

**An Efficient and Scalable One-Pot Double Michael Addition-
Dieckmann Condensation for the Synthesis of 4,4-
Disubstituted Cyclohexane β -Keto Esters**

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Supporting Information

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General Information

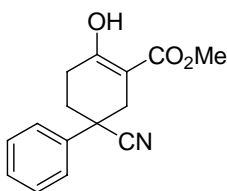
Commercial grade reagents were used without further purification. Purification of reaction products was carried out by flash chromatography using silica gel (230-400 mesh). Analytical thin-layer chromatography (TLC) was performed using pre-coated glass plates and visualized with ultraviolet light. For the solid compounds melting points were determined using a melting point apparatus and are reported as uncorrected. All ^1H NMR and ^{13}C NMR spectra were measured on a 400 MHz or 500 MHz spectrometer using either CDCl_3 or $\text{DMSO}-d_6$ as solvent. ^1H NMR chemical shifts are expressed in parts per million (δ) relative to CHCl_3 ($\delta = 7.26$) and DMSO ($\delta = 2.50$); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to CHCl_3 ($\delta = 77.0$) and DMSO ($\delta = 39.5$); Coupling constants in ^1H NMR spectra are expressed in Hertz.

General procedure A for the cyclization reaction (1.2 equiv. of *t*-BuOK):

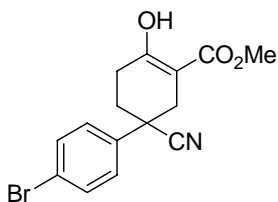
To a solution of arylacetonitrile or methyl arylacetate (1.0 equiv.) and methyl acrylate (2.0 equiv.) in THF (0.37 M) was added solid *t*-BuOK (1.2 equiv.). After being stirred for 0.25–3 h at 25 °C, the reaction mixture was quenched with acidified with 3 N HCl and extracted with CH₂Cl₂ (×3). The organic layers were combined, dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Purification of the crude product by flash chromatography on silica gel provided the title compounds.

General procedure B for the cyclization reaction (3.0 equiv. of *t*-BuOK):

To a solution of arylacetonitrile or methyl arylacetate (1.0 equiv.) and methyl acrylate (2.0 equiv.) in THF (0.37 M) was added solid *t*-BuOK (3.0 equiv.). After being stirred for 0.25–3 h at 25 °C, the reaction mixture was acidified with aqueous 3 N HCl and extracted with CH₂Cl₂ (×3). The organic layers were combined, dried with Na₂SO₄, filtered, and concentrated *in vacuo*. Purification of the crude product by flash chromatography on silica gel provided the title compounds.



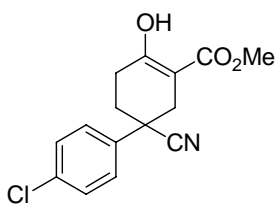
4-Phenyl-4-cyano-2-carbomethoxycyclohexanone (1a): Prepared according to general procedure **A**, 73%; Prepared according to general procedure **B**, 82%; White solid; Analytical data for **1a**: mp 96.2–97.8 °C; ¹H NMR (500 MHz, CDCl₃) δ 12.28 (s, 1 H), 7.53 (d, *J* = 8.3 Hz, 2 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.38 (dt, *J* = 8.3, 1.2 Hz, 1 H), 3.80 (s, 3 H), 3.03 (d, *J* = 16.1 Hz, 1 H), 2.85 (m, 1 H), 2.71 (dd, *J* = 16.1, 1.0 Hz, 1 H), 2.52 (m, 1 H), 2.32 (ABXY, *J*_{AB} = 13.2, *J*_{AX} = 6.1, *J*_{AY} = 3.1 Hz, 1 H) 2.24 (ABXY, *J*_{AB} = 13.2, *J*_{BX} = 11.9, *J*_{BY} = 5.6 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) 171.8, 170.7, 139.4, 129.1, 128.3, 125.6, 122.0, 95.0, 51.7, 41.2, 34.8, 31.5, 27.1; IR (neat, cm⁻¹) 2800-3100, 1660, 1617, 1443, 1354, 1291, 1219; MS (ESI) 256.0 [M-H]⁻; Anal. Calcd. for C₁₅H₁₅NO₃: C, 70.02; H, 5.88; N, 5.44; Found: C, 70.02; H, 5.88; N, 5.45.



4-(4-Bromophenyl)-4-cyano-2-carbomethoxycyclohexanone (1b): Prepared according to general procedure **A**, 88%; Prepared

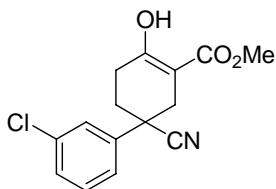
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according to general procedure **B**, 82%; Beige solid; Analytical data for **1b**: mp 161-165 °C; ¹H NMR (500 MHz, CDCl₃) δ 12.25 (s, 1 H), 7.55 (d, *J* = 8.6 Hz, 2 H), 7.38 (d, *J* = 8.6 Hz, 2 H), 3.78 (s, 3 H), 2.99 (d, *J* = 16.1 Hz, 1 H), 2.86-2.78 (m, 1 H), 2.65 (d, *J* = 16.1 Hz, 1 H), 2.49 (m, 1 H), 2.26 (m, 1 H), 2.08 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 170.5, 138.3, 132.3, 127.4, 122.5, 121.5, 94.8, 51.8, 40.9, 34.7, 31.5, 27.0; IR (neat, cm⁻¹) 2916, 2850, 1746, 1722, 1660, 1614, 1444, 1292, 1222, 808; LRMS (ESI): *m/z* = 336.1, 338.1 [M+H]⁺; Anal. Calcd. for C₁₅H₁₄BrNO₃: C, 53.59; H, 4.20; N, 4.17; Br, 23.77. Found: C, 53.42; H, 4.20; N, 4.08; Br, 23.58.



4-(4-Chlorophenyl)-4-cyano-2-carbomethoxycyclohexanone

(1c): Prepared according to general procedure **A**, 87%; Prepared according to general procedure **B**, 82%; White solid; Analytical data for **1c**: mp 150-152 °C; ¹H NMR (500 MHz, CDCl₃) δ 12.25 (s, 1 H), 7.44 (d, *J* = 8.6 Hz, 2 H), 7.39 (d, *J* = 8.6 Hz, 2 H), 3.78 (s, 3 H), 2.99 (d, *J* = 16.1 Hz, 1 H), 2.81 (m, 1 H), 2.64 (d, *J* = 16.1, Hz, 1 H), 2.50 (ddd, *J*=18.9, 5.4, 2.3 Hz, 1 H); 2.26 (m, 1 H), 2.08 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 171.8, 170.5, 137.8, 134.4, 129.3, 127.1, 121.6, 94.8, 51.8, 40.8, 34.7, 31.5, 27.0; IR (neat, cm⁻¹) 2947, 2900, 1660, 1617, 1439, 1291, 1280, 1220, 823, 752; LRMS (ESI): *m/z* = 292.1 [M+H]⁺; Anal. Calcd. for C₁₅H₁₄ClNO₃: C, 61.76; H, 4.78; N, 4.68; Cl, 12.15. Found: C, 61.58; H, 4.77; N, 4.68; Cl, 12.26.

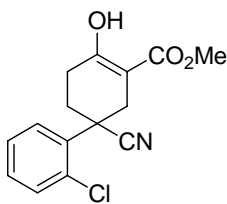


4-(3-Chlorophenyl)-4-cyano-2-carbomethoxycyclohexanone

(1d): Prepared according to general procedure **A**, 87%; Prepared according to general procedure **B**, 85%; White solid; Analytical data for **1d**: mp 130-133 °C; ¹H NMR (500 MHz, CDCl₃) δ 12.25 (s, 1 H), 7.50 (m, 1 H), 7.32 - 7.41 (m, 3 H), 3.78 (s, 3 H), 2.99 (d, *J* = 16.4 Hz, 1 H), 2.77 - 2.86 (m, 1 H), 2.64 (d, *J* = 16.1, 1 H), 2.50 (ddd, *J* = 16.1, 5.6, 2.4 Hz, 1 H), 2.29 (m, 1 H), 2.20 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 171.8, 170.5, 141.3, 135.1, 130.4, 128.7, 126.0, 124.0, 121.4, 94.8, 51.8, 41.1, 34.8, 31.4, 27.0; IR (neat, cm⁻¹) 2952, 2237, 1657, 1442, 1295, 1278, 1221, 755; LRMS (ESI): *m/z* = 292.1 [M+H]⁺; Anal. Calcd. for

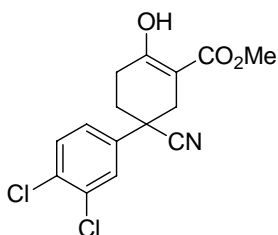
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C₁₅H₁₄ClNO₃: C, 61.76; H, 4.78; N, 4.68; Cl, 12.15. Found: C, 61.80; H, 4.83; N, 4.80; Cl, 12.14.



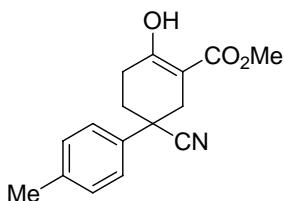
4-(2-Chlorophenyl)-4-cyano-2-carbomethoxycyclohexanone (1e):

Prepared according to general procedure **A**, 85%; Prepared according to general procedure **B**, 83%; White solid; Analytical data for **1e**: mp 119-122 °C; ¹H NMR (500 MHz, CDCl₃) δ 12.24 (s, 1 H), 7.48 (m, 1 H), 7.43 (m, 1 H), 7.31 (m, 2 H), 3.79 (s, 3 H), 3.34 (d, *J* = 14.7 Hz, 1 H), 2.81 (m, 2 H), 2.54 - 2.38 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 171.7, 170.5, 134.7, 133.4, 132.1, 129.7, 127.4, 120.5, 94.4, 51.7, 39.6, 31.8, 29.3, 26.6; IR (neat, cm⁻¹) 3421, 2359, 2341, 1663, 1617, 1443, 1265, 734, 703; LRMS (ESI): *m/z* = 292.1 [M+H]⁺; Anal. Calcd. for C₁₅H₁₄ClNO₃: C, 61.76; H, 4.84; N, 4.80; Cl, 12.15. Found: C, 61.73; H, 4.81; N, 4.82; Cl, 12.00.



4-(3,4-Dichlorophenyl)-4-cyano-2-carbomethoxycyclohexanone (1f):

Prepared according to general procedure **A**, 84%; Prepared according to general procedure **B**, 81%; White solid; Analytical data for **1f**: mp 116-119 °C; ¹H NMR (500 MHz, CDCl₃) δ 12.24 (s, 1 H), 7.59 (d, *J* = 2.2 Hz, 1 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 7.35 (dd, *J* = 8.4, 2.2 Hz, 1 H), 3.78 (s, 3 H), 2.99 (d, *J* = 16.1 Hz, 1 H), 2.86 - 2.76 (m, 1 H), 2.62 (d, *J* = 15.9 Hz, 1 H), 2.51 (m, 1 H), 2.27 (m, 1 H), 2.16 (m, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 171.5, 170.3, 139.4, 133.3, 132.7, 130.9, 127.8, 125.0, 121.0, 94.6, 51.7, 40.6, 34.6, 31.3, 26.9; IR (neat, cm⁻¹) 3367, 3056, 2946, 1662, 1620, 1447, 1273, 1224, 736; LRMS (ESI): *m/z* = 326.0, 328.0 [M+H]⁺; Anal. Calcd. for C₁₅H₁₃Cl₂NO₃: C, 55.23; H, 4.02; N, 4.29; Cl, 21.74. Found: C, 54.90; H, 4.00; N, 4.25; Cl, 22.07.

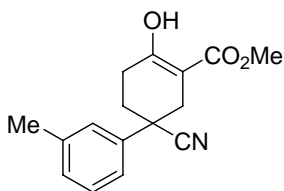


4-(4-Methylphenyl)-4-cyano-2-carbomethoxycyclohexanone (1g):

Prepared according to general procedure **A**, 89%; Prepared according to general procedure **B**, 86%; White solid; Analytical

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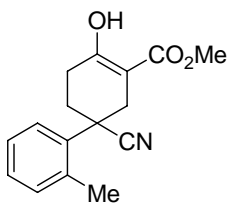
data for **1g**: mp 113-116 °C; ^1H NMR (500 MHz, CDCl_3) δ 12.26 (s, 1 H), 7.39 (d, $J = 8.3$ Hz, 2 H), 7.23 (d, $J = 8.3$ Hz, 2 H), 3.78 (s, 3 H), 3.00 (d, $J = 16.3$ Hz, 1 H), 2.83 (m, 1 H), 2.67 (d, $J = 16.1$ Hz, 1 H), 2.50 (m, 1 H), 2.37 (s, 3 H), 2.27 (m, 1 H), 2.22 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.8, 170.7, 138.2, 136.3, 129.8, 125.5, 122.2, 95.0, 51.8, 40.8, 34.8, 31.6, 27.1, 21.0; IR (neat, cm^{-1}) 3023, 2954, 1661, 1618, 1443, 1288, 1269, 1241, 1223, 814, 754; LRMS (ESI): $m/z = 272.0$ $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_3$: C, 70.83; H, 6.32; N, 5.16;. Found: C, 70.76; H, 6.31; N, 5.13.



4-(3-Methylphenyl)-4-cyano-2-carbomethoxycyclohexanone

(1h): Prepared according to general procedure **A**, 86%; Prepared according to general procedure **B**, 92%; White solid; Analytical data for **1h**: mp 150-152 °C; ^1H NMR (500 MHz, CDCl_3) δ

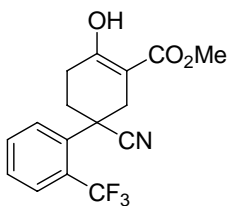
12.26 (s, 1 H), 7.30 (m, 3 H), 7.17 (m, 1 H), 3.78 (s, 3 H), 3.00 (d, $J = 16.1$ Hz, 1 H), 2.87 - 2.79 (m, 1 H), 2.68 (d, $J = 16.3$ Hz, 1 H), 2.52 (m, 1 H) 2.42 (s, 3 H), 2.25 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.9, 170.7, 139.3, 138.9, 129.1, 128.9, 126.4, 122.5, 122.1, 95.1, 51.8, 41.2, 34.9, 31.5, 27.2, 21.6; IR (neat, cm^{-1}) 3017, 2952, 1657, 1617, 1442, 1292, 1234, 1214, 750; LRMS (ESI): $m/z = 272.0$ $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.87; H, 6.31; N, 5.18.



4-(2-Methylphenyl)-4-cyano-2-carbomethoxycyclohexanone (1i):

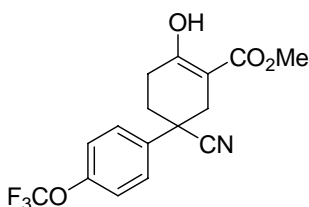
Prepared according to general procedure **B**, 76%; White solid; Analytical data for **1i** : mp 119-122 °C; ^1H NMR (400 MHz, CDCl_3)

δ 12.24 (s, 1 H), 7.24 (m, 4 H), 3.81 (s, 3 H), 3.23 (d, $J = 16.2$ Hz, 1 H), 2.82 (m, 1 H), 2.70 (s, 3 H), 2.66 (d, $J = 16.4$ Hz, 1 H), 2.45 (m, 2 H), 2.32 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.8, 170.3, 136.6, 136.0, 133.0, 128.3, 126.6, 125.2, 121.6, 94.7, 51.7, 38.8, 33.0, 30.5, 26.8, 21.2; IR (neat, cm^{-1}) 2954, 1662, 1620, 1443, 1293, 1272, 1220, 759, 727; LRMS (ESI): $m/z = 272$ $[\text{M}+\text{H}]^+$; Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.81; H, 6.32; N, 5.17



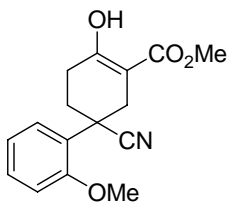
4-(2-Trifluoromethylphenyl)-4-cyano-2-carbomethoxycyclohexanone (1j): Prepared according to general procedure **A**, 80%; Prepared according to general procedure **B**, 84%; White solid; Analytical data for **1j**: mp 113-115 °C ¹H NMR (500

MHz, CDCl₃) δ 12.23 (s, 1 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.60 (m, 1 H), 7.52 (m, 1 H), 3.79 (s, 3 H), 3.20 (d, *J* = 16.6 Hz, 1 H), 2.88-2.79 (m, 2 H), 2.48-2.39 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 170.5, 136.3, 132.5, 129.3, 128.9, 128.2, 125.4, 123.2, 120.9, 94.7, 51.7, 40.2, 34.6, 31.1, 27.0; IR (neat, cm⁻¹) 3017, 2952, 1659, 1617, 1443, 1302, 1275, 1215, 1120, 751; LRMS (ESI): *m/z* = 326.0 [M+H]⁺; Anal. Calcd. for C₁₆H₁₄F₃NO₃: C, 59.08; H, 4.34; N, 4.31; F, 17.52. Found: C, 59.00; H, 4.33; N, 4.23; Cl, 17.28.



4-((Trifluoromethoxy)phenyl)-4-cyano-2-carbomethoxycyclohexanone (1k): Prepared according to general procedure **A**, 91%; Colorless oil; Analytical data for

1k: ¹H NMR (500 MHz, CDCl₃) δ 12.3 (s, 1 H), 7.55 (d, *J* = 8.8 Hz, 2 H), 7.28 (d, *J* = 8.8 Hz, 2 H), 7.98 (s, 1 H), 3.79 (s, 3 H), 3.03 (d, *J* = 15.9 Hz, 1 H), 2.89–2.80 (m, 1 H), 2.66 (d, *J* = 15.9 Hz, 1 H), 2.56–2.48 (m, 1 H), 2.33–2.27 (m, 1 H), 2.24–2.18 (m, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 170.9, 149.5, 148.0, 138.3, 127.7 (2C), 121.9 (2C), 121.9, 121.9, 95.2, 52.2, 41.2, 35.3, 31.9, 27.4; IR (neat): ν 1663, 1624, 1508, 1444, 1257, 1218, 1166; MS (ESI) 342 [M+H]⁺; Anal. Calcd for C₁₆H₁₄F₃NO₄: C, 56.31; H, 4.13; N, 4.10. Found: C, 56.46; H, 4.12; N, 4.13.

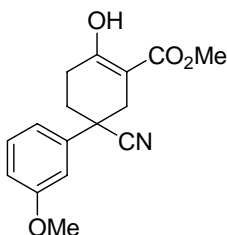


4-(2-Methoxyphenyl)-4-cyano-2-carbomethoxycyclohexanone (1l): Prepared according to general procedure **B**, 76%; Pale yellow solid; Analytical data for **1l**: mp 92-94 °C; ¹H NMR (500 MHz,

CDCl₃) δ 12.25 (s, 1 H), 7.36 (m, 2 H), 7.00 (m, 2 H), 3.96 (s, 3 H), 3.81 (s, 3 H), 3.19 (d, *J* = 16.4 Hz, 1 H), 2.80 (m, 2 H), 2.41 (m, 3 H). ¹³C NMR (125 MHz, CDCl₃) δ 172.5, 171.2, 157.9, 130.1, 126.9, 122.4, 121.3, 112.7, 99.9, 95.3, 56.1, 51.7, 38.6, 32.4, 29.5, 27.1; IR (cm⁻¹) 3054, 2949, 1660, 1618, 1441, 1293, 1245, 1217;

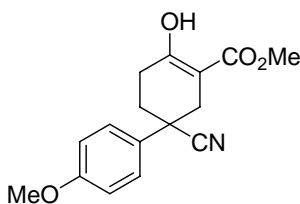
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MS (ESI) 288; $[M+H]^+$; Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89, H, 5.96, N, 4.88; found C, 66.98, H, 6.14, N, 4.78.



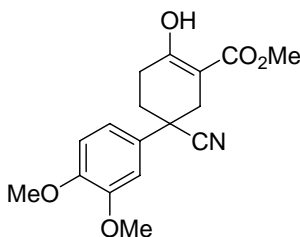
4-(3-Methoxyphenyl)-4-cyano-2-carbomethoxycyclohexanone

(1m): Prepared according to general procedure **B**, 87%; Pale yellow solid; Analytical data for **1m**: mp 97-101 °C 1H NMR (500 MHz, $CDCl_3$) δ 12.25 (s, 1 H), 7.34 (t, $J = 7.3$ Hz, 1 H), 7.08 (d, $J = 7.8$ Hz, 1 H), 7.05 (t, $J = 2.1$ Hz, 1 H), 6.89 (dd, $J = 8.3, 2.4$ Hz, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.01 (d, $J = 16.1$ Hz, 1 H), 2.83 (m, 1 H), 2.68 (dd, $J = 16.3, 1.3$ Hz, 1 H), 2.50 (ddd, $J = 18.9, 5.6, 2.4$ Hz, 1 H), 2.29 (m, 1 H), 2.20 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 171.0, 160.5, 141.2, 130.6, 122.3, 118.2, 112.6, 110.2, 95.4, 55.6, 52.2, 41.6, 35.2, 31.8, 27.6; IR (cm^{-1}) 2996, 2949, 2836, 1659, 1608, 1585, 1442, 1292, 1238, 1217, 1195; MS (ESI) 288 $[M+H]^+$; Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89, H, 5.96, N, 4.88; found C, 66.88, H, 5.95, N, 4.86.



4-(4-Methoxyphenyl)-4-cyano-2-

carbomethoxycyclohexanone (1n): Prepared according to general procedure **B**, 85%; Pale yellow oil; Analytical data for **1n**: 1H NMR (500 MHz, $CDCl_3$) δ 12.24 (s, 1 H), 7.42 (m, 2 H), 6.94 (m, 2 H), 3.83 (s, 3 H), 3.78 (s, 3 H), 2.99 (d, $J = 16.1$ Hz, 1 H), 2.81 (m, 1 H), 2.65 (d, $J = 16.3$ Hz, 1 H), 2.48 (ddd, $J = 18.8, 5.6, 2.9$ Hz, 1 H), 2.28 (m, 1 H), 2.17 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 171.1, 159.8, 131.6, 127.21, 122.7, 122.7, 114.8, 110.0, 104.3, 95.4, 55.7, 52.2, 40.7, 35.2, 32.1, 27.5; IR (cm^{-1}) 3012, 2952, 2838, 1660, 1615, 1514, 1443, 1293, 1253, 1221, 1186, 1032, 829; MS (ESI) 288 $[M+H]^+$; Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89, H, 5.96, N, 4.88; found C, 66.88, H, 5.95, N, 4.86.



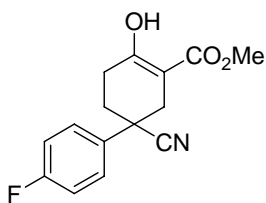
4-(3,

4-Dimethoxyphenyl)-4-cyano-2-

carbomethoxycyclohexanone (1o): Prepared according to general procedure **A**, 65%; Prepared according to general procedure **B**, 90%; Pale yellow solid; Analytical data for **1o**: mp

Supporting Information

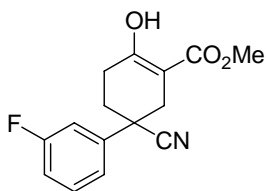
123-126 °C; ^1H NMR (500 MHz, CDCl_3) δ 12.23 (s, 1 H), 7.03 (m, 2 H), 6.86 (d, $J = 8.8$ Hz, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.76 (s, 3 H), 2.98 (d, $J = 16.4$ Hz, 1 H), 2.87-2.78 (m, 1 H), 2.67-2.61 (m, 1 H), 2.48 (ddd, $J = 18.8, 5.4, 2.4$ Hz, 1 H), 2.29-2.23 (m, 1 H), 2.16 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.8, 170.6, 149.2, 148.9, 131.6, 122.1, 117.6, 111.2, 109.2, 94.9, 55.9, 51.7, 40.7, 34.8, 31.6; IR (neat, cm^{-1}) 3483, 2369, 2330, 1662, 1617, 1519, 1444, 1265, 1220, 735; LCMS (ESI): $m/z = 318.1$ $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.17; H, 6.07; N, 4.40.



4-(4-Fluorophenyl)-4-cyano-2-carbomethoxycyclohexanone

(1p): Prepared according to general procedure **B**, 76%; White solid; Analytical data for **1p**: mp 97.3-99.1°C; ^1H NMR (CDCl_3 , 400 MHz) δ 12.26 (s, 1 H), 7.54 (dd, $J = 5.2, 8.8$ Hz, 2 H), 7.12 (dd, $J = 8.8, 8.8$ Hz, 2 H), 3.80 (s, 3 H), 3.02 (d, $J = 16.4$ Hz, 1 H), 2.83 (m, 1 H), 2.66 (d, $J = 16.4$ Hz, 1 H), 2.51-2.46 (m, 1 H), 2.35-2.26 (m, 2 H), 2.25-2.15 (m, 1 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 172.2, 170.9, 163.8, 161.8, 135.5, 127.9, 127.8, 122.5, 116.4, 95.3, 52.2, 41.0, 35.28, 32.1, 27.5; IR (neat, cm^{-1}) 1662 (st), 1220(st); M/S (ESI) 293.0 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{FNO}_3$: C, 65.45; H, 5.13; N, 5.09. Found: C, 65.40; H, 5.15; N, 5.22.

Large scale procedure for the synthesis of 1p: To a solution of 4-fluorophenylacetonitrile (50 g, 370 mmol) and methyl acrylate (66 mL, 741 mmol) in THF (1 L) at 0 °C was added solid *t*-BuOK (50 g, 444 mmol) portionwise, then warmed to 25 °C. After being stirred for 1 h at 25 °C, the reaction mixture was quenched with aqueous 3 N HCl (1.5 L) and extracted with 10% MeOH/ CH_2Cl_2 ($\times 3$). The organic layers were combined, dried with Na_2SO_4 , filtered, and concentrated *in vacuo* to afford the crude product 101.5 g, (white solid, >90% pure by NMR). This material was not subjected to further purification.

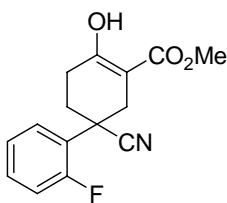


4-(3-Fluorophenyl)-4-cyano-2-carbomethoxycyclohexanone

(1q): Prepared according to general procedure **B**, 79%; White solid; Analytical data for **1q**: mp 105.5-107.3°C; ^1H NMR (CDCl_3 ,

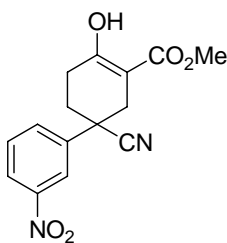
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400 MHz) δ 12.27 (s, 1 H), 7.45-7.37 (m, 1 H), 7.32 (d, $J = 7.6$ Hz, 1 H), 7.22 (ddd, $J = 2.4, 4.0, 7.6$ Hz, 1 H), 7.08 (ddd, $J = 2.0, 8.0, 8.4$ Hz, 1 H), 3.80 (s, 3 H), 3.02 (d, $J = 16.4$ Hz, 1 H), 2.99-2.79 (m, 1 H), 2.67 (d, $J = 16.4$ Hz, 1 H), 2.58-2.46 (m, 1 H), 2.35-2.26 (m, 1 H), 2.25-2.16 (m, 1 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 172.2, 170.9, 142.2, 131.2, 121.9, 121.8, 115.93, 115.8, 113.6, 113.4, 85.2, 52.2, 41.4, 35.1, 31.8, 27.4; IR (neat, cm^{-1}) 1661 (st), 1217 (st); M/S (ESI) 293.0 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{FNO}_3$: C, 65.43; H, 5.13; N, 5.09. Found: C, 65.43; H, 5.14; N, 5.17.



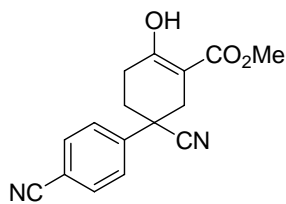
4-(2-Fluorophenyl)-4-cyano-2-carbomethoxycyclohexanone (1r):

Prepared according to general procedure **B**, 84%; White solid; Analytical data for **1r**: mp 106.5-108.2°C; ^1H NMR (CDCl_3 , 400 MHz) δ 12.26 (s, 1 H), 7.51 (ddd, $J = 1.2, 8.0, 8.0$ Hz, 1 H), 7.42-7.35 (m, 1 H), 7.25 – 7.12 (m, 2 H), 3.80 (s, 3 H), 3.10 (d, $J = 16.4$ Hz, 1 H), 2.90-2.78 (m, 2 H), 2.54-2.41 (m, 2 H), 2.40-2.30 (m, 1 H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 172.2, 170.9, 162.1, 160.1, 130.8, 127.9, 125.1, 121.3, 117.5, 117.3, 95.1, 52.2, 39.2, 32.6, 29.9, 27.2; IR (neat, cm^{-1}) 1662 (st), 1218 (st); M/S (ESI) 293.0 $[\text{M}+\text{H}]^+$. Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{FNO}_3$: C, 65.45; H, 5.13; N, 5.09. Found: C, 65.58; H, 5.21; N, 5.18.

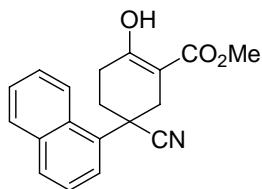


4-(3-Nitrophenyl)-4-cyano-2-carbomethoxycyclohexanone (1t):

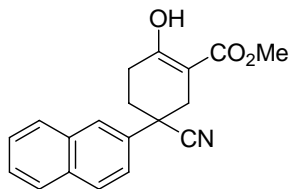
Prepared according to general procedure **B**, 6%; Pink solid; Analytical data for **1t**: mp 137-139 °C; ^1H NMR (400 MHz, CDCl_3) δ 12.27 (s, 1 H), 8.35 (s, 1 H), 8.25 (dd, $J = 8.2, 1.1$ Hz, 1 H), 7.93 (dd, $J = 7.8, 1.1$ Hz, 1 H), 7.65 (t, $J = 8.0$ Hz, 1 H), 3.80 (s, 3H), 3.07 (d, $J = 16.1$ Hz, 1 H), 2.86 (m, 1 H), 2.71 (d, $J = 16.1$ Hz, 1 H), 2.57 (m, 1 H), 2.31 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 170.4, 148.9, 141.6, 132.0, 130.3, 123.4, 120.9, 120.7, 94.6, 51.8, 41.2, 34.7, 31.5, 26.9; IR (neat, cm^{-1}) 2953, 1661, 1617, 1531, 1443, 1348, 1293, 1223, 735, 686; LRMS (ESI): $m/z = 303$ $[\text{M}+\text{H}]^+$; Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.69; H, 4.75; N, 9.16.

**4-(4-Cyanophenyl)-4-cyano-2-carbomethoxycyclohexanone**

(1u): Prepared according to general procedure **B**, 70%; White solid; Analytical data for **1u**: mp 162-164 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.11 (s, 1 H), 7.95 (d, *J* = 8.6 Hz, 2 H), 7.80 (d, *J* = 8.6 Hz, 2 H), 3.75 (s, 3 H), 2.91 (d, *J* = 15.6 Hz, 1 H), 2.72 (d, *J* = 15.6 Hz, 1 H), 2.54 (m, 2 H), 2.40 (m, 1 H), 2.29 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 170.4, 144.3, 133.0, 126.7, 121.0, 118.0, 115.0, 112.7, 94.7, 94.3, 51.9, 41.5, 34.6, 31.3, 26.9; IR (thin film, cm⁻¹) 2951, 2230, 1660, 1644, 1443, 1286, 1221, 816, 736; LRMS (ESI): *m/z* = 283 [M+H]⁺; Anal. Calcd for C₁₆H₁₄N₂O₃: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.02; H, 4.99; N, 9.91.

**4-(1-Naphthyl)-4-cyano-2-carbomethoxycyclohexanone (1v):**

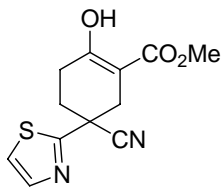
Prepared according to general procedure **B**, 84%; White solid; Analytical data for **1v**: mp 172-174 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.15 (s, 1 H), 8.50 (d, *J* = 8.6 Hz, 1 H), 8.04 (m, 2 H), 7.71 (m, 1 H), 7.59 (m, 3 H), 3.77 (s, 3 H), 3.37 (d, *J* = 16.2 Hz, 1 H), 2.79 (m, 2 H), 2.66 (m, 1 H), 2.49 (m, 2 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 171.8, 170.7, 134.6, 133.7, 130.1, 130.0, 129.9, 126.9, 126.3, 125.8, 124.3, 122.5, 95.1, 52.4, 38.5, 33.5, 30.7, 27.2; IR (neat, cm⁻¹) 1662, 1619, 1443, 1295, 1278, 1234, 1218, 800, 776; LRMS (ESI): *m/z* = 308 [M+H]⁺; Anal. Calcd for C₁₉H₁₇NO₃: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.00; H, 5.56; N, 4.51.

**4-(2-Naphthyl)-4-cyano-2-carbomethoxycyclohexanone (1w):**

Prepared according to general procedure **B**, 90%; White solid; Analytical data for **1w**: mp 132-134 °C; ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.16 (s, 1 H), 8.09 (m, 1 H), 8.02 (d, 2 H), 7.96 (m, 1 H), 7.73 (dd, *J* = 2.1, 8.7 Hz, 1 H), 7.58 (m, 2 H), 3.77 (s, 3 H), 2.99 (d, *J* = 15.9 Hz, 1 H), 2.84 (d, *J* = 15.9 Hz, 1 H), 2.69 (m, 1 H), 2.57 (m, 1 H), 2.41 (m, 2 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 171.8, 170.7, 136.9, 133.1, 132.8, 129.2, 128.5, 127.8, 127.1, 124.8, 124.1, 122.5, 95.3, 52.3, 39.4, 34.2, 30.6, 27.4; IR (neat, cm⁻¹) 1663, 1618,

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1443, 1348, 1295, 1278, 1219, 816, 720; LRMS (ESI): $m/z = 308 [M+H]^+$; Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.51; H, 5.59; N, 4.51.



4-(Thiazol-2-yl)-4-cyano-2-carbomethoxycyclohexanone (1x):

Prepared according to general procedure **A**, 82%; Yellow solid;

Analytical data for **1x**: mp 121-123 °C; 1H NMR (500 MHz, $CDCl_3$)

δ 12.27 (s, 1 H), 7.82 (d, $J = 3.2$ Hz, 1 H), δ 7.40 (d, $J = 3.2$ Hz, 1 H),

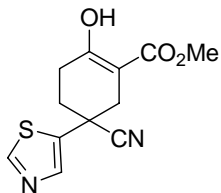
3.80 (s, 3 H), 3.20 (d, $J = 16.1$ Hz, 1 H), 2.98 (d, $J = 15.9$ Hz, 1 H) 2.81 (m, 1 H), 2.53

(m, 2 H), 2.39 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 170.8, 167.9, 143.6,

120.6, 110.4, 108.5, 100.0, 94.6, 52.2, 41.2, 34.2, 32.1, 26.9; IR (cm^{-1}) 3121, 3012, 2953,

2863, 1660, 1617, 1443, 1296, 1278, 1220; M/S (ESI) 265; $[M+H]^+$; Anal. Calcd for

$C_{12}H_{12}N_2O_3S$: C, 54.53, H, 4.58, N, 10.60; found C, 54.45, H, 4.56, N, 10.52.



4-(Thiazol-5-yl)-4-cyano-2-carbomethoxycyclohexanone (1y):

Prepared according to general procedure **A**, 88%; White solid;

Analytical data for **1y**: mp 82-83 °C; 1H NMR (500 MHz, $CDCl_3$) δ

12.3 (s, 1 H), 8.83 (s, 1 H), 7.98 (s, 1 H), 3.81 (s, 3 H), 3.17 (d, $J =$

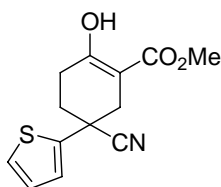
15.9 Hz, 1 H), 2.87-2.75 (m, 1 H), 2.76 (d, $J = 16.6$ Hz, 1 H), 2.55-2.43 (m, 2 H), 2.22-

2.18 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 170.7, 153.7, 141.4, 139.0, 120.8,

94.7, 52.3, 36.6, 36.1, 33.9, 27.1; IR (neat): ν 1655, 1618, 1443, 1297, 1219; MS (ESI)

265 $[M+H]^+$; Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60. Found: C,

54.45; H, 4.55; N, 10.44.



4-(Thiophen-2-yl)-4-cyano-2-carbomethoxycyclohexanone (1z):

Prepared according to general procedure **B**, 78%; White solid;

Analytical data for **1z**: mp 84-87 °C; 1H NMR (400 MHz, $CDCl_3$) δ

12.26 (s, 1 H), 7.30 (d, $J = 4.6$ Hz, 1 H), 7.19 (d, $J = 2.8$ Hz, 1 H),

7.01 (dd, $J = 5.0, 1.1$ Hz, 1 H), 3.79 (s, 3 H), 3.14 (d, $J = 16.3$ Hz, 1 H), 2.80 (m, 1 H),

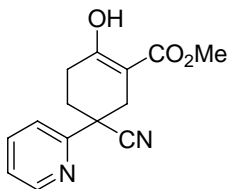
2.76 (d, $J = 15.9$ Hz, 1 H), 2.47 (m, 2 H), 2.19 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

172.1, 170.9, 143.6, 127.5, 125.7, 125.5, 121.7, 95.0, 52.3, 38.5, 36.0, 33.9, 27.3; IR (thin

film, cm^{-1}) 2951, 1660, 1620, 1443, 1296, 1277, 1217, 836, 706; LRMS (ESI): $m/z = 264$

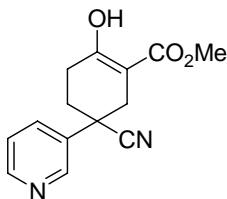
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$[M+H]^+$; Anal. Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.33; H, 4.98; N, 5.34.



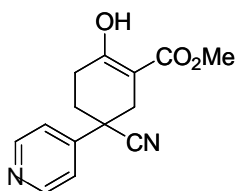
4-(Pyridin-2-yl)-4-cyano-2-carbomethoxycyclohexanone (1aa):

Prepared according to general procedure A, 87%; White solid; Analytical data for **1aa**: mp 81.2-82.2°C; 1H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1 H), 8.66 (d, $J = 4.0$ Hz, 1 H), 7.81 (dd, $J = 8.0$, 8.0 Hz, 1 H), 7.69 (d, $J = 8.0$ Hz, 1 H), 7.31 (m, 1 H), 3.80 (s, 3 H), 3.00 (br s, 2 H), 2.90-2.81 (m, 1 H), 2.59-2.43 (m, 2 H), 2.30 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 170.9, 158.0, 150.1, 137.8, 123.6, 122.1, 121.1, 95.3, 52.1, 43.9, 33.3, 30.8, 27.2; IR (CH_2Cl_2) 1660 (st), 1222 (st); M/S (ESI) 259.1 $[M+H]^+$. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.07; H, 5.44; N, 10.76.



4-(Pyridin-3-yl)-4-cyano-2-carbomethoxycyclohexanone (1bb):

Prepared according to general procedure A, 82%; White solid; Analytical data for **1bb**: mp 113.8-114.4°C 1H NMR (400 MHz, $CDCl_3$) δ 12.30 (s, 1 H), 8.82 (d, $J = 2.3$ Hz, 1 H), 8.67 (d, $J = 4.7$ Hz, 1 H), 7.88 (m, 1 H), 7.41 (m, 1 H), 3.82 (s, 3 H), 3.08 (d, $J = 16.2$ Hz, 1 H), 2.86 (m, 1 H), 2.75 (d, $J = 16.2$ Hz, 1 H), 2.56 (m, 1 H), 2.35 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 170.9, 150.3, 147.5, 135.3, 134.0, 124.1, 121.4, 95.1, 52.2, 40.1, 34.9, 31.6, 27.1; IR (neat, cm^{-1}) 1660 (st), 1223 (st); M/S (ESI) 259.1 $[M+H]^+$. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.10; H, 5.48; N, 10.80.

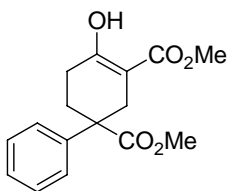


4-(Pyridin-4-yl)-4-cyano-2-carbomethoxycyclohexanone (1cc):

Prepared according to general procedure A, 86%; White solid; Analytical data for **1cc**: mp 130.7-131.1°C; 1H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1 H), 8.72 (d, $J = 6.0$ Hz, 2 H), 8.46 (d, $J = 6.0$ Hz, 2 H), 3.82 (s, 3 H), 3.03 (d, $J = 16.2$ Hz, 1 H), 2.84 (m, 1 H), 2.70 (d, $J = 16.2$ Hz, 1 H), 2.55 (m, 1 H), 2.32-2.21 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 170.8, 152.5, 151.4, 148.4, 123.6, 121.0, 95.0, 52.3, 41.5, 34.6, 31.5, 27.2; IR (neat, cm^{-1}) 1660,

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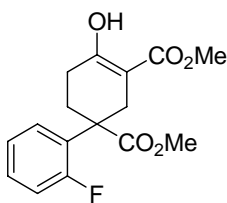
1222; M/S (ESI) 259.1 [M+H]⁺. Anal. Calcd for C₁₄H₁₄N₂O₃: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.11; H, 5.46; N, 10.74.



4-Phenyl-2, 4-biscarbomethoxycyclohexanone (11a): Yield: 89%;

Colorless oil; Analytical data for **11a**: ¹H NMR (400 MHz, CDCl₃) δ 12.14 (s, 1 H), 7.38-7.26 (m, 5 H), 3.82 (s, 3 H), 3.65 (s, 3 H), 3.10 (d, *J* = 16.1 Hz, 1 H), 2.75 (d, *J* = 16.1 Hz, 1 H), 2.48-2.39 (m, 2 H),

2.26-2.18 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 174.9, 172.5, 171.2, 141.2, 128.7, 127.2, 125.9, 95.9, 52.4, 51.6, 49.0, 30.6, 29.4, 26.6; IR (thin film, cm⁻¹) 2952, 1731, 1661, 1618, 1443, 1293, 1233, 1196, 733, 698; LRMS (ESI): *m/z* = 291 [M+H]⁺; Anal. Calcd. for C₁₆H₁₈O₅: C, 66.19; H, 6.25. Found: C, 65.04; H, 6.22.



4-(2-Fluorophenyl)-2, 4-biscarbomethoxycyclohexanone (11b):

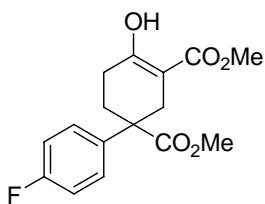
Yield: 75%; White solid. Analytical data for **11b**: mp 126-129 °C; ¹H NMR (400 MHz, CDCl₃) δ 12.13 (s, 1 H), 7.28-7.18 (m, 2 H), 7.11-7.00 (m, 2 H), 3.80 (s, 3 H), 3.67 (s, 3 H), 2.85 (br s, 2 H), 2.36-2.31

(m, 2 H), 2.28-2.25 (m, 1 H), 1.96-1.88 (m, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 175.2, 172.2, 171.4, 160.7 (d, *J* = 245 Hz), 129.0 (d, *J* = 8.6 Hz), 128.8 (d, *J* = 12.7 Hz), 128.0 (d, *J* = 4.4 Hz), 124.1 (d, *J* = 3.2 Hz), 115.9 (d, *J* = 22.6 Hz), 95.2, 52.4, 51.6, 46.7, 30.5, 28.0, 26.2; IR (thin film, cm⁻¹) 2954, 1737, 1660, 1616, 1443, 1286, 1234, 1215, 1194, 1105, 816, 754, 732; LRMS (ESI): *m/z* = 309 [M+H]⁺; Anal. Calcd for C₁₆H₁₇FO₅: C, 62.33; H, 5.56. Found: C, 62.03; H, 5.50.

Large scale procedure for the synthesis of 11b: To a solution of methyl 4-fluorophenylacetate (158 g, 940 mmol) and methyl acrylate (186 mL, 2.07 mmol) in THF (1.2 L) at 0 °C was added solid *t*-BuOK (26.4 g, 236 mmol). The reaction mixture was stirred for 15 min at 0 °C, then warmed to 25 °C. After being stirred an additional 1 h at 25 °C, the reaction was re-cooled to 0 °C and solid *t*-BuOK (100 g, 893 mmol) was added in portions. After being stirred for 1 h at 25 °C, the reaction mixture was quenched with aqueous NH₄Cl (1.5 L) and extracted with EtOAc (×3). The organic layers were combined, dried with Na₂SO₄, filtered, and concentrated *in vacuo* to afford the crude

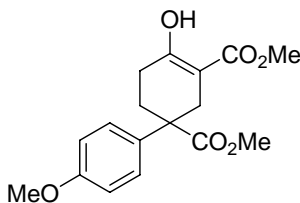
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product 285 g, (white solid, >90% pure by NMR). This material was not subjected to further purification.



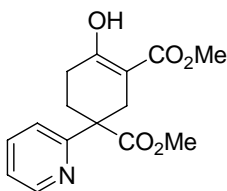
4-(4-Fluorophenyl)-2,4-biscarbomethoxycyclohexanone (11c):

Yield: 66%; White solid. Analytical data for **11c**: ^1H NMR (400 MHz, CDCl_3) δ 12.12 (s, 1 H), 7.34 (dd, $J = 8.3, 5.4$ Hz, 2 H), 7.02 (t, $J = 8.3$ Hz, 2 H), 3.81 (s, 3 H), 3.64 (s, 3 H), 3.08 (d, $J = 16.1$ Hz, 1 H), 2.72 (d, $J = 16.1$ Hz, 1 H), 2.42 (m, 2 H), 2.18 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.8, 172.4, 171.1, 163.1, 160.6, 136.9 (d, $J = 4.0$ Hz) 127.7 (d, $J = 9.0$ Hz), 115.5 (d, $J = 22.0$ Hz), 95.7, 52.2, 51.6, 48.4, 30.6, 29.5, 26.5; Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{FO}_5$: C, 62.33; H, 5.56. Found: C, 62.16; H, 5.65.



4-(4-Methoxyphenyl)-2,4-biscarbomethoxycyclohexanone (11d):

Yield: 89%; White solid; Analytical data for **11d**: mp 92-95 °C; ^1H NMR (500 MHz, CDCl_3) δ 12.12 (s, 1 H), 7.29 (d, $J = 8.8$ Hz, 2 H), 6.88 (d, $J = 8.8$ Hz, 2 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 3.65 (s, 3 H), 3.08 (dd, $J = 16.1$ Hz, 1.0 Hz, 1 H), 2.73 (d, $J = 16.1$ Hz, 1 H), 2.47-2.37 (m, 2 H), 2.24-2.16 (m, 2 H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.1, 172.4, 171.2, 158.6, 133.1, 127.0, 113.9, 95.8, 55.2, 52.3, 51.5, 48.1, 30.5, 29.5, 26.6; IR (neat, cm^{-1}) 3495, 3005, 2989, 2359, 2340, 1634, 1456, 1275, 1261, 764, 750; LCMS (ESI): $m/z = 289.1$ $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{17}\text{H}_{20}\text{O}_6$: C, 63.74; H, 6.29. Found: C, 63.64; H, 6.31.

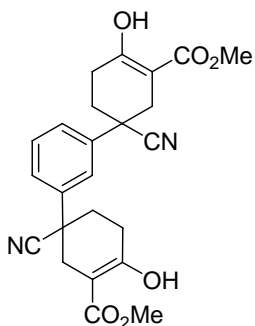


4-(Pyridin-2-yl)-2,4-biscarbomethoxycyclohexanone (11e):

Yield: 74%; Colorless oil; Analytical data for **11e**: ^1H NMR (400 MHz, CDCl_3) δ 12.08 (s, 1 H), 8.52 (d, $J = 3.8$ Hz, 1 H), 7.61 (dt, $J = 7.9, 1.8$ Hz, 1 H), 7.27 (d, $J = 8.0$ Hz, 1 H), 7.12 (dd, $J = 6.8, 5.0$ Hz, 1 H), 3.74 (s, 3 H), 3.61 (s, 3 H), 3.04 (d, $J = 16.1$ Hz, 1 H), 2.81 (d, $J = 16.1$ Hz, 1 H), 2.44-2.33 (m, 3 H), 2.19-2.13 (m, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 172.4, 171.1, 160.6, 149.2, 136.6, 122.0, 120.5, 95.6, 52.3, 52.1, 51.5, 30.0, 28.6, 26.5; IR (thin

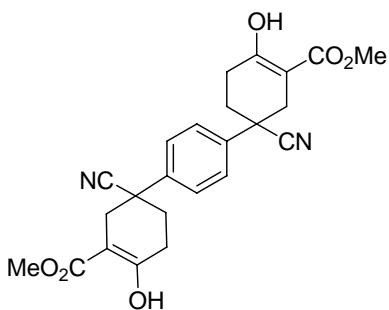
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film, cm^{-1}) 2954, 1732, 1660, 1617, 1442, 1291, 1232, 731; LRMS (ESI): $m/z = 292$ $[\text{M}+\text{H}]^+$; Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_5$: C, 61.85; H, 5.88; N 4.81. Found: C, 61.92; H, 5.90; N, 4.80.



(1,3)-Bis(4-phenyl-4-cyano-2-carbomethoxycyclohexanone)

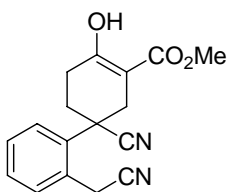
benzene (15): Yield: 63%; White solid; Analytical data for **15**: mp 164-169 °C; ^1H NMR (500 MHz, CDCl_3) δ 12.26 (s, 2 H), 7.65 (m, 1 H), 7.52 (m, 3 H), 3.79 (s, 6 H), 3.02 (d, $J = 16.1$ Hz, 2 H), 2.85 (m, 2 H), 2.68 (d, $J = 16.1$ Hz, 2 H), 2.53 (m, 2 H), 2.33-2.24 (m, 4 H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.7, 170.5, 139.6, 126.5, 121.6, 94.8, 51.8, 40.8, 34.7, 31.4, 26.9; IR (neat, cm^{-1}) 3406, 3357, 3058, 2945, 2321, 1661, 1620, 1442, 1267, 1225, 734; LRMS (ESI): $m/z = 437.1$ $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 65.73; H, 5.58; N, 6.30.



(1,4)-Bis(4-phenyl-4-cyano-2-

carbomethoxycyclohexanone) benzene (17): Yield: 59%; White solid; Analytical data for **17**: mp 200-204 °C; ^1H NMR (500 MHz, CDCl_3) δ 12.26 (s, 2 H), 7.57 (s, 4 H), 3.79 (s, 6 H), 3.02 (d, $J = 16.1$ Hz, 2 H), 2.86 (m, 2 H), 2.68 (d, $J = 16.1$ Hz, 2 H), 2.55 (m, 2 H) 2.26 (m, 4

H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.8, 170.5, 139.6, 126.5, 121.7, 94.9, 51.8, 40.9, 34.7, 31.4, 27.0; IR (neat, cm^{-1}) 3375, 3050, 2949, 2348, 1660, 1620, 1442, 1288, 1221, 733; LRMS (ESI): $m/z = 437.1$ $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 65.98; H, 5.48; N, 6.40.

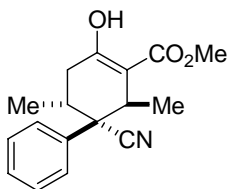


4-(2-(Cyanomethyl)phenyl)-2,4-biscarbomethoxycyclohexanone

(19): Yield: 25%; White solid; Analytical data for **19**: mp 176-180 °C; ^1H NMR (500 MHz, CDCl_3) δ 9.53 (s, 1 H), 7.50 (d, $J = 7.3$ Hz, 1 H), 7.39 (m, 1 H), 7.26 (m, 2 H), 3.67 (s, 3 H), 3.04 (m, 1 H), 2.87 (m, 1 H), 2.84-2.60 (m, 5 H) 1.73 (m, 1 H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.6, 169.0, 143.5, 137.6, 137.2, 129.5, 125.5, 122.7, 118.9, 118.8, 118.2, 51.9, 44.4, 31.8, 28.8, 28.2,

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28.1, 18.5; IR (neat, cm^{-1}) 3052, 2982, 2413, 2317, 1721, 1673, 1430, 1357, 1265, 736; LRMS (ESI): $m/z = 297.1$ $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.51; H, 5.50; N, 9.18.



4-Phenyl-4-cyano-3,5-dimethyl-2-carbomethoxycyclohexanone

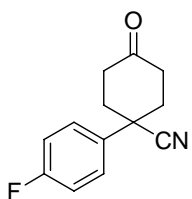
(20): pink solid. Analytical data for **20**: mp 127-130 °C; ^1H NMR (400 MHz, CDCl_3) δ 12.22 (s, 1 H), 7.29 (m, 5 H), 3.68 (s, 3 H), 2.94 (q, $J = 7.0$ Hz, 1 H), 2.72 (dq, $J = 19.2, 6.3$ Hz, 1 H), 2.59 (dd, $J = 19.2, 6.3$ Hz, 1 H), 2.41 (dd, $J = 19.2, 11.0$ Hz, 1 H), 1.02 (d, $J = 6.3$ Hz, 3 H), 0.67 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.8, 170.2, 136.1, 128.6, 128.1, 127.9, 121.7, 51.7, 51.6, 39.5, 35.5, 26.5, 17.6, 17.5; IR (thin film, cm^{-1}) 3054, 2986, 1659, 1620, 1441, 1264, 1223, 732, 703; LRMS (ESI): $m/z = 286.1$ $[\text{M}+\text{H}]^+$; Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_3$: C, 71.56; H, 6.71; N, 4.89. Found: C, 71.38; H, 6.76; N, 4.89.

General Method A for the decarboxylation reaction:

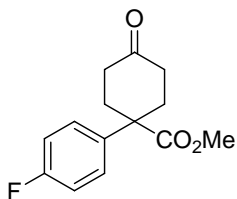
A mixture of β -keto ester (1.0 equiv.), NaCl (1.0 equiv.) and DMSO/ H_2O (100:1, 0.5 M total concentration) was heated to 150 °C for 2-6 h. The reaction was then cooled to 25 °C and diluted with H_2O and EtOAc. The aqueous layer was extracted with EtOAc ($\times 3$) and the combined organic layers were washed with brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. Purification of the crude product by flash chromatography on silica gel provided the title compounds.

General Method B for the decarboxylation reaction:

To a solution the β -keto ester (1.0 equiv.) in $\text{H}_2\text{O}/\text{THF}/\text{MeOH}$ (0.5 M total concentration) was added KOH (0.6 equiv.) and the reaction mixture was heated to 100 °C. After being stirred for 18 h at reflux, the reaction was cooled to 25 °C and diluted with water. The aqueous layer was extracted with EtOAc ($\times 3$) and the combined organic layers were washed with brine, dried with MgSO_4 , filtered, and concentrated *in vacuo*. Purification of the crude product by flash chromatography on silica gel provided the title compounds.

**4-Cyano, 4-(4-fluorophenyl)cyclohexanone (21) known compound:**

Prepared according to general method **A** using 4-(4-fluorophenyl)-4-cyano-2-carbomethoxycyclohexanone **1p** (7.0 g, 25.4 mmol), sodium chloride (1.5 g, 25.4 mmol), DMSO (50 mL) and H₂O (500 μL). Flash column chromatography on silica gel eluting with CH₂Cl₂ afforded 2.9 g of **21** (53%) as a pale yellow oil; Prepared according to general method **B** using 4-(4-fluorophenyl)-4-cyano-2-carbomethoxycyclohexanone **1p** (5.1 g, 18.0 mmol), solid KOH (311 mg, 5.56 mmol) in 2:1:1 H₂O/MeOH/THF (40 mL). Flash column chromatography on silica gel eluting with CH₂Cl₂ afforded 2.6 g of **21** (62%) as a pale yellow oil.; Analytical data for **21**: mp 80-84 °C ; ¹H NMR (500 MHz, DMSO-d₆) δ 7.39 (m, 2 H), 7.07 (m, 2 H), 2.76-2.56 (m, 2 H), 2.52-2.37 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 206.9, 163.5, 161.5, 134.5, 127.3 (*J* = 20.7 Hz), 121.1, 116.4, 116.2, 42.6, 38.6, 37.1; IR (neat, cm⁻¹) 2956, 2939, 2234, 1709, 1608, 1513, 1444, 1233, 1164, 841, 815. Anal. Calcd for C₁₃H₁₂FNO: C, 71.87; H, 5.57; N, 6.45. Found: C, 71.99; H, 5.56; N, 6.45.

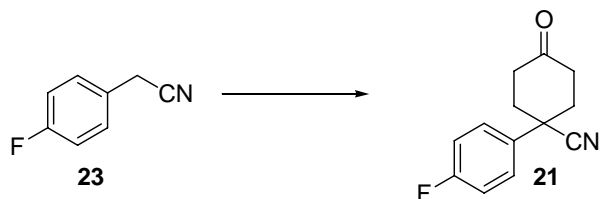
**4-Carboxymethyl, 4-(4-fluorophenyl)cyclohexanone (22) known compound:**

Prepared according to general method **A** using 4-(4-fluorophenyl)-2, 4-biscarbomethoxycyclohexanone **11c** (1.0 g, 3.25 mmol), sodium chloride (188 mg, 3.25 mmol), DMSO (6.5 mL) and H₂O (65 μL). Flash column chromatography on silica gel eluting with 9% EtOAc/hexanes afforded 610 mg of **22** (75%) as a white solid; Prepared according to general method **B** using 4-(4-fluorophenyl)-2, 4-biscarbomethoxycyclohexanone **11c** (86.7 g, 281 mmol), 1 M aqueous KOH (170 mL) in 1:1 MeOH/THF (370 mL). Flash column chromatography using a gradient elution (SiO₂, 10% to 25% EtOAc/hexanes) afforded 50 g of **22** (71%) as a white solid.; Analytical data for **22**: ¹H NMR (400 MHz, CDCl₃) δ 7.39 (ddd, *J* = 8.3, 3.2, 2.3 Hz, 2 H), 7.07 (t, *J* = 8.3, Hz, 2 H), 3.73 (s, 3H), 2.78 (m, 2 H), 2.55 (ABXY, *J*_{AB} = 16.0, *J*_{AX} = 10.5, *J*_{AY} = 5.5 Hz, 2 H) 2.43 (ABXY, *J*_{AB} = 16.6, *J*_{BX} = 15.2, *J*_{BY} = 5.5 Hz, 2 H), 2.23 (ddd, *J* = 17.6, 12.5, 5.1 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 209.9, 174.4, 163.2, 160.8, 136.7, 127.6 (d, *J* = 7.7 Hz), 115.7 (d, *J*

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= 20.7 Hz), 52.7, 49.4, 38.5, 34.2; Anal. Calcd for C₁₄H₁₅FO₃: C, 67.19; H, 6.04. Found: C, 67.14; H, 6.04.

One-pot double Michael addition–Dieckmann condensation–decarboxylation:

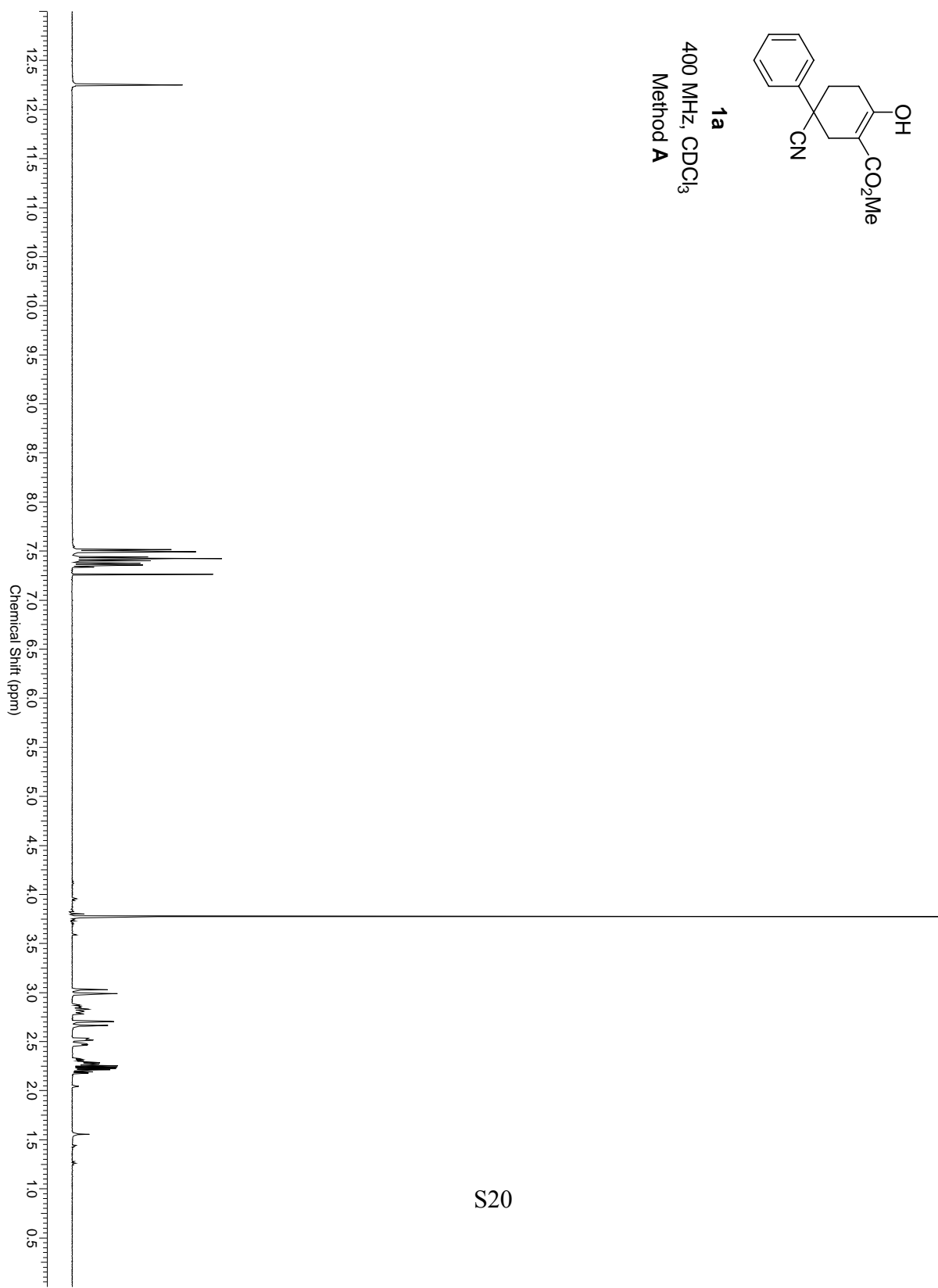


To a solution of 4-fluorophenylacetonitrile (5.0 g, 37.0 mmol) and methyl acrylate (6.6 mL, 74.0 mmol) in THF (100 mL) was added solid *t*-BuOK (5.0 g, 44.4 mmol). After being stirred for 30 min at 25 °C, the reaction mixture was diluted with H₂O (500 mL) and heated to 85 °C for 12 h. The reaction mixture was allowed to cool to 25 °C, acidified with 2 N HCl and extracted with CH₂Cl₂ (×3). The combined organic layers were washed with brine, dried with MgSO₄, and concentrated *in vacuo*. Purification of the crude product by flash chromatography using a gradient elution (SiO₂, 10% to 20% EtOAc/hexanes) afforded 5.6 g of **21** (70%) as a white solid.

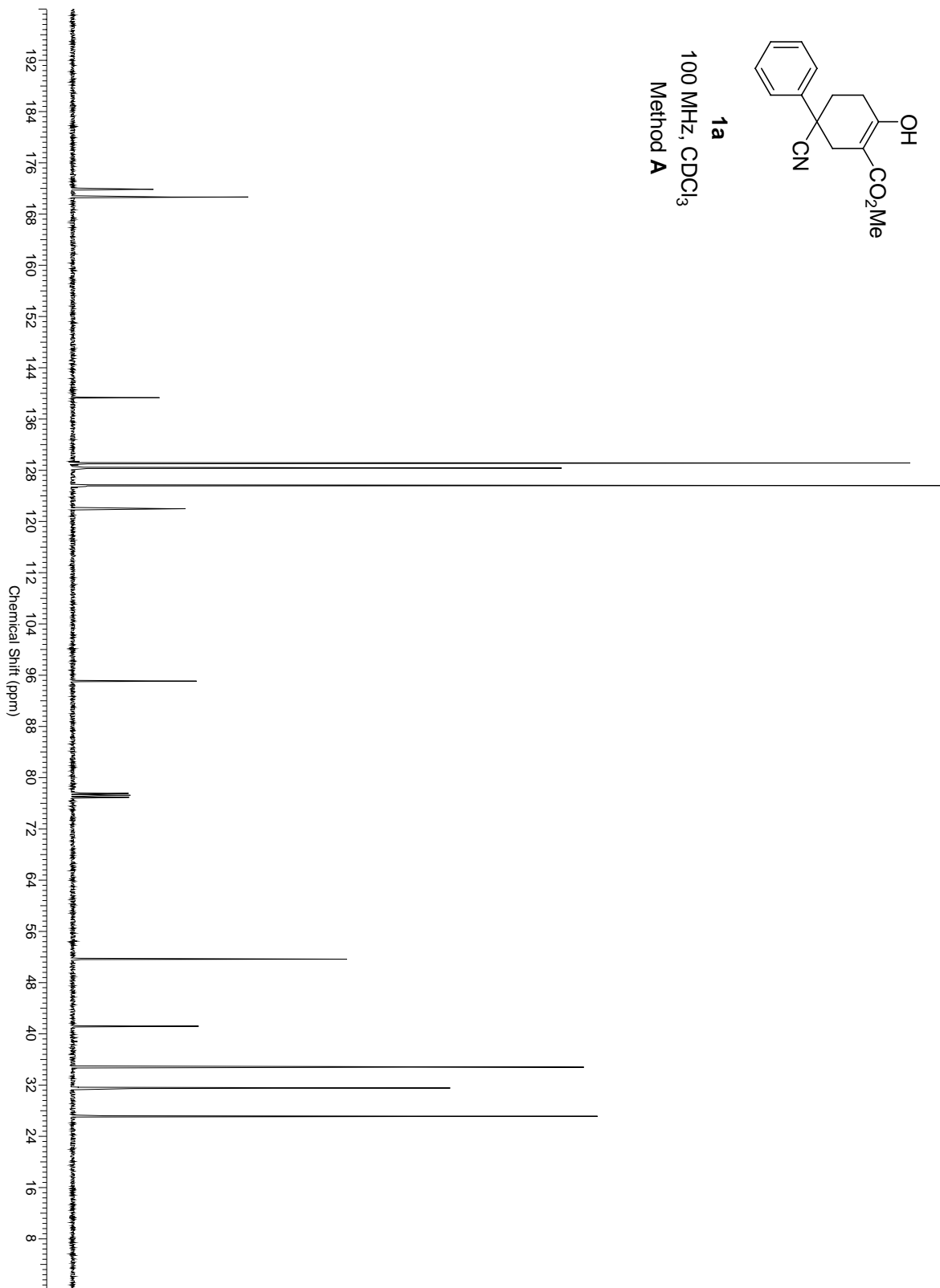


To a solution of methyl 4-fluorophenylacetate (1.0 g, 5.95 mmol) and methyl acrylate (1.1 mL, 11.9 mmol) in THF (13 mL) was added solid *t*-BuOK (800 mg, 7.1 mmol). After being stirred for 2 h at 25 °C, the reaction mixture was diluted with H₂O (65 mL) and heated to 85 °C for 5.5 h. The reaction mixture was allowed to cool to 25 °C, acidified with 2 N HCl and extracted with CH₂Cl₂ (×3). The combined organic layers were washed with brine, dried with MgSO₄, and concentrated *in vacuo*. Purification of the crude product by flash chromatography using a gradient elution (SiO₂, 10% to 25% EtOAc/hexanes) afforded 745 mg of **22** (50%) as a white solid.

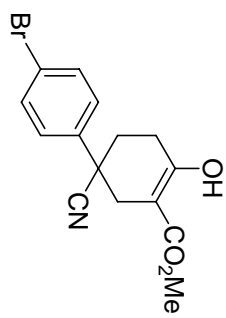
^1H and ^{13}C NMR spectra:



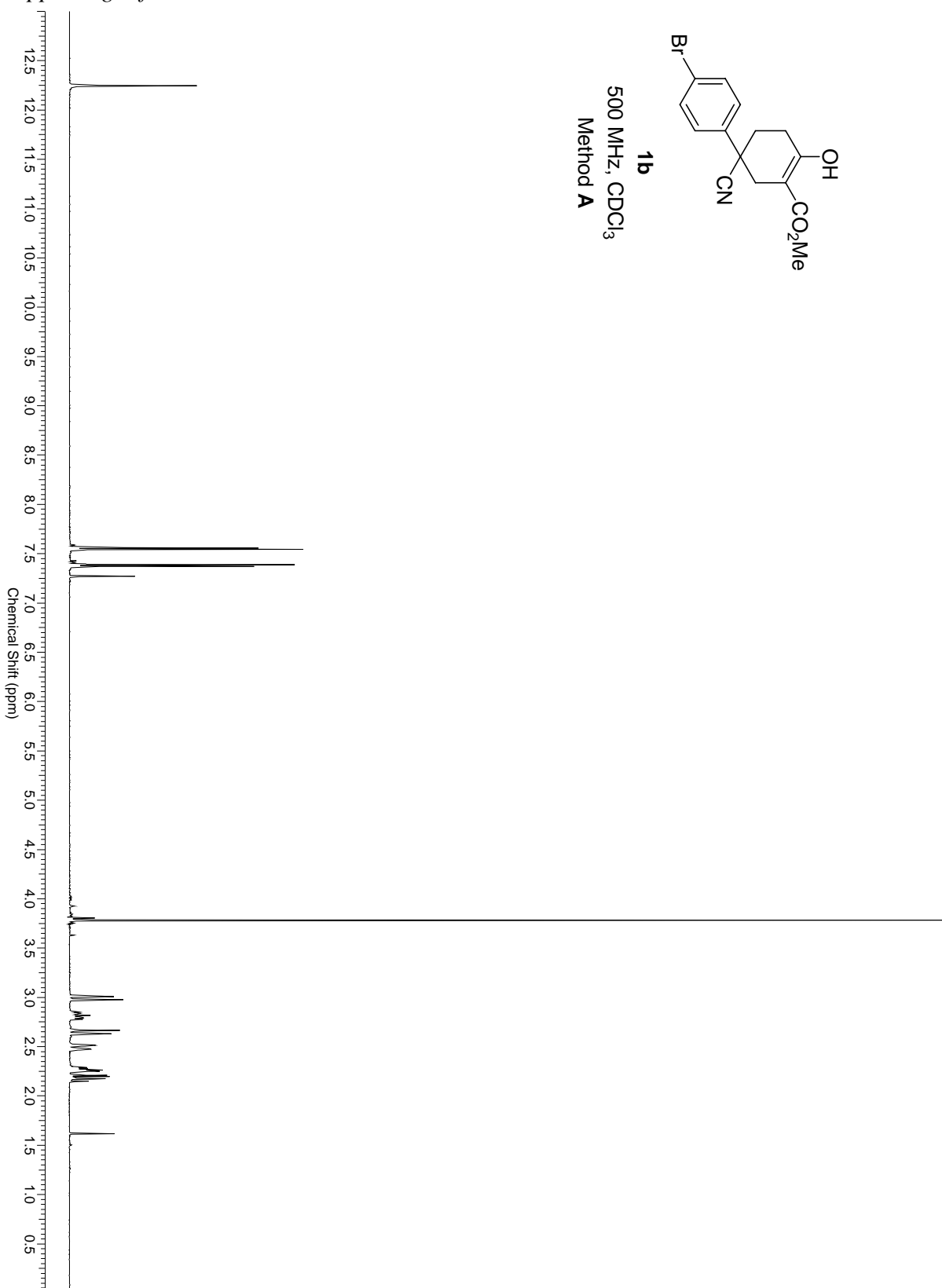
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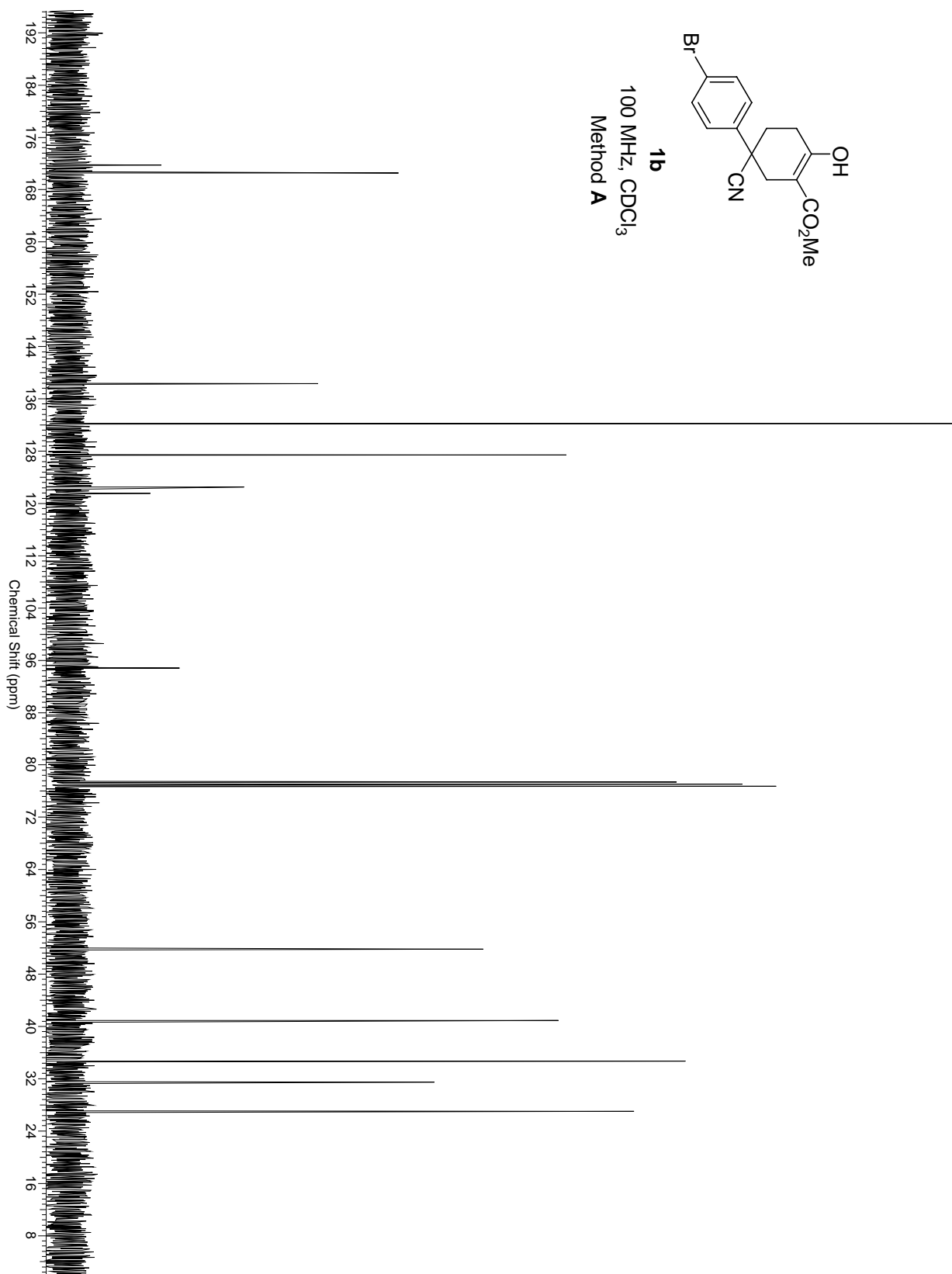
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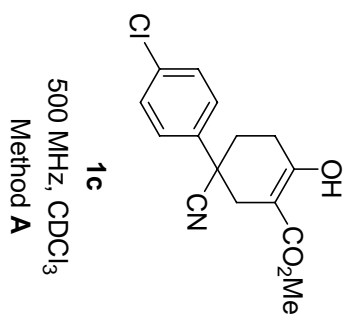
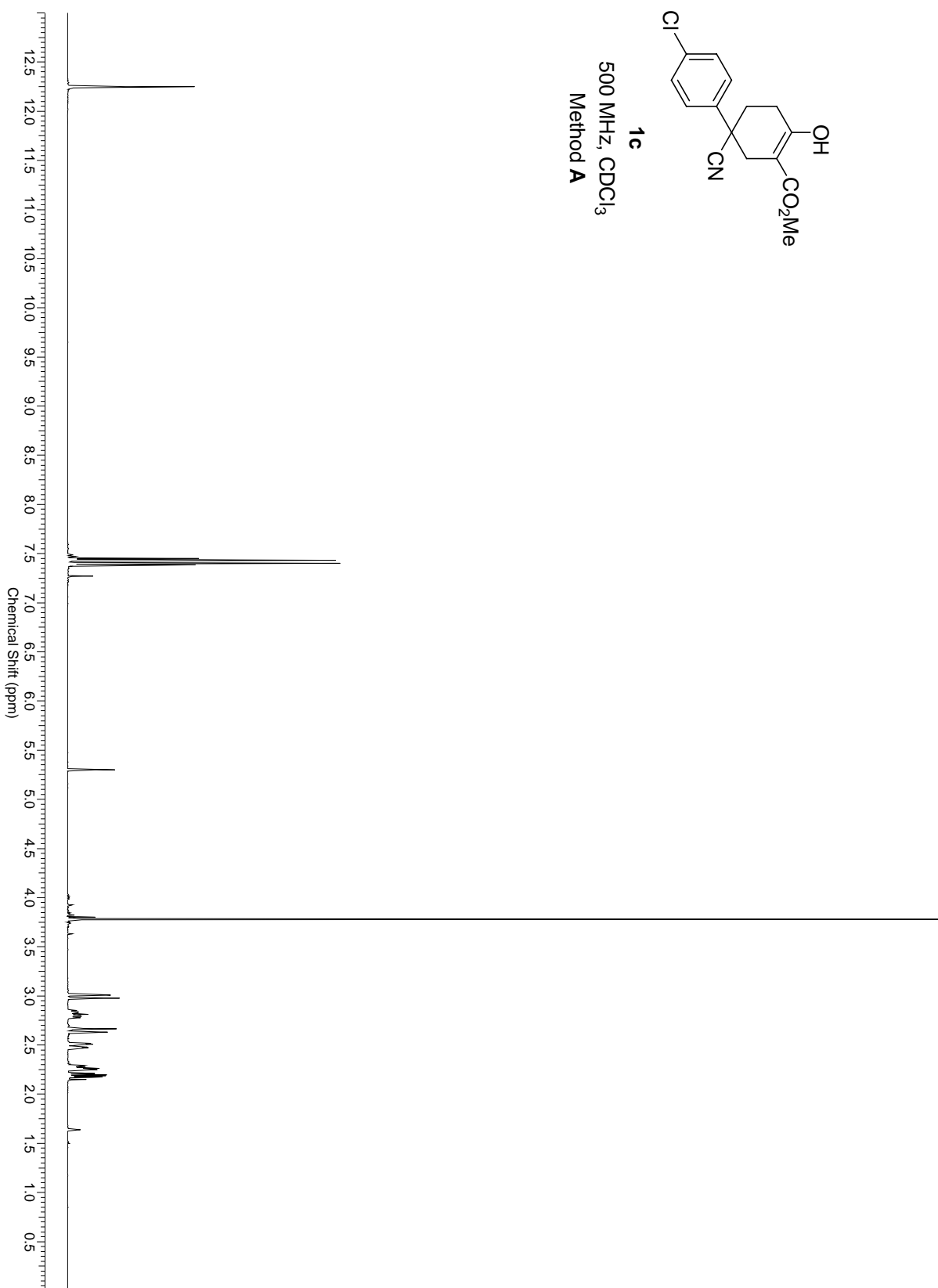
500 MHz, CDCl₃
Method A



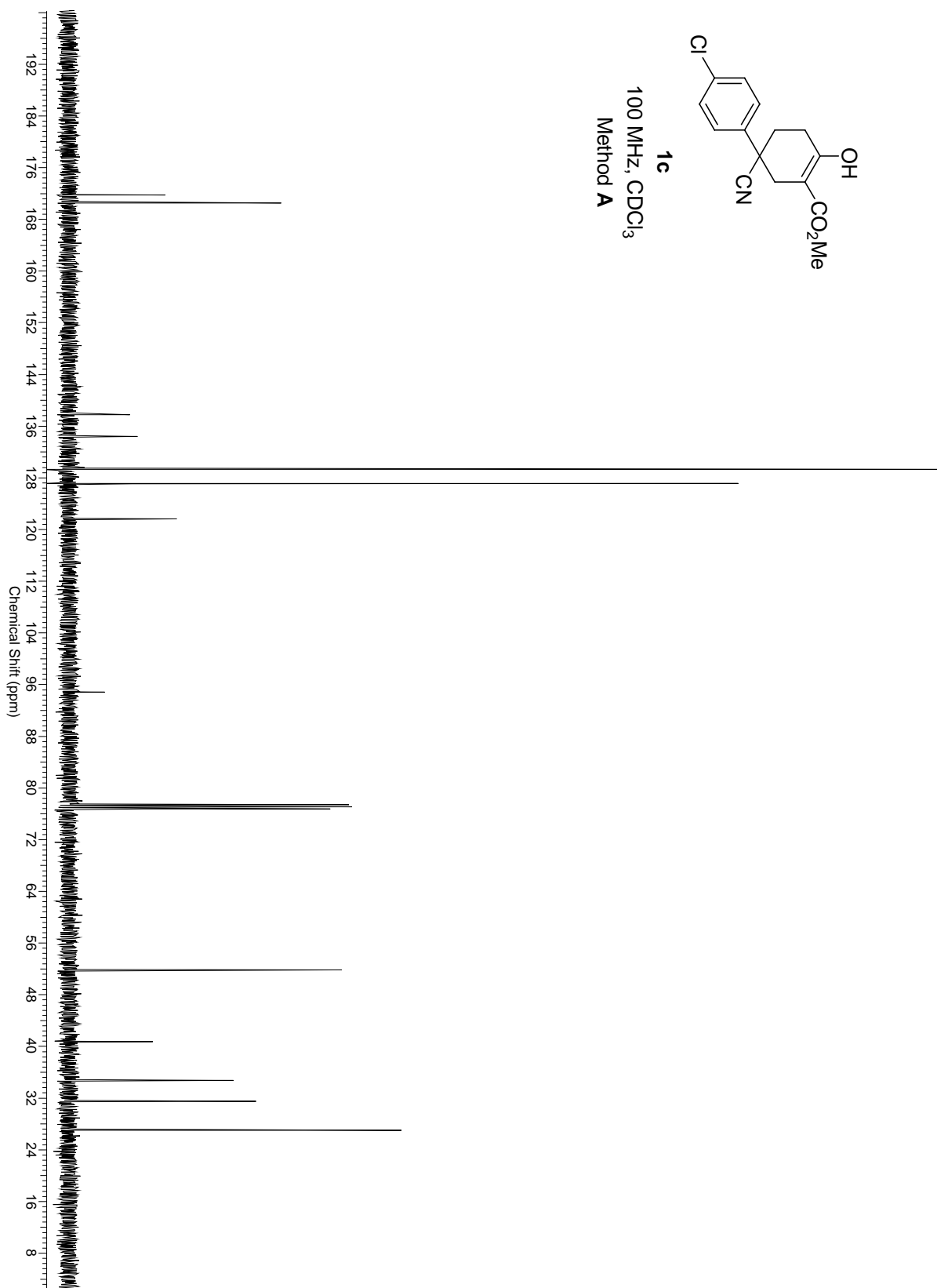
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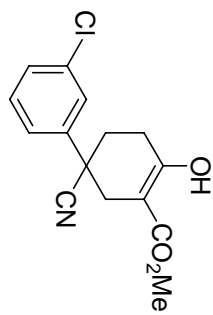
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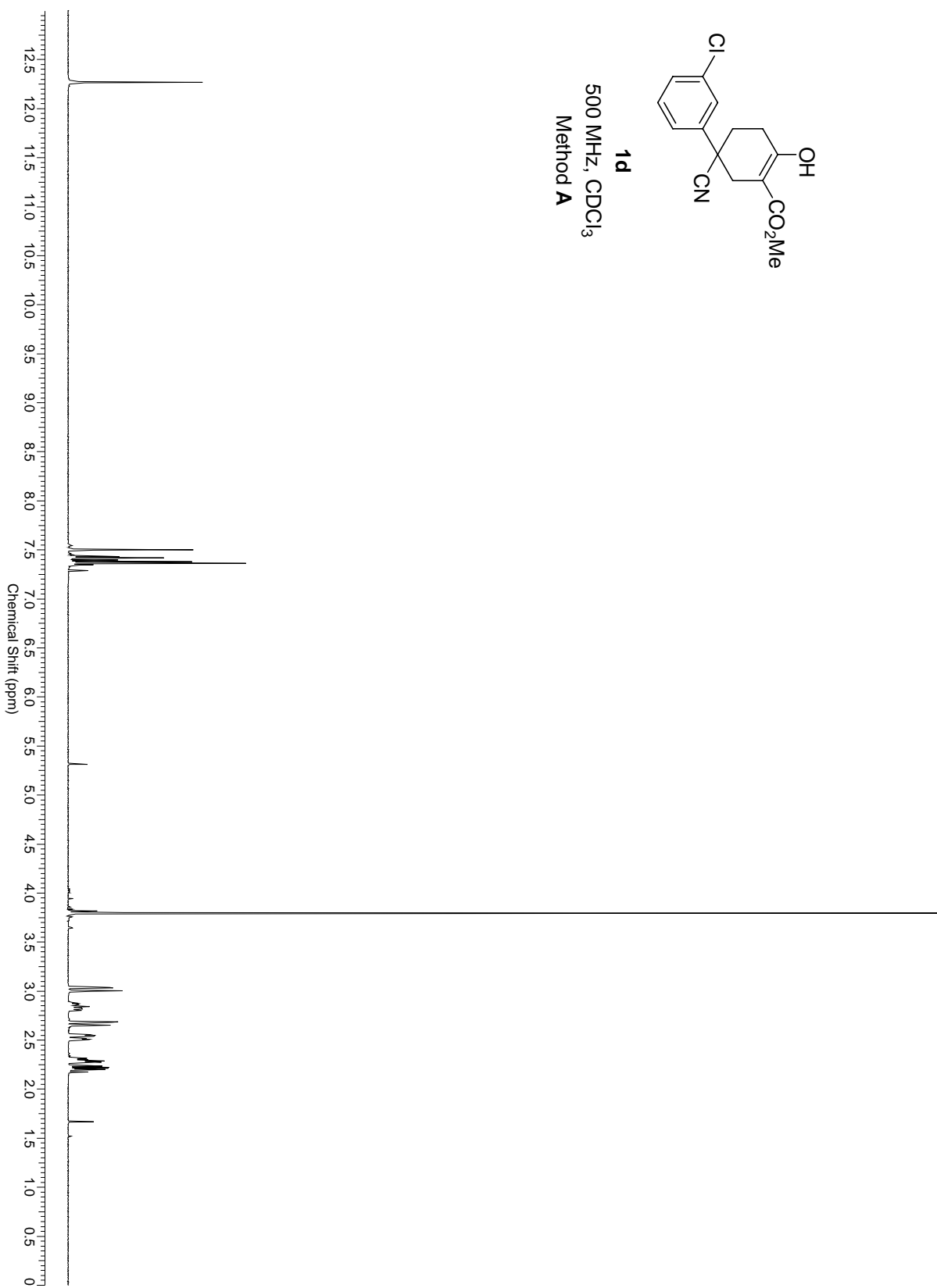
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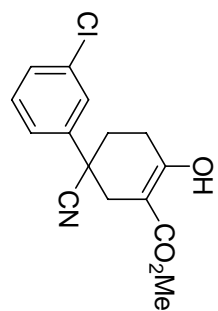
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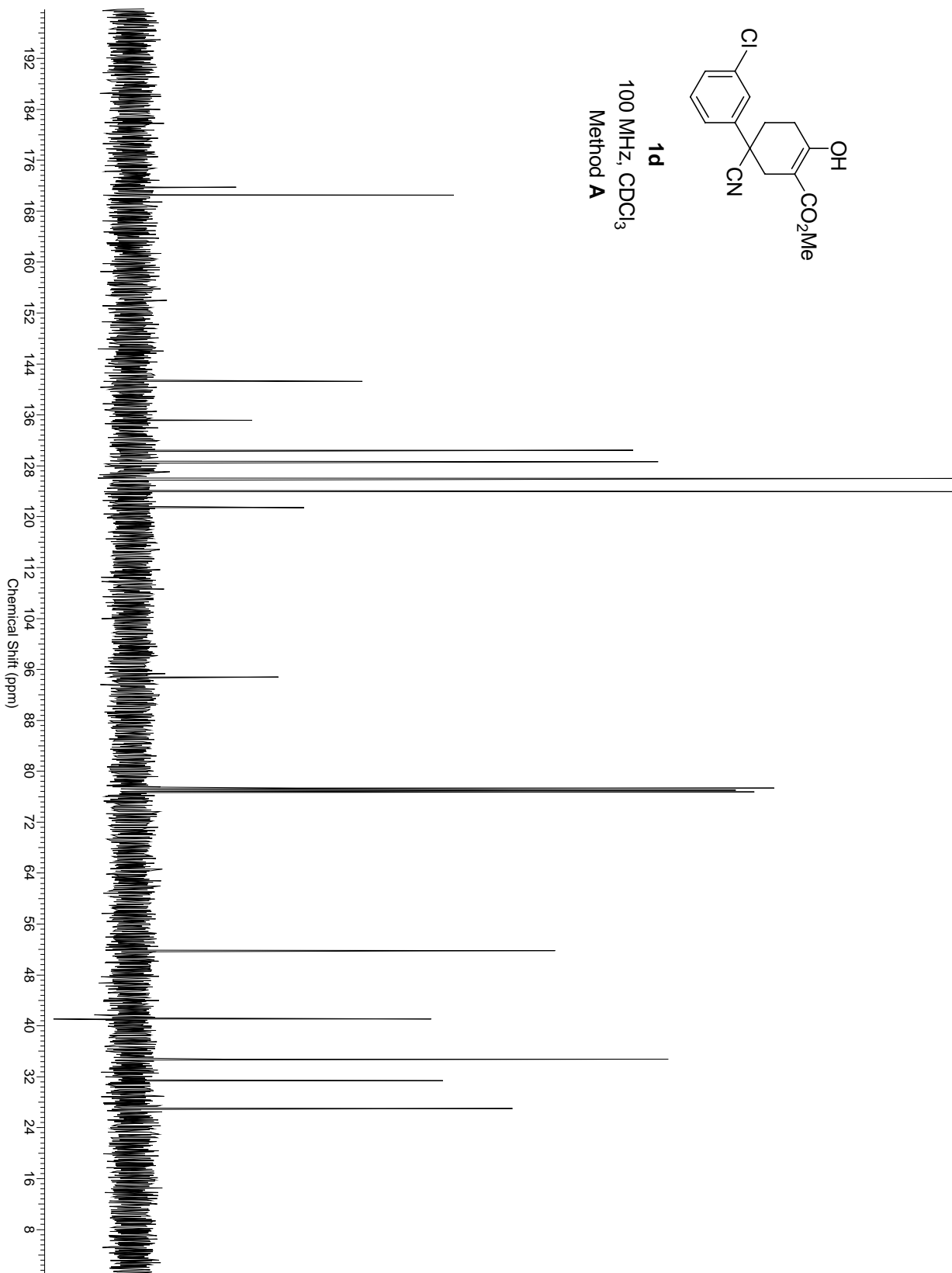
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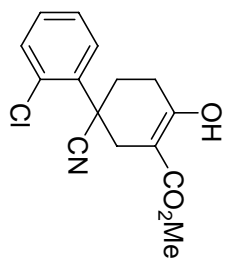
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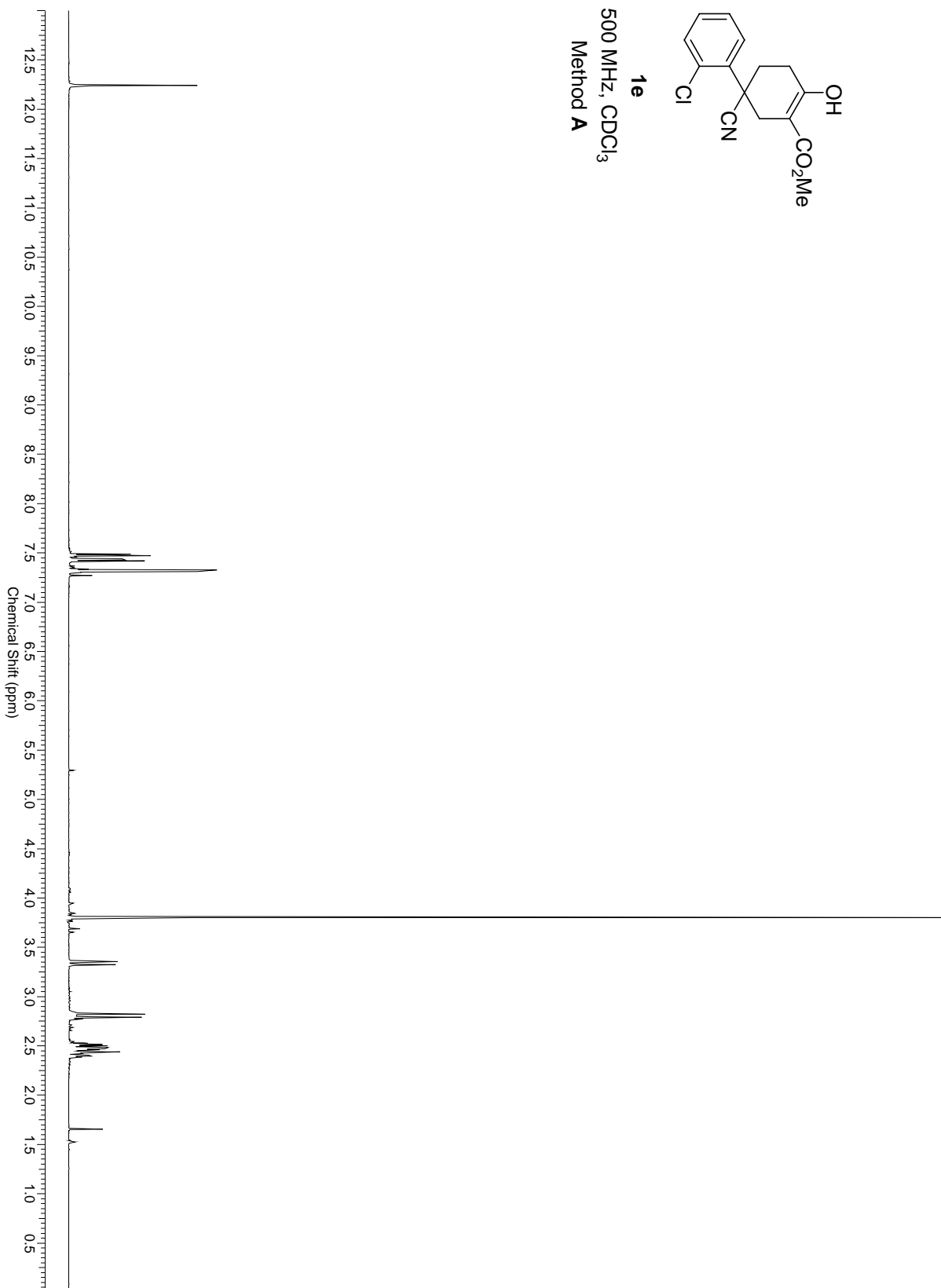
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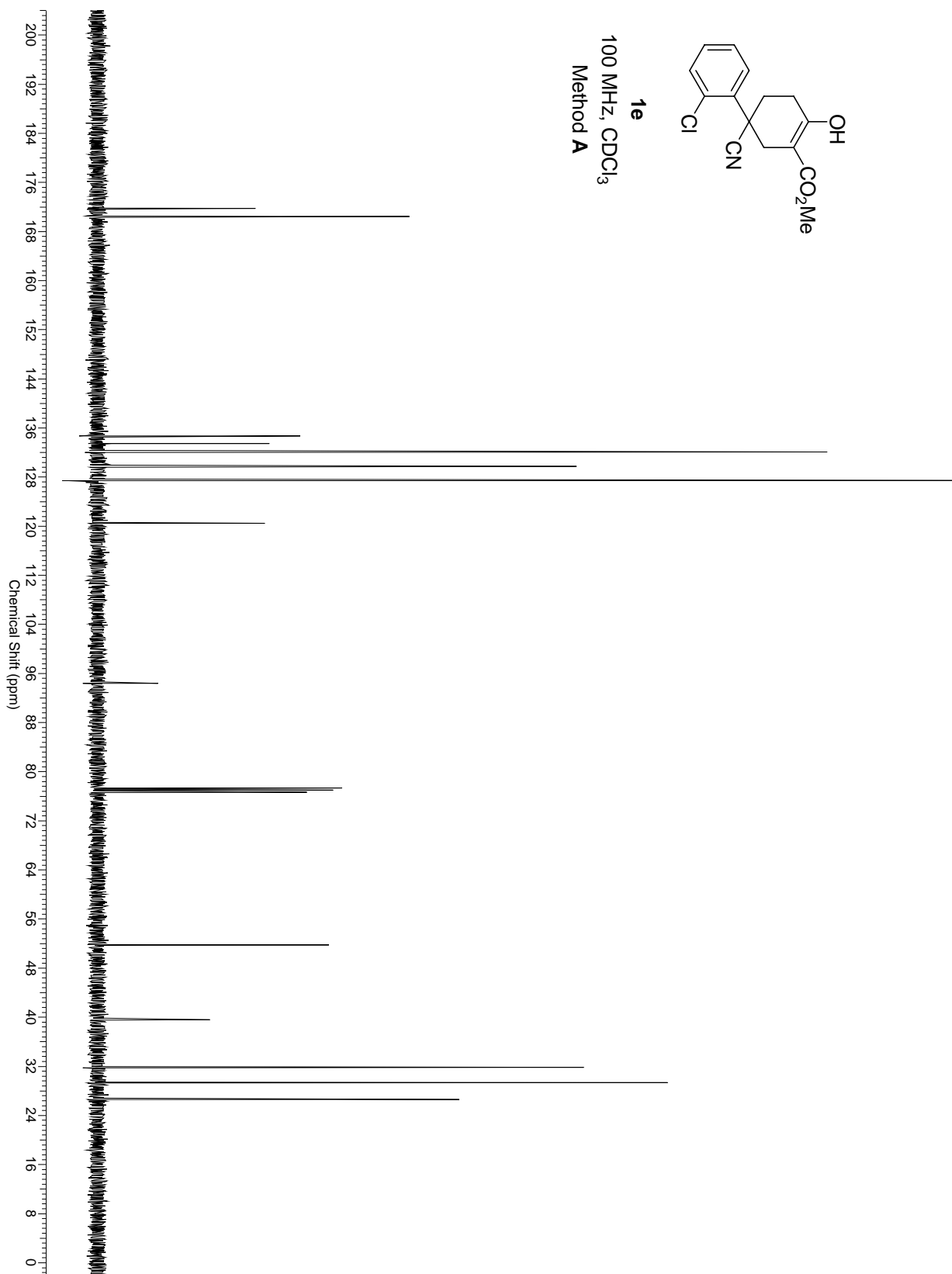
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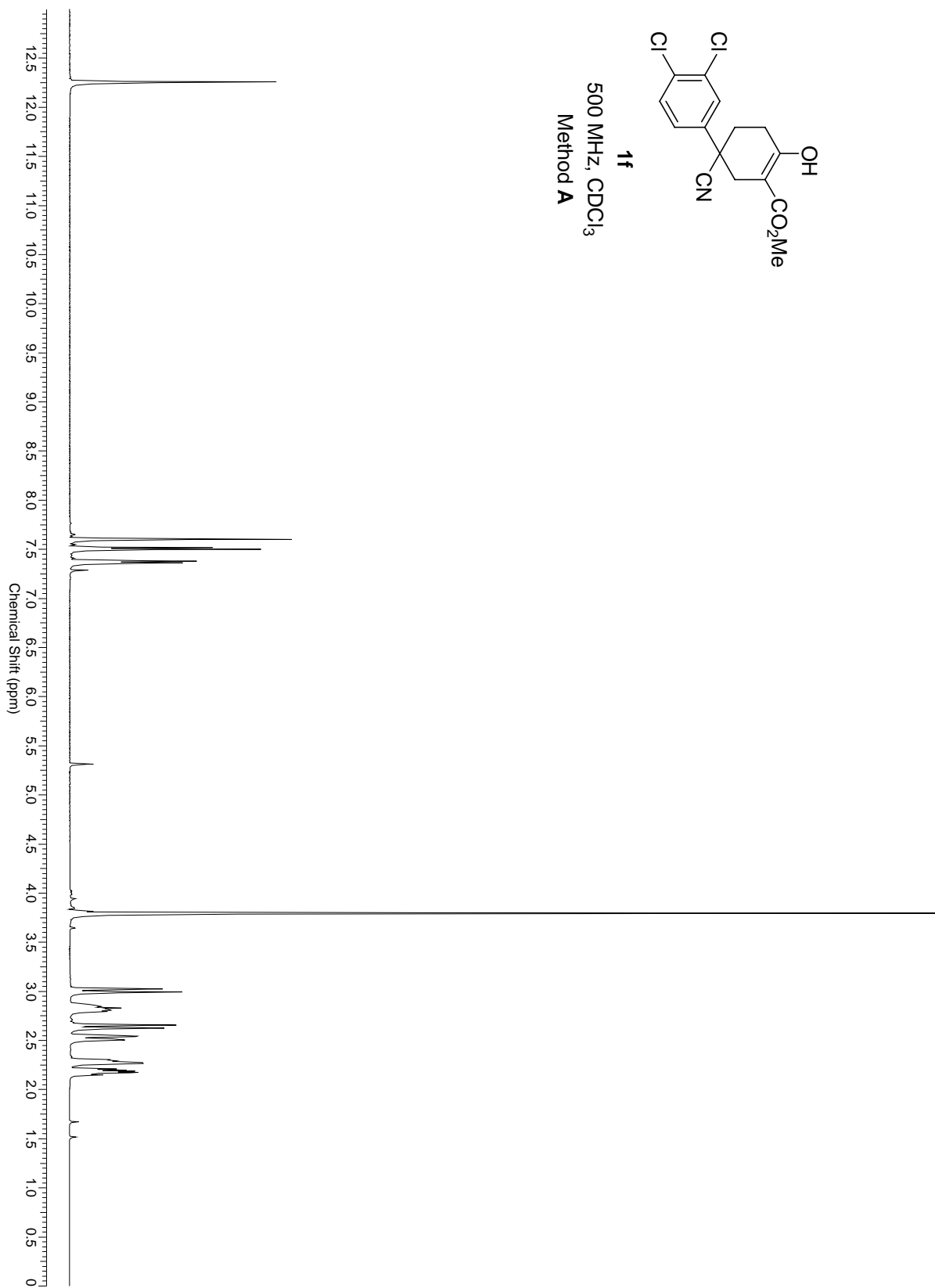
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Method A



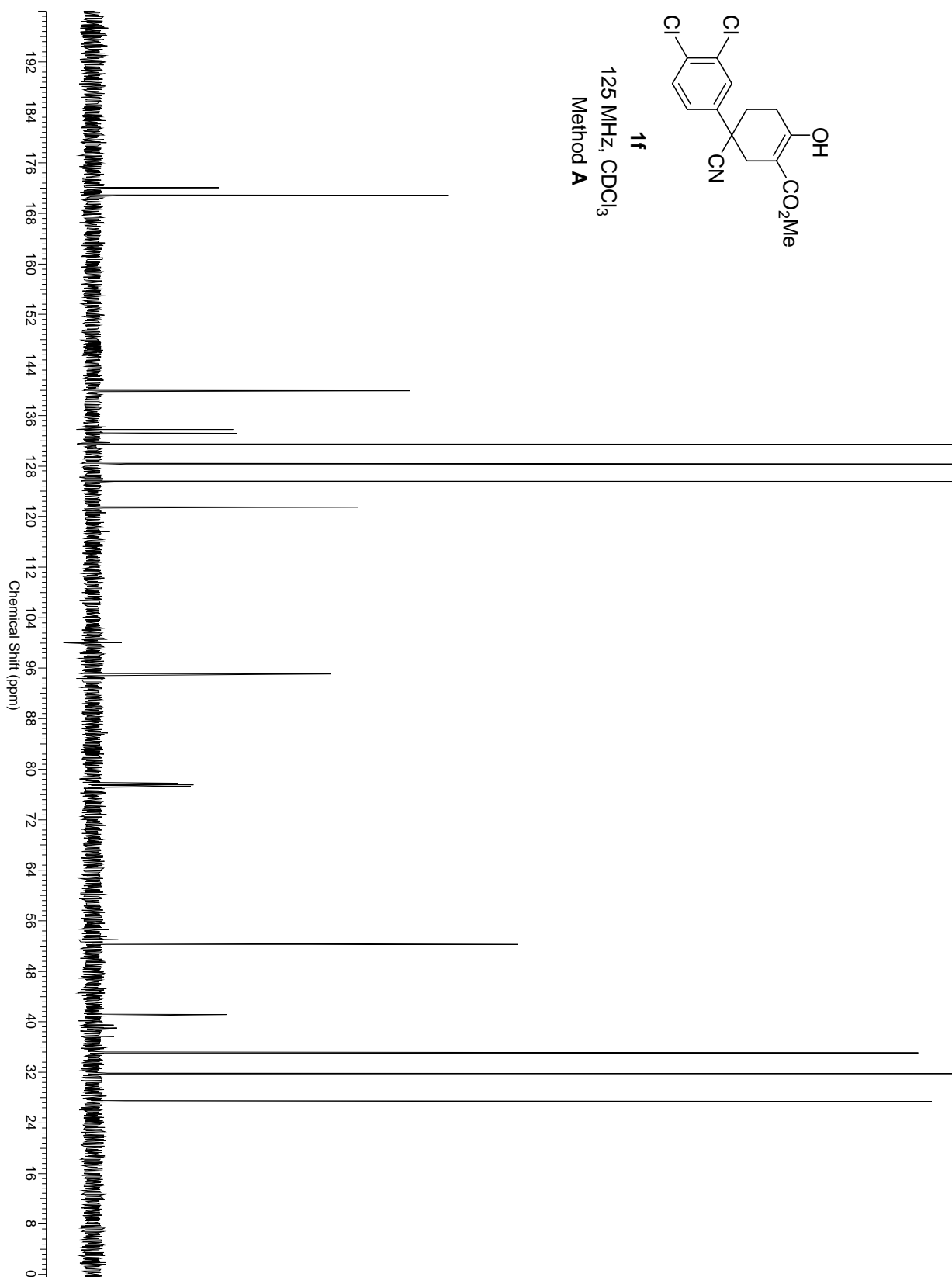
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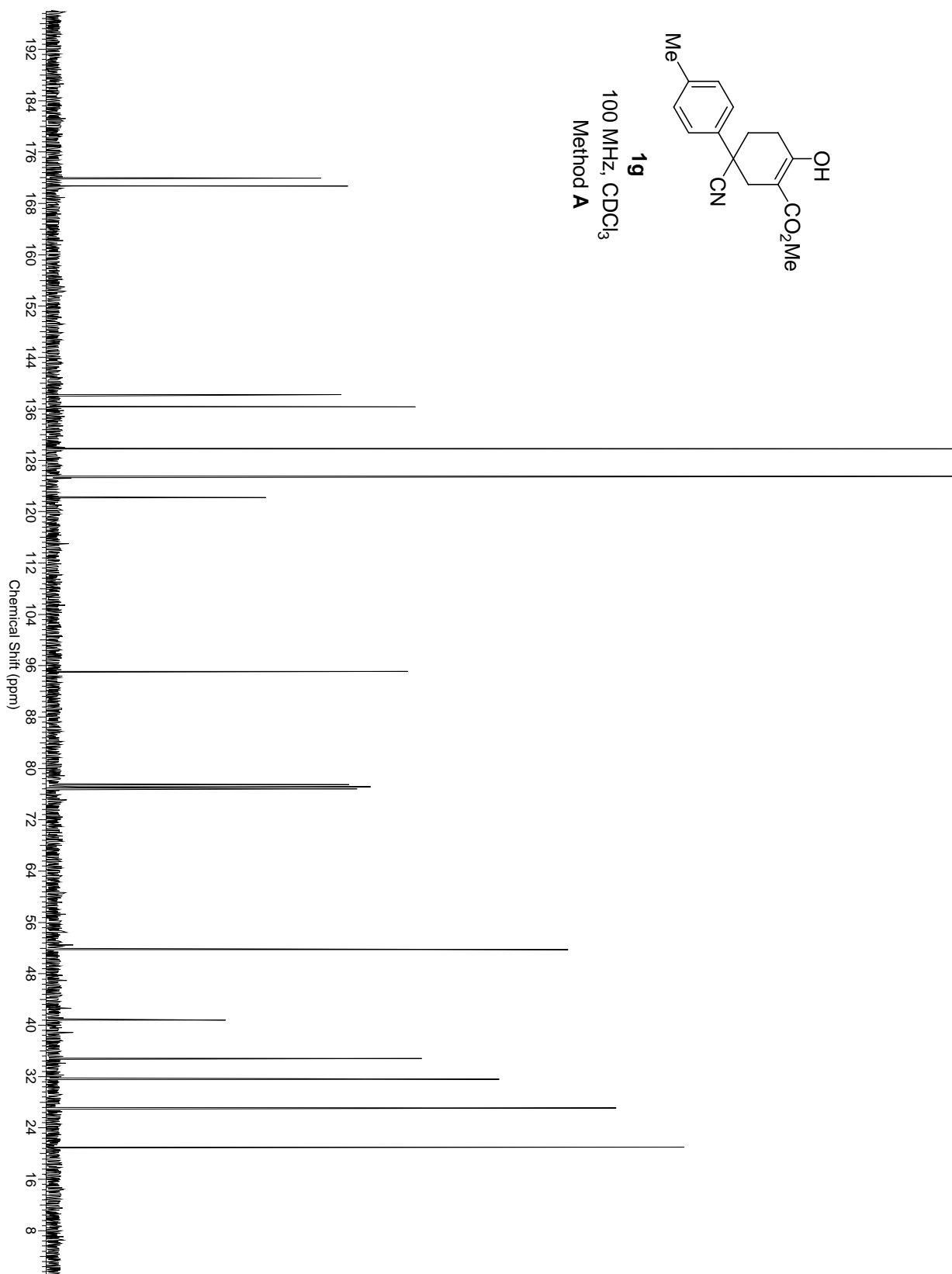
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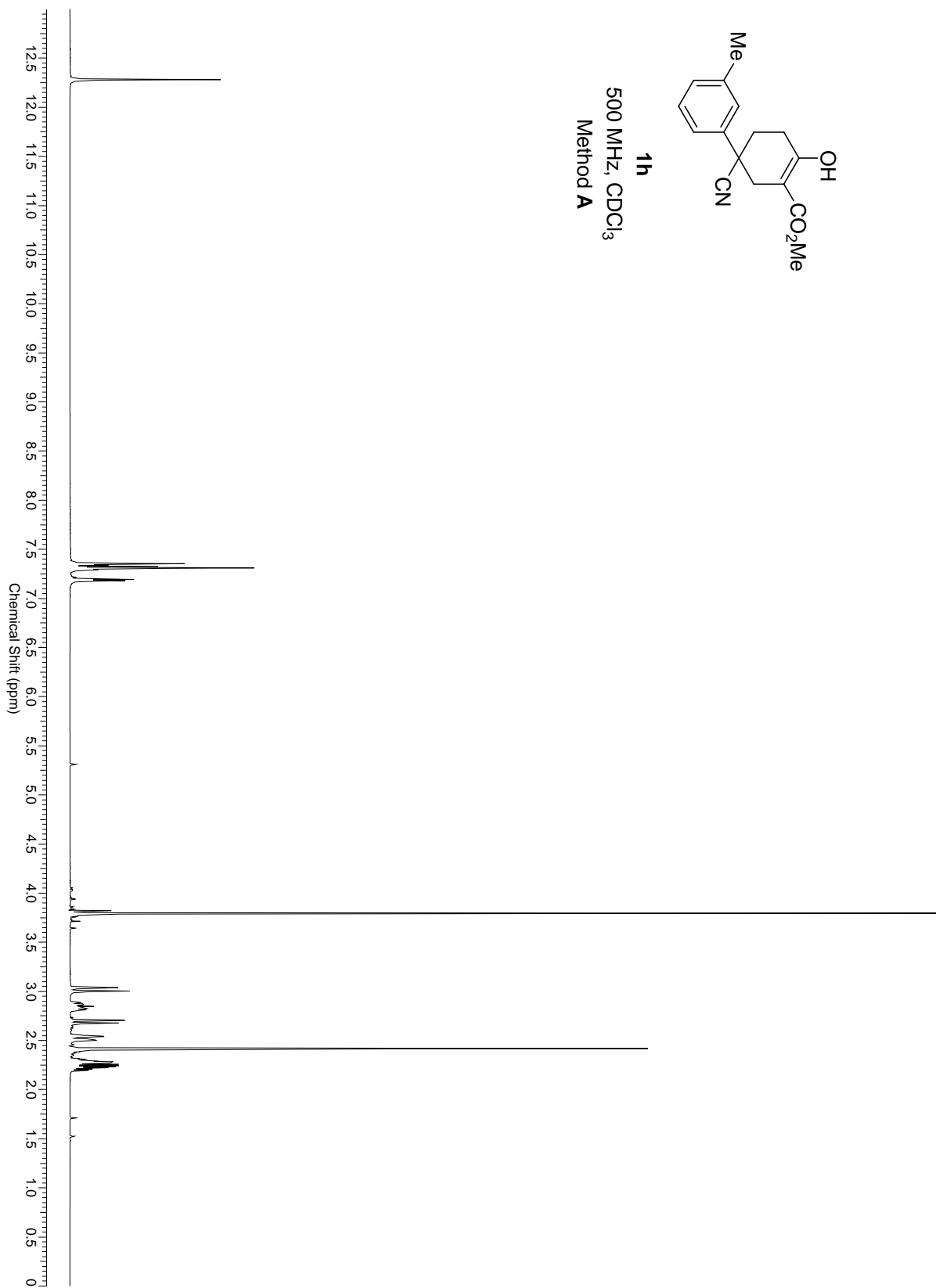
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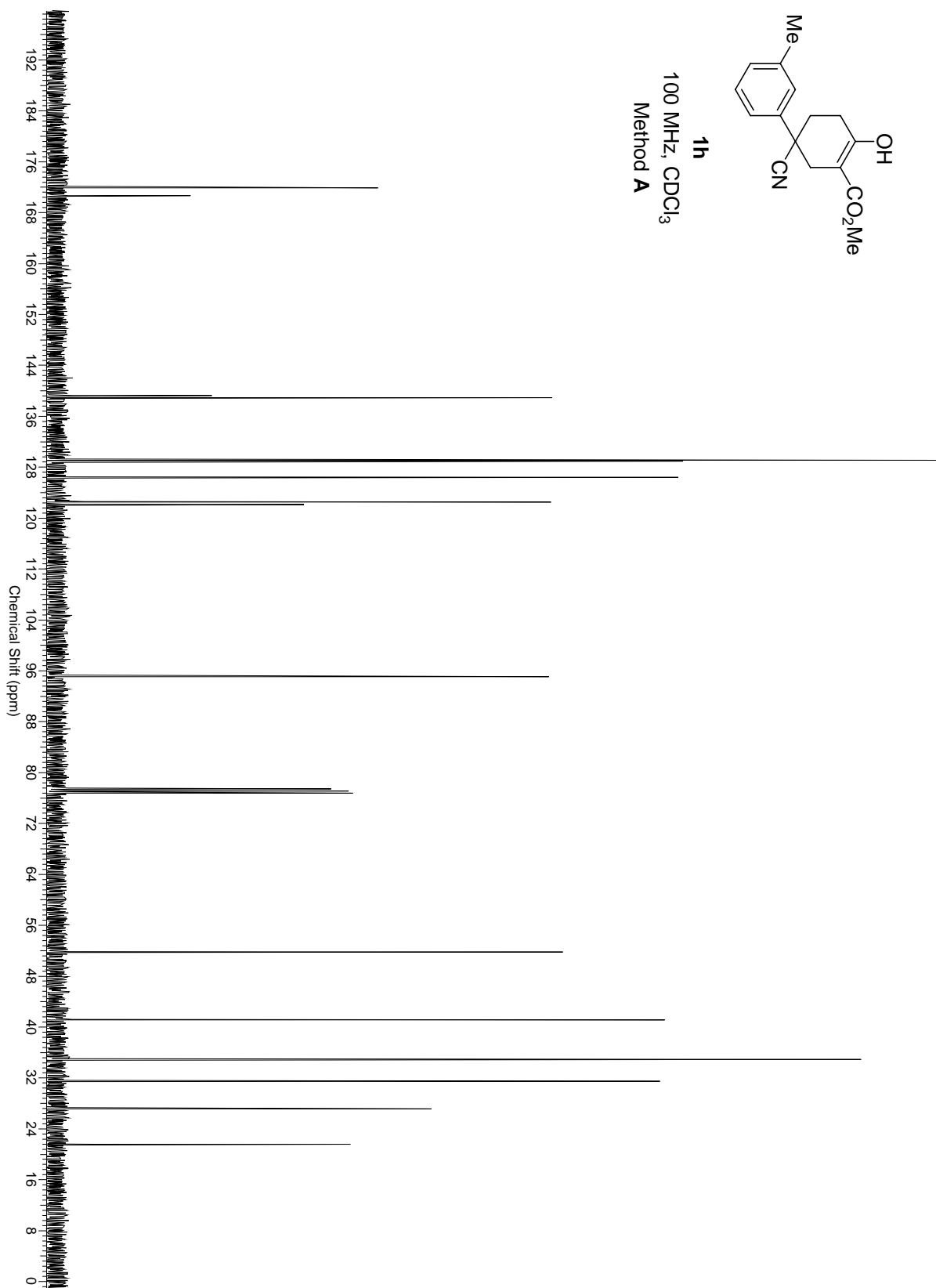
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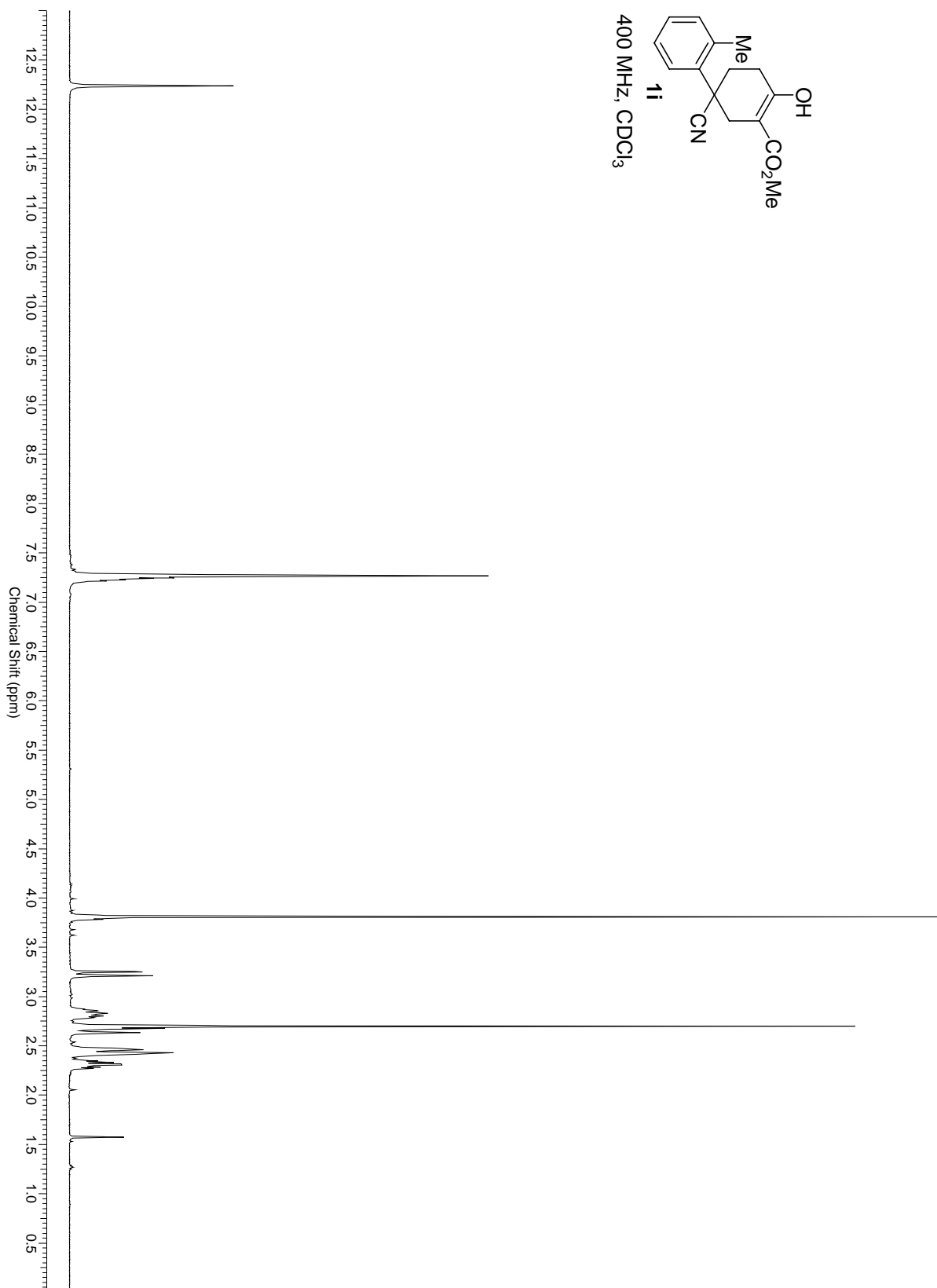
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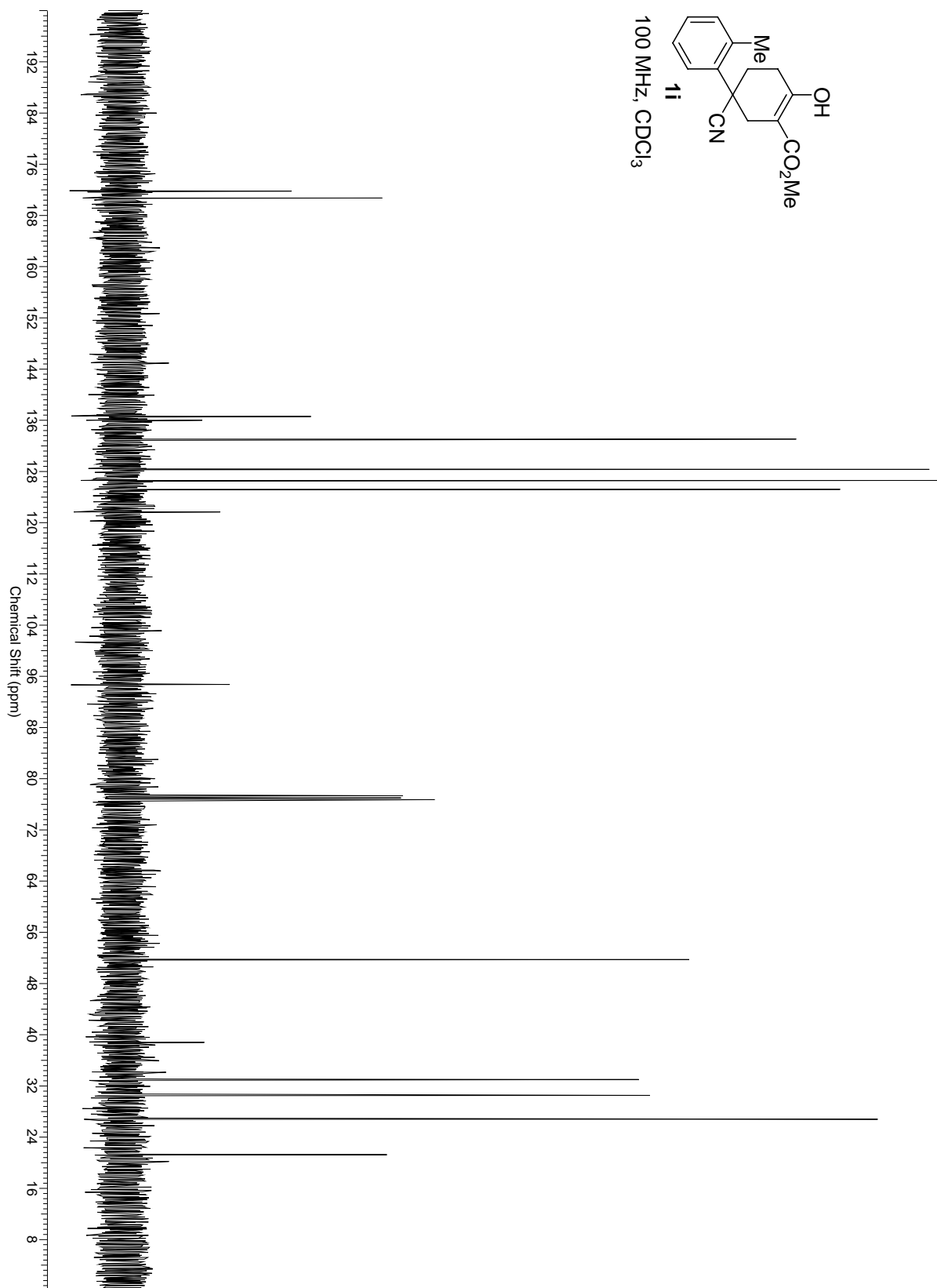
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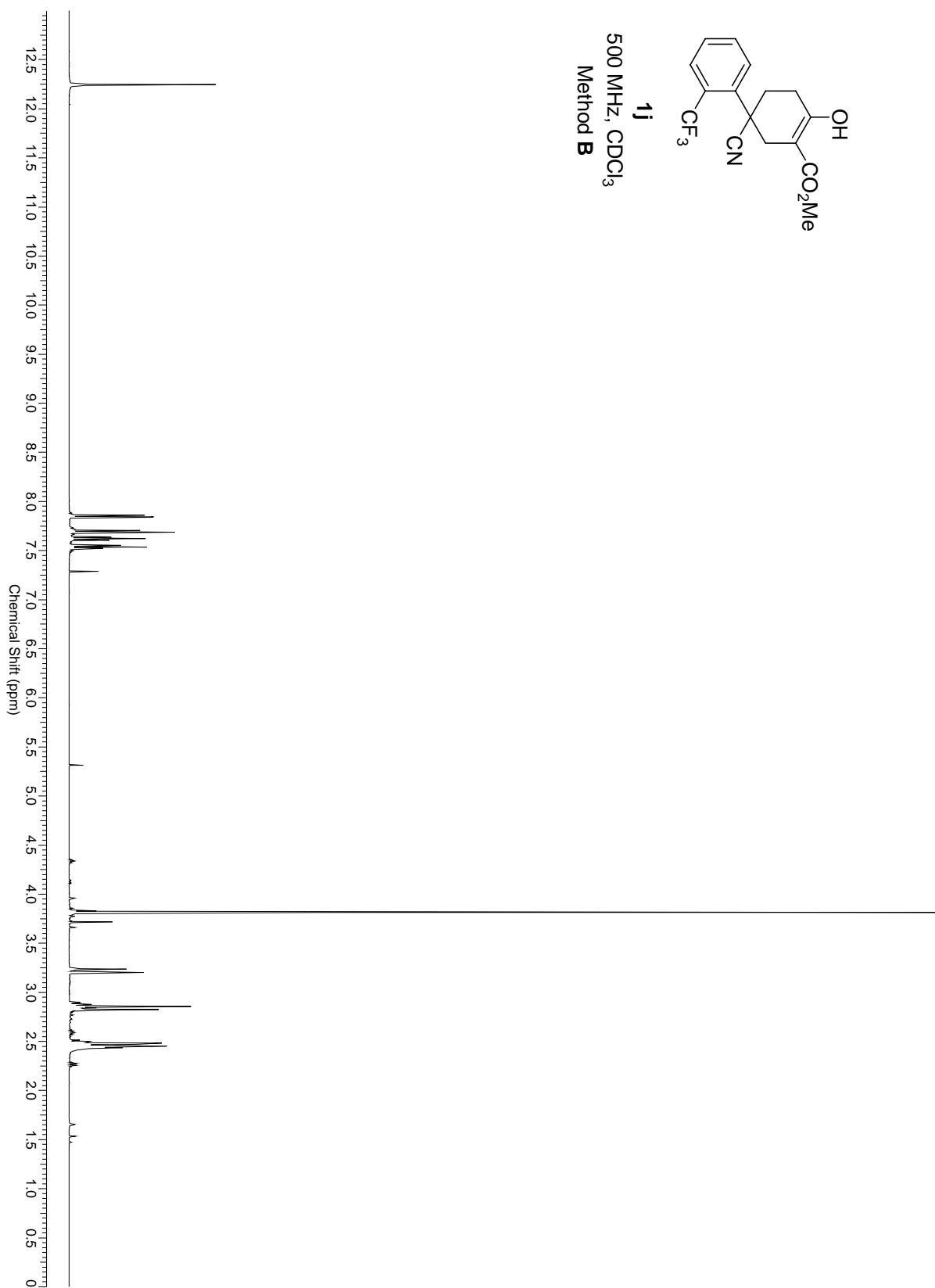
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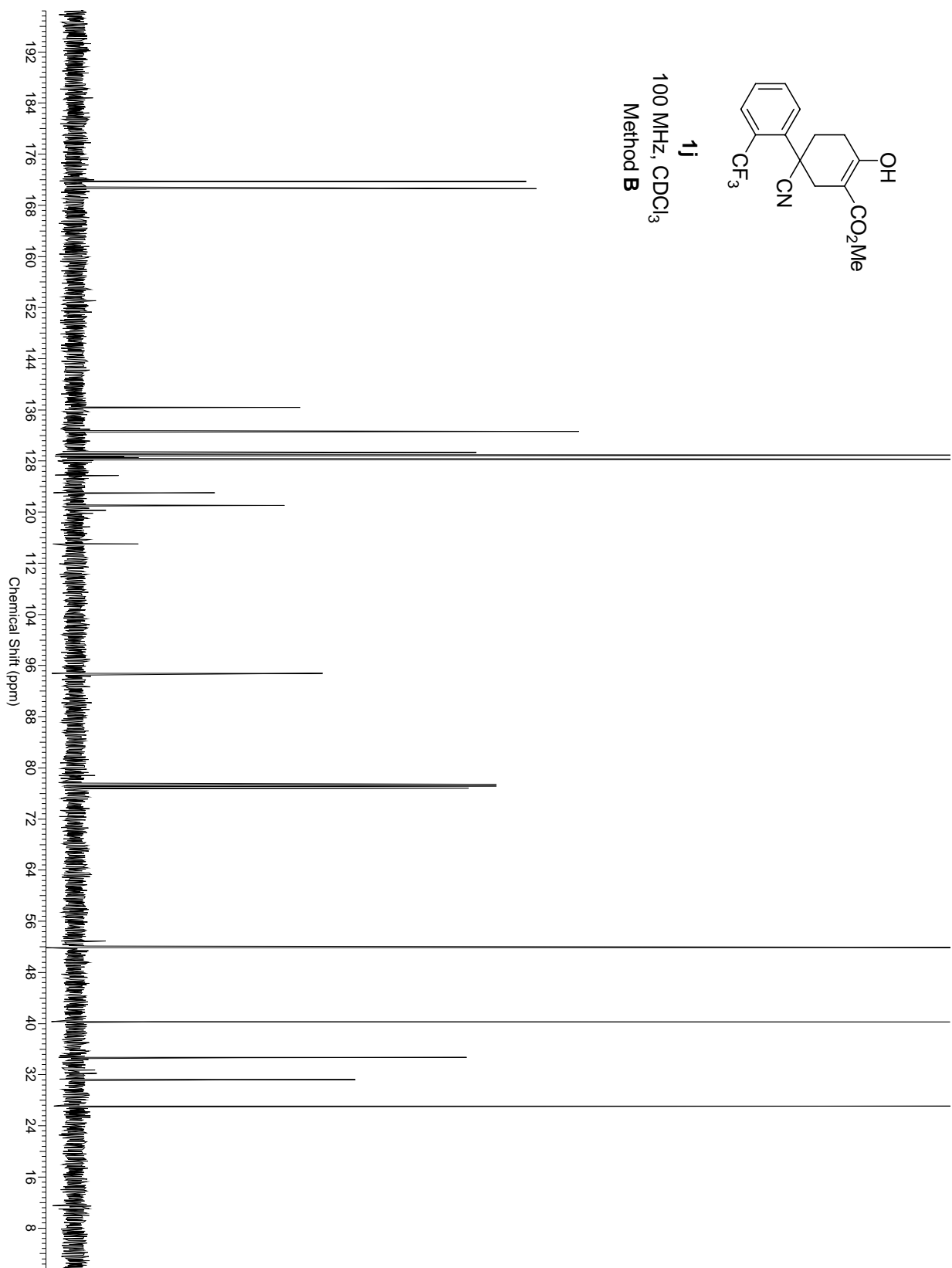
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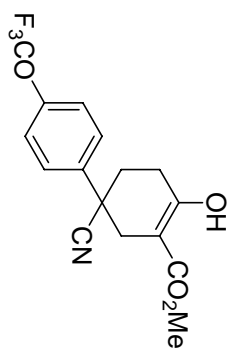
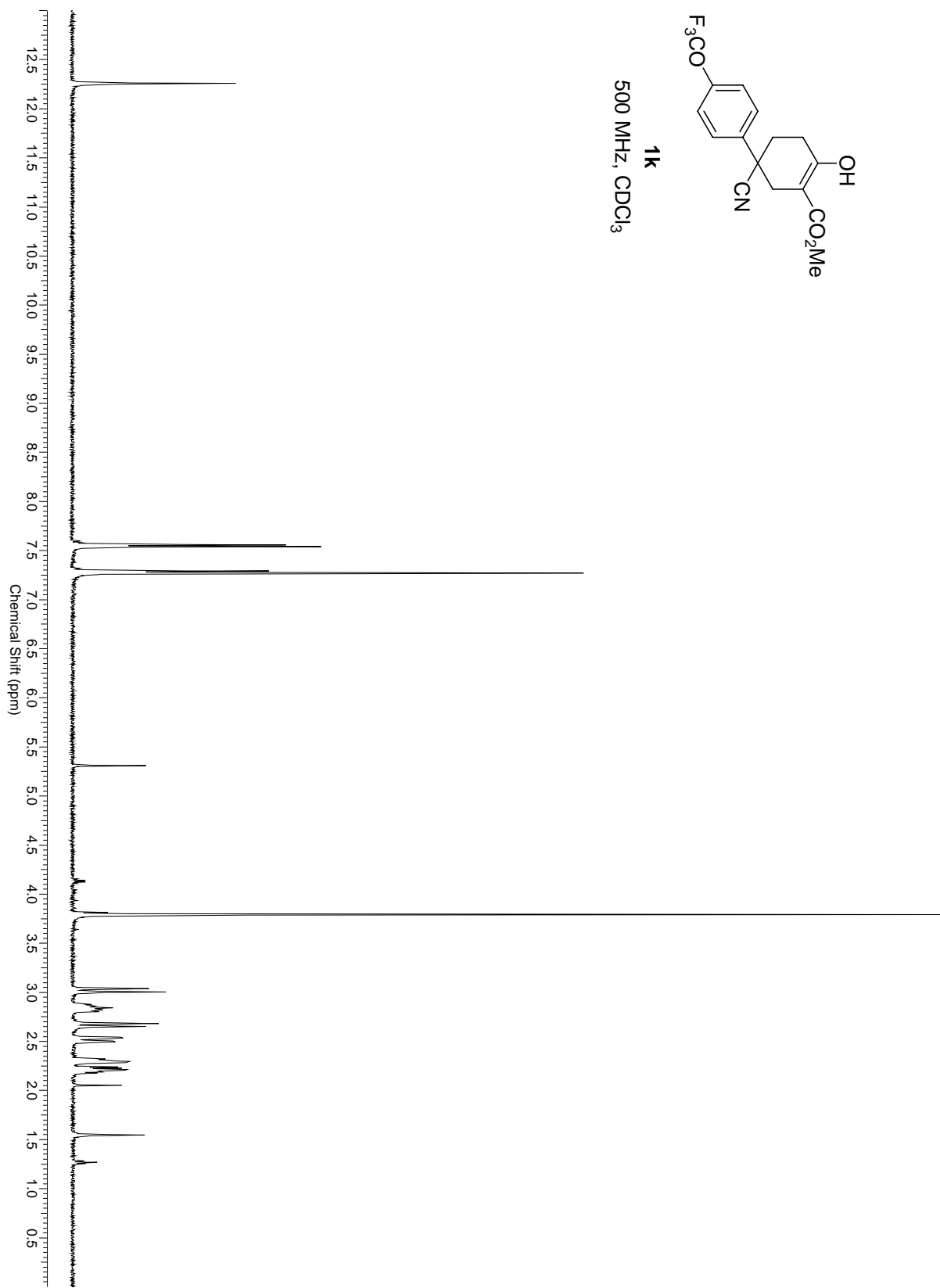
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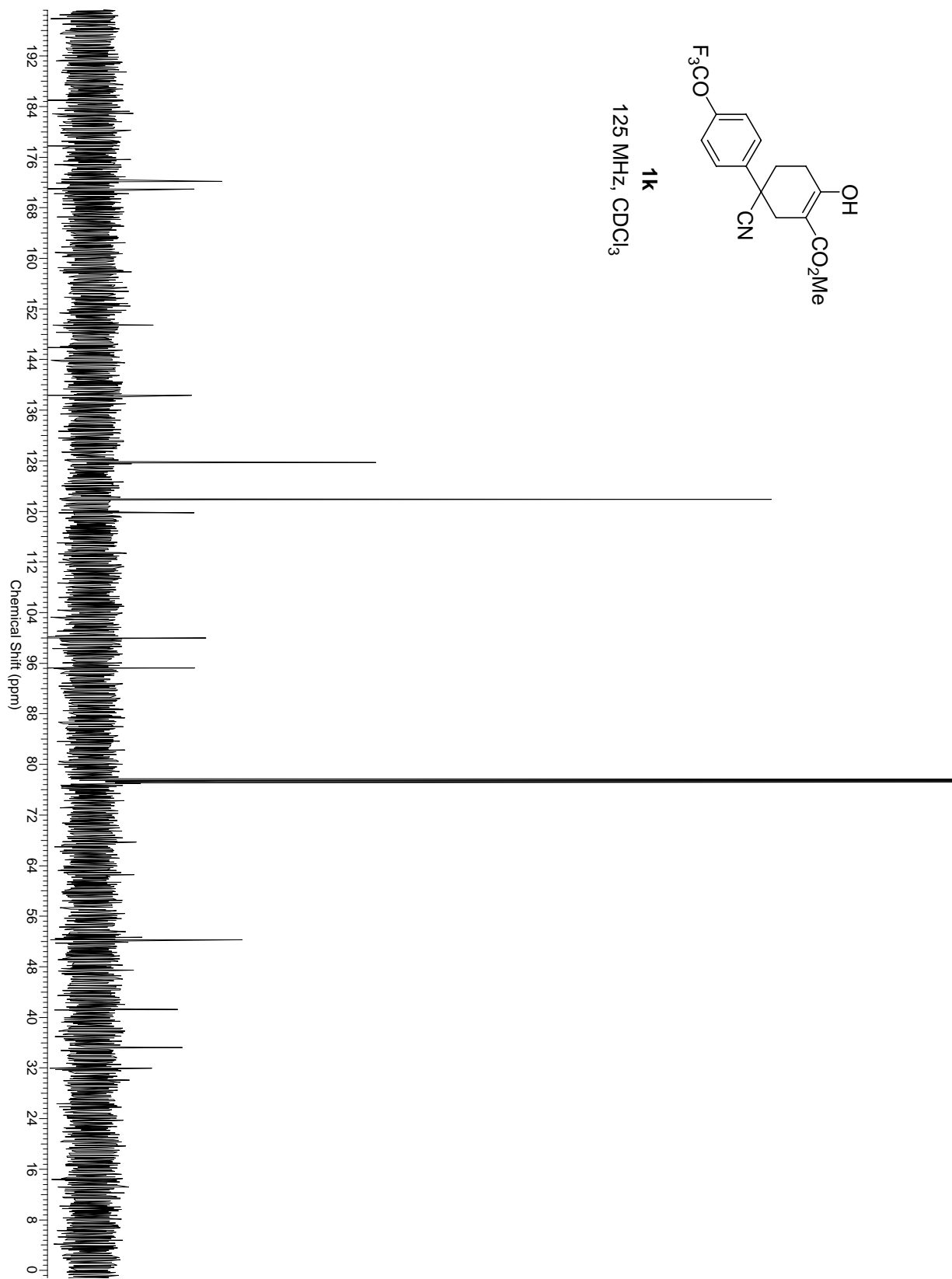
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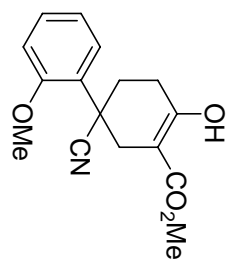
1k

500 MHz, CDCl₃

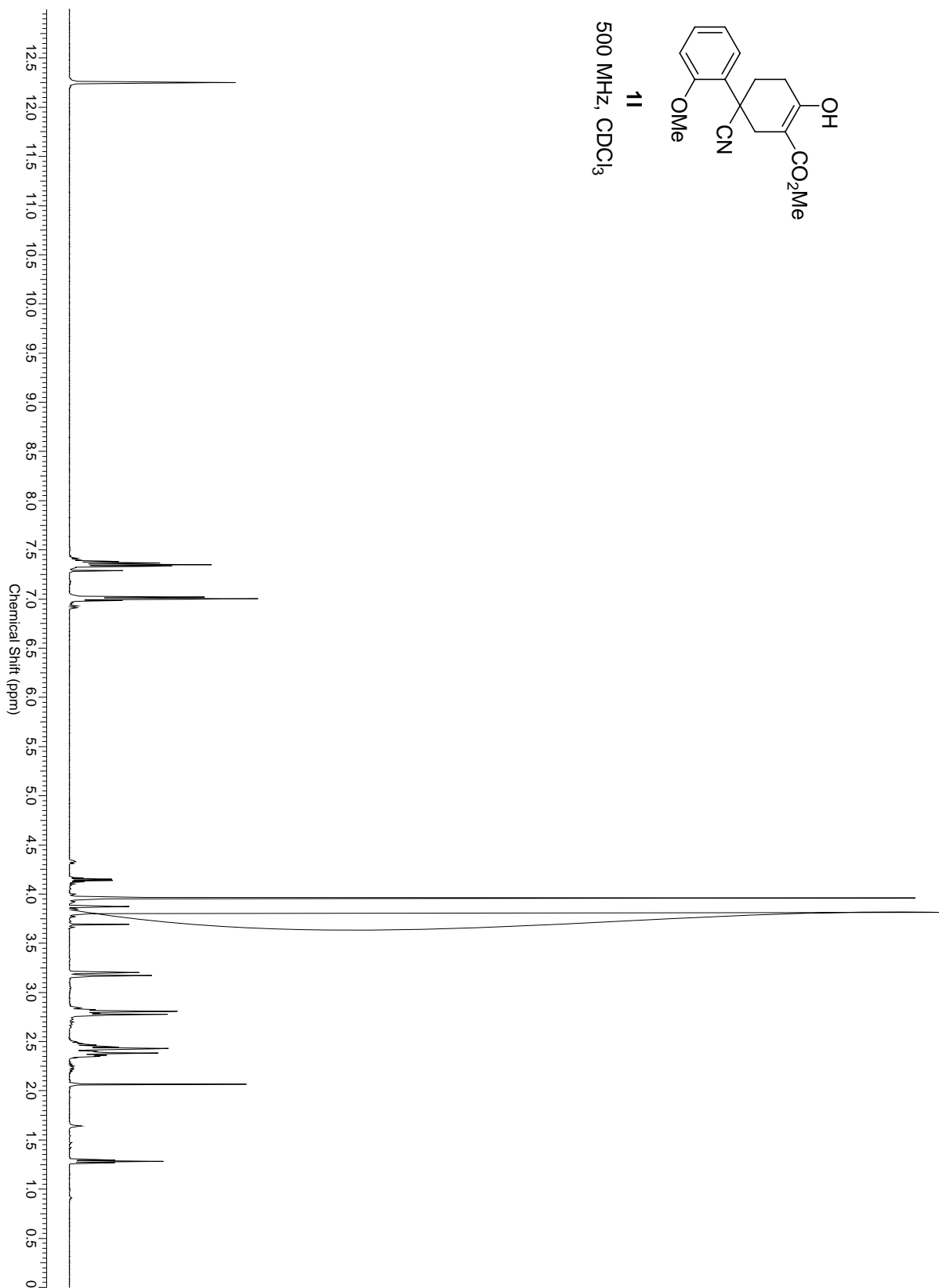
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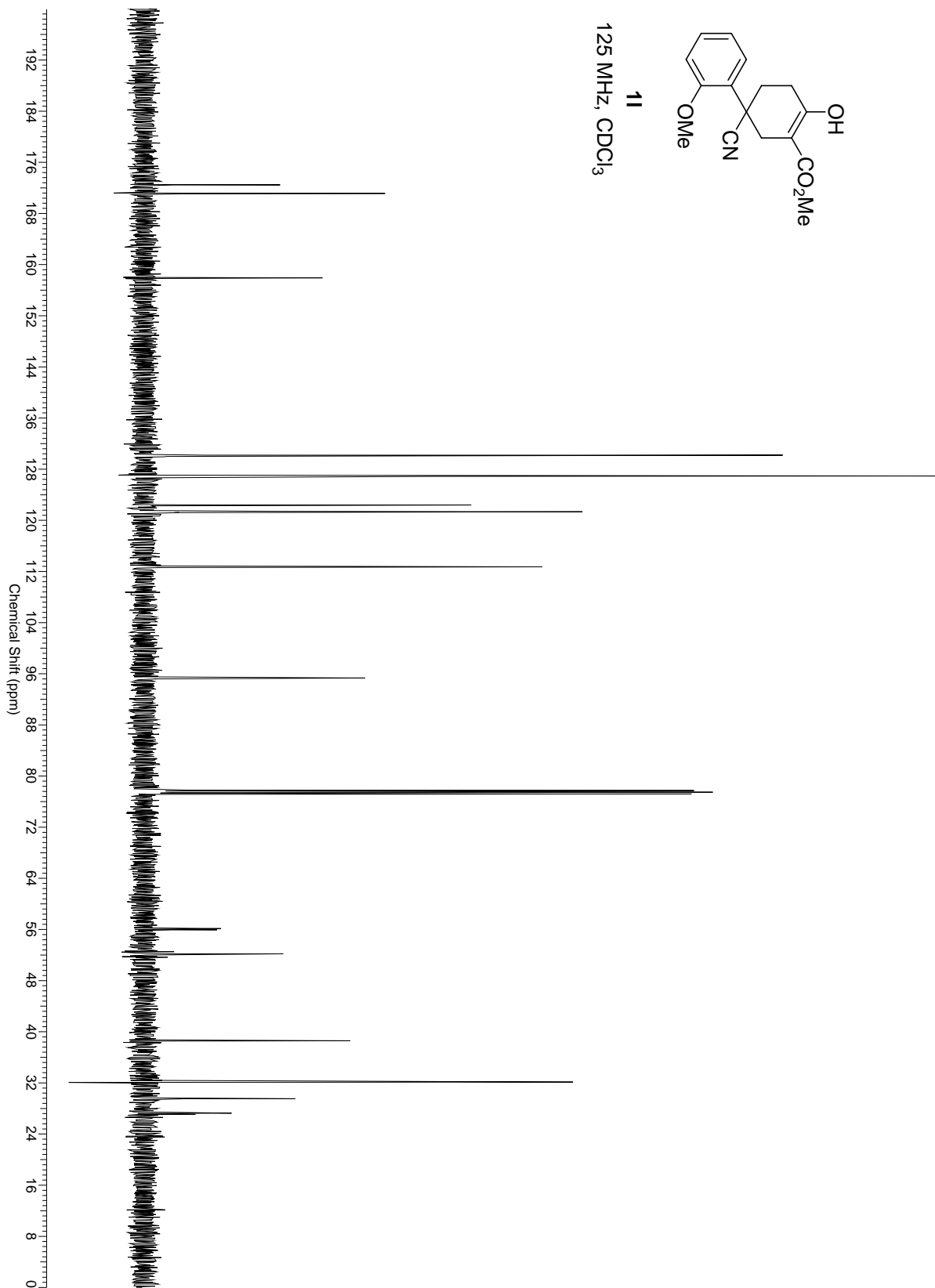
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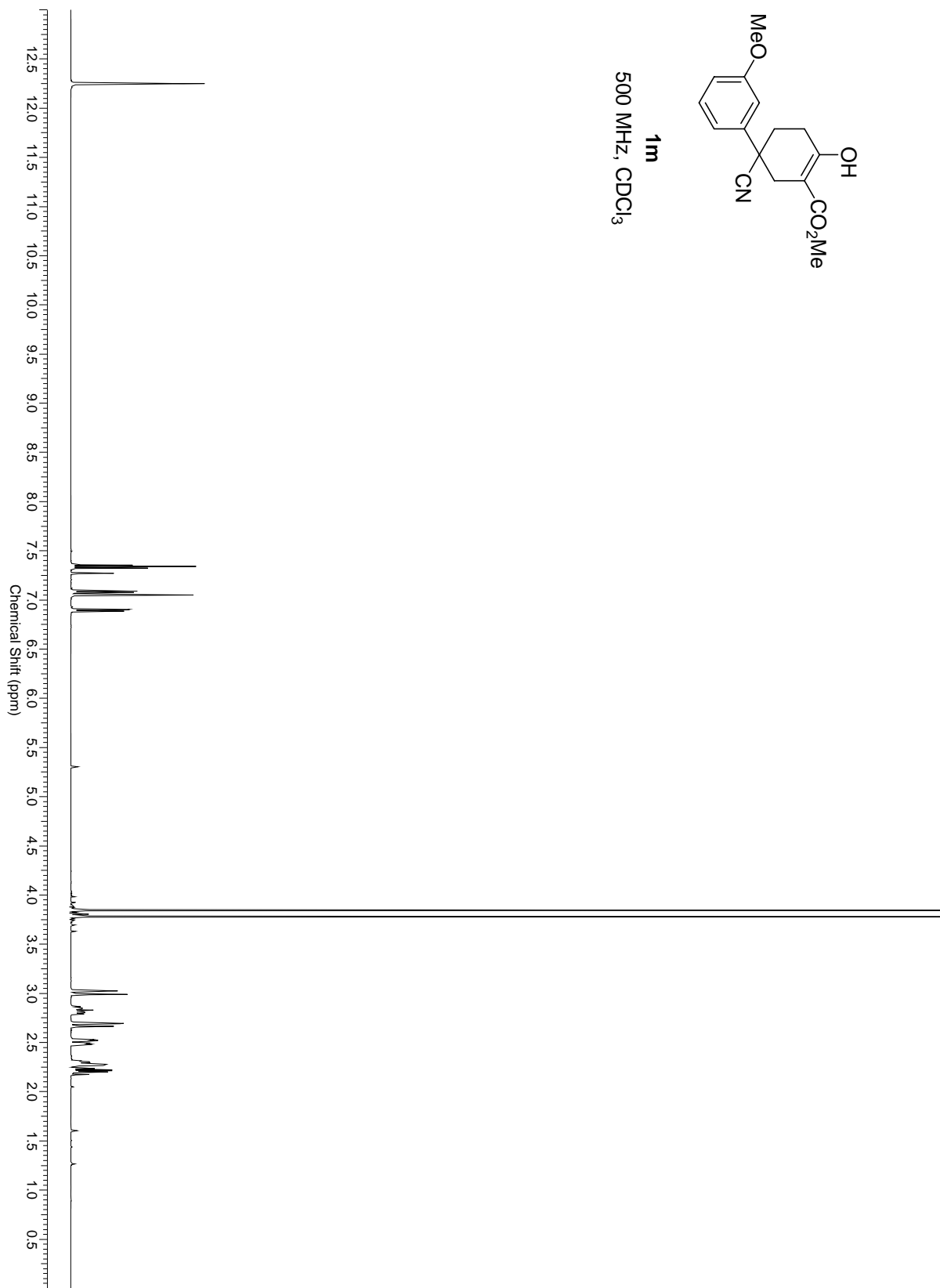
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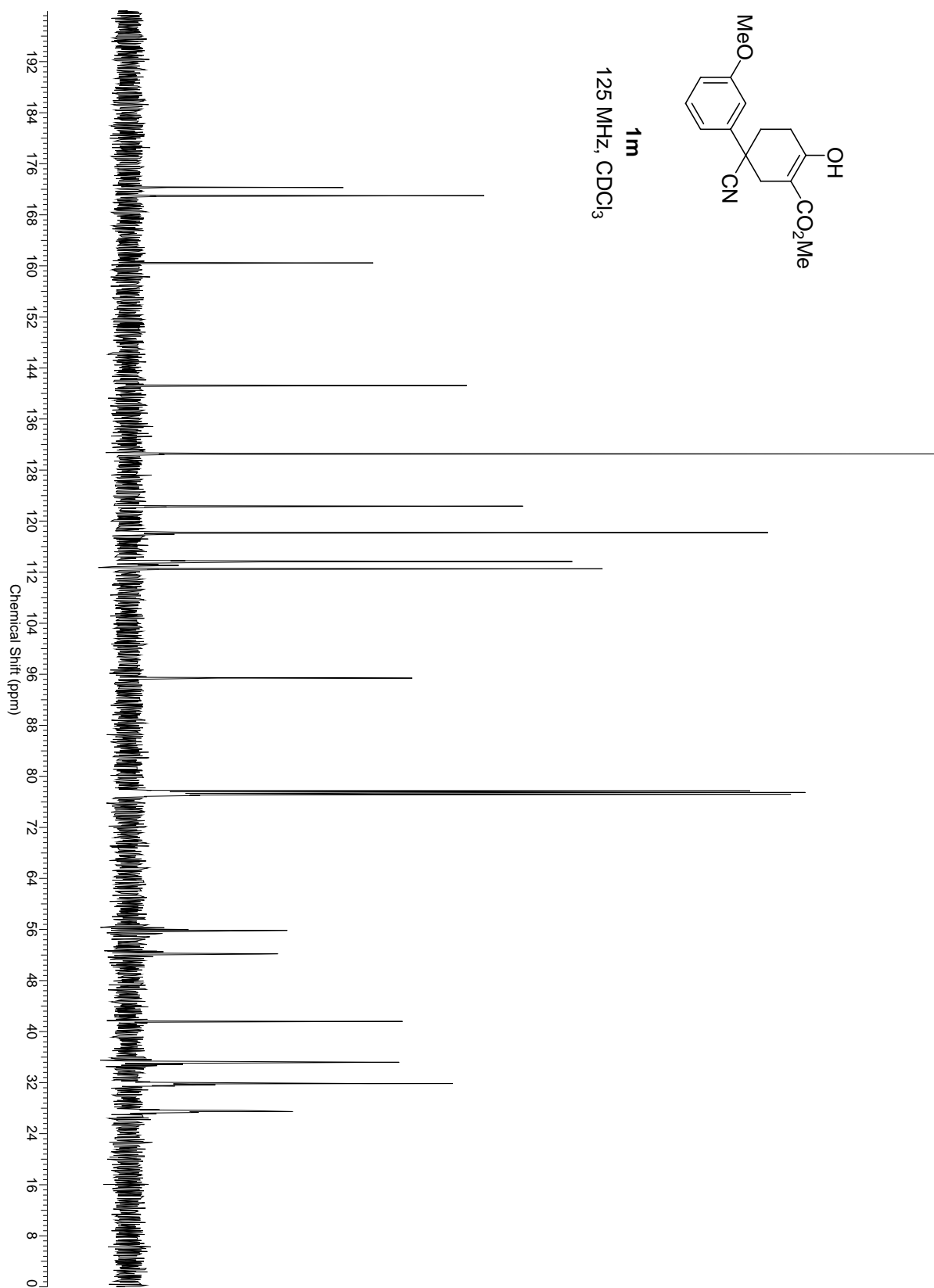
Supporting Information



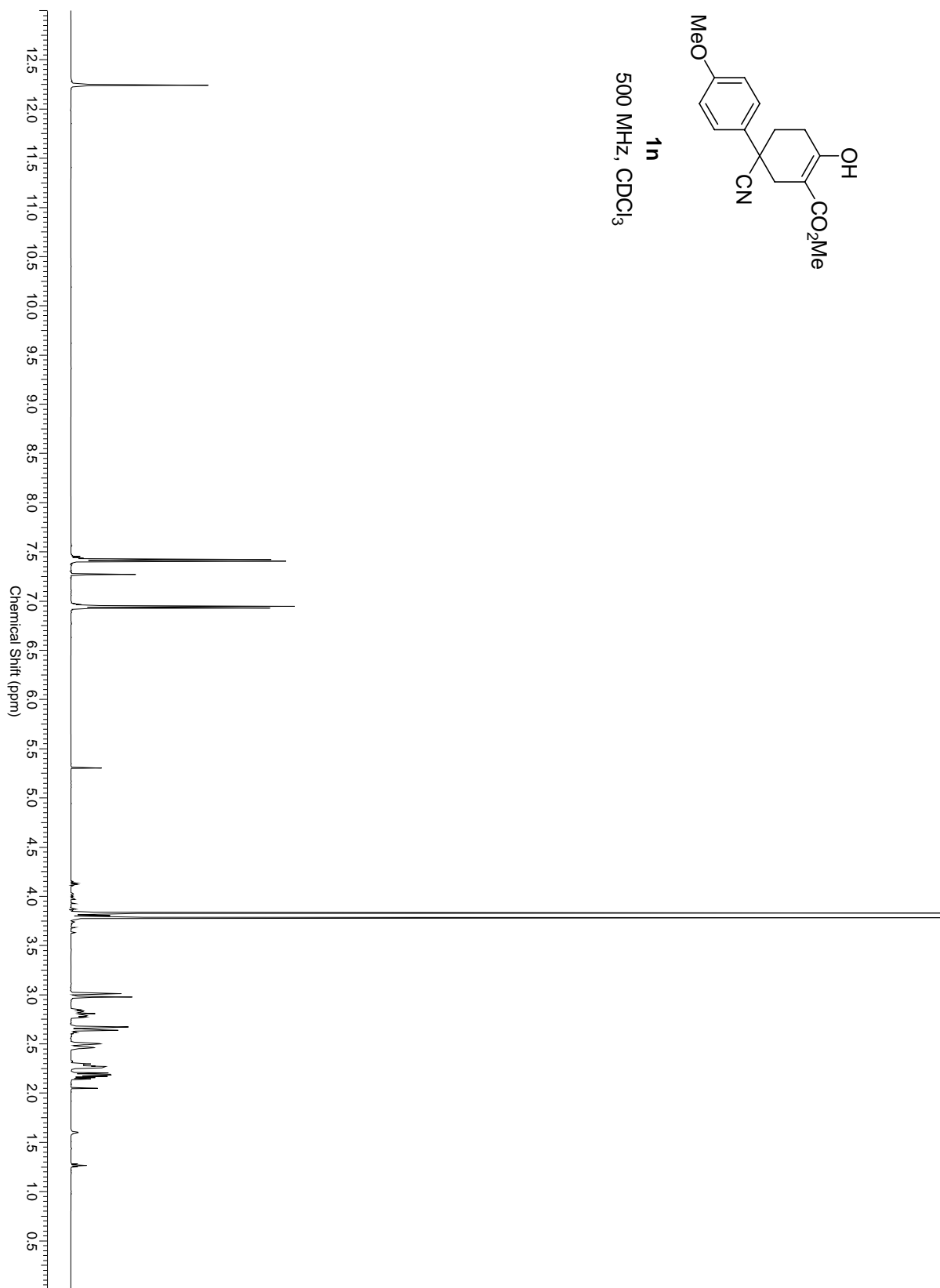
Supporting Information



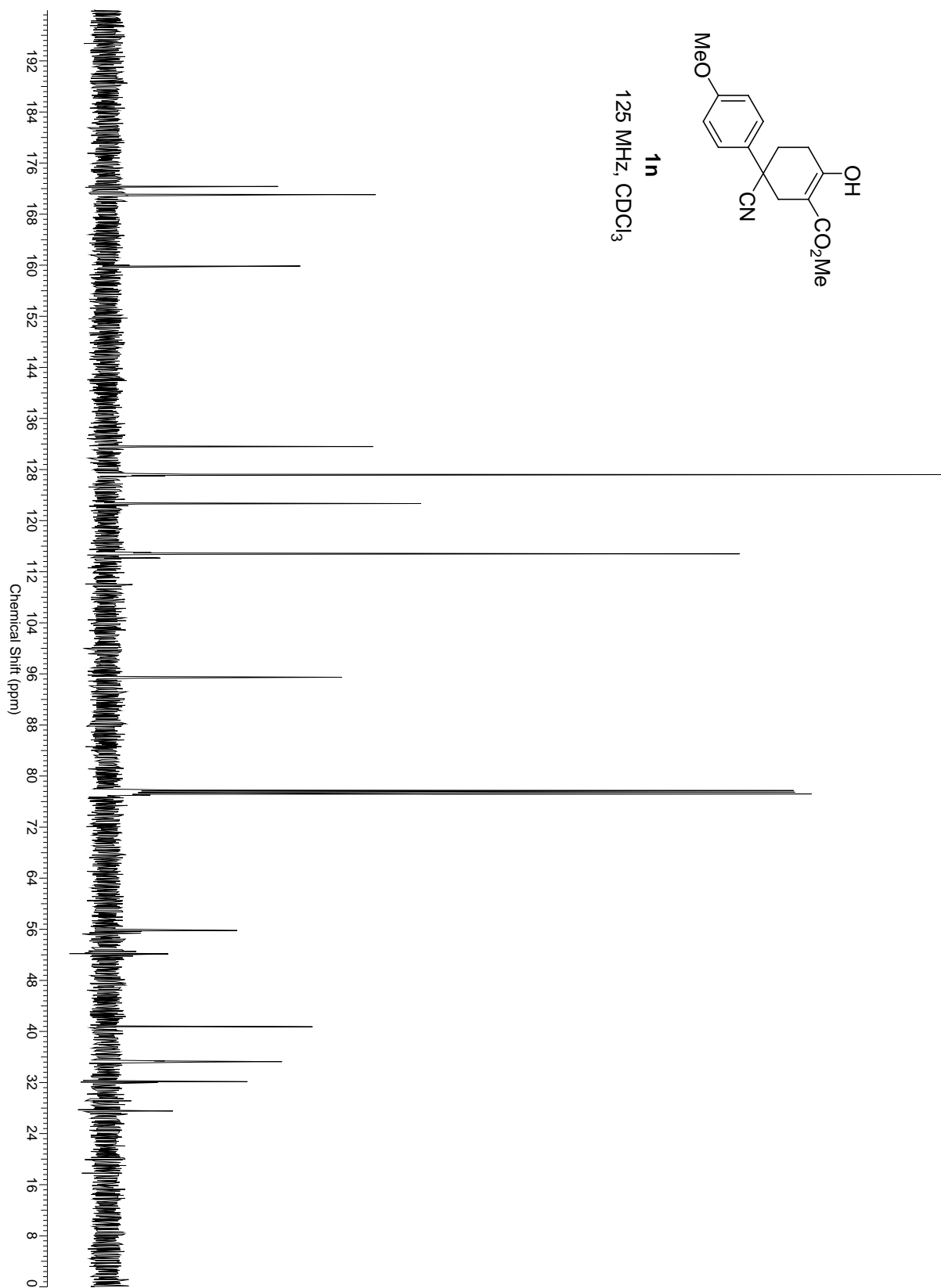
Supporting Information



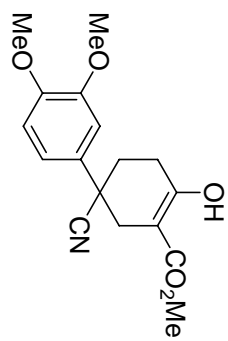
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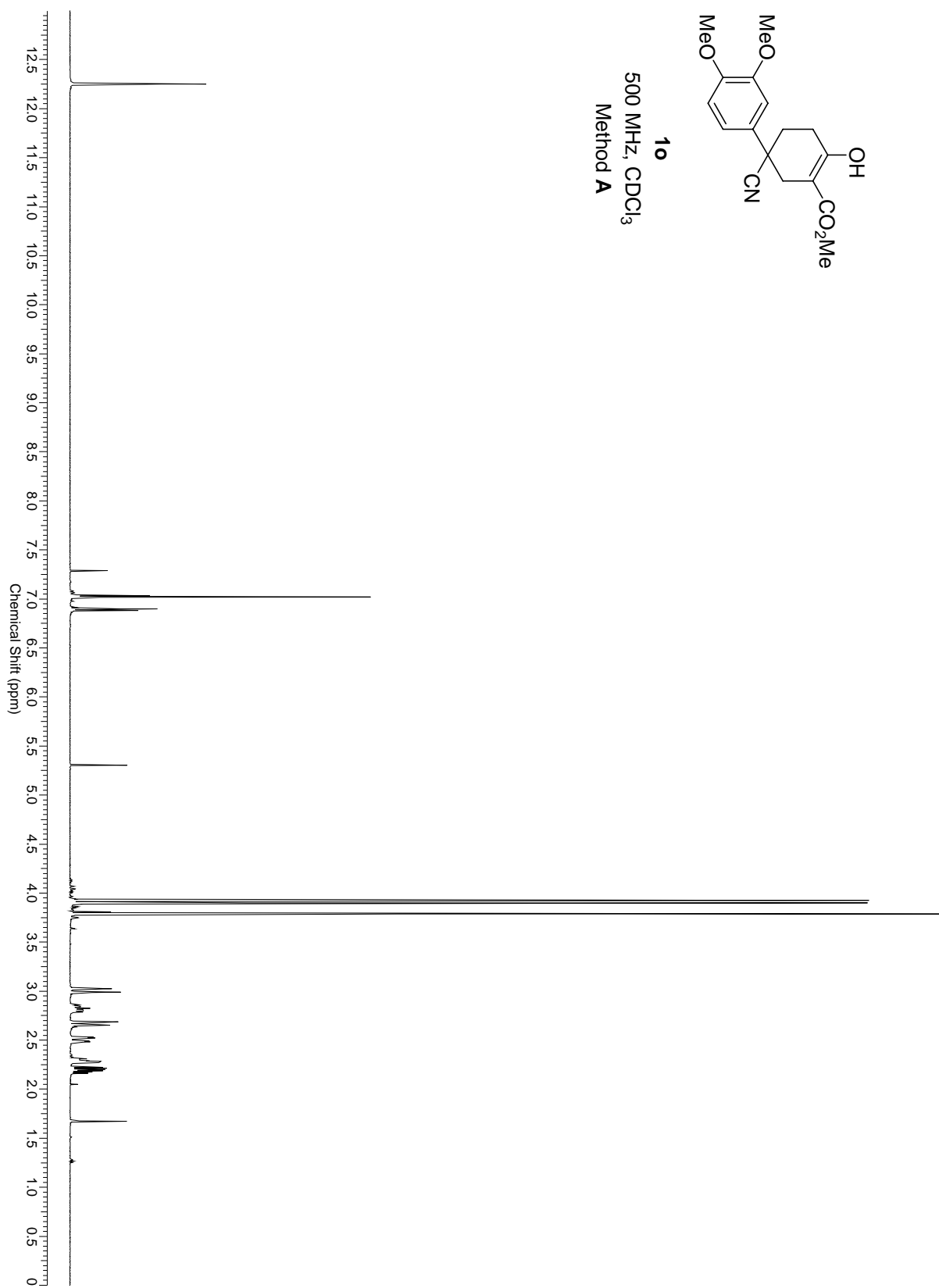
Supporting Information



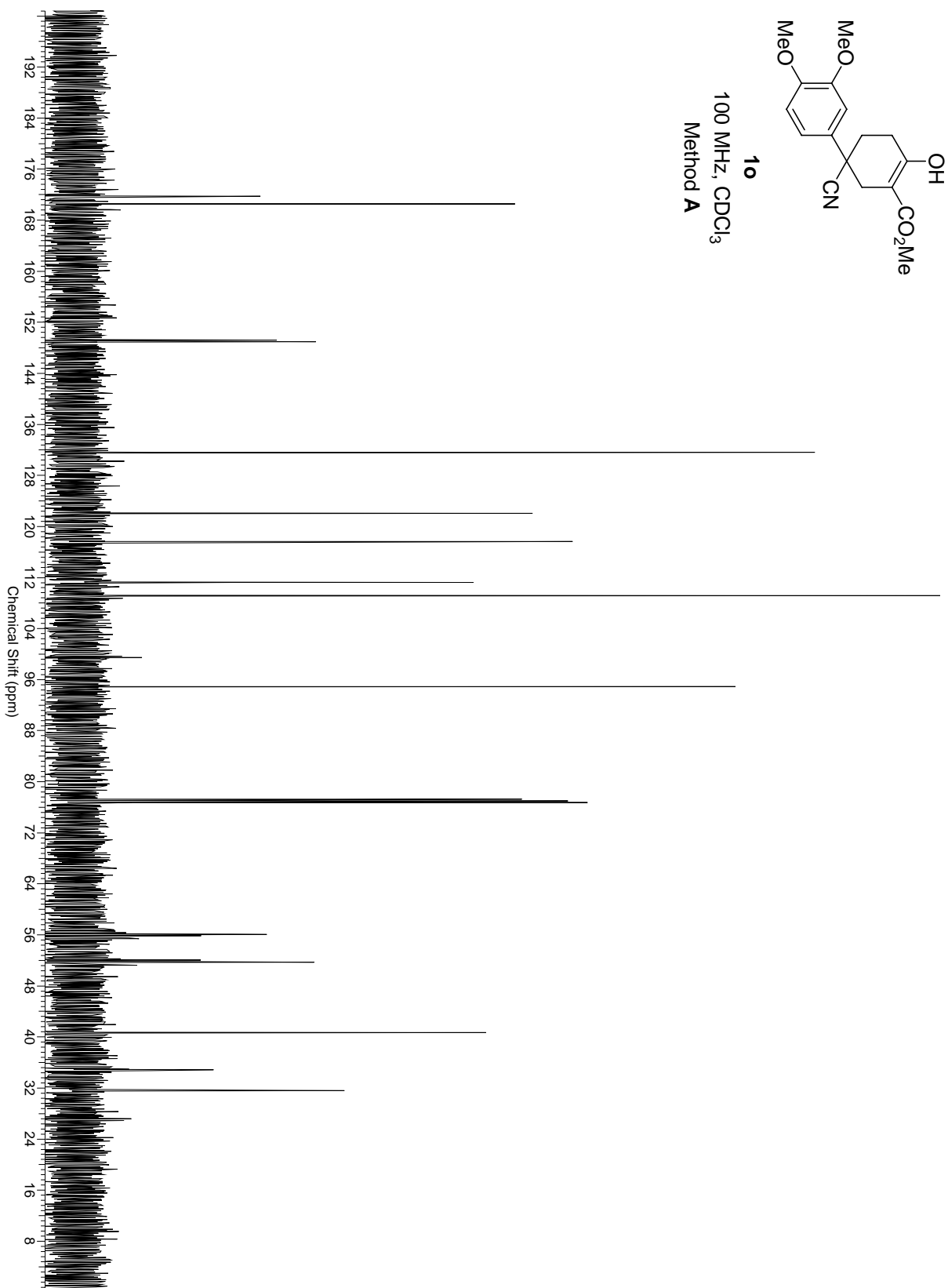
Supporting Information



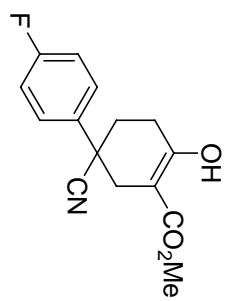
500 MHz, CDCl₃
Method A



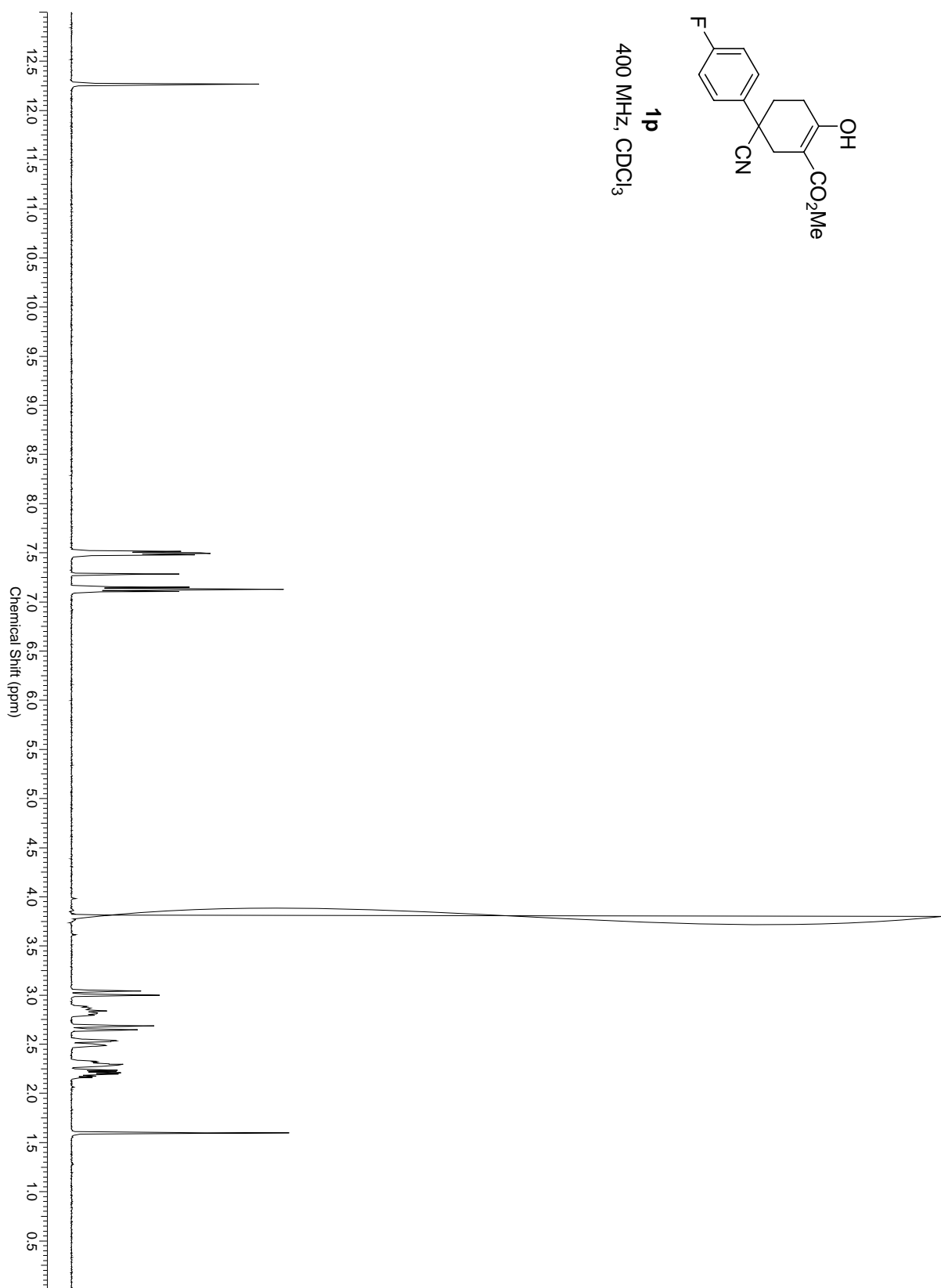
Supporting Information



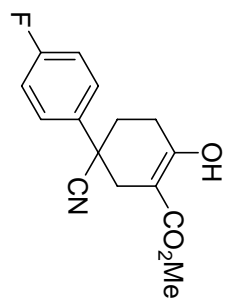
Supporting Information



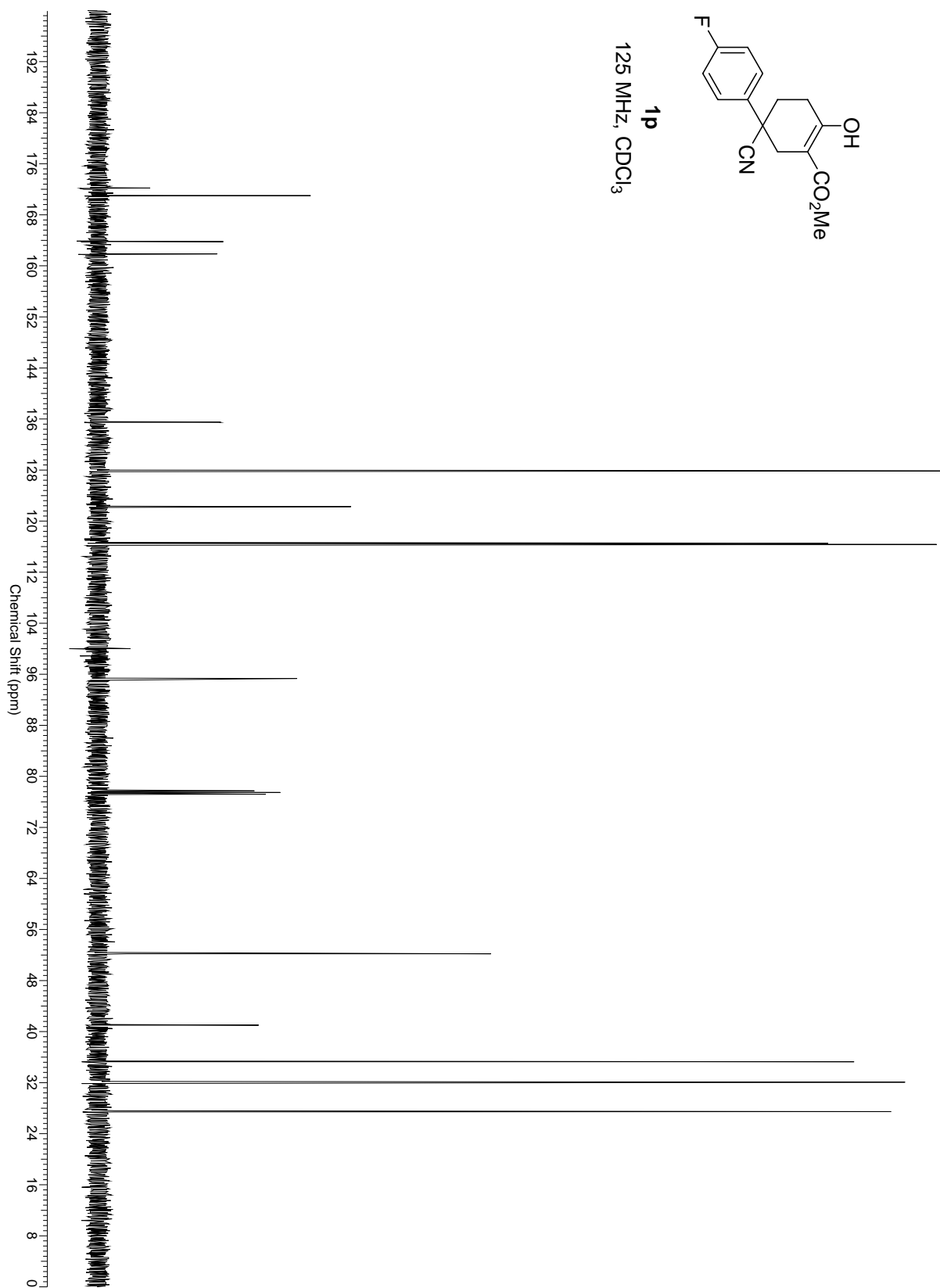
1p
400 MHz, CDCl_3



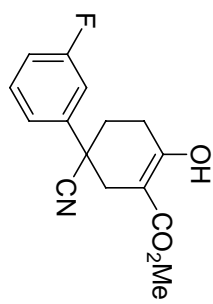
Supporting Information



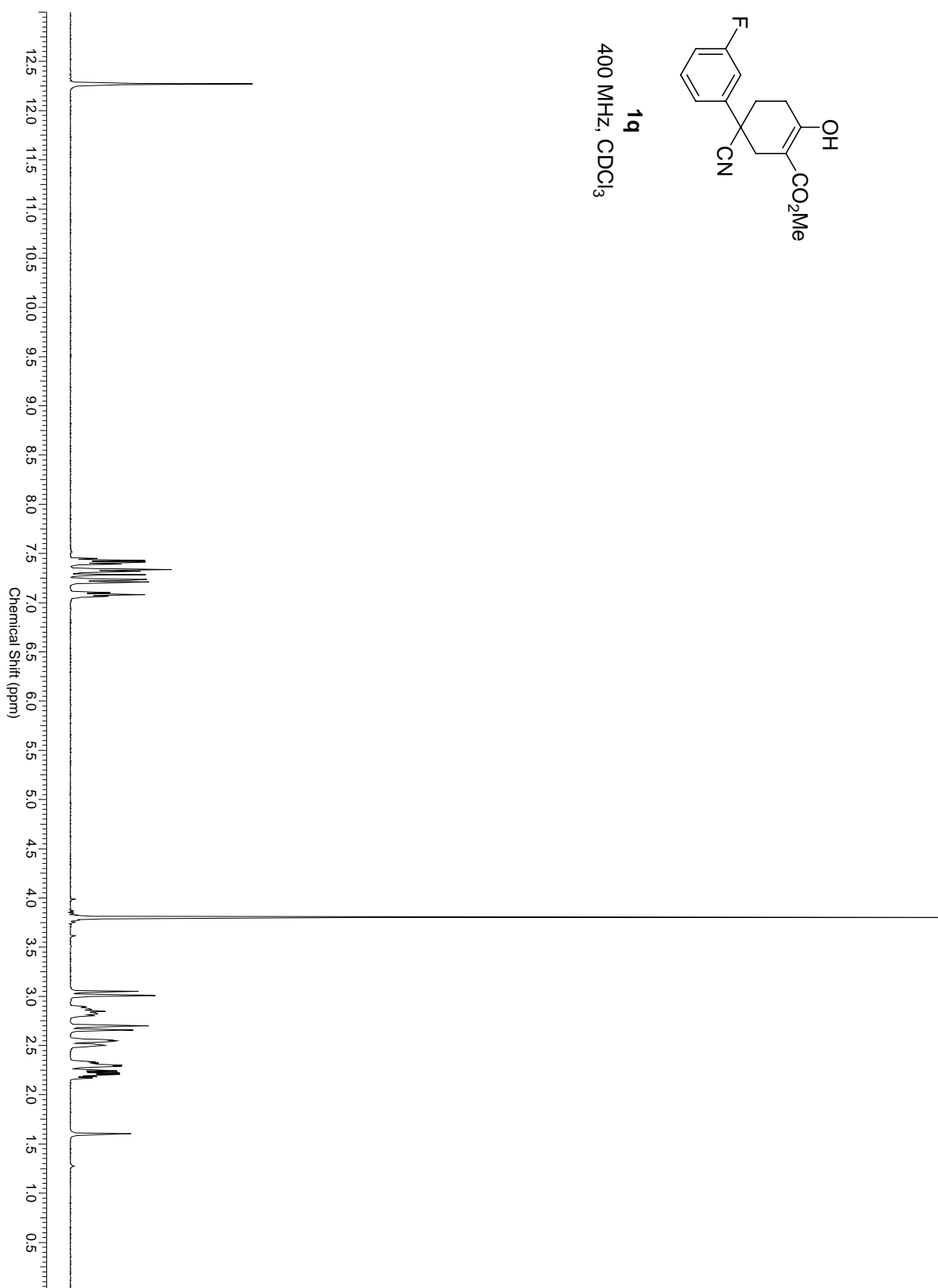
1p
125 MHz, CDCl₃



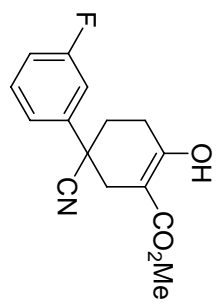
Supporting Information



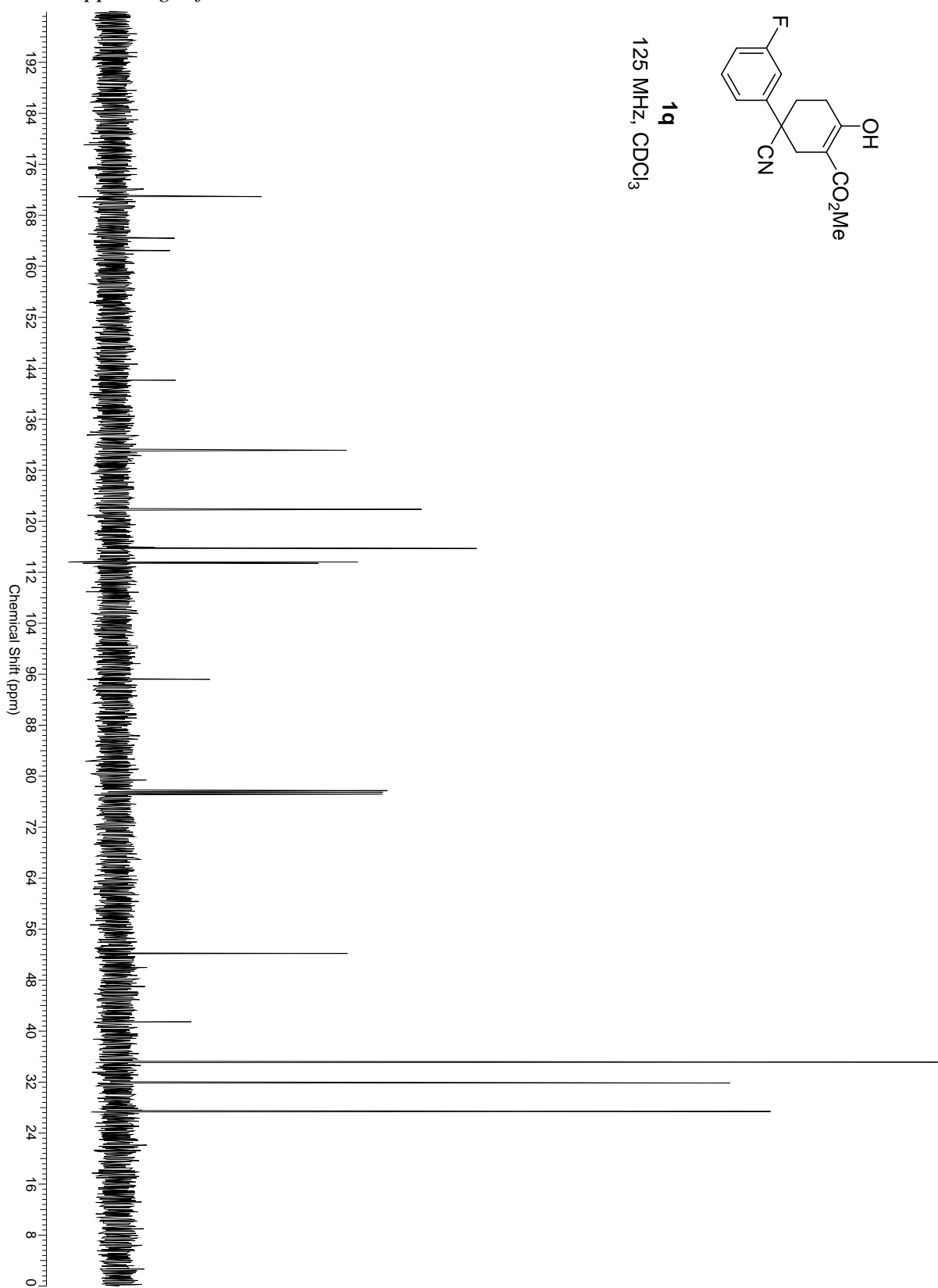
400 MHz, CDCl₃



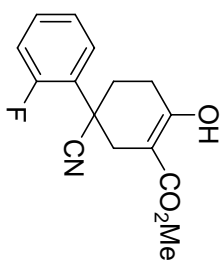
Supporting Information



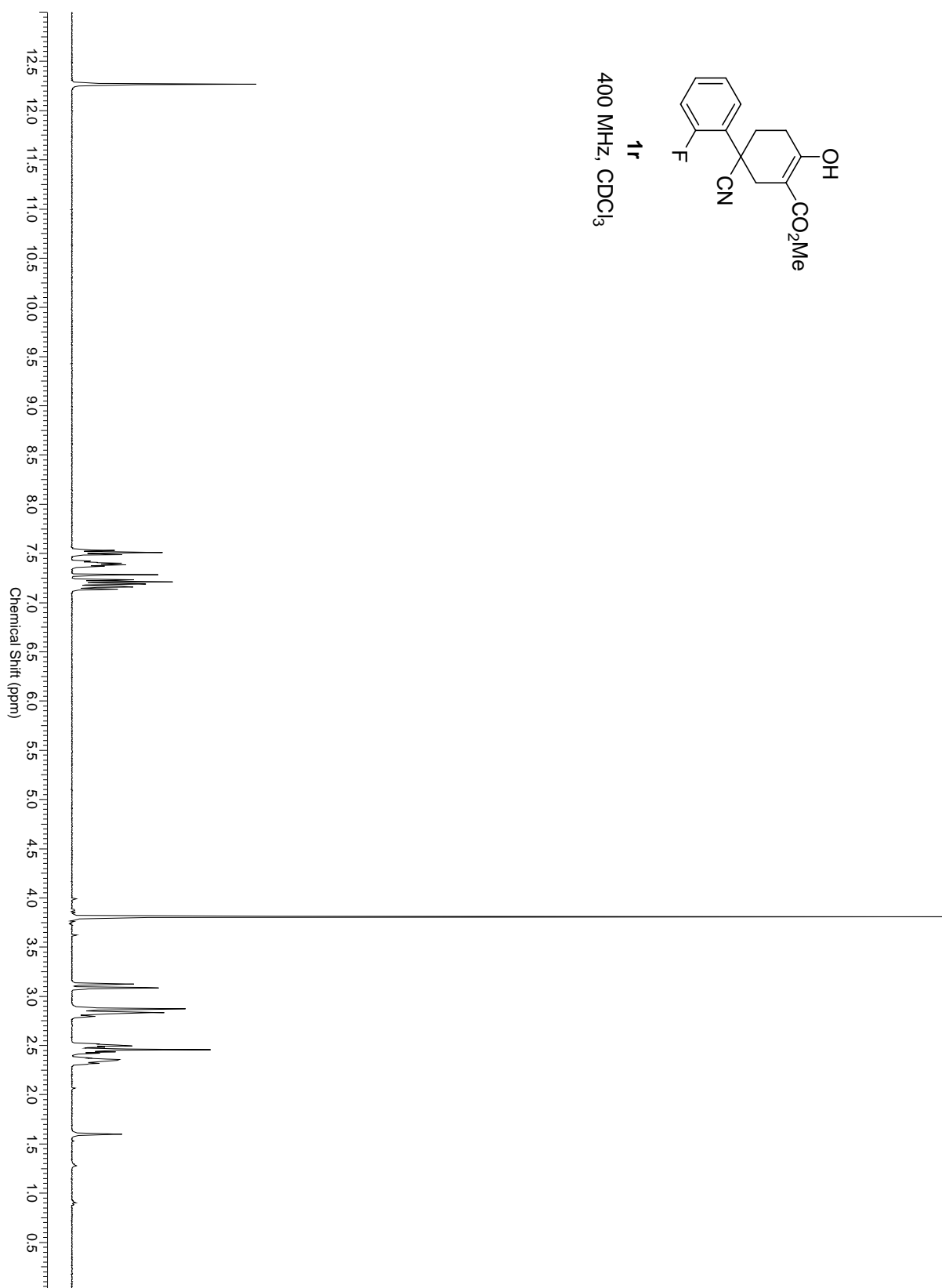
1q
125 MHz, CDCl₃



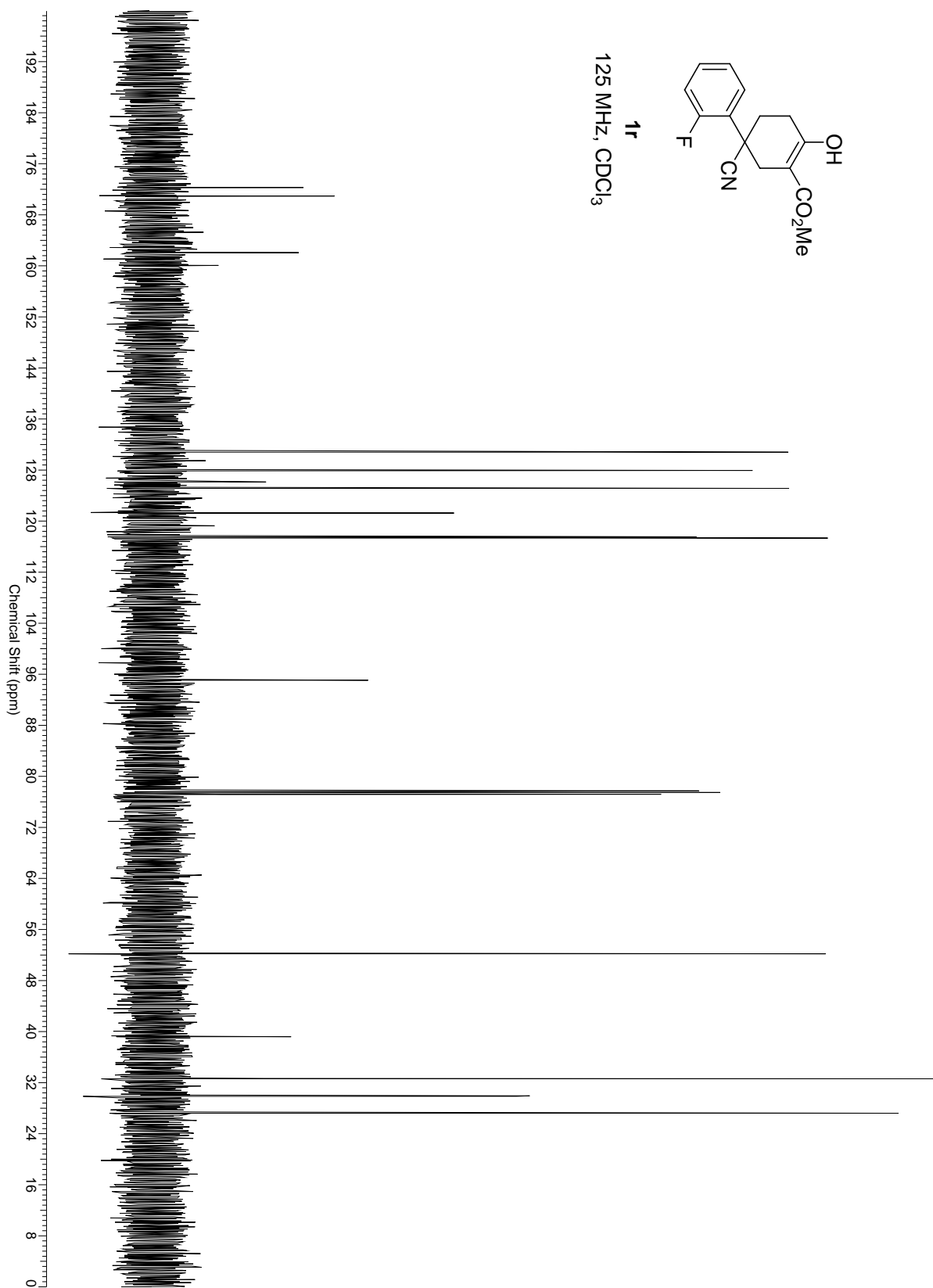
Supporting Information



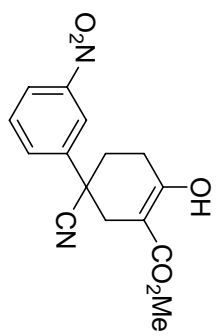
1r
400 MHz, CDCl₃



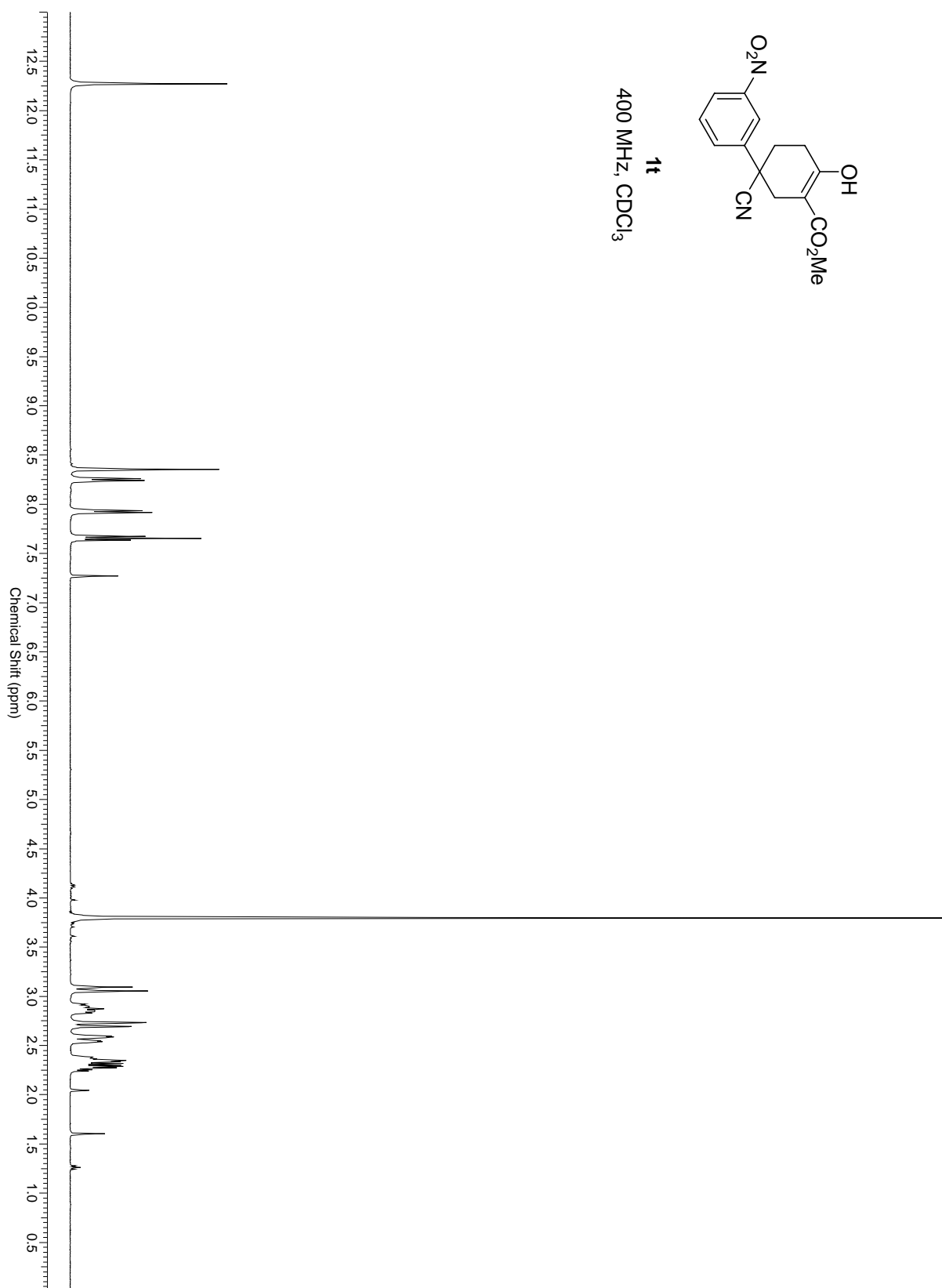
Supporting Information



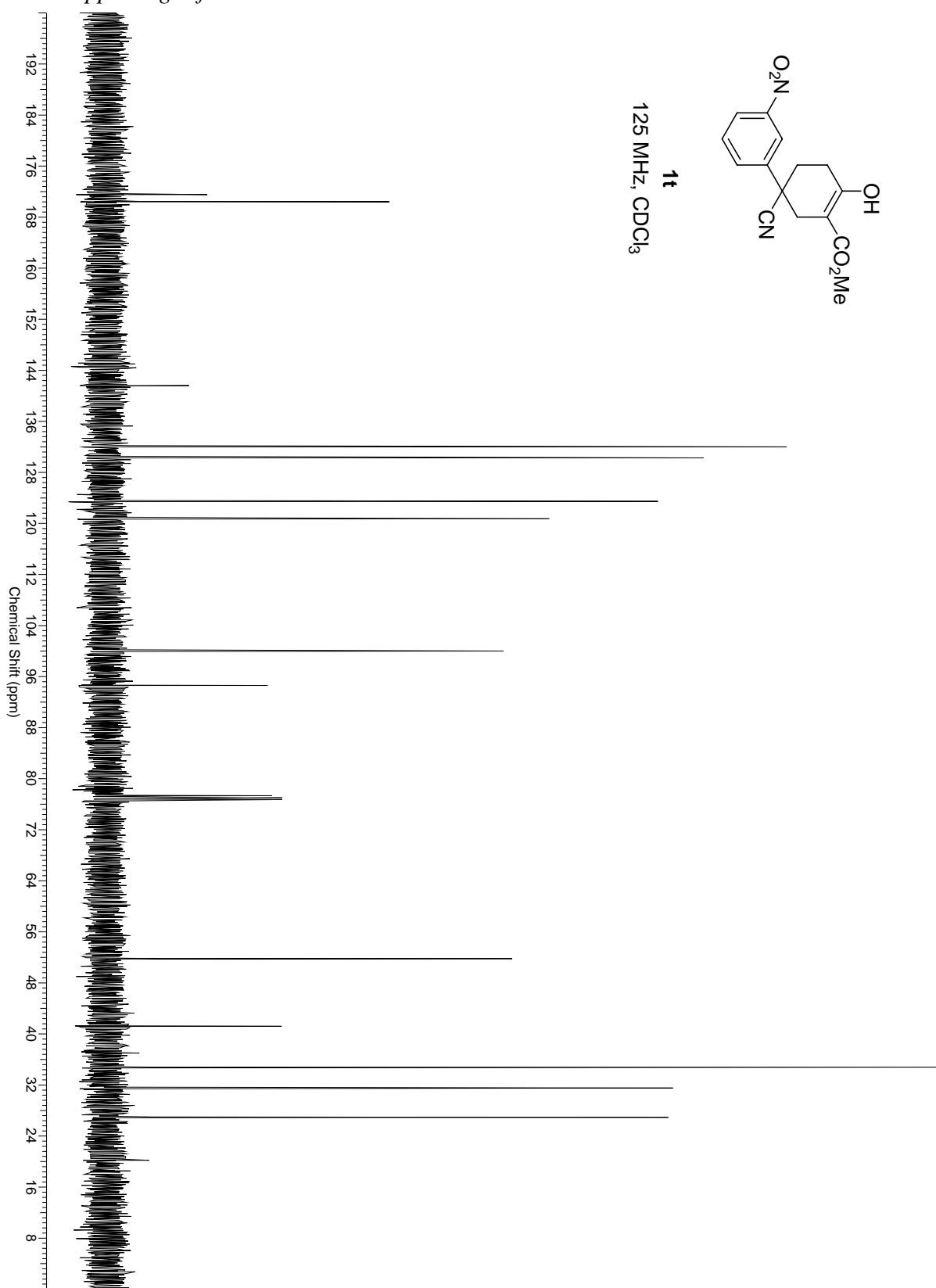
Supporting Information



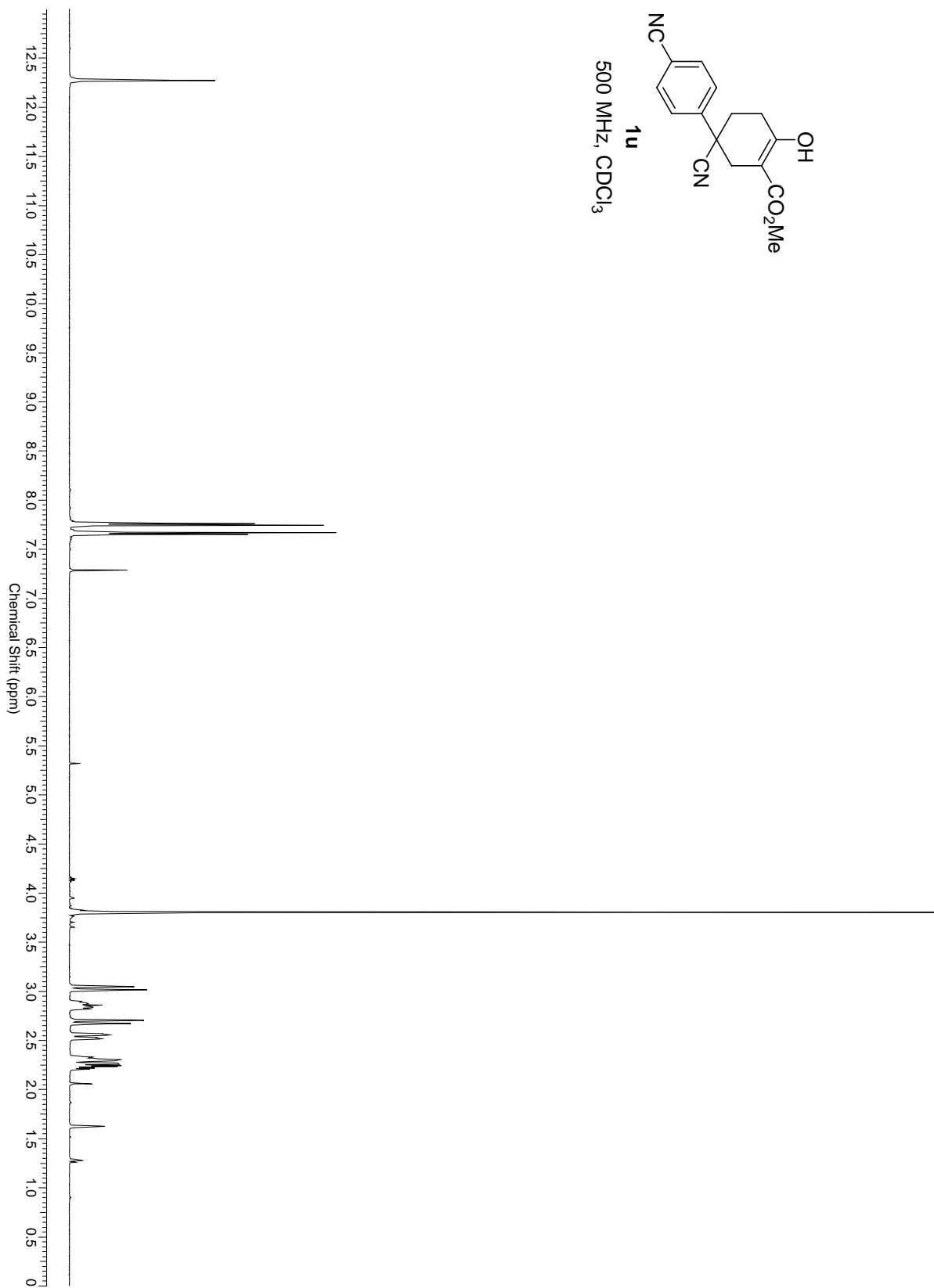
1t
400 MHz, CDCl₃



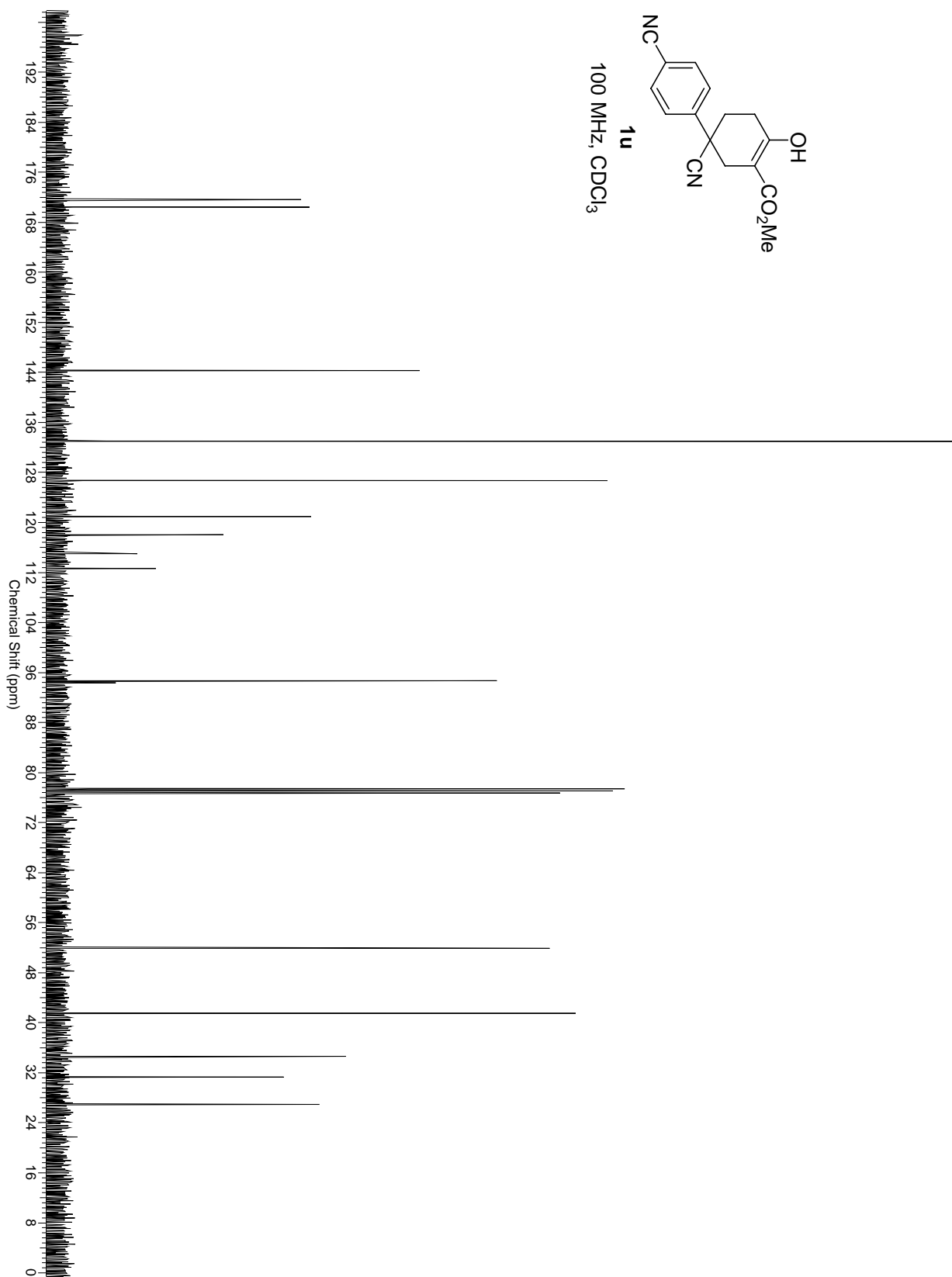
Supporting Information



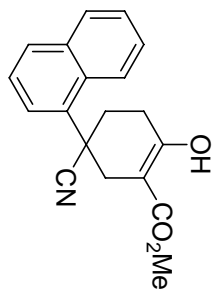
Supporting Information



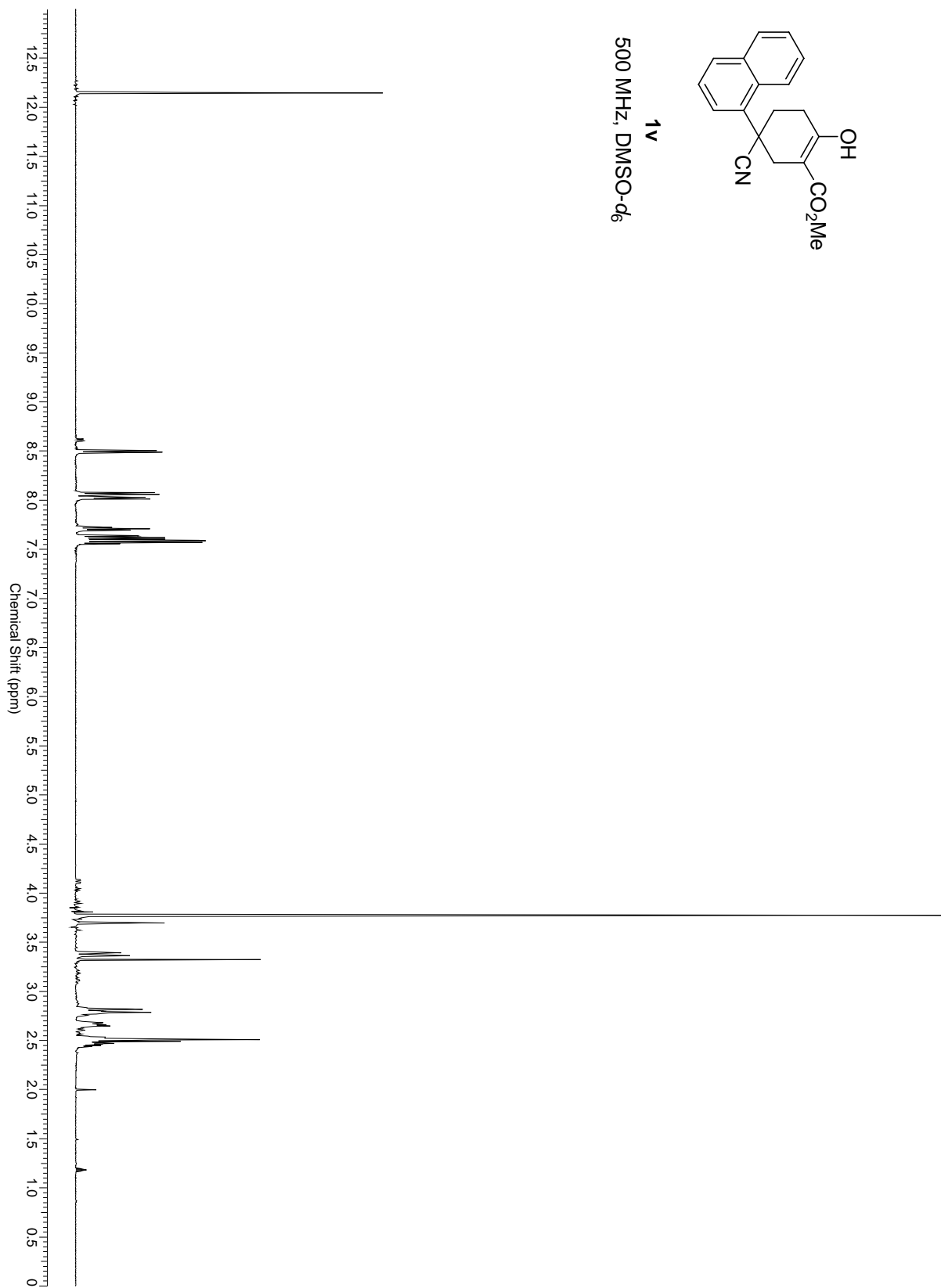
Supporting Information



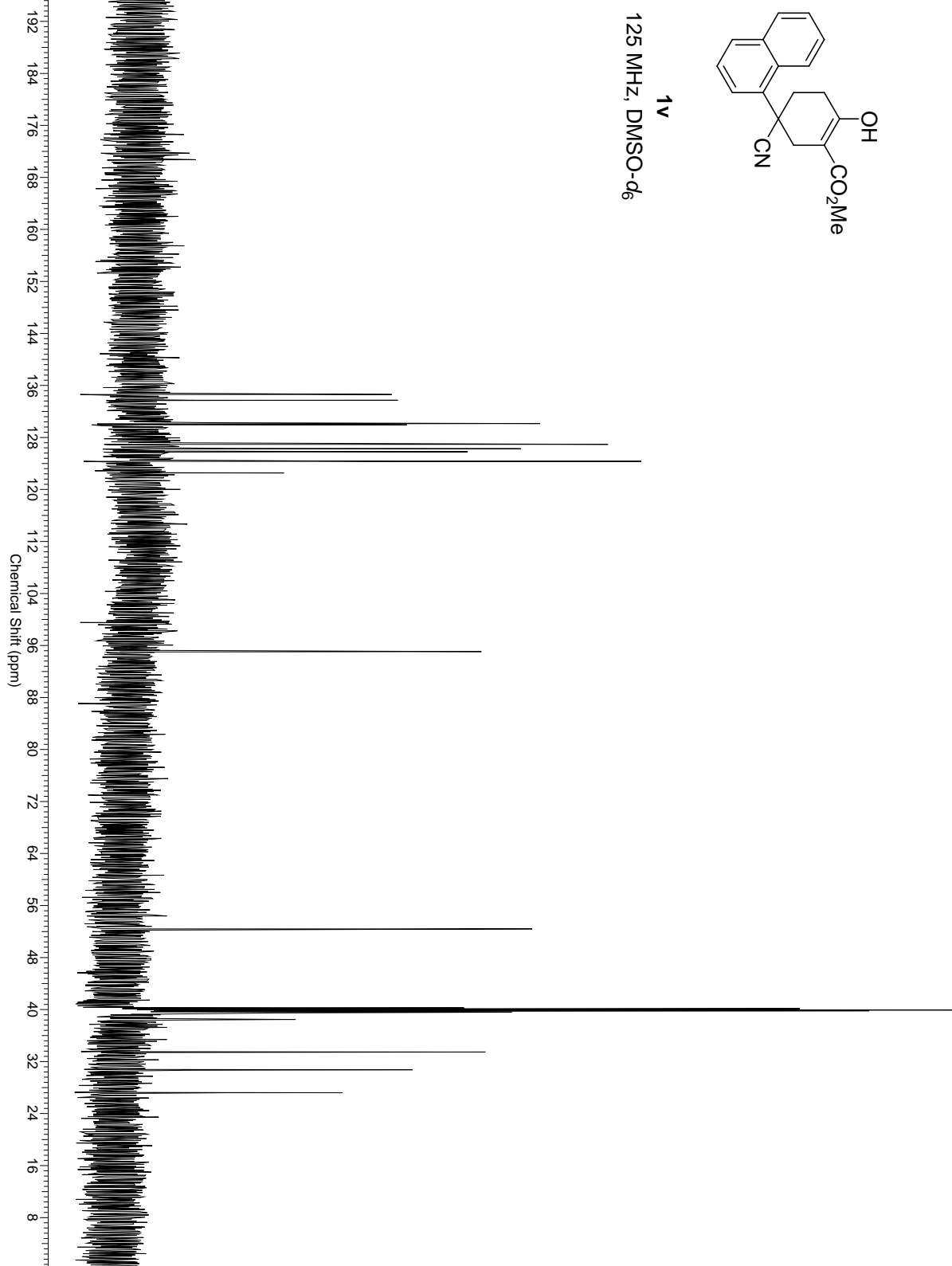
Supporting Information



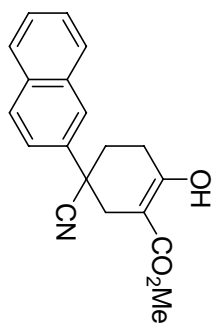
500 MHz, DMSO-*d*₆



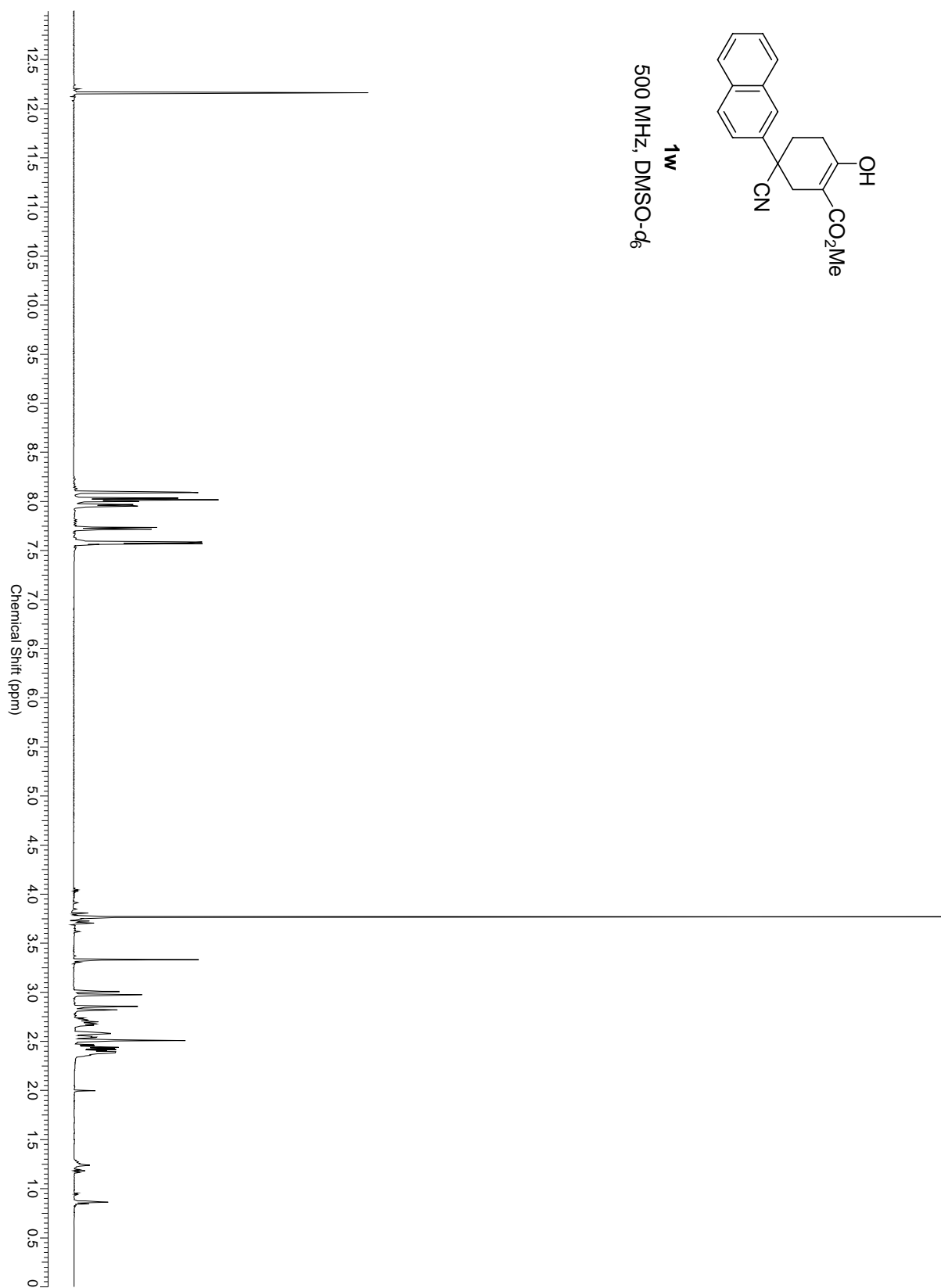
Supporting Information



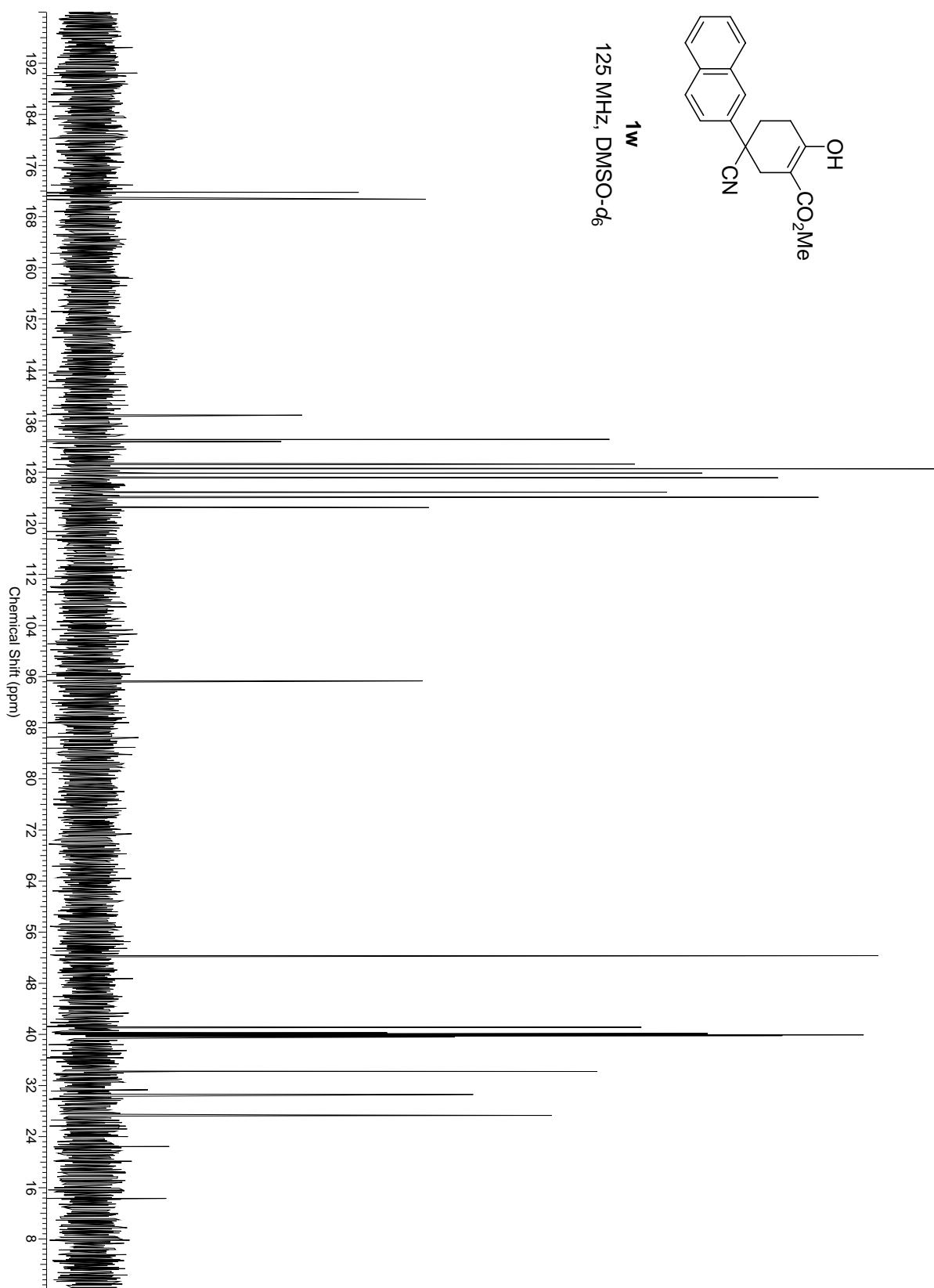
Supporting Information



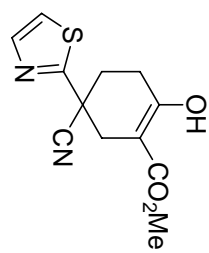
¹H
500 MHz, DMSO-d₆



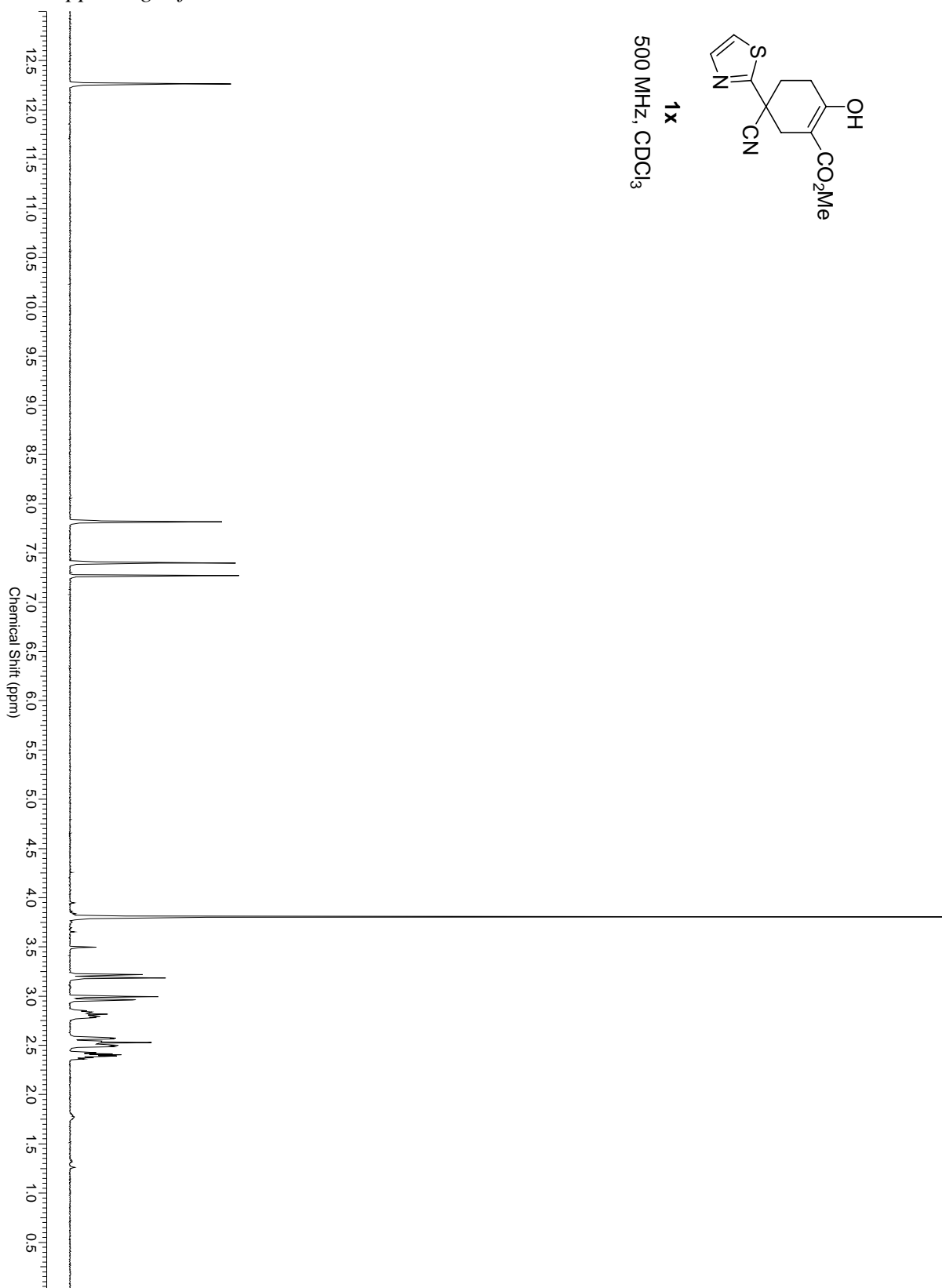
Supporting Information



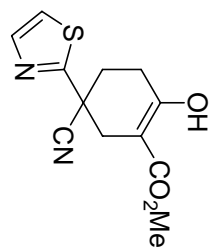
Supporting Information



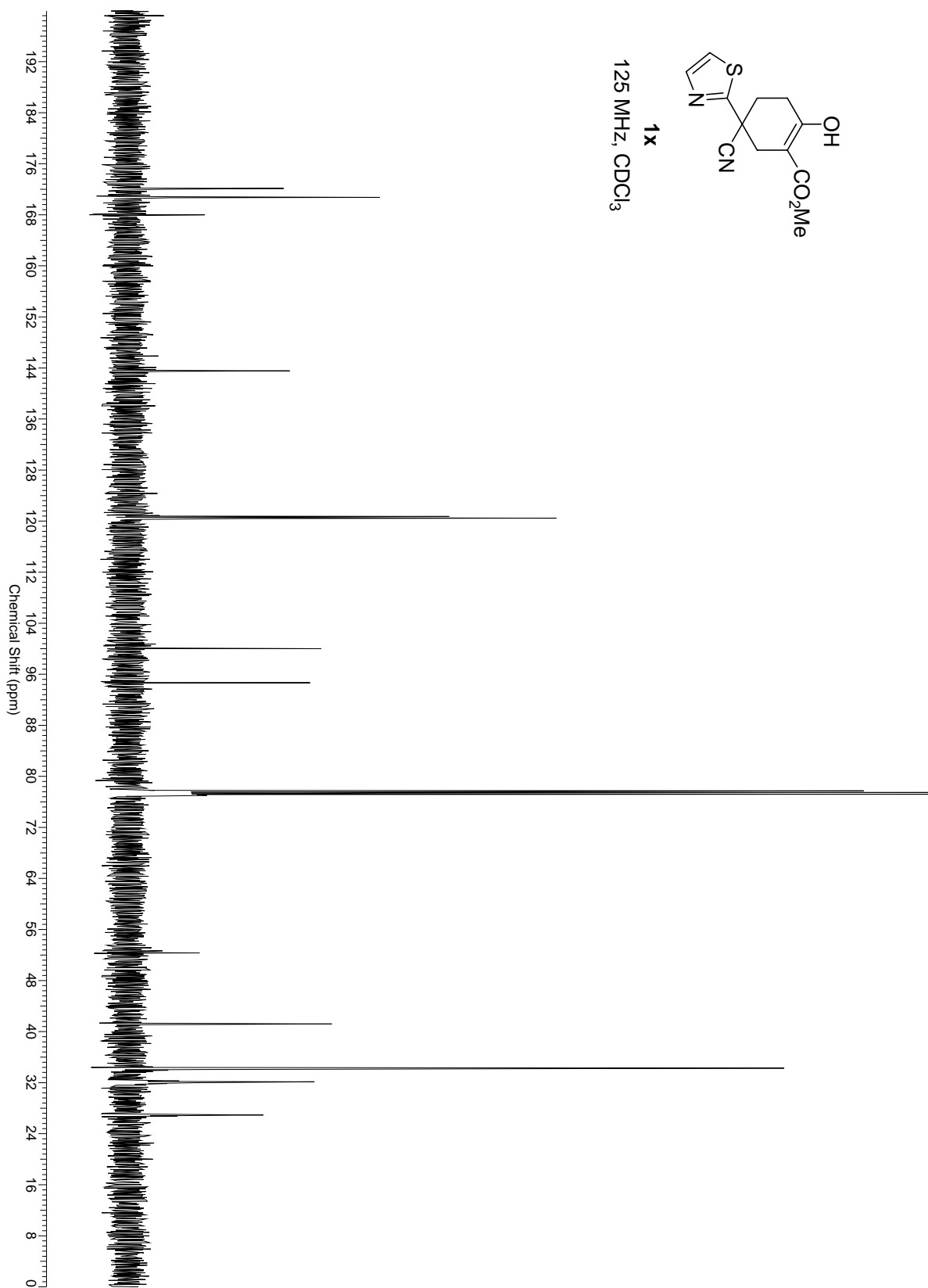
1x
500 MHz, CDCl₃



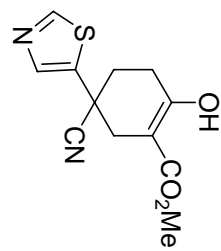
Supporting Information



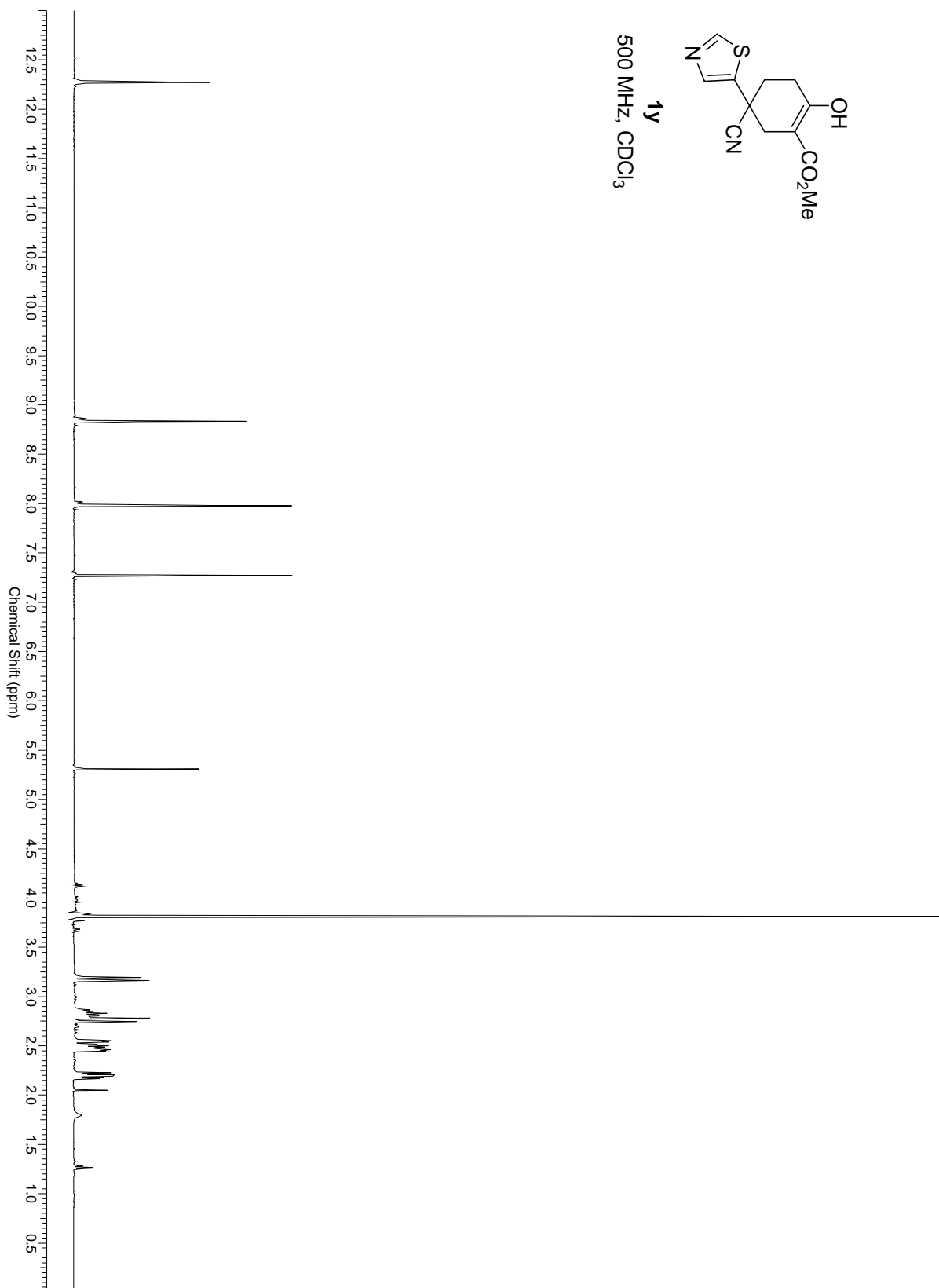
1x
125 MHz, CDCl₃



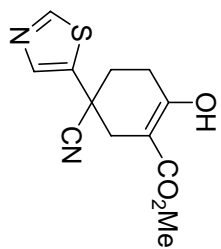
Supporting Information



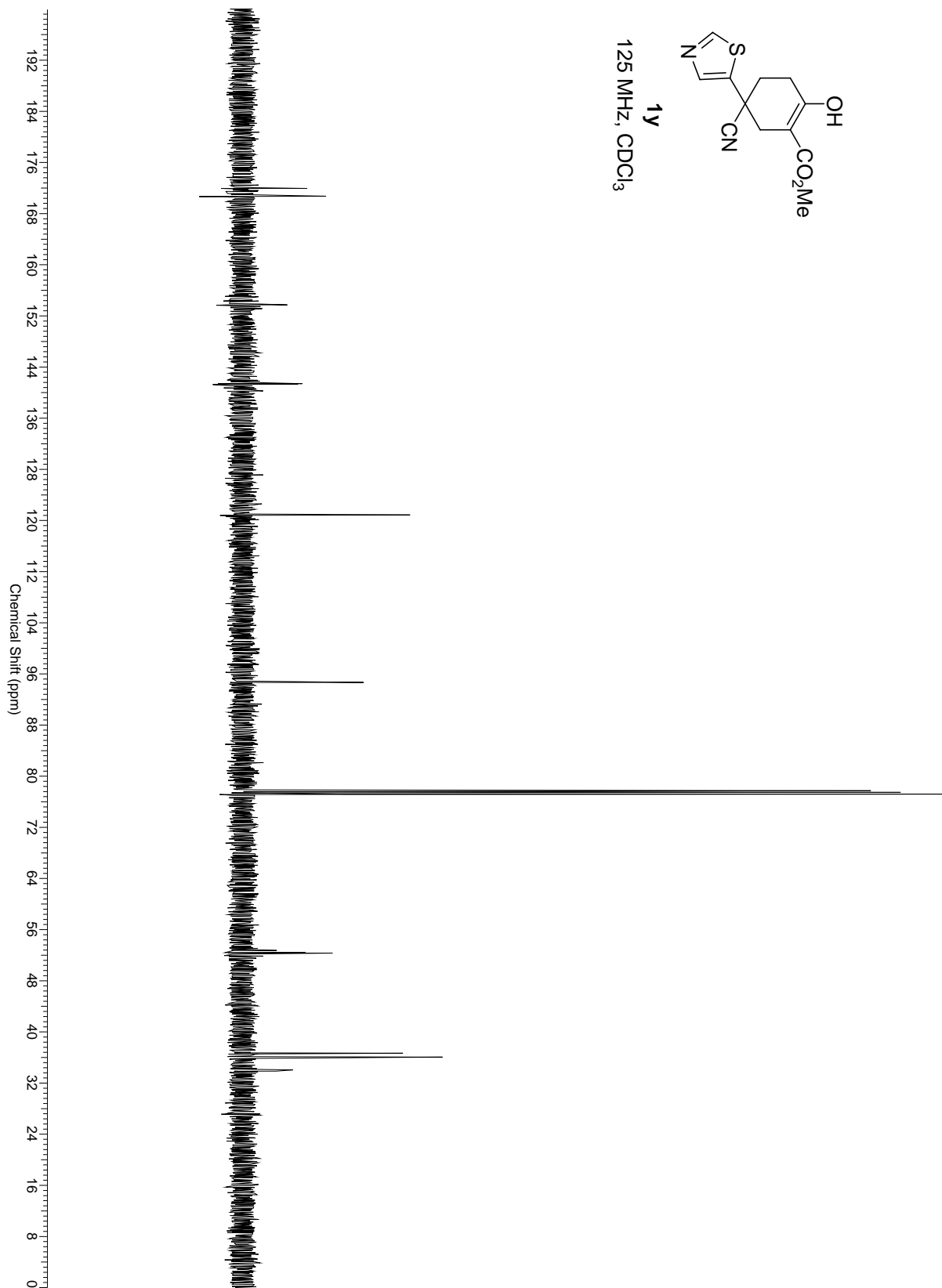
500 MHz, CDCl₃



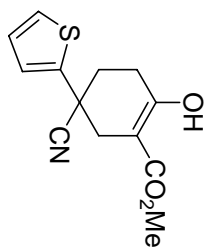
Supporting Information



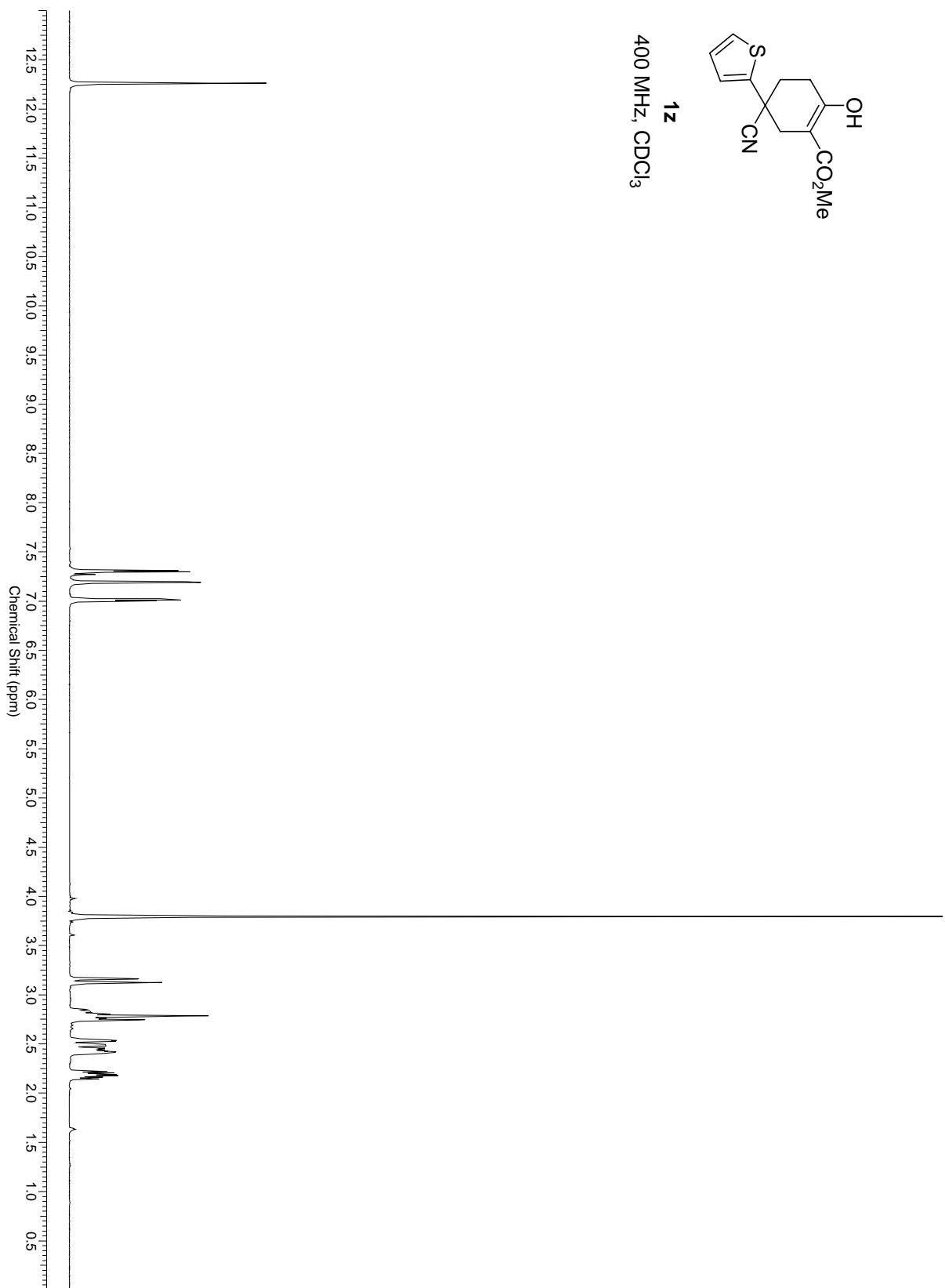
1y
125 MHz, CDCl₃



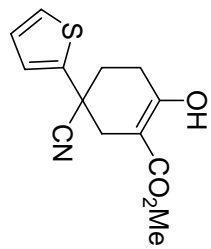
Supporting Information



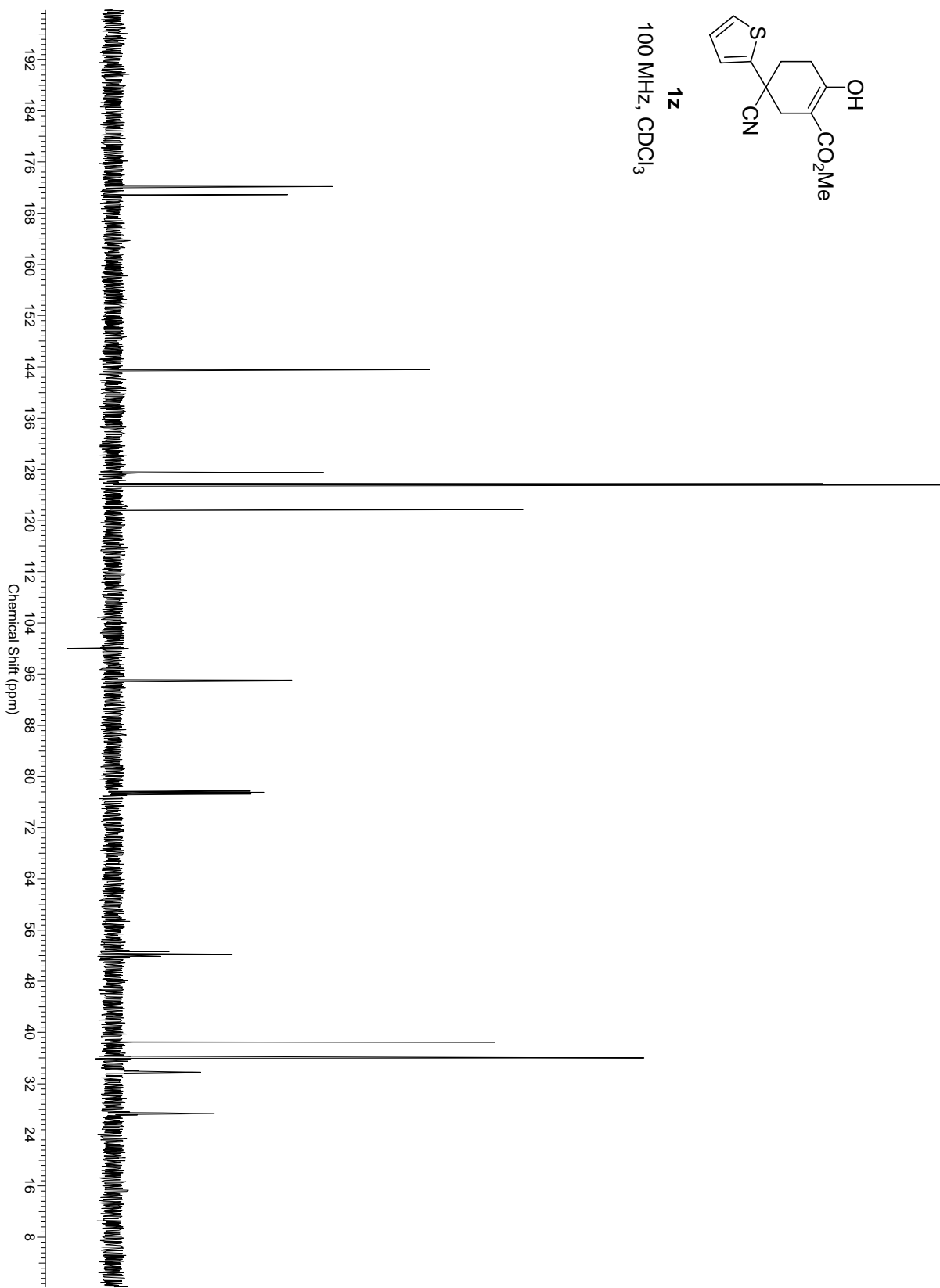
12
400 MHz, CDCl₃



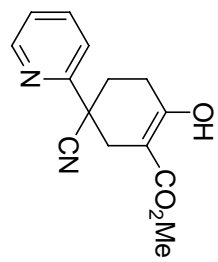
Supporting Information



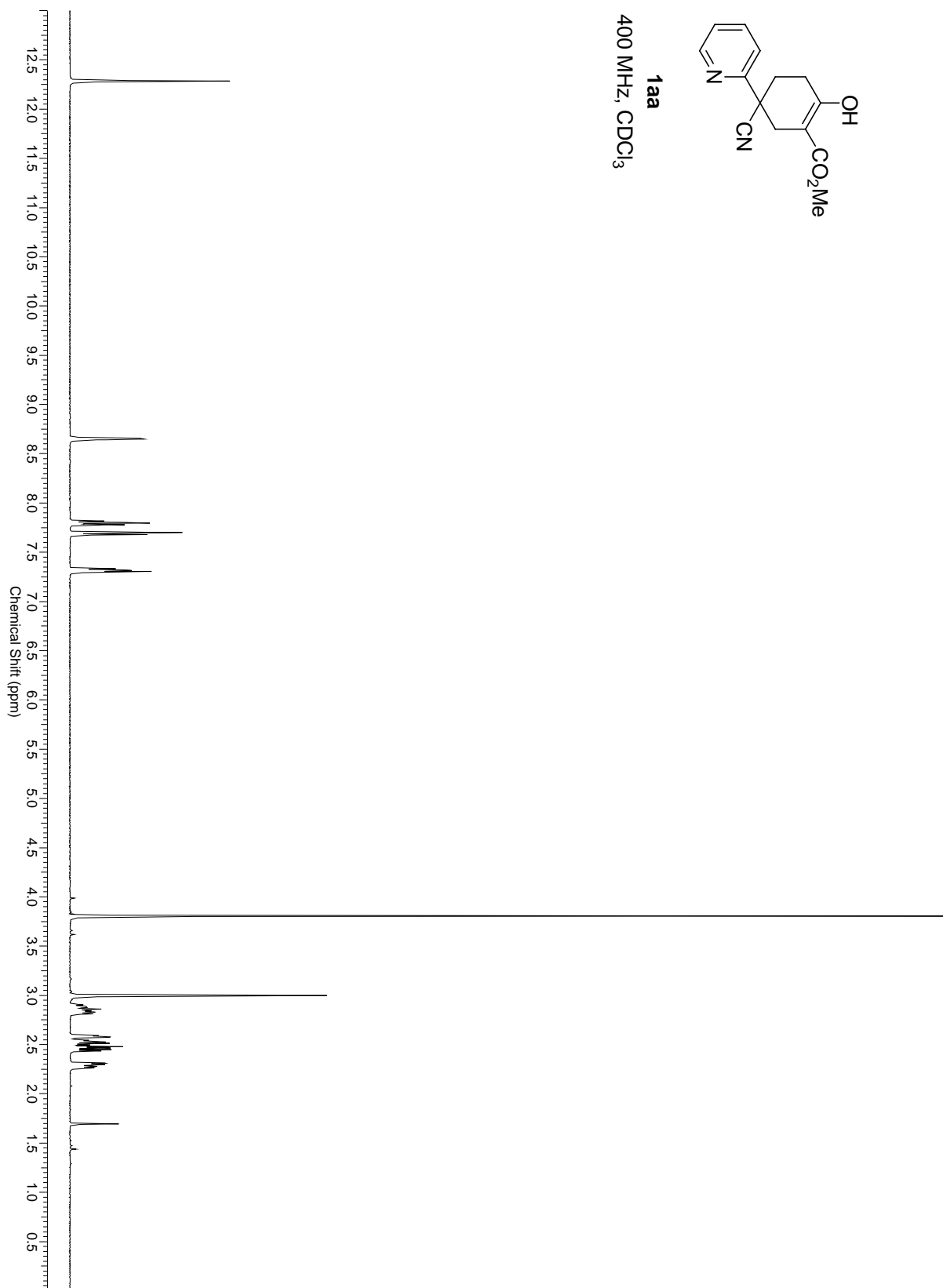
1z
100 MHz, CDCl₃



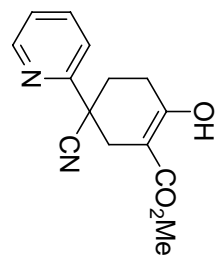
Supporting Information



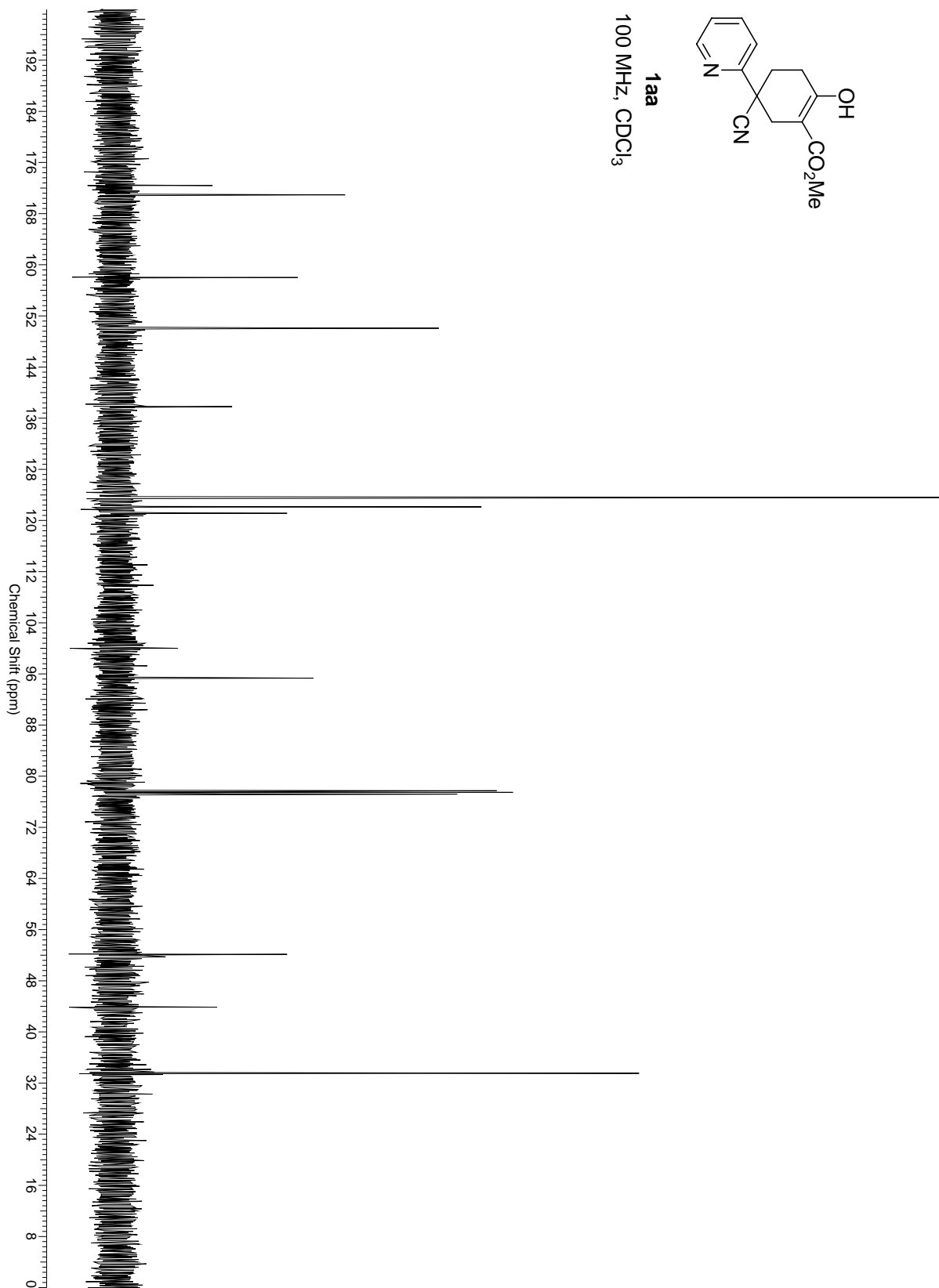
1aa
400 MHz, CDCl₃



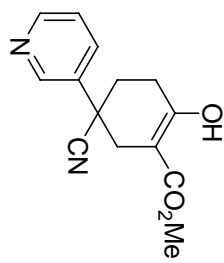
Supporting Information



1aa
100 MHz, CDCl₃

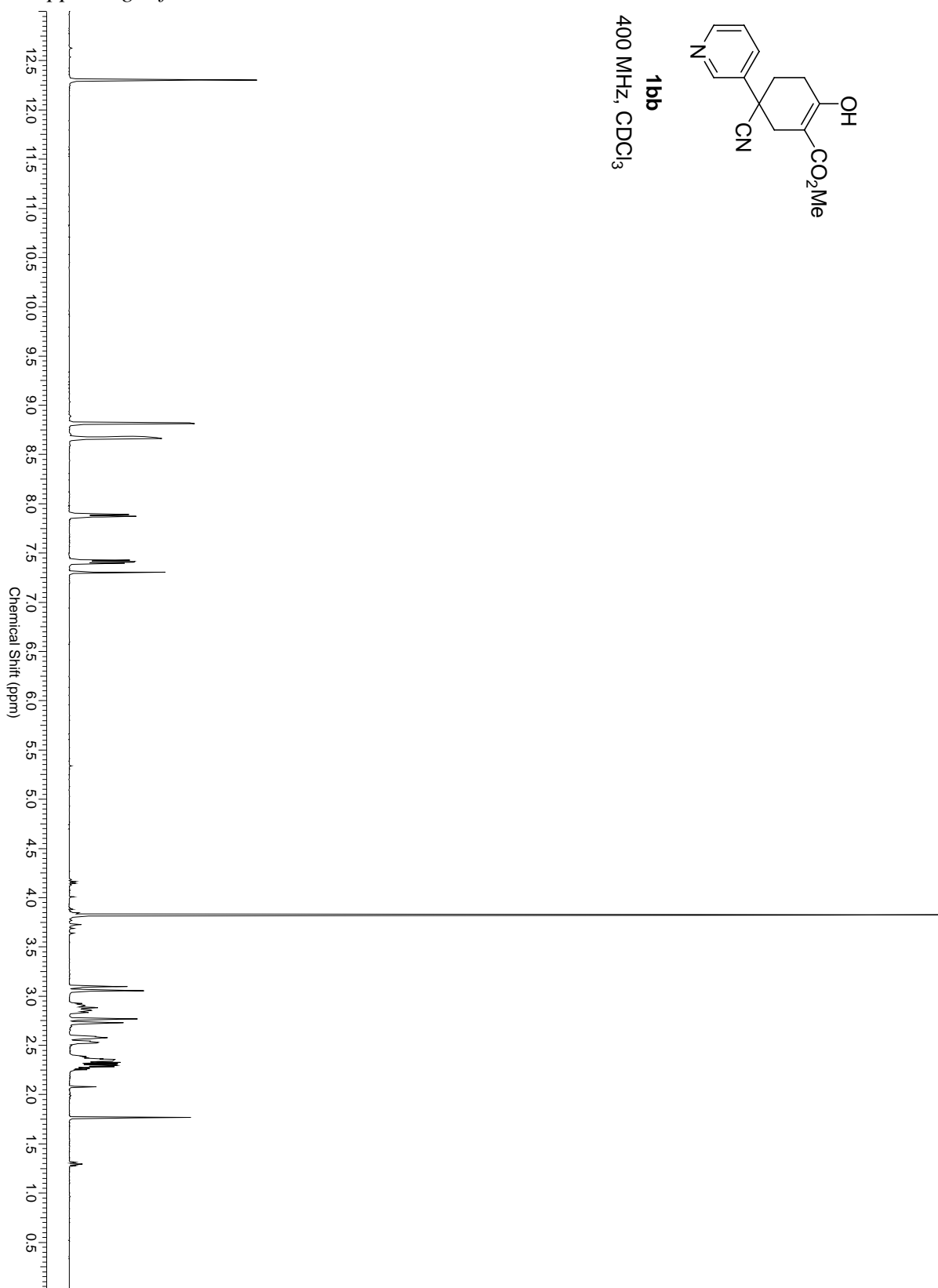


Supporting Information

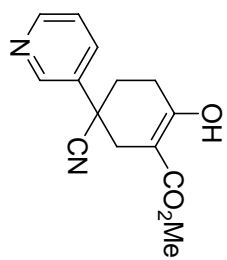


1bb

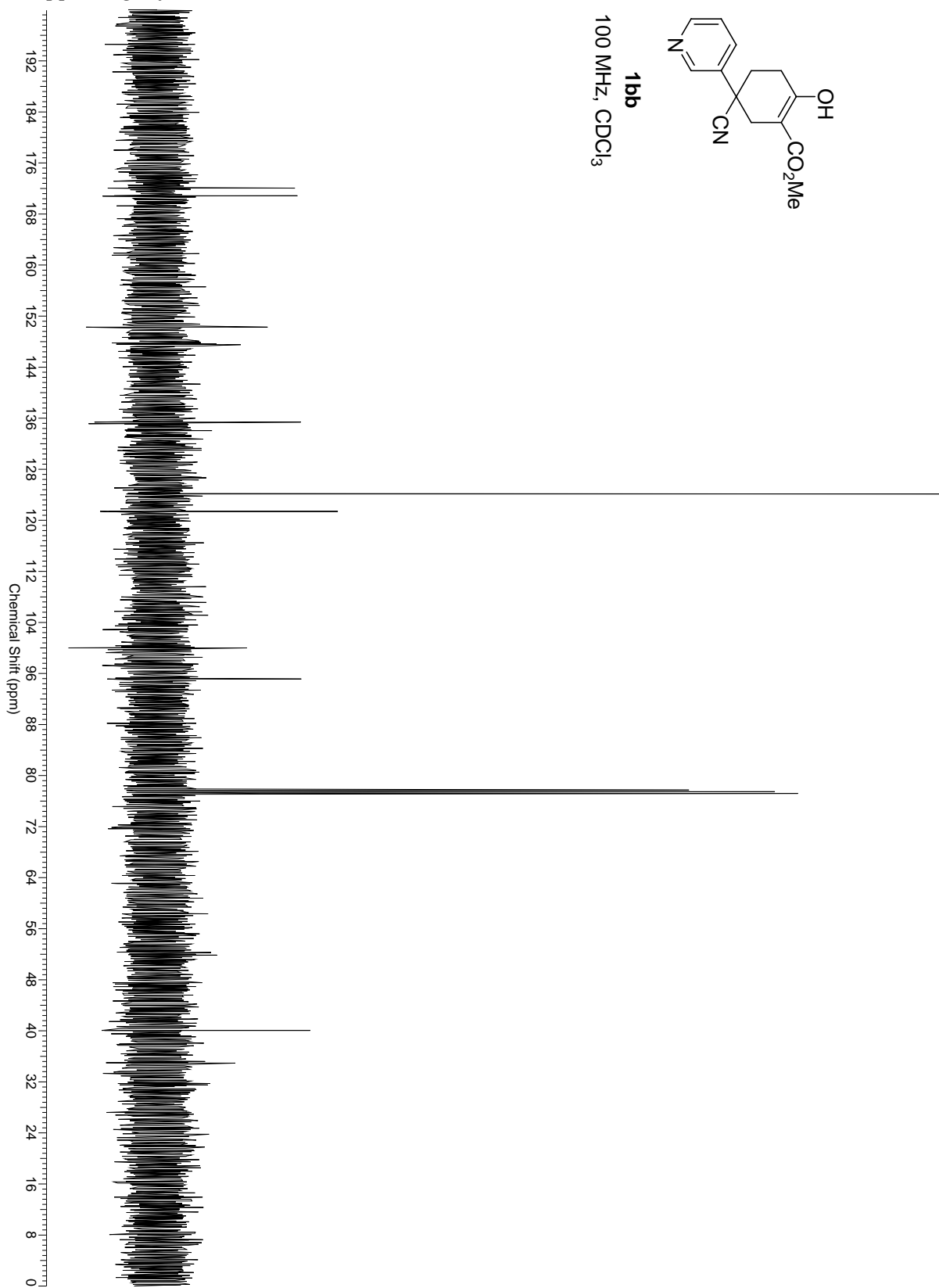
400 MHz, CDCl₃



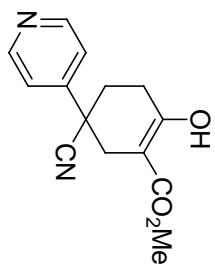
Supporting Information



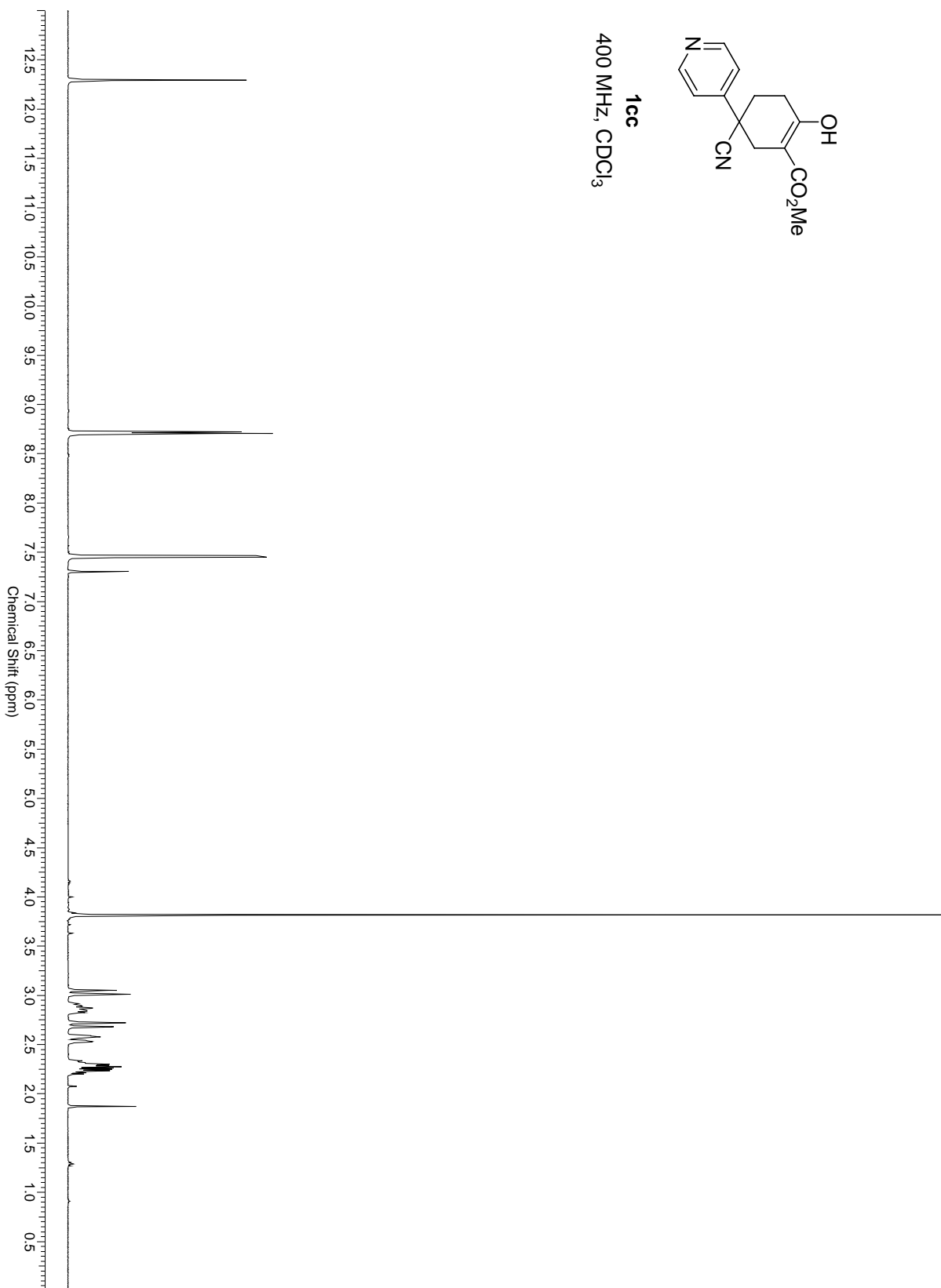
1bb
100 MHz, CDCl₃



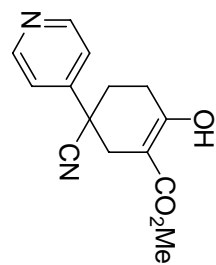
Supporting Information



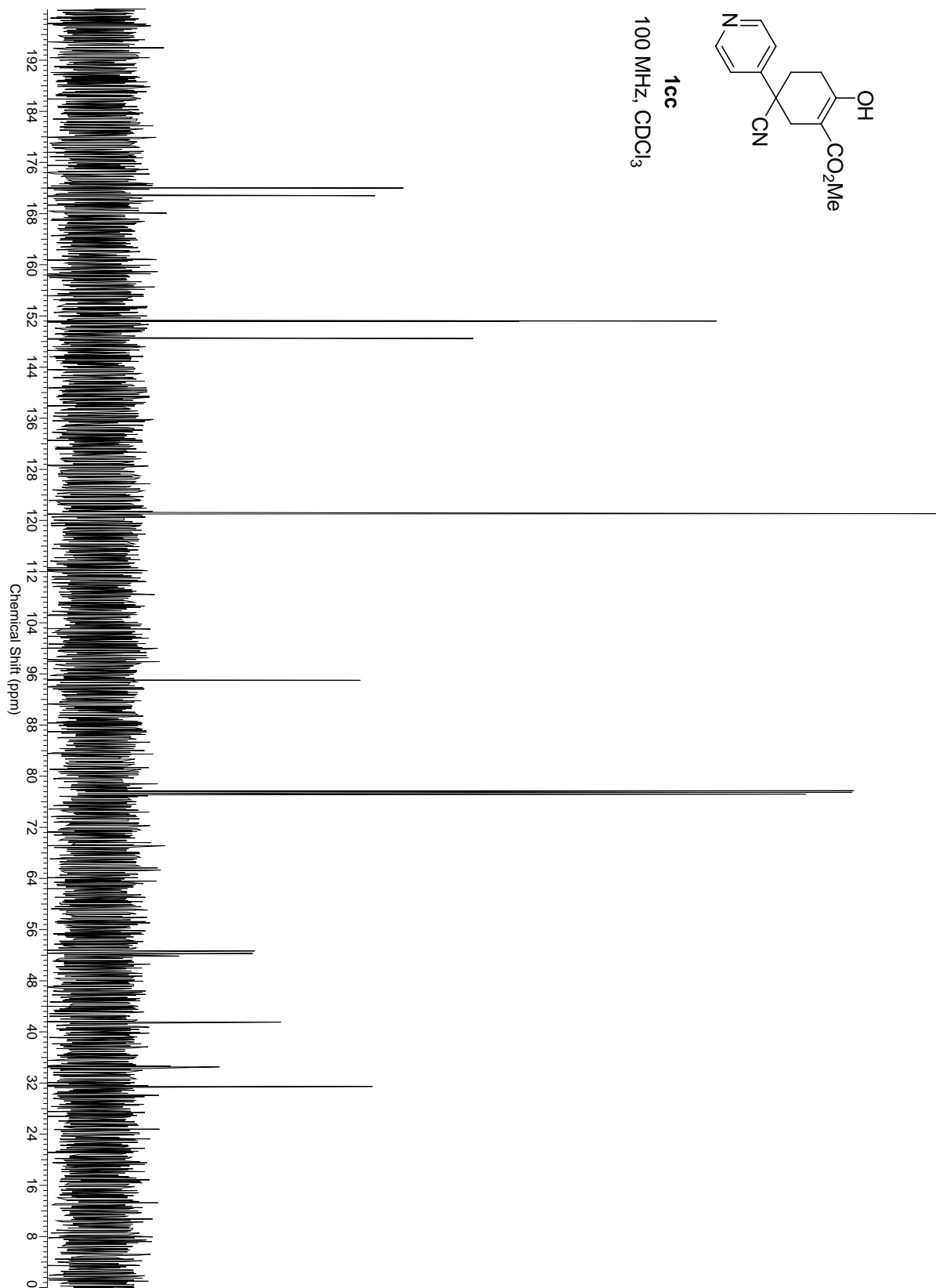
1cc
400 MHz, CDCl₃

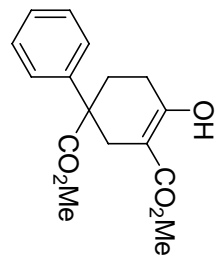


Supporting Information



1cc
100 MHz, CDCl₃

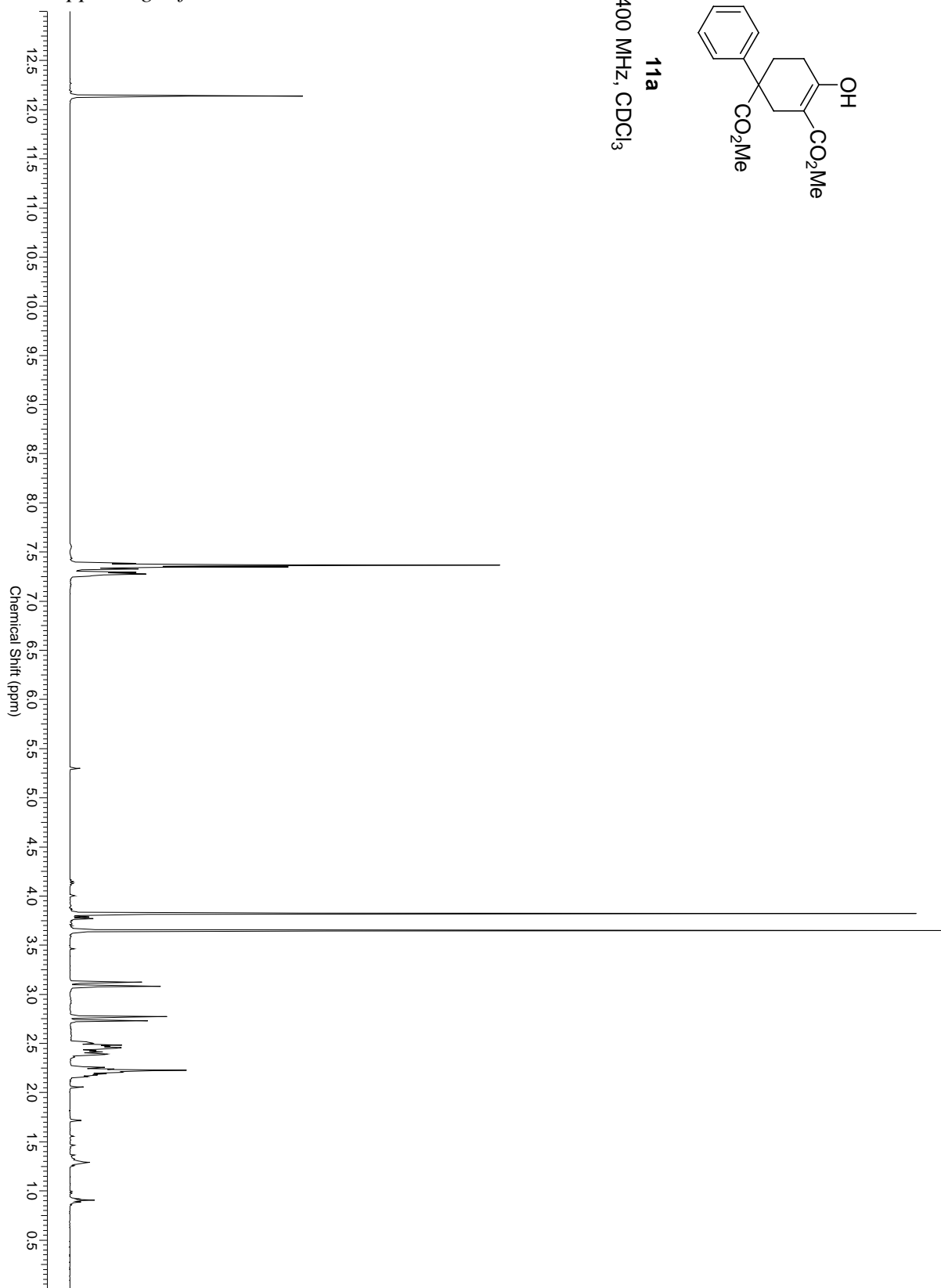




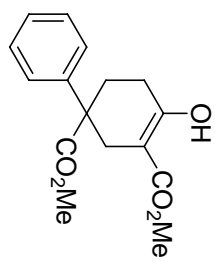
11a

400 MHz, CDCl₃

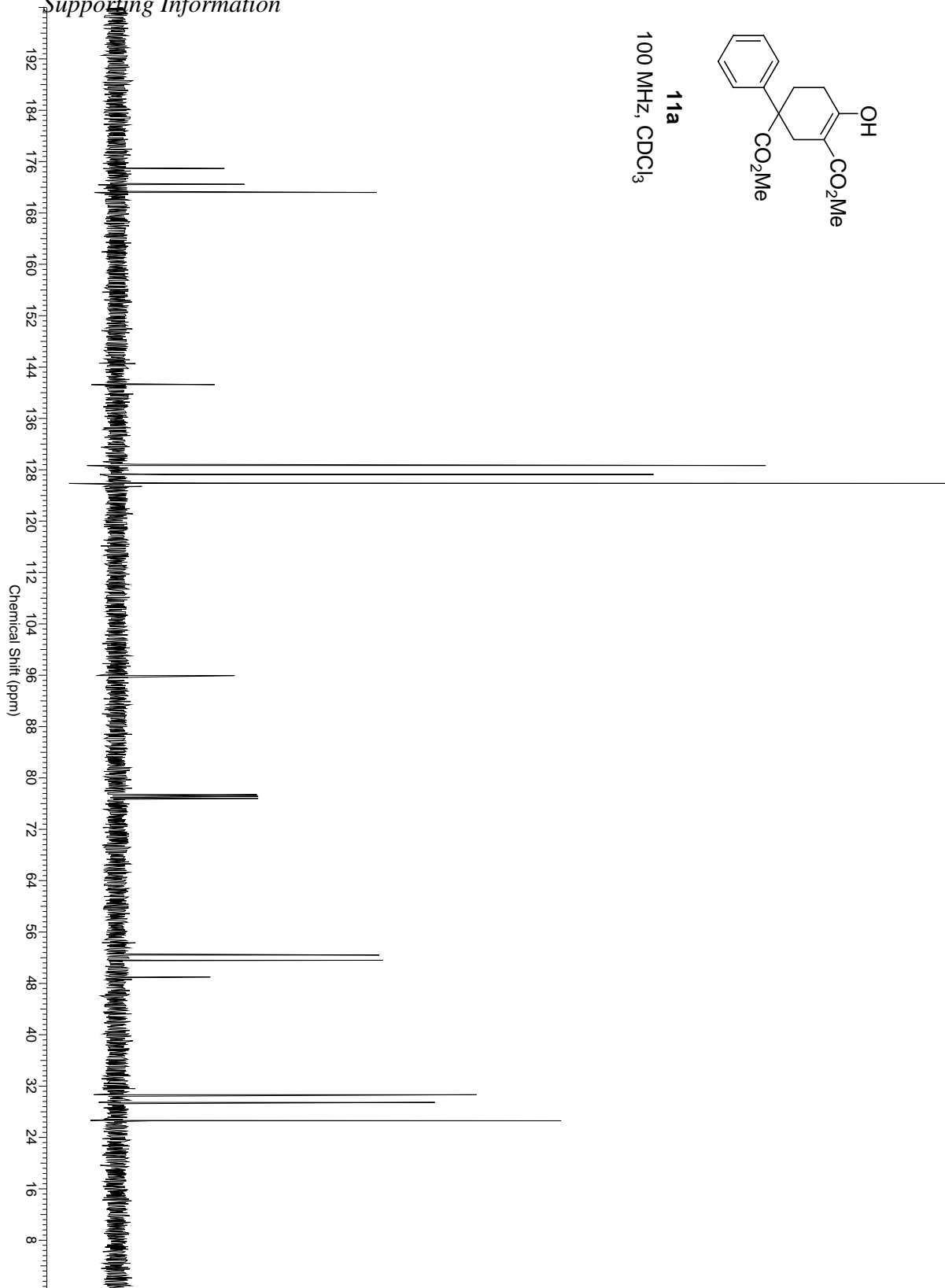
Supporting Information



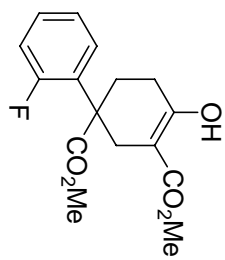
Supporting Information



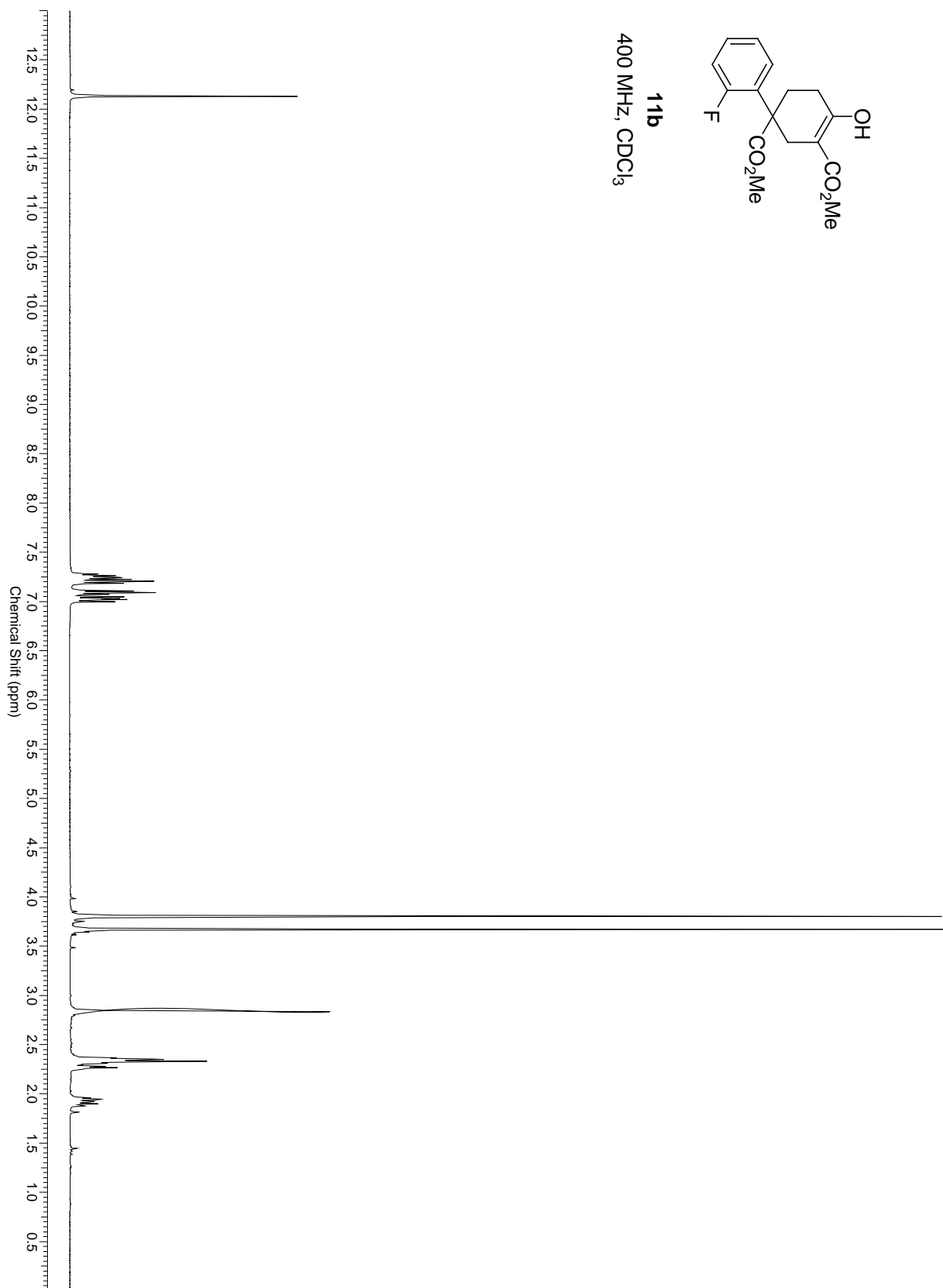
11a
100 MHz, CDCl₃



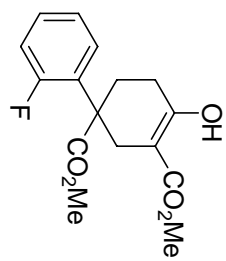
Supporting Information



11b
400 MHz, CDCl₃

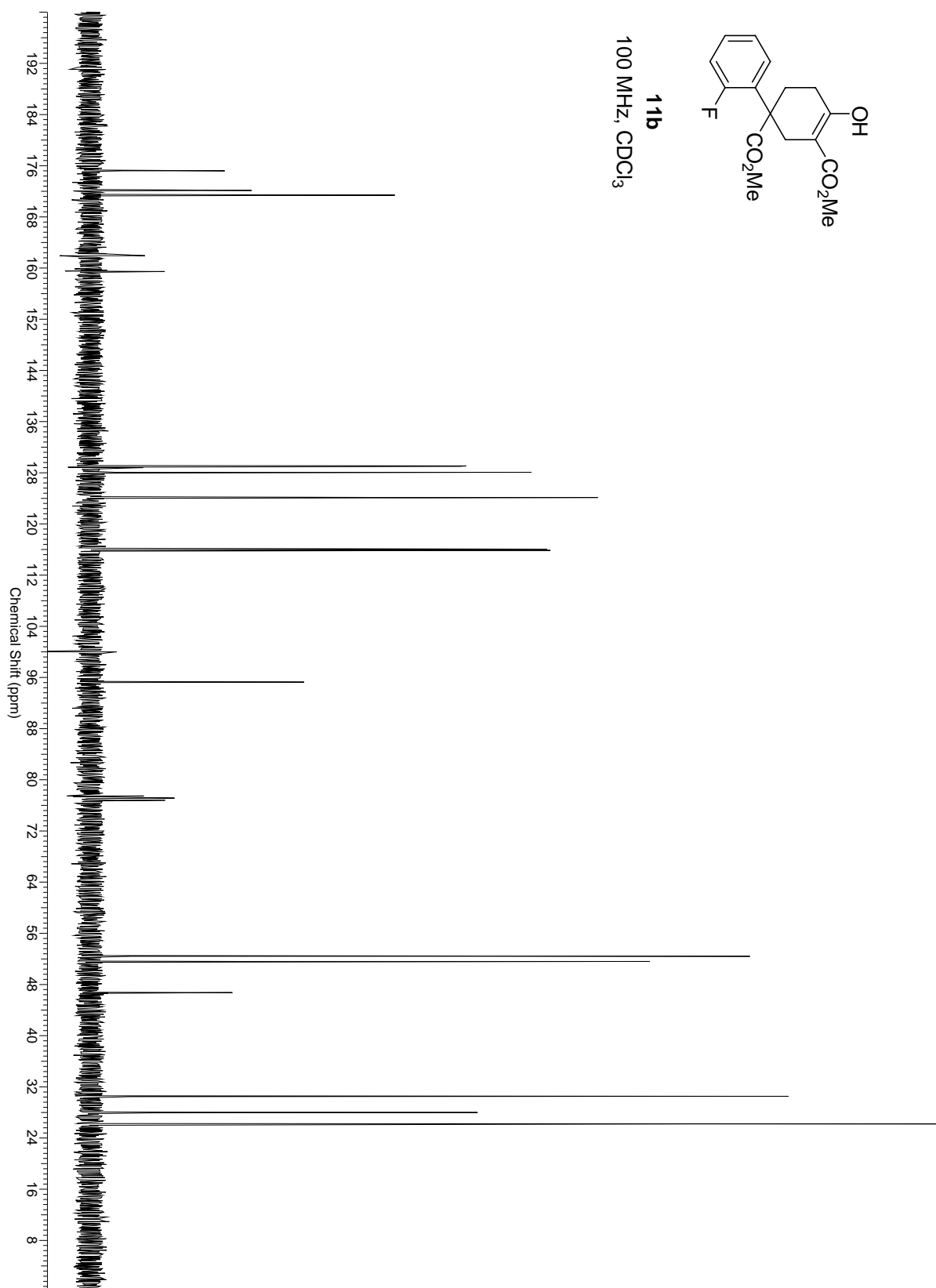


Supporting Information

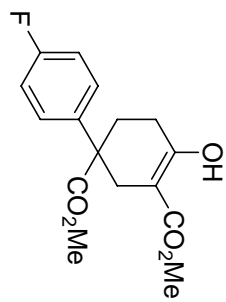


11b

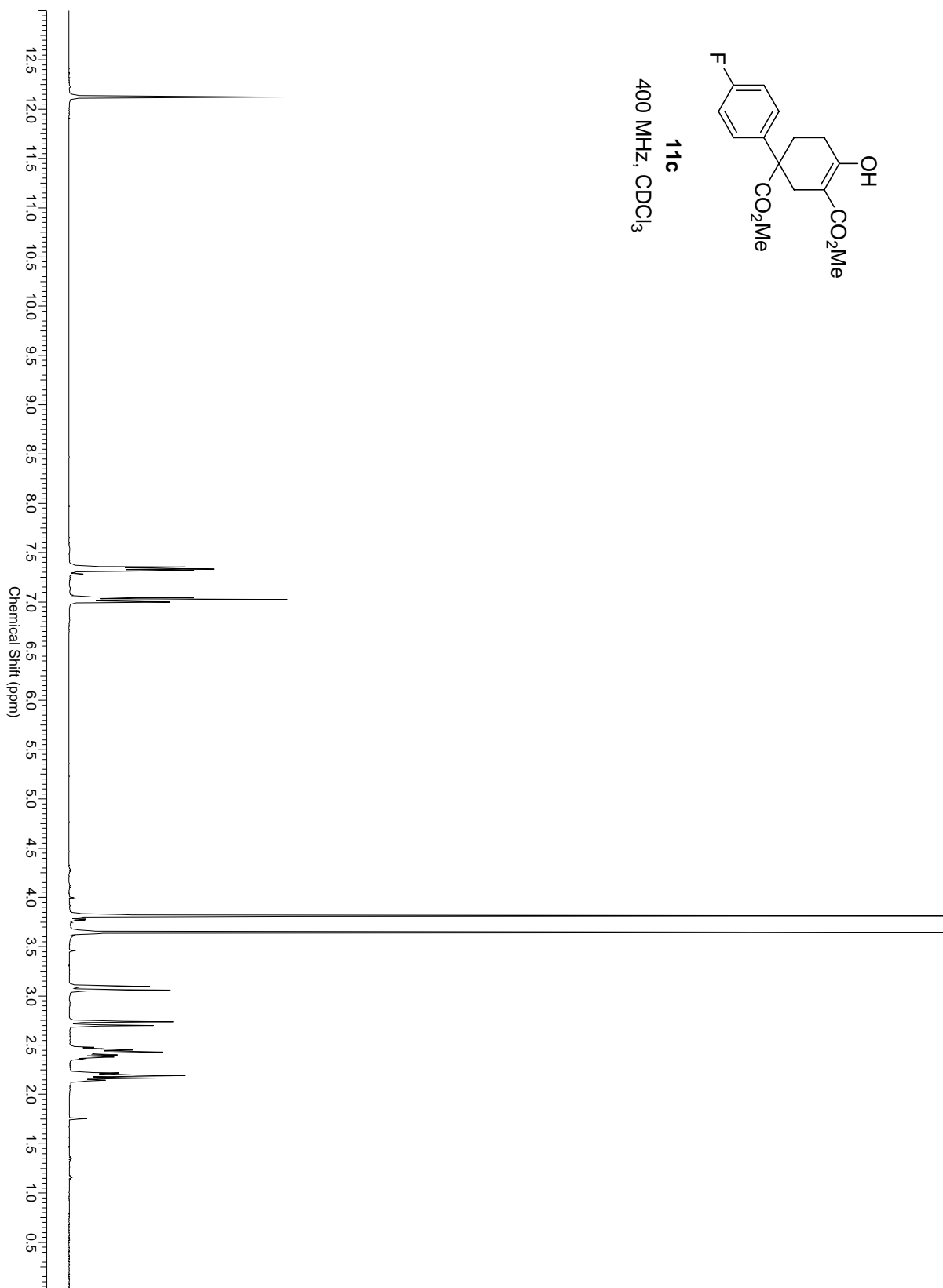
100 MHz, CDCl₃



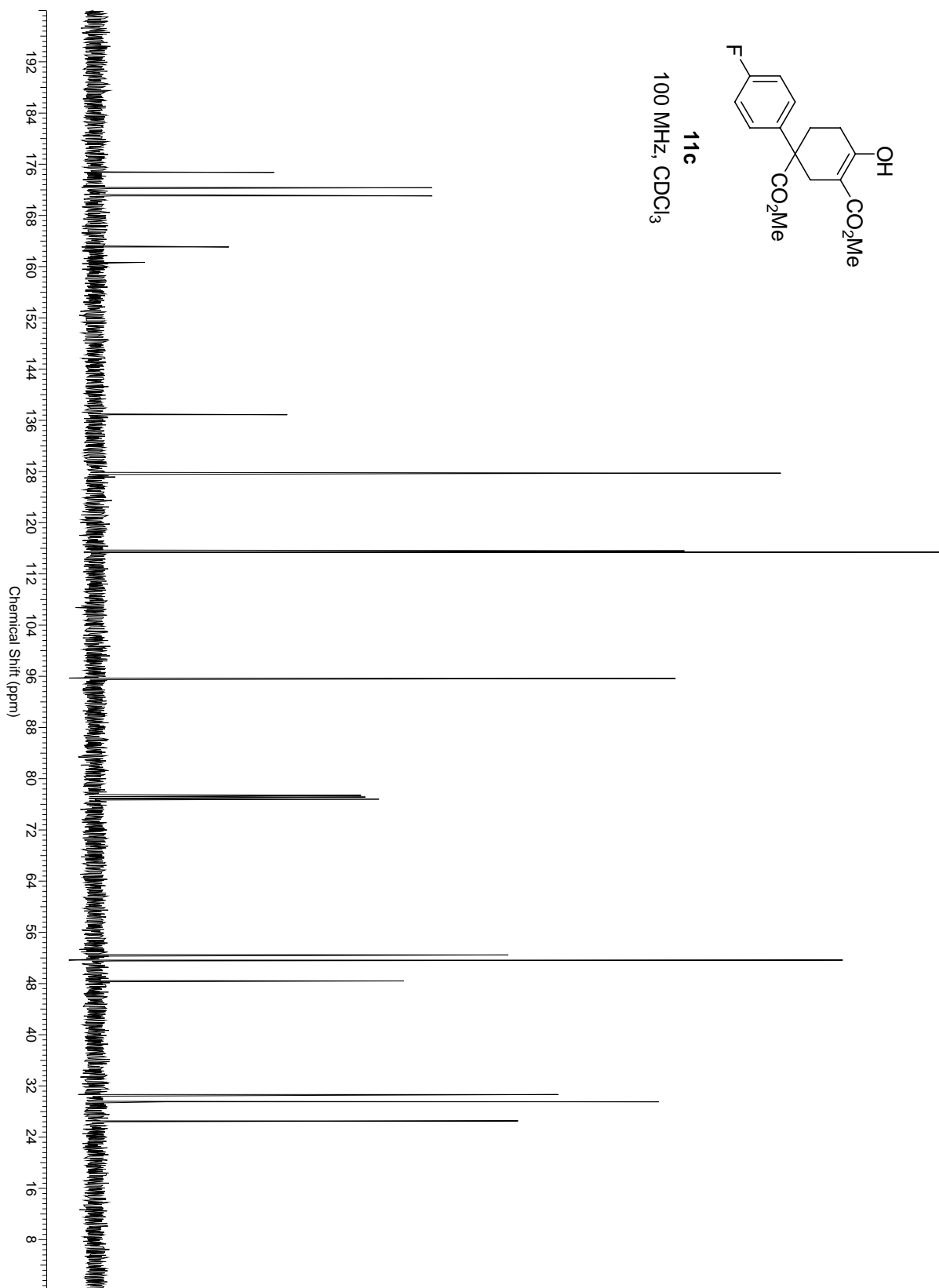
Supporting Information



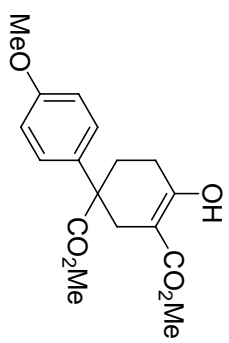
11c
400 MHz, CDCl₃



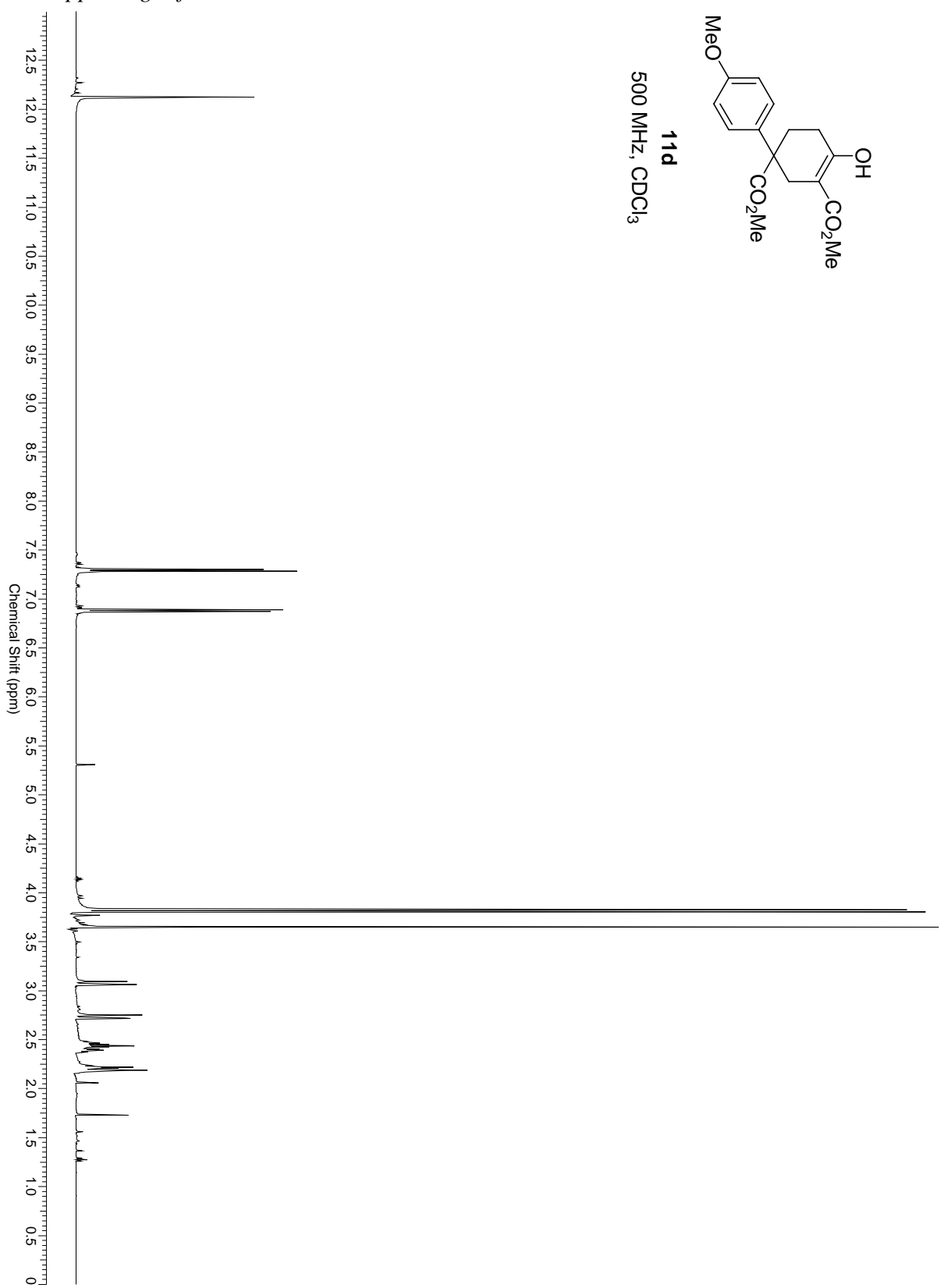
Supporting Information



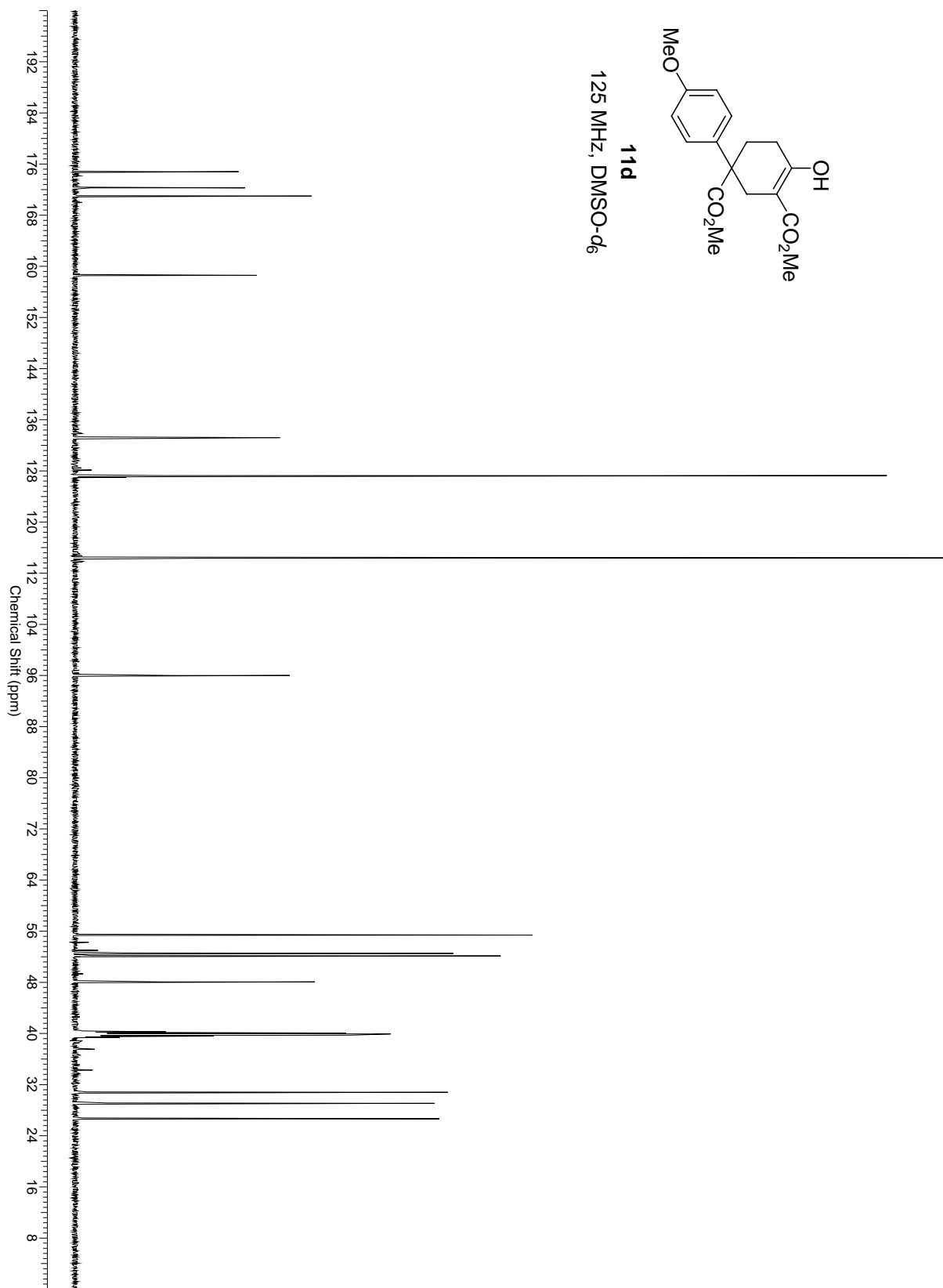
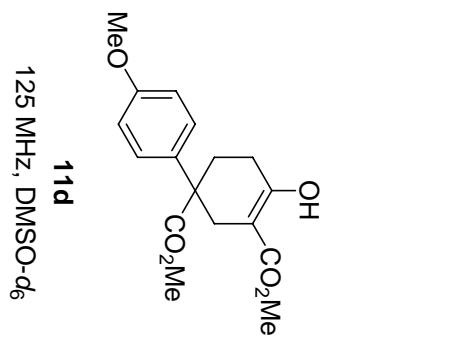
Supporting Information



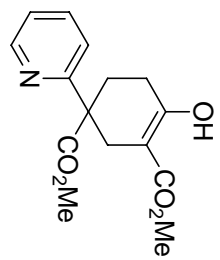
11d
500 MHz, CDCl₃



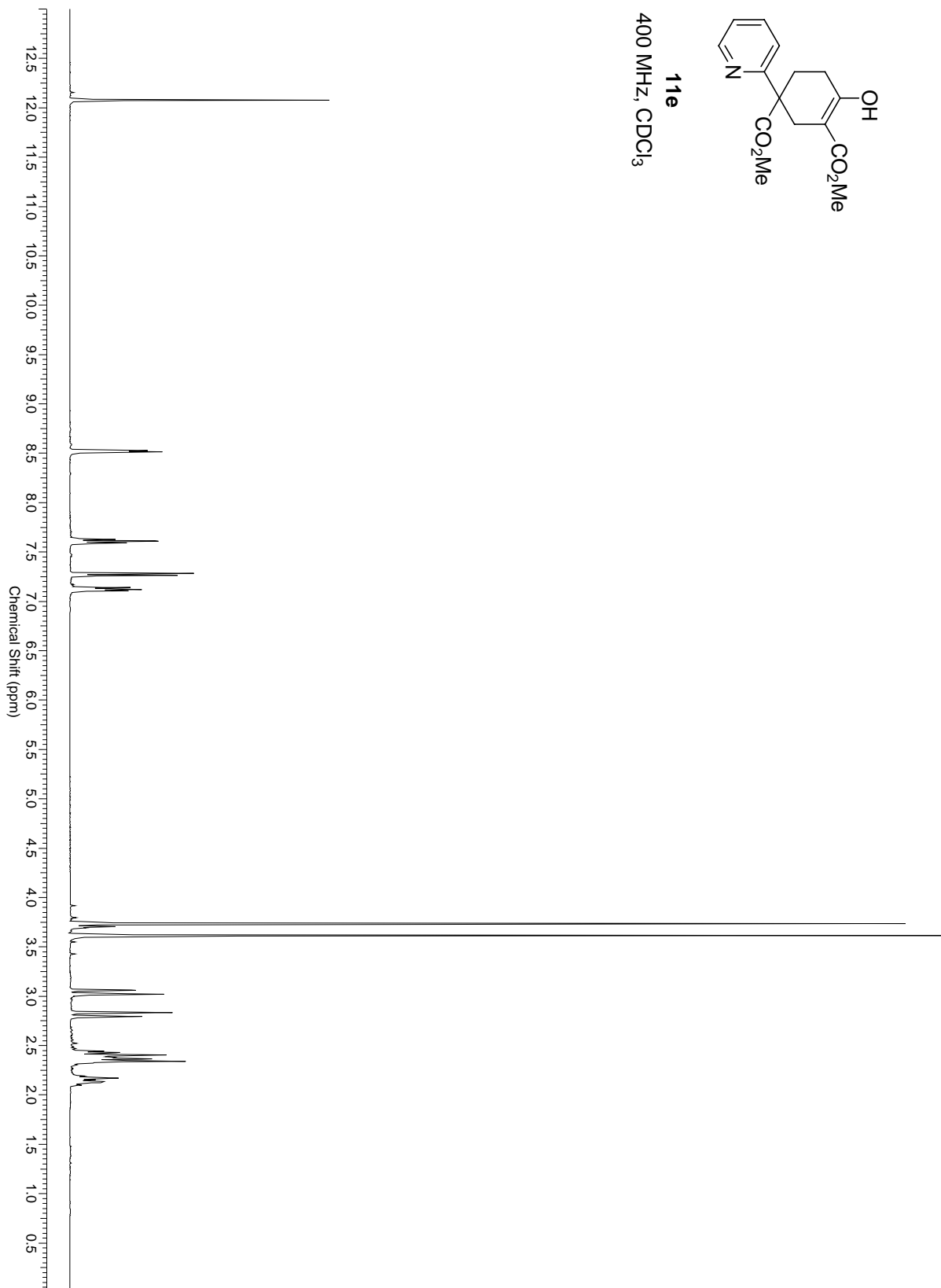
Supporting Information



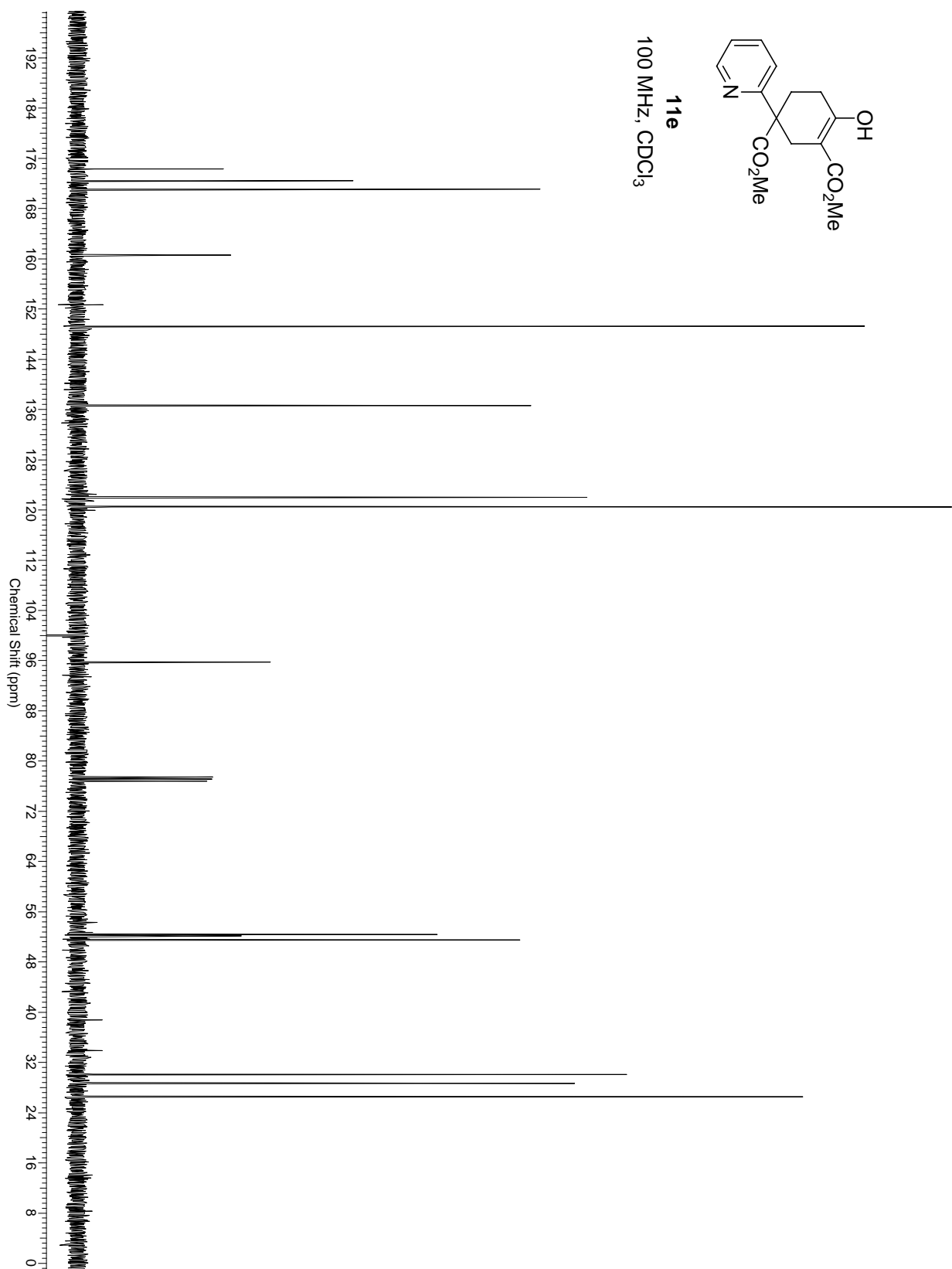
Supporting Information



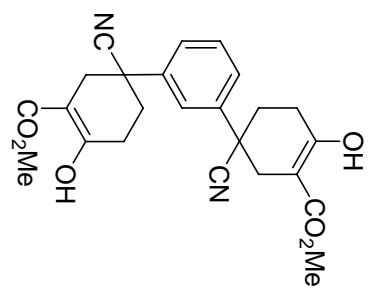
11e
400 MHz, CDCl₃



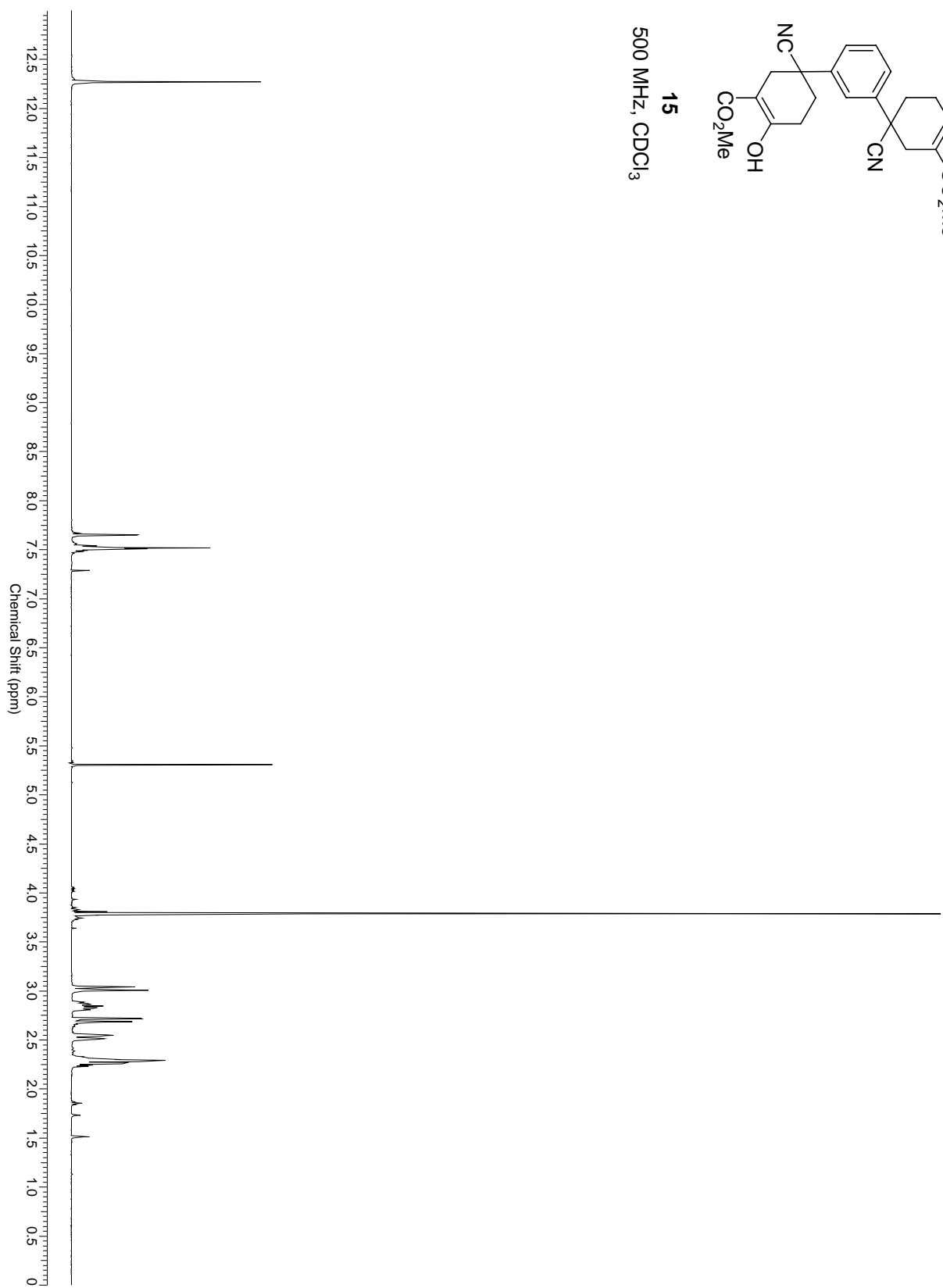
Supporting Information



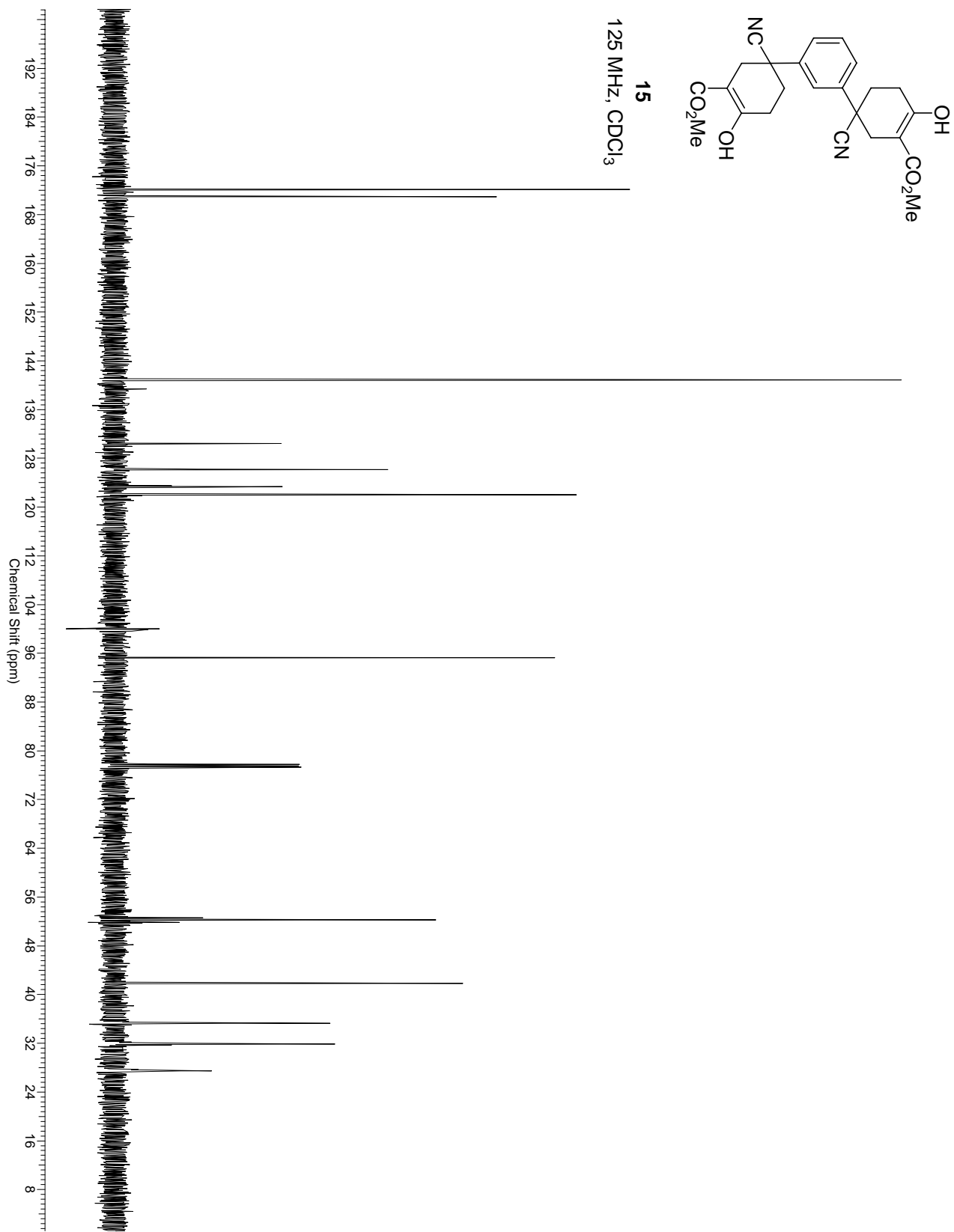
Supporting Information



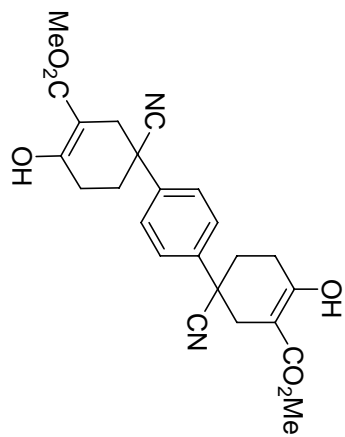
15
500 MHz, CDCl₃



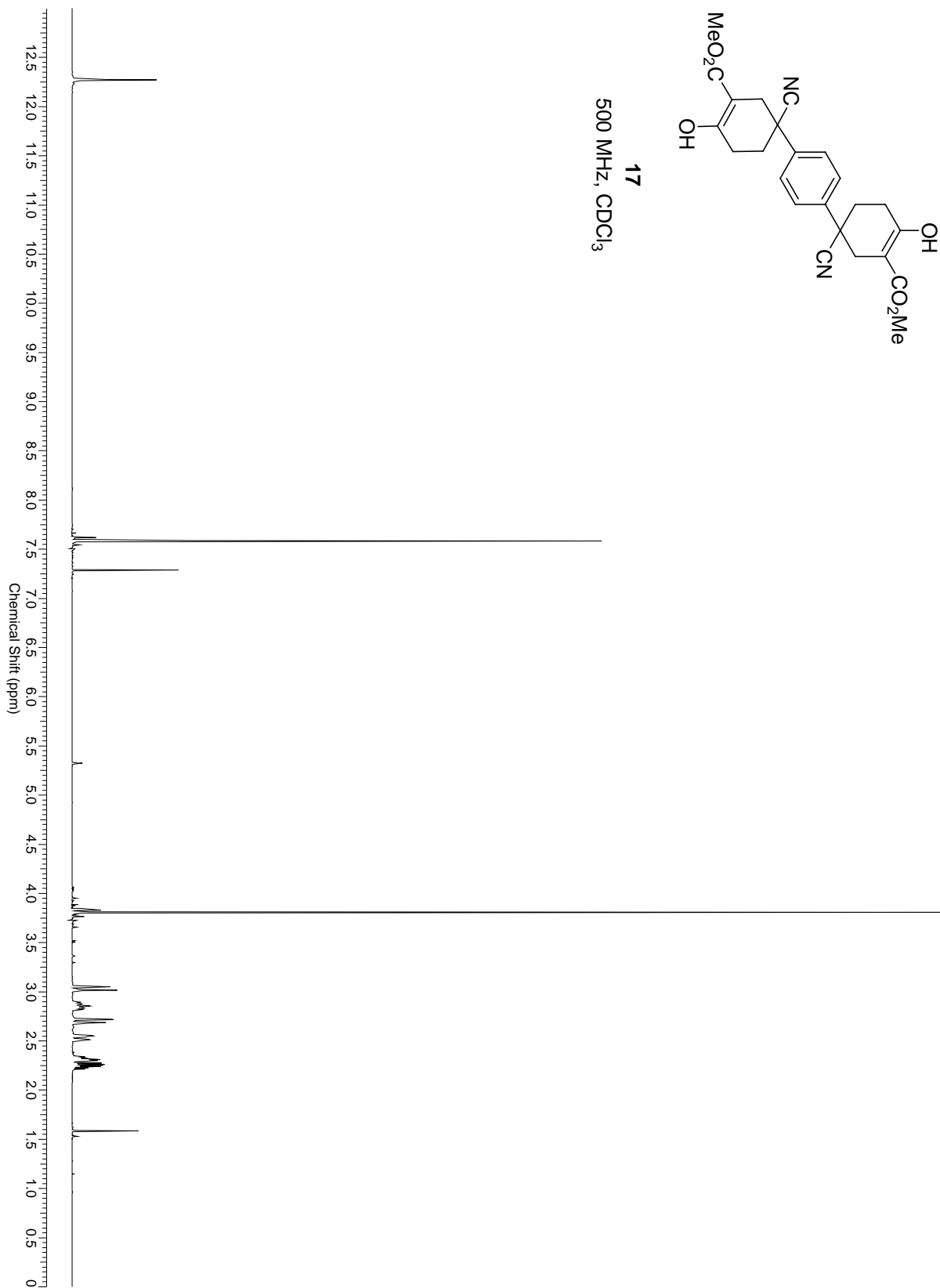
Supporting Information



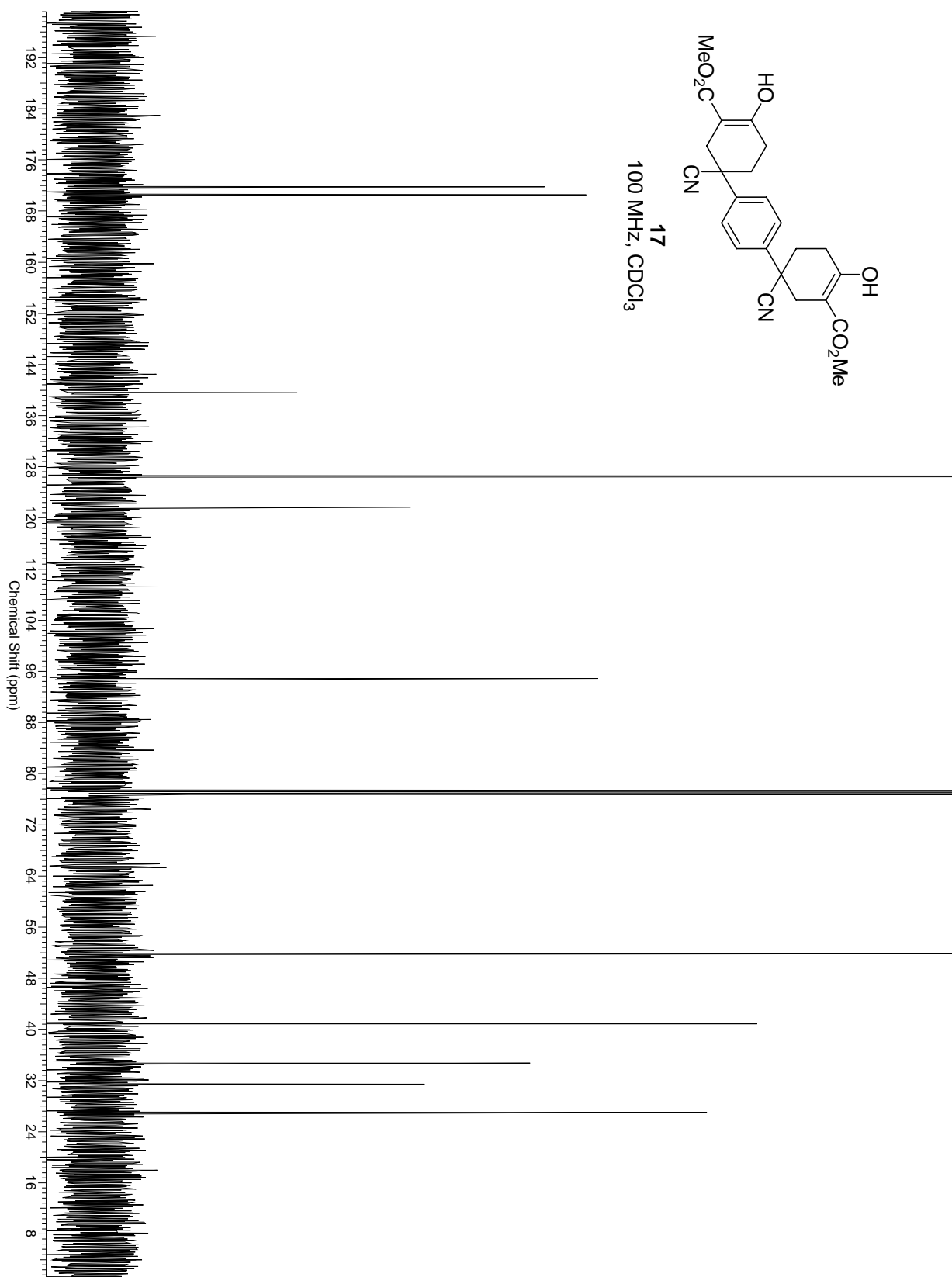
Supporting Information



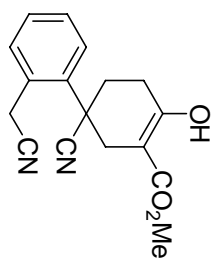
17
500 MHz, CDCl₃



Supporting Information

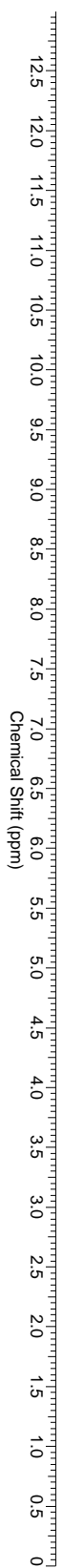


Supporting Information

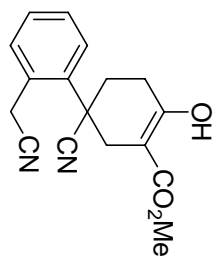


19

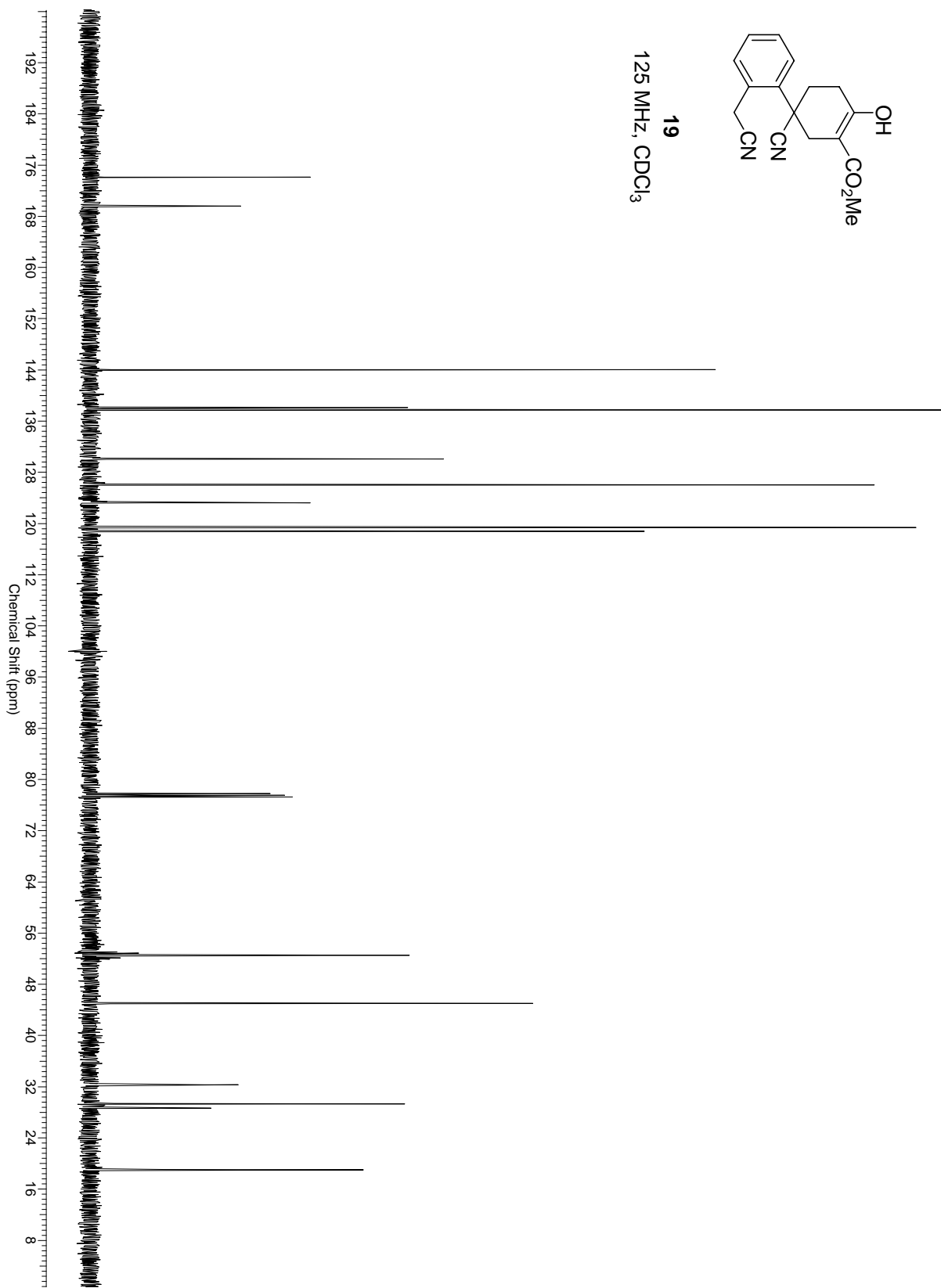
500 MHz, CDCl₃



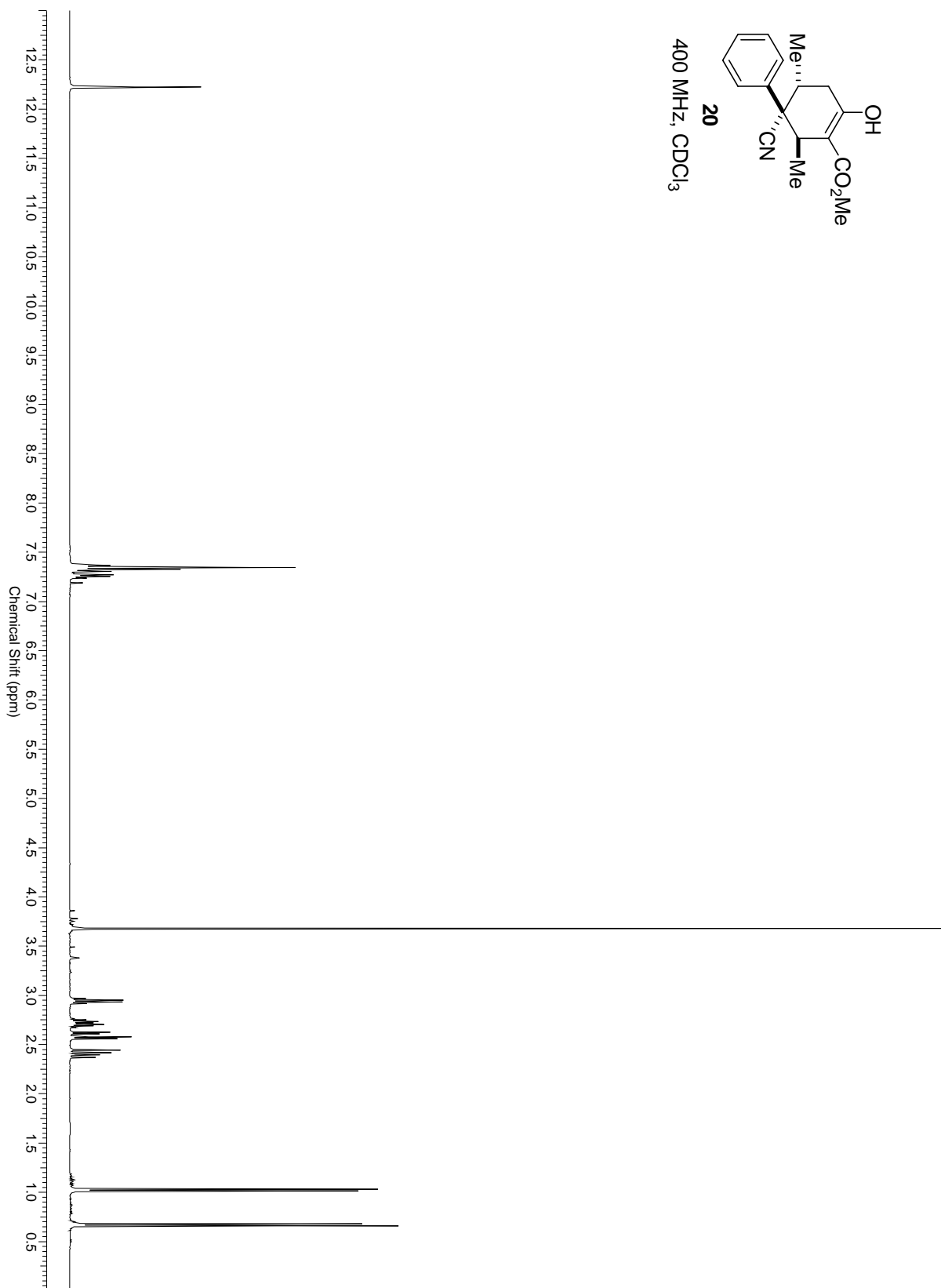
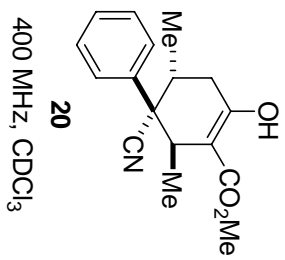
Supporting Information



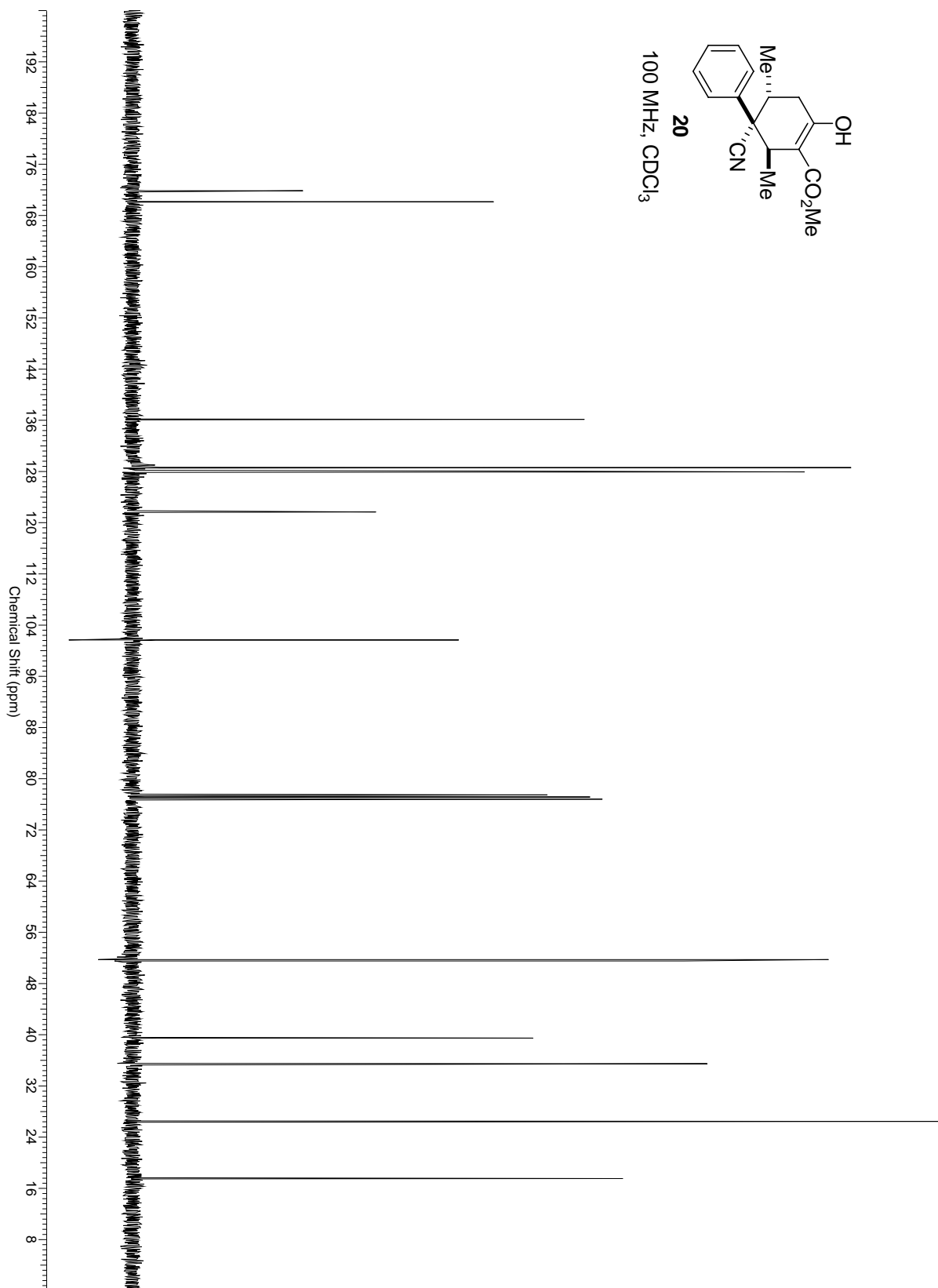
125 MHz, CDCl₃



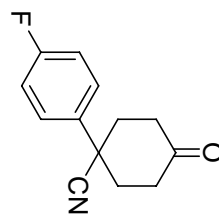
Supporting Information



Supporting Information

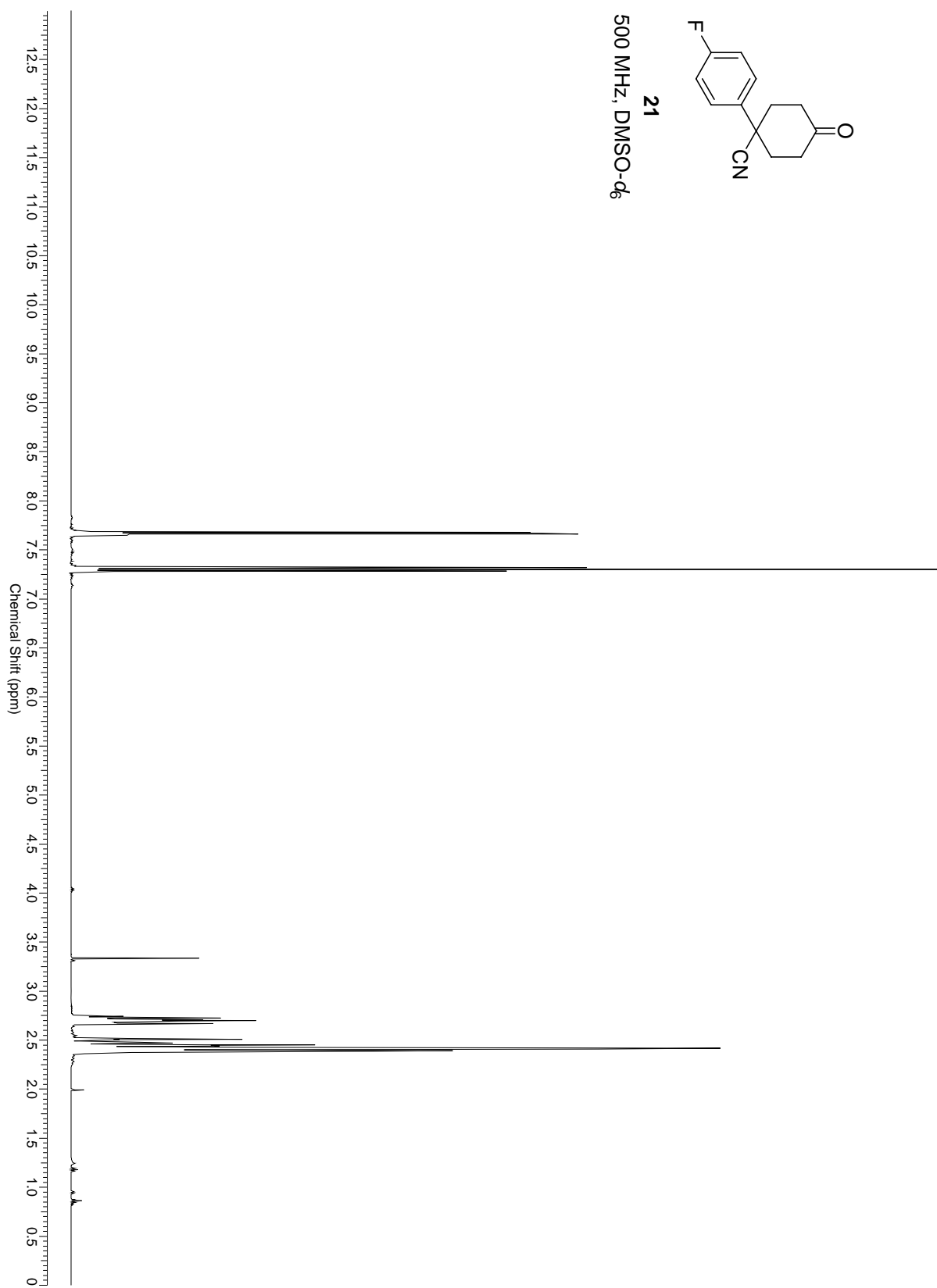


Supporting Information

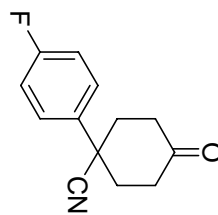


21

500 MHz, DMSO-*d*₆

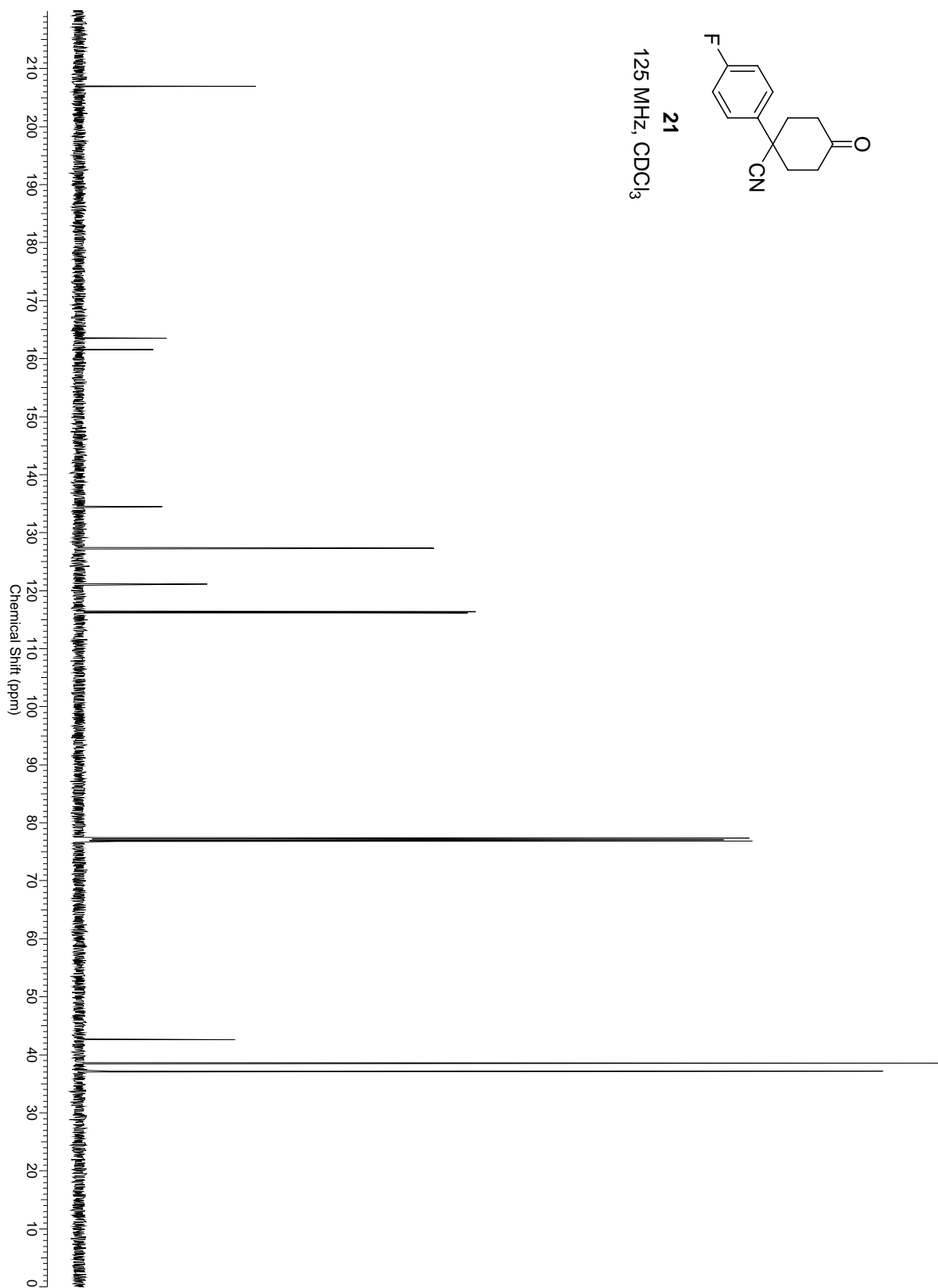


Supporting Information

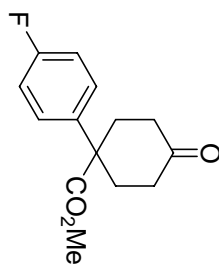


21

125 MHz, CDCl₃

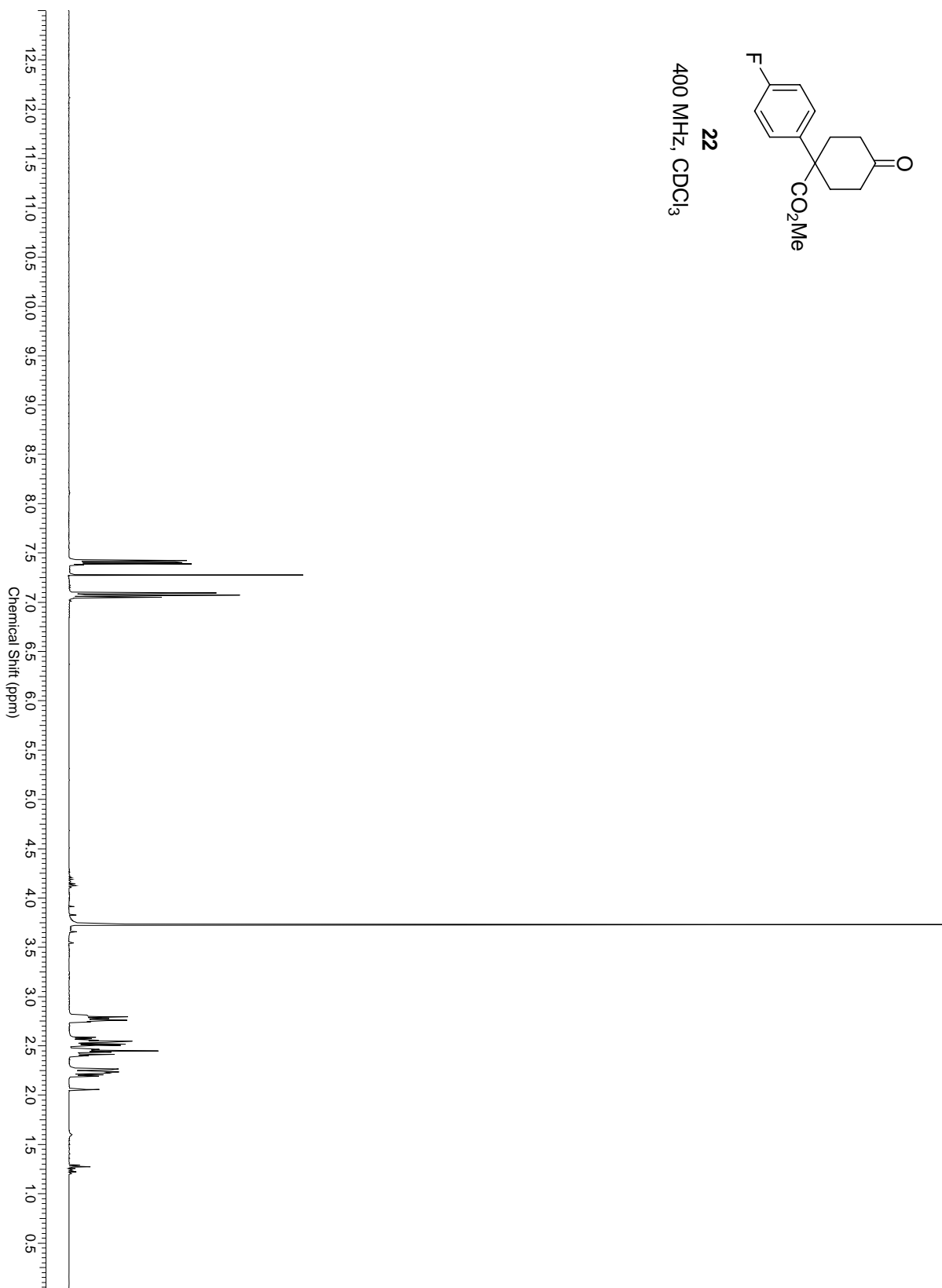


Supporting Information

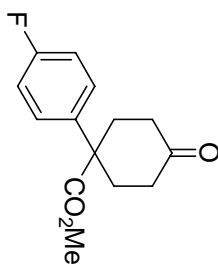
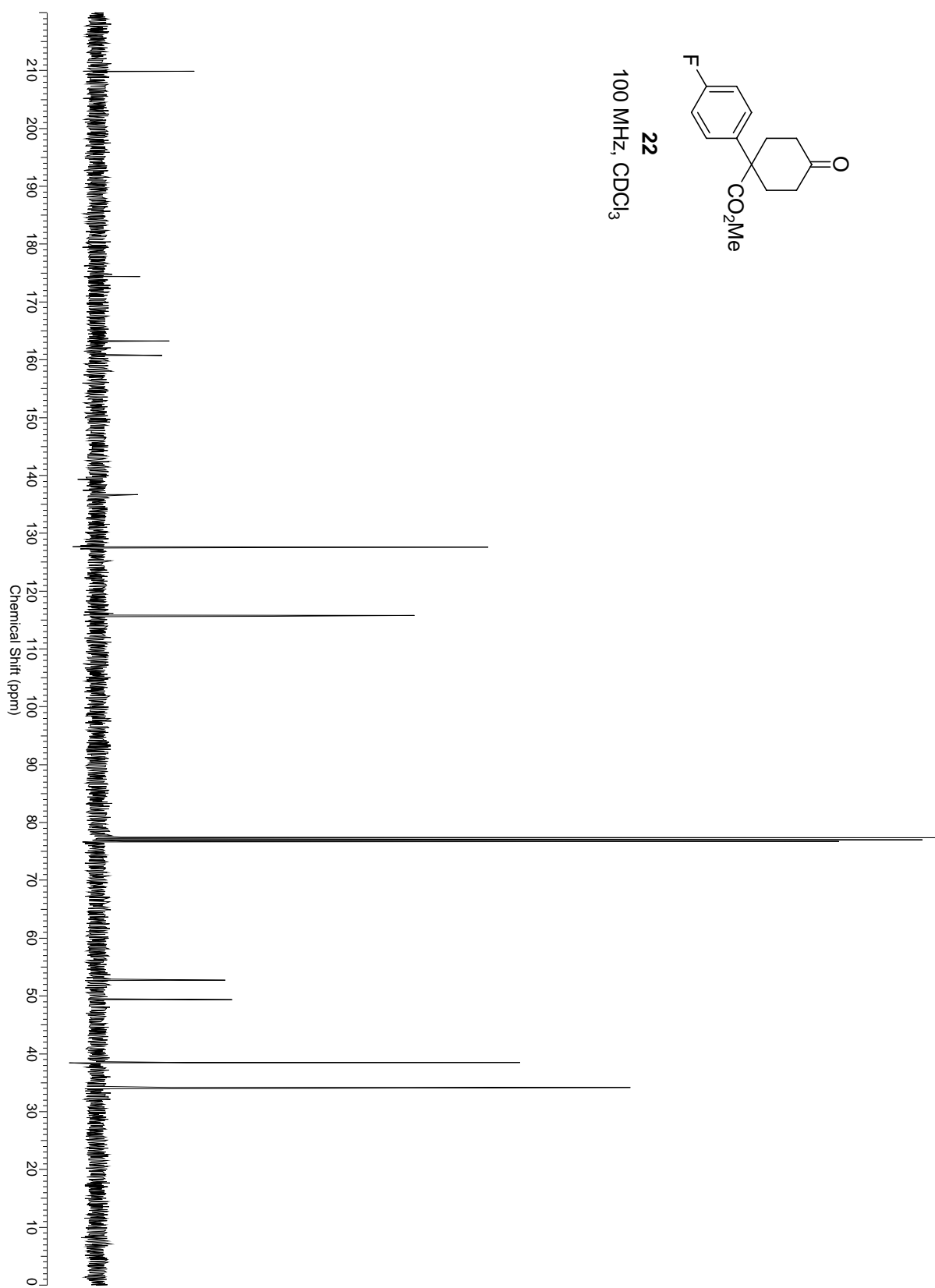


22

400 MHz, CDCl₃



Supporting Information



100 MHz, CDCl₃