

Supporting Information:

Synthesis of spirocyclic dihydropyrazoles from tosylhydrazones and electron-deficient alkenes.

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2. General Experimental Details

All reactions were conducted using standard Schlenk techniques. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F₂₅₄ pre-coated glass-backed plates and visualised by ultraviolet radiation (254 nm), potassium permanganate, ceric ammonium molybdate or iodine dispersed on silica, as appropriate. Flash column chromatography was performed using silica gel (particle size 40-63 nm) under air pressure. ¹H NMR spectra were recorded on a Bruker 400 MHz spectrometer. Chemical shifts are reported in ppm with the resonance resulting from incomplete deuteration of the solvent as the internal standard (CDCl₃: 7.26 ppm, *d*₆-DMSO: 2.50 ppm). ¹³C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (¹³CDCl₃: 77.0 ppm, t or ¹³C-*d*₆-DMSO: 39.5 ppm, septet). HRMS was performed on a Thermo LCQ Classic using electrospray ionisation or a Xevo G2-XS-TOF. HRMS signals are reported to 4 decimal places and are within ± 5 ppm of theoretical values. Infrared spectra were recorded neat as thin films on a Bruker Alpha Platinum-ATR and only selected peaks are reported.

3. Synthesis of sulfonylhydrazones **1a-1k**

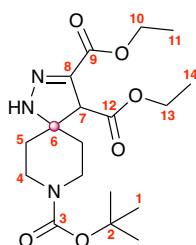
Sulfonylhydrazones **1a-1k** were prepared according to procedures described previously: **1a-c**, **1e-g** and **1i**¹; **1d** and **1h**²; **1j** and **1k**³.

4. Synthesis of spirocyclic dihydropyrazoles 5a-5o.

General procedure A:

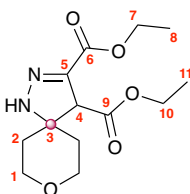
Sulfonylhydrazone (1.0 or 0.5 mmol, 1.0 equiv.), caesium fluoride (1.5 equiv.) and a magnetic stirbar were added to an oven-dried glass vial. The tube was evacuated and back-filled with nitrogen gas (x3 cycles) followed by addition of anhydrous DMSO (0.25 M with respect to sulfonylhydrazone) and the alkene (1.5 equiv.). The vial was sealed with a PTFE-silicone cap and heated to 110 °C. Once the reaction was complete by TLC, the vial was allowed to cool to room temperature and the contents partitioned between EtOAc (50 or 25 mL) and water (50 or 25 mL). The organic phase was washed with water (50 or 25 mL) and the combined aqueous phases extracted with EtOAc (50 or 25 mL). The combined organic layers were washed with aqueous lithium chloride solution (5%, 4 x 20 or 10 mL), followed by brine (50 or 25 mL) before being dried over anhydrous MgSO₄ and solvents removed *in vacuo* to provide a crude residue which was purified by flash column chromatography (30% EtOAc/hexanes) to yield the title compound.

8-(*tert*-Butyl) 3,4-diethyl 1,2,8-triazaspiro[4.5]dec-2-ene-3,4,8-tricarboxylate (5a).



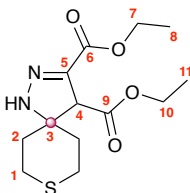
Isolated as a yellow oil (283 mg, 0.742 mmol, 74%) according to general procedure A. ¹H NMR (CDCl₃) δ 1.29 (3H, t, *J* 7.1 Hz, H14), 1.35 (3H, t, *J* 7.1 Hz, H11), 1.47 (9H, s, H1), 1.77 (4H, m, H5), 3.34 (2H, m, H4_a), 3.35 (2H, dt, *J* 5.2, 13.8 Hz, H4_b), 3.78 (1H, s, H7), 4.23 (2H, dq, *J* 2.4, 6.8 Hz, H13), 4.32 (2H, dq, *J* 2.4, 6.8 Hz, H10), 6.33 (1H, s, NH). ¹³C NMR (CDCl₃) δ 14.1 (C14), 14.2 (C11), 28.4 (C1), 31.7 (C5_a), 36.7 (C4), 57.9 (C7), 61.4 (C10), 61.5 (C13), 68.4 (C6), 80.1 (C2), 140.0 (C8), 154.5 (C3), 162.0 (C9), 168.2 (C12). FTIR (ν_{max} cm⁻¹) 2950 (w, CH_x), 1700 (s, C=O), 1300 (m, C-O), 1200 (m, C-N). *R*_f 0.44 (50% EtOAc/hexanes). HRMS (XEVO G2-XS QToF) calculated for C₁₈H₃₀N₃O₆ [M+H]⁺ 384.2135, found 384.2135.

Diethyl 8-oxa-1,2-diazaspiro[4.5]dec-2-ene-3,4-dicarboxylate (5b).



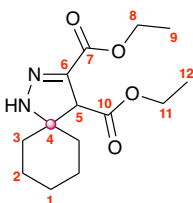
Isolated as a colourless oil (91.8 mg, 0.323 mmol, 65%) according to general procedure A. ^1H NMR (CDCl_3) δ 1.25 (3H, t, J 7.1 Hz, H11), 1.30 (3H, t, J 7.1 Hz, H8), 1.73 (2H, m, H2_{a1} & H2_{b1}), 1.84 (2H, m, H2_{a2} & H2_{b2}), 3.68 (2H, m, H1_{a1} & H1_{b1}), 3.77 (1H, s, H4), 3.80 (2H, br app. dd, J 12.3, 5.2 Hz, H1_{a2} & H1_{b2}), 4.19 (2H, m, H10), 4.27 (2H, m, H7), 6.70 (1H, br, NH). ^{13}C NMR (CDCl_3) δ 14.1 (C11), 14.2 (C8), 32.5 (C2_a), 37.6 (C2_b), 58.1 (C4), 61.3 (C7), 61.4 (C10), 64.0 (C1_a), 64.8 (C1_b), 67.5 (C3), 139.3 (C5), 162.1 (C6), 168.2 (C9). FTIR (ν_{max} cm^{-1}) 2963 (w, CH_x), 1733 (s, C=O), 1325 (m, C-O), 1210 (m, C-N). R_f 0.23 (50% EtOAc/hexanes). HRMS (XEVO G2-XS QToF) calculated for $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 285.1451, found 285.1451.

Diethyl 8-thia-1,2-diazaspiro[4.5]dec-2-ene-3,4-dicarboxylate (5c).



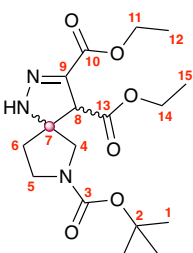
Isolated as a pale yellow oil (93.2 mg, 0.310 mmol, 62%) according to general procedure A. ^1H NMR (CDCl_3) δ 1.27 (3H, t, J 7.1 Hz, H11), 1.32 (3H, t, J 7.1 Hz, H8), 1.93–2.05 (4H, m, H2), 2.62–2.78 (4H, m, H1), 3.71 (1H, s, H4), 4.16–4.24 (2H, m, H10), 4.25–4.32 (2H, m, H7), 6.53 (1H, br, NH). ^{13}C NMR (CDCl_3) δ 14.1 (C11), 14.2 (C8), 24.6 (C1_a), 25.0 (C1_b), 33.1 (C2_a), 38.0 (C2_b), 59.0 (C4), 61.3 (C7), 61.5 (C10), 68.9 (C3), 139.6 (C5), 162.1 (C6), 168.1 (C9). FTIR (ν_{max} cm^{-1}) 2974 (w, CH_x), 1722 (s, C=O), 1319 (m, C-O), 1200 (m, C-N). R_f 0.50 (50% EtOAc/hexanes). HRMS (XEVO G2-XS QToF) calculated for $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 301.1144, found 304.1144.

Diethyl 1,2-diazaspiro[4.5]dec-2-ene-3,4-dicarboxylate (5d).



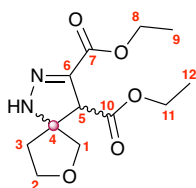
Isolated as a pale yellow oil (168 mg, 0.595 mmol, 60%) according to general procedure A. ^1H NMR (CDCl_3) δ 1.29 (3H, t, J 7.1 Hz, H12), 1.35 (3H, t, J 7.1 Hz, H9), 1.47–1.72 (10H, m, H1 – H3), 3.72 (1H, s, H5), 4.22 (2H, m, H11), 4.31 (2H, m, H8), 6.32 (1H, s, NH). ^{13}C NMR (CDCl_3) δ 14.1 (C12), 14.2 (C9), 22.6 (C1), 32.1 (C2), 24.8 (C1/C2_b), 37.6 (C3), 58.6 (C5), 61.1 (C8), 61.2 (C11), 70.2 (C4), 139.4 (C6), 162.4 (C7), 168.6 (C10). FTIR (ν_{max} cm^{-1}) 2978 (w, CH_x), 2866 (w, CH_x), 1732 (s, C=O), 1158 (m, C=N). R_f 0.50 (50% EtOAc/hexanes). HRMS (XEVO G2-XS QToF) calculated for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 283.1658, found 283.1658.

7-(*tert*-Butyl) 3,4-diethyl 1,2,7-triazaspiro[4.4]non-2-ene-3,4,7-tricarboxylate (5e).



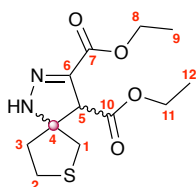
Isolated as a pale yellow oil (133 mg, 0.360 mmol, 72%) according to general procedure A. The compound is an approximate 3:2 mixture of diastereoisomers by ^1H NMR. ^1H NMR (CDCl_3) δ 1.29 (3H_{both}, t, J 7.1 Hz, H15_{both}), 1.35 (3H_{both}, t, J 7.1 Hz, H12_{both}), 1.47 (9H_{both}, s, H1), 2.01–2.17 (2H_{both}, m, H6_{both}), 3.39–3.49 (2H_{both}, br m, H4_{a,both} & H5_{a,both}), 3.53–3.60 (2H_{both}, H4_{b,both} & H5_{b,both}), 3.90 (1H_{maj}, br s, H8_{maj}), 3.93 (1H_{min}, br s, H8_{min}), 4.17–4.27 (2H_{both}, m, H14_{both}), 4.28–4.38 (2H_{both}, m, H11_{both}), 6.48 (1H, br, NH_{both}). ^{13}C NMR (CDCl_3) δ 14.16 (C15), 14.20 (C12), 28.4 (C1_{maj}), 28.5 (C1_{min}), 31.7 (C6_{maj}), 32.7 (C6_{min}), 44.1 (C5_{maj}), 44.5 (C5_{min}), 54.7 (C8_{maj}), 55.1 (C8_{min}), 57.3 (C4_{maj/min}), 57.9 (C4_{maj/min}), 61.4 (C11), 61.7 (C14), 77.2 (C7), 80.2 (C2), 139.8 (C9), 154.2 (C3), 161.7 (C10), 167.9 (C13). R_f 0.26 (50% EtOAc/hexanes). FTIR (ν_{max} cm^{-1}) 2978 (w, CH_x), 1692 (s, C=O), 1364 (m, C-O), 1148 (m, C-N). HRMS (XEVO G2-XS QToF) calculated for $\text{C}_{17}\text{H}_{28}\text{N}_3\text{O}_6$ $[\text{M}+\text{H}]^+$ 370.1978, found 370.1978.

Diethyl 7-oxa-1,2-diazaspiro[4.4]non-2-ene-3,4-dicarboxylate (5f).



Isolated as a yellow oil (67.2 mg, 0.249 mmol, 25%) according to general procedure A. The compound is an approximate 5:4 mixture of diastereoisomers by ^1H NMR. ^1H NMR (CDCl_3) 1.268 (3H_{min}, t, J 7.1 Hz, H12_{min}), 1.270 (3H_{maj}, t, J 7.1 Hz, H12_{maj}), 1.325 (3H_{min}, t, J 7.1 Hz, H9_{min}), 1.327 (3H_{maj}, t, J 7.1 Hz, H9_{maj}), 2.09 (1H_{maj}, dddd, J 13.4, 7.8, 5.5, 0.9 Hz, H3_{a,maj}), 2.26 (1H_{maj} + 2H_{min}, m, H3_{b,maj} & H3_{a&b,min}), 3.56 (1H_{maj}, d, J 9.2 Hz, H1_{a,maj}), 3.64 (1H_{min}, d, J 9.7 Hz, H1_{a,min}), 3.79 (1H_{min}, d, J 9.7 Hz, H1_{b,min}), 3.85 (1H_{maj}, s, H5_{maj}), 3.86 (1H_{maj}, d, J 9.6 Hz, H1_{b,maj}), 3.88-4.04 (2H_{maj} + 2H_{min}, m, H2), 4.03 (1H_{min}, s, H5_{min}), 4.21 (2H_{maj} + 2H_{min}, app. quint., J 6.9 Hz, H11), 4.29 (2H_{maj} + 2H_{min}, m, H8), 6.67 (1H_{min}, br s, NH_{min}), 6.74 (1H_{maj}, br s, NH_{maj}). ^{13}C NMR (CDCl_3) 14.09 (C12_{min}), 14.16 (C12_{maj}), 14.19 (C9), 33.3 (C3_{maj}), 39.9 (C3_{min}), 53.6 (C5_{maj}), 55.3 (C5_{min}), 61.33 (C8_{min}), 61.34 (C8_{maj}), 61.65 (C11_{maj}), 61.68 (C11_{min}), 66.5 (C2_{min}), 67.3 (C2_{maj}), 73.4 (C1_{min}), 75.8 (C4_{maj}), 75.9 (C4_{min}), 78.8 (C1_{maj}), 139.1 (C6_{min}), 139.3 (C6_{maj}), 161.7 (C7_{min}), 161.8 (C7_{maj}), 168.1 (C10_{min}), 168.3 (C10_{maj}). FTIR (ν_{max} cm^{-1}) 2981 (w, CH_x), 2937 (w, CH_x), 1703 (s, C=O), 1251 (m, C=N), 1169 (m, C-O). R_f 0.11 (30% EtOAc/hexanes). HRMS (XEVO G2-XS QToF) calculated for $\text{C}_{12}\text{H}_{19}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 271.1294, found 271.1294.

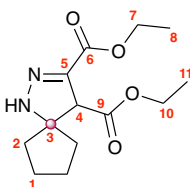
Diethyl 7-thia-1,2-diazaspiro[4.4]non-2-ene-3,4-dicarboxylate (5g).



Isolated as a pale yellow oil (78.3 mg, 0.273 mmol, 55%) according to general procedure A. The compound is a 5:4 mixture of diastereoisomers by ^1H NMR. ^1H NMR (CDCl_3) δ 1.26 (3H, t, J 7.1 Hz, H12_{maj/min}), 1.27 (3H, t, J 7.1 Hz, H12_{maj/min}), 1.32 (3H, t, J 7.1 Hz, H9_{maj/min}), 1.33 (3H, t, J 7.1 Hz, H9_{maj/min}), 2.03–2.20 (1H_{maj}+2H_{min}, m, H2_{a maj} & H2_{a&b min}), 2.34 (1H_{maj}, m, H2_{b maj}), 2.79 (1H_{maj}, br d, J 11.2 Hz, H4_{a maj}), 2.84–3.04 (3H_{maj} + 2H_{min}, m, H4_{b,maj} + H1_{all}), 3.96 (1H_{maj}, s, H5_{maj}), 3.99 (1H_{min}, s, H5_{min}), 4.16–4.24 (2H_{maj} + 2H_{min}, m, H11_{all}), 4.25–4.33

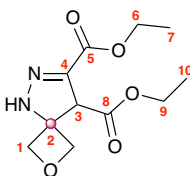
(2H_{maj} + 2H_{min}, m, H8_{all}). ¹³C NMR (CDCl₃) δ 14.11 (C9/C12), 14.14 (C9/C12), 14.2 (2 x C9/C12), 27.0 (C1_{either}/C4_{min}), 27.8 (C1_{either}/C4_{min}), 35.1 (C2_{min}), 37.3 (C4_{maj}), 41.0 (C2_{maj}), 42.8 (C1_{either}/C4_{min}), 55.3 (C5_{min}), 55.4 (C5_{maj}), 61.3 (C8_{maj}), 61.4 (C8_{min}), 61.6 (C11_{maj}), 61.7 (C11_{min}), 78.7 (C3_{maj}), 78.9 (C3_{min}), 139.7 (C6_{min}), 140.3 (C6_{maj}), 161.7 (C7_{min}), 161.8 (C7_{maj}), 168.0 (C10_{min}), 168.2 (C10_{maj}). FTIR (ν_{max} cm⁻¹) 2978 (w, CH_x), 1722 (s, C=O), 1320 (m, C-O), 1196 (m, C-N). R_f 0.50 (50% EtOAc/hexanes). HRMS (XEVO G2-XS QToF) calculated for C₁₂H₁₈N₂O₄S [M+H]⁺ 287.0979, found 287.0979.

Diethyl 1,2-diazaspiro[4.4]non-2-ene-3,4-dicarboxylate (5h).



Isolated as a colourless oil (105 mg, 0.391 mmol, 78%) according to general procedure A. ¹H NMR (CDCl₃) δ 1.26 (3H, t, *J* 7.1 Hz, H11), 1.33 (3H, t, *J* 7.1 Hz, H8), 1.70–1.86 (8H, m, H1 & H2), 3.80 (1H, s, H4), 4.19 (2H, m, H10), 4.29 (2H, m, H7). ¹³C NMR (CDCl₃) δ 14.17 (C11), 14.23 (C8), 22.5 (C1_a), 23.0 (C1_b), 33.6 (C2_a), 40.8 (C2_b), 57.3 (C4), 61.1 (C7), 61.2 (C10), 77.9 (C3), 139.1 (C5), 162.2 (C6), 168.9 (C9). FTIR (ν_{max} cm⁻¹) 2959 (w, CH_x), 1726 (s, C=O), 1372 (m, C-O), 1186 (m, C-N). R_f 0.50 (50% EtOAc/hexanes). HRMS (XEVO G2-XS QToF) calculated for C₁₃H₂₁N₂O₄ [M+H]⁺ 269.1478, found 269.1478.

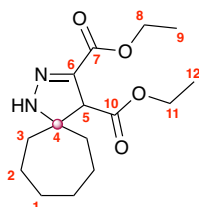
Diethyl 2-oxa-5,6-diazaspiro[3.4]oct-6-ene-7,8-dicarboxylate (5i).



Isolated as a colourless oil (32.0 mg, 0.125 mmol, 25%) according to general procedure A. ¹H NMR (CDCl₃) δ 1.32 (3H, t, *J* 7.1 Hz, H7/H10), 1.34 (3H, t, *J* 7.1 Hz, H7/H10), 4.18 (1H, s, H3), 4.24–4.34 (4H, m, H6 & H9), 4.71 (1H, dd, *J* 8.1, 0.4 Hz, H1_{a1}), 4.78 (1H, dd, *J* 7.3, 0.7 Hz, H1_{b1}), 4.82 (1H, br d, *J* 7.1 Hz, H1_{b2}), 4.89 (1H, br d, *J* 8.1 Hz, H1_{a2}), 7.06 (1H, br, NH). ¹³C NMR (CDCl₃) δ 14.17 (C7/C10), 14.19 (C7/C10), 56.7 (C3), 61.5 (C6), 62.0 (C9), 70.4

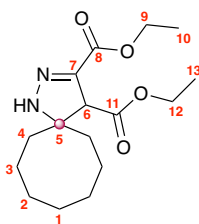
(C2), 79.6 (C1_a), 85.3 (C1_b), 139.0 (C4), 161.4 (C5), 167.6 (C8). FTIR (ν_{\max} cm⁻¹) 2981 (w, CH_x), 1722 (s, C=O), 1237 (m, C-O), 1189 (m, C-N). *R*_f 0.26 (50% EtOAc/hexanes). HRMS (XEVO G2-XS QTof) calculated for C₁₁H₁₆N₂O₅ [M+H]⁺ 257.0866, found 257.0866.

Diethyl 1,2-diazaspiro[4.6]undec-2-ene-3,4-dicarboxylate (5j).



Isolated as a pale yellow oil (88.9 mg, 0.300 mmol, 60%) according to general procedure A. ¹H NMR (CDCl₃) δ 1.20 (3H, t, *J* 7.1 Hz, H12), 1.25 (3H, t, *J* 7.1 Hz, H9), 1.43–1.61 (8H, m, H1 & H2), 1.66–1.88 (4H, m, H3), 3.65 (1H, s, H5), 4.12 (2H, m, H11), 4.21 (2H, m, H8). ¹³C NMR (CDCl₃) δ 14.1 (C12), 14.2 (C9), 21.9 (C1_a), 22.7 (C1_b), 29.1 (C2_a), 29.4 (C2_b), 35.2 (C3_a), 41.1 (C3_b), 59.7 (C5), 61.1 (C8), 61.2 (C11), 74.0 (C4), 138.8 (C6), 162.4 (C7), 168.8 (C10). FTIR (ν_{\max} cm⁻¹) 2981 (w, CH_x), 2933 (w, CH_x), 2859 (w, CH_x), 1722 (s, C=O), 1021 (m, C=N). *R*_f 0.50 (50% EtOAc/hexanes). HRMS (XEVO G2-XS QTof) calculated for C₁₅H₂₄N₂O₄ [M+H]⁺ 297.1814, found 297.1814.

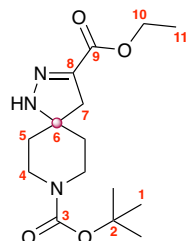
Diethyl 1,2-diazaspiro[4.7]dodec-2-ene-3,4-dicarboxylate (5k).



Isolated as a pale yellow oil (90.0 mg, 0.290 mmol, 58%) according to general procedure A. ¹H NMR (CDCl₃) δ 1.25 (3H, t, *J* 7.1 Hz, H13), 1.30 (3H, t, *J* 7.1 Hz, H10), 1.44–1.65 (8H, br m, H2–H3), 1.68–1.98 (6H, br m, H1 & H4), 2.02 (1H, s, NH), 3.69 (1H, s, H6), 4.17 (2H, m, H12), 4.25 (2H, m, H9). ¹³C NMR (CDCl₃) δ 14.1 (C13), 14.2 (C10), 21.9 (C3_a), 22.7 (C3_b), 29.1 (C2_a), 29.4 (C2_b), 35.2 (C1), 41.6 (C4), 59.7 (C6), 61.0 (C9), 61.2 (C12), 74.0 (C5), 138.8 (C7), 162.4 (C8), 168.8 (C12). *R*_f 0.59 (50% EtOAc/hexanes). FTIR (ν_{\max} cm⁻¹) 2983 (w, CH_x),

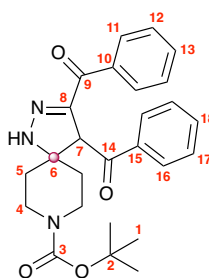
2857 (w, CH_x), 1730 (s, C=O), 1021 (m, C=N). HRMS (XEVO G2-XS QToF) calculated for C₁₆H₂₇N₂O₄ [M+H]⁺ 311.1698, found 311.1698.

8-(*tert*-Butyl) 3-ethyl 1,2,8-triazaspiro[4.5]dec-2-ene-3,8-dicarboxylate (5l).



Isolated as a viscous orange oil (163 mg, 0.530 mmol, 53%) according to general procedure A. ¹H NMR (CDCl₃) δ 1.27 (3H, t, *J* 7.1 Hz, H11), 1.39 (9H, s, H1), 1.61 (4H, m, H5), 2.74 (2H, s, H7), 3.12 (2H, qd, *J* 3.7, 9.1 Hz, H4_a), 3.64 (2H, m, H4_b), 6.08 (1H, s, NH). ¹³C NMR (CDCl₃) main peaks; δ 14.3 (C11), 28.4 (C1), 35.9 (C5), 40.7 (C4), 40.9 (C7), 61.2 (C10), 66.3 (C2), 79.9 (C6), 141.5 (C8), 154.5 (C9), 162.8 (C3). *R*_f 0.579 (30% EtOAc/hexanes). FTIR (ν_{max} cm⁻¹) 2974 (w, CH_x), 2933 (w, CH_x), 1689 (s, C=O), 1241 (s, C=N), 1152 (s, C-O). HRMS (XEVO G2-XS QToF) calculated for C₁₅H₂₆N₃O₄ [M+H]⁺ 340.1794, found: 340.1794.

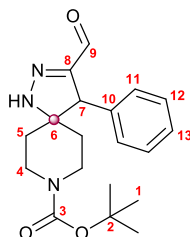
***tert*-Butyl 3,4-dibenzoyl-1,2,8-triazaspiro[4.5]dec-2-ene-8-carboxylate (5m).**



Isolated as a dark red amorphous solid (53.2 mg, 0.119 mmol, 45%) according to general procedure A. ¹H NMR (CDCl₃) δ 1.44 (9H, s, H1), 1.65 (1H, br m, H5_{a1}), 1.77 (1H, br m, H5_{a2}), 1.90 (2H, br m, H5_b), 3.09 (1H, br m, H4_{a1}), 3.26 (1H, br m, H4_{b1}), 3.59 (1H, br d, H4_{a2}), 3.86 (1H, br, H4_{b2}), 5.07 (1H, s, H7), 6.84 (1H, br s, NH), 7.44 (2H, t, *J* 7.6 Hz, H12/H17 a), 7.54 (3H, t, *J* 7.4 Hz, H12/17 b & H13), 7.65 (1H, t, *J* 7.3 Hz, H18), 8.06 (2H, d, *J* 7.5 Hz, H16), 8.17 (2H, d, *J* 7.3 Hz, H11). ¹³C NMR (CDCl₃) δ 28.3 (C1), 31.8 (C5_a), 37.2 (C5_b), 40.0 (br, C4_b), 41.5 (br, C4_b), 58.9 (C7), 67.9 (C6), 80.2 (C2), 128.1 (C12/C17 a), 128.6 (C16),

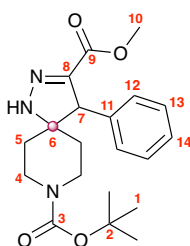
129.0 (C12/C17 b), 130.0 (C18), 132.6 (C13), 133.7 (C18), 136.5 (C5/C10 a), 137.3 (C5/C10 b), 149.8 (C8), 154.5 (C3), 186.9 (C9), 196.0 (C14). R_f 0.45 (30% EtOAc/hexanes). FTIR (ν_{\max} cm^{-1}) 2974 (w, CH_x), 2867 (w, CH_x), 1673 (s, $\text{C}=\text{O}$), 1276 (m, $\text{C}=\text{N}$), 1156 (m, $\text{C}-\text{O}$). HRMS (XEVO G2-XS QTof) calculated for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$ 448.2236, found 448.2236.

***tert*-Butyl 3-formyl-4-phenyl-1,2,8-triazaspiro[4.5]dec-2-ene-8-carboxylate (5n).**



Isolated as an orange amorphous solid (0.183 g, 0.534 mmol, 54%) according to general procedure A. ^1H NMR (CDCl_3) δ 1.28 (2H, app. q, J 6.68 Hz, H5_a), 1.35 (9H, s, H1), 1.64 (2H, t, J 5.44 Hz, H5_b), 3.16 (2H, m, H4_a), 3.41 (1H, m, H4_{b1}), 3.54 (1H, m, H4_{b2}), 3.98 (1H, s, H7), 6.87 (1H, s, NH), 6.96 (2H, br d, J 6.9 Hz, H13), 7.21 (4H, m, H11 & H12), 9.67 (1H, s, H9). ^{13}C NMR (CDCl_3) δ 28.4 (C1), 30.9 (C5_a), 36.3 (C5_b), 39.8 (br, C4_b), 41.2 (br, C4_a), 54.8 (C7), 69.0 (C6), 80.0 (C2), 127.7 (C13), 128.5 (br, C11), 128.8 (C12), 134.4 (C10), 153.4 (C8), 154.5 (C3), 186.4 (C9). R_f 0.59 (30% EtOAc/hexanes). FTIR (ν_{\max} cm^{-1}) 2967 (w, CH_x), 2922 (w, CH_x), 2863 (w, CH_x (aromatic)), 1655 (s, $\text{C}=\text{O}$), 1244 (m, $\text{C}-\text{O}$), 1156 (m, $\text{C}-\text{N}$). HRMS (XEVO G2-XS QTof) calculated for $\text{C}_{19}\text{H}_{26}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 344.1974, found 344.1974.

8-(*tert*-Butyl) 3-methyl 4-phenyl-1,2,8-triazaspiro[4.5]dec-2-ene-3,8-dicarboxylate (5o).

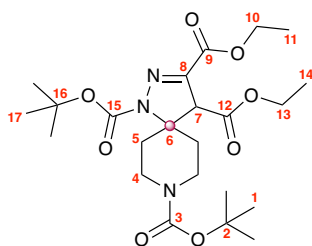


Isolated as an orange amorphous solid (77.5 mg, 0.208 mmol, 21%) according to general procedure A. ^1H NMR (CDCl_3) δ 1.34 (2H, m, H5_a), 1.42 (9H, s, H1), 1.73 (2H, m, H5_b), 3.22 (2H, m, H4_a), 3.55 (2H, m, H4_b), 3.74 (3H, s, H10), 4.03 (1H, s, H7), 6.25 (1H, br, NH), 7.10 (2H, br d, J 7.1 Hz, H12), 7.30 (3H, m, H13 & H14). ^{13}C NMR (CDCl_3) δ 28.4 (C1), 31.0 (C5_a), 36.2 (C5_b), 40.0 (C4_b), 41.1 (C4_a), 52.1 (C10), 57.5 (C7), 68.2 (C6), 79.9 (C2), 127.8

(C14), 128.6 (C12), 128.8 (C13), 134.8 (C11), 145.2 (C8), 154.5 (C3), 162.7 (C9). R_f 0.20 (30% EtOAc/hexanes). FTIR (ν_{\max} cm^{-1}) 2974 (w, CH_x), 2930 (w, CH_x), 1685 (s, C=O), 1234 (m, C-N), 1163 (m, C-O). HRMS (XEVO G2-XS QTof) calculated for $\text{C}_{20}\text{H}_{28}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$ 374.2080, found 374.2080.

5. Synthesis of compounds 6-9

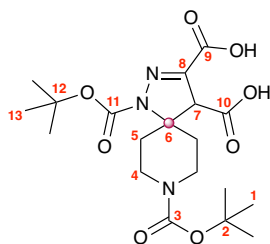
1,8-Di-*tert*-butyl 3,4-diethyl 1,2,8-triazaspiro[4.5]dec-2-ene-1,3,4,8-tetracarboxylate (6).



Adapted from a known procedure.⁴ To a solution of compound **5a** (0.191 g, 0.50 mmol, 1.0 equiv.) in CH₂Cl₂ (5 mL) was added NEt₃ (0.139 mL, 0.101 g, 1.0 mmol, 2.0 equiv.) and DMAP (6.1 mg, 0.05 mmol, 0.1 equiv.) followed by Boc₂O (120 mg, 0.55 mmol, 1.1 equiv.) and the reaction mixture was allowed to stir at room temperature. After 12 h, the mixture was partitioned between CH₂Cl₂ (25 mL) and water (25 mL). The aqueous layer was extracted with CH₂Cl₂ (25 mL). The combined organic phases were washed with brine (25 mL) and dried over anhydrous MgSO₄ before being filtered and the solvents removed *in vacuo* to give a residue which was purified by flash column chromatography (30% EtOAc / hexanes) to provide compound **6** as an orange amorphous solid (0.125 g, 0.258 mmol, 52%).

¹H NMR (CDCl₃) δ 1.24 (3H, t, *J* 7.1 Hz, H14), 1.31 (3H, t, *J* 7.1 Hz, H11), 1.42 (9H, s, H1), 1.45-1.55 (1H, br, H5_{a1}), 1.51 (1H, s, H17), 1.81 (1H, br, H5_{b1}), 2.43 (1H, br, H5_{a2}), 2.85 (3H, br, H4_{a1} & H4_{b1} & H5_{b2}), 3.93-4.24 (2H, br, H4_{a2} & H4_{b2}), 4.03 (1H, br s, H7), 4.19 (2H, q, *J* 7.1 Hz, H13), 4.28 (2H, m, H10). ¹³C NMR (CDCl₃) δ 13.99 (C14), 14.04 (C11), 28.1 (C16), 28.3 (C1), 29.3 (br, C5_b), 32.9 (br, C5_a), 39.3 (br, C4_a, rotamer 1), 40.2 (br, C4_a, rotamer 2), 40.6 (br, C4_b, rotamer 1), 41.7 (br, C4_b, rotamer 2), 58.7 (C7), 61.9 (C13), 71.6 (C6), 79.8 (C2), 83.3 (C16), 141.0 (C8), 150.4 (C15), 154.2 (C3), 161.5 (C9), 167.6 (C12). *R*_f 0.573 (30% EtOAc/hexanes). FTIR (ν_{max} cm⁻¹) 2974 (w, CH_x), 2933 (w, CH_x), 1692 (s, C=O), 1241 (m, C=N), 1126 (s, C-O). HRMS (XEVO G2-XS QToF) calculated for C₂₃H₃₈N₃O₈ [M+H]⁺ 484.2659, found 484.2659.

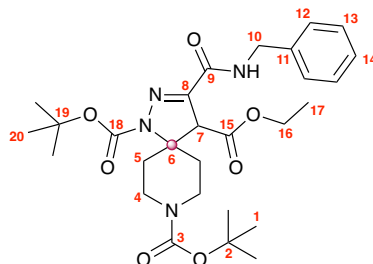
1,8-Bis(*tert*-butoxycarbonyl)-1,2,8-triazaspiro[4.5]dec-2-ene-3,4-dicarboxylic acid (7)



Adapted from a known procedure.⁵ To compound **6** (121 mg, 0.25 mmol, 1.0 equiv.) in MeOH (5 mL) was added KOH (0.25 g, 4.46 mmol, 18 equiv.) and the solution heated to 80 °C. After 3 h, the reaction mixture was concentrated *in vacuo*. The residue was resuspended in water (10 mL) and washed with Et₂O (10 mL). The aqueous layer was acidified with 3M aqueous HCl and extracted with Et₂O (3 x 10 mL). The combined organic layers were dried with MgSO₄ and solvents removed *in vacuo* to afford **7** as a yellow powder (76.2 mg, 0.178 mmol, 72%) without further purification.

¹H NMR (CDCl₃); δ 1.41 (9H, s, H1), 1.47 (9H, s, H13), 1.65 (1H, br d, *J* 12.6 Hz, H5_{a1}), 1.75 (1H, br d, *J* 12.6 Hz, H5_{b1}), 2.12 (2H, app. td, *J* 12.6, 2.9 Hz, H5_{a2}), 2.67-2.75 (1H, br, H5_{b2}), 2.80-3.00 (2H, br, H4a), 3.80-4.00 (2H, br, H4b), 4.07 (1H, s, H7), 13.0-13.6 (2H, br, 2 x OH). ¹³C NMR (CDCl₃); δ 28.3 (C1), 28.5 (C13), 29.4 (C5), 40.9 (C4), 58.8 (C7), 71.08 (C6), 79.4 (C2), 82.5 (C12), 144.0 (C8), 154.1 (C11), 163.0 (C3), 169.9 (C9 + C10). *R*_f 0.108 (30% EtOAc/hexanes). FTIR (*ν*_{max} cm⁻¹) 3630 (b, OH), 2971 (w, CH_x), 2926 (w, CH_x), 1689 (s, C=O), 1241 (m, C=N), 1129 (m, C-O). HRMS (XEVO G2-XS QToF) calculated for C₁₉H₂₉N₃O₈ [M+H]⁺ 428.2062, found 428.2062.

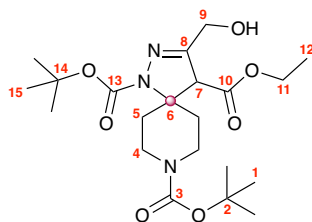
1,8-Di-*tert*-butyl 4-ethyl 3-(benzylcarbamoyl)-1,2,8-triazaspiro[4.5]dec-2-ene-1,4,8-tricarboxylate (8).



Adapted from a known procedure.⁶ To compound **6** (121 mg, 0.25 mmol, 1.0 equiv.) in methanol (1 mL) was added benzylamine (53.5 mg, 0.50 mmol, 2.0 equiv.) and the mixture was heated to 60 °C. After 12 h, the mixture was concentrated *in vacuo* and the residue partitioned between Et₂O (25 mL) and water (25 mL). The aqueous phase was extracted with Et₂O (2 x 25 mL) and the combined organic phases were washed with saturated aqueous Na₂CO₃ (25 mL) before being dried over MgSO₄. Solvents were removed *in vacuo* to provide a residue which was purified by flash column chromatography (30% EtOAc/hexanes) to provide compound **8** as a viscous yellow oil (102 mg, 0.205 mmol, 75%).

¹H NMR (CDCl₃); δ 1.29 (3H, t, *J* 7.1 Hz, H17), 1.47 (9H, s, H1/H20 a), 1.53 (10H, s, H1/H20 b & H5_{a1}), 1.87 (1H, br, H5_{b1}), 2.39 (1H, br, H5_{a2}), 2.70-3.05 (3H, br, H5_{b2}, H4_{a1} & H4_{b1}), 4.00-4.20 (1H, br, H4_{a2}), 4.20 (1H, s, H7), 4.25 (2H, q, *J* 7.1 Hz, H16), 4.48 (1H, dd, *J* 14.8, 5.9 Hz, H10_a), 4.57 (1H, dd, *J* 14.8, 6.3 Hz, H10_b), 7.14 (1H, br t, *J* 5.4 Hz, NH), 7.30 (5H, m, H12, H13 & H14). ¹³C NMR (CDCl₃); δ 14.0 (C17), 28.2 (C1/C20 b), 28.4 (C1/C20 a), 29.4 (br, C5b rotamer 1), 29.7 (br, C5b rotamer 2), 32.9 (br, C5a rotamer 1), 33.2 (C5a rotamer 2), 39.4 (br, C4a rotamer 1), 40.4 (C4a rotamer 2), 40.7 (C4b rotamer 1), 41.8 (br, C4b rotamer 2), 43.4 (C10), 58.4 (br, C7), 61.9 (C16), 71.5 (C6), 79.9 (C2/C19 a), 83.2 (C2/C19 b), 127.6 (C14), 127.9 (C12), 128.7 (C13), 137.5 (C11), 144.6 (C8), 150.7 (C3/C18), 154.2 (C3/C18), 160.5 (C9), 167.8 (C15). *R*_f 0.41 (30% EtOAc/hexanes). FTIR (ν_{max} cm⁻¹) 2974 (w, CH_x), 2930 (w, CH_x), 1666 (s, C=O), 1245 (m, C=N), 1133 (m, C-O). HRMS (XEVO G2-XS QTof) calculated for C₂₈H₄₁N₄O₇ [M+H]⁺ 545.1870, found 545.1870.

1,8-Di-*tert*-butyl 4-ethyl 3-(hydroxymethyl)-1,2,8-triazaspiro[4.5]dec-2-ene-1,4,8-tricarboxylate (9).

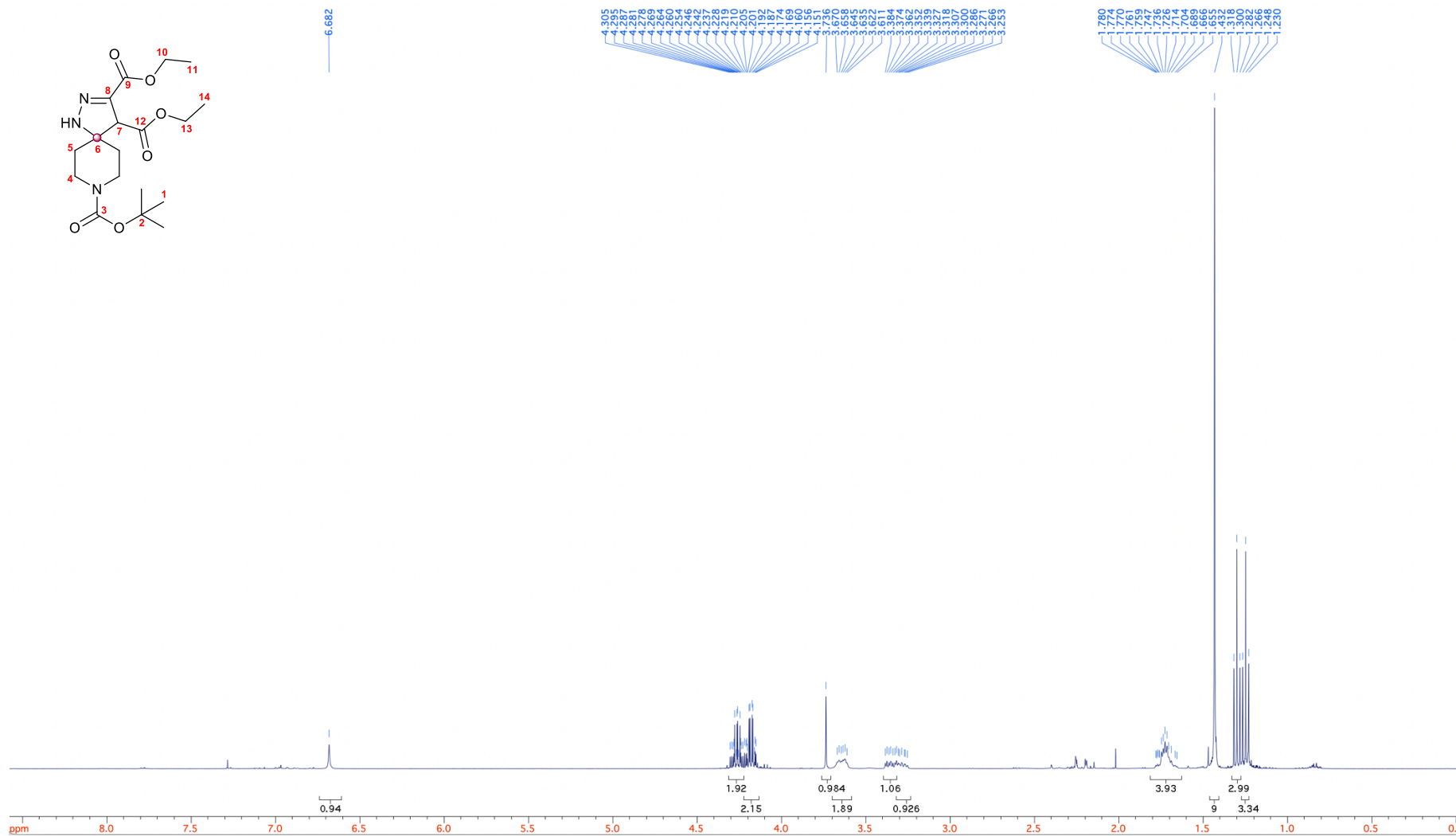


Adapted from a known procedure.⁵ To compound **6** (0.221 g, 0.5 mmol, 1.0 equiv.) in MeOH (5 mL) was added NaBH₄ (38.0 mg, 1.0 mmol, 2.0 equiv.) and the mixture was stirred at room temperature. After 12 h, the mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (10 mL) and water (10 mL). The aqueous phase was extracted with EtOAc (10 mL) followed by 5:1 CH₂Cl₂:MeOH (2 x 30 mL). The combined organic phases were dried over anhydrous MgSO₄ and solvents removed *in vacuo* to give a residue which was purified by flash column chromatography to yield compound **9** as a viscous yellow oil (65.3 mg, 0.148 mmol, 30%).

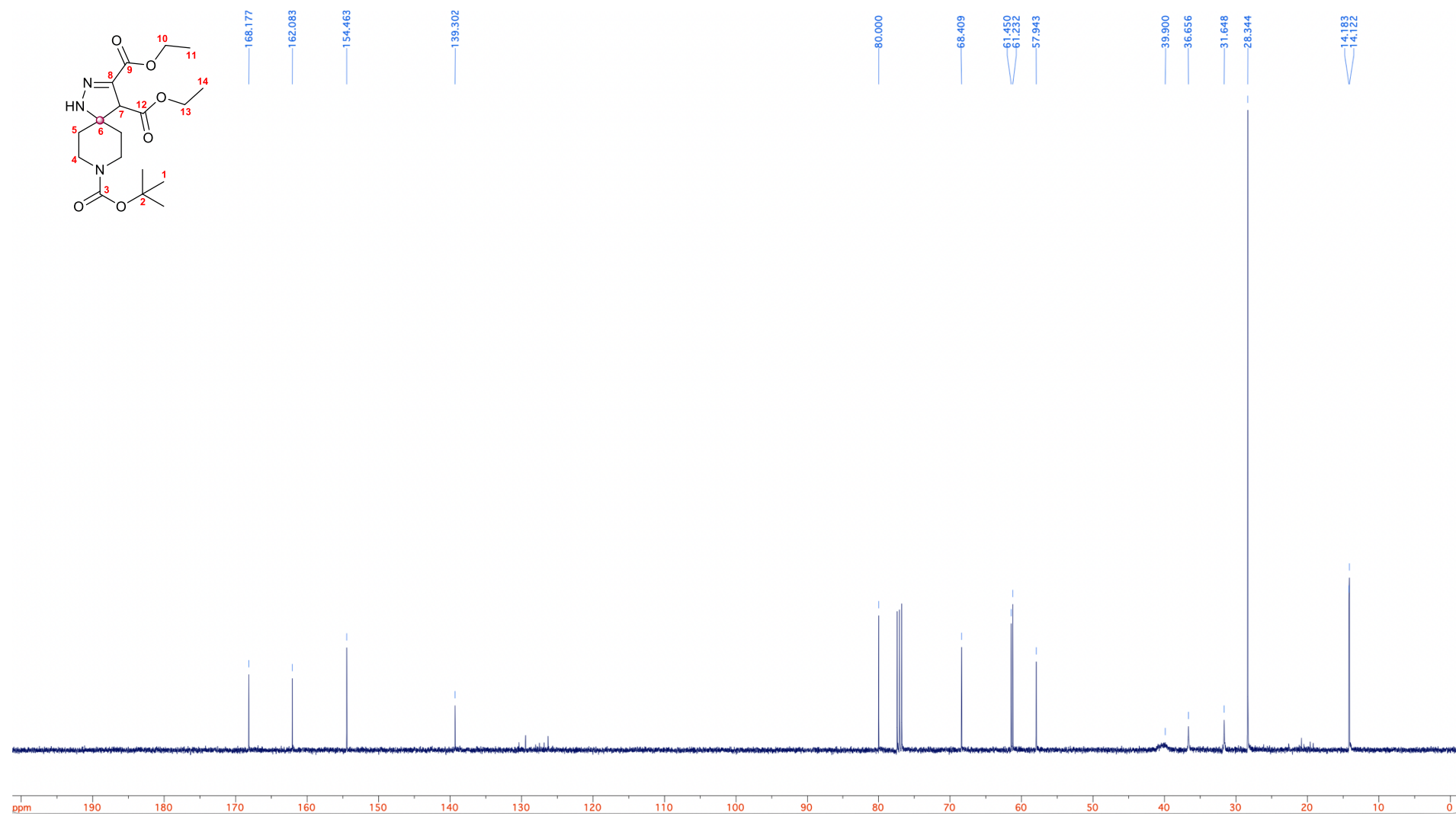
¹H NMR (CDCl₃); δ 1.30 (3H, t, *J* 7.1 Hz, H12), 1.47 (11H, s, H1/H13 & H5a), 1.54 (9H, s, H1/H13), 1.86 (2H, br m, H5b), 3.03 (2H, br ddd, *J* 13.3, 10.1, 3.1 Hz, H4a), 3.84 (2H, br m, H4b), 3.95 (1H, br s, H7), 4.23 (2H, q, *J* 7.1 Hz, H11), 4.40 (1H, d, *J* 14.8 Hz, H9a), 4.42 (1H, d, *J* 15.0 Hz, H9b). ¹³C NMR (CDCl₃); δ 14.1 (C12), 28.3 (C1/C13), 28.4 (C1/C13), 34.1 (C5), 41.2 (br, C4), 59.4 (br, C7), 59.8 (C9), 61.9 (C11), 69.5 (C6), 79.6 (C2/C14), 79.9 (C2/C14), 151.4 (C8), 154.3 (C3/C13), 154.8 (C3/C13), 168.1 (C10). *R*_f 0.04 (30% EtOAc/hexanes). FTIR (ν_{max} cm⁻¹) 3414 (b, O-H), (w, CH_x), 2974 (w, CH_x), 2930 (w, CH_x), 1733 (s, C=O), 1629 (s, C=O), 1244 (m, C=N), 1156 (m, C-O). HRMS (XEVO G2-XS QTof) calculated for C₂₁H₃₆N₃O₇ [M+H]⁺ 442.2553, found 442.2553.

6. ^1H and ^{13}C NMR Spectra for synthesised compounds

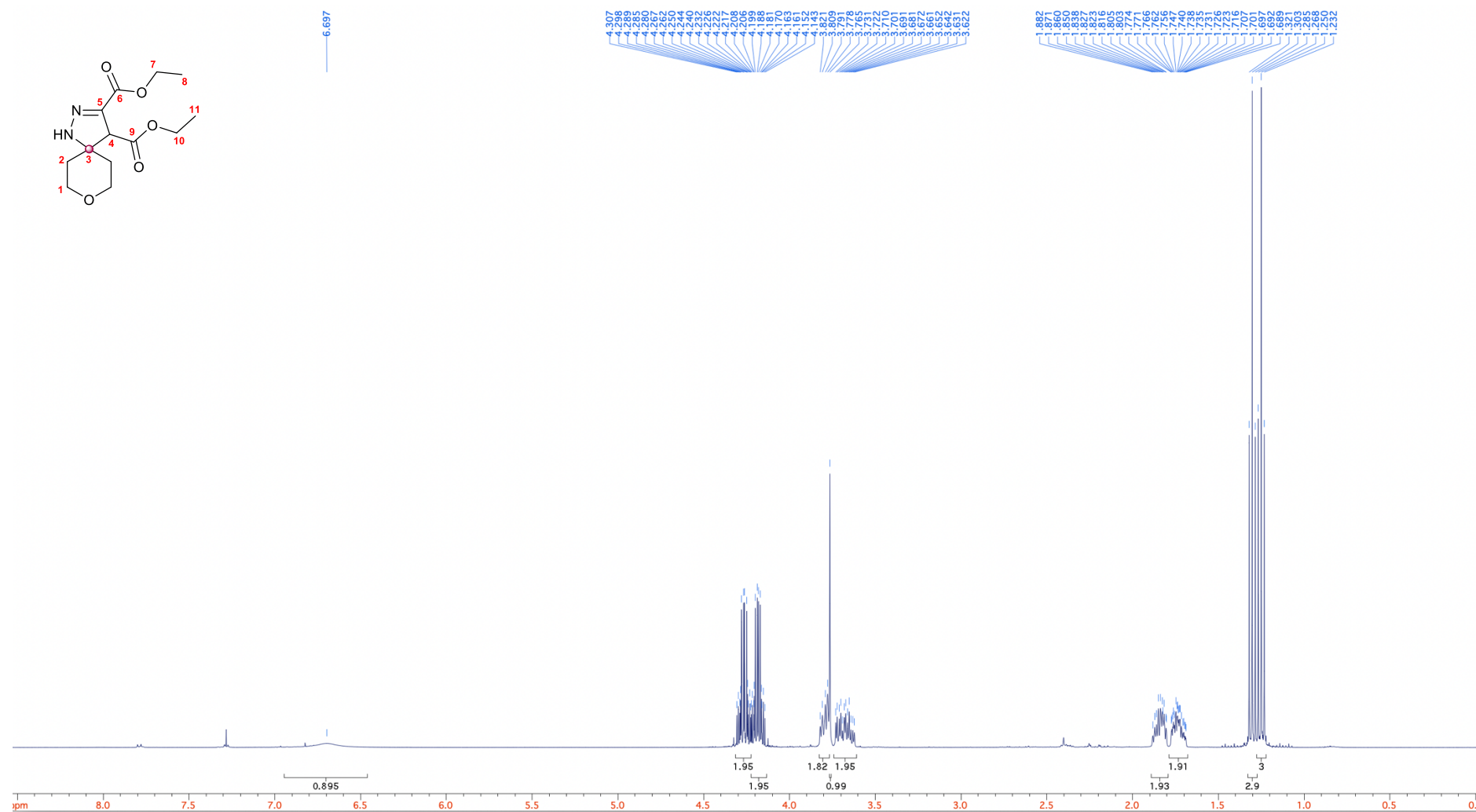
Compound **5a** ^1H NMR (400 MHz, CDCl_3)



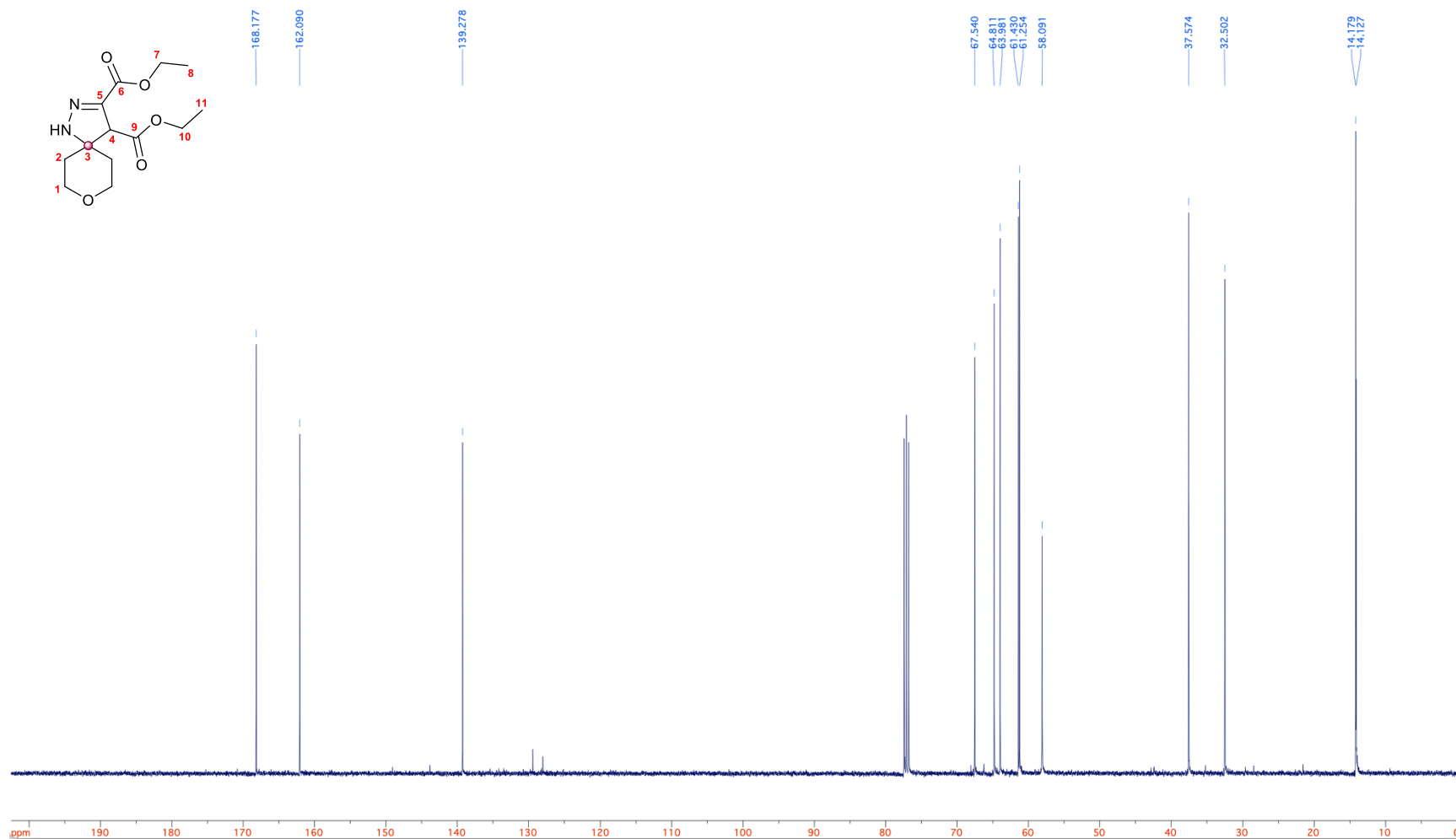
Compound **5a** ^{13}C NMR (100 MHz, CDCl_3)



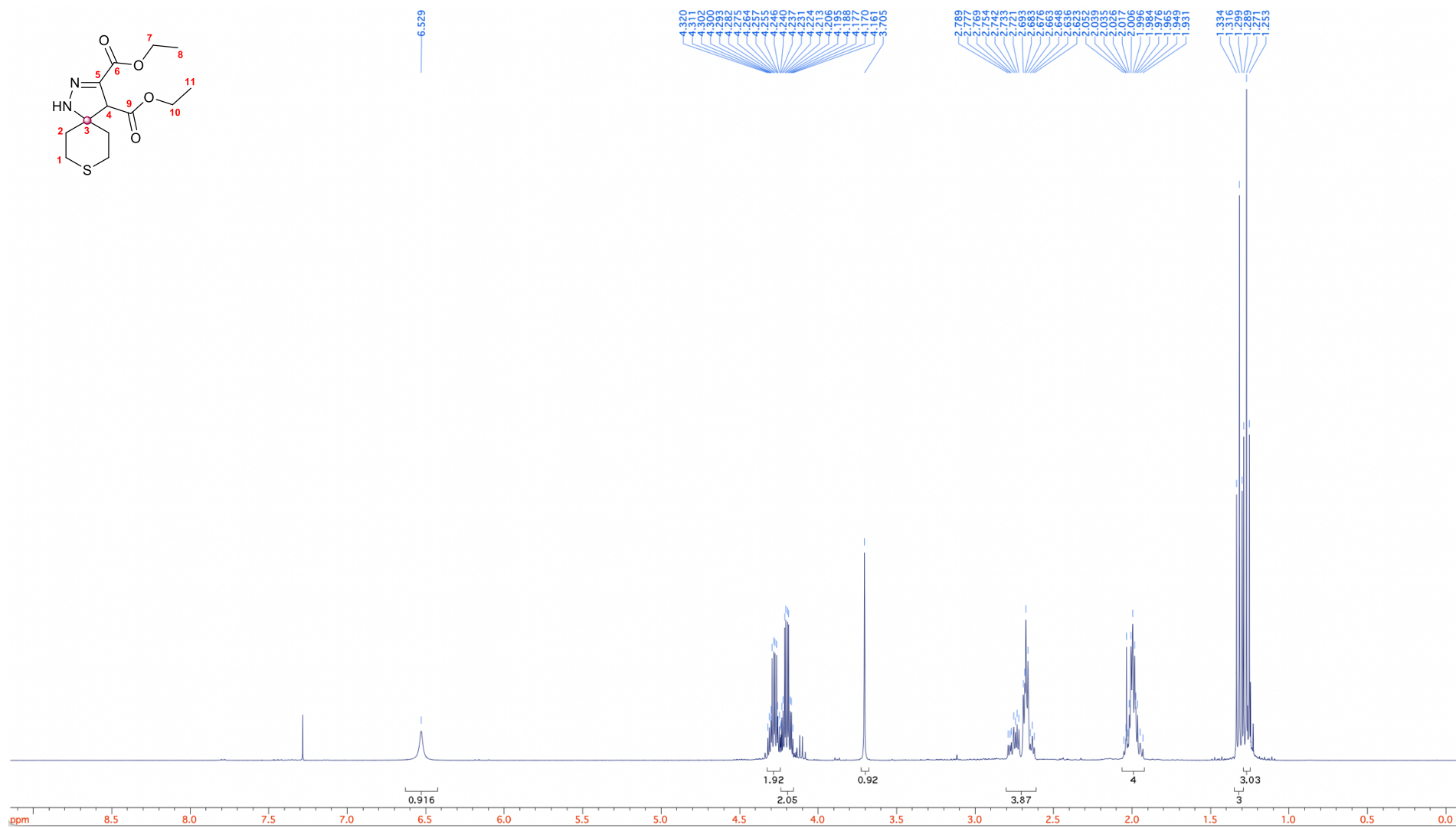
Compound **5b** ^1H NMR (400 MHz, CDCl_3)



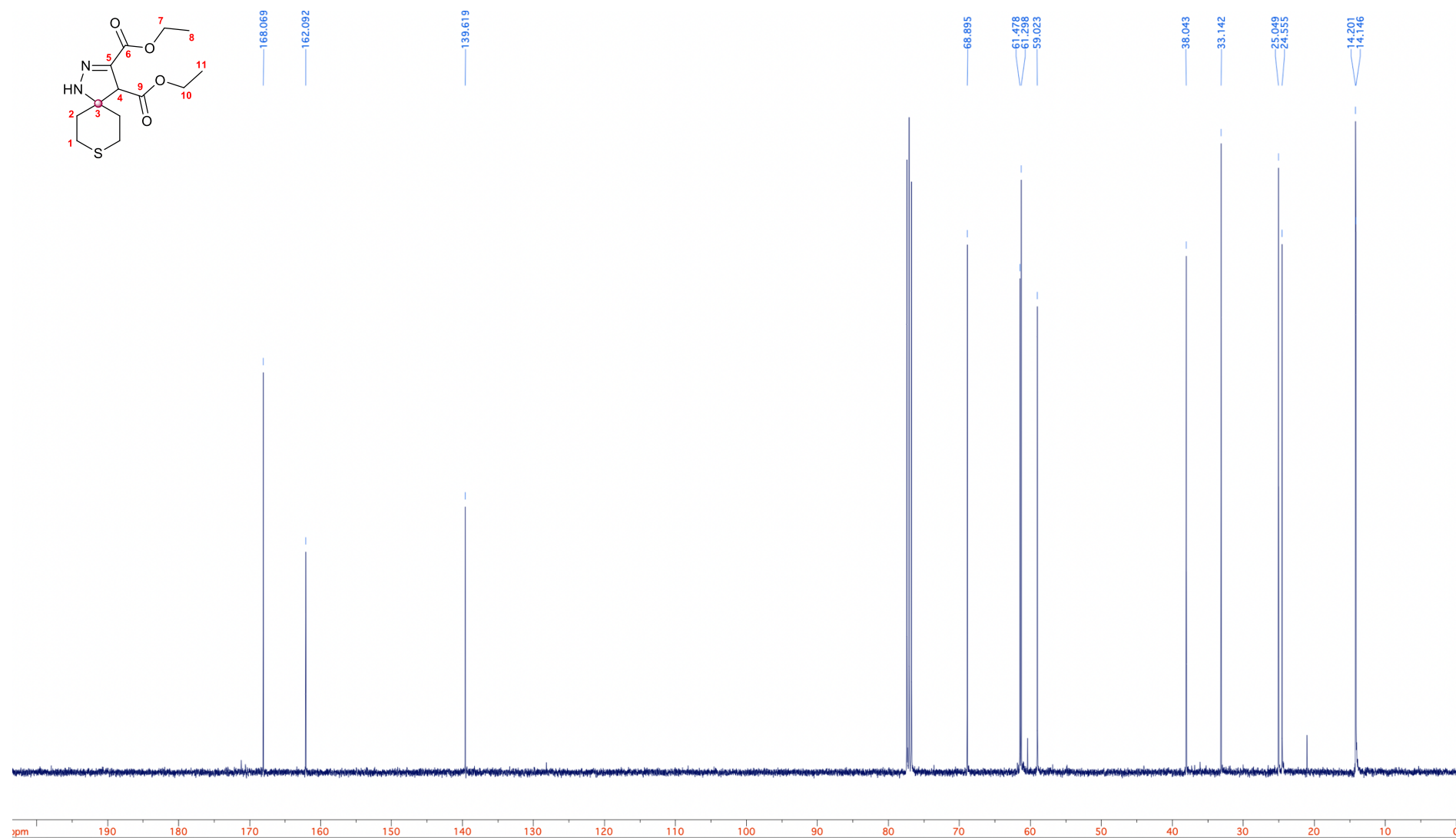
Compound **5b** ^{13}C NMR (100 MHz, CDCl_3)



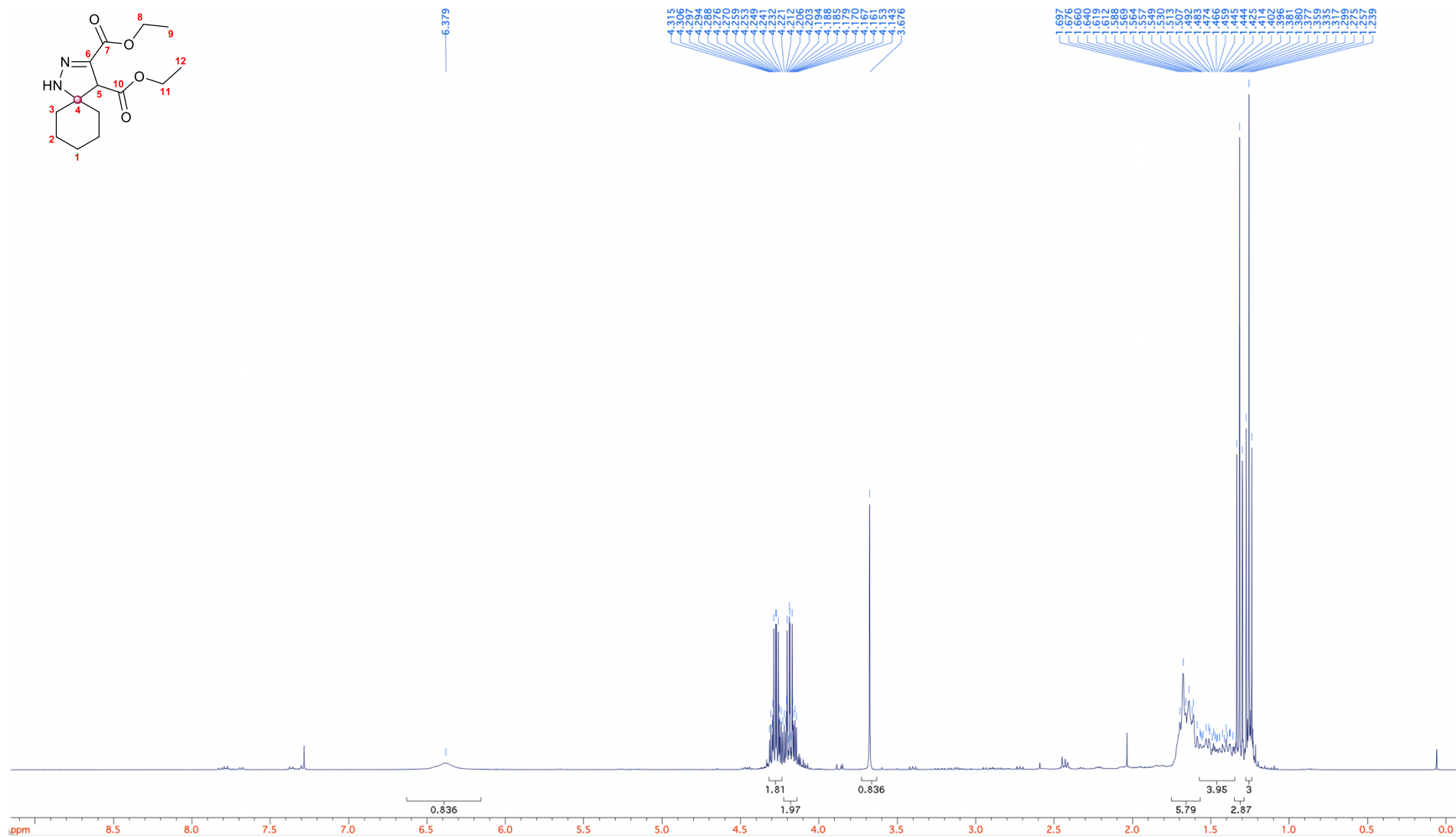
Compound **5c** ^1H NMR (400 MHz, CDCl_3)



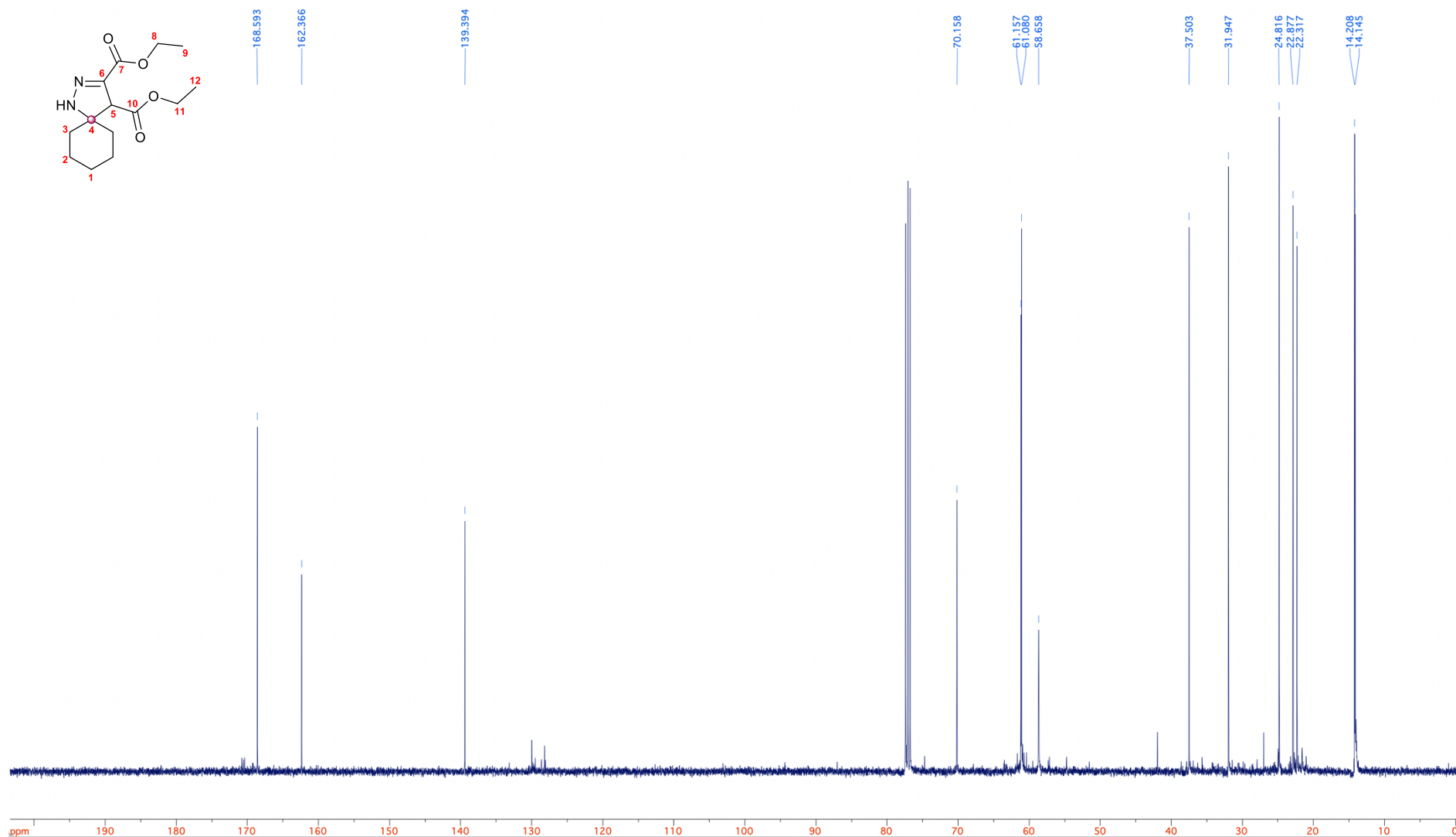
Compound **5c** ^{13}C NMR (100 MHz, CDCl_3)



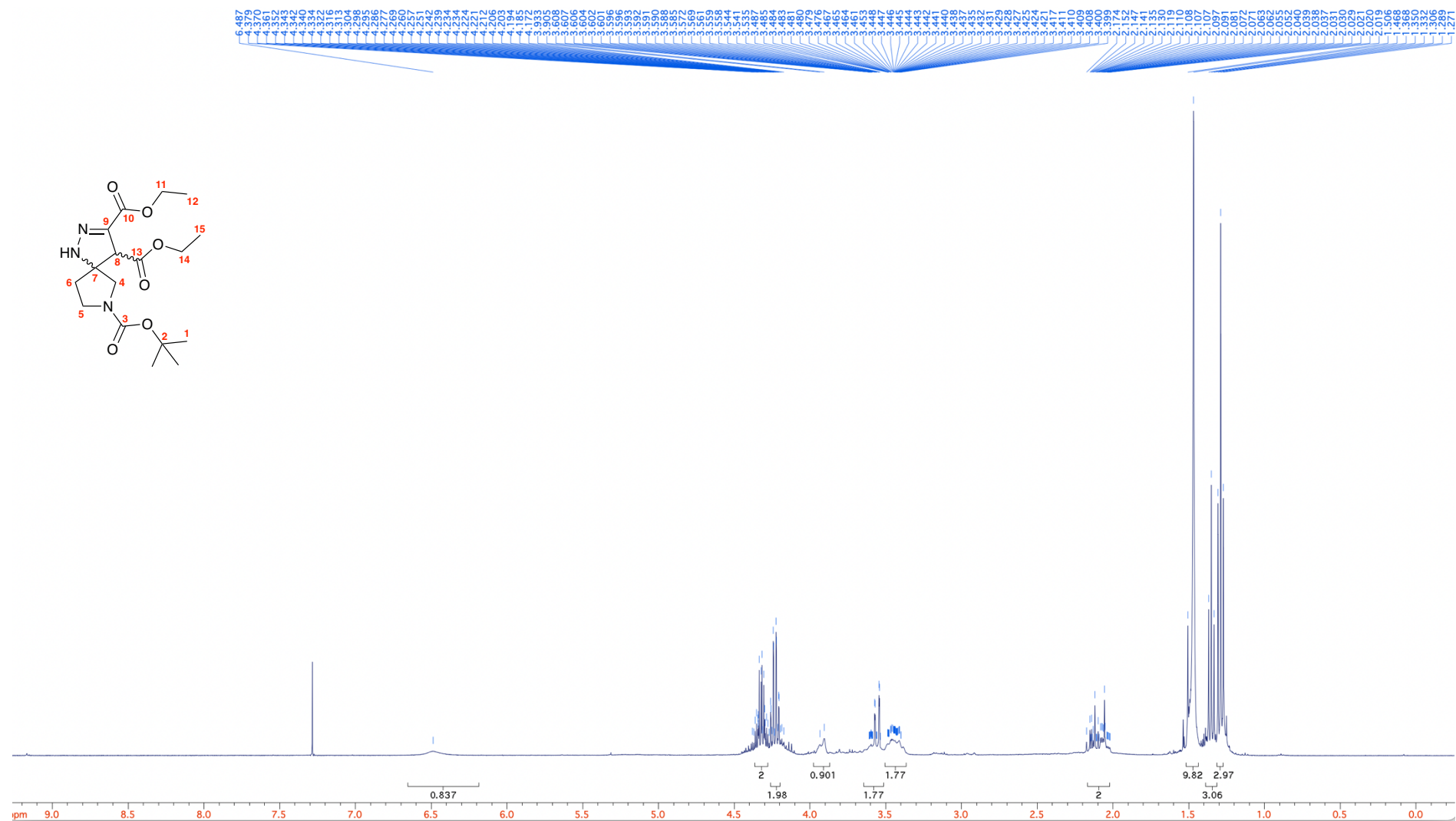
Compound **5d** ^1H NMR (400 MHz, CDCl_3)



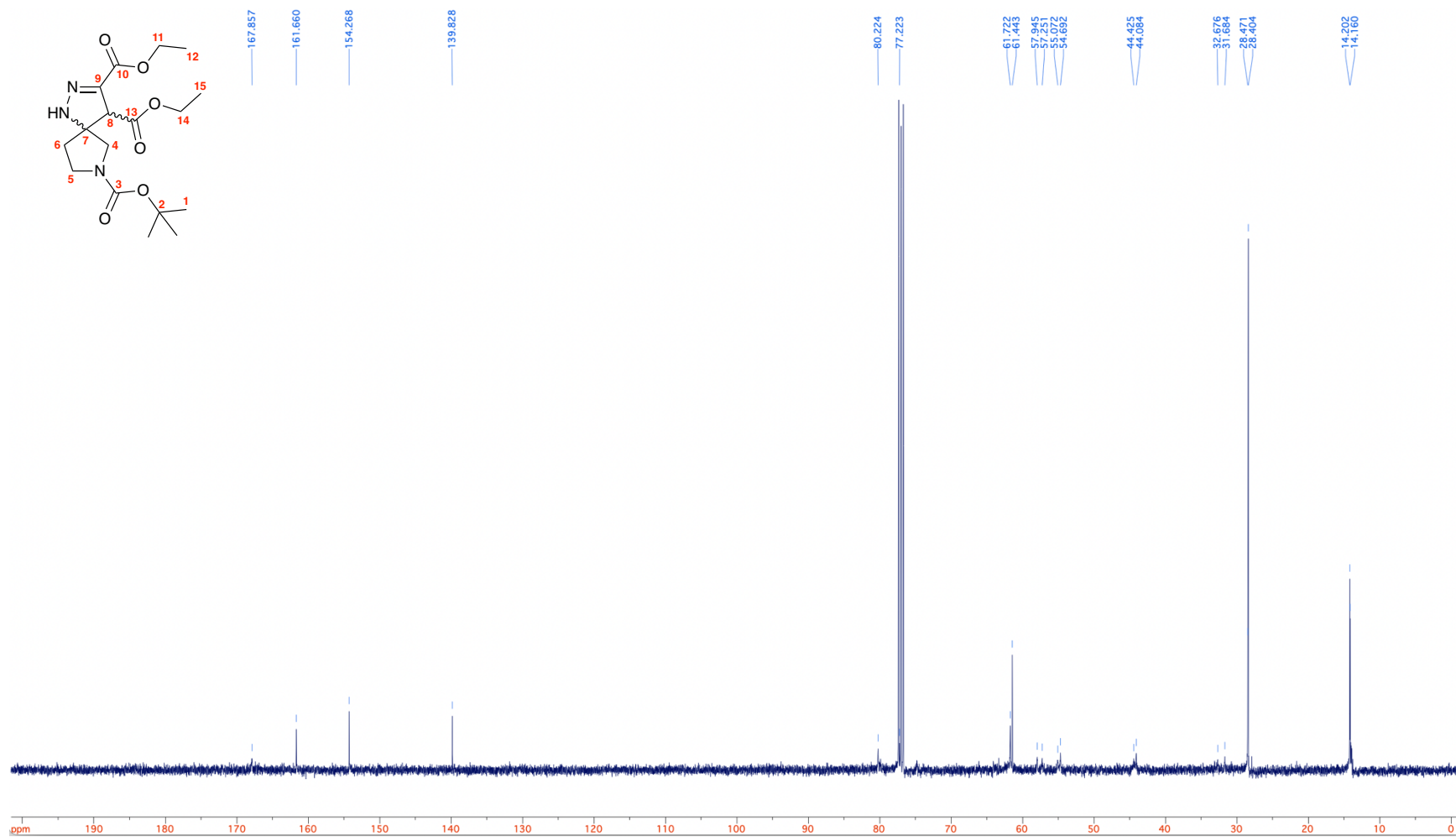
Compound **5d** ^{13}C NMR (100 MHz, CDCl_3)



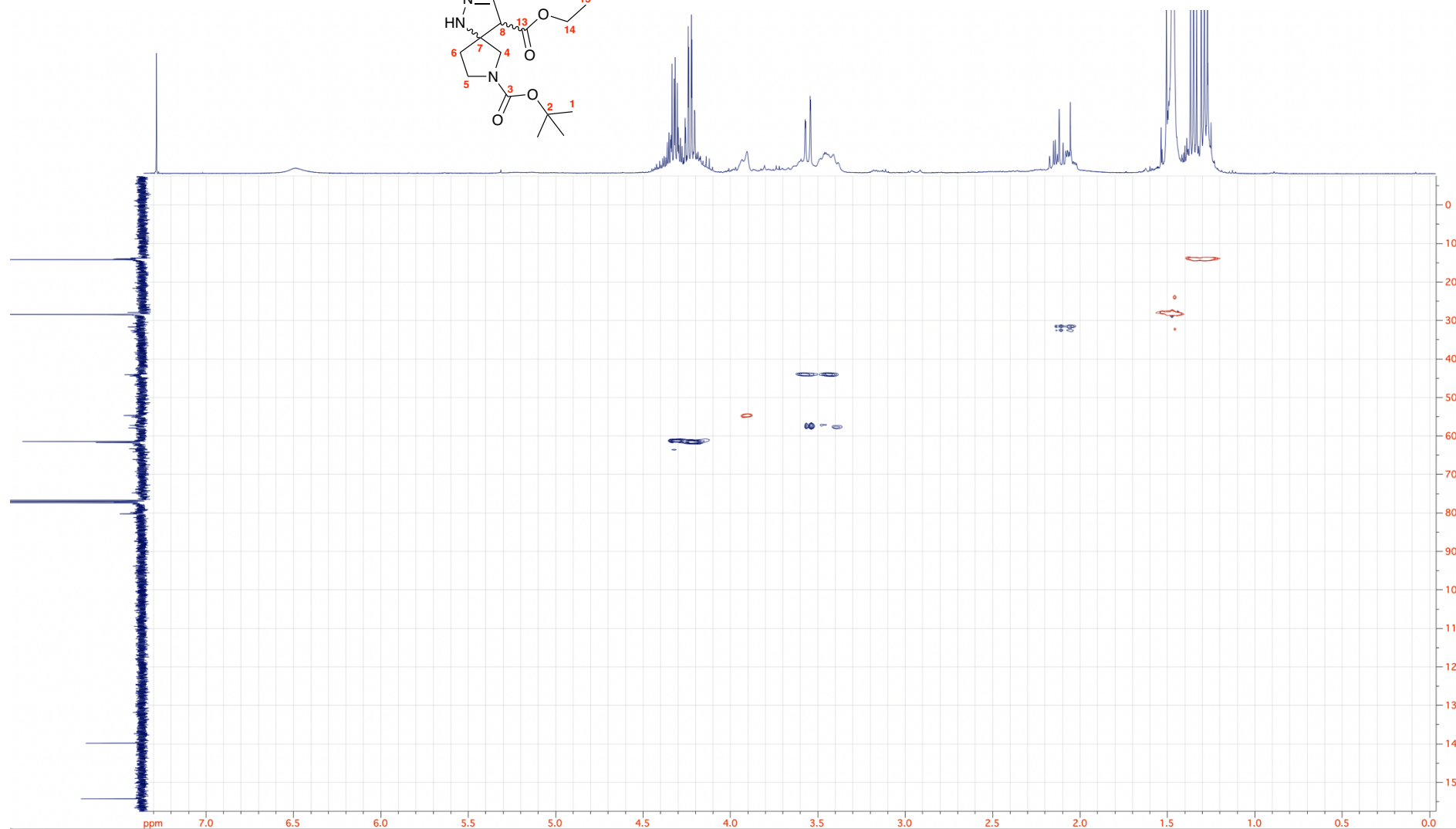
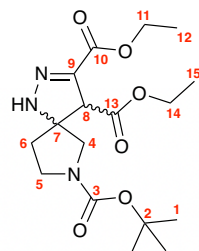
Compound **5e** ^1H NMR (400 MHz, CDCl_3)



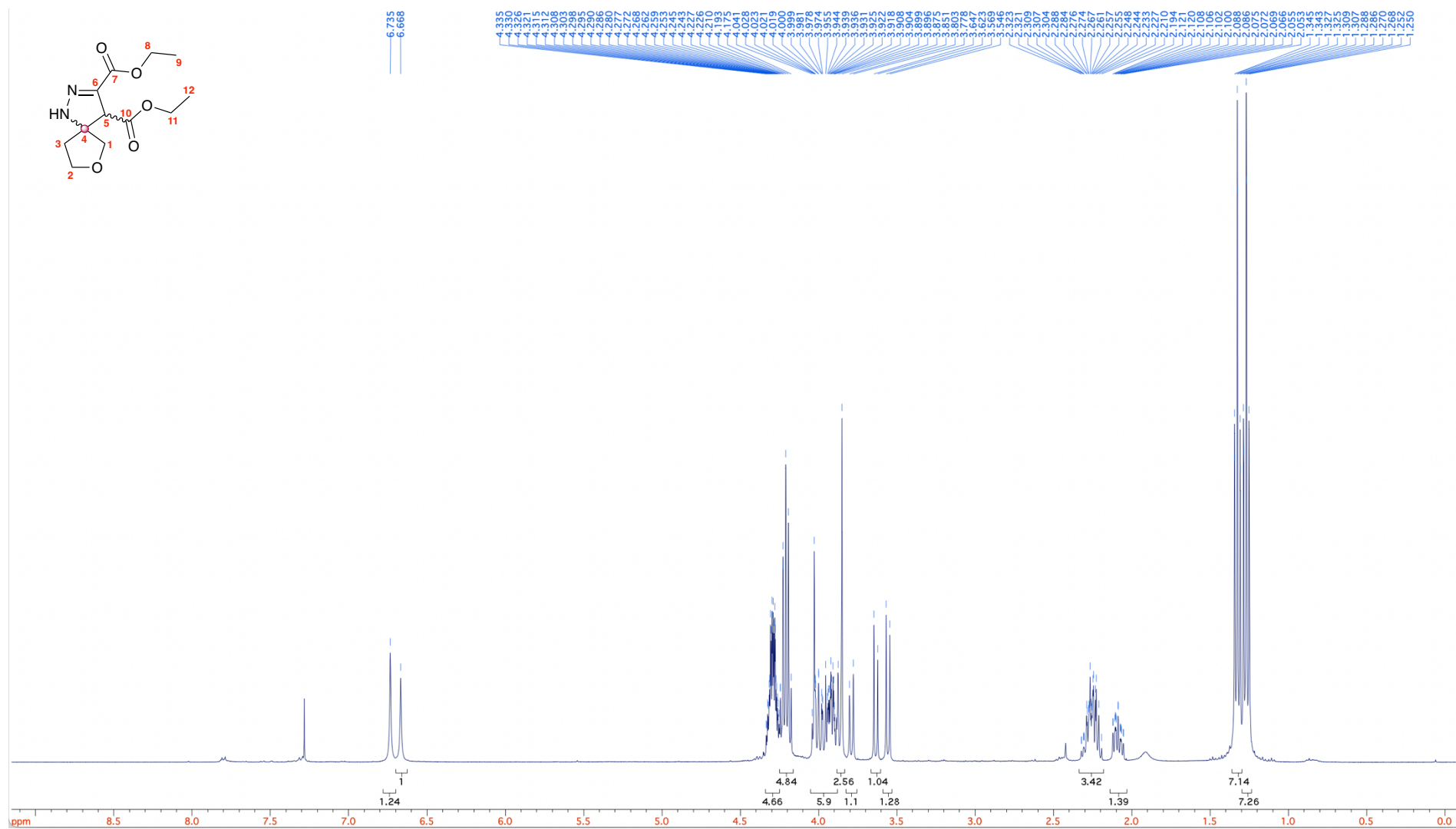
Compound **5e** ^{13}C NMR (100 MHz, CDCl_3)



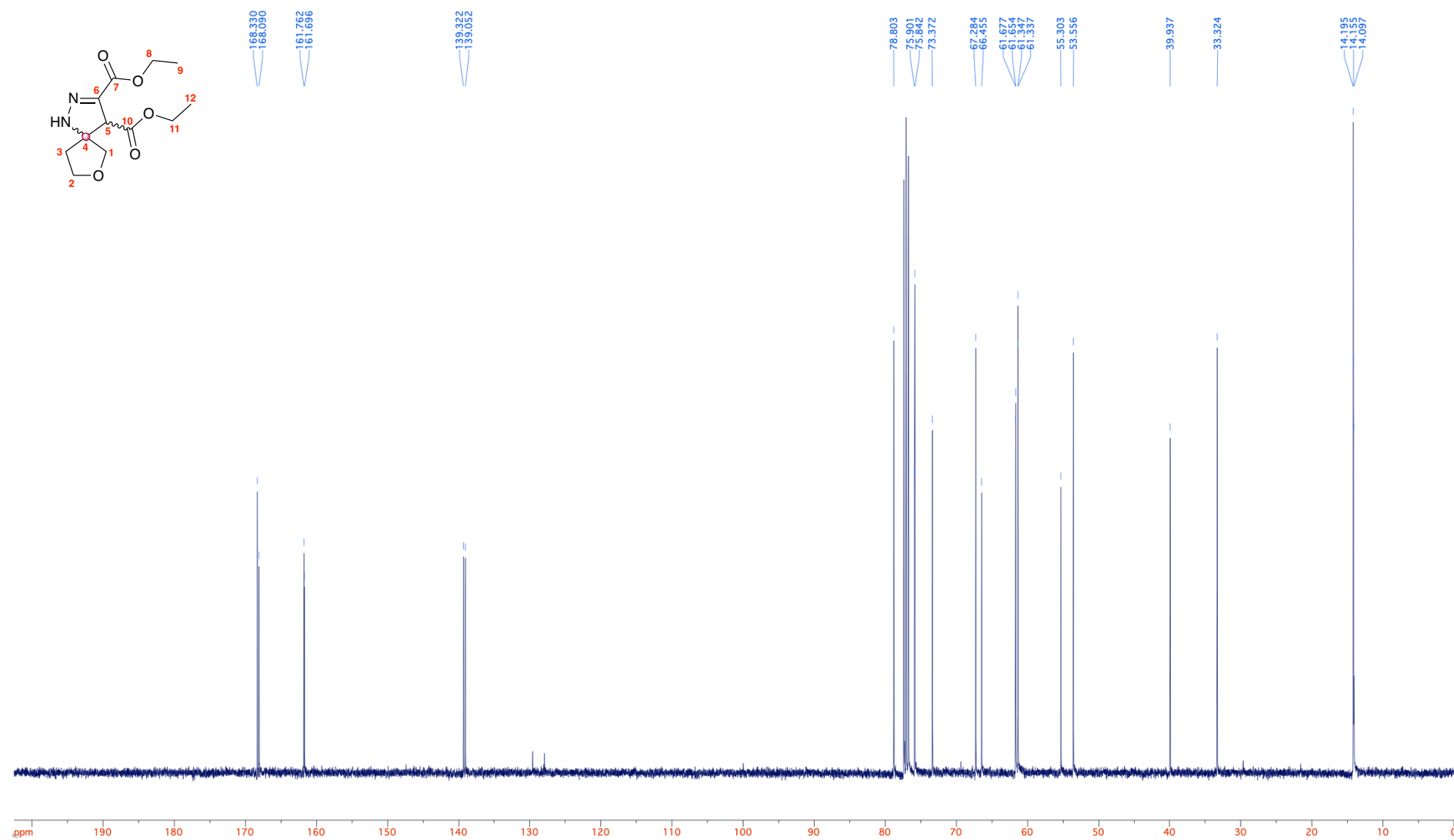
Compound **5e** HSQC (400/100 MHz, CDCl₃)



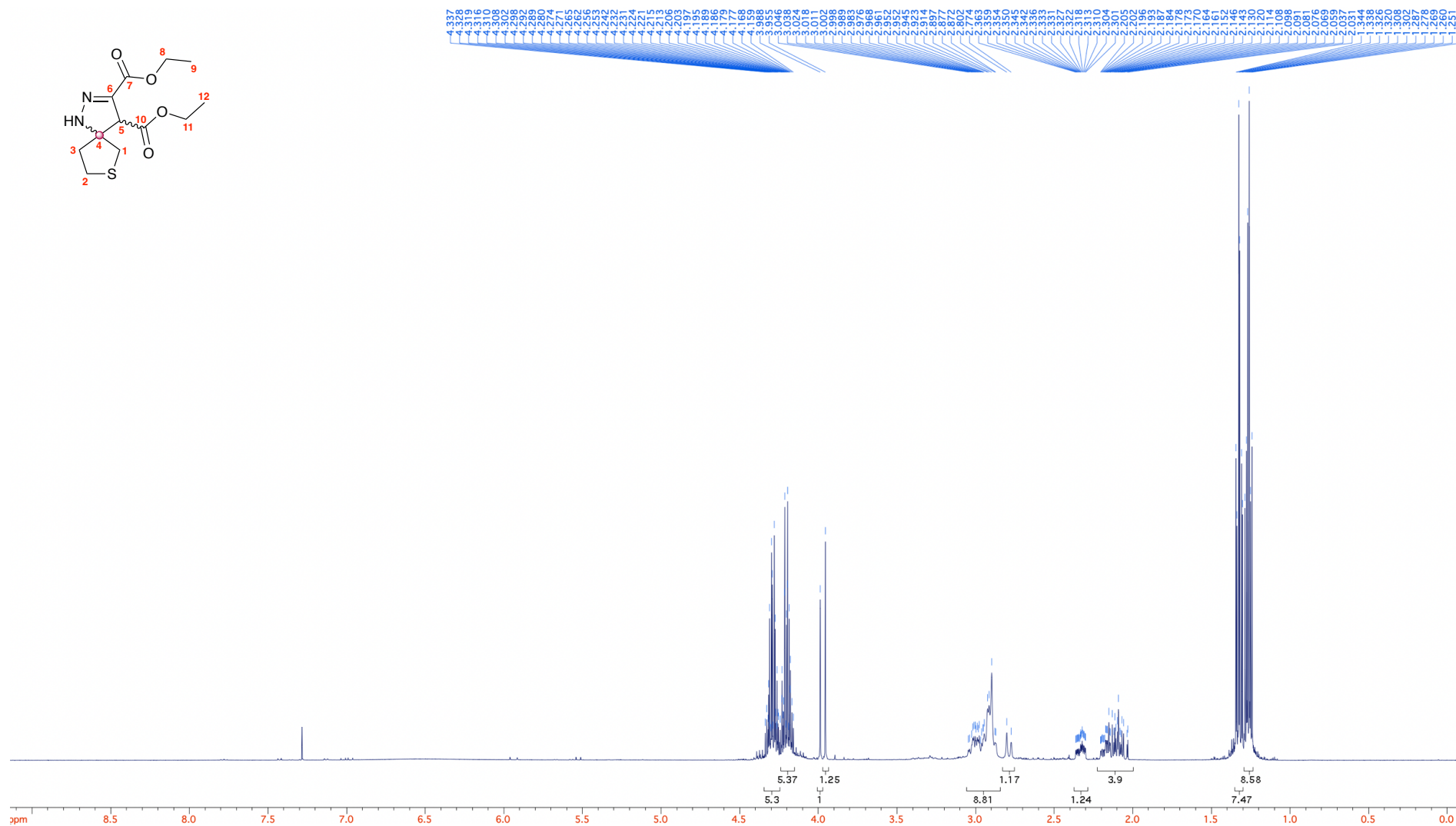
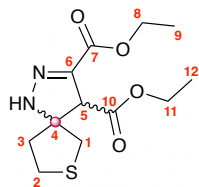
Compound **5f** ^1H NMR (400 MHz, CDCl_3)



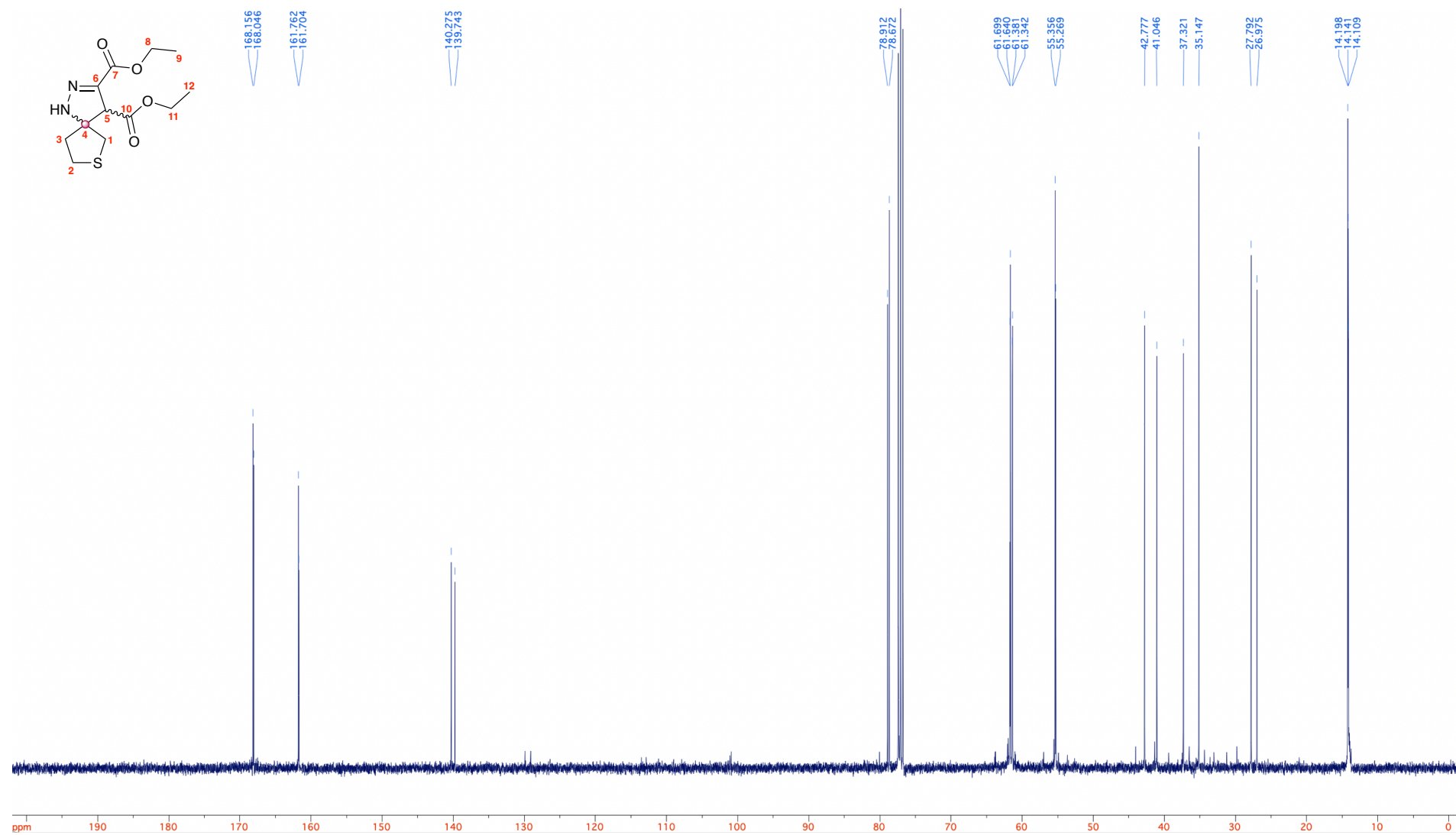
Compound **5f** ^{13}C NMR (100 MHz, CDCl_3)



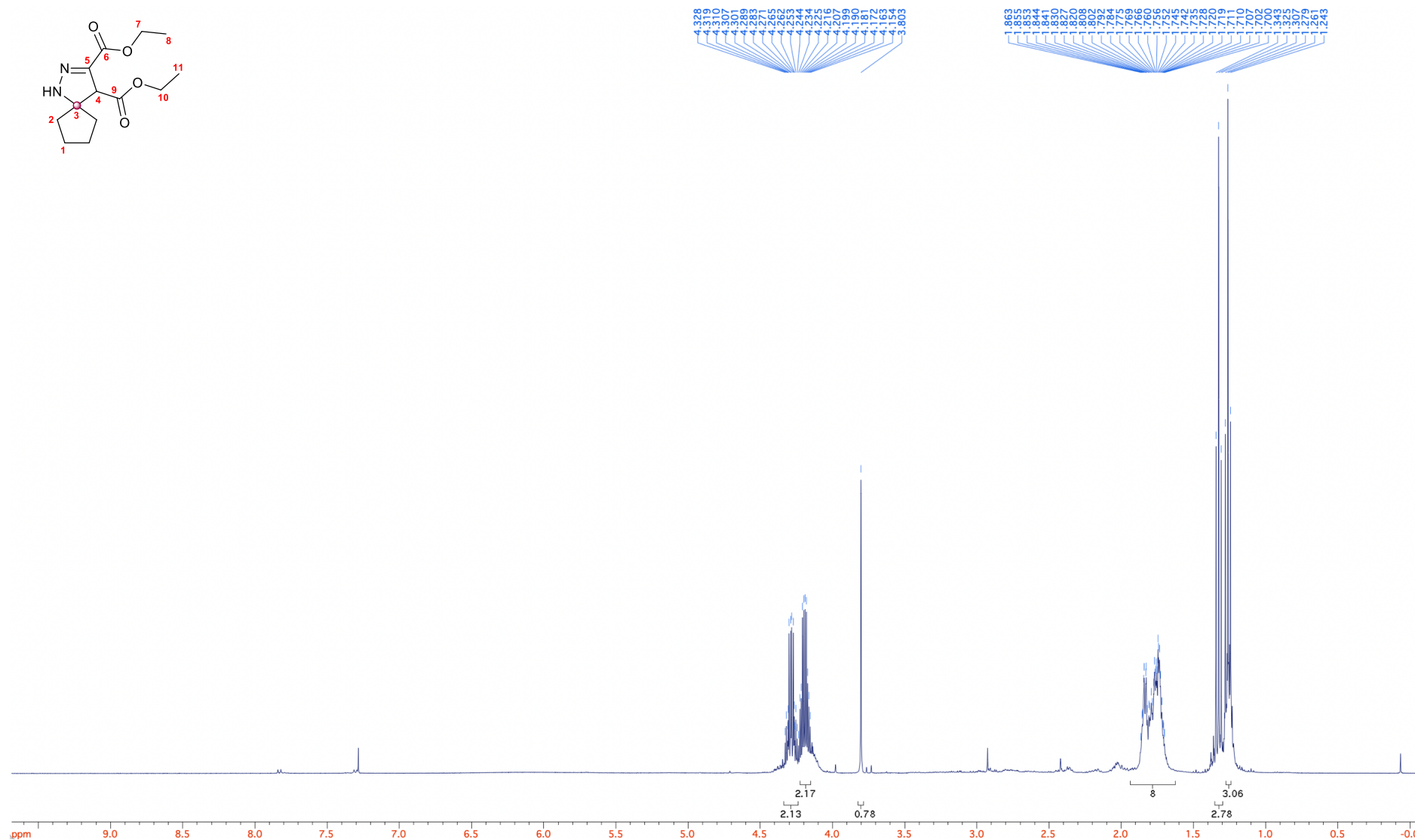
Compound **5g** ^1H NMR (400 MHz, CDCl_3)



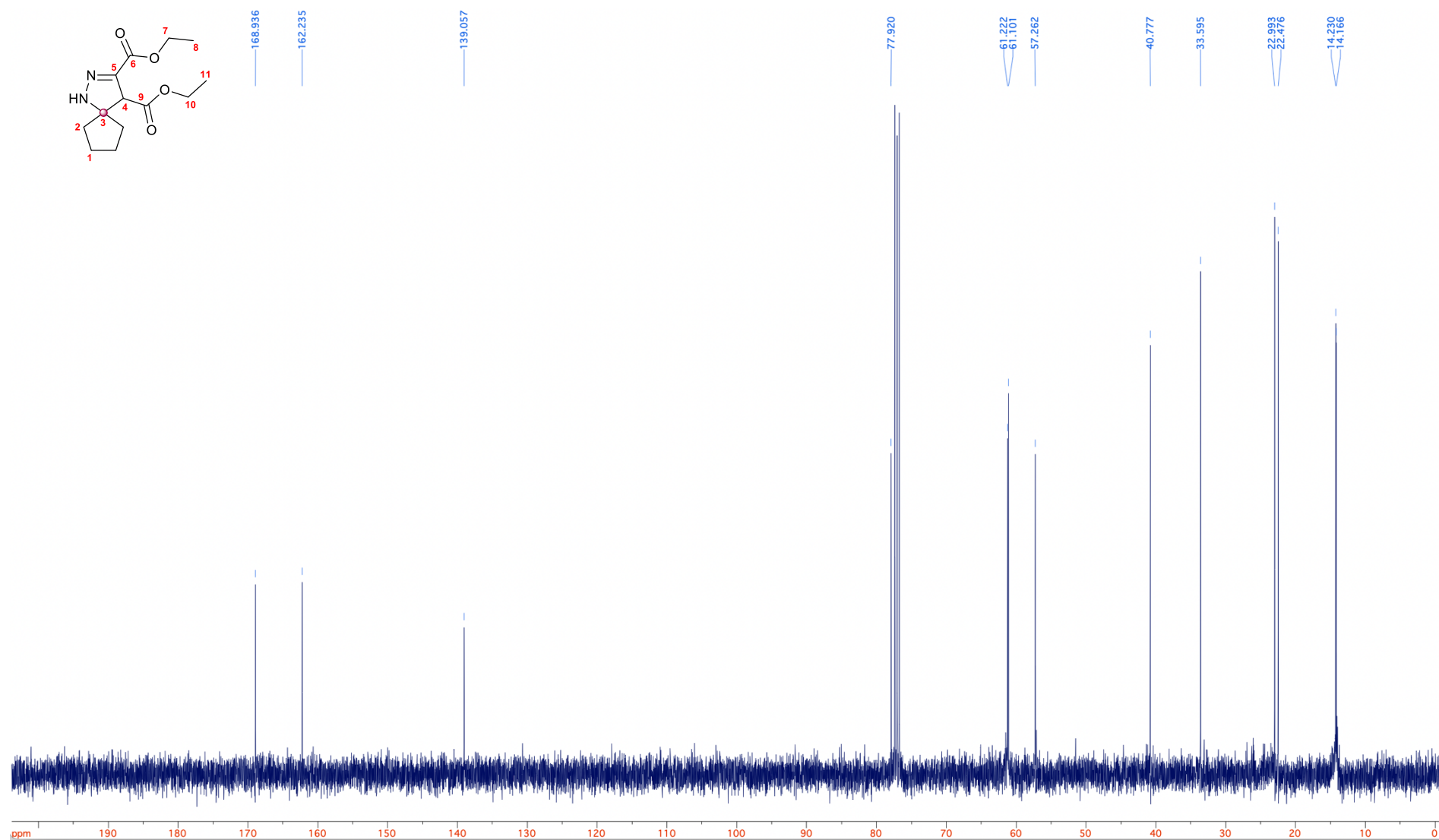
Compound **5g** ^{13}C NMR (100 MHz, CDCl_3)



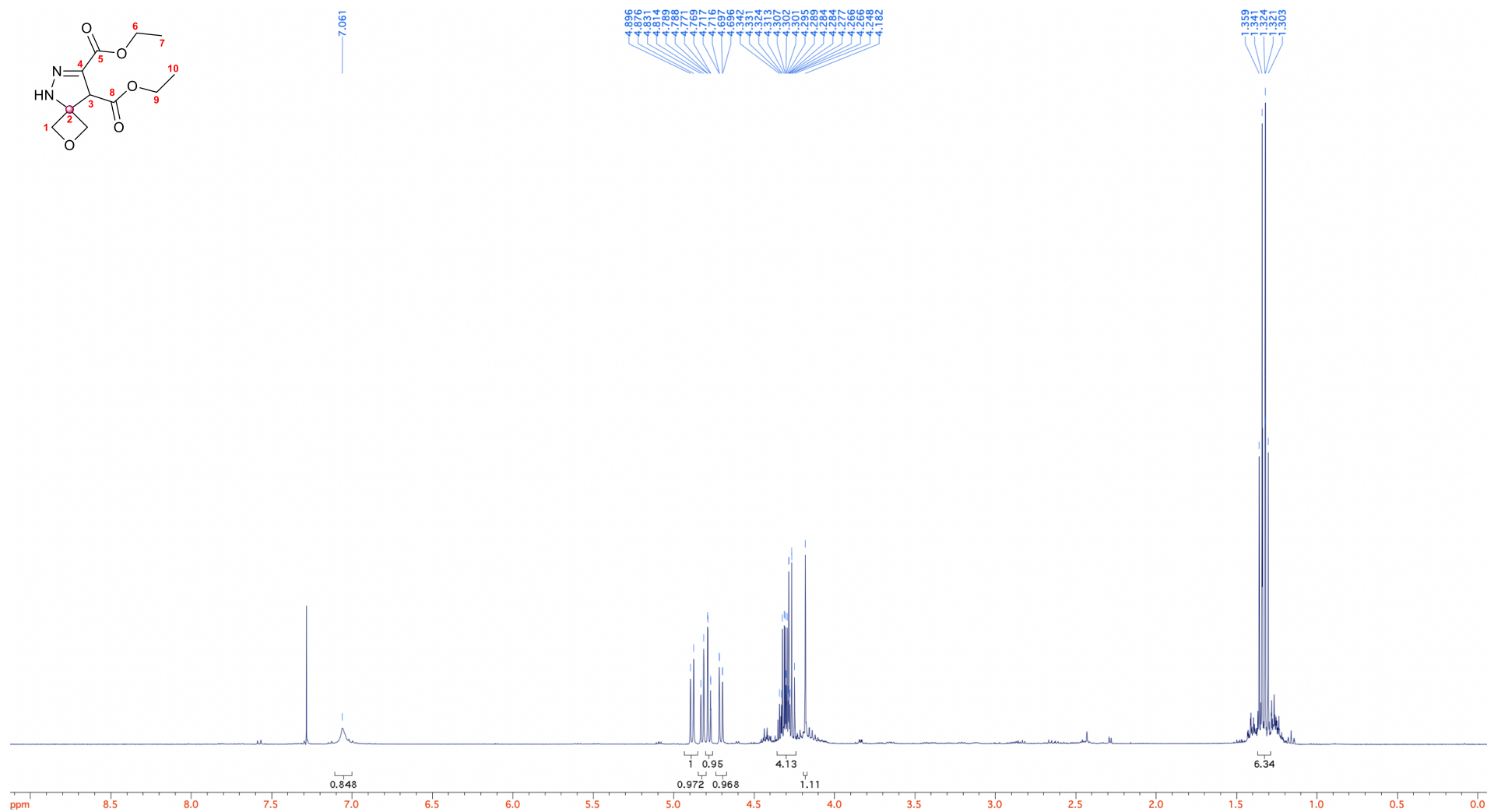
Compound **5h** ^1H NMR (400 MHz, CDCl_3)



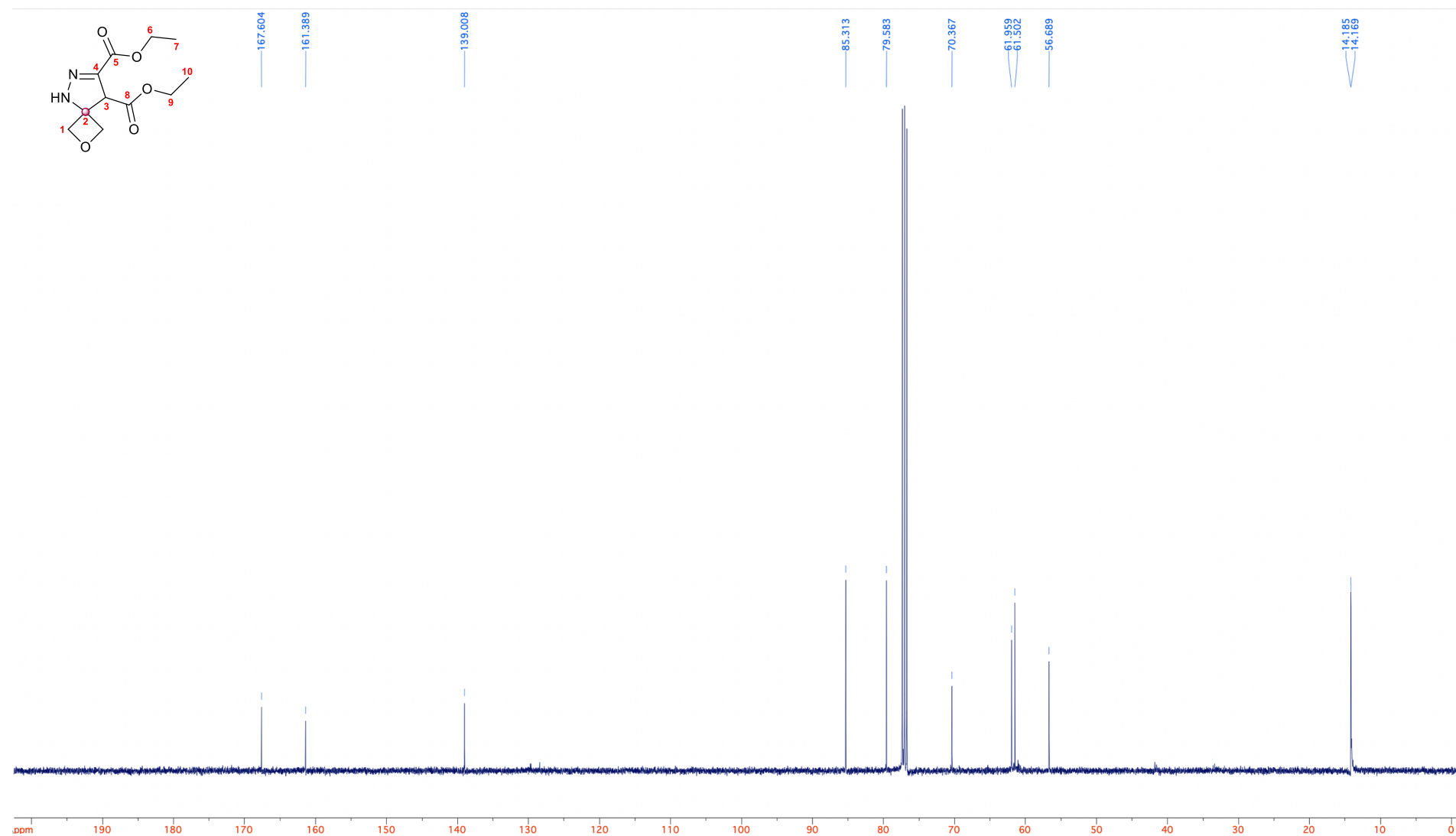
Compound **5h** ^{13}C NMR (100 MHz, CDCl_3)



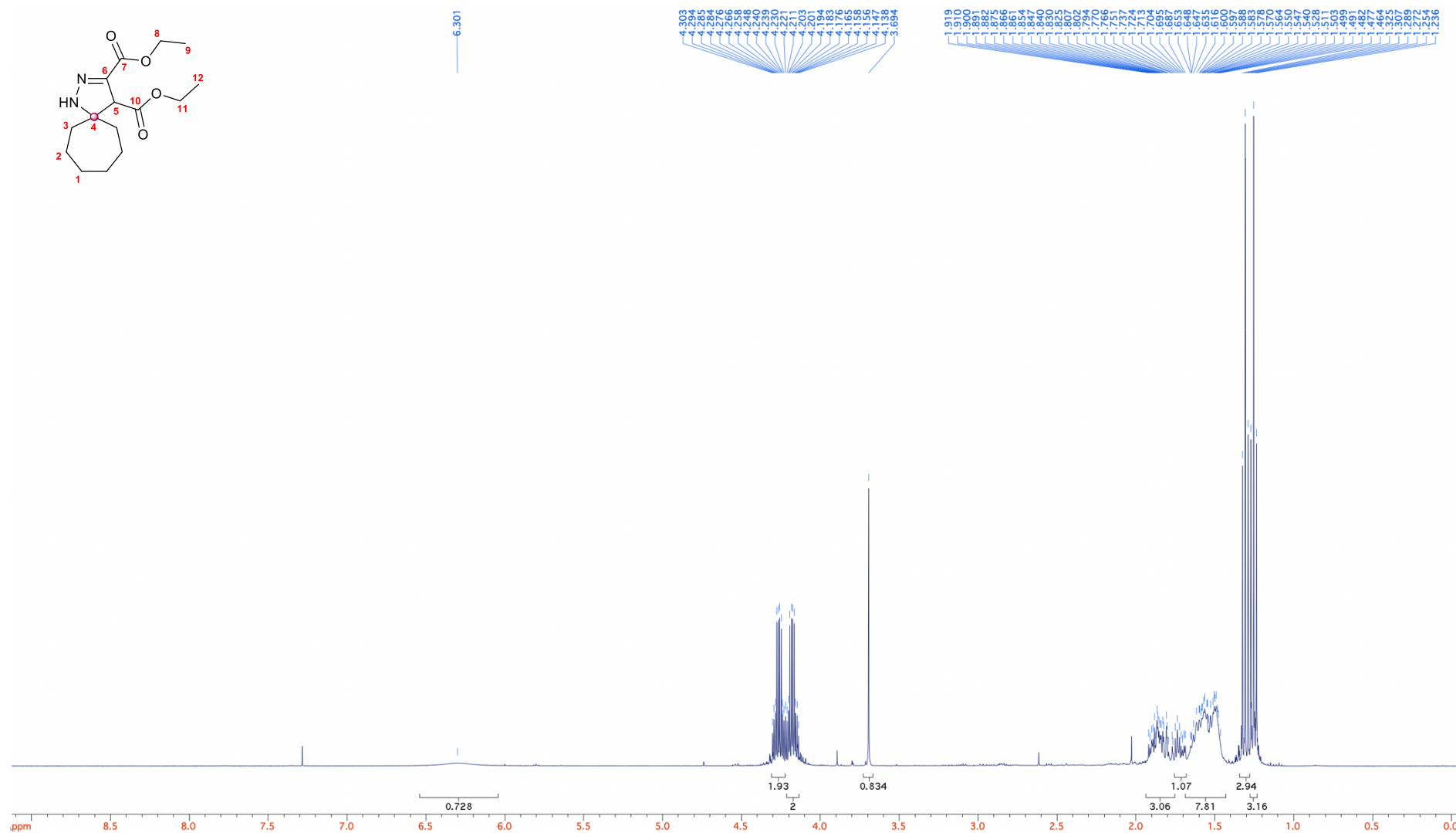
Compound **5i** ^1H NMR (400 MHz, CDCl_3)



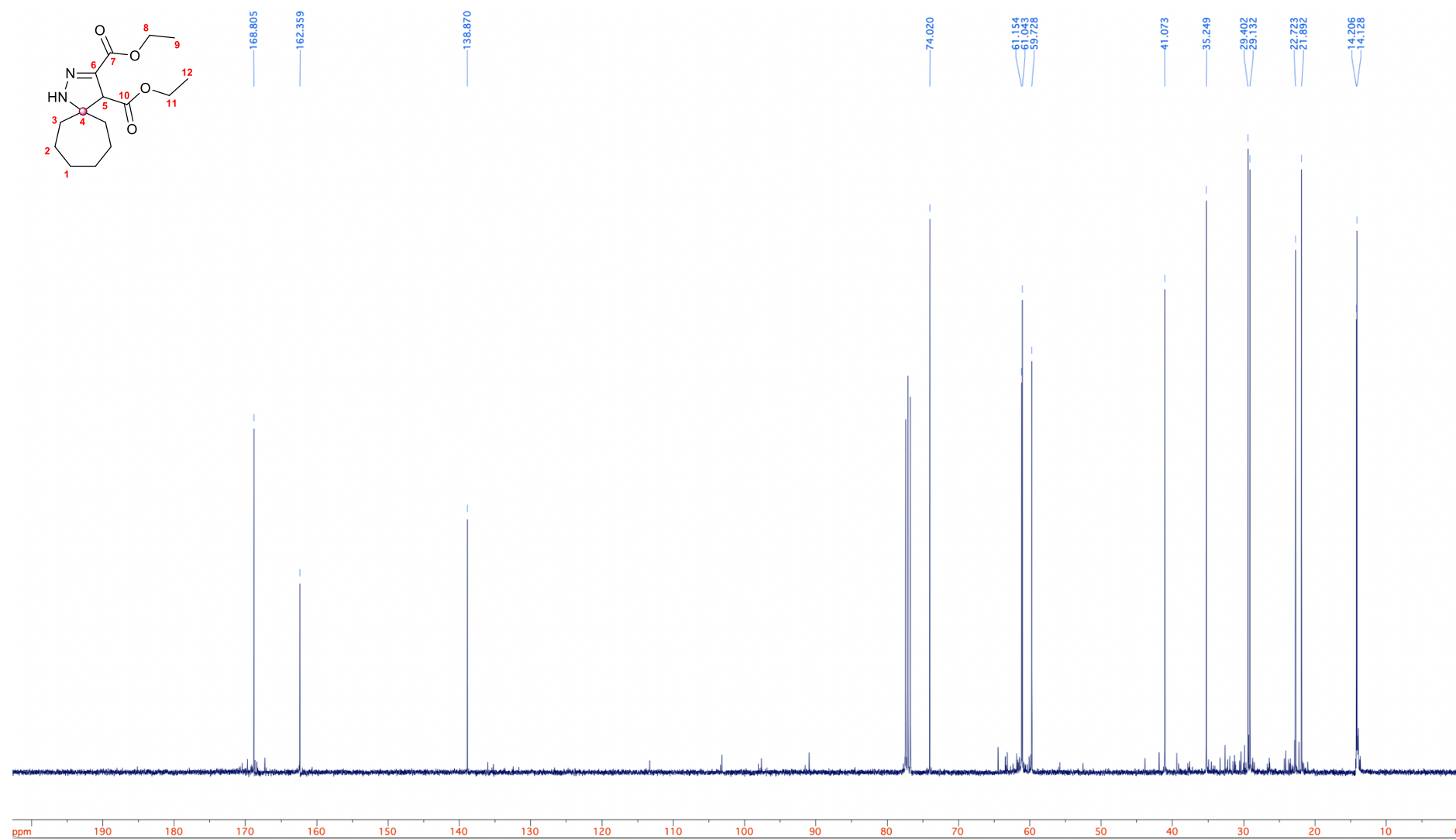
Compound **5i** ^{13}C NMR (100 MHz, CDCl_3)



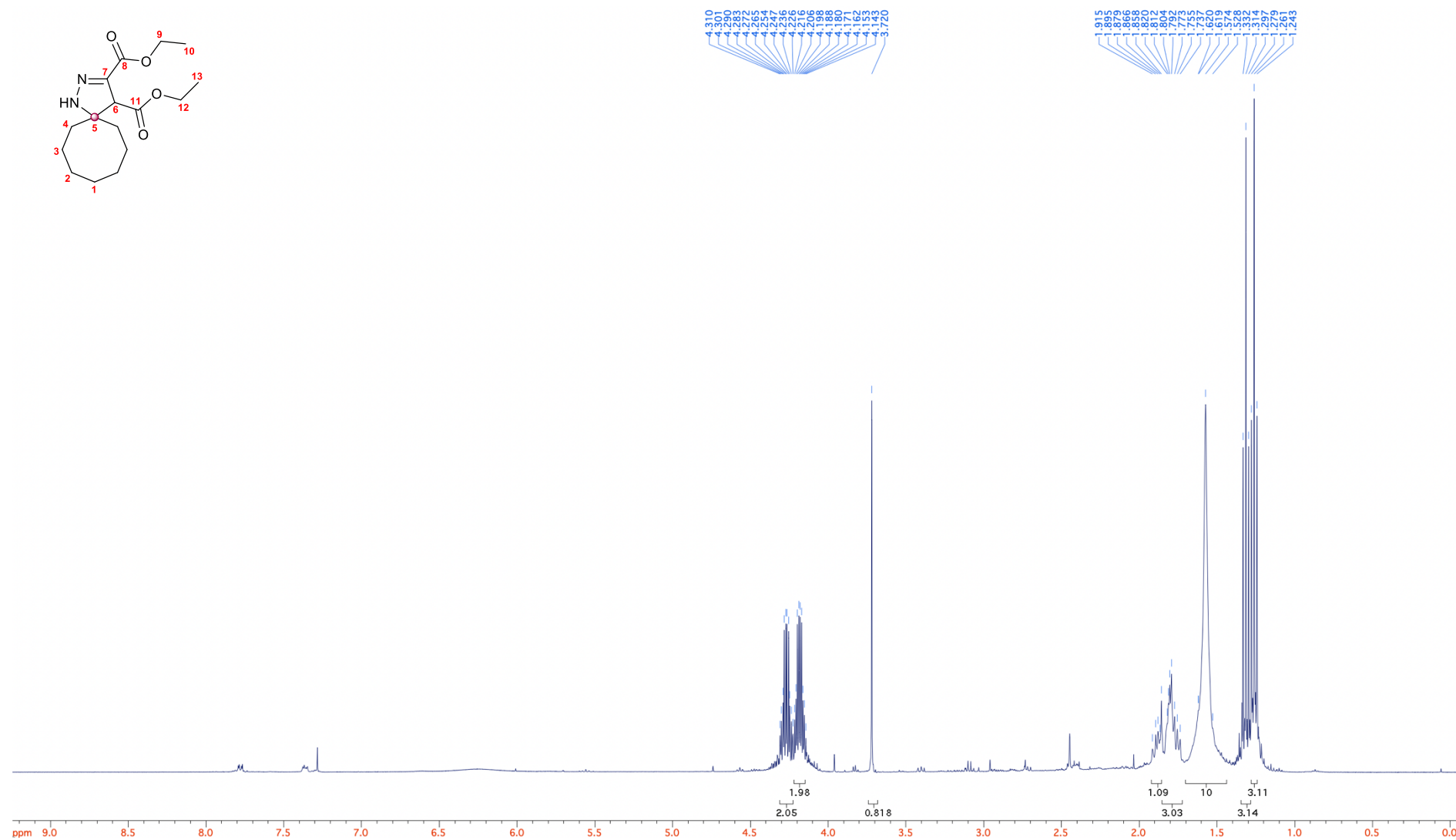
Compound **5j** ^1H NMR (400 MHz, CDCl_3)



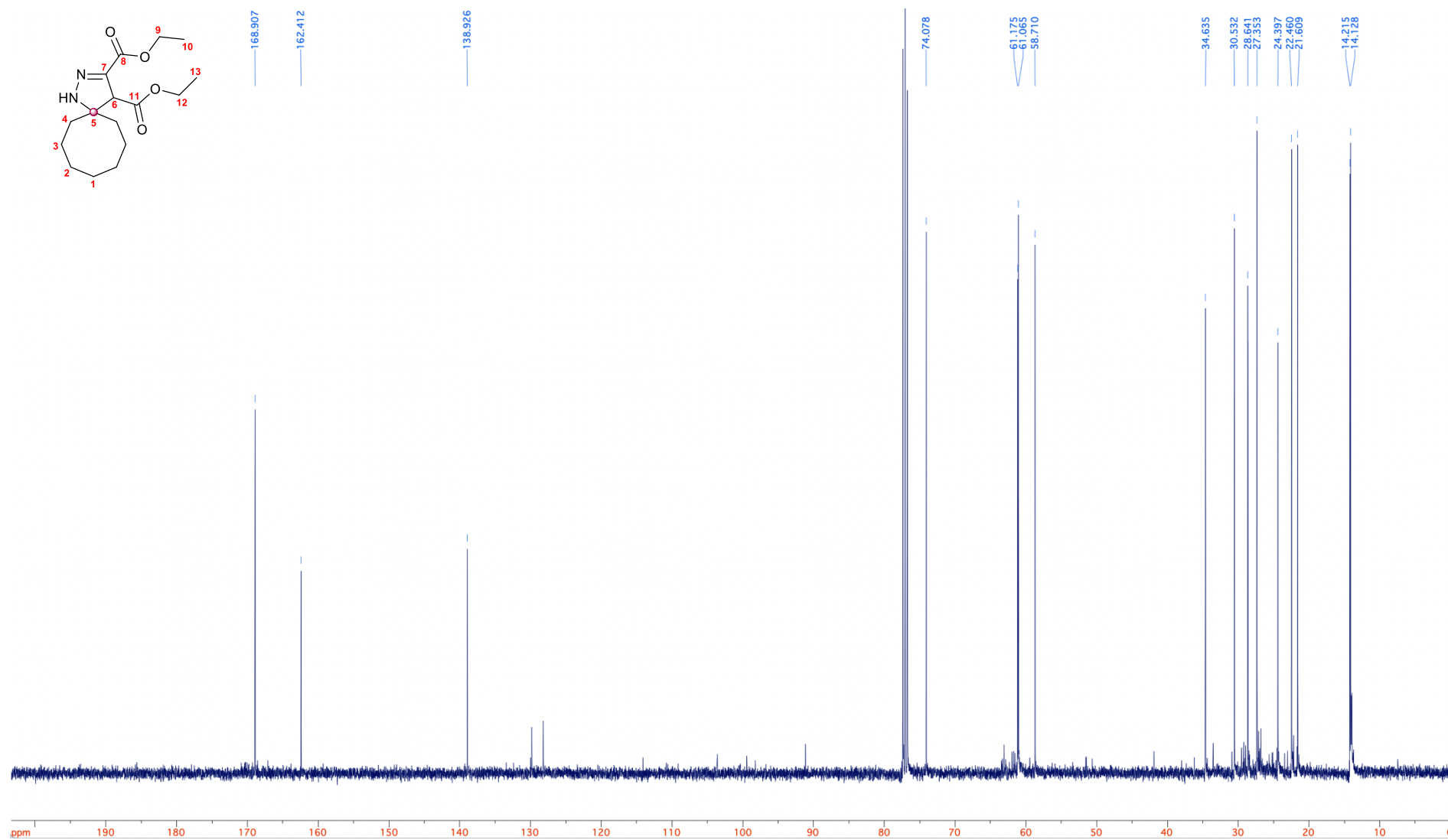
Compound **5j** ^{13}C NMR (100 MHz, CDCl_3)



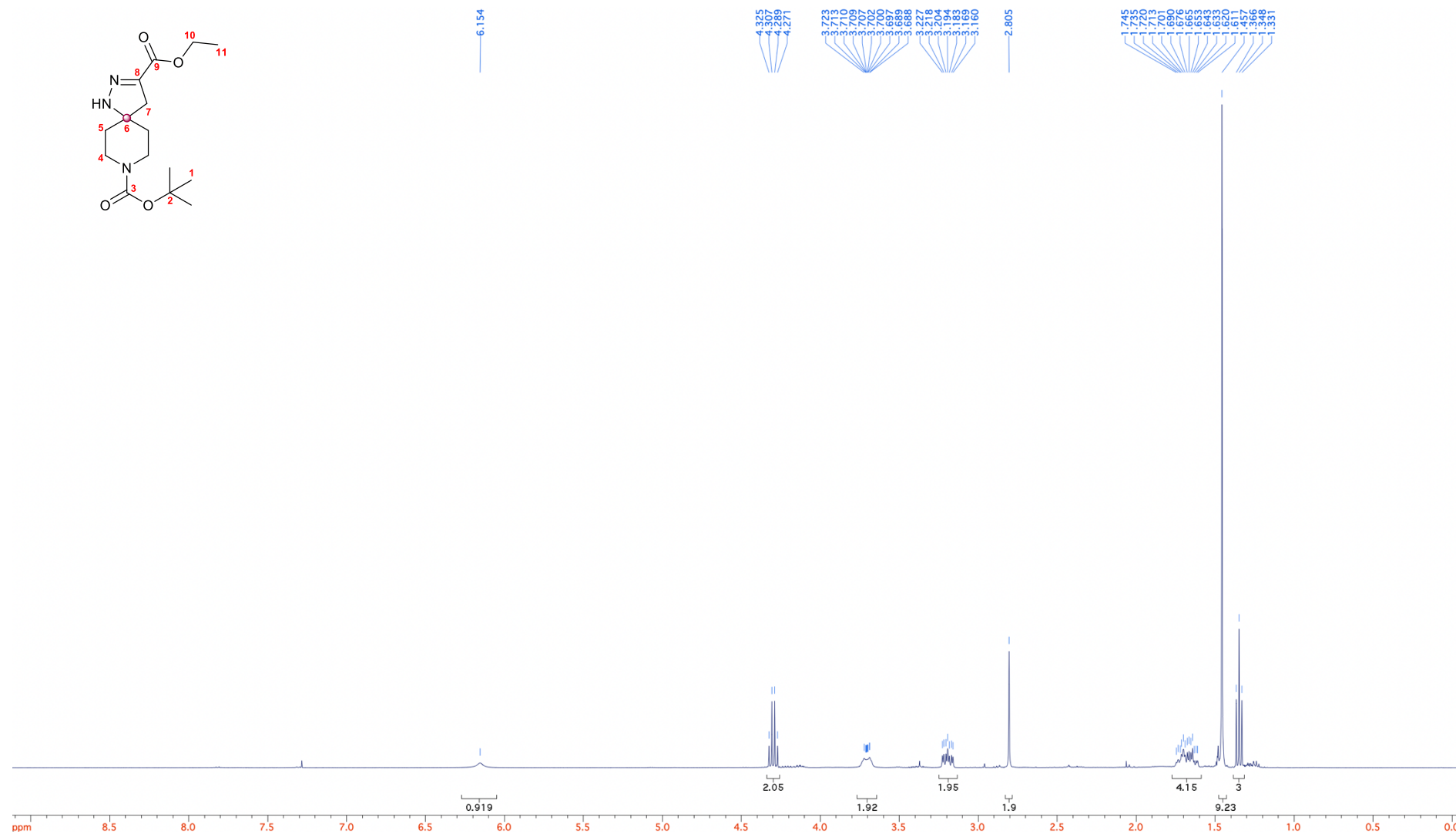
Compound **5k** ^1H NMR (400 MHz, CDCl_3)



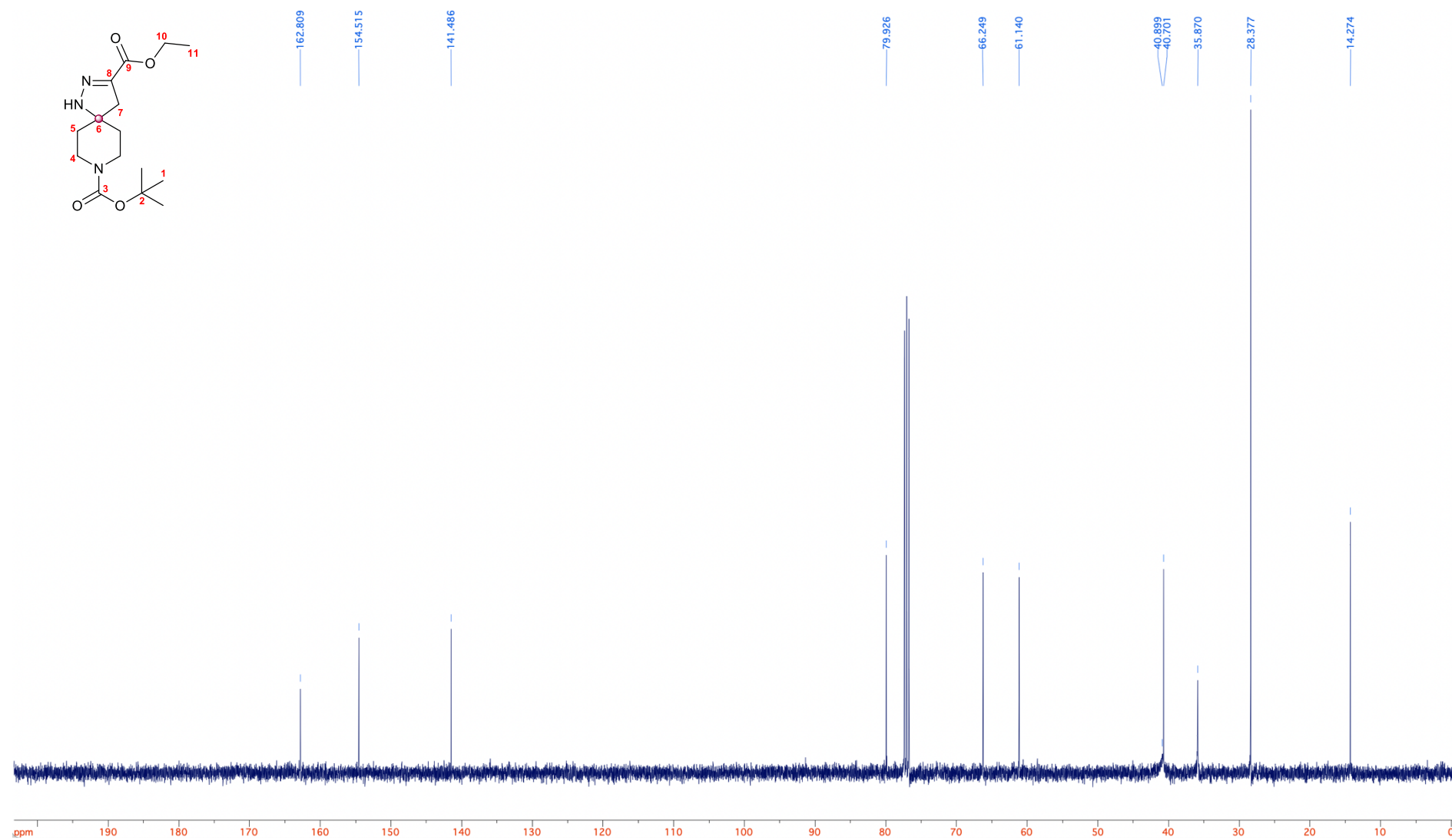
Compound **5k** ^{13}C NMR (100 MHz, CDCl_3)



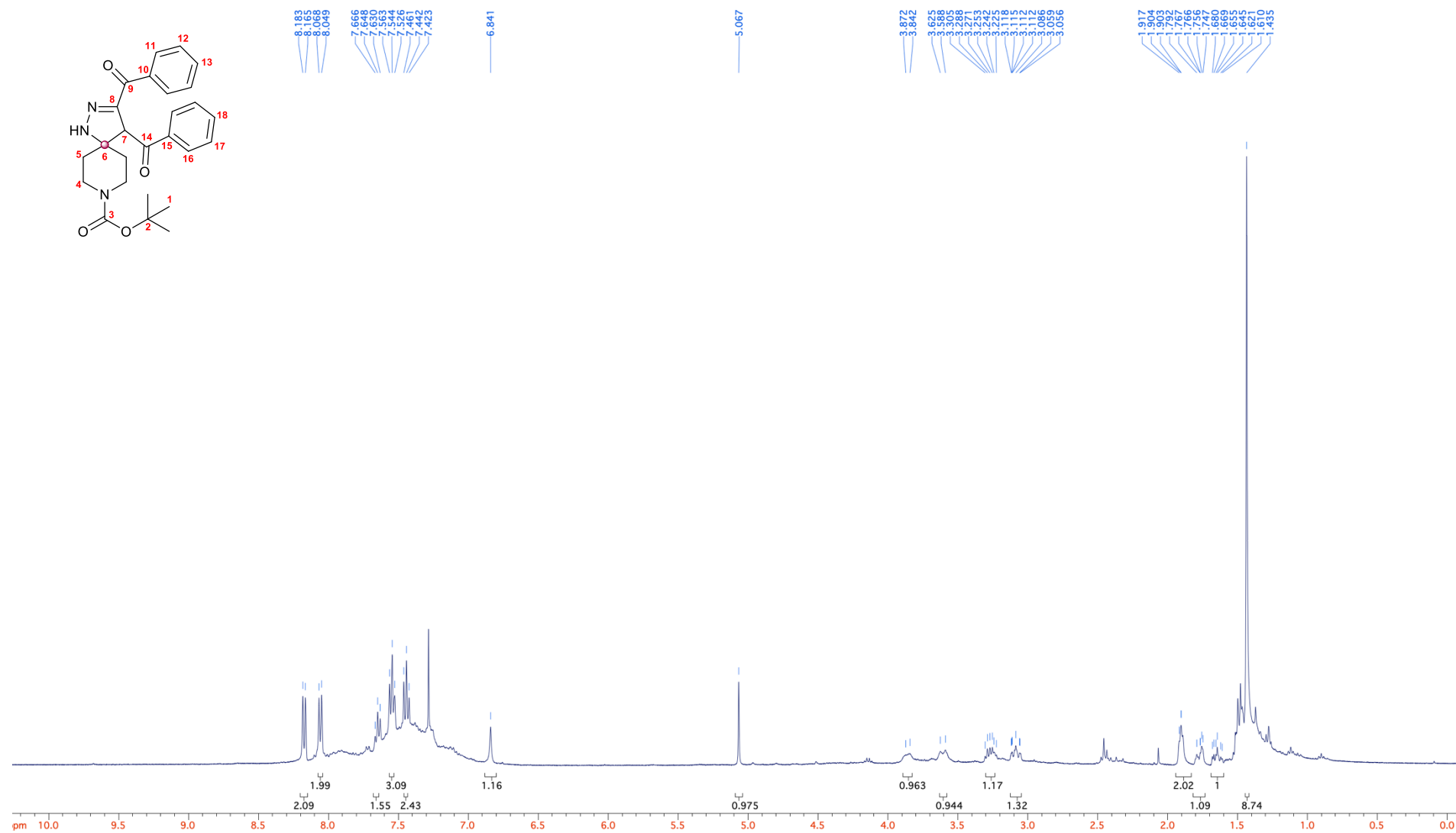
Compound **5I** ^1H NMR (400 MHz, CDCl_3)



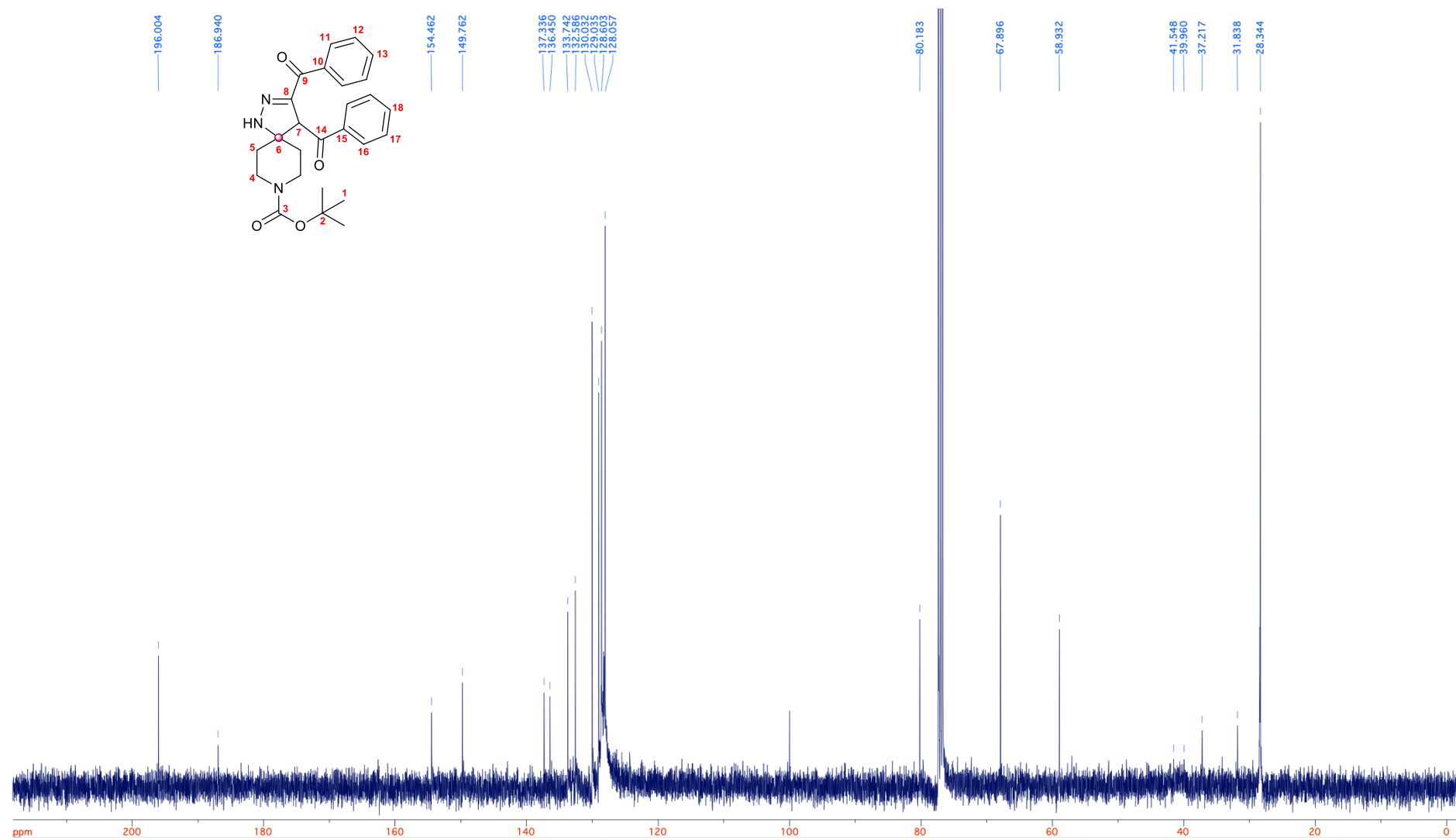
Compound **5I** ^{13}C NMR (100 MHz, CDCl_3)



Compound **5m** ^1H NMR (400 MHz, CDCl_3)



Compound **5m** ^{13}C NMR (100 MHz, CDCl_3)



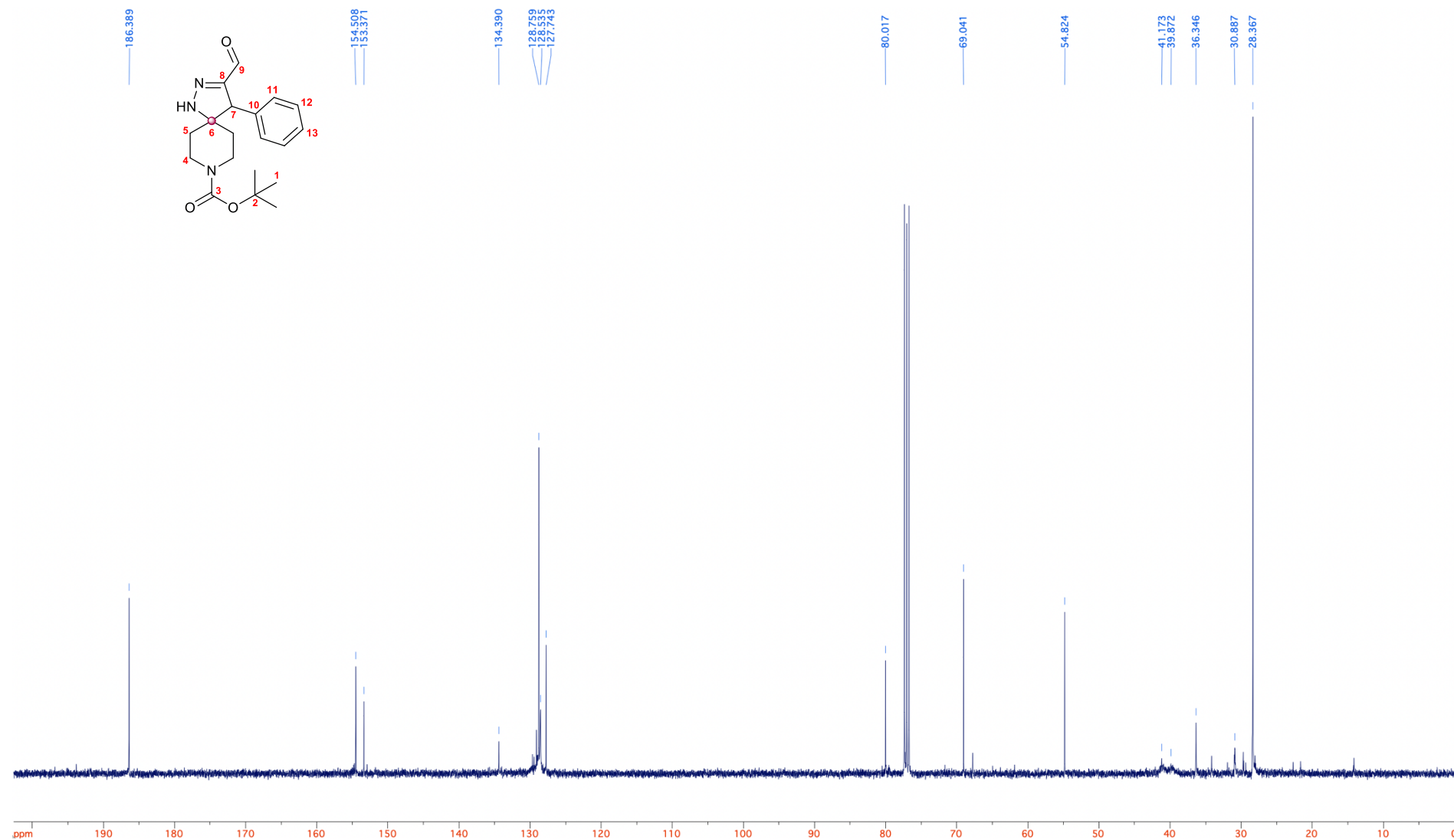
The chemical structure of compound 10 is shown in the top left corner. It is a 1,4-dihydropyridine derivative with a 4-tert-butyl-1H-imidazole-2-carboxamide group at position 4 and a 3-phenylpropyl group at position 2. The structure is labeled with red numbers 1 through 13 corresponding to the peaks in the spectrum.

The ¹H NMR spectrum (400 MHz, CDCl₃) is displayed below the structure. The x-axis represents the chemical shift in ppm, ranging from 0 to 10.0. The spectrum shows several peaks, with the following assignments and integrations:

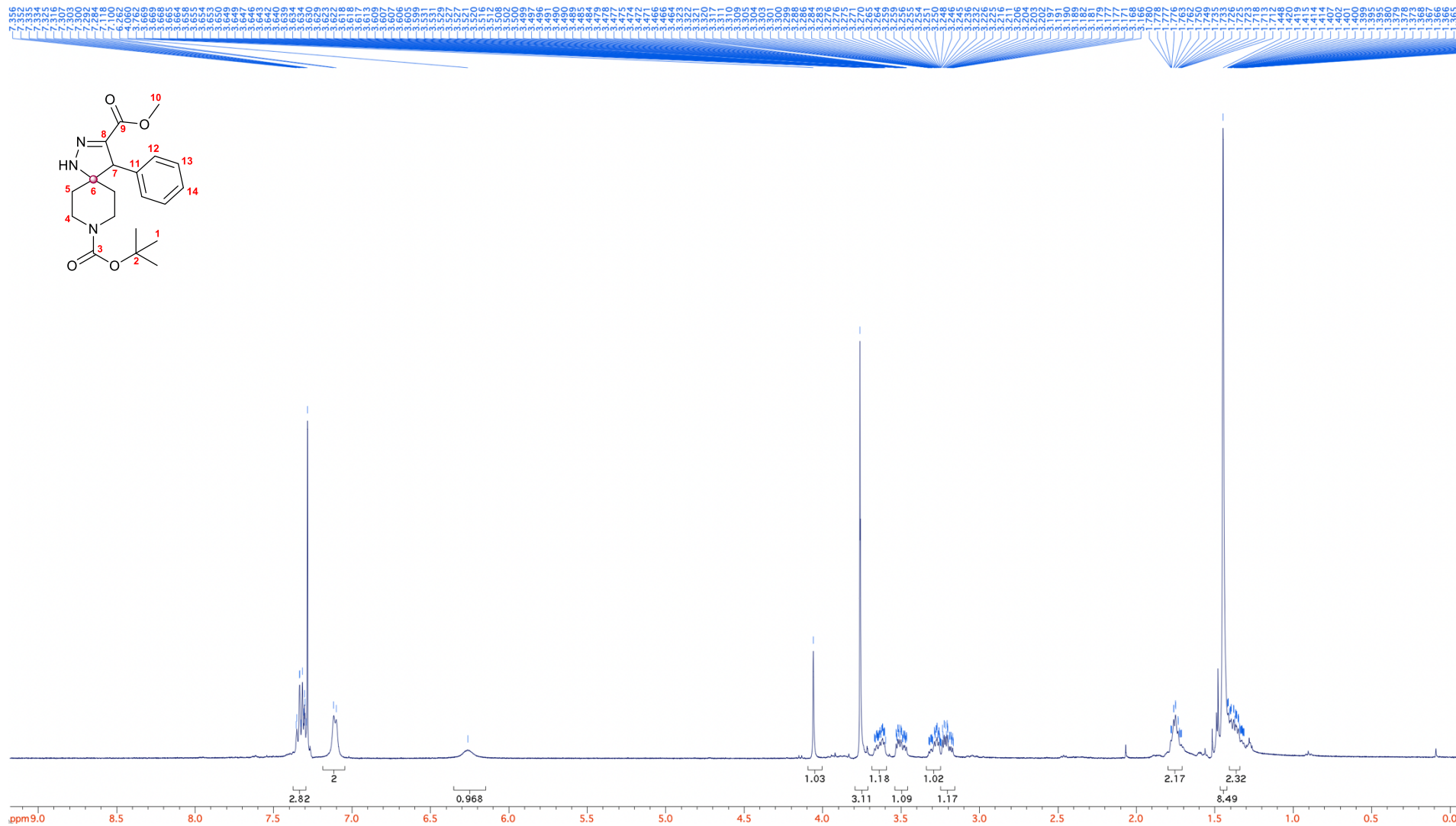
- Peak 1 (9.751 ppm, 1H, s): NH of the imidazole ring.
- Peak 2 (7.241 ppm, 2H, d): Aromatic protons of the phenyl ring (positions 10 and 11).
- Peak 3 (7.066 ppm, 1H, d): Aromatic proton of the phenyl ring (position 12).
- Peak 4 (7.066 ppm, 1H, d): Aromatic proton of the phenyl ring (position 13).
- Peak 5 (4.070 ppm, 2H, t): CH₂ protons adjacent to the nitrogen atom (positions 5 and 6).
- Peak 6 (3.662 ppm, 2H, t): CH₂ protons adjacent to the carbonyl group (positions 7 and 8).
- Peak 7 (3.344 ppm, 2H, t): CH₂ protons adjacent to the carbonyl group (positions 9 and 10).
- Peak 8 (3.155 ppm, 2H, t): CH₂ protons adjacent to the carbonyl group (positions 11 and 12).
- Peak 9 (2.870 ppm, 3H, s): Methyl protons of the tert-butyl group (position 13).
- Peak 10 (2.320 ppm, 3H, s): Methyl protons of the tert-butyl group (position 13).
- Peak 11 (1.443 ppm, 9H, s): Methyl protons of the tert-butyl group (position 13).

The spectrum shows a complex pattern of peaks, with the most prominent signals being the aromatic protons (peaks 2, 3, and 4) and the aliphatic protons (peaks 5, 6, 7, 8, 9, 10, 11, 12, and 13).

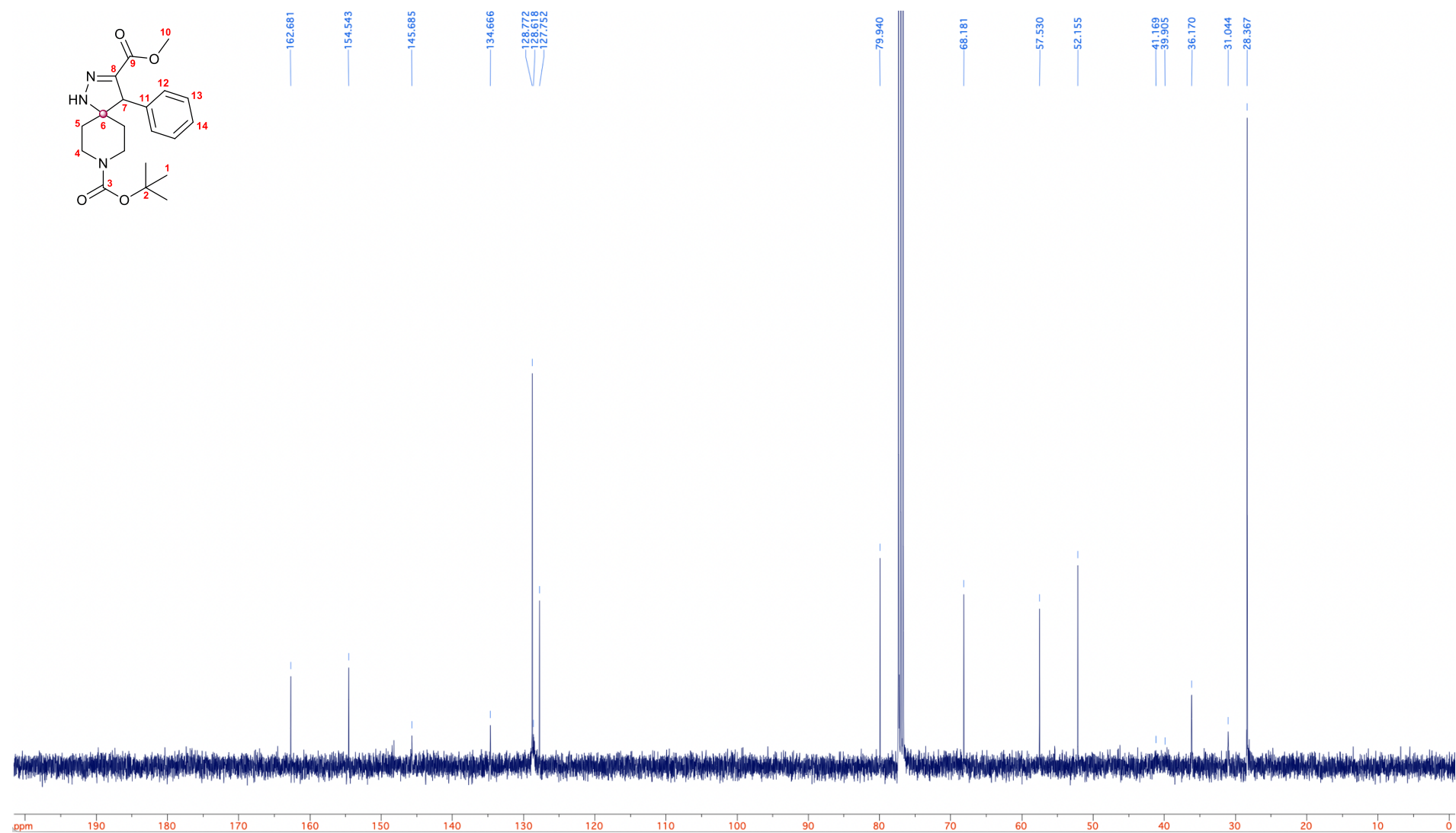
Compound **5n** ^{13}C NMR (100 MHz, CDCl_3)



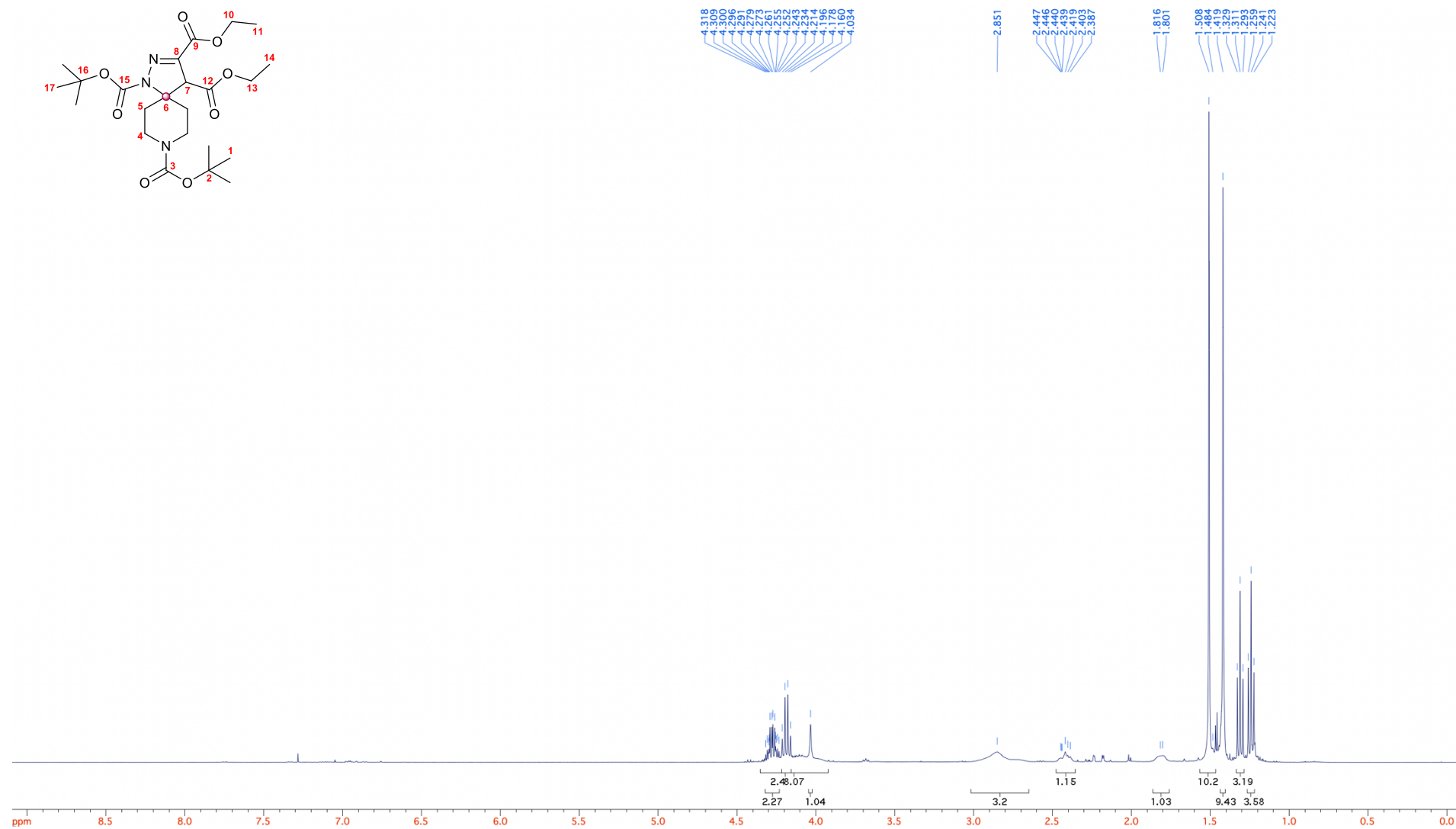
Compound **5o** ^1H NMR (400 MHz, CDCl_3)



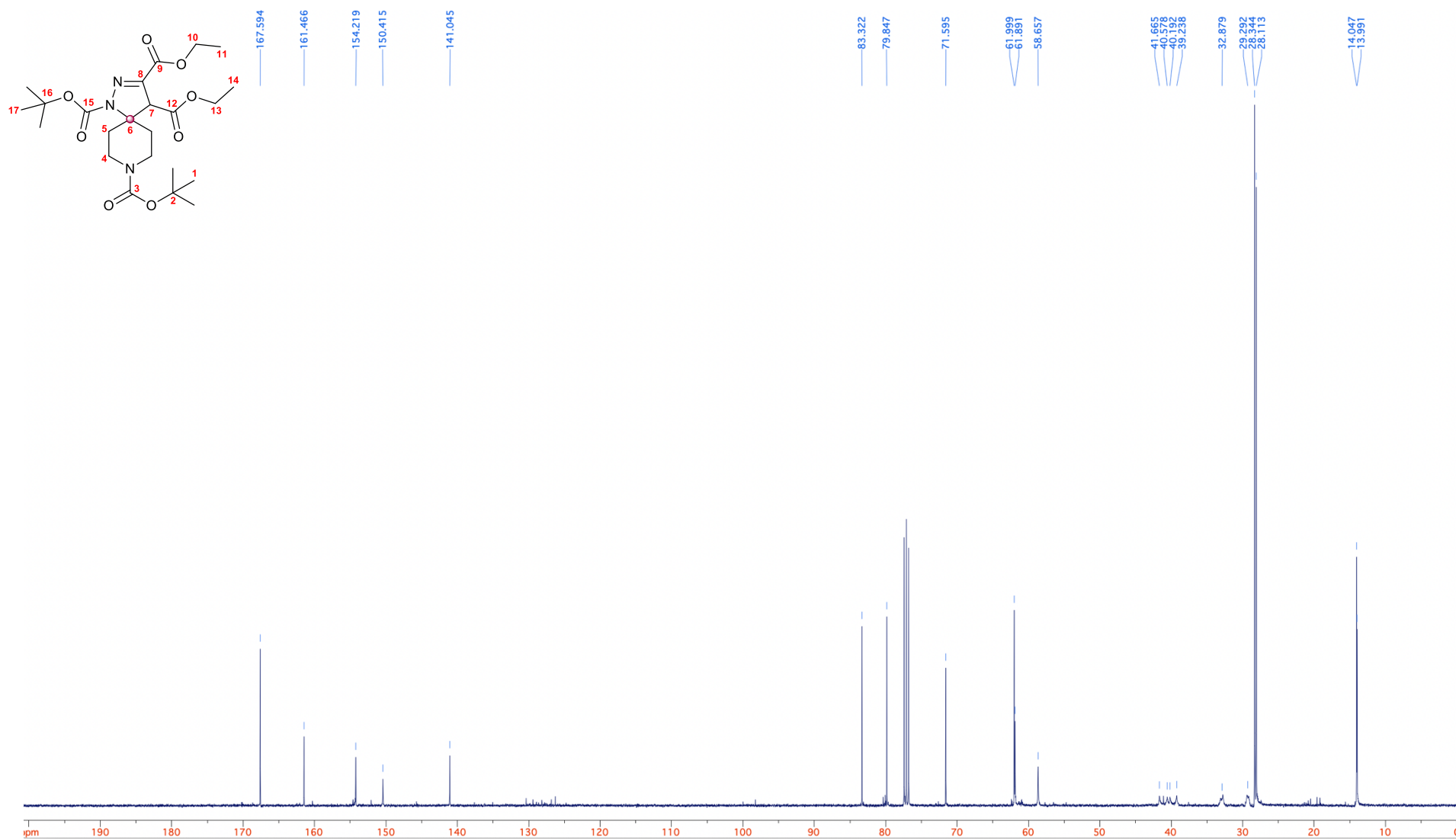
Compound **5o** ^{13}C NMR (100 MHz, CDCl_3)



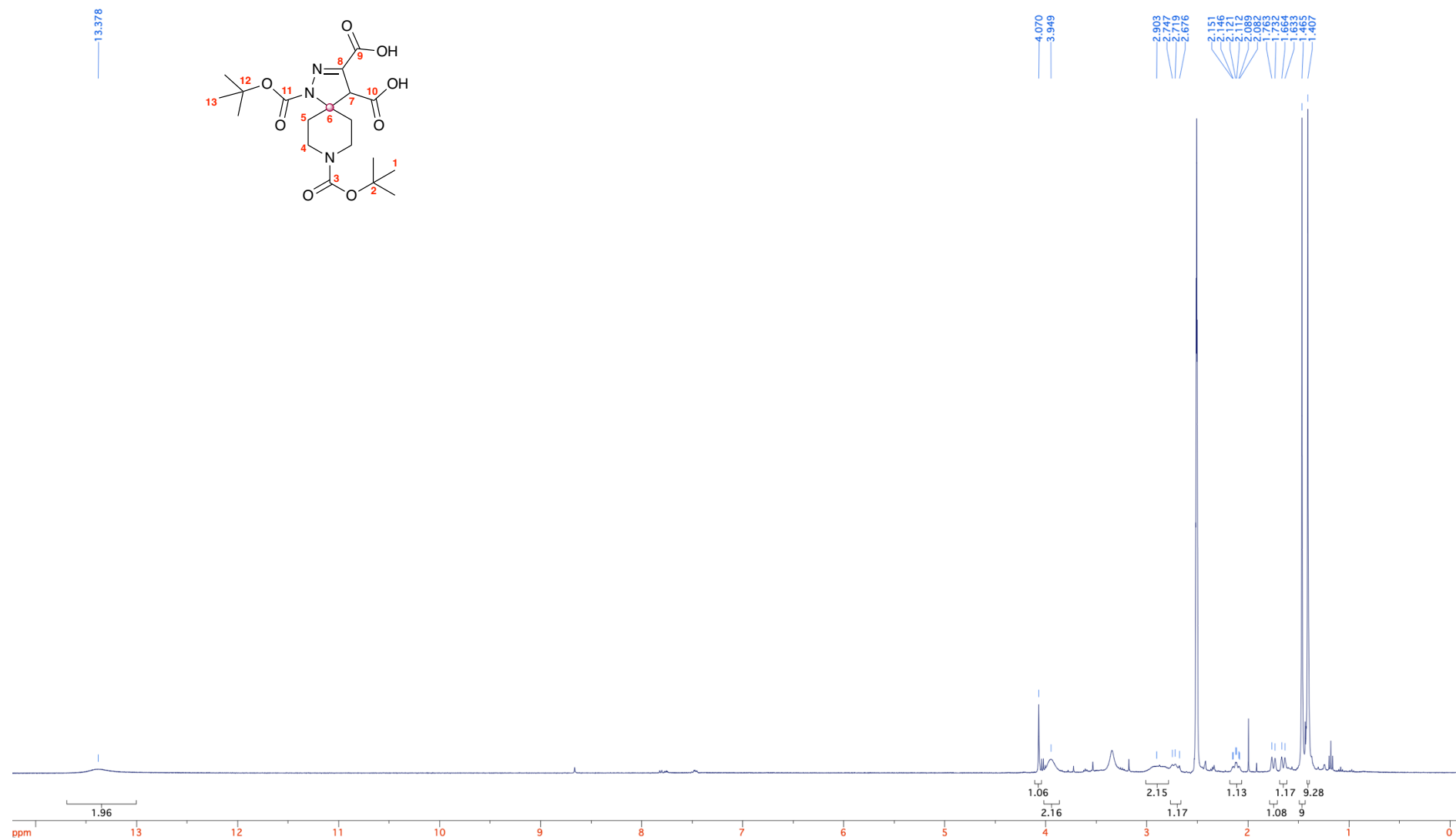
Compound **6** ^1H NMR (400 MHz, CDCl_3)



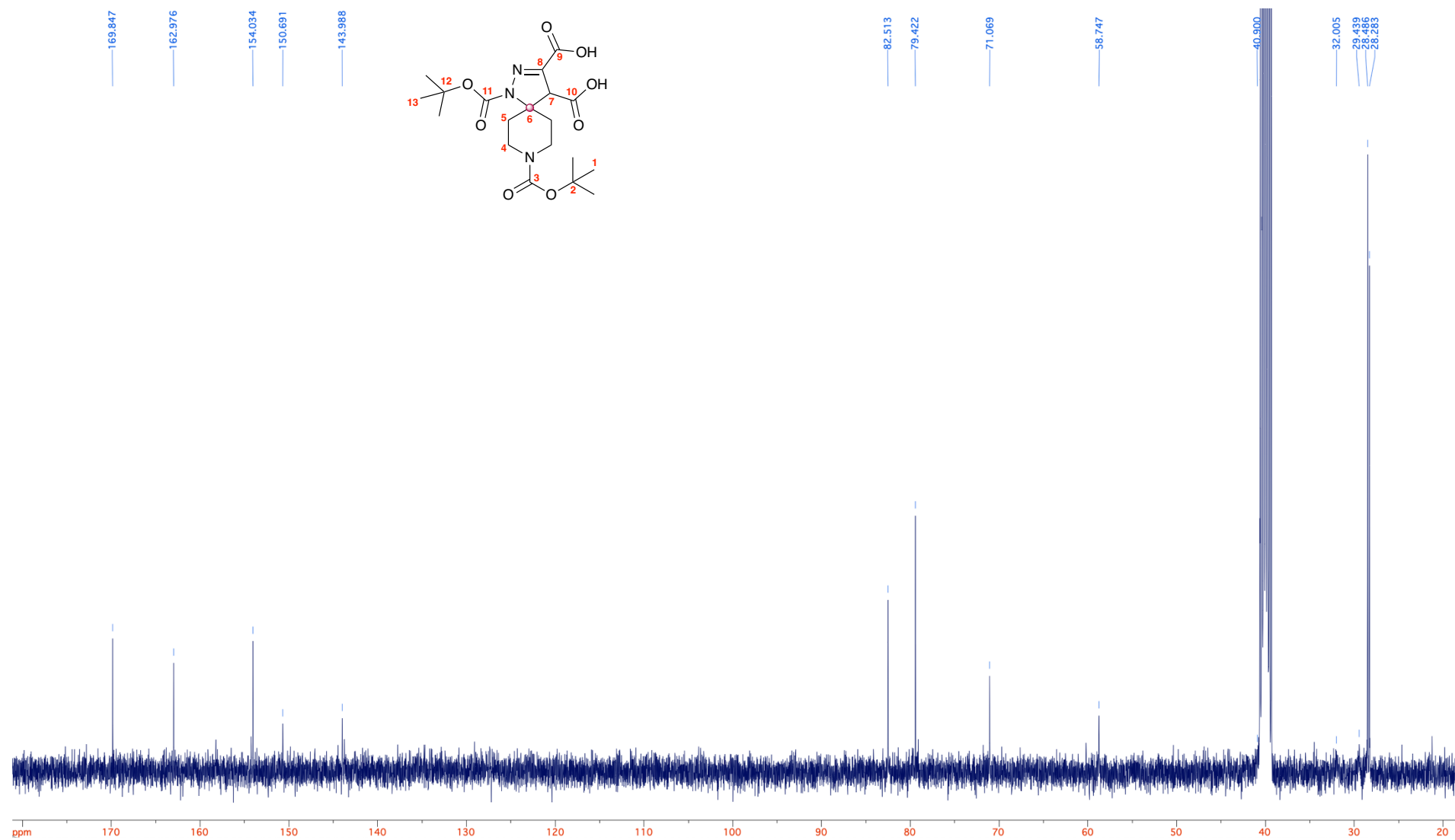
Compound **6** ^{13}C NMR (100 MHz, CDCl_3)



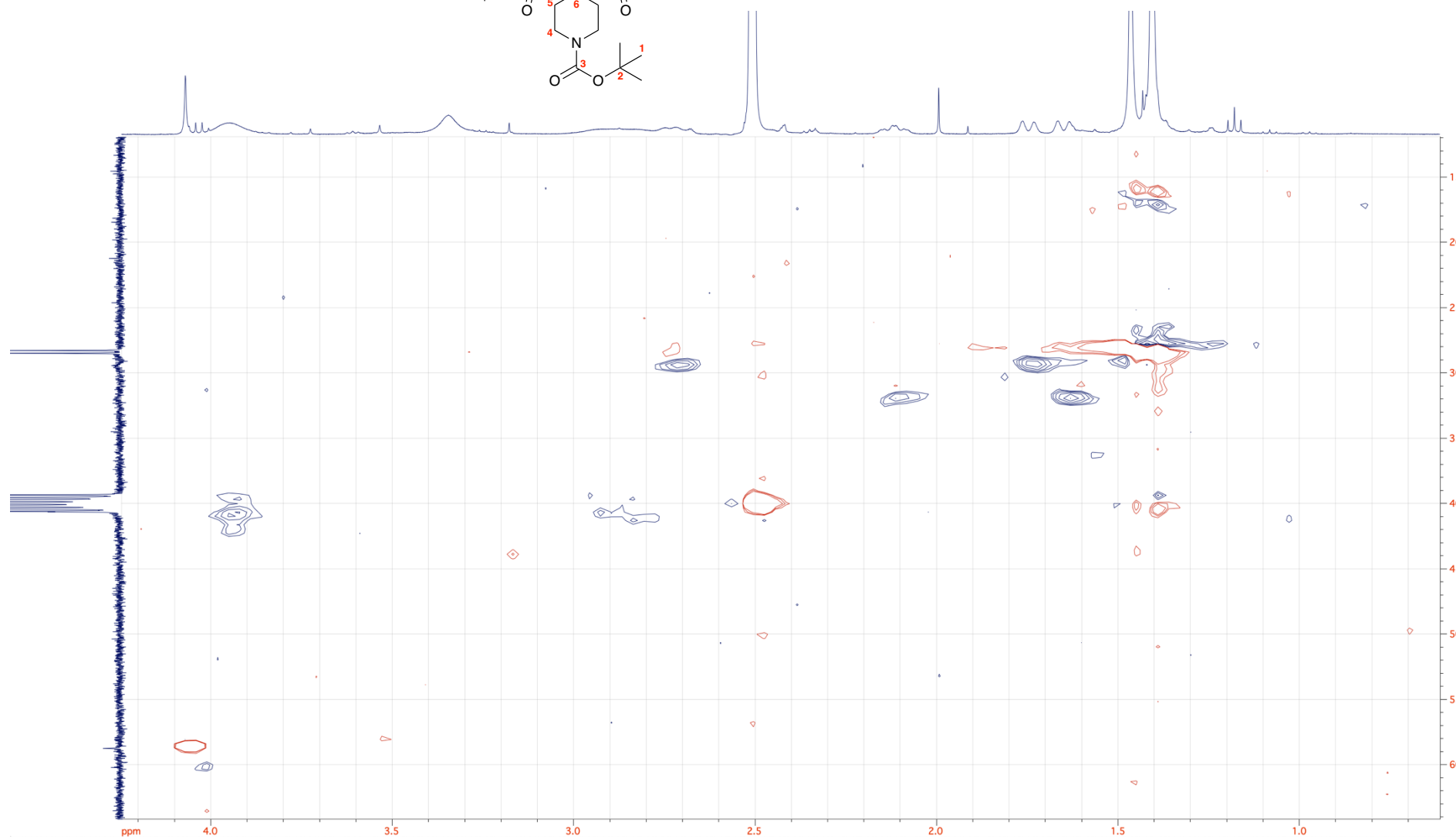
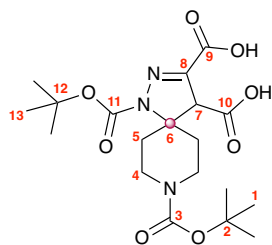
Compound **7** ^1H NMR (400 MHz, d_6 -DMSO)



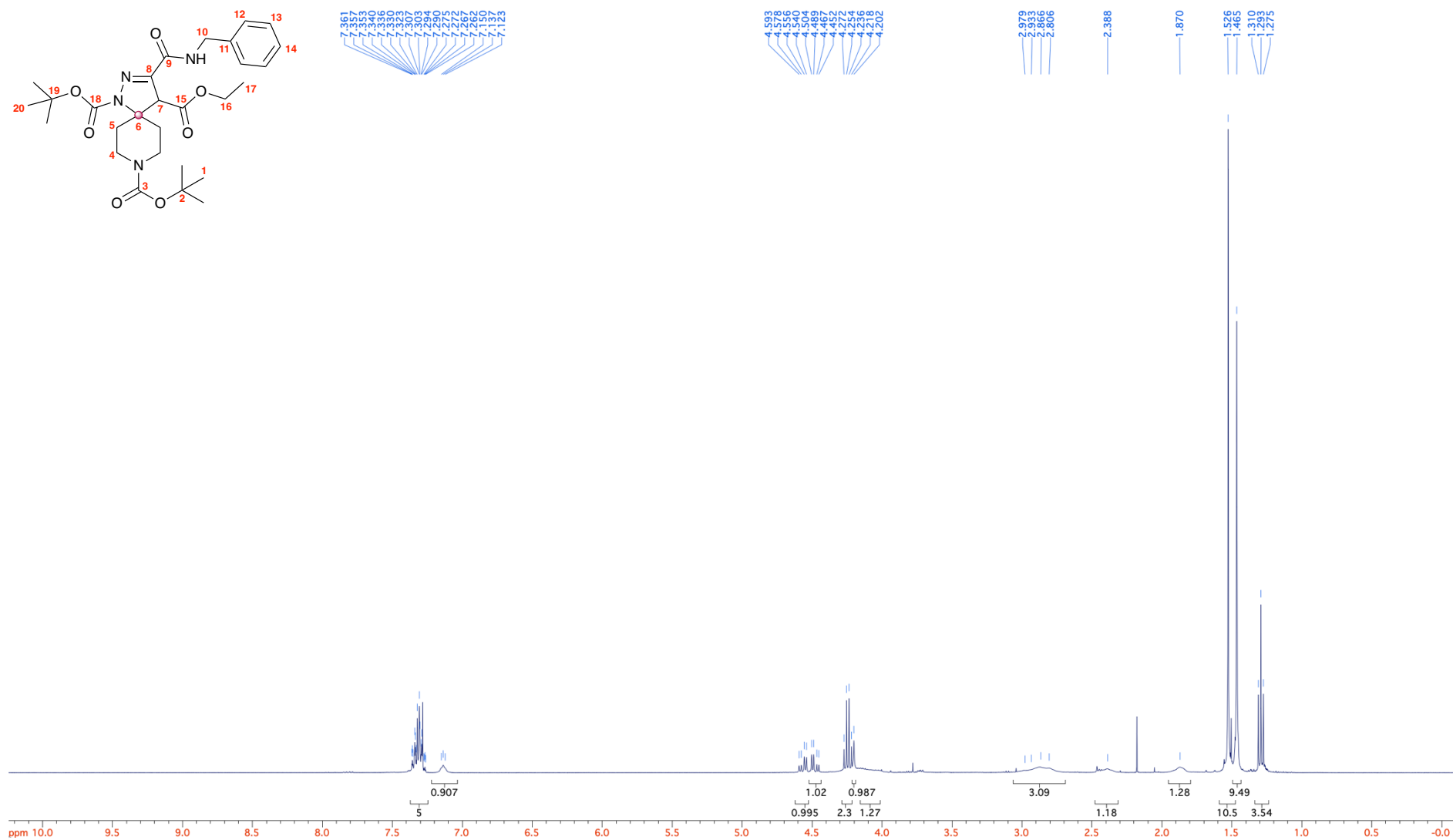
Compound 7 ^{13}C NMR (100 MHz, d_6 -DMSO)



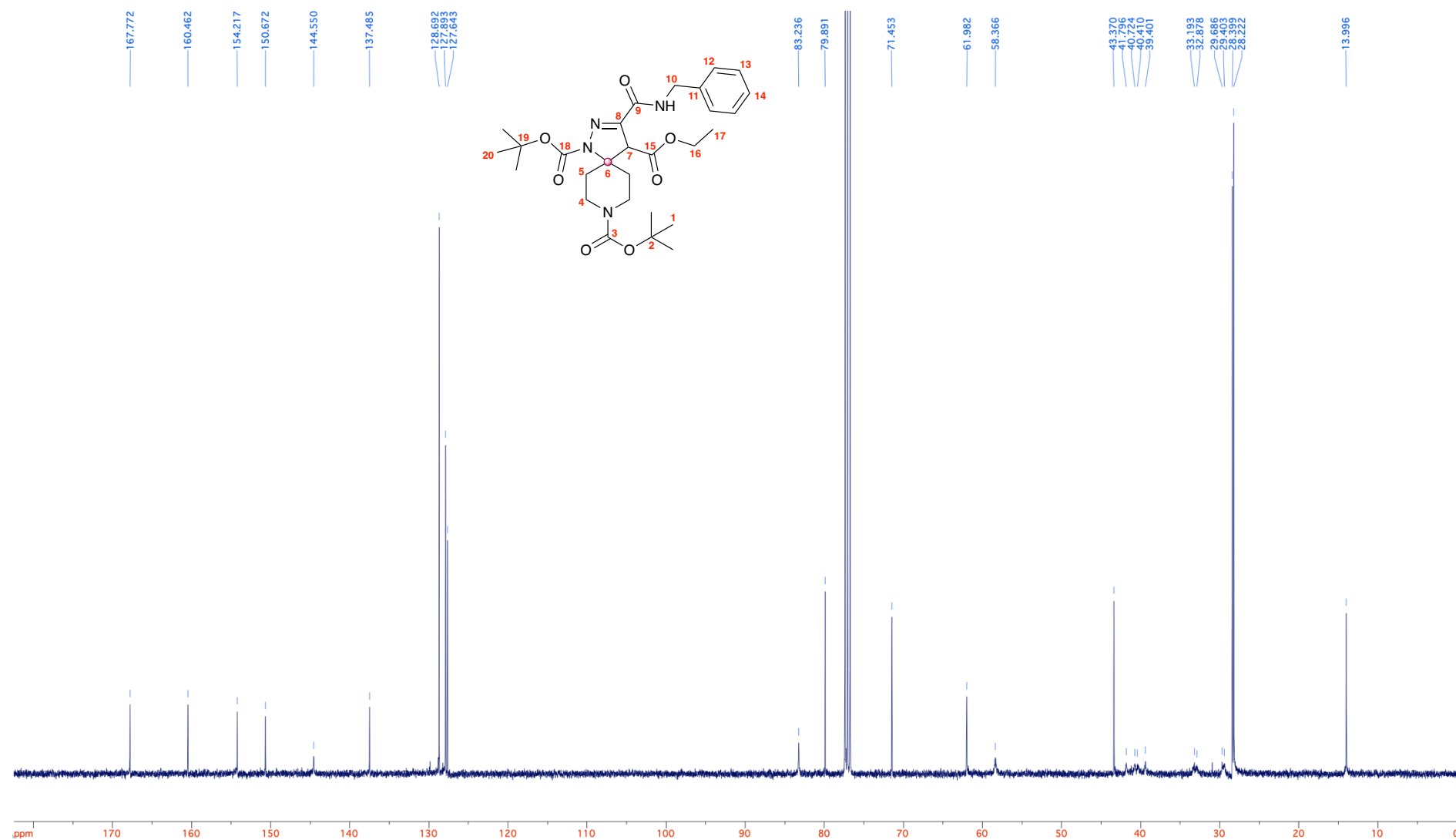
Compound 7 HSQC (400/100 MHz, *d*₆-DMSO)



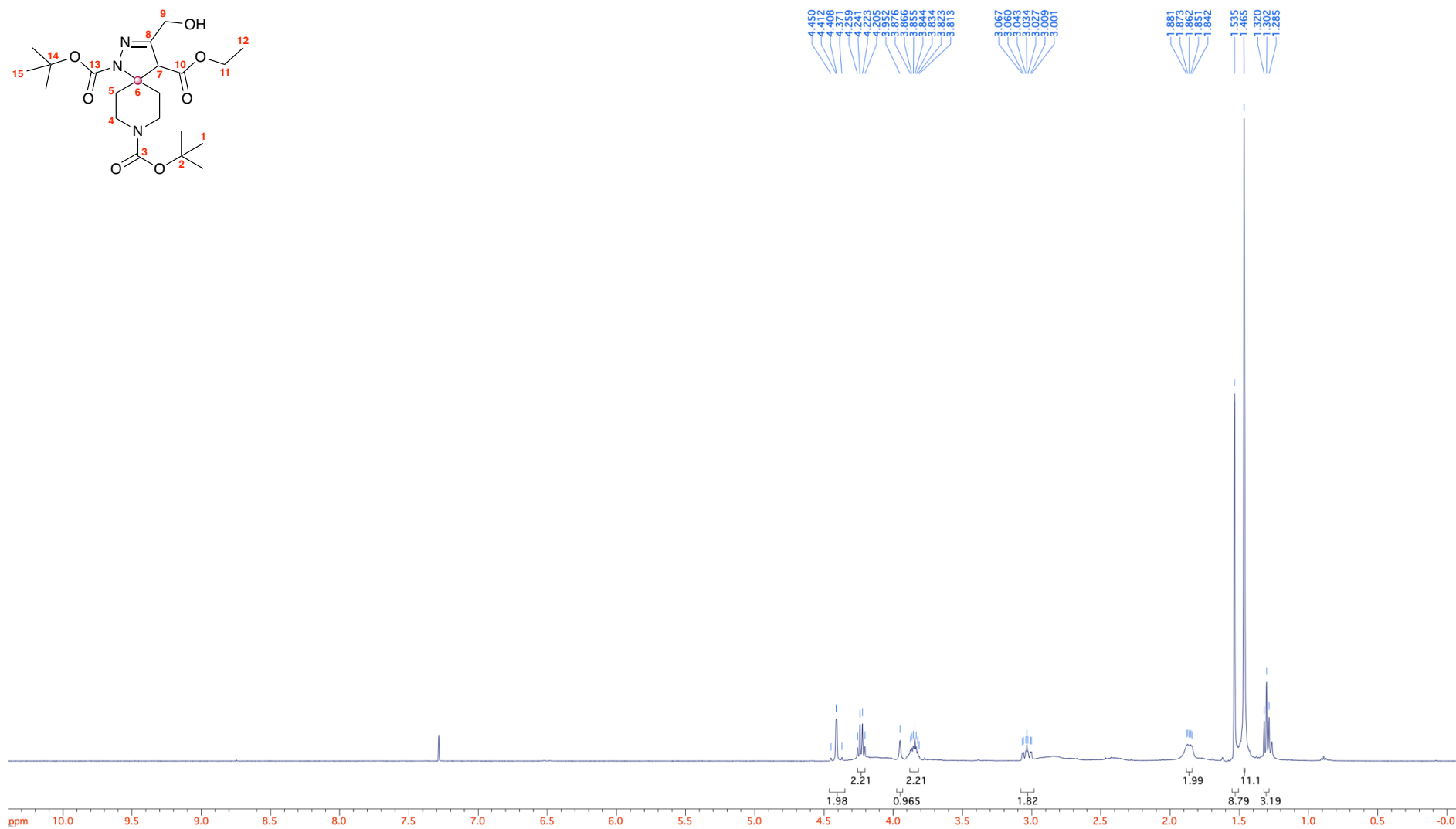
Compound **8** ^1H NMR (400 MHz, CDCl_3)



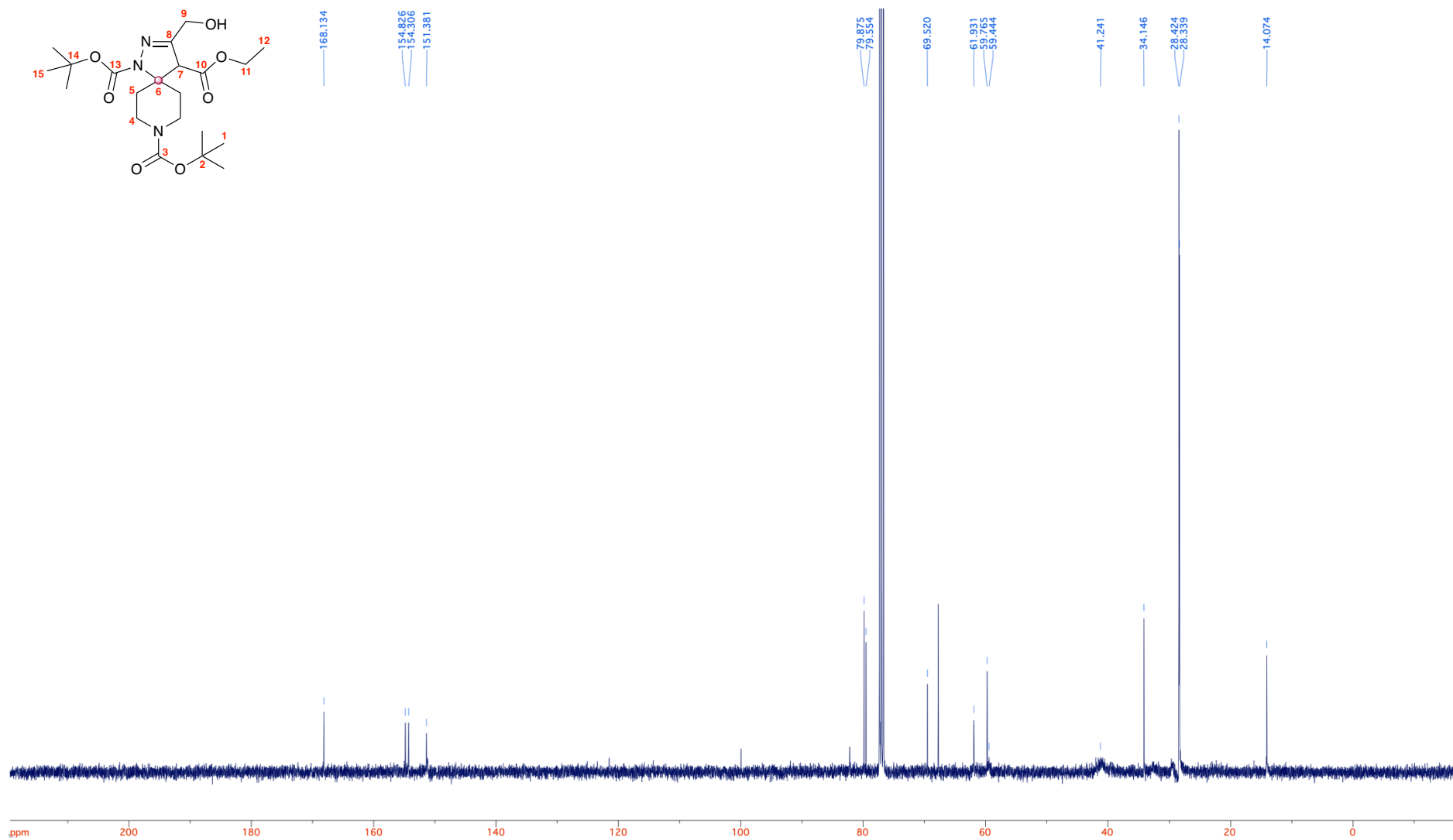
Compound **8** ^{13}C NMR (100 MHz, CDCl_3)



Compound **9** ^1H NMR (400 MHz, CDCl_3)



Compound **9** ^{13}C NMR (100 MHz, CDCl_3)



7. SI References

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