# An Ugi Reaction Incorporating a Redox-Neutral Amine C–H Functionalization Step

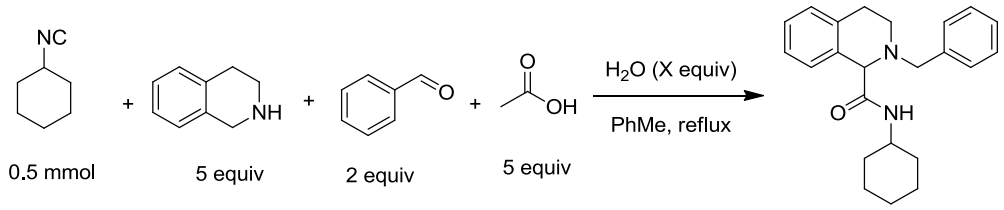
Zhengbo Zhu and Daniel Seidel*

*Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, United States*

## Supporting Information

**General Information:** Reagents and solvents were purchased from commercial sources and were purified by distillation or recrystallization prior to use unless stated otherwise. Cyclohexyl isocyanide was used as received. Benzyl isocyanide[1] and isocyanobenzene[2] were prepared following literature procedures. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 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 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. Chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, m = multiplet, comp = complex, br = broad, coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra ($^{13}$C-NMR) spectra were recorded on a Varian VNMRS-500 MHz. Chemical shifts are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

**Table S1**: Additional optimization data for 1,2,3,4-tetrahydroisoquinoline.[a]




| Entry | Molarity (M) | X | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 0.25 | - | 2 | 65 |
| 2 | 0.25 | 10 | 2 | 61 |
| 3 | 0.5 | - | 2 | 54 |
| 4 | 0.5 | 10 | 2 | 50 |
| 5 | 0.1 | - | 3 | 58 |
| 6 | 0.1 | 10 | 3 | 69 |
| 7 | 0.1 | 5 | 3 | 65 |
| 8 | 0.1 | 15 | 3 | 64 |
| 9[c] | 0.1 | 10 | 3 | 27 |

[a.]Reactions were performed on a 0.5 mmol scale. All substrates were mixed directly. [b.]Isolated yields. [c.]With 2 equiv of 1,2,3,4-tetrahydroisoquinoline.

**General procedure A for the redox-neutral α-amidation:**

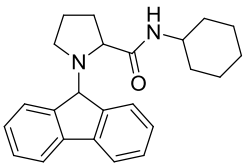
To a solution of 9*H*-fluoren-9-one (180 mg, 1 mmol, 2 equiv) in toluene (2 mL, 0.25 M) was added the pyrrolidine (0.21 mL, 2.5 mmol, 5 equiv), isocyanide (0.5 mmol, 1 equiv) and acetic acid (0.14 mL, 2.5 mmol, 5 equiv). The resulting mixture was heated at reflux until the isocyanide was consumed as indicated by TLC. The reaction mixture was then allowed to cool to room temperature, diluted with 5 mL EtOAc, and washed with saturated aqueous $NaHCO_3$ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography.

**General procedure B for the redox-neutral α-amidation:**

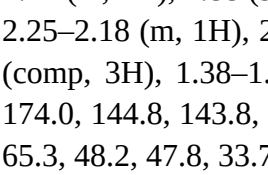
To a solution of the aldehyde (1 mmol, 2 equiv) in toluene (5 mL, 0.1 M) was added the amine (2.5 mmol, 5 equiv), isocyanide (0.5 mmol, 1 equiv), acetic acid (0.14 mL, 2.5 mmol, 5 equiv) and distilled water (90 µL, 5 mmol, 10 equiv). The resulting mixture was heated at reflux until

the isocyanide was consumed as indicated by TLC. The reaction mixture was then allowed to cool to room temperature, diluted with 5 mL EtOAc, and washed with saturated aqueous $NaHCO_3$ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography.

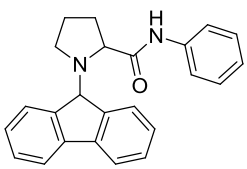
***N*-cyclohexyl-1-(9*H*-fluoren-9-yl)pyrrolidine-2-carboxamide 1a:** Following the general procedure A, cyclohexyl isocyanide, 9*H*-fluoren-9-one and pyrrolidine were heated at reflux for 18 h. Product **1a** was obtained as a yellow solid in 89% yield (160 mg), ($R_f$ = 0.28 in hexane/EtOAc 80:20 v/v); mp = 113–115 °C; IR (KBr) 3310, 2931, 2848, 1637, 1522, 1449, 1302, 1154, 1127, 741, 731, 624; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.65 (d, *J* = 8.8 Hz, 1H), 7.58–7.55 (comp, 2H), 7.50–7.46 (m, 1H), 7.44–7.40 (m, 1H), 7.30–7.20 (comp, 3H), 7.17–7.12 (m, 1H), 4.88 (s, 1H), 3.89 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.77–3.68 (m, 1H), 2.60–2.55 (m, 1H), 2.25–2.18 (m, 1H), 2.12–2.02 (m, 1H), 1.93–1.83 (comp, 3H), 1.71–1.61 (comp, 2H), 1.59–1.47 (comp, 3H), 1.38–1.27 (comp, 2H), 1.24–1.10 (comp, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 174.0, 144.8, 143.8, 141.6, 140.7, 128.62, 128.61, 127.7, 127.5, 126.0, 124.7, 120.3, 120.2, 66.0, 65.3, 48.2, 47.8, 33.7, 33.6, 31.8, 25.8, 25.2, 25.1, 24.7; *m/z* (ESI–MS) 361.0 $[M + H]^+$.



***N*-benzyl-1-(9*H*-fluoren-9-yl)pyrrolidine-2-carboxamide 1b:** Following the general procedure A, benzyl isocyanide, 9*H*-fluoren-9-one and pyrrolidine were heated at reflux for 20 h. Product **1b** was obtained as a yellow solid in 65% yield (119 mg), ($R_f$ = 0.26 in hexane/EtOAc 80:20 v/v); mp = 119–120 °C; IR (KBr) 3351, 3028, 2933, 2877, 1649, 1518, 1450, 1359, 1298, 1201, 1126, 754, 733, 620, 478; $^1$H NMR ($CDCl_3$, 500 MHz) δ 8.14–8.08 (m, 1H), 7.70–7.65 (comp, 2H), 7.58–7.54 (m, 1H), 7.41–7.16 (comp, 10H), 5.03 (s, 1H), 4.59 (dd, *J* = 14.7, 6.2 Hz, 1H), 4.50 (dd, *J* = 14.7, 5.4 Hz, 1H), 4.08 (dd, *J* = 9.8, 3.5 Hz, 1H), 2.70–2.65 (m, 1H), 2.40–2.33 (m, 1H), 2.29–2.17 (m, 1H), 2.10–2.03 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.1, 144.5, 143.7, 141.6, 140.6, 138.6, 129.1, 128.7, 128.6, 127.9, 127.8, 127.6, 127.5, 125.8, 124.9, 120.3, 120.1, 66.1, 65.3, 48.3, 43.5, 31.8, 24.9; *m/z* (ESI–MS) 369.4 $[M + H]^+$.



**1-(9*H*-fluoren-9-yl)-*N*-phenylpyrrolidine-2-carboxamide 1c:** Following the general procedure A, isocyanobenzene, 9*H*-fluoren-9-one and pyrrolidine were heated at reflux for 19 h. Product **1c** was obtained as a yellow solid in 29% yield (52 mg), ($R_f$ = 0.55 in hexane/EtOAc 80:20 v/v); mp = 152–154 °C; IR (KBr) 3284, 2964, 2839, 1681, 1601, 1518, 1442, 1311, 1258, 1080, 1025, 744, 500; $^1$H NMR ($CDCl_3$, 500 MHz) δ 9.81 (s, 1H), 7.65–7.60 (comp, 3H), 7.59–7.54 (comp, 2H), 7.36–7.28 (comp, 5H), 7.22–7.16 (comp, 2H), 7.10–7.05 (m, 1H), 5.04 (s, 1H), 4.04 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.77–2.72 (m, 1H), 2.39–2.32 (m, 1H), 2.22–



2.13 (m, 1H), 2.10–2.03 (m, 1H), 1.67–1.61 (comp, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.3, 144.4, 143.4, 141.7, 140.8, 138.0, 129.4, 128.82, 128.81, 127.8, 127.6, 125.8, 124.8, 124.4, 120.4, 120.3, 119.5, 66.2, 65.8, 48.5, 31.9, 24.9.; *m/z* (ESI–MS) 355.4 $[M + H]^+$.

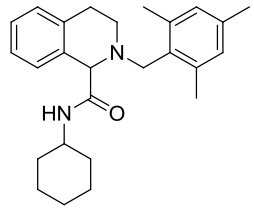
***N*-cyclohexyl-1-(2,4,6-trimethylbenzyl)pyrrolidine-2-carboxamide 1d:** Following the general procedure B, cyclohexyl isocyanide, mesitaldehyde and pyrrolidine were heated at reflux for 12 h. Product **1d** was obtained as a white solid in 68% yield (112 mg), ($R_f$ = 0.18 in hexane/EtOAc 80:20 v/v); mp = 113–115 °C; IR (KBr) 3324, 2937, 2851, 2797, 1648, 1525, 1450, 1318, 1173, 1150, 1113, 885, 849, 668; $^1$H NMR ($CDCl_3$, 500 MHz) δ 6.90 (d, *J* = 9.0 Hz, 1H), 6.81 (s, 2H), 3.74 (d, *J* = 12.9 Hz, 1H), 3.67 (d, *J* = 12.9 Hz, 1H), 3.56–3.47 (m, 1H), 3.16 (dd, *J* = 10.4, 4.1 Hz, 1H), 2.99–2.93 (m, 1H), 2.56–2.46 (m, 1H), 2.36 (s, 6H), 2.28–2.18 (comp, 4H), 1.92–1.84 (m, 1H), 1.81–1.70 (comp, 2H), 1.68–1.52 (comp, 5H), 1.35–1.20 (comp, 2H), 1.15–0.90 (comp, 2H), 0.82–0.72 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 174.1, 137.3, 136.8, 132.3, 129.5, 68.3, 54.9, 53.7, 47.6, 33.4, 32.7, 31.6, 25.8, 25.11, 25.10, 24.4, 21.0, 20.7; *m/z* (ESI–MS) 329.0 $[M + H]^+$.

***N*-cyclohexyl-1-(2,6-dichlorobenzyl)pyrrolidine-2-carboxamide 1e:** Following the general procedure B, cyclohexyl isocyanide, 2,6-dichlorobenzaldehyde and pyrrolidine were heated at reflux for 12 h. Product **1e** was obtained as a yellow solid in 60% yield (106 mg), ($R_f$ = 0.24 in hexane/EtOAc 80:20 v/v); mp = 108–109 °C; IR (KBr) 3310, 2934, 2844, 2364, 1641, 1521, 1451, 1293, 1153, 743, 728, 620; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, *J* = 8.2 Hz, 1H), 7.26–7.22 (comp, 2H), 7.10 (dd, *J* = 8.5, 7.6 Hz, 1H), 4.00 (d, *J* = 12.4 Hz, 1H), 3.92 (d, *J* = 12.4 Hz, 1H), 3.55–3.45 (m, 1H), 3.31 (dd, *J* = 10.3, 3.4 Hz, 1H), 3.03–2.96 (m, 1H), 2.63 (ddd, *J* = 10.8, 9.0, 5.8 Hz, 1H), 2.22–2.12 (m, 1H), 1.93–1.86 (m, 1H), 1.79–1.67 (comp, 2H), 1.66–1.49 (comp, 5H), 1.30–1.17 (comp, 2H), 1.12–0.97 (comp, 2H), 0.91–0.81 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.7, 136.6, 134.2, 129.3, 128.8, 66.9, 54.7, 54.0, 47.6, 33.5, 32.9, 31.6, 25.8, 25.18, 25.16, 24.5; *m/z* (ESI–MS) ($^{35}$Cl) 354.98 $[M + H]^+$, ($^{37}$Cl) 357.0 $[M + H]^+$.

***N*-cyclohexyl-2-(2,6-dichlorobenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1f:** Following the general procedure B, cyclohexyl isocyanide, 2,6-dichlorobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1f** was obtained as a yellow solid in 68% yield (142 mg), ($R_f$ = 0.29 in hexane/EtOAc 90:10 v/v); mp = 65–66 °C; IR (KBr) 3271, 2930, 2852, 1671, 1648, 1508, 1450, 1091, 745, 435; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.54–7.48 (comp, 2H), 7.35–7.31 (comp, 2H), 7.21–7.14 (comp, 3H), 7.09–7.05 (m , 1H), 4.17 (s, 1H), 4.13 (d, *J* = 12.7 Hz, 1H), 3.99 (d, *J* = 12.6 Hz, 1H), 3.64–3.55 (m, 1H), 3.05 (ddd, *J* = 12.3, 8.0, 4.5 Hz, 1H), 2.96 (ddd, *J* = 16.0, 8.0, 4.3 Hz, 1H), 2.92–2.84 (m, 1H), 2.67 (app dt, *J* = 16.0, 5.4 Hz, 1H), 1.81–1.70 (comp, 2H), 1.68–1.50 (comp, 3H), 1.35–1.22 (comp, 2H), 1.19–1.01 (comp, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ

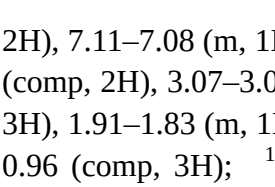
170.9, 137.2, 134.2, 134.0, 132.2, 130.1, 129.6, 128.9, 128.4, 127.0, 126.0, 66.0, 53.4, 48.1, 46.3, 33.2, 32.8, 26.2, 25.8, 25.0, 24.9; *m/z* (ESI–MS) ($^{35}$Cl) 417.72 [M + H ]$^+$, ($^{37}$Cl) 419.9 [M + H ]$^+$.

**_N_-cyclohexyl-2-(2,4,6-trimethylbenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1g:**

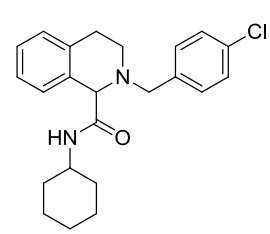


Following the general procedure B, cyclohexyl isocyanide, mesitaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1g** was obtained as a white solid in 64% yield (124 mg), ($R_f$ = 0.37 in hexane/EtOAc 90:10 v/v); mp = 150–151 °C; IR (KBr) 3322, 2927, 2849, 1644, 1521, 1450, 1319, 1231, 1136, 1103, 1073, 1031, 852, 745, 433; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.48–7.45 (m, 1H), 7.22–7.16 (comp, 2H), 7.11–7.08 (m, 1H), 6.90–6.85 (comp,3H), 4.09 (s, 1H), 3.95 (d, *J* = 12.6 Hz, 1H), 3.73–3.62 (comp, 2H), 3.07–3.00 (m, 1H), 2.89–2.81 (m, 1H), 2.77–2.66 (comp, 2H), 2.33 (s, 6H), 2.29 (s, 3H), 1.91–1.83 (m, 1H), 1.81–1.74 (m, 1H), 1.72–1.55 (comp, 3H), 1.41–1.25 (comp, 2H), 1.21–0.96 (comp, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.7, 138.2, 137.2, 134.2, 132.8, 131.2, 129.5, 128.9, 128.7, 127.0, 126.2, 67.8, 52.8, 48.2, 46.1, 33.1, 32.9, 27.2, 25.8, 25.0, 24.9, 21.1, 20.7; *m/z* (ESI–MS) 391.2 [M + H ]$^+$.

**2-benzyl-_N_-cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1h:** Following the general procedure B, cyclohexyl isocyanide, benzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1h** was obtained as a white solid in 69% yield (120 mg), ($R_f$ = 0.27 in hexane/EtOAc 90:10 v/v); mp = 117–119 °C; IR (KBr) 3346, 3023, 2936, 2849, 2802, 1663, 1510, 1491, 1450, 1148, 753, 695, 607, 550; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.61–7.56 (m, 1H), 7.40–7.28 (comp, 5H), 7.19–7.15 (comp, 2H), 7.12–7.06 (comp, 2H), 4.18 (s, 1H), 3.95 (d, *J* = 13.5 Hz, 1H), 3.79–3.69 (m, 1H), 3.46 (d, *J* = 13.5 Hz, 1H), 3.07 (ddd, *J* = 11.5, 5.0, 3.5 Hz, 1H), 2.92 (ddd, *J* = 15.9, 10.6, 5.0 Hz, 1H), 2.70 (app dt, *J* = 16.1, 3.5 Hz, 1H), 2.46 (app td, *J* = 11.1, 3.4 Hz, 1H), 1.94–1.87 (m, 1H), 1.79–1.73 (m, 1H), 1.71–1.54 (comp, 3H), 1.40–1.26 (comp, 2H), 1.21–1.08 (comp, 2H), 1.06–0.97(m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.1, 138.1, 134.1, 132.8, 128.9, 128.8, 128.7, 127.6, 127.5, 127.0, 126.4, 68.7, 60.3, 48.0, 46.8, 33.2, 33.1, 29.0, 25.8, 25.0, 24.9; *m/z* (ESI–MS) 349.0 [M + H ]$^+$.



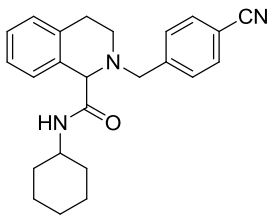
**2-(4-chlorobenzyl)-_N_-cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1i:**



Following the general procedure B, cyclohexyl isocyanide, 4-chlorobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1i** was obtained as a white solid in 76% yield (145 mg), ($R_f$ = 0.27 in hexane/EtOAc 90:10 v/v); mp = 103–105 °C; IR (KBr) 3264, 3070, 2930, 2851, 1648, 1635, 1552, 1490, 1449, 1090, 1014, 741, 485; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.57–7.52 (m, 1H), 7.35–7.31 (comp, 2H), 7.29–7.24 (comp, 2H), 7.19–7.13 (comp, 2H), 7.10–7.05 (m, 1H), 6.95 (d,

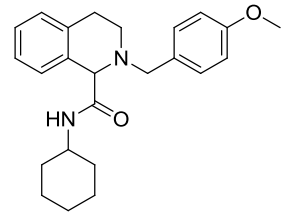
J = 8.6 Hz, 1H), 4.16 (s, 1H), 3.89 (d, *J* = 13.7 Hz, 1H), 3.79–3.69 (m, 1H), 3.44 (d, *J* = 13.7 Hz, 1H), 3.06–3.00 (m, 1H), 2.91 (ddd, *J* = 15.9, 10.6, 5.0 Hz, 1H), 2.70 (app dt, *J* = 16.2, 3.5 Hz, 1H) , 2.44 (app td, *J* = 11.0, 3.5 Hz, 1H), 1.91–1.84 (m, 1H), 1.78–1.71 (m, 1H), 1.70–1.53 (comp, 3H), 1.39–1.24 (comp, 2H), 1.18–1.07 (comp, 2H), 1.04–0.94 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.0, 136.5, 133.9, 133.4, 132.6, 130.2, 128.9, 128.8, 127.4, 127.1, 126.4, 68.7, 59.5, 48.0, 46.8, 33.3, 33.1, 29.0, 25.7, 25.0, 24.9; *m/z* (ESI–MS) ($^{35}$Cl) 383.14 $[M + H]^+$, ($^{37}$Cl) 385.1 $[M + H]^+$.

**2-(4-cyanobenzyl)-*N*-cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1j:**

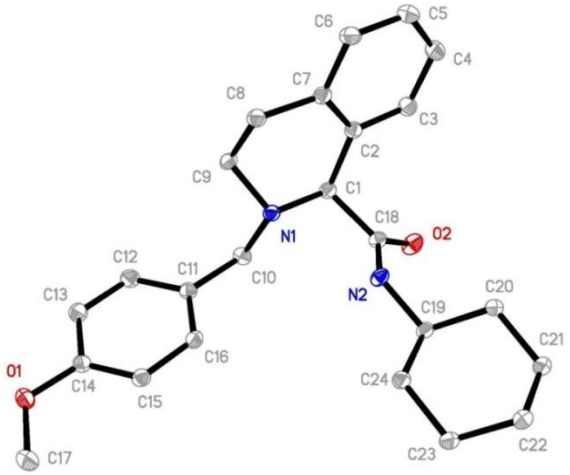



Following the general procedure B, cyclohexyl isocyanide, 4-formylbenzonitrile and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1j** was obtained as a yellow oil in 67% yield (125 mg), ($R_f$ = 0.10 in hexane/EtOAc 90:10 v/v); IR (KBr) 3373, 2931, 2854, 2228, 1656, 1510, 1451, 1386, 1311, 1151, 1093, 890, 815, 736; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.69–7.63 (comp, 2H), 7.52–7.48 (m, 1H), 7.47–7.43 (comp, 2H), 7.20–7.13 (comp , 2H), 7.11–7.05 (m, 1H), 6.78 (d, *J* = 8.6 Hz, 1H) 4.17 (s, 1H), 3.96 (d, *J* = 14.4 Hz, 1H), 3.76–3.66 (m, 1H), 3.55 (d, *J* = 14.4 Hz, 1H) , 3.02–2.90 (comp, 2H), 2.72 (app dt, *J* = 16.2, 3.0 Hz, 1H), 2.48 (m, 1H), 1.85–1.78 (m, 1H), 1.77–1.71 (m, 1H), 1.68–1.52 (comp, 3H), 1.38–1.23 (comp, 2H), 1.16–1.03 (comp, 2H), 1.02–0.92 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.7, 143.7, 133.6, 132.6, 132.4, 129.3, 128.8, 127.3, 127.2, 126.6, 118.9, 111.6, 68.9, 59.7, 48.0, 47.2, 33.3, 33.0, 28.9, 25.7, 25.0, 24.8; *m/z* (ESI–MS) 374.6 $[M + H]^+$.

***N*-cyclohexyl-2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1k:**

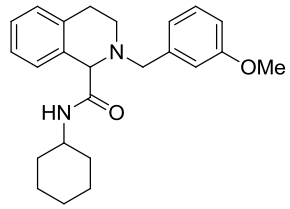



Following the general procedure B, cyclohexyl isocyanide, 4-methoxybenzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1k** was obtained as a white solid in 68% yield (130 mg), ($R_f$ = 0.20 in hexane/EtOAc 90:10 v/v); mp = 133–135 °C; IR (KBr) 3368, 2931, 2856, 2834, 2354, 1670, 1611, 1508, 1443, 1247, 1173, 1080, 1032, 813, 752, 525; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.60–7.55 (m, 1H), 7.26–7.22 (comp, 2H), 7.18–7.14 (comp, 2H), 7.13–7.05 (comp, 2H), 6.92–6.88 (comp, 2H), 4.15 (s, 1H), 3.88 (d, *J* = 13.3 Hz, 1H), 3.82 (s, 3H), 3.78–3.70 (m, 1H), 3.40 (d, *J* = 13.3 Hz, 1H), 3.06 (ddd, *J* = 11.5, 5.0, 3.6 Hz, 1H), 2.89 (ddd, *J* = 16.2, 10.5, 5.0 Hz, 1H), 2.69 (app dt, *J* = 16.1, 3.5 Hz, 1H), 2.43 (app td, *J* = 11.1, 3.4 Hz, 1H), 1.96–1.89 (m, 1H), 1.79–1.54 (comp, 4H), 1.41–1.26 (comp, 2H), 1.22–1.09 (comp, 2H), 1.06–0.96 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.2, 159.2, 134.2, 132.8, 130.2, 129.9, 128.7, 127.5, 127.0, 126.4, 114.1, 68.5, 59.6, 55.5, 48.0, 46.6, 33.3, 33.1, 29.0, 25.8, 25.1, 24.9; *m/z* (ESI–MS) 379.0 $[M + H]^+$. X-ray quality crystals of **1k** were obtained from hexane/dichloromethane through slow diffusion at room temperature.



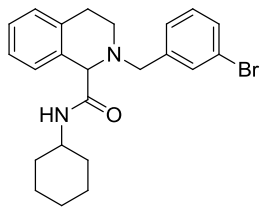

The requisite CIF has been submitted to the journal and deposited with the CCDC (deposition # 1441887).

***N*-cyclohexyl-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1l:**




Following the general procedure B, cyclohexyl isocyanide, 3-methoxybenzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1l** was obtained as a white solid in 74% yield (140 mg), ($R_f$ = 0.19 in hexane/EtOAc 90:10 v/v); mp = 90–92 °C; IR (KBr) 3310, 3052, 3019, 2933, 2849, 1648, 1522, 1487, 1449, 1277, 1153, 1049, 778, 750, 688, 568, 435; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.60–7.56 (m, 1H), 7.31–7.25 (m, 1H), 7.18–7.06 (comp, 4H), 6.95–6.88 (comp, 2H), 6.86–6.82 (m, 1H), 4.17 (s, 1H), 3.92 (d, *J* = 13.6 Hz, 1H), 3.81 (s, 3H), 3.78–3.69 (m, 1H), 3.42 (d, *J* = 13.6 Hz, 1H), 3.07 (ddd, *J* = 11.5, 5.0, 3.5 Hz, 1H), 2.92 (ddd, *J* = 15.9, 10.7, 5.0 Hz, 1H), 2.69 (app dt, *J* = 16.2, 3.5 Hz, 1H) , 2.44 (app td, *J* = 11.1, 3.4 Hz, 1H), 1.93–1.87 (m, 1H), 1.79–1.72 (m, 1H), 1.70–1.53 (comp, 3H), 1.39–1.25 (comp, 2H), 1.20–1.07 (comp, 2H), 1.05–0.96 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.2, 160.0, 139.7, 134.1, 132.7, 129.8, 128.8, 127.4, 127.0, 126.4, 121.2, 114.6, 112.8, 68.7, 60.2, 55.4, 48.0, 46.8, 33.2, 33.1, 29.0, 25.8, 25.1, 24.9; *m/z* (ESI–MS) 379.4 [M + H ]$^+$.

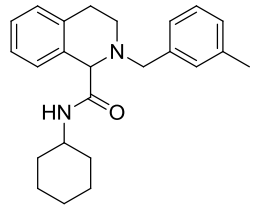
**2-(3-bromobenzyl)-*N*-cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1m:**




Following the general procedure B, cyclohexyl isocyanide, 3-bromobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1m** was obtained as a yellow solid in 74% yield (158 mg), ($R_f$ = 0.21 in hexane/EtOAc 90:10 v/v); mp = 83–85 °C; IR (KBr) 3262, 3063, 2928, 2851, 1648, 1560, 1445, 1244, 1088, 925, 882, 777, 740, 669, 425; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.57–7.53 (m, 1H),

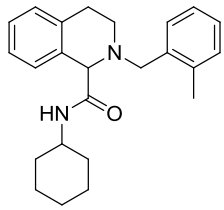
7.52–7.50 (m, 1H), 7.42 (app dt, *J* = 7.3, 1.9 Hz, 1H), 7.26–7.20 (comp, 2H), 7.18–7.14 (comp, 2H), 7.10–7.06 (m, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 4.16 (s, 1H), 3.89 (d, *J* = 13.7 Hz, 1H), 3.78–3.69 (m, 1H), 3.44 (d, *J* = 13.8 Hz, 1H), 3.04 (ddd, *J* = 11.5, 5.1, 3.7 Hz, 1H), 2.92 (ddd, *J* = 15.8, 10.5, 5.0 Hz, 1H), 2.71 (app dt, *J* = 16.2, 3.6 Hz, 1H), 2.47 (ddd, *J* = 11.4, 10.5, 3.5 Hz, 1H), 1.91–1.85 (m, 1H), 1.78–1.71 (m, 1H), 1.70–1.52 (comp, 3H), 1.40–1.25 (comp, 2H), 1.21–1.09 (comp, 2H), 1.06–0.96 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.9, 140.6, 133.9, 132.5, 131.8, 130.8, 130.3, 128.8, 127.49, 127.46, 127.1, 126.4, 123.0, 68.7, 59.6, 48.0, 47.0, 33.2, 33.0, 28.9, 25.7, 25.0, 24.8; *m/z* (ESI–MS) ($^{79}$Br) 427.13 [M + H ]$^+$, ($^{81}$Br) 429.1 [M + H ]$^+$.

***N*-cyclohexyl-2-(3-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1n:**



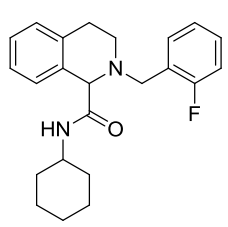

Following the general procedure B, cyclohexyl isocyanide, 3-methylbenzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1n** was obtained as a white solid in 72% yield (130 mg), ($R_f$ = 0.29 in hexane/EtOAc 90:10 v/v); mp = 103–104 °C; IR (KBr) 3375, 2927, 2856, 1668, 1506, 1452, 1365, 1139, 1083, 789, 755, 748, 701, 571, 538, 440; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.52–7.48 (m, 1H), 7.19–7.14 (m, 1H), 7.11–6.97 (comp, 7H), 4.08 (s, 1H), 3.82 (d, *J* = 13.4 Hz, 1H), 3.70–3.61 (m, 1H), 3.32 (d, *J* = 13.4 Hz, 1H), 2.98 (ddd, *J* = 11.5, 5.0, 3.6 Hz, 1H), 2.82 (ddd, *J* = 15.8, 10.6, 4.9 Hz, 1H), 2.61 (app dt, *J* = 16.1, 3.5 Hz, 1H), 2.35 (app td, *J* = 11.1, 3.4 Hz, 1H), 2.28 (s, 3H), 1.87–1.80 (m, 1H), 1.71–1.44 (comp, 4H), 1.32–1.17 (comp, 2H), 1.14–1.00 (comp, 2H), 0.98–0.88 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.2, 138.4, 138.0, 134.2, 132.8, 129.8, 128.74, 128.67, 128.4, 127.5, 127.0, 126.4, 126.0, 68.6, 60.3, 48.0, 46.7, 33.2, 33.1, 29.0, 25.8, 25.0, 24.9, 21.8; *m/z* (ESI–MS) 363.2 [M + H ]$^+$.

***N*-cyclohexyl-2-(2-methylbenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1o:**



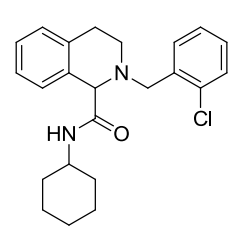

Following the general procedure B, cyclohexyl isocyanide, 2-methylbenzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1o** was obtained as a white solid in 64% yield (115 mg), ($R_f$ = 0.34 in hexane/EtOAc 90:10 v/v); mp = 101–102 °C; IR (KBr) 3273, 3065, 2931, 1635, 1551, 1496, 1451, 1229, 1085, 887, 741, 684; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.50–7.46 (m, 1H), 7.29–7.25 (m, 1H), 7.14–7.06 (comp, 5H), 7.02–6.99 (m, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 4.11 (s, 1H), 3.73 (d, *J* = 14.0 Hz, 1H), 3.63 – 3.55 (m, 1H), 3.50 (d, *J* = 14.0 Hz, 1H), 2.97 (app dt, J = 11.7, 4.7 Hz, 1H), 2.83 (ddd, J = 15.3, 9.8, 5.0 Hz, 1H), 2.66 (app dt, *J* = 16.2, 4.1 Hz, 1H), 2.43 (ddd, J = 11.7, 9.8, 3.7 Hz, 1H), 2.26 (s, 3H), 1.71–1.61 (comp, 2H), 1.54–1.40 (comp, 3H), 1.25–1.14 (comp, 2H), 1.05–0.83 (comp, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.0, 136.9, 136.3, 134.1, 132.8, 130.7, 128.7, 128.6, 127.9, 127.5, 127.0, 126.4, 126.3, 69.0, 57.6, 48.0, 47.0, 33.0, 32.9, 28.5, 25.7, 24.9, 24.83, 19.7; *m/z* (ESI–MS) 363.2 [M + H ]$^+$.

***N*-cyclohexyl-2-(2-fluorobenzyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1p:**



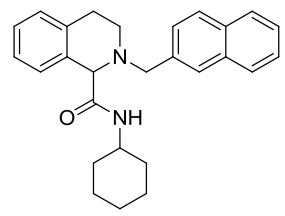
Following the general procedure B, cyclohexyl isocyanide, 2-fluorobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3h. Product **1p** was obtained as a yellow oil in 82% yield (150 mg), ($R_f$ = 0.39 in hexane/EtOAc 90:10 v/v); IR (KBr) 3374, 3064, 2931, 2854, 2359, 1671, 1510, 1492, 1453, 1368, 1229, 1098, 1085, 1033, 890, 757; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.64–7.59 (m, 1H), 7.36–7.27 (comp, 2H), 7.22–7.18 (m, 1H), 7.17–7.11 (comp, 3H), 7.10–7.03 (comp, 2H), 4.17 (s, 1H), 3.97 (d, *J* = 13.3 Hz, 1H), 3.76–3.66 (m, 1H), 3.54 (d, *J* = 13.3 Hz, 1H), 3.03 (ddd, *J* = 11.4, 4.9, 3.5 Hz, 1H), 2.90 (ddd, *J* = 15.9, 10.8, 5.0 Hz, 1H), 2.68 (app dt, *J* = 16.1, 3.4 Hz, 1H), 2.46 (app td, *J* = 11.1, 3.3 Hz, 1H), 1.97–1.89 (m, 1H), 1.76–1.53 (comp, 4H), 1.39–1.23 (comp, 2H), 1.21–1.07 (comp, 2H), 1.06–0.97 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.9, 161.9 (d, $J_{C\text{-}F}$ = 247.1 Hz), 134.1, 132.8, 131.8 (d, $J_{C\text{-}F}$ = 4.6 Hz), 129.6 (d, $J_{C\text{-}F}$ = 8.3 Hz), 128.6, 127.5, 127.0, 126.4, 124.7 (d, $J_{C\text{-}F}$ = 14.4 Hz), 124.3 (d, $J_{C\text{-}F}$ = 3.5 Hz), 115.9 (d, $J_{C\text{-}F}$ = 22.0 Hz), 68.8, 54.4, 48.2, 46.8, 33.0, 32.9, 29.0, 25.8, 25.1, 25.0; *m/z* (ESI–MS) 367.2 $[M + H]^+$.

**2-(2-chlorobenzyl)-*N*-cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1q:**



Following the general procedure B, cyclohexyl isocyanide, 2-chlorobenzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1q** was obtained as a white solid in 75% yield (143 mg), ($R_f$ = 0.24 in hexane/EtOAc 90:10 v/v); mp = 117–118 °C; IR (KBr) 3289, 2930, 2853, 1636, 1549, 1442, 1230, 1035, 748, 696; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.60–7.56 (m, 1H), 7.43–7.37 (comp, 2H), 7.30–7.22 (comp, 2H), 7.21–7.15 (comp, 3H), 7.12–7.07 (m, 1H), 4.21 (s, 1H), 3.87 (d, *J* = 14.1 Hz, 1H), 3.81 (d, *J* = 14.1 Hz, 1H), 3.70–3.61 (m, 1H), 3.07 (app dt, *J* = 11.9, 5.0 Hz, 1H), 2.90 (ddd, *J* = 14.7, 9.3, 4.9 Hz, 1H), 2.79 (app dt, *J* = 16.3, 4.4 Hz, 1H) , 2.63 (ddd, *J* = 11.8, 9.3, 3.8 Hz, 1H), 1.79–1.70 (comp, 2H), 1.64–1.49 (comp, 3H), 1.34–1.22 (comp, 2H), 1.15–0.95 (comp, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.6, 135.8, 134.7, 134.0, 132.6, 130.5, 130.1, 129.0, 128.7, 128.3, 127.13, 127.06, 126.3, 68.0, 57.3, 48.0, 47.1, 33.0, 32.9, 28.1, 25.8, 24.94, 24.86; *m/z* (ESI–MS) ($^{35}$Cl) 383.14 $[M + H]^+$, ($^{37}$Cl) 385.2 $[M + H]^+$.

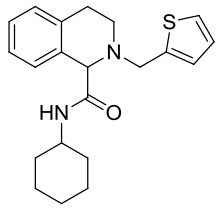
***N*-cyclohexyl-2-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1r:**



Following the general procedure B, cyclohexyl isocyanide, 2-naphthaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1r** was obtained as a white solid in 71% yield (141 mg), ($R_f$ = 0.26 in hexane/EtOAc 90:10 v/v); mp = 150–151 °C; IR (KBr) 3379, 3023, 2923, 1668, 1504, 1451, 857, 816, 759, 480; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.90–7.83 (comp, 3H), 7.80–7.78 (m, 1H), 7.65–7.61 (m, 1H), 7.55–7.47 (comp, 3H), 7.23–7.16 (comp, 3H), 7.13–7.08 (m, 1H), 4.7 (s, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 3.85–3.75 (m, 1H), 3.64 (d, *J* = 13.5 Hz, 1H), 3.14 (ddd, *J* = 11.6, 5.0, 3.7 Hz, 1H), 2.94 (ddd, *J* = 15.8, 10.5, 5.0 Hz, 1H), 2.73 (app dt, *J* = 16.2, 3.6 Hz, 1H), 2.56–

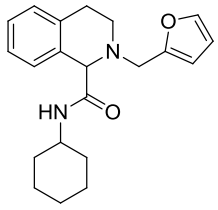
2.49 (m, 1H), 1.99–1.92 (m, 1H), 1.84–1.77 (m, 1H), 1.74–1.56 (comp, 3H), 1.43–1.03 (comp, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.1, 135.7, 134.1, 133.6, 133.1, 132.8, 128.8, 128.6, 127.96, 127.95, 127.8, 127.6, 127.1, 126.8, 126.5, 126.4, 126.2, 68.8, 60.4, 48.0, 46.9, 33.3, 33.2, 29.0, 25.8, 25.0, 24.9; *m/z* (ESI–MS) 399.4 $[M + H]^+$.

***N*-cyclohexyl-2-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1s:**



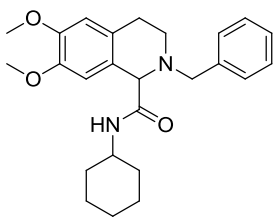
Following the general procedure B, cyclohexyl isocyanide, thiophene-2-carbaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1s** was obtained as a yellow solid in 76% yield (135 mg), ($R_f$ = 0.24 in hexane/EtOAc 90:10 v/v); mp = 100–102 °C; IR (KBr) 3372, 2932, 2856, 1670, 1507, 1452, 1369, 1140, 754, 733, 709; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.61–7.56 (m, 1H), 7.28–7.25 (m, 1H), 7.19–7.05 (comp, 4H), 6.98–6.94 (comp, 2H), 4.20 (s, 1H), 4.00 (d, *J* = 14.1 Hz, 1H), 3.78–3.68 (comp, 2H), 3.17 (ddd, *J* = 11.6, 5.1, 3.7 Hz, 1H), 2.93 (ddd, *J* = 15.8, 10.5, 5.0 Hz, 1H), 2.72 (app dt, *J* = 16.2, 3.6 Hz, 1H), 2.51 (app td, *J* = 11.0, 3.4 Hz, 1H), 1.98–1.91 (m, 1H), 1.79–1.54 (comp, 4H), 1.40–1.00 (comp, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.8, 142.1, 134.0, 132.5, 128.7, 127.6, 127.1, 126.9, 126.5, 126.4, 125.2, 68.2, 54.7, 48.2, 46.8, 33.2, 33.0, 29.0, 25.8, 25.1, 25.0; *m/z* (ESI–MS) 355.3 $[M + H]^+$.

***N*-cyclohexyl-2-(furan-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1t:**



Following the general procedure B, cyclohexyl isocyanide, furan-2-carbaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1t** was obtained as a yellow oil in 68% yield (115 mg), ($R_f$ = 0.19 in hexane/EtOAc 90:10 v/v); IR (KBr) 3370, 2930, 2853, 1671, 1508, 1452, 1313, 1149, 1010, 910, 880, 805, 735; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.65–7.60 (m, 1H), 7.41–7.37 (m, 1H), 7. 31–7.27 (m, 1H), 7.18–7.12 (comp, 2H), 7.09–7.04 (m, 1H), 6.36–6.32 (m, 1H), 6.28–6.24 (m,1H), 4.18 (s, 1H), 3.82 (d, *J* = 14.4 Hz, 1H), 3.77–3.68 (m, 1H), 3.56 (d, *J* = 14.5 Hz, 1H), 3.13 (ddd, *J* = 11.2, 5.0, 3.1 Hz, 1H), 2.94 (ddd, *J* = 16.1, 11.2, 5.1 Hz, 1H), 2.70 (app dt, *J* = 16.1, 3.3 Hz, 1H), 2.54 (app td, *J* = 11.3, 3.3 Hz, 1H), 1.99–1.91 (m, 1H), 1.76–1.67 (comp, 2H), 1.65–1.54 (comp, 2H), 1.42–1.11 (comp, 4H), 1.08–0.97(m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.9, 151.6, 142.6, 134.0, 132.7, 128.6, 127.5, 126.9, 126.4, 110.4, 109.4, 67.6, 52.5, 48.0, 47.2, 33.0, 29.4, 25.8, 25.0, 24.9; *m/z* (ESI–MS) 339.1 $[M + H]^+$.

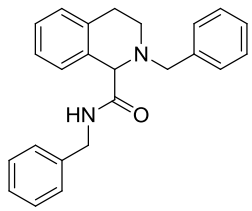
**2-benzyl-*N*-cyclohexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1u:**



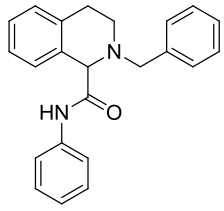
Following the general procedure B, cyclohexyl isocyanide, benzaldehyde and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1u** was obtained as a white solid in 94% yield (192 mg), ($R_f$ = 0.21 in hexane/EtOAc 80:20 v/v); mp = 135–137 °C; IR (KBr) 3380, 3322, 2928, 2849, 1648, 1606, 1518, 1453, 1254, 1229, 1131, 1020, 755, 730, 697; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.26 (comp, 5H),

7.12–7.07 (comp, 2H), 6.54 (s, 1H), 4.07 (s, 1H), 3.92 (d, *J* = 13.5 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.76–3.67 (m, 1H), 3.43 (d, *J* = 13.5 Hz, 1H), 3.03 (ddd, *J* = 11.4, 5.0, 3.7 Hz, 1H), 2.82 (ddd, *J* = 15.7, 10.3, 4.8 Hz, 1H), 2.60 (app dt, *J* = 15.9, 3.6 Hz, 1H), 2.43 (app td, *J* = 11.0, 3.5 Hz, 1H), 1.93–1.85 (m, 1H), 1.81–2.73 (m, 1H), 1.70–1.52(comp, 3H), 1.38–1.23 (comp, 2H), 1.39–1.24 (comp, 2H), 1.19–0.96 (comp, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.3, 148.1, 147.6, 138.1, 128.9, 128.7, 127.6, 126.1, 124.6, 111.1, 110.1, 68.2, 60.2, 56.1, 56.0, 48.0, 46.9, 33.2, 33.1, 28.4, 25.8, 25.0, 24.9; *m/z* (ESI–MS) 409.0 $[M + H]^+$.

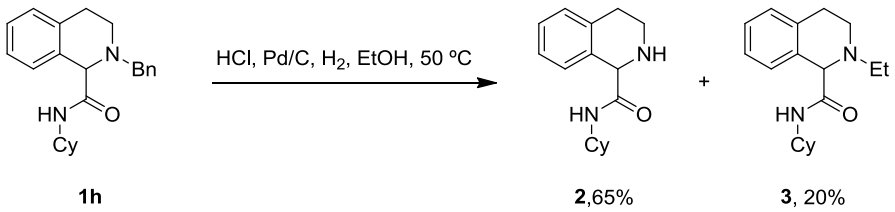
***N*,2-dibenzyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1v:** Following the general procedure B, benzyl isocyanide, benzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1v** was obtained as a yellow solid in 85% yield (151 mg), ($R_f$ = 0.22 in hexane/EtOAc 90:10 v/v); mp = 130–131 °C; IR (KBr) 3338, 3029, 2921, 2807, 1655, 1523, 1492, 1453, 1426, 1273, 1030, 755, 734, 696, 430; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.71–7.67 (m, 1H), 7.62–7.57 (m, 1H), 7.35–7.17 (comp, 12H), 7.16–7.11 (m, 1H), 4.63 (dd, *J* = 14.8, 6.8 Hz, 1H), 4.36–4.28 (comp, 2H), 3.95 (d, *J* = 13.4 Hz, 1H), 3.51 (d, *J* = 13.5 Hz, 1H), 3.11 (ddd, *J* = 11.5, 4.9, 3.6 Hz, 1H), 2.93 (ddd, *J* = 15.8, 10.6, 4.9 Hz, 1H), 2.73 (app dt, *J* = 16.2, 3.6 Hz, 1H), 2.50 (app td, *J* = 11.1, 3.4 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.2, 138.7, 137.7, 134.3, 132.6, 129.2, 128.94, 128.87, 128.7, 128.0, 127.8, 127.70, 127.68, 127.2, 126.5, 68.6, 60.4, 46.7, 43.5, 29.0; *m/z* (ESI–MS) 357.2$[M + H]^+$.




**2-benzyl-*N*-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide 1w:** Following the general procedure B, isocyanobenzene, benzaldehyde and 1,2,3,4-tetrahydroisoquinoline were heated at reflux for 3 h. Product **1w** was obtained as a white solid in 53% yield (90 mg), ($R_f$ = 0.45 in hexane/EtOAc 90:10 v/v); mp = 117–119 °C; IR (KBr) 3328, 2813, 1676, 1604, 1523, 1493, 1439, 1313, 1153, 1128, 755, 747, 692, 535; $^1$H NMR ($CDCl_3$, 500 MHz) δ 9.28 (s, 1H), 7.69–7.64 (m, 1H), 7.58–7.53 (comp, 2H), 7.43–7.28 (comp, 7H), 7.24–7.18 (comp, 2H), 7.15–7.05 (comp, 2H), 4.35 (s, 1H), 4.01 (d, *J* = 13.6 Hz, 1H), 3.61 (d, *J* = 13.5 Hz, 1H), 3.20 (ddd, *J* = 11.6, 5.0, 3.9 Hz, 1H), 2.99 (ddd, *J* = 15.8, 10.5, 5.0 Hz, 1H), 2.79 (app dt, *J* = 16.2, 3.6 Hz, 1H), 2.59 (app td, *J* = 11.1, 3.4 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.1, 138.1, 137.5, 134.3, 131.8, 129.23, 129.15, 128.92, 128.88, 127.90, 127.85, 127.4, 126.6, 124.3, 119.6, 68.9, 60.6, 46.7, 28.9; *m/z* (ESI–MS) 343.1 $[M + H]^+$.



***N*-cyclohexyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (2) and *N*-cyclohexyl-2-ethyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3):**

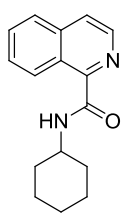



**1h** **2**,65% **3**, 20%

Following a modified literature procedure,[3] a solution of **1h** (62 mg, 0.18 mmol) in MeOH (5 mL) was treated with methanolic HCl (1.2 equiv). The solvent was subsequently removed under reduced pressure to obtain the hydrochloride salt, which was dissolved in EtOH (5 mL). To this solution was added 10% Pd/C (10 mg) and it was stirred for 20 h at 50 °C under an atmosphere of hydrogen. The reaction mixture was allowed to cool to room temperature and filtered through Celite. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel. Product **2** was obtained as a white solid in 65% yield (30 mg), ($R_f$ = 0.52 in EtOAc/MeOH 90:10 v/v); mp = 130–132 °C; IR (KBr) 3283, 3057, 3017, 2929, 2854, 1644, 1545, 1449, 1247, 985, 890, 735, 693, 645, 443; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.54–7.49 (m, 1H), 7.19–7.14 (comp, 2H), 7.10–7.06 (m, 1H), 7.04–6.96 (m, 1H), 4.50 (s, 1H), 3.78–3.68 (m, 1H), 3.12–3.03 (comp, 2H), 2.89–2.81 (m, 1H), 2.79–2.70 (m, 1H), 2.16 (br s, 1H) 1.93–1.86 (m, 1H), 1.83–1.75 (m, 1H), 1.71–1.53 (comp, 3H), 1.41–1.25 (comp, 2H), 1.20–1.02 (comp, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.9, 134.8, 133.1, 129.2, 128.1, 127.1, 126.1, 60.4, 48.1, 41.5, 33.2, 33.1, 29.6, 25.8, 25.0, 24.9.; *m/z* (ESI–MS) 259.1 $[M + H]^+$.

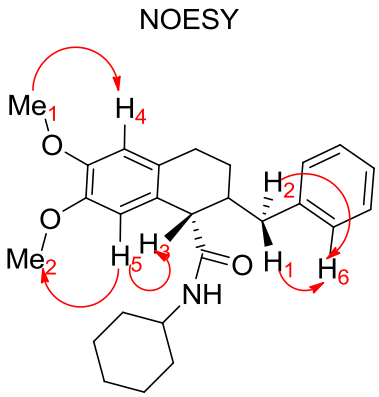
In addition, product **3** was obtained as a white solid in 20% yield (10 mg), ($R_f$ = 0.12 in hexane/EtOAc 90:10 v/v); mp = 88–89 °C; IR (KBr) 3275, 3067, 2931, 2852, 1637, 1536, 1448, 1248, 1095, 930, 888, 735; $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.60–7.56 (m, 1H), 7.17–7.05 (comp, 4H), 4.06 (s, 1H), 3.75–3.65 (m, 1H), 3.17 (ddd, *J* = 11.3, 4.9, 3.2 Hz, 1H), 2.95 (ddd, *J* = 16.0, 11.2, 4.9 Hz, 1H), 2.77–2.65 (comp, 2H), 2.54–2.43 (comp, 2H), 1.94–1.89 (m, 1H), 1.72–1.53 (comp, 5H), 1.41–1.24 (comp, 2H), 1.20–1.09 (comp, 4H), 1.02–0.94 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.6, 134.3, 133.1, 128.5, 127.5, 126.8, 126.3, 68.5, 50.3, 47.8, 46.5, 33.2, 33.0, 29.5, 25.8, 25.0, 24.9, 12.6.; *m/z* (ESI–MS) 287.1 $[M + H]^+$.

***N*-cyclohexylisoquinoline-1-carboxamide 4:** Following a modified literature procedure,[4] to a solution of **1k** (76 mg, 0.2 mmol) in mesitylene (2 mL, 0.1 M) was added 10% Pd/C (43 mg) and the mixture was stirred under reflux for 4 h. The reaction mixture was allowed to cool to room temperature, diluted with 5 mL of EtOAc and a few drops of triethylamine, and then filtered through Celite. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel. Product **4** was obtained as a white solid in 71% yield (36 mg), ($R_f$ = 0.45 in



hexane/EtOAc 90:10 v/v); mp = 118–120 °C; IR (KBr) 3355, 2923, 2856, 1654, 1513, 1451, 1383, 1341, 1313, 1251, 1148, 763, 625, 513; $^{1}$H NMR ($CDCl_3$, 500 MHz) δ 9.62–9.59 (m, 1H), 8.44 (d, *J* = 5.5 Hz, 1H), 8.14–8.06 (m, 1H), 7.84–7.80 (m, 1H), 7.78–7.74 (m, 1H), 7.72–7.63 (comp, 2H), 4.06–3.97 (m, 1H), 2.11–2.04 (comp, 2H), 1.83–1.75 (comp, 2H), 1.70–1.62 (m, 1H), 1.52–1.32 (comp, 4H), 1.30–1.20 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 165.4, 148.9, 140.4, 137.6, 130.6, 128.7, 128.2, 127.3, 126.9, 124.3, 48.5, 33.3, 25.9, 25.2.; *m/z* (ESI–MS) 277.6 $[M + Na]^+$.

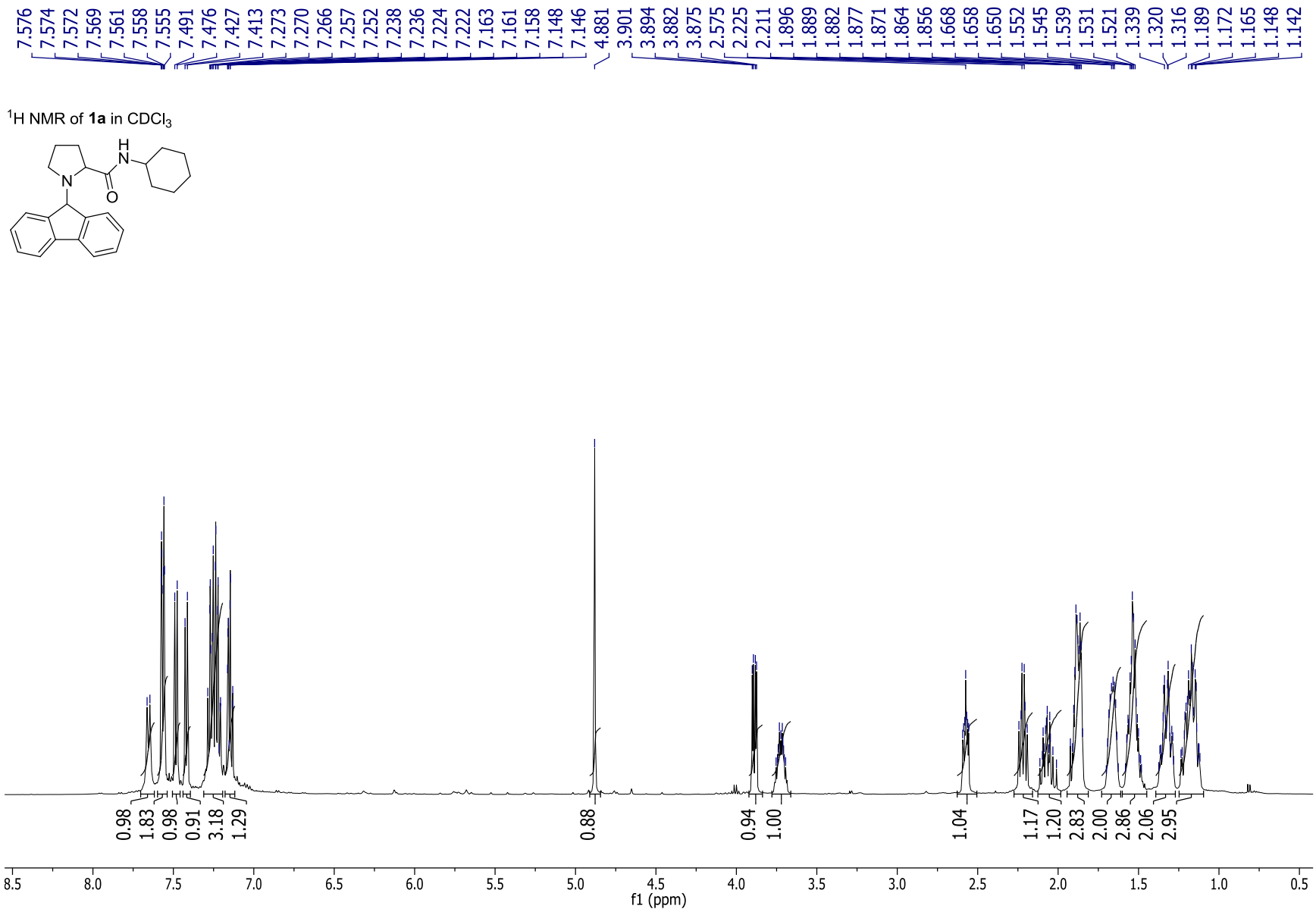
**2D-NMR Analysis for Compound 1u, Selected Interactions (in $CDCl_3$):**



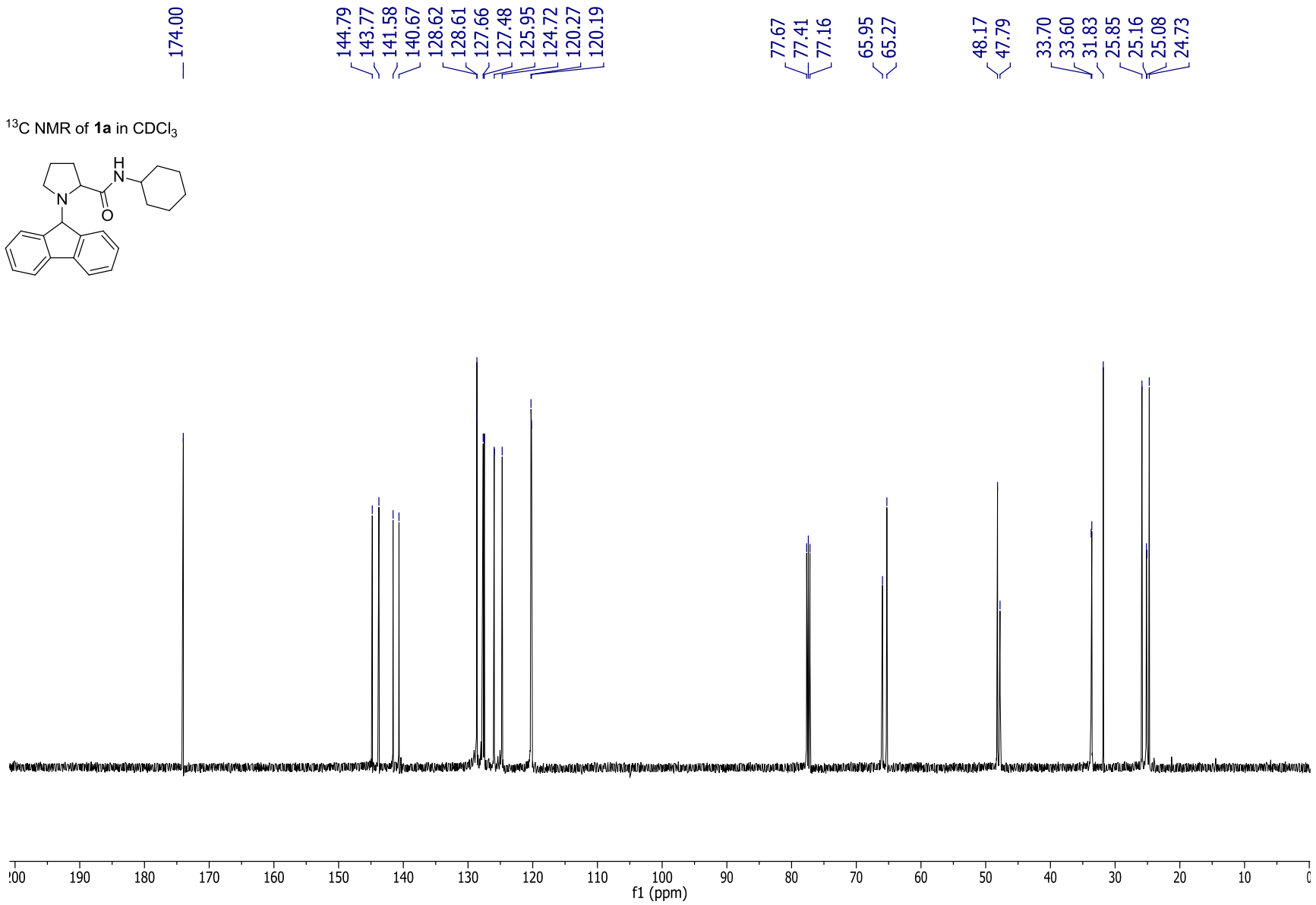

| Protons | Chemical Shifts (ppm) |
|---|---|
| H1,H2 | 3.43, 3.92 |
| Me1 | 3.83 |
| Me2 | 3.84 |
| H3 | 4.07 |
| H4 | 6.54 |
| H5 | 7.12–7.07 |
| H6 | 7.38–7.26 |

## References:

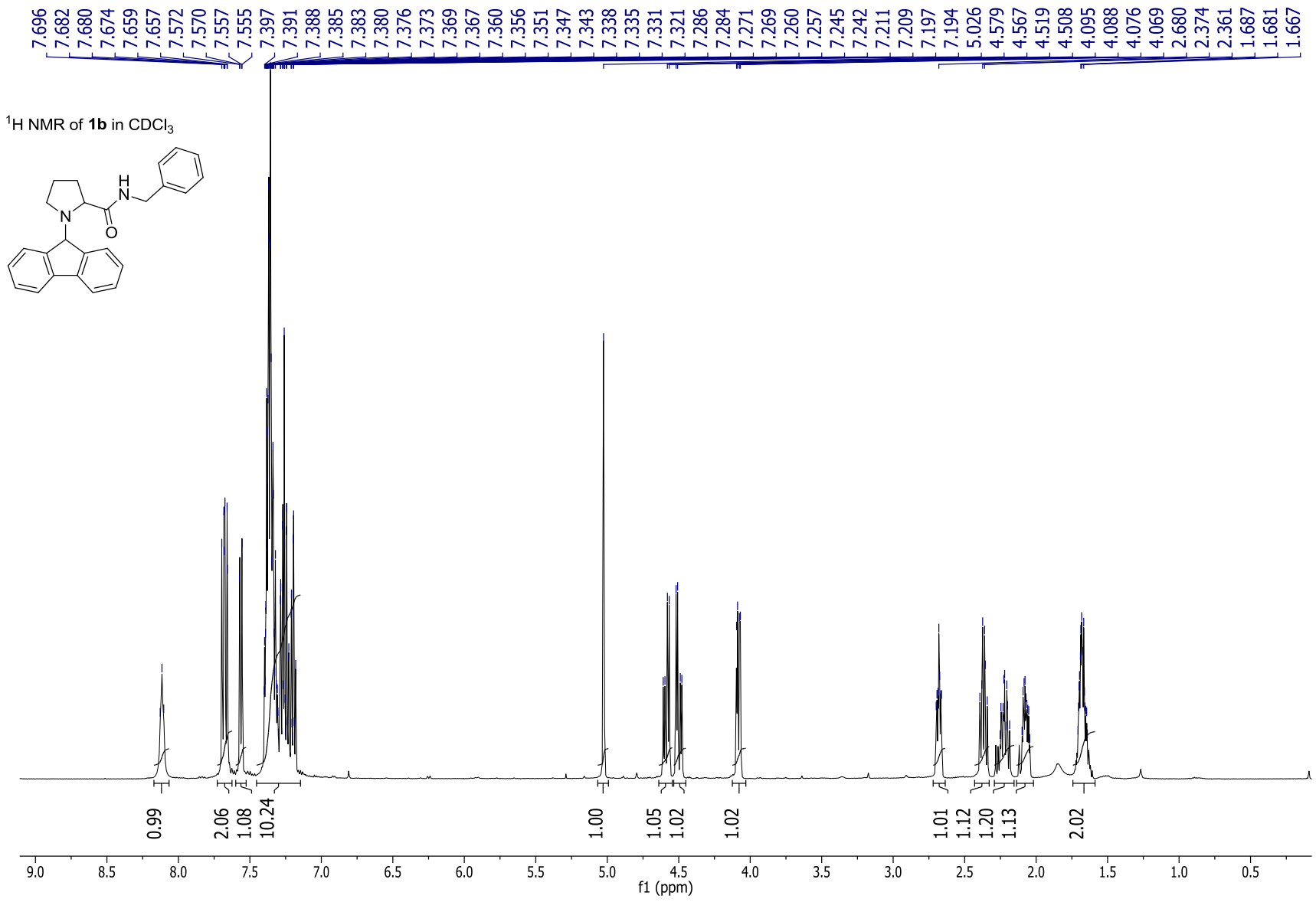

1. Sehlinge, A.; Espinosa, L.; Meier, M. *Macromolecules* **2013**, *46*, 6031.
2. Janza, B.; Studer, A. *Org. Lett*. **2006**, *8*, 1875.
3. Nussbaumer, P.; Dechat. T, *Monatsh. Chem*. **2001**, *132*, 1047.
4. Teske, J.; Deiters, A. *J. Org. Chem*. **2008**, *73*, 342.
5. Popovici-Muller, J.; Saunders, J.; Salituro, F.; Travins, J.; Yan, S.; Zhao, F.; Gross, S.; Dang, L.; Yen, K.; Yang, H.; Straley, K.; Jin, S.; Kunii, K.; Fantin, V.; Zhang, S.; Pan, Q.; Shi, D.; Biller, S.; Su, S. *ACS Med. Chem. Lett*. **2012**, *3*, 850.
6. Fañanás-Mastral, M.; Teichert, J.; Fernández-Salas, J.; Heijnen, D.; Feringa, B. *Org. Biomol. Chem*. **2013**, *11*, 4521.

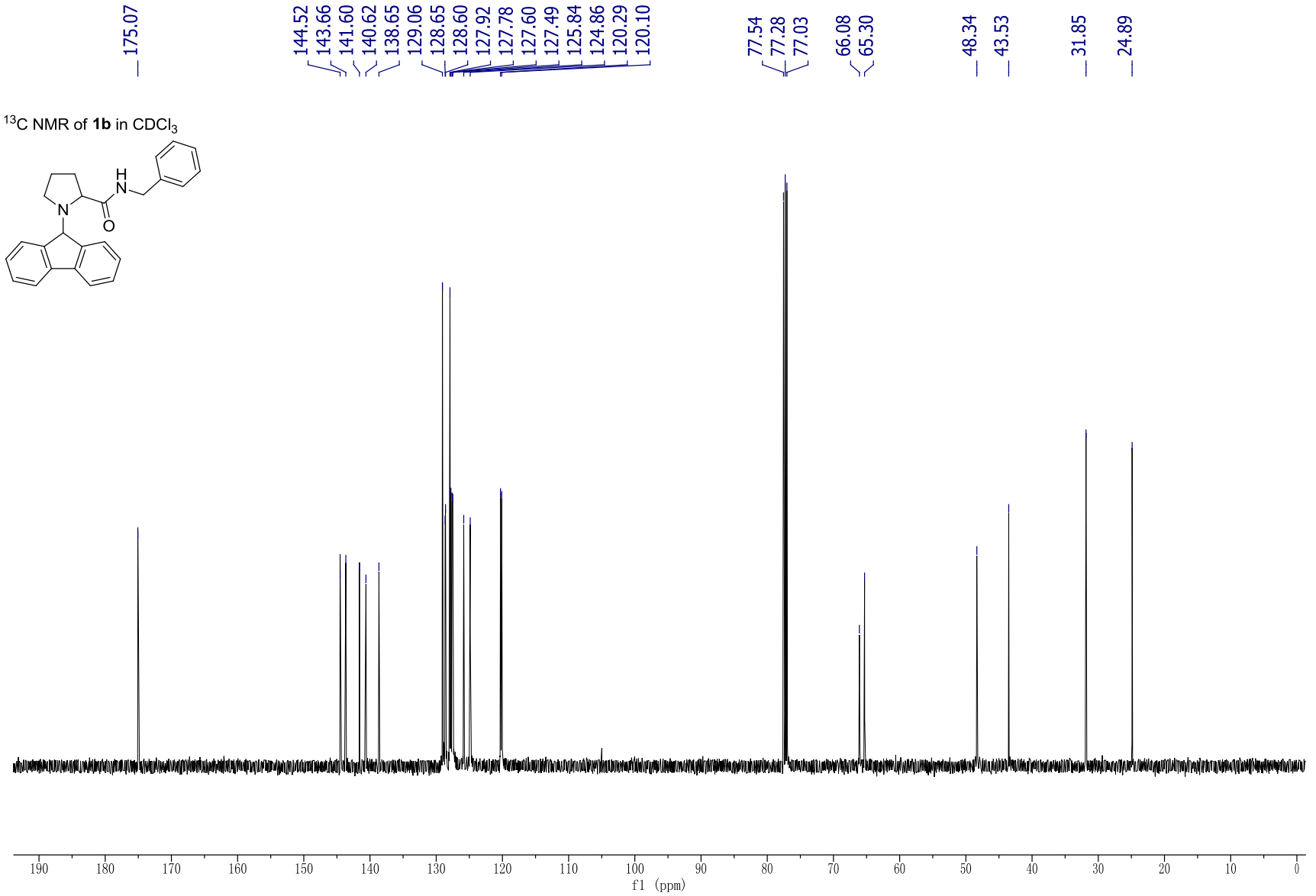


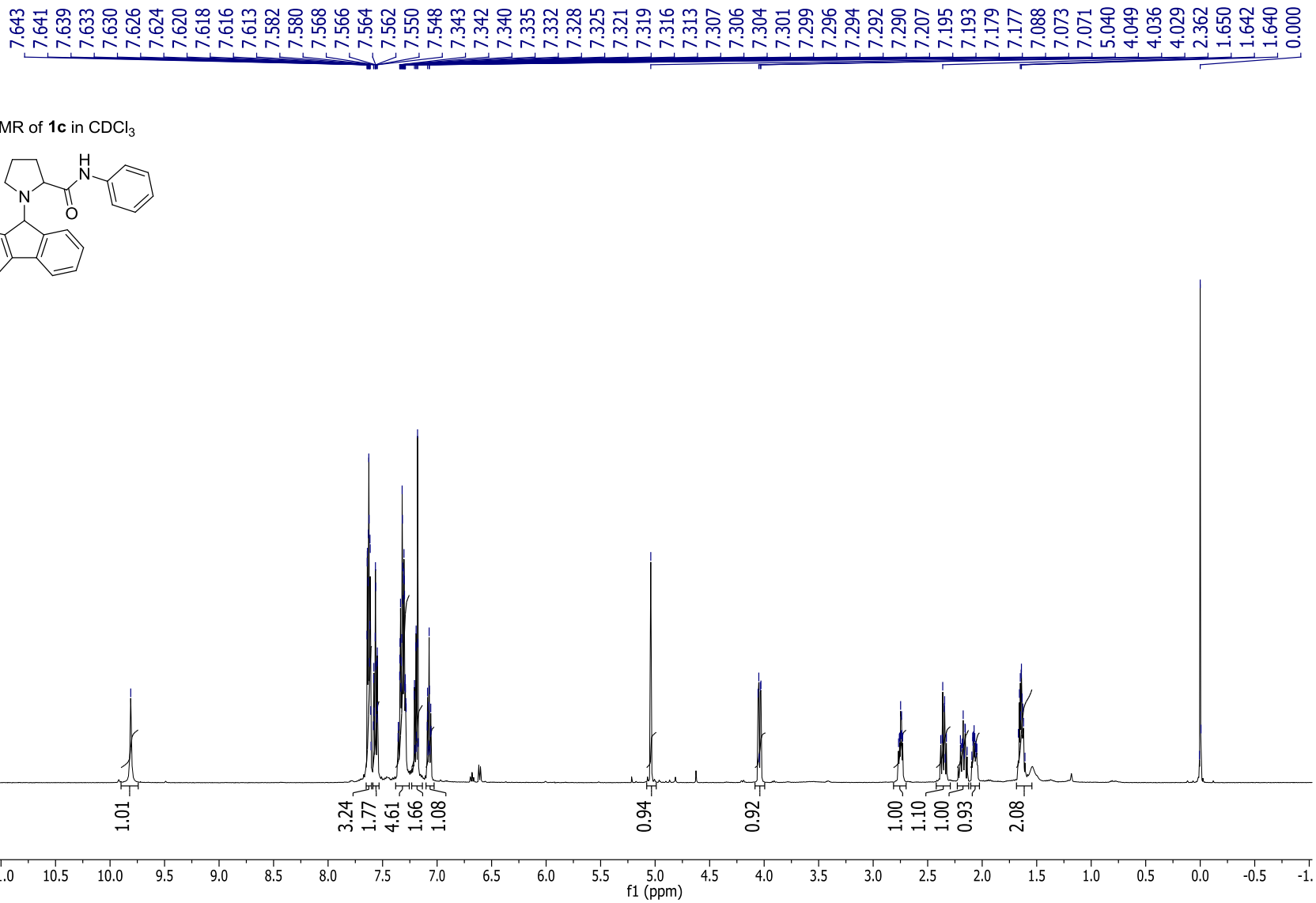

$^1$H NMR of **1a** in $CDCl_3$

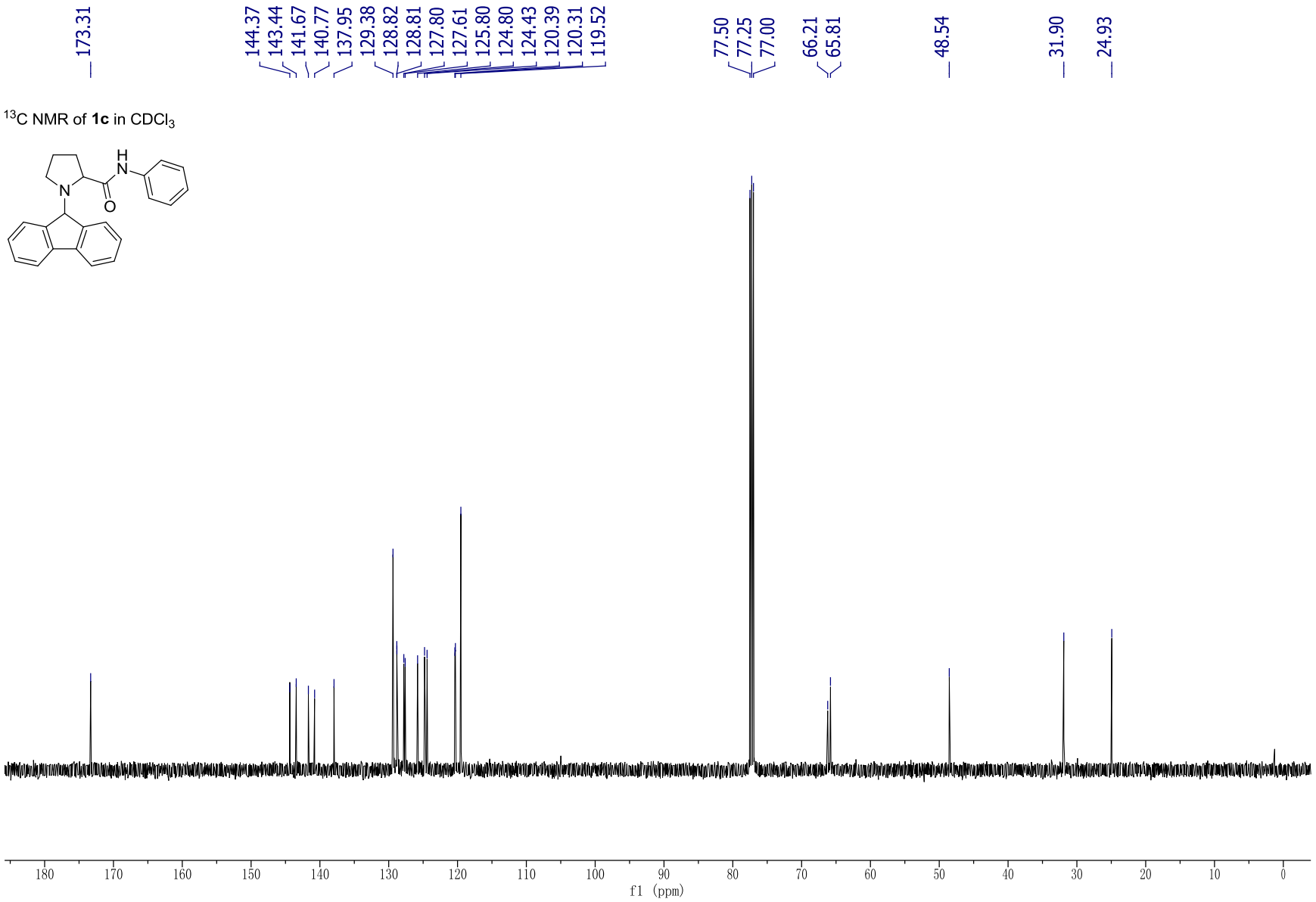


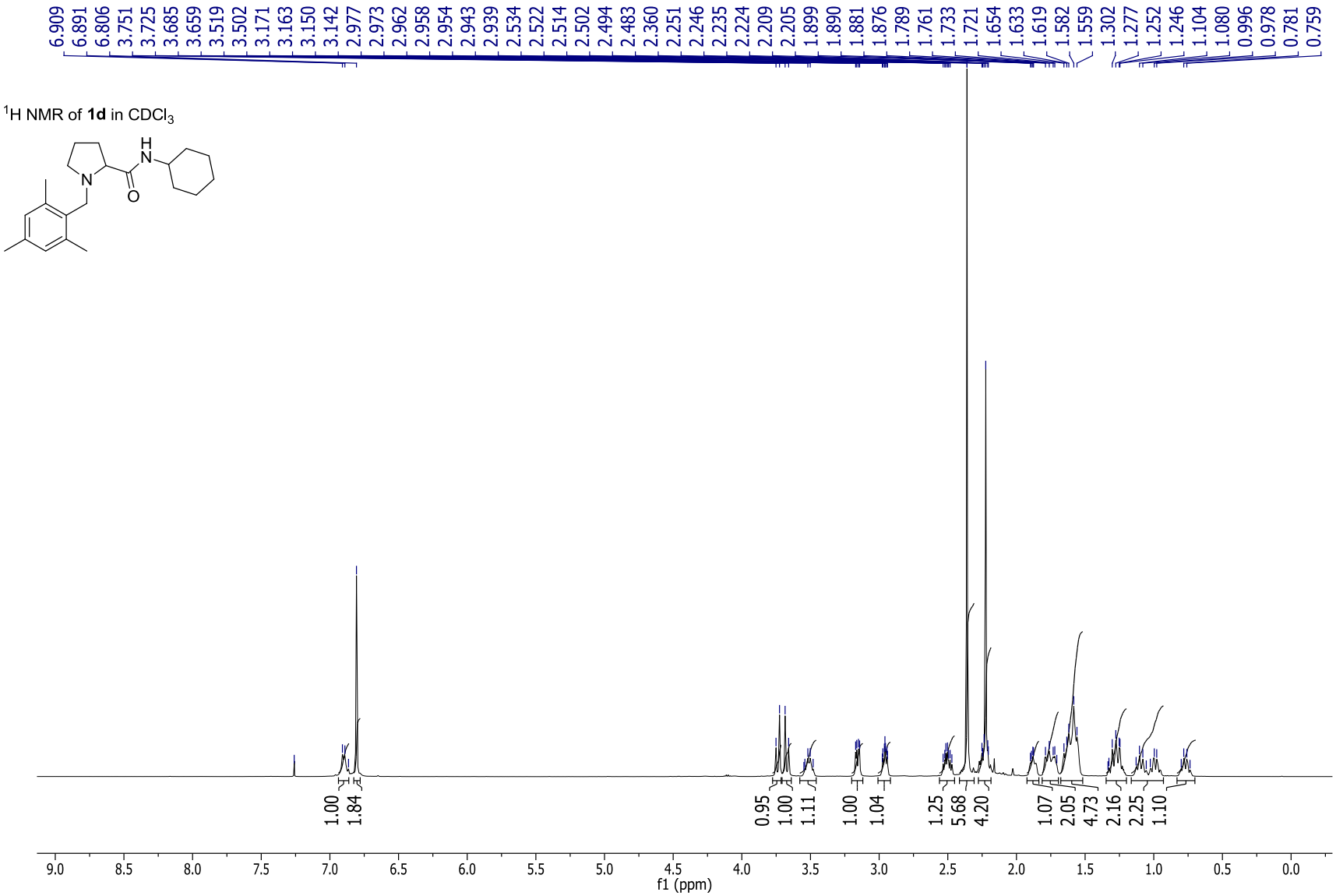

$^{13}C$ NMR of **1a** in $CDCl_3$


7.696
7.682
7.680
7.674
7.659
7.657
7.572
7.570
7.557
7.555
7.397
7.391
7.388
7.385
7.383
7.380
7.376
7.373
7.369
7.367
7.360
7.356
7.351
7.347
7.343
7.338
7.335
7.331
7.321
7.286
7.284
7.271
7.269
7.260
7.257
7.245
7.242
7.211
7.209
7.197
7.194
5.026
4.579
4.567
4.519
4.508
4.095
4.088
4.076
4.069
2.680
2.374
2.361
1.687
1.681
1.667
$^1$H NMR of **1b** in $CDCl_3$
0.99
2.06
1.08
10.24
1.00
1.05
1.02
1.02
1.01
1.12
1.20
1.13
2.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

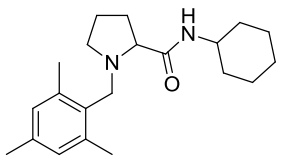

175.07
144.52
143.66
141.60
140.62
138.65
129.06
128.65
128.60
127.92
127.78
127.60
127.49
125.84
124.86
120.29
120.10
77.54
77.28
77.03
66.08
65.30
48.34
43.53
31.85
24.89
13C NMR of 1b in CDCl3
H
N
N
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

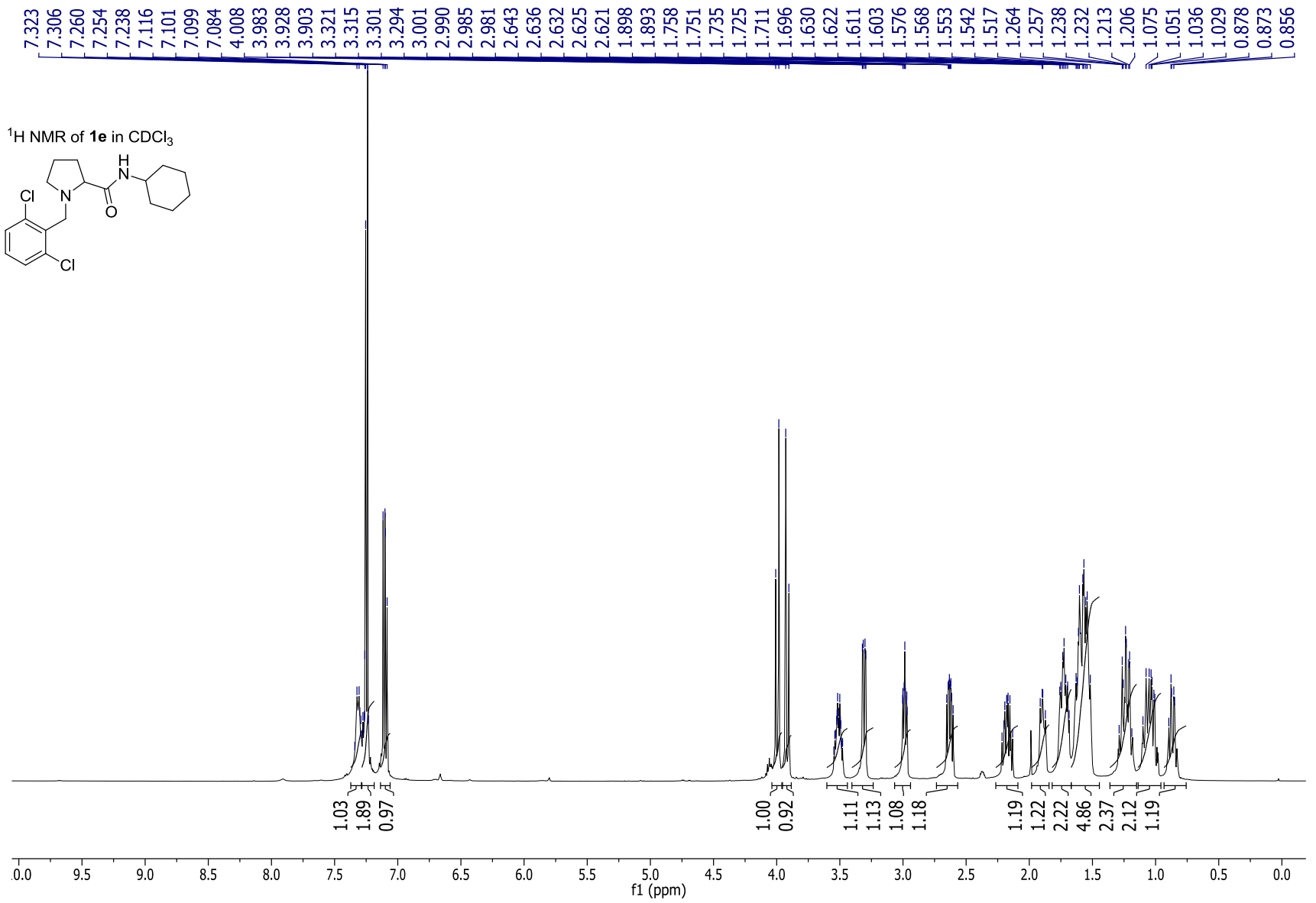

7.643
7.641
7.639
7.633
7.630
7.626
7.624
7.620
7.618
7.616
7.613
7.582
7.580
7.568
7.566
7.564
7.562
7.550
7.548
7.343
7.342
7.340
7.335
7.332
7.328
7.325
7.321
7.319
7.316
7.313
7.307
7.306
7.304
7.301
7.299
7.296
7.294
7.292
7.290
7.207
7.195
7.193
7.179
7.177
7.088
7.073
7.071
5.040
4.049
4.036
4.029
2.362
1.650
1.642
1.640
0.000
1H NMR of 1c in CDCl3
H
N
N
O
1.01
3.24
1.77
4.61
1.66
1.08
0.94
0.92
1.00
1.10
1.00
0.93
2.08
f1 (ppm)

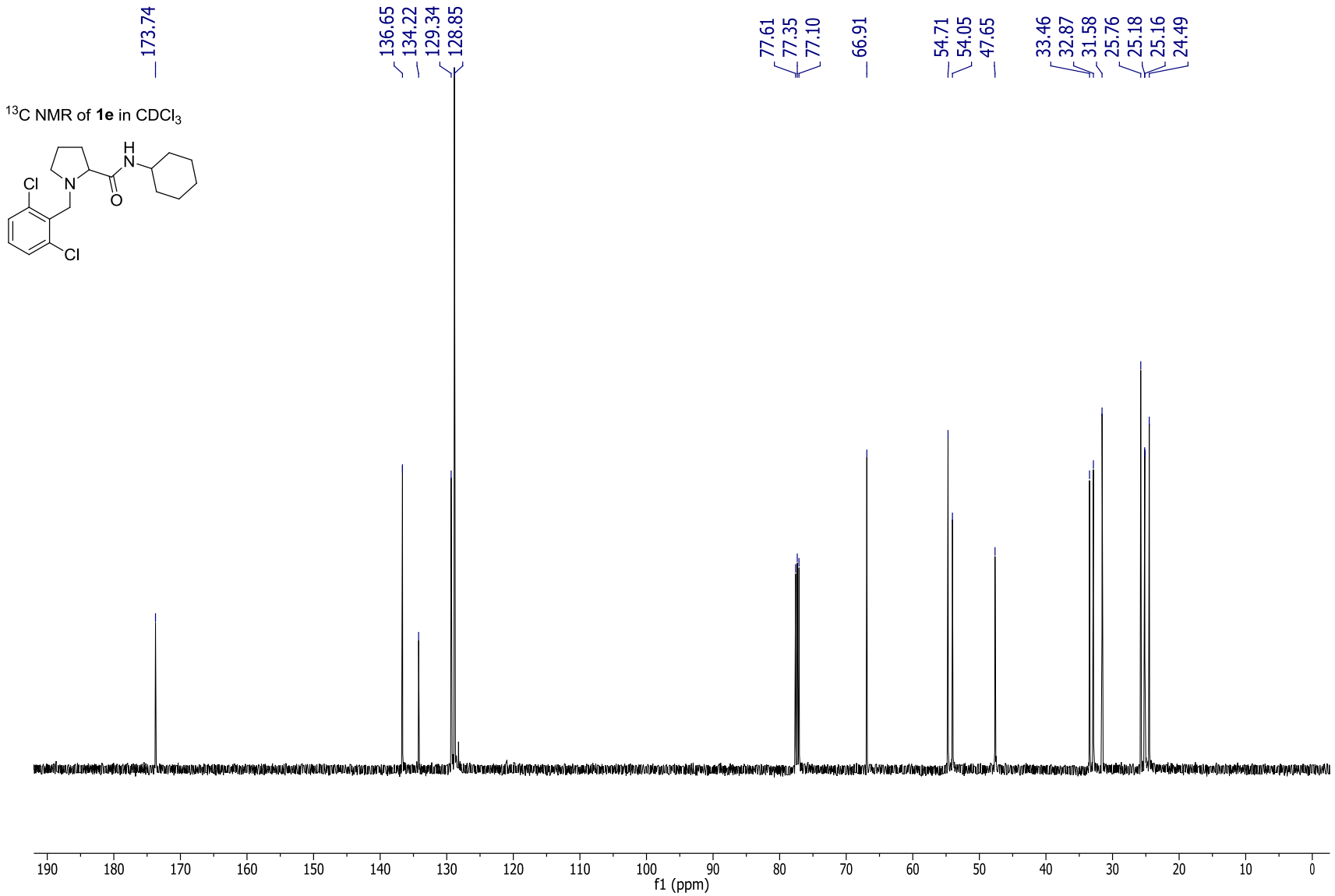

173.31
144.37
143.44
141.67
140.77
137.95
129.38
128.82
128.81
127.80
127.61
125.80
124.80
124.43
120.39
120.31
119.52
77.50
77.25
77.00
66.21
65.81
48.54
31.90
24.93
$^{13}$C NMR of **1c** in $CDCl_3$
H
N
N
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

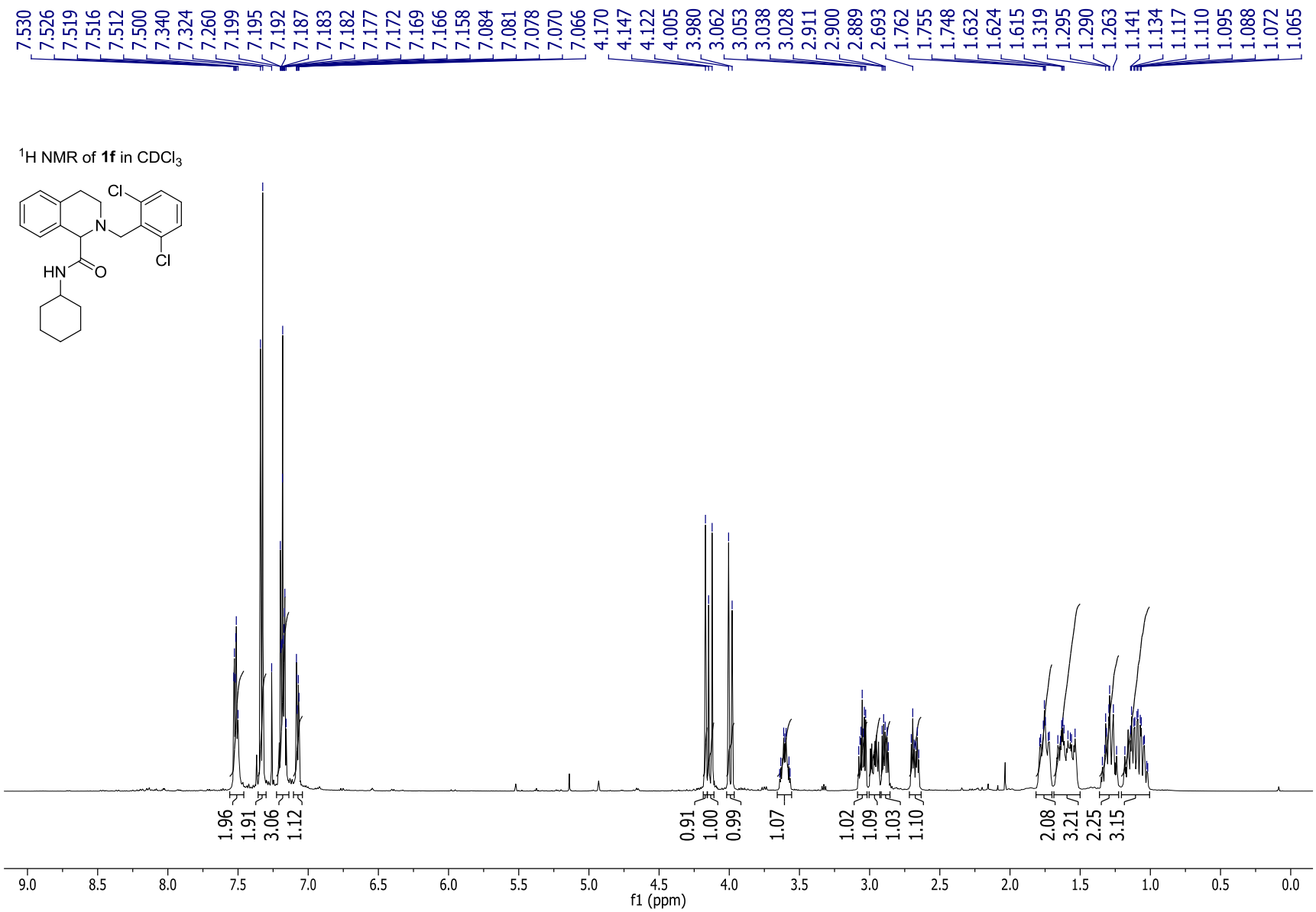

6.909
6.891
6.806
3.751
3.725
3.685
3.659
3.519
3.502
3.171
3.163
3.150
3.142
2.977
2.973
2.962
2.958
2.954
2.943
2.939
2.534
2.522
2.514
2.502
2.494
2.483
2.360
2.251
2.246
2.235
2.224
2.209
2.205
1.899
1.890
1.881
1.876
1.789
1.761
1.733
1.721
1.654
1.633
1.619
1.582
1.559
1.302
1.277
1.252
1.246
1.104
1.080
0.996
0.978
0.781
0.759
1H NMR of 1d in CDCl3
H
N
N
O
1.00
1.84
0.95
1.00
1.11
1.00
1.04
1.25
5.68
4.20
1.07
2.05
4.73
2.16
2.25
1.10
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)

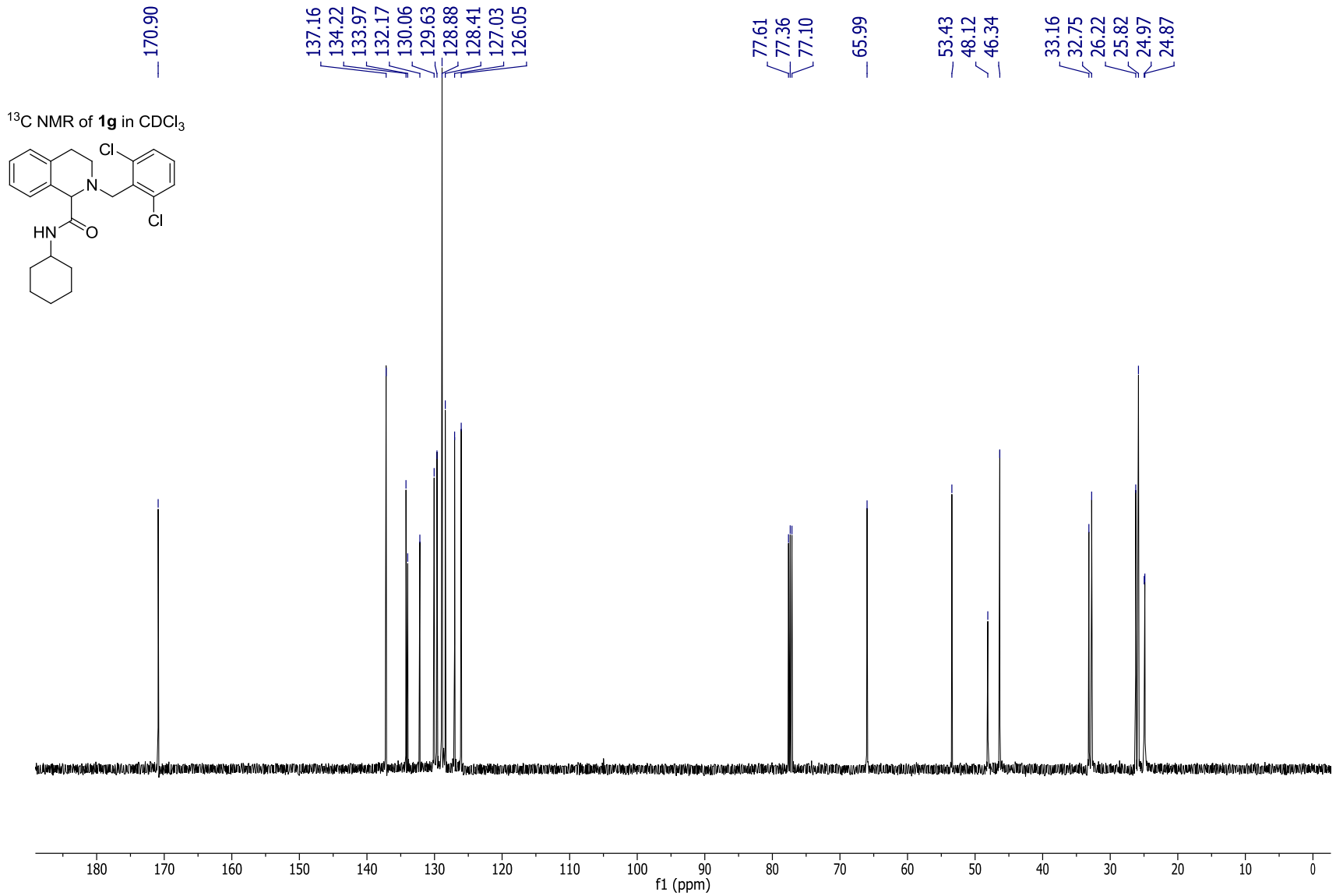
$^{13}$C NMR of **1d** in $CDCl_3$

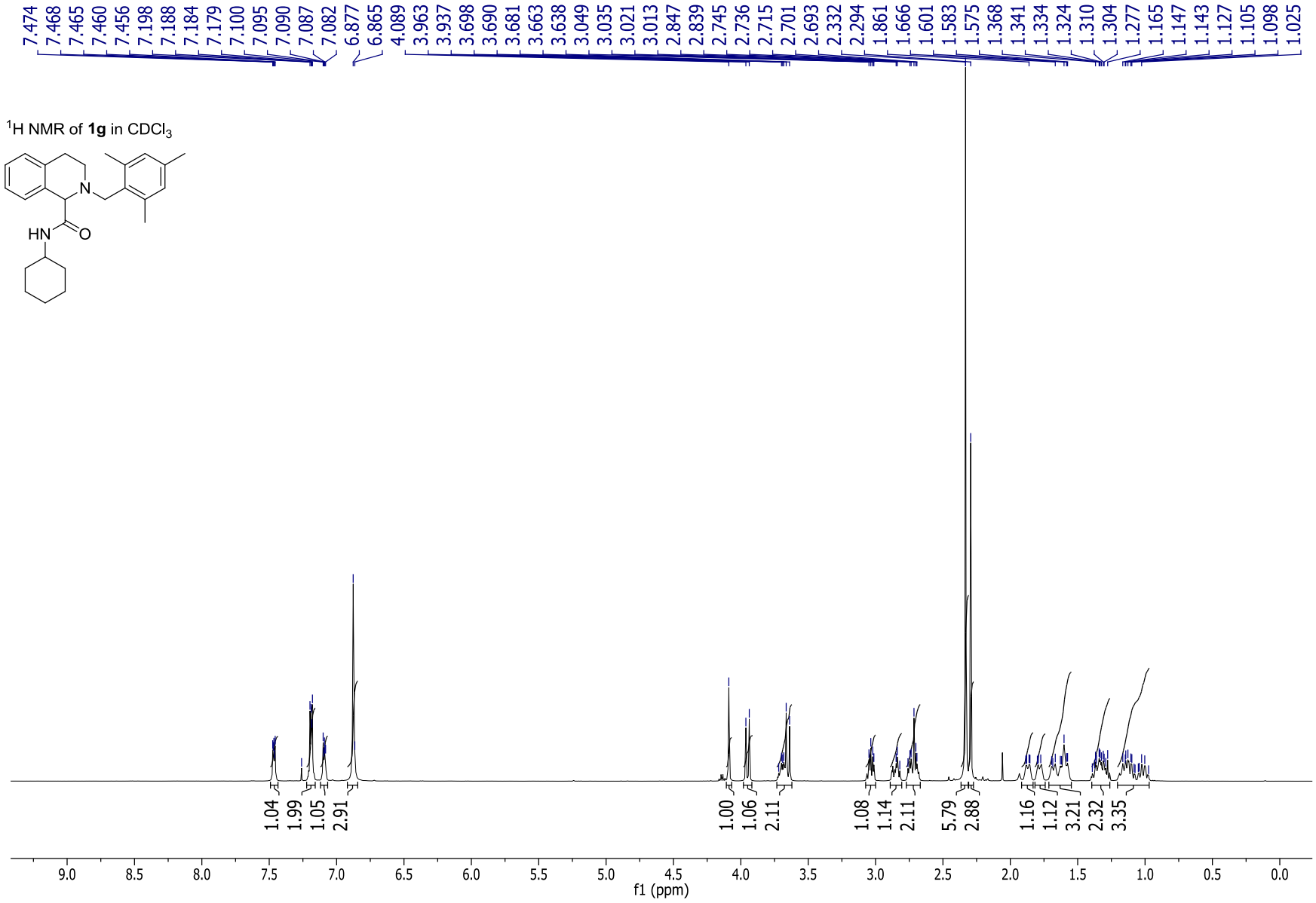


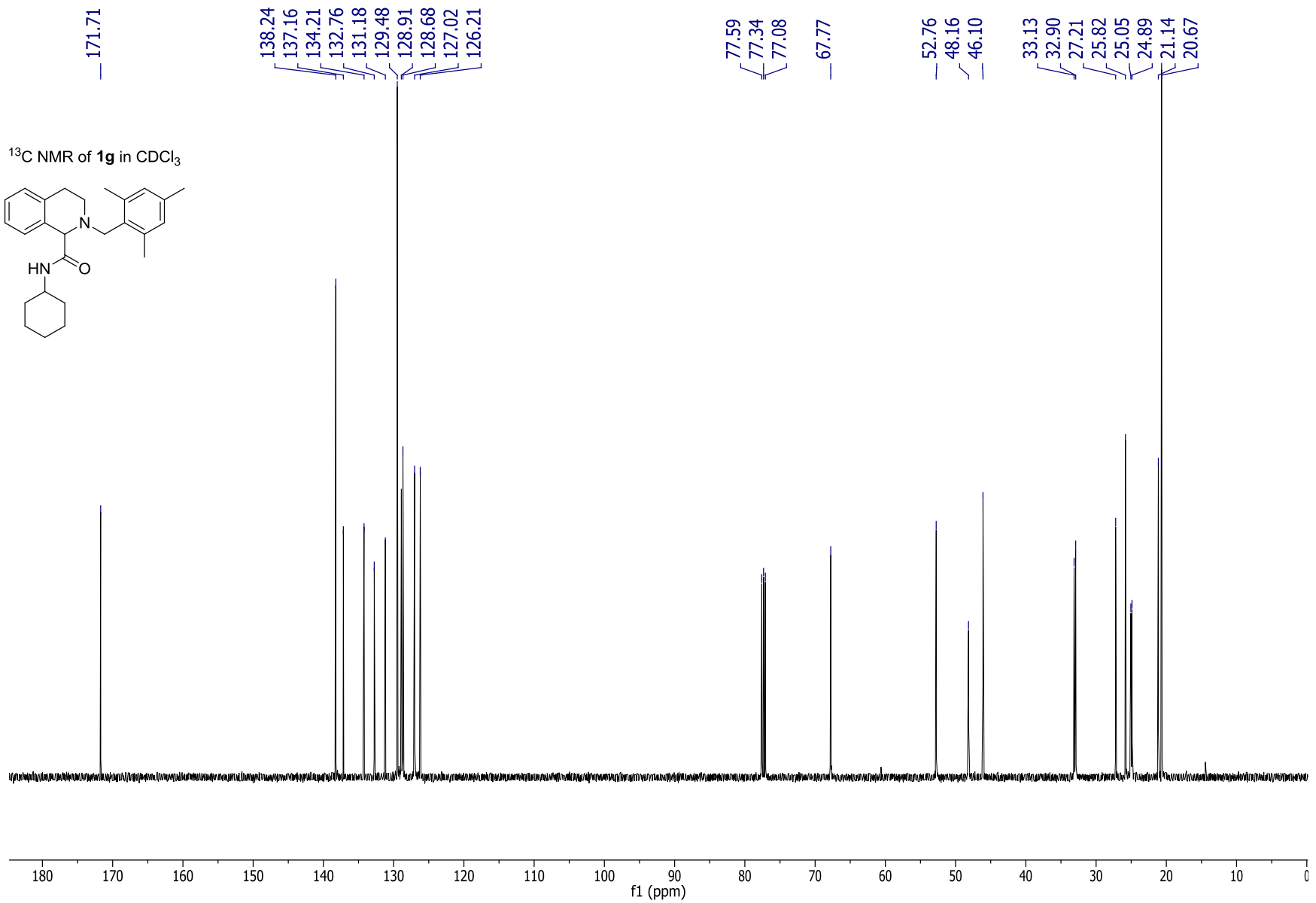

7.323
7.306
7.260
7.254
7.238
7.116
7.101
7.099
7.084
4.008
3.983
3.928
3.903
3.321
3.315
3.301
3.294
3.001
2.990
2.985
2.981
2.643
2.636
2.632
2.625
2.621
1.898
1.893
1.758
1.751
1.735
1.725
1.711
1.696
1.630
1.622
1.611
1.603
1.576
1.568
1.553
1.542
1.517
1.264
1.257
1.238
1.232
1.213
1.206
1.075
1.051
1.036
1.029
0.878
0.873
0.856
$^1$H NMR of **1e** in $CDCl_3$
Cl
N
H
N
O
Cl
1.03
1.89
0.97
1.00
0.92
1.11
1.13
1.08
1.18
1.19
1.22
2.22
4.86
2.37
2.12
1.19
f1 (ppm)

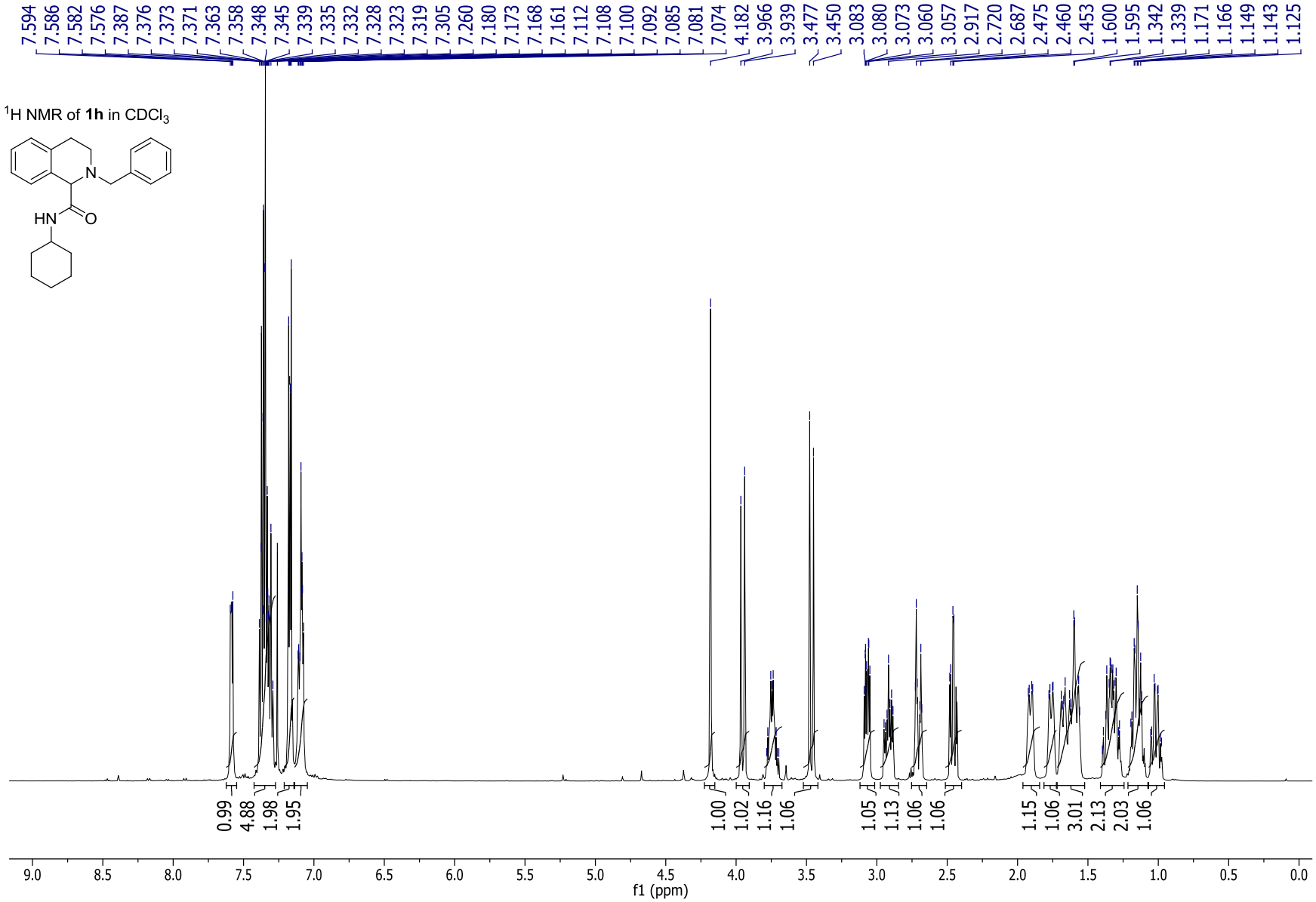

$^{13}$C NMR of **1e** in $CDCl_3$
173.74
136.65
134.22
129.34
128.85
77.61
77.35
77.10
66.91
54.71
54.05
47.65
33.46
32.87
31.58
25.76
25.18
25.16
24.49
Cl
N
O
H
N
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

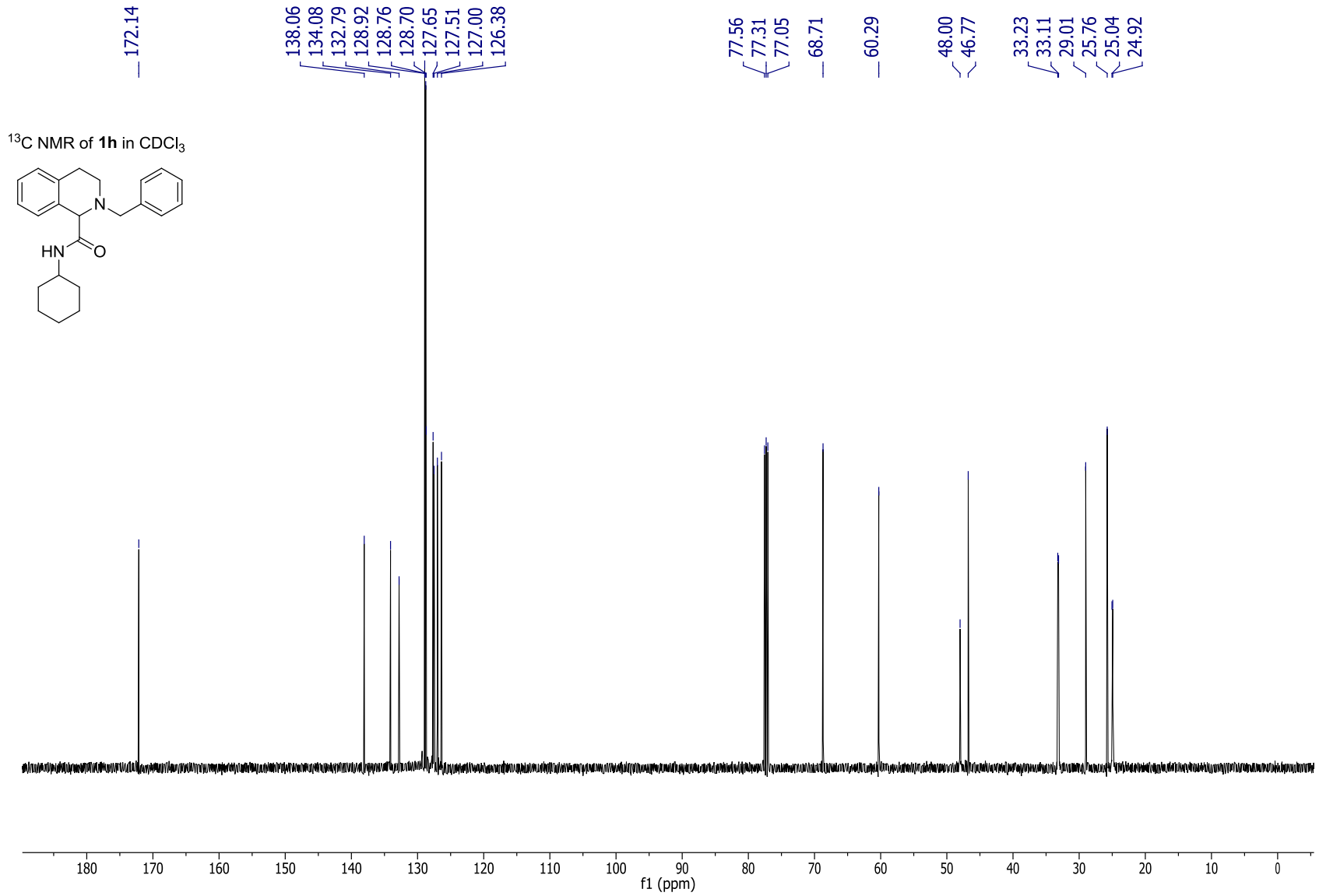

7.530
7.526
7.519
7.516
7.512
7.500
7.340
7.324
7.260
7.199
7.195
7.192
7.187
7.183
7.182
7.177
7.172
7.169
7.166
7.158
7.084
7.081
7.078
7.070
7.066
4.170
4.147
4.122
4.005
3.980
3.062
3.053
3.038
3.028
2.911
2.900
2.889
2.693
1.762
1.755
1.748
1.632
1.624
1.615
1.319
1.295
1.290
1.263
1.141
1.134
1.117
1.110
1.095
1.088
1.072
1.065
1H NMR of 1f in CDCl3
Cl
N
Cl
HN
O
1.96
1.91
3.06
1.12
0.91
1.00
0.99
1.07
1.02
1.09
1.03
1.10
2.08
3.21
2.25
3.15
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)

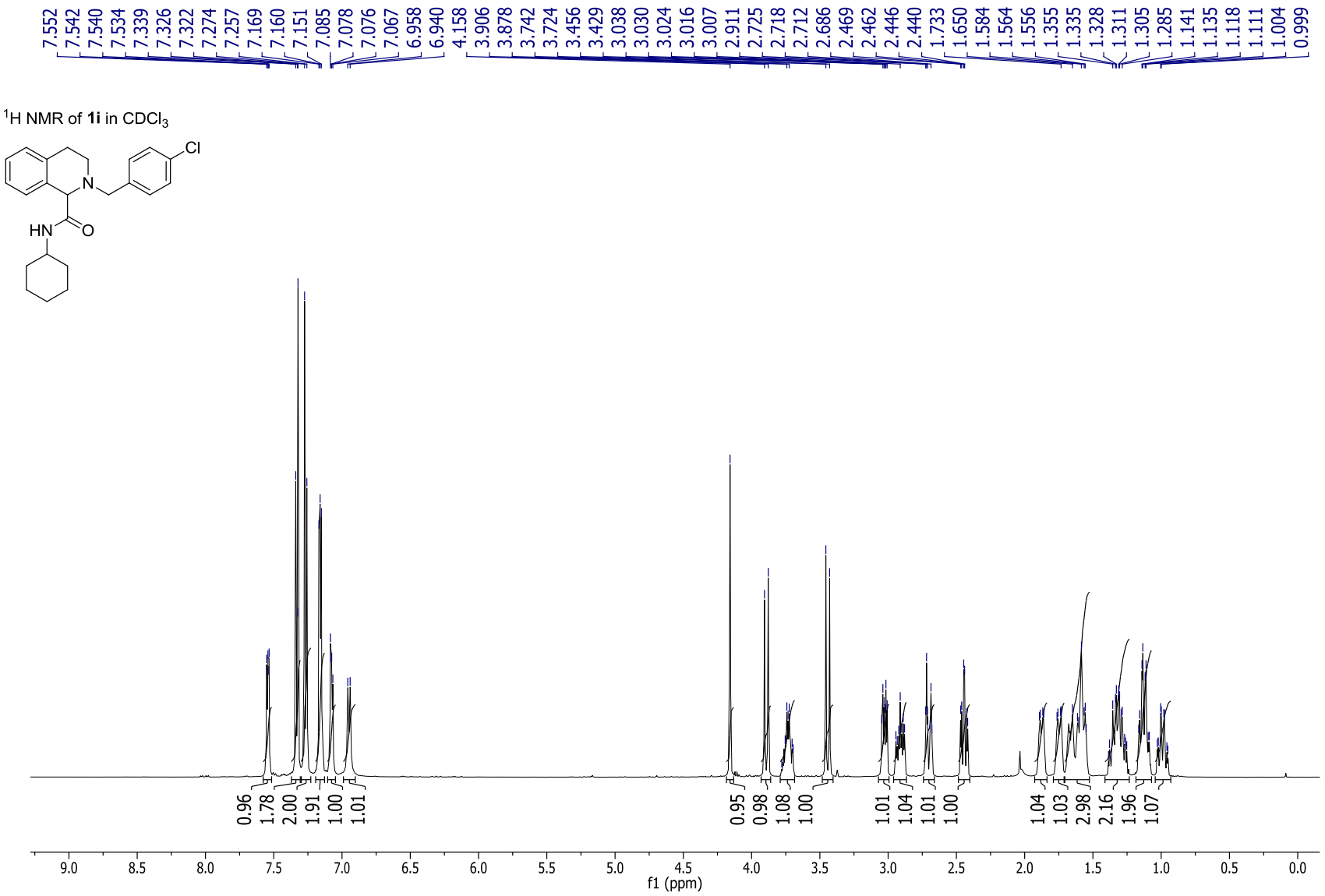

170.90
137.16
134.22
133.97
132.17
130.06
129.63
128.88
128.41
127.03
126.05
77.61
77.36
77.10
65.99
53.43
48.12
46.34
33.16
32.75
26.22
25.82
24.97
24.87
13C NMR of 1g in CDCl3
Cl
N
Cl
HN
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

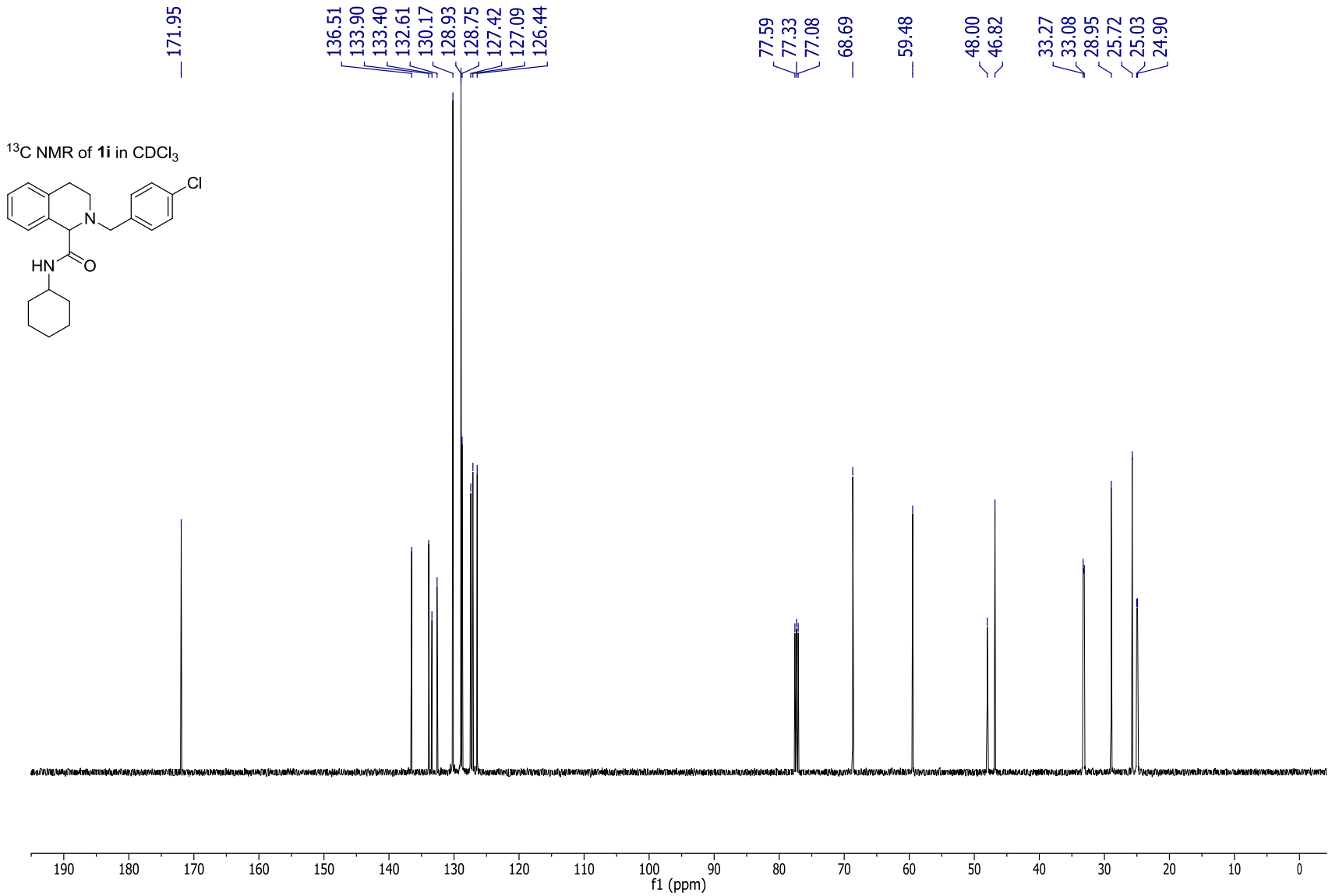

7.474
7.468
7.465
7.460
7.456
7.198
7.188
7.184
7.179
7.100
7.095
7.090
7.087
7.082
6.877
6.865
4.089
3.963
3.937
3.698
3.690
3.681
3.663
3.638
3.049
3.035
3.021
3.013
2.847
2.839
2.745
2.736
2.715
2.701
2.693
2.332
2.294
1.861
1.666
1.601
1.583
1.575
1.368
1.341
1.334
1.324
1.310
1.304
1.277
1.165
1.147
1.143
1.127
1.105
1.098
1.025
1H NMR of 1g in CDCl3
N
HN
O
1.04
1.99
1.05
2.91
1.00
1.06
2.11
1.08
1.14
2.11
5.79
2.88
1.16
1.12
3.21
2.32
3.35
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)

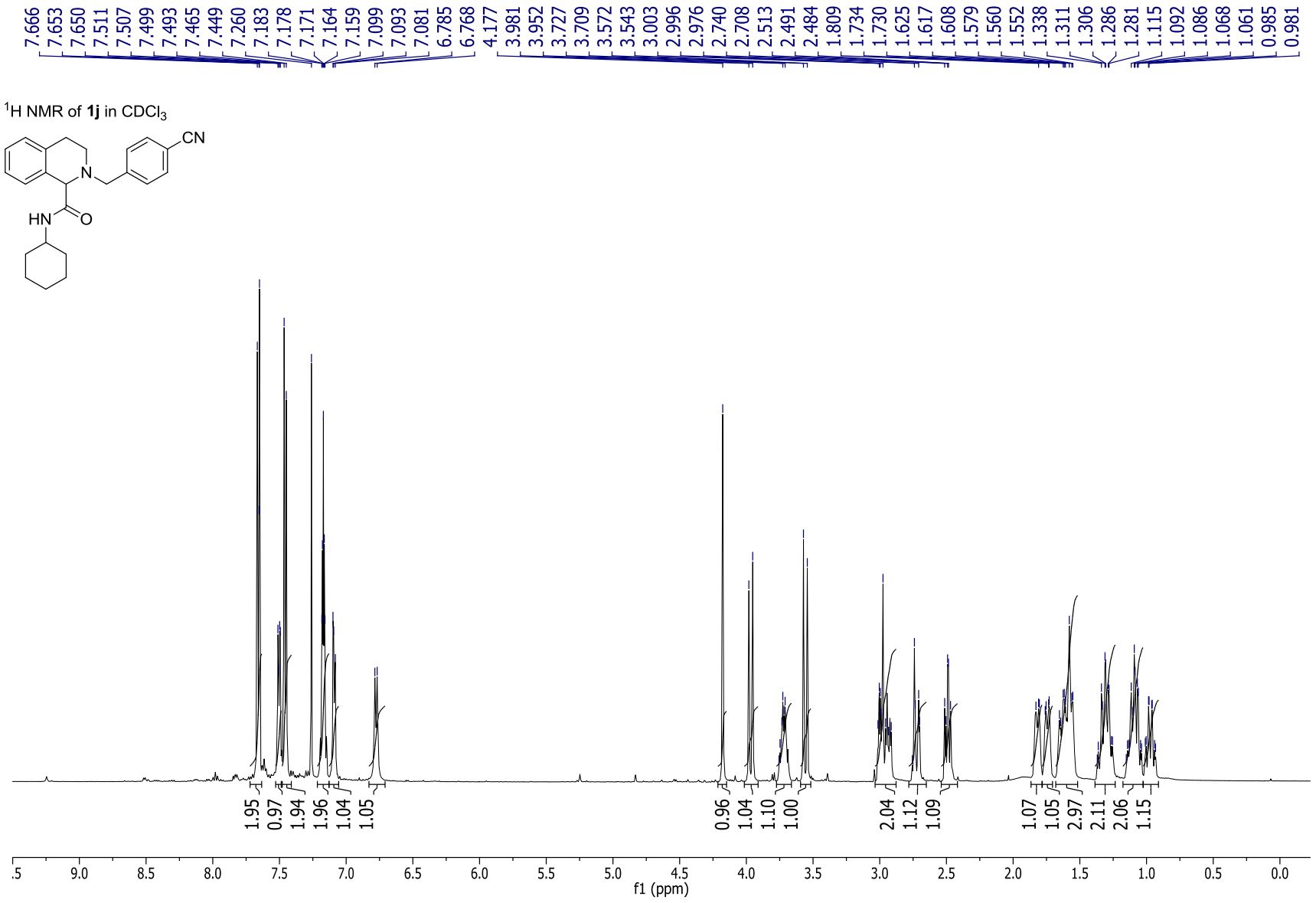

171.71
138.24
137.16
134.21
132.76
131.18
129.48
128.91
128.68
127.02
126.21
77.59
77.34
77.08
67.77
52.76
48.16
46.10
33.13
32.90
27.21
25.82
25.05
24.89
21.14
20.67
13C NMR of 1g in CDCl3
N
HN
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

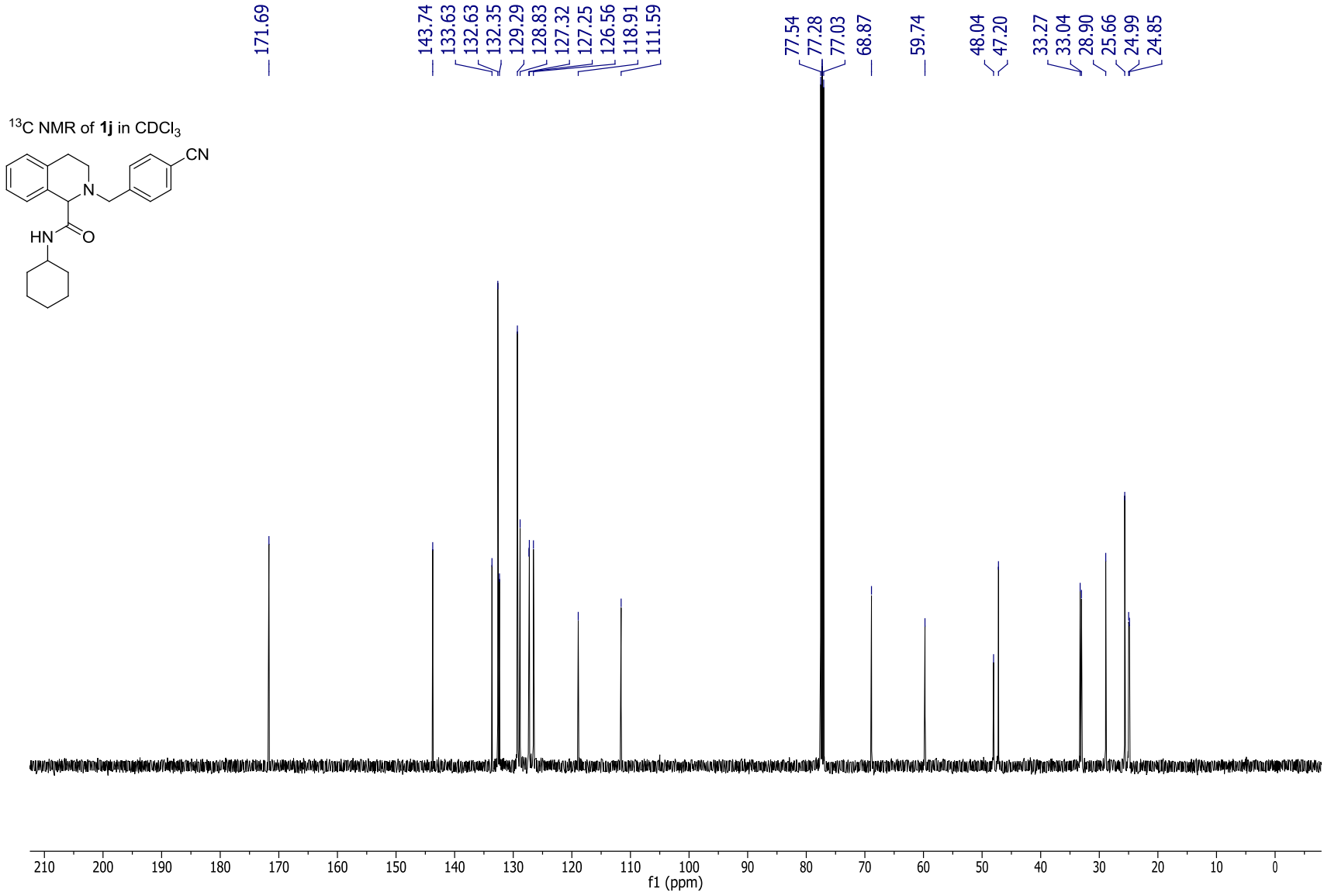

$^1$H NMR of **1h** in $CDCl_3$
7.594
7.586
7.582
7.576
7.387
7.376
7.373
7.371
7.363
7.358
7.348
7.345
7.339
7.335
7.332
7.328
7.323
7.319
7.305
7.260
7.180
7.173
7.168
7.161
7.112
7.108
7.100
7.092
7.085
7.081
7.074
4.182
3.966
3.939
3.477
3.450
3.083
3.080
3.073
3.060
3.057
2.917
2.720
2.687
2.475
2.460
2.453
1.600
1.595
1.342
1.339
1.171
1.166
1.149
1.143
1.125
HN
O
N
0.99
4.88
1.98
1.95
1.00
1.02
1.16
1.06
1.05
1.13
1.06
1.06
1.15
1.06
3.01
2.13
2.03
1.06
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

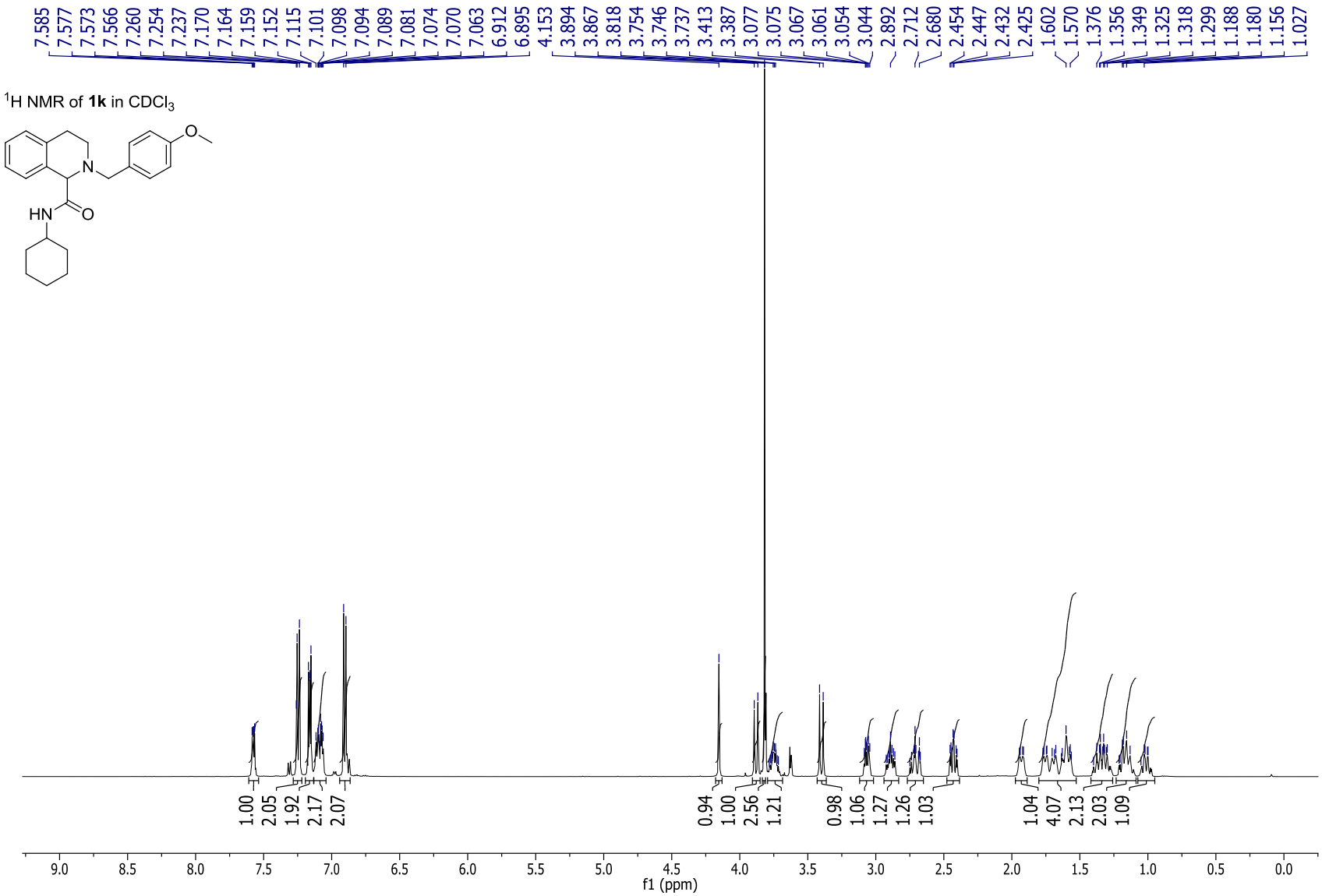

172.14
138.06
134.08
132.79
128.92
128.76
128.70
127.65
127.51
127.00
126.38
77.56
77.31
77.05
68.71
60.29
48.00
46.77
33.23
33.11
29.01
25.76
25.04
24.92
13C NMR of 1h in CDCl3
N
HN
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

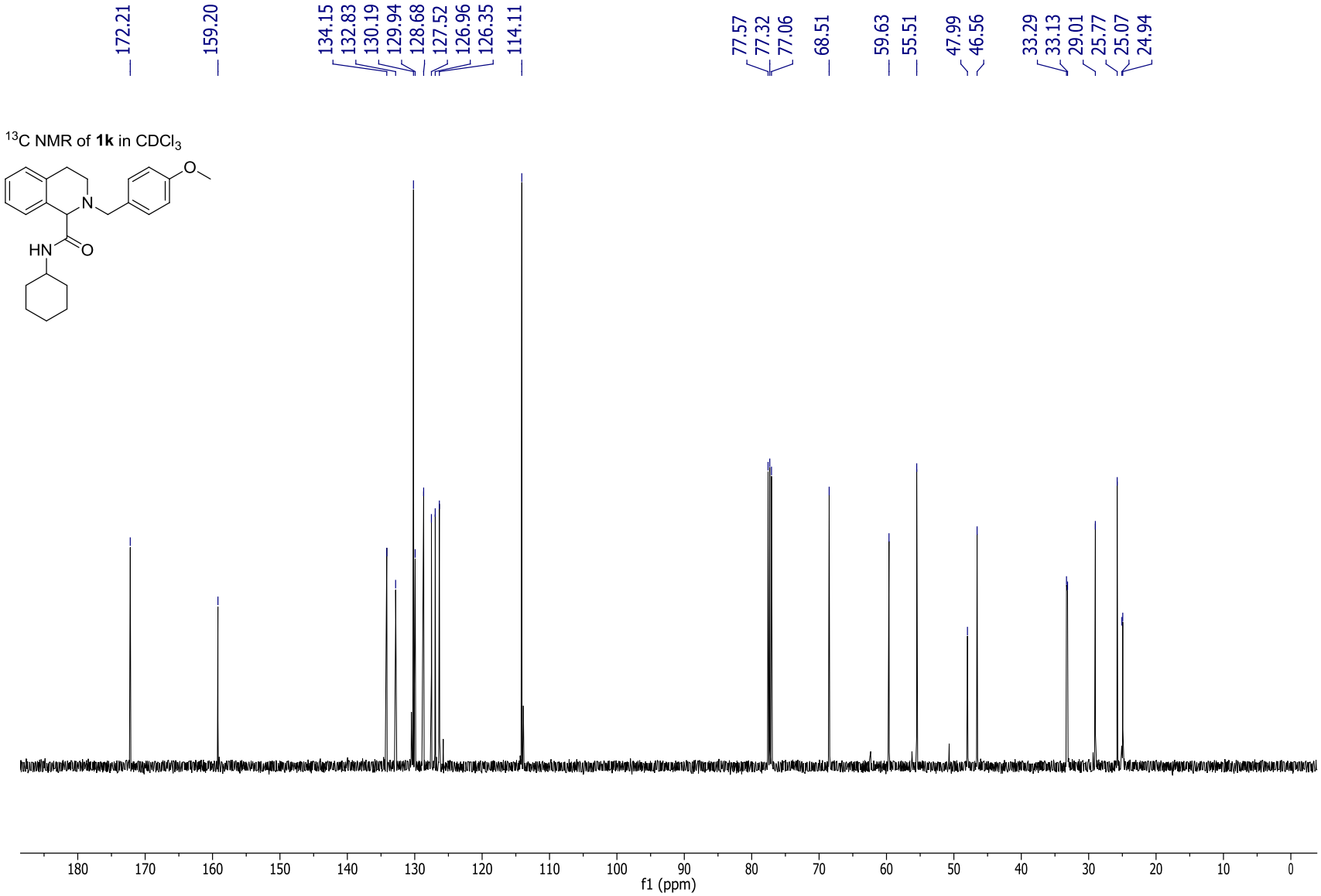

7.552
7.542
7.540
7.534
7.339
7.326
7.322
7.274
7.257
7.169
7.160
7.151
7.085
7.078
7.076
7.067
6.958
6.940
4.158
3.906
3.878
3.742
3.724
3.456
3.429
3.038
3.030
3.024
3.016
3.007
2.911
2.725
2.718
2.712
2.686
2.469
2.462
2.446
2.440
1.733
1.650
1.584
1.564
1.556
1.355
1.335
1.328
1.311
1.305
1.285
1.141
1.135
1.118
1.111
1.004
0.999
1H NMR of 1i in CDCl3
Cl
N
HN
O
0.96
1.78
2.00
1.91
1.00
1.01
0.95
0.98
1.08
1.00
1.01
1.04
1.01
1.00
1.04
1.03
2.98
2.16
1.96
1.07
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)

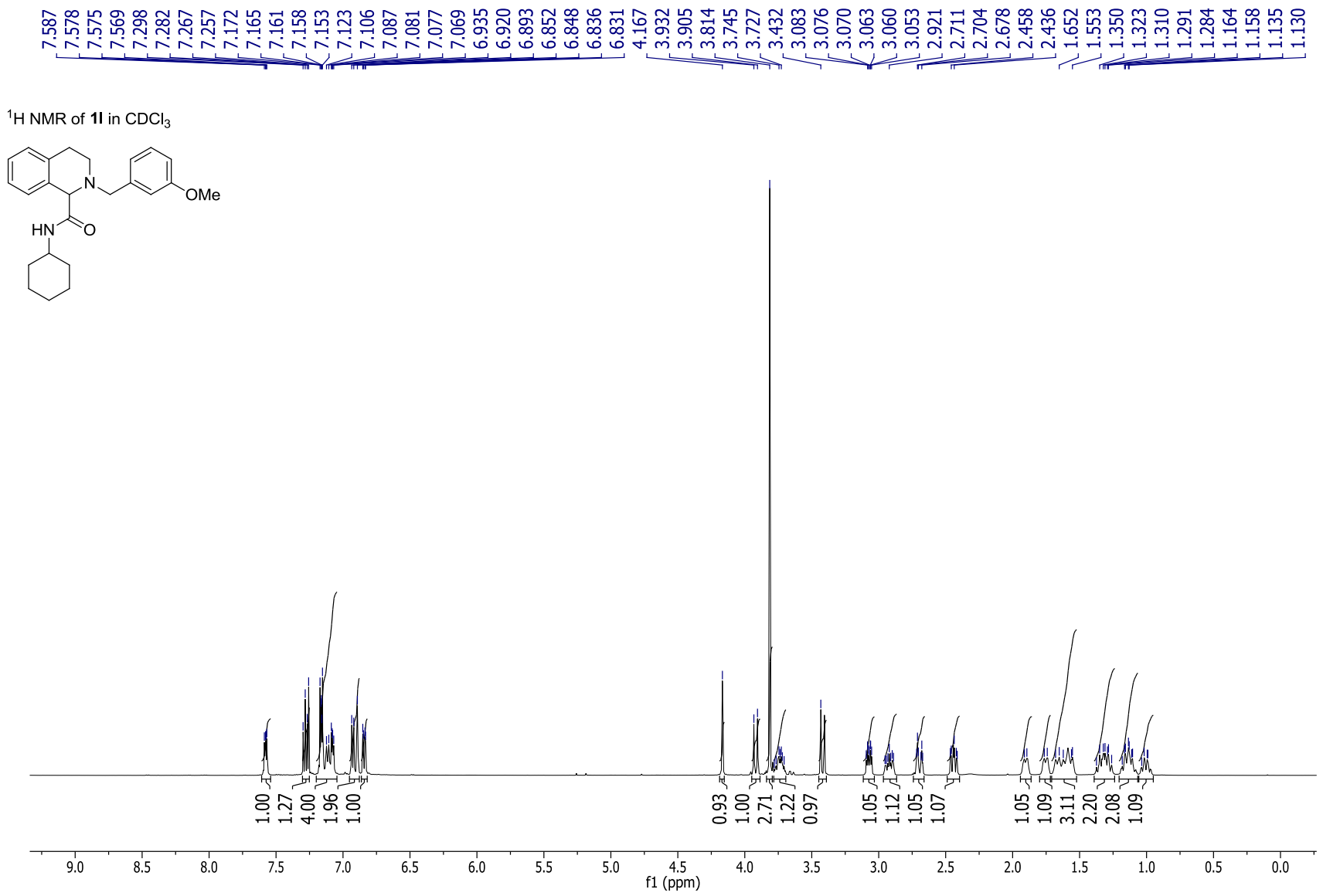

171.95
136.51
133.90
133.40
132.61
130.17
128.93
128.75
127.42
127.09
126.44
77.59
77.33
77.08
68.69
59.48
48.00
46.82
33.27
33.08
28.95
25.72
25.03
24.90
13C NMR of 1i in CDCl3
Cl
N
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

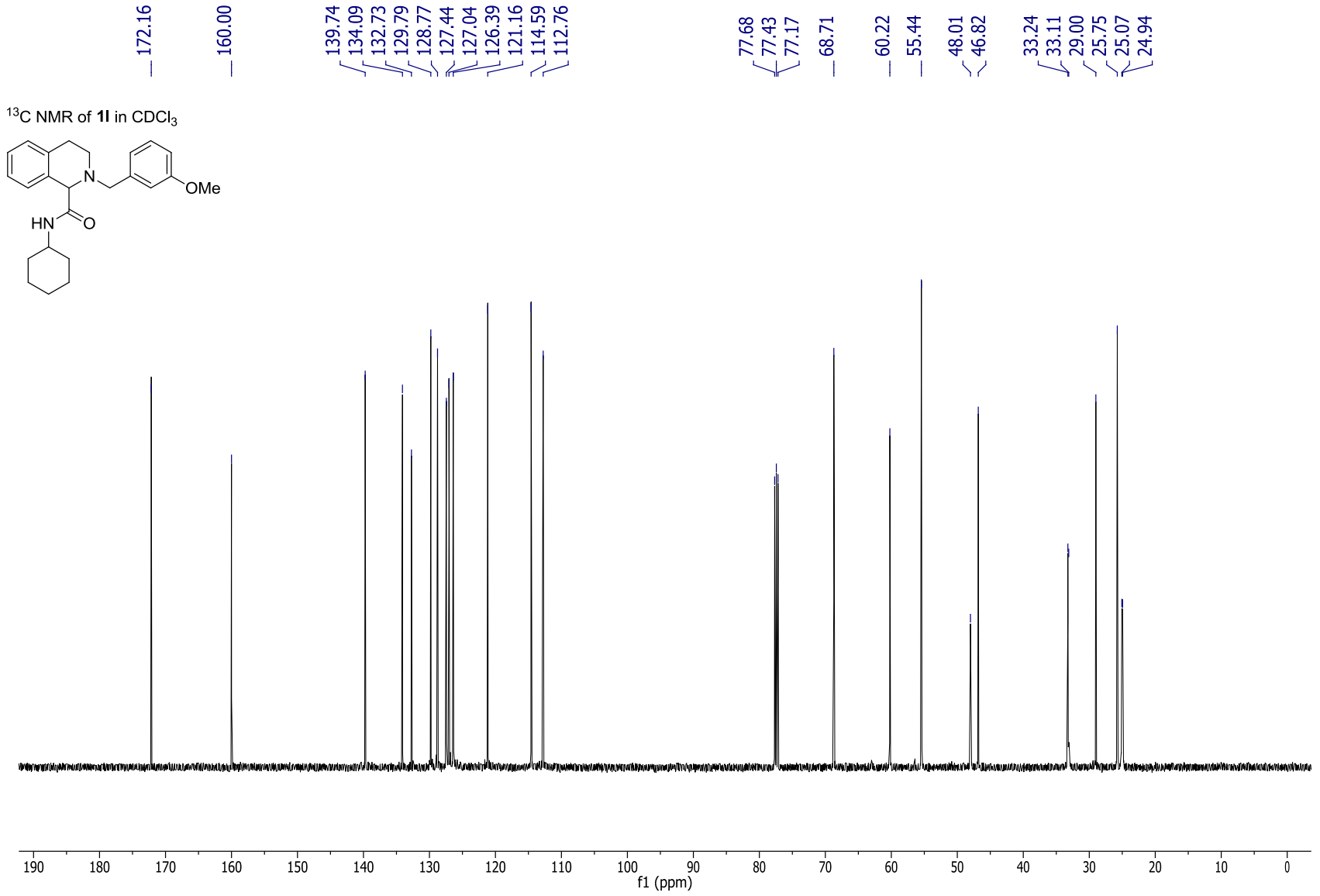

7.666
7.653
7.650
7.511
7.507
7.499
7.493
7.465
7.449
7.260
7.183
7.178
7.171
7.164
7.159
7.099
7.093
7.081
6.785
6.768
4.177
3.981
3.952
3.727
3.709
3.572
3.543
3.003
2.996
2.976
2.740
2.708
2.513
2.491
2.484
1.809
1.734
1.730
1.625
1.617
1.608
1.579
1.560
1.552
1.338
1.311
1.306
1.286
1.281
1.115
1.092
1.086
1.068
1.061
0.985
0.981
1H NMR of 1j in CDCl3
CN
N
HN
O
1.95
0.97
1.94
1.96
1.04
1.05
0.96
1.04
1.10
1.00
2.04
1.12
1.09
1.07
1.05
2.97
2.11
2.06
1.15
f1 (ppm)

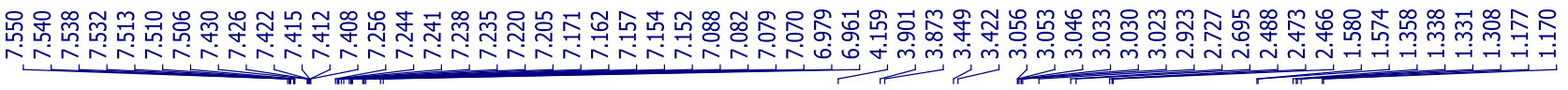

171.69
143.74
133.63
132.63
132.35
129.29
128.83
127.32
127.25
126.56
118.91
111.59
77.54
77.28
77.03
68.87
59.74
48.04
47.20
33.27
33.04
28.90
25.66
24.99
24.85
13C NMR of 1j in CDCl3
CN
N
HN
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.585
7.577
7.573
7.566
7.260
7.254
7.237
7.170
7.164
7.159
7.152
7.115
7.101
7.098
7.094
7.089
7.081
7.074
7.070
7.063
6.912
6.895
4.153
3.894
3.867
3.818
3.754
3.746
3.737
3.413
3.387
3.077
3.075
3.067
3.061
3.054
3.044
2.892
2.712
2.680
2.454
2.447
2.432
2.425
1.602
1.570
1.376
1.356
1.349
1.325
1.318
1.299
1.188
1.180
1.156
1.027
1H NMR of 1k in CDCl3
O
N
HN
O
1.00
2.05
1.92
2.17
2.07
0.94
1.00
2.56
1.21
0.98
1.06
1.27
1.26
1.03
1.04
4.07
2.13
2.03
1.09
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)

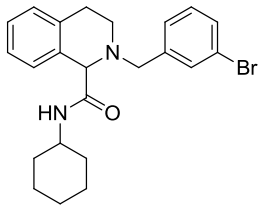

172.21
159.20
134.15
132.83
130.19
129.94
128.68
127.52
126.96
126.35
114.11
77.57
77.32
77.06
68.51
59.63
55.51
47.99
46.56
33.29
33.13
29.01
25.77
25.07
24.94
13C NMR of 1k in CDCl3
O
N
HN
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

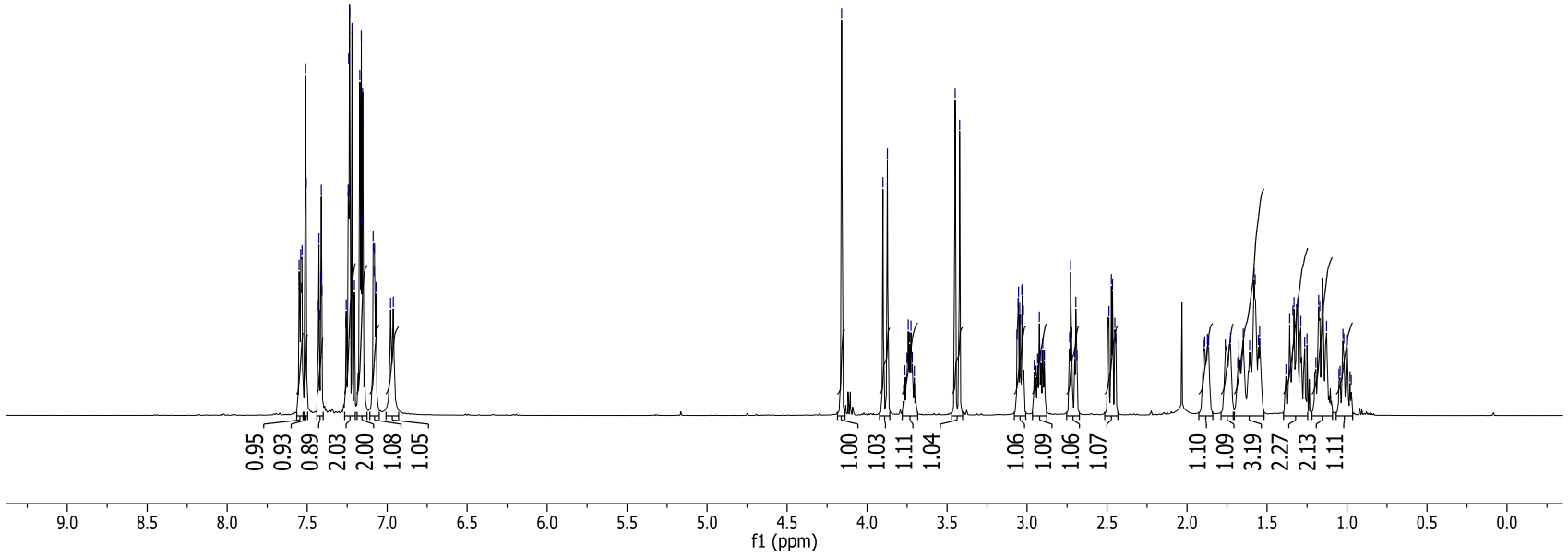

7.587
7.578
7.575
7.569
7.298
7.282
7.267
7.257
7.172
7.165
7.161
7.158
7.153
7.123
7.106
7.087
7.081
7.077
7.069
6.935
6.920
6.893
6.852
6.848
6.836
6.831
4.167
3.932
3.905
3.814
3.745
3.727
3.432
3.083
3.076
3.070
3.063
3.060
3.053
2.921
2.711
2.704
2.678
2.458
2.436
1.652
1.553
1.350
1.323
1.310
1.291
1.284
1.164
1.158
1.135
1.130
1H NMR of 1l in CDCl3
N
OMe
HN
O
1.00
1.27
4.00
1.96
1.00
0.93
1.00
2.71
1.22
0.97
1.05
1.12
1.05
1.07
1.05
1.09
3.11
2.20
2.08
1.09
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)

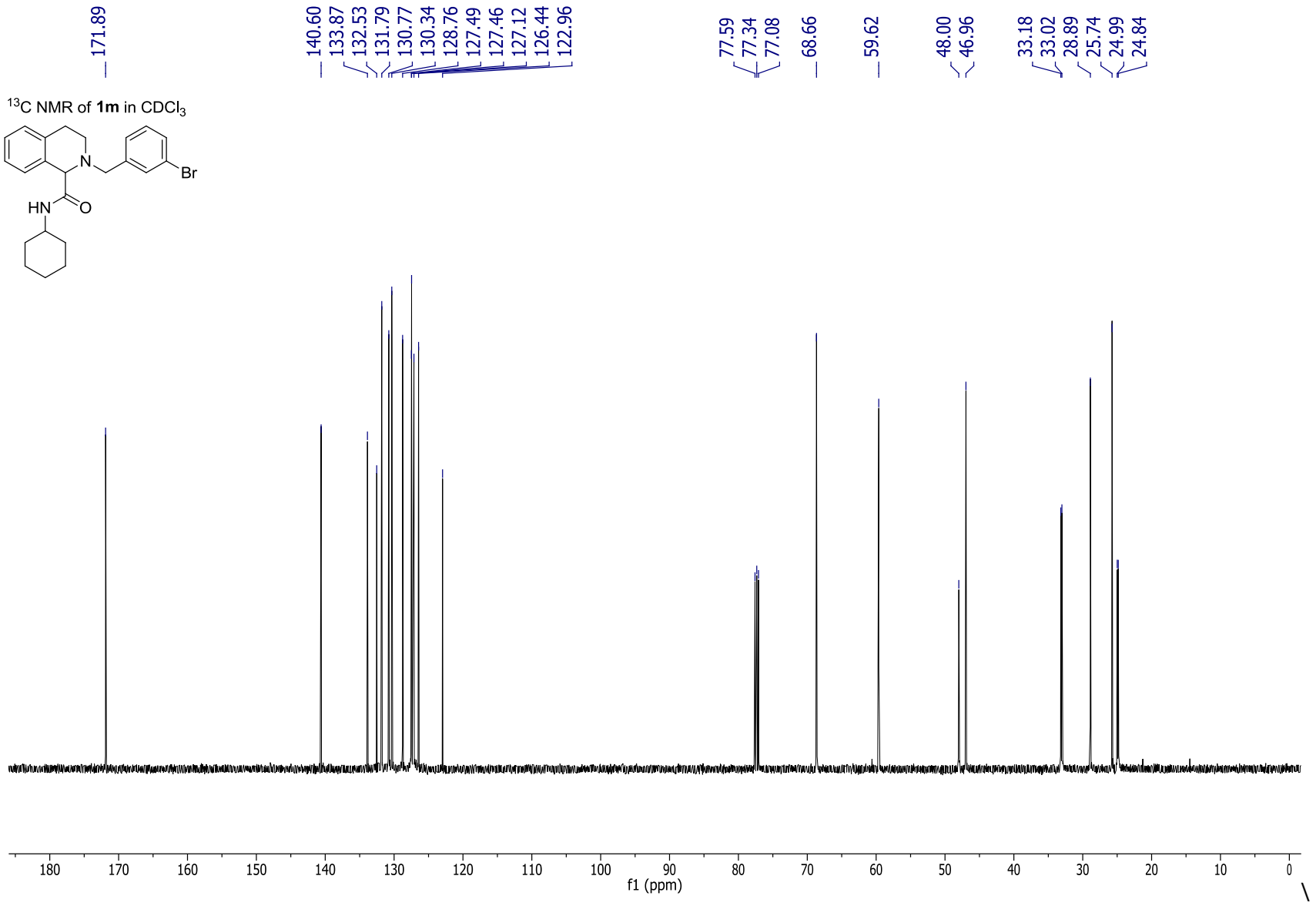

172.16
160.00
139.74
134.09
132.73
129.79
128.77
127.44
127.04
126.39
121.16
114.59
112.76
77.68
77.43
77.17
68.71
60.22
55.44
48.01
46.82
33.24
33.11
29.00
25.75
25.07
24.94
13C NMR of 1l in CDCl3
N
OMe
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

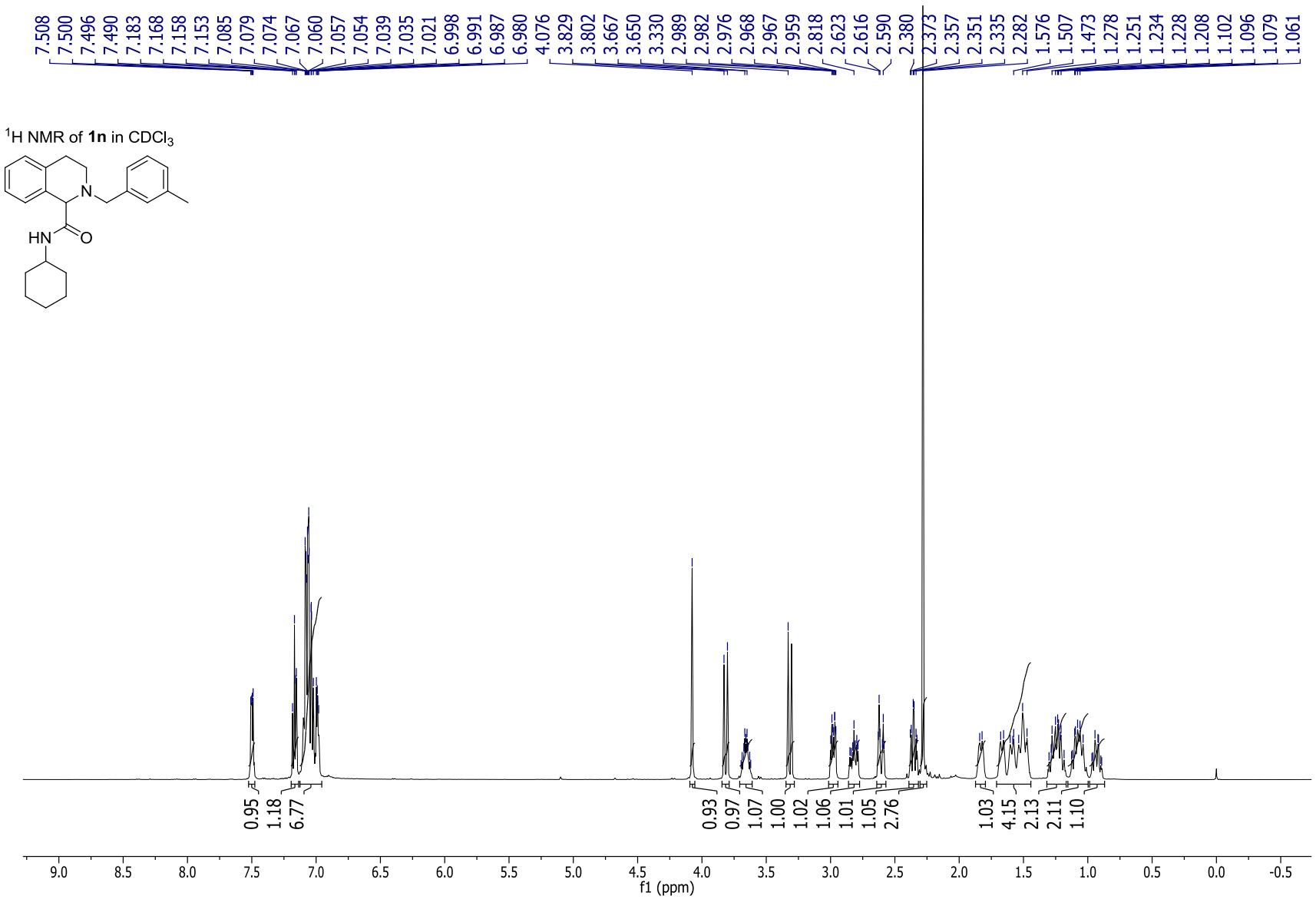


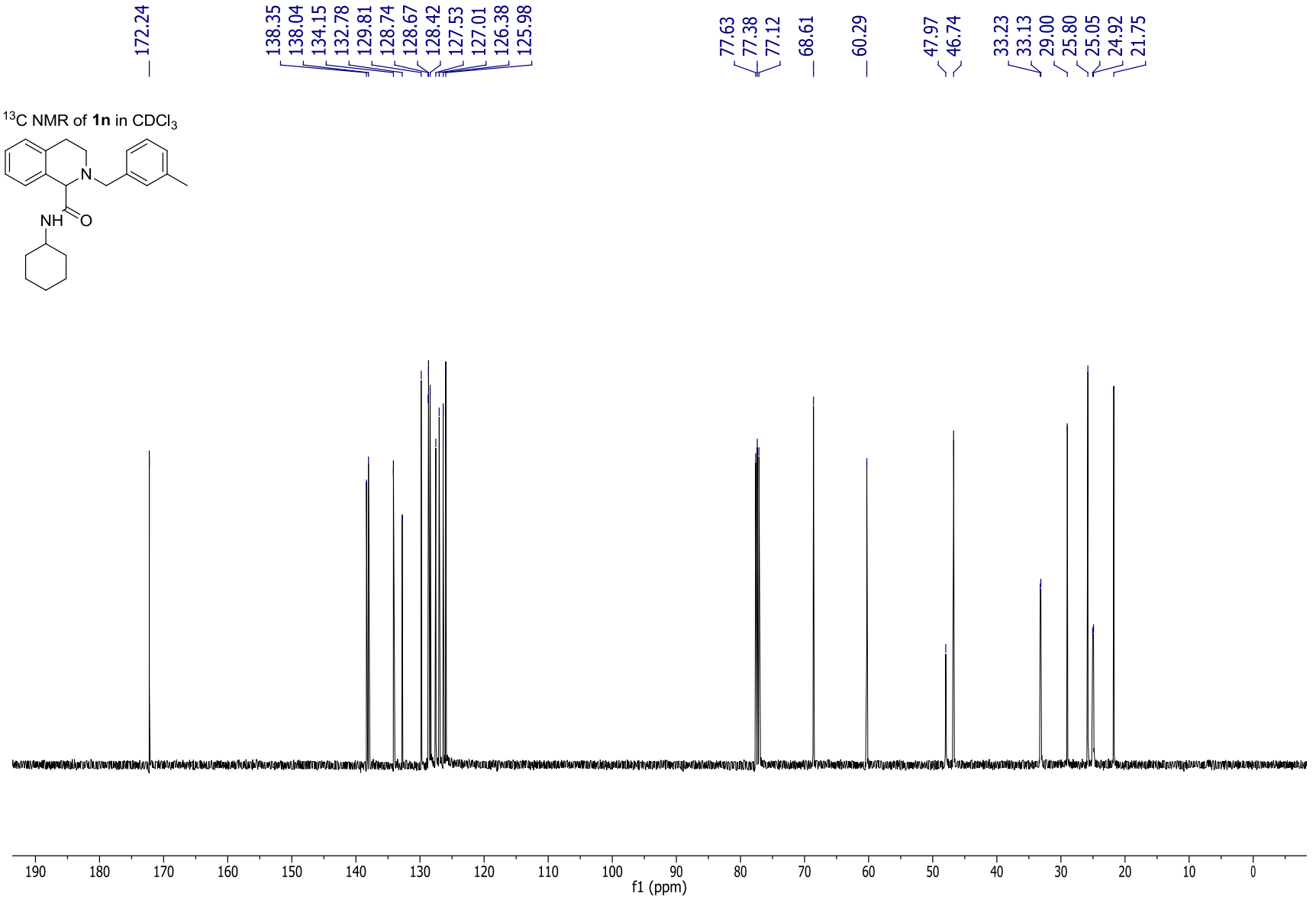

$^1$H NMR of **1m** in $CDCl_3$

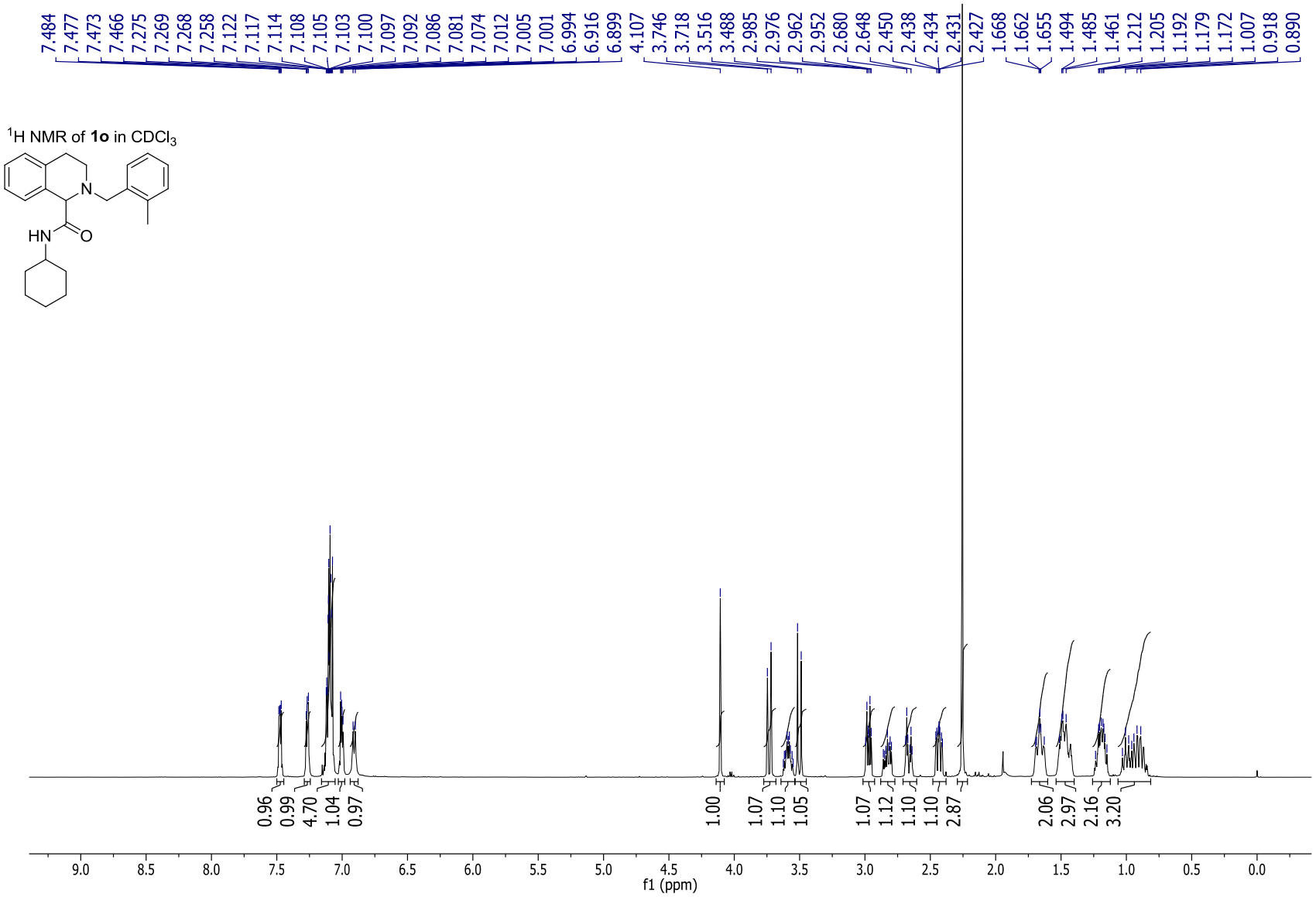


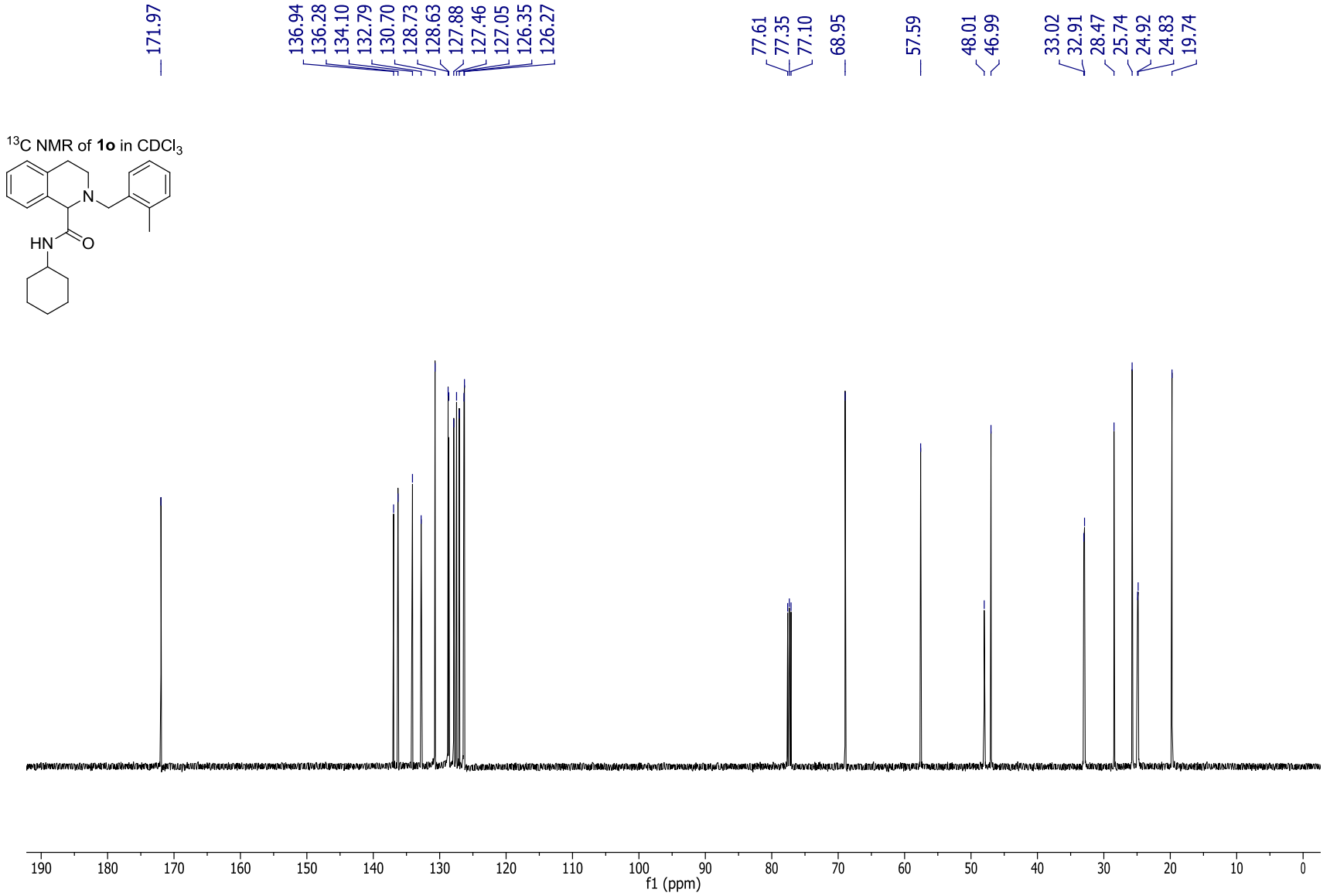



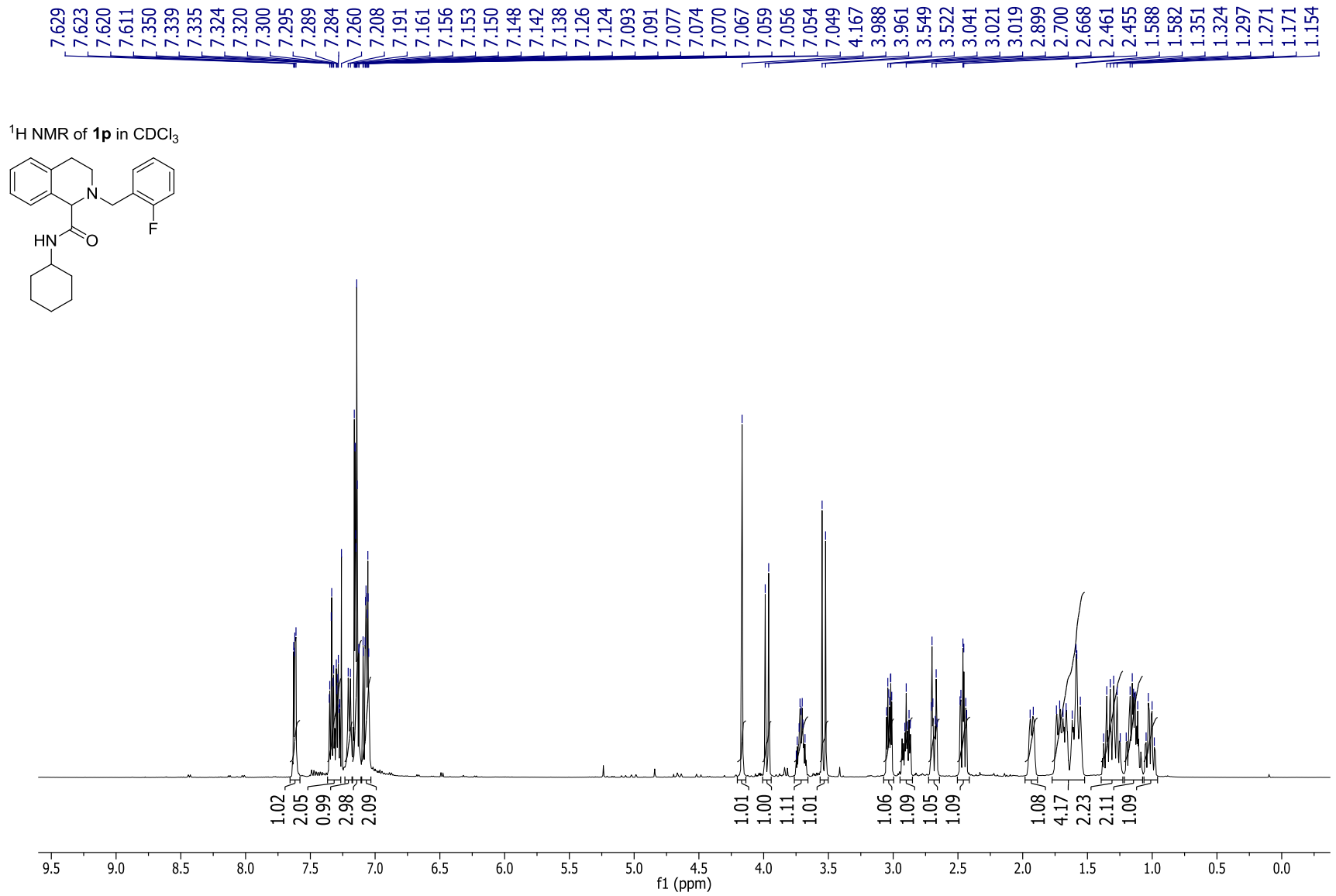

171.89
140.60
133.87
132.53
131.79
130.77
130.34
128.76
127.49
127.46
127.12
126.44
122.96
77.59
77.34
77.08
68.66
59.62
48.00
46.96
33.18
33.02
28.89
25.74
24.99
24.84
13C NMR of 1m in CDCl3
N
Br
HN
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

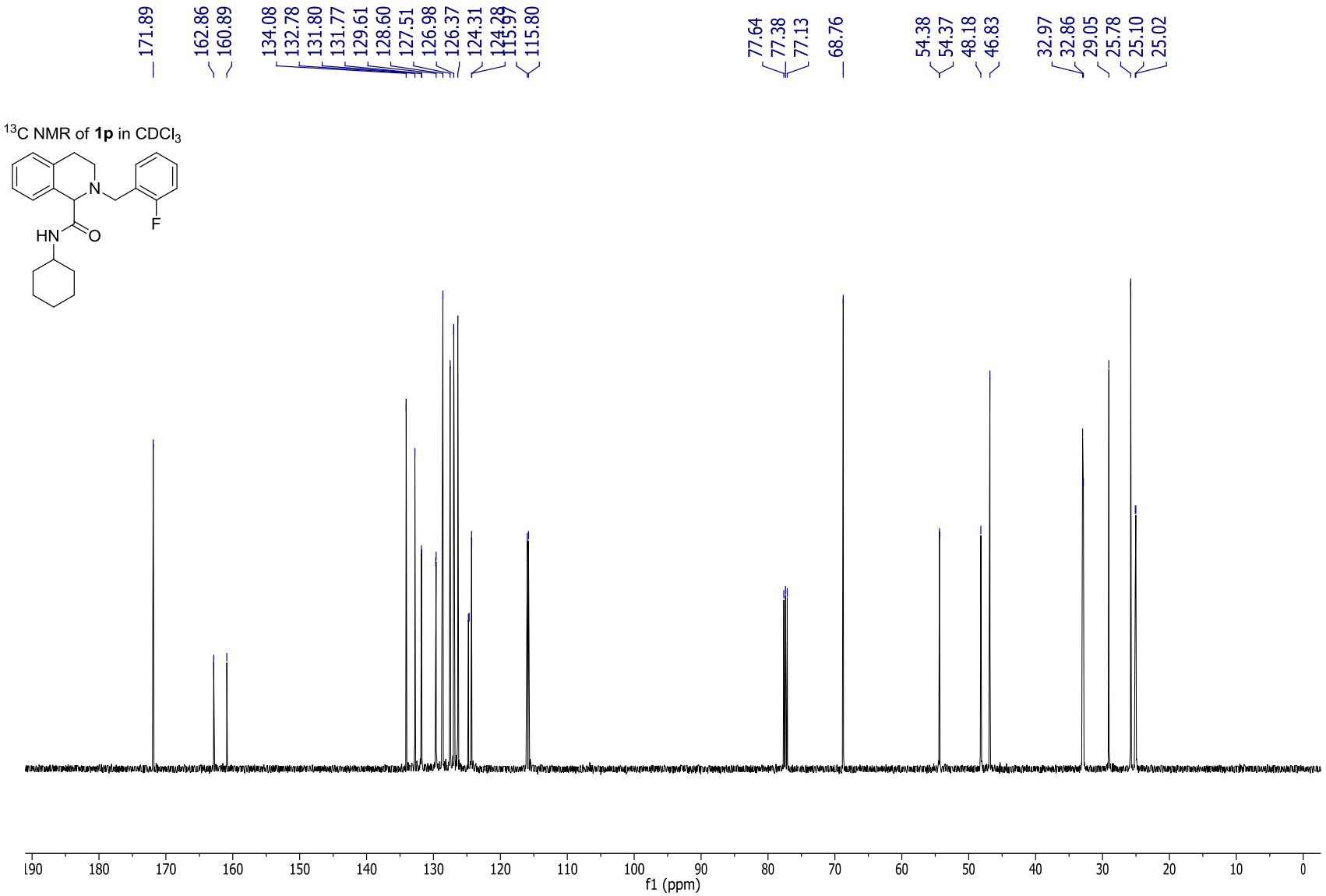

7.508
7.500
7.496
7.490
7.183
7.168
7.158
7.153
7.085
7.079
7.074
7.067
7.060
7.057
7.054
7.039
7.035
7.021
6.998
6.991
6.987
6.980
4.076
3.829
3.802
3.667
3.650
3.330
2.989
2.982
2.976
2.968
2.967
2.959
2.818
2.623
2.616
2.590
2.380
2.373
2.357
2.351
2.335
2.282
1.576
1.507
1.473
1.278
1.251
1.234
1.228
1.208
1.102
1.096
1.079
1.061
$^1$H NMR of **1n** in $CDCl_3$
N
HN
O
0.95
1.18
6.77
0.93
0.97
1.07
1.00
1.02
1.06
1.01
1.05
2.76
1.03
4.15
2.13
2.11
1.10
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
-0.5
f1 (ppm)

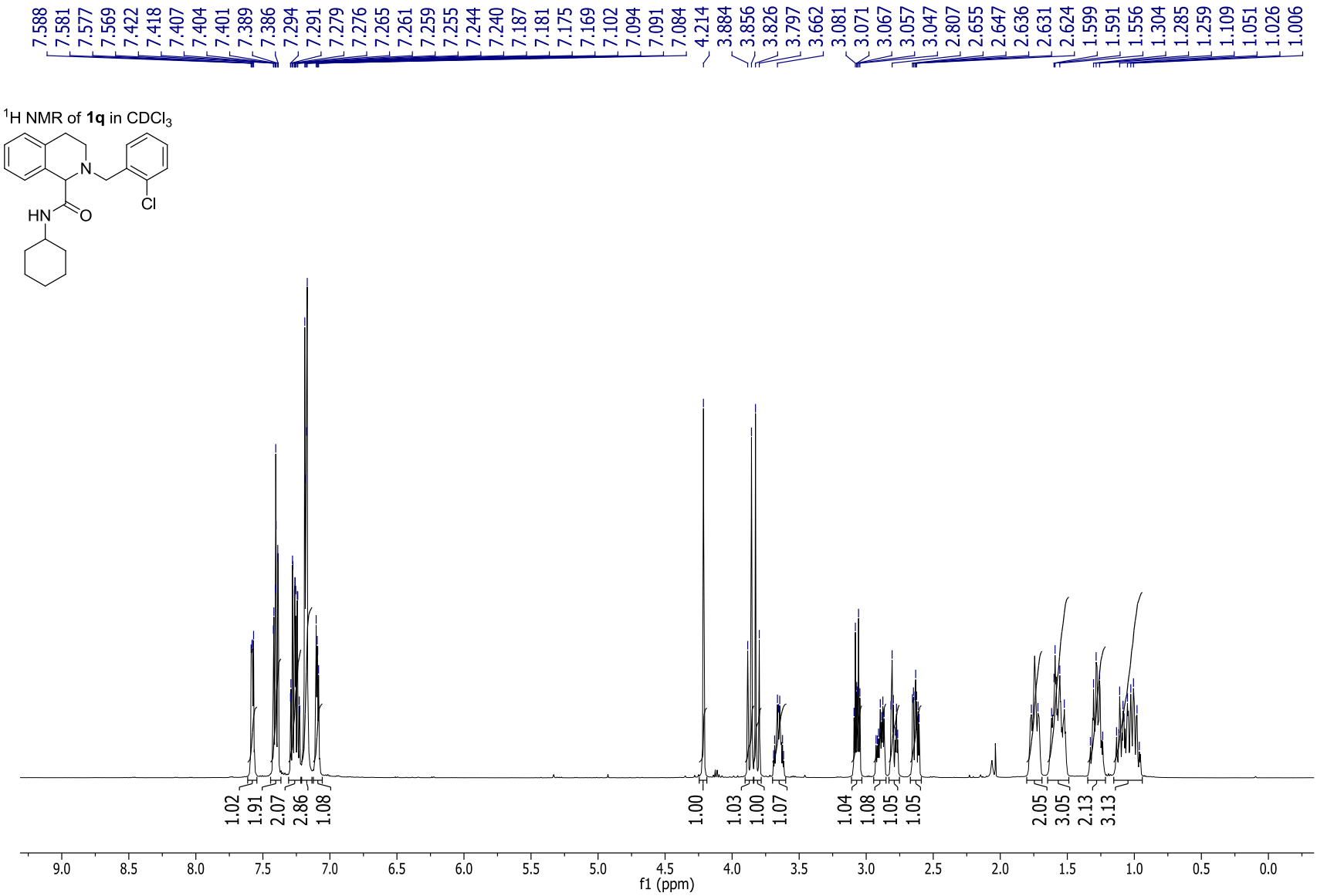

172.24
138.35
138.04
134.15
132.78
129.81
128.74
128.67
128.42
127.53
127.01
126.38
125.98
77.63
77.38
77.12
68.61
60.29
47.97
46.74
33.23
33.13
29.00
25.80
25.05
24.92
21.75
13C NMR of 1n in CDCl3
N
NH
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

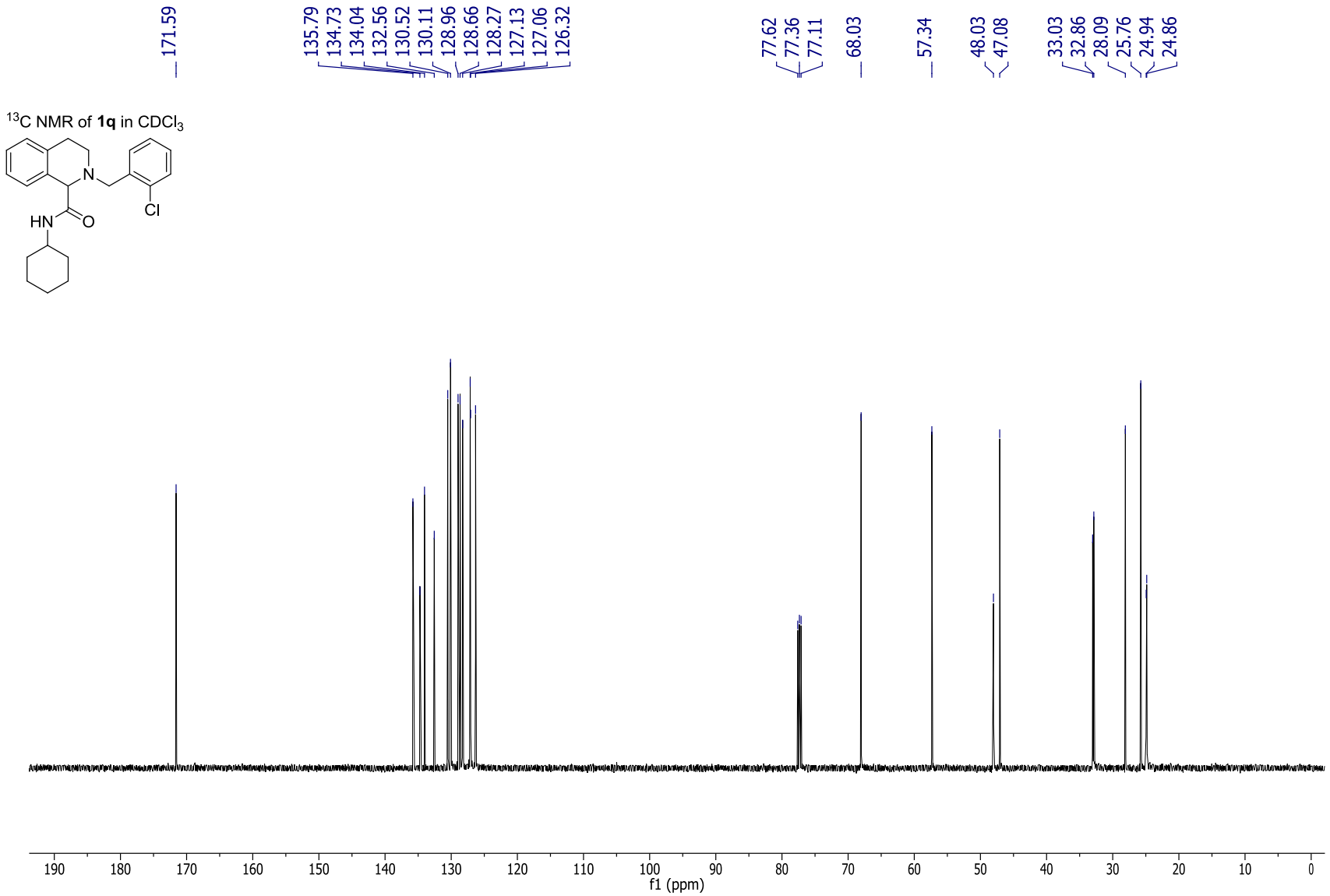

7.484
7.477
7.473
7.466
7.275
7.269
7.268
7.258
7.122
7.117
7.114
7.108
7.105
7.103
7.100
7.097
7.092
7.086
7.081
7.074
7.012
7.005
7.001
6.994
6.916
6.899
4.107
3.746
3.718
3.516
3.488
2.985
2.976
2.962
2.952
2.680
2.648
2.450
2.438
2.434
2.431
2.427
1.668
1.662
1.655
1.494
1.485
1.461
1.212
1.205
1.192
1.179
1.172
1.007
0.918
0.890
$^1$H NMR of **1o** in $CDCl_3$
N
HN
O
0.96
0.99
4.70
1.04
0.97
1.00
1.07
1.10
1.05
1.07
1.12
1.10
1.10
2.87
2.06
2.97
2.16
3.20
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)

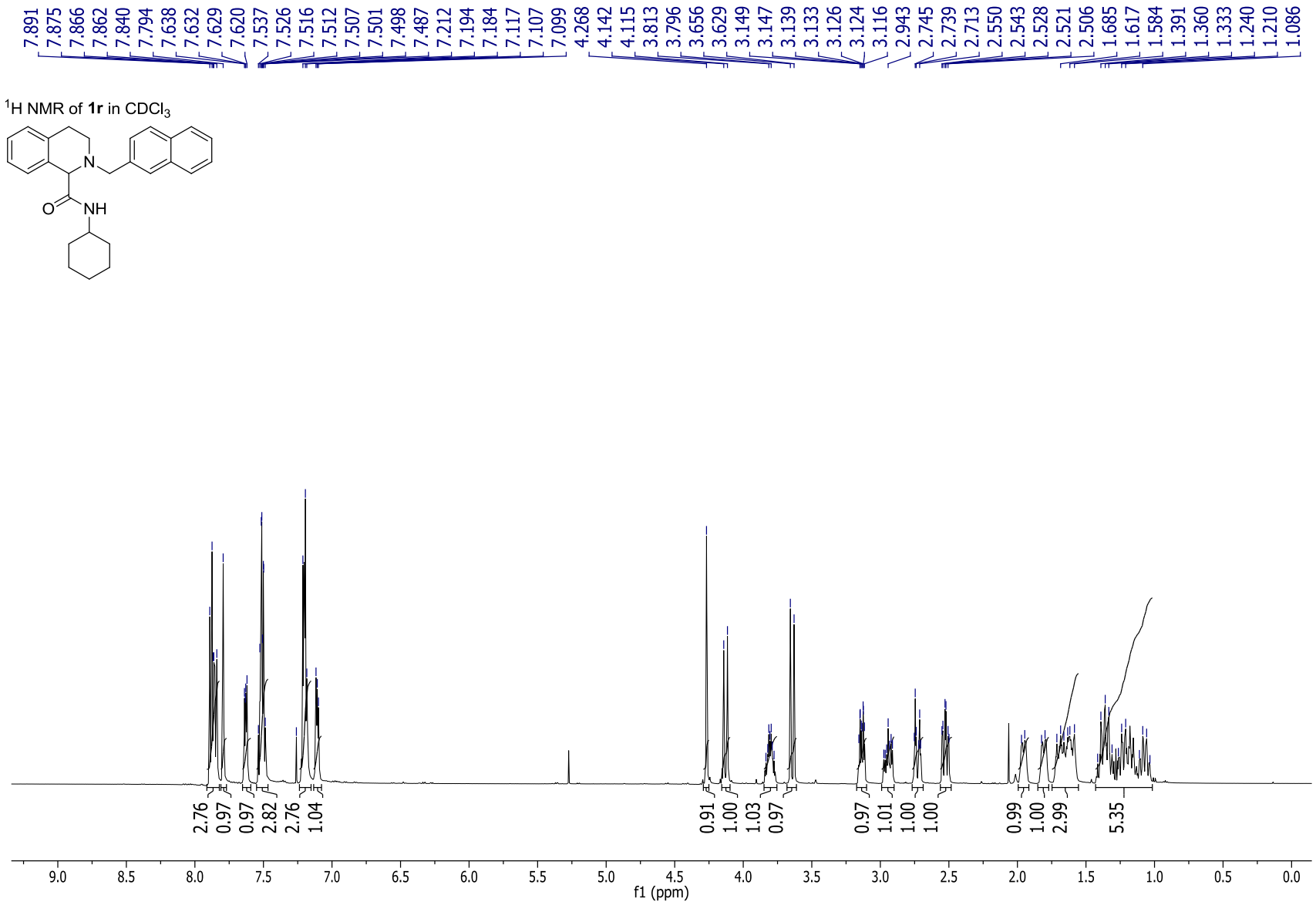

171.97
136.94
136.28
134.10
132.79
130.70
128.73
128.63
127.88
127.46
127.05
126.35
126.27
77.61
77.35
77.10
68.95
57.59
48.01
46.99
33.02
32.91
28.47
25.74
24.92
24.83
19.74
13C NMR of 1o in CDCl3
N
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

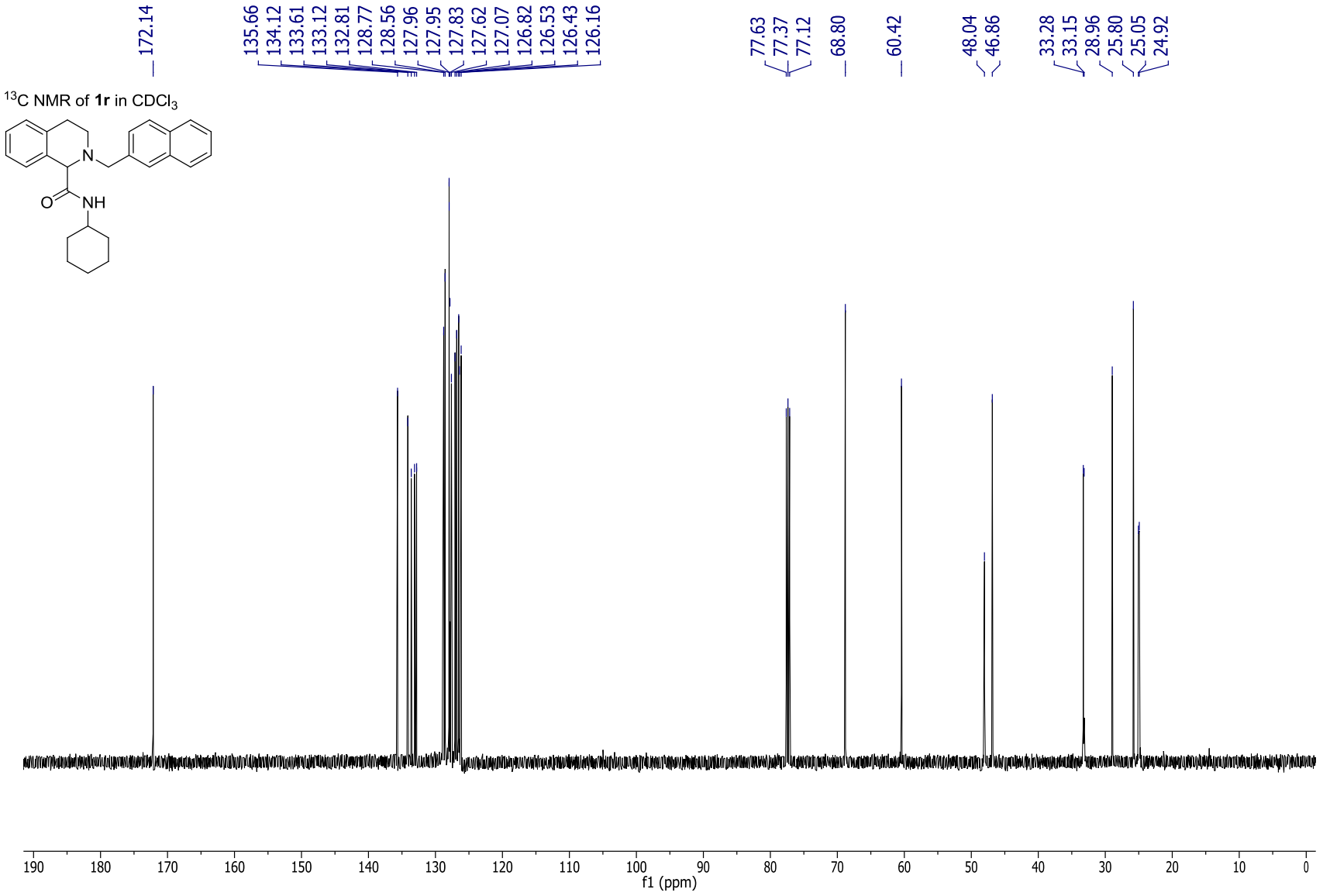

7.629
7.623
7.620
7.611
7.350
7.339
7.335
7.324
7.320
7.300
7.295
7.289
7.284
7.260
7.208
7.191
7.161
7.156
7.153
7.150
7.148
7.142
7.138
7.126
7.124
7.093
7.091
7.077
7.074
7.070
7.067
7.059
7.056
7.054
7.049
4.167
3.988
3.961
3.549
3.522
3.041
3.021
3.019
2.899
2.700
2.668
2.461
2.455
1.588
1.582
1.351
1.324
1.297
1.271
1.171
1.154
1H NMR of 1p in CDCl3
N
F
HN
O
1.02
2.05
0.99
2.98
2.09
1.01
1.00
1.11
1.01
1.06
1.09
1.05
1.09
1.08
4.17
2.23
2.11
1.09
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)

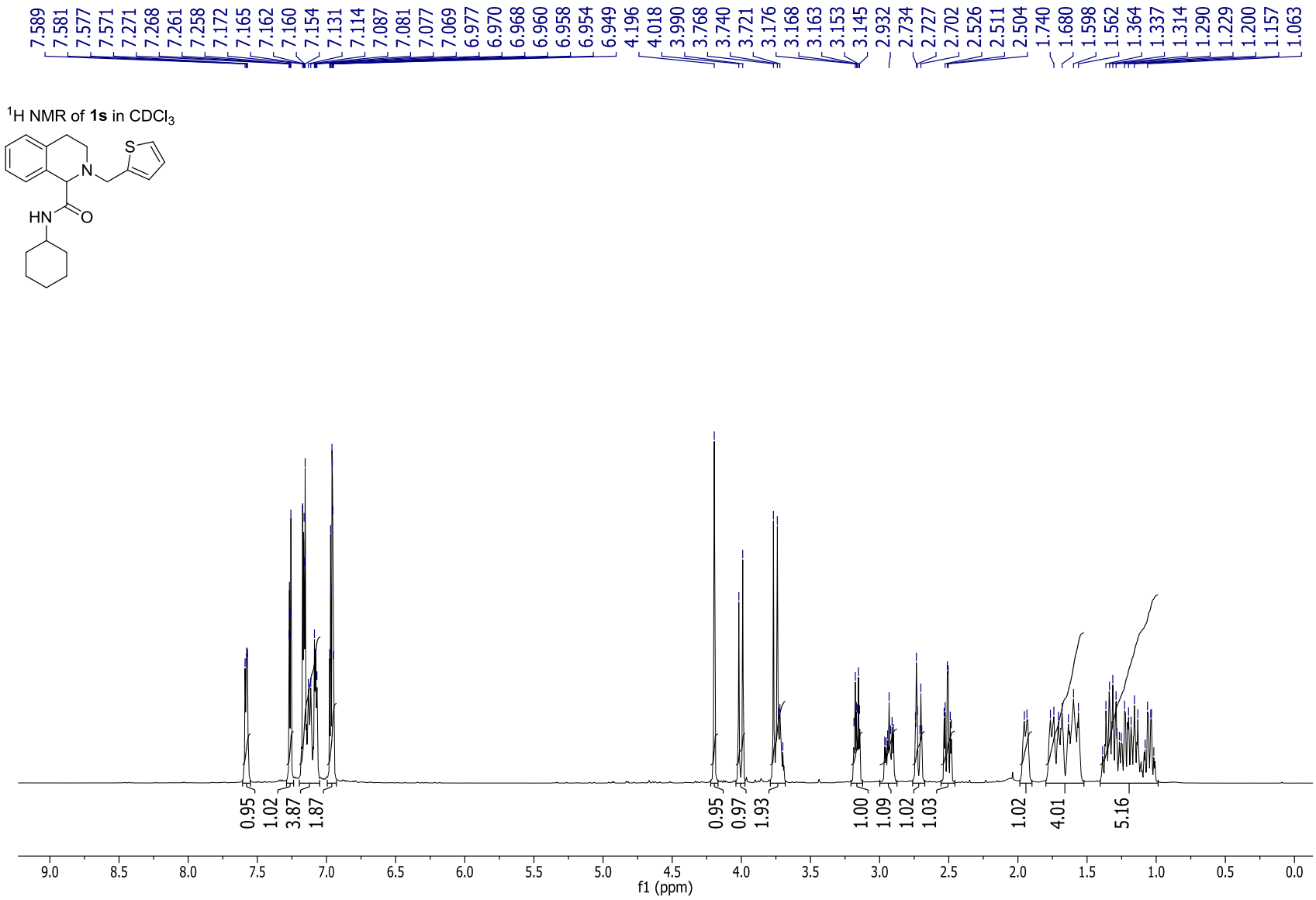

171.89
162.86
160.89
134.08
132.78
131.80
131.77
129.61
128.60
127.51
126.98
126.37
124.31
124.28
115.97
115.80
77.64
77.38
77.13
68.76
54.38
54.37
48.18
46.83
32.97
32.86
29.05
25.78
25.10
25.02
13C NMR of 1p in CDCl3
N
HN
O
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

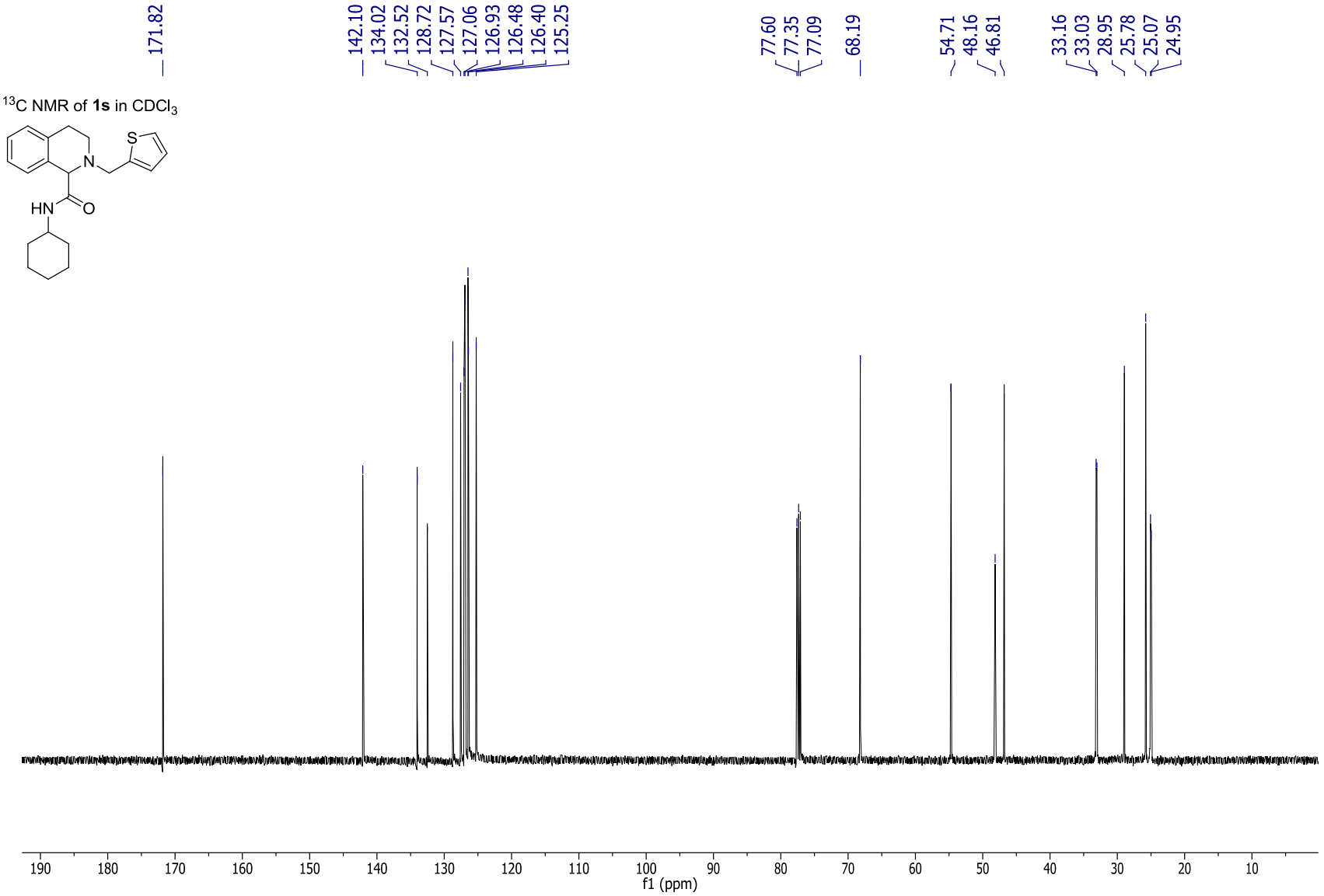

7.588
7.581
7.577
7.569
7.422
7.418
7.407
7.404
7.401
7.389
7.386
7.294
7.291
7.279
7.276
7.265
7.261
7.259
7.255
7.244
7.240
7.187
7.181
7.175
7.169
7.102
7.094
7.091
7.084
4.214
3.884
3.856
3.826
3.797
3.662
3.081
3.071
3.067
3.057
3.047
2.807
2.655
2.647
2.636
2.631
2.624
1.599
1.591
1.556
1.304
1.285
1.259
1.109
1.051
1.026
1.006
1H NMR of 1q in CDCl3
N
Cl
HN
O
1.02
1.91
2.07
2.86
1.08
1.00
1.03
1.00
1.07
1.04
1.08
1.05
1.05
2.05
3.05
2.13
3.13
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)

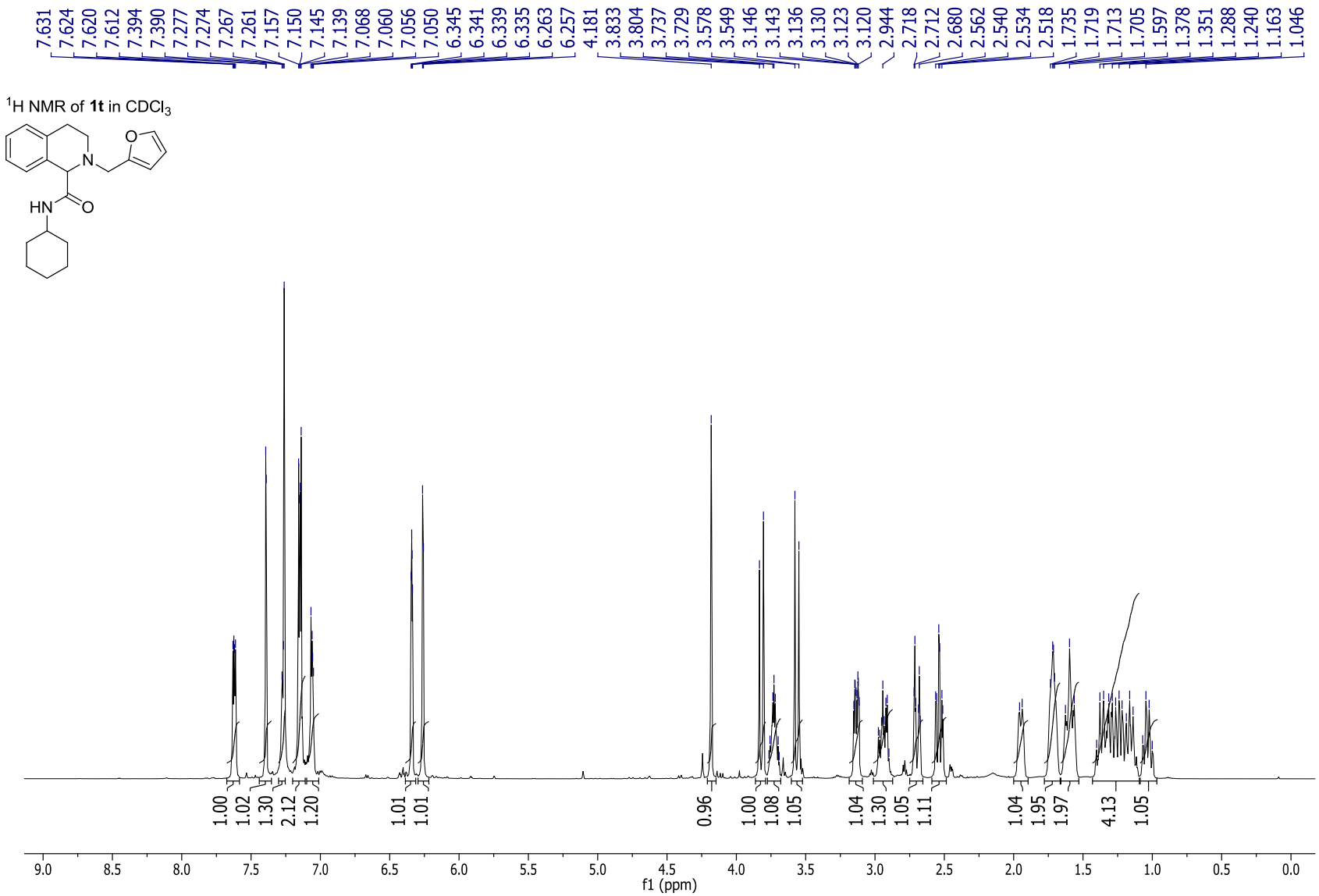

171.59
135.79
134.73
134.04
132.56
130.52
130.11
128.96
128.66
128.27
127.13
127.06
126.32
77.62
77.36
77.11
68.03
57.34
48.03
47.08
33.03
32.86
28.09
25.76
24.94
24.86
13C NMR of 1q in CDCl3
N
Cl
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.891
7.875
7.866
7.862
7.840
7.794
7.638
7.632
7.629
7.620
7.537
7.526
7.516
7.512
7.507
7.501
7.498
7.487
7.212
7.194
7.184
7.117
7.107
7.099
4.268
4.142
4.115
3.813
3.796
3.656
3.629
3.149
3.147
3.139
3.133
3.126
3.124
3.116
2.943
2.745
2.739
2.713
2.550
2.543
2.528
2.521
2.506
1.685
1.617
1.584
1.391
1.360
1.333
1.240
1.210
1.086
1H NMR of 1r in CDCl3
N
O
NH
2.76
0.97
0.97
2.82
2.76
1.04
0.91
1.00
1.03
0.97
0.97
1.01
1.00
1.00
0.99
1.00
2.99
5.35
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)

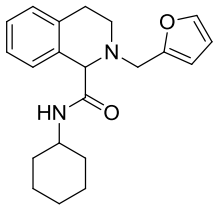

172.14
135.66
134.12
133.61
133.12
132.81
128.77
128.56
127.96
127.95
127.83
127.62
127.07
126.82
126.53
126.43
126.16
77.63
77.37
77.12
68.80
60.42
48.04
46.86
33.28
33.15
28.96
25.80
25.05
24.92
13C NMR of 1r in CDCl3
N
O
NH
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

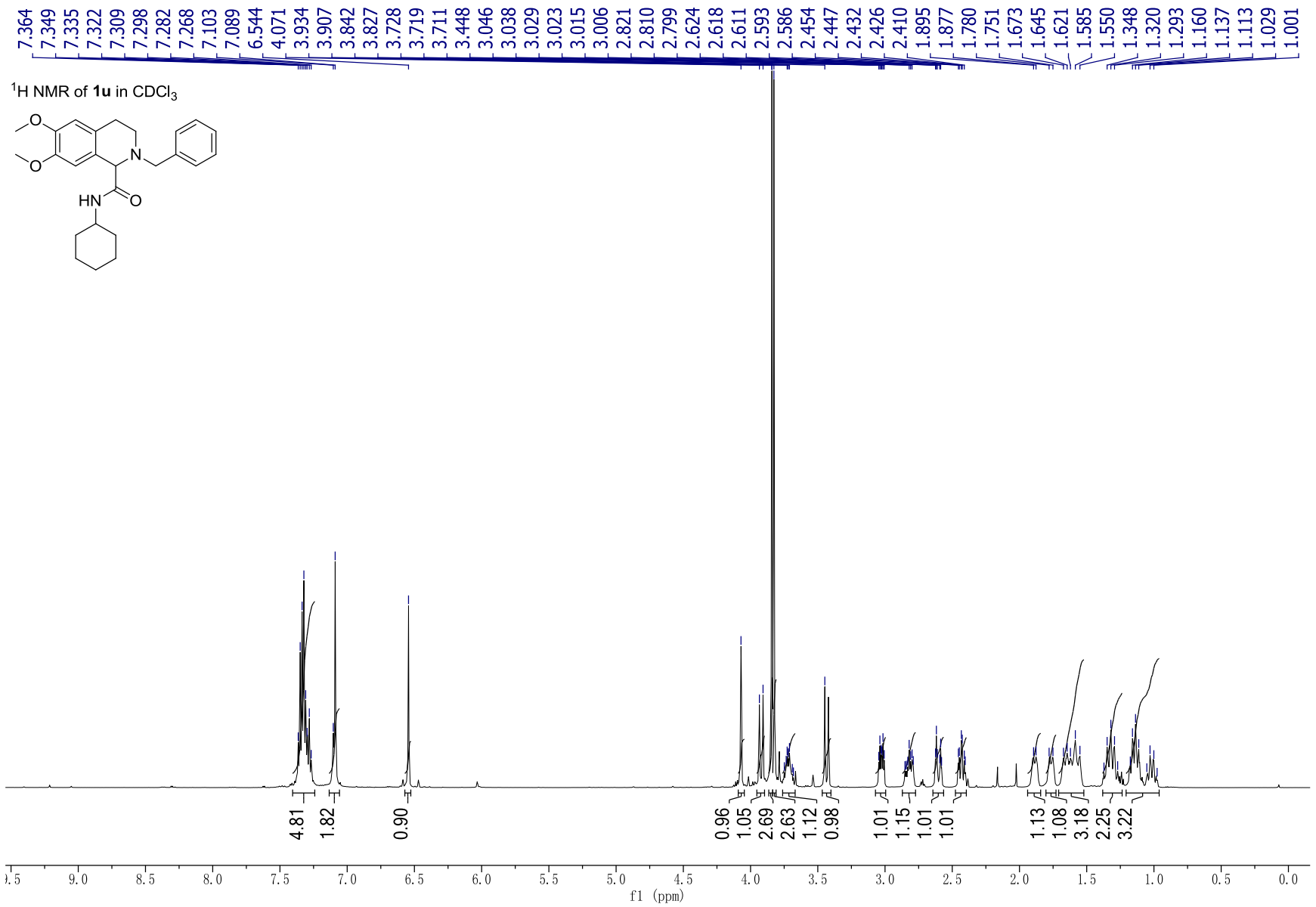

7.589
7.581
7.577
7.571
7.271
7.268
7.261
7.258
7.172
7.165
7.162
7.160
7.154
7.131
7.114
7.087
7.081
7.077
7.069
6.977
6.970
6.968
6.960
6.958
6.954
6.949
4.196
4.018
3.990
3.768
3.740
3.721
3.176
3.168
3.163
3.153
3.145
2.932
2.734
2.727
2.702
2.526
2.511
2.504
1.740
1.680
1.598
1.562
1.364
1.337
1.314
1.290
1.229
1.200
1.157
1.063
1H NMR of 1s in CDCl3
S
N
HN
O
0.95
1.02
3.87
1.87
0.95
0.97
1.93
1.00
1.09
1.02
1.03
1.02
4.01
5.16
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)

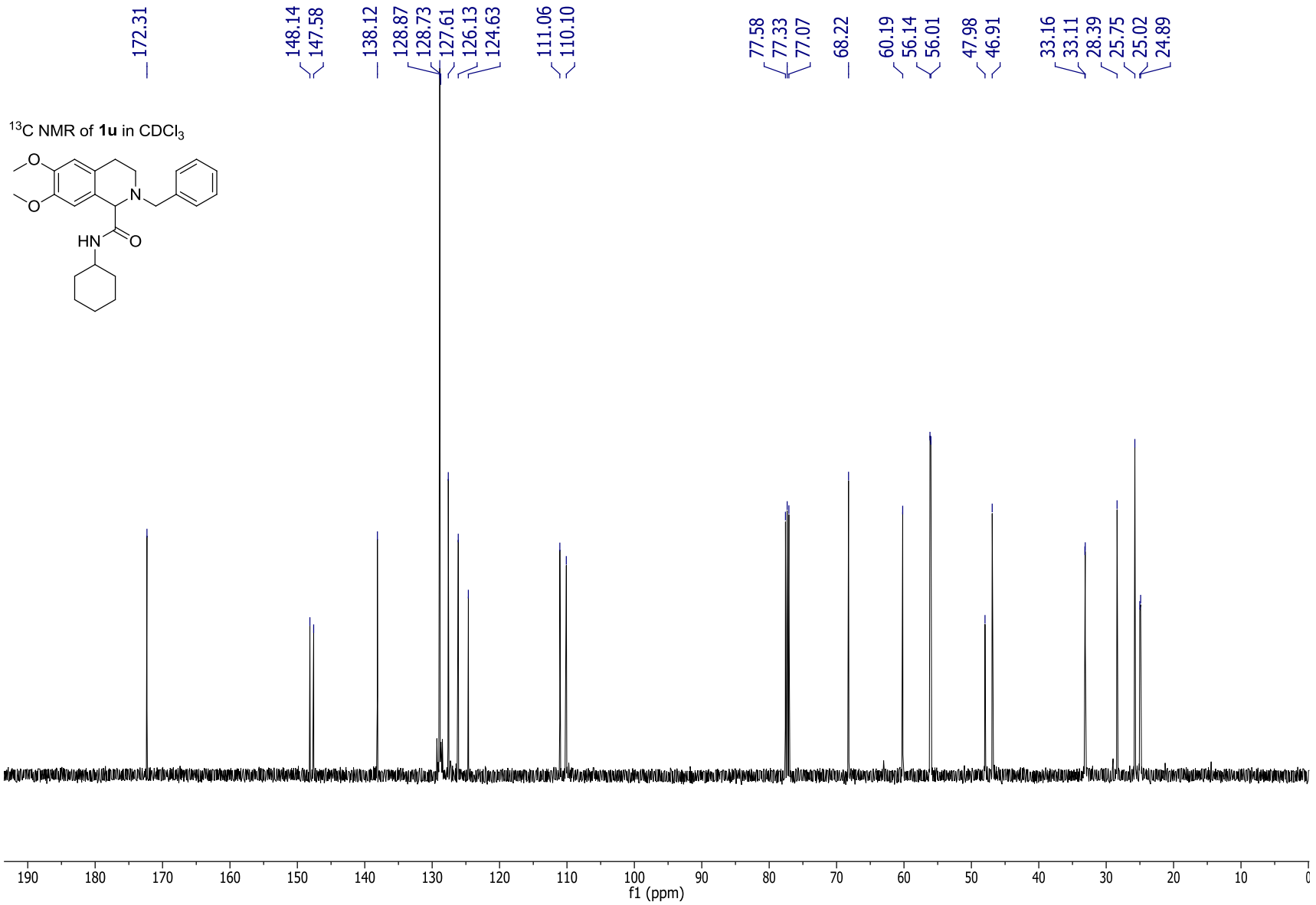

171.82
142.10
134.02
132.52
128.72
127.57
127.06
126.93
126.48
126.40
125.25
77.60
77.35
77.09
68.19
54.71
48.16
46.81
33.16
33.03
28.95
25.78
25.07
24.95
13C NMR of 1s in CDCl3
S
N
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

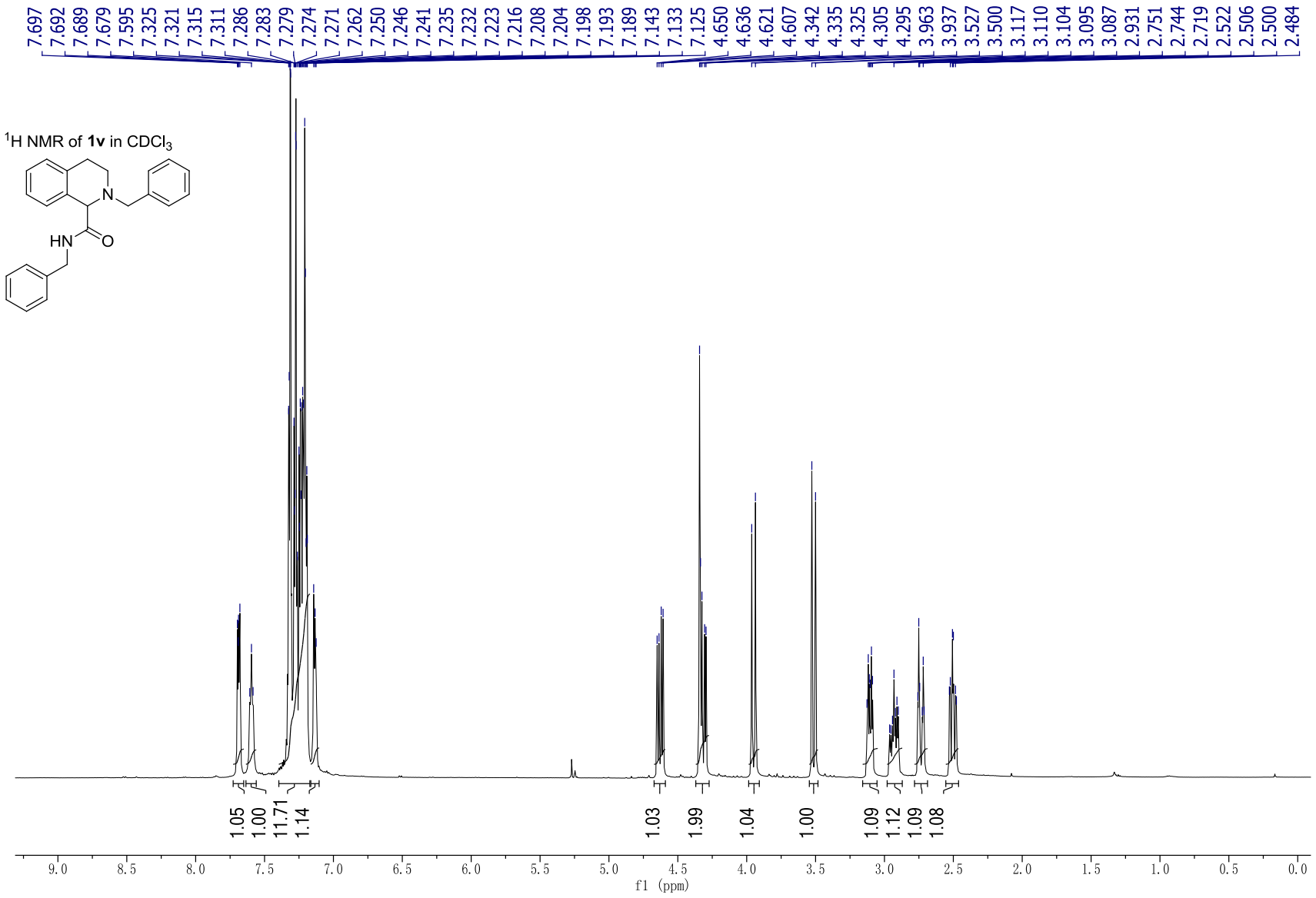

7.631 7.624 7.620 7.612 7.394 7.390 7.277 7.274 7.267 7.261 7.157 7.150 7.145 7.139 7.068 7.060 7.056 7.050 6.345 6.341 6.339 6.335 6.263 6.257 4.181 3.833 3.804 3.737 3.729 3.578 3.549 3.146 3.143 3.136 3.130 3.123 3.120 2.944 2.718 2.712 2.680 2.562 2.540 2.534 2.518 1.735 1.719 1.713 1.705 1.597 1.378 1.351 1.288 1.240 1.163 1.046
1H NMR of 1t in CDCl3
O
N
HN
O
1.00 1.02 1.30 2.12 1.20 1.01 1.01 0.96 1.00 1.08 1.05 1.04 1.30 1.05 1.11 1.04 1.95 1.97 4.13 1.05
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)

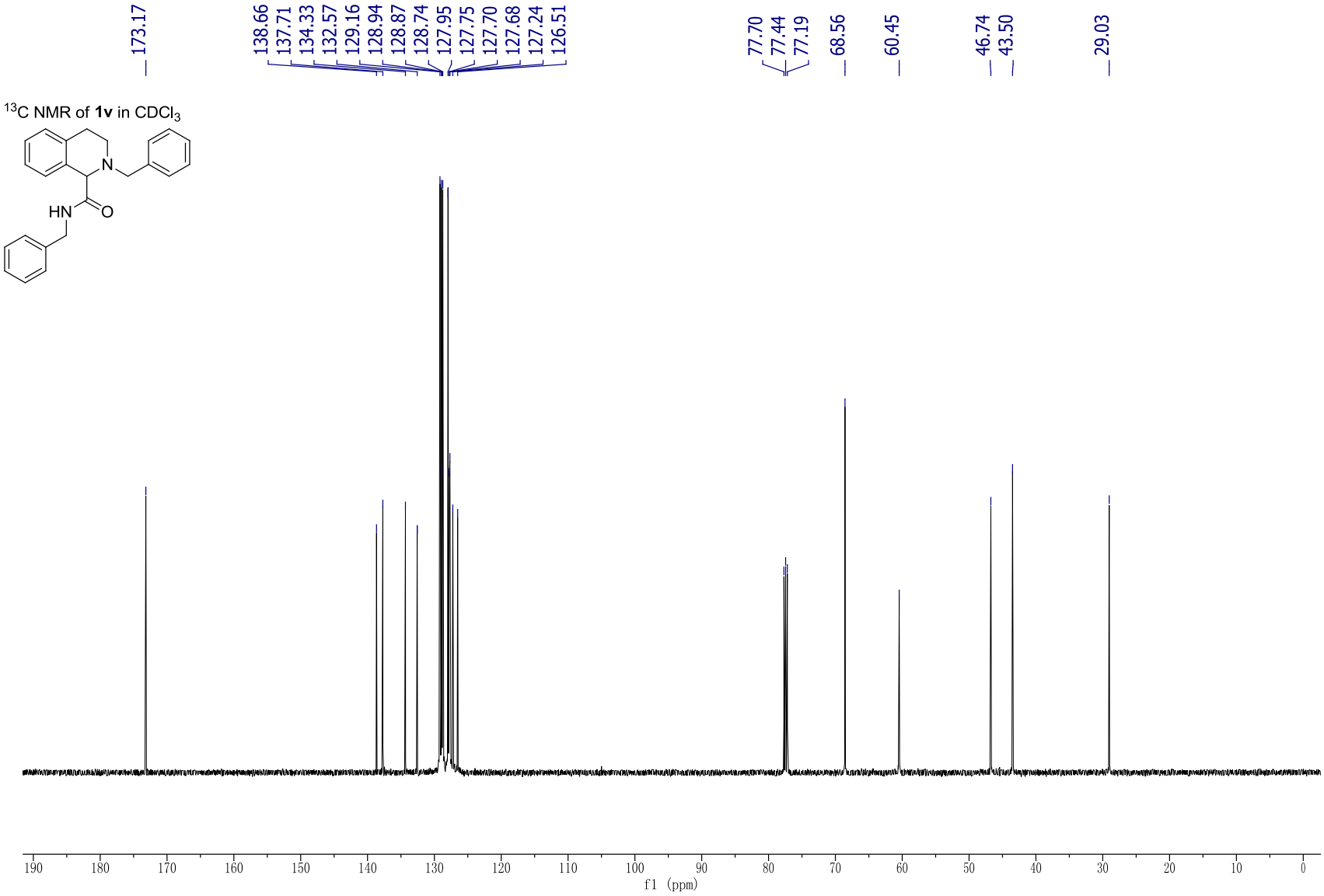
$^{13}$C NMR of **1t** in $CDCl_3$

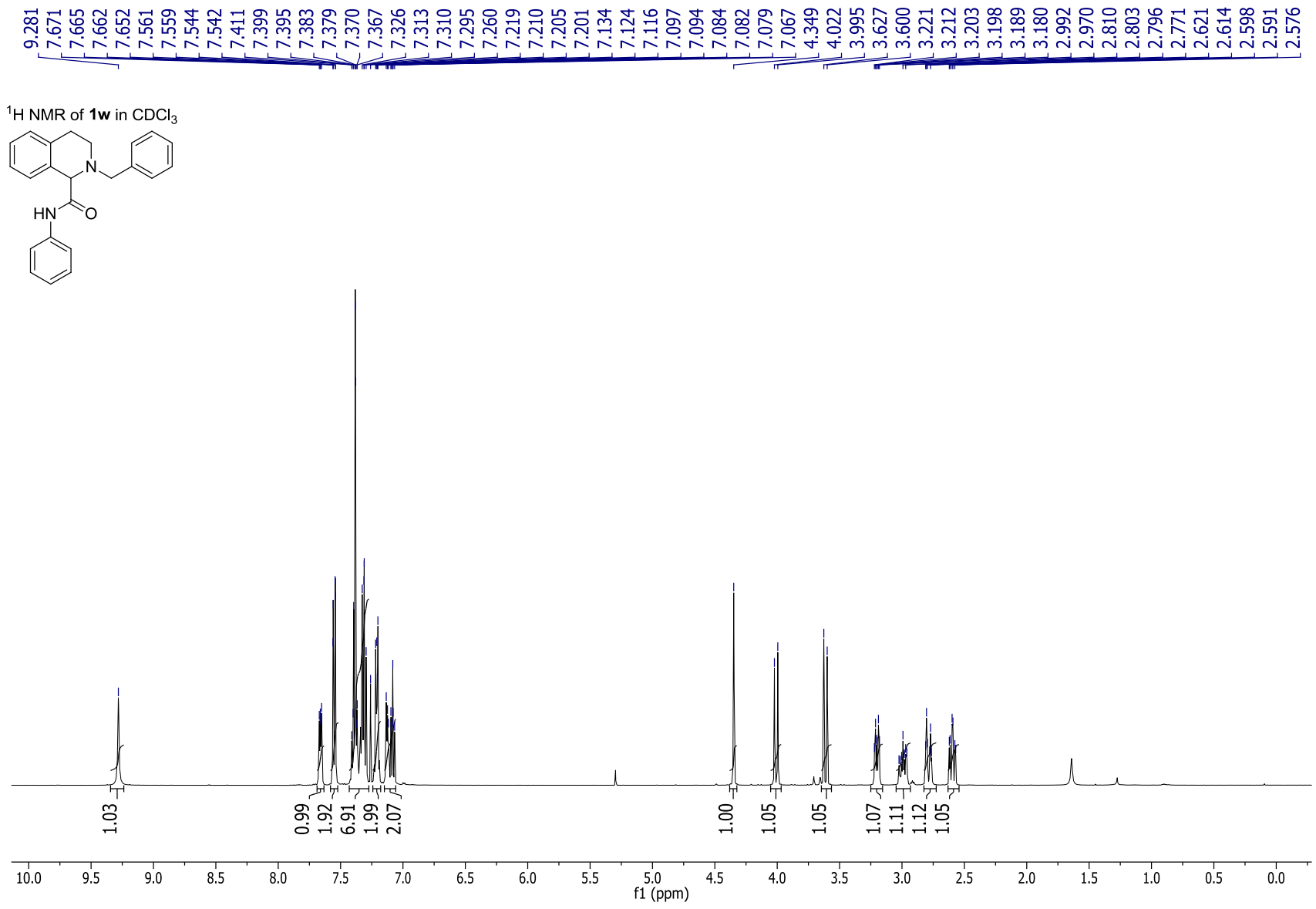


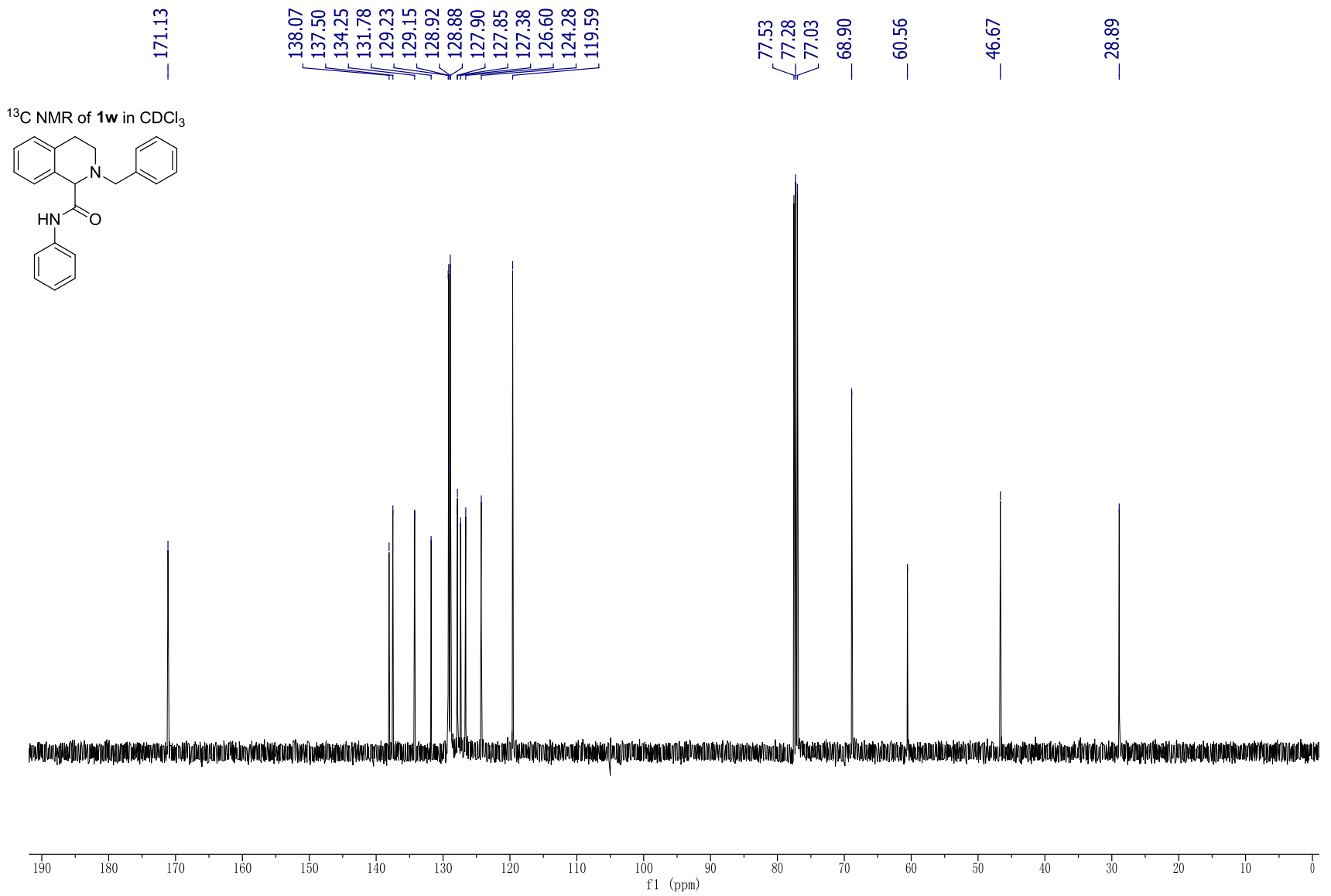

7.364
7.349
7.335
7.322
7.309
7.298
7.282
7.268
7.103
7.089
6.544
4.071
3.934
3.907
3.842
3.827
3.728
3.719
3.711
3.448
3.046
3.038
3.029
3.023
3.015
3.006
2.821
2.810
2.799
2.624
2.618
2.611
2.593
2.586
2.454
2.447
2.432
2.426
2.410
1.895
1.877
1.780
1.751
1.673
1.645
1.621
1.585
1.550
1.348
1.320
1.293
1.160
1.137
1.113
1.029
1.001
1H NMR of 1u in CDCl3
O
O
N
HN
O
4.81
1.82
0.90
0.96
1.05
2.69
2.63
1.12
0.98
1.01
1.15
1.01
1.01
1.13
1.08
3.18
2.25
3.22
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)

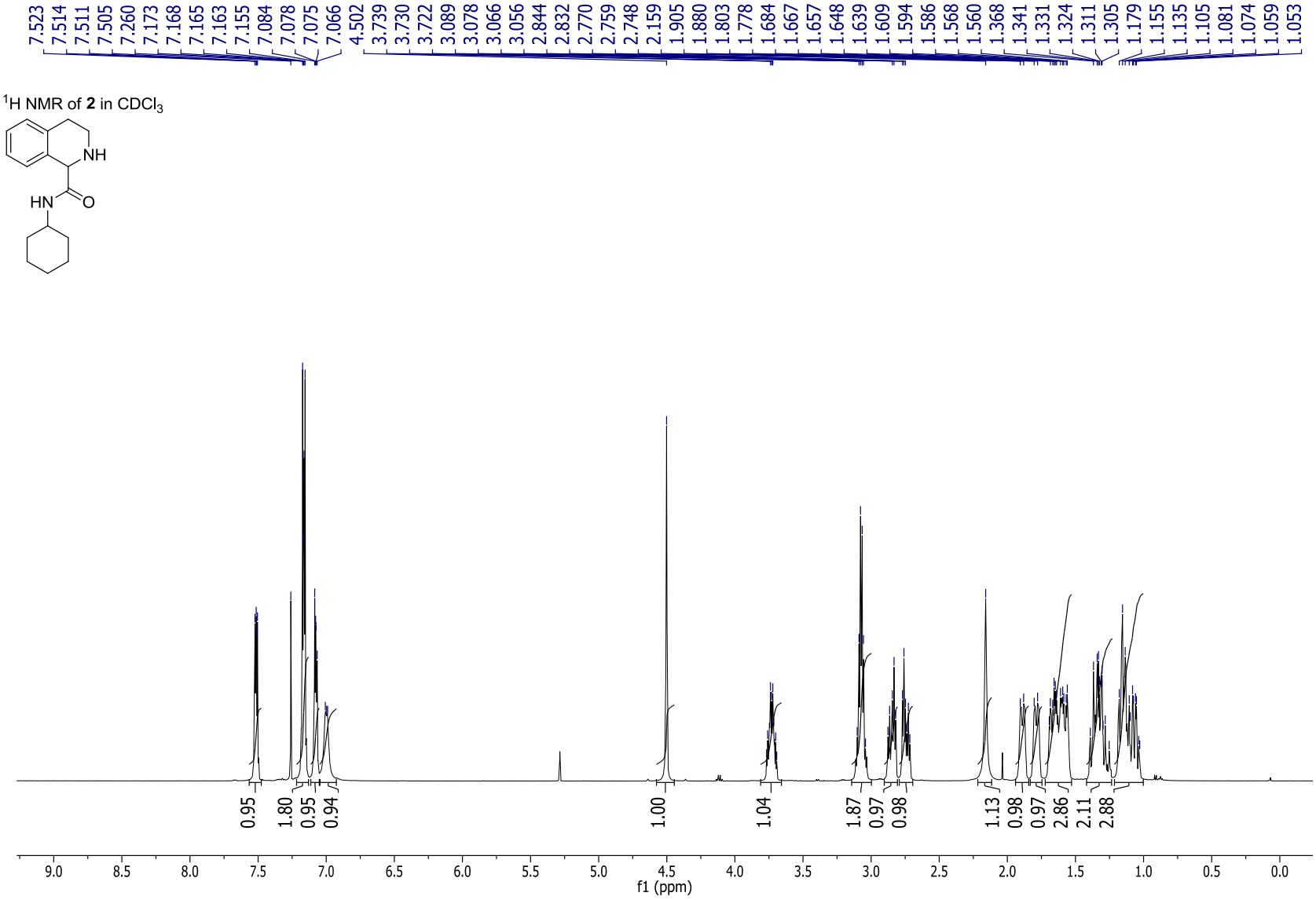

172.31
148.14
147.58
138.12
128.87
128.73
127.61
126.13
124.63
111.06
110.10
77.58
77.33
77.07
68.22
60.19
56.14
56.01
47.98
46.91
33.16
33.11
28.39
25.75
25.02
24.89
13C NMR of 1u in CDCl3
O
O
N
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

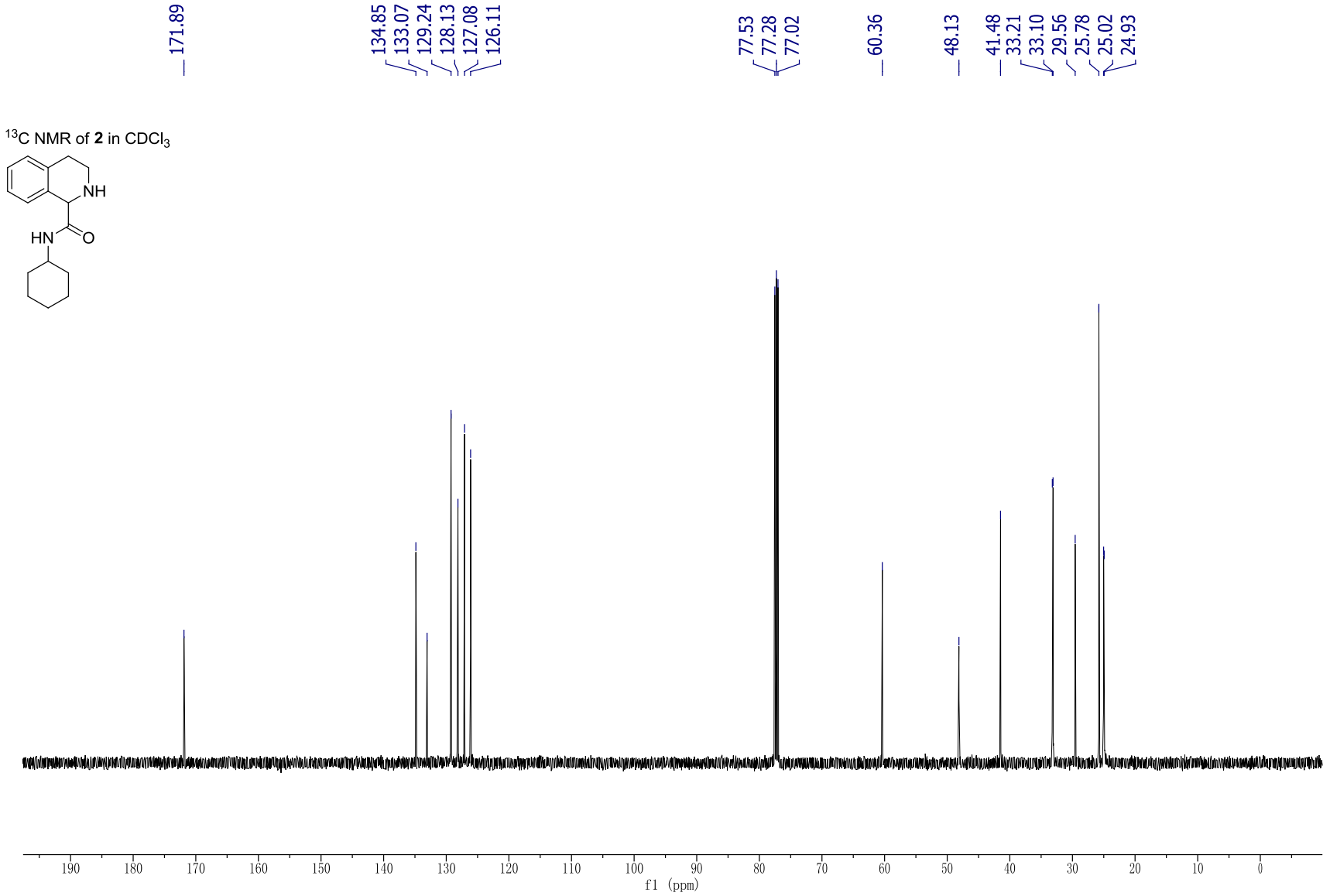

7.697
7.692
7.689
7.679
7.595
7.325
7.321
7.315
7.311
7.286
7.283
7.279
7.274
7.271
7.262
7.250
7.246
7.241
7.235
7.232
7.223
7.216
7.208
7.204
7.198
7.193
7.189
7.143
7.133
7.125
4.650
4.636
4.621
4.607
4.342
4.335
4.325
4.305
4.295
3.963
3.937
3.527
3.500
3.117
3.110
3.104
3.095
3.087
2.931
2.751
2.744
2.719
2.522
2.506
2.500
2.484
1H NMR of 1v in CDCl3
HN
O
N
1.05
1.00
11.71
1.14
1.03
1.99
1.04
1.00
1.09
1.12
1.09
1.08
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)

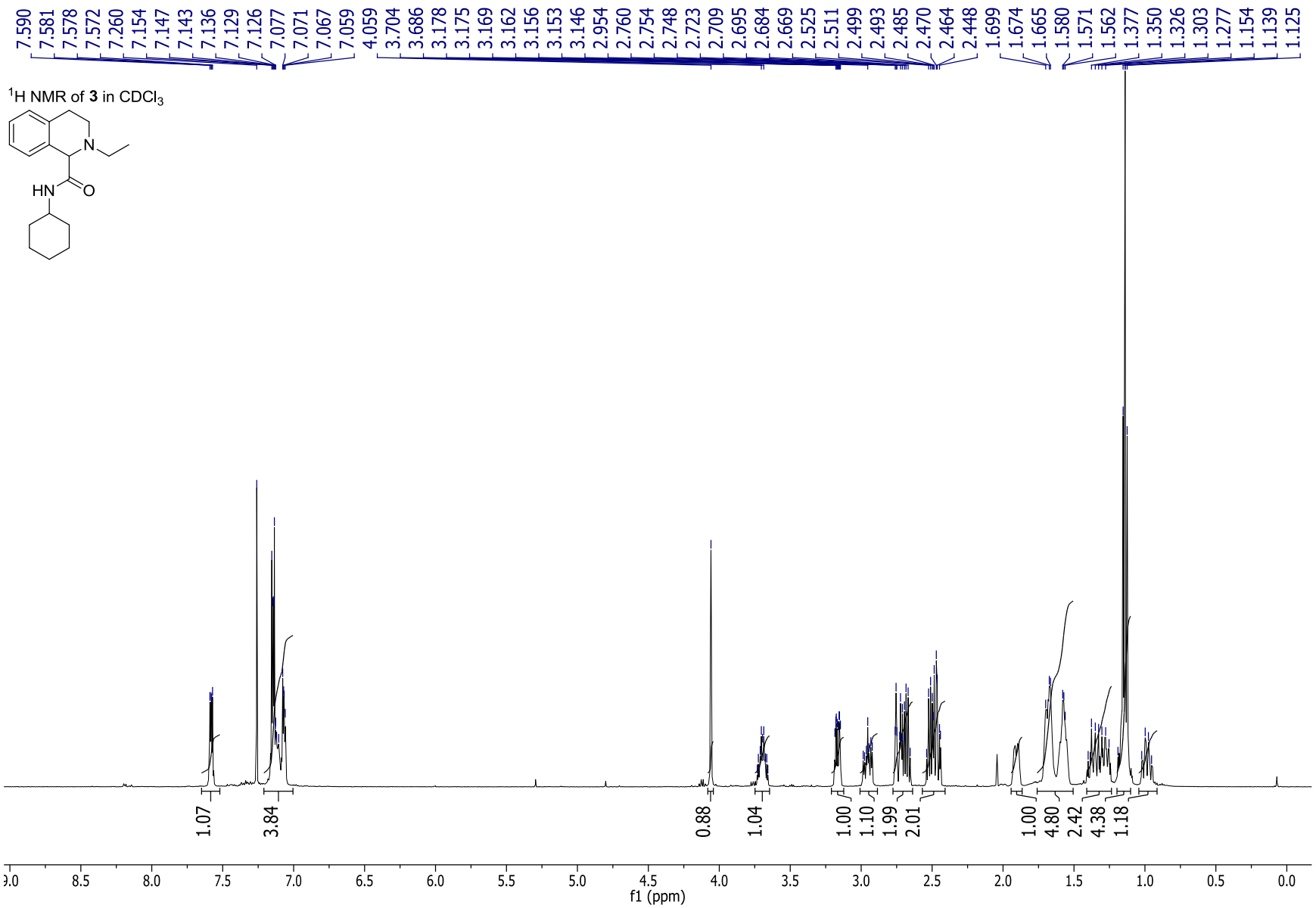

173.17
138.66
137.71
134.33
132.57
129.16
128.94
128.87
128.74
127.95
127.75
127.70
127.68
127.24
126.51
77.70
77.44
77.19
68.56
60.45
46.74
43.50
29.03
13C NMR of 1v in CDCl3
N
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

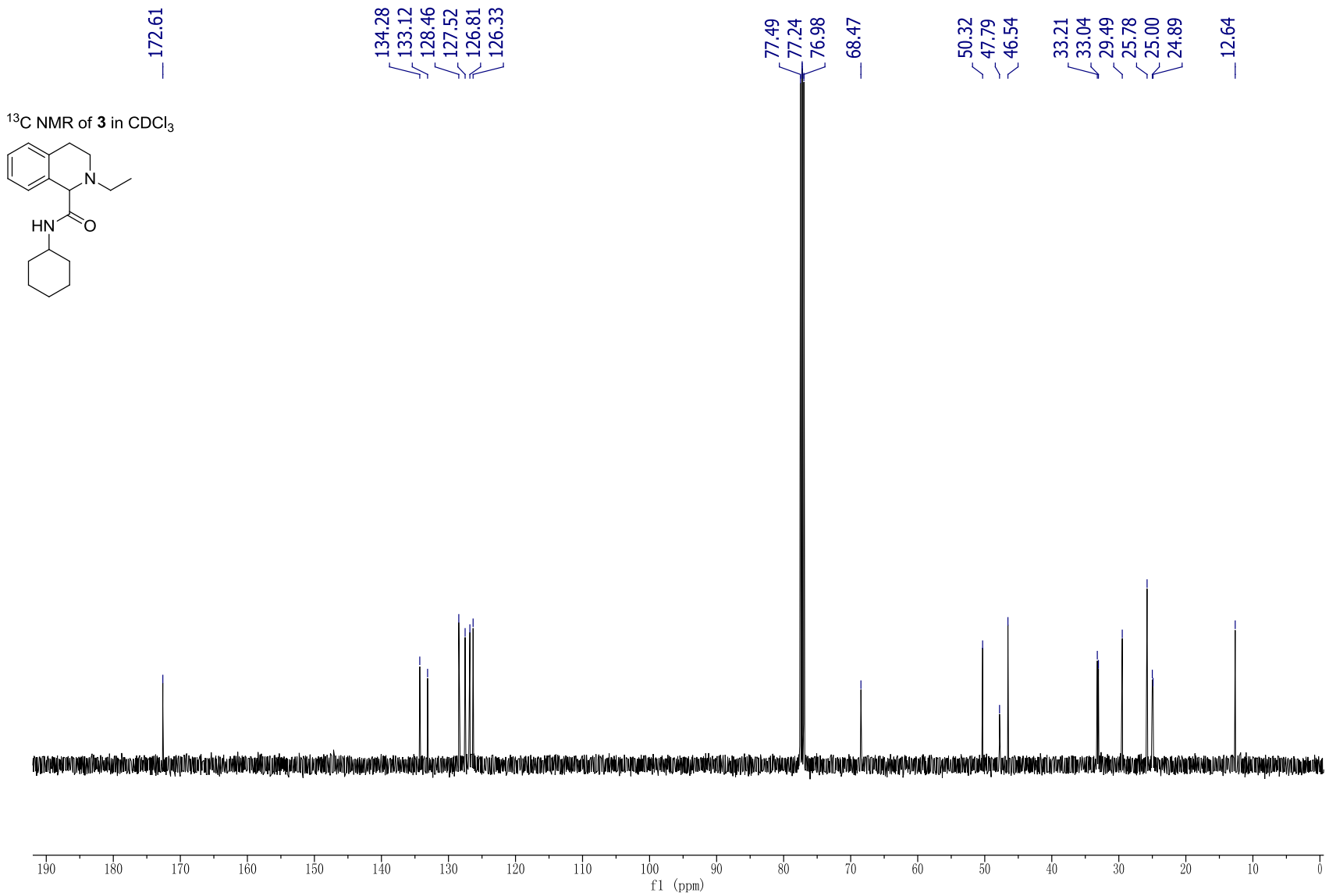

9.281
7.671
7.665
7.662
7.652
7.561
7.559
7.544
7.542
7.411
7.399
7.395
7.383
7.379
7.370
7.367
7.326
7.313
7.310
7.295
7.260
7.219
7.210
7.205
7.201
7.134
7.124
7.116
7.097
7.094
7.084
7.082
7.079
7.067
4.349
4.022
3.995
3.627
3.600
3.221
3.212
3.203
3.198
3.189
3.180
2.992
2.970
2.810
2.803
2.796
2.771
2.621
2.614
2.598
2.591
2.576
1H NMR of 1w in CDCl3
HN
O
N
1.03
0.99
1.92
6.91
1.99
2.07
1.00
1.05
1.05
1.07
1.11
1.12
1.05
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)

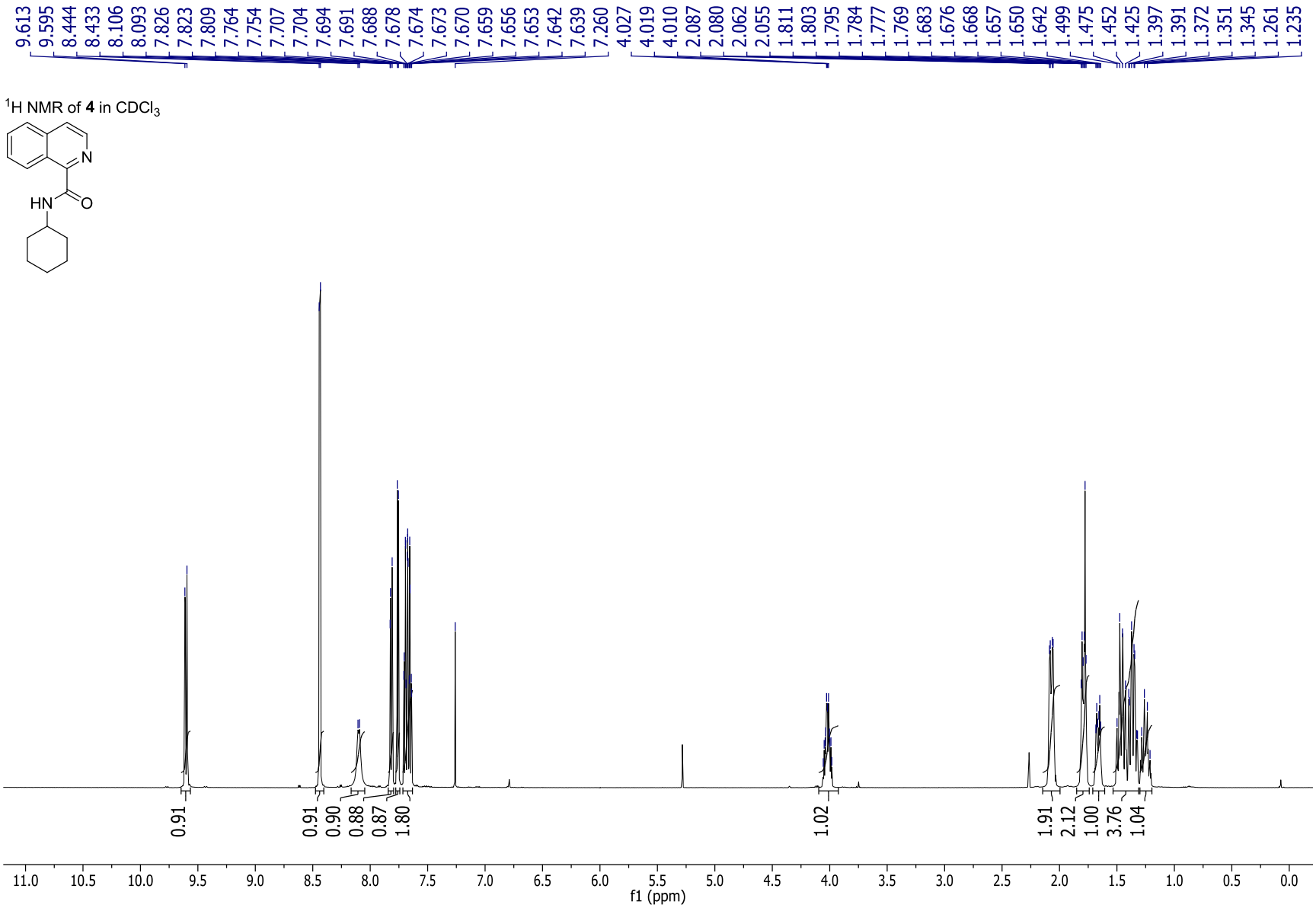

171.13
138.07
137.50
134.25
131.78
129.23
129.15
128.92
128.88
127.90
127.85
127.38
126.60
124.28
119.59
77.53
77.28
77.03
68.90
60.56
46.67
28.89
13C NMR of 1w in CDCl3
N
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

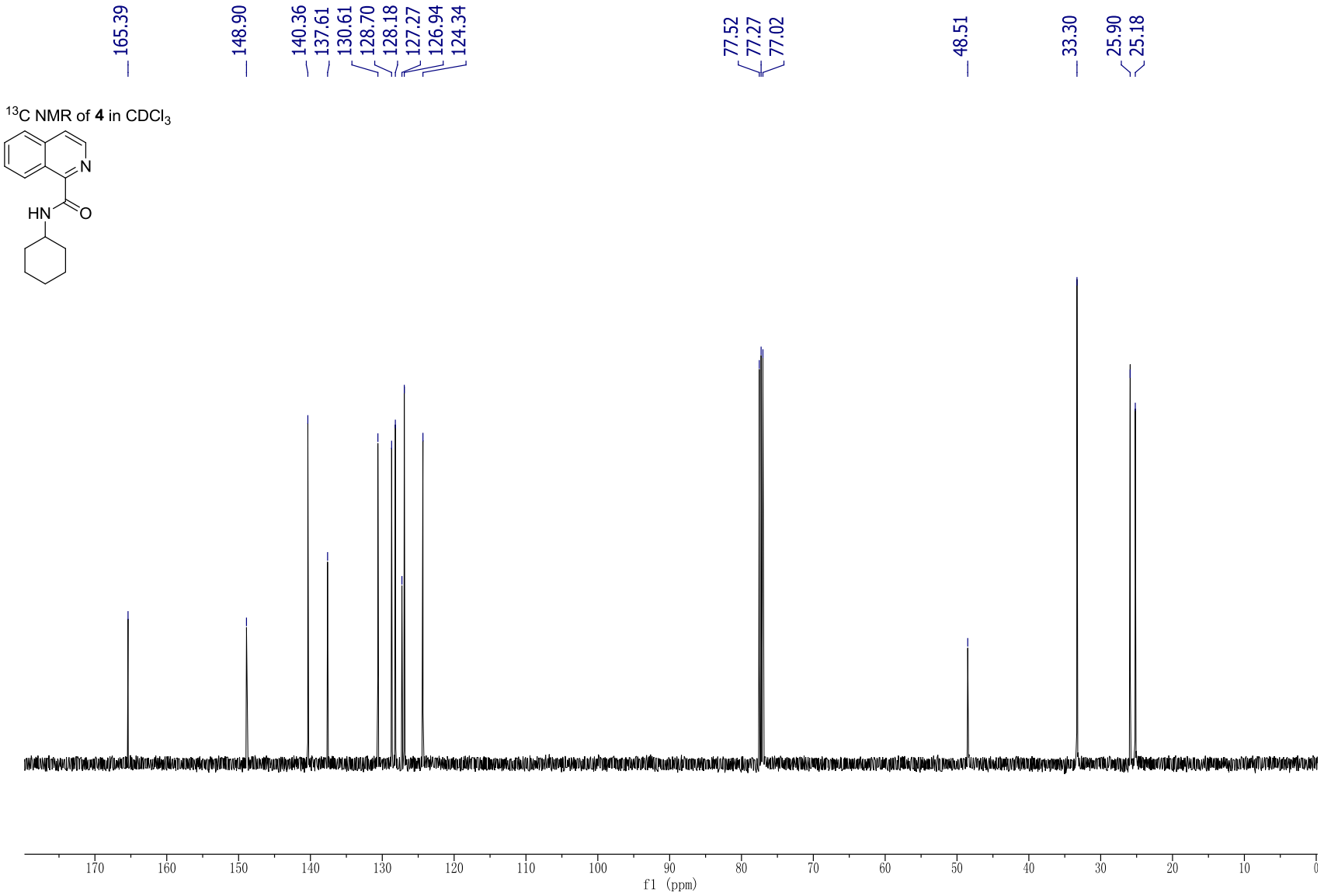

7.523
7.514
7.511
7.505
7.260
7.173
7.168
7.165
7.163
7.155
7.084
7.078
7.075
7.066
4.502
3.739
3.730
3.722
3.089
3.078
3.066
3.056
2.844
2.832
2.770
2.759
2.748
2.159
1.905
1.880
1.803
1.778
1.684
1.667
1.657
1.648
1.639
1.609
1.594
1.586
1.568
1.560
1.368
1.341
1.331
1.324
1.311
1.305
1.179
1.155
1.135
1.105
1.081
1.074
1.059
1.053
$^1$H NMR of **2** in $CDCl_3$
NH
HN
O
0.95
1.80
0.95
0.94
1.00
1.04
1.87
0.97
0.98
1.13
0.98
0.97
2.86
2.11
2.88
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)


171.89
134.85
133.07
129.24
128.13
127.08
126.11
77.53
77.28
77.02
60.36
48.13
41.48
33.21
33.10
29.56
25.78
25.02
24.93
13C NMR of 2 in CDCl3
NH
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

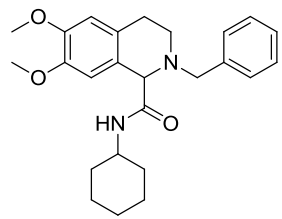

7.590
7.581
7.578
7.572
7.260
7.154
7.147
7.143
7.136
7.129
7.126
7.077
7.071
7.067
7.059
4.059
3.704
3.686
3.178
3.175
3.169
3.162
3.156
3.153
3.146
2.954
2.760
2.754
2.748
2.723
2.709
2.695
2.684
2.669
2.525
2.511
2.499
2.493
2.485
2.470
2.464
2.448
1.699
1.674
1.665
1.580
1.571
1.562
1.377
1.350
1.326
1.303
1.277
1.154
1.139
1.125
$^1$H NMR of **3** in $CDCl_3$
N
HN
O
1.07
3.84
0.88
1.04
1.00
1.10
1.99
2.01
1.00
4.80
2.42
4.38
1.18
f1 (ppm)

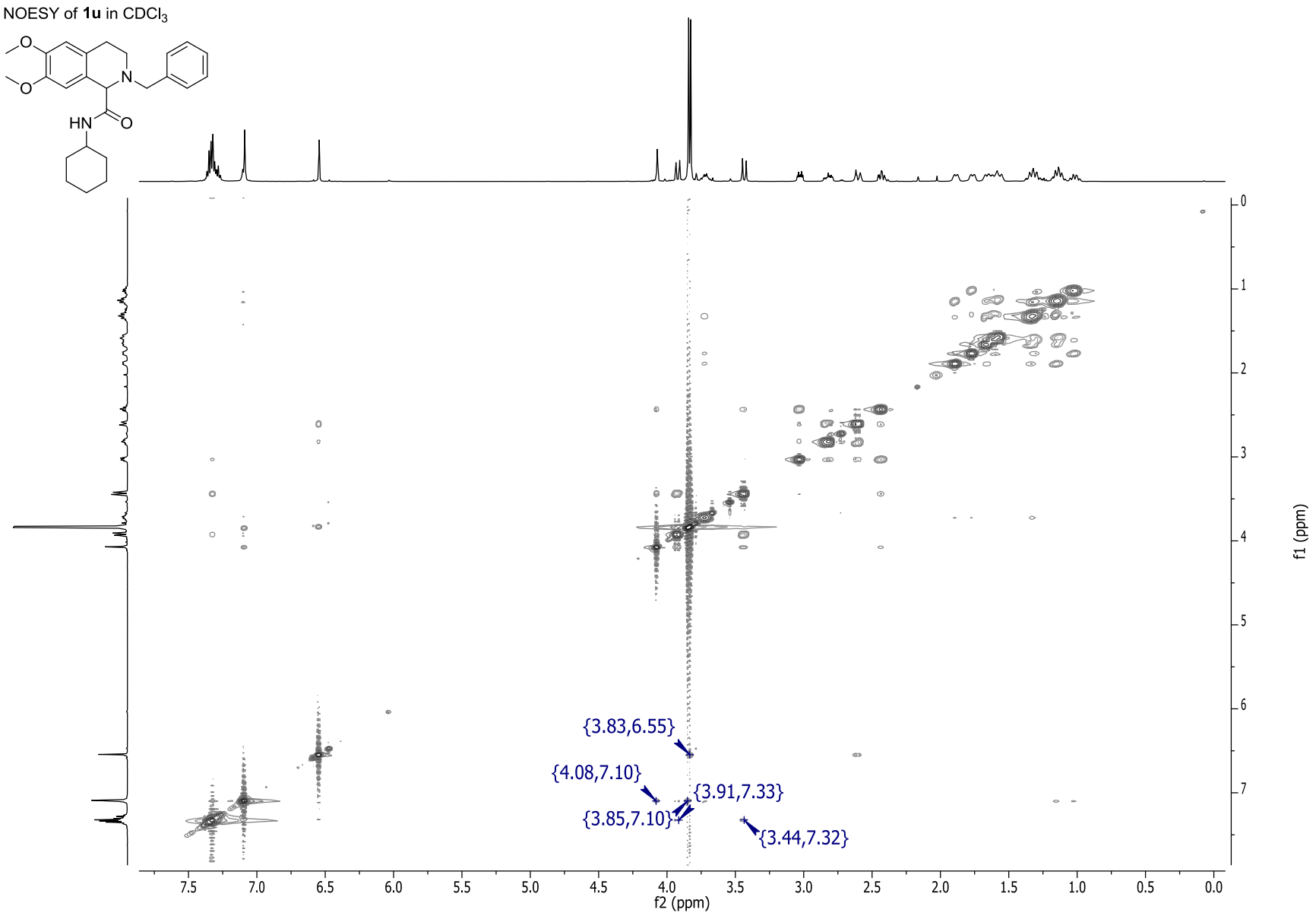

172.61
134.28
133.12
128.46
127.52
126.81
126.33
77.49
77.24
76.98
68.47
50.32
47.79
46.54
33.21
33.04
29.49
25.78
25.00
24.89
12.64
13C NMR of 3 in CDCl3
N
HN
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


9.613
9.595
8.444
8.433
8.106
8.093
7.826
7.823
7.809
7.764
7.754
7.707
7.704
7.694
7.691
7.688
7.678
7.674
7.673
7.670
7.659
7.656
7.653
7.642
7.639
7.260
4.027
4.019
4.010
2.087
2.080
2.062
2.055
1.811
1.803
1.795
1.784
1.777
1.769
1.683
1.676
1.668
1.657
1.650
1.642
1.499
1.475
1.452
1.425
1.397
1.391
1.372
1.351
1.345
1.261
1.235
$^1$H NMR of **4** in $CDCl_3$
N
HN
O
0.91
0.91
0.90
0.88
0.87
1.80
1.02
1.91
2.12
1.00
3.76
1.04
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)


165.39
148.90
140.36
137.61
130.61
128.70
128.18
127.27
126.94
124.34
77.52
77.27
77.02
48.51
33.30
25.90
25.18
$^{13}$C NMR of **4** in $CDCl_3$
N
HN
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

GCOSY of **1u** in $CDCl_3$




NOESY of **1u** in $CDCl_3$
O
O
N
HN
O
{3.83,6.55}
{4.08,7.10}
{3.91,7.33}
{3.85,7.10}
{3.44,7.32}
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
f2 (ppm)
0
1
2
3
4
5
6
7
f1 (ppm)