

Supporting Information

Cobalt-Catalyzed Alkylation of Drug-Like Molecules and Pharmaceuticals Using Heterocyclic Phosphonium Salts

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1. General Information

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz), an Agilent Inova 400 (400 MHz) spectrometer, or a Bruker AV-111 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in CDCl_3 (7.26 ppm), $(\text{CD}_3)_2\text{SO}$ (2.50 ppm) and coupling constants (J) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants, proton assignment). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz), an Agilent Inova 400 (100 MHz) spectrometer, or a Bruker AV-111 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.01 ppm relative to the residual solvent peaks in CDCl_3 (77.00 ppm).

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}).

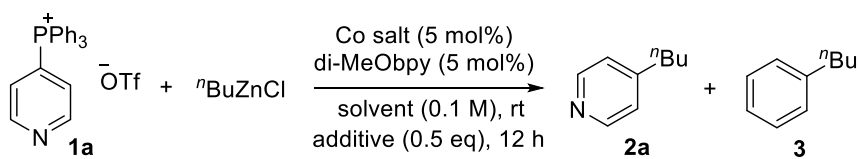
Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Silicycle silica gel Siliacflash P60 40-63 μm (230-400 mesh) under a positive pressure of air. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate.



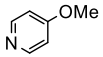
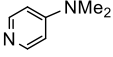



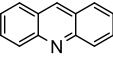
Tetrahydrofuran (THF) were dried and distilled using standard methods¹. Bis(1,5-cyclooctadiene)nickel(0) $[\text{Ni}(\text{COD})_2]$ was purchased from Strem Chemicals, Palladium(II) acetate $[\text{Pd}(\text{OAc})_2]$ (>99.9% trace metals basis), Cobalt(III) acetylacetonate $[\text{Co}(\text{acac})_3]$ (99.99% trace metals basis), 1,3-Bis(2,6-diisopropylphenyl)imidazolinium Chloride ($\text{SIPr}\cdot\text{HCl}$), 1,3-Bis(2,4,6-trimethylphenyl)imidazolinium chloride ($\text{SIMes}\cdot\text{HCl}$) and

isopropylmagnesium chloride solution [i PrMgCl] (2.0 M in THF) were purchased from Sigma Aldrich chemical company. 2,2'-Bipyridine and 4,4'-dimethoxy-2,2'-bipyridine were purchased from Oakwood Chemicals. All reagents were purchased at the highest commercial quality and used without further purification. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^1H NMR spectra taken from reaction samples, gas chromatography (GC) and gas chromatography-mass spectrometry (GCMS) using a 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.

PPh₃ (99%) was purchased from Oakwood Chemicals and is most effective when crushed to a powder before use. Tf₂O (99%) was purchased from Oakwood Chemicals and used without further purification but was routinely stored in a -20 °C fridge. ZnCl₂ (anhydrous, free-flowing, Redi-DriTM, reagent grade, $\geq 98\%$) was purchased from Sigma Aldrich chemical company and used without further purification but was routinely stored in a glovebox. Zn (dust, <10 μm , $\geq 98\%$) was purchased from Sigma Aldrich chemical company, activated by diluted HCl, and stored in a glovebox. LiCl was dried under high vacuum for 4 h at 140 °C and stored in a glovebox. *N*-methylimidazole was distilled and stored in a glovebox. NEt₃ and DBU were distilled before use.

2. Optimization of additives

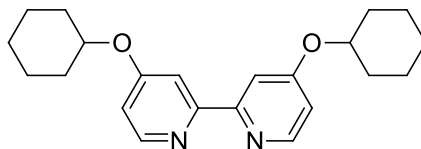


entry	catalyst	solvent	additive	GC yield 2a	GC yield 3
1	Co(acac) ₃	THF	---	47%	<1%
2	CoCl ₂	THF	---	42%	<1%
3	CoBr ₂	THF	---	41%	<1%
4	Co(acac) ₃	toluene	---	39%	<1%
5	Co(acac) ₃	dioxane	---	43%	<1%
6	Co(acac) ₃	DCM	---	12%	<1%
7	Co(acac) ₃	CH ₃ CN	---	10%	<1%
8	Co(acac) ₃	THF		51%	<1%
9	Co(acac) ₃	THF		50%	<1%
10	Co(acac) ₃	THF		54%	<1%
11	Co(acac) ₃	THF		59%	<1%
12	Co(acac) ₃	THF		50%	<1%
13	Co(acac) ₃	THF		48%	<1%
14	Co(acac) ₃	THF		48%	<1%
15	Co(acac) ₃	THF		40%	<1%
16	Co(acac) ₃	THF	DBU	42%	<1%
17	Co(acac) ₃	THF	DABCO	40%	<1%
18	Co(acac) ₃	THF	quinuclidine	48%	<1%
19	Co(acac) ₃	THF	imidazole	36%	<1%
20	Co(acac) ₃	THF	<i>N</i> -methylimidazole	61%	<1%
21	Co(acac) ₃	THF	<i>N</i> -methylimidazole (1 eq.)	64%	<1%
22	Co(acac) ₃	THF	<i>N</i> -methylimidazole (1.5 eq.)	67%	<1%
23	Co(acac) ₃	THF	<i>N</i> -methylimidazole (2 eq.)	67%	<1%
24	Co(acac) ₃	THF	ZnCl ₂	26%	<1%

3. Preparation of Ligand and Heterocyclic Phosphonium Salt

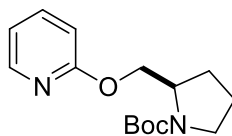
Precursors

4,4'-Bis(cyclohexyloxy)-2,2'-bipyridine (L3)



Cyclohexanol (1.50 mL, 14.20 mmol) was added dropwise under N₂ to a suspension of NaH (60%) (568 mg, 14.20 mmol) in anhydrous DMF (105 mL). After stirring at 80 °C for 1 h, 4,4'-dichloro-2,2'-bipyridine (788 mg, 3.50 mmol) was added in one portion and the mixture was stirred at 80 °C for 16 hours. The reaction mixture was quenched with cold H₂O and extracted with CH₂Cl₂ (3 x 50 mL). The organic extracts were washed with H₂O (3 x 100 mL), dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude material was purified by recrystallization (CH₂Cl₂ and hexanes) to give the title compound as colorless crystals (987 mg, 2.80 mmol, 80% yield). mp 152-154 °C; IR ν_{max} /cm⁻¹ (film): 2935, 2859, 1584, 1551, 1456, 1393, 1372, 1291, 1236, 1043, 1019, 988, 969, 894, 884, 858, 829; ¹H NMR (400 MHz, CDCl₃) δ : 8.44 (2H, d, *J* = 5.7 Hz), 7.92 (2H, s), 6.81 (2H, dd, *J* = 5.7, 2.1 Hz), 4.57-4.51 (2H, m), 2.04-1.97 (4H, m), 1.84-1.78 (4H, m), 1.63-1.54 (6H, m), 1.48-1.29 (6H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 164.98, 157.95, 150.19, 111.82, 107.69, 74.94, 31.40, 25.44, 23.45; *m/z* LRMS (ESI + APCI) found [M + H]⁺ 353.3, C₂₂H₂₉N₂O₂⁺ requires 353.2.

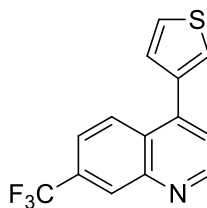
(*R*)-Tert-butyl 2-((pyridin-2-yloxy)methyl)pyrrolidine-1-carboxylate



Boc-D-Prolinol (1.21 g, 6.00 mmol) was added portions under N₂ to a suspension of NaH (60%) (288 mg, 7.20 mmol) in anhydrous DMF (15 mL). After stirring at rt for 30 min, 2-fluoropyridine (620 μ L, 7.20 mmol) was added dropwise and the mixture was stirred at rt overnight. The reaction mixture was quenched with cold H₂O and extracted with CH₂Cl₂ (3 x 50 mL). The organic extracts were washed with H₂O (3 x

100 mL), dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in CH_2Cl_2) to give the title compound as a colorless oil (835 mg, 3.00 mmol, 50% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2972, 2879, 1689, 1593, 1570, 1475, 1431, 1364, 1308, 1284, 1272, 1249, 1165, 1139, 1106, 1041, 1017, 987, 910, 864, 776, 735; ^1H NMR (400 MHz, CDCl_3) δ : 8.11 (1H, dd, $J = 5.0, 1.5$ Hz), 7.52 (1H, dt, $J = 7.6, 1.4$ Hz), 6.82 (1H, t, $J = 5.7$ Hz), 6.70 (1H, d, $J = 8.4$ Hz), 4.37-4.35 (1H, m), 4.21-4.11 (2H, m), 3.37 (2H, br s), 1.98-1.90 (3H, m), 1.83-1.77 (1H, m), 1.43 (9H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.70, 154.48, 146.81, 138.44, 116.67, 110.89, 79.32, 66.05, 56.00, 46.36, 28.74, 28.45, 22.91; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 279.2, $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_3^+$ requires 279.2.

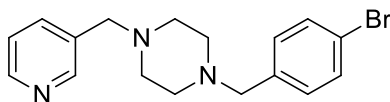
4-(Thiophen-3-yl)-7-(trifluoromethyl)quinoline



To a 100 mL round bottom flask under N_2 , 4-chloro-7-(trifluoromethyl)quinoline (973 mg, 4.20 mmol), thiophen-3-ylboronic acid (699 mg, 5.46 mmol), $\text{Pd}(\text{PPh}_3)_4$ (97 mg, 0.08 mmol), K_2CO_3 (1.74 g, 12.6 mmol), 12 mL of H_2O (degassed) and 36 mL of 1,4-dioxane (degassed) were added. The reaction mixture was then heated to reflux and allowed to stir for 12 hours prior to quenching with H_2O (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 16% EtOAc in hexanes) to provide the title compound as brown solid (1.147 g, 4.12 mmol, 98% yield). mp 91-93 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3104, 3064, 1584, 1566, 1506, 1459, 1373, 1325, 1290, 1244, 1219, 1207, 1191, 1156, 1059, 902, 884, 853, 833, 815, 794, 784, 767, 740; ^1H NMR (400 MHz, CDCl_3) δ : 9.01 (1H, d, $J = 4.4$ Hz), 8.47 (1H, s), 8.21 (1H, d, $J = 8.8$ Hz), 7.70 (1H, dd, $J = 8.8, 1.2$ Hz), 7.56-7.54 (2H, m), 7.50 (1H, d, $J = 4.4$ Hz), 7.34 (1H, dd, $J = 4.5, 1.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 151.32, 147.78, 143.26, 137.63, 131.11 (q, $J = 32.6$ Hz), 128.57, 128.31, 127.69 (q, $J = 4.3$ Hz), 127.06, 126.75, 125.39, 123.88 (q, $J = 271.1$ Hz), 122.63, 122.21 (q, $J = 3.1$ Hz);

^{19}F NMR (365 MHz, CDCl_3) δ : -62.76 ; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 280.1, $\text{C}_{14}\text{H}_9\text{F}_3\text{NS}^+$ requires 280.0.

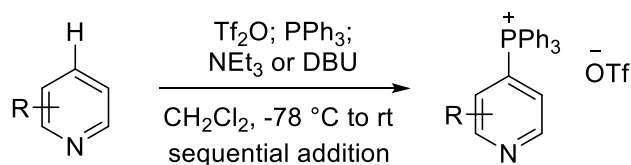
1-(4-Bromobenzyl)-4-(pyridin-3-ylmethyl)piperazine



To a 50 °C solution of 1-(4-bromobenzyl)piperazine (2.55 g, 10.00 mmol) and Et_3N (4.50 mL, 32.00 mmol) in EtOH (180 mL), 3-(chloromethyl)pyridine hydrochloride (2.79 g, 17 mmol) in EtOH (20 mL) was added dropwise, and then the reaction mixture was allowed to stir at 60 °C for 24 hours. After cooling to room temperature, the solvent was removed under vacuum. The residue was treated with water (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: EtOAc to 5% Et_3N in EtOAc) to provide the title compound as light yellow oil (2.718 g, 7.80 mmol, 78% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3026, 2935, 2806, 2767, 1674, 1575, 1485, 1456, 1423, 1405, 1371, 1343, 1291, 1134, 1100, 1068, 1027, 928, 838, 792, 712; ^1H NMR (400 MHz, CDCl_3) δ : 8.53 (1H, d, $J = 1.8$ Hz), 8.50 (1H, dd, $J = 4.8, 1.6$ Hz), 7.65 (1H, td, $J = 7.8, 1.9$ Hz), 7.42 (2H, d, $J = 8.3$ Hz), 7.24 (1H, dd, $J = 8.0, 4.8$ Hz), 7.19 (2H, d, $J = 8.3$ Hz), 3.51 (2H, s), 3.45 (2H, s), 2.46 (8H, br s); ^{13}C NMR (100 MHz, CDCl_3) δ : 150.48, 148.58, 137.19, 136.65, 133.54, 131.27, 130.73, 123.23, 120.79, 62.19, 60.13, 52.97, 52.92; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 346.1, $\text{C}_{17}\text{H}_{21}\text{BrN}_3^+$ requires 346.1.

4. Preparation of Heterocyclic Phosphonium Salts

General Procedure A



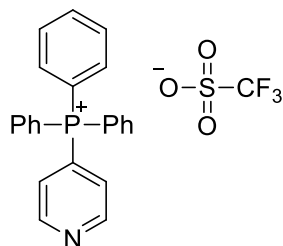
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel

cooled to $-78\text{ }^{\circ}\text{C}$ and Ti_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before PPh_3 (1.1 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at $-78\text{ }^{\circ}\text{C}$. The stated organic base (NEt_3 or DBU, 1.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (approximately 15–30 minutes). The reaction mixture was quenched with H_2O (approximately the same volume as CH_2Cl_2) and the mixture was transferred to a separatory funnel. The mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed three times with H_2O . The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo* to approximately 2–10 mL (depending on the scale of the reaction). An excess of chilled Et_2O ($0\text{ }^{\circ}\text{C}$) was added to the concentrated solution that was then placed in a $-20\text{ }^{\circ}\text{C}$ refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O ($0\text{ }^{\circ}\text{C}$) and dried *in vacuo* to provide the pure phosphonium salt.

Notes.

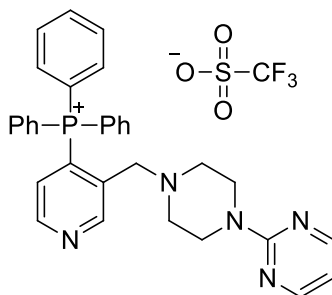
- 1) PPh_3 was crushed into a powder prior to use.
- 2) Certain substrates require longer periods for the precipitation step and specific cases are indicated below.
- 3) In a small number of cases, residual CH_2Cl_2 or Et_2O can become trapped in the phosphonium salt products. In these cases, heating the salts under vacuum ($50\text{--}100\text{ }^{\circ}\text{C}$) removed the solvent.
- 4) In order to evaluate regioselectivity from the crude reaction mixtures, a duplicate reaction was performed and aliquots taken after addition of the organic base and warming to room temperature. These aliquots were concentrated *in vacuo* and analyzed by ^1H and ^{31}P NMR.

Triphenyl(pyridin-4-yl)phosphonium trifluoromethanesulfonate (1a)



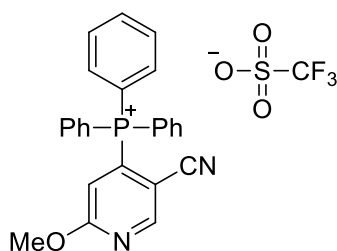
Prepared according to our previous report.² ¹H NMR (400 MHz, CDCl₃) δ : 9.02 (2H, dd, J = 5.8, 5.2 Hz), 7.94-7.90 (3H, m), 7.83-7.78 (6H, m), 7.69-7.59 (8H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 151.62 (d, J = 9.9 Hz), 136.16 (d, J = 3.1 Hz), 134.41 (d, J = 10.5 Hz), 130.96 (d, J = 13.1 Hz), 128.39 (d, J = 83.6 Hz), 127.18 (d, J = 7.9 Hz), 121.22 (q, J = 319.5 Hz), 115.57 (d, J = 89.1 Hz). The spectroscopic data is in agreement with our reported synthesis.²

Triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (1b)



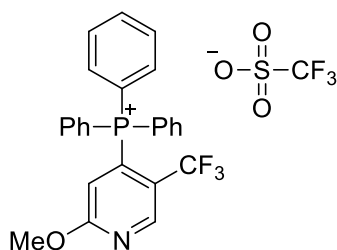
Prepared according to our previous report.² ¹H NMR (400 MHz, CDCl₃) δ : 9.15 (1H, d, J = 6.7 Hz), 8.85 (1H, app t, J = 4.5 Hz), 8.23 (2H, d, J = 4.7 Hz), 7.89-7.86 (3H, m), 7.81-7.69 (12H, m), 7.22 (1H, dd, J = 15.8, 5.1 Hz), 6.45 (1H, t, J = 4.7 Hz), 3.42 (4H, s), 3.17 (2H, s), 1.93 (4H, t, J = 4.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 161.17, 157.49, 153.37 (d, J = 8.2 Hz), 150.76 (d, J = 10.6 Hz), 136.99 (d, J = 5.8 Hz), 135.72 (d, J = 3.0 Hz), 133.99 (d, J = 10.2 Hz), 130.89 (d, J = 13.0 Hz), 129.06 (d, J = 9.7 Hz), 126.61 (d, J = 82.4 Hz), 120.72 (q, J = 319.5 Hz), 116.86 (d, J = 88.9 Hz), 110.07, 59.13 (d, J = 3.0 Hz), 52.47, 42.81. The spectroscopic data is in agreement with our reported synthesis.²

**(5-Cyano-2-methoxypyridin-4-yl)triphenylphosphonium
trifluoromethanesulfonate (1c)**



Prepared according to general procedure A using 6-methoxynicotinonitrile (403 mg, 3.00 mmol), Tf₂O (504 μ L, 3.00 mmol), PPh₃ (866 mg, 3.30 mmol), DBU (450 μ L, 3.00 mmol) and CH₂Cl₂ (30 mL). After the purification procedure, the title compound was isolated as a white solid (1.17 g, 2.16 mmol, 72% yield). mp 83–88 °C; IR ν_{max} /cm⁻¹ (film): 2225, 1579, 1532, 1482, 1438, 1360, 1260, 1223, 1147, 1106, 1070, 1029, 996, 877, 754, 724, 688, 635; ¹H NMR (400 MHz, CDCl₃) δ : 8.76 (1H, t, *J* = 6.1 Hz), 7.94–7.89 (3H, m), 7.83–7.74 (12H, m), 6.87 (1H, d, *J* = 16.3 Hz), 4.08 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 166.43 (d, *J* = 14.6 Hz), 155.64 (d, *J* = 7.3 Hz), 136.29 (d, *J* = 3.0 Hz), 134.59 (d, *J* = 10.8 Hz), 132.31 (d, *J* = 83.5 Hz), 130.97 (d, *J* = 13.4 Hz), 121.00–120.86 (m), 120.65 (q, *J* = 319.5 Hz), 114.48 (d, *J* = 89.5 Hz), 114.23 (d, *J* = 4.4 Hz), 103.03 (d, *J* = 4.2 Hz), 55.53 (d, *J* = 9.3 Hz); ¹⁹F NMR (365 MHz, CDCl₃) δ : –78.28; ³¹P NMR (162 MHz, CDCl₃) δ : 22.81; *m/z* LRMS (ESI + APCI) found [M-OTf]⁺ 395.2, C₂₅H₂₀N₂OP⁺ requires 395.1.

**(2-Methoxy-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium
trifluoromethanesulfonate (1d)**

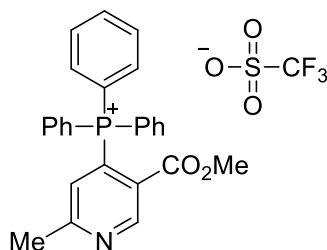


Prepared according to general procedure A using 2-methoxy-5-(trifluoromethyl)pyridine (532 mg, 3.00 mmol), Tf₂O (504 μ L, 3.00 mmol), PPh₃ (866 mg, 3.30 mmol), DBU (450 μ L, 3.00 mmol) and CH₂Cl₂ (30 mL). After the purification procedure, the title compound was isolated as a white solid

S10

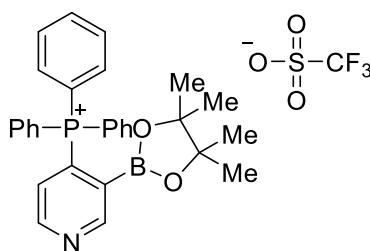
(1.54 g, 2.61 mmol, 87% yield). mp 73–78 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 1585, 1541, 1493, 1439, 1364, 1303, 1223, 1142, 1107, 1029, 878, 754, 722, 690, 636; ^1H NMR (400 MHz, CDCl_3) δ : 8.82 (1H, t, $J = 7.2$ Hz), 7.90–7.86 (3H, m), 7.79–7.66 (12H, m), 6.71 (1H, dd, $J = 17.9, 3.4$ Hz), 4.06 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 166.69 (d, $J = 14.7$ Hz), 150.16 (q, $J = 5.3$ Hz), 135.88 (d, $J = 2.9$ Hz), 134.31 (d, $J = 10.6$ Hz), 130.66 (d, $J = 13.3$ Hz), 128.11 (d, $J = 79.7$ Hz), 122.72 (qd, $J = 272.5, 1.9$ Hz), 121.26–121.11 (m), 120.72 (q, $J = 319.5$ Hz), 119.23 (qd, $J = 33.2, 4.2$ Hz), 116.28 (d, $J = 89.9$ Hz), 55.20 (d, $J = 15.0$ Hz); ^{19}F NMR (365 MHz, CDCl_3) δ : –52.81 (d, $J = 2.2$ Hz), –78.27; ^{31}P NMR (162 MHz, CDCl_3) δ : 27.07; m/z LRMS (ESI + APCI) found $[\text{M-OTf}]^+ 438.2$, $\text{C}_{25}\text{H}_{20}\text{F}_3\text{NOP}^+$ requires 438.1.

(5-(Methoxycarbonyl)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1e)



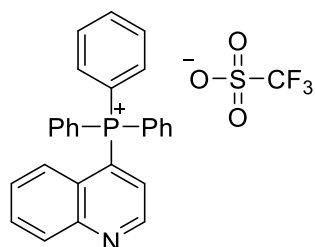
Prepared according to our previous report.² ^1H NMR (400 MHz, CDCl_3) δ : 9.42 (1H, d, $J = 6.4$ Hz), 7.84–7.80 (3H, m), 7.73–7.68 (6H, m), 7.63–7.57 (6H, m), 7.13 (1H, d, $J = 16.4$ Hz), 3.52 (3H, s), 2.68 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 166.40 (d, $J = 10.4$ Hz), 164.31 (d, $J = 1.7$ Hz), 152.61 (d, $J = 6.2$ Hz), 135.01 (d, $J = 3.1$ Hz), 133.71 (d, $J = 10.3$ Hz), 130.72 (d, $J = 8.9$ Hz), 130.27 (d, $J = 13.3$ Hz), 129.31 (d, $J = 82.4$ Hz), 124.45 (d, $J = 3.1$ Hz), 120.74 (q, $J = 319.5$ Hz), 118.35 (d, $J = 92.4$ Hz), 53.25, 25.26 (d, $J = 1.0$ Hz). The spectroscopic data is in agreement with our reported synthesis.²

Triphenyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (1f)



Prepared according to general procedure A using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (615 mg, 3.00 mmol), Tf_2O (504 μL , 3.00 mmol), PPh_3 (866 mg, 3.30 mmol), DBU (450 μL , 3.00 mmol) and CH_2Cl_2 (30 mL). After the purification procedure, the title compound was isolated as a white solid (1.22 g, 1.98 mmol, 66% yield). mp 200–204 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3060, 2982, 1568, 1537, 1480, 1440, 1418, 1400, 1382, 1374, 1359, 1342, 1262, 1223, 1153, 1124, 1105, 1083, 1045, 1030, 963, 852, 827, 756, 720, 689, 660; ^1H NMR (400 MHz, CDCl_3) δ : 9.43 (1H, d, $J = 5.8$ Hz), 9.01 (1H, d, $J = 4.8$ Hz), 7.89–7.84 (3H, m), 7.76–7.71 (6H, m), 7.64–7.57 (6H, m), 7.18 (1H, dd, $J = 15.2, 5.0$ Hz), 0.79 (12H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.03 (d, $J = 10.2$ Hz), 154.17 (d, $J = 10.2$ Hz), 135.32 (d, $J = 3.0$ Hz), 134.10 (d, $J = 10.2$ Hz), 132.75 (d, $J = 81.3$ Hz), 130.38 (d, $J = 13.2$ Hz), 129.72 (d, $J = 10.5$ Hz), 120.77 (q, $J = 319.6$ Hz), 118.35 (d, $J = 89.7$ Hz), 85.43 (2C), 23.99; ^{19}F NMR (365 MHz, CDCl_3) δ : –78.10; ^{31}P NMR (162 MHz, CDCl_3) δ : 24.89; m/z LRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 466.3, $\text{C}_{29}\text{H}_{30}\text{BNO}_2\text{P}^+$ requires 466.3.

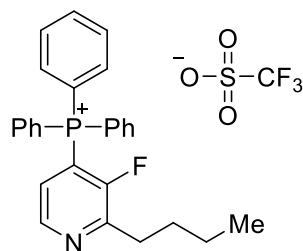
Triphenyl(quinolin-4-yl)phosphonium trifluoromethanesulfonate (1g)



An oven dried 100 mL round bottom flask equipped with a stir bar was charged with quinoline (450 μL , 3.00 mmol) and placed under a nitrogen atmosphere. CH_2Cl_2 (30 mL) was added, the reaction vessel cooled to –78 °C and Tf_2O (504 μL , 3.00 mmol)

was added dropwise over 5 minutes. The reaction was stirred for 30 min before PPh₃ (866 mg, 3.30 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 min at –78 °C. After EtN₃ (420 µL, 3.00 mmol) was added dropwise via syringe, the reaction was stirred at –50 °C for 2 hours, then allowed to warm to room temperature and stirred for another 30 min. The reaction mixture was quenched with H₂O (approximately the same volume as CH₂Cl₂) and the mixture was transferred to a separatory funnel. The mixture was diluted CH₂Cl₂ and the resulting organic layer was washed six times with H₂O. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* to approximately 5 mL. An excess of chilled Et₂O (0 °C) was added to the concentrated solution that was then placed in a –20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et₂O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt as a light yellow solid (664 mg, 1.23 mmol, 41% yield). mp 75–80 °C; IR ν_{max} /cm^{–1} (film): 3062, 1610, 1586, 1500, 1484, 1438, 1347, 1260, 1222, 1146, 1105, 1029, 996, 753, 722, 688, 635; ¹H NMR (400 MHz, CDCl₃) δ : 9.20 (1H, t, *J* = 4.4 Hz), 8.36 (1H, dt, *J* = 8.5, 1.6 Hz), 7.92–7.84 (4H, m), 7.79–7.74 (6H, m), 7.71–7.66 (6H, m), 7.49–7.42 (6H, m), 7.38 (1H, d, *J* = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 150.11 (d, *J* = 12.2 Hz), 148.67 (q, *J* = 7.0 Hz), 136.03 (d, *J* = 3.1 Hz), 134.25 (d, *J* = 10.5 Hz), 131.82 (d, *J* = 2.4 Hz), 131.20, 131.03 (d, *J* = 13.0 Hz), 130.56 (d, *J* = 8.8 Hz), 129.37, 125.91 (d, *J* = 6.1 Hz), 125.59 (d, *J* = 6.5 Hz), 124.15 (d, *J* = 81.7 Hz), 120.76 (q, *J* = 319.2 Hz), 116.42 (d, *J* = 88.4 Hz); ¹⁹F NMR (365 MHz, CDCl₃) δ : –78.11; ³¹P NMR (162 MHz, CDCl₃) δ : 21.74; *m/z* LRMS (ESI + APCI) found [M–OTf]⁺ 390.2, C₂₇H₂₁NP⁺ requires 390.1.

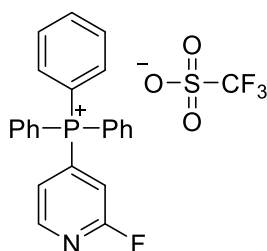
(2-Butyl-3-fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1h)



Prepared according to our previous report.² ¹H NMR (400 MHz, CDCl₃) δ : 8.73 (1H, t, *J* = 4.0 Hz), 7.94–7.90 (3H, m), 7.82–7.78 (6H, m), 7.69–7.64 (6H, m), 7.12 (1H, dt, *J*

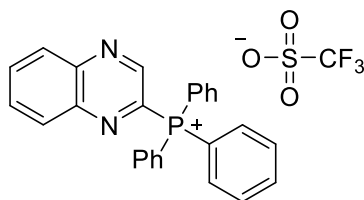
= 14.0, 4.7 Hz), 2.95 (2H, td, $J = 7.6, 2.5$ Hz), 1.73 (2H, qn, $J = 7.5$ Hz), 1.37 (2H, sext, $J = 7.5$ Hz), 0.92 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 156.80 (d, $J = 263.2$ Hz), 153.64 (dd, $J = 16.0, 4.0$ Hz), 147.23 (dd, $J = 10.7, 6.6$ Hz), 136.16 (d, $J = 3.1$ Hz), 133.98 (d, $J = 10.7$ Hz), 130.96 (d, $J = 13.4$ Hz), 125.87 (dd, $J = 6.0, 2.3$ Hz), 120.75 (q, $J = 319.5$ Hz), 115.64 (dd, $J = 83.5, 15.0$ Hz), 115.30 (d, $J = 90.6$ Hz), 31.07, 30.01, 22.18, 13.61. The spectroscopic data is in agreement with our reported synthesis.²

(2-Fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1i)



Prepared according to our previous report.³ ^1H NMR (400 MHz, CDCl_3) δ : 8.67 (1H, app t, $J = 5.3$ Hz), 7.99-7.88 (3H, m), 7.87-7.75 (6H, m), 7.74-7.60 (7H, m), 7.10 (1H, d, $J = 13.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.28 (dd, $J = 245.4, 16.9$ Hz), 150.63 (dd, $J = 13.7, 12.7$ Hz), 136.09 (d, $J = 3.2$ Hz), 134.21 (d, $J = 10.7$ Hz), 133.95 (dd, $J = 84.4, 6.6$ Hz), 130.81 (d, $J = 13.8$ Hz), 125.18 (dd, $J = 8.2, 5.1$ Hz), 122.44 (q, $J = 321.6$ Hz), 114.81 (d, $J = 90.1$ Hz), 114.19 (dd, $J = 40.3, 10.2$ Hz). The spectroscopic data is in agreement with our reported synthesis.³

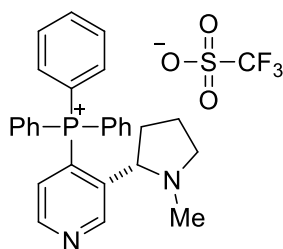
Triphenyl(quinoxalin-2-yl)phosphonium trifluoromethanesulfonate (1j)



Prepared according to our previous report.⁴ ^1H NMR (400 MHz, CDCl_3) δ : 8.99 (1H, s), 8.27-8.22 (2H, m), 8.09-8.01 (2H, m), 7.93-7.90 (3H, m), 7.79-7.72 (12H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 145.86 (d, $J = 25.4$ Hz), 143.38 (d, $J = 2.8$ Hz), 142.70 (d, $J = 17.3$ Hz), 140.83 (d, $J = 111.6$ Hz), 136.16 (d, $J = 3.1$ Hz), 134.98, 134.66 (d, $J = 10.5$ Hz), 133.08, 130.86 (d, $J = 13.0$ Hz), 130.19 (d, $J = 2.0$ Hz), 129.85 (d, $J = 2.3$

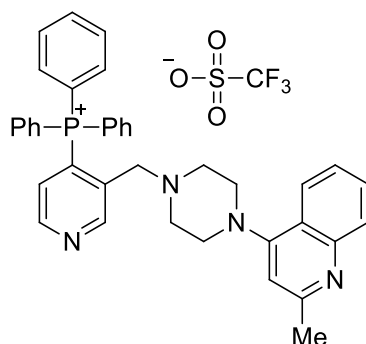
Hz), 120.76 (q, $J = 319.5$ Hz), 116.03 (d, $J = 88.1$ Hz). The spectroscopic data is in agreement with our reported synthesis.⁴

(S)-(3-(1-methylpyrrolidin-2-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1k)



Prepared according to our previous report.³ ¹H NMR (400 MHz, CDCl₃) δ : 9.37 (1H, d, $J = 6.9$ Hz), 8.79 (1H, app t, $J = 4.6$ Hz), 7.96-7.62 (15H, m), 7.12 (1H, dd, $J = 15.5, 5.1$ Hz), 3.10-2.93 (2H, m), 1.99 (1H, app q, $J = 8.5$ Hz), 1.87-1.67 (4H, m), 1.49-1.23 (2H, m), 1.01-0.83 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 153.01 (d, $J = 8.1$ Hz), 149.96 (d, $J = 10.6$ Hz), 144.24 (d, $J = 6.7$ Hz), 135.99 (d, $J = 3.0$ Hz), 134.39 (d, $J = 10.2$ Hz), 131.05 (d, $J = 13.0$ Hz), 127.53 (d, $J = 9.9$ Hz), 126.24 (d, $J = 81.6$ Hz), 120.83 (q, $J = 321.3$ Hz), 116.74 (d, $J = 88.5$ Hz), 66.03 (d, $J = 4.9$ Hz), 55.97, 39.39, 35.43, 22.93. The spectroscopic data is in agreement with our reported synthesis.³

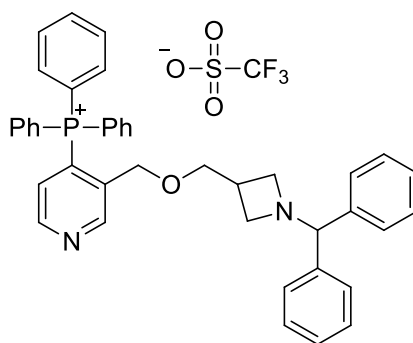
(3-((4-(2-Methylquinolin-4-yl)piperazin-1-yl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1l)



Prepared according to our previous report.² ¹H NMR (400 MHz, CDCl₃) δ : 9.15 (1H, d, $J = 6.8$ Hz), 8.84 (1H, app t, $J = 4.6$ Hz), 7.91-7.70 (17H, m), 7.54 (1H, dd, $J = 7.8, 7.4$ Hz), 7.33 (1H, dd, $J = 7.6, 7.5$ Hz), 7.20 (1H, dd, $J = 15.6, 5.0$ Hz), 6.59 (1H, s),

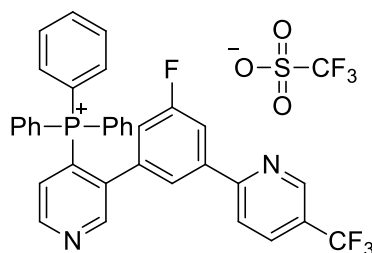
3.26 (2H, s), 2.81 (4H, s), 2.62 (3H, s), 2.16 (4H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.11, 156.40, 153.46 (d, $J = 8.3$ Hz), 150.81 (d, $J = 10.6$ Hz), 148.38, 136.99 (d, $J = 5.7$ Hz), 135.71 (d, $J = 2.9$ Hz), 134.01 (d, $J = 10.2$ Hz), 130.97 (d, $J = 13.0$ Hz), 129.28, 129.09 (d, $J = 9.8$ Hz), 128.46, 126.67 (d, $J = 81.7$ Hz), 124.58, 123.20, 121.28, 120.80 (q, $J = 319.4$ Hz), 117.00 (d, $J = 88.9$ Hz), 109.22, 59.10 (d, $J = 3.3$ Hz), 52.69, 51.18, 25.09. The spectroscopic data is in agreement with our reported synthesis.²

(3-(((1-Benzhydrylazetidin-3-yl)methoxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1m)



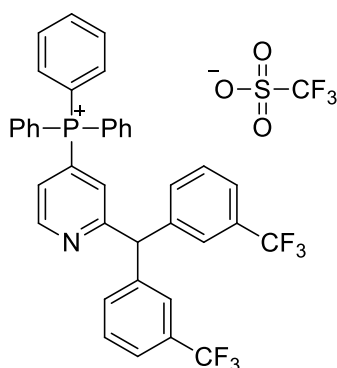
Prepared according to our previous report.² ^1H NMR (400 MHz, CDCl_3) δ : 8.97 (1H, d, $J = 6.5$ Hz), 8.80 (1H, app t, $J = 4.7$ Hz), 7.83-7.79 (3H, m), 7.73-7.68 (6H, m), 7.63-7.58 (6H, m), 7.30 (4H, d, $J = 7.3$ Hz), 7.23 (4H, dd, $J = 7.7, 7.3$ Hz), 7.17-7.08 (3H, m), 4.19 (1H, s), 4.14 (2H, s), 2.93 (2H, d, $J = 7.3$ Hz), 2.84 (2H, t, $J = 7.6$ Hz), 2.46 (2H, dd, $J = 6.6, 6.2$ Hz), 1.99 (1H, sept, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 152.09 (d, $J = 8.2$ Hz), 151.11 (d, $J = 10.6$ Hz), 141.74, 136.69 (d, $J = 5.4$ Hz), 135.54 (d, $J = 3.0$ Hz), 133.94 (d, $J = 10.3$ Hz), 130.57 (d, $J = 13.0$ Hz), 128.74 (d, $J = 9.7$ Hz), 128.23, 127.27, 126.94, 125.33 (d, $J = 82.4$ Hz), 120.76 (q, $J = 319.6$ Hz), 117.15 (d, $J = 89.8$ Hz), 77.44, 73.84, 69.12 (d, $J = 3.6$ Hz), 55.92, 28.62. The spectroscopic data is in agreement with our reported synthesis.²

(3-(3-Fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1n)



Prepared according to our previous report.⁵ ¹H NMR (400 MHz, CDCl₃) δ : 8.98 (1H, app t, J = 4.8 Hz), 8.78 (1H, d, J = 6.8 Hz), 8.72 (1H, br s), 7.98 (1H, dd, J = 8.3, 1.8 Hz), 7.77-7.56 (17H, m), 7.51-7.42 (2H, m), 6.53 (1H, d, J = 8.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 162.25 (d, J = 249.6 Hz), 156.95, 153.34, 150.62 (d, J = 10.3 Hz), 146.22 (q, J = 4.1 Hz), 139.97 (d, J = 8.1 Hz), 139.84 (dd, J = 6.7, 2.1 Hz), 137.12 (dd, J = 8.3, 4.2 Hz), 135.42 (d, J = 3.1 Hz), 134.66-134.28 (2C, m), 130.65 (d, J = 13.1 Hz), 128.45 (d, J = 9.3 Hz), 126.68 (d, J = 83.3 Hz), 125.79 (q, J = 33.2 Hz), 124.82-124.63 (m), 123.41 (q, J = 272.3 Hz), 120.81 (q, J = 321.0 Hz), 120.50, 117.49 (d, J = 23.1 Hz), 116.89 (d, J = 88.8 Hz), 114.59 (d, J = 23.0 Hz). The spectroscopic data is in agreement with our reported synthesis.⁵

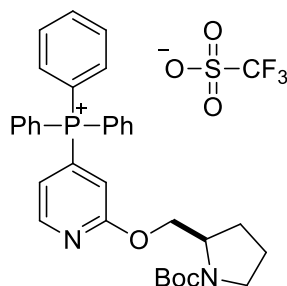
(2-(Bis(3-(trifluoromethyl)phenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1o)



Prepared according to our previous report.⁵ ¹H NMR (400 MHz, CDCl₃) δ : 8.99 (1H, app t, J = 5.1 Hz), 7.91-7.80 (3H, m), 7.78-7.66 (6H, m), 7.63-7.37 (15H, m), 7.29 (1H, d, J = 13.8 Hz), 5.97 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 164.02 (d, J = 9.8 Hz), 151.56 (d, J = 10.4 Hz), 141.69, 136.10 (d, J = 3.1 Hz), 134.31 (d, J = 10.5 Hz), 132.90 (d, J = 1.1 Hz), 130.89 (d, J = 13.1 Hz), 130.73 (q, J = 32.2 Hz), 129.99,

129.57 (d, $J = 83.7$ Hz), 126.99 (d, $J = 8.7$ Hz), 125.65-125.39 (2C, m), 124.04 (q, $J = 3.8$ Hz), 123.83 (q, $J = 272.5$ Hz), 120.78 (q, $J = 321.2$ Hz), 115.44 (d, $J = 89.5$ Hz), 57.75. The spectroscopic data is in agreement with our reported synthesis.⁵

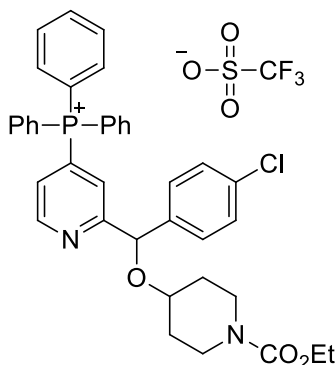
(*R*)-(2-((1-(Tert-butoxycarbonyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1p)



Prepared according to general procedure A using (*R*)-tert-butyl 2-((pyridin-2-yloxy)methyl)pyrrolidine-1-carboxylate (696 mg, 2.50 mmol), TiF_2O (420 μL , 2.50 mmol), PPh_3 (721 mg, 2.75 mmol), DBU (375 μL , 2.50 mmol) and CH_2Cl_2 (25 mL). After the purification procedure (The concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of chilled Et_2O /Hexanes = 1/1 (0 °C). The mixture was then placed in a -20 °C refrigerator overnight. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O /Hexanes = 1/1 (0 °C). The solid was redissolved in approximately 2 mL of CH_2Cl_2 and was precipitated a second time via dropwise addition to an excess of chilled Et_2O /Hexanes = 1/1 (0 °C). The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.), the title compound was isolated as a white solid (1.419 g, 2.05 mmol, 82% yield). mp 85–89 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2973, 1683, 1585, 1541, 1438, 1395, 1367, 1313, 1261, 1222, 1148, 1107, 1029, 996, 862, 753, 723, 689, 635; ^1H NMR (400 MHz, CDCl_3) δ : 8.52 (1H, t, $J = 5.0$ Hz), 7.94-7.90 (3H, m), 7.82-7.79 (6H, m), 7.67-7.62 (6H, m), 7.10 (1H, br s), 6.81 (1H, $J = 14.5$ Hz), 4.48 (1H, dd, $J = 10.4, 4.1$ Hz), 4.30 (1H, t, $J = 7.8$ Hz), 4.18-4.12 (1H, m), 3.48-3.33 (2H, m), 1.94-1.87 (4H, m), 1.42 (9H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.19, 164.03, 154.29, 149.71 (d, $J = 12.3$ Hz), 136.07 (d, $J = 1.0$ Hz), 134.22 (d, $J = 10.3$ Hz), 130.85 (d, $J = 13.0$ Hz), 120.69 (q, $J = 319.5$ Hz), 119.00, 116.02 (d, $J = 11.0$ Hz), 115.52 (d, $J = 89.2$ Hz), 79.36, 67.17, 55.38, 46.24, 28.25, 27.78, 23.43-22.74 (rot); ^{19}F NMR (365 MHz, CDCl_3) δ : -78.14; ^{31}P NMR (162 MHz, CDCl_3) δ : 22.32; m/z LRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 539.3,

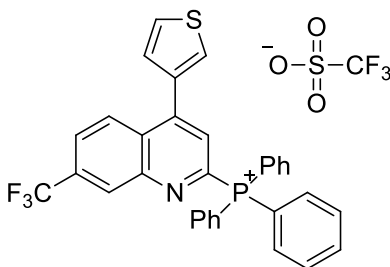
C₃₃H₃₆N₂O₃P⁺ requires 539.2.

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



Prepared according to our previous report.⁵ ¹H NMR (400 MHz, CDCl₃) δ: 8.90 (1H, t, *J* = 5.1 Hz), 7.94-7.86 (3H, m), 7.82-7.73 (6H, m), 7.71-7.59 (7H, m), 7.49 (1H, ddd, *J* = 12.6, 5.0, 1.1 Hz), 7.34-7.25 (4H, m), 5.71 (1H, s), 4.11 (2H, q, *J* = 7.1 Hz), 3.70-3.60 (1H, m), 3.55-3.42 (2H, m), 3.25-3.12 (2H, m), 1.79-1.56 (2H, m), 1.54-1.37 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 164.37 (d, *J* = 9.6 Hz), 155.43, 151.10 (d, *J* = 10.5 Hz), 138.68, 136.16 (d, *J* = 3.1 Hz), 134.53 (d, *J* = 10.5 Hz), 134.01, 130.95 (d, *J* = 13.1 Hz), 129.28 (d, *J* = 84.1 Hz), 128.81, 128.47, 125.92 (d, *J* = 8.4 Hz), 123.86 (d, *J* = 9.1 Hz), 120.83 (q, *J* = 321.2 Hz), 115.80 (d, *J* = 89.4 Hz), 79.94, 72.82, 61.29, 40.69 (rot), 40.66, 31.29, 30.35 (rot), 14.68. The spectroscopic data is in agreement with our reported synthesis.⁴

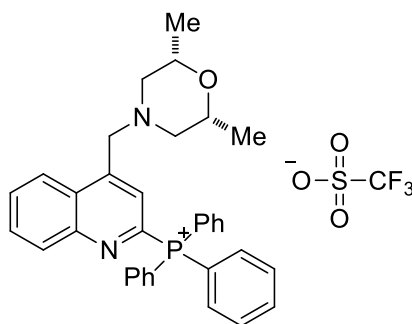
Triphenyl(4-(thiophen-3-yl)-7-(trifluoromethyl)quinolin-2-yl)phosphonium trifluoromethanesulfonate (1r)



An oven dried 100 mL round bottom flask equipped with a stir bar was charged with 4-(thiophen-3-yl)-7-(trifluoromethyl)quinoline (805 mg, 2.88 mmol), PPh₃ (831 mg,

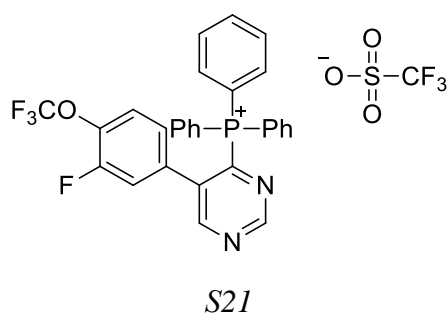
3.17 mmol) and placed under a nitrogen atmosphere. CH₂Cl₂ (29 mL) was added, the reaction vessel cooled to –50 °C and Tf₂O (484 µL, 2.88 mmol) was added dropwise over 5 minutes. The reaction was stirred for 1 hour before cooled to –78 °C. Then DBU (432 µL, 2.88 mmol) was added dropwise via syringe, the reaction was allowed to warm to room temperature. The reaction mixture was quenched with H₂O (approximately the same volume as CH₂Cl₂) and the mixture was transferred to a separatory funnel. The mixture was diluted with CH₂Cl₂ and the resulting organic layer was washed three times with H₂O. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* to approximately 5 mL. An excess of chilled Et₂O (0 °C) was added to the concentrated solution that was then placed in a –20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et₂O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt as an off-white solid (1.68 g, 2.33 mmol, 81% yield). mp 234-237 °C; IR ν_{max} /cm^{–1} (film): 3064, 1739, 1575, 1540, 1501, 1484, 1439, 1421, 1378, 1335, 1224, 1167, 1140, 1108, 1065, 1030, 997, 918, 835, 797, 785, 748, 728, 701, 689, 663, 631; ¹H NMR (400 MHz, CDCl₃) δ : 8.52 (1H, s), 8.40 (1H, d, *J* = 8.9 Hz), 7.92-7.87 (4H, m), 7.82-7.75 (14H, m), 7.55 (1H, dd, *J* = 4.7, 3.0 Hz), 7.34 (1H, *J* = 4.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 148.55, 148.32, 147.51, 146.52 (d, *J* = 10.5 Hz), 146.35, 135.86 (d, *J* = 2.9 Hz), 135.47 (d, *J* = 1.5 Hz), 134.69 (d, *J* = 10.1 Hz), 133.22 (q, *J* = 33.2 Hz), 130.65 (d, *J* = 12.9 Hz), 128.64 (d, *J* = 2.4 Hz), 128.31, 128.12, 128.01, 127.76, 125.91-125.62 (m), 123.17 (q, *J* = 271.7 Hz), 120.71 (q, *J* = 319.6 Hz), 116.66 (d, *J* = 88.0 Hz); ¹⁹F NMR (365 MHz, CDCl₃) δ : –63.08, –78.20; ³¹P NMR (162 MHz, CDCl₃) δ : 15.62; *m/z* LRMS (ESI + APCI) found [M-OTf]⁺ 540.2, C₃₂H₂₂F₃NPS⁺ requires 540.1.

(4-(((2*R*,6*S*)-2,6-Dimethylmorpholino)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (1s)



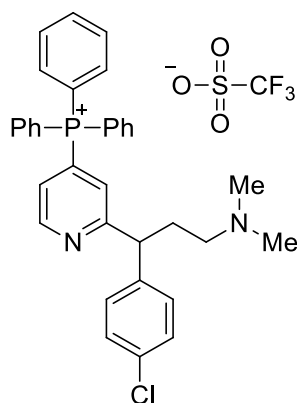
An oven dried 50 mL round bottom flask equipped with a stir bar was charged with (2*R*,6*S*)-2,6-dimethyl-4-(quinolin-4-ylmethyl)morpholine (385 mg, 1.50 mmol), PPh₃ (433 mg, 1.65 mmol) and placed under a nitrogen atmosphere. CH₂Cl₂ (15 mL) was added, the reaction vessel cooled to –50 °C and Tf₂O (252 µL, 1.50 mmol) was added dropwise over 5 minutes. The reaction was stirred for 1 hour before cooled to –78 °C. Then DBU (225 µL, 1.50 mmol) was added dropwise via syringe, the reaction was allowed to warm to room temperature. The reaction mixture was quenched with H₂O (approximately the same volume as CH₂Cl₂) and the mixture was transferred to a separatory funnel. The mixture was diluted with CH₂Cl₂ and the resulting organic layer was washed three times with H₂O. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* to approximately 3 mL. An excess of chilled Et₂O/hexanes = 1:1 (0 °C) was added to the concentrated solution that was then placed in a –20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et₂O/hexanes = 1:1 (0 °C) and dried *in vacuo* to provide the pure phosphonium salt as a white solid (921 mg, 1.38 mmol, 92% yield). mp 188-195 °C; IR ν_{max} /cm^{–1} (film): 3072, 2971, 2936, 2844, 1576, 1545, 1505, 1483, 1457, 1438, 1369, 1322, 1266, 1220, 1110, 1082, 997, 981, 882, 857, 833, 762, 751, 726; ¹H NMR (400 MHz, CDCl₃) δ : 8.28 (1H, d, *J* = 8.4 Hz), 8.24 (1H, d, *J* = 8.4 Hz), 7.94-7.90 (4H, m), 7.84-7.76 (14H, m), 4.03 (2H, s), 3.48-3.41 (2H, m), 2.60 (2H, d, *J* = 10.7 Hz), 1.92 (2H, t, *J* = 10.6 Hz), 1.10 (6H, d, *J* = 6.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 148.83 (d, *J* = 22.1 Hz), 148.03 (d, *J* = 10.1 Hz), 145.07, 143.90, 135.60, 134.51 (d, *J* = 9.9 Hz), 131.65, 130.72, 130.43 (d, *J* = 12.7 Hz), 127.68 (d, *J* = 2.9 Hz), 123.80, 123.36 (dd, *J* = 27.4, 4.0 Hz), 120.74 (q, *J* = 319.7 Hz), 117.23 (d, *J* = 87.7 Hz), 71.49 (d, *J* = 3.8 Hz), 59.19, 57.89, 18.79; ¹⁹F NMR (365 MHz, CDCl₃) δ : –78.07; ³¹P NMR (162 MHz, CDCl₃) δ : 14.48; *m/z* LRMS (ESI + APCI) found [M-OTf]⁺ 517.3, C₃₄H₃₄N₂OP⁺ requires 517.2.

(5-(3-Fluoro-4-(trifluoromethoxy)phenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1t)



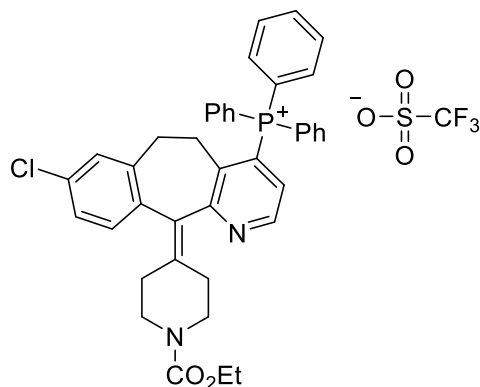
Prepared according to our previous report.⁵ ¹H NMR (400 MHz, CDCl₃) δ: 9.50 (1H, s), 8.90 (1H, d, *J* = 8.8 Hz), 7.82-7.51 (16H, m), 6.98 (1H, d, *J* = 8.6 Hz), 6.35 (1H, d, *J* = 10.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 162.00 (d, *J* = 5.3 Hz), 158.21 (d, *J* = 248.49 Hz), 157.73 (d, *J* = 16.6 Hz), 151.69 (d, *J* = 116.9 Hz), 150.75 (dd, *J* = 10.8, 1.6 Hz), 135.26 (d, *J* = 3.0 Hz), 135.04, 134.85 (d, *J* = 10.3 Hz), 132.95 (d, *J* = 2.4 Hz), 129.93 (d, *J* = 13.2 Hz), 120.54 (q, *J* = 321.1 Hz), 119.84 (q, *J* = 259.5 Hz), 118.78 (d, *J* = 15.1 Hz), 117.36, 116.46 (d, *J* = 88.8 Hz), 107.87 (d, *J* = 25.4 Hz). The spectroscopic data is in agreement with our reported synthesis.⁵

(2-(1-(4-Chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1u)



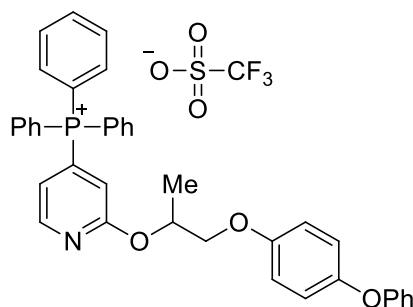
Prepared according to our previous report.³ ¹H NMR (400 MHz, CDCl₃) δ: 8.97 (1H, app t, *J* = 5.1 Hz), 7.93-7.86 (3H, m), 7.80-7.70 (6H, m), 7.61-7.50 (6H, m), 7.39 (1H, ddd, *J* = 12.8, 5.1, 1.5 Hz), 7.25-7.16 (5H, m), 4.28 (1H, app t, *J* = 6.8 Hz), 2.56-2.43 (1H, m), 2.32-2.11 (9H, m); ¹³C NMR (100 MHz, CDCl₃) δ: 165.55 (d, *J* = 9.9 Hz), 150.97 (d, *J* = 9.9 Hz), 140.26, 135.82 (d, *J* = 3.1 Hz), 134.02 (d, *J* = 10.7 Hz), 132.25, 130.61 (d, *J* = 13.0 Hz), 128.92 (d, *J* = 85.5 Hz), 128.75, 127.92, 126.26 (d, *J* = 8.4 Hz), 124.42 (d, *J* = 7.6 Hz), 120.46 (q, *J* = 321.2 Hz), 115.31 (d, *J* = 89.3 Hz), 56.73, 49.77, 44.88, 31.99. The spectroscopic data is in agreement with our reported synthesis.³

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



Prepared according to our previous report.³ ¹H NMR (400 MHz, CDCl₃) δ: 8.73 (1H, app t, *J* = 5.0 Hz), 7.97-7.87 (3H, m), 7.86-7.74 (6H, m), 7.73-7.60 (6H, m), 7.16-7.01 (3H, m), 6.71 (1H, s), 4.14 (2H, q, *J* = 7.0 Hz), 3.84-3.61 (2H, m), 3.45- 3.20 (3H, m), 2.75 (1H, dt, *J* = 17.4, 4.7 Hz), 2.58 (1H, dt, *J* = 14.9, 4.7 Hz), 2.53-2.30 (3H, m), 2.26-2.09 (1H, m), 1.60-1.43 (1H, m), 1.25 (3H, t, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 163.64 (d, *J* = 8.3 Hz), 155.37, 149.08 (d, *J* = 11.4 Hz), 139.23, 136.84, 136.66 (d, *J* = 6.8 Hz), 136.06 (d, *J* = 3.1 Hz), 134.21 (d, *J* = 10.7 Hz), 133.95, 133.57, 132.37, 131.58, 131.13 (d, *J* = 13.0 Hz), 129.85, 127.22 (d, *J* = 10.0 Hz), 127.01 (d, *J* = 82.2 Hz), 126.43, 120.78 (q, *J* = 321.3 Hz), 116.42 (d, *J* = 88.5 Hz), 61.39, 44.65, 44.41, 30.74, 30.46, 30.39, 29.39, 14.59. The spectroscopic data is in agreement with our reported synthesis.³

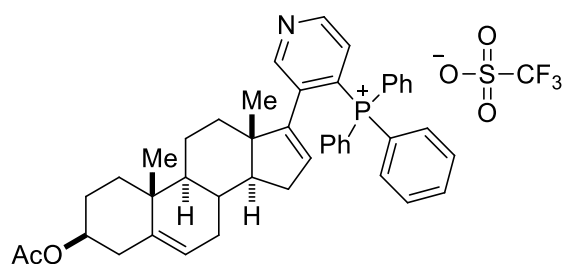
(2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1w)



Prepared according to our previous report.⁴ ¹H NMR (400 MHz, CDCl₃) δ: 8.55 (1H,

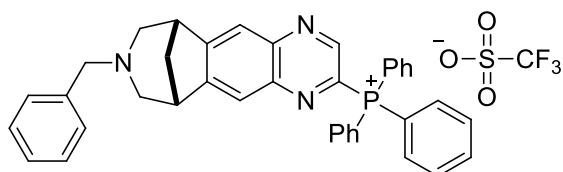
app t, $J = 5.3$ Hz), 7.93-7.87 (3H, m), 7.82-7.74 (6H, m), 7.67-7.59 (6H, m), 7.30-7.23 (2H, m), 7.13 (1H, ddd, $J = 11.7, 5.3, 1.2$ Hz), 7.02 (1H, t, $J = 7.4$ Hz), 6.94-6.77 (7H, m), 5.66 (1H, sext, $J = 5.3$ Hz), 4.18-4.07 (2H, m), 1.48 (3H, d, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.72 (d, $J = 15.9$ Hz), 158.13, 154.71, 150.29, 149.77 (d, $J = 12.1$ Hz), 136.11 (d, $J = 3.0$ Hz), 134.32 (d, $J = 10.6$ Hz), 130.91 (d, $J = 13.0$ Hz), 130.78 (d, $J = 84.2$ Hz), 129.50, 122.43, 120.78 (q, $J = 321.2$ Hz), 120.56, 119.08 (d, $J = 8.1$ Hz), 117.47, 116.55 (d, $J = 10.0$ Hz), 115.62 (d, $J = 89.4$ Hz), 115.61, 71.50, 70.49, 16.41. The spectroscopic data is in agreement with our reported synthesis.⁴

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



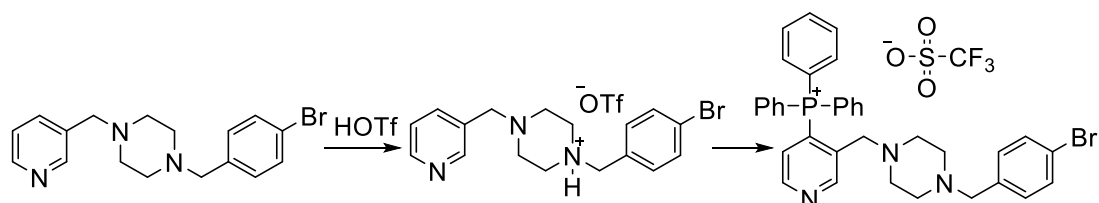
Prepared according to our previous report.⁴ ^1H NMR (400 MHz, CDCl_3) δ : 8.99 (1H, d, $J = 7.2$ Hz), 8.72 (1H, app t, $J = 4.1$ Hz), 7.88-7.59 (15H, m), 7.27 (1H, dd, $J = 15.7, 5.2$ Hz), 5.55 (1H, s), 5.28 (1H, d, $J = 3.4$ Hz), 4.58 (1H, m), 2.33-2.18 (2H, m), 1.99 (3H, s), 1.87-1.30 (10H, m), 1.24-1.01 (5H, m), 0.94 (3H, s), 0.79 (1H, td, $J = 12.1, 3.7$ Hz), 0.57 (1H, td, $J = 11.2, 3.9$ Hz), -0.22 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.37, 150.59 (d, $J = 7.5$ Hz), 149.00 (d, $J = 4.2$ Hz), 148.68 (d, $J = 10.8$ Hz), 139.88, 139.11, 137.35 (d, $J = 6.1$ Hz), 135.54 (d, $J = 2.9$ Hz), 134.22 (d, $J = 9.9$ Hz), 130.83 (d, $J = 13.0$ Hz), 129.95 (d, $J = 10.5$ Hz), 125.23 (d, $J = 83.7$ Hz), 121.56, 120.74 (q, $J = 321.2$ Hz), 117.96 (d, $J = 89.6$ Hz), 73.46, 55.28, 49.70, 48.71, 37.88, 36.76, 36.42, 33.51, 32.43, 30.97, 29.74, 27.50, 21.27, 20.25, 18.95, 18.64. The spectroscopic data is in agreement with our reported synthesis.⁴

((rac)-8-Benzyl-7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxalin-2-yl)triphenylphosphonium trifluoromethanesulfonate (1y)



Prepared according to our previous report.⁴ ¹H NMR (400 MHz, DMSO-d₆) δ: 9.09 (1H, s), 8.10-7.72 (17H, m), 7.20-7.05 (3H, m), 6.92-6.80 (2H, m), 3.55-3.27 (4H, m), 3.03-2.87 (2H, m), 2.66-2.42 (2H, m), 2.29-2.15 (1H, m), 1.87 (1H, d, *J* = 10.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 144.90 (d, *J* = 23.5 Hz), 144.21, 143.45 (d, *J* = 16.9 Hz), 137.51, 136.00 (d, *J* = 2.9 Hz), 134.55 (d, *J* = 10.9 Hz), 130.72 (d, *J* = 13.0 Hz), 129.20-126.21 (3C, m), 120.69, 120.67 (q, *J* = 321.5 Hz), 116.42 (d, *J* = 88.3 Hz), 61.29, 57.90-56.06 (2C, m), 43.14-40.43 (3C, m) The spectroscopic data is in agreement with our reported synthesis.⁴

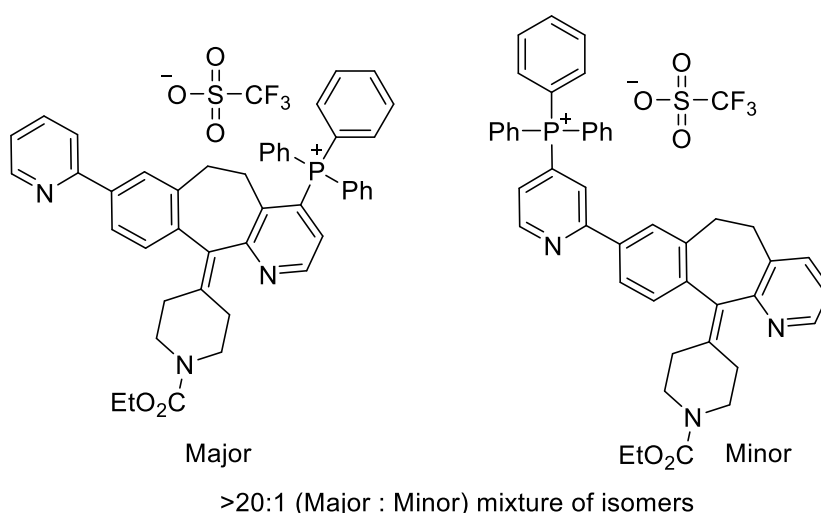
(3-((4-(4-Bromobenzyl)piperazin-1-yl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1aq)



1-(4-bromobenzyl)-4-(pyridin-3-ylmethyl)piperazine (346 mg, 1.00 mmol) was dissolved in Et₂O (1.5 mL) and cooled to 0 °C. Trifluoromethanesulfonic acid (89 μL, 1.00 mmol) was added dropwise, the ice bath was removed and the solution was stirred for 10 minutes at room temperature. The solution was concentrated *in vacuo* and the resulting acid salt was subjected to general procedure A (except that after PPh₃ was added, the reaction mixture was stirred for 30 min at –50 °C) using Tf₂O (168 μL, 1.00 mmol), PPh₃ (289 mg, 1.10 mmol), DBU (300 μL, 2.00 mmol) and CH₂Cl₂ (10 mL). After the purification procedure, the title compound was isolated as an off-white solid (468 mg, 0.62 mmol, 62% yield). mp 95-99 °C; IR *v*_{max}/cm^{–1} (film): 3059, 2939, 2822, 1572, 1485, 1459, 1438, 1404, 1347, 1311, 1223, 1187, 1147, 1099, 1070, 1030, 1006, 927, 842, 753, 715, 689, 636; ¹H NMR (400 MHz, CDCl₃) δ: 9.08 (1H, d, *J* = 6.8 Hz), 8.84 (1H, t, *J* = 4.7 Hz), 7.89-7.85 (3H, m), 7.80-7.68 (12H, m),

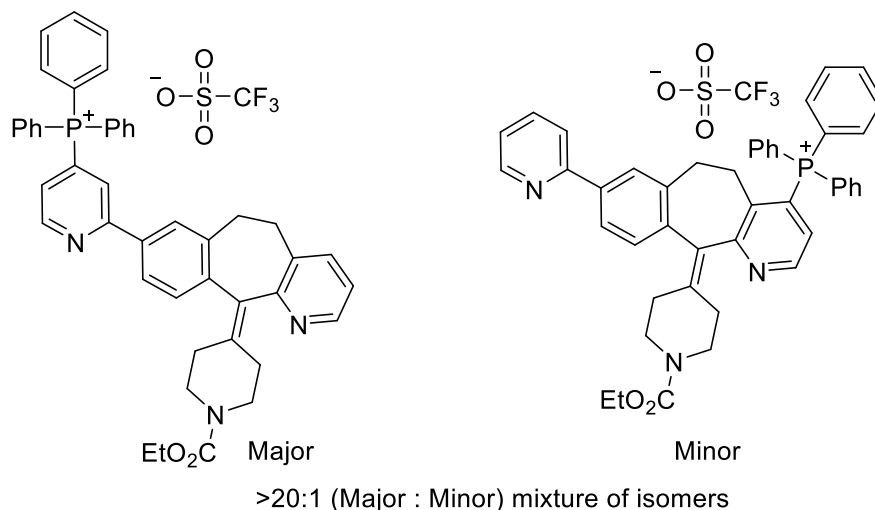
7.39 (2H, d, $J = 8.3$ Hz), 7.21 (1H, dd, $J = 15.7, 5.0$ Hz), 7.08 (2H, d, $J = 8.3$ Hz), 3.26 (2H, s), 3.10 (2H, s), 2.02-1.91 (8H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 153.37 (d, $J = 8.2$ Hz), 150.67 (d, $J = 10.8$ Hz), 137.29 (d, $J = 5.7$ Hz), 136.54, 133.62 (d, $J = 2.8$ Hz), 133.90 (d, $J = 10.2$ Hz), 131.13, 130.86 (d, $J = 13.0$ Hz), 130.63, 129.11 (d, $J = 9.8$ Hz), 126.56 (d, $J = 81.7$ Hz), 120.78 (q, $J = 319.6$ Hz), 120.72, 116.99 (d, $J = 89.1$ Hz), 61.64, 59.01 (d, $J = 3.3$ Hz), 52.61, 51.81; ^{19}F NMR (365 MHz, CDCl_3) δ : -78.05; ^{31}P NMR (162 MHz, CDCl_3) δ : 21.19; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 606.3, $\text{C}_{35}\text{H}_{34}\text{BrN}_3\text{P}^+$ requires 606.2.

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



Prepared according to our previous report.⁶ Major isomer, ^1H NMR (400 MHz, CDCl_3) δ : 8.75 (1H, app t, $J = 4.5$ Hz), 8.67 (1H, d, $J = 3.3$ Hz), 8.06-7.56 (18H, m), 7.44 (1H, s), 7.35-7.17 (2H, m), 7.05 (1H, dd, $J = 14.9, 5.1$ Hz), 4.16 (2H, q, $J = 7.0$ Hz), 3.90-3.62 (2H, m), 3.54-3.24 (3H, m), 3.03-2.81 (1H, m), 2.74-2.35 (4H, m), 2.32-2.07 (1H, m), 1.91-1.67 (1H, m), 1.28 (3H, t, $J = 7.0$ Hz); Major isomer, ^{13}C NMR (100 MHz, CDCl_3) δ : 163.8 (d, $J = 8.5$ Hz), 156.2, 155.4, 149.4, 149.0 (d, $J = 11.5$ Hz), 139.1-138.7 (2C), 137.2 (d, $J = 7.1$ Hz), 136.1 (d, $J = 2.1$ Hz), 135.4, 134.2 (d, $J = 10.5$ Hz), 133.2 (d, $J = 2.1$ Hz), 131.1 (d, $J = 13.0$ Hz), 130.8, 128.6, 126.8 (d, $J = 81.4$ Hz), 127.1 (d, $J = 9.8$ Hz), 124.7, 122.4, 120.8 (q, $J = 321.3$ Hz), 120.5, 116.5 (d, $J = 88.8$ Hz), 61.4, 44.7, 44.8, 30.8, 30.8, 30.5, 29.8, 14.6. The spectroscopic data is in agreement with our reported synthesis.⁶

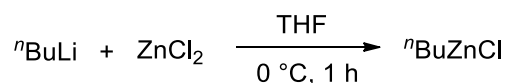
(2-(11-(1-(Ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-8-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (1as)



Prepared according to our previous report.⁶ Major isomer, ¹H NMR (400 MHz, CDCl₃) δ: 9.07 (1H, app t, *J* = 4.9 Hz), 8.39 (1H, dd, *J* = 5.0, 1.4 Hz), 7.98-7.89 (3H, m), 7.86 (1H, d, *J* = 1.5 Hz), 7.85-7.76 (7H, m), 7.75-7.65 (6H, m), 7.59 (1H, dd, *J* = 7.9, 1.8 Hz), 7.54-7.44 (2H, m), 7.29 (1H, d, *J* = 8.0 Hz), 7.11 (1H, dd, *J* = 7.7, 4.8 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.94-3.69 (2H, m), 3.57-3.30 (2H, m), 3.23-3.03 (2H, m), 3.03-2.82 (2H, m), 2.61-2.24 (4H, m), 1.24 (3H, t, *J* = 7.1 Hz); Major isomer, ¹³C NMR (100 MHz, CDCl₃) δ: 159.0 (d, *J* = 10.3 Hz), 151.7 (d, *J* = 11.2 Hz), 156.4, 155.4, 146.2, 141.7, 139.0, 138.0, 137.9, 136.2 (d, *J* = 2.9 Hz), 136.1 (d, *J* = 1.5 Hz), 134.5 (d, *J* = 10.7 Hz), 134.2, 133.8, 131.0 (d, *J* = 13.1 Hz), 129.9, 129.3 (d, *J* = 83.6 Hz), 125.2 (d, *J* = 8.4 Hz), 124.7, 123.2 (d, *J* = 8.8 Hz), 122.4, 120.8 (q, *J* = 320.8 Hz), 115.7 (d, *J* = 89.2 Hz), 61.2, 44.7, 31.7, 31.5, 30.7, 30.5, 14.6. The spectroscopic data is in agreement with our reported synthesis.²

5. Preparation of Alkyl Zinc Reagents

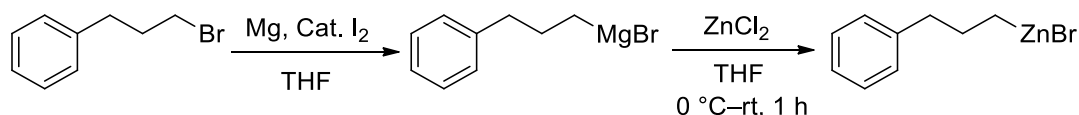
n-Butylzinc chloride



An oven-dried 50 mL round bottomed flask was charged with anhydrous ZnCl₂ (1.36 g, 10.00 mmol) and anhydrous THF (20 mL). The colorless solution was cooled to 0 °C, ⁿBuLi (2.5 M in hexanes, 4.00 mL, 10.00 mmol) was added dropwise, and the reaction mixture was stirred for 1 hour. The concentration of resulting n-butylzinc chloride solution (0.40 M) was determined by titration following the procedure of

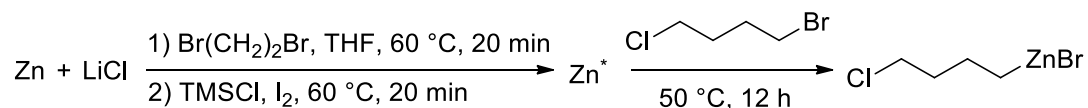
Knochel⁷: A flame-dried 8 mL vial was charged with I₂ (51 mg, 0.20 mmol) and flushed with N₂. The iodine was dissolved in 2.0 mL of a 0.5 M solution of LiCl in anhydrous THF. The solution was cooled to 0 °C using an ice bath and the n-butylzinc chloride solution was added dropwise until the brown red/brownish color had disappeared.

(3-Phenylpropyl)zinc bromide



Two round-bottom flasks were flame-dried and allowed to cool under vacuum. Both flasks were then backfilled with N₂. One flask was charged with Mg turnings (292 mg, 12.00 mmol) and I₂ (20 mg, 0.08 mmol). In the other flame-dried flask, (3-bromopropyl)benzene (1.22 mL, 8.00 mmol) was dissolved in anhydrous THF (8 mL) to make a 1.0 M solution of (3-bromopropyl)benzene in THF. A small portion of (3-bromopropyl)benzene solution (approx. 1 mL) was added to the Mg and I₂, and the mixture was stirred. The flask was heated gently with a heat gun until the dark brown color disappeared. The rest of (3-bromopropyl)benzene solution was added dropwise while the flask was heated with a heat gun. After 2 hours stirring at room temperature, the resulting solution of Grignard reagent (8.20 mL) was titrated with I₂ to afford the concentration (0.80 M). To a separate flame-dried round-bottom flask, ZnCl₂ (894 mg, 1.66 M in THF, 6.56 mmol) was added and cooled to 0 °C. A portion of the solution of (3-phenylpropyl)magnesium bromide (6.56 mmol) was added dropwise to the ZnCl₂ solution, and the mixture was allowed to warm to rt and stirred for 1 hour. The concentration of the resulting (3-phenylpropyl)zinc bromide (0.49 M) was determined according to the procedure for titration of n-butylzinc chloride.

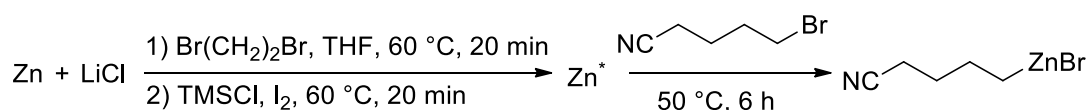
(4-Chlorobutyl)zinc bromide



In a glovebox, a 50 mL round-bottom flask equipped with a magnetic stir bar was charged with LiCl (170 mg, 4.00 mmol) and zinc dust (390 mg, 6.00 mmol) then sealed with a rubber septum and moved outside the glovebox. Under high vacuum,

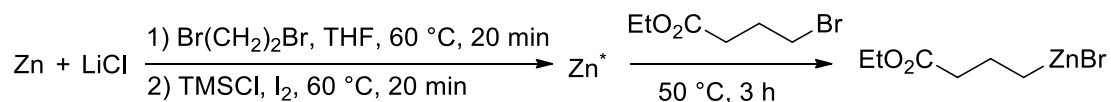
the flask was heated with a heat gun for 15 min with occasional stirring then cooled to room temperature and backfilled with N₂. After repeating this process once more, THF (4 mL) and 1,2-dibromoethane (17 µL, 0.20 mmol) were added via syringe and the reaction mixture was heated at 60 °C for 20 min. After cooling to room temperature, chlorotrimethylsilane (5 µL, 0.04 mmol) and a solution of iodine (5 mg, 0.02 mmol) in THF (160 µL) were added via syringe. The reaction mixture was heated at 60 °C for 20 min and then cooled to room temperature. 1-Bromo-4-chlorobutane (0.46 mL, 4.00 mmol) was added dropwise over 5 min after which the flask was sealed with vinyl tape and allowed to stir at 50 °C for 12 hours at which time it was cooled to room temperature and allowed to stand for 6 hours. The concentration of (4-chlorobutyl)zinc bromide (0.80 M) was determined according to the procedure for titration of n-butylzinc chloride.

(4-Cyanobutyl)zinc bromide



This compound was prepared according to the procedure for synthesis of (4-chlorobutyl)zinc bromide, using LiCl (170 mg, 4.00 mmol), zinc dust (390 mg, 6.00 mmol), THF (4 mL), 1,2-dibromoethane (17 µL, 0.20 mmol), chlorotrimethylsilane (5 µL, 0.04 mmol), a solution of iodine (5 mg, 0.02 mmol) in THF (160 µL) and 5-bromopentanenitrile (0.47 mL, 4.00 mmol). The concentration of the resulting (4-cyanobutyl)zinc bromide is 0.59 M.

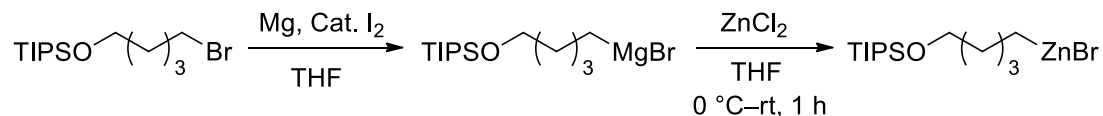
(4-Ethoxy-4-oxobutyl)zinc bromide



This compound was prepared according to the procedure for synthesis of (4-chlorobutyl)zinc bromide, using LiCl (170 mg, 4.00 mmol), zinc dust (390 mg, 6.00 mmol), THF (4 mL), 1,2-dibromoethane (17 µL, 0.20 mmol), chlorotrimethylsilane (5 µL, 0.04 mmol), a solution of iodine (5 mg, 0.02 mmol) in THF (160 µL) and ethyl 4-bromobutanoate (0.58 mL, 4.00 mmol). The concentration

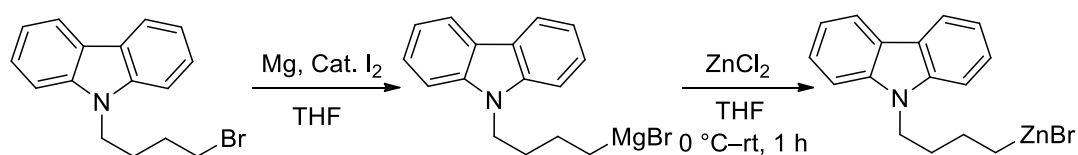
of the resulting (4-ethoxy-4-oxobutyl)zinc bromide is 0.53 M.

(5-((Triisopropylsilyl)oxy)pentyl)zinc bromide



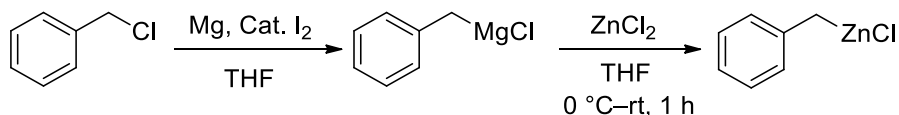
This compound was prepared according to the procedure for synthesis of (3-phenylpropyl)zinc reagent, using Mg turnings (183 mg, 7.50 mmol), I₂ (13 mg, 0.05 mmol), ((5-bromopentyl)oxy)triisopropylsilane (1.62 g, 5.00 mmol), anhydrous THF (5 mL) and ZnCl₂ (564 mg, 1.66 M in THF, 4.14 mmol). The concentration of the resulting (5-((triisopropylsilyl)oxy)pentyl)zinc bromide is 0.37 M.

(4-(9H-Carbazol-9-yl)butyl)zinc bromide



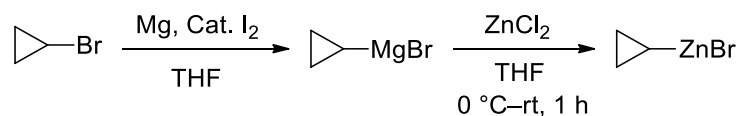
This compound was prepared according to the procedure for synthesis of (3-phenylpropyl)zinc reagent, using Mg turnings (183 mg, 7.50 mmol), I₂ (13 mg, 0.05 mmol), 9-(4-bromobutyl)-9H-carbazole (1.51 g, 5.00 mmol), anhydrous THF (5 mL) and ZnCl₂ (516 mg, 1.66 M in THF, 3.79 mmol). The concentration of the resulting (4-(9H-carbazol-9-yl)butyl)zinc bromide is 0.50 M.

Benzylzinc chloride



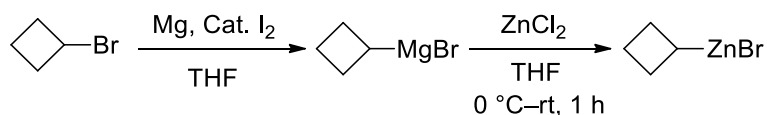
This compound was prepared according to the procedure for synthesis of (3-phenylpropyl)zinc reagent, using Mg turnings (292 mg, 12.00 mmol), I₂ (20 mg, 0.08 mmol), benzyl chloride (0.92 mL, 8.00 mmol), anhydrous THF (8 mL) and ZnCl₂ (609 mg, 1.66 M in THF, 4.47 mmol). The concentration of the resulting benzylzinc chloride is 0.49 M.

Cyclopropylzinc bromide



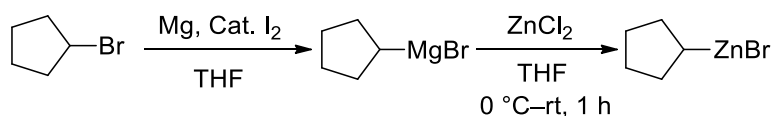
This compound was prepared according to the procedure for synthesis of (3-phenylpropyl)zinc reagent, using Mg turnings (292 mg, 12.00 mmol), I₂ (20 mg, 0.08 mmol), cyclopropyl bromide (0.64 mL, 8.00 mmol), anhydrous THF (8 mL) and ZnCl₂ (679 mg, 1.66 M in THF, 4.98 mmol). The concentration of the resulting cyclopropylzinc bromide is 0.21 M.

Cyclobutylzinc bromide



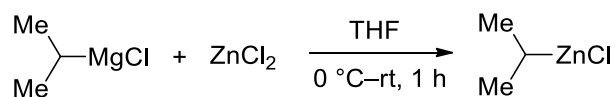
This compound was prepared according to the procedure for synthesis of (3-phenylpropyl)zinc reagent, using Mg turnings (292 mg, 12.00 mmol), I₂ (20 mg, 0.08 mmol), cyclobutyl bromide (0.68 mL, 8.00 mmol), anhydrous THF (8 mL) and ZnCl₂ (796 mg, 1.66 M in THF, 5.84 mmol). The concentration of the resulting cyclobutylzinc bromide is 0.53 M.

Cyclopentylzinc bromide



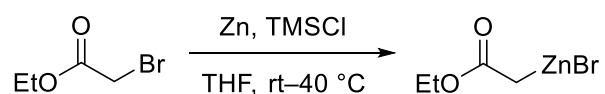
This compound was prepared according to the procedure for synthesis of (3-phenylpropyl)zinc reagent, using Mg turnings (292 mg, 12.00 mmol), I₂ (20 mg, 0.08 mmol), cyclopentyl bromide (0.86 mL, 8.00 mmol), anhydrous THF (8 mL) and ZnCl₂ (478 mg, 1.66 M in THF, 3.51 mmol). The concentration of the resulting cyclobutylzinc bromide is 0.40 M.

Isopropylzinc chloride



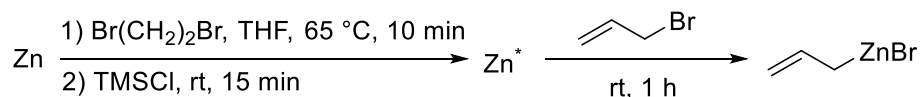
An oven-dried 25 mL round bottomed flask was charged with anhydrous ZnCl_2 (314 mg, 2.30 mmol) and anhydrous THF (5 mL). The colorless solution was cooled to 0 °C, isopropylmagnesium chloride (2.0 M in THF, 1.15 mL, 2.30 mmol) was added dropwise. Then the reaction mixture was warmed up to room temperature and stirred for 1 hour. The concentration of the resulting isopropylzinc chloride (0.35 M) was determined according to the procedure for titration of n-butylzinc chloride.

(2-Ethoxy-2-oxoethyl)zinc bromide



In a glovebox, an 8 mL vial equipped with a magnetic stir bar was charged with zinc dust (455 mg, 7.00 mmol) then sealed with a rubber septum and moved outside the glovebox. Under high vacuum, the flask was heated with a heat gun for 15 min with occasional stirring then cooled to room temperature and backfilled with N_2 . After repeating this process once more, THF (4.2 mL) and chlorotrimethylsilane (43 μL , 0.34 mmol) were added via syringe and the reaction mixture was stirred at room temperature for 20 min. Then, a solution of ethyl 2-bromoacetate (555 μL , 5.00 mmol) in THF (1.7 mL) was added dropwise over 30 min after which the vial was sealed with vinyl tape and allowed to stir at 40 °C for 30 min at which time it was cooled to room temperature and allowed to stand for 1 hour. The concentration of (2-ethoxy-2-oxoethyl)zinc bromide (0.54 M) was determined according to the procedure for titration of n-butylzinc chloride.

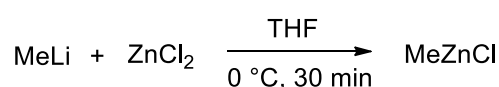
(4-Chlorobutyl)zinc bromide



In a glovebox, an vial equipped with a magnetic stir bar was charged with zinc dust (390 mg, 6.00 mmol) then sealed with a rubber septum and moved outside the glovebox. Under high vacuum, the flask was heated with a heat gun for 15 min with occasional stirring then cooled to room temperature and backfilled with N_2 . After repeating this process once more, THF (1 mL) and 1,2-dibromoethane (51 μL , 0.60 mmol) were added via syringe and the reaction mixture was heated at 65 °C for 10

min. After cooling to room temperature, chlorotrimethylsilane (51 μ L, 0.40 mmol) in THF (0.5 mL) were added via syringe. The reaction mixture was stirred at room temperature for 15 min. A solution of allyl bromide (433 μ L, 5.00 mmol) in THF (2.5 mL) was added dropwise over 30 min after which the flask was sealed with vinyl tape and stirred for another 30 min at room temperature, and then allowed to stand for 1 hour. The concentration of allyliczinc bromide (1.00 M) was determined according to the procedure for titration of n-butylzinc chloride.

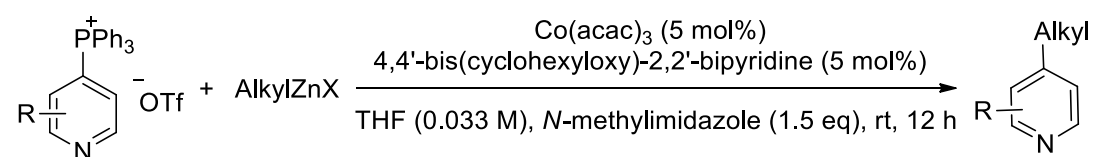
Methylzinc chloride



An oven-dried 50 mL round bottomed flask was charged with anhydrous ZnCl_2 (682 mg, 5.00 mmol) and anhydrous THF (10 mL). The colorless solution was cooled to 0 $^\circ\text{C}$, 1.6 M MeLi in diethyl ether (3.13 mL, 5.00 mmol) was added dropwise, and the reaction mixture was stirred for 30 min. The concentration of resulting methylzinc chloride solution (0.49 M) was determined according to the procedure for titration of n-butylzinc chloride.

6. Preparation of alkylated pyridines

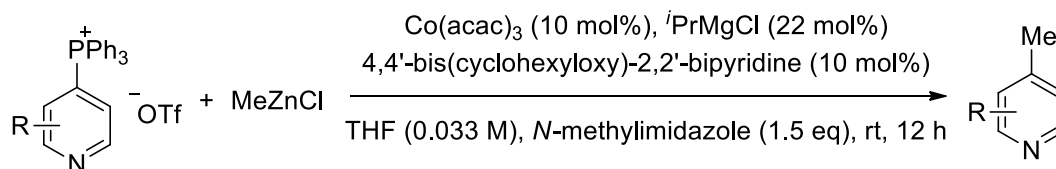
General Procedure B



An oven dried 8 mL vial with a septa cap was charged with a phosphonium salt (1.0 equiv), $\text{Co}(\text{acac})_3$ (5 mol%) and 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (5 mol%). The vial was then evacuated and backfilled with N_2 three times. THF (0.033 M), Alkylzinc reagent (2 equiv) and *N*-methylimidazole (1.5 equiv) were added sequentially under N_2 . And then the vial was sealed with a new septa cap and the reaction mixture was stirred at room temperature for 12 hours. The reaction was quenched with H_2O , the aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried with MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified

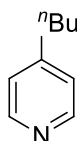
by flash column chromatography under the stated conditions to provide the alkylated pyridine product.

General Procedure C



An oven dried 8 mL vial with a septa cap was charged with a phosphonium salt (1.0 equiv), $\text{Co}(\text{acac})_3$ (10 mol%) and 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (10 mol%). The vial was then evacuated and backfilled with N_2 three times. THF (0.033 M), Methylzinc chloride (3 equiv), *N*-methylimidazole (1.5 equiv) and $i\text{PrMgCl}$ (22 mol%) were added sequentially under N_2 . Then the vial was sealed with a new septa cap and the reaction mixture was stirred at room temperature for 12 hours. The reaction was quenched with H_2O , the aqueous layer was separated and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried with MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the methylated pyridine product.

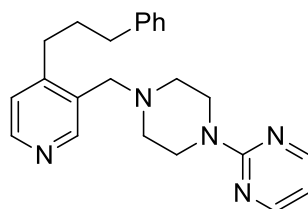
4-Butylpyridine (2a)



Prepared according to general procedure B using triphenyl(pyridin-4-yl)phosphonium trifluoromethanesulfonate (98 mg, 0.20 mmol), $n\text{BuZnCl}$ (0.40 mmol), $\text{Co}(\text{acac})_3$ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μL , 0.30 mmol) and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 17% Acetone in Hexanes) afforded the title compound as an orange oil (21 mg, 0.16 mmol, 78% yield). ^1H NMR (400 MHz, CDCl_3) δ : 8.46 (2H, d, $J = 5.8$ Hz), 7.08 (2H, d, $J = 5.5$ Hz), 2.58 (2H, t, $J = 7.8$ Hz), 1.59 (2H, qn, $J = 7.4$ Hz), 1.34 (2H, sext, $J = 7.4$ Hz), 0.91 (3H, t, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 151.62, 149.57, 123.83, 34.87, 32.35, S34

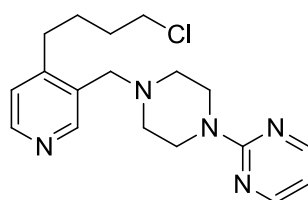
22.19, 13.77. The spectroscopic data is in agreement with previous reported synthesis.⁸

2-(4-((4-(3-Phenylpropyl)pyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2b)



Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), (4-chlorobutyl)zinc chloride (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol) and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: EtOAc to 2% Et₃N in EtOAc) afforded the title compound as an orange oil (49 mg, 0.13 mmol, 65% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3023, 2933, 2853, 1679, 1583, 1545, 1494, 1446, 1392, 1357, 1305, 1256, 1126, 1080, 1003, 981, 954, 796, 747, 699, 638; ¹H NMR (400 MHz, CDCl₃) δ : 8.42-8.39 (2H, m), 8.29 (2H, d, *J* = 4.7 Hz), 7.28 (2H, dd, *J* = 7.8, 7.3 Hz), 7.19 (3H, d, *J* = 6.2 Hz), 7.11 (1H, d, *J* = 5.0 Hz), 6.46 (1H, t, *J* = 5.1 Hz), 3.73 (4H, t, *J* = 4.7 Hz), 3.40 (2H, s), 2.77-2.69 (4H, m), 2.38 (4H, t, *J* = 4.9 Hz), 1.95 (2H, qn, *J* = 7.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 161.54, 157.62, 151.20, 151.04, 148.88, 141.65, 131.32, 128.40, 128.35, 125.93, 124.15, 109.71, 58.05, 52.81, 43.63, 35.78, 31.78, 31.16; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 374.3, C₂₃H₂₈N₅⁺ requires 374.2.

2-(4-((4-(4-Chlorobutyl)pyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2c)

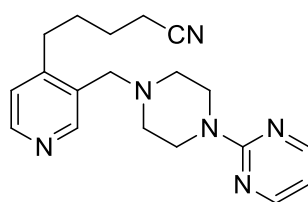


Prepared according to general procedure B using

S35

triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), (4-chlorobutyl)zinc chloride (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), ⁱPrMgCl (11 μ L, 0.022 mmol) and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: EtOAc to 2% Et₃N in EtOAc) afforded the title compound as an orange oil (54 mg, 0.16 mmol, 78% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2937, 2852, 1676, 1583, 1545, 1491, 1445, 1392, 1357, 1305, 1256, 1221, 1126, 1004, 981, 954, 796, 733, 638; ¹H NMR (400 MHz, CDCl₃) δ : 8.42 (2H, br s), 8.28 (2H, d, *J* = 4.7 Hz), 7.11 (1H, d, *J* = 4.7 Hz), 6.46 (1H, t, *J* = 4.8 Hz), 3.78 (4H, t, *J* = 4.9 Hz), 3.56 (2H, t, *J* = 6.0 Hz), 3.51 (2H, s), 2.76 (2H, dd, *J* = 7.8, 7.1 Hz), 2.48 (4H, t, *J* = 5.0 Hz), 1.89-1.76 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 161.59, 157.64, 151.21, 150.67, 148.99, 131.31, 124.07, 109.80, 58.26, 52.94, 44.61, 43.65, 32.28, 30.89, 27.25; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 346.3, C₁₈H₂₅ClN₅⁺ requires 346.2.

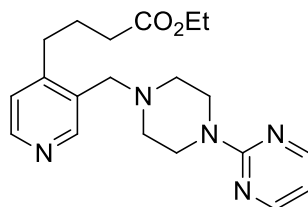
5-(3-((4-(Pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)pentanenitrile (2d)



Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), (4-chlorobutyl)zinc chloride (0.40 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), ⁱPrMgCl (22 μ L, 0.044 mmol) and THF (0.033 M) at 50 °C for 12 hours. Flash column chromatography (silica gel: EtOAc to 2% Et₃N in EtOAc) afforded the title compound as an orange oil (42 mg, 0.12 mmol, 62% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2936, 2855, 2244, 1583, 1545, 1491, 1446, 1392, 1356, 1305, 1256, 1221, 1126, 1079, 1003, 981, 954, 834, 796, 638; ¹H NMR (400 MHz, CDCl₃) δ : 8.44-8.42 (2H, m), 8.28 (2H, d, *J* = 4.7 Hz), 7.11 (1H, d, *J* = 4.8 Hz), 6.46 (1H, t, *J* = 4.7 Hz), 3.77 (4H, t, *J* = 4.7 Hz), 3.50 (2H, s), 3.79 (2H, dd, *J* = 7.9, 7.2 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 2.38 (2H, dd, *J* = 6.9, 6.6 Hz), 1.84-1.72 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 161.57, 157.63, 151.30, 150.06, 149.09, 131.26, 123.95, 119.31, 109.85, 58.31, 52.94, 43.65, 30.77, 28.89, 25.17, 17.03; *m/z* S36

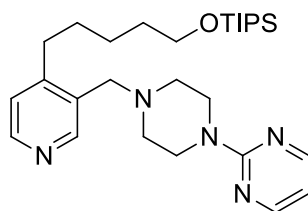
LRMS (ESI + APCI) found $[M+H]^+$ 337.3, $C_{19}H_{25}N_6^+$ requires 337.2.

Ethyl 4-(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)butanoate (2e)



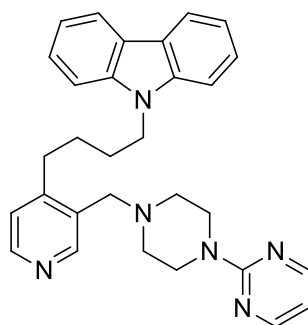
Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), (4-ethoxy-4-oxobutyl)zinc bromide (0.60 mmol), $Co(acac)_3$ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), $iPrMgCl$ (22 μ L, 0.044 mmol) and THF (0.033 M) at 50 °C for 24 hours. Flash column chromatography (silica gel: EtOAc to 2% Et_3N in EtOAc) afforded the title compound as an orange oil (31 mg, 0.09 mmol, 42% yield). IR ν_{max}/cm^{-1} (film): 2936, 1728, 1583, 1546, 1492, 1446, 1392, 1357, 1305, 1256, 1182, 1004, 981, 954, 796; 1H NMR (400 MHz, $CDCl_3$) δ : 8.43-8.42 (2H, m), 8.28 (2H, d, $J = 4.7$ Hz), 7.12 (1H, d, $J = 4.9$ Hz), 6.46 (1H, t, $J = 4.7$ Hz), 4.11 (1H, q, $J = 7.1$ Hz), 3.78 (4H, t, $J = 4.8$ Hz), 3.52 (2H, s), 2.77 (2H, t, $J = 7.8$ Hz), 2.49 (4H, t, $J = 4.9$ Hz), 2.37 (2H, t, $J = 7.3$ Hz), 2.00-1.94 (2H, m), 1.23 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 173.07, 161.59, 157.65, 151.11, 150.50, 148.89, 131.41, 124.26, 109.81, 60.37, 58.05, 52.90, 43.62, 33.89, 31.13, 25.33, 14.20; m/z LRMS (ESI + APCI) found $[M+H]^+$ 370.3, $C_{20}H_{28}N_5O_2^+$ requires 370.2.

2-(4-((4-(5-((Triisopropylsilyl)oxy)pentyl)pyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2f)



Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), (5-((triisopropylsilyl)oxy)pentyl)zinc bromide (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), *i*PrMgCl (11 μ L, 0.022 mmol) and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: EtOAc to 1% Et₃N in EtOAc) afforded the title compound as an orange oil (64 mg, 0.13 mmol, 64% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2938, 2863, 1584, 1546, 1496, 1446, 1391, 1357, 1306, 1257, 1105, 1005, 982, 954, 881, 796, 679; ¹H NMR (400 MHz, CDCl₃) δ : 8.43-8.40 (2H, m), 8.29 (2H, d, *J* = 4.7 Hz), 7.11 (1H, d, *J* = 5.0 Hz), 6.46 (1H, t, *J* = 4.7 Hz), 3.78 (4H, t, *J* = 4.8 Hz), 3.67 (2H, t, *J* = 6.4 Hz), 3.51 (2H, s), 2.73 (2H, t, *J* = 7.7 Hz), 2.48 (4H, t, *J* = 4.9 Hz), 1.69-1.54 (4H, m), 1.49-1.41 (2H, m), 1.11-1.00 (21H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 161.62, 157.64, 151.56, 150.94, 148.70, 131.35, 124.18, 109.77, 63.16, 58.11, 52.96, 43.70, 32.82, 31.86, 30.06, 25.97, 17.99, 11.95; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 498.4, C₂₈H₄₈N₅OSi⁺ requires 498.4.

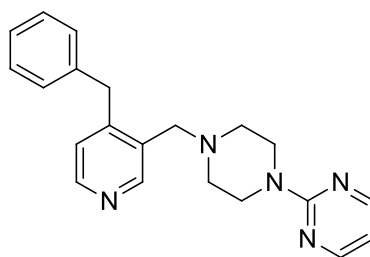
9-(4-(3-((4-(Pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)butyl)-9H-carbazole (2g)



Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), (4-(9H-carbazol-9-yl)butyl)zinc bromide (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), *i*PrMgCl (11 μ L, 0.022 mmol) and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 20% Acetone in hexanes to 33% Acetone in hexanes) afforded the title compound as an orange oil (71

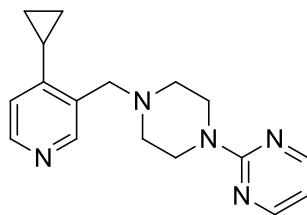
mg, 0.15 mmol, 74% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3046, 2935, 2852, 1626, 1584, 1545, 1483, 1449, 1392, 1356, 1325, 1306, 1256, 1152, 1121, 1064, 1003, 982, 954, 796, 749, 723; ^1H NMR (400 MHz, CDCl_3) δ : 8.38-8.36 (2H, m), 8.32 (2H, d, $J = 4.7$ Hz), 8.02 (2H, d, $J = 7.7$ Hz), 7.42 (2H, dt, $J = 7.6, 1.1$ Hz), 7.36 (2H, d, $J = 8.1$ Hz), 7.19 (2H, dt, $J = 7.4, 1.0$ Hz), 6.99 (2H, d, $J = 5.0$ Hz), 6.49 (1H, t, $J = 4.7$ Hz), 4.36 (2H, t, $J = 6.8$ Hz), 3.55 (4H, t, $J = 4.8$ Hz), 3.37 (2H, s), 2.68 (2H, t, $J = 7.8$ Hz), 2.34 (4H, t, $J = 5.0$ Hz), 2.05-1.95 (2H, m), 1.73-1.66 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 161.49, 157.56, 151.01, 150.68, 148.86, 140.22, 131.27, 125.56, 124.02, 122.74, 120.35, 118.79, 109.73, 108.41, 58.19, 52.77, 43.41, 42.69, 31.63, 29.08, 27.84; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 477.3, $\text{C}_{30}\text{H}_{33}\text{N}_6^+$ requires 477.3.

2-((4-(4-Benzylpyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2h)



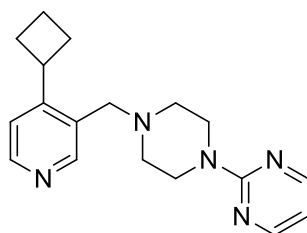
Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), benzylzinc chloride (0.40 mmol), $\text{Co}(\text{acac})_3$ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μL , 0.30 mmol), and THF (0.033 M) at 50 $^\circ\text{C}$ for 12 hours. Flash column chromatography (silica gel: 33% EtOAc, 10% Et_3N in hexanes) afforded the title compound as an orange solid (35 mg, 0.10 mmol, 51% yield). mp 95-99 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3391, 3026, 2994, 2959, 2934, 2827, 1669, 1581, 1547, 1473, 1441, 1374, 1356, 1305, 1269, 1253, 1223, 1205, 1180, 1147, 1126, 1091, 1056, 1027, 1005, 981, 953, 920, 847, 800, 790, 729, 698, 653, 637, 619; ^1H NMR (400 MHz, CDCl_3) δ : 8.45 (2H, br s), 8.29 (2H, d, $J = 4.7$ Hz), 7.31-7.20 (3H, m), 7.14 (2H, d, $J = 7.2$ Hz), 7.04 (1H, d, $J = 4.7$ Hz), 6.47 (1H, t, $J = 4.7$ Hz), 4.19 (2H, s), 3.77 (4H, t, $J = 4.9$ Hz), 3.48 (2H, s), 2.46 (4H, t, $J = 5.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 161.61, 157.65, 151.19, 149.55, 149.15, 138.90, 131.66, 128.94, 128.55, 126.41, 125.21, 109.79, 58.36, 52.92, 43.64, 37.78; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 346.3, $\text{C}_{21}\text{H}_{24}\text{N}_5^+$ requires 346.2.

2-(4-((4-Cyclopropylpyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2i)



Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), cyclopropylzinc chloride (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: EtOAc to 2% Et₃N in EtOAc) afforded the title compound as an orange oil (53 mg, 0.18 mmol, 90% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3377, 2998, 2837, 2810, 1673, 1583, 1545, 1492, 1445, 1392, 1357, 1305, 1257, 1223, 1124, 1042, 1004, 981, 953, 902, 796; ¹H NMR (400 MHz, CDCl₃) δ : 8.38-8.35 (2H, m), 8.27 (2H, d, J = 4.7 Hz), 6.74 (1H, d, J = 5.1 Hz), 6.44 (1H, t, J = 4.7 Hz), 3.78 (4H, t, J = 5.0 Hz), 3.63 (2H, s), 2.50 (4H, t, J = 5.0 Hz), 2.31-2.24 (1H, m), 1.06-1.01 (2H, m), 0.74-0.70 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 161.56, 157.60, 152.52, 150.38, 148.96, 132.08, 118.51, 109.69, 58.14, 52.94, 43.88, 11.49, 8.88; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 296.3, C₁₇H₂₂N₅⁺ requires 296.2.

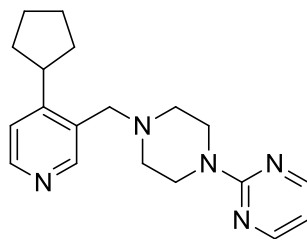
2-(4-((4-Cyclobutylpyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2j)



Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), cyclobutylzinc chloride (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room

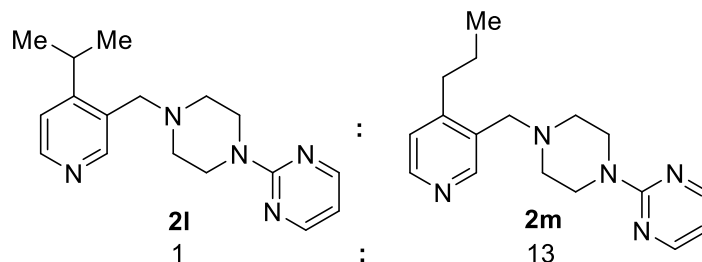
temperature for 12 hours. Flash column chromatography (silica gel: 33% EtOAc and 10% Et₃N in hexanes) afforded the title compound as an orange oil (53 mg, 0.17 mmol, 86% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2937, 2854, 1676, 1583, 1545, 1488, 1444, 1392, 1356, 1306, 1256, 1221, 1127, 1062, 1004, 981, 954, 828, 796, 730, 638; ¹H NMR (400 MHz, CDCl₃) δ : 8.47-8.42 (2H, m), 8.27 (2H, d, J = 4.7 Hz), 7.23 (1H, d, J = 5.0 Hz), 6.44 (1H, t, J = 4.7 Hz), 3.88 (1H, qn, J = 8.1 Hz), 3.78 (4H, t, J = 5.0 Hz), 3.45 (2H, s), 2.44 (4H, t, J = 5.0 Hz), 2.39-2.32 (2H, m), 2.18-2.00 (3H, m), 1.89-1.82 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 161.60, 157.61, 153.50, 150.58, 149.04, 130.79, 120.92, 109.72, 58.05, 52.99, 43.69, 36.74, 28.58, 18.23; m/z LRMS (ESI + APCI) found $[M+H]^+$ 310.3, C₁₈H₂₄N₅⁺ requires 310.2.

2-(4-((4-Cyclopentylpyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2k)



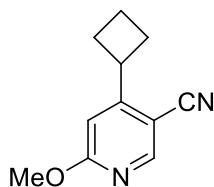
Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), cyclopentylzinc chloride (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 33% EtOAc and 5% Et₃N in hexanes) afforded the title compound as a light yellow oil (7 mg, 0.02 mmol, 11% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3367, 2946, 2865, 1673, 1583, 1546, 1489, 1445, 1392, 1357, 1306, 1256, 1221, 1127, 1060, 1004, 981, 954, 796, 638; ¹H NMR (400 MHz, CDCl₃) δ : 8.45-8.41 (2H, m), 8.30 (2H, d, J = 4.7 Hz), 7.22 (1H, d, J = 5.1 Hz), 6.47 (1H, t, J = 4.7 Hz), 3.79 (4H, t, J = 5.0 Hz), 3.56 (2H, s), 3.42 (1H, qn, J = 8.5 Hz), 2.49 (4H, t, J = 5.0 Hz), 2.10-2.05 (2H, m), 1.90-1.80 (2H, m), 1.76-1.66 (2H, m), 1.63-1.52 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 161.68, 157.68, 156.13, 150.84, 149.00, 131.22, 121.17, 109.82, 58.31, 52.88, 43.80, 40.35, 34.60, 26.03; m/z LRMS (ESI + APCI) found $[M+H]^+$ 324.3, C₁₉H₂₆N₅⁺ requires 324.2.

2-(4-((4-Isopropylpyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2l) and 2-(4-((4-Propylpyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2m)



Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), isopropylzinc chloride (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: EtOAc to 2% Et₃N in EtOAc) afforded the mixture of isomers as an orange oil (41 mg, 0.14 mmol, 68% yield). Mixture, IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2957, 2870, 1675, 1583, 1545, 1491, 1445, 1392, 1357, 1305, 1256, 1128, 1004, 981, 954, 796; Major isomer, ¹H NMR (400 MHz, CDCl₃) δ : 8.44-8.40 (2H, m), 8.28 (2H, d, J = 4.8 Hz), 7.10 (1H, d, J = 4.8 Hz), 6.46 (1H, t, J = 4.7 Hz), 3.78 (4H, t, J = 4.9 Hz), 3.51 (2H, s), 2.77 (2H, t, J = 7.8 Hz), 2.69 (2H, t, J = 7.7 Hz), 2.49 (4H, t, J = 4.7 Hz), 1.65 (2H, sext, J = 7.7 Hz), 0.98 (3H, t, J = 7.3 Hz); Major isomer, ¹³C NMR (100 MHz, CDCl₃) δ : 161.63, 157.65, 151.34, 150.94, 148.67, 131.41, 124.15, 109.78, 58.03, 52.94, 43.70, 33.79, 23.32, 14.14; m/z LRMS (ESI + APCI) found $[M+H]^+$ 298.3, C₁₇H₂₄N₅⁺ requires 298.2.

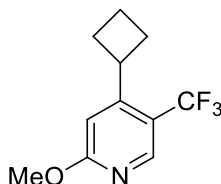
4-Cyclobutyl-6-methoxynicotinonitrile (2n)



Prepared according to general procedure B using (5-cyano-2-methoxypyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (109 mg, 0.20 mmol), cyclobutylzinc bromide (0.60 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol),

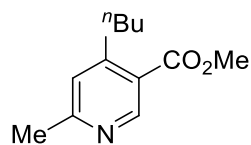
N-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a colorless oil (16 mg, 0.09 mmol, 42% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2982, 2948, 2869, 2223, 1600, 1540, 1485, 1445, 1374, 1312, 1279, 1241, 1200, 1143, 1035, 1003, 932, 867; ^1H NMR (400 MHz, CDCl_3) δ : 8.36 (1H, s), 6.70 (1H, s), 3.97 (3H, s), 3.74 (1H, qn, $J = 8.0$ Hz), 2.51-2.44 (2H, m), 2.18-2.03 (3H, m), 1.93-1.85 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 166.57, 159.66, 152.31, 116.83, 108.44, 102.02, 54.12, 38.01, 28.77, 28.09, 18.10; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 189.1, $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}^+$ requires 189.1.

4-Cyclobutyl-2-methoxy-5-(trifluoromethyl)pyridine (2o)



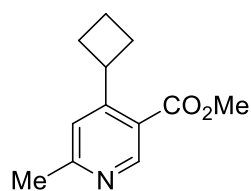
Prepared according to general procedure B using (2-methoxy-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (118 mg, 0.20 mmol), cyclobutylzinc bromide (0.60 mmol), $\text{Co}(\text{acac})_3$ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 16% CH_2Cl_2 in hexanes) afforded the title compound as a colorless oil (17 mg, 0.07 mmol, 37% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2983, 2950, 2867, 1611, 1550, 1497, 1446, 1388, 1304, 1231, 1164, 1138, 1112, 1063, 1027, 939, 867; ^1H NMR (400 MHz, CDCl_3) δ : 8.35 (1H, s), 6.83 (1H, s), 3.97 (3H, s), 3.77 (1H, qn, $J = 8.0$ Hz), 2.38-2.31 (2H, m), 2.18-1.98 (3H, m), 1.89-1.81 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 166.78, 155.44, 145.33 (q, $J = 6.8$ Hz), 124.55 (q, $J = 270.8$ Hz), 117.89 (q, $J = 30.2$ Hz), 109.28, 53.79, 36.51 (q, $J = 1.4$ Hz), 29.14, 17.94, ^{19}F NMR (365 MHz, CDCl_3) δ : -59.48; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 232.1, $\text{C}_{11}\text{H}_{13}\text{F}_3\text{NO}^+$ requires 232.1.

Methyl 4-butyl-6-methylnicotinate (2p)



Prepared according to general procedure B using (5-(methoxycarbonyl)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (113 mg, 0.20 mmol), ⁿBuZnCl (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μL, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a colorless oil (27 mg, 0.13 mmol, 64% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2955, 2930, 2861, 1722, 1598, 1549, 1433, 1379, 1278, 1190, 1165, 1095, 1079; ¹H NMR (400 MHz, CDCl₃) δ : 8.93 (1H, s), 7.02 (1H, s), 3.89 (3H, s), 2.92 (2H, t, J = 7.8 Hz), 2.54 (3H, s), 1.59-1.51 (2H, m), 1.39 (2H, qn, J = 7.2 Hz), 0.93 (3H, t, J = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 166.68, 161.63, 154.07, 151.47, 124.87, 122.67, 51.93, 33.49, 32.90, 24.40, 22.72, 13.85; m/z LRMS (ESI + APCI) found $[M+H]^+$ 208.2, C₁₂H₁₈NO₂⁺ requires 208.1.

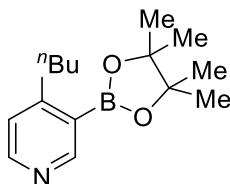
Methyl 4-cyclobutyl-6-methylnicotinate (2q)



Prepared according to general procedure B using (5-(methoxycarbonyl)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (113 mg, 0.20 mmol), cyclobutylzinc bromide (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μL, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a colorless oil (33 mg, 0.16 mmol, 80% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2973, 2867, 1712, 1595, 1540, 1486, 1432, 1385, 1360, 1310, 1277, 1239, 1186, 1163, 1088, 1038, 968, 939, 876, 836, 794; ¹H NMR (400 MHz, CDCl₃) δ : 8.84 (1H, s), 7.16 (1H, s), 4.16 (1H, qn, J = 8.0 Hz), 3.88 (3H, s),

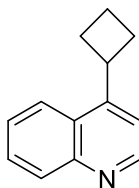
2.58 (3H, s), 2.40-2.33 (2H, m), 2.12-1.99 (3H, m), 1.84-1.77 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 166.81, 161.88, 155.78, 150.81, 122.23, 121.16, 52.00, 37.64, 28.57, 24.66, 18.12; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 206.1, $\text{C}_{12}\text{H}_{16}\text{NO}_2^+$ requires 206.1.

4-Butyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2r)



Prepared according to general procedure B using triphenyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (123 mg, 0.20 mmol), $n\text{BuZnCl}$ (0.40 mmol), $\text{Co}(\text{acac})_3$ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), N -methylimidazole (24 μL , 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 20% Acetone in hexanes) afforded the title compound as a colorless oil (27 mg, 0.10 mmol, 51% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2956, 2925, 2870, 1729, 1611, 1553, 1458, 1410, 1381, 1370, 1358, 1274, 1153, 1094, 1024, 962, 886, 848, 836, 797, 746, 724, 676; ^1H NMR (400 MHz, CDCl_3) δ : 8.84 (1H, s), 8.49 (1H, d, $J = 5.2$ Hz), 7.07 (1H, d, $J = 5.2$ Hz), 2.84 (2H, t, $J = 7.3$ Hz), 1.53 (2H, qn, $J = 7.6$ Hz), 1.42-1.35 (14H, m), 0.92 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.89, 156.35, 151.34, 124.19, 83.74 (2C), 34.91, 34.42, 24.82, 22.62, 13.87; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 262.3, $\text{C}_{15}\text{H}_{25}\text{BNO}_2^+$ requires 262.2.

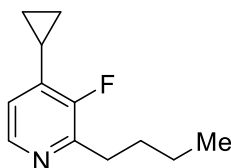
4-Cyclobutylquinoline (2s)



Prepared according to general procedure B using triphenyl(quinolin-4-yl)phosphonium trifluoromethanesulfonate (108 mg, 0.20 mmol),

cyclobutylzinc bromide (0.60 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at 50 °C for 12 hours. Flash column chromatography (silica gel: 5% EtOAc in CH₂Cl₂ to 9% EtOAc in CH₂Cl₂) afforded the title compound as a yellow oil (22 mg, 0.12 mmol, 60% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3061, 3031, 2964, 2935, 2863, 1589, 1568, 1507, 1461, 1443, 1420, 1391, 1328, 1306, 1246, 1139, 1021, 906, 867, 843, 759; ¹H NMR (400 MHz, CDCl₃) δ : 8.85 (1H, d, *J* = 4.5 Hz), 8.11 (1H, d, *J* = 8.3 Hz), 7.92 (1H, d, *J* = 8.4 Hz), 7.68 (1H, dt, *J* = 7.6, 1.4 Hz), 7.52 (1H, dt, *J* = 7.6, 1.3 Hz), 7.27 (1H, d, *J* = 8.4 Hz), 4.15 (1H, qn, *J* = 8.5 Hz), 2.59-2.52 (2H, m), 2.36-2.13 (3H, m), 1.98-1.91 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 151.26, 150.37, 148.17, 130.11, 128.86, 126.98, 126.03, 124.01, 117.61, 37.17, 28.76, 18.64; *m/z* LRMS (ESI + APCI) found [M + H]⁺ 184.2, C₁₃H₁₄N⁺ requires 184.1.

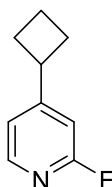
2-Butyl-4-cyclopropyl-3-fluoropyridine (2t)



Prepared according to general procedure B using (2-butyl-3-fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (113 mg, 0.20 mmol), cyclopropylzinc bromide (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 22 hours. Flash column chromatography (silica gel: 2.5% EtOAc in CH₂Cl₂) afforded the title compound as a colorless oil (28 mg, 0.14 mmol, 71% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3087, 3012, 2957, 2929, 2861, 1609, 1477, 1459, 1429, 1367, 1284, 1193, 1178, 1122, 1103, 1051, 1023, 956, 888, 867, 816; ¹H NMR (400 MHz, CDCl₃) δ : 8.14 (1H, d, *J* = 5.1 Hz), 6.56 (1H, t, *J* = 5.4 Hz), 2.81 (2H, dt, *J* = 7.8, 2.7 Hz), 2.15-2.08 (1H, m), 1.73-1.65 (2H, m), 1.39 (2H, qn, *J* = 7.3 Hz), 1.11-1.06 (2H, m), 0.94 (3H, t, *J* = 7.3 Hz), 0.81-0.77 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 157.00 (d, *J* = 250.6 Hz), 149.70 (d, *J* = 16.7 Hz), 144.38 (d, *J* = 6.3 Hz), 139.54 (d, *J* = 13.3 Hz), 117.38, 31.34, 30.74, 22.55, 13.88, 9.33, 8.14, 8.08; ¹⁹F NMR (365 MHz, CDCl₃) δ : -135.67 (t, *J* = 2.5 Hz); *m/z* LRMS (ESI + APCI) found [M+H]⁺ 194.2, C₁₁H₁₃N₂O⁺

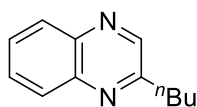
requires 194.1.

4-Cyclobutyl-2-fluoropyridine (2u)



Prepared according to general procedure B using (2-fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (102 mg, 0.20 mmol), cyclopropylzinc bromide (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: CH₂Cl₂) afforded the title compound as a colorless oil (11 mg, 0.07 mmol, 36% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2970, 2943, 2869, 1609, 1562, 1553, 1480, 1407, 1275, 1246, 1153, 1115, 1014, 950, 865, 832; ¹H NMR (400 MHz, CDCl₃) δ : 8.09 (1H, d, J = 5.2 Hz), 6.99 (1H, d, J = 5.1 Hz), 6.73 (1H, s), 3.55 (1H, qn, J = 8.5 Hz), 2.42-2.34 (2H, m), 2.19-2.01 (3H, m), 1.95-1.85 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 164.18 (d, J = 236.6 Hz), 161.11 (d, J = 7.4 Hz), 147.23 (d, J = 15.3 Hz), 119.51 (d, J = 4.3 Hz), 106.91 (d, J = 36.6 Hz), 39.19 (d, J = 3.0 Hz), 30.74, 28.86, 18.26; ¹⁹F NMR (365 MHz, CDCl₃) δ : -69.17; m/z LRMS (ESI + APCI) found [M+H]⁺ 152.2, C₉H₁₁FN⁺ requires 152.1.

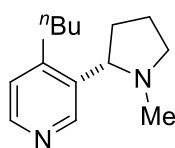
2-Butylquinoxaline (2v)



Prepared according to general procedure B using triphenyl(quinoxalin-2-yl)phosphonium trifluoromethanesulfonate (108 mg, 0.20 mmol), ⁿBuZnCl (0.60 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 14 hours. Flash column chromatography (silica gel: 5% EtOAc in CH₂Cl₂) afforded the title compound as a

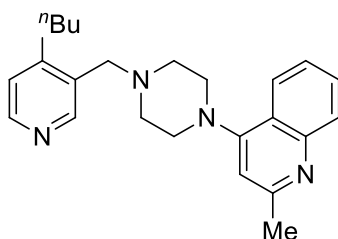
light yellow oil (17 mg, 0.09 mmol, 45% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3062, 2956, 2928, 2859, 1735, 1559, 1491, 1464, 1409, 1365, 1269, 1180, 1124, 1012, 981, 758; ^1H NMR (400 MHz, CDCl_3) δ : 8.74 (1H, s), 8.08-8.03 (2H, m), 7.76-7.68 (2H, m), 3.02 (2H, t, $J = 7.7$ Hz), 1.87-1.80 (2H, m), 1.46 (2H, sext, $J = 7.4$ Hz), 0.98 (2H, t, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 157.70, 145.83, 142.21, 141.21, 129.89, 129.17, 128.88, 128.86, 36.24, 31.62, 22.56, 13.87. The spectroscopic data is in agreement with previous reported synthesis.⁹

(S)-4-Butyl-3-(1-methylpyrrolidin-2-yl)pyridine (2w)



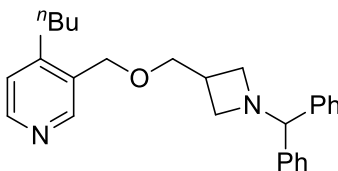
Prepared according to general procedure B using (S)-(3-(1-methylpyrrolidin-2-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (115 mg, 0.20 mmol), $n\text{BuZnCl}$ (0.40 mmol), $\text{Co}(\text{acac})_3$ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μL , 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 50% acetone in hexanes) afforded the title compound as a yellow oil (27 mg, 0.12 mmol, 61% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2955, 2931, 2871, 2777, 1727, 1592, 1557, 1456, 1406, 1377, 1209, 1154, 1115, 1085, 1043, 900, 829, 729; ^1H NMR (400 MHz, CDCl_3) δ : 8.71 (1H, s), 8.35 (1H, d, $J = 5.0$ Hz), 7.01 (1H, d, $J = 5.0$ Hz), 3.32 (1H, t, $J = 4.4$ Hz), 3.25 (1H, dd, $J = 8.1, 8.5$ Hz), 2.63 (2H, t, $J = 7.9$ Hz), 2.31-2.17 (5H, m), 2.02-1.90 (1H, m), 1.85-1.76 (1H, m), 1.70-1.51 (3H, m), 1.40 (2H, sext, $J = 7.3$ Hz), 0.94 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 149.45, 149.19, 147.52, 136.51, 123.58, 65.23, 56.95, 40.59, 34.67, 32.82, 31.43, 22.71, 22.66, 13.92; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 219.2, $\text{C}_{14}\text{H}_{23}\text{N}_2^+$ requires 219.2.

4-(4-((4-Butylpyridin-3-yl)methyl)piperazin-1-yl)-2-methylquinoline (2x)



Prepared according to general procedure B using (3-((4-(2-methylquinolin-4-yl)piperazin-1-yl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (146 mg, 0.20 mmol), *n*BuZnCl (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: EtOAc to 2% Et₃N in EtOAc) afforded the title compound as a yellow oil (55 mg, 0.15 mmol, 74% yield). IR ν_{max} /cm⁻¹ (film): 3380, 3057, 2953, 2929, 2870, 2820, 1588, 1560, 1505, 1455, 1415, 1377, 1348, 1303, 1287, 1224, 1191, 1133, 1095, 1023, 1004, 981, 927, 888, 827, 766, 728; ¹H NMR (400 MHz, CDCl₃) δ : 8.46 (1H, s), 8.41 (1H, d, *J* = 5.0 Hz), 7.95 (2H, d, *J* = 8.6 Hz), 7.59 (1H, dd, *J* = 8.0, 7.3 Hz), 7.39 (1H, dd, *J* = 7.7, 7.6 Hz), 7.10 (1H, d, *J* = 5.0 Hz), 6.69 (1H, s), 3.60 (2H, s), 3.18 (4H, br s), 2.75-2.71 (6H, m), 2.65 (3H, s), 1.61 (2H, qn, *J* = 7.1 Hz), 1.42 (2H, sext, *J* = 7.4 Hz), 0.96 (3H, t, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 159.30, 156.78, 151.50, 151.00, 149.17, 148.80, 131.20, 129.10, 128.94, 124.41, 124.11, 123.37, 121.75, 109.28, 57.97, 53.05, 52.11, 32.26, 31.47, 25.56, 22.73, 13.93; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 375.3, C₂₄H₃₁N₄⁺ requires 375.2.

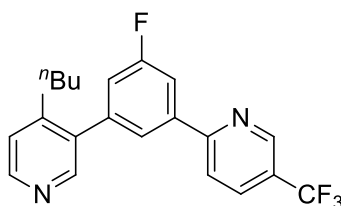
3-(((1-Benzhydrylazetid-3-yl)methoxy)methyl)-4-butylpyridine (2y)



Prepared according to general procedure B using (3-(((1-benzhydrylazetid-3-yl)methoxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (151 mg, 0.20 mmol), *n*BuZnCl (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol),

N-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 33% acetone in hexanes) two times afforded the title compound as a light yellow oil (56 mg, 0.14 mmol, 70% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3058, 3025, 2953, 2929, 2857, 1659, 1595, 1490, 1451, 1410, 1365, 1345, 1307, 1275, 1204, 1171, 1089, 1028, 971, 923, 831, 744, 703; ^1H NMR (400 MHz, CDCl_3) δ : 8.48 (1H, s), 8.45 (1H, d, $J = 5.0$ Hz), 7.39 (4H, d, $J = 7.6$ Hz), 7.26 (4H, dd, $J = 7.8, 7.3$ Hz), 7.17 (2H, dd, $J = 7.4, 7.1$ Hz), 7.11 (1H, d, $J = 5.0$ Hz), 4.53 (2H, s), 4.34 (1H, s), 3.64 (2H, d, $J = 6.6$ Hz), 3.29 (2H, t, $J = 7.6$ Hz), 2.90 (2H, dd, $J = 6.7, 7.0$ Hz), 2.78-2.70 (1H, m), 2.65 (2H, t, $J = 7.8$ Hz), 1.58 (2H, qn, $J = 7.2$ Hz), 1.38 (2H, sext, $J = 7.5$ Hz), 0.92 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 150.83, 150.12, 149.41, 142.17, 131.30, 128.31, 127.44, 126.95, 123.91, 77.96, 73.11, 68.85, 56.46, 32.10, 31.38, 29.74, 22.65, 13.86; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 401.3, $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}^+$ requires 401.3.

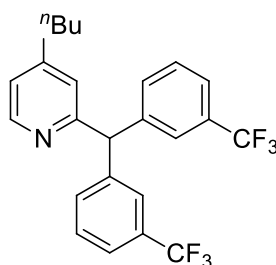
2-(3-(4-Butylpyridin-3-yl)-5-fluorophenyl)-5-(trifluoromethyl)pyridine (2z)



Prepared according to general procedure B using (3-(3-fluoro-5-(5-(trifluoromethyl)pyridin-2-yl)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (146 mg, 0.20 mmol), $n\text{BuZnCl}$ (0.40 mmol), $\text{Co}(\text{acac})_3$ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 33% EtOAc in hexanes) afforded the title compound as a white solid (32 mg, 0.084 mmol, 42% yield). mp 44-46 $^{\circ}\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3089, 3054, 2961, 2933, 2870, 1613, 1596, 1572, 1490, 1468, 1425, 1402, 1383, 1313, 1264, 1249, 1227, 1163, 1136, 1061, 1040, 1014, 935, 918, 877, 851, 833, 770, 694; ^1H NMR (400 MHz, CDCl_3) δ : 8.95 (1H, s), 8.53 (2H, d, $J = 18.3$ Hz), 8.01 (1H, dd, $J = 8.3, 1.7$ Hz), 7.87-7.79 (3H, m), 7.26 (1H, s), 7.14 (1H, d, $J = 8.7$ Hz), 2.61 (2H, t, $J = 7.8$ Hz), 1.51 (2H, qn, $J = 7.3$ Hz), 1.25 (2H, sext, $J = 7.4$ Hz), 0.81 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.05 (d, $J = 246.3$ Hz), 158.75 (q, $J = 1.4$ Hz), 149.86, 149.14, 149.12, 146.75 (q, J

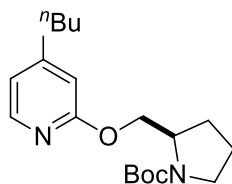
= 4.1 Hz), 140.81 (d, $J = 8.1$ Hz), 140.17 (d, $J = 8.1$ Hz), 136.13, 134.18 (q, $J = 3.5$ Hz), 128.77, 125.61 (q, $J = 33.0$ Hz), 123.98 (d, $J = 2.7$ Hz), 123.53 (q, $J = 270.9$ Hz), 120.01, 117.89 (d, $J = 21.8$ Hz), 113.45 (d, $J = 22.9$ Hz), 32.40, 32.01, 22.36, 13.70; ^{19}F NMR (365 MHz, CDCl_3) δ : -62.38, -112.05 (t, $J = 9.0$ Hz); m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 375.3, $\text{C}_{21}\text{H}_{19}\text{F}_4\text{N}_2^+$ requires 375.1.

2-(Bis(3-(trifluoromethyl)phenyl)methyl)-4-butylpyridine (2aa)



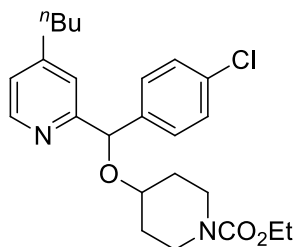
Prepared according to general procedure B using (2-(bis(3-(trifluoromethyl)phenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (158 mg, 0.20 mmol), $n\text{BuZnCl}$ (0.40 mmol), $\text{Co}(\text{acac})_3$ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), N -methylimidazole (24 μL , 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a colorless oil (59 mg, 0.13 mmol, 67% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2933, 2862, 1601, 1558, 1447, 1410, 1326, 1161, 1120, 1095, 1074, 919, 838, 805, 701; ^1H NMR (400 MHz, CDCl_3) δ : 8.50 (1H, d, $J = 5.0$ Hz), 7.52 (2H, d, $J = 7.6$ Hz), 7.47-7.37 (6H, m), 7.03 (1H, d, $J = 5.0$ Hz), 6.93 (1H, s), 5.70 (1H, s), 2.57 (2H, t, $J = 7.6$ Hz), 1.57 (2H, qn, $J = 7.3$ Hz), 1.33 (2H, sext, $J = 7.4$ Hz), 0.91 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 160.95, 152.84, 149.71, 143.08, 132.63 (d, $J = 1.0$ Hz), 130.87 (q, $J = 32.1$ Hz), 129.00, 125.96 (q, $J = 3.8$ Hz), 124.05 (q, $J = 271.1$ Hz), 123.97, 123.76 (q, $J = 3.7$ Hz), 122.30, 58.64, 34.97, 32.34, 22.20, 13.75; ^{19}F NMR (365 MHz, CDCl_3) δ : -62.62; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 438.3, $\text{C}_{24}\text{H}_{22}\text{F}_6\text{N}^+$ requires 438.2.

(*R*)-Tert-butyl 2-(((4-butylpyridin-2-yl)oxy)methyl)pyrrolidine-1-carboxylate (2ab)



Prepared according to general procedure B using (*R*)-(2-((1-(tert-butoxycarbonyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (138 mg, 0.20 mmol), ⁿBuZnCl (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μL, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a colorless oil (40 mg, 0.12 mmol, 60% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2957, 2930, 2873, 1692, 1609, 1558, 1478, 1455, 1416, 1388, 1364, 1314, 1286, 1249, 1156, 1105, 1035, 990, 862, 772; ¹H NMR (400 MHz, CDCl₃) δ : 7.99 (1H, d, *J* = 5.2 Hz), 6.68 (1H, d, *J* = 1.5 Hz), 6.53 (1H, s), 4.40-4.33 (1H, m), 4.19-4.12 (2H, m), 3.38 (2H, br s), 2.53 (2H, d, *J* = 7.6 Hz), 1.97-1.91 (3H, m), 1.86-1.80 (1H, m), 1.57 (2H, qn, *J* = 7.2 Hz), 1.44 (9H, s), 1.33 (2H, sext, *J* = 7.4 Hz), 0.91 (3H, t, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 164.06, 154.59, 154.50, 146.37, 117.59, 110.22, 79.32, 66.07, 56.09, 46.38, 34.79, 32.22, 28.76, 28.47, 22.93, 22.21, 13.81; *m/z* LRMS (ESI + APCI) found [M + H]⁺ 335.3, C₁₉H₃₁N₂O₃⁺ requires 335.2.

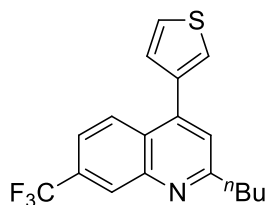
Ethyl 4-((4-butylpyridin-2-yl)(4-chlorophenyl)methoxy)piperidine-1-carboxylate (2ac)



Prepared according to general procedure B using (2-((4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (138 mg, 0.20 mmol), ⁿBuZnCl (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μL, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a colorless oil (40 mg, 0.12 mmol, 60% yield).

enylphosphonium trifluoromethanesulfonate (157 mg, 0.20 mmol), *n*BuZnCl (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 16% acetone in hexanes) two times afforded the title compound as a colorless oil (48 mg, 0.11 mmol, 56% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2929, 2860, 1695, 1601, 1557, 1488, 1468, 1430, 1380, 1354, 1333, 1272, 1226, 1170, 1085, 1029, 1014, 994, 964, 937, 827, 767; ¹H NMR (400 MHz, CDCl₃) δ : 8.37 (1H, d, *J* = 5.0 Hz), 7.35 (2H, d, *J* = 8.5 Hz), 7.31 (1H, s), 7.27 (2H, d, *J* = 8.4 Hz), 6.98 (1H, d, *J* = 4.8 Hz), 5.58 (1H, s), 4.11 (2H, q, *J* = 7.1 Hz), 3.77-3.75 (2H, m), 3.64-3.59 (1H, m), 3.22-3.14 (2H, m), 2.59 (2H, t, *J* = 7.7 Hz), 1.86-1.77 (2H, m), 1.71-1.54 (4H, m), 1.34 (2H, sext, *J* = 7.4 Hz), 1.24 (3H, t, *J* = 7.1 Hz), 0.92 (3H, t, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 161.55, 155.48, 152.82, 148.71, 140.24, 133.22, 128.47, 128.06, 122.78, 120.53, 81.04, 72.59, 61.21, 41.07, 41.03, 35.09, 32.33, 31.12, 31.00, 22.24, 14.66, 13.78; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 431.4, C₂₄H₃₂ClN₂O₃⁺ requires 431.2.

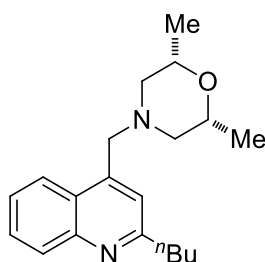
2-Butyl-4-(thiophen-3-yl)-7-(trifluoromethyl)quinolone (2ad)



Prepared according to general procedure B using triphenyl(4-(thiophen-3-yl)-7-(trifluoromethyl)quinolin-2-yl)phosphonium trifluoromethanesulfonate (138 mg, 0.20 mmol), *n*BuZnCl (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. First flash column chromatography (silica gel: 50% CH₂Cl₂ in hexanes to 67% CH₂Cl₂ in hexanes), then second flash column chromatography (silica gel: 5% Et₂O in hexanes) afforded the title compound as a colorless oil (52 mg, 0.16 mmol, 78% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3103, 2956, 2929, 1595, 1558, 1509, 1465, 1434, 1411, 1371, 1336, 1297, 1247, 1207, 1169, 1151, 1122, 1062, 959, 905, 867, 832, 796, 771, 732, 693, 668; ¹H NMR (400 MHz, CDCl₃) δ : 8.42 (1H, s), 8.14 (1H, d, *J* = 4.8 Hz), 7.63 (1H, dd, *J* = 4.8, 3.2 Hz), 7.55-7.53 (2H, m), 7.39 (1H, s), 7.33 (1H, dd, *J* = 4.7,

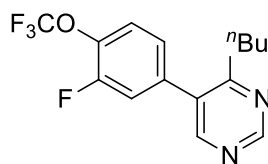
3.4 Hz), 3.01 (2H, t, $J = 7.8$ Hz), 1.85 (2H, qn, $J = 7.5$ Hz), 1.47 (2H, sext, $J = 7.5$ Hz), 0.98 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.29, 147.58, 143.19, 137.99, 130.98 (q, $J = 32.5$ Hz), 128.65, 127.12 (q, $J = 4.4$ Hz), 126.93 (d, $J = 1.0$ Hz), 126.72, 126.58, 125.13, 124.03 (q, $J = 271.0$ Hz), 123.03, 121.31 (q, $J = 3.0$ Hz), 38.97, 31.91, 22.66, 13.94; ^{19}F NMR (365 MHz, CDCl_3) δ : -62.70; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 336.2, $\text{C}_{18}\text{H}_{17}\text{F}_3\text{NS}^+$ requires 336.1.

(2*R*,6*S*)-4-((2-Butylquinolin-4-yl)methyl)-2,6-dimethylmorpholine (2ae)



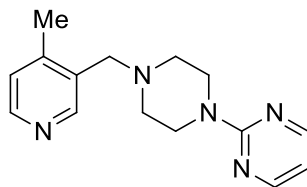
Prepared according to general procedure B using 4-(((2*R*,6*S*)-2,6-dimethylmorpholino)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), $n\text{BuZnCl}$ (0.40 mmol), $\text{Co}(\text{acac})_3$ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μL , 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a yellow solid (42 mg, 0.14 mmol, 68% yield). mp 55-57 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3060, 2964, 2925, 2856, 2814, 2777, 1733, 1605, 1563, 1506, 1456, 1416, 1369, 1322, 1293, 1284, 1244, 1220, 1178, 1144, 1046, 1021, 985, 965, 934, 917, 891, 873, 835, 819, 767, 758; ^1H NMR (400 MHz, CDCl_3) δ : 8.19 (1H, d, $J = 8.4$ Hz), 8.05 (1H, d, $J = 8.4$ Hz), 7.66 (1H, dd, $J = 8.1, 7.2$ Hz), 7.47 (1H, dd, $J = 8.0, 7.3$ Hz), 7.28 (1H, s), 3.83 (2H, s), 3.73-3.65 (2H, m), 2.96 (2H, t, $J = 7.9$ Hz), 2.72 (2H, $J = 10.7$ Hz), 1.89-1.76 (4H, m), 1.44 (2H, sext, $J = 7.5$ Hz), 1.14 (6H, d, $J = 6.3$ Hz), 0.96 (3H, t, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 162.61, 148.20, 143.32, 129.27, 128.96, 126.12, 125.31, 124.03, 121.70, 71.66, 59.84, 59.66, 39.01, 32.10, 22.64, 19.05, 13.96; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 313.3, $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}^+$ requires 313.2.

4-Butyl-5-(3-fluoro-4-(trifluoromethoxy)phenyl)pyrimidine (2af)



Prepared according to general procedure B using (5-(3-fluoro-4-(trifluoromethoxy)phenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (134 mg, 0.20 mmol), ⁿBuZnCl (0.60 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μL, 0.30 mmol), and THF (0.033 M) at 50 °C for 12 hours. Flash column chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a colorless oil (23 mg, 0.07 mmol, 37% yield). IR ν_{max} /cm⁻¹ (film): 3039, 2960, 2932, 2873, 1623, 1587, 1570, 1542, 1504, 1444, 1420, 1400, 1318, 1250, 1211, 1168, 1111, 1002, 983, 934, 861, 823, 764, 715, 696; ¹H NMR (400 MHz, CDCl₃) δ : 9.16 (1H, s), 8.50 (1H, br s), 7.29 (1H, t, *J* = 8.3 Hz), 7.16 (1H, d, *J* = 8.7 Hz), 7.12 (1H, d, *J* = 9.8 Hz), 2.65 (2H, t, *J* = 7.7 Hz), 1.65 (2H, qn, *J* = 7.4 Hz), 1.26 (2H, sext, *J* = 7.5 Hz), 0.82 (3H, t, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 169.06, 159.60 (d, *J* = 249.2 Hz), 158.30, 156.97, 150.17 (d, *J* = 12.5 Hz), 132.07 (d, *J* = 4.1 Hz), 127.79, 122.18 (d, *J* = 16.5 Hz), 120.29 (q, *J* = 257.7 Hz), 116.82 (dd, *J* = 1.0, 3.9 Hz), 109.33 (d, *J* = 26.9 Hz), 34.73 (d, *J* = 1.4 Hz), 30.36, 22.39, 13.67; ¹⁹F NMR (365 MHz, CDCl₃) δ : -58.03, -109.52 (t, *J* = 8.6 Hz); *m/z* LRMS (ESI + APCI) found [M+H]⁺ 315.1, C₁₅H₁₅F₄N₂O⁺ requires 315.1.

2-(4-((4-Methylpyridin-3-yl)methyl)piperazin-1-yl)pyrimidine (2ag)

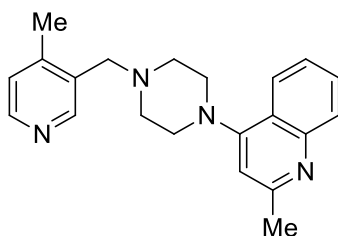


Prepared according to general procedure C using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), MeZnCl (0.60 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μL, 0.30 mmol), ⁱPrMgCl (22 μL, 0.044 mmol) and THF (0.033 M) at 50 °C for 12 hours. Flash column chromatography (silica gel: EtOAc to

S55

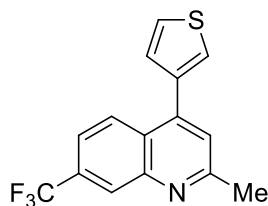
2% Et₃N in EtOAc) afforded the title compound as a light brown solid (42 mg, 0.15 mmol, 77% yield). mp 81-84 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3025, 3002, 2933, 2817, 2774, 1579, 1543, 1485, 1436, 1391, 1358, 1347, 1315, 1305, 1293, 1270, 1254, 1223, 1195, 1147, 1119, 1080, 1059, 1002, 980, 954, 858, 829, 793, 736, 638; ¹H NMR (400 MHz, CDCl₃) δ : 8.40-8.36 (2H, m), 8.27 (2H, d, J = 4.7 Hz), 7.08 (1H, d, J = 4.7 Hz), 6.45 (1H, t, J = 4.7 Hz), 3.77 (4H, t, J = 4.9 Hz), 3.48 (2H, s), 2.47 (4H, t, J = 5.0 Hz), 2.39 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 161.57, 157.62, 150.54, 148.67, 147.10, 131.87, 125.36, 109.73, 58.31, 52.91, 43.66, 18.70; m/z LRMS (ESI + APCI) found [M+H]⁺ 270.2, C₁₅H₂₀N₅⁺ requires 270.2.

2-Methyl-4-(4-((4-methylpyridin-3-yl)methyl)piperazin-1-yl)quinoline (2ah)



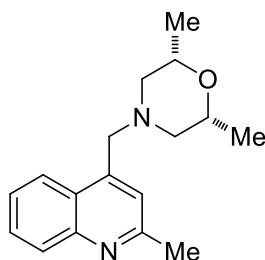
Prepared according to general procedure C using (3-((4-(2-methylquinolin-4-yl)piperazin-1-yl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (146 mg, 0.20 mmol), MeZnCl (0.60 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), ^{*i*}PrMgCl (22 μ L, 0.044 mmol) and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: EtOAc to 2% Et₃N in EtOAc) afforded the title compound as a light yellow oil (40 mg, 0.12 mmol, 59% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3058, 2940, 2818, 2767, 1587, 1560, 1503, 1452, 1415, 1381, 1366, 1348, 1333, 1319, 1303, 1286, 1247, 1227, 1196, 1133, 1121, 1095, 1059, 1022, 1004, 980, 934, 887, 854, 834, 820, 797, 771, 730; ¹H NMR (400 MHz, CDCl₃) δ : 8.50-8.44 (2H, m), 7.97 (2H, t, J = 7.4 Hz), 7.61 (1H, dt, J = 7.0, 1.0 Hz), 7.41 (1H, dd, J = 8.0, 0.8 Hz), 7.12 (1H, br s), 6.71 (1H, s), 3.61 (2H, s), 3.21 (4H, br s), 2.74-2.73 (4H, m), 2.67 (3H, s), 2.42 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 159.27, 156.96, 150.55, 149.00, 148.75, 147.20, 131.91, 129.10, 128.98, 125.52, 124.52, 123.44, 121.75, 109.31, 58.26, 53.06, 52.14, 25.48, 18.74; m/z LRMS (ESI + APCI) found [M+H]⁺ 333.3, C₂₁H₂₅N₄⁺ requires 333.2.

2-Methyl-4-(thiophen-3-yl)-7-(trifluoromethyl)quinolone (2ai)



Prepared according to general procedure C using triphenyl(4-(thiophen-3-yl)-7-(trifluoromethyl)quinolin-2-yl)phosphonium trifluoromethanesulfonate (138 mg, 0.20 mmol), MeZnCl (0.60 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), *i*PrMgCl (22 μ L, 0.044 mmol) and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a light yellow solid (36 mg, 0.12 mmol, 61% yield). mp 61-64 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3104, 2924, 1597, 1558, 1512, 1426, 1372, 1360, 1335, 1295, 1251, 1237, 1208, 1183, 1143, 1113, 1077, 1064, 1020, 958, 904, 890, 869, 840, 831, 817, 796, 784, 774, 726, 711, 682, 664; ¹H NMR (400 MHz, CDCl₃) δ : 8.38 (1H, s), 8.13 (1H, d, *J* = 4.8 Hz), 7.62 (1H, dd, *J* = 4.8, 1.5 Hz), 7.54-7.51 (2H, m), 7.38 (1H, s), 7.32 (1H, dd, *J* = 4.8, 1.6 Hz), 2.78 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 160.23, 147.54, 143.21, 137.82, 131.07 (q, *J* = 32.4 Hz), 128.60, 126.80 (q, *J* = 4.2 Hz), 126.75 (2C), 126.63, 125.18, 123.99 (q, *J* = 270.8 Hz), 123.60, 121.37 (q, *J* = 3.1 Hz), 25.31; ¹⁹F NMR (365 MHz, CDCl₃) δ : -62.70; *m/z* LRMS (ESI + APCI) found [M + H]⁺ 294.1, C₁₅H₁₁F₃NS⁺ requires 294.0.

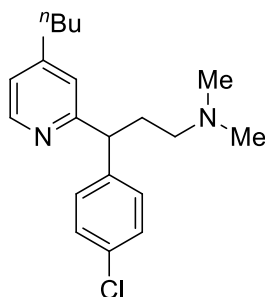
(2*R*,6*S*)-4-((2-Methylquinolin-4-yl)methyl)-2,6-dimethylmorpholine (2aj)



Prepared according to general procedure C using 4-(((2*R*,6*S*)-2,6-dimethylmorpholino)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (133 mg, 0.20 mmol), MeZnCl (0.60 mmol), Co(acac)₃ (7.1

mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), i PrMgCl (22 μ L, 0.044 mmol) and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 33% EtOAc in hexanes to 50% EtOAc in hexanes) afforded the title compound as a light yellow solid (33 mg, 0.12 mmol, 60% yield). mp 101-104 $^{\circ}$ C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3056, 2970, 2931, 2859, 2813, 2771, 1607, 1565, 1508, 1454, 1415, 1375, 1322, 1295, 1281, 1242, 1219, 1178, 1141, 1084, 1022, 993, 968, 890, 877, 868, 854, 836, 755; ^1H NMR (400 MHz, CDCl_3) δ : 8.19 (1H, dd, $J = 8.4, 0.7$ Hz), 8.02 (1H, d, $J = 8.2$ Hz), 7.66 (1H, dt, $J = 7.0, 1.4$ Hz), 7.48 (1H, dt, $J = 7.0, 1.1$ Hz), 7.28 (1H, s), 3.83 (2H, s), 3.83 (3H, s), 3.71-3.67 (2H, m), 2.73-2.70 (2H, m), 1.86 (2H, dd, $J = 10.8, 10.6$ Hz), 1.14 (6H, d, $J = 6.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.54, 148.12, 143.47, 129.12, 129.05, 125.91, 125.39, 124.05, 122.29, 71.66, 59.78, 59.67, 25.34, 19.05; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 271.2, $\text{C}_{17}\text{H}_{23}\text{N}_2\text{O}^+$ requires 271.2.

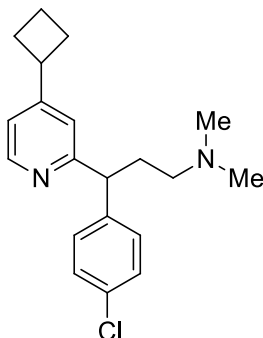
3-(4-Butylpyridin-2-yl)-3-(4-chlorophenyl)-*N,N*-dimethylpropan-1-amine (2ak)



Prepared according to general procedure B using (2-(1-(4-chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (137 mg, 0.20 mmol), $n\text{BuZnCl}$ (0.60 mmol), $\text{Co}(\text{acac})_3$ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 16 hours. Flash column chromatography (silica gel: 5% Et_3N in EtOAc) afforded the title compound as a yellow oil (46 mg, 0.14 mmol, 70% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3388, 2931, 2857, 2814, 2764, 1601, 1556, 1489, 1459, 1405, 1377, 1263, 1142, 1090, 1042, 1014, 830; ^1H NMR (400 MHz, CDCl_3) δ : 8.42 (1H, d, $J = 5.0$ Hz), 7.29 (2H, d, $J = 8.3$ Hz), 7.23 (2H, d, $J = 8.4$ Hz), 6.95 (1H, s), 6.91 (1H, d, $J = 4.9$ Hz), 4.07 (1H, t, $J = 6.8$ Hz), 2.53 (2H, t, $J = 7.8$ Hz), 2.41-2.33 (1H, m), 2.18-2.16 (9H, m), 1.55 (2H, qn, $J = 7.5$ Hz), 1.32 (2H, sext, $J = 7.4$ Hz), 0.90 (3H, t, $J = 7.3$ Hz); ^{13}C NMR

(100 MHz, CDCl₃) δ : 162.81, 152.21, 149.15, 142.38, 132.03, 129.37, 128.50, 122.88, 121.69, 57.69, 50.49, 45.46, 34.94, 32.97, 32.38, 22.28, 13.81; m/z LRMS (ESI + APCI) found $[M + H]^+$ 331.2, C₂₁H₂₈N₂⁺ requires 331.2.

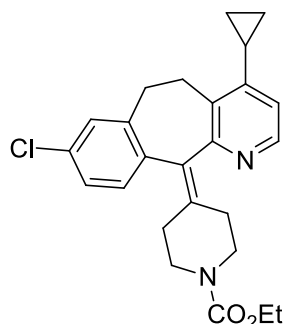
3-(4-Chlorophenyl)-3-(4-cyclobutylpyridin-2-yl)-N,N-dimethylpropan-1-amine (2al)



Prepared according to general procedure B using (2-(1-(4-chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (137 mg, 0.20 mmol), cyclobutylzinc bromide (0.60 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 5% Et₃N in EtOAc) afforded the title compound as a yellow oil (47 mg, 0.15 mmol, 72% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2938, 2853, 2814, 2764, 1600, 1552, 1488, 1460, 1404, 1263, 1142, 1090, 1041, 1014, 824; ¹H NMR (400 MHz, CDCl₃) δ : 8.44 (1H, d, J = 5.0 Hz), 7.29 (2H, d, J = 8.4 Hz), 7.23 (2H, d, J = 8.5 Hz), 6.95-6.93 (2H, m), 4.07 (1H, t, J = 6.9 Hz), 3.44 (1H, qn, J = 8.5 Hz), 2.44-2.28 (3H, m), 2.18-2.14 (9H, m), 2.11-1.98 (3H, m), 1.87-1.80 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 162.72, 155.40, 149.14, 142.35, 132.01, 129.34, 128.48, 120.68, 119.50, 57.65, 50.52, 45.42, 39.30, 32.94, 28.88, 18.27; m/z LRMS (ESI + APCI) found $[M + H]^+$ 329.3, C₂₁H₂₆N₂⁺ requires 329.2.

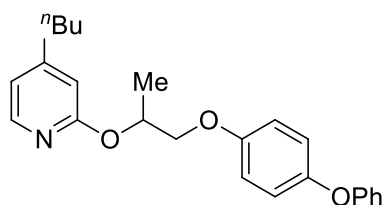
Ethyl

4-(8-chloro-4-cyclopropyl-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11(6H)-ylidene)piperidine-1-carboxylate (2am)



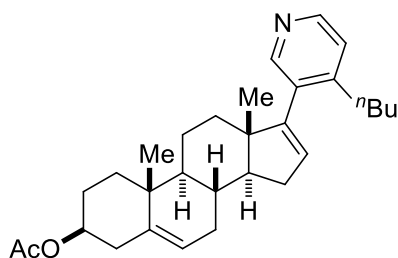
Prepared according to general procedure B using (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (159 mg, 0.20 mmol), cyclopropylzinc bromide (0.60 mmol), Co(acac)₃ (7.1 mg, 0.02 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (7.1 mg, 0.02 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 24 hours. Flash column chromatography (silica gel: 16% Acetone in hexanes) afforded the title compound as a colorless oil (72 mg, 0.17 mmol, 85% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2976, 2907, 1690, 1581, 1553, 1474, 1429, 1385, 1324, 1277, 1222, 1170, 1113, 1061, 1025, 985, 907, 832, 766, 727; ¹H NMR (400 MHz, CDCl₃) δ : 8.27 (1H, d, J = 5.1 Hz), 7.15-7.11 (3H, m), 6.72 (1H, d, J = 5.1 Hz), 4.12 (2H, q, J = 7.1 Hz), 3.79 (2H, br s), 3.45-3.38 (1H, m), 3.35-3.28 (1H, m), 3.18-3.10 (3H, m), 2.89-2.82 (1H, m), 2.48-2.25 (4H, m), 1.92-1.85 (1H, m), 1.24 (3H, t, J = 7.1 Hz), 1.06-0.96 (2H, m), 0.73-0.63 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 157.12, 155.47, 150.81, 146.66, 139.49, 137.47, 136.68, 134.66, 132.77, 132.64, 130.54, 128.98, 126.01, 118.78, 61.26, 44.75, 44.70, 31.43, 30.62, 30.56, 27.47, 14.65, 12.46, 7.83, 7.76; m/z LRMS (ESI + APCI) found $[M + H]^+$ 423.3, C₂₅H₂₈ClN₂O₂⁺ requires 423.2.

4-Butyl-2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (2an)



Prepared according to general procedure B using (2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (146 mg, 0.20 mmol), *n*BuZnCl (0.40 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (24 μ L, 0.30 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography (silica gel: 5% acetone in hexanes) afforded the title compound as a colorless oil (45 mg, 0.12 mmol, 59% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2955, 2930, 2870, 2360, 2340, 1608, 1557, 1503, 1487, 1413, 1378, 1313, 1286, 1217, 1157, 1121, 1074, 1043, 993, 871, 840, 748, 690; ¹H NMR (400 MHz, CDCl₃) δ : 8.03 (1H, d, *J* = 5.2 Hz), 7.32-7.28 (2H, m), 7.04 (1H, t, *J* = 7.4 Hz), 6.98-6.92 (6H, m), 6.71 (1H, dd, *J* = 2.7, 5.2 Hz), 6.58 (1H, s), 5.58 (1H, sext, *J* = 6.3 Hz), 4.20 (1H, dd, *J* = 1.2, 9.9 Hz), 4.08 (1H, dd, *J* = 1.3, 9.9 Hz), 2.55 (2H, t, *J* = 7.6 Hz), 1.60 (2H, qn, *J* = 7.3 Hz), 1.49 (3H, d, *J* = 6.4 Hz), 1.36 (2H, sext, *J* = 7.4 Hz), 0.93 (3H, t, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 163.44, 158.48, 155.24, 154.78, 150.20, 146.31, 129.56, 122.37, 120.72, 117.64, 117.57, 115.77, 110.94, 71.08, 69.12, 34.80, 32.19, 22.23, 17.04, 13.84; *m/z* LRMS (ESI + APCI) found [M + H]⁺ 378.3, C₂₄H₂₈NO₃⁺ requires 378.2.

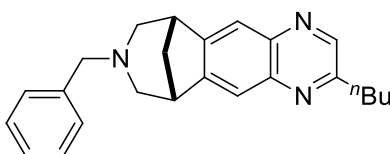
(3*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-(4-Butylpyridin-3-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (2ao)



Prepared according to general procedure B using (3-((3*S*,9*S*,10*R*,13*S*,14*S*)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (80 mg, 0.10 mmol), *n*BuZnCl (0.30 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (12 μ L, 0.15 mmol), and THF (0.033 M) at room temperature for 12 hours. Flash column chromatography three times (silica gel: 16% acetone in hexanes) followed by flash column chromatography (silica gel: Et₂O) afforded the

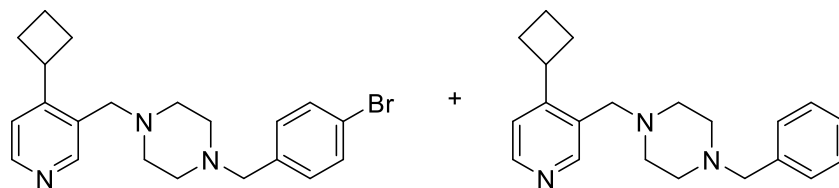
title compound as a white solid (23 mg, 0.05 mmol, 52% yield). mp 124-126 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3041, 2953, 2929, 2856, 1725, 1584, 1457, 1438, 1400, 1368, 1236, 1123, 1097, 1031, 960, 913, 886, 834, 821, 739; ^1H NMR (400 MHz, CDCl_3) δ : 8.36 (1H, s), 8.28 (1H, s), 7.14 (1H, d, $J = 4.0$ Hz), 5.64 (1H, s), 5.42 (1H, d, $J = 4.7$ Hz), 4.65-4.57 (1H, m), 2.58 (2H, t, $J = 7.6$ Hz), 2.39-2.28 (3H, m), 2.13-2.03 (5H, m), 1.88-1.83 (2H, m), 1.78-1.68 (2H, m), 1.65-1.45 (8H, m), 1.35 (2H, sext, $J = 7.5$ Hz), 1.19-1.06 (5H, m), 0.94-0.90 (6H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.49, 150.52, 150.22, 149.47, 147.66, 140.04, 133.17, 130.40, 123.62, 122.29, 73.85, 57.17, 50.42, 49.37, 38.13, 36.92, 36.83, 34.74, 33.12, 32.43, 32.22, 31.63, 30.80, 27.72, 22.64, 21.41, 20.69, 19.22, 16.27, 13.91; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 448.4, $\text{C}_{30}\text{H}_{42}\text{NO}_2^+$ requires 448.3.

(6*S*,10*R*)-8-Benzyl-2-butyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline (2ap)



Prepared according to general procedure B using ((6*S*,10*R*)-8-benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxalin-2-yl)triphenylphosphonium trifluoromethanesulfonate (71 mg, 0.10 mmol), $n\text{BuZnCl}$ (0.30 mmol), $\text{Co}(\text{acac})_3$ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.6 mg, 0.01 mmol), *N*-methylimidazole (12 μL , 0.15 mmol), and THF (0.033 M) at room temperature for 16 hours. Flash column chromatography (silica gel: 33% EtOAc in hexanes) afforded the title compound as a brown oil (19 mg, 0.05 mmol, 54% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3286, 3026, 2952, 2869, 2790, 1718, 1667, 1555, 1472, 1453, 1359, 1284, 1132, 1064, 1026, 988, 922, 873, 781, 726, 697; ^1H NMR (400 MHz, CDCl_3) δ : 8.66 (1H, s), 7.73 (2H, d, $J = 6.3$ Hz), 7.11-7.10 (3H, m), 6.85-6.84 (2H, m), 3.48 (2H, s), 3.33 (2H, s), 3.02-2.97 (4H, m), 2.55 (2H, dd, $J = 6.8, 7.0$ Hz), 2.34-2.29 (1H, m), 1.88-1.81 (3H, m), 1.48 (2H, sext, $J = 7.6$ Hz), 0.99 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 155.89, 150.63, 149.52, 143.95, 142.51, 141.44, 138.26, 128.30, 127.97, 126.59, 120.19, 119.97, 61.57, 57.46, 57.35, 43.25, 41.34, 41.20, 36.08, 31.87, 22.60, 13.92; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 358.3, $\text{C}_{24}\text{H}_{28}\text{N}_3^+$ requires 358.2.

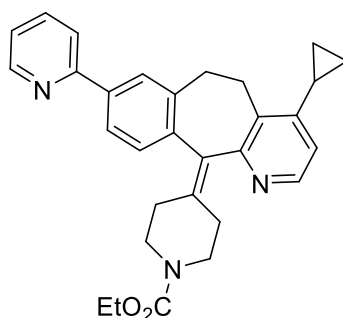
1-(4-Bromobenzyl)-4-((4-cyclobutylpyridin-3-yl)methyl)piperazine (2aq) and 1-benzyl-4-((4-cyclobutylpyridin-3-yl)methyl)piperazine (2ar)



Prepared according to general procedure B using 3-((4-(4-bromobenzyl)piperazin-1-yl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (76 mg, 0.10 mmol), cyclobutylzinc chloride (0.20 mmol), Co(acac)₃ (1.8 mg, 0.005 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (1.8 mg, 0.005 mmol), *N*-methylimidazole (12 μ L, 0.15 mmol), and THF (0.033 M) at room temperature for 80 mins. Flash column chromatography (silica gel: EtOAc to 2% Et₃N in EtOAc) afforded a mixture of compounds as an orange oil (30 mg, 0.08 mmol, 75% yield). Mixture, IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2936, 2867, 2807, 1671, 1591, 1554, 1485, 1457, 1406, 1343, 1312, 1289, 1134, 1068, 1008, 928, 836, 790, 730, 647, 577; Major product, ¹H NMR (400 MHz, CDCl₃) δ : 8.45 (1H, d, *J* = 5.0 Hz), 8.39 (1H, s), 7.42 (2H, d, *J* = 8.2 Hz), 7.22-7.17 (3H, m), 3.89-3.80 (1H, m), 3.42 (4H, s), 2.42-2.32 (10H, m), 2.17-2.00 (3H, m), 1.89-1.83 (1H, m); Major product, ¹³C NMR (100 MHz, CDCl₃) δ : 153.42, 150.56, 148.90, 137.32, 131.26, 131.06, 130.72, 120.83, 120.75, 62.22, 57.87, 53.12 (2C), 36.76, 28.60, 18.26; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 400.2, C₂₁H₂₇BrN₃⁺ requires 400.1.

Ethyl

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

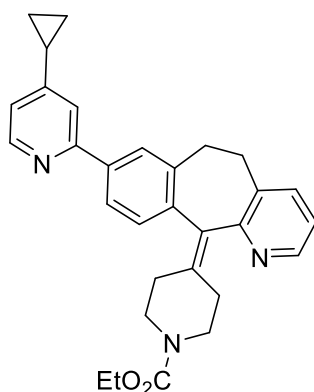


Prepared according to general procedure B using

(11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-8-(pyridin-2-yl)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (84 mg, 0.10 mmol), cyclopropylzinc bromide (0.30 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.5 mg, 0.01 mmol), *N*-methylimidazole (12 μ L, 0.15 mmol), and THF (0.033 M) at 50 °C for 24 hours. First preparative thin-layer chromatography (silica gel: 75% Acetone in hexanes), and second flash column chromatography (silica gel: 2.5% MeOH in CH₂Cl₂ to 5% MeOH in CH₂Cl₂) afforded the title compound as a colorless oil (25 mg, 0.05 mmol, 54% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2922, 2853, 1690, 1585, 1553, 1464, 1431, 1276, 1223, 1169, 1112, 1029, 985, 907, 779, 725; ¹H NMR (400 MHz, CDCl₃) δ : 8.67 (1H, d, *J* = 4.6 Hz), 8.29 (1H, d, *J* = 5.2 Hz), 7.87 (1H, d, *J* = 1.9 Hz), 7.75-7.67 (3H, m), 7.30 (1H, d, *J* = 7.9 Hz), 7.21 (1H, dt, *J* = 4.8, 1.5 Hz), 6.73 (1H, d, *J* = 5.1 Hz), 4.14 (2H, q, *J* = 7.1 Hz), 3.83 (2H, br s), 3.58-3.50 (1H, m), 3.41-3.34 (1H, m), 3.24-3.12 (3H, m), 3.05-2.98 (1H, m), 2.52-2.31 (4H, m), 1.95-1.88 (1H, m), 1.25 (3H, t, *J* = 6.9 Hz), 1.05-0.99 (2H, m), 0.77-0.71 (1H, m), 0.68-0.62 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 157.16, 155.52, 149.62, 146.50, 139.95, 138.43, 138.26, 136.71, 133.07, 132.13, 132.03, 129.68, 128.53, 128.41, 127.61, 124.42, 122.01, 120.40, 118.74, 61.25, 44.83, 44.79, 31.65, 30.74, 30.64, 27.85, 14.67, 12.54, 7.89, 7.70; *m/z* LRMS (ESI + APCI) found [M + H]⁺ 466.3, C₃₀H₃₂N₃O₂⁺ requires 466.2.

Ethyl

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



Prepared according to general procedure B using (2-(11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-8-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate

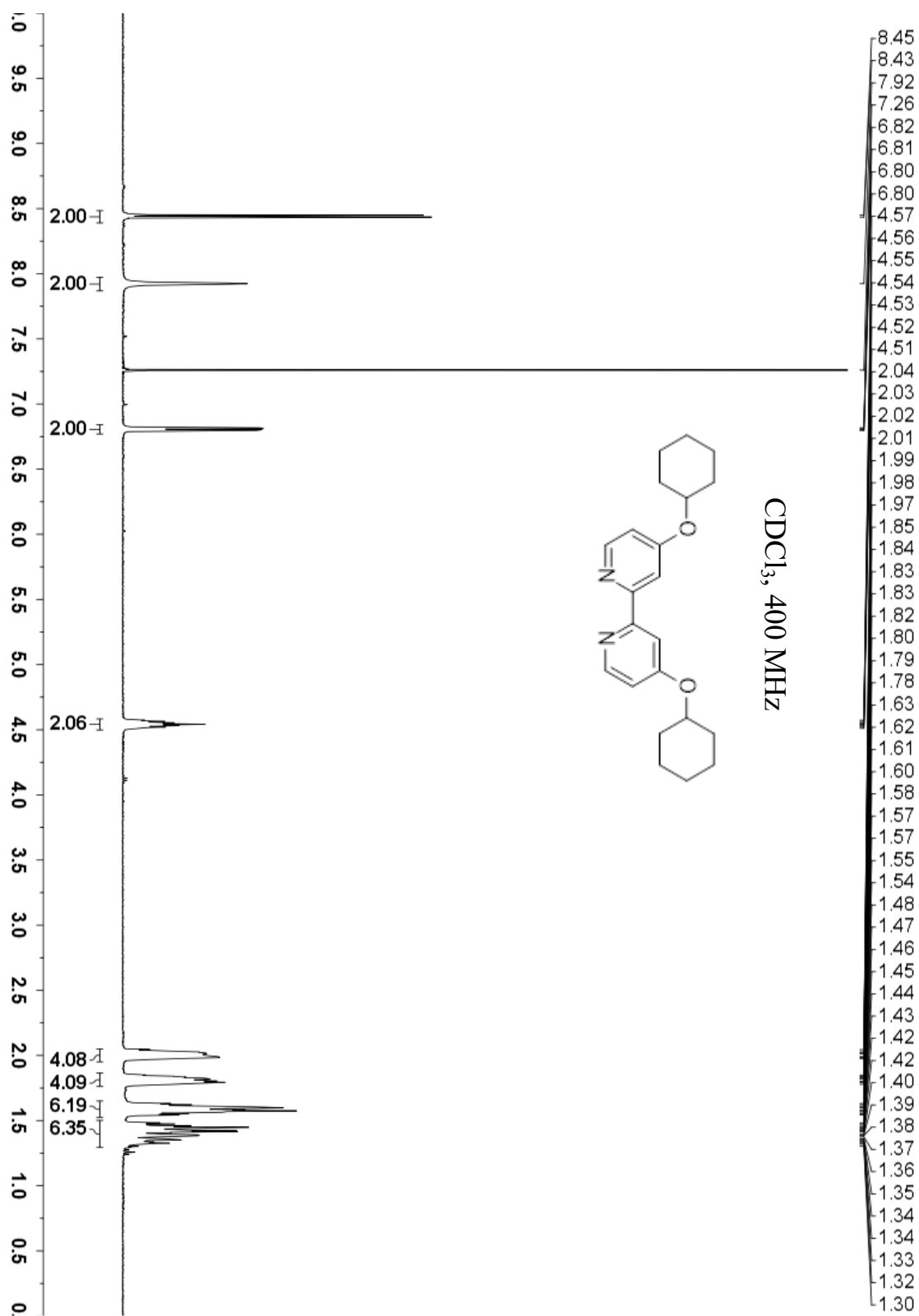
S64

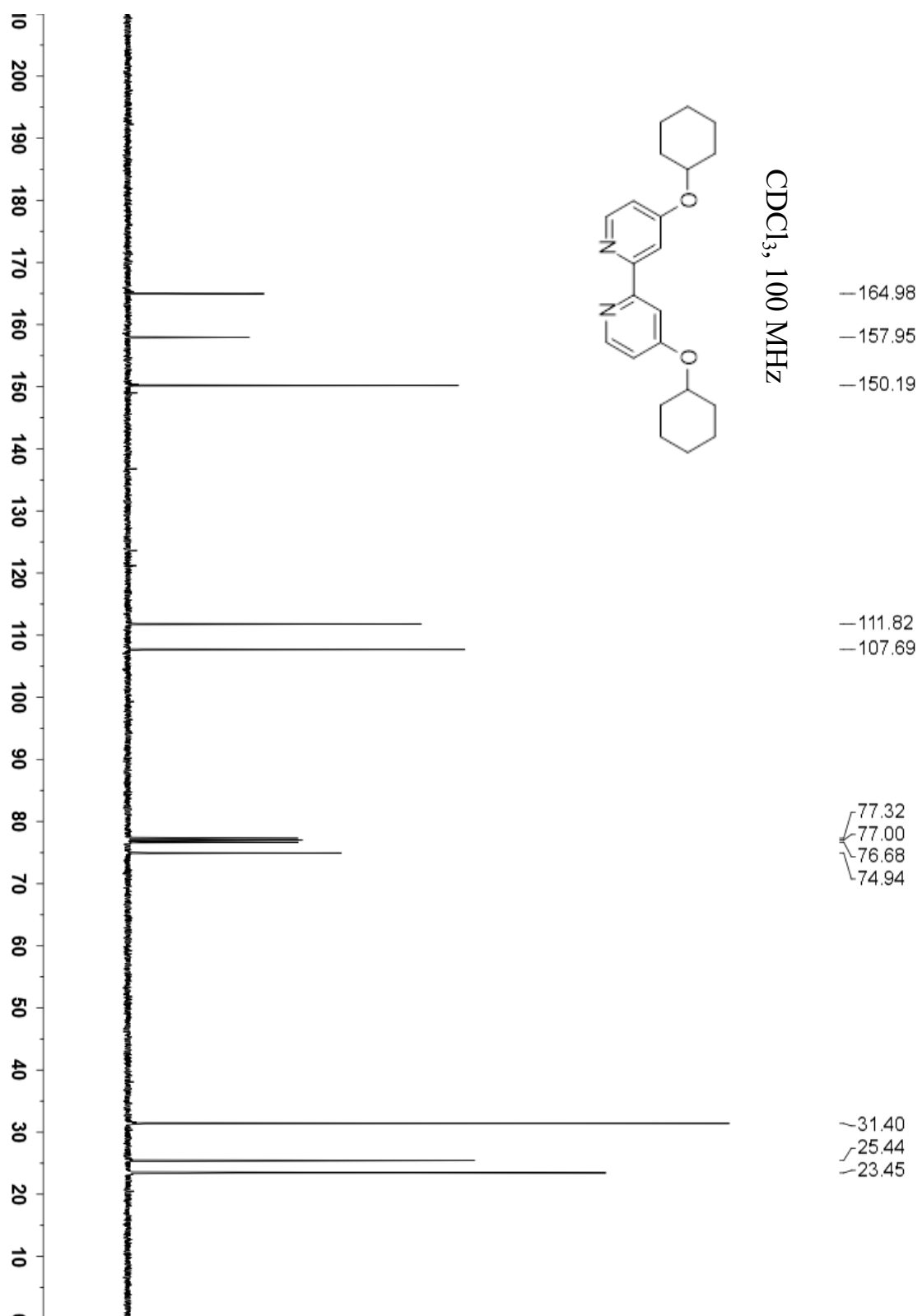
(84 mg, 0.10 mmol), cyclopropylzinc bromide (0.30 mmol), Co(acac)₃ (3.6 mg, 0.01 mmol), 4,4'-bis(cyclohexyloxy)-2,2'-bipyridine (3.5 mg, 0.01 mmol), *N*-methylimidazole (12 μ L, 0.15 mmol), and THF (0.033 M) at 50 °C for 22 hours. First flash column chromatography (silica gel: 50% Acetone in hexanes), and second flash column chromatography (silica gel: 2.5% MeOH in CH₂Cl₂ to 5% MeOH in CH₂Cl₂) afforded the title compound as a colorless oil (28 mg, 0.06 mmol, 60% yield). IR ν_{max} /cm⁻¹ (film): 2920, 2854, 1690, 1599, 1550, 1471, 1433, 1384, 1324, 1276, 1225, 1170, 1112, 1023, 995, 913, 823, 765, 727; ¹H NMR (400 MHz, CDCl₃) δ : 8.48 (1H, d, *J* = 5.2 Hz), 8.40 (1H, dd, *J* = 4.8, 1.7 Hz), 7.83 (1H, d, *J* = 1.9 Hz), 7.69 (1H, dd, *J* = 7.9, 2.0 Hz), 7.44 (1H, dd, *J* = 7.7, 1.7 Hz), 7.36 (1H, d, *J* = 1.6 Hz), 7.28 (1H, d, *J* = 7.9 Hz), 7.08 (1H, dd, *J* = 7.7, 4.8 Hz), 6.86 (1H, dd, *J* = 5.2, 1.7 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.82 (2H, br s), 3.53-3.45 (1H, m), 3.42-3.35 (1H, m), 3.17-3.10 (2H, m), 2.97-2.86 (2H, m), 2.54-2.47 (1H, m), 2.41-2.31 (3H, m), 1.94-1.87 (1H, m), 1.25 (3H, t, *J* = 7.1 Hz), 1.12-1.07 (2H, m), 0.85-0.81 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 157.25, 156.93, 155.51, 154.40, 149.29, 146.56, 139.91, 138.76, 138.18, 137.49, 137.06, 135.04, 133.69, 129.58, 127.64, 124.51, 122.12, 119.05, 117.73, 61.26, 44.86, 44.84, 31.91, 31.77, 30.79, 30.54, 15.17, 14.66, 10.39; *m/z* LRMS (ESI + APCI) found [M + H]⁺ 466.4, C₃₀H₃₂N₃O₂⁺ requires 466.2.

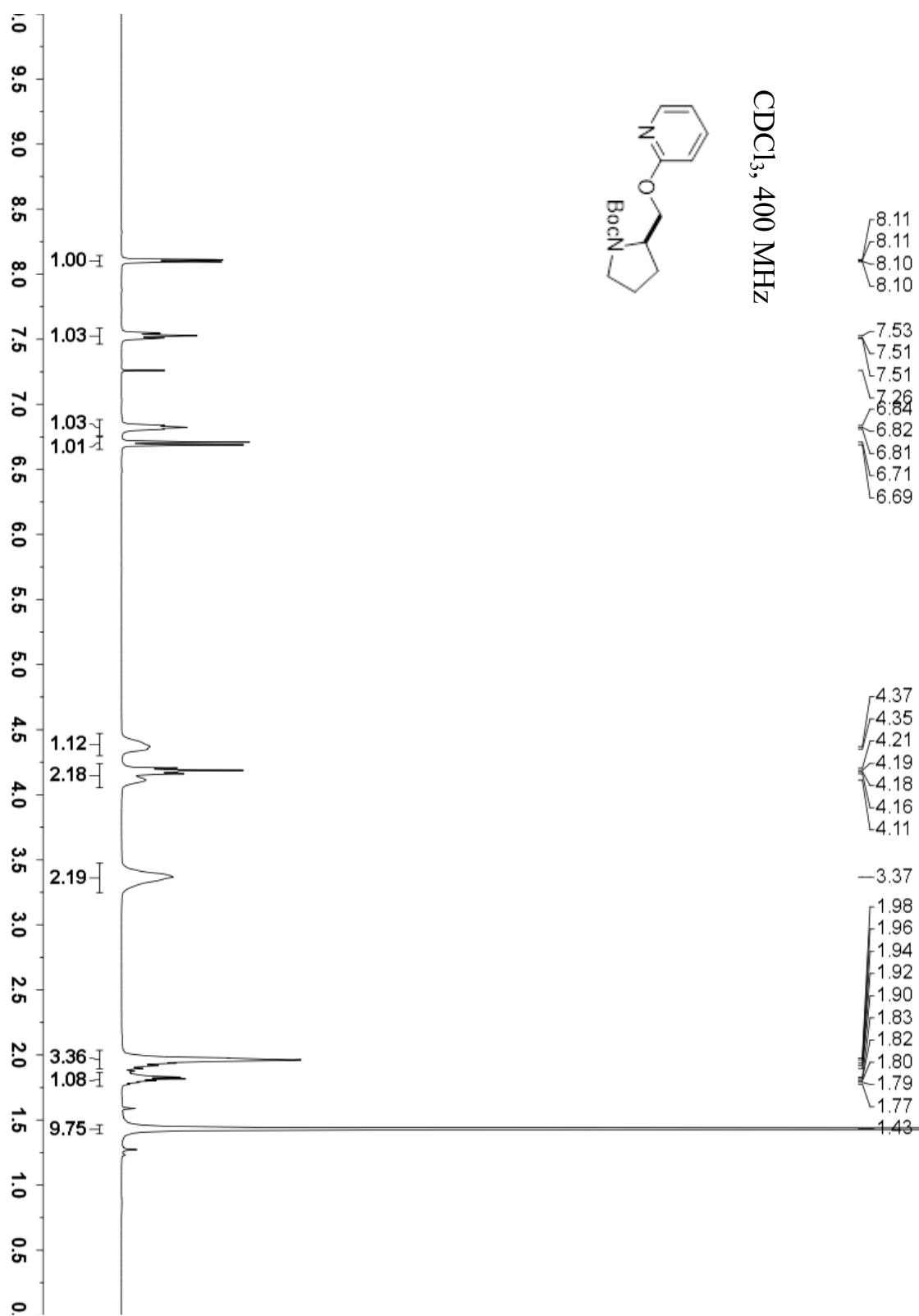
7. References

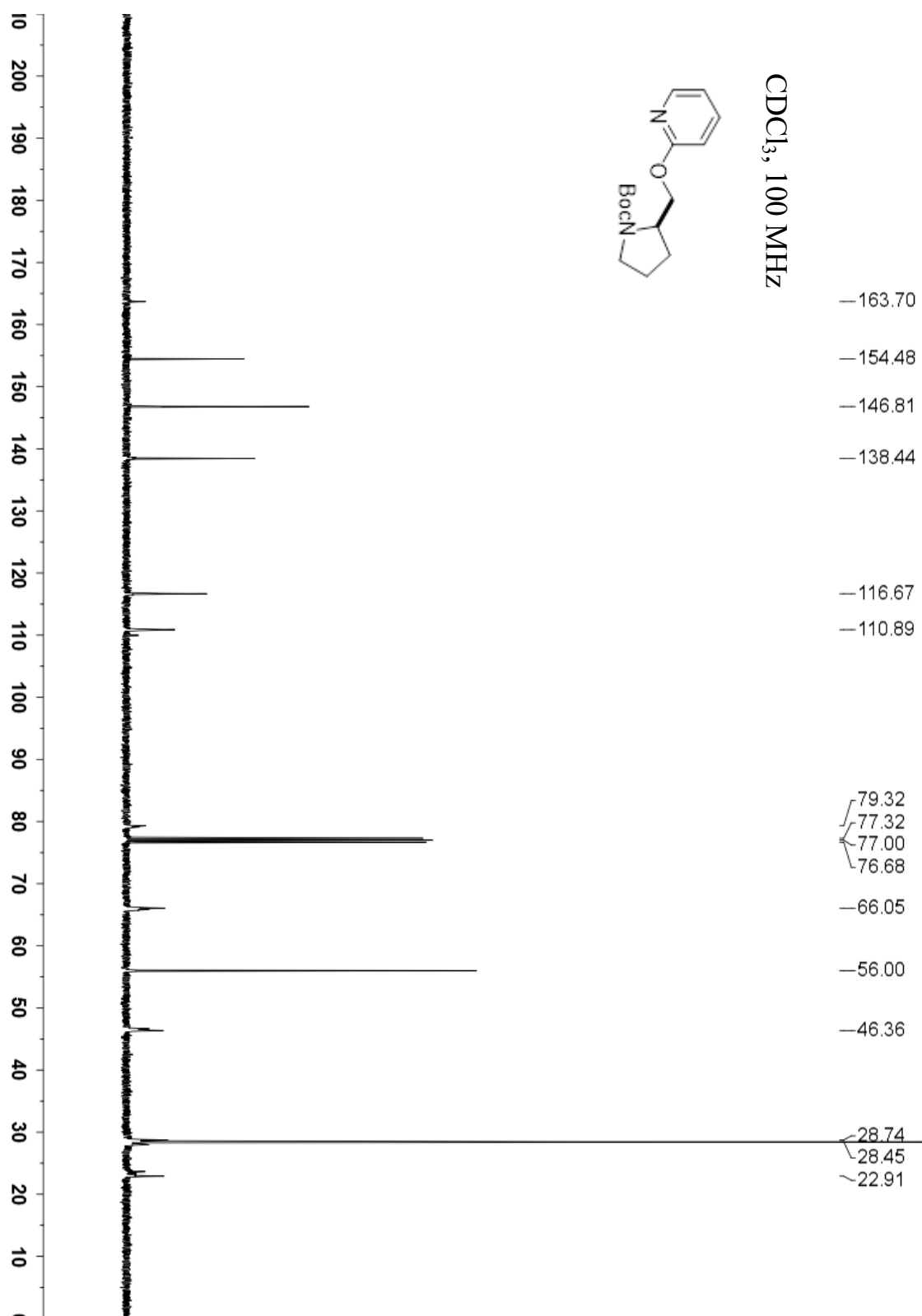
- (1) Perrin, D. D.; Amarego, W. L. F. *Purification of Laboratory Chemicals*. Pergamon, Press, Oxford. ed. 3, **1988**; pp 293-294.
- (2) Zhang, X.; McNally, A. Phosphonium Salts as Pseudohalides: Regioselective Nickel-Catalyzed Cross-Coupling of Complex Pyridines and Diazines. *Angew. Chem., Int. Ed.* **2017**, *56*, 9833-9836.
- (3) Hilton, M. C.; Dolewski, R. D.; McNally, A. Selective Functionalization of Pyridines via Heterocyclic Phosphonium Salts. *J. Am. Chem. Soc.* **2016**, *138*, 13806-13809.
- (4) Koniarczyk, J. L.; Hesk, D.; Overgard, A.; Davies, I. W.; McNally, A. A General Strategy for Site-Selective Incorporation of Deuterium and Tritium into Pyridines, Diazines and Pharmaceuticals. *J. Am. Chem. Soc.* **2018**, *140*, 1990-1993.
- (5) Patel, C.; Mohnike, M.; Hilton, M. C.; McNally, A. A Strategy to Aminate Pyridines, Diazines, and Pharmaceuticals via Heterocyclic Phosphonium Salts. *Org. Lett.* **2018**, *20*, 2607-2610.
- (6) Dolewski, R. D.; Fricke, P. J.; McNally, A. Site-Selective Switching Strategies to Functionalize Polyazines. *J. Am. Chem. Soc.* **2018**, *140*, 8020-8026.
- (7) Krasovskiy, A.; Knochel, P. Convenient Titration Method for Organometallic Zinc, Magnesium, and Lanthanide Reagents. *Synthesis* **2006**, *5*, 890-891.
- (8) Obando, D.; Pantarat, N.; Handke, R.; Koda, Y.; Widmer, F.; Djordjevic, J. T.; Ellis, D. H.; Sorrell, T. C.; Jolliffe, K. A. Synthesis, Antifungal, Haemolytic and Cytotoxic Activities of A Series of Bis(alkylpyridinium)alkanes. *Biorg. Med. Chem.* **2009**, *17*, 6329-6339.
- (9) Cho, C. S.; Oh, S. G. Copper-Catalyzed Oxidative Cyclization of α -Hydroxyketones with *o*-Phenylenediamines Leading to Quinoxalines. *J. Mol. Catal. A-Chem* **2007**, *276*, 205-210.

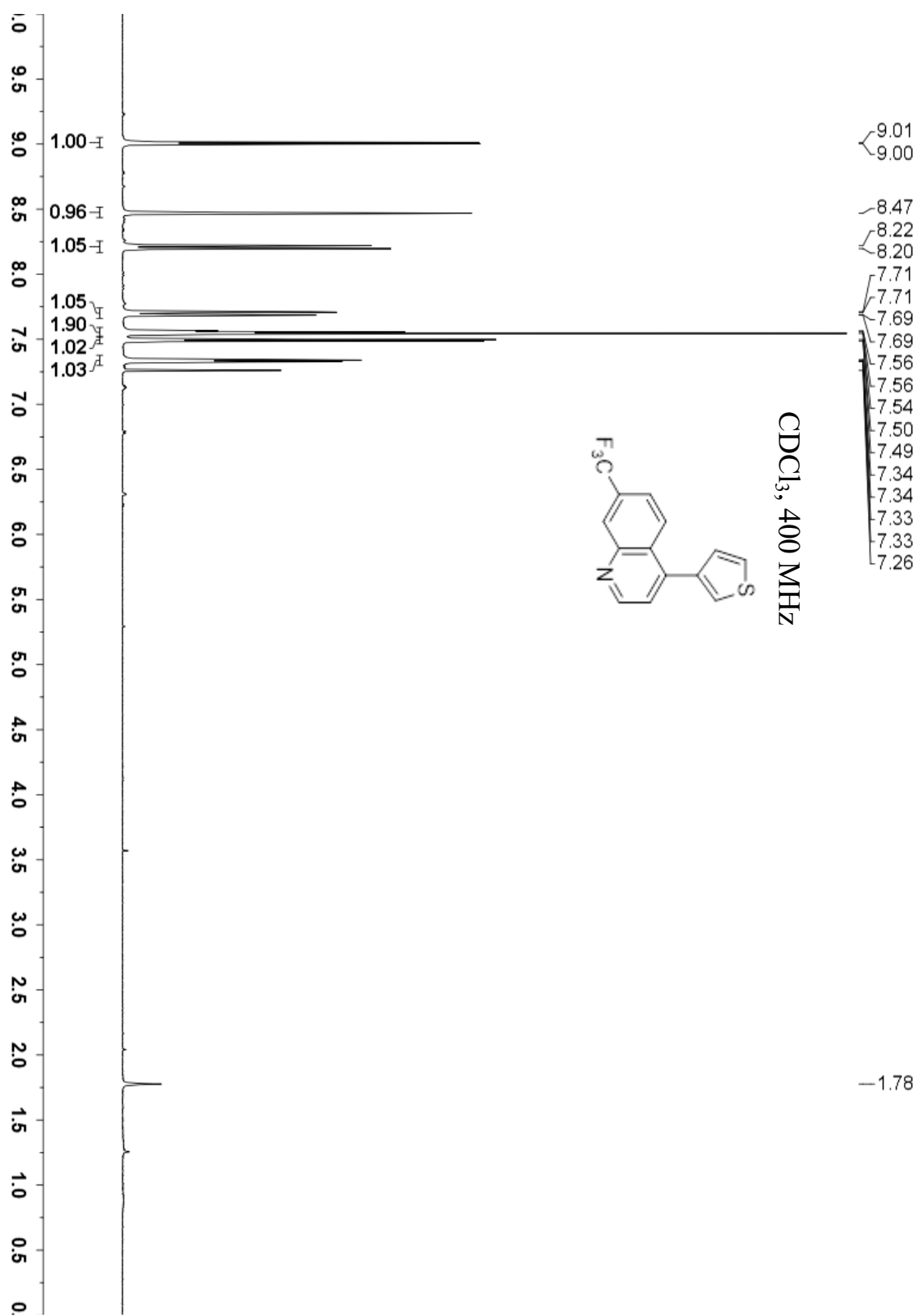
8. ^1H , ^{13}C , ^{19}F and ^{31}P spectra

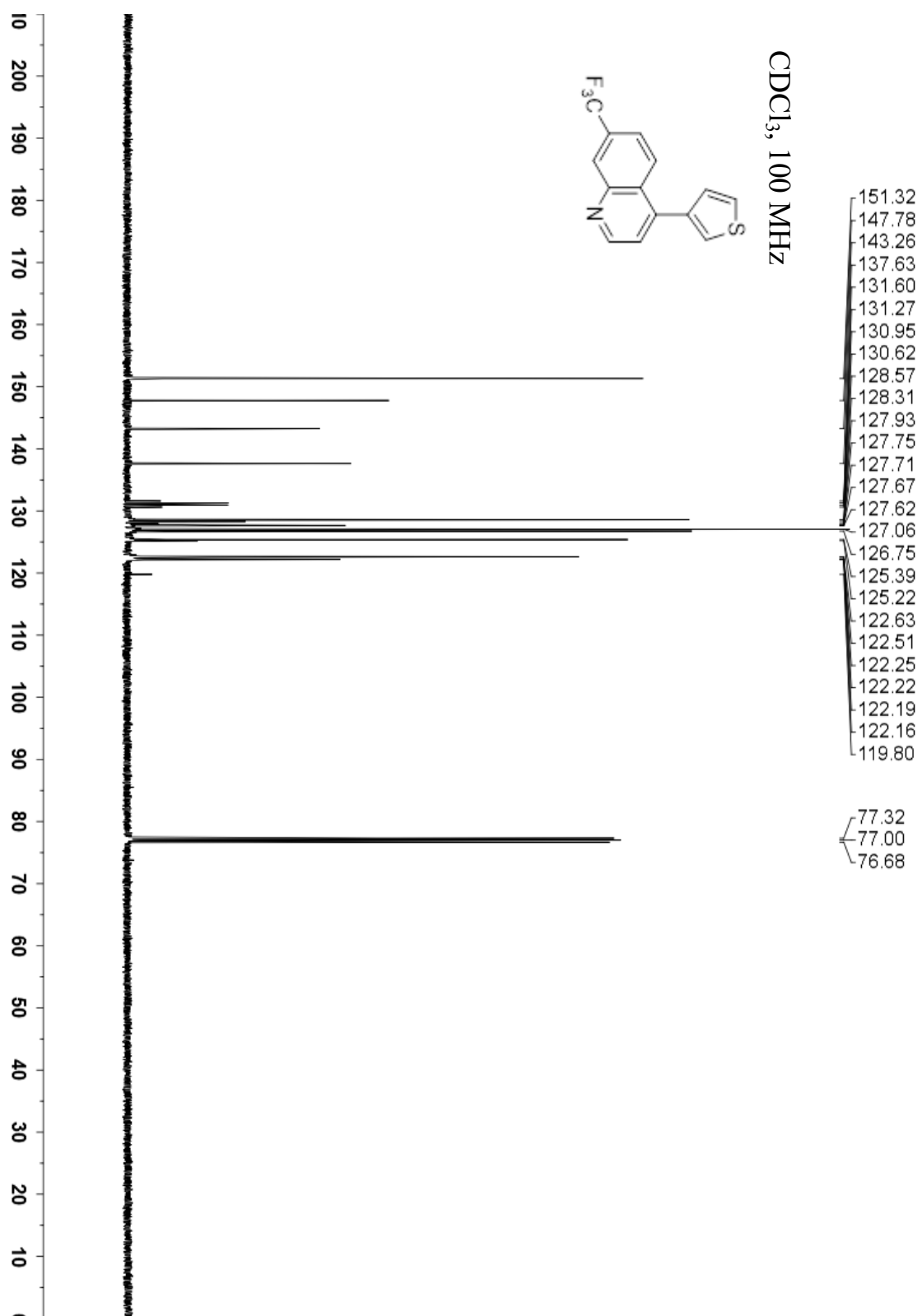




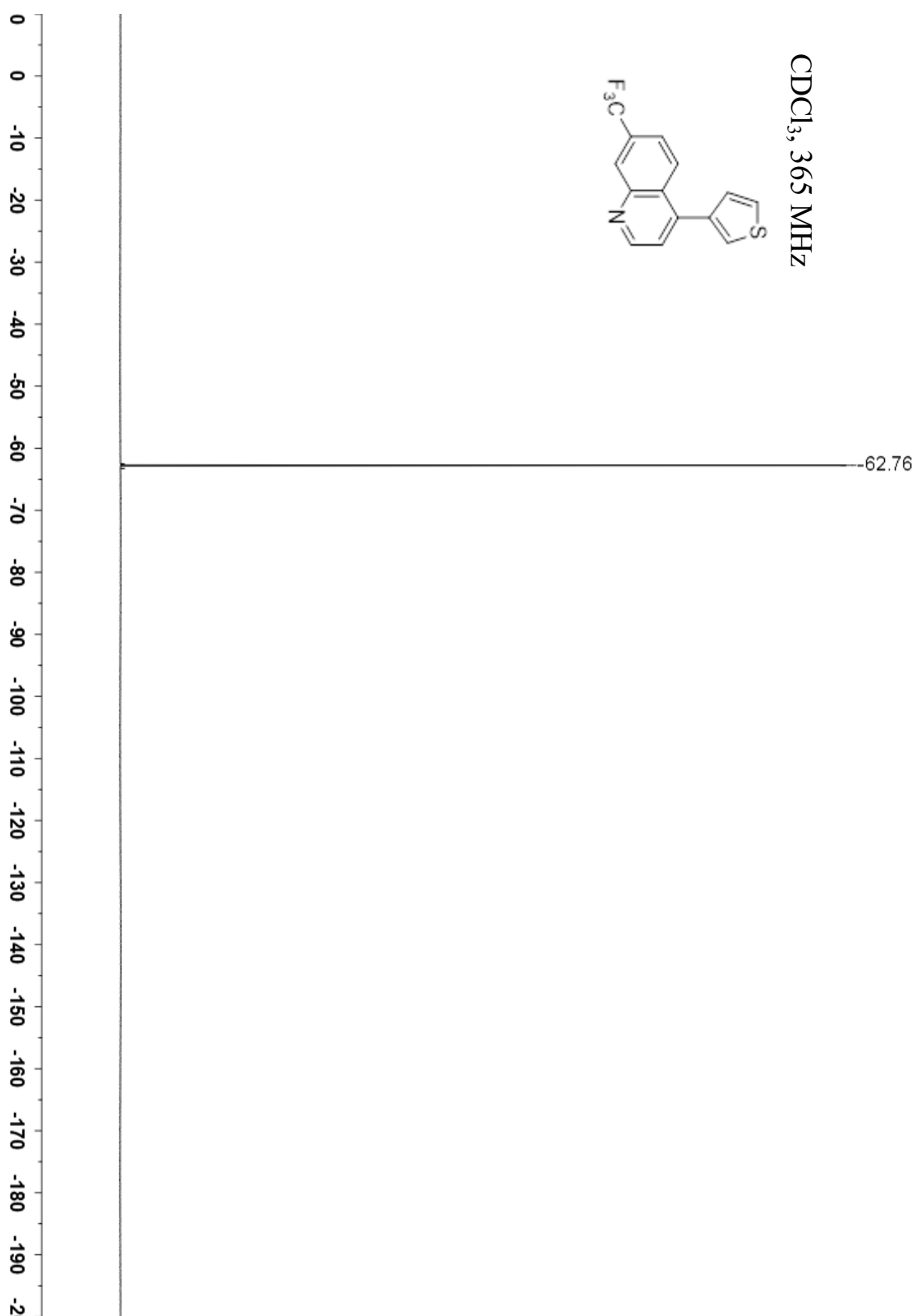
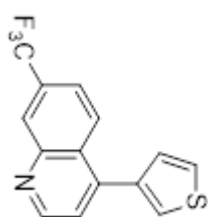


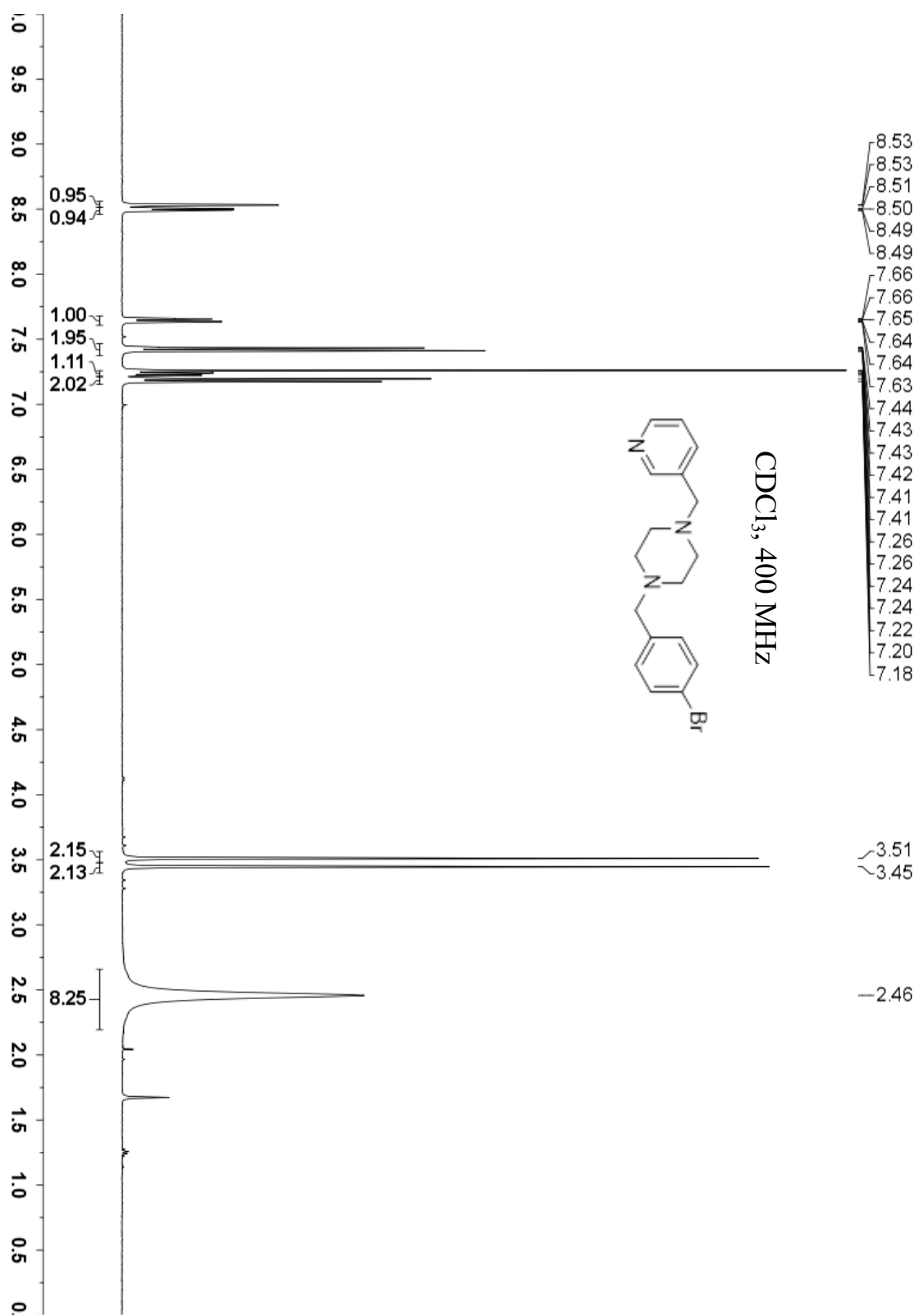


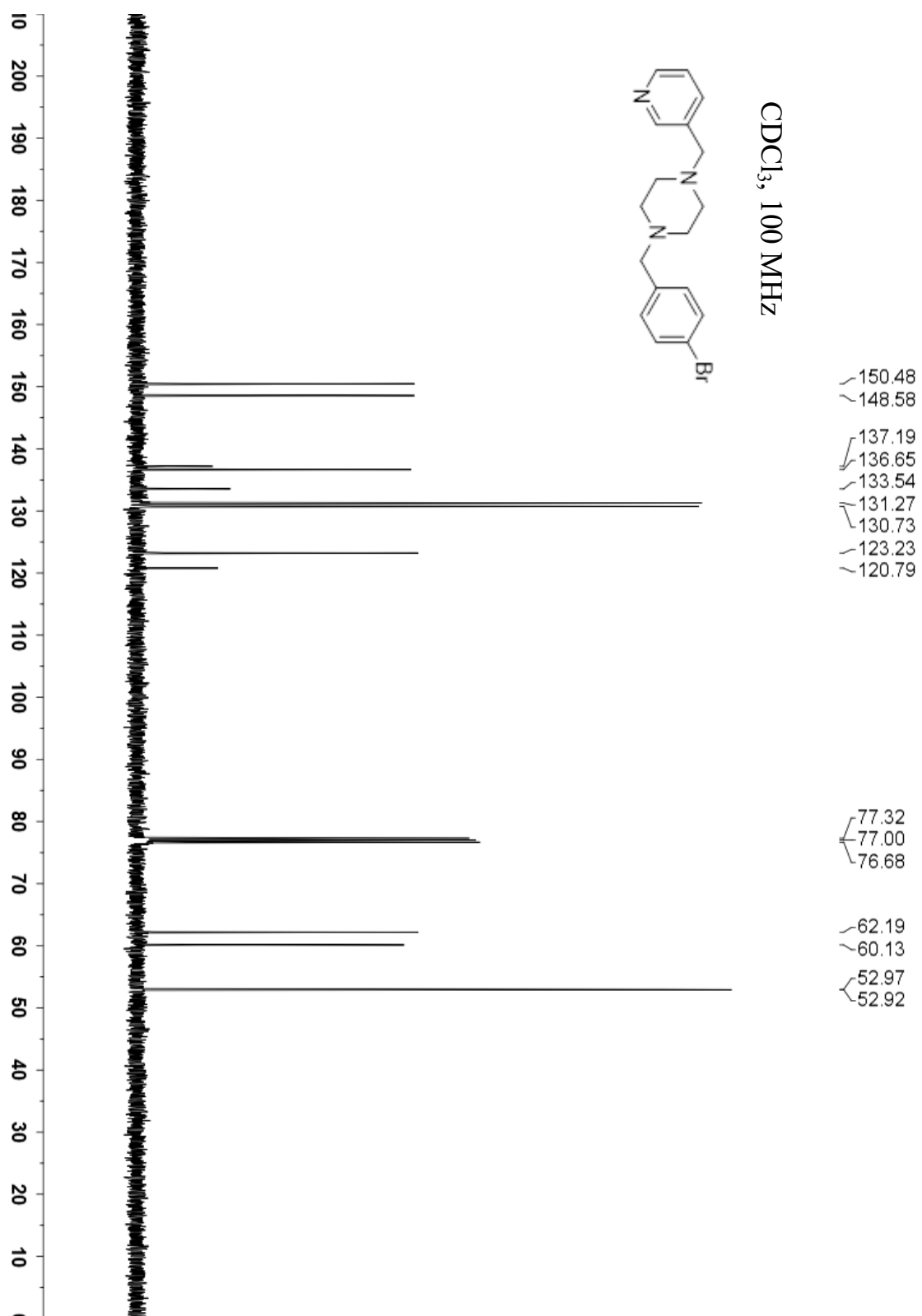


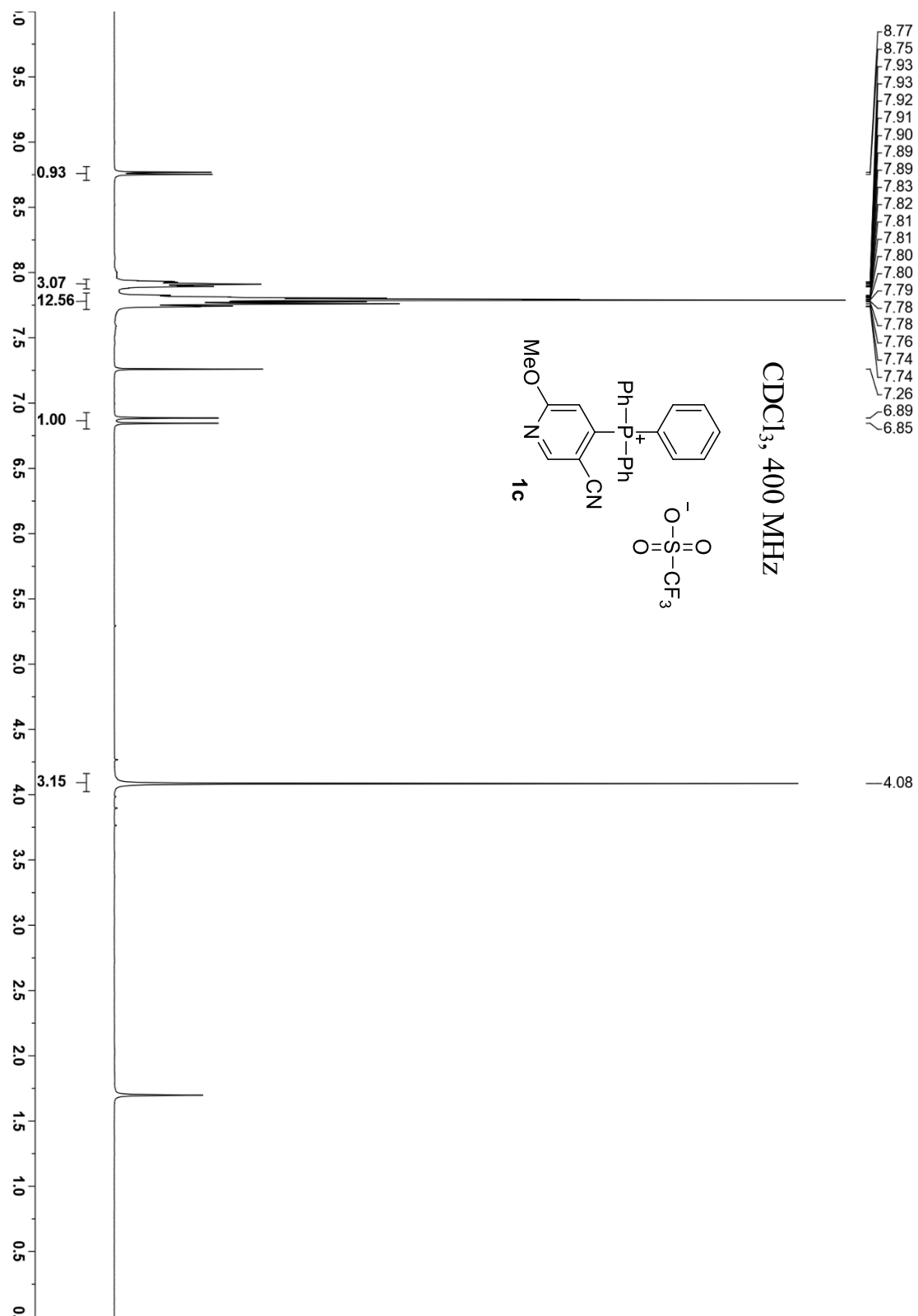


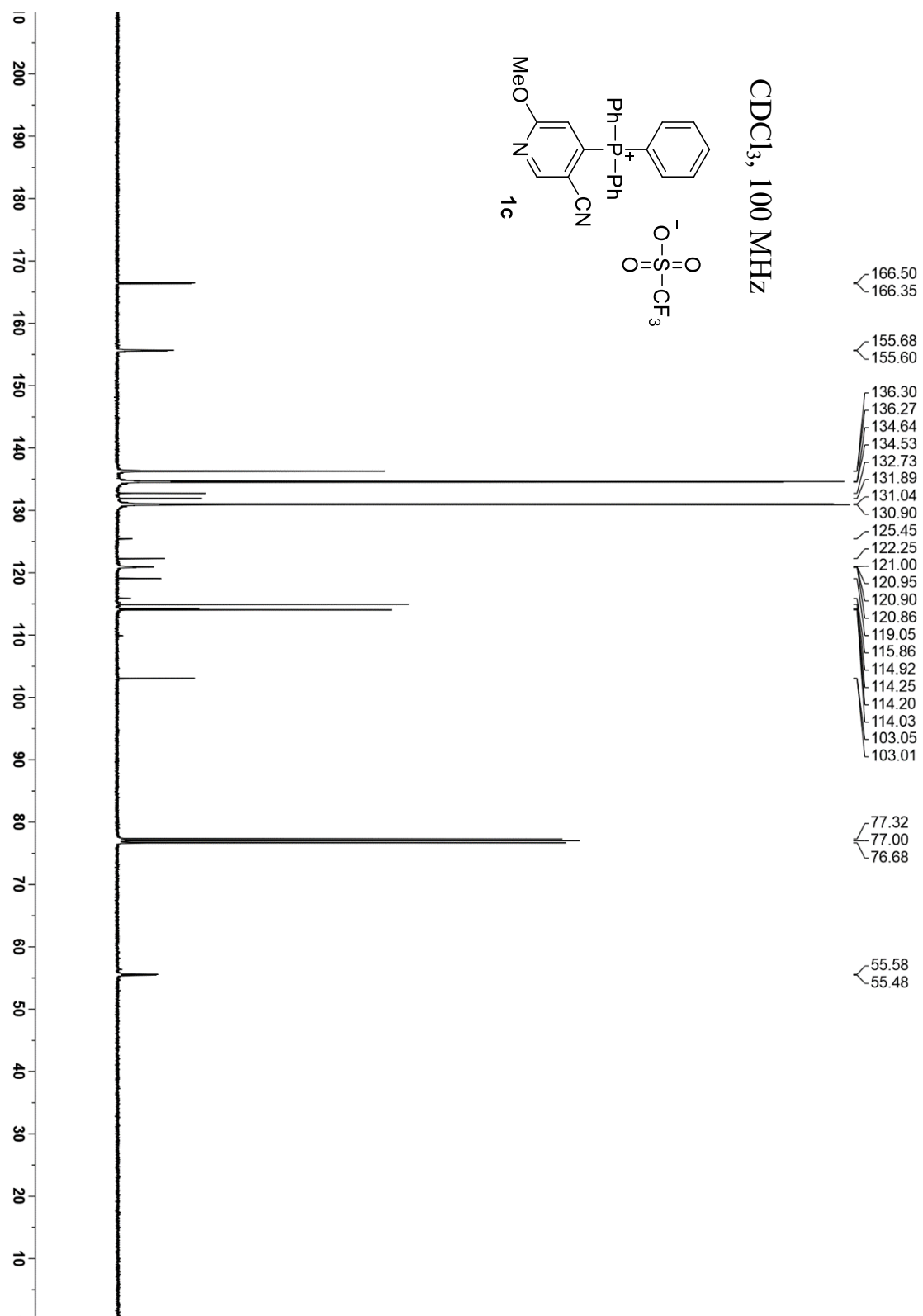
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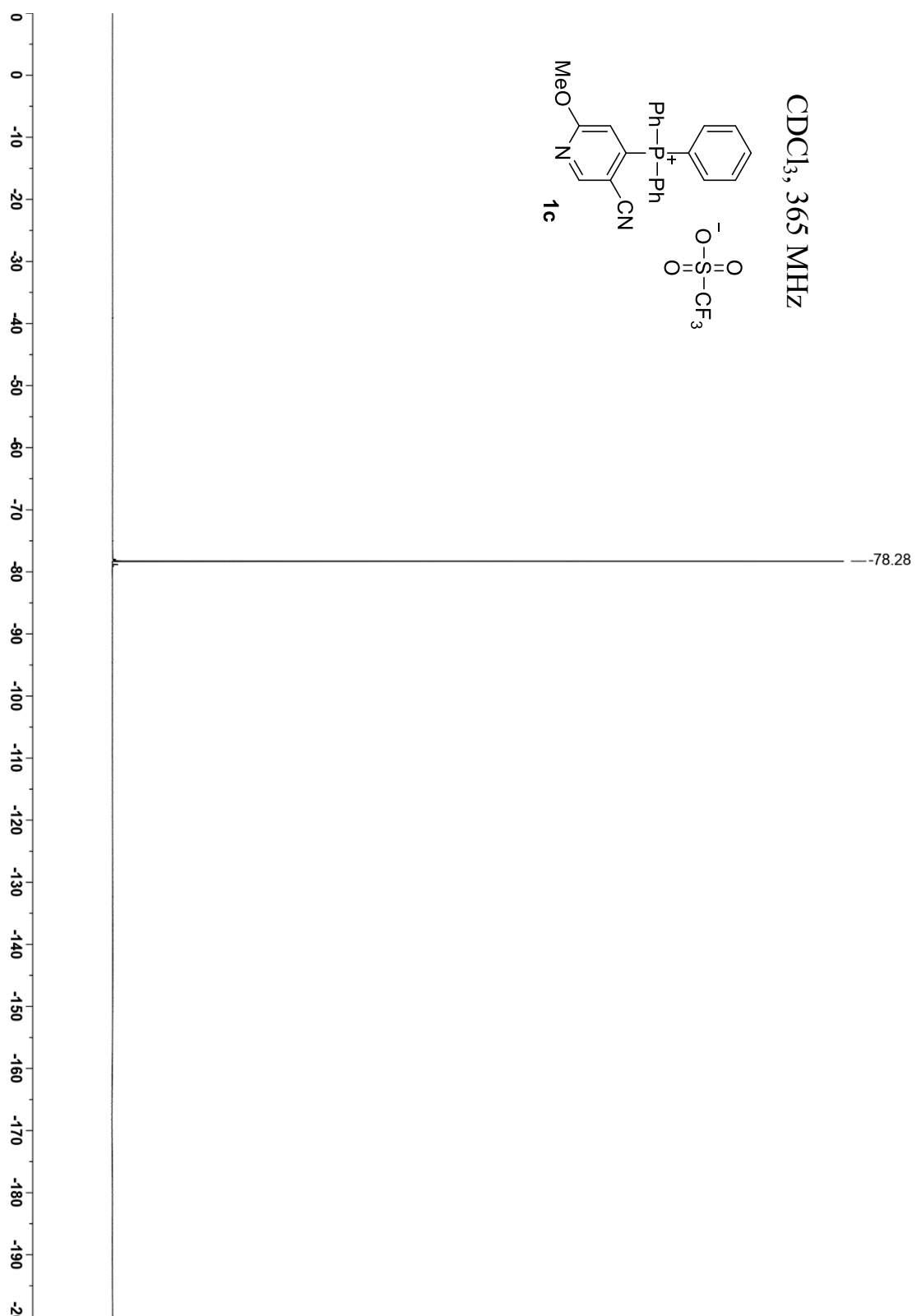
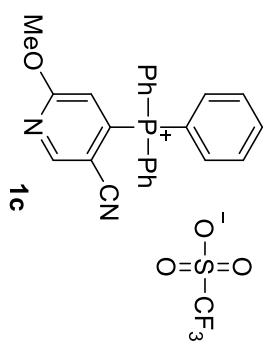




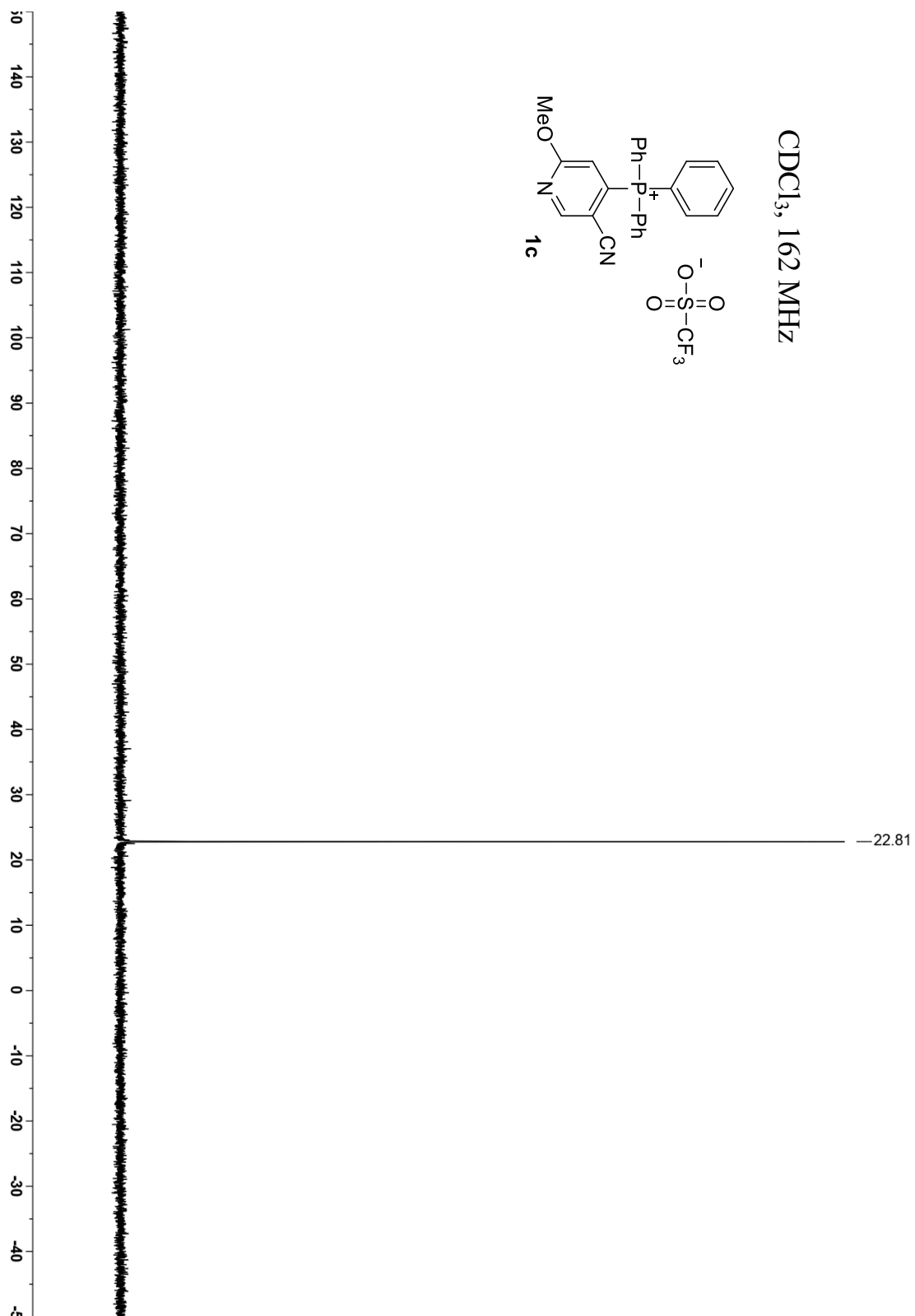
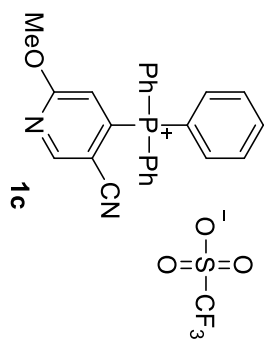


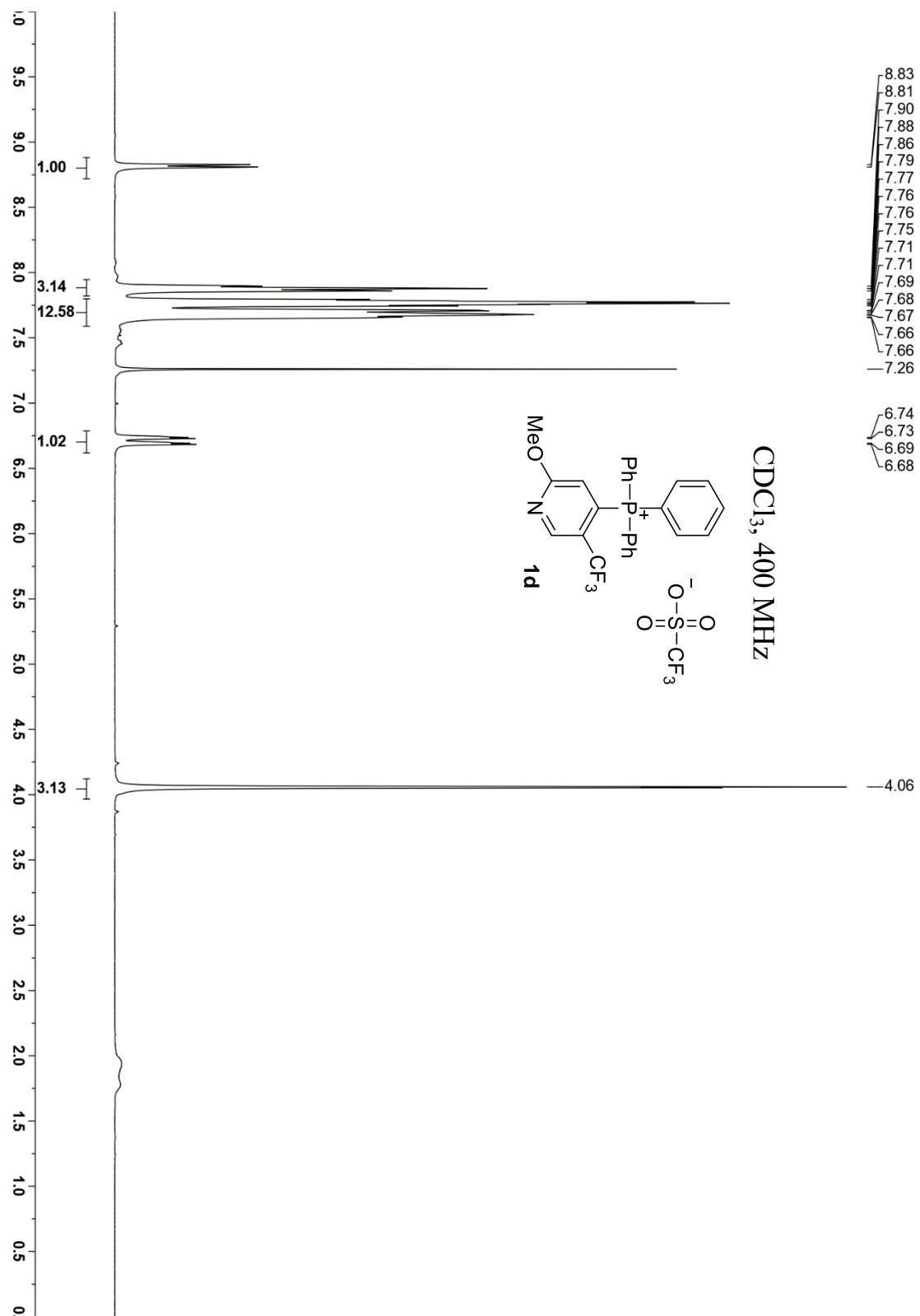


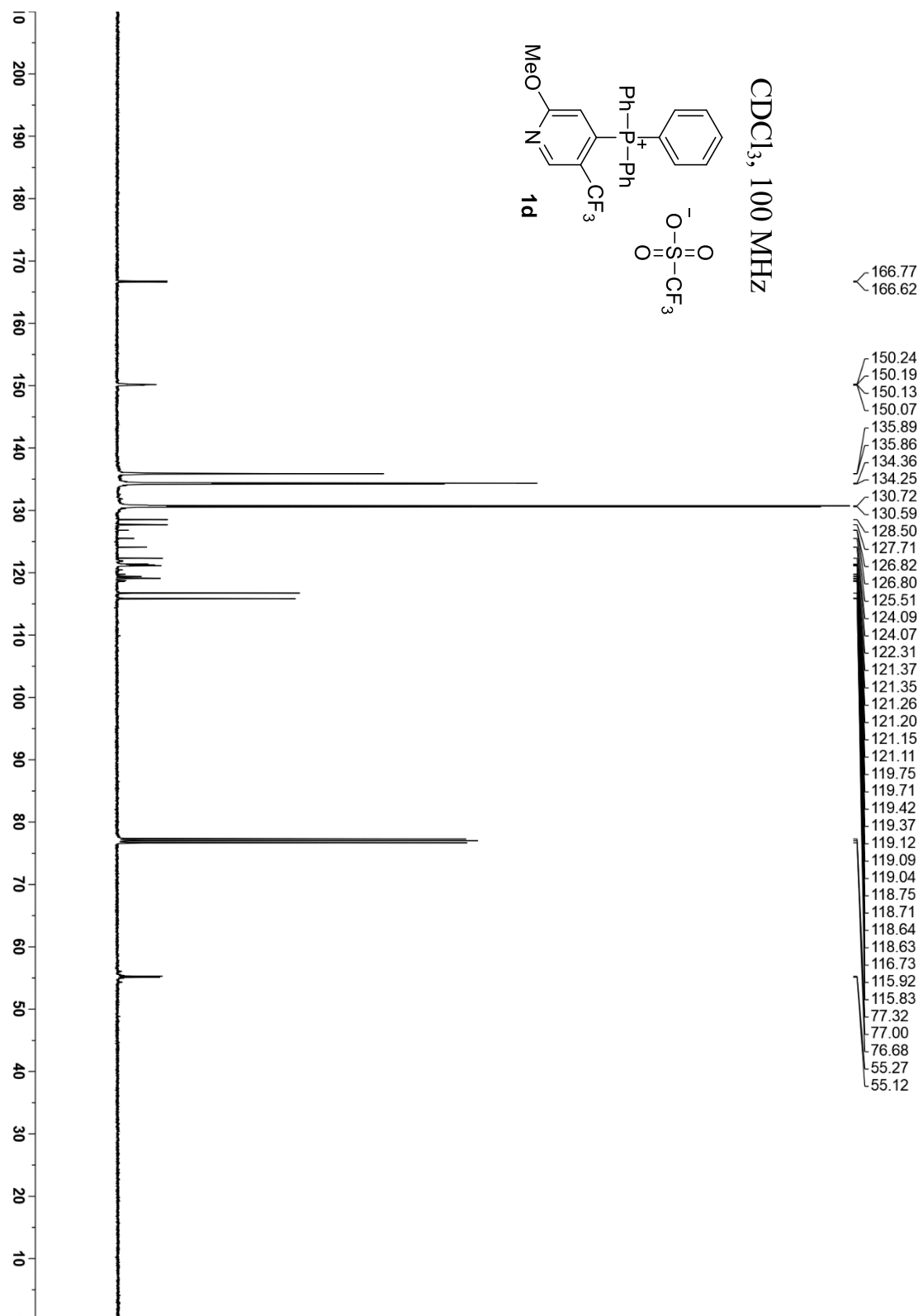
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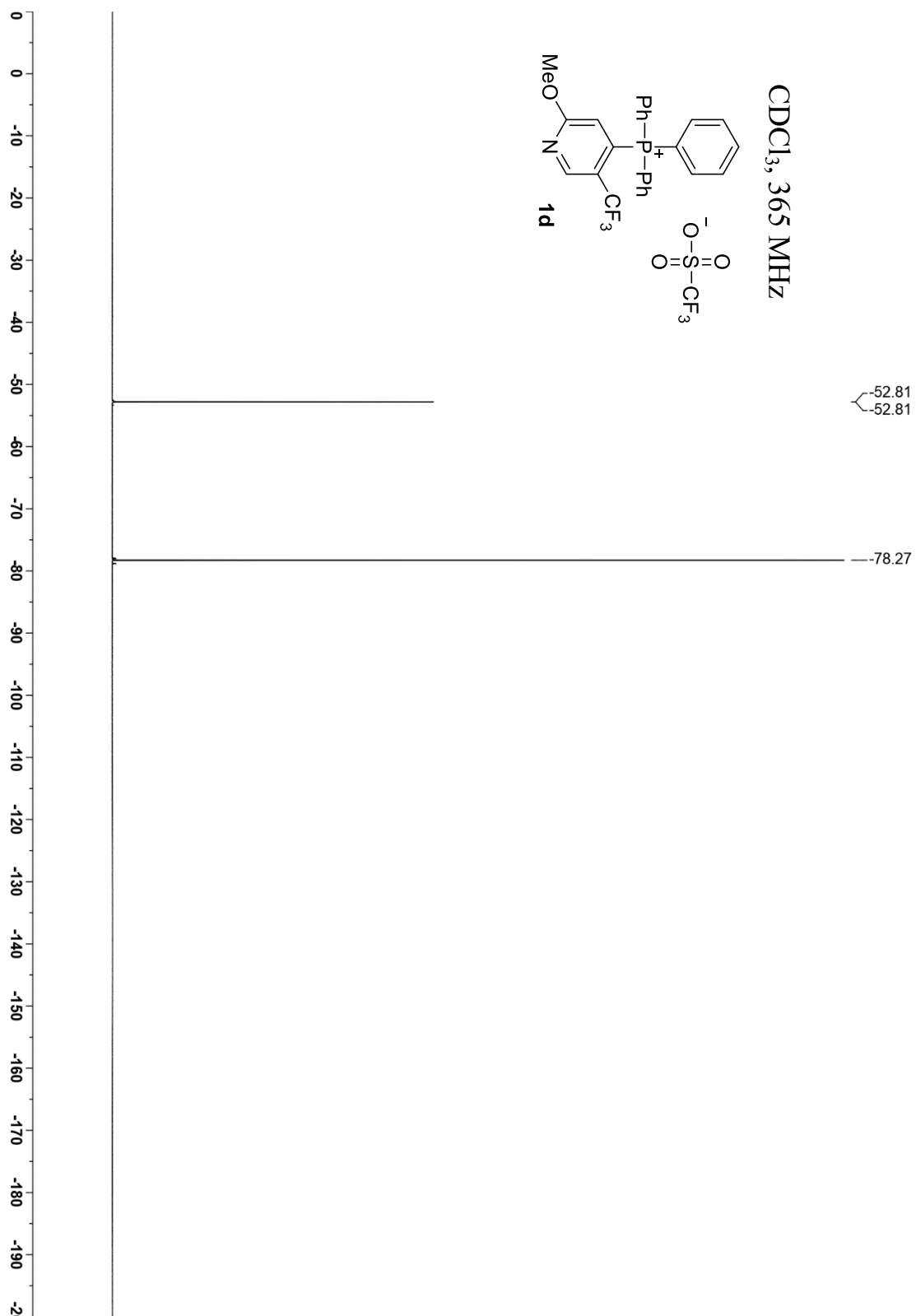


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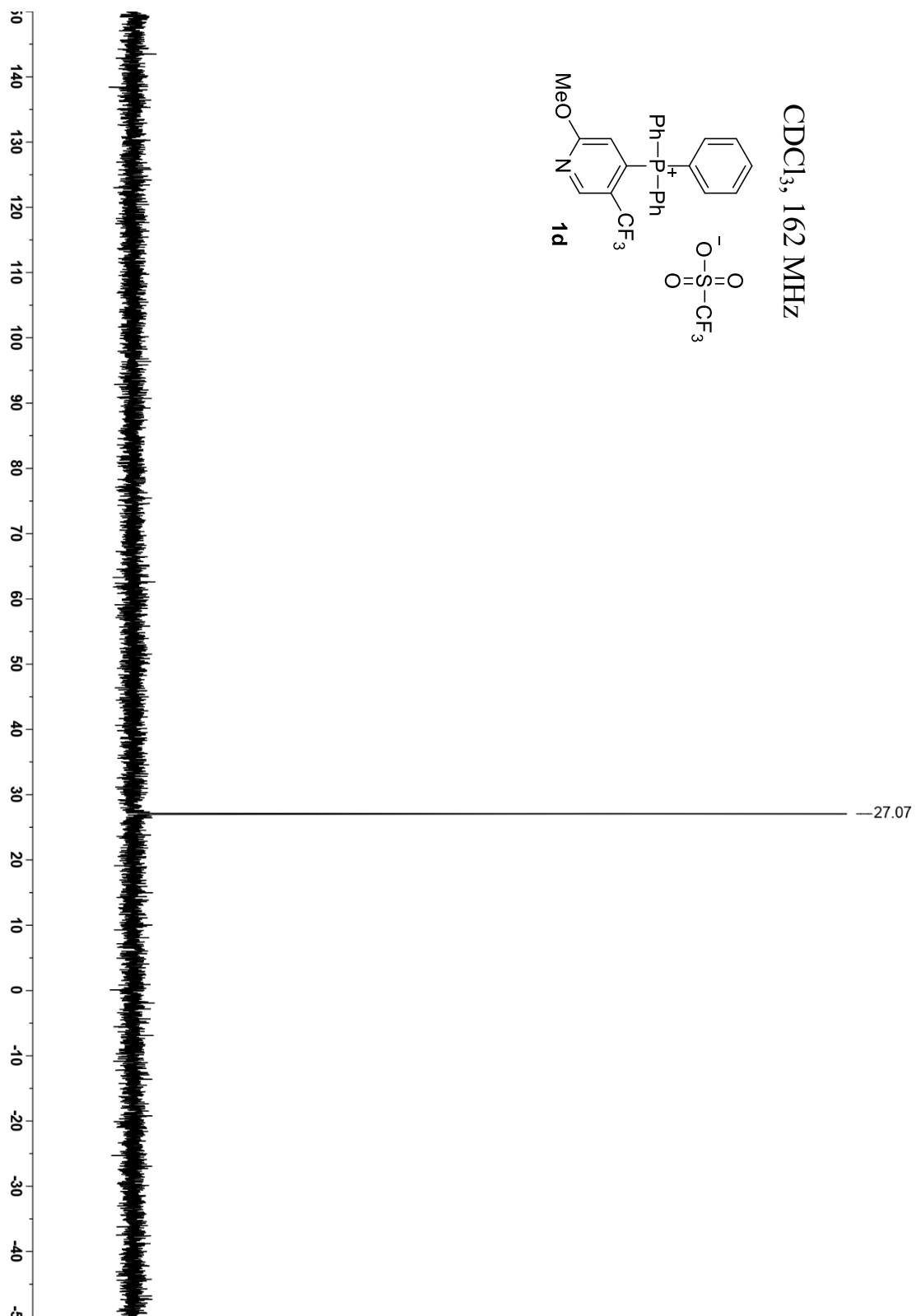
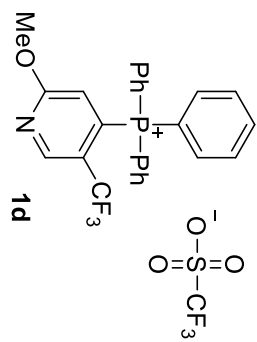


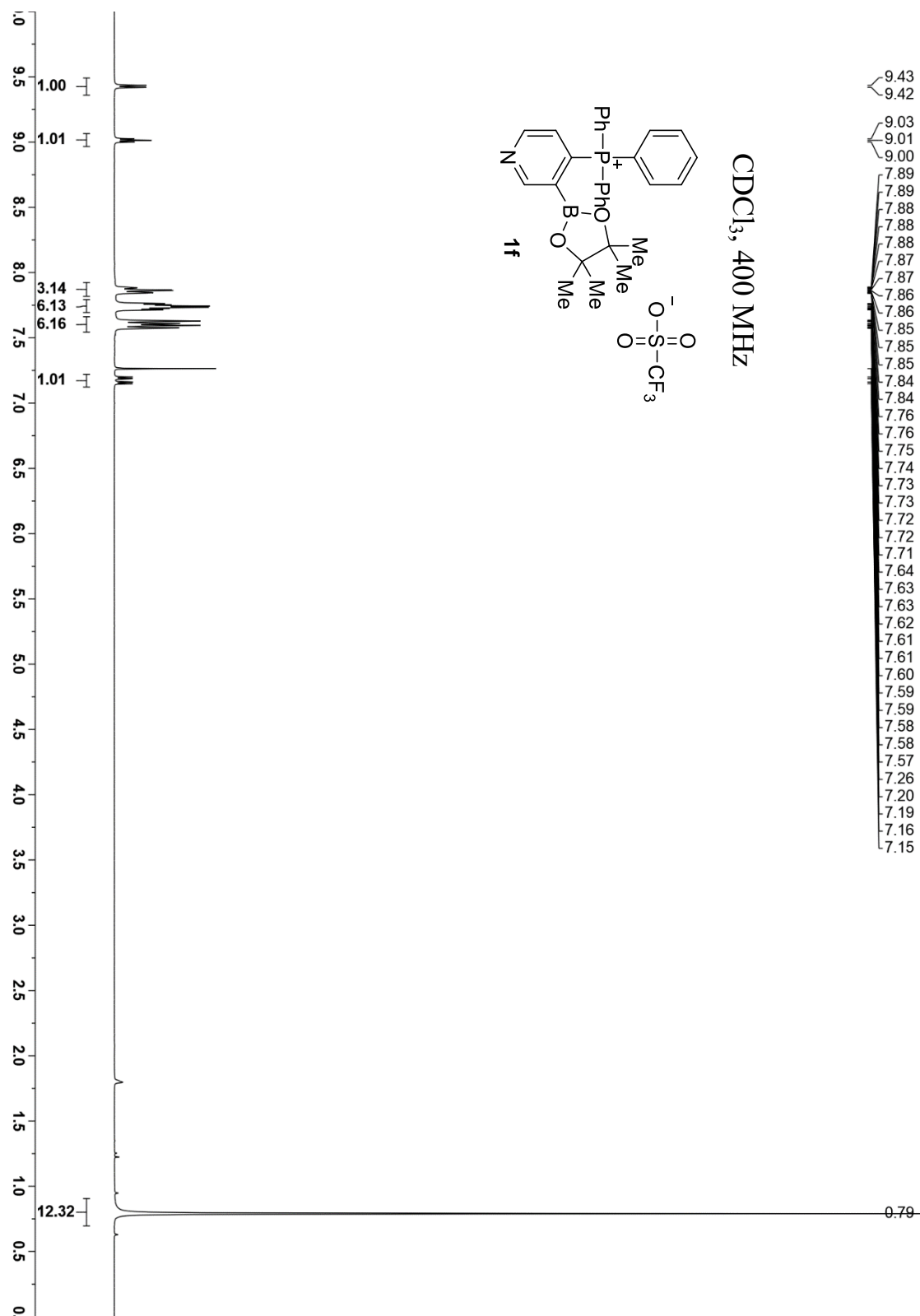


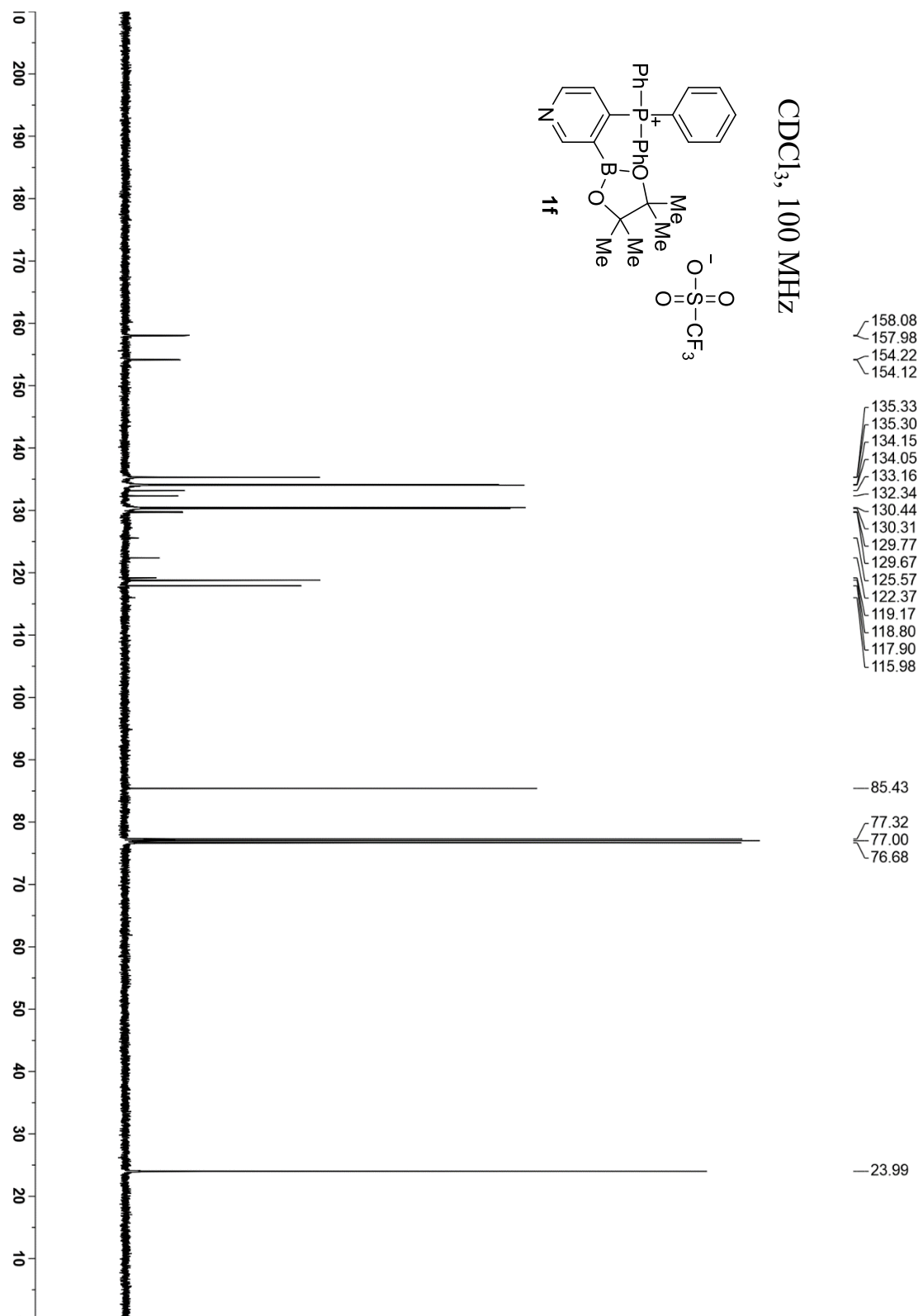




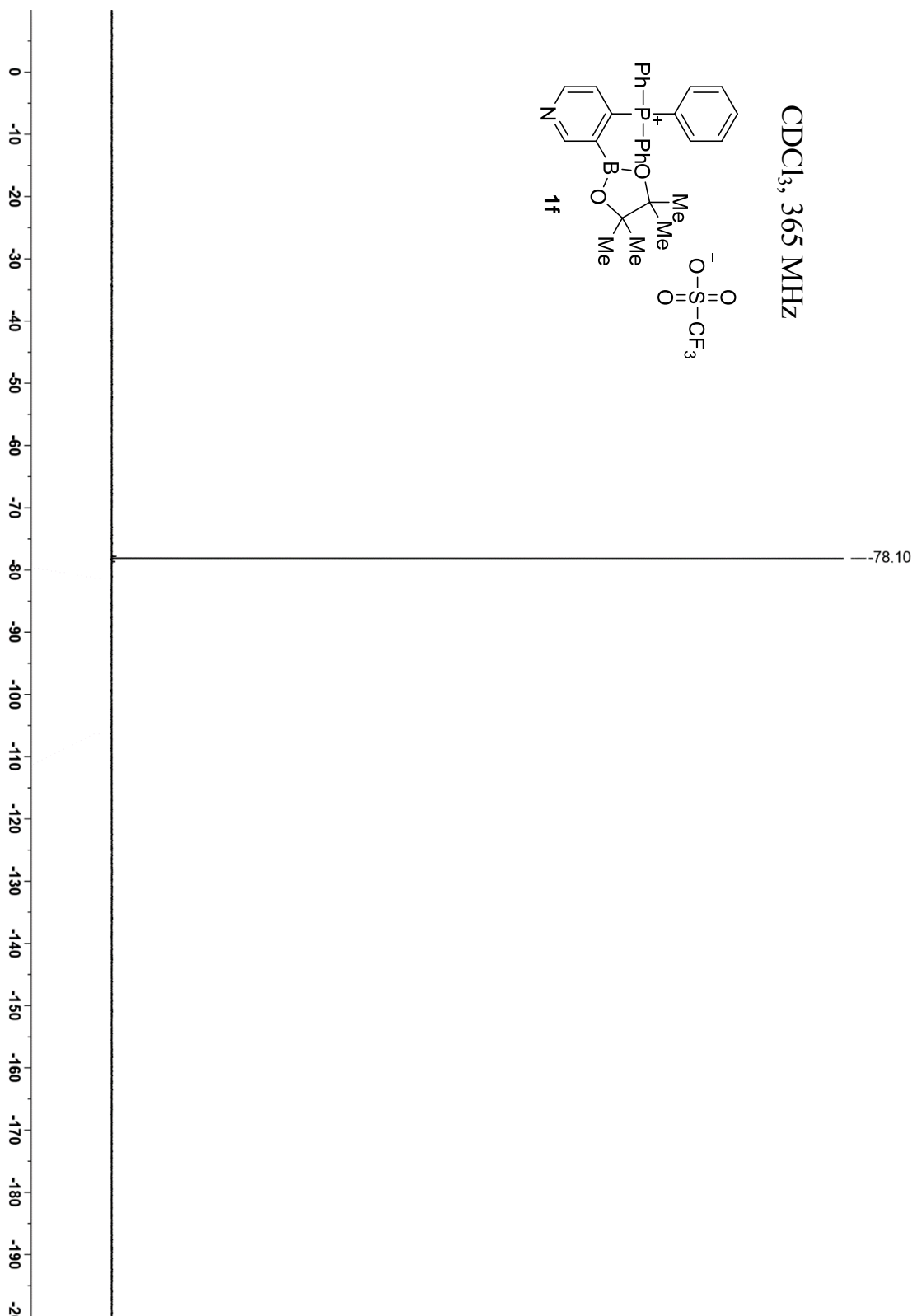
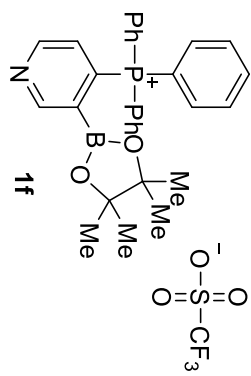
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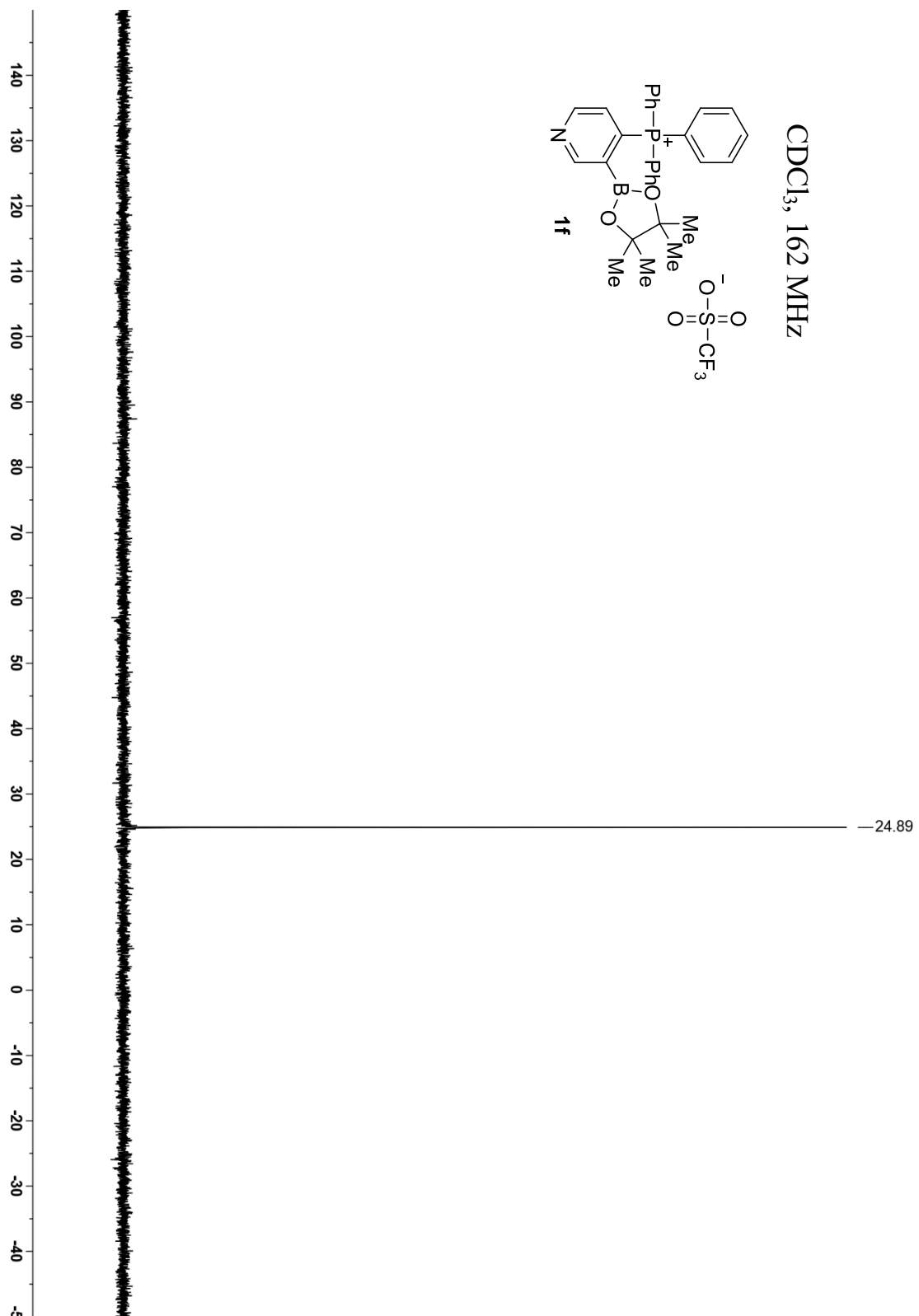
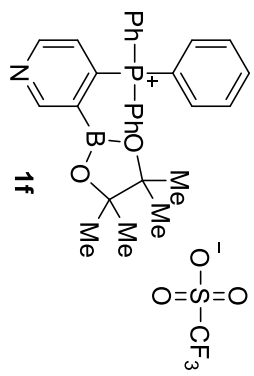


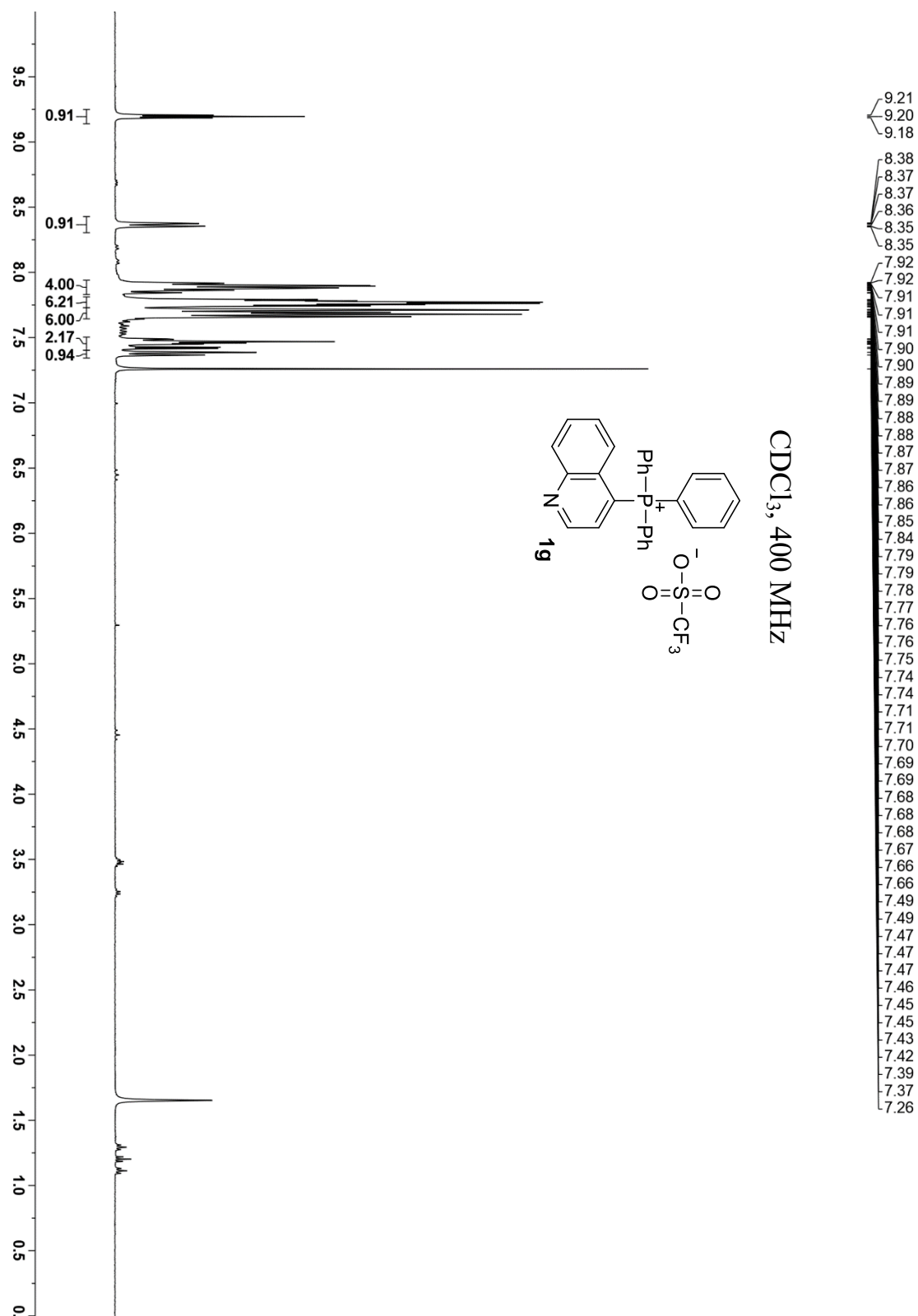


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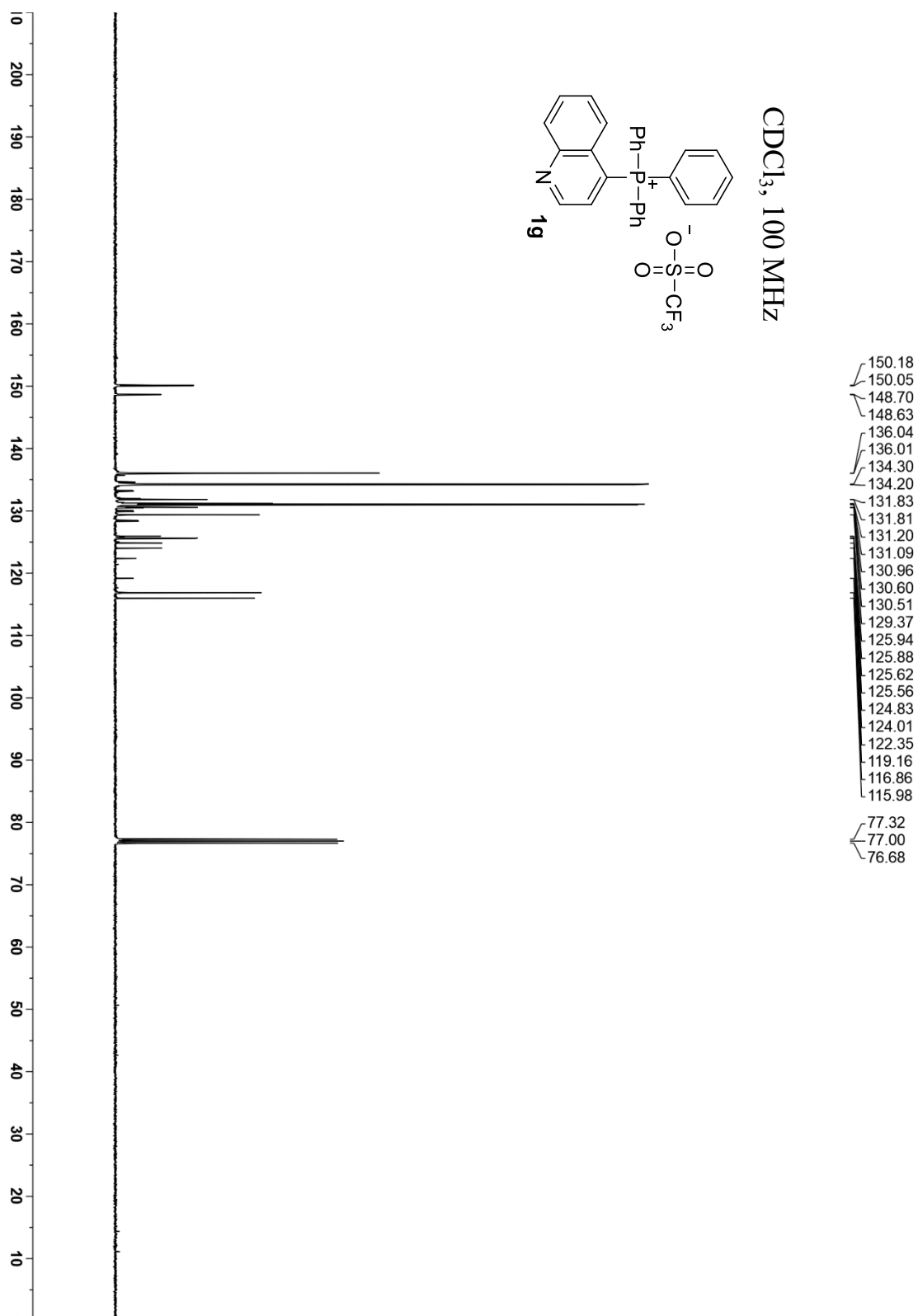
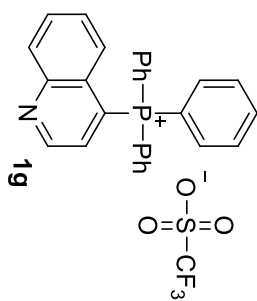


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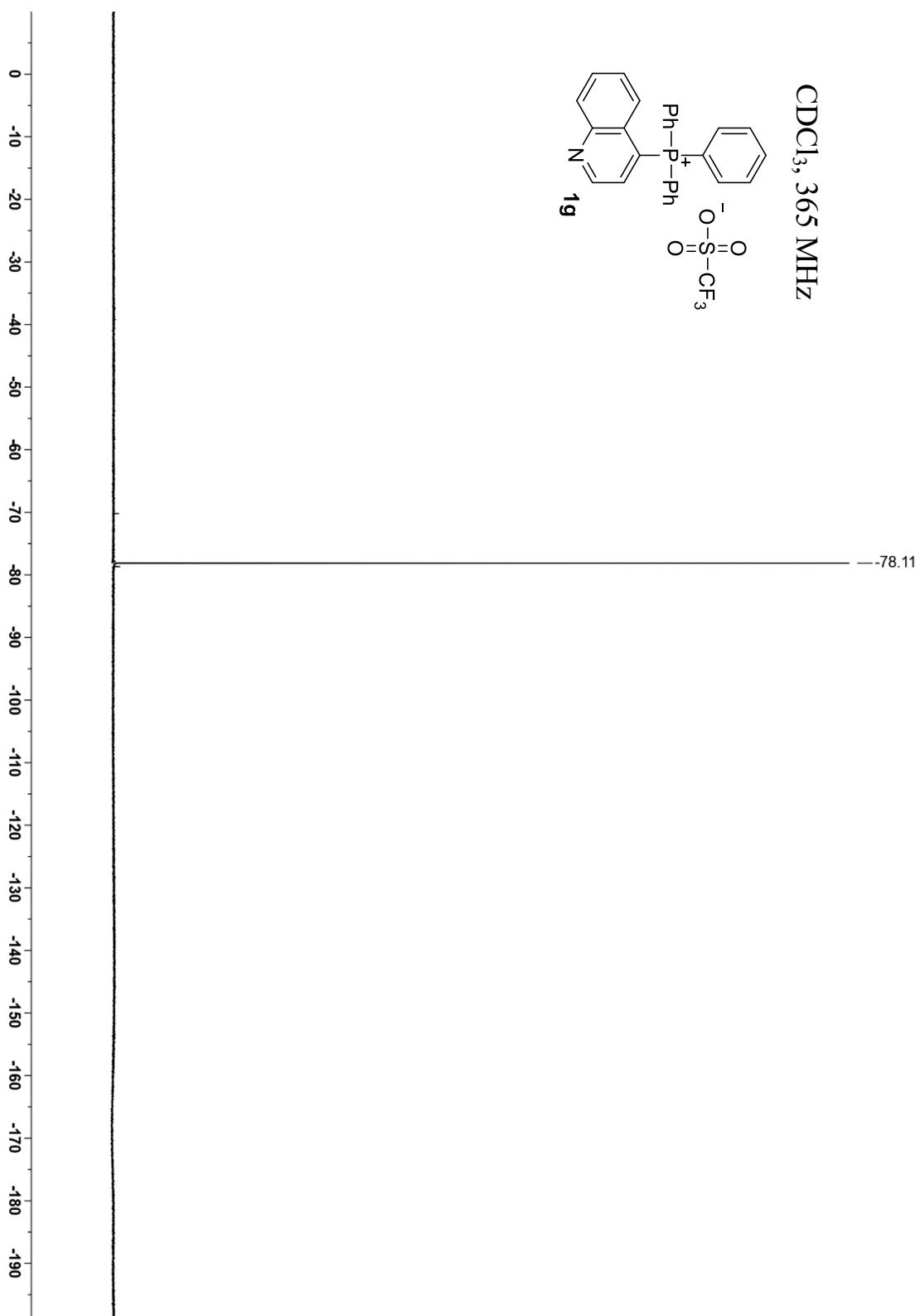
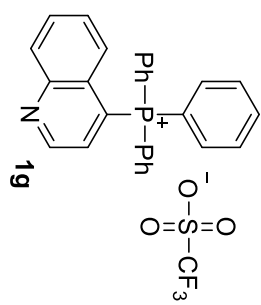




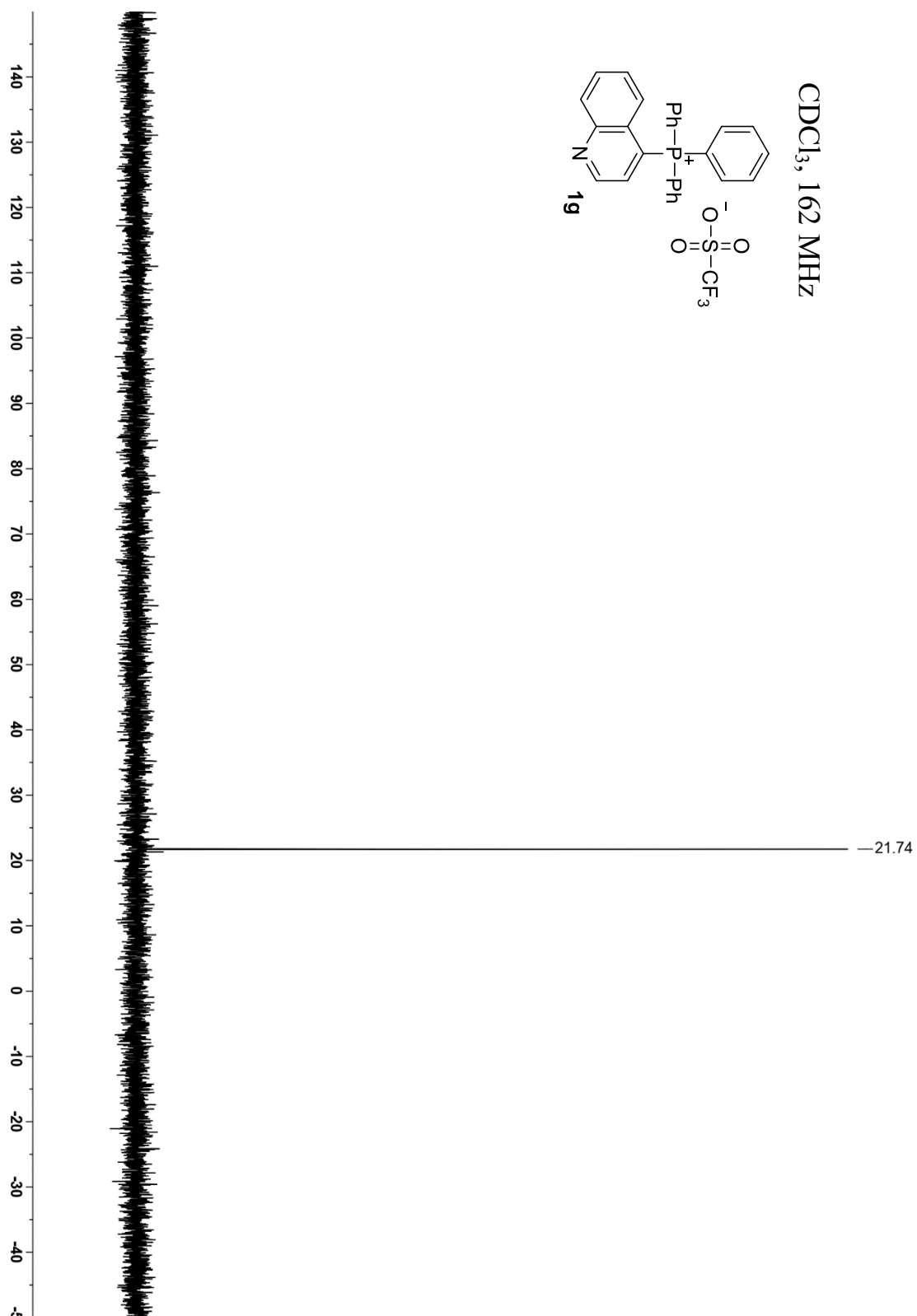
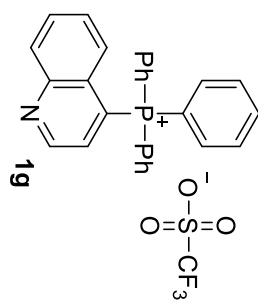
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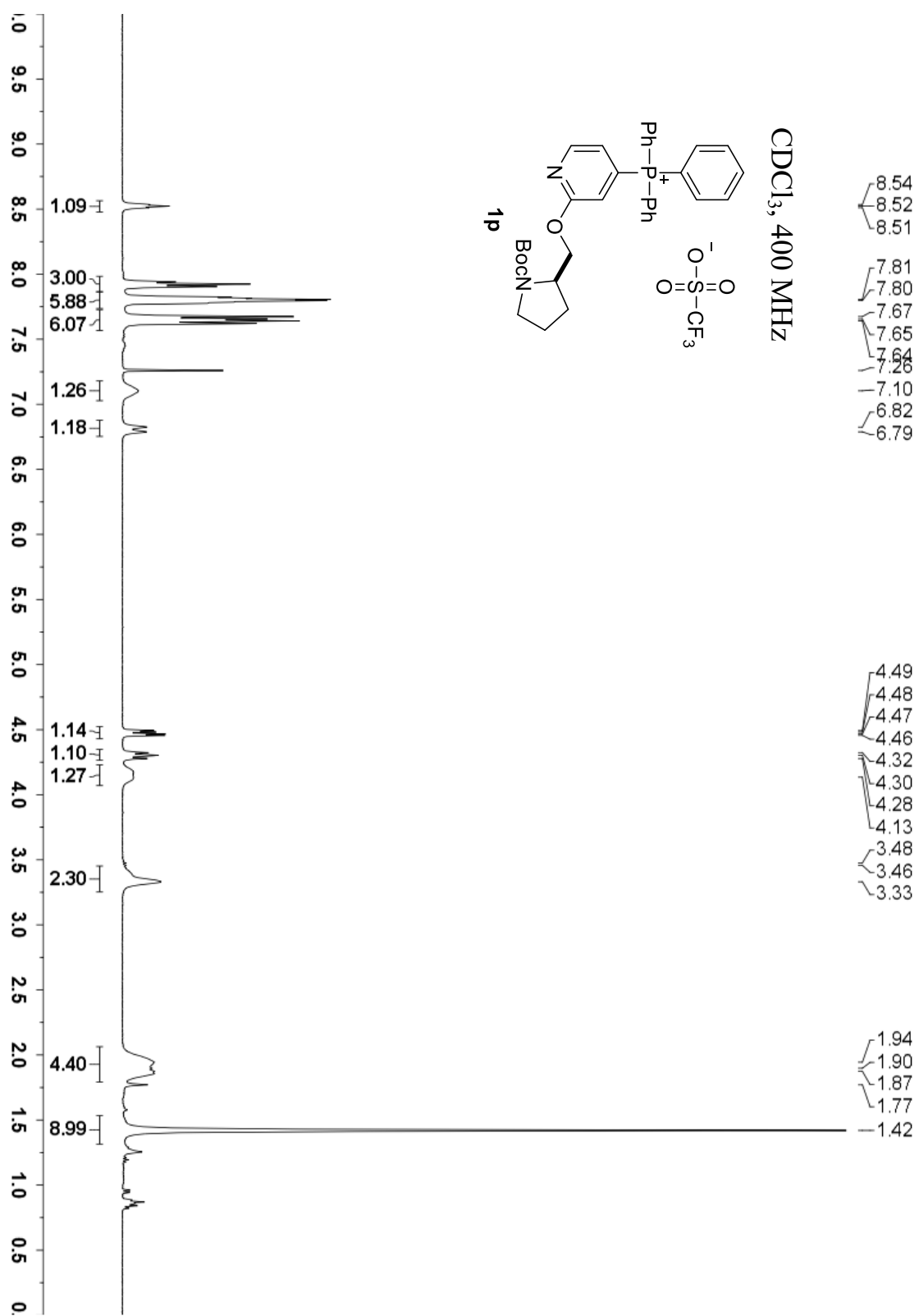


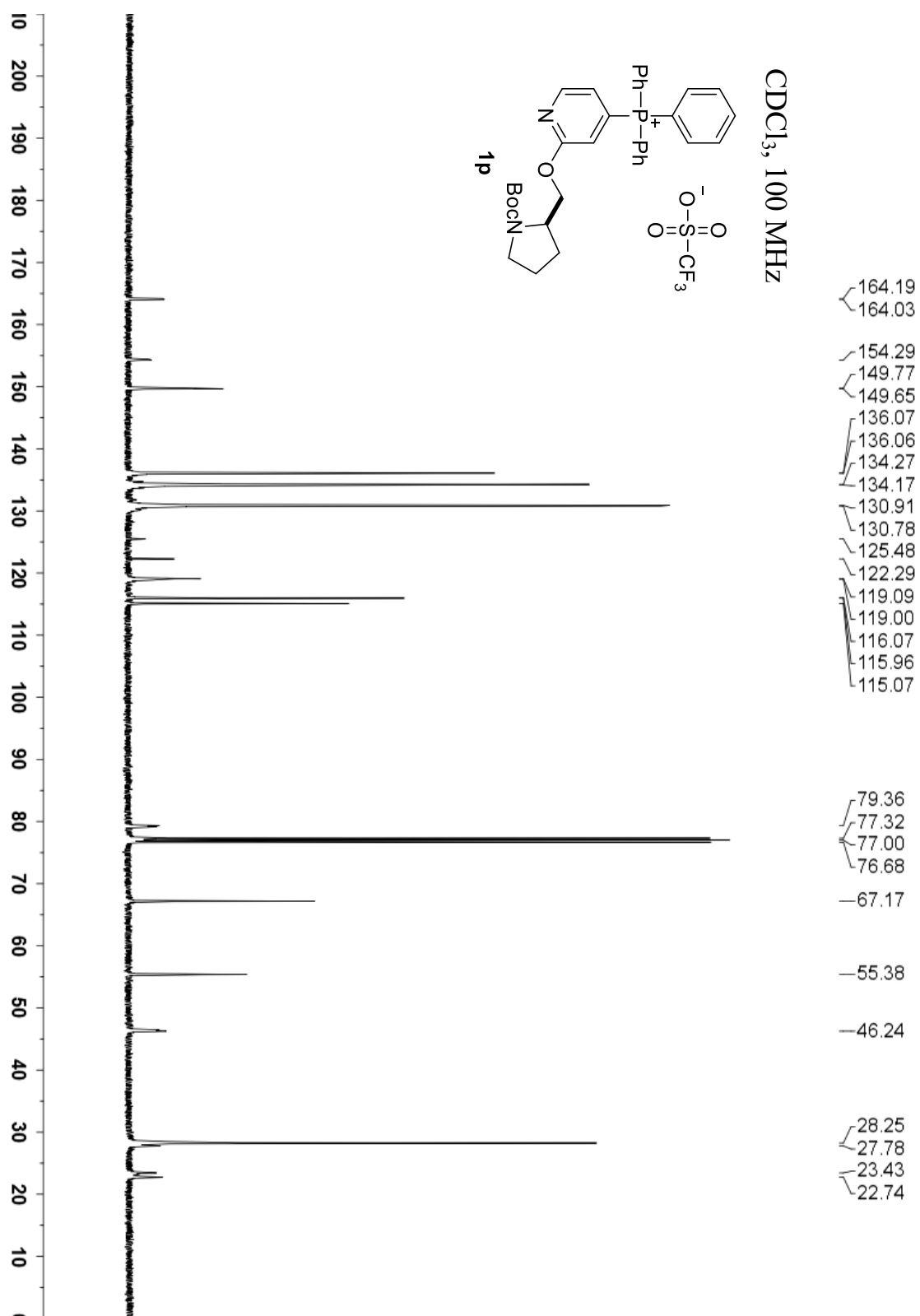
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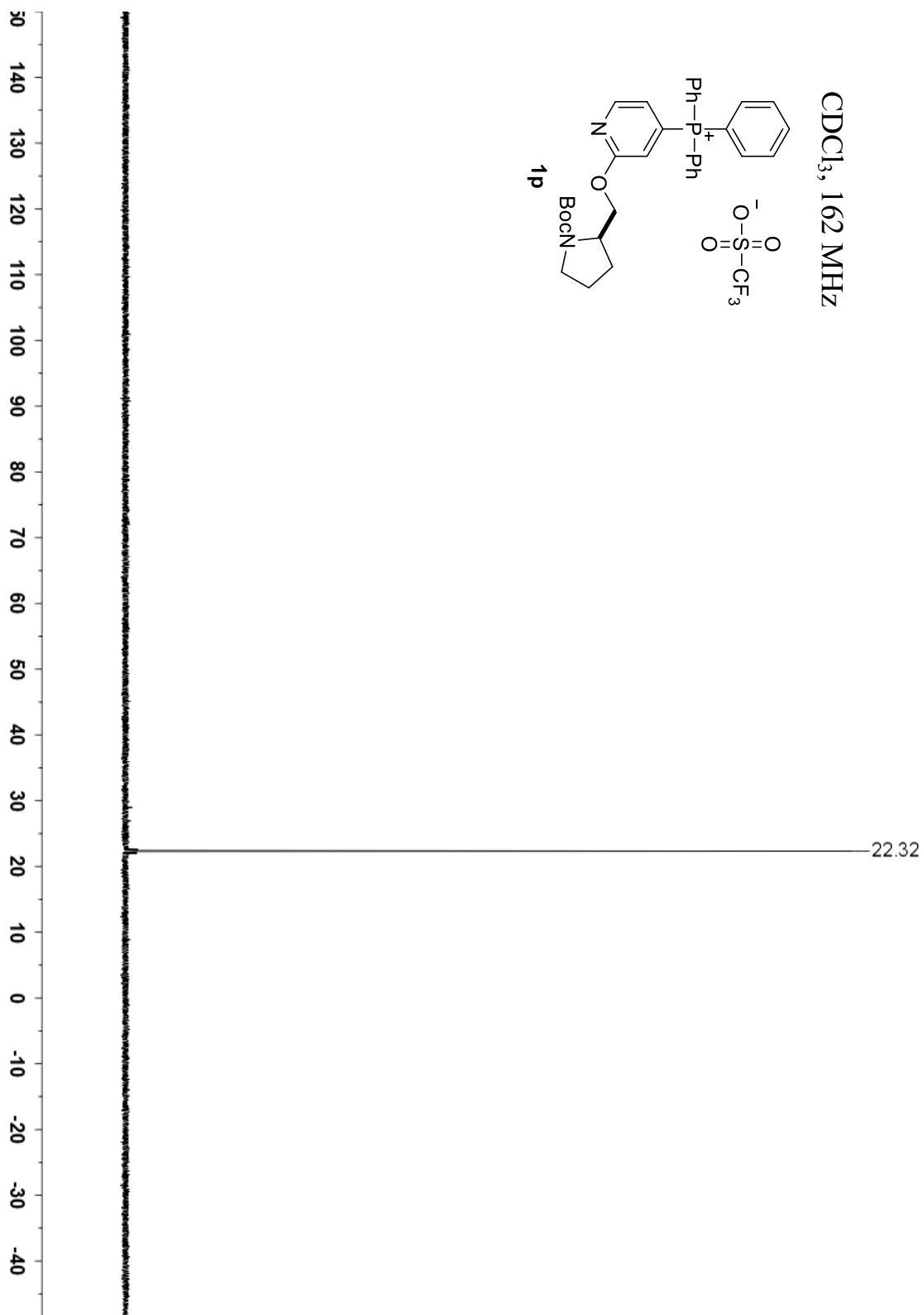
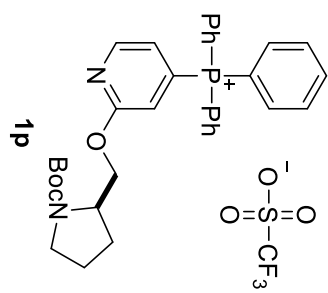
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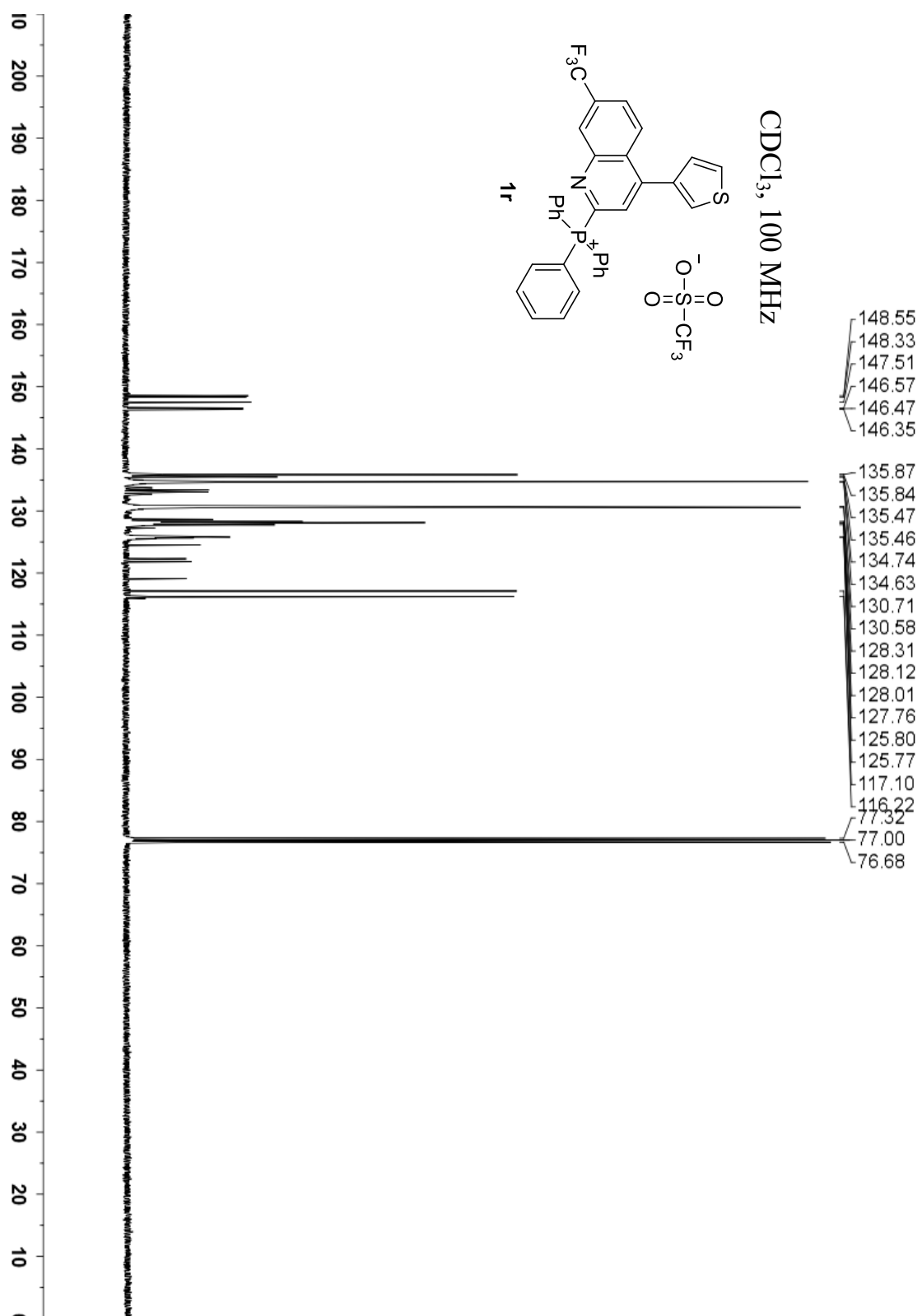


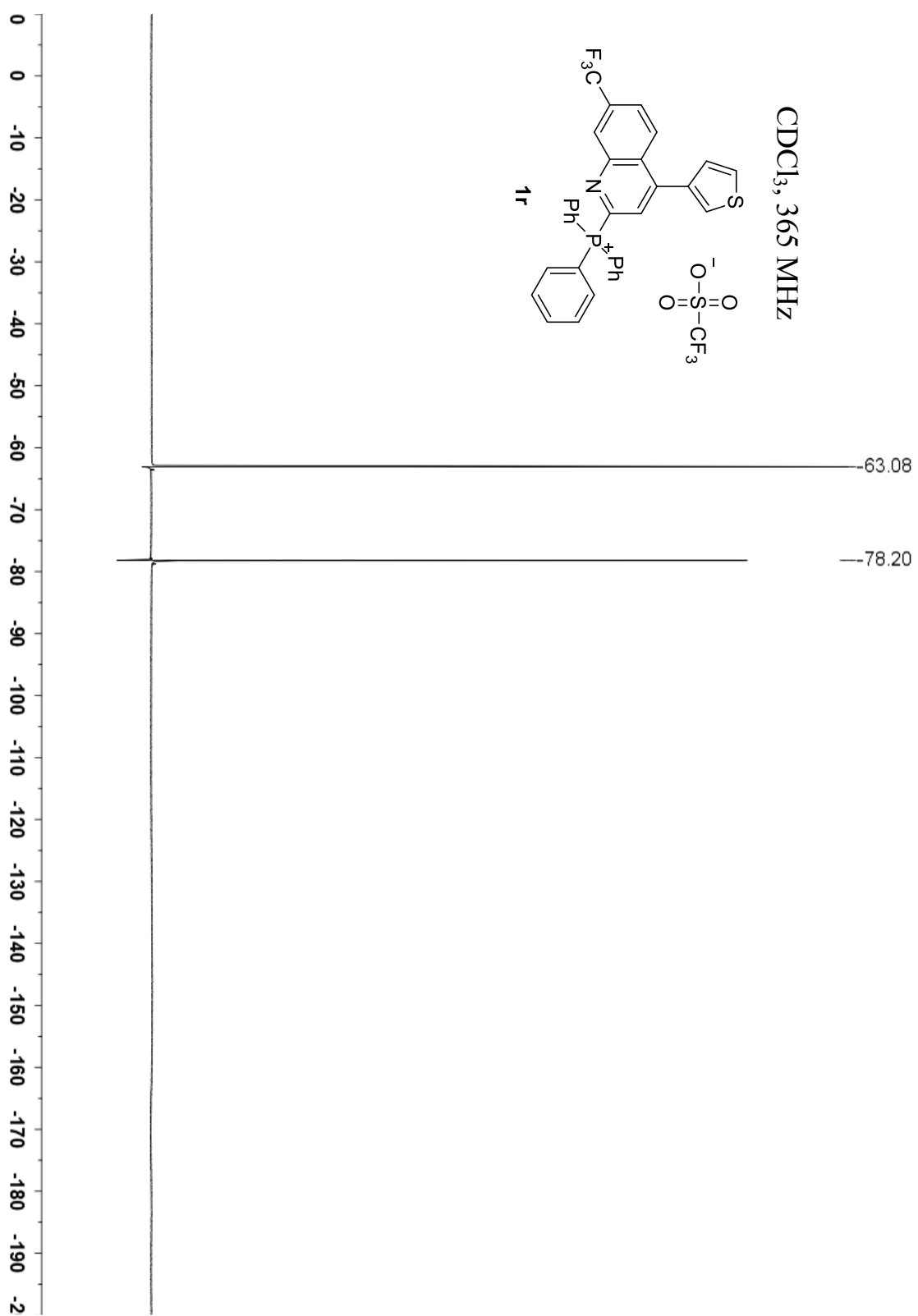
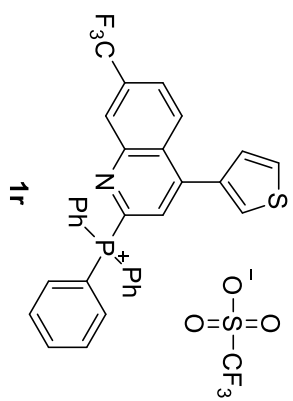




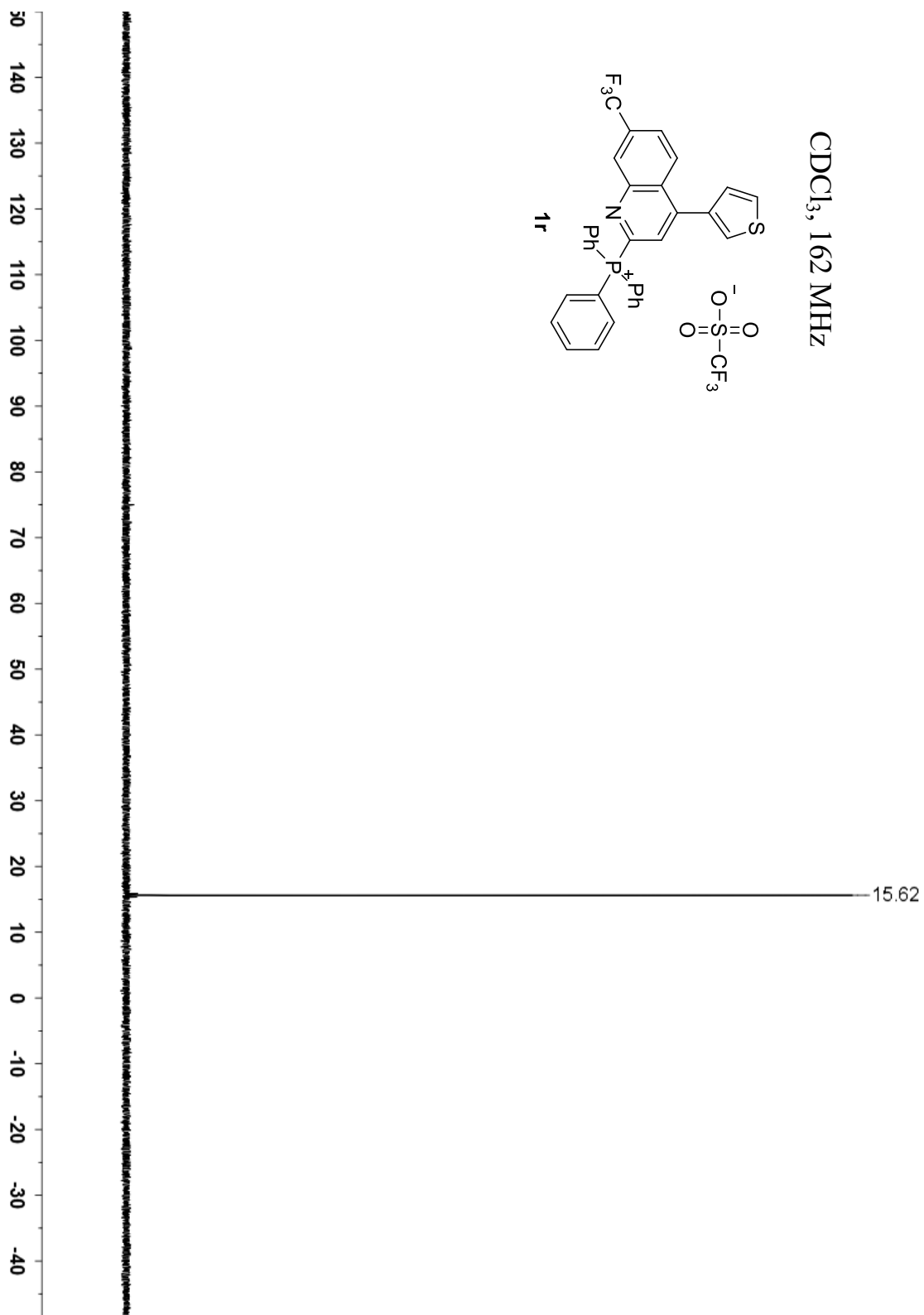
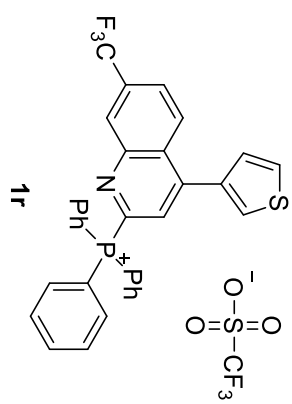
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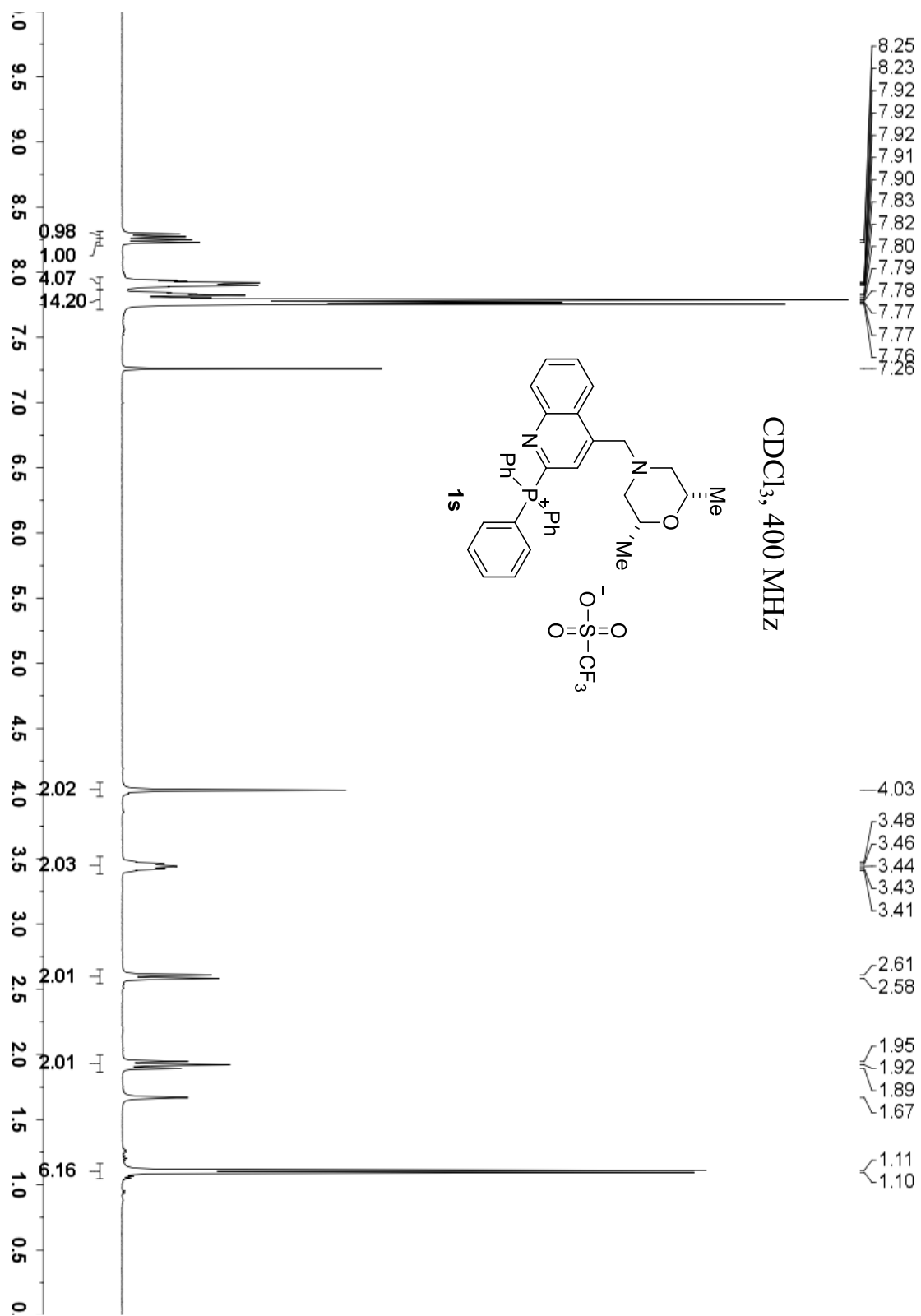




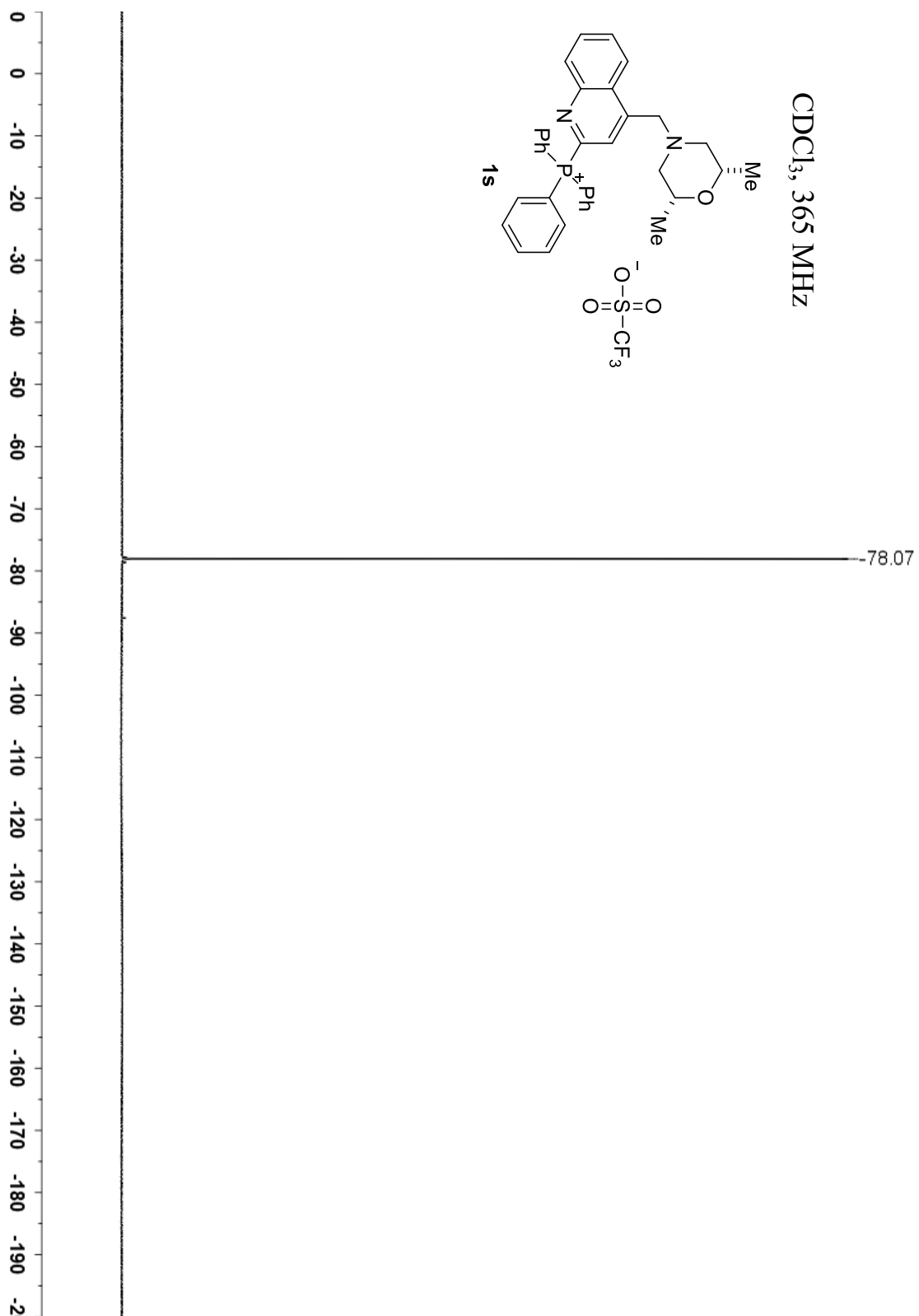
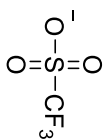
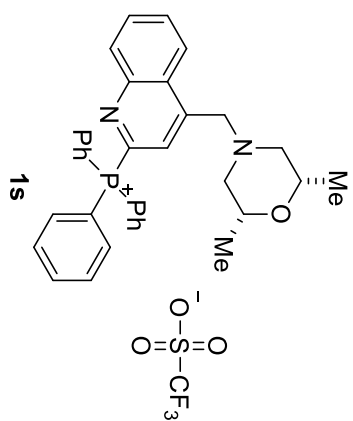
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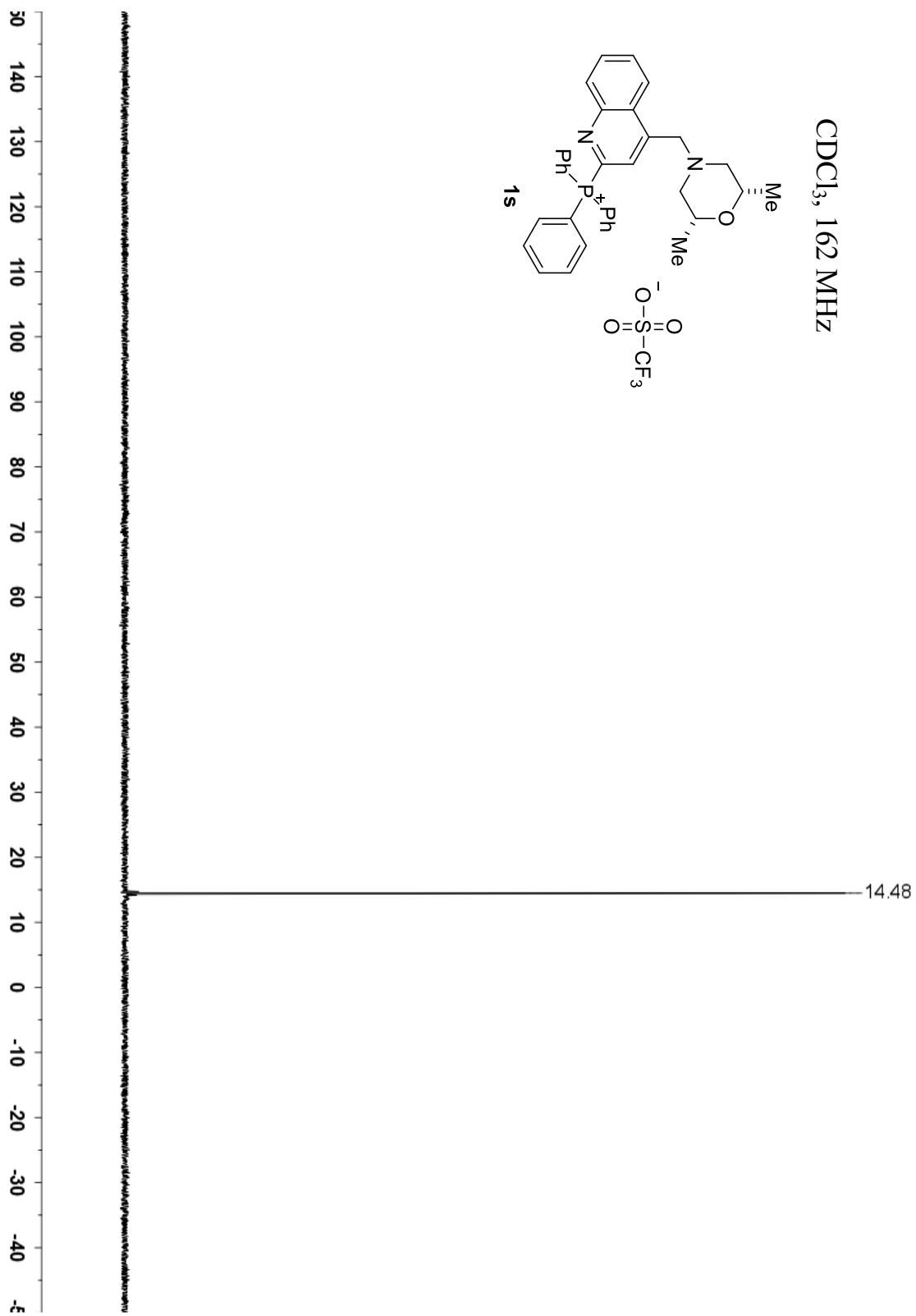
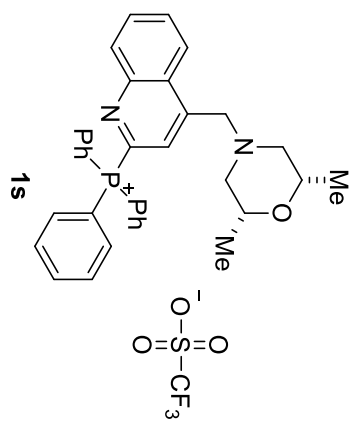


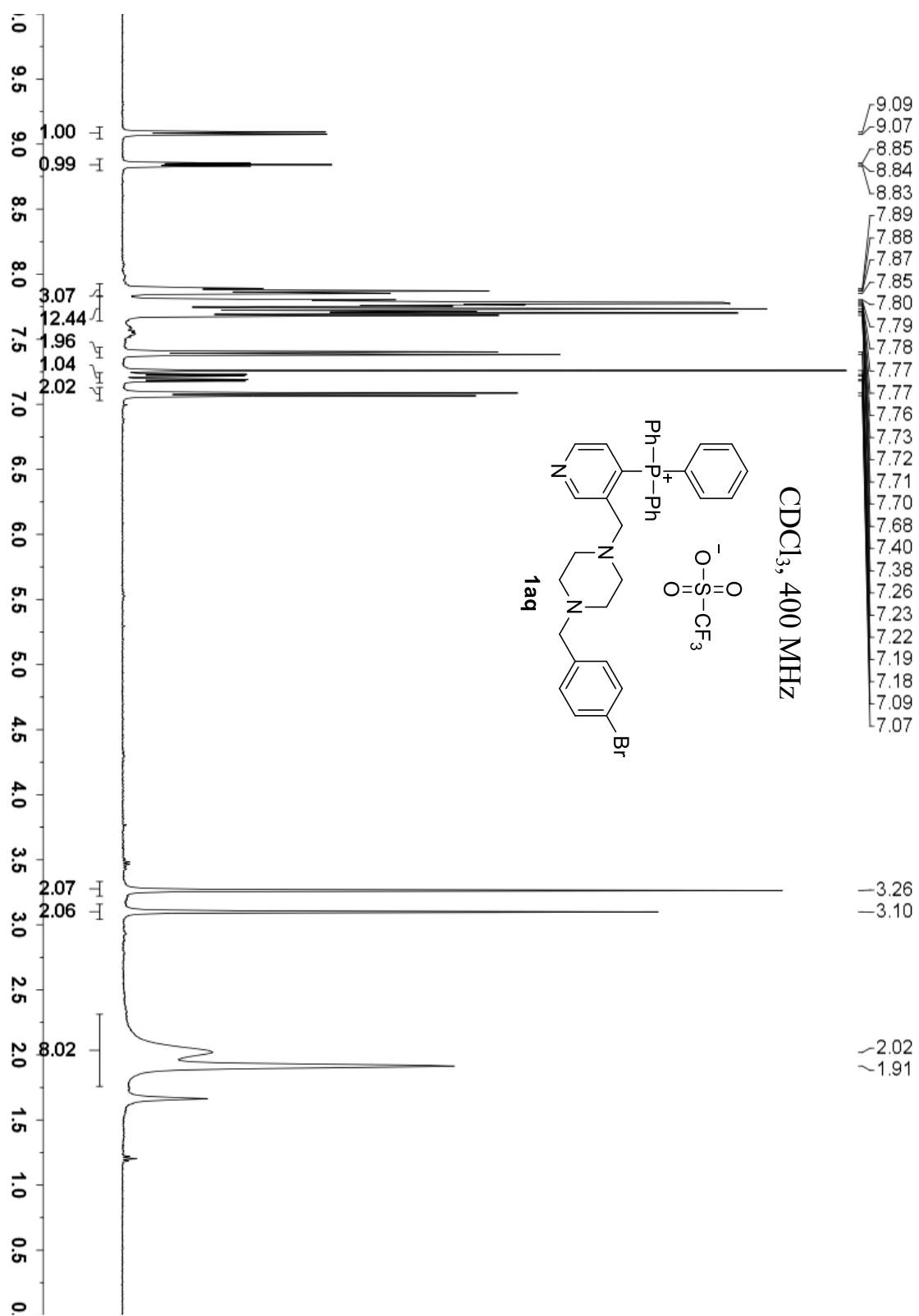


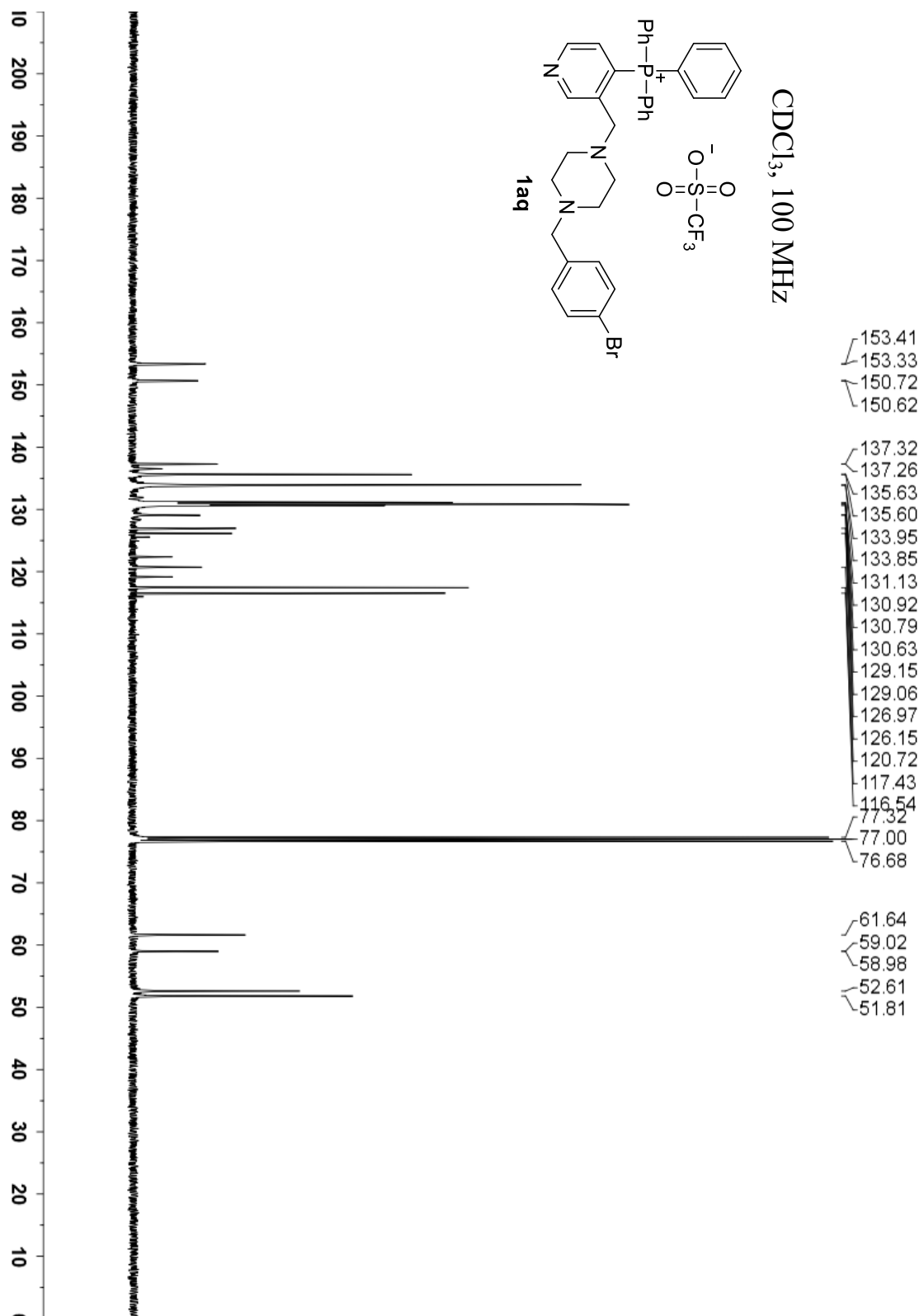
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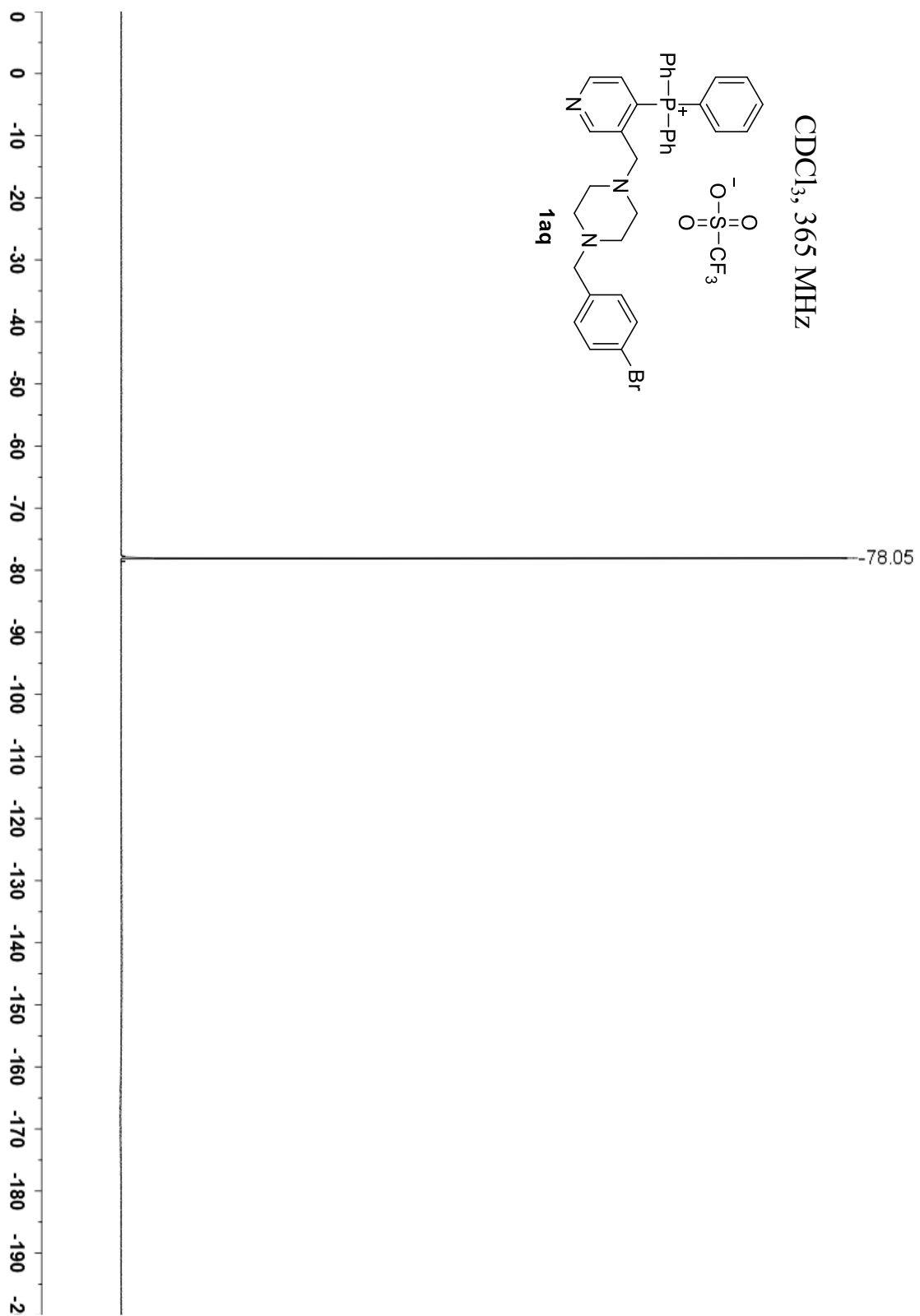
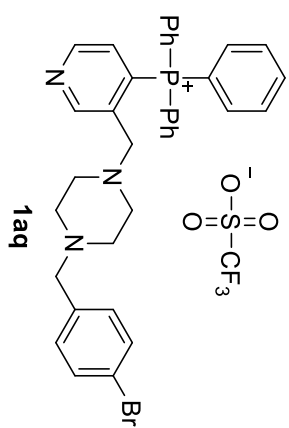
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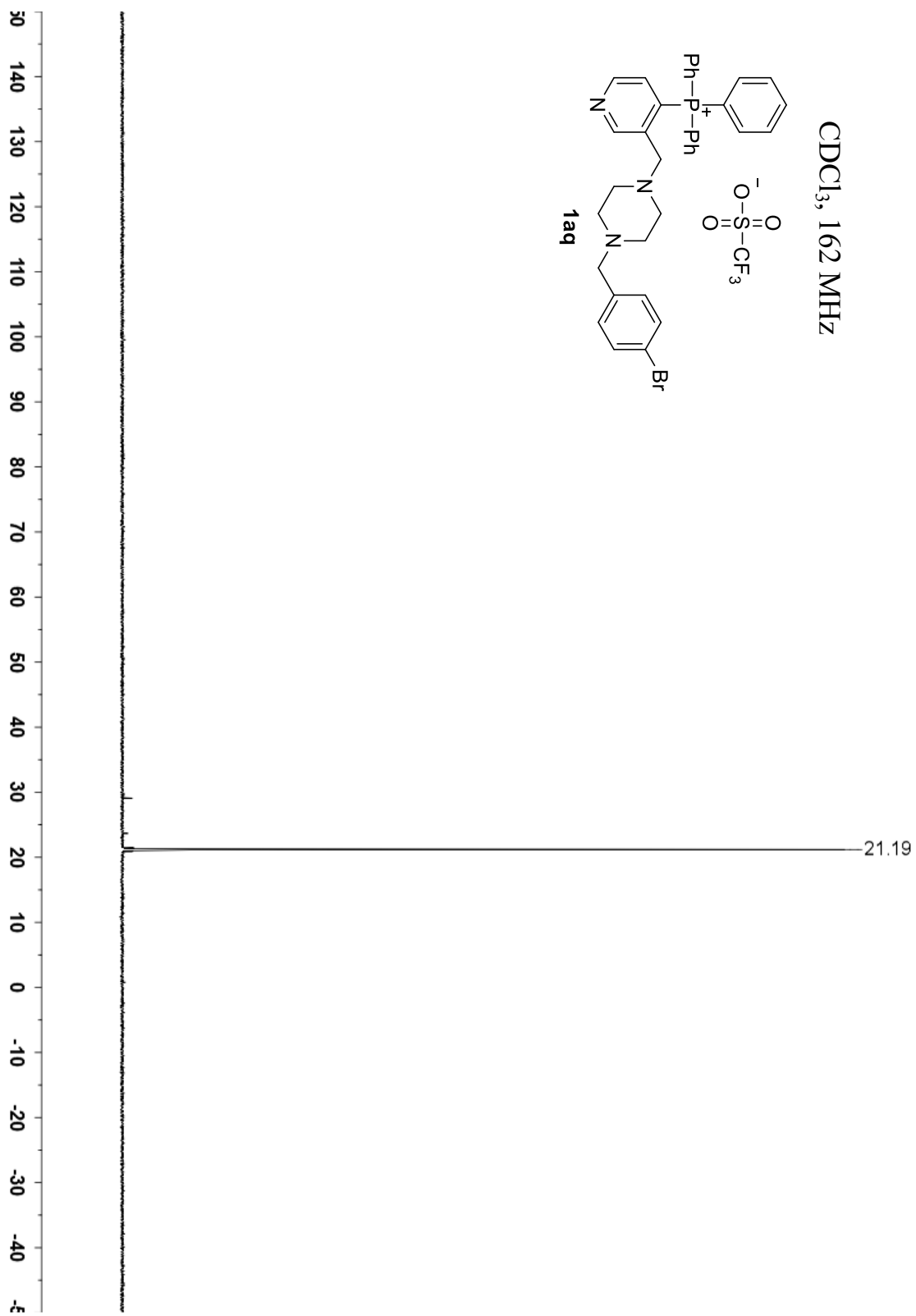
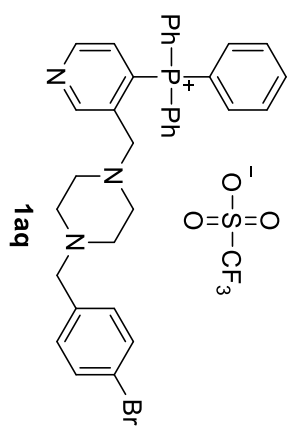


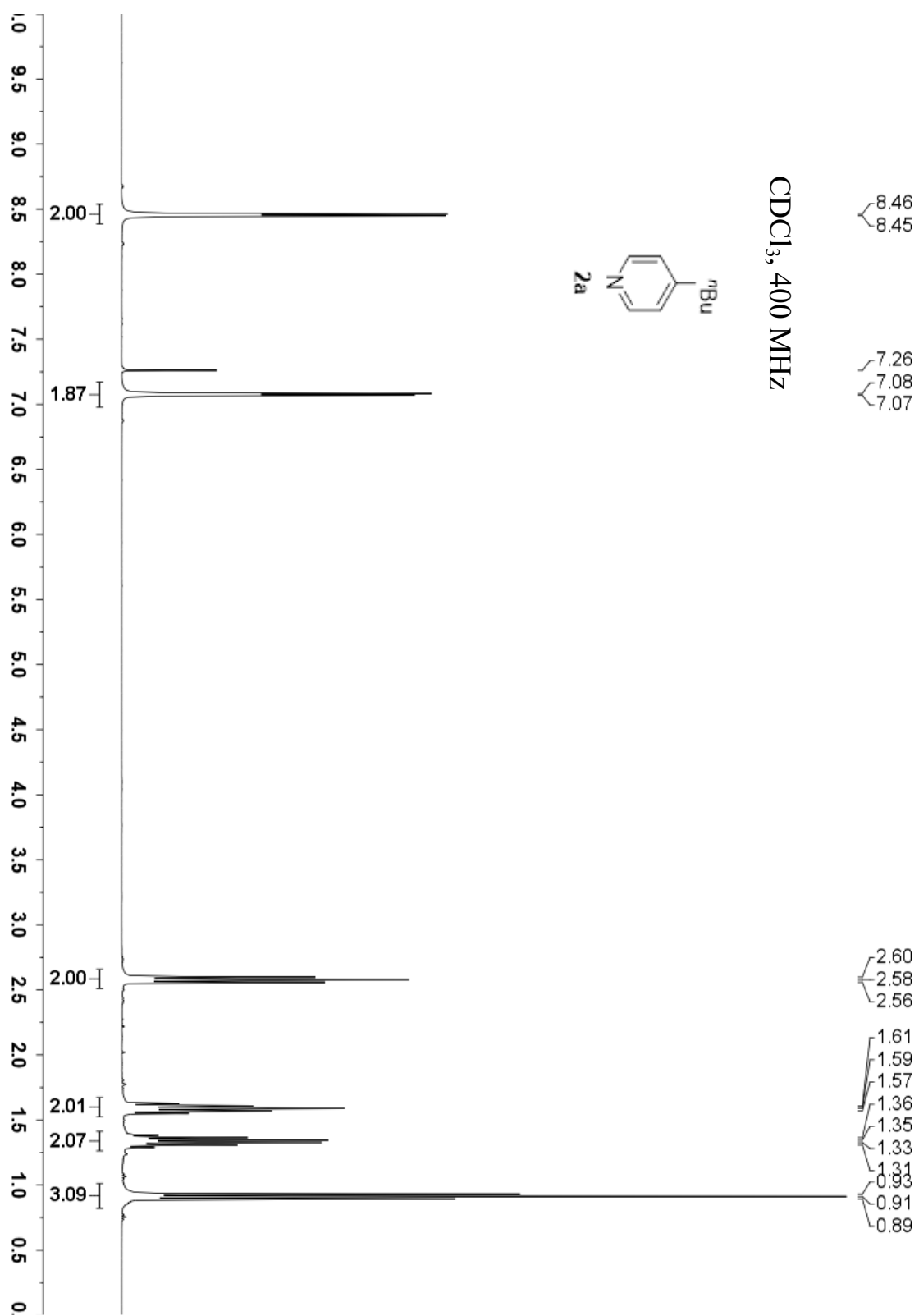


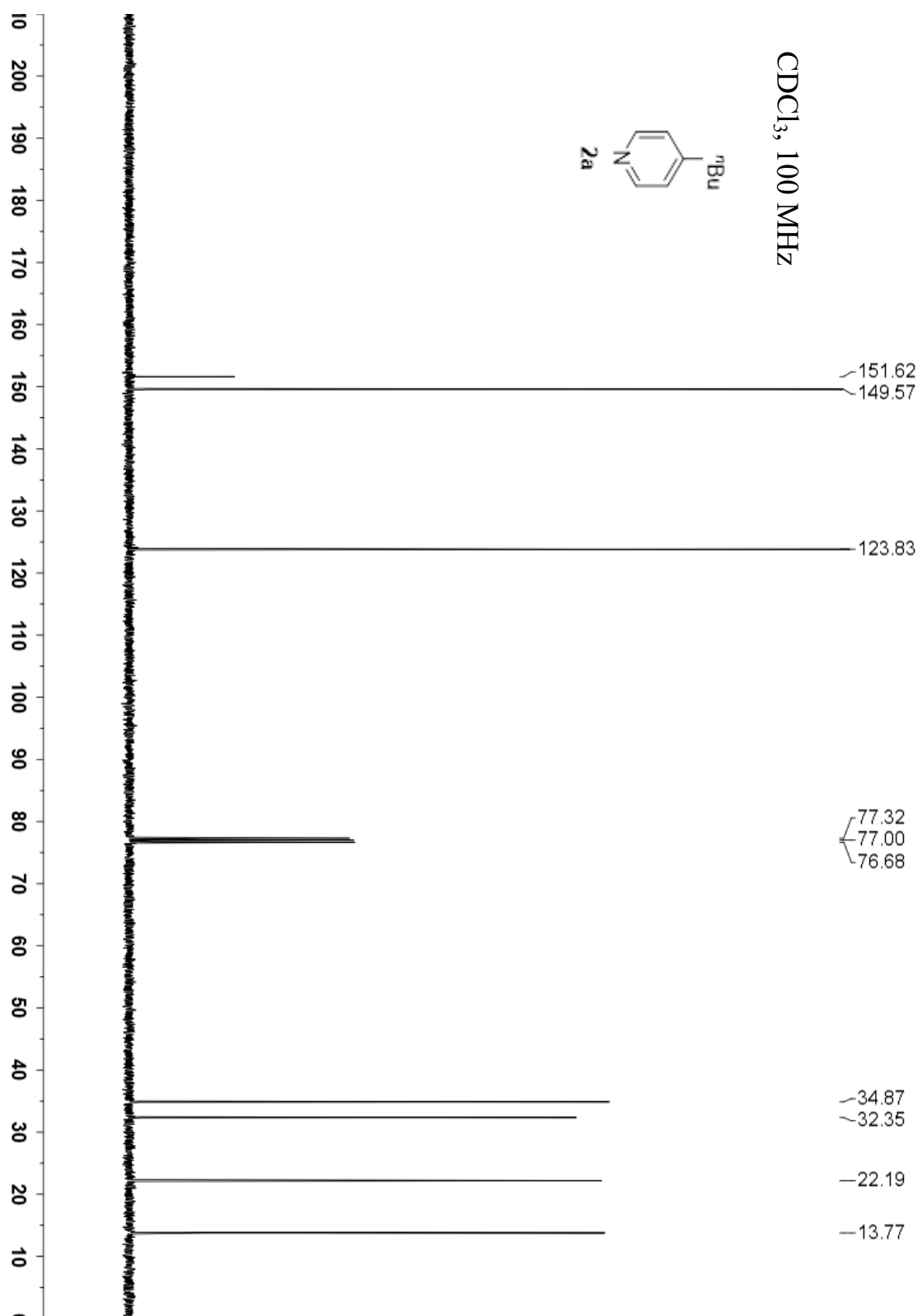
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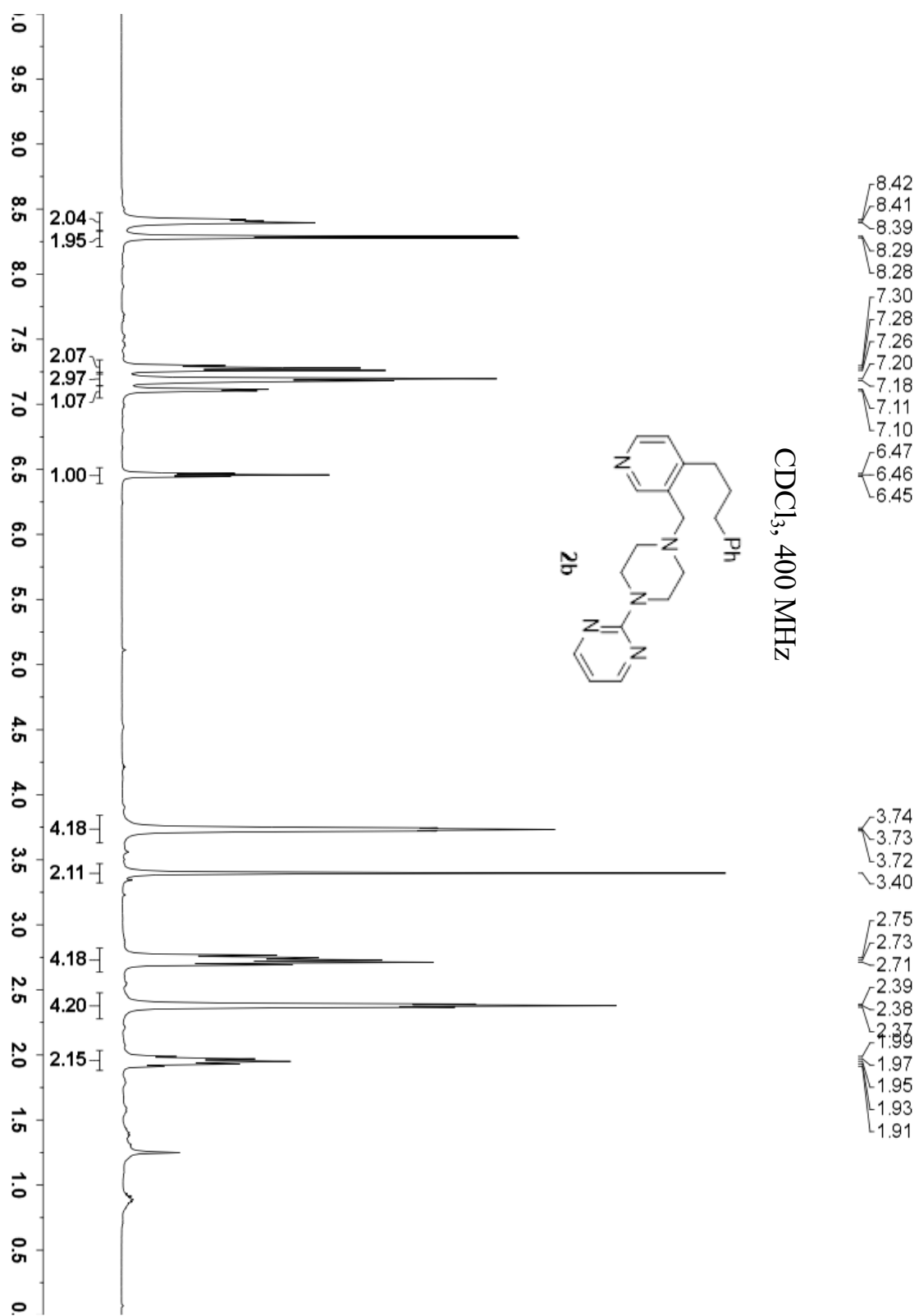


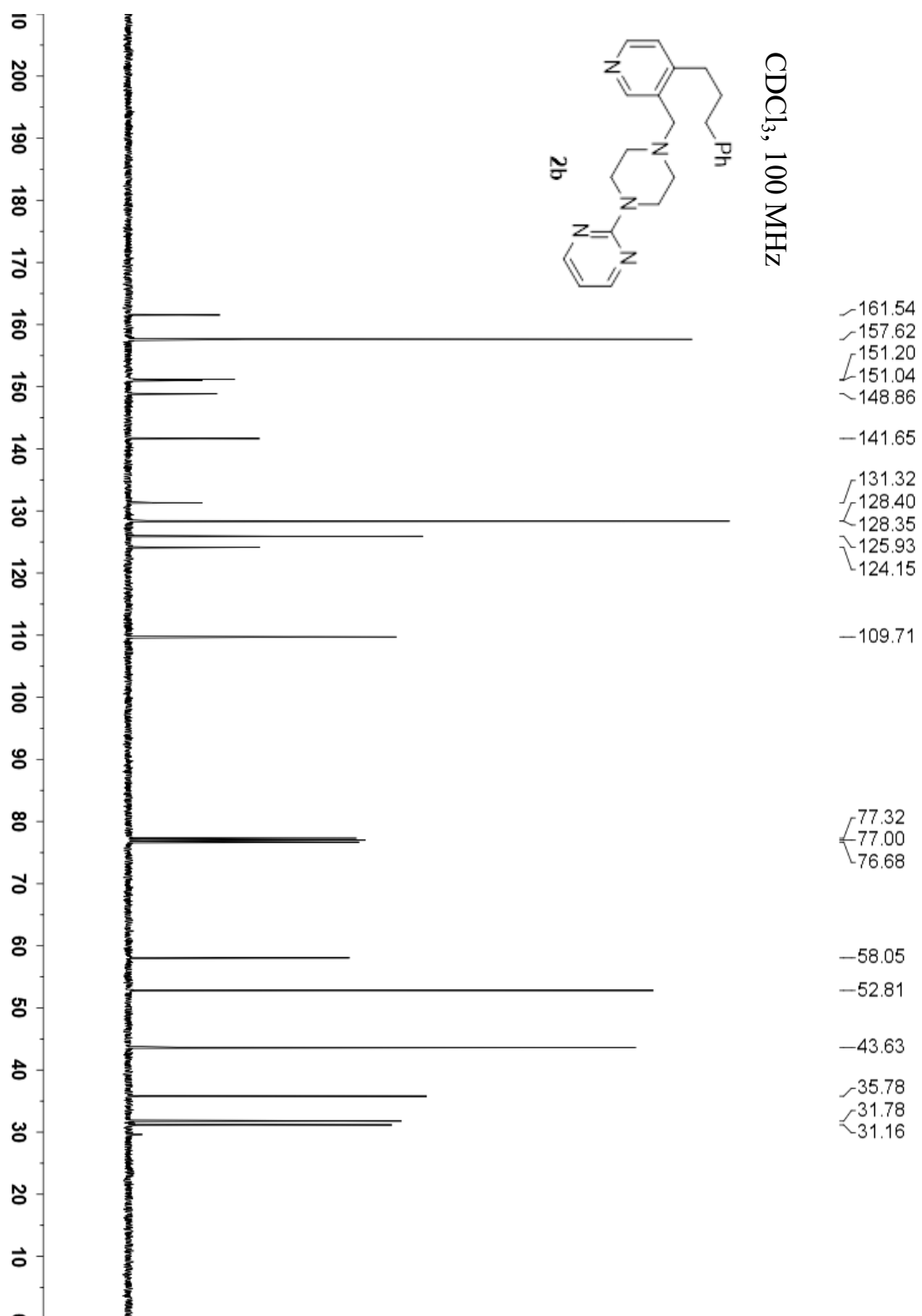
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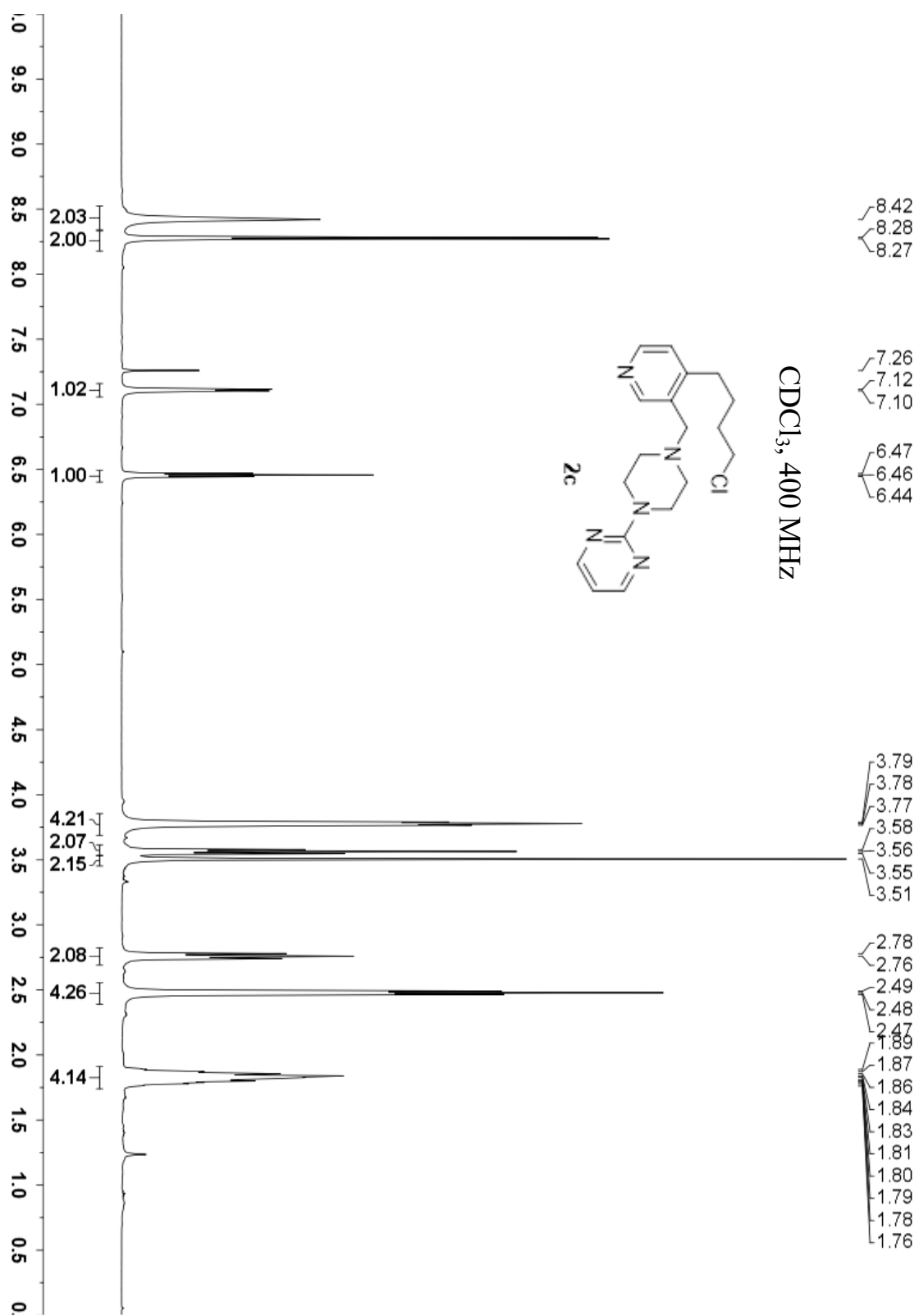


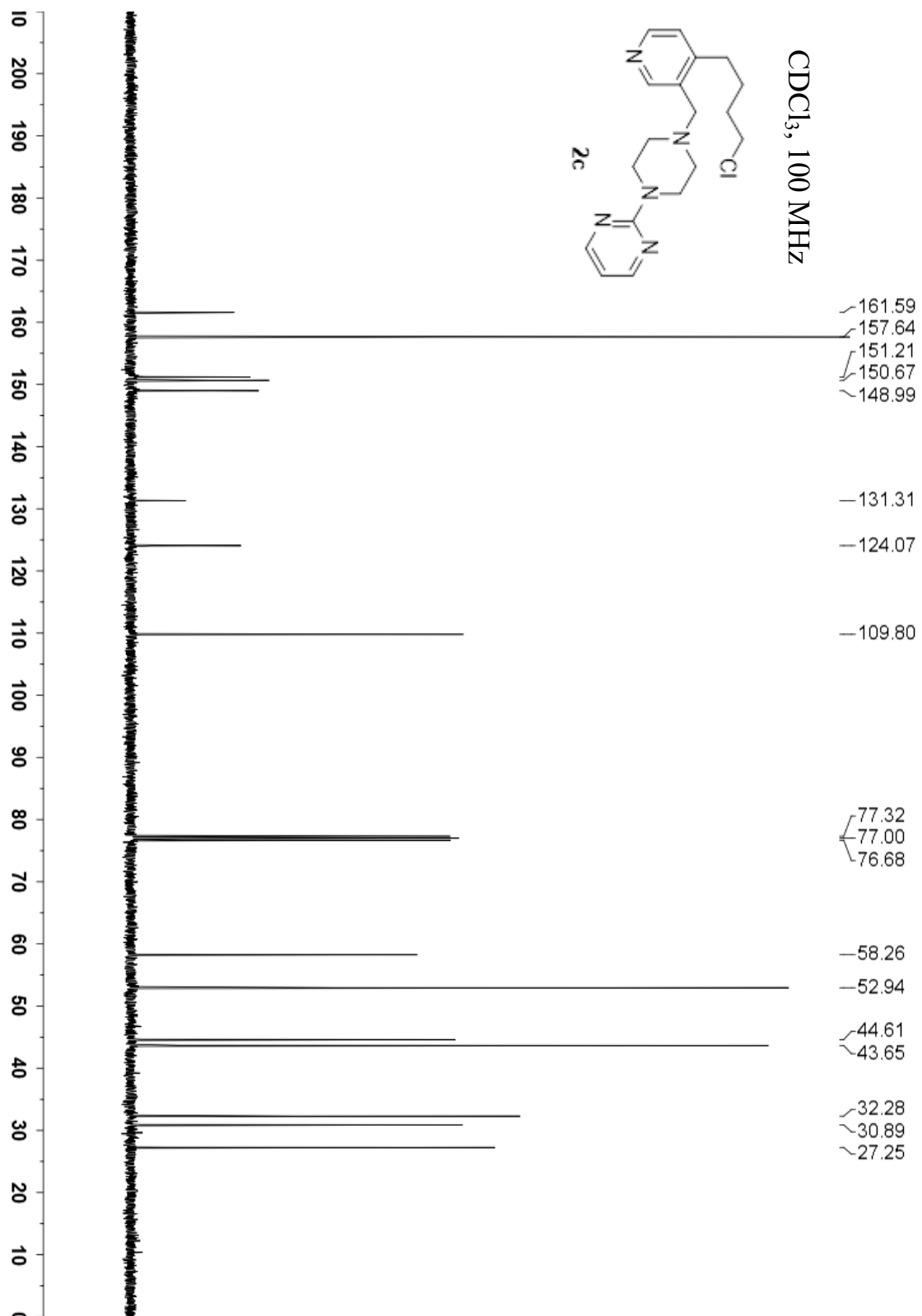


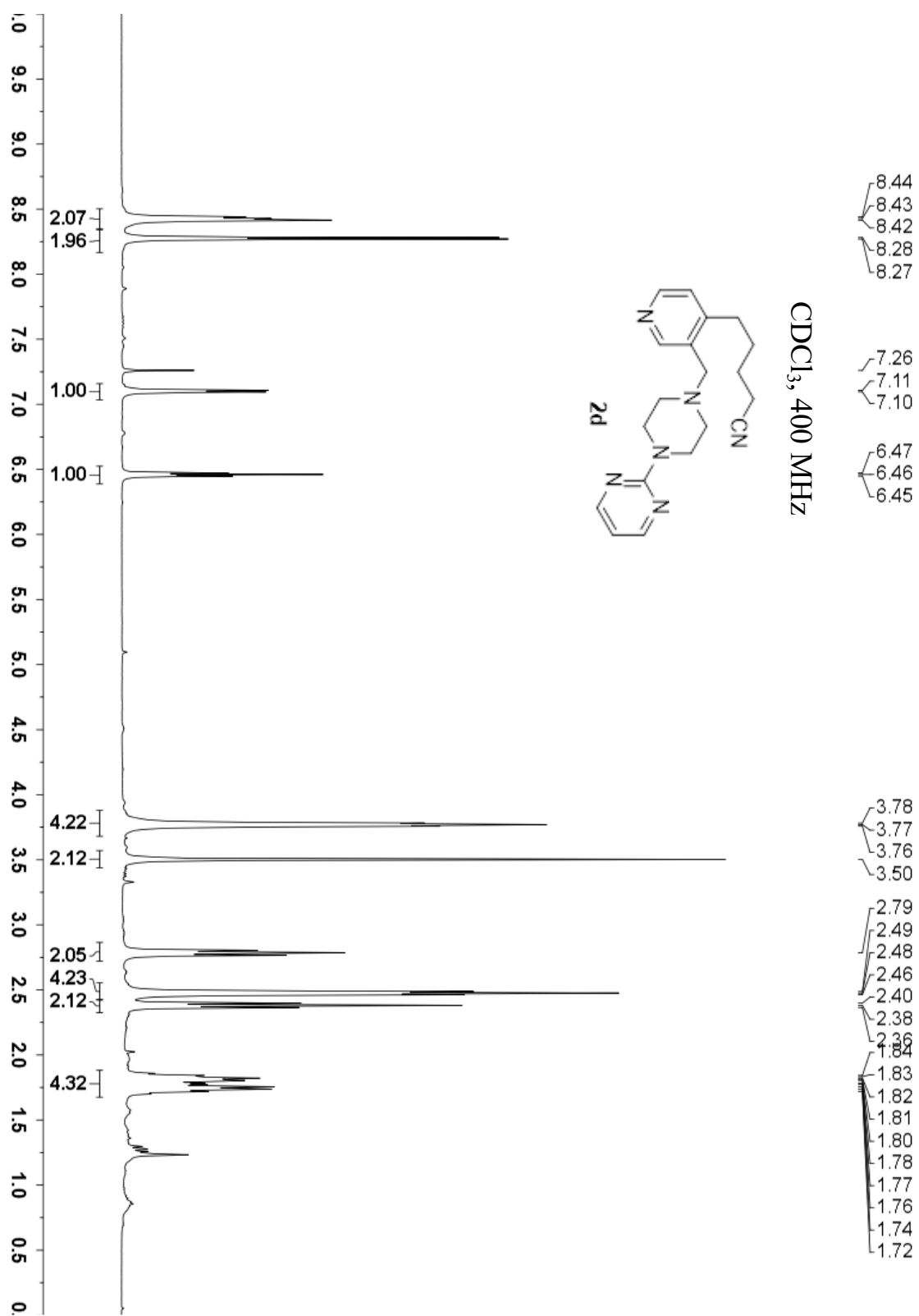


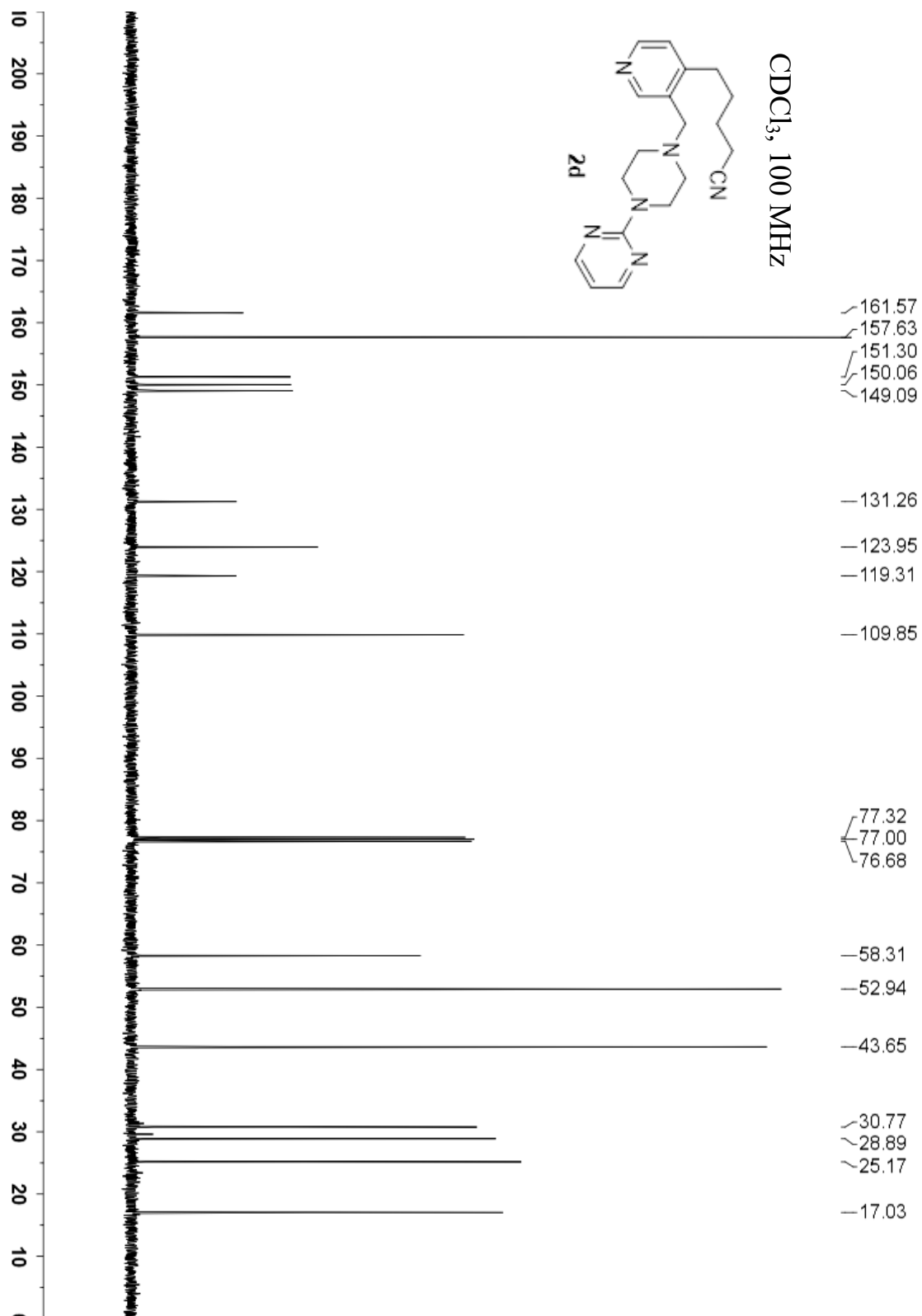


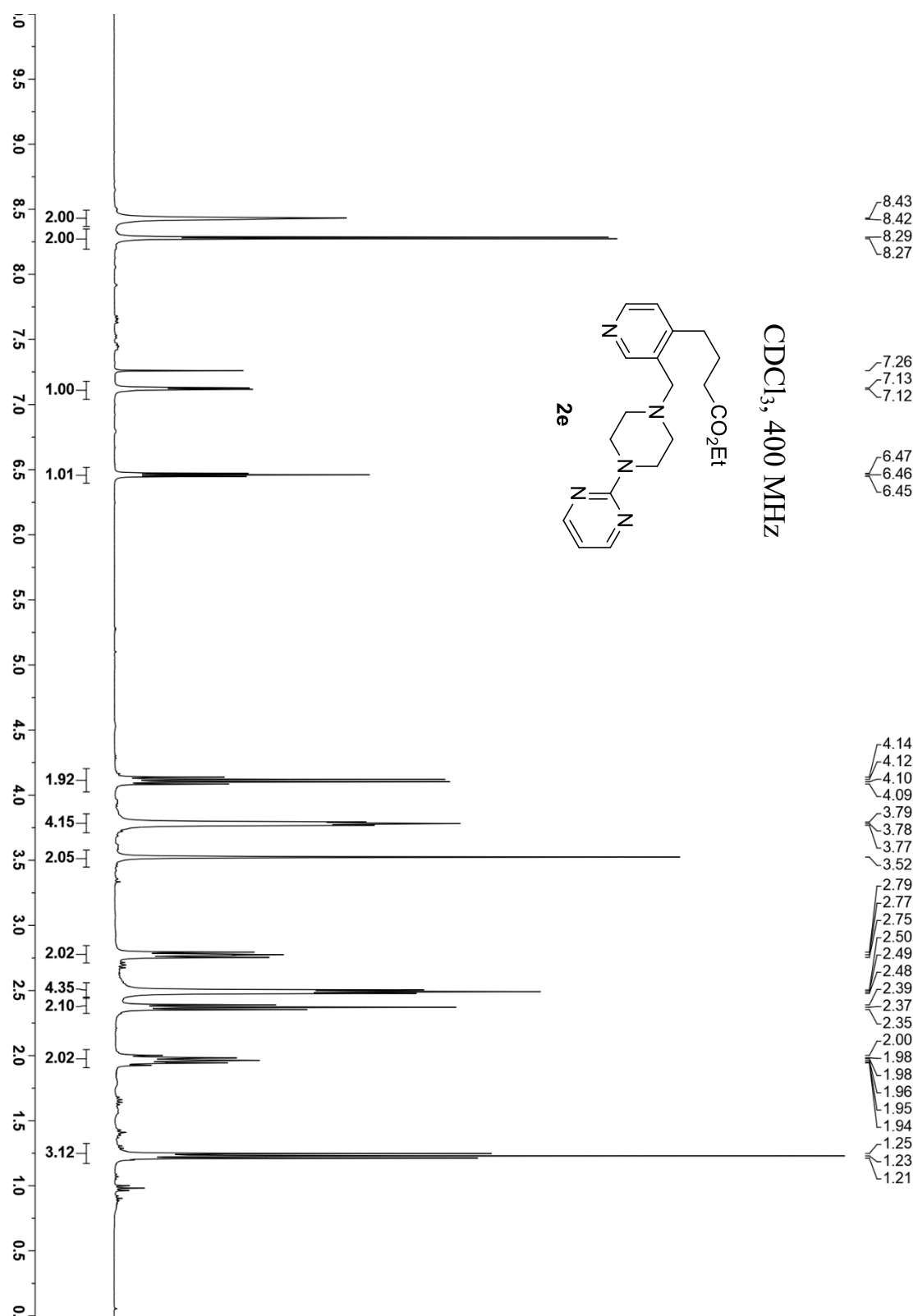


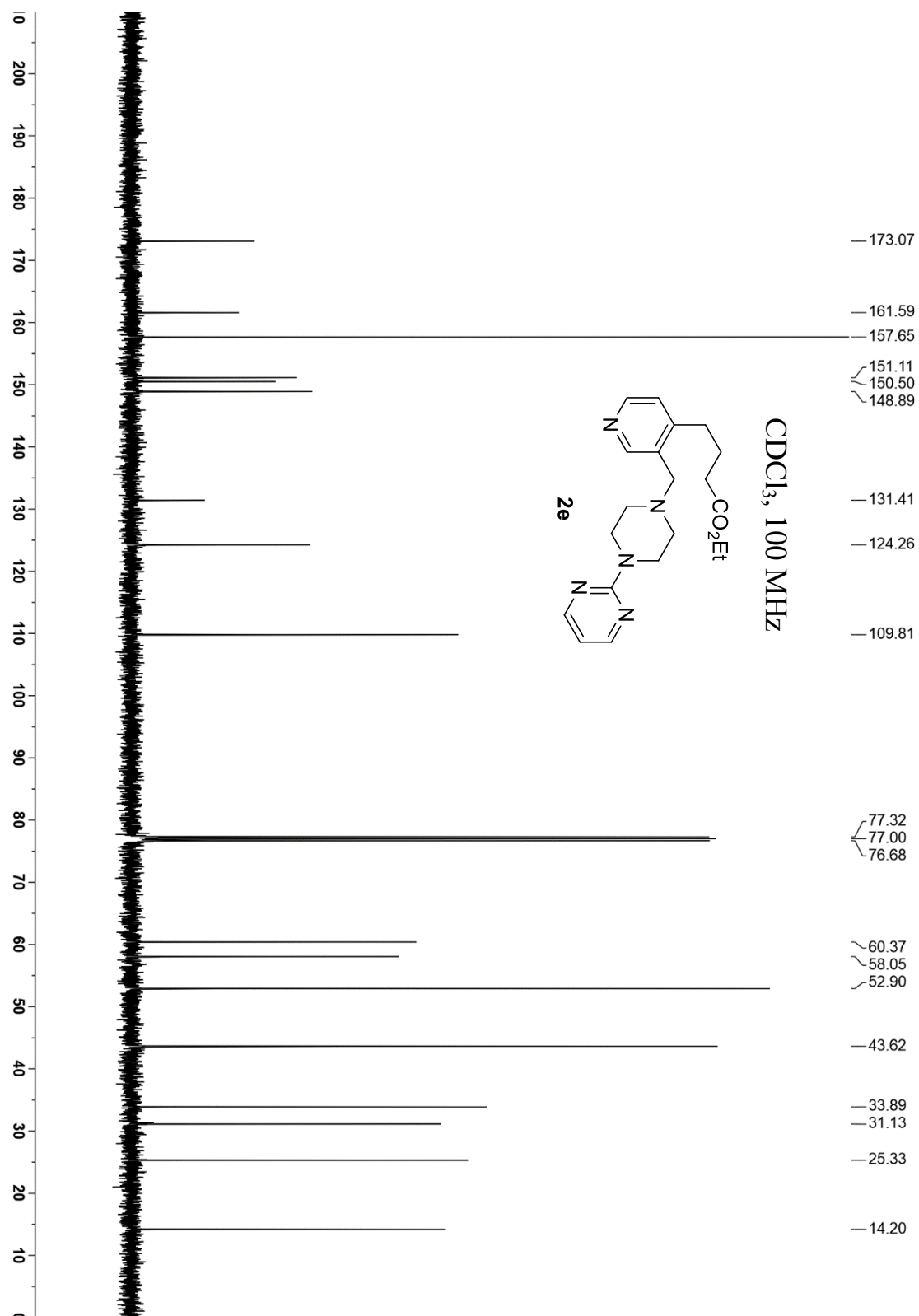


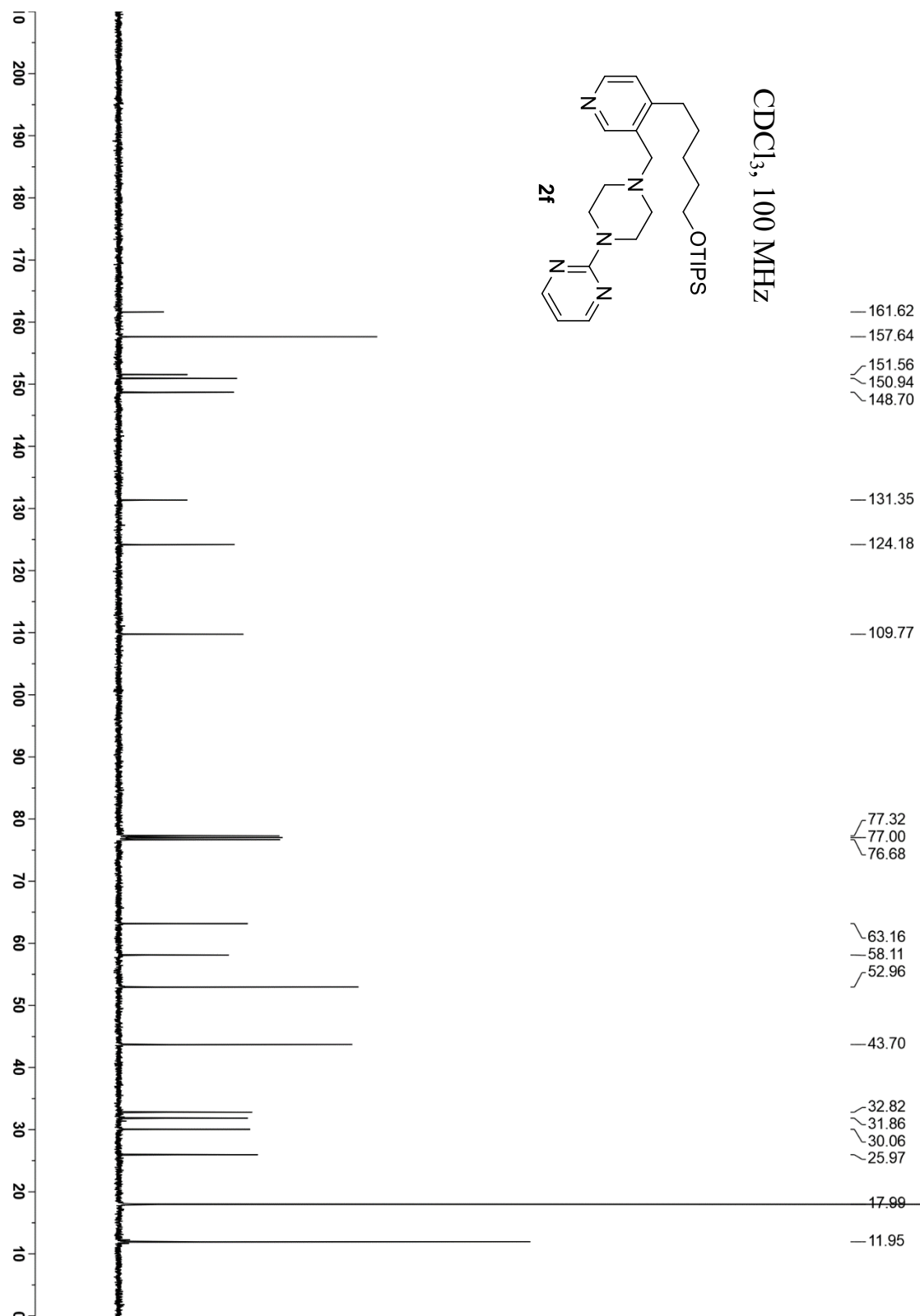


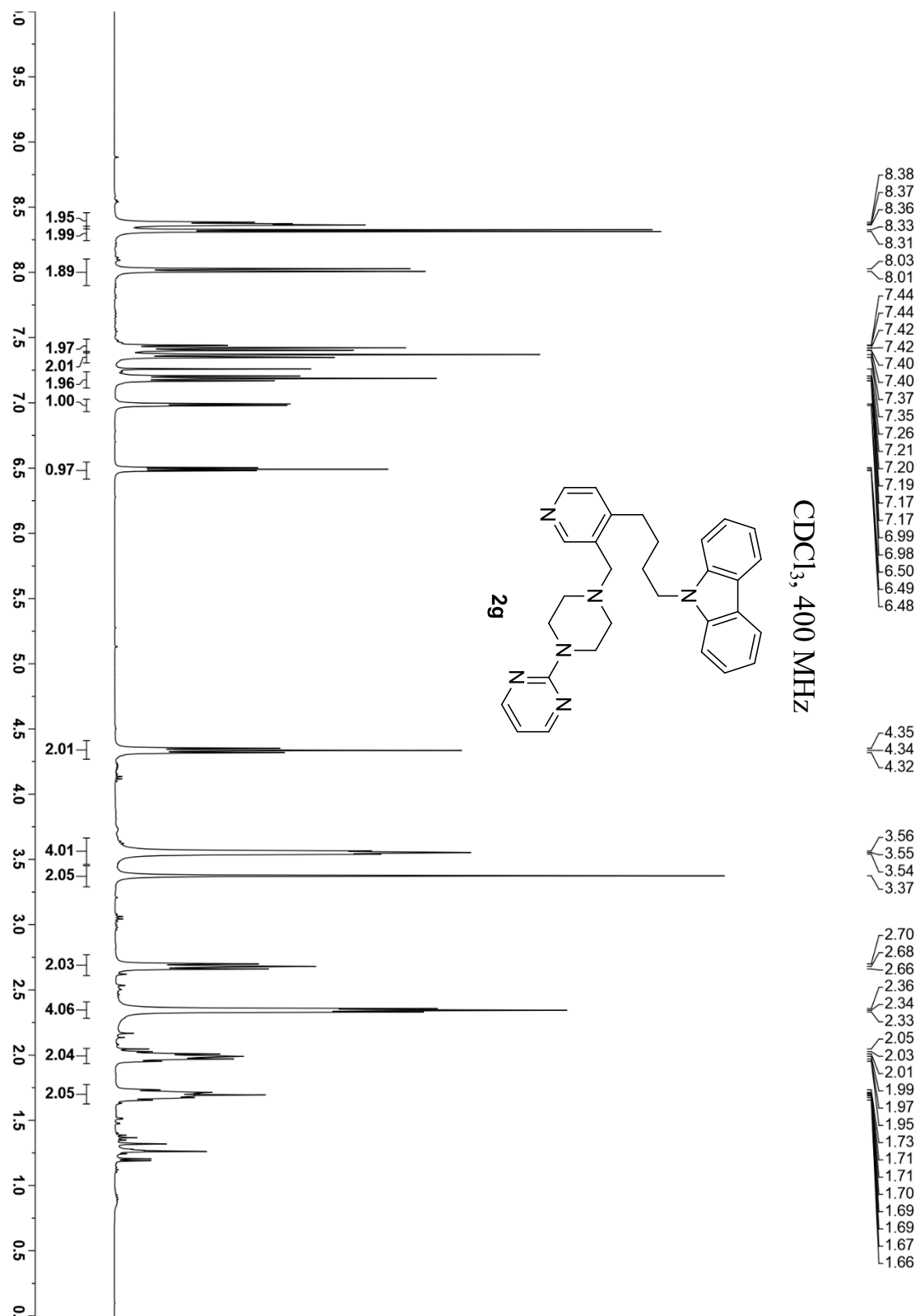


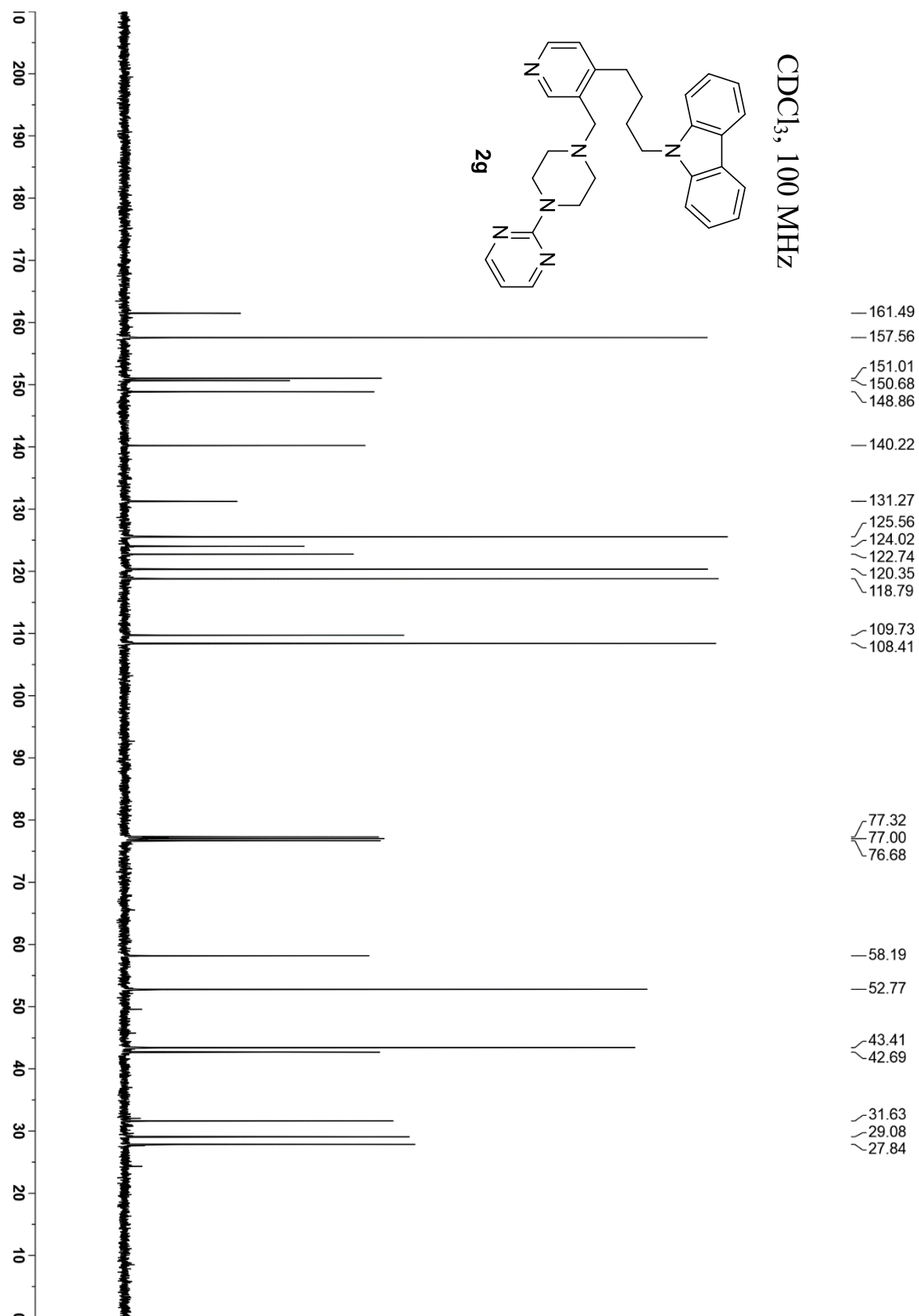


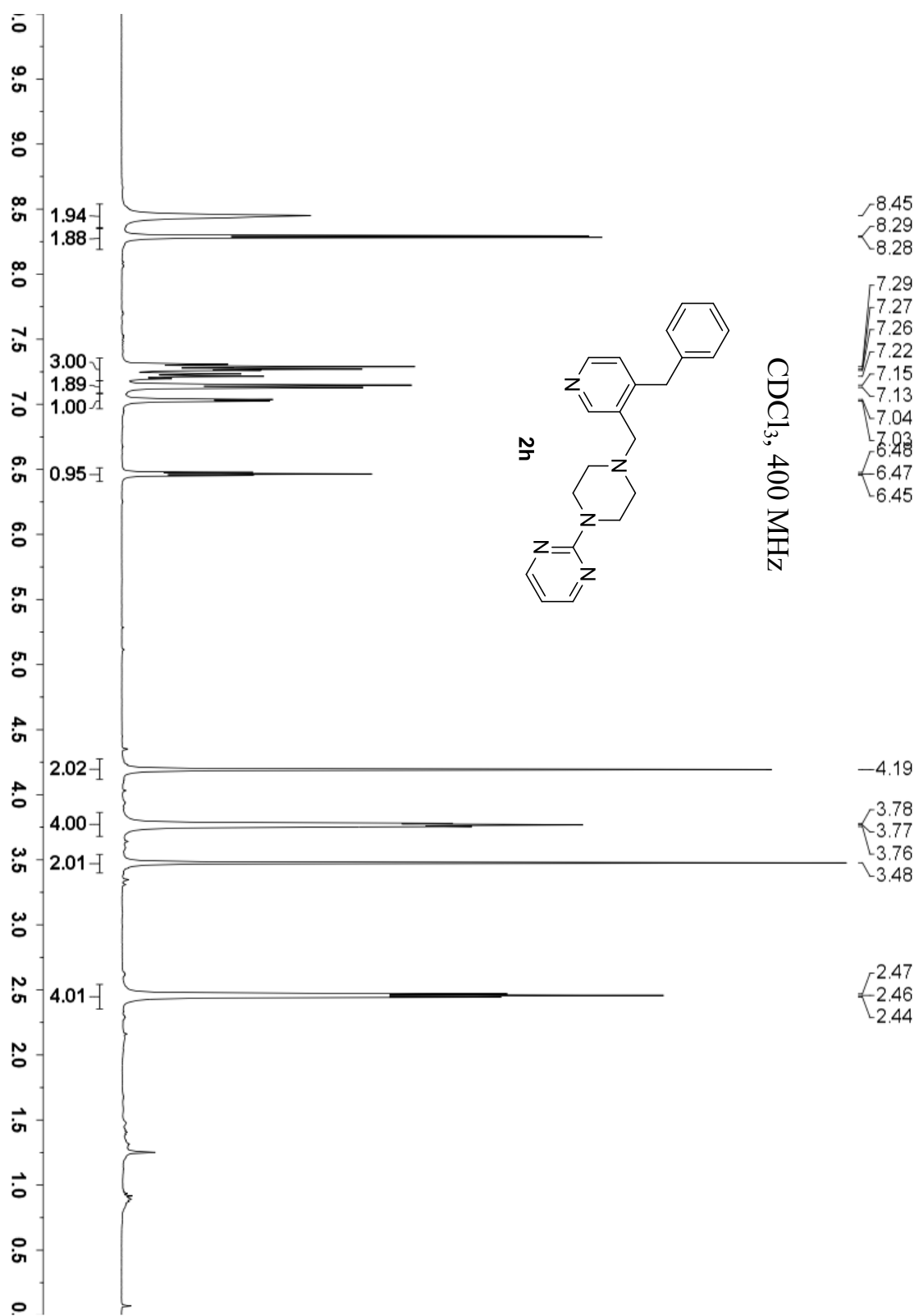


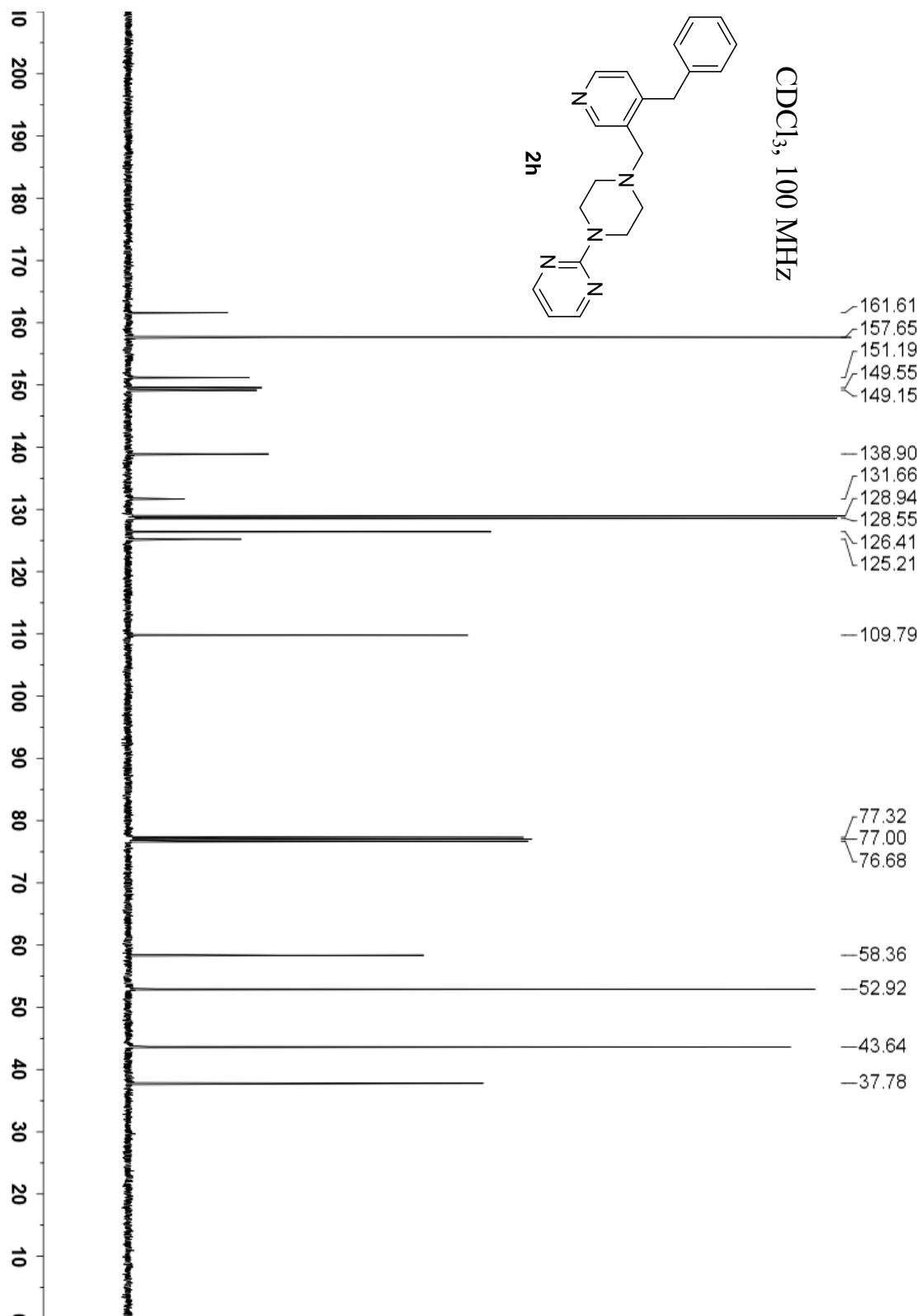


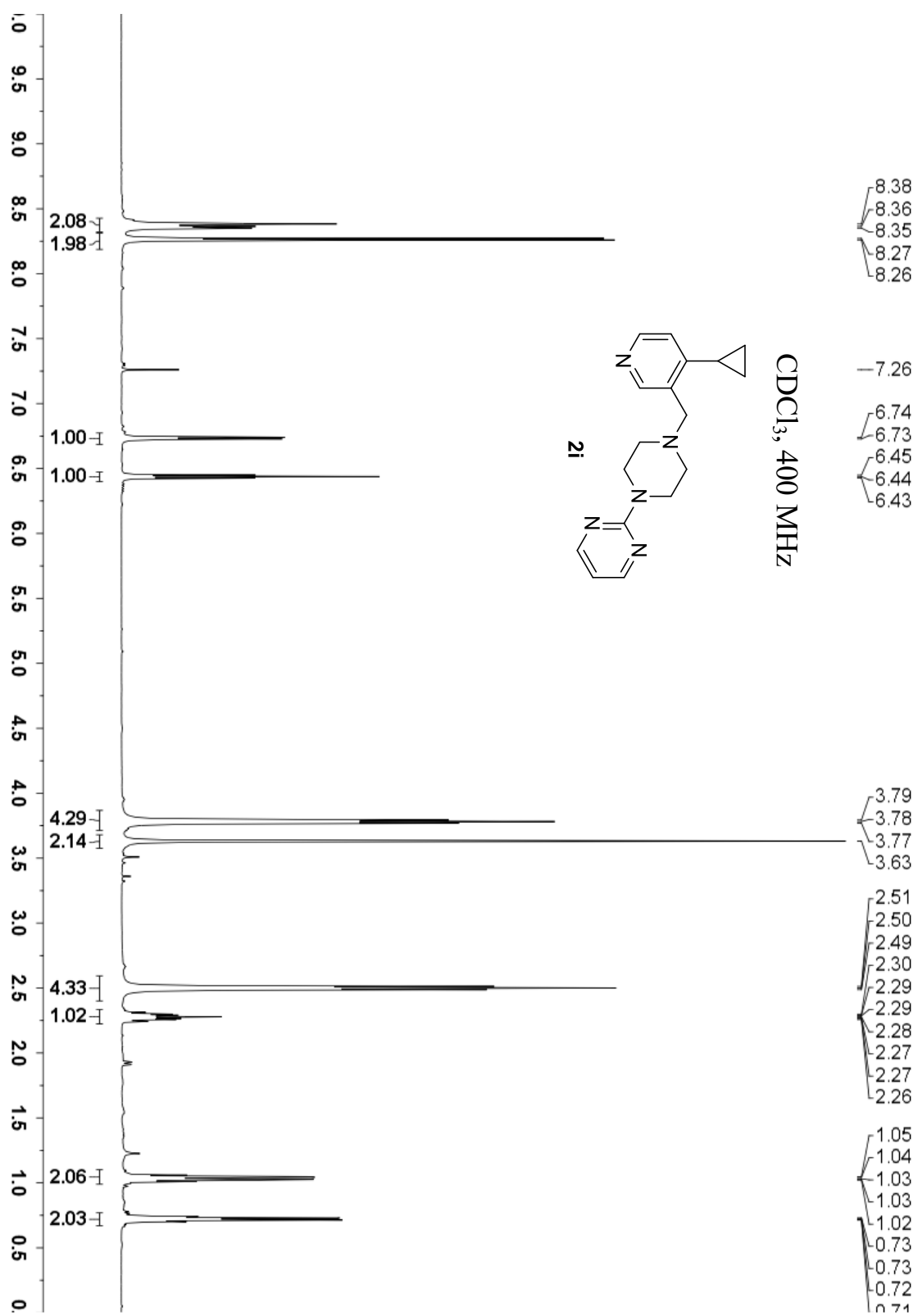


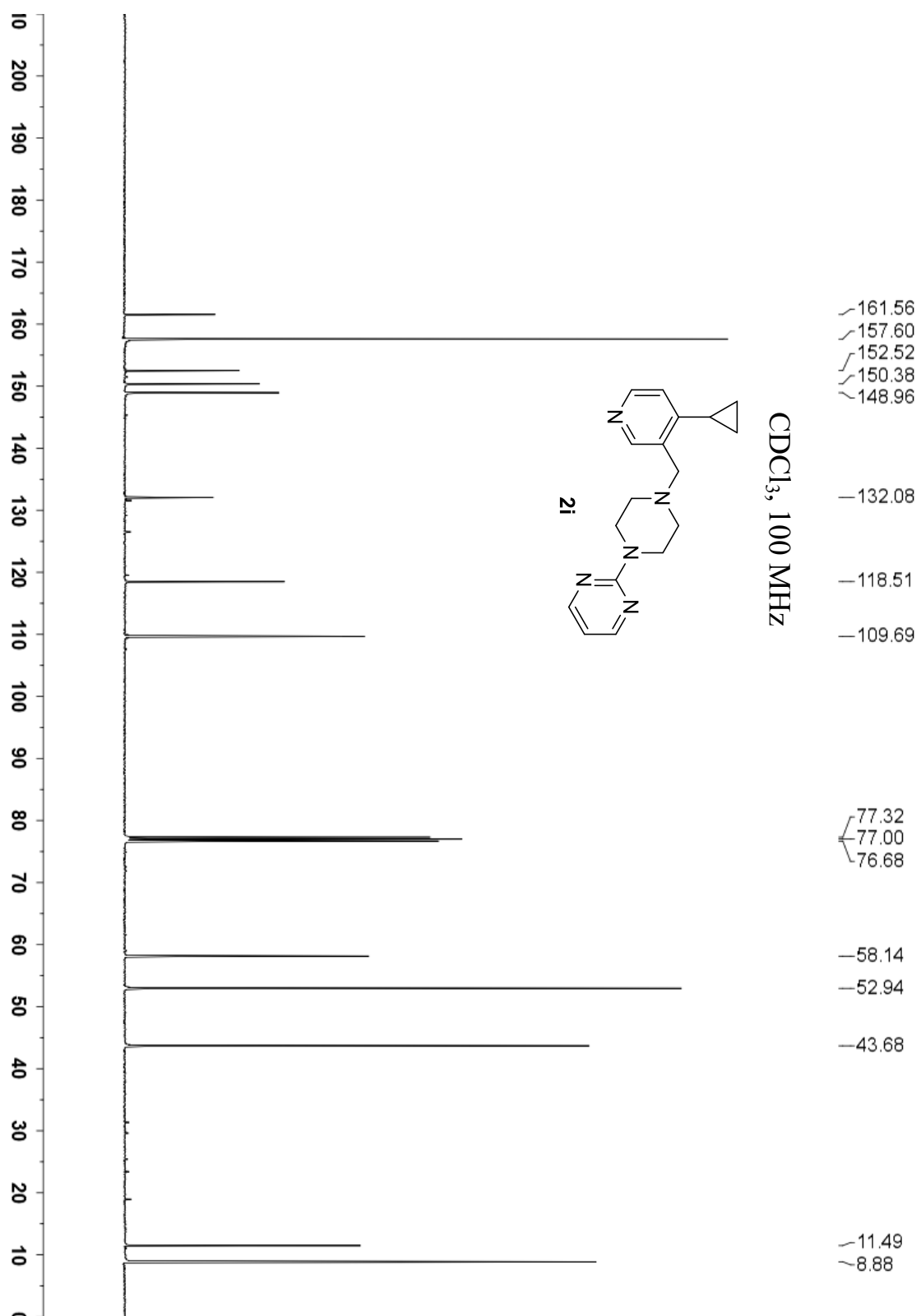


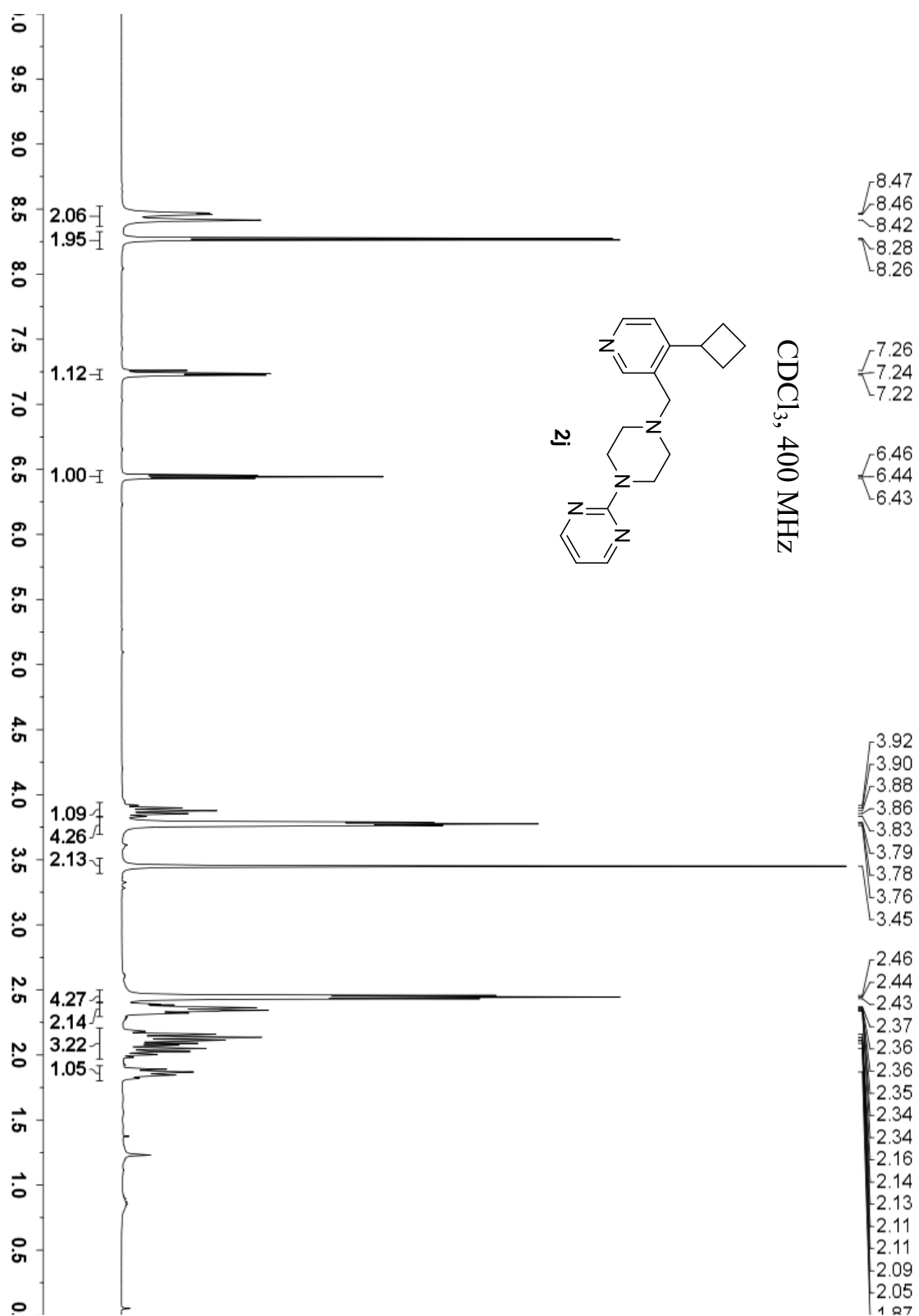


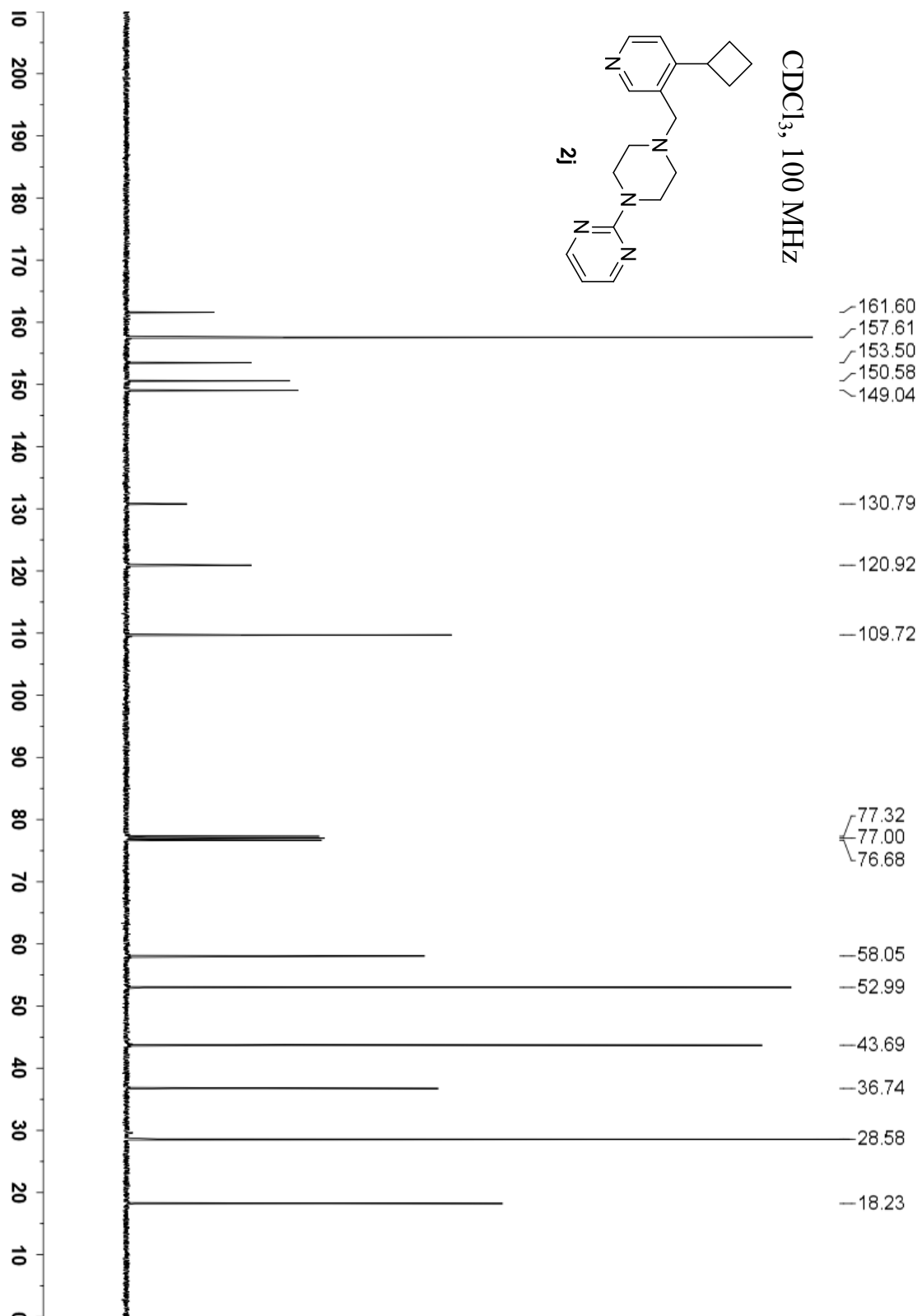


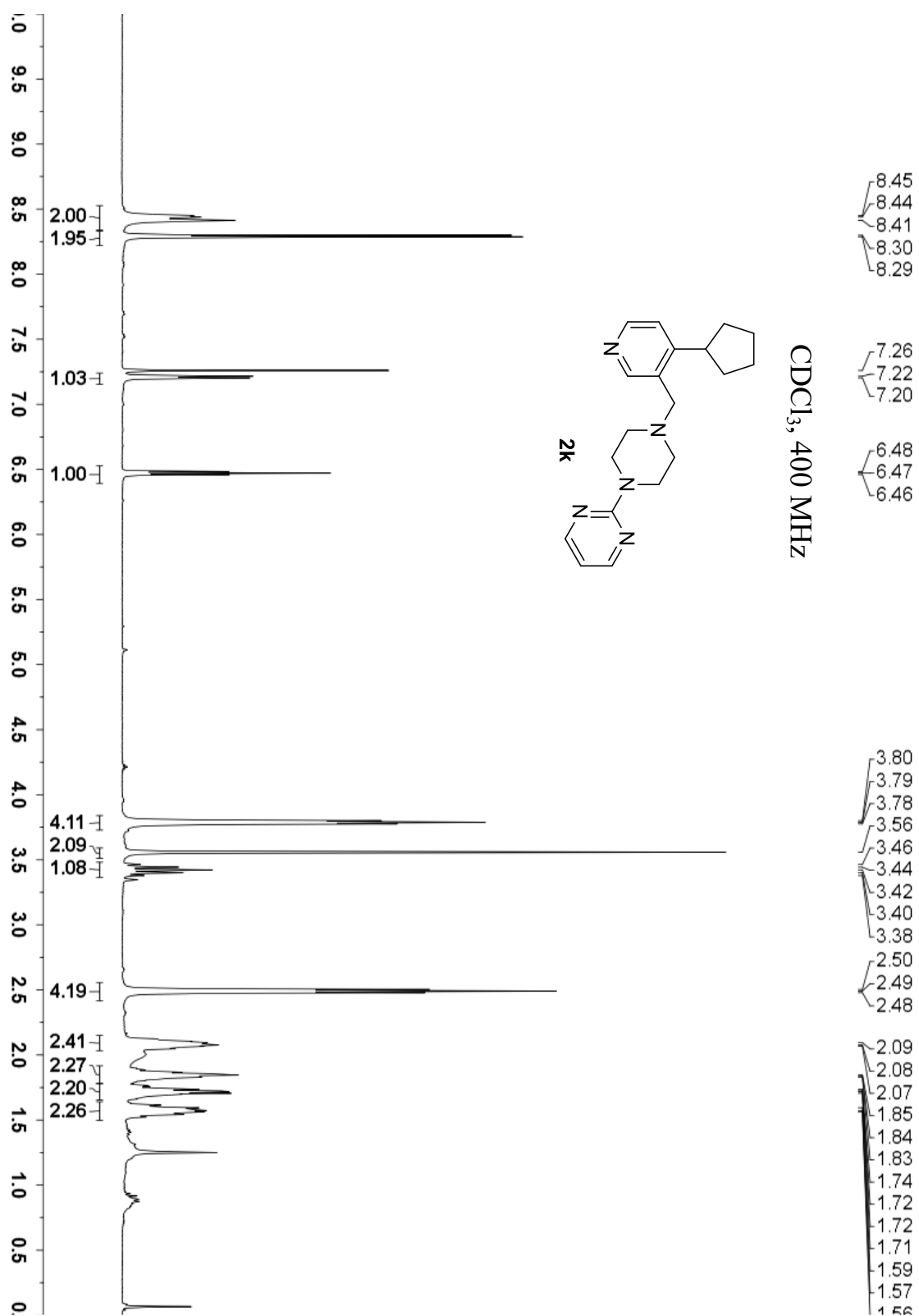


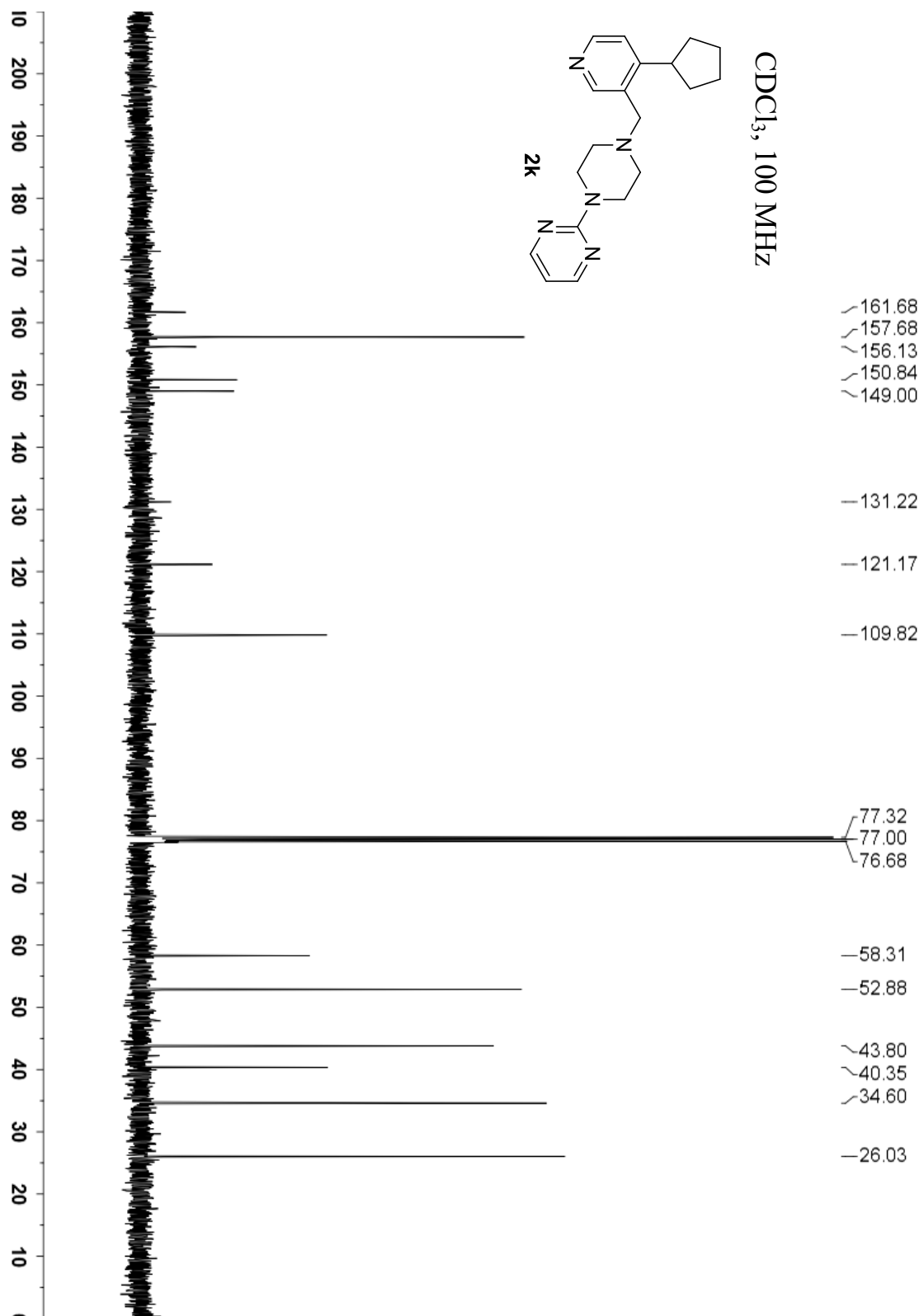


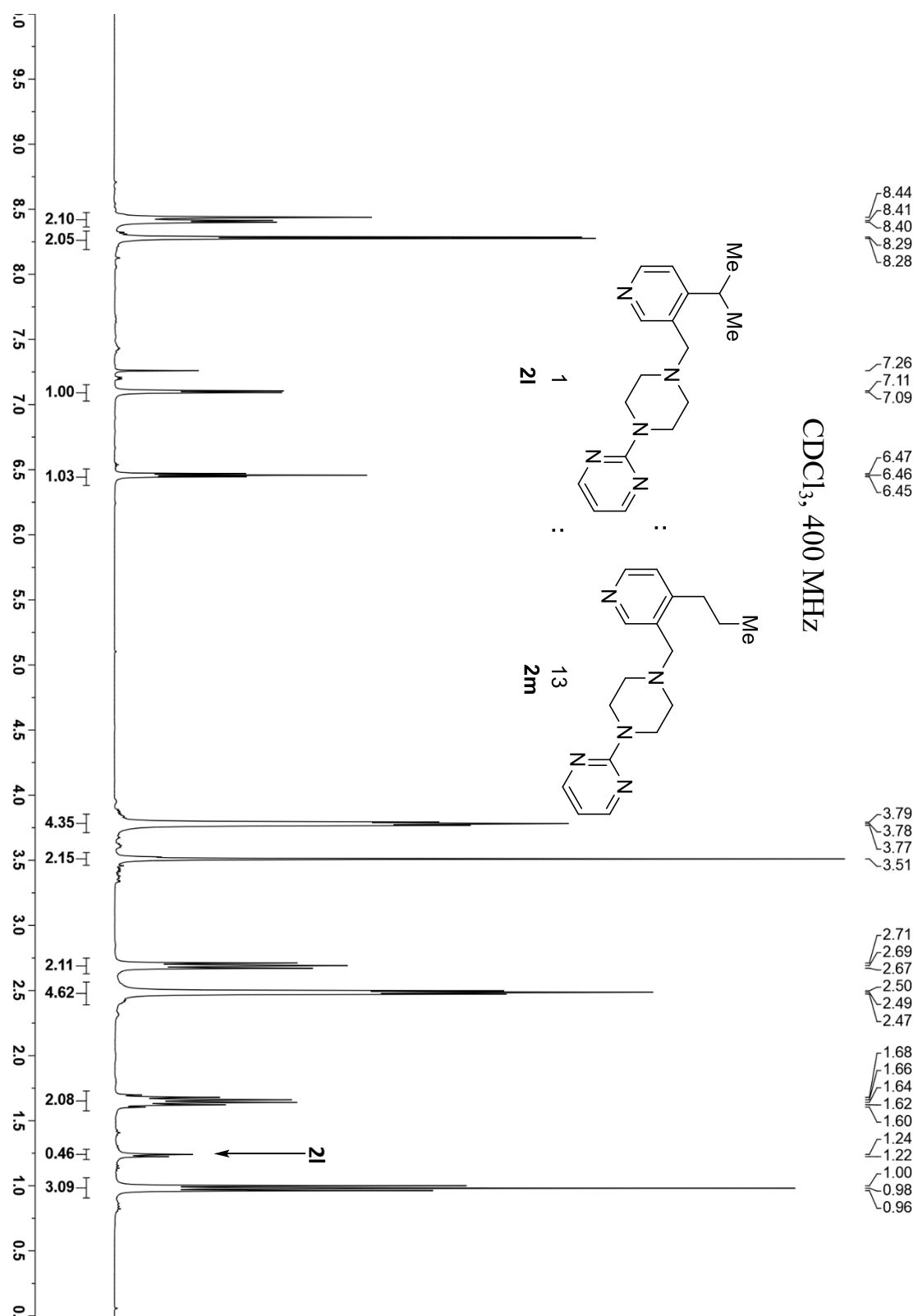


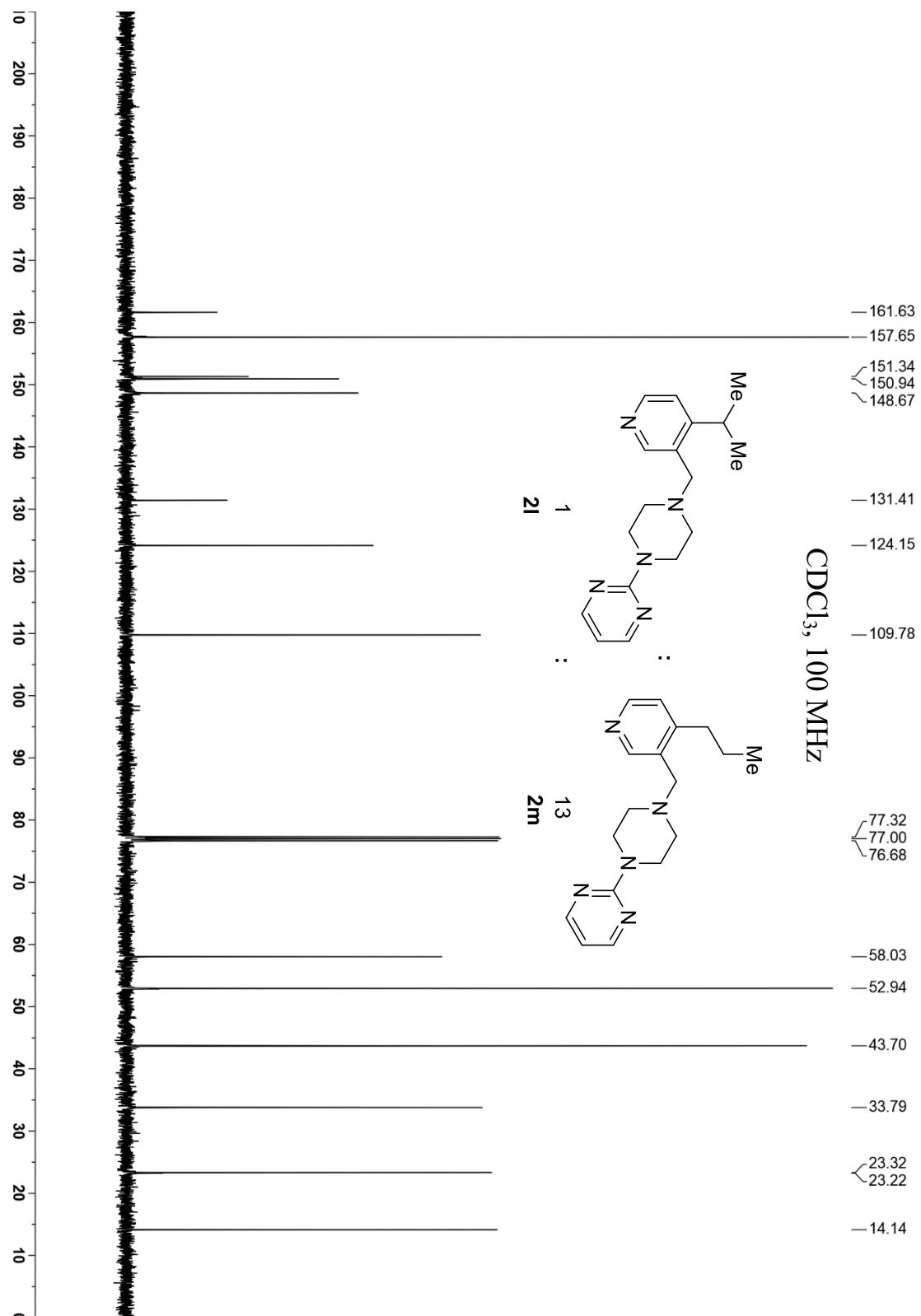


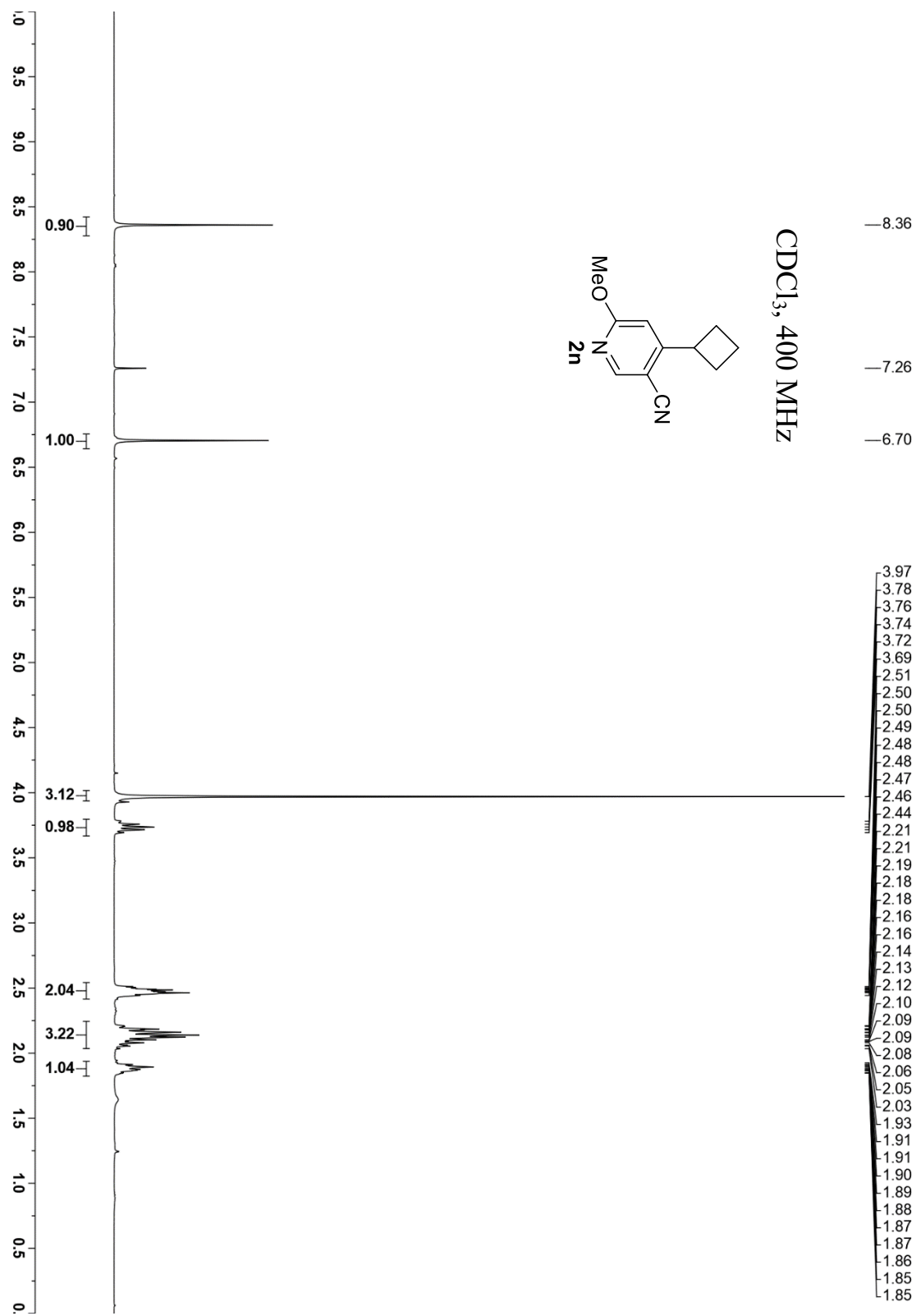


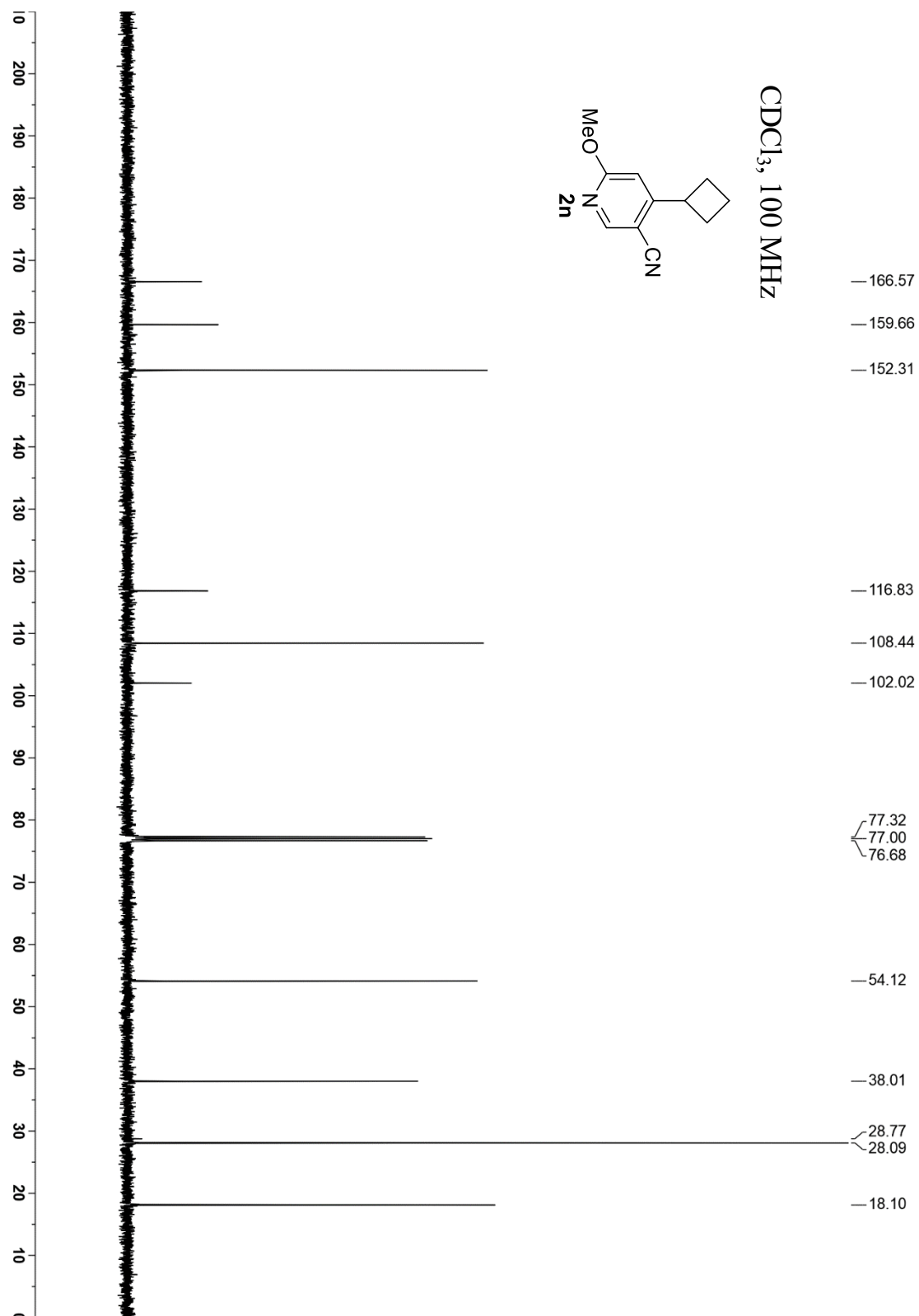


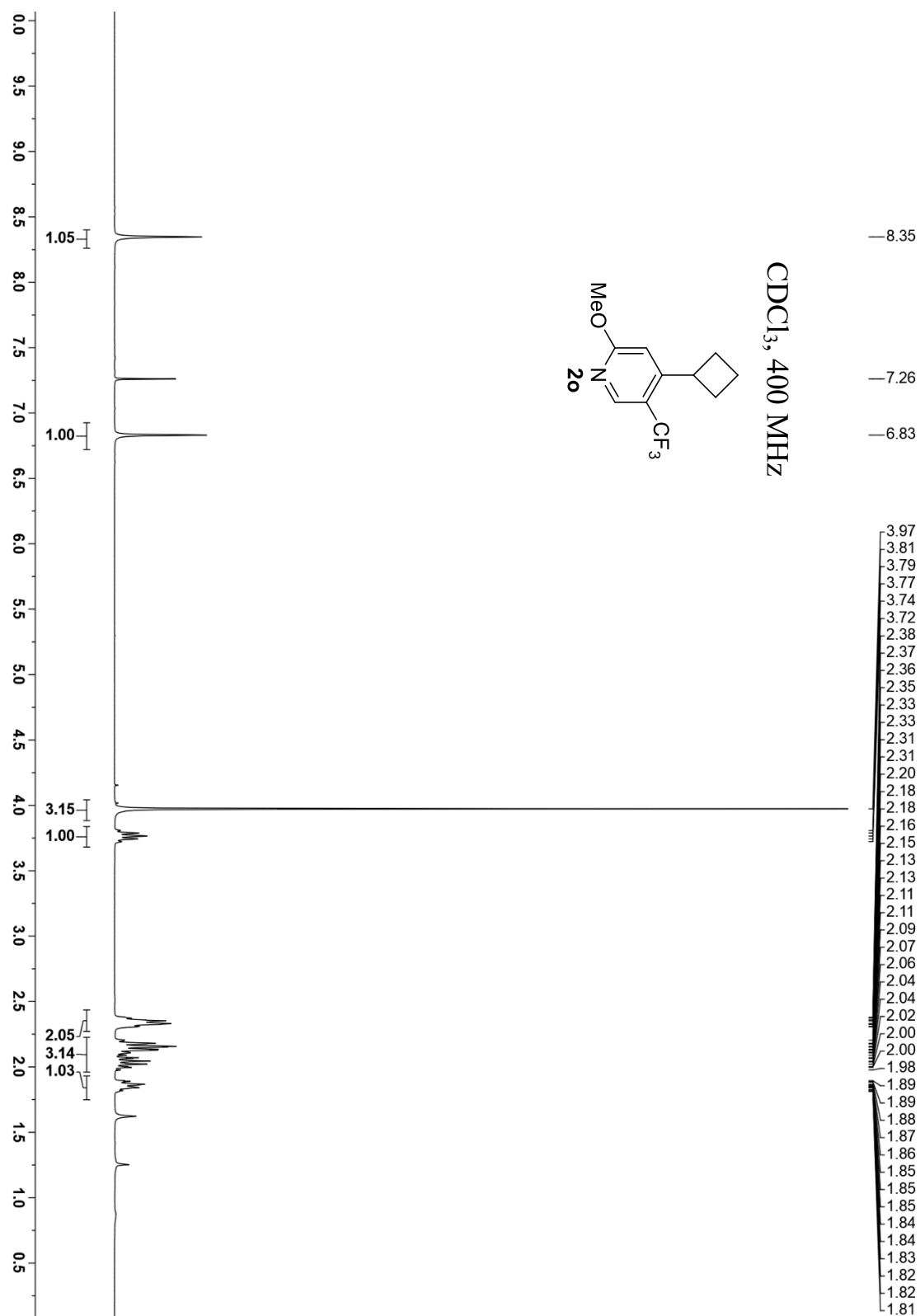


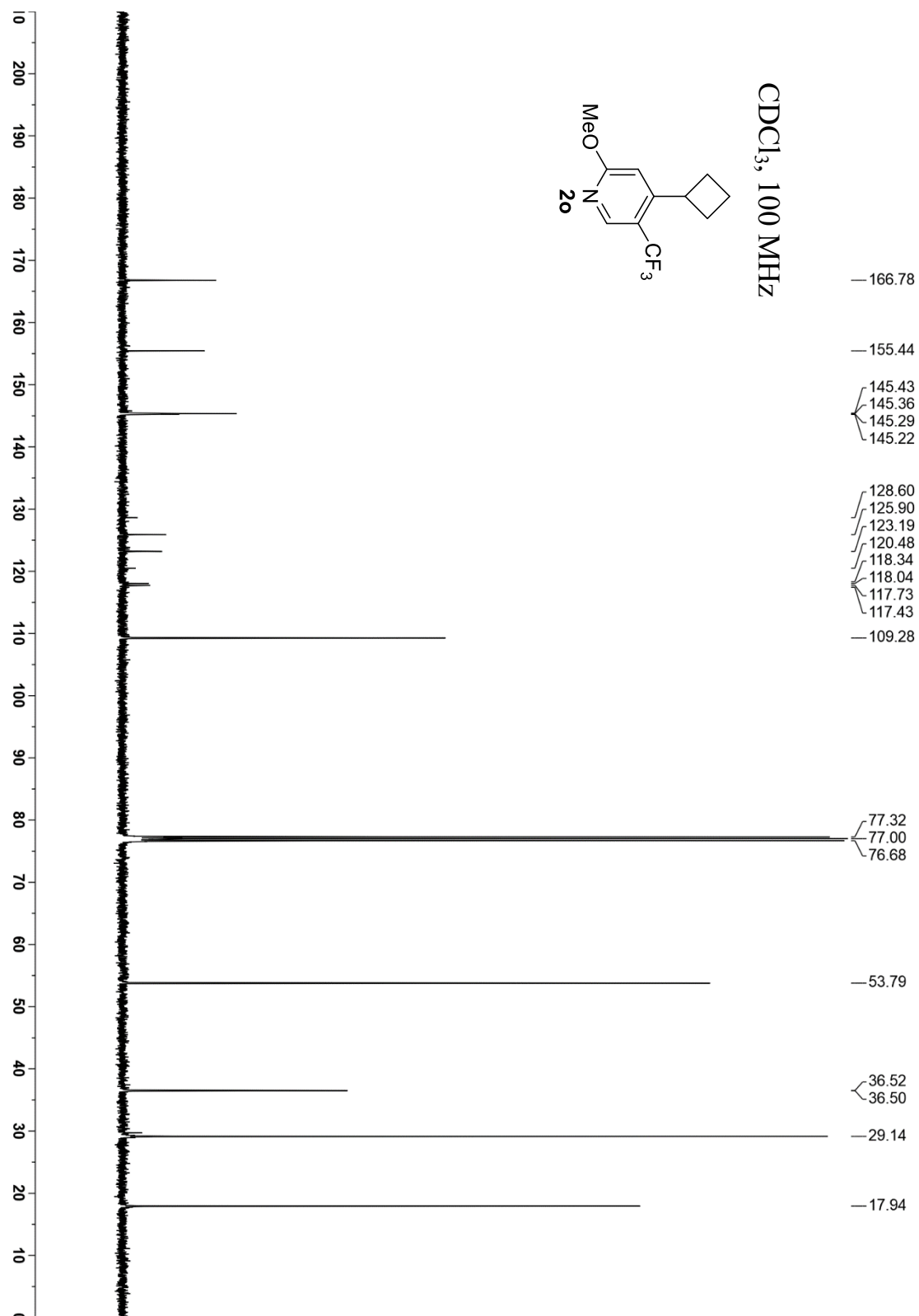




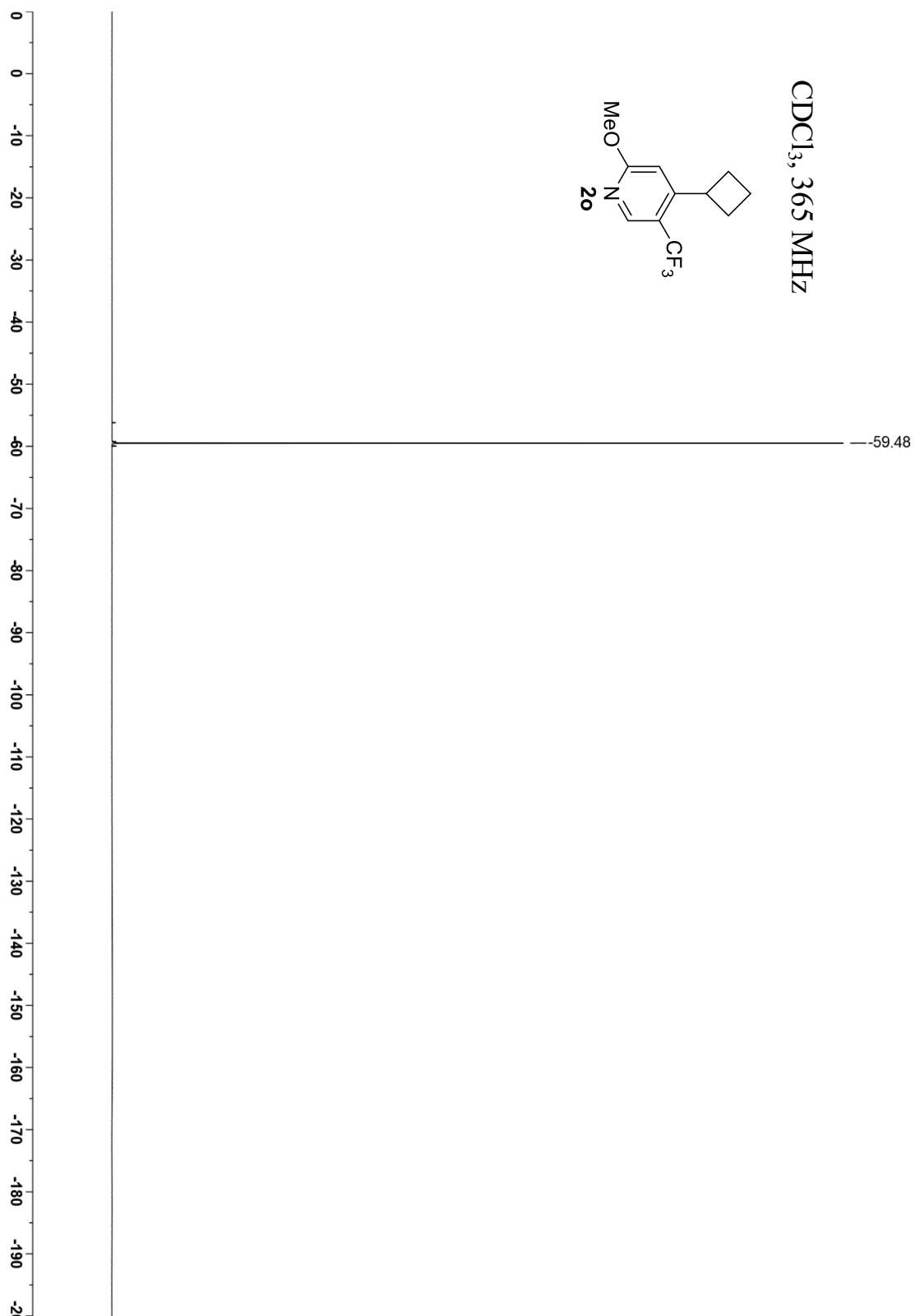
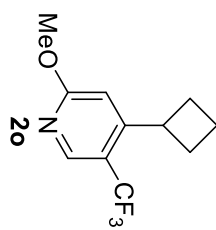


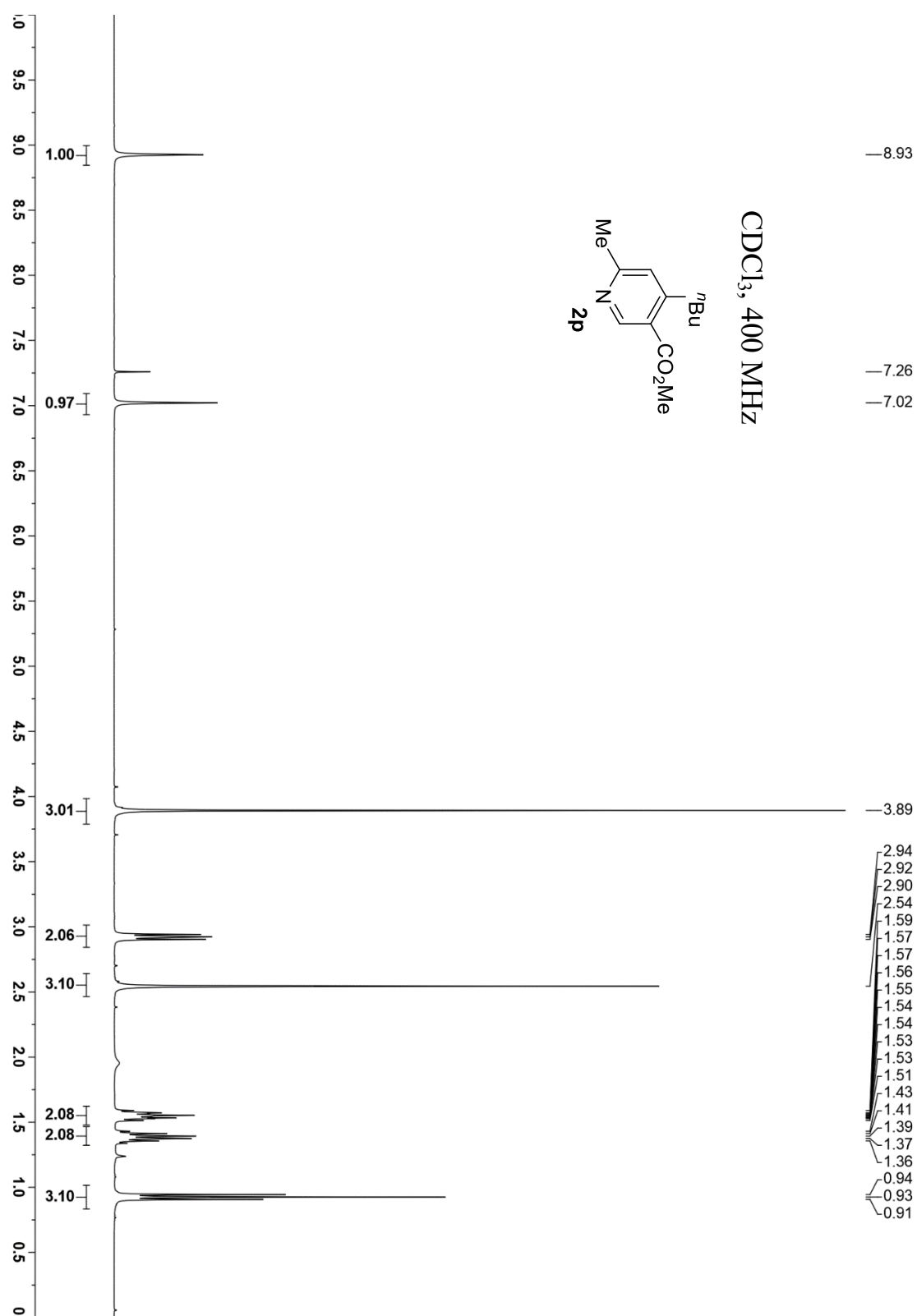


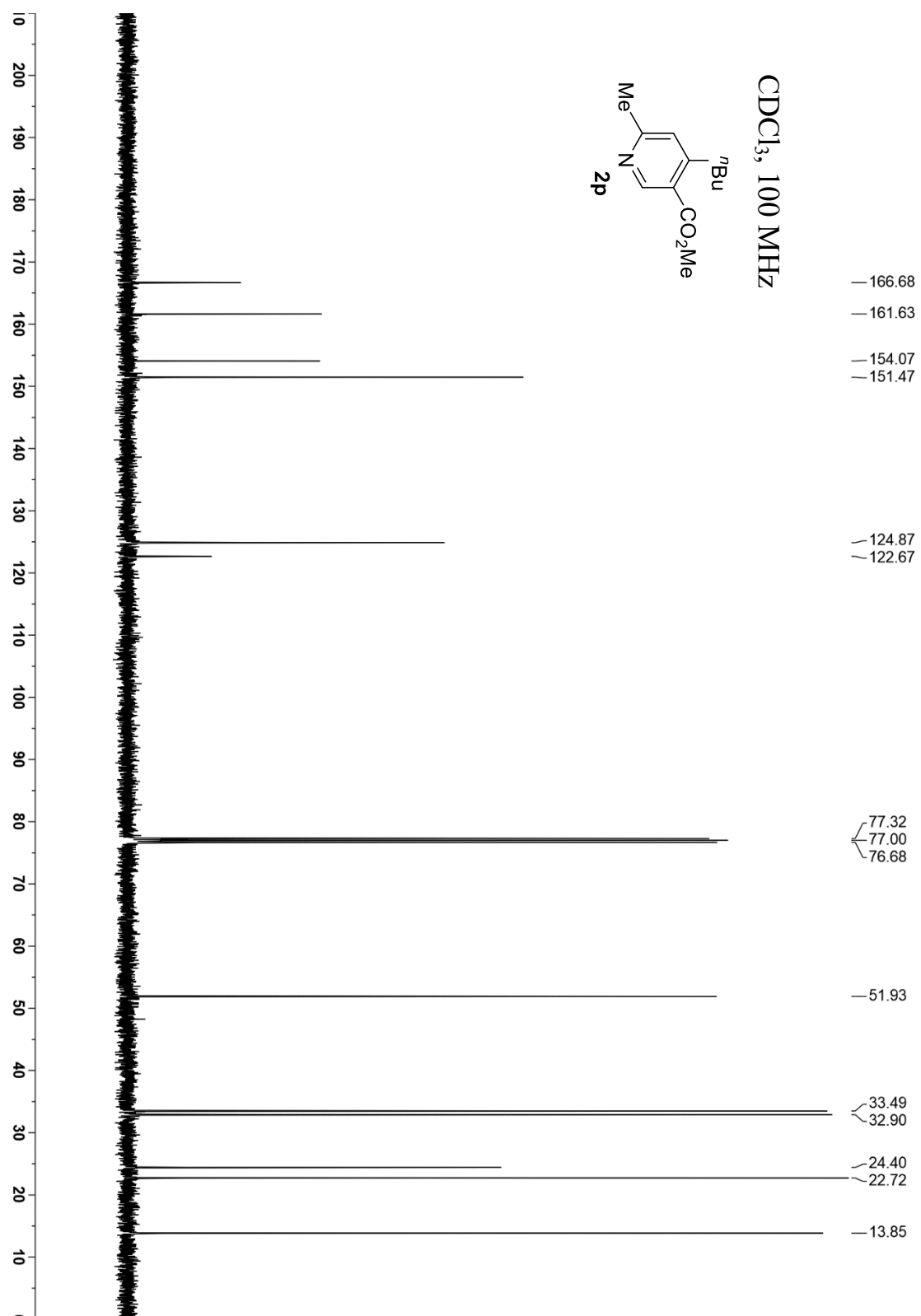


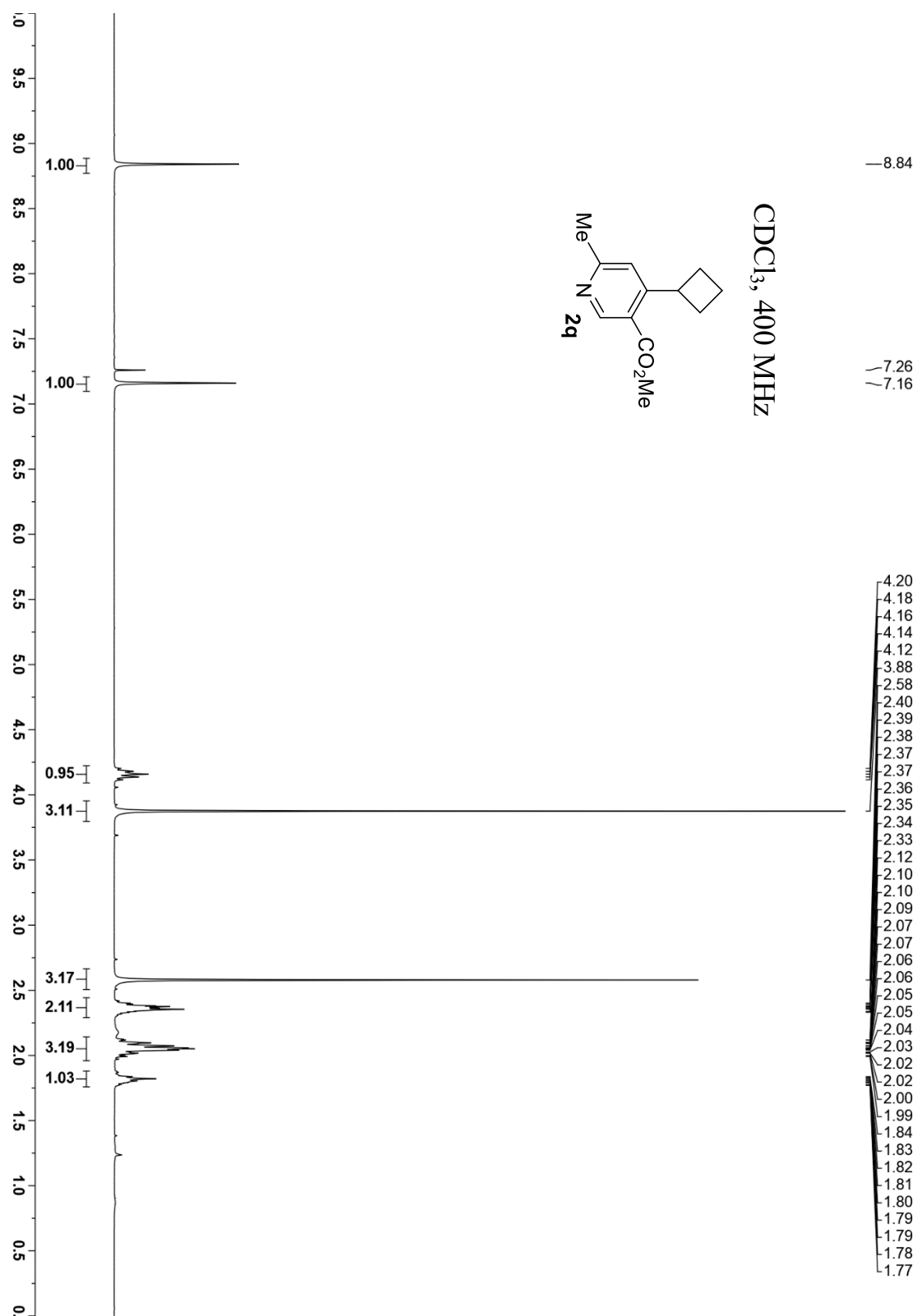


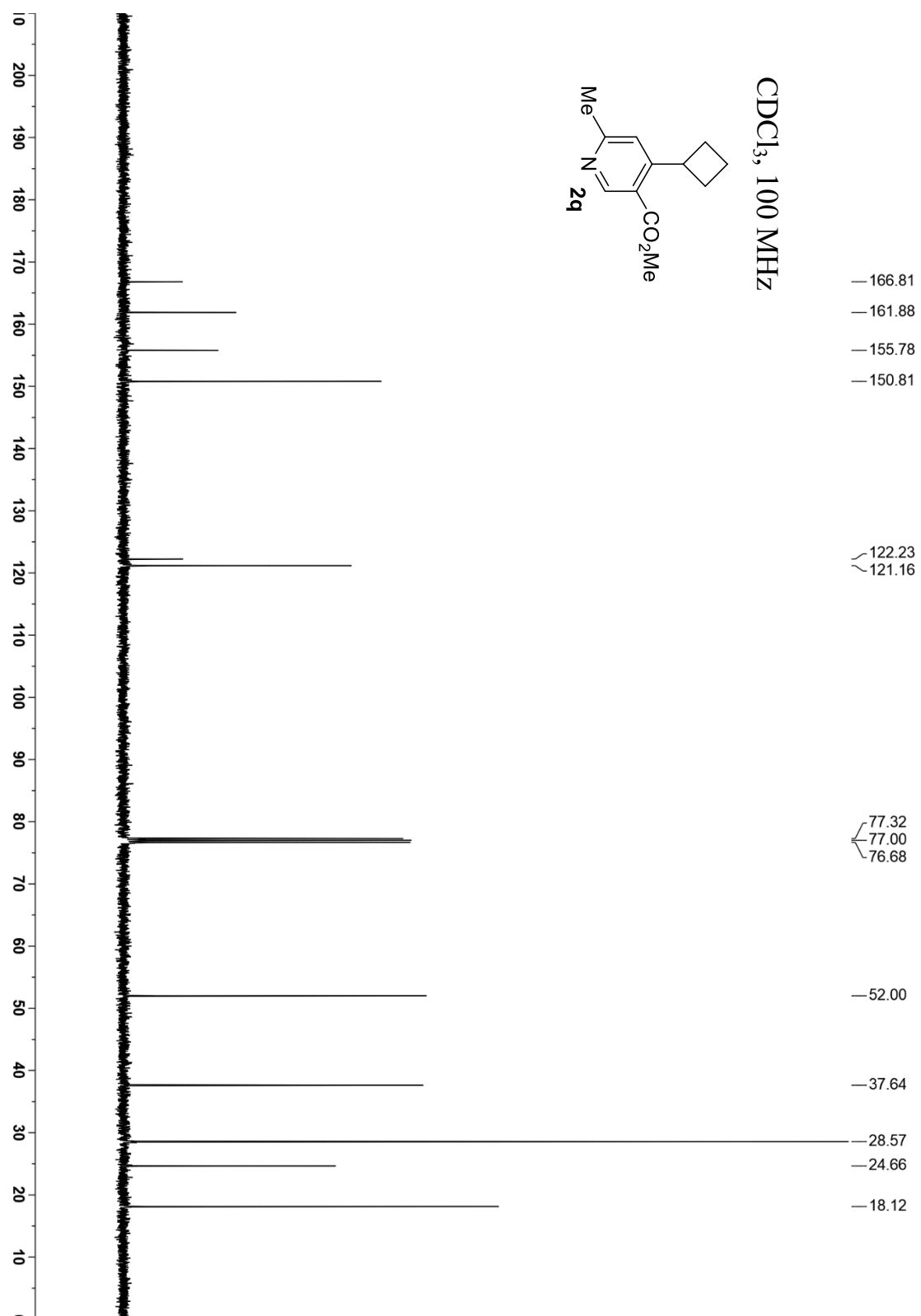
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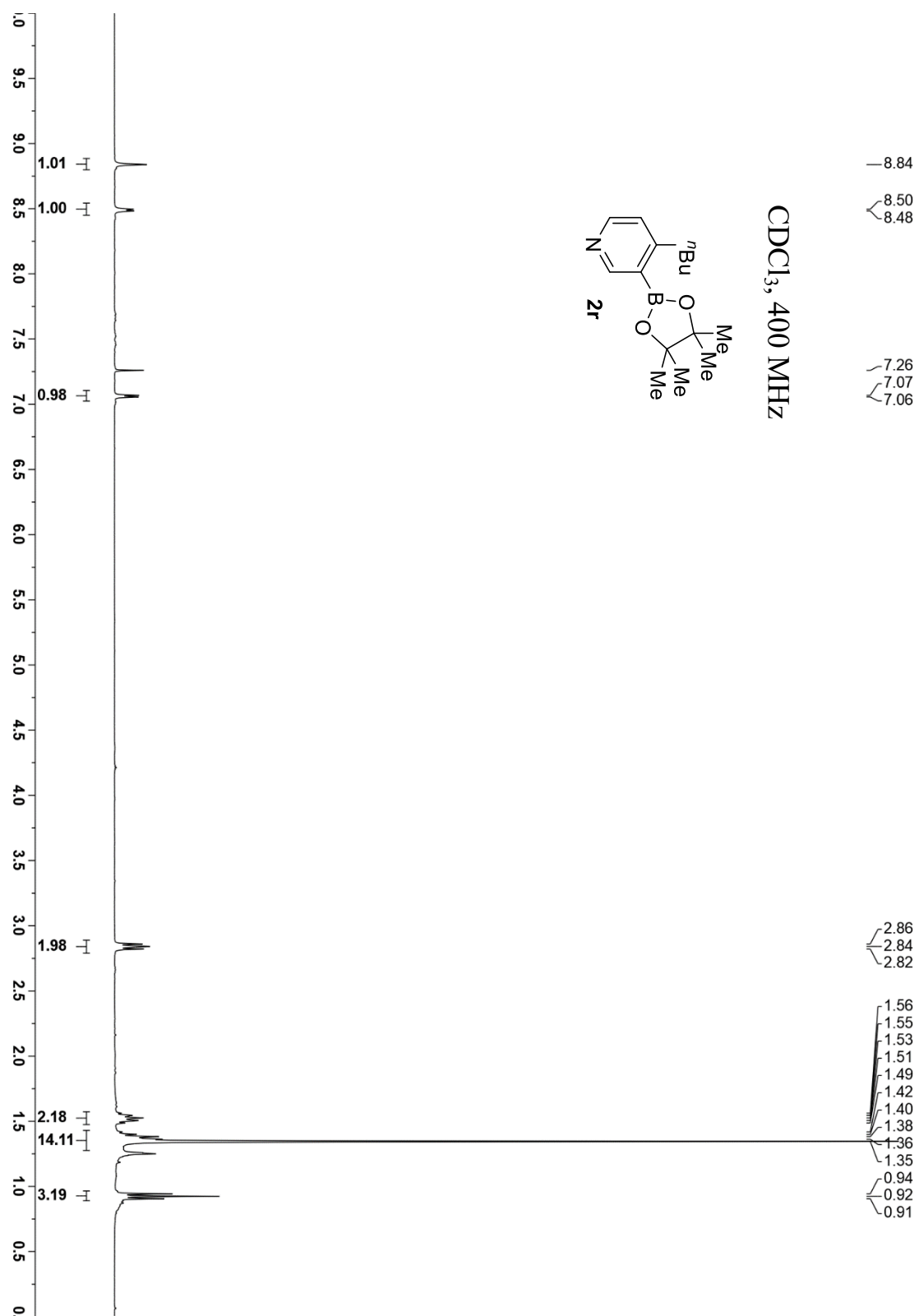


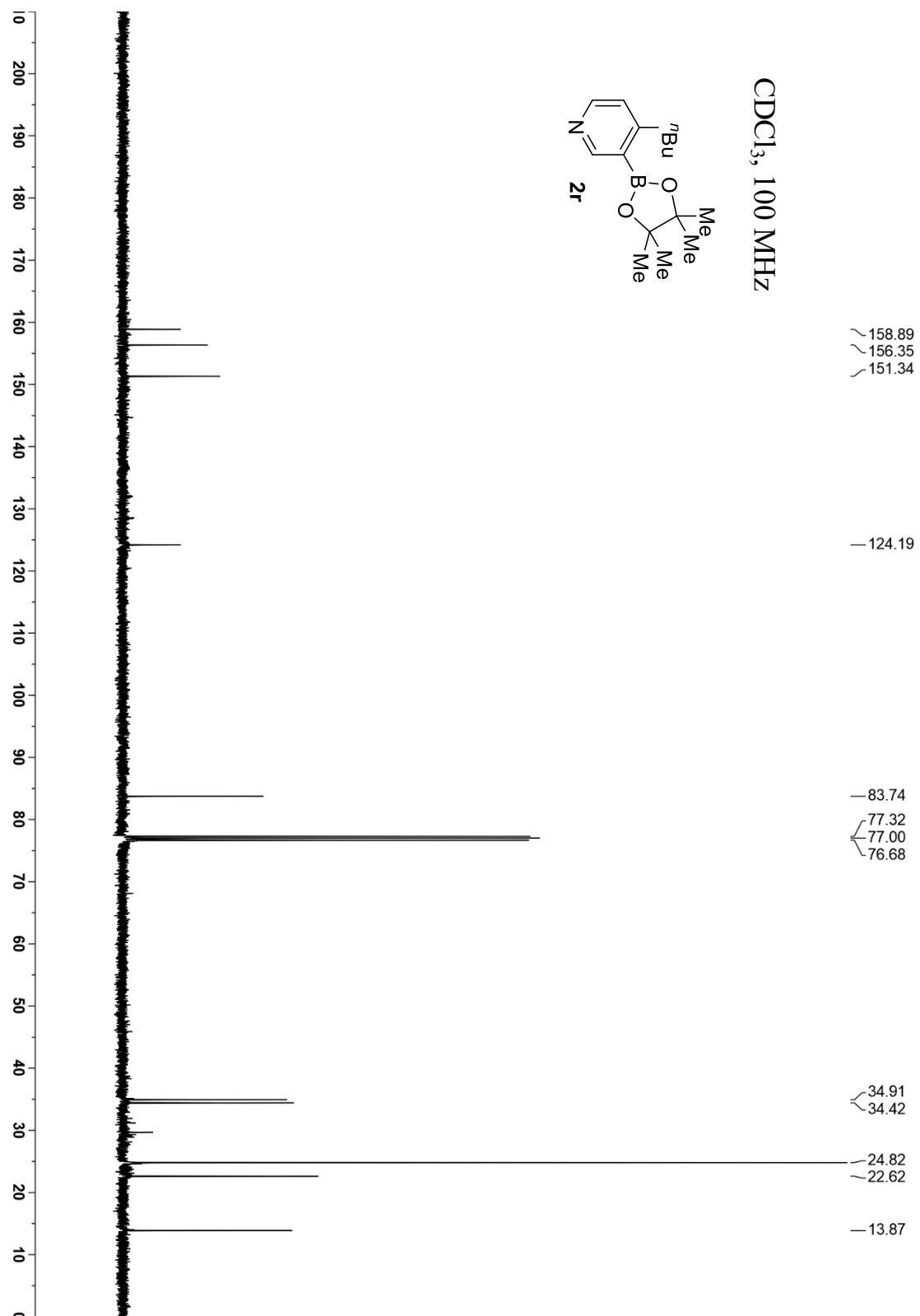


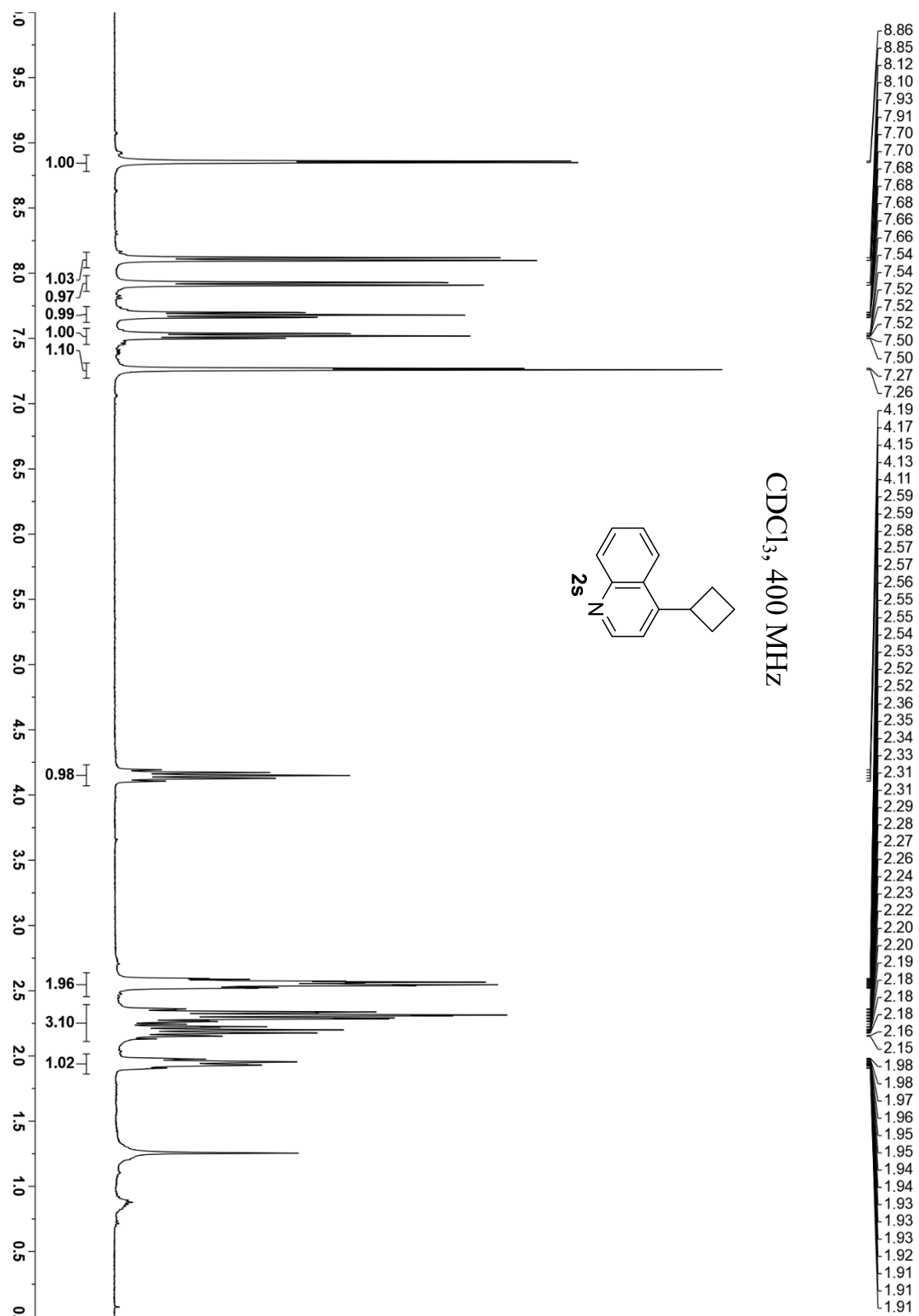


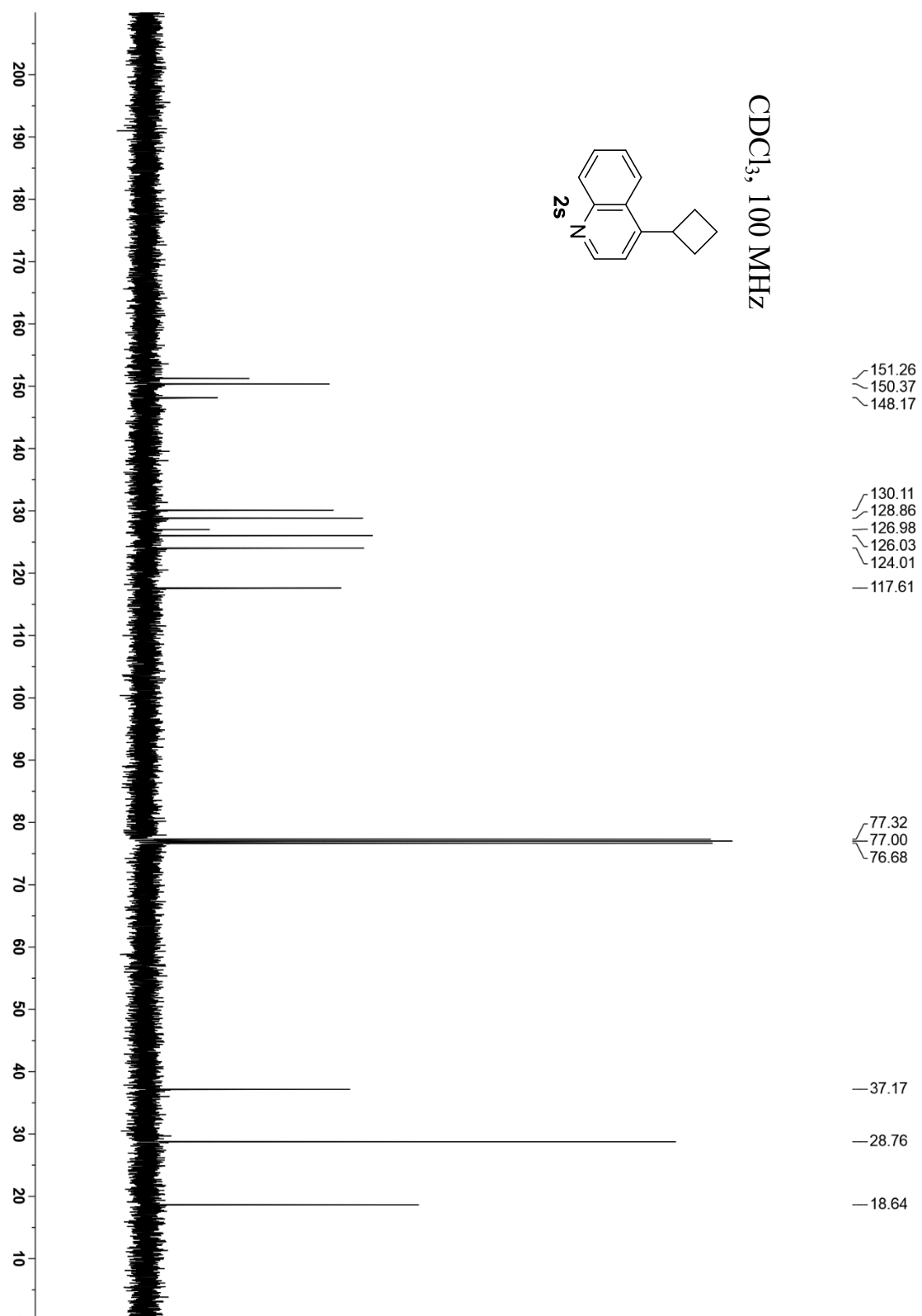


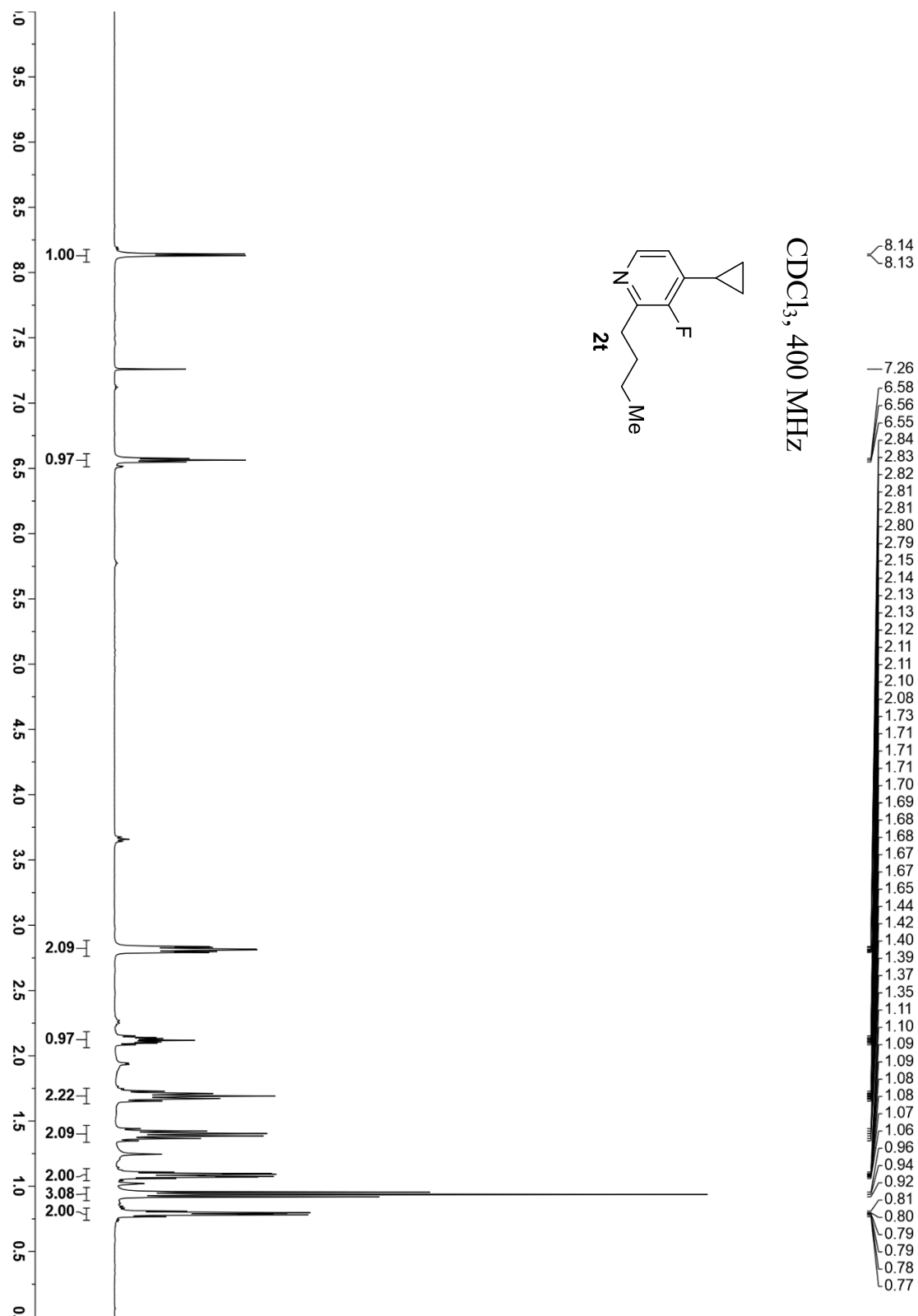


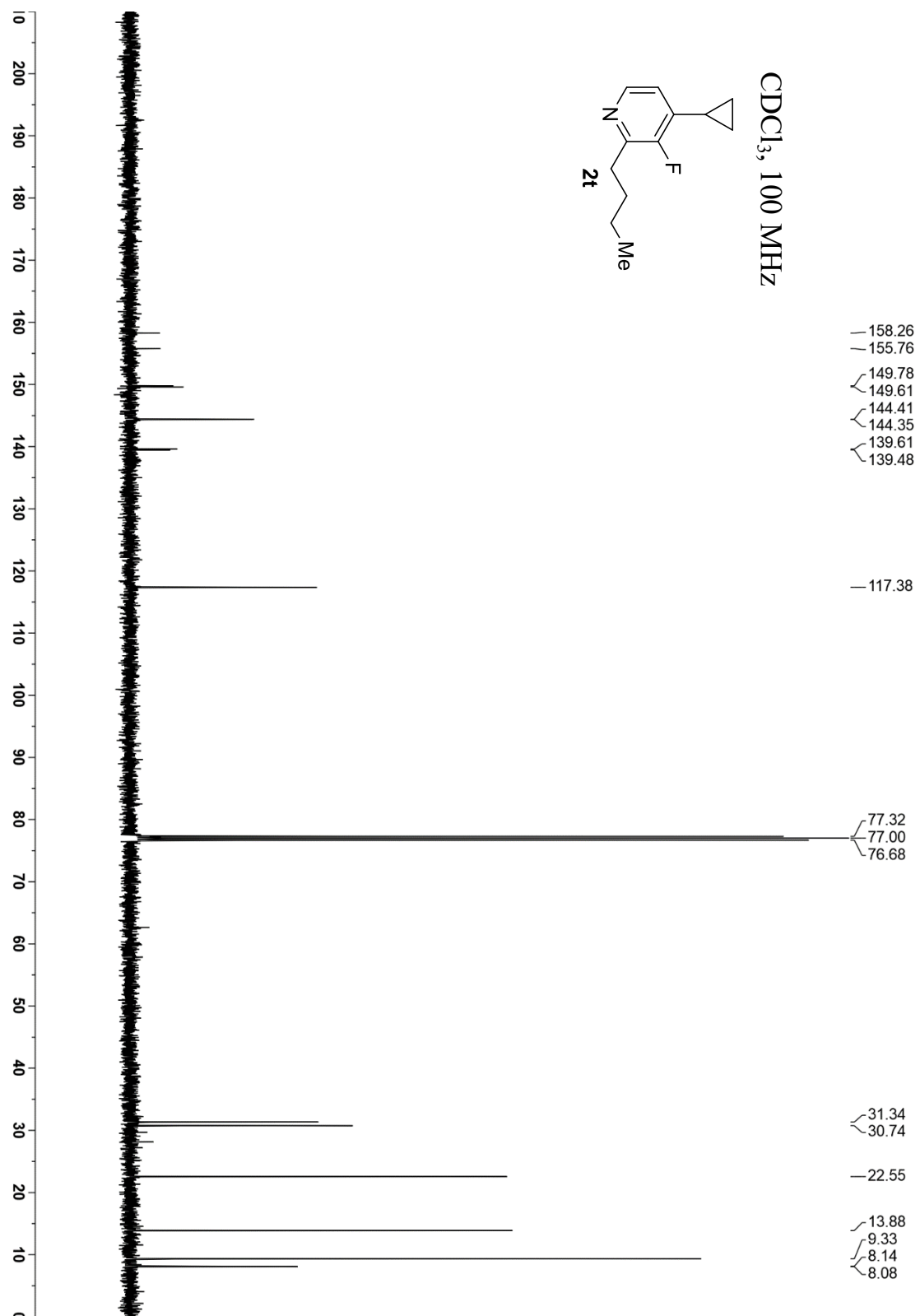




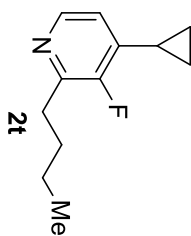




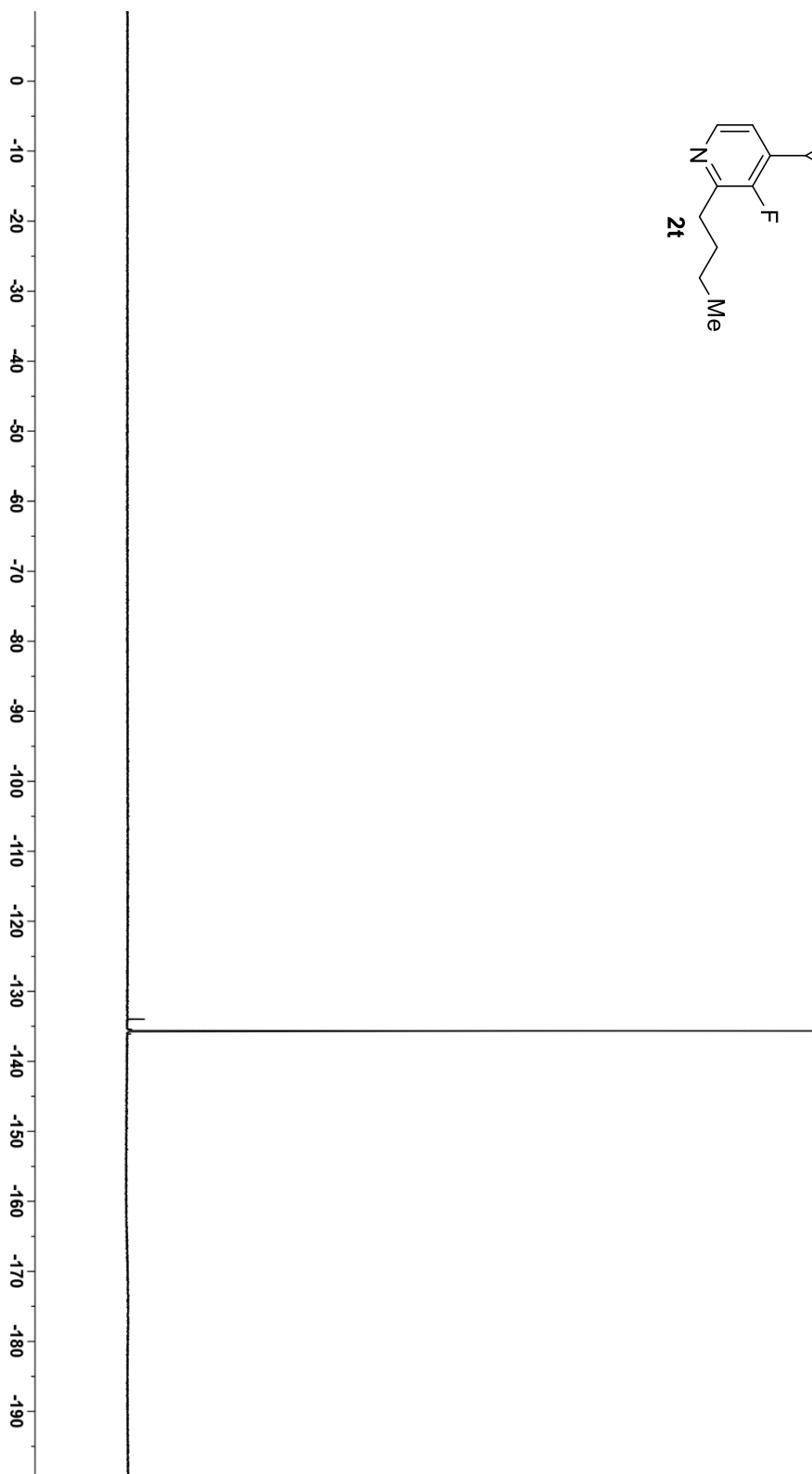


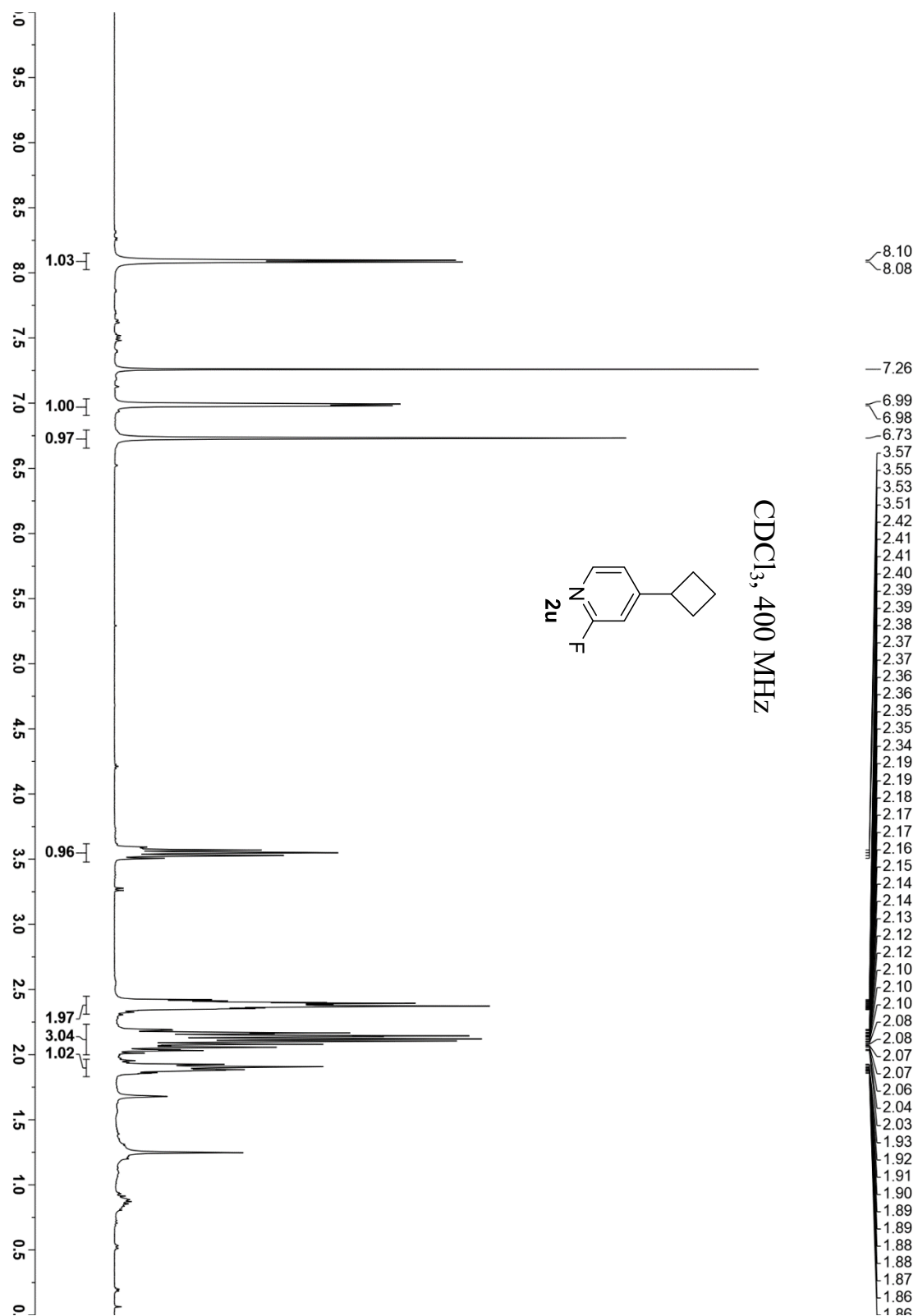


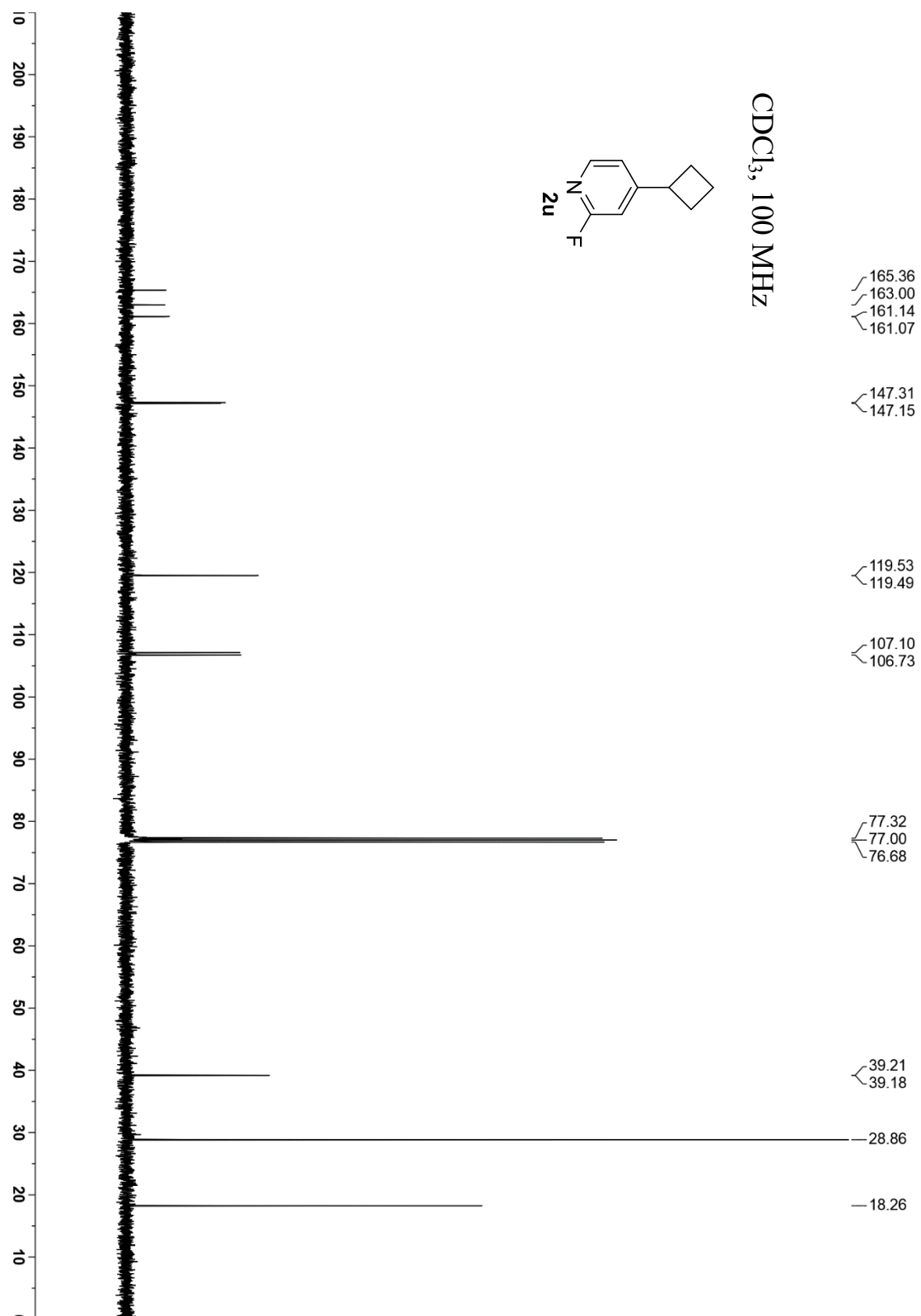
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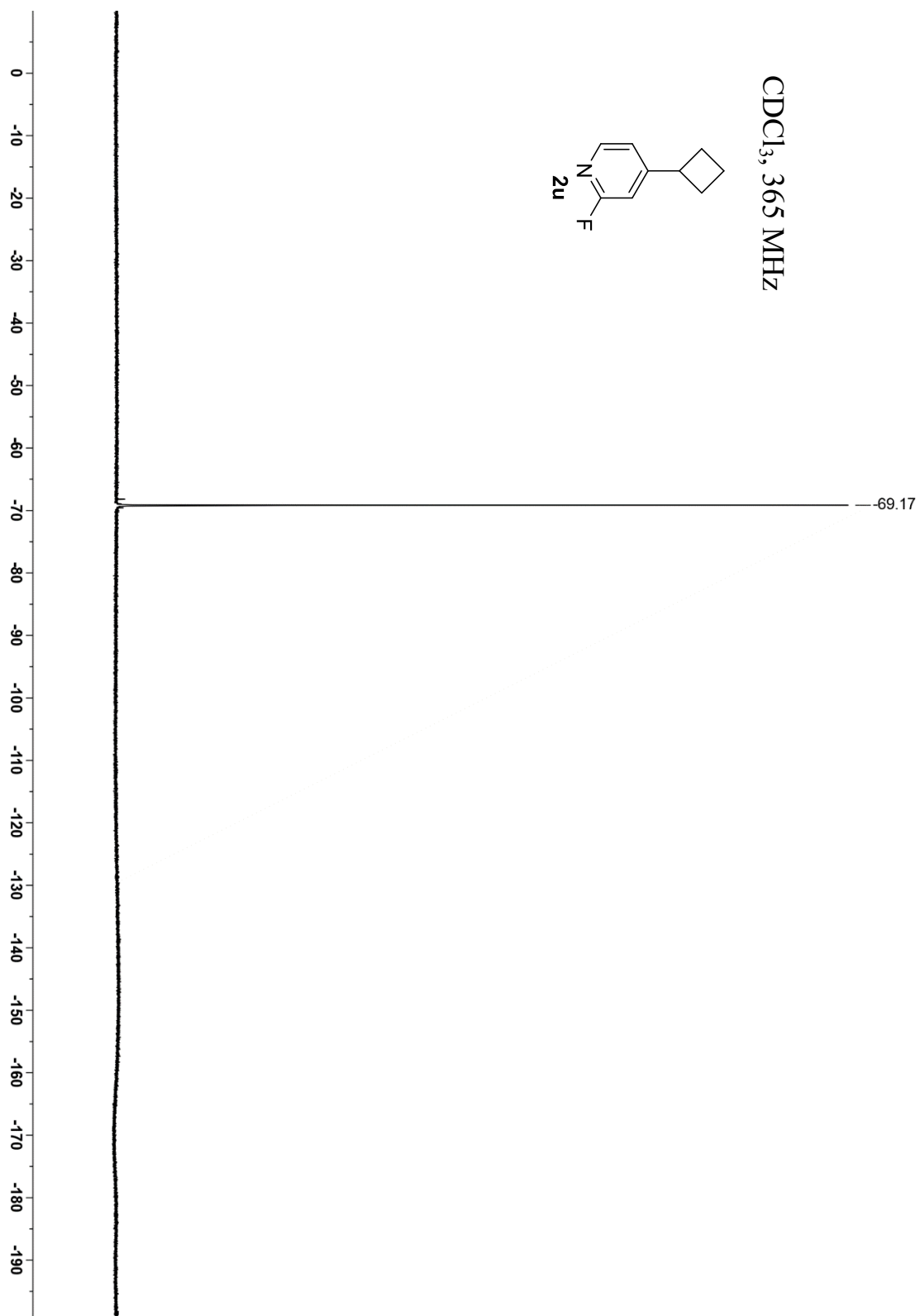
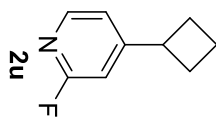
-135.66
-135.67
-135.68

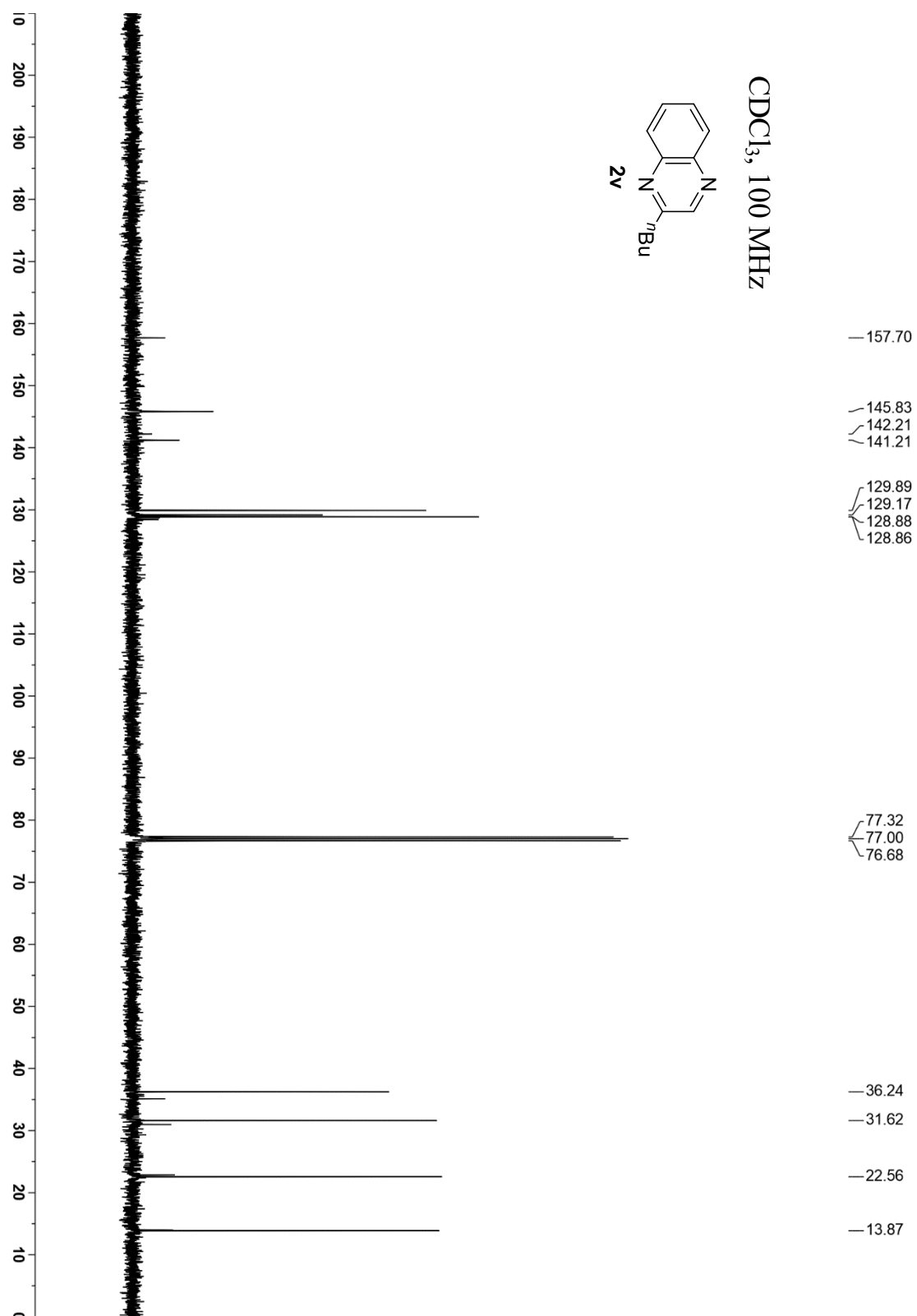


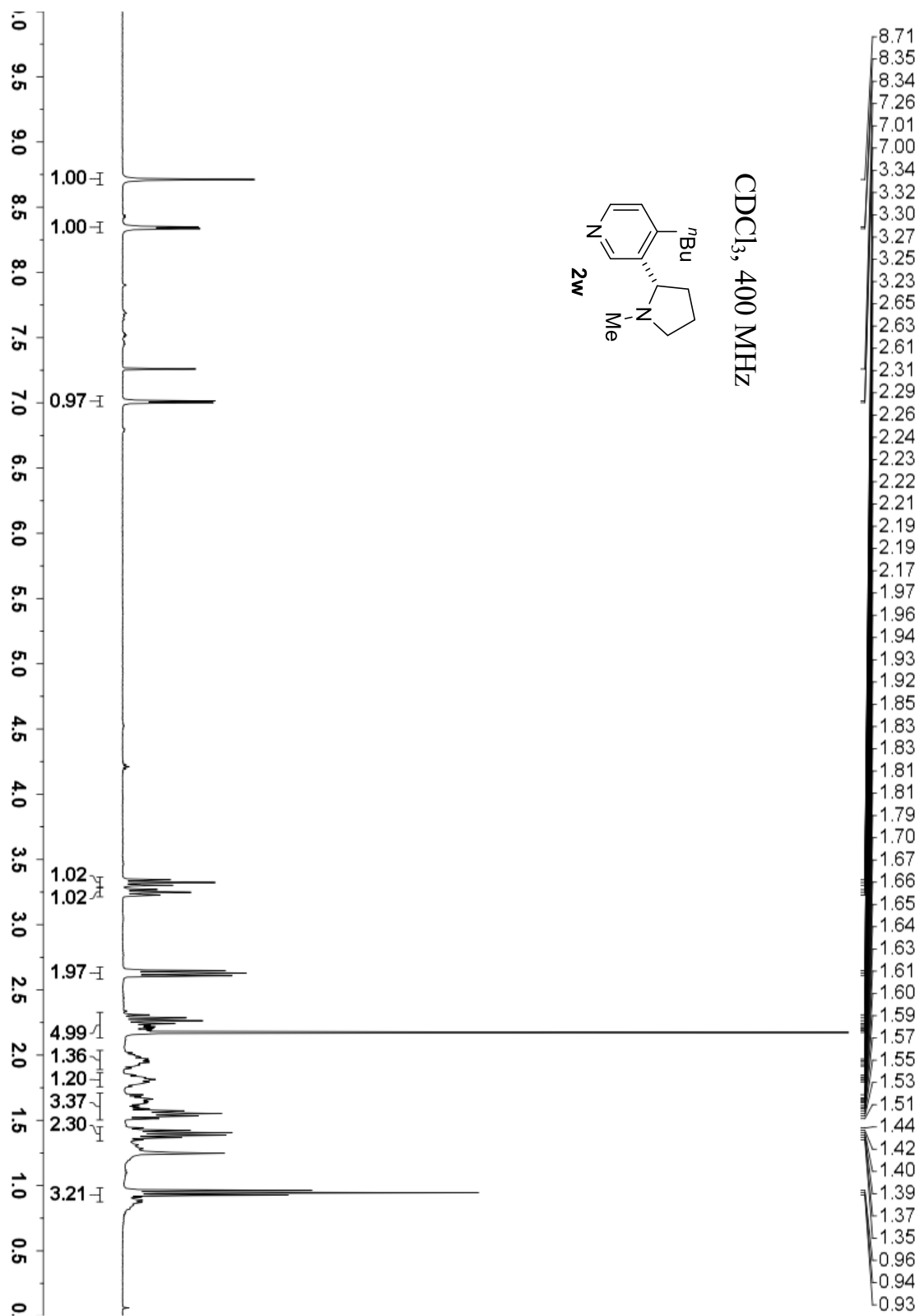


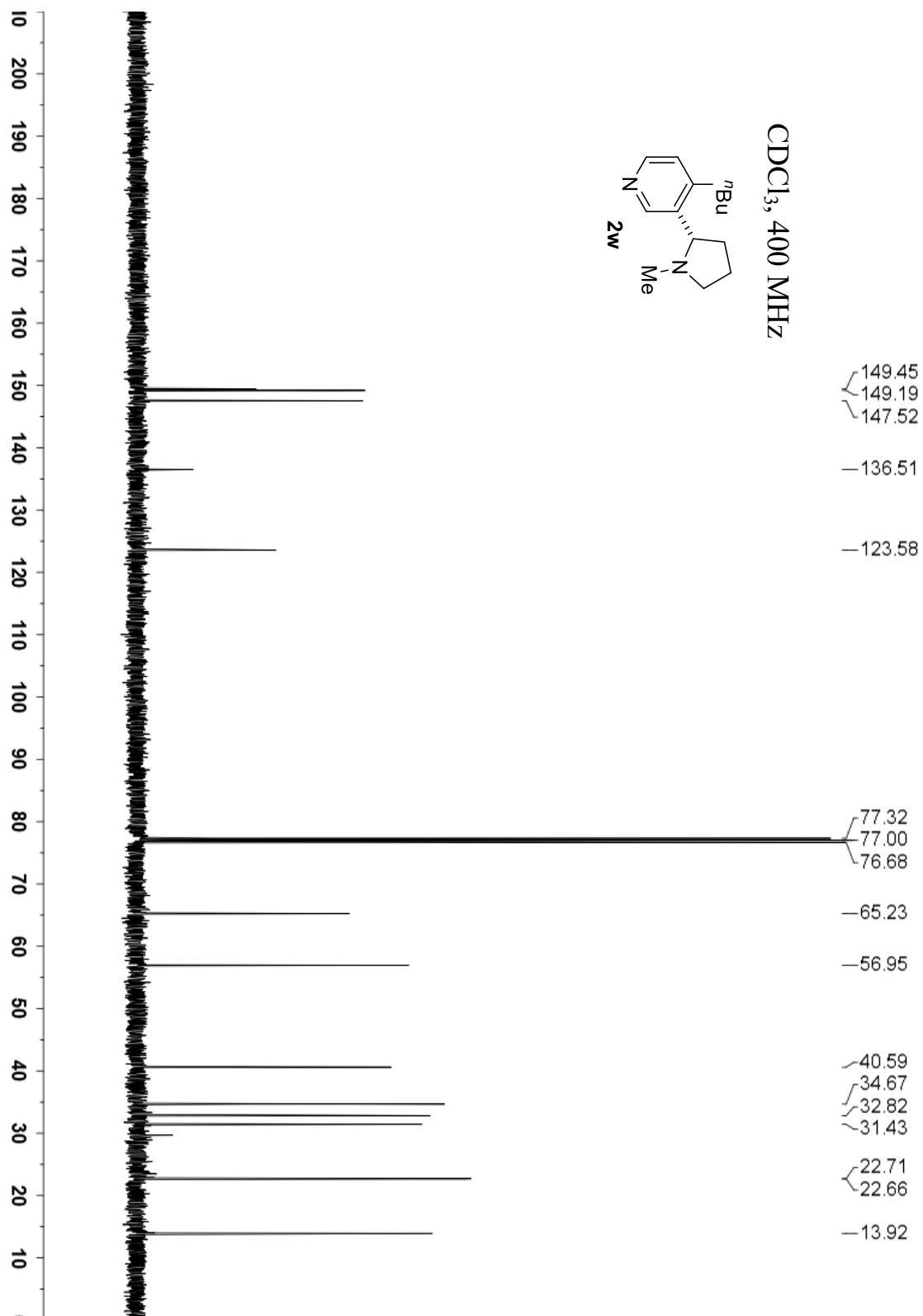


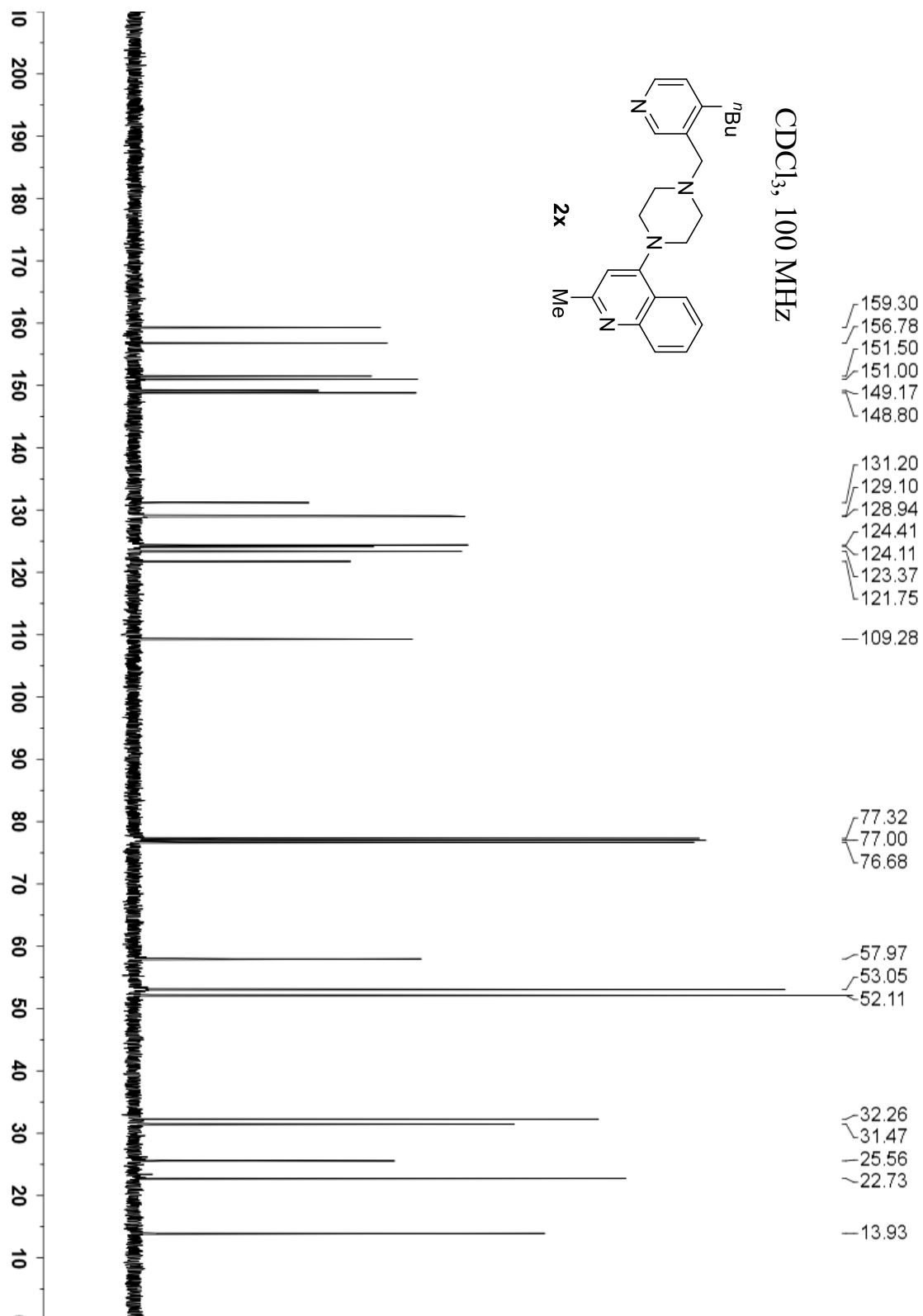
CDCl₃, 365 MHz

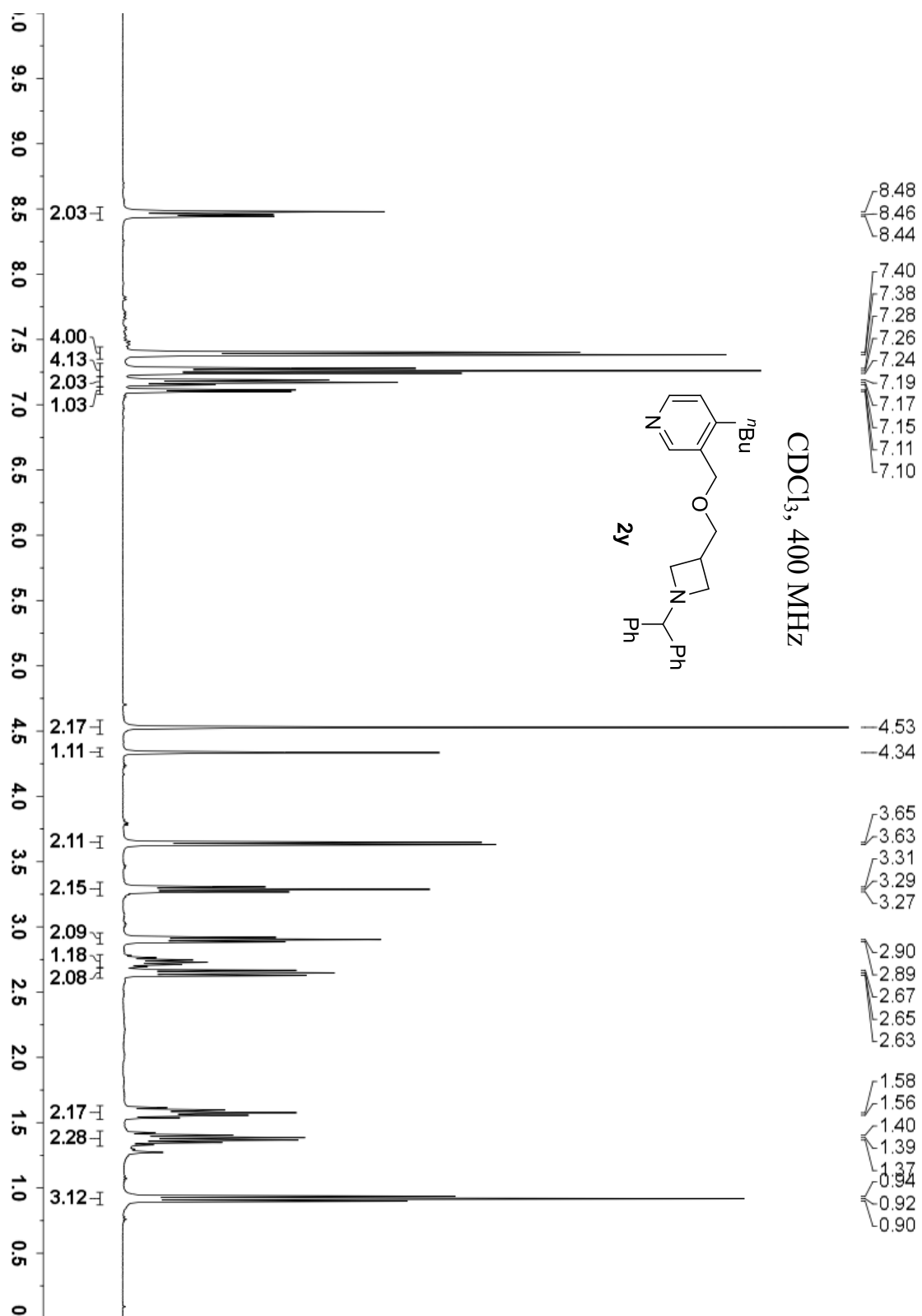


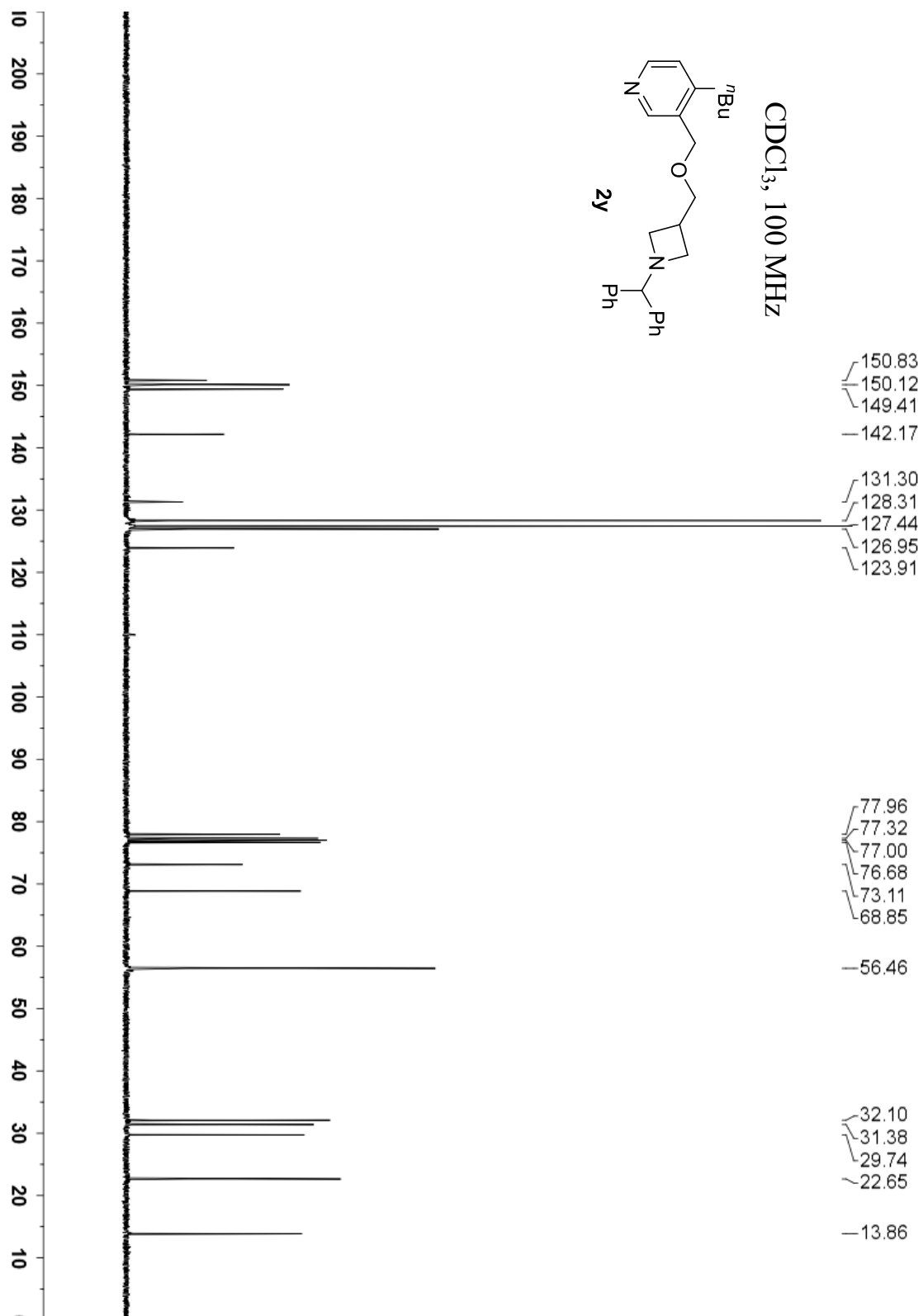


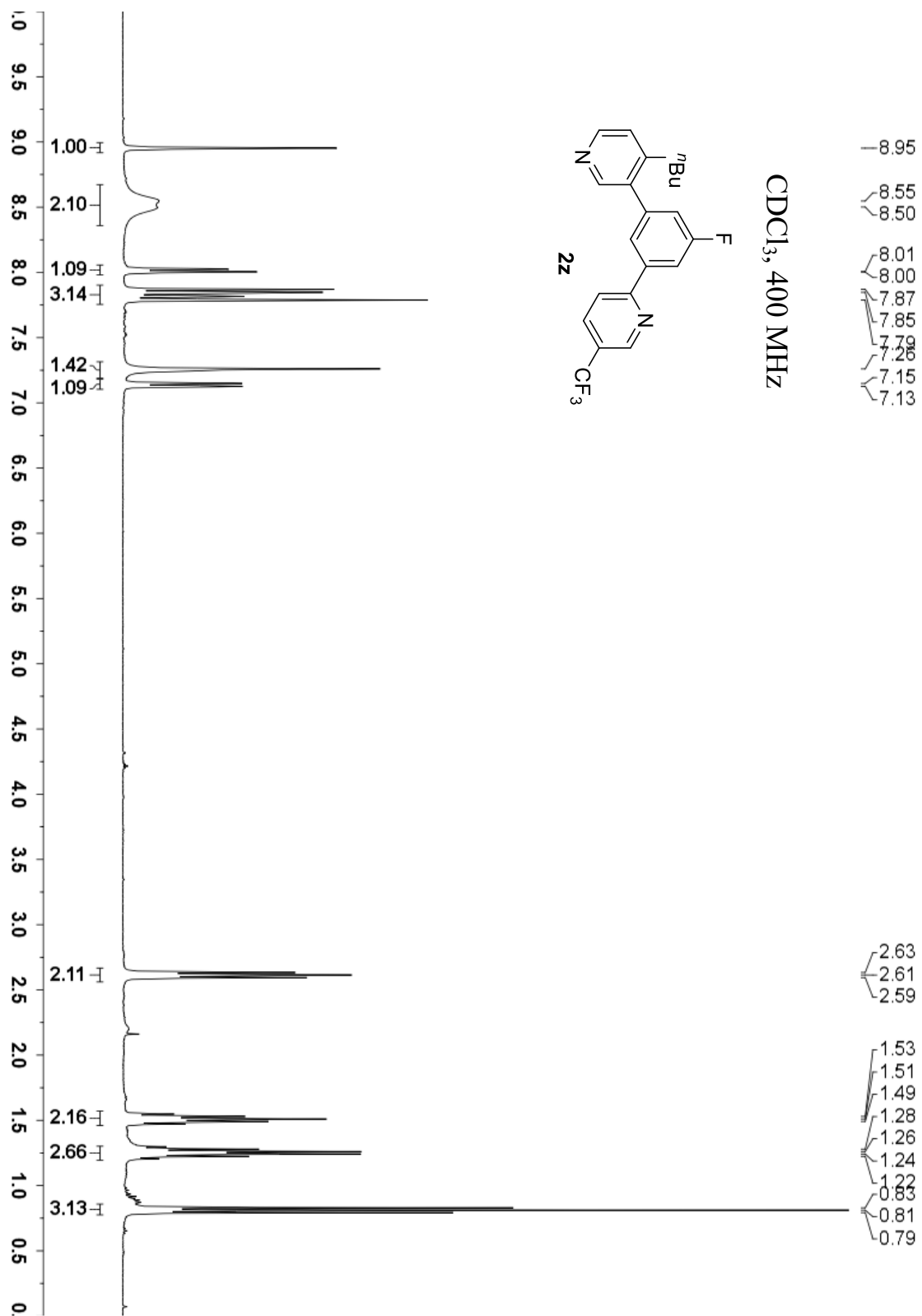


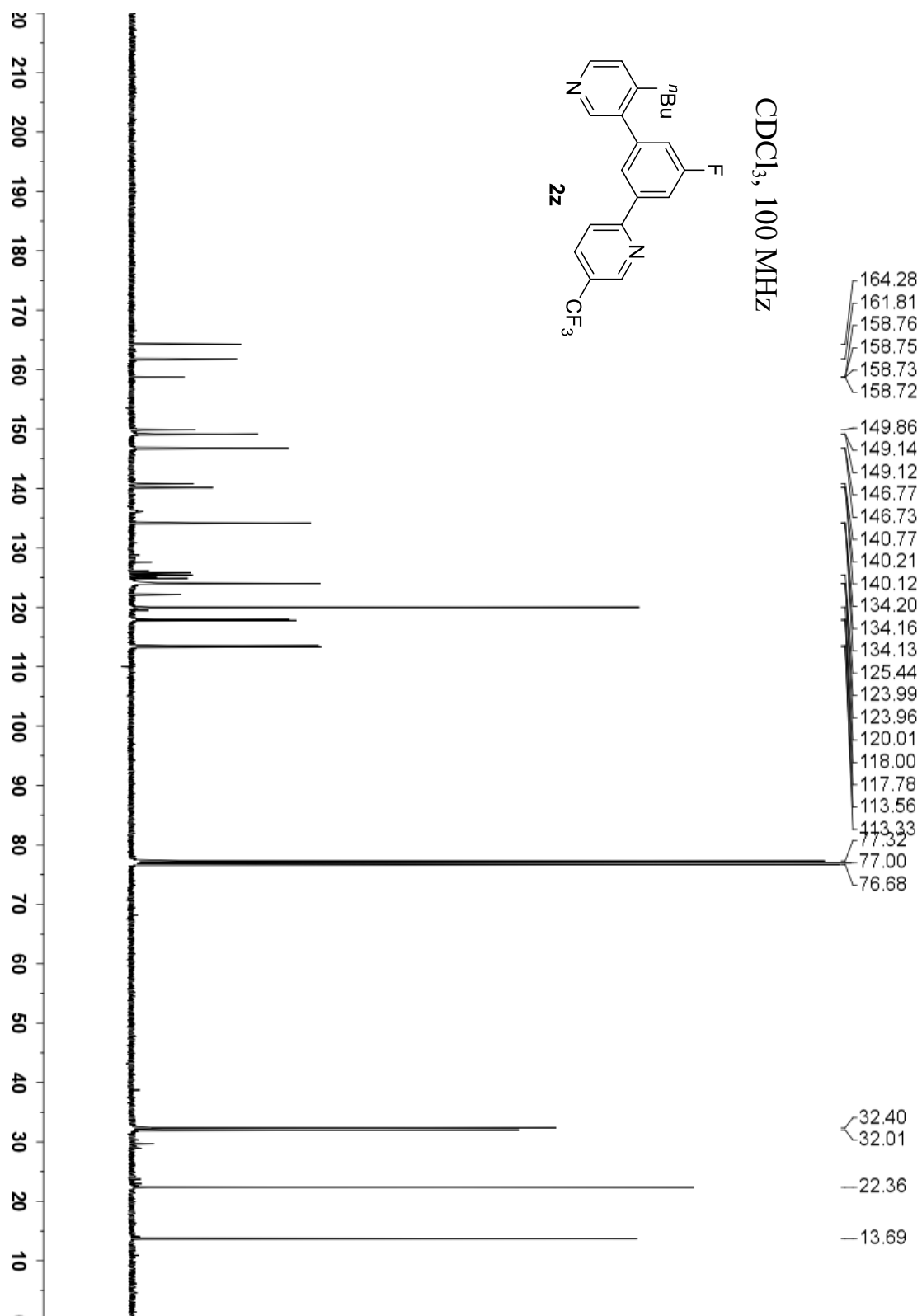




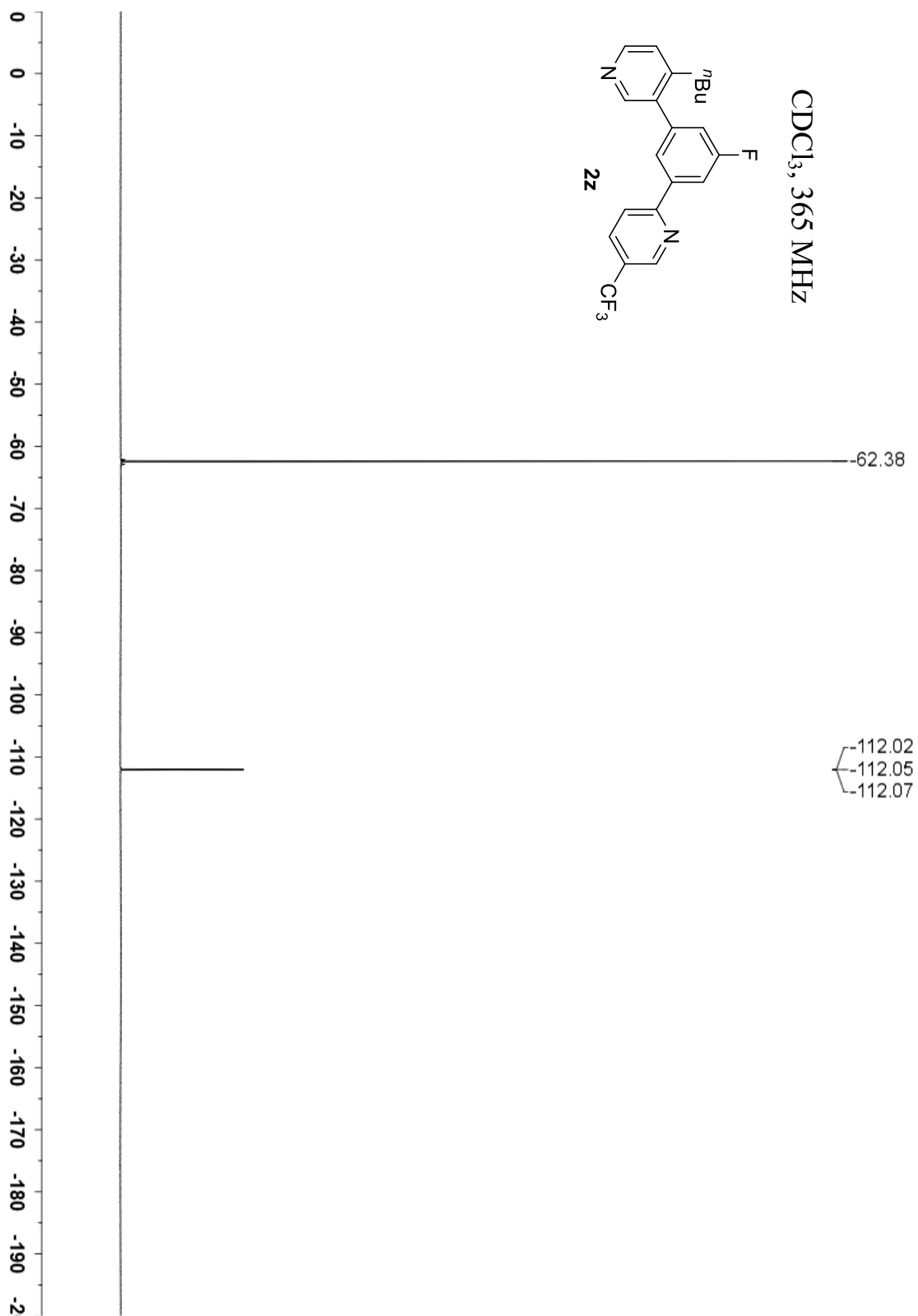
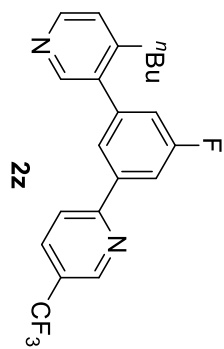


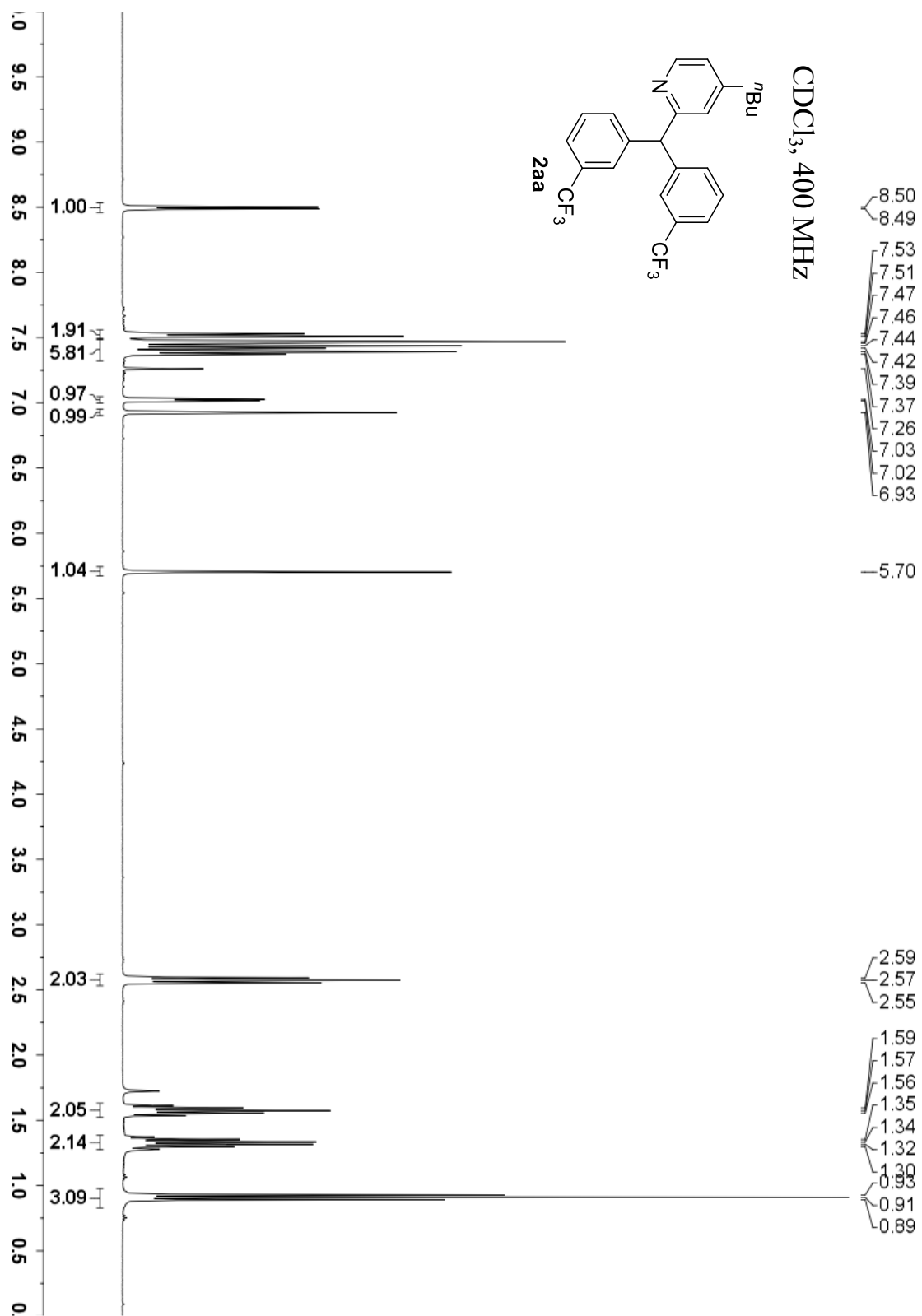


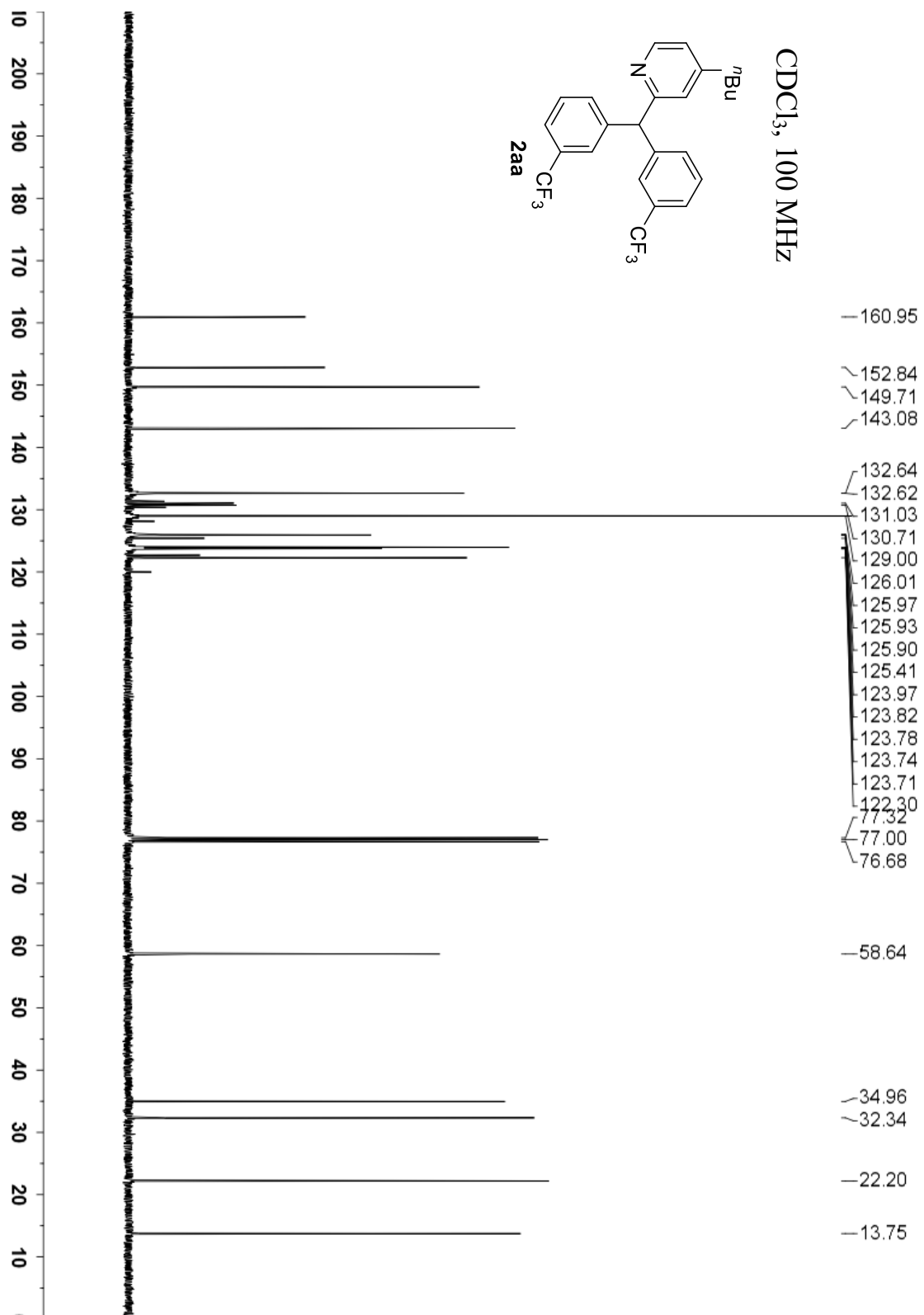




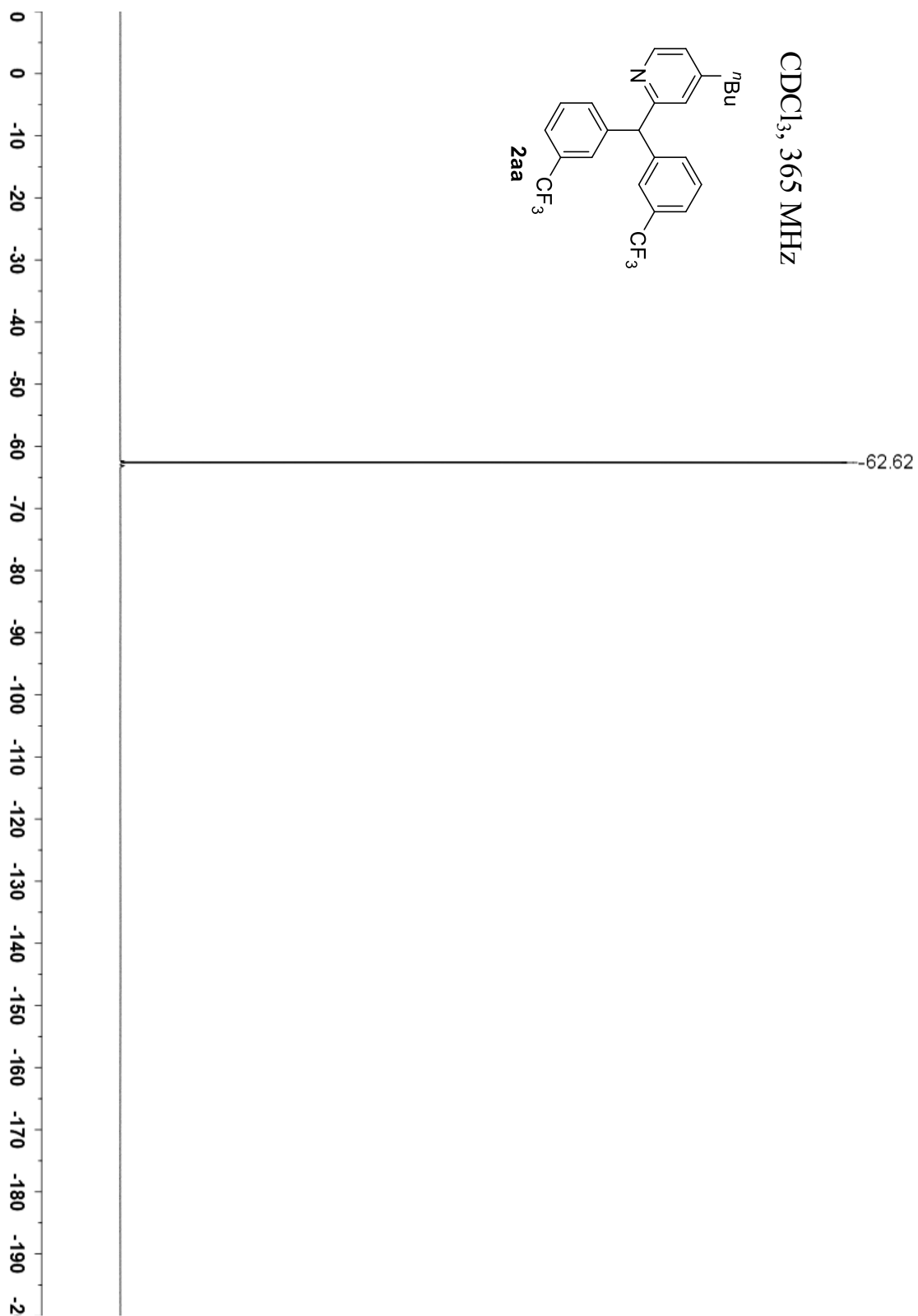
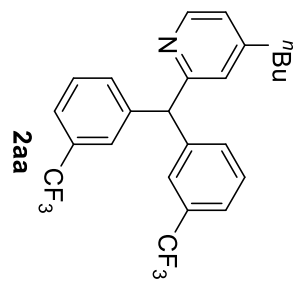
CDCl₃, 365 MHz

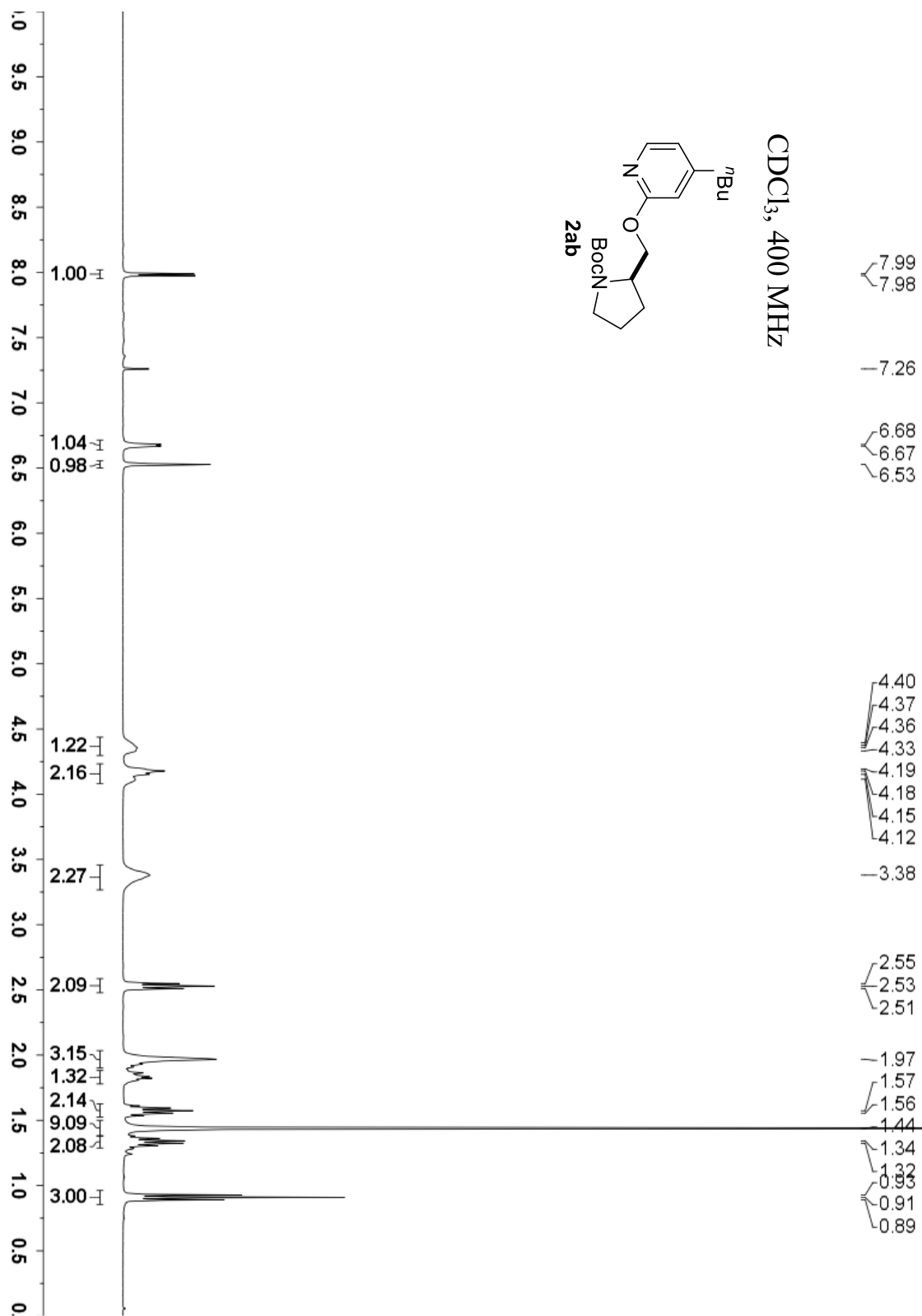


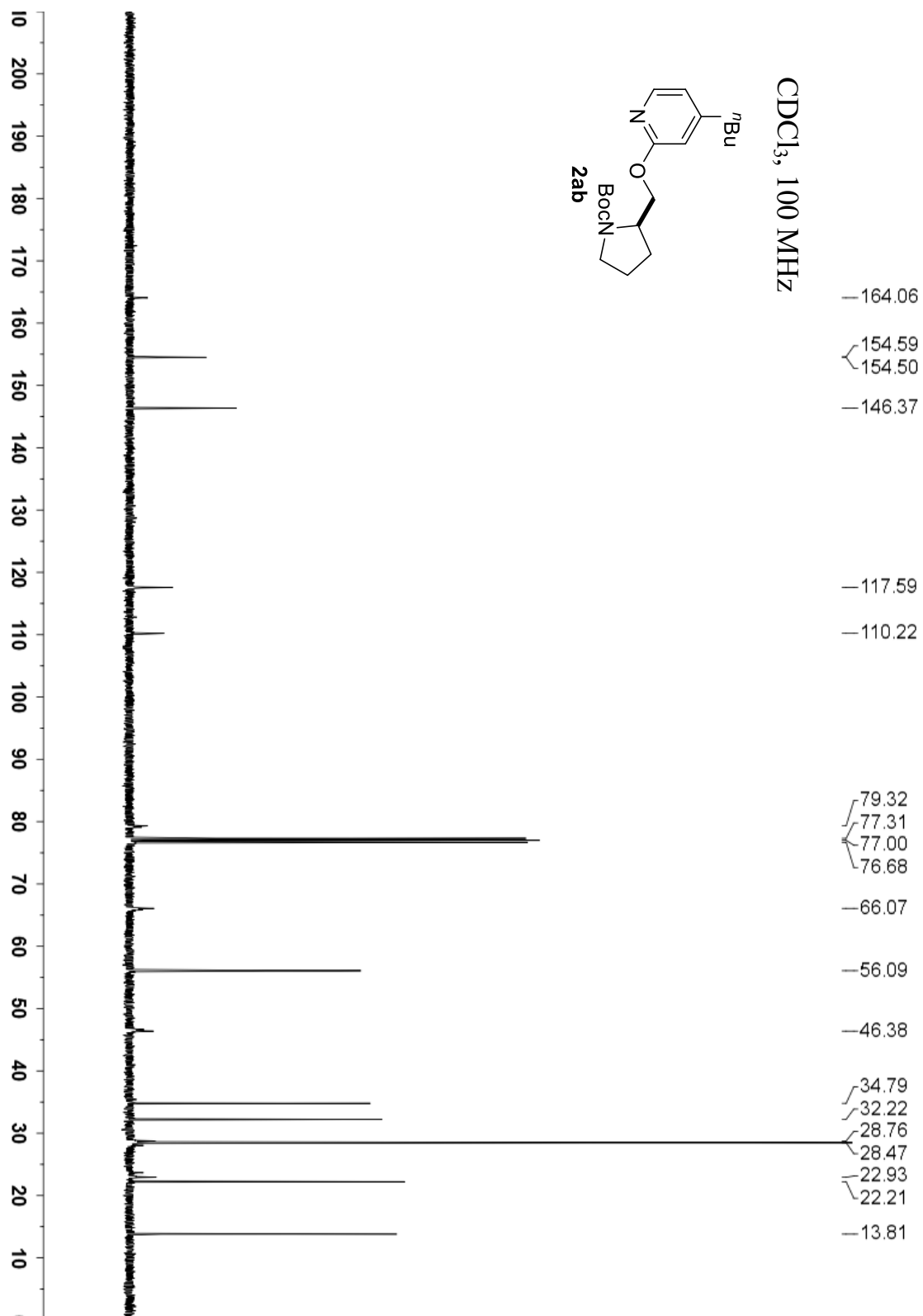


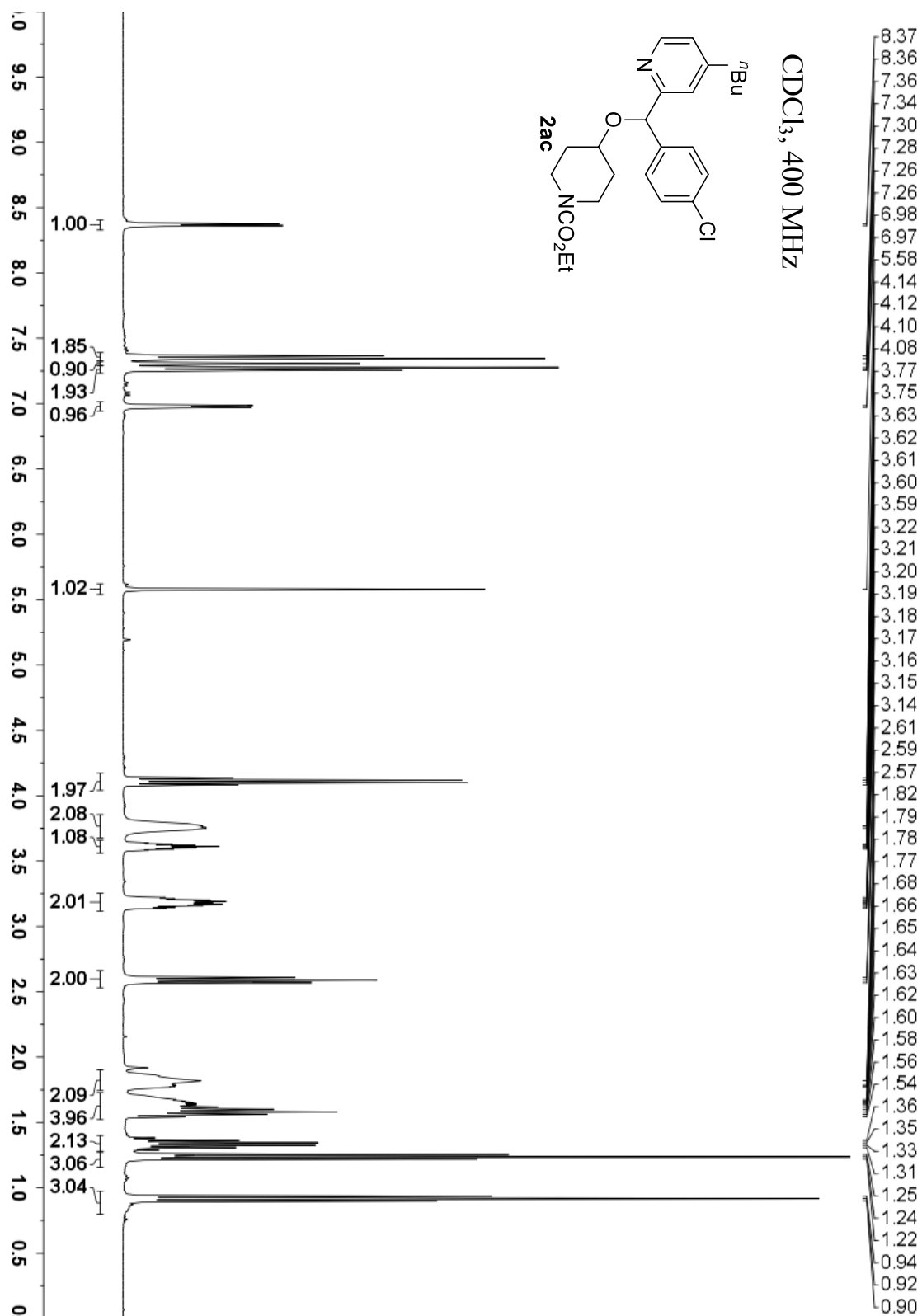


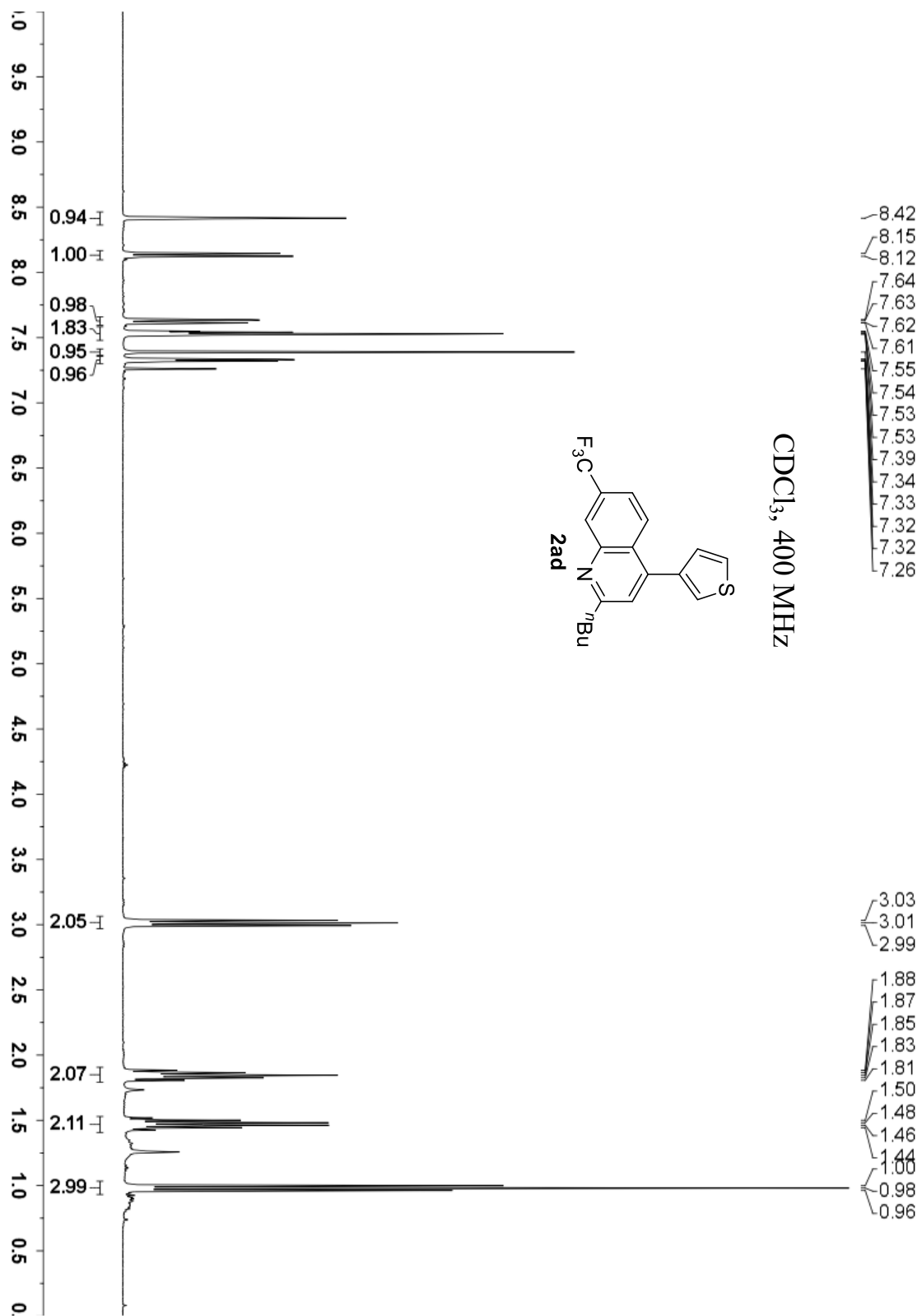
CDCl₃, 365 MHz

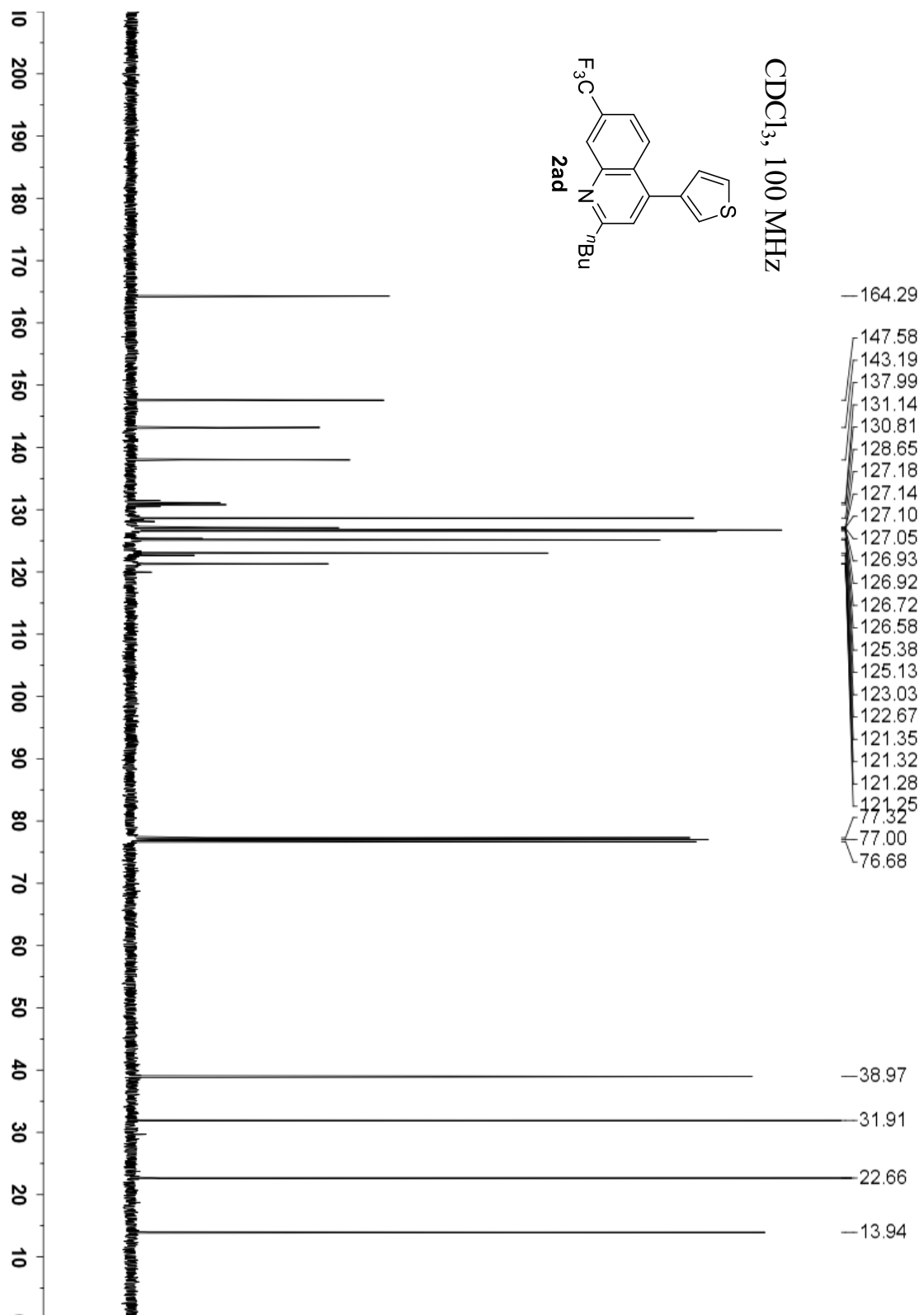




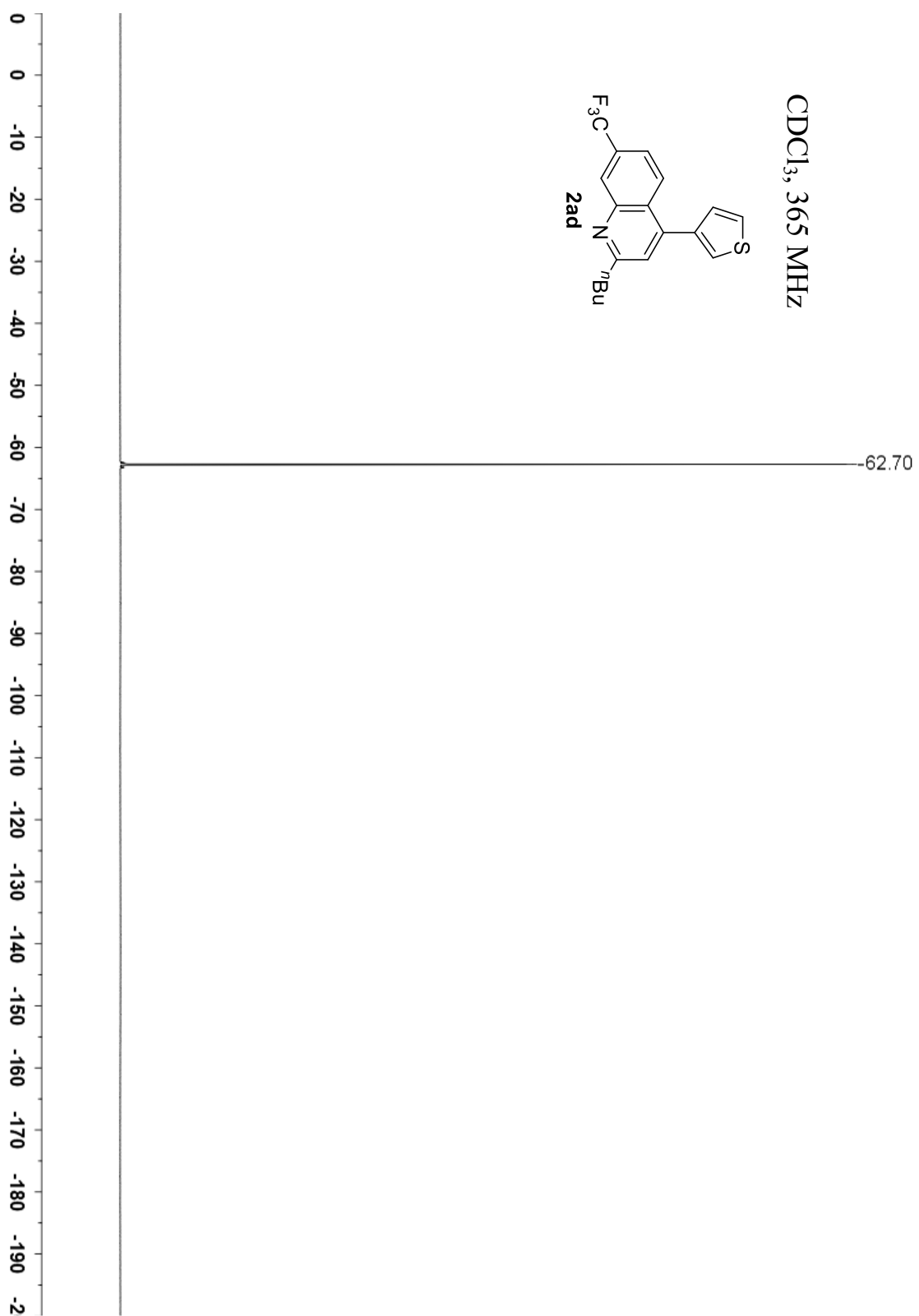
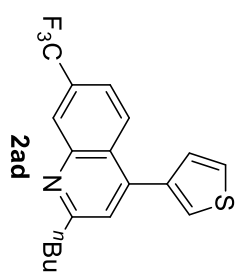


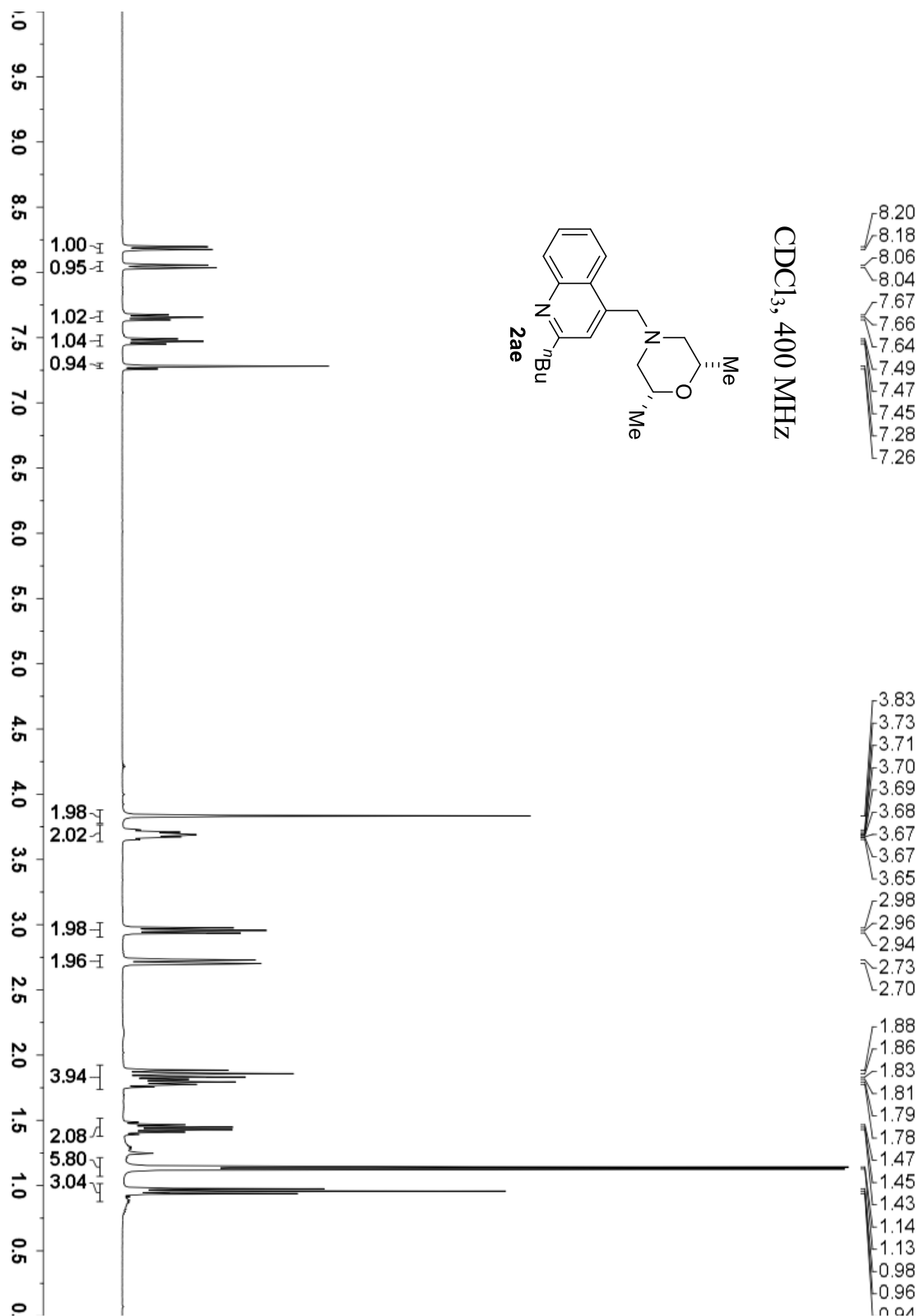


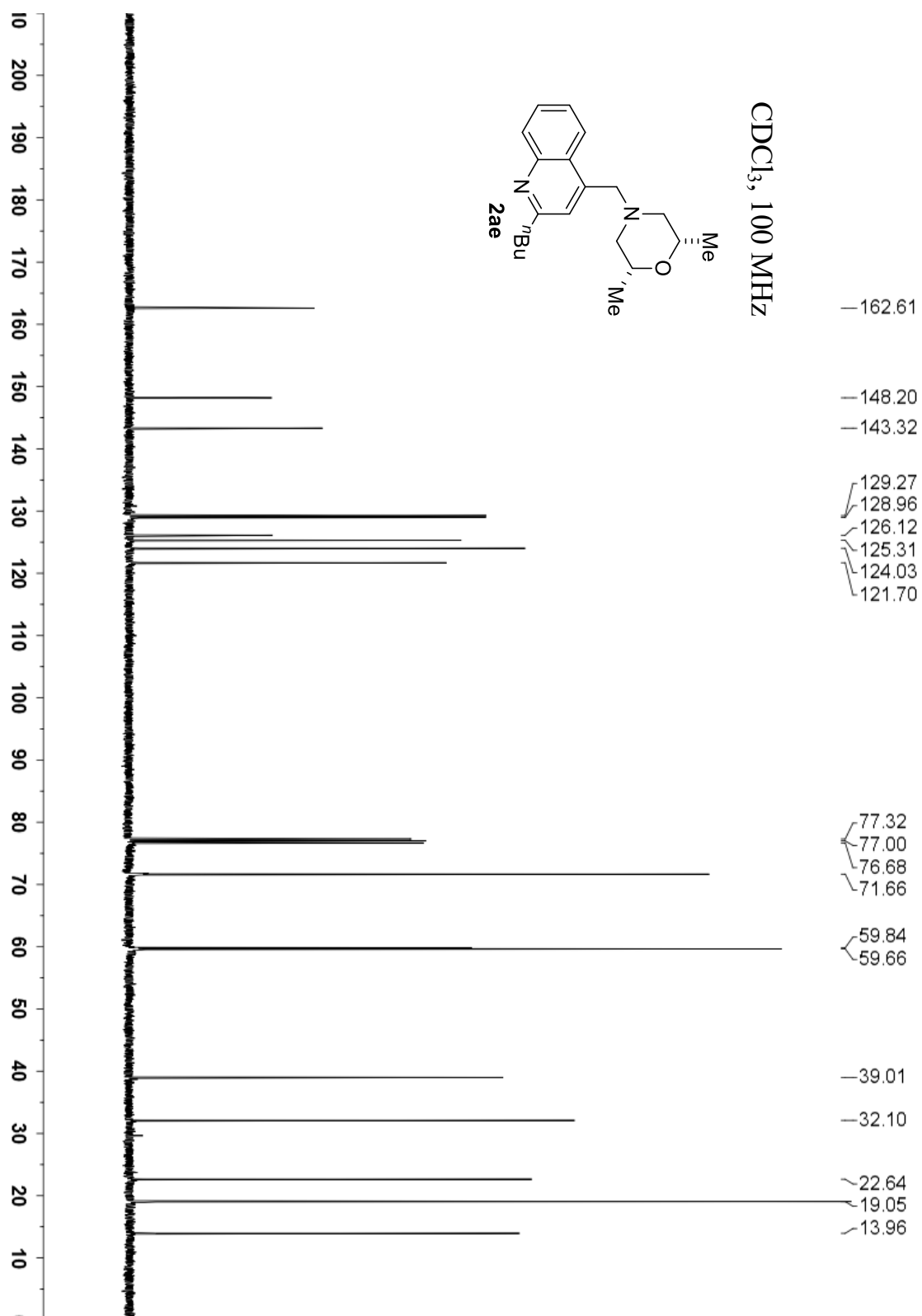


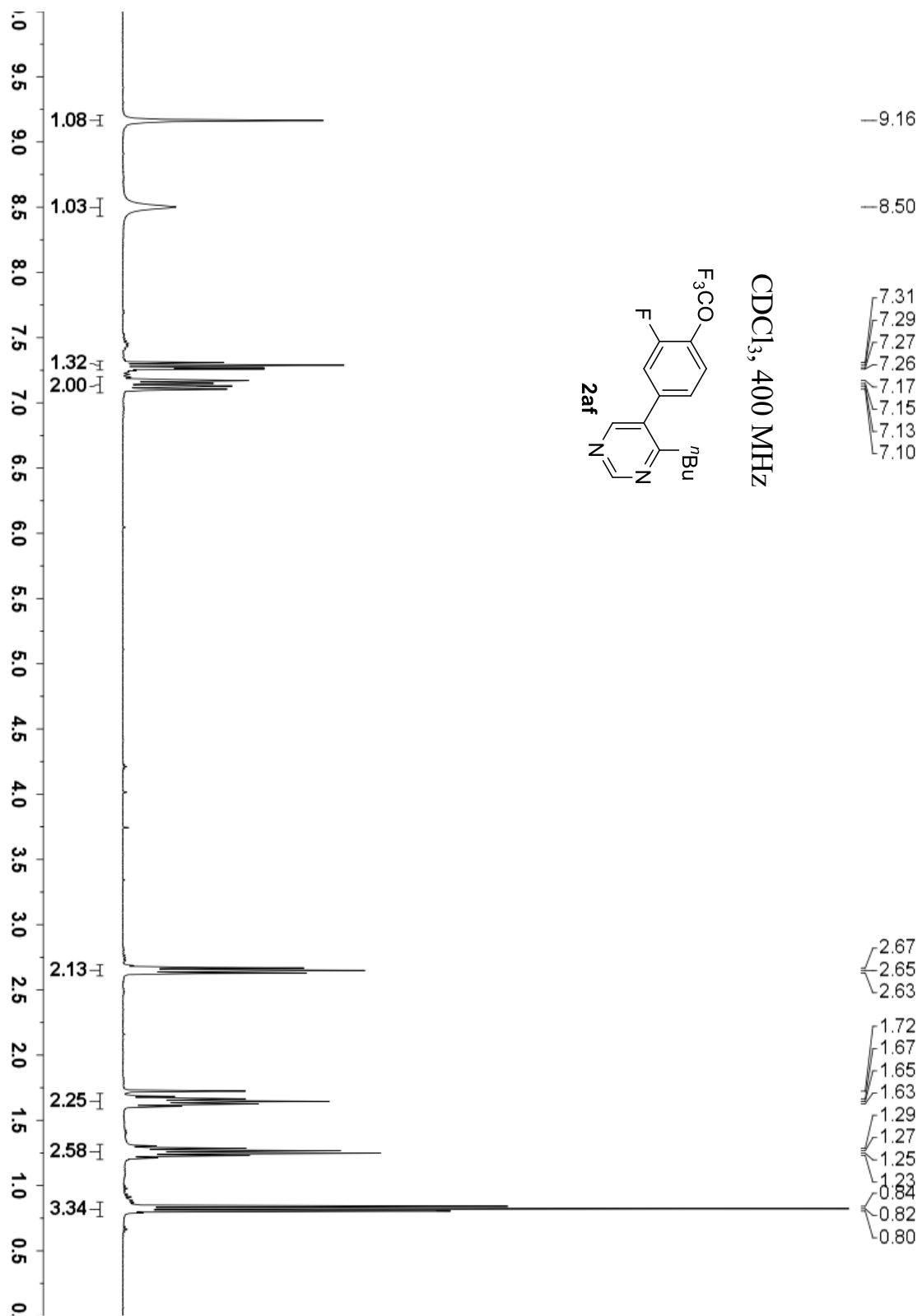


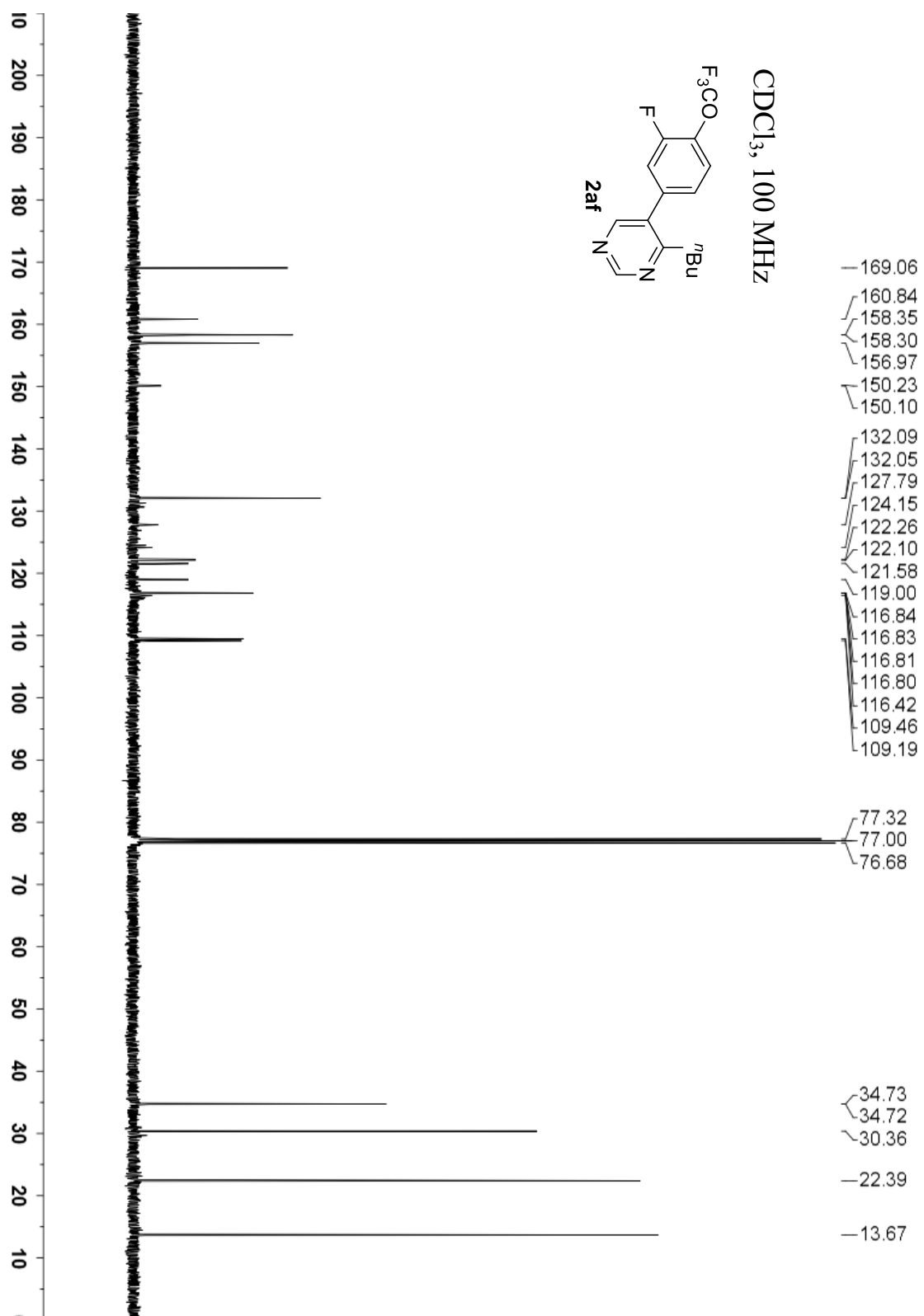
CDCl₃, 365 MHz

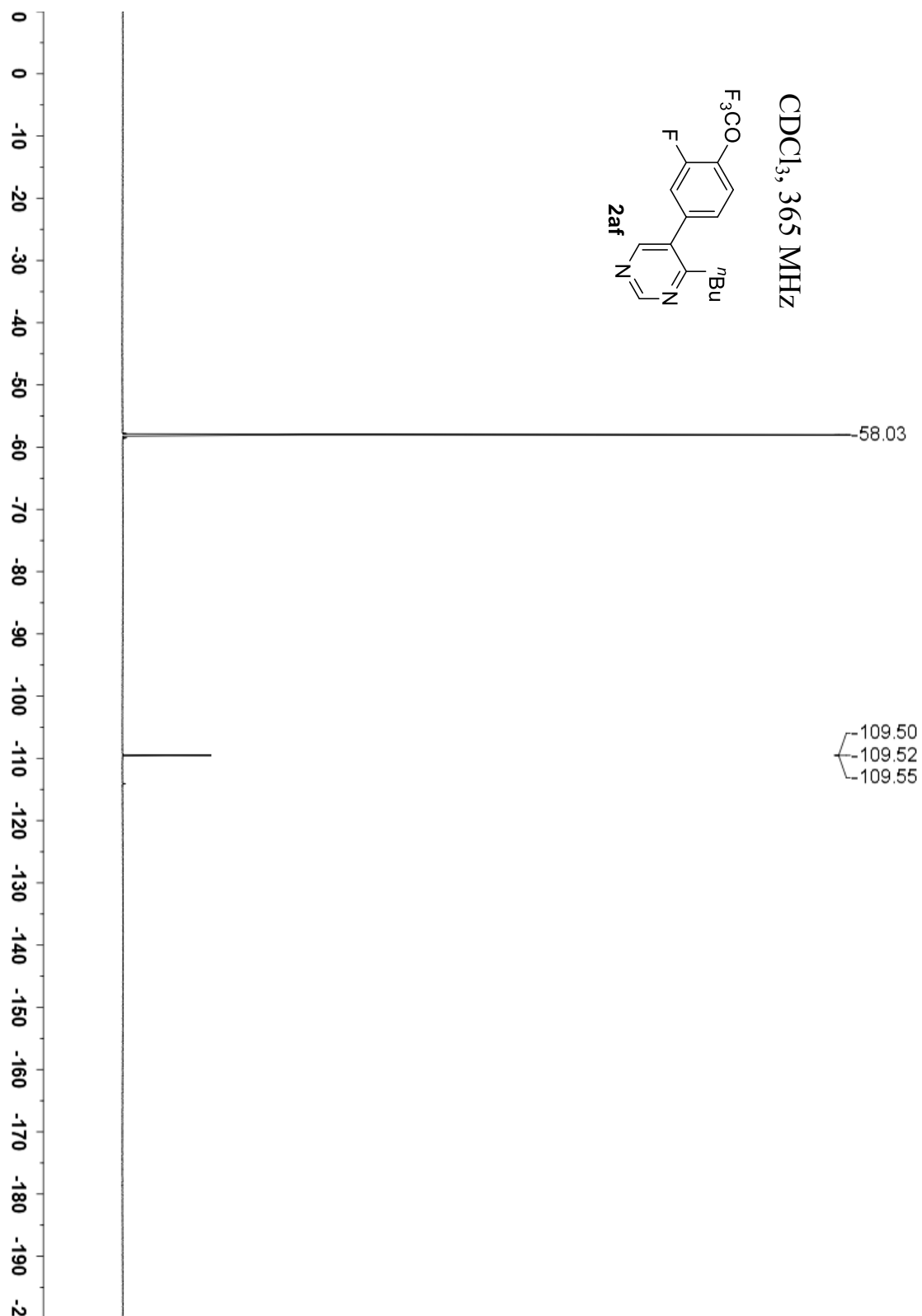


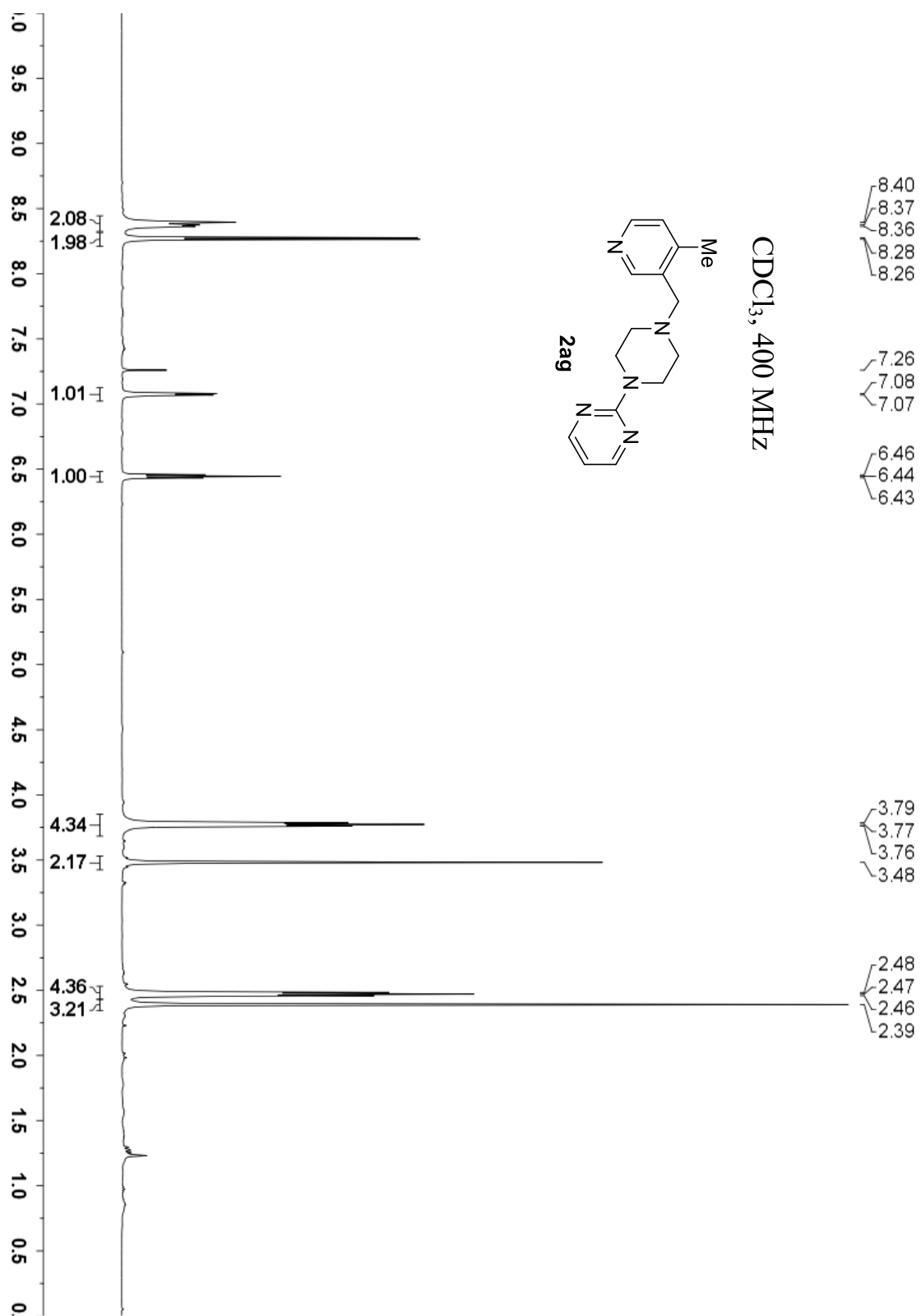


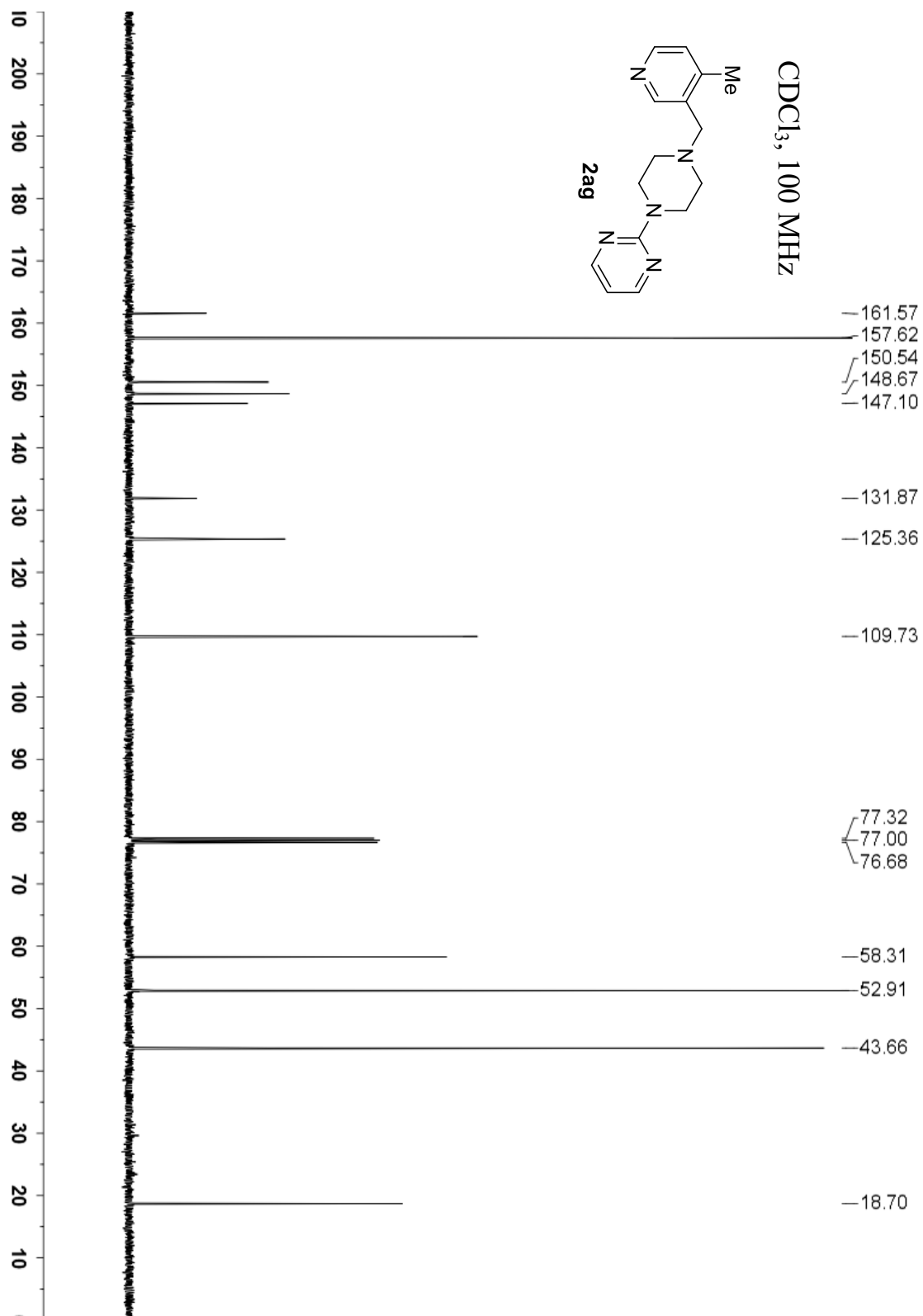


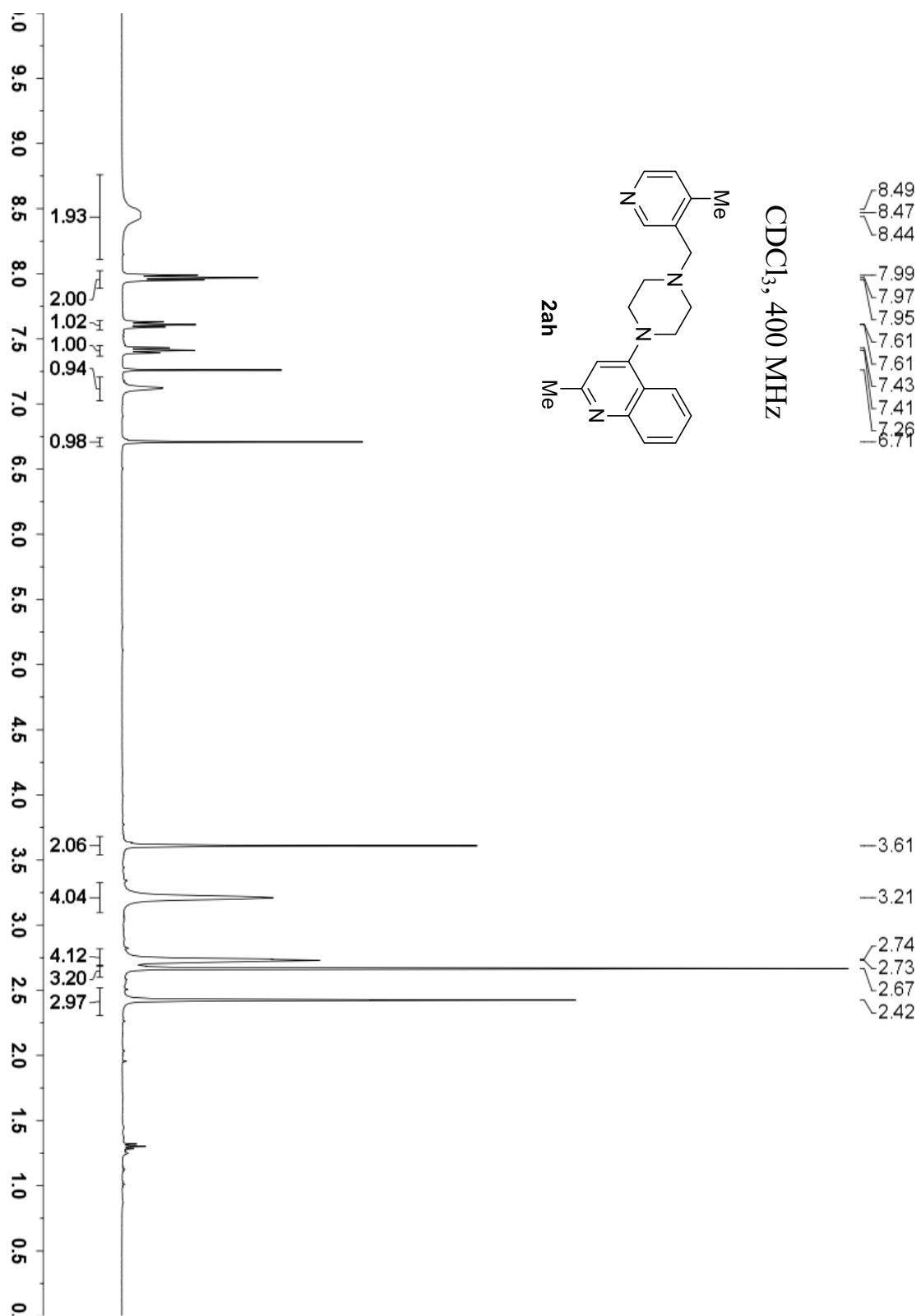


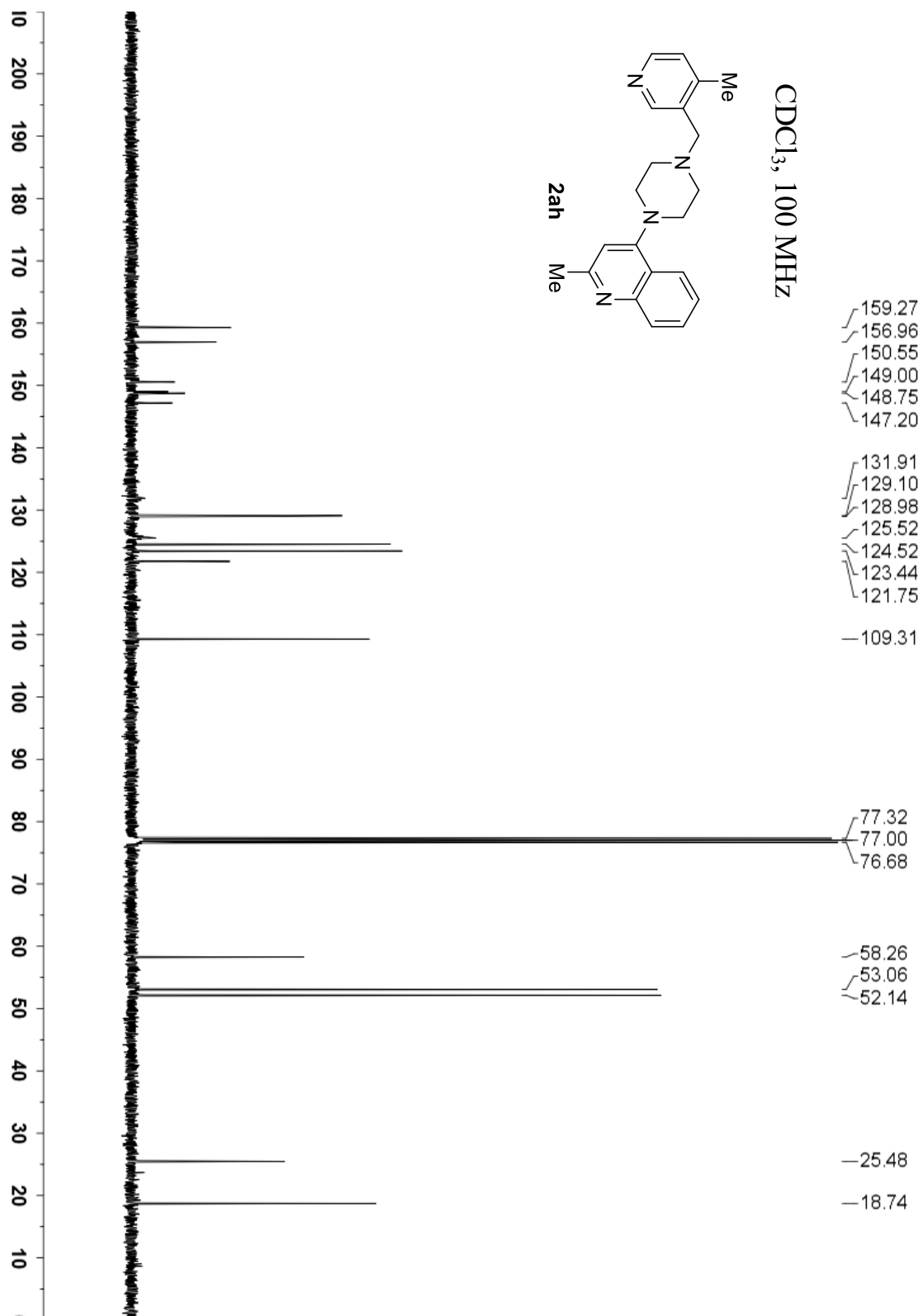


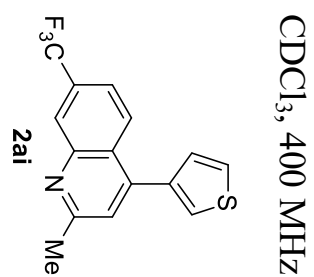




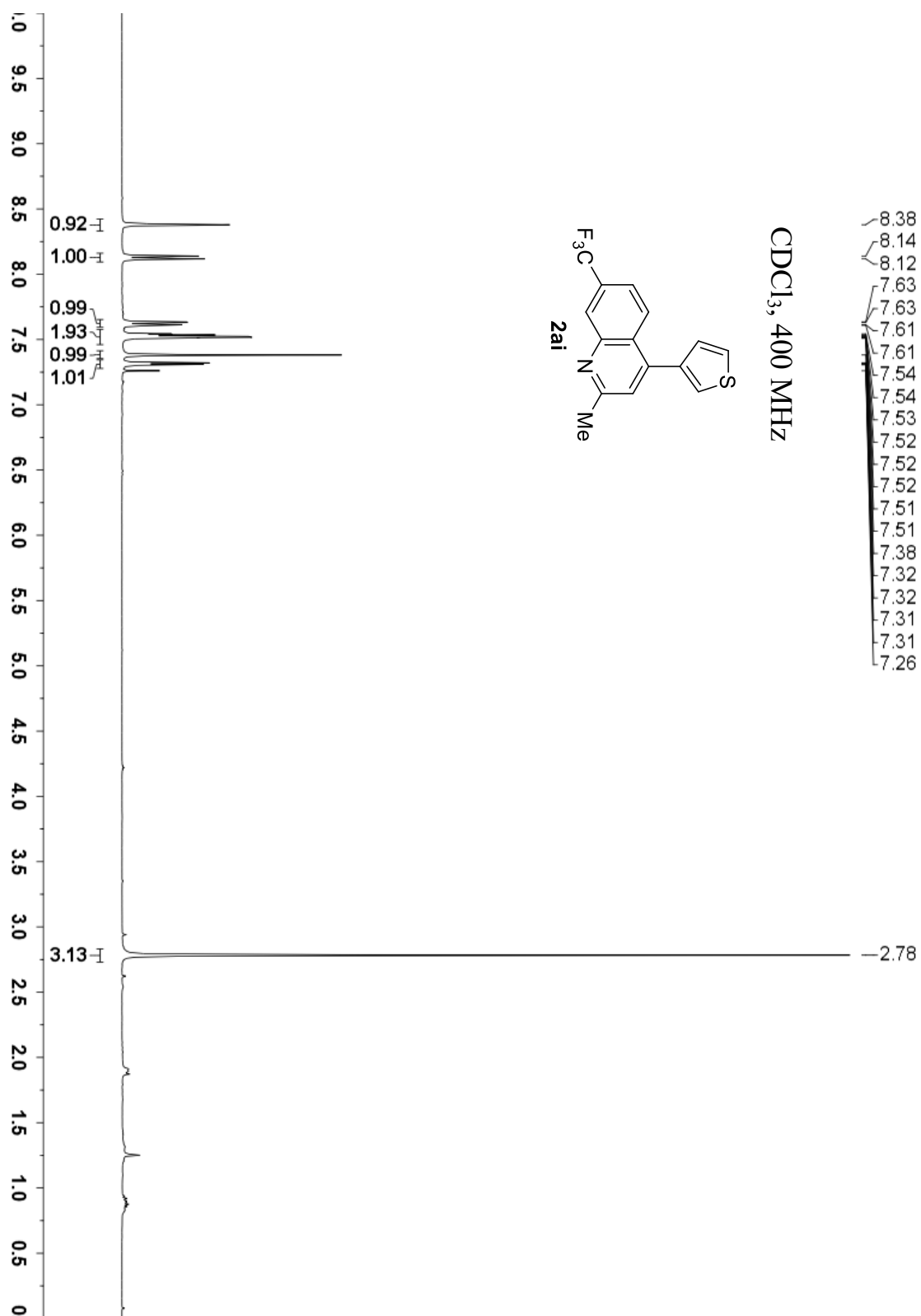


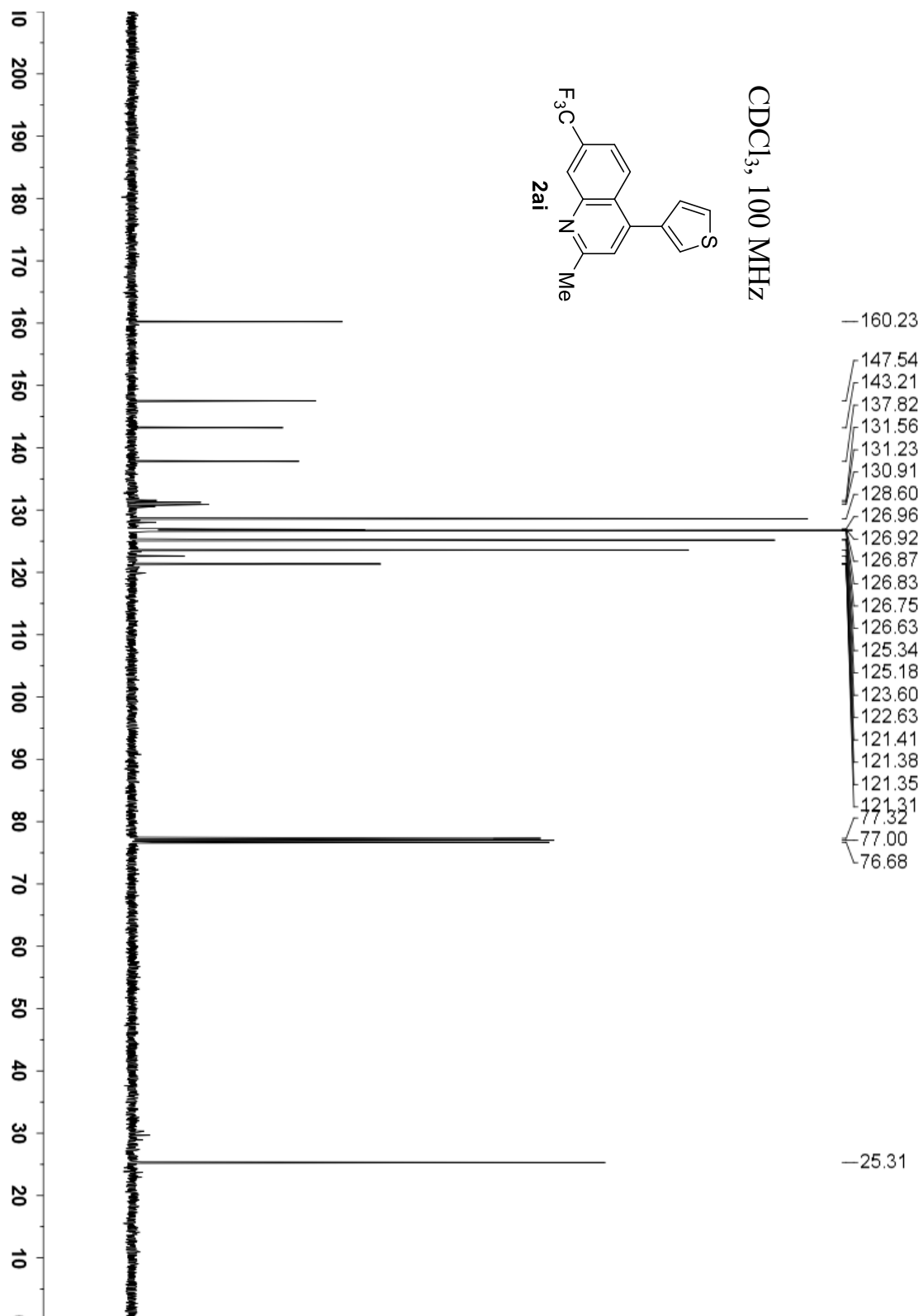






8.38
8.14
8.12
7.63
7.63
7.61
7.61
7.54
7.54
7.53
7.52
7.52
7.52
7.51
7.51
7.38
7.32
7.32
7.31
7.31
7.26





CDCl₃, 365 MHz

