Predicting and Optimizing Asymmetric Catalyst Performance Using the Principles of Experimental Design and Steric Parameters

Supporting Information

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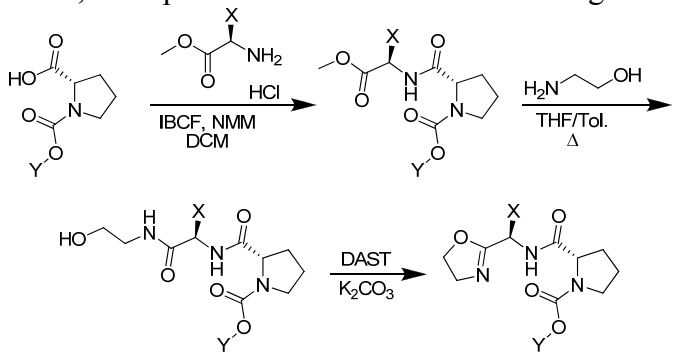
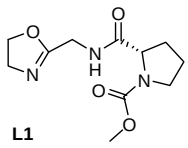
General Information: Unless otherwise noted, all reactions were performed under a nitrogen atmosphere with stirring. Toluene, dichloromethane, dichloroethane and THF were dried before use by passing through a column of activated alumina. Methanol was distilled from magnesium methoxide. Triethylamine was distilled from CaH_2. Benzaldehyde was purified by aqueous base wash, drying with sodium sulfate, and followed by fractional distillation. Acetophenone was purified by drying over Na_2SO_4 then fractional distillation. Methyl Ethyl Ketone was purified by two sequential fractional distillations. Allyl bromide was purified by drying over magnesium sulfate, filtration and fractional distillation. $CrCl_3(THF)_3$ was prepared by soxhlet extraction of anhydrous $CrCl_3$ with anhydrous THF. All other reagents were purchased from commercial sources and used without further purification. Yields were calculated for material judged homogeneous by thin-layer chromatography and NMR. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained either with potassium permanganate, phosphomolybdic acid, or ninhydrin. Flash column chromatography was performed with EcoChrom MP Silitech 32-63D 60Å silica gel, slurry packed with solvents indicated in glass columns. Nuclear magnetic resonance spectra were acquired at 300, 400, or 500 MHz for ^1H, and 75, 100, or 125 MHz for ^{13}C and 50°C. Chemical shifts for proton nuclear magnetic resonance (^1H NMR) spectra are reported in parts per million downfield relative to the line of $CHCl_3$ singlet at 7.24 ppm. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the center-line of the $CDCl_3$ triplet at 77.23 ppm. The abbreviations s, d, t, p, sep, dd, td, bs, and m stand for the resonance multiplicities singlet, doublet, triplet, pentet, septet, doublet of doublets, triplet of doublets, broad singlet, and multiplet, respectively. Optical rotations were obtained (Na D line) using a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length. Concentrations are reported in g/100 mL. SFC (super critical fluid chromatography) analysis was performed at 25 °C or 40 °C, using a Thar instrument fitted with chiral stationary phase (as indicated). Melting points were obtained on an electrothermal melting point apparatus and are uncorrected. Unless otherwise noted, glassware for all reactions was oven-dried at 110 ^oC and cooled in a dry atmosphere prior to use.

Ligand Synthesis: Ligands were prepared according to previously published[1-4] synthetic routes. Herein, we report characterization of all new ligands.



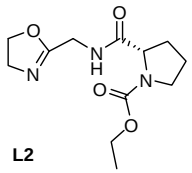
(S)-methyl 2-((4,5-dihydrooxazol-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (L1):[5]


L1

The product of the DAST cyclization, was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give

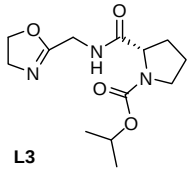
0.301 g of **L1.** R_f = 0.3 w/ 10% MeOH/DCM, yellow oil, $[\alpha]^{20}_D$ = –69.5° (c = 0.965, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.99 (bs, 1 H), 4.16 (s, 1 H), 4.12 (s, 1H), 3.855 (d, *J* = 4, 2 H), 3.65 (td, *J* = 9.6, 1.6; 2 H), 3.53 (s, 3 H), 3.34 (bs, 2 H), 2.1-1.65 (m, 4 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 171.9, 164.5, 67.9, 60.5, 54.0, 52.5, 46.9, 36.7, 28.9, 24.0. HRMS $C_{11}H_{17}N_3O_4$ $(M+H)^+$ calcd. 256.1297, obsvd. 256.1300.

(S)-ethyl 2-((4,5-dihydrooxazol-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (L2):[5]


L2

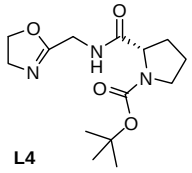
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.150 g of **L2.** R_f = 0.4 w/ 10% MeOH/DCM, yellow oil, $[\alpha]^{20}_D$ = –69.7° (c = 1.095, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.02 (bs, 1H), 4.16 (s, 1H), 4.11 (t, *J* = 9.6, 2H), 3.96 (m, 2H), 3.85 (s, 2H), 3.65 (dt, *J* = 9.6,1.6; 2H), 3.33 (bs, 2H), 2.1-1.65 (m, 4H), 1.071 (t, *J* = 7.2, 3H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 172.0, 164.5, 67.9, 61.3, 60.4, 54.0, 46.9, 36.7, 28.9, 24.0, 14.3. HRMS $C_{12}H_{19}N_3O_4$ $(M+H)^+$ calcd. 270.1454, obsvd. 270.1451.

(S)-isopropyl 2-((4,5-dihydrooxazol-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (L3): [5]


L3

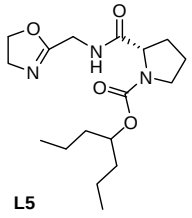
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.190 g of **L3.** R_f = 0.4 w/ 10% MeOH/DCM, yellow oil, $[\alpha]^{20}_D$ = –0.4° (c = 0.055, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.08 (bs, 1H), 4.81 (sep, *J* = 6.4, 1H), 4.17 (m, 3H), 3.92 (d, *J* = 4.8, 2H), 3.71 (dt, *J* = 9.6, 1.6; 2H), 3.37 (bs, 2H), 2.2-1.7 (m, 4H), 1.13 (m, 6H), ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 172.1, 164.6, 69.0, 68.1, 60.5, 54.1, 47.0, 36.9, 28.5, 24.1, 22.1. HRMS $C_{13}H_{21}N_3O_4$ $(M+H)^+$ calcd. 284.1610, obsvd. 284.1606.

(S)-tert-butyl 2-((4,5-dihydrooxazol-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (L4): [5]


L4

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.167 g of **L4.** R_f = 0.4 w/ 10% MeOH/DCM, yellow oil, $[\alpha]^{20}_D$ = –11.8° (c = 0.195, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.63 (bs, 1H), 4.23 (m, 1H), 4.23 (t, *J* = 9.2, 2H), 3.99 (m, 2H), 3.77 (t, *J* = 9.6, 2H), 3.40 (bs, 2H), 2.29-1.75 (bs, 4H), 1.41 (s, 9H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 172.5, 164.8, 80.6, 68.3, 60.7, 54.3, 47.2, 37.1, 28.5, 24.3. HRMS $C_{14}H_{23}N_3O_4$ $(M+H)^+$ calcd. 298.1767, obsvd. 298.1765.

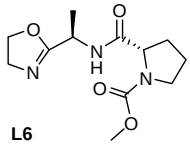
(S)-heptan-4-yl 2-((4,5-dihydrooxazol-2-yl)methylcarbamoyl)pyrrolidine-1-carboxylate (L5): [5]


L5

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.175 g of **L5.** R_f = 0.6 w/ 10% MeOH/DCM, yellow oil, $[\alpha]^{20}_D$ = –9.7° (c = 0.230, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.91 (bs, 1H), 4.75 (m, 1H), 4.23 (m, 3H), 3.98 (s, 2H), 3.77 (t, *J* = 9.6, 2H), 3.45 (bs, 2H), 2.3-1.78 (m, 4H), 1.47 (m, 4H), 1.29 (m 4H), 0.85 (m, 6H). ^{13}C-NMR

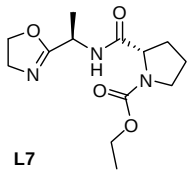
{^{1}H} (100 MHz, $CDCl_3$) δ = 167.3, 75.7, 68.3, 60.7, 54.3, 47.2, 37.1, 36.7, 24.4, 18.7, 18.6, 14.1. HRMS $C_{17}H_{29}N_3O_4$ $(M+H)^+$ calcd. 340.2236, obsvd. 340.2239.

(S)-methyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)ethylcarbamoyl)pyrrolidine-1-carboxylate (L6): [5]


L6

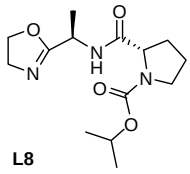
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.365 g of **L6.** R_f = 0.4 w/ 10% MeOH/DCM, white solid, MP = 102-105 °C . $[\alpha]^{20}_D$ = –9.2° (c = 0.140, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.91 (bs, 1H), 4.61 (p, *J* = 6.8, 1H), 4.23 (m, 3H), 3.77 (t, *J* = 10, 2H), 3.66 (s, 3H), 3.47 (bs, 2H), 2.2-1.75 (m, 4H), 1.33 (d, *J* = 7.2, 3H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 171.6, 168.4, 68.4, 61.1, 54.3, 52.8, 47.4, 43.8, 30.2, 24.2, 19.1. HRMS $C_{12}H_{19}N_3O_4$ $(M+H)^+$ calcd. 270.1454, obsvd. 270.1453.

(S)-ethyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)ethylcarbamoyl)pyrrolidine-1-carboxylate (L7): [5]


L7

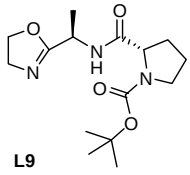
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.278 g of **L7.** R_f = 0.4 w/ 10% MeOH/DCM, white solid, MP = 93-94 °C . $[\alpha]^{20}_D$ = –13.8° (c = 0.225, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.86 (bs, 1H), 4.57 (p, *J* = 11.2, 1H), 4.19 (t, *J* = 9.6, 2H), 4.06 (m, 1H), 3.73 (t, *J* = 9.6, 2H), 3.43 (bs, 2H), 2.20-1.70 (m, 4H), 1.29 (d, *J* = 7.2, 3H), 1.17 (m, 3H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ =171.5, 168.3, 68.3, 61.6, 60.9, 54.2, 47.2, 43.6, 29.7, 24.1, 19.1, 14.7. HRMS $C_{13}H_{21}N_3O_4$ $(M+H)^+$ calcd. 284.1610, obsvd. 284.1609.

(S)-isopropyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)ethylcarbamoyl)pyrrolidine-1-carboxylate (L8): [5]


L8

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.285 g of **L8.** R_f = 0.5 w/ 10% MeOH/DCM, white solid, MP = 79-80 °C . $[\alpha]^{20}_D$ = –9.5° (c = 0.165, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.65 (bs, 1H), 4.88 (sep, *J* = 6, 1H), 4.62 (p, *J* = 7, 1H), 4.22 (m, 3H), 3.76 (t, *J* = 9.6, 2H), 3.45 (bs, 2H), 2.30-1.75 (m, 4H), 1.33 (d, *J* = 6.8, 3H), 1.19 (t, *J* = 6.8, 6H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 171.7, 168.4, 69.2, 68.4, 61.0, 54.3, 47.2, 43.7, 29.8, 24.1, 22.3, 22.3, 19.2. HRMS $C_{14}H_{23}N_3O_4$ $(M+H)^+$ calcd. 298.1767, obsvd. 298.1765.

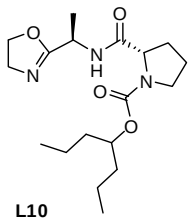
(S)-tert-butyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)ethylcarbamoyl)pyrrolidine-1-carboxylate (L9): [5]


L9

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.325 g of **L9.** R_f = 0.5 w/ 10% MeOH/DCM, white solid, MP = 91-94 °C . $[\alpha]^{20}_D$ = –14.4° (c = 0.195, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.65 (bs, 1H), 4.63 (p, *J* = 8, 1H), 4.22 (m, 3H), 3.76 (t, *J* = 8.8, 2H), 3.42 (bs, 2H), 2.3-1.73 (m, 4H), 1.41 (s, 9H), 1.35 (dd, *J* = 4.8, 2; 3H).

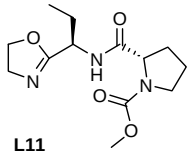
^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 174.1, 168.3, 80.5, 68.4, 54.3, 47.2, 43.7, 28.5, 24.1, 19.3. HRMS $C_{15}H_{25}N_3O_4$ $(M+H)^+$ calcd. 312.1923, obsvd. 312.1922.

(S)-heptan-4-yl 2-((R)-1-(4,5-dihydrooxazol-2-yl)ethylcarbamoyl)pyrrolidine-1-carboxylate (L10): [5]


L10

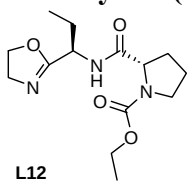
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.125 g of **L10.** R_f = 0.5 w/ 10% MeOH/DCM, white solid, MP = 91-93 °C . $[\alpha]^{20}_D$ = –5° (c = 0.090, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.68 (bs, 1H), 4.80 (m, 1H), 4.65 (p, *J* = 7.2, 1H), 4.25 (m, 3H), 3.79 (t, *J* = 10.4, 2H), 3.49 (bs, 2H), 2.35-1.78 (m, 4H), 1.60-1.25 (m, 8H), 0.89 (t, *J* = 7.2, 6H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 168.5, 164.3, 75.8, 68.5, 61.1, 54.4, 47.3, 43.8, 36.8, 19.2, 18.8, 14.2, 14.2. HRMS $C_{17}H_{29}N_3O_4$ $(M+H)^+$ calcd. 354.2393, obsvd. 354.2390.

(S)-methyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)propylcarbamoyl)pyrrolidine-1-carboxylate (L11): [5]


L11

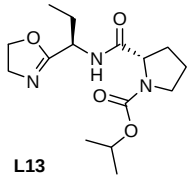
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.213 g of **L11.** R_f = 0.5 w/ 10% MeOH/DCM, white solid, MP = 109-110 °C . $[\alpha]^{20}_D$ = –8.2° (c = 0.125, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.65 (bs, 1H), 4.60 (q, *J* = 6.8, 1H), 4.25 (m, 3H), 3.79 (t, *J* = 9.6, 2H), 3.69 (s, 3H), 3.50 (bs, 2H), 2.20-1.80 (m, 4H), 1.66 (sep, *J* = 7.2, 1H), 0.86 (t, *J* = 7.6, 3H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 167.5, 68.3, 61.2, 54.4, 52.9, 48.8, 47.5, 29.8, 26.1, 24.9, 24.2, 9.3. HRMS $C_{13}H_{21}N_3O_4$ $(M+H)^+$ calcd. 284.1610, obsvd. 284.1609.

(S)-ethyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)propylcarbamoyl)pyrrolidine-1-carboxylate (L12): [5]


L12

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.315 g of **L12.** R_f = 0.5 w/ 10% MeOH/DCM, white solid, MP = 99-101 °C . $[\alpha]^{20}_D$ = –2.9° (c = 0.050, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.65 (bs, 1H), 4.61 (q, *J* = 6.8, 1H), 4.24 (m, 3H), 4.13 (q, *J* = 6.8, 1H), 3.79 (t, *J* = 9.6, 2H), 3.50 (bs, 2H), 2.25-1.79 (m, 4H), 1.66 (sep, *J* = 7.2, 1H), 1.23 (t, *J* = 7.2, 3H), 0.869 (t, *J* = 7.6, 3H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 165.4, 68.3, 61.8, 61.1, 54.4, 48.8, 47.4, 26.2, 24.3, 14.8, 9.4. HRMS $C_{14}H_{23}N_3O_4$ $(M+H)^+$ calcd. 298.1767, obsvd. 298.1769.

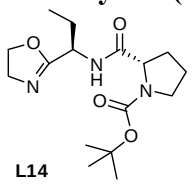
(S)-isopropyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)propylcarbamoyl)pyrrolidine-1-carboxylate (L13): [5]


L13

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.190 g of **L13.** R_f = 0.5 w/ 10% MeOH/DCM, white solid, MP = 92-93 °C . $[\alpha]^{20}_D$ = –5.1° (c = 0.09, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.67 (bs, 1H), 4.92 (sep, *J* = 10.4, 1H), 4.69 (q, *J* = 6.8, 1H), 4.31-4.21 (m, 3H), 3.80 (t, *J* = 9.6, 2H), 3.49 (bs, 2H), 2.30-1.80 (m, 4H), 1.652

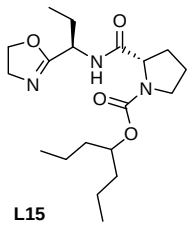
(sep, J = 8, 1H), 1.22 (t, J = 5.6, 3H), 0.89 (t, J = 7.2, 3H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 170.9, 167.5, 69.3, 68.3, 61.1, 54.4, 48.9, 47.4, 26.3, 24.2, 22.4, 22.3, 9.5. HRMS $C_{15}H_{25}N_3O_4$ $(M+H)^+$ calcd. 312.1923, obsvd. 312.1921.

(S)-tert-butyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)propylcarbamoyl)pyrrolidine-1-carboxylate (L14): [5]


L14

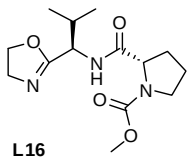
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 5-10% MeOH/DCM as eluent to give 0.330 g of **L14.** R_f = 0.5 w/ 10% MeOH/DCM, white solid, MP = 131-132 °C . $[\alpha]^{20}_D$ = –4.5° (c = 0.080, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.98 (bs, 1H), 4.61 (q, J = 7.2, 1H), 4.24 (m, 3H), 3.79 (t, J = 9.6, 2H), 3.45 (bs, 2H), 2.30-1.80 (m, 4H), 1.68 (sep, J = 7.2, 1H), 1.44 (s, 9H), 0.89 (t, J = 7.2, 3H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 172.7, 167.5, 94.7, 68.2, 61.1, 54.4, 48.8, 47.3, 28.6, 26.3, 24.1, 9.5. HRMS $C_{16}H_{27}N_3O_4$ $(M+H)^+$ calcd. 326.2080, obsvd. 326.2079.

(S)-heptan-4-yl 2-((R)-1-(4,5-dihydrooxazol-2-yl)propylcarbamoyl)pyrrolidine-1-carboxylate (L15): [5]


L15

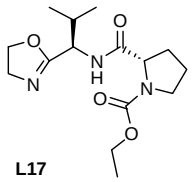
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 1-10% MeOH/DCM as eluent to give 0.198 g of **L15.** R_f = 0.6 w/ 50% Acetone/Hexanes, white solid, MP = 74-75 °C . $[\alpha]^{20}_D$ = –6.1° (c = 0.130, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.67 (bs, 1H), 4.79 (m, 1H), 4.59 (q, J = 7.2, 1H), 4.31-4.20 (m, 3H), 3.78 (t, J = 9.6, 2H), 3.49 (bs, 2H), 2.32-1.78 (m, 4H), 1.65 (sep, J = 7.2, 1H), 1.49 (m, 4H), 1.30 (m, 4H), 0.87 (m, 6H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 174.6, 167.5, 75.7, 68.3, 61.0, 54.6, 48.9, 47.4, 36.8, 36.8, 26.3, 24.1, 18.8, 18.7, 14.2, 14.1, 9.5. HRMS $C_{19}H_{33}N_3O_4$ $(M+H)^+$ calcd. 368.2549, obsvd. 368.2552.

(S)-methyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (L16): [2]


L16

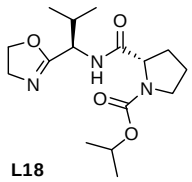
L16 was synthesized according to previously published methods and the physical data matched to previously published spectra.

(S)-ethyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (L17): [2]


L17

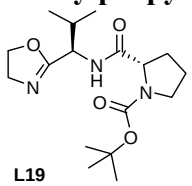
L17 was synthesized according to previously published methods and the physical data matched to previously published spectra.

(S)-isopropyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (L18): [2]


L18

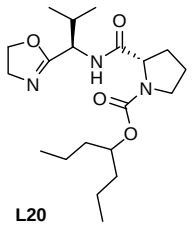
L18 was synthesized according to previously published methods and the physical data matched to previously published spectra.

(S)-tert-butyl 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (L19): [4]


L19

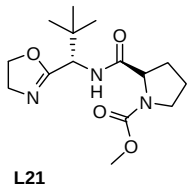
L19 was synthesized according to previously published methods and the physical data matched to previously published spectra.

(S)-heptan-4-yl 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (L20): [5]


L20

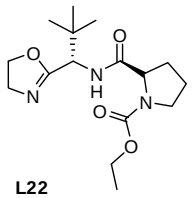
L20 The product of the DAST cyclization was purified flash silica-gel column chromatography with 1-10% MeOH/DCM as eluent to give 0.300 g of **L20.** R_f = 0.7 w/ 10% MeOH/DCM, white solid, MP = 75-77 °C . $[\alpha]^{20}_D$ = –3.6° (c = 0.080, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 6.86 (bs, 1H), 4.80 (td, *J* = 7.2, 5.5; 1H), 4.57 (q, *J* = 5.1, 1H), 4.34 (d, *J* = 5.6, 1H), 4.22 (td, *J* = 9, 3; 2H), 3.79 (t, *J* = 9.6, 2H), 3.50 (m, 2H), 2.40-1.80 (m, 4H), 1.50 (m, 4H), 1.33 (m, 4H), 0.90 (m, 6H). ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) δ = 172.8, 167.1, 75.8, 68.1, 61.1, 54.3, 52.7, 47.3, 36.9, 36.8, 31.8, 18.9, 18.8, 18.7, 17.9, 14.2, 14.2. HRMS $C_{20}H_{35}N_3O_4$ $(M+H)^+$ calcd. 382.2706, obsvd. 382.2708.

(S)-methyl 2-((S)-1-(4,5-dihydrooxazol-2-yl)-2,2-dimethylpropylcarbamoyl)pyrrolidine-1-carboxylate (L21): [5,8]


L21

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 50% Acetone/Hexane as eluent to give 0.140 g of **L21.** R_f = 0.4 w/ 50% Acetone/Hexanes, white solid, MP = 133-135 °C . $[\alpha]^{20}_D$ = +3.4° (c = 0.055, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.71 (bs, 1H), 4.52 (d, *J* = 8, 1H), 4.21 (m, 3H), 3.79 (m, 2H), 3.69 (s, 3H), 3.51 (bs, 2H), 2.20-1.80 (m, 4H), 0.94 (s, 9H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 171.5, 166.8, 67.7, 61.3, 55.5, 54.3, 52.9, 47.5, 35.5, 26.7, 24.2. HRMS $C_{15}H_{25}N_3O_4$ $(M+H)^+$ calcd. 312.1923, obsvd. 312.1924.

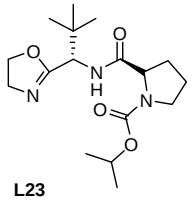
(S)-ethyl 2-((S)-1-(4,5-dihydrooxazol-2-yl)-2,2-dimethylpropylcarbamoyl)pyrrolidine-1-carboxylate (L22): [5,8]


L22

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 50% Acetone/Hexane as eluent to give 0.320 g of **L22.** R_f = 0.45 w/ 10% Acetone/Hexanes, white solid, MP = 134-136 °C . $[\alpha]^{20}_D$ = +5.8° (c = 0.105, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.73 (bs, 1H), 4.53 (d, *J* = 9.6, 1H), 4.33 (d, *J* = 7.2, 1H),

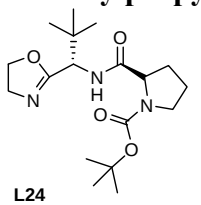
4.17 (m, 4H), 3.80 (m, 2H), 3.51 (bs, 2H), 2.25-1.80 (m, 4H), 1.24 (t, J = 7.2, 3H), 0.96 (s, 9H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 180.0, 166.8, 67.7, 61.9, 61.2, 55.2, 54.4, 47.43, 41.4, 26.7, 24.2, 14.9. HRMS $C_{16}H_{27}N_3O_4$ $(M+H)^+$ calcd. 326.2080, obsvd. 326.2078.

(S)-isopropyl 2-((S)-1-(4,5-dihydrooxazol-2-yl)-2,2-dimethylpropylcarbamoyl)pyrrolidine-1-carboxylate (L23): [5,8]


L23

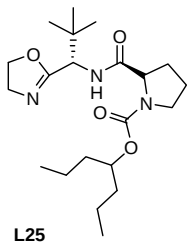
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 50% Acetone/Hexane as eluent to give 0.290 g of **L23.** R_f = 0.55 w/ 50% Acetone/Hexanes, white solid, MP = 148-150 °C . $[\alpha]^{20}_D$ = +5.4° (c = 0.090, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.98 (bs, 1H), 4.92 (sep, J = 6.4, 1H), 4.53 (d, J = 9.6, 1H), 4.58 (d, J = 6.8, 1H), 4.23 (m, 2H), 3.79 (m, 2H), 3.49 (bs, 2H), 2.28-1.80 (m, 4H), 1.23 (d, J = 6, 6H), 0.96 (s, 9H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 171.3, 166.8, 94.7, 69.4, 67.6, 61.1, 55.5, 54.5, 47.4, 35.5, 26.8, 22.4, 22.4. HRMS $C_{17}H_{29}N_3O_4$ $(M+H)^+$ calcd. 340.2236, obsvd. 340.2242.

(S)-tert-butyl 2-((S)-1-(4,5-dihydrooxazol-2-yl)-2,2-dimethylpropylcarbamoyl)pyrrolidine-1-carboxylate (L24): [5,8]


L24

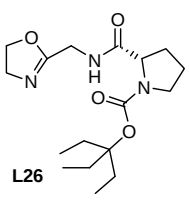
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 50% Acetone/Hexane as eluent to give 0.300 g of **L24.** R_f = 0.5 w/ 10% Acetone/Hexanes, white solid, MP = 141-143 °C . $[\alpha]^{20}_D$ = +6.1° (c = 0.095, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.97 (bs, 1H), 4.52 (d, J = 9.6, 1H), 4.21 (m, 3H), 3.82 (m, 2H), 3.44 (bs, 2H), 2.25-1.80 (m, 4H), 1.44 (s, 9H), 0.96 (s, 9H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 166.8, 67.6, 61.4, 55.5, 54.3, 47.3, 41.9, 35.4, 28.6, 26.7, 24.1. HRMS $C_{18}H_{31}N_3O_4$ $(M+H)^+$ calcd. 354.2392, obsvd. 354.2390.

(S)-heptan-4-yl 2-((S)-1-(4,5-dihydrooxazol-2-yl)-2,2-dimethylpropylcarbamoyl)pyrrolidine-1-carboxylate (L25): [5,8]


L25

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 50% Acetone/Hexane as eluent to give 0.210 g of **L25.** R_f = 0.6 w/ 10% MeOH/DCM, white solid, MP = 103-105 °C. $[\alpha]^{20}_D$ = +2.7° (c = 0.070, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.99 (bs, 1H), 4.75 (m, 1H), 4.47 (t, J = 9.6), 1H), 4.29 (m, 1H), 4.15 (m, 2H), 3.75 (m, 2H), 3.44 (bs, 2H), 2.3-1.75 (m, 4H), 1.46 (m, 4H), 1.28 (m, 4H), 0.89 (m, 9H), 0.83 (m, 6H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 172.1, 166.7, 75.7, 67.5, 66.9, 55.5, 54.2, 47.2, 36.8, 36.7, 35.3, 26.7, 24.1, 18.7, 18.7, 14.1. HRMS $C_{21}H_{37}N_3O_4$ $(M+H)^+$ calcd. 396.2862, obsvd. 396.2859.

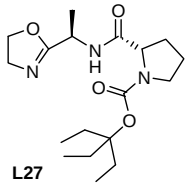
(S)-1-(3,3-diethylpentanoyl)-N-((4,5-dihydrooxazol-2-yl)methyl)pyrrolidine-2-carboxamide (L26): [5]


L26

The product of the DAST cyclization was purified by flash silica-gel column chromatography with 1-5% MeOH/DCM as eluent to give 0.182 g of **L26.** R_f = 0.6 w/ 10% MeOH/DCM, yellow oil. $[\alpha]^{20}_D$ = -34.7° (c = 0.11, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.67 (bs, 1H), 4.627 (m,

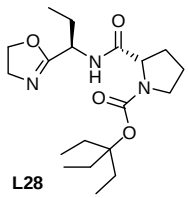
1H), 4.23 (m, 3H), 3.77 (t, *J* = 9.2, 2H), 3.43 (bs, 2H), 2.23-1.8 (m, 4H), 1.79 (q, *J* = 7, 4H), 1.34 (d, *J* = 7.2, 3H), 0.783 (t, *J* = 7.2, 9H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 168.4, 68.4, 60.5, 54.4, 47.3, 47.2, 43.7, 28.3, 27.4, 24.2, 19.2, 7.8. HRMS $C_{21}H_{37}N_3O_4$ $(M+H)^+$ calcd. 340.2236, obsvd. 340.2237.

(S)-3-ethylpentan-3-yl 2-((R)-1-(4,5-dihydrooxazol-2-yl)ethylcarbamoyl)pyrrolidine-1-carboxylate (L27): [5]


L27

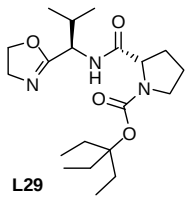
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 1-5% MeOH/DCM as eluent to give 0.304 g of **L27.** R_f = 0.7 w/ 10% MeOH/DCM, white solid, MP = 88-90 °C. $[\alpha]^{20}_D$ = -44.0° (c = 0.310, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.68 (bs, 1H), 4.63 (m, 1H), 4.23 (m, 3H), 3.77 (t, *J* = 9.2, 2H), 3.43 (bs, 2H), 2.23-1.80 (m, 4H), 1.79 (q, *J* = 7, 6H), 1.34 (d, *J* = 7.2, 3H), 0.78 (t, *J* = 7, 9H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 168.4, 68.4, 60.5, 54.4, 47.3, 43.7, 28.3, 27.4, 24.2, 19.2, 7.8. HRMS $C_{21}H_{37}N_3O_4$ $(M+H)^+$ calcd. 354.2393, obsvd. 354.2396.

(S)-3-ethylpentan-3-yl 2-((R)-1-(4,5-dihydrooxazol-2-yl)propylcarbamoyl)pyrrolidine-1-carboxylate (L28): [5]


L28

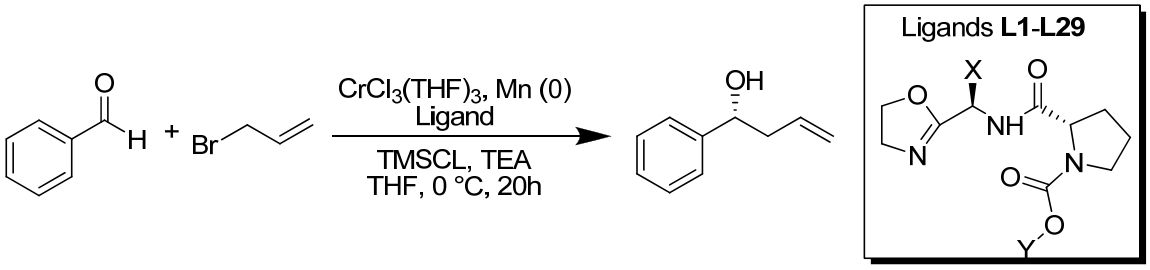
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 1-5% MeOH/DCM as eluent to give 0.252 g of **L28.** R_f = 0.7 w/ 10% MeOH/DCM, white solid, MP = 99-103 °C. $[\alpha]^{20}_D$ = -35.9° (c = .350, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.74 (bs, 1H), 4.58 (m, 1H), 4.22 (m, 3H), 3.77 (t, *J* = 9.6, 2H), 3.44 (bs, 2H), 2.32-1.80 (m, 4H), 1.80 (q, *J* = 7.2, 6H), 0.87 (m, 3H), 0.79 (t, *J* = 7.2, 9H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 167.5, 68.2, 54.4, 48.8, 43.7, 47.2, 27.4, 26.3, 24.4, 9.6, 7.9. HRMS $C_{21}H_{37}N_3O_4$ $(M+H)^+$ calcd. 368.2548, obsvd. 368.2549.

(S)-3-ethylpentan-3-yl 2-((R)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (L29): [5]


L29

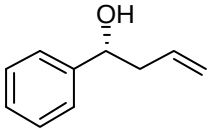
The product of the DAST cyclization was purified by flash silica-gel column chromatography with 1-5% MeOH/DCM as eluent to give 0.252 g of **L29.** R_f = 0.7 w/ 10% MeOH/DCM, white solid, MP = 87-88 °C. $[\alpha]^{20}_D$ = 37.0° (c = 0.275, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.76 (bs, 1H), 4.56 (m, 1H), 4.30 (d, *J* = 7.6, 1H), 4.22 (m, 2H), 3.77 (t, *J* = 9.2, 2H), 3.44 (bs, 2H), 2.30-1.90 (m, 5H), 1.82 (q, *J* = 7.2, 6H), 0.91 (m, 6H), 0.81 (t, *J* = 7.2, 9H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 170.9, 167.0, 68.0, 54.3, 52.8, 47.4, 47.3, 31.8, 27.5, 19.0, 18.1, 8.0. HRMS $C_{21}H_{37}N_3O_4$ $(M+H)^+$ calcd. 382.2706, obsvd. 382.2710.

Allylation of Benzaldehyde:



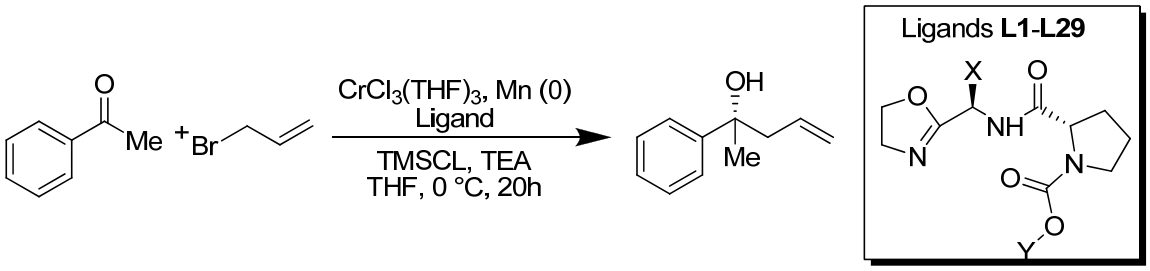
To an oven dried 1.5 dram vial with stir bar, was added $CrCl_3(THF)_3$ (9.4 mg, 0.025mmol, 0.1 eq.), manganese powder (27.5 mg, 0.5 mmol, 2 eq.), and ligand (0.0275 mmol, 0.11 eq.). The vial was then fitted with a Tefton septum and cap. The vial was further sealed by wrapping the cap with Teflon tape. The vial was then purged under vacuum and flushed with argon gas 3 times. Under an atmosphere of argon, a standard solution of THF/TEA (0.6% TEA/THF, or 7.5 *u*L per 1.25 ml, in the test reaction 1.25 ml of this solution was added to each vial) was added. The reaction was then stirred for 3-5 minutes and TMSCl (124 *u*L, 1 mmol, 4 eq.) was added dropwise. The reaction was then allowed to stir for 20 minutes at RT. After 20 minutes, the reaction had turned dark grey. The vial was transported to a cold bath at 0 °C and allowed to equilibrate for 10 minutes. After equilibration, allyl bromide (45 *u*L, 0.5 mmol, 2 eq.) was added. The reaction was then allowed to stir for another 20 minutes and finally benzaldehyde was added. The reaction was then stirred vigorously for 20h and slowly turned light gray or greenish gray. The reaction was quenched by slow addition of a saturated sodium bicarbonate solution (approx. 1 mL). The mixture was separated and the aqueous layer washed with diethyl ether (1x1ml). The organic layers were combined and passed over a Celite plug and collected. The organic layer was then dried with sodium sulfate and passed over a silica plug. The silica was rinsed with diethyl ether (~1mL). Samples of the corresponding enantiomeric products were then prepped for analysis without consideration for yield.

(R)-1-phenylbut-3-en-1-ol:



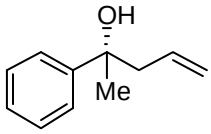
All physical data obtained from the above reaction was consistent with (R)-1-phenylbut-3-en-1-ol please see previous publications[6] for characterization.

Allylation of Acetophenone:

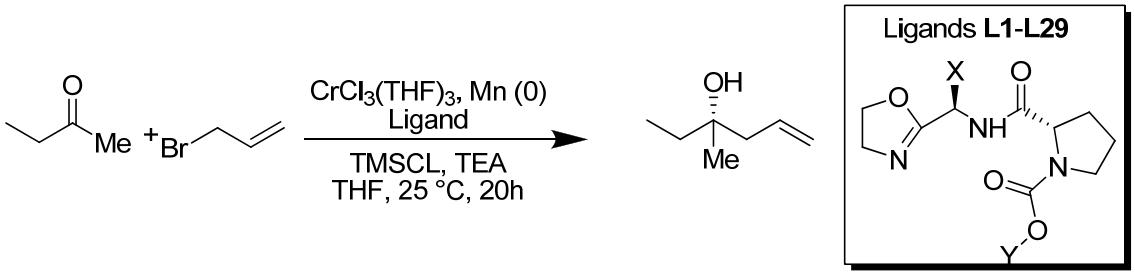


To an oven dried 1.5 dram vial with stir bar, was added $CrCl_3(THF)_3$ (9.4 mg, 0.025mmol, 0.1 eq.), 325 mesh manganese powder (27.5 mg, 0.5 mmol, 2 eq.), and ligand (.0275 mmol, 0.11 eq.). The vial was then fitted with a Tefton septum and cap. The vial was further sealed by wrapping the cap with Teflon tape. The vial was then purged under vacuum and flushed with argon gas 3 times. Under an atmosphere of argon, a standard solution of THF/TEA (0.6% TEA/THF, or 7.5 *u*L per 1.25 ml, in the test reaction 1.25 ml of this solution was added to each vial) was added. The reaction was then stirred for 3-5 minutes and TMSCl (124 *u*L, 1 mmol, 4 eq.) was added dropwise. The reaction was then allowed to stir for 20 minutes at RT. After 20 minutes, the reaction had turned dark grey. The vial was transported to a cold bath at 0 °C and allowed to equilibrate for 10 minutes. After equilibration, allyl bromide (45 *u*L, 0.5 mmol, 2 eq.) was added. The reaction was then allowed to stir for another 20 minutes and finally acetophenone was added. The reaction was then stirred vigorously for 20h and slowly turned light gray or greenish gray. The reaction was quenched by slow addition of a saturated sodium bicarbonate solution (approx. 1 mL). The mixture was separated and the aqueous layer washed with diethyl ether (1x1ml). The organic layers were combined and passed over a Celite plug and collected. The organic layer was then dried with sodium sulfate and passed over a silica plug. The silica was rinsed with diethyl ether (~1mL). Samples of the corresponding enantiomeric products were then prepped for analysis without consideration for yield.

(S) 2-phenylpent-4-en-2-ol:

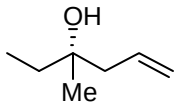


All physical data obtained from the above reaction was consistent with (S)-2-phenylpent-4-en-2-ol please see previous publications[6] for characterization.



To an oven dried 1.5 dram vial with stir bar, was added $CrCl_3(THF)_3$ (9.4 mg, 0.025mmol, 0.1 eq.), 325 mesh manganese powder (27.5 mg, 0.5 mmol, 2 eq.), and ligand (.0275 mmol, 0.11 eq.). The vial was then fitted with a Tefton septum and cap. The vial was further sealed by wrapping the cap with Teflon tape. The vial was then purged under vacuum and flushed with argon gas 3 times. Under an atmosphere of argon, a standard solution of THF/TEA (0.6% TEA/THF, or 7.5 *u*L per 1.25 ml, in the test reaction 1.25 ml of this solution was to each vial) was added. The reaction was then stirred for 3-5 minutes and TMSCl (124 *u*L, 1 mmol, 4 eq.) was added dropwise. The reaction was then allowed to stir for 20 minutes at RT. After 20 minutes, the reaction had turned dark grey. Allyl bromide (45 *u*L, 0.5 mmol, 2 eq.) was added. The reaction was then allowed to stir for another 20 minutes and finally methyl ethyl ketone was added. The reaction was then stirred vigorously for 20h and slowly turned light gray or greenish gray. The reaction was quenched by slow addition of a saturated sodium bicarbonate solution (approx. 1 mL). The mixture was separated and the aqueous layer washed with diethyl ether (1x1ml). The organic layers were combined and passed over a Celite plug and collected. The organic layer was then dried with sodium sulfate and passed over a silica plug. The silica was rinsed with diethyl ether (~1mL). Samples of the corresponding enantiomeric products were then prepped for analysis without consideration for yield.

3-methylhex-5-en-3-ol: All spectrographic data was consistant with previously published results.



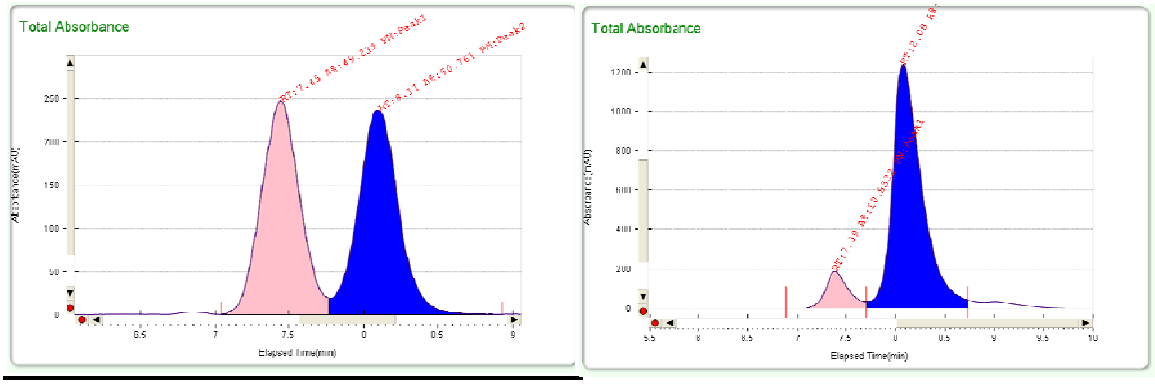
SFC Analysis:

Enantiomeric analysis for (R)-1-phenylbut-3-en-1-ol were carried using a Thar SFC system. Concentrations of approximately 5-10 mg/mL sample were loaded. Injections were made at 5 *u*L sample loading on a Chiralcel OJ-H (0.46cm x 25 cm) column. The chiral separation was carried out using 1% MeOH at 40 °C. Peak 1 R_T: 7.43 min, Peak 2 R_T: 8.11.

Table 1. Tabulated SFC enantiomeric ratio determination results for benzaldehyde.

Ligand	Peak 1	Peak 2	Ligand	Peak 1	Peak 2
L1	49	51	**L16**	37.5	62.5
L2	36.5	63.5	**L17**	16.5	83.5
L3	38.5	61.5	**L18**	14.5	85.5
L4	15	85	**L19**	8.5	91.5
L5	22.25	73.25	**L20**	24.3	75.7
L6	44	56	**L21**	39.6	60.4
L7	39	61	**L22**	41	59
L8	35.5	64.5	**L23**	35.25	64.75
L9	17	83	**L24**	35	65
L10	12	88	**L25**	31.5	68.5
L11	39	61	**L26**	42.5	57.5
L12	25.5	74.5	**L27**	34	66
L13	16.5	83.5	**L28**	44?	56?
L14	9.5	90.5	**L29**	40	60
L15	11	89			

Example Chromatograms



Acetophenone was separated according to previously publish means. [2]

Table 2. Tabulated SFC enantiomeric ratio determination results for acetophenone.

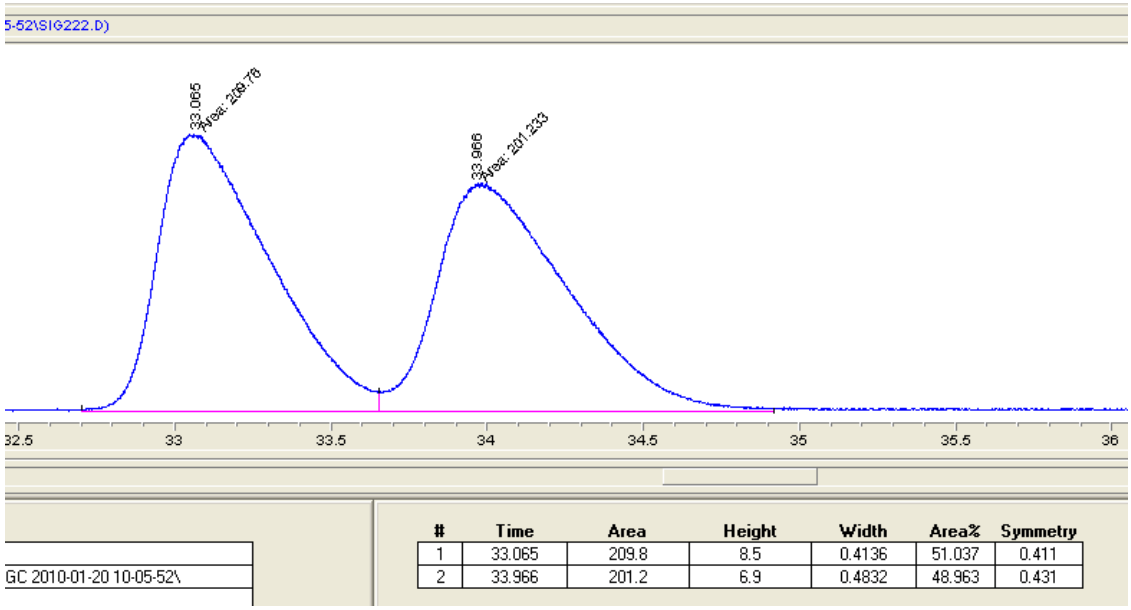
Ligand	Peak 1	Peak 2	Ligand	Peak 1	Peak 2
L1	20	80	**L16**	21	79
L2	21.5	78.5	**L17**	25	75
L3	24	76	**L18**	29.5	70.5
L4	90	10	**L19**	95.5	4.5
L5	29	71	**L20**	42.5	57.5
L6	22	78	**L21**	39	61
L7	19	81	**L22**	43	57
L8	18.5	81.5	**L23**	46.5	53.5
L9	92.5	7.5	**L24**	77	23
L10	31.5	69.5	**L25**	59.5	40.5
L11	16	84	**L26**	78	22
L12	18	82	**L27**	88	12
L13	21.5	78.5	**L28**	88	12
L14	92.5	7.5	**L29**	91	9
L15	29.5	70.5			

Methyl Ethyl Ketone was separated by gas chromatography with a chiral stationary phase. A J&W Scientific 19091G-B213 HP-Chiral-20B cylcodex-B column was used. The length was 30m and I.D. was 0.320 mm. The run was isocratic at 45 °C and 0.6 mL/min flow rate for a 1 *u*l injection. The average retention time was 33.5 min and 34.5 min.

Table 3. Tabulated GC enantiomeric ratio determination results for MEK.

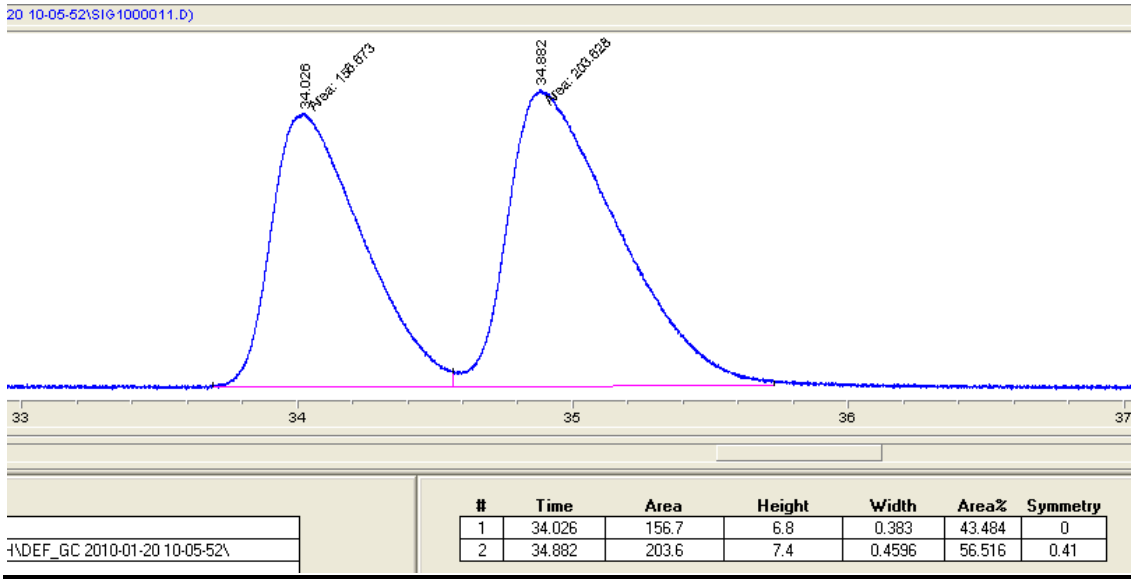
Ligand	Peak 1	Peak 2	Ligand	Peak 1	Peak 2
L1	34	66	**L16**	34	66
L2	37	63	**L17**	38	62
L3	32	68	**L18**	38	62
L4	50	50	**L19**	62	38
L5	35	65	**L20**	43	57
L6	30	70	**L21**	45	55
L7	33	67	**L22**	47	53
L8	32	68	**L23**	50	50
L9	54	46	**L24**	55	45
L10	36	64	**L25**	53	47
L11	32	68	**L26**	50	50
L12	33	67	**L27**	54	46
L13	34	64	**L28**	57	43
L14	56	44	**L29**	63	37
L15	38.5	61.5			

Racemic



#	Time	Area	Height	Width	Area%	Symmetry
1	33.065	209.8	8.5	0.4136	51.037	0.411
2	33.966	201.2	6.9	0.4832	48.963	0.431

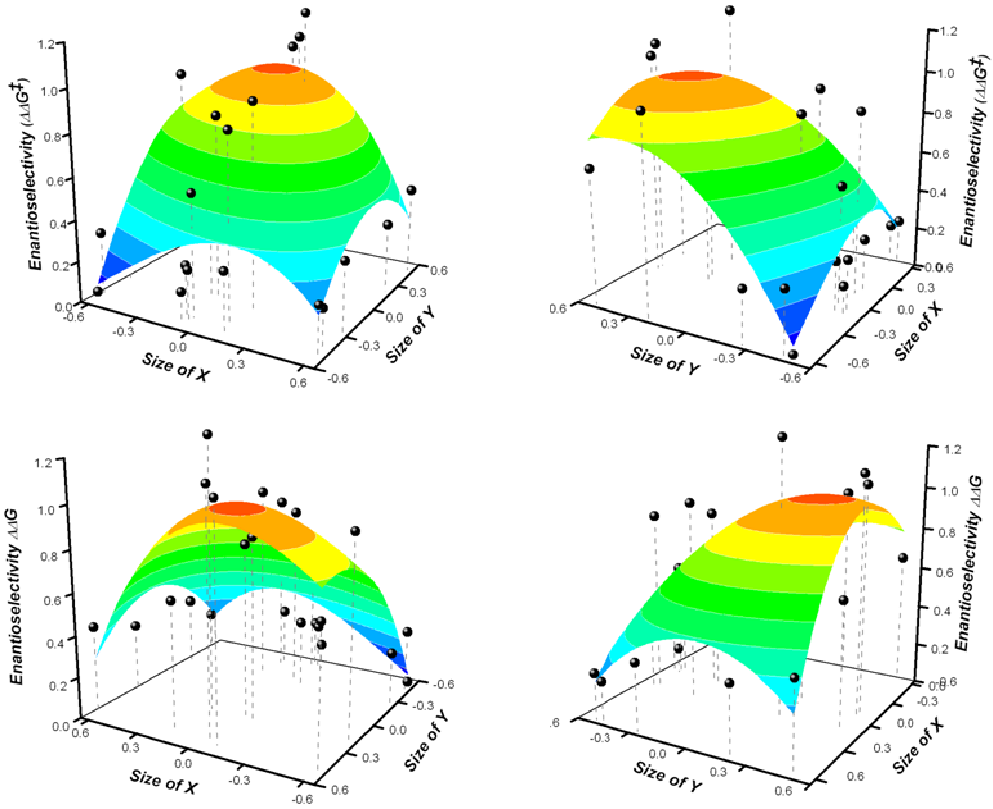
Selective



#	Time	Area	Height	Width	Area%	Symmetry
1	34.026	156.7	6.8	0.383	43.484	0
2	34.882	203.6	7.4	0.4596	56.516	0.41

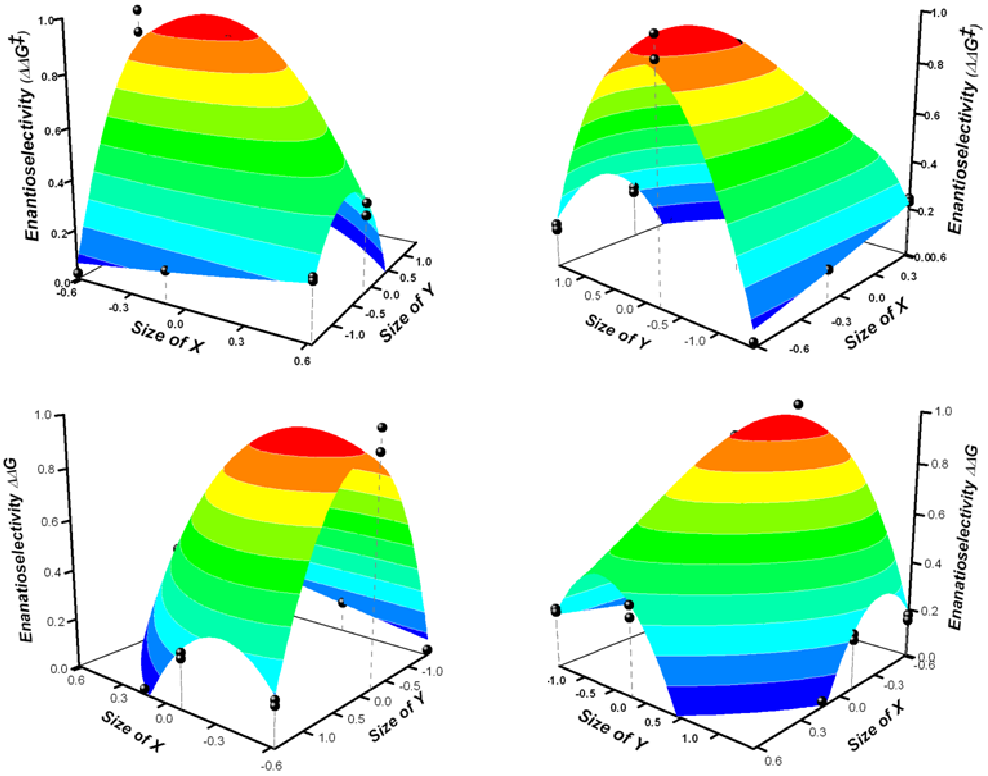
Graphical Representations:

Benzaldehyde 5×5



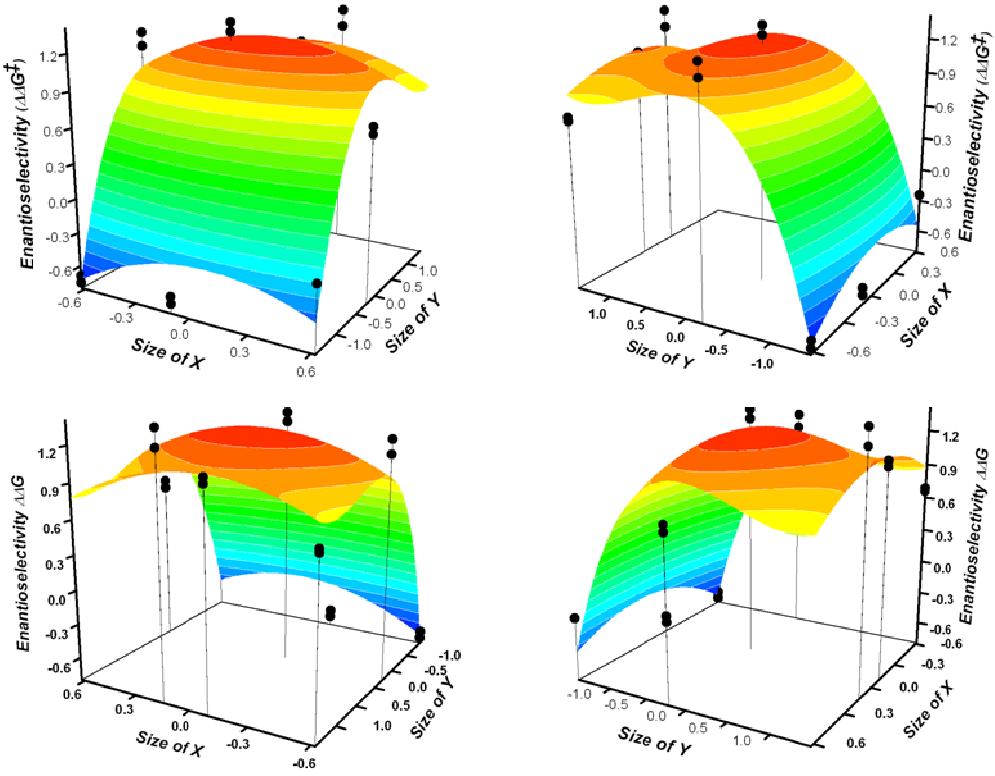
Sequential 90° Rotations

Benzaldehyde 3×3



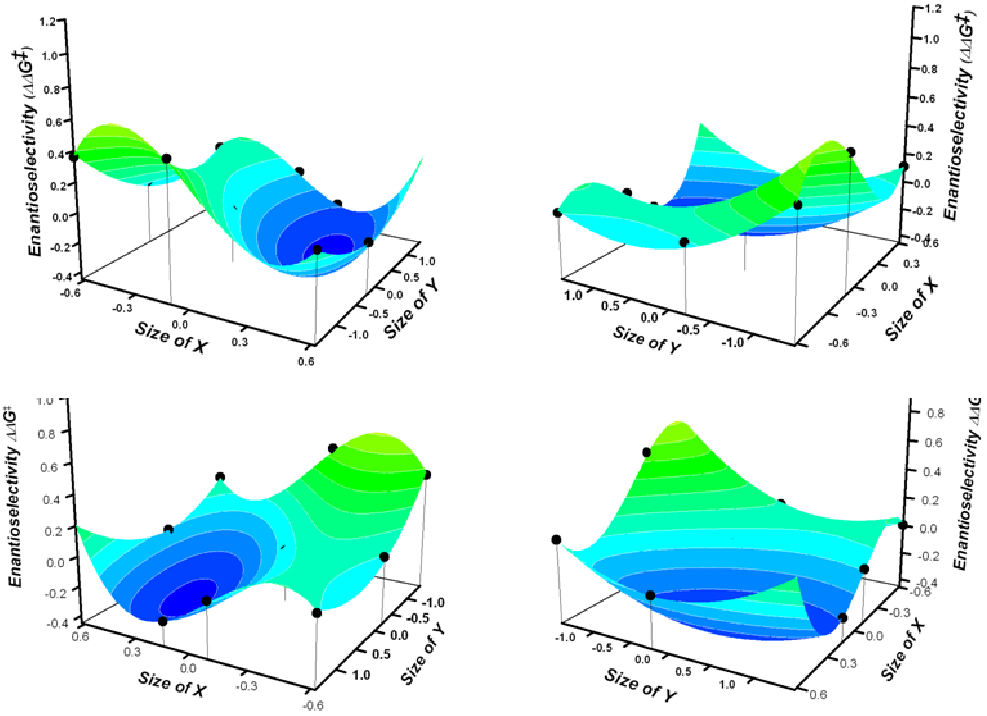
Sequential 90° Rotations

Acetophenone 3×3



Sequential 90° Rotations

Methyl Ethyl Ketone 3×3



Sequential 90° Rotations

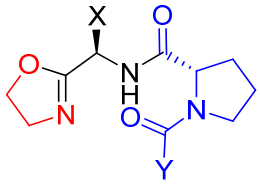
Data & Statistical Analysis:[7]

A detailed step by step summary of how the model for the 3 x 3 prediction of the best catalyst for benzaldehyde will be given followed by summaries of the key statistics for the other models.

3 x 3 Prediction of the Best Catalyst for Benzaldehyde

DATA SET

X Position	Adj. Charton Value	Y Position	Adj. Charton Value	Delta G in Kcal/mol
H	-0.62	Me	-1.45	0.0217
H	-0.62	tBu	-0.21	0.98475
H	-0.62	CEt_3	1.45	0.1529
Me	-0.1	Me	-1.45	0.13082
Me	-0.1	tBu	-0.21	0.89955
Me	-0.1	CEt_3	1.45	0.21996
tBu	0.62	Me	-1.45	0.22901
tBu	0.62	tBu	-0.21	0.35982
iPr	0.14	CEt_3	1.45	0.0217
H	-0.62	Me	-1.45	0.0217
H	-0.62	tBu	-0.21	0.89955
H	-0.62	CEt_3	1.45	0.1751
Me	-0.1	Me	-1.45	0.13082
Me	-0.1	tBu	-0.21	0.82258
Me	-0.1	CEt_3	1.45	0.19744
tBu	0.62	Me	-1.45	0.24266
tBu	0.62	tBu	-0.21	0.31212
iPr	0.14	CEt_3	1.45	0.0217



The data set consists of the 9 ligands listed but each replicate run is included in order to create enough degrees of freedom to create a polynomial model. To develop a linear least squares model first we must define a few matrices. The design matrix is the matrix where each row represents the values of the factor combinations used in each experiment:

z0	X	Y	X^2	Y^2	XY	X^3	Y^3	YX^2	XY^2
1	-0.62	-1.45	0.3844	2.1025	0.899	-0.23833	-3.04863	-0.55738	-1.30355
1	-0.62	-0.21	0.3844	0.0441	0.1302	-0.23833	-0.00926	-0.08072	-0.02734
1	-0.62	1.45	0.3844	2.1025	-0.899	-0.23833	3.048625	0.55738	-1.30355
1	-0.1	-1.45	0.01	2.1025	0.145	-0.001	-3.04863	-0.0145	-0.21025
1	-0.1	-0.21	0.01	0.0441	0.021	-0.001	-0.00926	-0.0021	-0.00441
1	-0.1	1.45	0.01	2.1025	-0.145	-0.001	3.048625	0.0145	-0.21025
1	0.62	-1.45	0.3844	2.1025	-0.899	0.238328	-3.04863	-0.55738	1.30355
1	0.62	-0.21	0.3844	0.0441	-0.1302	0.238328	-0.00926	-0.08072	0.027342
1	0.14	1.45	0.0196	2.1025	0.203	0.002744	3.048625	0.02842	0.29435
1	-0.62	-1.45	0.3844	2.1025	0.899	-0.23833	-3.04863	-0.55738	-1.30355
1	-0.62	-0.21	0.3844	0.0441	0.1302	-0.23833	-0.00926	-0.08072	-0.02734
1	-0.62	1.45	0.3844	2.1025	-0.899	-0.23833	3.048625	0.55738	-1.30355
1	-0.1	-1.45	0.01	2.1025	0.145	-0.001	-3.04863	-0.0145	-0.21025
1	-0.1	-0.21	0.01	0.0441	0.021	-0.001	-0.00926	-0.0021	-0.00441
1	-0.1	1.45	0.01	2.1025	-0.145	-0.001	3.048625	0.0145	-0.21025
1	0.62	-1.45	0.3844	2.1025	-0.899	0.238328	-3.04863	-0.55738	1.30355
1	0.62	-0.21	0.3844	0.0441	-0.1302	0.238328	-0.00926	-0.08072	0.027342
1	0.14	1.45	0.0196	2.1025	0.203	0.002744	3.048625	0.02842	0.29435

The design matrix was created by taking each individual term and performing the mathematical function described at the top of the column. The column for x^2 is simply the value of X for the ligand squared, for YX^2 it is the value for Y multiplied by the value for (X^2). It is important that the design matrix values match up with their corresponding $\Delta\Delta G^{\ddagger}$ values in the response matrix, as we are essentially solving a system of equations. A response matrix is also created which consists of the measured enantiomeric ratios given as $\Delta\Delta G^{\ddagger}$ values.

0.021702
0.984751
0.152897
0.130825
0.899549
0.219955
0.229012
0.359821
0.021702
0.021702
0.899549
0.175097
0.130825
0.822582
0.197442
0.242656
0.312121
0.021702

The response matrix is given the designation Y and the design matrix given the designation X and the two are manipulated according to the least squares regression:

$$C = (X^TX)^{-1}(X^TY)$$

Above C represents the solved matrix of coefficient values. For the values in the design matrix and response matrix above, the following C was calculated.

Z0 = 0.8481

X = -0.6502

Y = 0.1011

X^2 = -0.5049

Y^2 = -0.3302

XY = -0.2812

X^3 = 0.2625

Y^3 = -0.0391

YX^2 =-0.3313

XY^2 = 0.152

Which can be substituted into the original equation to give:

$$\Delta\Delta G^{\ddagger} = 0.8481 - .6502x + 0.1011y - 0.5049x^2 - 0.3302y^2 - 0.2812xy + 0.2625x^3 - 0.0391y^3 - 0.3313yx^2 - 0.152xy^2$$

The next step would be the calculation of each of the errors for each of the terms. Examination of the errors reveals which terms to eliminate. The variance and covariance matrix (V) for these coefficients can be calculated by the equation

$V = (X^TX)^{-1}$

For our example V =

-0.0450	0.0000	-0.2143	-0.0000	0.0214	-0.0000	-0.0000	0.1019	-0.0000	-0.0000
0.0000	0.0000	0.0000	-0.0000	-0.0000	-0.0000	-0.0000	-0.0000	-0.0000	-0.0000
-0.2143	0.0000	-1.0206	-0.0000	0.1019	-0.0000	-0.0000	0.4854	-0.0000	-0.0000
-0.0000	-0.0000	-0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.0214	-0.0000	0.1019	0.0000	-0.0102	0.0000	0.0000	-0.0485	0.0000	0.0000
-0.0000	-0.0000	-0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
-0.0000	-0.0000	-0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.1019	-0.0000	0.4854	0.0000	-0.0485	0.0000	0.0000	-0.2309	0.0000	0.0000
-0.0000	-0.0000	-0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
-0.0000	-0.0000	-0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

The diagonal values highlighted along this matrix represent the non-scaled errors associated with each coefficient value. Overall, the lack of information on the diagonal represents an over fitting of the data (insufficient degrees of freedom to pass the *f* test for statistical significance). To simplify the model, all of the third order terms were removed to give a new design matrix:

z0	X	y	X^2	Y^2	XY
1	-0.62	-1.45	0.3844	2.1025	0.899
1	-0.62	-0.21	0.3844	0.0441	0.1302
1	-0.62	1.45	0.3844	2.1025	-0.899
1	-0.1	-1.45	0.01	2.1025	0.145
1	-0.1	-0.21	0.01	0.0441	0.021
1	-0.1	1.45	0.01	2.1025	-0.145
1	0.62	-1.45	0.3844	2.1025	-0.899
1	0.62	-0.21	0.3844	0.0441	-0.1302
1	0.14	1.45	0.0196	2.1025	0.203
1	-0.62	-1.45	0.3844	2.1025	0.899
1	-0.62	-0.21	0.3844	0.0441	0.1302
1	-0.62	1.45	0.3844	2.1025	-0.899
1	-0.1	-1.45	0.01	2.1025	0.145
1	-0.1	-0.21	0.01	0.0441	0.021
1	-0.1	1.45	0.01	2.1025	-0.145
1	0.62	-1.45	0.3844	2.1025	-0.899
1	0.62	-0.21	0.3844	0.0441	-0.1302
1	0.14	1.45	0.0196	2.1025	0.203

The coefficient values were calculated for this matrix along with the same response matrix Y to give matrix C:

0.8396
-0.3068
-0.0663
-0.5194
-0.3184
-0.2492

These values of coefficients give the following covariance matrix:

Z0	X	Y	X^2	Y^2	XY
0.3120	-0.0585	-0.0275	-0.5559	-0.1044	-0.0833
-0.0585	0.3657	0.0523	0.3051	0.0281	0.1707
-0.0275	0.0523	0.0561	0.1555	0.0046	0.0621
-0.5559	0.3051	0.1555	2.2815	0.0860	0.3791
-0.1044	0.0281	0.0046	0.0860	0.0640	0.0309
-0.0833	0.1707	0.0621	0.3791	0.0309	0.3248

Analysis of this matrix shows that the X^2 term has the largest amount of error. Looking at the covariance we see that the X^2 term has a large degree of covariance with the offset or z0 term. Our first iteration we will eliminate this term giving a new design matrix:

z0	X	Y	Y^2	XY
1	-0.62	-1.45	2.1025	0.899
1	-0.62	-0.21	0.0441	0.1302
1	-0.62	1.45	2.1025	-0.899
1	-0.1	-1.45	2.1025	0.145
1	-0.1	-0.21	0.0441	0.021
1	-0.1	1.45	2.1025	-0.145

1	0.62	-1.45	2.1025	-0.899
1	0.62	-0.21	0.0441	-0.1302
1	0.14	1.45	2.1025	0.203
1	-0.62	-1.45	2.1025	0.899
1	-0.62	-0.21	0.0441	0.1302
1	-0.62	1.45	2.1025	-0.899
1	-0.1	-1.45	2.1025	0.145
1	-0.1	-0.21	0.0441	0.021
1	-0.1	1.45	2.1025	-0.145
1	0.62	-1.45	2.1025	-0.899
1	0.62	-0.21	0.0441	-0.1302
1	0.14	1.45	2.1025	0.203

The matrix of coefficients for this design matrix was:

z0 = 0.7130
X = -0.2373
Y = -0.0309
Y^2 = -0.2988
XY =-0.1629

The covariance matrix was:

z0	X	Y	Y^2	XY
0.1766	0.0159	0.0104	-0.0835	0.0091
0.0159	0.3249	0.0315	0.0166	0.1201
0.0104	0.0315	0.0455	-0.0012	0.0363
-0.0835	0.0166	-0.0012	0.0608	0.0166
0.0091	0.1201	0.0363	0.0166	0.2618

Analysis of these matrices reveals that the X term has the largest error but a couple of other factors need to be considered the Y term has a large relative error and its coefficient value has a minimal effect on the overall model so elimination of this term gives the following design matrix:

z0	X	Y^2	XY
1	-0.62	2.1025	0.899
1	-0.62	0.0441	0.1302
1	-0.62	2.1025	-0.899
1	-0.1	2.1025	0.145
1	-0.1	0.0441	0.021
1	-0.1	2.1025	-0.145
1	0.62	2.1025	-0.899
1	0.62	0.0441	-0.1302
1	0.14	2.1025	0.203
1	-0.62	2.1025	0.899
1	-0.62	0.0441	0.1302
1	-0.62	2.1025	-0.899
1	-0.1	2.1025	0.145
1	-0.1	0.0441	0.021

1	-0.1	2.1025	-0.145
1	0.62	2.1025	-0.899
1	0.62	0.0441	-0.1302
1	0.14	2.1025	0.203

Which gives the following coeffecients:

$Z0 = 0.7200$
$X = -0.2159$
$Y^2 = -0.2997$
$XY = -0.1383$

And the covariance matrix:

z0	X	Y^2	XY
0.1742	0.0087	-0.0832	0.0008
0.0087	0.3031	0.0174	0.0949
-0.0832	0.0174	0.0607	0.0176
0.0008	0.0949	0.0176	0.2329

At this point reevaluating the model can prove helpful. Inclusion of each of the terms which have been eliminated until now shows that reinclusion of the X^2 term gives an overall decrease of error. The design matrix is now:

z0	X	X^2	Y^2	XY
1	-0.62	0.3844	2.1025	0.899
1	-0.62	0.3844	0.0441	0.1302
1	-0.62	0.3844	2.1025	-0.899
1	-0.1	0.01	2.1025	0.145
1	-0.1	0.01	0.0441	0.021
1	-0.1	0.01	2.1025	-0.145
1	0.62	0.3844	2.1025	-0.899
1	0.62	0.3844	0.0441	-0.1302
1	0.14	0.0196	2.1025	0.203
1	-0.62	0.3844	2.1025	0.899
1	-0.62	0.3844	0.0441	0.1302
1	-0.62	0.3844	2.1025	-0.899
1	-0.1	0.01	2.1025	0.145
1	-0.1	0.01	0.0441	0.021
1	-0.1	0.01	2.1025	-0.145
1	0.62	0.3844	2.1025	-0.899
1	0.62	0.3844	0.0441	-0.1302
1	0.14	0.0196	2.1025	0.203

This design matrix gives the following matrix of coeffecients:

$Z0 = 0.8071$
$X = -0.2450$
$X^2 = -0.3358$
$Y^2 = -0.3130$
$XY = -0.1758$

And the covariance matrix:

z0	X	X^2	Y^2	XY
0.2986	-0.0328	-0.0797	-0.1022	-0.0529
-0.0328	0.3169	0.1601	0.0238	0.1128
-0.0797	0.1601	0.8505	0.0732	0.2069
-0.1022	0.0238	0.0732	0.0636	0.0258
-0.0529	0.1128	0.2069	0.0258	0.2560

Evaluation of this shows a good model and systematic inclusion of the 3rd order terms reveals that inclusion of the YX^2 term leads to the best overall model in terms of error.

z0	X	X^2	Y^2	XY	YX^2
1	-0.62	0.3844	2.1025	0.899	-0.55738
1	-0.62	0.3844	0.0441	0.1302	-0.08072
1	-0.62	0.3844	2.1025	-0.899	0.55738
1	-0.1	0.01	2.1025	0.145	-0.0145
1	-0.1	0.01	0.0441	0.021	-0.0021
1	-0.1	0.01	2.1025	-0.145	0.0145
1	0.62	0.3844	2.1025	-0.899	-0.55738
1	0.62	0.3844	0.0441	-0.1302	-0.08072
1	0.14	0.0196	2.1025	0.203	0.02842
1	-0.62	0.3844	2.1025	0.899	-0.55738
1	-0.62	0.3844	0.0441	0.1302	-0.08072
1	-0.62	0.3844	2.1025	-0.899	0.55738
1	-0.1	0.01	2.1025	0.145	-0.0145
1	-0.1	0.01	0.0441	0.021	-0.0021
1	-0.1	0.01	2.1025	-0.145	0.0145
1	0.62	0.3844	2.1025	-0.899	-0.55738
1	0.62	0.3844	0.0441	-0.1302	-0.08072
1	0.14	0.0196	2.1025	0.203	0.02842

This design matrix give the coefficient matrix:

Z0 = 0.895
X = -0.489
X^2 = -0.813
Y^2 = -0.361
XY = -0.422
YX^2 = -0.571

And the covariance matrix:

z0	X	X^2	Y^2	XY	YX^2
0.3311	-0.1221	-0.6554	-0.1197	-0.1435	-0.2100
-0.1221	0.5617	0.6415	0.0718	0.3612	0.5758
-0.6554	0.6415	0.7975	0.1676	0.6954	1.1325
-0.1197	0.0718	0.1676	0.0730	0.0745	0.1129
-0.1435	0.3612	0.6954	0.0745	0.5080	0.5843
-0.2100	0.5758	1.1325	0.1129	0.5843	0.3544

Final Equation:

$$\Delta\Delta G^{\ddagger} = 0.895 - 0.489X - 0.813X^2 - 0.361Y^2 - 0.422XY - 0.571YX^2$$

Additional iterative manipulations were performed as above and this model resulted in the lowest error overall.

The following key statistics were calculated with this model

Sum of Square due to experimental error (SS_{pe}):

0.0083

Sum of Squares due to Lack of Fit (SS_{lof})

0.0645
$S_r^2 = 0.006$
$R^2 = 0.99$
F test for goodness of fit gave
$F_{(5,12)} = 61.6$
This result is highly significant at the 95% confidence level
The error associated with any value can be calculated according to the following equation:

$$Z \pm (f * s_r^2 * (X_0(X' * X)^{-1} X_0'))^{1/2}$$

Where Z is the estimated value given by the model equation, *f* is the appropriate Fisher value at the desired confidence interval and X_0 is the row vector for the calculated factor level.
The reader is referred to the Table 1 of the manuscript for comparison of all the predicted values and all of the measured values along with the

3 x 3 Acetophenone Model

X Position	Adj. Charton Value	Y Position	Adj. Charton Value	Delta G in Kcal/mol
H	-0.62	Me	-1.45	-0.78659
H	-0.62	tBu	-0.21	-0.11392
H	-0.62	CEt3	1.45	0.78659
Me	-0.1	Me	-1.45	-0.78659
Me	-0.1	tBu	-0.21	-0.11392
Me	-0.1	CEt3	1.45	0.78659
tBu	0.62	Me	-1.45	-0.78659
tBu	0.62	tBu	-0.21	-0.11392
iPr	0.14	CEt3	1.45	0.78659
H	-0.62	Me	-1.45	-0.78659
H	-0.62	tBu	-0.21	-0.11392
H	-0.62	CEt3	1.45	0.78659
Me	-0.1	Me	-1.45	-0.78659
Me	-0.1	tBu	-0.21	-0.11392
Me	-0.1	CEt3	1.45	0.78659
tBu	0.62	Me	-1.45	-0.78659
tBu	0.62	tBu	-0.21	-0.11392
iPr	0.14	CEt3	1.45	0.78659

Final Design Matrix

z0	X	X2	Y2	XY	Y3
1	-0.62	0.3844	2.1025	0.899	-3.04863
1	-0.62	0.3844	0.0441	0.1302	-0.00926
1	-0.62	0.3844	2.1025	-0.899	3.048625
1	-0.1	0.01	2.1025	0.145	-3.04863
1	-0.1	0.01	0.0441	0.021	-0.00926
1	-0.1	0.01	2.1025	-0.145	3.048625
1	0.62	0.3844	2.1025	-0.899	-3.04863
1	0.62	0.3844	0.0441	-0.1302	-0.00926
1	0.14	0.0196	2.1025	0.203	3.048625
1	-0.62	0.3844	2.1025	0.899	-3.04863
1	-0.62	0.3844	0.0441	0.1302	-0.00926
1	-0.62	0.3844	2.1025	-0.899	3.048625
1	-0.1	0.01	2.1025	0.145	-3.04863
1	-0.1	0.01	0.0441	0.021	-0.00926
1	-0.1	0.01	2.1025	-0.145	3.048625
1	0.62	0.3844	2.1025	-0.899	-3.04863
1	0.62	0.3844	0.0441	-0.1302	-0.00926
1	0.14	0.0196	2.1025	0.203	3.048625

Final Response Matrix

-0.75203
1.255091
0.686594
-0.71874
1.403217
1.080845
-0.24266
0.686594
1.403217
-0.68659
1.134177
0.65548
-0.65548
1.324914
1.031224
-0.24266
0.625301
1.255091

The Coefficient Matrix

1.2824
0.0335
-0.7240
-0.4322
-0.0730
0.2397

3

The uncorrected Varience-Covarience Matrix

0.3260	-0.0695	-0.5885	-0.1093	-0.0964	-0.0187
-0.0695	0.3657	0.3051	0.0333	0.1707	0.0249
-0.5885	0.3051	0.2815	0.1016	0.3791	0.0739
-0.1093	0.0333	0.1016	0.0655	0.0371	0.0049
-0.0964	0.1707	0.3791	0.0371	0.3248	0.0295
-0.0187	0.0249	0.0739	0.0049	0.0295	0.0127

Final Equation

$$\Delta\Delta G^{\ddagger} = 1.282 + 0.034X - 0.724X^2 - 0.432Y^2 - 0.073XY + 0.240Y$$

The following key statistics were calculated with this model

Sum of Square due to experimental error (SS_{pe}):

0.029

Sum of Squares due to Lack of Fit (SS_{lof})

0.986

$S_r^2 = 0.084$

$R^2 = 0.91$

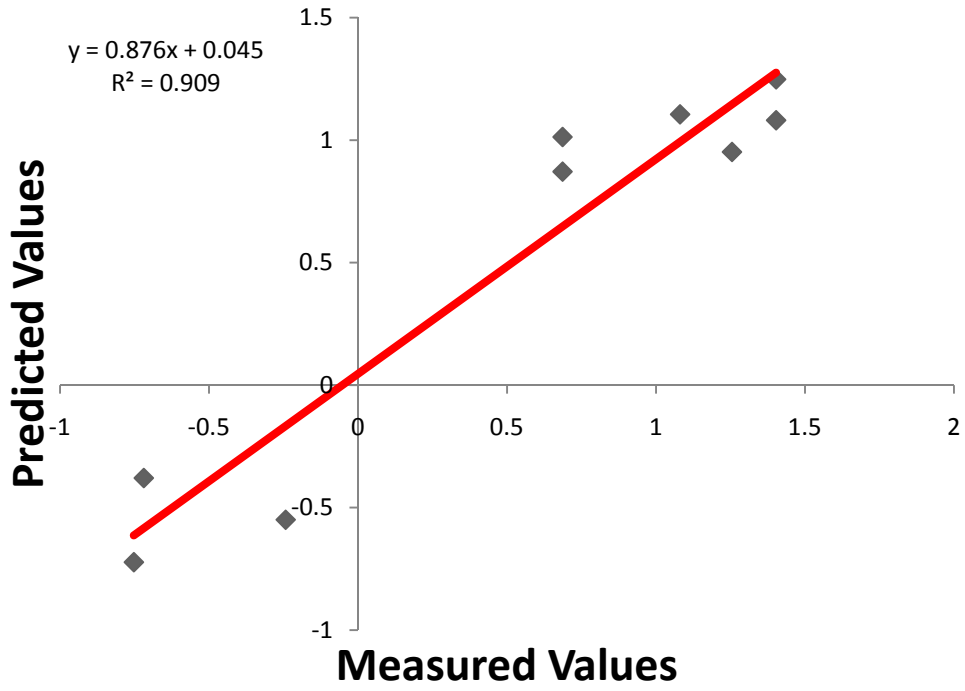
F test for goodness of fit gave

$F_{(5,12)} = 24.77297$

Significant at the 95% confidence interval.

Comparison of measured er to predicted er:

Measured			*Predicted*		
R	**S**	**ΔΔG‡**	**R**	**S**	**ΔΔG‡**
20	80	-0.75203	21	79	-0.72296
91	9	1.255091	85	15	0.951836
78	22	0.686594	83	17	0.871631
21	79	-0.71874	33	67	-0.37918
93	7	1.403217	91	9	1.248553
88	12	1.080845	88	12	1.105335
39	61	-0.24266	27	73	-0.54955
78	22	0.686594	87	13	1.013005
93	7	1.403217	88	12	1.081141
22	78	-0.68659	21	79	-0.72296
89	11	1.134177	85	15	0.951836
77	23	0.65548	83	17	0.871631
23	77	-0.65548	33	67	-0.37918
92	8	1.324914	91	9	1.248553
87	13	1.031224	88	12	1.105335
39	61	-0.24266	27	73	-0.54955
76	24	0.625301	87	13	1.013005
91	9	1.255091	88	12	1.081141



MEK Allylation

X Position	Adj. Charton Value	Y Position	Adj. Charton Value	Delta G in Kcal/mol
H	-0.62	Me	-1.45	0.359821
H	-0.62	tBu	-0.21	0
H	-0.62	CEt3	1.45	0
Me	-0.1	Me	-1.45	0.459639
Me	-0.1	tBu	-0.21	-0.08698
Me	-0.1	CEt3	1.45	-0.08698
tBu	0.62	Me	-1.45	0.108859
tBu	0.62	tBu	-0.21	-0.10886
iPr	0.14	CEt3	1.45	-0.28871
H	-0.62	Me	-1.45	0.359821
H	-0.62	tBu	-0.21	0
H	-0.62	CEt3	1.45	0
Me	-0.1	Me	-1.45	0.459639
Me	-0.1	tBu	-0.21	-0.08698
Me	-0.1	CEt3	1.45	-0.08698
tBu	0.62	Me	-1.45	0.108859
tBu	0.62	tBu	-0.21	-0.10886
iPr	0.14	CEt3	1.45	-0.28871

Final Design Matrix

z0	X	Y	X^2	Y^2	XY	X^3	YX^2
1	-0.62	-1.45	0.3844	2.1025	0.899	-0.23833	-0.55738
1	-0.62	-0.21	0.3844	0.0441	0.1302	-0.23833	-0.08072
1	-0.62	1.45	0.3844	2.1025	-0.899	-0.23833	0.55738
1	-0.1	-1.45	0.01	2.1025	0.145	-0.001	-0.0145
1	-0.1	-0.21	0.01	0.0441	0.021	-0.001	-0.0021
1	-0.1	1.45	0.01	2.1025	-0.145	-0.001	0.0145
1	0.62	-1.45	0.3844	2.1025	-0.899	0.238328	-0.55738
1	0.62	-0.21	0.3844	0.0441	-0.1302	0.238328	-0.08072
1	0.14	1.45	0.0196	2.1025	0.203	0.002744	0.02842
1	-0.62	-1.45	0.3844	2.1025	0.899	-0.23833	-0.55738
1	-0.62	-0.21	0.3844	0.0441	0.1302	-0.23833	-0.08072
1	-0.62	1.45	0.3844	2.1025	-0.899	-0.23833	0.55738
1	-0.1	-1.45	0.01	2.1025	0.145	-0.001	-0.0145
1	-0.1	-0.21	0.01	0.0441	0.021	-0.001	-0.0021
1	-0.1	1.45	0.01	2.1025	-0.145	-0.001	0.0145
1	0.62	-1.45	0.3844	2.1025	-0.899	0.238328	-0.55738
1	0.62	-0.21	0.3844	0.0441	-0.1302	0.238328	-0.08072
1	0.14	1.45	0.0196	2.1025	0.203	0.002744	0.02842

Final Response Matrix

0.359821
0
0
0.459639
-0.08698
-0.08698
0.108859
-0.10886
-0.28871
0.359821
0
0
0.459639
-0.08698
-0.08698
0.108859
-0.10886
-0.28871

Coefficients and Associated Errors

Coeff
-0.200
-1.03628
-0.1773
0.2938
0.1260
0.1286
2.6119
0.3412

Final Equation

$$\Delta\Delta G^{\ddagger} = -0.200 - 1.036X - 0.177Y + 0.294X^2 + 0.126Y^2 + 0.129XY + 2.6120X^3 + 0.341YX^2$$

The following key statistics were calculated with this model

Sum of Square due to experimental error (SS_{pe}):

0.00

Sum of Squares due to Lack of Fit (SS_{lof})

0.986

$S_r^2 = 0.0008$

$R^2 = 0.98$

F test for goodness of fit gave

$F_{(5, 9)} = 131$

Highly significant at the 95% confidence interval.

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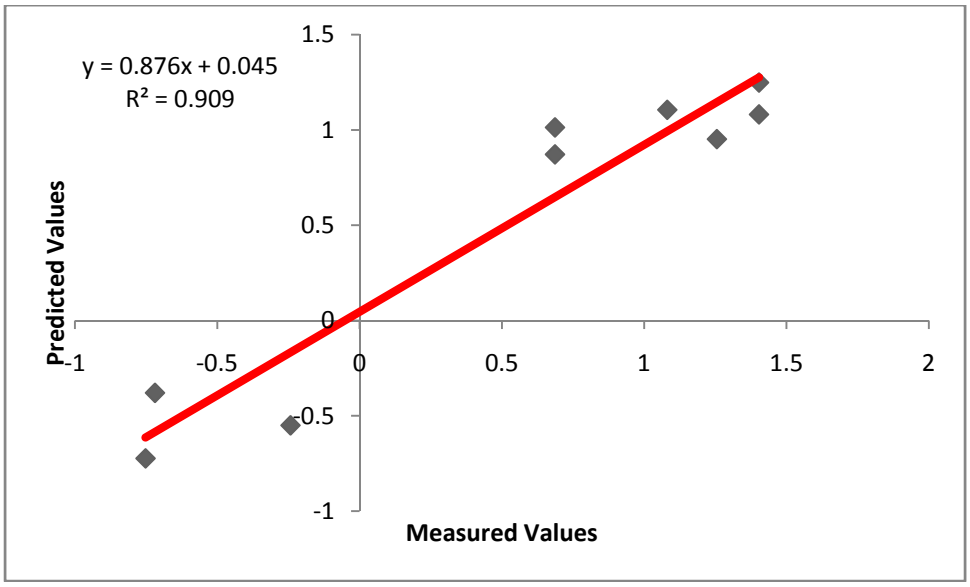
Measured			*Predicted*		
R	**S**	**ΔΔG‡**	**R**	**S**	**ΔΔG‡**
34	66	0.359821	67	33	0.38029
50	50	0	48	52	-0.03518
50	50	0	51	49	0.015181
30	70	0.459639	69	31	0.439254
54	46	-0.08698	48	52	-0.05135
54	46	-0.08698	45	55	-0.10157
45	55	0.108859	55	45	0.108734
55	45	-0.10886	45	55	-0.10839
63	37	-0.28871	37	63	-0.28797
34	66	0.359821	67	33	0.38029
50	50	0	48	52	-0.03518
50	50	0	51	49	0.015181
30	70	0.459639	69	31	0.439254
54	46	-0.08698	48	52	-0.05135
54	46	-0.08698	45	55	-0.10157
45	55	0.108859	55	45	0.108734
55	45	-0.10886	45	55	-0.10839
63	37	-0.28871	37	63	-0.28797



5x5 Benzaldehyde

X Pos.	Adj. Charton Value	Y Pos.	Adj. Charton Value	Delta G
H	-0.62	Me	-0.51	0.021702
H	-0.62	Et	-0.47	0.300384
H	-0.62	*i*Pr	-0.27	0.254084
H	-0.62	*t*Bu	0.21	0.940979
H	-0.62	Hep	0.51	0.64638
Me	-0.1	Me	-0.51	0.130825
Me	-0.1	Et	-0.47	0.242656
Me	-0.1	*i*Pr	-0.27	0.32393
Me	-0.1	*t*Bu	0.21	0.860165
Me	-0.1	Hep	0.51	1.080845
Et	-0.06	Me	-0.51	0.242656
Et	-0.06	Et	-0.47	0.5816
Et	-0.06	*i*Pr	-0.27	0.879617
Et	-0.06	*t*Bu	0.21	0.822582
Et	-0.06	Hep	0.51	1.134177
*i*Pr	0.14	Me	-0.51	0.277111
*i*Pr	0.14	Et	-0.47	0.879617
*i*Pr	0.14	*i*Pr	-0.27	0.962552
*i*Pr	0.14	*t*Bu	0.21	1.289071
*i*Pr	0.14	Hep	0.51	0.616416
*t*Bu	0.62	Me	-0.51	0.229012
*t*Bu	0.62	Et	-0.47	0.197442
*t*Bu	0.62	*i*Pr	-0.27	0.329862
*t*Bu	0.62	*t*Bu	0.21	0.335814
*t*Bu	0.62	Hep	0.51	0.42142

Design Matrix

Z0	Y	X^2	Y^2	XY	X^3	YX^2
1	-0.51	0.3844	0.2601	0.3162	-0.23833	-0.19604
1	-0.47	0.3844	0.2209	0.2914	-0.23833	-0.18067
1	-0.27	0.3844	0.0729	0.1674	-0.23833	-0.10379
1	0.21	0.3844	0.0441	-0.1302	-0.23833	0.080724
1	0.51	0.3844	0.2601	-0.3162	-0.23833	0.196044
1	-0.51	0.01	0.2601	0.051	-0.001	-0.0051
1	-0.47	0.01	0.2209	0.047	-0.001	-0.0047
1	-0.27	0.01	0.0729	0.027	-0.001	-0.0027
1	0.21	0.01	0.0441	-0.021	-0.001	0.0021
1	0.51	0.01	0.2601	-0.051	-0.001	0.0051
1	-0.51	0.0036	0.2601	0.0306	-0.00022	-0.00184
1	-0.47	0.0036	0.2209	0.0282	-0.00022	-0.00169
1	-0.27	0.0036	0.0729	0.0162	-0.00022	-0.00097
1	0.21	0.0036	0.0441	-0.0126	-0.00022	0.000756
1	0.51	0.0036	0.2601	-0.0306	-0.00022	0.001836
1	-0.51	0.0196	0.2601	-0.0714	0.002744	-0.01
1	-0.47	0.0196	0.2209	-0.0658	0.002744	-0.00921
1	-0.27	0.0196	0.0729	-0.0378	0.002744	-0.00529
1	0.21	0.0196	0.0441	0.0294	0.002744	0.004116
1	0.51	0.0196	0.2601	0.0714	0.002744	0.009996
1	-0.51	0.3844	0.2601	-0.3162	0.238328	-0.19604
1	-0.47	0.3844	0.2209	-0.2914	0.238328	-0.18067
1	-0.27	0.3844	0.0729	-0.1674	0.238328	-0.10379
1	0.21	0.3844	0.0441	0.1302	0.238328	0.080724
1	0.51	0.3844	0.2601	0.3162	0.238328	0.196044

Response Matrix

0.021702
0.300384
0.254084
0.940979
0.64638
0.130825
0.242656
0.32393
0.860165
1.080845
0.242656
0.5816
0.879617
0.822582
1.134177
0.277111
0.879617
0.962552
1.289071
0.616416
0.229012
0.197442
0.329862
0.335814
0.42142

Coefficient Matrix

0.9311
0.5757
-0.9053
-1.0053
-0.5018
-0.4069
-0.4751

Covariance Matrix

0.2066	0.0242	-0.2051	-0.7764	-0.0002	-0.0009	-0.1267
0.0242	0.4451	-0.1267	0.1338	0.0132	0.0037	-0.1954
-0.2051	-0.1267	0.2786	0.0000	0.0005	0.0023	0.7897
-0.7764	0.1338	0.0000	0.6065	0.0000	0.0000	0.0000
-0.0002	0.0132	0.0005	0.0000	0.5512	0.4284	-0.0439
-0.0009	0.0037	0.0023	0.0000	0.4284	0.8788	-0.0121
-0.1267	-0.1954	0.7897	0.0000	-0.0439	-0.0121	0.4513

$$\Delta\Delta G^{\ddagger} = 0.931 + 0.576Y - 0.905X^2 - 1.005Y^2 - 0.502XY - 0.407X^3 - 0.475YX^2$$

The following key statistics were calculated with this model

Sum of Square due to experimental error (SS_{pe}):

0.029

Sum of Squares due to Lack of Fit (SS_{lof})

0.872

$S_r^2 = 0.021$

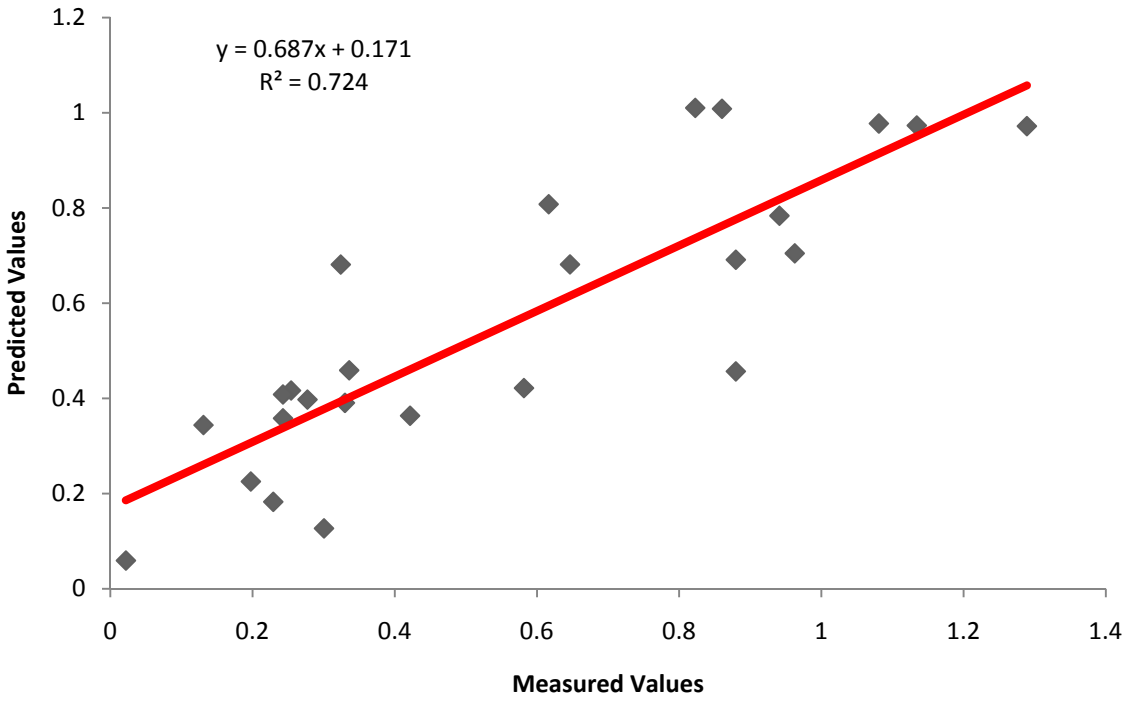
$R^2 = 0.64$

F test for goodness of fit gave

$F_{(5, 9)} = 16.1$

Significant at the 90% confidence interval.

Substituent		***Measured***			***Predicted***		
X	**Y**	**R**	**S**	**$\Delta\Delta G^{\ddagger}$**	**R**	**S**	**$\Delta\Delta G^{\ddagger}$**
H	Me	49	51	0.021702	47	53	0.059345
H	Et	37	64	0.300384	44	56	0.126927
H	iPr	39	62	0.254084	32	68	0.416597
H	tBu	15	85	0.940979	19	81	0.783773
H	Hep	22	73	0.64638	22	78	0.681496
Me	Me	44	56	0.130825	35	65	0.344017
Me	Et	39	61	0.242656	32	68	0.408271
Me	iPr	36	65	0.32393	22	78	0.681301
Me	tBu	17	83	0.860165	13	87	1.008541
Me	Hep	12	88	1.080845	14	86	0.977577
Et	Me	39	61	0.242656	34	66	0.35818
Et	Et	26	75	0.5816	31	69	0.421753
Et	iPr	17	84	0.879617	22	78	0.691375
Et	tBu	18	82	0.822582	13	87	1.010436
Et	Hep	11	89	1.134177	14	86	0.973474
iPr	Me	38	63	0.277111	32	68	0.397576
iPr	Et	17	84	0.879617	30	70	0.456828
iPr	iPr	15	86	0.962552	21	79	0.70485
iPr	tBu	9	92	1.289071	14	86	0.972071
iPr	Hep	24	76	0.616416	18	82	0.808031
tBu	Me	40	60	0.229012	42	58	0.182811
tBu	Et	41	59	0.197442	40	60	0.225494
tBu	iPr	35	65	0.329862	33	67	0.390668
tBu	tBu	35	65	0.335814	30	70	0.459054
tBu	Hep	32	69	0.42142	34	66	0.363624


y = 0.687x + 0.171
R² = 0.724
Predicted Values
Measured Values
0
0.2
0.4
0.6
0.8
1
1.2
1.4

References:

(1) Miller, J. J.; Rajaram, S.; Pfaffenroth, C.; Sigman, M. S. (2009) Synthesis of amine functionalized oxazolines with applications in asymmetric catalysis. *Tetrahedron* 65: 3110-3119.

(2) Miller, J. J.; Sigman, M. S. (2008) Quantitatively Correlating the Effect of Ligand-Substituent Size in Asymmetric Catalysis Using Linear Free Energy Relationships. *Angew. Chem., Int. Ed.* 47: 771-774.

(3) Rajaram, S.; Sigman, M. S. (2005) Design of Hydrogen Bond Catalysts Based on a Modular Oxazoline Template: Application to an Enantioselective Hetero Diels−Alder Reaction. *Org. Lett.* 7: 5473-5475.

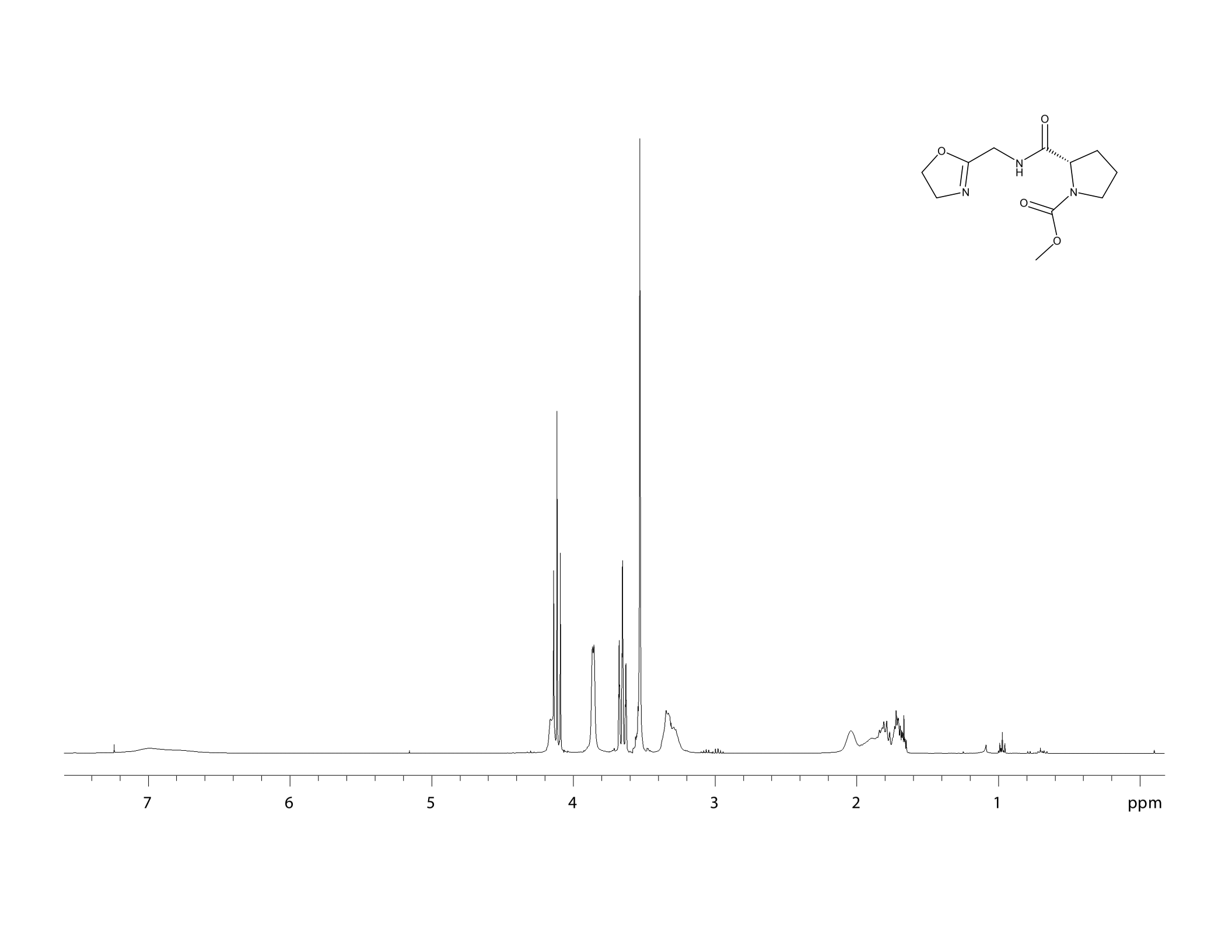
(4) Miller, J. J.; Sigman, M. S. (2007) Design and Synthesis of Modular Oxazoline Ligands for the Enantioselective Chromium-Catalyzed Addition of Allyl Bromide to Ketones. *J. Am. Chem. Soc.* 129: 2752-2753.

(5) All carbons where not observed in the ^{13}C NMR even with increased delay times (d1 = 25 sec) and extended experiment length (> 12h) and increased concentration.

(6)Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593-5601.

(7) (a) Deming, S. N.; Morgan, S. L. (1993) *Experimental design: a chemometric approach; Data Handling in Science and Technology*, *Vol. 11*, (Elsevier: Amsterdam-London-New York-Tokyo). (b) Deming, S. N. (1983) *Chemometrics. Mathematics and Statistics in Chemistry*, ed. Kowalski, B. R. (D. Riedel Publishing Company, Dordrecht) pp. 267-304. (c) Argawal, A. K.; Brisk, M. L. (1985) Sequential Experimental Design for Precise Parameter Estimation. *Ind. Eng. Chem. Process. Des. Dev.* 24: 203-210. (d) Issanchou, S.; Cognet, P.; Cabassud, M. (2005) Sequential Experimental Design Strategy for Rapid Kinetic Modeling of Chemical Synthesis. *AIChE J.* 51: 1773-1781.

(8) Ligands **L21**-**L25** were synthesized as their opposite enantiomer due to the prohibitive cost of D-TLE. The sign of the reported values were changed (in terms of $\Delta\Delta G^{\ddagger}$) to account for this.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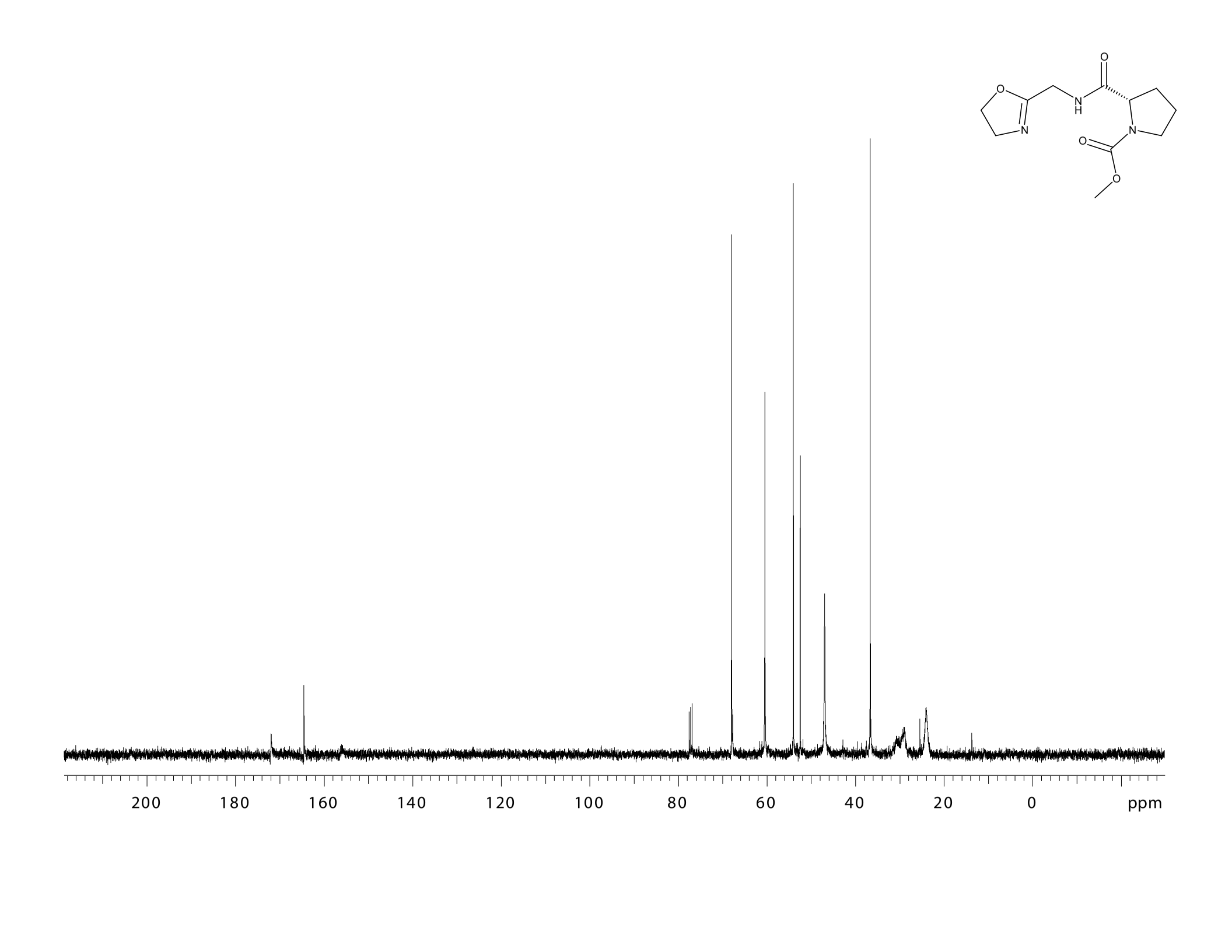
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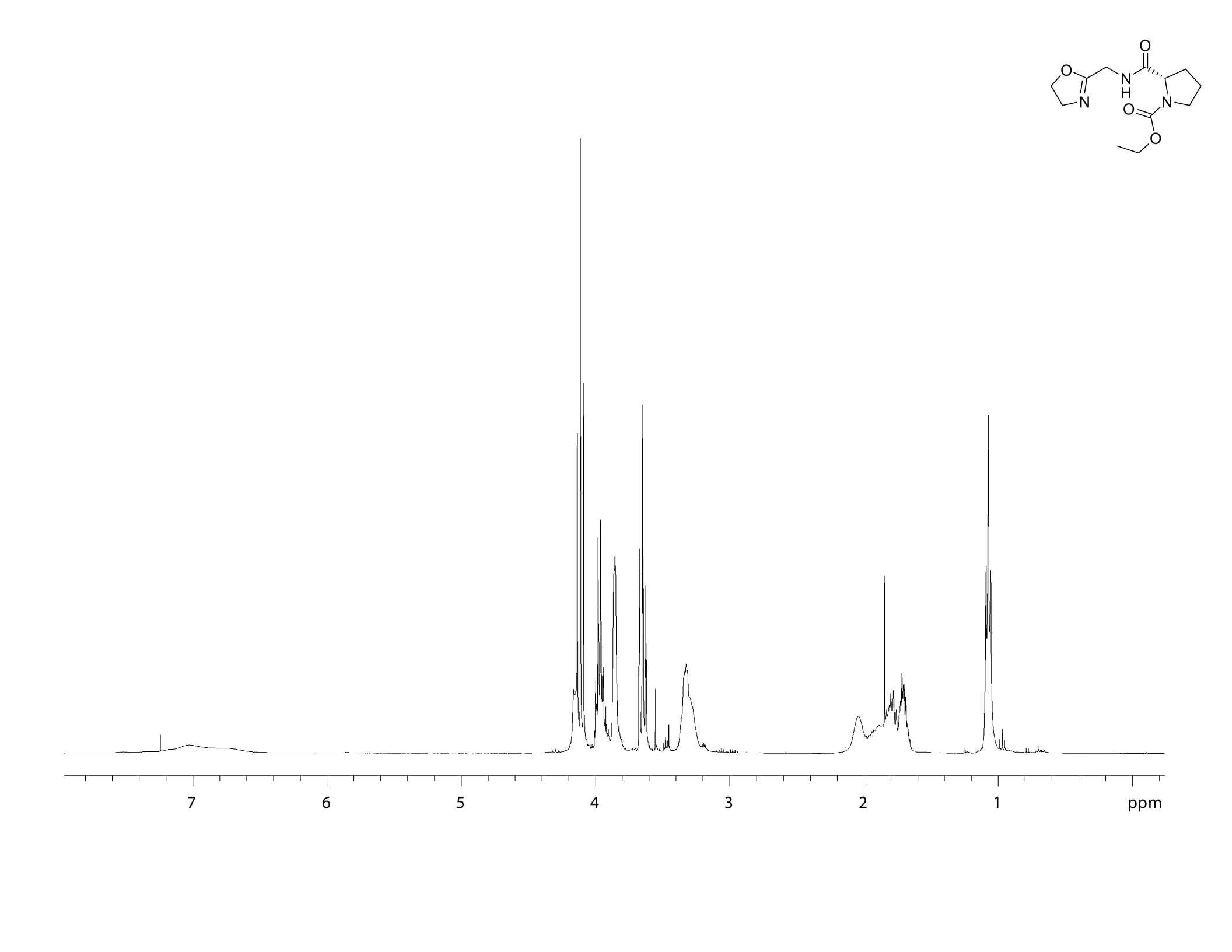
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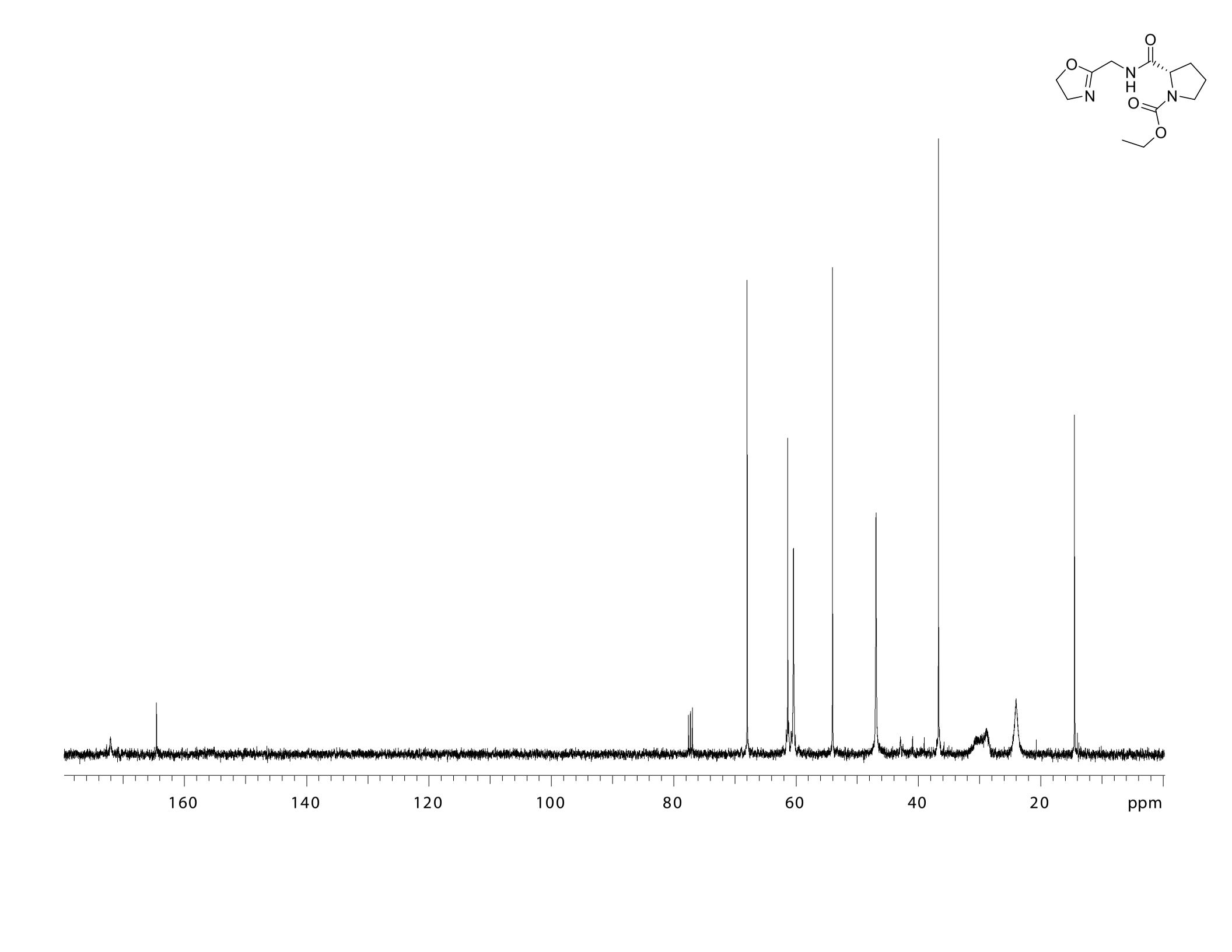
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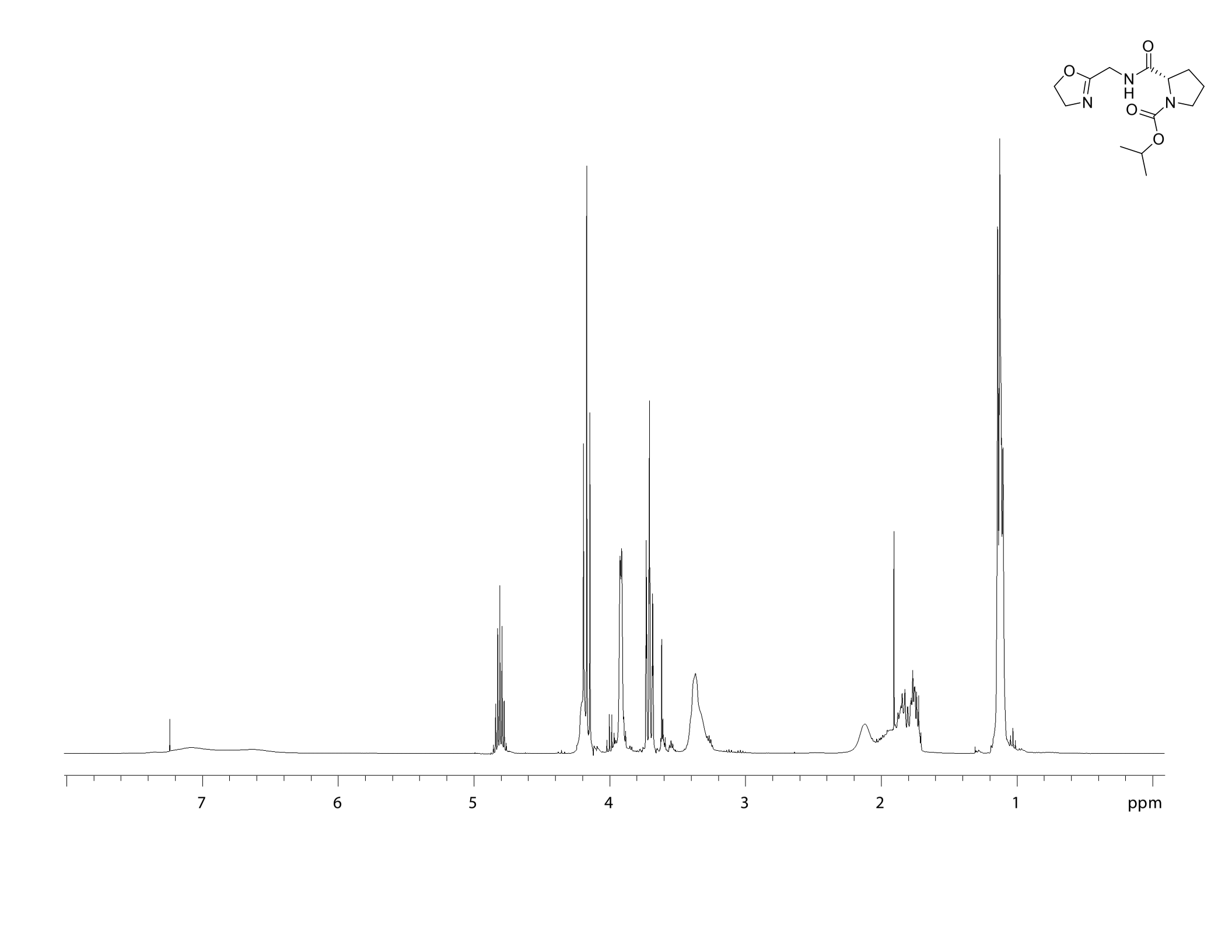
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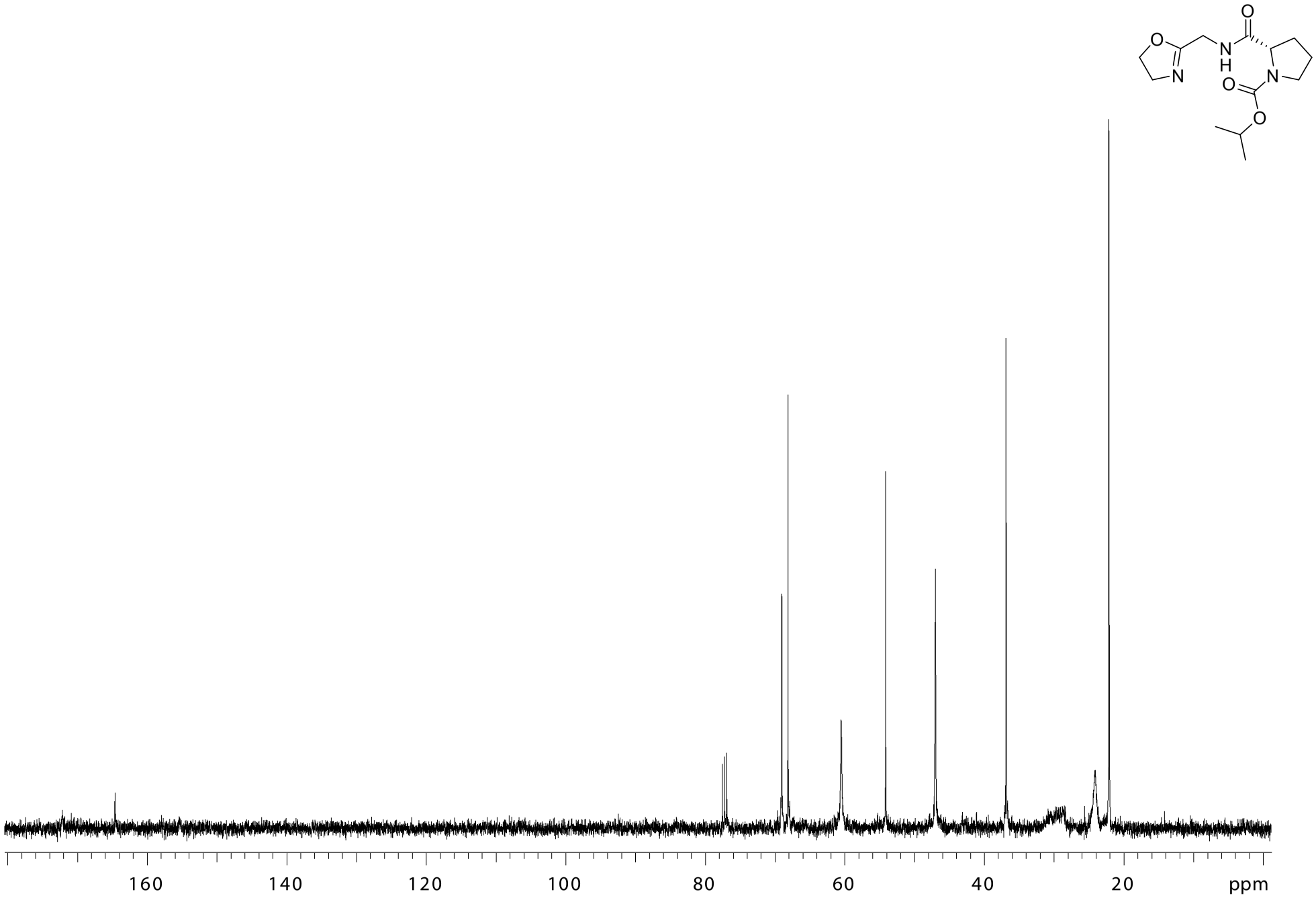
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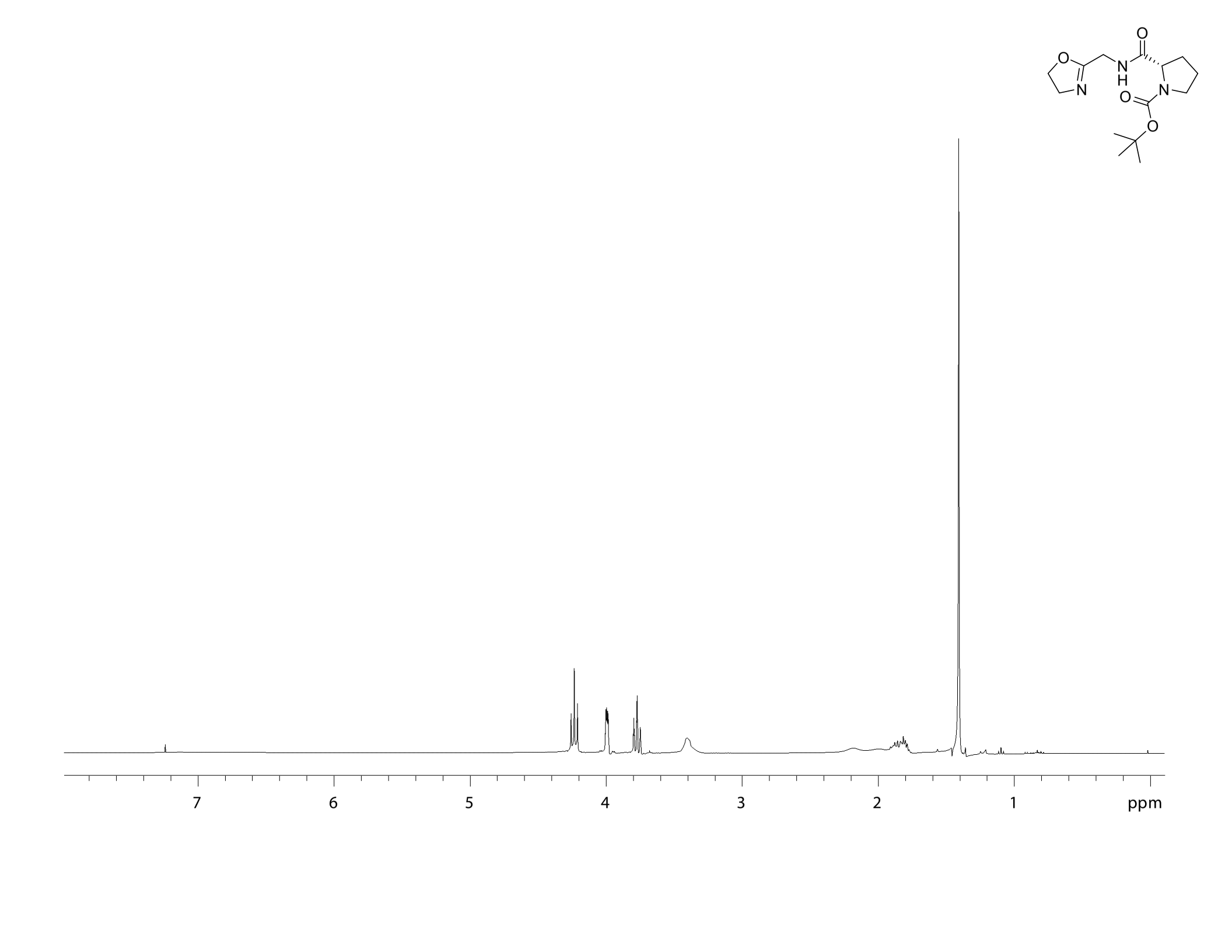
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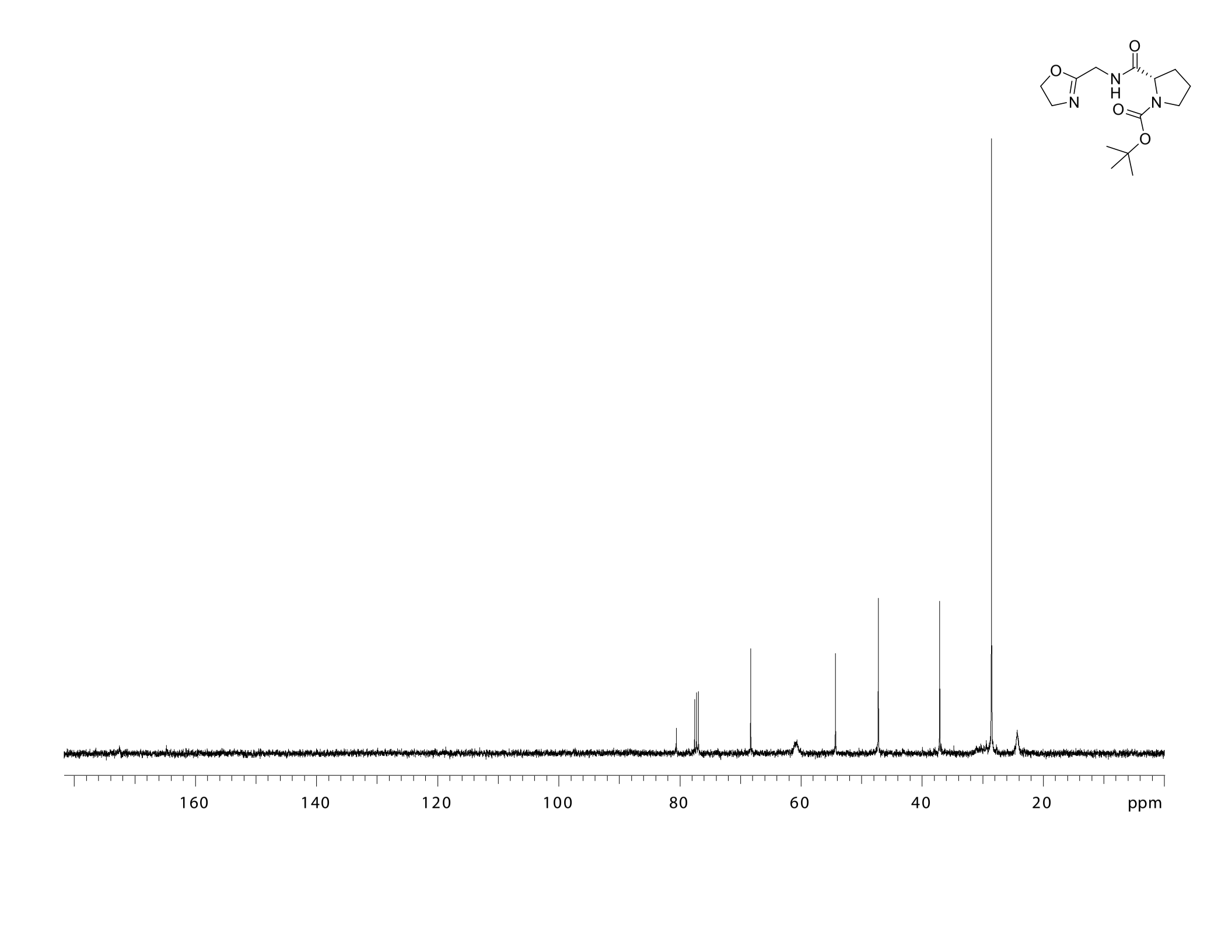
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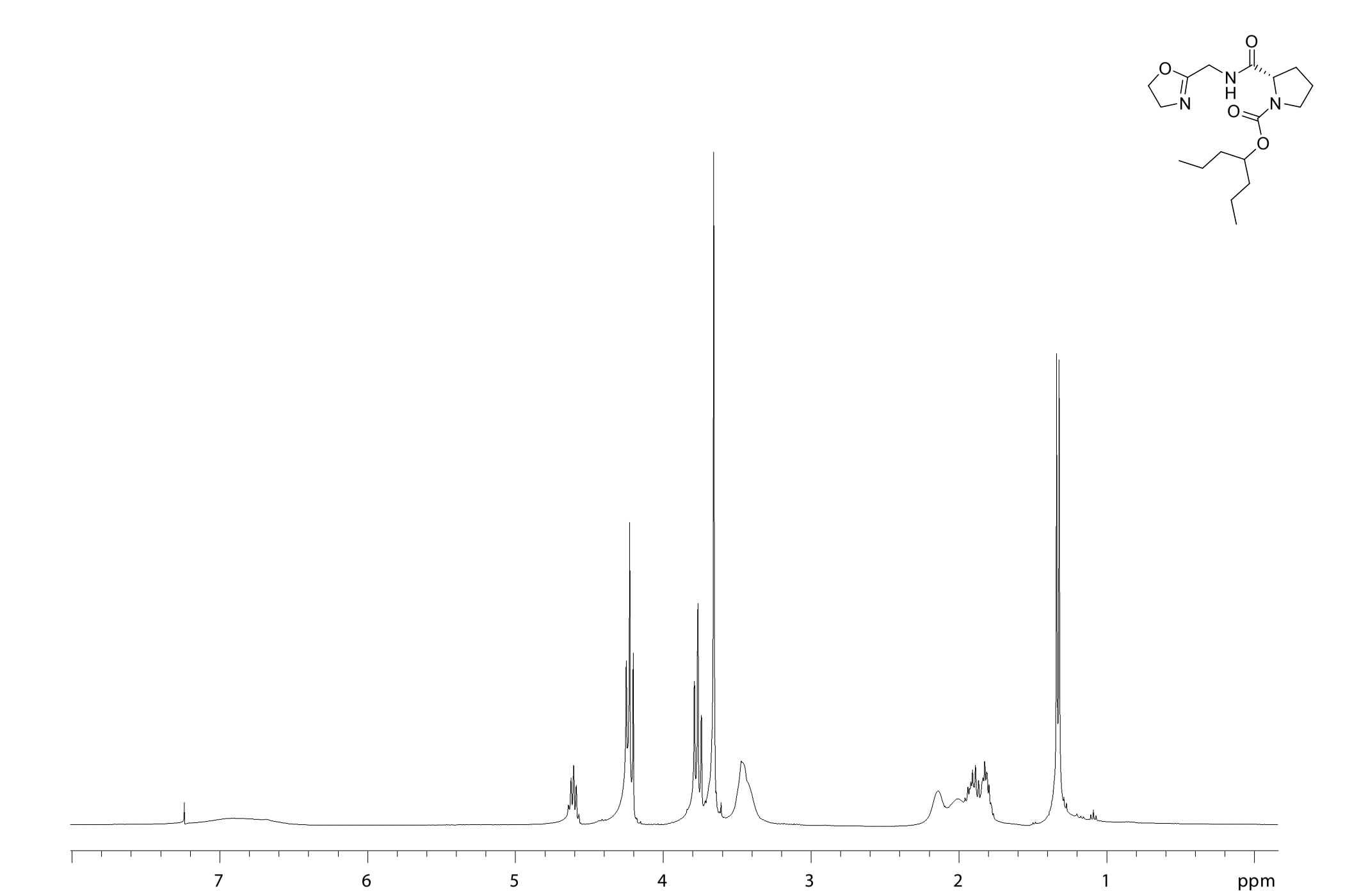
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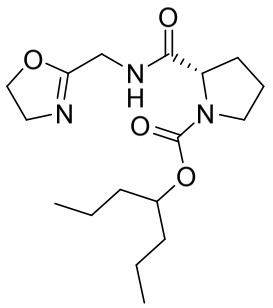
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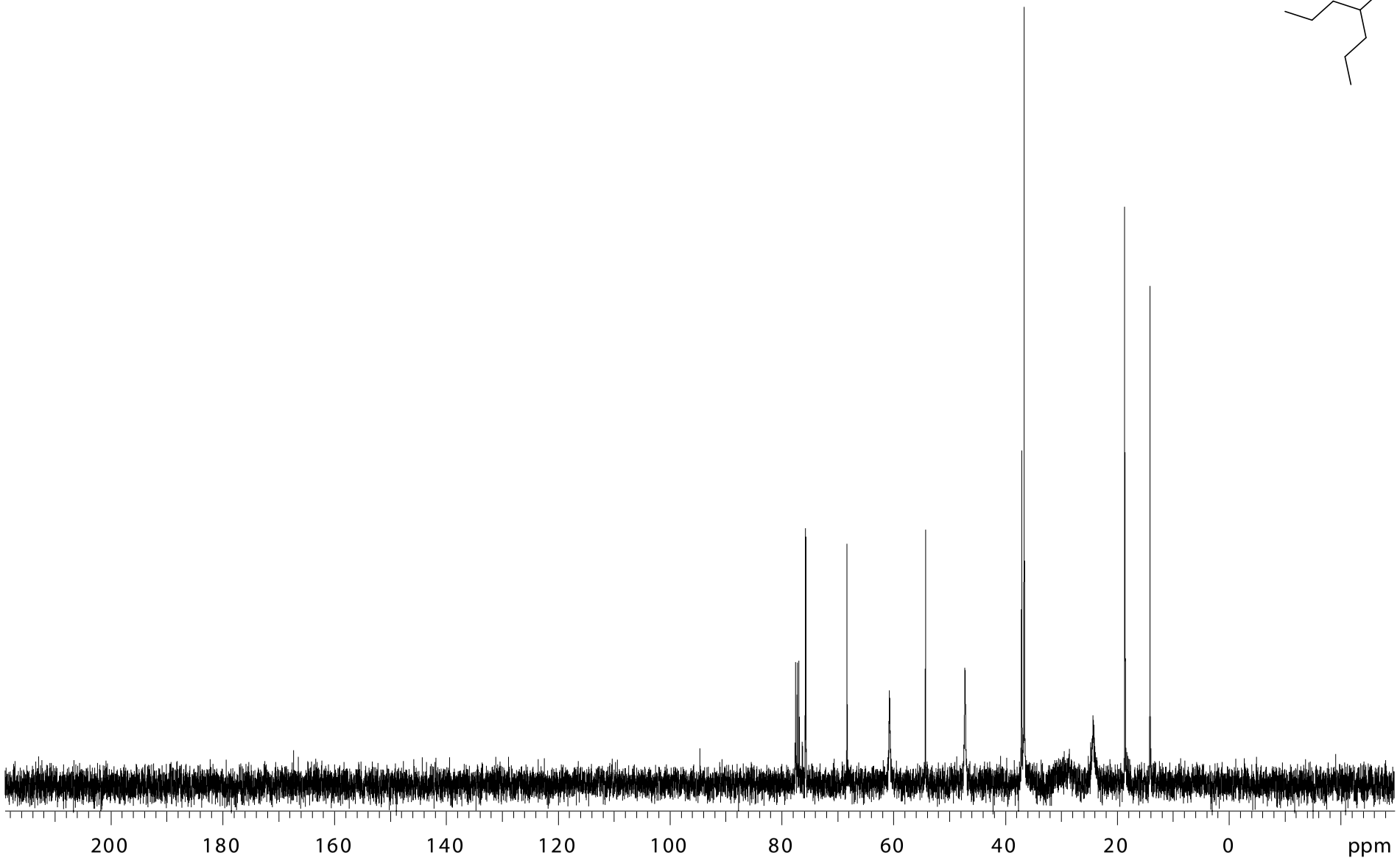
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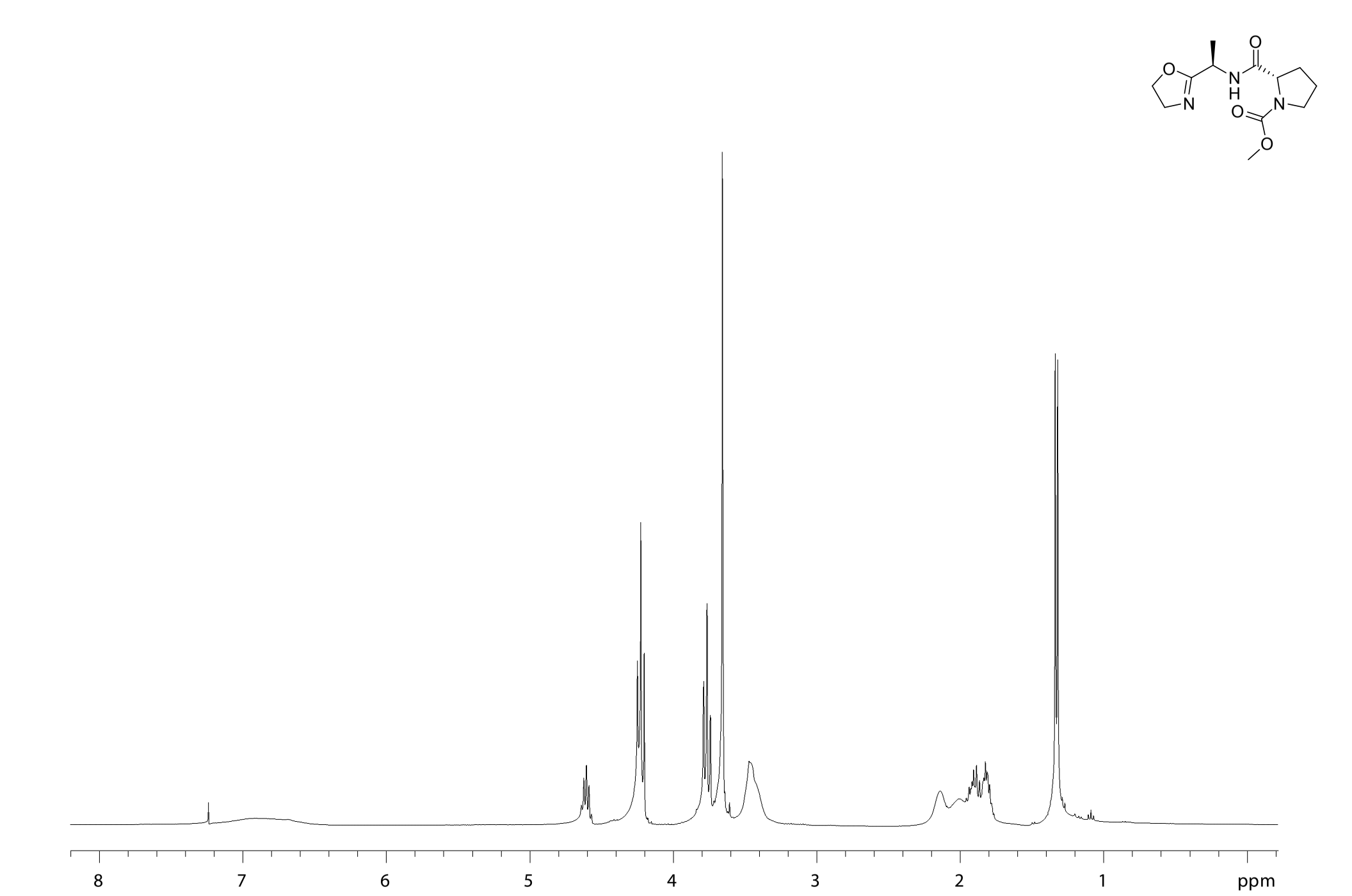
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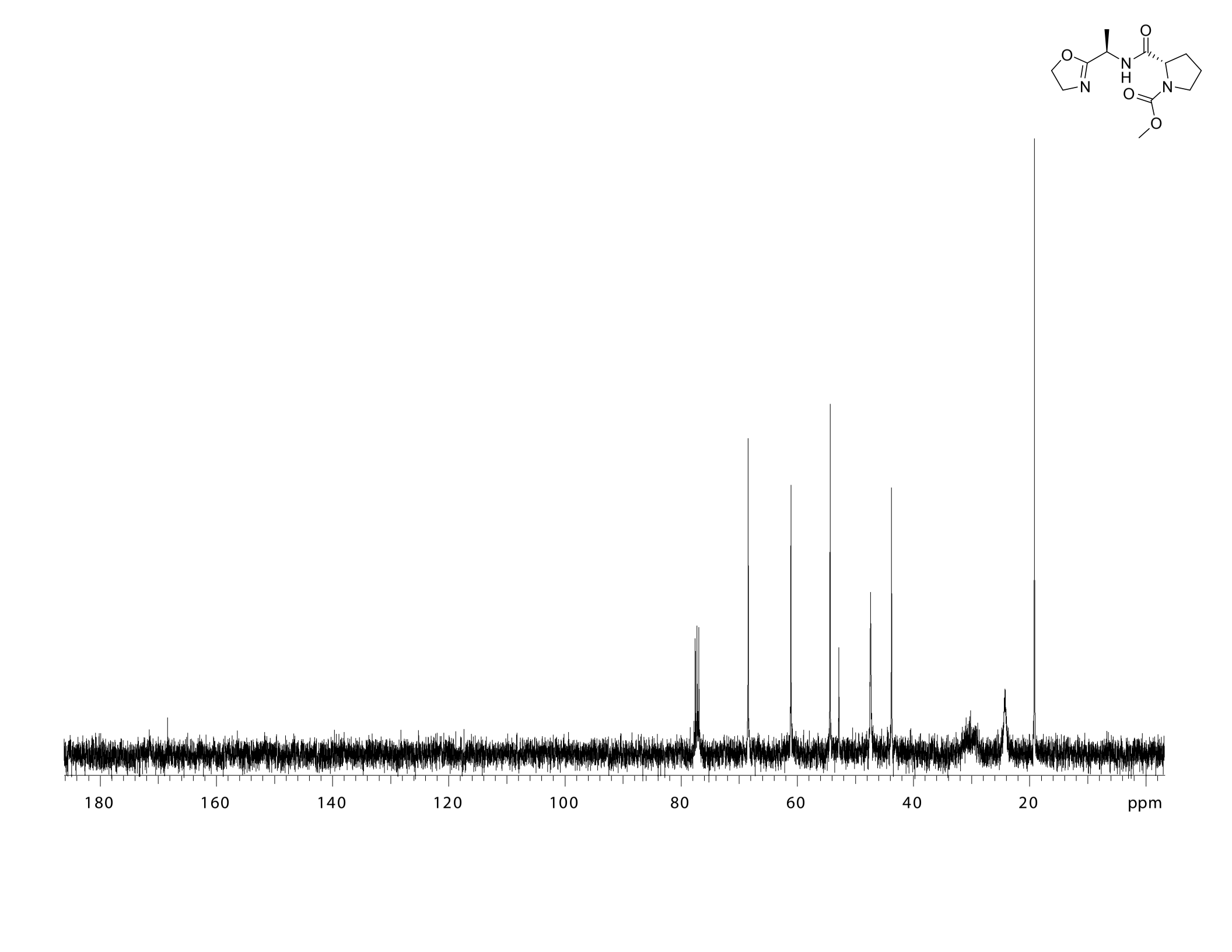
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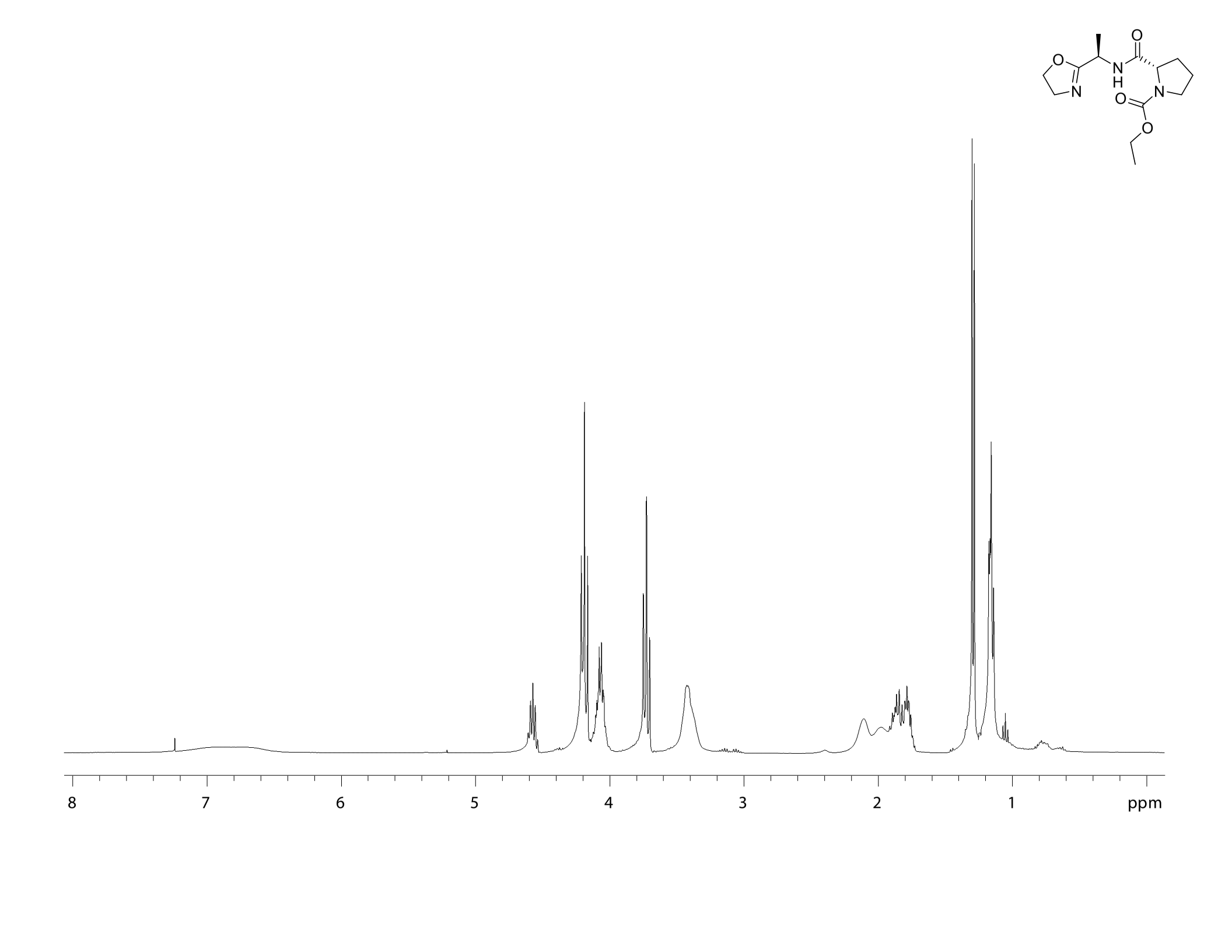
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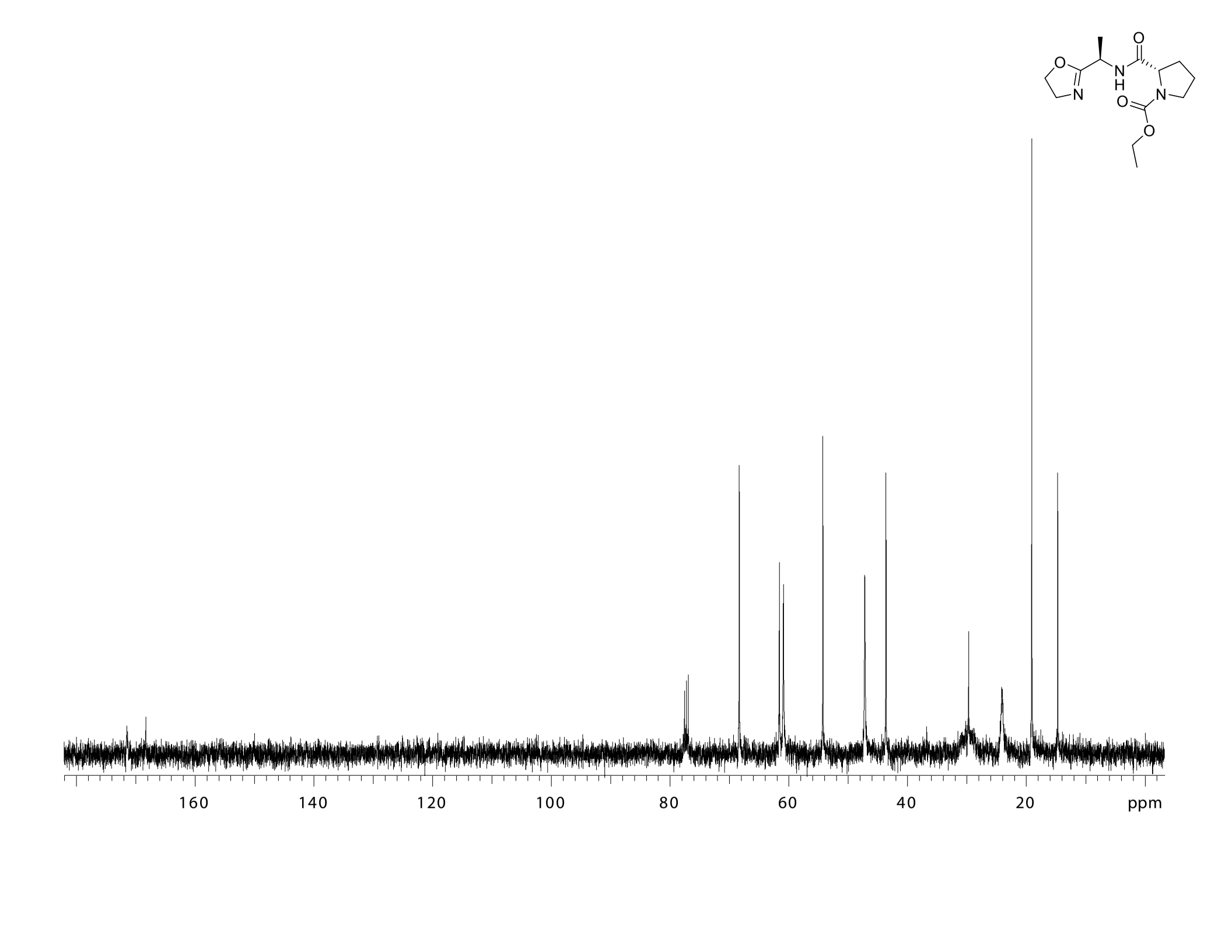
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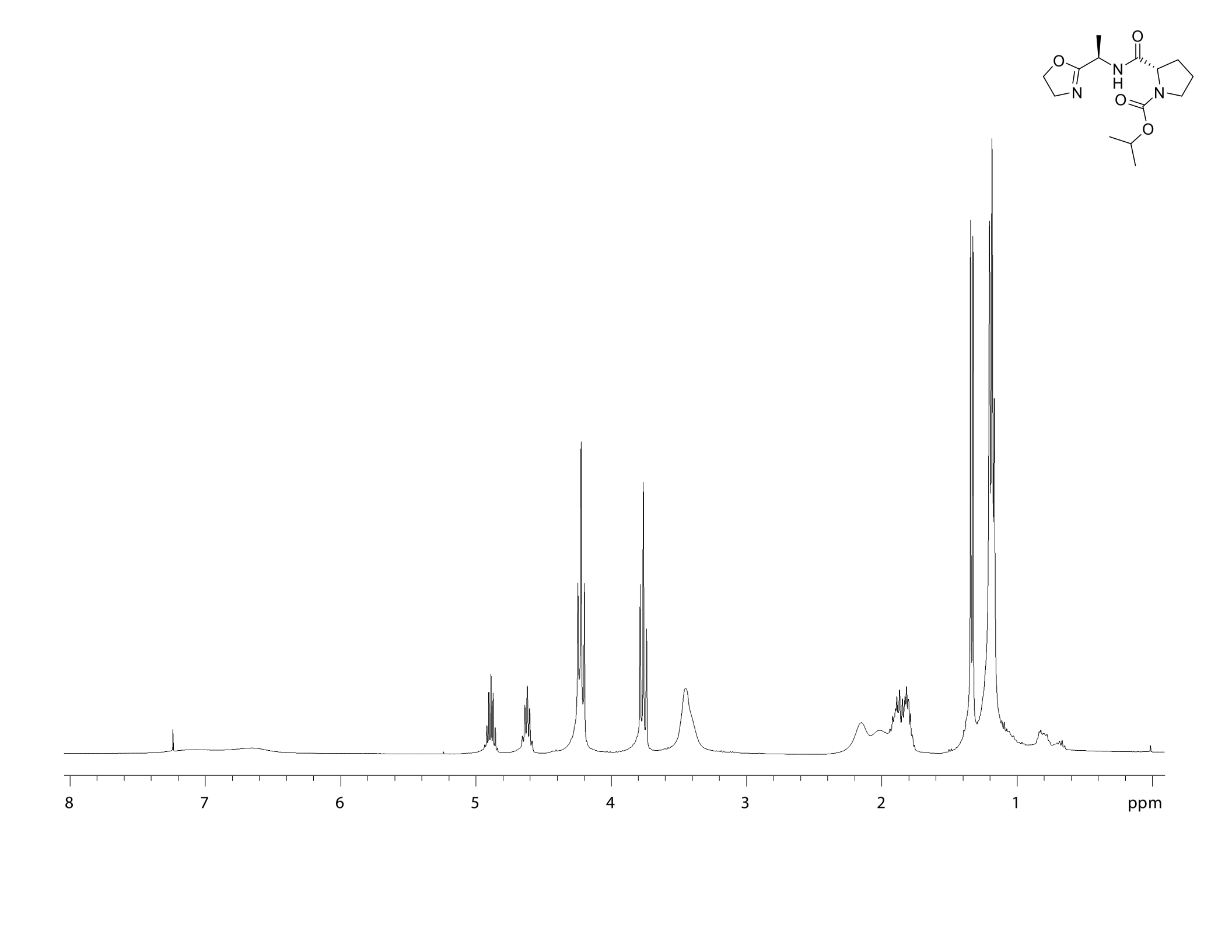
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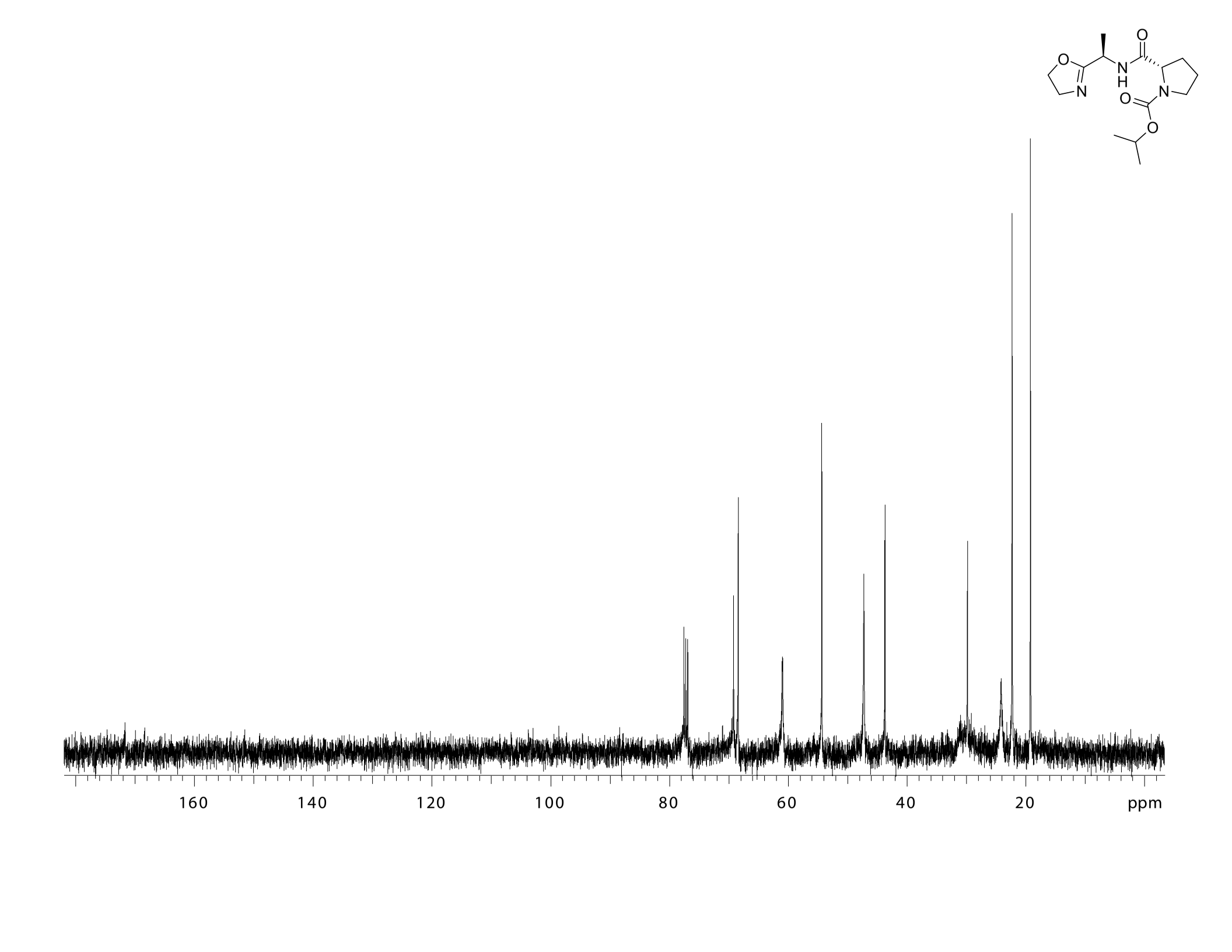
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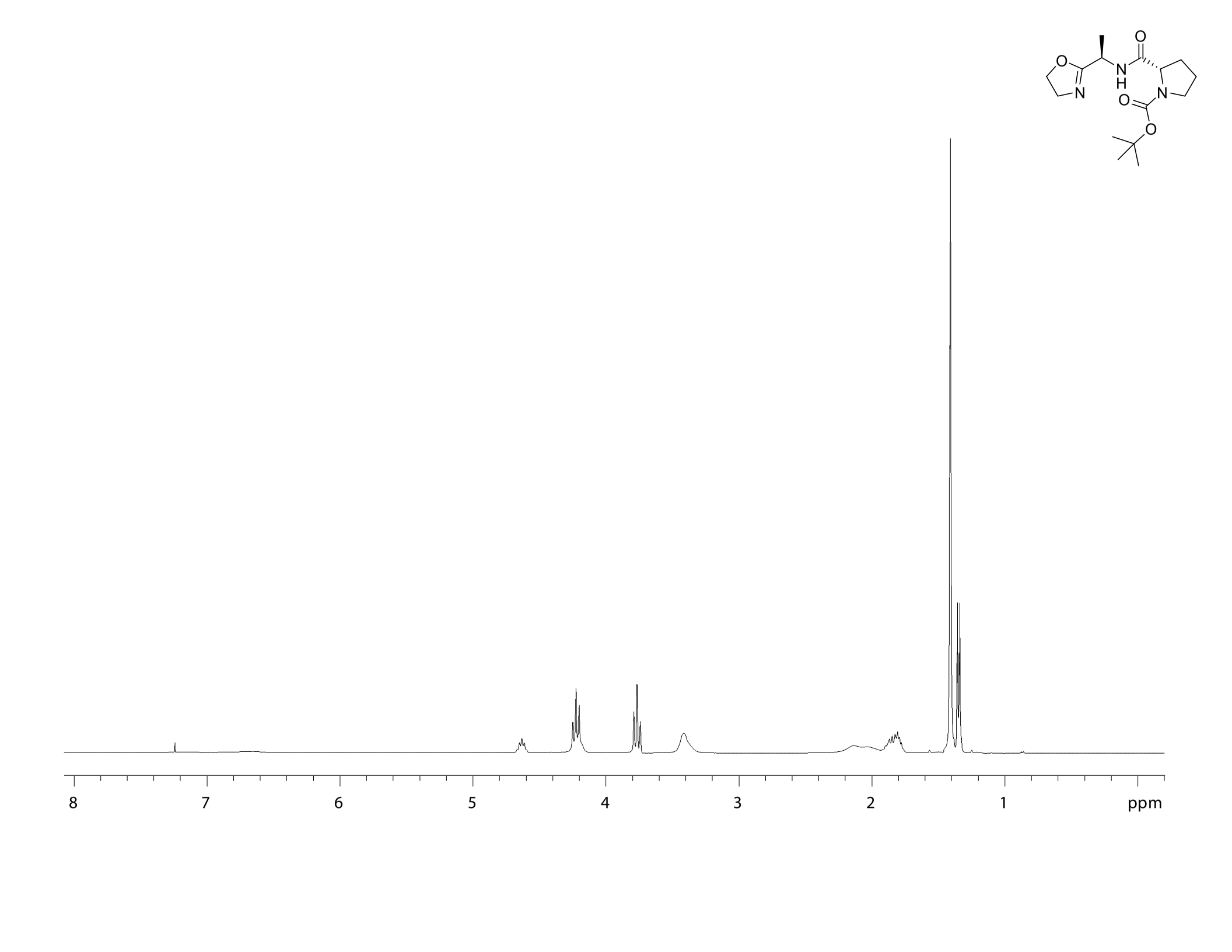
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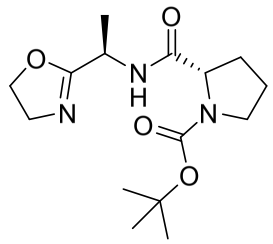
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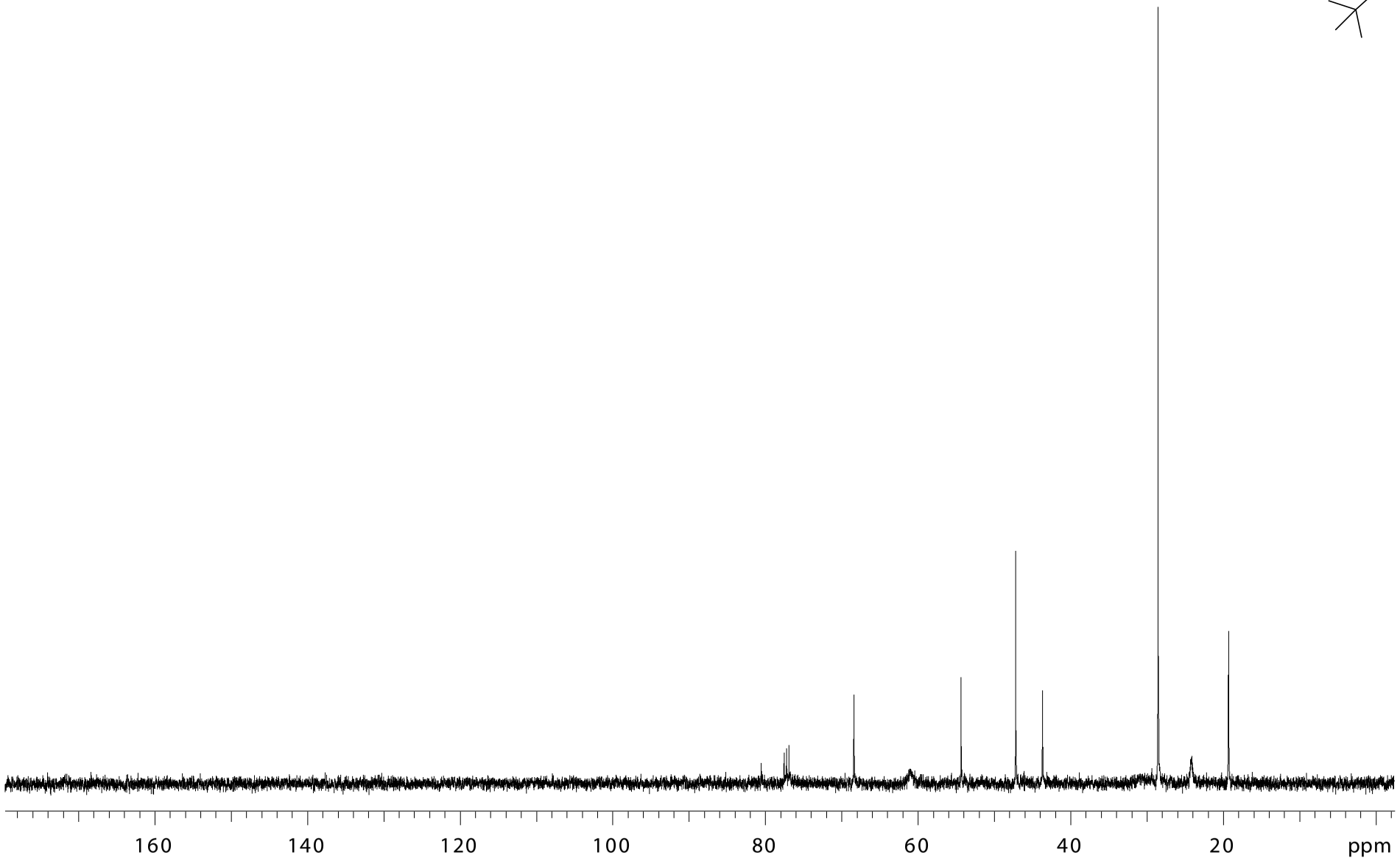
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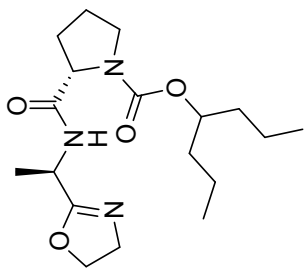


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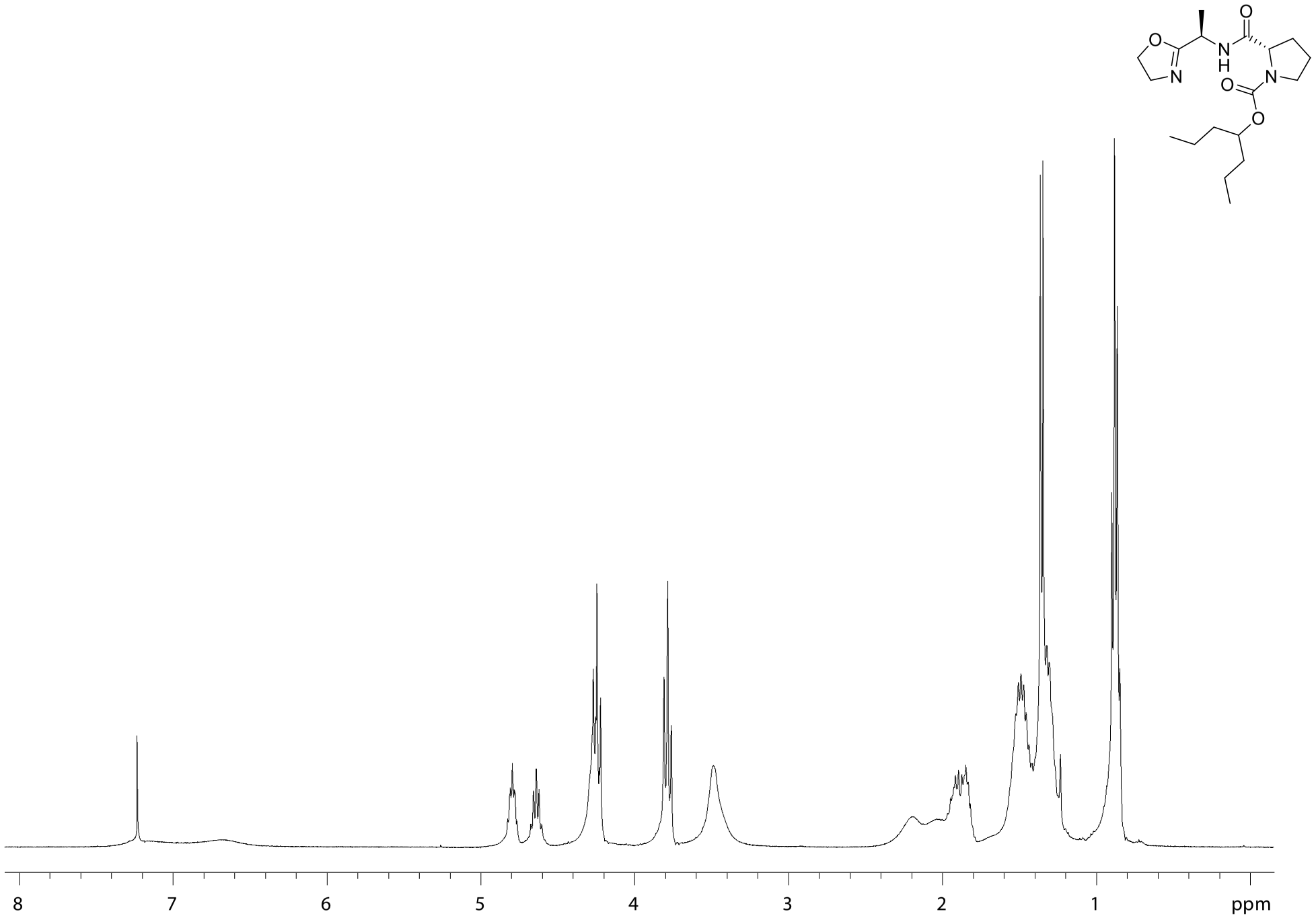
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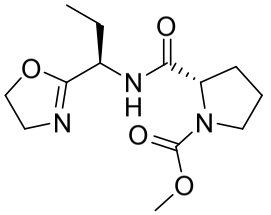
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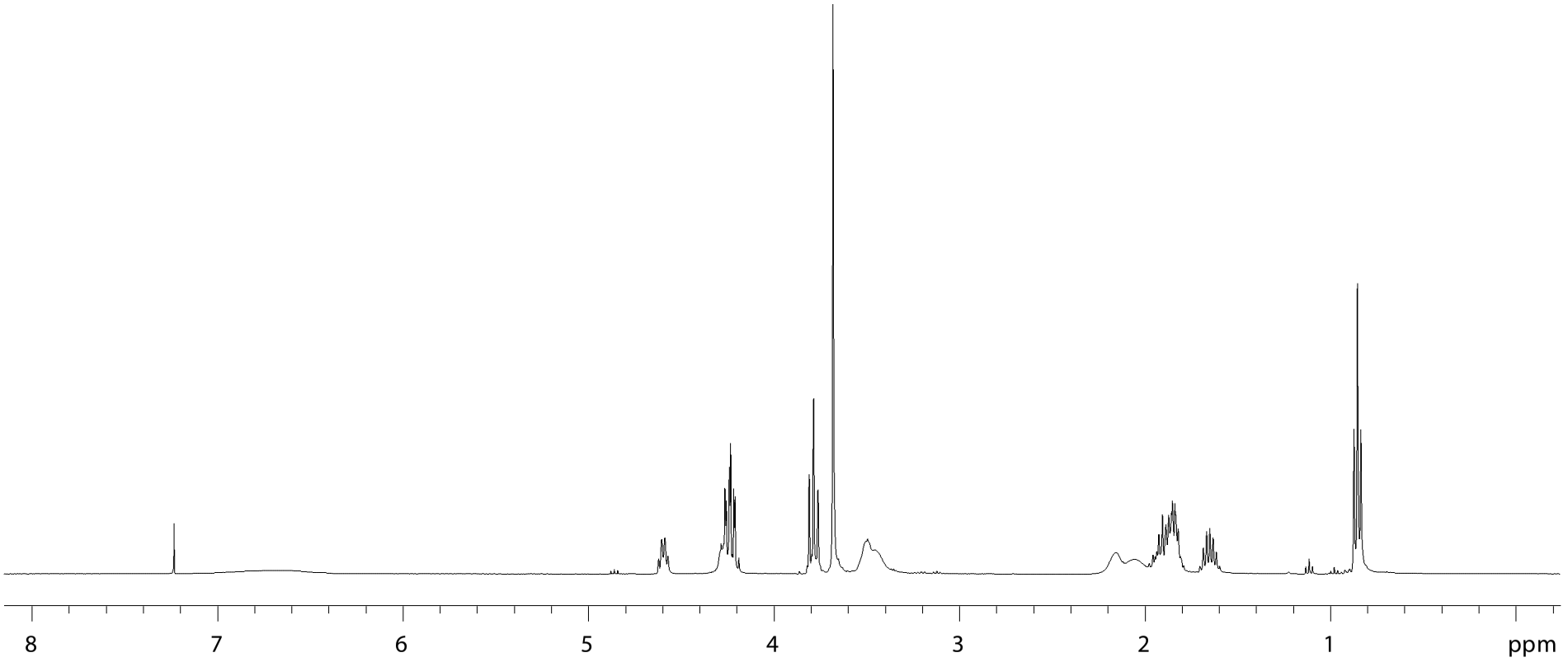
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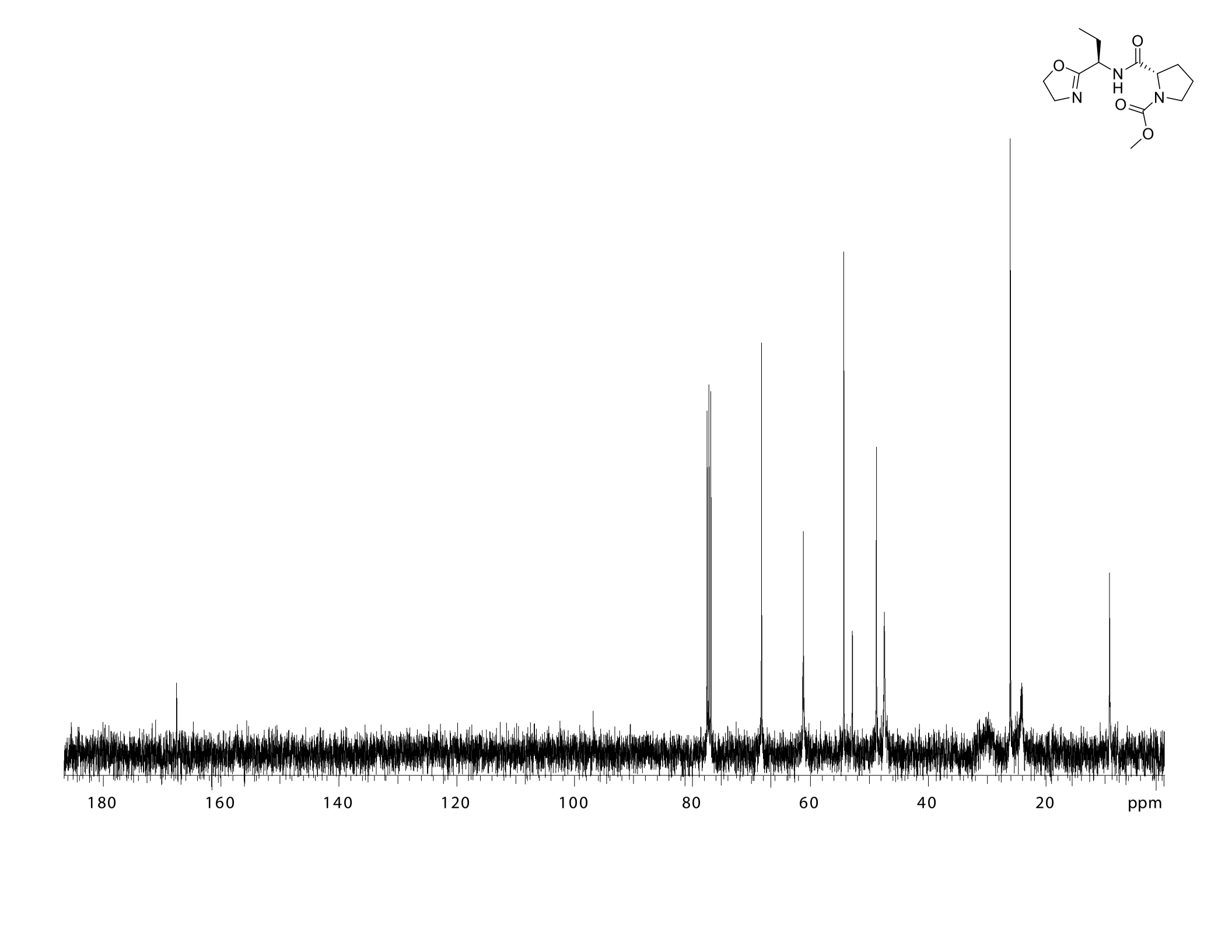
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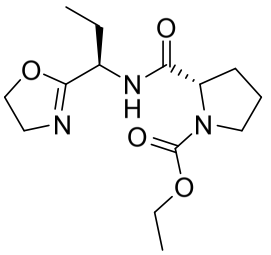
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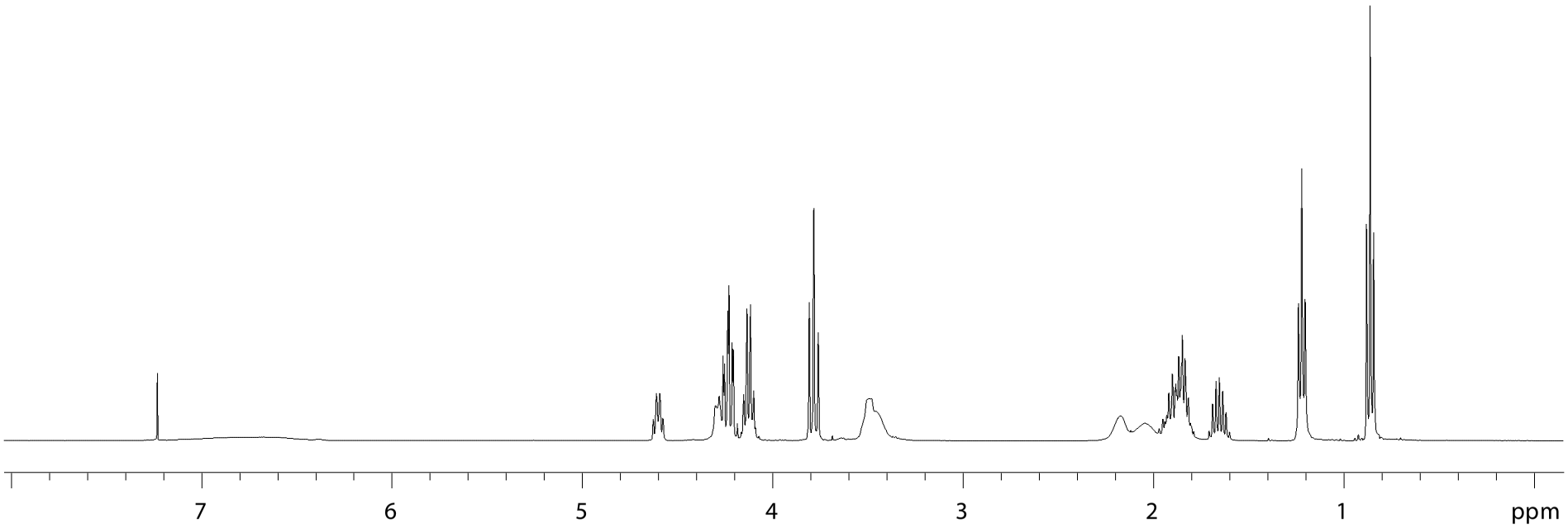
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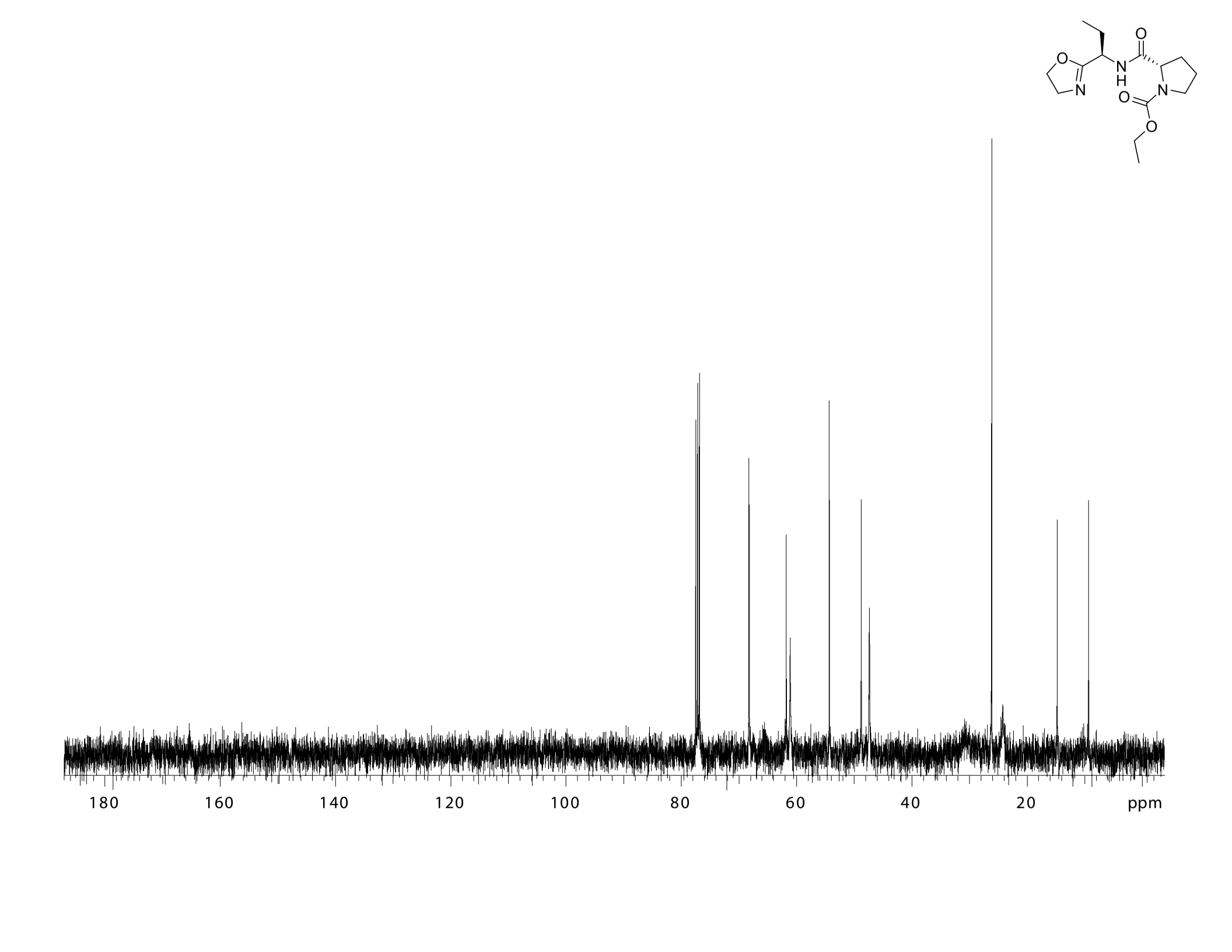
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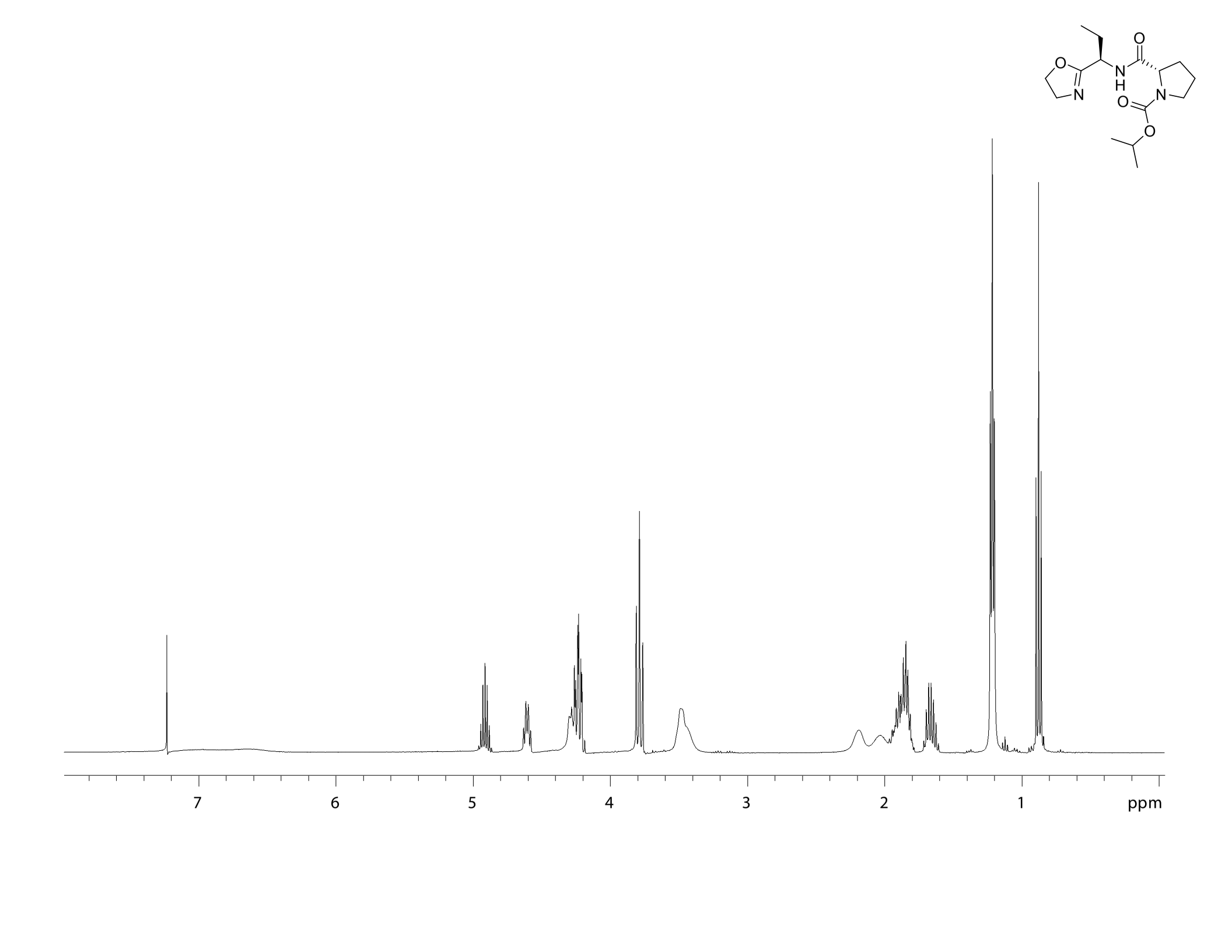
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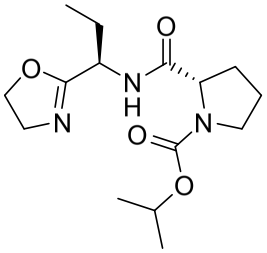
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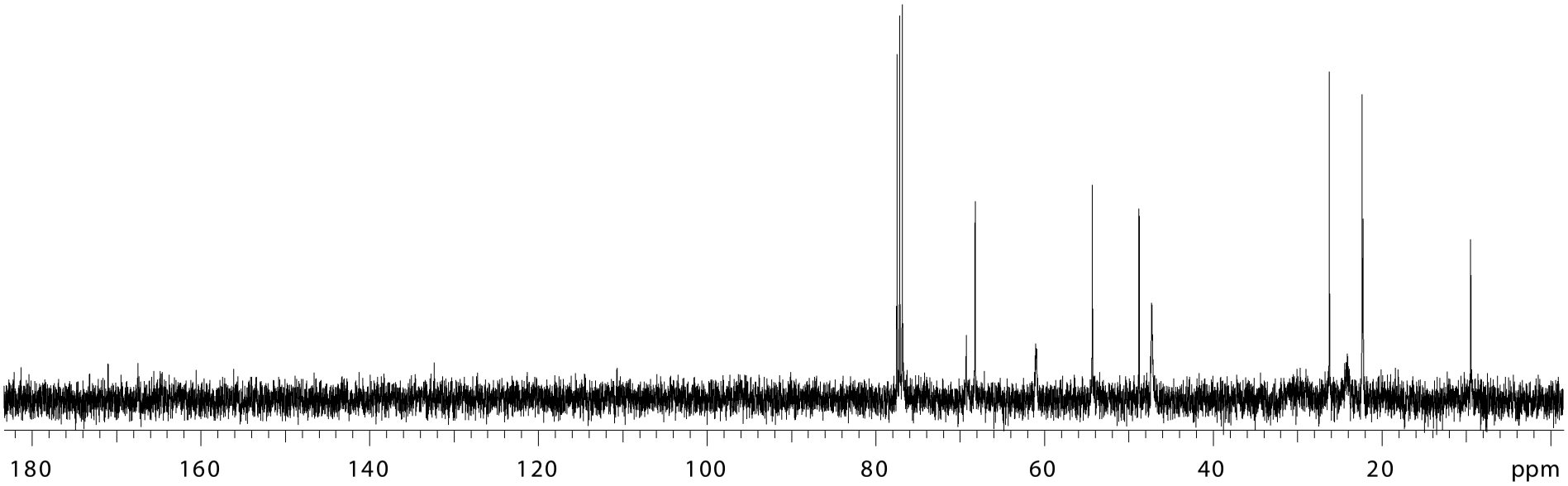
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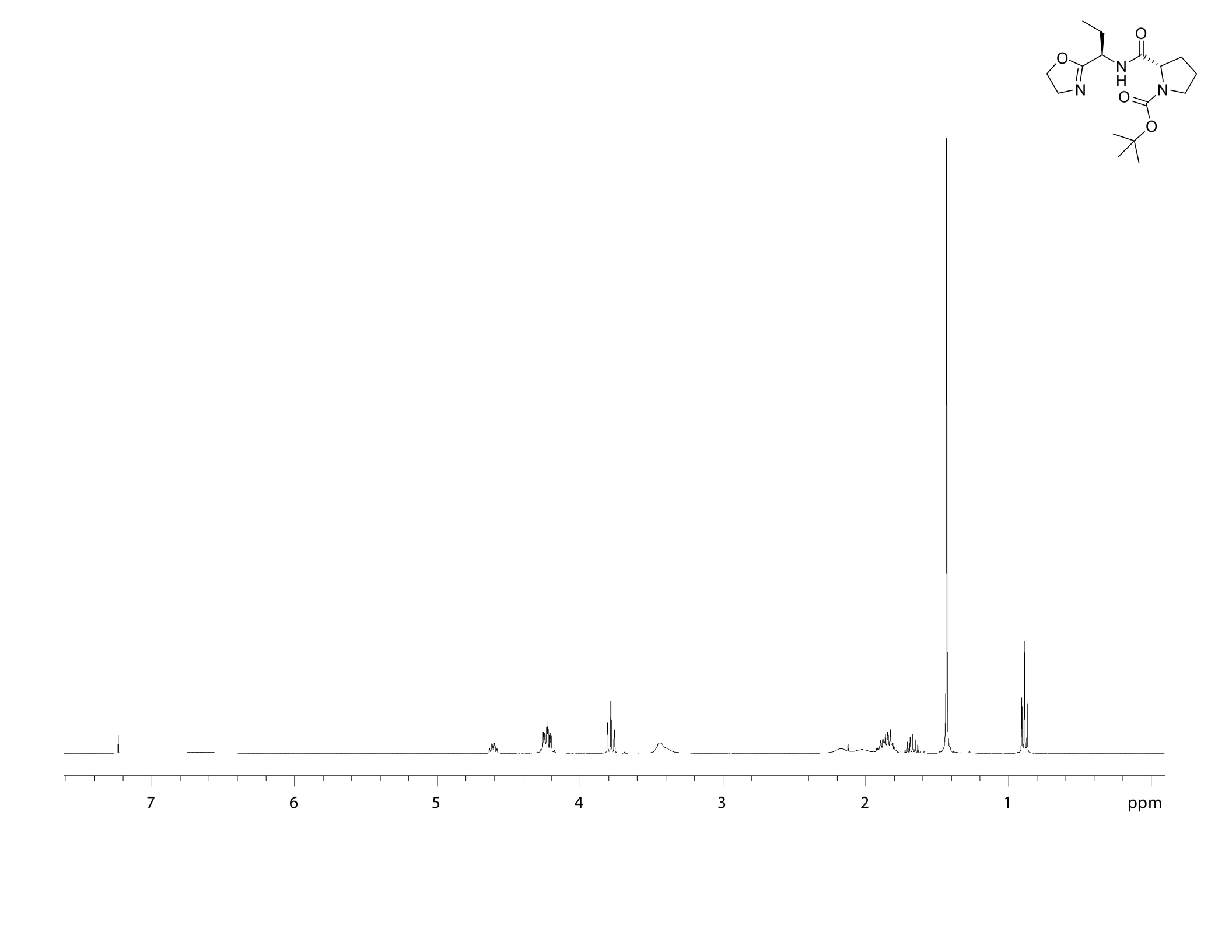
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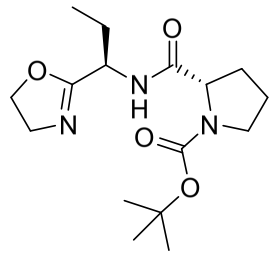
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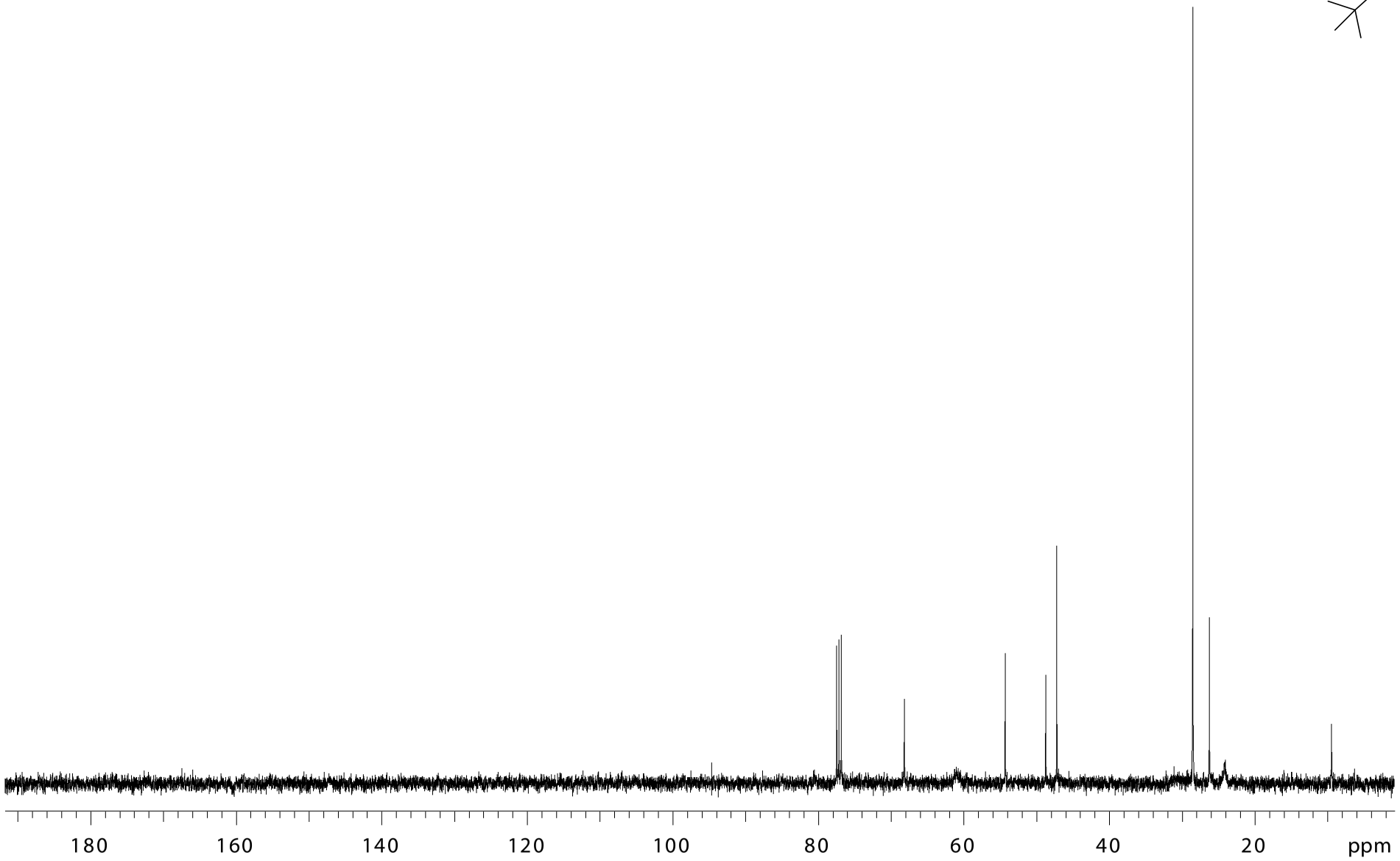
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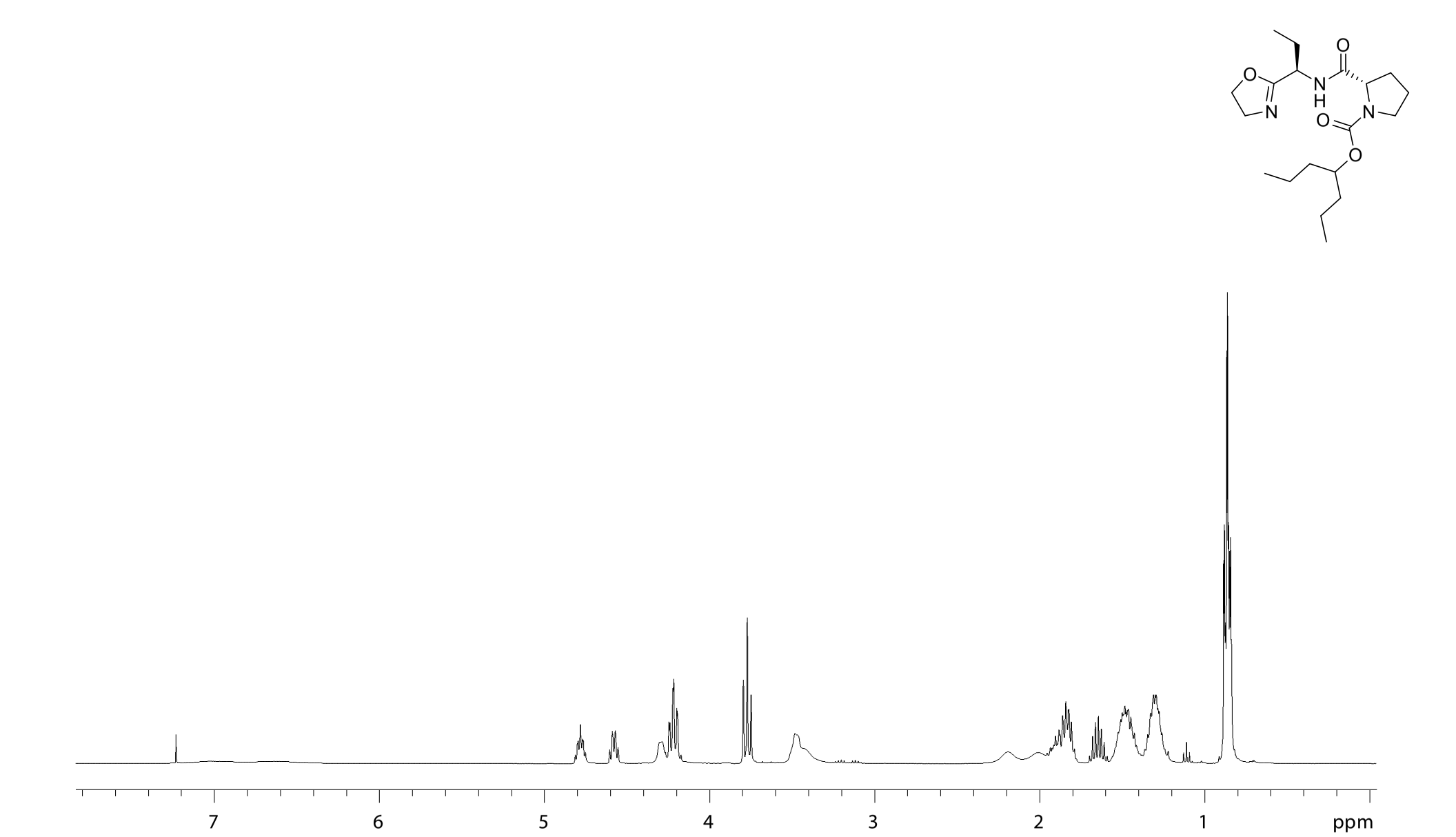
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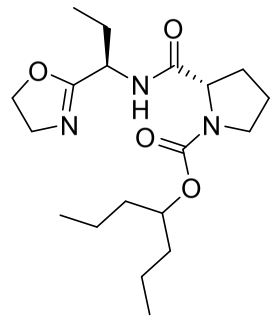
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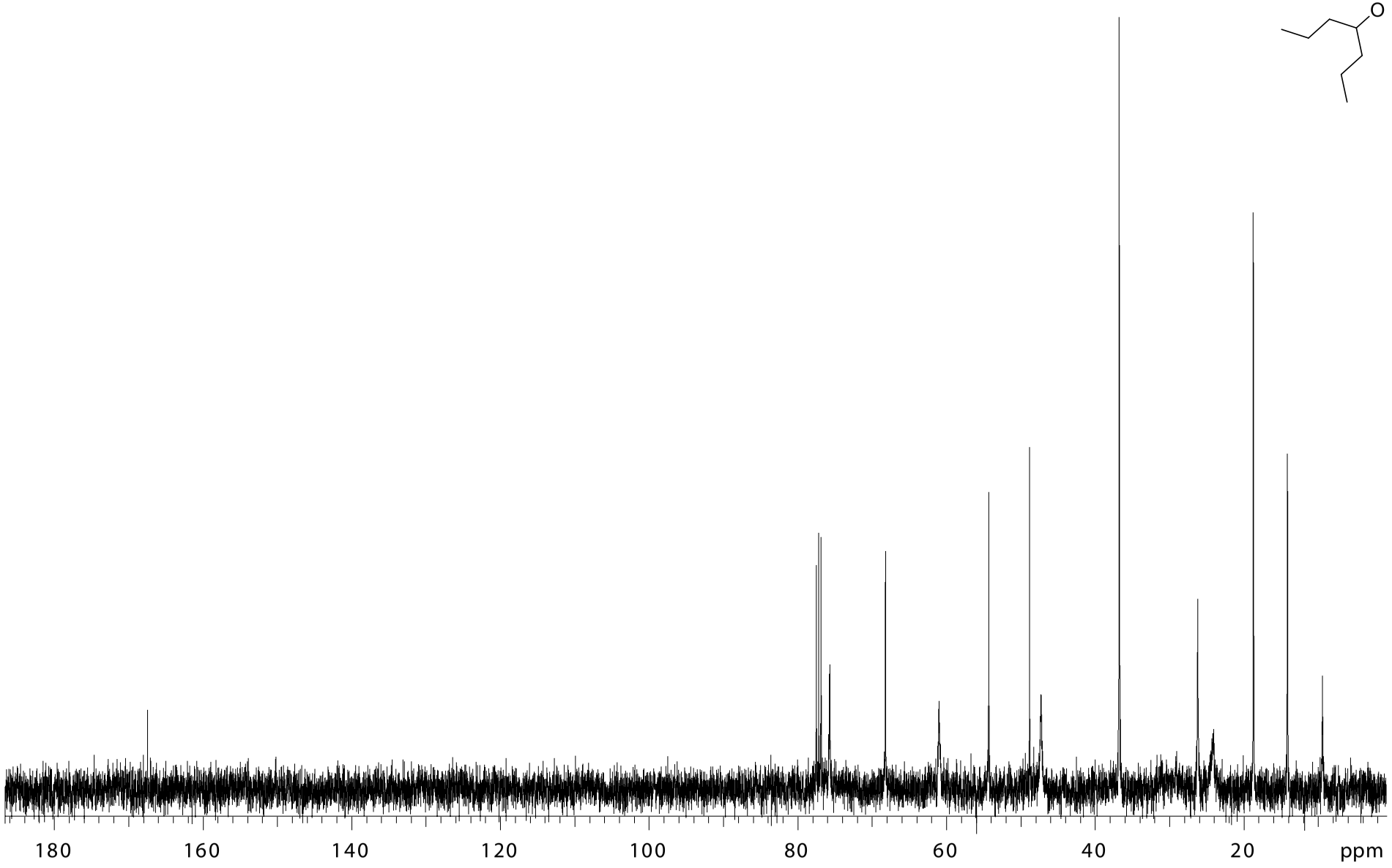
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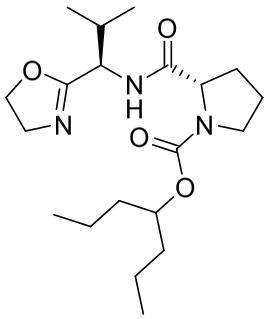
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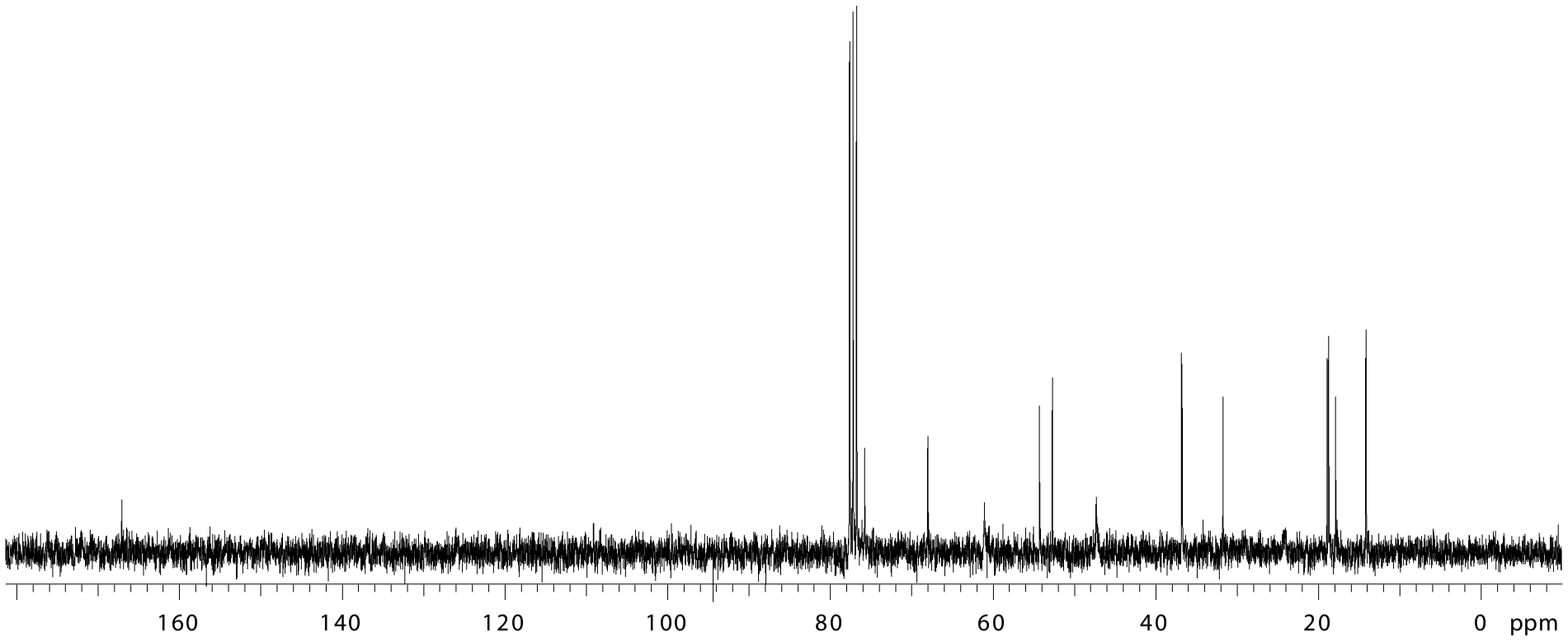
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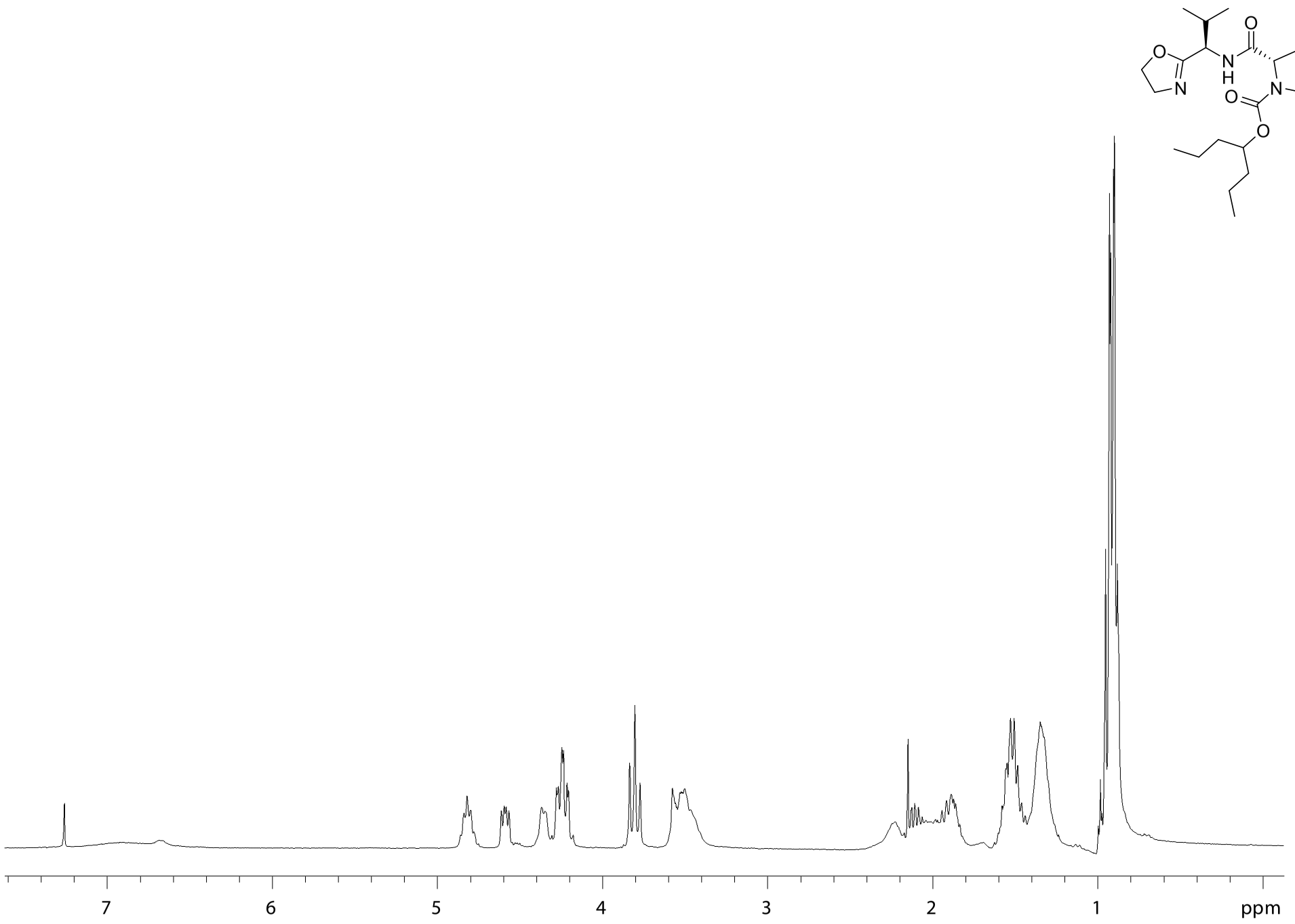
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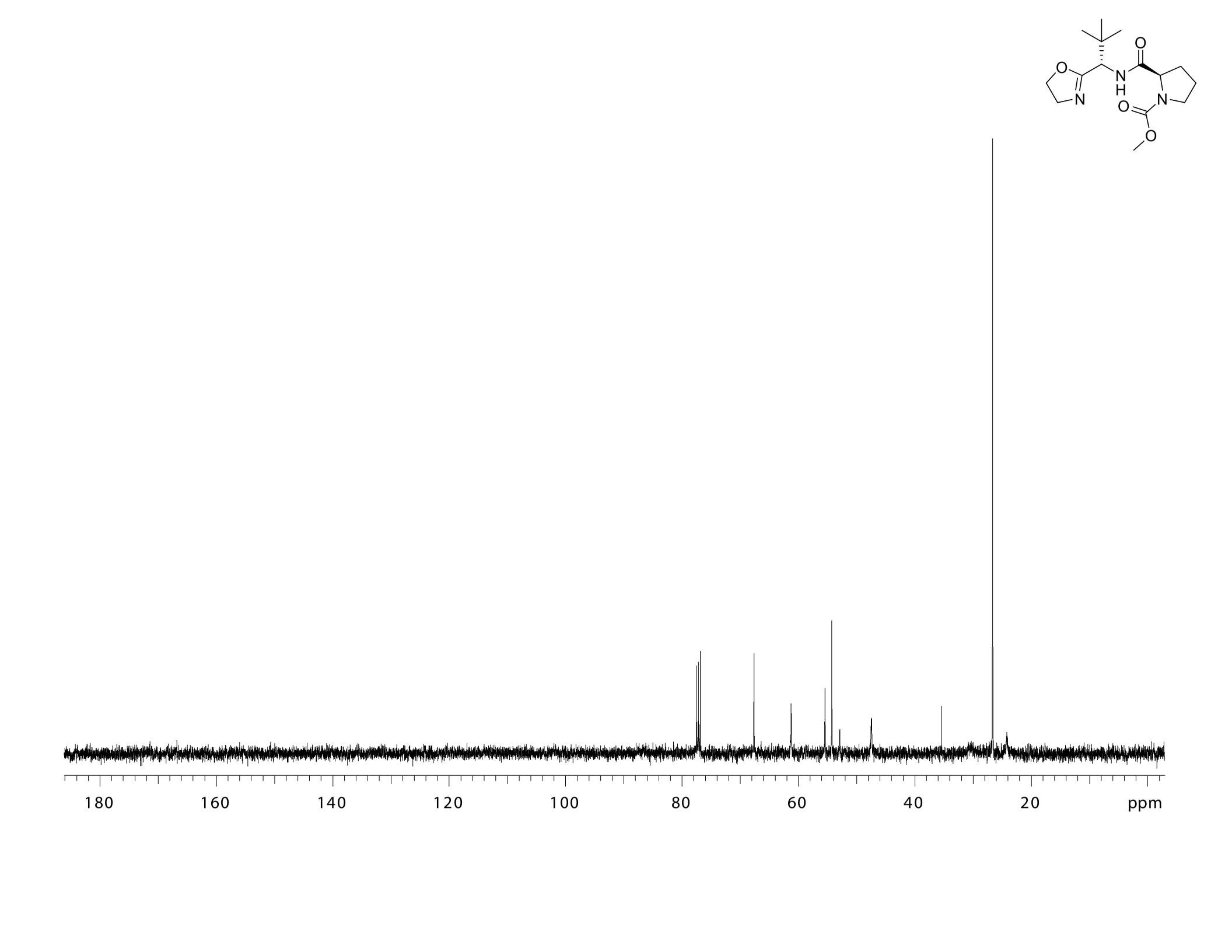
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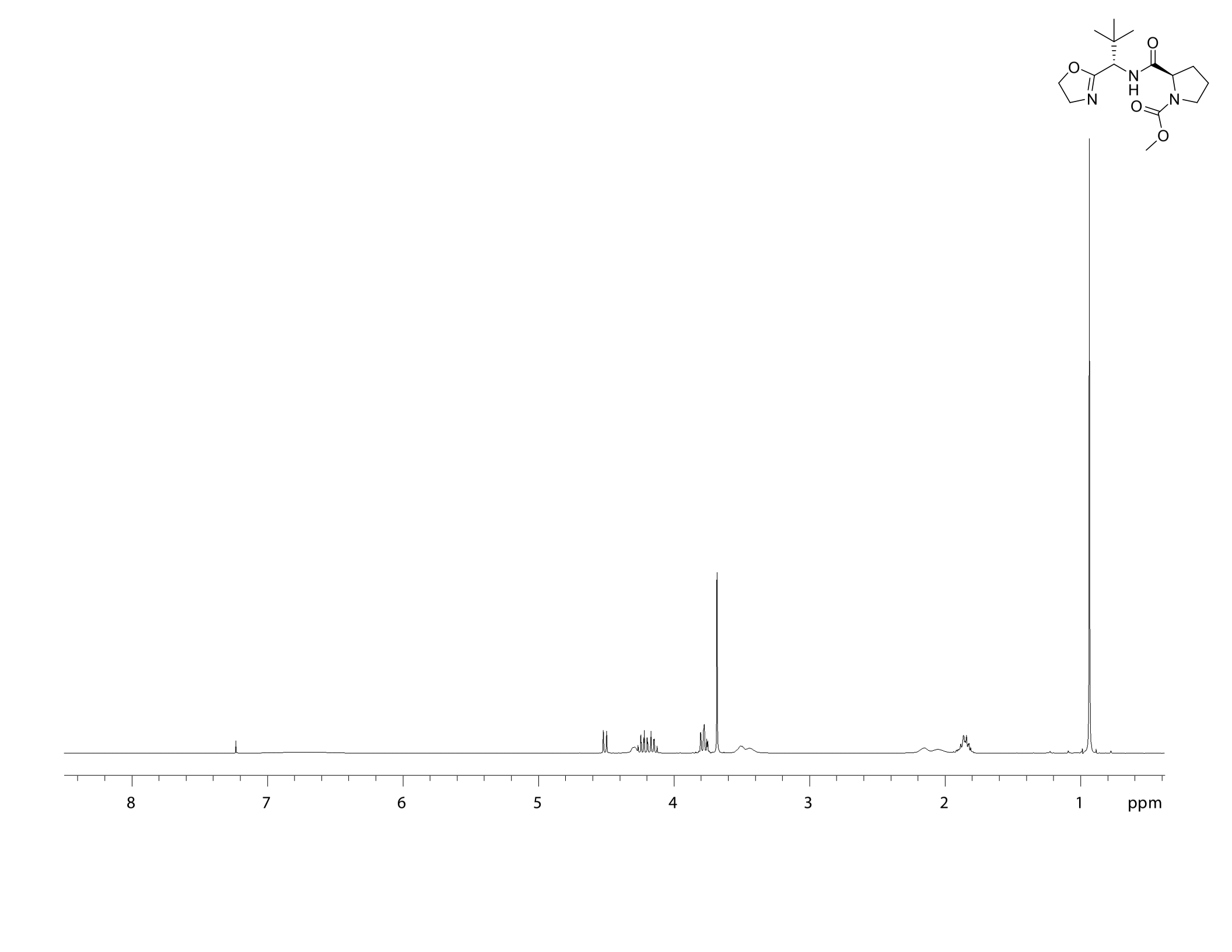
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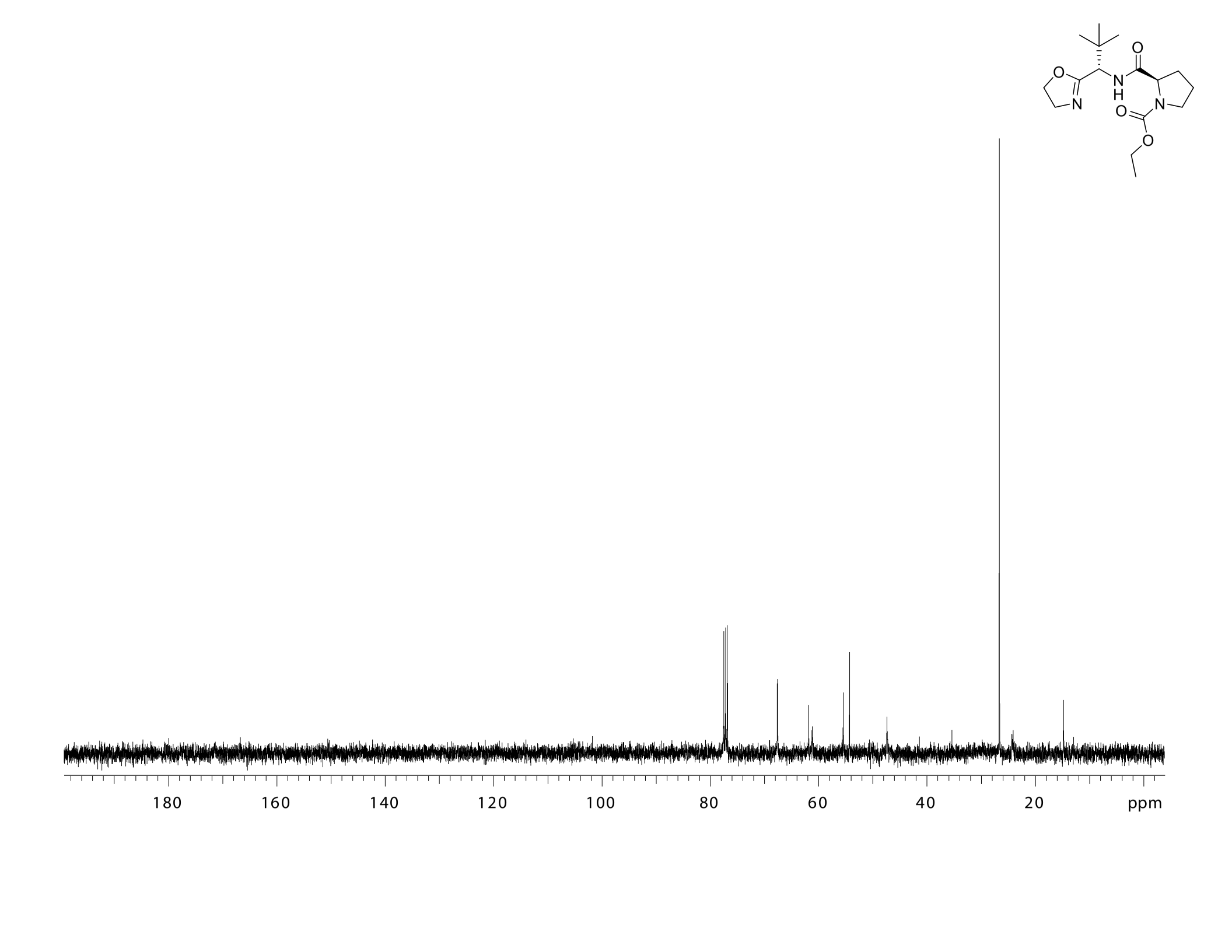
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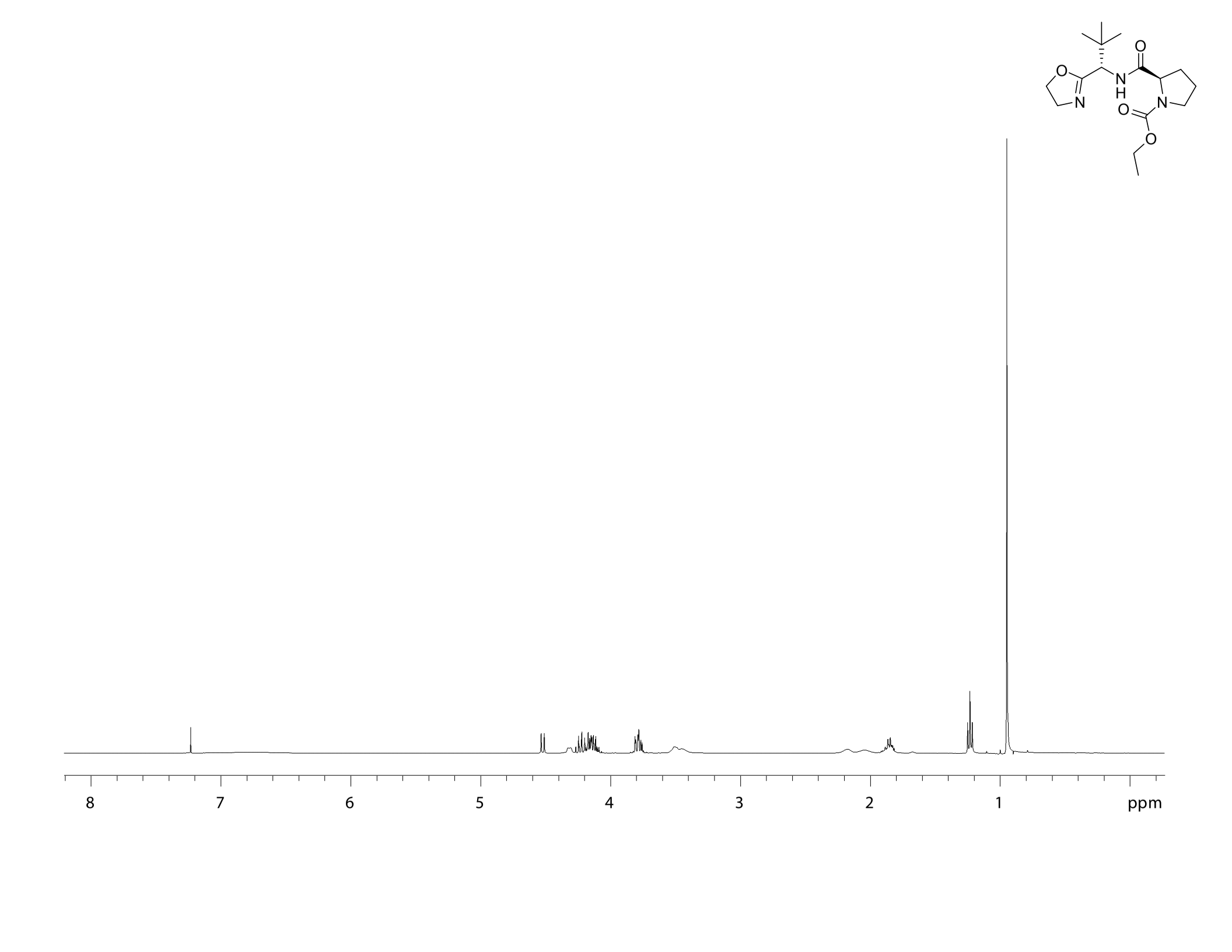
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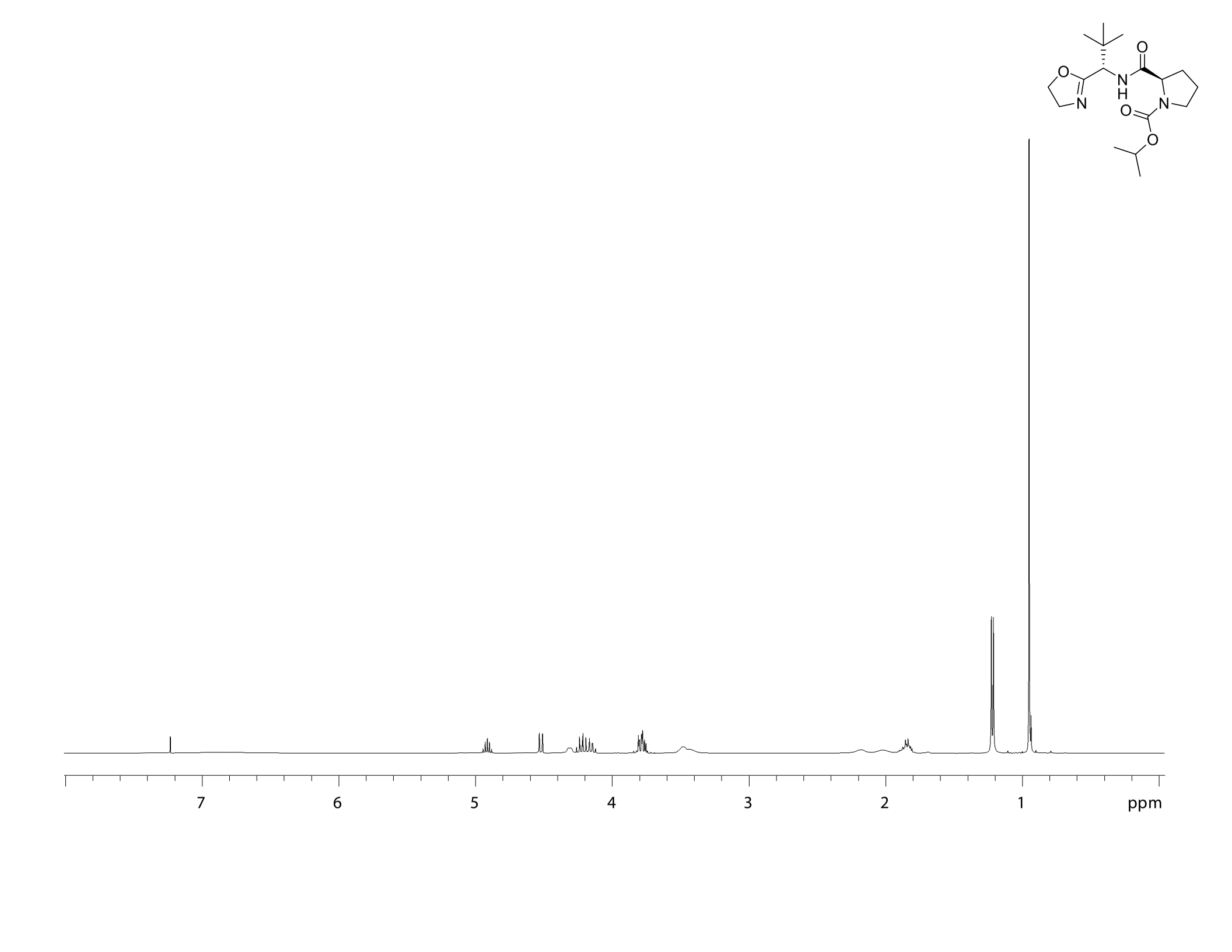
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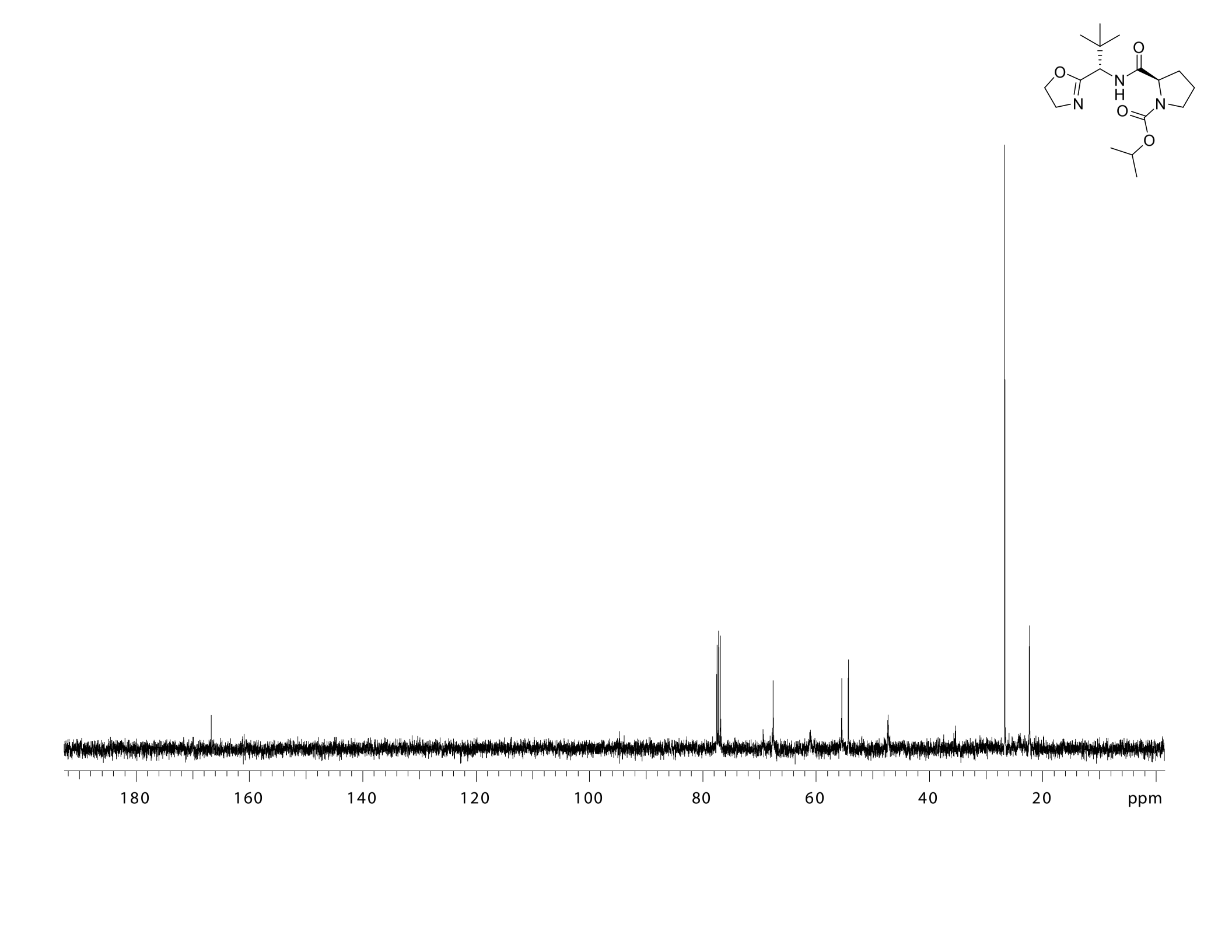
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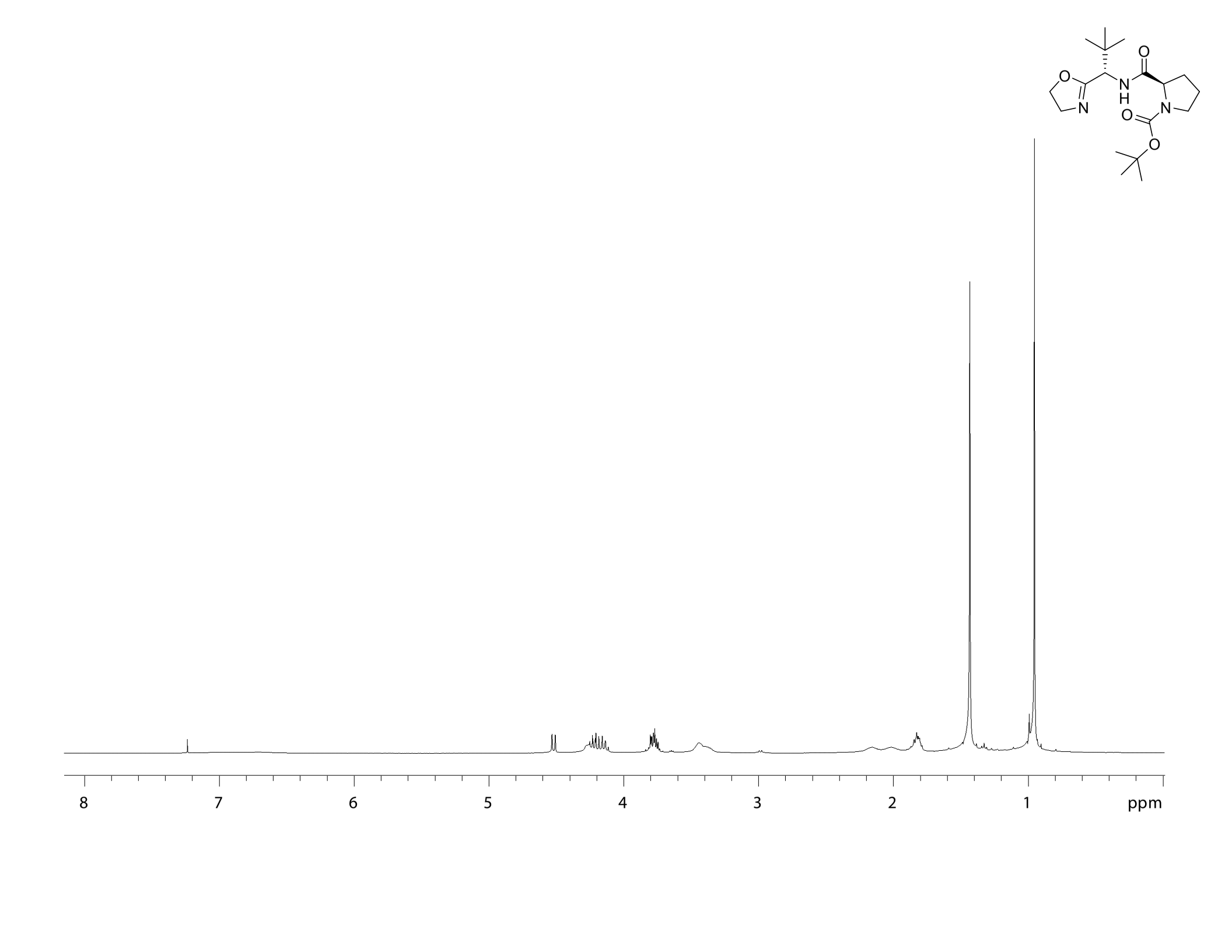
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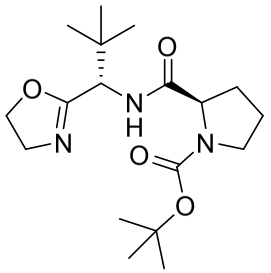
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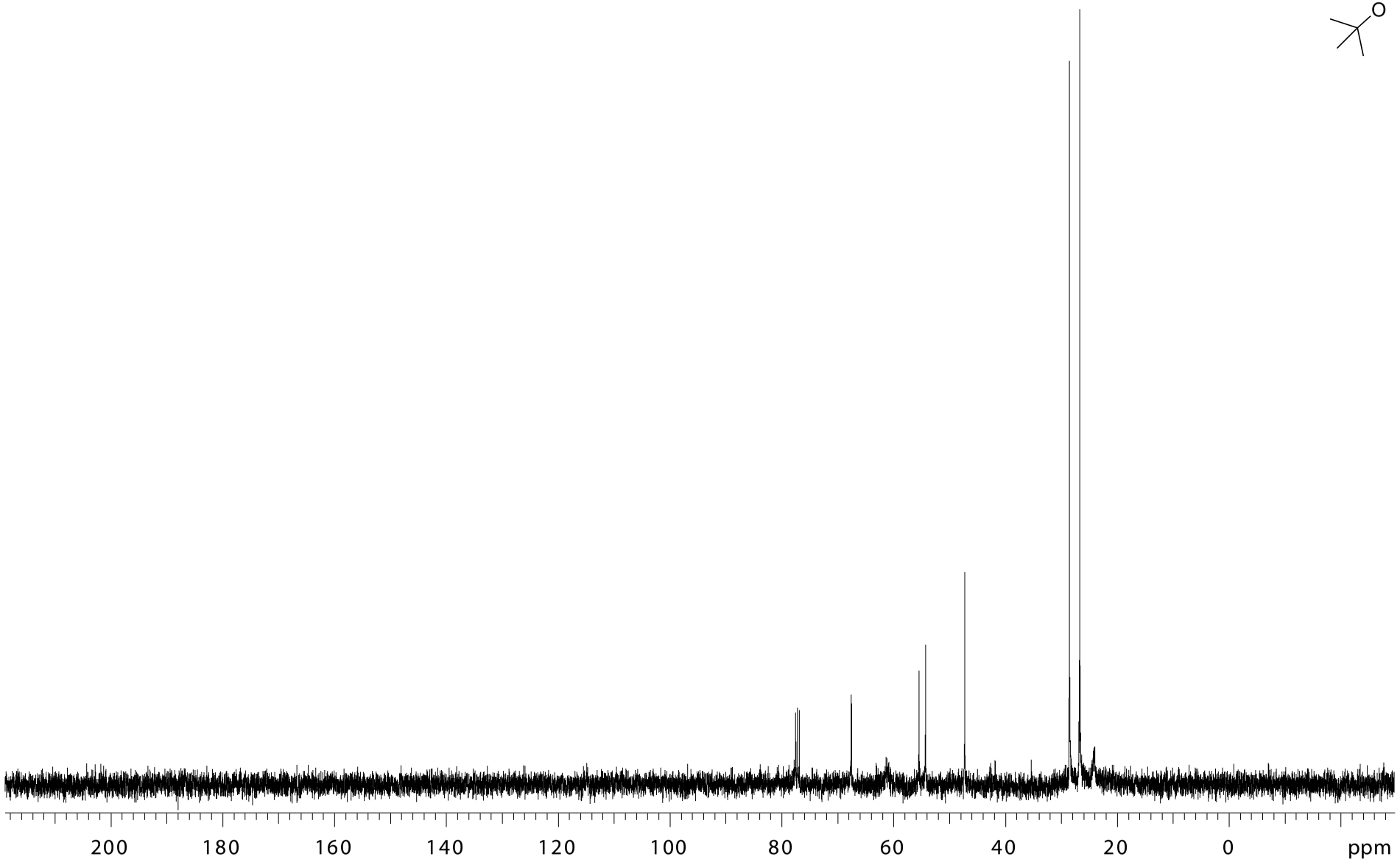
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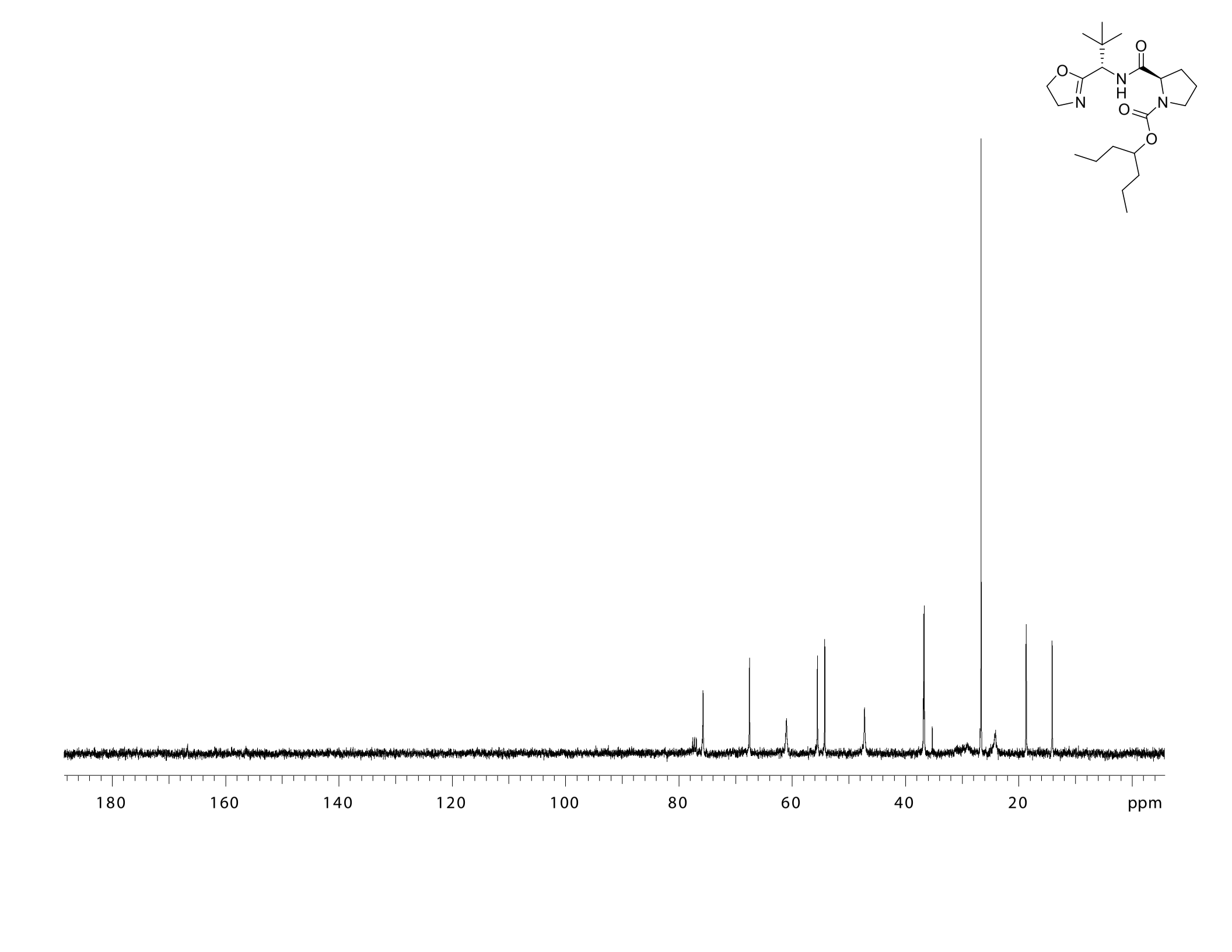
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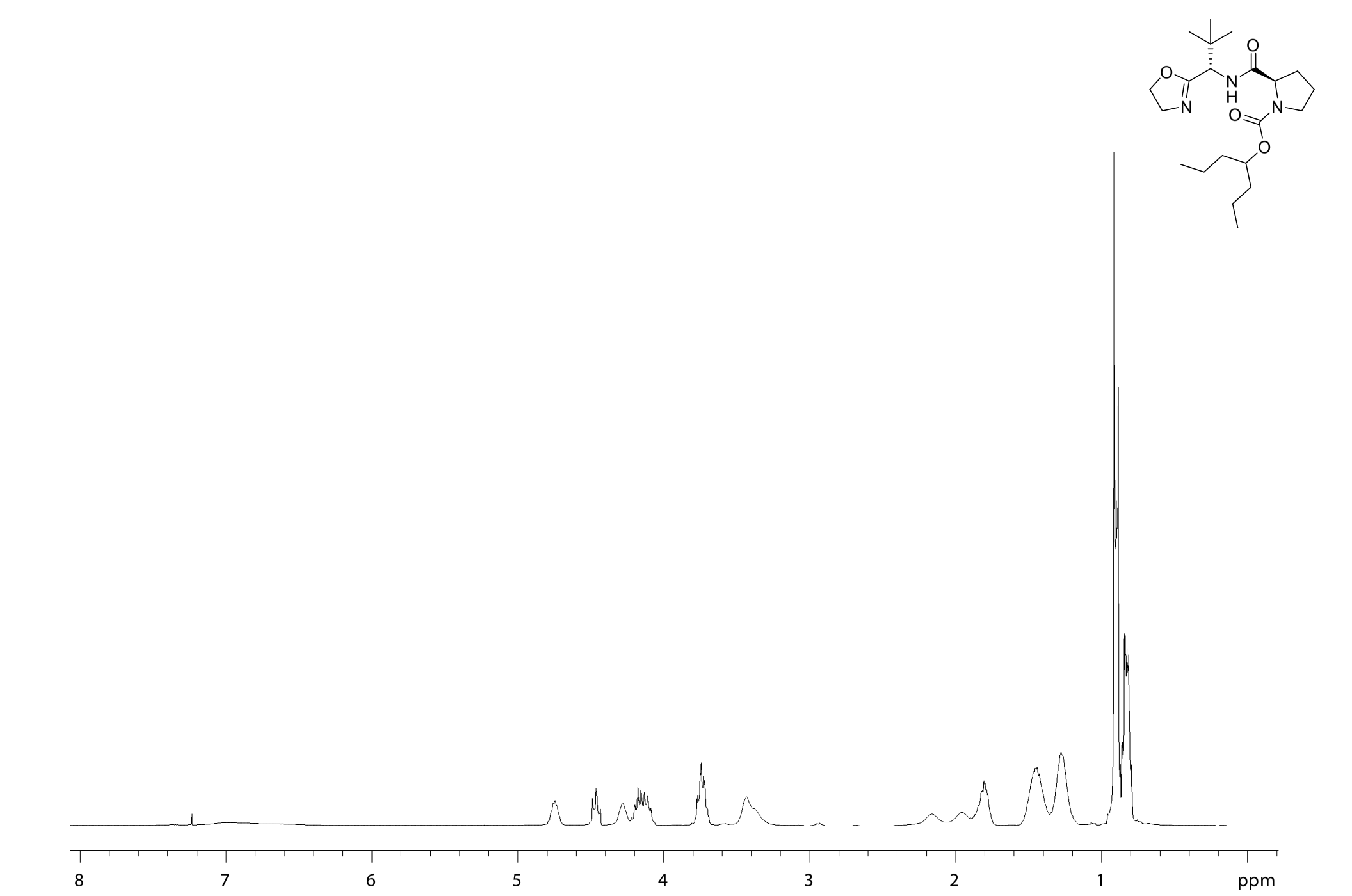
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