Direct Formation of Oxocarbenium Ions under Weakly Acidic Conditions: Catalytic Enantioselective Oxa-Pictet–Spengler Reactions

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Supporting Information

Table of Contents

I. General information ... S2

II. Reaction optimization ... S3

Evaluation of other anion binding catalysts ... S3

Evaluation of other amine salts ... S5

III. Mechanistic studies ... S6

Evaluation of pyridinium salts with different p*K*a values ... S6

Nonlinear effects study ... S6

IV. Synthesis of catalysts ... S7

V. Preparation and characterization data of products ... S11

VI. HPLC profiles of products ... S17

VII. NMR spectra ... S33

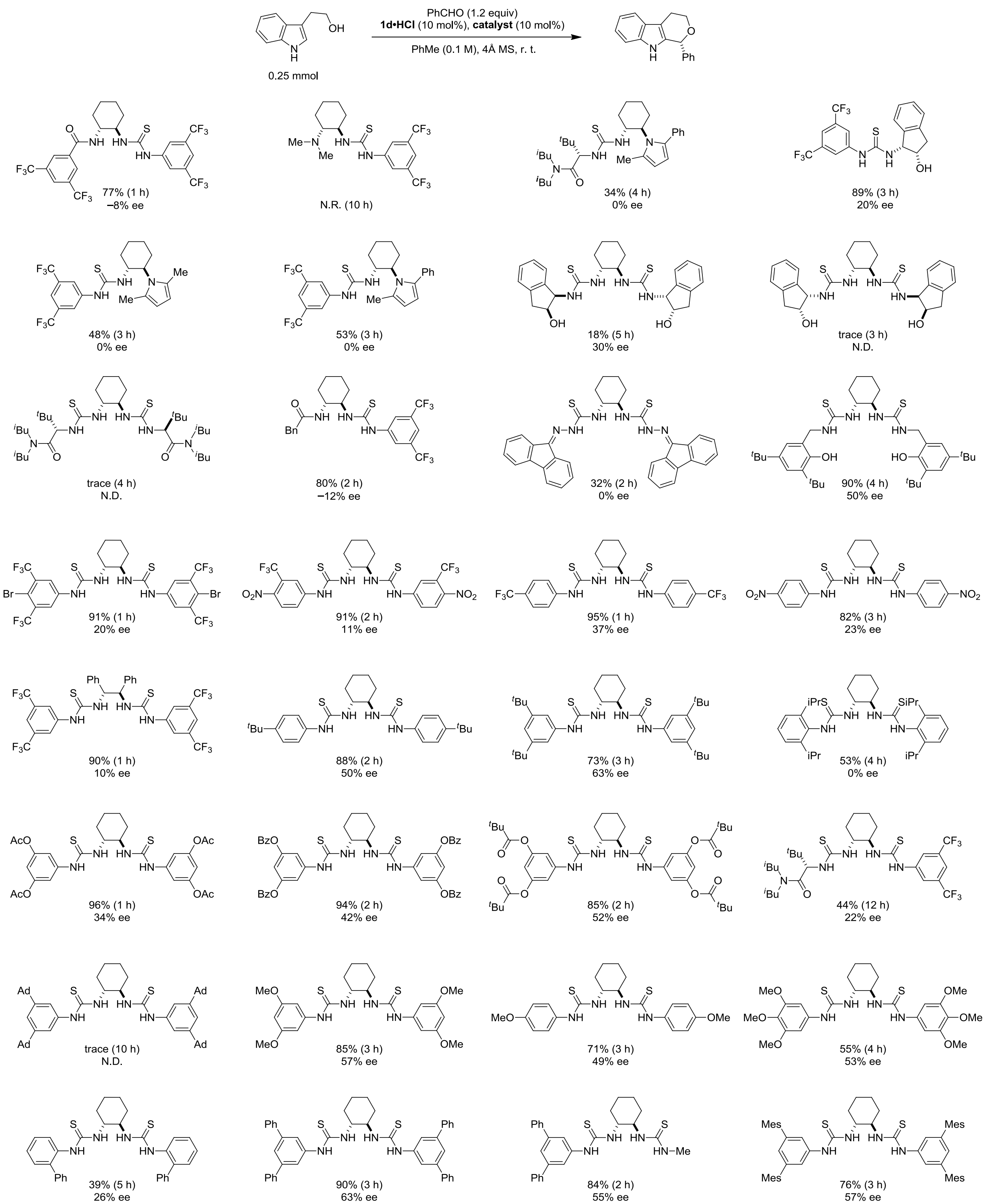
VIII. References ... S93

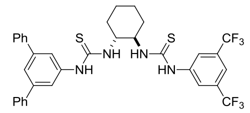
I. General information:

Reagents and solvents were purchased from commercial sources and were purified by distillation or recrystallization prior to use. Toluene was freshly distilled from sodium under nitrogen prior to use. Reactions were run under a nitrogen atmosphere. Purification of reaction products was carried out by flash column chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and potassium permanganate or Dragendorff-Munier stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm, CD_3OD at 3.31 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, m = multiplet, comp = complex; integration; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm, $(CD_3)_2SO$ at 39.52 ppm, CD_3OD at 49.00 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. HPLC analysis was carried out on an Agilent 1100 series instrument with auto sampler and multiple wavelength detectors. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P–2000 polarimeter at 589 nm and at 20 °C. Compounds **1c**,[1] **1d**,[2] **1i**,[3] **2a**,[4] **2b**,[5] **2c**,[6] **2d**,[7] **2e**[8] were prepared according to reported procedures.

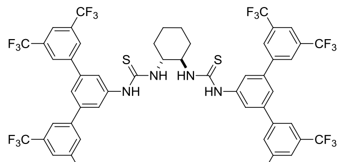
II. Reaction optimization

Evaluation of other anion binding catalysts

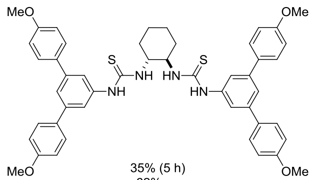




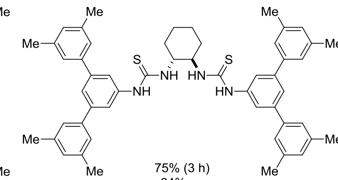
92% (1.5 h)
58% ee



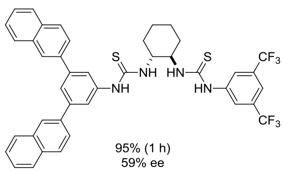
88% (1 h)
49% ee



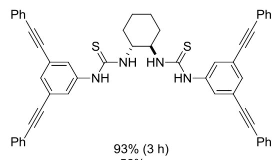
35% (5 h)
62% ee



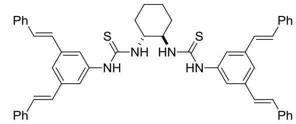
75% (3 h)
64% ee



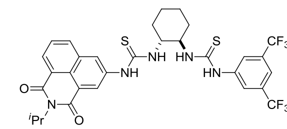
95% (1 h)
59% ee



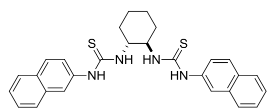
93% (3 h)
56% ee



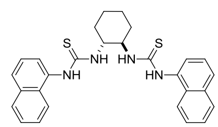
80% (2 h)
55% ee



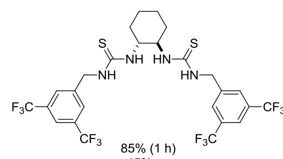
91% (3 h)
50% ee



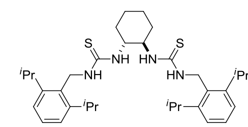
86% (2 h)
49% ee



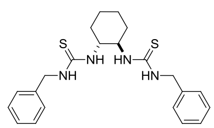
56% (3 h)
36% ee



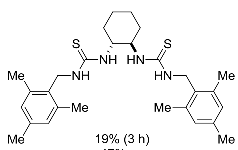
85% (1 h)
45% ee



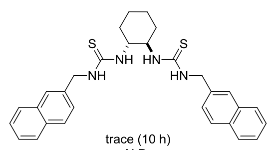
13% (3 h)
0% ee



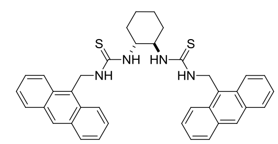
43% (4 h)
46% ee



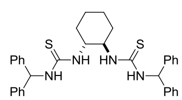
19% (3 h)
47% ee



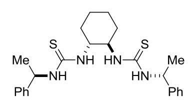
trace (10 h)
N.D.



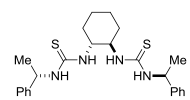
trace (10 h)
N.D.



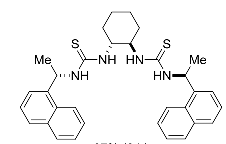
80% (2 h)
52% ee



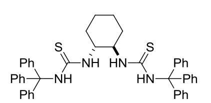
87% (2 h)
47% ee



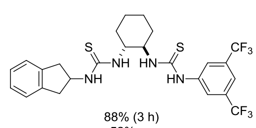
84% (2 h)
57% ee



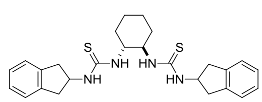
87% (2 h)
55% ee



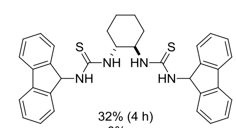
trace (4 h)
N.D.



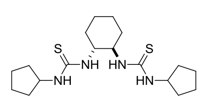
88% (3 h)
52% ee



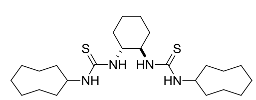
51% (24 h)
59% ee



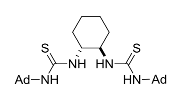
32% (4 h)
0% ee



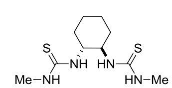
83% (4 h)
61% ee



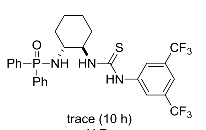
87% (4 h)
59% ee



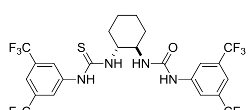
88% (4 h)
58% ee



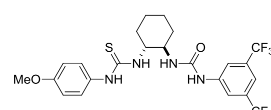
80% (2 h)
43% ee



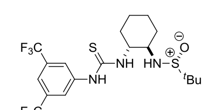
trace (10 h)
N.D.



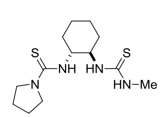
53% (4 h)
21% ee



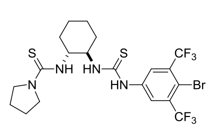
88% (3 h)
39% ee



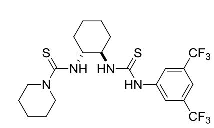
trace (10 h)
N.D.



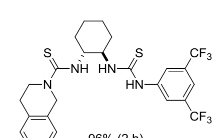
78% (4 h)
59% ee



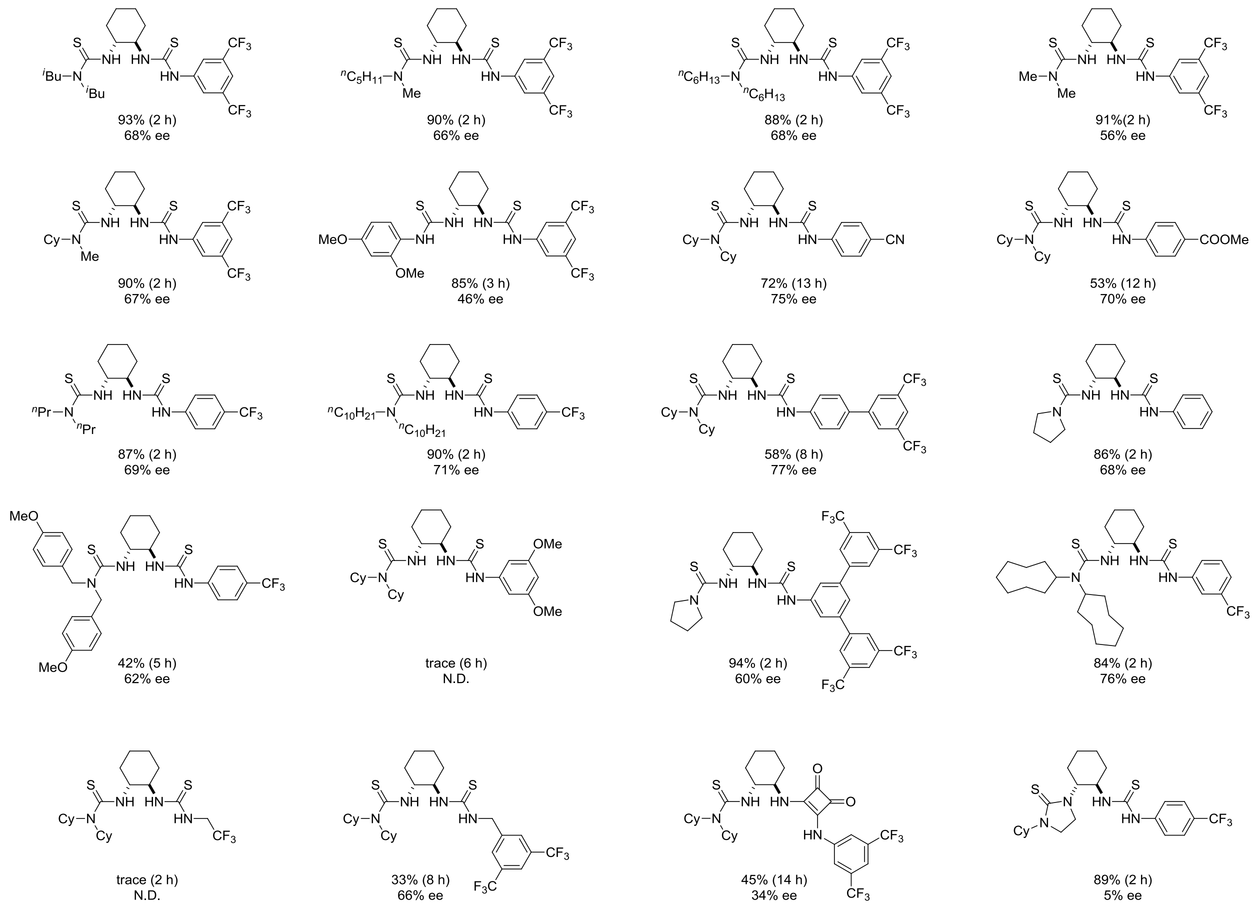
87% (2 h)
62% ee



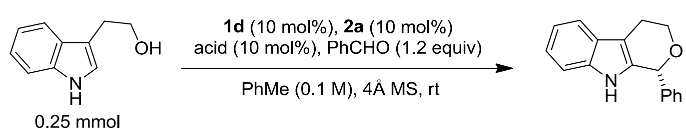
90% (2 h)
66% ee



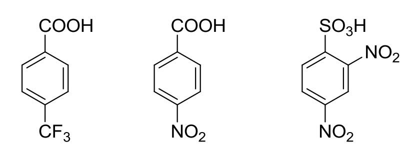
96% (2 h)
60% ee



Evaluation of other amine salts



p-TSA	$CHCl_2COOH$	CH_3SO_3H	CBr_3COOH
82% (1 h) 27% ee	6% (24 h) 36% ee	11% (16 h) 28% ee	63% (16 h) 34% ee

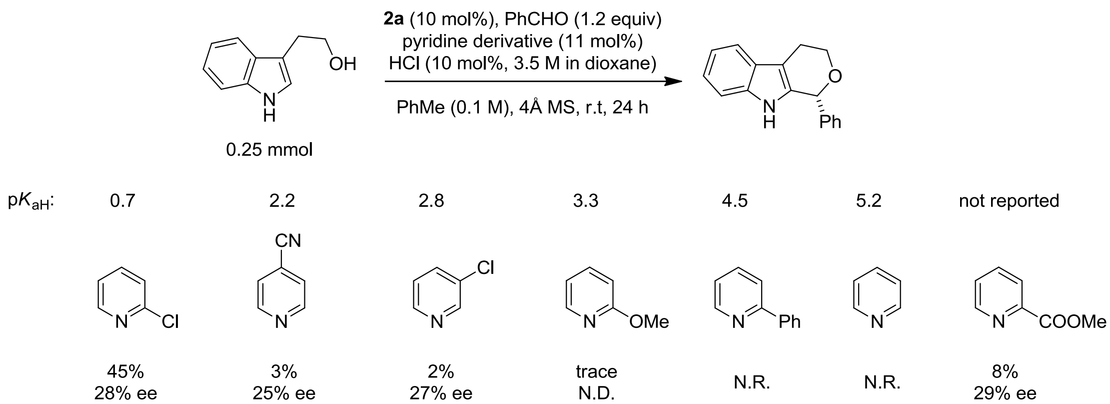


N.R. (8 h) N.R. (8 h) 96% (2 h) 30% ee

III. Mechanistic studies

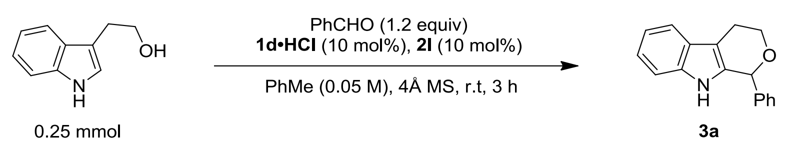
Evaluation of pyridinium salts with different pK_a values[9-12]

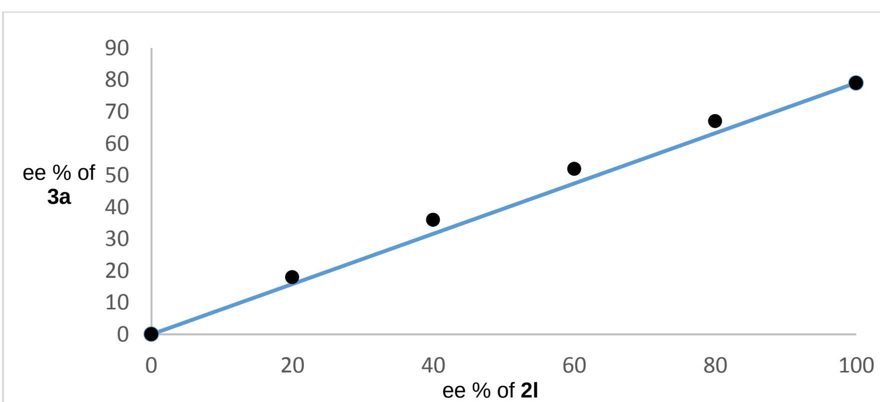
To a flame dried vial was added the pyridine derivative (0.0275 mmol, 11 mol %), thiourea catalyst **2a** (16 mg, 0.025 mmol, 10 mol %), tryptophol (40 mg, 0.25 mmol, 1 equiv), 4Å MS (100 mg) and dry toluene (2.5 mL, 0.1 M). The resulting mixture was stirred under nitrogen and HCl (10 mol%, 3.5 M in dioxane) was added followed by benzaldehyde (30 μL, 0.3 mmol, 1.2 equiv). The reaction was stirred for 24 hours before being quenched with triethylamine (40 μL). The resulting mixture was directly purified by flash chromatography on silica gel topped with Celite.



Nonlinear effects study

Following general procedure **C** for the enantioselective oxa-Pictet–Spengler reaction (see below), the reaction was set up using catalyst **2l** with 0%, 20%, 40%, 60%, 80%, > 99% ee at room temperature.



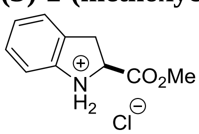


IV. Synthesis of catalysts

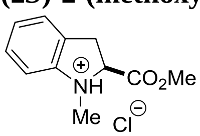
General procedure A for the synthesis of amine salts

To a solution of the corresponding amine (5.33 mmol, 1 equiv) in diethyl ether (10.7 mL, 0.5 M) was added HCl (4 M in dioxane, 1.33 mL, 5.33 mmol, 1 equiv) and the resulting mixture was stirred vigorously for 10 min. After filtration, the solid was washed with cold (~ 0 °C) diethyl ether (3×5 mL) and dried under vacuum to afford the amine salt.

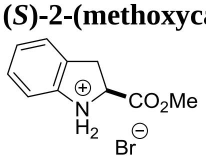
(*S*)-2-(methoxycarbonyl)indolin-1-ium chloride (1d·HCl): Following general procedure **A**, **1d·HCl** was obtained as a white solid in 95% yield; mp = 161–163 ºC; $[\alpha]_D^{20}$ –73.2 (c 0.5, $CHCl_3$); IR (KBr) 3119, 3054, 2957, 2359, 1741, 1506, 1391, 1236, 1143, 1021, 860, 758, 420 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.61 (br s, 3H, contains water), 7.28 (app d, *J* = 7.4 Hz, 1H), 7.22 (app td, *J* = 7.8, 1.2 Hz, 1H), 7.17–7.05 (comp, 2H), 4.78 (dd, *J* = 9.8, 6.9 Hz, 1H), 3.73 (s, 3H), 3.44 (dd, *J* = 16.2, 9.8 Hz, 1H), 3.28 (dd, *J* = 16.2, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 170.56, 141.63, 131.11, 127.96, 125.25, 125.02, 115.68, 58.98, 52.78, 32.73; *m/z* (ESI-MS) 178.1 $[M – Cl]^+$.



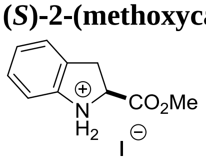
(2*S*)-2-(methoxycarbonyl)-1-methylindolin-1-ium chloride (1i·HCl): Following general procedure **A**, **1i·HCl** was obtained as a white solid in 70% yield; mp = 101–103 ºC; $[\alpha]_D^{20}$ –58.3 (c 0.5, MeOH); IR (KBr) 3400, 2904, 1738, 1486, 1428, 1368, 1343, 1251, 1128, 995, 825, 803, 763, 605, 513, 428 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.83 (br s, 2H, contains water), 7.07–6.93 (comp, 2H), 6.60 (app td, *J* = 7.4, 1.0 Hz, 1H), 6.49 (app d, *J* = 7.8 Hz, 1H), 4.14 (dd, *J* = 10.1, 8.4 Hz, 1H), 3.69 (s, 3H), 3.30 (dd, *J* = 16.0, 10.2 Hz, 1H), 2.98 (dd, *J* = 15.9, 8.4 Hz, 1H), 2.75 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 172.52, 151.98, 127.57, 126.89, 123.89, 117.67, 106.67, 66.72, 51.90, 34.39, 32.75; *m/z* (ESI-MS) 192.1 $[M – Cl]^+$.



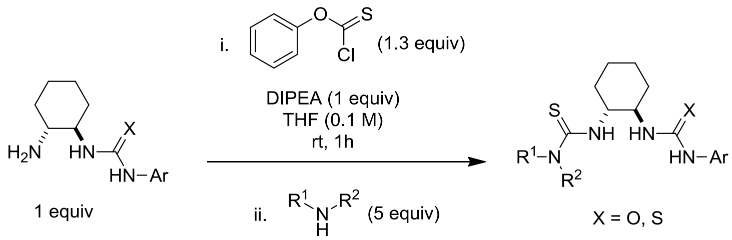
(*S*)-2-(methoxycarbonyl)indolin-1-ium bromide (1d·HBr): Following general procedure **A**, except for using HBr (48% in water), **1d·HBr** was obtained as a white solid in 77% yield; mp = 172–174 ºC; $[\alpha]_D^{20}$ –50.7 (c 0.5, MeOH); IR (KBr) 3092, 3054, 2997, 2954, 2587, 2514, 1738, 1503, 1378, 1348, 1231, 1020, 860, 753 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) 7.54–7.49 (comp, 3H), 7.49–7.44 (m, 1H), 5.13 (dd, *J* = 9.5, 7.3 Hz, 1H), 3.91 (s, 3H), 3.73 (dd, *J* = 16.5, 9.5 Hz, 1H), 3.54 (dd, *J* = 16.3, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.91, 136.81, 134.85, 131.27, 130.04, 127.32, 120.19, 61.28, 54.18, 33.93; *m/z* (ESI-MS) 178.2 $[M – Br]^+$.



(*S*)-2-(methoxycarbonyl)indolin-1-ium iodide (1d·HI): Following general procedure **A**, except for using HI (57% in water), **1d·HI** was obtained as a yellow solid in 87% yield; mp = 145–147 ºC; $[\alpha]_D^{20}$ –39.8 (c 0.5, MeOH); IR (KBr) 3417, 3379, 2942, 2914, 2464, 1756, 1428, 1351, 1283, 1246, 1208, 1161, 1001, 763 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 7.14 (app d, *J* = 7.2 Hz, 1H), 7.07 (app td, *J* = 7.8, 1.1 Hz, 1H), 6.86–6.78 (comp, 2H), 6.50 (br s, 4H, contains water), 4.60 (dd, *J* = 10.2, 6.4 Hz, 1H), 3.70 (s, 3H), 3.37 (dd, *J* = 16.2, 10.2 Hz, 1H), 3.17 (dd, *J* = 16.2, 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 172.51, 146.54, 128.44, 127.62, 124.66, 121.03, 111.73, 59.18, 52.34, 32.99; *m/z* (ESI-MS) 178.4 $[M – I]^+$.

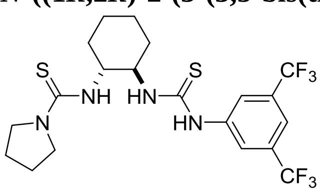


General procedure B for the synthesis of thiourea catalysts

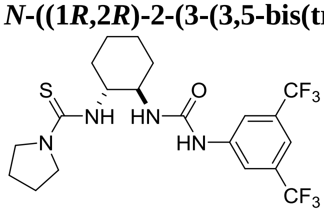


To a solution of amino(thio)urea[13,14] (0.39 mmol, 1 equiv) in dry THF (3.9 mL, 0.1 M) was added *o*-phenyl chlorothionoformate (70 µL, 0.51 mmol, 1.3 equiv) and *N*,*N*-diisopropylethylamine (68 µL, 0.39 mmol, 1 equiv). The resulting solution was stirred at room temperature for 1 h, followed by addition of the amine (1.95 mmol, 5 equiv). The resulting mixture was stirred at room temperature for the indicated time. Subsequently, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and filtered. The resulting solution was then concentrated under reduced pressure and purified by flash chromatography on silica gel.

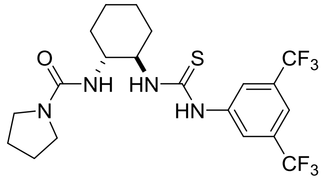
***N*-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)pyrrolidine-1-carbothioamide (2f):** Following general procedure **B**, the reaction was stirred at room temperature for 2 hours and **2f** was isolated as a white solid in 88% yield; mp = 171–173 ºC; R_f = 0.30 (Hexanes/EtOAc 70:30 v/v); $[\alpha]_D^{20}$ +68.2 (c 0.5, $CHCl_3$); IR (KBr) 3246, 3048, 2938, 2861, 1545, 1385, 1277, 1178, 1132, 971, 885, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.37 (d, *J* = 8.3 Hz, 1H), 8.25 (s, 2H), 7.57 (s, 1H), 7.09 (d, *J* = 5.9 Hz, 1H), 4.73–4.60 (m, 1H), 4.07–3.82 (comp, 2H), 3.65–3.42 (comp, 2H), 3.42–3.25 (m, 1H), 2.72–2.58 (m, 1H), 2.28–2.16 (m, 1H), 2.13–1.72 (comp, 6H), 1.73–1.61 (m, 1H), 1.51–1.37 (m, 1H), 1.37–1.17 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.42, 175.90, 140.77, 131.79 (q, $J_{C\text{-}F}$ = 33.5 Hz), 123.23 (q, $J_{C\text{-}F}$ = 272.8 Hz), 122.25, 117.62, 62.38, 56.43, 52.58, 48.57, 32.77, 32.74, 26.03, 25.07, 24.77, 24.54; *m/z* (ESI-MS) 497.1 $[M – H]^–$.



***N*-((1*R*,2*R*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)cyclohexyl)pyrrolidine-1-carbothioamide (2g):** Following general procedure **B**, the reaction was stirred at room temperature for 2 hours and **2g** was isolated as a white solid in 66% yield; mp > 200 ºC; R_f = 0.28 (Hexanes/EtOAc 70:30 v/v); $[\alpha]_D^{20}$ +31.9 (c 0.5, $CHCl_3$); IR (KBr) 3349, 3307, 3282, 3207, 3087, 2938, 1697, 1571, 1474, 1391, 1275, 1186, 1130, 1023, 895, 870, 703, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.00 (s, 2H), 7.41 (s, 1H), 6.95 (d, *J* = 5.5 Hz, 1H), 6.90 (d, *J* = 7.3 Hz, 1H), 4.14–3.92 (m, 1H), 3.91–3.71 (comp, 2H), 3.66–3.50 (m, 1H), 3.49–3.28 (comp, 2H), 2.69–2.58 (m, 1H), 2.21–2.14 (m, 1H), 2.14–1.96 (m, 1H), 1.95–1.75 (comp, 5H), 1.64–1.52 (m, 1H), 1.47–1.37 (m, 1H), 1.37–1.24 (m, 1H), 1.23–1.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.22, 156.72, 141.52, 132.25 (q, $J_{C\text{-}F}$ = 33.2 Hz), 123.39 (q, $J_{C\text{-}F}$ = 272.7 Hz), 117.48, 115.03, 62.88, 53.01, 52.36, 47.42, 32.74, 32.63, 25.77, 25.31, 24.79, 24.58; *m/z* (ESI-MS) 481.2 $[M – H]^–$.

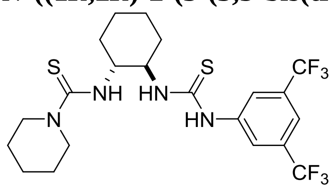


N-((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)pyrrolidine-1-carboxamide



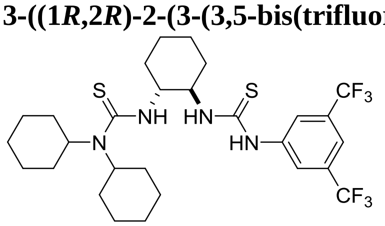
(2h): Following general procedure **B**, except for using phenyl chloroformate, the reaction was stirred at room temperature for 2 days and **2h** was isolated as a white solid in 44% yield; mp = 188–190 ºC; R_f = 0.18 (Hexanes/EtOAc 40:60 v/v); $[\alpha]_D^{20}$ +41.7 (c 0.5, $CHCl_3$); IR (KBr) 3300, 3097, 2938, 2859, 1618, 1535, 1474, 1396, 1278, 1181, 1131, 968, 880, 678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.21 (d, J = 9.1 Hz, 1H), 7.97 (s, 2H), 7.56 (s, 1H), 5.00 (d, J = 8.8 Hz, 1H), 4.69–4.54 (m, 1H), 3.68–3.58 (m, 1H), 3.46–3.30 (comp, 2H), 3.21–3.02 (comp, 2H), 2.28–2.18 (m, 1H), 2.14–2.05 (m, 1H), 1.98–1.67 (comp, 6H), 1.55–1.28 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.08, 157.40, 141.11, 131.53 (q, J_{C-F} = 33.4 Hz), 124.27, 123.26 (q, J_{C-F} = 271.3 Hz), 117.87, 57.39, 56.25, 46.33, 33.77, 32.65, 25.34, 24.94; *m/z* (ESI-MS) 481.2 $[M – H]^-$.

N-((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)piperidine-1-carbothioamide



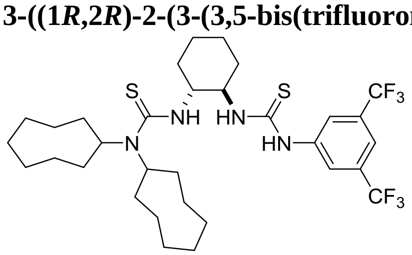
(2i): Following general procedure **B**, the reaction was stirred at room temperature for 5 hours and **2i** was isolated as a white solid in 69% yield; mp = 96–98 ºC; R_f = 0.21 (Hexanes/EtOAc 80:20 v/v); $[\alpha]_D^{20}$ +93.1 (c 0.5, $CHCl_3$); IR (KBr) 3266, 3042, 2939, 2859, 1541, 1474, 1385, 1333, 1277, 1178, 1132, 968, 885, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.18 (s, 2H), 7.57 (s, 1H), 7.33 (d, J = 5.8 Hz, 1H), 4.71–4.59 (m, 1H), 4.18–4.06 (m, 1H), 3.94–3.78 (comp, 2H), 3.78–3.66 (comp, 2H), 2.69–2.57 (m, 1H), 2.27–2.17 (m, 1H), 1.97–1.79 (comp, 2H), 1.76–1.38 (comp, 8H), 1.38–1.18 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.49, 177.86, 140.65, 131.82 (q, J_{C-F} = 33.5 Hz), 123.22 (q, J_{C-F} = 272.9 Hz), 122.53, 117.81, 62.76, 56.63, 49.61, 32.63, 32.51, 25.54, 25.07, 24.76, 24.17; *m/z* (ESI-MS) 511.1 $[M – H]^-$.

3-((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-1,1-dicyclohexylthiourea (2j):



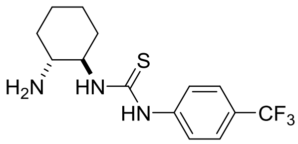
Following general procedure **B**, the reaction was stirred at room temperature for 24 hours and **2j** was isolated as a white solid in 66% yield; mp = 98–100 ºC; R_f = 0.36 (Hexanes/EtOAc 90:10 v/v); $[\alpha]_D^{20}$ –27.1 (c 0.5, $CHCl_3$); IR (KBr) 3442, 3247, 2935, 2857, 1534, 1473, 1383, 1323, 1278, 1178, 1135, 968, 885, 675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40–8.17 (comp, 2H), 7.91 (s, 2H), 7.60 (s, 1H), 5.61 (d, J = 8.4 Hz, 1H), 4.72–4.58 (m, 1H), 4.49–3.94 (comp, 3H), 2.43–2.28 (m, 1H), 2.25–2.13 (m, 1H), 1.95–1.46 (comp, 16H), 1.46–1.15 (comp, 8H), 1.12–1.00 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.72, 180.50, 140.24, 132.05 (q, J_{C-F} = 36.6 Hz), 123.58, 123.18 (q, J_{C-F} = 272.7 Hz), 118.33, 61.17, 59.75, 57.86, 32.76, 32.05, 31.55, 30.94, 26.16, 25.50, 25.05, 24.48; *m/z* (ESI-MS) 607.1 $[M – H]^-$.

3-((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-1,1-dicyclooctylthiourea (2k):

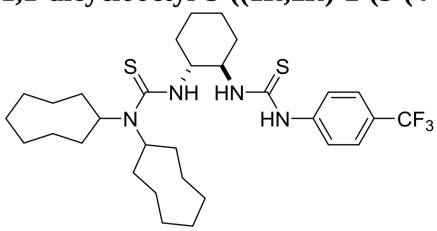


Following general procedure **B** (using 2.5 equivalents of dicyclooctylamine[15]), the reaction was stirred at room temperature for 2 days to afford **2k** as a white solid in 61% yield; mp = 105–108 ºC; R_f = 0.33 (Hexanes/EtOAc 85:15 v/v); $[\alpha]_D^{20}$ –31.4 (c 0.5, $CHCl_3$); IR (KBr) 3437, 3247, 2926, 2855, 1534, 1473, 1384, 1323, 1277, 1178, 1135, 973, 880, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.18 (s, 1H), 7.93 (s, 2H), 7.58 (s, 1H), 5.61 (s, 1H), 5.20–5.06 (m, 1H), 4.70–4.56 (m, 1H), 4.33–4.19 (m, 1H), 3.66–3.50 (m, 1H), 2.44–2.28 (m, 1H), 2.16–2.07 (m, 1H), 2.05–1.05 (comp, 34H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.38, 178.22, 140.41, 131.99 (q, J_{C-F} = 33.4 Hz), 123.33, 123.20 (q, J_{C-F} = 272.9 Hz), 118.09, 62.07, 61.65, 57.59, 56.82, 34.42, 33.79, 32.83, 32.69, 32.28, 32.02, 26.48, 26.23, 26.04, 25.05, 24.80, 24.45; *m/z* (ESI-MS) 663.2 $[M – H]^-$.

1-((1*R*,2*R*)-2-thioureidocyclohexyl)-3-(4-(trifluoromethyl)phenyl)thiourea: Following a procedure for a closely related product,[16] (1*R*,2*R*)-cyclohexane-1,2-diamine (2.24 g, 19.6 mmol, 1.5 equiv), dissolved in a minimum amount of CH_2Cl_2 (ca. 1 mL), was cooled to 0 ºC. 1-Isothiocyanato-4-(trifluoromethyl)benzene (2.66 g, 13.1 mmol, 1 equiv), dissolved in 262 mL CH_2Cl_2, was added dropwise over 1 hour. The resulting mixture was allowed to warm to room temperature and concentrated under reduced pressure. Purification by flash chromatography on silica gel afforded the desired product as a white solid in 87% yield; mp = 144–146 ºC; R_f = 0.10 ($MeOH/CH_2Cl_2/Et_3N$ 10:89:1 v/v/v); $[\alpha]_D^{20}$ +125.5 (c 0.5, $CHCl_3$); IR (KBr) 3259, 2937, 2854, 1613, 1523, 1341, 1161, 1111, 1068, 1008, 825, 708 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 7.79 (app d, J = 8.2 Hz, 2H), 7.60 (app d, J = 8.4 Hz, 2H), 4.08–3.75 (m, 1H), 2.62–2.52 (m, 1H), 2.23–1.99 (m, 1H), 1.92–1.78 (m, 1H), 1.73–1.50 (comp, 2H), 1.34–0.98 (comp, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 180.31, 143.76, 125.36, 124.46 (q, J_{C-F} = 271.3 Hz), 123.25 (q, J_{C-F} = 31.9 Hz), 121.57, 60.08, 54.02, 35.05, 31.05, 24.62.; *m/z* (ESI-MS) 318.1 $[M + H]^-$.



1,1-dicyclooctyl-3-((1*R*,2*R*)-2-(3-(4-(trifluoromethyl)phenyl)thioureido)cyclohexyl)thiourea (2l): Following general procedure **B** (using 2.5 equivalents of dicyclooctylamine[15]), the reaction was stirred at 50 ºC for 24 hours to afford **2l** as a white solid in 65% yield; mp = 110–112 ºC; R_f = 0.31 (Hexanes/EtOAc 85:15 v/v); $[\alpha]_D^{20}$ –25.1 (c 0.5, $CHCl_3$); IR (KBr) 3432, 3222, 2924, 2847, 1614, 1522, 1441, 1324, 1124, 1067, 1011, 948, 828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.71 (s, 1H), 7.59 (app d, *J* = 8.3 Hz, 2H), 7.44 (app d, *J* = 8.3 Hz, 2H), 5.65 (s, 1H), 5.18–5.05 (m, 1H), 4.81–4.68 (m, 1H), 4.35–4.22 (m, 1H), 3.67–3.50 (m, 1H), 2.44–2.31 (m, 1H), 2.15–2.06 (m, 1H), 2.05–1.23 (m, 34H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.85, 178.51, 140.74, 127.17 (q, J_{C-F} = 33.3 Hz), 126.56, 124.06 (q, J_{C-F} = 270 Hz), 123.36, 61.71, 61.48, 57.33, 56.60, 34.33, 33.82, 32.94, 32.66, 32.36, 32.07, 26.59, 26.27, 25.05, 24.90, 24.52; *m/z* (ESI-MS) 595.3 $[M – H]^-$.

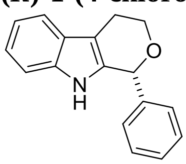


V Preparation and characterization data of products:

General procedure C for the enantioselective oxa-Pictet–Spengler reaction

To a flame dried vial was added amine salt **1d·HCl** (5.3 mg, 0.025 mmol, 10 mol %), thiourea catalyst **2l** (15 mg, 0.025 mmol, 10 mol %), tryptophol (40 mg, 0.25 mmol, 1 equiv), 4Å MS (100 mg) and dry toluene (5 mL, 0.05 M). The resulting mixture was stirred under nitrogen and cooled to –30 ºC over 15 minutes. Aldehyde (0.3 mmol, 1.2 equiv) was then added and the reaction was stirred for the indicated time before being quenched with triethylamine (40 μL). The resulting mixture was directly purified by flash chromatography on silica gel topped with Celite.

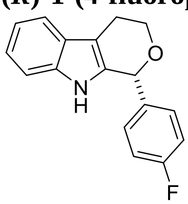
(*R*)-1-(4-chlorophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3a): Following general procedure **C**,



the reaction was run for 2 days and **3a** was obtained as a white solid in 90% yield; mp = 153–155 ºC; R_f = 0.32 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –15.7 (c 0.5, $CHCl_3$, 91% ee); IR (KBr) 3397, 3032, 2909, 2837, 1446, 1311, 1273, 1251, 1136, 1083, 1048, 978, 738, 693, 470 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (app dd, *J* = 7.0, 2.1 Hz, 1H), 7.46 (br s, 1H), 7.42–7.36 (comp, 5H), 7.25–7.19 (m, 1H), 7.19–7.11 (comp, 2H), 5.80 (app t, *J* = 1.9 Hz, 1H), 4.34 (ddd, *J* = 11.2, 5.4, 2.9 Hz, 1H), 4.00 (ddd, *J* = 11.3, 9.6, 4.0 Hz, 1H), 3.12 (dddd, *J* = 15.2, 9.7, 5.4, 2.1 Hz, 1H), 2.84 (dddd, *J* = 15.4, 4.1, 3.0, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.59, 136.16, 133.74, 129.06, 128.94, 128.57, 127.14, 122.08, 119.78, 118.47, 111.13, 108.91, 76.28, 65.00, 22.44; *m/z* (ESI-MS) 250.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 14.7 min (minor) and t_R = 19.6 min (major).

The absolute configuration was assigned by analogy.

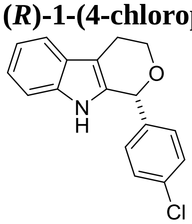
(*R*)-1-(4-fluorophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3b): Following general procedure **C**,



the reaction was run for 2 days and **3b** was obtained as a white solid in 82% yield; mp = 116–118 ºC; R_f = 0.21 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –8.1 (c 0.5, $CHCl_3$, 90% ee); IR (KBr) 3389, 3292, 3047, 2957, 2914, 2847, 1713, 1606, 1509, 1446, 1224, 1153, 1071, 1043, 830, 743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 1H), 7.44 (br s, 1H), 7.38–7.32 (comp, 2H), 7.27–7.23 (m, 1H), 7.21–7.12 (comp, 2H), 7.11–7.04 (comp, 2H), 5.78 (t, *J* = 1.9 Hz, 1H), 4.31 (ddd, *J* = 11.3, 5.4, 3.0 Hz, 1H), 3.99 (ddd, *J* = 11.3, 9.6, 4.0 Hz, 1H), 3.10 (dddd, *J* = 15.2, 9.6, 5.4, 2.1 Hz, 1H), 2.84 (dddd, *J* = 15.4, 4.0, 3.0, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.03 (d, $J_{C\text{-}F}$ = 247.7 Hz), 136.05, 135.37 (d, $J_{C\text{-}F}$ = 3.2 Hz), 133.28, 130.28 (d, $J_{C\text{-}F}$ = 8.3 Hz), 126.96, 122.11, 119.76, 118.39, 115.71 (d, $J_{C\text{-}F}$ = 21.6 Hz), 111.01, 109.01, 75.37, 64.82, 22.26; *m/z* (ESI-MS) 268.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 15.7 min (major) and t_R = 18.2 min (minor).

The absolute configuration was assigned by analogy.

(*R*)-1-(4-chlorophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3c): Following general procedure **C**,

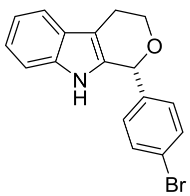


the reaction was run for 2 days and **3c** was obtained as a white solid in 91% yield; mp = 101–103 ºC; R_f = 0.28 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –9.3 (c 0.5, $CHCl_3$, 94% ee); IR (KBr) 3393, 3307, 3052, 2919, 2834, 1713, 1611, 1490, 1451, 1246, 1087, 1015, 815, 743, 510 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (app dd, *J* = 7.6, 1.2 Hz, 1H), 7.45 (br s, 1H), 7.38–7.34 (comp, 2H), 7.33–7.29 (comp, 2H), 7.26–7.22 (m, 1H), 7.20–7.13 (comp, 2H), 5.76 (app t, *J* = 1.9 Hz, 1H), 4.30 (ddd, *J* = 11.3, 5.4, 3.1 Hz, 1H), 3.98 (ddd, *J* = 11.4, 9.5, 4.1 Hz, 1H), 3.09 (dddd, *J* = 15.0, 9.5, 5.3, 2.0 Hz, 1H), 2.90–2.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.14, 136.20, 134.91, 133.14, 129.93, 129.11, 127.06, 122.29, 119.92, 118.54, 111.16, 109.13, 75.47, 64.90, 22.37; *m/z* (ESI-MS) 284.2 $[M + H]^+$; HPLC: Daicel Chiralpak

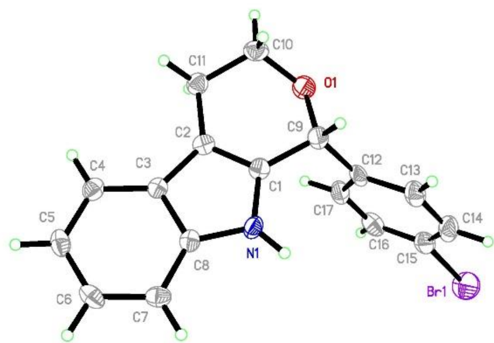
AS-H, *n*-hexane/*i*-PrOH = 93/7, Flow rate = 0.2 mL/min, UV = 280.16 nm, t_R = 66.4 min (minor) and t_R = 69.8 min (major).

The absolute configuration was assigned by analogy.

(*R*)-1-(4-bromophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3d): Following general procedure **C**, the reaction was run for 2 days and **3d** was obtained as a white solid in 91% yield; mp = 116–118 ºC; R_f = 0.25 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –7.2 (c 0.5, $CHCl_3$, 93% ee); IR (KBr) 3394, 3312, 3062, 2962, 2914, 2852, 2369, 2341, 1716, 1506, 1481, 1451, 1253, 1073, 1043, 1011, 810, 735, 508 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 1H), 7.53–7.49 (comp, 2H), 7.44 (br s, 1H), 7.26–7.23 (comp, 3H), 7.20–7.12 (comp, 2H), 5.75 (app t, *J* = 1.9 Hz, 1H), 4.30 (ddd, *J* = 11.3, 5.4, 3.0 Hz, 1H), 3.98 (ddd, *J* = 11.3, 9.5, 4.1 Hz, 1H), 3.09 (dddd, *J* = 15.4, 9.5, 5.4, 2.0 Hz, 1H), 2.84 (dddd, *J* = 15.5, 4.1, 3.1, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.65, 136.20, 133.07, 132.08, 130.23, 127.05, 123.11, 122.31, 119.92, 118.55, 111.16, 109.13, 75.53, 64.91, 22.37; *m/z* (ESI-MS) 328.3 (^{79}Br) $[M + H]^+$, 330.3 (^{81}Br) $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 0.2 mL/min, UV = 280.16 nm, t_R = 55.0 min (minor) and t_R = 59.5 min (major).

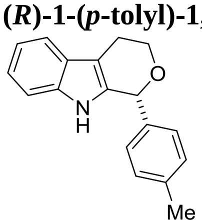


The absolute configuration of **3d** was assigned by X-ray crystallography:



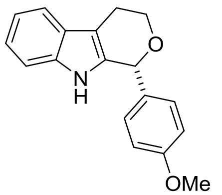
Compound **3d** was crystallized from MeOH through slow evaporation at room temperature. The requisite CIF has been submitted to the journal.

(*R*)-1-(*p*-tolyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3e): Following general procedure **C**, the reaction was run for 2 days and **3e** was obtained as a white solid in 90% yield; mp = 179–180 ºC; R_f = 0.24 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –2.4 (c 0.5, $CHCl_3$, 95% ee); IR (KBr) 3394, 2947, 2909, 2859, 2819, 1446, 1298, 1081, 1041, 808, 740, 455 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (app d, *J* = 6.5 Hz, 1H), 7.49 (br s, 1H), 7.33–7.24 (comp, 2H), 7.24–7.19 (comp, 3H), 7.19–7.13 (comp, 2H), 5.76 (s, 1H), 4.32 (ddd, *J* = 11.4, 5.5, 3.2 Hz, 1H), 3.99 (ddd, *J* = 11.3, 9.6, 4.1 Hz, 1H), 3.16–3.06 (m, 1H), 2.89–2.81 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.86, 136.61, 136.11, 133.90, 129.53, 128.55, 127.13, 121.96, 119.69, 118.40, 111.10, 108.82, 75.98, 64.78, 22.42, 21.35; *m/z* (ESI-MS) 264.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 11.9 min (minor) and t_R = 18.3 min (major).



The absolute configuration was assigned by analogy.

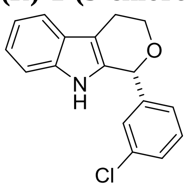
(*R*)-1-(4-methoxyphenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3f): Following general procedure **C**,



the reaction was run for 3 days and **3f** was obtained as a white solid in 84% yield; mp = 115–117 ºC; R_f = 0.26 (Hexanes/EtOAc 80:20 v/v); $[\alpha]^D_{20}$ +0.6 (c 0.5, $CHCl_3$, 84% ee); IR (KBr) 3392, 2949, 2907, 2837, 1611, 1448, 1301, 1243, 1173, 1078, 1033, 968, 830, 735, 465, 508, 473 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.54 (m, 1H), 7.46 (br s, 1H), 7.32–7.27 (comp, 2H), 7.25–7.22 (m, 1H), 7.19–7.11 (comp, 2H), 6.92–6.88 (comp, 2H), 5.76 (app t, *J* = 1.9 Hz, 1H), 4.31 (ddd, *J* = 11.2, 5.3, 3.1 Hz, 1H), 3.98 (ddd, *J* = 11.2, 9.4, 4.1 Hz, 1H), 3.82 (s, 3H), 3.09 (dddd, *J* = 15.0, 9.5, 5.4, 2.1 Hz, 1H), 2.842 (dddd, *J* = 15.4, 4.0, 3.1, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.17, 136.11, 133.98, 131.75, 129.99, 127.14, 121.99, 119.71, 118.41, 114.22, 111.10, 108.94, 75.73, 64.79, 55.45, 22.44; *m/z* (ESI-MS) 280.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 20.8 min (minor) and t_R = 31.3 min (major).

The absolute configuration was assigned by analogy.

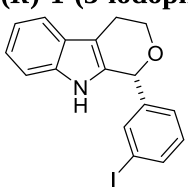
(*R*)-1-(3-chlorophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3g): Following general procedure **C**,



the reaction was run for 2 days and **3g** was obtained as a white solid in 73% yield; mp = 157–160 ºC; R_f = 0.18 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –3.6 (c 0.5, $CHCl_3$, 82% ee); IR (KBr) 3394, 3052, 2957, 2922, 2837, 1718, 1621, 1596, 1571, 1461, 1433, 1296, 1253, 1078, 1041, 855, 790, 740, 705, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (ddd, *J* = 7.4, 1.5, 0.8 Hz, 1H), 7.45 (br s, 1H), 7.39–7.34 (comp, 2H), 7.34–7.30 (m, 1H), 7.29–7.23 (comp, 2H), 7.21–7.11 (comp, 2H), 5.77 (app t, *J* = 2.0 Hz, 1H), 4.32 (ddd, *J* = 11.3, 5.4, 3.0 Hz, 1H), 3.99 (ddd, *J* = 11.3, 9.5, 4.1 Hz, 1H), 3.10 (dddd, *J* = 15.1, 9.5, 5.4, 2.0 Hz, 1H), 2.89–2.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.75, 136.29, 134.95, 132.94, 130.22, 129.23, 128.59, 127.10, 126.62, 122.36, 119.96, 118.58, 111.21, 109.19, 75.61, 65.00, 22.38; *m/z* (ESI-MS) 284.1 $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 8.3 min (minor) and t_R = 10.6 min (major).

The absolute configuration was assigned by analogy.

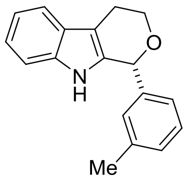
(*R*)-1-(3-iodophenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3h): Following general procedure **C**, the



reaction was run for 3 days and **3h** was obtained as a white solid in 78% yield; mp = 158–160 ºC; R_f = 0.17 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ +3.1 (c 0.5, $CHCl_3$, 85% ee); IR (KBr) 3399, 2957, 2914, 2864, 2822, 1568, 1468, 1296, 1076, 1056, 800, 745, 675, 465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78–7.67 (comp, 2H), 7.58 (app d, *J* = 7.2 Hz, 1H), 7.48 (br s, 1H), 7.34 (app d, *J* = 7.8 Hz, 1H), 7.25 (app d, *J* = 8.2 Hz, 1H), 7.22–7.14 (comp, 2H), 7.12 (app t, *J* = 7.7 Hz, 1H), 5.71 (app t, *J* = 1.9 Hz, 1H), 4.31 (ddd, *J* = 11.3, 5.3, 2.9 Hz, 1H), 3.98 (ddd, *J* = 11.3, 9.6, 4.1 Hz, 1H), 3.11 (dddd, *J* = 15.2, 9.7, 5.4, 2.1 Hz, 1H), 2.89–2.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.94, 138.11, 137.32, 136.22, 132.87, 130.62, 127.77, 127.01, 122.30, 119.90, 118.54, 111.21, 109.10, 94.86, 75.46, 64.99, 22.33; *m/z* (ESI-MS) 376.0 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 14.2 min (minor) and t_R = 17.1 min (major).

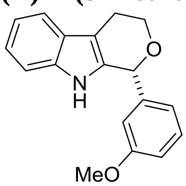
The absolute configuration was assigned by analogy.

(*R*)-1-(m-tolyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3i): Following general procedure **C**, the reaction was run for 2 days and **3i** was obtained as a white solid in 86% yield; mp = 126–128 ºC; R_f = 0.17 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –4.9 (c 0.5, $CHCl_3$, 86% ee); IR (KBr) 3399, 3024, 2962, 2917, 2832, 1611, 1466, 1443, 1368, 1291, 1276, 1138, 1076, 1043, 748, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.55 (m, 1H), 7.47 (br s, 1H), 7.32–7.27 (m, 1H), 7.27–7.22 (m, 1H), 7.22–7.12 (comp, 5H), 5.76 (app t, *J* = 2.0 Hz, 1H), 4.35 (ddd, *J* = 11.5, 5.5, 2.8 Hz, 1H), 4.05–3.93 (m, 1H), 3.19–3.05 (m, 1H), 2.84 (dddd, *J* = 15.5, 3.9, 2.7, 1.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.48, 138.76, 136.14, 133.91, 129.84, 129.10, 128.78, 127.17, 125.67, 122.02, 119.75, 118.45, 111.14, 108.79, 76.37, 65.10, 22.44, 21.51; *m/z* (ESI-MS) 264.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254.16 nm, t_R = 11.4 min (minor) and t_R = 19.7 min (major).



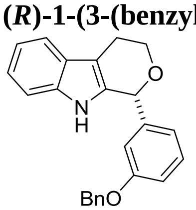
The absolute configuration was assigned by analogy.

(*R*)-1-(3-methoxyphenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3j): Following general procedure **C**, the reaction was run for 2 days and **3j** was obtained as a white solid in 82% yield; mp = 107–109 ºC; R_f = 0.14 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –2.6 (c 0.5, $CHCl_3$, 86% ee); IR (KBr) 3284, 3049, 2939, 2894, 2844, 1606, 1581, 1491, 1448, 1276, 1228, 1151, 1041, 875, 805, 763, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (app dd, *J* = 7.5, 1.5 Hz, 1H), 7.47 (br s, 1H), 7.34–7.27 (m, 1H), 7.24 (app dd, *J* = 6.9, 1.4 Hz, 1H), 7.19–7.11 (comp, 2H), 6.98 (app dt, *J* = 7.5, 1.2 Hz, 1H), 6.95–6.89 (comp, 2H), 5.77 (app t, *J* = 1.9 Hz, 1H), 4.36 (ddd, *J* = 11.3, 5.5, 2.8 Hz, 1H), 4.00 (ddd, *J* = 11.3, 9.8, 4.0 Hz, 1H), 3.78 (s, 3H), 3.12 (dddd, *J* = 15.3, 9.8, 5.5, 2.1 Hz, 1H), 2.83 (dddd, *J* = 15.4, 4.3, 2.7, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.19, 141.19, 136.20, 133.72, 129.95, 127.22, 122.09, 120.70, 119.78, 118.46, 114.78, 113.67, 111.16, 108.76, 76.27, 65.12, 55.44, 22.43; *m/z* (ESI-MS) 280.3 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 15.8 min (minor) and t_R = 30.7 min (major).



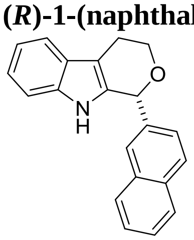
The absolute configuration was assigned by analogy.

(*R*)-1-(3-(benzyloxy)phenyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3k): Following general procedure **C**, the reaction was run for 3 days and **3k** was obtained as a white solid in 87% yield; mp = 154–156 ºC; R_f = 0.15 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –9.0 (c 0.5, $CHCl_3$, 90% ee); IR (KBr) 3439, 3059, 3032, 2959, 2917, 2857, 1586, 1491, 1446, 1256, 1153, 1071, 1038, 735, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.54 (m, 1H), 7.44–7.37 (comp, 3H), 7.37–7.33 (comp, 2H), 7.33–7.28 (comp, 2H), 7.25–7.22 (m, 1H), 7.19–7.11 (comp, 2H), 7.03–6.94 (comp, 3H), 5.77 (app t, *J* = 1.8 Hz, 1H), 5.05 (d, *J* = 11.6 Hz, 1H), 5.02 (d, *J* = 11.5 Hz, 1H), 4.34 (ddd, *J* = 11.4, 5.4, 2.8 Hz, 1H), 4.02–3.95 (m, 1H), 3.15–3.04 (m, 1H), 2.87–2.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.31, 141.19, 136.90, 136.17, 133.65, 130.04, 128.70, 128.14, 127.70, 127.19, 122.10, 120.95, 119.80, 118.48, 115.61, 114.61, 111.19, 108.78, 76.21, 70.15, 65.13, 22.43; *m/z* (ESI-MS) 356.3 $[M + H]^+$; HPLC: Daicel Chiralpak AS-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254.16 nm, t_R = 12.0 min (minor) and t_R = 15.8 min (major).



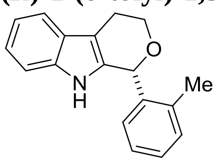
The absolute configuration was assigned by analogy.

(*R*)-1-(naphthalen-2-yl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3l): Following general procedure **C**, the reaction was run for 2 days and **3l** was obtained as a white solid in 86% yield; mp = 185–187 ºC; R_f = 0.21 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –104.6 (c 0.5, $CHCl_3$, 88% ee); IR (KBr) 3378, 3042, 2961, 2889, 2839, 1506, 1466, 1449, 1370, 1293, 1253, 1141, 1073, 1048, 863, 824, 739, 484 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90–7.81 (comp, 4H), 7.64–7.58 (m, 1H), 7.56–7.50 (comp, 2H), 7.49–7.44 (comp, 2H), 7.23–7.14 (comp, 3H), 5.94 (app t, *J* = 1.9 Hz, 1H), 4.37 (ddd, *J* = 11.3, 5.4, 3.0 Hz, 1H), 4.04 (ddd, *J* = 11.2, 9.5, 4.1 Hz, 1H), 3.16 (dddd, *J* = 15.2, 9.5, 5.4, 2.1 Hz, 1H), 2.95–2.79 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.02, 136.21, 133.73, 133.28, 128.94, 128.22, 127.89, 127.72, 127.18, 126.61, 126.50, 125.99, 122.11, 119.80, 118.50, 111.18, 108.94, 76.36, 64.95, 22.47; *m/z* (ESI-MS) 300.1 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 20.0 min (minor) and t_R = 25.0 min (major).



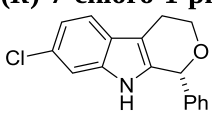
The absolute configuration was assigned by analogy.

(*R*)-1-(o-tolyl)-1,3,4,9-tetrahydropyrano[3,4-b]indole (3m): Following general procedure **C**, the reaction was run for 2 days and **3m** was obtained as a white solid in 91% yield; mp = 98–100 ºC; R_f = 0.26 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –4.5 (c 0.5, $CHCl_3$, 48% ee); IR (KBr) 3397, 3289, 3052, 2954, 2909, 2847, 1453, 1303, 1256, 1076, 1041, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60–7.54 (m, 1H), 7.47 (br s, 1H), 7.30–7.22 (comp, 3H), 7.20–7.10 (comp, 4H), 6.02 (app t, *J* = 2.1 Hz, 1H), 4.29 (ddd, *J* = 11.3, 5.2, 3.5 Hz, 1H), 3.99 (ddd, *J* = 11.4, 9.0, 4.1 Hz, 1H), 3.08 (dddd, *J* = 16.1, 9.0, 5.3, 1.9 Hz, 1H), 2.87 (app dtd, *J* = 15.4, 4.0, 1.8 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.83, 137.15, 136.09, 133.58, 131.26, 129.49, 128.95, 127.15, 126.17, 121.99, 119.77, 118.39, 111.11, 109.21, 73.98, 64.70, 22.47, 19.14; *m/z* (ESI-MS) 264.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 10.5 min (minor) and t_R = 16.6 min (major).



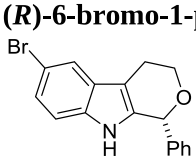
The absolute configuration was assigned by analogy.

(*R*)-7-chloro-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (3n): Following general procedure **C**, the reaction was run for 4 days and **3n** was obtained as a white solid in 89% yield; mp = 106–108 ºC; R_f = 0.18 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ +25.2 (c 0.5, $CHCl_3$, 94% ee); IR (KBr) 3414, 3279, 2964, 2917, 2837, 1451, 1301, 1241, 1146, 1051, 903, 850, 803, 755, 690 cm^{-1}; ^1H NMR (500 MHz) δ 7.45 (s, 1H), 7.44 (br s, 1H), 7.41–7.33 (comp, 5H), 7.22–7.19 (m, 1H), 7.11–7.08 (m, 1H), 5.76 (app t, *J* = 1.9 Hz, 1H), 4.32 (ddd, *J* = 11.4, 5.5, 2.9 Hz, 1H), 3.98 (ddd, *J* = 11.3, 9.8, 4.0 Hz, 1H), 3.15–3.00 (m, 1H), 2.85–2.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.27, 136.48, 134.47, 129.20, 129.03, 128.51, 127.82, 125.79, 120.46, 119.28, 111.14, 109.02, 76.14, 64.89, 22.30; *m/z* (ESI-MS) 284.2 $[M + H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254.16 nm, t_R = 9.9 min (minor) and t_R = 14.1 min (major).



The absolute configuration was assigned by analogy.

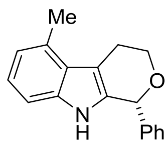
(*R*)-6-bromo-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (3o): Following general procedure **C**, the reaction was run for 4 days and **3o** was obtained as a white solid in 91% yield; mp = 100–102 ºC; R_f = 0.21 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^{D}_{20}$ –62.5 (c 0.5, $CHCl_3$, 92% ee); IR (KBr) 3414, 3282, 2954, 2917, 2842, 1451, 1296, 1078, 1043, 986, 793 ,698 cm^{-1}; ^1H NMR (500 MHz) δ 7.67 (s, 1H), 7.46 (br s, 1H), 7.43–7.33 (comp, 5H), 7.25–7.21 (m, 1H), 7.12–7.08 (m, 1H), 5.78 (app t, *J* = 2.0 Hz, 1H), 4.33 (ddd, *J* = 11.5, 5.5, 2.8 Hz, 1H), 4.02–3.94 (m, 1H), 3.06 (dddd, *J* = 15.5, 9.6, 5.6, 2.0 Hz, 1H), 2.81–2.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.25, 135.24, 134.78, 129.21, 129.06, 128.98, 128.47, 124.88, 121.22, 113.04, 112.52, 108.66,



76.20, 65.00, 22.29; *m/z* (ESI-MS) 328.1 (^{79}Br) [M + H]$^+$, 330.1 (^{81}Br) [M + H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 13.9 min (minor) and t_R = 21.1 min (major).

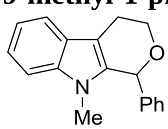
The absolute configuration was assigned by analogy.

(*R*)-5-methyl-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (3p): Following general procedure **C**, the reaction was run for 4 days and **3p** was obtained as a white solid in 75% yield; mp = 155–158 ºC; R_f = 0.20 (Hexanes/EtOAc 90:10 v/v); $[\alpha]^D_{20}$ –45.9 (c 0.5, $CHCl_3$, 81% ee); IR (KBr) 3294, 2979, 2937, 2849, 1443, 1373, 1333, 1141, 1073, 1041, 976, 750, 698 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.47–7.32 (comp, 6H), 7.08–6.98 (comp, 2H), 6.87–6.82 (m, 1H), 5.80 (app t, *J* = 1.9 Hz, 1H), 4.31 (ddd, *J* = 11.4, 5.5, 2.9 Hz, 1H), 3.98 (ddd, *J* = 11.3, 9.7, 4.0 Hz, 1H), 3.35 (dddd, *J* = 15.3, 9.8, 5.5, 2.2 Hz, 1H), 3.14–3.06 (m, 1H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.69, 136.10, 133.29, 130.74, 129.06, 128.96, 128.58, 126.21, 122.09, 120.93, 109.15, 108.86, 76.44, 65.24, 24.95, 19.71; *m/z* (ESI-MS) 264.1 [M + H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 19.1 min (major) and t_R = 26.7 min (minor).

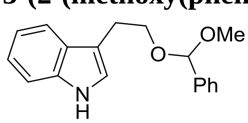


The absolute configuration was assigned by analogy.

9-methyl-1-phenyl-1,3,4,9-tetrahydropyrano[3,4-b]indole (3q): Following general procedure **C**, the reaction was run at room temperature for 24 hours and **3q** was obtained as a white solid in 62 % yield; mp = 103–105 ºC; R_f = 0.36 (Hexanes/EtOAc 90:10 v/v); IR (KBr) 3029, 2977, 2917, 2854, 1466, 1378, 1258, 1183, 1056, 898, 735, 698, 615, 503 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.63–7.60 (m, 1H), 7.41–7.35 (comp, 3H), 7.34–7.29 (comp, 2H), 7.29–7.28 (m, 1H), 7.28–7.23 (m, 1H), 7.20–7.15 (m, 1H), 5.92 (app t, *J* = 1.3 Hz, 1H), 4.04 (app dt, *J* = 11.4, 5.6 Hz, 1H), 3.94 (app dt, *J* = 11.3, 5.2 Hz, 1H), 3.28 (s, 3H), 2.99–2.95 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.65, 137.30, 134.09, 129.09, 128.85, 128.78, 126.60, 121.61, 119.26, 118.43, 109.00, 108.59, 74.66, 62.13, 30.29, 22.50; *m/z* (ESI-MS) 264.2 [M + H]$^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 280.16 nm, t_R = 9.8 min and 13.3 min.

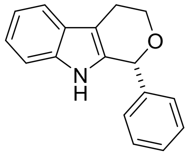


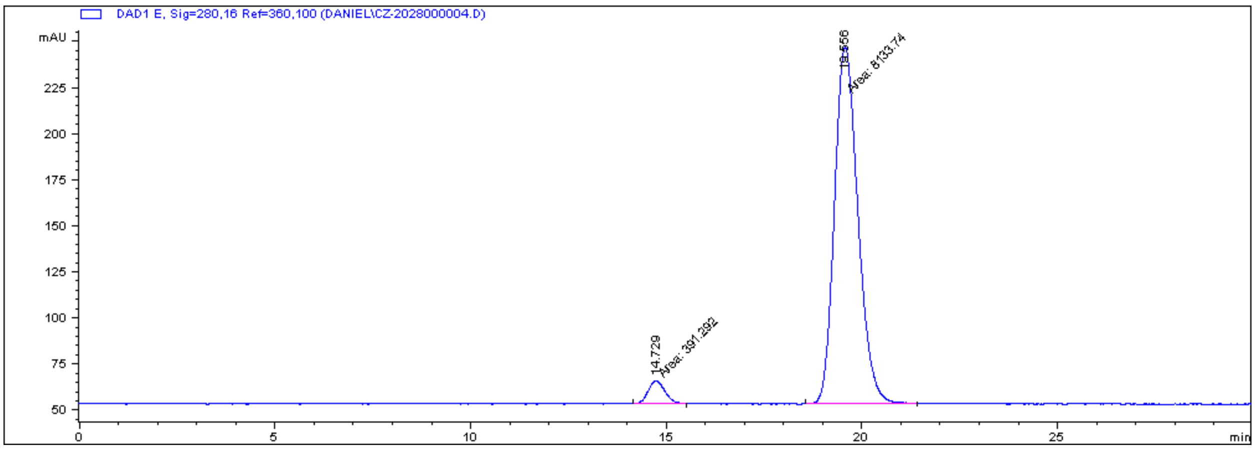
3-(2-(methoxy(phenyl)methoxy)ethyl)-1H-indole (4): To a solution of tryptophol (0.5 g, 3.1 mmol, 1 equiv) in CH_2Cl_2 (62 mL, 0.05 M) was added benzaldehyde dimethyl acetal (0.70 mL, 4.65 mmol, 1.5 equiv) and pyridinium *p*-toluenesulfonate (39 mg, 0.16 mmol, 5 mol%). The reaction mixture was stirred at room temperature for 1 hour before being quenched with trimethylamine (0.1 mL). The resulting mixture was then concentrated under reduced pressure and purified by flash chromatography on silica gel to afford **4** as a colorless oil in 16% yield. R_f = 0.31 (Hexanes/EtOAc 85:15 v/v); IR (film) 3409, 3054, 2927, 2872, 2361, 1453, 1418, 1353, 1203, 1098, 1043, 740, 703 cm^{-1}; ^{1}H NMR (500 MHz) δ 7.97 (br s, 1H), 7.63–7.60 (m, 1H), 7.51–7.46 (comp, 2H), 7.41–7.30 (comp, 4H), 7.20 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 7.05–7.03 (m, 1H), 5.52 (s, 1H), 3.90 (app dt, *J* = 9.4, 7.2 Hz, 1H), 3.81 (app dt, *J* = 9.5, 7.2 Hz, 1H), 3.32 (s, 3H), 3.15–3.10 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.55, 136.24, 128.51, 128.30, 127.65, 126.82, 122.14, 122.00, 119.33, 118.92, 113.01, 111.17, 102.69, 66.08, 52.80, 25.93; *m/z* (ESI-MS) 250.1 [M – OMe]$^+$.



VI. HPLC profiles of products

HPLC profile of **3a**





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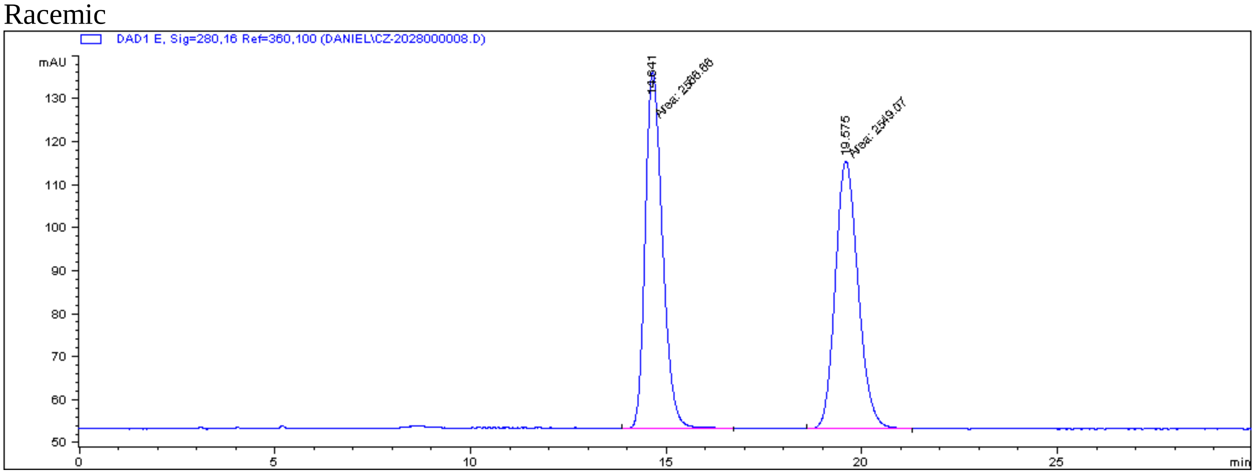
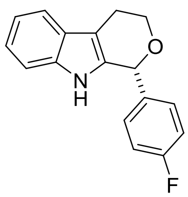
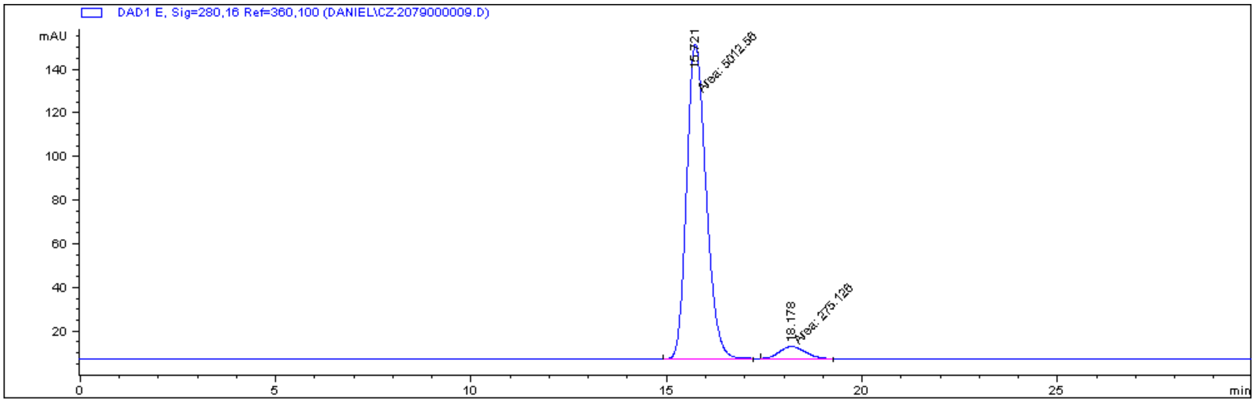


HPLC Profile of **3b**





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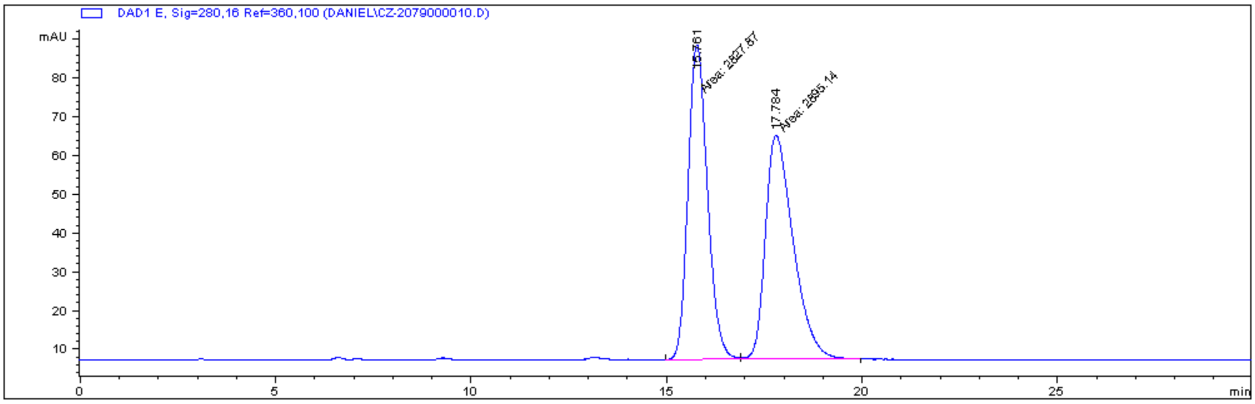
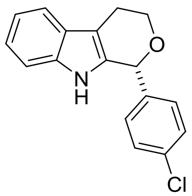
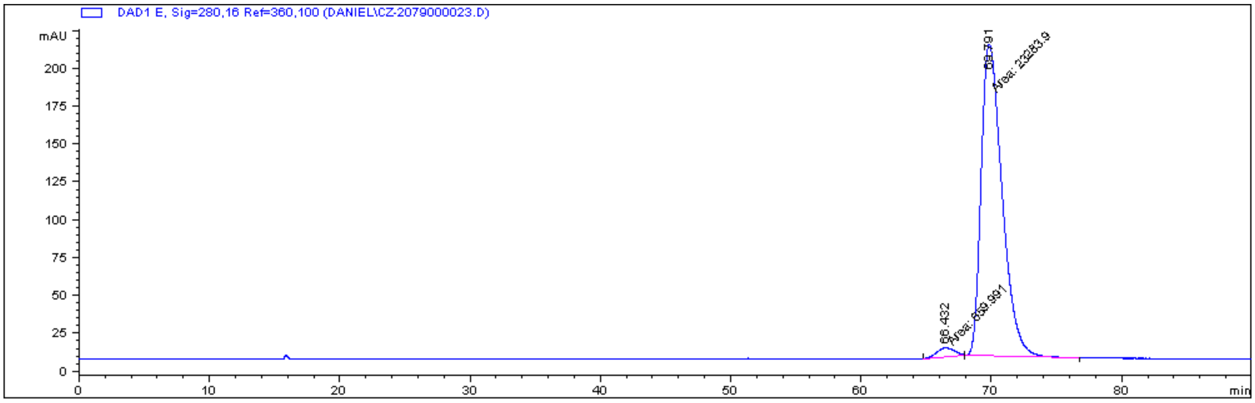


HPLC Profile of **3c**





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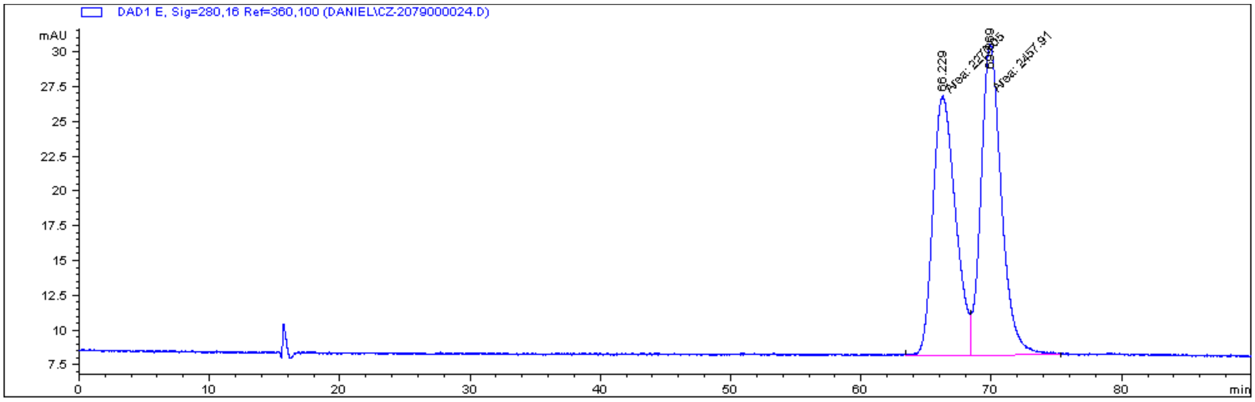
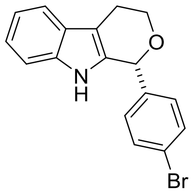
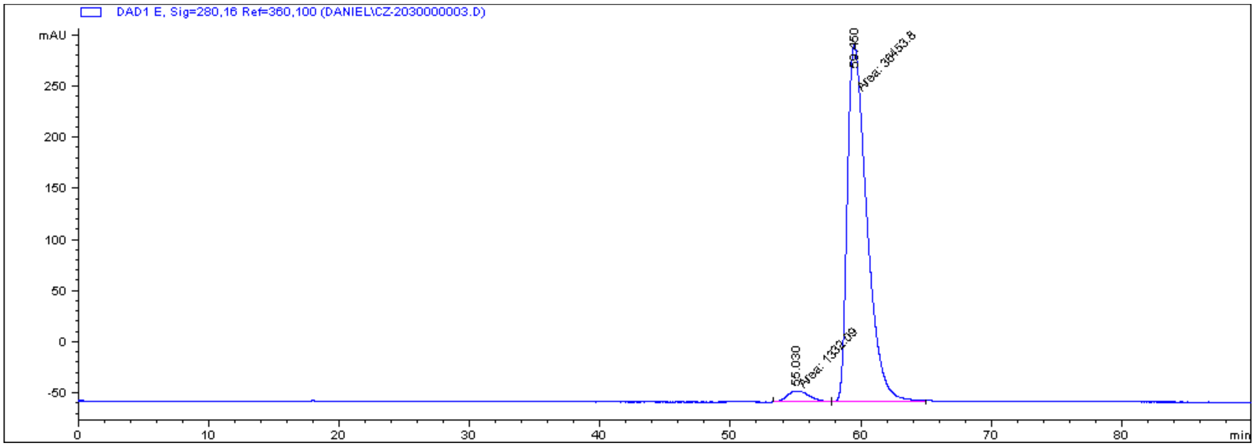


HPLC Profile of **3d**





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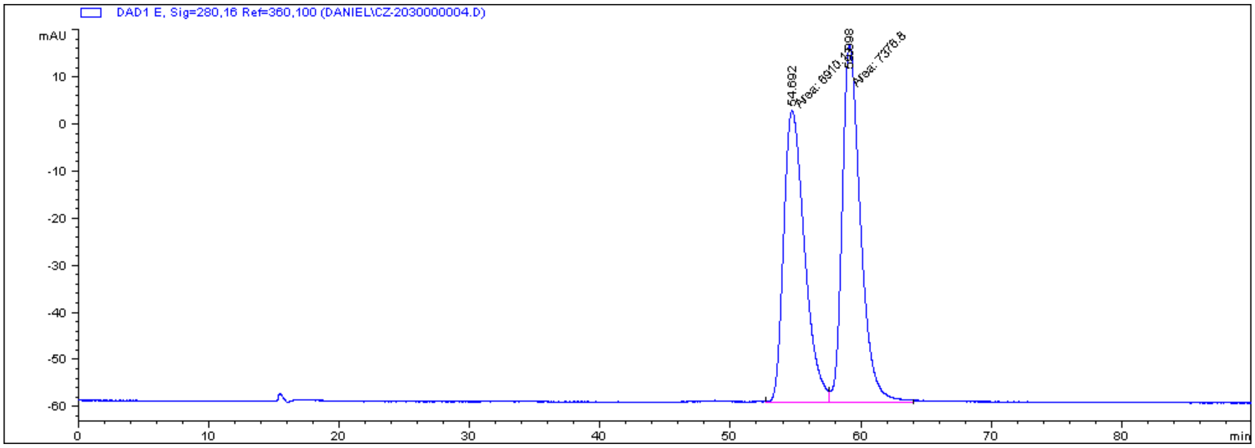
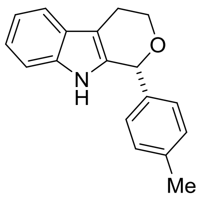
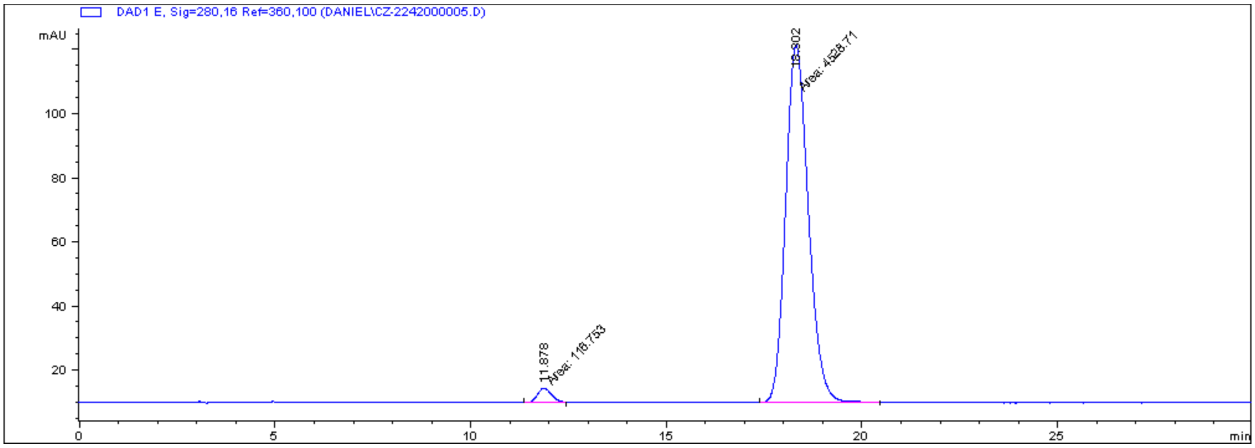


HPLC Profile of **3e**





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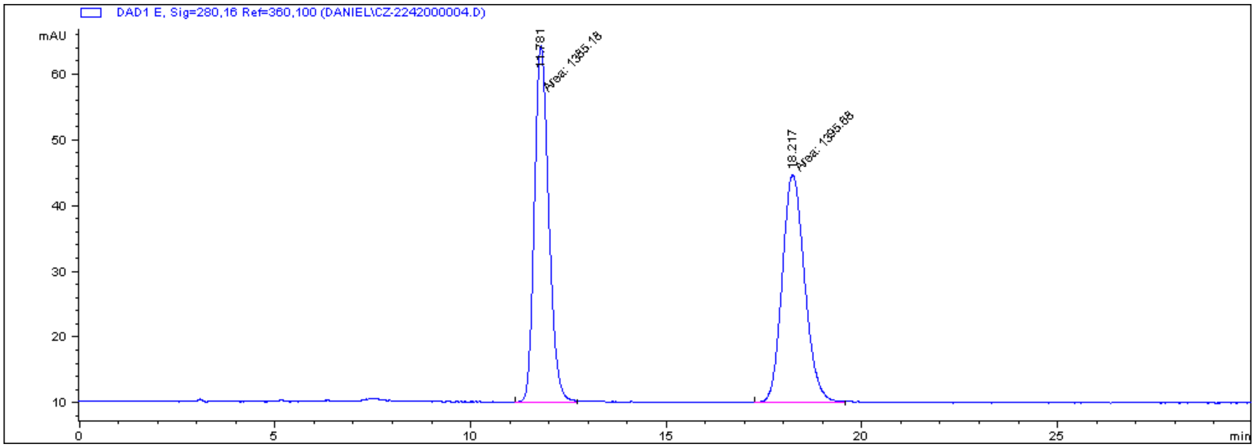
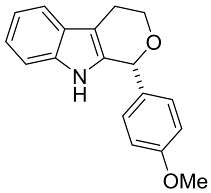
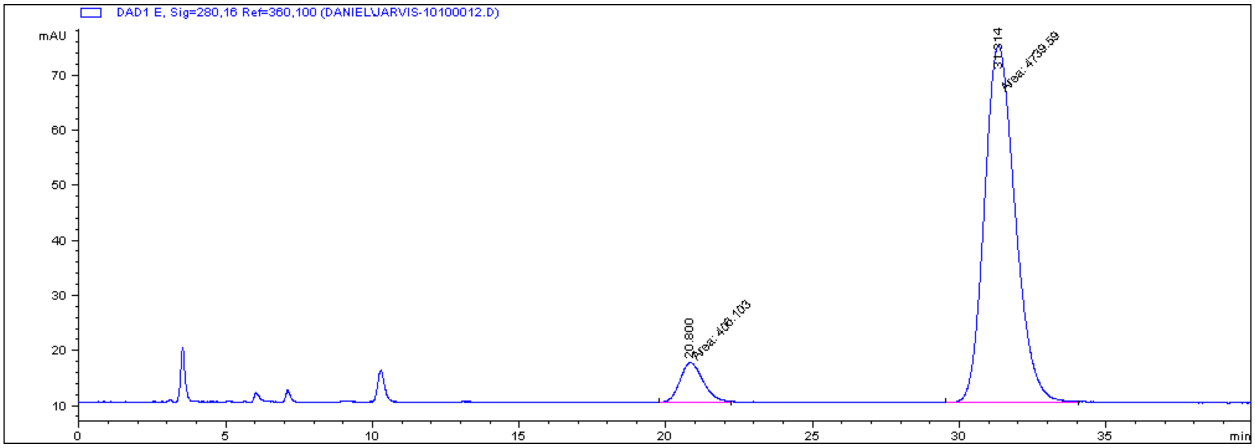


HPLC Profile of **3f**





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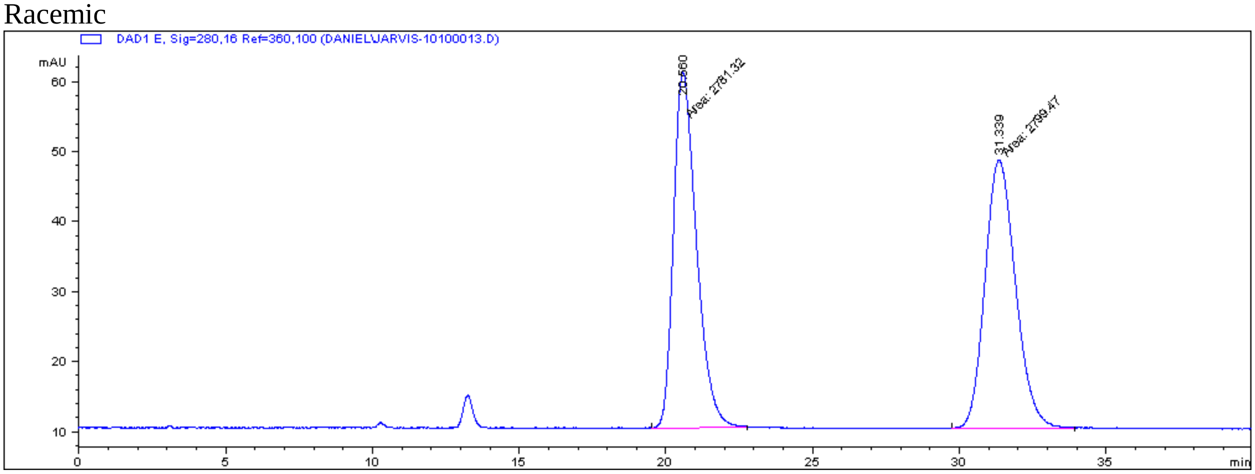
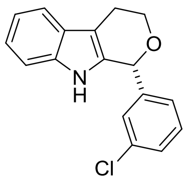
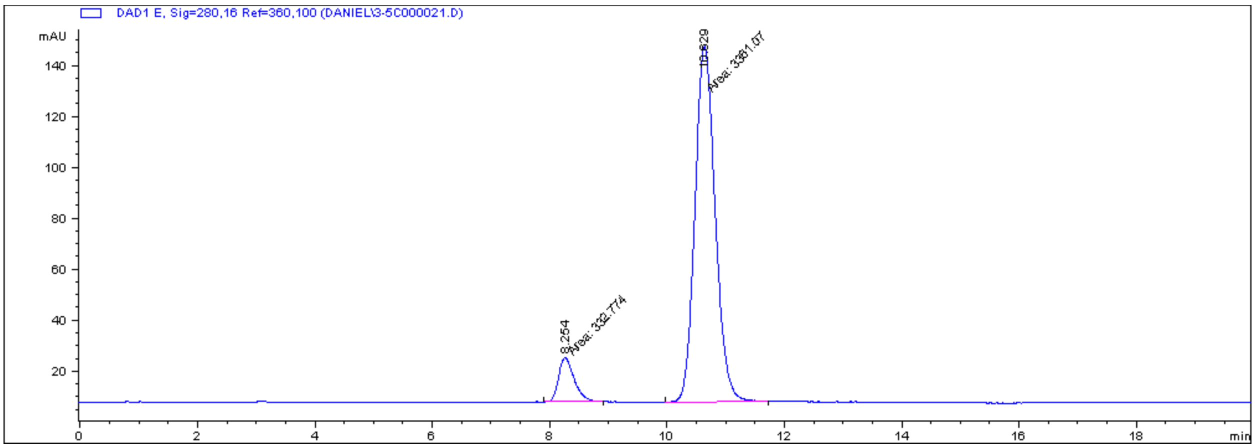


HPLC Profile of **3g**





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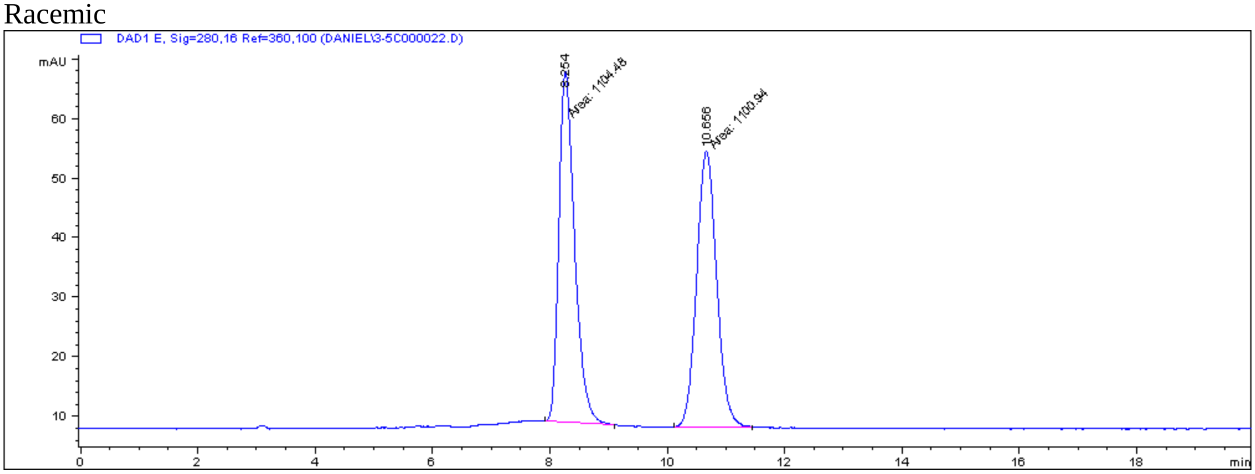
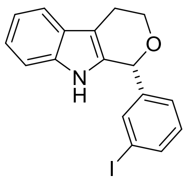
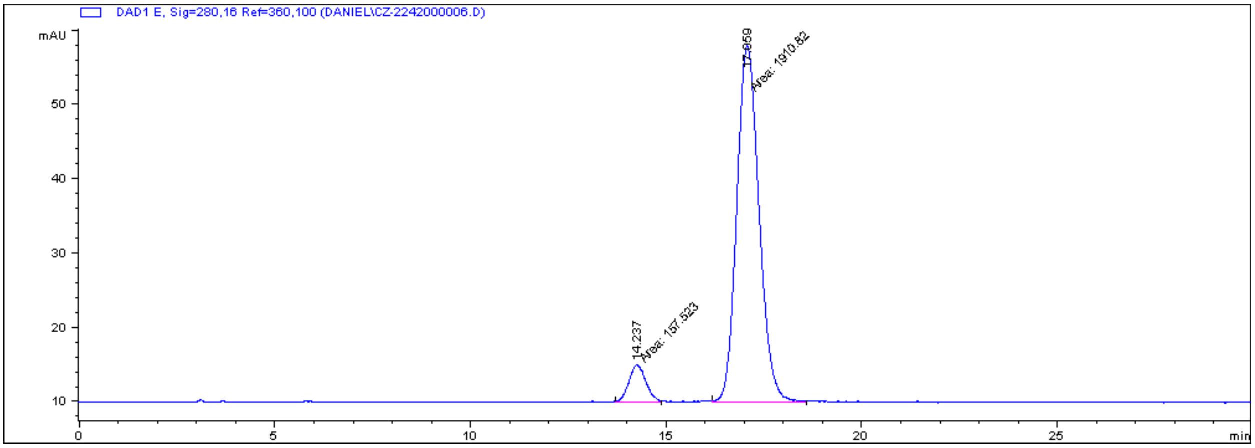


HPLC Profile of **3h**





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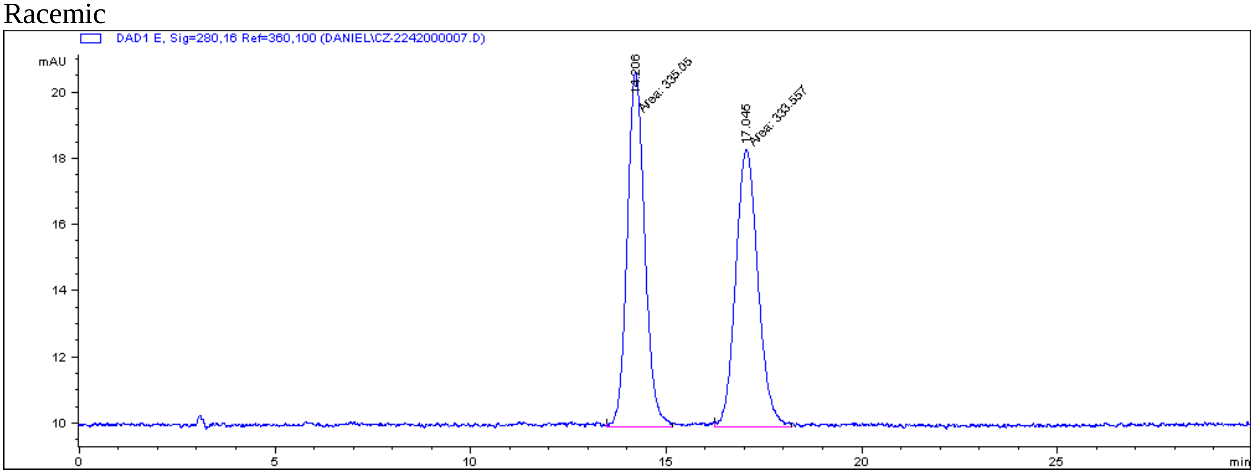
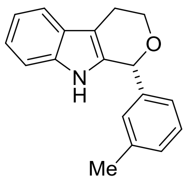
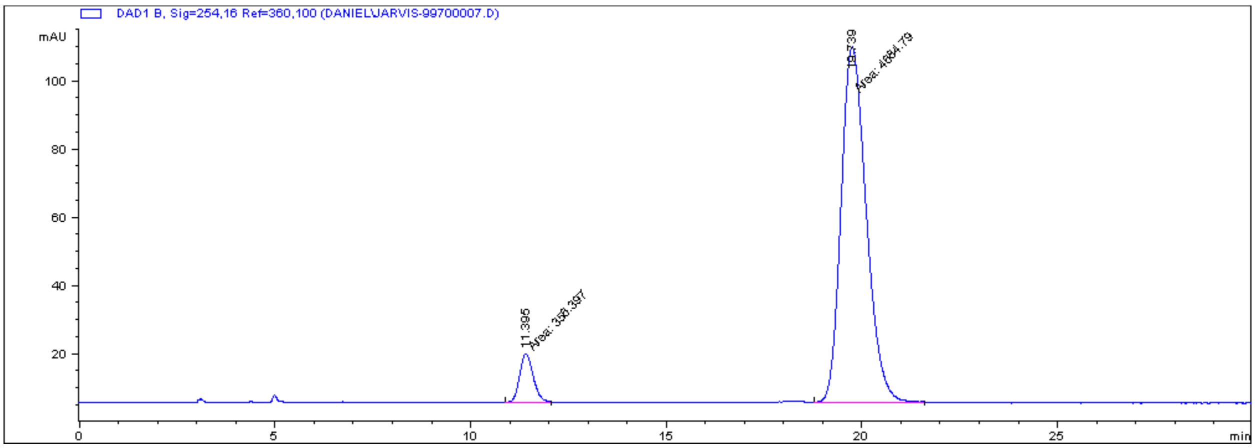


HPLC Profile of **3i**





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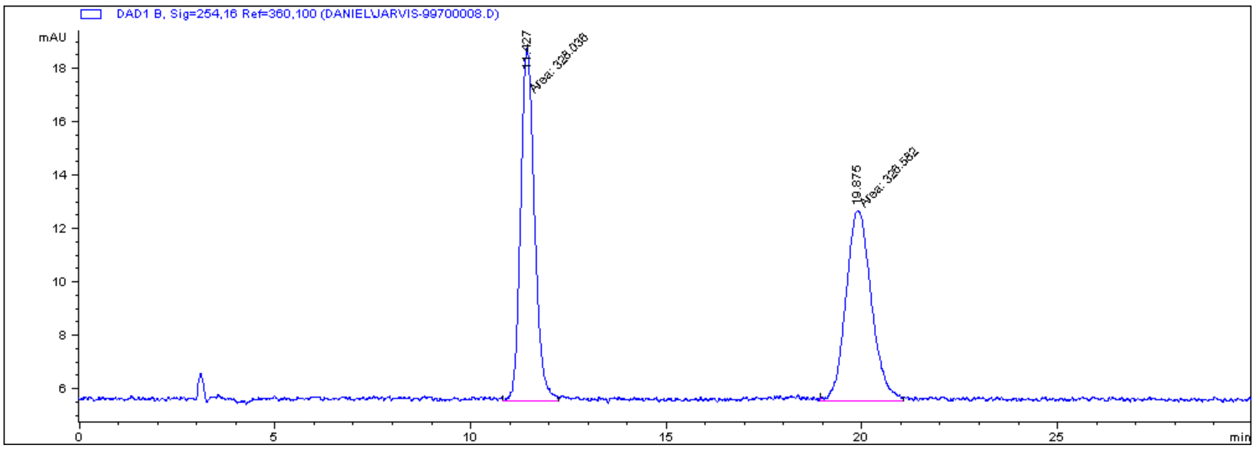
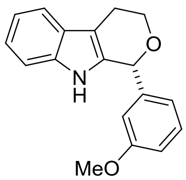
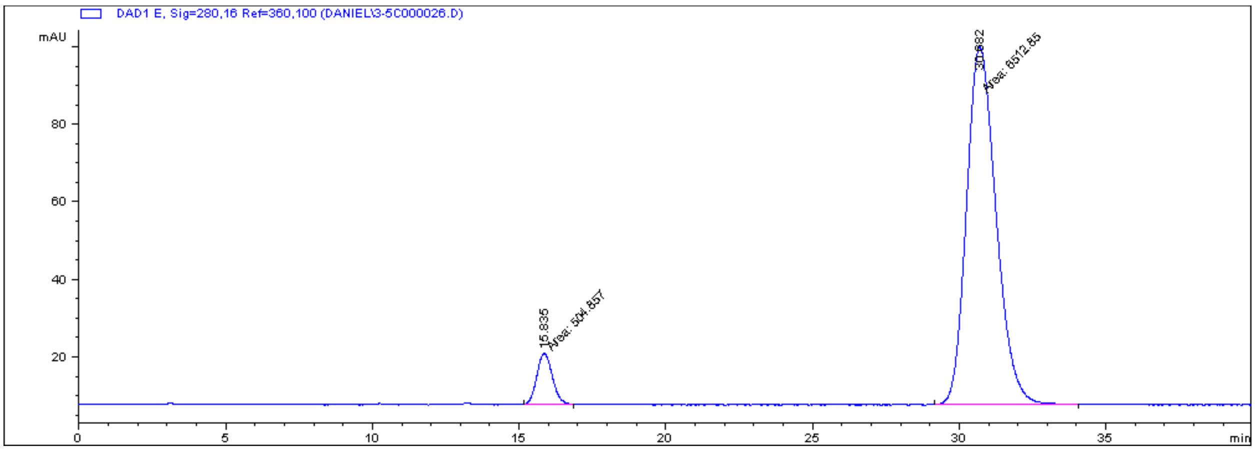


HPLC Profile of **3j**





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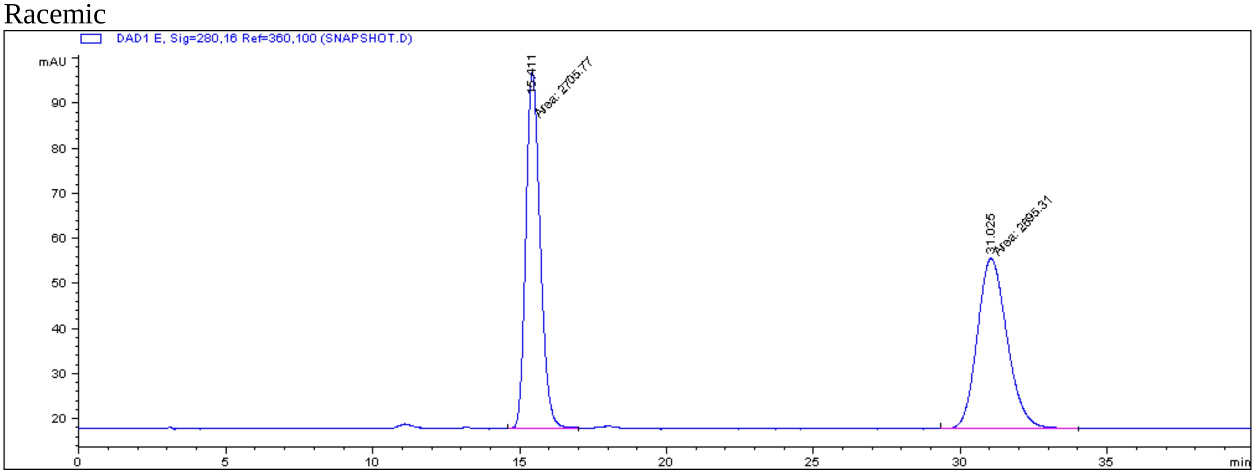
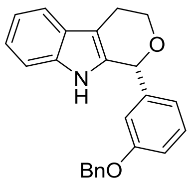
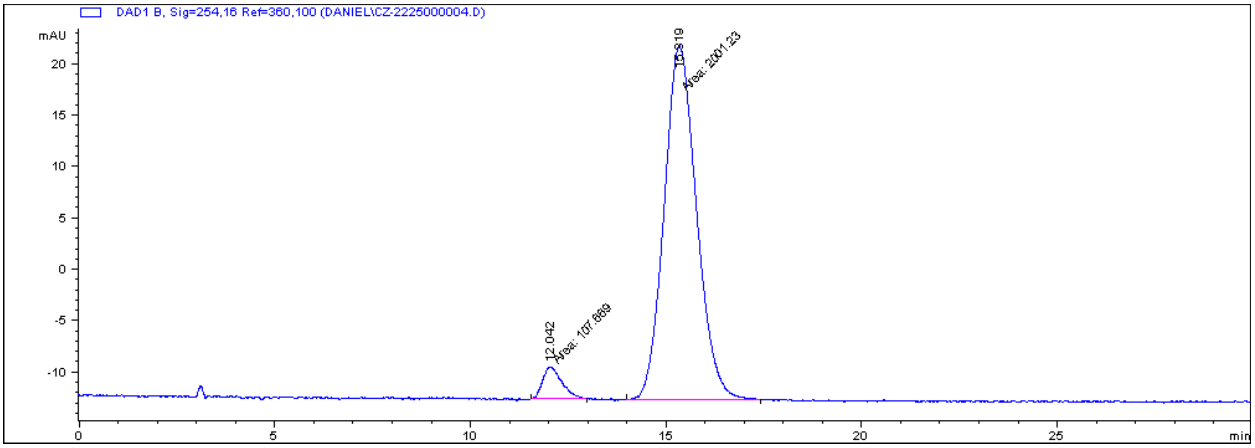


HPLC Profile of **3k**





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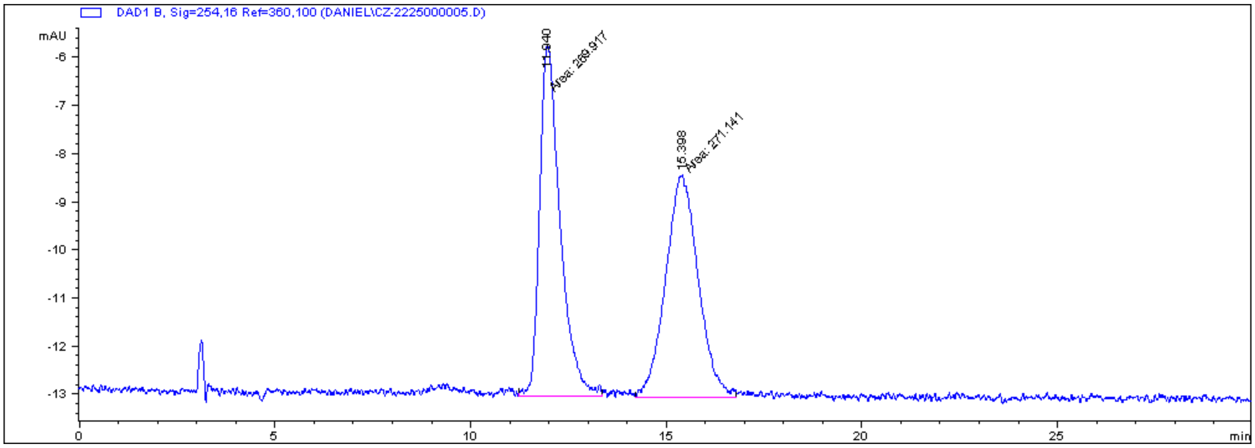
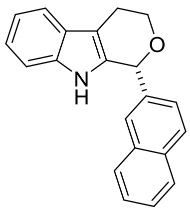
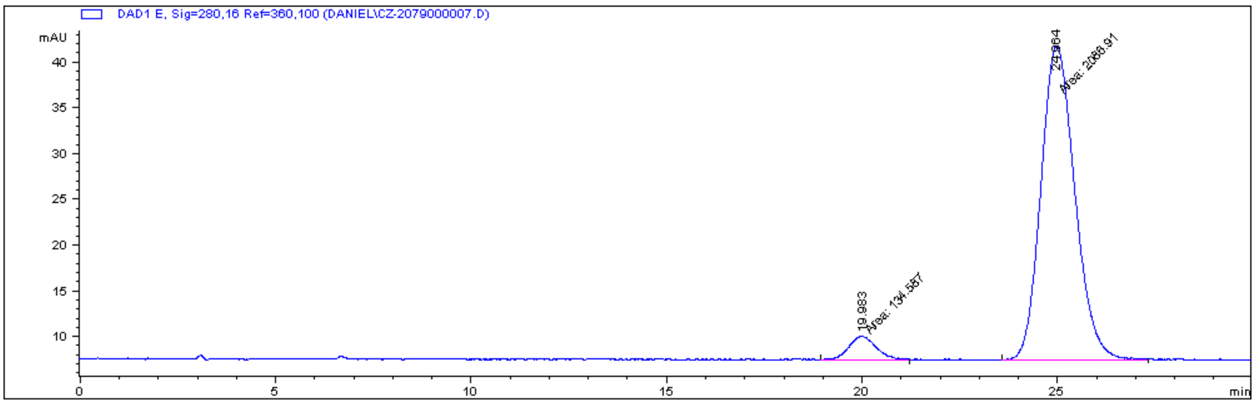


HPLC Profile of **3l**





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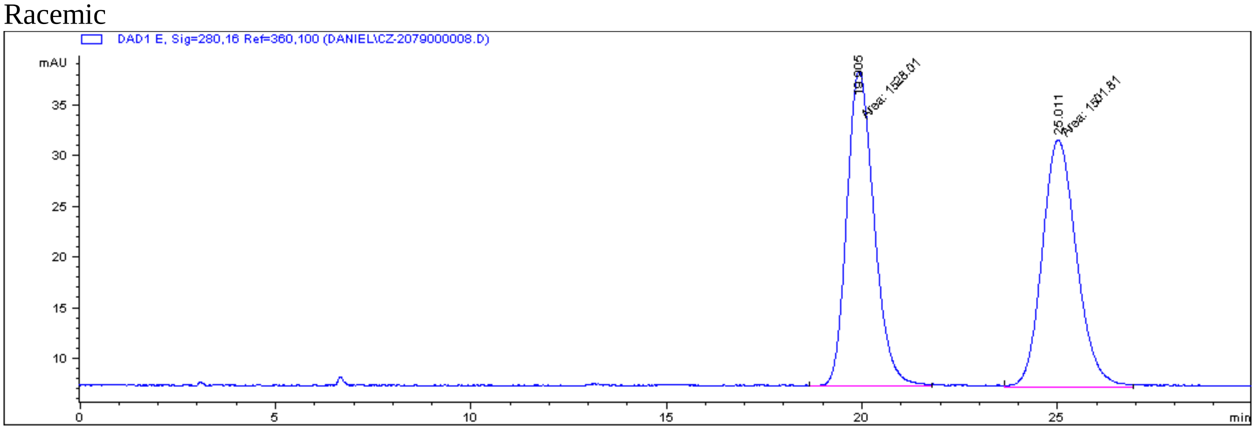
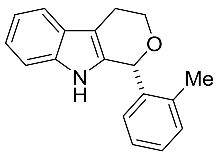
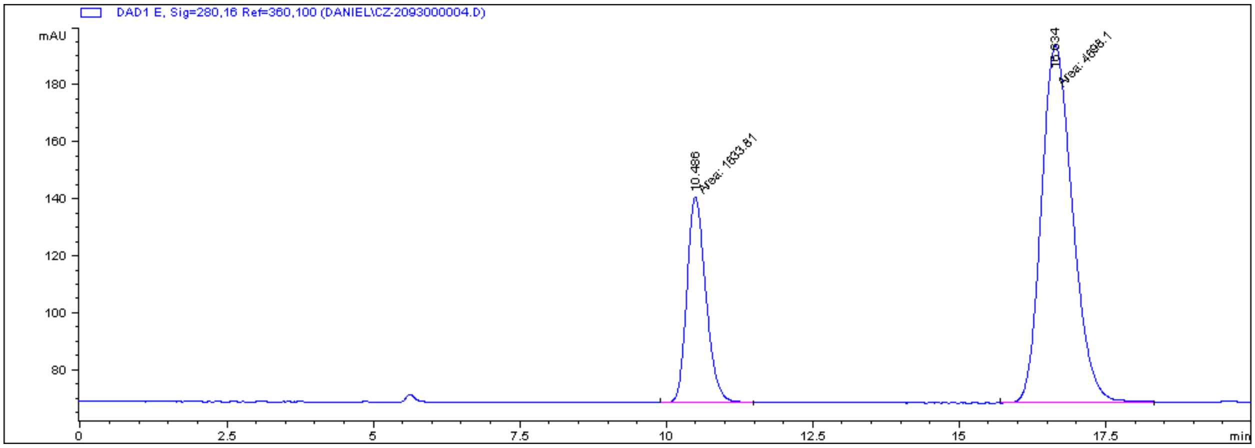


HPLC Profile of **3m**





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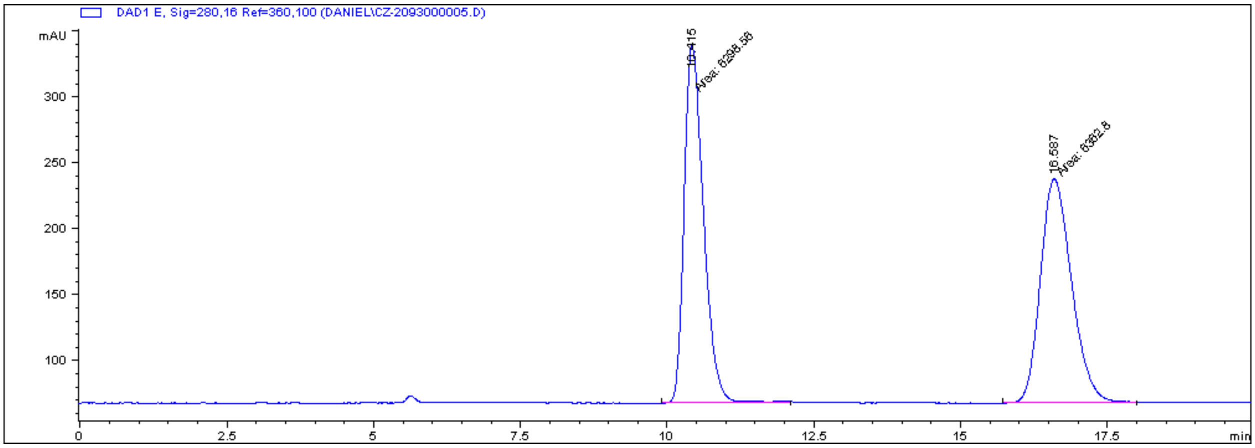
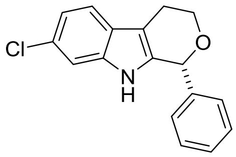
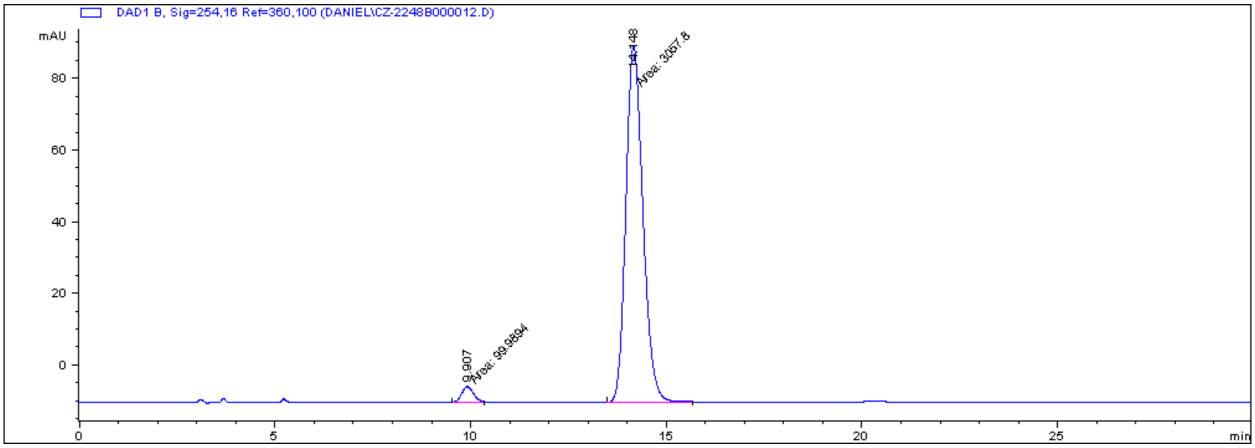


HPLC Profile of **3n**





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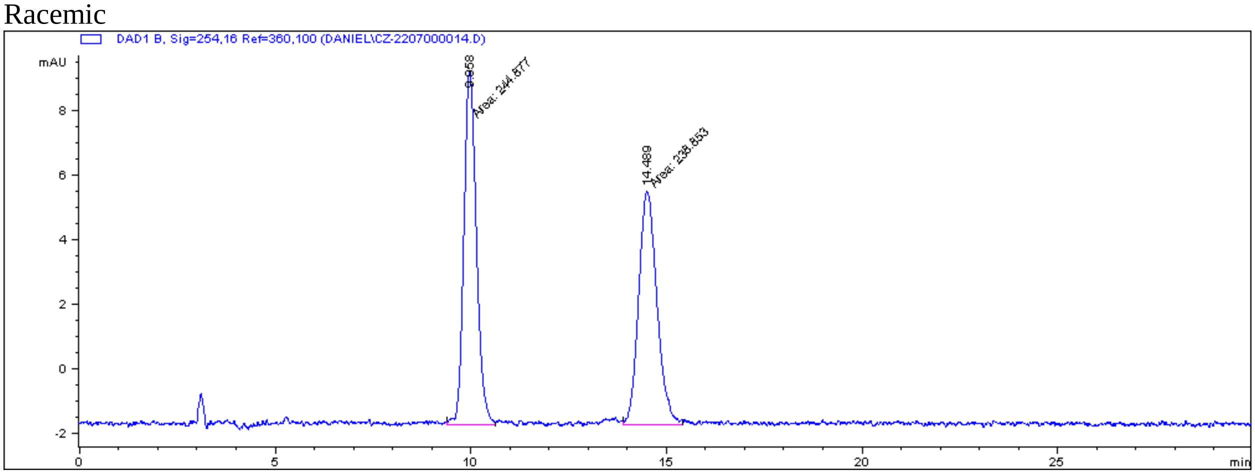
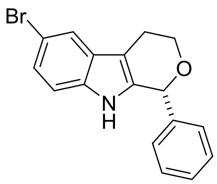
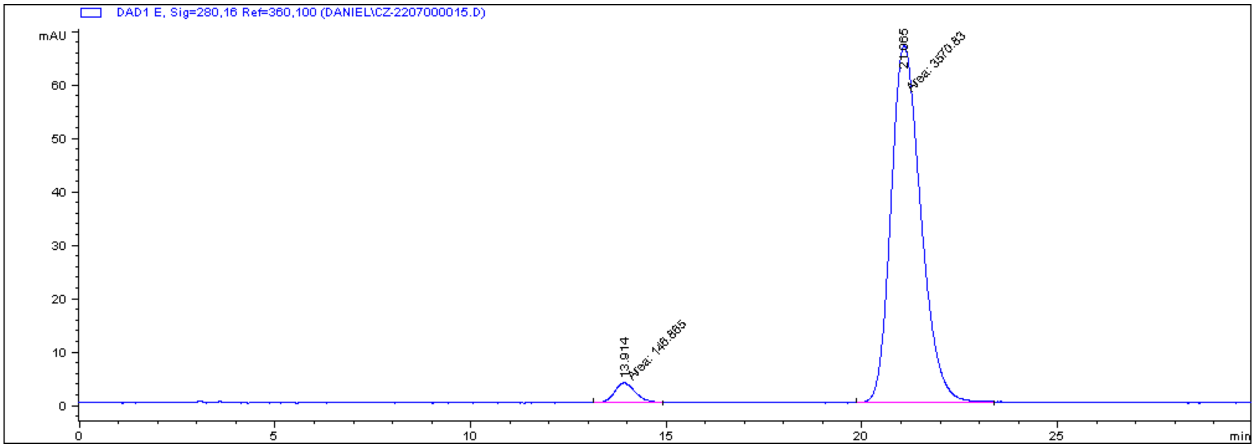


HPLC Profile of **3o**





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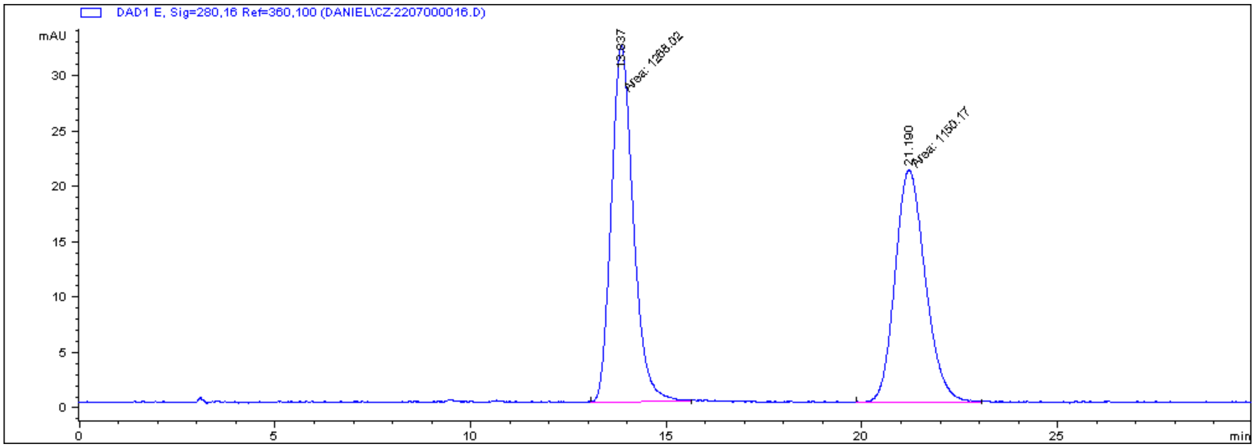
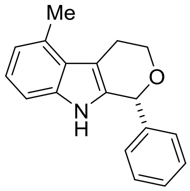
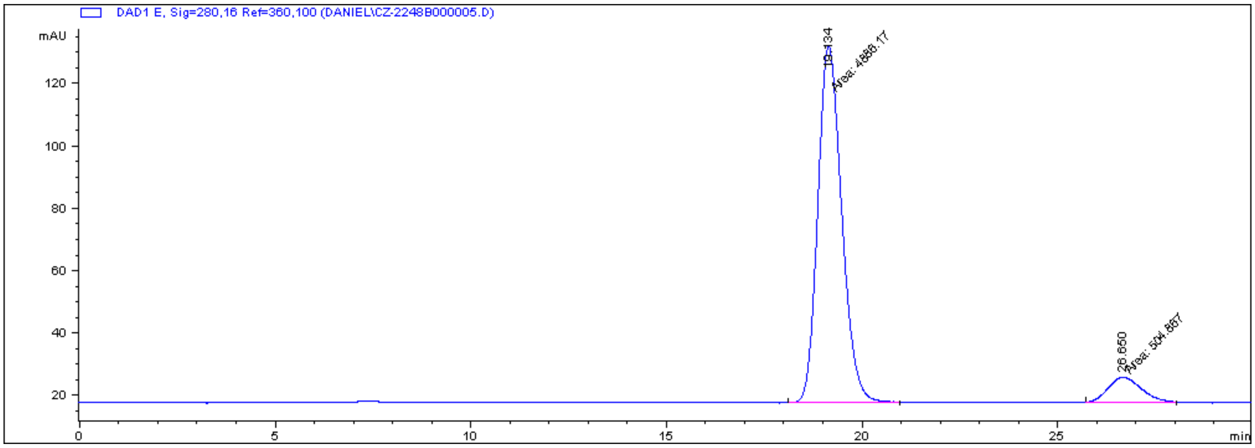
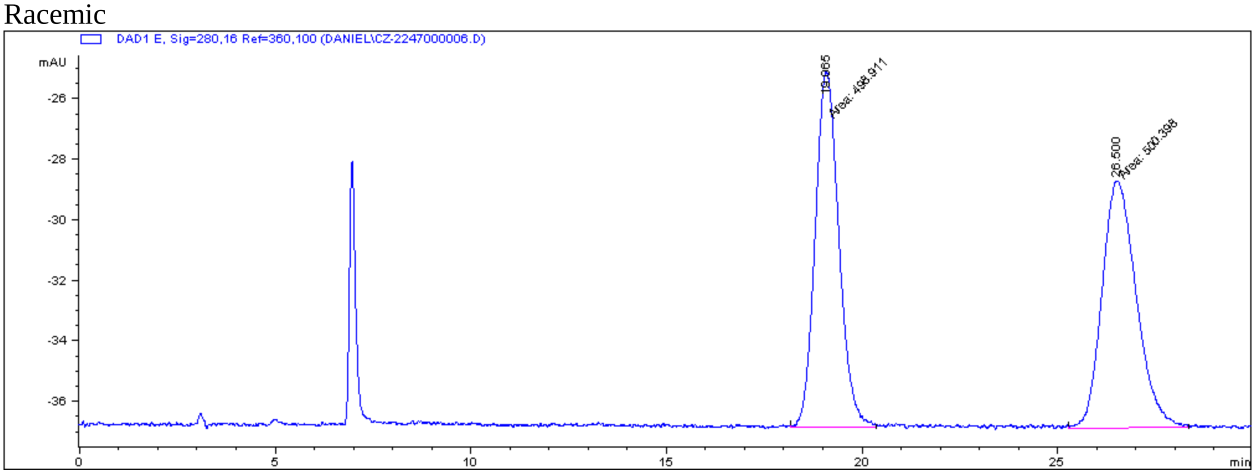


HPLC Profile of **3p**

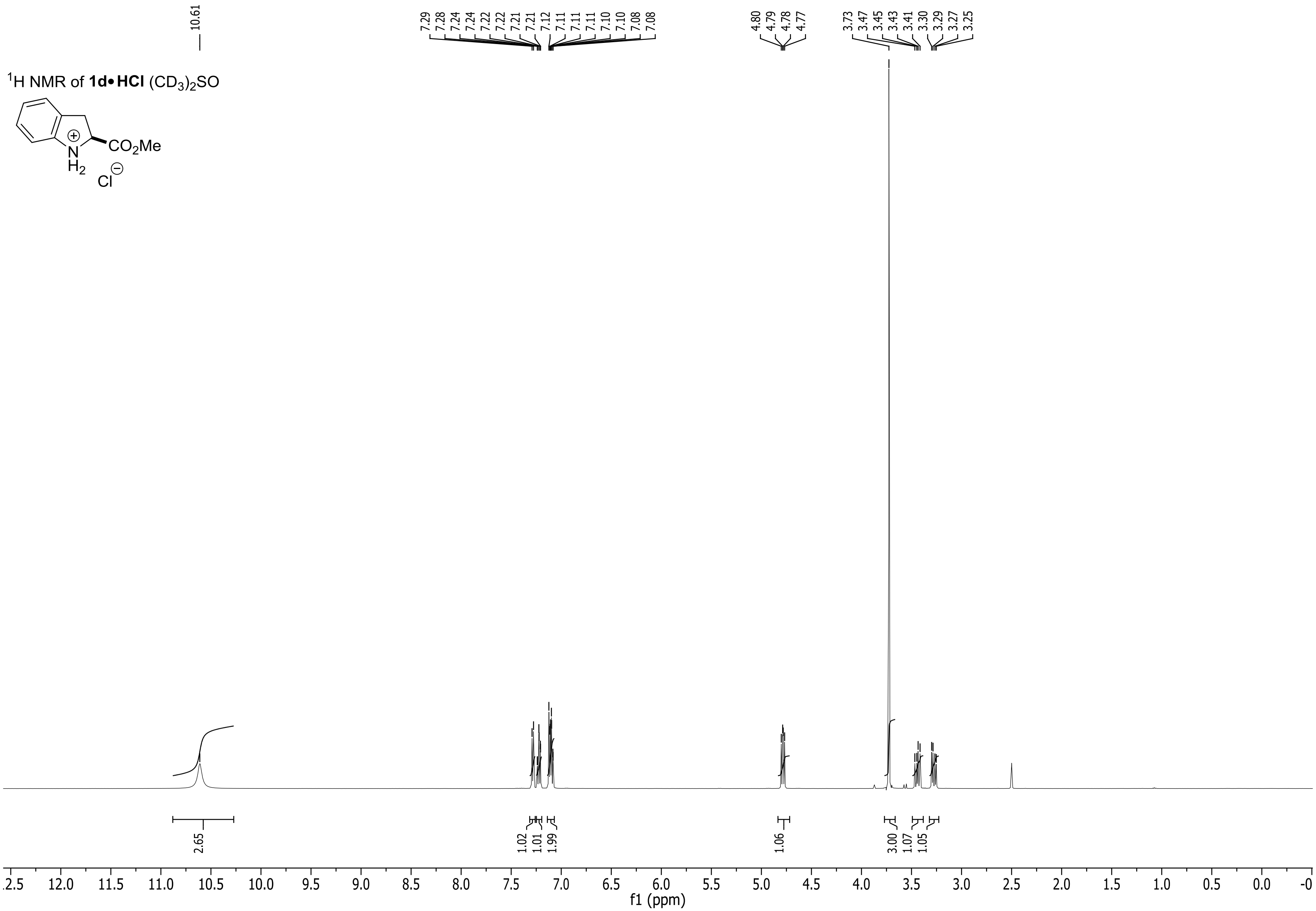




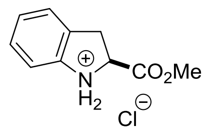
Racemic

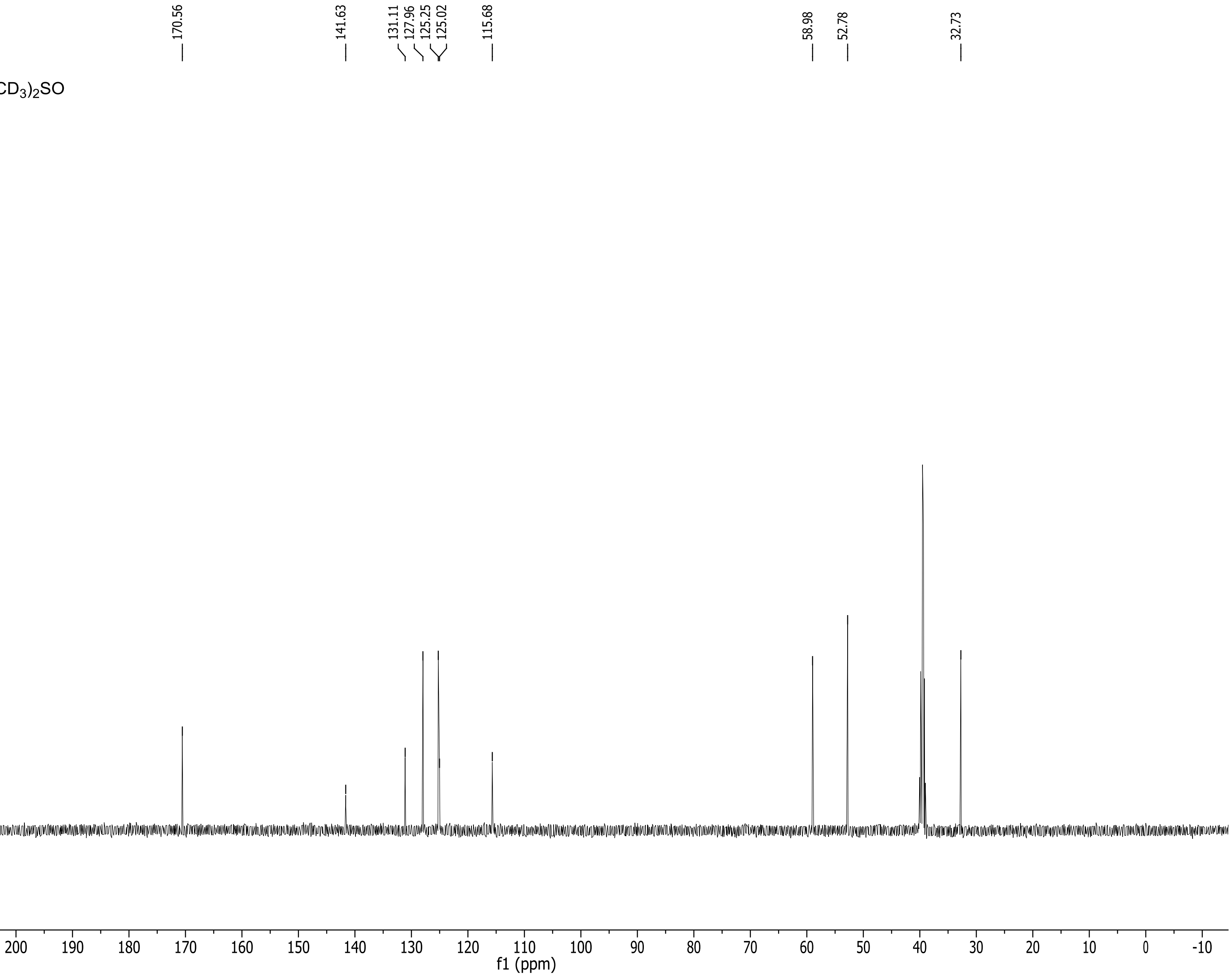


VII. NMR spectra

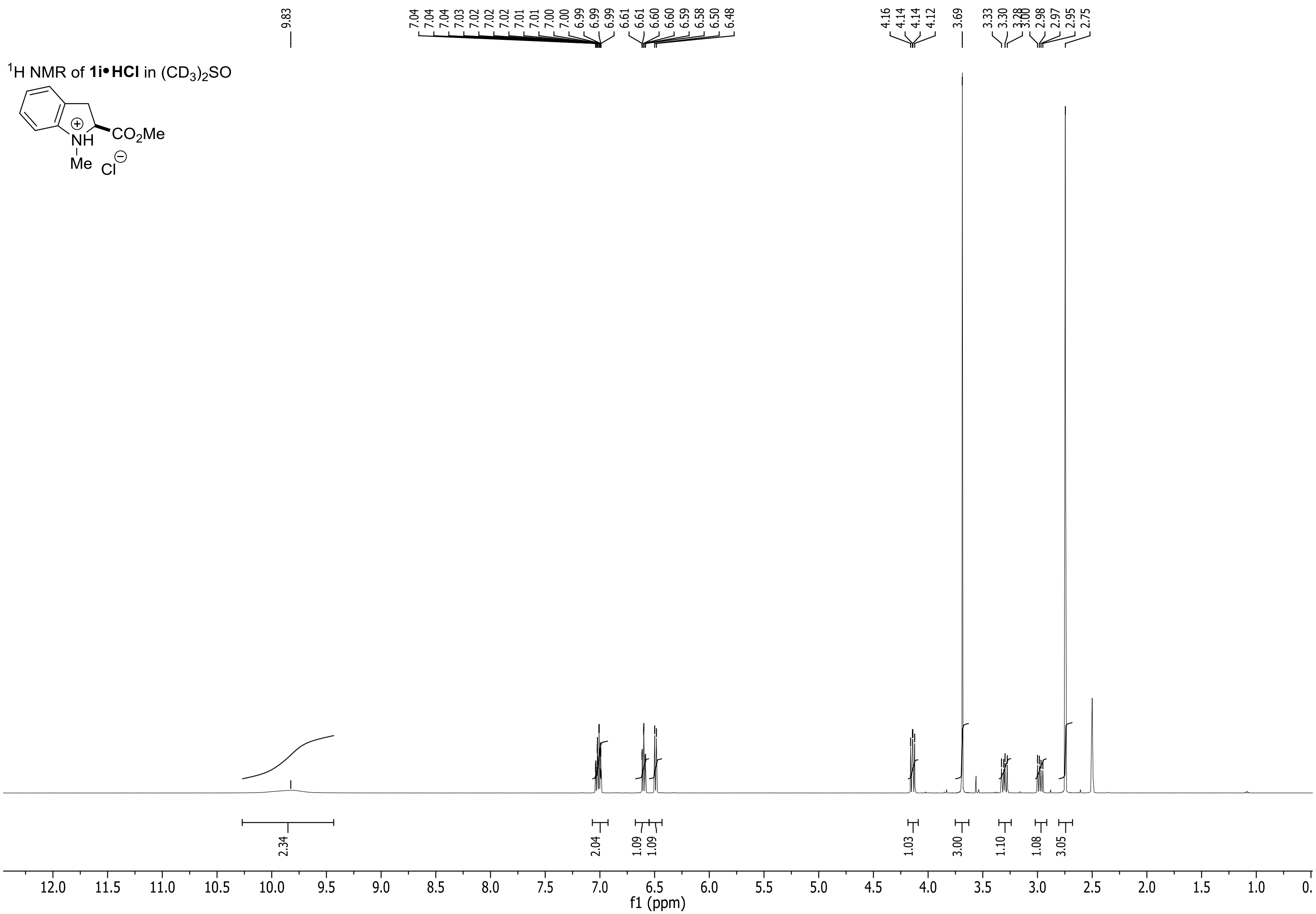


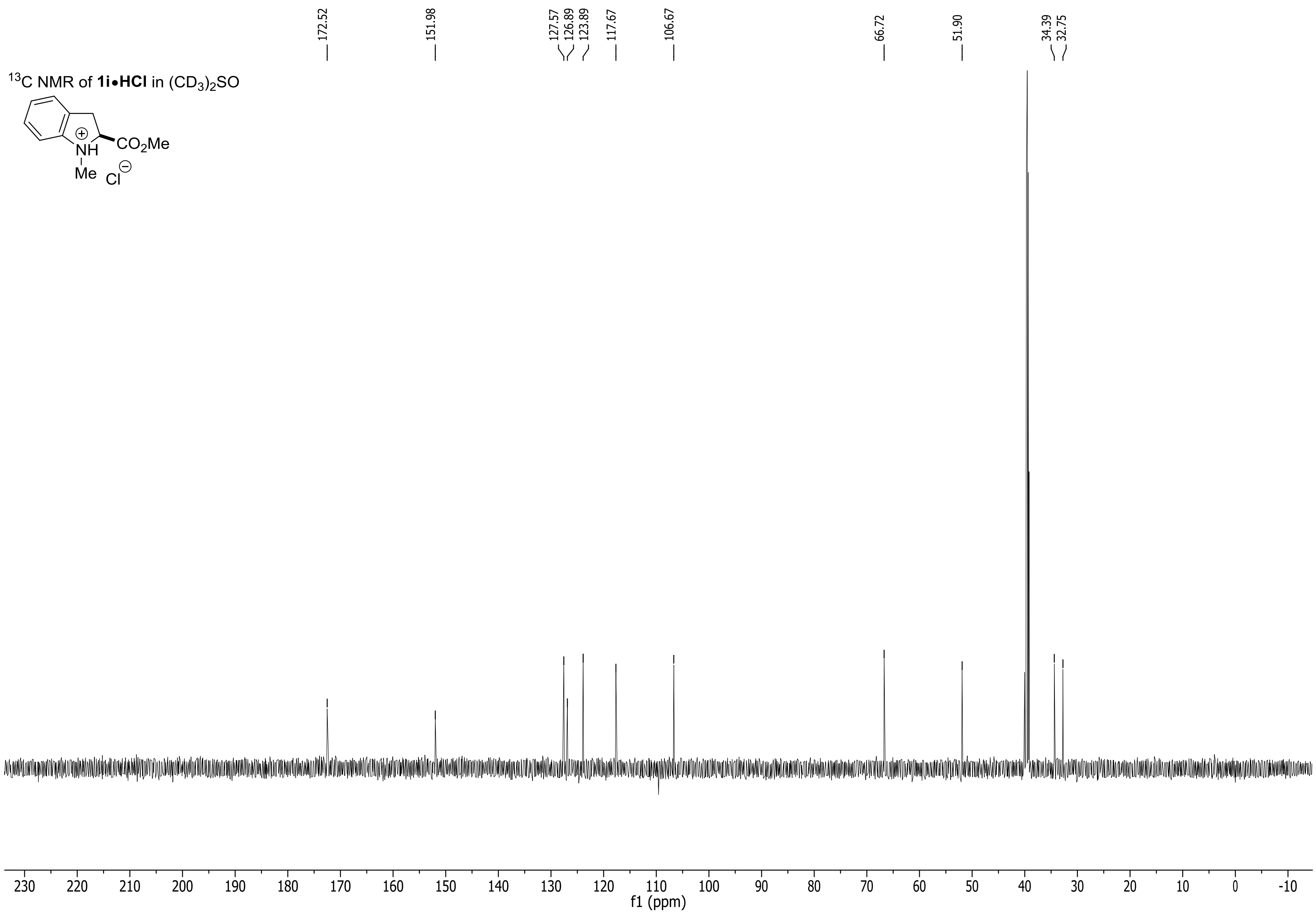
^{13}C NMR of **1d•HCl** $(CD_3)_2SO$

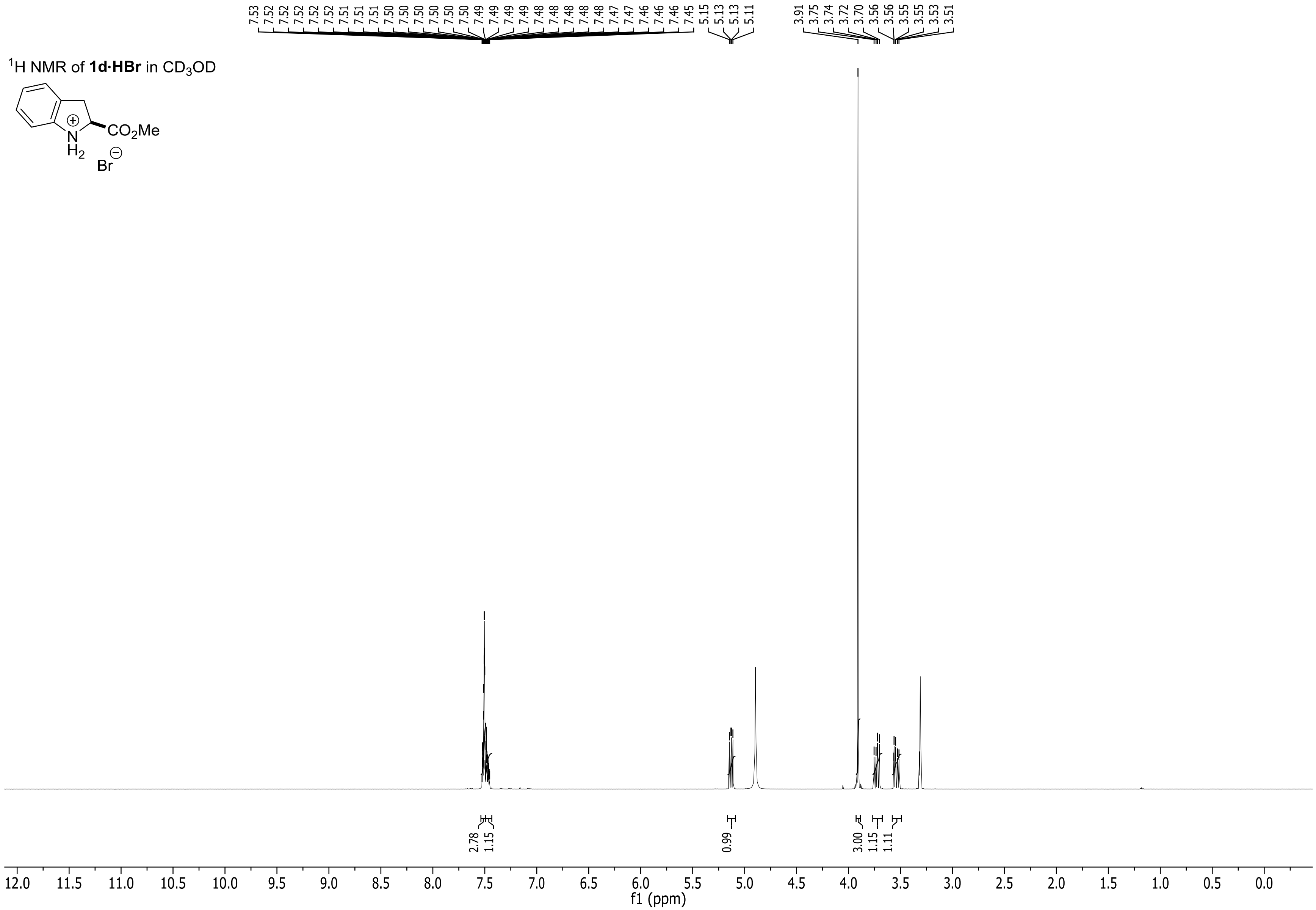




[1]H NMR of **1i•HCl** in $(CD_3)_2SO$

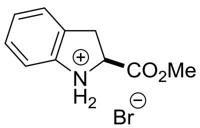


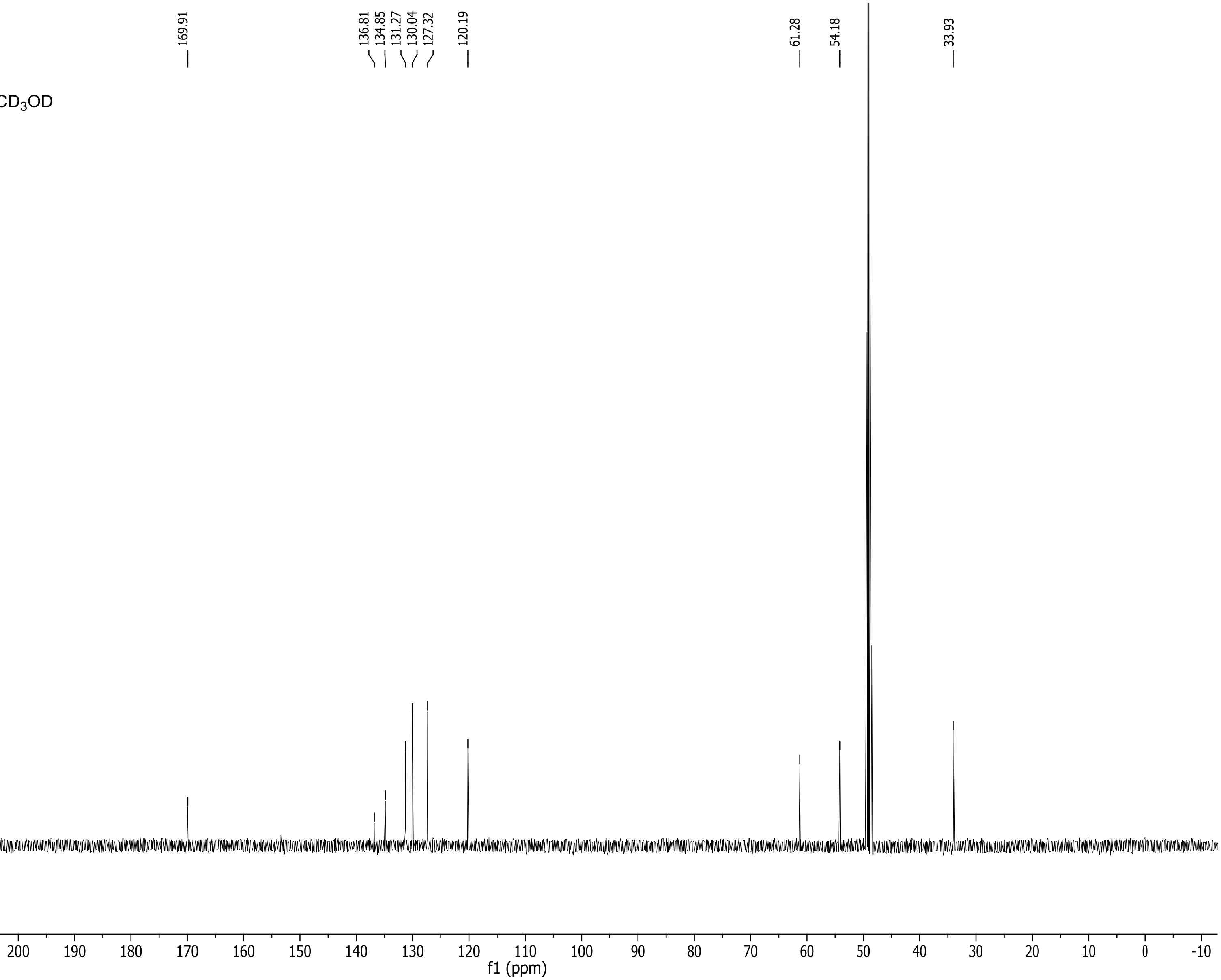

13C NMR of 1i•HCl in (CD3)2SO
CO2Me
NH
Me
Cl
172.52
151.98
127.57
126.89
123.89
117.67
106.67
66.72
51.90
34.39
32.75
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



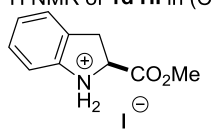
¹H NMR of 1d·HBr in CD3OD
CO2Me
N
H2
Br
7.53 7.52 7.52 7.52 7.52 7.52 7.51 7.51 7.51 7.50 7.50 7.50 7.50 7.50 7.50 7.49 7.49 7.49 7.49 7.48 7.48 7.48 7.48 7.48 7.47 7.47 7.46 7.46 7.46 7.45 5.15 5.13 5.13 5.11
3.91 3.75 3.74 3.72 3.70 3.56 3.56 3.55 3.55 3.53 3.51
2.78 1.15 0.99 3.00 1.15 1.11
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

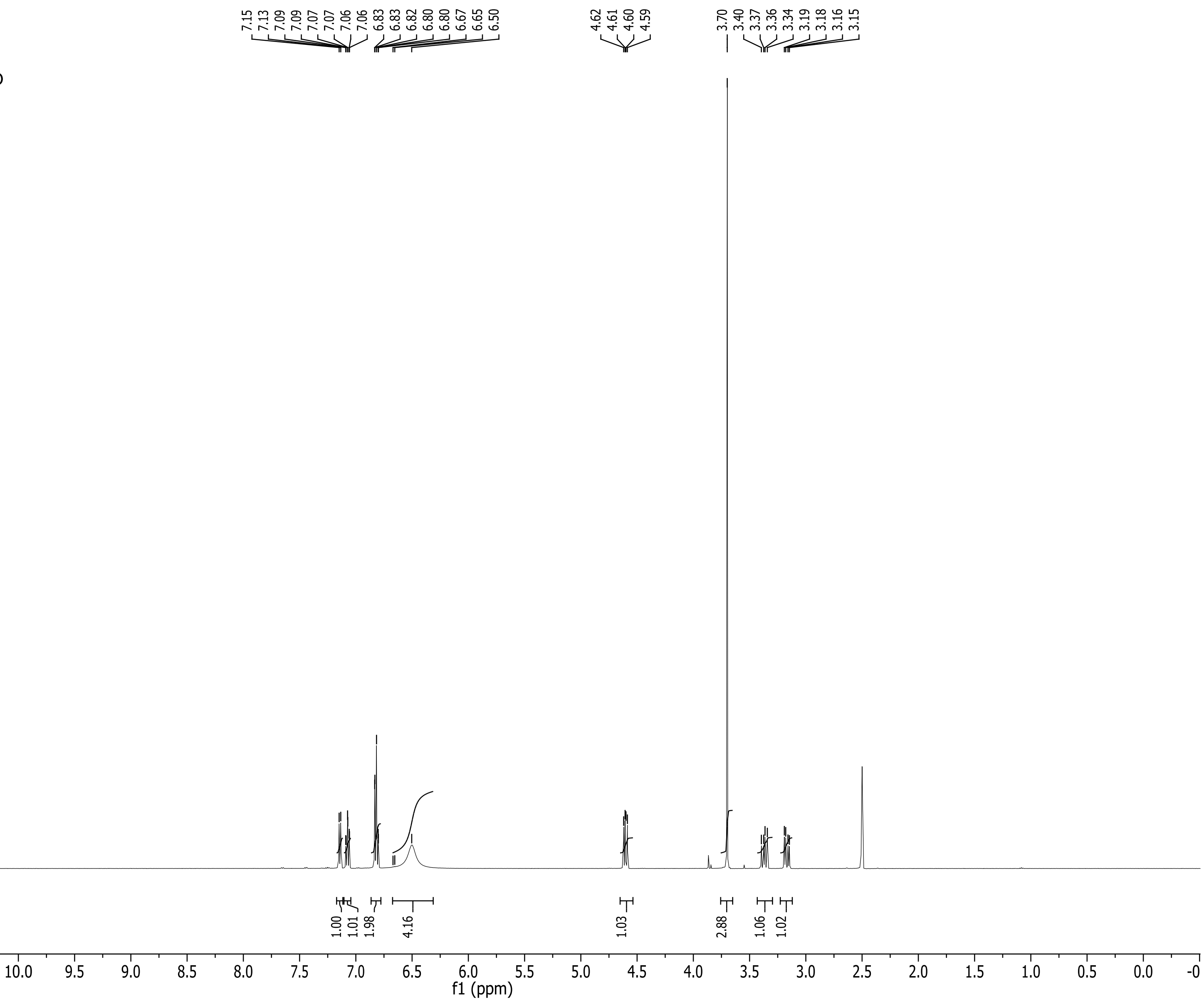
^{13}C NMR of **1d·HBr** in CD_3OD

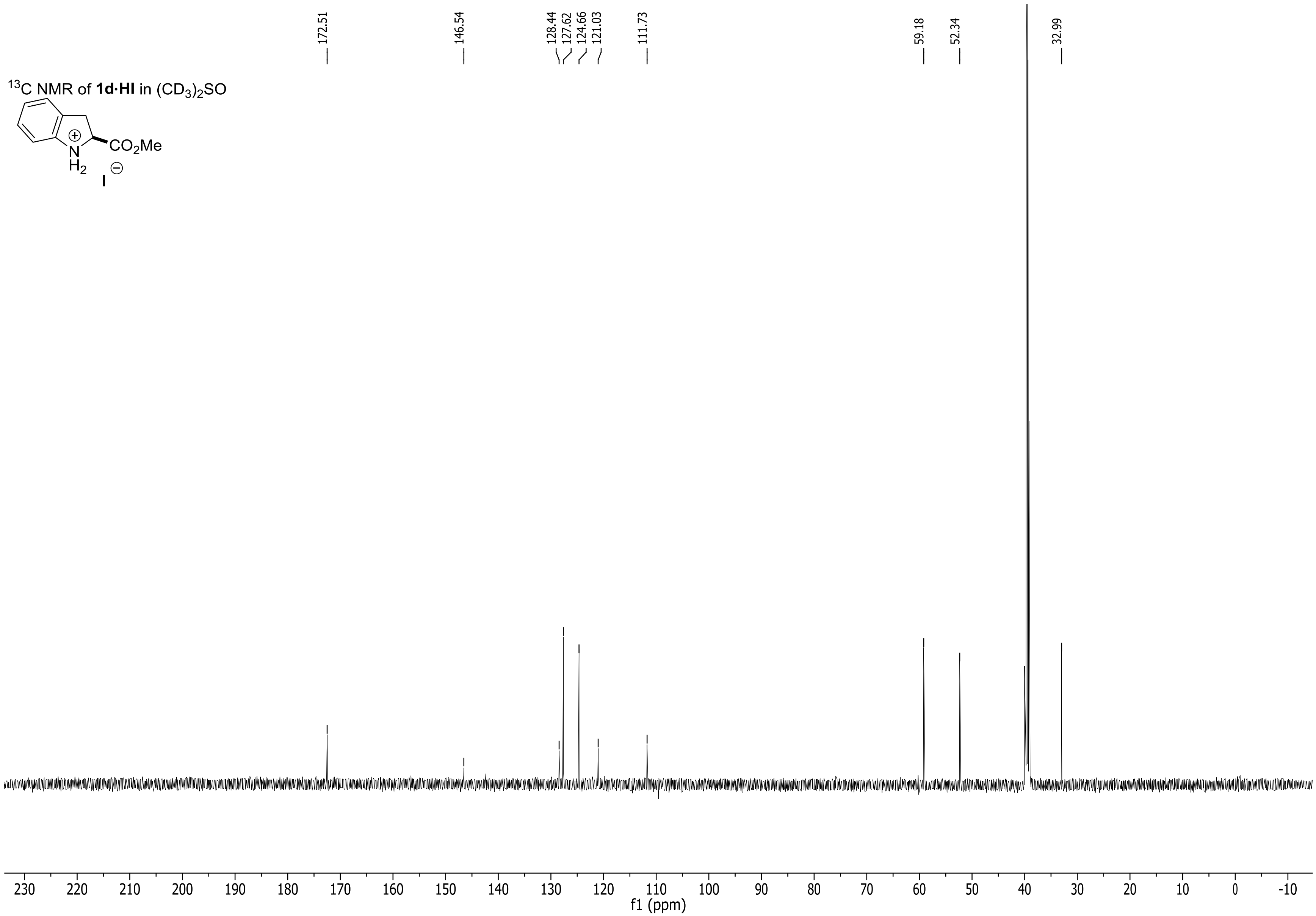




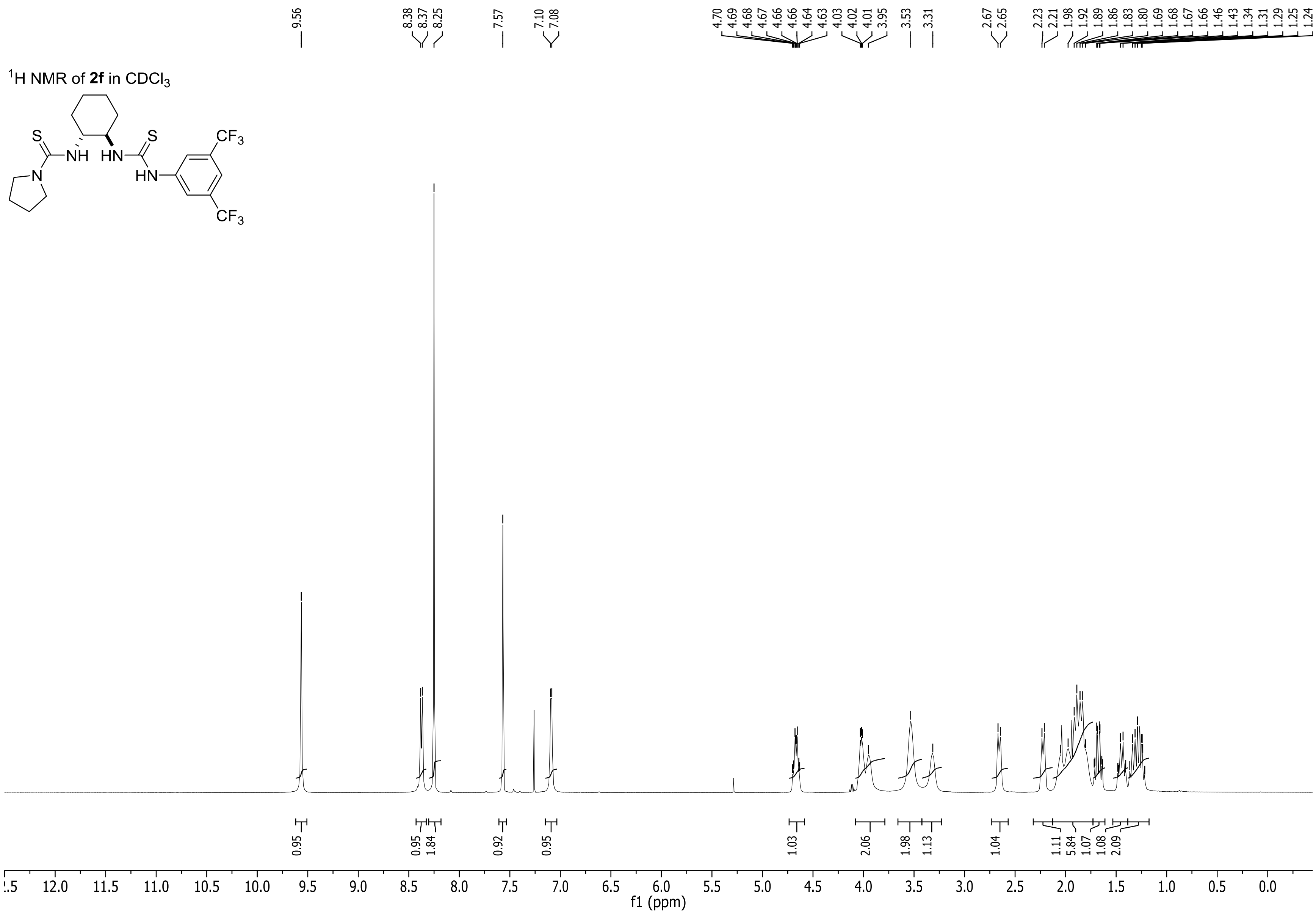
^{1}H NMR of **1d·HI** in $(CD_3)_2SO$





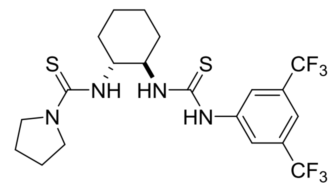


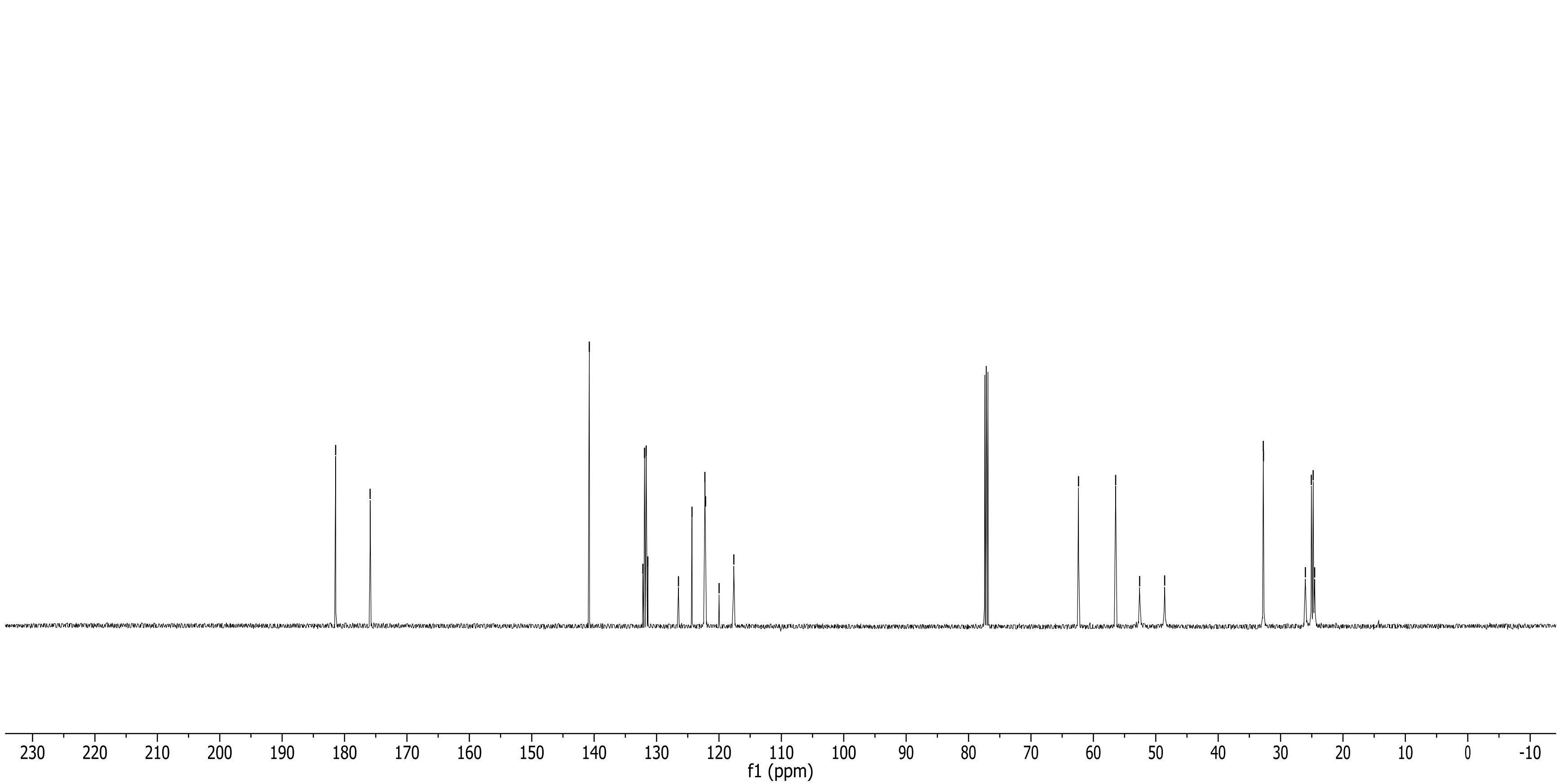
13C NMR of 1d·HI in (CD3)2SO
CO2Me
N
H2
I
172.51
146.54
128.44
127.62
124.66
121.03
111.73
59.18
52.34
32.99
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



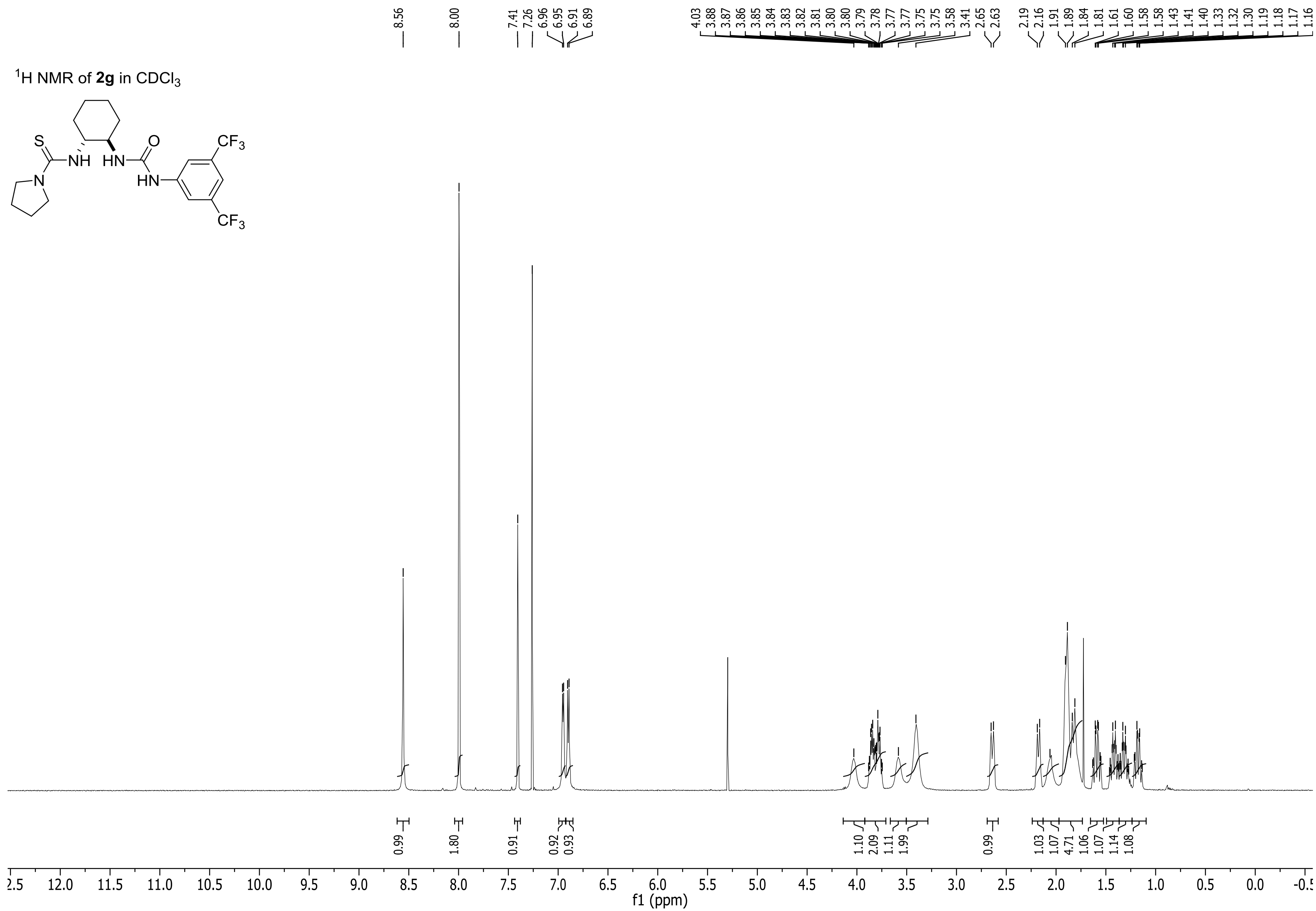
^{1}H NMR of **2f** in $CDCl_3$
9.56
8.38 8.37 8.25
7.57
7.10 7.08
4.70 4.69 4.68 4.67 4.66 4.64 4.63 4.03 4.02 4.01 3.95 3.53 3.31
2.67 2.65
2.23 2.21 1.98 1.92 1.89 1.86 1.83 1.80 1.69 1.68 1.67 1.66 1.46 1.43 1.34 1.31 1.29 1.25 1.24
0.95 0.95 1.84 0.92 0.95 1.03 2.06 1.98 1.13 1.04 1.11 5.84 1.07 1.08 2.09
f1 (ppm)

^{13}C NMR of **2f** in $CDCl_3$

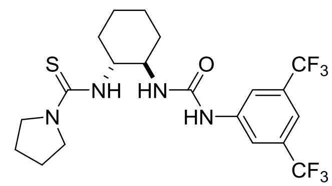


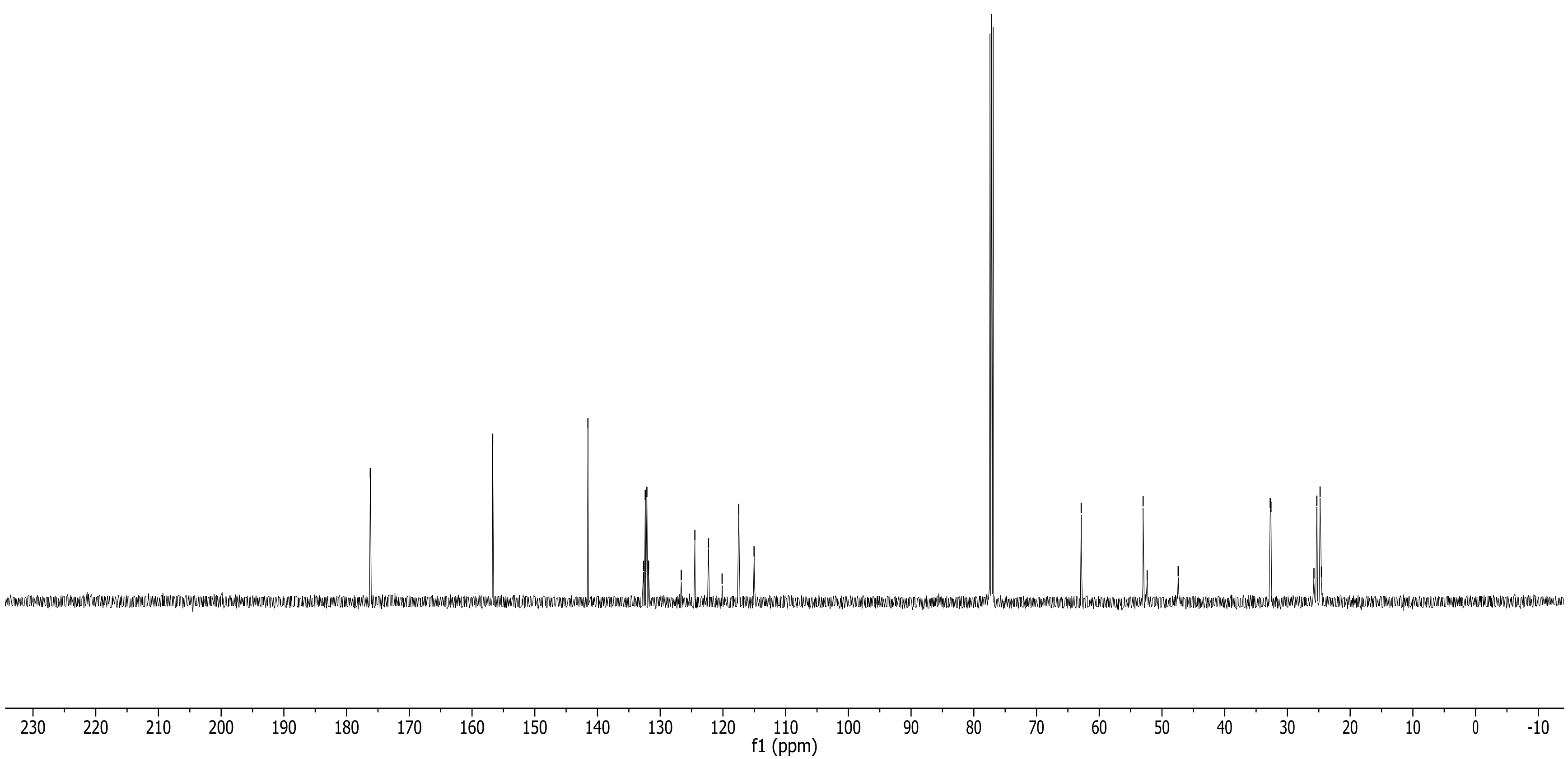


^{1}H NMR of **2g** in $CDCl_3$

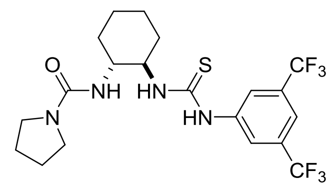


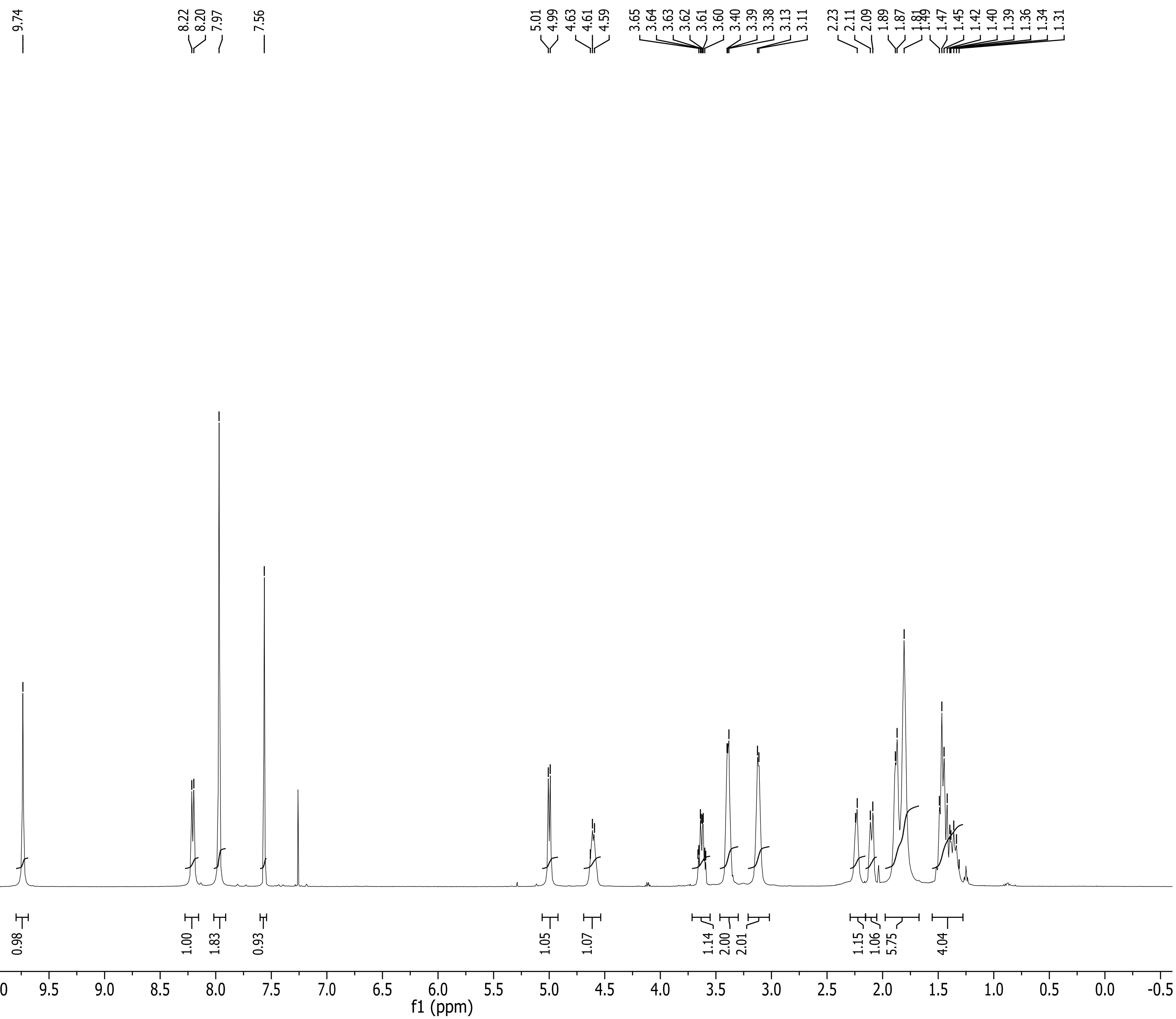
^{13}C NMR of **2g** in $CDCl_3$



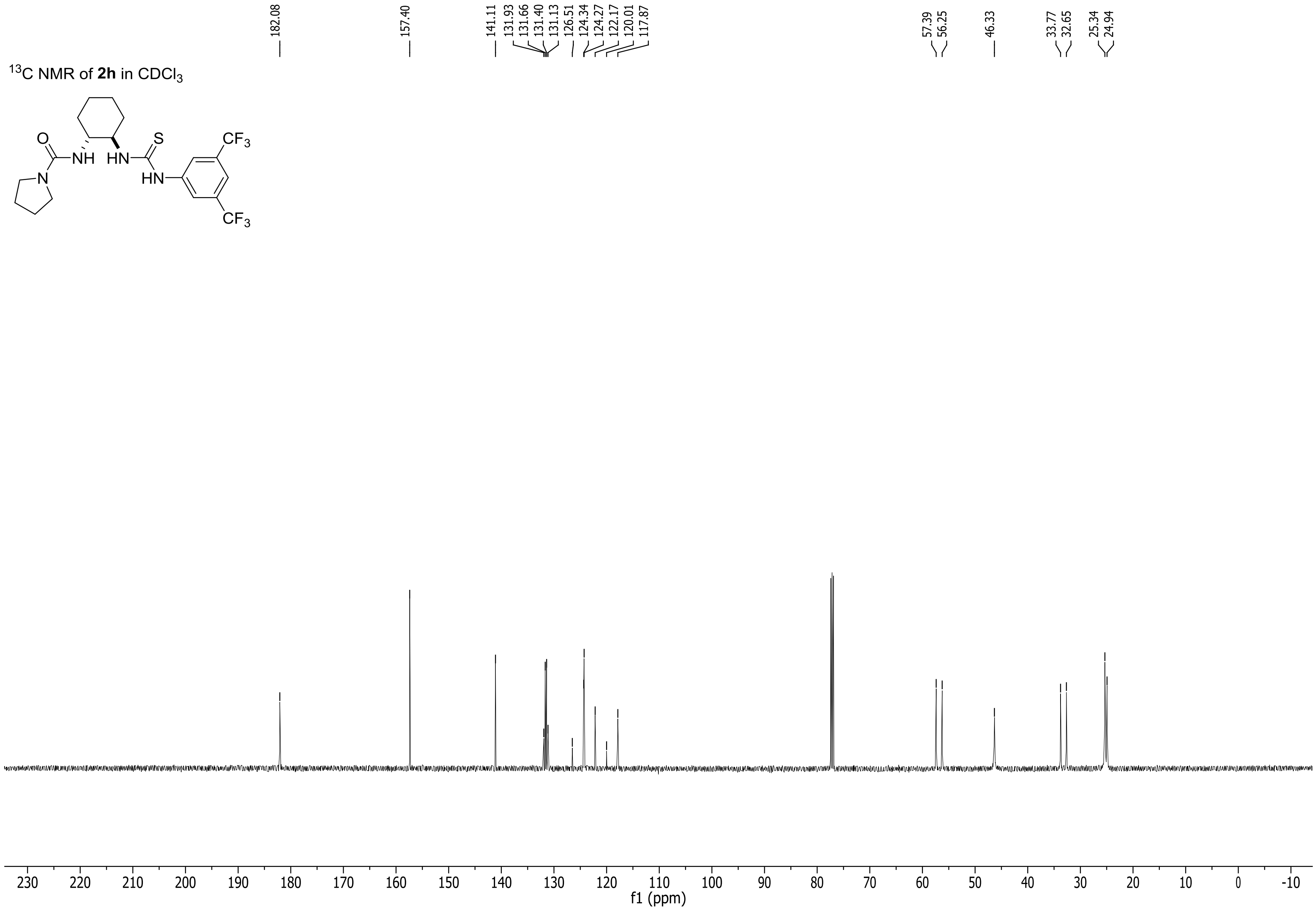


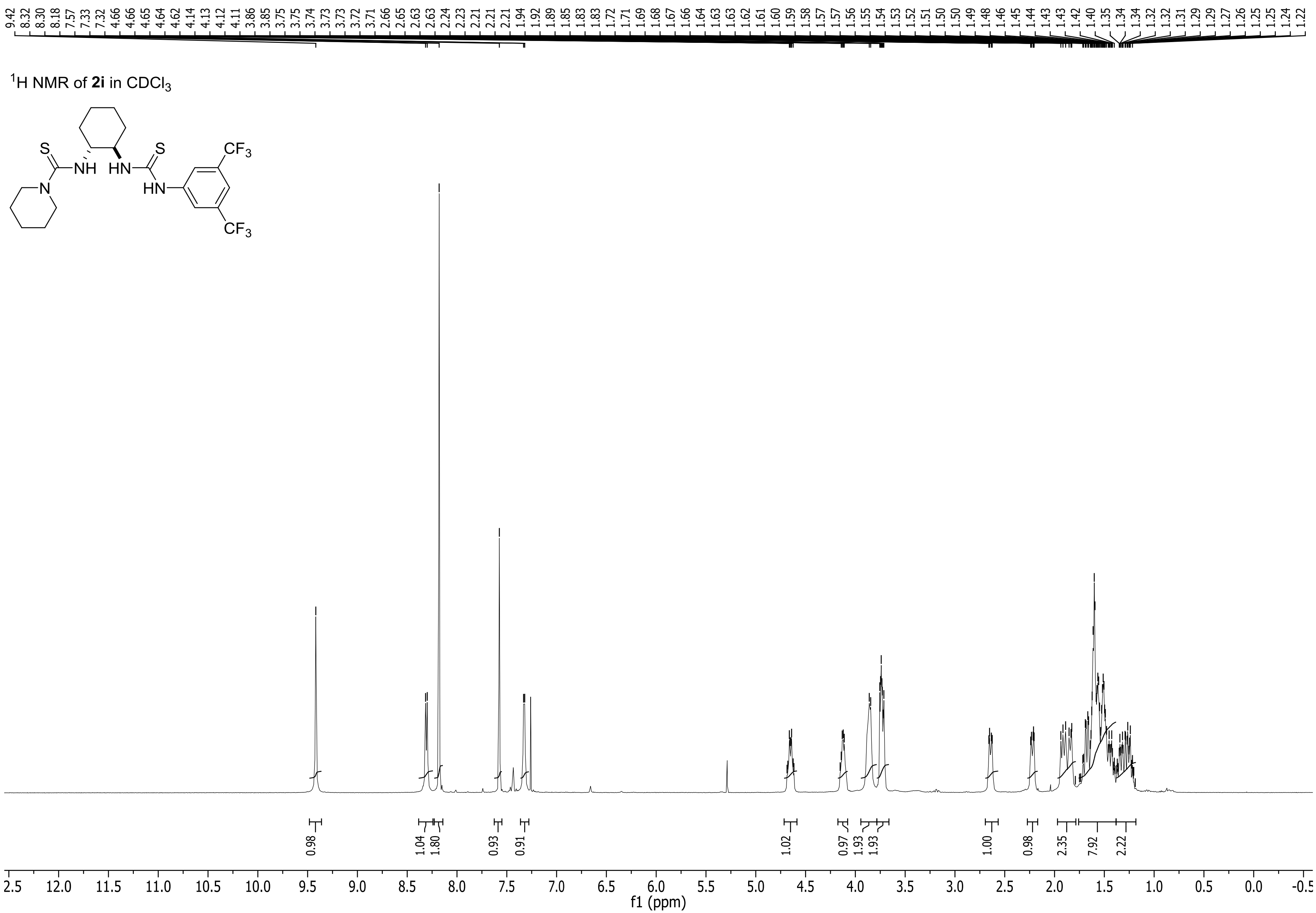
^1H NMR of **2h** in $CDCl_3$





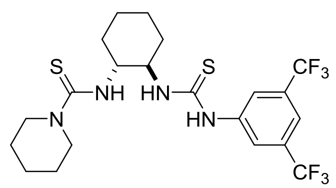
^{13}C NMR of **2h** in $CDCl_3$

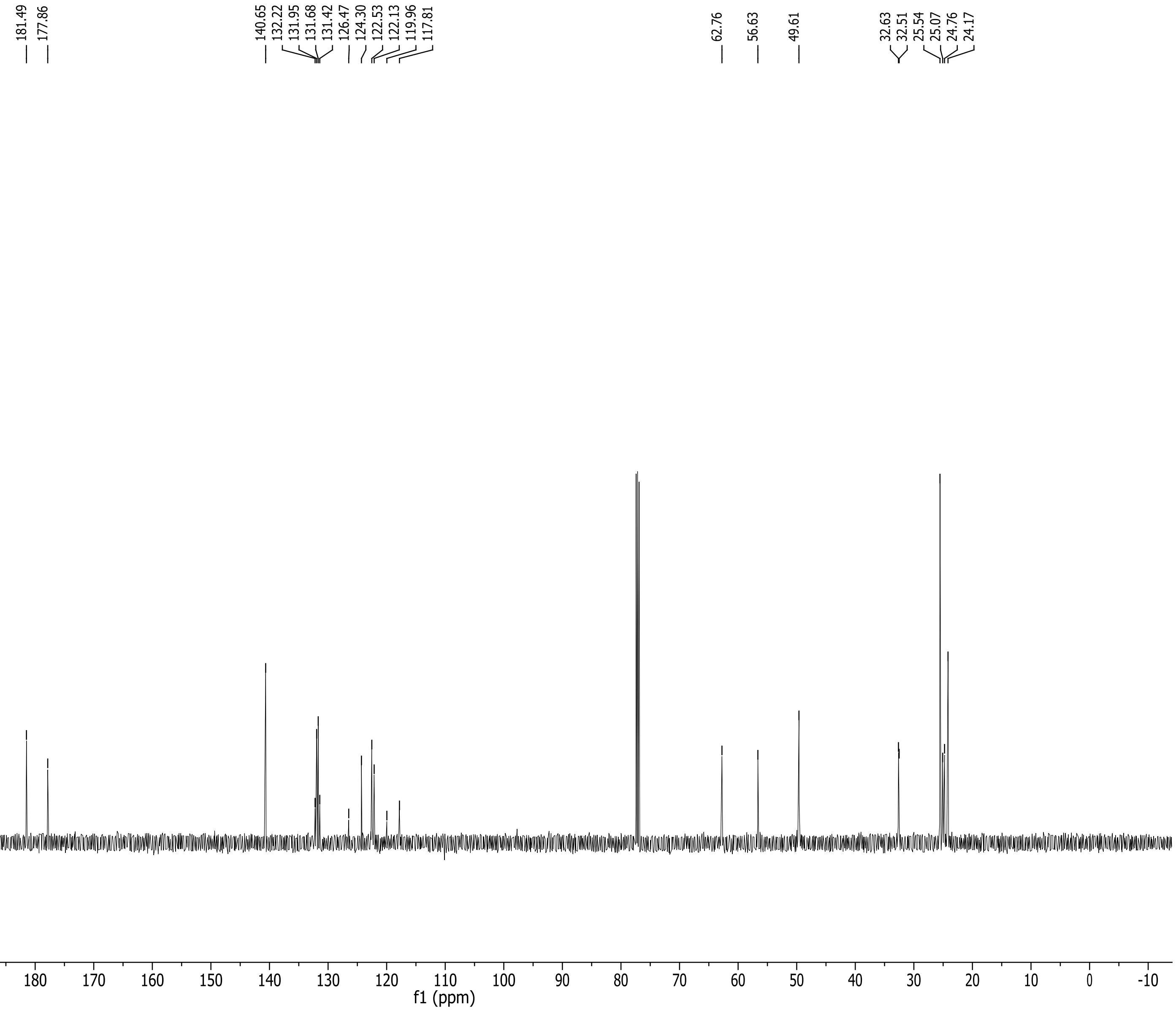




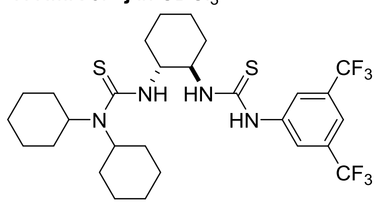
¹H NMR of 2i in CDCl3
f1 (ppm)

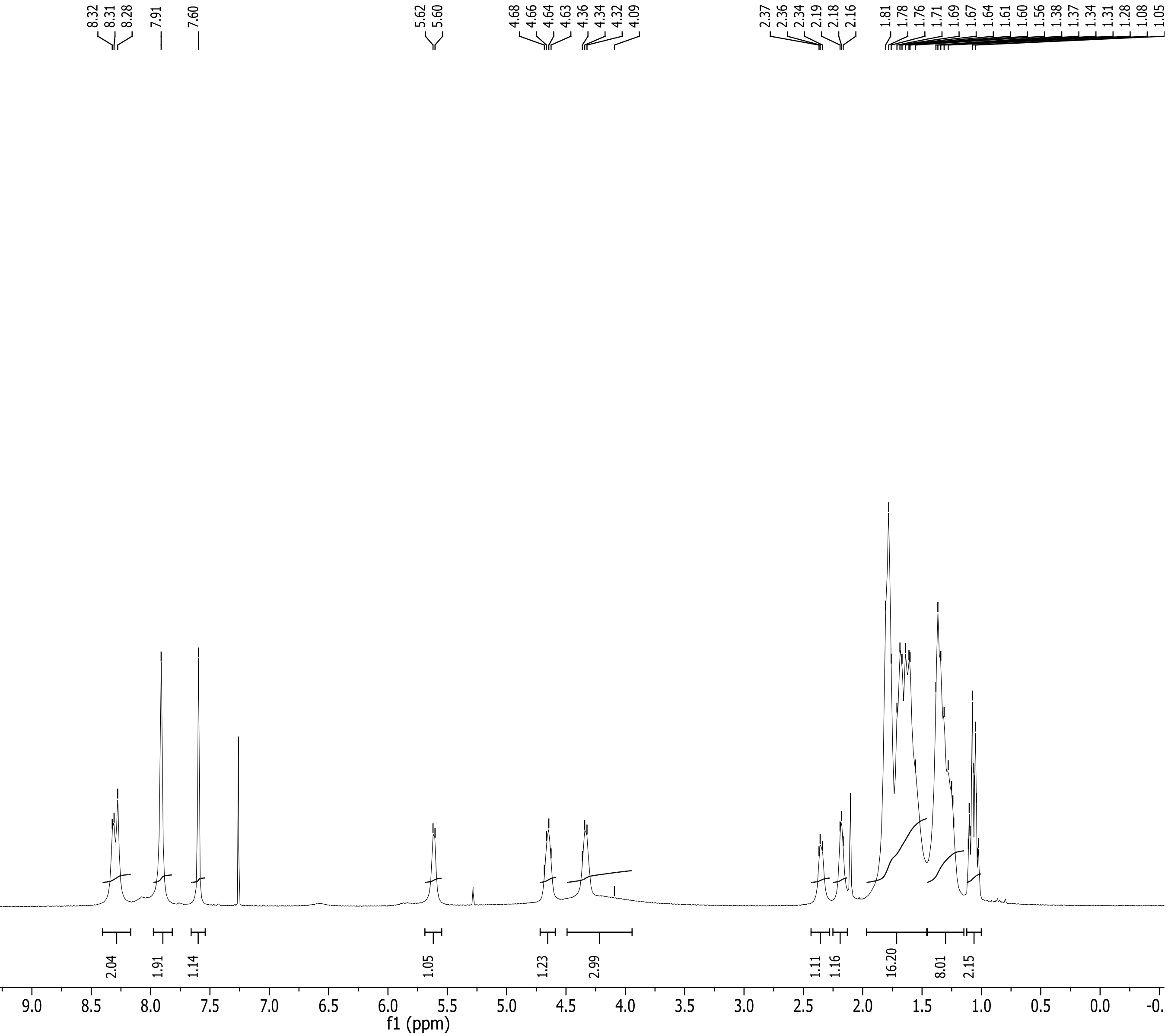
^{13}C NMR of **2i** in $CDCl_3$

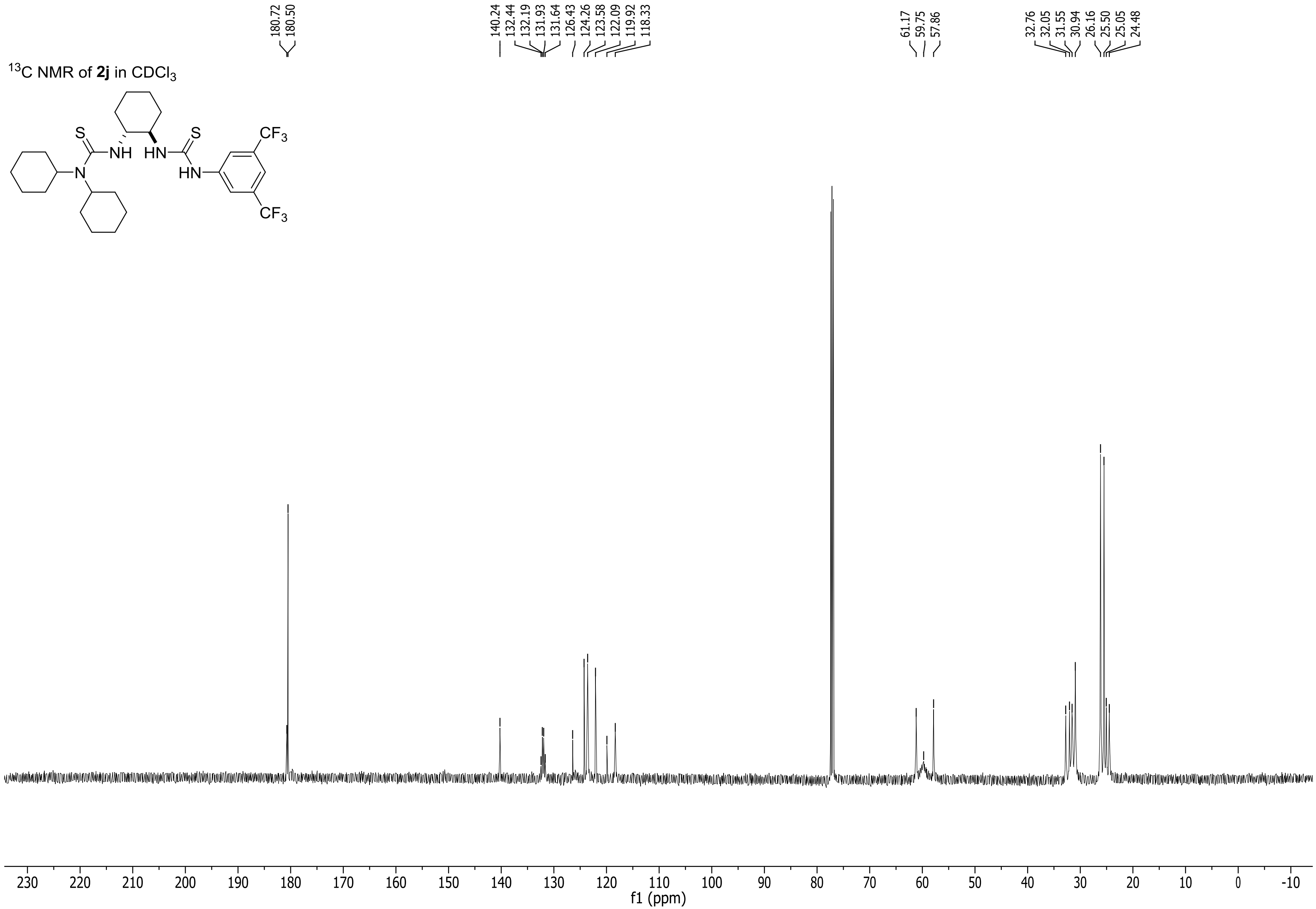




[1]H NMR of **2j** in $CDCl_3$

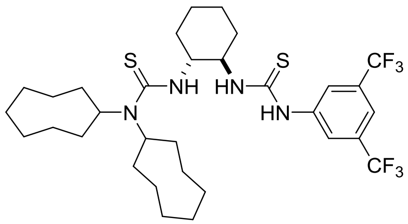


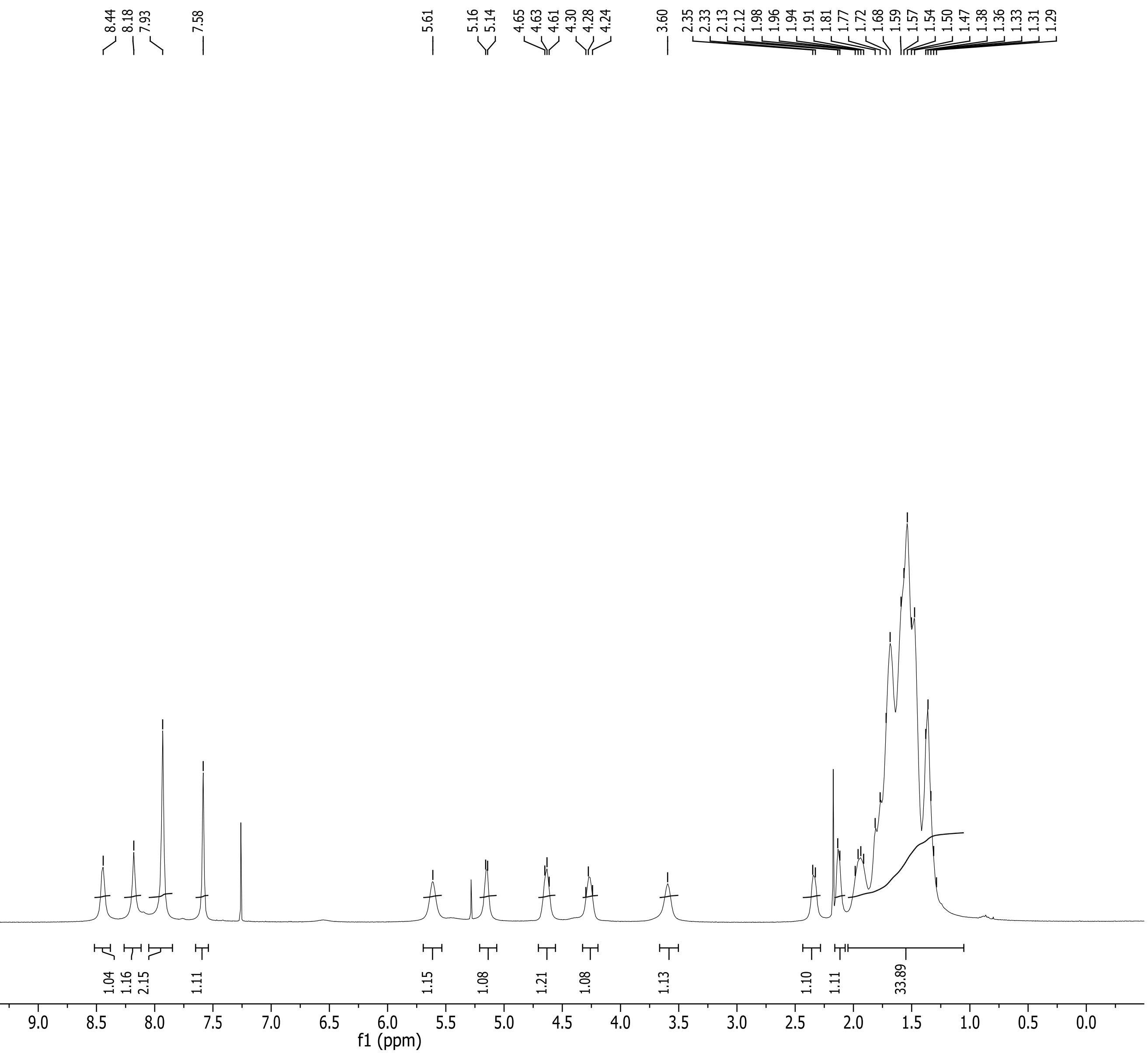




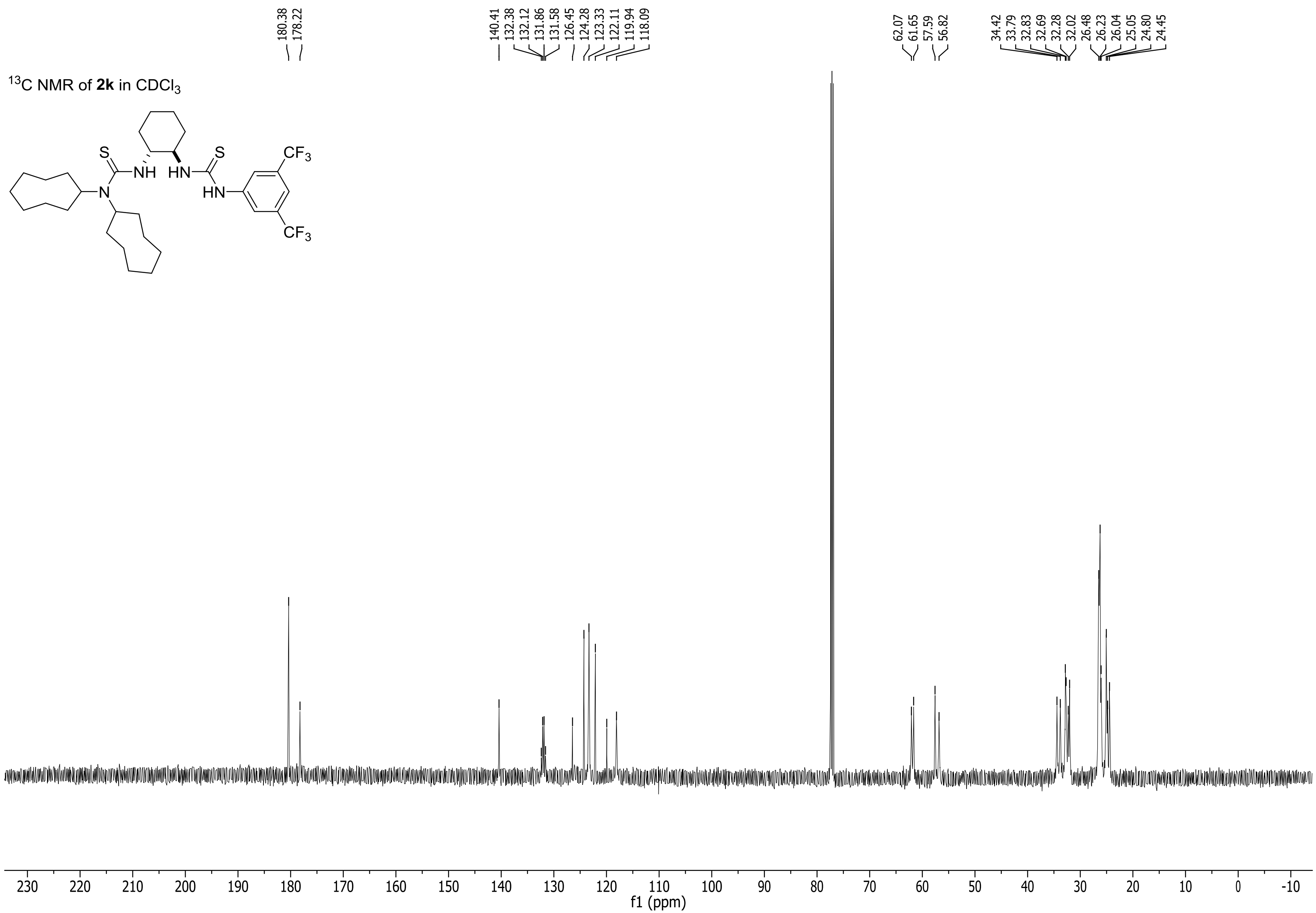
180.72
180.50
140.24
132.44
132.19
131.93
131.64
126.43
124.26
123.58
122.09
119.92
118.33
61.17
59.75
57.86
32.76
32.05
31.55
30.94
26.16
25.50
25.05
24.48
^{13}C NMR of **2j** in CDCl$_3$
S
S
CF$_3$
NH
HN
N
HN
CF$_3$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

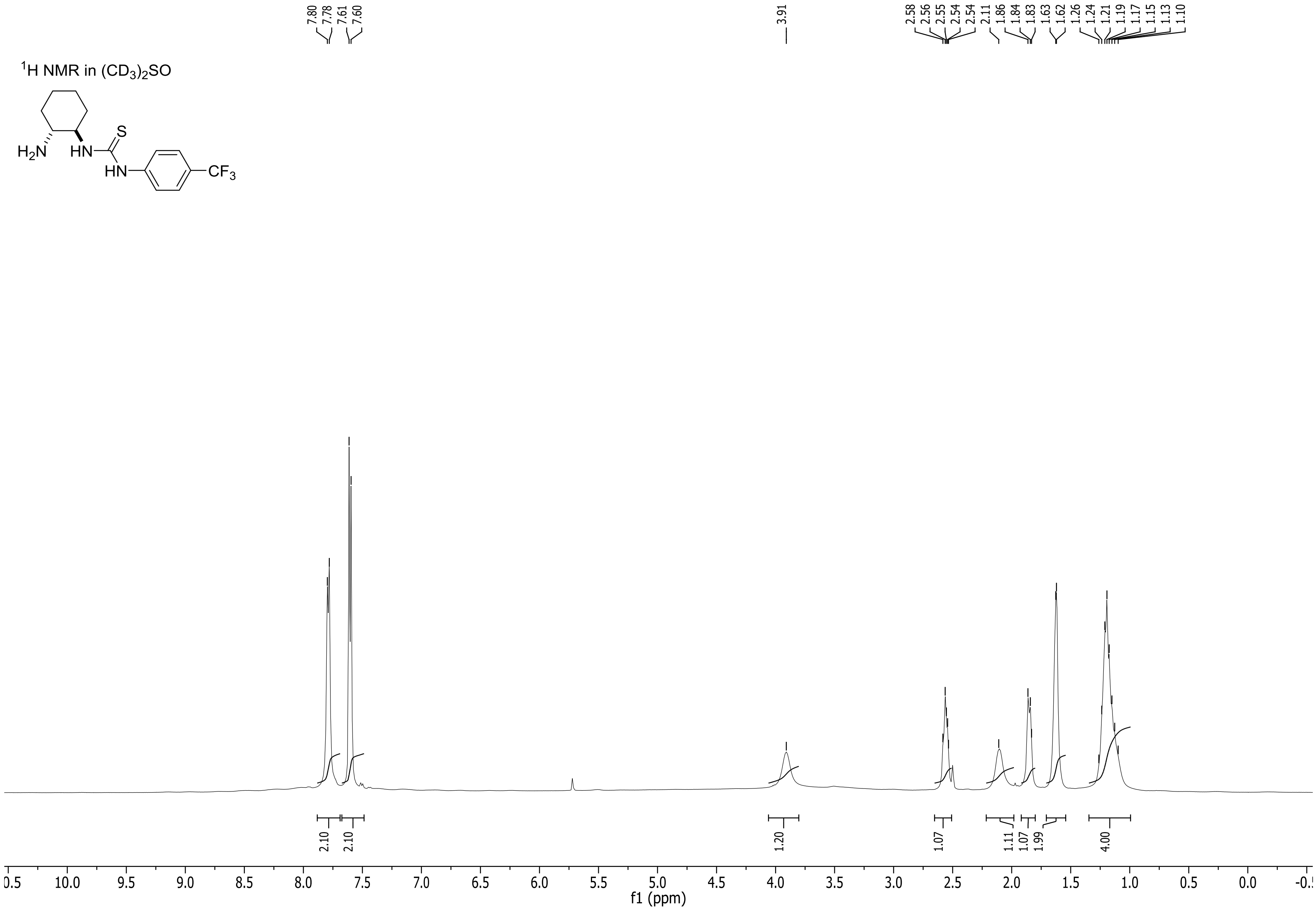
^{1}H NMR of **2k** in $CDCl_3$



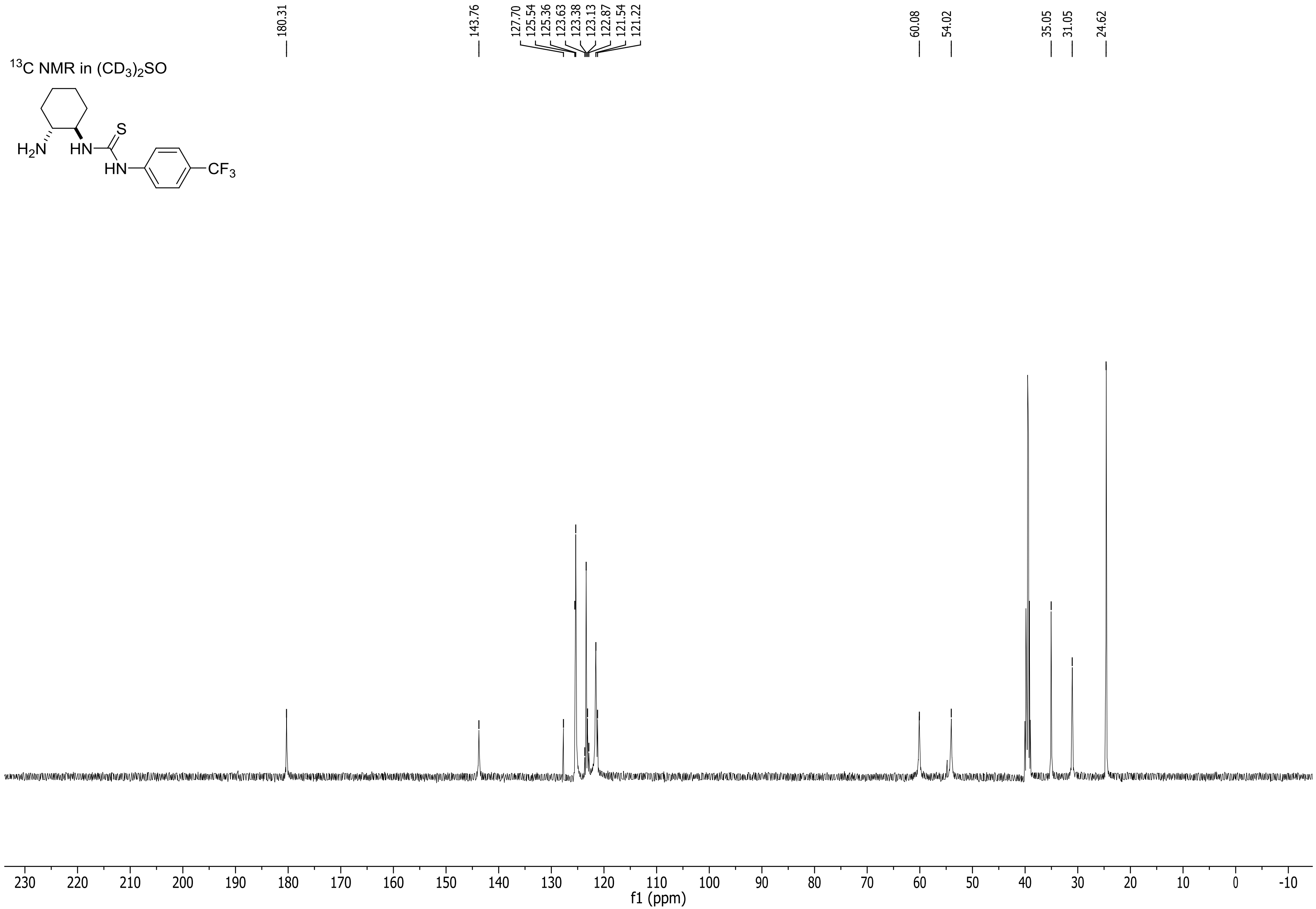


^{13}C NMR of **2k** in $CDCl_3$

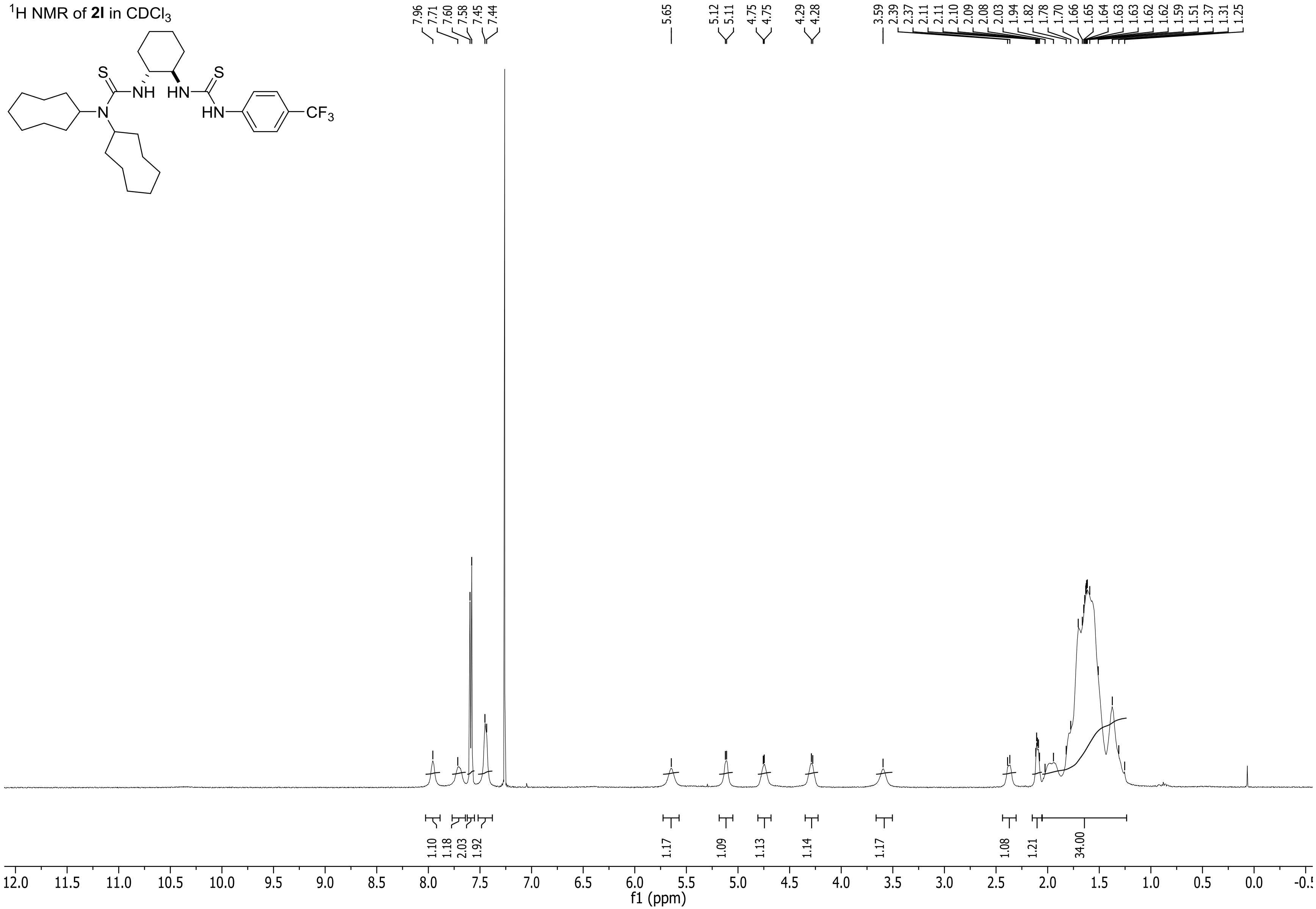


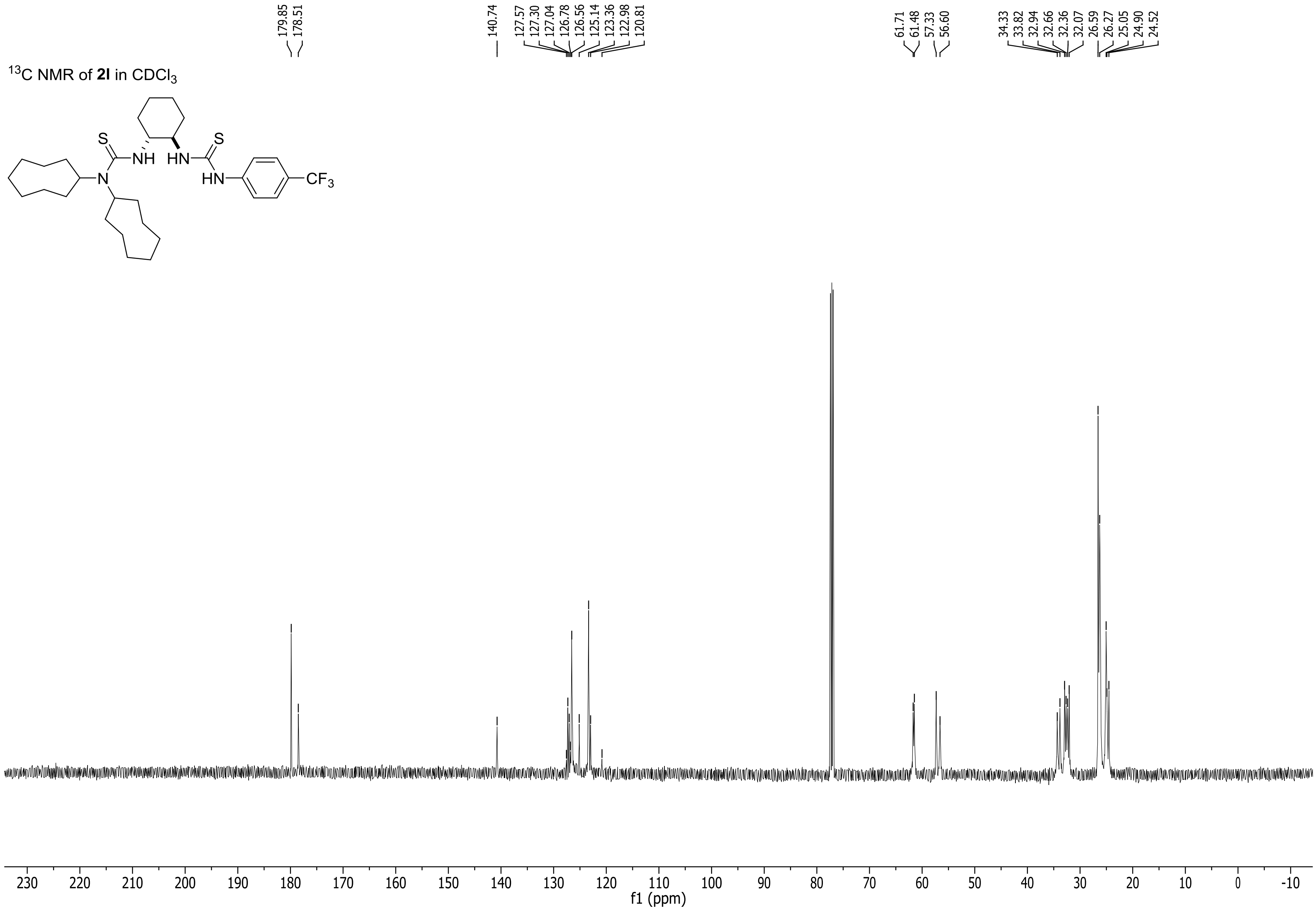


1H NMR in (CD3)2SO
7.80
7.78
7.61
7.60
3.91
2.58
2.56
2.55
2.54
2.54
2.11
1.86
1.84
1.83
1.63
1.62
1.26
1.24
1.21
1.19
1.17
1.15
1.13
1.10
2.10
2.10
1.20
1.07
1.11
1.07
1.99
4.00
f1 (ppm)


^{13}C NMR in $(CD_3)_2SO$
H_2N
HN
S
HN
CF_3
180.31
143.76
127.70
125.54
125.36
123.63
123.38
123.13
122.87
121.54
121.22
60.08
54.02
35.05
31.05
24.62
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

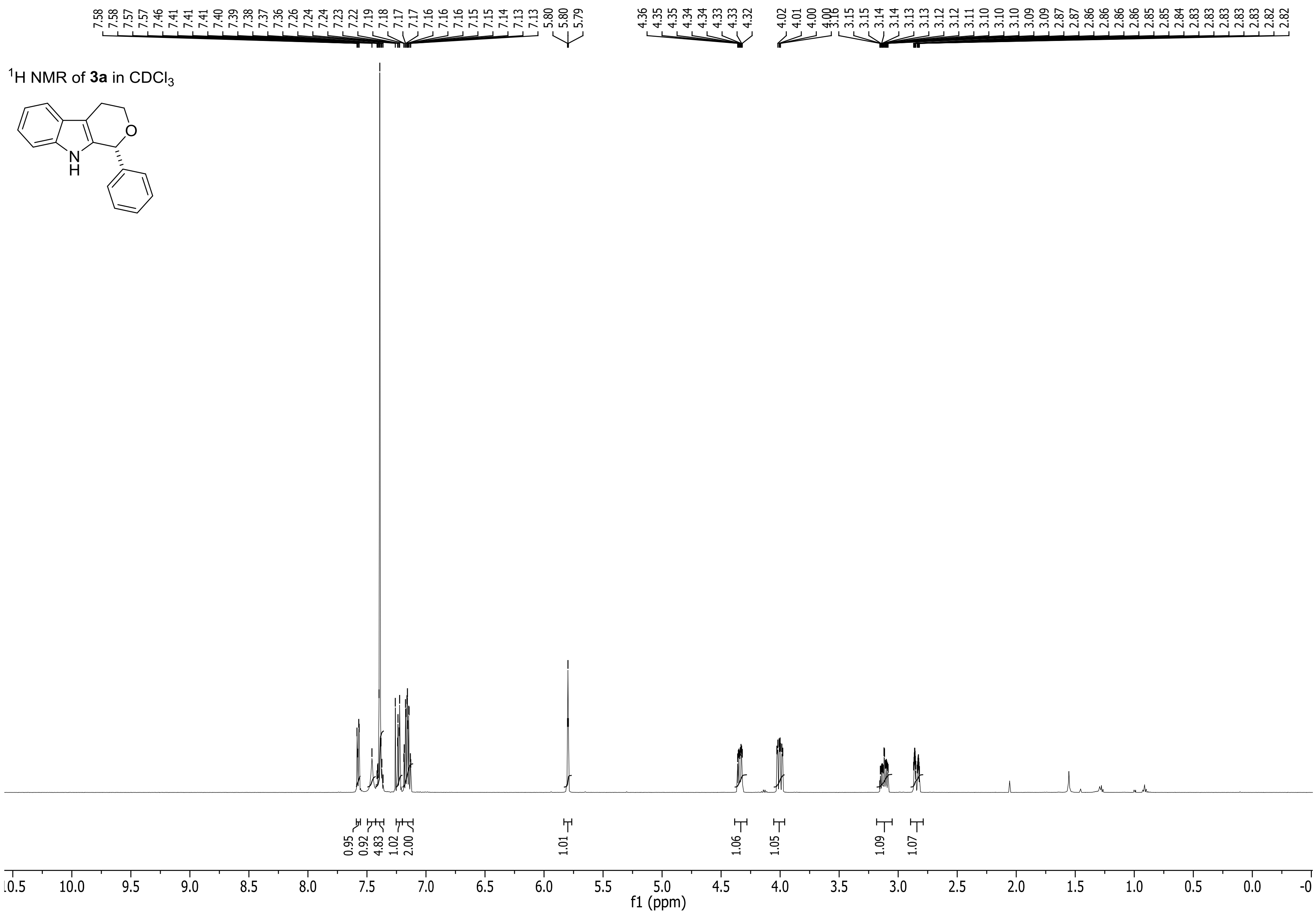
^{1}H NMR of **2l** in $CDCl_3$



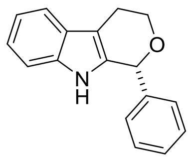


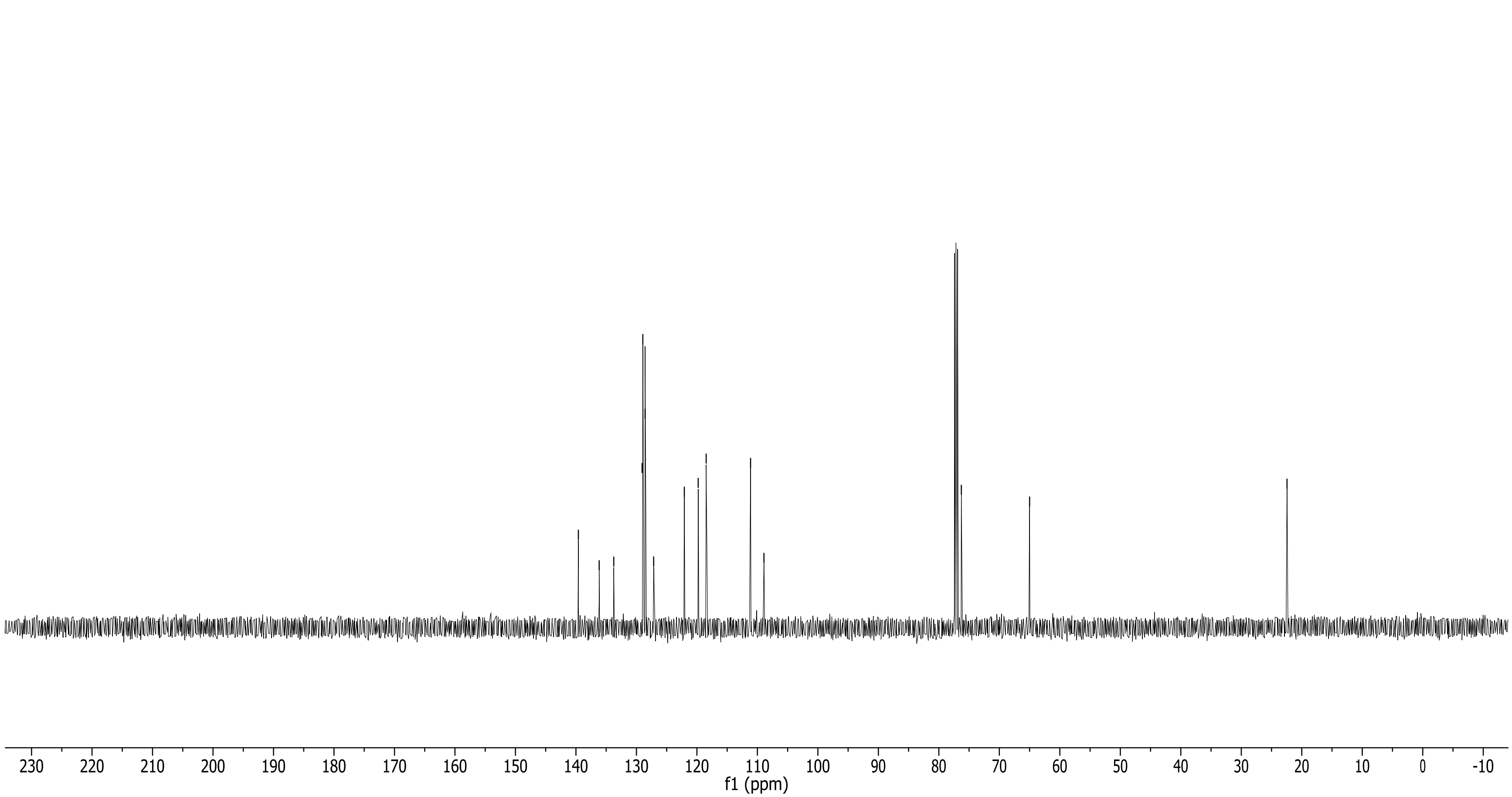
179.85
178.51
140.74
127.57
127.30
127.04
126.78
126.56
125.14
123.36
122.98
120.81
61.71
61.48
57.33
56.60
34.33
33.82
32.94
32.66
32.36
32.07
26.59
26.27
25.05
24.90
24.52
^{13}C NMR of **2l** in CDCl$_3$
S
NH
HN
S
N
HN
CF$_3$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

[1]H NMR of **3a** in $CDCl_3$

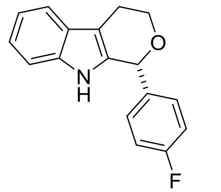


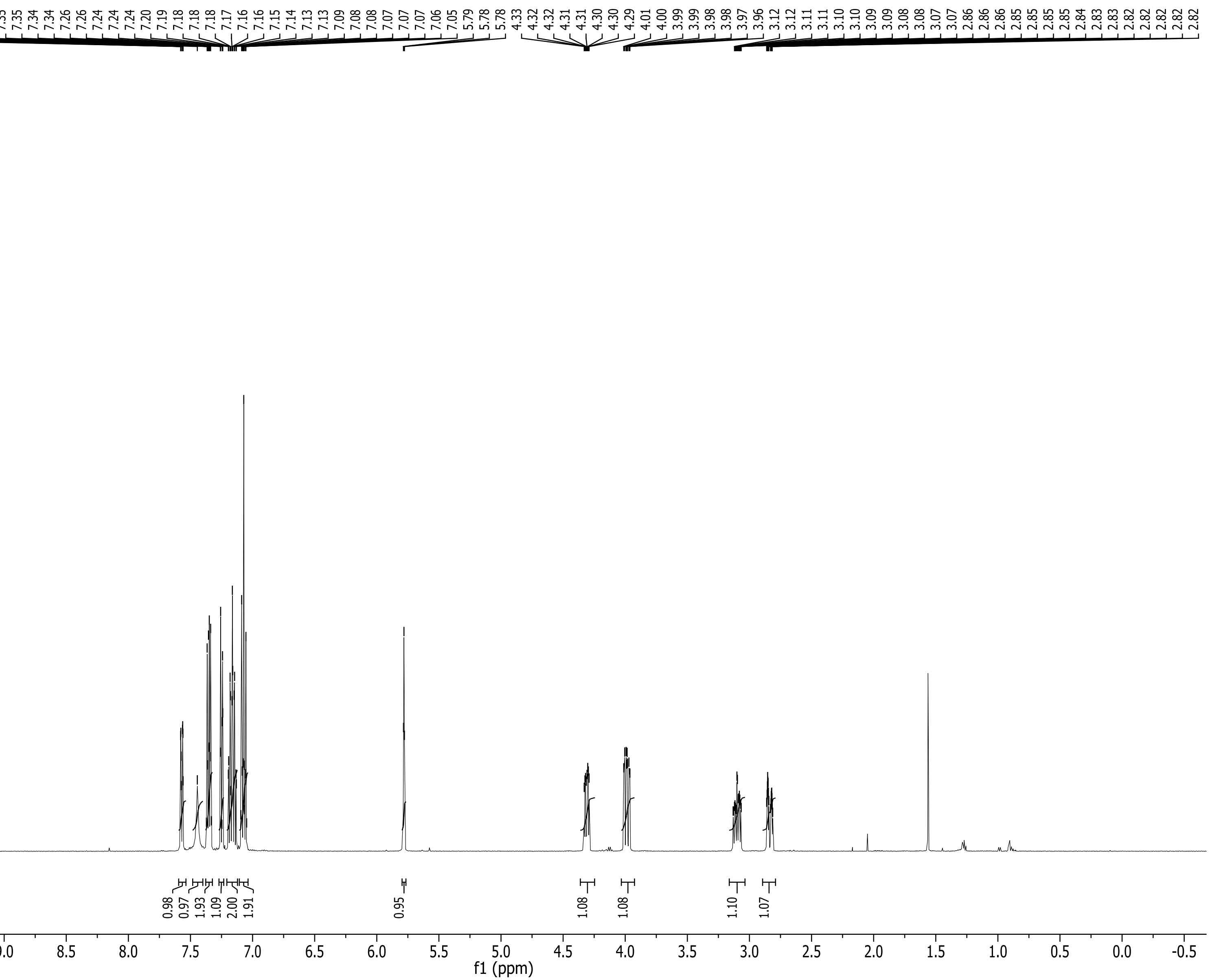
^{13}C NMR of **3a** in $CDCl_3$



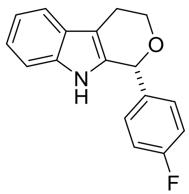


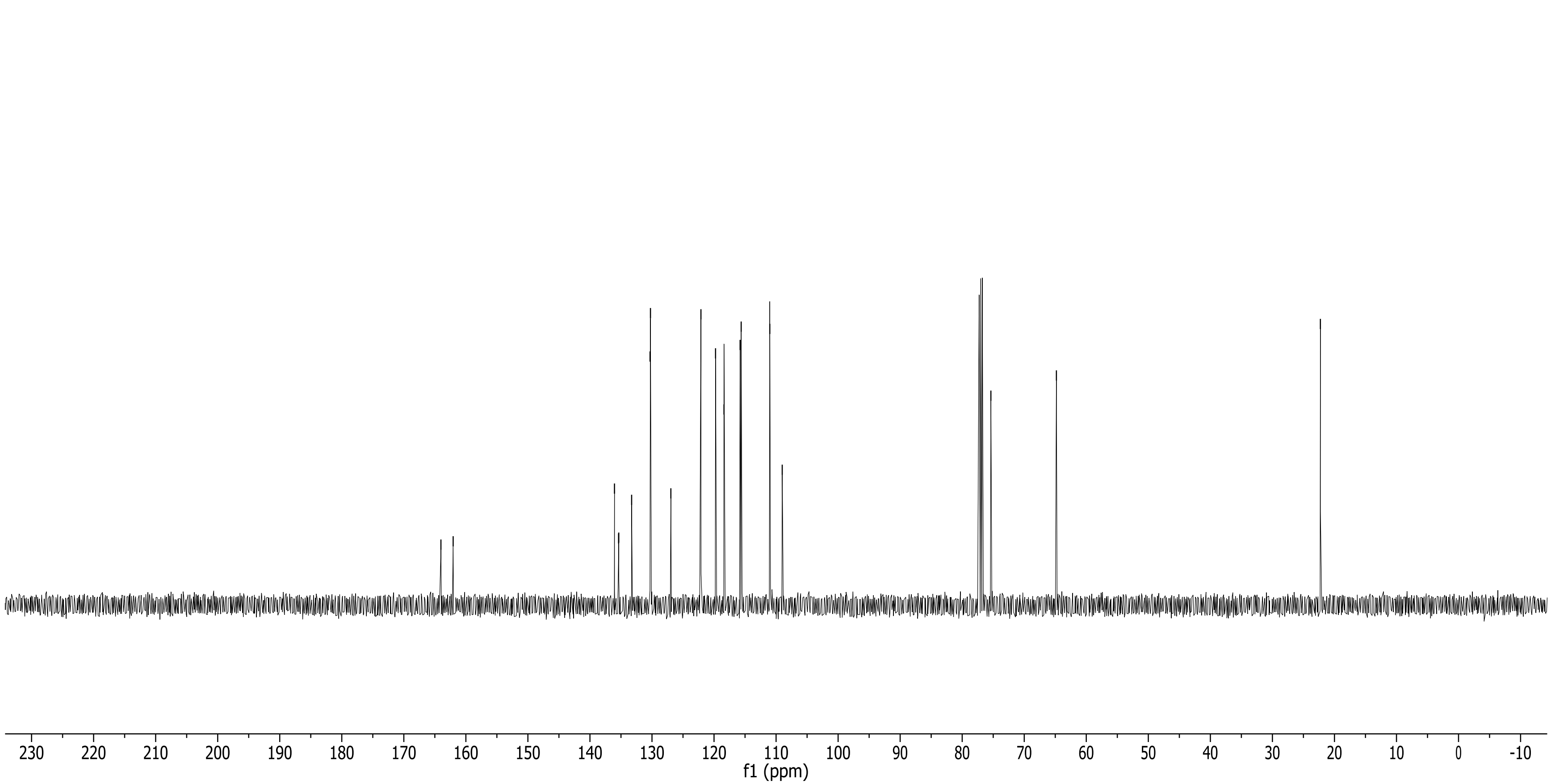
[1]H NMR of **3b** in $CDCl_3$



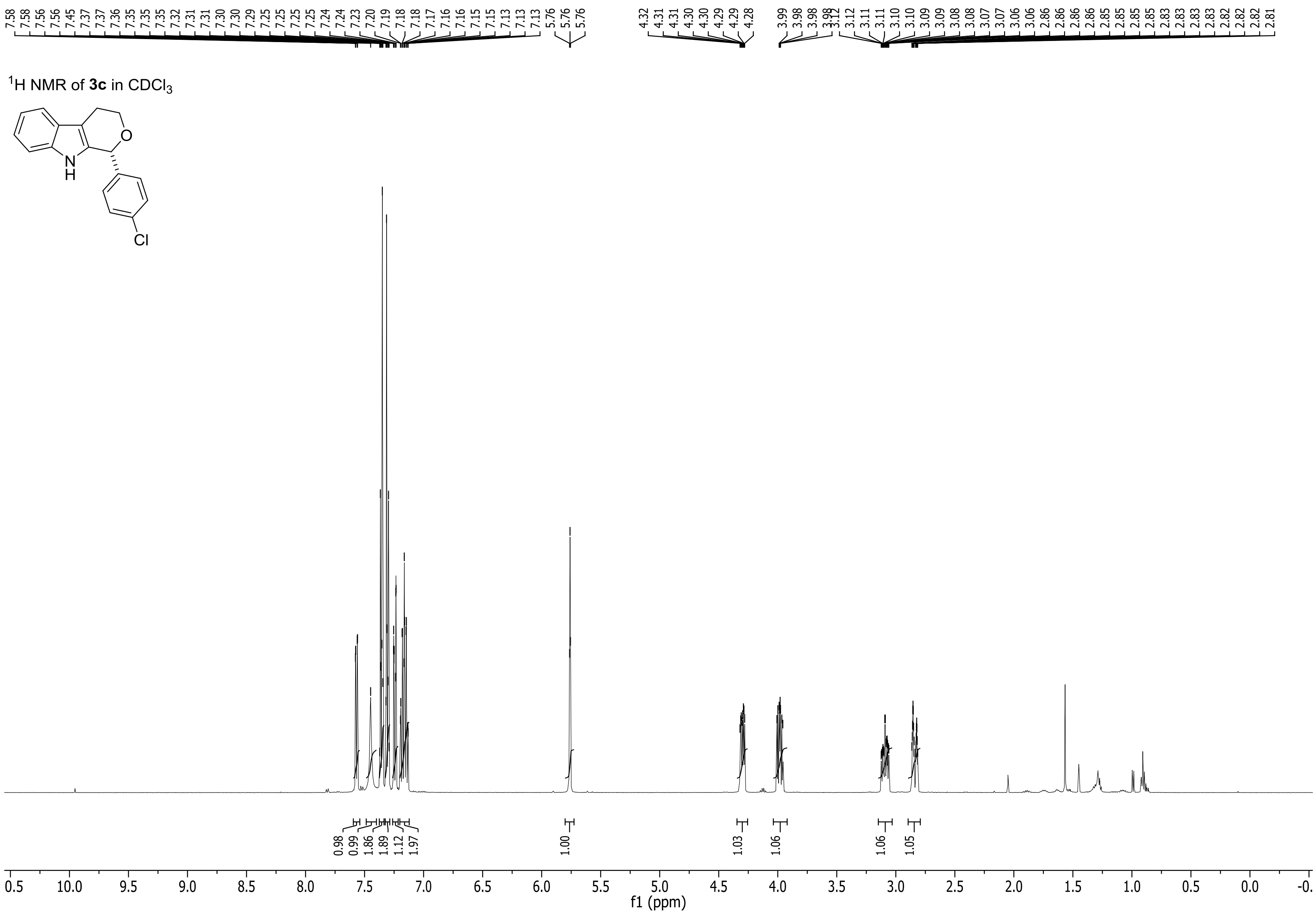


^{13}C NMR of **3b** in $CDCl_3$

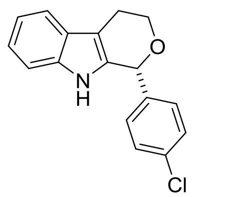


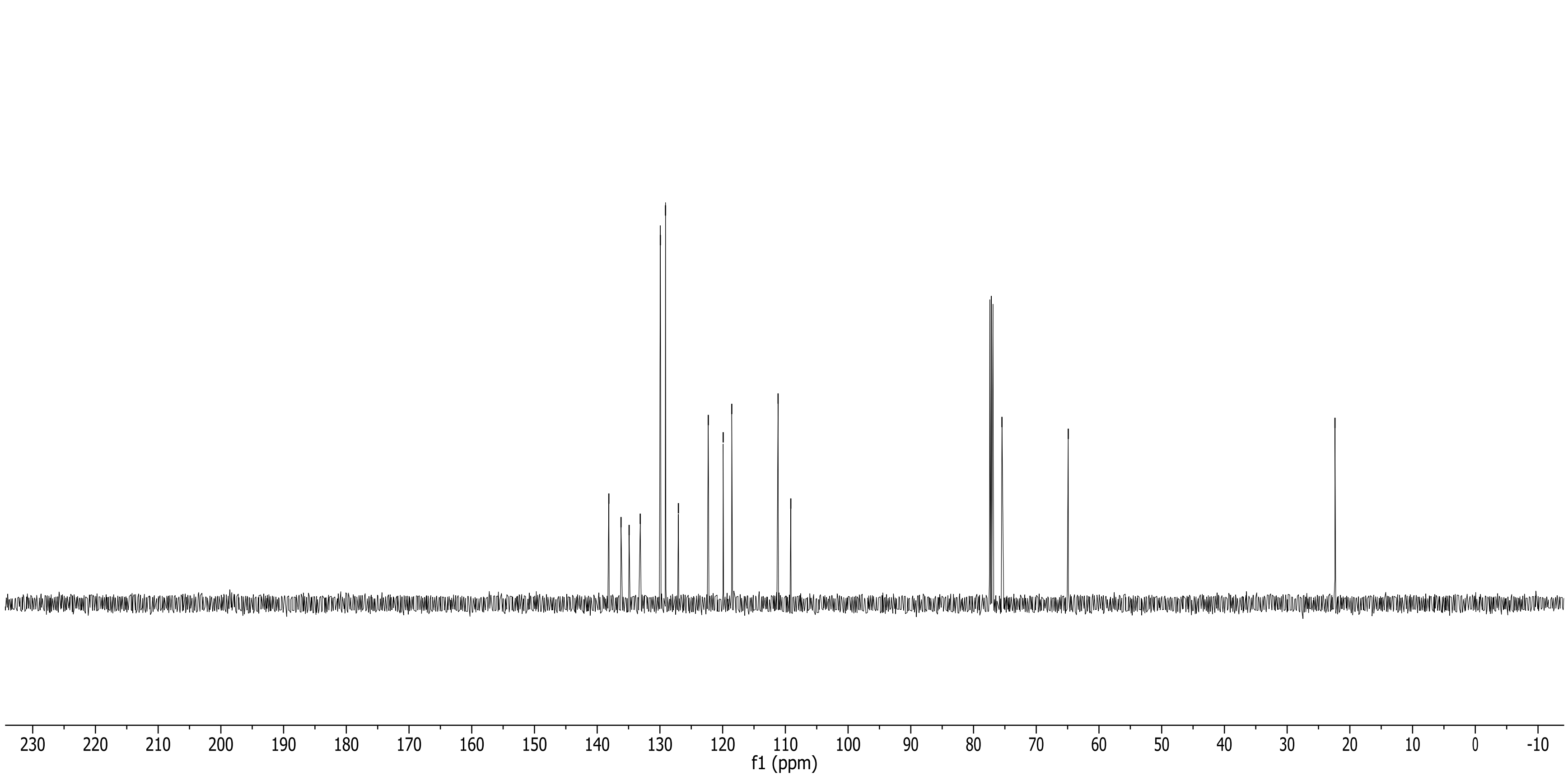


^1H NMR of **3c** in $CDCl_3$

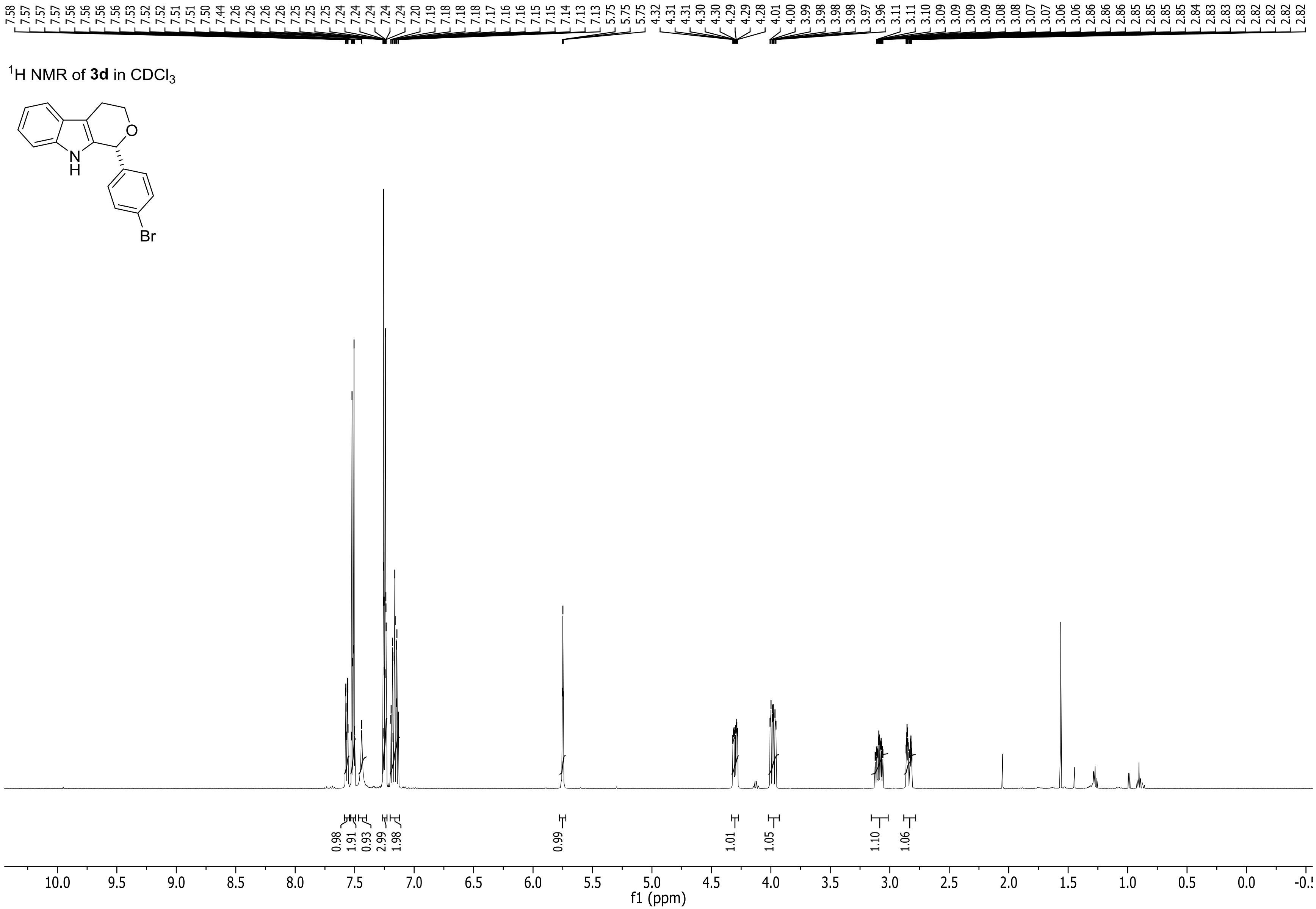


^{13}C NMR of **3c** in $CDCl_3$

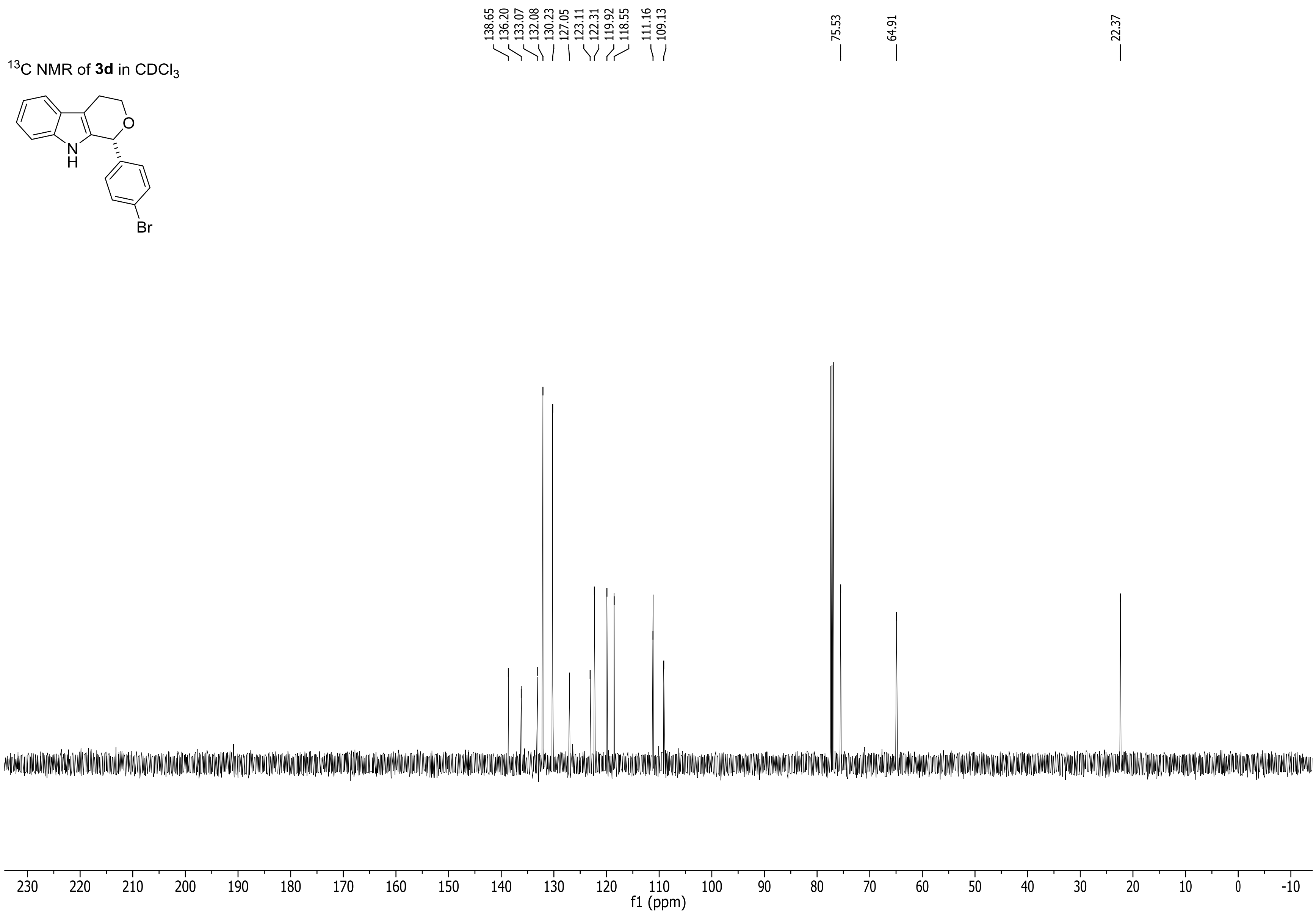




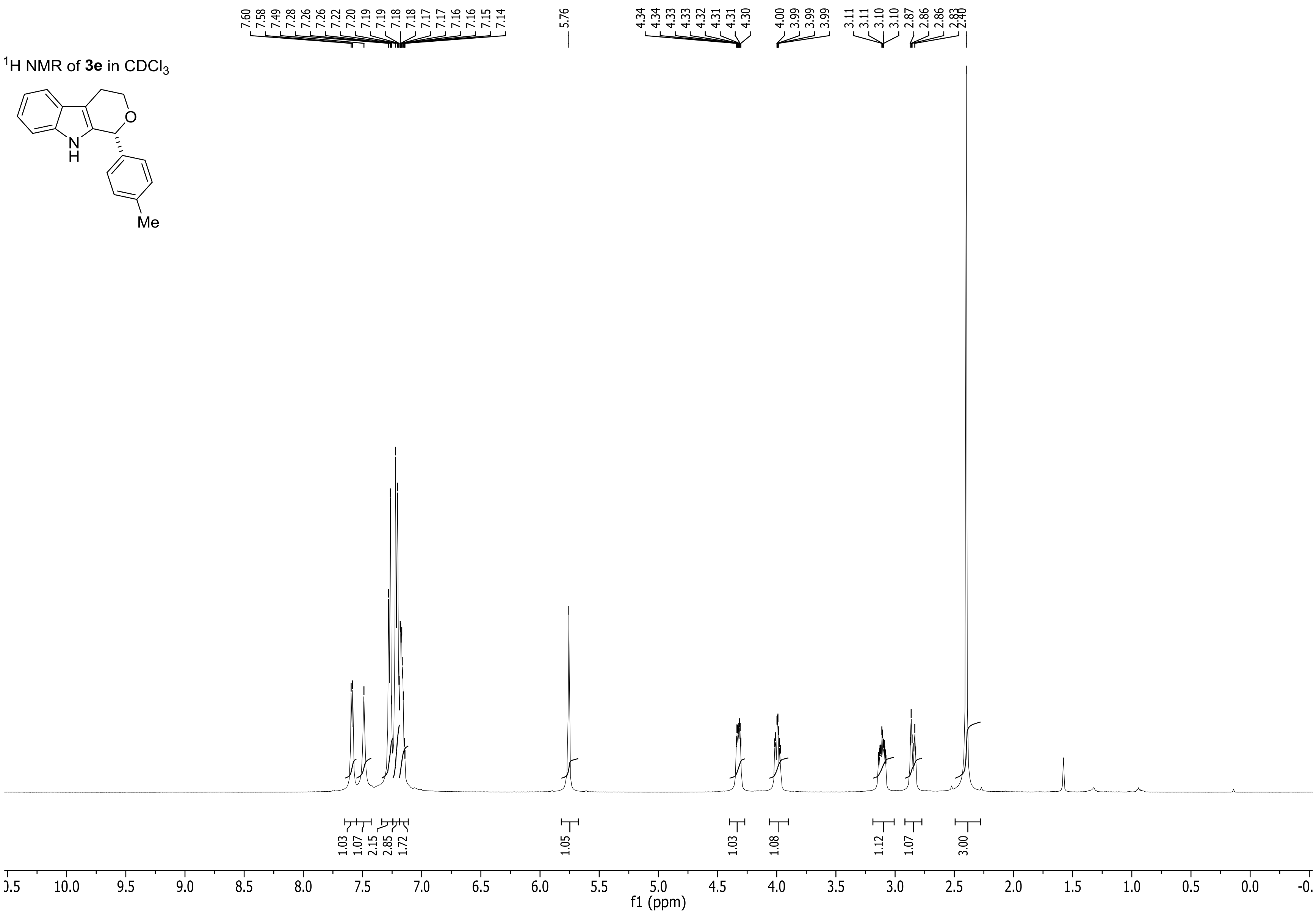
^1H NMR of **3d** in $CDCl_3$



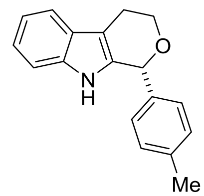
^{13}C NMR of **3d** in $CDCl_3$

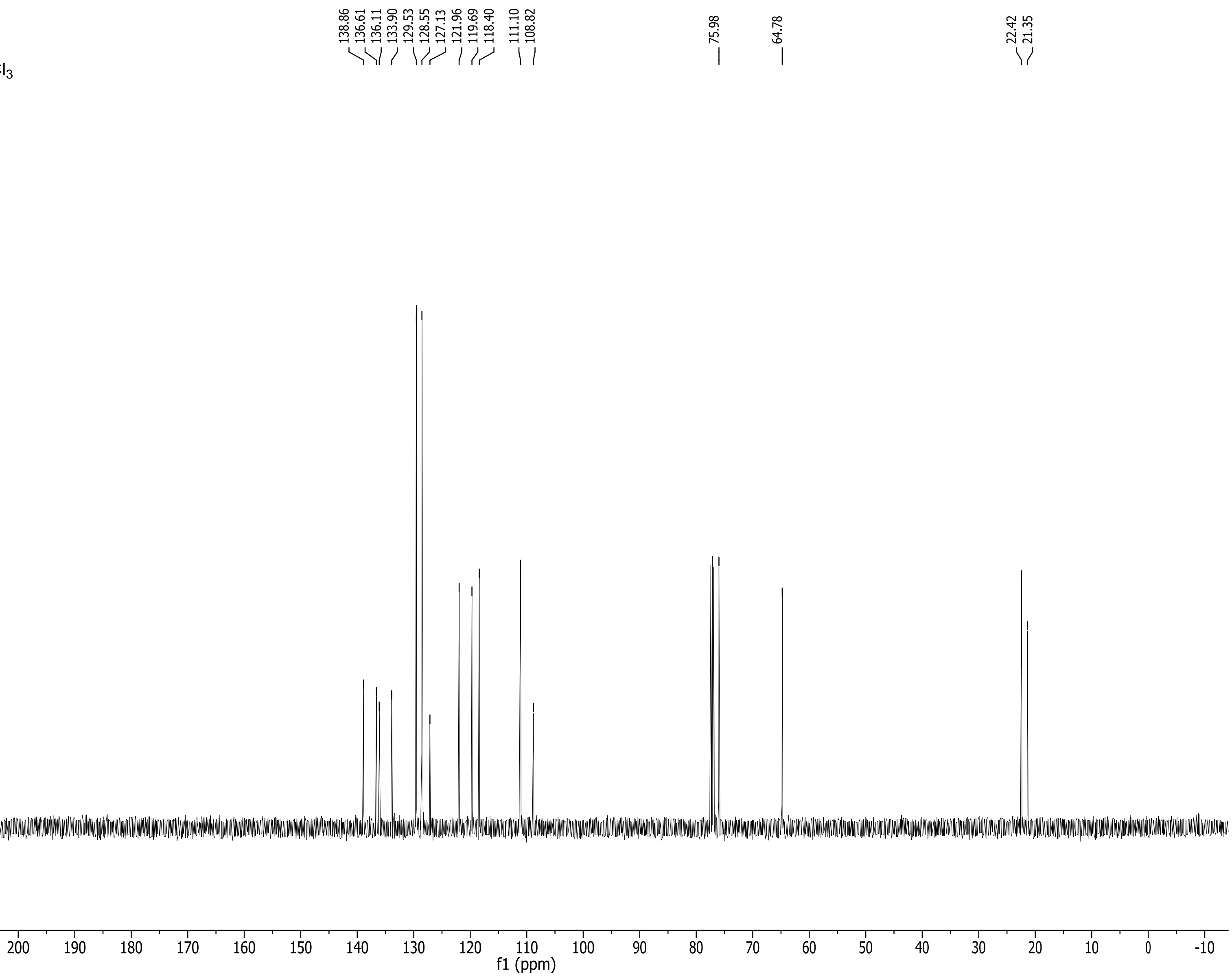


[1]H NMR of **3e** in $CDCl_3$

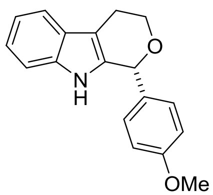


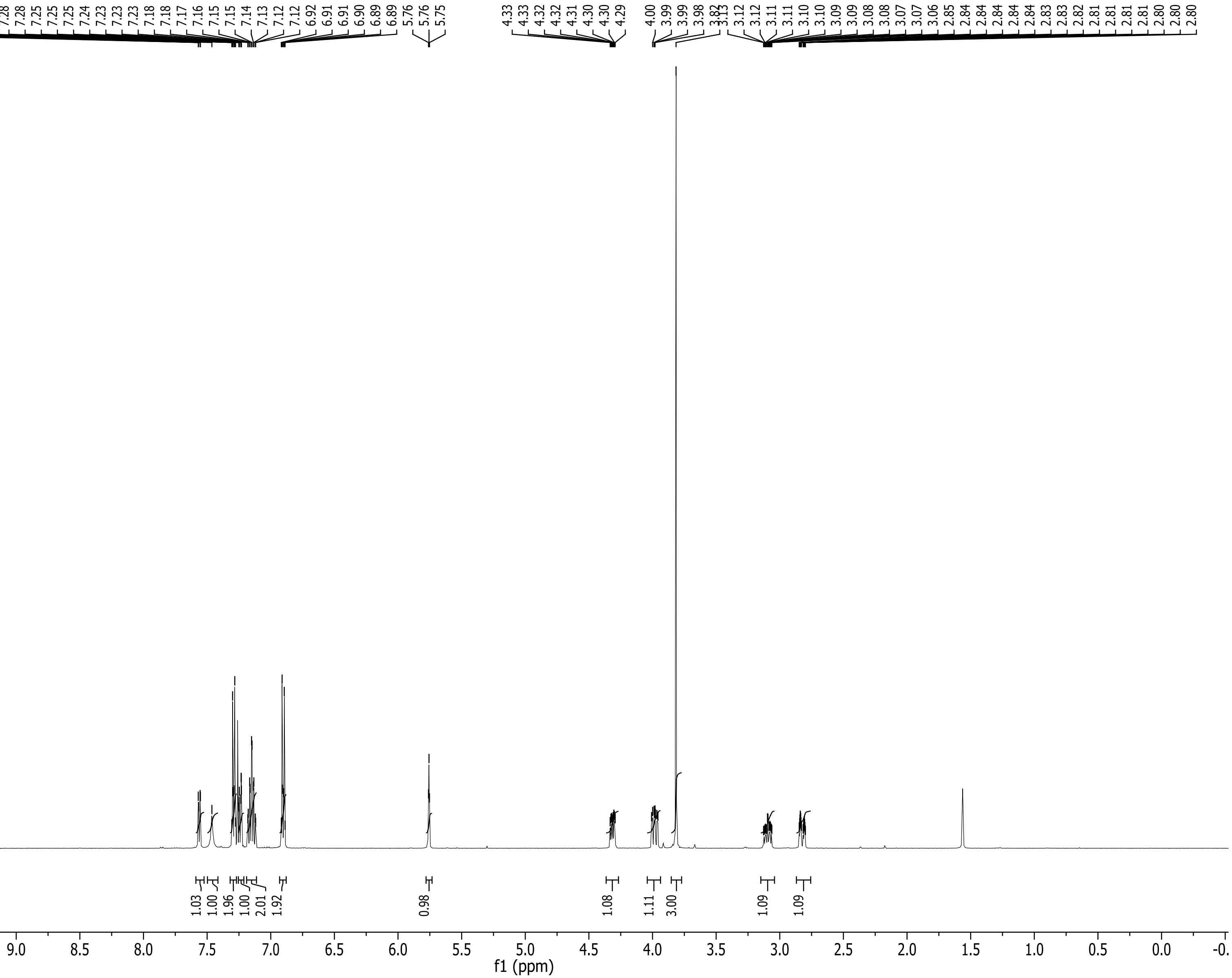
^{13}C NMR of **3e** in $CDCl_3$



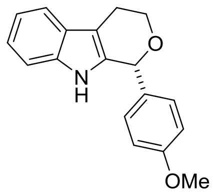


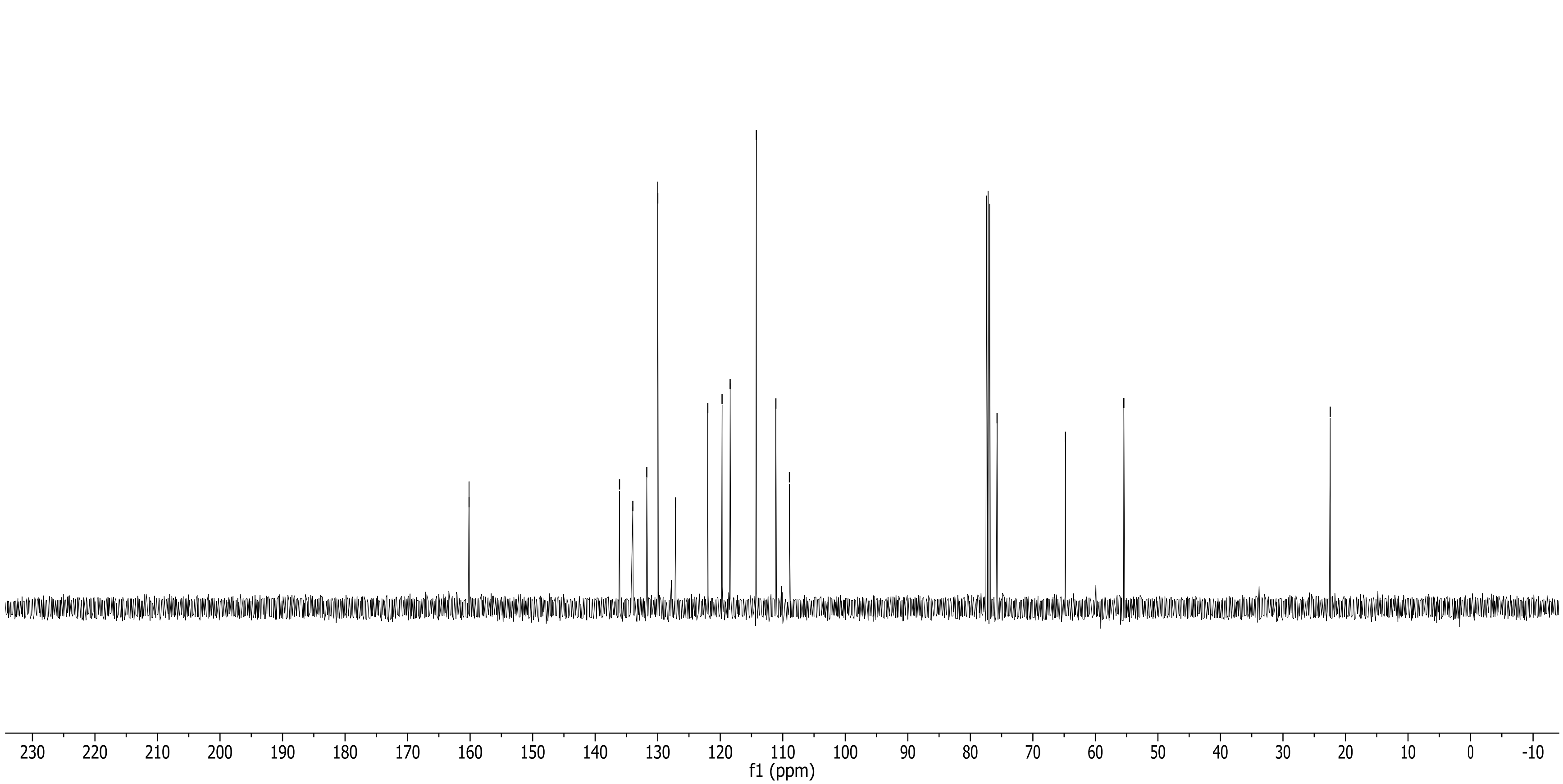
^{1}H NMR of **3f** in $CDCl_3$



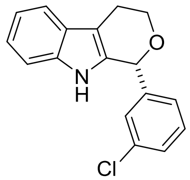


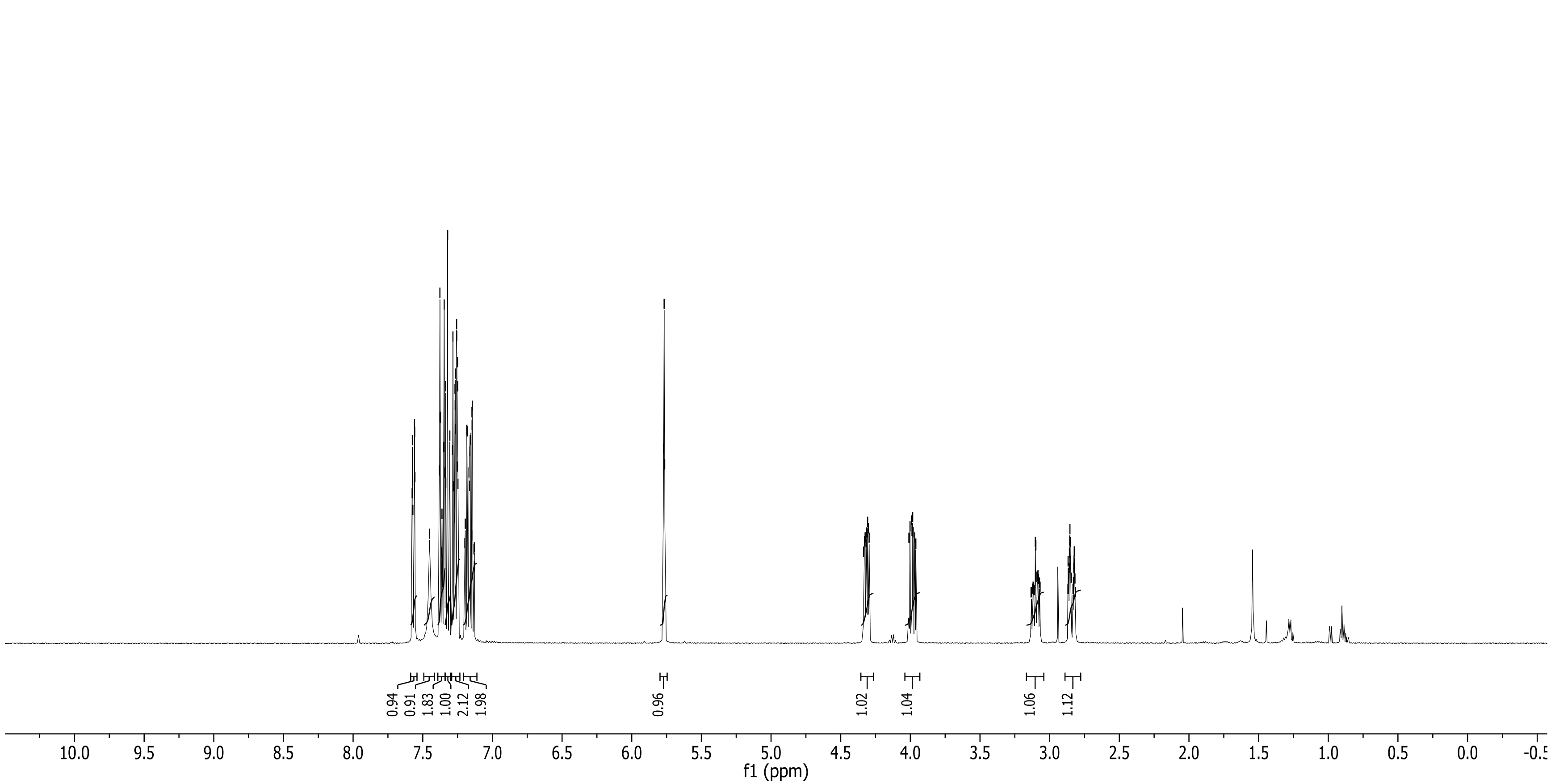
^{13}C NMR of **3f** in $CDCl_3$



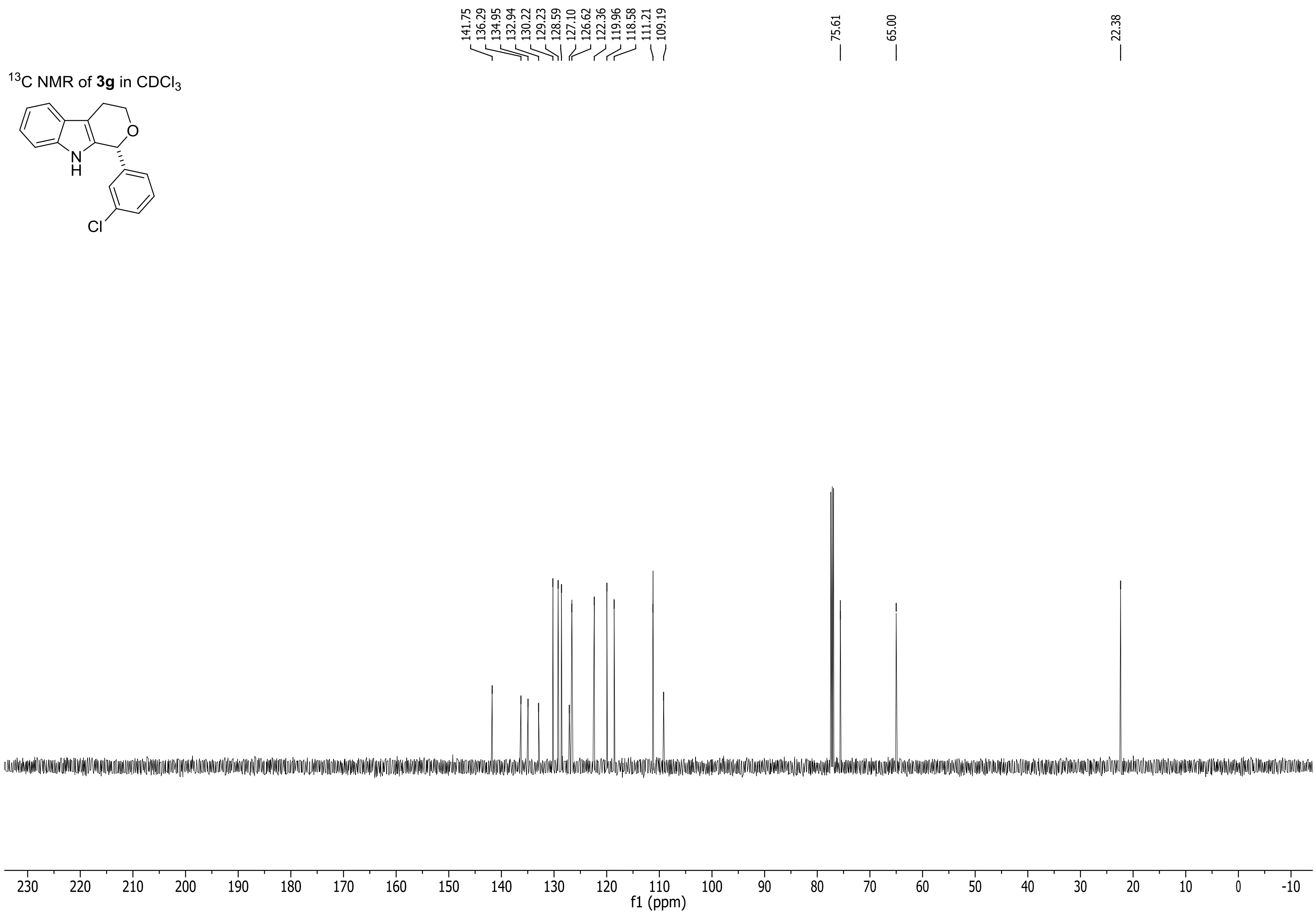


^{1}H NMR of **3g** in $CDCl_3$

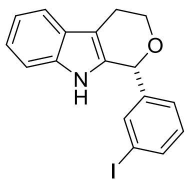


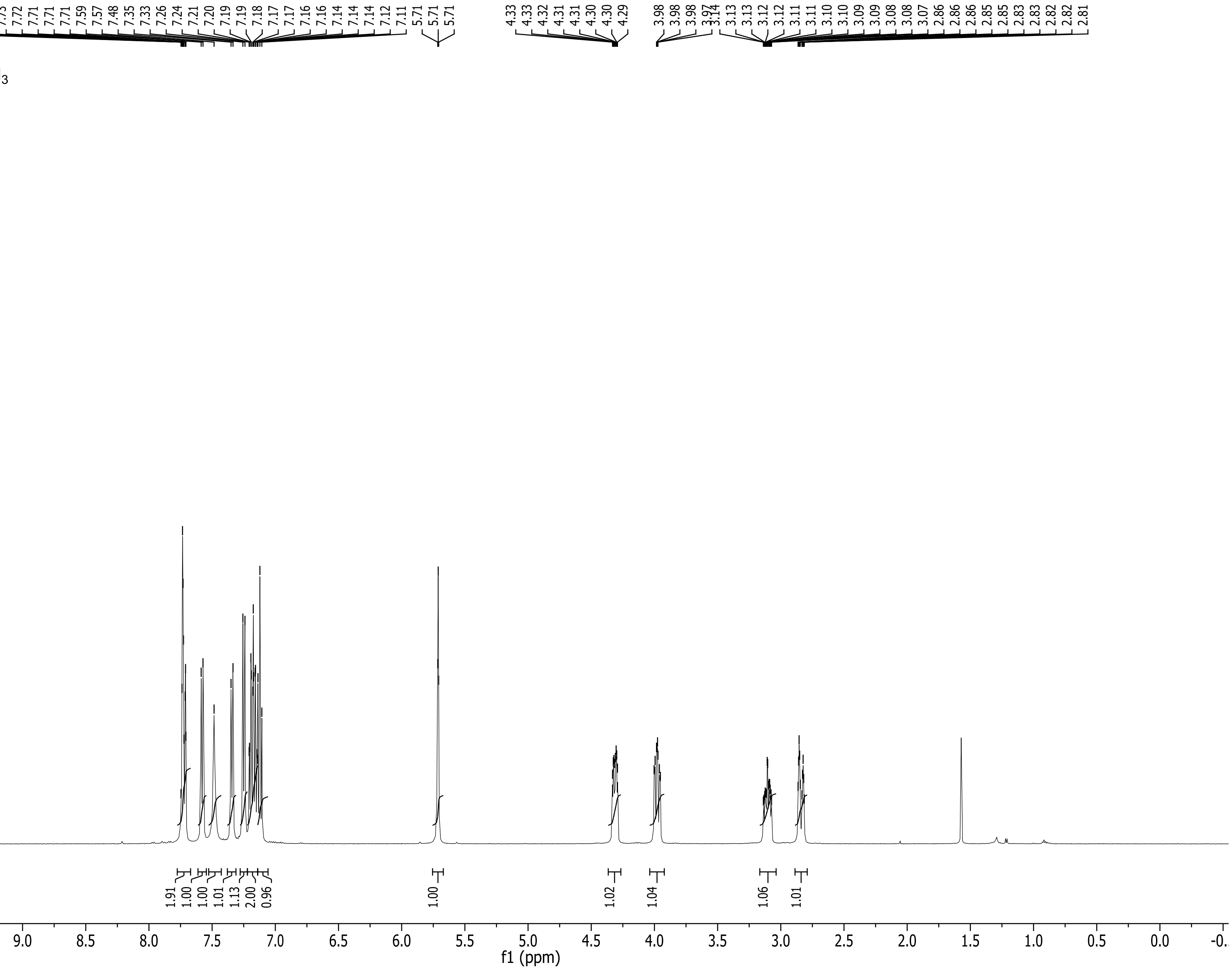


^{13}C NMR of **3g** in $CDCl_3$

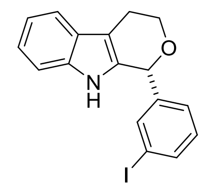


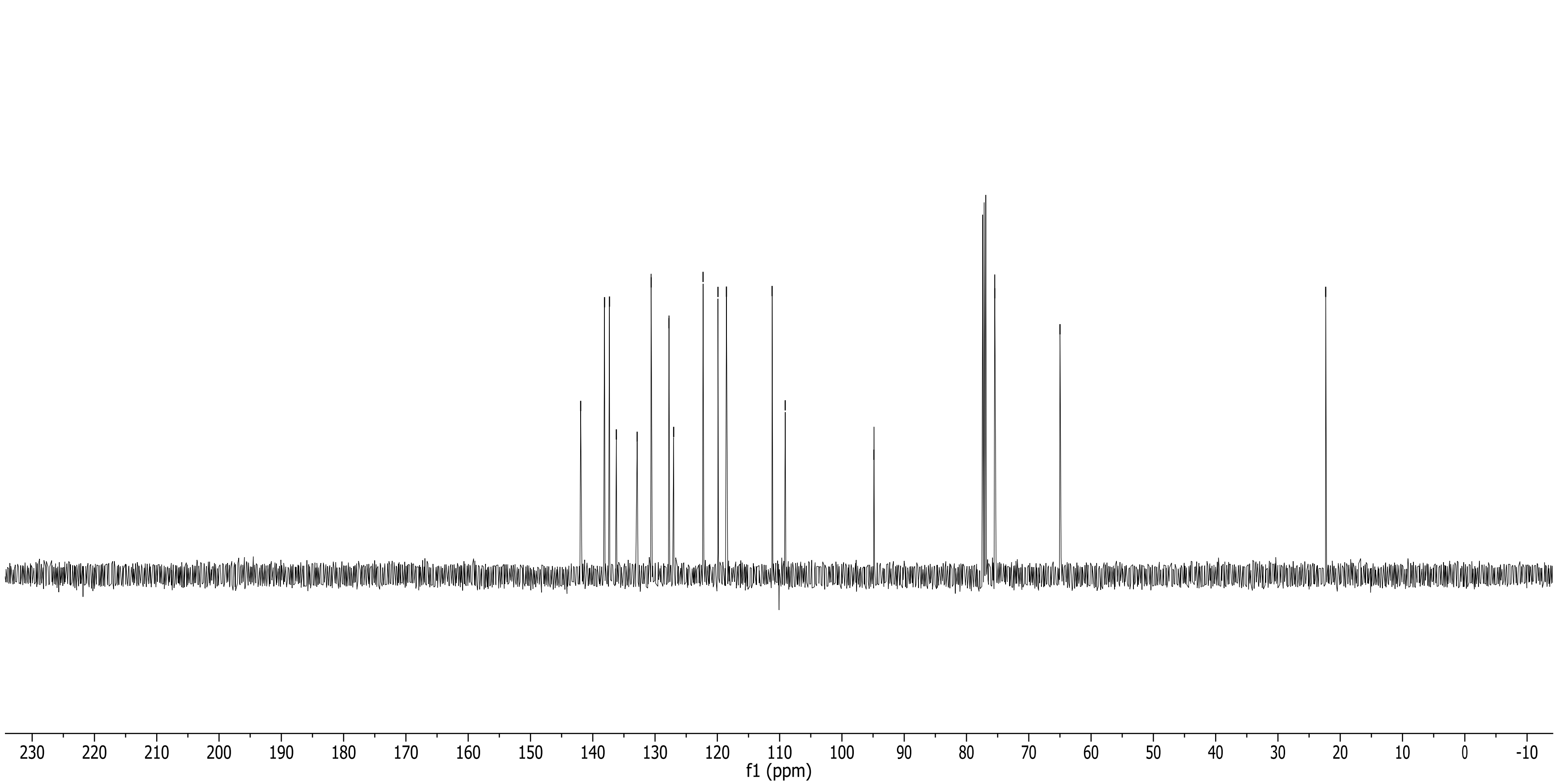
^{1}H NMR of **3h** in $CDCl_3$



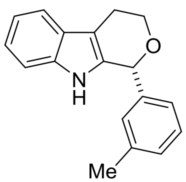


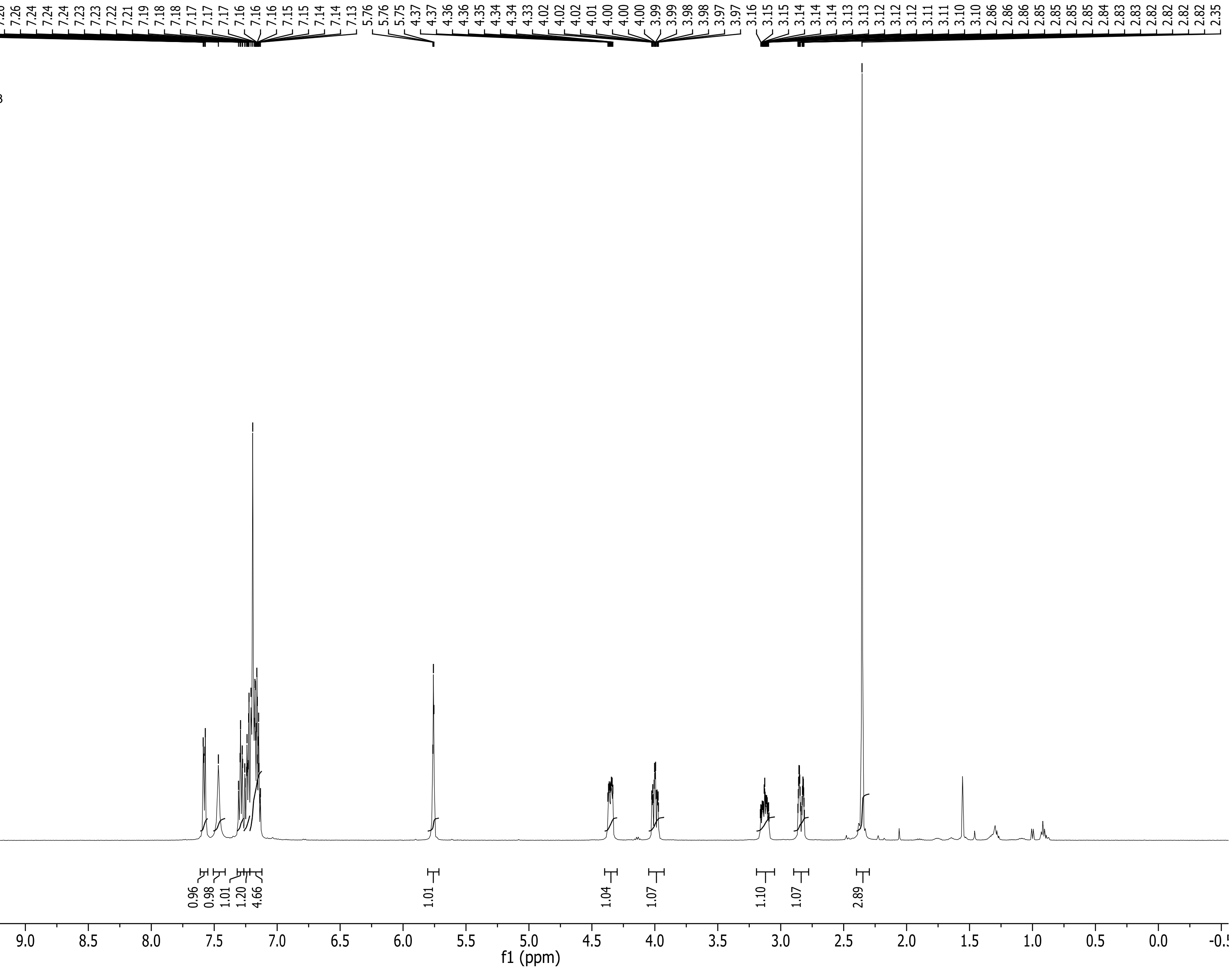
^{13}C NMR of **3h** in $CDCl_3$



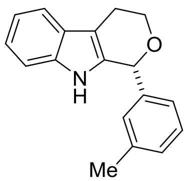


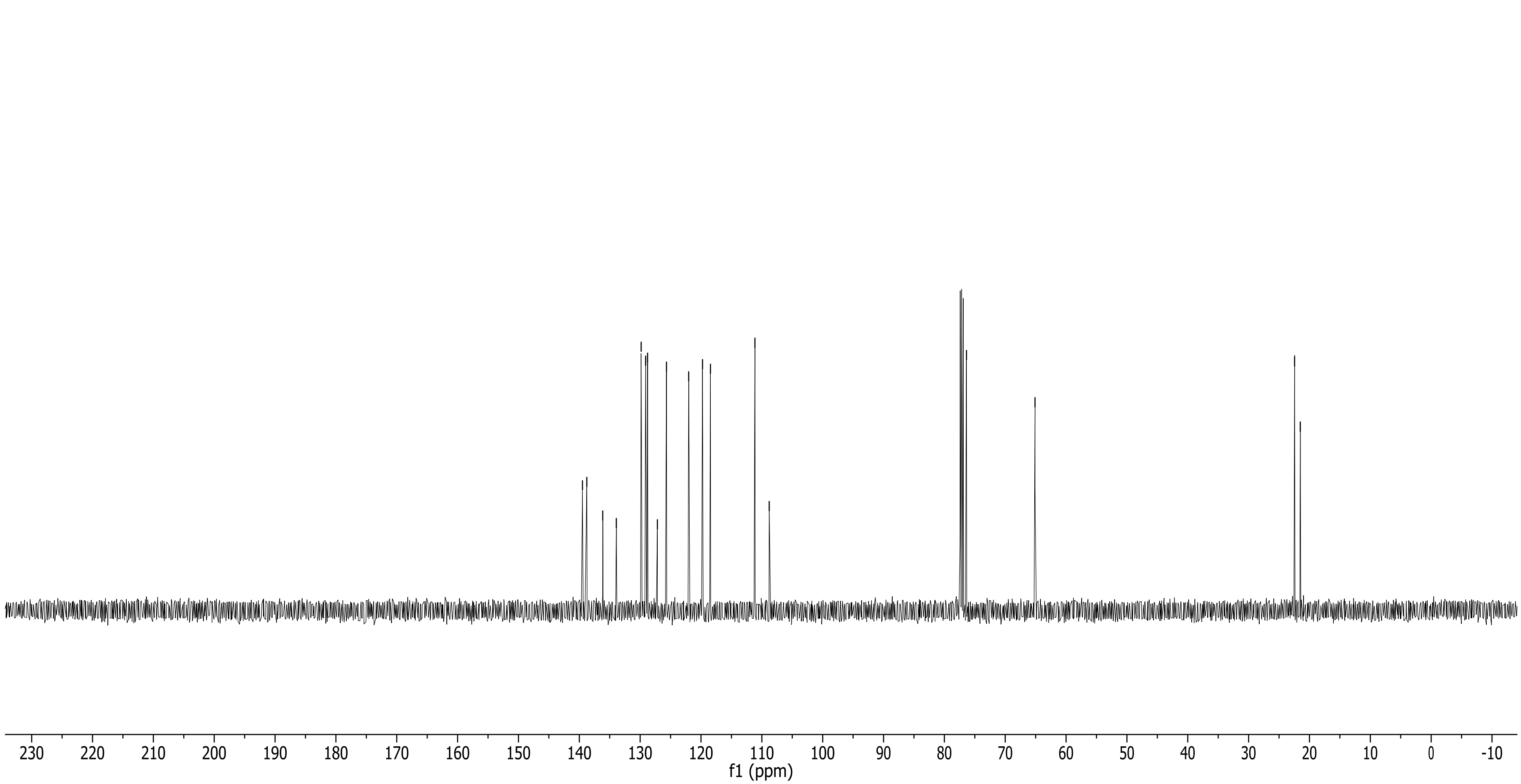
^{1}H NMR of **3i** in $CDCl_3$



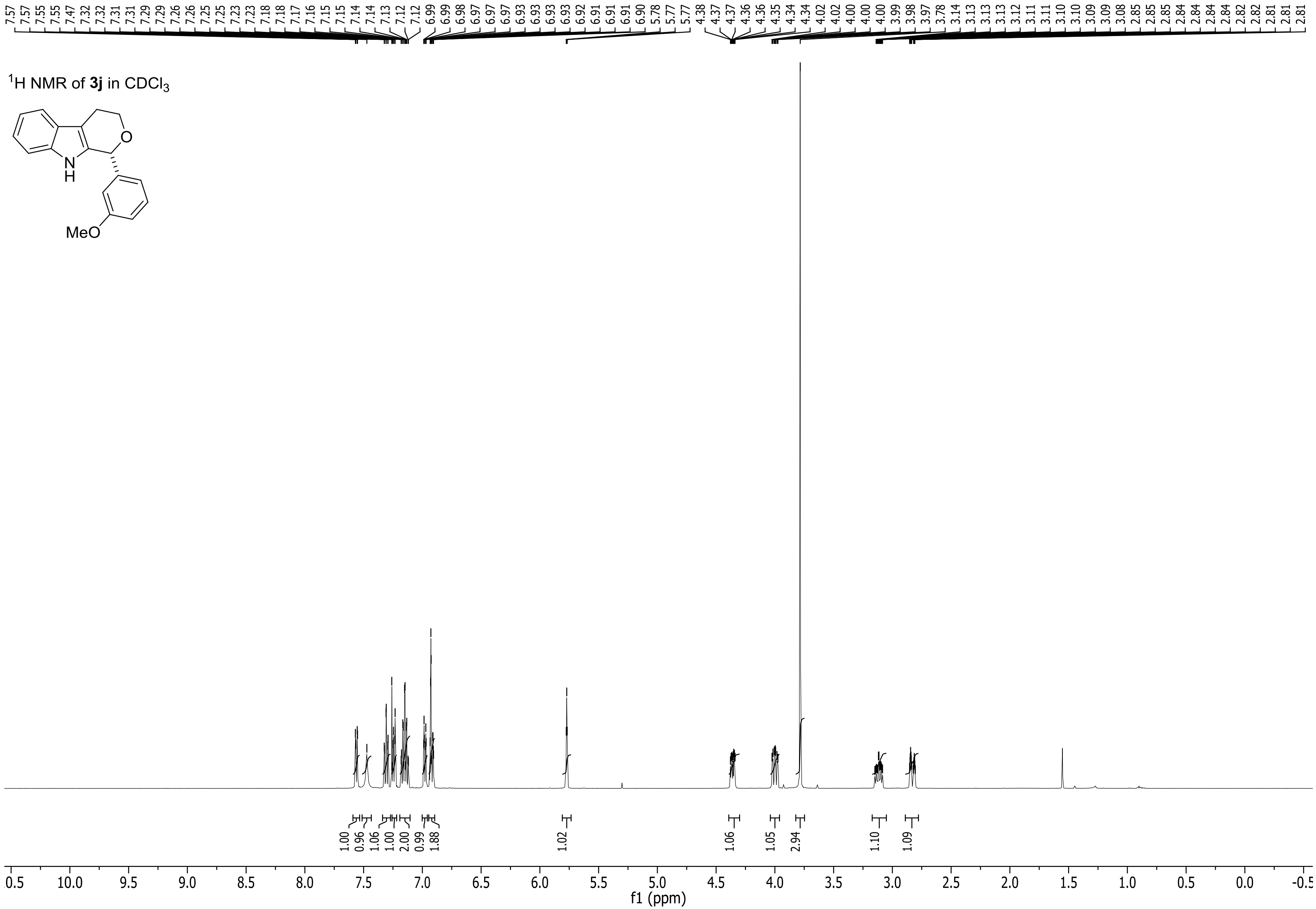


^{13}C NMR of **3i** in $CDCl_3$

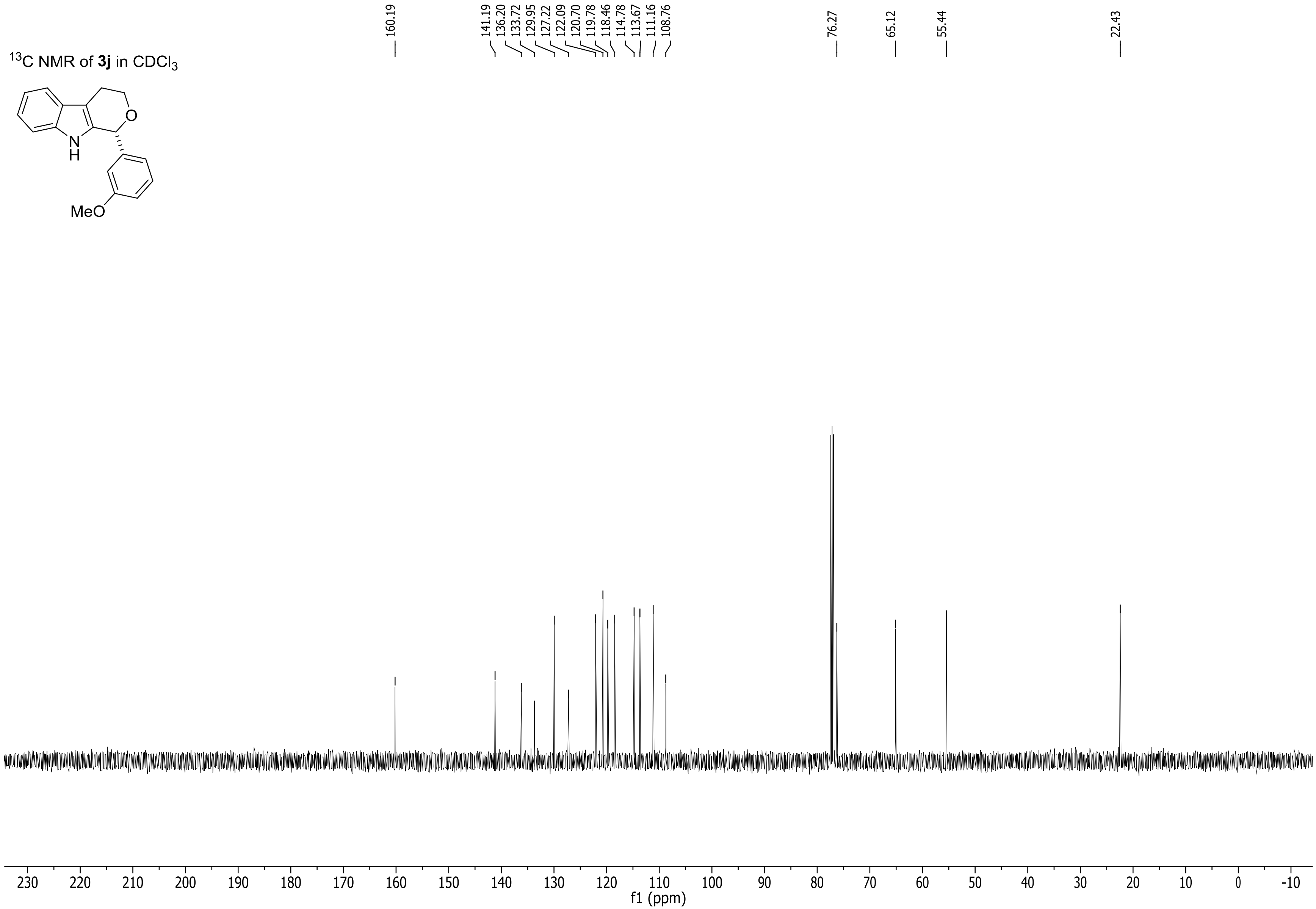




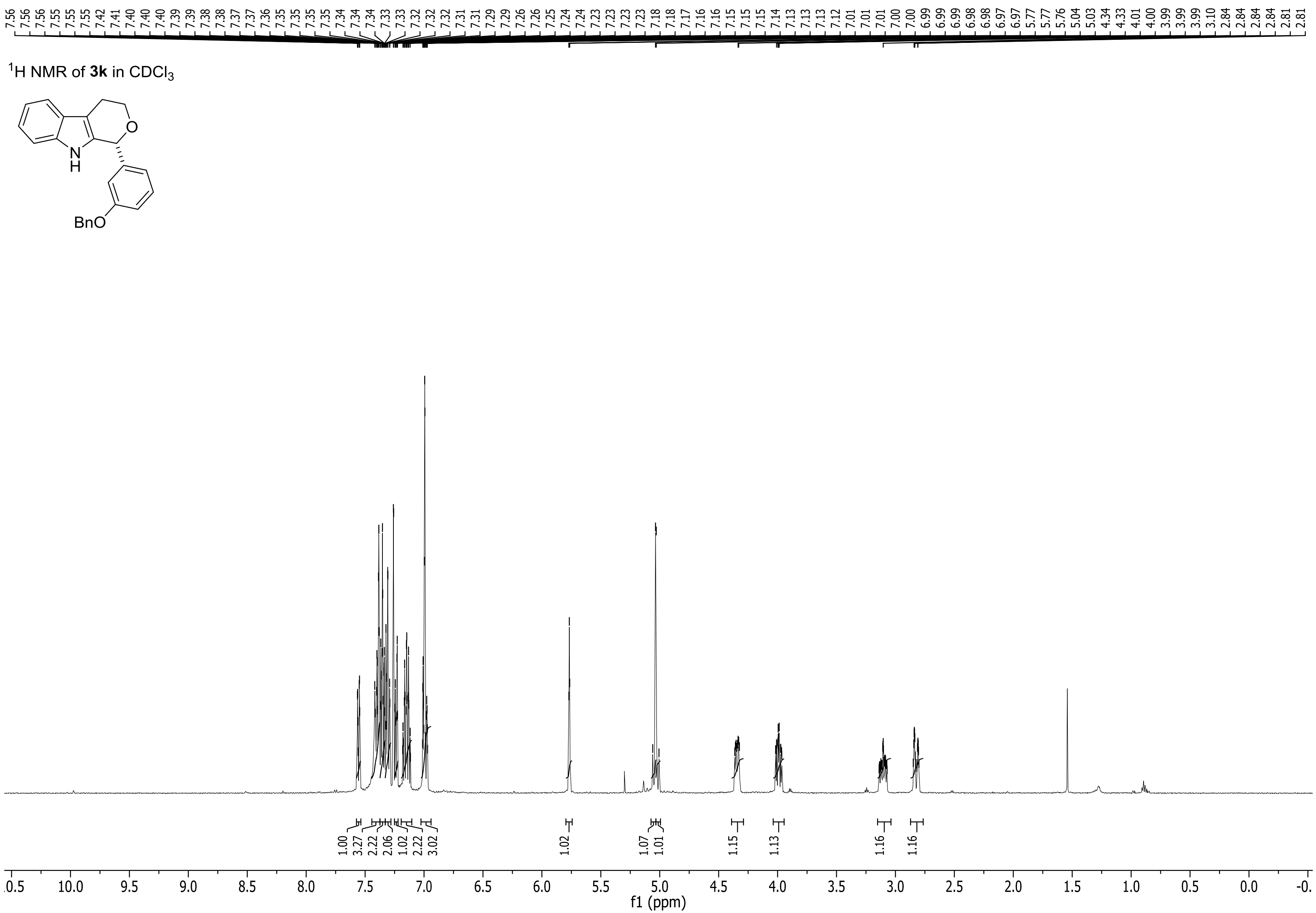
[1]H NMR of **3j** in $CDCl_3$



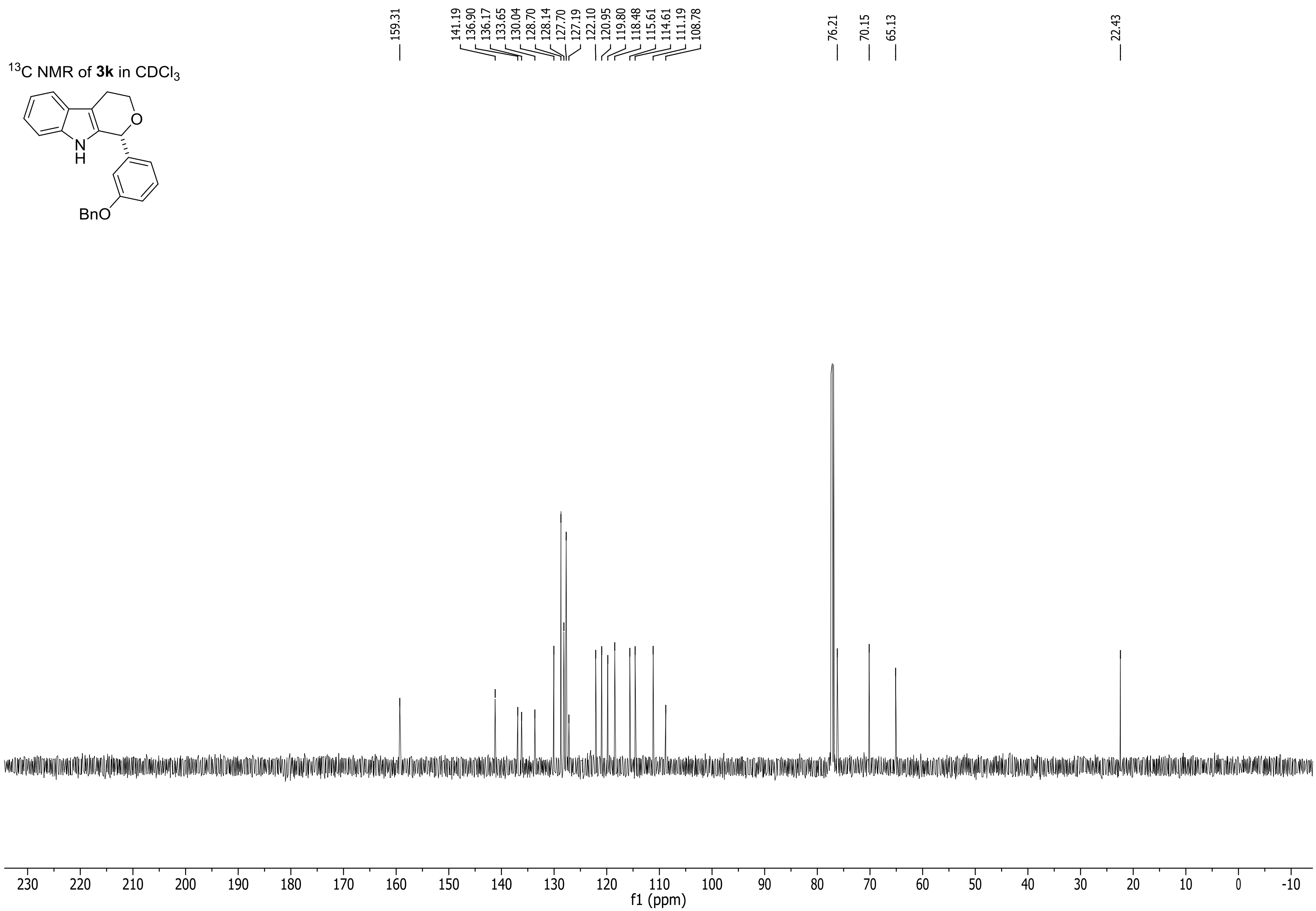
^{13}C NMR of **3j** in $CDCl_3$



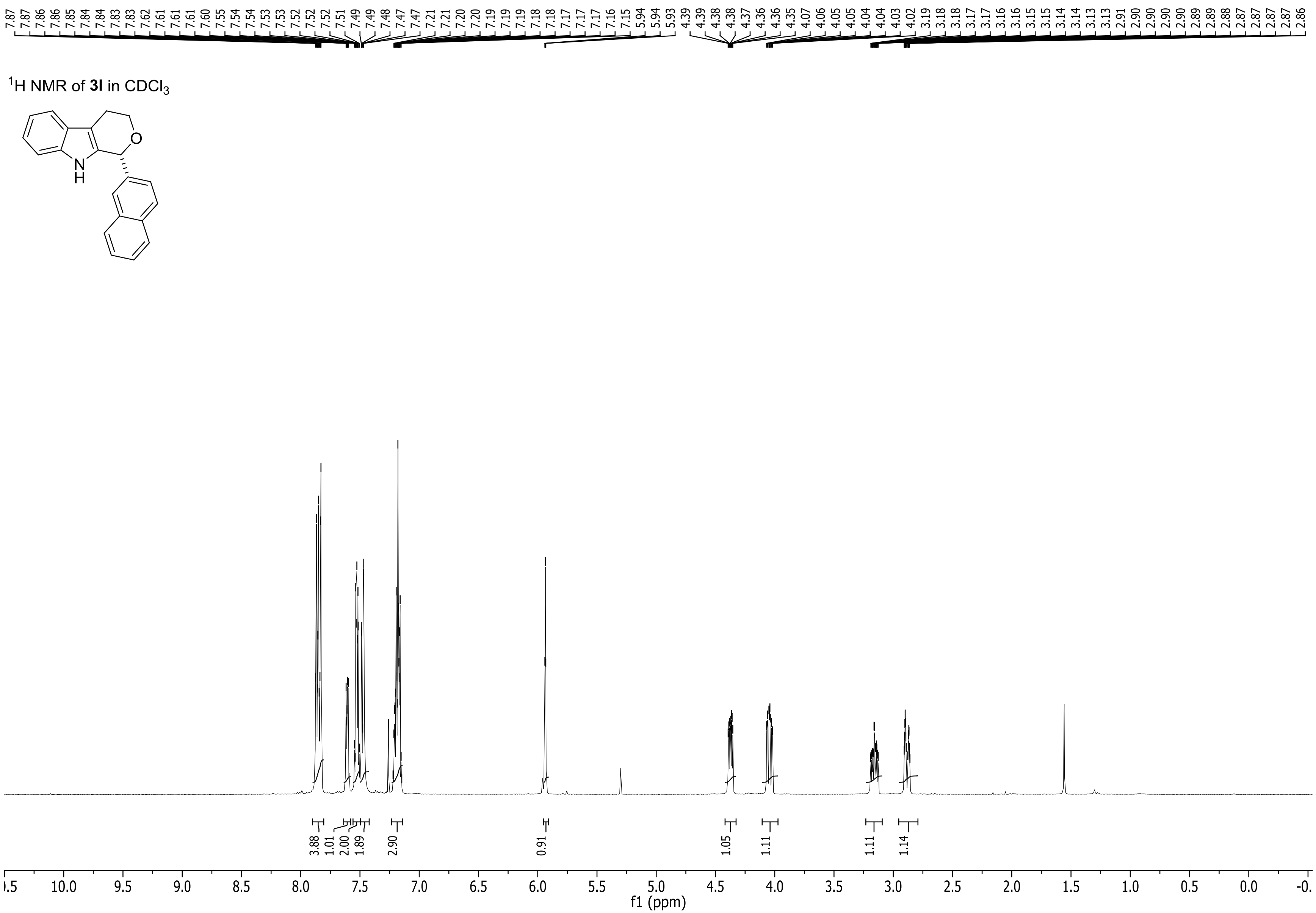
^{1}H NMR of **3k** in $CDCl_3$



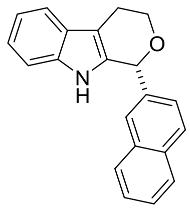
^{13}C NMR of **3k** in $CDCl_3$

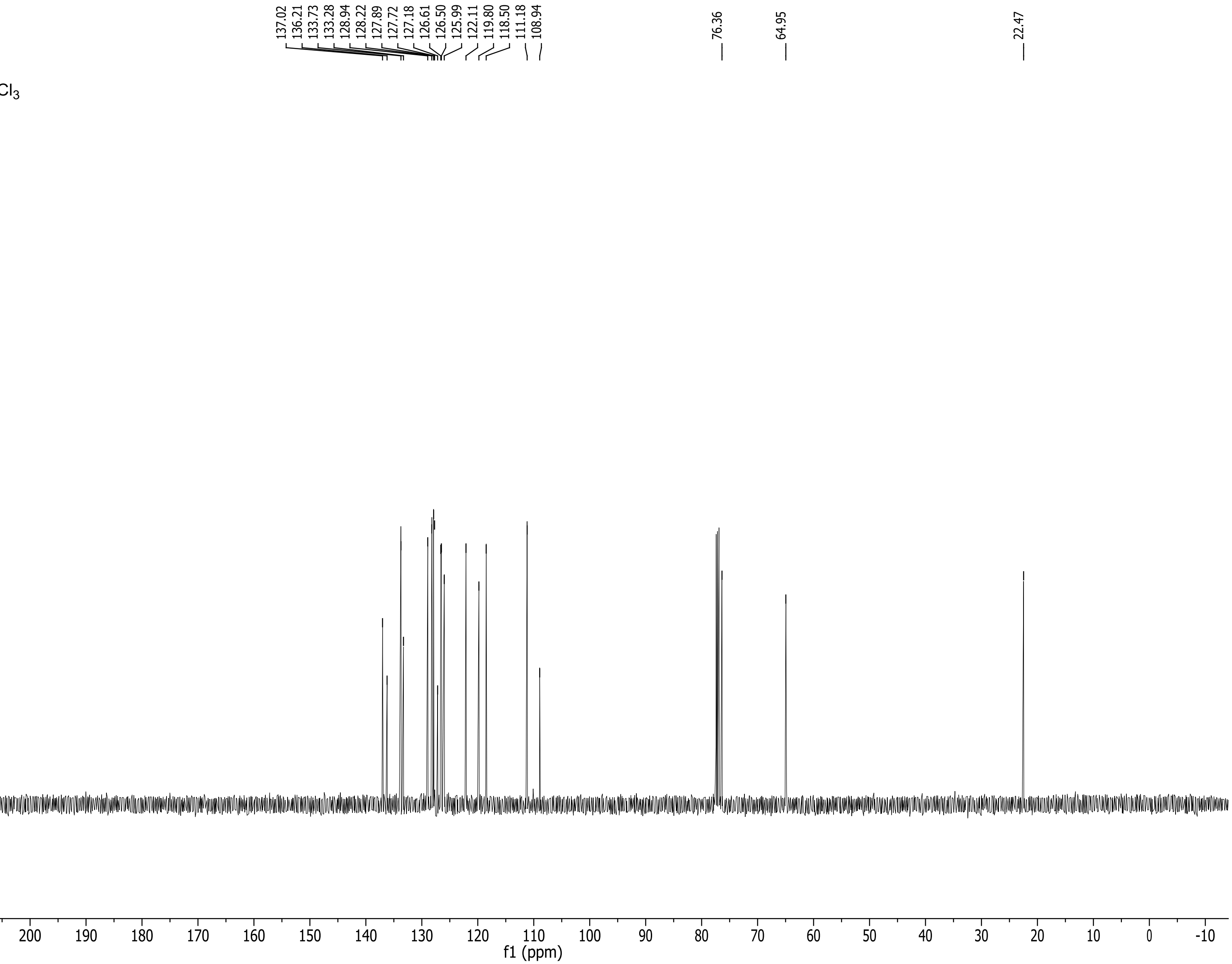


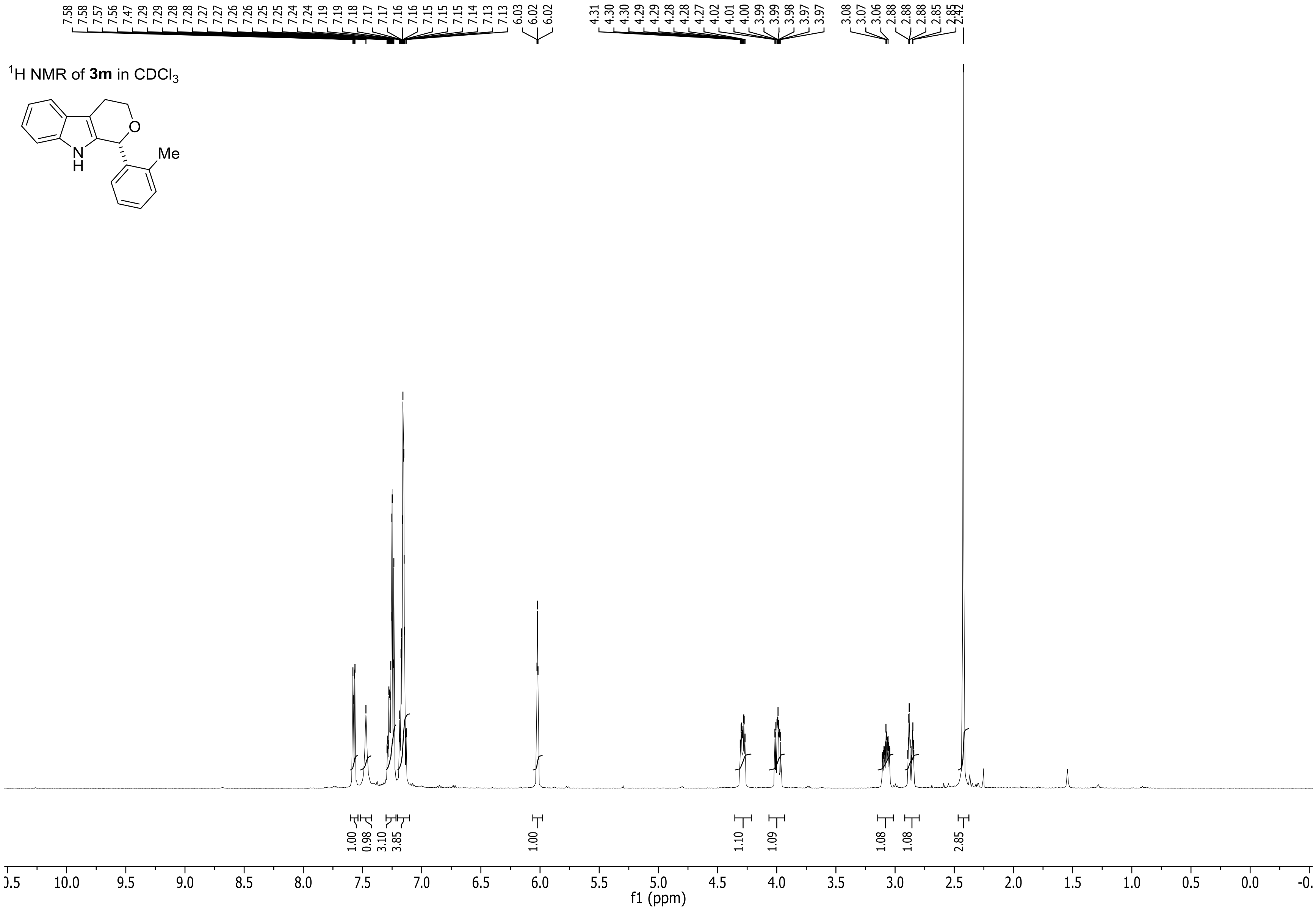
[1]H NMR of **3l** in $CDCl_3$



^{13}C NMR of **3l** in $CDCl_3$

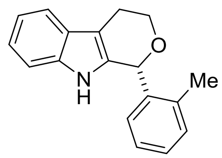


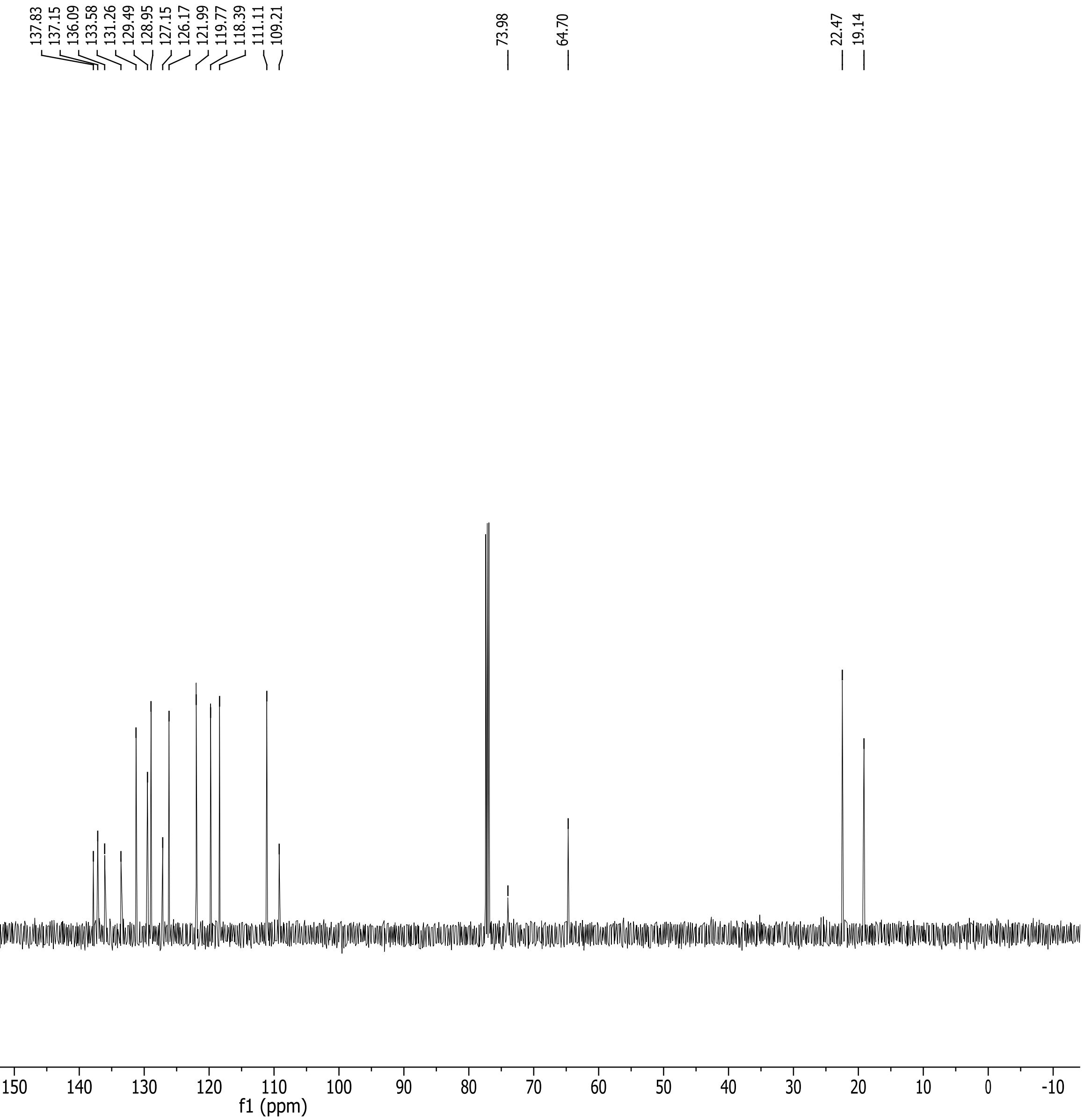




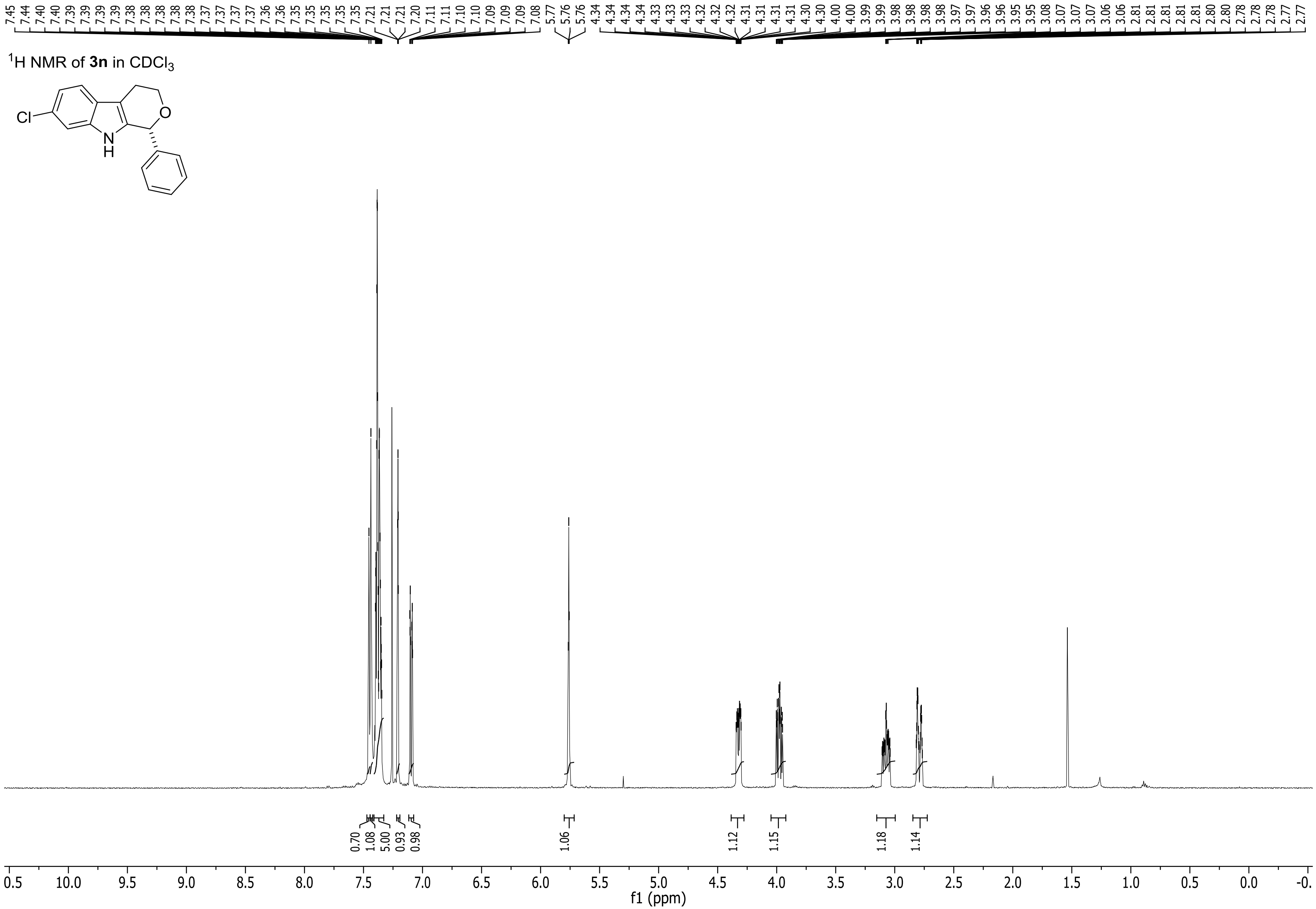
^{1}H NMR of **3m** in CDCl$_3$
O
Me
N
H
f1 (ppm)

^{13}C NMR of **3m** in $CDCl_3$

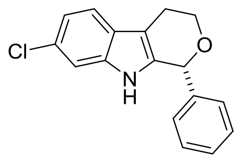


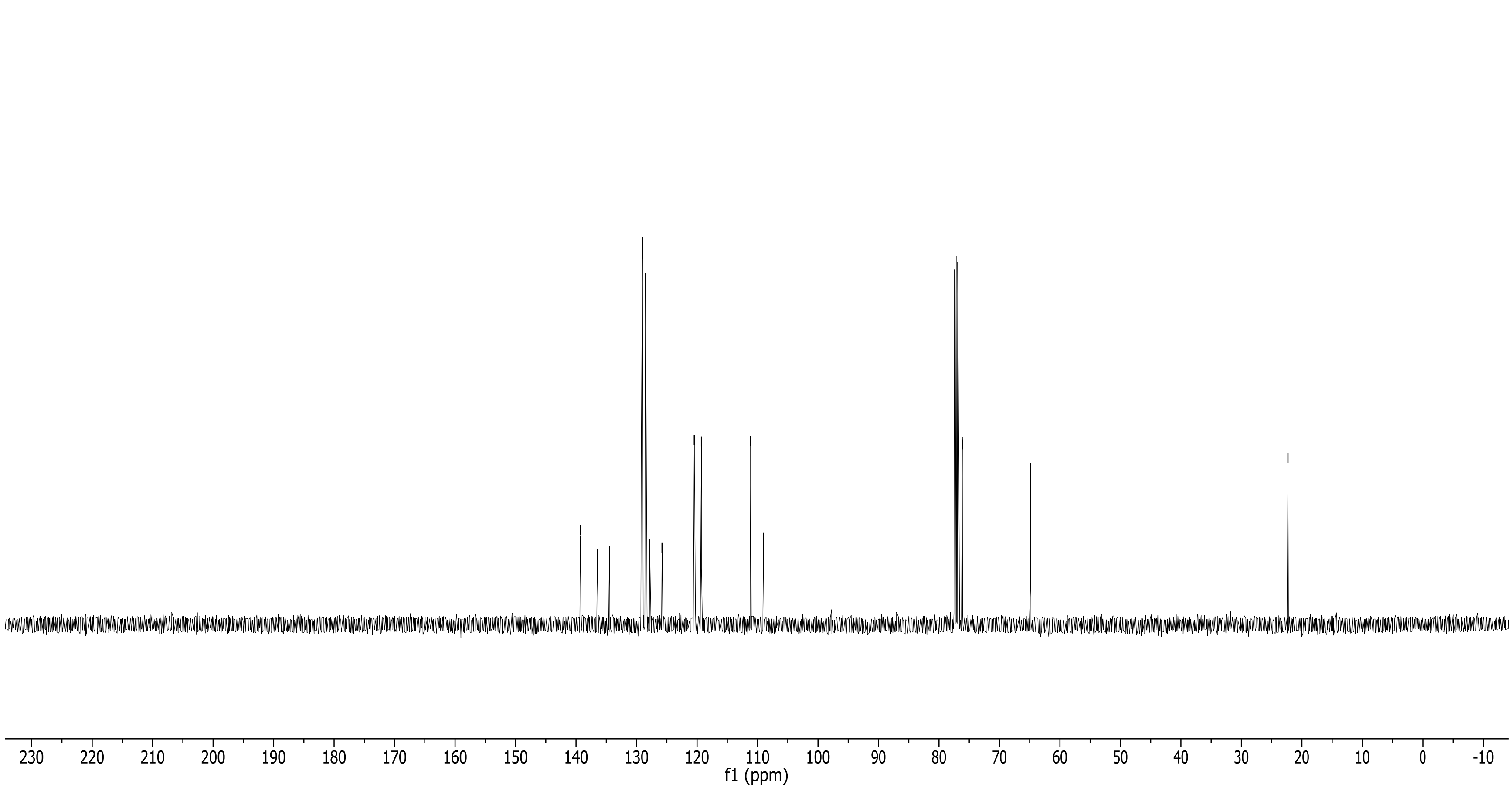


¹H NMR of **3n** in $CDCl_3$

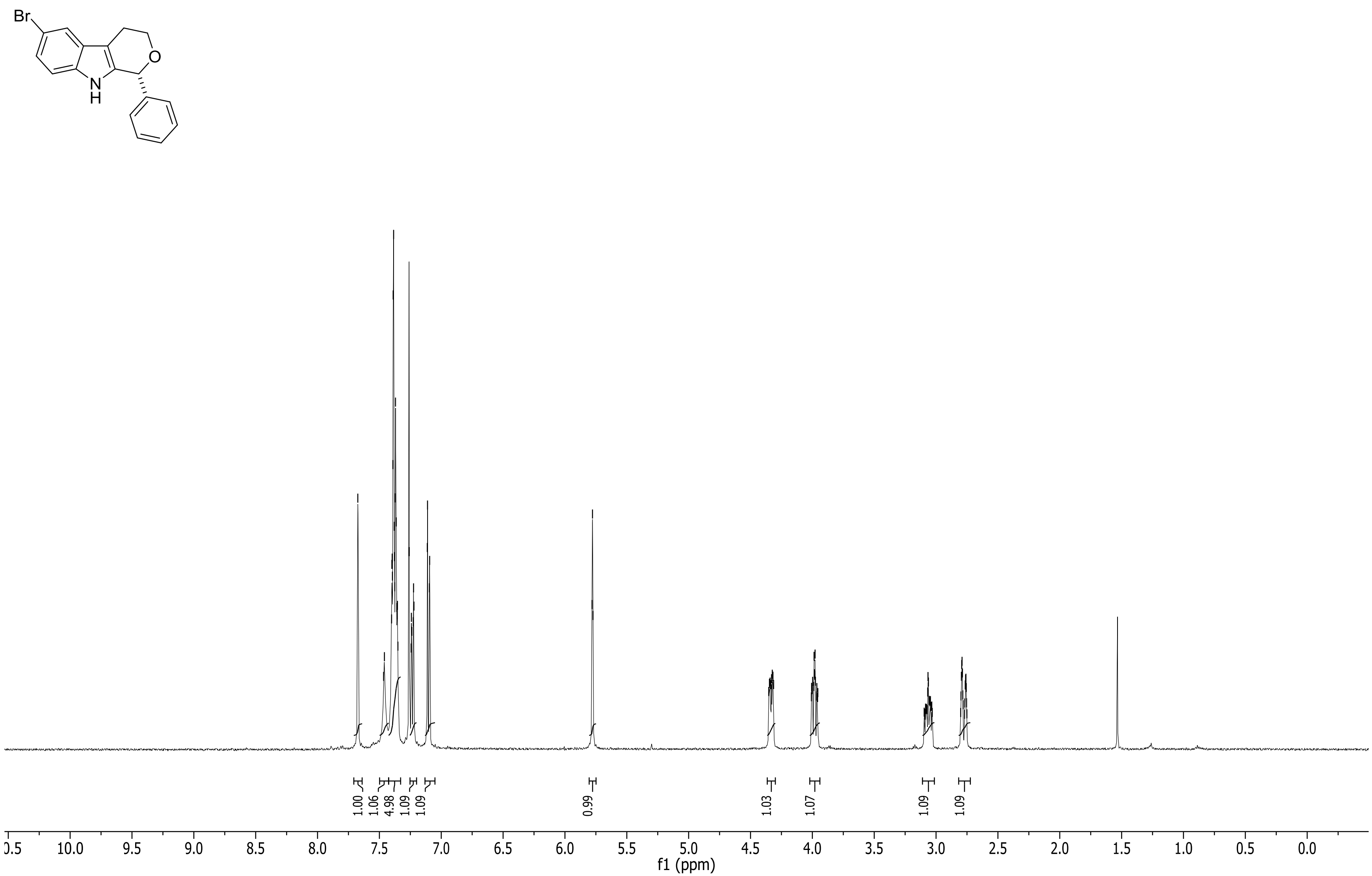


^{13}C NMR of **3n** in $CDCl_3$

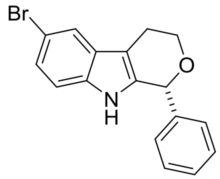


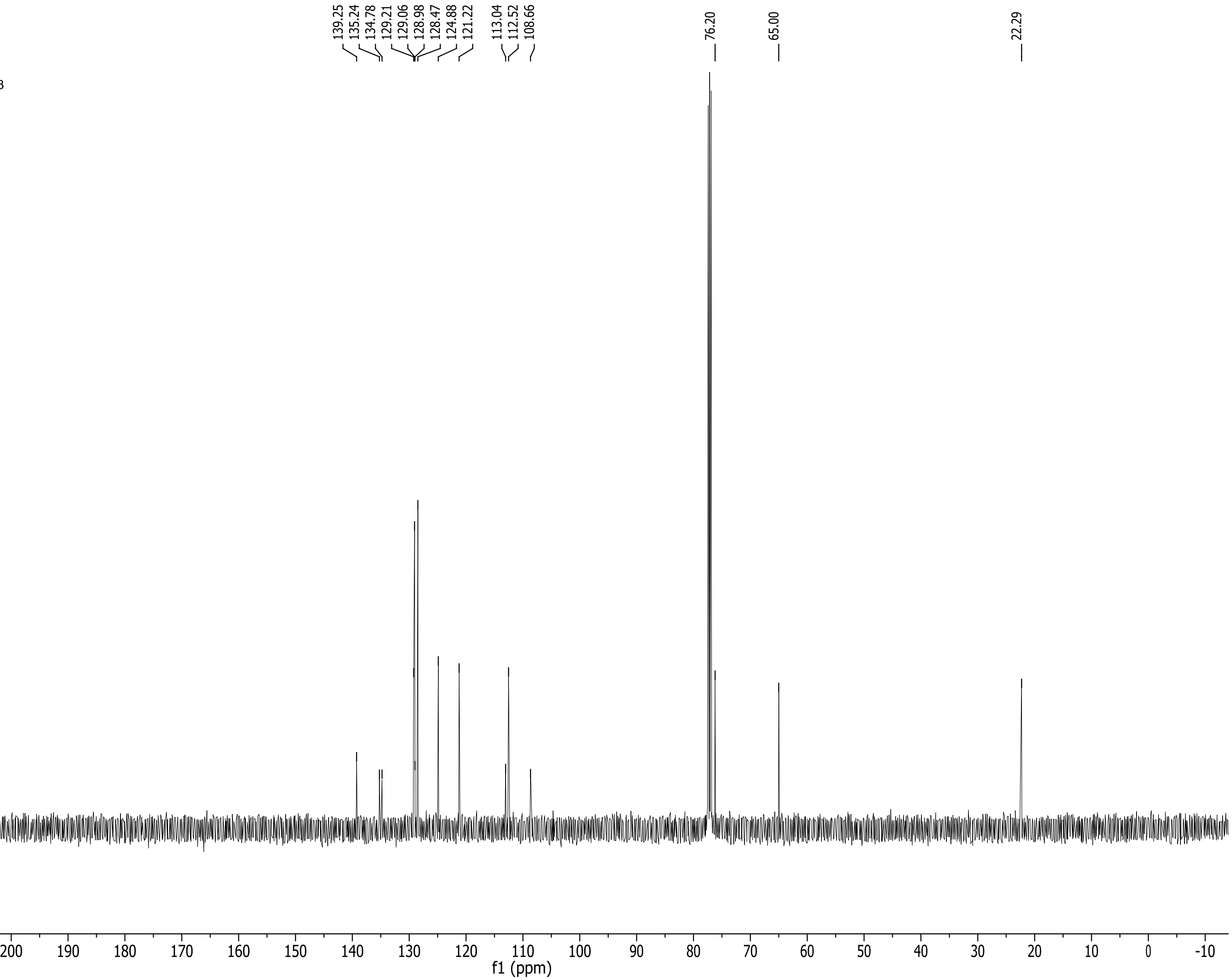


^{1}H NMR of **3o** in $CDCl_3$

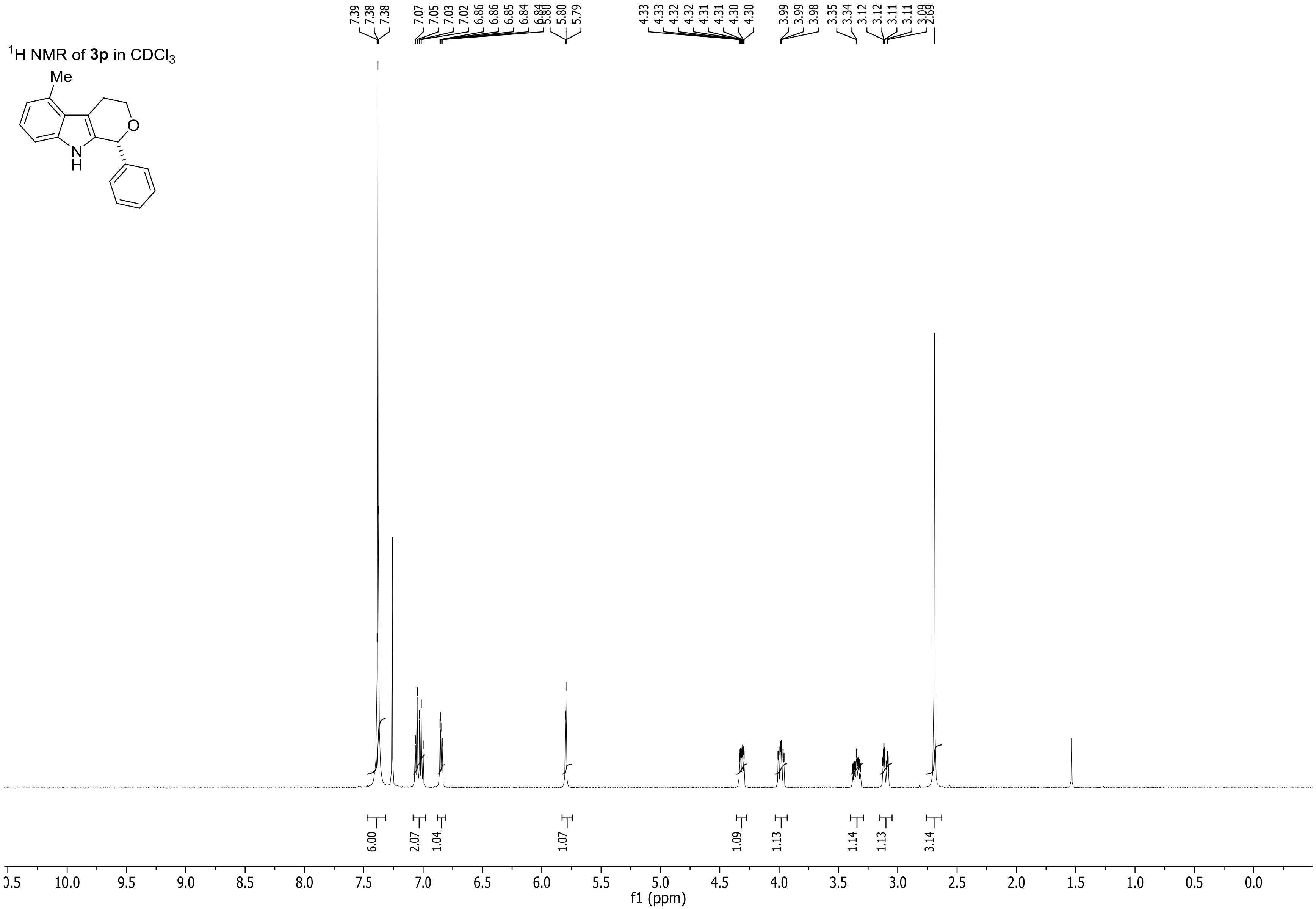


^{13}C NMR of **3o** in $CDCl_3$

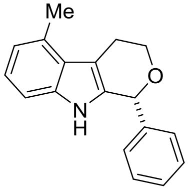


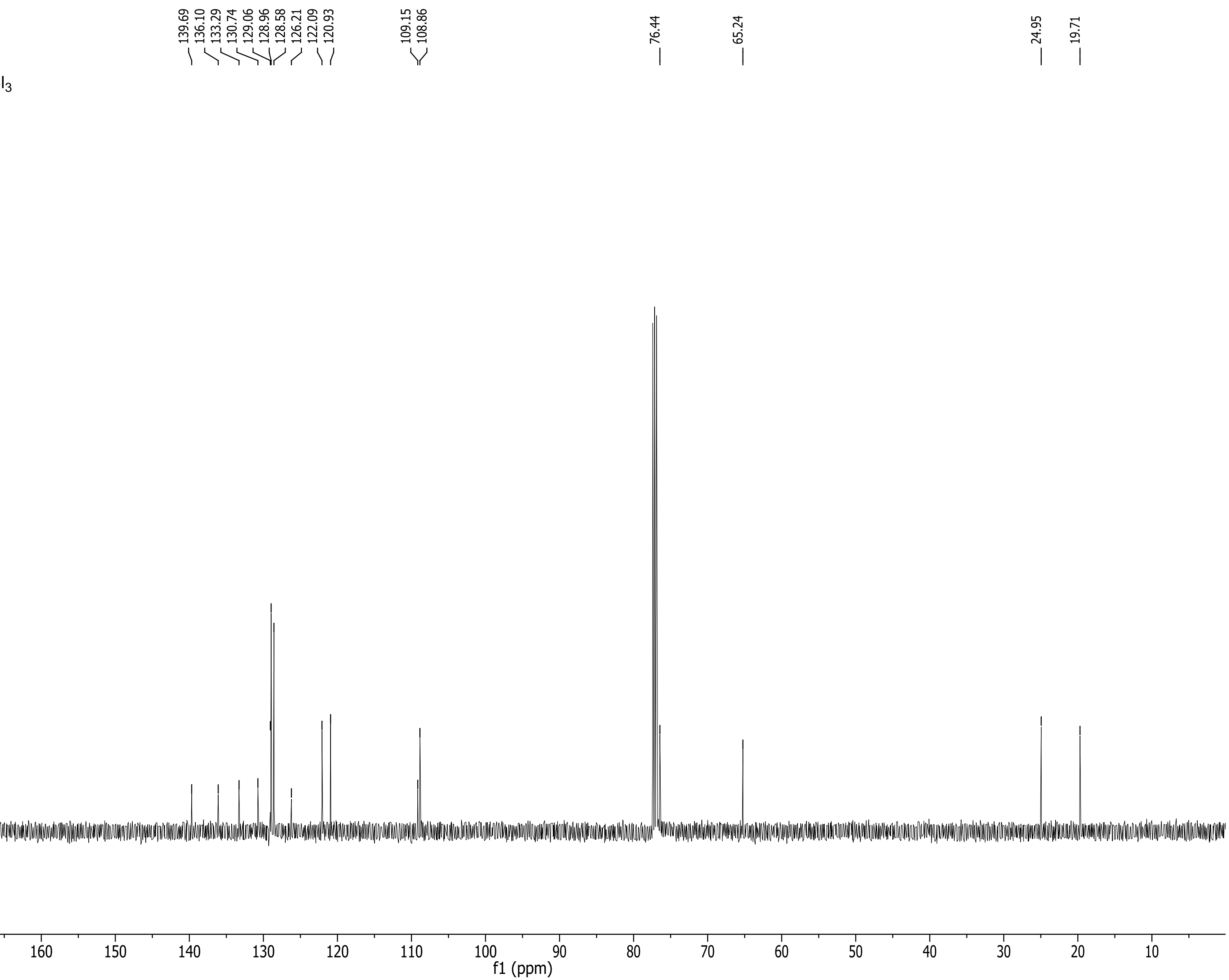


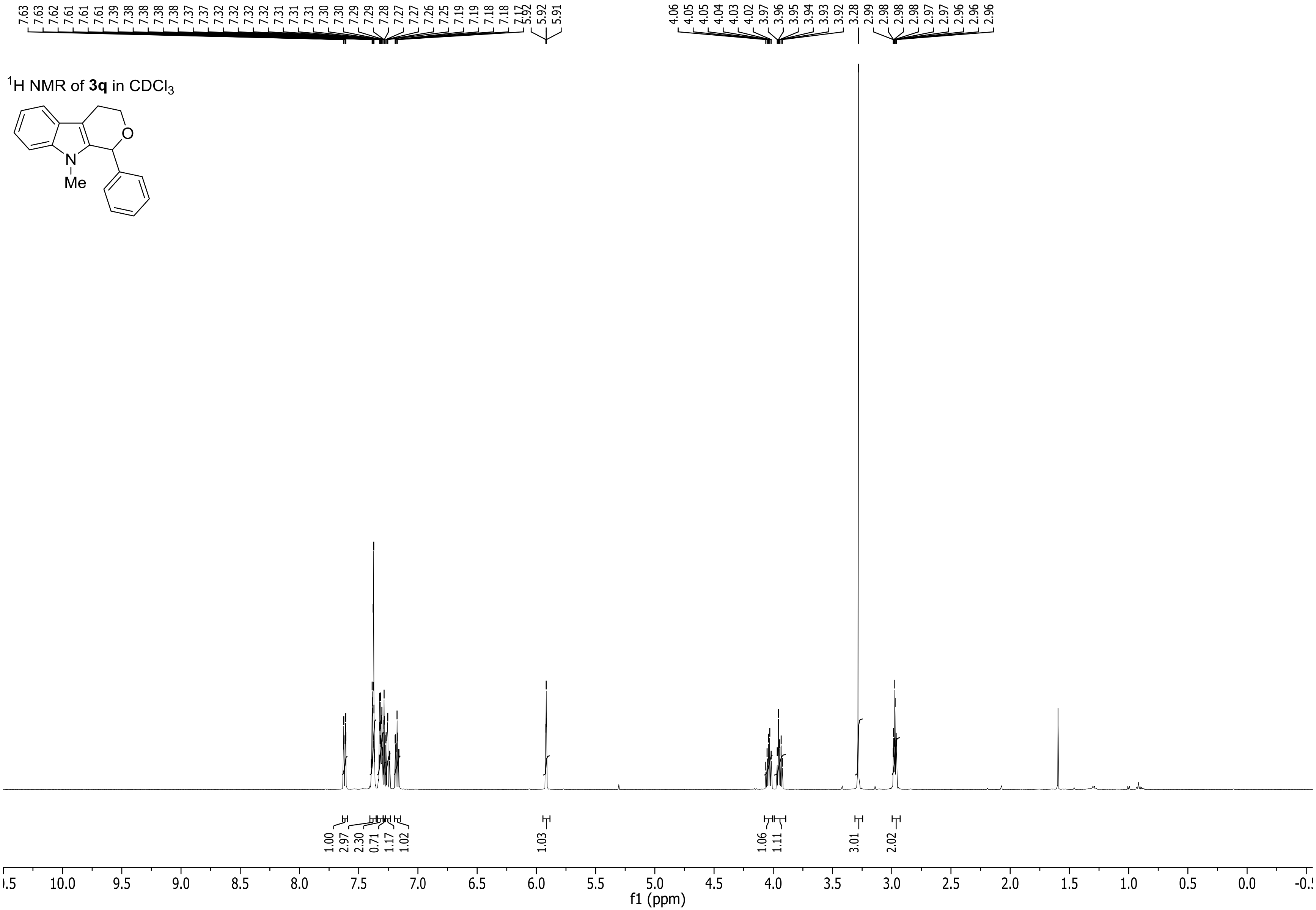
^{1}H NMR of **3p** in $CDCl_3$



^{13}C NMR of **3p** in $CDCl_3$

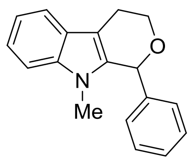


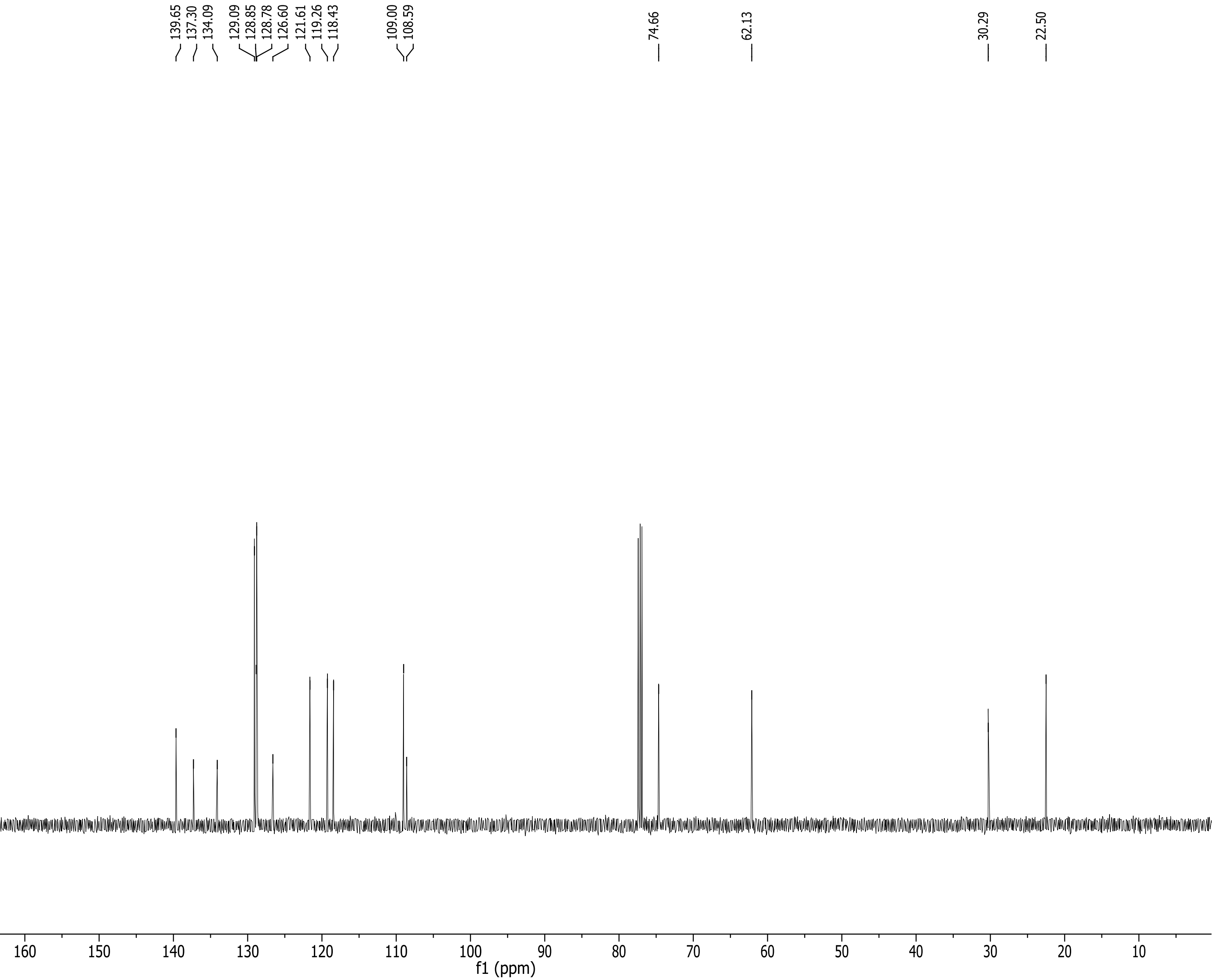


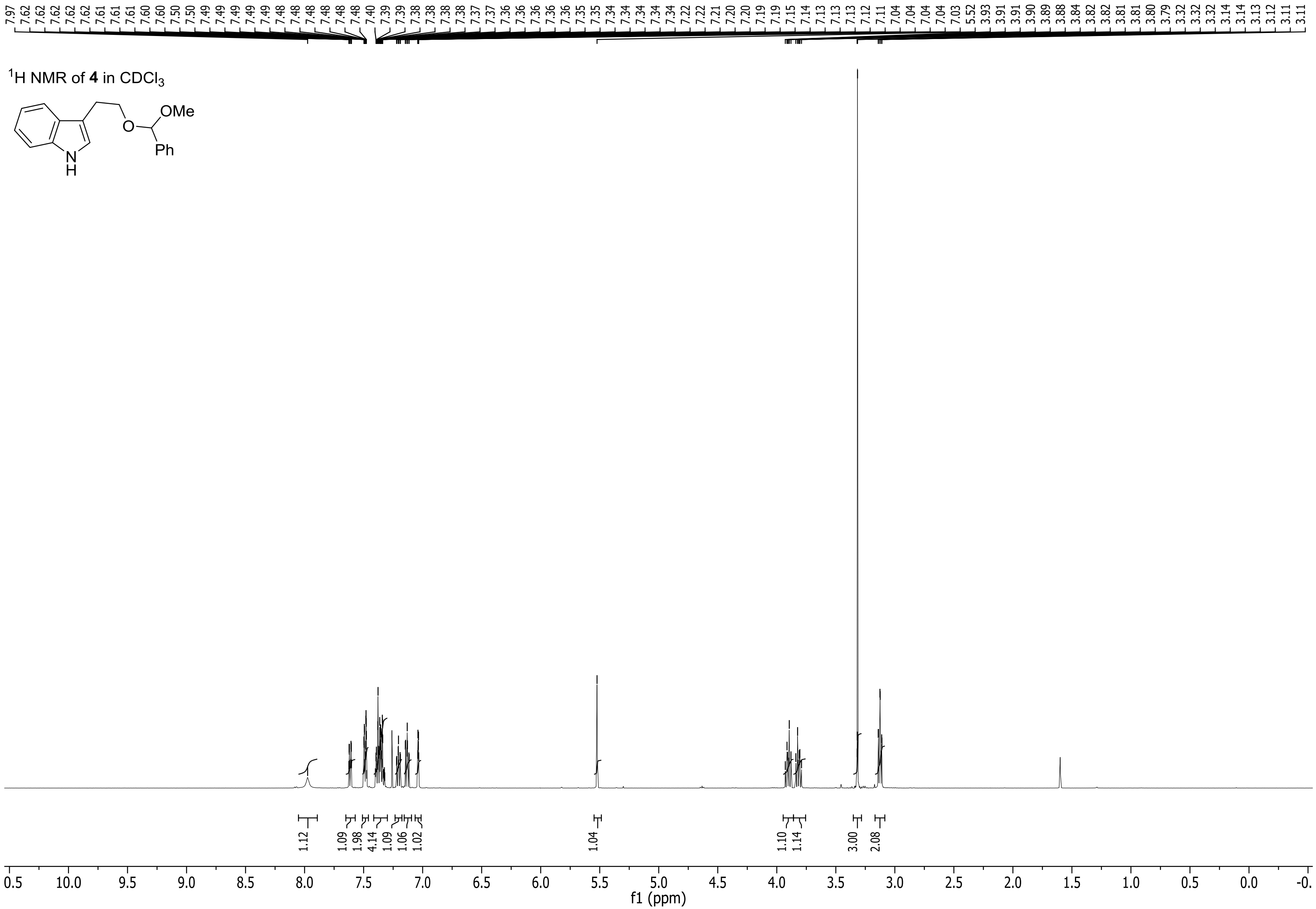


1H NMR of 3q in CDCl3
N
Me
O
7.63 7.63 7.62 7.61 7.61 7.61 7.39 7.38 7.38 7.38 7.38 7.37 7.37 7.32 7.32 7.32 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.27 7.26 7.25 7.19 7.19 7.18 7.17 5.92 5.92 5.91
4.06 4.05 4.05 4.04 4.03 4.02 3.97 3.96 3.95 3.94 3.93 3.92 3.28 2.99 2.98 2.98 2.98 2.97 2.97 2.96 2.96 2.96
1.00 2.97 2.30 0.71 1.17 1.02 1.03 1.06 1.11 3.01 2.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

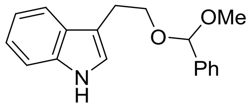
^{13}C NMR of **3q** in $CDCl_3$

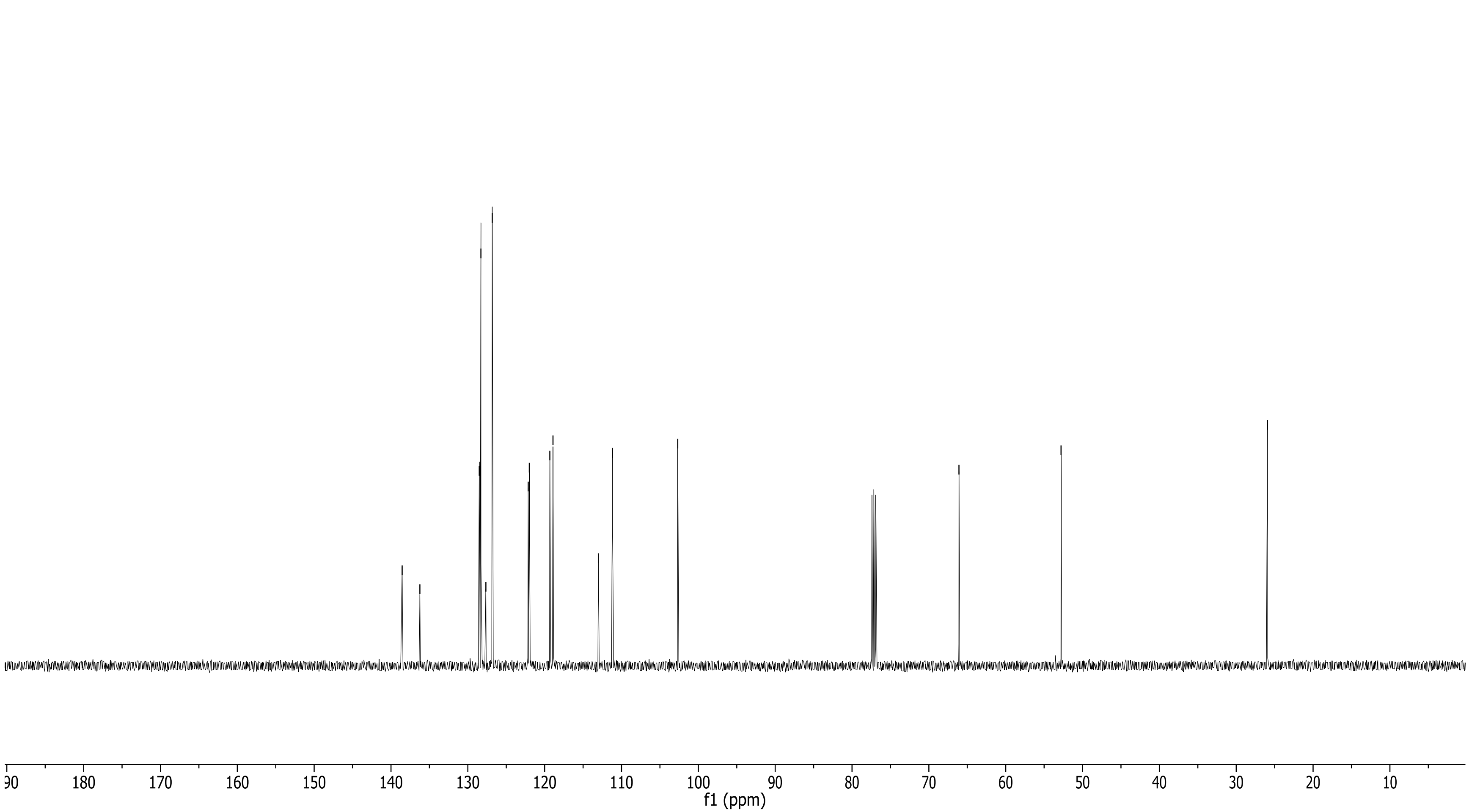





7.97 7.62 7.62 7.62 7.62 7.62 7.61 7.61 7.60 7.50 7.50 7.49 7.49 7.49 7.49 7.49 7.48 7.48 7.48 7.48 7.48 7.48 7.40 7.39 7.39 7.38 7.38 7.38 7.38 7.37 7.36 7.36 7.36 7.36 7.36 7.35 7.35 7.34 7.34 7.34 7.34 7.34 7.22 7.22 7.21 7.20 7.20 7.19 7.19 7.15 7.14 7.13 7.13 7.13 7.12 7.11 7.04 7.04 7.04 7.04 7.03 5.52 3.93 3.91 3.91 3.90 3.89 3.88 3.84 3.82 3.81 3.81 3.80 3.79 3.32 3.32 3.32 3.14 3.14 3.13 3.12 3.11 3.11
1H NMR of 4 in CDCl3
OMe
O
Ph
N
H
1.12
1.09
1.98
4.14
1.09
1.06
1.02
1.04
1.10
1.14
3.00
2.08
f1 (ppm)

^{13}C NMR of **4** in $CDCl_3$





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