Supporting Online Material for

Non-Symmetrical Bis-Azine Biaryls from Chloroazines: A Strategy Using Phosphorus Ligand-Coupling

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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). DEPT135, NOE experiments and 2–dimensional experiments (COSY, HMBC, and HSQC) were used to support assignments where appropriate.

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

Analytical thin layer chromatography (TLC) was performed using pre–coated glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Silicycle 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.

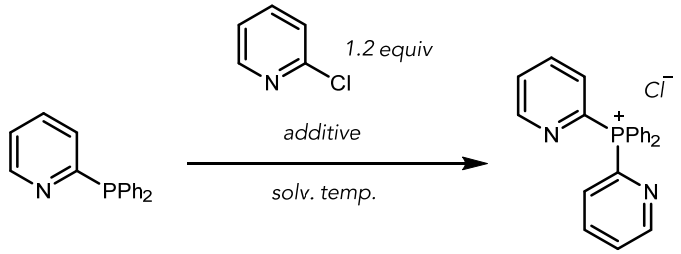
Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Ethyl acetate (EtOAc), 1,2–Dichloroethane (DCE), 1,4–

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

$HPPh_2$ (99%) was purchased from Oakwood Chemicals and stored in a glovebox. (2,2,2)-Trifluoroethanol (TFE) was purchased from Oakwood Chemicals and used without further purification. Anhydrous chlorobenzene (>99.8%) was purchased from Sigma Aldrich chemical company and used without further purification. HCl (4.0 M in dioxanes) and trifluoromethanesulfonic acid (98%) were purchased from Sigma Aldrich chemical company and used without further purification but were routinely stored in a –20 ºC fridge. KPF_6 (>99%) was purchased from Sigma Aldrich chemical company and used without further purification but was routinely stored in a desiccator. NaOTf was purchased from Oakwood Chemicals and used without further purification but was routinely stored in a desiccator.

2. Optimization Studies

Table S1: Phosphonium Salt Formation using SNAr Conditions

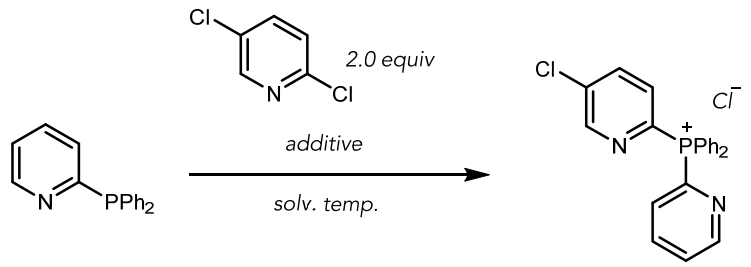


Entry	Solvent	Temp. °C	Conc. (M)	Acid	Yield (%)*
1	TFE	80	0.4	TfOH	n.d.†
2	2-Cl-pyridine (neat)	120	0.4	None	n.d.†
3	2-F-pyridine (neat)	120	0.4	None	n.d.†
4	2-Cl-pyridine (neat)	120	0.4	TfOH	73
5	2-F-pyridine (neat)	120	0.4	TfOH	80
6	DMSO	80	0.4	TfOH	n.d.†
7	DMF	80	0.4	TfOH	3
8	ACN	80	0.4	TfOH	11
9	EtOAc	80	0.4	TfOH	6
10	ACN	100	2.0	TfOH	25
11	EtOAc	100	2.0	TfOH	25
12	ethylene glycol	120	0.4	TfOH	7
13	dioxanes	100	0.4	TfOH	8
14	dioxanes‡	100	2.0	TfOH	22
15	dioxanes	100	2.0	TfOH	30
16	dioxanes	120	2.0	TfOH	90
17	dioxanes	120	2.0	HCl	89
18	**dioxanes⁂**	**120**	**2.0**	**TfOH**	**92**
19	**dioxanes⁂**	**120**	**2.0**	**HCl**	**93**

*^{1}H NMR yields shown using 1,3,5-trimethoxybenzene as an internal standard. †Products were not detected by LCMS or ^{1}H NMR. ‡2-Fluoropyridine used instead of 2-chloropyridine. ⁂NaOTf (2.4 eq) added from the beginning of the reaction.

Note: These conditions were found to work extremely well for the synthesis of 2,4'-phosphonium salts, however, were found to lack generality for 2,2'- bipyridine phosphonium salts. This led to an additional optimization and modified conditions for 2,2'- bipyridine phosphonium salts (**Table S2**).

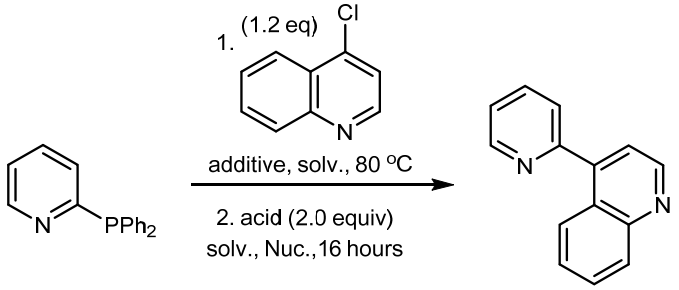
Table S2: 2,2' Bipyridine: Phosphonium Salt Formation using S_NAr Conditions



Entry	Solvent	Additive	Temp. °C	Conc. (M)	Acid	Yield (%)*
1	dioxane/tol. (1:1)	NaOTf	120	2	HCl	43
2	dioxane/tol. (1:1)	KPF_6	120	2	HCl	49
3	dioxane/tol. (1:1)	NaOTf	120	2	TfOH	42
4	dioxane/tol. (1:1)	none	120	2	TfOH	57
5	dioxane	none	120	2	TfOH	46
6	tol.	none	120	2	TfOH	60
7	tol.	KPF_6	120	2	TfOH	66
8	tol.	none	130	2	TfOH	70
9	PhCl	none	120	2	TfOH	51
10	PhCl	none	130	2	TfOH	67
11	PhCl	none	140	2	TfOH	69†
12	**PhCl**	**KPF_6**	**130**	**2**	**TfOH**	**81**
13	PhCl	KPF_6‡	130	2	TfOH	73
14	PhCl	$NaPF_6$	130	2	TfOH	79
15	PhCl	$LiPF_6$	130	2	TfOH	78

*^{1}H NMR yields shown using triphenylmethane as an internal standard. †Undesired phosphonium salt observed see **Challenges and Limitations** for example. ‡1.5 equivalents of KPF_6 was used instead of 1.0 equivalents.

Table S3: Heterobiaryl Synthesis by Phosphonium Salt Formation and Ligand Coupling

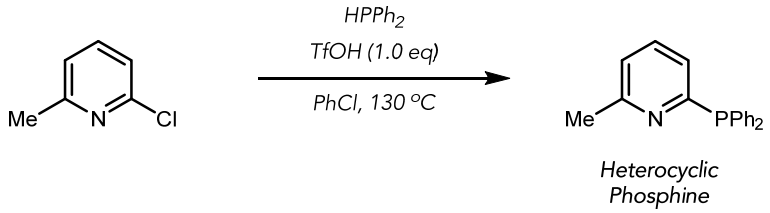


Entry	Additive	Acid	Solvent	Nuc. (eq)	Yield (%)*
1	None	TfOH	TFE	None	n.d.†
2	AgOTf‡	TfOH	TFE	None	n.d.†
3	AgOTf‡	TfOH	ACN	H_2O (10)	55

4	AgOTf‡	TfOH	EtOAc	H_2O (10)	37
5	AgOTf‡	TfOH	TFE	H_2O (5)	17
6	AgOTf‡	TfOH	TFE	H_2O (10)	23
7	AgOTf‡	TfOH	TFE	H_2O (20)	18
8	AgOTf‡	TfOH	TFE	EtOH (10)	n.d.
9	AgOTf‡	TfOH	TFE	EtOH (20)	n.d.
10	AgOTf	TfOH	TFE	H_2O (10)	n.d.
11	AgOTf	HCl	TFE	H_2O (10)	n.d.
12	**NaOTf**	**TfOH**	**TFE**	**H_2O (10)**	**83**
13	**NaOTf**	**HCl**	**TFE**	**H_2O (10)**	**85**

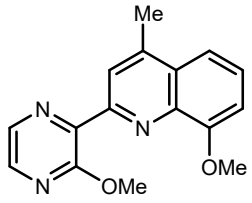
*^{1}H NMR yields shown using 1,3,5-trimethoxybenzene as an internal standard. †Products were not detected by LCMS or ^{1}H NMR. ‡AgOTf was added after salt formation was observed to be complete by LCMS.

Table S4: Phosphine Synthesis: $HPPh_2$ Hold Study

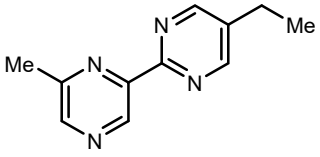


Entry	*$HPPh_2$ Hold Time**	*^{1}H NMR Yield (%)*
1	*No Hold*	*98%*
2	*1 week*	*90%*

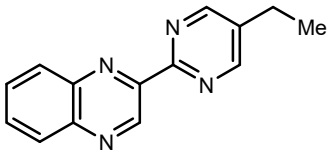
^{1}H NMR yields shown using 1,3,5-trimethoxybenzene as an internal standard. *$HPPh_2$ was obtained from the glove box and stored in an oven-dried 8mL vial under N_2 at –20 °C. Entry 1 was used immediately and entry 2 was stored for 1 week prior to use.



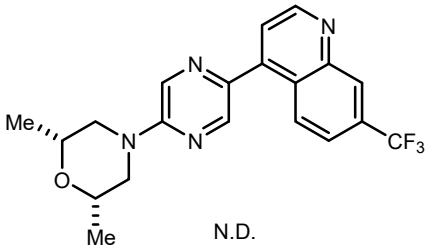
22% yield (isolated)



<3% yield



N.D.



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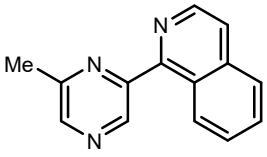

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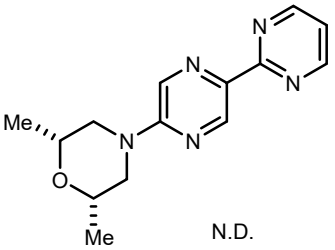

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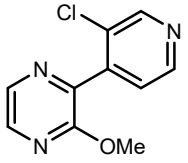

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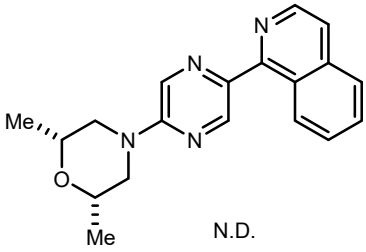

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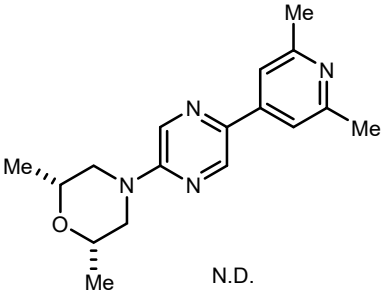

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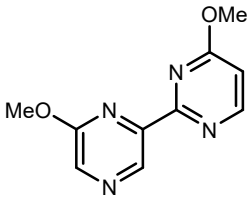

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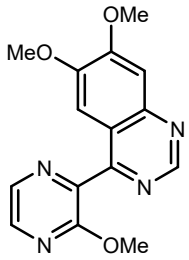
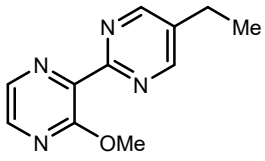
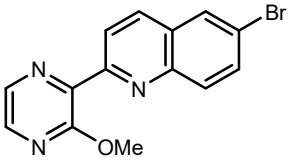


N.D.



N.D.

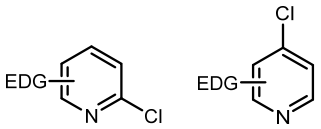


N.D.

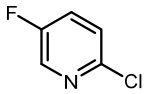
Scheme S1: Pyrazine Coupling Results/Challenges.

3. Challenges and Limitations

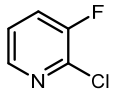
Phosphine/Phosphonium Salt Formation: Guidelines/Challenges



-Poor reactivity towards phosphine formation; low yields result; EDG located not on the azine ring are tolerated; phosphonium formation proceeds slowly

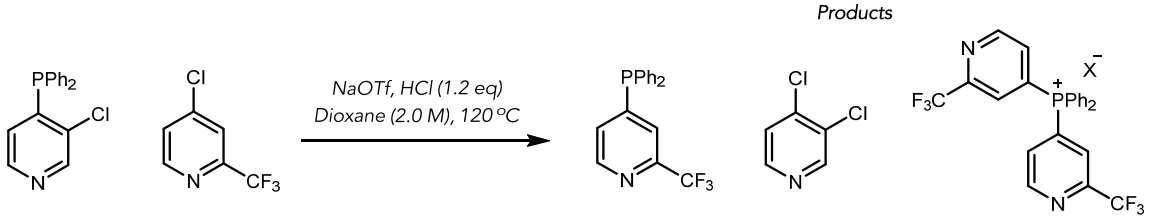


-Low yield observed for phosphine formation.

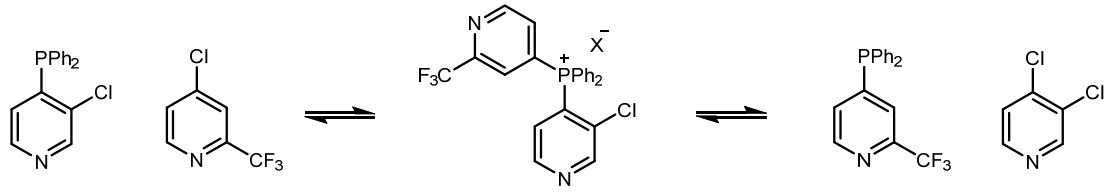


-Unexpected oxidation after isolation for phosphine formation. Reaction can be performed in one-pot (no phosphine isolation) to avoid oxidation

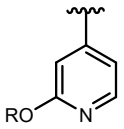
Phosphine transfer: Reaction equilibrium



-In this particular example; we observed phosphine transfer which we speculate results from an equilibrium between the phosphonium salt and a heteroaryl chloride along with a heteroaryl phosphine
-When paired with other heteroarenes, both azines were shown to be competent coupling partners (3a and 3c)

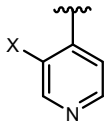


Ligand Coupling: Guidelines/Challenges



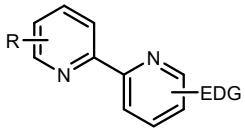
R= alkyl

-Dealkylation observed in some cases with HCl. Using TfOH as the acid resolves this issue

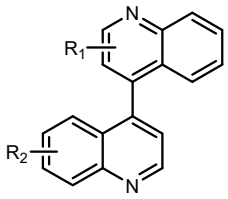


X= Br or I

-Dehalogenation observed under ligand-coupling conditions



-Slow reaction rate for ligand-coupling reaction



-No desired coupling observed; phosphonium salt remained or reversion to SM observed

Notes:

-The ligand-coupling reaction was typically able to achieve the desired heterobiaryl product with yields varying based on the pyridine substitutuents over substitution elsewhere in the molecule.

-Ligand-coupling together 2 deficient pyridines (3 or more EWG directly attached to the pyridines) have been seen to give lower than expected yields for the ligand coupled product.

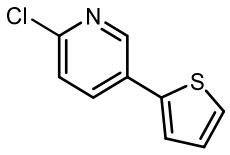
-An excess of basic nitrogens (5+ between the two coupling partners) results in slower reaction rates.

-When using conditions B', it was found that using a 1:1 TFE/toluene mixture is successful at limiting the amount of phosphine transfer/promote ligand-coupling over retro-S_NAr. This solvent mixture does result in slightly lower yields for the desired product in most cases.

-When preparing a phosphine for use in the coupling reaction, it is recommended to make the less S_NAr active partner into the phosphine. This allows one to use the most mild conditions possible for salt formation/coupling and will minimize the amount of phosphine transfer observed.

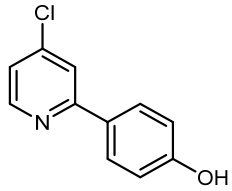
4. Preparation of Heteroaryl Precursors

2-Chloro-5-(thiophen-2-yl)pyridine



An oven dried 80 mL pressure tube was charged with (6-chloropyridin-3-yl)boronic acid (1.18 g, 7.50 mmol), Na_2CO_3 (1.06 g, 10.00 mmol), $Pd(PPh_3)_4$ (578 mg, 0.50 mmol), and subjected to three cycles of vacuum/nitrogen backfill. 2-bromothiophene (0.484 mL, 5.00 mmol) was charged to the tube followed by degassed H_2O (5 mL) and degassed dioxanes (24 mL). The mixture was heated at 80 °C for 24 hours, then cooled to room temperature and diluted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted 2x with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as a white crystalline solid (0.550 g, 2.81 mmol, 56% yield). mp 45-46 °C; IR ν_{max}/cm^{-1} (film): 3104, 3071, 2924, 1581, 1303, 931, 641; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, d, *J* = 2.6 Hz), 7.82 (1H, dd, *J* = 8.3, 2.6 Hz), 7.37 (1H, dd, *J* = 5.1, 1.2 Hz), 7.37-7.29 (2H, m), 7.12 (1H, dd, *J* = 5.1, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.1, 146.7, 139.1, 135.9, 129.6, 128.6, 126.6, 124.8, 124.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 196.1, $C_9H_7ClNS^+$ requires 196.0.

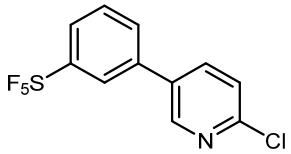
4-(4-Chloropyridin-2-yl)phenol



An oven dried 80 mL pressure tube was charged with (4-hydroxyphenyl)boronic acid (762 mg, 5.52 mmol), K_2CO_3 (2.29 g, 16.57 mmol), $Pd(OAc)_2$ (62 mg, 0.28 mmol), triphenylphosphine (290 mg, 1.11 mmol) and subjected to three cycles of vacuum/nitrogen backfill. 2-Bromo-4-chloropyridine (1.06 g, 5.52 mmol) was charged to the tube followed by H_2O (8 mL) and dimethoxyethane (8 mL). The mixture was heated at 85 ºC for 24.5 hours. Additional (4-hydroxyphenyl)boronic acid (381 mg, 2.76 mmol) was added and then the mixture was heated at 85 ºC for 3 hours. Additional (4-hydroxyphenyl)boronic acid (762 mg, 5.52 mmol) was added again and then the mixture was heated at 85 ºC for 6.5 hours, then cooled to room temperature and diluted with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted 2x with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered over a frit, and concentrated in vacuo. Flash column chromatography (silica gel, gradient elution: 20% EtOAc in hexanes to 25% EtOAc in hexanes) afforded the title compound as a yellow crystalline solid (633 mg, 3.08 mmol, 56% yield). mp 175-178 ºC; IR ν_{max}/cm^{-1} (film): 3055, 2926, 2589, 1608, 1575, 1565, 1548, 1517, 1435, 1381, 1283, 1240, 1229, 1169, 1100, 815; ^1H NMR (400 MHz, DMSO-d_6) δ: 9.85 (1H, s), 8.54 (1H, d, *J* = 5.3 Hz), 8.05–7.88 (3H, m), 7.35 (1H, dd, *J* = 5.5, 1.9 Hz), 6.87 (2H, d, *J*

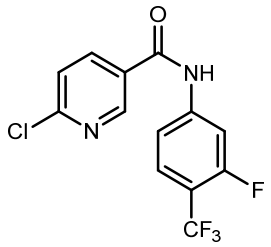
= 8.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.2, 158.0, 150.6, 143.7, 128.3, 128.2, 121.3, 118.9, 115.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 206.1, $C_{11}H_9ClNO^+$ requires 206.0.

2-Chloro-5-(3-(pentafluoro-λ^6-sulfaneyl)phenyl)pyridine



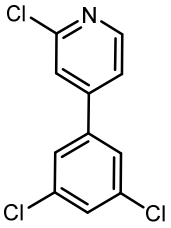
Prepared according to an established procedure[2] using (3-bromophenyl)pentafluoro-λ^6-sulfane (939 mg, 3.32 mmol), (6-chloropyridin-3-yl)boronic acid (601 mg, 3.82 mmol), $Pd_2(dba)_3$ (30 mg, 0.033 mmol), tricyclohexylphosphane (26 mg, 0.093 mmol), aqueous K_3PO_4 (1.25 M, 4.5 mL, 5.64 mmol), and dioxanes (9 mL). Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (274 mg, 0.87 mmol, 26% yield). mp 95-96 ºC; IR ν_{max}/cm^{-1} (film): 3085, 3038, 2923, 1557, 1457, 1429, 1370, 1105, 860, 833, 796, 781; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 2.4 Hz), 7.90 (1H, t, *J* = 1.9 Hz), 7.84-7.78 (2H, m), 7.69 (1H, d, *J* = 7.9 Hz), 7.60 (1H, t, *J* = 8.0 Hz), 7.44 (1H, dd, *J* = 8.3, 0.5 Hz); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 154.8 (app t, *J* = 1.7 Hz), 151.6, 148.2, 137.8, 137.4, 134.1, 130.3, 129.8, 126.0 (app qn, *J* = 4.6 Hz), 124.8 (app qn, *J* = 4.6 Hz), 124.7; ^{19}F NMR (365 MHz, $CDCl_3$) δ: 83.70 (qn, *J* = 148.7 Hz), 62.72 (d, *J* = 150.1 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 316.1, $C_{11}H_8ClF_5NS^+$ requires 316.0.

6-Chloro-N-(3-fluoro-4-(trifluoromethyl)phenyl)nicotinamide



An oven dried 100 mL round bottom flask was charged with 3-fluoro-4-(trifluoromethyl)aniline (896 mg, 5.00 mmol) and THF (25 mL) under N_2. K_2CO_3 (1.382g, 10.00 mmol) was added to the flask at room temperature followed by 6-chloronicotinoyl chloride (880 mg, 5.00 mmol). After 20 hours stirring at room temperature, the reaction mixture was filtered and the filtrate was cooled to 0 ºC and water was added until a yellow oil formed. The mixture was concentrated down to remove the THF until a pale yellow precipitated. The solution was filtered and the solid collected. Flash column chromatography (silica gel: 40% Et_2O in toluene) afforded the title compound as a white crystalline solid (1.03 g, 3.25 mmol, 65% yield). mp 185-186 ºC; IR ν_{max}/cm^{-1} (film): 3279, 3103, 2923, 1350, 866, 730, 541; ^{1}H NMR (400 MHz, MeCN-d_3) δ: 9.18 (1H, s), 8.88 (1H, d, *J* = 2.5 Hz), 8.22 (1H, dd, *J* = 8.4, 2.5 Hz), 7.89 (1H, d, *J* = 12.5 Hz), 7.66 (1H, t, *J* = 8.4 Hz), 7.61-7.52 (2H, m); ^{13}C NMR (100 MHz, CD_3OD) δ: 165.6, 161.2 (dd, *J* = 252.2, 2.4 Hz), 155.5, 150.2, 145.4, 140.0, 130.8, 129.0-127.4 (m), 125.5, 121.5 (q, *J* = 270.1), 116.6 (d, *J* = 3.4 Hz), 114.3 (dd, *J* = 33.3, 12.8 Hz), 109.4 (d, *J* = 25.8 Hz); ^{19}F NMR (365 MHz, MeCN-d_3) δ: –61.28 (d, *J* = 12.4 Hz), –114.76 (qd, *J* = 12.7, 8.2 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 319.0, $C_{13}H_8ClF_4N_2O^+$ requires 319.0.

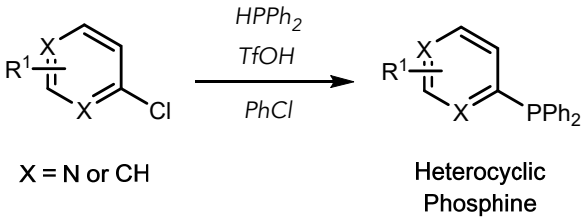
2-Chloro-4-(3,5-dichlorophenyl)pyridine



An oven dried 80 mL pressure tube was charged with (3,5-dichlorophenyl)boronic acid (840 mg, 4.40 mmol), K_2CO_3 (1.66 g, 12.00 mmol), $Pd(OAc)_2$ (45 mg, 0.20 mmol), triphenylphosphine (210 mg, 0.80 mmol) and subjected to three cycles of vacuum/nitrogen backfill. 2-Chloro-4-bromopyridine (0.44 mL, 4.00 mmol) was charged to the tube followed by degassed H_2O (14 mL) and degassed dimethoxyethane (14 mL). The mixture was heated at 80 °C for 24 hours, then cooled to room temperature and diluted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted 2x with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered over a frit, and concentrated *in vacuo*. Flash column chromatography (silica gel neutralized with NEt_3: 1% EtOAc in hexanes) afforded the title compound as a white crystalline solid (0.932 g, 3.61 mmol, 90% yield). mp 101-103 °C; IR ν_{max}/cm^{-1} (film): 3082, 3052, 3020, 1938, 1430, 1483, 885, 541; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.46 (1H, dd, J = 5.1, 0.7 Hz), 7.54 (1H, d, J = 2.0 Hz), 7.42-7.33 (2H, m), 7.32-7.23 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.8, 149.7, 149.1, 135.9, 135.2, 133.1, 131.6, 130.4, 127.8, 124.8, 123.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 258.0, $C_{11}H_7Cl_3N^+$ requires 258.0.

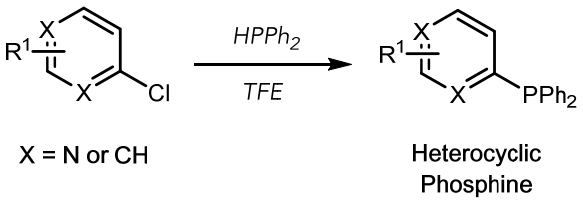
5. Preparation of Heteroaryl Phosphines

General Procedure A (pyridine heterocyclic phosphine)



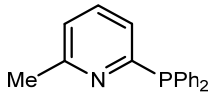
An oven dried 8 mL vial equipped with a stir bar was charged with the heterocycle (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, chlorobenzene (2.0 M) was added, followed by diphenylphosphine (1.2 equiv), and trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to 130 °C and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl phosphine product.

General Procedure B (quinoline/diazine heterocyclic phosphine)



An oven dried 8 mL vial (< 1.0 mmol) or 15 mL pressure tube (1.0-4.0 mmol) equipped with a stir bar was charged with the heterocycle (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and TFE (0.4 M) was added, followed by diphenylphosphine (1.2 equiv). The reaction was heated to 80 ºC and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl phosphine product.

2-(Diphenylphosphaneyl)-6-methylpyridine (2a)

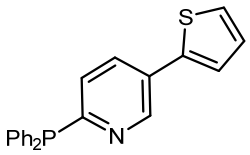


Prepared according to general procedure A using 2-chloro-6-methylpyridine (0.22 mL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 µL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 ºC for 21 hours. Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (522 mg, 1.88 mmol, 94% yield). mp 80-82 ºC; IR ν_{max}/cm^{-1} (film): 3048, 3001, 2961, 1576, 1555, 1443, 1433, 1094, 796, 754, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (1H, td, J = 7.2, 1.2 Hz), 7.40-7.29 (10H, m), 7.03 (1H, d, J = 7.8 Hz), 6.82 (1H, d, J = 7.6 Hz), 2.57 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2 (d, J = 7.3 Hz), 159.1 (d, J = 14.5 Hz), 136.7 (d, J = 11.2 Hz), 136.0, 134.2 (d, J = 19.5 Hz), 129.0, 128.6 (d, J = 7.1 Hz), 125.0 (d, J = 11.6 Hz), 122.1, 24.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –4.96; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 278.1, $C_{18}H_{17}NP^+$ requires 278.1.

Scale-Up:

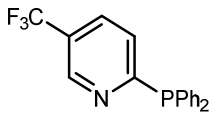
Prepared according to general procedure A (40 mL pressure tube) using 2-chloro-6-methylpyridine (1.11 mL, 10.00 mmol), diphenylphosphane (2.09 mL, 10.00 mmol), trifluoromethanesulfonic acid (883 µL, 10.00 mmol), and chlorobenzene (5.0 mL) at 130 ºC for 16 hours. Flash column chromatography (silica gel, gradient elution: 7.5% EtOAc in hexanes) afforded the title compound as a white powder (2.397 g, 8.60 mmol, 86% yield). Spectral data is consistent with compound **2a**.

2-(Diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (2b)



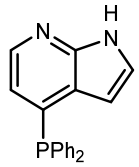
Prepared according to general procedure A using 2-chloro-5-(thiophen-2-yl)pyridine (391 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 ºC for 21 hours. Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (610 mg, 1.77 mmol, 88% yield). mp 89-91 ºC; IR ν_{max}/cm^{-1} (film): 3053, 1544, 1478, 1458, 1432, 1378, 1267, 1206, 1095, 1025, 850, 828; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99(1H, d, *J* = 2.0 Hz), 7.74 (1H, dt, *J* = 8.1, 2.0 Hz), 7.47-7.32 (12H, m), 7.14-7.07 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6 (d, *J* = 3.1 Hz), 147.4 (d, *J* = 13.0 Hz), 140.3, 136.2 (d, *J* = 10.7 Hz), 134.3 (d, *J* = 19.8 Hz), 132.5 (d, *J* = 2.3 Hz), 129.2, 128.9, 128.8 (d, *J* = 6.9 Hz), 128.4, 128.0 (d, *J* = 16.8 Hz), 126.3, 124.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –4.05; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 346.1, $C_{21}H_{17}NPS^+$ requires 346.1.

2-(Diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (2c)



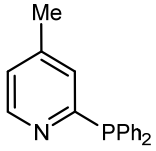
Prepared according to general procedure A using 2-chloro-5-trifluoromethylpyridine (363 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 ºC for 15.5 hours. Flash column chromatography (silica gel, gradient elution: 1% EtOAc in hexanes to 2% EtOAc in hexanes) afforded the title compound as a yellow oil (590 mg, 1.78 mmol, 89% yield). IR ν_{max}/cm^{-1} (film): 3055, 3003, 2359, 1955, 1881, 1684, 1594, 1558, 1479, 1281, 938, 578; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, s), 7.76 (1H, d, *J* = 8.1), 7.48-7.31 (10H, m), 7.19 (1H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.7 (d, *J* = 2.2 Hz), 146.8 (dd, *J* = 11.7, 4.0 Hz), 135.2 (d, *J* = 9.9), 134.5 (d, *J* = 20.3 Hz), 132.9-132.6 (m), 132.3 (d, *J* = 9.6 Hz), 129.7, 129.0 (d, *J* = 7.5 Hz), 127.3 (d, *J* = 16.1 Hz), 123.7 (q, *J* = 272.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.51; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –2.34; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 332.1, $C_{18}H_{14}F_3NP^+$ requires 332.1.

4-(Diphenylphosphaneyl)-1H-pyrrolo[2,3-b]pyridine (2d)



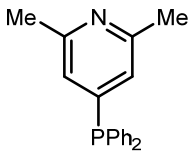
Prepared according to general procedure A using 4-chloro-1H-pyrrolo[2,3-b]pyridine (305 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol, trifluoromethanesulfonic acid (177 μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 20 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a faint yellow crystalline solid (550 mg, 1.82 mmol, 91% yield). mp 146-148 °C; IR ν_{max}/cm^{-1} (film): 3119, 3069, 3054, 2902, 2802, 2763, 1592, 1182, 792, 611; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76 (1H, s), 8.20 (1H, d, *J* = 4.9 Hz), 7.46-7.31 (11H, m), 6.71-6.57 (1H, m), 6.28 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.6 (d, *J* = 6.9 Hz), 142.2, 140.5 (d, *J* = 17.2 Hz), 135.2 (d, *J* = 20.3 Hz), 134.4 (d, *J* = 20.3 Hz), 129.4, 128.8 (d, *J* = 7.7 Hz), 125.4, 123.3, 119.2 (d, *J* = 4.4 Hz), 101.2 (d, *J* = 6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: –12.55; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 303.1, $C_{19}H_{16}N_2P^+$ requires 303.1.

2-(Diphenylphosphaneyl)-4-methylpyridine (2e)



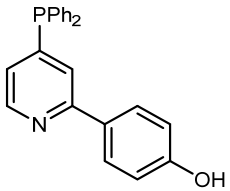
Prepared according to general procedure A using 2-chloro-4-methylpyridine (0.22 mL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 14 hours. Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 15% EtOAc in hexanes) afforded the title compound as a white powder (523 mg, 1.89 mmol, 94% yield). mp 69-71 °C; IR ν_{max}/cm^{-1} (film): 3066, 3045, 2922, 1584, 1547, 1477, 1457, 1434, 1388, 1373, 1311, 1089, 1025, 999, 826, 752 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (1H, d, *J* = 4.6 Hz), 7.44-7.29 (10H, m), 7.00 (1H, d, *J* = 4.1 Hz), 6.93 (1H, s), 2.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4 (d, *J* = 4.6 Hz), 150.2 (d, *J* = 13.0 Hz), 146.9 (d, *J* = 2.6 Hz), 136.4 (d, *J* = 10.8 Hz), 134.2 (d, *J* = 19.8 Hz), 129.1, 128.9 (d, *J* = 16.4 Hz), 128.7 (d, *J* = 6.9 Hz), 123.4, 21.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –4.06; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 278.2, $C_{18}H_{17}NP^+$ requires 278.1.

4-(Diphenylphosphaneyl)-2,6-dimethylpyridine (2f)



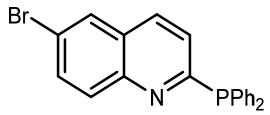
Prepared according to general procedure A using 4-chloro-2,6-dimethylpyridine (283 mL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 20 hours. Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as a white crystalline solid (582 mg, 2.00 mmol, 99% yield). mp 118-119 °C; IR ν_{max}/cm^{-1} (film): 3069, 3052, 3000, 2984, 2954, 2916, 2361, 1739, 1675, 1158, 831, 618, 542; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.29 (10H, m), 6.79 (2H, d, J = 7.2 Hz), 2.46 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5 (d, J = 5.1 Hz),149.0 (d, J = 16.2 Hz), 135.4 (d, J = 10.0 Hz), 134.3 (d, J = 20.3 Hz), 129.5, 128.9 (d, J = 7.5 Hz), 123.9 (d, J = 15.9 Hz), 24.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –6.96; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 292.2, $C_{19}H_{19}NP^+$ requires 292.1.

4-(4-(Diphenylphosphaneyl)pyridin-2-yl)phenol (2g)



Prepared according to general procedure A using 4-(4-chloropyridin-2-yl)phenol (206 mg, 1.00 mmol), diphenylphosphane (0.21 mL, 1.20 mmol), trifluoromethanesulfonic acid (88 μL, 1.00 mmol), and chlorobenzene (0.5 mL) at 130 °C for 2 hours. Flash column chromatography (silica gel, gradient elution: 30% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white powder (293 mg, 0.83 mmol, 83% yield). mp 196-198 °C; IR ν_{max}/cm^{-1} (film): 3004, 2794, 2663, 2591, 2479, 1608, 1579, 1518, 1435, 1376, 1278, 1241, 1174, 1000, 824; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.76 (1H, s), 8.54 (1H, dd, J = 5.1, 2.5 Hz), 7.76 (2H, d, J = 8.7 Hz), 7.53 (1H, d, J = 7.6 Hz), 7.50–7.41 (m, 6H), 7.41–7.29 (m, 4H), 6.91 (1H, ddd, J = 6.2, 4.9, 1.4 Hz), 6.82 (2H, d, J = 8.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.7, 155.9 (d, J = 5.4 Hz), 149.2 (d, J = 4.1 Hz), 148.6 (d, J = 17.3 Hz), 134.7 (d, J = 10.4 Hz), 133.8 (d, J = 20.3 Hz), 129.7, 129.3–128.6 (2C, m), 127.9, 124.3 (d, J = 13.0 Hz), 122.1 (d, J = 18.8 Hz), 115.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –6.32; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 356.2, $C_{23}H_{19}NOP^+$ requires 356.1.

6-Bromo-2-(diphenylphosphaneyl)quinoline (2h)

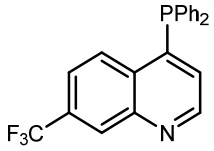


Prepared according to general procedure B using 2-chloro-6-bromoquinoline (485 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 19 hours. Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as an orange viscous oil (748 mg, 1.90 mmol, 95% yield). IR ν_{max}/cm^{-1} (film): 3047, 3006, 2967, 2929, 2872, 223, 1963, 1575, 1537, 1286, 999; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (1H, d, *J* = 9.01), 7.95-7.88 (2H, m), 7.76 (1H, dd, *J* = 9.0, 2.2 Hz), 7.52-7.30 (10H, m), 7.20 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.9 (d, *J* = 1.54 Hz), 147.2 (d, *J* = 14.4 Hz), 136.1 (d, *J* = 11.1 Hz), 134.4 (d, *J* = 19.8 Hz) 134.4 (d, *J* = 2.6 Hz), 133.3, 131.5, 129.8, 129.3, 128.8 (d, *J* = 7.2 Hz), 128.0, 125.2 (d, *J* = 14.7 Hz), 120.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –1.83; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 392.1, $C_{21}H_{16}BrNP^+$ requires 392.0.

Scale-Up:

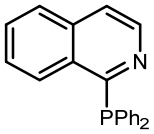
Prepared according to general procedure B (using 40 mL pressure tube) using 2-chloro-6-bromoquinoline (2.425 g, 10.00 mmol), diphenylphosphane (2.09 mL, 12.00 mmol), and TFE (25.0 mL) at 80 °C for 19 hours. Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as an orange viscous oil (3.513 g, 8.95 mmol, 90% yield). Spectral data is consistent with compound **2h**.

4-(diphenylphosphaneyl)-7-(trifluoromethyl)quinoline (2i)



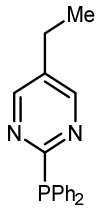
Prepared according to general procedure B using 4-chloro-7-(trifluoromethyl)quinoline (926 mg, 4.00 mmol), diphenylphosphane (0.84 mL, 4.80 mmol), and TFE (10.0 mL) at 80 °C for 16 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as an faint yellow solid (1.30 g, 3.41 mmol, 85% yield). mp 86-89 °C; IR ν_{max}/cm^{-1} (film): 3074, 3052, 3016, 1569, 1505, 1478, 1433, 1206, 856, 600, 529; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.84 (1H, dd, *J* = 4.4, 1.2 Hz), 8.44 (1H, s), 8.34 (1H, dd, *J* = 8.8, 3.4 Hz), 7.62 (1H, dd, *J* = 8.8, 2.0 Hz), 7.46-7.27 (10H, m), 6.93 (1H, t, *J* = 4.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.1, 147.6 (d, *J* = 22.5 Hz), 146.8 (d, *J* = 2.7 Hz), 134.5 (d, *J* = 20.5 Hz), 133.9 (d, *J* = 8.3 Hz), 131.5 (d, *J* = 3.5 Hz), 131.4 (d, *J* = 47.7 Hz), 129.2, 129.2 (d, *J* = 7.6 Hz), 128.2-127.9 (m), 127.6 (d, *J* = 22.0 Hz), 127.1, 124.0 (q, *J* = 272.5 Hz), 122.6-122.2 (m); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.75 ^{31}P NMR (162 MHz, $CDCl_3$) δ: –14.95; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 382.2, $C_{22}H_{16}F_3NP^+$ requires 382.1.

1-(diphenylphosphaneyl)isoquinoline (2j)



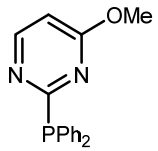
Prepared according to general procedure B using 1-chloro-isoquinoline (328 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 16.5 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as an white crystalline solid (579 mg, 1.86 mmol, 93% yield). mp 143-145; °C IR ν_{max}/cm^{-1} (film): 3069, 3046, 3004, 2924, 2361, 2340, 1577, 1543, 1492, 1434, 1304, 828, 694, 672, 546, 539, 527; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66-8.56 (2 H, m), 7.82 (1H, d, *J* = 8.2 Hz), 7.65 (1H, t, *J* = 7.5 Hz), 7.58 (1H, d, *J* = 5.6 Hz), 7.52 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz), 7.45-7.29 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8 (d, *J* = 10.0 Hz), 143.4 (d, *J* = 4.1 Hz), 136.1 (d, *J* = 6.9 Hz), 135.5 (d, *J* = 4.0 Hz), 134.6 (d, *J* = 20.0 Hz), 132.2 (d, *J* = 29.0 Hz), 130.1 (d, *J* = 1.3 Hz), 129.0, 128.5 (d, *J* = 7.6 Hz), 127.5 (d, *J* = 2.0 Hz), 127.3 (d, *J* = 1.8 Hz), 127.1 (d, *J* = 23.0 Hz), 120.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –8.33; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 314.2, $C_{21}H_{17}NP^+$ requires 314.1.

2-(Diphenylphosphaneyl)-5-ethylpyrimidine (2k)



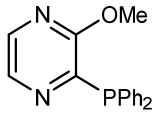
Prepared according to general procedure B using 2-chloro-5-ethylpyrimidine (243 μL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 19 hours. Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a white crystalline solid (478 mg, 1.64 mmol, 82% yield). mp 78-80 °C; IR ν_{max}/cm^{-1} (film): 3070, 3045, 3006, 2929, 1962, 1536, 1208, 1100, 816; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (2H, s), 7.59-7.43 (4H, m), 7.42-7.30 (6H, m), 2.62 (2H, q, *J* = 7.63 Hz), 1.27 (3H, t, *J* = 7.63 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.8 (d, *J* = 12.4 Hz), 156.3 (d, *J* = 6.7 Hz), 135.9 (d, *J* = 20.1 Hz), 134.6 (d, *J* = 20.1 Hz), 134.1, 129.3, 128.6 (d, *J* = 7.6 Hz), 23.6, 14.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –0.70; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 293.2, $C_{18}H_{18}N_2P^+$ requires 293.2.

2-(Diphenylphosphaneyl)-4-methoxypyrimidine (2l)



Prepared according to general procedure B using 2-chloro-4-methoxypyrimidine (723 mg, 5.00 mmol), diphenylphosphane (1.04 mL, 6.00 mmol, and TFE (13.50 mL) at 80 °C for 19.5 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a clear oil (1.10 g, 3.75 mmol, 75% yield). IR ν_{max}/cm^{-1} (film): 3052, 3002, 2950, 2363, 2153, 1963, 1907, 1825, 1683, 1610, 782, 617, 578; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (1H, dd, *J* = 5.8, 0.7 Hz), 7.59-7.47 (4H, m), 7.40-7.30 (6H, m), 6.54 (1H, dd, *J* = 5.8, 0.9 Hz), 3.75 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.0 (d, *J* = 12.4 Hz), 168.2 (d, *J* = 6.2 Hz), 156.8 (d, *J* = 7.6 Hz), 135.7 (d, *J* = 7.6 Hz), 134.7 (d, *J* = 19.8 Hz), 129.1, 128.3 (d, *J* = 7.6 Hz), 106.1 (d, *J* = 2.0 Hz), 53.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –1.62; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 295.1, $C_{17}H_{16}N_2OP^+$ requires 295.1.

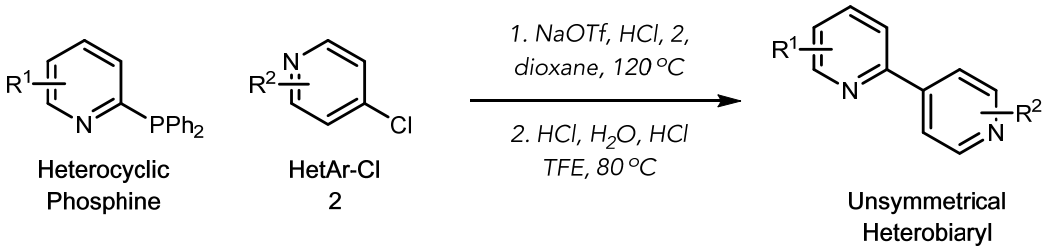
2-(Diphenylphosphaneyl)-3-methoxypyrazine (2m)



Prepared according to general procedure B using 2-chloro-3-methoxypyrazine (434 mg, 3.00 mmol), diphenylphosphane (0.63 mL, 3.60 mmol, and TFE (7.5 mL) at 80 °C for 2 hours. Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (549 mg, 1.87 mmol, 62% yield). mp 104-105 °C; IR ν_{max}/cm^{-1} (film): 3052, 2943, 1515, 1479, 1454, 1434, 1368, 1353, 1297, 1220, 1179, 1157, 1099, 999, 866, 747; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (1H, d, *J* = 2.7 Hz), 8.01 (1H, d, *J* = 2.8 Hz), 7.44–7.29 (10H, m), 3.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.7 (d, *J* = 21.8 Hz), 148.6 (d, *J* = 13.4 Hz), 139.6, 137.6, 134.6 (d, *J* = 7.2 Hz), 134.3 (d, *J* = 20.2 Hz), 129.0, 128.3 (d, *J* = 7.6 Hz), 53.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ: –10.32; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 295.1, $C_{17}H_{16}N_2OP^+$ requires 295.1.

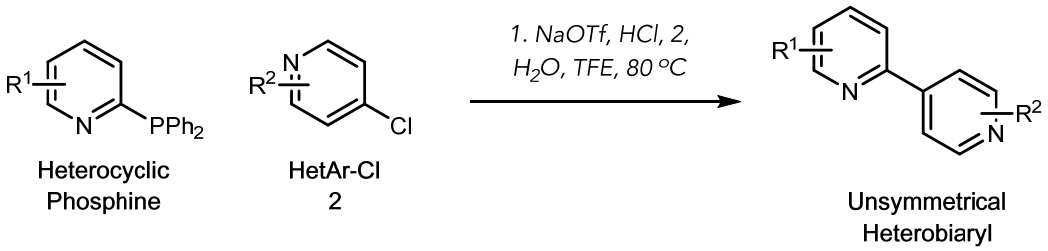
6. Preparation of Heterobiaryls

General Procedure A′ (2,4′ or 4,4′-bipyridine synthesis)



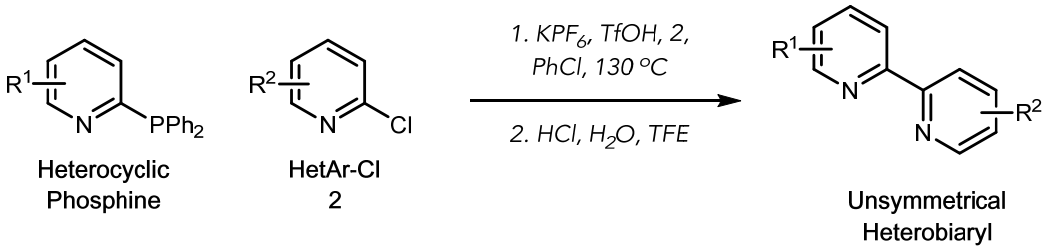
An oven dried 8 mL vial with a septa cap was charged with the heterocyclic phosphine (1.0 equiv), sodium trifluoromethanesulfonate (3.2 equiv) and heteroaryl chloride 2 (1.2 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then dioxane (2.0M) and 4.0M HCl in dioxane (1.0 equiv) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 120 ºC and allowed to stir for the stated time. The reaction was allowed to cool to room temperature before the septa cap was removed and 4.0M HCl in dioxanes (1.0 equiv), H_2O (10 equiv), and TFE (dilute to 0.4M) were quickly added. The reaction vial was heated to 80 ºC and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

General Procedure B′ (Couplings involving quinolines/diazines)



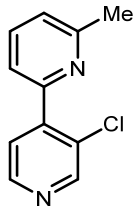
An oven dried 8 mL vial with a septa cap was charged with the heterocyclic phosphine (1.0 equiv), sodium trifluoromethanesulfonate (2.2 equiv) and heteroaryl chloride 2 (1.2 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then TFE (0.4M), H_2O (10 equiv), and HCl (1.2 equiv) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 80 ºC and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

General Procedure C′ (2,2′-bipyridines synthesis)



An oven dried 8 mL vial with a septa cap was charged with the heterocyclic phosphine (1.0 equiv), potassium hexafluorophosphate (1.0 equiv), and heteroaryl chloride 2 (2.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then chlorobenzene (2.0M) and trifluoromethanesulfonic acid (1.2 equiv) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 130 ºC for the stated time. The reaction was then allowed to cool to room temperature. The septa cap was removed and 4.0M HCl in dioxanes (1.0 equiv), H_2O (10 equiv), and TFE (dilute to 0.4M) were quickly added. The reaction vial was then heated at 80 ºC for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

3'-Chloro-6-methyl-2,4'-bipyridine (3a)

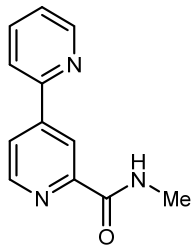


Prepared according to general procedure A′ using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 3,4-dichloropyridine (44 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and dioxanes (0.13 mL) at 120 ºC for 17 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 ºC for 22 hours. Flash column chromatography (silica gel: 45% EtOAc in hexanes) afforded the title compound as a white crystalline solid (41 mg, 0.20 mmol, 81% yield). mp 59-60 ºC; IR ν_{max}/cm^{-1} (film): 3063, 3035, 3014, 3002, 2958, 1371, 1248, 980, 750, 742, 613; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, s), 8.57 (1H, d, J = 5.0 Hz), 7.70 (1H, t, J = 7.8 Hz), 7.57 (1H, d, J = 4.9 Hz), 7.52 (1H, d, J = 7.7 Hz), 7.23 (1H, d, J = 7.7 Hz), 2.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 153.6, 150.4, 148.2, 146.3, 136.6, 129.9, 125.5, 123.3, 121.7, 24.8; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 205.1, $C_{11}H_{10}ClN_2^+$ requires 205.1.

Scale-Up:

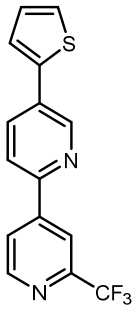
Prepared according to general procedure A′ (using 40 mL pressure tube) using 2-(diphenylphosphaneyl)-6-methylpyridine (1.387 g, 5.00 mmol), 3,4-dichloropyridine (888 mg, 6.00 mmol), sodium trifluoromethanesulfonate (2.754 g, 16.00 mmol), 4.0M HCl in dioxanes (1.25 mL, 5.00 mmol), and dioxanes (2.50 mL) at 120 °C for 36 hours; then H_2O (900 μL, 50.00 mmol), 4.0M HCl in dioxanes (1.25 mL, 5.00 mmol), and TFE (10.0 mL) at 80 °C for 23 hours. Flash column chromatography (silica gel: 35% EtOAc in hexanes) afforded the title compound as a white crystalline solid (756 mg, mmol, 74% yield). Spectral data is consistent with compound **2a**.

N-methyl-[2,4'-bipyridine]-2'-carboxamide (3b)



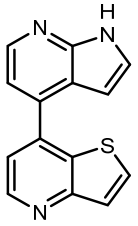
Prepared according to general procedure A′ except with additional 4.0M HCl in dioxanes (1.2 equiv.) using 2-(diphenylphosphaneyl)pyridine (66 mg, 0.25 mmol), 4-chloro-N-methylpicolinamide (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (75 μL, 0.3 mmol), and dioxanes (0.13 mL) at 120 °C for 22 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 25.5 hours. Flash column chromatography (silica gel: 70% EtOAc in hexanes) afforded the title compound as a colorless oil (42 mg, 0.20 mmol, 79% yield). IR ν_{max}/cm^{-1} (film): 3404, 3053, 2926, 1670, 1603, 1587, 1533, 1461, 1433, 1412, 1265, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, d, *J* = 4.9 Hz), 8.69 (1H, d, *J* = 1.8 Hz), 8.63 (1H, d, *J* = 5.1 Hz), 8.16 (1H, dd, *J* = 5.1, 1.9 Hz), 8.08 (1H, br s), 7.91 (1H, d, *J* = 7.9 Hz), 7.86–7.77 (1H, m), 7.34 (1H, ddd, *J* = 7.5, 4.8, 1.1 Hz), 3.05 (3H, d, *J* = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9, 153.9, 150.6, 150.1, 148.8, 147.9, 137.1, 124.1, 123.5, 121.1, 119.2, 26.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 214.1, $C_{12}H_{12}N_3O^+$ requires 214.1.

5-(Thiophen-2-yl)-2'-(trifluoromethyl)-2,4'-bipyridine (3c)



Prepared according to general procedure A′ using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 4-chloro-2-(trifluoromethyl)pyridine (31 μL, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and dioxanes (0.13 mL) at 120 °C for 24 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a faint yellow crystalline solid (44 mg, 0.14 mmol, 57% yield). mp 93-94 °C; IR ν_{max}/cm^{-1} (film): 3071, 3046, 2954, 2922, 2851, 1606, 1572, 1471, 958, 856, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, dd, *J* = 2.4, 0.9 Hz), 8.84 (1H, d, *J* = 5.1 Hz), 8.37 (1H, dd, *J* = 1.7, 0.8 Hz), 8.12 (1H, dd, *J* = 5.1, 1.7 Hz), 8.03 (1H, dd, *J* = 8.3, 2.4 Hz), 7.88 (1H, dd, *J* = 8.3, 0.9 Hz), 7.51-7.41 (2H, m), 7.18 (1H, dd, *J* = 5.1, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.7, 150.9, 149.4 (d, *J* = 34.54 Hz), 147.8, 147.5, 139.7, 134.1, 131.5, 128.8, 127.2, 125.2, 123.4, 123.3, 121.9 (q, *J* = 274.34 Hz), 117.9 (d, *J* = 2.57 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –67.99; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 307.1, $C_{15}H_{10}F_3N_2S^+$ requires 307.1.

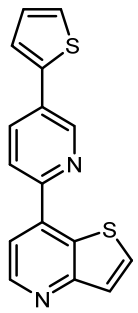
7-(1H-pyrrolo[2,3-b]pyridin-4-yl)thieno[3,2-b]pyridine (3d)



Prepared according to general procedure A′ using 4-(diphenylphosphaneyl)-1H-pyrrolo[2,3-b]pyridine (76 mg, 0.25 mmol), 7-chlorothieno[3,2-b]pyridine (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and dioxanes (0.13 mL) at 120 °C for 18.5 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 24 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as an white crystalline solid (37 mg, 0.15 mmol, 58% yield). mp 250-251 °C; IR ν_{max}/cm^{-1} (film): 3122, 2996, 2924, 2860, 2762, 2710, 2215, 2041, 1557, 1541, 1325; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.79 (1H, s), 8.85 (1H, d, *J* = 4.8 Hz), 8.50 (1H, d, *J* = 5.0 Hz), 7.81 (1H, d, *J* = 5.6 Hz), 7.68 (1H, d, *J* = 5.6 Hz), 7.52 (1H, d,

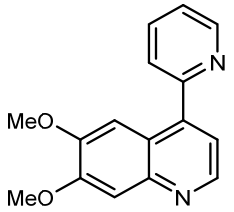
J = 4.7 Hz), 7.50-7.42 (2H, m), 6.55 (1H, dd, *J* = 3.6, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4, 149.5, 147.8, 143.4, 141.8, 138.5, 132.3, 131.3, 126.0, 125.7, 118.8, 118.3, 115.2, 100.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 252.1, $C_{14}H_{10}N_3S^+$ requires 252.1.

7-(5-(Thiophen-2-yl)pyridin-2-yl)thieno[3,2-b]pyridine (3e)



Prepared according to general procedure A′ using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 7-chlorothieno[3,2-b]pyridine (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and dioxanes (0.13 mL) at 120 °C for 12 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a bright yellow crystalline solid (55 mg, 0.19 mmol, 75% yield). mp 129-130 °C; IR ν_{max}/cm^{-1} (film): 3089, 3063, 3041, 3004, 2975, 2923, 2852, 2520, 2157, 1555, 1389, 1139, 1026, 832, 674; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 (1H, dd, *J* = 2.1, 1.1 Hz), 8.83 (1H, d, *J* = 4.9 Hz), 8.12-8.02 (2H, m), 7.90 (1H, d, *J* = 5.7 Hz), 7.76 (1H, d, *J* = 4.9 Hz), 7.64 (1H, d, *J* = 5.7 Hz), 7.50 (1H, dd, *J* = 3.6, 1.1 Hz), 7.43 (1H, dd, *J* = 5.0 Hz), 7.18 (1H, dd, *J* = 5.1, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4, 152.5, 147.5, 146.0, 140.0, 139.9, 134.6, 133.7, 130.5, 129.8, 128.7, 126.8, 124.9, 124.8, 121.2, 115.0; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 295.1, $C_{16}H_{11}N_2S_2^+$ requires 295.0.

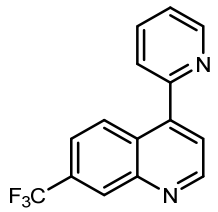
6,7-Dimethoxy-4-(pyridin-2-yl)quinoline (3f)



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)pyridine (66 mg, 0.25 mmol), 4-chloro-6,7-dimethoxyquinoline (67 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), and TFE (0.63 mL) at 80 ºC for 18.5 hours; then H_2O (45 μL, 2.5 mmol) and 4.0M HCl (75 μL, 0.3 mmol) at 80 ºC for 21 hours. Flash column chromatography (neutral alumnia, gradient elution: 50% EtOAc in hexanes to 80% EtOAc in hexanes) afforded the title compound as an off-white powder (39 mg, 0.14 mmol, 58% yield). mp 62-65 ºC; IR ν_{max}/cm^{-1} (film): 3018, 2922, 2851, 1504, 1490, 1473, 1432, 1421, 1351, 1244, 1217,

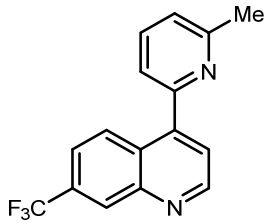
1126, 1013, 847, 795; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, *J* = 4.8 Hz), 8.78 (1H, d, *J* = 4.6 Hz), 7.87 (1H, td, *J* = 7.7, 1.8 Hz), 7.62 (1H, d, *J* = 7.8 Hz), 7.54-7.46 (2H, m), 7.39 (1H, ddd, *J* = 7.7, 4.9, 0.9 Hz), 7.34 (1H, d, *J* = 4.6 Hz), 4.04 (3H, s) 3.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 157.5, 152.4, 150.2, 149.8, 147.8, 146.4, 144.3, 137.0, 124.7, 123.1, 121.6, 120.0, 108.4, 103.4, 56.2, 56.0; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 267.1, $C_{16}H_{15}N_2O_2^+$ requires 267.1.

4-(Pyridin-2-yl)-7-(trifluoromethyl)quinoline (3g)



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)pyridine (63 mg, 0.25 mmol), 4-chloro-7-(trifluoromethyl)quinoline (69 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 17 hours. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a white crystalline solid (55 mg, 0.20 mmol, 81% yield). mp 77-79 °C; IR ν_{max}/cm^{-1} (film): 3053, 3024, 2957, 2925, 2852, 1183, 973, 646, 601, 547; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.10 (1H, d, *J* = 4.4 Hz), 8.85 (1H, d, *J* = 4.5 Hz), 8.59 (1H, s), 8.32 (1H, d, *J* = 8.9), 7.92 (1H, td, *J* = 7.7, 1.8 Hz), 7.72 (1H, dd, *J* = 8.4, 1.9 Hz), 7.68-7.60 (2H, m), 7.50-7.55 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.1, 151.5, 150.2, 148.2, 146.3, 131.3 (d, *J* = 32.7 Hz), 129.5 (q, *J* = 274.6 Hz), 128.0-127.7 (2C, m), 127.4, 125.4, 124.9, 123.6, 123.1, 122.9-122.6 (m); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.83; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 275.1, $C_{15}H_{10}F_3N_2^+$ requires 275.1.

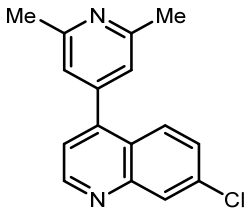
4-(6-Methylpyridin-2-yl)-7-(trifluoromethyl)quinoline (3h)



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 4-chloro-7-(trifluoromethyl)quinoline (69 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 15.5 hours. Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as an white crystalline solid (53 mg, 0.19 mmol, 73% yield). mp 54-55 °C; IR ν_{max}/cm^{-1} (film): 3053, 2954, 2856, 1655, 1637, 1623, 1574, 1555, 1368, 1080, 872, 662; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, d, *J* = 4.4 Hz), 8.48 (1H, dd, *J* = 2.0, 1.0 Hz), 8.32-8.26 (1H, m), 7.80 (1H, t, *J* = 7.7 Hz), 7.71 (1H, dd, *J* = 8.9,

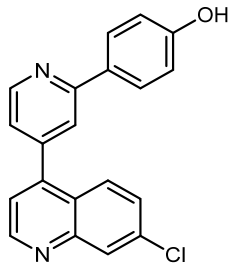
1.9 Hz), 7.62 (1H, d, J = 4.4 Hz), 7.42 (1H, d, J = 7.6 Hz), 7.31 (1H, d, J = 7.8 Hz), 2.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 155.4, 151.5, 148.1, 146.7, 137.3, 131.3 (q, J = 32.85 Hz), 128.0-127.7 (2C, m), 127.5, 124.1 (q, J = 272.54 Hz), 123.2, 123.1, 122.7-122.5 (m), 121.9, 24.8; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.81; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 289.2, $C_{16}H_{12}F_3N_2^+$ requires 289.1.

7-Chloro-4-(2,6-dimethylpyridin-4-yl)quinoline (3i)



Prepared according to general procedure B′ using 4-(diphenylphosphaneyl)-2,6-dimethylpyridine (73 mg, 0.25 mmol), 4,7-dichloroquinoline (60 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 14 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a white crystalline solid (46 mg, 0.17 mmol, 69% yield). mp 88-90 °C; IR ν_{max}/cm^{-1} (film): 3361, 3087, 3040, 3026, 2961, 2857, 1551, 1349, 822, 735, 656, 591; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, s), 8.19 (1H, d, J = 2.1 Hz), 7.77 (1H, d, J = 9.0 Hz), 7.49 (1H, dd, J = 9.0, 2.2 Hz), 7.30 (1H, d, J = 4.4 Hz), 7.07 (2H, s), 2.64 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 151.1, 149.2, 146.5, 146.1, 135.8, 129.1, 128.2, 126.9, 124.6, 121.1, 120.8, 24.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 269.1, $C_{16}H_{14}ClN_2^+$ requires 269.1.

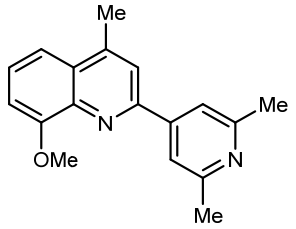
4-(4-(7-Chloroquinolin-4-yl)pyridin-2-yl)phenol (3j)



Prepared according to general procedure B′ using 4-(4-(diphenylphosphaneyl)pyridin-2-yl)phenol (71 mg, 0.20 mmol), 4,7-dichloroquinoline (48 mg, 0.24 mmol), sodium trifluoromethanesulfonate (76 mg, 0.44 mmol), 4.0M HCl in dioxanes (60 μL, 0.24 mmol), H_2O (36 μL, 2.0 mmol), and TFE (0.5 mL) at 80 °C for 44.5 hours. Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the title compound as an off-white powder (50 mg, 0.15 mmol, 75% yield). mp 258-260 °C; IR ν_{max}/cm^{-1} (film): 3033, 2921, 2850, 1608, 1580, 1539, 1520, 1451, 1419, 1382, 1274, 1240, 1179, 878, 833, 822; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.78

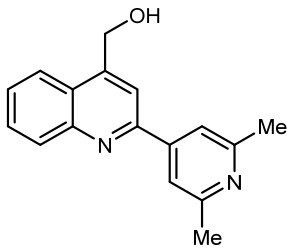
(1H, s), 9.04 (1H, d, J = 4.4 Hz), 8.77 (1H, dd, J = 4.9, 0.8 Hz), 8.20 (1H, d, J = 2.2 Hz), 8.07–8.00 (2H, m), 7.98 (1H, s), 7.89 (1H, d, J = 9.0 Hz), 7.71–7.57 (2H, m), 7.42 (1H, dd, J = 4.9, 1.5 Hz), 6.87 (2H, d, J = 8.7 Hz); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 158.8, 156.8, 151.5, 149.7, 148.4, 145.5, 145.4, 134.4, 129.2, 128.3, 128.1, 128.0, 127.3, 124.0, 121.8, 119.4, 115.5; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 333.1, $C_{20}H_{14}ClN_2O^+$ requires 333.1.

2-(2,6-Dimethylpyridin-4-yl)-8-methoxy-4-methylquinoline (3k)



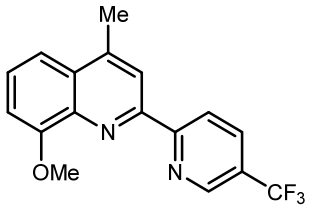
Prepared according to general procedure B′ using 4-(diphenylphosphaneyl)-2,6-dimethylpyridine (73 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 ºC for 25.5 hours. Flash column chromatography (silica gel: 20% EtOAc in hexanes) followed by a second flash column (silica gel, gradient elution: 1% MeOH and 1% acetic acid in CH_2Cl_2 to 5% MeOH and 1% acetic acid in CH_2Cl_2) and then dilution with a saturated aqueous solution of Na_2CO_3 and extraction with CH_2Cl_2 (3x) afforded the title compound as a tan powder (43 mg, 0.15 mmol, 61% yield). mp 148-150 ºC; IR ν_{max}/cm^{-1} (film): 3056, 2920, 2851, 1602, 1588, 1573, 1546, 1510, 1471, 1459, 1418, 1389, 1260, 1207, 1154, 1106, 852, 804; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77-7.70 (3H, m), 7.57 (1H, dd, J = 8.5, 1.1 Hz), 7.50 (1H, t, J = 7.7 Hz), 7.08 (1H, dd, J = 7.6, 0.8 Hz), 4.10 (3H, s), 2.75 (3H, d, 0.6 Hz), 2.63 (6H, s); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 158.5, 156.1, 153.7, 147.5, 145.5, 140.1, 129.1, 127.1, 120.2, 118.5, 115.6, 108.0, 56.3, 24.7, 19.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 279.2, $C_{18}H_{19}N_2O^+$ requires 279.2.

(2-(2,6-Dimethylpyridin-4-yl)quinolin-4-yl)methanol (3l)



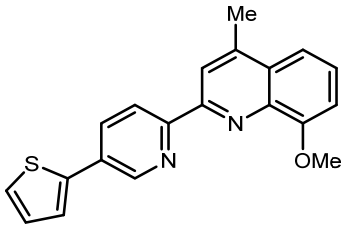
Prepared according to general procedure B′ using 4-(diphenylphosphaneyl)-2,6-dimethylpyridine (73 mg, 0.25 mmol), (2-chloroquinolin-4-yl)methanol (58 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 ºC for 44 hours. Flash column chromatography (silica gel: EtOAc) afforded the title compound as a white powder (33 mg, 0.13 mmol, 50% yield). mp 152-154 ºC; IR ν_{max}/cm^{-1} (film): 3253, 2897, 2841, 1610, 1598, 1549, 1510, 1443, 1429, 1390, 1221, 1098, 861, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (1H, dd, *J* = 8.5, 1.2 Hz), 7.92 (1H, dd, *J* = 8.5, 1.4 Hz), 7.88 (1H, s), 7.74 (1H, ddd, *J* = 8.4, 6.8, 1.4 Hz), 7.62 (2H, s), 7.56 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz), 5.23 (2H, d, *J* = 1.1 Hz), 4.07 (1H, br s), 2.55 (6H, s); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 158.3, 154.8, 147.9, 147.6, 147.5, 130.4, 129.8, 127.1, 125.4, 122.7, 118.4, 115.7, 61.4, 24.3; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 265.2, $C_{17}H_{17}N_2O^+$ requires 265.1.

8-Methoxy-4-methyl-2-(5-(trifluoromethyl)pyridin-2-yl)quinoline (3m)



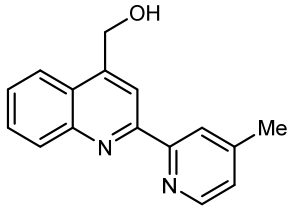
Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (83 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 ºC for 18 hours. Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a faint yellow solid (49 mg, 0.16 mmol, 61% yield). mp 105-108 ºC; IR ν_{max}/cm^{-1} (film): 2958, 2919, 2815, 2829, 1603, 1576, 1554, 1507, 1452, 1212, 980, 777, 694, 639; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, dq, *J* = 2.4, 0.9 Hz), 8.84 (1H, dt, *J* = 8.3, 0.8 Hz), 8.47 (1H, q, *J* = 1.0 Hz), 8.07 (1H, ddd, *J* = 8.3, 2.4, 0.7 Hz), 7.61 (1H, dd, *J* = 8.5, 1.2 Hz), 7.53 (1H, dd, *J* = 8.5, 7.6 Hz), 7.10 (1H, dd, *J* = 7.7, 1.2 Hz), 4.13 (3H, s), 2.80 (3H, d, *J* = 0.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8 (d, *J* = 1.7 Hz), 156.2, 153.1, 146.1 (q, *J* = 4.2 Hz), 145.7, 139.9, 134.1 (q, *J* = 3.5 Hz), 129.9, 127.5, 126.5 (q, *J* =32.9 Hz), 123.9 (q, *J* = 272.2 Hz), 121.9, 120.3, 115.9, 108.1, 56.4, 19.7; ^{9}F NMR (365 MHz, $CDCl_3$) δ: −62.27; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 319.1, $C_{17}H_{14}F_3N_2O^+$ requires 319.1.

8-Methoxy-4-methyl-2-(5-(thiophen-2-yl)pyridin-2-yl)quinoline (3n)



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 18 hours. Flash column chromatography (silica gel: 60% EtOAc in Et_2O) followed by a second flash column (silica gel neutralized with NEt_3: gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a yellow amorphous solid (42 mg, 0.13 mmol, 50% yield). IR ν_{max}/cm^{-1} (film): 3070, 2956, 2934, 2832, 1600, 1567, 1546, 1126, 958, 814, 663, 647; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98 (1H, dd, *J* = 2.4, 0.8 Hz), 8.74 (1H, dd, *J* = 8.3, 0.8 Hz), 8.48 (1H, s), 8.04 (1H, dd, *J* = 8.3, 2.4 Hz), 7.61 (1H, dd, *J* = 8.5, 1.2 Hz), 7.55-7.44 (2H, m), 7.40 (1H, dd, *J* = 5.1, 1.1 Hz), 7.16 (1H, dd, *J* = 5.1, 3.6 Hz), 7.09 (1H, dd, *J* = 7.7. 1.2 Hz), 4.13 (3H, s), 2.80 (3H, d, *J* = 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.1, 155.3, 154.1, 146.1, 145.1, 145.2, 140.6, 139.9, 133.8, 130.6, 129.6, 128.5, 126.8, 126.3, 124.5, 122.2, 120.1, 115.9, 107.9, 56.4, 19.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 333.2, $C_{20}H_{17}N_2OS^+$ requires 333.1.

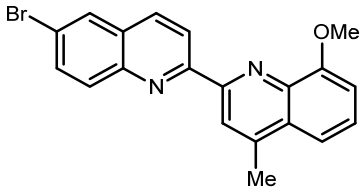
(2-(4-Methylpyridin-2-yl)quinolin-4-yl)methanol (3o)



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)-4-methylpyridine (69 mg, 0.25 mmol), (2-chloroquinolin-4-yl)methanol (58 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 ºC for 43 hours. Flash column chromatography (silica gel: 4% MeOH in CH_2Cl_2) followed by a second flash column (silica gel: 3% MeOH in CH_2Cl_2) afforded the title compound as an off-white powder (26 mg, 0.10 mmol, 42% yield). mp 154-157 ºC; IR ν_{max}/cm^{-1} (film): 3292, 2923, 2852, 1602, 1555, 1509, 1480, 1447, 1332, 1093, 1080, 826, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, s), 8.56 (1H, d, *J* = 5.0 Hz), 8.41 (1H, d, *J* = 1.7 Hz), 8.17 (1H, dd, *J* = 8.4, 1.3 Hz), 7.95 (1H, dd, *J* = 8.4, 1.4 Hz), 7.70 (1H, ddd, *J* = 8.4, 6.8, 1.4 Hz), 7.52 (1H, ddd, *J* = 8.2, 6.8, 1.3 Hz), 7.18 (1H, dd, *J* = 5.1, 1.7 Hz), 5.20 (2H, s), 3.14 (1H, br s), 2.48 (3H, s); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 156.2, 156.0, 148.9, 148.4, 147.9, 146.7, 130.4,

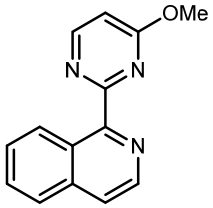
129.4, 126.9, 126.0, 125.2, 123.1, 122.7, 116.7, 62.4, 21.3; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 251.1, $C_{16}H_{15}N_2O^+$ requires 251.1.

6'-Bromo-8-methoxy-4-methyl-2,2'-biquinoline (3p)



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 18 hours. Flash column chromatography (silica gel: 60% EtOAc in hexanes) followed by a second flash column (silica gel: gradient elution: CH_2Cl_2 to 2% MeOH in CH_2Cl_2) afforded the title compound as an orange crystalline solid (60 mg, 0.16 mmol, 63% yield). mp 173-174 °C; IR ν_{max}/cm^{-1} (film): 3496, 3061, 3010, 2969, 2941, 2835, 1592, 1560, 1546, 1402, 1318, 1160, 884; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, dd, *J* = 8.6, 1.9 Hz), 8.70 (1H, s), 8.22 (1H, dd, *J* = 8.7, 1.8 Hz), 8.10 (1H, d, *J* = 8.9 Hz), 8.04 (1H, d, *J* = 2.1 Hz), 7.81 (1H, dt. *J* = 9.1, 2.1 Hz), 7.63 (1H, d, *J* = 8.4 Hz), 7.54 (1H, dt, *J* = 8.0, 1.9 Hz), 7.12 (1H, d, *J* = 7.7 Hz), 4.15 (3H, d, *J* = 1.9 Hz), 2.84 (3H, d, *J* = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.0, 156.2, 154.1, 146.6, 145.3, 139.9, 135.7, 133.0, 131.6, 129.9, 129.8, 129.6, 127.2, 120.8, 120.8, 120.4, 115.9, 108.0, 56.4, 19.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 379.1, $C_{20}H_{16}BrN_2O^+$ requires 379.0.

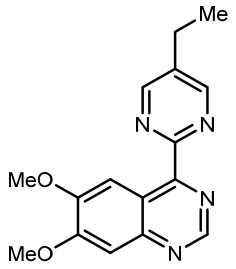
1-(4-Methoxypyrimidin-2-yl)isoquinoline (3r)



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)-4-methoxypyrimidine (74 mg, 0.25 mmol), 1-chloroisoquinoline (49 mg, 0.30 mmol), sodium trifluoromethanesulfonate (43 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 17.5 hours. Flash column chromatography (silica gel: 3% MeOH in CH_2Cl_2) followed by a second flash column (silica gel: 2.5% MeOH in CH_2Cl_2) afforded the title compound as an off-white amorphous solid (34 mg, 0.14 mmol, 58% yield). mp 146-148 °C; IR ν_{max}/cm^{-1} (film): 3053, 2954, 2856, 1655, 1637, 1623, 1574, 1080, 872, 528; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (2H, m), 8.48 (1H, dd, *J* = 8.6, 1.1 Hz). 7.89 (1H, dt, *J* = 8.3, 1.1 Hz), 7.76 (1H, dd, *J* = 5.6, 1.0 Hz), 7.70 (1H, ddd, *J* = 8.2, 6.8, 1.2 Hz), 7.59 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz), 6.84 (1H, d, *J* = 5.8 Hz), 4.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.8,

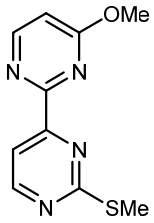
165.1, 157.7, 156.1, 142.3, 137.2, 130.2, 127.7, 127.2, 127.2, 126.7, 122.0, 107.6, 54.2; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 238.1, $C_{14}H_{12}N_3O^+$ requires 238.1.

4-(5-Ethylpyrimidin-2-yl)-6,7-dimethoxyquinazoline (3s)



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)-5-ethylpyrimidine (73 mg, 0.25 mmol), 4-chloro-6,7-dimethoxyquinazoline (67 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 12 hours. Flash column chromatography (silica gel: 4% MeOH in CH_2Cl_2) afforded the title compound as a yellow crystalline solid (40 mg, 0.14 mmol, 54% yield). mp 163-164 °C; IR ν_{max}/cm^{-1} (film): 3090, 3043, 3009, 2928, 1557, 1341, 940, 827, 630, 599, 562; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.34 (1H, s), 8.89 (2H, s), 8.21 (1H, s), 7.42 (1H, s), 4.09 (3H, s), 4.01 (3H, s), 2.82 (2H, q, J = 7.6 Hz), 1.40 (3H, t, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2, 159.0, 157.1 (2C), 156.1, 153.7, 151.0, 151.0, 137.6, 119.1, 107.1, 104.4, 56.6, 56.3, 23.8, 14.9,; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 297.2, $C_{16}H_{17}N_4O_2^+$ requires 297.1.

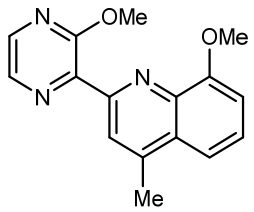
4-Methoxy-2'-(methylthio)-2,4'-bipyrimidine (3t)



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)-4-methoxypyrimidine (74 mg, 0.25 mmol), 4-chloro-2-(methylthio)pyrimidine (35 μL, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 13 hours. Flash column chromatography (silica gel, gradient elution: 20% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white powder (23 mg, 0.10 mmol, 38% yield). mp 93-95 °C; IR ν_{max}/cm^{-1} (film): 3068, 3035, 2993, 2952, 2923, 2852, 1567, 1553, 1536, 1469, 1370, 1337, 1286, 1207, 843, 788; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, d, J = 5.1 Hz), 8.65 (1H, d, J = 5.7 Hz), 7.99 (1H, d, J = 5.1 Hz), 6.81 (1H, d, J = 5.8 Hz), 4.10 (3H, s), 2.66 (3H, s); ^{13}C NMR (100 MHz , $CDCl_3$)

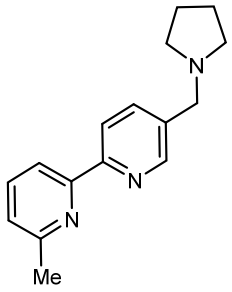
δ: 173.8, 170.1, 162.0, 161.8, 158.5, 158.1, 114.9, 109.1, 54.0, 14.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 235.1, $C_{10}H_{11}N_4OS^+$ requires 235.1.

8-Methoxy-2-(3-methoxypyrazin-2-yl)-4-methylquinoline



Prepared according to general procedure B′ using 2-(diphenylphosphaneyl)-3-methoxypyrazine (74 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL, 0.30 mmol), H_2O (45 μL, 2.5 mmol), and TFE (0.63 mL) at 80 ºC for 20 hours. Flash column chromatography (neutral alumnia: 60% EtOAc in hexanes) afforded the title compound as a tan solid (16 mg, 0.06 mmol, 22% yield). mp 143-145 ºC; IR ν_{max}/cm^{-1} (film): 3050, 2948, 2832, 1611, 1534, 1505, 1462, 1386, 1341, 1294, 1259, 1154, 1110, 1044, 1003, 919, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (1H, d, *J* = 2.6 Hz), 8.16 (1H, d, *J* = 2.6 Hz), 7.91 (1H, s), 7.58 (1H, d, *J* = 8.4 Hz), 7.51 (1H, t, *J* = 8.0 Hz), 7.06 (1H, d, *J* = 7.6 Hz), 4.14–4.02 (6H, m), 2.76 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 156.3, 152.8, 144.4, 142.9, 140.6, 139.9, 136.6, 128.9, 127.1, 123.0, 115.2, 107.5, 56.0, 54.0, 19.5.; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 282.1, $C_{16}H_{16}N_3O_2^+$ requires 282.1.

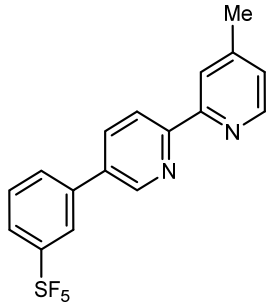
6'-Methyl-5-(pyrrolidin-1-ylmethyl)-2,2'-bipyridine (3u)



Prepared according to general procedure C′ using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 2-chloro-5-(pyrrolidin-1-ylmethyl)pyridine (98 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (71 μL, 0.80 mmol), and chlorobenzene (0.13 mL) at 130 ºC for 39.5 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 ºC for 24 hours. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then gradient elution: 30% EtOAc in hexanes to 70% EtOAc in hexanes) afforded the title compound as an orange oil (22 mg, 0.09 mmol, 35% yield). IR ν_{max}/cm^{-1} (film): 3057, 2960, 2786, 1593, 1573, 1560, 1454

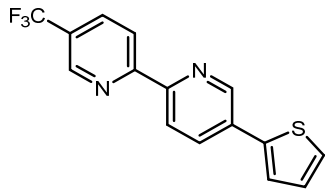
1410, 1347, 1080, 1025, 800, 759; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, *J* = 1.7 Hz), 8.35 (1H, d, *J* = 8.1 Hz), 8.14 (1H, d, *J* = 7.8 Hz), 7.81 (1H, dd, *J* = 8.1, 2.1 Hz), 7.68 (1H, t, *J* = 7.7 Hz), 7.15 (1H, d, J = 7.6 Hz), 3.69 (2H, s), 2.62 (3H, s), 2.58-2.50 (4H, m), 1.83-1.77 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1, 155.7, 155.6, 149.7, 137.6, 137.2, 134.5, 123.2, 121.0, 118.2, 57.7, 54.2, 24.8, 23.6; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 254.2, $C_{16}H_{20}N_3^+$ requires 254.2.

4-Methyl-5'-(3-(pentafluoro-λ^6-sulfaneyl)phenyl)-2,2'-bipyridine (3v)



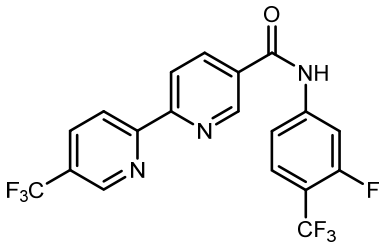
Prepared according to general procedure C′ using 2-(diphenylphosphaneyl)-4-methylpyridine (69 mg, 0.25 mmol), 2-chloro-5-(3-(pentafluoro-λ^6-sulfaneyl)phenyl)pyridine (158 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 ºC for 39 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 ºC for 22 hours. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a light tan powder (48 mg, 0.13 mmol, 51% yield). mp 129-131 ºC; IR ν_{max}/cm^{-1} (film): 3022, 2923, 2852, 1606, 1595, 1465, 1435, 1368, 1115, 859, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.89 (1H, s), 8.66-8.44 (2H, m), 8.29 (1H, s), 8.11-7.93 (2H, m), 7.89-7.72 (2H, m), 7.60 (1H, t, *J* = 7.8 Hz), 7.17 (1H, d, *J* = 3.6 Hz), 2.46 (3H, s); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 156.2, 155.3, 154.9 (app t, *J* = 17.4 Hz), 149.2, 148.5, 147.7, 139.0, 135.6, 134.8, 130.3, 129.7, 125.6 (app qn, *J* = 4.5 Hz), 125.2, 124.8 (app qn, *J* = 4.5 Hz), 122.2, 121.4, 21.4; ^{19}F NMR (365 MHz, $CDCl_3$) δ: 83.77 (qn, *J* = 151.8 Hz), 62.75 (d, *J* = 150.0 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 373.2, $C_{17}H_{14}F_5N_2S^+$ requires 373.1.

5-(Thiophen-2-yl)-5'-(trifluoromethyl)-2,2'-bipyridine (3w)



Prepared according to general procedure C′ using 2-(diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (83 mg, 0.25 mmol), 2-chloro-5-(thiophen-2-yl)pyridine (98 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 °C for 45 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 19 hours. Flash column chromatography (silica gel: 2% EtOAc in hexanes) afforded the title compound as a white crystalline solid (41 mg, 0.13 mmol, 53% yield). IR ν_{max}/cm^{-1} (film): 3124, 3067, 2921, 1599, 1579, 1548, 1530, 1468, 1209, 782, 751, 644; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.98 (1H, dd, *J* = 2.4, 0.8 Hz), 8.93 (1H, dt, *J* = 2.5, 0.9 Hz), 8.58 (1H, dt, *J* = 8.4, 0.8 Hz), 8.49 (1H, dd, *J* = 8.3, 0.8 Hz), 8.09-7.99 (2H, m), 7.47 (1H, dd, *J* = 3.6, 1.1 Hz), 7.42 (1H, dd, *J* = 5.1, 1.1 Hz), 7.17 (1H, dd, *J* = 5.1, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.9, 153.4, 146.6, 146.3 (q, *J* = 4.1 Hz), 140.2, 134.2, (q, *J* = 3.5 Hz), 134.0, 131.4, 128.6, 126.8, 126.4 (q, *J* = 33.00 Hz), 124.9, 123.9 (q, *J* = 272.1 Hz), 121.9, 120.7; ^{19}F NMR (365 MHz, $CDCl_3$) δ: −62.32; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 307.1, $C_{15}H_{10}F_3N_2S^+$ requires 307.1.

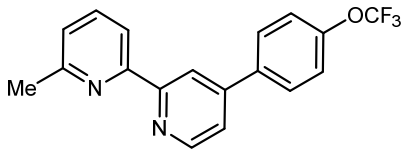
N-(3-fluoro-4-(trifluoromethyl)phenyl)-5'-(trifluoromethyl)-[2,2'-bipyridine]-5-carboxamide (3x)



Prepared according to general procedure C′ using 2-(diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (66 mg, 0.20 mmol), 6-chloro-N-(3-fluoro-4-(trifluoromethyl)phenyl)nicotinamide (128 mg, 0.40 mmol), potassium hexafluorophosphate (36 mg, 0.20 mmol), trifluoromethanesulfonic acid (21 μL, 0.24 mmol), and chlorobenzene (0.13 mL) at 130 °C for 45 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 19 hours. Preparatory thin layer chromatography (40% EtOAc in hexanes) followed by flash column chromatography (silica gel: 1% MeOH in CH_2Cl_2) afforded the title compound as a white amorphous solid (40 mg, 0.09 mmol, 47% yield). IR ν_{max}/cm^{-1} (film): 3853, 3750, 2923, 2852, 2359, 2342, 1733, 1652, 1598, 1540, 1468, 1426, 1132, 1083, 820, 552, 532; ^1H NMR (400 MHz, DMSO-d_6) δ: 11.06 (1H, s), 9.27 (1H, d, *J* = 2.2 Hz), 9.15 (1H, s), 8.67 (1H, d, *J* = 8.4 Hz), 8.61 (1H, d, *J* = 8.3 Hz), 8.54 (1H, dd, *J* = 8.3, 2.2 Hz), 8.43 (1H, dd, *J* = 8.5, 2.4 Hz), 8.02 (1H, dd, *J* = 13.6, 1.9 Hz), 7.86-7.74 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6)

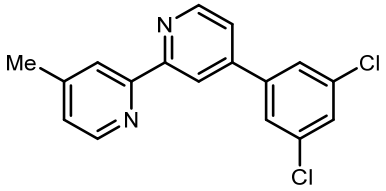
δ: 164.4, 160.3, 157.8, 156.2, 149.1, 146.4 (d, J = 4.1 Hz), 144.6 (d, J = 11.9 Hz), 137.3, 135.2 (d, J = 3.7 Hz), 130.7, 127.9 (2C, m), 125.7 (d, J = 32.5 Hz), 123.7 (q, J = 272.3 Hz), 122.8 (q, J = 270.59 Hz), 121.1 (d, J = 41.7 Hz), 115.8 (d, J = 3.0 Hz), 110.9 (d, J = 32.8 Hz), 107.7 (d, J = 25.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –59.19 (d, J = 12.0 Hz), –60.89, –114.19 (tt, J = 13.0, 6.7 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 430.2, $C_{19}H_{11}F_7N_3O^+$ requires 430.1.

6'-Methyl-4-(4-(trifluoromethoxy)phenyl)-2,2'-bipyridine (3y)



Prepared according to general procedure C′ using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 2-chloro-4-(4-(trifluoromethoxy)phenyl)pyridine (137 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 ºC for 39.5 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 ºC for 27 hours. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3: 10% EtOAc in hexanes) afforded the title compound as colorless crystals (47 mg, 0.14 mmol, 57% yield). mp 46-48 ºC; IR ν_{max}/cm^{-1} (film): 3055, 3012, 2920, 1587, 1511, 1459, 1271, 1208, 1150, 1106, 1086, 834, 803; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, dd, J = 5.1, 0.8 Hz), 8.67-8.62 (1H, m), 8.23 (1H, d, J = 7.8 Hz), 7.84-7.75 (2H, m), 7.73 (1H, t, J = 7.7), 7.48 (1H, dd, J = 5.1, 1.9 Hz), 7.36 (2H, dq, J = 8.6, 1.0 Hz), 7.20 (1H, d, J = 7.6 Hz), 2.66 (3H, s); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 158.2, 157.4, 155.5, 150.0 (q, J = 1.9 Hz), 149.9, 148.0, 137.4, 137.3, 128.8, 124.5, 121.5, 121.4, 120.6 (q, J = 257.7 Hz), 119.2, 118.4, 24.8; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –57.76; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 331.2, $C_{18}H_{14}F_3N_2O^+$ requires 331.1.

4-(3,5-Dichlorophenyl)-4'-methyl-2,2'-bipyridine (3z)

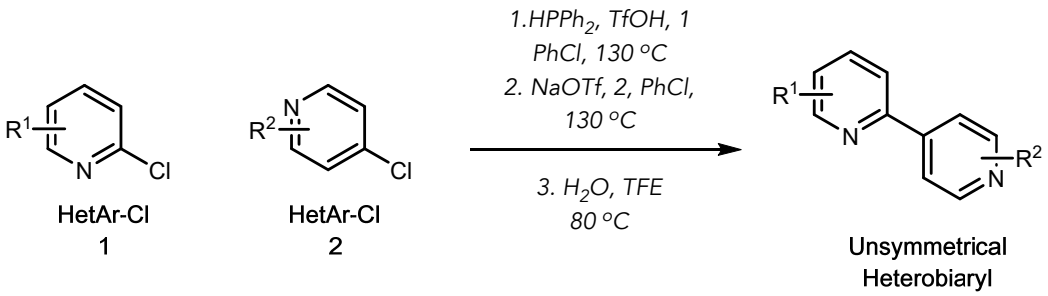


Prepared according to general procedure C′ using 2-(diphenylphosphaneyl)-4-methylpyridine (69 mg, 0.25 mmol), 2-chloro-4-(3,5-dichlorophenyl)pyridine (129 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 ºC for 43 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 μL, 0.25 mmol), and TFE (0.50 mL) at 80 ºC for 20 hours. Flash column chromatography (silica gel: 2% MeOH in Et_2O) followed by a second flash column (silica gel: 2% MeOH in CH_2Cl_2) afforded the title compound as a white amorphous solid (46 mg, 0.15 mmol, 58% yield). IR ν_{max}/cm^{-1} (film): 3054, 3011, 2922, 2855, 1670, 1595, 1556, 1490, 1138, 849, 720,

650, 533; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, dd, *J* = 5.0, 0.8 Hz), 8.53 (1H, dd, *J* = 4.9, 0.8 Hz), 8.44 (1H, dd, *J* = 1.7, 0.8 Hz), 8.28 (1H, dt, *J* = 1.6, 0.8 Hz), 7.52 (1H, dd, *J* = 1.8, 0.7 Hz), 7.42-7.32 (3H, m), 7.15 (1H, ddd, *J* = 5.0, 1.7, 0.8 Hz), 2.45 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.7, 155.7, 149.2, 149.1, 148.4, 147.2, 136.8, 135.2, 133.1, 131.9, 130.1, 127.6, 125.1, 124.2, 122.2 121.8, 21.4; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 315.1, $C_{17}H_{13}Cl_2N_2^+$ requires 315.0.

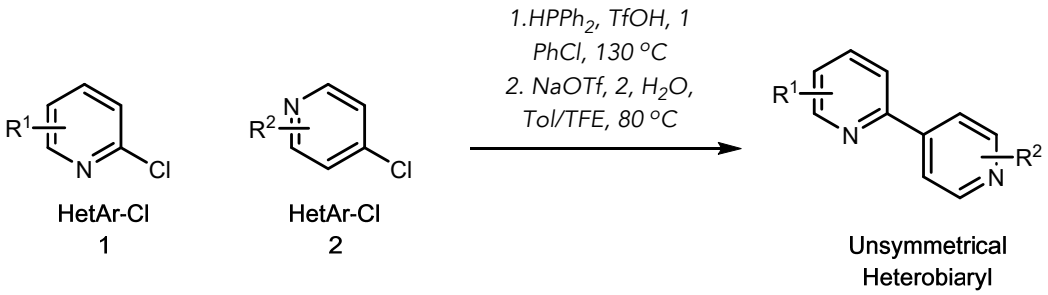
7. Preparation of Heterobiaryls (one-pot synthesis)

General Procedure D (2,4′ or 4,4′-bipyridines one-pot synthesis)



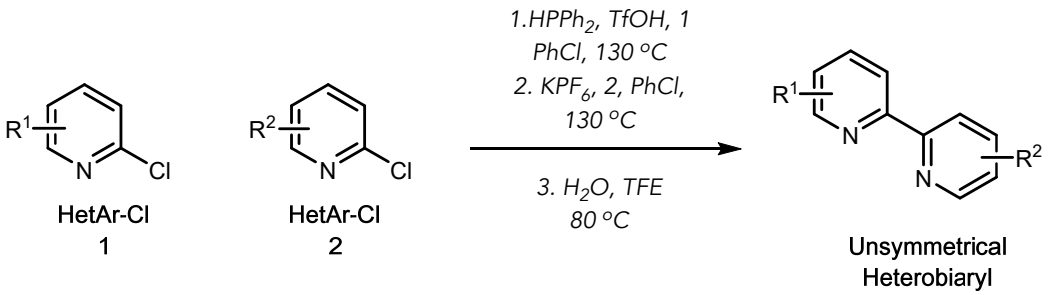
An oven dried 8 mL vial equipped with a stir bar was charged with heteroaryl chloride 1 (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and chlorobenzene (2.0 M) was added, followed by diphenylphosphine (1.0 equiv) and trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to 130 ºC and allowed to stir for the stated time. The reaction was then cooled to room temperature. The vial cap was removed and sodium trifluoromethanesulfonate (2.0 equiv) and heteroaryl chloride 2 (1.2 equiv) were quickly added. The vial was then placed in a pre-heated oil bath at 130 ºC and allowed to stir for the stated time. The reaction was then cooled to room temperature and the vial cap was removed and H_2O (10 equiv) and TFE (dilute to 0.4M) were added to the reaction vial quickly. The vial heated to 80 ºC and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl product.

General Procedure D′ (Couplings with quinolines/diazines one-pot synthesis)



An oven dried 8 mL vial equipped with a stir bar was charged with heteroaryl chloride 1 (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and chlorobenzene (2.0 M) was added, followed by diphenylphosphine (1.0 equiv) and trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to 130 °C and allowed to stir for the stated time. The reaction was then cooled to room temperature. The vial cap was removed and sodium trifluoromethanesulfonate (2.0 equiv), H_2O (10 equiv), HetAr-Cl 2 (1.2 equiv), 50:50 toluene/TFE (dilute to 0.4M) were quickly added. The vial heated to 80 °C and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl product.

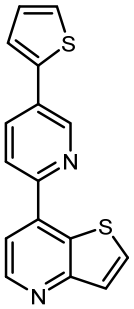
General Procedure D″ (2,2′-bipyridines one-pot synthesis)



An oven dried 8 mL vial equipped with a stir bar was charged with heteroaryl chloride 1 (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and chlorobenzene (2.0 M) was added, followed by diphenylphosphine (1.0 equiv) and trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to 130 °C and allowed to stir for the stated time. The reaction was then cooled to room temperature. The vial cap was removed and potassium hexafluorophosphate (2.0 equiv) and HetAr-Cl 2 (2.0 equiv) were quickly added. The vial was heated to 130 °C and allowed to stir for the stated time. The reaction was then cooled to room temperature and the vial cap was removed. H_2O (10 equiv) and TFE (dilute to 0.4M) were added to the reaction vial quickly. The vial heated to 80 °C and allowed to stir for the stated time.

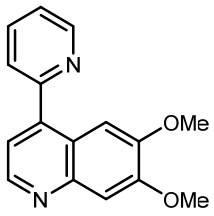
The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl product.

7-(5-(Thiophen-2-yl)pyridin-2-yl)thieno[3,2-b]pyridine (3e)



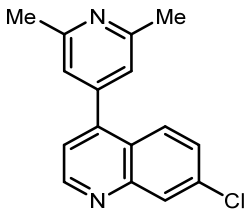
Prepared according to general procedure D using 2-chloro-5-(thiophen-2-yl)pyridine (49 mg, 0.25 mmol), diphenylphosphane (44 μL, 0.25 mmol), trifluoromethanesulfonic acid (22 μL, 0.25 mmol), and chlorobenzene (0.13 mL) at 130 °C for 16 hours; then 7-chlorothieno[3,2-b]pyridine (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (86 mg, 0.50 mmol) at 130 °C for 12 hours; then H_2O (45 μL, 2.5 mmol) and TFE (0.50 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a bright yellow crystalline solid (49 mg, 0.17 mmol, 67% yield). Spectral data is consistent with compound **3e**.

6,7-Dimethoxy-4-(pyridin-2-yl)quinoline (3f)



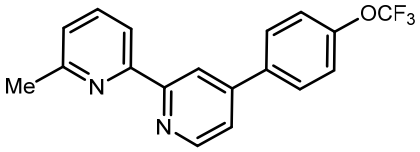
Prepared according to general procedure D′ using 2-chloropyridine (24 μL, 0.25 mmol), diphenylphosphane (44 μL, 0.25 mmol), trifluoromethanesulfonic acid (22 μL, 0.25 mmol), and chlorobenzene (0.13 mL) at 130 °C for 16 hours; then 4-chloro-6,7-dimethoxyquinoline (67 mg, 0.30 mmol), sodium trifluoromethanesulfonate (86 mg, 0.50 mmol), H_2O (45 μL, 2.5 mmol), TFE (0.25 mL), and toluene (0.25 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 75% EtOAc in CH_2Cl_2) followed by a second flash column (neutral alumina: 75% EtOAc in hexanes) afforded the title compound as a tan crystalline solid (31 mg, 0.12 mmol, 47% yield). Spectral data is consistent with compound **3f**.

7-Chloro-4-(2,6-dimethylpyridin-4-yl)quinoline (3i)



Prepared according to general procedure D″ using 4-chloro-2,6-dimethylpyridine (31 μL, 0.25 mmol), diphenylphosphane (44 μL, 0.25 mmol), trifluoromethanesulfonic acid (22 μL, 0.25 mmol), and chlorobenzene (0.13 mL) at 130 °C for 16 hours; then 4,7-dichloroquinoline (60 mg, 0.30 mmol), sodium trifluoromethanesulfonate (86 mg, 0.50 mmol), H_2O (45 μL, 2.5 mmol), TFE (0.25 mL), and toluene (0.25 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) followed by a second flash column (silica gel: 100% Et_2O) afforded the title compound as a white crystalline solid (40 mg, 0.15 mmol, 59% yield). Spectral data is consistent with compound **3i**.

6'-Methyl-4-(4-(trifluoromethoxy)phenyl)-2,2'-bipyridine (3y)

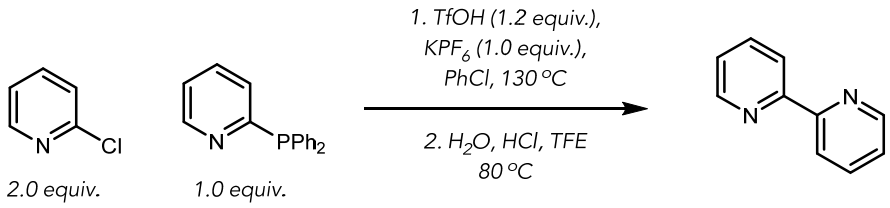


Prepared according to general procedure D″ using 2-chloro-6-methylpyridine (27 μL, 0.25 mmol), diphenylphosphane (44 μL, 0.25 mmol), trifluoromethanesulfonic acid (22 μL, 0.25 mmol), and chlorobenzene (0.13 mL) at 130 °C for 16 hours; then 2-chloro-4-(4-(trifluoromethoxy)phenyl)pyridine (137 mg, 0.50 mmol), potassium hexafluorophosphate (92 mg, 0.50 mmol) at 130 ºC for 41 hours; then H_2O (45 μL, 2.5 mmol) and TFE (0.50 mL) at 80 ºC for 23 hours. Flash column chromatography (silica gel: 30% EtOAc in hexanes) followed by a second flash column (silica gel neutralized with NEt_3: 10% EtOAc in hexanes) afforded the title compound as colorless crystals (36 mg, 0.11 mmol, 43% yield). Spectral data is consistent with compound **3y**.

8. Other Attributes of the Ligand-Coupling Process

Air Compatibility

Table S5: Nitrogen versus air atmosphere study.



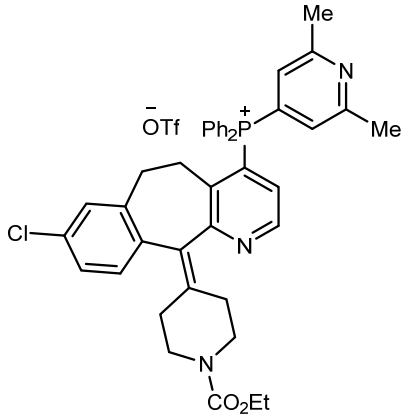
2.0 equiv. 1.0 equiv.

Entry	Atmosphere	Yield
1	N_2	65%
2	N_2	67%
3	air	66%
4	air	68%

Reaction ran on 0.5 mmol scale using **Conditions C'** under either N_2 or air atmosphere. ^{1}H NMR yields shown using 1,3,5-trimethoxybenzene as an internal standard.

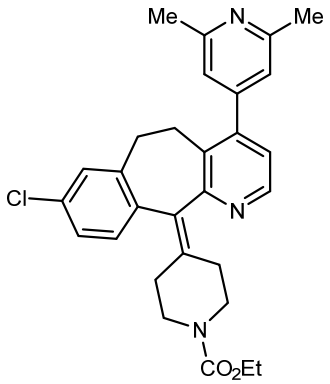
Combining C-H and S_NAr protocols to Synthesize Novel Bipyridines

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



An oven dried round bottom flask equipped with a stir bar was charged with loratadine (456 mg, 1.19 mmol) and placed under a nitrogen atmosphere. CH_2Cl_2 (12 mL) was added, the reaction vessel cooled to –78 ºC and Tf_2O (200 µL, 1.19 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the mixture was warmed to –50 ºC and then the 4-(diphenylphosphaneyl)-2,6-dimethylpyridine (382 mg, 1.31 mmol) was added in one portion as a solid. The reaction was subjected to three rapid cycles of vacuum / nitrogen backfill and was stirred for a further 30 minutes at –50 ºC. The reaction was cooled to –78 ºC and DBU (0.18 mL, 1.19 mmol) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O (3x). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to approximately 5 mL. The concentrated reaction mixture was added dropwise to an excess of chilled Et_2O (0 ºC) that was then placed in a –20 ºC refrigerator for approximately 12 hours. The suspension was filtered on a frit, the solid washed with Et_2O and dried *in vacuo* to provide the pure phosphonium salt as a white solid (762 mg, 0.93 mmol, 78%). mp 138-142 ºC; IR ν_{max}/cm^{-1} (film): 3061, 2976, 2909, 1688, 1584, 1554, 1479, 1438, 1388, 1260, 1222, 1147, 1107, 1029, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (1H, t, *J* = 4.8 Hz), 8.00-7.90 (2H, m), 7.88-7.80 (4H, m), 7.78-7.65 (5H, m), 7.21-7.02 (5H, m), 6.75 (1H, d, *J* = 2.1 Hz), 4.14 (2H, q, *J* = 7.1 Hz), 3.84-3.68 (1H, m), 3.39-3.22 (3H, m), 2.81 (1H, dt, *J* = 17.4, 5.3 Hz), 2.59-2.34 (3H, m), 2.23 (1H, s), 1.58 (1H, ddd, *J* = 17.1, 11.6, 5.2 Hz), 1.26 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5 (d, *J* = 8.4 Hz), 161.2 (d, *J* = 10.9 Hz), 155.4, 149.4 (d, *J* = 11.5 Hz), 139.4, 136.9, 136.7-136.3 (2C, m), 134.4 (dd, *J* = 10.6, 2.1 Hz), 134.2, 133.7, 132.4 (d, *J* = 2.2 Hz), 131.6, 131.4 (d, *J* = 13.2 Hz), 129.8, 127.7 (d, *J* = 82.7 Hz), 127.5 (d, *J* = 10.3 Hz), 126.6, 125.8 (d, *J* = 82.2 Hz), 123.3 (d, *J* = 8.4 Hz), 120.7 (q, *J* = 321.2 Hz), 115.1 (d, *J* = 88.0 Hz), 115.0 (d, *J* = 88.2 Hz), 44.7, 44.5, 31.1-30.2 (3C, m), 29.5, 24.9 (2C, m), 14.6.; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.18; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.47; *m/z* LRMS (ESI + APCI) found $[M\text{-}OTf]^+$ 672.3, $C_{41}H_{40}ClN_3O_2P^+$ requires 672.3.

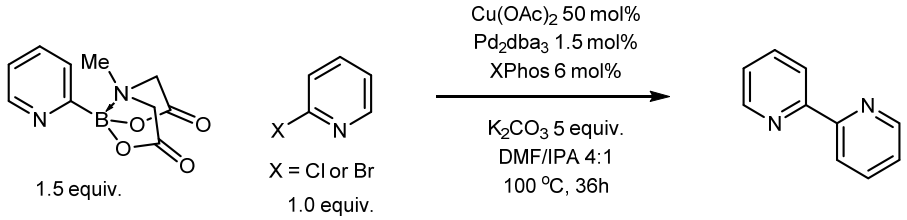
Ethyl 4-(8-chloro-4-(2,6-dimethylpyridin-4-yl)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (3ab)



Prepared according to established procedure.[3] An oven dried 8 mL vial with a septa cap was charged with (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)(2,6-dimethylpyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (206 mg, 0.25 mmol) and EtOH (0.63 mL). The vial was subjected to three rapid cycles of vacuum / nitrogen backfill and then TfOH (44 μL, 0.5 mmol) was added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 80 ºC for 40 hours. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (MgSO4), filtered and concentrated *in vacuo*. Flash column chromatography (neutral alumina, gradient elution: 20% EtOAc in hexanes to EtOAc) followed by a second flash column (silica gel, gradient elution: 2% MeOH in CH_2Cl_2 to 4% MeOH in CH_2Cl_2) afforded the title compound as a colorless oil (101 mg, 0.21 mmol, 83% yield). IR ν_{max}/cm^{-1} (film): 3049, 2978, 2910, 1689, 1608, 1579, 1561, 1542, 1477, 1430, 1386, 1325, 1277, 1222, 1172, 1117, 1062, 1028, 990, 732; ^1H NMR (400 MHz, $CDCl_3$) d: 8.41 (1H, d, J = 5.0 Hz), 7.13-7.07 (3H, m), 6.96 (1H, d, J = 5.0 Hz), 6.86 (2H, s), 4.11 (2H, q, J = 7.1 Hz), 3.78 (2H, br s), 3.42-3.04 (4H, m), 2.75 (2H, m), 2.56 (s, 6H), 2.40 (3H, m), 2.30-2.14 (1H, m), 1.22 (4H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 158.2, 155.5, 147.7, 147.6, 146.7, 138.8, 137.2, 136.0, 134.4, 133.1, 131.4, 130.5, 129.8, 126.2, 122.7, 119.9, 61.4, 44.9, 44.7, 32.3, 30.7, 30.6, 27.5, 24.6, 14.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 488.3, $C_{29}H_{31}ClN_3O_2^+$ requires 488.2.

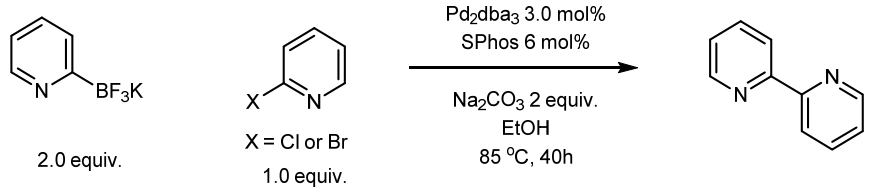
9. Compatibility and Comparison to Metal-Catalyzed Cross-Coupling Reactions

BMIDA Cross Coupling



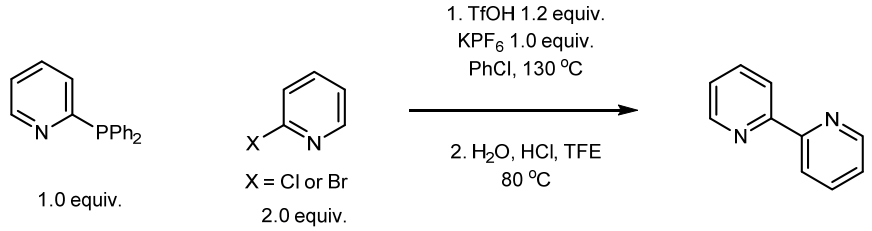
Prepared according to established procedure.[4] An 8 mL oven dried vial equipped with a stir bar was purged with nitrogen and charged with 6-methyl-2-(pyridin-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (70 mg, 0.30 mmol), 2-chloropyridine (19 mL, 0.20 mmol) or 2-bromopyridine (19 mL, 0.20 mmol), $Cu(OAc)_2$ (18 mg, 0.10 mmol), K_2CO_3 (138 mg, 1.0 mmol), and isopropylalcohol (400 uL). In a separate 8 mL oven dried vial in a glove box, Pd_2dba_3 (2.7 mg, 0.003 mmol, 1.5 mol%), XPhos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, 5.7 mg, 0.01 mmol, 6.0 mol%), and DMF (1.6 mL) were stirred together at 100 °C for 10 minutes. This mixture was then transferred to the other 8 mL vial while mixture was soluble in DMF (around 40 °C for transfer). Reaction was then allowed to stir at 100 °C for 36 hours. Reaction was cooled to room temperature and quenched with 10% NaOH in H_2O and aqueous layer was extracted 3x with Et_2O. The combined organic layers were dried with $MgSO_4$ and concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (34 mg, 0.20 mmol) was added as an internal standard and the ^1H NMR yield was determined to be 39% for 2-chloropyridine and 38% for 2-bromopyridine.

BF_3K Cross Coupling



Prepared according to established procedure.[5] An 8 mL oven dried vial equipped with a stir bar was purged with nitrogen and charged with 2-(trifluoro-l^4-boraneyl)pyridine, potassium salt (93 mg, 0.50 mmol), 2-chloropyridine (23 mL, 0.25 mmol) or 2-bromopyridine (24 mL, 0.25 mmol), Na_2CO_3 (53mg, 0.5 mmol), $Pd(OAc)_2$ (1.7 mg, 0.008 mmol, 3.0 mol%), and SPhos (2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 6.2 mg, 0.016 mmol, 6 mol%) and EtOH (2.0 mL). Reaction was then heated to 80 °C for 40 hours. Reaction was cooled to room temperature and filtered through a pad of silica gel eluting with EtOAc. The filtrate was concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard and the ^1H NMR yield was determined to be 15% for 2-chloropyridine and 5% for 2-bromopyridine.

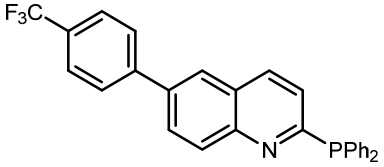
Tandem S_NAr-Ligand-Coupling



Prepared according to general procedure C′ using 2-(diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (66 mg, 0.25 mmol), 2-chloropyridine (47 μL, 0.50 mmol) or 2-bromopyridine (48 μL, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 °C for 41 hours; then H_2O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 mL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 23 hours. 1,3,5-Trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard and the ^{1}H NMR yield was determined to be 68% for 2-chloropyridine and 67% for 2-bromopyridine.

Phosphine Compatibility: Suzuki-Miyaura Reaction

2-(Diphenylphosphaneyl)-6-(4-(trifluoromethyl)phenyl)quinoline (2n)

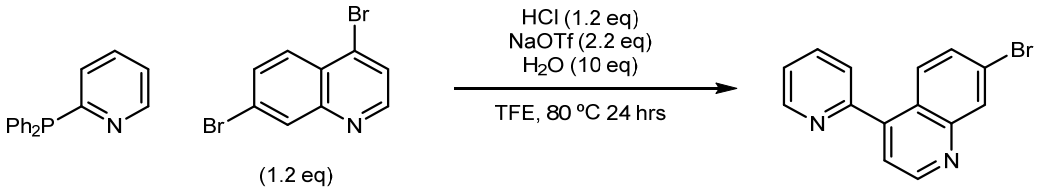


Prepared according to an established procedure[2] using 6-bromo-2-(diphenylphosphaneyl)quinoline (784 mg, 2.00 mmol), (4-(trifluoromethyl)phenyl)boronic acid (454 mg, 2.40 mmol), $Pd_2(dba)_3$ (18 mg, 0.02 mmol), tricyclohexylphosphane (14 mg, 0.048 mmol), aqueous K_3PO_4 (1.25 M, 2.7 mL, 3.40 mmol), and dioxanes (5.3 mL). Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes) afforded the title compound as a faint yellow powder (631 mg, 1.38 mmol, 69% yield). mp 130-131 °C; IR ν_{max}/cm^{-1} (film): 3071, 3040, 1615, 1550, 1456, 1386, 1257, 895, 753, 546; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (1H, d, *J* = 8.7 Hz), 8.07 (1H, dd, *J* = 8.6, 1.8 Hz), 8.01-7.92 (2H, m), 7.81 (2H, d, *J* = 8.2 Hz), 7.75 (2H, d, *J* = 8.3 Hz), 7.55-7.35 (10H, m), 7.24 (1H, d, *J* = 8.4 Hz); ^{13}C NMR (100 MHz , $CDCl_3$) δ: 165.9 (d, *J* = 2.1 Hz), 148.3 (d, *J* = 14.5 Hz), 138.1, 136.2 (d, *J* = 11.2), 135.7 (d, *J* = 2.8 Hz), 134.4 (d, *J* = 19.7 Hz), 132.3 (d, *J* = 9.4 Hz), 130.5, 129.9 (q, *J* = 32.5 Hz), 129.3, 129.2, 128.8 (d, *J* = 7.2 Hz), 127.8, 127.0, 126.0, 125.96, 125.0 (d, *J* = 14.3 Hz), 124.3 (q, *J* = 272.1 Hz),; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.39; ^{31}P NMR (365 MHz, $CDCl_3$) δ: –1.80; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 458.2, $C_{28}H_{20}F_3NP^+$ requires 458.1.

Note: Other reaction conditions for Suzuki-Miyaura reaction gave undesired oxidation of phosphine product/reactivity on the C-P bond. It is recommended to use this set of conditions and to vigorously degas all solvents prior to use in reaction.

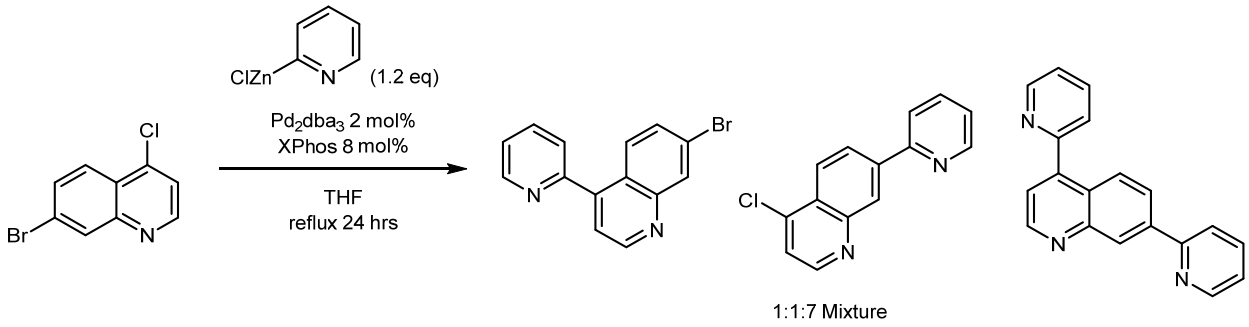
11. Halide Selectivity: Comparison to Metal-Catalysis

Tandem S_NAr-Ligand-Coupling



Prepared according to general procedure B′. An oven dried 8 mL vial with a septa cap was charged with 2-(diphenylphosphaneyl)pyridine (63 mg, 0.25 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), and 4,7-dibromoquinoline (86 mg, 0.30 mmol). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then TFE (0.63 mL), H_2O (45 µL, 2.5 mmol), and 4.0M HCl in dioxanes (75 µL, 0.30 mmol) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 80 ºC and allowed to stir for 24 hours. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). 1,3,5-Trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard and the ^1H NMR yield was determined to be 81%.

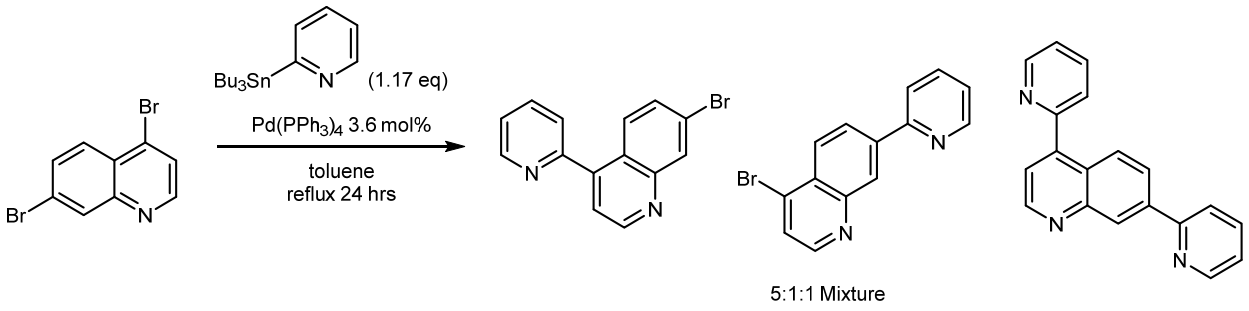
Negishi Coupling:



Prepared according to established procedure.[6] A 5 mL oven dried round-bottom flask equipped with a stir bar was purged with nitrogen and charged with 2.0M iPrMgCl in THF (550 µL, 1.10 mmol) and 2-bromopyridine (97 µL, 1.00 mmol) was added dropwise over 20 minutes at room temperature. Mixture was allowed to stir at room temperature for 4 hours prior to dropwise addition of $ZnCl_2$ in THF (164 mg, 1.20 mmol, 0.5M, 2.40 mL). A separate 10 mL two-necked flask fitted with a reflux condenser was charged with Pd_2dba_3 (4.6 mg, 0.01 mmol, 2.0 mol%), XPhos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, 9.5 mg, 0.02 mmol, 8.0 mol%) and THF (630 µL). Flask was then heated to 65 ºC and stirred for 15 minutes prior to addition of 7-bromo-4-chloroquinoline (61 mg, 0.25 mmol). Mixture was allowed to stir for 20 minutes at 65 ºC before addition of pyridin-2-ylzinc(II) chloride in THF (0.33M, 900 µL, 1.20 mmol). Reaction was stirred at 65 ºC for 24 hours prior to cooling to room temperature. After reaching room temperature, reaction was quenched with saturated aqueous solution of $NaHCO_3$ and the organic

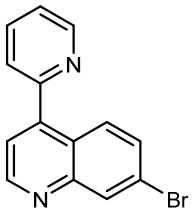
layer was separated. The aqueous layer was extracted 3x with EtOAc and the organic layers were combined and washed with H_2O. The organic layer was then dried with $MgSO_4$ and concentrated *in vacuo*. 1,3,5-trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard and the ^{1}H NMR yield was determined to be 7%, 5%, and 38% respectively (1:1:7). Starting material remaining (25%) was observed by ^{1}H NMR.

Stille Coupling



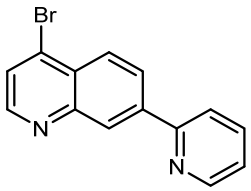
Prepared according to established procedure.[7] An 8 mL oven dried vial equipped with a stir bar was charged with 4,7-dibromoquinoline (72 mg, 0.25 mmol), $Pd(PPh_3)_4$ (10 mg, 0.009 mmol), toluene (0.72 mL), and subjected to three cycles of vacuum/nitrogen backfill. 2-(tributylstannyl)pyridine (95 µL, 0.29 mmol) was added via a syringe before the reaction was heated to reflux for 24 hours. After cooling to room temperature, 1,3,5-trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard. ^{1}H NMR yield of 7-bromo-4-(pyridin-2-yl)quinoline, 4-bromo-7-(pyridin-2-yl)quinoline, and 4,7-di(pyridin-2-yl)quinoline was determined to be 61%, 14%, and 13% respectively (5:1:1). The crude material was purified by flash column chromatography (silica gel, gradient elution: 30% EtOAc in hexanes to 40% EtOAc in hexanes) followed by a second flash column (neutral alumina, gradient elution: 25% EtOAc in hexanes to 30% EtOAc in hexanes) to afford the title compounds.

7-Bromo-4-(pyridin-2-yl)quinoline (3ac)



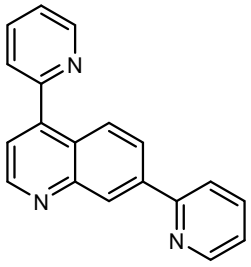
The title compound was isolated as an off white solid. mp 120-122 ºC; IR ν_{max}/cm^{-1} (film): 3084, 3052, 2924, 2853, 1580, 1567, 1557, 1468, 1433, 1409, 1368, 1348, 1276, 1188, 1152, 1093, 1046, 990, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98 (1H, d, *J* = 4.5 Hz), 8.82 (1H, dd, *J* = 4.9, 1.6 Hz), 8.36 (1H, d, *J* = 2.0 Hz), 8.04 (1H, d, *J* = 9.1 Hz), 7.88 (1H, td, *J* = 7.7, 1.8 Hz), 7.71–7.57 (2H, m), 7.51 (1H, d, *J* = 4.4 Hz), 7.42 (1H, dd, *J* = 7.7, 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.3, 151.1, 150.1, 149.7, 146.4, 137.1, 132.3, 130.6, 127.4, 124.9, 124.9, 123.8, 123.5, 121.7, 77.5, 77.2, 76.8; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 285.1, $C_{14}H_{10}BrN_2^+$ requires 285.0.

4-Bromo-7-(pyridin-2-yl)quinoline (3ae)



The title compound was isolated as a white solid. mp 107-109 ºC; IR ν_{max}/cm^{-1} (film): 3051, 1618, 1587, 1548, 1503, 1474, 1413, 1343, 1184, 767; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77–8.67 (2H, m), 8.64 (1H, d, *J* = 1.6 Hz), 8.45–8.30 (2H, m), 8.09 (1H, dt, *J* = 8.0, 1.1 Hz), 7.98 (1H, td, *J* = 7.7, 1.8 Hz), 7.91 (1H, d, *J* = 4.8 Hz), 7.46 (1H, ddd, *J* = 7.5, 4.9, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.0, 151.7, 150.9, 149.8, 142.9, 139.1, 135.5, 129.4, 128.5, 128.1, 128.1, 127.1, 124.7, 123.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 285.0, $C_{14}H_{10}BrN_2^+$ requires 285.0.

4,7-Di(pyridin-2-yl)quinoline (3af)



The title compound was isolated as a tan oil. IR ν_{max}/cm^{-1} (film): 3391, 3053, 2924, 2852, 1583, 1566, 1470, 1431, 1413, 1378, 992, 776; ^{1}H NMR (400 MHz, MeOD) δ: 9.02 (1 H, d, *J* = 4.5 Hz), 8.80 (1H, ddd, *J* = 5.0, 1.8, 0.9 Hz), 8.71 (2H, d, *J* = 2.1 Hz), 8.27 (1H, dd, *J* = 8.9, 1.9 Hz), 8.18 (1H, d, *J* = 8.9 Hz), 8.14–8.03 (2H, m), 7.98 (1H, td, *J* = 7.7, 1.8 Hz), 7.81 (1H, d, *J* = 7.9 Hz), 7.66 (1H, d, *J* = 4.5 Hz), 7.61 (1H, ddd, *J* = 7.7, 4.9, 1.2 Hz), 7.44 (1H, ddd, *J* = 7.5, 4.9, 1.1 Hz); ^{13}C NMR (100 MHz, MeOD) δ: 157.4, 157.2, 151.7, 150.8, 150.6, 149.7, 148.0, 142.0, 139.2, 139.0, 127.9, 127.6, 127.6, 127.3, 126.6, 125.2, 124.5, 123.2, 123.0; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 284.2, $C_{19}H_{14}N_3^+$ requires 284.1.

8. References

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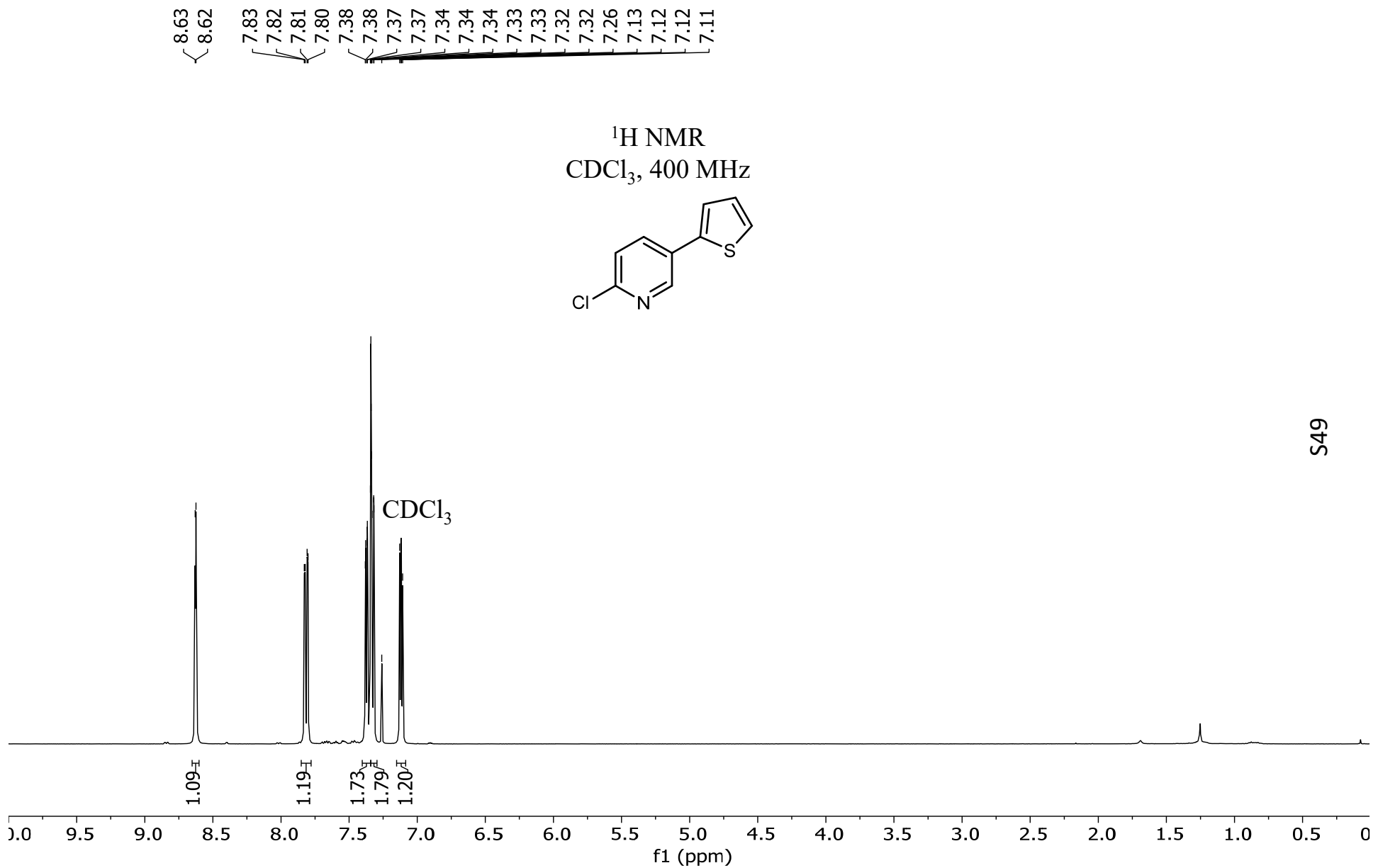
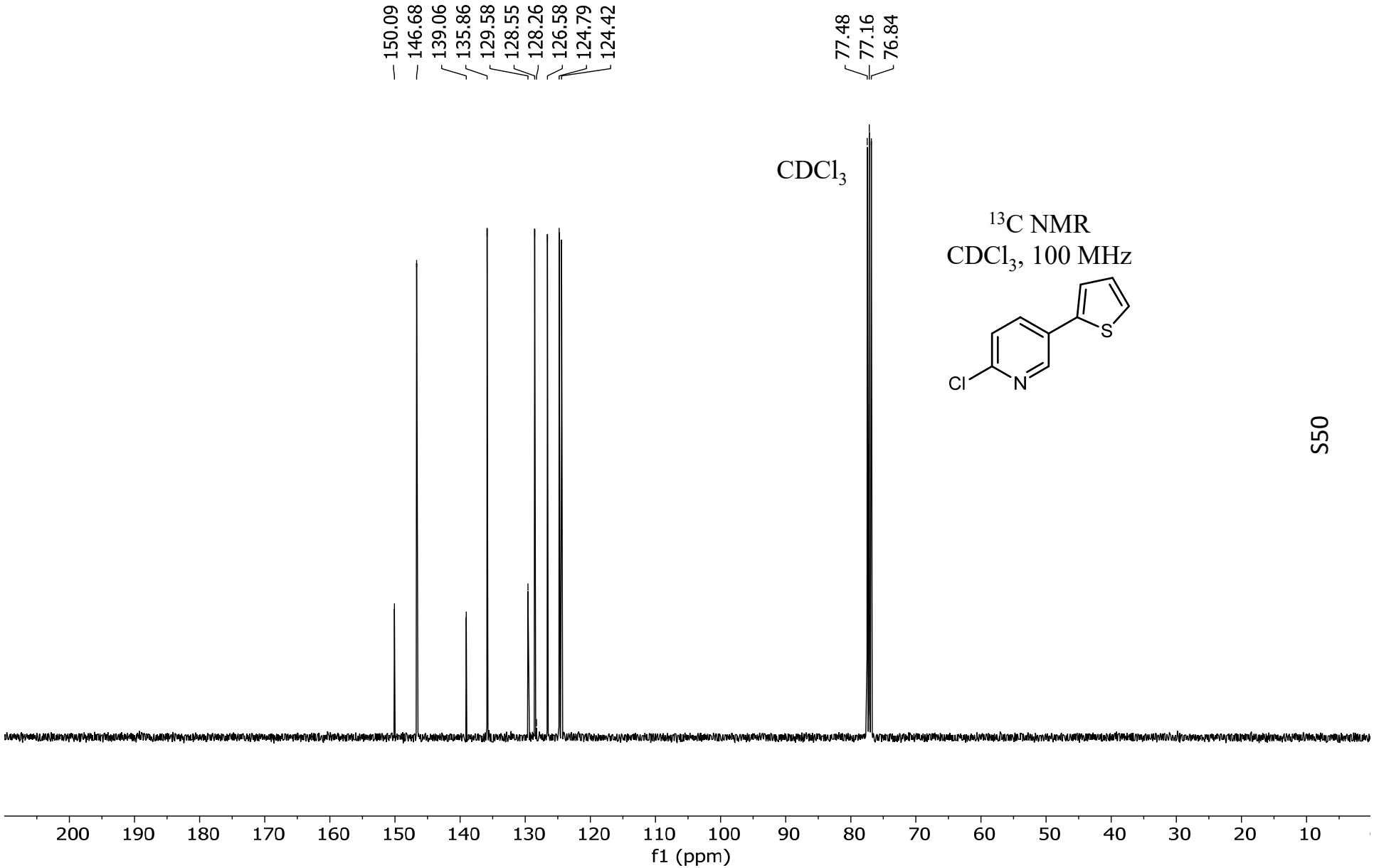
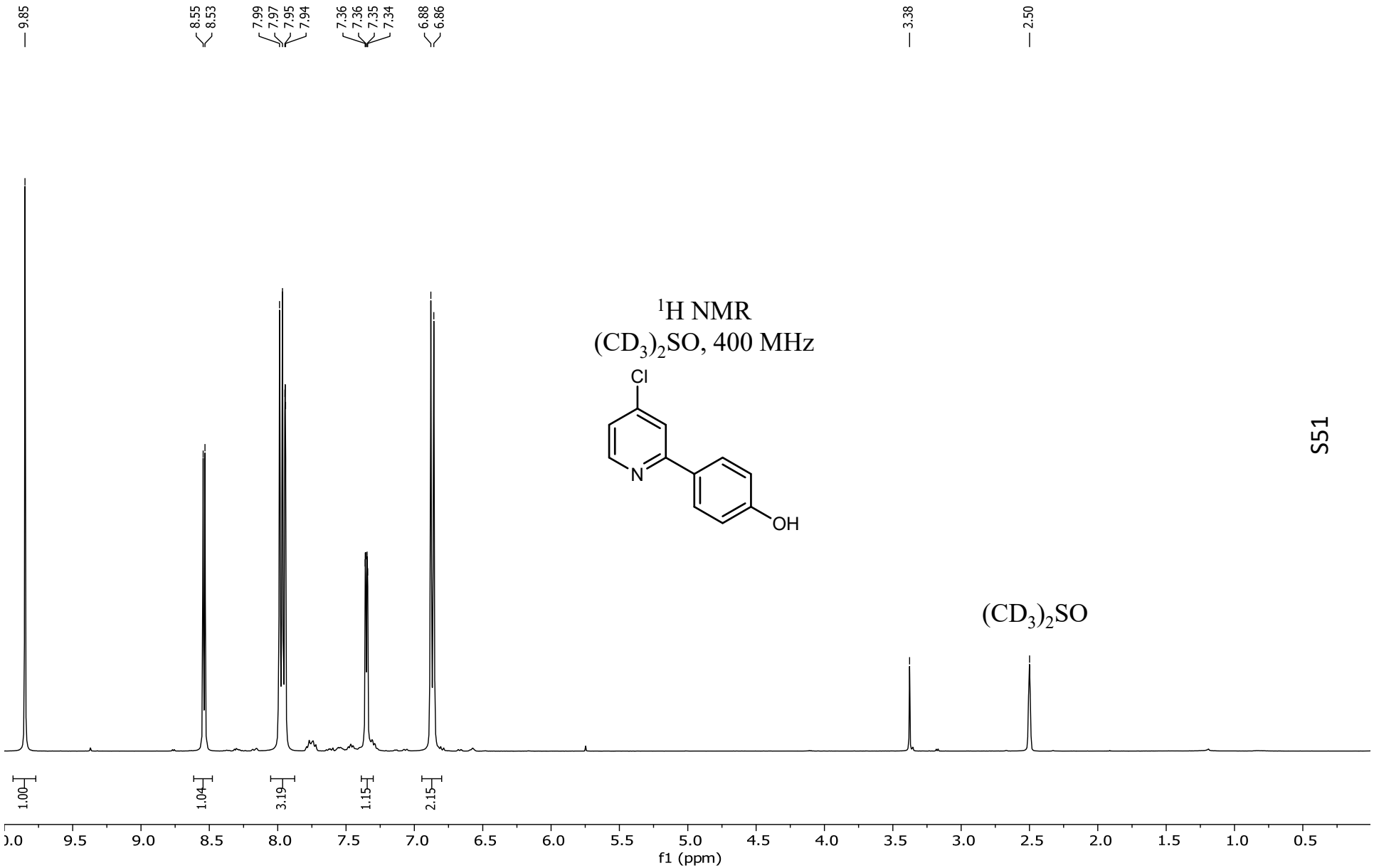
9. ^{1}H, ^{13}C, ^{19}F and ^{31}P Spectra


8.63
8.62
7.83
7.82
7.81
7.80
7.38
7.38
7.37
7.37
7.34
7.34
7.34
7.33
7.33
7.32
7.32
7.26
7.13
7.12
7.12
7.11
1H NMR
CDCl3, 400 MHz
Cl
N
S
CDCl3
1.09
1.19
1.73
1.79
1.20
f1 (ppm)


150.09
146.68
139.06
135.86
129.58
128.55
128.26
126.58
124.79
124.42
77.48
77.16
76.84
CDCl3
13C NMR
CDCl3, 100 MHz
Cl
N
S
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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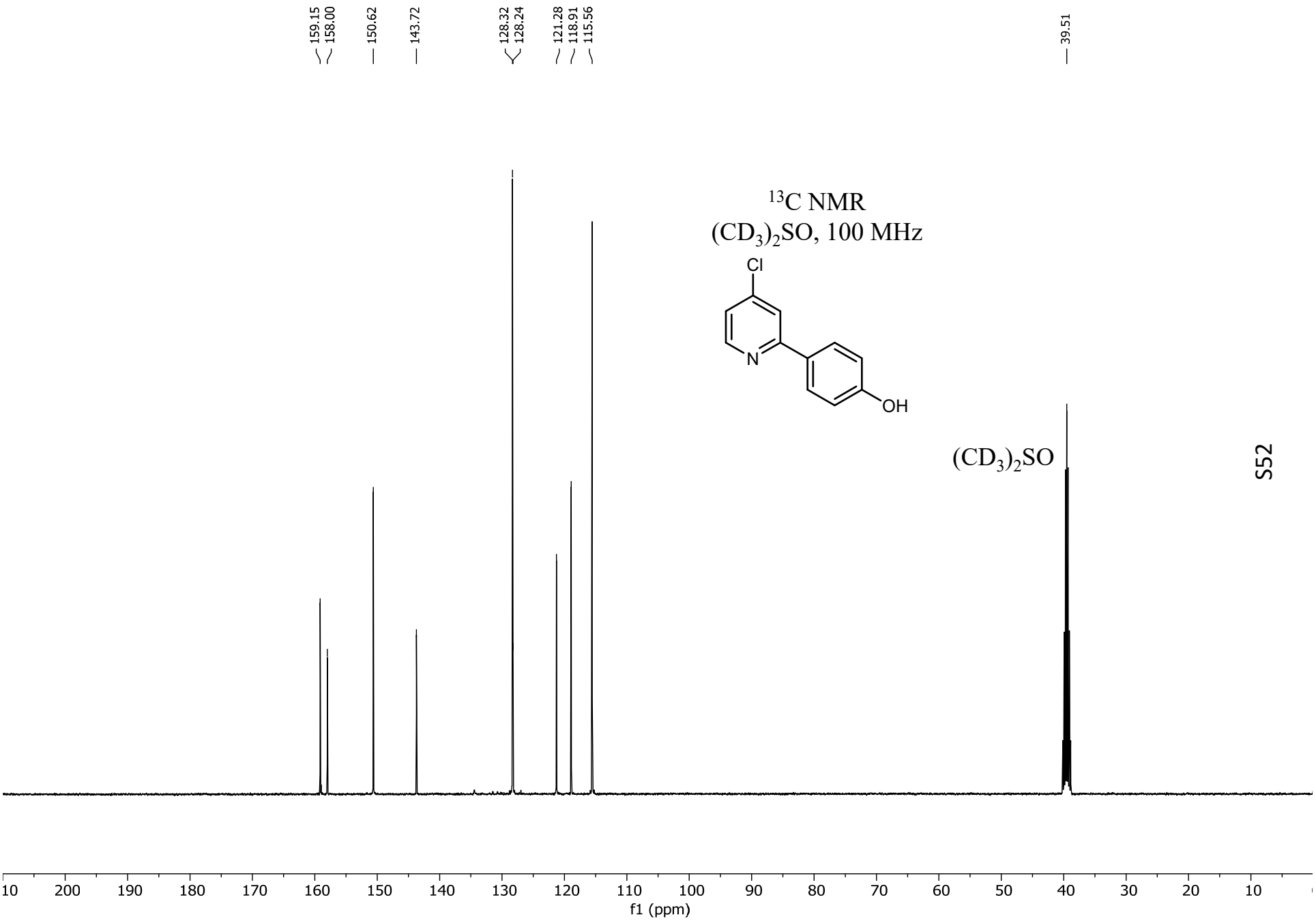
8.55
8.53
7.99
7.97
7.95
7.94
7.36
7.36
7.35
7.34
6.88
6.86
3.38
2.50
^{1}H NMR
$(CD_3)_2SO$, 400 MHz
Cl
N
OH
$(CD_3)_2SO$
1.00
1.04
3.19
1.15
2.15
f1 (ppm)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158.00
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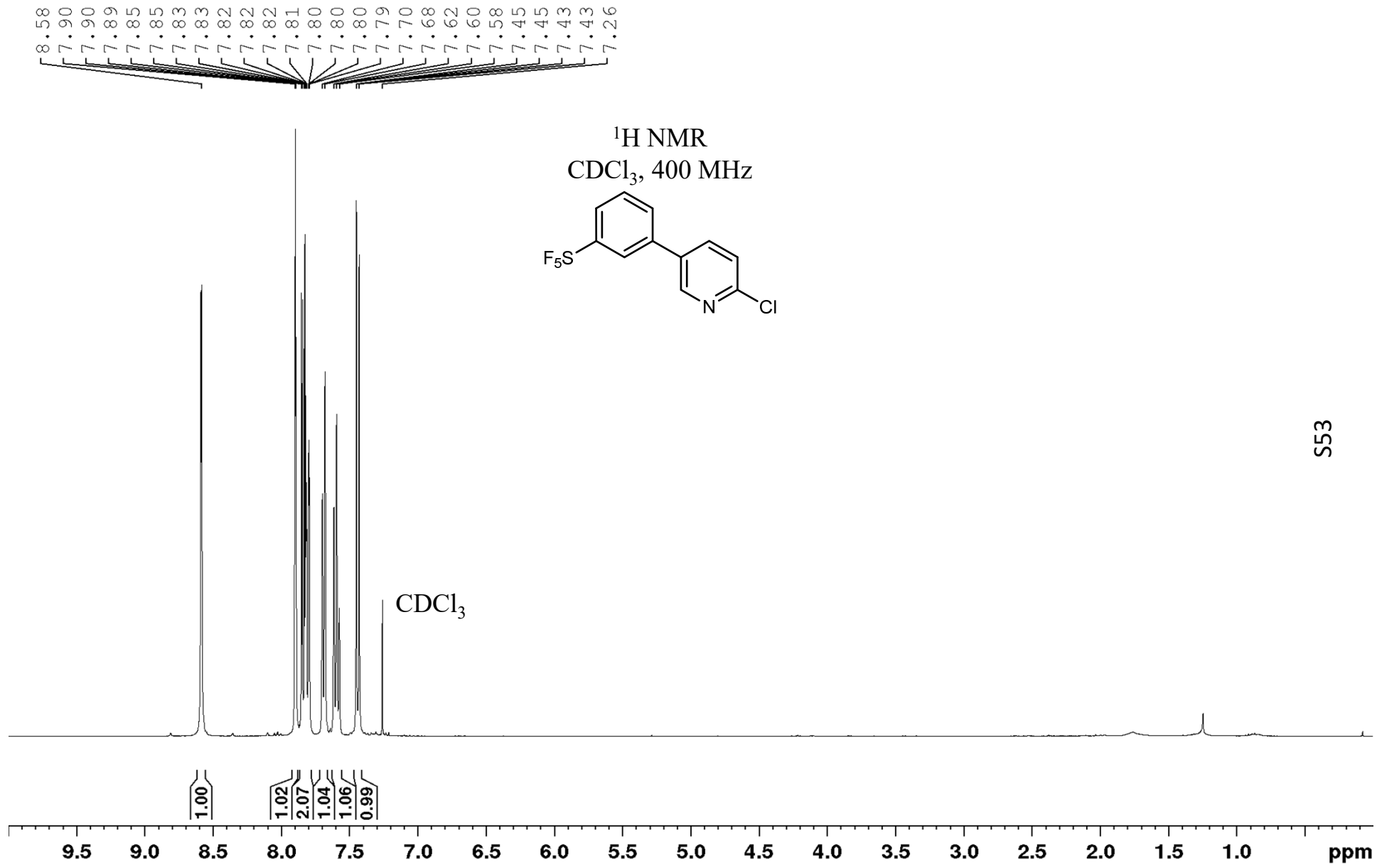
143.72
128.32
128.24
121.28
118.91
115.56
39.51
^{13}C NMR
$(CD_3)_2SO$, 100 MHz
Cl
N
OH
$(CD_3)_2SO$
S52
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


8.58
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7.85
7.85
7.83
7.83
7.82
7.82
7.82
7.81
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7.80
7.80
7.79
7.70
7.68
7.62
7.60
7.58
7.45
7.45
7.43
7.43
7.26
1H NMR
CDCl3, 400 MHz
F5S
N
Cl
CDCl3
1.00
1.02
2.07
1.04
1.06
0.99
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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5.0
4.5
4.0
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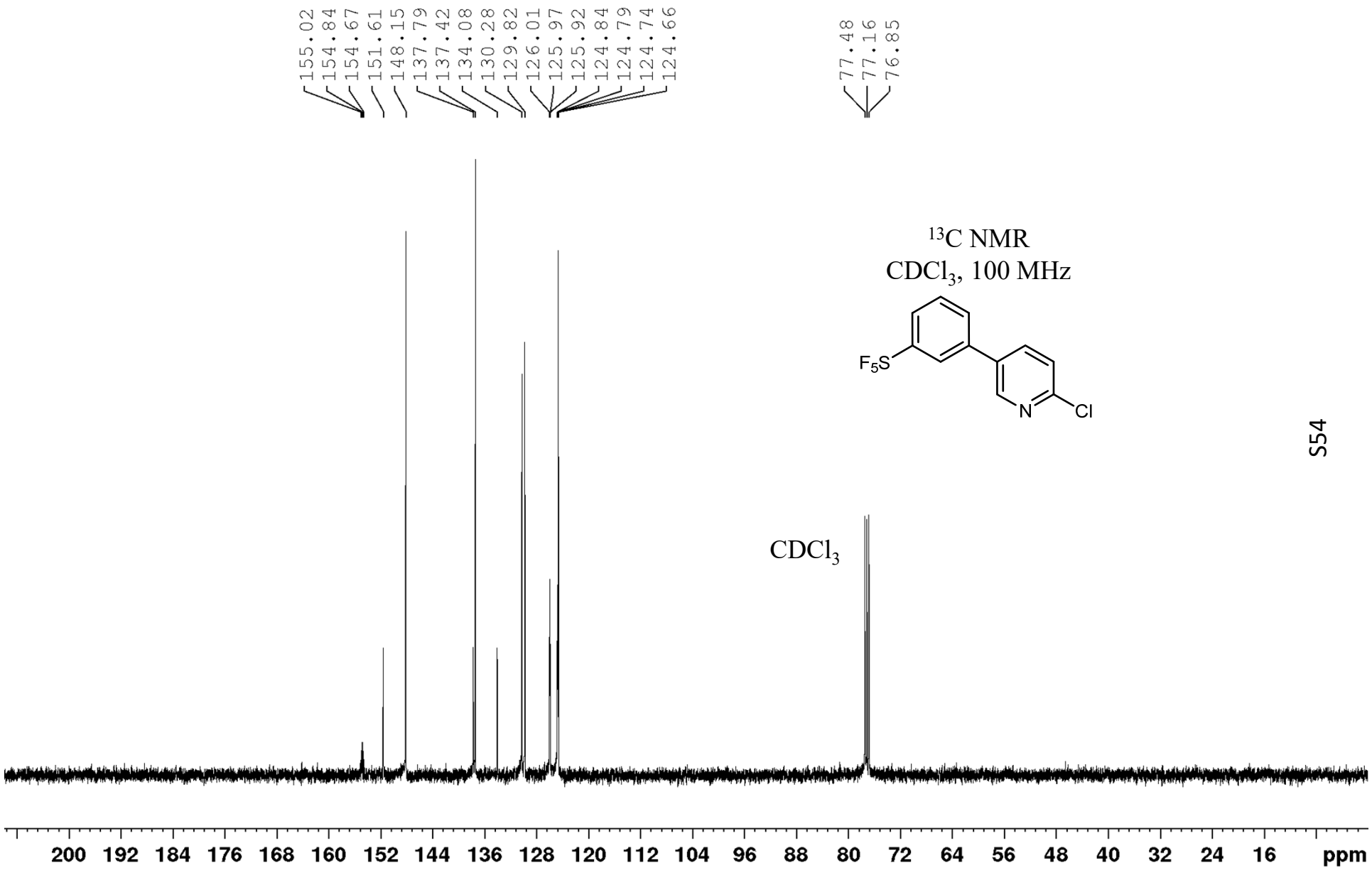
3.0
2.5
2.0
1.5
1.0
ppm


155.02
154.84
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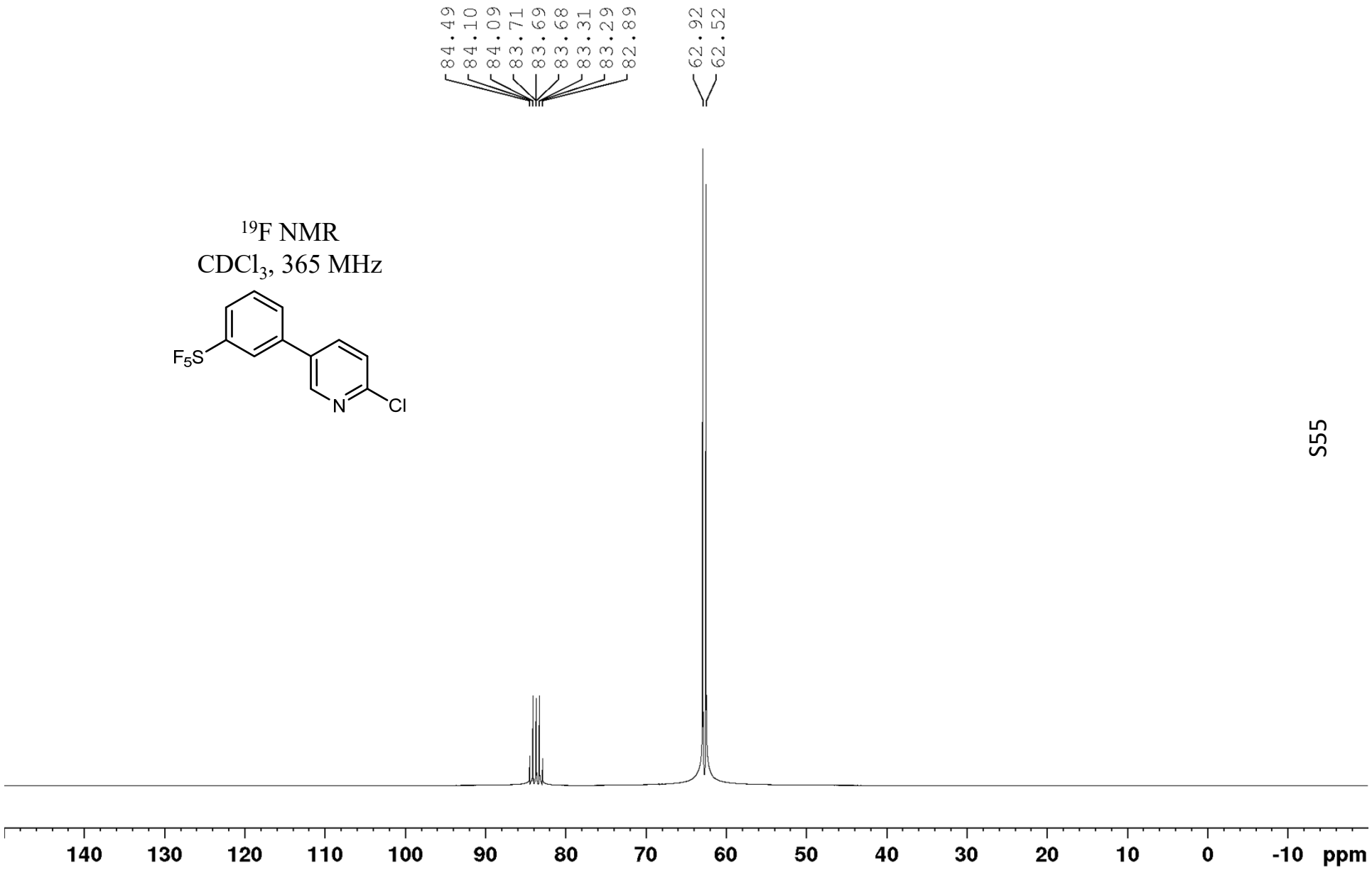
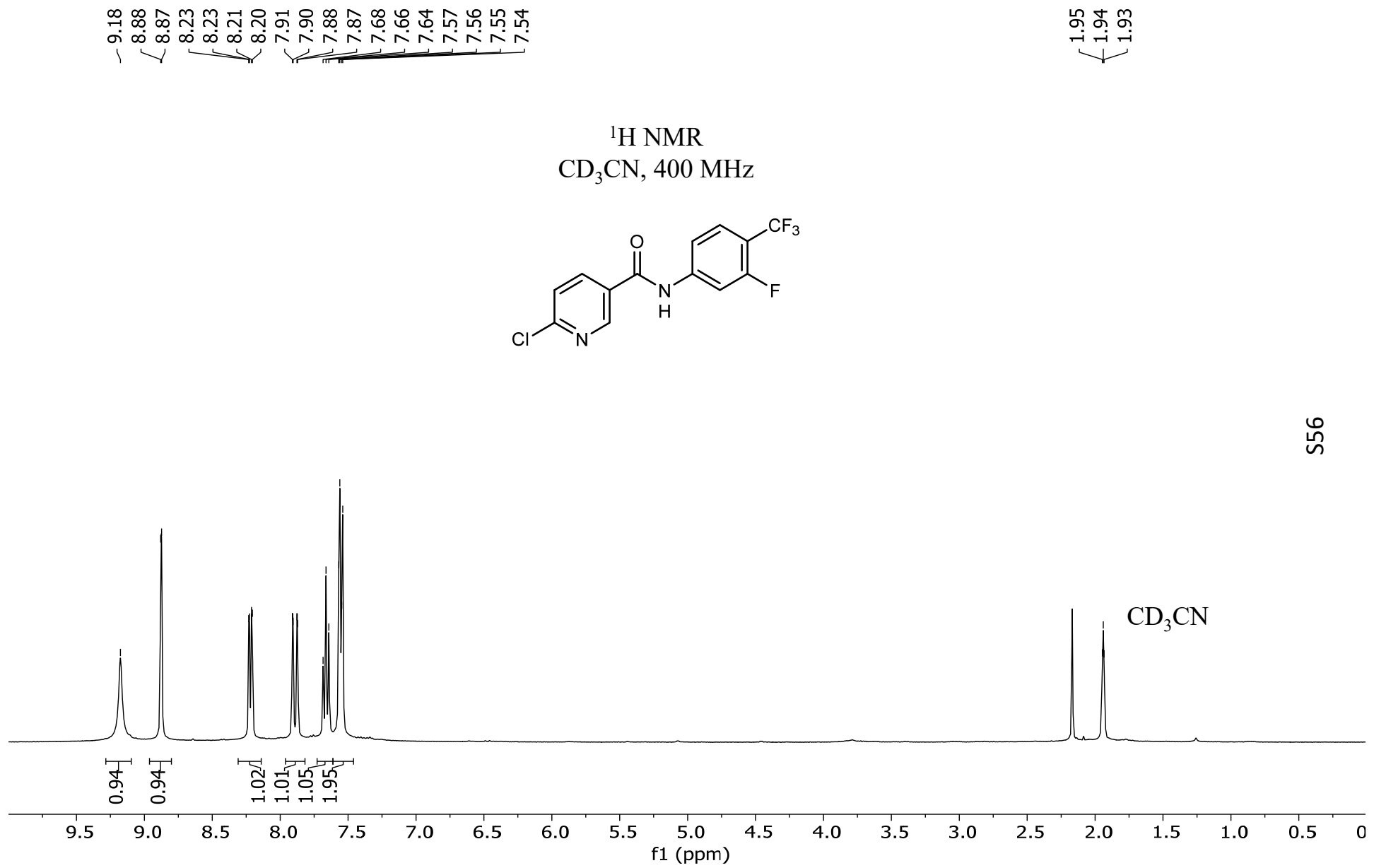
151.61
148.15
137.79
137.42
134.08
130.28
129.82
126.01
125.97
125.92
124.84
124.79
124.74
124.66
77.48
77.16
76.85
^{13}C NMR
$CDCl_3$, 100 MHz
F_5S
N
Cl
$CDCl_3$
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


84.49
84.10
84.09
83.71
83.69
83.68
83.31
83.29
82.89
62.92
62.52
^{19}F NMR
$CDCl_3$, 365 MHz
F_5S
N
Cl
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


9.18
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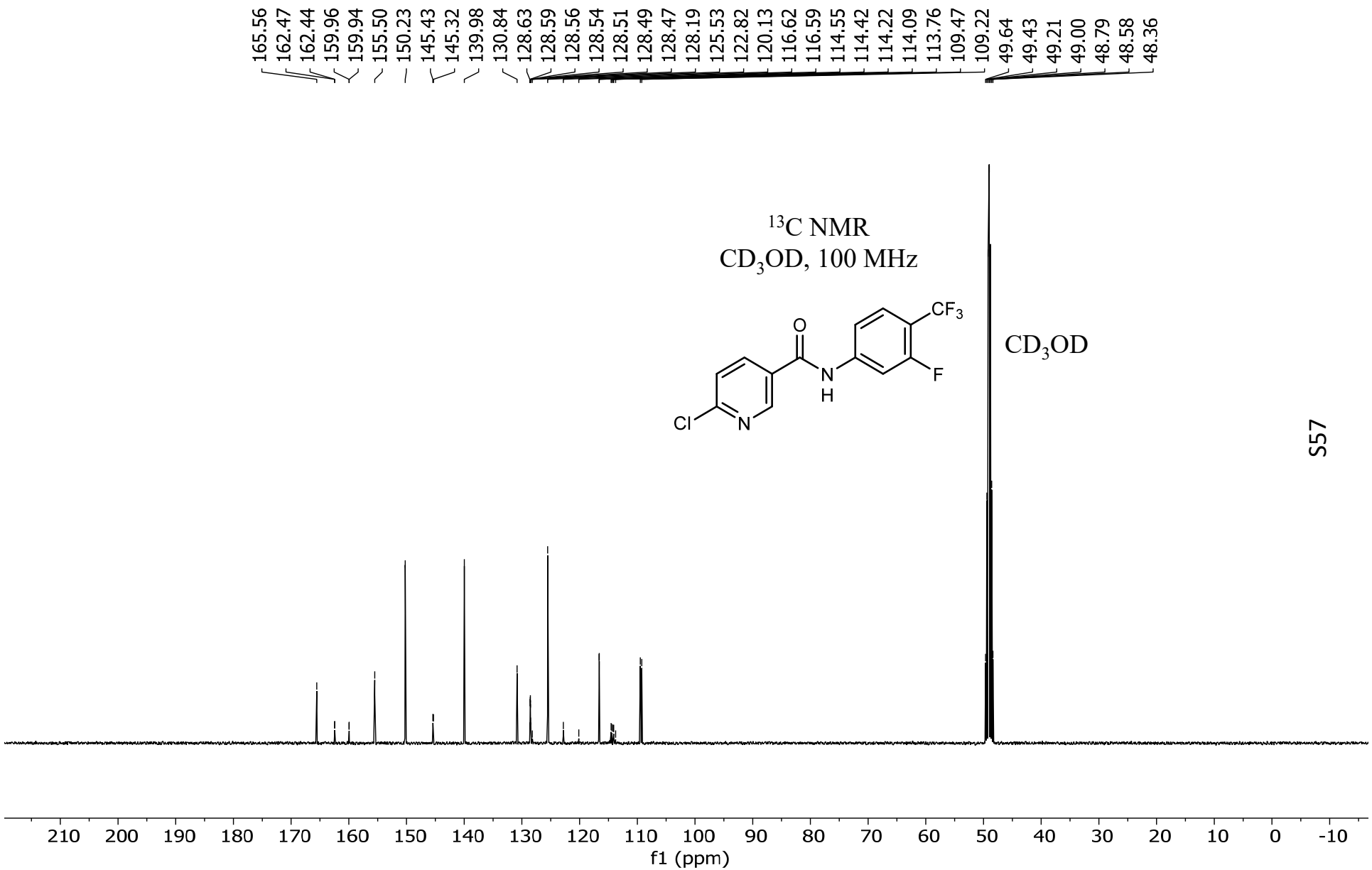
8.87
8.23
8.23
8.21
8.20
7.91
7.90
7.88
7.87
7.68
7.66
7.64
7.57
7.56
7.55
7.54
1.95
1.94
1.93
^{1}H NMR
CD_3CN, 400 MHz
O
N
H
Cl
N
CF_3
F
S56
CD_3CN
0.94
0.94
1.02
1.01
1.05
1.95
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)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155.50
150.23
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139.98
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128.56
128.54
128.51
128.49
128.47
128.19
125.53
122.82
120.13
116.62
116.59
114.55
114.42
114.22
114.09
113.76
109.47
109.22
49.64
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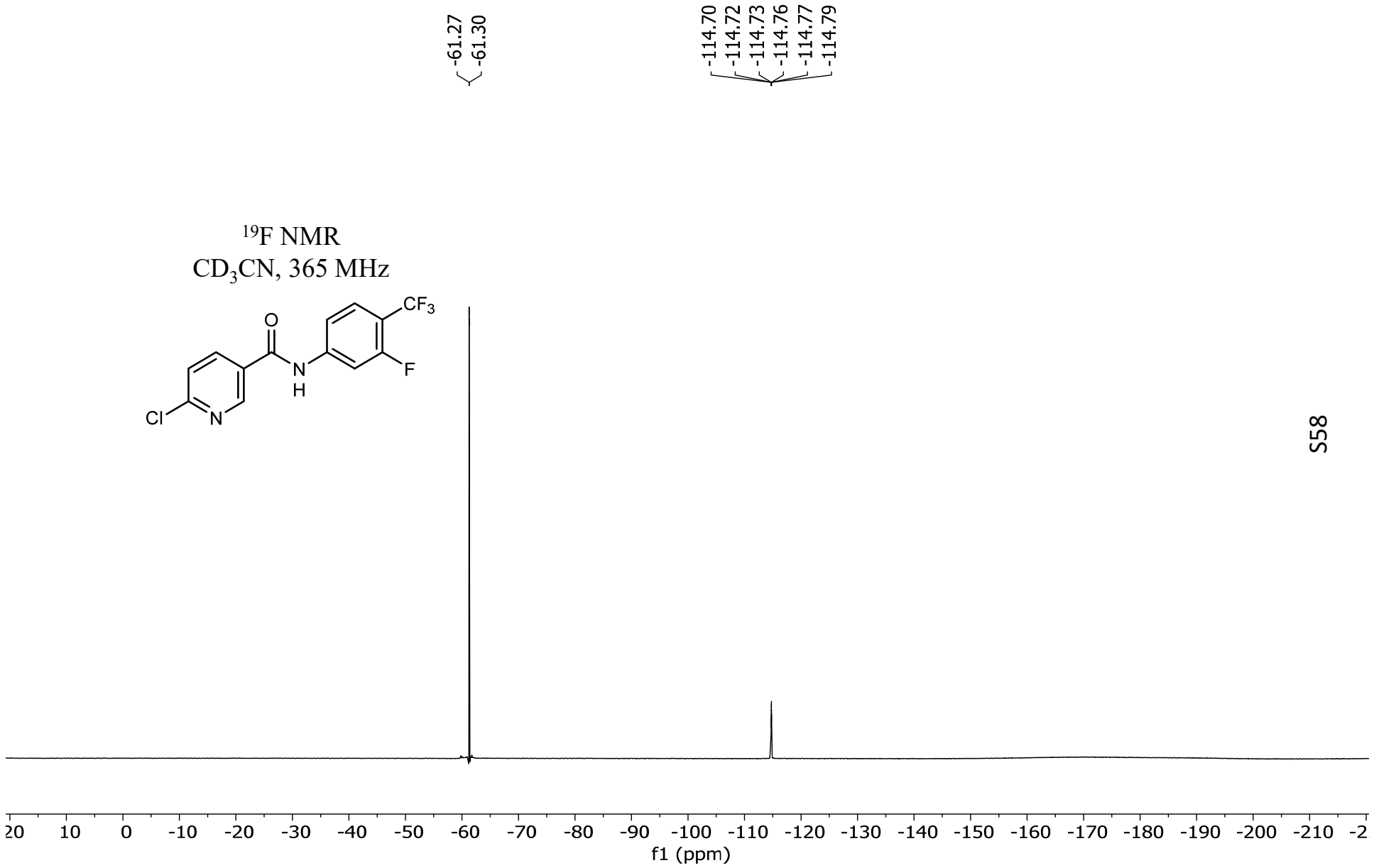
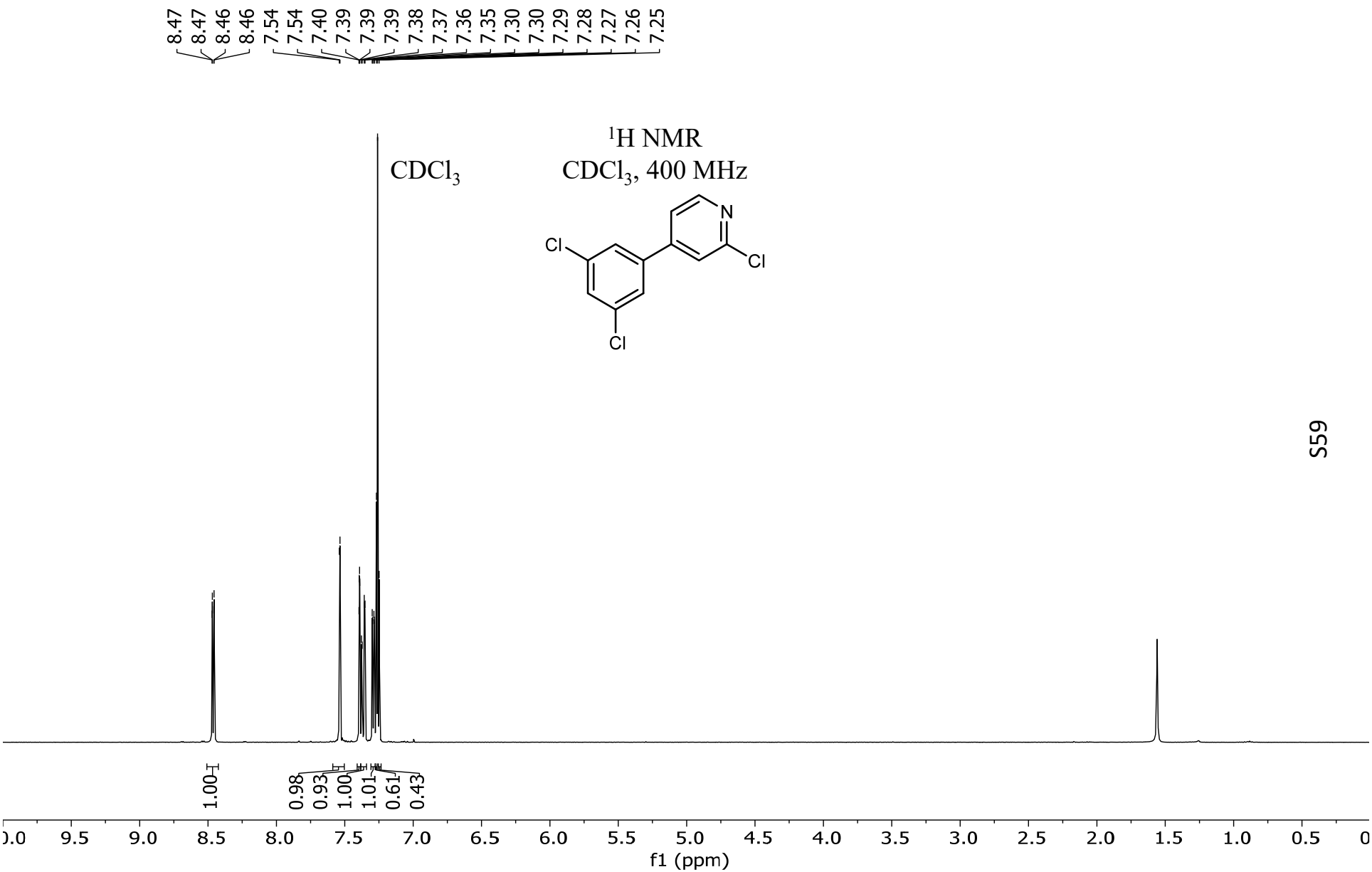
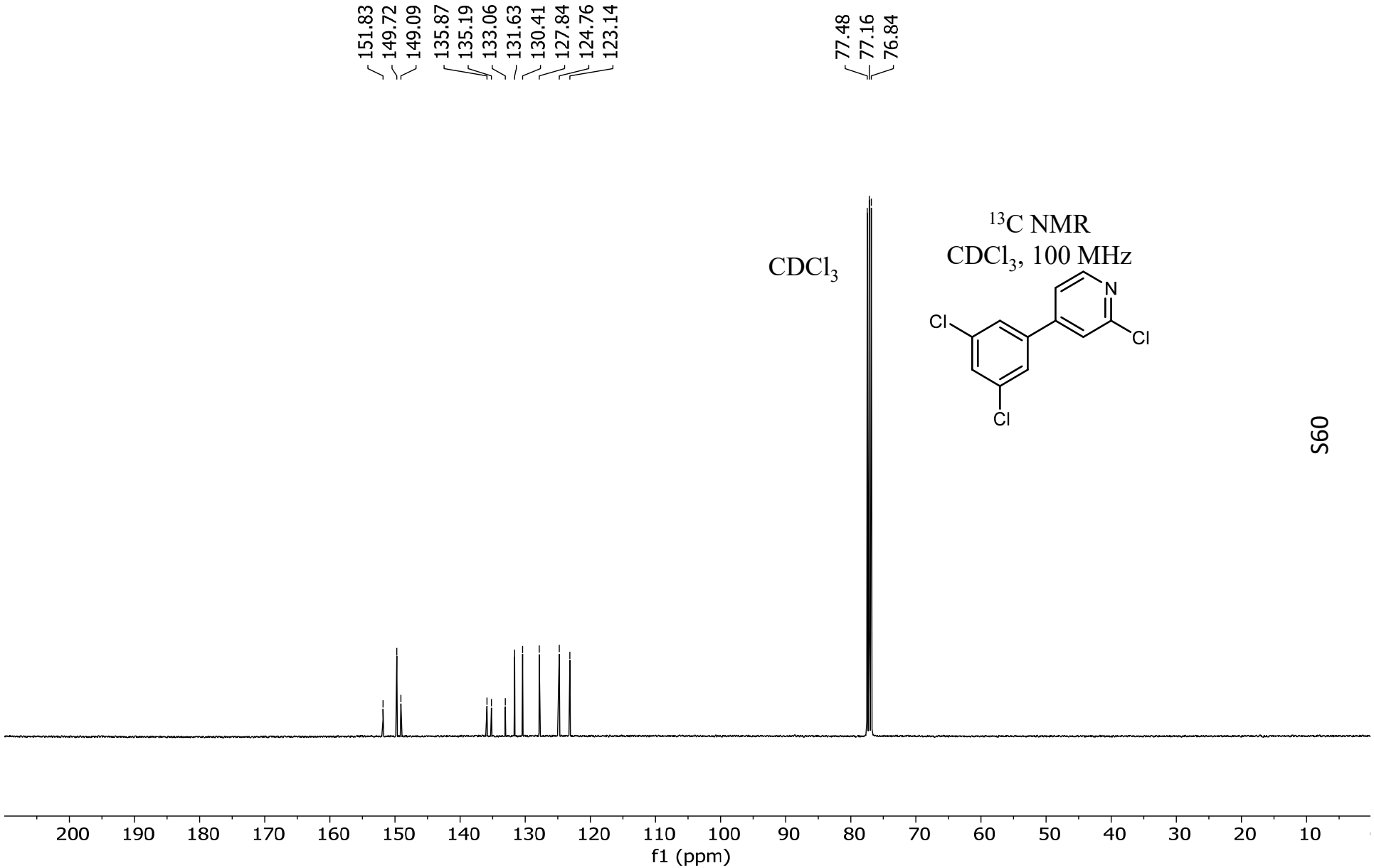
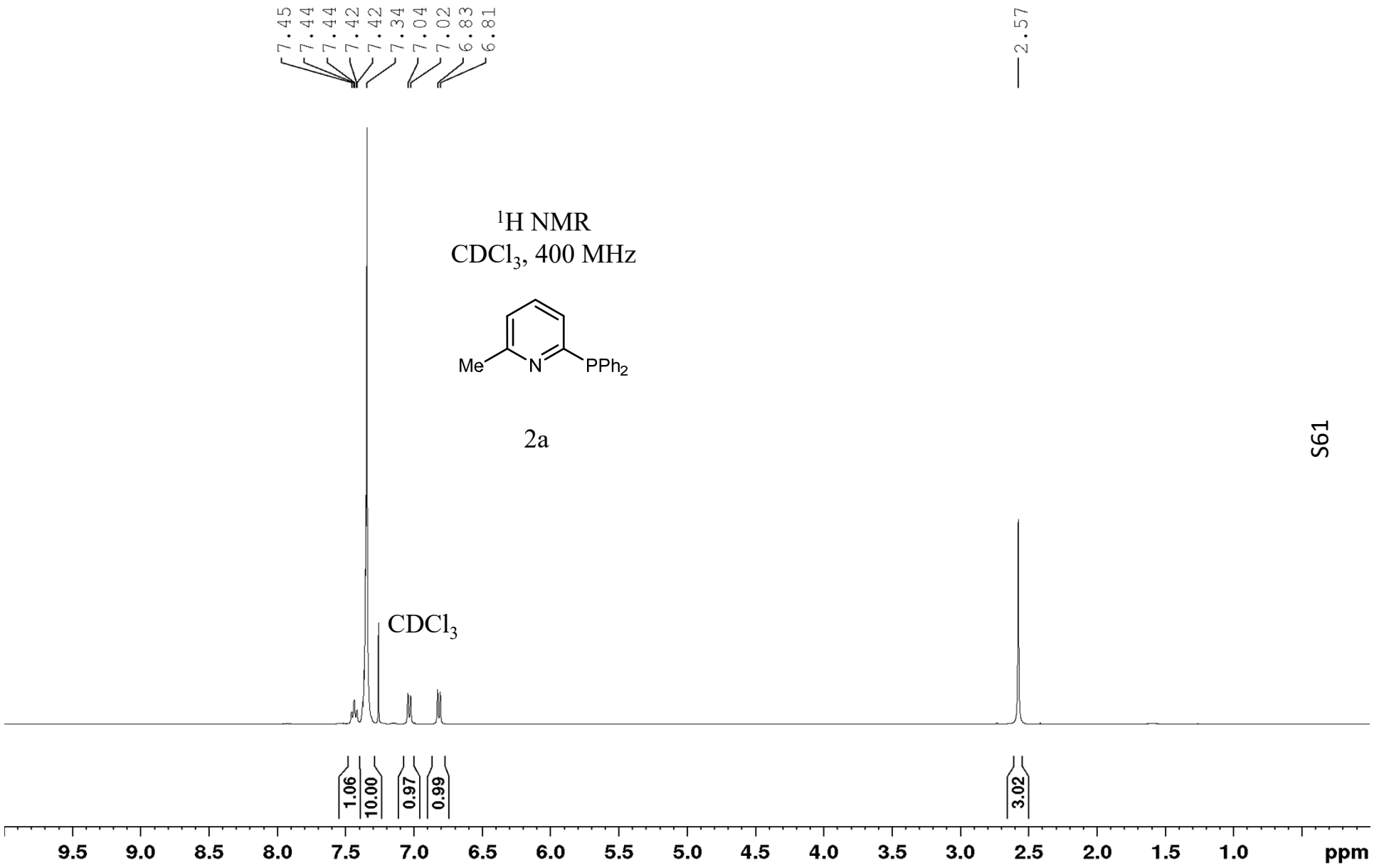
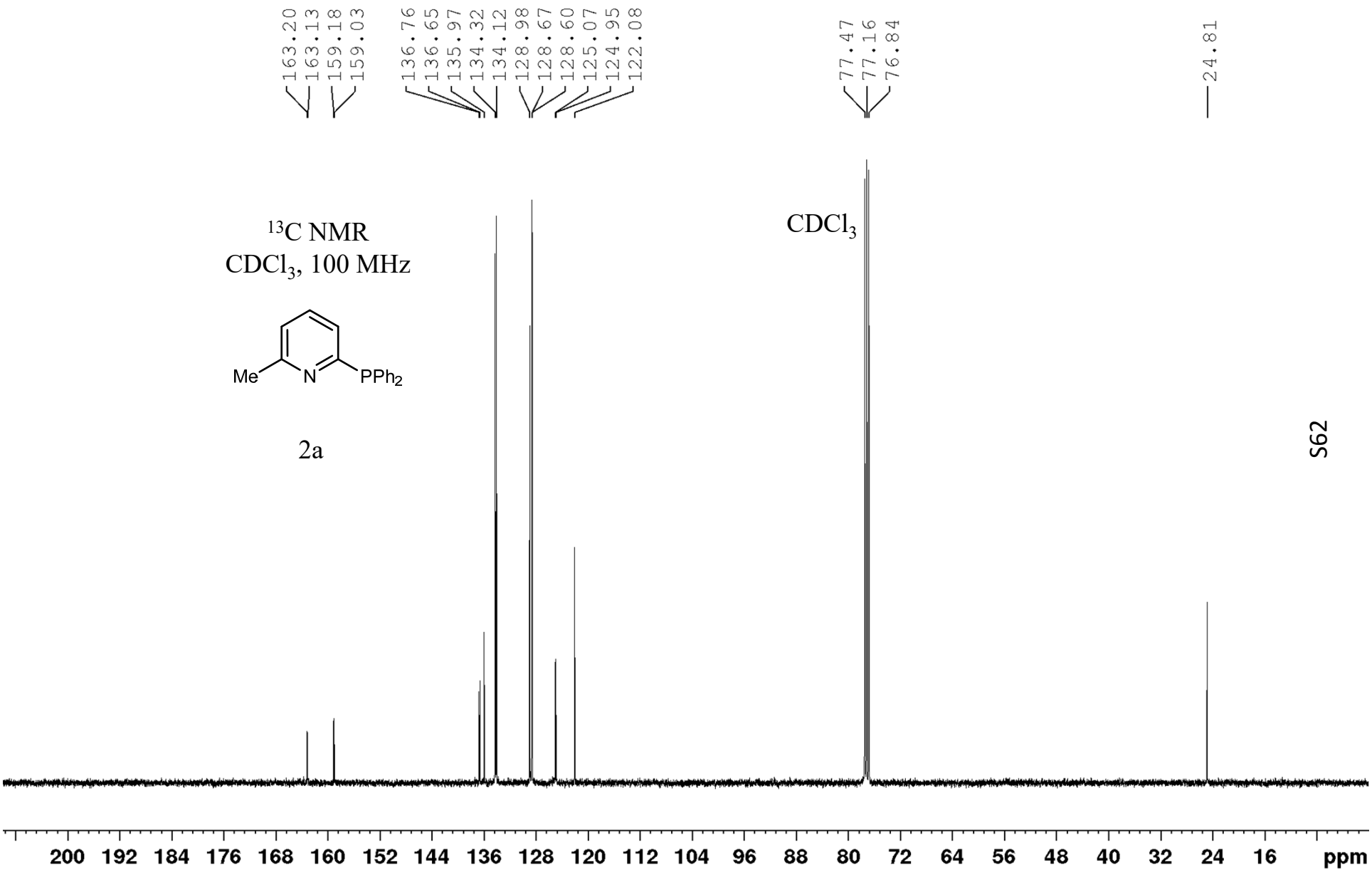
CD_3OD, 100 MHz
CD_3OD
S57
f1 (ppm)

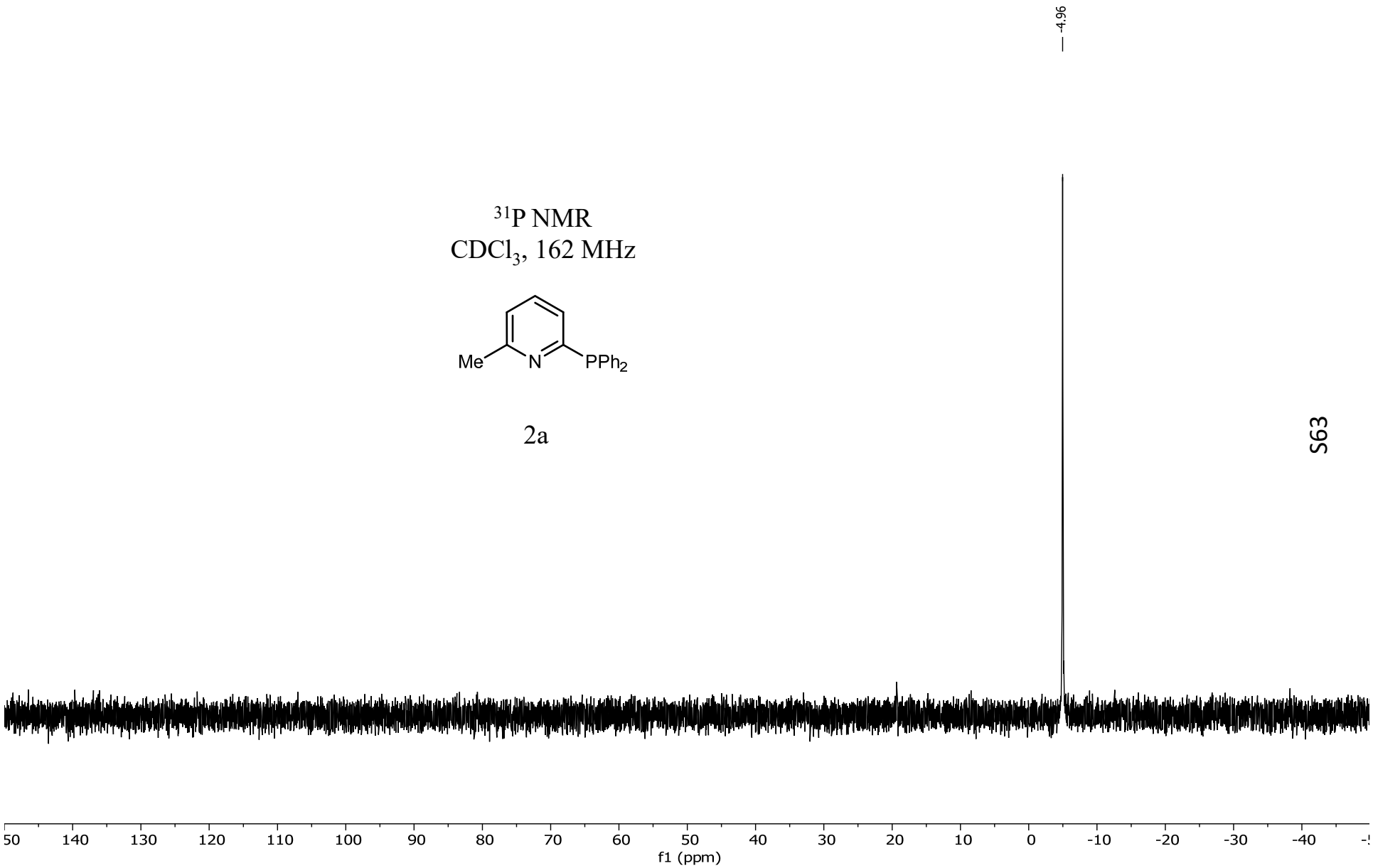

-61.27
-61.30
-114.70
-114.72
-114.73
-114.76
-114.77
-114.79
19F NMR
CD3CN, 365 MHz
CF3
O
N
H
F
Cl
N
f1 (ppm)

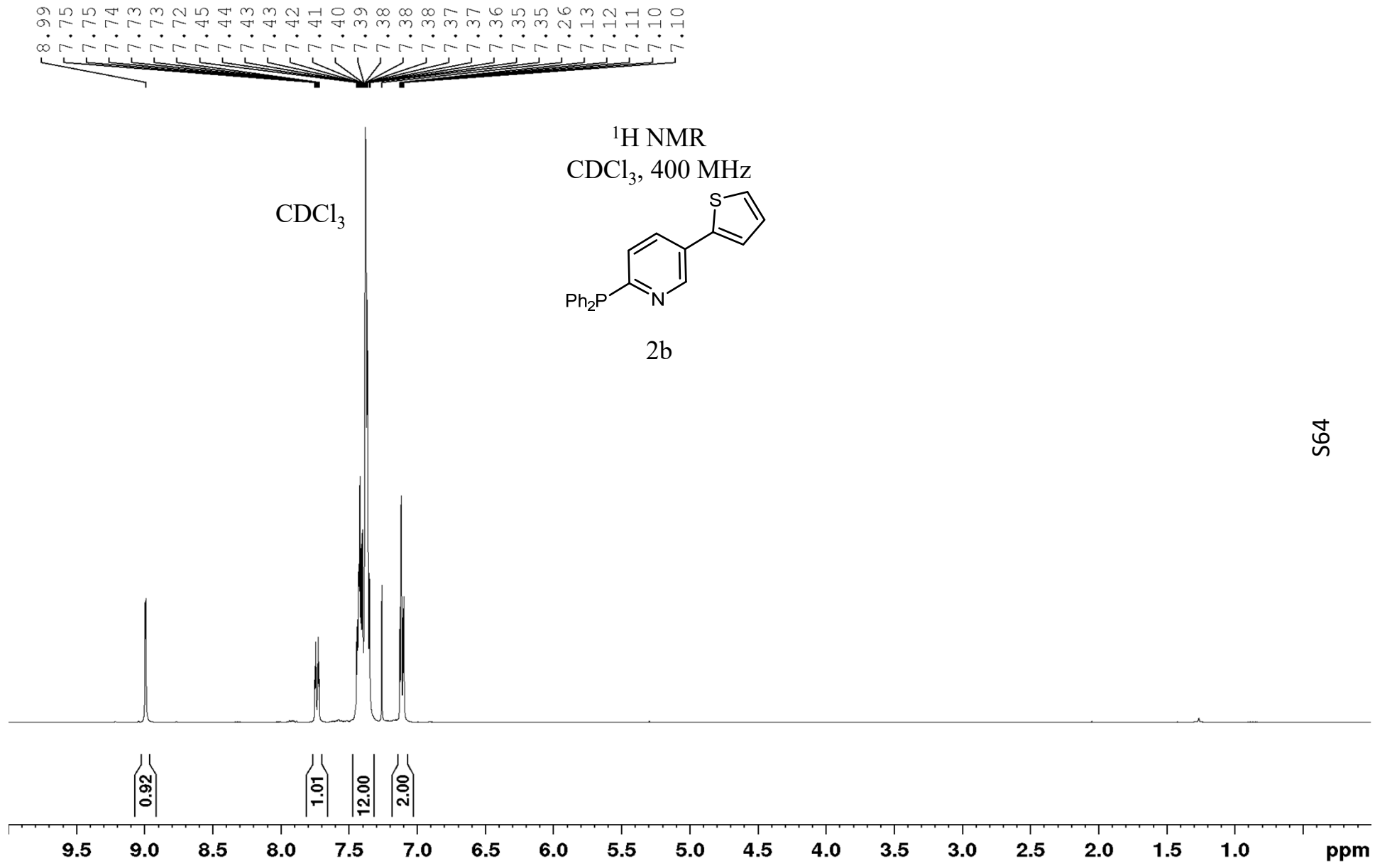

8.47
8.47
8.46
8.46
7.54
7.54
7.40
7.39
7.39
7.39
7.38
7.37
7.36
7.35
7.30
7.30
7.29
7.28
7.27
7.26
7.25
CDCl3
1H NMR
CDCl3, 400 MHz
N
Cl
Cl
Cl
1.00
0.98
0.93
1.00
1.01
0.61
0.43
f1 (ppm)

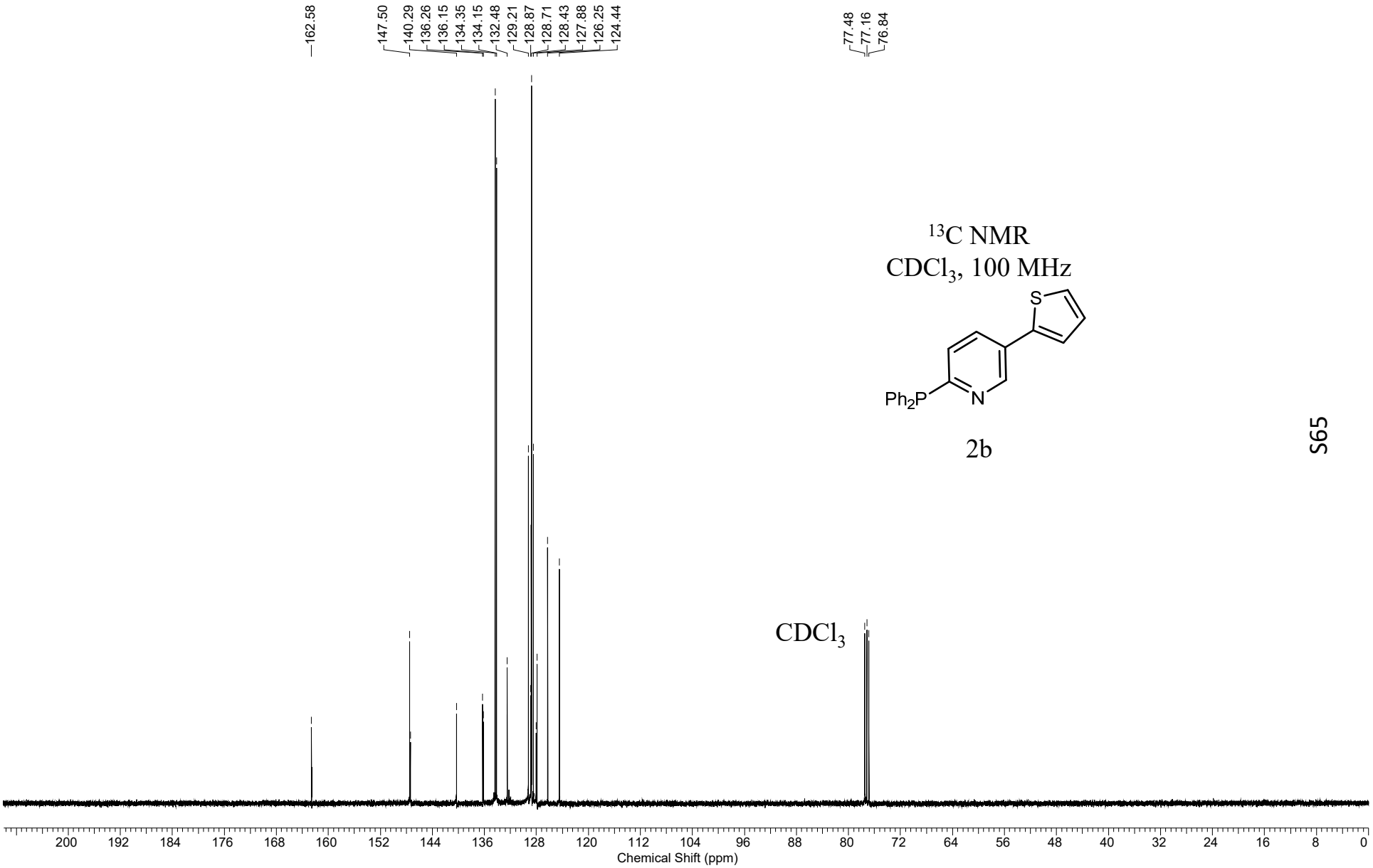

151.83
149.72
149.09
135.87
135.19
133.06
131.63
130.41
127.84
124.76
123.14
77.48
77.16
76.84
CDCl3
13C NMR
CDCl3, 100 MHz
N
Cl
Cl
Cl
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

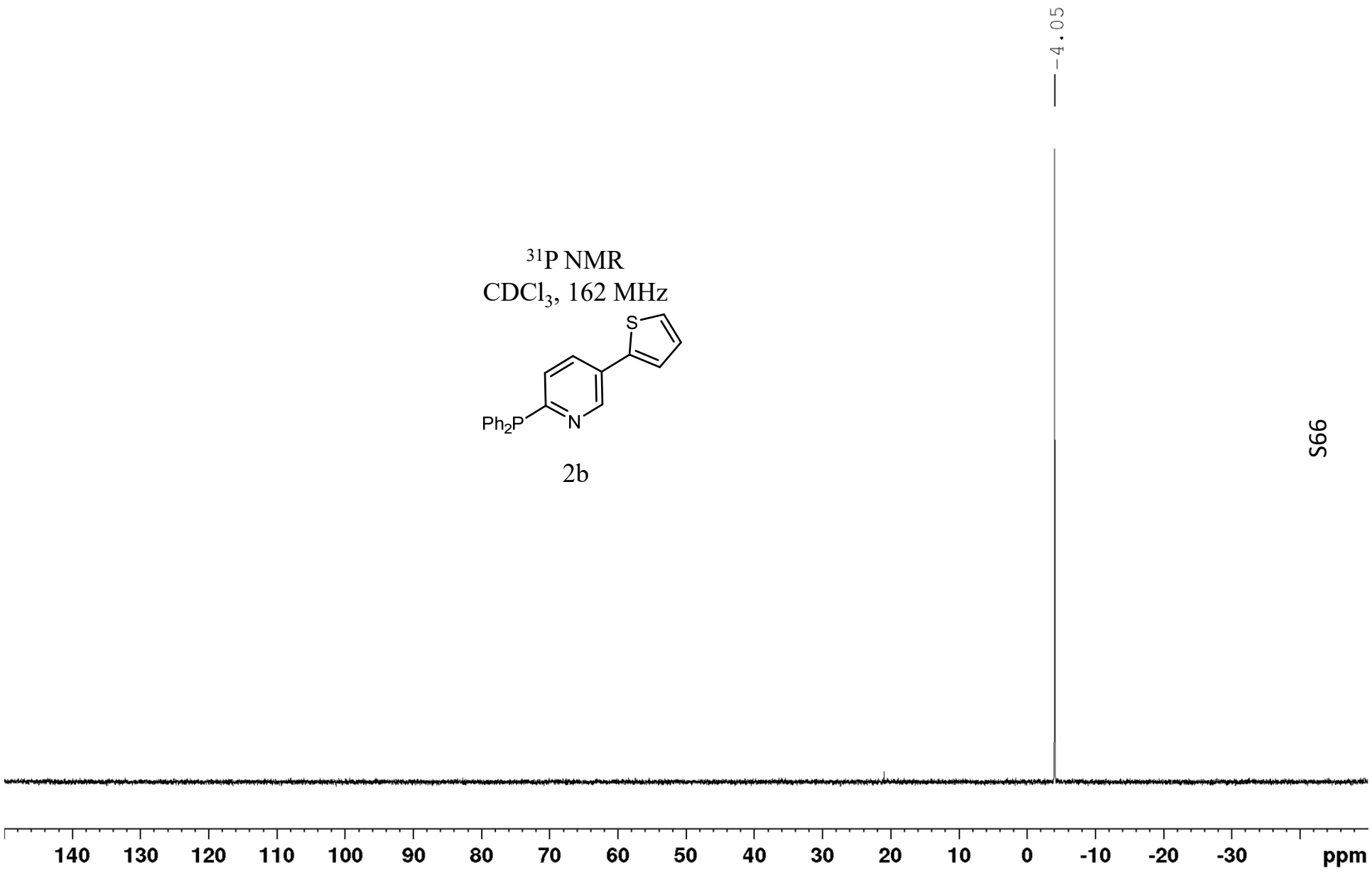

7.45
7.44
7.44
7.42
7.42
7.34
7.04
7.02
6.83
6.81
2.57
^{1}H NMR
$CDCl_3$, 400 MHz
Me
N
PPh_2
2a
$CDCl_3$
1.06
10.00
0.97
0.99
3.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

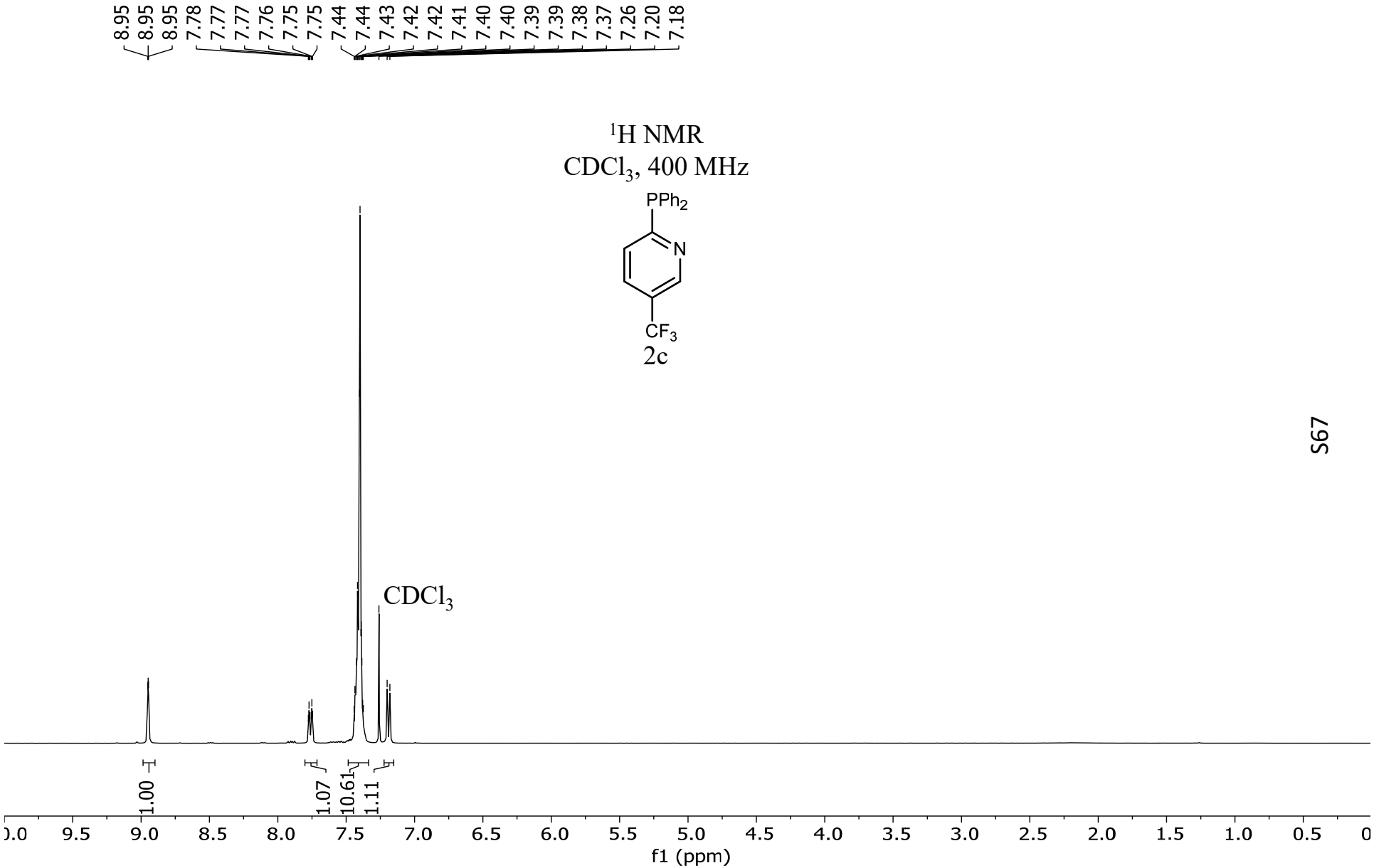

163.20
163.13
159.18
159.03
136.76
136.65
135.97
134.32
134.12
128.98
128.67
128.60
125.07
124.95
122.08
77.47
77.16
76.84
24.81
^{13}C NMR
$CDCl_3$, 100 MHz
Me
N
PPh_2
2a
$CDCl_3$
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

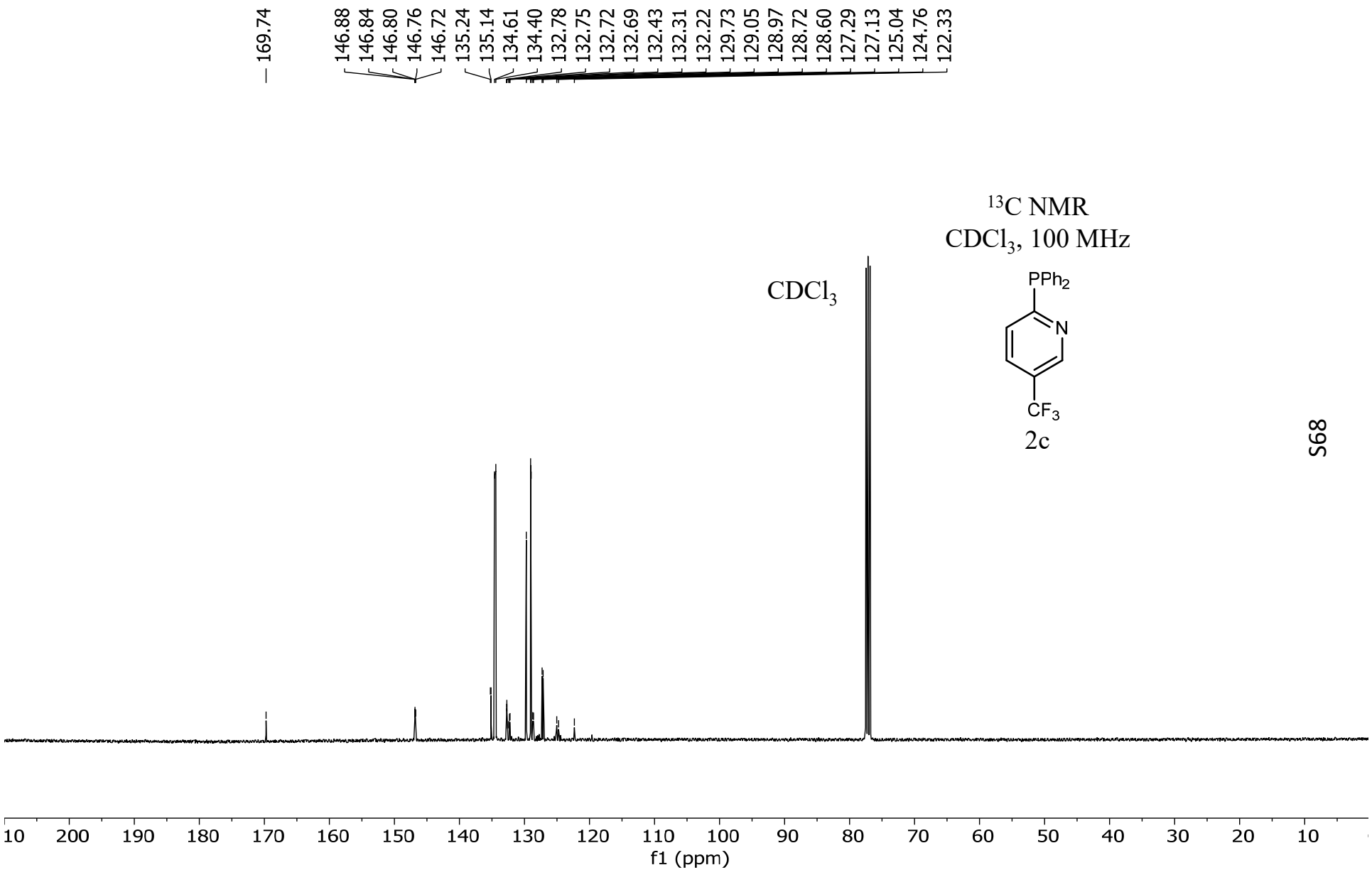

-4.96
31P NMR
CDCl3, 162 MHz
Me
N
PPh2
2a
S63
50
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
f1 (ppm)

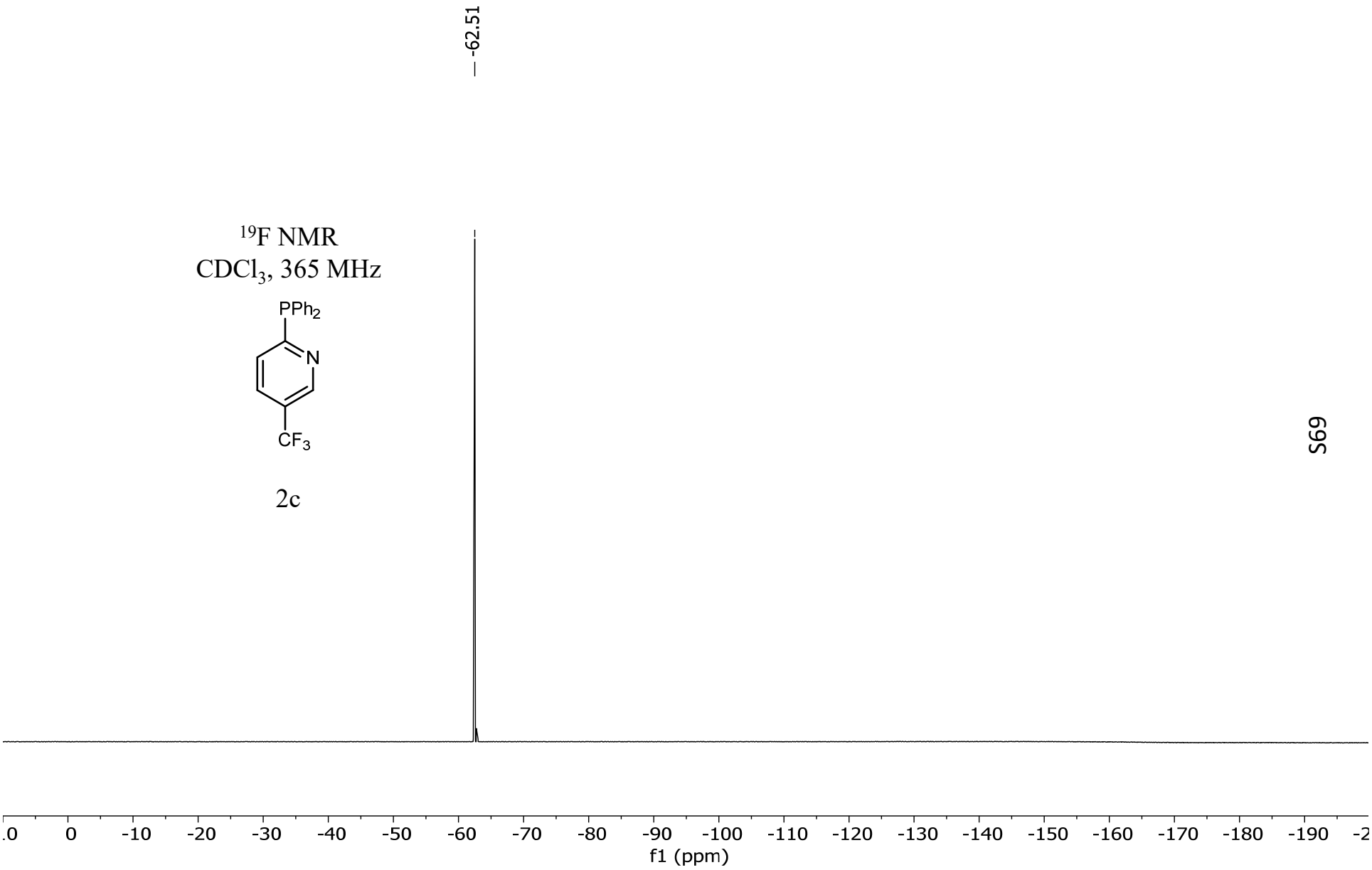

8.99
7.75
7.75
7.74
7.73
7.73
7.72
7.45
7.44
7.43
7.43
7.42
7.41
7.40
7.39
7.38
7.38
7.38
7.37
7.37
7.36
7.35
7.35
7.26
7.13
7.12
7.11
7.10
7.10
^{1}H NMR
$CDCl_3$, 400 MHz
$CDCl_3$
S
Ph_2P
N
2b
0.92
1.01
12.00
2.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


162.58
147.50
140.29
136.26
136.15
134.35
134.15
132.48
129.21
128.87
128.71
128.43
127.88
126.25
124.44
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
S
Ph_2P
N
2b
$CDCl_3$
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

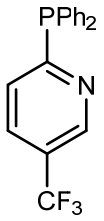

-4.05
^{31}P NMR
$CDCl_3$, 162 MHz
S
Ph_2P
N
2b
S66
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
ppm


8.95
8.95
8.95
7.78
7.77
7.77
7.76
7.75
7.75
7.44
7.44
7.43
7.42
7.42
7.41
7.40
7.40
7.39
7.39
7.38
7.37
7.26
7.20
7.18
1H NMR
CDCl3, 400 MHz
PPh2
N
CF3
2c
CDCl3
1.00
1.07
10.61
1.11
f1 (ppm)

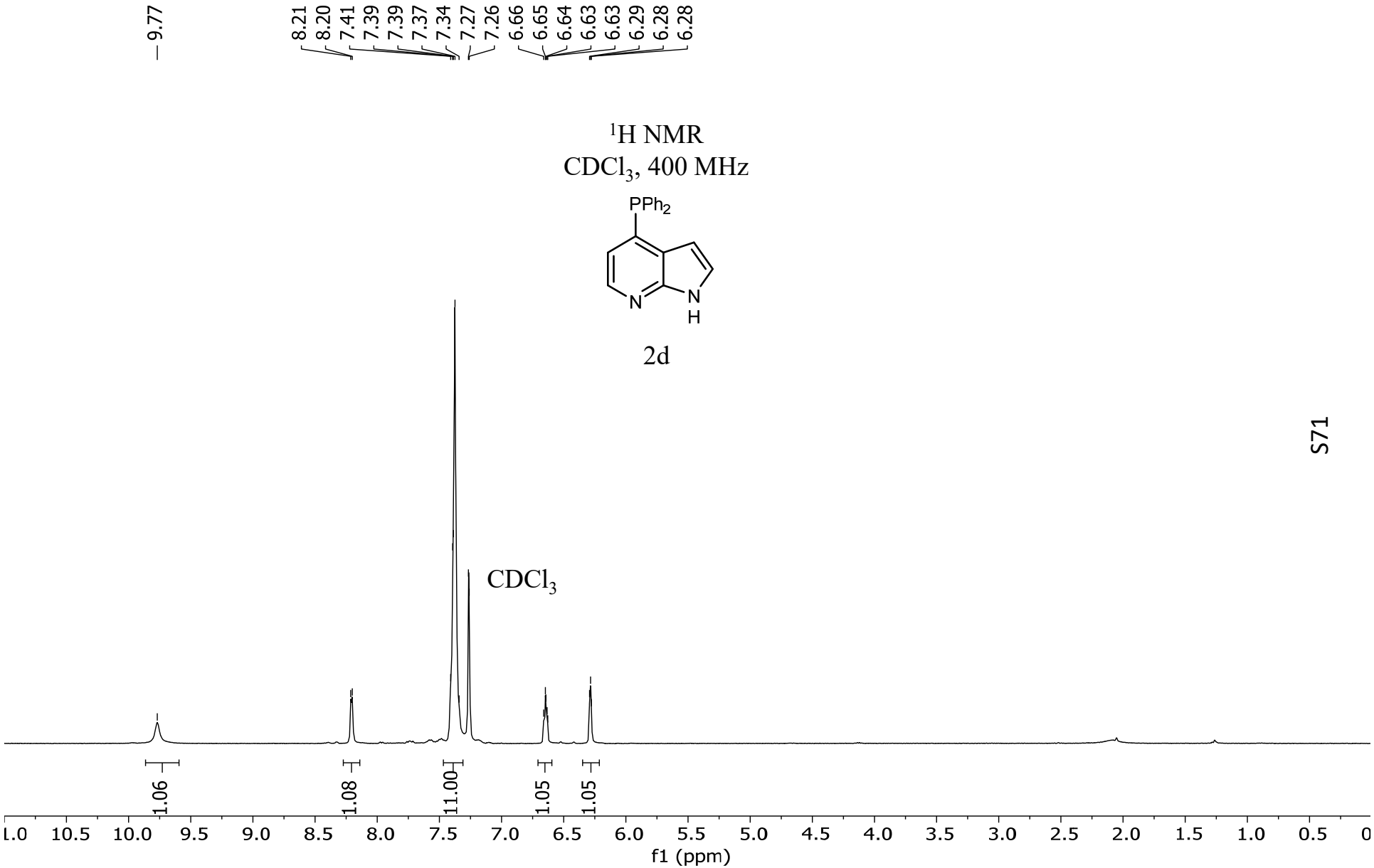

169.74
146.88
146.84
146.80
146.76
146.72
135.24
135.14
134.61
134.40
132.78
132.75
132.72
132.69
132.43
132.31
132.22
129.73
129.05
128.97
128.72
128.60
127.29
127.13
125.04
124.76
122.33
13C NMR
CDCl3, 100 MHz
CDCl3
PPh2
N
CF3
2c
S68
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

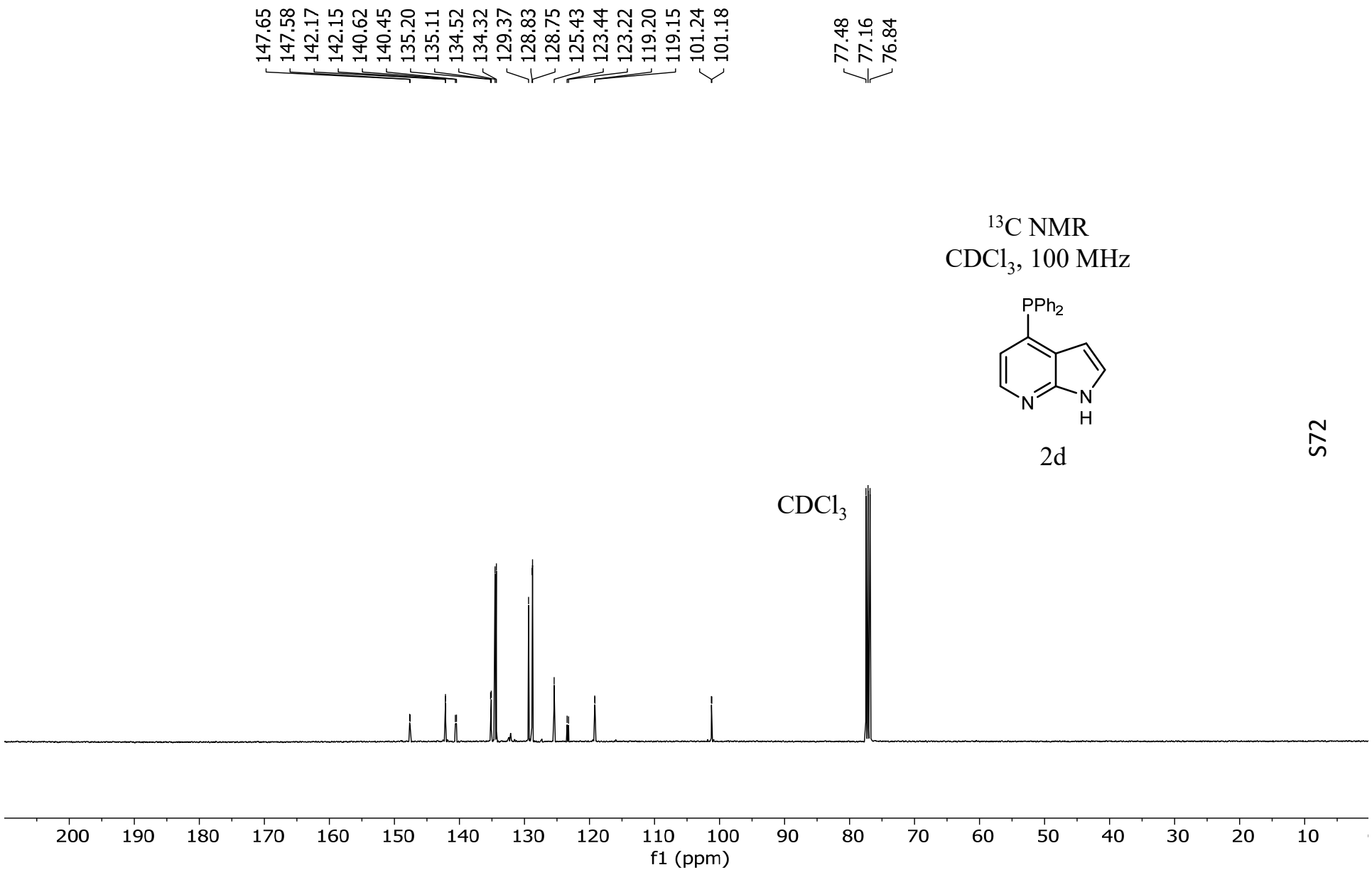

-62.51
19F NMR
CDCl3, 365 MHz
PPh2
N
CF3
2c
S69
.0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2
f1 (ppm)

^{31}P NMR
$CDCl_3$, 162 MHz

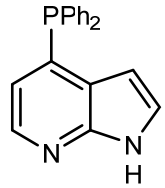


2c

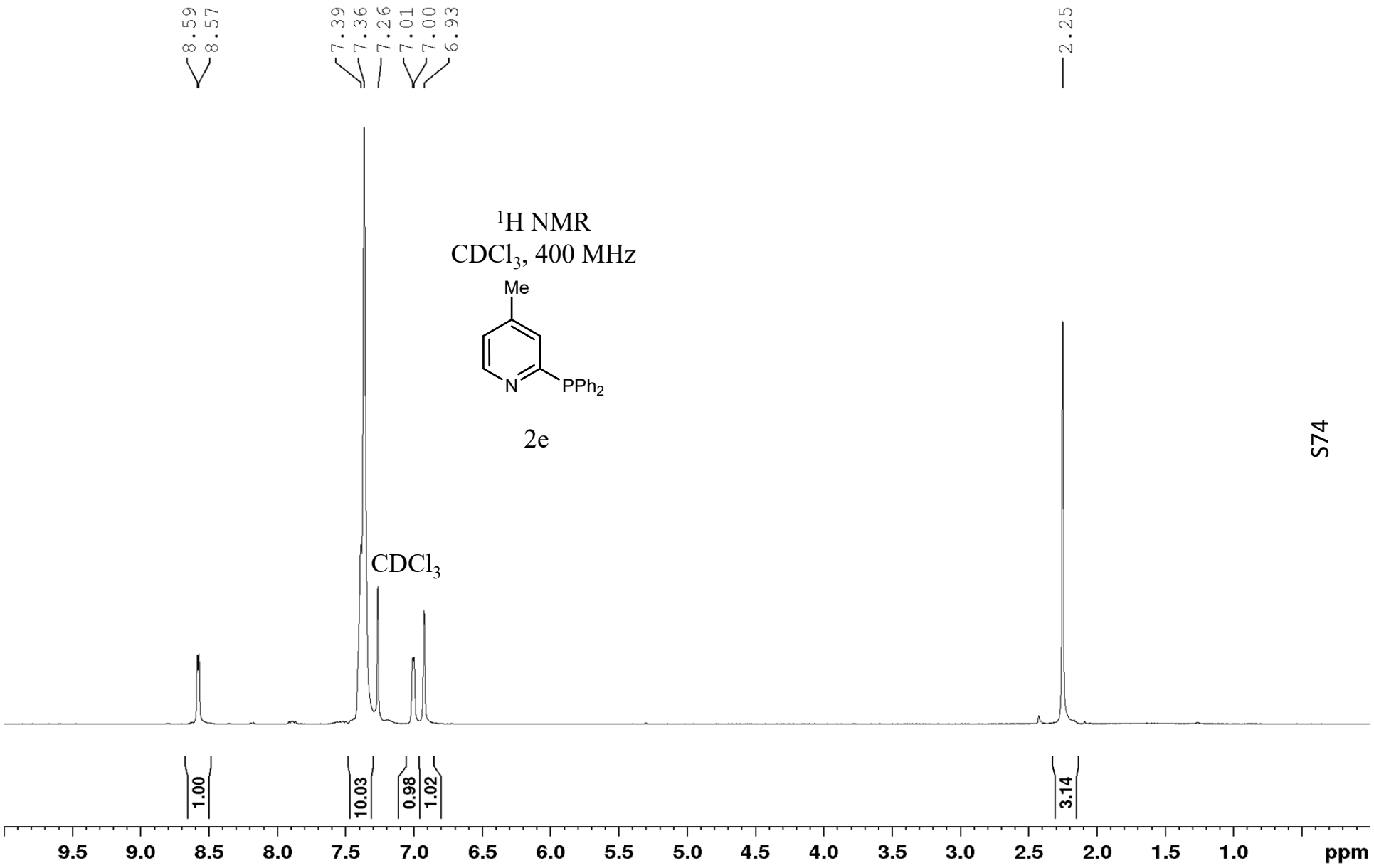

9.77
8.21
8.20
7.41
7.39
7.39
7.37
7.34
7.27
7.26
6.66
6.65
6.64
6.63
6.63
6.29
6.28
6.28
1H NMR
CDCl3, 400 MHz
PPh2
N
N
H
2d
CDCl3
1.06
1.08
11.00
1.05
1.05
f1 (ppm)

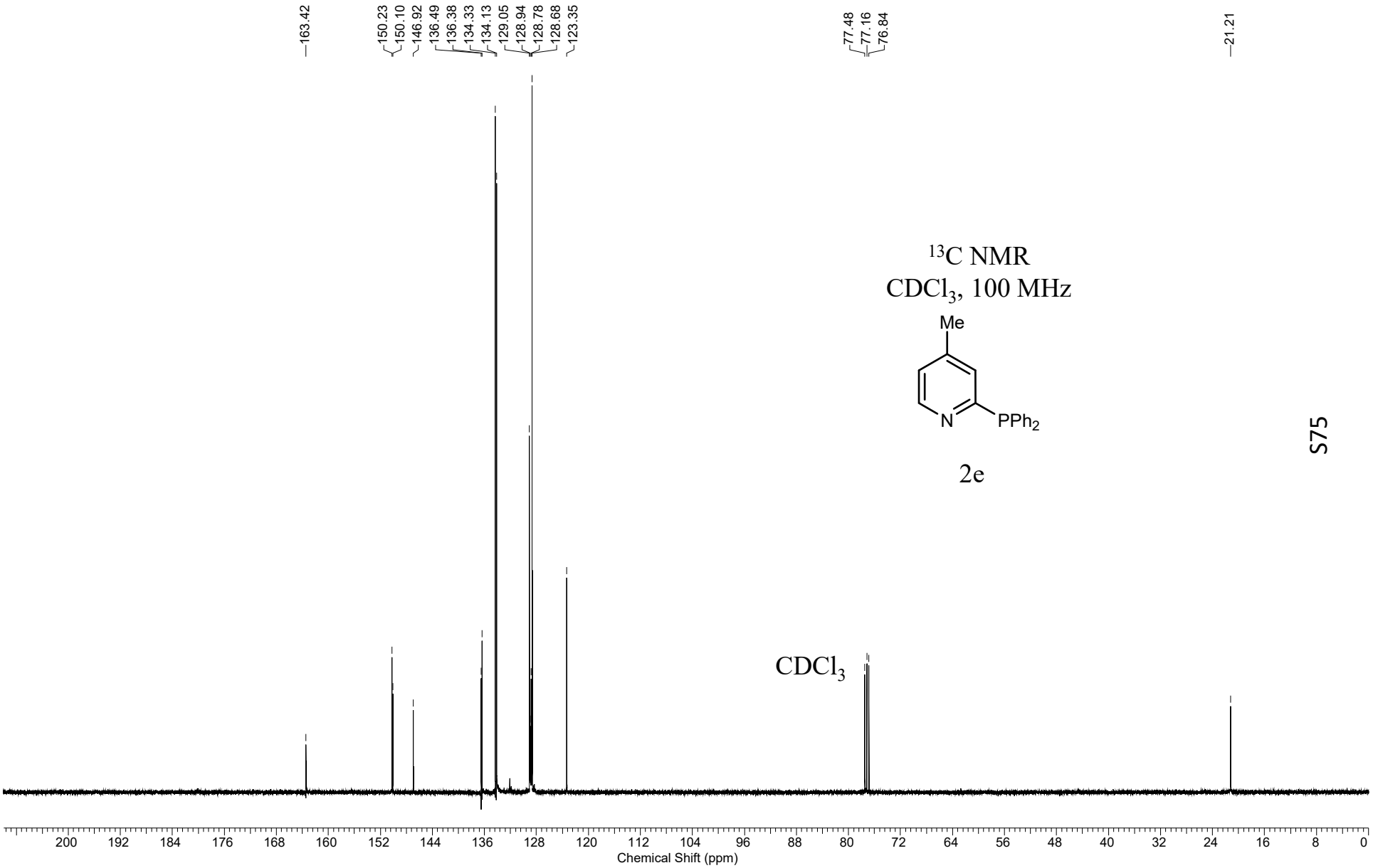

147.65
147.58
142.17
142.15
140.62
140.45
135.20
135.11
134.52
134.32
129.37
128.83
128.75
125.43
123.44
123.22
119.20
119.15
101.24
101.18
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
PPh$_2$
N
N
H
2d
$CDCl_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

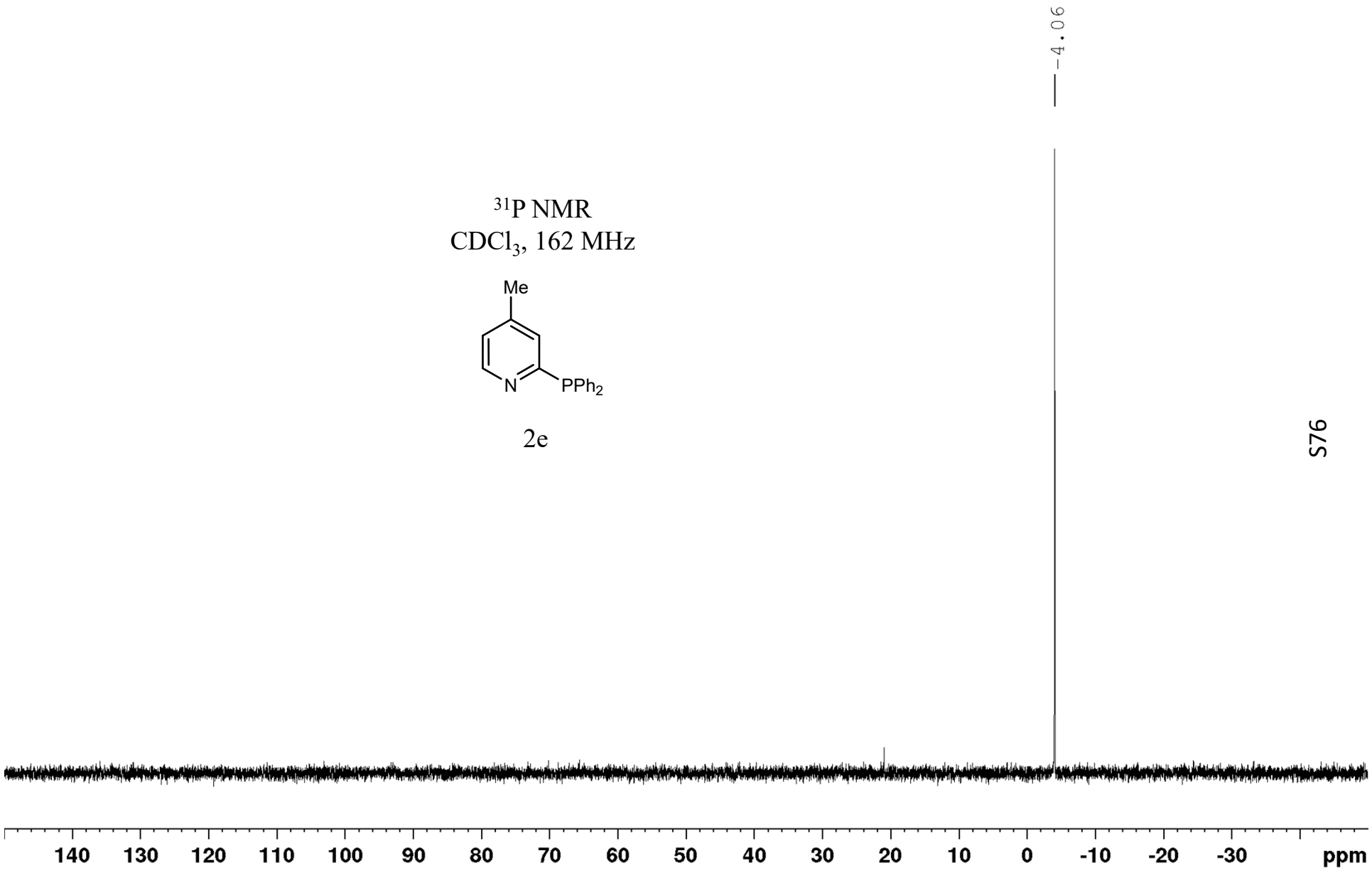
^{31}P NMR
$CDCl_3$, 162 MHz

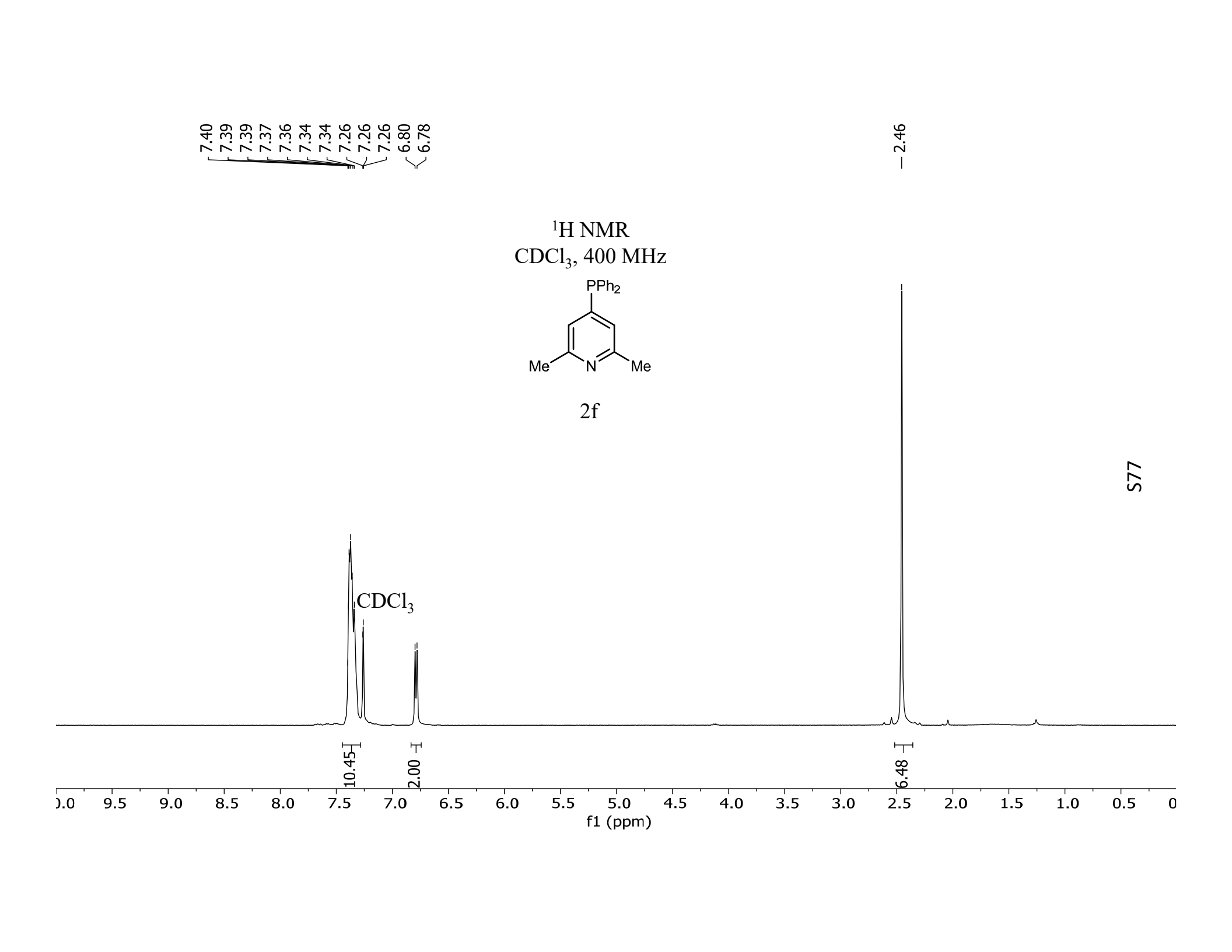


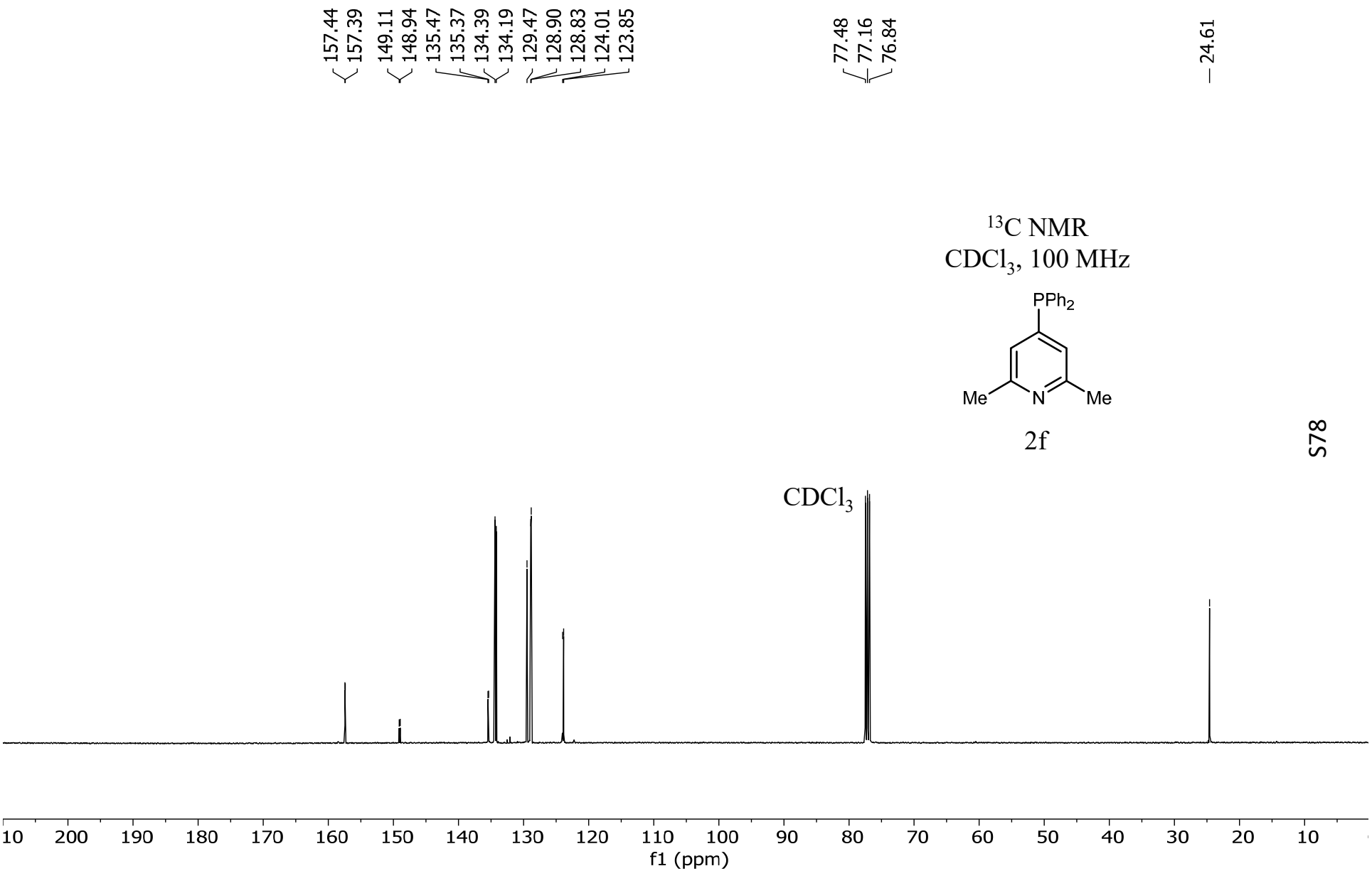
2d


8.59
8.57
7.39
7.36
7.26
7.01
7.00
6.93
2.25
^{1}H NMR
$CDCl_3$, 400 MHz
Me
N
PPh_2
2e
$CDCl_3$
1.00
10.03
0.98
1.02
3.14
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

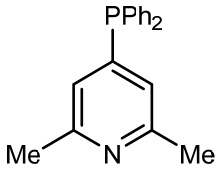

163.42
150.23
150.10
146.92
136.49
136.38
134.33
134.13
129.05
128.94
128.78
128.68
123.35
77.48
77.16
76.84
21.21
^{13}C NMR
$CDCl_3$, 100 MHz
Me
N
PPh_2
2e
$CDCl_3$
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)


-4.06
^{31}P NMR
$CDCl_3$, 162 MHz
Me
N
PPh_2
2e
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
ppm

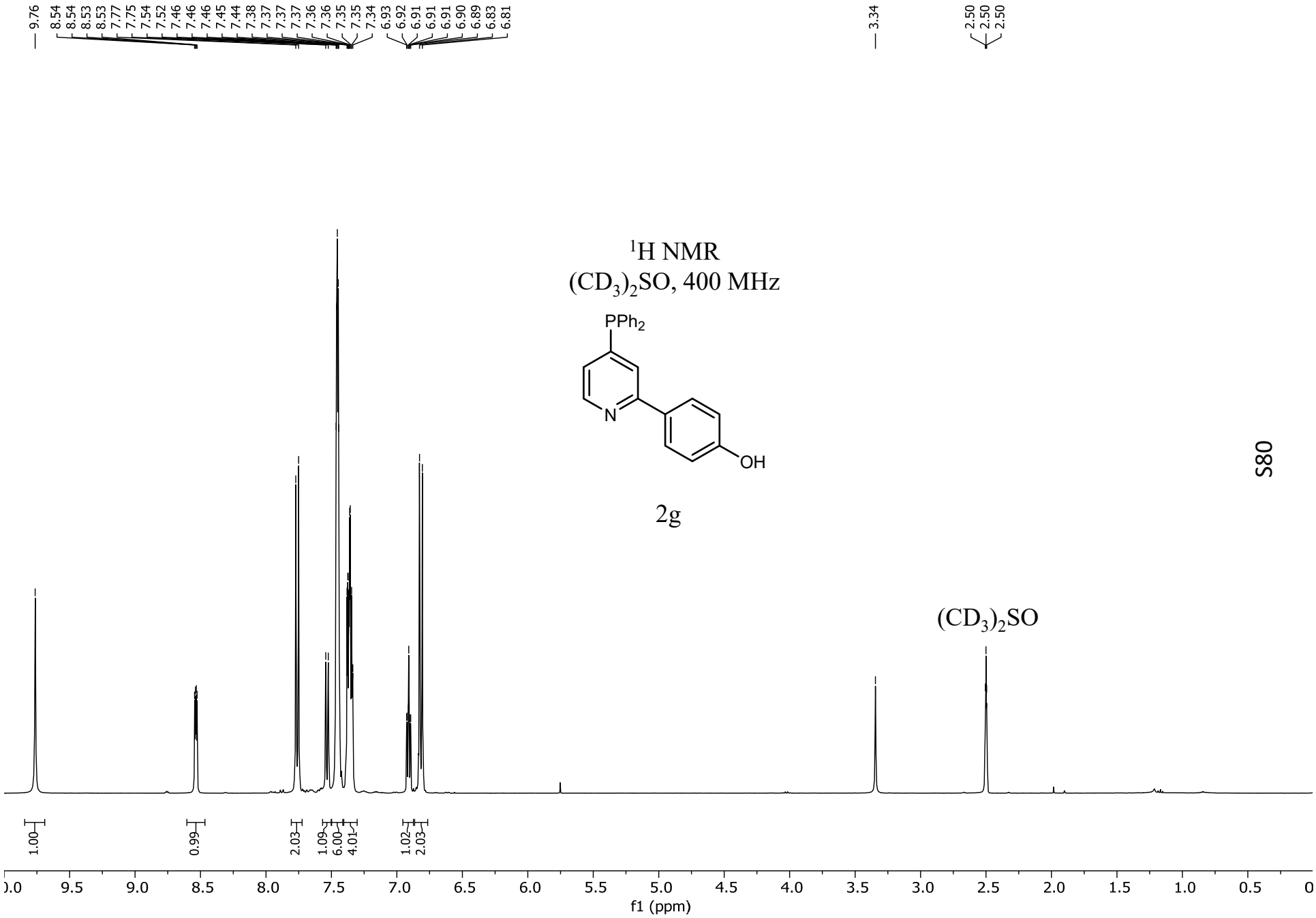

7.40
7.39
7.39
7.37
7.36
7.34
7.34
7.26
7.26
7.26
6.80
6.78
2.46
^{1}H NMR
$CDCl_3$, 400 MHz
PPh2
Me
N
Me
2f
S77
$CDCl_3$
10.45
2.00
6.48
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

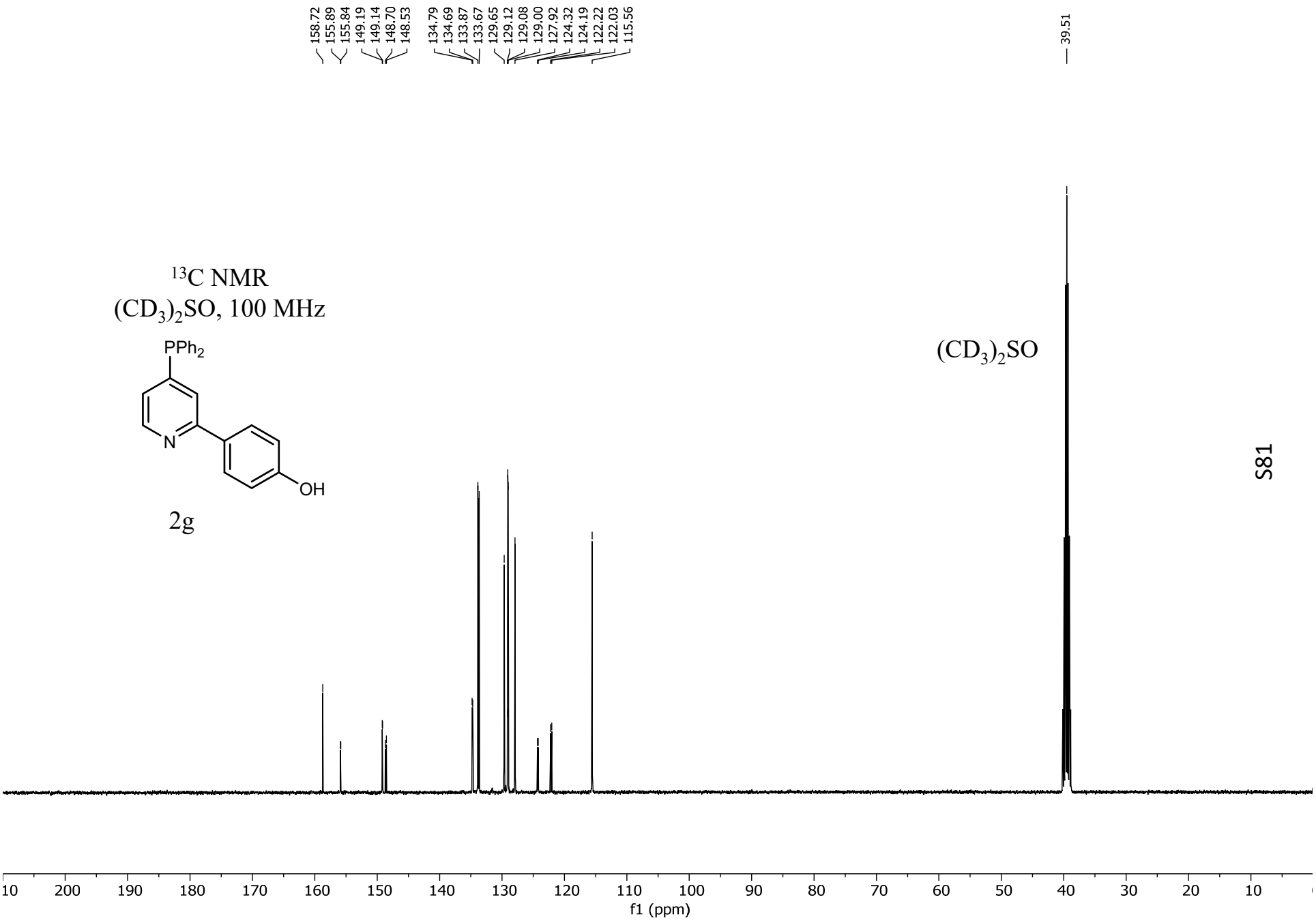

157.44
157.39
149.11
148.94
135.47
135.37
134.39
134.19
129.47
128.90
128.83
124.01
123.85
77.48
77.16
76.84
24.61
^{13}C NMR
$CDCl_3$, 100 MHz
PPh2
Me
N
Me
2f
$CDCl_3$
f1 (ppm)

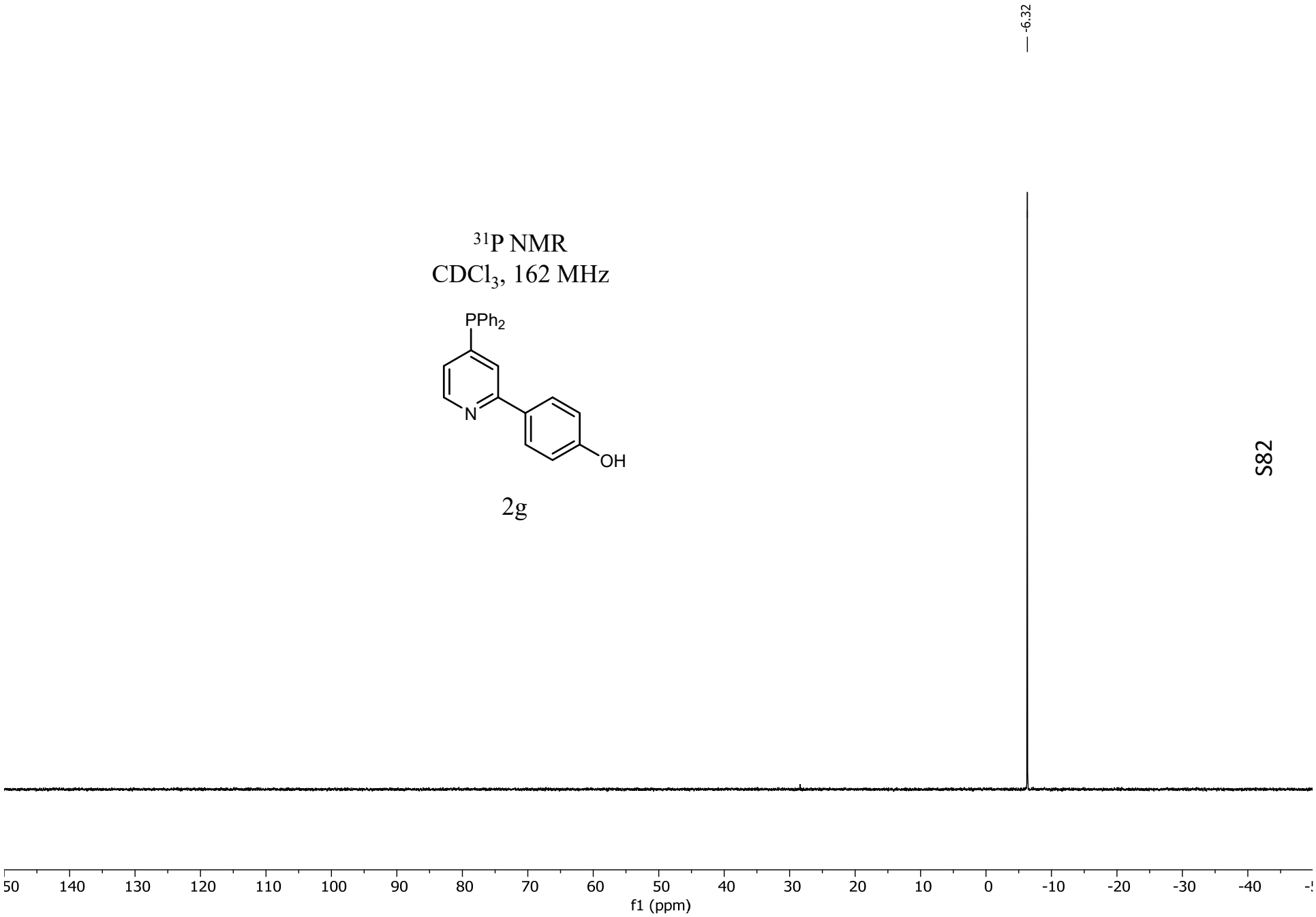
^{31}P NMR
$CDCl_3$, 162 MHz

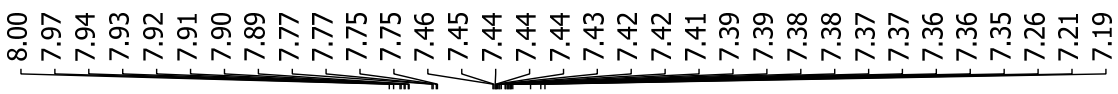


2f

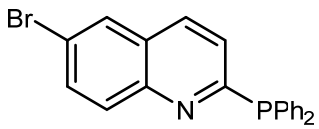

9.76
8.54
8.54
8.53
8.53
7.77
7.75
7.54
7.52
7.46
7.46
7.45
7.44
7.38
7.37
7.37
7.37
7.36
7.36
7.35
7.35
7.34
6.93
6.92
6.91
6.91
6.91
6.90
6.89
6.83
6.81
3.34
2.50
2.50
2.50
1H NMR
(CD3)2SO, 400 MHz
PPh2
N
OH
2g
S80
(CD3)2SO
1.00
0.99
2.03
1.09
6.00
4.01
1.02
2.03
f1 (ppm)


158.72
155.89
155.84
149.19
149.14
148.70
148.53
134.79
134.69
133.87
133.67
129.65
129.12
129.08
129.00
127.92
124.32
124.19
122.22
122.03
115.56
39.51
^{13}C NMR
$(CD_3)_2SO$, 100 MHz
PPh$_2$
N
OH
2g
$(CD_3)_2SO$
f1 (ppm)

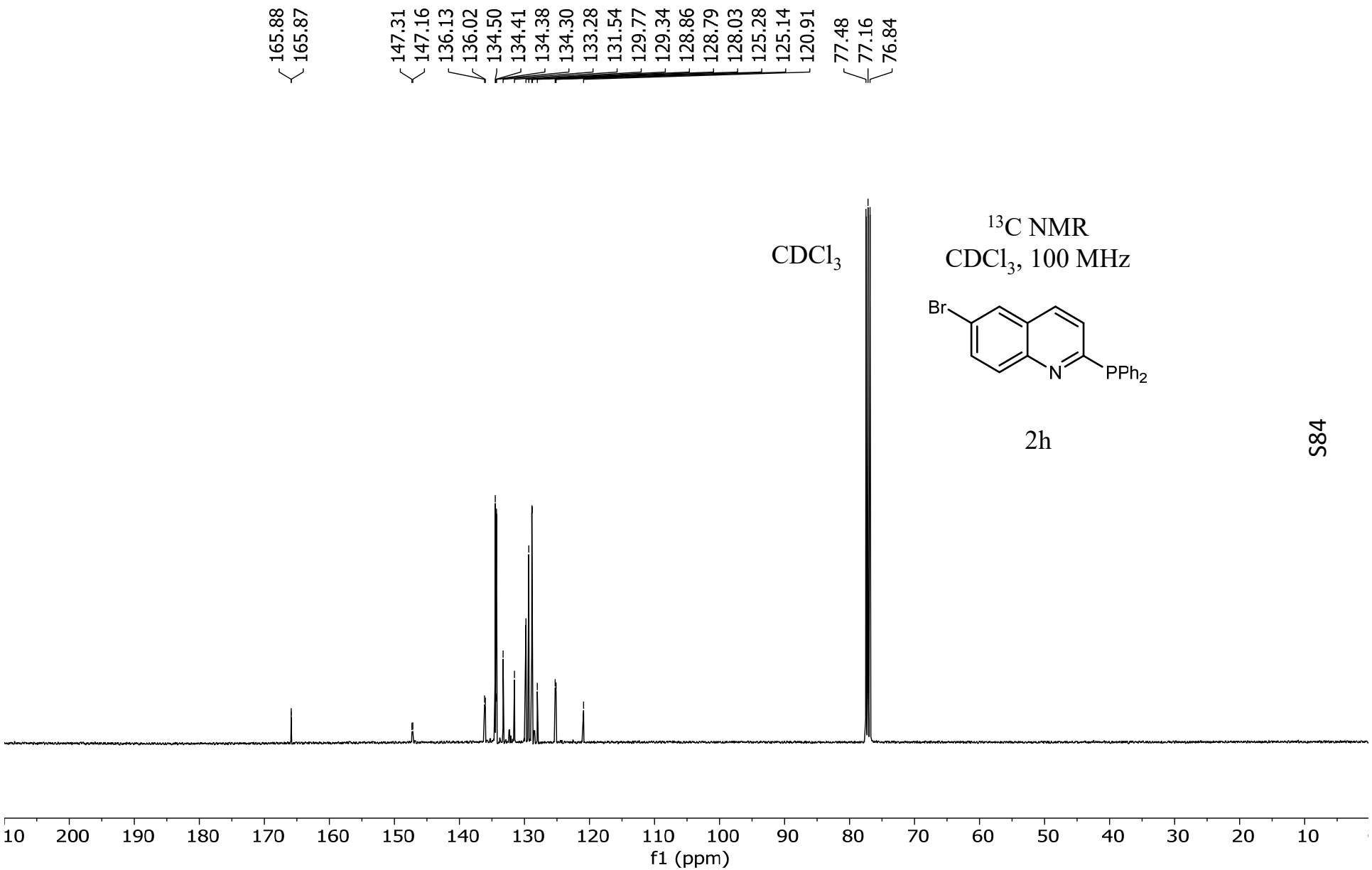

-6.32
31P NMR
CDCl3, 162 MHz
PPh2
N
OH
2g
S82
50
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
f1 (ppm)



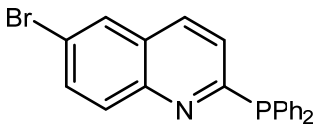
^{1}H NMR
$CDCl_3$, 400 MHz



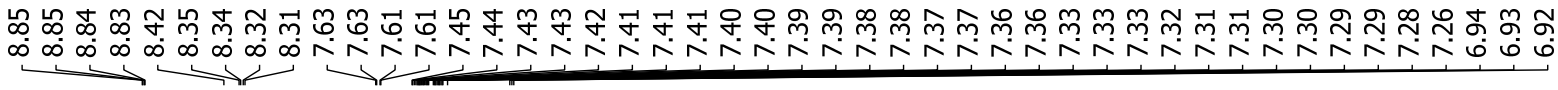
2h


165.88
165.87
147.31
147.16
136.13
136.02
134.50
134.41
134.38
134.30
133.28
131.54
129.77
129.34
128.86
128.79
128.03
125.28
125.14
120.91
77.48
77.16
76.84
CDCl3
13C NMR
CDCl3, 100 MHz
Br
N
PPh2
2h
S84
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{31}P NMR
$CDCl_3$, 162 MHz

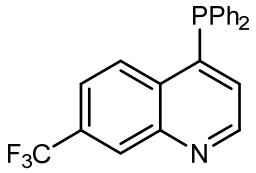


2h

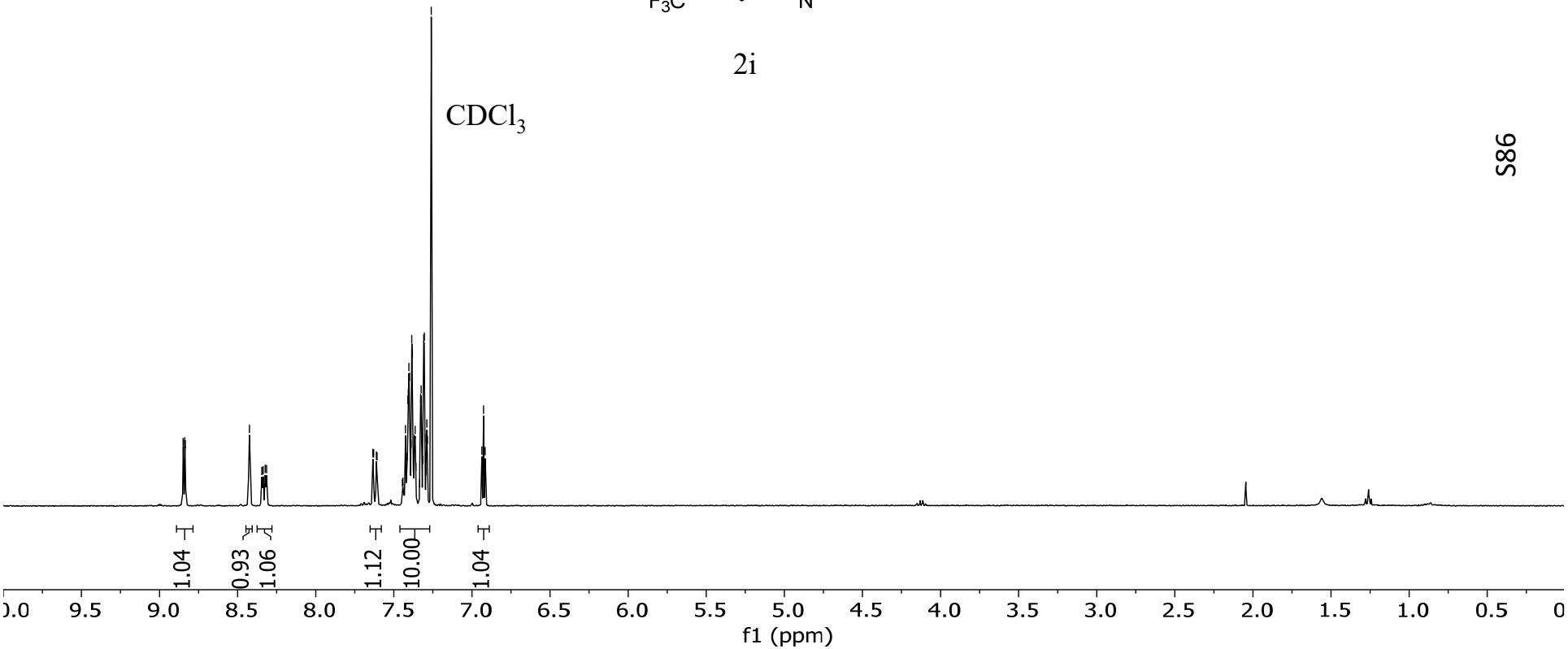


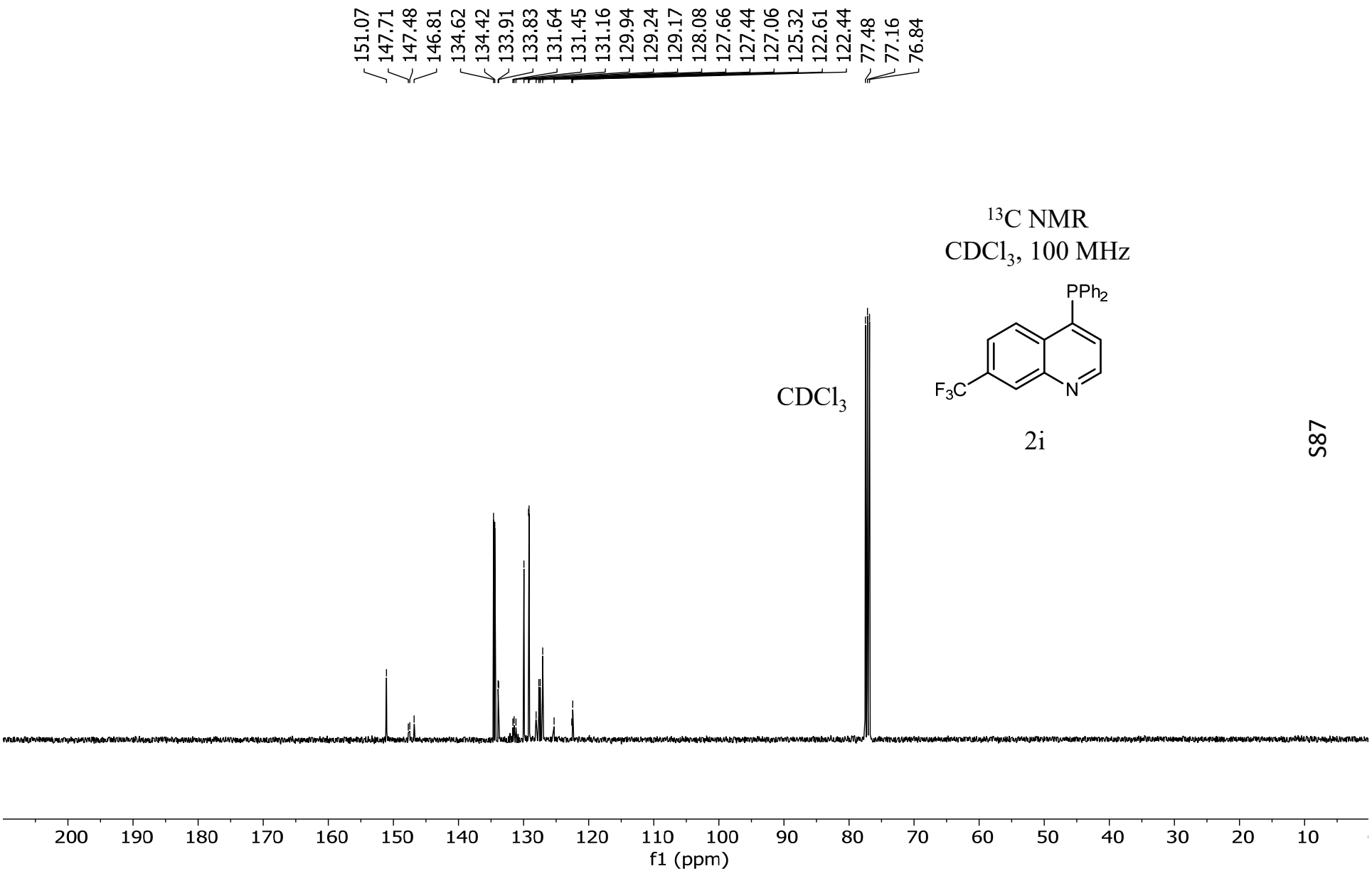
^{1}H NMR

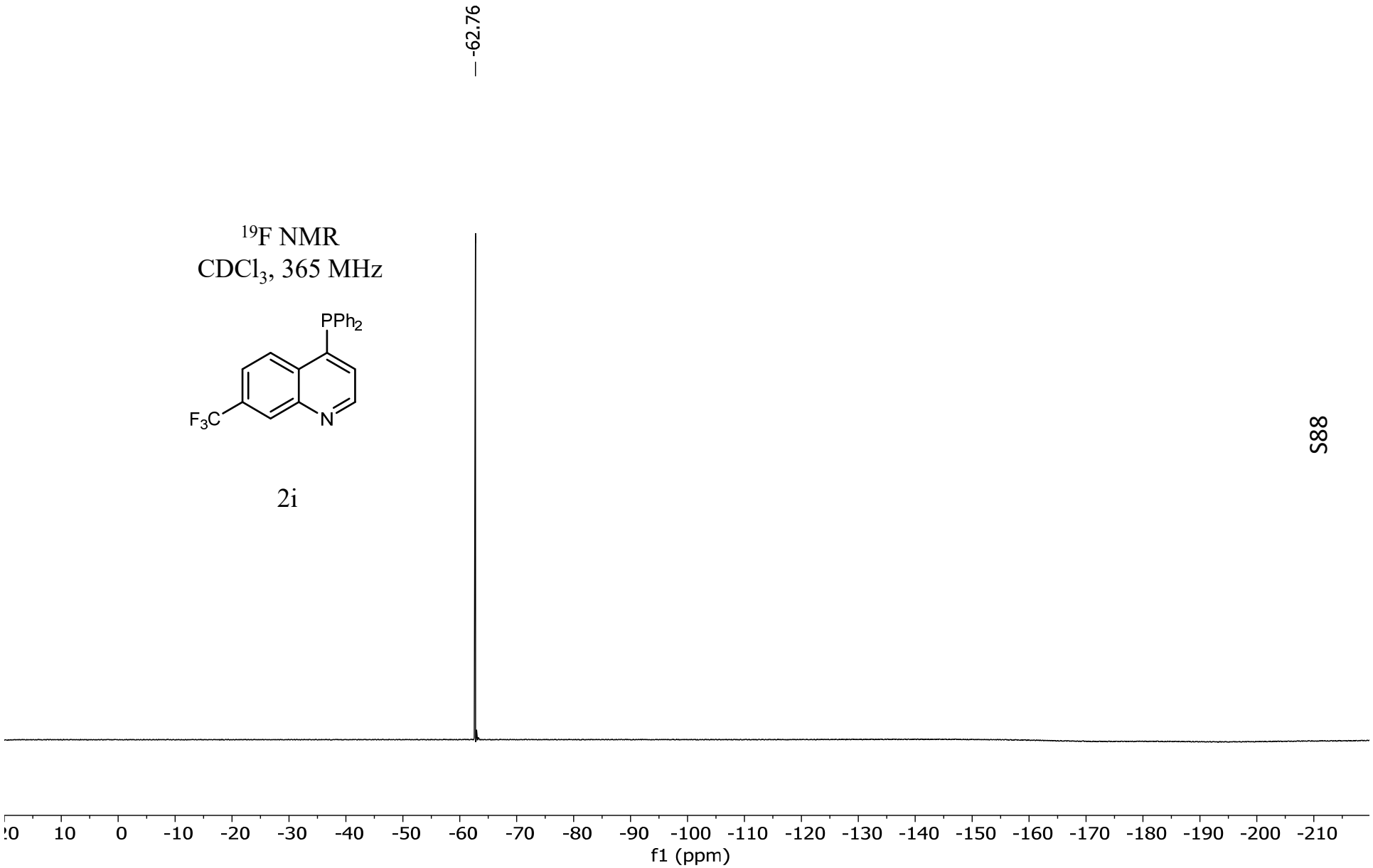
$CDCl_3$, 400 MHz



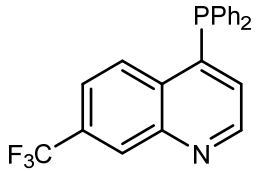
2i



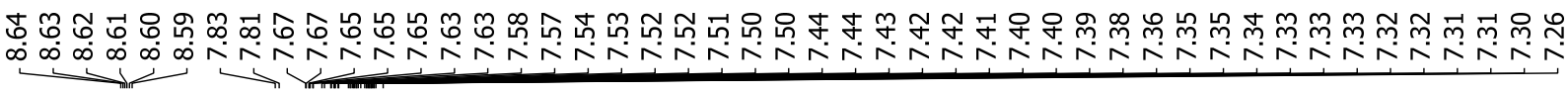

151.07
147.71
147.48
146.81
134.62
134.42
133.91
133.83
131.64
131.45
131.16
129.94
129.24
129.17
128.08
127.66
127.44
127.06
125.32
122.61
122.44
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
PPh$_2$
F$_3$C
N
2i
S87
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


-62.76
^{19}F NMR
$CDCl_3$, 365 MHz
PPh_2
F_3C
N
2i
S88
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)

^{31}P NMR
$CDCl_3$, 162 MHz

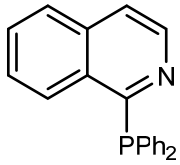


2i

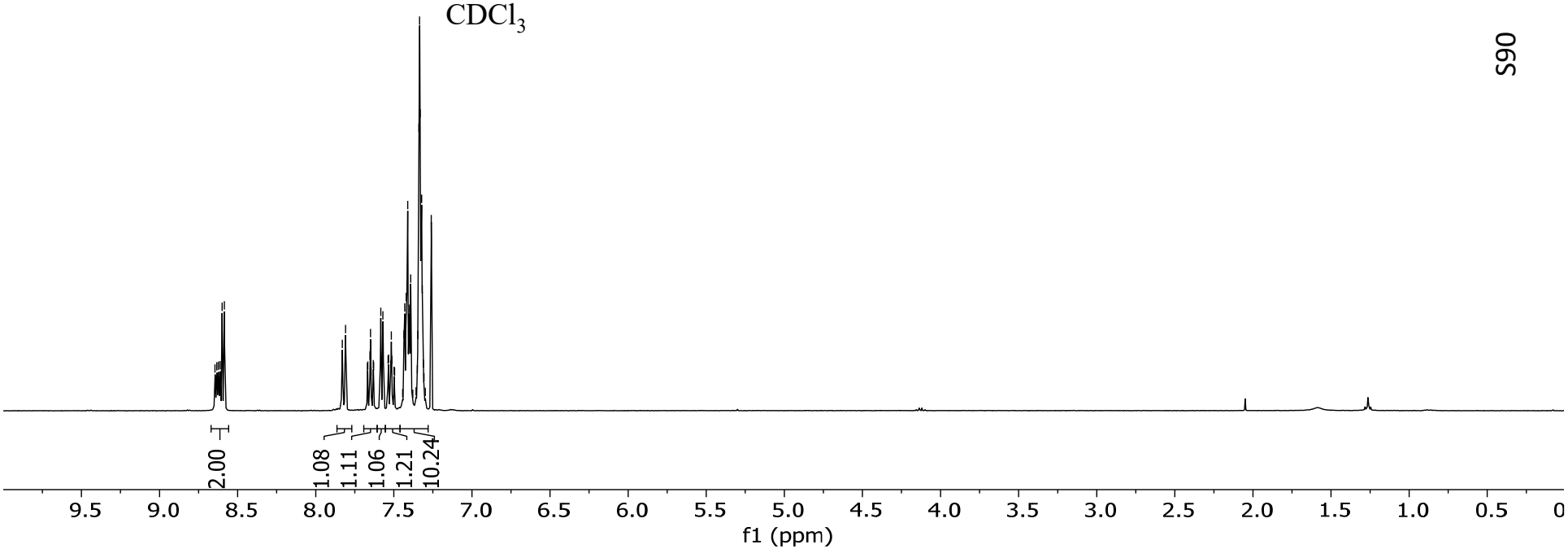


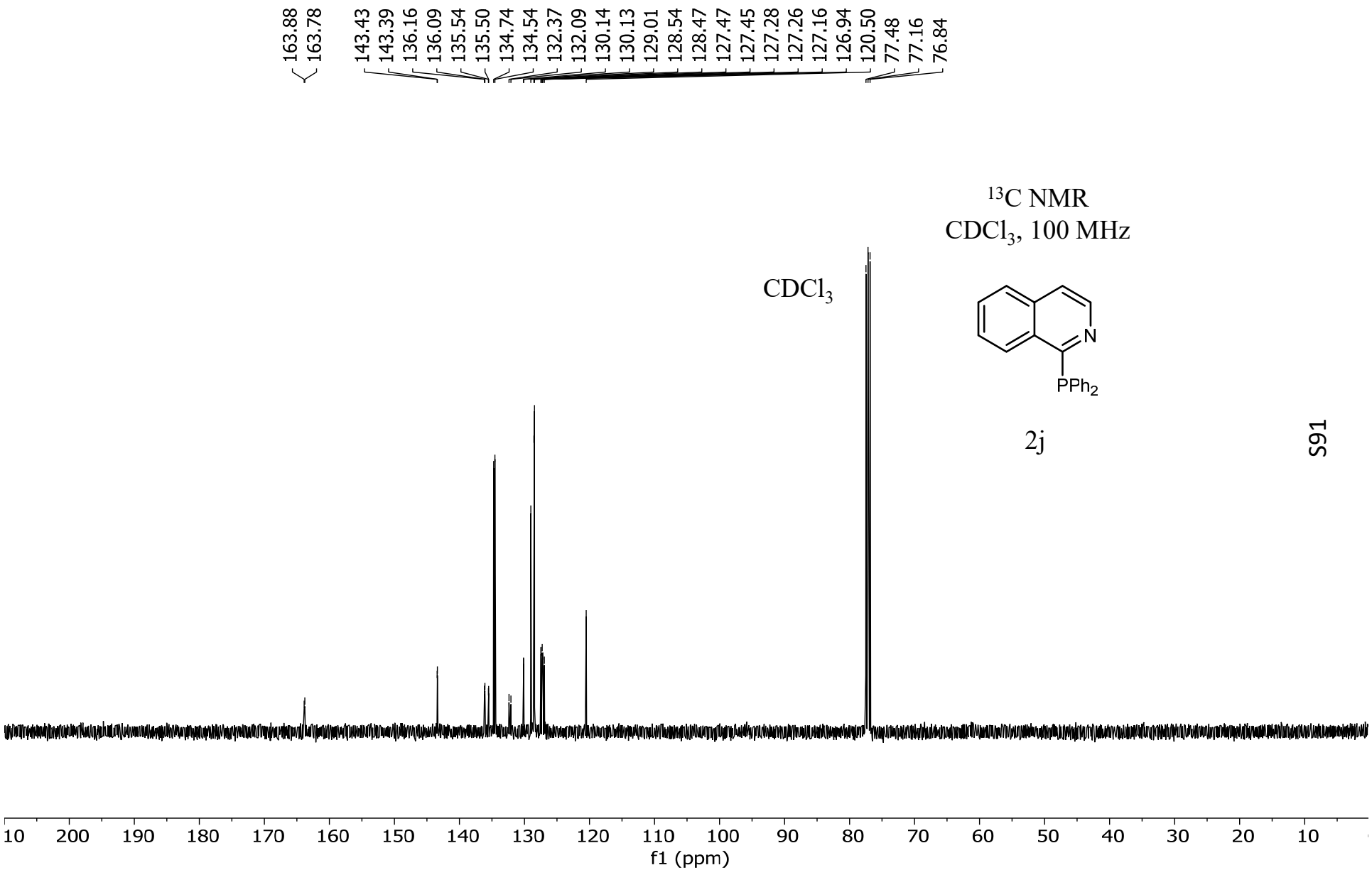
^{1}H NMR

$CDCl_3$, 400 MHz

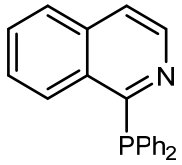


2j

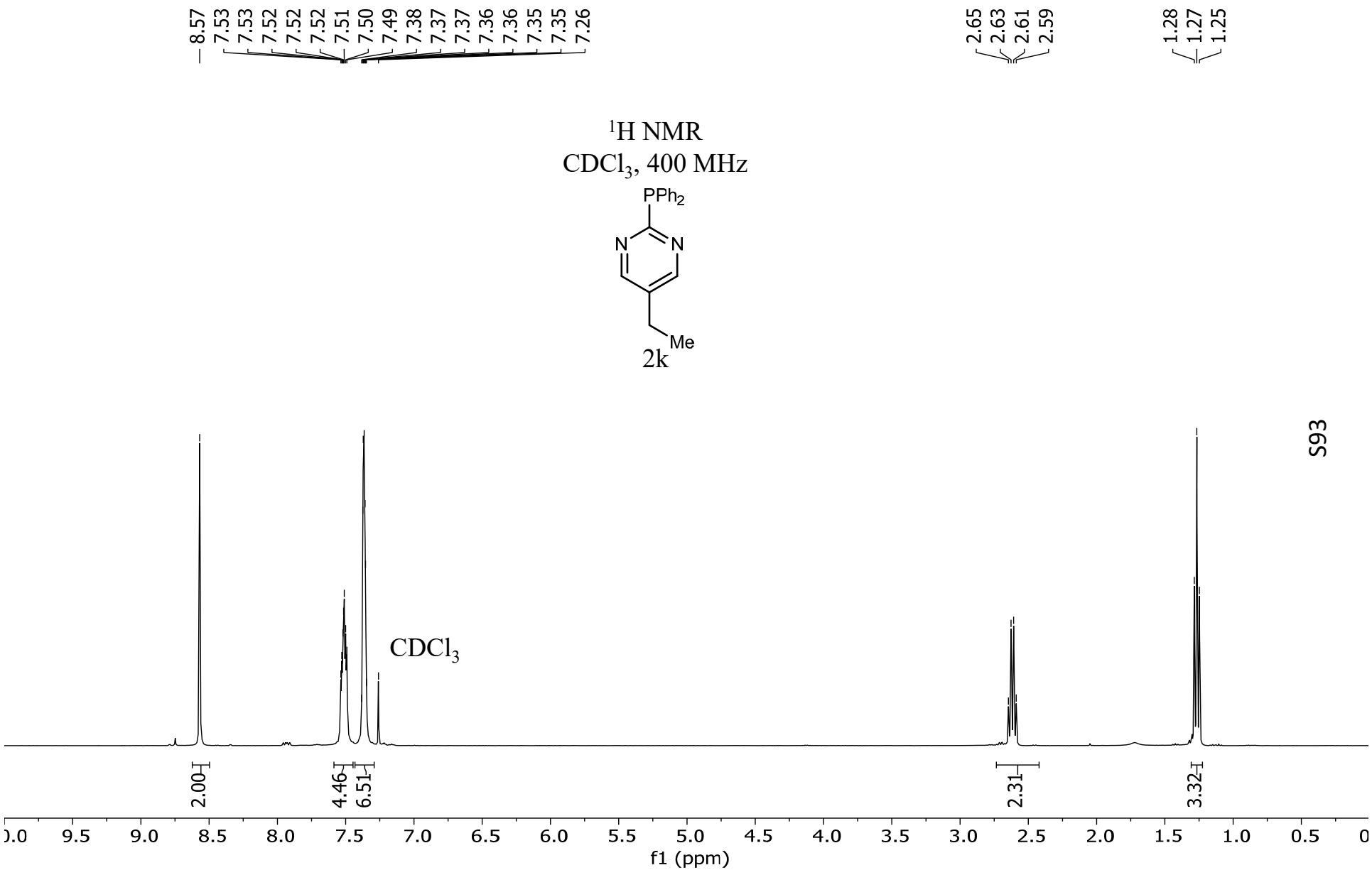


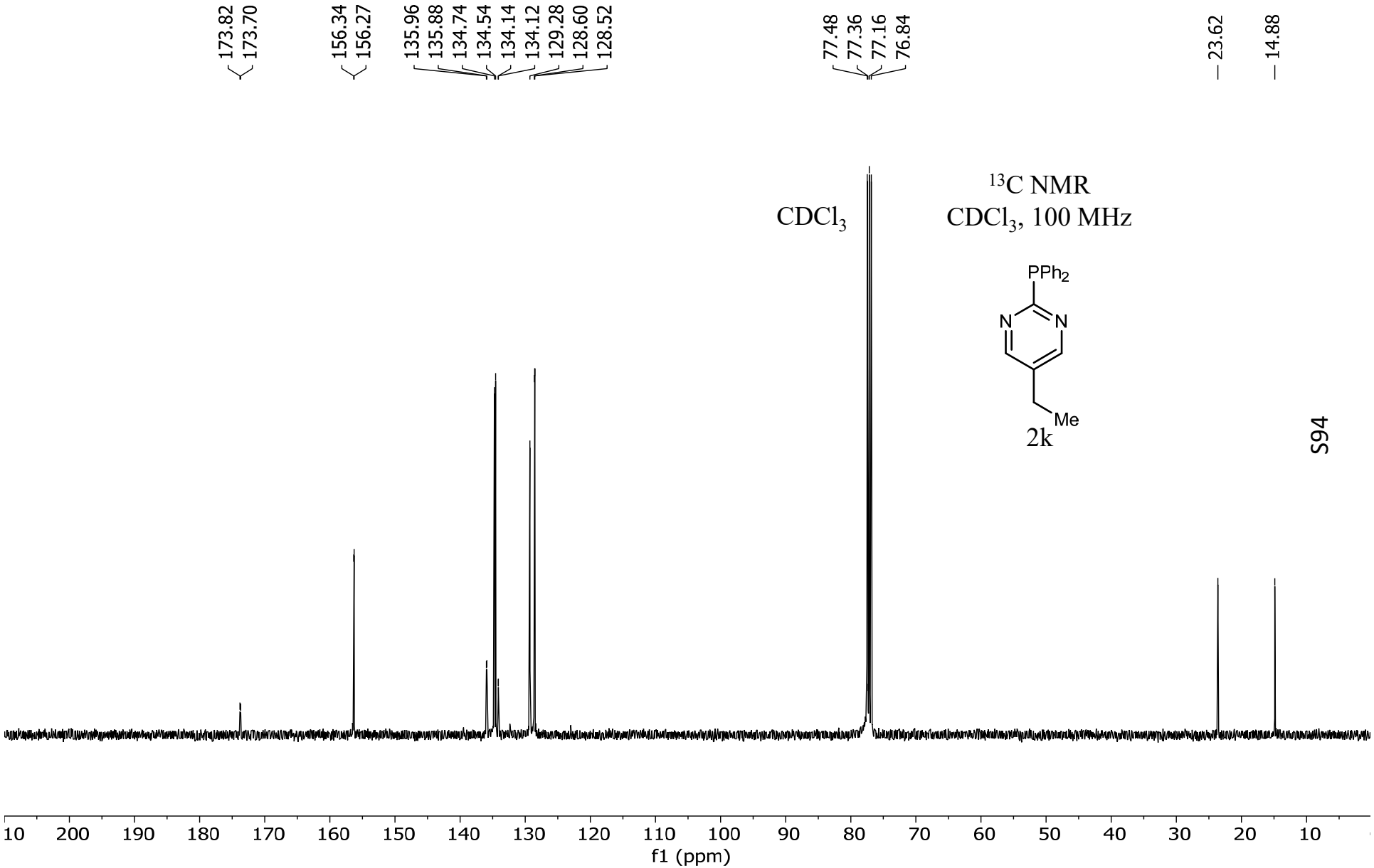

163.88
163.78
143.43
143.39
136.16
136.09
135.54
135.50
134.74
134.54
132.37
132.09
130.14
130.13
129.01
128.54
128.47
127.47
127.45
127.28
127.26
127.16
126.94
120.50
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
CDCl3
N
PPh2
2j
S91
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{31}P NMR
$CDCl_3$, 162 MHz



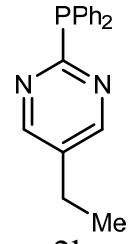
2j


8.57
7.53
7.53
7.52
7.52
7.52
7.51
7.50
7.49
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.26
2.65
2.63
2.61
2.59
1.28
1.27
1.25
1H NMR
CDCl3, 400 MHz
PPh2
N
N
Me
2k
S93
CDCl3
2.00
4.46
6.51
2.31
3.32
f1 (ppm)

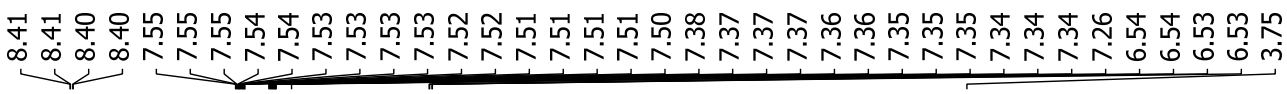

173.82
173.70
156.34
156.27
135.96
135.88
134.74
134.54
134.14
134.12
129.28
128.60
128.52
77.48
77.36
77.16
76.84
23.62
14.88
CDCl3
13C NMR
CDCl3, 100 MHz
PPh2
N
N
Me
2k
S94
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{31}P NMR

$CDCl_3$, 162 MHz

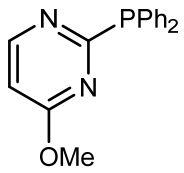


2k

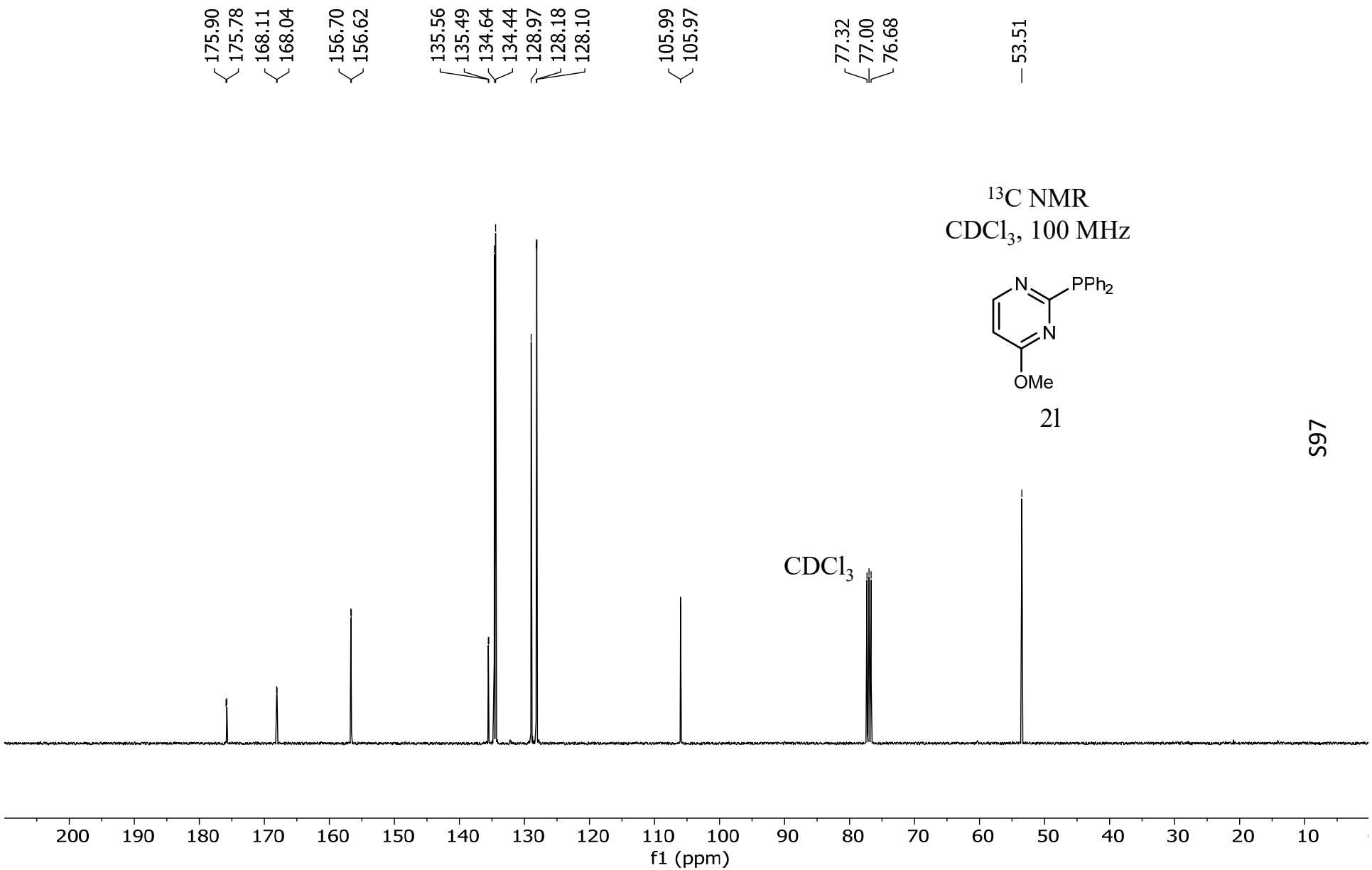


^{1}H NMR

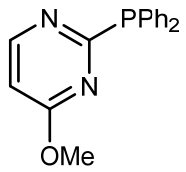
$CDCl_3$, 400 MHz



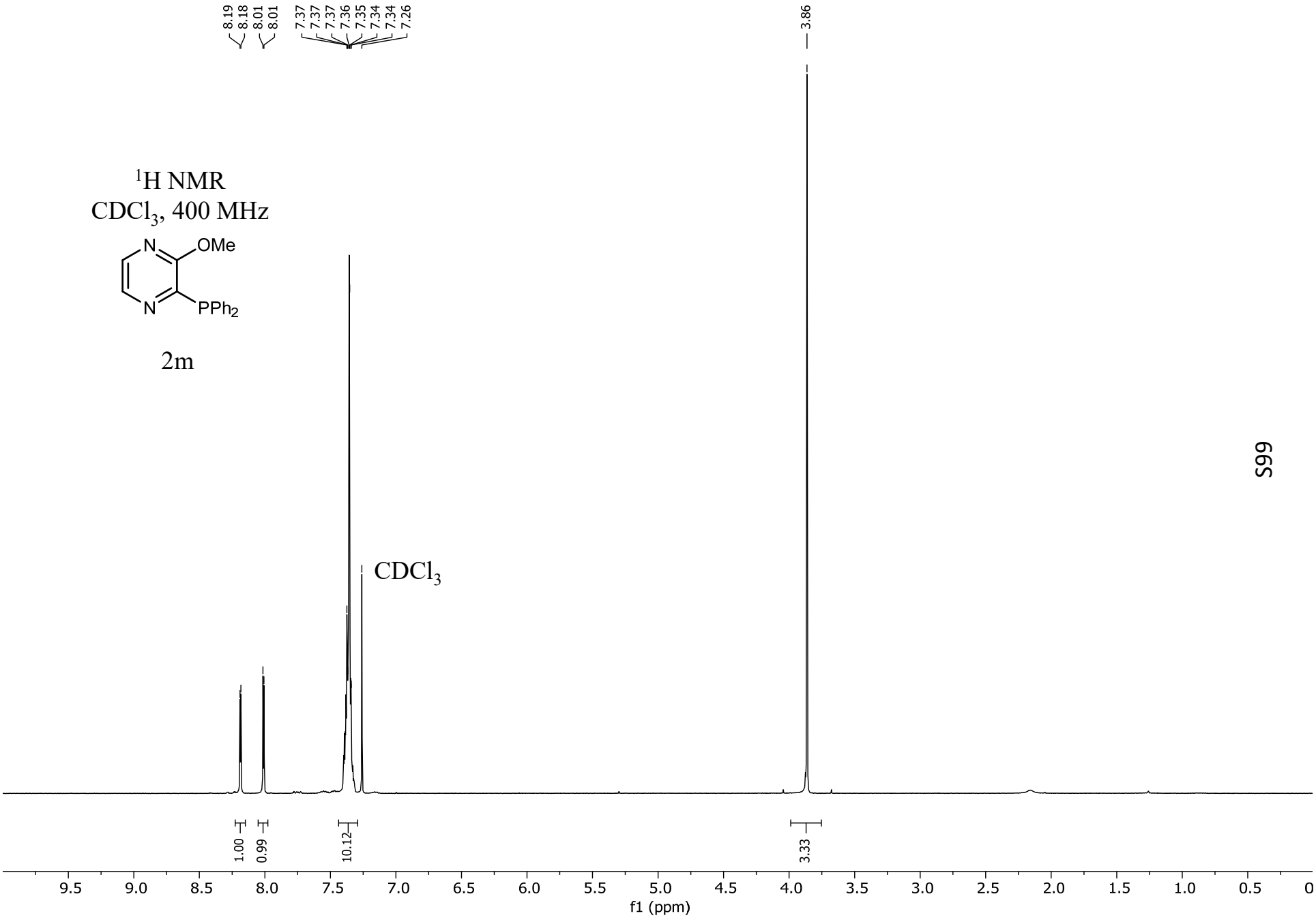
2l

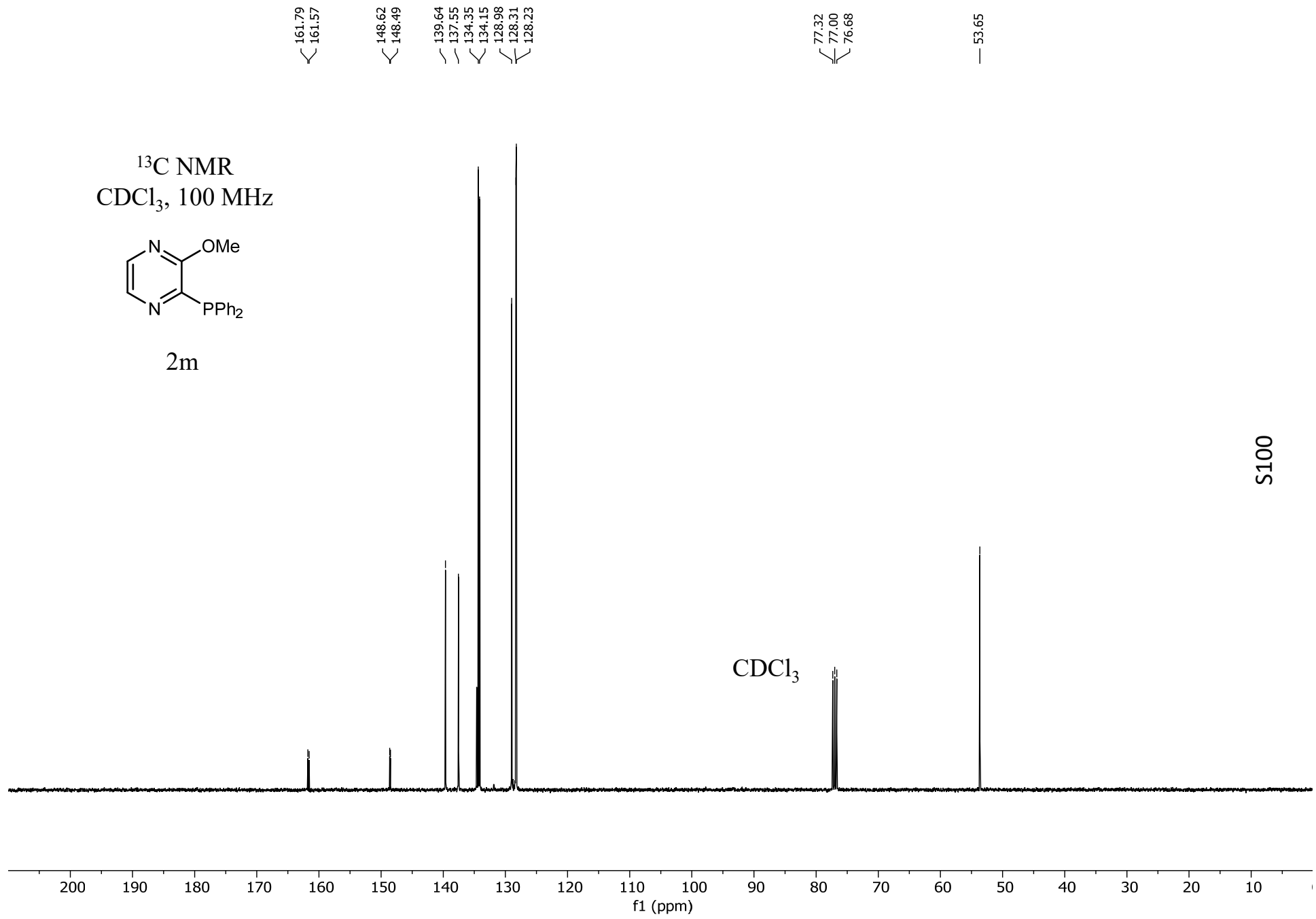

175.90
175.78
168.11
168.04
156.70
156.62
135.56
135.49
134.64
134.44
128.97
128.18
128.10
105.99
105.97
77.32
77.00
76.68
53.51
13C NMR
CDCl3, 100 MHz
N
PPh2
N
OMe
21
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{31}P NMR
$CDCl_3$, 162 MHz

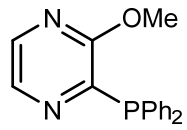


2l

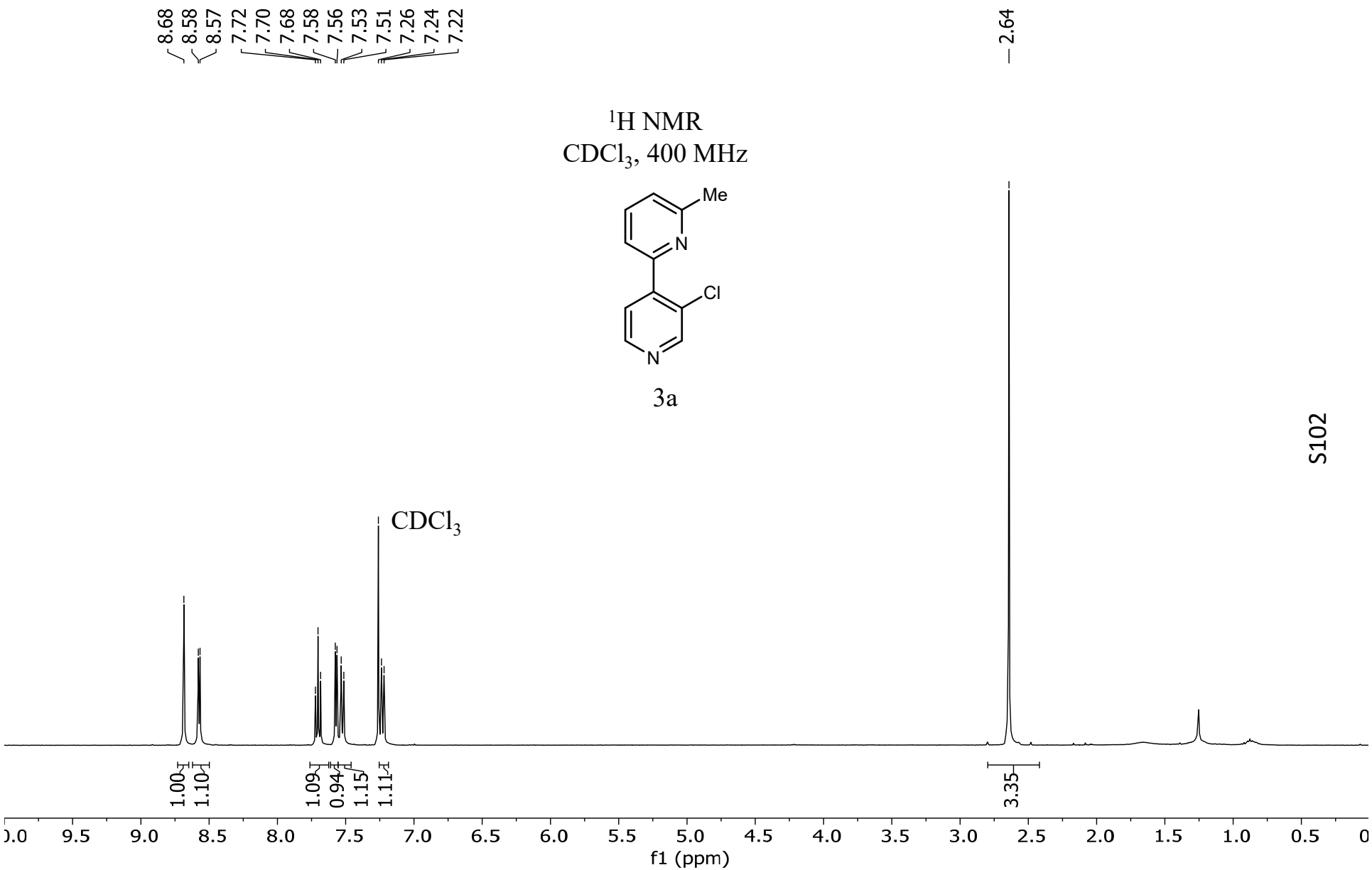

8.19
8.18
8.01
8.01
7.37
7.37
7.37
7.36
7.35
7.34
7.34
7.26
3.86
^{1}H NMR
$CDCl_3$, 400 MHz
N
OMe
N
PPh_2
2m
$CDCl_3$
S99
1.00
0.99
10.12
3.33
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

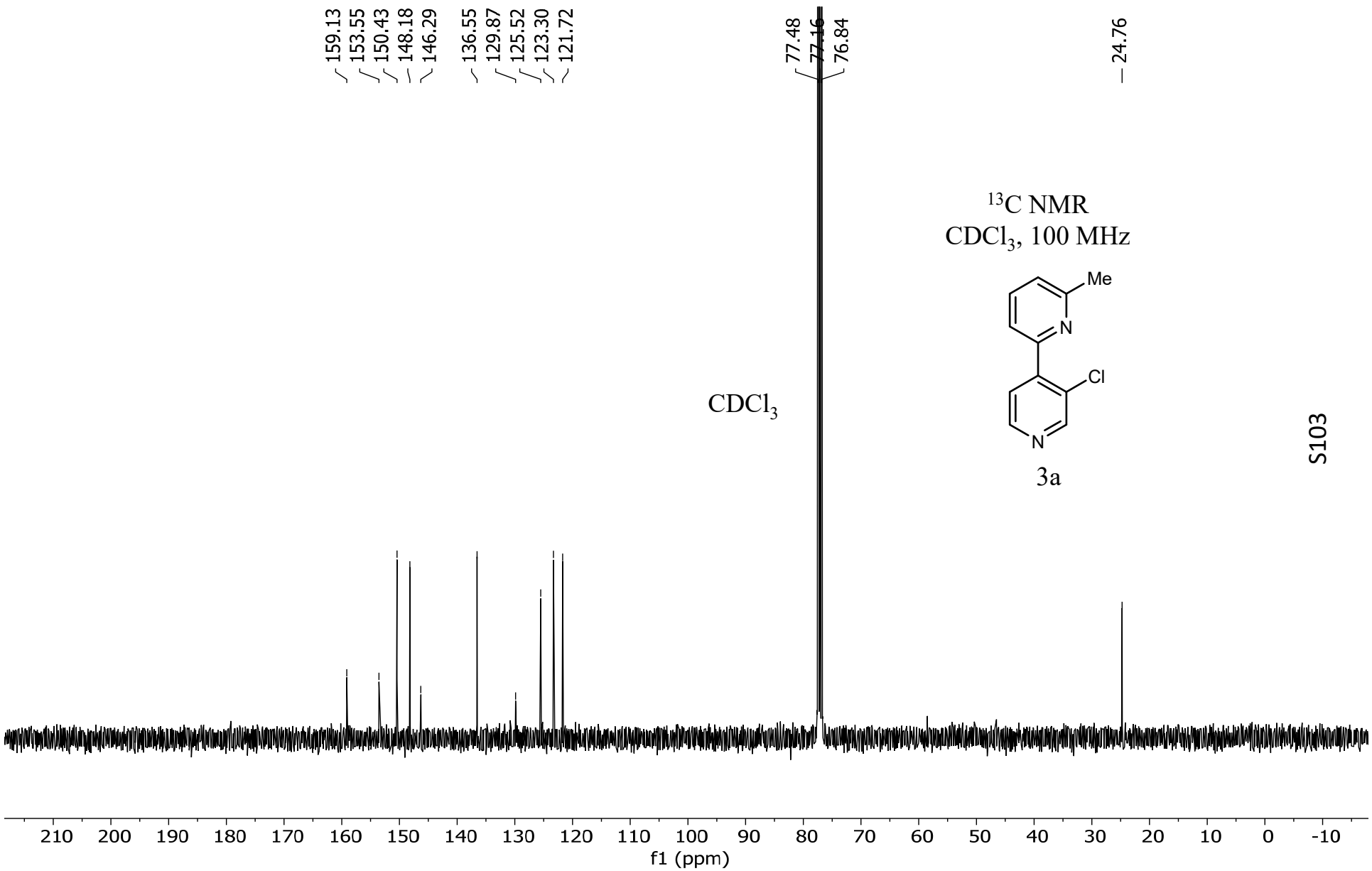

161.79
161.57
148.62
148.49
139.64
137.55
134.35
134.15
128.98
128.31
128.23
77.32
77.00
76.68
53.65
13C NMR
CDCl3, 100 MHz
N
OMe
N
PPh2
2m
S100
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

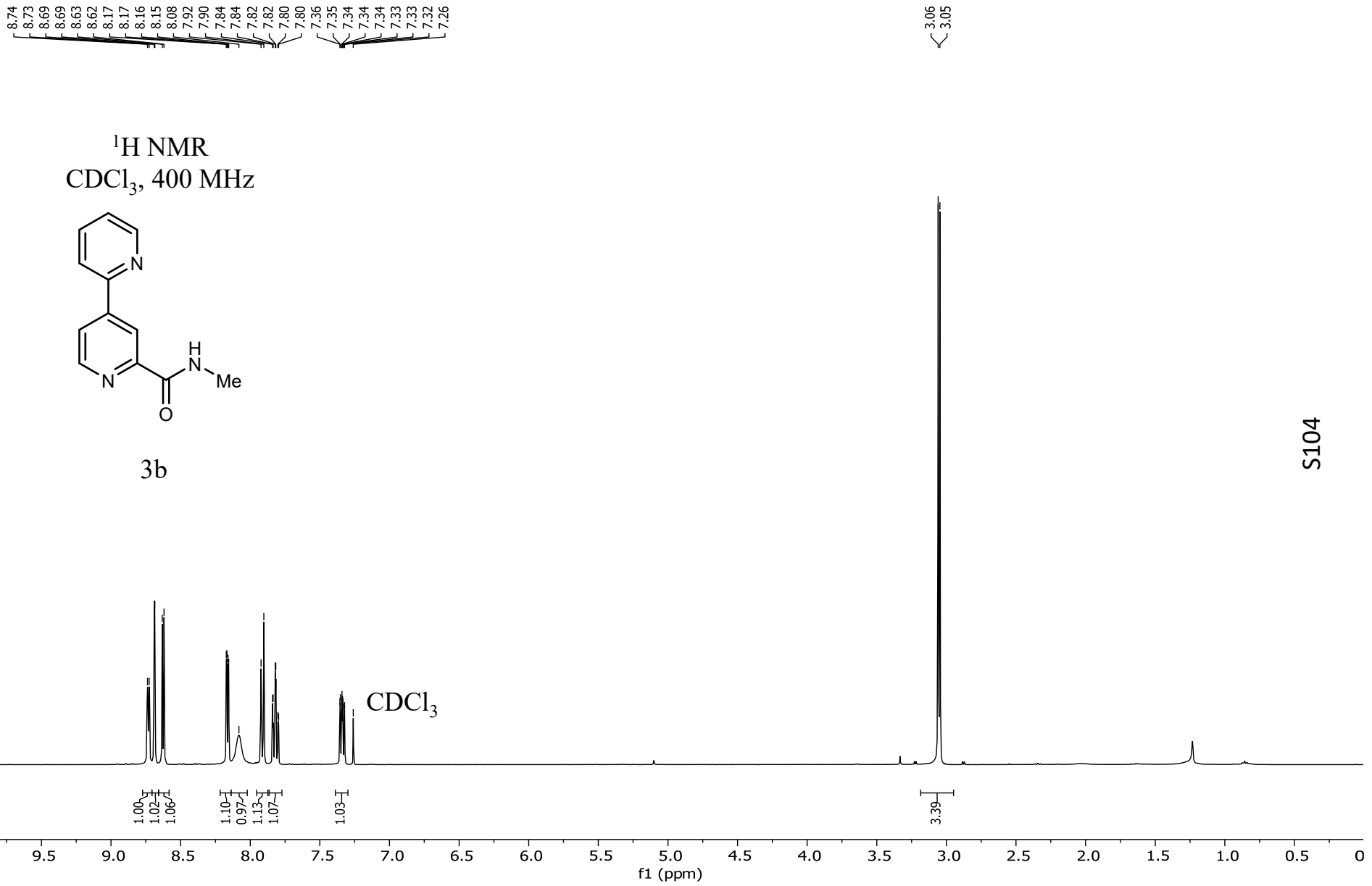
^{31}P NMR
$CDCl_3$, 162 MHz

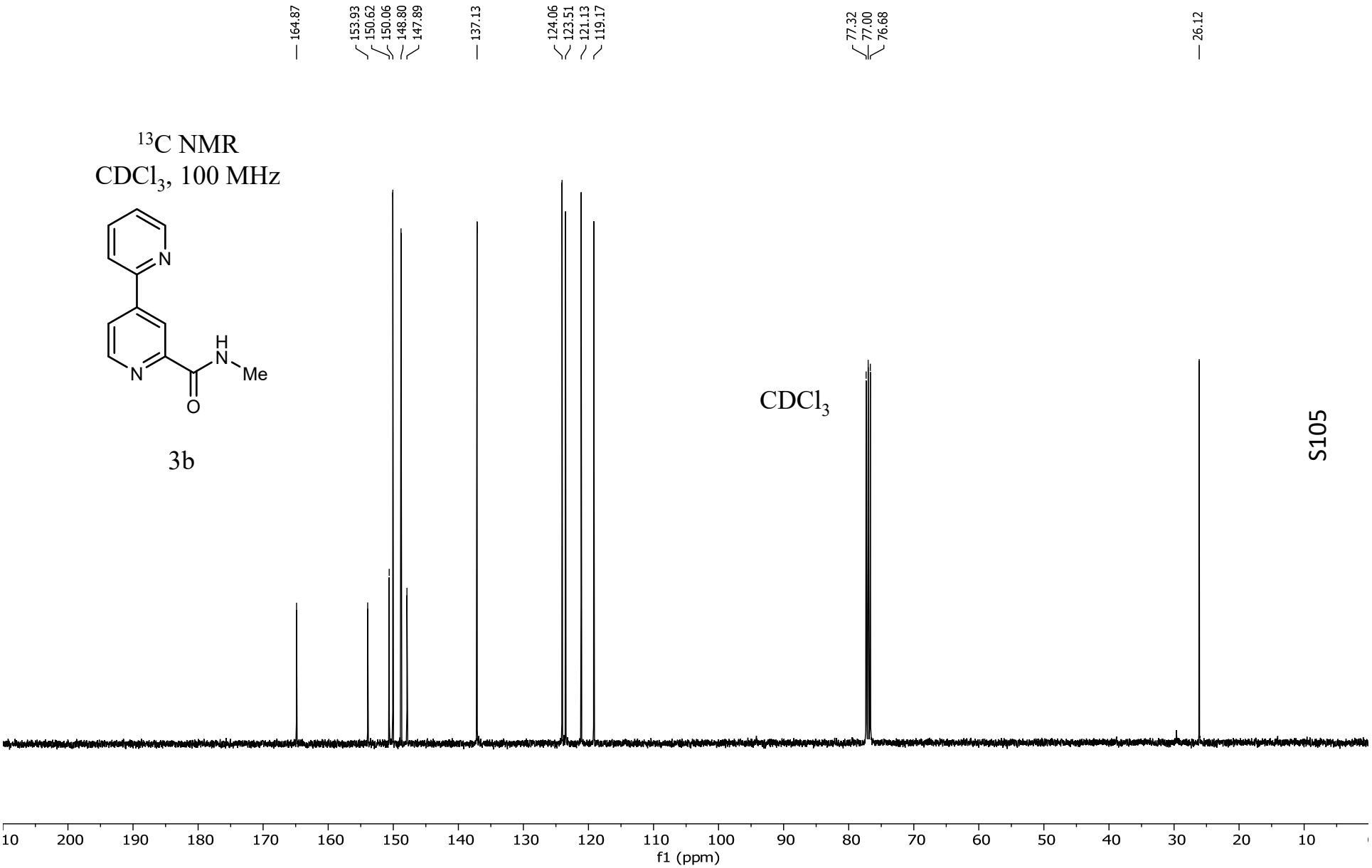


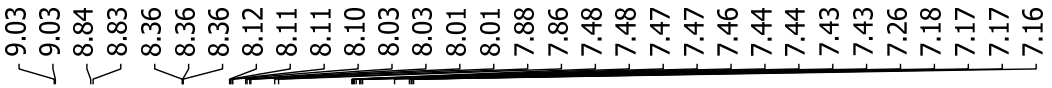
2m


8.68
8.58
8.57
7.72
7.70
7.68
7.58
7.56
7.53
7.51
7.26
7.24
7.22
2.64
^{1}H NMR
$CDCl_3$, 400 MHz
Me
N
Cl
N
3a
S102
$CDCl_3$
1.00
1.10
1.09
0.94
1.15
1.11
3.35
f1 (ppm)

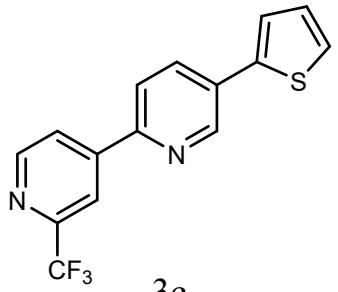

159.13
153.55
150.43
148.18
146.29
136.55
129.87
125.52
123.30
121.72
77.48
77.16
76.84
24.76
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
Me
N
Cl
N
3a
S103
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.74
8.73
8.69
8.69
8.63
8.62
8.17
8.17
8.16
8.15
8.08
7.92
7.90
7.84
7.84
7.82
7.82
7.80
7.80
7.36
7.35
7.34
7.34
7.34
7.33
7.33
7.32
7.26
3.06
3.05
1H NMR
CDCl3, 400 MHz
N
H
N
Me
N
O
3b
S104
CDCl3
1.00
1.02
1.06
1.10
0.97
1.13
1.07
1.03
3.39
f1 (ppm)

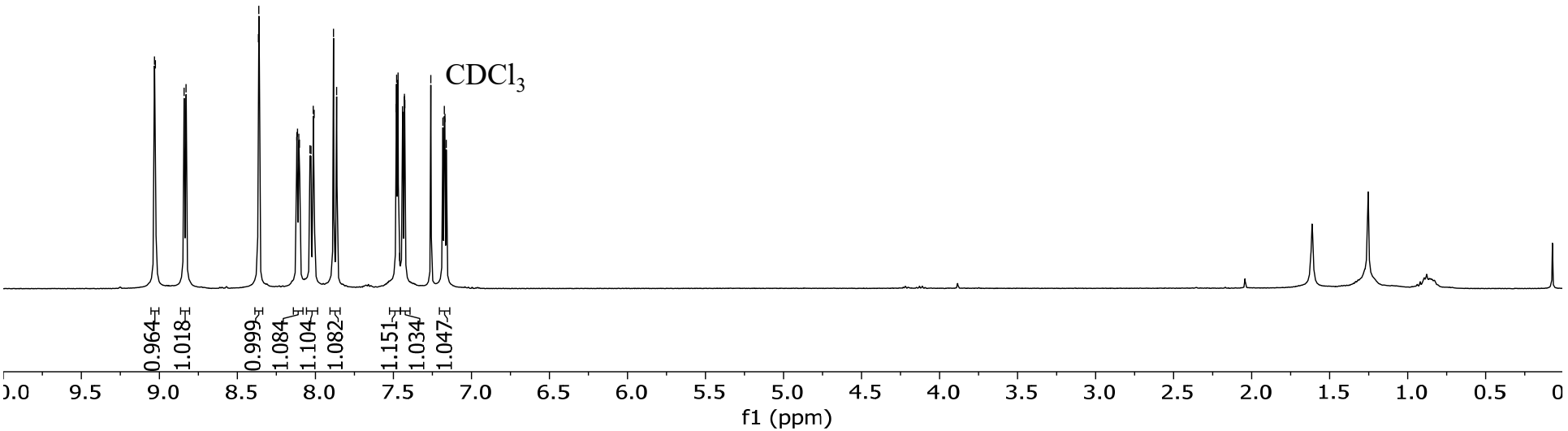

164.87
153.93
150.62
150.06
148.80
147.89
137.13
124.06
123.51
121.13
119.17
77.32
77.00
76.68
26.12
13C NMR
CDCl3, 100 MHz
N
N
H
N
Me
O
3b
CDCl3
S105
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

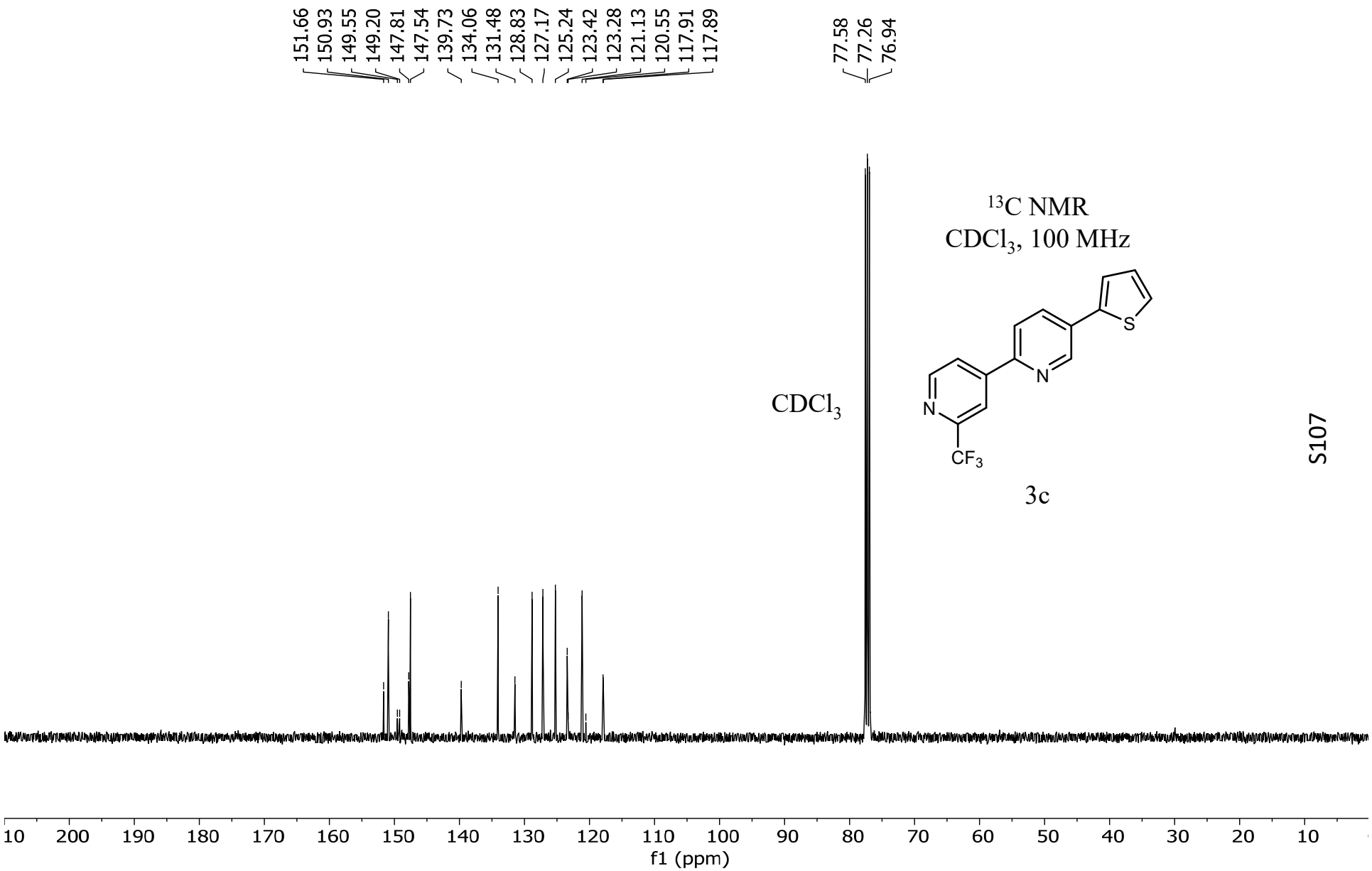


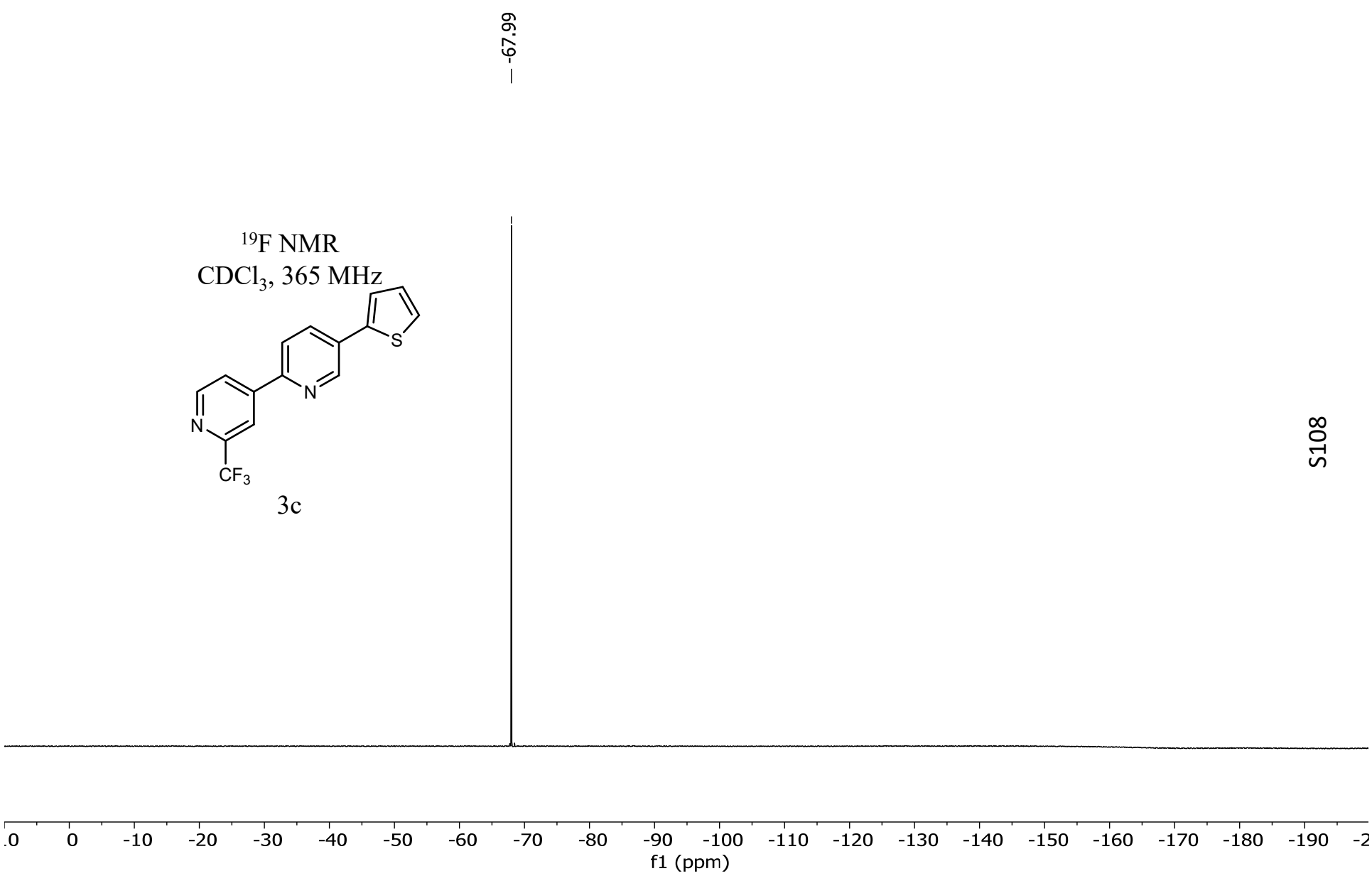
^{1}H NMR
$CDCl_3$, 400 MHz

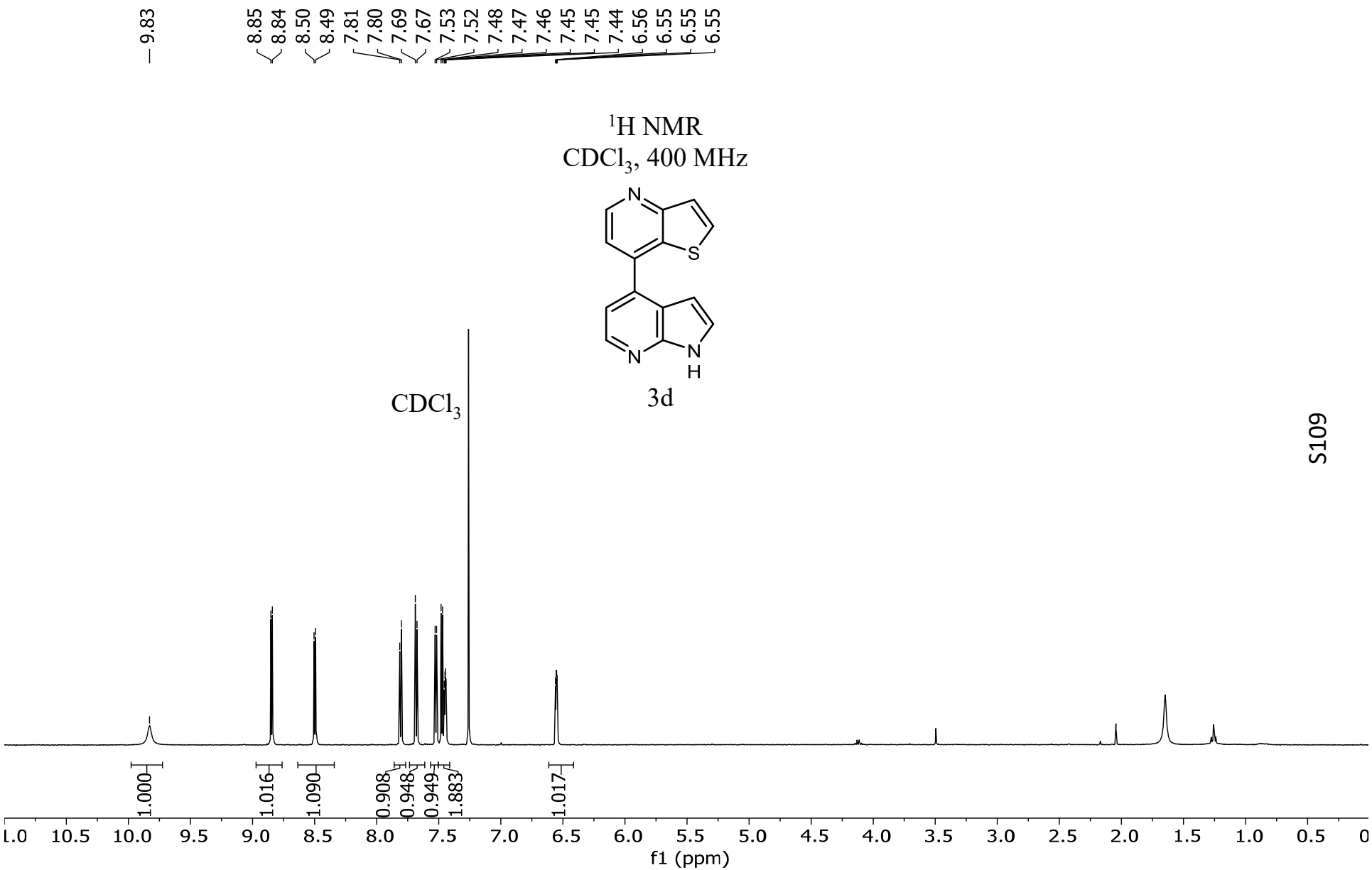


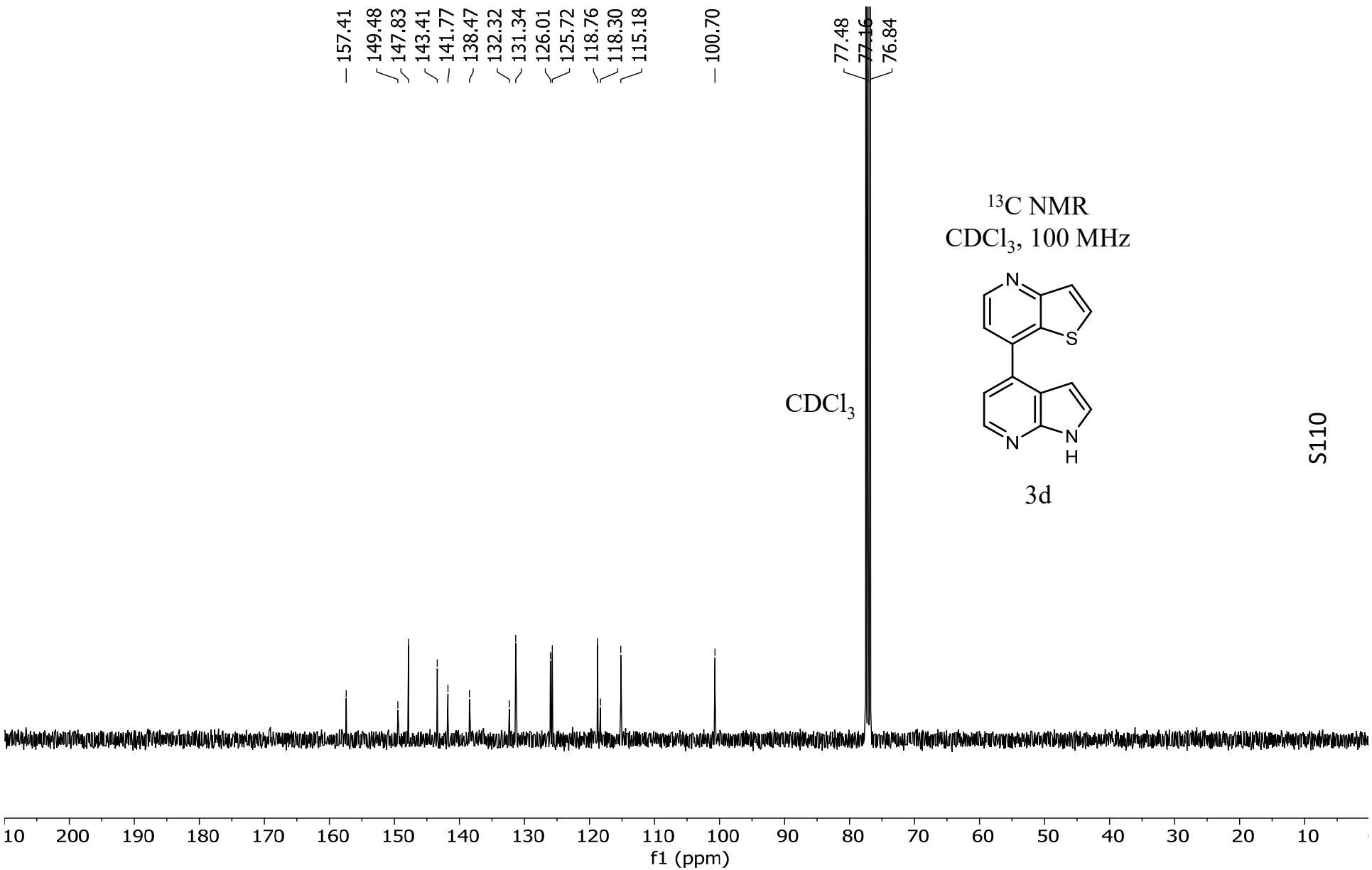
3c

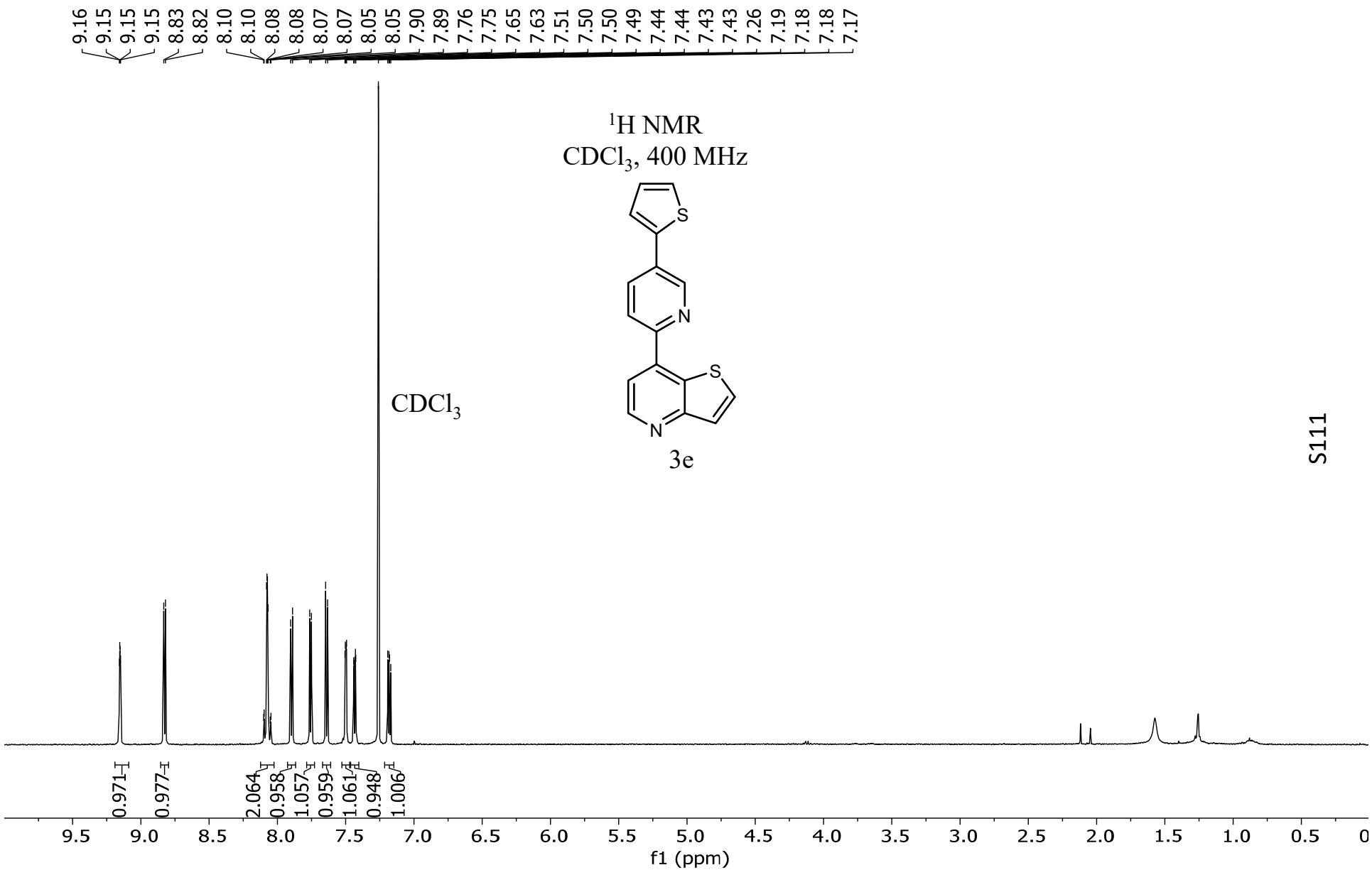


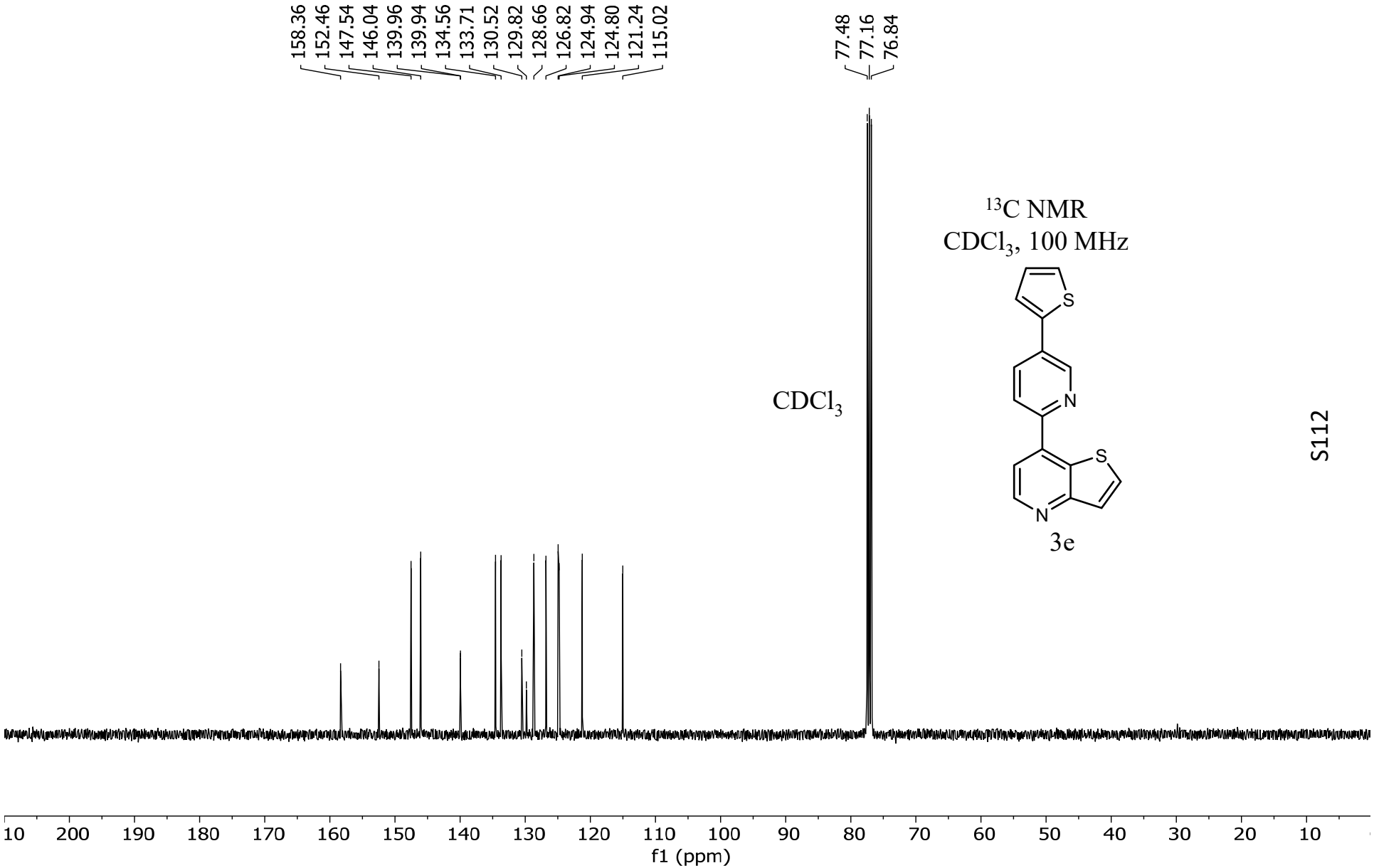

151.66
150.93
149.55
149.20
147.81
147.54
139.73
134.06
131.48
128.83
127.17
125.24
123.42
123.28
121.13
120.55
117.91
117.89
77.58
77.26
76.94
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
N
N
S
CF_3
3c
S107
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

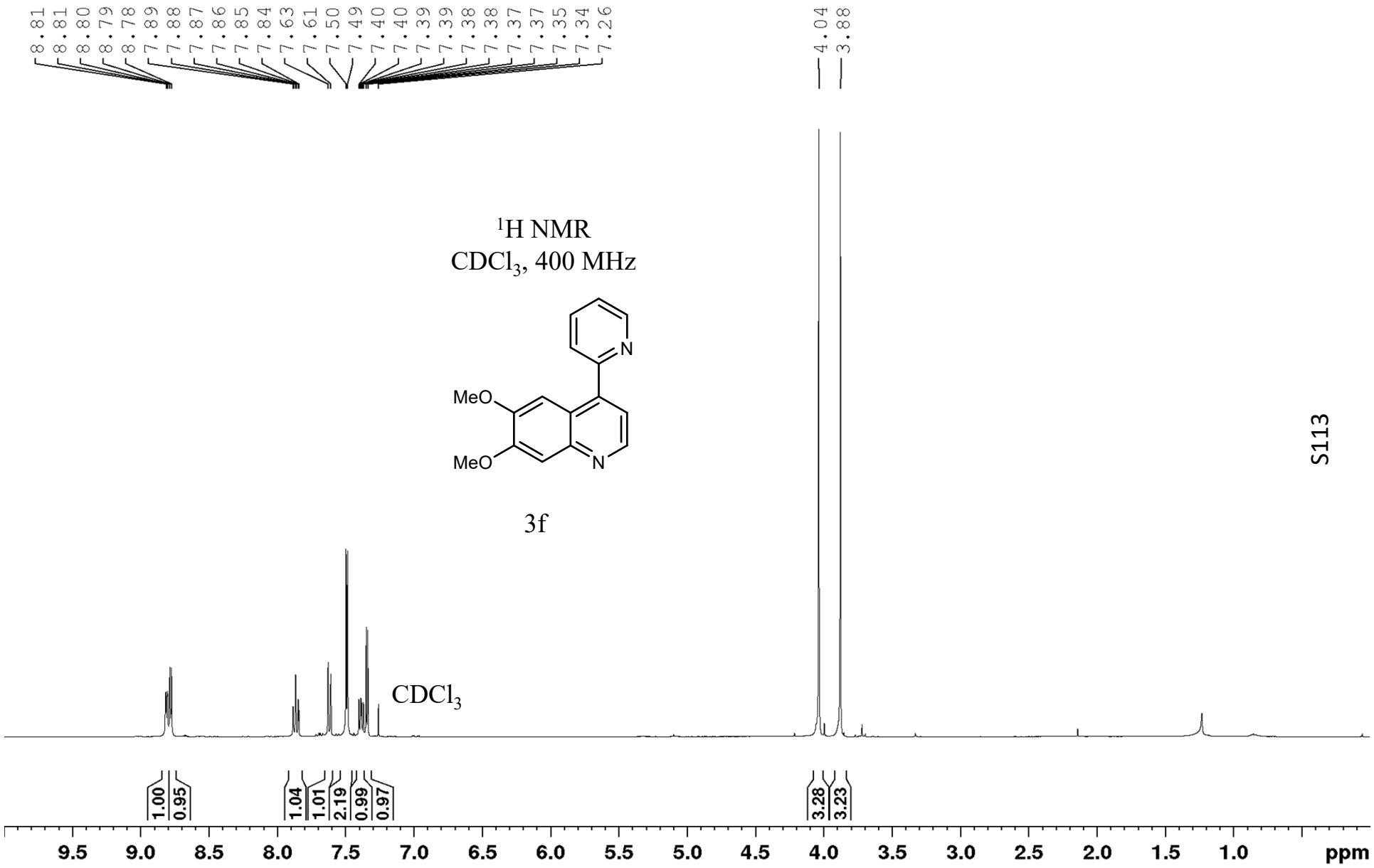

-67.99
^{19}F NMR
$CDCl_3$, 365 MHz
N
N
S
CF_3
3c
S108
.0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-2
f1 (ppm)

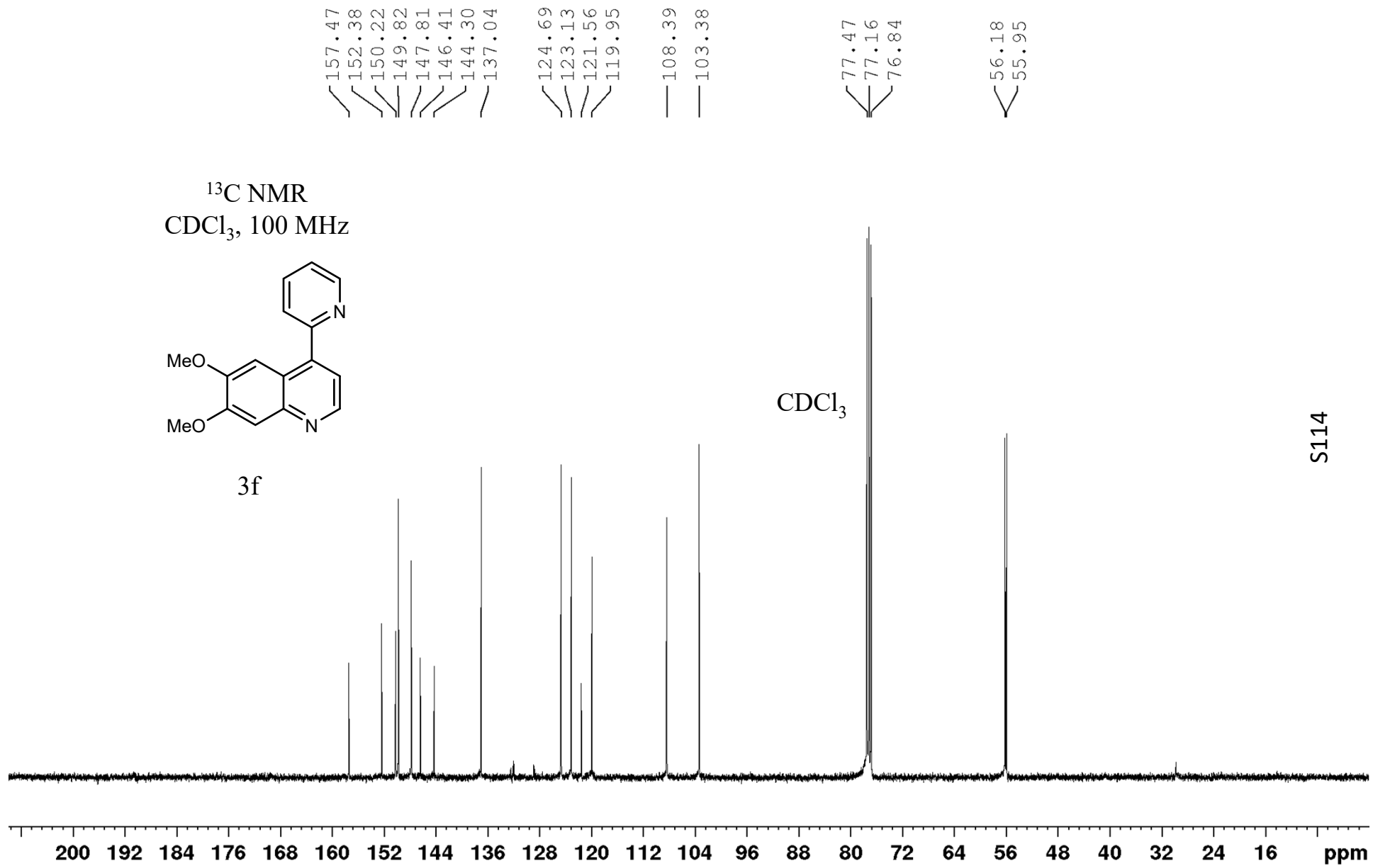

9.83
8.85
8.84
8.50
8.49
7.81
7.80
7.69
7.67
7.53
7.52
7.48
7.47
7.46
7.45
7.45
7.44
6.56
6.55
6.55
6.55
1H NMR
CDCl3, 400 MHz
N
S
N
N
H
3d
CDCl3
1.000
1.016
1.090
0.908
0.948
0.949
1.883
1.017
f1 (ppm)

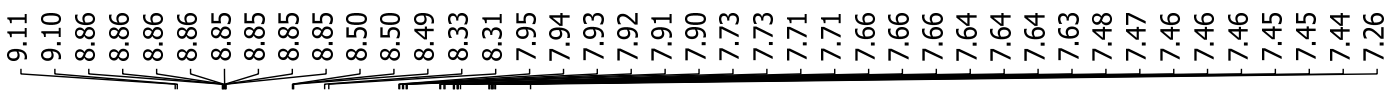

157.41
149.48
147.83
143.41
141.77
138.47
132.32
131.34
126.01
125.72
118.76
118.30
115.18
100.70
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
N
S
N
N
H
3d
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


9.16
9.15
9.15
9.15
8.83
8.82
8.10
8.10
8.08
8.08
8.07
8.07
8.05
8.05
7.90
7.89
7.76
7.75
7.65
7.63
7.51
7.50
7.50
7.49
7.44
7.44
7.43
7.43
7.26
7.19
7.18
7.18
7.17
^{1}H NMR
$CDCl_3$, 400 MHz
$CDCl_3$
3e
S111
0.971
0.977
2.064
0.958
1.057
0.959
1.061
0.948
1.006
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)


158.36
152.46
147.54
146.04
139.96
139.94
134.56
133.71
130.52
129.82
128.66
126.82
124.94
124.80
121.24
115.02
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
S
N
S
N
3e
S112
f1 (ppm)

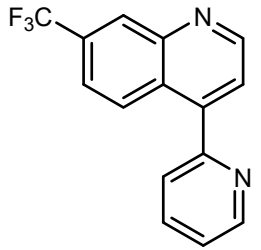

8.81
8.81
8.80
8.79
8.78
7.89
7.88
7.87
7.86
7.85
7.84
7.63
7.61
7.50
7.49
7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.37
7.35
7.34
7.26
4.04
3.88
^{1}H NMR
$CDCl_3$, 400 MHz
MeO
MeO
N
N
3f
S113
$CDCl_3$
1.00
0.95
1.04
1.01
2.19
0.99
0.97
3.28
3.23
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


157.47
152.38
150.22
149.82
147.81
146.41
144.30
137.04
124.69
123.13
121.56
119.95
108.39
103.38
77.47
77.16
76.84
56.18
55.95
^{13}C NMR
$CDCl_3$, 100 MHz
MeO
MeO
N
N
3f
$CDCl_3$
S114
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

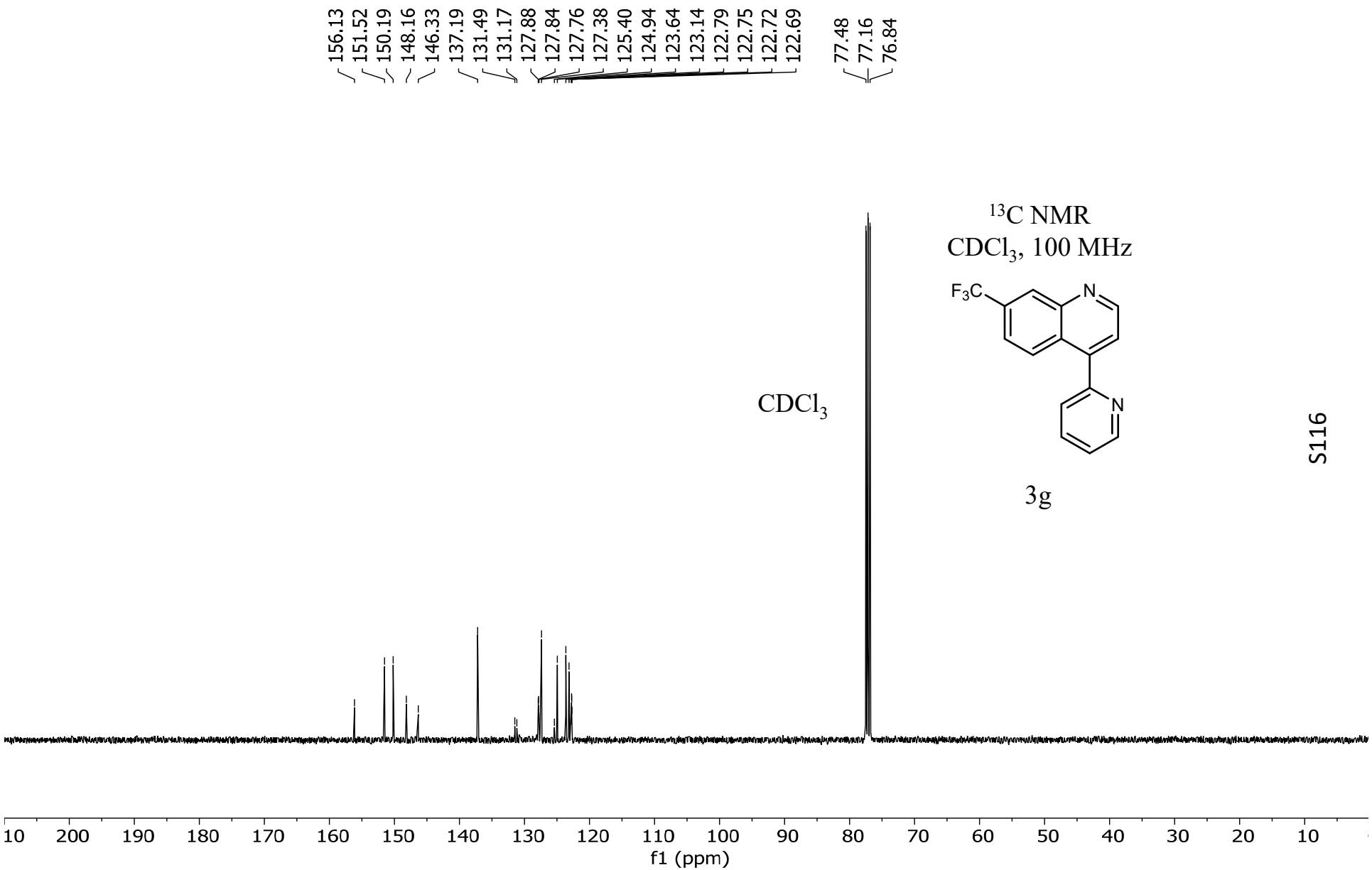


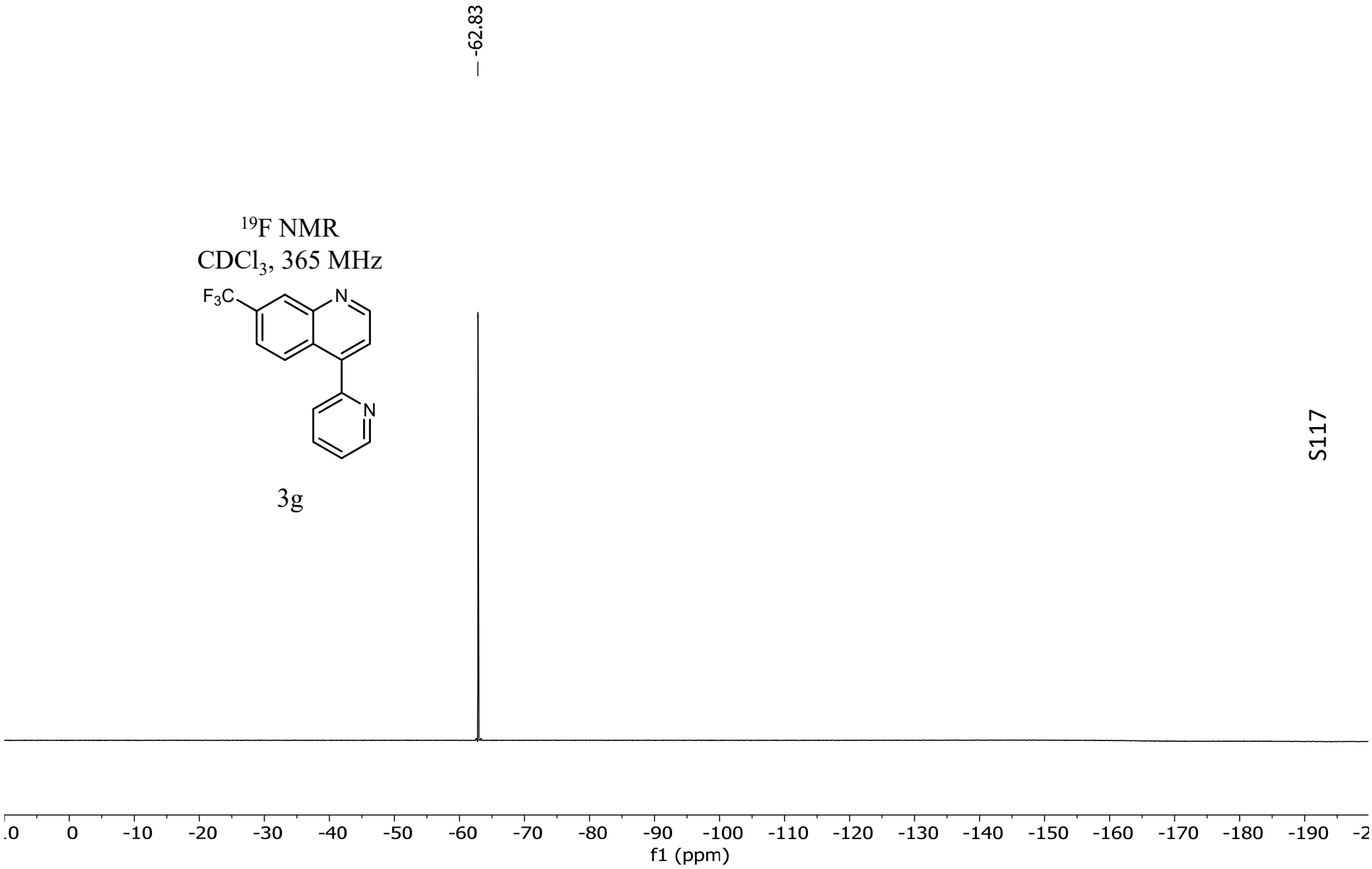
^{1}H NMR

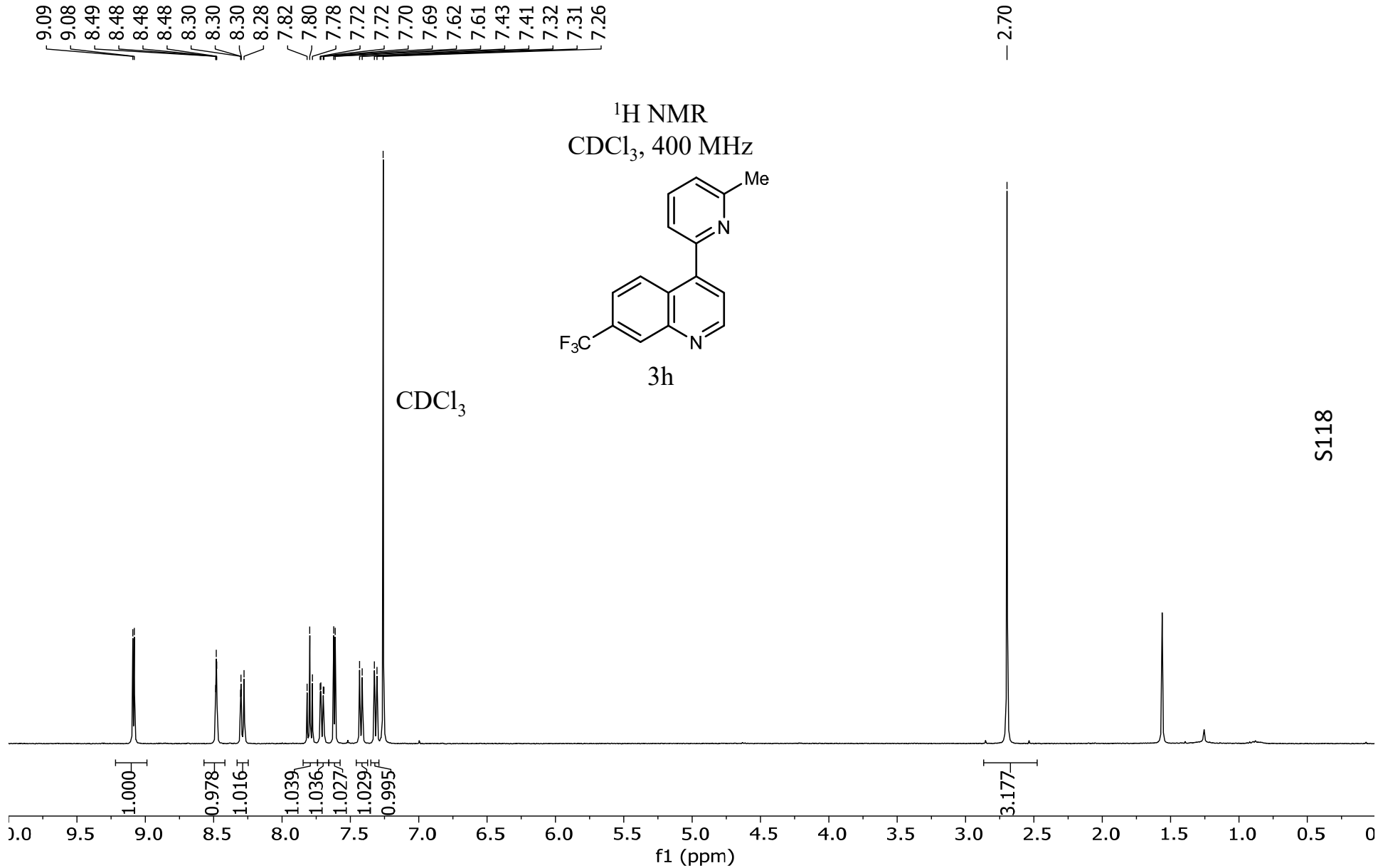
$CDCl_3$, 400 MHz

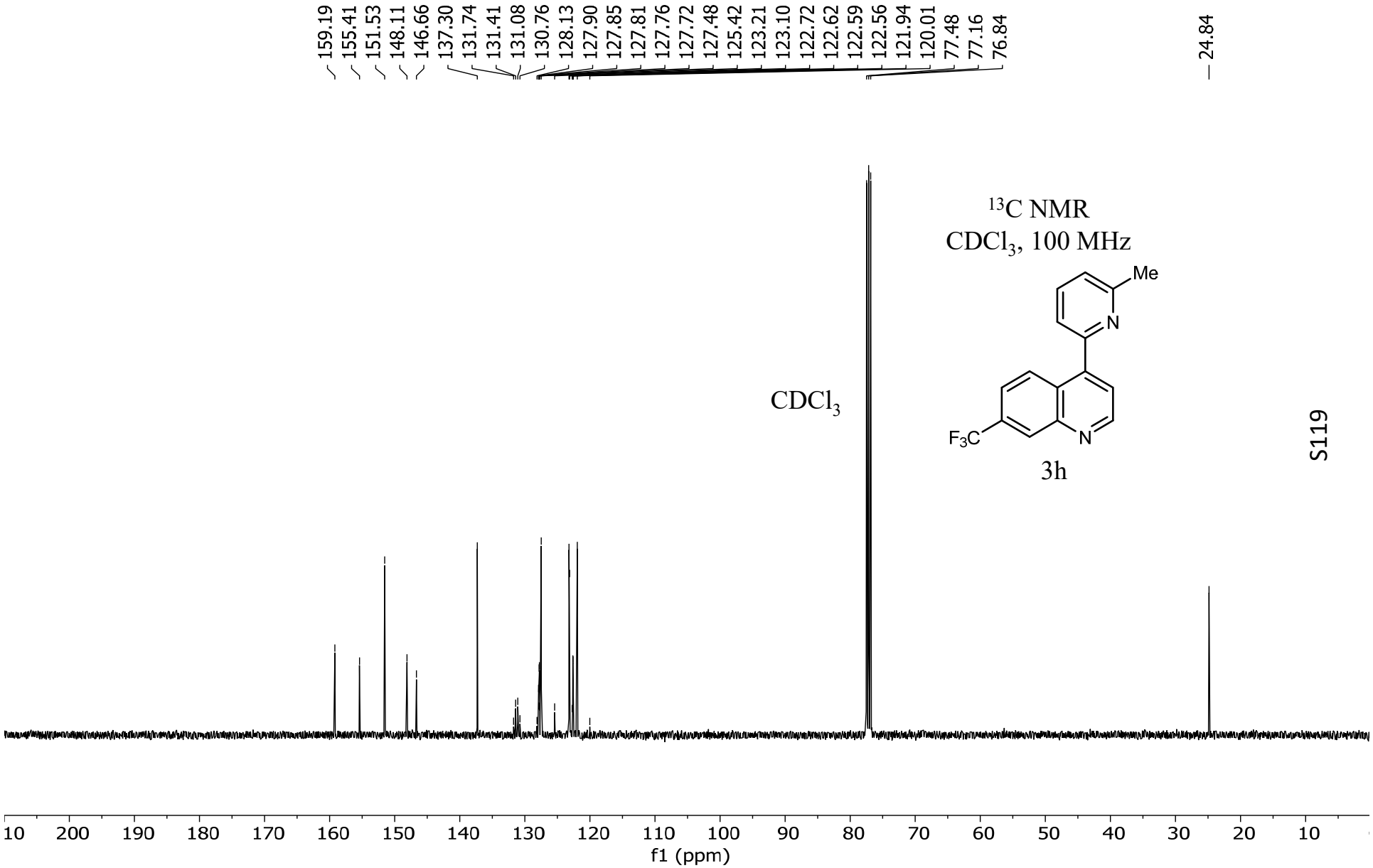


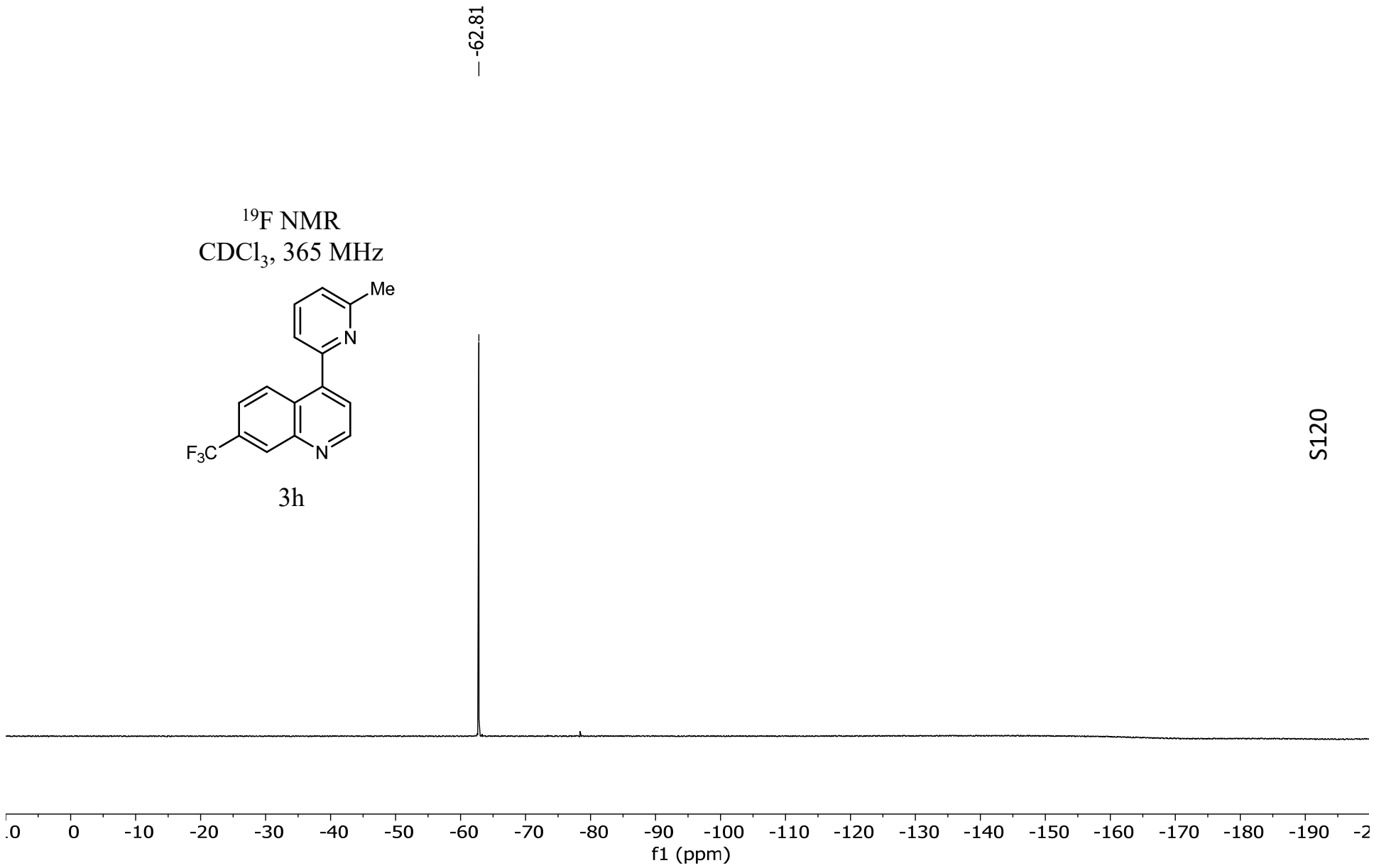
3g

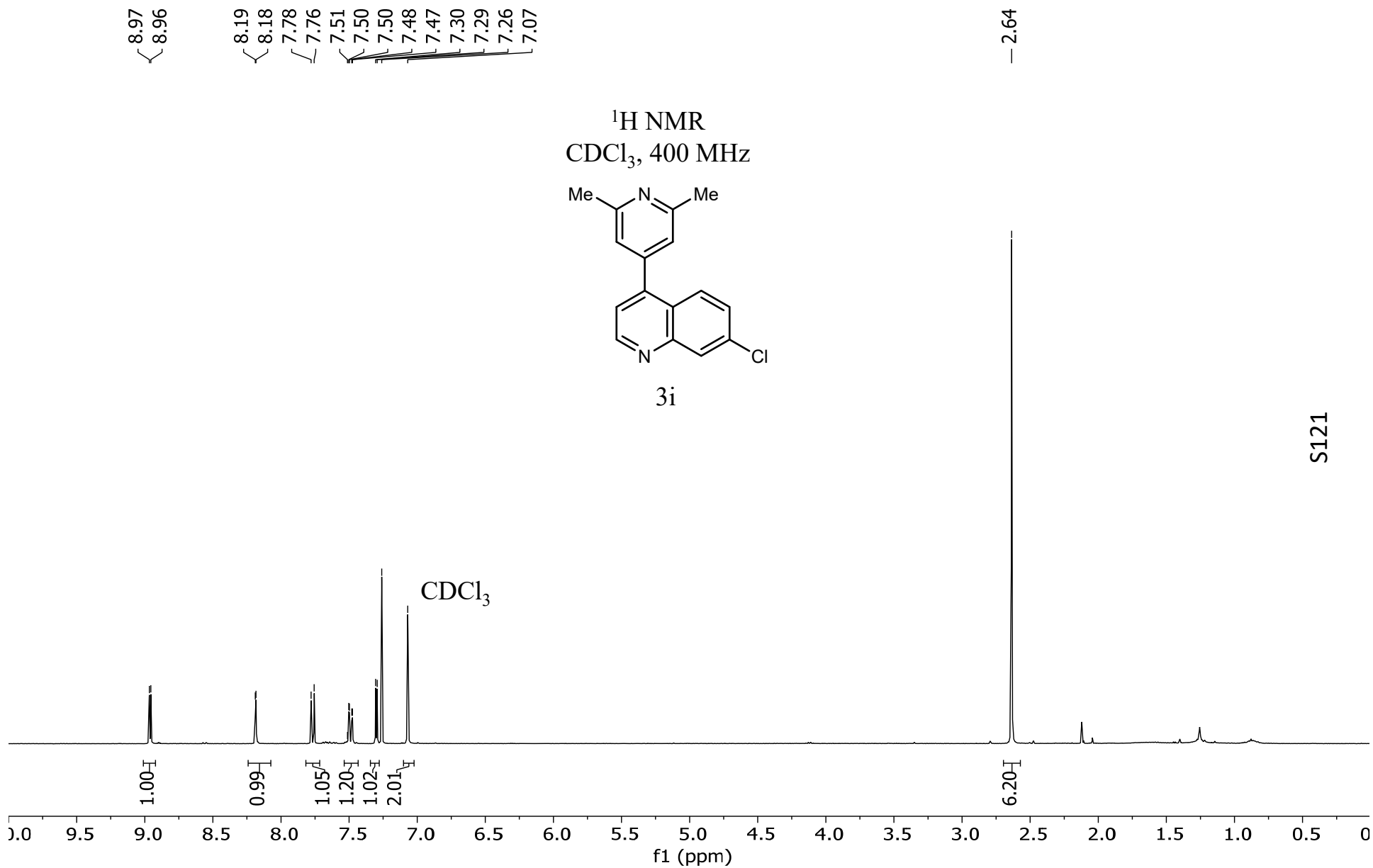

156.13
151.52
150.19
148.16
146.33
137.19
131.49
131.17
127.88
127.84
127.76
127.38
125.40
124.94
123.64
123.14
122.79
122.75
122.72
122.69
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
F_3C
N
N
3g
S116
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

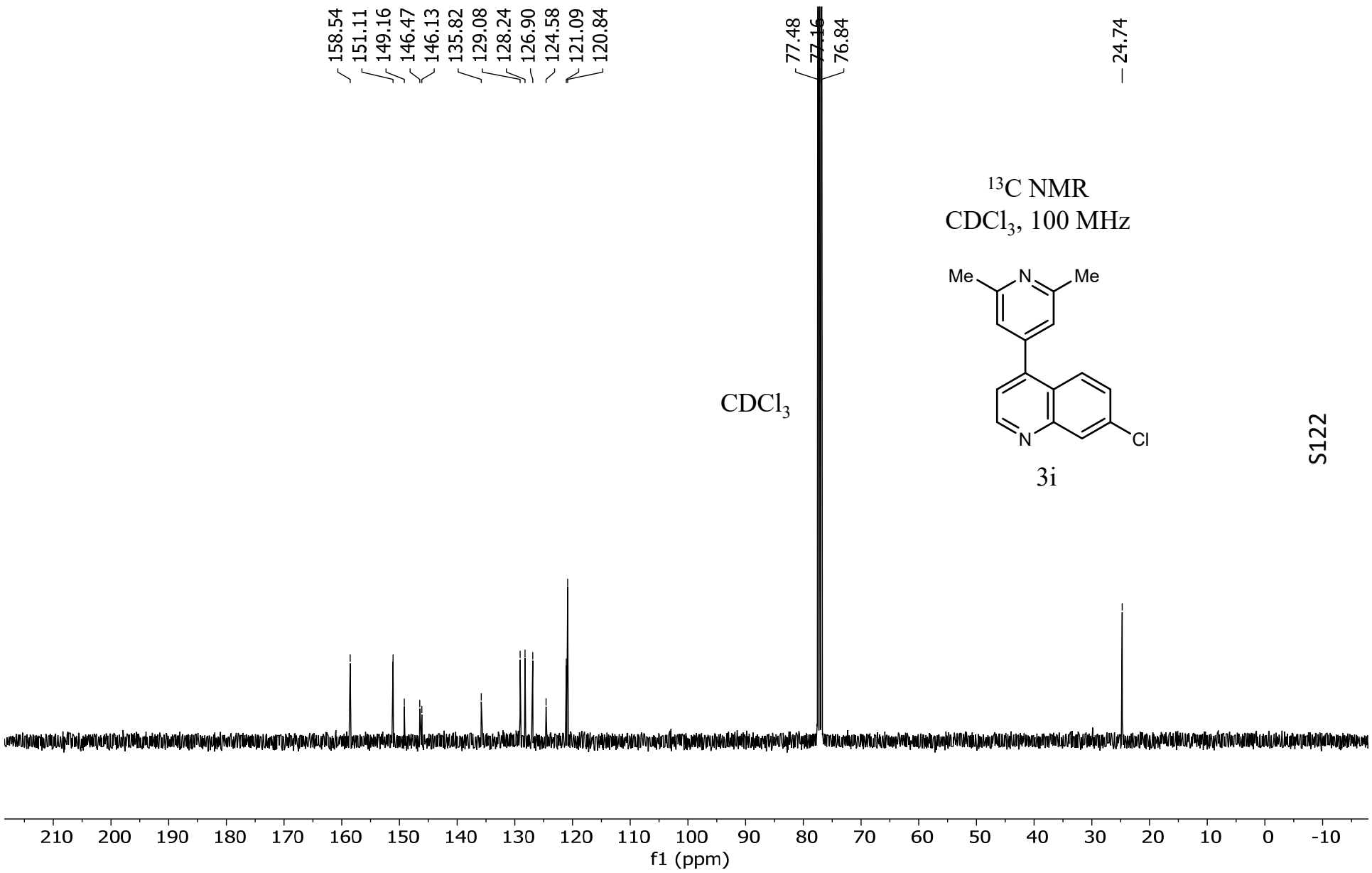

-62.83
^{19}F NMR
$CDCl_3$, 365 MHz
F_3C
N
N
3g
S117
.0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-2
f1 (ppm)

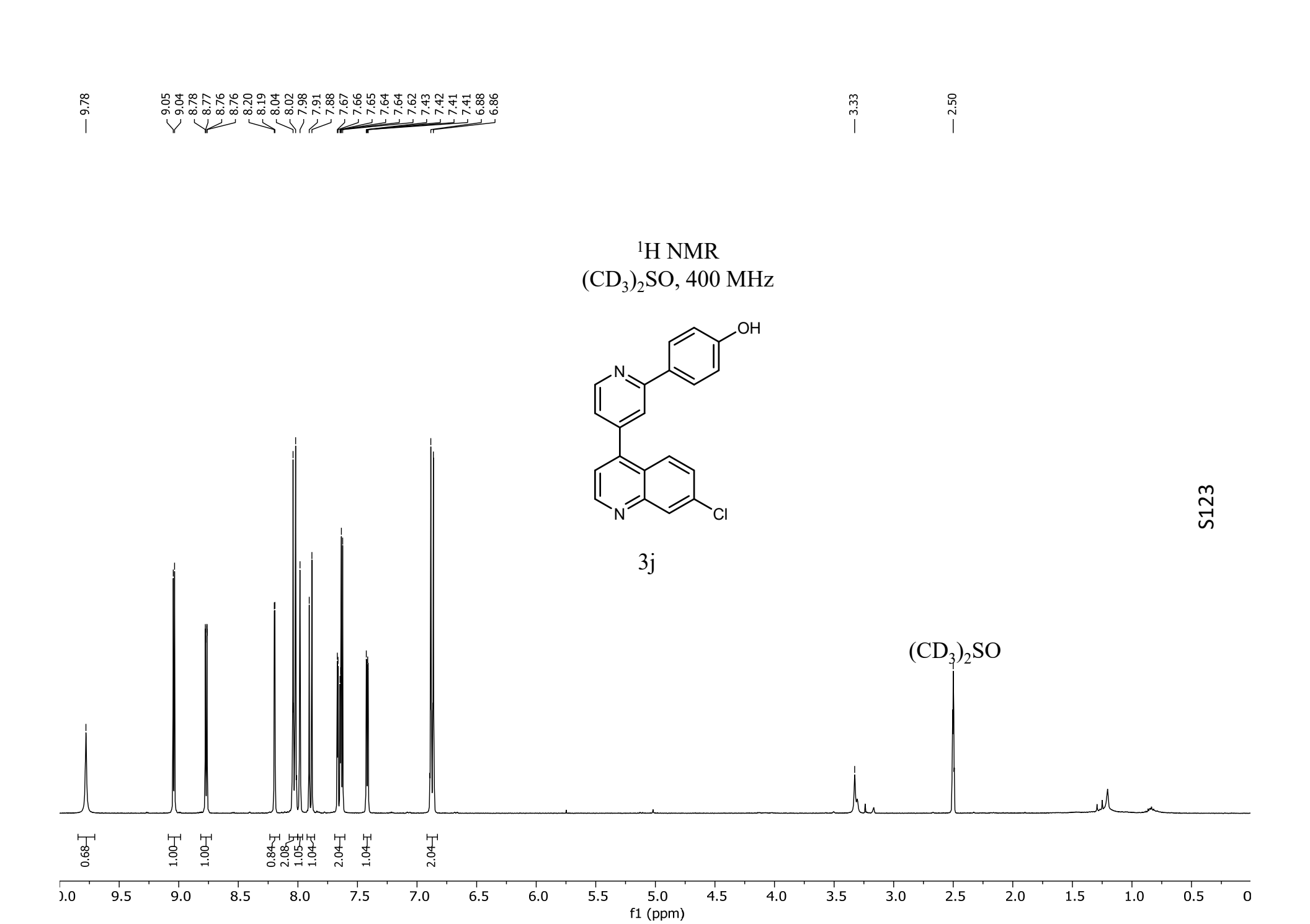

9.09
9.08
8.49
8.48
8.48
8.48
8.30
8.30
8.30
8.28
7.82
7.80
7.78
7.72
7.72
7.70
7.69
7.62
7.61
7.43
7.41
7.32
7.31
7.26
2.70
1H NMR
CDCl3, 400 MHz
Me
N
F3C
N
3h
CDCl3
S118
1.000
0.978
1.016
1.039
1.036
1.027
1.029
0.995
3.177
f1 (ppm)

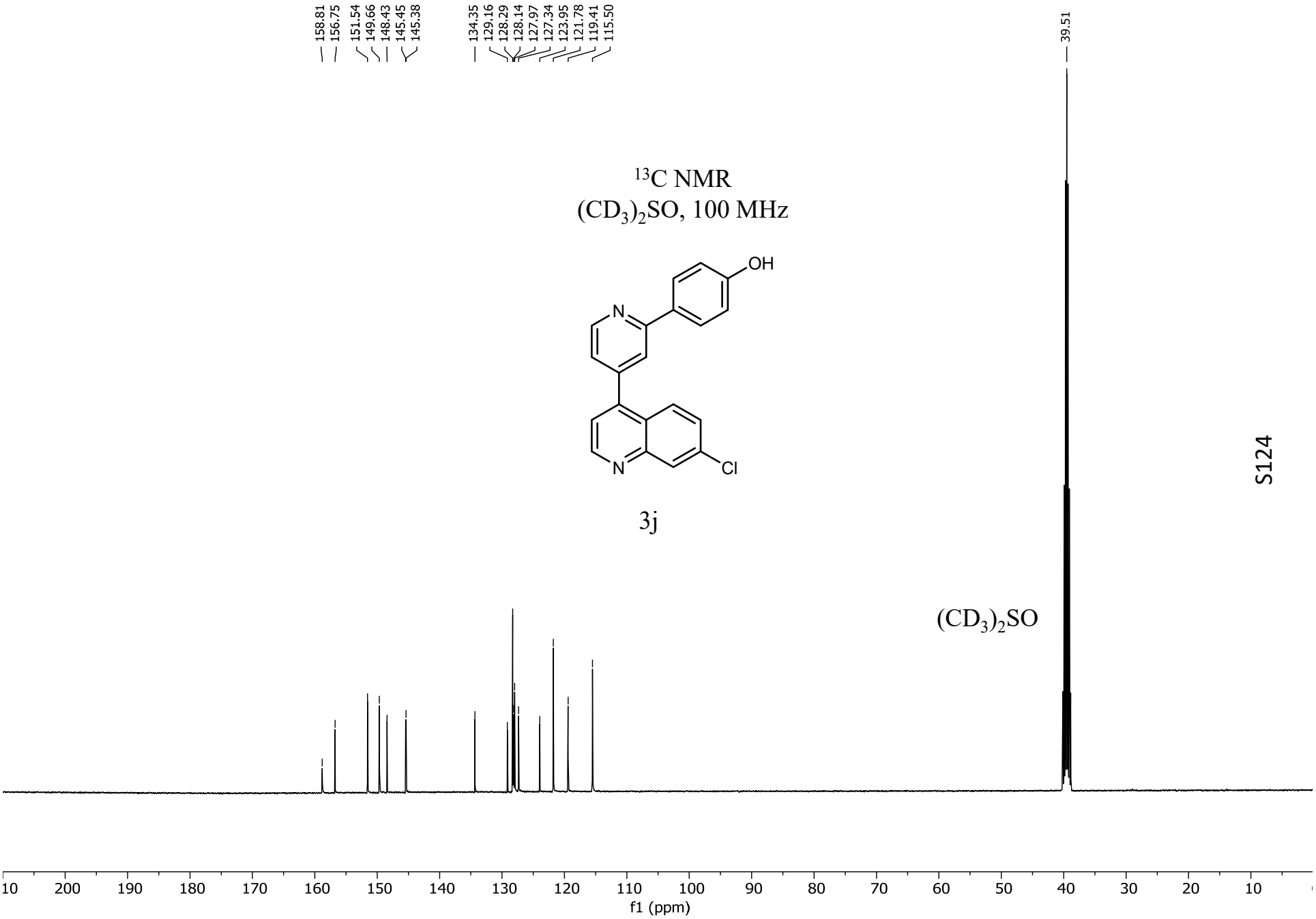

159.19
155.41
151.53
148.11
146.66
137.30
131.74
131.41
131.08
130.76
128.13
127.90
127.85
127.81
127.76
127.72
127.48
125.42
123.21
123.10
122.72
122.62
122.59
122.56
121.94
120.01
77.48
77.16
76.84
24.84
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
Me
N
F_3C
N
3h
S119
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

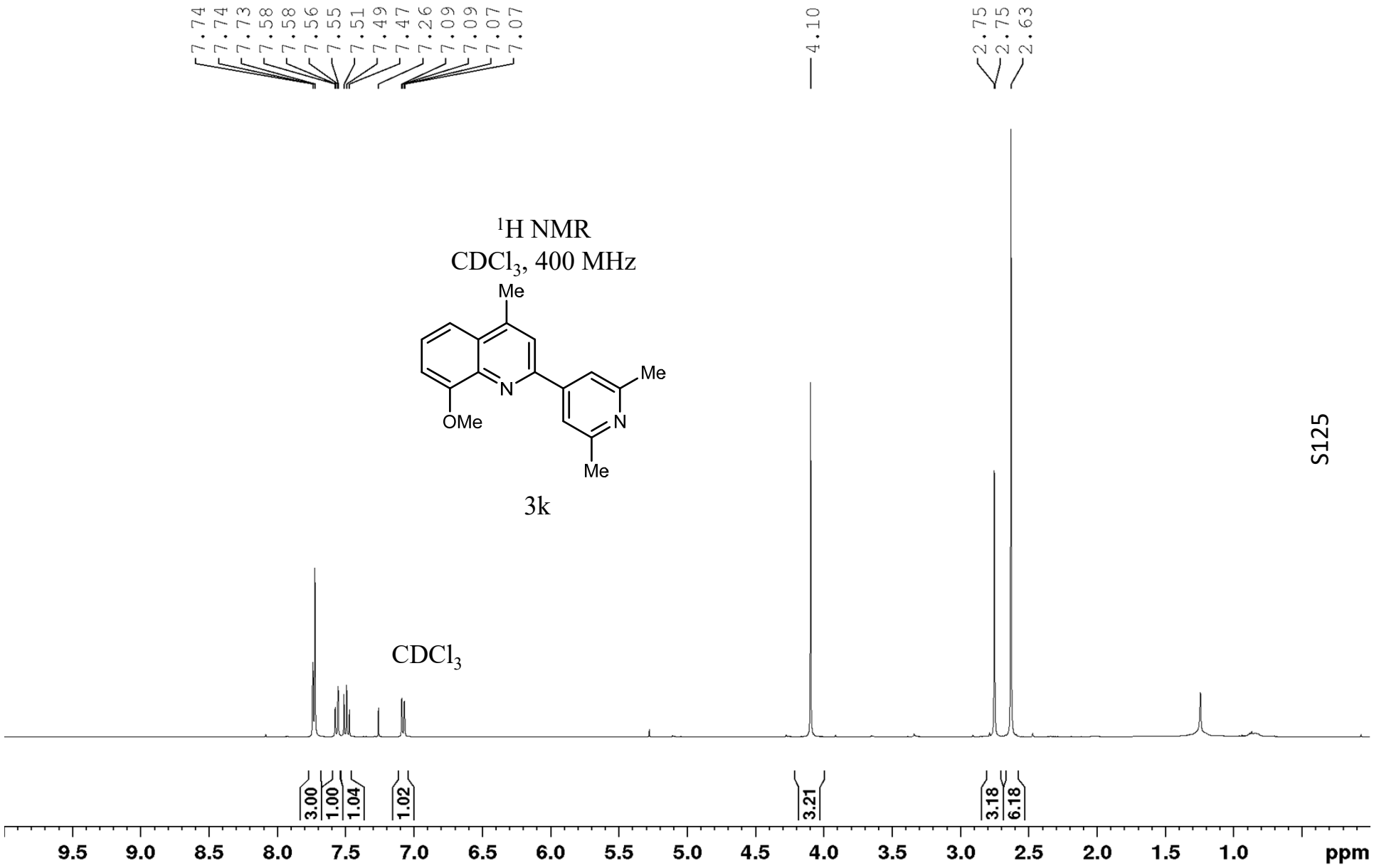

-62.81
^{19}F NMR
$CDCl_3$, 365 MHz
Me
N
F_3C
N
3h
S120
.0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-2
f1 (ppm)

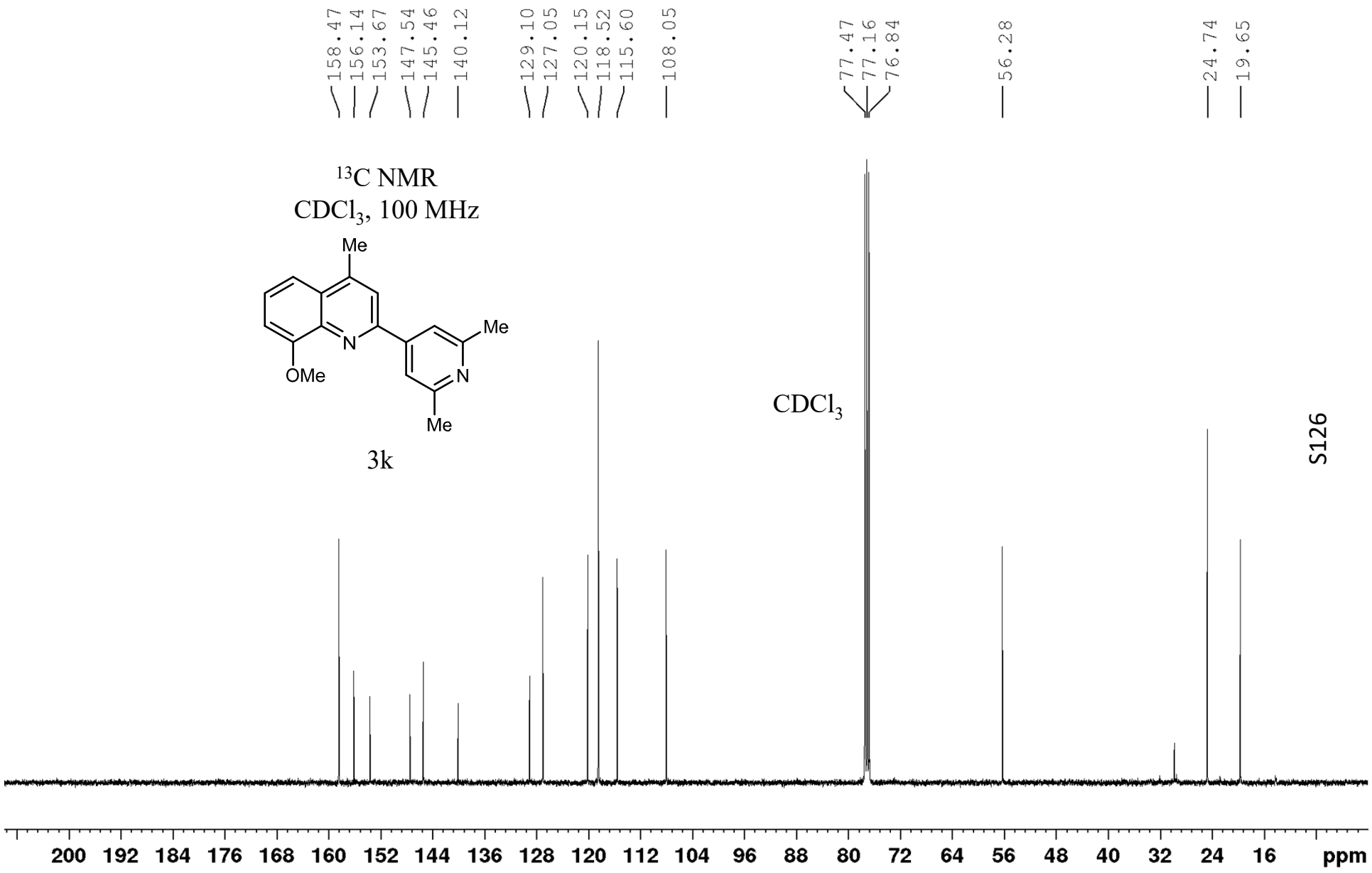

8.97
8.96
8.19
8.18
7.78
7.76
7.51
7.50
7.50
7.48
7.47
7.30
7.29
7.26
7.07
2.64
^{1}H NMR
$CDCl_3$, 400 MHz
Me
N
Me
N
Cl
3i
S121
$CDCl_3$
1.00
0.99
1.05
1.20
1.02
2.01
6.20
f1 (ppm)

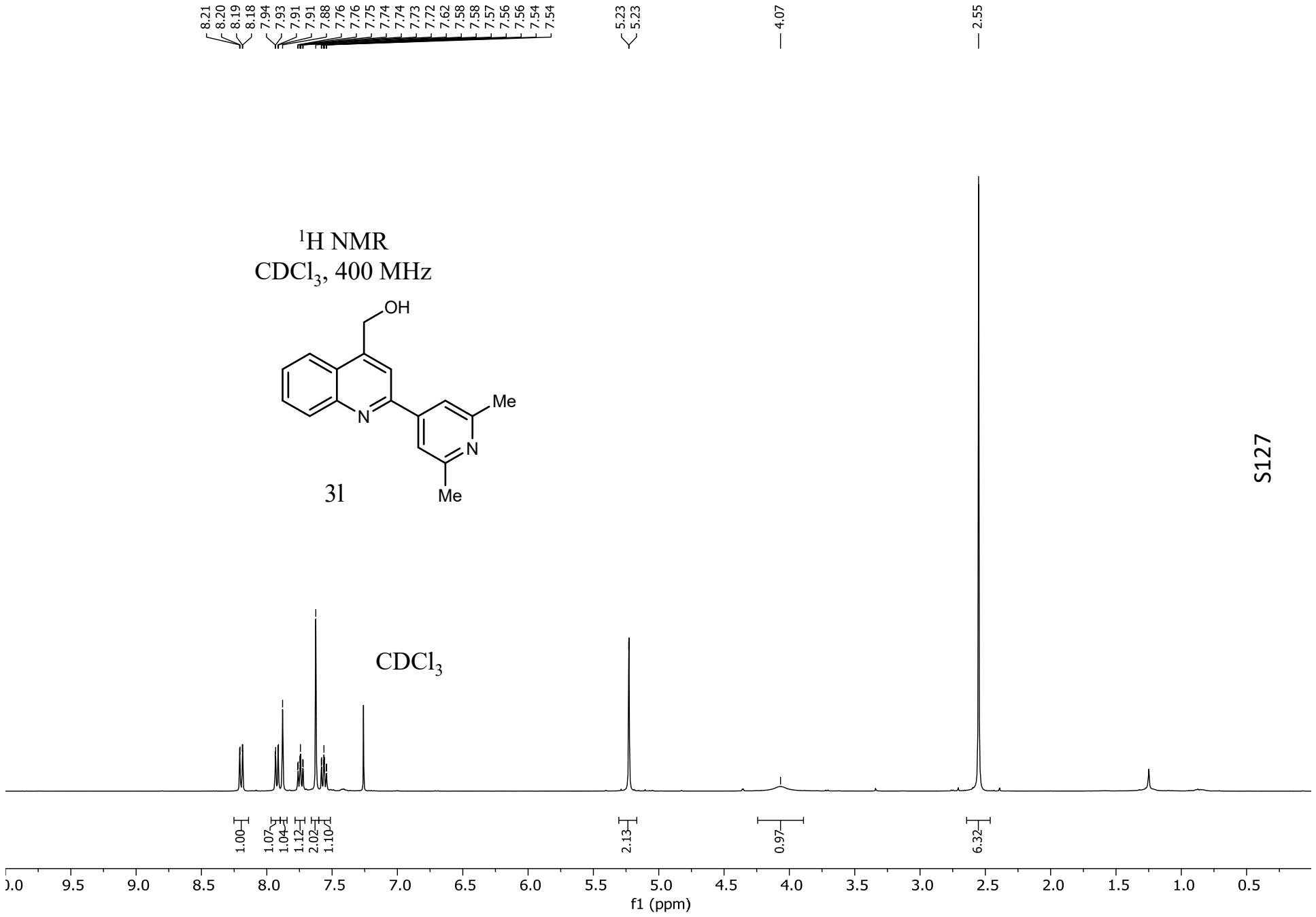

158.54
151.11
149.16
146.47
146.13
135.82
129.08
128.24
126.90
124.58
121.09
120.84
77.48
77.16
76.84
24.74
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
Me
N
Me
N
Cl
3i
S122
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


9.78
9.05
9.04
8.78
8.77
8.76
8.76
8.20
8.19
8.04
8.02
7.98
7.91
7.88
7.67
7.66
7.65
7.64
7.64
7.62
7.43
7.42
7.41
7.41
6.88
6.86
3.33
2.50
1H NMR
(CD3)2SO, 400 MHz
OH
N
N
Cl
3j
S123
(CD3)2SO
0.68
1.00
1.00
0.84
2.08
1.05
1.04
2.04
1.04
2.04
f1 (ppm)


158.81
156.75
151.54
149.66
148.43
145.45
145.38
134.35
129.16
128.29
128.14
127.97
127.34
123.95
121.78
119.41
115.50
39.51
^{13}C NMR
$(CD_3)_2SO$, 100 MHz
OH
N
N
Cl
3j
$(CD_3)_2SO$
S124
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

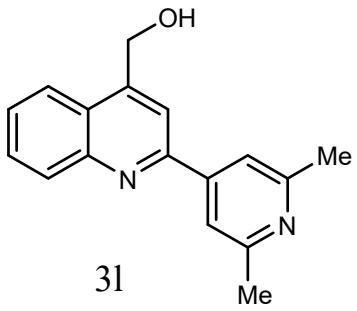

7.74
7.74
7.73
7.58
7.58
7.56
7.55
7.51
7.49
7.47
7.26
7.09
7.09
7.07
7.07
4.10
2.75
2.75
2.63
^{1}H NMR
$CDCl_3$, 400 MHz
Me
N
Me
OMe
N
Me
3k
S125
$CDCl_3$
3.00
1.00
1.04
1.02
3.21
3.18
6.18
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


158.47
156.14
153.67
147.54
145.46
140.12
129.10
127.05
120.15
118.52
115.60
108.05
77.47
77.16
76.84
56.28
24.74
19.65
13C NMR
CDCl3, 100 MHz
Me
Me
N
OMe
N
Me
3k
CDCl3
S126
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.21
8.20
8.19
8.18
7.94
7.93
7.91
7.91
7.88
7.76
7.76
7.75
7.74
7.74
7.73
7.72
7.62
7.58
7.58
7.57
7.56
7.56
7.54
7.54
5.23
5.23
4.07
2.55
1H NMR
CDCl3, 400 MHz
OH
N
Me
N
Me
31
CDCl3
S127
1.00
1.07
1.04
1.12
2.02
1.10
2.13
0.97
6.32
f1 (ppm)

158.29
154.84
147.90
147.56
147.51
130.43
129.75
127.08
125.35
122.68
118.42
115.70
61.36
24.32

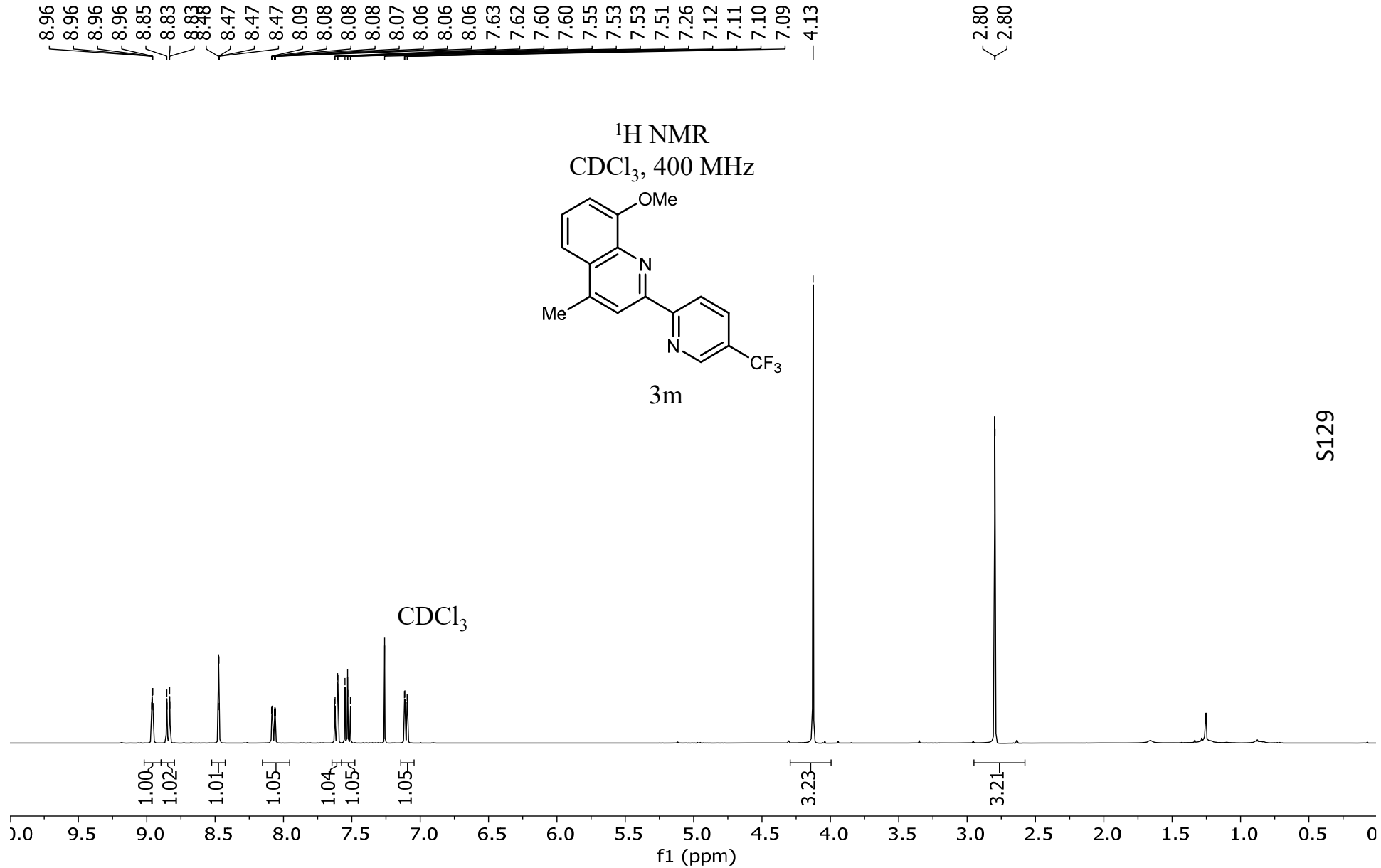
^{13}C NMR
$CDCl_3$, 100 MHz

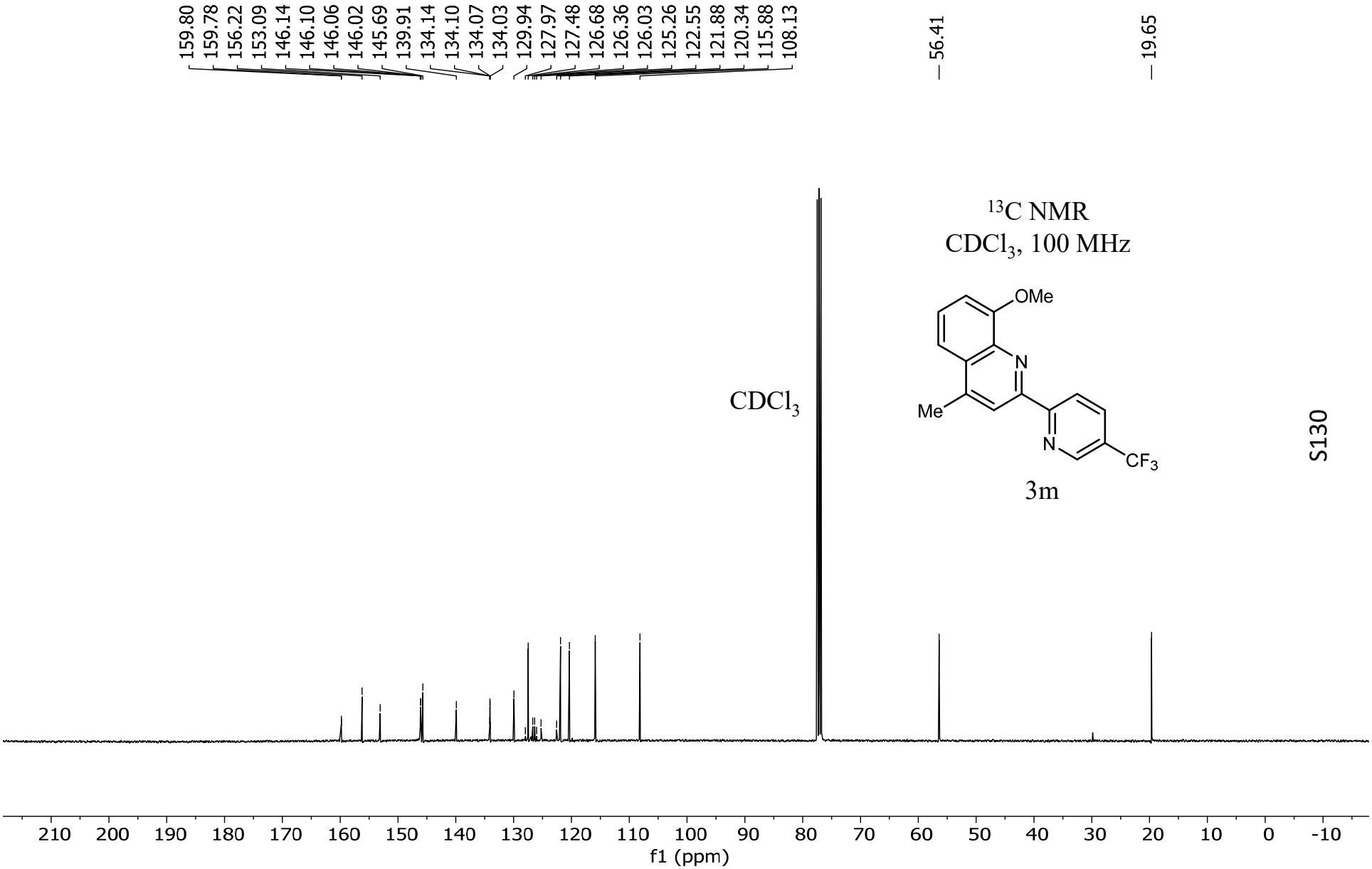


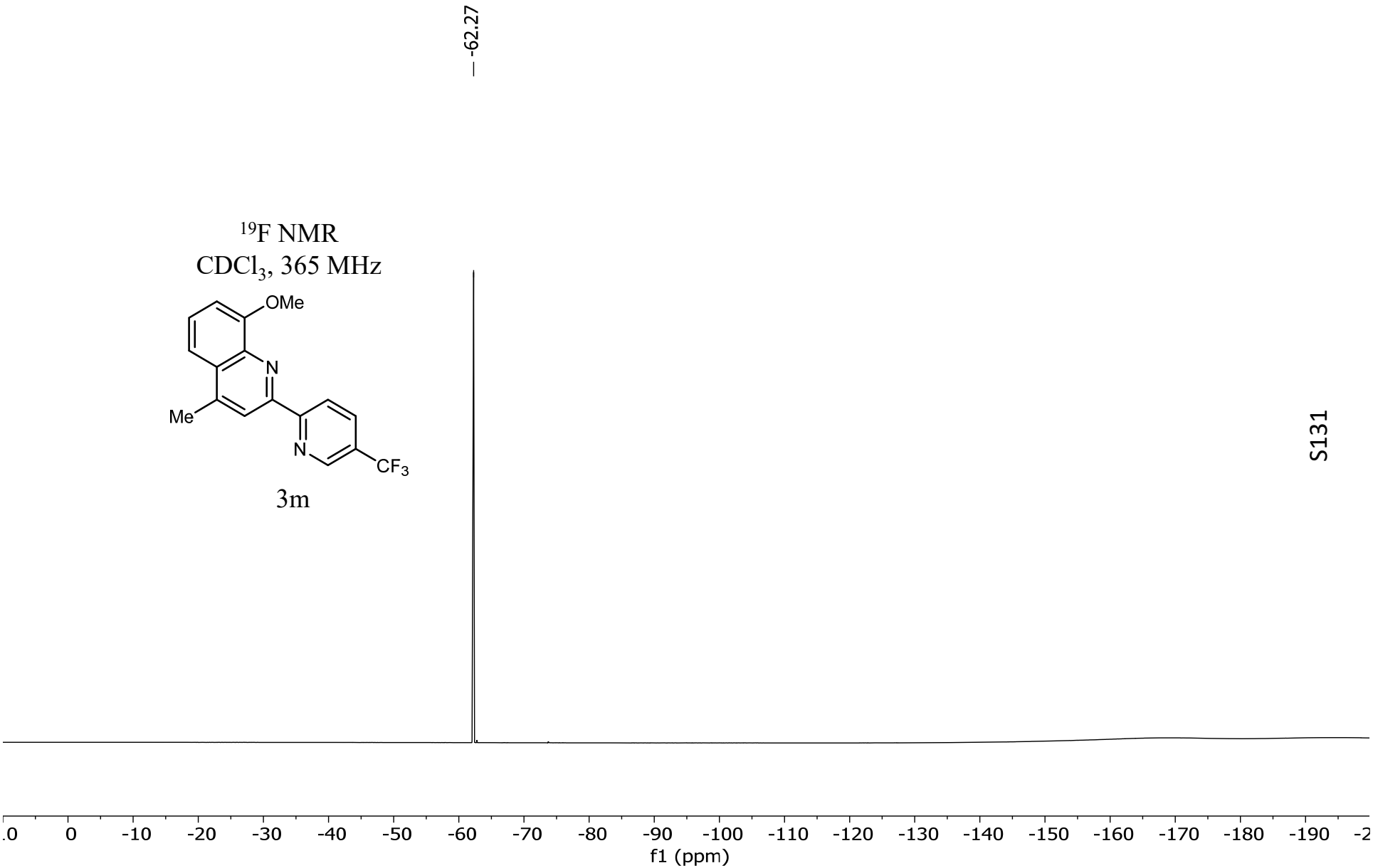
3l

$CDCl_3$

S128


8.96
8.96
8.96
8.96
8.85
8.83
8.48
8.47
8.47
8.47
8.09
8.08
8.08
8.08
8.07
8.06
8.06
8.06
7.63
7.62
7.60
7.60
7.55
7.53
7.53
7.51
7.26
7.12
7.11
7.10
7.09
4.13
2.80
2.80
1H NMR
CDCl3, 400 MHz
OMe
N
Me
N
CF3
3m
S129
CDCl3
1.00
1.02
1.01
1.05
1.04
1.05
1.05
3.23
3.21
f1 (ppm)

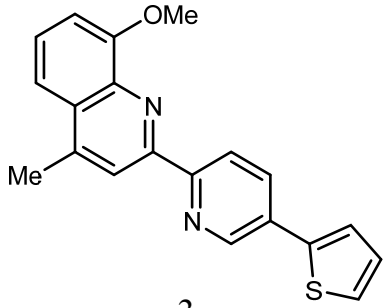

159.80
159.78
156.22
153.09
146.14
146.10
146.06
146.02
145.69
139.91
134.14
134.10
134.07
134.03
129.94
127.97
127.48
126.68
126.36
126.03
125.26
122.55
121.88
120.34
115.88
108.13
56.41
19.65
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
OMe
N
Me
N
CF_3
3m
S130
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


-62.27
19F NMR
CDCl3, 365 MHz
OMe
N
Me
N
CF3
3m
S131
.0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-2
f1 (ppm)

8.99 8.99 8.98 8.98 8.75 8.73 8.73 8.48 8.48 8.02 8.05 8.04 8.03 7.62 7.62 7.60 7.60 7.52 7.50 7.50 7.48 7.47 7.47 7.47 7.46 7.41 7.40 7.39 7.39 7.26 7.17 7.16 7.16 7.15 7.11 7.10 7.09 7.08 4.13 2.80 2.80

^{1}H NMR

$CDCl_3$, 400 MHz



3n

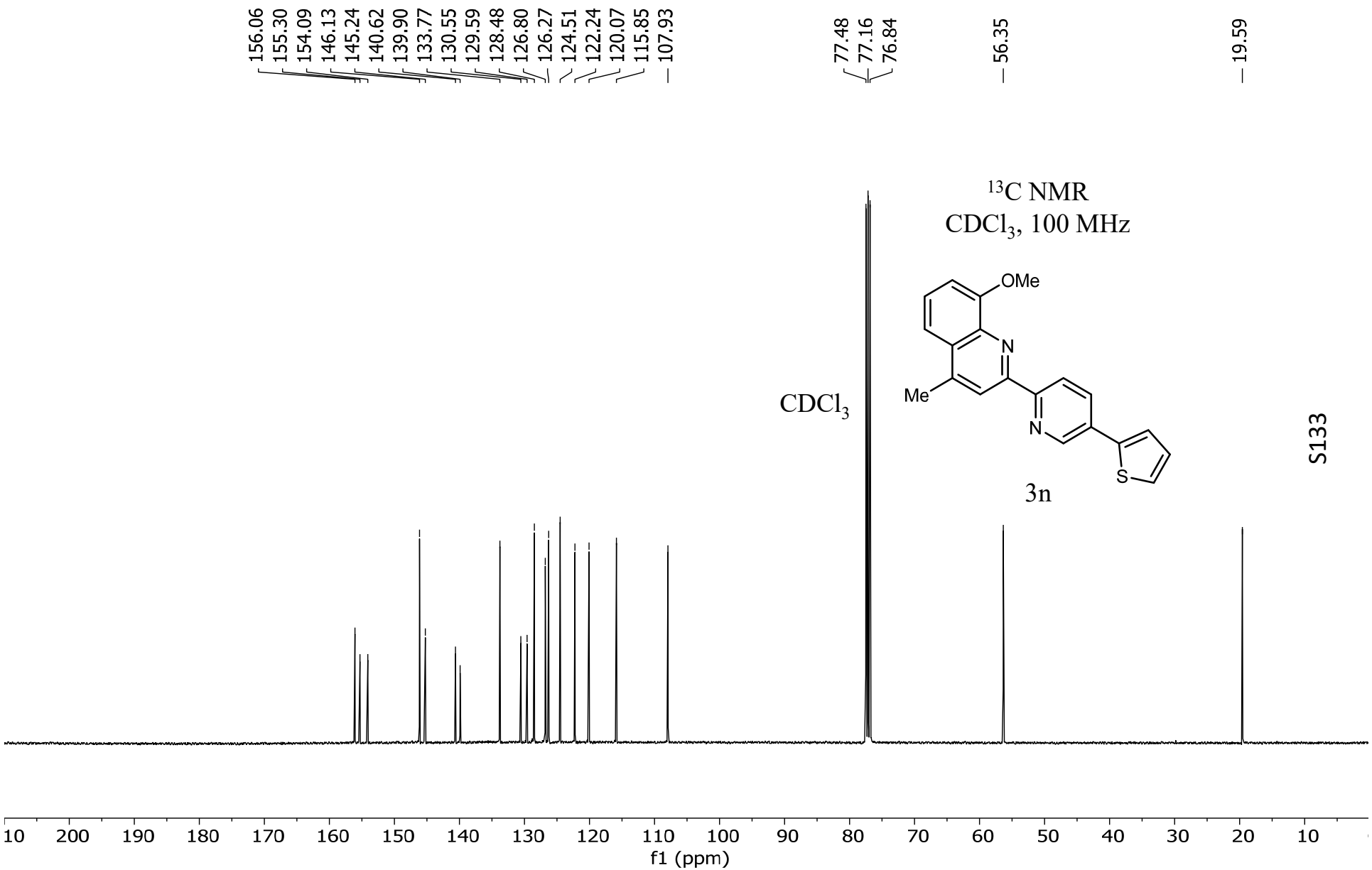
$CDCl_3$

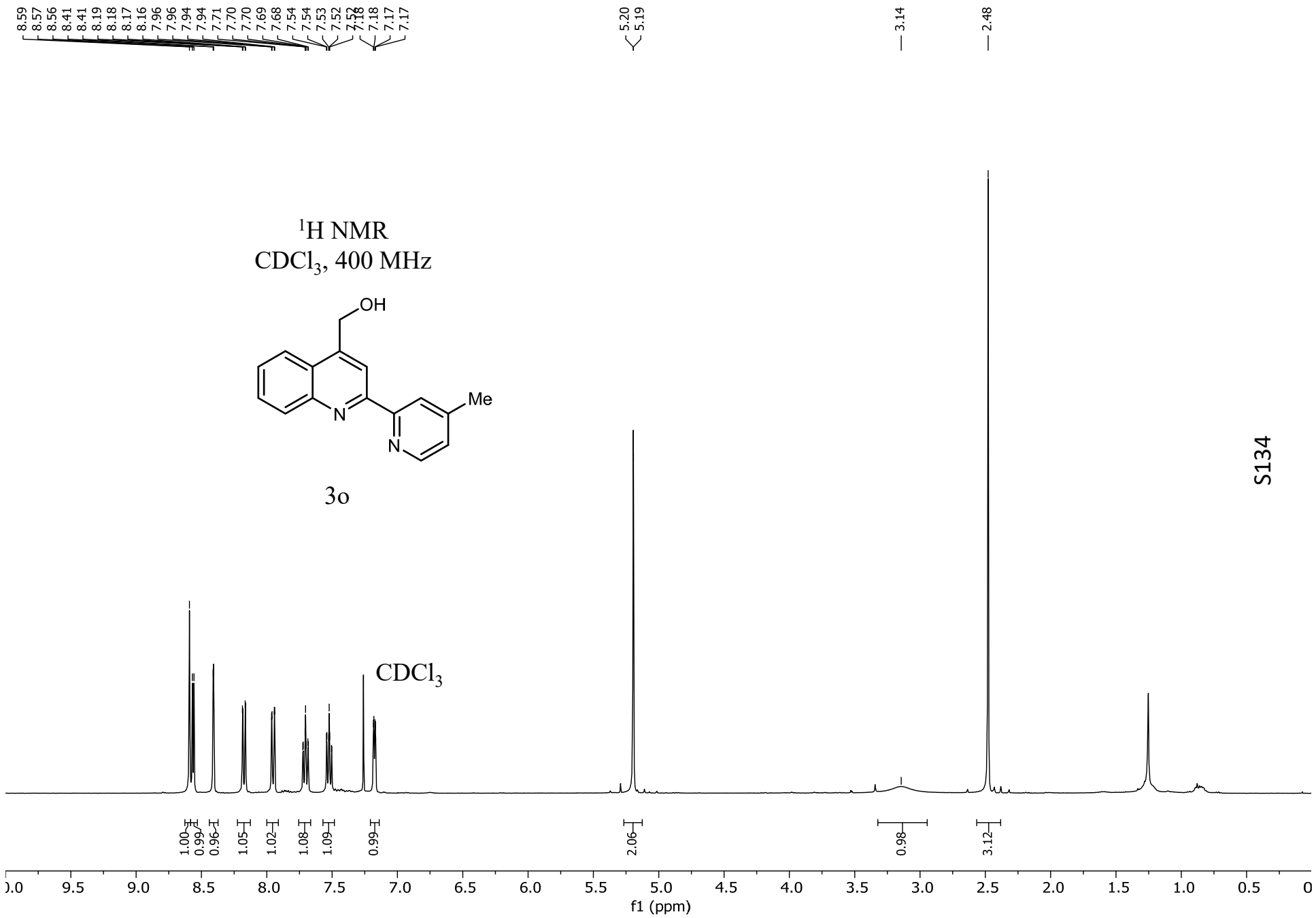
S132

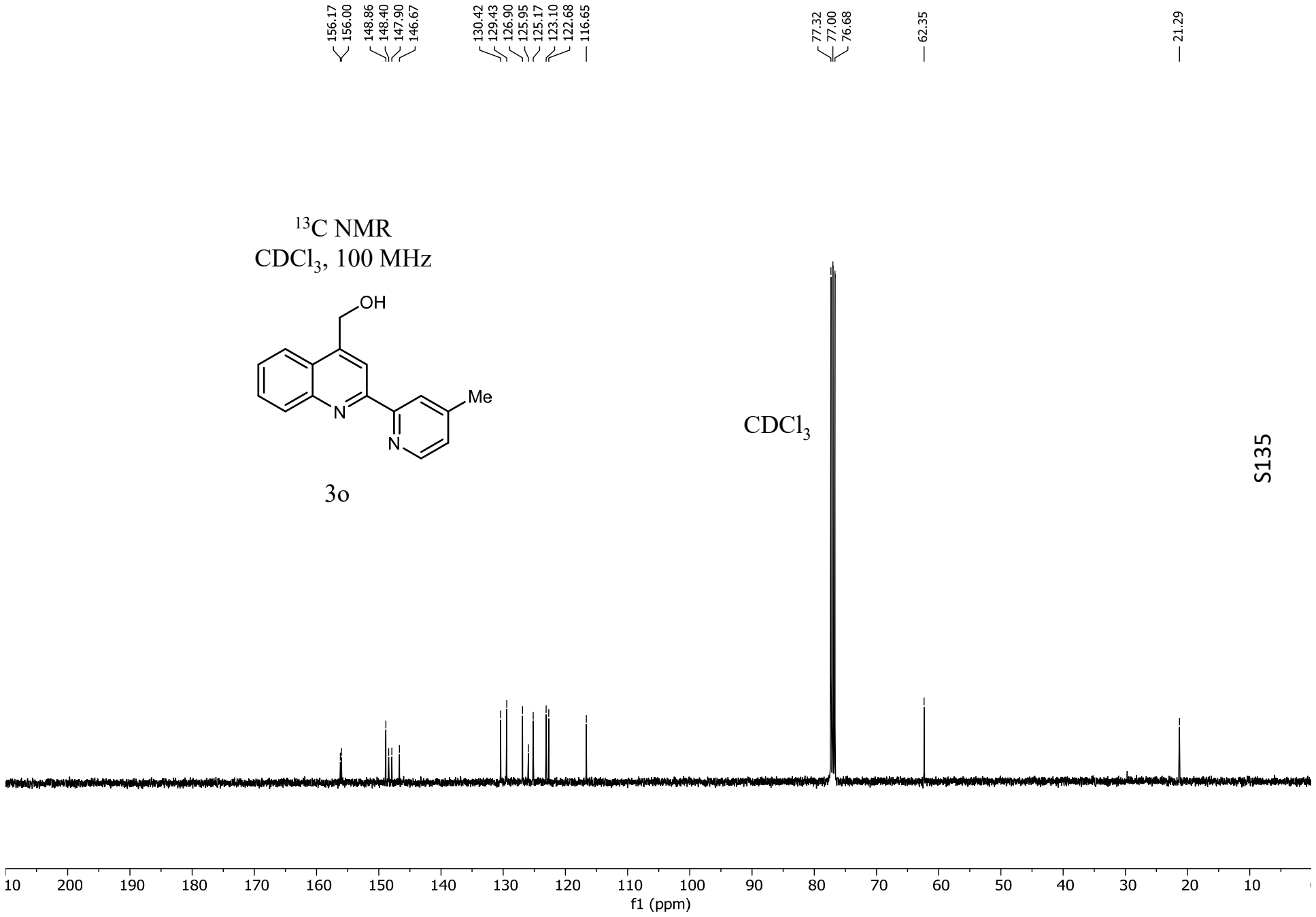
1.00 1.03 0.98 1.03 1.05 2.14 0.99 1.04 1.04 3.22 3.18

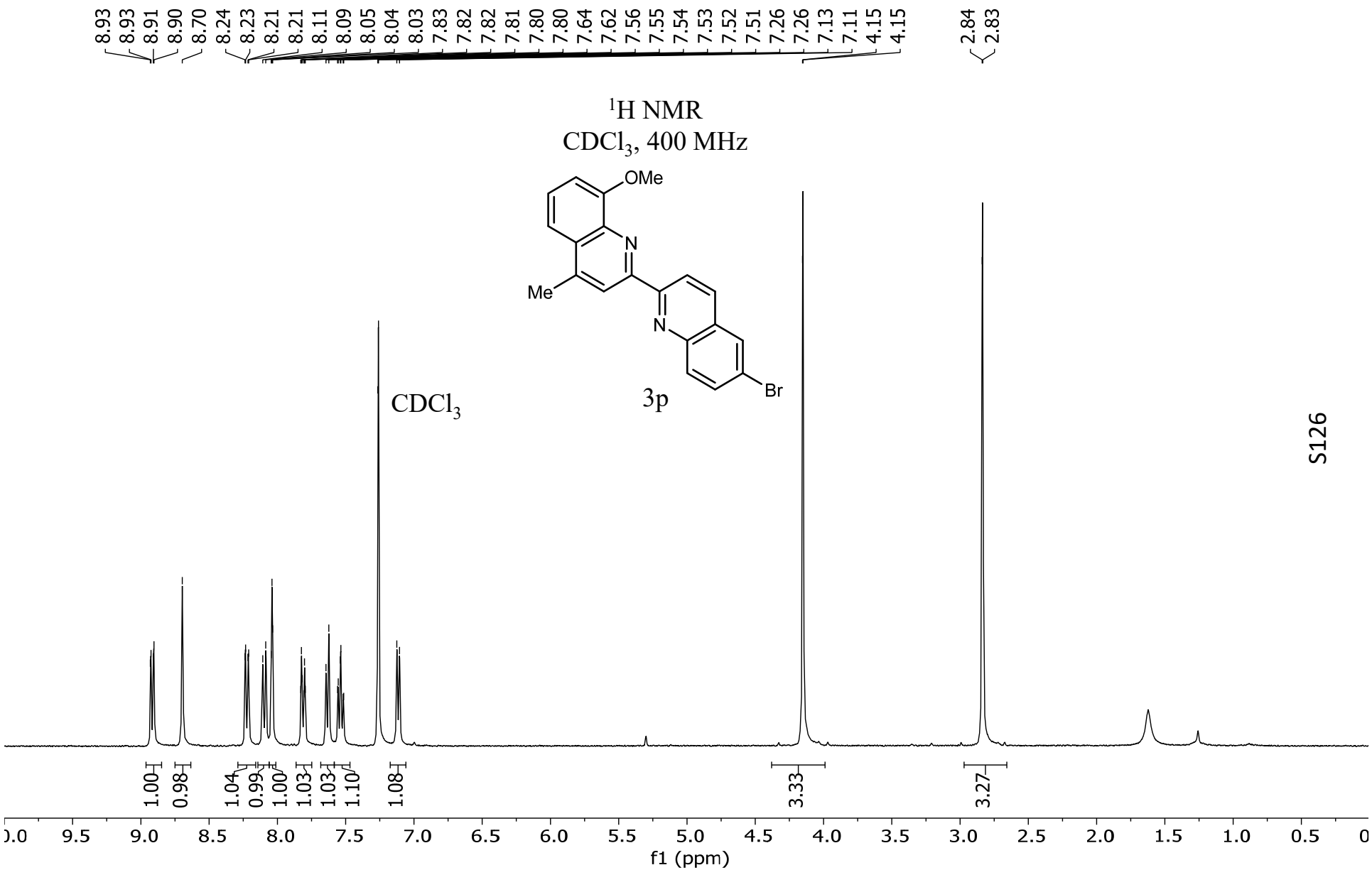
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

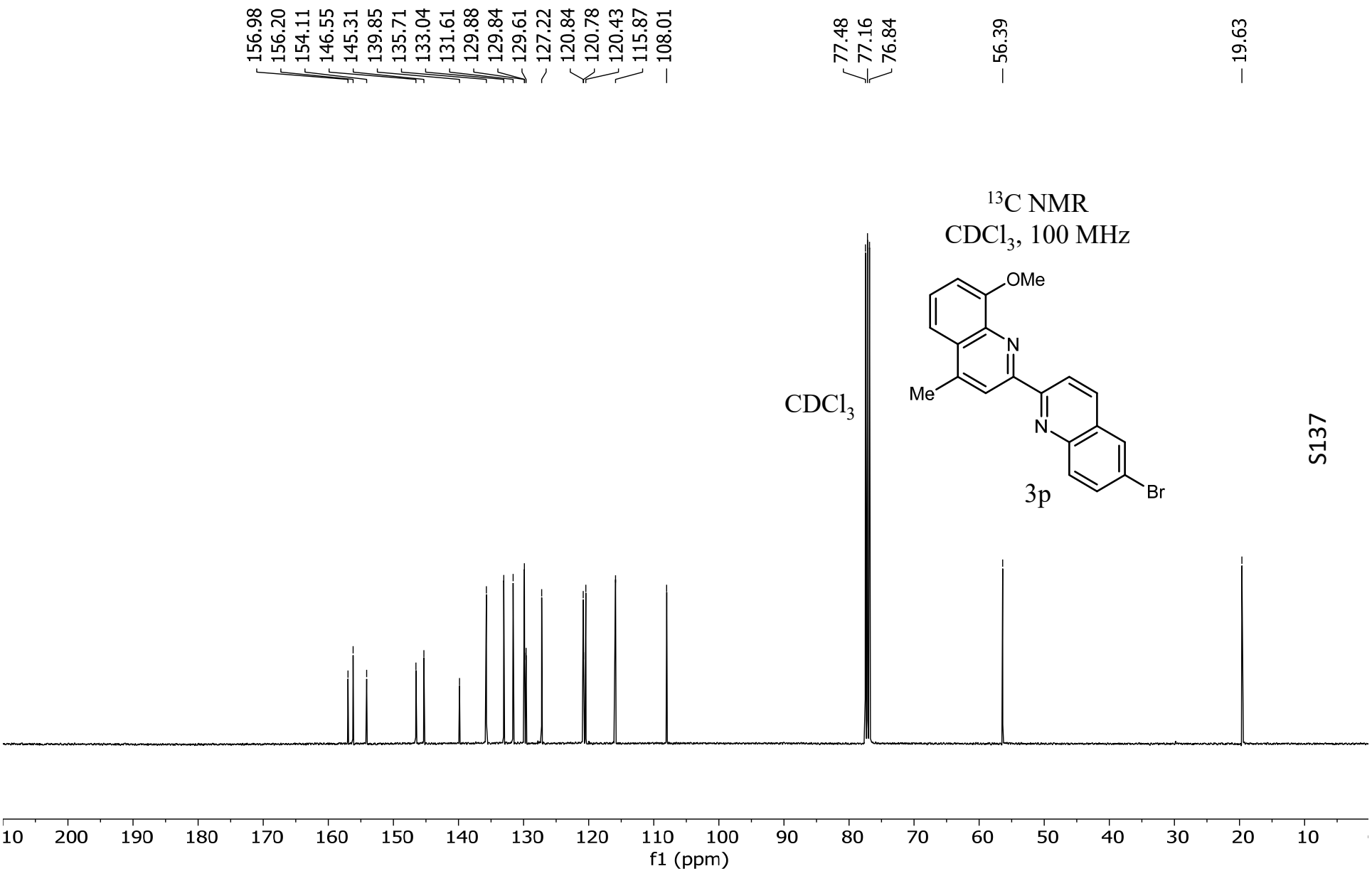
f1 (ppm)

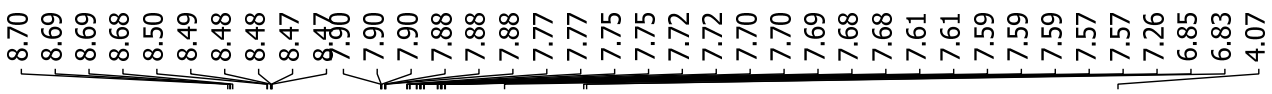

156.06
155.30
154.09
146.13
145.24
140.62
139.90
133.77
130.55
129.59
128.48
126.80
126.27
124.51
122.24
120.07
115.85
107.93
77.48
77.16
76.84
56.35
19.59
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
OMe
N
Me
N
S
3n
S133
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


8.59
8.57
8.56
8.41
8.41
8.19
8.18
8.17
8.16
7.96
7.96
7.94
7.94
7.71
7.70
7.70
7.69
7.68
7.54
7.54
7.53
7.52
7.52
7.18
7.18
7.17
7.17
5.20
5.19
3.14
2.48
^{1}H NMR
$CDCl_3$, 400 MHz
OH
Me
N
N
3o
$CDCl_3$
S134
1.00
0.99
0.96
1.05
1.02
1.08
1.09
0.99
2.06
0.98
3.12
f1 (ppm)


156.17
156.00
148.86
148.40
147.90
146.67
130.42
129.43
126.90
125.95
125.17
123.10
122.68
116.65
77.32
77.00
76.68
62.35
21.29
^{13}C NMR
$CDCl_3$, 100 MHz
OH
Me
N
N
3o
$CDCl_3$
S135
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

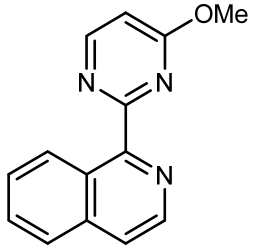

8.93
8.93
8.91
8.90
8.70
8.24
8.23
8.21
8.21
8.11
8.09
8.05
8.04
8.03
7.83
7.82
7.82
7.81
7.80
7.80
7.64
7.62
7.56
7.55
7.54
7.53
7.52
7.51
7.26
7.26
7.13
7.11
4.15
4.15
2.84
2.83
1H NMR
CDCl3, 400 MHz
OMe
N
Me
N
Br
3p
CDCl3
S126
1.00
0.98
1.04
0.99
1.00
1.03
1.03
1.10
1.08
3.33
3.27
f1 (ppm)


156.98
156.20
154.11
146.55
145.31
139.85
135.71
133.04
131.61
129.88
129.84
129.61
127.22
120.84
120.78
120.43
115.87
108.01
77.48
77.16
76.84
56.39
19.63
13C NMR
CDCl3, 100 MHz
CDCl3
OMe
N
Me
N
Br
3p
S137
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



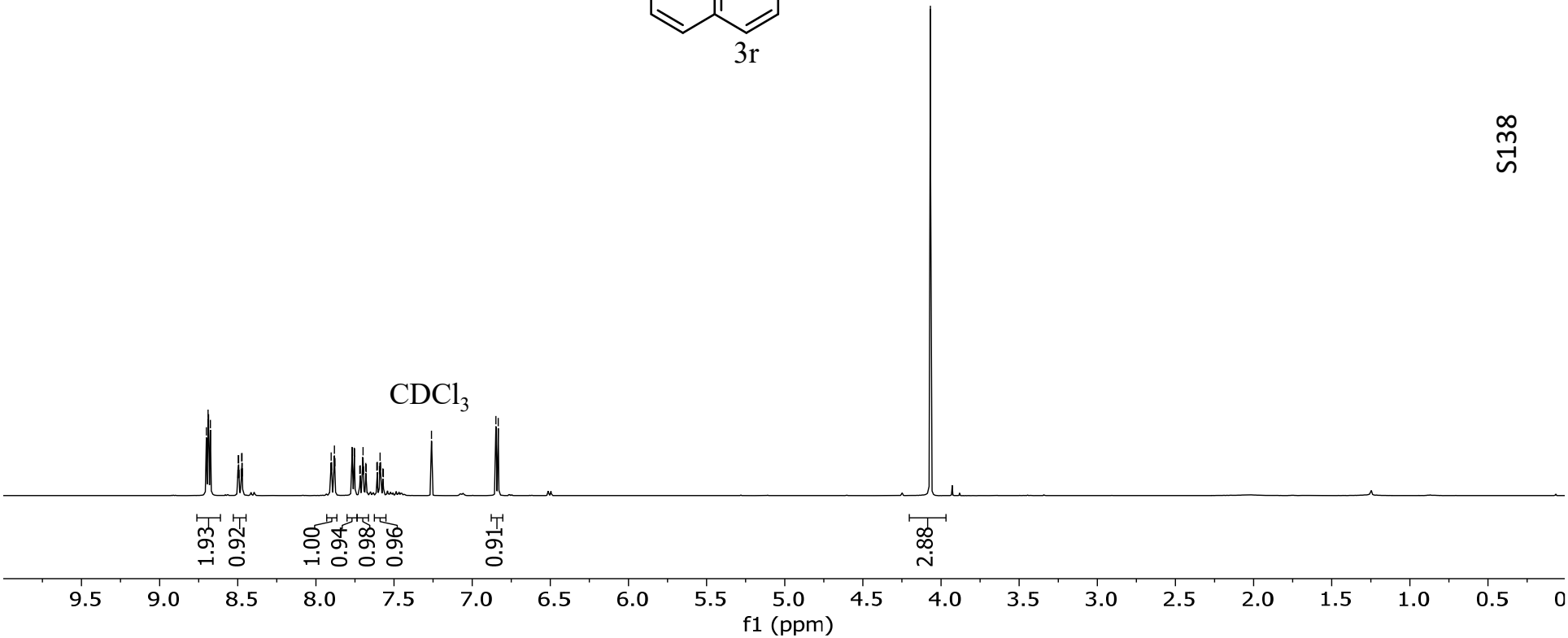
^{1}H NMR

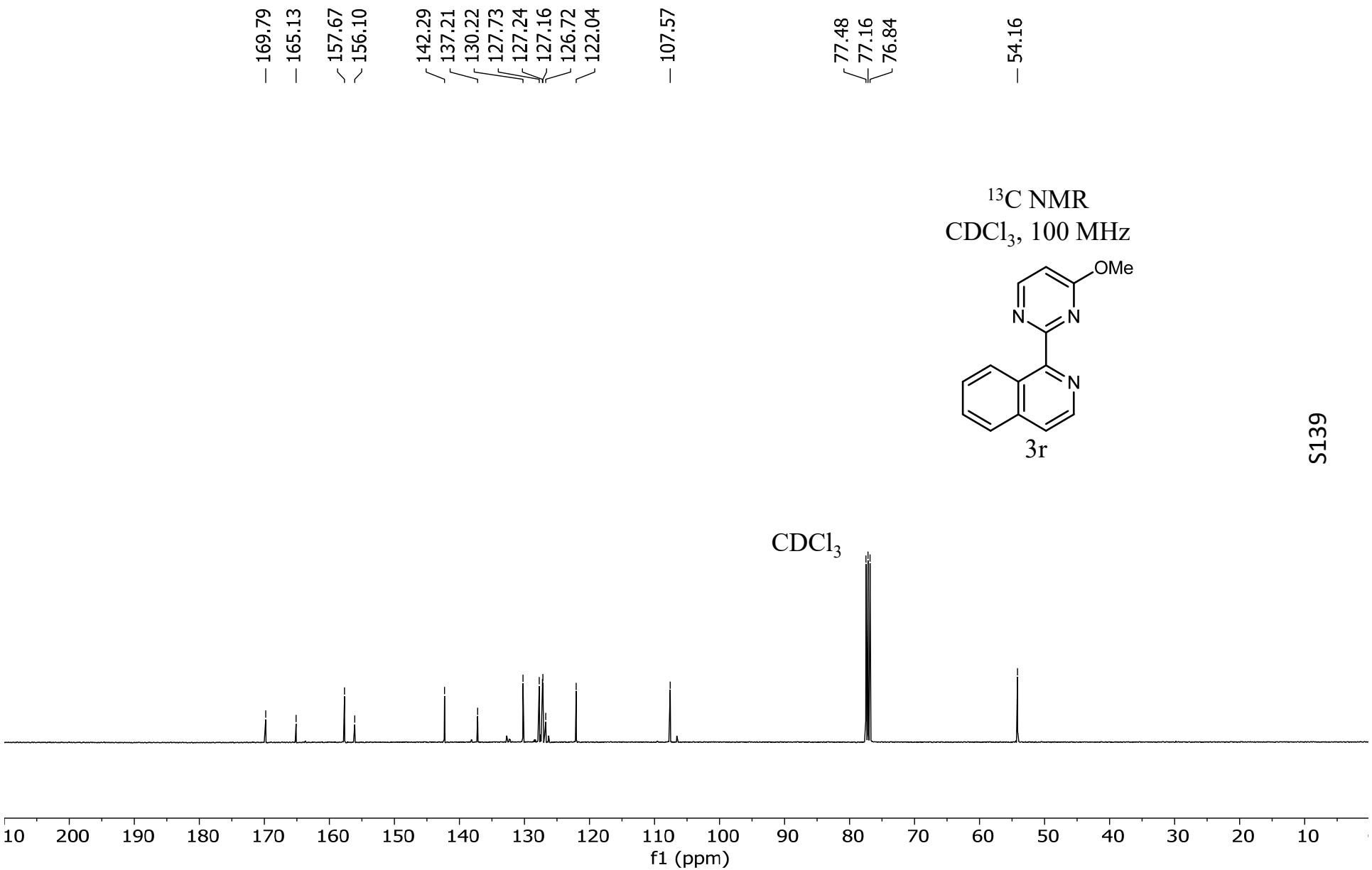
$CDCl_3$, 400 MHz

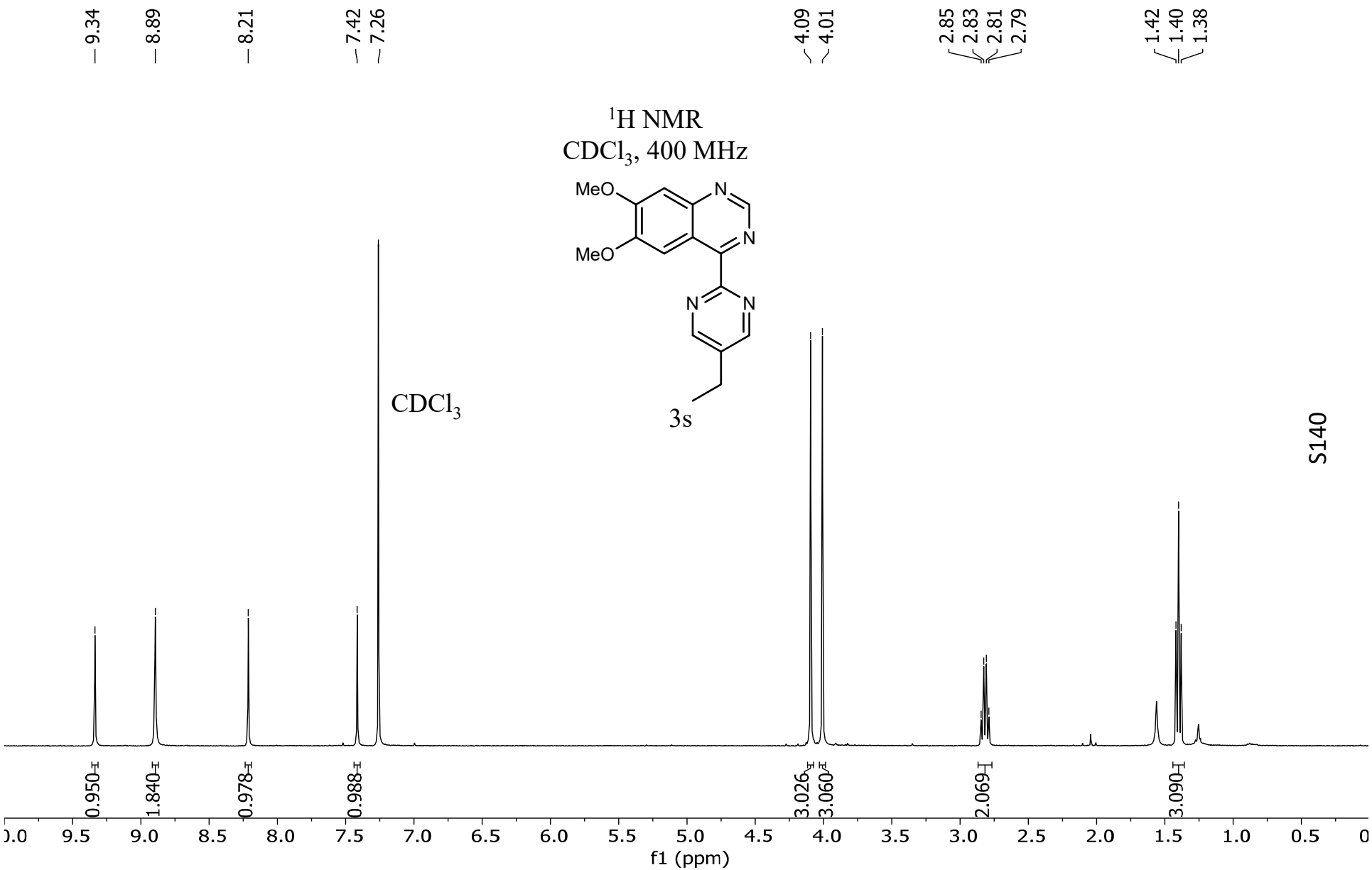


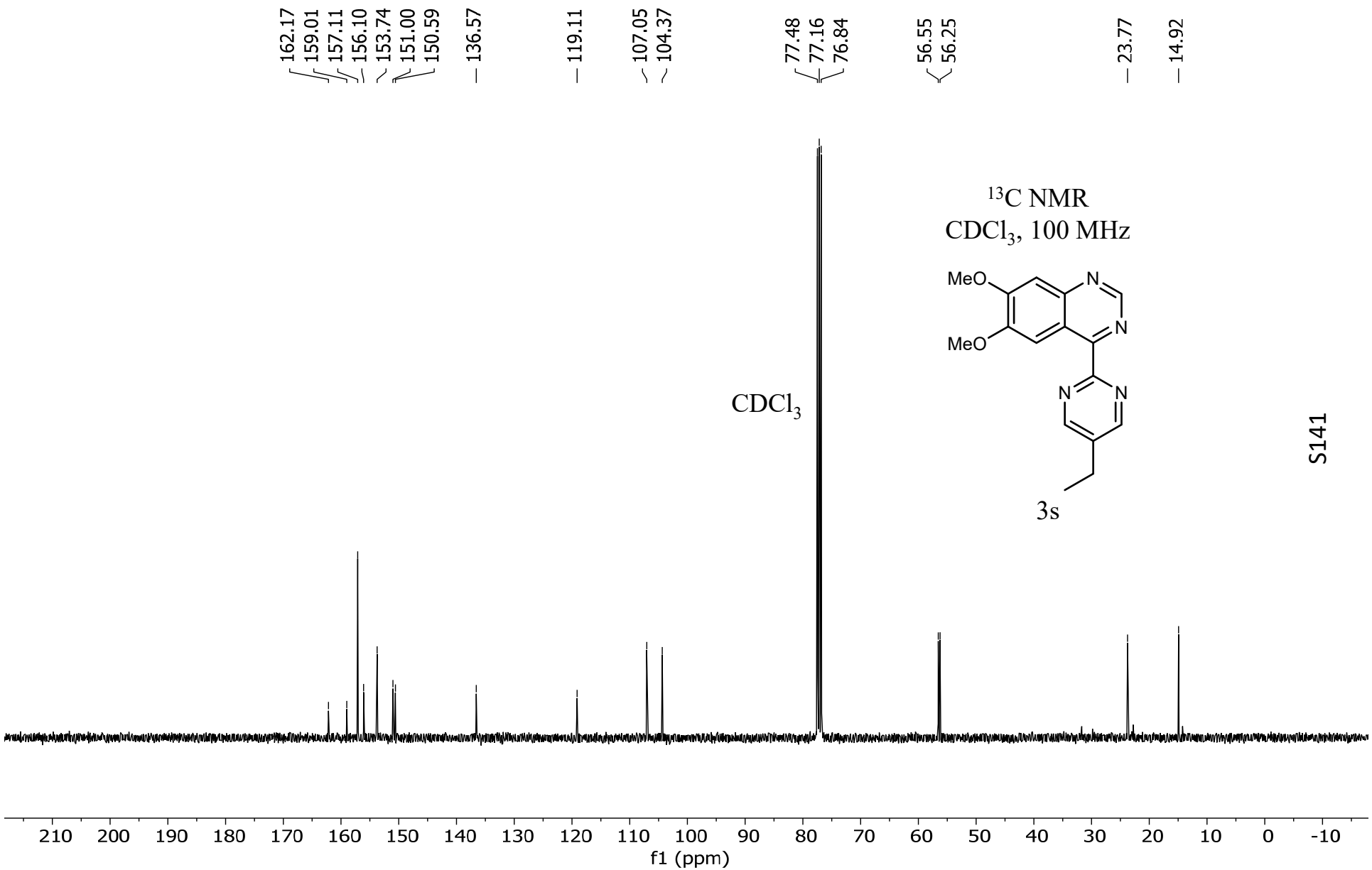
3r

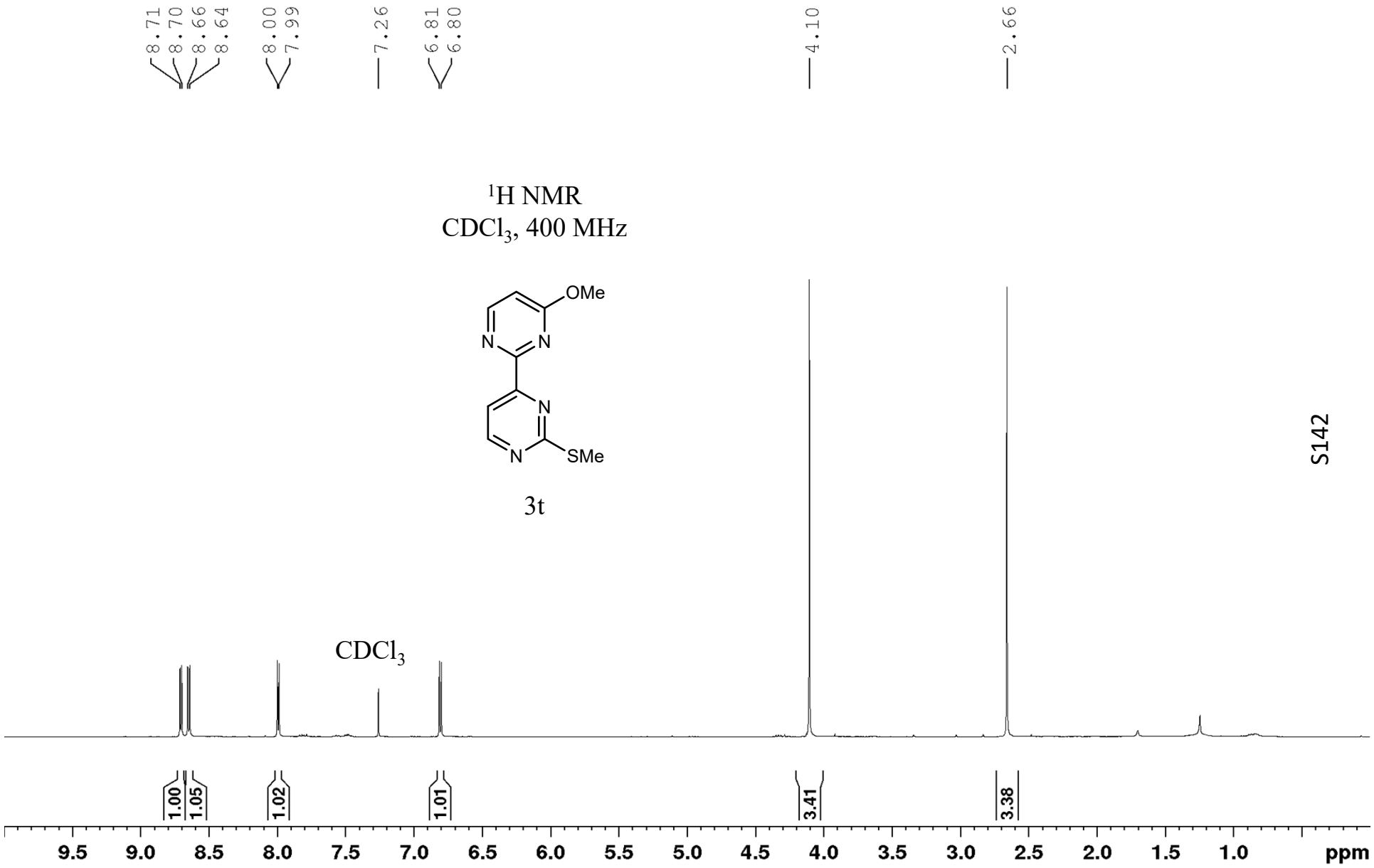
S138

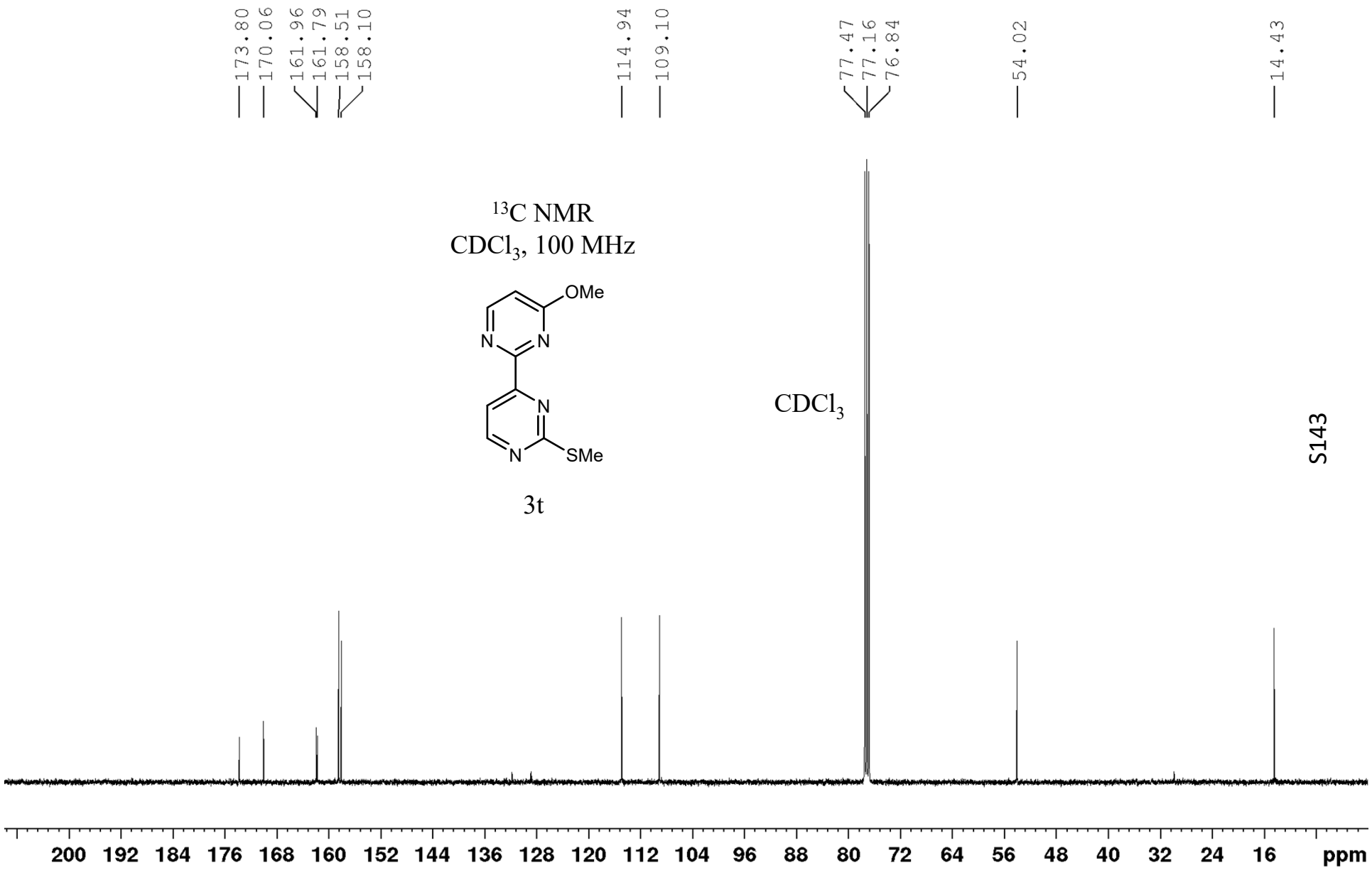


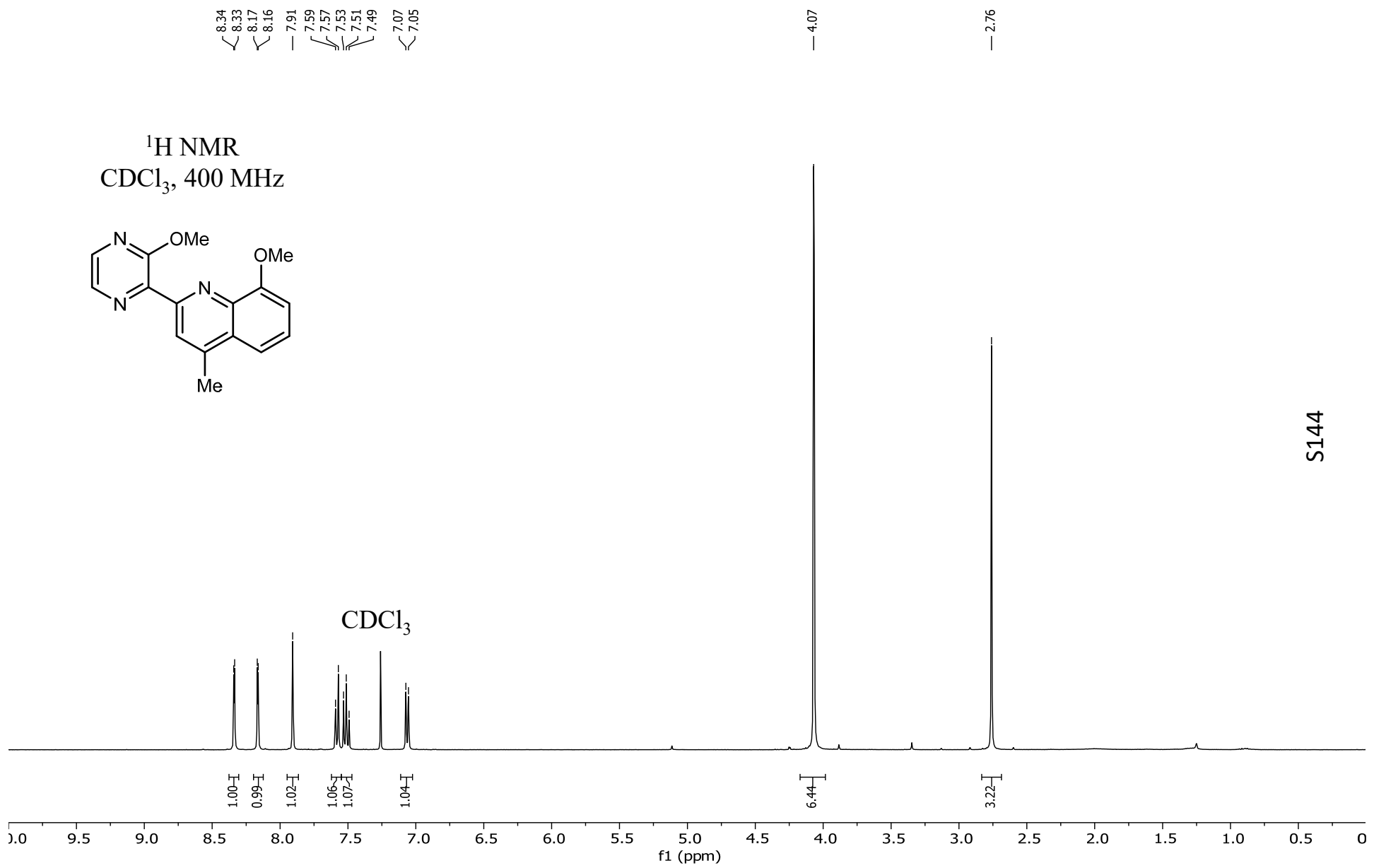

169.79
165.13
157.67
156.10
142.29
137.21
130.22
127.73
127.24
127.16
126.72
122.04
107.57
77.48
77.16
76.84
54.16
13C NMR
CDCl3, 100 MHz
OMe
N
N
N
3r
CDCl3
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


9.34
8.89
8.21
7.42
7.26
4.09
4.01
2.85
2.83
2.81
2.79
1.42
1.40
1.38
^{1}H NMR
$CDCl_3$, 400 MHz
MeO
MeO
N
N
N
N
$CDCl_3$
3s
S140
0.950
1.840
0.978
0.988
3.026
3.060
2.069
3.090
f1 (ppm)


162.17
159.01
157.11
156.10
153.74
151.00
150.59
136.57
119.11
107.05
104.37
77.48
77.16
76.84
56.55
56.25
23.77
14.92
^{13}C NMR
$CDCl_3$, 100 MHz
MeO
MeO
N
N
N
N
$CDCl_3$
3s
S141
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

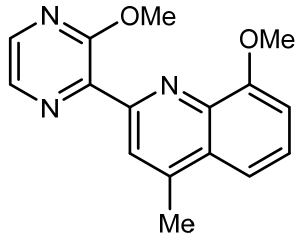

8.71
8.70
8.66
8.64
8.00
7.99
7.26
6.81
6.80
4.10
2.66
1H NMR
CDCl3, 400 MHz
OMe
N
N
N
N
SMe
3t
S142
CDCl3
1.00
1.05
1.02
1.01
3.41
3.38
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


173.80
170.06
161.96
161.79
158.51
158.10
114.94
109.10
77.47
77.16
76.84
54.02
14.43
13C NMR
CDCl3, 100 MHz
OMe
N
N
N
N
SMe
3t
CDCl3
S143
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm


8.34
8.33
8.17
8.16
7.91
7.59
7.57
7.53
7.51
7.49
7.07
7.05
4.07
2.76
1H NMR
CDCl3, 400 MHz
N
OMe
OMe
N
N
Me
CDCl3
S144
1.00
0.99
1.02
1.06
1.07
1.04
6.44
3.22
f1 (ppm)

158.84
156.26
152.76
144.39
142.92
140.56
139.94
136.61
128.88
127.11
122.98
115.24
107.54
77.32
77.00
76.68
55.98
54.02
19.45

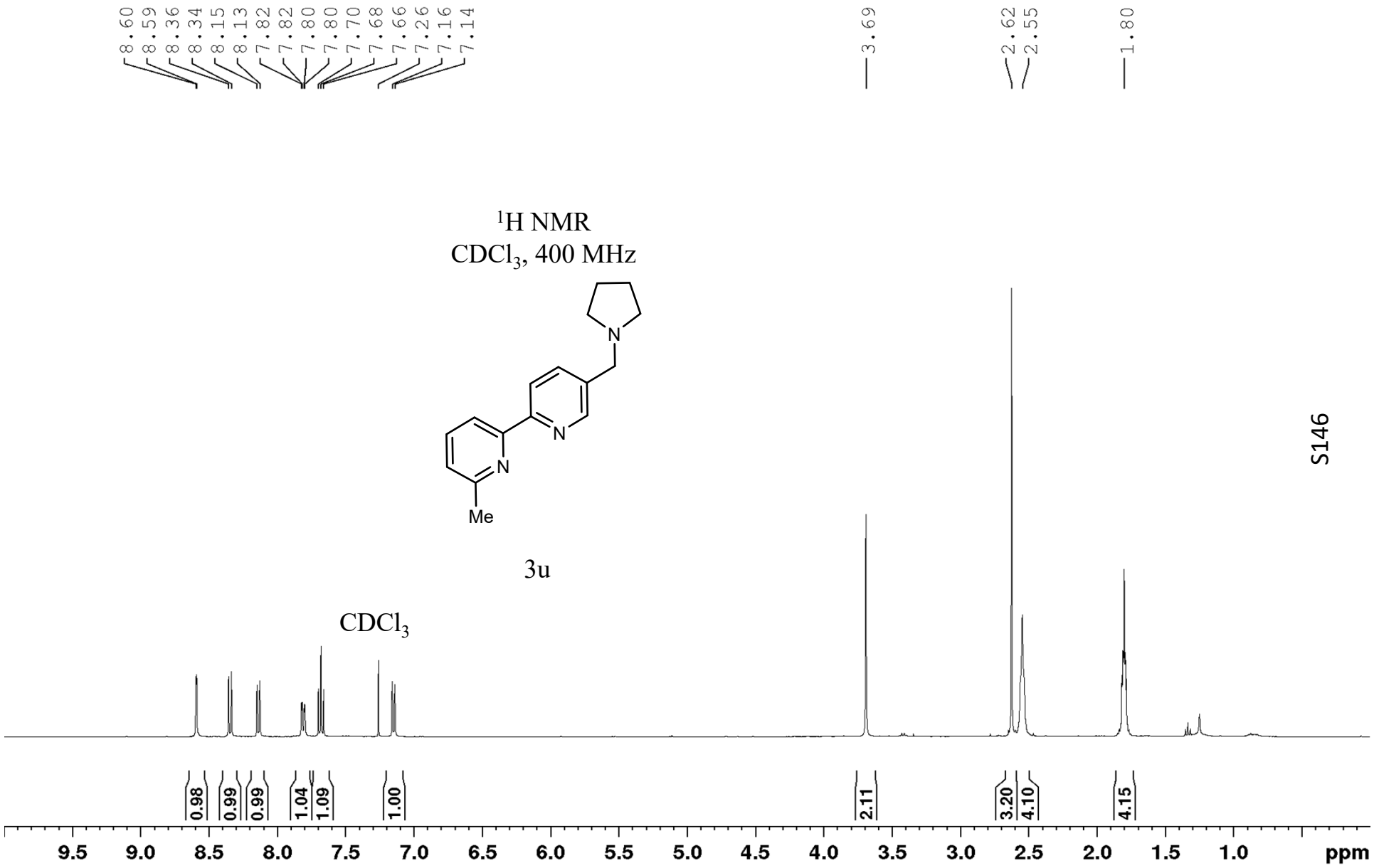
^{13}C NMR
$CDCl_3$, 100 MHz

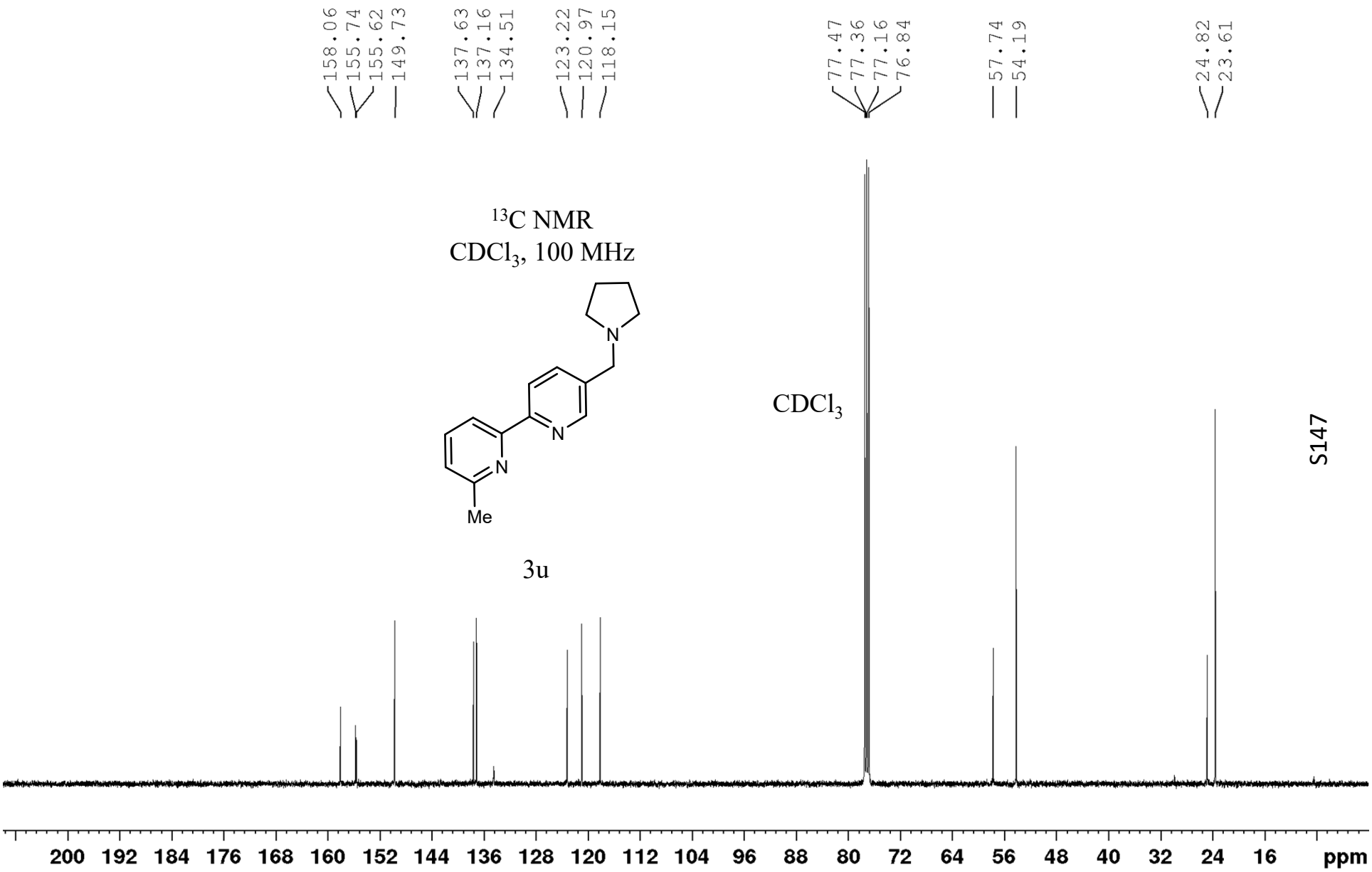


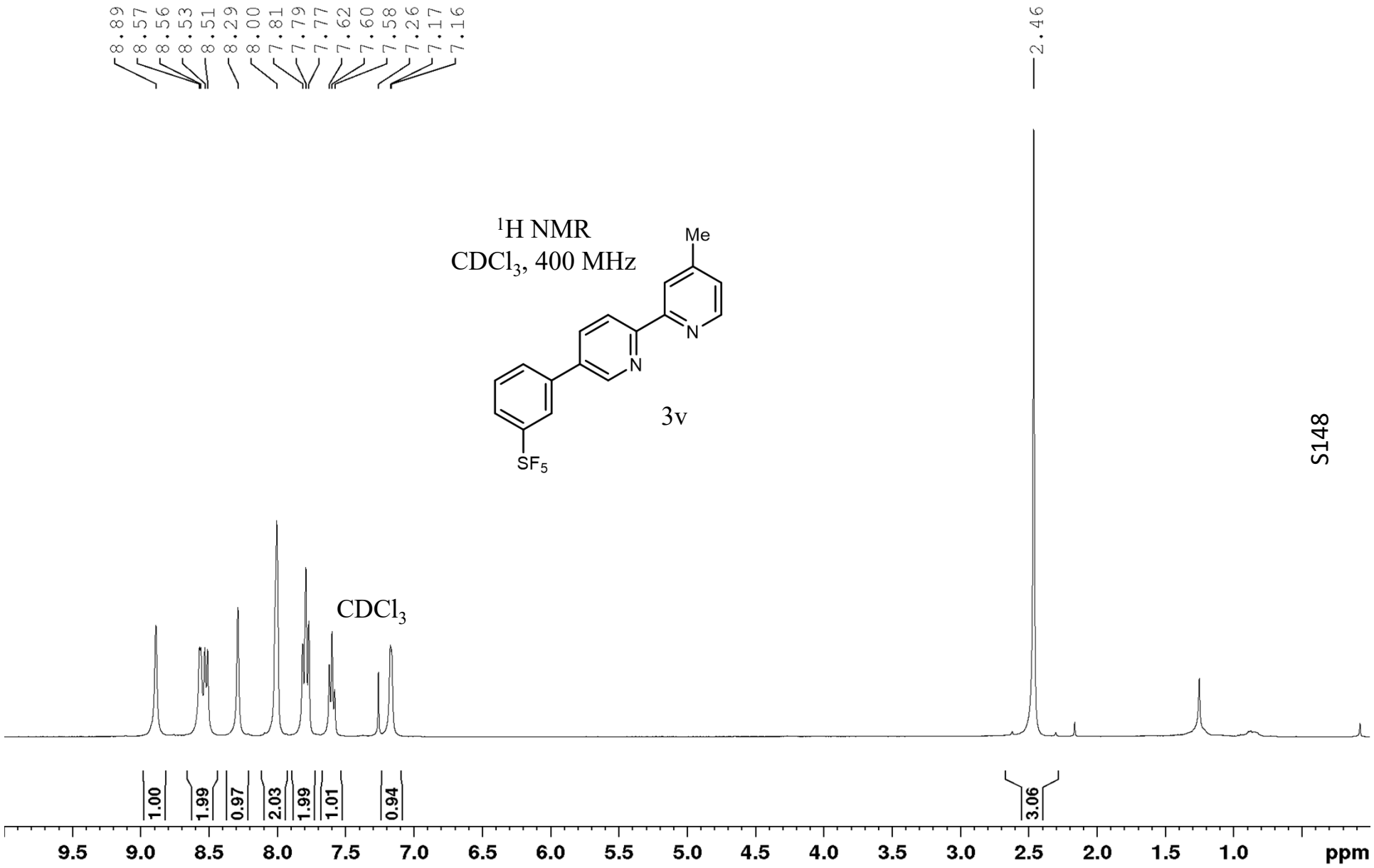
$CDCl_3$

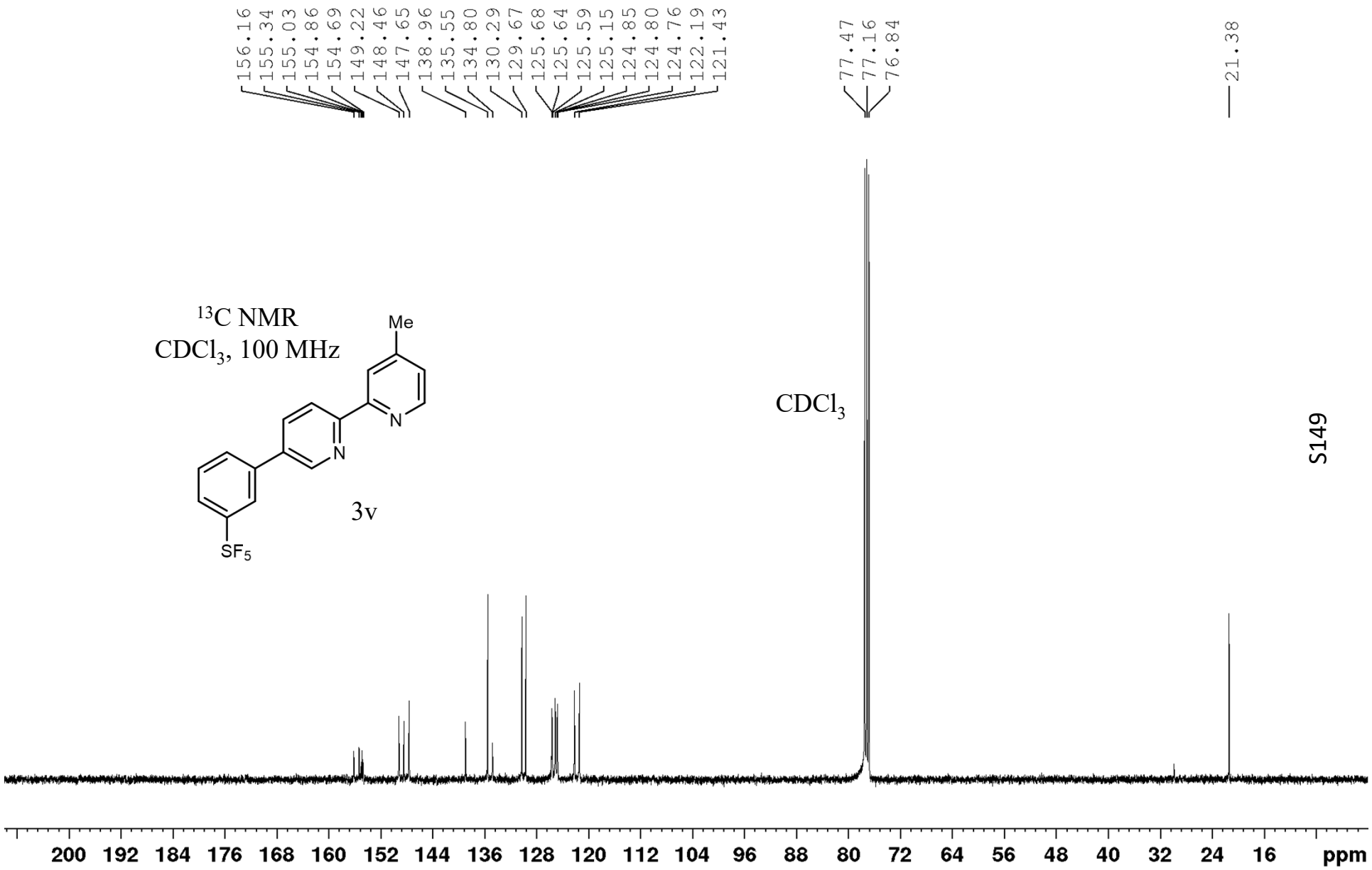
S145

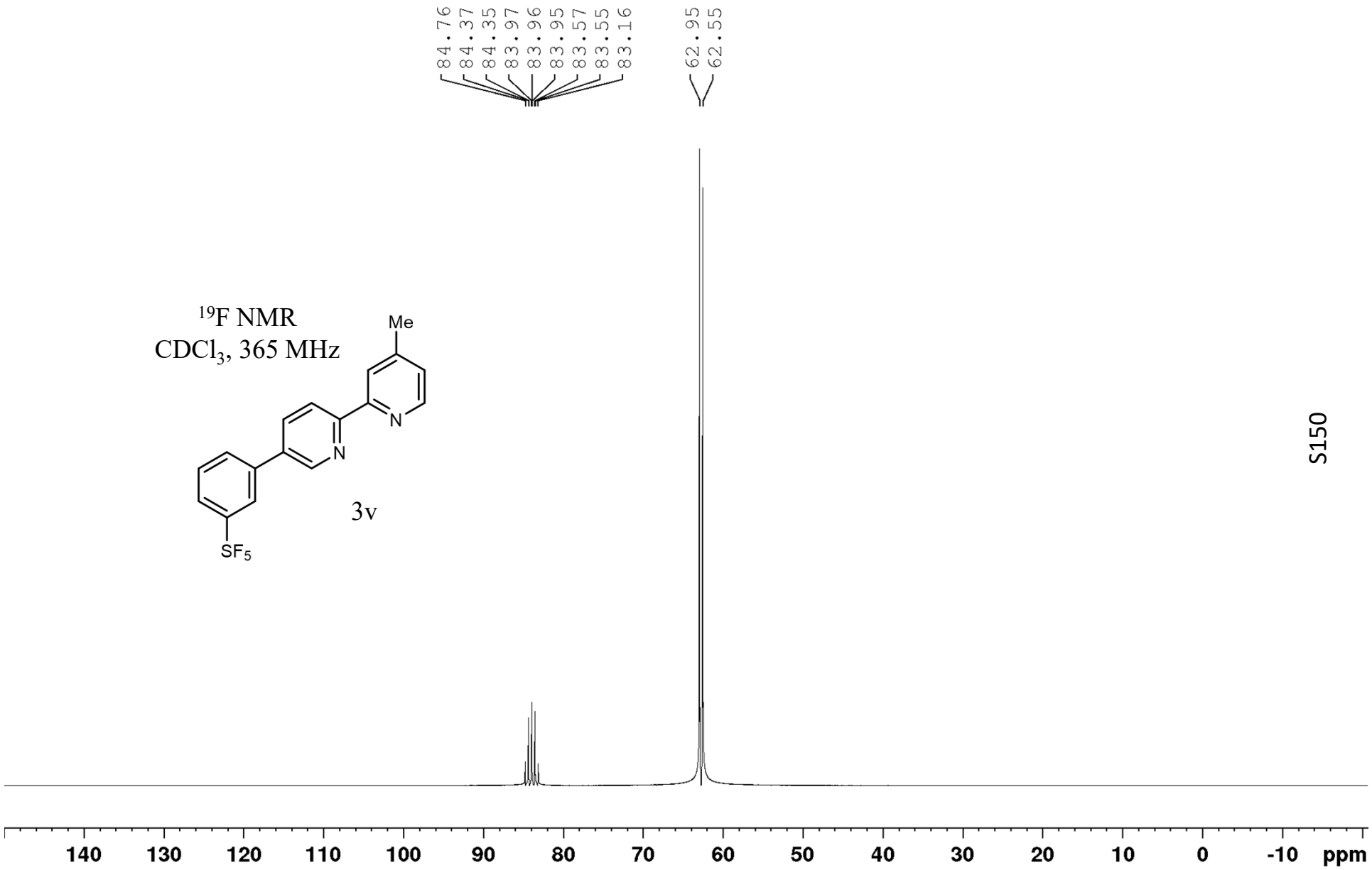
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

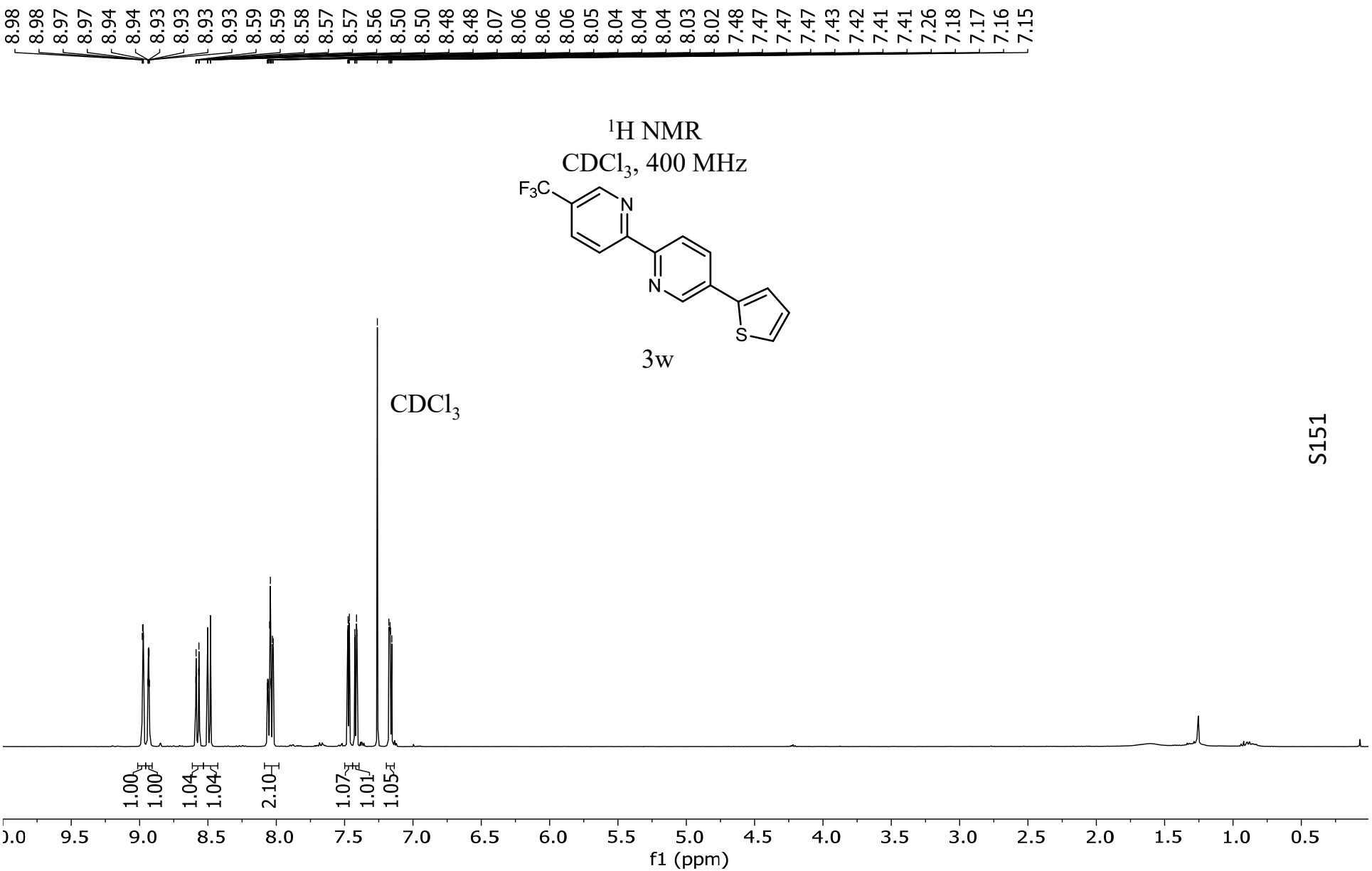

8.60
8.59
8.36
8.34
8.15
8.13
7.82
7.82
7.80
7.80
7.70
7.68
7.66
7.26
7.16
7.14
3.69
2.62
2.55
1.80
^{1}H NMR
$CDCl_3$, 400 MHz
N
N
N
Me
3u
$CDCl_3$
S146
0.98
0.99
0.99
1.04
1.09
1.00
2.11
3.20
4.10
4.15
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

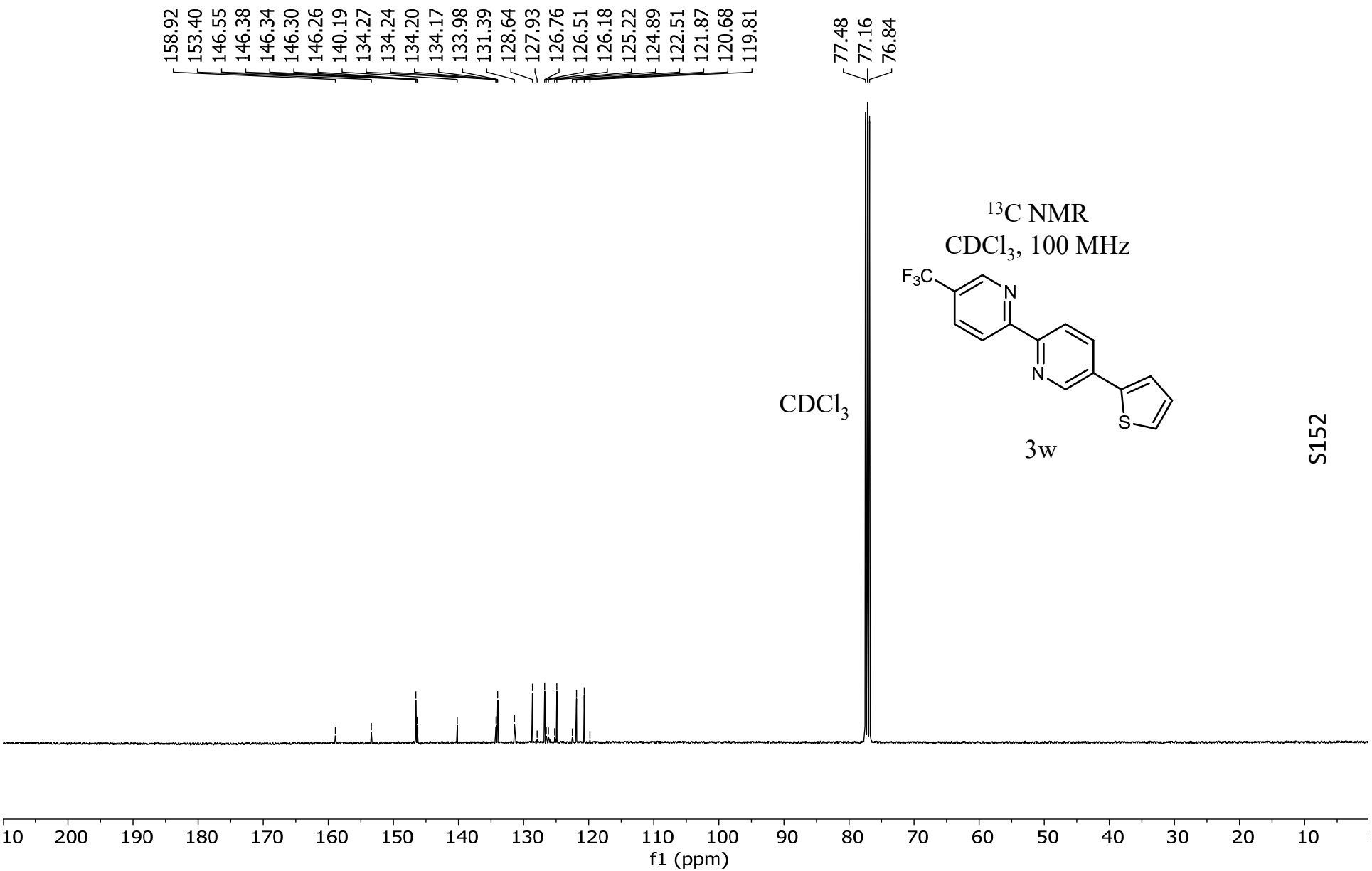

158.06
155.74
155.62
149.73
137.63
137.16
134.51
123.22
120.97
118.15
77.47
77.36
77.16
76.84
57.74
54.19
24.82
23.61
^{13}C NMR
$CDCl_3$, 100 MHz
N
N
N
Me
3u
$CDCl_3$
S147
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

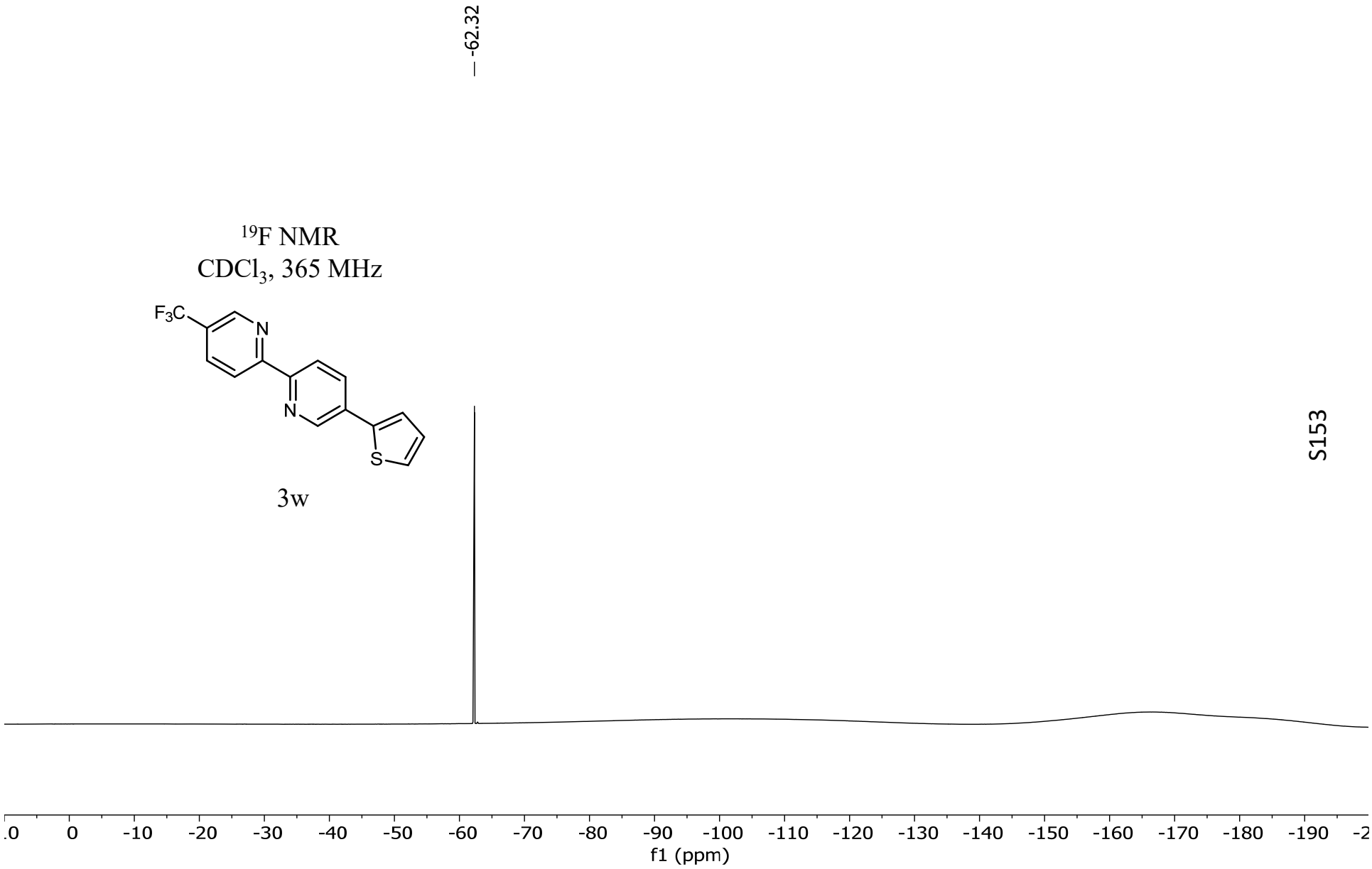

8.89
8.57
8.56
8.53
8.51
8.29
8.00
7.81
7.79
7.77
7.62
7.60
7.58
7.26
7.17
7.16
2.46
1H NMR
CDCl3, 400 MHz
Me
N
N
SF5
3v
S148
CDCl3
1.00
1.99
0.97
2.03
1.99
1.01
0.94
3.06
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

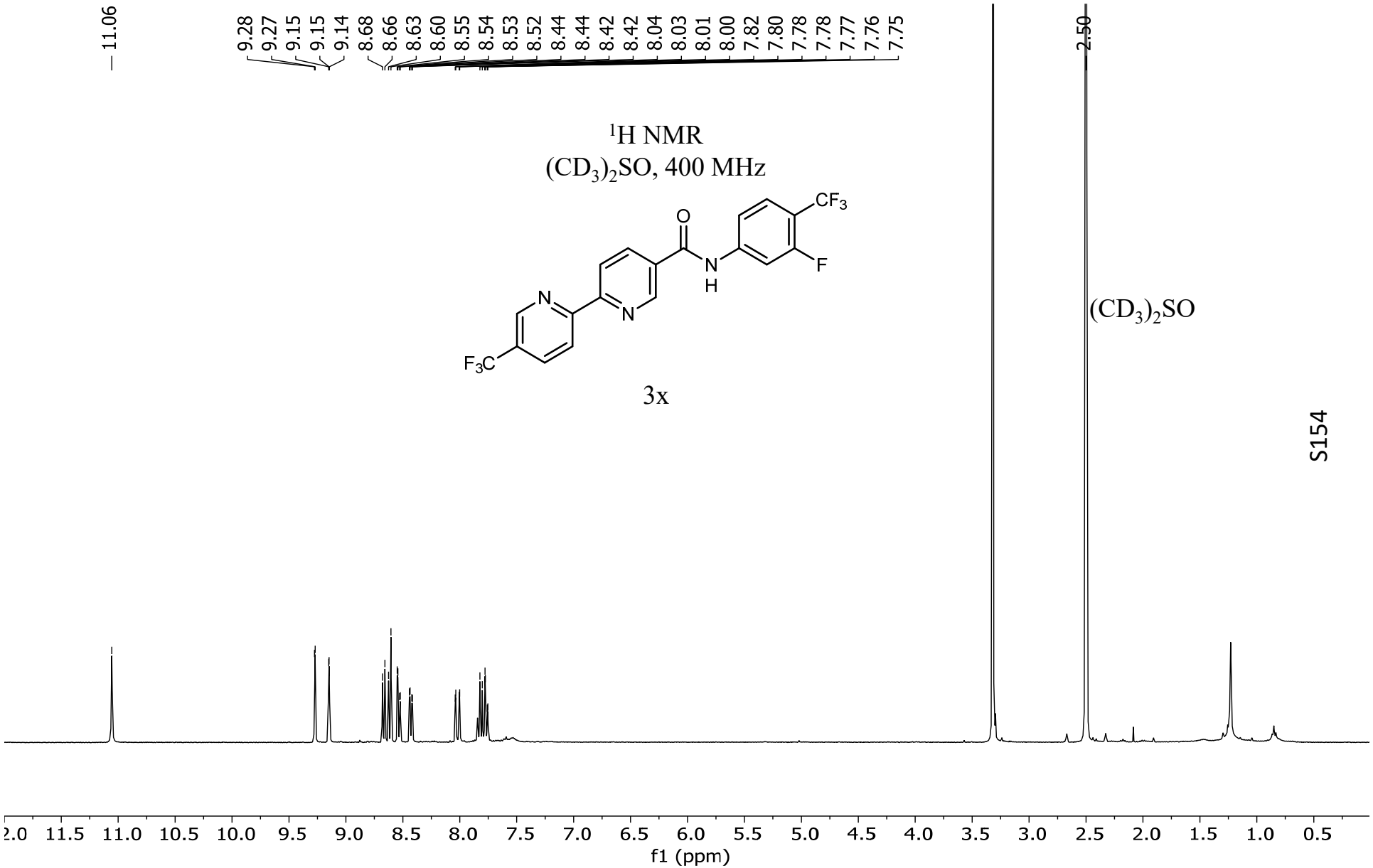

156.16
155.34
155.03
154.86
154.69
149.22
148.46
147.65
138.96
135.55
134.80
130.29
129.67
125.68
125.64
125.59
125.15
124.85
124.80
124.76
122.19
121.43
77.47
77.16
76.84
21.38
13C NMR
CDCl3, 100 MHz
Me
N
N
SF5
3v
CDCl3
S149
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 ppm

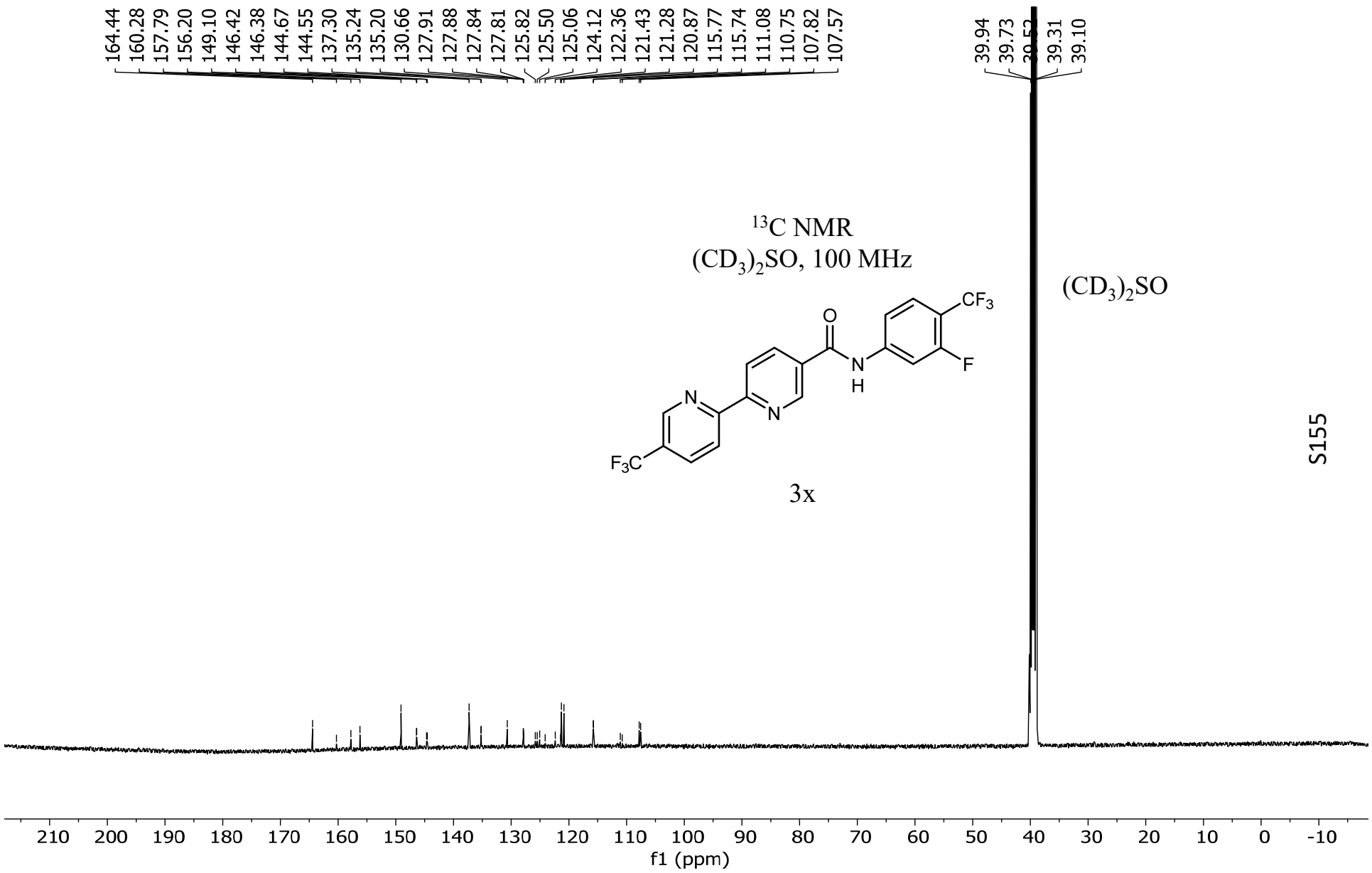

84.76
84.37
84.35
83.97
83.96
83.95
83.57
83.55
83.16
62.95
62.55
19F NMR
CDCl3, 365 MHz
Me
N
N
SF5
3v
S150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm

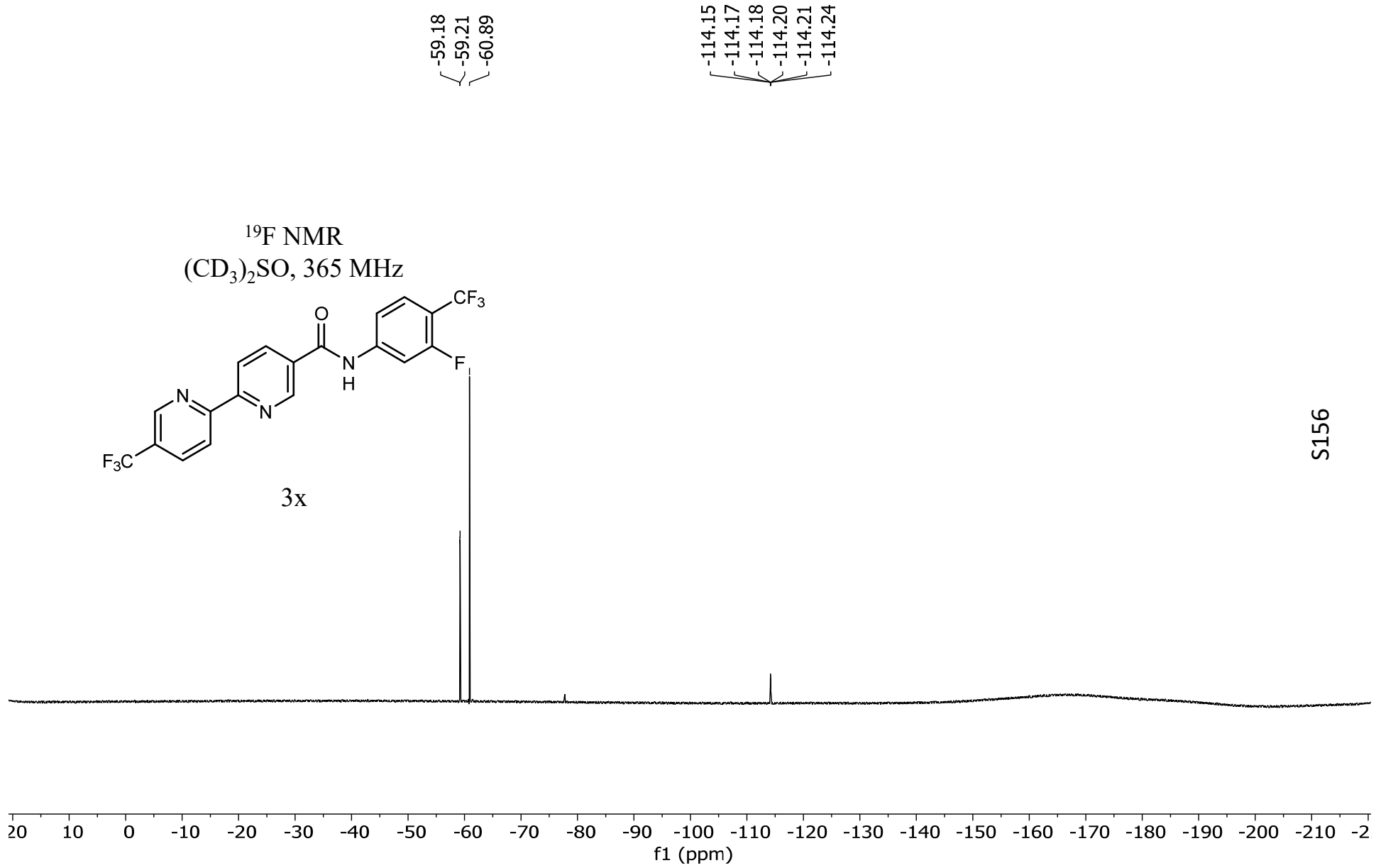

8.98
8.98
8.97
8.97
8.94
8.94
8.93
8.93
8.93
8.93
8.59
8.59
8.58
8.57
8.57
8.56
8.50
8.50
8.48
8.48
8.07
8.06
8.06
8.06
8.05
8.04
8.04
8.04
8.03
8.02
7.48
7.47
7.47
7.47
7.43
7.42
7.41
7.41
7.26
7.18
7.17
7.16
7.15
1H NMR
CDCl3, 400 MHz
F3C
N
N
S
3w
CDCl3
S151
1.00
1.00
1.04
1.04
2.10
1.07
1.01
1.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

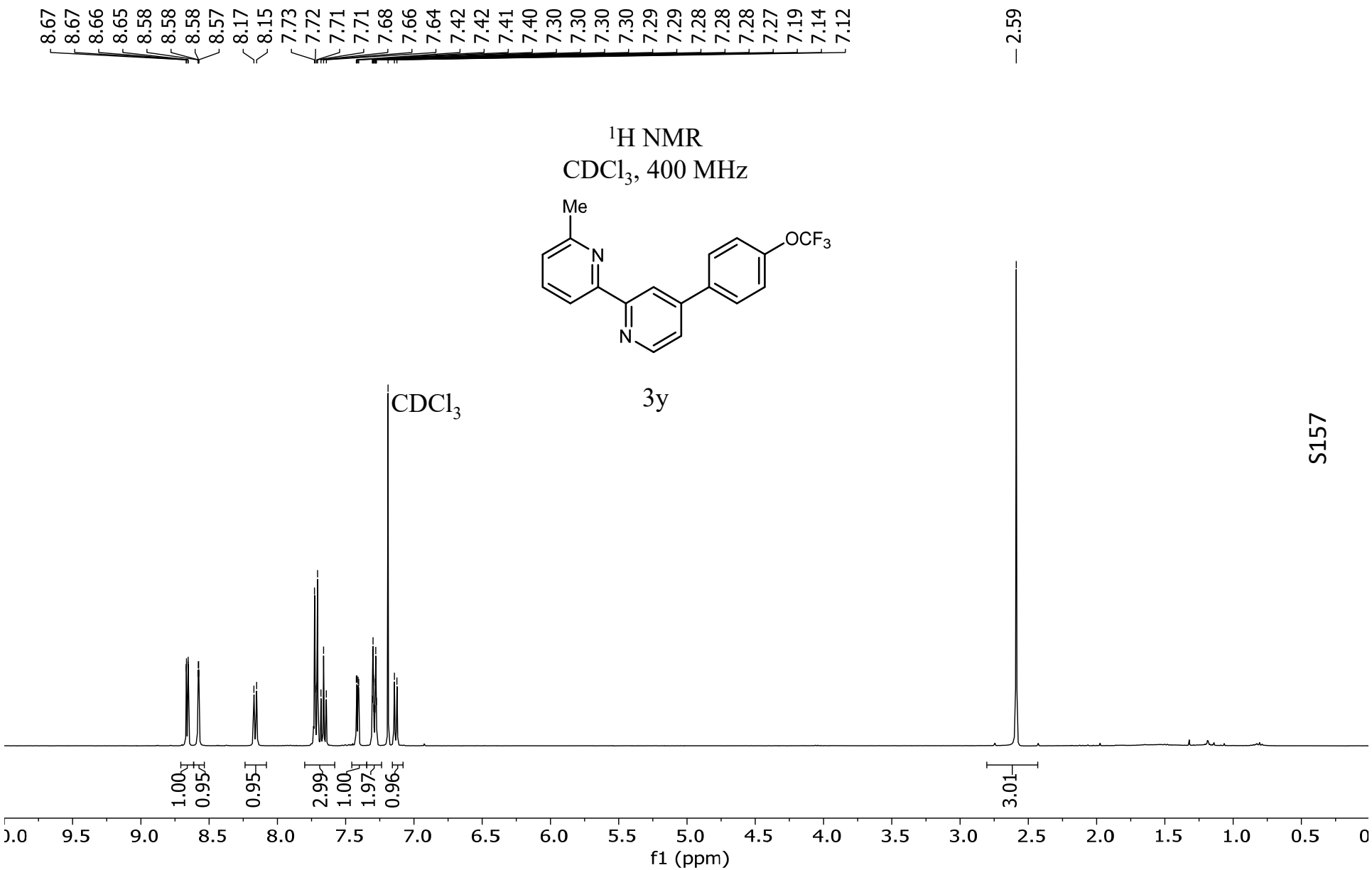

158.92
153.40
146.55
146.38
146.34
146.30
146.26
140.19
134.27
134.24
134.20
134.17
133.98
131.39
128.64
127.93
126.76
126.51
126.18
125.22
124.89
122.51
121.87
120.68
119.81
77.48
77.16
76.84
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
3w
S152
f1 (ppm)

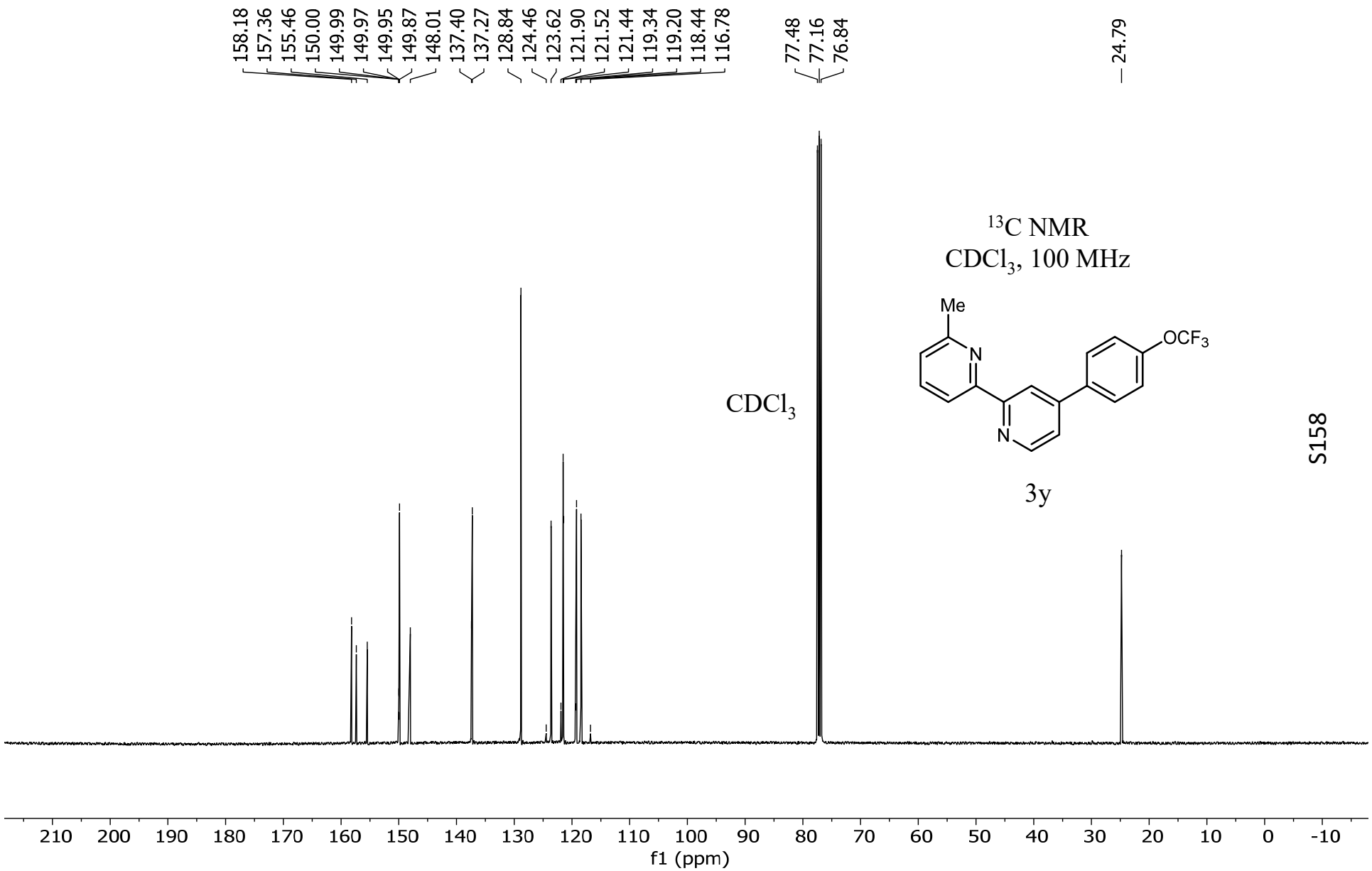

-62.32
^{19}F NMR
$CDCl_3$, 365 MHz
F_3C
N
N
S
3w
S153
.0
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-2
f1 (ppm)


11.06
9.28
9.27
9.15
9.15
9.14
8.68
8.66
8.63
8.60
8.55
8.54
8.53
8.52
8.44
8.44
8.42
8.42
8.04
8.03
8.01
8.00
7.82
7.80
7.78
7.78
7.77
7.76
7.75
2.50
1H NMR
(CD3)2SO, 400 MHz
CF3
O
N
H
F
N
N
F3C
3x
(CD3)2SO
S154
f1 (ppm)

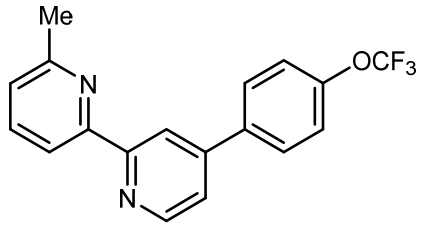

164.44
160.28
157.79
156.20
149.10
146.42
146.38
144.67
144.55
137.30
135.24
135.20
130.66
127.91
127.88
127.84
127.81
125.82
125.50
125.06
124.12
122.36
121.43
121.28
120.87
115.77
115.74
111.08
110.75
107.82
107.57
39.94
39.73
39.52
39.31
39.10
^{13}C NMR
$(CD_3)_2SO$, 100 MHz
$(CD_3)_2SO$
S155
3x
f1 (ppm)


-59.18
-59.21
-60.89
-114.15
-114.17
-114.18
-114.20
-114.21
-114.24
19F NMR
(CD3)2SO, 365 MHz
CF3
O
N
H
F
N
N
F3C
3x
S156
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -2
f1 (ppm)

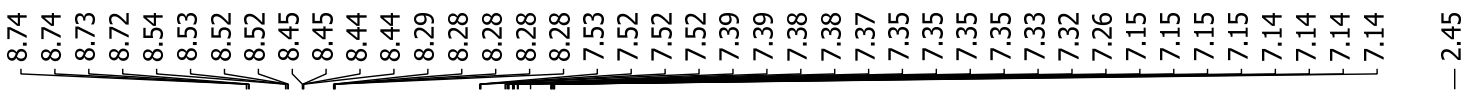

8.67
8.67
8.66
8.65
8.58
8.58
8.58
8.57
8.17
8.15
7.73
7.72
7.71
7.71
7.68
7.66
7.64
7.42
7.42
7.41
7.40
7.30
7.30
7.30
7.30
7.29
7.29
7.28
7.28
7.28
7.27
7.19
7.14
7.12
2.59
1H NMR
CDCl3, 400 MHz
Me
N
N
OCF3
3y
CDCl3
S157
1.00
0.95
0.95
2.99
1.00
1.97
0.96
3.01
f1 (ppm)


158.18
157.36
155.46
150.00
149.99
149.97
149.95
149.87
148.01
137.40
137.27
128.84
124.46
123.62
121.90
121.52
121.44
119.34
119.20
118.44
116.78
77.48
77.16
76.84
24.79
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
Me
N
N
OCF_3
3y
S158
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

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

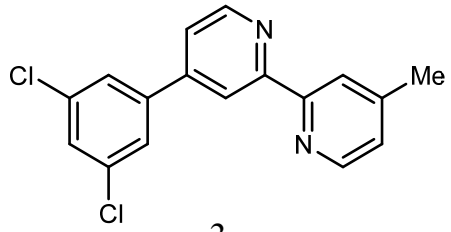


3y



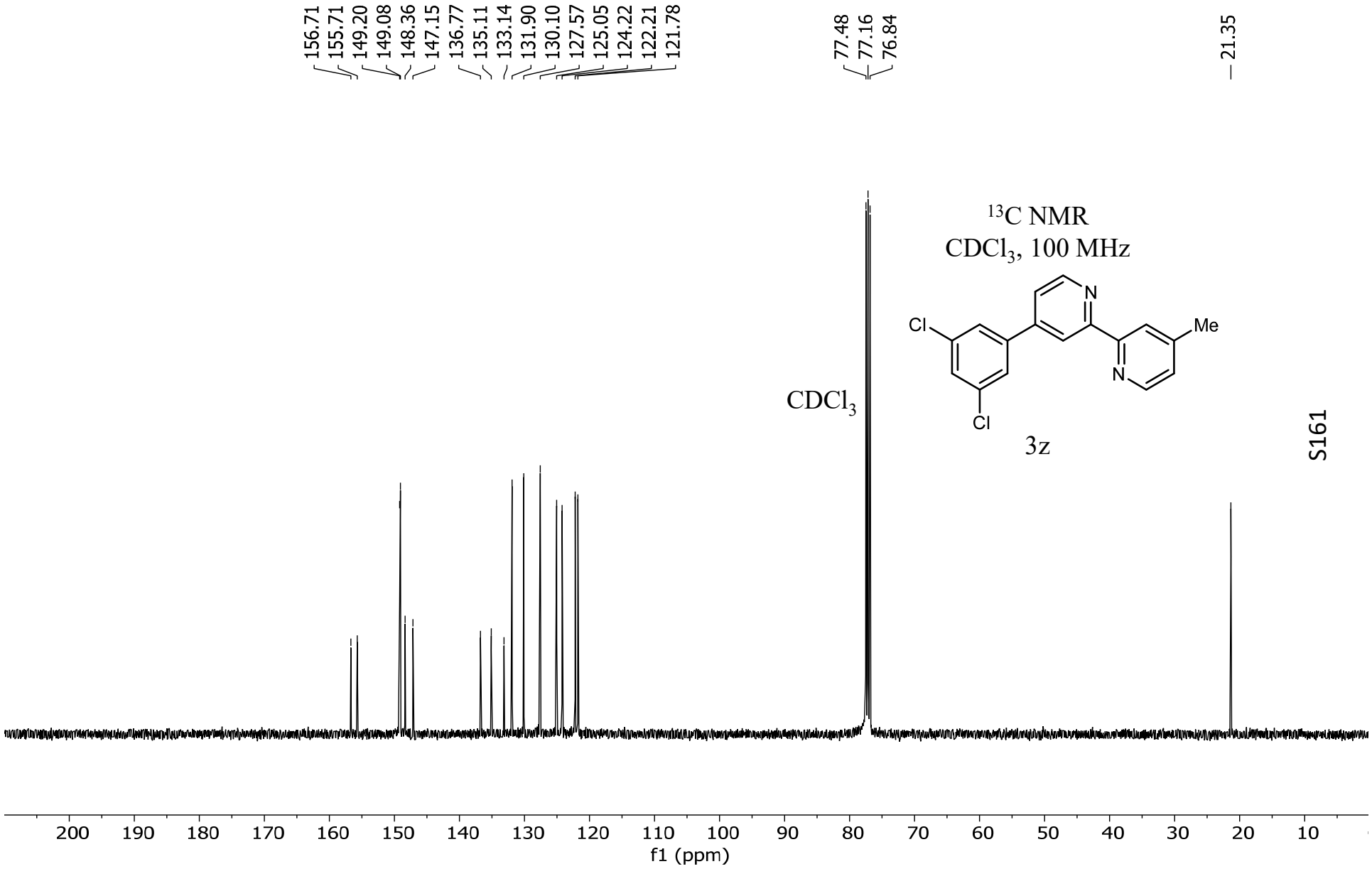
^{1}H NMR

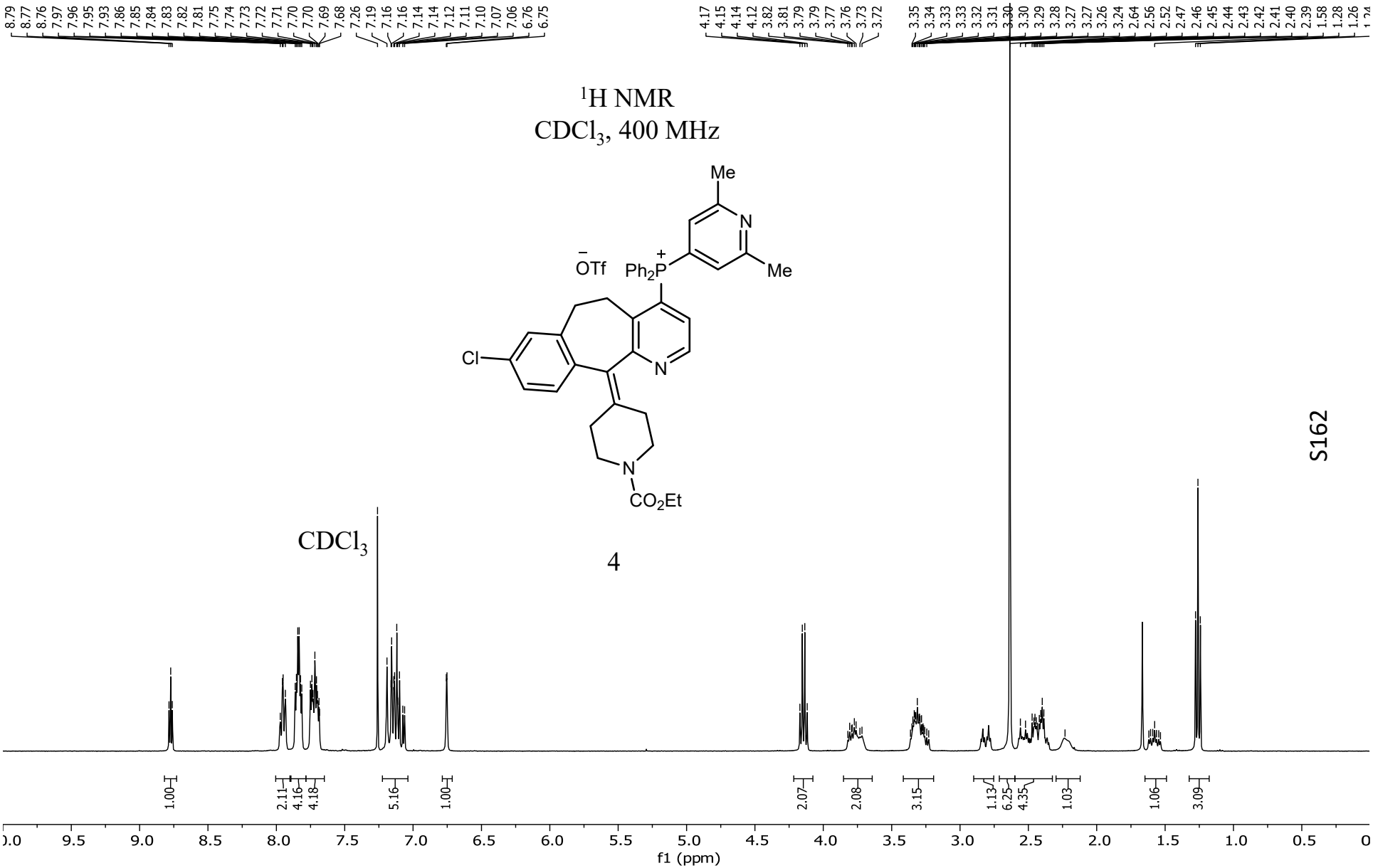
$CDCl_3$, 400 MHz

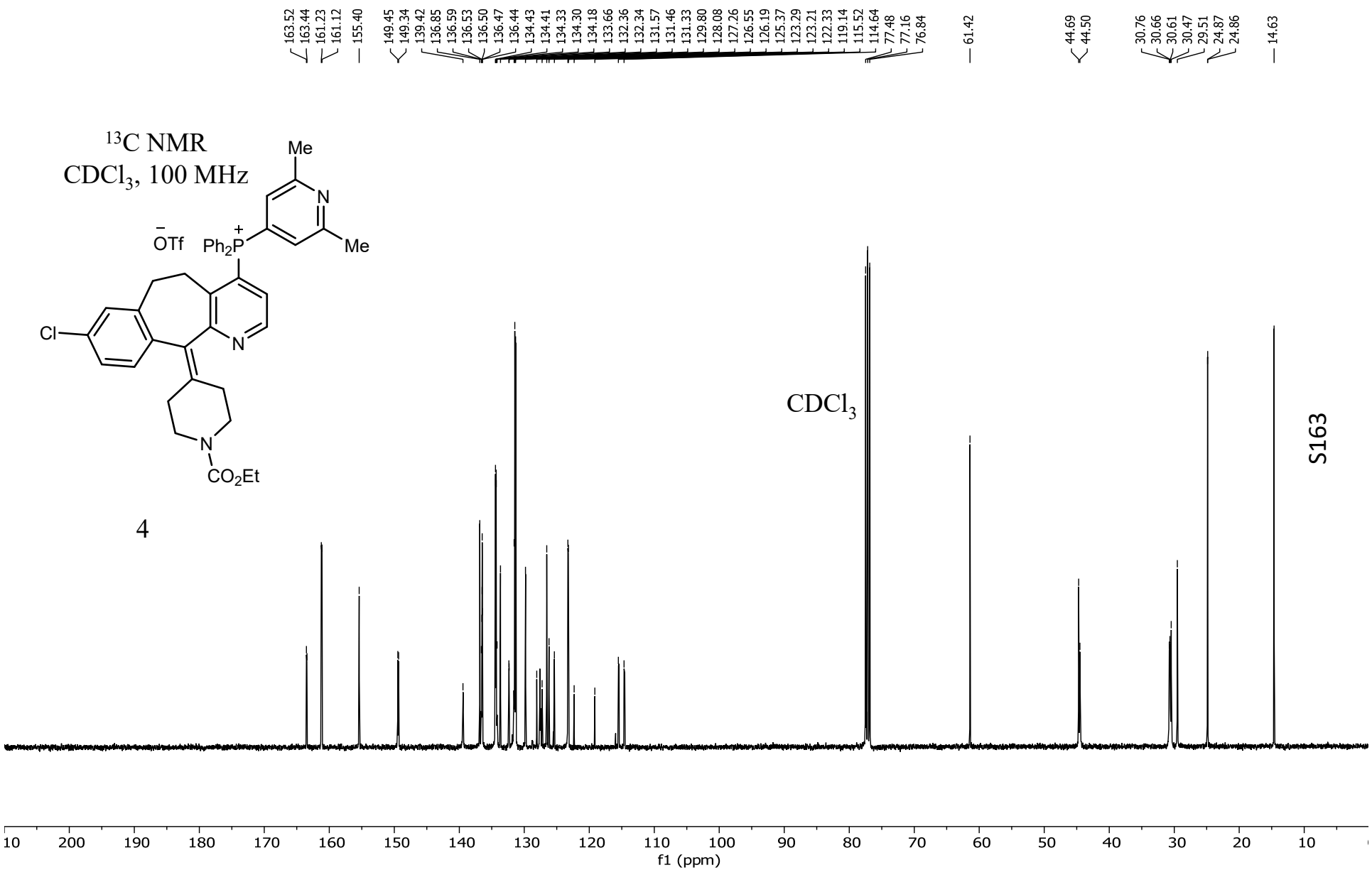


3z

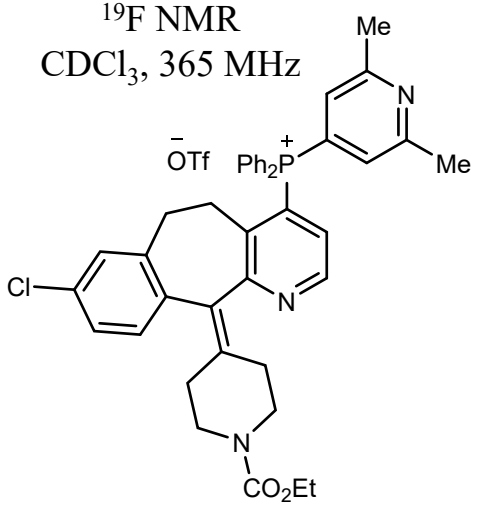
S160


156.71
155.71
149.20
149.08
148.36
147.15
136.77
135.11
133.14
131.90
130.10
127.57
125.05
124.22
122.21
121.78
77.48
77.16
76.84
21.35
^{13}C NMR
$CDCl_3$, 100 MHz
$CDCl_3$
Cl
Cl
N
N
Me
3z
S161
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
Me
N
Me
OTf
Ph_2P
Cl
N
N
CO_2Et
4
$CDCl_3$
S162
f1 (ppm)

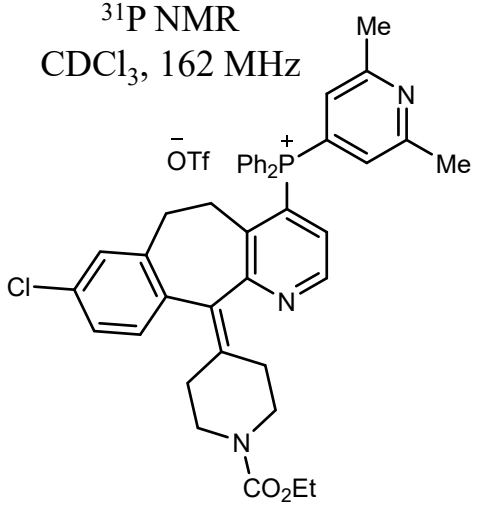

163.52
163.44
161.23
161.12
155.40
149.45
149.34
139.42
136.85
136.59
136.53
136.50
136.47
136.44
134.43
134.41
134.33
134.30
134.18
133.66
132.36
132.34
131.57
131.46
131.33
129.80
128.08
127.26
126.55
126.19
125.37
123.29
123.21
122.33
119.14
115.52
114.64
77.48
77.16
76.84
61.42
44.69
44.50
30.76
30.66
30.61
30.47
29.51
24.87
24.86
14.63
13C NMR
CDCl3, 100 MHz
Me
N
OTf
Ph2P
Me
Cl
N
N
CO2Et
4
CDCl3
S163
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

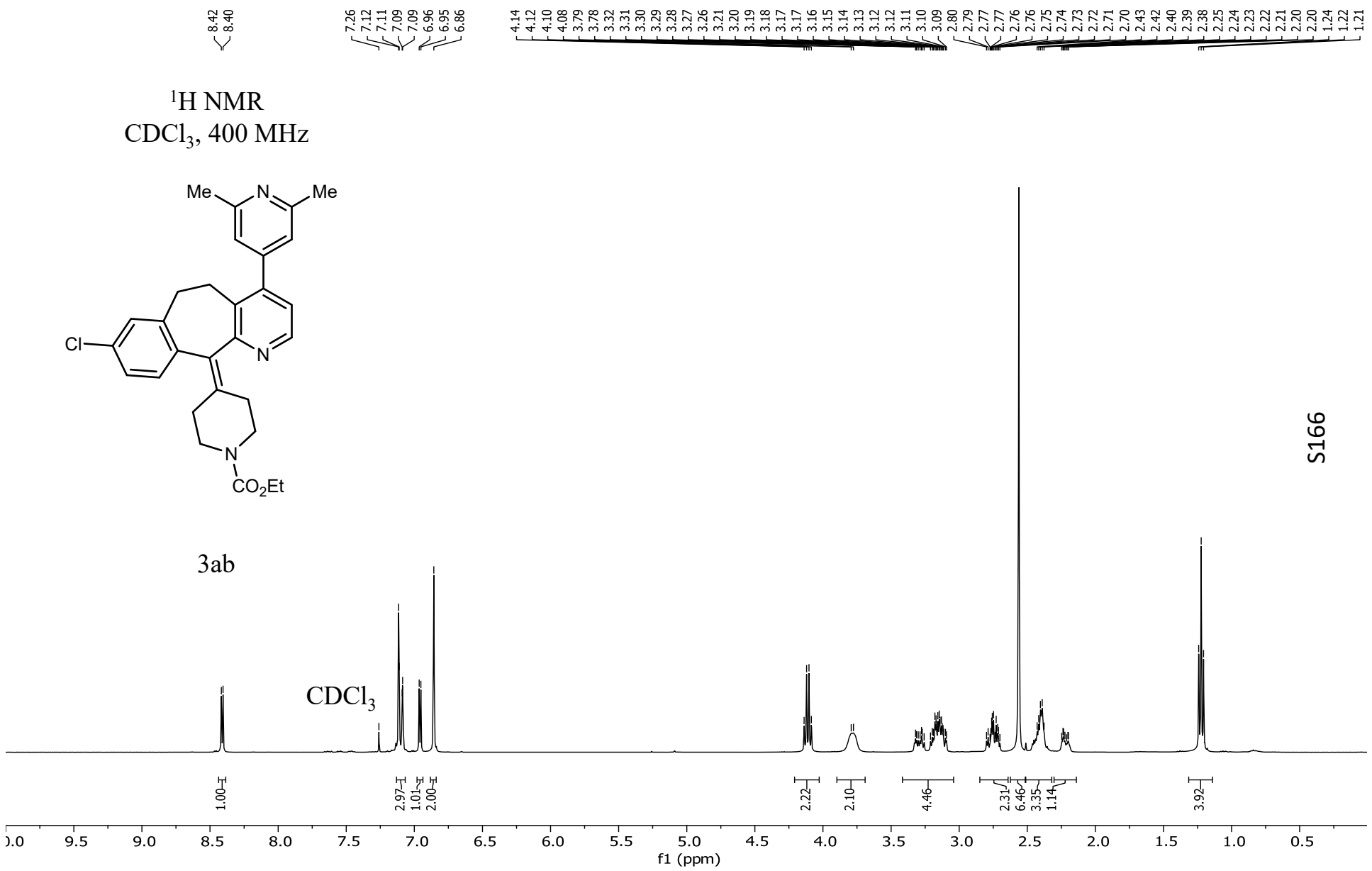


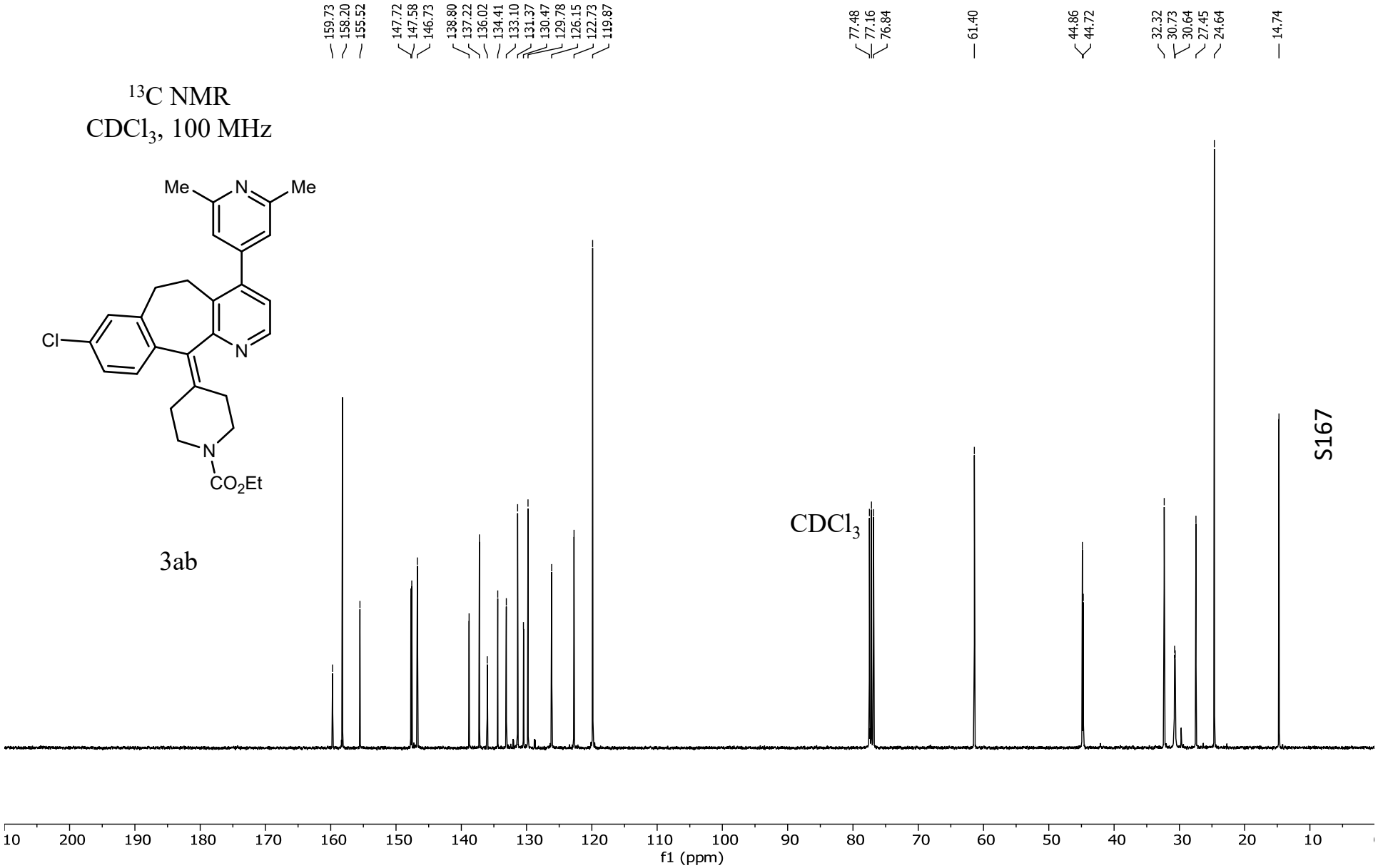
4

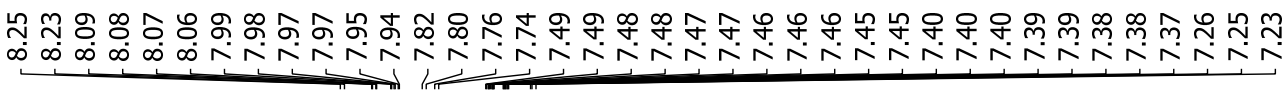
^{31}P NMR
$CDCl_3$, 162 MHz



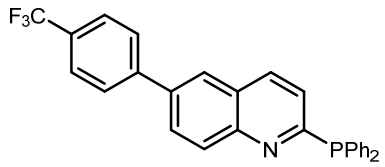
4


8.42
8.40
7.26
7.12
7.11
7.09
7.09
6.96
6.95
6.86
4.14
4.12
4.10
4.08
3.79
3.78
3.32
3.31
3.30
3.29
3.28
3.27
3.26
3.21
3.20
3.19
3.18
3.17
3.17
3.16
3.15
3.14
3.13
3.12
3.12
3.11
3.10
3.09
2.80
2.79
2.77
2.77
2.76
2.76
2.75
2.74
2.73
2.72
2.71
2.70
2.43
2.42
2.40
2.39
2.38
2.25
2.24
2.23
2.22
2.21
2.20
2.20
1.24
1.22
1.21
1H NMR
CDCl3, 400 MHz
Me
N
Me
Cl
N
N
CO2Et
3ab
S166
CDCl3
1.00
2.97
1.01
2.00
2.22
2.10
4.46
2.31
6.46
3.35
1.14
3.92
f1 (ppm)

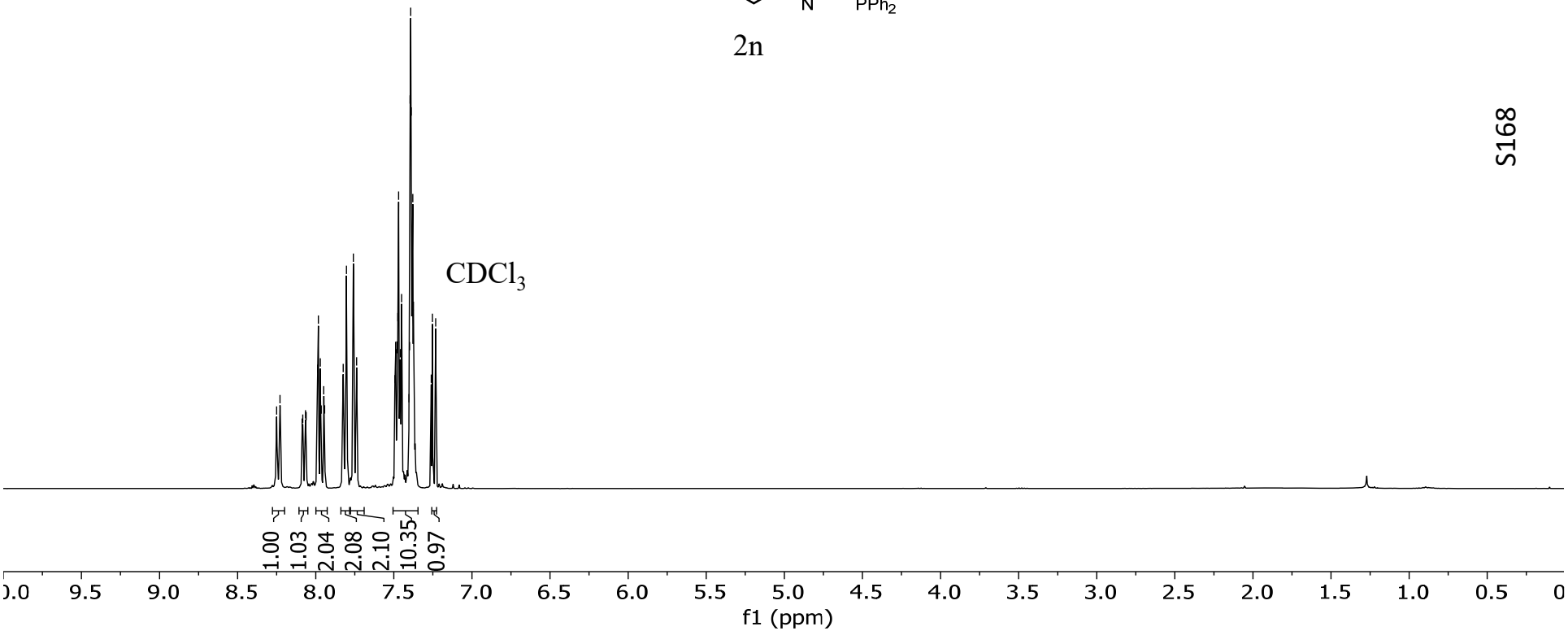

159.73
158.20
155.52
147.72
147.58
146.73
138.80
137.22
136.02
134.41
133.10
131.37
130.47
129.78
126.15
122.73
119.87
77.48
77.16
76.84
61.40
44.86
44.72
32.32
30.73
30.64
27.45
24.64
14.74
^{13}C NMR
$CDCl_3$, 100 MHz
Me
N
Me
Cl
N
N
CO_2Et
3ab
$CDCl_3$
S167
f1 (ppm)

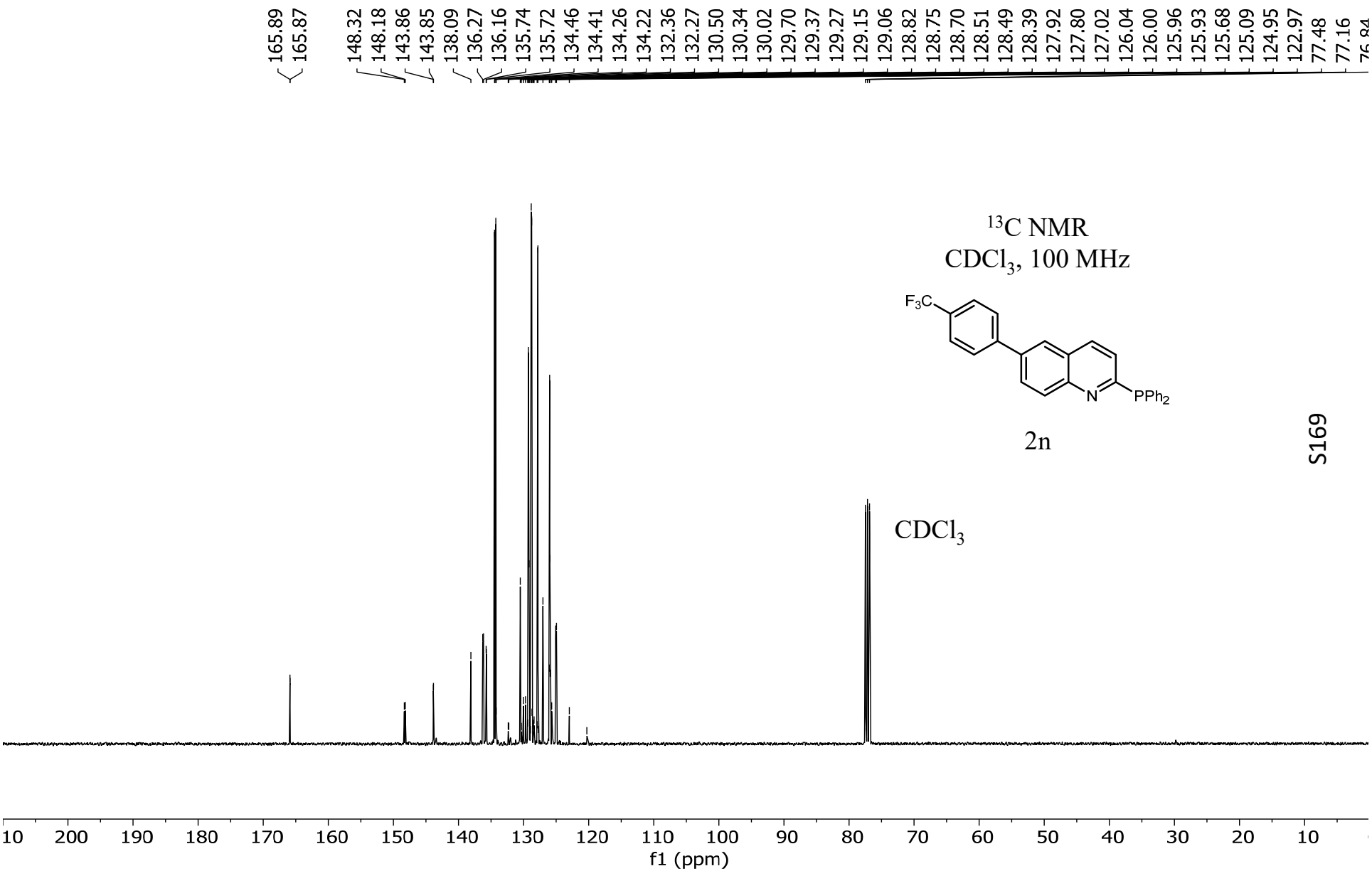


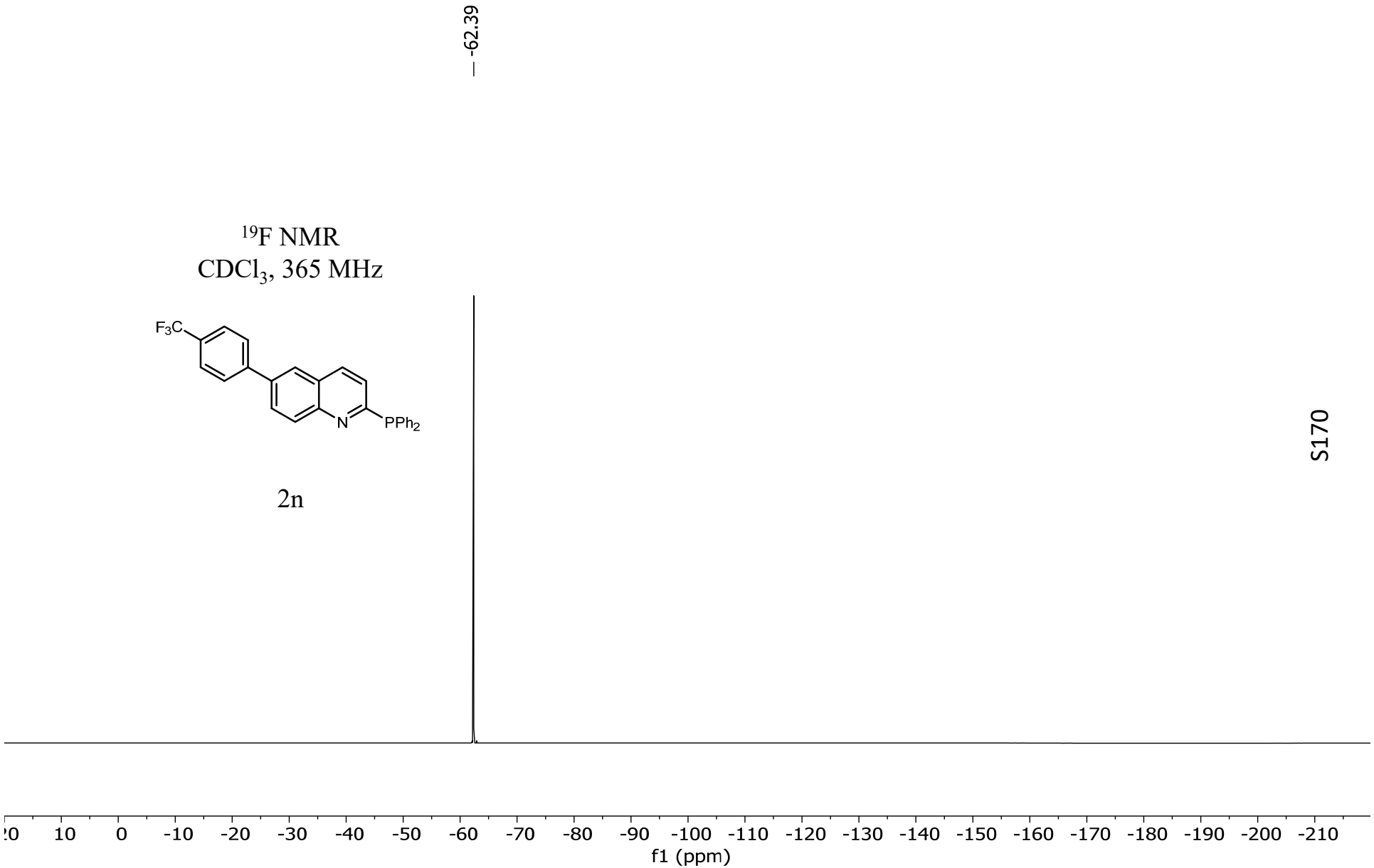
^{1}H NMR
$CDCl_3$, 400 MHz



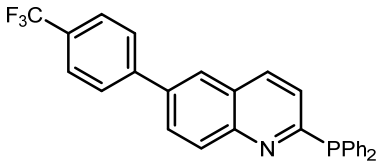
2n



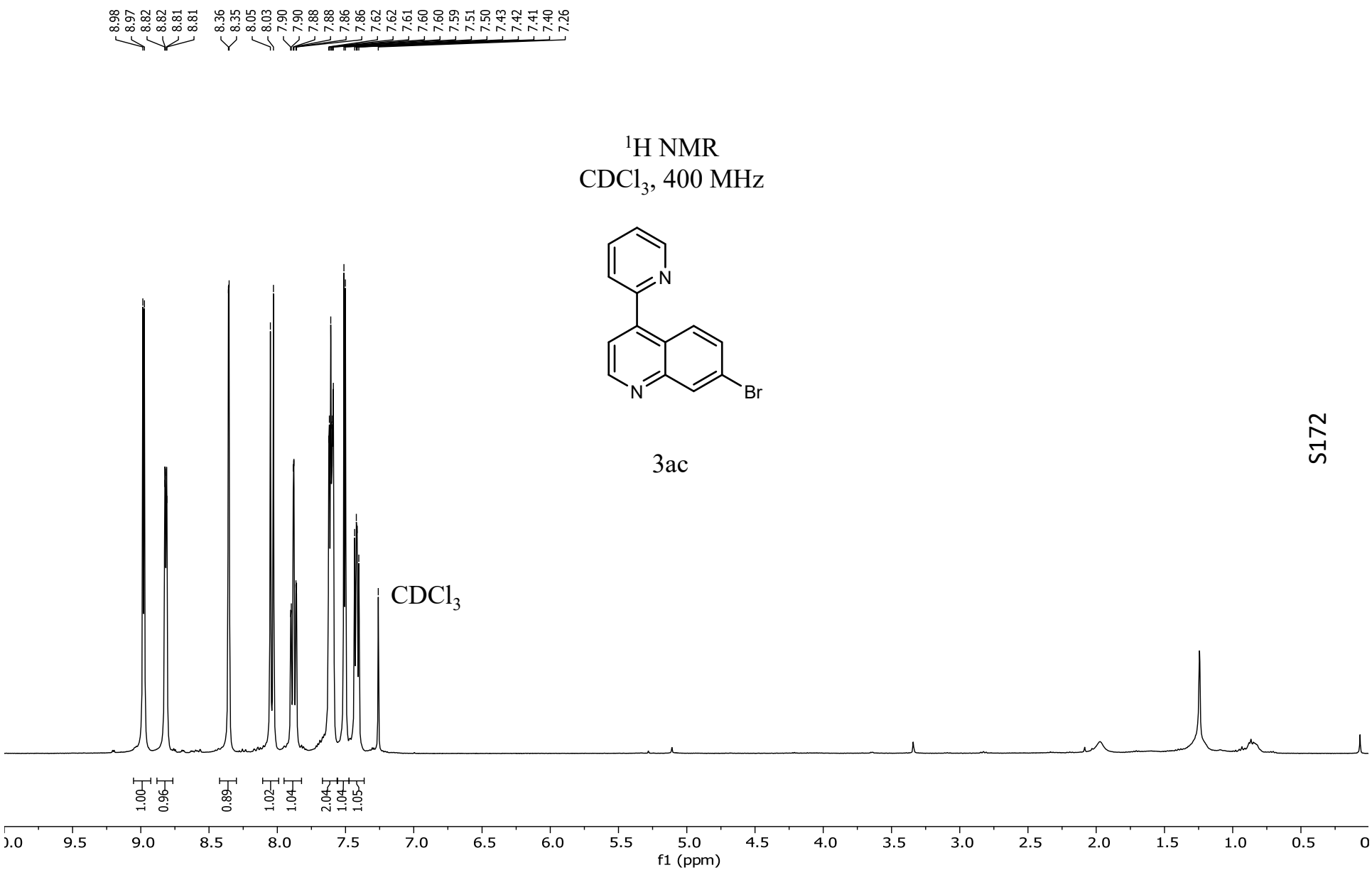

165.89
165.87
148.32
148.18
143.86
143.85
138.09
136.27
136.16
135.74
135.72
134.46
134.41
134.26
134.22
132.36
132.27
130.50
130.34
130.02
129.70
129.37
129.27
129.15
129.06
128.82
128.75
128.70
128.51
128.49
128.39
127.92
127.80
127.02
126.04
126.00
125.96
125.93
125.68
125.09
124.95
122.97
77.48
77.16
^{13}C NMR
$CDCl_3$, 100 MHz
F_3C
N
PPh_2
2n
S169
$CDCl_3$
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


-62.39
^{19}F NMR
$CDCl_3$, 365 MHz
F_3C
N
PPh_2
2n
S170
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)

^{31}P NMR
$CDCl_3$, 162 MHz

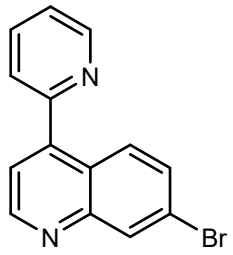


2n

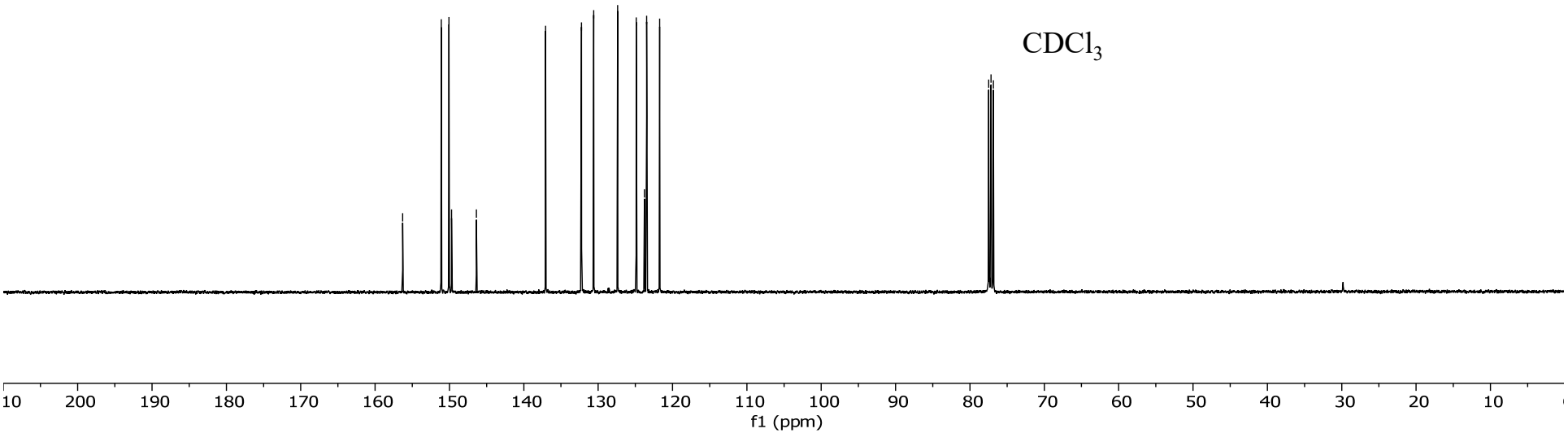

8.98
8.97
8.82
8.82
8.81
8.81
8.36
8.35
8.05
8.03
7.90
7.90
7.88
7.88
7.86
7.86
7.62
7.62
7.61
7.60
7.60
7.59
7.51
7.50
7.43
7.42
7.41
7.40
7.26
1H NMR
CDCl3, 400 MHz
N
N
Br
3ac
S172
CDCl3
1.00
0.96
0.89
1.02
1.04
2.04
1.04
1.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)

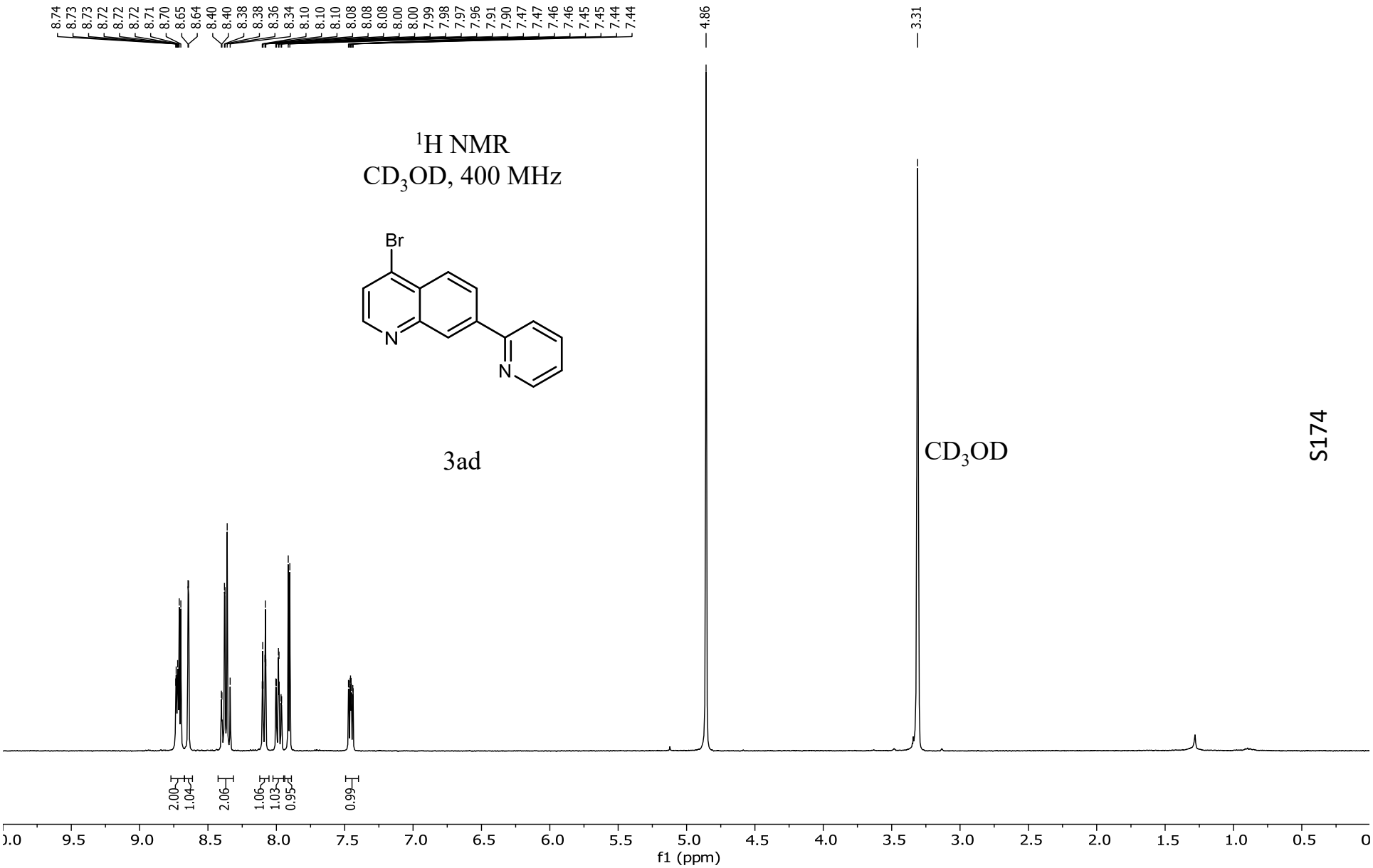
156.29
151.11
150.06
149.72
146.38
137.07
132.25
130.61
127.39
124.88
124.85
123.77
123.48
121.74
77.48
77.16
76.84

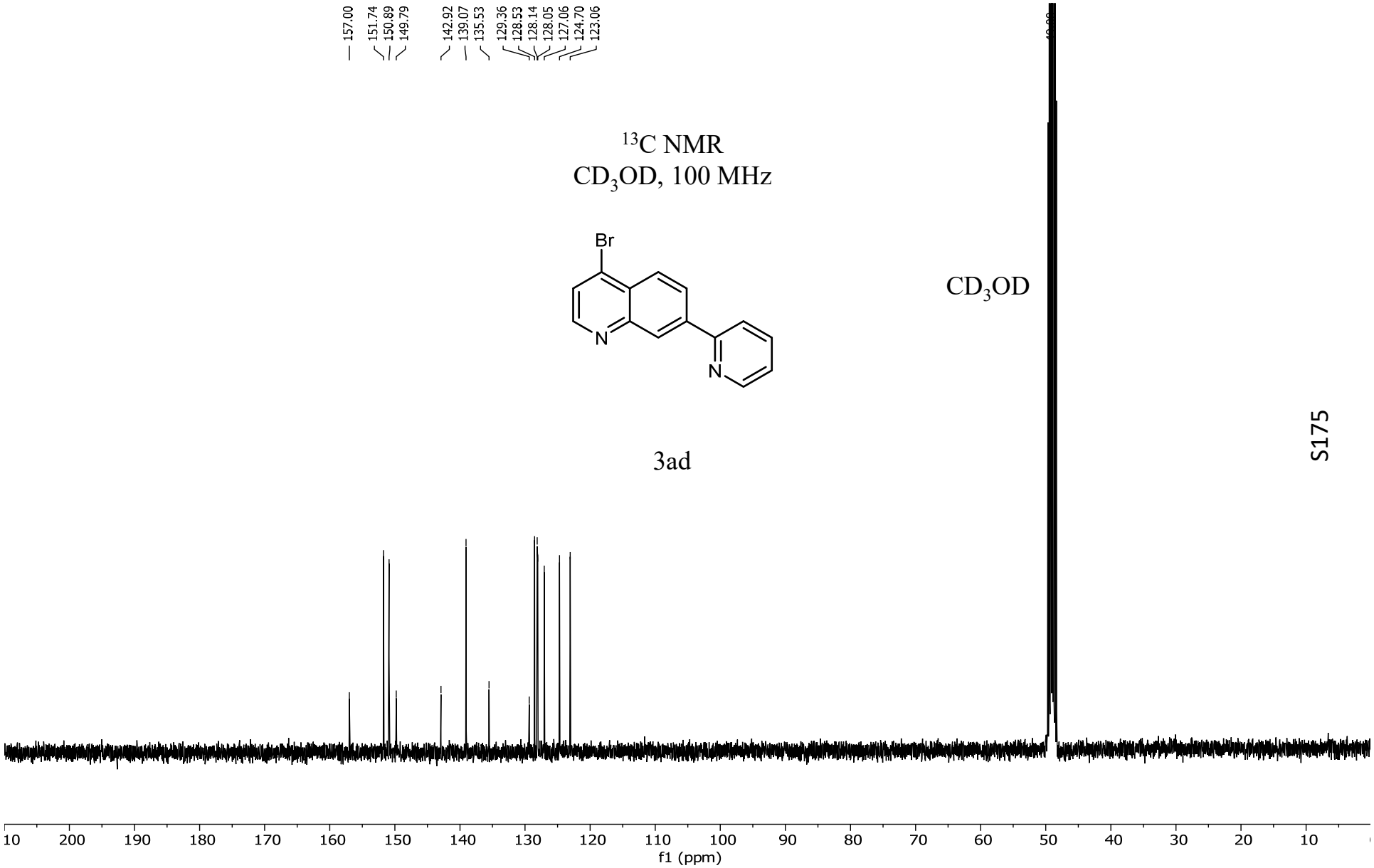
^{13}C NMR
$CDCl_3$, 100 MHz

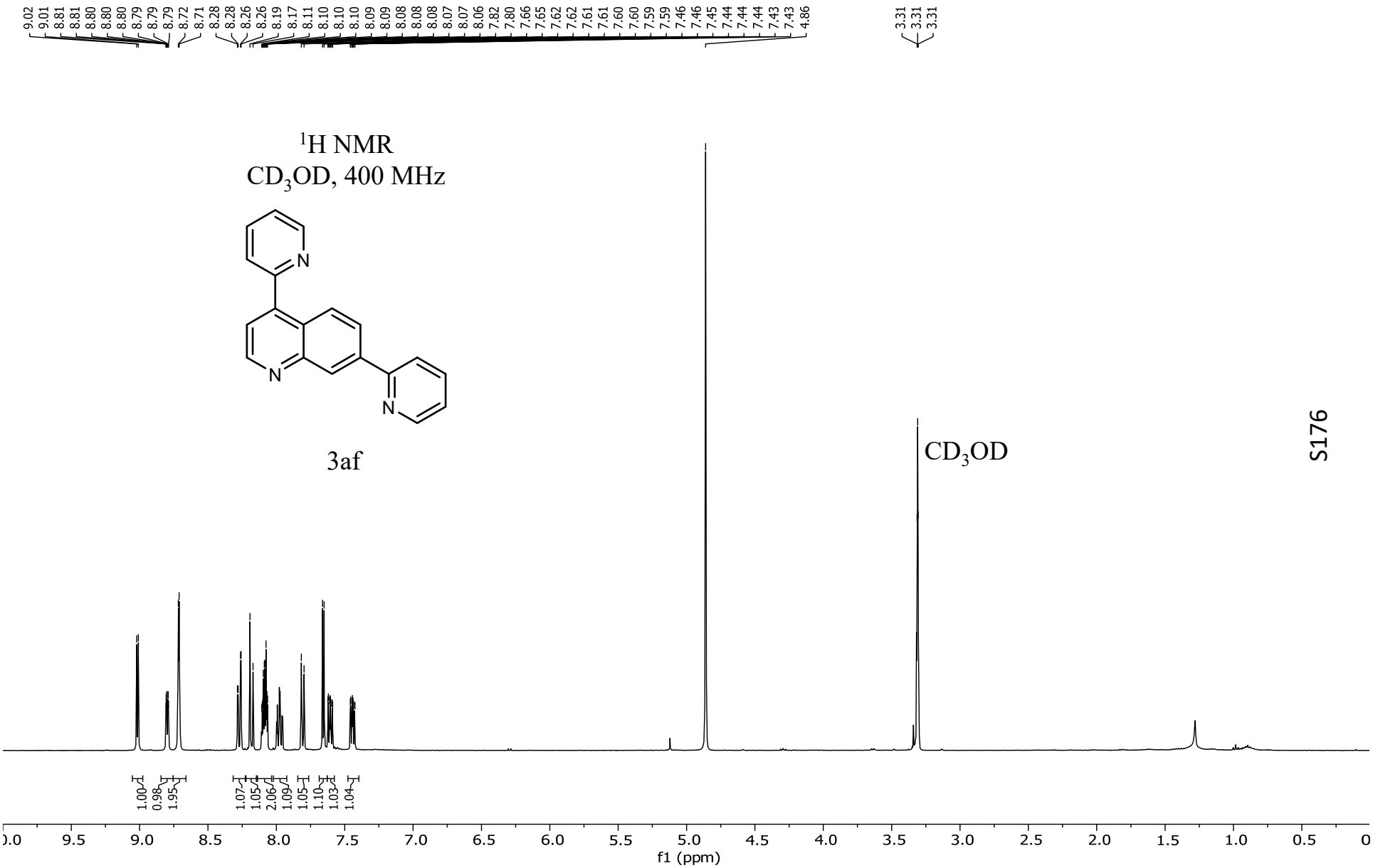


3ac

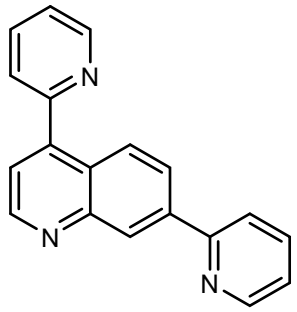



8.74
8.73
8.73
8.72
8.72
8.72
8.71
8.70
8.65
8.64
8.40
8.40
8.38
8.38
8.36
8.34
8.10
8.10
8.08
8.08
8.08
8.00
8.00
7.99
7.98
7.97
7.96
7.91
7.90
7.47
7.47
7.46
7.46
7.45
7.45
7.44
7.44
4.86
3.31
1H NMR
CD3OD, 400 MHz
Br
N
N
3ad
CD3OD
S174
2.00
1.04
2.06
1.06
1.03
0.95
0.99
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)


157.00
151.74
150.89
149.79
142.92
139.07
135.53
129.36
128.53
128.14
128.05
127.06
124.70
123.06
^{13}C NMR
CD_3OD, 100 MHz
Br
N
N
CD_3OD
3ad
S175
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


9.02
9.01
8.81
8.81
8.80
8.80
8.80
8.79
8.79
8.79
8.72
8.71
8.28
8.28
8.26
8.26
8.19
8.17
8.11
8.10
8.10
8.10
8.09
8.09
8.08
8.08
8.08
8.07
8.07
8.06
7.82
7.80
7.66
7.65
7.62
7.62
7.61
7.61
7.60
7.60
7.59
7.59
7.46
7.45
7.44
7.44
7.44
7.43
7.43
4.86
3.31
3.31
3.31
1H NMR
CD3OD, 400 MHz
N
N
N
3af
CD3OD
S176
1.00
0.98
1.95
1.07
1.05
2.06
1.09
1.05
1.10
1.03
1.04
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)

^{13}C NMR
CD_3OD, 100 MHz



3af

157.42
157.16
151.69
150.81
150.64
149.66
147.99
141.98
139.17
139.04
127.88
127.63
127.55
127.27
126.61
125.20
124.52
123.22
122.99

CD_3OD

S177