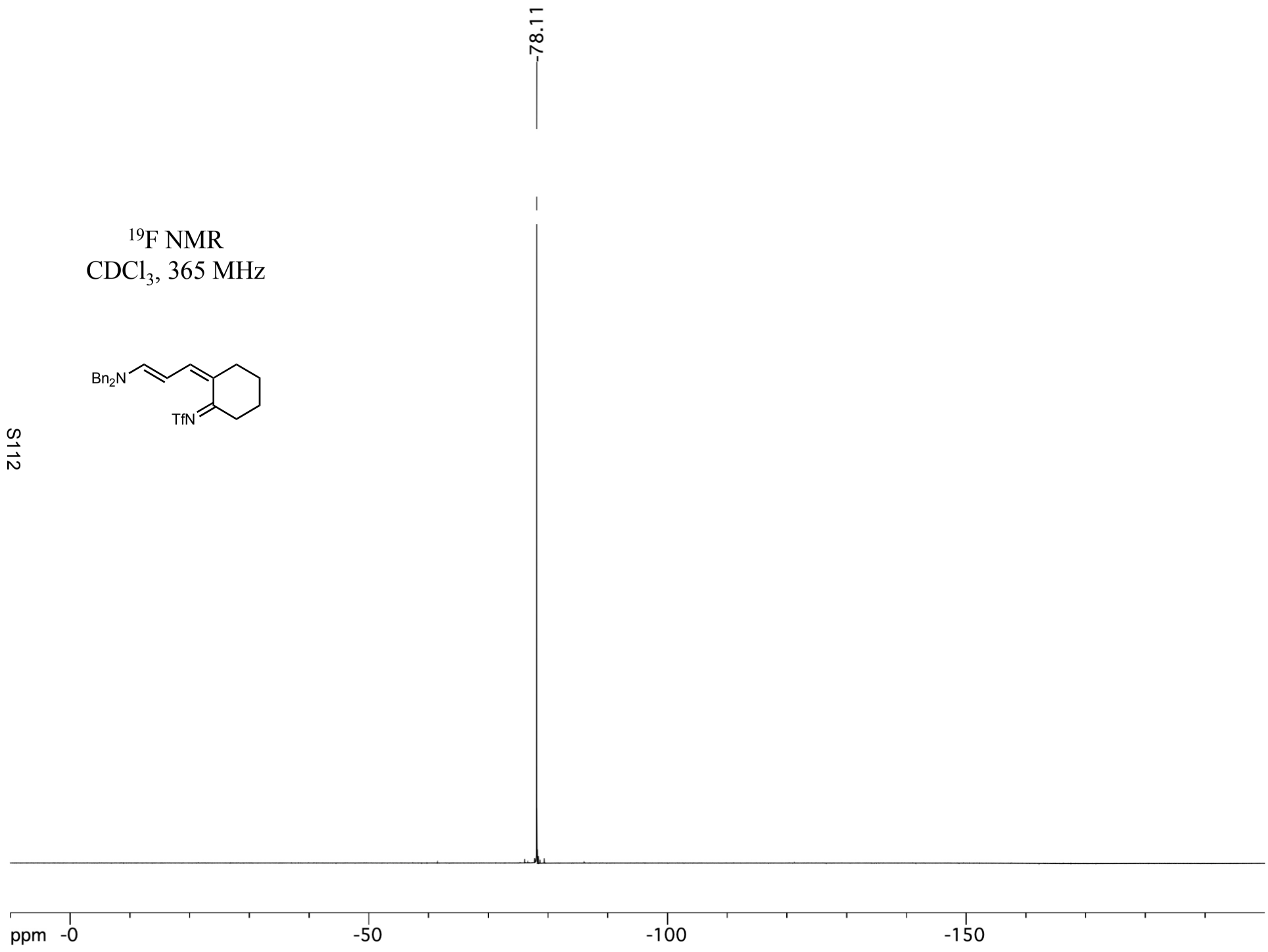

144.72
137.99
133.46
132.67
129.01
128.50
128.37
127.65
126.90
125.76
124.69
124.18
121.46
118.23
115.00
110.32
77.48
77.16
76.84
73.43
51.78
^{13}C NMR
$CDCl_3$, 100 MHz
NO_2
N
Tf
NBn_2
ppm 200
150
100
50
0

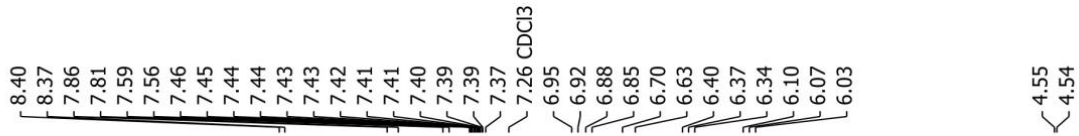
^{19}F NMR
$CDCl_3$, 365 MHz



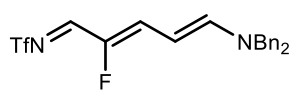

8.53
8.50
8.35
8.32
7.44
7.42
7.40
7.39
7.38
7.36
7.34
7.32
7.25
7.23
6.01
5.98
5.95
4.80
4.72
2.78
2.77
2.76
2.50
2.20
2.19
2.17
1.61
1.59
1.58
^{1}H NMR
$CDCl_3$, 400 MHz
Bn_2N
TfN
S110
0.984
2.06
1.98
1.99
3.99
1
8.39
0.953
1.96
2.01
ppm
9
8
7
6
5
4
3
2
1
0


174.18
164.80
156.00
134.82
134.35
129.96
128.88
128.76
128.44
127.85
127.36
124.84
121.63
118.42
117.63
115.20
103.48
59.86
51.60
40.14
39.93
39.72
39.51
39.30
39.09
38.88
32.71
24.44
21.84
21.49
^{13}C NMR
$CDCl_3$, 100 MHz
Bn_2N
TfN
ppm 200
150
100
50
0

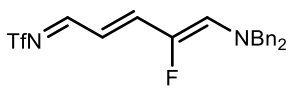

-78.11
^{19}F NMR
$CDCl_3$, 365 MHz
Bn_2N
TfN
ppm -0
-50
-100
-150



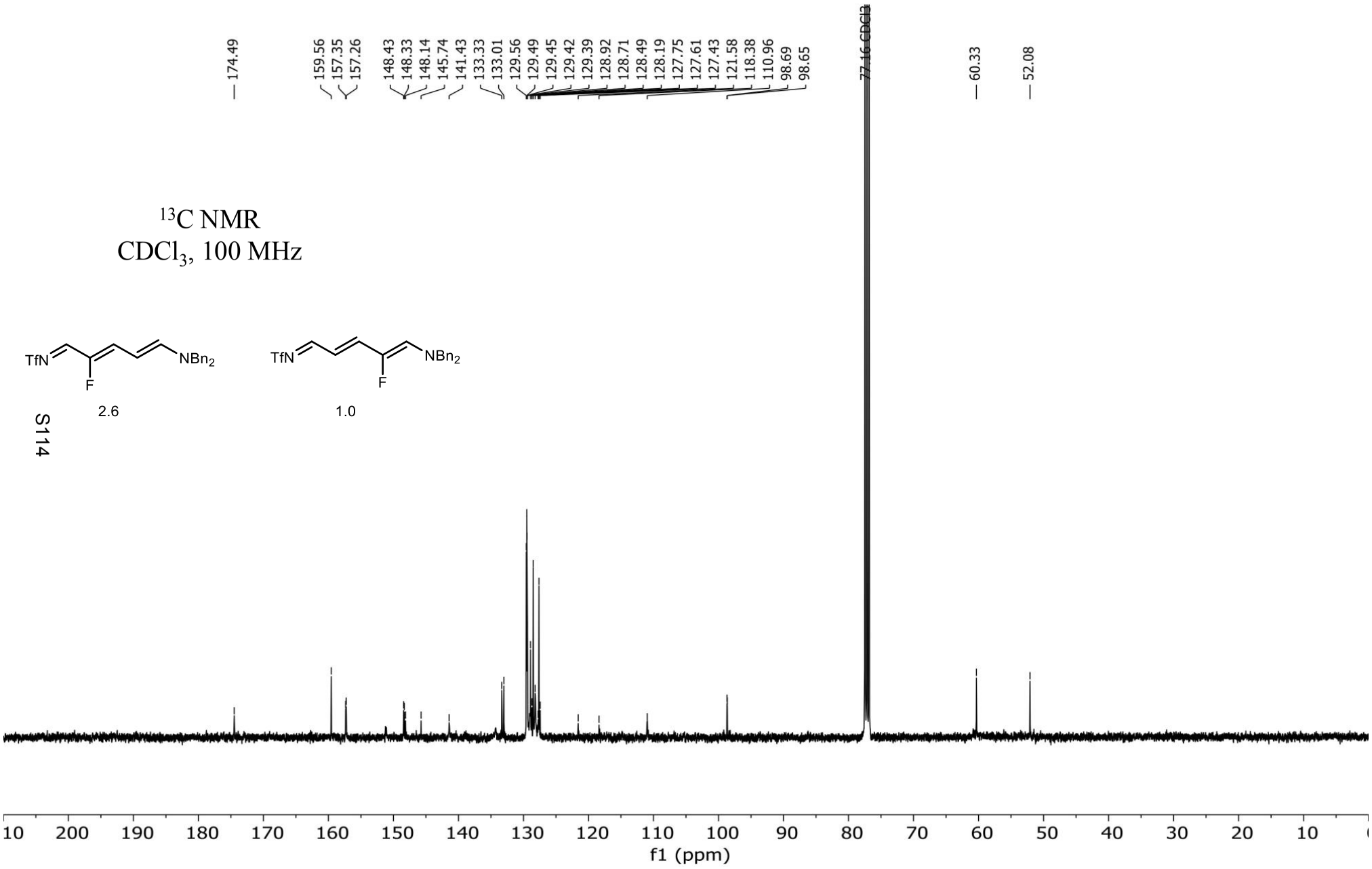
^{1}H NMR
$CDCl_3$, 400 MHz



2.6



1.0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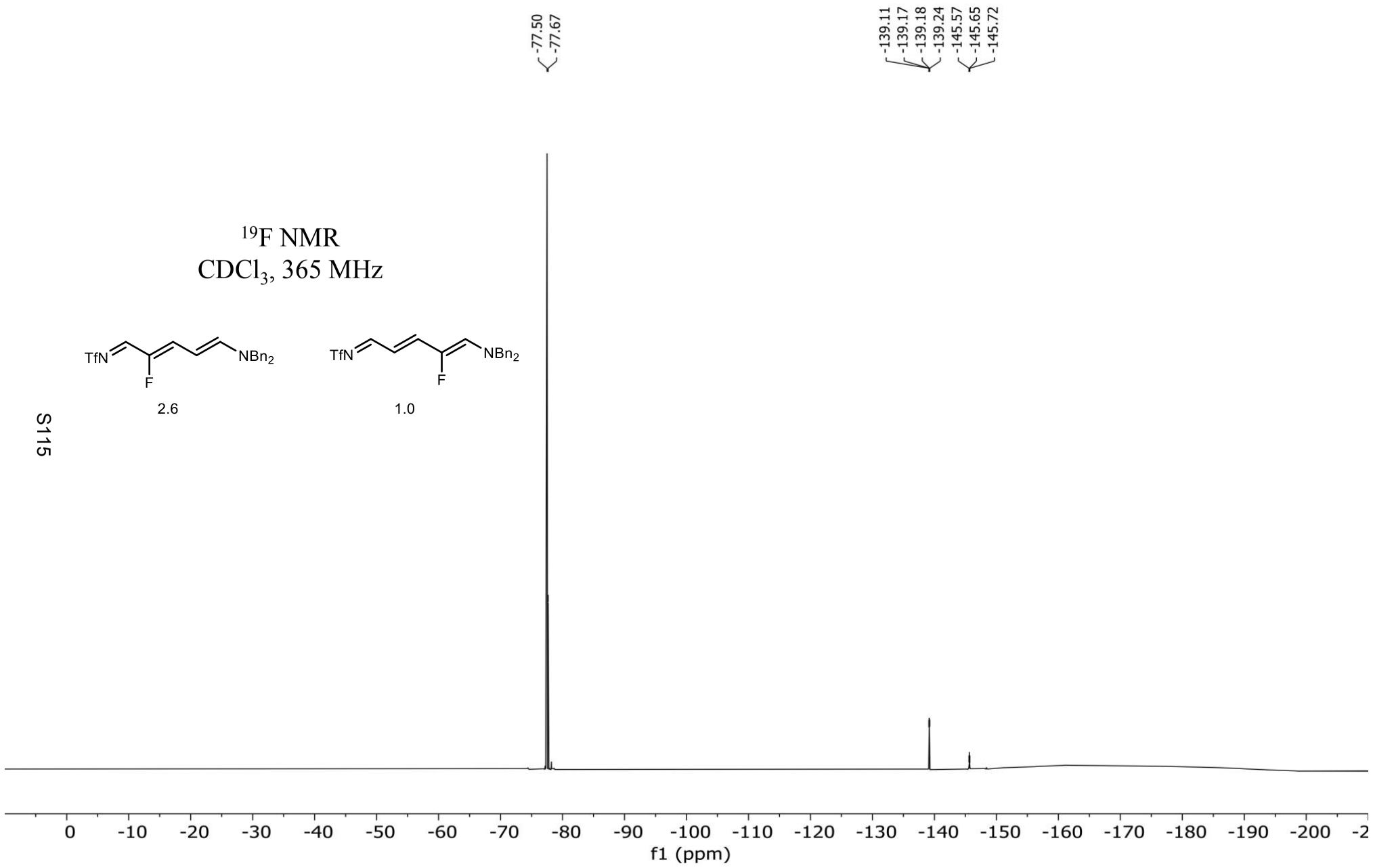
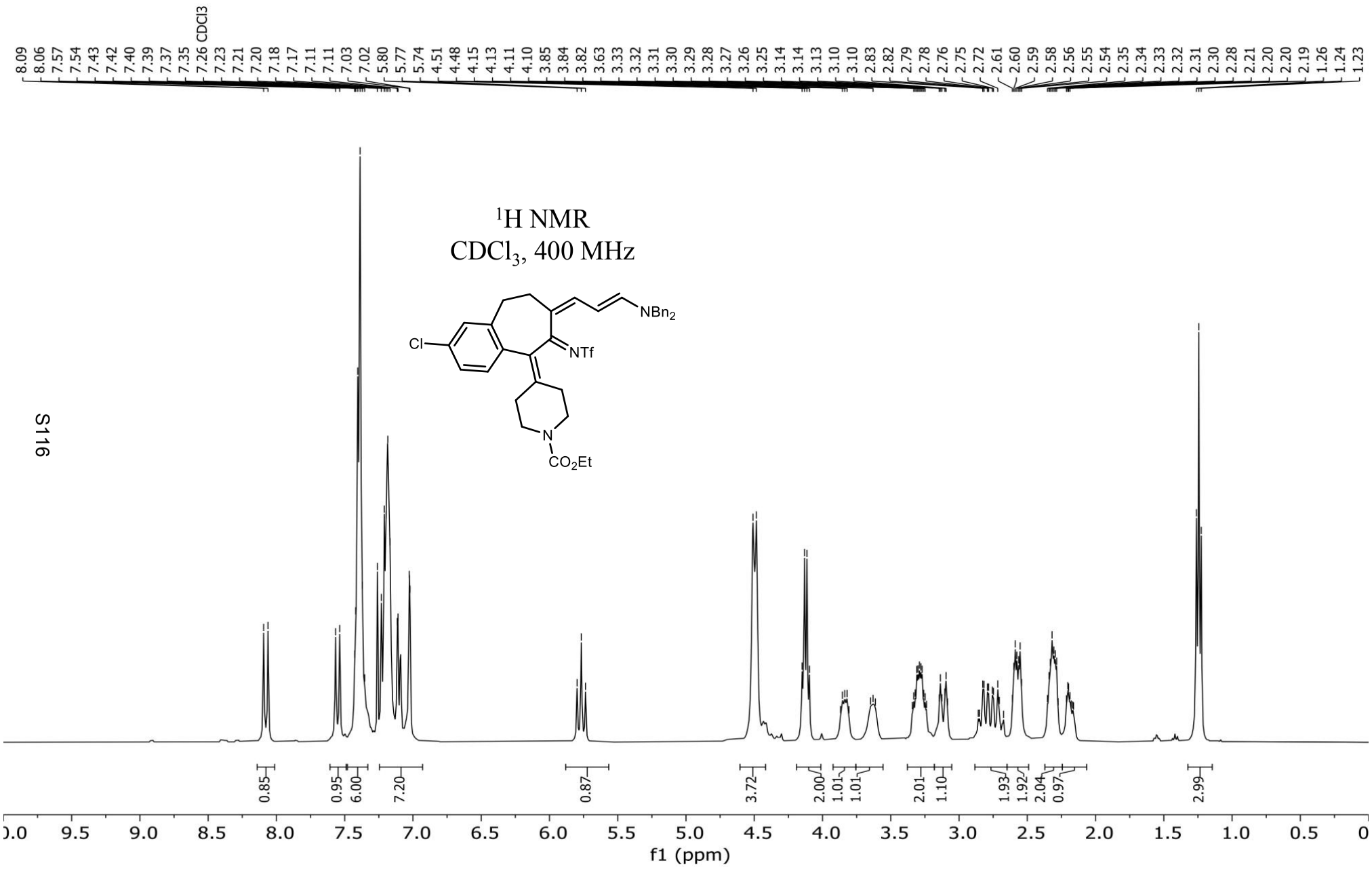
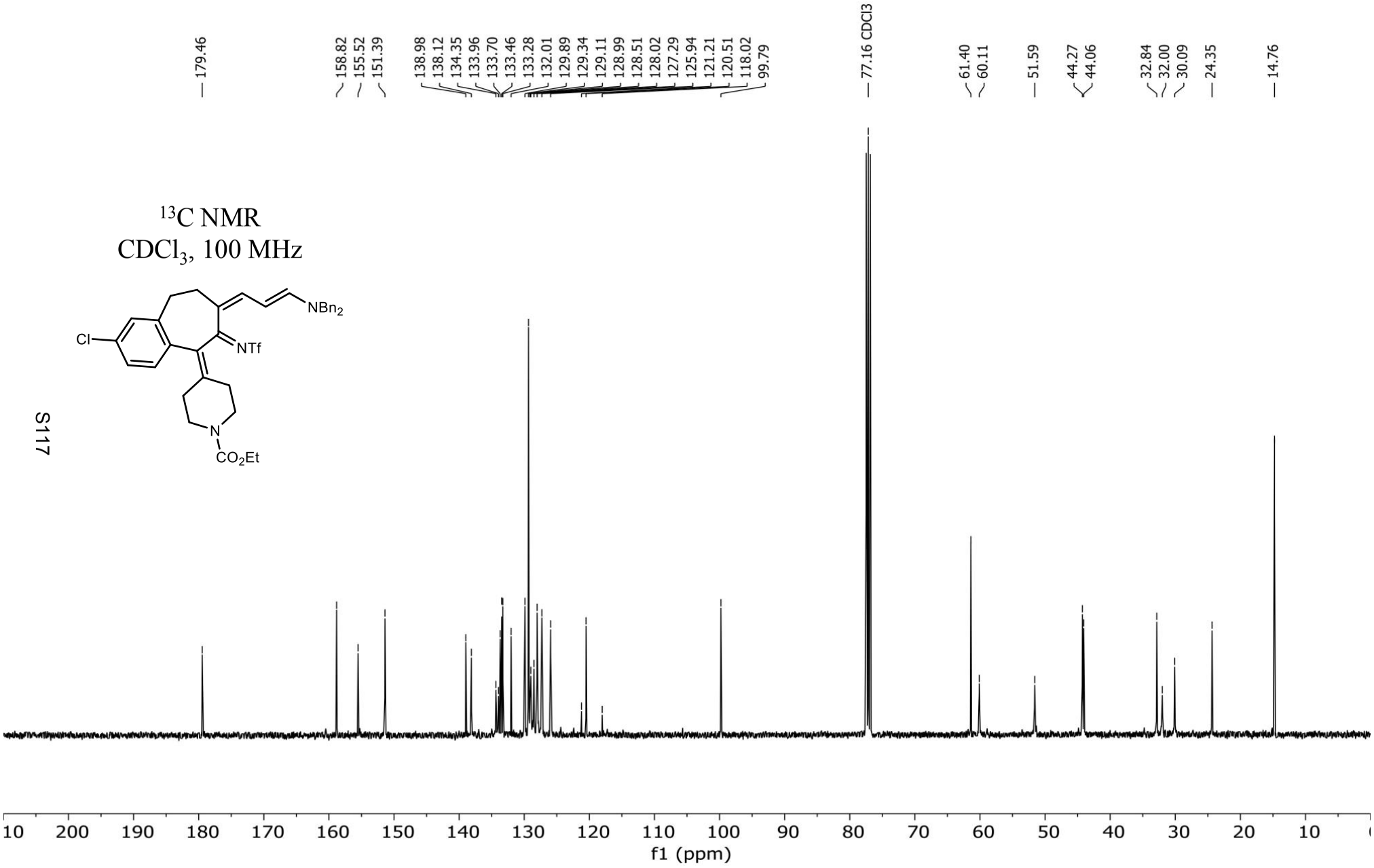
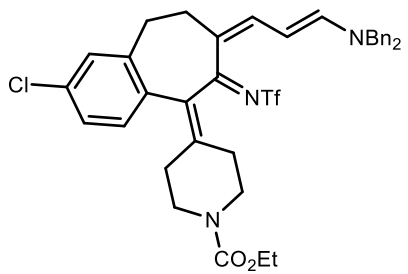
159.56
157.35
157.26
148.43
148.33
148.14
145.74
141.43
133.33
133.01
129.56
129.49
129.45
129.42
129.39
128.92
128.71
128.49
128.19
127.75
127.61
127.43
121.58
118.38
110.96
98.69
98.65
77.16 CDCl3
60.33
52.08
13C NMR
CDCl3, 100 MHz
TfN
NBn2
F
2.6
TfN
NBn2
F
1.0
f1 (ppm)

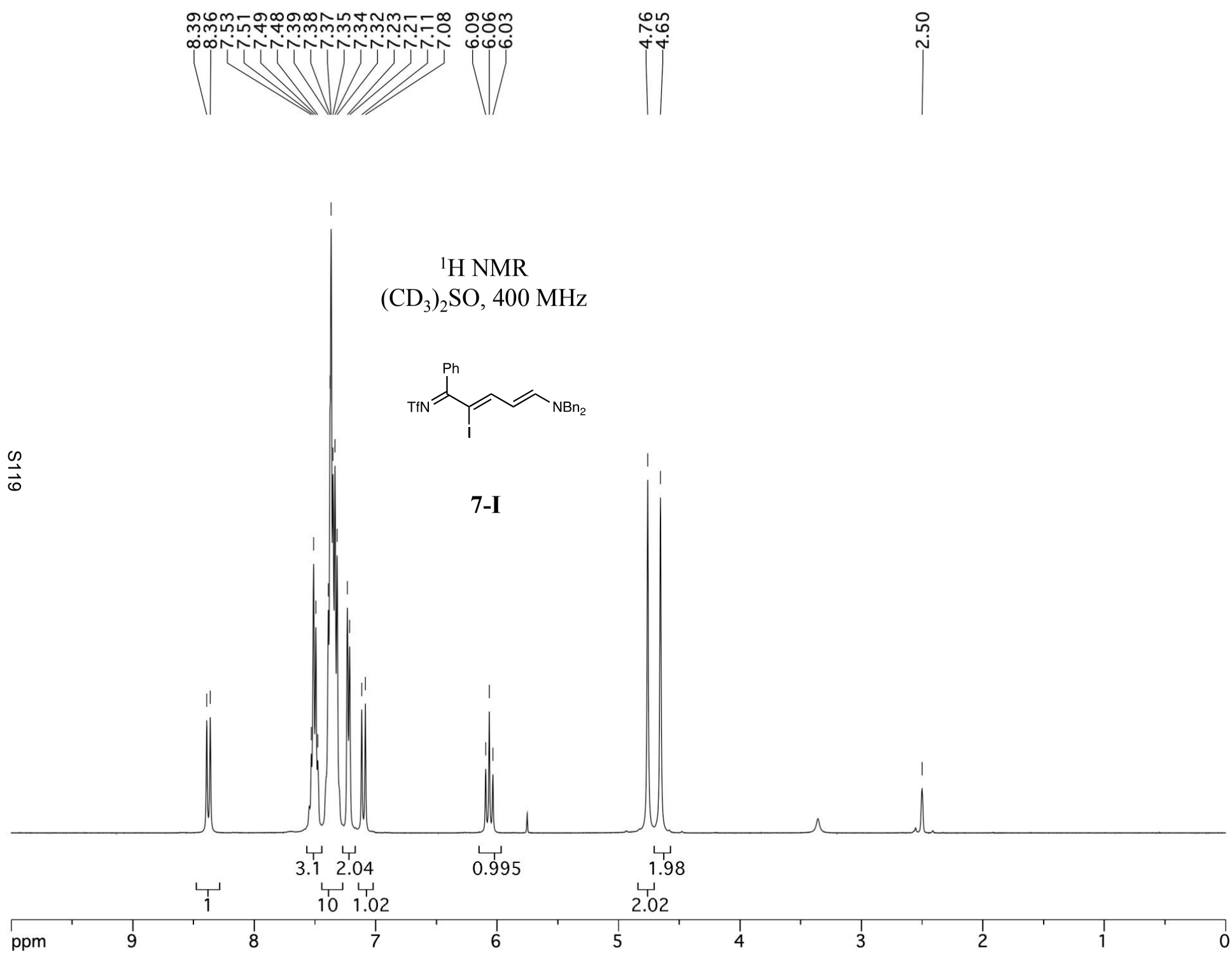

-77.50
-77.67
-139.11
-139.17
-139.18
-139.24
-145.57
-145.65
-145.72
19F NMR
CDCl3, 365 MHz
TfN
NBn2
F
2.6
TfN
NBn2
F
1.0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

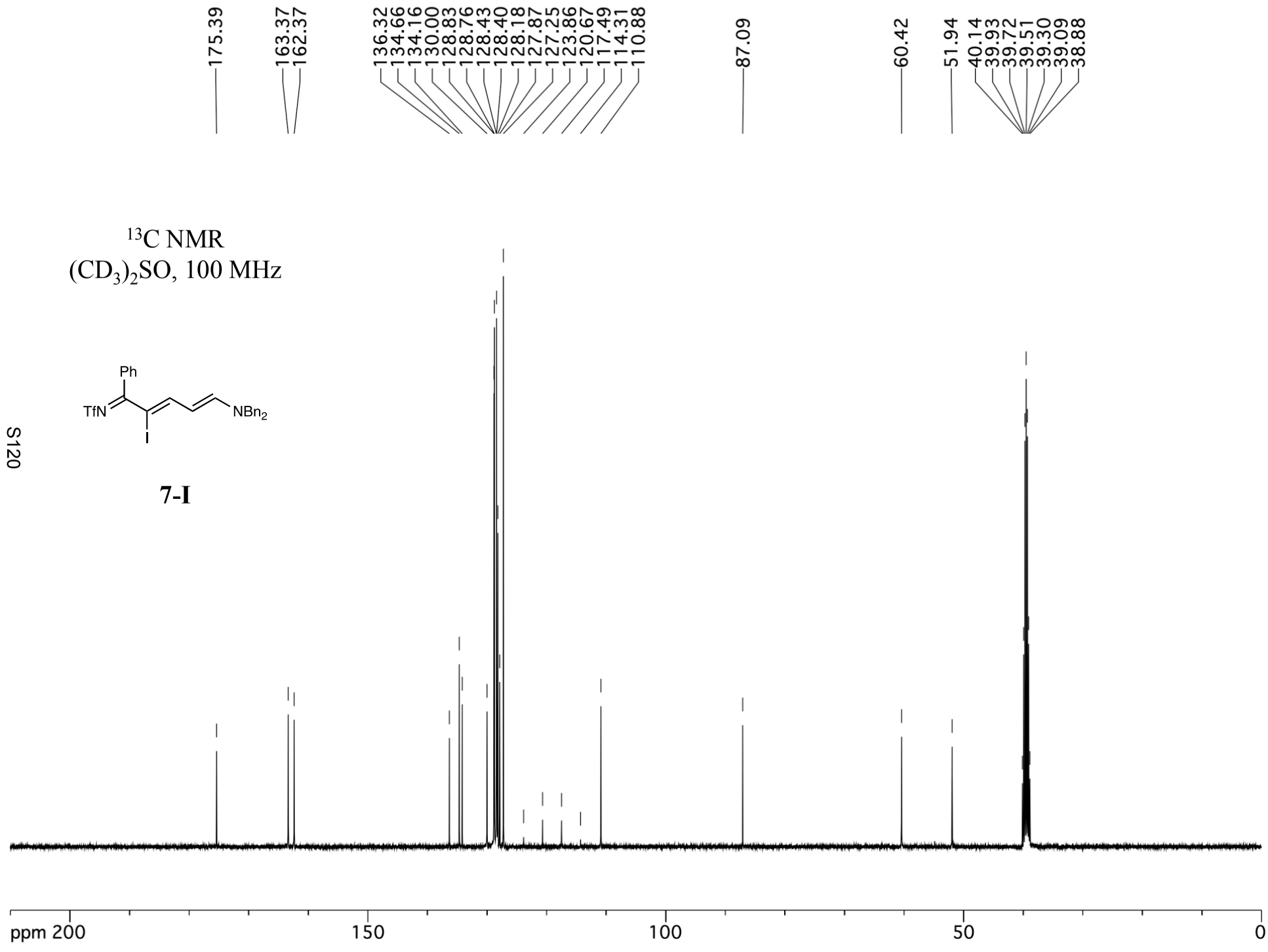

8.09 8.06 7.57 7.54 7.43 7.42 7.40 7.39 7.37 7.35 CDCl3 7.26 7.23 7.21 7.20 7.18 7.17 7.11 7.11 7.03 7.02 5.80 5.77 5.74 4.51 4.48 4.15 4.13 4.11 4.10 3.85 3.84 3.82 3.63 3.33 3.32 3.31 3.30 3.29 3.28 3.27 3.26 3.25 3.14 3.14 3.13 3.10 3.10 2.83 2.82 2.79 2.78 2.76 2.75 2.72 2.61 2.60 2.59 2.58 2.56 2.55 2.54 2.35 2.34 2.33 2.32 2.31 2.30 2.28 2.21 2.20 2.20 2.19 1.26 1.24 1.23
^{1}H NMR
$CDCl_3$, 400 MHz
NBn2
Cl
NTf
N
CO2Et
0.85 0.95 6.00 7.20 0.87 3.72 2.00 1.01 1.01 2.01 1.10 1.93 1.92 2.04 0.97 2.99
f1 (ppm)


179.46
158.82
155.52
151.39
138.98
138.12
134.35
133.96
133.70
133.46
133.28
132.01
129.89
129.34
129.11
128.99
128.51
128.02
127.29
125.94
121.21
120.51
118.02
99.79
77.16 CDCl3
61.40
60.11
51.59
44.27
44.06
32.84
32.00
30.09
24.35
14.76
13C NMR
CDCl3, 100 MHz
NBn2
Cl
NTf
N
CO2Et
f1 (ppm)

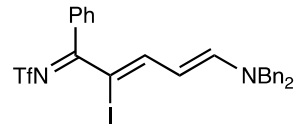
^{19}F NMR
$CDCl_3$, 365 MHz



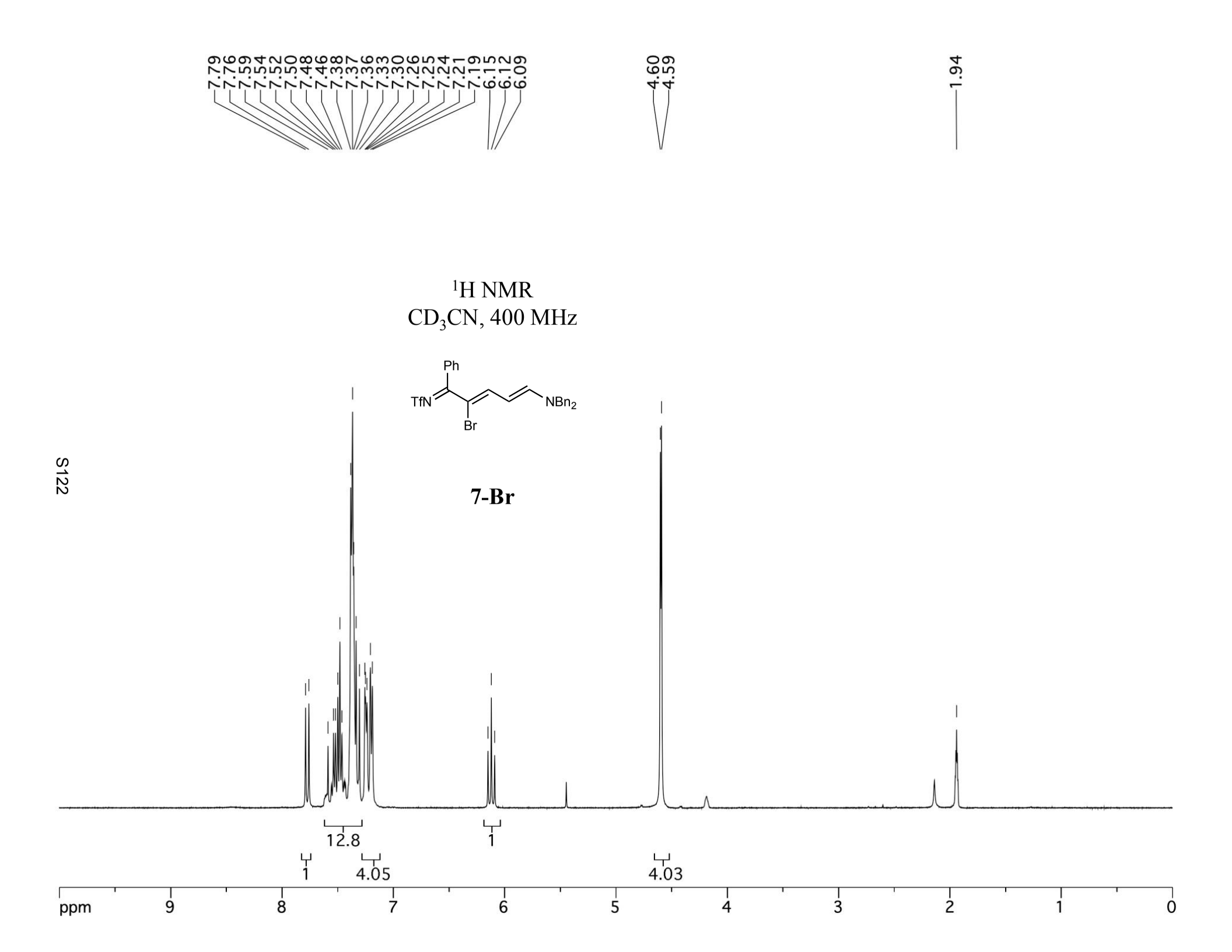

8.39
8.36
7.53
7.51
7.49
7.48
7.39
7.38
7.37
7.35
7.34
7.32
7.23
7.21
7.11
7.08
6.09
6.06
6.03
4.76
4.65
2.50
^{1}H NMR
$(CD_3)_2SO$, 400 MHz
Ph
TfN
NBn$_2$
I
7-I
S119
3.1
2.04
0.995
1.98
1
10
1.02
2.02
ppm
9
8
7
6
5
4
3
2
1
0


175.39
163.37
162.37
136.32
134.66
134.16
130.00
128.83
128.76
128.43
128.40
128.18
127.87
127.25
123.86
120.67
117.49
114.31
110.88
87.09
60.42
51.94
40.14
39.93
39.72
39.51
39.30
39.09
38.88
^{13}C NMR
$(CD_3)_2SO$, 100 MHz
Ph
TfN
NBn$_2$
I
7-I
S120
ppm 200
150
100
50
0

^{19}F NMR
$(CD_3)_2SO$, 365 MHz

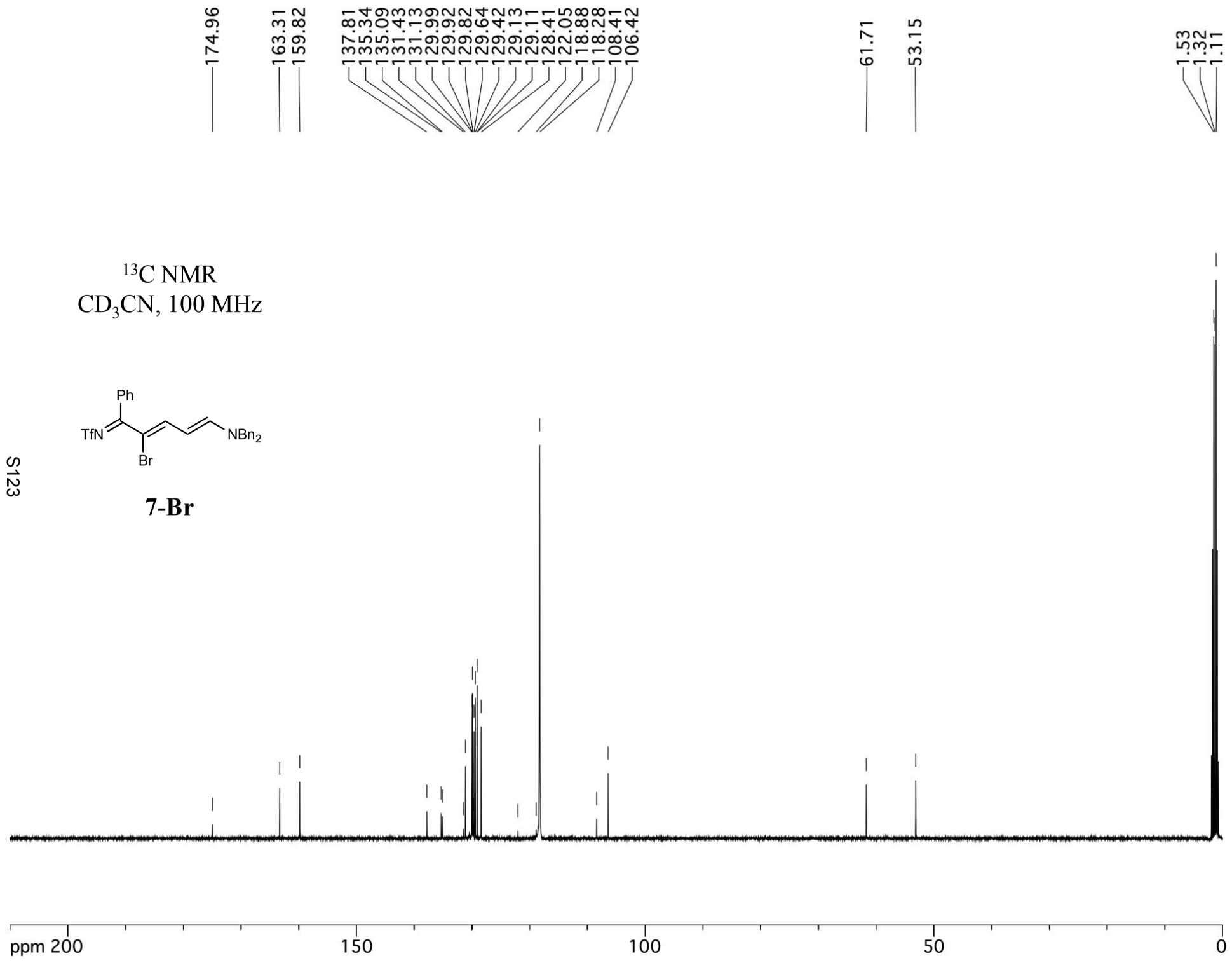


7-I

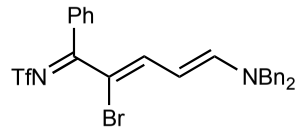


^{1}H NMR
CD_3CN, 400 MHz

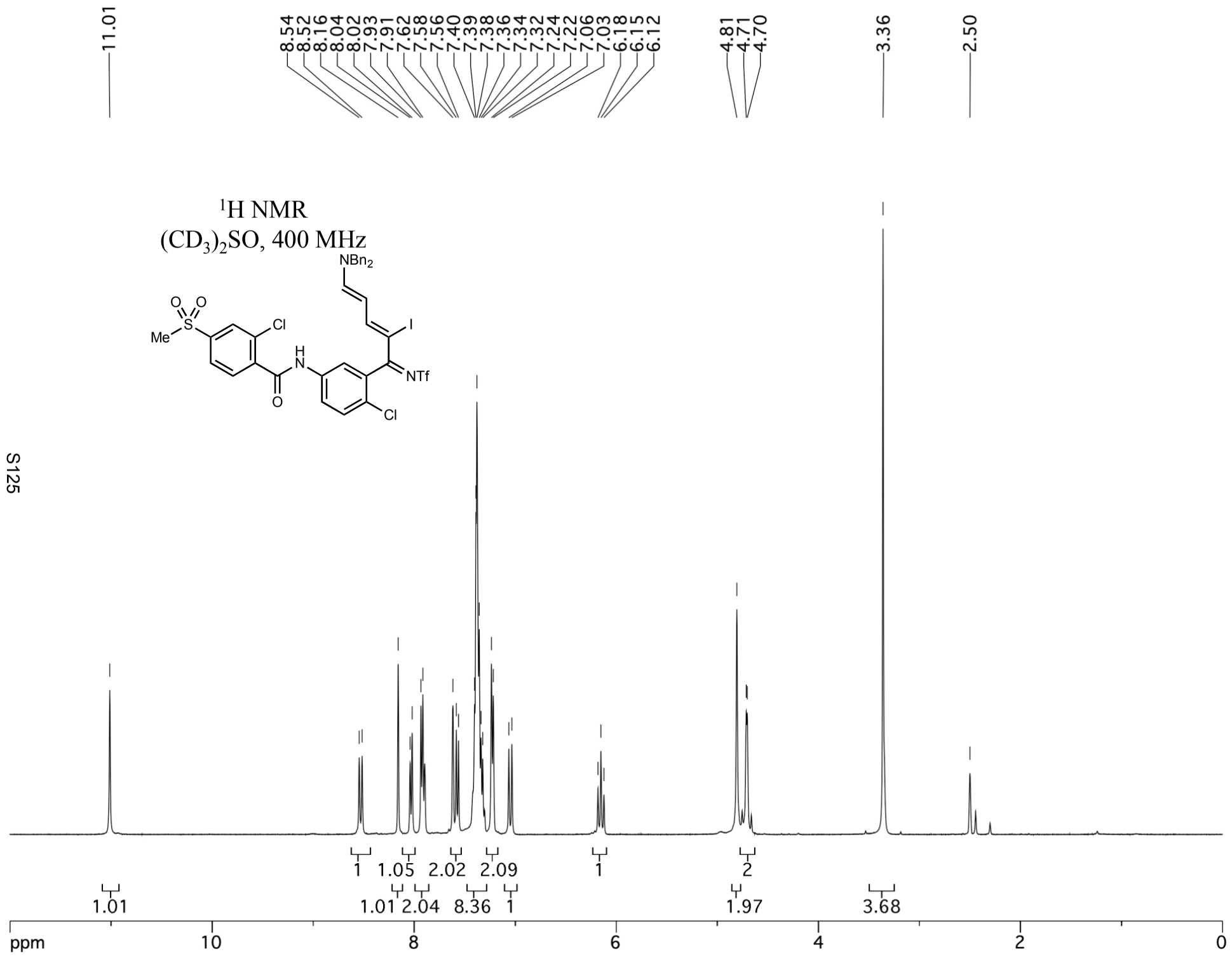
7-Br

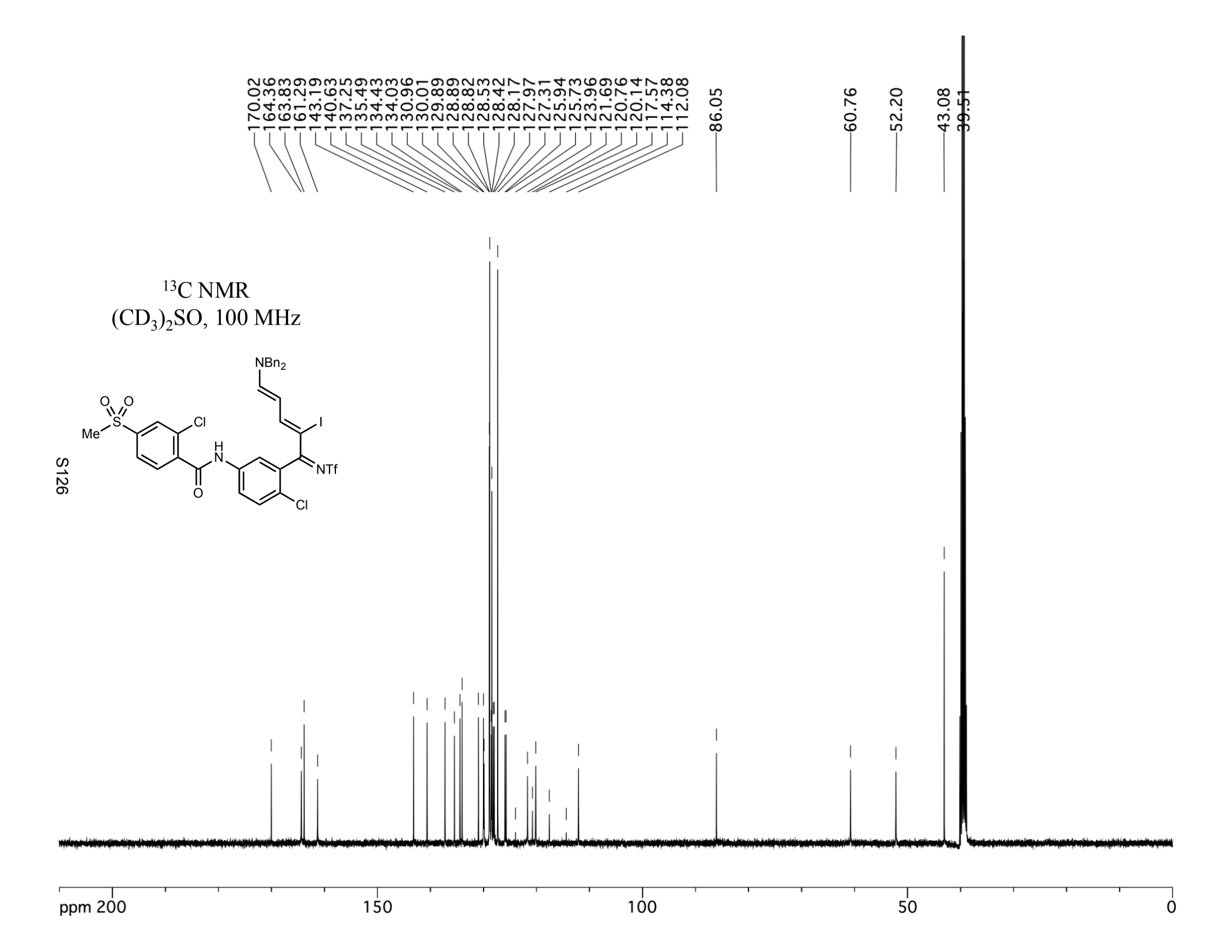

174.96
163.31
159.82
137.81
135.34
135.09
131.43
131.13
129.99
129.92
129.82
129.64
129.42
129.13
129.11
128.41
122.05
118.88
118.28
108.41
106.42
61.71
53.15
1.53
1.32
1.11
13C NMR
CD3CN, 100 MHz
Ph
TfN
NBn2
Br
7-Br
S123
ppm 200
150
100
50
0

^{19}F NMR
CD_3CN, 365 MHz

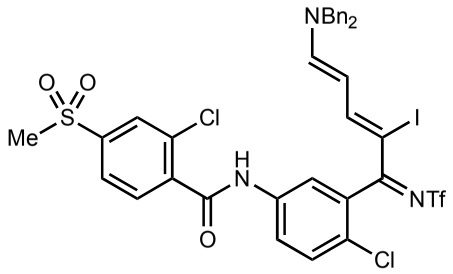


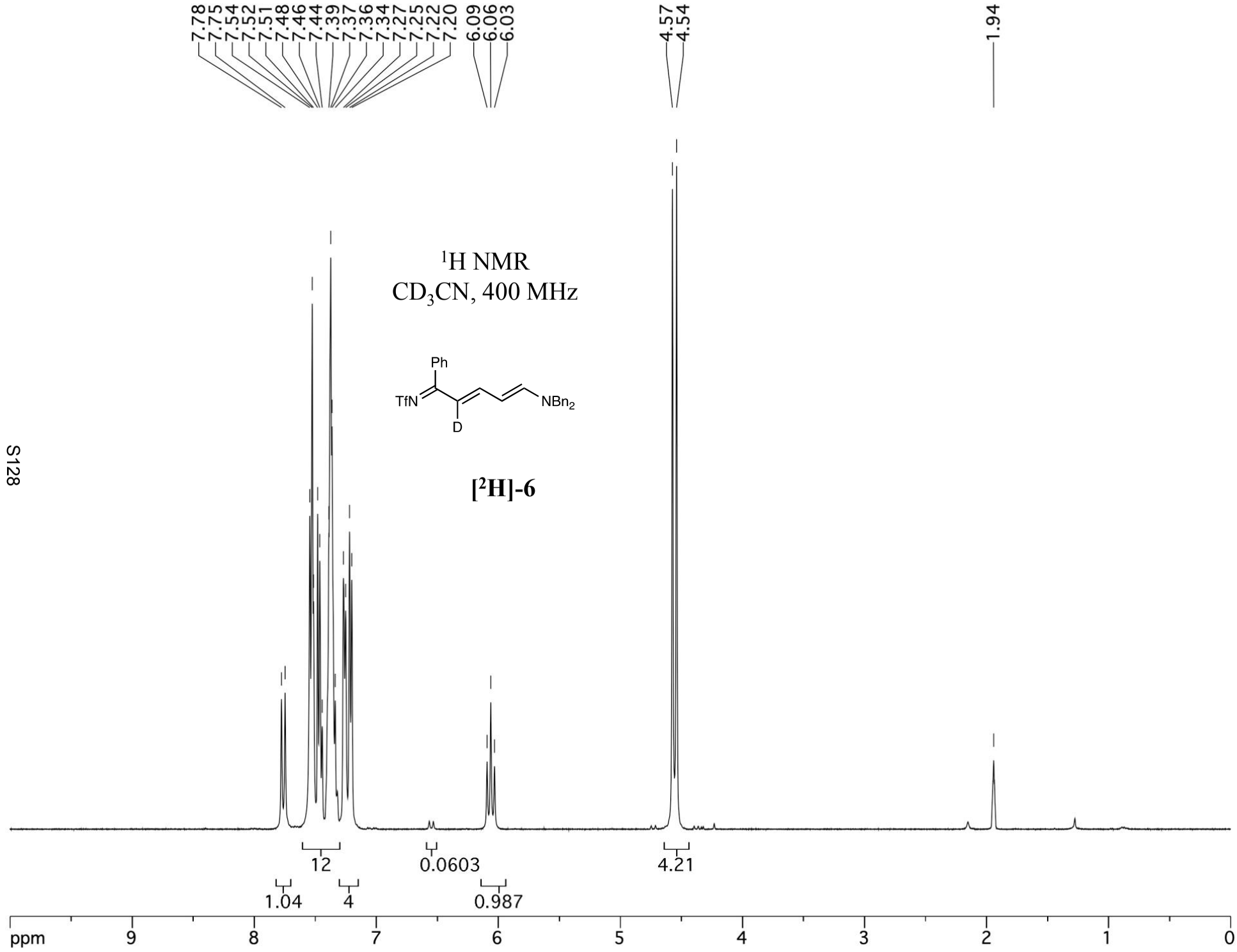
7-Br

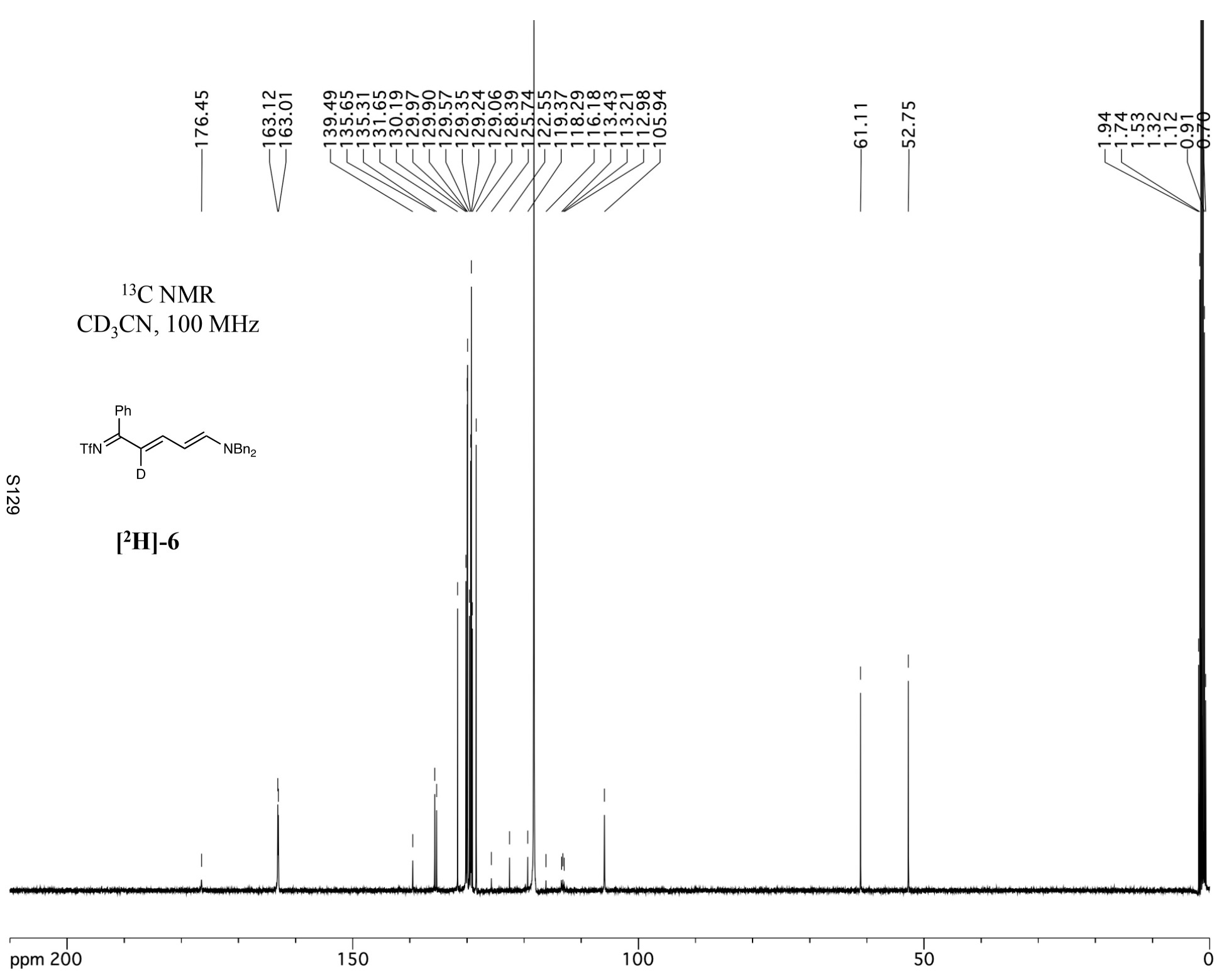

11.01
8.54
8.52
8.16
8.04
8.02
7.93
7.91
7.62
7.58
7.56
7.40
7.39
7.38
7.36
7.34
7.32
7.24
7.22
7.06
7.03
6.18
6.15
6.12
4.81
4.71
4.70
3.36
2.50
1H NMR
(CD3)2SO, 400 MHz
NBn2
I
NTf
Cl
Me
S
O
O
H
N
O
Cl
1
1.05
2.02
2.09
1
2
1.01
1.01
2.04
8.36
1
1.97
3.68
ppm
10
8
6
4
2
0


170.02
164.36
163.83
161.29
143.19
140.63
137.25
135.49
134.43
134.03
130.96
130.01
129.89
128.89
128.82
128.53
128.42
128.17
127.97
127.31
125.94
125.73
123.96
121.69
120.76
120.14
117.57
114.38
112.08
86.05
60.76
52.20
43.08
39.51
^{13}C NMR
$(CD_3)_2SO$, 100 MHz
NBn$_2$
Me
S
O
O
Cl
I
H
N
NTf
O
Cl
ppm 200
150
100
50
0

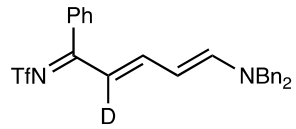
^{19}F NMR
$(CD_3)_2SO$, 365 MHz



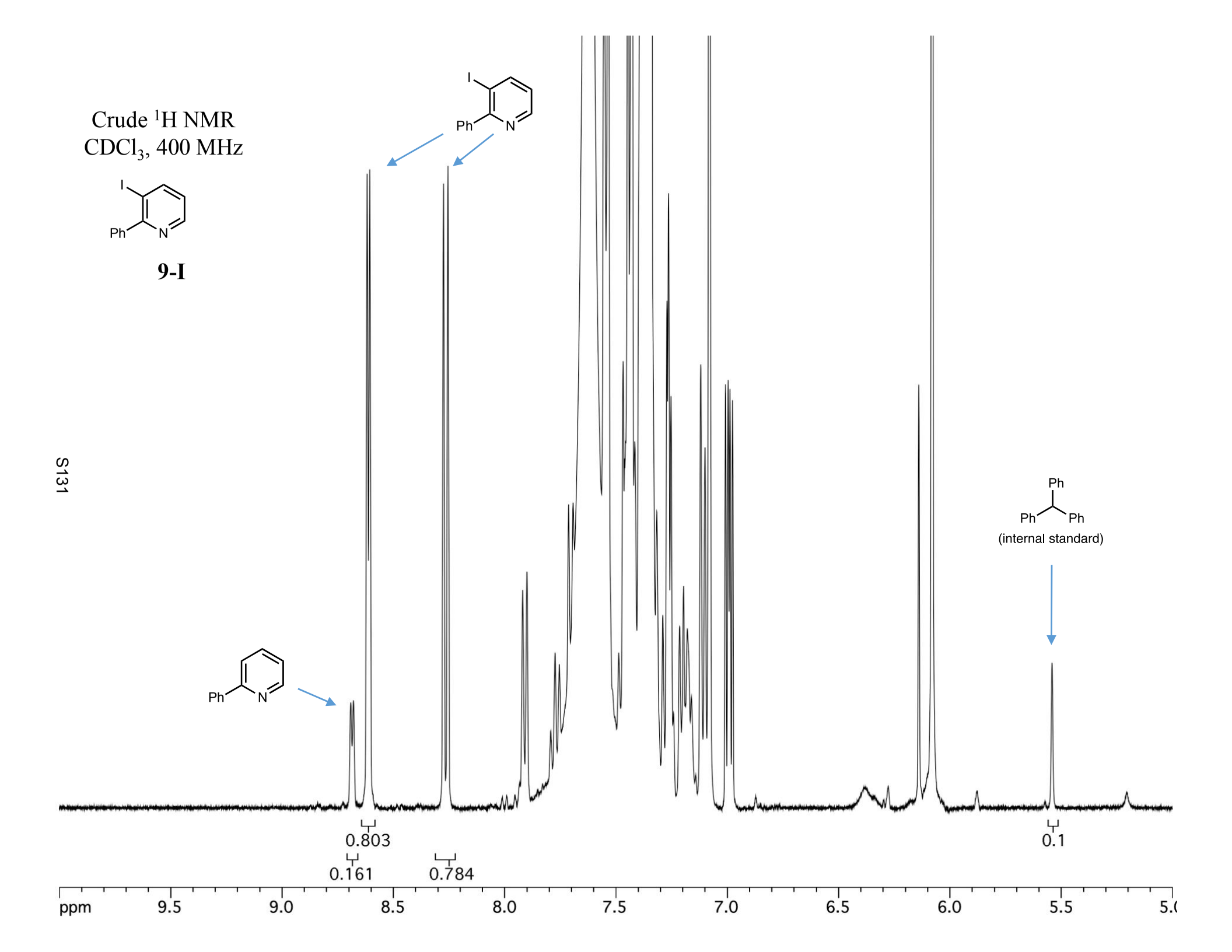

7.78
7.75
7.54
7.52
7.51
7.48
7.46
7.44
7.39
7.37
7.36
7.34
7.27
7.25
7.22
7.20
6.09
6.06
6.03
4.57
4.54
1.94
^{1}H NMR
CD_3CN, 400 MHz
Ph
TfN
NBn$_2$
D
[^{2}H]-6
12
0.0603
4.21
1.04
4
0.987
ppm
9
8
7
6
5
4
3
2
1
0

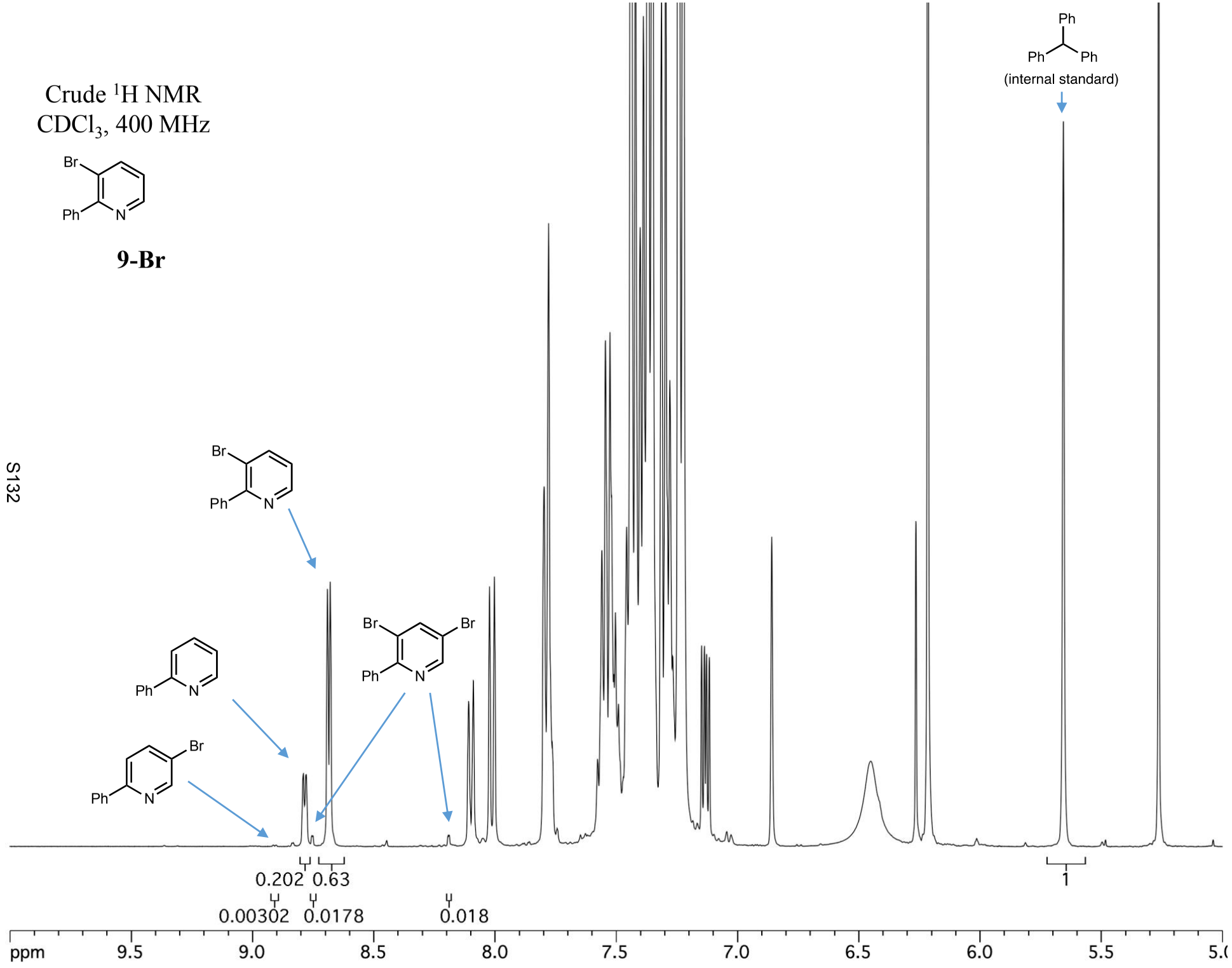

176.45
163.12
163.01
139.49
135.65
135.31
131.65
130.19
129.97
129.90
129.57
129.35
129.24
129.06
128.39
125.74
122.55
119.37
118.29
116.18
113.43
113.21
112.98
105.94
61.11
52.75
1.94
1.74
1.53
1.32
1.12
0.91
0.70
^{13}C NMR
CD_3CN, 100 MHz
Ph
TfN
NBn$_2$
D
S129
[^{2}H]-6
ppm 200
150
100
50
0

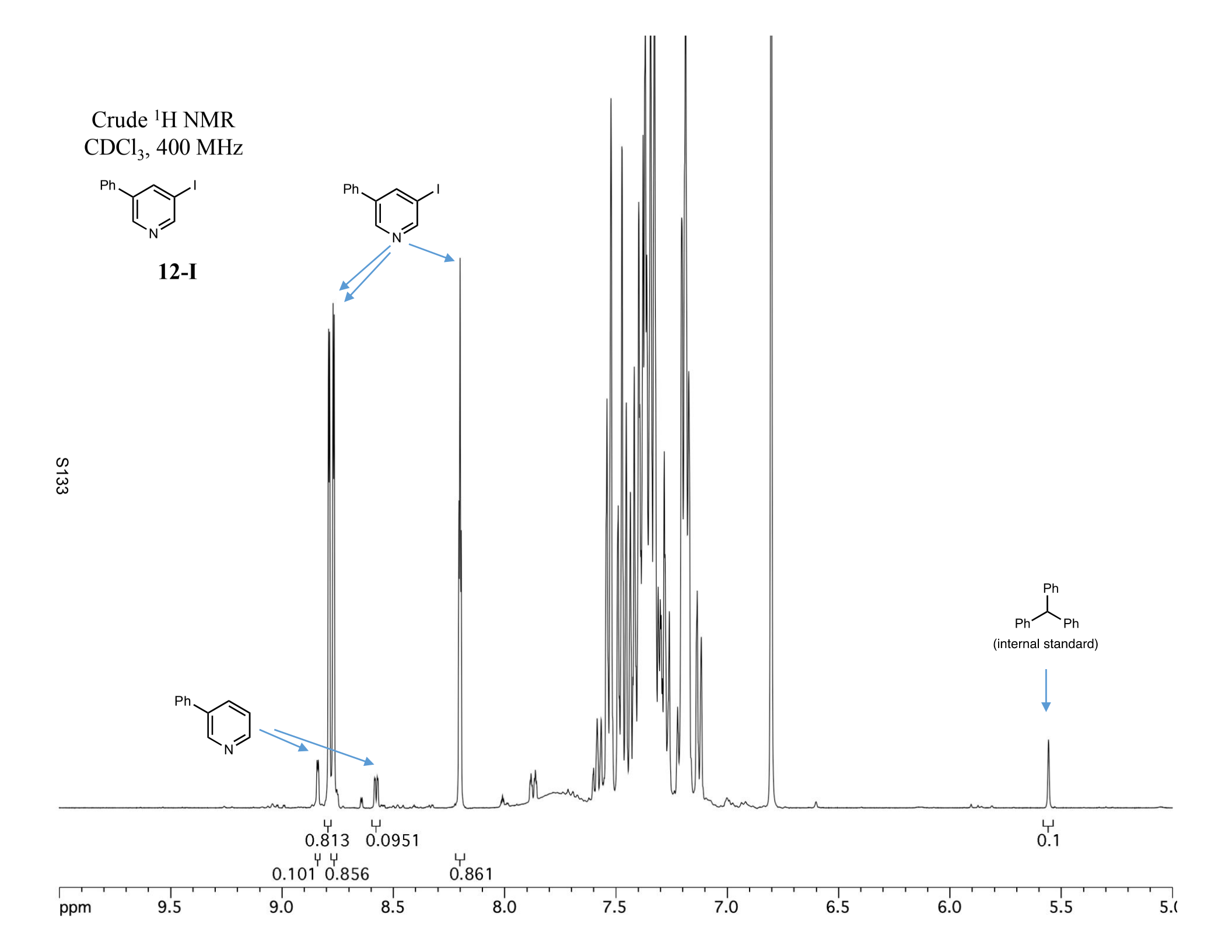
^{19}F NMR
CD_3CN, 365 MHz

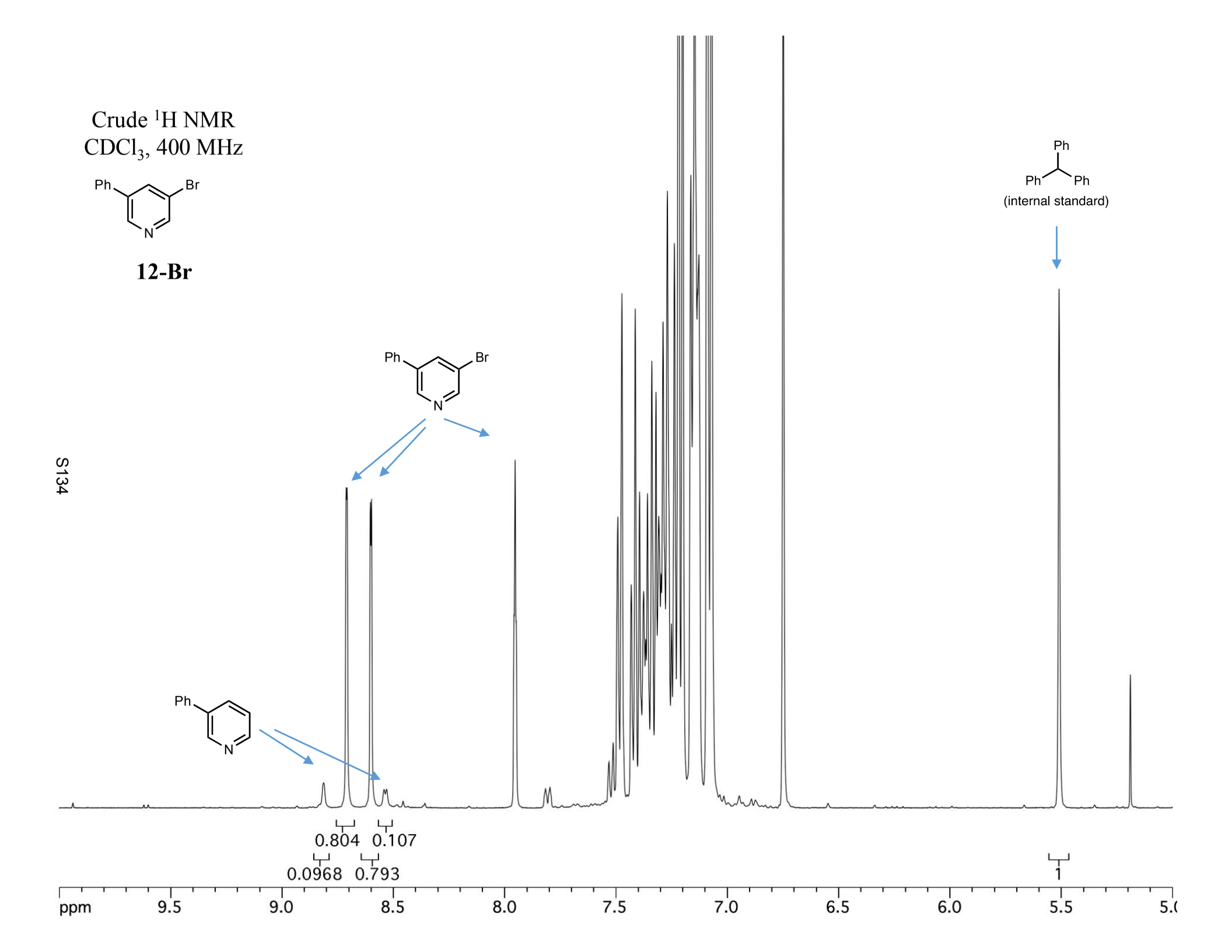


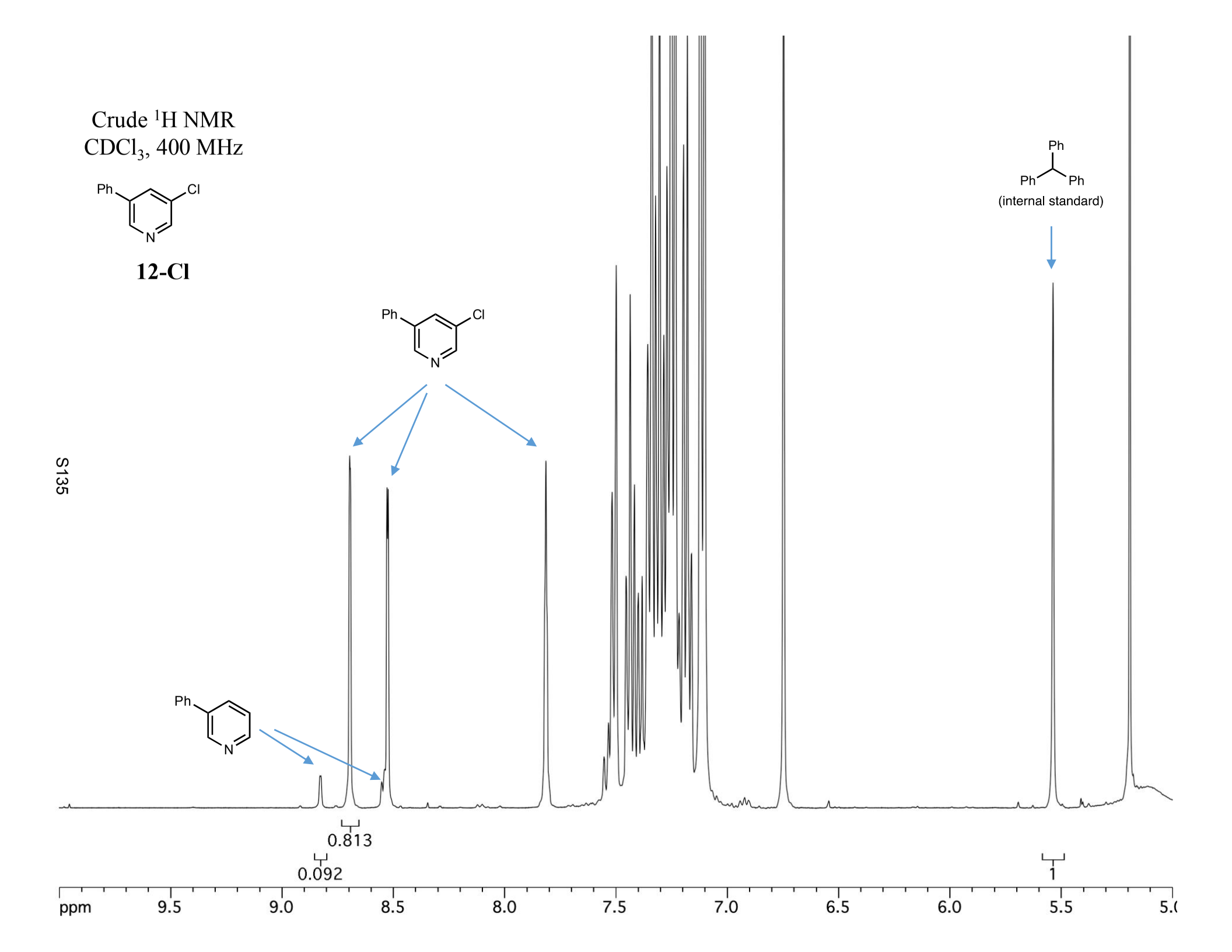
[^{2}H]-6

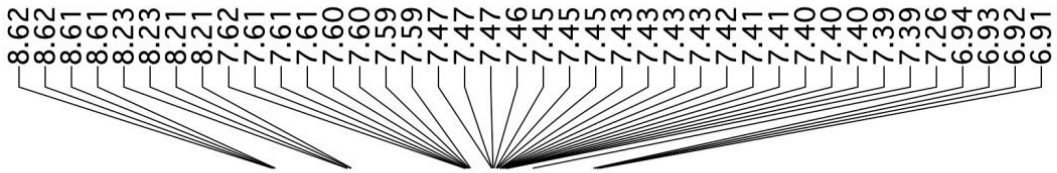

Crude ^{1}H NMR
$CDCl_3$, 400 MHz
I
Ph
N
9-I
S131
Ph
Ph
Ph
(internal standard)
0.803
0.161
0.784
0.1
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5


Crude ^{1}H NMR
$CDCl_3$, 400 MHz
Br
Ph
N
9-Br
Ph
Ph
Ph
(internal standard)
S132
0.202
0.63
1
0.00302
0.0178
0.018
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5

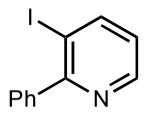

Crude ^{1}H NMR
$CDCl_3$, 400 MHz
Ph
I
N
12-I
Ph
I
N
Ph
N
Ph
Ph
Ph
(internal standard)
S133
0.813
0.0951
0.101
0.856
0.861
0.1
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5


Crude ^{1}H NMR
$CDCl_3$, 400 MHz
Ph
Br
N
12-Br
Ph
Ph
Ph
(internal standard)
Ph
Br
N
Ph
N
S134
0.804
0.107
0.0968
0.793
1
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5

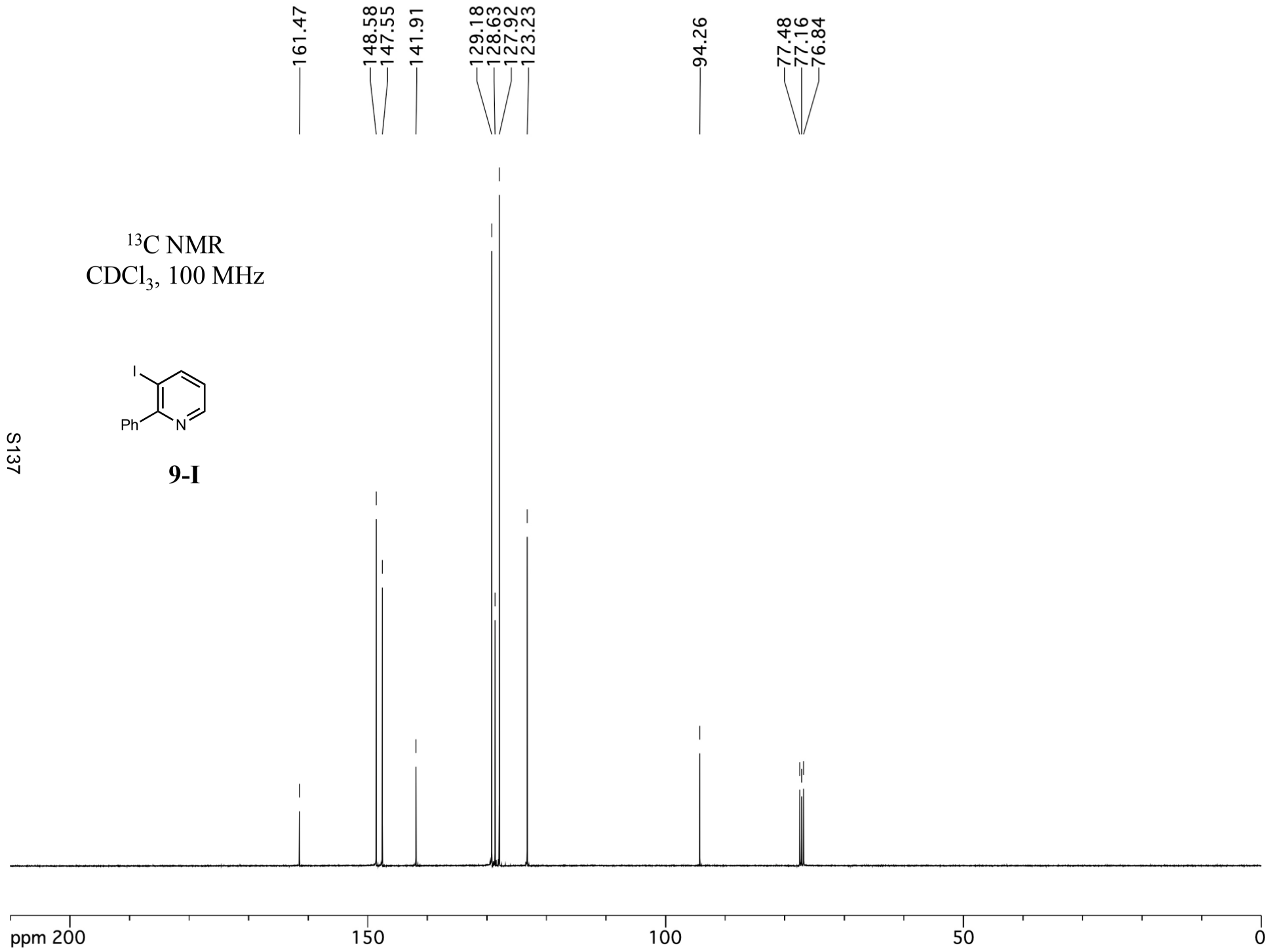

Crude ^{1}H NMR
$CDCl_3$, 400 MHz
Ph
Cl
N
12-Cl
Ph
Cl
N
Ph
N
Ph
Ph
Ph
(internal standard)
S135
0.813
0.092
1
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5

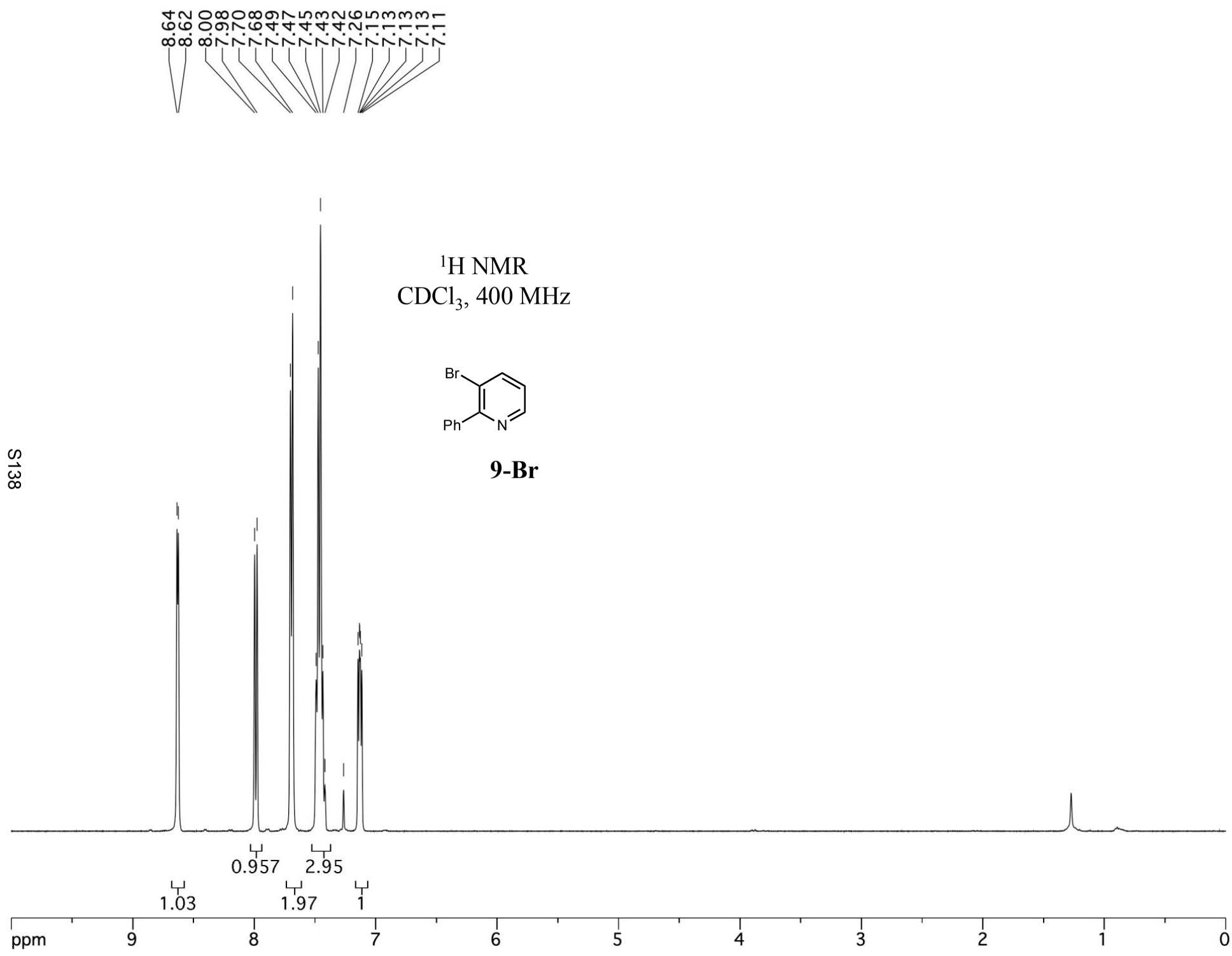


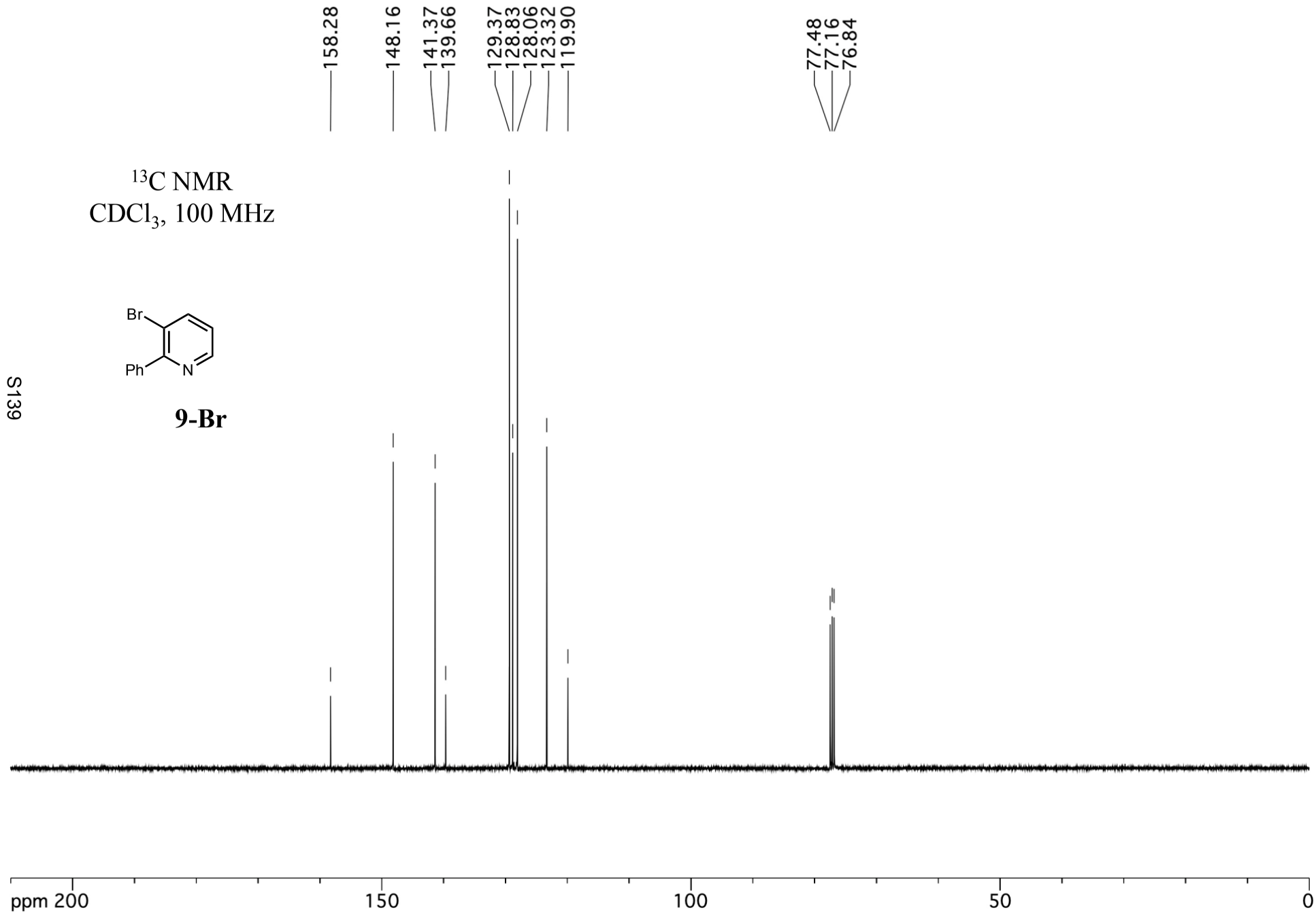
^{1}H NMR
$CDCl_3$, 400 MHz

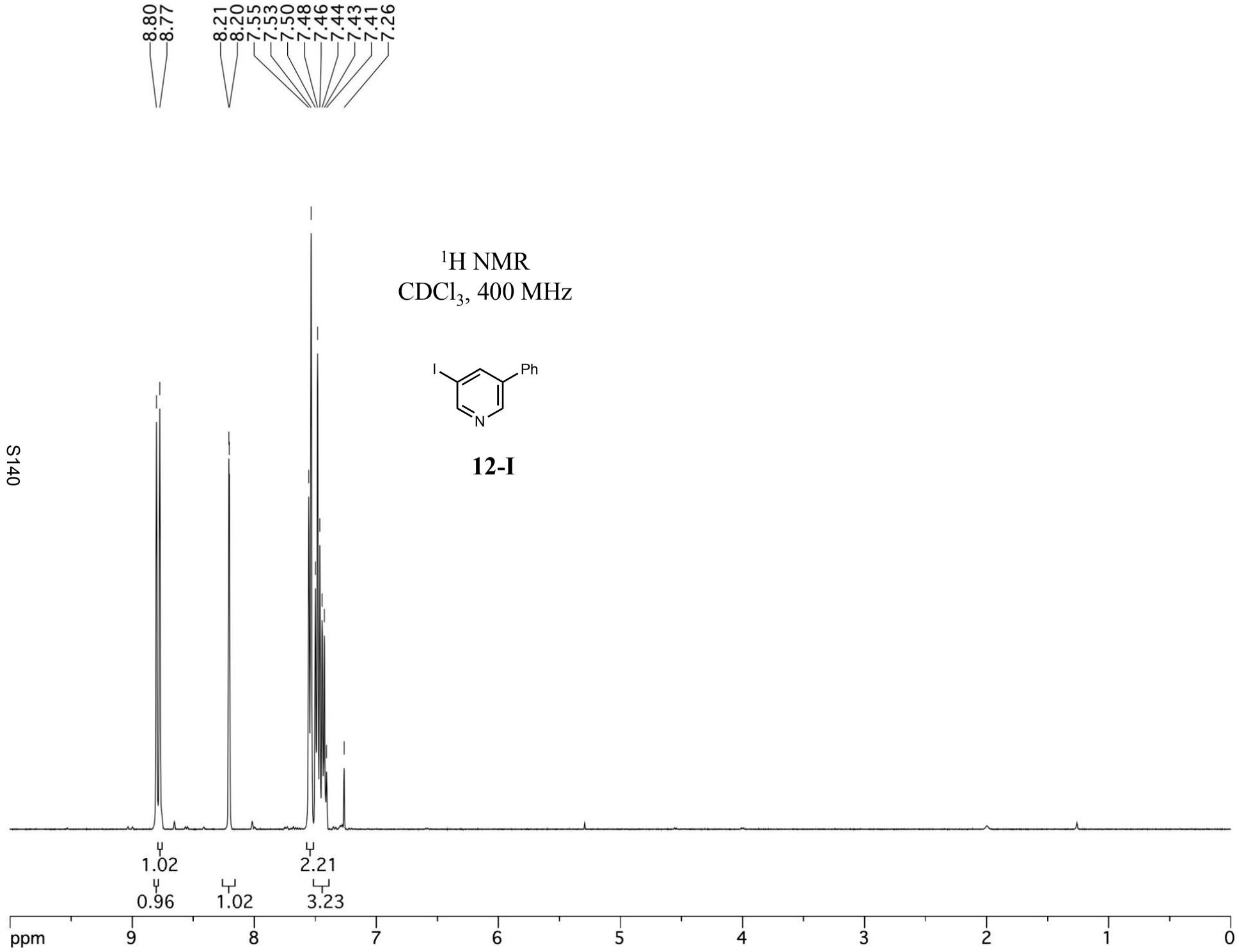


9-I


161.47
148.58
147.55
141.91
129.18
128.63
127.92
123.23
94.26
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
I
Ph
N
9-I
ppm 200
150
100
50
0

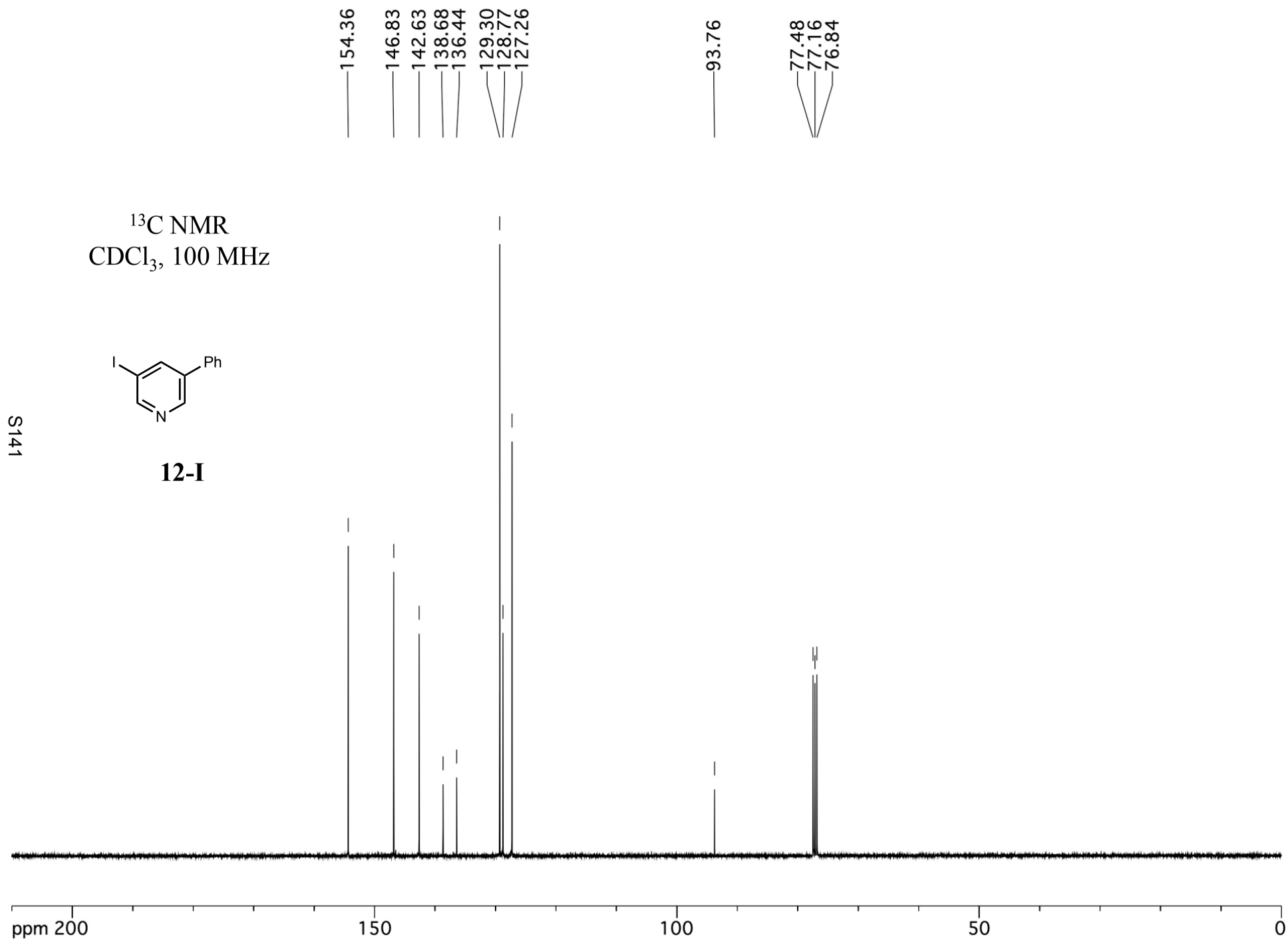

8.64
8.62
8.00
7.98
7.70
7.68
7.49
7.47
7.45
7.43
7.42
7.26
7.15
7.13
7.13
7.13
7.11
^{1}H NMR
$CDCl_3$, 400 MHz
Br
Ph
N
9-Br
S138
0.957
2.95
1.03
1.97
1
ppm
9
8
7
6
5
4
3
2
1
0

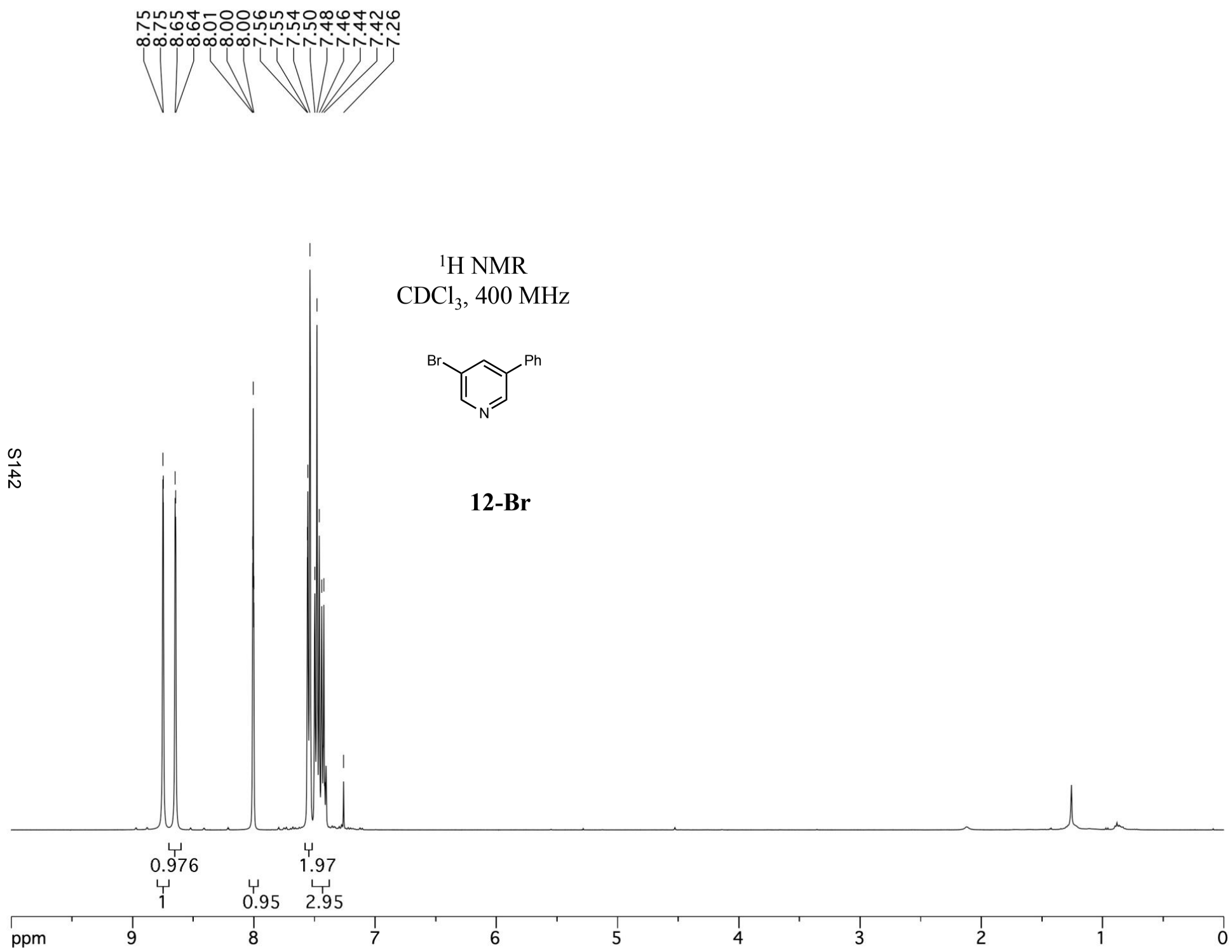

158.28
148.16
141.37
139.66
129.37
128.83
128.06
123.32
119.90
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
Ph
N
9-Br
ppm 200
150
100
50
0



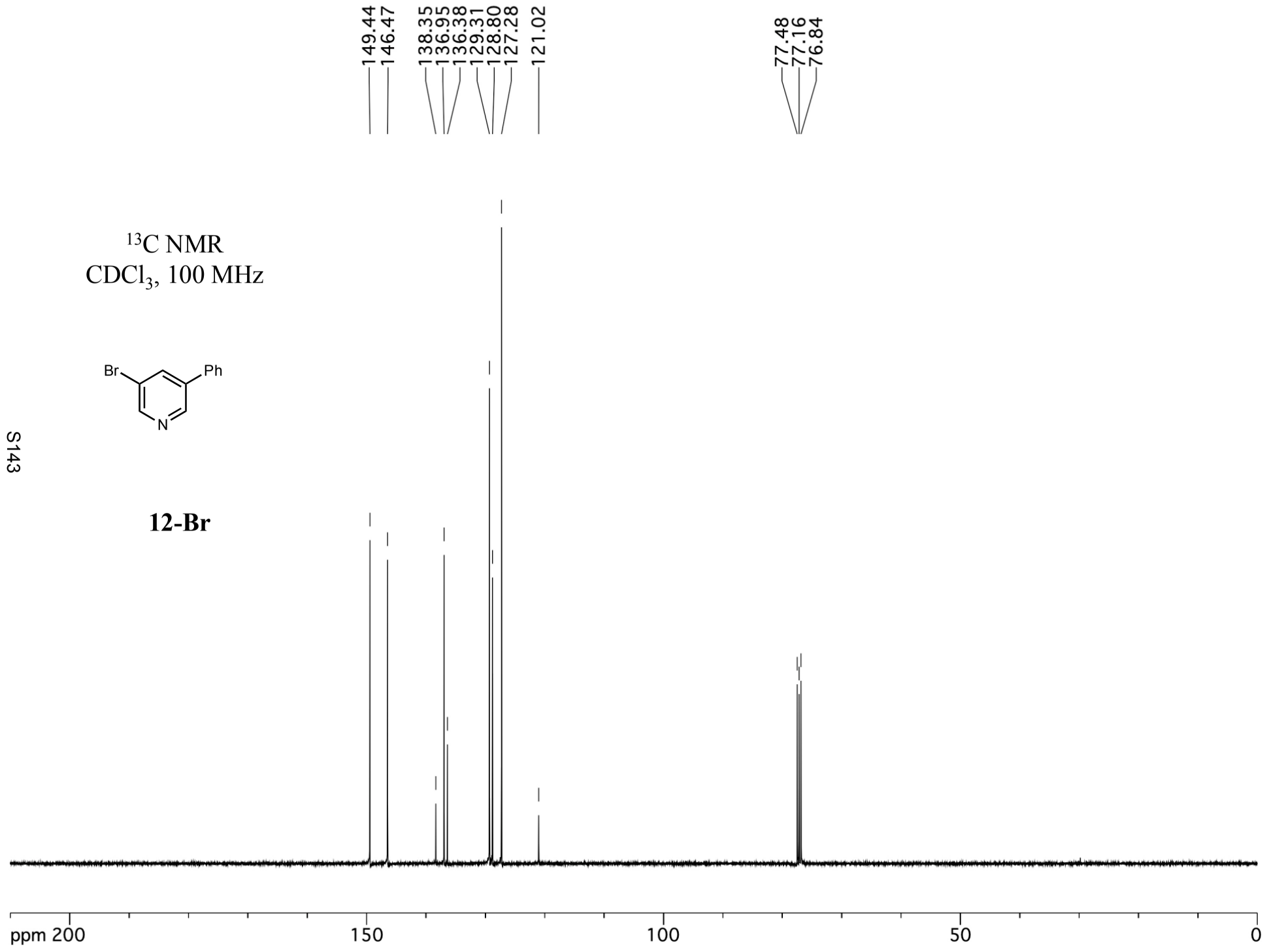
^{1}H NMR
$CDCl_3$, 400 MHz

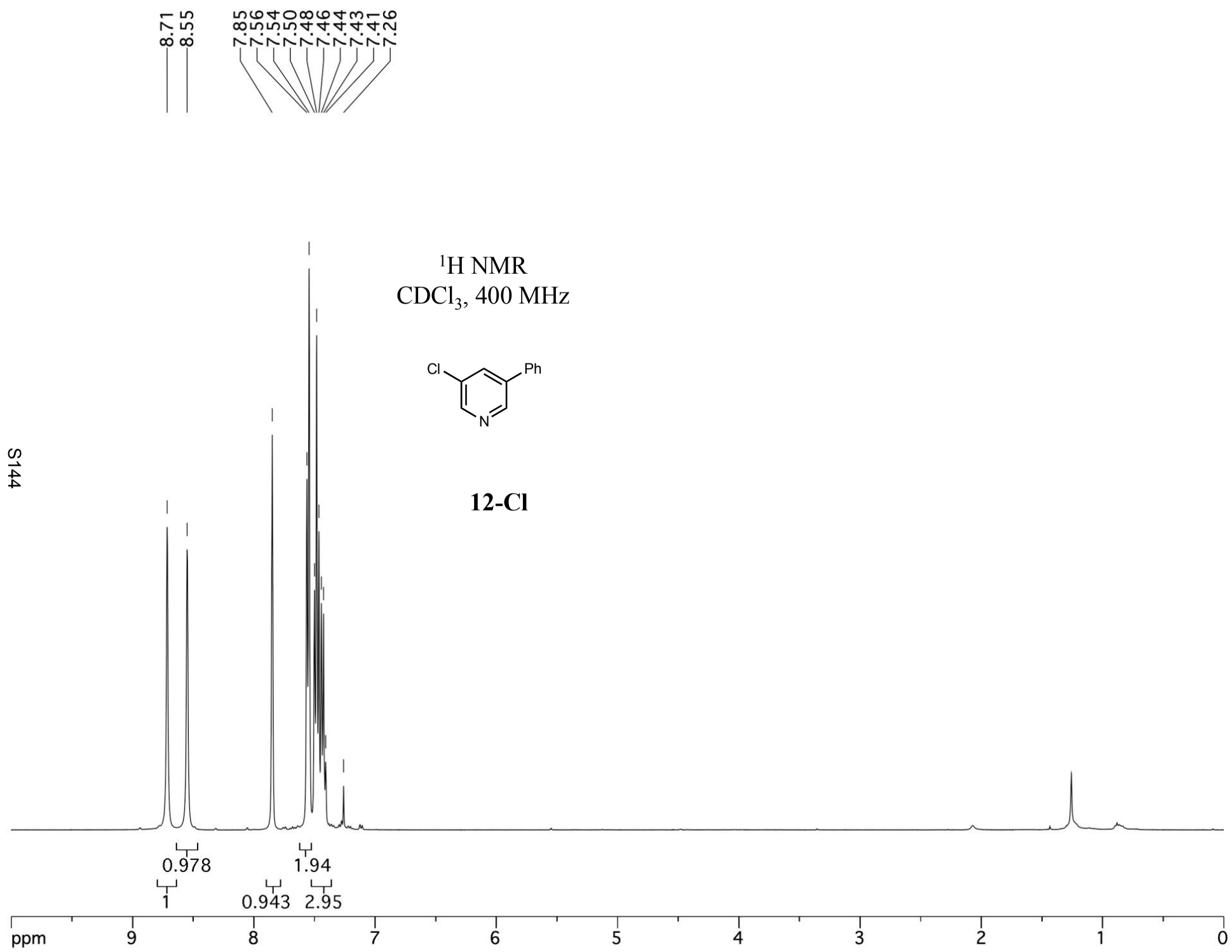
12-I

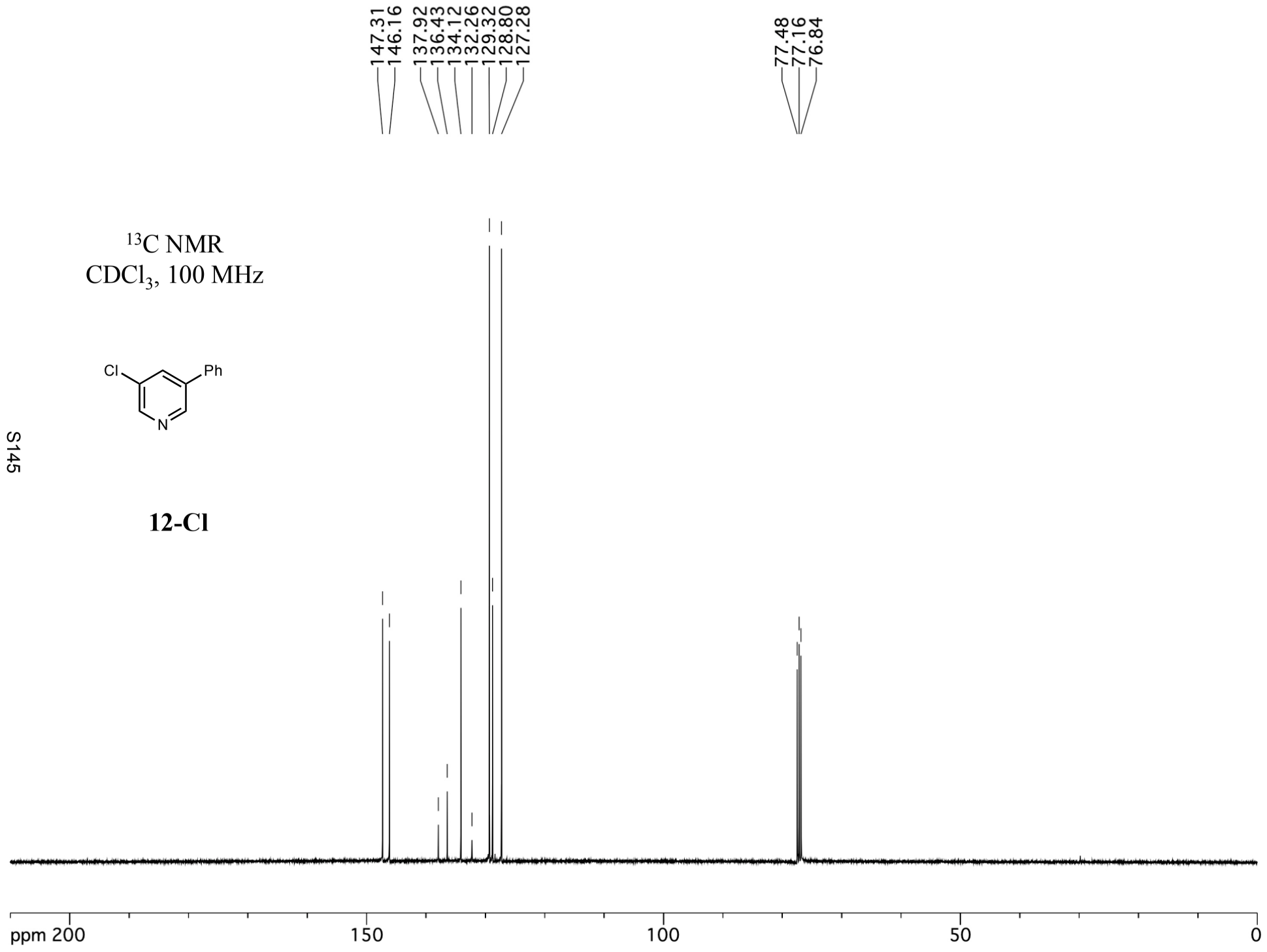

154.36
146.83
142.63
138.68
136.44
129.30
128.77
127.26
93.76
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
I
Ph
N
12-I
ppm 200
150
100
50
0

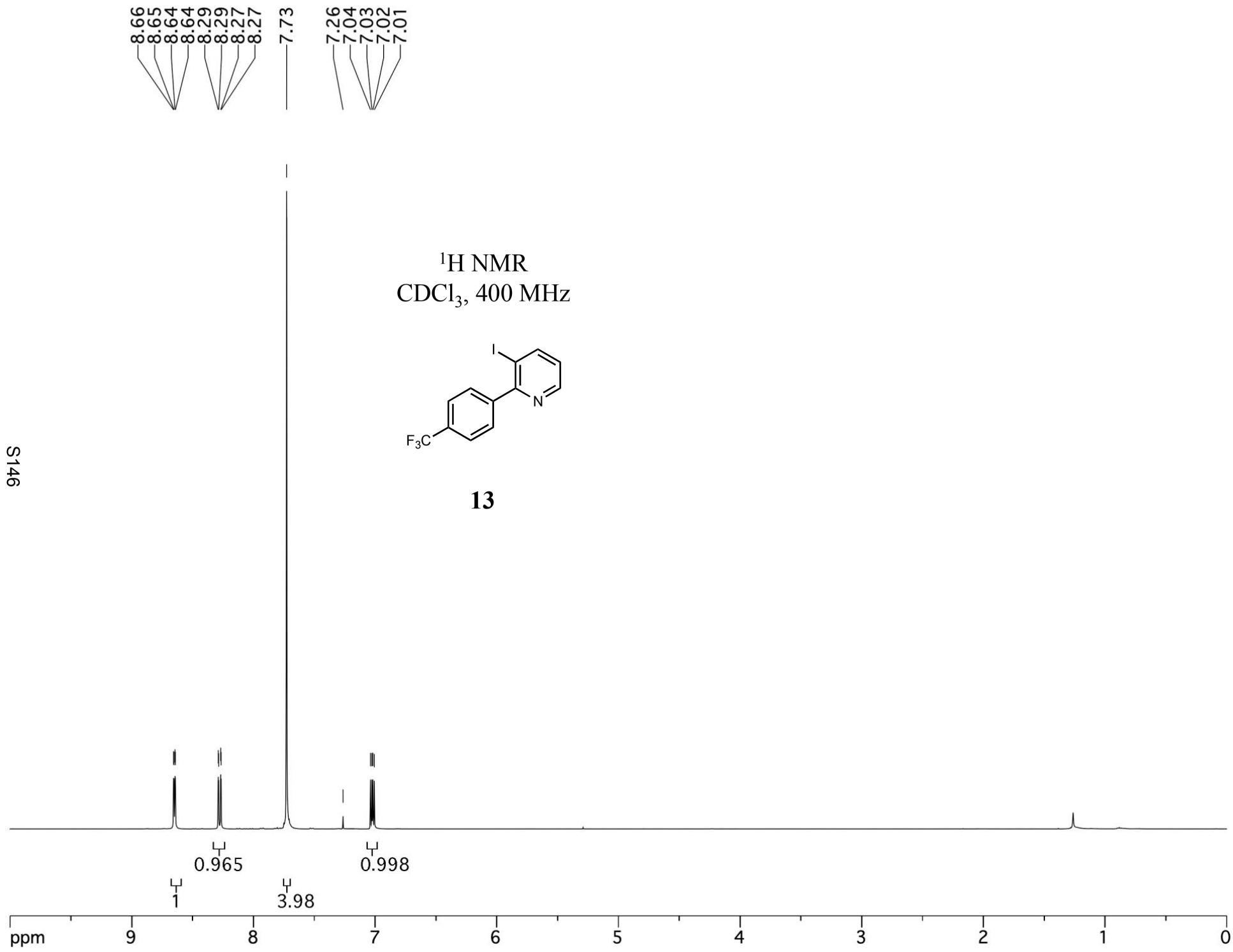

8.75
8.75
8.65
8.64
8.01
8.00
8.00
7.56
7.55
7.54
7.50
7.48
7.46
7.44
7.42
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Br
Ph
N
S142
0.976
1.97
1
0.95
2.95
ppm
9
8
7
6
5
4
3
2
1
0

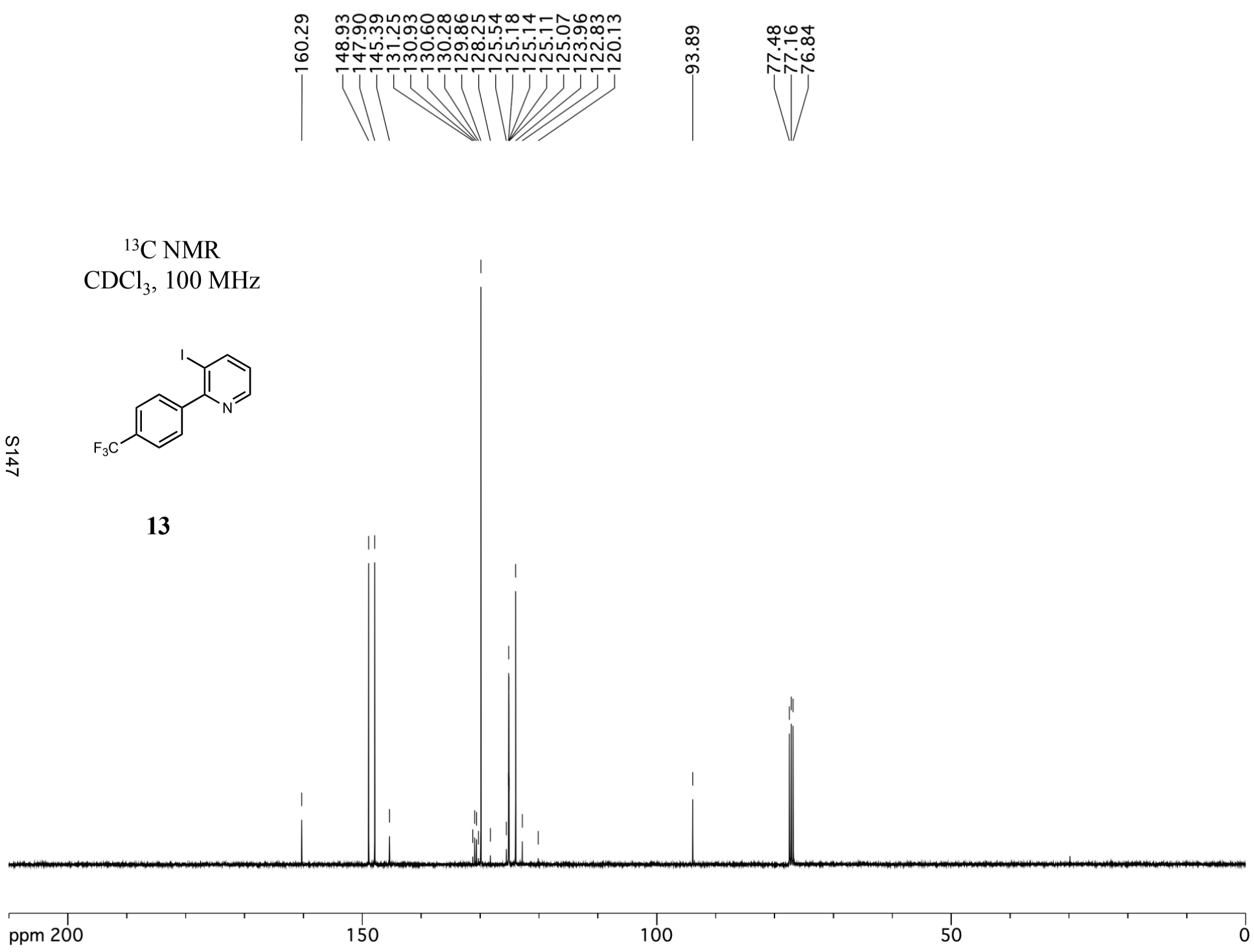
12-Br

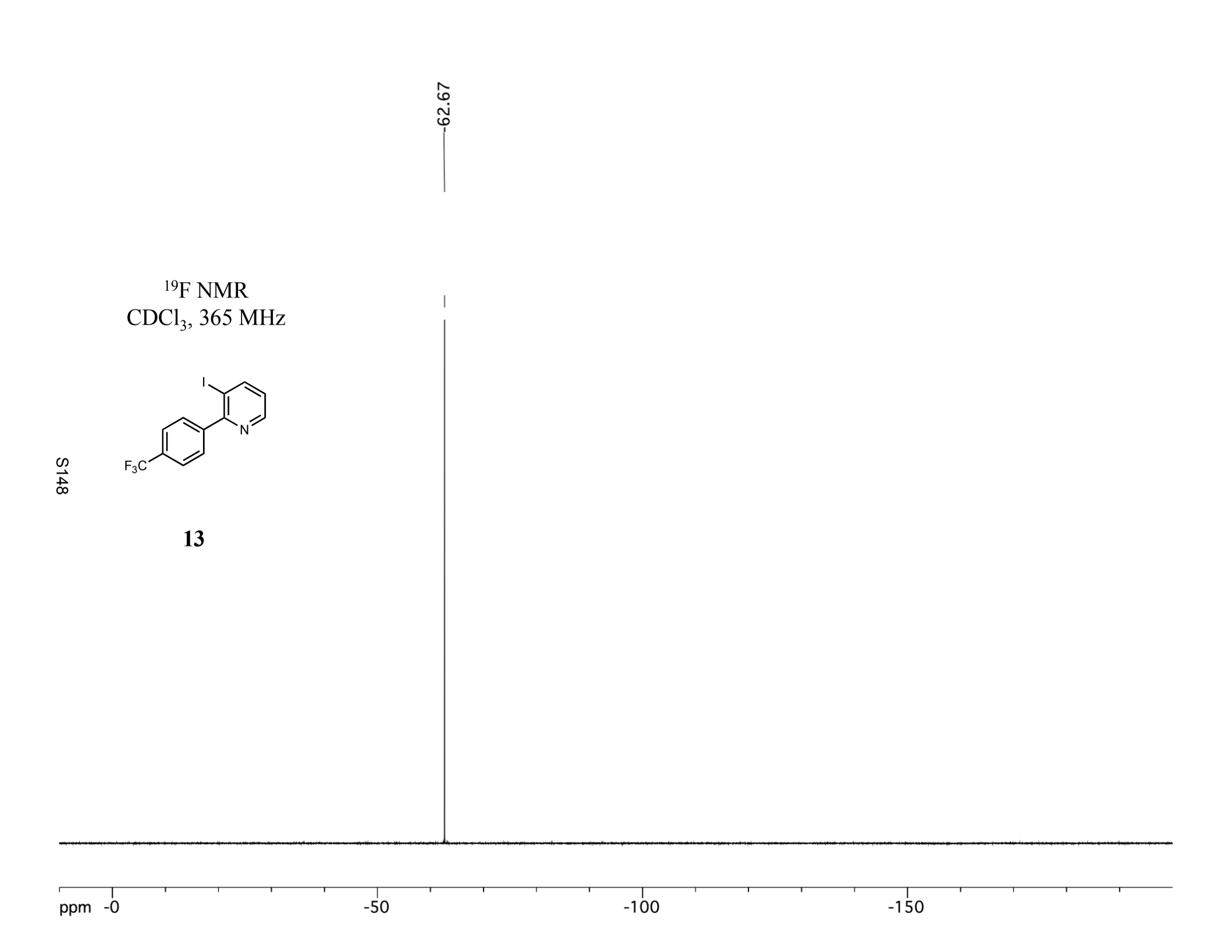

149.44
146.47
138.35
136.95
136.38
129.31
128.80
127.28
121.02
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
Ph
N
S143
12-Br
ppm 200
150
100
50
0

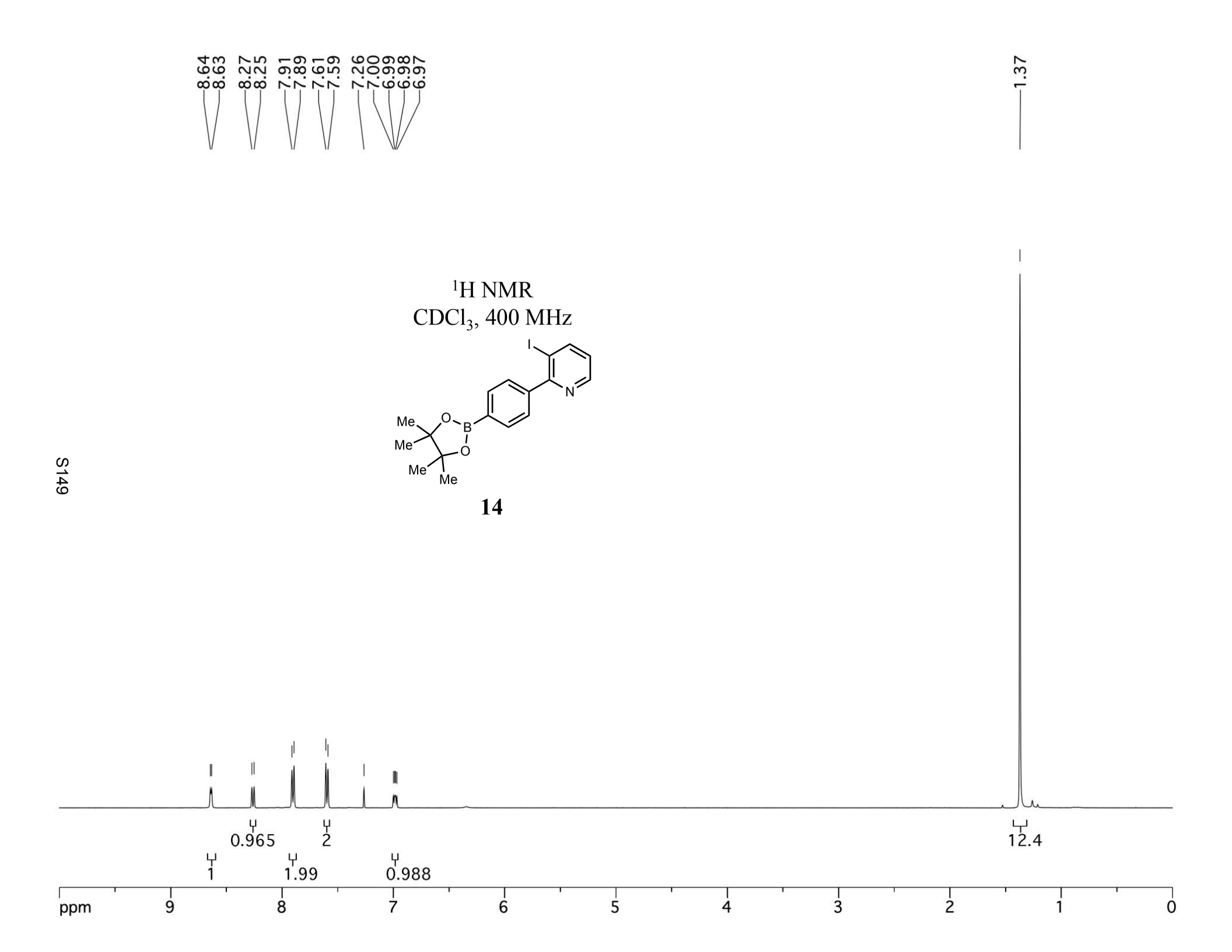

8.71
8.55
7.85
7.56
7.54
7.50
7.48
7.46
7.44
7.43
7.41
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Cl
Ph
N
12-Cl
0.978
1.94
1
0.943
2.95
ppm
9
8
7
6
5
4
3
2
1
0

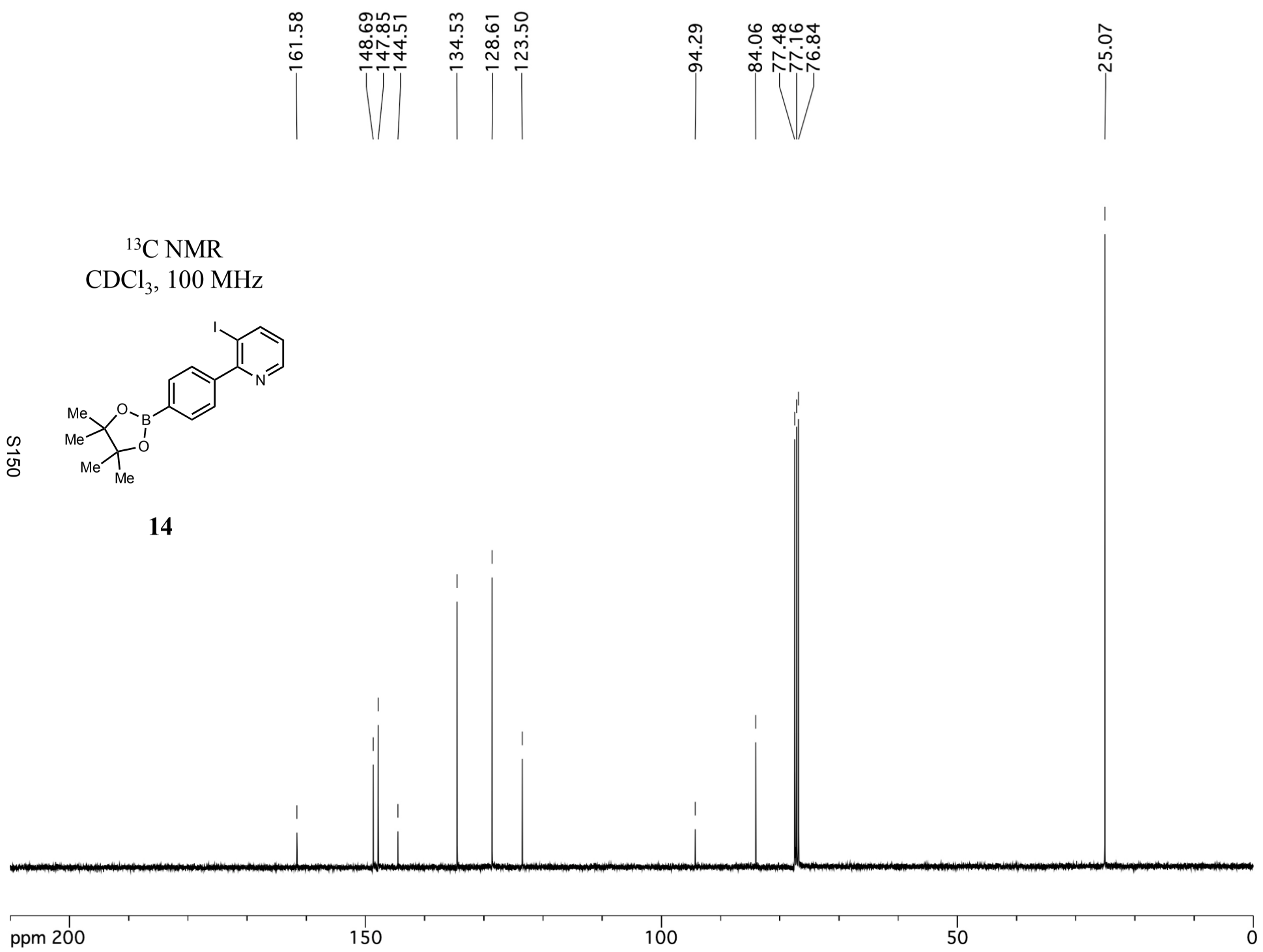

147.31
146.16
137.92
136.43
134.12
132.26
129.32
128.80
127.28
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
Ph
N
S145
12-Cl
ppm 200
150
100
50
0

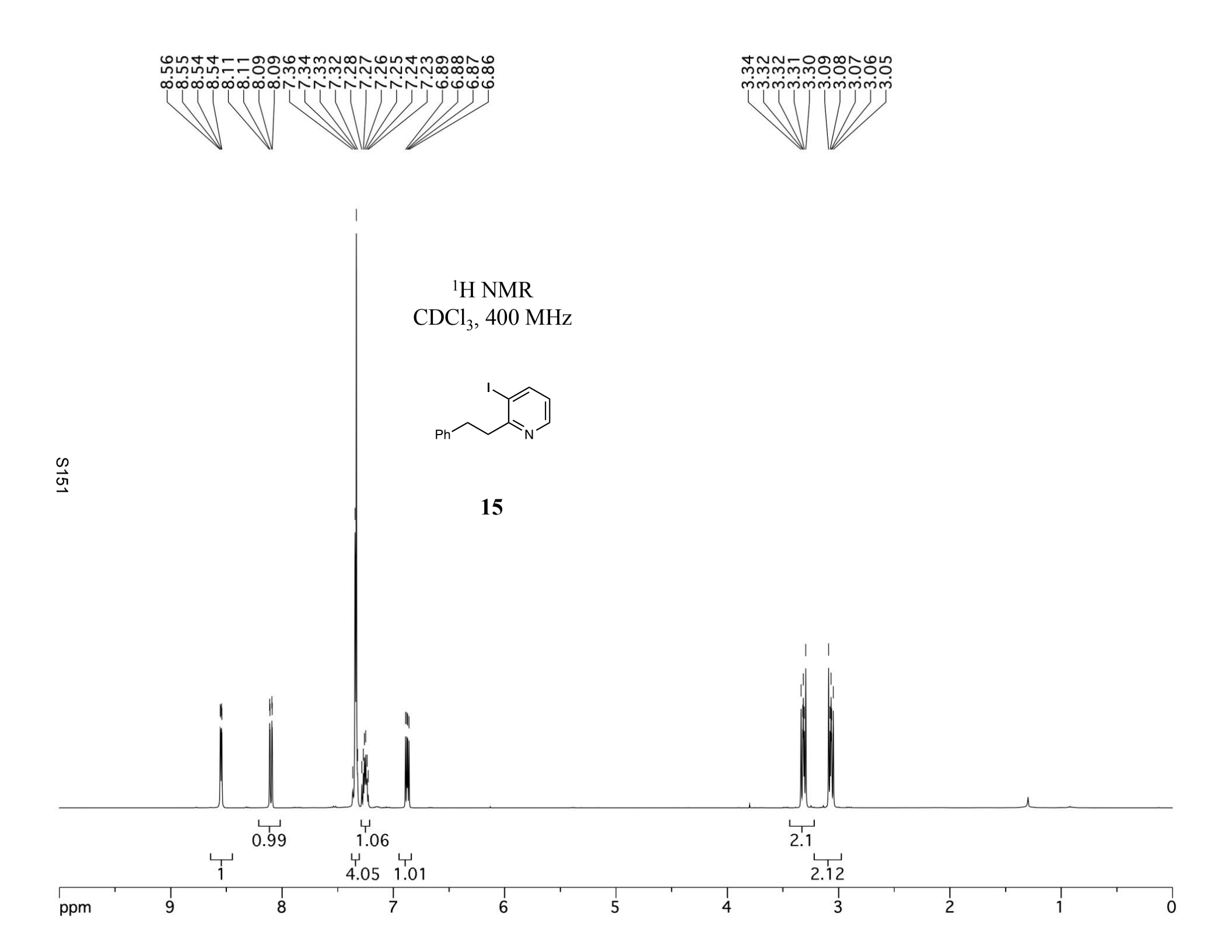

8.66
8.65
8.64
8.64
8.29
8.29
8.27
8.27
7.73
7.26
7.04
7.03
7.02
7.01
^{1}H NMR
$CDCl_3$, 400 MHz
I
N
F_3C
13
0.965
0.998
1
3.98
ppm
9
8
7
6
5
4
3
2
1
0

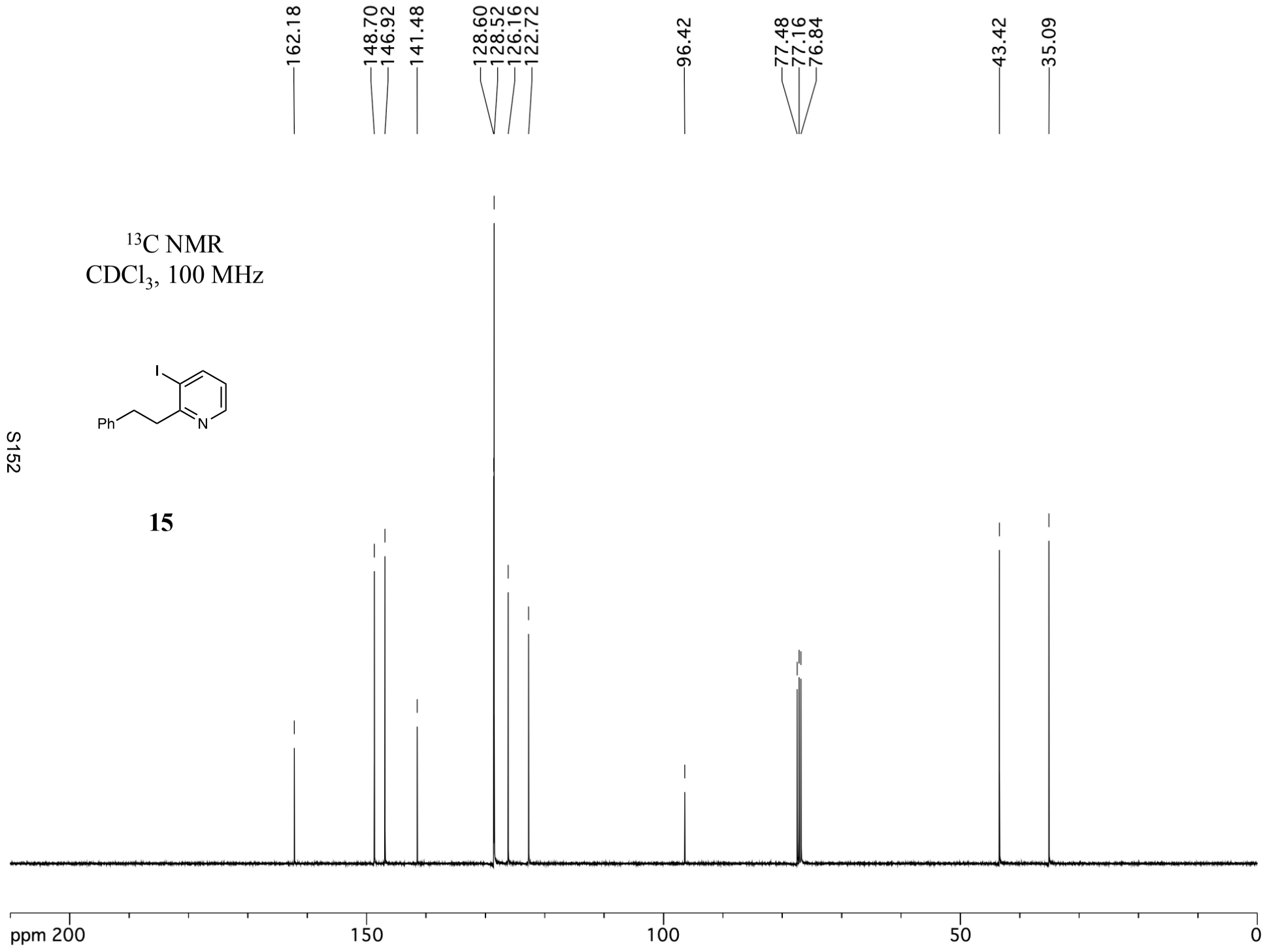

160.29
148.93
147.90
145.39
131.25
130.93
130.60
130.28
129.86
128.25
125.54
125.18
125.14
125.11
125.07
123.96
122.83
120.13
93.89
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
I
N
F_3C
13
ppm 200
150
100
50
0

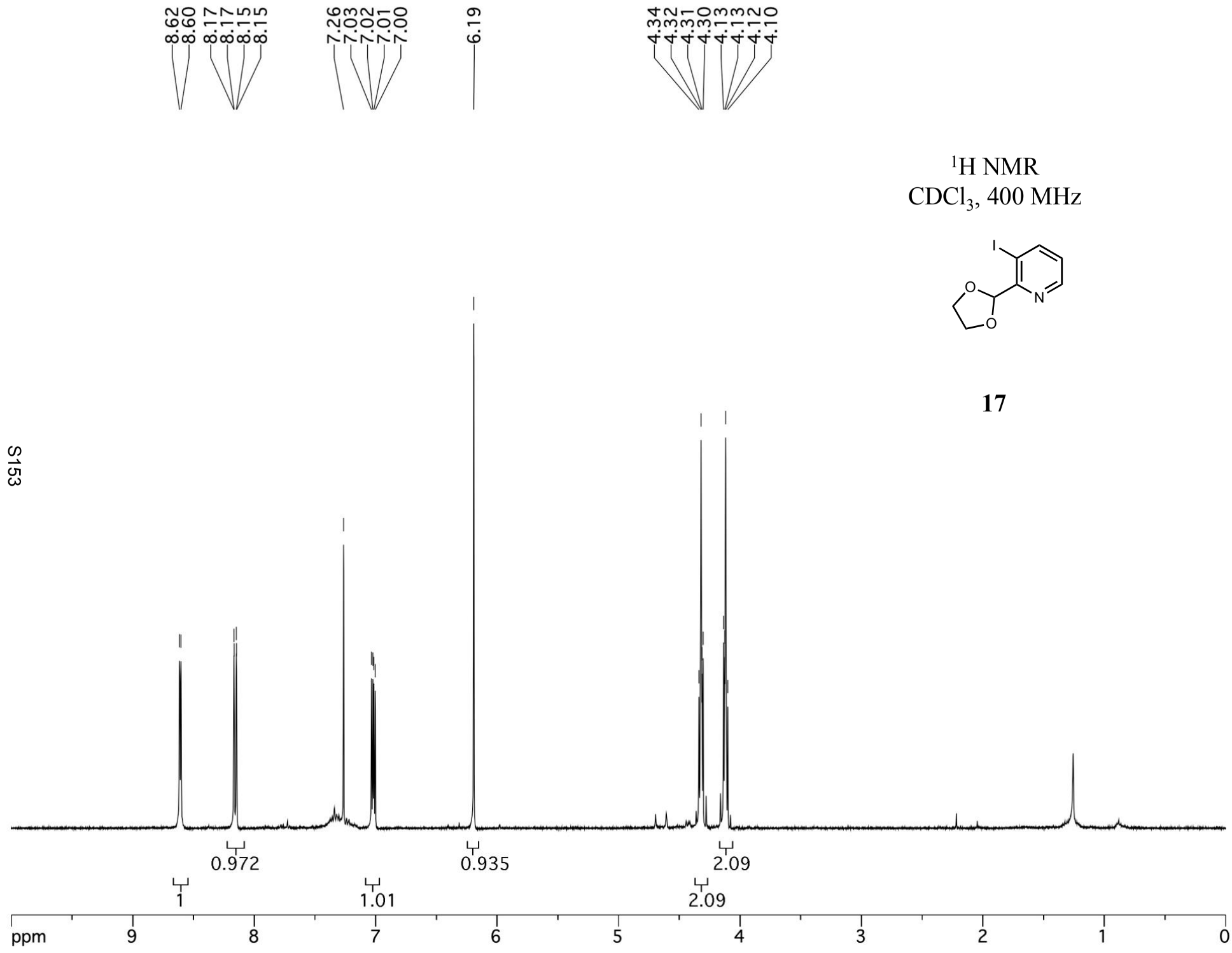

-62.67
^{19}F NMR
$CDCl_3$, 365 MHz
I
N
F_3C
13
ppm -0
-50
-100
-150


8.64
8.63
8.27
8.25
7.91
7.89
7.61
7.59
7.26
7.00
6.99
6.98
6.97
1.37
^{1}H NMR
$CDCl_3$, 400 MHz
I
N
O
B
O
Me
Me
Me
Me
14
S149
0.965
2
12.4
1
1.99
0.988
ppm
9
8
7
6
5
4
3
2
1
0


161.58
148.69
147.85
144.51
134.53
128.61
123.50
94.29
84.06
77.48
77.16
76.84
25.07
13C NMR
CDCl3, 100 MHz
I
N
O
B
O
Me
Me
Me
Me
14
S150
ppm 200
150
100
50
0

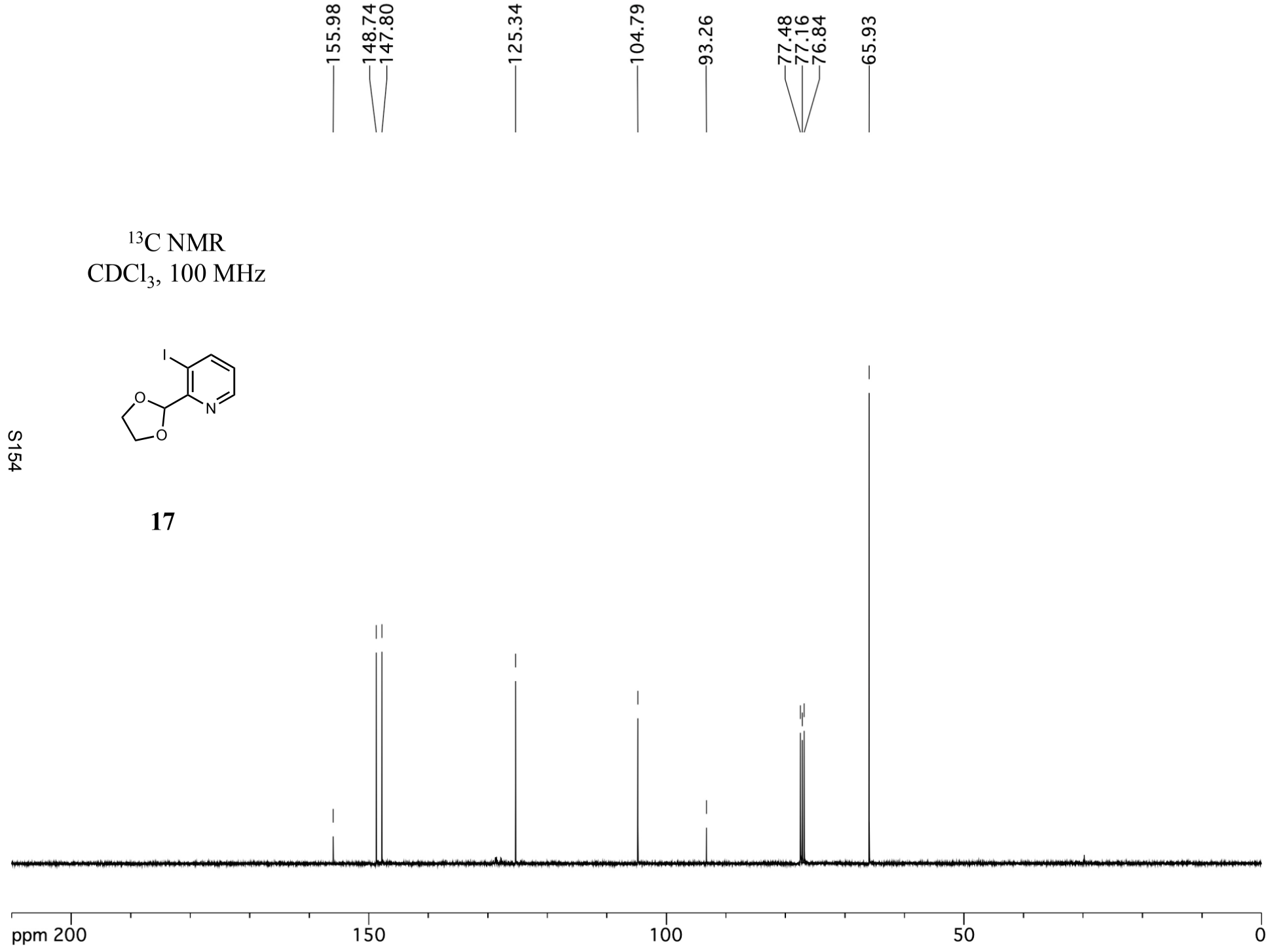

8.56
8.55
8.54
8.54
8.11
8.11
8.09
8.09
7.36
7.34
7.33
7.32
7.28
7.27
7.26
7.25
7.24
7.23
6.89
6.88
6.87
6.86
3.34
3.32
3.32
3.31
3.30
3.09
3.08
3.07
3.06
3.05
^{1}H NMR
$CDCl_3$, 400 MHz
I
Ph
N
15
S151
0.99
1.06
2.1
1
4.05
1.01
2.12
ppm
9
8
7
6
5
4
3
2
1
0


162.18
148.70
146.92
141.48
128.60
128.52
126.16
122.72
96.42
77.48
77.16
76.84
43.42
35.09
13C NMR
CDCl3, 100 MHz
I
Ph
N
S152
15
ppm 200
150
100
50
0



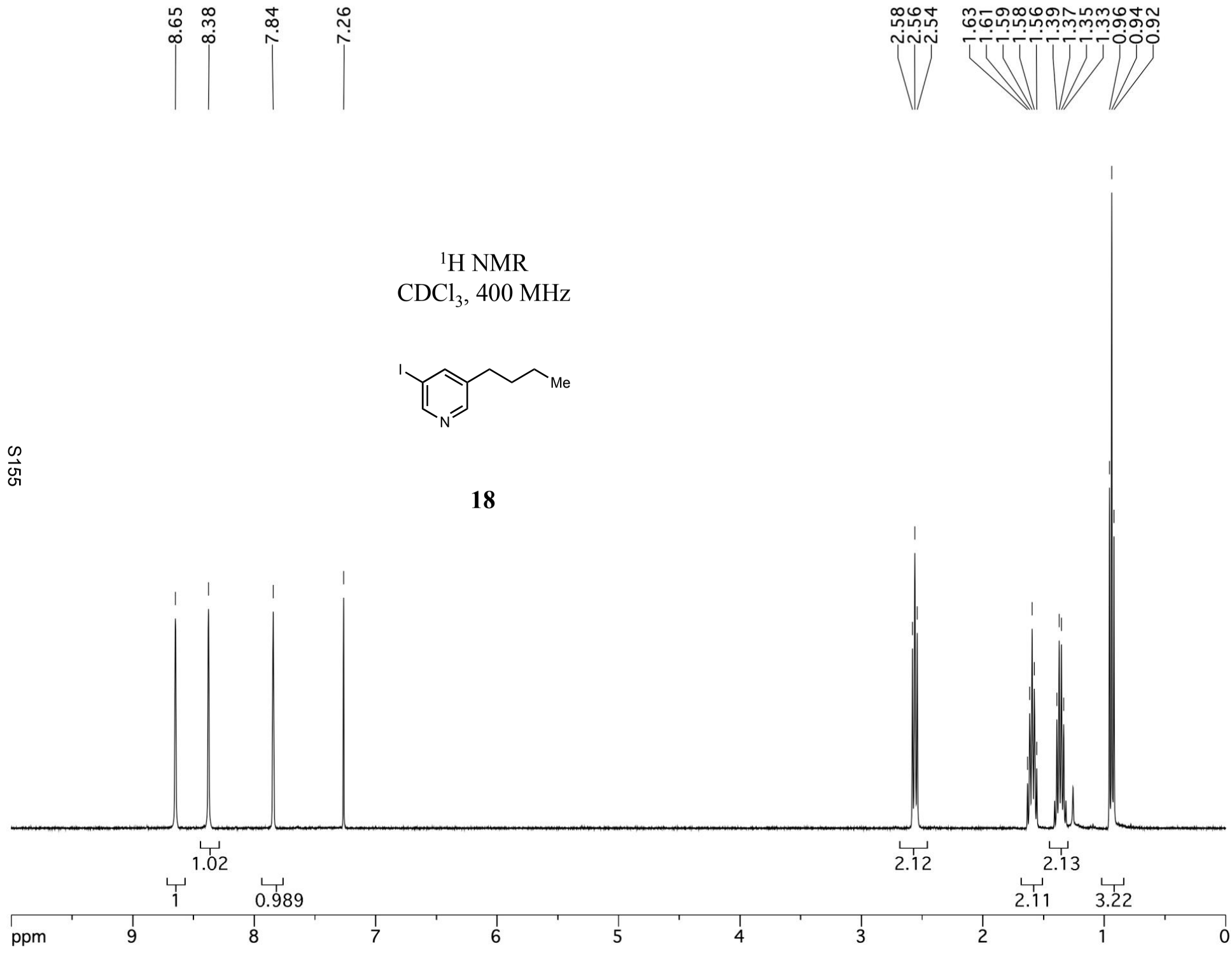
^{1}H NMR
$CDCl_3$, 400 MHz

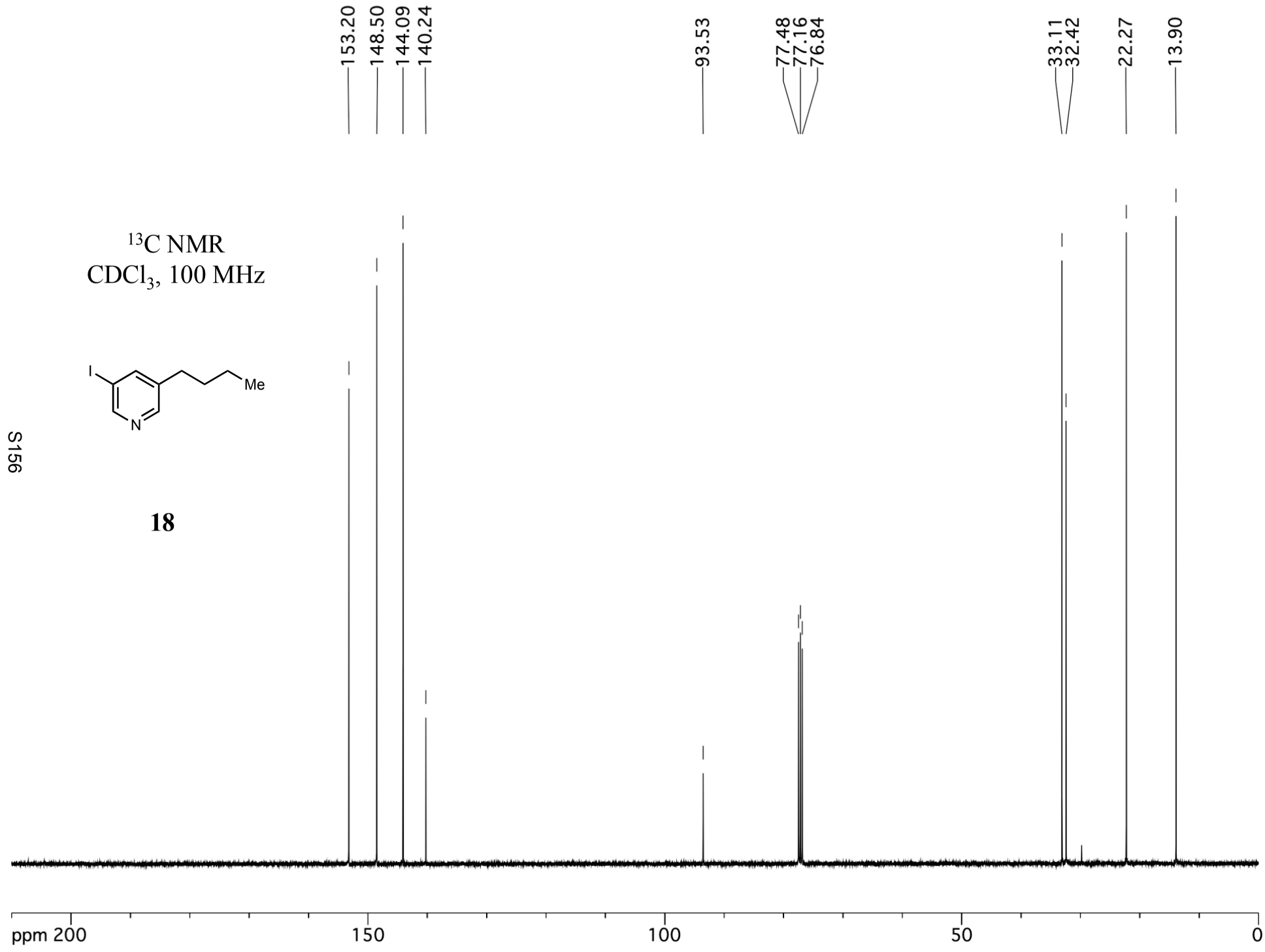
17

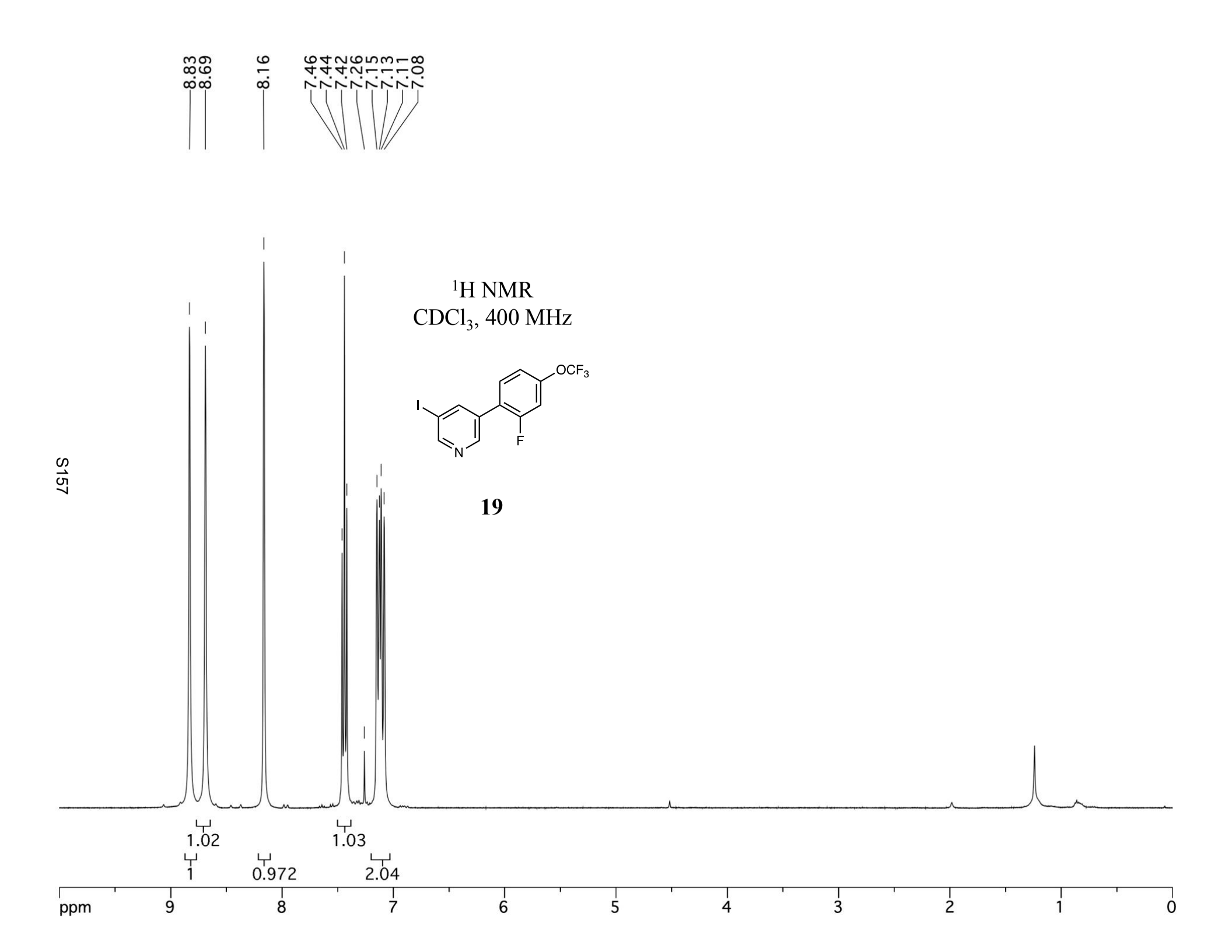


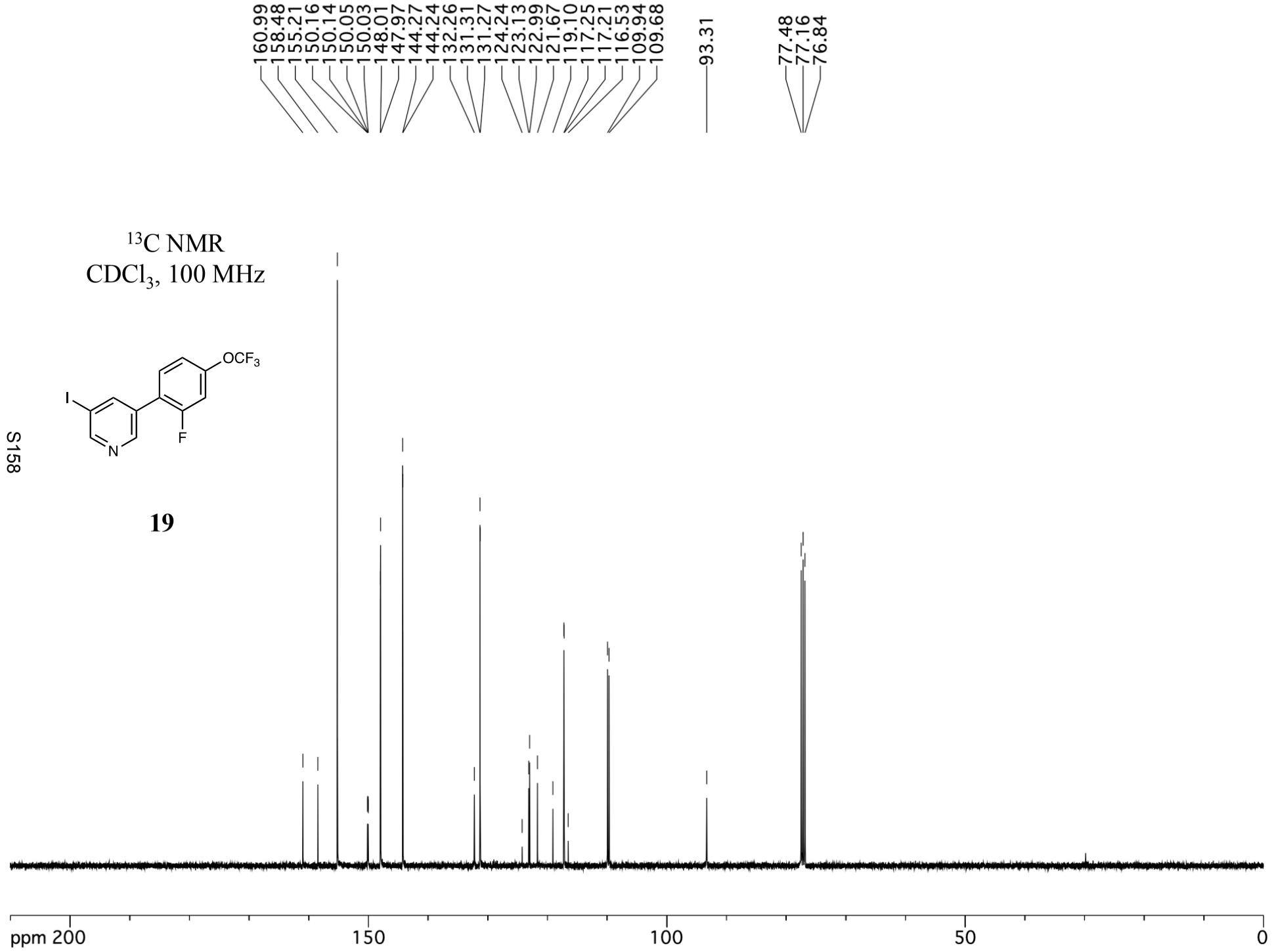
^{13}C NMR
$CDCl_3$, 100 MHz

17

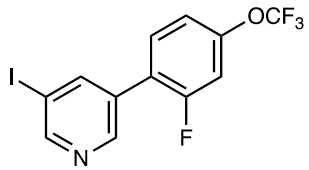

8.65
8.38
7.84
7.26
2.58
2.56
2.54
1.63
1.61
1.59
1.58
1.56
1.39
1.37
1.35
1.33
0.96
0.94
0.92
1H NMR
CDCl3, 400 MHz
I
Me
N
18
1
1.02
0.989
2.12
2.13
2.11
3.22
ppm
9
8
7
6
5
4
3
2
1
0


153.20
148.50
144.09
140.24
93.53
77.48
77.16
76.84
33.11
32.42
22.27
13.90
^{13}C NMR
$CDCl_3$, 100 MHz
I
Me
N
S156
18
ppm 200
150
100
50
0


8.83
8.69
8.16
7.46
7.44
7.42
7.26
7.15
7.13
7.11
7.08
^{1}H NMR
$CDCl_3$, 400 MHz
OCF_3
I
F
N
19
1.02
1.03
1
0.972
2.04
ppm
9
8
7
6
5
4
3
2
1
0


160.99
158.48
155.21
150.16
150.14
150.05
150.03
148.01
147.97
144.27
144.24
132.26
131.31
131.27
124.24
123.13
122.99
121.67
119.10
117.25
117.21
116.53
109.94
109.68
93.31
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
OCF_3
I
F
N
19
S158
ppm 200
150
100
50
0

^{19}F NMR
$CDCl_3$, 365 MHz



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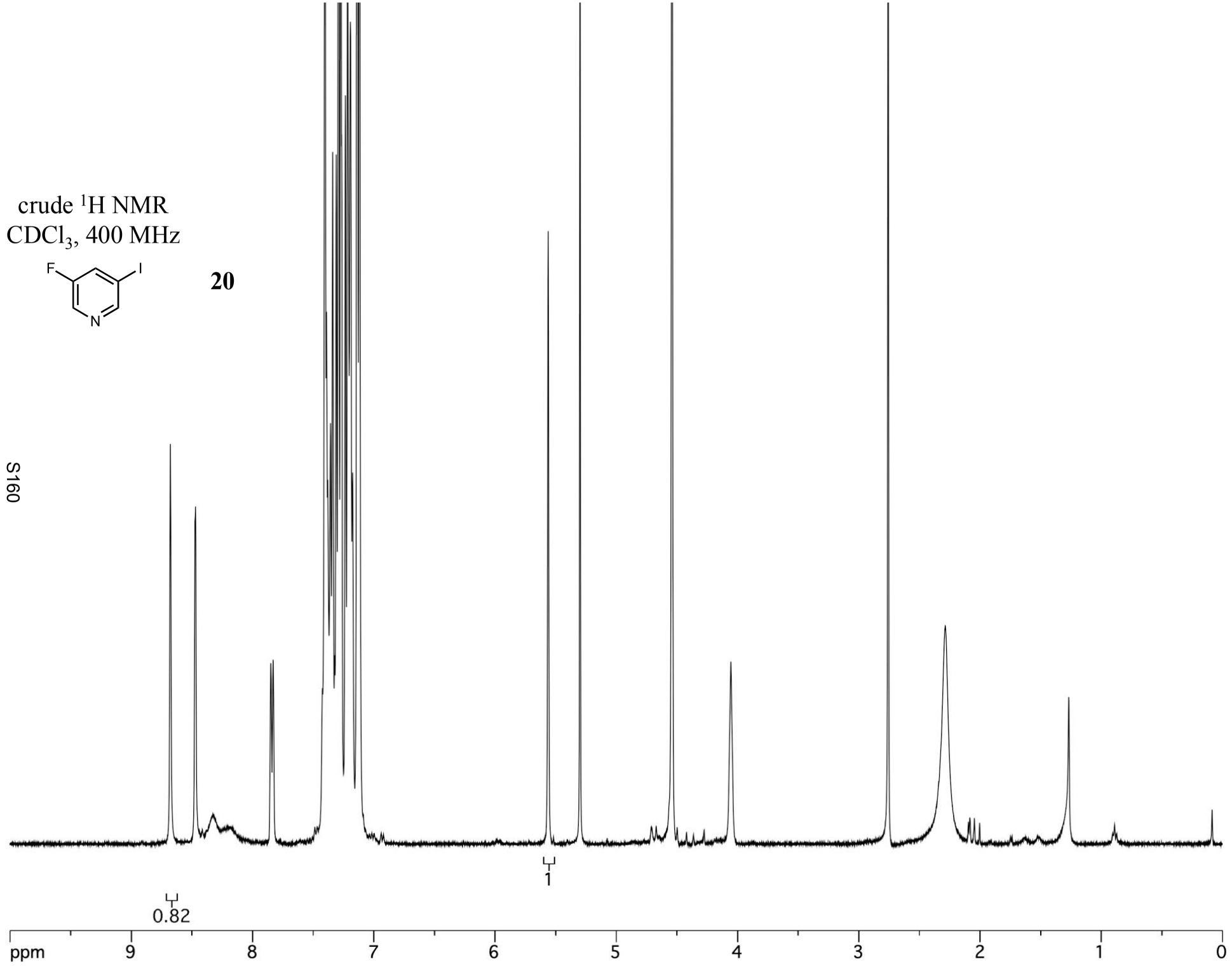
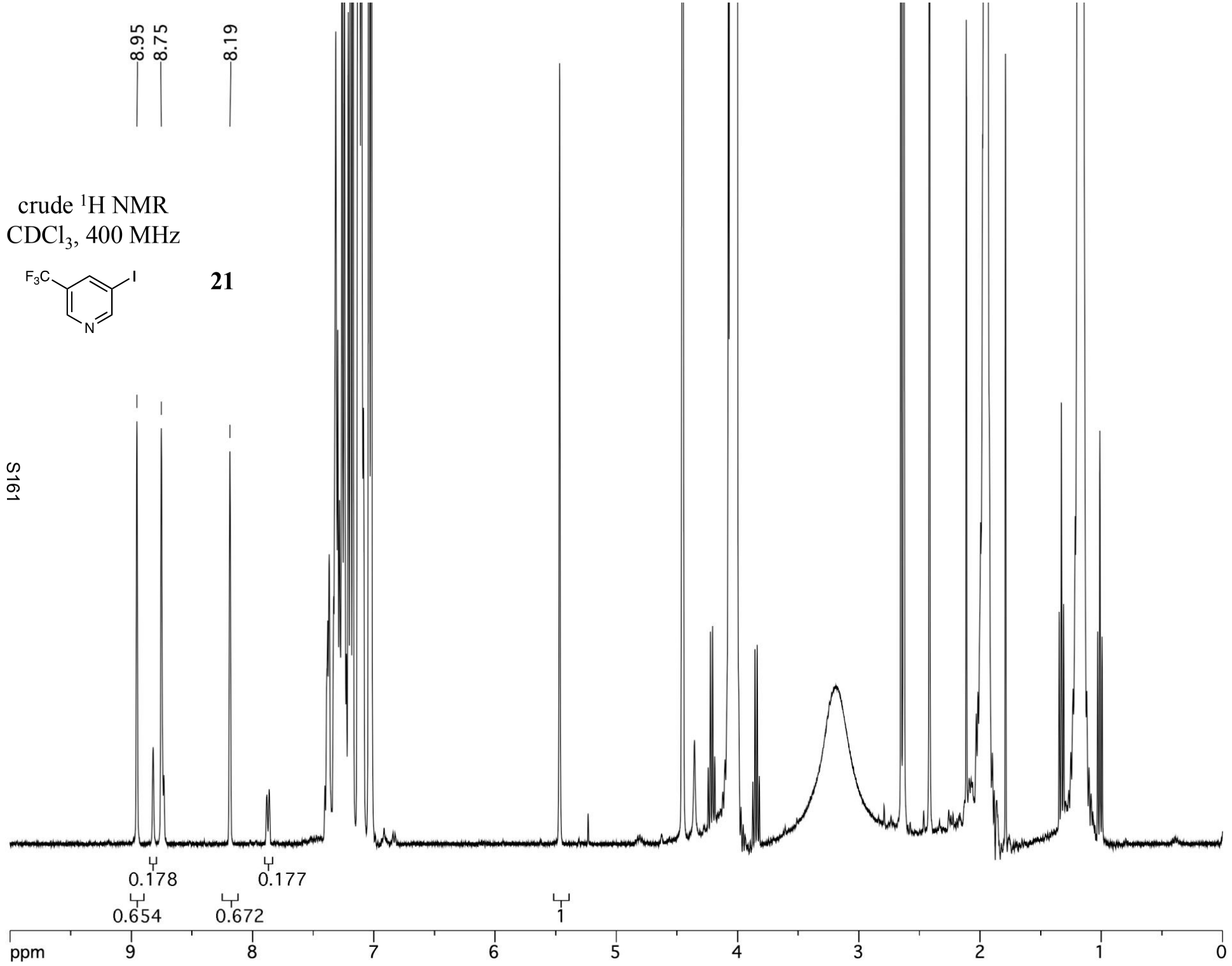
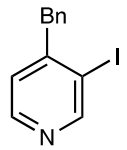
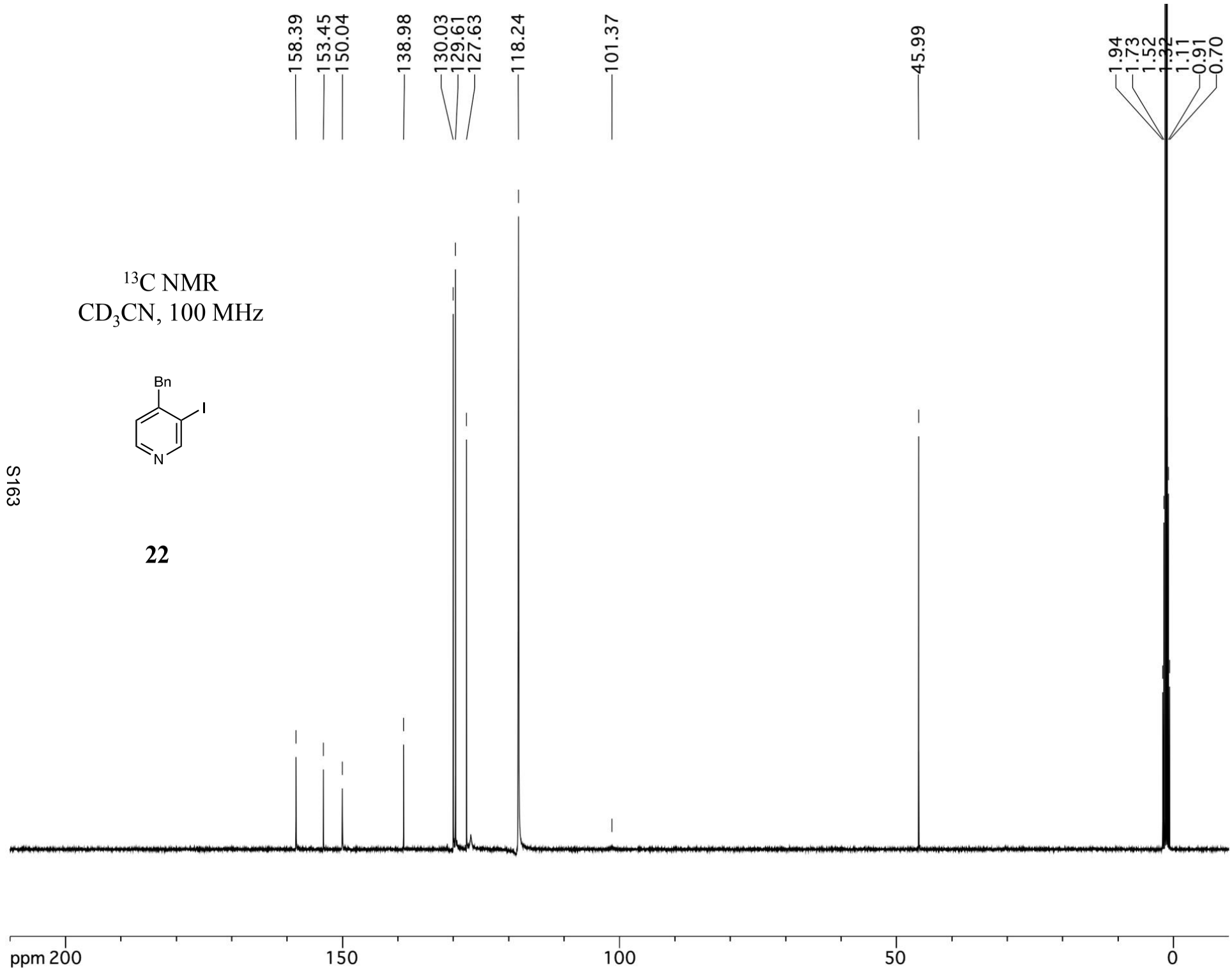

crude ^{1}H NMR
$CDCl_3$, 400 MHz
F
I
N
20
S160
0.82
1
ppm
9
8
7
6
5
4
3
2
1
0

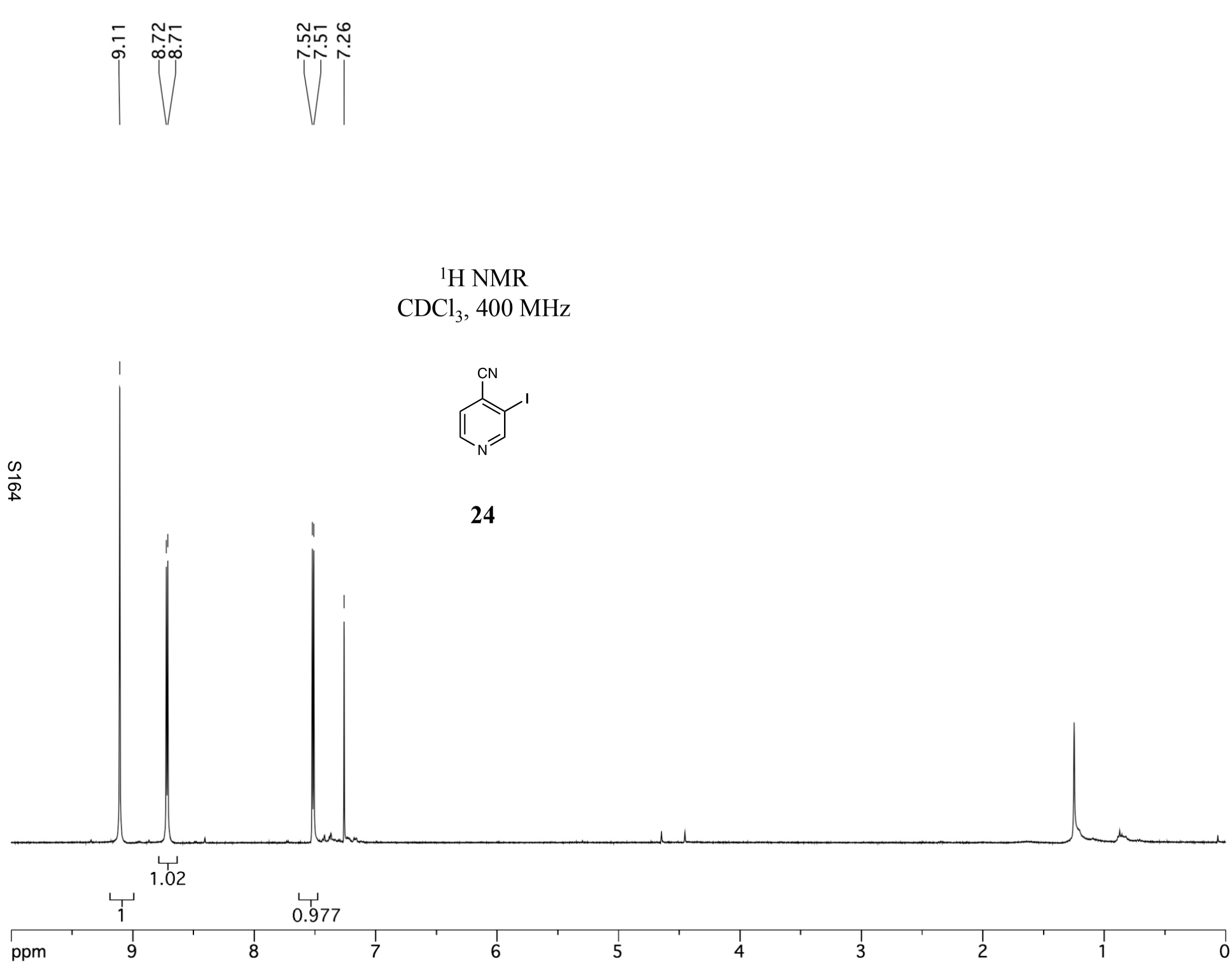

8.95
8.75
8.19
crude ^{1}H NMR
$CDCl_3$, 400 MHz
F_3C
I
N
21
S161
0.178
0.177
0.654
0.672
1
ppm
9
8
7
6
5
4
3
2
1
0

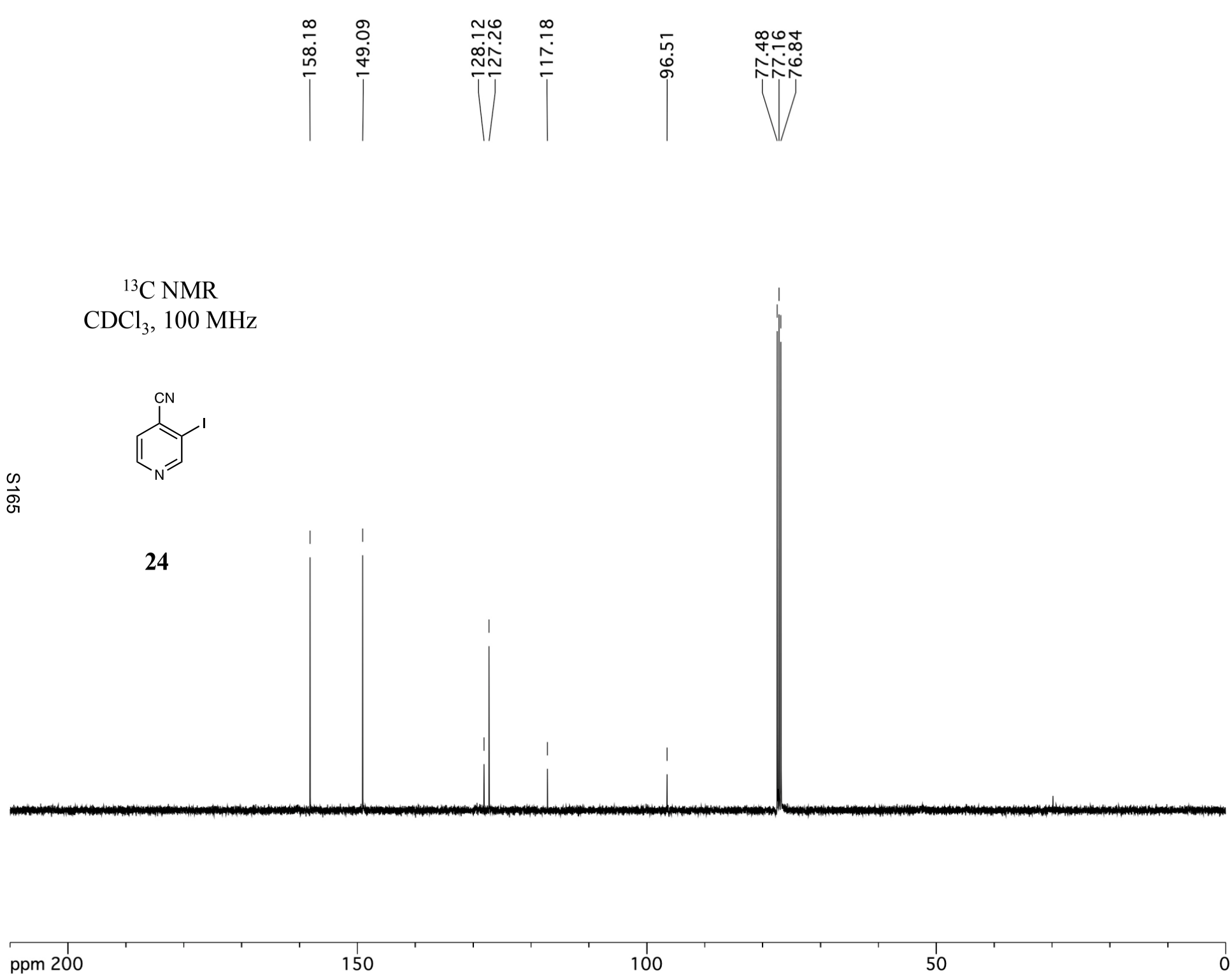
^{1}H NMR
CD_3CN, 400 MHz

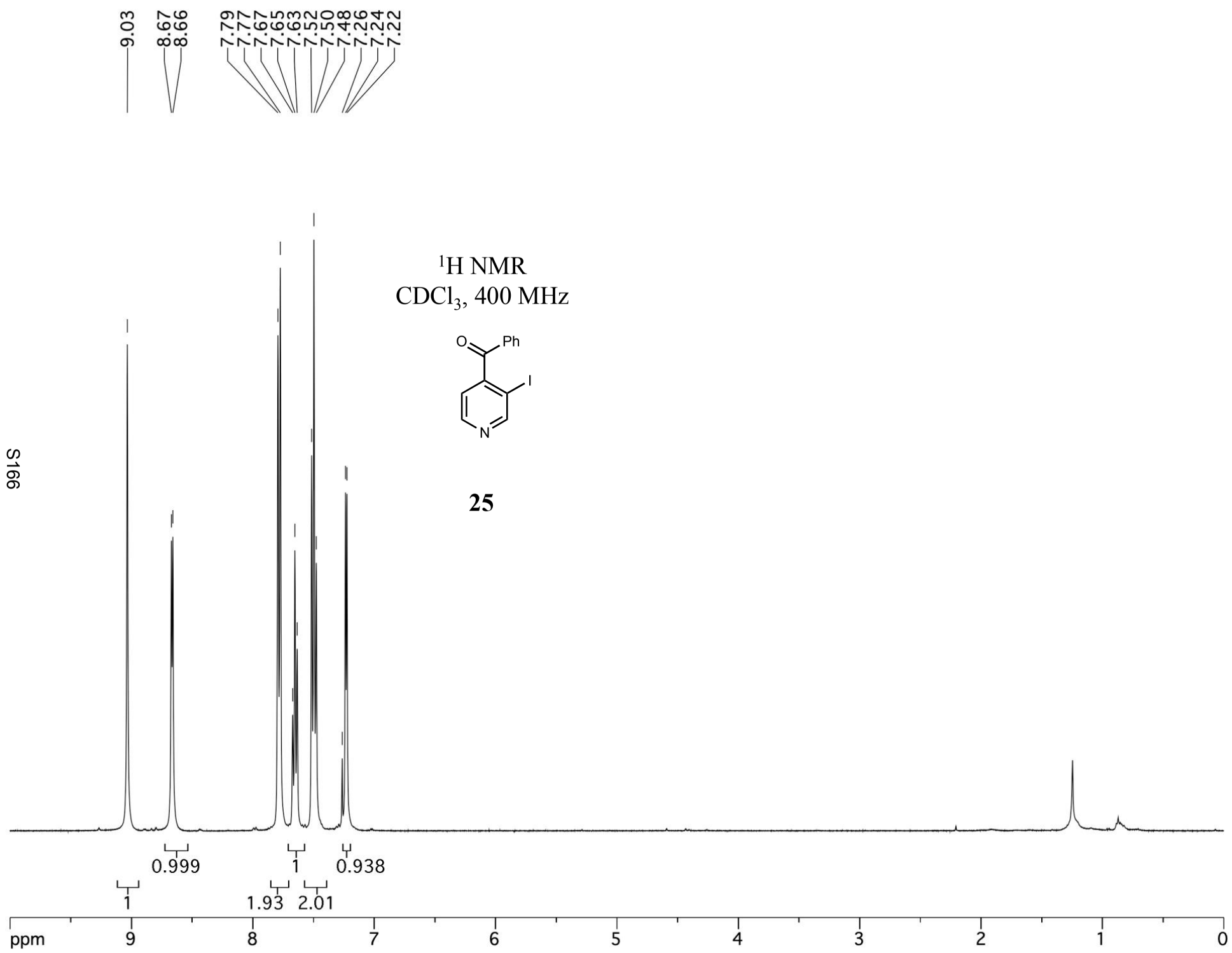


22


158.39
153.45
150.04
138.98
130.03
129.61
127.63
118.24
101.37
45.99
1.94
1.73
1.52
1.32
1.11
0.91
0.70
^{13}C NMR
CD_3CN, 100 MHz
Bn
I
N
22
ppm 200
150
100
50
0

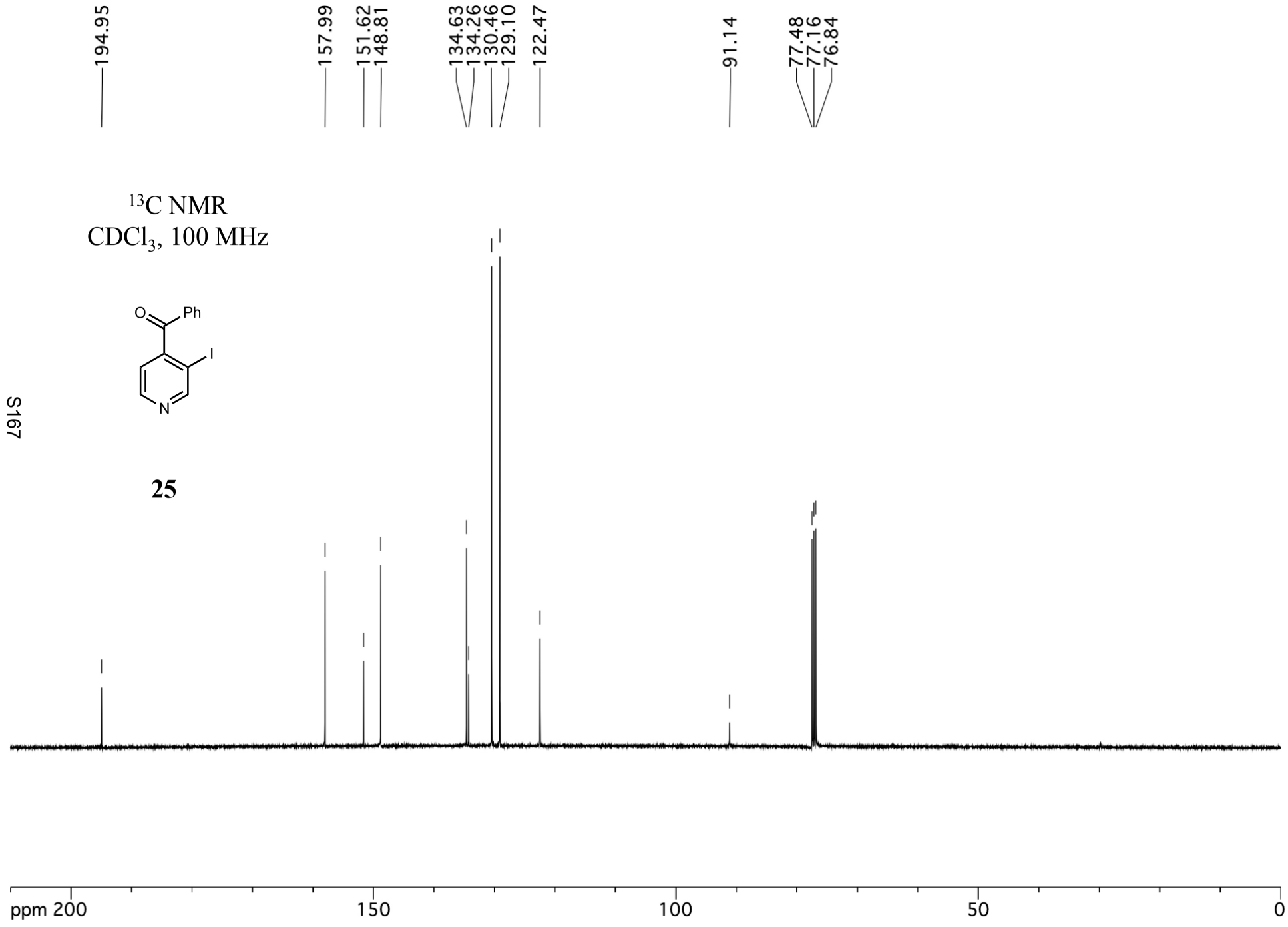

9.11
8.72
8.71
7.52
7.51
7.26
1H NMR
CDCl3, 400 MHz
CN
I
N
24
S164
1.02
1
0.977
ppm
9
8
7
6
5
4
3
2
1
0

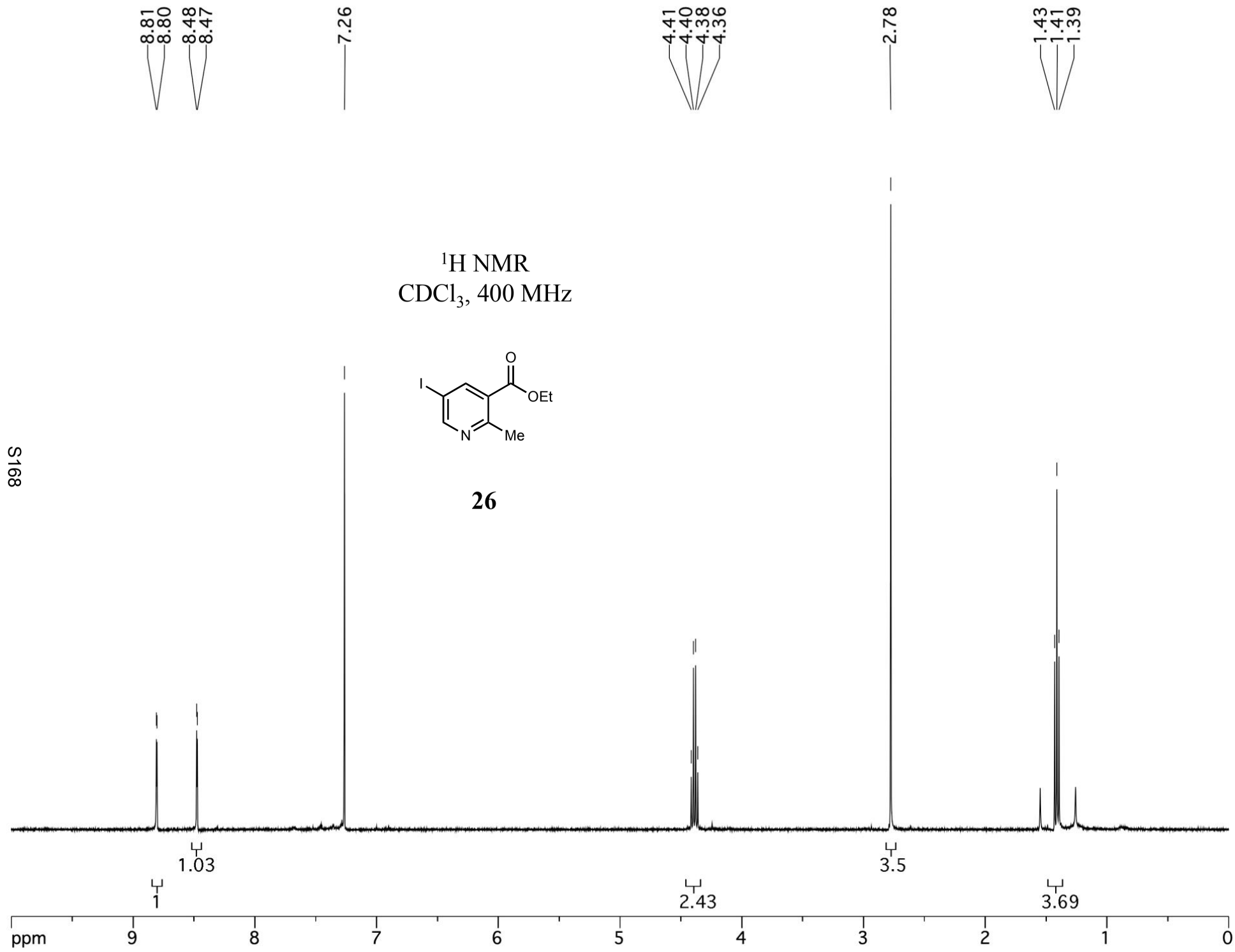

158.18
149.09
128.12
127.26
117.18
96.51
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
CN
I
N
24
ppm 200
150
100
50
0

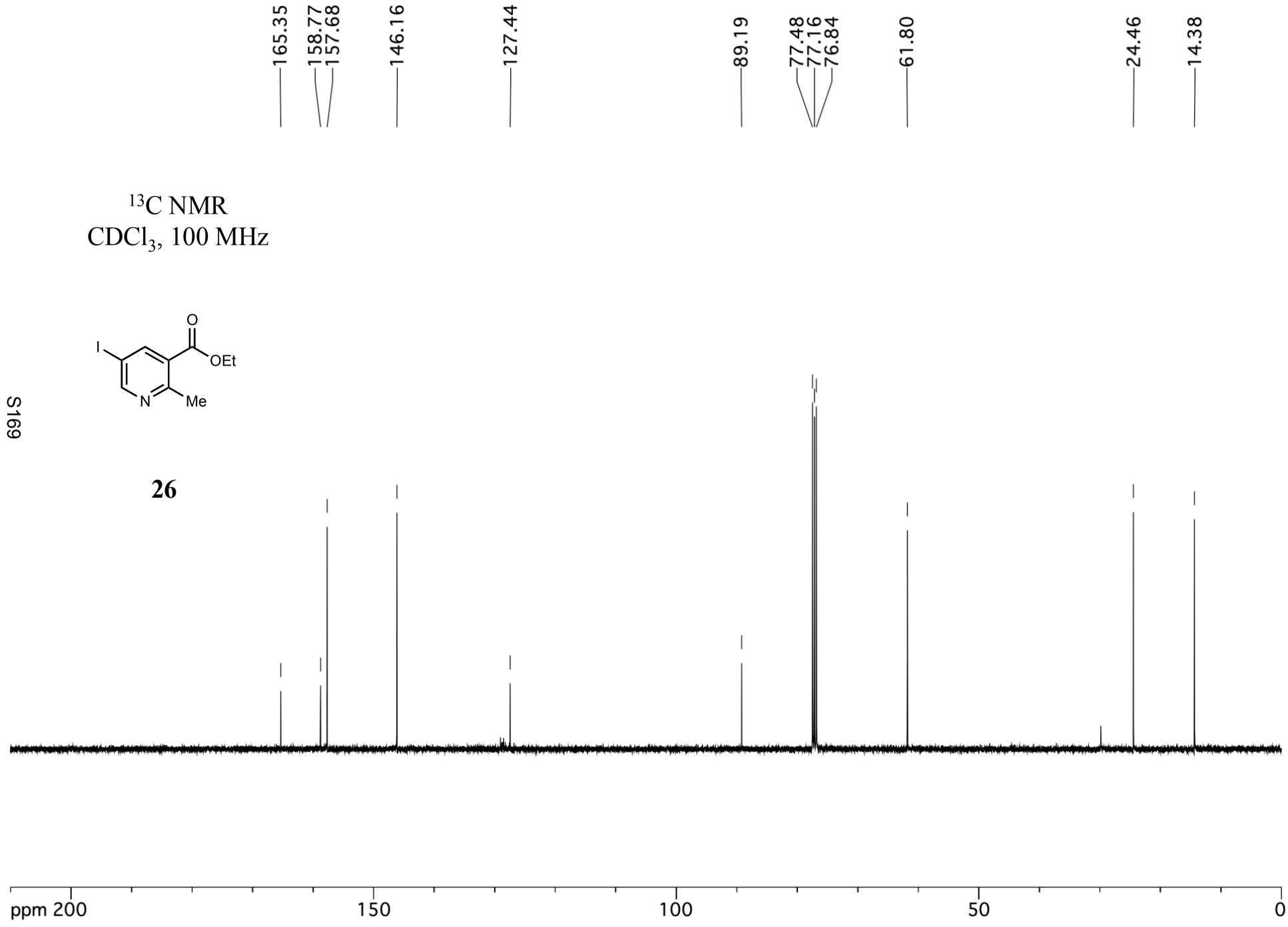


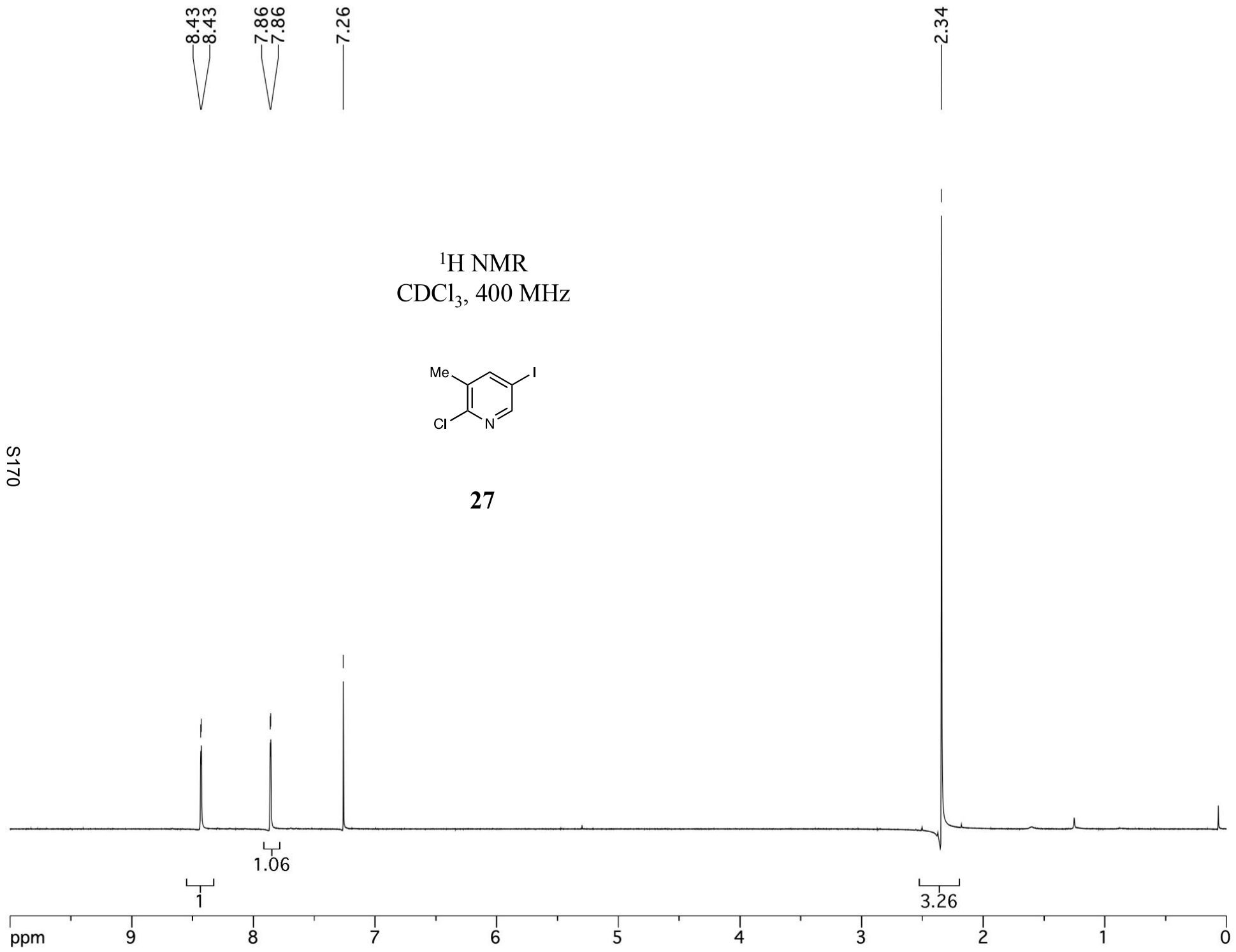
^{1}H NMR
$CDCl_3$, 400 MHz

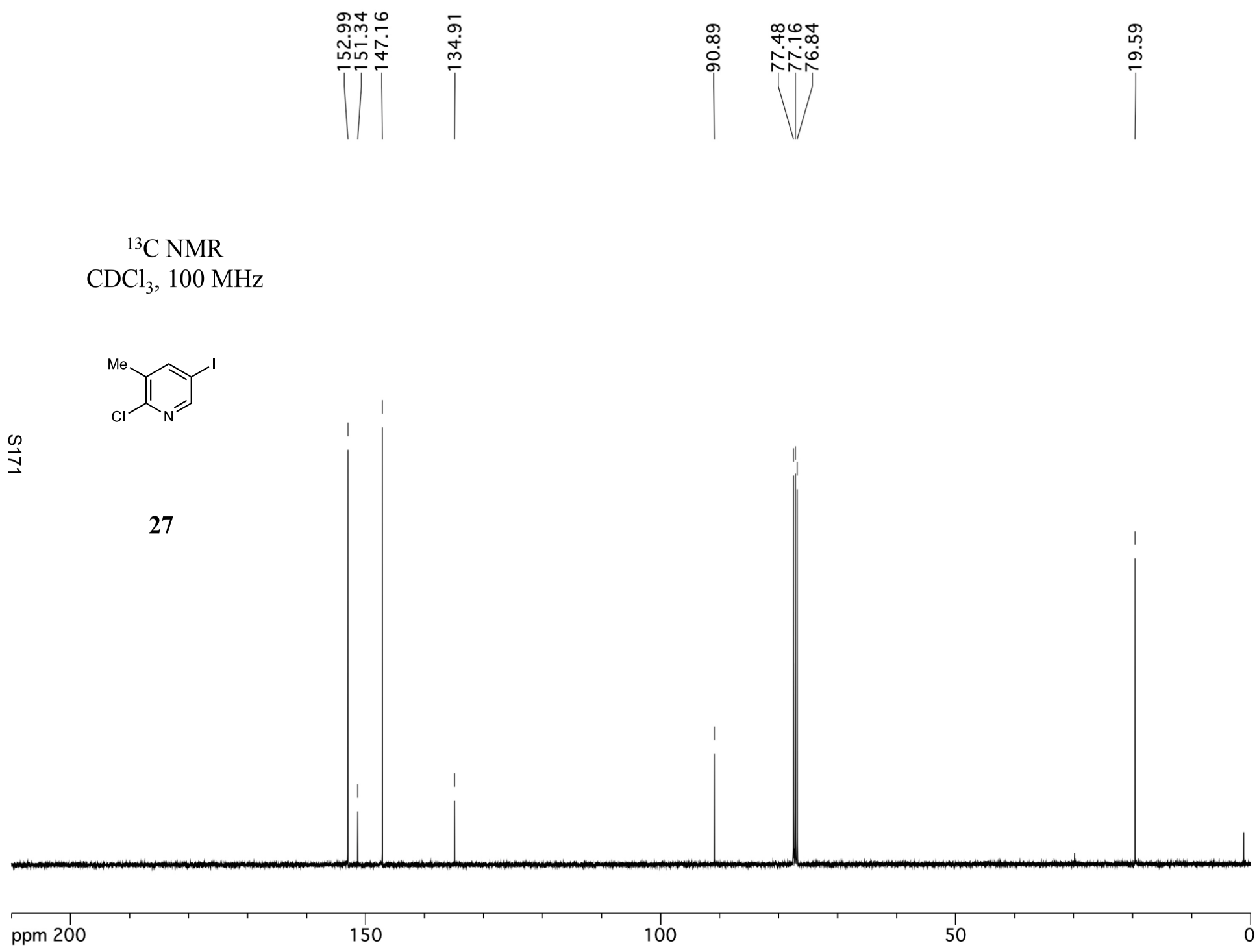
25

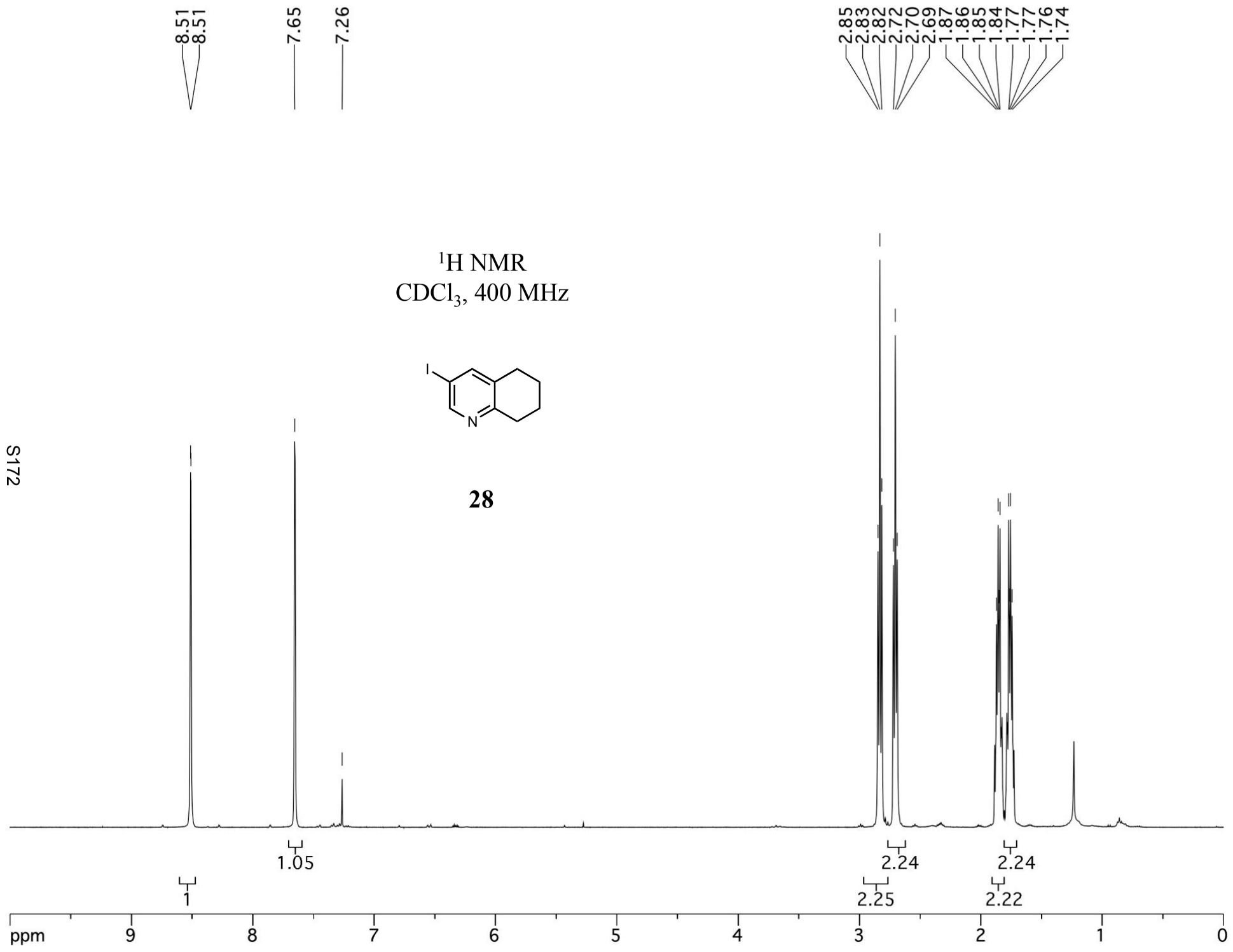

194.95
157.99
151.62
148.81
134.63
134.26
130.46
129.10
122.47
91.14
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
O
Ph
I
N
25
S167
ppm 200
150
100
50
0

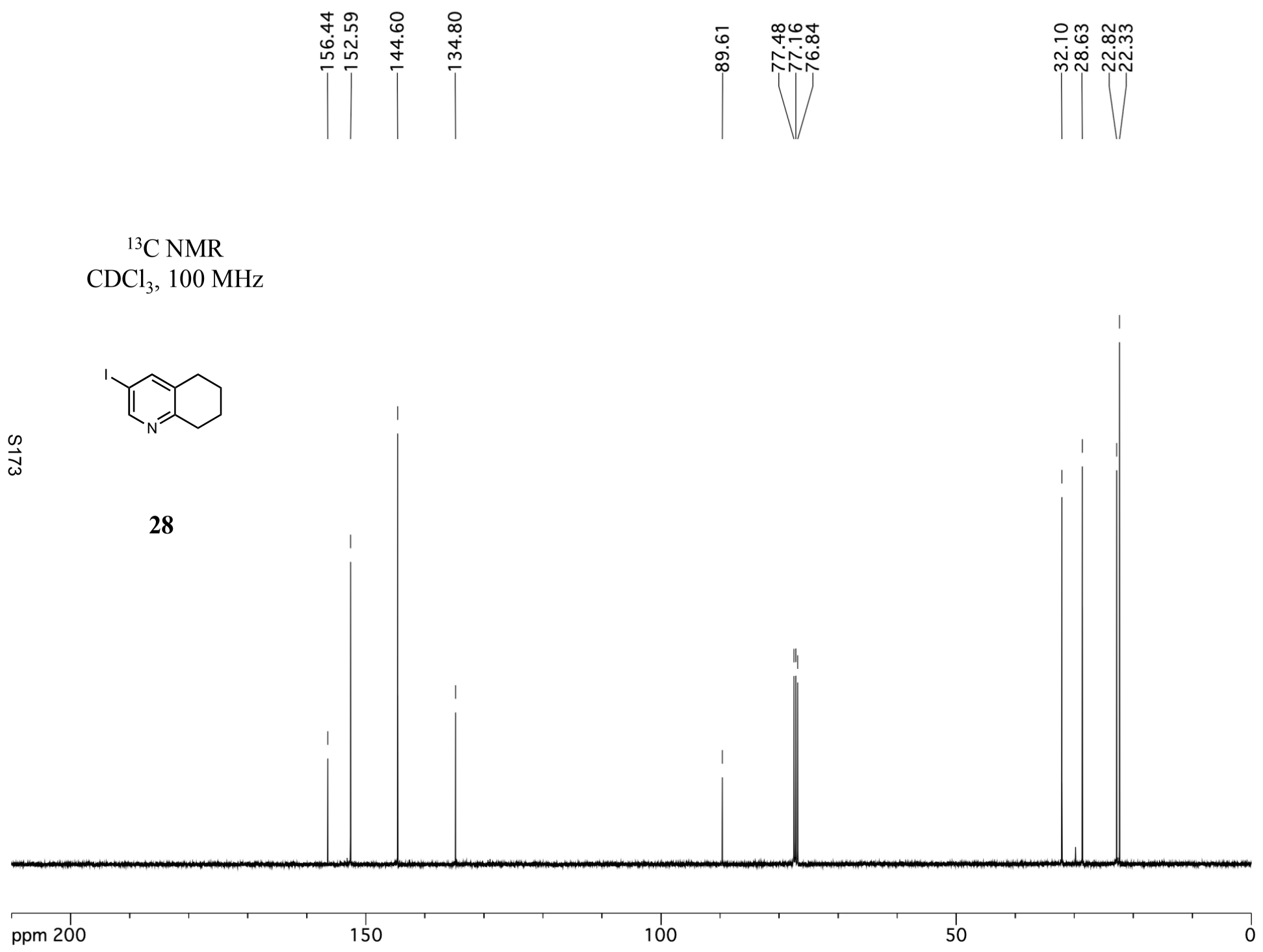

8.81
8.80
8.48
8.47
7.26
4.41
4.40
4.38
4.36
2.78
1.43
1.41
1.39
^{1}H NMR
$CDCl_3$, 400 MHz
I
O
OEt
N
Me
26
S168
1.03
3.5
1
2.43
3.69
ppm
9
8
7
6
5
4
3
2
1
0

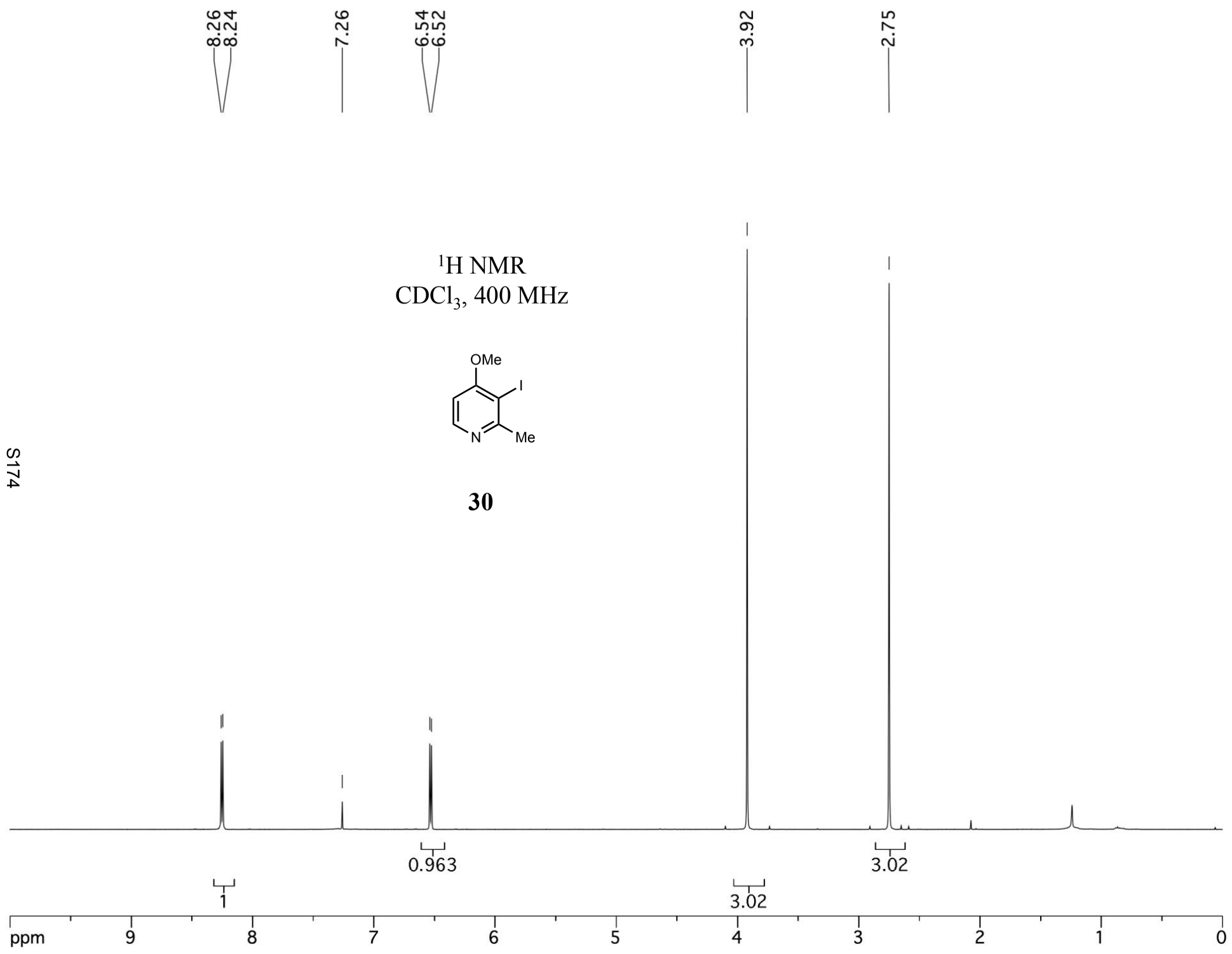

165.35
158.77
157.68
146.16
127.44
89.19
77.48
77.16
76.84
61.80
24.46
14.38
^{13}C NMR
$CDCl_3$, 100 MHz
O
I
OEt
N
Me
26
ppm 200
150
100
50
0


8.43
8.43
7.86
7.86
7.26
2.34
^{1}H NMR
$CDCl_3$, 400 MHz
Me
I
Cl
N
S170
27
1.06
1
3.26
ppm
9
8
7
6
5
4
3
2
1
0


152.99
151.34
147.16
134.91
90.89
77.48
77.16
76.84
19.59
^{13}C NMR
$CDCl_3$, 100 MHz
Me
I
Cl
N
S171
27
ppm 200
150
100
50
0

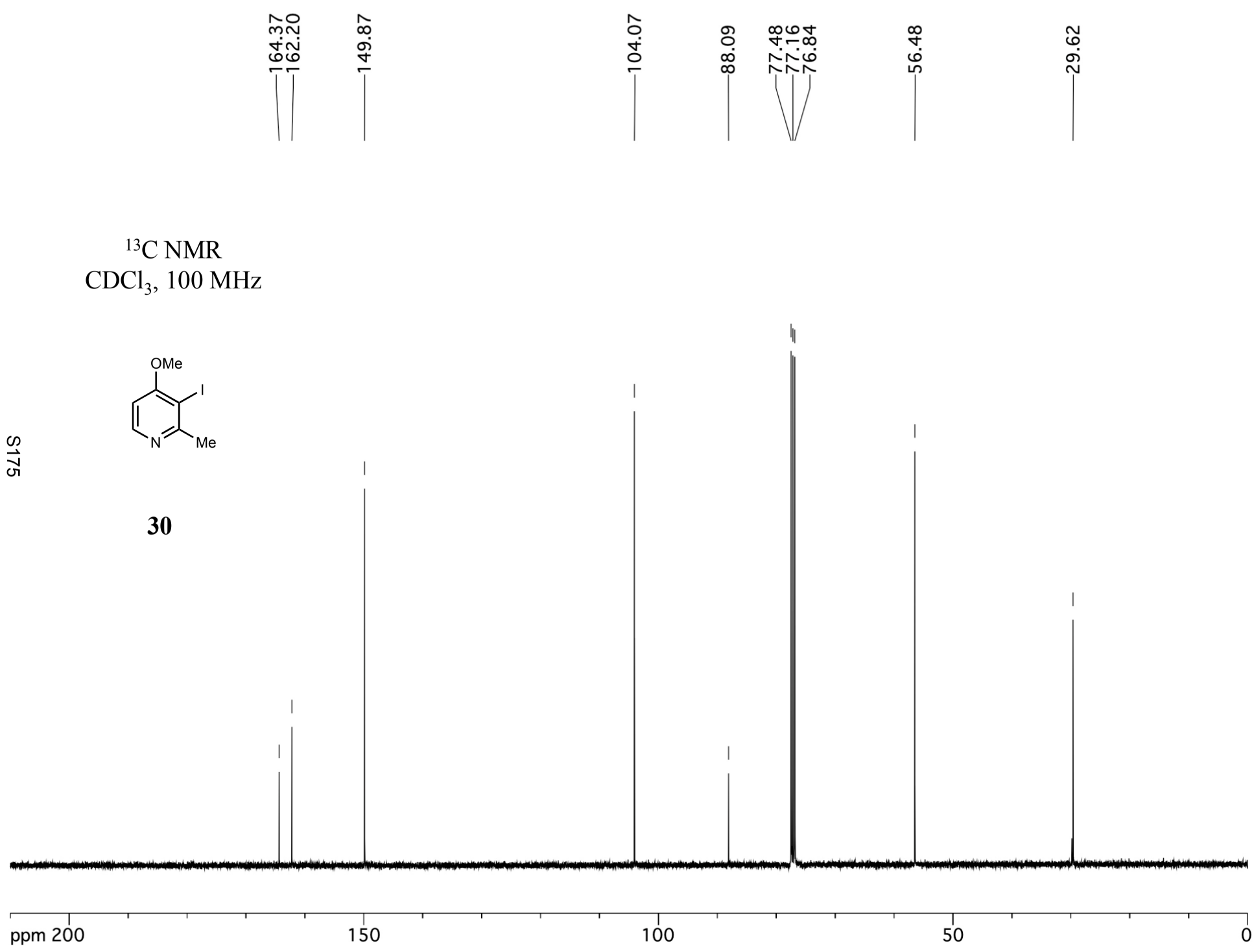

8.51
8.51
7.65
7.26
2.85
2.83
2.82
2.72
2.70
2.69
1.87
1.86
1.85
1.84
1.77
1.77
1.76
1.74
^{1}H NMR
$CDCl_3$, 400 MHz
I
N
28
S172
1
1.05
2.25
2.24
2.22
2.24
ppm
9
8
7
6
5
4
3
2
1
0

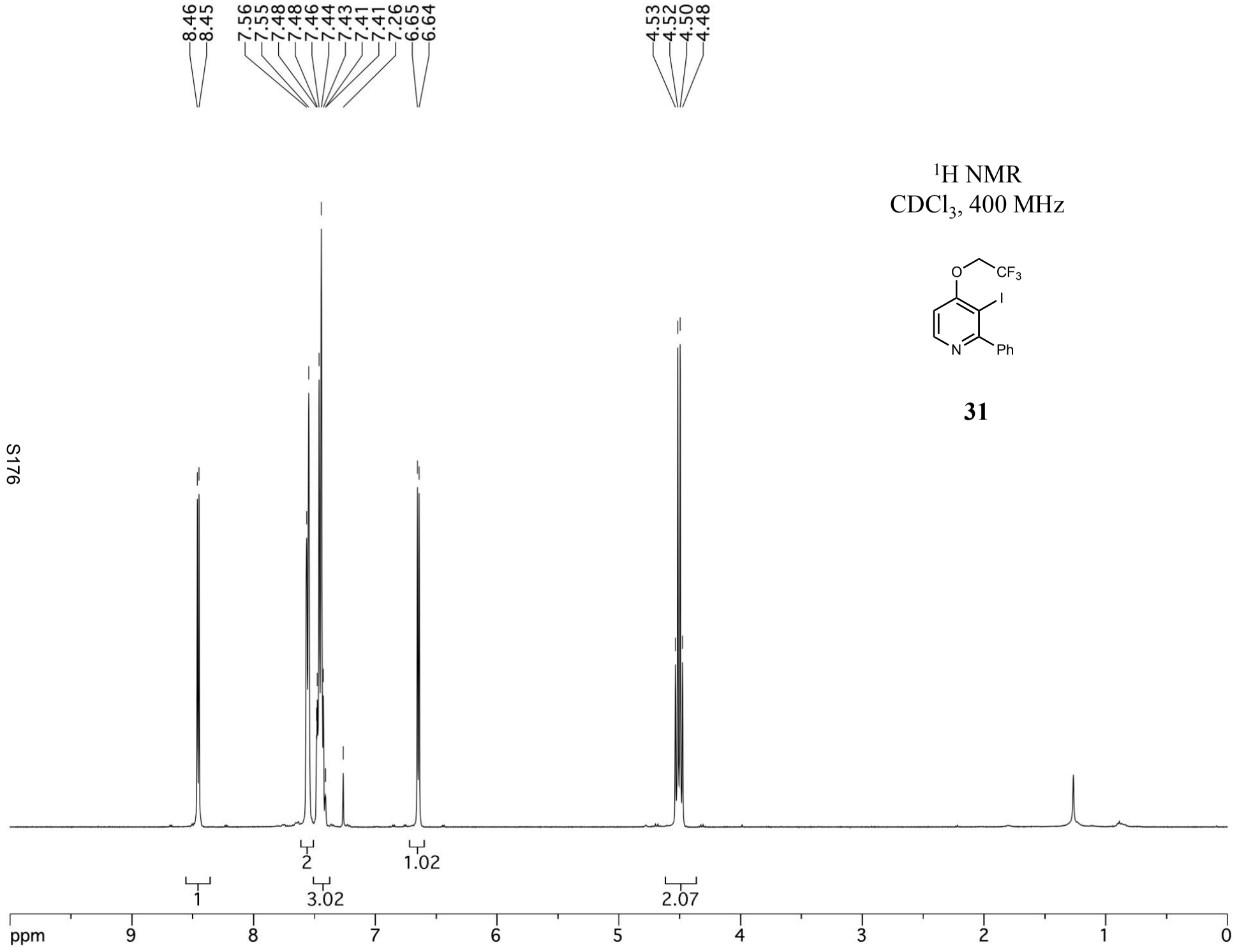

156.44
152.59
144.60
134.80
89.61
77.48
77.16
76.84
32.10
28.63
22.82
22.33
^{13}C NMR
$CDCl_3$, 100 MHz
I
N
S173
28
ppm 200
150
100
50
0



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

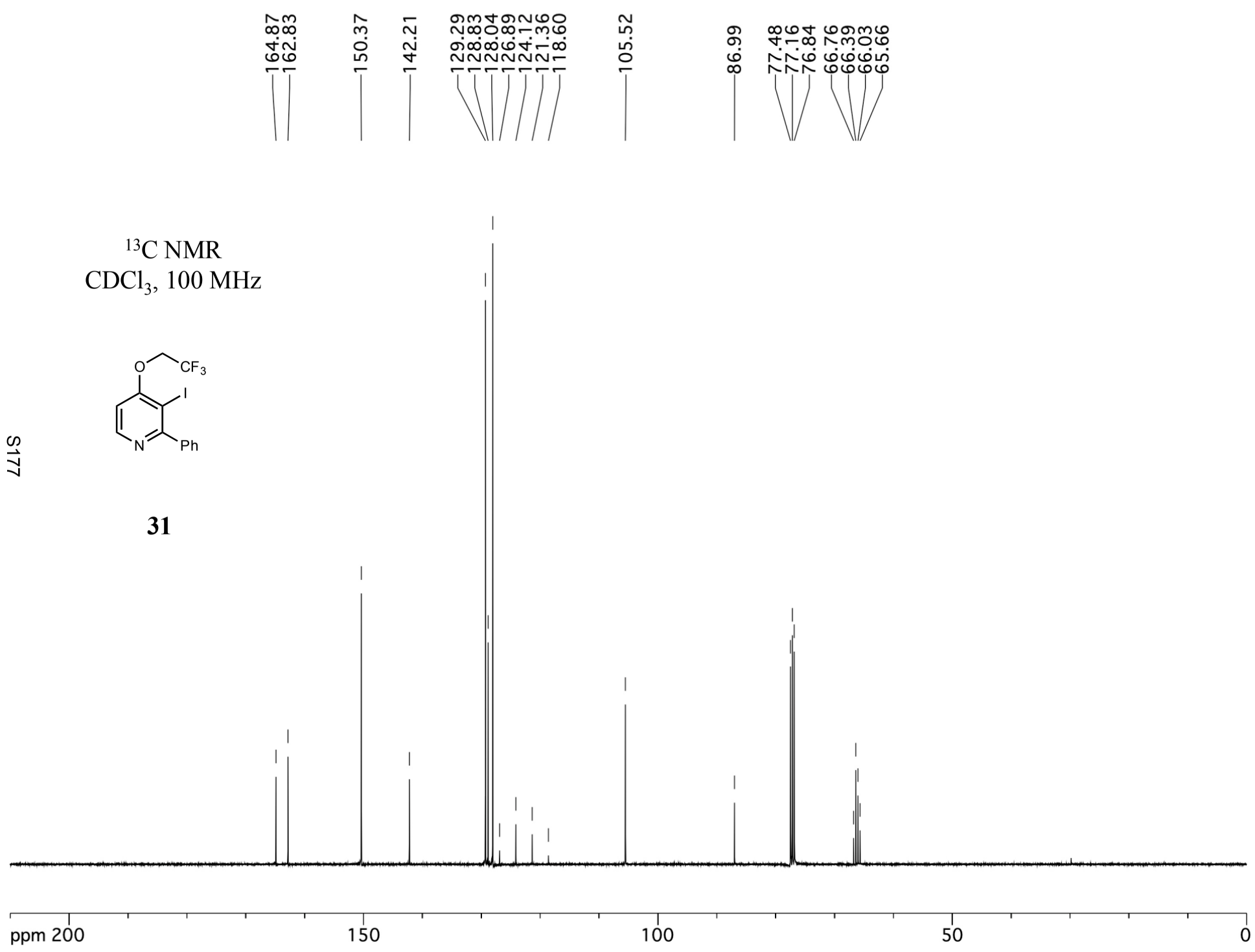
30


164.37
162.20
149.87
104.07
88.09
77.48
77.16
76.84
56.48
29.62
^{13}C NMR
$CDCl_3$, 100 MHz
OMe
I
N
Me
30
S175
ppm 200
150
100
50
0

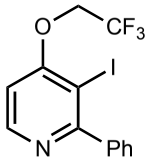


^{1}H NMR
$CDCl_3$, 400 MHz

31


164.87
162.83
150.37
142.21
129.29
128.83
128.04
126.89
124.12
121.36
118.60
105.52
86.99
77.48
77.16
76.84
66.76
66.39
66.03
65.66
^{13}C NMR
$CDCl_3$, 100 MHz
O
CF_3
I
N
Ph
S177
31
ppm 200
150
100
50
0

^{19}F NMR
$CDCl_3$, 365 MHz



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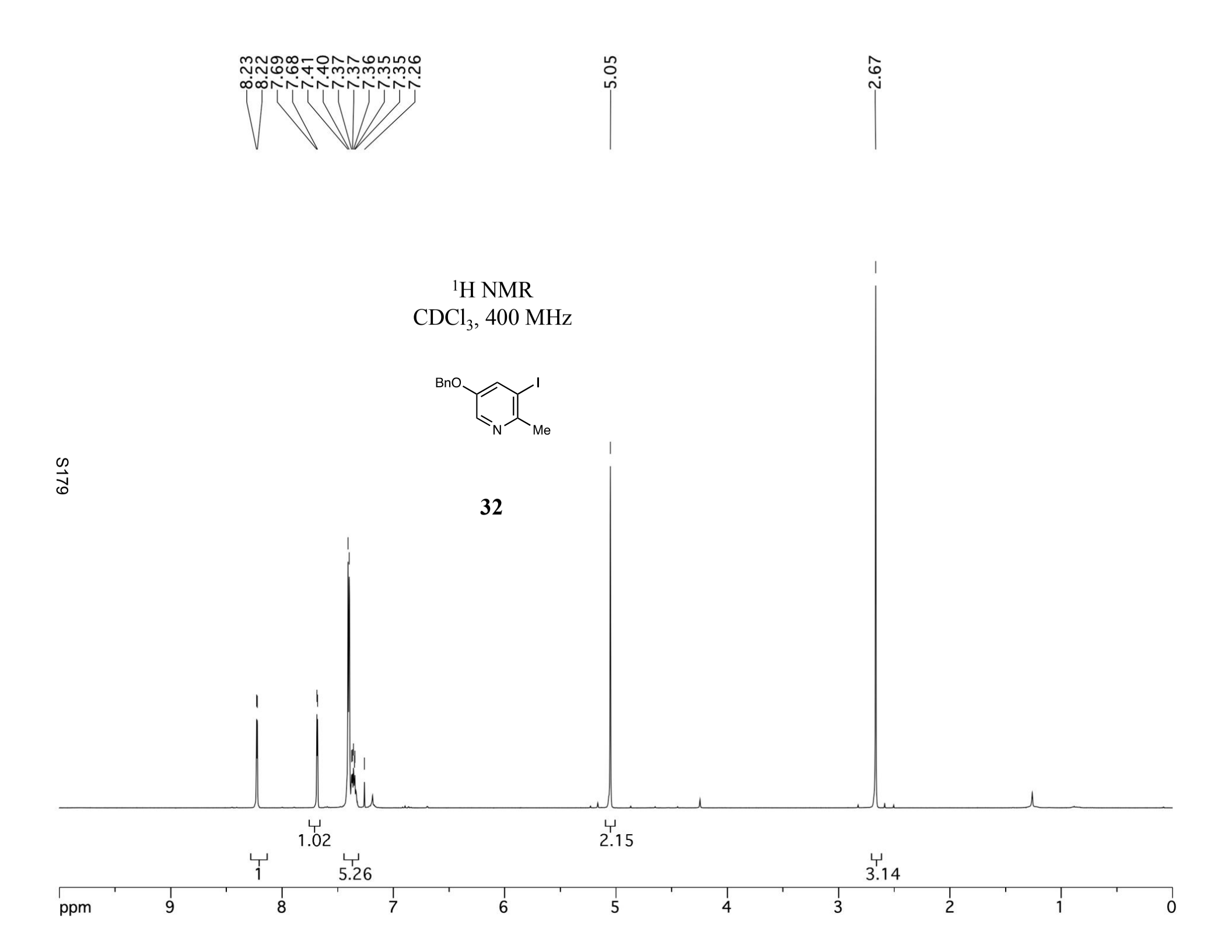
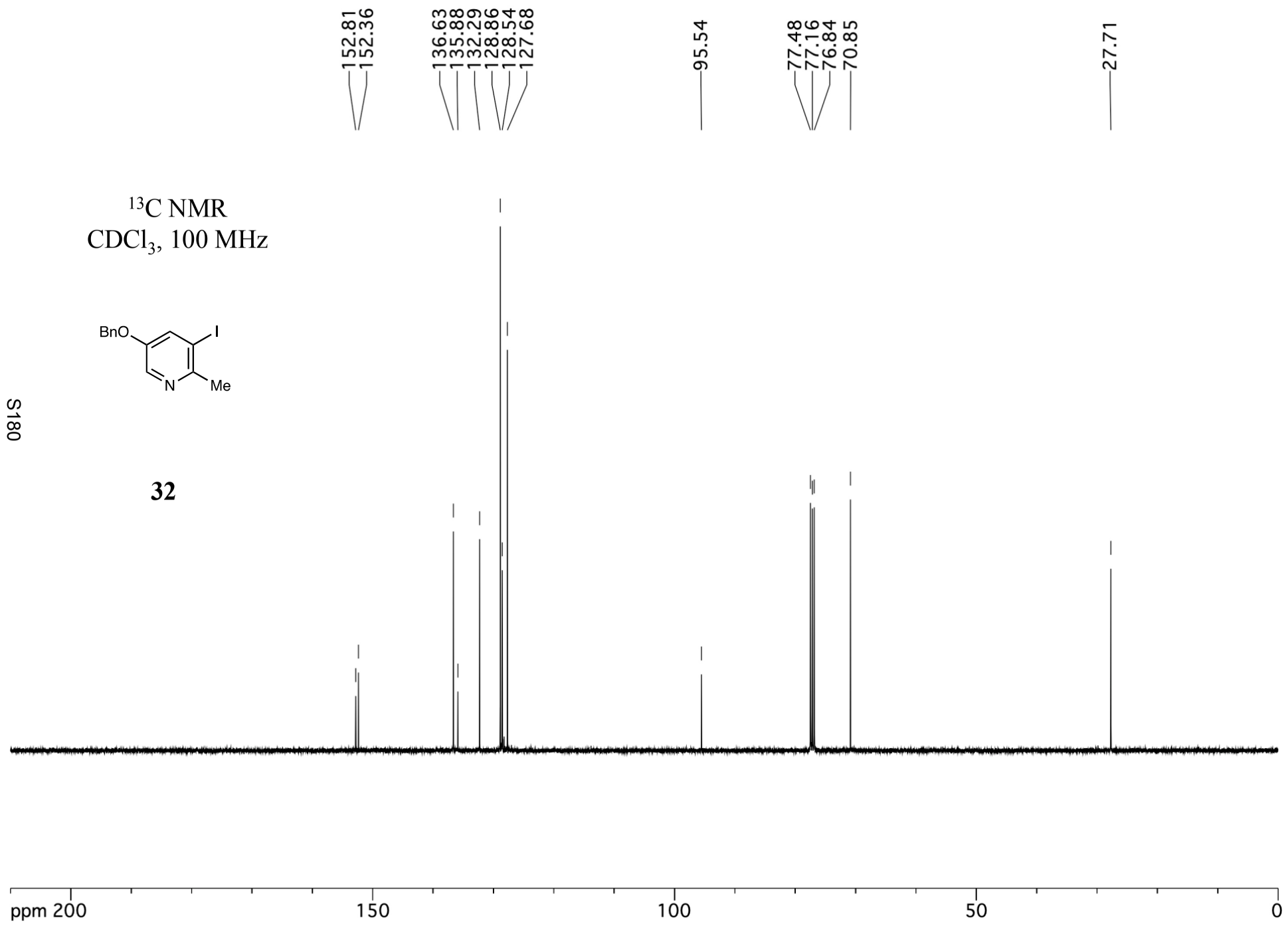
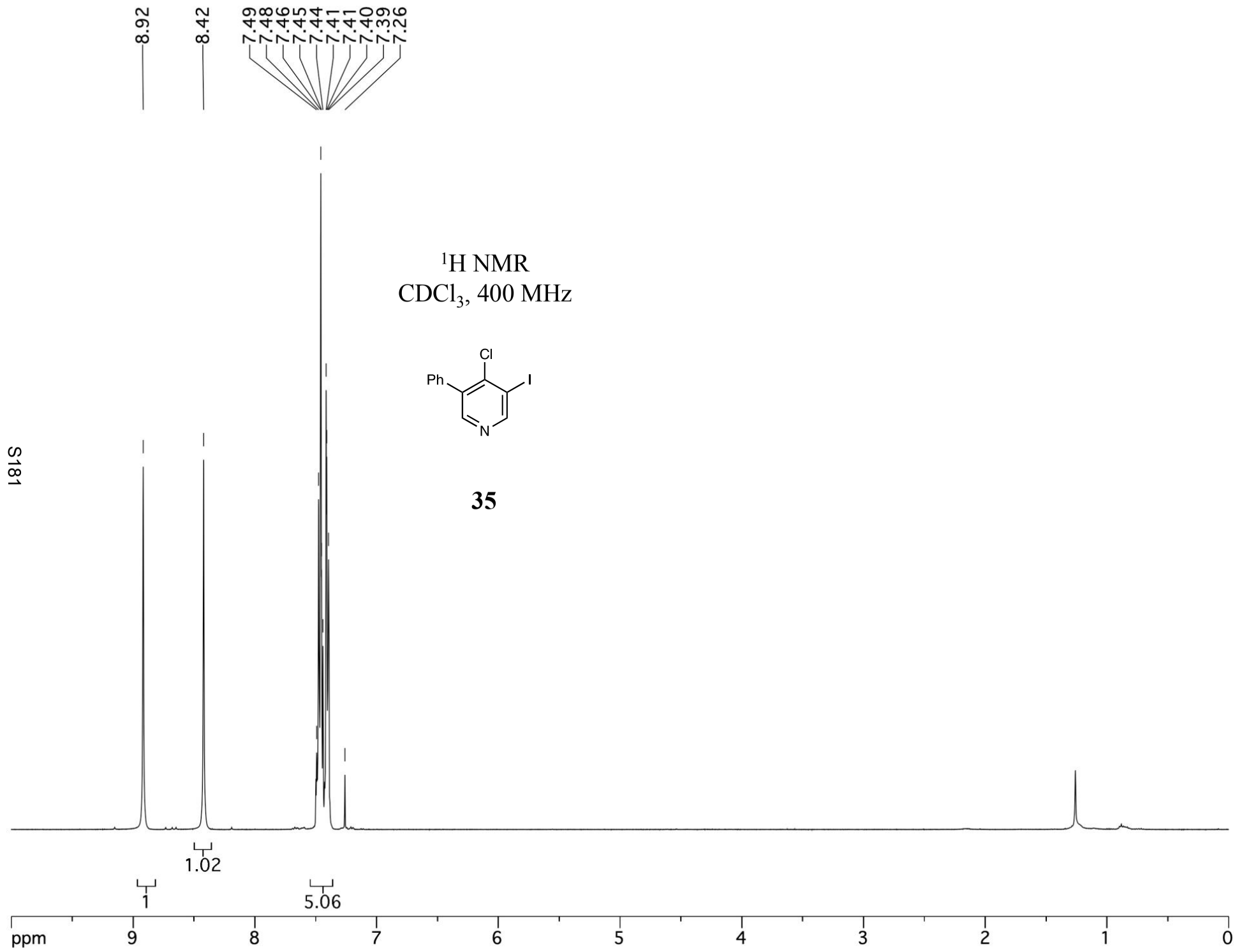
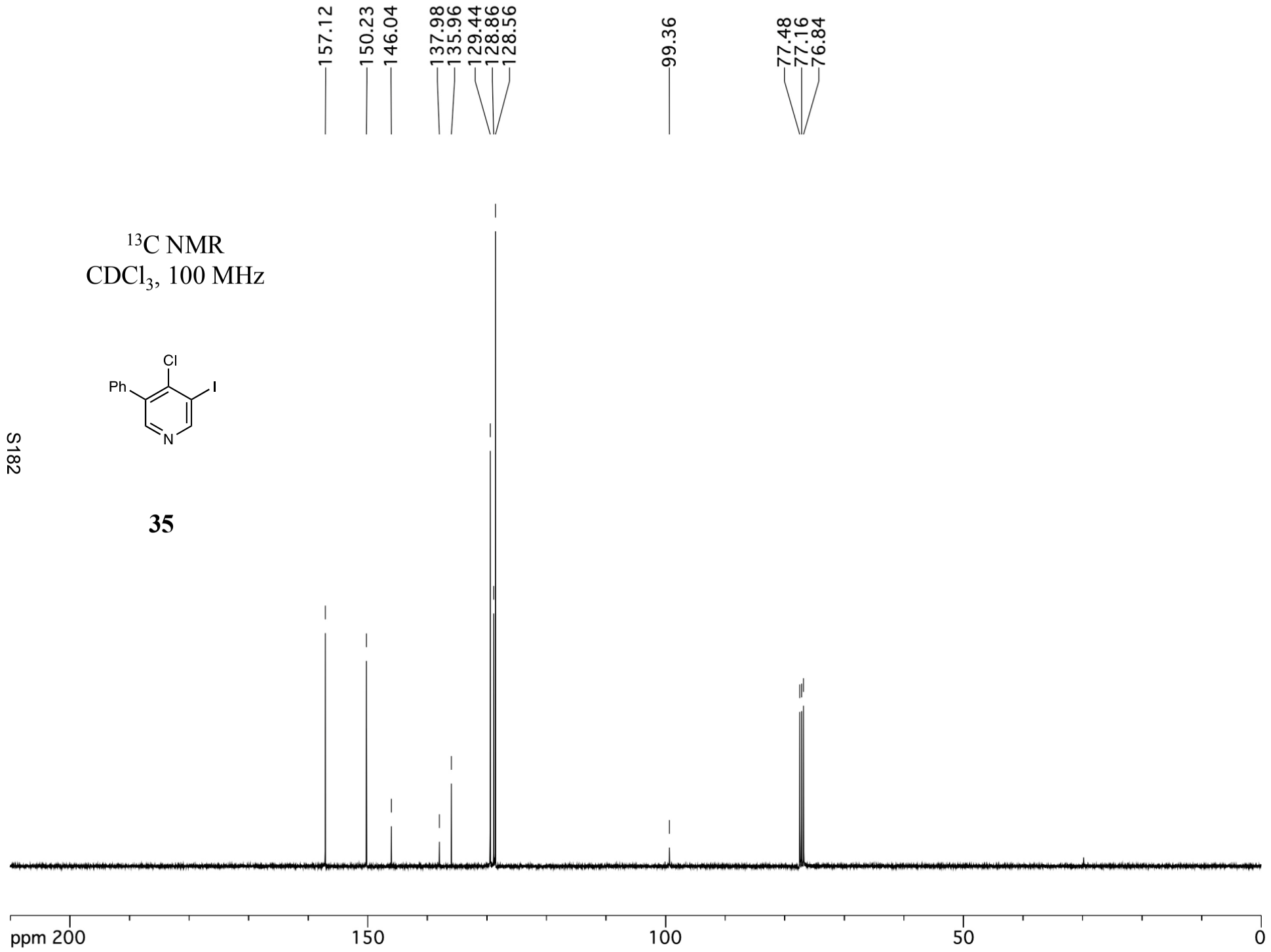
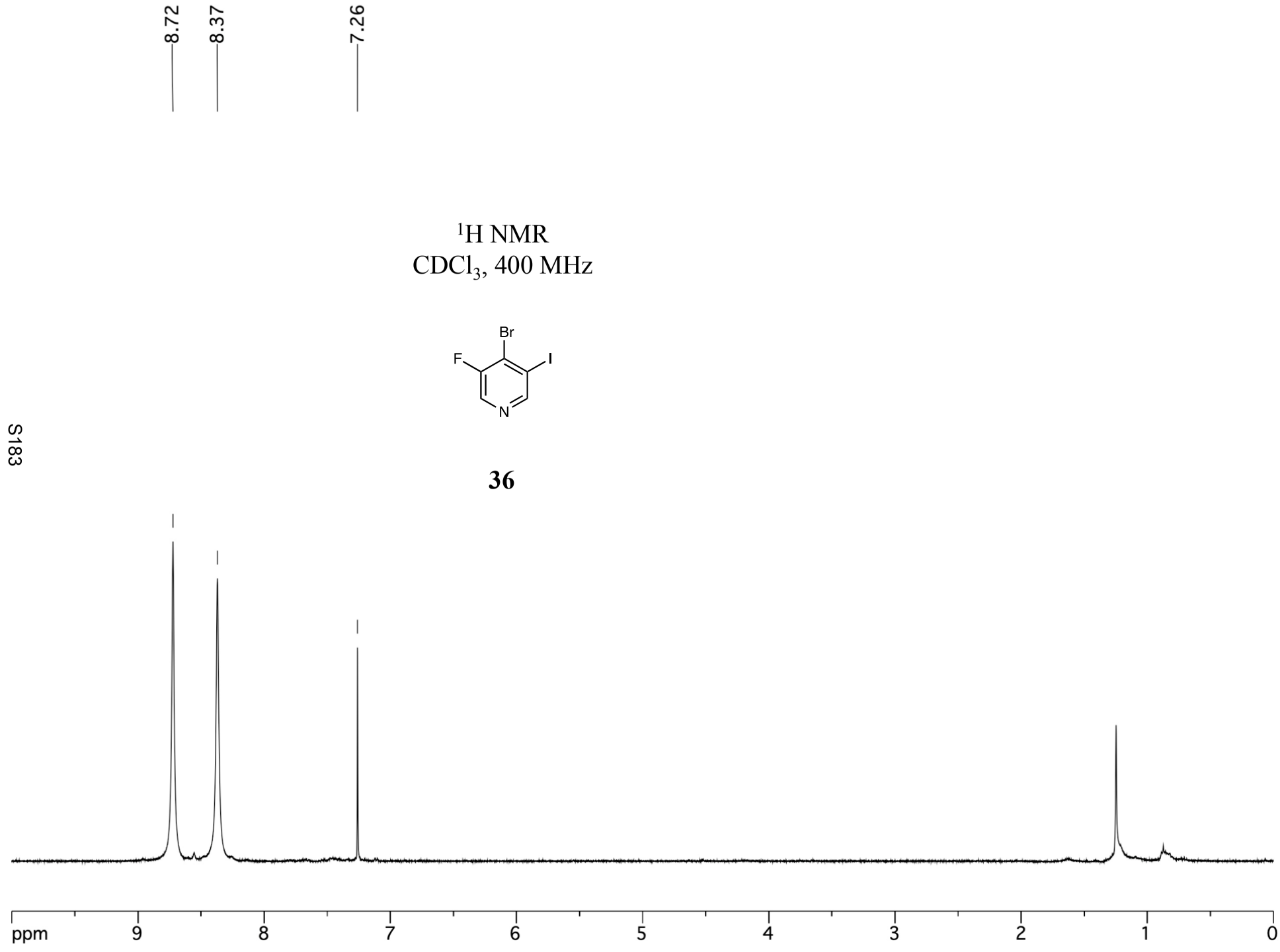

8.23
8.22
7.69
7.68
7.41
7.40
7.37
7.37
7.36
7.35
7.35
7.26
5.05
2.67
^{1}H NMR
$CDCl_3$, 400 MHz
BnO
I
N
Me
32
S179
1.02
2.15
1
5.26
3.14
ppm
9
8
7
6
5
4
3
2
1
0


152.81
152.36
136.63
135.88
132.29
128.86
128.54
127.68
95.54
77.48
77.16
76.84
70.85
27.71
^{13}C NMR
$CDCl_3$, 100 MHz
BnO
I
N
Me
S180
32
ppm 200
150
100
50
0

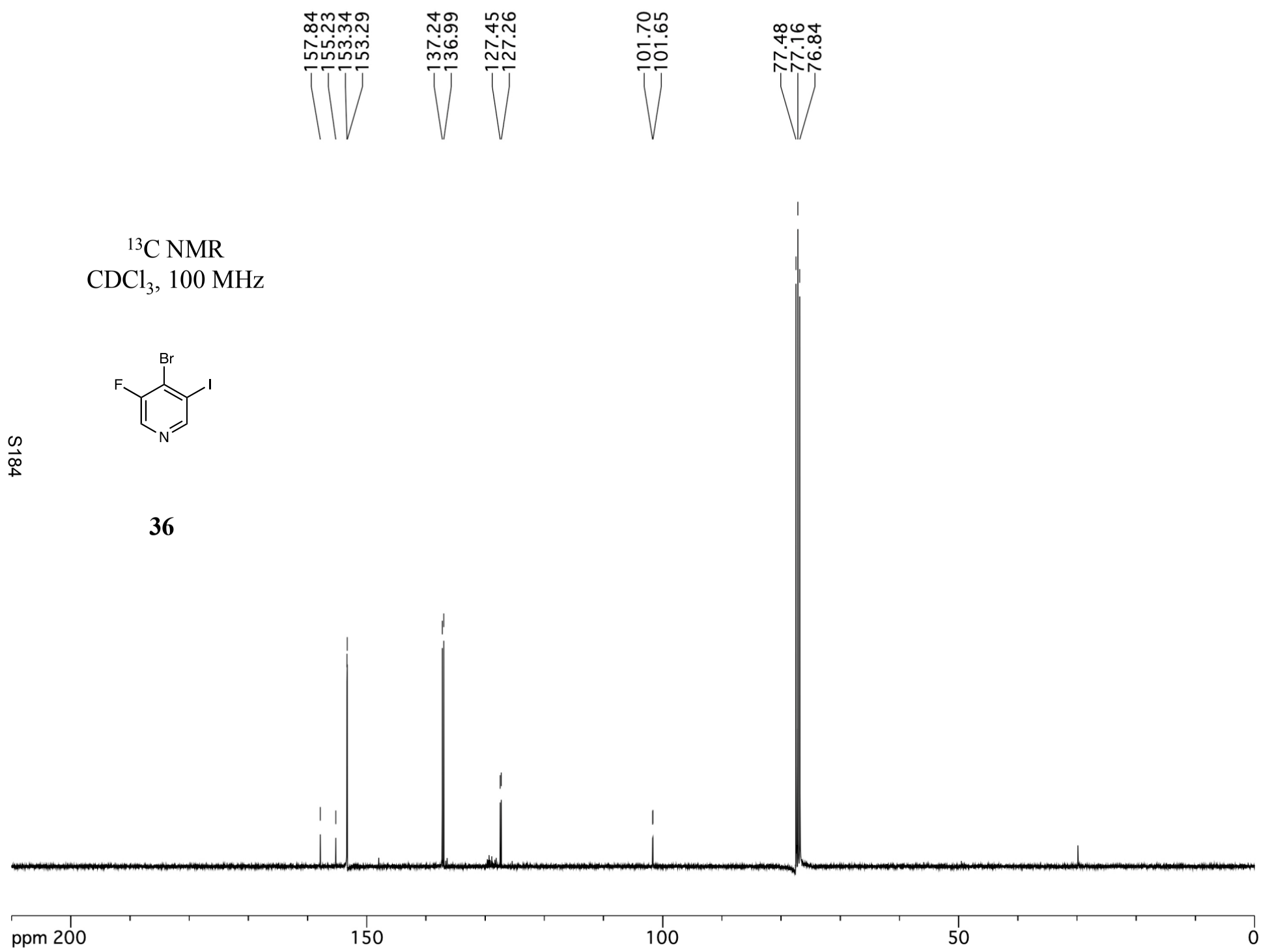

8.92
8.42
7.49
7.48
7.46
7.45
7.44
7.41
7.41
7.40
7.39
7.26
1H NMR
CDCl3, 400 MHz
Cl
Ph
I
N
35
S181
1.02
1
5.06
ppm
9
8
7
6
5
4
3
2
1
0


157.12
150.23
146.04
137.98
135.96
129.44
128.86
128.56
99.36
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
Ph
I
N
S182
35
ppm 200
150
100
50
0



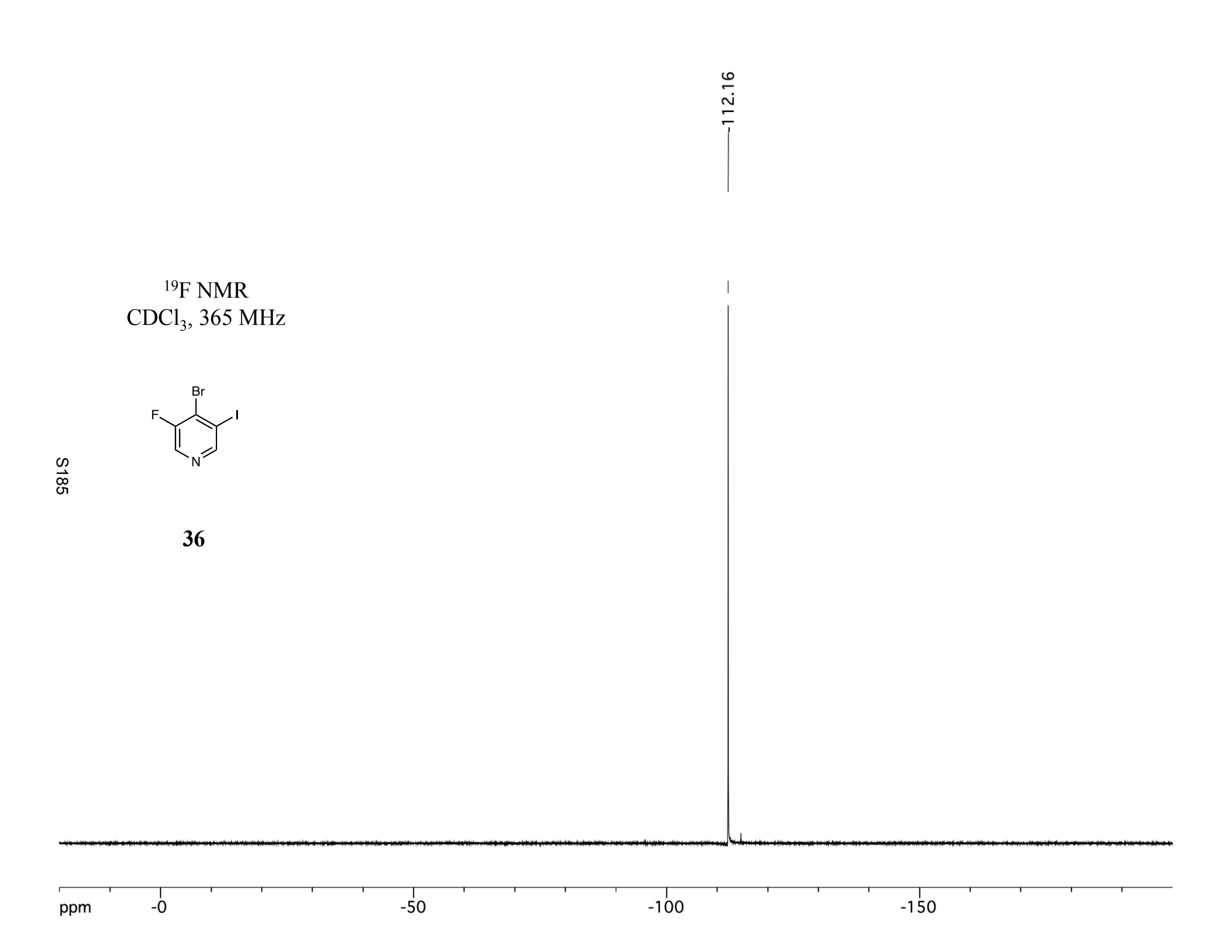
^{1}H NMR
$CDCl_3$, 400 MHz

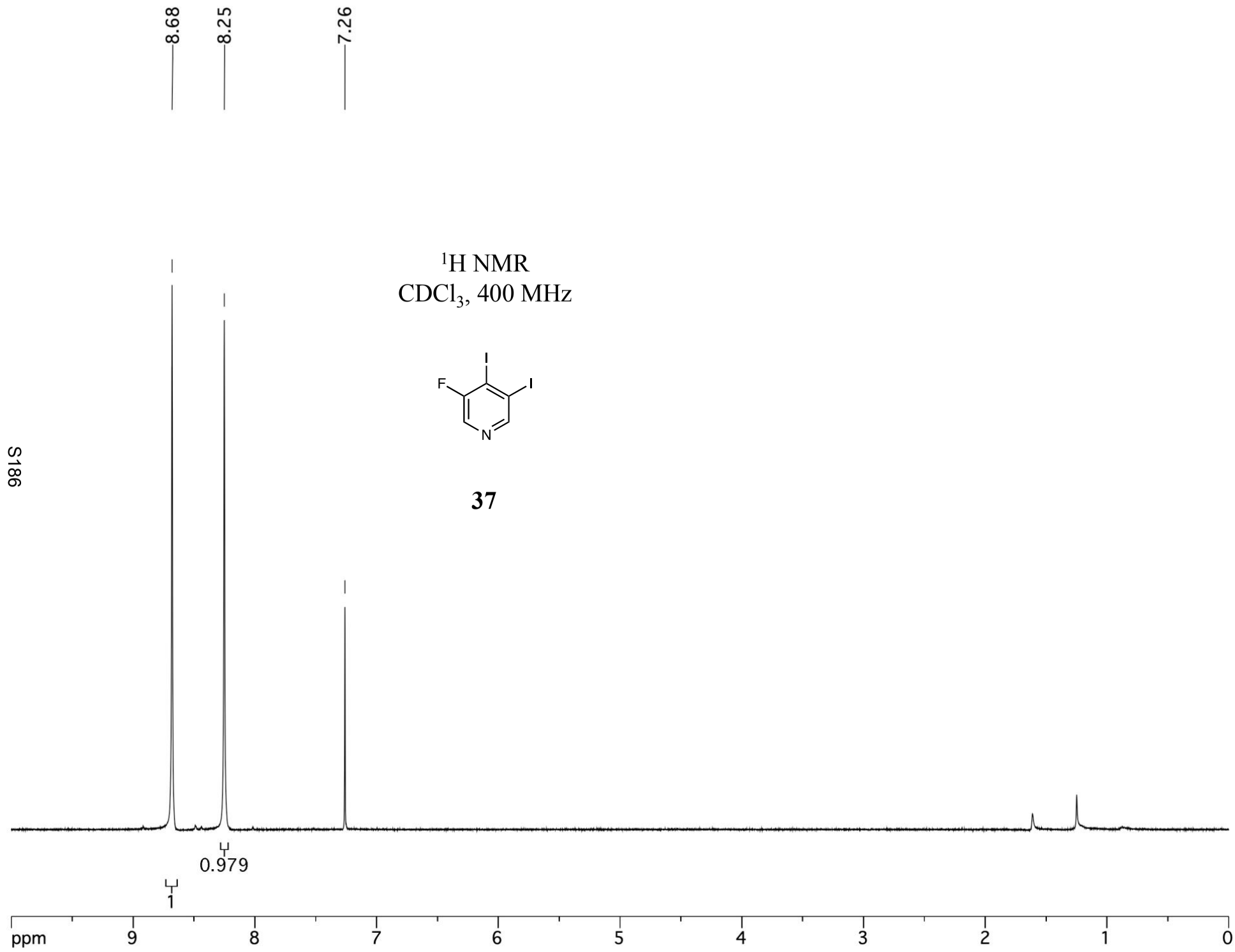
36

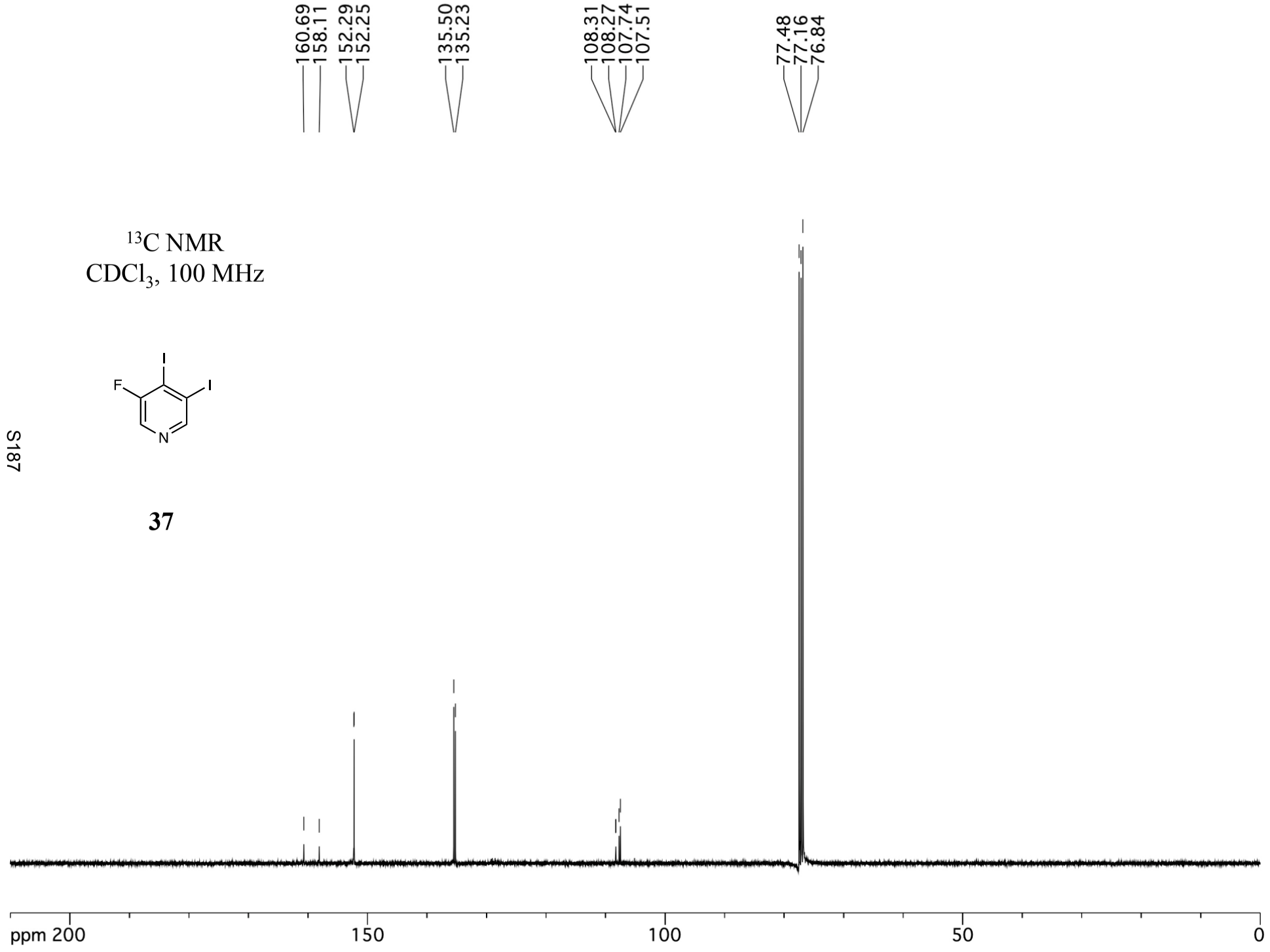

157.84
155.23
153.34
153.29
137.24
136.99
127.45
127.26
101.70
101.65
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
F
I
N
ppm 200
150
100
50
0

S184

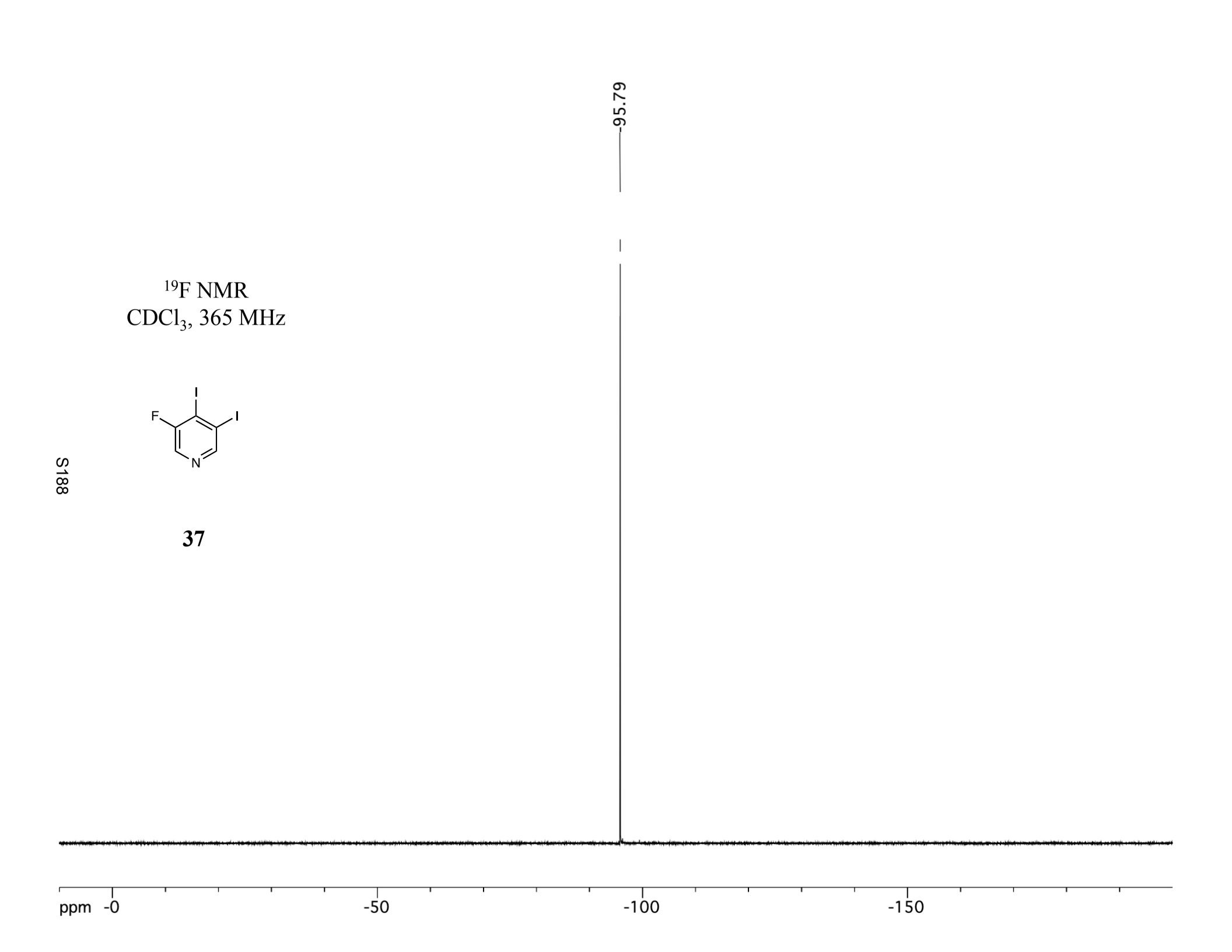
36

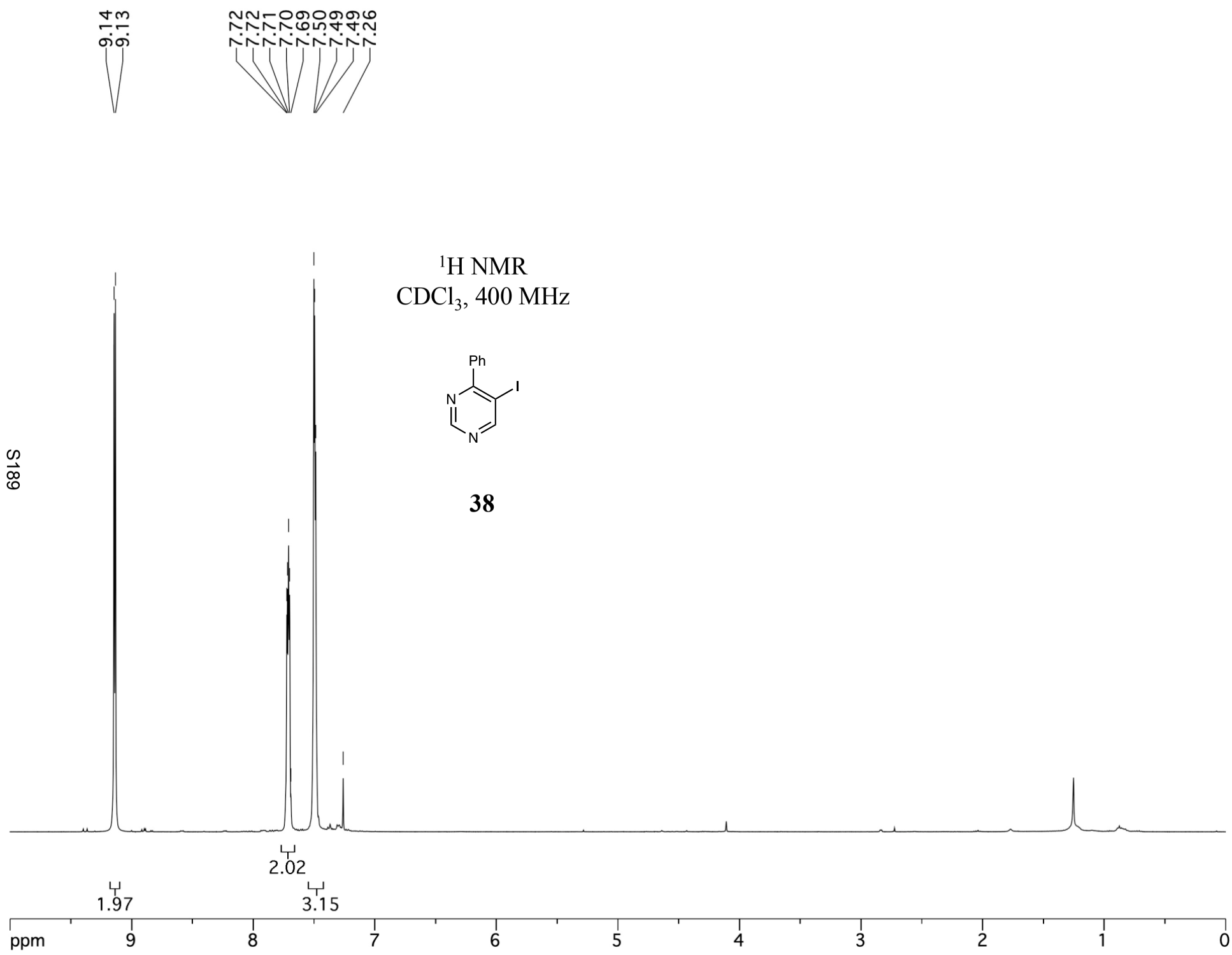

-112.16
^{19}F NMR
$CDCl_3$, 365 MHz
Br
F
I
N
S185
36
ppm
-0
-50
-100
-150

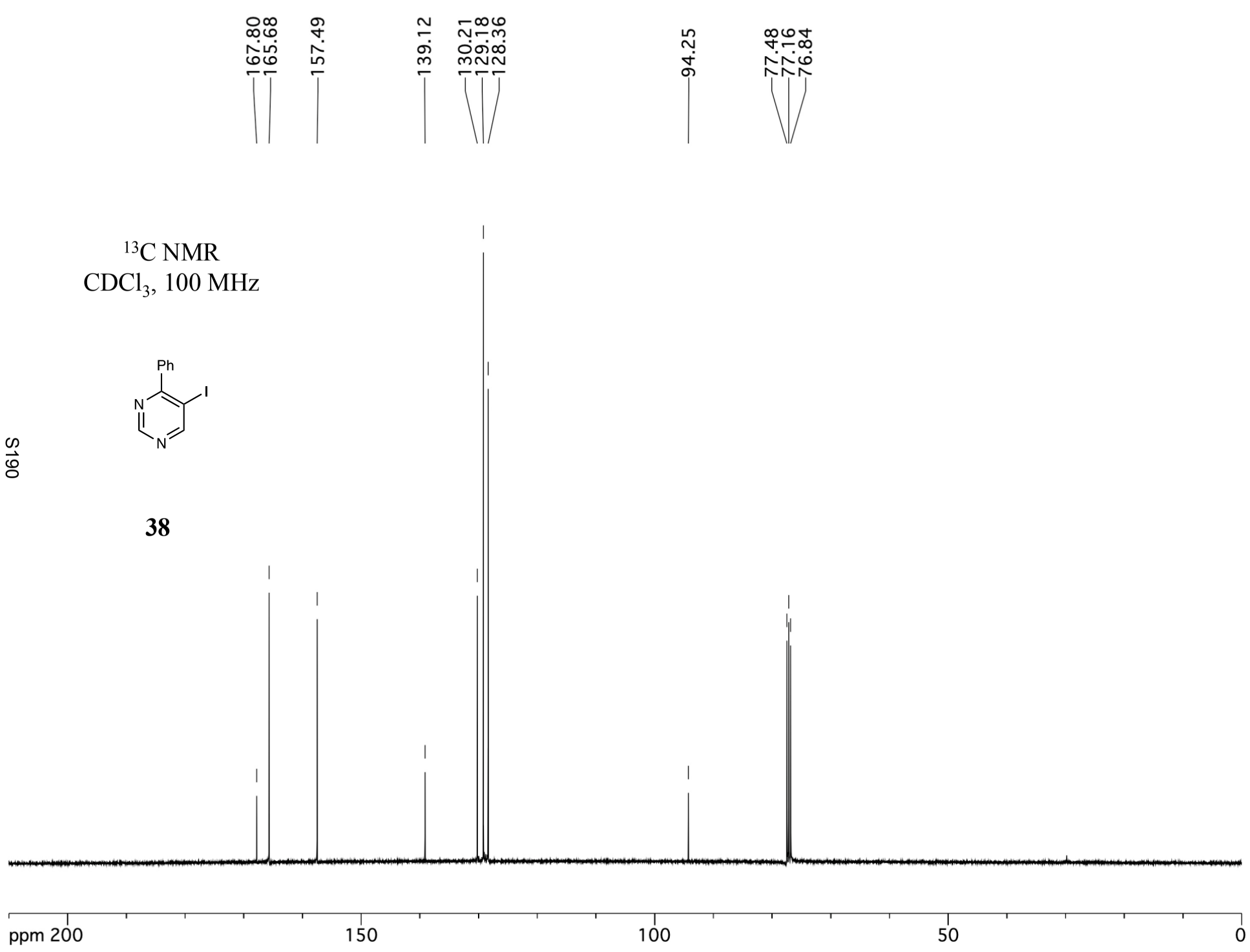

8.68
8.25
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
I
F
I
N
S186
37
1
0.979
ppm
9
8
7
6
5
4
3
2
1
0

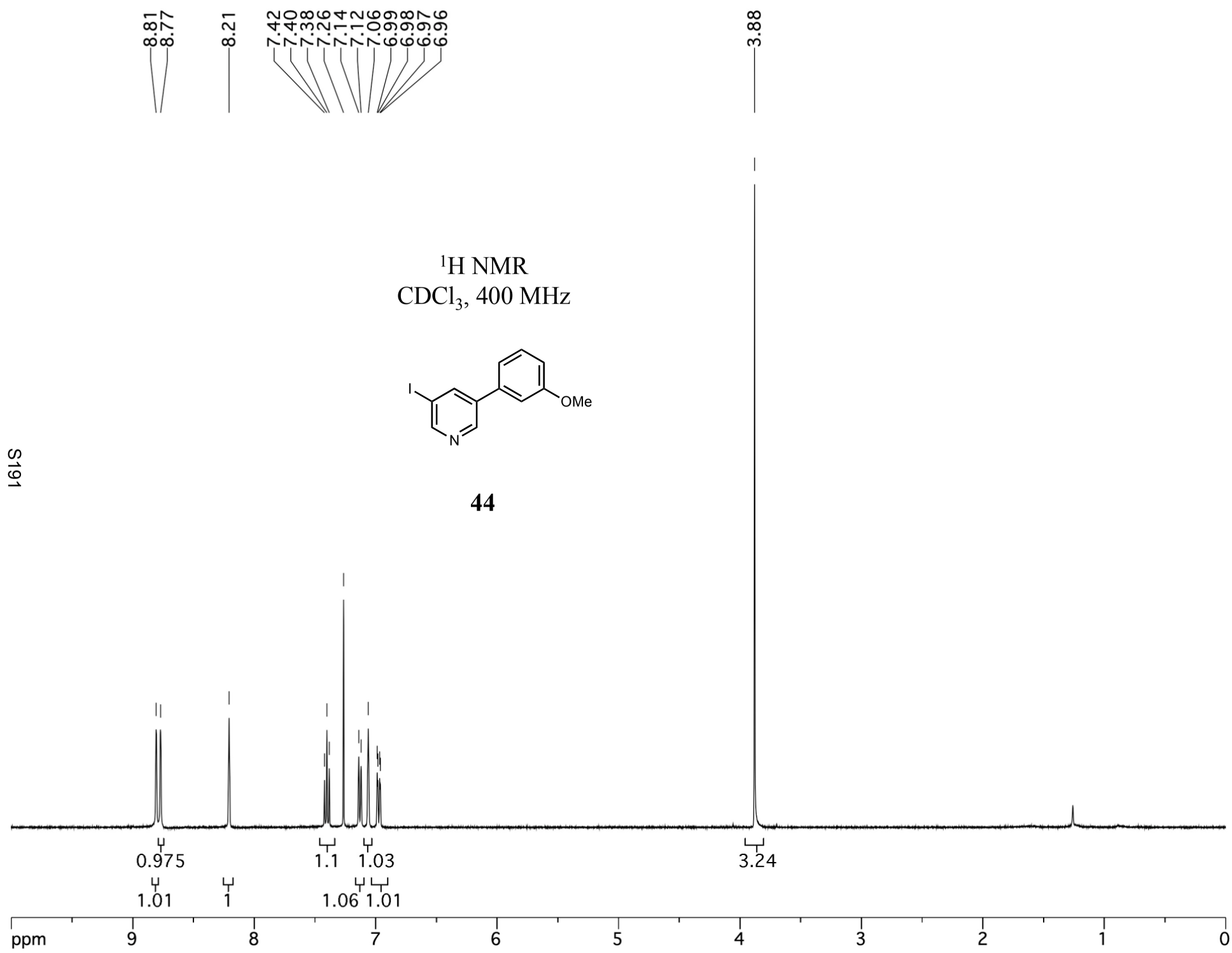

160.69
158.11
152.29
152.25
135.50
135.23
108.31
108.27
107.74
107.51
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
F
I
I
N
ppm 200
150
100
50
0

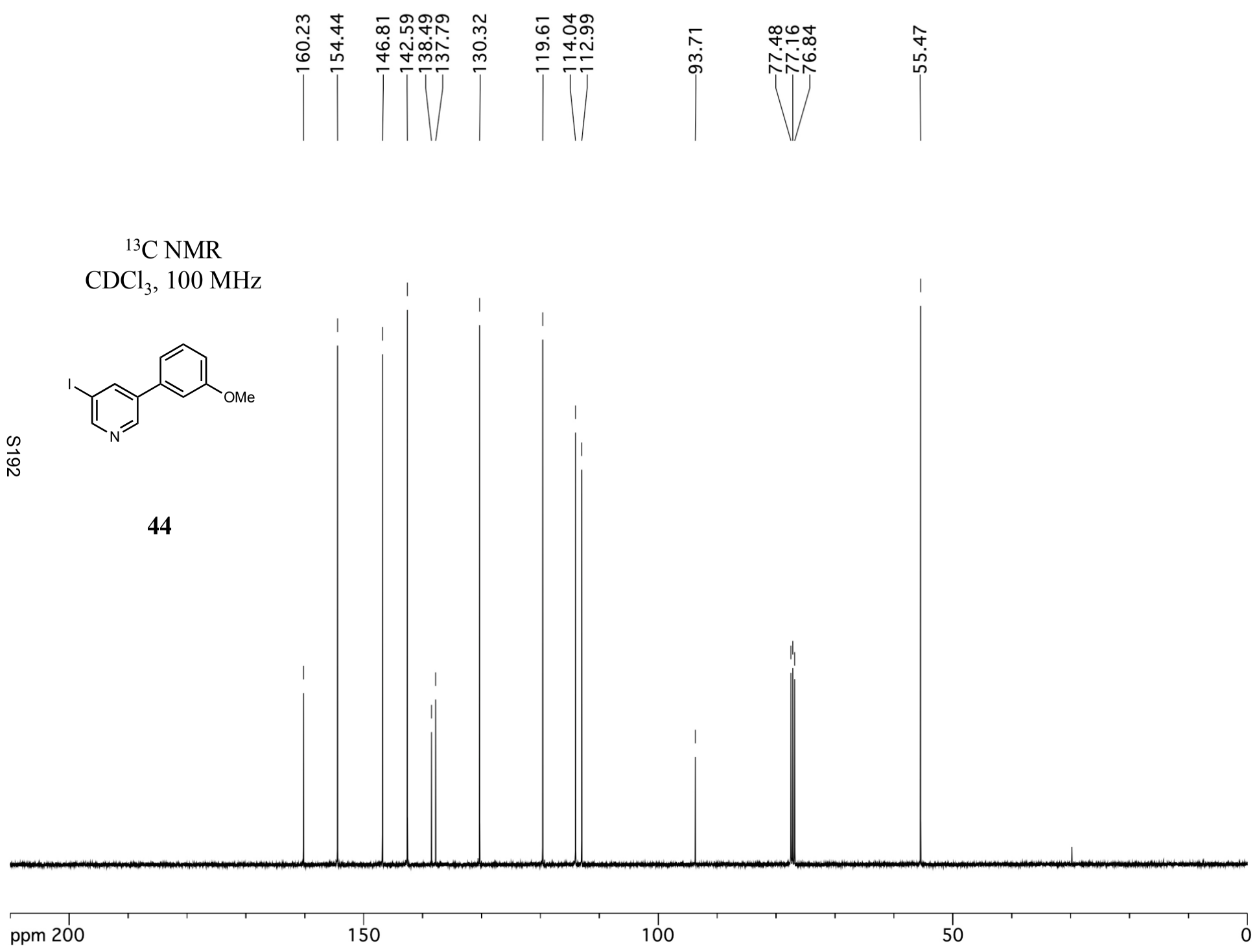
37

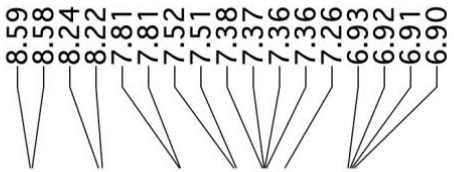

-95.79
^{19}F NMR
$CDCl_3$, 365 MHz
F
I
I
N
S188
37
ppm -0
-50
-100
-150


9.14
9.13
7.72
7.72
7.71
7.70
7.69
7.50
7.49
7.49
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Ph
I
N
N
38
S189
2.02
1.97
3.15
ppm
9
8
7
6
5
4
3
2
1
0

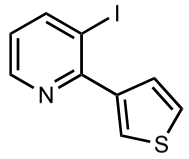

167.80
165.68
157.49
139.12
130.21
129.18
128.36
94.25
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Ph
I
N
N
38
S190
ppm 200
150
100
50
0


8.81
8.77
8.21
7.42
7.40
7.38
7.26
7.14
7.12
7.06
6.99
6.98
6.97
6.96
3.88
^{1}H NMR
$CDCl_3$, 400 MHz
I
OMe
N
44
S191
0.975
1.1
1.03
3.24
1.01
1
1.06
1.01
ppm
9
8
7
6
5
4
3
2
1
0


160.23
154.44
146.81
142.59
138.49
137.79
130.32
119.61
114.04
112.99
93.71
77.48
77.16
76.84
55.47
^{13}C NMR
$CDCl_3$, 100 MHz
I
OMe
N
S192
44
ppm 200
150
100
50
0



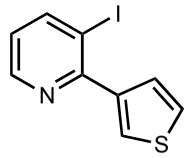
^{1}H NMR
$CDCl_3$, 400 MHz



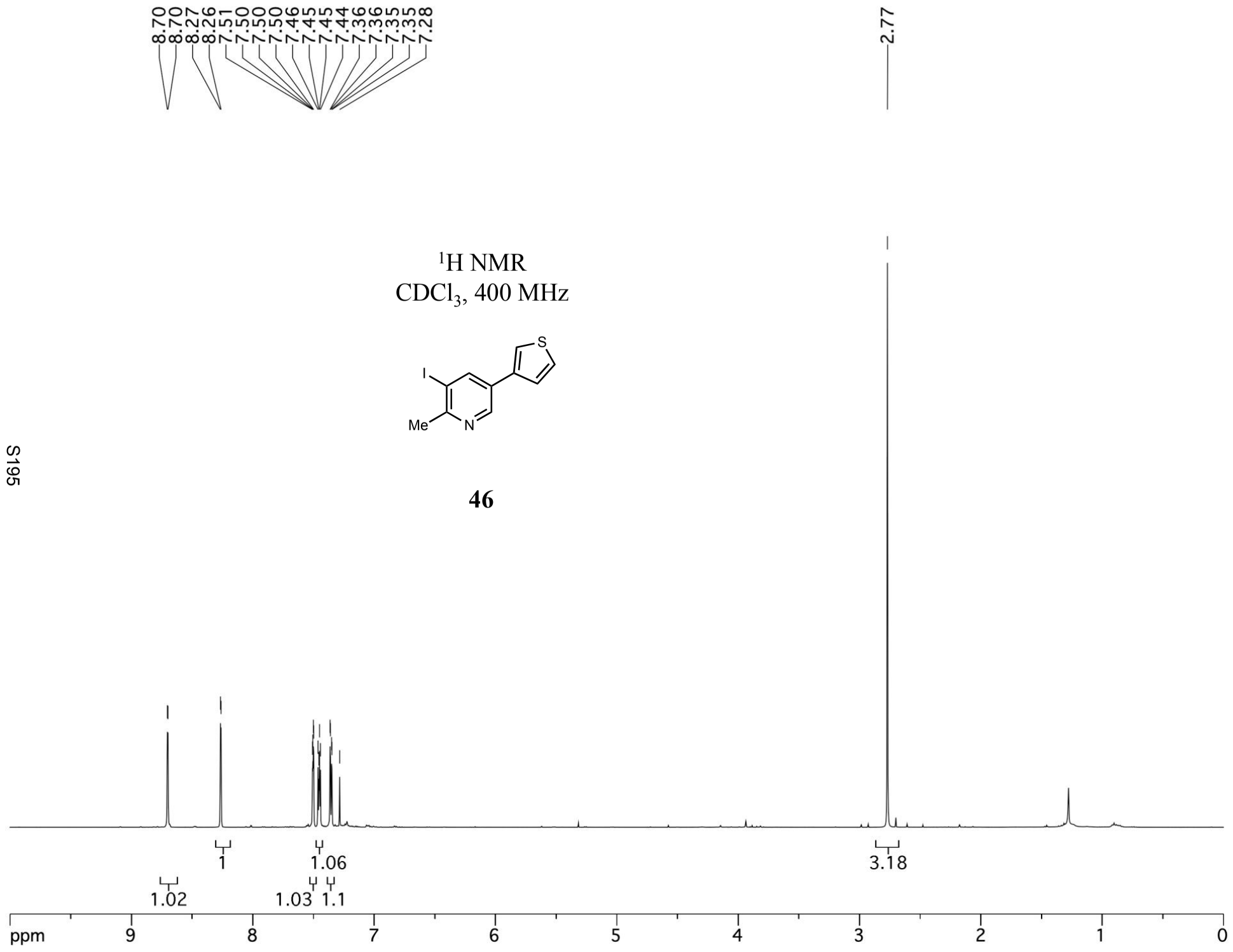
45

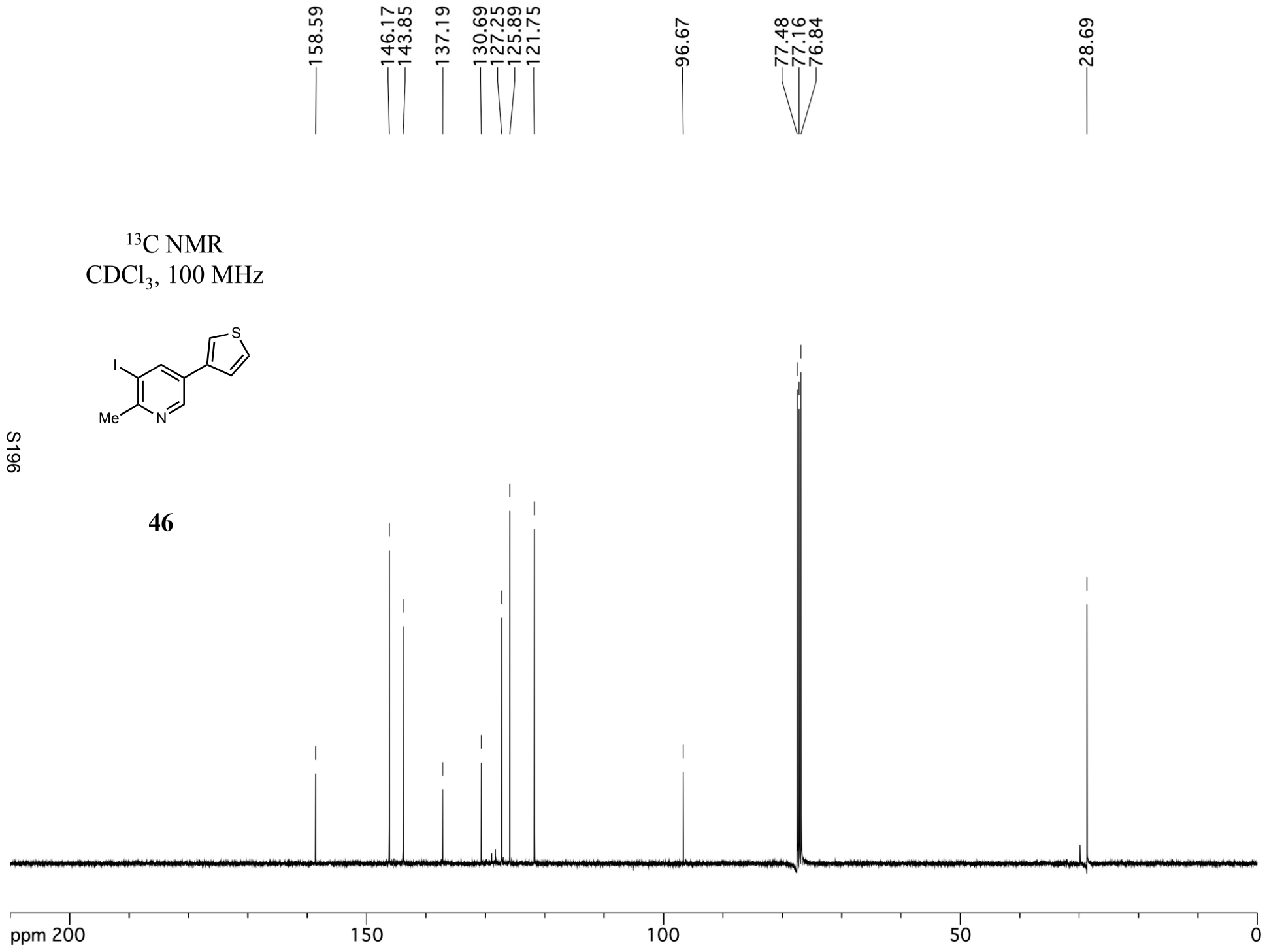
156.79
148.60
148.05
142.51
128.91
126.58
124.99
123.12
93.71
77.48
77.16
76.84

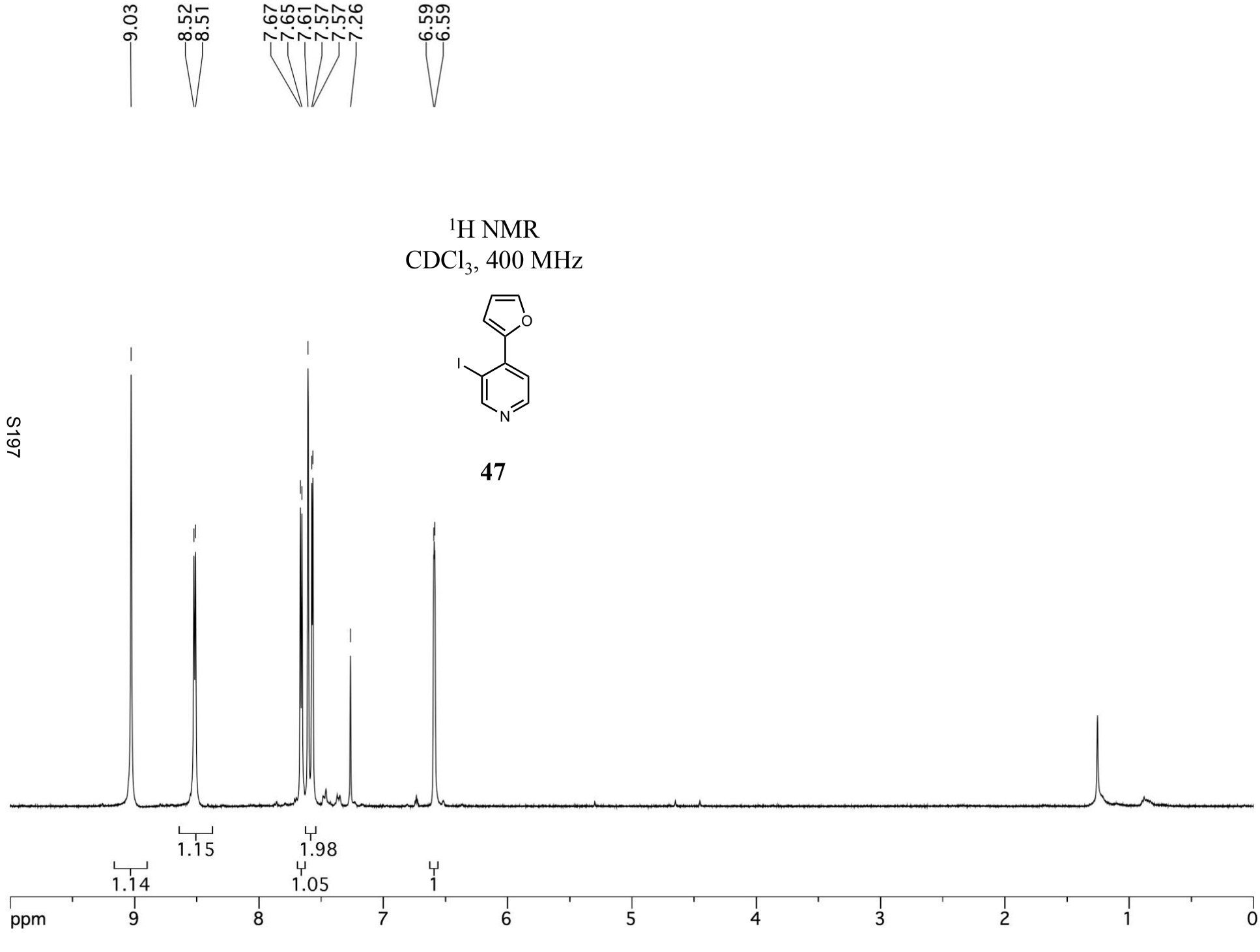
^{13}C NMR
$CDCl_3$, 100 MHz



45

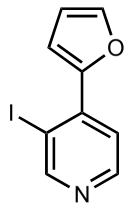

8.70
8.70
8.27
8.26
7.51
7.50
7.50
7.50
7.46
7.45
7.45
7.44
7.36
7.36
7.35
7.35
7.28
2.77
1H NMR
CDCl3, 400 MHz
S
I
Me
N
46
S195
1.02
1
1.03
1.06
1.1
3.18
ppm
9
8
7
6
5
4
3
2
1
0


158.59
146.17
143.85
137.19
130.69
127.25
125.89
121.75
96.67
77.48
77.16
76.84
28.69
^{13}C NMR
$CDCl_3$, 100 MHz
S
I
Me
N
S196
46
ppm 200
150
100
50
0

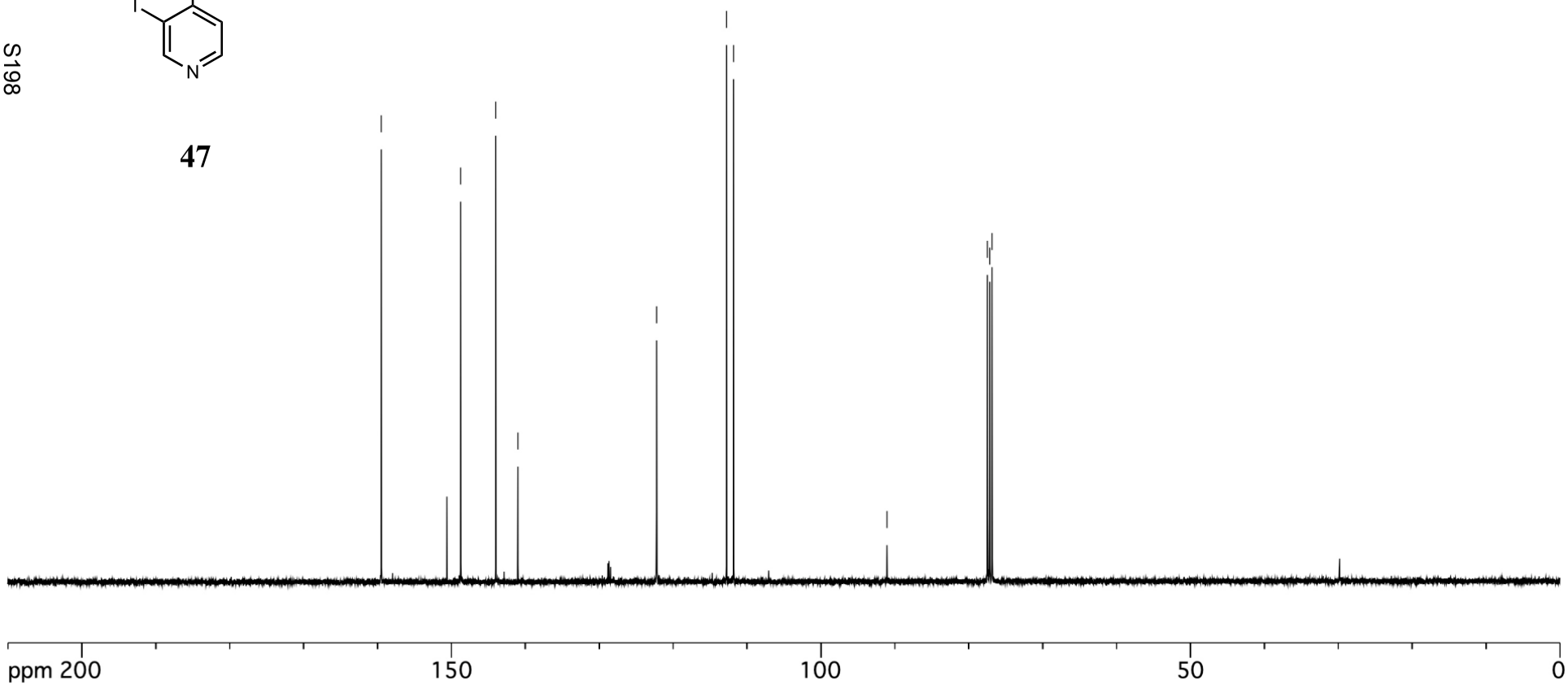

9.03
8.52
8.51
7.67
7.65
7.61
7.57
7.57
7.26
6.59
6.59
^{1}H NMR
$CDCl_3$, 400 MHz
O
I
N
47
S197
1.14
1.15
1.98
1.05
1
ppm
9
8
7
6
5
4
3
2
1
0

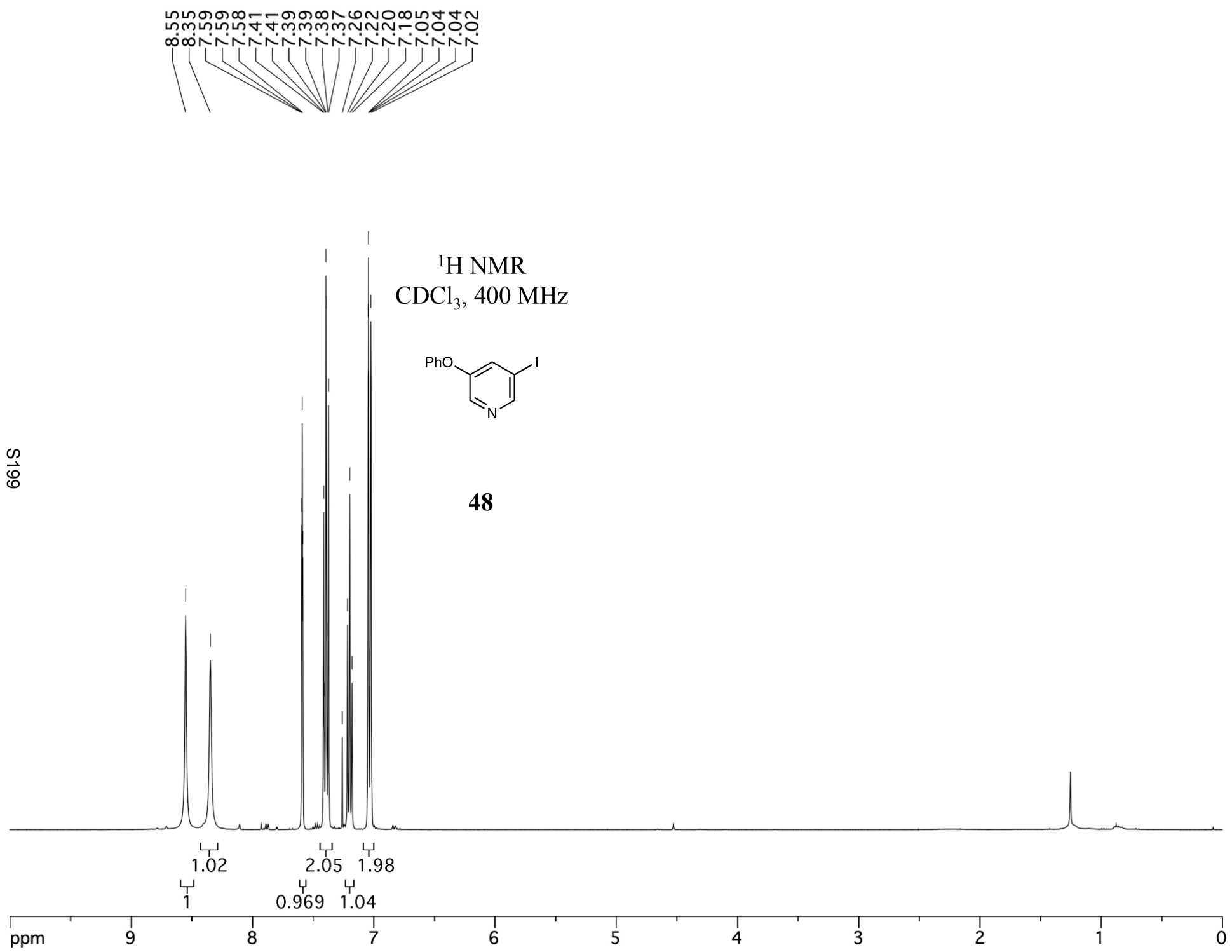
159.49
148.75
144.00
141.00
122.23
112.77
111.82
91.06
77.48
77.16
76.84

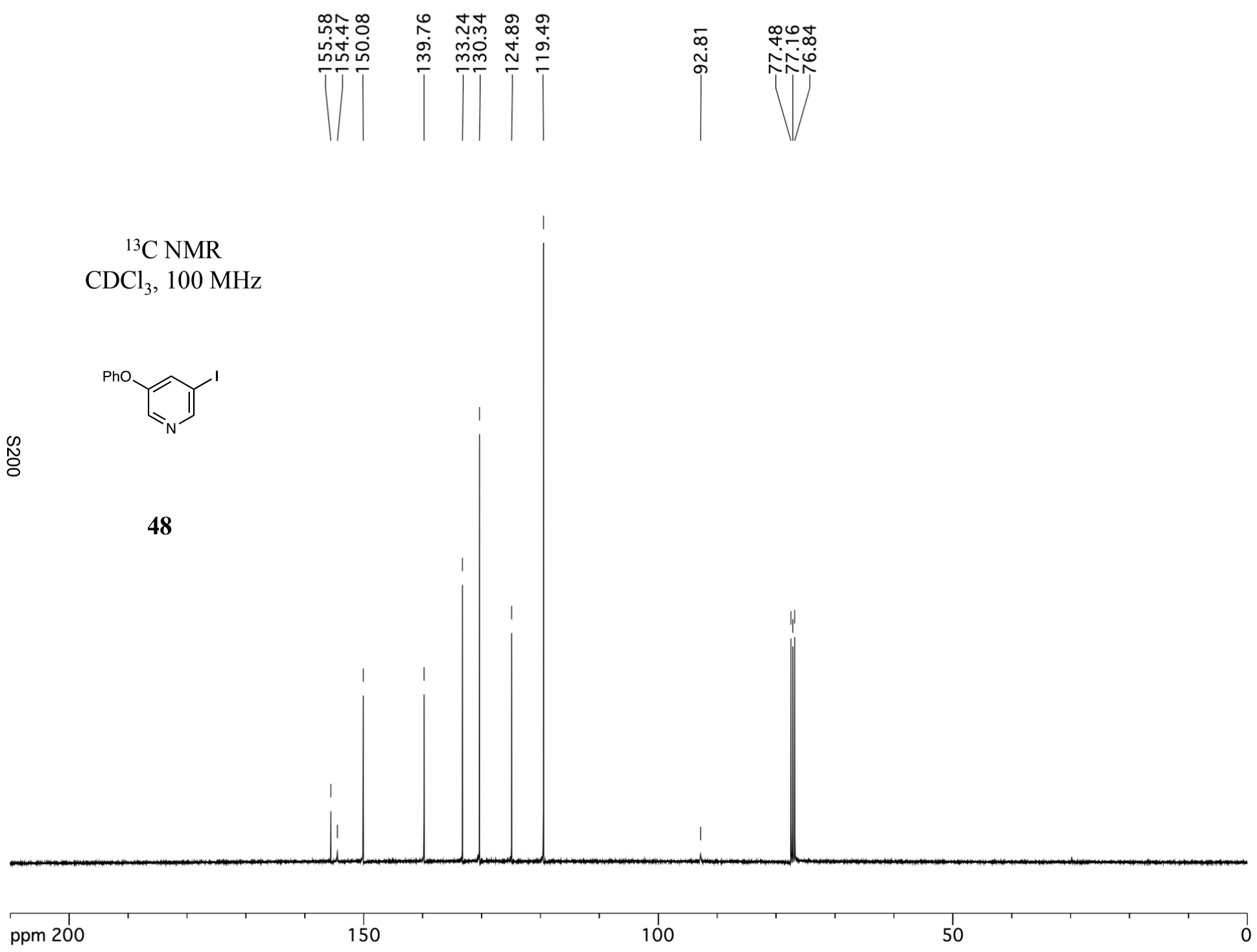
^{13}C NMR
$CDCl_3$, 100 MHz

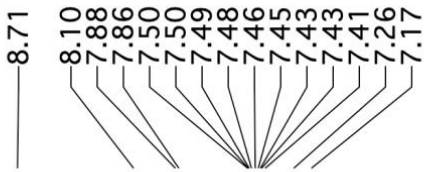


47

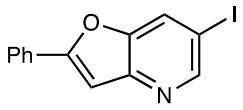



8.55
8.35
7.59
7.59
7.58
7.41
7.41
7.39
7.39
7.38
7.37
7.26
7.22
7.20
7.18
7.05
7.04
7.04
7.02
^{1}H NMR
$CDCl_3$, 400 MHz
PhO
I
N
48
S199
1.02
2.05
1.98
1
0.969
1.04
ppm
9
8
7
6
5
4
3
2
1
0


155.58
154.47
150.08
139.76
133.24
130.34
124.89
119.49
92.81
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
PhO
I
N
S200
48
ppm 200
150
100
50
0



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



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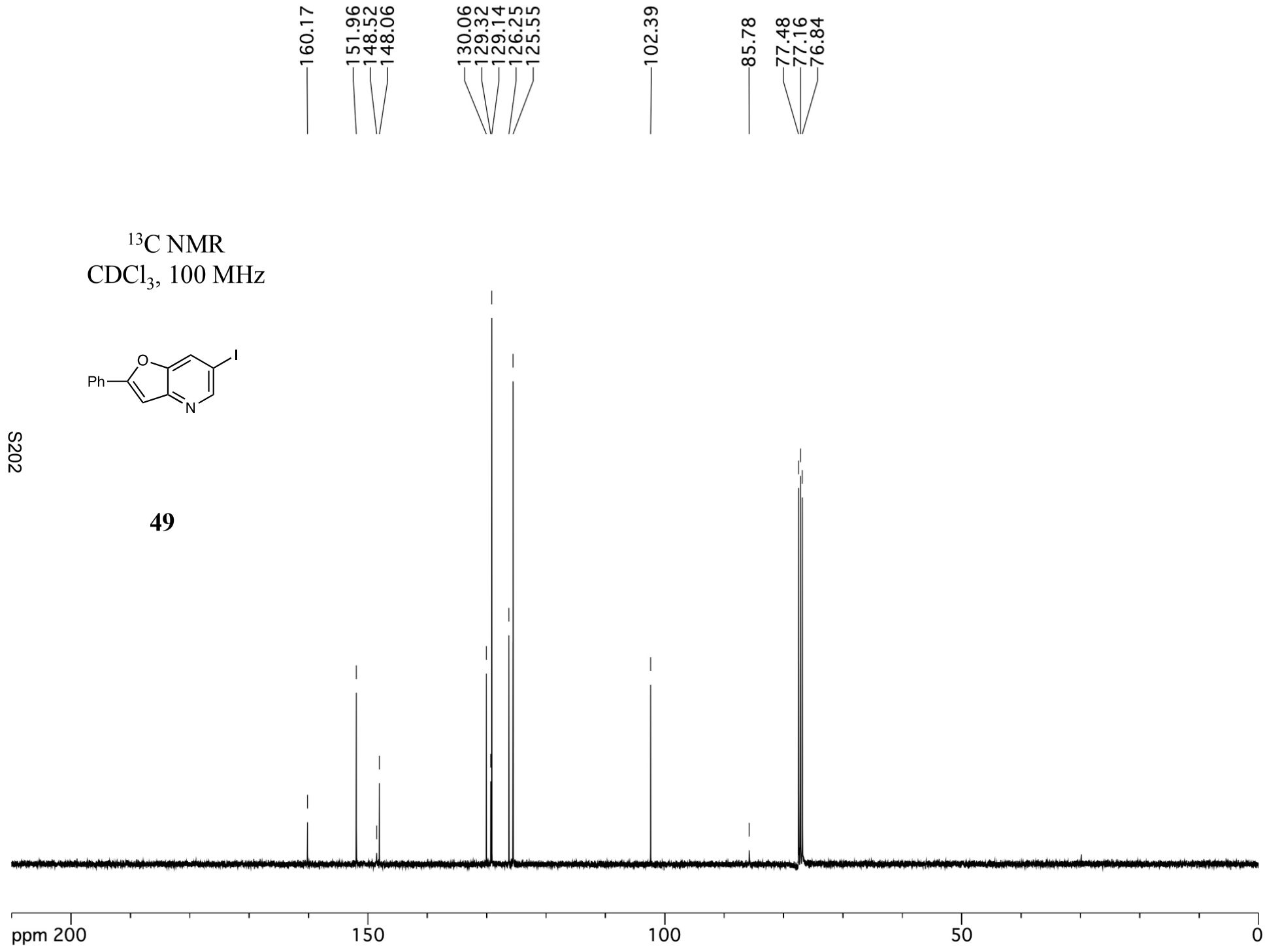
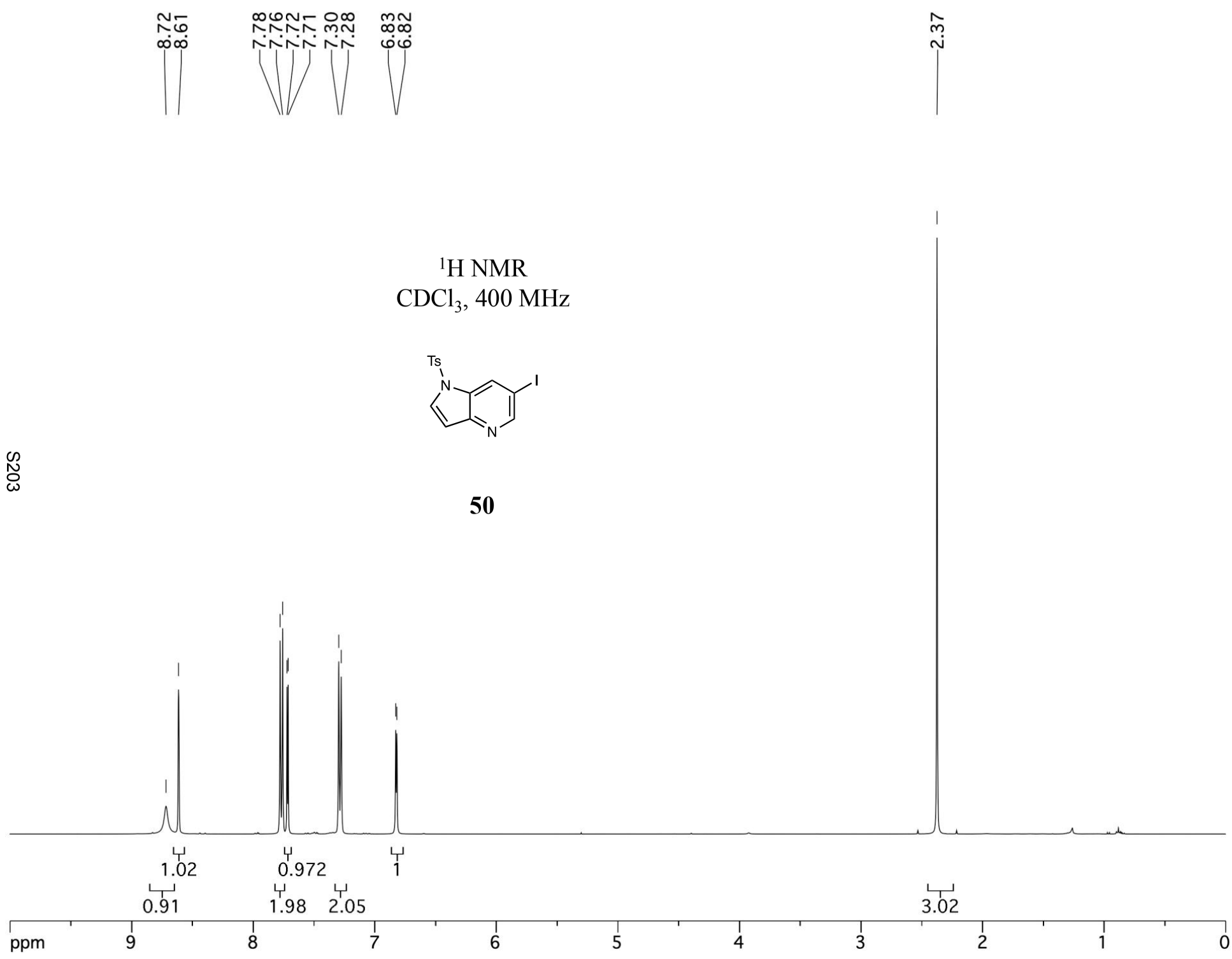
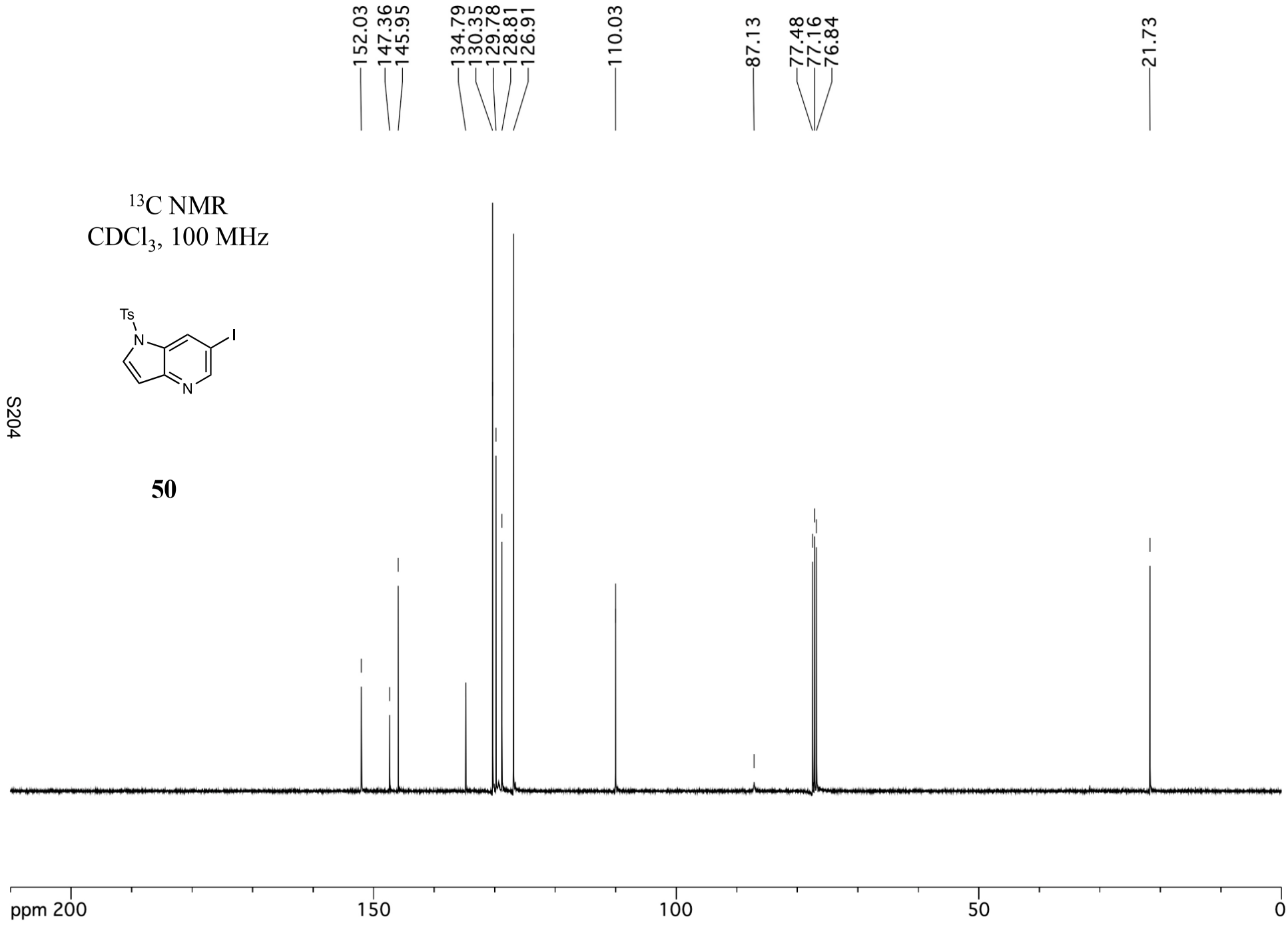
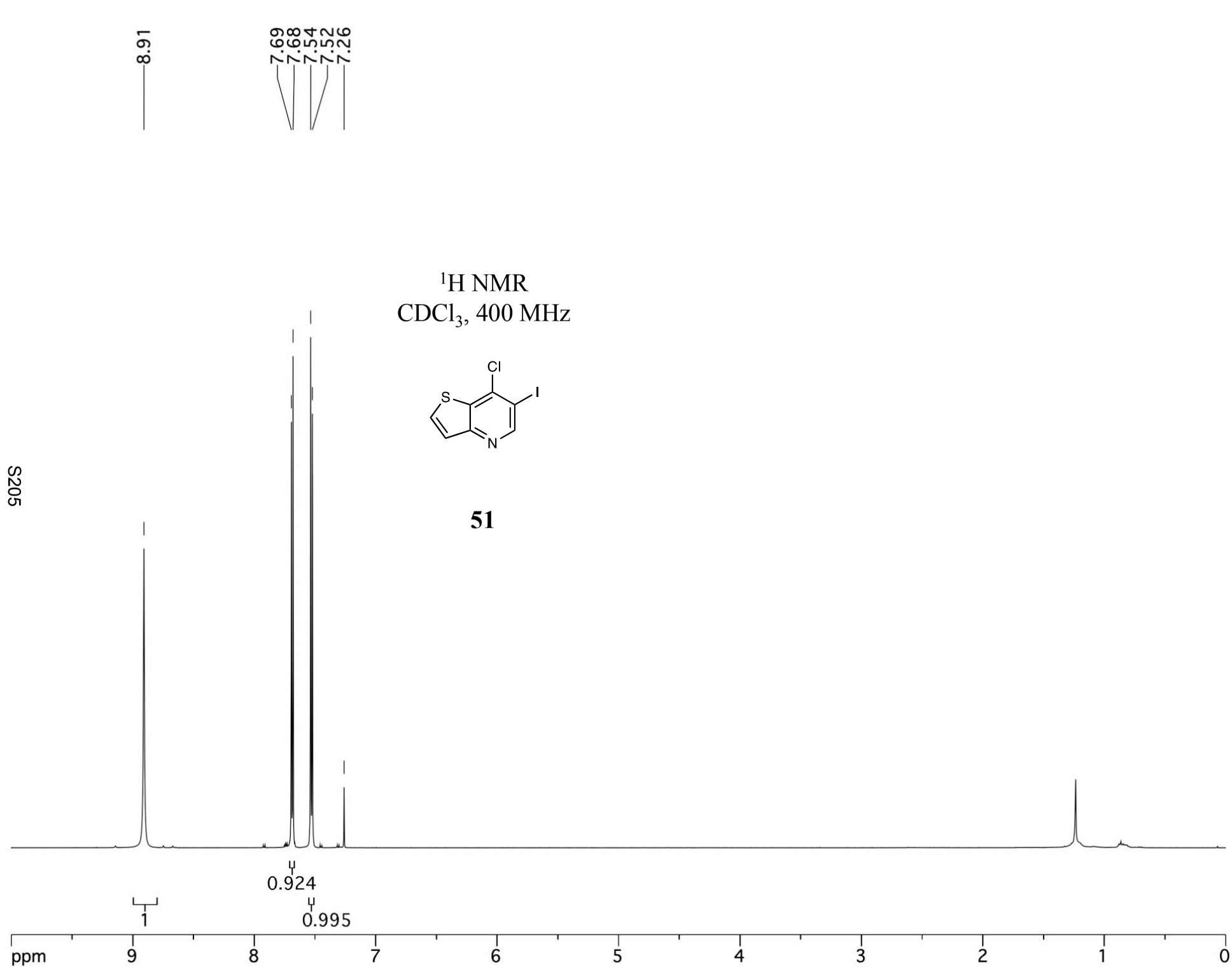
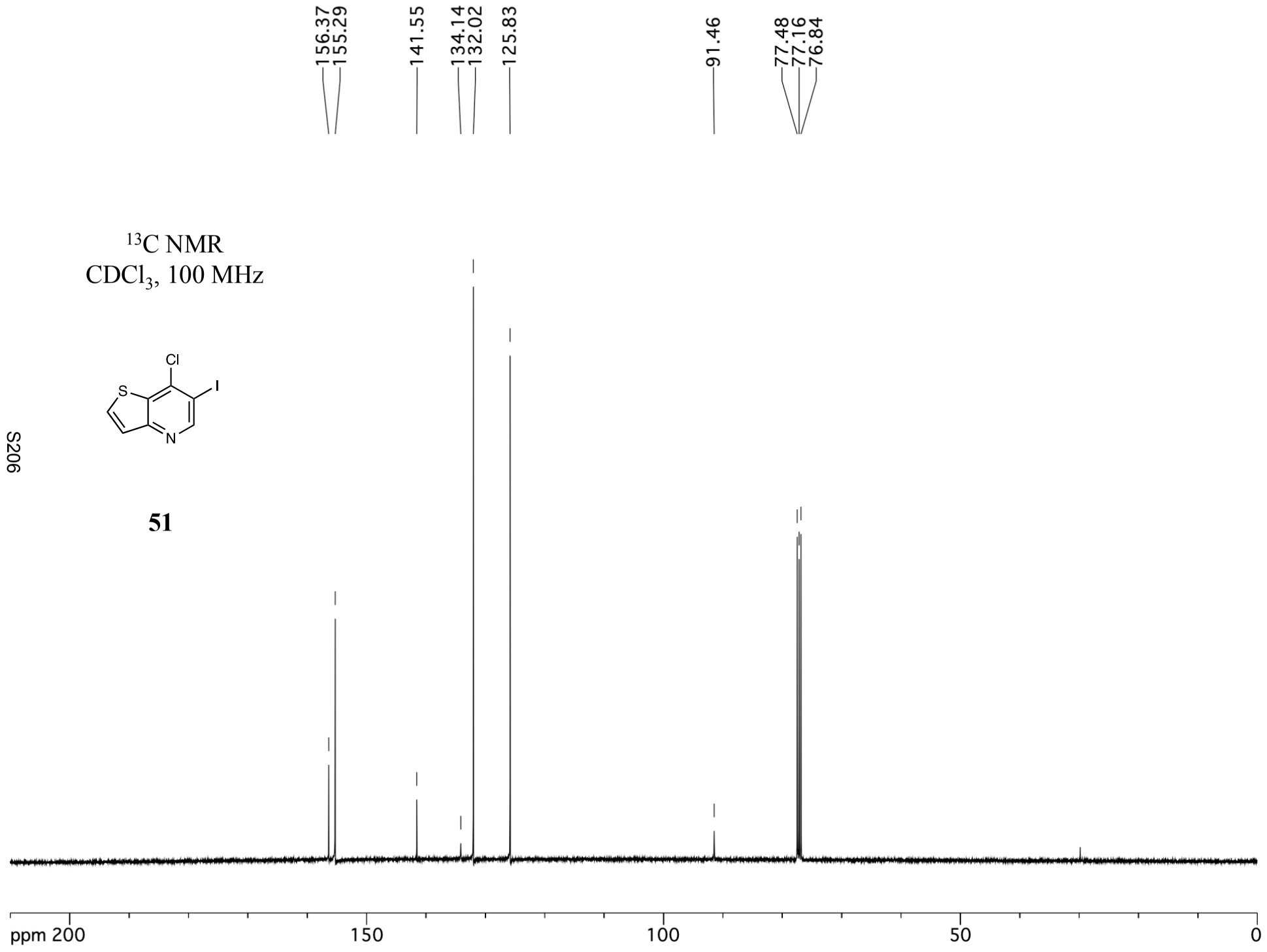
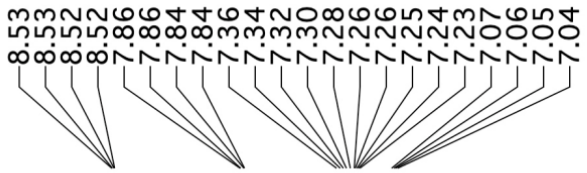

160.17
151.96
148.52
148.06
130.06
129.32
129.14
126.25
125.55
102.39
85.78
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Ph
O
N
I
S202
49
ppm 200
150
100
50
0

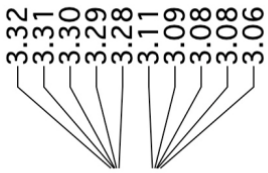

8.72
8.61
7.78
7.76
7.72
7.71
7.30
7.28
6.83
6.82
2.37
1H NMR
CDCl3, 400 MHz
Ts
N
I
N
S203
50
1.02
0.972
1
0.91
1.98
2.05
3.02
ppm
9
8
7
6
5
4
3
2
1
0


152.03
147.36
145.95
134.79
130.35
129.78
128.81
126.91
110.03
87.13
77.48
77.16
76.84
21.73
^{13}C NMR
$CDCl_3$, 100 MHz
Ts
N
I
N
S204
50
ppm 200
150
100
50
0

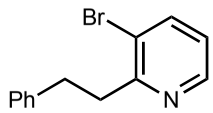

8.91
7.69
7.68
7.54
7.52
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Cl
S
I
N
S205
51
0.924
1
0.995
ppm
9
8
7
6
5
4
3
2
1
0


156.37
155.29
141.55
134.14
132.02
125.83
91.46
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
S
I
N
S206
51
ppm 200
150
100
50
0

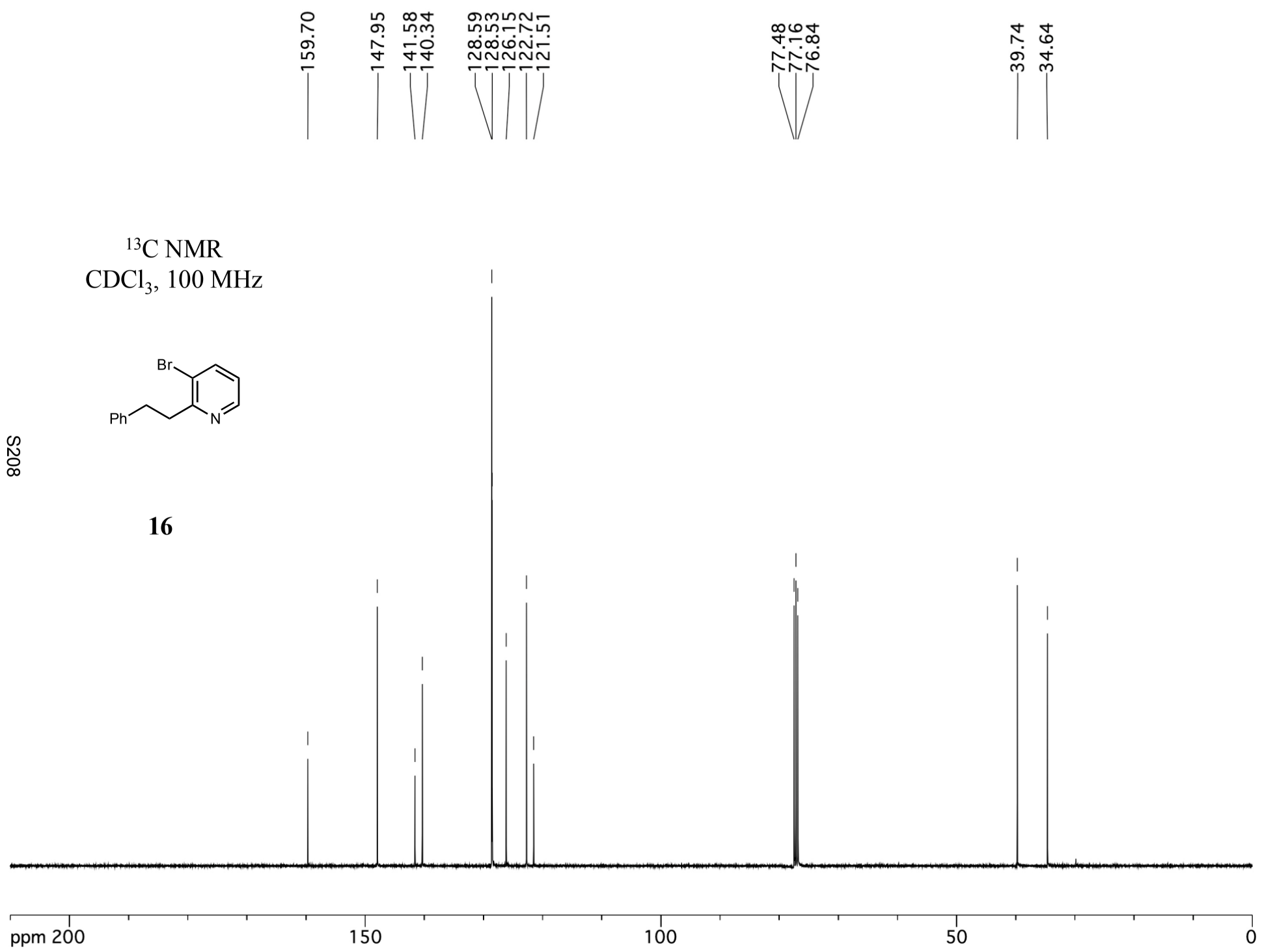


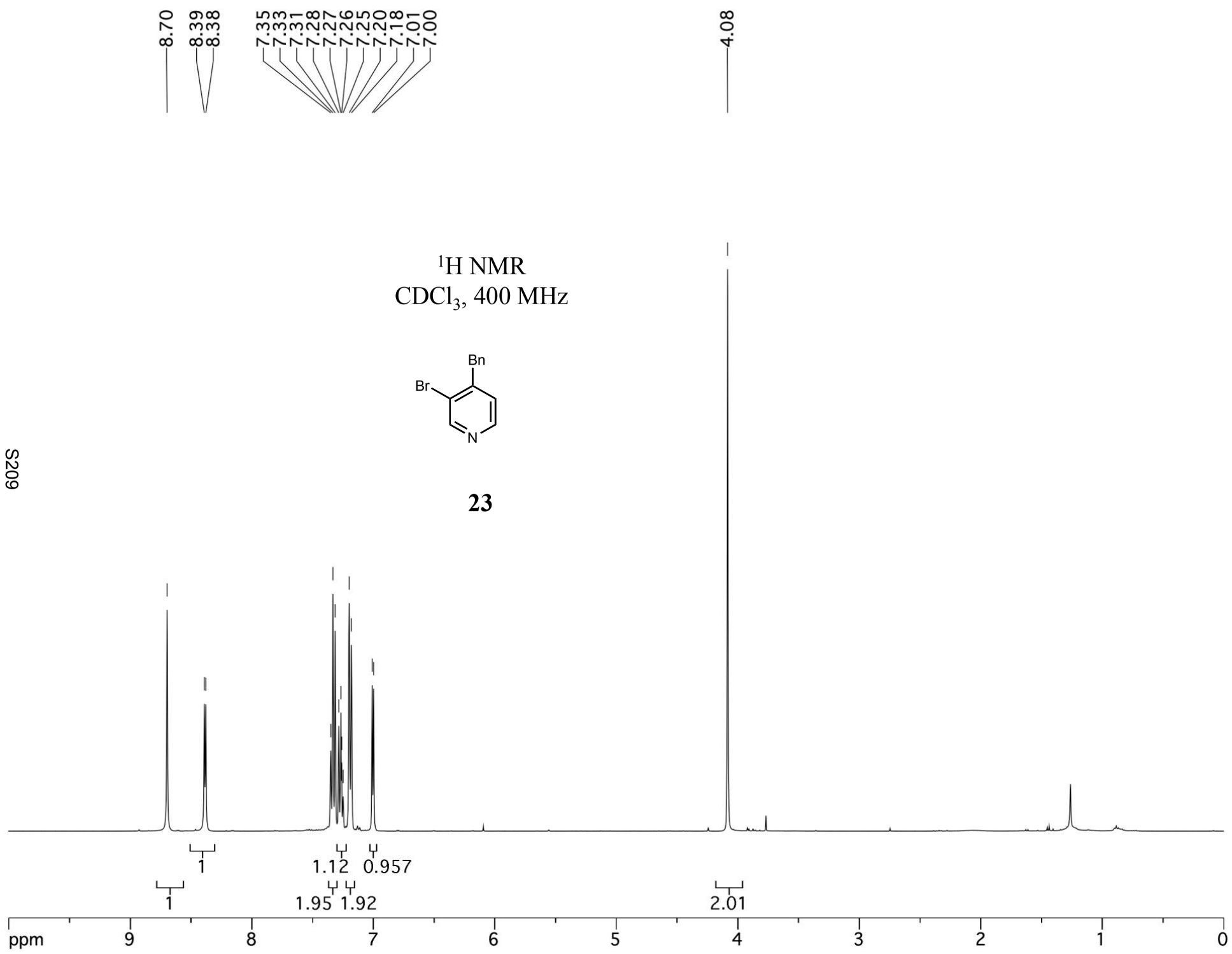


^{1}H NMR
$CDCl_3$, 400 MHz



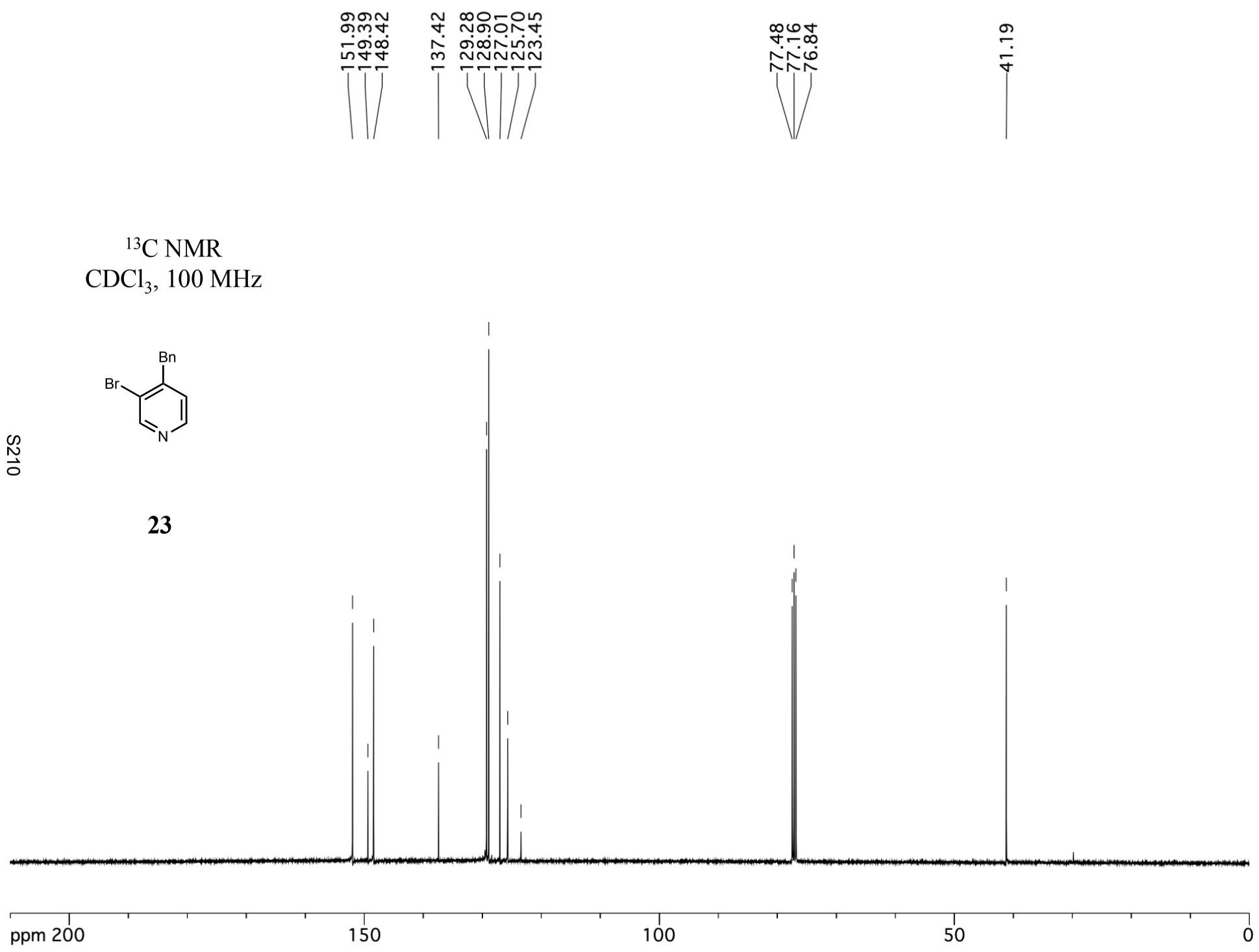
16

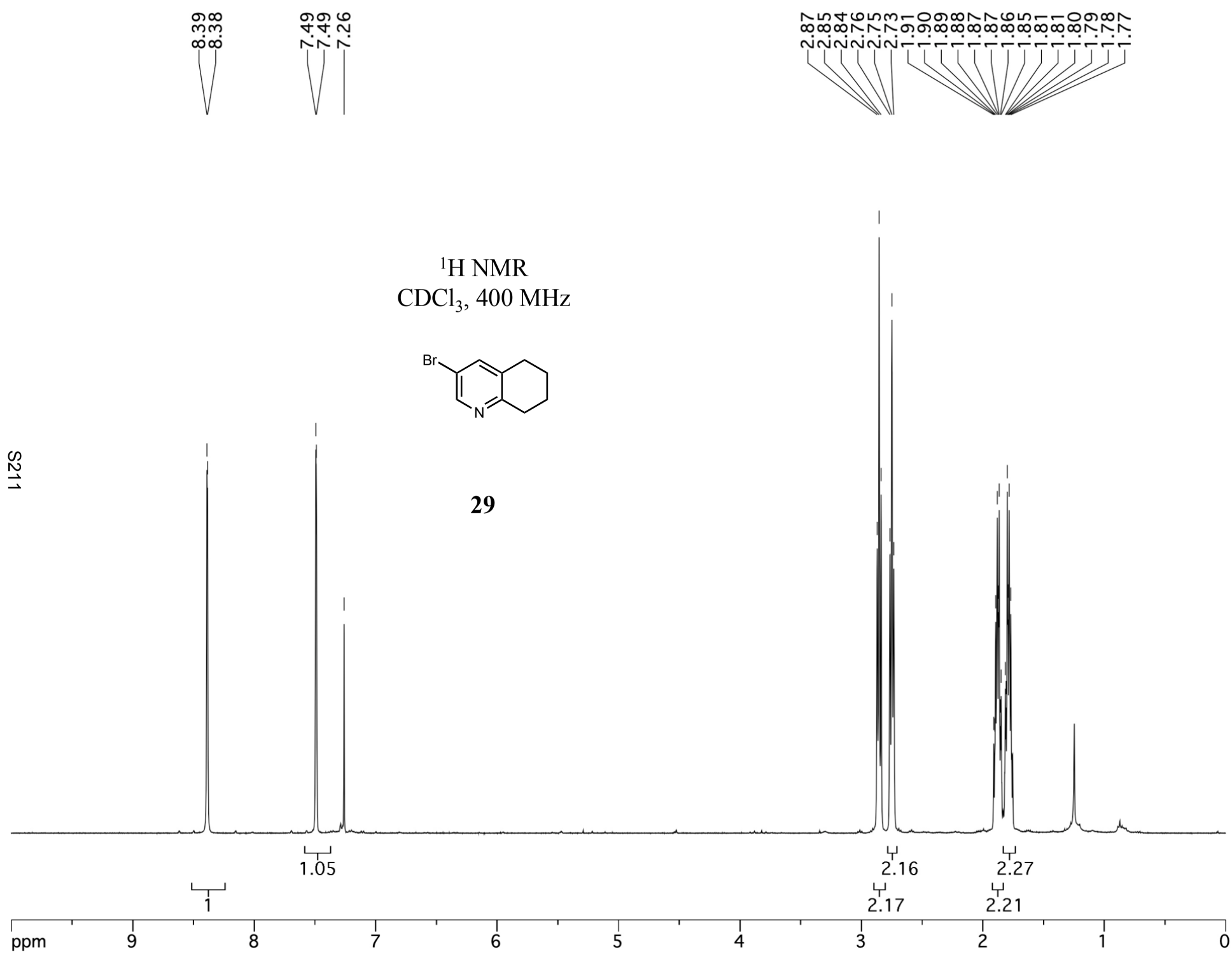

159.70
147.95
141.58
140.34
128.59
128.53
126.15
122.72
121.51
77.48
77.16
76.84
39.74
34.64
^{13}C NMR
$CDCl_3$, 100 MHz
Br
Ph
N
S208
16
ppm 200
150
100
50
0

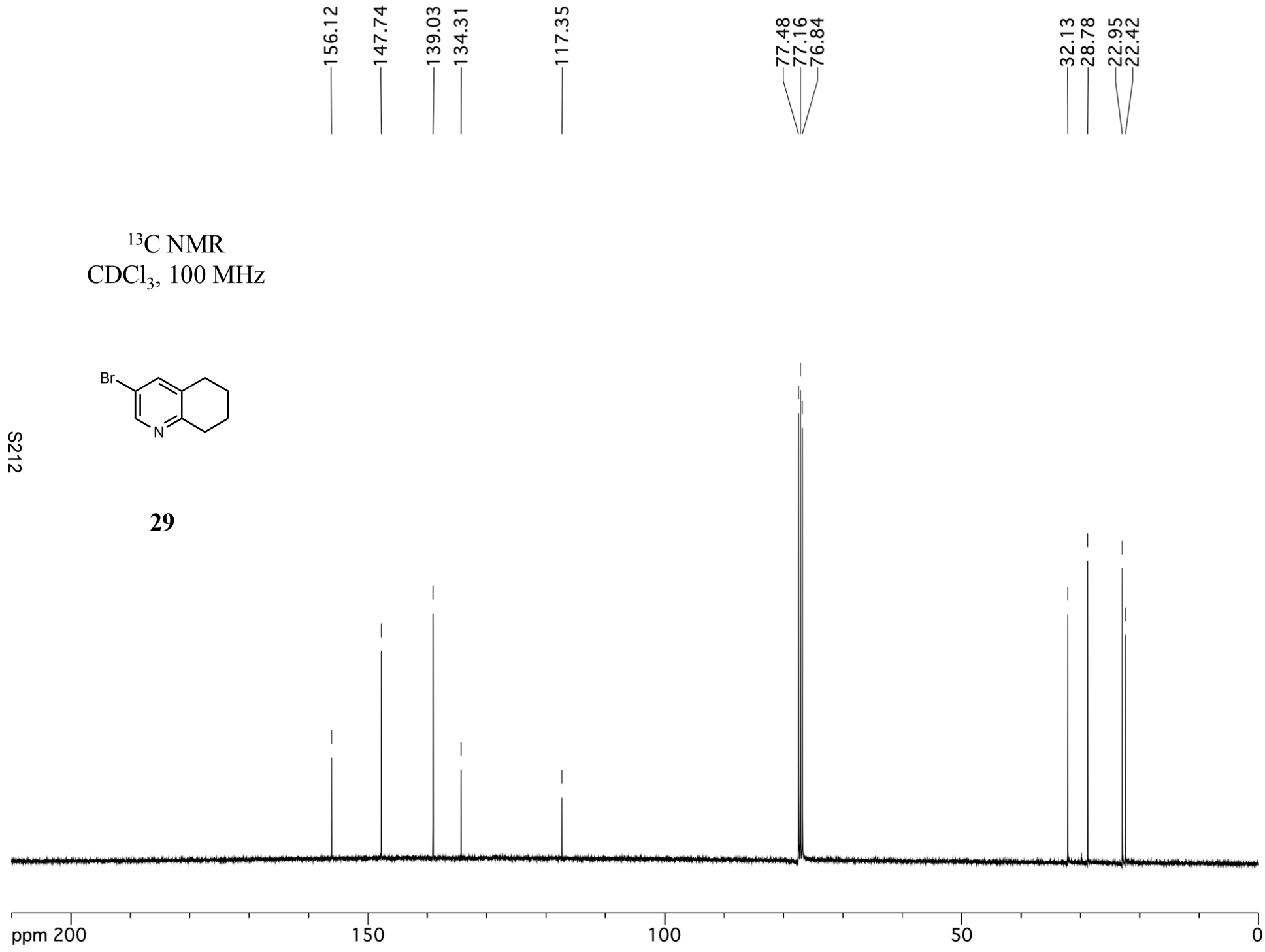


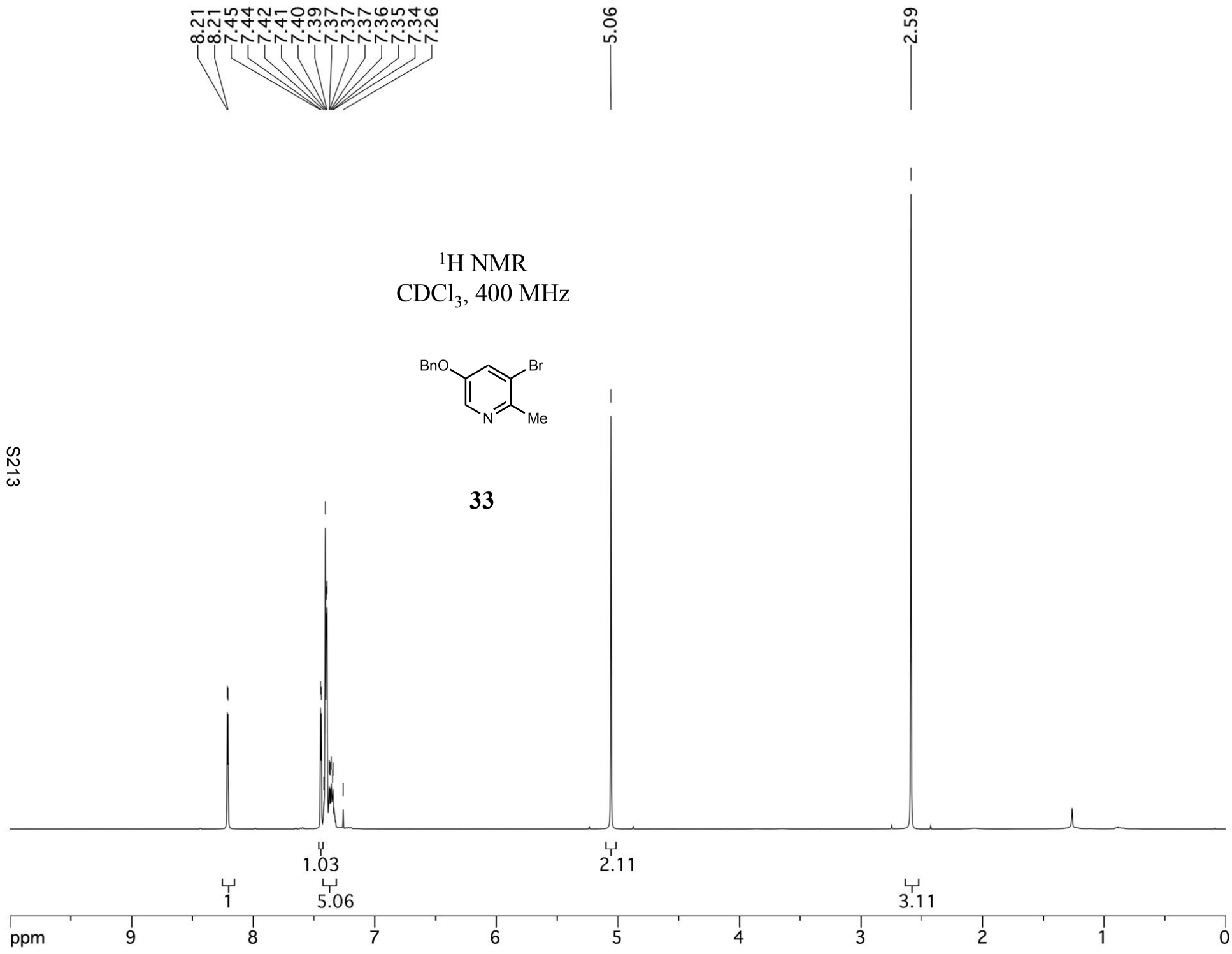
^{1}H NMR
$CDCl_3$, 400 MHz

23


151.99
149.39
148.42
137.42
129.28
128.90
127.01
125.70
123.45
77.48
77.16
76.84
41.19
^{13}C NMR
$CDCl_3$, 100 MHz
Bn
Br
N
S210
23
ppm 200
150
100
50
0

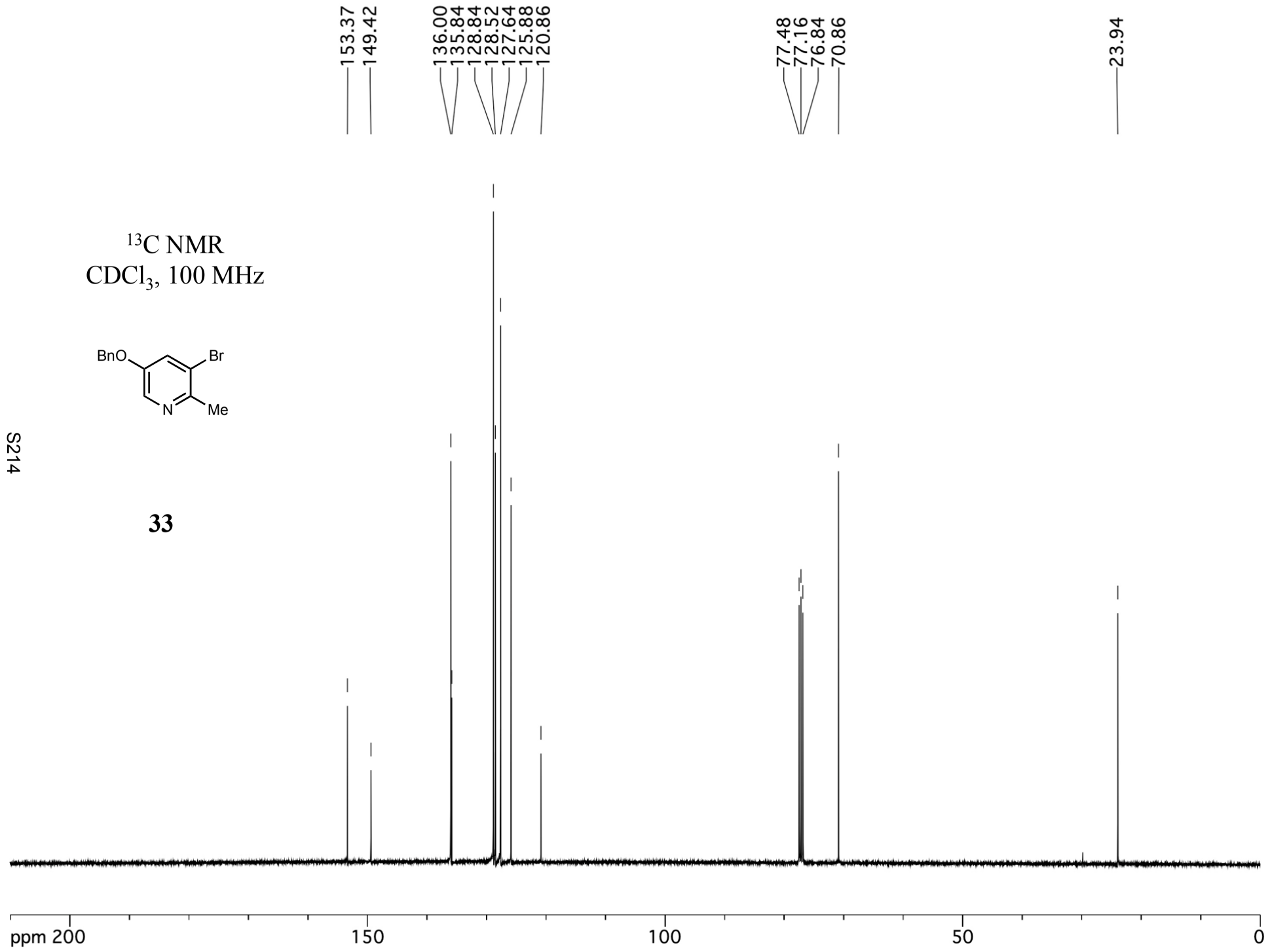

8.39
8.38
7.49
7.49
7.26
2.87
2.85
2.84
2.76
2.75
2.73
1.91
1.90
1.89
1.88
1.87
1.87
1.86
1.85
1.81
1.81
1.80
1.79
1.78
1.77
^{1}H NMR
$CDCl_3$, 400 MHz
Br
N
29
S211
1.05
2.16
2.27
1
2.17
2.21
ppm
9
8
7
6
5
4
3
2
1
0

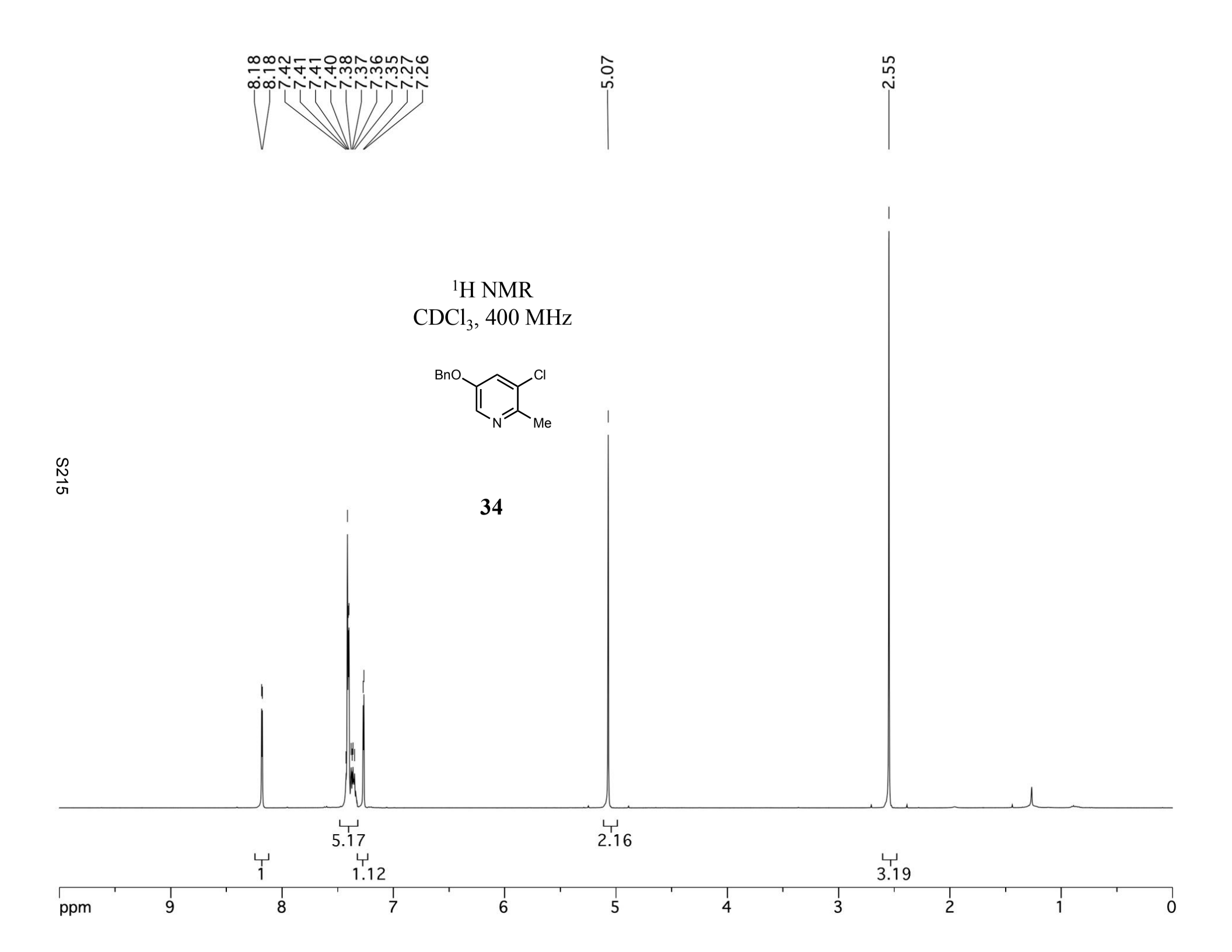

156.12
147.74
139.03
134.31
117.35
77.48
77.16
76.84
32.13
28.78
22.95
22.42
^{13}C NMR
$CDCl_3$, 100 MHz
Br
N
S212
29
ppm 200
150
100
50
0

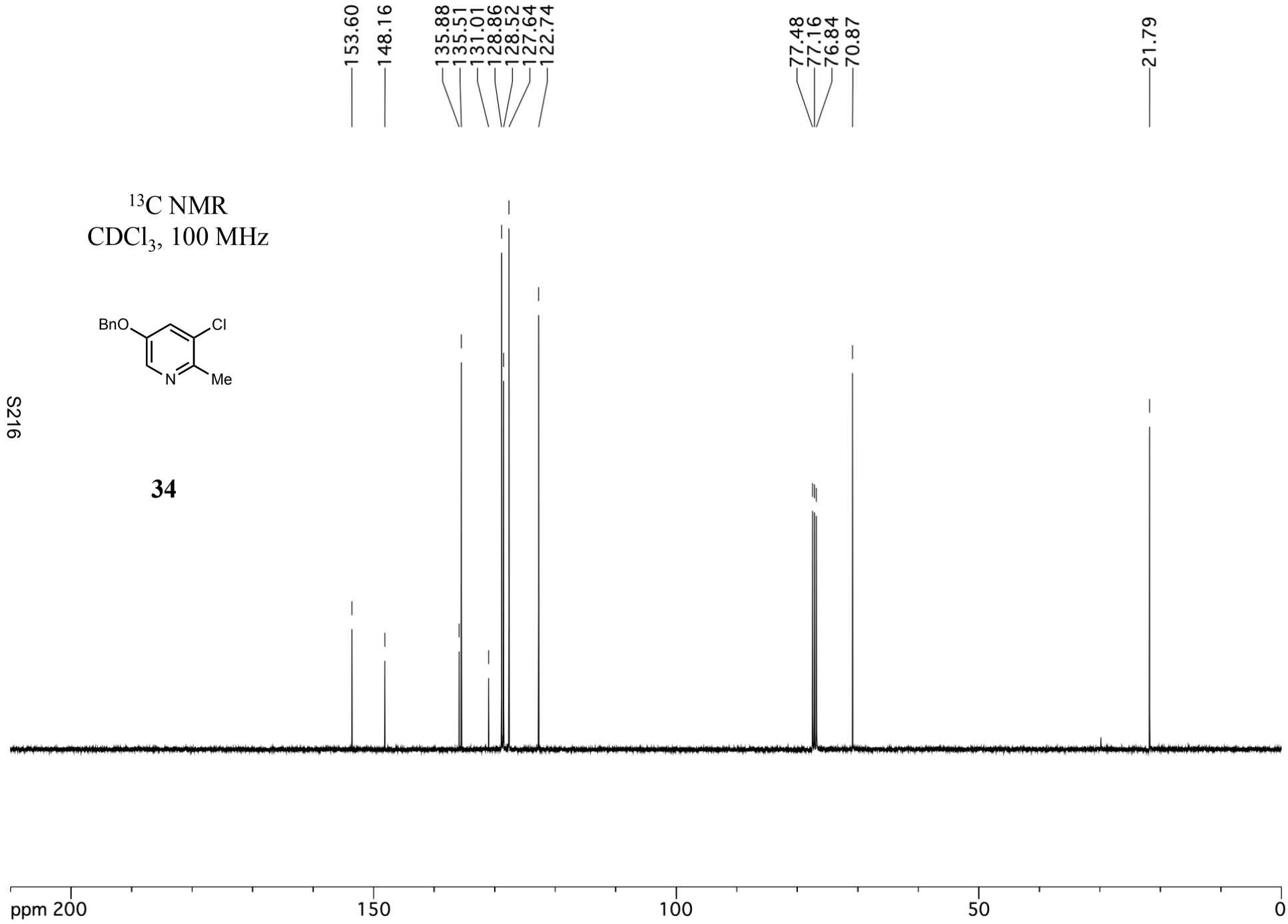


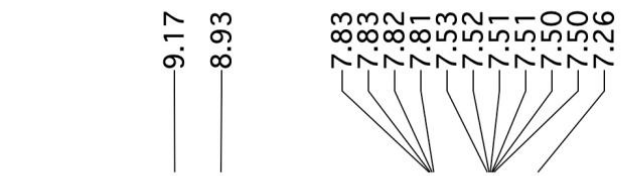
^{1}H NMR
$CDCl_3$, 400 MHz

33

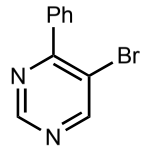

153.37
149.42
136.00
135.84
128.84
128.52
127.64
125.88
120.86
77.48
77.16
76.84
70.86
23.94
13C NMR
CDCl3, 100 MHz
BnO
Br
N
Me
33
ppm 200
150
100
50
0


8.18
8.18
7.42
7.41
7.41
7.40
7.38
7.37
7.36
7.35
7.27
7.26
5.07
2.55
1H NMR
CDCl3, 400 MHz
BnO
Cl
N
Me
34
S215
5.17
2.16
1
1.12
3.19
ppm
9
8
7
6
5
4
3
2
1
0


153.60
148.16
135.88
135.51
131.01
128.86
128.52
127.64
122.74
77.48
77.16
76.84
70.87
21.79
13C NMR
CDCl3, 100 MHz
BnO
Cl
N
Me
34
S216
ppm 200
150
100
50
0



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



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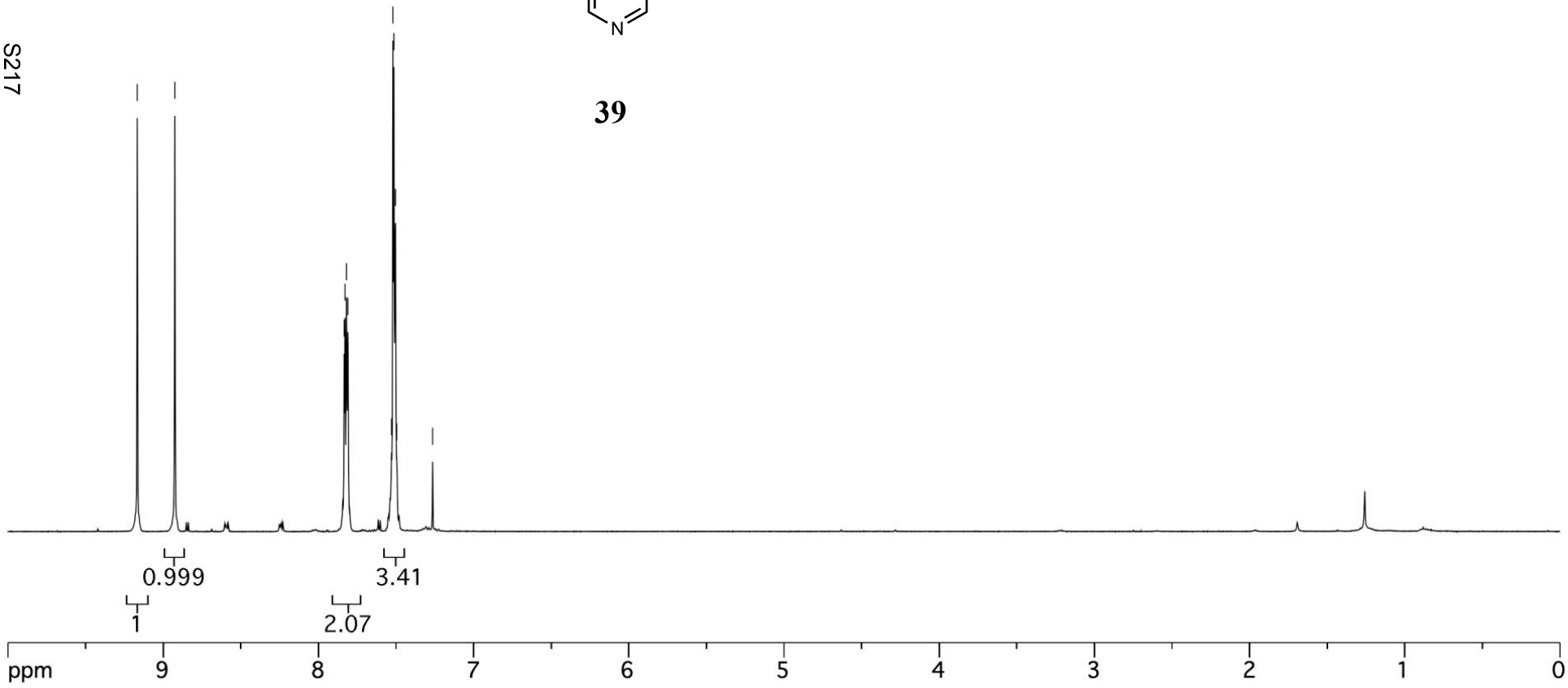
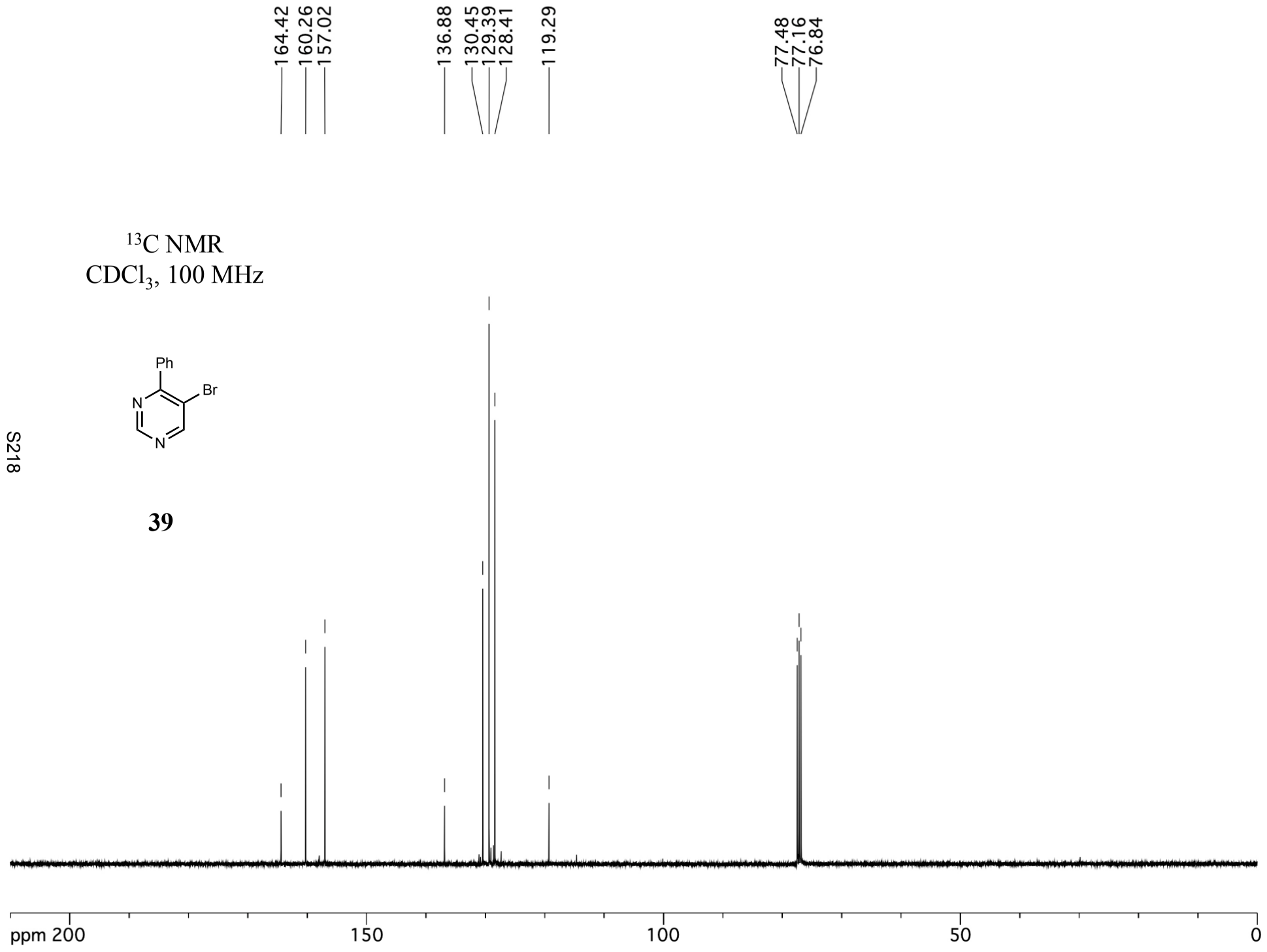
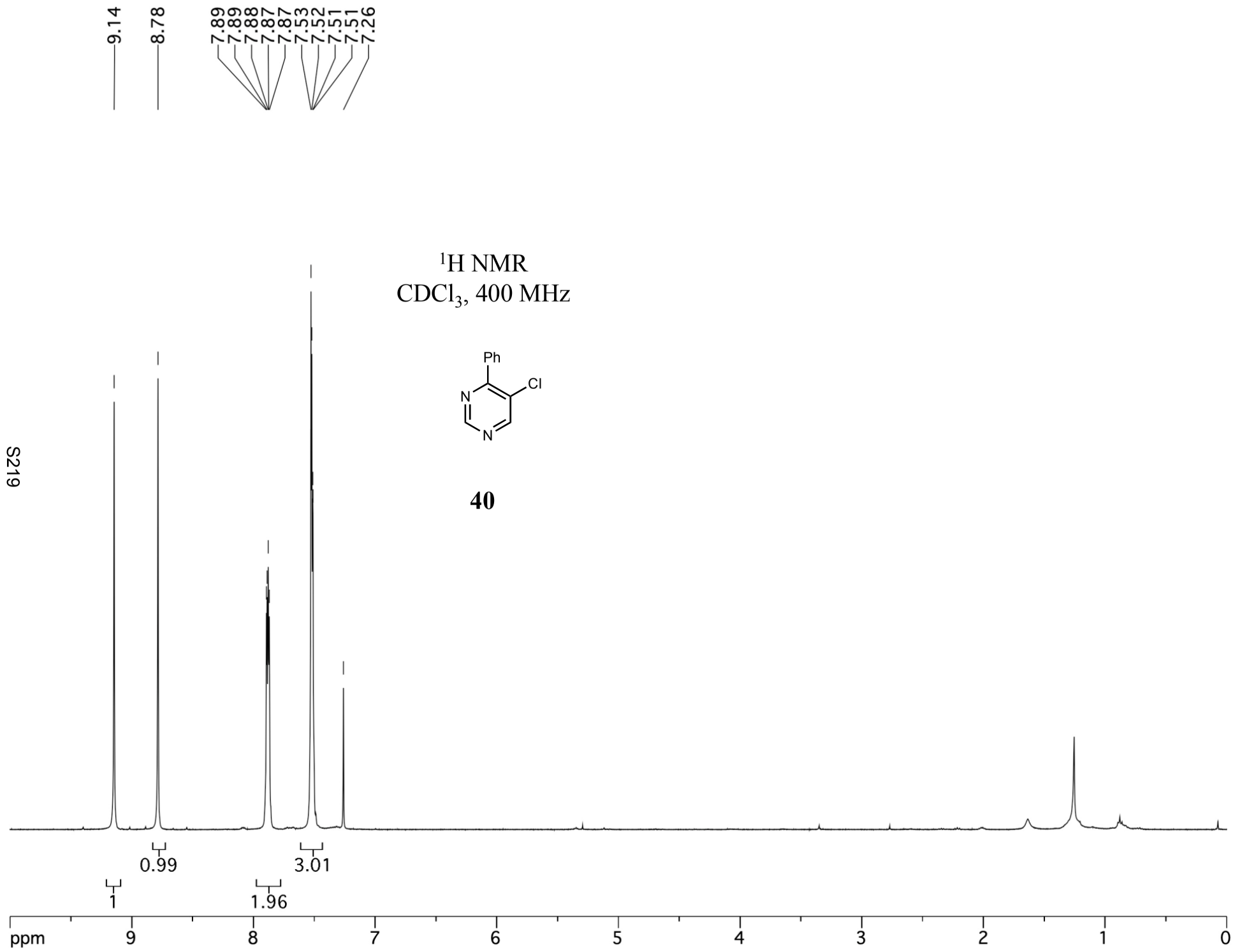
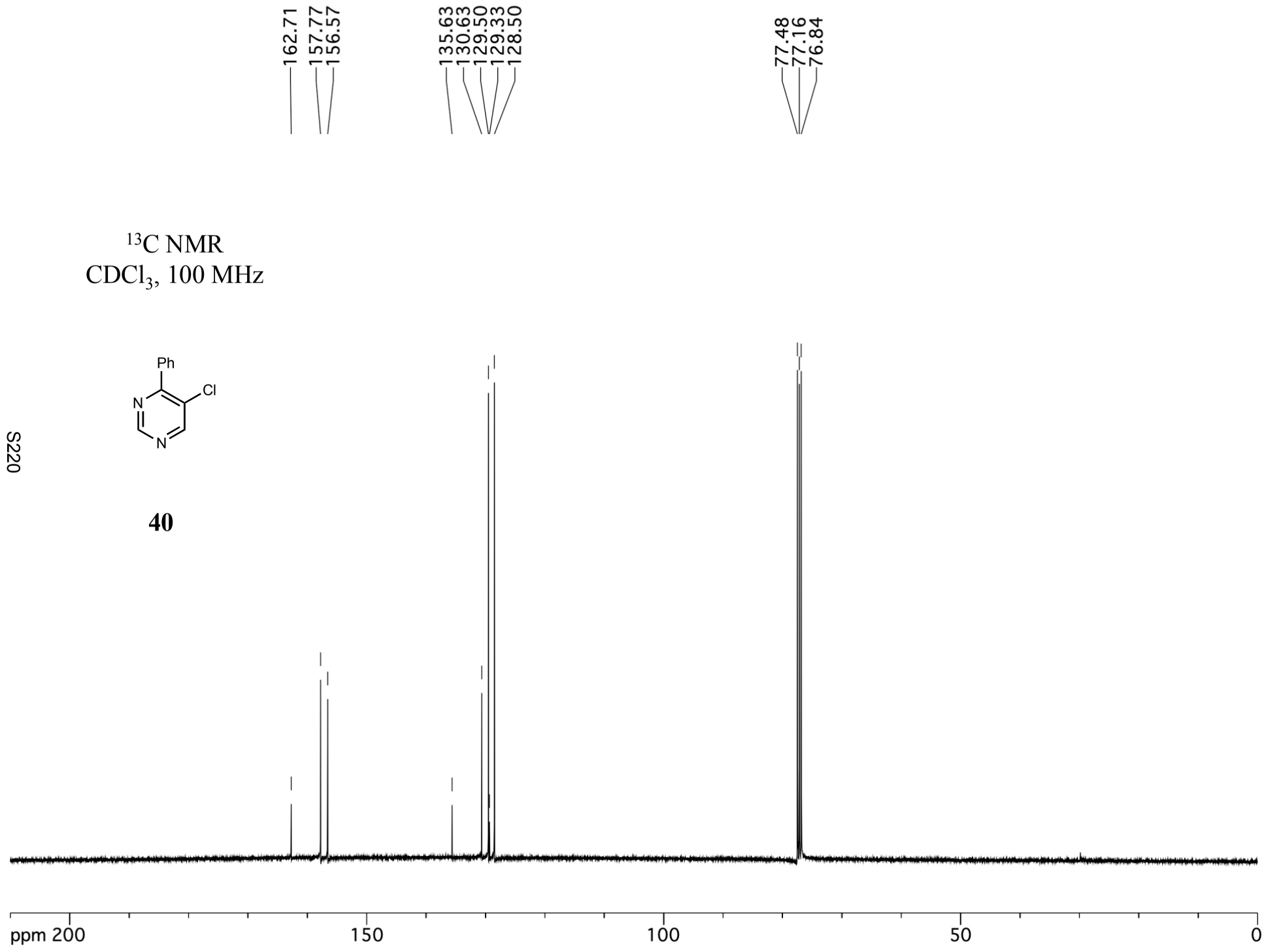
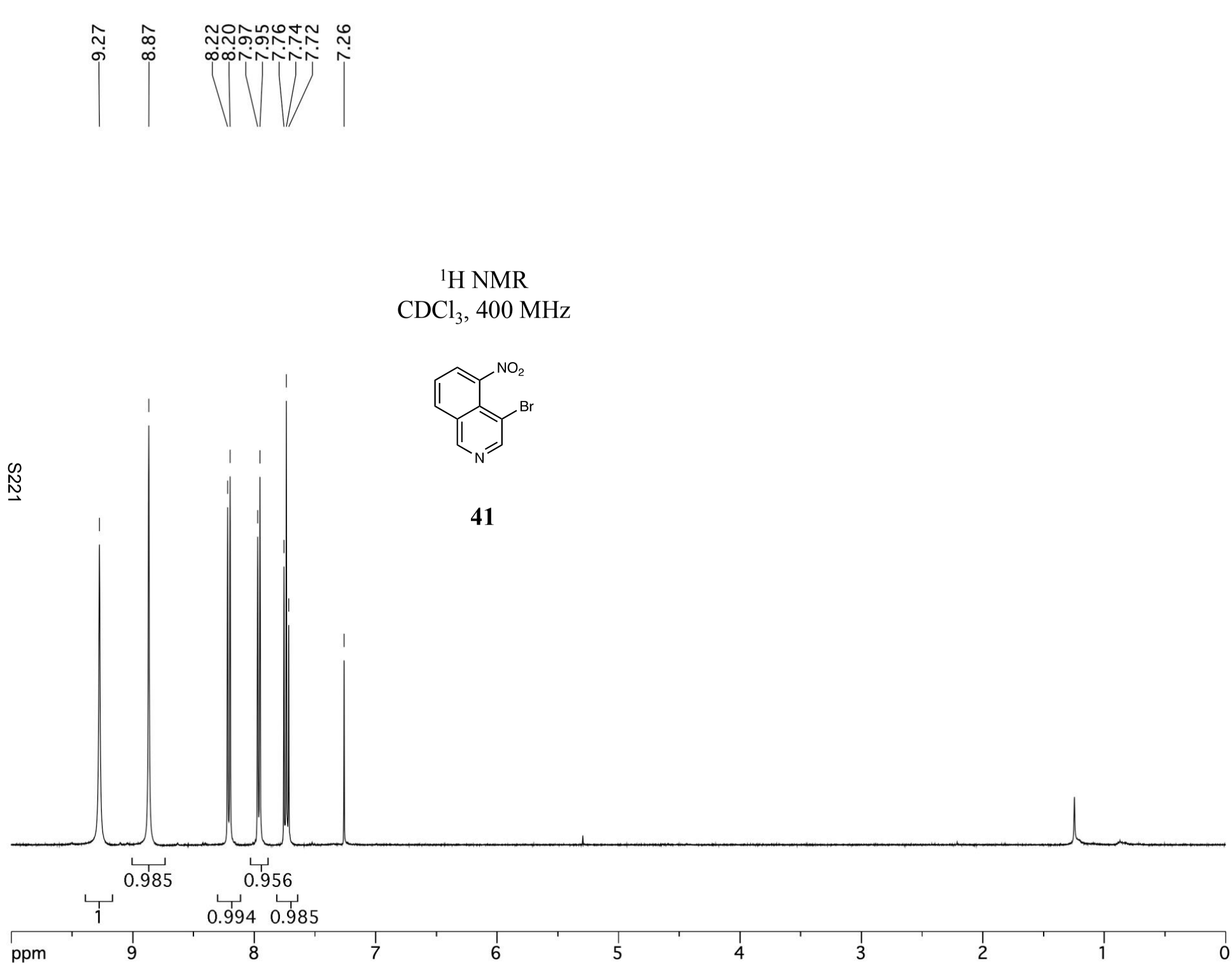



164.42
160.26
157.02
136.88
130.45
129.39
128.41
119.29
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Ph
Br
N
N
S218
39
ppm 200
150
100
50
0

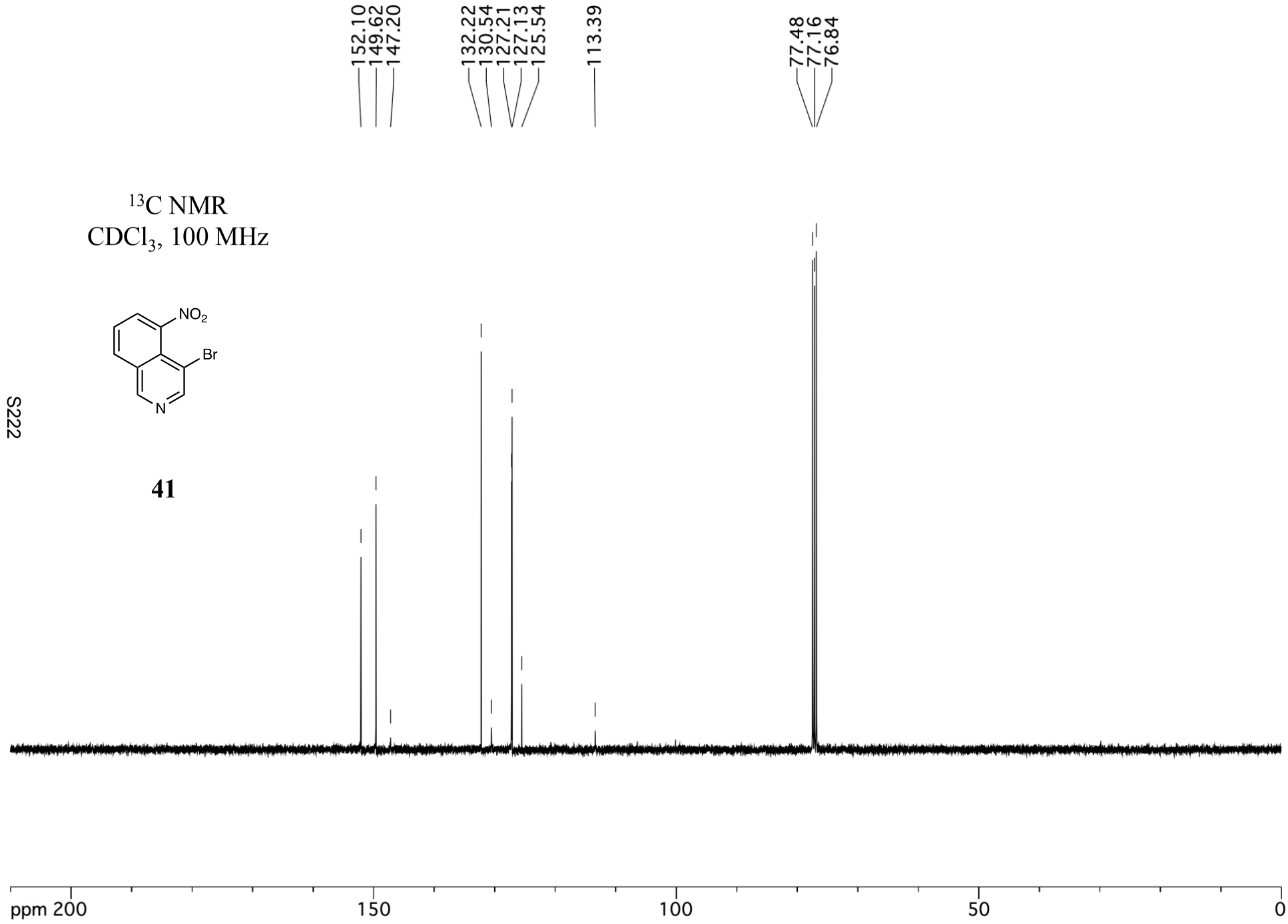

9.14
8.78
7.89
7.89
7.88
7.87
7.87
7.53
7.52
7.51
7.51
7.26
^{1}H NMR
$CDCl_3$, 400 MHz
Ph
Cl
N
N
40
S219
0.99
3.01
1
1.96
ppm
9
8
7
6
5
4
3
2
1
0

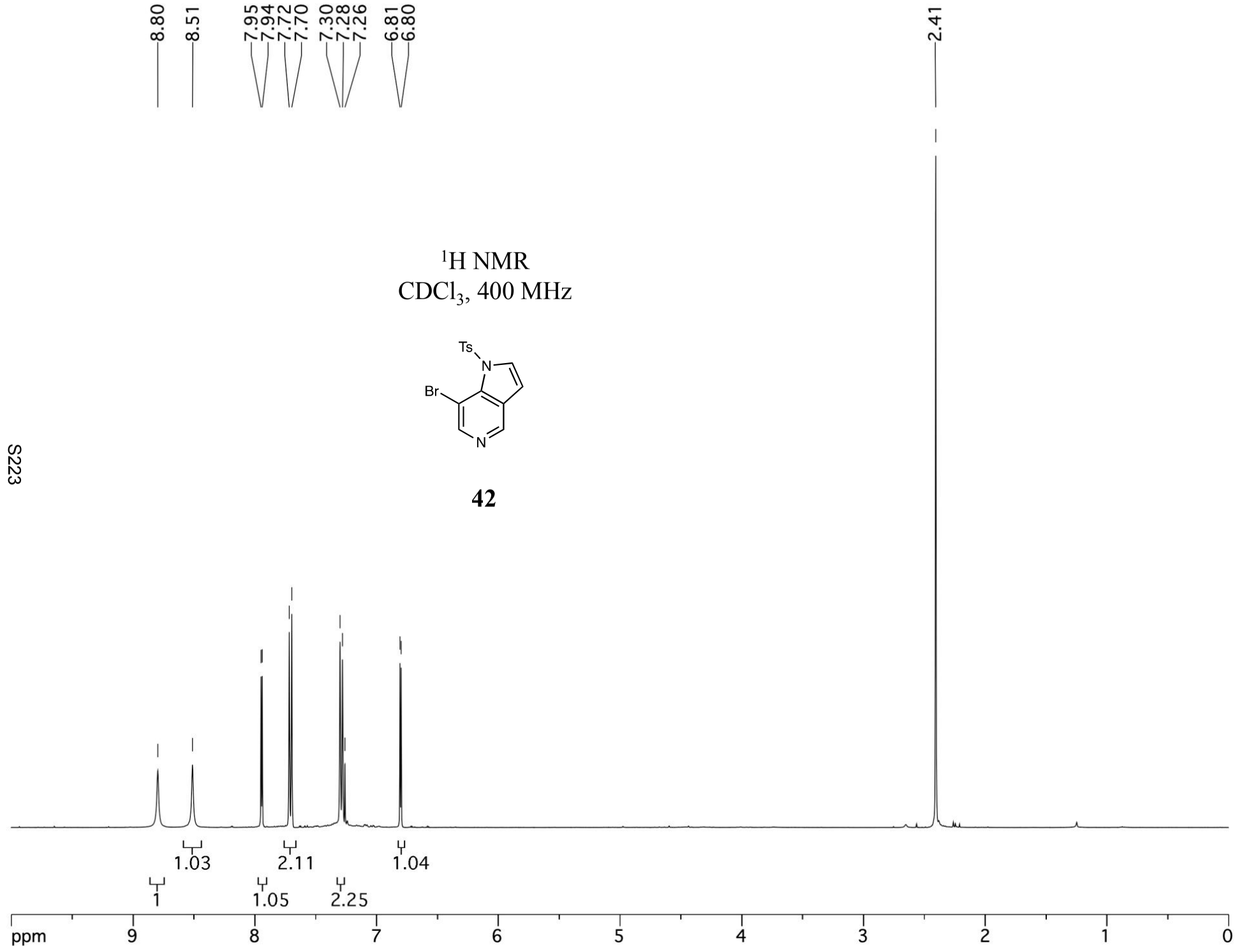

162.71
157.77
156.57
135.63
130.63
129.50
129.33
128.50
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Ph
Cl
N
N
S220
40
ppm 200
150
100
50
0

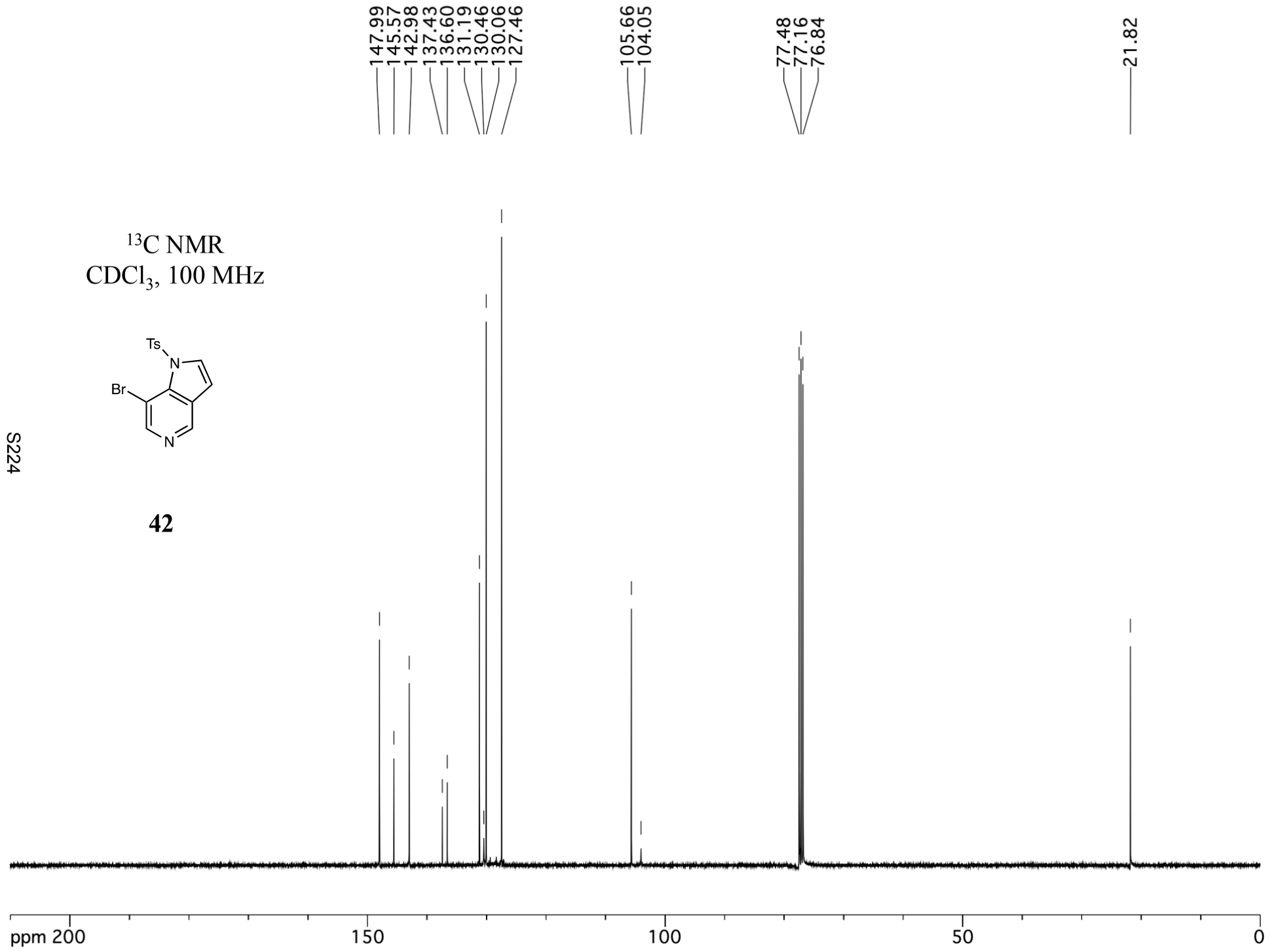


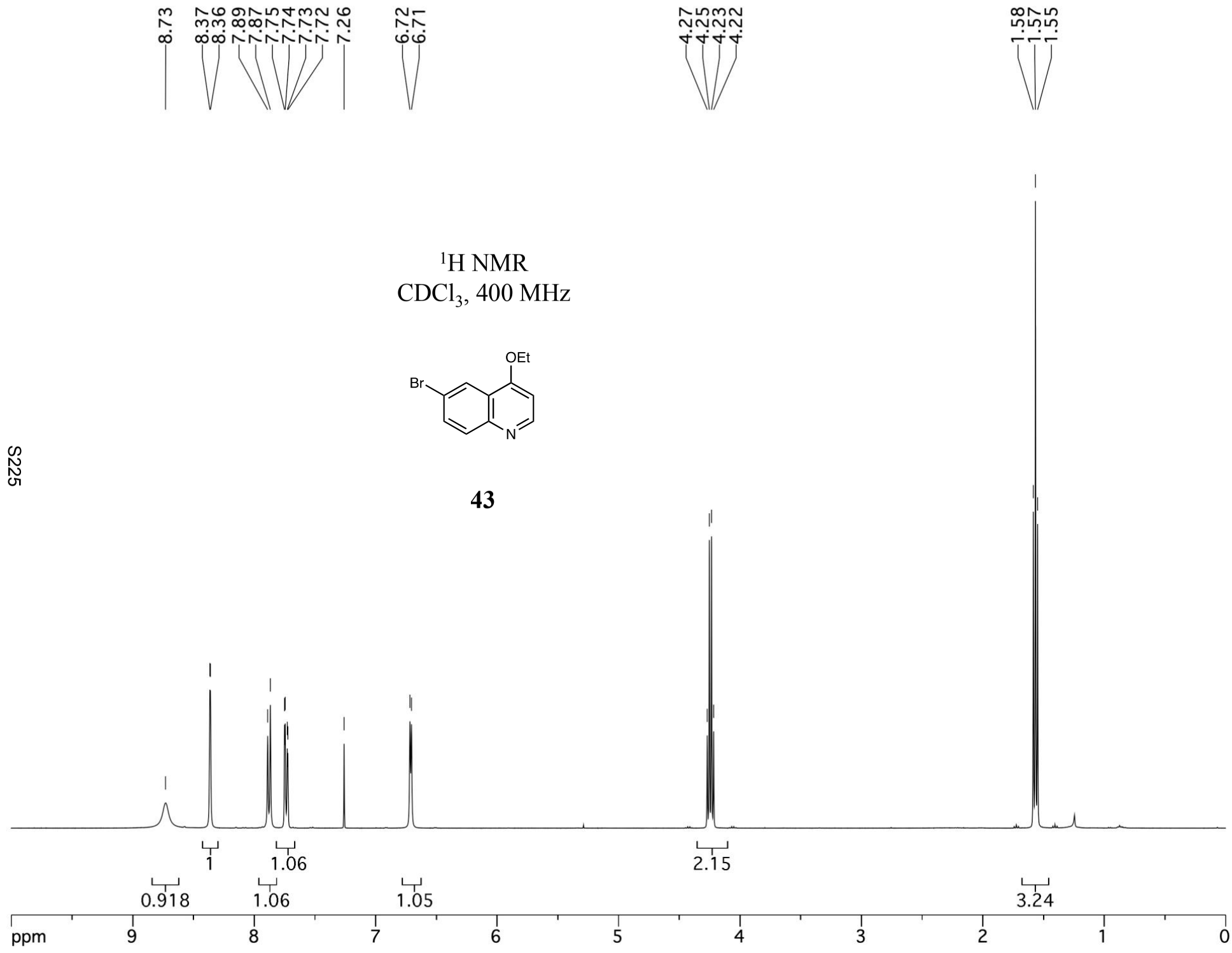
^{1}H NMR
$CDCl_3$, 400 MHz

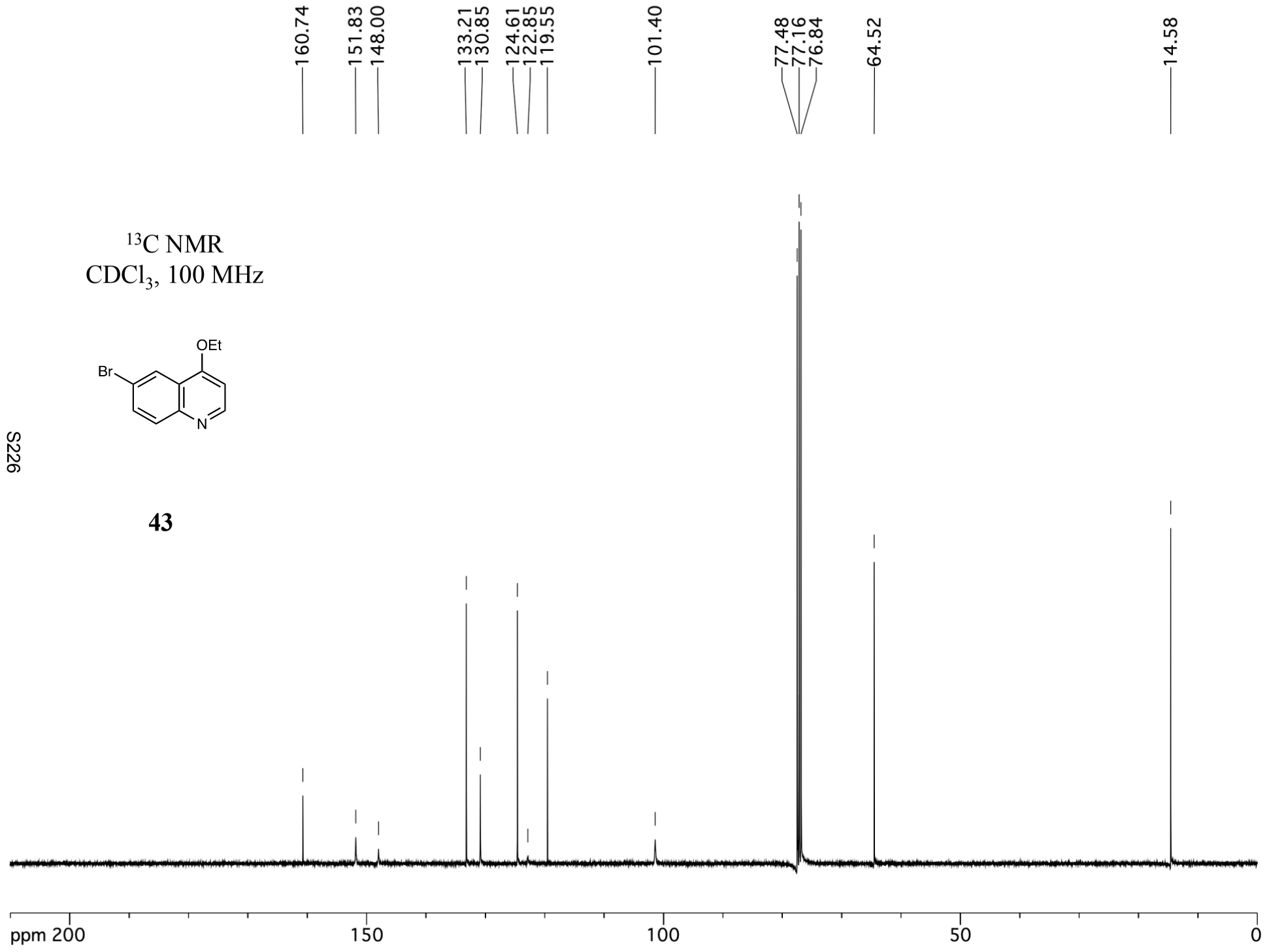
41

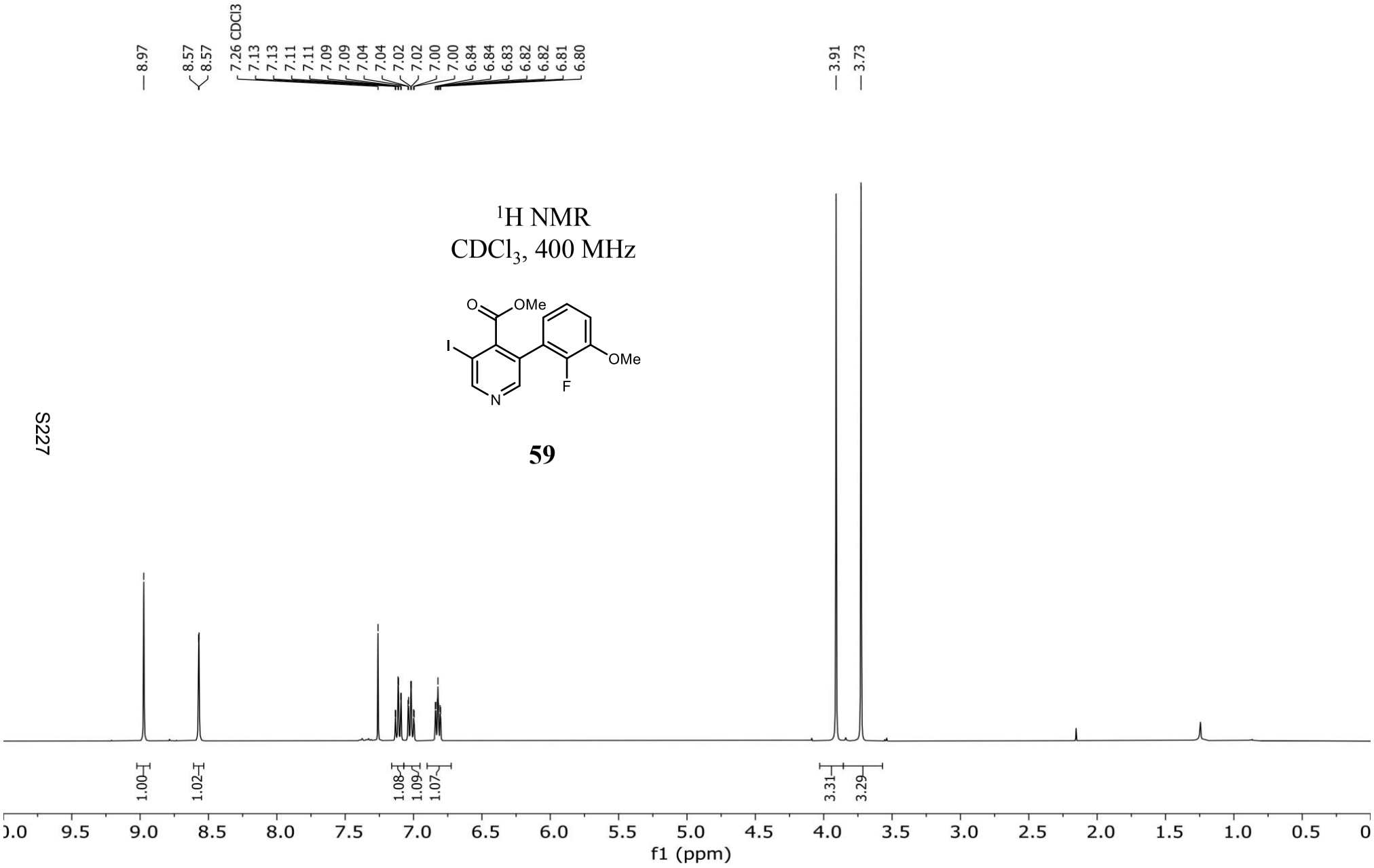

152.10
149.62
147.20
132.22
130.54
127.21
127.13
125.54
113.39
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
NO_2
Br
N
S222
41
ppm 200
150
100
50
0


8.80
8.51
7.95
7.94
7.72
7.70
7.30
7.28
7.26
6.81
6.80
2.41
1H NMR
CDCl3, 400 MHz
Ts
N
Br
N
42
S223
1.03
2.11
1.04
1
1.05
2.25
ppm
9
8
7
6
5
4
3
2
1
0


147.99
145.57
142.98
137.43
136.60
131.19
130.46
130.06
127.46
105.66
104.05
77.48
77.16
76.84
21.82
^{13}C NMR
$CDCl_3$, 100 MHz
Ts
N
Br
N
S224
42
ppm 200
150
100
50
0

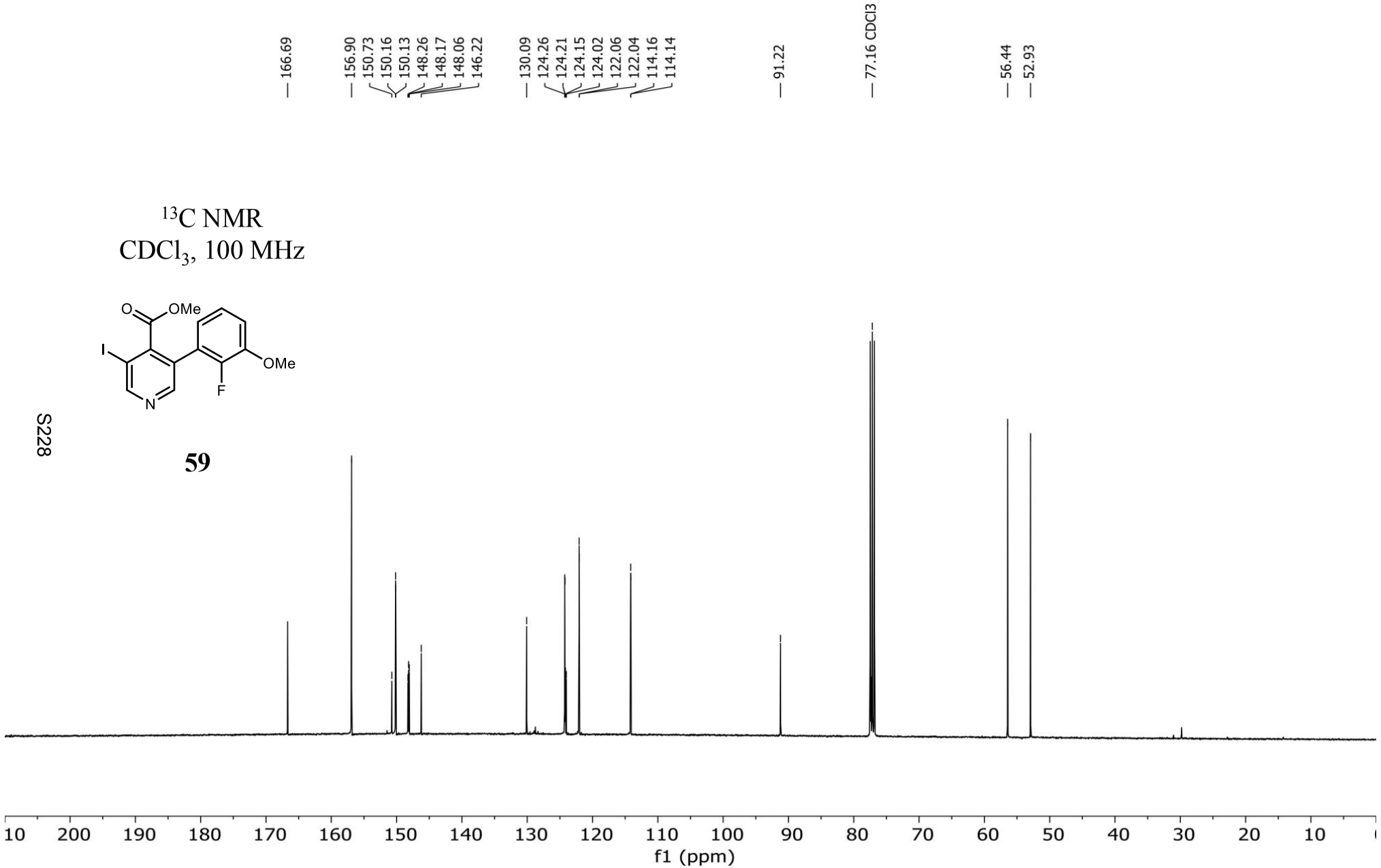

8.73
8.37
8.36
7.89
7.87
7.75
7.74
7.73
7.72
7.26
6.72
6.71
4.27
4.25
4.23
4.22
1.58
1.57
1.55
1H NMR
CDCl3, 400 MHz
OEt
Br
N
43
S225
1
1.06
2.15
0.918
1.06
1.05
3.24
ppm
9
8
7
6
5
4
3
2
1
0


160.74
151.83
148.00
133.21
130.85
124.61
122.85
119.55
101.40
77.48
77.16
76.84
64.52
14.58
^{13}C NMR
$CDCl_3$, 100 MHz
OEt
Br
N
S226
43
ppm 200
150
100
50
0

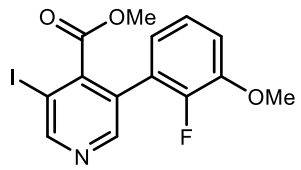


^{1}H NMR
$CDCl_3$, 400 MHz

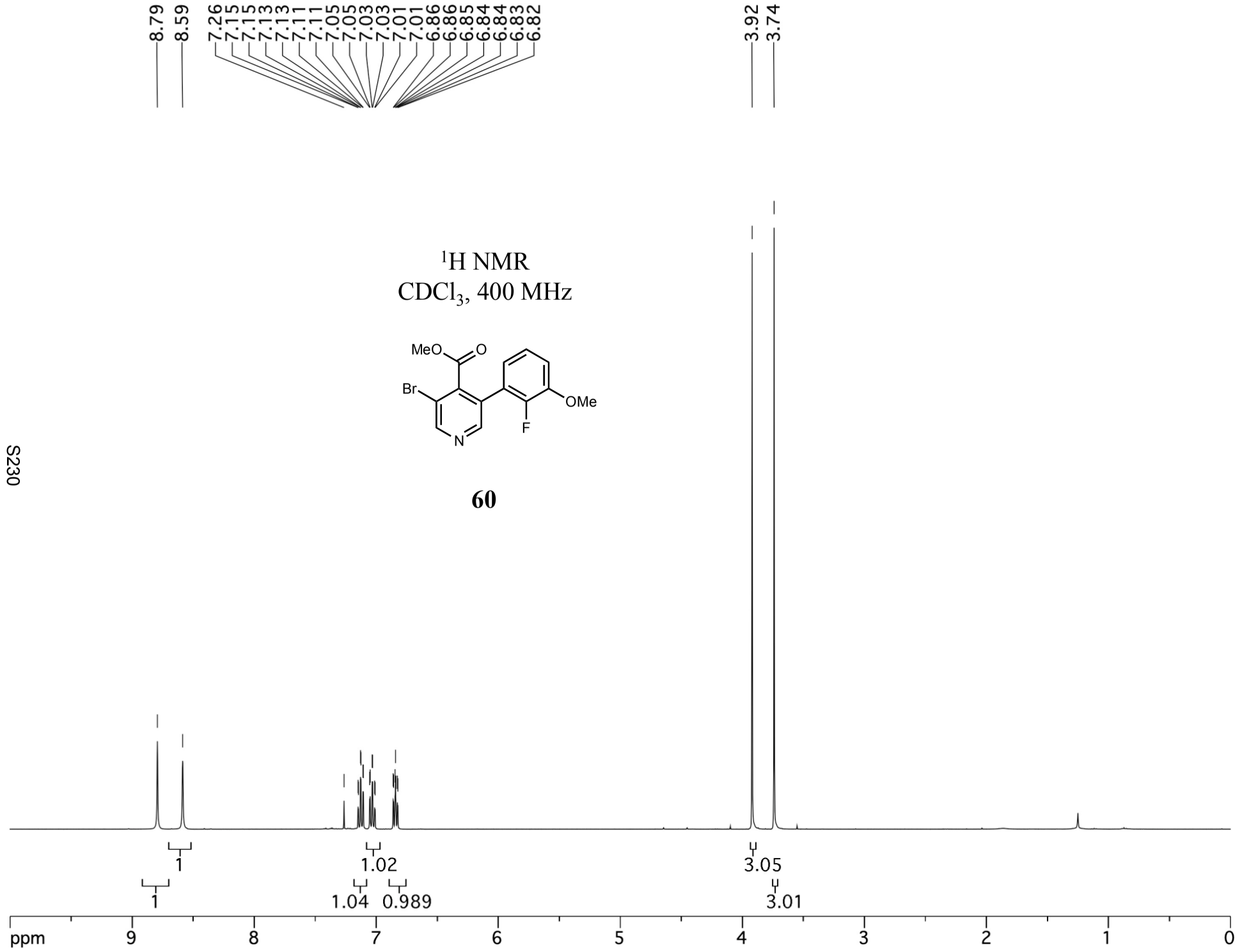
59


166.69
156.90
150.73
150.16
150.13
148.26
148.17
148.06
146.22
130.09
124.26
124.21
124.15
124.02
122.06
122.04
114.16
114.14
91.22
77.16 CDCl3
56.44
52.93
13C NMR
CDCl3, 100 MHz
O
OMe
I
OMe
F
N
59
S228
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{19}F NMR
$CDCl_3$, 365 MHz

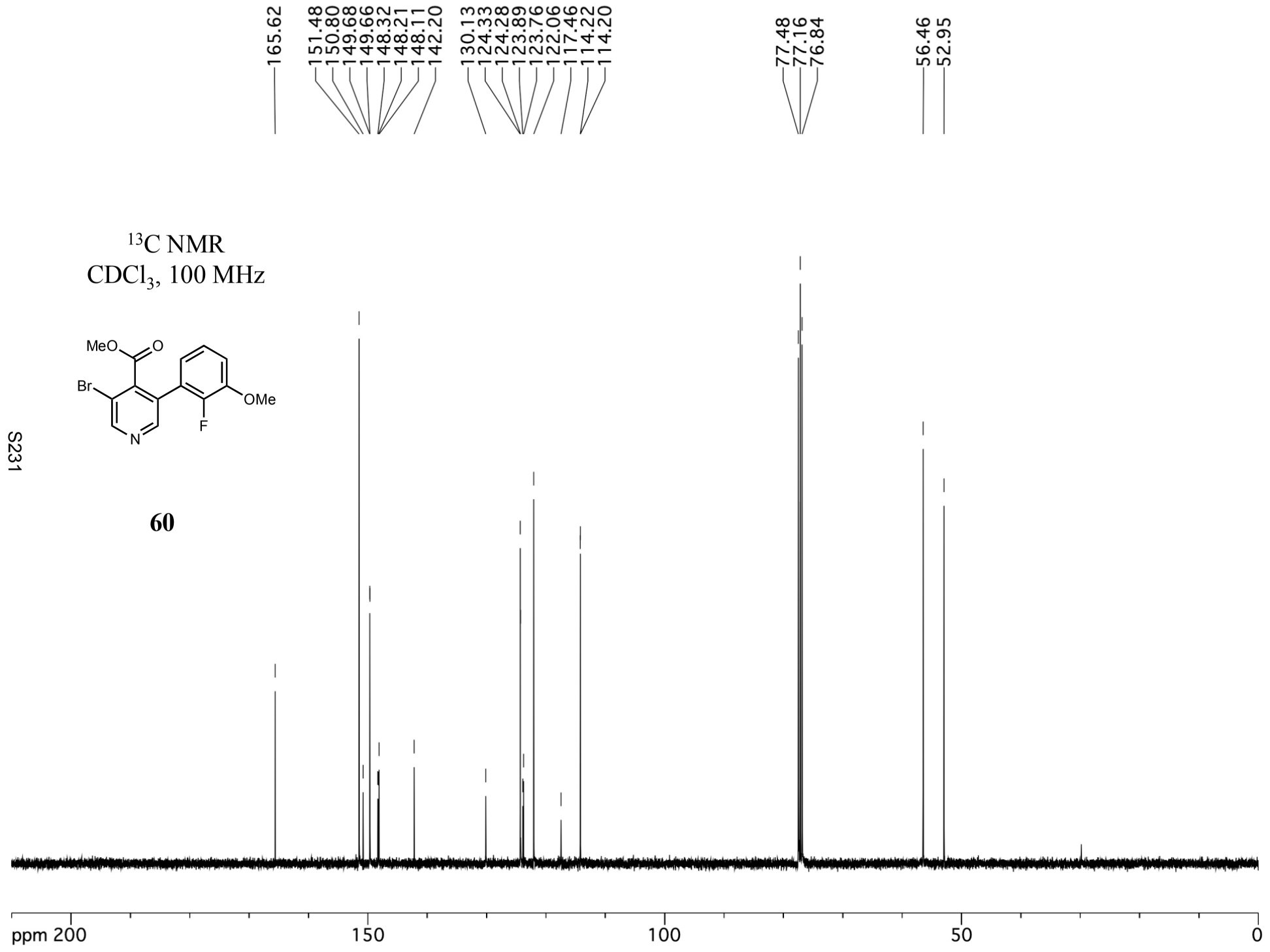


59

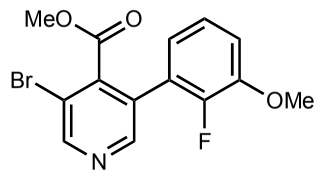


^{1}H NMR
$CDCl_3$, 400 MHz

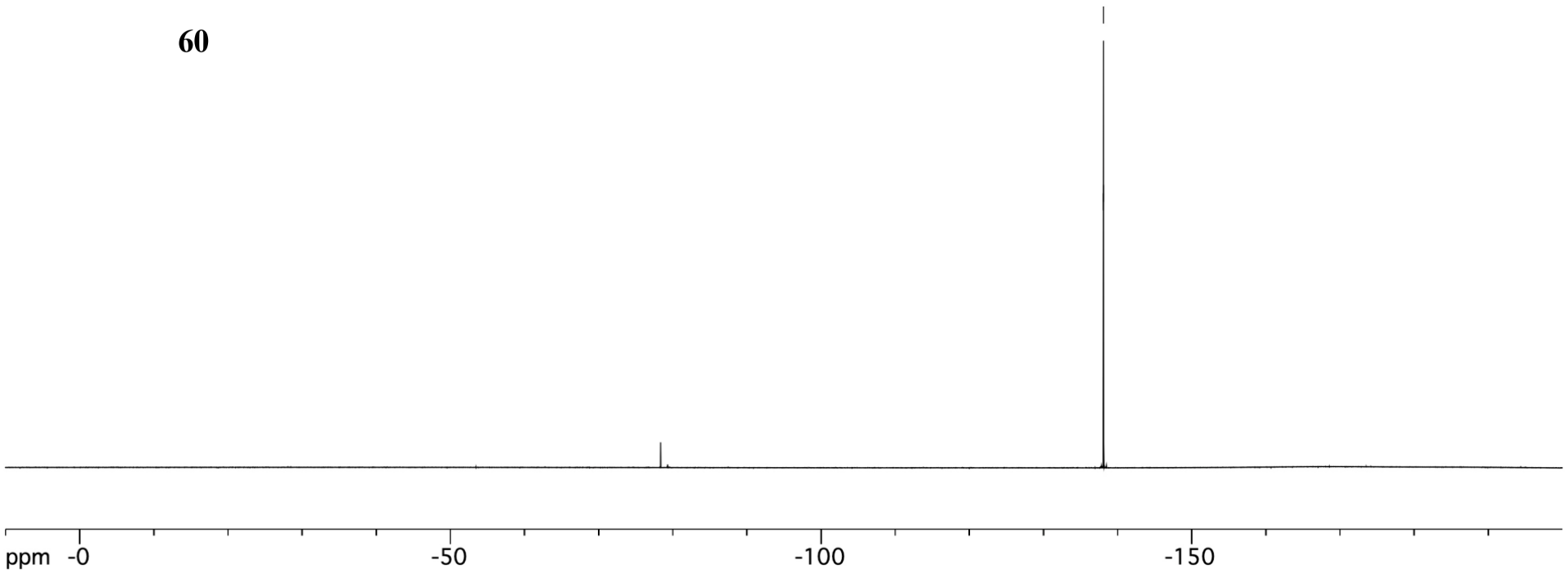
60

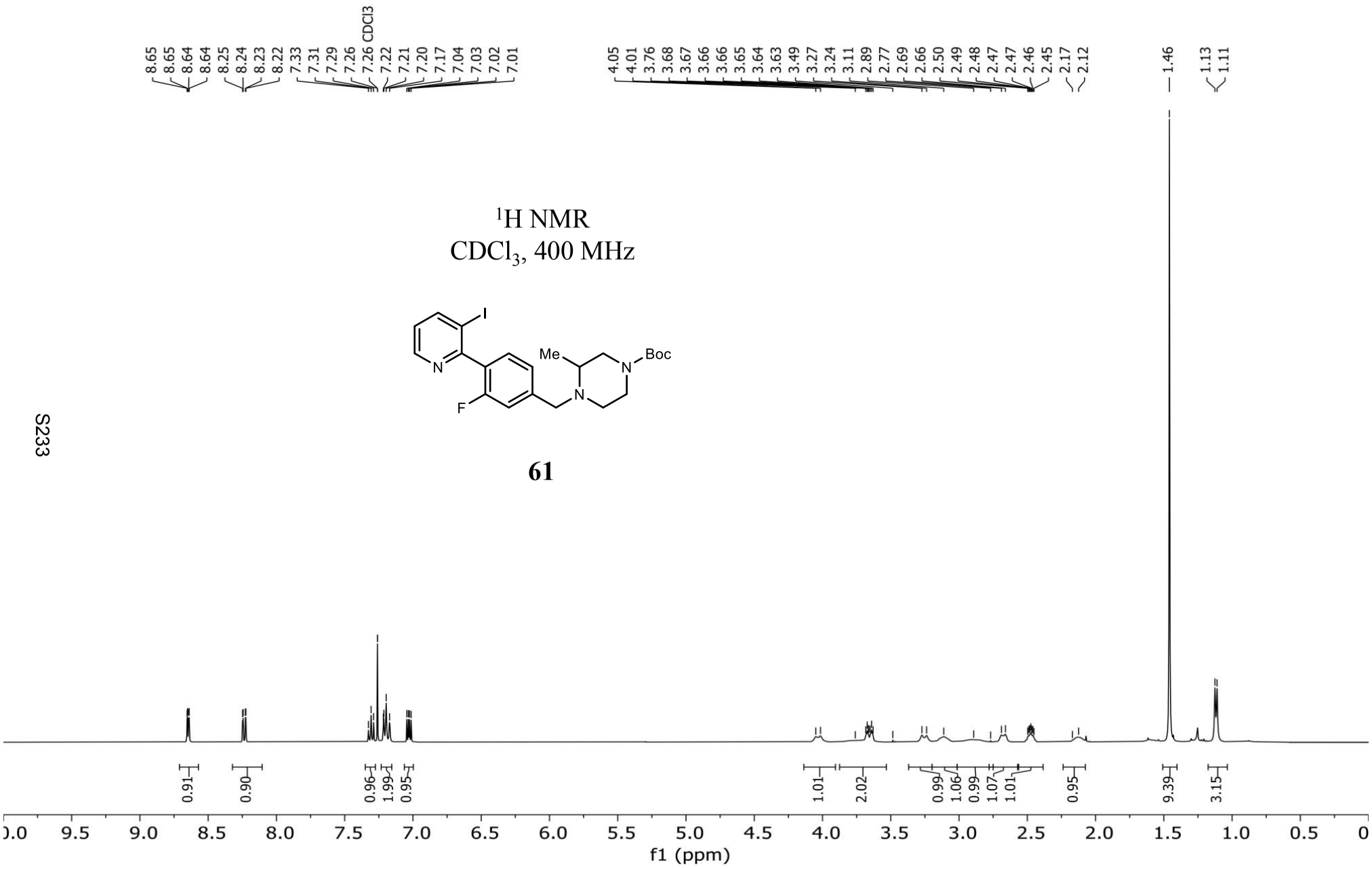

165.62
151.48
150.80
149.68
149.66
148.32
148.21
148.11
142.20
130.13
124.33
124.28
123.89
123.76
122.06
117.46
114.22
114.20
77.48
77.16
76.84
56.46
52.95
^{13}C NMR
$CDCl_3$, 100 MHz
MeO
O
Br
OMe
F
N
60
S231
ppm 200
150
100
50
0

^{19}F NMR
$CDCl_3$, 365 MHz



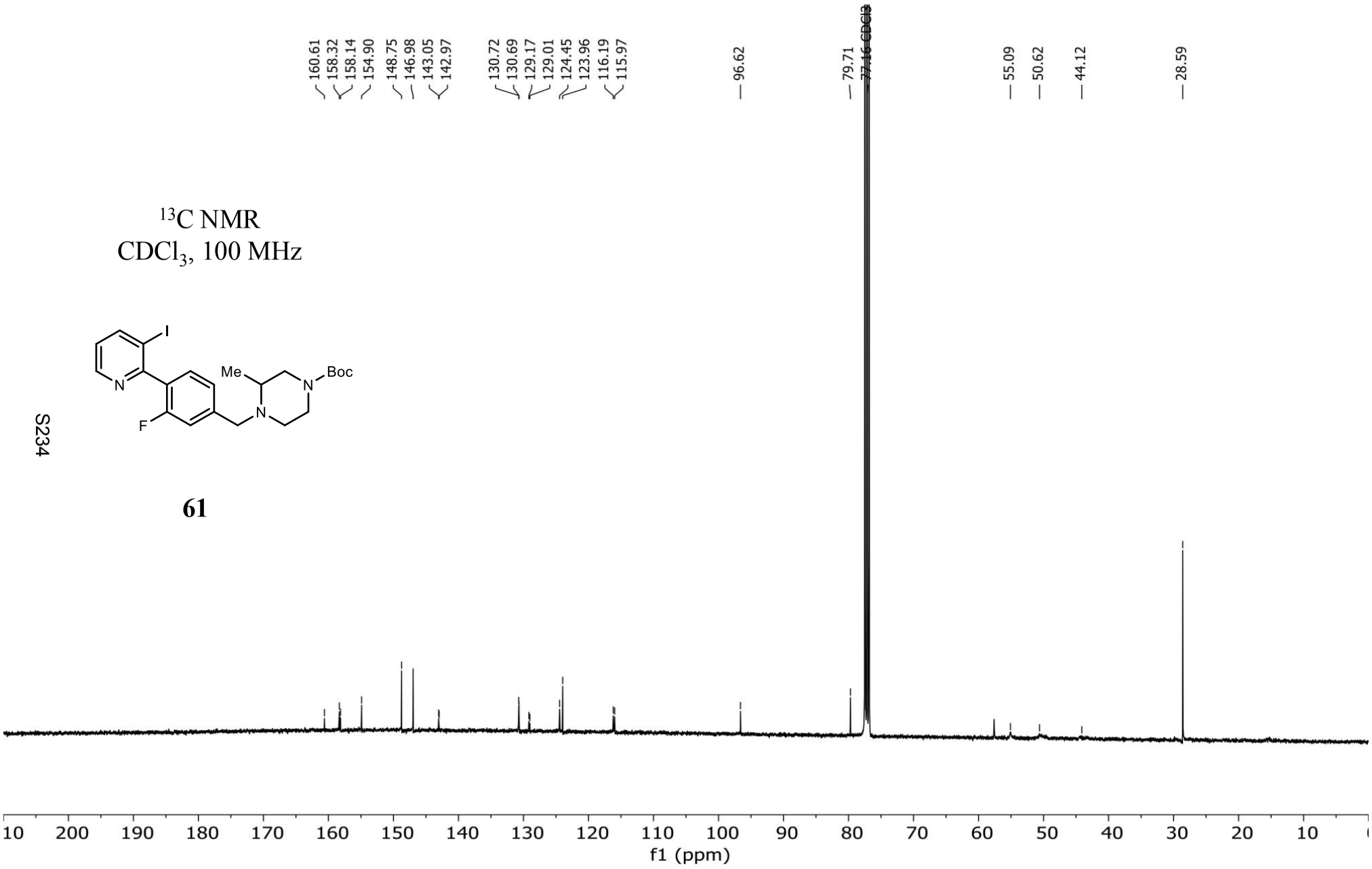
60



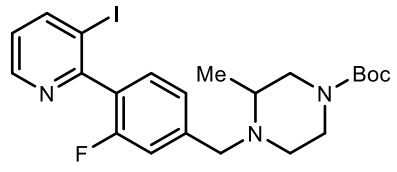


^{1}H NMR
$CDCl_3$, 400 MHz

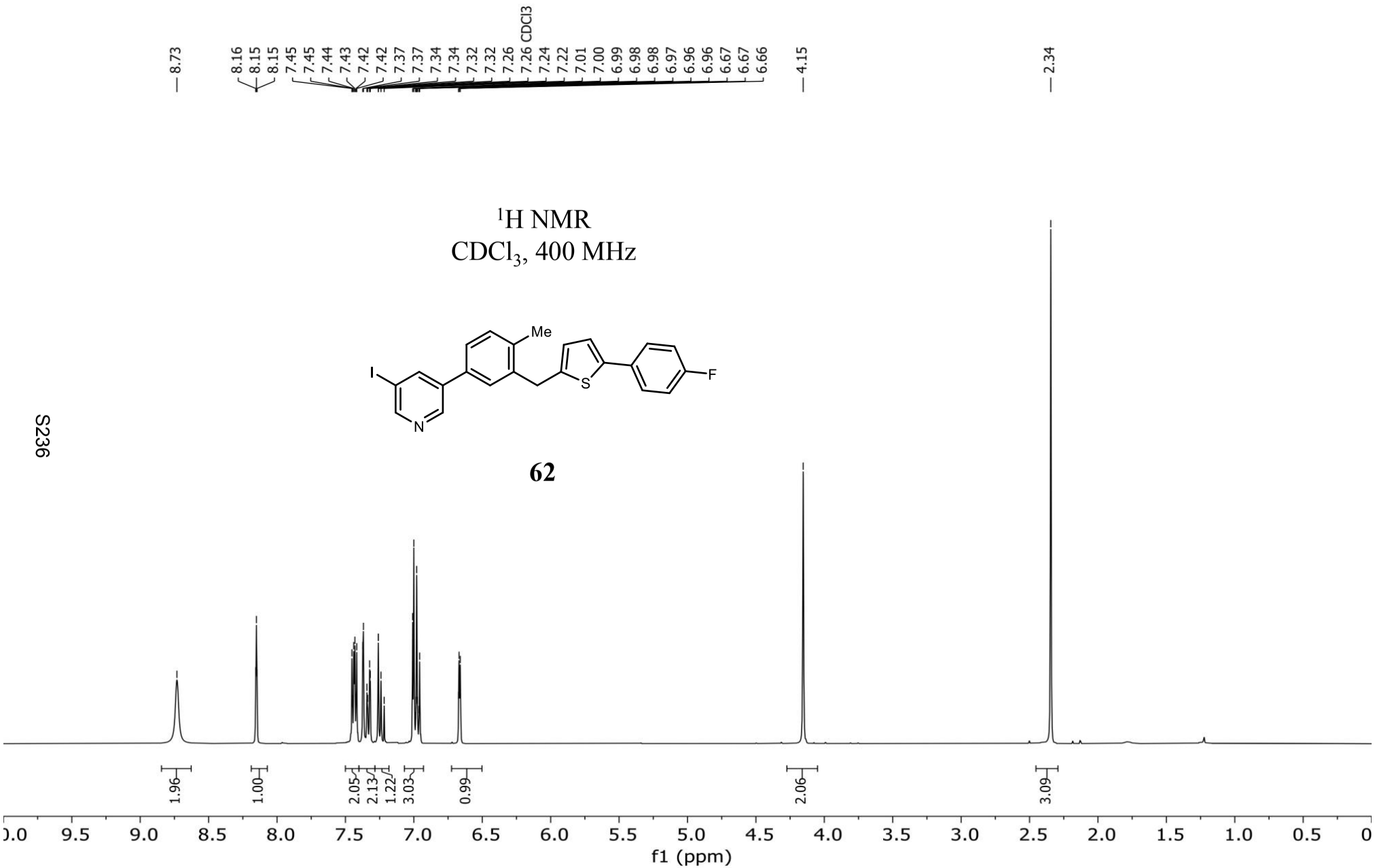
61

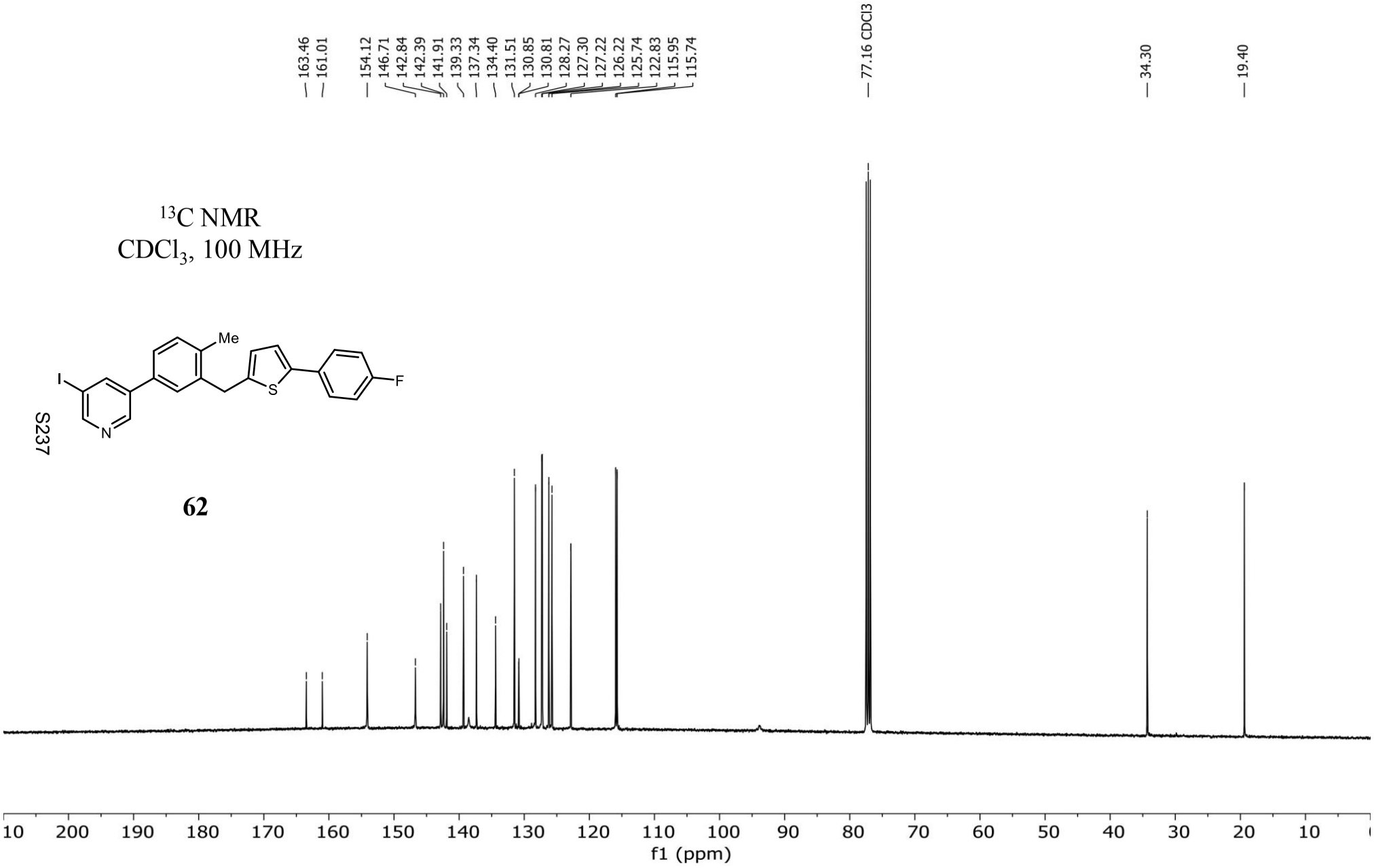

160.61
158.32
158.14
154.90
148.75
146.98
143.05
142.97
130.72
130.69
129.17
129.01
124.45
123.96
116.19
115.97
96.62
79.71
77.16 CDCl3
55.09
50.62
44.12
28.59
13C NMR
CDCl3, 100 MHz
I
N
Me
N
Boc
N
F
61
f1 (ppm)

^{19}F NMR
$CDCl_3$, 365 MHz

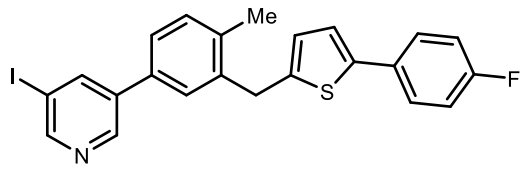


61

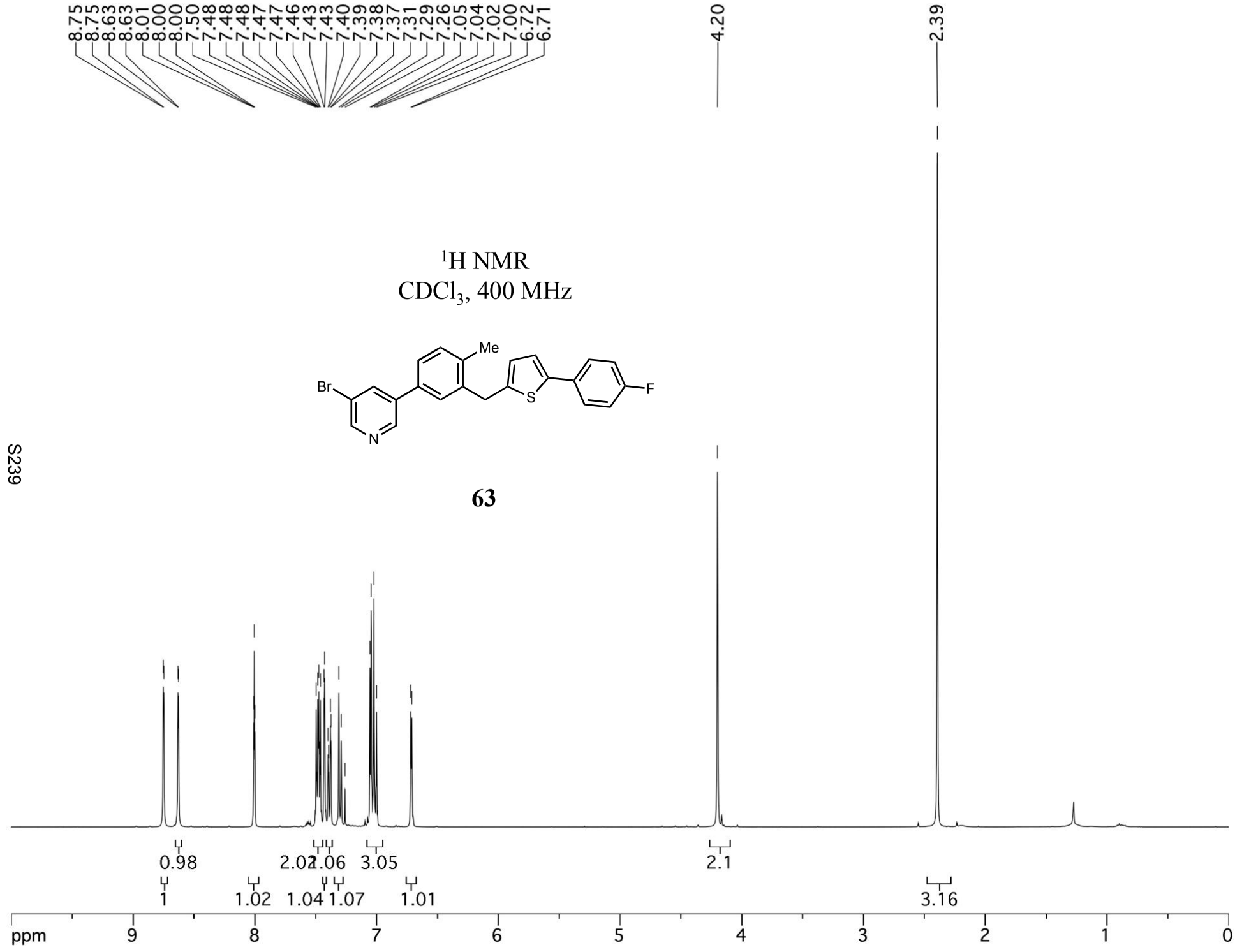

8.73
8.16
8.15
8.15
7.45
7.45
7.44
7.43
7.42
7.42
7.37
7.37
7.34
7.34
7.32
7.32
7.26 CDCl3
7.24
7.22
7.01
7.00
6.99
6.98
6.98
6.97
6.96
6.96
6.67
6.67
6.66
4.15
2.34
1H NMR
CDCl3, 400 MHz
Me
I
S
F
N
62
S236
1.96
1.00
2.05
2.13
1.22
3.03
0.99
2.06
3.09
f1 (ppm)


163.46
161.01
154.12
146.71
142.84
142.39
141.91
139.33
137.34
134.40
131.51
130.85
130.81
128.27
127.30
127.22
126.22
125.74
122.83
115.95
115.74
77.16 CDCl3
34.30
19.40
13C NMR
CDCl3, 100 MHz
Me
I
S
F
N
62
f1 (ppm)

^{19}F NMR
$CDCl_3$, 365 MHz

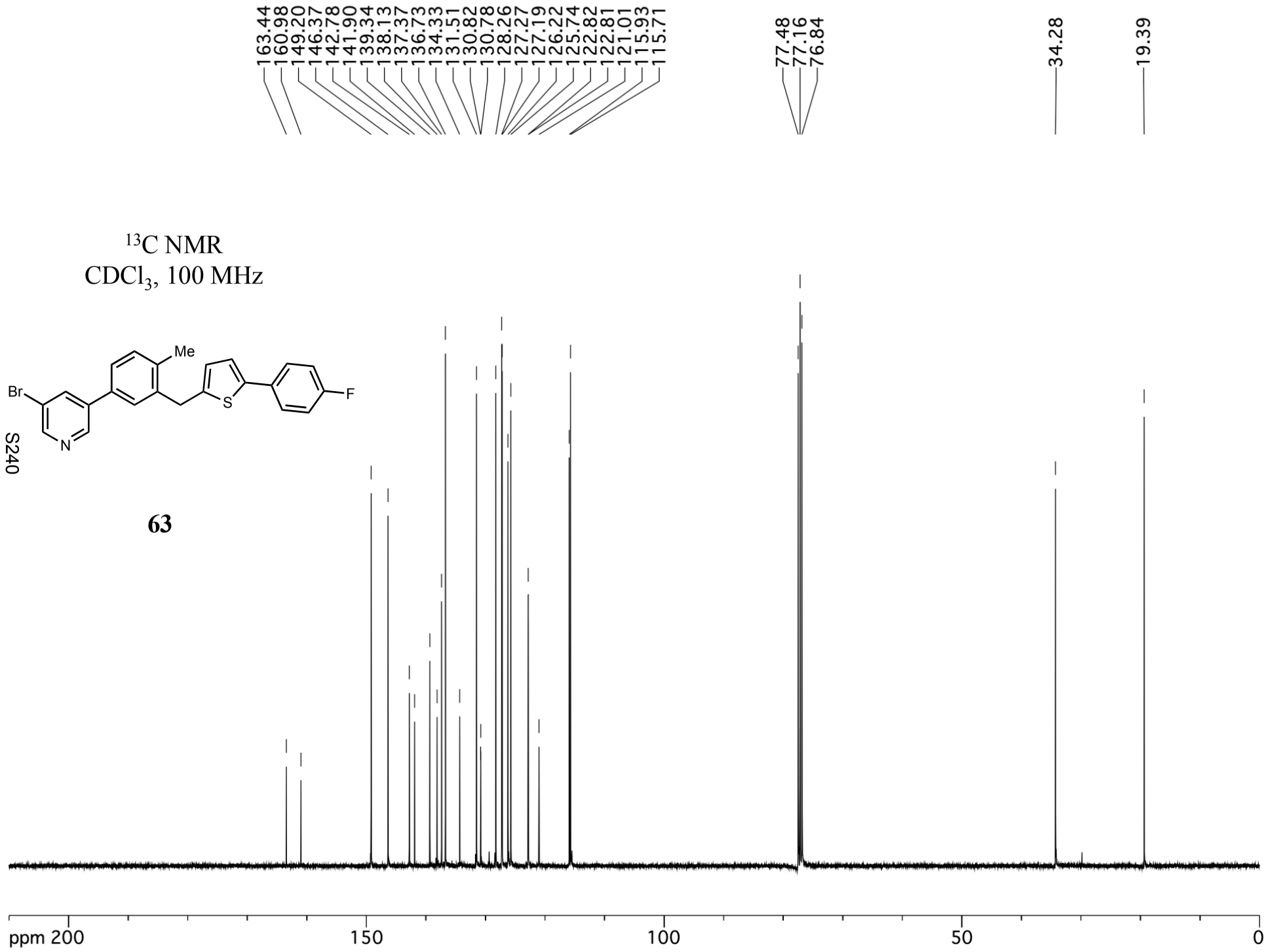


62

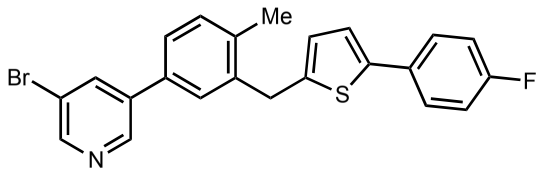


^{1}H NMR
$CDCl_3$, 400 MHz

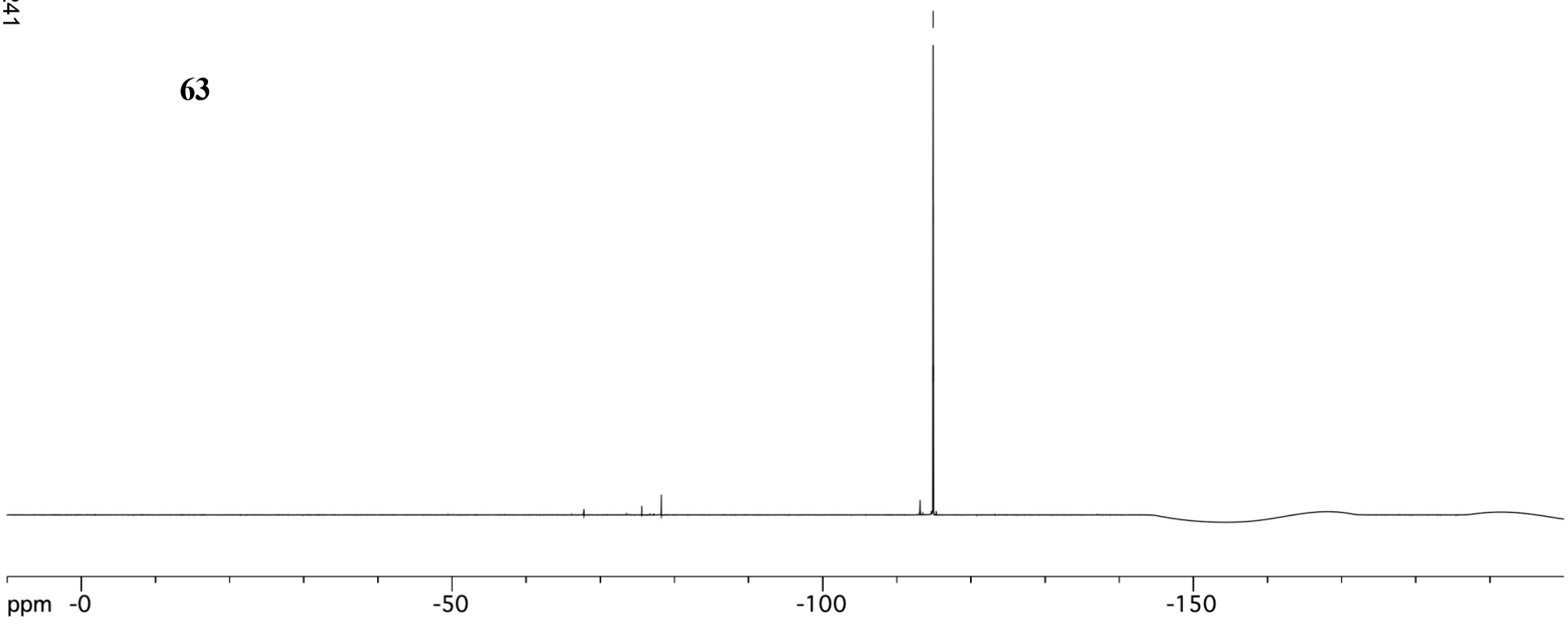
63

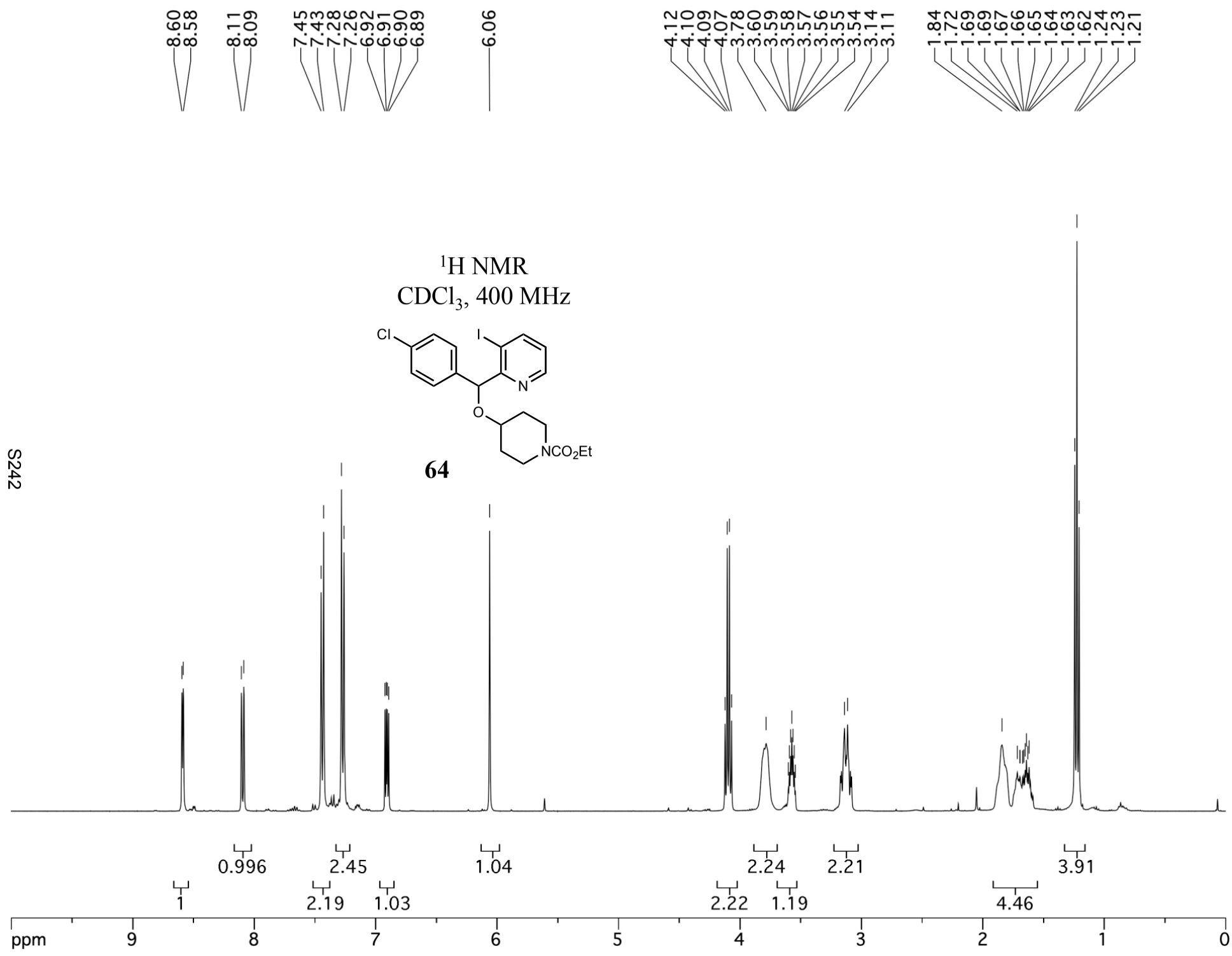

163.44
160.98
149.20
146.37
142.78
141.90
139.34
138.13
137.37
136.73
134.33
131.51
130.82
130.78
128.26
127.27
127.19
126.22
125.74
122.82
122.81
121.01
115.93
115.71
77.48
77.16
76.84
34.28
19.39
^{13}C NMR
$CDCl_3$, 100 MHz
Me
Br
S
F
N
S240
63
ppm 200
150
100
50
0

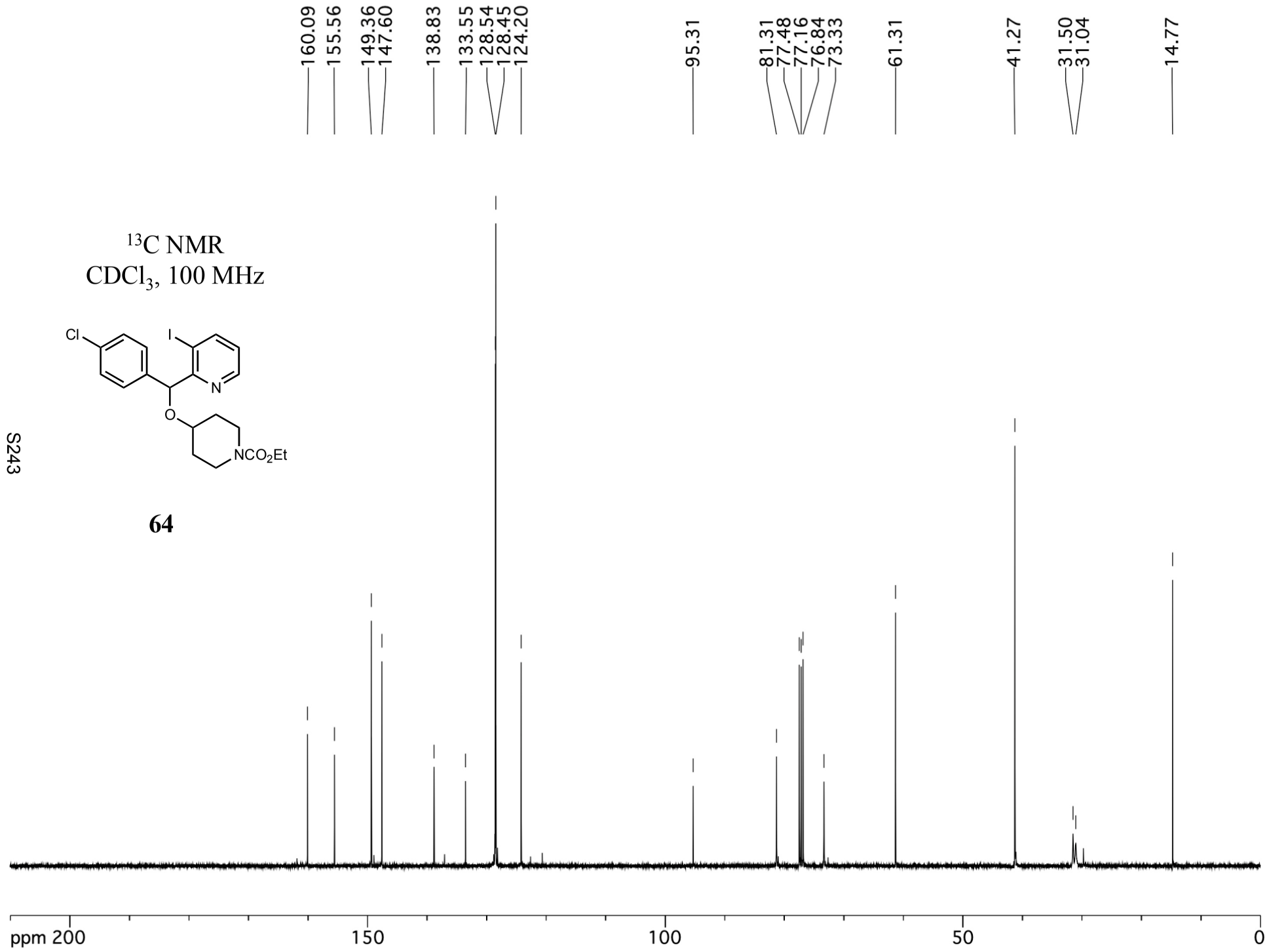
^{19}F NMR
$CDCl_3$, 365 MHz



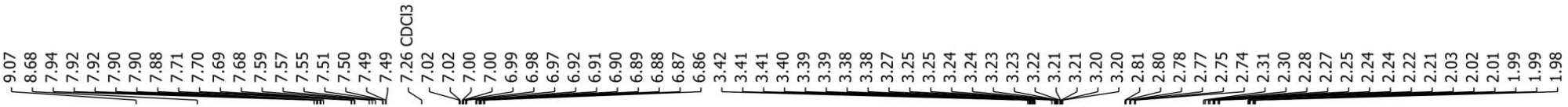
63



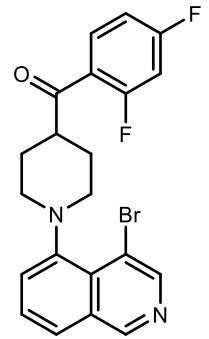

8.60
8.58
8.11
8.09
7.45
7.43
7.28
7.26
6.92
6.91
6.90
6.89
6.06
4.12
4.10
4.09
4.07
3.78
3.60
3.59
3.58
3.57
3.56
3.55
3.54
3.14
3.11
1.84
1.72
1.69
1.69
1.67
1.66
1.65
1.64
1.63
1.62
1.24
1.23
1.21
^{1}H NMR
$CDCl_3$, 400 MHz
Cl
I
N
O
NCO_2Et
64
S242
0.996
2.45
1.04
2.24
2.21
3.91
1
2.19
1.03
2.22
1.19
4.46
ppm
9
8
7
6
5
4
3
2
1
0


160.09
155.56
149.36
147.60
138.83
133.55
128.54
128.45
124.20
95.31
81.31
77.48
77.16
76.84
73.33
61.31
41.27
31.50
31.04
14.77
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
I
N
O
NCO_2Et
S243
ppm 200
150
100
50
0

64



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



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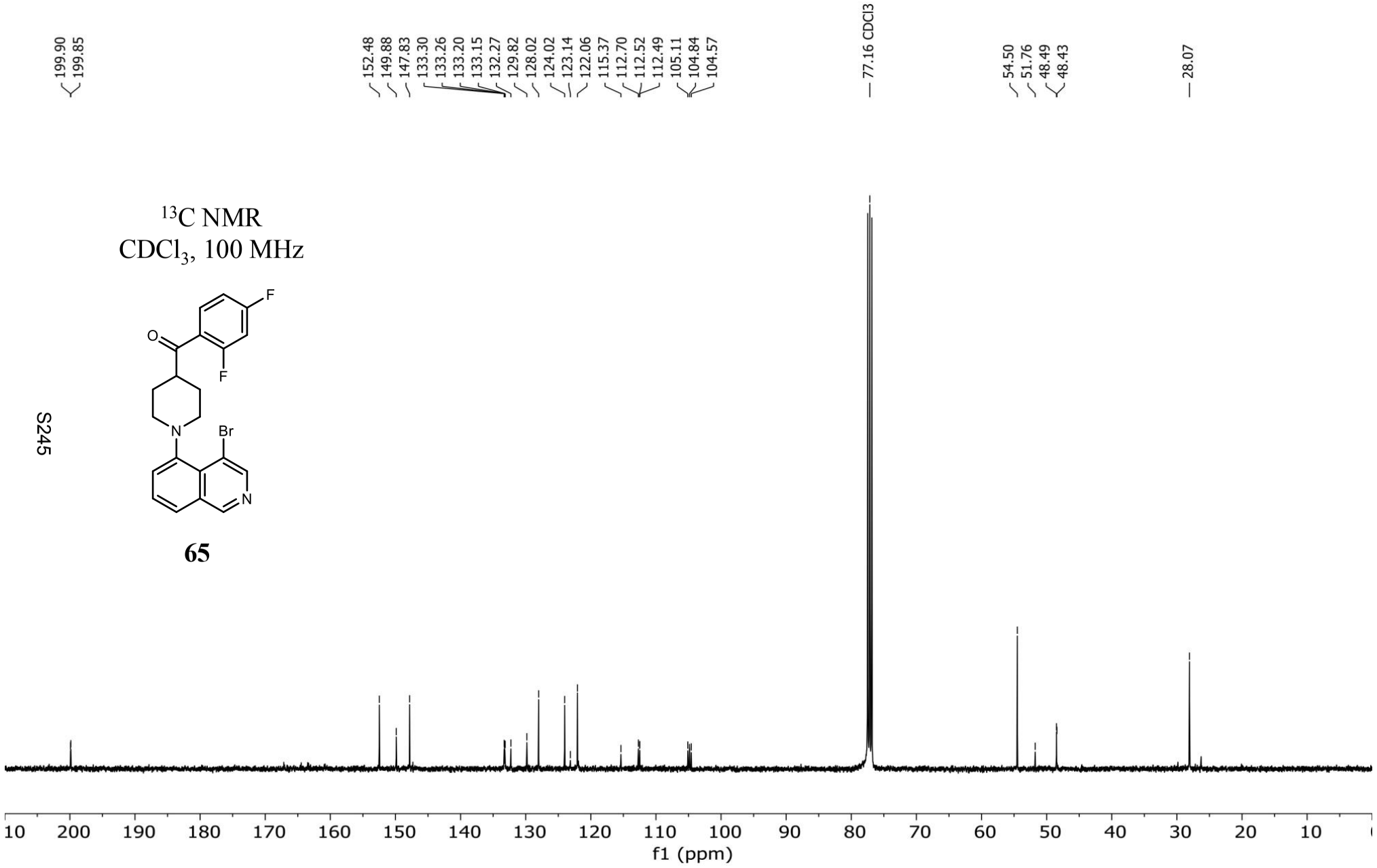
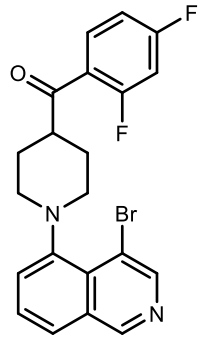

199.90
199.85
152.48
149.88
147.83
133.30
133.26
133.20
133.15
132.27
129.82
128.02
124.02
123.14
122.06
115.37
112.70
112.52
112.49
105.11
104.84
104.57
77.16 CDCl3
54.50
51.76
48.49
48.43
28.07
13C NMR
CDCl3, 100 MHz
F
O
F
N
Br
N
65
f1 (ppm)

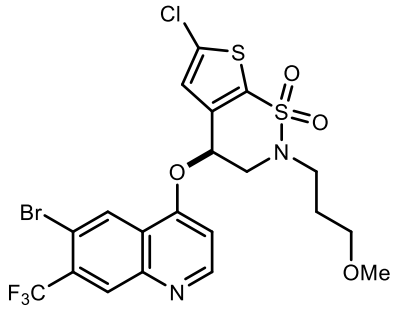
^{19}F NMR

$CDCl_3$, 365 MHz



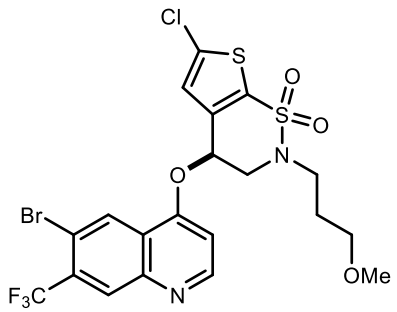
65

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



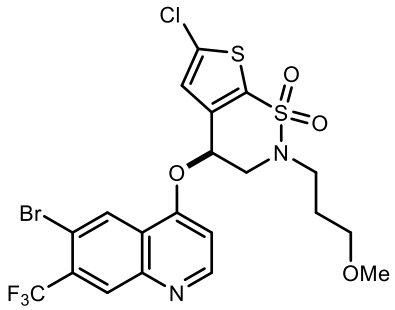
66

^{13}C NMR
$CDCl_3$, 100 MHz



66

^{19}F NMR
$CDCl_3$, 365 MHz



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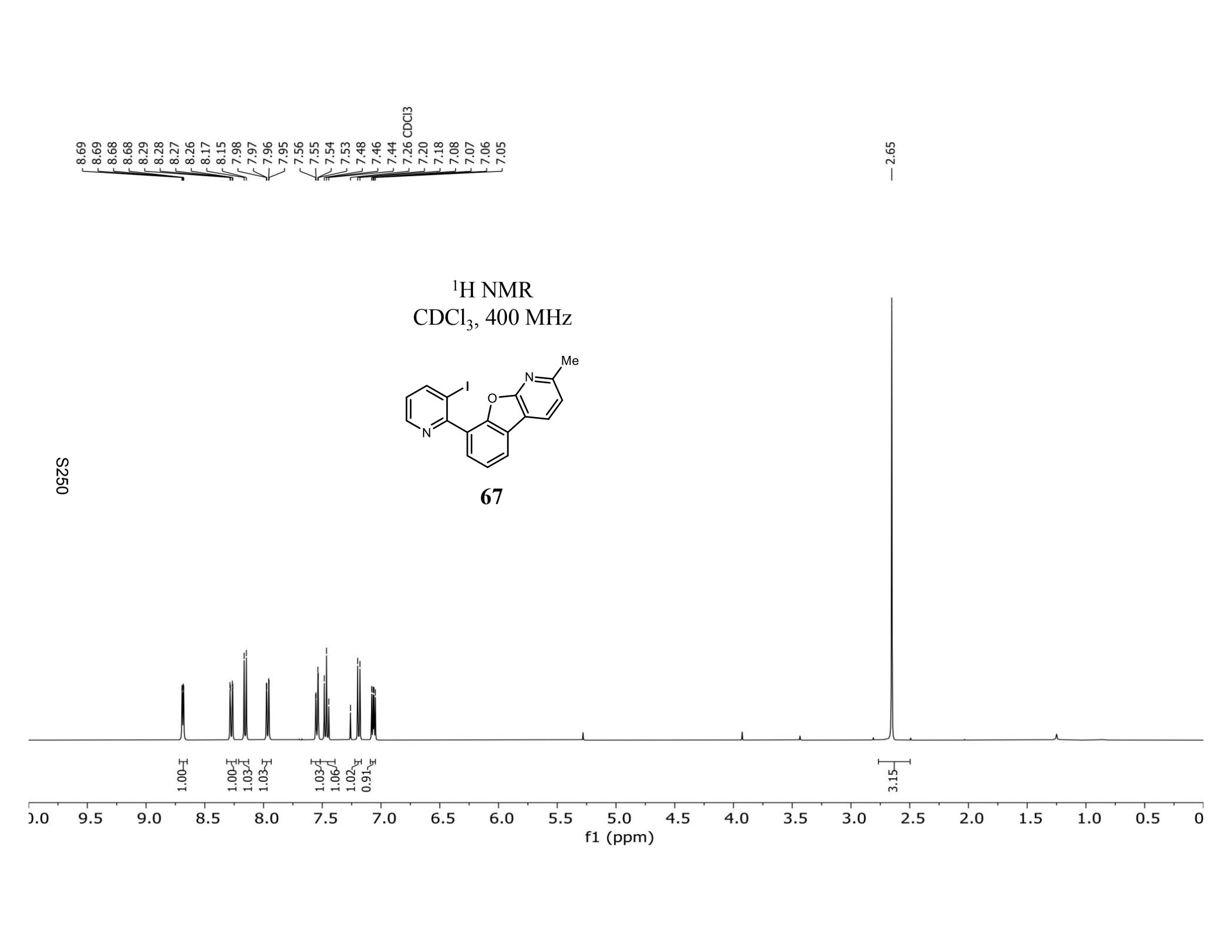
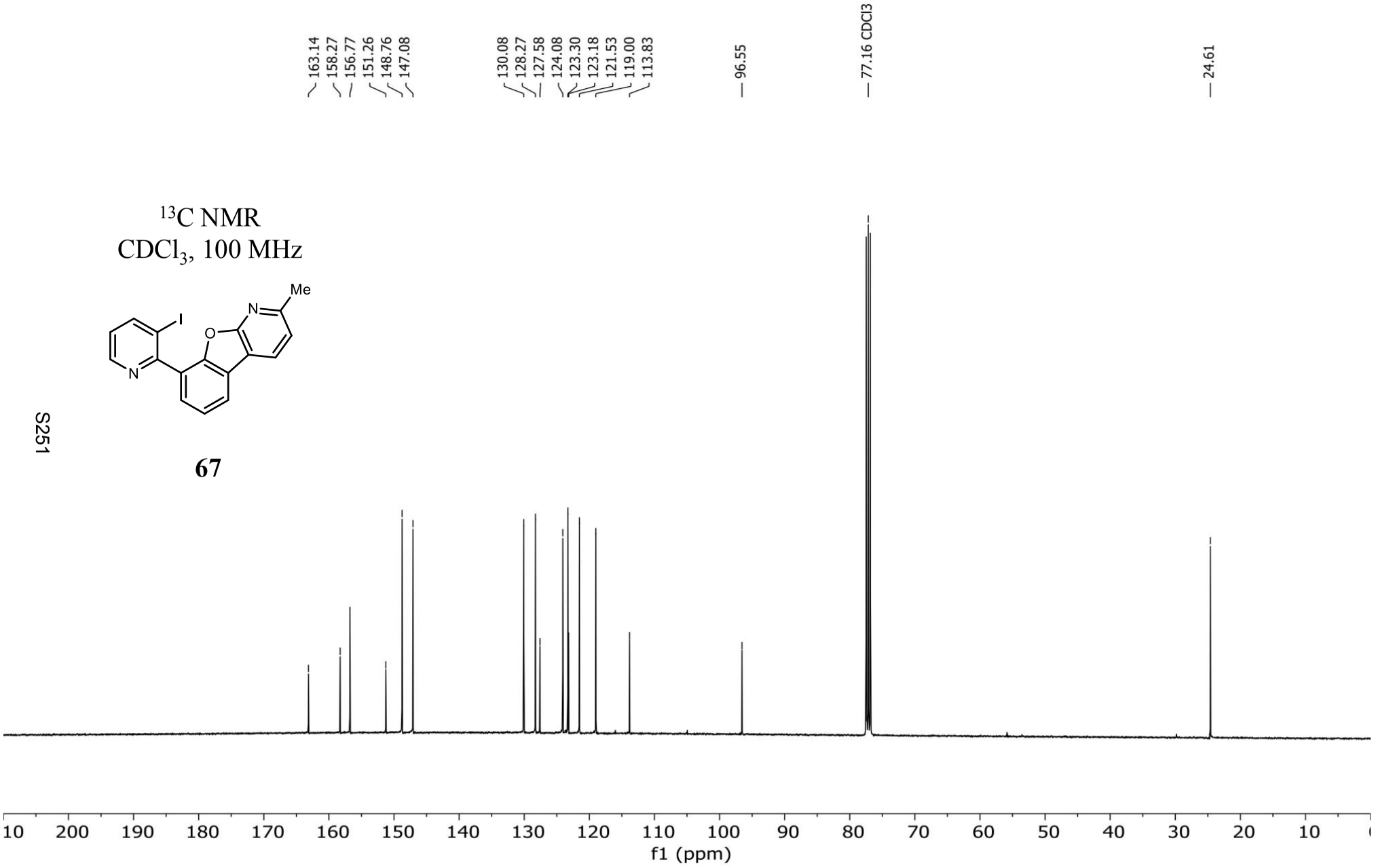
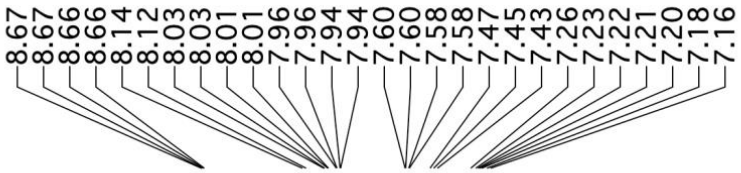
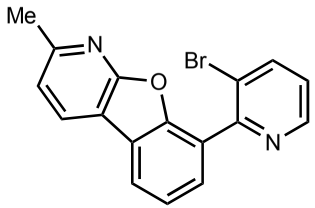

8.69
8.69
8.68
8.68
8.29
8.28
8.27
8.26
8.17
8.15
7.98
7.97
7.96
7.95
7.56
7.55
7.54
7.53
7.48
7.46
7.44
7.26 CDCl3
7.20
7.18
7.08
7.07
7.06
7.05
2.65
1H NMR
CDCl3, 400 MHz
Me
N
I
O
N
67
S250
1.00
1.00
1.03
1.03
1.03
1.06
1.02
0.91
3.15
f1 (ppm)


163.14
158.27
156.77
151.26
148.76
147.08
130.08
128.27
127.58
124.08
123.30
123.18
121.53
119.00
113.83
96.55
77.16 CDCl3
24.61
^{13}C NMR
$CDCl_3$, 100 MHz
Me
N
I
O
N
67
S251
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

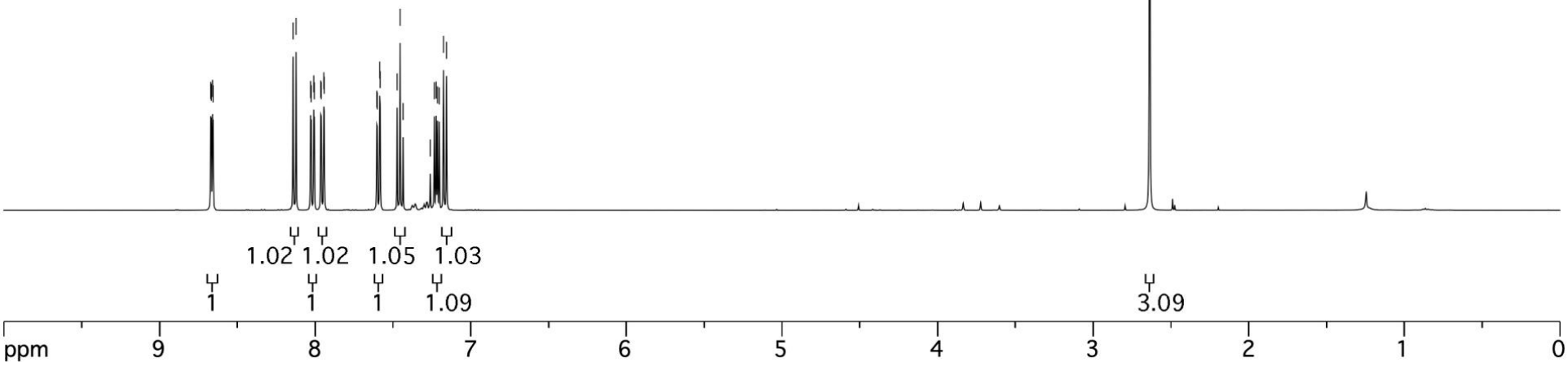


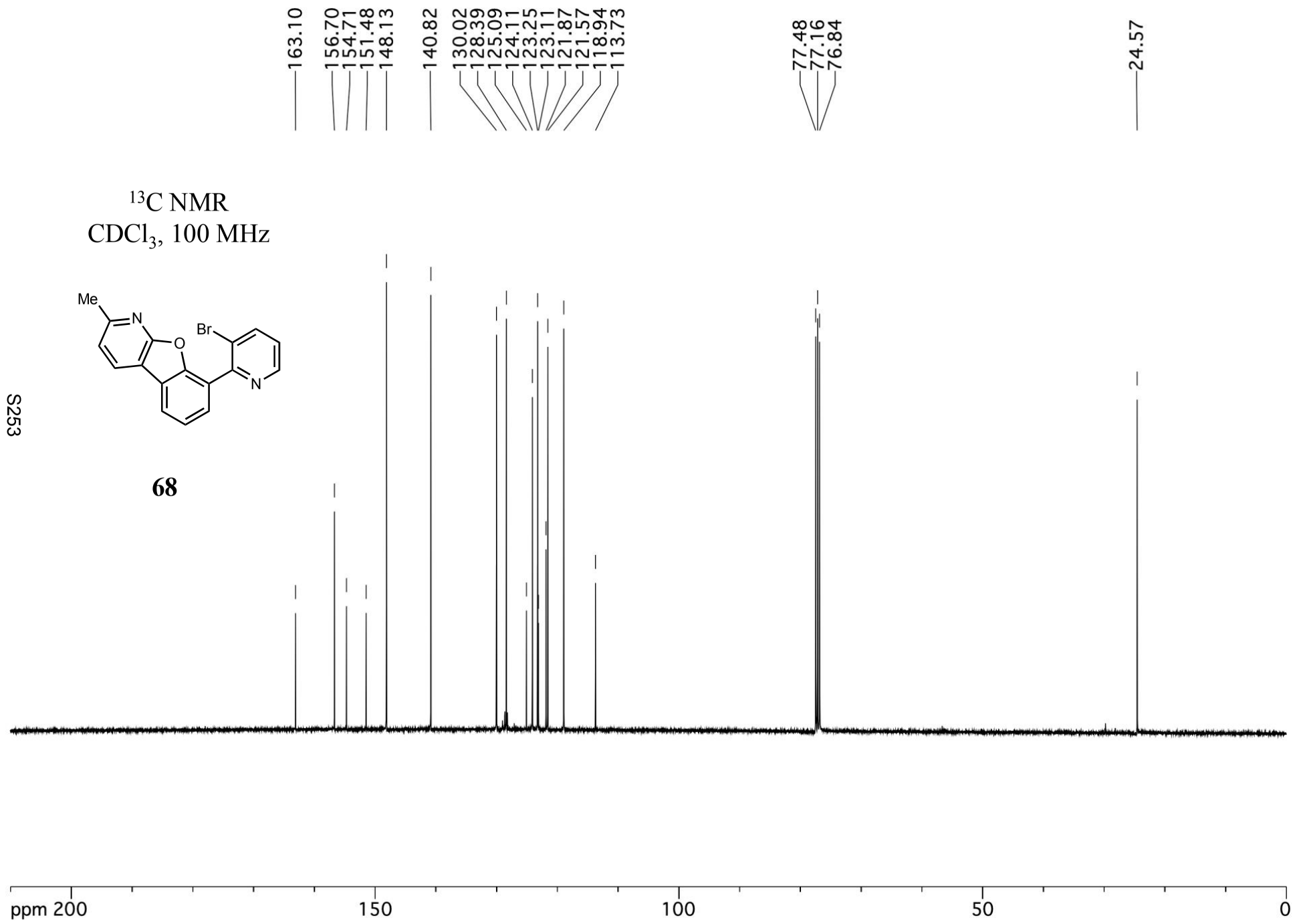
^{1}H NMR
$CDCl_3$, 400 MHz



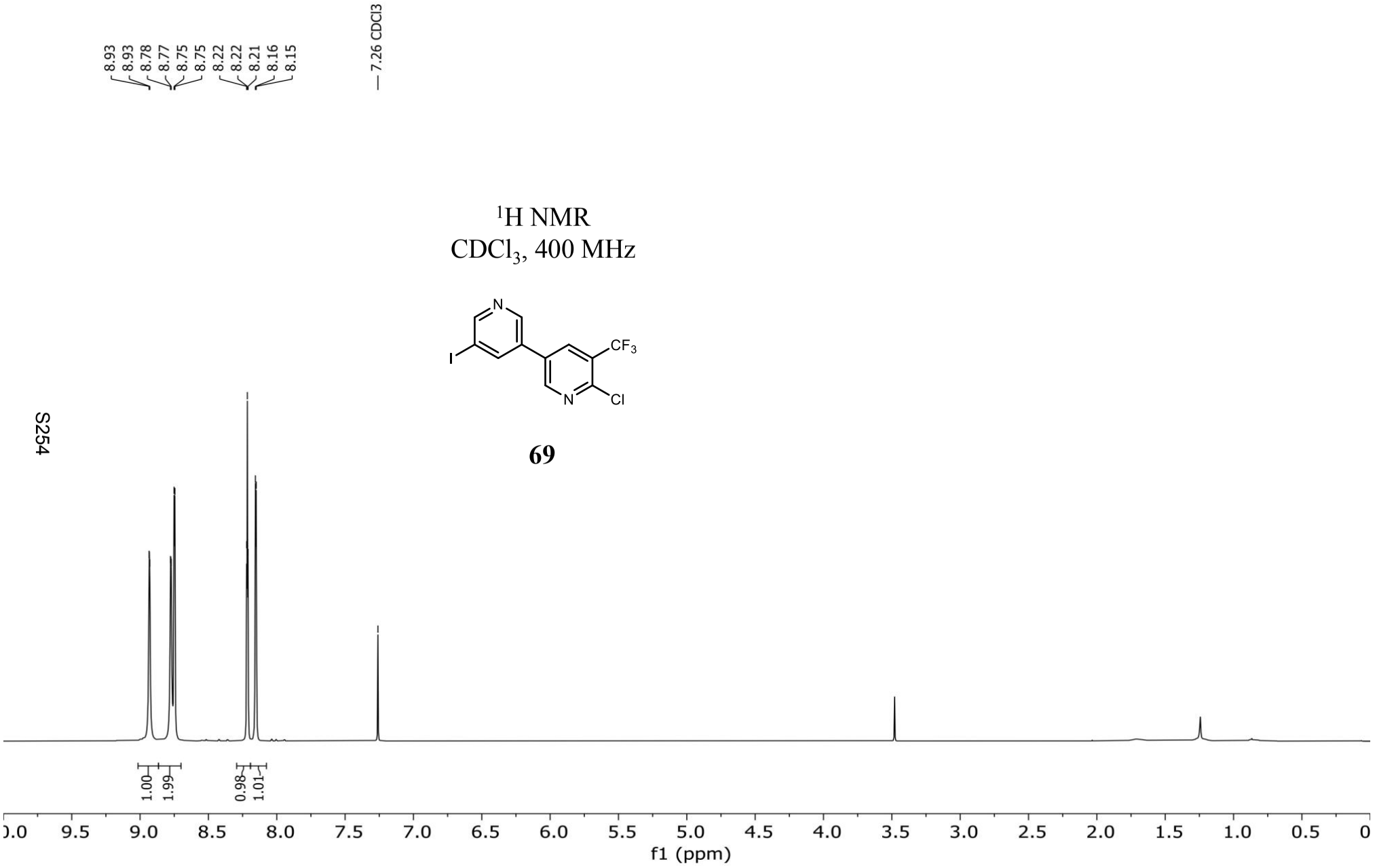
68

S252



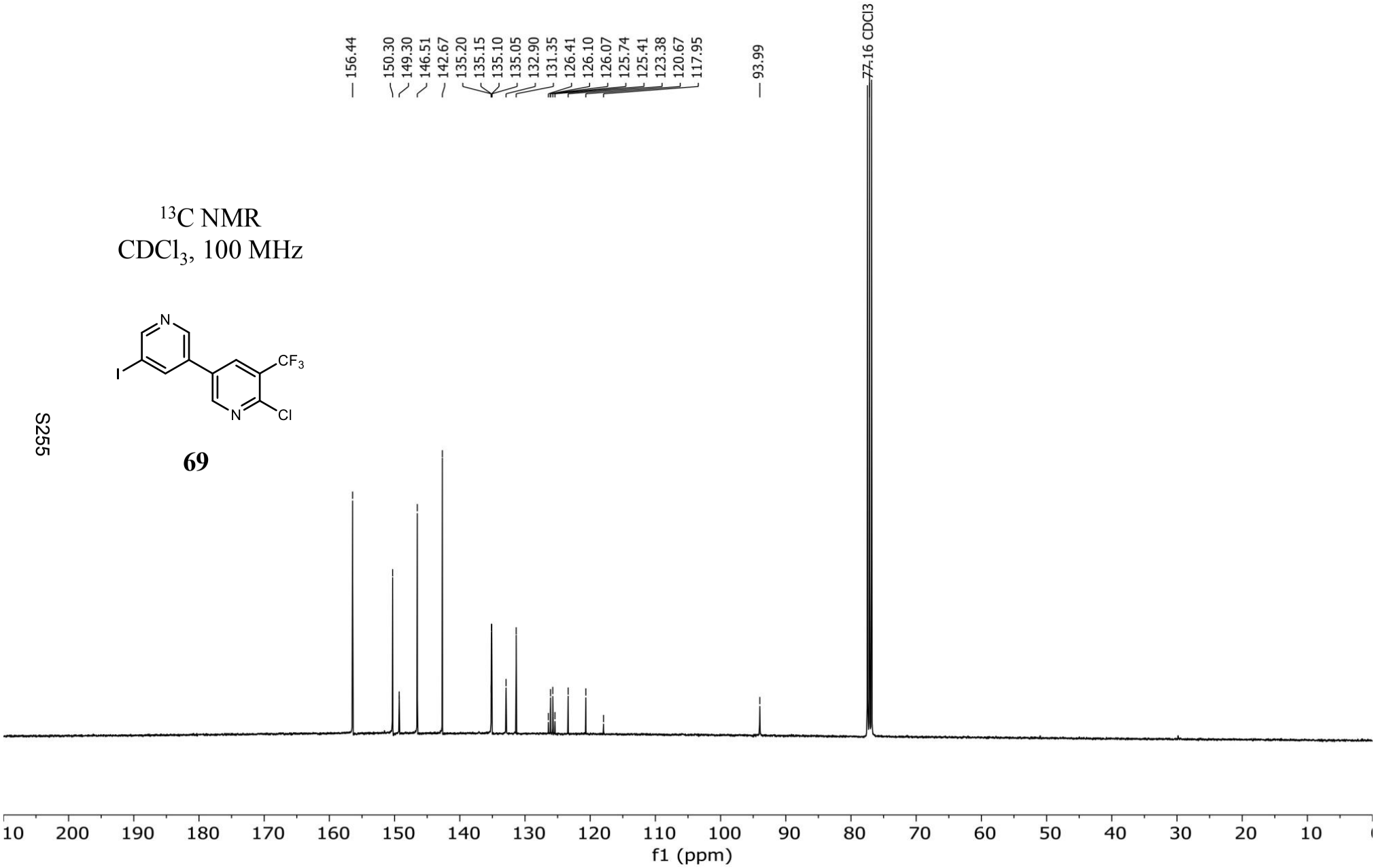

163.10
156.70
154.71
151.48
148.13
140.82
130.02
128.39
125.09
124.11
123.25
123.11
121.87
121.57
118.94
113.73
77.48
77.16
76.84
24.57
^{13}C NMR
$CDCl_3$, 100 MHz
Me
N
O
Br
N
S253
ppm 200
150
100
50
0

68

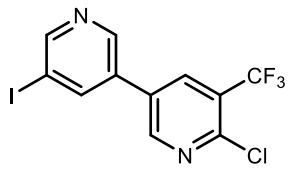


^{1}H NMR
$CDCl_3$, 400 MHz

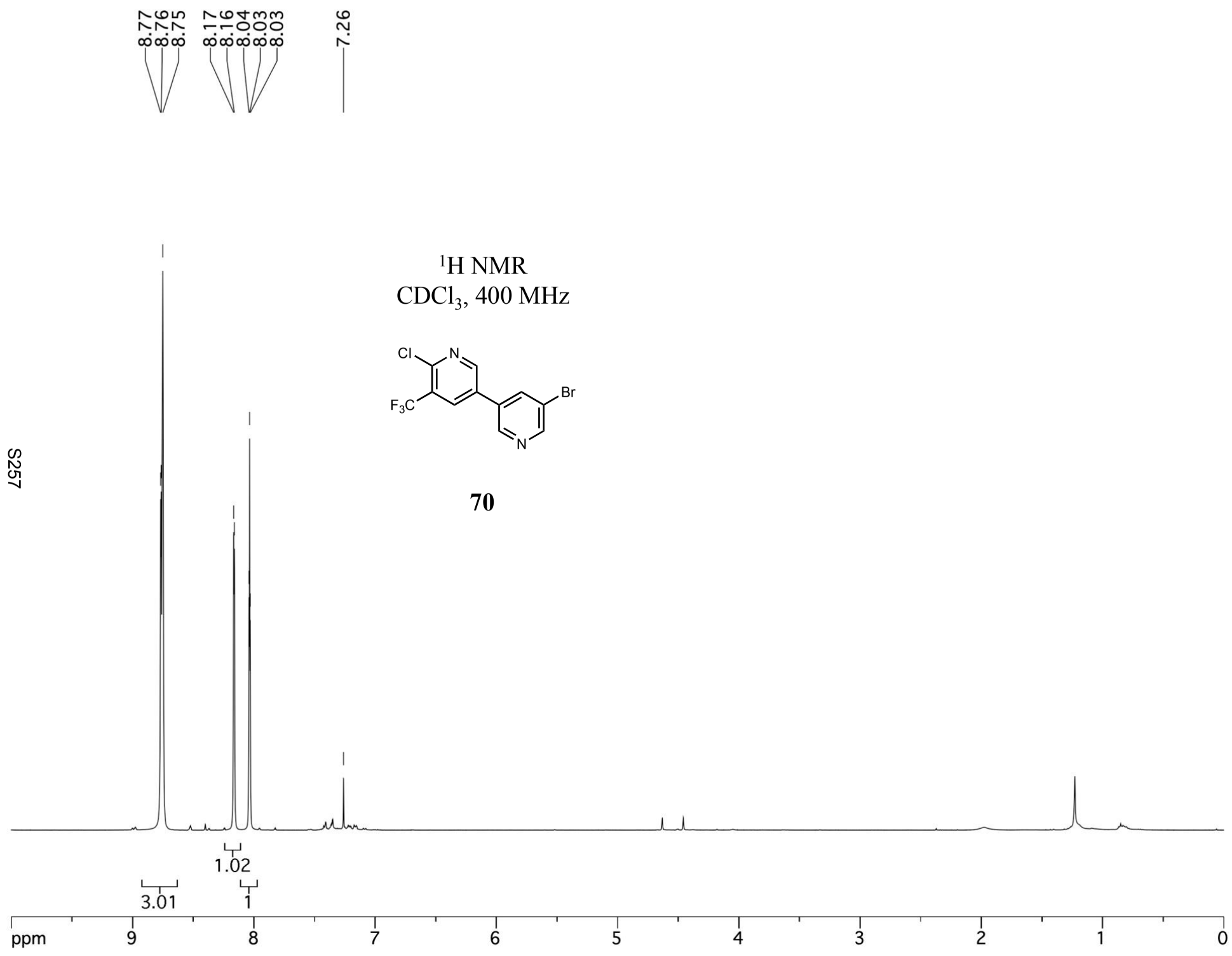
69

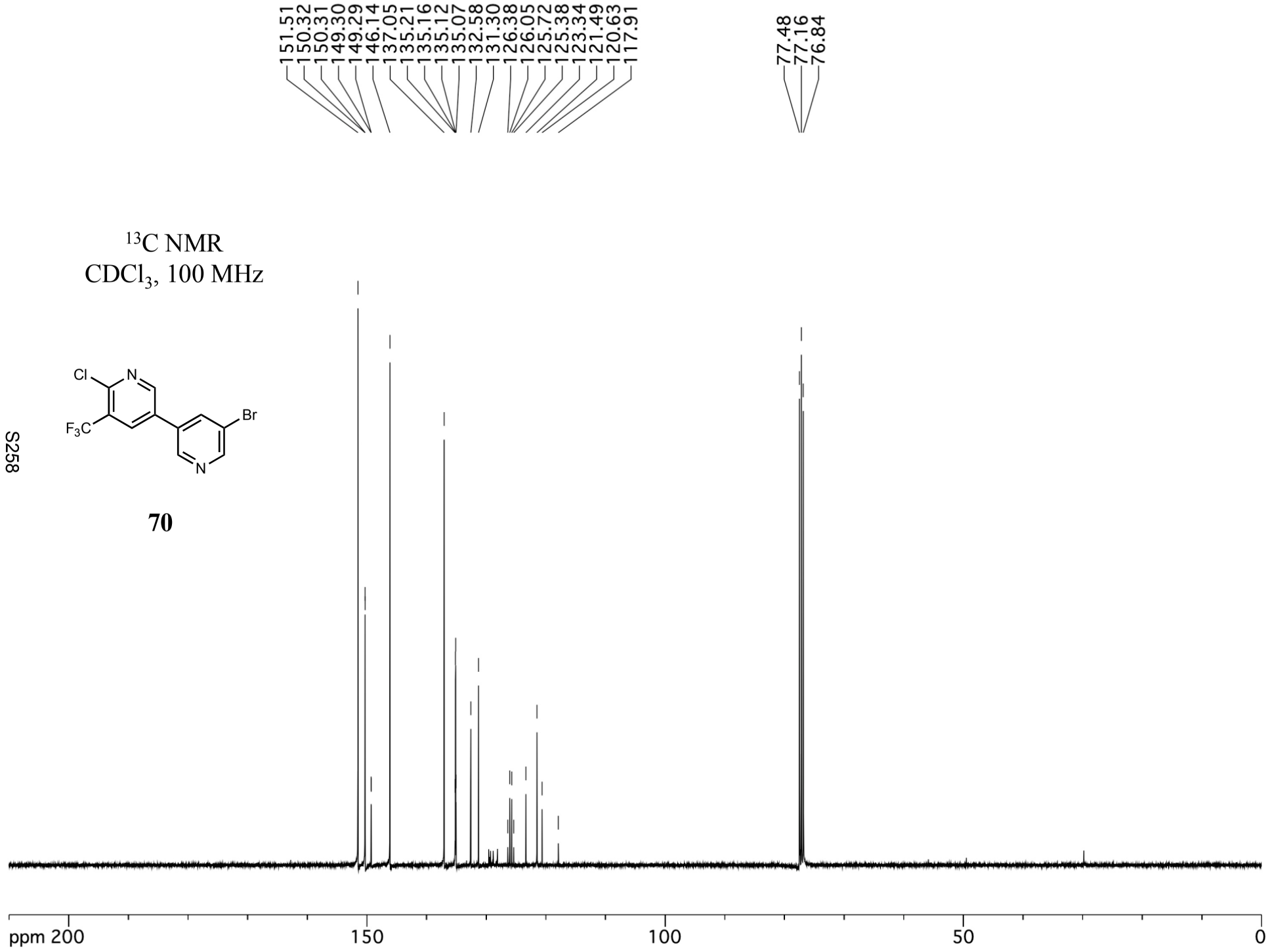

156.44
150.30
149.30
146.51
142.67
135.20
135.15
135.10
135.05
132.90
131.35
126.41
126.10
126.07
125.74
125.41
123.38
120.67
117.95
93.99
77.16 CDCl3
^{13}C NMR
$CDCl_3$, 100 MHz
N
I
CF_3
N
Cl
69
f1 (ppm)

^{19}F NMR
$CDCl_3$, 365 MHz

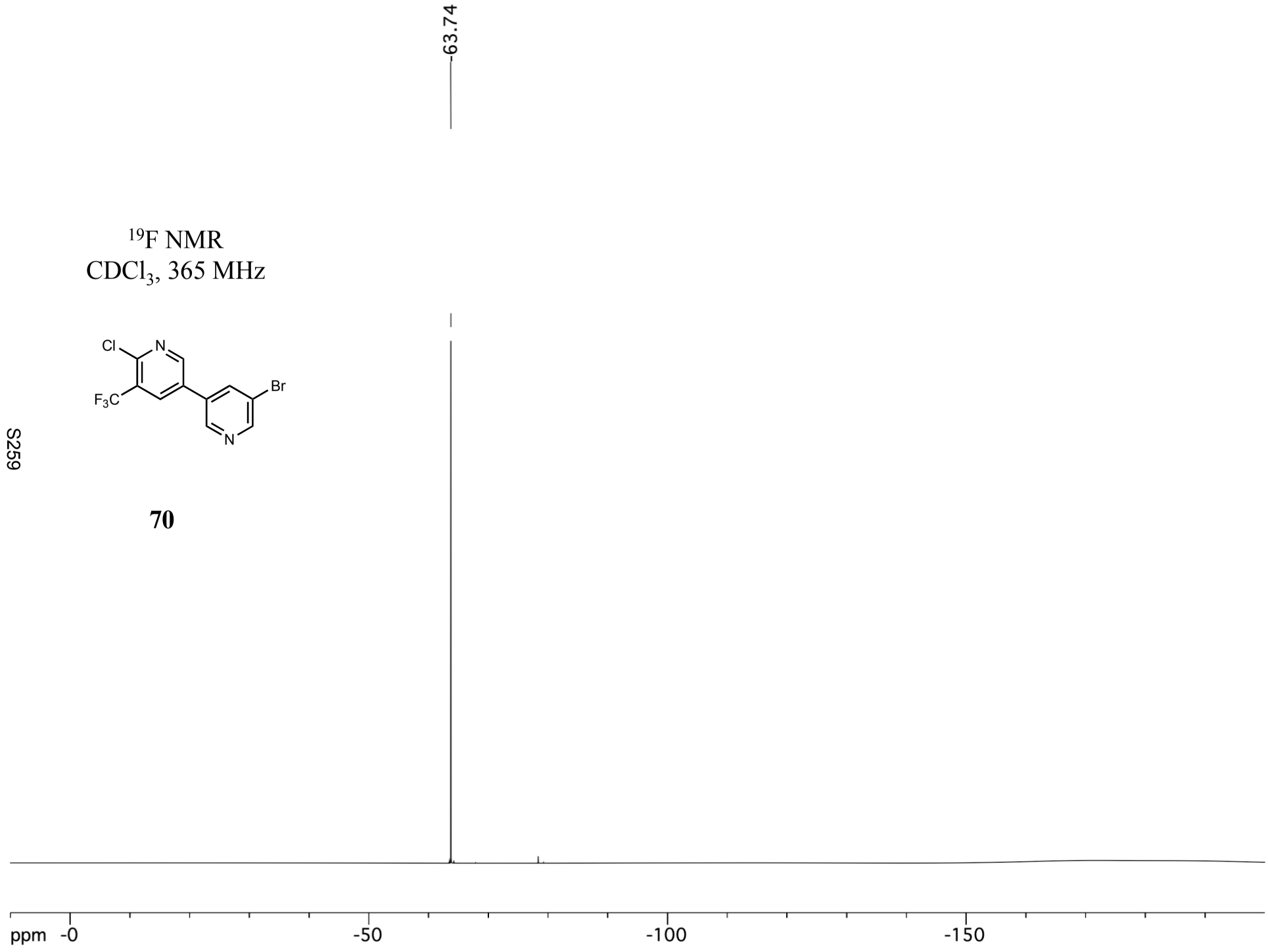


69


8.77
8.76
8.75
8.17
8.16
8.04
8.03
8.03
7.26
1H NMR
CDCl3, 400 MHz
Cl
N
F3C
Br
N
70
S257
1.02
3.01
1
ppm
9
8
7
6
5
4
3
2
1
0


151.51
150.32
150.31
149.30
149.29
146.14
137.05
135.21
135.16
135.12
135.07
132.58
131.30
126.38
126.05
125.72
125.38
123.34
121.49
120.63
117.91
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
N
F_3C
Br
N
S258
ppm 200
150
100
50
0

70



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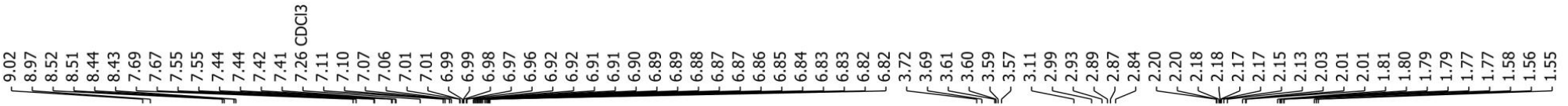
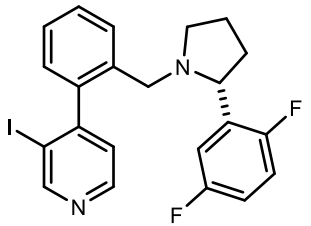
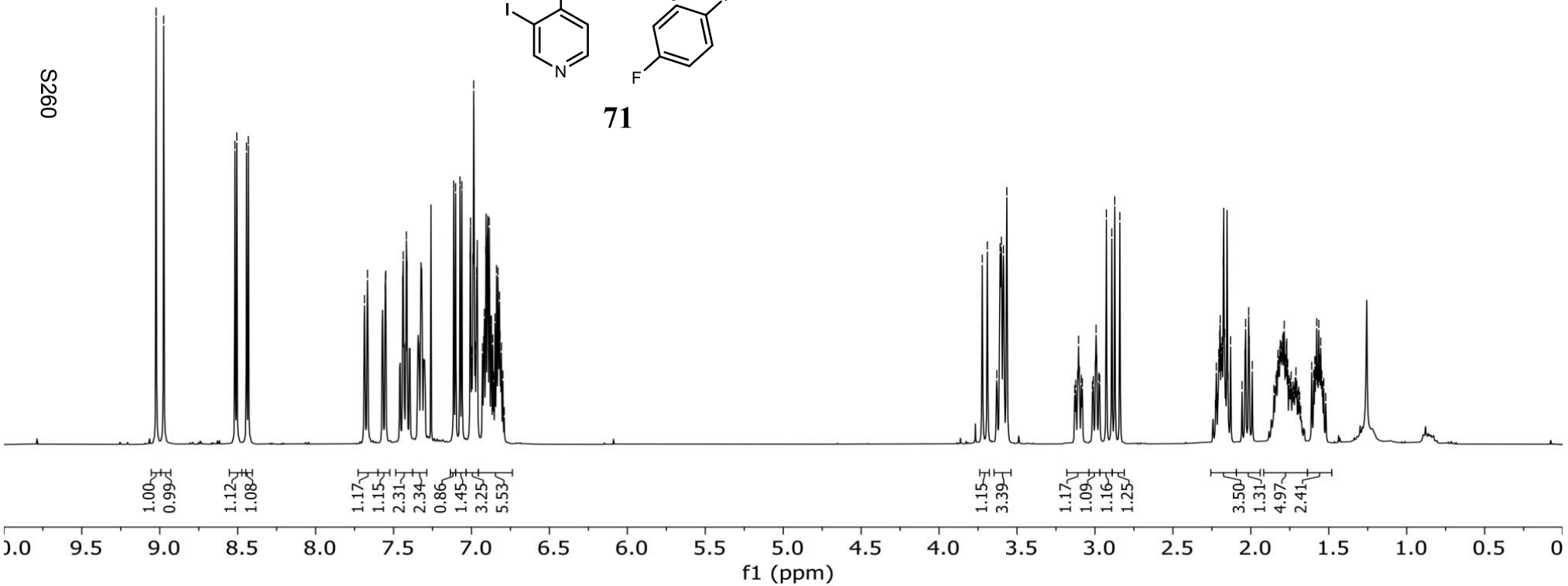


^{1}H NMR
$CDCl_3$, 400 MHz



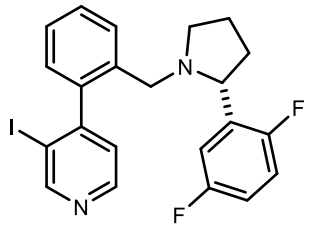
71

S260

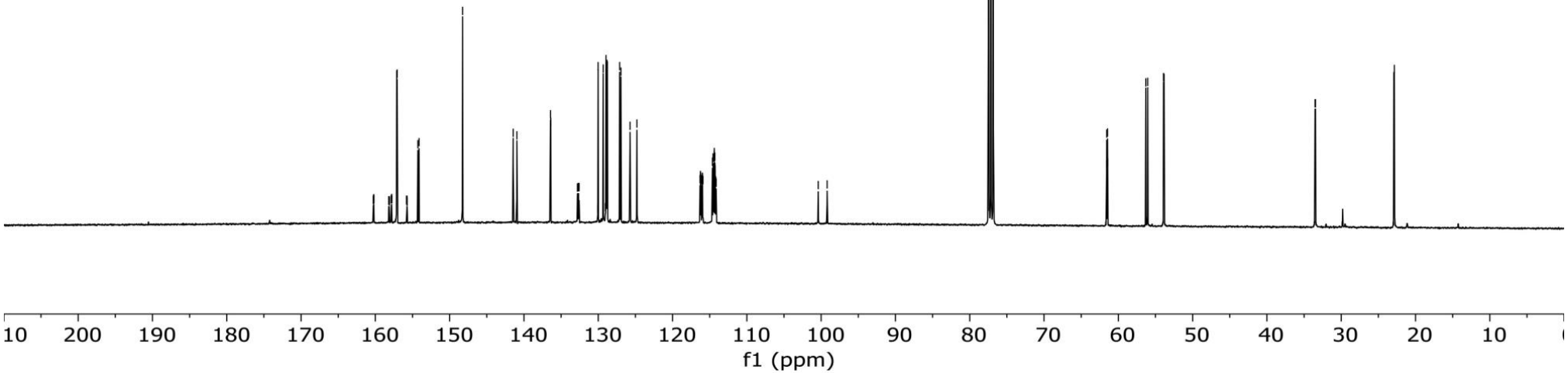


160.28
160.26
160.21
160.18
158.20
158.18
158.14
158.11
157.88
157.85
157.80
157.78
157.13
157.07
155.81
155.78
155.74
154.28
154.12
148.26
141.45
140.96
136.43
136.40
132.80
132.73
132.65
132.58
130.01
129.33
128.95
128.91
128.82
128.77
127.12
126.95
125.72
124.80
116.30
116.24
116.21
116.15
116.05
115.99
115.96
115.90
114.63
114.55
114.52
114.47
114.42
114.39
114.38
114.30
114.28
114.23
114.18
114.13
100.39
99.19
77.16 CDCl3
61.58
61.56
61.55
61.47
61.46
61.44
56.30
56.04
53.92
53.84
33.53
33.47
22.92
22.85

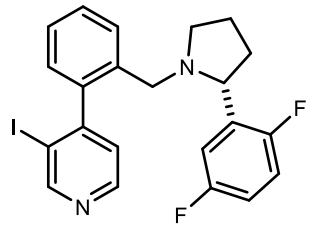
^{13}C NMR
$CDCl_3$, 100 MHz



71



^{19}F NMR
$CDCl_3$, 365 MHz



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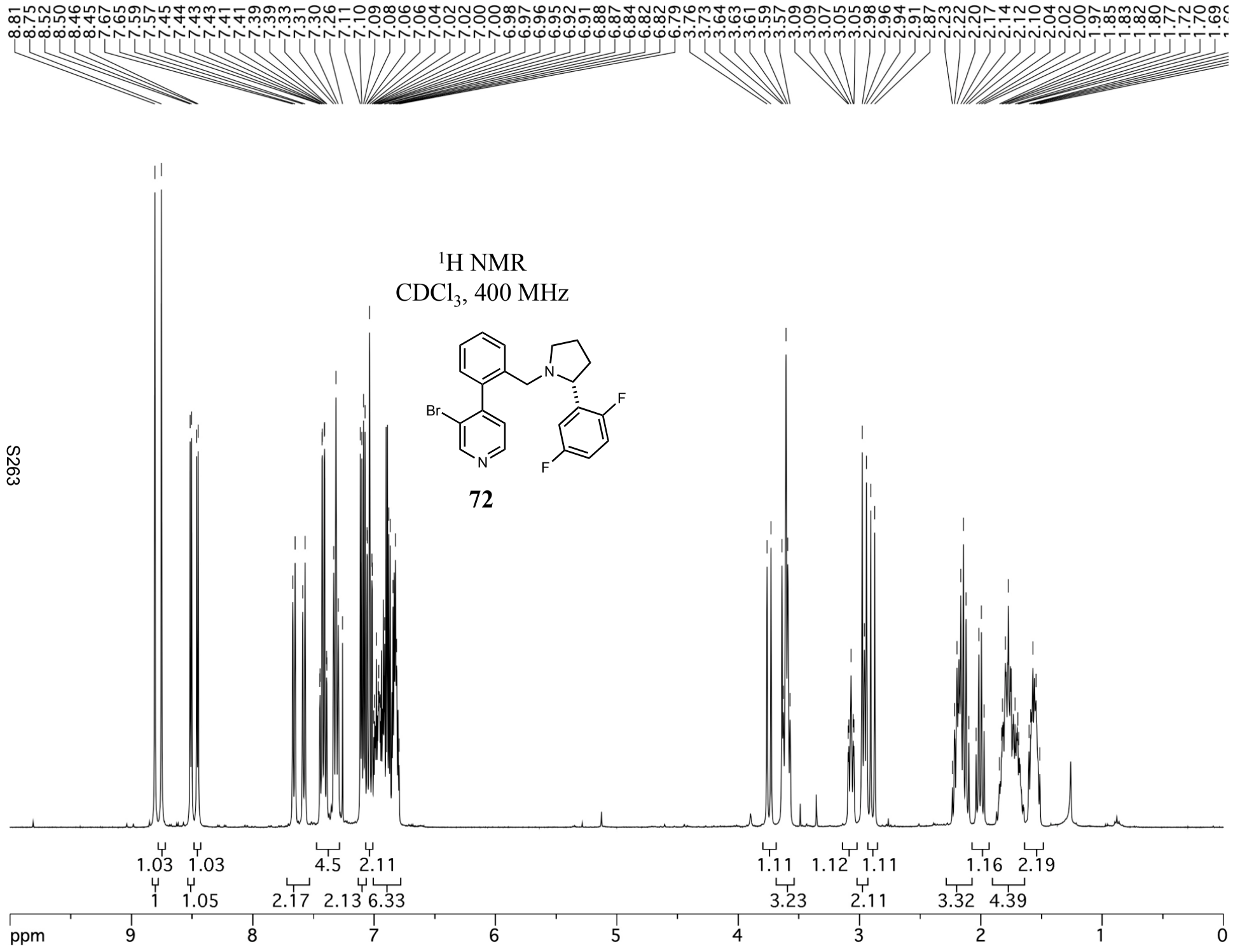
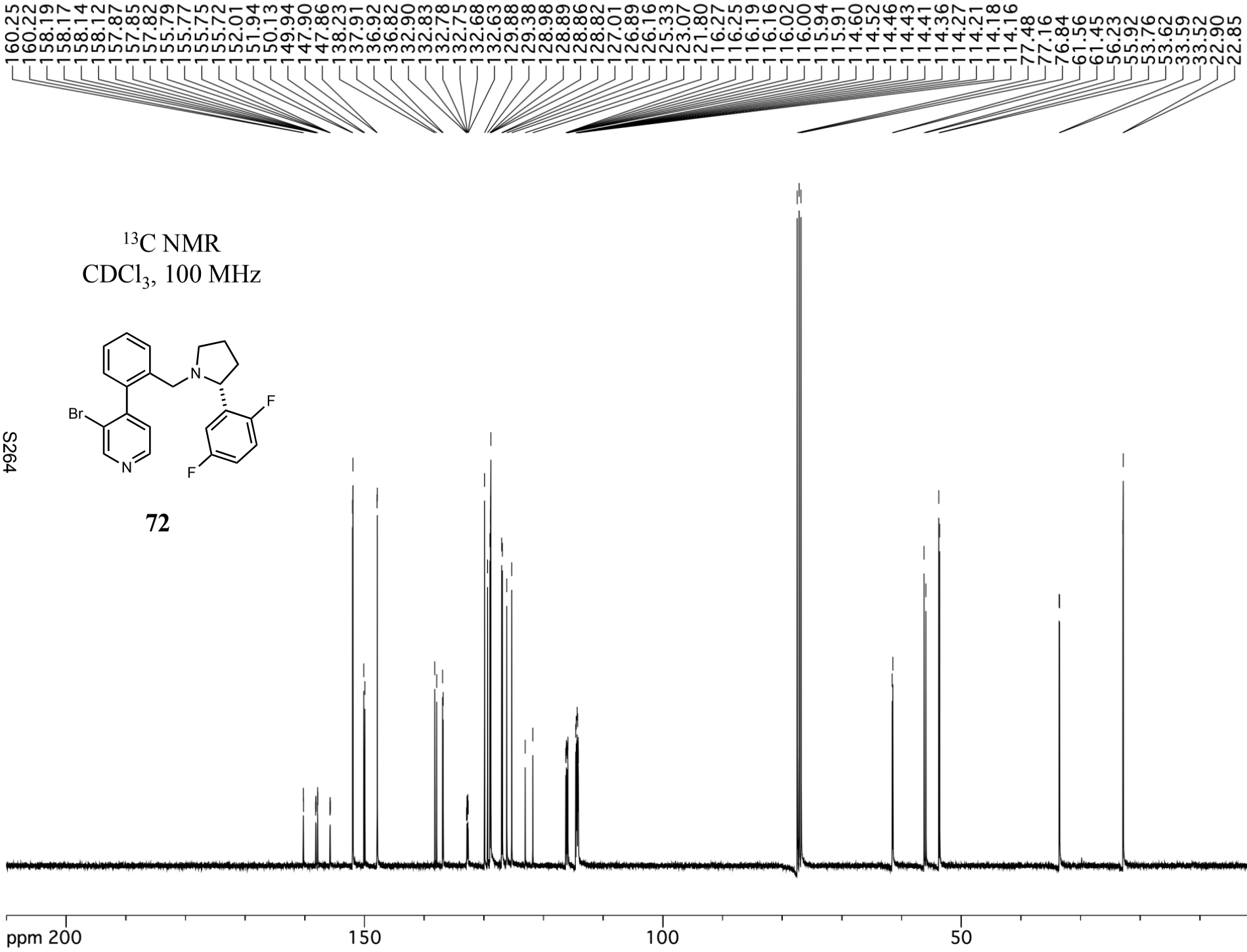

8.81 8.75 8.52 8.50 8.46 8.45 7.67 7.65 7.59 7.57 7.45 7.44 7.43 7.43 7.41 7.41 7.39 7.39 7.33 7.31 7.30 7.26 7.11 7.10 7.09 7.08 7.06 7.06 7.04 7.02 7.00 7.00 6.98 6.97 6.96 6.95 6.92 6.91 6.88 6.87 6.84 6.82 6.82 6.79 3.76 3.73 3.64 3.63 3.61 3.59 3.57 3.09 3.09 3.07 3.05 3.05 2.98 2.96 2.94 2.91 2.87 2.23 2.22 2.20 2.17 2.14 2.12 2.10 2.04 2.02 2.00 1.97 1.85 1.83 1.82 1.80 1.77 1.72 1.70 1.69
S263
^{1}H NMR
$CDCl_3$, 400 MHz
Br
N
F
F
N
72
1.03 1.03 4.5 2.11 1.11 1.12 1.11 1.16 2.19
1 1.05 2.17 2.13 6.33 3.23 2.11 3.32 4.39
ppm 9 8 7 6 5 4 3 2 1 0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160.22
158.19
158.17
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158.12
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157.85
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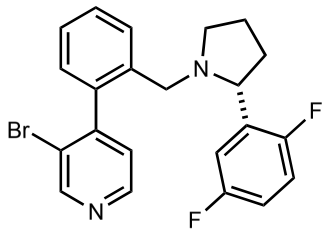
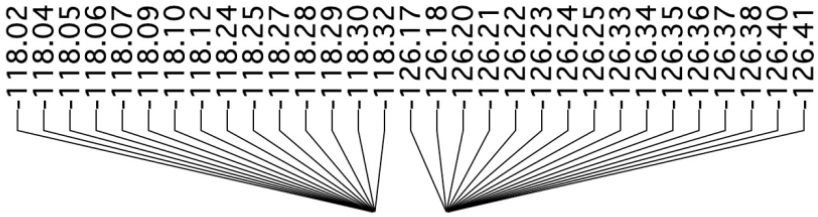
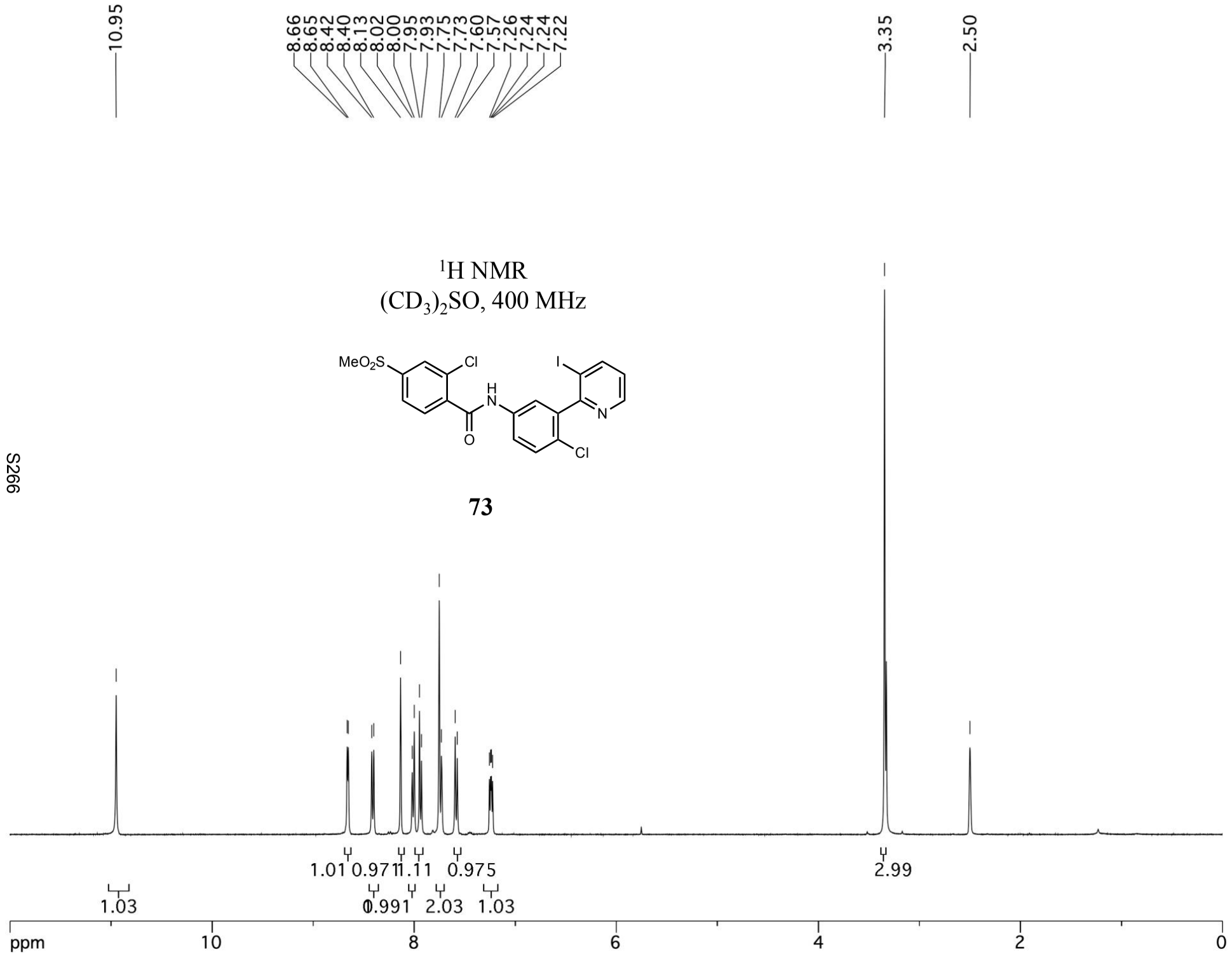
155.77
155.75
155.72
152.01
151.94
150.13
149.94
147.90
147.86
138.23
137.91
136.92
136.82
132.90
132.83
132.78
132.75
132.68
132.63
129.88
129.38
128.98
128.89
128.86
128.82
127.01
126.89
126.16
125.33
123.07
121.80
116.27
116.25
116.19
116.16
116.02
116.00
115.94
115.91
114.60
114.52
114.46
114.43
114.41
114.36
114.27
114.21
114.18
77.48
77.16
76.84
61.56
61.45
56.23
55.92
53.76
53.62
33.59
33.52
22.90
22.85
^{13}C NMR
$CDCl_3$, 100 MHz
Br
N
N
F
F
72
S264
ppm 200
150
100
50
0

^{19}F NMR
$CDCl_3$, 365 MHz



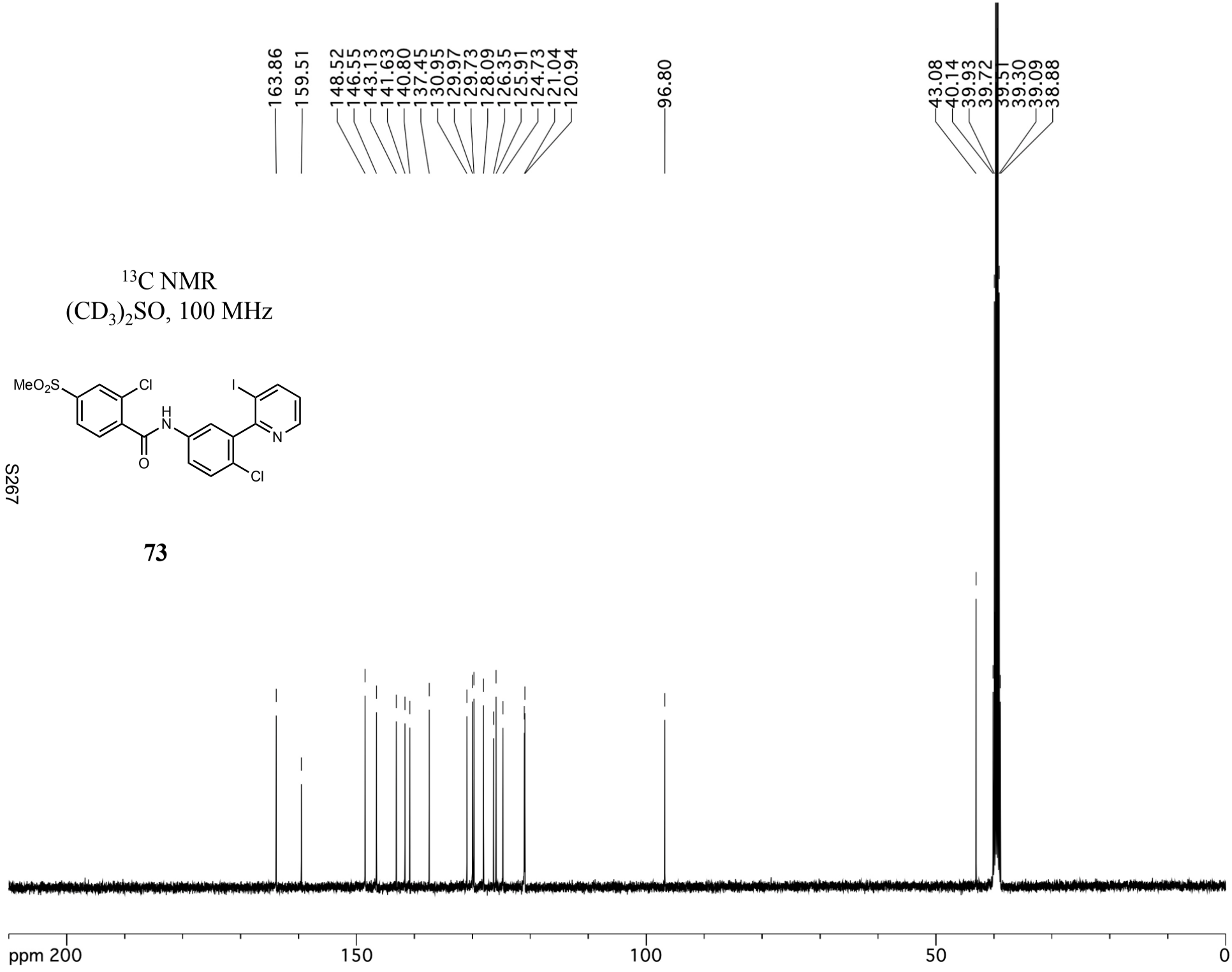
72

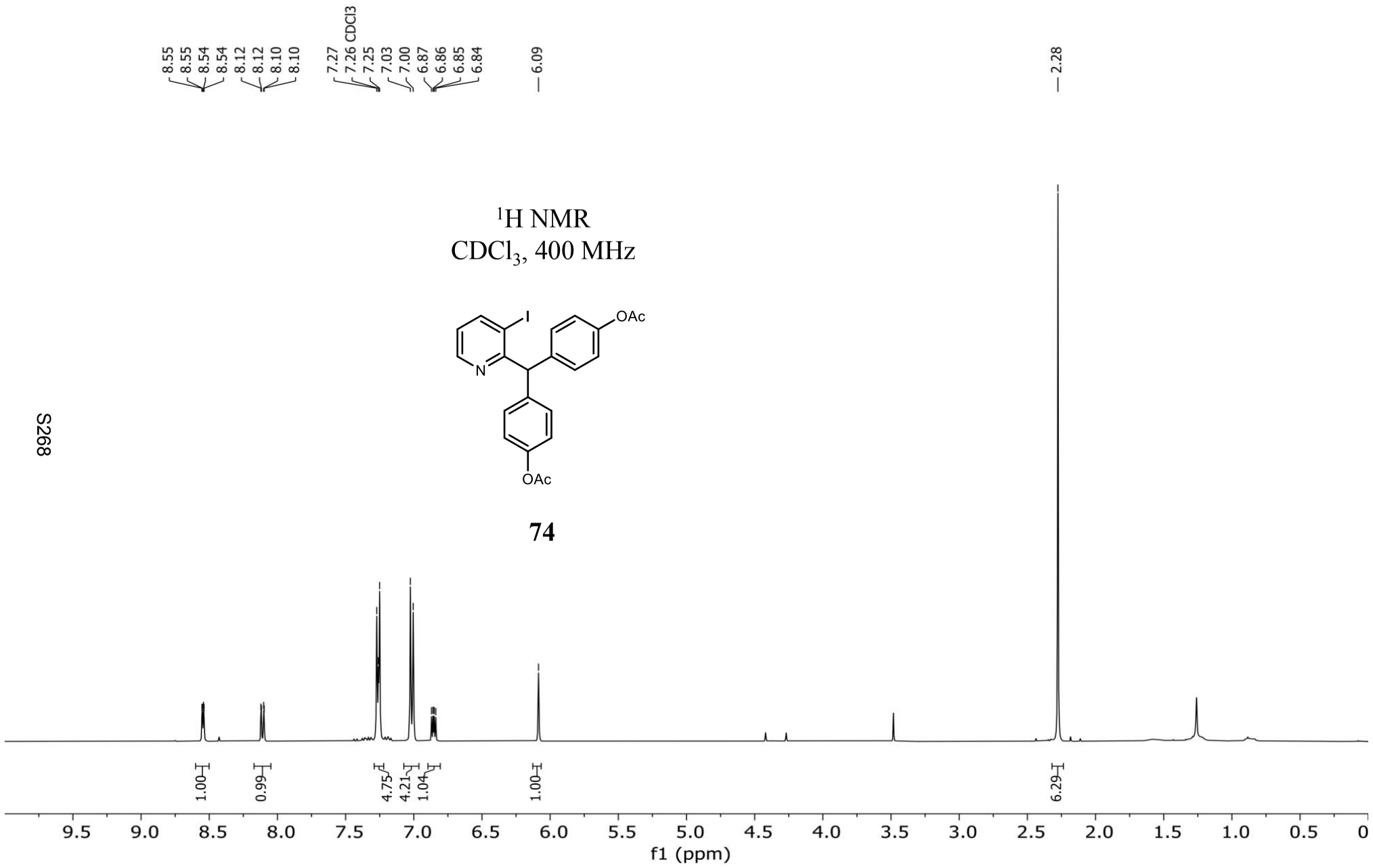


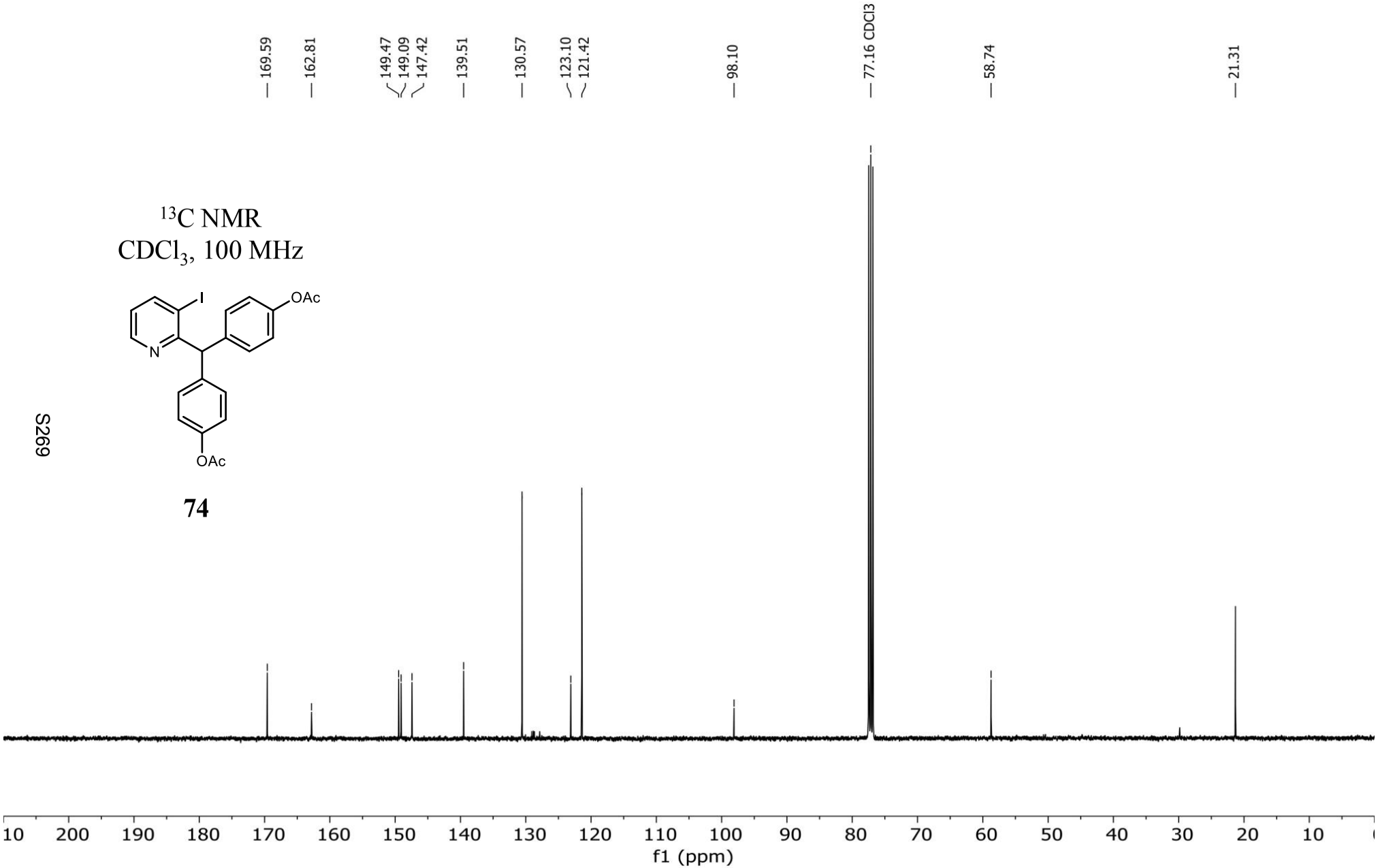


^{1}H NMR
$(CD_3)_2SO$, 400 MHz

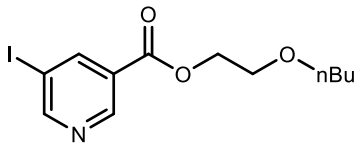
73


163.86
159.51
148.52
146.55
143.13
141.63
140.80
137.45
130.95
129.97
129.73
128.09
126.35
125.91
124.73
121.04
120.94
96.80
43.08
40.14
39.93
39.72
39.51
39.30
39.09
38.88
^{13}C NMR
$(CD_3)_2SO$, 100 MHz
MeO_2S
Cl
I
H
N
O
N
Cl
S267
73
ppm 200
150
100
50
0

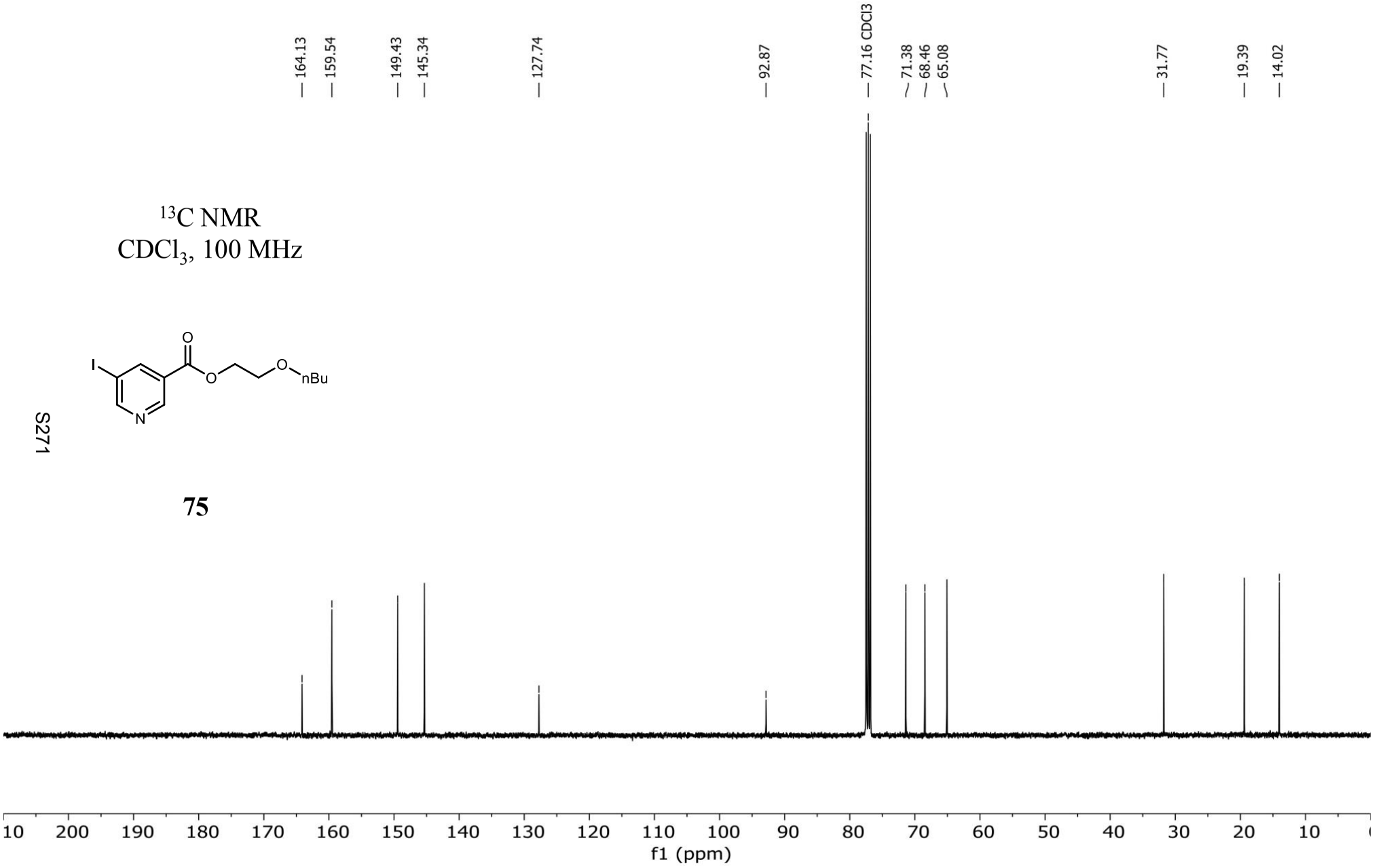

8.55
8.55
8.54
8.54
8.12
8.12
8.10
8.10
7.27
7.26 CDCl3
7.25
7.03
7.00
6.87
6.86
6.85
6.84
6.09
2.28
1H NMR
CDCl3, 400 MHz
I
OAc
N
OAc
74
1.00
0.99
4.75
4.21
1.04
1.00
6.29
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

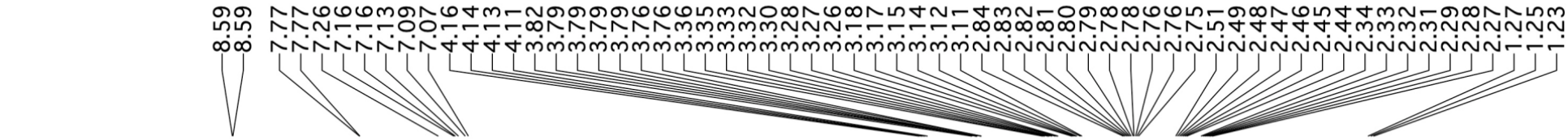

169.59
162.81
149.47
149.09
147.42
139.51
130.57
123.10
121.42
98.10
77.16 CDCl3
58.74
21.31
13C NMR
CDCl3, 100 MHz
I
OAc
N
OAc
74
S269
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

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

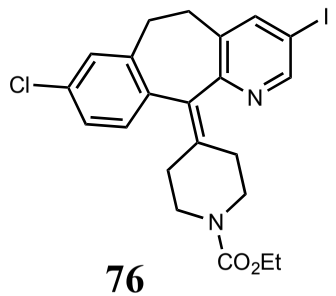


75

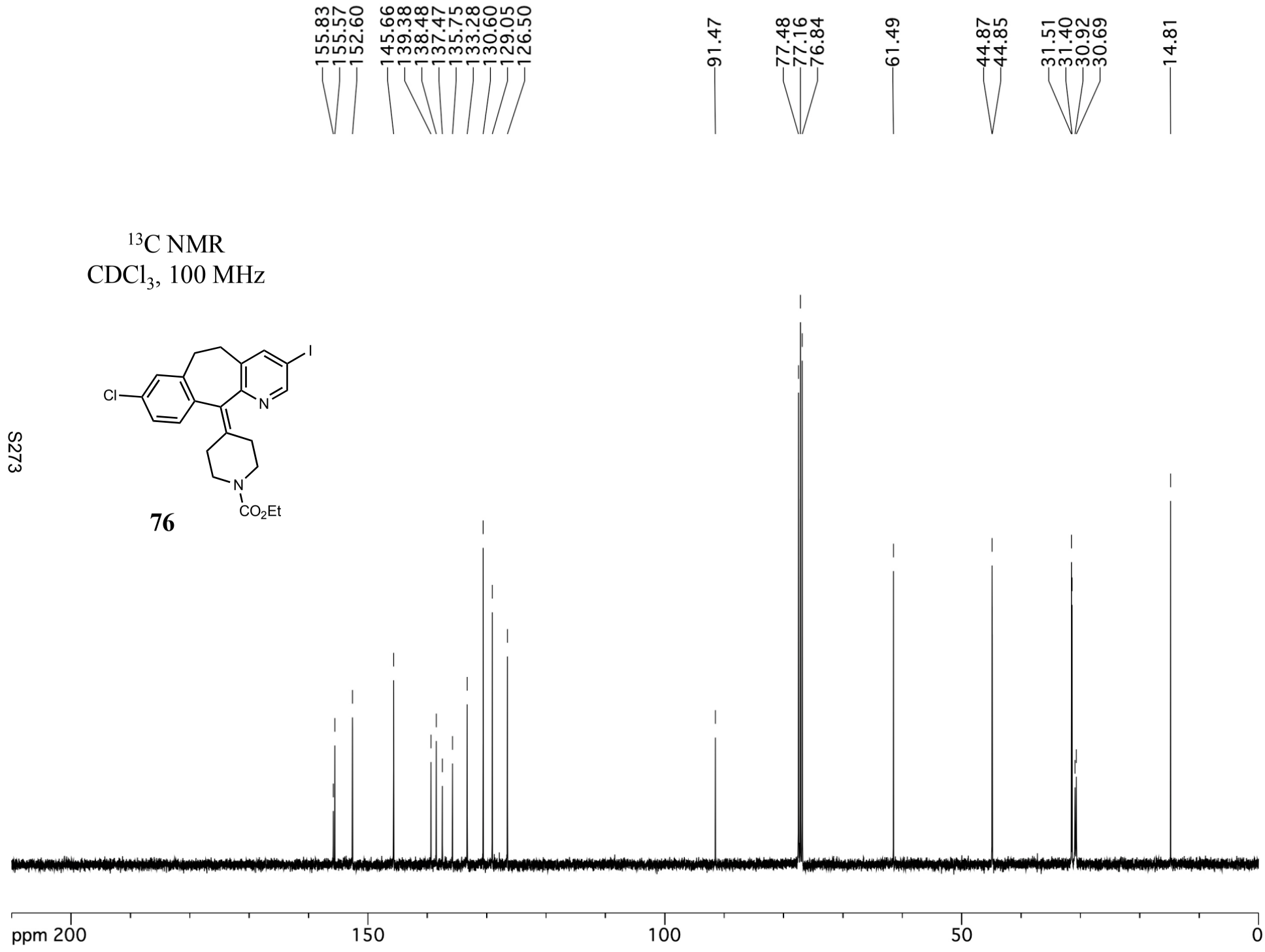

164.13
159.54
149.43
145.34
127.74
92.87
77.16 CDCl3
71.38
68.46
65.08
31.77
19.39
14.02
^{13}C NMR
$CDCl_3$, 100 MHz
I
O
O
O
nBu
N
S271
75
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

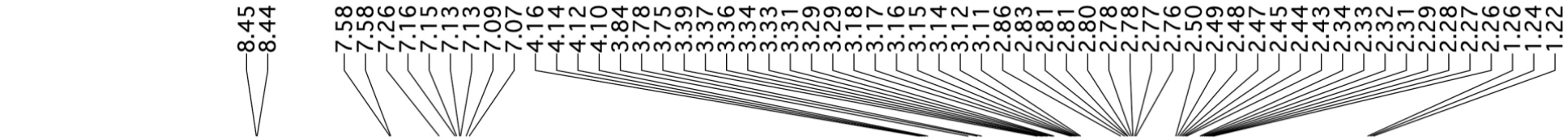


^{1}H NMR
$CDCl_3$, 400 MHz

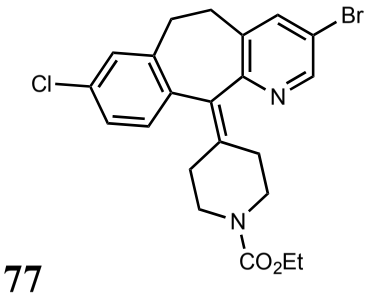


76

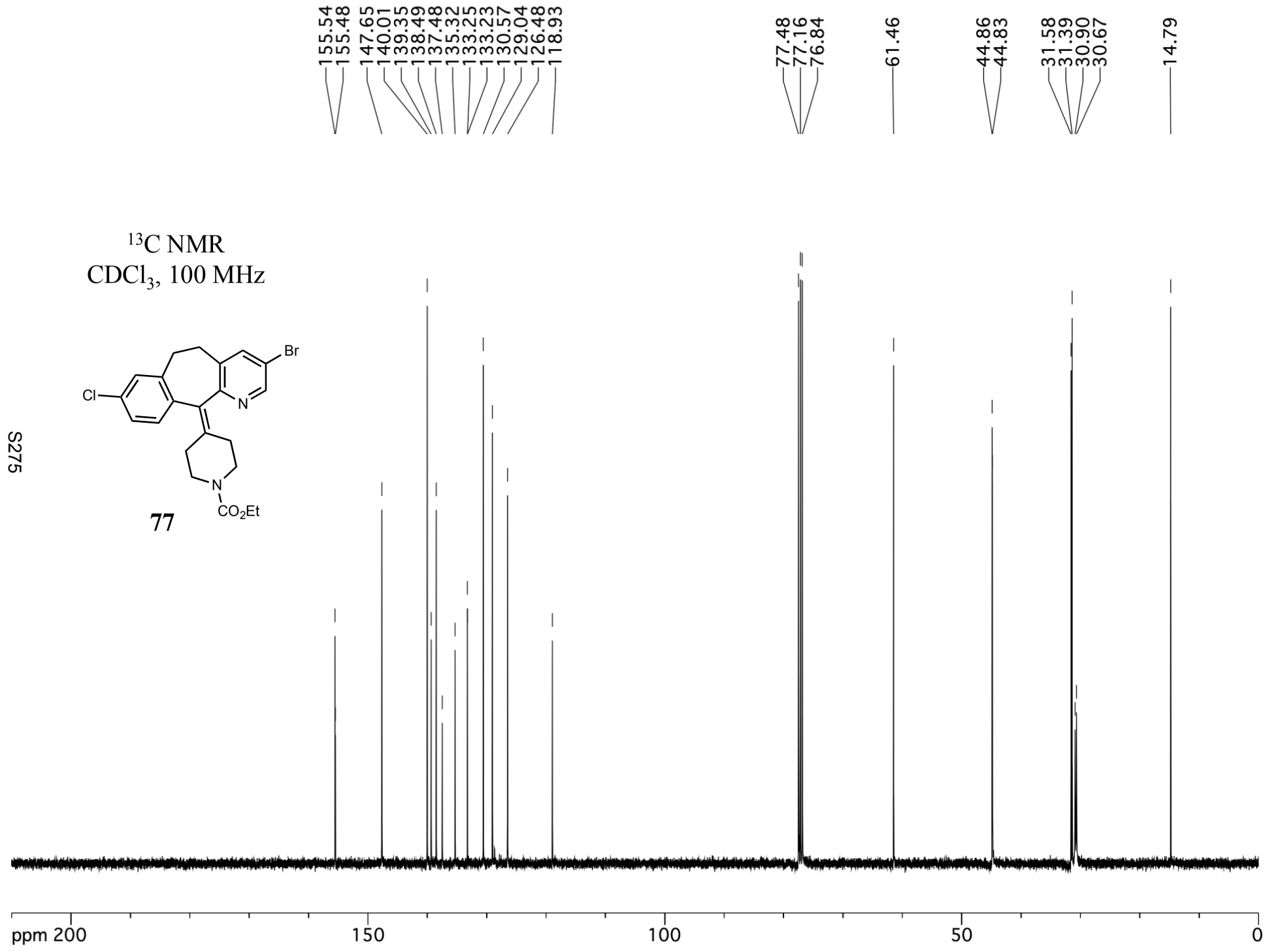

155.83
155.57
152.60
145.66
139.38
138.48
137.47
135.75
133.28
130.60
129.05
126.50
91.47
77.48
77.16
76.84
61.49
44.87
44.85
31.51
31.40
30.92
30.69
14.81
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
I
N
N
CO_2Et
76
S273
ppm 200
150
100
50
0

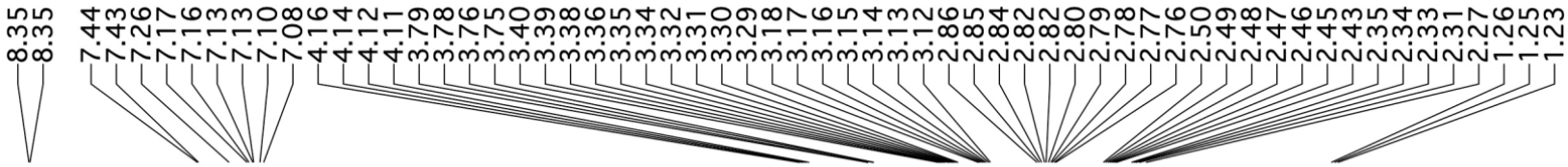


^{1}H NMR
$CDCl_3$, 400 MHz

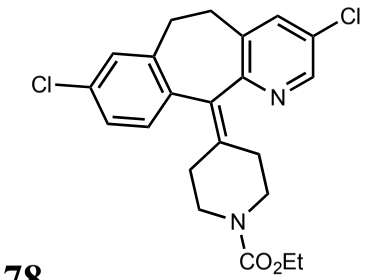


77

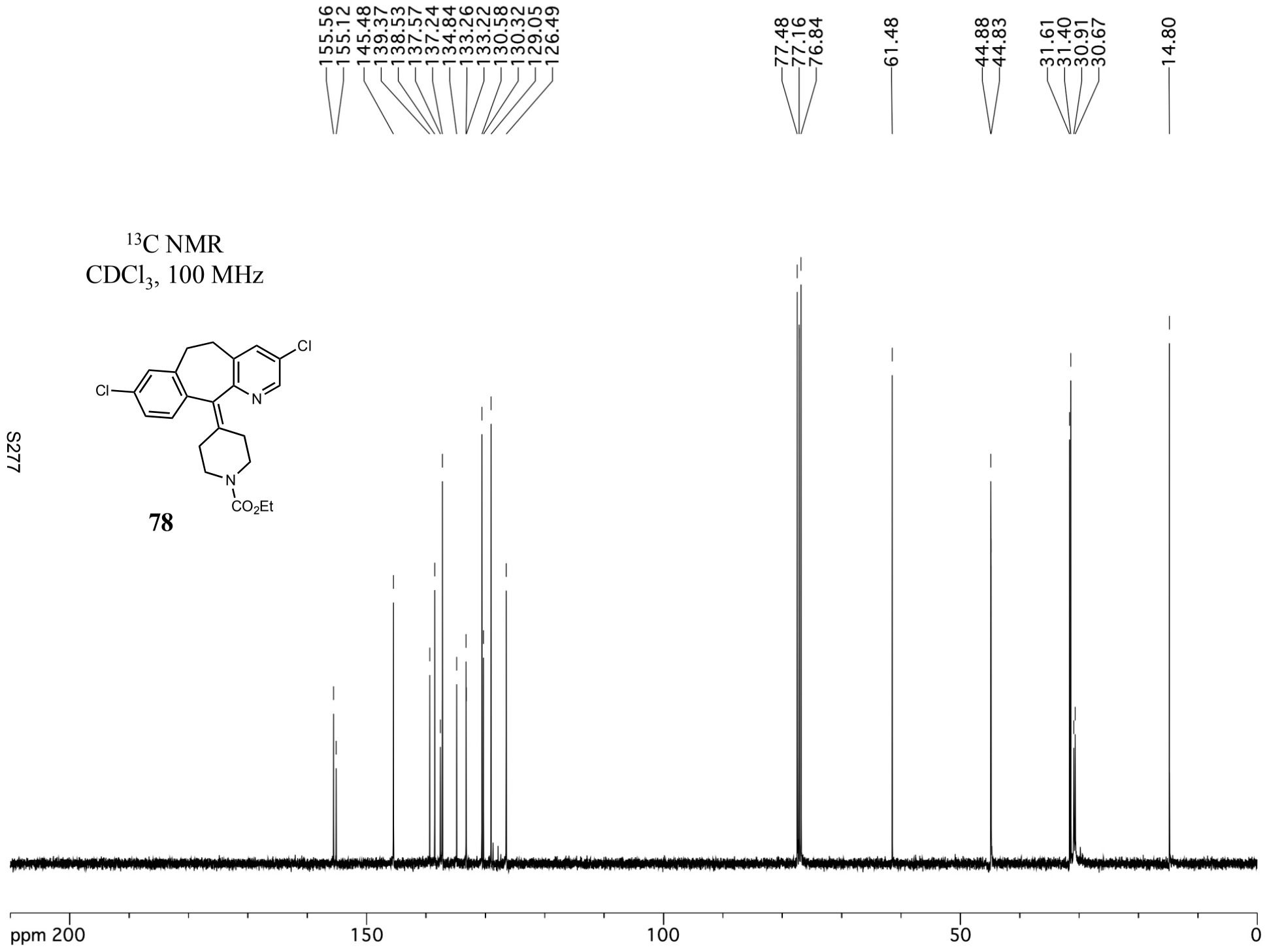

155.54
155.48
147.65
140.01
139.35
138.49
137.48
135.32
133.25
133.23
130.57
129.04
126.48
118.93
77.48
77.16
76.84
61.46
44.86
44.83
31.58
31.39
30.90
30.67
14.79
^{13}C NMR
$CDCl_3$, 100 MHz
Br
Cl
N
N
CO_2Et
77
S275
ppm 200
150
100
50
0

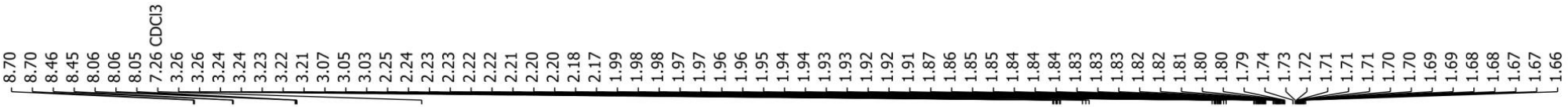


^{1}H NMR
$CDCl_3$, 400 MHz

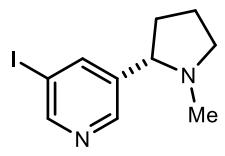


78


155.56
155.12
145.48
139.37
138.53
137.57
137.24
134.84
133.26
133.22
130.58
130.32
129.05
126.49
77.48
77.16
76.84
61.48
44.88
44.83
31.61
31.40
30.91
30.67
14.80
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
Cl
N
N
CO_2Et
78
S277
ppm 200
150
100
50
0

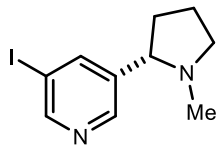


^{1}H NMR
$CDCl_3$, 400 MHz



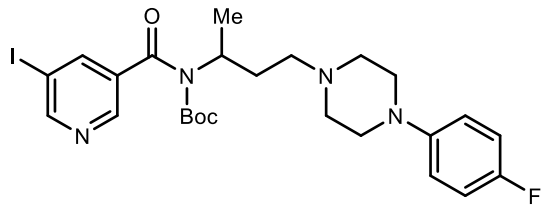
79

^{13}C NMR
$CDCl_3$, 100 MHz

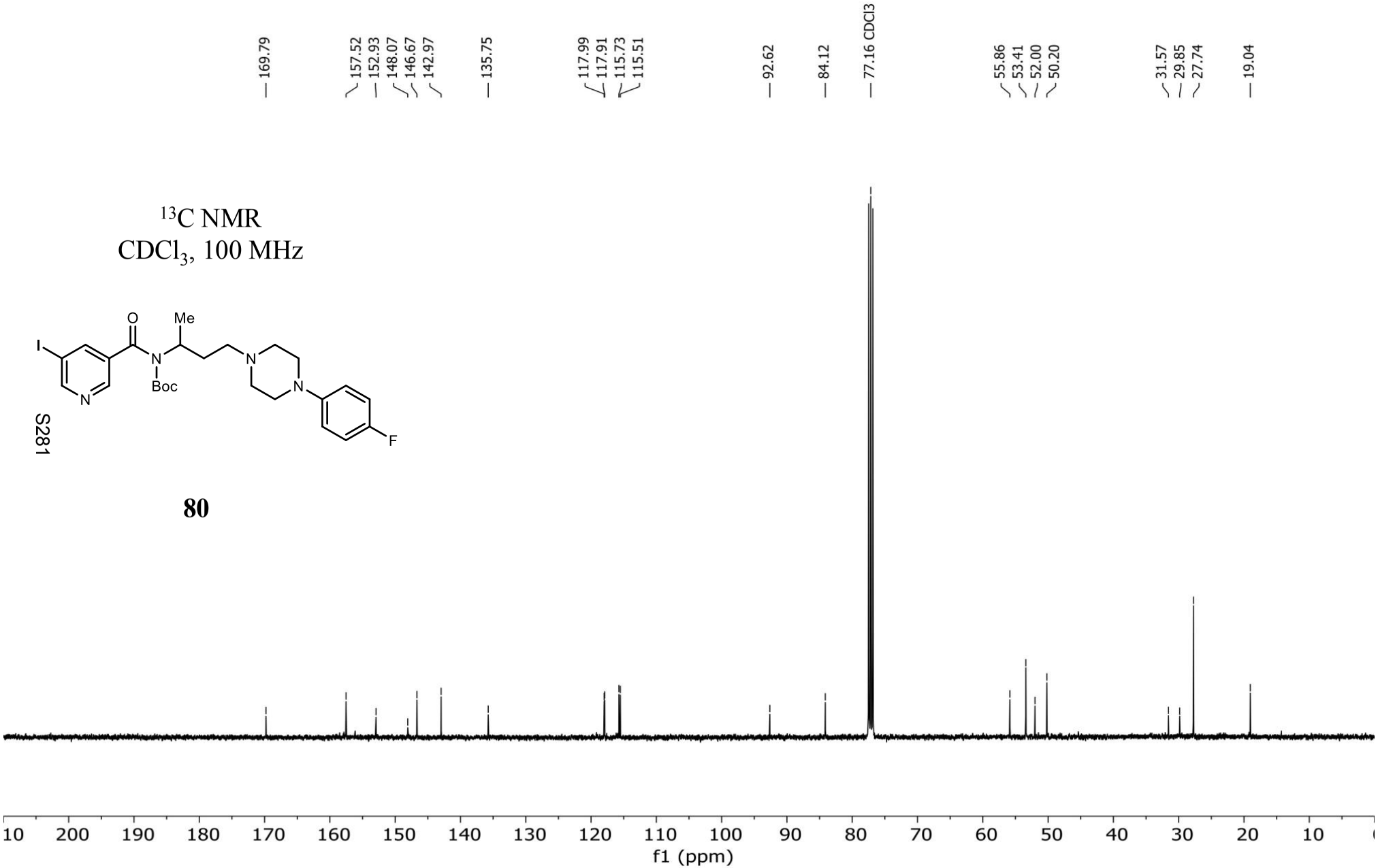


79

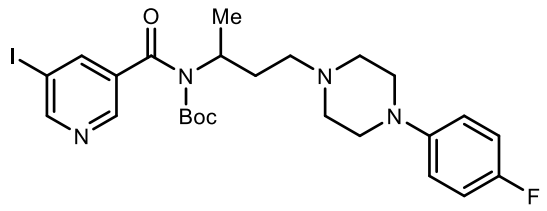
^{1}H NMR
$CDCl_3$, 400 MHz



80


169.79
157.52
152.93
148.07
146.67
142.97
135.75
117.99
117.91
115.73
115.51
92.62
84.12
77.16 CDCl3
55.86
53.41
52.00
50.20
31.57
29.85
27.74
19.04
13C NMR
CDCl3, 100 MHz
O
Me
I
N
N
Boc
N
N
F
S281
80
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{19}F NMR
$CDCl_3$, 365 MHz



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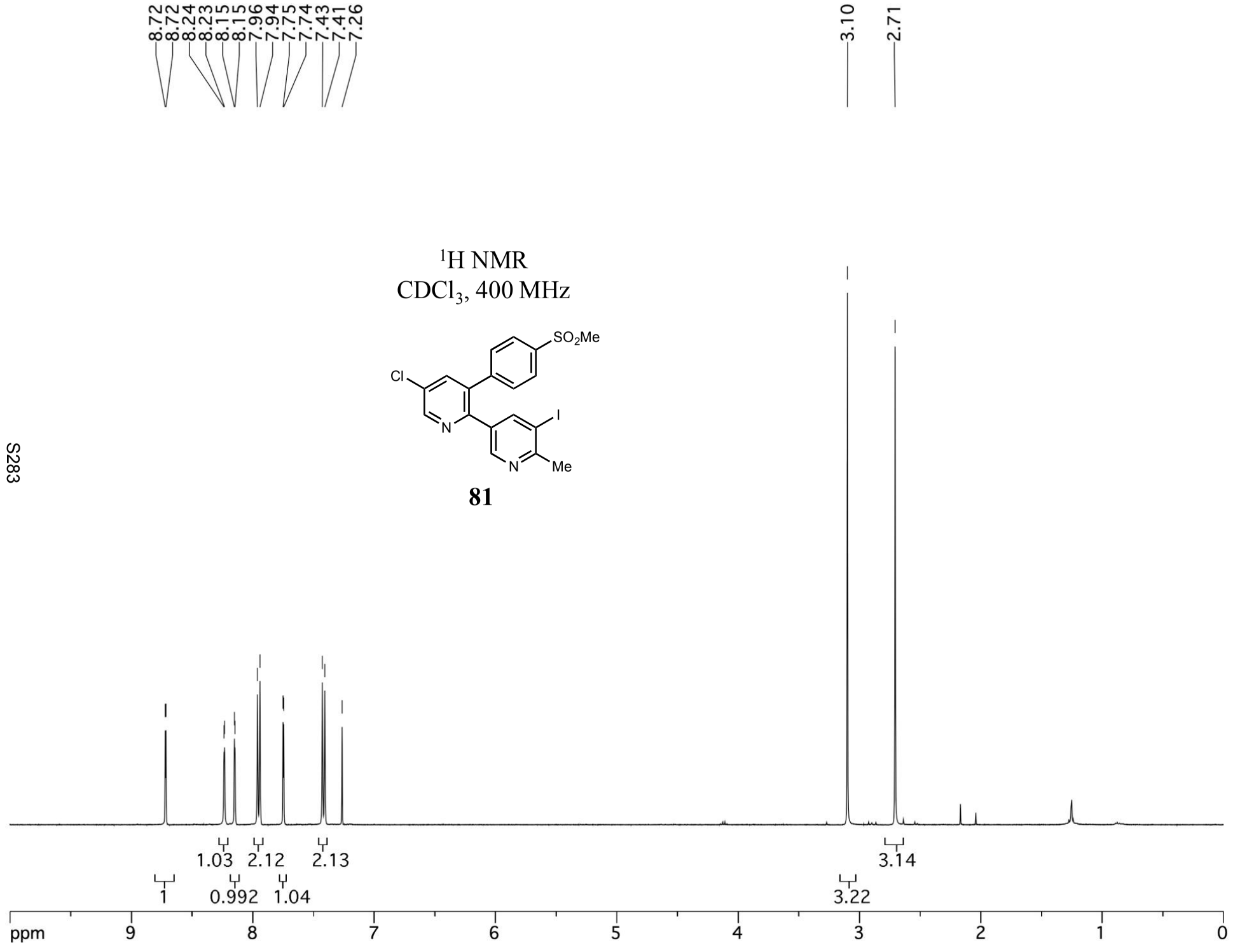
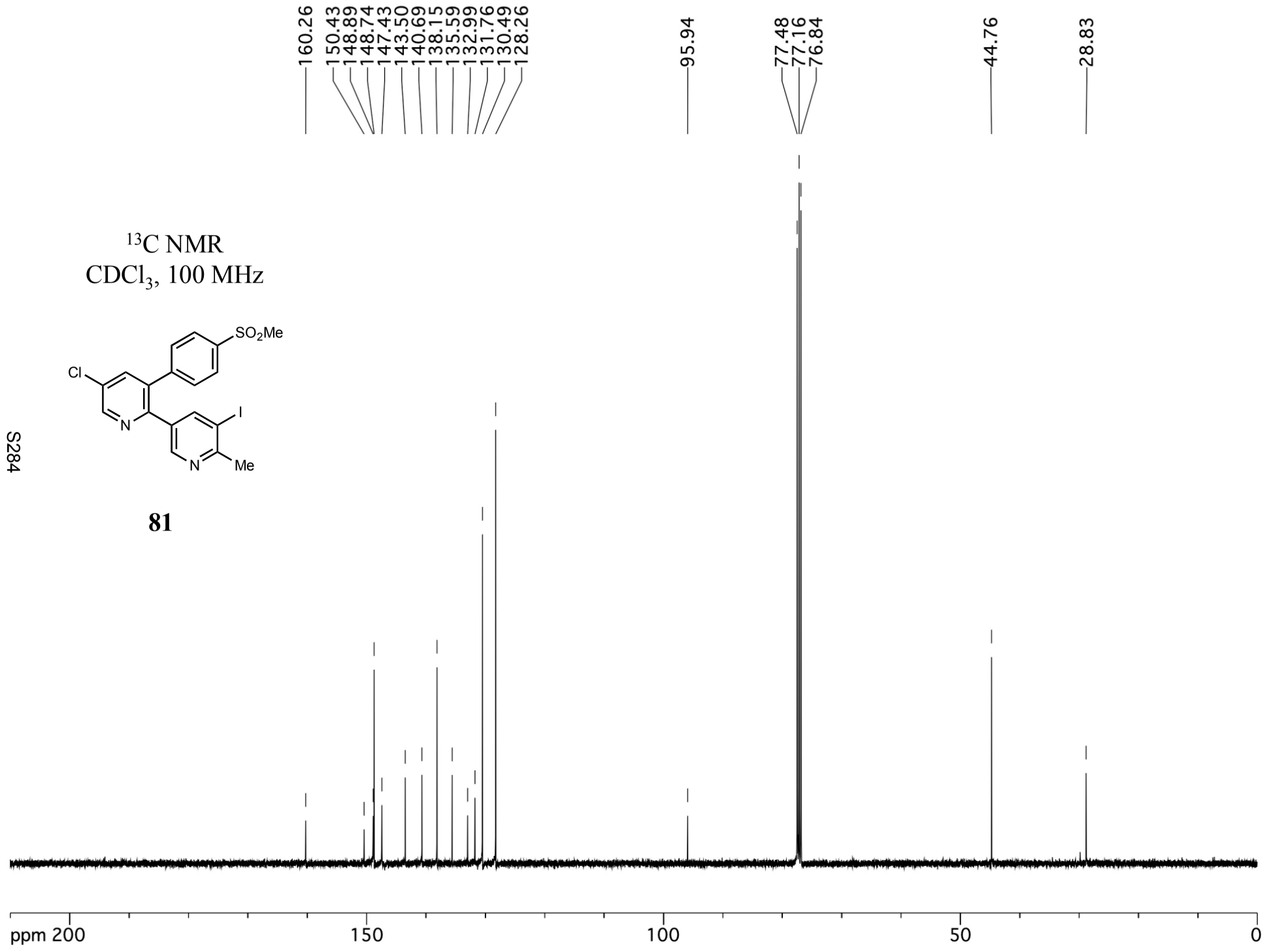
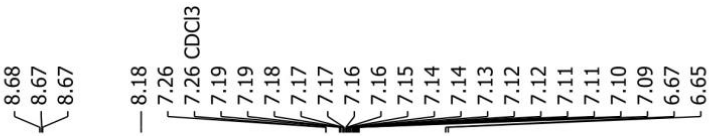
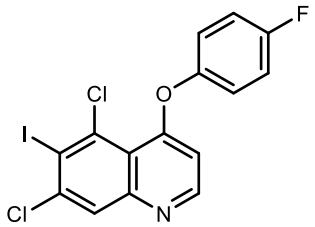

8.72
8.72
8.24
8.23
8.15
8.15
7.96
7.94
7.75
7.74
7.43
7.41
7.26
3.10
2.71
1H NMR
CDCl3, 400 MHz
SO2Me
Cl
I
N
N
Me
81
1.03
2.12
2.13
3.14
1
0.992
1.04
3.22
ppm
9
8
7
6
5
4
3
2
1
0


160.26
150.43
148.89
148.74
147.43
143.50
140.69
138.15
135.59
132.99
131.76
130.49
128.26
95.94
77.48
77.16
76.84
44.76
28.83
^{13}C NMR
$CDCl_3$, 100 MHz
SO_2Me
Cl
I
N
N
Me
ppm 200
150
100
50
0

81



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



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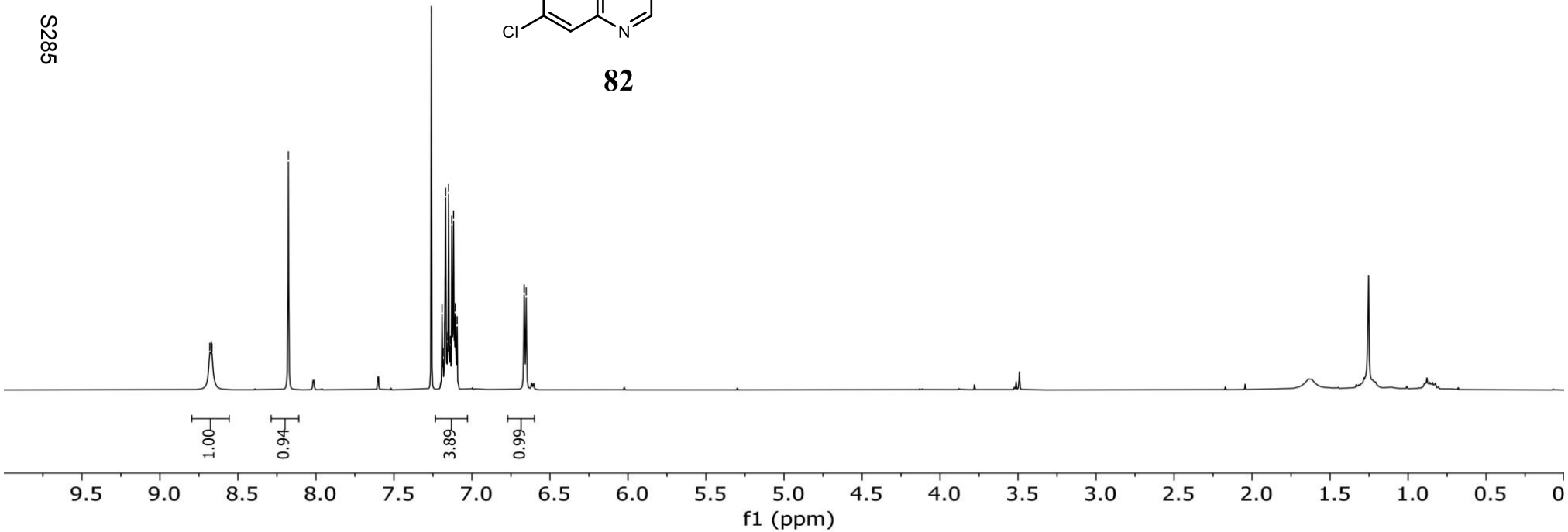
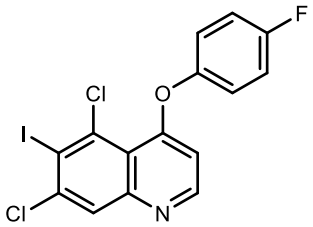
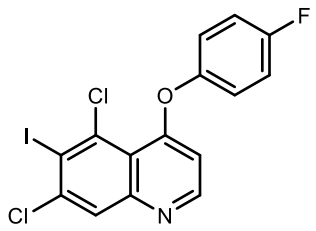


^{13}C NMR
$CDCl_3$, 100 MHz

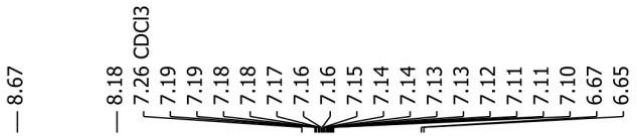


82

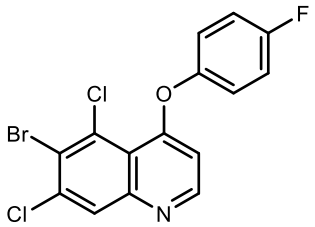
^{19}F NMR
$CDCl_3$, 365 MHz



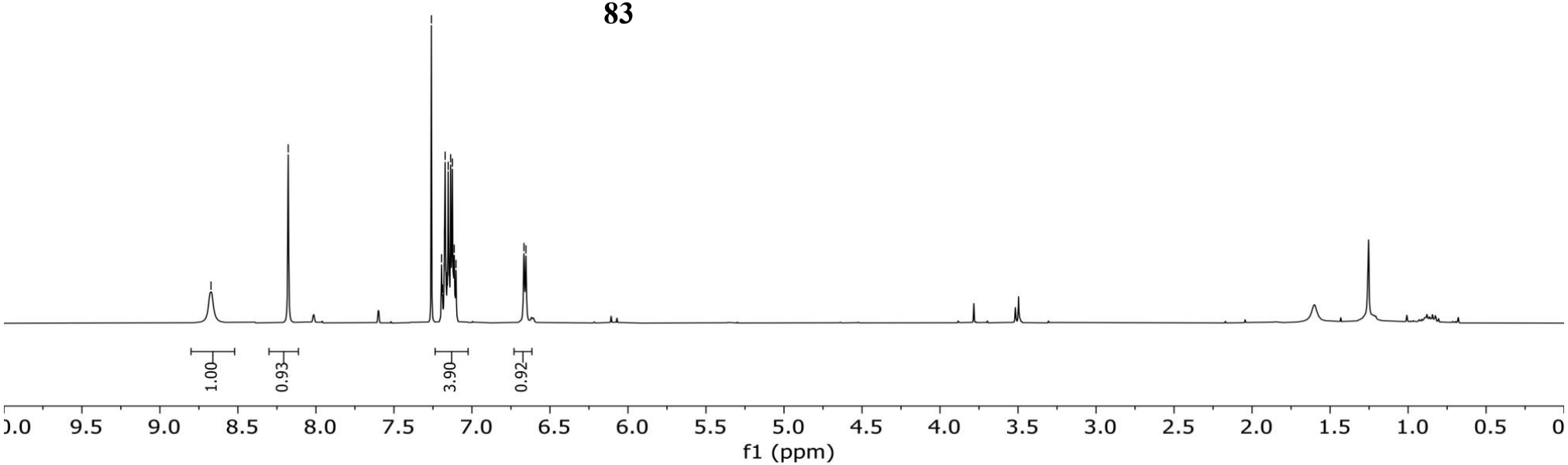
82



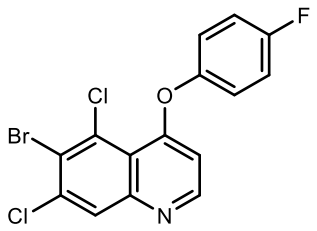
^{1}H NMR
$CDCl_3$, 400 MHz



83

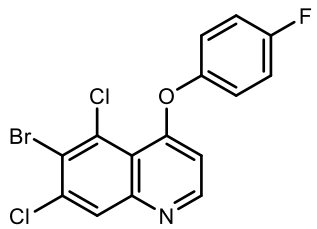


^{13}C NMR
$CDCl_3$, 100 MHz

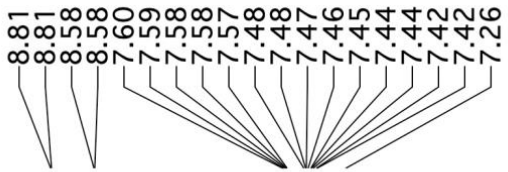


83

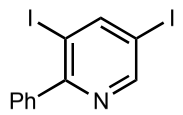
^{19}F NMR
$CDCl_3$, 365 MHz



83



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

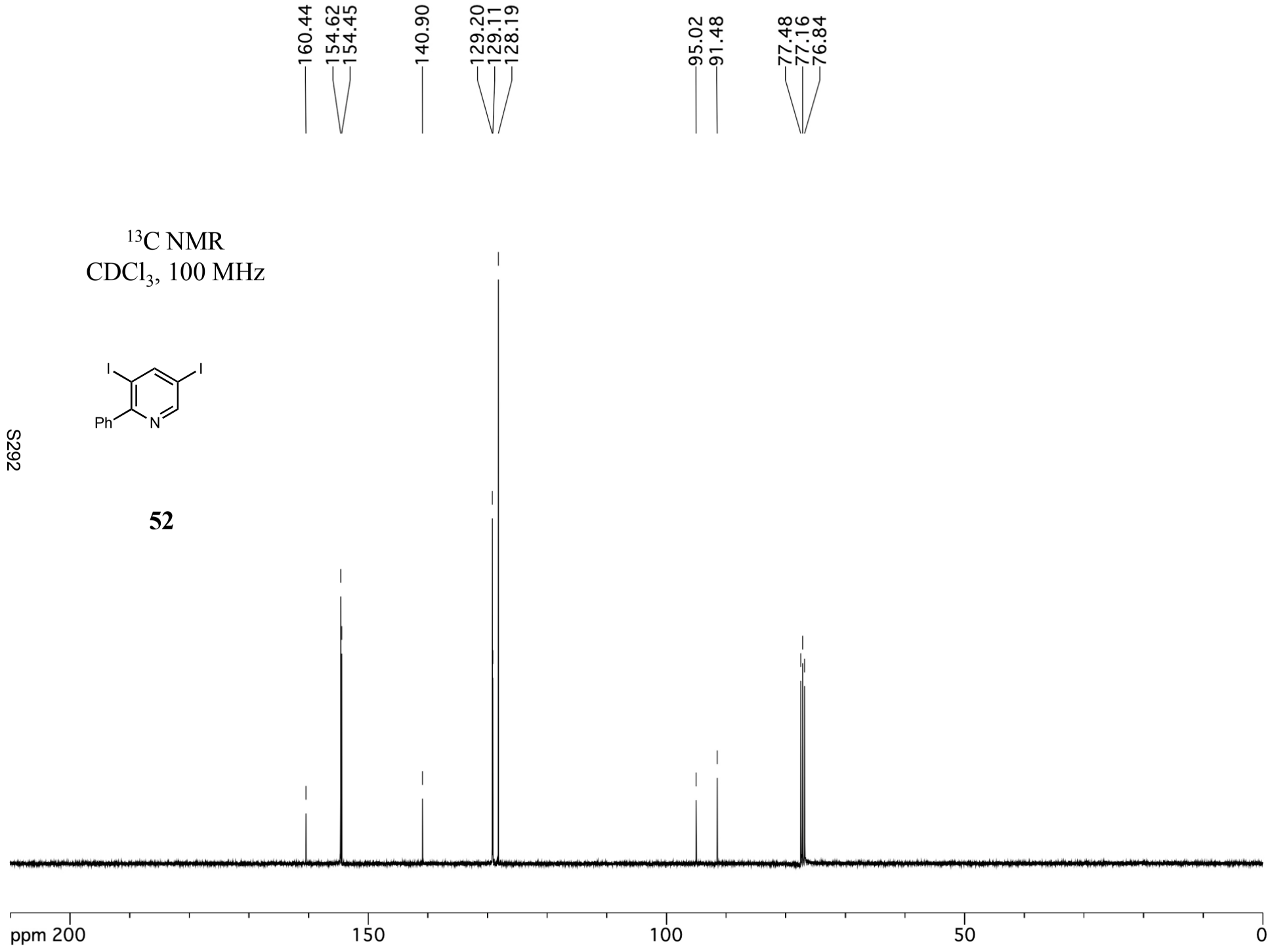


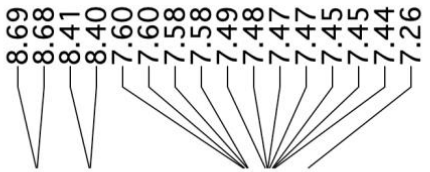
52

S291

0.931
3.18
1
2.11

ppm 9 8 7 6 5 4 3 2 1 0


160.44
154.62
154.45
140.90
129.20
129.11
128.19
95.02
91.48
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
I
I
Ph
N
S292
52
ppm 200
150
100
50
0



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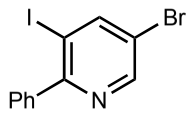
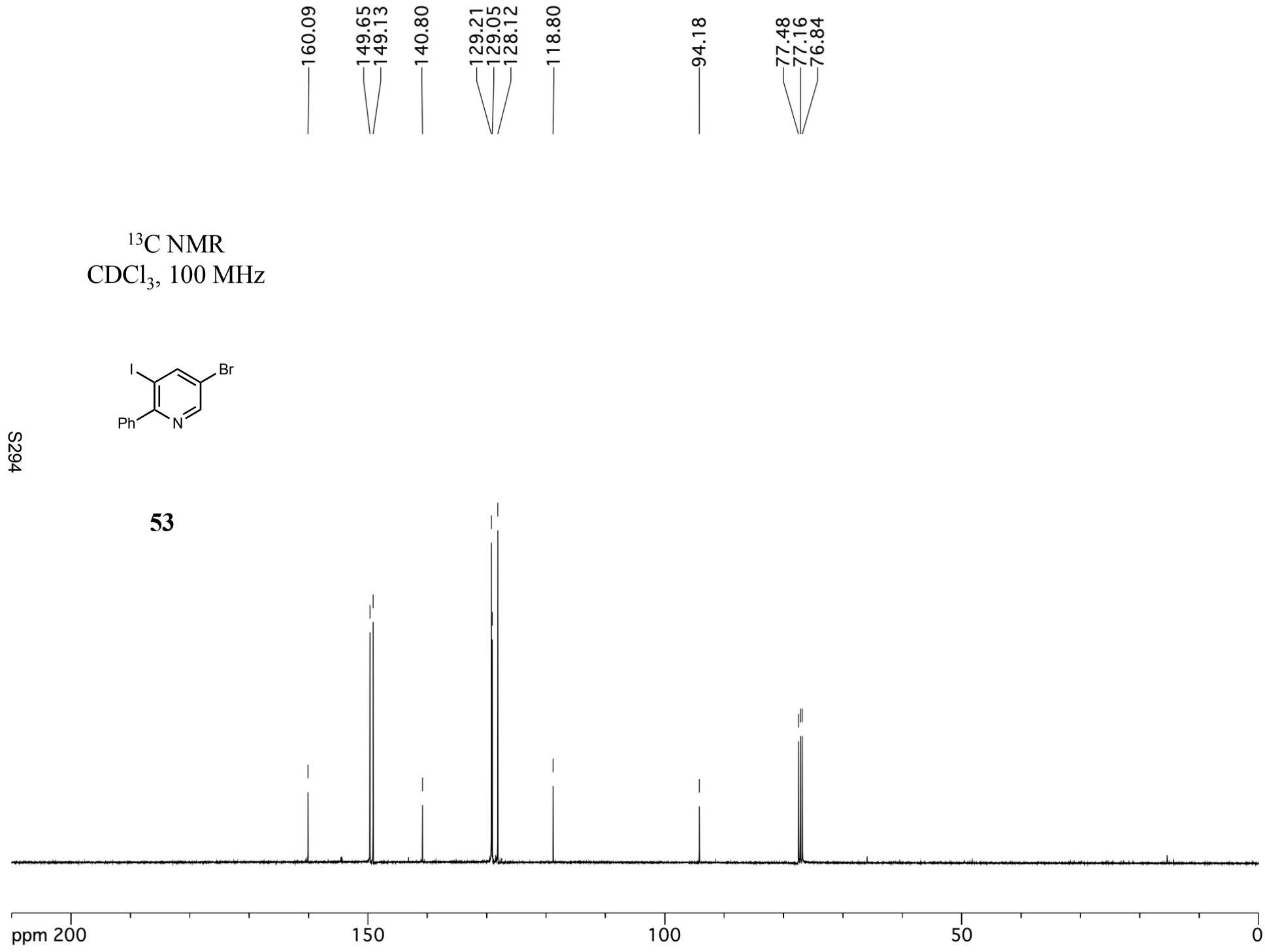
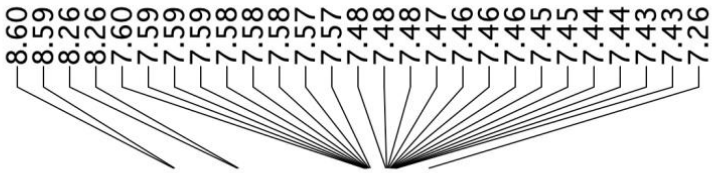
$CDCl_3$, 400 MHz

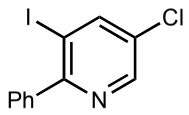


53

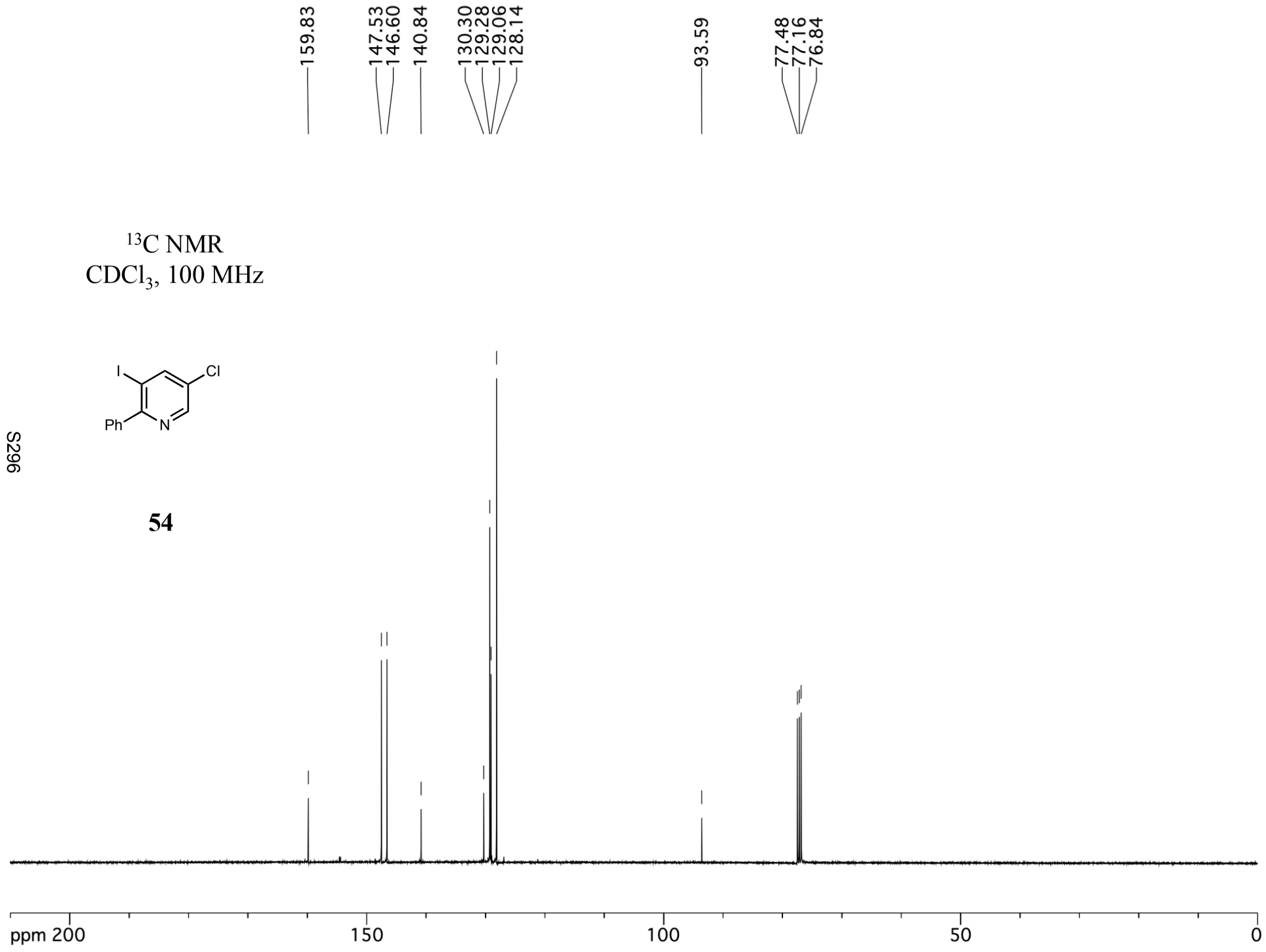

160.09
149.65
149.13
140.80
129.21
129.05
128.12
118.80
94.18
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
I
Br
Ph
N
S294
53
ppm 200
150
100
50
0



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



54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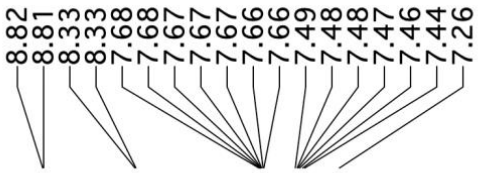
147.53
146.60
140.84
130.30
129.28
129.06
128.14
93.59
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
I
Cl
Ph
N
S296
54
ppm 200
150
100
50
0



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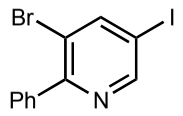

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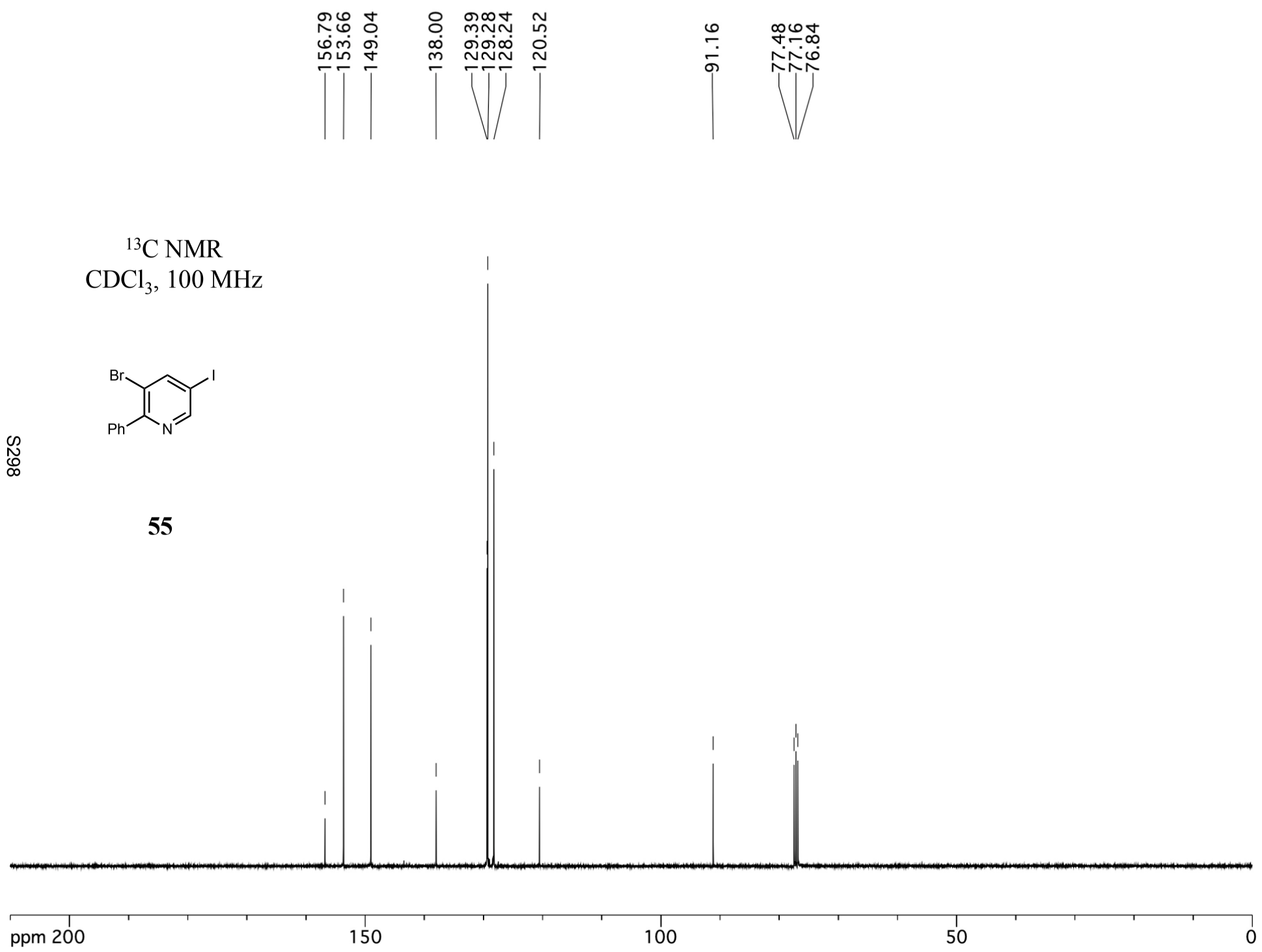
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153.66
149.04
138.00
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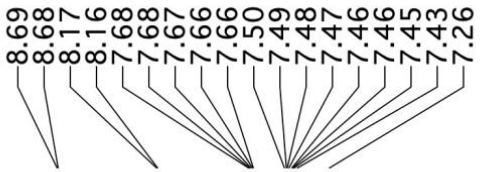
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
I
Ph
N
S298
55
ppm 200
150
100
50
0



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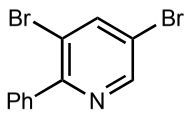
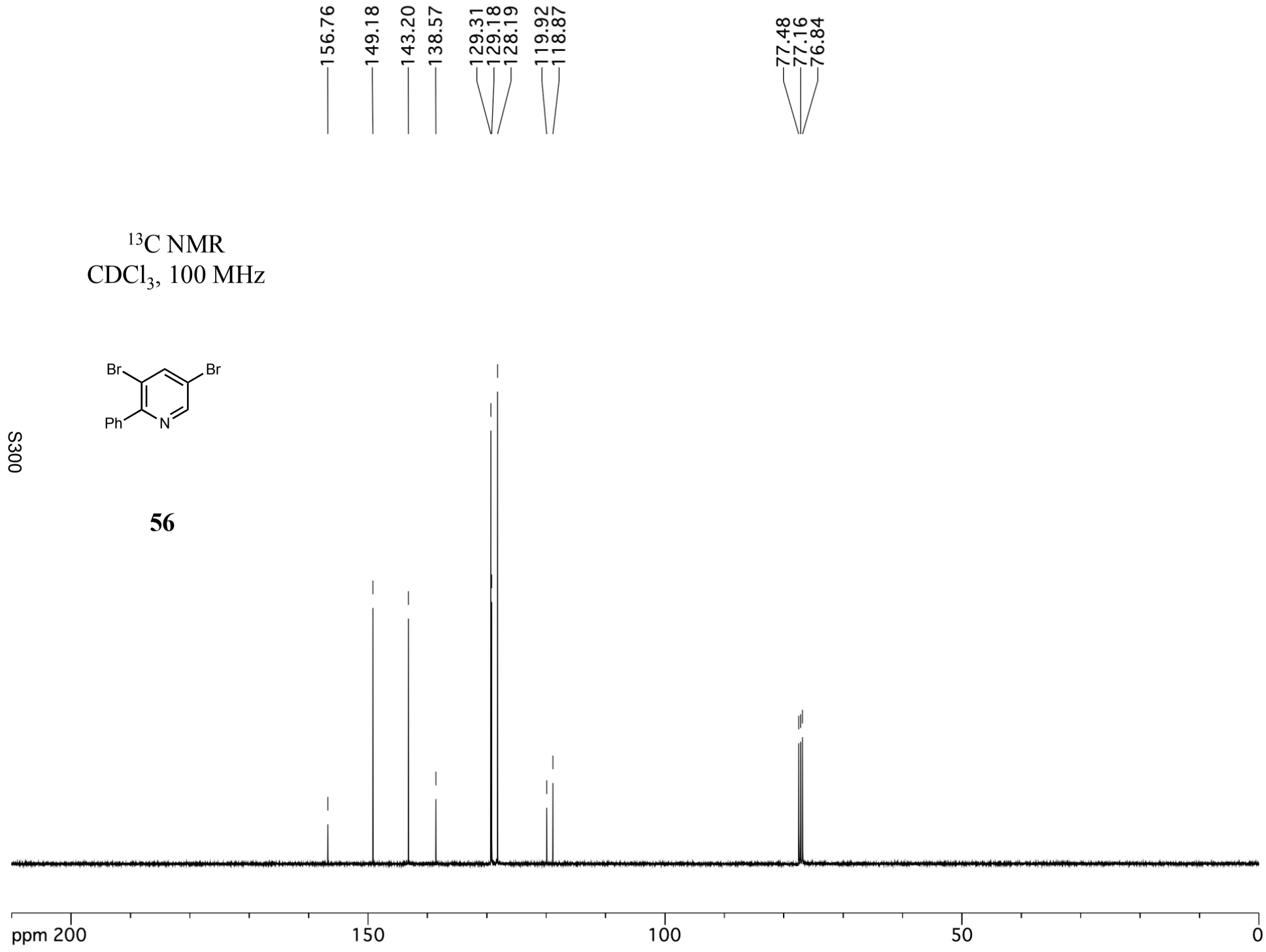
$CDCl_3$, 400 MHz



56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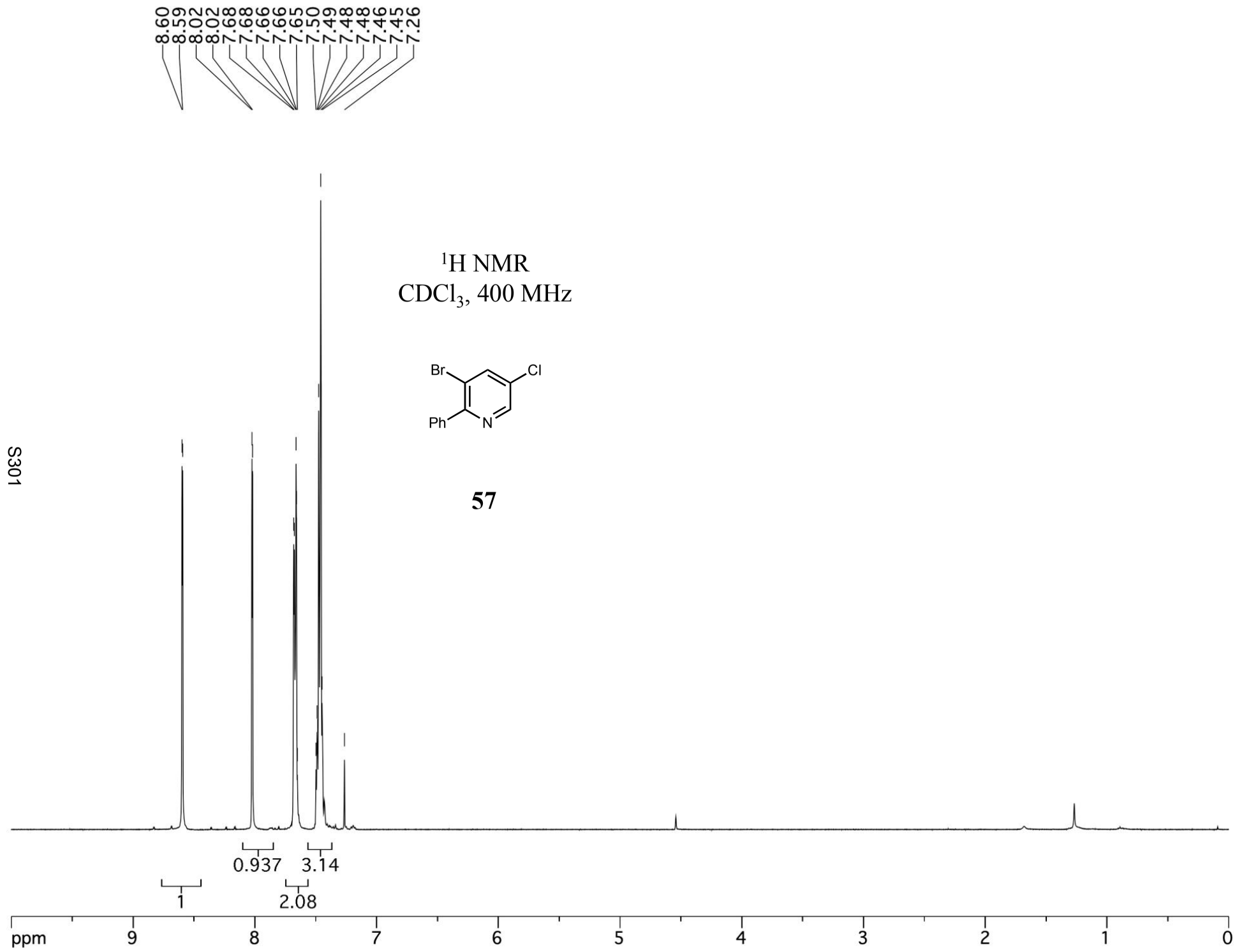
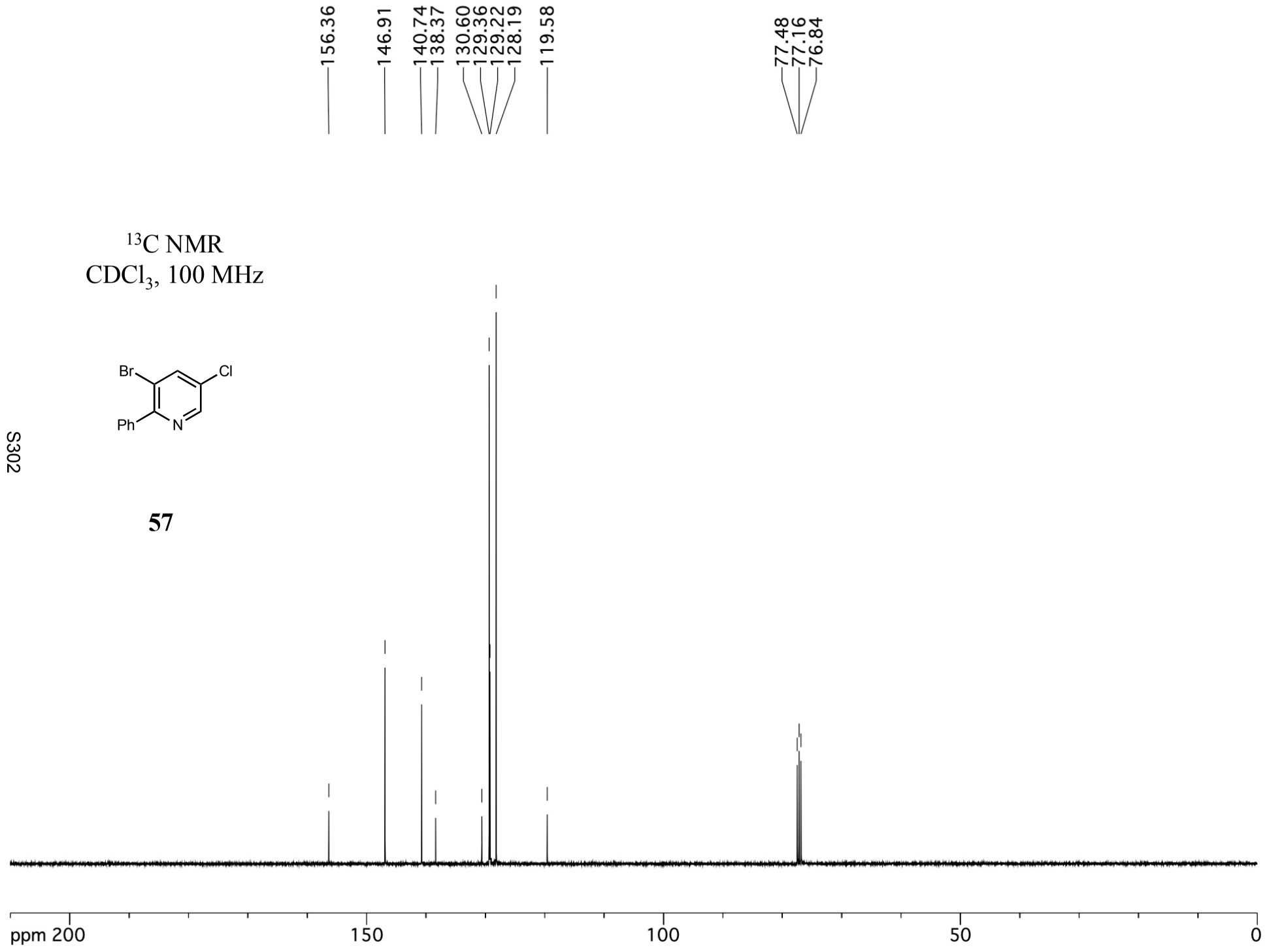
149.18
143.20
138.57
129.31
129.18
128.19
119.92
118.87
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
Br
Ph
N
S300
56
ppm 200
150
100
50
0



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

57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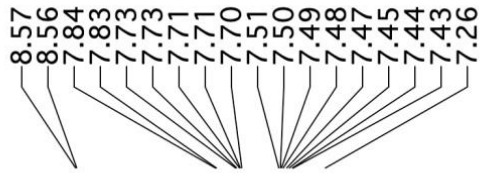
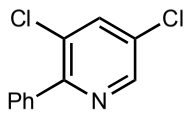
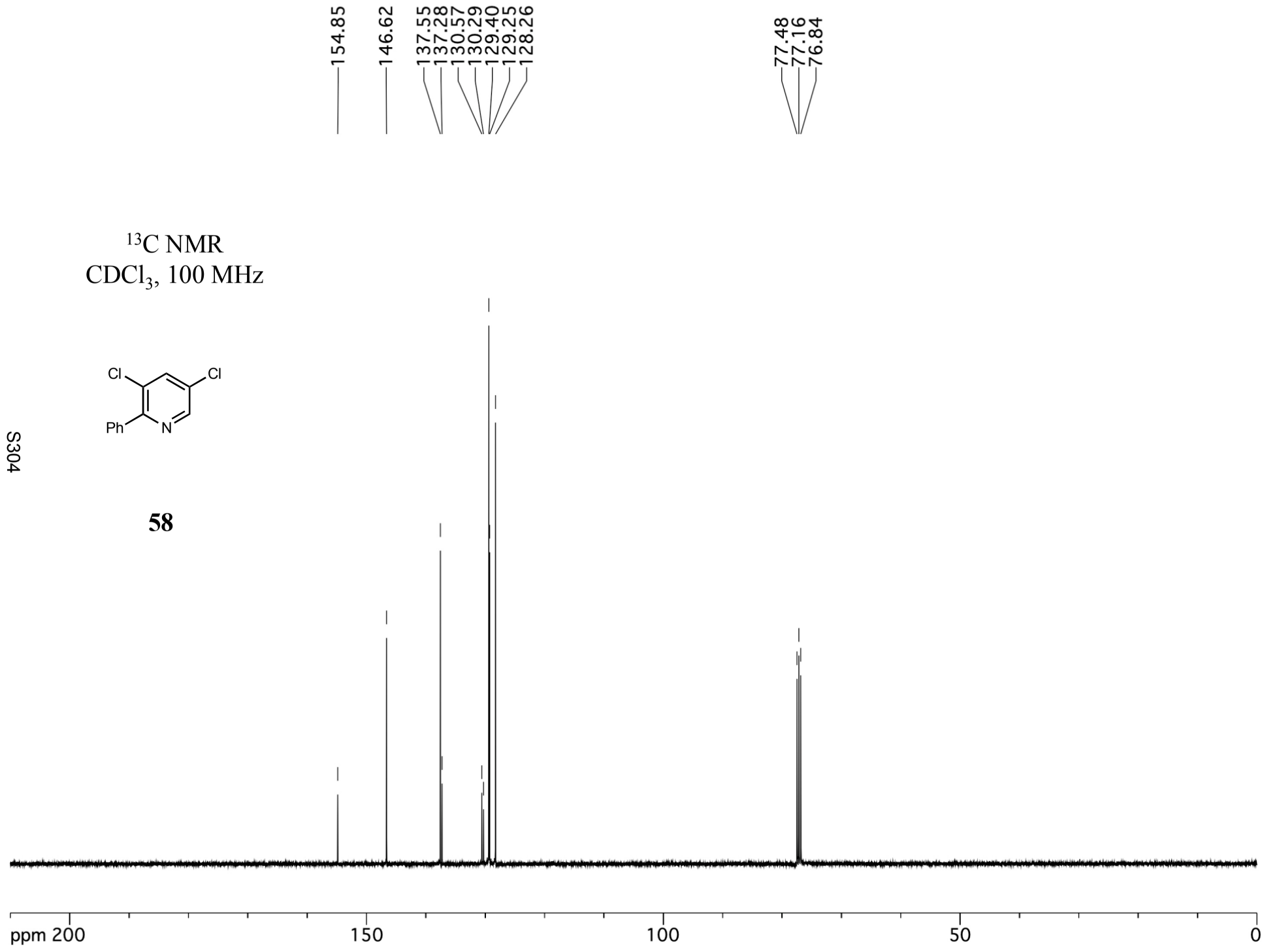
146.91
140.74
138.37
130.60
129.36
129.22
128.19
119.58
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Br
Cl
Ph
N
S302
57
ppm 200
150
100
50
0



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



58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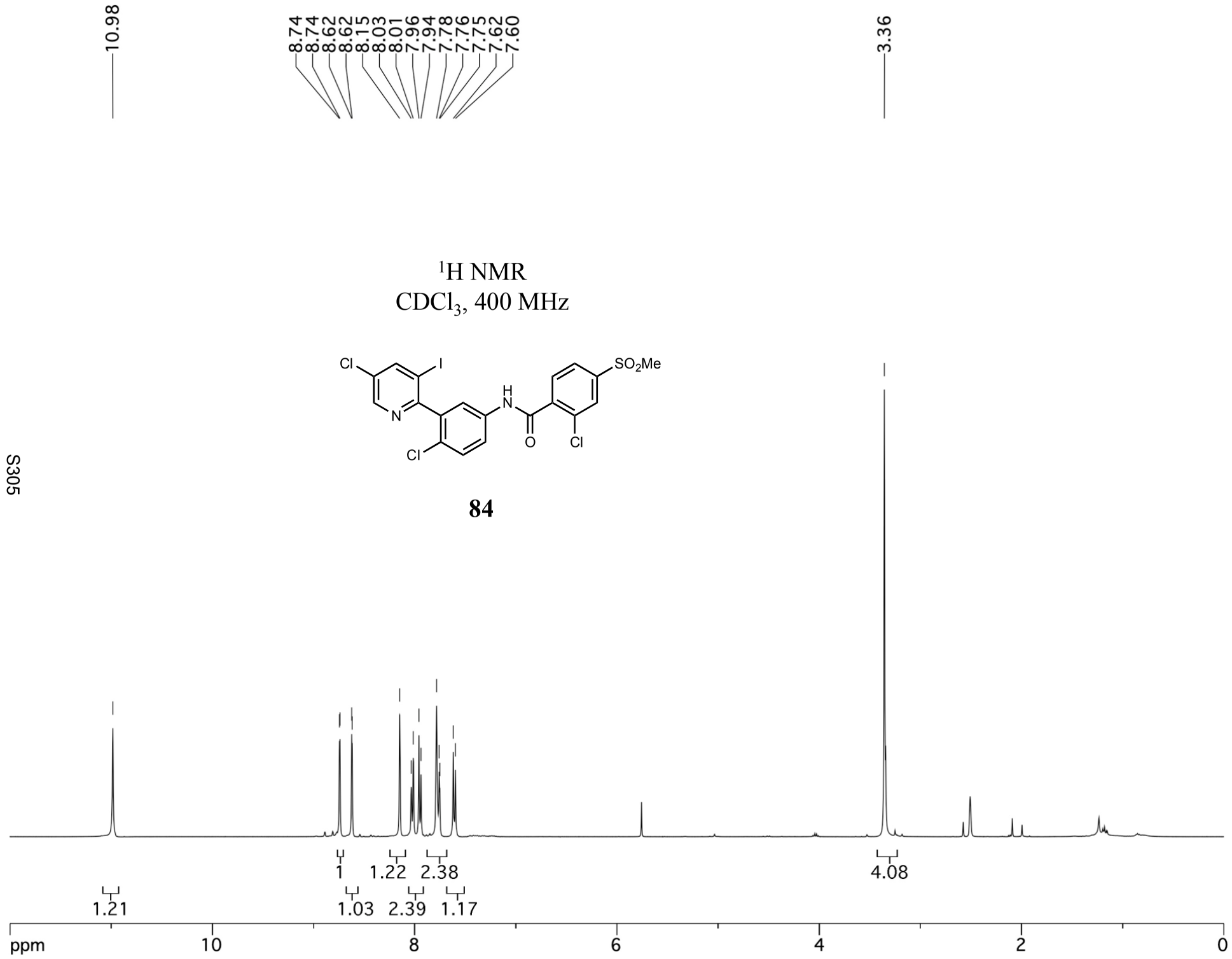
146.62
137.55
137.28
130.57
130.29
129.40
129.25
128.26
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
Cl
Ph
N
58
ppm 200
150
100
50
0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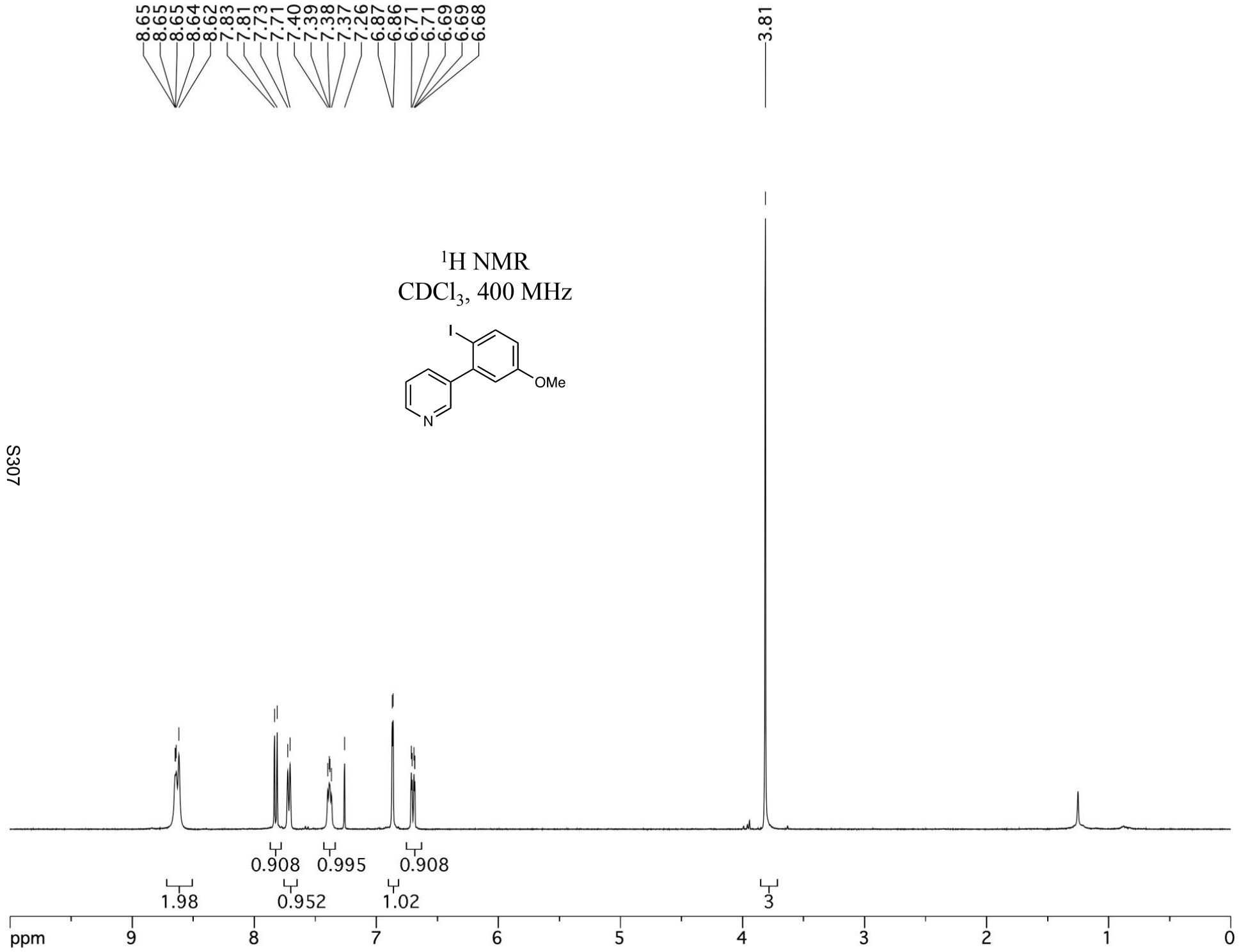
8.74
8.74
8.62
8.62
8.15
8.03
8.01
7.96
7.94
7.78
7.76
7.75
7.62
7.60
3.36
1H NMR
CDCl3, 400 MHz
Cl
I
N
H
N
O
Cl
Cl
SO2Me
S305
1.21
1
1.03
1.22
2.39
2.38
1.17
4.08
ppm
10
8
6
4
2
0

84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8.65
8.65
8.64
8.62
7.83
7.81
7.73
7.71
7.40
7.39
7.38
7.37
7.26
6.87
6.86
6.71
6.71
6.69
6.69
6.68
3.81
^{1}H NMR
$CDCl_3$, 400 MHz
I
OMe
N
0.908
0.995
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0.952
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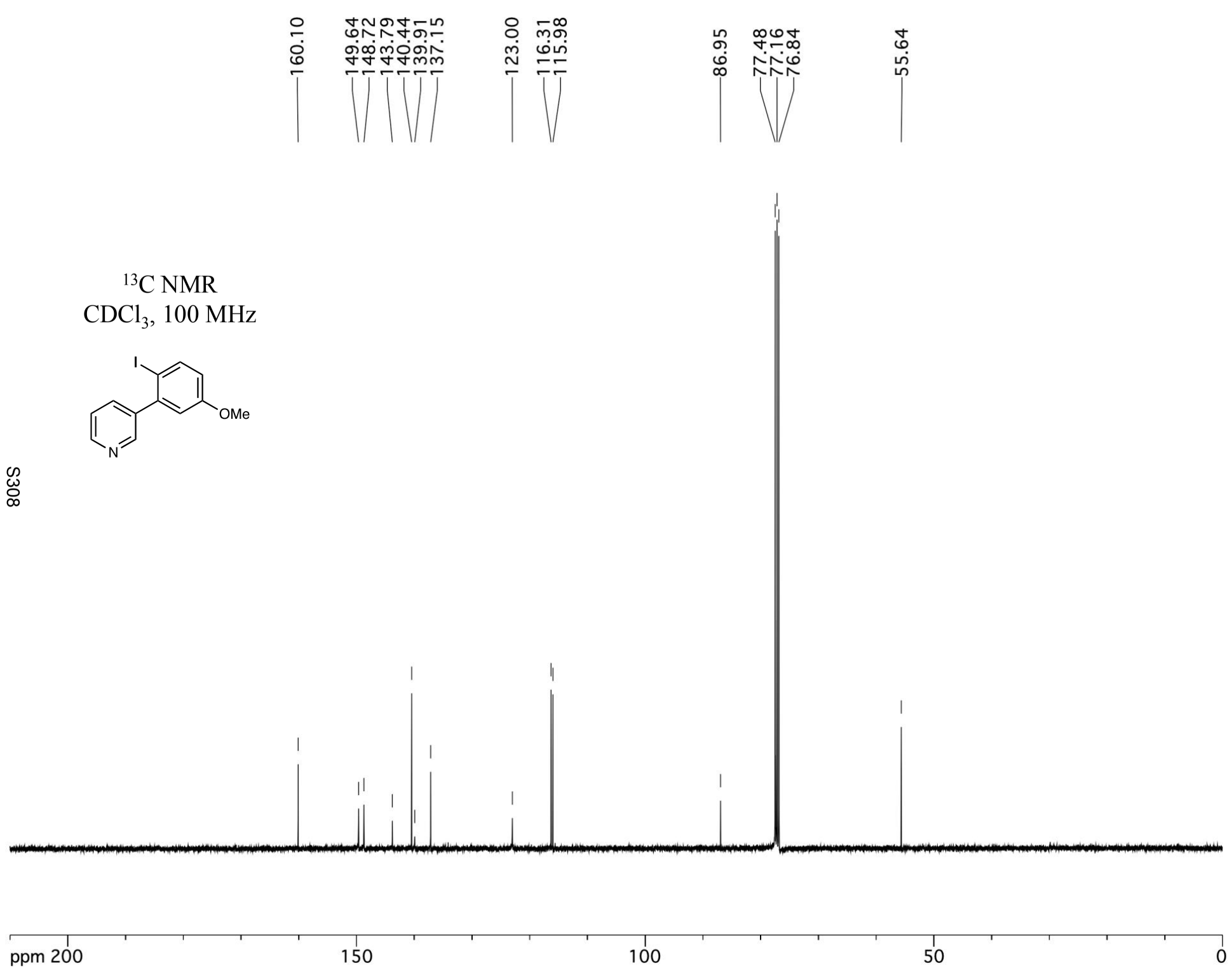
3
ppm
9
8
7
6
5
4
3
2
1
0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149.64
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143.79
140.44
139.91
137.15
123.00
116.31
115.98
86.95
77.48
77.16
76.84
55.64
^{13}C NMR
$CDCl_3$, 100 MHz
I
OMe
N
S308
ppm 200
150
100
50
0

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