Supporting Information

Oxa-spirocycles: synthesis, properties and applications

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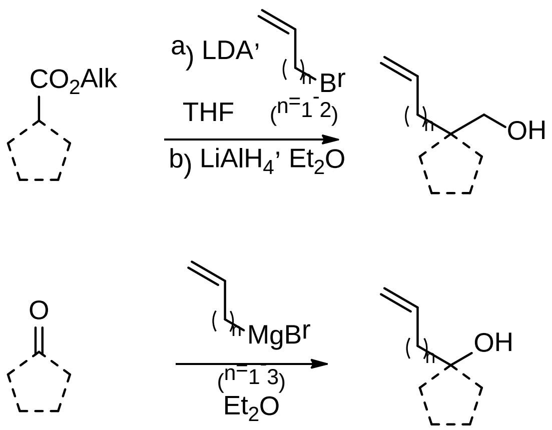
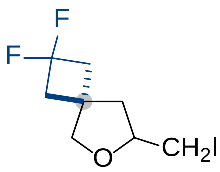
Experimental Section. Data description and procedures

General Considerations. All chemicals were provided by Enamine Ltd. (www.enamine.net). All solvents were treated according to standard methods. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. Product purification was performed using silica gel column chromatography. TLC-characterization was performed with pre-coated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100-200 mesh). ^{1}H-NMR spectra were recorded at 400, 500 or 600 MHz (Varian); ^{19}F-NMR spectra were recorded at 376 MHz (Varian) and ^{13}C NMR spectra were recorded at 100, 126 or 151 MHz (Varian). ^{1}H-NMR chemical shifts are calibrated using residual undeuterated solvents $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). ^{13}C-NMR chemical shifts for ^{13}C-NMR are reported relative to the central $CHCl_3$ (δ = 77.16 ppm) or DMSO (δ = 39.52 ppm). Coupling constants are given in Hz. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments.

All starting materials for iodocyclization were taken from stock at Enamine Ltd. (www.enamine.net). >80% of them could be obtained following these sequences:

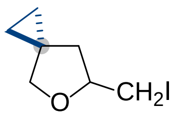


General procedure A for synthesis 4a-31a (**4a** as an example. Scale: 0.1 mol for all derivatives). *Note*: Boc-derivatives **8a**, **10a**, **14a**, **16a**, **17a**, **21a** and **29a** were purified via column chromatography; eluent: hexane.



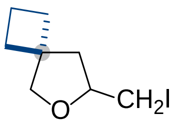
2,2-Difluoro-7-(iodomethyl)-6-oxaspiro[3.4]octane (4a)

In a flask fitted with a magnetic bar, (16.2 g, 0.1 mol, 1.0 equiv) of alcohol was dissolved in 150 mL of dry CH_3CN under an argon atmosphere, and (25.2 g, 0.3 mol, 3.0 equiv) of $NaHCO_3$ was added. The resulting mixture was stirred at room temperature for 5 min and cooled to 0 °C, then I_2 (76.2 g, 0.3 mol, 3.0 equiv) was added. The reaction mixture was left to warm to room temperature for 1 h. The mixture was diluted with MTBE and washed with a 10% sodium thiosulfate solution until the color disappeared. The aqueous layer was extracted several times with MTBE. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The final product was purified by distillation. Yield: 26.2 g, 91%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.11 – 4.00 (m, 1H), 3.93 (d, *J* = 8.7 Hz, 1H), 3.85 (d, *J* = 8.7 Hz, 1H), 3.31 – 3.17 (m, 2H), 2.69 – 2.48 (m, 4H), 2.28 (dd, *J* = 12.9, 6.6 Hz, 1H), 1.86 (dd, *J* = 12.8, 8.0 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 119.0 (t, *J* = 278.2 Hz), 78.6 (dd, *J* = 5.3, 2.0 Hz), 78.3, 46.0 (t, *J* = 22.6 Hz), 45.0 (d, *J* = 3.4 Hz), 43.8 (t, *J* = 23.1 Hz), 35.6 (t, *J* = 9.9 Hz), 9.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -91.5 (dd, *J* = 538.9, 196.2 Hz) ppm. GCMS (M): 288. HRMS (ESI): calc'd for $C_8H_{12}F_2IO$ $[M+H]^+$ 288.9901; found 288.9905.



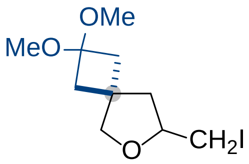
6-(Iodomethyl)-5-oxaspiro[2.4]heptane (5a)

General procedure A was used. Yield: 19.5 g, 82%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.30 – 4.16 (m, 1H), 3.82 (d, *J* = 8.0 Hz, 1H), 3.68 (d, *J* = 8.0 Hz, 1H), 3.39 – 3.17 (m, 2H), 2.01 (dd, *J* = 12.4, 6.6 Hz, 1H), 1.81 (dd, *J* = 12.4, 6.8 Hz, 1H), 0.73 – 0.46 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 79.5, 75.9, 41.1, 22.5, 10.8, 10.4, 10.1 ppm. GCMS (M): 238. HRMS (ESI): calc'd for $C_7H_{12}IO$ $[M+H]^+$ 238.9933; found 238.9930.



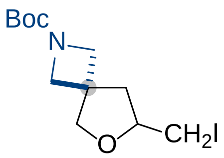
7-(Iodomethyl)-6-oxaspiro[3.4]octane (6a)

General procedure A was used. Yield: 23.2 g, 92%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.11 – 3.94 (m, 1H), 3.91 – 3.69 (m, 2H), 3.21 (qd, *J* = 9.8, 6.1 Hz, 2H), 2.20 (dd, *J* = 12.5, 6.4 Hz, 1H), 2.07 – 1.48 (m, 7H), 1.70 (dd, *J* = 12.5, 7.9 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 79.7, 78.4, 46.6, 45.6, 33.1, 30.9, 16.6, 10.6 ppm. GCMS (M): 252. HRMS (ESI): calc'd for $C_8H_{14}IO$ $[M+H]^+$ 253.0089; found 253.0082.



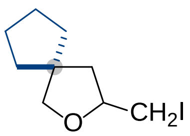
7-(Iodomethyl)-2,2-dimethoxy-6-oxaspiro[3.4]octane (7a)

General procedure A was used. Yield: 23.4 g, 75%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.10 – 3.96 (m, 1H), 3.86 (d, *J* = 8.5 Hz, 1H), 3.80 (d, *J* = 8.5 Hz, 1H), 3.27 – 3.18 (m, 2H), 3.14 (s, 3H), 3.12 (s, 3H), 2.26 – 2.07 (m, 5H), 1.77 (dd, *J* = 12.7, 7.9 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 99.4, 79.6, 78.4, 48.7, 48.7, 45.8, 42.8, 40.7, 37.1, 10.3 ppm. HRMS (ESI): calc'd for $C_{10}H_{18}IO_3$ $[M+H]^+$ 313.0301; found 313.0307.



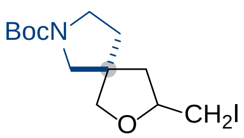
***Tert*-butyl 7-(iodomethyl)-6-oxa-2-azaspiro[3.4]octane-2-carboxylate (8a)**

General procedure A was used. Yield: 29.3 g, 83%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.05 – 3.98 (m, 2H), 3.95 – 3.82 (m, 5H), 3.26 – 3.15 (m, 2H), 2.34 (dd, *J* = 13.0, 6.7 Hz, 1H), 1.92 (dd, *J* = 13.0, 7.7 Hz, 1H), 1.43 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.3, 79.9, 78.3, 77.8, 59.7 (br s), 58.2 (br s), 43.8, 41.0, 28.5, 9.7 ppm. LCMS $(M+H)^+$: 354. HRMS (ESI): calc'd for $C_{12}H_{21}INO_3$ $[M+H]^+$ 354.0566; found 354.0560.



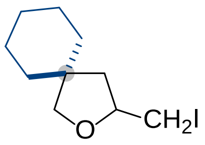
3-(Iodomethyl)-2-oxaspiro[4.4]nonane (9a)

General procedure A was used. Yield: 24.7 g, 93%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.16 – 3.98 (m, 1H), 3.71 (d, *J* = 8.0 Hz, 1H), 3.63 (d, *J* = 8.0 Hz, 1H), 3.34 – 3.12 (m, 2H), 2.04 (dd, *J* = 12.3, 6.4 Hz, 1H), 1.86 – 1.26 (m, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 79.4, 78.8, 51.6, 45.8, 37.8, 36.2, 24.9, 10.9 ppm. GCMS (M): 266. HRMS (ESI): calc'd for $C_9H_{16}IO$ $[M+H]^+$ 267.0246; found 267.0244.



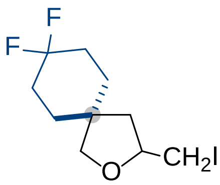
***Tert*-butyl-3-(iodomethyl)-2-oxa-7-azaspiro[4.4]nonane-7-carboxylate (10a)**

General procedure A was used. Yield: 30 g, 82%, yellow oil. Mixture of stereoisomers (d.r. = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.17 – 4.02 (m, 1H), 3.87 – 3.76 (m, 1H), 3.76 – 3.65 (m, 1H), 3.48 – 3.13 (m, 6H), 2.21 – 2.06 (m, 1H), 1.97 – 1.78 (m, 2H), 1.74 – 1.57 (m, 1H), 1.45 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.7, 154.6, 79.6, 78.5, 78.4, 76.8, 55.5 (br s), 50.2 (br s), 45.2, 45.1, 43.0, 42.8, 28.6, 10.1, 9.8 ppm. HRMS (ESI): calc'd for $C_{13}H_{23}INO_3$ $[M+H]^+$ 368.0723; found 368.0727.



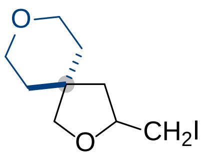
3-(Iodomethyl)-2-oxaspiro[4.5]decane (11a)

General procedure A was used. Yield: 26.6 g, 95%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.13 – 3.99 (m, 1H), 3.71 – 3.58 (m, 2H), 3.31 – 3.15 (m, 2H), 2.01 (dd, *J* = 12.6, 6.6 Hz, 1H), 1.49 – 1.36 (m, 11H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 79.0, 78.2, 44.9, 44.7, 36.5, 35.6, 26.1, 24.2, 23.5, 10.9 ppm. GCMS (M): 280. HRMS (ESI): calc'd for $C_{10}H_{18}IO$ $[M+H]^+$ 281.0402; found 281.0400.



8,8-Difluoro-3-(iodomethyl)-2-oxaspiro[4.5]decane (12a)

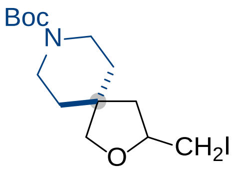
General procedure A was used. Yield: 29.4 g, 93%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 – 4.01 (m, 1H), 3.74 (d, *J* = 8.6 Hz, 1H), 3.68 (d, *J* = 8.8 Hz, 1H), 3.33 – 3.19 (m, 2H), 2.06 (dd, *J* = 12.7, 6.7 Hz, 1H), 2.00 – 1.78 (m, 4H), 1.77 – 1.63 (m, 4H), 1.47 (dd, *J* = 12.7, 8.6 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 123.1 (t, *J* = 241.0 Hz), 78.1, 77.8, 43.5, 43.5, 32.2 (t, *J* = 4.8 Hz), 31.9 (t, *J* = 24.3 Hz), 31.3 (t, *J* = 6.6 Hz), 31.3 (t, *J* = 24.4 Hz), 10.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -98.2 (s) ppm. GCMS (M): 316. HRMS (ESI): calc'd for $C_{10}H_{16}F_2IO$ $[M+H]^+$ 317.0214; found 317.0218.



3-(Iodomethyl)-2,8-dioxaspiro[4.5]decane (13a)

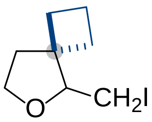
General procedure A was used. Yield: 24.5 g, 87%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 – 4.00 (m, 1H), 3.73 (s, 2H), 3.69 – 3.58 (m, 4H), 3.29 – 3.18 (m, 2H), 2.12 (dd, *J* = 12.7, 6.6

Hz, 1H), 1.66 – 1.52 (m, 4H), 1.47 (dd, J = 12.7, 8.6 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 78.4, 78.0, 65.8, 65.4, 44.4, 42.3, 36.2, 35.7, 10.5 ppm. GCMS (M): 282. HRMS (ESI): calc'd for $C_9H_{16}IO_2$ [M+H]$^+$ 283.0195; found 283.0190.



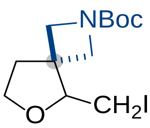
***Tert*-butyl 3-(iodomethyl)-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (14a)**

General procedure A was used. Yield: 34.7 g, 91%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.13 – 4.01 (m, 1H), 3.76 – 3.64 (m, 2H), 3.47 – 3.22 (m, 6H), 2.06 (dd, J = 12.7, 6.7 Hz, 1H), 1.59 – 1.50 (m, 4H), 1.47 – 1.39 (m, 10H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.9, 79.7, 78.1, 78.0, 43.8, 43.2, 41.9, 41.3, 35.4, 34.7, 28.6, 10.4 ppm. HRMS (ESI): calc'd for $C_{14}H_{25}INO_3$ [M+H]$^+$ 382.0879; found 382.0875.



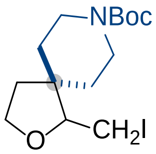
5-(Iodomethyl)-6-oxaspiro[3.4]octane (15a)

General procedure A was used. Yield: 14.9 g, 59%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.92 – 3.79 (m, 2H), 3.78 – 3.67 (m, 1H), 3.32 (dd, J = 10.3, 3.7 Hz, 1H), 3.05 (dd, J = 10.1, 8.6 Hz, 1H), 2.22 – 1.73 (m, 8H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 85.5, 65.8, 48.7, 39.5, 33.2, 28.0, 16.8, 7.3 ppm. GCMS (M): 252. HRMS (ESI): calc'd for $C_8H_{14}IO$ [M+H]$^+$ 253.0089; found 253.0093.



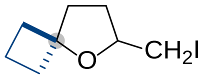
***Tert*-butyl 5-(iodomethyl)-6-oxa-2-azaspiro[3.4]octane-2-carboxylate (16a)**

General procedure A was used. Yield: 22.2 g, 63%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.09 – 3.68 (m, 7H), 3.35 (dd, J = 10.6, 3.9 Hz, 1H), 3.16 (dd, J = 10.5, 7.6 Hz, 1H), 2.34 – 2.16 (m, 2H), 1.44 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.4, 83.6, 80.0, 65.8, 59.9, 55.0, 43.4, 39.1, 28.5, 5.2 ppm. GCMS (M): 353. HRMS (ESI): calc'd for $C_{12}H_{21}INO_3$ [M+H]$^+$ 354.566; found 354.0564.



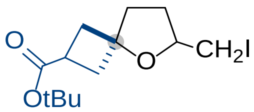
***Tert*-butyl 1-(iodomethyl)-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (17a)**

General procedure A was used. Yield: 27.1 g, 71%, yellow solid, mp = 96-97 °C. ^{1}H NMR (400 MHz, CDC_3) δ = 4.06 – 3.82 (m, 4H), 3.72 (dd, *J* = 9.8, 2.9 Hz, 1H), 3.22 (dd, *J* = 10.4, 3.1 Hz, 1H), 3.09 (t, *J* = 10.1 Hz, 1H), 2.87 (t, *J* = 11.3 Hz, 2H), 2.08 – 1.98 (m, 1H), 1.88 – 1.77 (m, 1H), 1.62 – 1.54 (m, 1H), 1.50 – 1.33 (m, 12H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.8, 87.3, 79.8, 65.5, 44.6, 41.0, 34.8, 29.7, 28.6, 4.5 ppm. HRMS (ESI): calc'd for $C_{14}H_{25}INO_3$ $[M+H]^+$ 382.0879; found 382.0870.



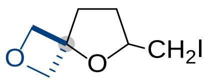
6-(Iodomethyl)-5-oxaspiro[3.4]octane (18a)

General procedure A was used. Yield: 21.9 g, 87%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.10 – 3.96 (m, 1H), 3.25 (dd, *J* = 9.8, 4.5 Hz, 1H), 3.09 (dd, *J* = 9.7, 7.7 Hz, 1H), 2.31 – 2.17 (m, 2H), 2.18 – 1.88 (m, 5H), 1.76 – 1.62 (m, 2H), 1.56 – 1.42 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 84.5, 78.4, 36.9, 36.7, 35.8, 31.5, 12.7, 11.3 ppm. GCMS (M): 252. HRMS (ESI): calc'd for $C_8H_{14}IO$ $[M+H]^+$ 253.0089; found 253.0086.



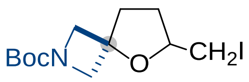
***Tert*-butyl 6-(iodomethyl)-5-oxaspiro[3.4]octane-2-carboxylate (19a)**

General procedure A was used. Yield: 24.3 g, 69%, yellow oil. Mixture of stereoisomers (d.r. = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.08 – 3.93 (m, 1H), 3.25 (dd, *J* = 9.8, 4.2 Hz, 1H), 3.14 – 3.05 (m, 1H), 2.57 – 2.39 (m, 3H), 2.28 – 1.87 (m, 5H), 1.75 – 1.63 (m, 1H), 1.44, 1.42 (2×s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 175.3, 173.8, 83.3, 80.4, 80.0, 78.6, 78.4, 40.5, 39.29, 39.25, 38.4, 37.8, 36.7, 31.6, 31.5, 31.3, 30.6, 28.2, 11.1 ppm. HRMS (ESI): calc'd for $C_{13}H_{22}IO_3$ $[M+H]^+$ 353.0614; found 353.0610.



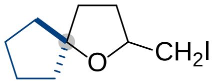
6-(Iodomethyl)-2,5-dioxaspiro[3.4]octane (20a)

General procedure A was used. Yield: 11.4 g, 45%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.79 (t, *J* = 7.0 Hz, 2H), 4.50 (d, *J* = 6.6 Hz, 2H), 4.06 – 3.93 (m, 1H), 3.25 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.15 (dd, J = 10.1, 6.8 Hz, 1H), 2.43 – 2.28 (m, 1H), 2.24 – 2.05 (m, 2H), 1.79 – 1.61 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 84.7, 83.5, 83.3, 79.0, 35.4, 31.6, 10.6 ppm. HRMS (ESI): calc'd for $C_7H_{12}IO_2$ $[M+H]^+$ 254.9882; found 254.9885.



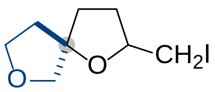
Tert-butyl 6-(iodomethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (21a)

General procedure A was used. Yield: 26.1 g, 74%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.10 – 3.96 (m, 3H), 3.83 (dd, J = 9.0, 2.8 Hz, 2H), 3.26 (dd, J = 10.1, 4.4 Hz, 1H), 3.16 (dd, J = 10.1, 6.8 Hz, 1H), 2.28 – 2.01 (m, 3H), 1.80 – 1.64 (m, 1H), 1.42 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.5, 79.7, 79.2, 79.1, 62.9, 61.9, 36.2, 31.7, 28.5, 10.3 ppm. HRMS (ESI): calc'd for $C_{12}H_{21}INO_3$ $[M+H]^+$ 354.0566; found 354.0560.



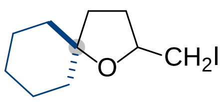
2-(Iodomethyl)-1-oxaspiro[4.4]nonane (22a)

General procedure A was used. Yield: 24.5 g, 92%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.24 – 4.04 (m, 1H), 3.43 (dd, J = 9.9, 4.5 Hz, 1H), 3.29 (dd, J = 9.8, 7.3 Hz, 1H), 2.23 – 2.04 (m, 1H), 1.91 – 1.66 (m, 7H), 1.67 – 1.49 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 92.8, 77.6, 39.1, 38.4, 36.4, 36.4, 31.0, 24.2 ppm. HRMS (ESI): calc'd for $C_9H_{16}IO$ $[M+H]^+$ 267.0246; found 267.0249.



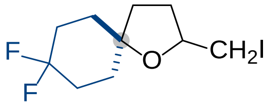
2-(Iodomethyl)-1,7-dioxaspiro[4.4]nonane (23a)

General procedure A was used. Yield: 21.2 g, 81%, brown oil. Mixture of stereoisomers (d.r. = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.27 – 4.14 (m, 1H), 4.01 – 3.83 (m, 2H), 3.83 – 3.73 (m, 1H), 3.60 (dd, J = 41.3, 9.2 Hz, 1H), 3.51 – 3.41 (m, 1H), 3.39 – 3.26 (m, 1H), 2.24 – 1.73 (m, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 90.7, 90.65, 78.1, 78.0, 77.5, 77.1, 68.0, 39.3, 38.8, 35.9, 35.8, 34.0, 33.5, 30.8, 30.7 ppm. HRMS (ESI): calc'd for $C_8H_{14}IO_2$ $[M+H]^+$ 269.0038; found 269.0031.



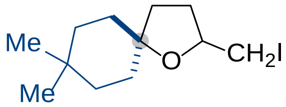
2-(Iodomethyl)-1-oxaspiro[4.5]decane (24a)

General procedure A was used. Yield: 25.2 g, 90%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.25 – 4.13 (m, 1H), 3.44 (dd, J = 9.9, 4.5 Hz, 1H), 3.29 (dd, J = 9.9, 7.3 Hz, 1H), 2.17 – 2.03 (m, 1H), 1.87 – 1.61 (m, 5H), 1.60 – 1.45 (m, 4H), 1.42 – 1.22 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 83.8, 76.8, 38.0, 36.9, 35.9, 35.0, 29.8, 25.1, 23.5, 23.3 ppm. HRMS (ESI): calc'd for $C_{10}H_{18}IO$ [M+H]$^+$ 281.0402; found 281.0407.



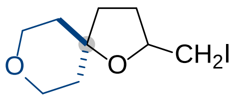
8,8-Difluoro-2-(iodomethyl)-1-oxaspiro[4.5]decane (25a)

General procedure A was used. Yield: 26.9 g, 85%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.04 – 3.86 (m, 1H), 3.28 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.19 (dd, *J* = 9.9, 6.8 Hz, 1H), 2.28 – 2.01 (m, 3H), 1.95 – 1.58 (m, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 123.6 (dd, *J* = 242.3, 239.1 Hz), 81.7, 77.8, 36.6, 34.5 (d, *J* = 8.2 Hz), 33.4 (d, *J* = 8.6 Hz), 31.8, 30.8 (t, *J* = 24.4 Hz), 11.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -94.1 (d, *J* = 238.1 Hz), -103.4 (d, *J* = 233.7 Hz) ppm. GCMS (M): 316. HRMS (ESI): calc'd for $C_{10}H_{16}F_2IO$ [M+H]$^+$ 317.0214; found 317.0210.



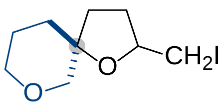
2-(Iodomethyl)-8,8-dimethyl-1-oxaspiro[4.5]decane (26a)

General procedure A was used. Yield: 27.1 g, 88%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.04 – 3.94 (m, 1H), 3.29 (dd, *J* = 9.7, 4.1 Hz, 1H), 3.13 (dd, *J* = 9.7, 7.7 Hz, 1H), 2.20 – 2.01 (m, 1H), 1.85 – 1.38 (m, 9H), 1.28 – 1.11 (m, 2H), 0.92 (s, 3H), 0.88 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 84.6, 77.5, 36.8, 36.6, 35.8, 34.7, 33.6, 31.9, 29.7, 28.4 (br s), 11.9 ppm. GCMS (M): 308. HRMS (ESI): calc'd for $C_{12}H_{22}IO$ [M+H]$^+$ 309.0715; found 309.0711.



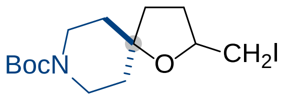
2-(Iodomethyl)-1,8-dioxaspiro[4.5]decane (27a)

General procedure A was used. Yield: 22.8 g, 81%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.26 – 4.16 (m, 1H), 3.86 – 3.70 (m, 2H), 3.69 – 3.53 (m, 2H), 3.44 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.33 (dd, *J* = 10.0, 6.9 Hz, 1H), 2.19 – 2.03 (m, 1H), 1.92 – 1.72 (m, 3H), 1.71 – 1.55 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 80.4, 76.9, 64.9, 64.8, 38.0, 37.0, 35.9, 35.7, 29.3 ppm. HRMS (ESI): calc'd for $C_9H_{16}IO_2$ [M+H]$^+$ 283.0195; found 283.0197.



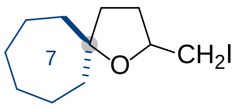
2-(Iodomethyl)-1,7-dioxaspiro[4.5]decane (28a)

General procedure A was used. Yield: 22.3 g, 79%, brown oil. Mixture of stereoisomers (d.r. = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.09 – 3.97 (m, 1H), 3.72 – 3.25 (m, 5H), 3.22 – 3.08 (m, 1H), 2.22 – 1.50 (m, 8H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 81.38, 81.35, 78.2, 78.1, 77.2, 75.2, 74.4, 67.9, 67.9, 35.9, 35.4, 34.1, 33.6, 31.9, 31.4, 24.3, 24.2, 11.4, 10.8 ppm. GCMS (M): 282. HRMS (ESI): calc'd for $C_9H_{16}IO_2$ $[M+H]^+$ 283.0195; found 283.0191.



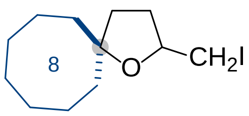
***Tert*-butyl 2-(iodomethyl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (29a)**

General procedure A was used. Yield: 35.8 g, 94%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.06 – 3.95 (m, 1H), 3.64 – 3.51 (m, 2H), 3.38 – 3.25 (m, 3H), 3.17 (dd, J = 9.9, 7.1 Hz, 1H), 2.23 – 2.10 (m, 1H), 1.84 – 1.48 (m, 7H), 1.44 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.0, 81.9, 79.5, 77.7, 41.3, 41.2, 37.8, 36.7, 36.6, 31.6, 28.6, 11.5 ppm. HRMS (ESI): calc'd for $C_{14}H_{25}INO_3$ $[M+H]^+$ 382.0879; found 382.0877.



2-(Iodomethyl)-1-oxaspiro[4.6]undecane (30a)

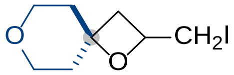
General procedure A was used. Yield: 27.9 g, 95%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.21 – 4.09 (m, 1H), 3.43 (dd, J = 9.9, 4.3 Hz, 1H), 3.29 (dd, J = 9.9, 7.2 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.78 – 1.31 (m, 14H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 88.1, 77.5, 41.6, 40.5, 37.7, 36.5, 30.3, 29.5, 29.5, 23.3, 23.0 ppm. HRMS (ESI): calc'd for $C_{11}H_{20}IO$ $[M+H]^+$ 295.0559; found 295.0555.



2-(Iodomethyl)-1-oxaspiro[4.7]dodecane (31a)

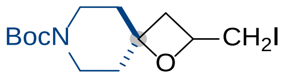
General procedure A was used. Yield: 29.6 g, 96%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.03 – 3.91 (m, 1H), 3.29 (dd, J = 9.6, 3.7 Hz, 1H), 3.18 – 3.04 (m, 1H), 2.19 – 2.04 (m, 1H), 1.85 – 1.40 (m, 17H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 88.2, 77.5, 37.0, 36.9, 35.9, 32.1, 28.5, 28.3, 24.8, 23.0, 22.7, 12.0 ppm. HRMS (ESI): calc'd for $C_{12}H_{22}IO$ $[M+H]^+$ 309.0715; found 309.0709.

General procedure B for synthesis 32a and **33a** (**32a** as an example)



2-(Iodomethyl)-1,7-dioxaspiro[3.5]nonane (32a)

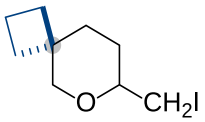
In a flask fitted with a magnetic bar, (10.6 g, 74.6 mmol, 1.0 equiv) of 4-allyltetrahydro-2*H*-pyran-4-ol was dissolved in 200 mL of dry CH_3CN under an argon atmosphere, and (18.8 g, 223.8 mmol, 3.0 equiv) of $NaHCO_3$ was added. The resulting mixture was stirred at room temperature for 5 min, cooled to 0 °C and covered from light, then I_2 (56.8 g, 223.8 mmol, 3.0 equiv) was added. The reaction mixture was left to warm to room temperature and stirred overnight. The mixture was diluted with MTBE and washed with a 10% sodium thiosulfate solution until the color disappeared. The aqueous layer was extracted several times with MTBE. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The final product was purified by column chromatography (hexane/EtOAc, 7:3). Yield: 4.8 g, 24%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.71 – 4.57 (m, 1H), 3.82 – 3.70 (m, 2H), 3.62 – 3.45 (m, 2H), 3.43 – 3.31 (m, 1H), 3.25 (t, *J* = 9.0 Hz, 1H), 2.48 (dd, *J* = 11.2, 7.7 Hz, 1H), 2.06 (dd, *J* = 11.3, 6.7 Hz, 1H), 1.98 – 1.65 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 78.2, 74.3, 64.4, 63.9, 40.5, 38.9, 38.4, 11.8 ppm. GCMS (M): 268. HRMS (ESI): calc'd for $C_8H_{14}IO_2$ $[M+H]^+$ 269.0038; found 269.0031.



***Tert*-butyl 2-(iodomethyl)-1-oxa-7-azaspiro[3.5]nonane-7-carboxylate (33a)**

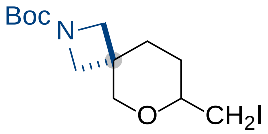
General procedure B was used. Scale: 0.1 mol. Yield: 7.7 g, 21%, beige solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.75 – 4.49 (m, 1H), 3.58 – 3.30 (m, 5H), 3.24 (t, *J* = 9.0 Hz, 1H), 2.45 (dd, *J* = 11.3, 7.6 Hz, 1H), 2.11 – 1.94 (m, 1H), 1.92 – 1.62 (m, 4H), 1.43 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.8, 79.7, 79.1, 74.3, 40.7 (br s), 39.8 (br s), 38.5, 37.3, 28.5, 11.7 ppm. HRMS (ESI): calc'd for $C_{13}H_{23}INO_3$ $[M+H]^+$ 368.0723; found 368.0721.

General procedure C for synthesis **34a-48a** (**34a** as an example. Scale: 0.1 mol for all derivatives)



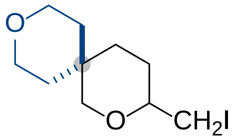
7-(Iodomethyl)-6-oxaspiro[3.5]nonane (34a)

In a flask fitted with a magnetic stirring bar, (14.0 g, 0.1 mol, 1.0 equiv) of (1-(but-3-en-1-yl)cyclobutyl)methanol was dissolved in 200 mL of dry CH_3CN under an argon atmosphere, and (41.4 g, 0.3 mol, 3 equiv) of K_2CO_3 was added. The resulting mixture was stirred at room temperature for 1 h, and (76.2 g, 0.3 mol, 3.0 equiv) of I_2 was added. The reaction mixture was left to warm to room temperature for 24 h, then extra of K_2CO_3 (13.8 g, 0.1 mol, 1.0 equiv) and I_2 and (25.4 g, 0.1 mol, 1.0 equiv) were added to the mixture. The mixture was stirring for additional 24 h. The mixture was diluted with MTBE and washed with a 10% sodium thiosulfate solution until the color disappeared. The aqueous layer was extracted several times with MTBE. The combined extracts were dried, filtered, and concentrated under reduced pressure. Yield: 12.8 g, 48%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.90 (dd, *J* = 11.2, 2.2 Hz, 1H), 3.49 – 3.38 (m, 1H), 3.36 – 3.29 (m, 2H), 3.26 (d, *J* = 11.2 Hz, 1H), 2.09 – 1.93 (m, 1H), 1.94 – 1.82 (m, 3H), 1.82 – 1.69 (m, 1H), 1.69 – 1.50 (m, 3H), 1.50 – 1.21 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 76.8, 76.5, 37.9, 35.7, 35.4, 30.3, 28.9, 27.1, 15.4 ppm. HRMS (ESI): calc'd for $C_9H_{16}IO$ $[M+H]^+$ 267.0246; found 267.0249.



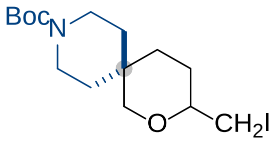
***Tert*-butyl 7-(iodomethyl)-6-oxa-2-azaspiro[3.5]nonane-2-carboxylate (35a)**

General procedure C was used. Yield: 23.1 g, 63%, beige solid, mp = 84-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.00 (dd, *J* = 11.4, 2.2 Hz, 1H), 3.83 (d, *J* = 8.5 Hz, 1H), 3.62 (d, *J* = 8.4 Hz, 1H), 3.56 – 3.38 (m, 3H), 3.30 – 3.19 (m, 1H), 3.21 – 3.08 (m, 2H), 2.07 – 1.89 (m, 1H), 1.88 – 1.72 (m, 1H), 1.69 – 1.53 (m, 1H), 1.42 (s, 9H), 1.36 – 1.21 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.5, 79.6, 76.4, 74.5, 58.5, 55.5, 33.5, 32.8, 28.5, 8.8 ppm. HRMS (ESI): calc'd for $C_{13}H_{23}INO_3$ $[M+H]^+$ 368.0723; found 368.0718.



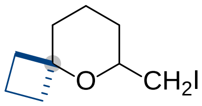
3-(Iodomethyl)-2,9-dioxaspiro[5.5]undecane (36a)

General procedure C was used. Yield: 17.8 g, 60%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.96 (dd, *J* = 11.5, 2.4 Hz, 1H), 3.75 – 3.60 (m, 3H), 3.60 – 3.52 (m, 1H), 3.52 – 3.43 (m, 1H), 3.38 (d, *J* = 5.3 Hz, 2H), 3.18 (d, *J* = 11.5 Hz, 1H), 1.88 (dd, *J* = 13.3, 3.0 Hz, 1H), 1.81 – 1.70 (m, 1H), 1.67 – 1.51 (m, 3H), 1.39 – 1.21 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 75.7, 64.0, 63.4, 35.9, 35.8, 34.0, 31.6, 30.3, 25.7 ppm. HRMS (ESI): calc'd for $C_{10}H_{18}IO_2$ $[M+H]^+$ 297.0351; found 297.0347.



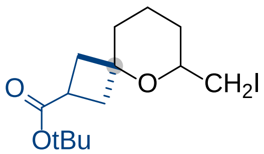
***Tert*-butyl 3-(iodomethyl)-2-oxa-9-azaspiro[5.5]undecane-9-carboxylate (37a)**

General procedure C was used. Yield: 24.1 g, 61%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.85 (dd, *J* = 11.5, 2.5 Hz, 1H), 3.47 – 3.03 (m, 8H), 1.80 (dd, *J* = 13.2, 3.0 Hz, 1H), 1.74 – 1.49 (m, 4H), 1.44 (s, 9H), 1.33 (td, *J* = 13.3, 4.5 Hz, 1H), 1.23 (t, *J* = 5.9 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.0, 79.5, 75.7, 39.8, 39.3, 35.0, 33.3, 31.0, 30.7, 28.6, 27.4, 9.8 ppm. LCMS $(M+H)^+$: 296. HRMS (ESI): calc'd for $C_{15}H_{27}INO_3$ $[M+H]^+$ 396.1036; found 396.1032.



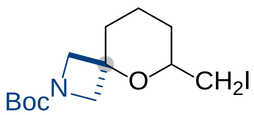
6-(Iodomethyl)-5-oxaspiro[3.5]nonane (38a)

General procedure C was used. Yield: 12.6 g, 47%, orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.40 – 3.31 (m, 1H), 3.13 (d, *J* = 5.9 Hz, 2H), 2.21 – 2.08 (m, 1H), 2.01 – 1.85 (m, 3H), 1.83 – 1.67 (m, 4H), 1.62 – 1.50 (m, 2H), 1.45 – 1.32 (m, 1H), 1.22 – 1.08 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 77.8, 71.9, 35.0, 33.0, 31.12, 31.09, 20.1, 12.9, 10.4 ppm. GCMS (M): 266. HRMS (ESI): calc'd for $C_9H_{16}IO$ $[M+H]^+$ 267.0246; found 267.0240.



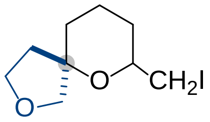
***Tert*-butyl 6-(iodomethyl)-5-oxaspiro[3.5]nonane-2-carboxylate (39a)**

General procedure C was used. Yield: 16.5 g, 45%, colorless oil. Mixture of stereoisomers (d.r. = 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.39 – 3.02 (m, 3H), 2.64 – 2.51 (m, 1H), 2.39 – 2.29 (m, 1H), 2.30 – 1.97 (m, 3H), 1.81 – 1.50 (m, 4H), 1.41 (s, 9H), 1.28 – 0.88 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 175.4, 174.2, 80.4, 80.3, 73.5, 72.1, 72.0, 38.5, 37.7, 34.9, 34.6, 33.7, 33.0, 31.7, 31.0, 30.9, 28.2, 20.1, 19.8, 10.2, 9.9 ppm. HRMS (ESI): calc'd for $C_{14}H_{24}IO_3$ $[M+H]^+$ 367.0770; found 367.0777.



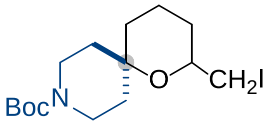
***Tert*-butyl 6-(iodomethyl)-5-oxa-2-azaspiro[3.5]nonane-2-carboxylate (40a)**

General procedure C was used. Yield: 18.7 g, 51%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.85 (dd, *J* = 16.9, 8.8 Hz, 2H), 3.71 (d, *J* = 8.9 Hz, 2H), 3.38 – 3.26 (m, 1H), 3.16 (d, *J* = 5.6 Hz, 1H), 1.80 (t, *J* = 9.3 Hz, 3H), 1.62 – 1.47 (m, 2H), 1.41 (s, 9H), 1.34 – 1.17 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.6, 79.7, 73.2, 61.0, 58.4, 32.6, 30.5, 28.5, 20.0, 9.2, 3.9 ppm. HRMS (ESI): calc'd for $C_{13}H_{23}INO_3$ $[M+H]^+$ 368.0723; found 368.0720.



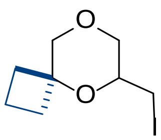
7-(Iodomethyl)-2,6-dioxaspiro[4.5]decane (41a)

General procedure C was used. Yield: 14.3 g, 51%, brown oil. Mixture of stereoisomers (d.r. = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.08 – 3.72 (m, 3H), 3.58 (dd, *J* = 13.8, 9.4 Hz, 1H), 3.54 – 3.36 (m, 1H), 3.15 (dd, *J* = 5.7, 1.8 Hz, 2H), 2.28 – 1.96 (m, 1H), 1.90 – 1.81 (m, 2H), 1.80 – 1.31 (m, 4H), 1.28 – 1.07 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 83.9, 83.7, 79.8, 73.4, 72.7, 72.6, 68.3, 67.0, 41.4, 33.8, 32.9, 32.0, 31.2, 31.1, 21.6, 21.1, 10.5, 10.3 ppm. GCMS (M): 282. HRMS (ESI): calc'd for $C_9H_{16}IO_2$ $[M+H]^+$ 283.0195; found 283.0190.



***Tert*-butyl 2-(iodomethyl)-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (42a)**

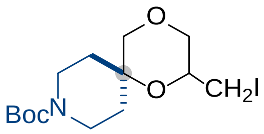
General procedure C was used. Yield: 25.3 g, 64%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.83 – 3.74 (m, 2H), 3.61 – 3.50 (m, 1H), 3.36 – 3.25 (m, 1H), 3.21 – 3.14 (m, 2H), 3.11 – 3.03 (m, 1H), 2.15 (d, *J* = 14.2 Hz, 1H), 1.83 – 1.73 (m, 1H), 1.68 – 1.61 (m, 2H), 1.56 – 1.46 (m, 2H), 1.45 (s, 9H), 1.39 – 1.03 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.1, 79.3, 71.6, 69.9, 39.4, 39.2, 35.5, 31.8, 29.4, 28.6, 19.1, 10.6 ppm. HRMS (ESI): calc'd for $C_{15}H_{27}INO_3$ $[M+H]^+$ 396.1036; found 396.1040.



6-(Iodomethyl)-5,8-dioxaspiro[3.5]nonane (43a)

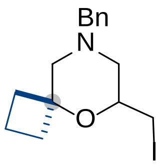
General procedure C was used. Yield: 15.5 g, 58%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.92 (dd, *J* = 11.2, 2.3 Hz, 1H), 3.73 (d, *J* = 11.4 Hz, 1H), 3.71 – 3.60 (m, 1H), 3.32 (dd, *J* = 11.4, 2.0 Hz, 1H), 3.21 (t, *J* = 10.5 Hz, 1H), 3.04 (dd, *J* = 6.3, 1.9 Hz, 2H), 2.33 – 2.20 (m, 1H), 2.14 –

1.97 (m, 2H), 1.91 – 1.75 (m, 2H), 1.62 – 1.50 (m, 1H) ppm. GCMS (M): 268. HRMS (ESI): calc'd for $C_{15}H_{27}INO_3$ $[M+H]^+$ 269.0038; found 269.0033.



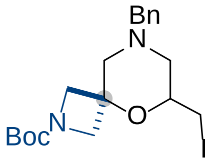
Tert-butyl 2-(iodomethyl)-1,4-dioxa-9-azaspiro[5.5]undecane-9-carboxylate (44a)

General procedure C was used. Yield: 25 g, 63%, yellow solid, mp = 65-66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.01 – 3.90 (m, 1H), 3.89 – 3.75 (m, 3H), 3.47 (d, J = 11.4 Hz, 1H), 3.30 – 2.96 (m, 6H), 2.32 (d, J = 14.2 Hz, 1H), 1.45 (s, 9H), 1.43 – 1.23 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.0, 79.6, 74.2, 70.9, 70.8, 68.1, 39.2, 38.6, 34.0, 28.9, 28.6, 3.6 ppm. GCMS (M): 397. HRMS (ESI): calc'd for $C_{14}H_{25}INO_4$ $[M+H]^+$ 398.0828; found 398.0821.



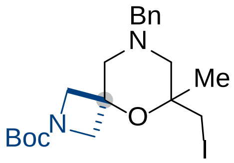
8-Benzyl-6-(iodomethyl)-5-oxa-8-azaspiro[3.5]nonane (45a)

General procedure C was used. Yield: 18.9 g, 53%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 – 7.24 (m, 5H), 3.60 – 3.32 (m, 4H), 2.67 (dd, J = 23.1, 11.3 Hz, 2H), 2.27 (q, J = 10.3 Hz, 1H), 2.14 (d, J = 11.5 Hz, 2H), 2.08 (d, J = 10.0 Hz, 1H), 1.95 – 1.84 (m, 1H), 1.75 – 1.61 (m, 1H), 1.48 – 1.31 (m, 1H), 1.28 – 1.26 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 128.9, 128.5, 127.3, 75.0, 73.1, 62.7, 60.7, 60.1, 35.1, 34.6, 16.5, 13.7 ppm. HRMS (ESI): calc'd for $C_{15}H_{21}INO$ $[M+H]^+$ 358.0668; found 358.0660.



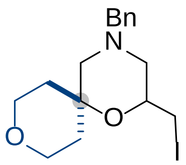
Tert-butyl 8-benzyl-6-(iodomethyl)-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (46a)

General procedure C was used. Yield: 26.6 g, 58%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 – 7.27 (m, J = 13.6, 6.5 Hz, 5H), 3.83 (q, J = 8.7 Hz, 3H), 3.65 (d, J = 9.4 Hz, 1H), 3.63 – 3.51 (m, 2H), 3.46 (d, J = 13.1 Hz, 1H), 3.13 (d, J = 5.7 Hz, 2H), 2.93 (d, J = 11.2 Hz, 1H), 2.81 (d, J = 11.3 Hz, 1H), 2.10 (d, J = 11.0 Hz, 1H), 1.92 (t, J = 10.5 Hz, 1H), 1.42 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.5, 137.5, 129.0, 128.6, 127.6, 79.8, 72.0, 62.6, 58.2, 57.2, 28.5, 5.0 ppm. HRMS (ESI): calc'd for $C_{19}H_{28}IN_2O_3$ $[M+H]^+$ 459.1145; found 459.1141.



***Tert*-butyl 8-benzyl-6-(iodomethyl)-6-methyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (47a)**

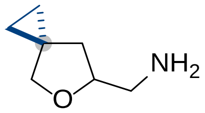
General procedure C was used. Yield: 31.6 g, 67%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.27 (m, 5H), 3.83 (q, J = 8.7 Hz, 3H), 3.71 – 3.53 (m, 3H), 3.46 (d, J = 13.1 Hz, 1H), 3.13 (d, J = 5.7 Hz, 2H), 2.93 (d, J = 11.2 Hz, 1H), 2.81 (d, J = 11.3 Hz, 1H), 2.10 (d, J = 11.0 Hz, 1H), 1.92 (t, J = 10.5 Hz, 1H), 1.42 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.5, 137.5, 129.0, 128.6, 127.6, 79.8, 72.0, 62.6, 58.2, 57.2, 28.5, 5.0 ppm. HRMS (ESI): calc'd for $C_{20}H_{30}IN_2O_3$ $[M+H]^+$ 473.1301; found 473.1309.



4-Benzyl-2-(iodomethyl)-1,9-dioxa-4-azaspiro[5.5]undecane (48a)

General procedure C was used. Yield: 27.9 g, 72%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.28 (m, 5H), 3.88 (t, J = 10.0 Hz, 1H), 3.79 (t, J = 9.9 Hz, 1H), 3.59 – 3.44 (m, 4H), 3.40 (d, J = 9.8 Hz, 1H), 3.30 (d, J = 9.9 Hz, 1H), 2.51 (d, J = 11.2 Hz, 1H), 2.36 – 2.20 (m, 3H), 1.88 (d, J = 12.7 Hz, 1H), 1.78 (d, J = 12.2 Hz, 1H), 1.67 – 1.54 (m, 2H), 1.26 (t, J = 6.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.2, 128.8, 128.5, 127.4, 72.2, 71.0, 64.3, 64.3, 62.7, 62.2, 61.1, 37.9, 37.7, 18.6 ppm. HRMS (ESI): calc'd for $C_{16}H_{23}INO_2$ $[M+H]^+$ 388.0773; found 388.0768.

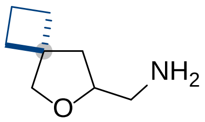
General procedure D for synthesis 5b, **32b** and **33b** (**5b** as an example. Scale: 0.01 mol for all derivatives).



(5-Oxaspiro[2.4]heptan-6-yl)methanamine (5b)

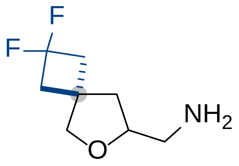
A mixture of **5a** (2.4 g, 0.01 mol, 1.0 equiv) and NaN_3 (2 g, 0.03 mol, 3.0 equiv) in DMF (50 mL) was heated and stirred at 50 °C for 15 h. The reaction mixture was cooled to room temperature and poured into cold water (100 mL). The aqueous mixture was extracted with MTBE (4 × 50 mL) and the organic extract was back-washed with water (3×20 mL), brine, dried over Na_2SO_4, and the solvent was partially evaporated under reduced pressure to afford the solution of the desired compound. To a solution of triphenylphosphine (3.9 g, 0.015 mol, 1.5 equiv) and H_2O (0.5 g, 0.03 mol, 3.0 equiv) in THF (20 mL) was added a solution of the appropriate azide (1.53g, 0.01 mol, 1.0 equiv) in THF dropwise. The mixture was stirred at 50 °C for 16 h. The mixture was concentrated under reduced pressure and H_2O (0.5 g, 0.03 mol, 3.0 equiv) was added. The mixture was washed with MTBE (3 × 20 mL) and partitioned. The aqueous layer was concentrated, washed with pentane and filtered. The filtrate was combined with organic layers and concentrated under reduced pressure. The crude product was purified by distillation to afford the desired product. Yield: 0.7 g, 56%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.20 – 4.04 (m, 1H), 3.67 (d, *J* = 8.0 Hz, 1H), 3.60 (d, *J* = 8.0 Hz, 1H), 2.89 – 2.71 (m, 2H), 2.55 (s, 2H), 1.83 (dd, *J* = 12.2, 6.8 Hz, 1H), 1.65 (dd, *J* = 12.1, 7.3 Hz, 1H), 0.68 – 0.43 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 80.9, 75.0, 46.2, 38.2, 22.4, 11.0, 10.7 ppm. HRMS (ESI): calc'd for $C_7H_{14}NO$ $[M+H]^+$ 128.1075; found 128.1078.

General procedure E for synthesis 4b, 6b-31b and **34b-44b** (**6b** as an example. Scale: 0.01 mol for all derivatives).



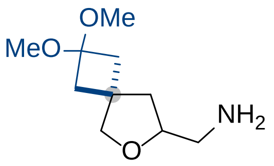
(6-Oxaspiro[3.4]octan-7-yl)methanamine hydrochloride (6b)

To a solution of **6a** (2.5 g, 0.01 mol, 1.0 equiv) in 50 mL of DMSO was added NaN_3 (1.0 g, 0.015 mol, 1.5 equiv). The mixture was heated at 85 °C for 24 h. The mixture was diluted with water (100 mL) and extracted with MTBE (6 times). The combined organic phases were washed with brine (3 times), dried over Na_2SO_4, filtered and partially concentrated under reduced pressure. The azide was stored as a solution in MeOH. To a solution of azide (1.67 g, 0.009 mol, 1.0 equiv) in 50 mL of MeOH was added and Pd/C (5%), (0.2 g). The mixture was stirred under H_2-ballon at room temperature overnight. The reaction was monitored by TLC. After consumption of all starting material, Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in cold EtOAc and 5M HCl in dioxane was added dropwise to achieve a slightly acidic pH. The precipitate was filtered and dried. Yield: 1.6 g, 90%, brown solid, mp = 118-119 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.22 (s, 3H), 4.11 – 3.98 (m, 1H), 3.75 – 3.62 (m, 2H), 2.92 – 2.80 (m, 1H), 2.78 – 2.66 (m, 1H), 2.08 (dd, *J* = 12.5, 6.8 Hz, 1H), 2.00 – 1.91 (m, 4H), 1.89 – 1.74 (m, 2H), 1.74 – 1.61 (m, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 77.8, 74.4, 45.4, 42.6, 41.7, 32.1, 30.2, 15.9 ppm. LCMS $(M+H)^+$: 142. HRMS (ESI): calc'd for $C_8H_{16}NO$ $[M+H]^+$ 142.1232; found 142.1237.



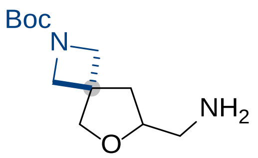
(2,2-Difluoro-6-oxaspiro[3.4]octan-7-yl)methanamine hydrochloride (4b)

General procedure E was used. Yield: 1.6 g, 77%, brown solid, mp = 207-209 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.27 (s, 3H), 4.21 – 4.05 (m, 1H), 3.79 (d, *J* = 8.6 Hz, 1H), 3.72 (d, *J* = 8.6 Hz, 1H), 2.99 – 2.84 (m, 1H), 2.84 – 2.73 (m, 1H), 2.71 – 2.55 (m, 4H), 2.18 (dd, *J* = 12.7, 7.0 Hz, 1H), 1.88 (dd, *J* = 12.8, 7.7 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ = 119.9 (t, *J* = 277.6 Hz), 76.8, 74.7, 44.6 (t, *J* = 21.9 Hz), 43.0 (t, *J* = 22.4 Hz), 42.3, 40.8, 34.5 (t, *J* = 10.3 Hz) ppm. LCMS (M+H)$^+$: 178. HRMS (ESI): calc'd for $C_8H_{14}F_2NO$ [M+H]$^+$ 178.1043; found 178.1041.



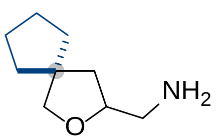
(2,2-Dimethoxy-6-oxaspiro[3.4]octan-7-yl)methanamine (7b)

General procedure E was used. Yield: 1.8 g, 89%, yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 3.98 – 3.85 (m, 1H), 3.72 (q, *J* = 8.5 Hz, 2H), 3.12 (s, 3H), 3.11 (s, 3H), 2.77 (dd, *J* = 13.1, 3.9 Hz, 1H), 2.67 (dd, *J* = 13.1, 7.0 Hz, 1H), 2.23 – 2.06 (m, 4H), 2.02 (dd, *J* = 12.5, 6.7 Hz, 1H), 1.70 – 1.65 (m, 1H), 1.64 (s, 2H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ = 143.2, 99.5, 80.5, 78.9, 48.6, 48.6, 46.6, 42.7, 42.6, 41.1, 36.7 ppm. LCMS (M+H)$^+$: 202. HRMS (ESI): calc'd for $C_{10}H_{20}NO_3$ [M+H]$^+$ 202.1443; found 202.1440.



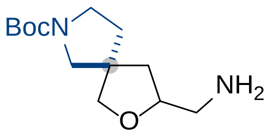
***Tert*-butyl 7-(aminomethyl)-6-oxa-2-azaspiro[3.4]octane-2-carboxylate (8b)**

General procedure E was used. Yield: 2.3 g, 95%, yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 3.98 – 3.87 (m, 2H), 3.87 – 3.81 (m, 5H), 2.79 (dd, *J* = 13.1, 3.6 Hz, 1H), 2.66 (dd, *J* = 13.1, 6.8 Hz, 1H), 2.15 (dd, *J* = 12.7, 6.8 Hz, 1H), 1.83 (dd, *J* = 12.7, 7.9 Hz, 1H), 1.46 (s, 2H), 1.41 (s, 9H) ppm. ^{13}C NMR (151 MHz, CDCl$_3$) δ = 156.3, 80.6, 79.7, 77.1, 59.2 (br s), 46.2, 40.7, 40.6, 28.4 ppm. HRMS (ESI): calc'd for $C_{12}H_{23}N_2O_3$ [M+H]$^+$ 243.1709; found 243.1707.



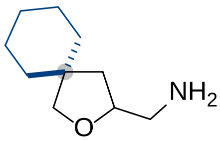
(2-Oxaspiro[4.4]nonan-3-yl)methanamine (9b)

General procedure E was used. Yield: 1.4 g, 87%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.01 – 3.89 (m, 1H), 3.55 (dd, J = 18.3, 8.1 Hz, 2H), 2.77 (dd, J = 13.1, 3.9 Hz, 1H), 2.70 (dd, J = 13.0, 7.0 Hz, 1H), 1.82 (dd, J = 12.1, 6.6 Hz, 1H), 1.64 (s, 2H), 1.64 – 1.46 (m, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.2, 80.9, 78.6, 51.0, 46.8, 42.4, 37.7, 36.6, 24.88, 24.86 ppm. LCMS $(M+H)^+$: 156. HRMS (ESI): calc'd for C9H18NO $[M+H]^+$ 156.1388; found 156.1387.



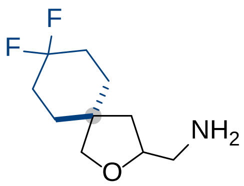
***Tert*-butyl-3-(aminomethyl)-2-oxa-7-azaspiro[4.4]nonane-7-carboxylate (10b)**

General procedure E was used. Yield: 2.1 g, 81%, colorless oil. Mixture of stereoisomers (d.r. = 5:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.96 (br s, 1H), 3.72 – 3.52 (m, 2H), 3.47 – 3.15 (m, 4H), 2.79 (dd, J = 13.1, 3.7 Hz, 1H), 2.70 (dd, J = 13.1, 6.9 Hz, 1H), 1.98 – 1.73 (m, 3H), 1.64 – 1.51 (m, 1H), 1.46 (s, 2H), 1.41 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 154.63, 154.58, 80.82, 80.75, 79.4, 76.5, 76.3, 76.0, 55.8, 55.4, 55.1, 50.3, 50.1, 49.4, 46.5, 45.4, 45.1, 39.6, 39.4, 35.6, 34.9, 34.5, 28.6 ppm. GCMS (M): 256. HRMS (ESI): calc'd for $C_{13}H_{25}N_2O_3$ $[M+H]^+$ 257.1865; found 257.1868.



(2-Oxaspiro[4.5]decan-3-yl)methanamine (11b)

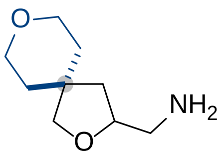
General procedure E was used. Yield: 1.4 g, 80%, colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.85 – 3.71 (m, 1H), 3.45 (d, J = 8.3 Hz, 1H), 3.40 (d, J = 8.3 Hz, 1H), 2.55 (d, J = 5.5 Hz, 2H), 1.74 (dd, J = 12.3, 6.8 Hz, 1H), 1.66 – 1.46 (m, 1H), 1.44 – 1.22 (m, 12H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 80.0, 77.3, 46.5, 43.2, 36.1, 35.1, 25.6, 23.5, 23.1 ppm. LCMS $(M+H)^+$: 170. HRMS (ESI): calc'd for $C_{10}H_{20}NO$ $[M+H]^+$ 170.1545; found 170.1540.



(8,8-Difluoro-2-oxaspiro[4.5]decan-3-yl)methanamine hydrochloride (12b)

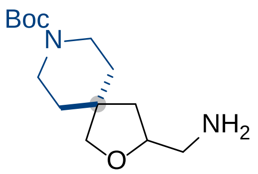
General procedure E was used. Yield: 22.9 g, 95%, beige solid, mp = 122-123 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.24 (s, 3H), 4.24 – 4.07 (m, 1H), 3.58 (q, J = 8.7 Hz, 2H), 3.37 (s, 2H), 2.89 (s, 1H), 2.87 – 2.73 (m, 1H), 2.02 – 1.76 (m, 4H), 1.59 (dd, J = 13.2, 7.2 Hz, 3H), 1.49 (dd, J =

12.7, 8.4 Hz, 1H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 124.0 (t, *J* = 240.2 Hz), 76.0, 74.5, 42.5, 42.3, 31.4 (t, *J* = 4.8 Hz), 31.1 (t, *J* = 23.7 Hz), 30.7 (t, *J* = 23.7 Hz), 30.6 (t, *J* = 4.9 Hz) ppm. LCMS (M+H)$^+$: 206. HRMS (ESI): calc'd for $C_{10}H_{18}F_2NO$ [M+H]$^+$ 206.1356; found 206.1353.



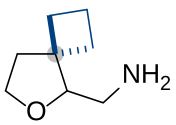
(2,8-Dioxaspiro[4.5]decan-3-yl)methanamine hydrochloride (13b)

General procedure E was used. Yield: 1.6 g, 78%, beige solid, mp = 158-160 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.27 (s, 3H), 4.24 – 4.08 (m, 1H), 3.72 – 3.42 (m, 6H), 2.89 (br s, 1H), 2.80 (br s, 1H), 1.98 (dd, *J* = 12.6, 7.1 Hz, 1H), 1.64 – 1.36 (m, 5H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 76.8, 74.3, 64.8, 64.4, 42.6, 41.2, 35.3, 34.9 ppm. LCMS (M+H)$^+$: 172. HRMS (ESI): calc'd for $C_9H_{18}NO_2$ [M+H]$^+$ 172.1338; found 172.1334.



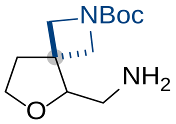
***Tert*-butyl 3-(aminomethyl)-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (14b)**

General procedure E was used. Yield: 2.4 g, 88%, colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.89 – 3.75 (m, 1H), 3.47 (dd, *J* = 22.4, 8.5 Hz, 2H), 3.41 – 3.31 (m, 2H), 3.28 – 3.15 (m, 2H), 2.56 (d, *J* = 5.4 Hz, 2H), 1.81 (dd, *J* = 12.4, 6.9 Hz, 1H), 1.51 – 1.39 (m, 4H), 1.39 (s, 9H), 1.36 – 1.23 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 153.8, 80.0, 78.4, 76.5, 46.3, 41.8, 35.0, 34.1, 28.1 ppm. HRMS (ESI): calc'd for $C_{14}H_{27}N_2O_3$ [M+H]$^+$ 271.2022; found 271.2016.



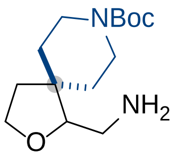
(6-Oxaspiro[3.4]octan-5-yl)methanamine hydrochloride (15b)

General procedure E was used. Yield: 1.6 g, 90%, white solid. ^{1}H NMR (500 MHz, CD_3OD) δ = 3.96 – 3.88 (m, 1H), 3.85 (dd, *J* = 11.0, 2.5 Hz, 1H), 3.77 (q, *J* = 8.3 Hz, 1H), 3.14 (d, *J* = 12.5 Hz, 1H), 2.70 (t, *J* = 11.8 Hz, 1H), 2.23 – 1.92 (m, 6H), 1.91 – 1.77 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 73.2, 57.8, 33.1, 30.0, 24.5, 18.7, 7.9 ppm. LCMS (M+H)$^+$: 142. HRMS (ESI): calc'd for $C_8H_{16}NO$ [M+H]$^+$ 142.1232; found 142.1235.



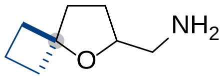
***Tert*-butyl 5-(aminomethyl)-6-oxa-2-azaspiro[3.4]octane-2-carboxylate (16b)**

General procedure E was used. Yield: 1.9 g, 79%, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.00 (d, *J* = 8.9 Hz, 1H), 3.91 – 3.84 (m, 2H), 3.83 (d, *J* = 3.5 Hz, 1H), 3.77 – 3.72 (m, 2H), 3.71 (d, *J* = 9.0 Hz, 1H), 2.94 (d, *J* = 11.5 Hz, 1H), 2.72 (dd, *J* = 12.9, 8.1 Hz, 1H), 2.26 – 2.09 (m, 2H), 1.46 (s, 2H), 1.43 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.5, 85.6, 79.8, 65.8, 59.9 (br s), 55.3 (br s), 43.5, 42.0, 39.4, 28.5 ppm. LCMS $(M+H)^+$: 243. HRMS (ESI): calc'd for $C_{12}H_{23}N_2O_3$ $[M+H]^+$ 243.1709; found 243.1705.



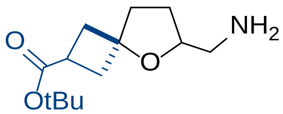
***Tert*-butyl 1-(aminomethyl)-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (17b)**

General procedure E was used. Yield: 2 g, 75%, white solid. ^{1}H NMR (500 MHz, CD_3OD) δ = 4.08 – 3.99 (m, 1H), 3.94 – 3.80 (m, 3H), 3.72 (dd, *J* = 11.0, 1.7 Hz, 1H), 3.17 – 2.96 (m, 3H), 2.90 (t, *J* = 11.9 Hz, 1H), 2.07 – 1.91 (m, 2H), 1.61 – 1.47 (m, 3H), 1.45 (s, 9H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 146.9, 74.0, 71.6, 57.7, 35.4, 32.7 (br s), 31.8, 25.8, 25.6, 21.6, 19.2 ppm. LCMS $(M+H)^+$: 271. HRMS (ESI): calc'd for $C_{14}H_{27}N_2O_3$ $[M+H]^+$ 271.2022; found 271.2018.



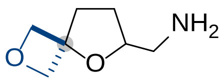
(5-Oxaspiro[3.4]octan-6-yl)methanamine hydrochloride (18b)

General procedure E was used. Yield: 1.6 g, 90%, brown solid, mp = 88-89 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.21 (s, 3H), 4.16 – 3.97 (m, 1H), 2.82 (br s, 1H), 2.72 – 2.56 (m, 1H), 2.22 – 2.05 (m, 2H), 2.04 – 1.80 (m, 5H), 1.72 – 1.54 (m, 2H), 1.53 – 1.34 (m, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 83.3, 74.4, 43.4, 35.7, 35.5, 35.2, 27.8, 12.2 ppm. LCMS $(M+H)^+$: 142. HRMS (ESI): calc'd for $C_8H_{16}NO$ $[M+H]^+$ 142.1232; found 142.1234.



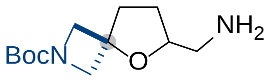
***Tert*-butyl 6-(aminomethyl)-5-oxaspiro[3.4]octane-2-carboxylate (19b)**

General procedure E was used. Yield: 1.8 g, 76%, brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.88 – 3.76 (m, 1H), 2.95 – 2.82 (m, 1H), 2.67 – 2.51 (m, 3H), 2.40 – 2.27 (m, 1H), 2.25 – 2.06 (m, 4H), 1.93 – 1.76 (m, 3H), 1.62 – 1.49 (m, 1H), 1.39 (s, 9H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 173.5, 79.8, 79.5, 78.3, 46.2, 38.8, 36.0, 29.6, 27.7 ppm. HRMS (ESI): calc'd for $C_{13}H_{24}NO_3$ $[M+H]^+$ 242.1756; found 242.1750.



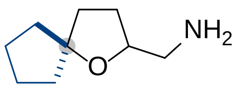
(2,5-Dioxaspiro[3.4]octan-6-yl)methanamine (20b)

General procedure E was used. Yield: 1.3 g, 90%, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.75 (d, *J* = 6.5 Hz, 1H), 4.68 (d, *J* = 6.4 Hz, 1H), 4.48 (t, *J* = 7.4 Hz, 1H), 3.97 – 3.85 (m, 1H), 2.73 (dd, *J* = 13.1, 4.0 Hz, 1H), 2.58 (dd, *J* = 13.1, 6.9 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.16 – 1.98 (m, 1H), 1.94 – 1.83 (m, 1H), 1.63 – 1.48 (m, 1H), 1.42 (s, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 84.4, 83.8, 82.3, 81.4, 46.7, 35.3, 28.0 ppm. GCMS (M): 143. HRMS (ESI): calc'd for $C_7H_{14}NO_2$ $[M+H]^+$ 144.1025; found 144.1027.



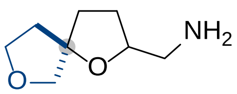
***Tert*-butyl 6-(aminomethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (21b)**

General procedure E was used. Yield: 1.9 g, 79%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.97 (dd, *J* = 16.1, 8.9 Hz, 3H), 3.82 (d, *J* = 8.9 Hz, 2H), 2.78 (dd, *J* = 13.1, 3.9 Hz, 1H), 2.64 (dd, *J* = 13.1, 6.9 Hz, 1H), 2.14 – 2.02 (m, 2H), 2.01 – 1.90 (m, 1H), 1.67 (br s, 2H), 1.61 – 1.53 (m, 1H), 1.41 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.5, 81.4, 79.6, 78.2, 62.1 (br s), 46.7, 36.1, 28.5, 28.1 ppm. HRMS (ESI): calc'd for $C_{12}H_{23}N_2O_3$ $[M+H]^+$ 243.1709; found 243.1700.



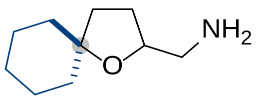
(1-Oxaspiro[4.4]nonan-2-yl)methanamine hydrochloride (22b)

General procedure E was used. Yield: 1.8 g, 95%, yellow solid, mp = 143-144 °C. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.22 (s, 3H), 4.13 – 4.02 (m, 1H), 2.92 – 2.78 (m, 1H), 2.75 – 2.62 (m, 1H), 2.52 – 2.43 (m, 1H), 2.07 – 1.91 (m, 1H), 1.89 – 1.41 (m, 10H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 91.7, 73.8, 43.3, 38.2, 37.6, 35.4, 28.9, 23.6, 23.6 ppm. LCMS $(M+H)^+$: 156. HRMS (ESI): calc'd for $C_9H_{18}NO$ $[M+H]^+$ 156.1388; found 156.1390.



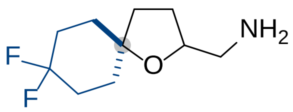
1,7-Dioxaspiro[4.4]nonan-2-yl)methanamine (23b)

General procedure E was used. Yield: 1.4 g, 74%, colorless oil. Mixture of stereoisomers (d.r. = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.99 – 3.82 (m, 3H), 3.74 (dd, J = 21.7, 9.1 Hz, 1H), 3.56 (dd, J = 39.6, 9.1 Hz, 1H), 2.84 – 2.72 (m, 1H), 2.73 – 2.63 (m, 1H), 2.12 – 2.00 (m, 1H), 1.98 – 1.88 (m, 3H), 1.87 – 1.73 (m, 1H), 1.72 – 1.56 (m, 1H), 1.52 (s, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 89.6, 89.5, 80.6, 80.4, 77.6, 77.1, 68.0, 67.93, 46.82, 46.80, 39.4, 38.7, 34.1, 33.6, 29.0 ppm. GCMS (M): 157. HRMS (ESI): calc'd for $C_8H_{16}NO_2$ $[M+H]^+$ 158.1181; found 158.1177.



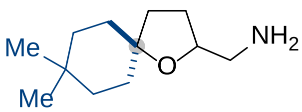
(1-Oxaspiro[4.5]decan-2-yl)methanamine hydrochloride (24b)

General procedure E was used. Yield: 1.9 g, 87%, brown solid, mp = 175-177 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.17 (s, 3H), 4.15 – 3.99 (m, 1H), 2.91 – 2.78 (m, 1H), 2.78 – 2.61 (m, 1H), 2.50 – 2.42 (m, 1H), 2.08 – 1.93 (m, 1H), 1.77 – 1.51 (m, 5H), 1.49 – 1.42 (m, 3H), 1.40 – 1.16 (m, 4H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 83.3, 73.7, 43.5, 37.9, 36.7, 35.1, 28.4, 25.2, 23.4, 23.2 ppm. LCMS $(M+H)^+$: 170. HRMS (ESI): calc'd for $C_{10}H_{20}NO$ $[M+H]^+$ 170.1545; found 170.1547.



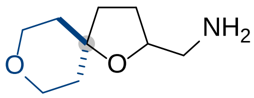
(8,8-Difluoro-1-oxaspiro[4.5]decan-2-yl)methanamine hydrochloride (25b)

General procedure E was used. Yield: 1.7 g, 72%, brown solid, mp = 140-142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.21 (br s, 3H), 4.17 – 4.04 (m, 1H), 2.96 – 2.86 (m, 1H), 2.78 – 2.67 (m, 1H), 2.27 – 1.94 (m, 3H), 1.94 – 1.40 (m, 9H) ppm. ^{13}C NMR (126 MHz, DMSO) δ = 124.1 (t, J = 240.0 Hz), 80.8, 74.3, 43.3, 35.2, 33.6 (d, J = 8.0 Hz), 32.4 (d, J = 8.1 Hz), 30.3 (t, J = 23.9 Hz), 28.2 ppm. HRMS (ESI): calc'd for $C_{10}H_{18}F_2NO$ $[M+H]^+$ 206.1356; found 206.1349.



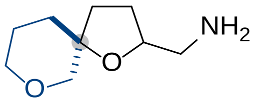
(8,8-Dimethyl-1-oxaspiro[4.5]decan-2-yl)methanamine hydrochloride (26b)

General procedure E was used. Yield: 1.7 g, 69%, yellow solid, mp = 194-195 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.17 (s, 3H), 4.14 – 4.02 (m, 1H), 2.89 – 2.78 (m, 1H), 2.77 – 2.66 (m, 1H), 2.07 – 1.90 (m, 1H), 1.74 – 1.62 (m, 3H), 1.59 – 1.35 (m, 6H), 1.14 (t, J = 9.5 Hz, 2H), 0.89 (s, 3H), 0.87 (s, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 83.1, 73.7, 43.4, 36.1, 35.9, 35.1, 33.7, 32.6, 29.2, 28.3 ppm. LCMS $(M+H)^+$: 198. HRMS (ESI): calc'd for $C_{12}H_{24}NO$ $[M+H]^+$ 198.1858; found 198.1853.



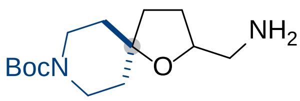
(1,8-Dioxaspiro[4.5]decan-2-yl)methanamine hydrochloride (27b)

General procedure E was used. Yield: 1.8 g, 88%, yellow solid, mp = 134-135 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.23 (s, 3H), 4.18 – 4.05 (m, 1H), 3.78 – 3.59 (m, 2H), 3.54 – 3.36 (m, 2H), 2.95 – 2.80 (m, 1H), 2.81 – 2.66 (m, 1H), 2.13 – 1.95 (m, 1H), 1.82 – 1.68 (m, 3H), 1.57 (t, *J* = 5.3 Hz, 2H), 1.53 (t, *J* = 5.6 Hz, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 80.4, 73.9, 64.6, 64.4, 43.3, 38.0, 37.0, 35.3, 28.1 ppm. LCMS $(M+H)^+$: 172. HRMS (ESI): calc'd for $C_9H_{18}NO_2$ $[M+H]^+$ 172.1338; found 172.1335.



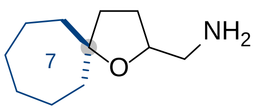
1,7-Dioxaspiro[4.5]decan-2-yl)methanamine (28b)

General procedure E was used. Yield: 1.3 g, 73%, colorless oil. Mixture of stereoisomers (d.r. = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.99 – 3.87 (m, 1H), 3.64 – 3.45 (m, 2H), 3.40 – 3.36 (m, 1H), 3.35 – 3.19 (m, 1H), 2.80 – 2.70 (m, 1H), 2.69 – 2.55 (m, 1H), 1.96 – 1.89 (m, 1H), 1.85 – 1.45 (m, 7H), 1.40 (s, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 80.4, 80.3, 79.8, 79.7, 75.1, 74.3, 67.9, 67.8, 46.9, 46.8, 35.8, 35.2, 34.2, 33.8, 28.3, 28.0, 24.3, 24.2 ppm. GCMS (M): 171. HRMS (ESI): calc'd for $C_9H_{18}NO_2$ $[M+H]^+$ 172.1338; found 172.1335.



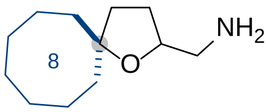
***Tert*-butyl 2-(aminomethyl)-1-oxa-8-azaspiro[4.5]decane-8-carboxylate (29b)**

General procedure E was used. Yield: 2.4 g, 91%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.06 – 3.95 (m, 1H), 3.60 (br s, 1H), 3.51 (br s, 3H), 3.37 – 3.26 (m, 2H), 2.84 (dd, *J* = 12.8, 3.6 Hz, 1H), 2.69 (dd, *J* = 12.8, 6.9 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.78 – 1.64 (m, 3H), 1.59 – 1.45 (m, 4H), 1.40 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.0, 80.8, 79.4, 78.3, 46.3, 41.0 (br s), 37.7, 36.6, 36.3, 28.6, 28.4 ppm. LCMS $(M+H)^+$: 271. HRMS (ESI): calc'd for $C_{14}H_{27}N_2O_3$ $[M+H]^+$ 271.2022; found 271.2016.



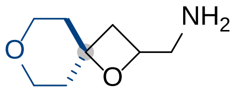
(1-Oxaspiro[4.6]undecan-2-yl)methanamine hydrochloride (30b)

General procedure E was used. Yield: 1.7 g, 78%, beige solid, mp = 183-184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.17 (s, 3H), 4.12 – 3.97 (m, 1H), 2.99 – 2.75 (m,1H), 2.78 – 2.58 (m, 1H), 2.08 – 1.89 (m, 1H), 1.76 – 1.37 (m, 12H), 1.37 – 1.18 (m, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 86.8, 73.8, 43.3, 40.9, 37.1, 28.8, 28.3, 22.7, 22.3 ppm. LCMS $(M+H)^+$: 184. HRMS (ESI): calc'd for: $C_{11}H_{22}NO$ $[M+H]^+$ 184.1701; found 184.1706.



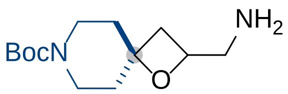
(1-Oxaspiro[4.7]dodecan-2-yl)methanamine hydrochloride (31b)

General procedure E was used. Yield: 2.1 g, 90%, yellow solid, mp = 142-143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.18 (s, 3H), 4.14 – 4.00 (m, 1H), 3.54 (br s, 1H), 2.89 – 2.78 (m, 1H), 2.76 – 2.62 (m, 1H), 2.07 – 1.91 (m, 1H), 1.79 – 1.32 (m, 16H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 86.6, 73.7, 43.3, 36.2, 36.1, 34.9, 28.6, 27.9, 27.7, 24.2, 22.4, 22.2 ppm. LCMS $(M+H)^+$: 198. HRMS (ESI): calc'd for: $C_{12}H_{24}NO$ $[M+H]^+$ 198.1858; found 198.1860.



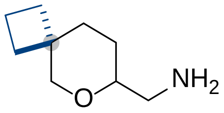
(1,7-Dioxaspiro[3.5]nonan-2-yl)methanamine (32b)

General procedure D was applied. The final product was purified by distillation. Yield: 1.2 g, 45%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.63 – 4.50 (m, 1H), 3.79 – 3.68 (m, 2H), 3.57 – 3.47 (m, 2H), 2.91 – 2.75 (m, 2H), 2.31 (dd, *J* = 11.0, 7.7 Hz, 1H), 2.13 (dd, *J* = 11.0, 7.1 Hz, 1H), 1.93 – 1.83 (m, 2H), 1.80 – 1.70 (m, 2H), 1.50 (s, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 79.1, 76.1, 74.3, 64.4, 64.0, 48.3, 40.1, 38.8, 34.6 ppm. LCMS $(M+H)^+$: 158. HRMS (ESI): calc'd for $C_8H_{16}NO_2$ $[M+H]^+$ 158.1181; found 158.1184.



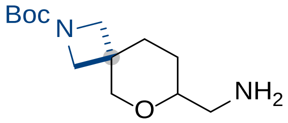
***Tert*-butyl 2-(aminomethyl)-1-oxa-7-azaspiro[3.5]nonane-7-carboxylate (33b)**

General procedure D was applied. The final product was purified by column chromatography (hexane/EtOAc, 8:2 + 1.5% Et_3N). Yield: 0.8 g, 32%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.64 – 4.51 (m, 1H), 3.47 – 3.33 (m, 4H), 2.92 – 2.77 (m, 2H), 2.33 – 2.23 (m, 1H), 2.16 – 2.08 (m, 1H), 1.92 – 1.82 (m, 1H), 1.82 – 1.72 (m, 2H), 1.70 – 1.62 (m, 1H), 1.59 – 1.49 (m, 2H), 1.42 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.9, 80.0, 79.6, 76.1, 48.3, 40.1, 38.9, 37.6, 34.2, 28.5 ppm. LCMS $(M+H)^+$: 257. HRMS (ESI): calc'd for: $C_{13}H_{25}N_2O_3$ $[M+H]^+$ 257.1865; found 257.1860.



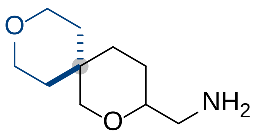
(6-Oxaspiro[3.5]nonan-7-yl)methanamine hydrochloride (34b)

General procedure E was used. Yield: 1.7 g, 89%, white solid, mp = 180-182 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.21 (s, 3H), 3.79 (d, *J* = 11.0 Hz, 1H), 3.46 (t, *J* = 9.5 Hz, 1H), 3.38 (s, 1H), 3.15 (d, *J* = 11.1 Hz, 1H), 2.82 (s, 1H), 2.65 (s, 1H), 2.06 – 1.76 (m, 4H), 1.77 – 1.63 (m, 1H), 1.64 – 1.54 (m, 2H), 1.49 (d, *J* = 12.7 Hz, 1H), 1.38 (t, *J* = 12.9 Hz, 1H), 1.29 – 1.07 (m, 1H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ = 75.0, 73.1, 42.8, 37.3, 34.3, 29.8, 28.4, 25.2, 14.9 ppm. HRMS (ESI): calc'd for: $C_9H_{18}NO$ $[M+H]^+$ 156.1388; found 156.1388.



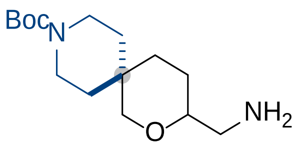
***Tert*-butyl 7-(aminomethyl)-6-oxa-2-azaspiro[3.5]nonane-2-carboxylate (35b)**

General procedure E was used. Yield: 2 g, 79%, white solid, mp = 56-58 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 3.94 (dd, *J* = 11.2, 1.9 Hz, 1H), 3.78 (d, *J* = 8.4 Hz, 1H), 3.59 (d, *J* = 8.4 Hz, 1H), 3.48 – 3.40 (m, 2H), 3.35 (d, *J* = 11.3 Hz, 1H), 3.21 – 3.11 (m, 1H), 2.69 – 2.57 (m, 2H), 2.03 – 1.93 (m, 1H), 1.63 – 1.44 (m, 2H), 1.39 (s, 9H), 1.31 (s, 2H), 1.27 – 1.14 (m, 1H) ppm. ^{13}C NMR (126 MHz, CDCl$_3$) δ = 156.5, 79.4, 78.9, 74.3, 59.0 (br s), 55.7 (br s), 47.0, 33.8, 32.9, 28.5, 25.9 ppm. LCMS $(M+H)^+$: 257. HRMS (ESI): calc'd for: $C_{13}H_{25}N_2O_3$ $[M+H]^+$ 257.1865; found 257.1868.



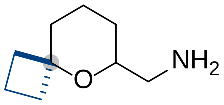
(2,9-Dioxaspiro[5.5]undecan-3-yl)methanamine (36b)

General procedure E was used. Yield: 1.7g, 86%, yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ = 3.87 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.70 – 3.63 (m, 2H), 3.62 – 3.46 (m, 2H), 3.25 – 3.16 (m, 1H), 3.11 (d, *J* = 11.4 Hz, 1H), 2.67 (d, *J* = 5.6 Hz, 2H), 1.83 (dd, *J* = 13.1, 3.1 Hz, 1H), 1.78 – 1.67 (m, 1H), 1.61 – 1.52 (m, 1H), 1.53 – 1.33 (m, 4H), 1.31 – 1.19 (m, 3H) ppm. ^{13}C NMR (151 MHz, CDCl$_3$) δ = 80.2, 75.6, 63.9, 63.3, 47.3, 36.0, 34.0, 31.7, 30.4, 24.6 ppm. GCMS (M): 185. HRMS (ESI): calc'd for $C_{10}H_{20}NO_2$ $[M+H]^+$ 186.1494; found 186.1487.



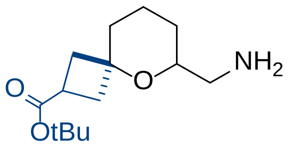
***Tert*-butyl 3-(aminomethyl)-2-oxa-9-azaspiro[5.5]undecane-9-carboxylate (37b)**

General procedure E was used. Yield: 1.7 g, 84%, colorless oil. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 3.72 (dd, *J* = 11.2, 2.2 Hz, 1H), 3.33 – 3.20 (m, 4H), 3.16 – 3.07 (m, 1H), 3.03 (d, *J* = 11.3 Hz, 1H), 2.56 – 2.50 (m, 2H), 2.50 – 2.45 (m, 1H), 1.81 – 1.67 (m, 1H), 1.57 – 1.40 (m, 3H), 1.38 (s, 9H), 1.35 – 1.11 (m, 5H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ = 153.9, 79.8, 78.4, 74.4, 46.9, 34.7, 32.4, 30.7, 30.2, 28.1, 24.3 ppm. LCMS (M+H)$^+$: 185. HRMS (ESI): calc'd for: $C_{15}H_{29}N_2O_3$ [M+H]$^+$ 285.2178; found 285.2179.



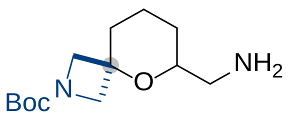
(5-Oxaspiro[3.5]nonan-6-yl)methanamine hydrochloride (38b)

General procedure E was used. Yield: 1.8 g, 94%, yellow solid, mp = 171-172 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.17 (br s, 3H), 3.53 (t, *J* = 10.0 Hz, 1H), 3.38 (s, 1H), 2.82 (s, 1H), 2.63 (s, 1H), 2.15 – 2.00 (m, 1H), 2.02 – 1.87 (m, 2H), 1.86 – 1.59 (m, 4H), 1.59 – 1.38 (m, 2H), 1.33 – 1.19 (m, 1H), 1.14 – 0.91 (m, 1H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ = 76.6, 67.9, 42.9, 34.2, 32.7, 30.3, 27.8, 19.2 12.2 ppm. LCMS (M+H)$^+$: 156. HRMS (ESI): calc'd for: $C_9H_{18}NO$ [M+H]$^+$ 156.1388; found 156.1382.



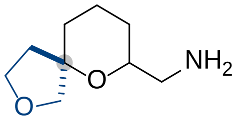
***Tert*-butyl 6-(aminomethyl)-5-oxaspiro[3.5]nonane-2-carboxylate (39b)**

General procedure E was used. Yield: 2.4 g, 93%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.36 – 3.23 (m, 1H), 2.70 – 2.63 (m, 2H), 2.65 – 2.54 (m, 1H), 2.36 – 2.23 (m, 2H), 2.21 – 2.04 (m, 2H), 1.83 (br s, 2H), 1.76 – 1.62 (m, 2H), 1.61 – 1.47 (m, 1H), 1.44 (s, 9H), 1.28 – 1.13 (m, 2H) ppm. HRMS (ESI): calc'd for: $C_{14}H_{26}NO_3$ [M+H]$^+$ 256.1913; found 256.1907.



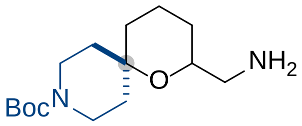
***Tert*-butyl 6-(aminomethyl)-5-oxa-2-azaspiro[3.5]nonane-2-carboxylate (40b)**

General procedure E was used. Yield: 2.2 g, 87%, white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.86 – 3.77 (m, 2H), 3.69 (t, *J* = 9.5 Hz, 2H), 3.35 – 3.20 (m, 1H), 2.68 (d, *J* = 5.7 Hz, 2H), 1.83 (d, *J* = 10.9 Hz, 1H), 1.78 (d, *J* = 10.8 Hz, 1H), 1.59 – 1.42 (m, 5H), 1.41 (s, 9H), 1.25 – 1.13 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.6, 79.6, 75.3, 72.4, 60.7 (br s), 58.5 (br s), 47.2, 33.1, 28.5, 27.9, 20.0 ppm. LCMS $(M+H)^+$: 257. HRMS (ESI): calc'd for: $C_{13}H_{25}N_2O_3$ $[M+H]^+$ 257.1865; found 257.1861.



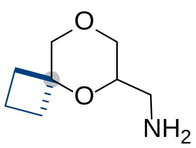
2,6-Dioxaspiro[4.5]decan-7-yl)methanamine hydrochloride (41b)

General procedure E was used. Yield: 1.9 g, 92%, beige solid, mp = 168-170 °C. Mixture of stereoisomers (d.r. = 1:1). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.16 (s, 3H), 3.87 (t, J = 8.6 Hz, 1H), 3.81 – 3.60 (m, 3H), 3.53 (d, J = 9.4 Hz), 3.44 (d, J = 9.1 Hz, 1H), 2.93 – 2.78 (m, 1H), 2.75 – 2.57 (m, 1H), 2.28 – 2.14 (m), 2.04 – 1.84 (m, 1H), 1.82 – 1.63 (m, 2H), 1.62 – 1.24 (m, 4H), 1.17 – 1.05 (m, 1H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 83.1, 82.8, 78.7, 72.5, 69.0, 68.6, 67.4, 65.9, 43.2, 43.1, 40.8, 33.1, 32.6, 31.5, 27.8, 27.7, 20.4, 20.1 ppm. LCMS $(M+H)^+$: 172. HRMS (ESI): calc'd for: $C_9H_{18}NO_2$ $[M+H]^+$ 172.1338; found 172.1336.



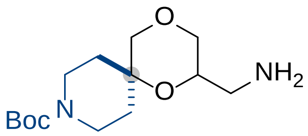
***Tert*-butyl 2-(aminomethyl)-1-oxa-9-azaspiro[5.5]undecane-9-carboxylate (42b)**

General procedure E was used. Yield: 2.4 g, 84%, brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.73 (br s, 2H), 3.50 – 3.39 (m, 1H), 3.19 (br s, 1H), 2.98 (t, J = 11.3 Hz, 1H), 2.64 (d, J = 5.5 Hz, 2H), 2.20 – 2.11 (m, 1H), 1.66 – 1.58 (m, 2H), 1.58 – 1.44 (m, 6H), 1.43 (s, 9H), 1.35 – 1.07 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.1, 79.3, 71.4, 70.3, 48.0, 39.5, 35.8, 29.3, 29.1, 28.6, 18.9 ppm. LCMS $(M+H)^+$: 285. HRMS (ESI): calc'd for: $C_{15}H_{29}N_2O_3$ $[M+H]^+$ 285.2178; found 285.2184.



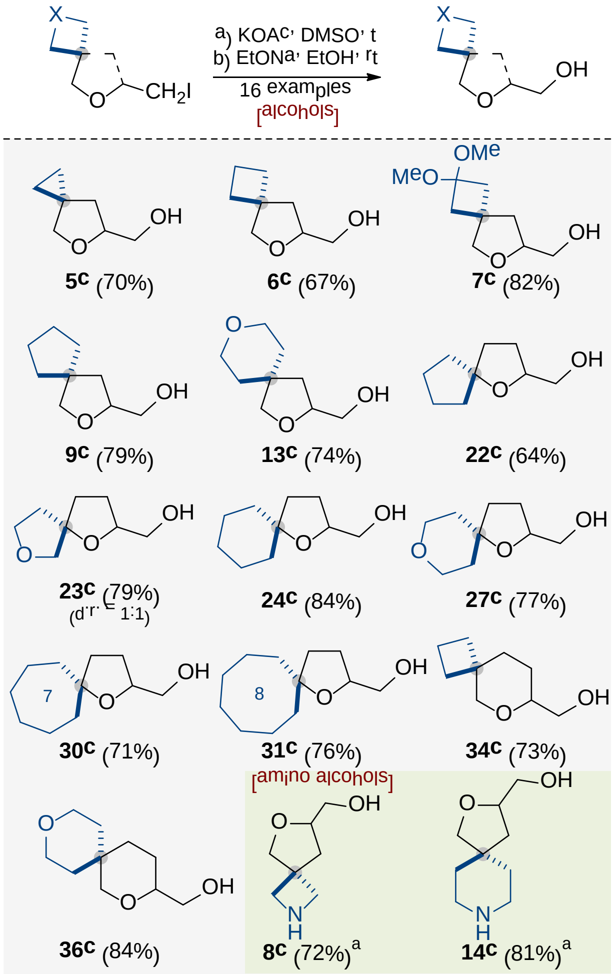
(5,8-Dioxaspiro[3.5]nonan-6-yl)methanamine hydrochloride (43b)

General procedure E was used. Yield: 1.4 g, 72%, yellow solid, mp 140-141 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 8.25 (br s, 3H), 3.81 (t, J = 9.4 Hz, 1H), 3.73 (t, J = 12.0 Hz, 2H), 3.24 – 3.06 (m, 2H), 2.85 (d, J = 11.3 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.17 – 2.06 (m, 1H), 2.06 – 1.88 (m, 2H), 1.83 – 1.65 (m, 2H), 1.64 – 1.47 (m, 1H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 74.7, 70.8, 67.2, 66.9, 30.0, 29.9, 12.1 ppm. HRMS (ESI): calc'd for $C_8H_{16}NO_2$ $[M+H]^+$ 158.1181; found 158.1177.



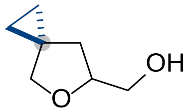
***Tert*-butyl 2-(aminomethyl)-1,4-dioxa-9-azaspiro[5.5]undecane-9-carboxylate (44b)**

General procedure E was used. Yield: 2.2 g, 78%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.92 – 3.58 (m, 5H), 3.51 (d, *J* = 11.4 Hz, 1H), 3.25 – 3.12 (m, 3H), 3.04 (t, *J* = 11.2 Hz, 1H), 2.67 – 2.61 (m, 2H), 2.32 (d, *J* = 13.9 Hz, 1H), 1.43 (s, 9H), 1.42 – 1.32 (m, 5H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.0, 79.5, 74.2, 69.7, 69.6, 69.5, 43.6, 39.0 (br s), 34.1, 28.8, 28.6 ppm. LCMS $(M+H)^+$: 287. HRMS (ESI): calc'd for: $C_{14}H_{27}N_2O_4$ $[M+H]^+$ 287.1971; found 287.1973.



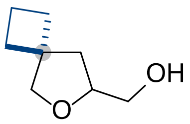
Scheme SI-1. Synthesis of *oxa*-spirocyclic alcohols **5c-7c**, **9c**, **8c**, **13c**, **14c**, **22c-24c**, **27c**, **30c**, **31c**, **34c**, **36c**. ([a]) After acidic *N*-Boc deprotection.

General procedure F for synthesis 5c-7c, 9c, 8c, 13c, 14c, 22c-24c, 27c, 30c, 31c, 34c and **36c** (**5c** as an example. Scale: 0.1 mol for all derivatives).



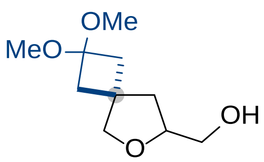
(5-Oxaspiro[2.4]heptan-6-yl)methanol (5c)

To a solution of **5a** (23.8 g, 0.1 mol, 1.0 equiv) in DMSO (130 mL) was added KOAc (29.4 g, 0.3 mol, 3.0 equiv). The mixture was vigorously stirred at 90 °C for 24 h. The mixture was diluted with water (130 mL) and extracted with MTBE (5 times). The combined organic layers were washed with brine (3 times), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title product as yellow oil. The residue (17.0 g, 0.1 mol, 1.0 equiv) was dissolved in EtOH (200 mL) and EtONa (10.2 g, 0.15 mol, 1.5 equiv) was added in portions at 5-10 °C under Ar. The mixture was vigorously stirred overnight at room temperature. After that NH_4Cl (5.3 g, 0.1 mol, 1.0 equiv) was added, and the mixture was stirred for 2 h at room temperature. The precipitate was filtered, washed with MTBE. The filtrate was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title product as brown oil. The final product was purified by column chromatography (hexane/EtOAc, gradient, 4:1 to 1:3). Yield: 8.9 g, 70%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.32 – 4.15 (m, 1H), 3.73 – 3.56 (m, 4H), 2.25 (s, 1H), 1.88 – 1.69 (m, 2H), 0.79 – 0.39 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.2, 80.3, 75.3, 65.0, 36.6, 22.6, 11.1, 10.6 ppm. HRMS (ESI): calc'd for: $C_7H_{13}O_2$ $[M+H]^+$ 129.0916; found 129.0914.



(6-Oxaspiro[3.4]octan-7-yl)methanol (6c)

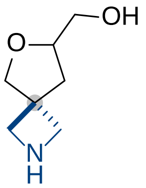
General procedure F was used. Yield: 9.5 g, 67%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.06 – 3.98 (m, 1H), 3.73 (s, 2H), 3.63 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.46 (dd, *J* = 11.6, 6.0 Hz, 1H), 2.29 (s, 1H), 2.02 – 1.93 (m, 5H), 1.93 – 1.79 (m, 2H), 1.70 (dd, *J* = 12.4, 8.1 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 79.3, 79.0, 65.1, 46.2, 40.8, 32.8, 31.1, 16.4 ppm. GCMS (M): 142. HRMS (ESI): calc'd for $C_8H_{15}O_2$ $[M+H]^+$ 143.1072; found 143.1075.



(2,2-Dimethoxy-6-oxaspiro[3.4]octan-7-yl)methanol (7c)

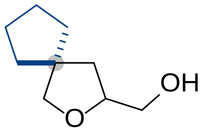
General procedure F was used. Yield: 16.5 g, 82%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 – 3.99 (m, 1H), 3.83 – 3.70 (m, 2H), 3.65 (dd, *J* = 11.7, 3.0 Hz, 1H), 3.53 – 3.41 (m, 1H), 3.13 (s, 3H), 3.12 (s, 3H), 2.29 (br s, 1H), 2.22 – 2.09 (m, 4H), 2.00 (dd, *J* = 12.6, 7.0 Hz, 1H), 1.79 (dd,

J = 12.5, 8.1 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 99.4, 79.4, 79.1, 64.9, 48.7, 48.6, 42.4, 40.97, 40.96, 36.7 ppm. HRMS (ESI): calc'd for $C_{10}H_{19}O_4$ $[M+H]^+$ 203.1283; found 203.1280.



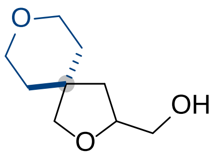
(6-Oxa-2-azaspiro[3.4]octan-7-yl)methanol (8c)

General procedure F was used. Yield: 10.3 g, 72%, yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.92 – 3.76 (m, 4H), 3.70 (d, J = 8.5 Hz, 1H), 3.57 – 3.40 (m, 3H), 3.31 (d, J = 4.9 Hz, 2H), 2.07 (dd, J = 12.6, 7.1 Hz, 1H), 1.80 (dd, J = 12.6, 7.3 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 79.2, 76.7, 63.6, 56.0 (br s), 55.7 (br s), 39.5 ppm. LCMS $(M+H)^+$: 144. HRMS (ESI): calc'd for: $C_7H_{14}NO_2$ $[M+H]^+$ 144.1025; found 144.1020.



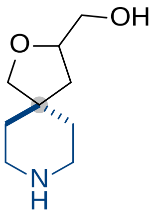
(2-Oxaspiro[4.4]nonan-3-yl)methanol (9c)

General procedure F was used. Yield: 12.3 g, 79%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.17 – 4.03 (m, 1H), 3.67 (dd, J = 11.7, 3.1 Hz, 1H), 3.59 (q, J = 8.1 Hz, 2H), 3.51 (dd, J = 11.6, 6.1 Hz, 1H), 2.66 (br s, 1H), 1.80 (dd, J = 12.2, 6.8 Hz, 1H), 1.72 – 1.35 (m, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 79.9, 78.7, 65.2, 51.1, 40.6, 37.6, 36.3, 24.9, 24.9 ppm. HRMS (ESI): calc'd for $C_9H_{17}O_2$ $[M+H]^+$ 157.1229; found 157.1223.



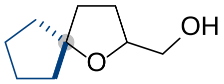
(2,8-Dioxaspiro[4.5]decan-3-yl)methanol (13c)

General procedure F was used. Yield: 12.7 g, 74%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.16 – 3.99 (m, 1H), 3.72 – 3.56 (m, 7H), 3.55 – 3.43 (m, 1H), 2.38 (br s, 1H), 1.87 (dd, J = 12.5, 7.0 Hz, 1H), 1.66 – 1.36 (m, 5H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 79.2, 78.0, 65.8, 65.5, 64.9, 41.7, 39.0, 36.1, 35.6 ppm. GCMS (M): 172. HRMS (ESI): calc'd for $C_9H_{17}O_3$ $[M+H]^+$ 173.1178; found 173.1175.



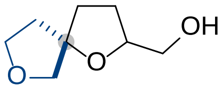
(2-Oxa-8-azaspiro[4.5]decan-3-yl)methanol (14c)

General procedure F was used. Yield: 13.8 g, 81%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.16 – 3.97 (m, 1H), 3.72 – 3.53 (m, 3H), 3.53 – 3.41 (m, 1H), 2.91 – 2.65 (m, 6H), 1.82 (dd, *J* = 12.5, 7.0 Hz, 1H), 1.63 – 1.51 (m, 3H), 1.47 (dd, *J* = 12.5, 8.9 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 79.3, 78.1, 64.9, 44.2, 43.8, 42.6, 39.4, 36.3, 35.6 ppm. GCMS (M): 171. HRMS (ESI): calc'd for $C_9H_{18}NO_2$ $[M+H]^+$ 172.1338; found 172.1331.



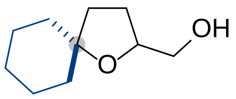
(1-Oxaspiro[4.4]nonan-2-yl)methanol (22c)

General procedure F was used. Yield: 10 g, 64%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.05 – 3.96 (m, 1H), 3.61 (dd, *J* = 11.4, 3.4 Hz, 1H), 3.45 (dd, *J* = 11.4, 5.7 Hz, 1H), 2.44 (s, 1H), 1.98 – 1.87 (m, 1H), 1.84 – 1.63 (m, 7H), 1.62 – 1.39 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 92.0, 78.6, 65.5, 38.9, 38.2, 36.6, 27.8, 24.1 ppm. GCMS (M): 156. HRMS (ESI): calc'd for $C_9H_{17}O_2$ $[M+H]^+$ 157.1229; found 157.1225.



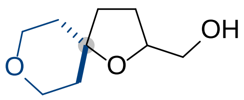
1,7-Dioxaspiro[4.4]nonan-2-yl)methanol (23c)

General procedure F was used. Yield: 12.5 g, 79%, colorless oil. Mixture of stereoisomers (d.r. = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.15 – 4.00 (m, 1H), 3.99 – 3.82 (m, 2H), 3.77 (dd, *J* = 15.9, 9.2 Hz, 1H), 3.71 – 3.43 (m, 3H), 2.28 (br s, 1H), 2.14 – 2.02 (m, 1H), 2.02 – 1.67 (m, 5H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 90.0, 89.9, 79.5, 79.3, 77.4, 77.0, 68.0, 68.0, 65.1, 39.3, 38.6, 34.0, 33.6, 27.6, 27.6 ppm. GCMS (M): 158. HRMS (ESI): calc'd for $C_8H_{15}O_3$ $[M+H]^+$ 159.1021; found 159.1023.



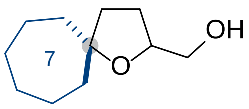
(1-Oxaspiro[4.5]decan-2-yl)methanol (24c)

General procedure F was used. Yield: 14.3 g, 84%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.13 – 4.00 (m, 1H), 3.65 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.45 (dd, *J* = 11.3, 5.5 Hz, 1H), 2.12 (br s, 1H), 1.98 – 1.84 (m, 1H), 1.78 – 1.63 (m, 5H), 1.59 – 1.45 (m, 4H), 1.42 – 1.27 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 83.5, 78.3, 65.4, 38.5, 37.4, 36.1, 27.2, 25.8, 24.2, 23.9 ppm. GCMS (M): 170. HRMS (ESI): calc'd for $C_{10}H_{19}O_2$ $[M+H]^+$ 171.1385; found 171.1388.



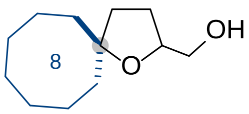
(1,8-Dioxaspiro[4.5]decan-2-yl)methanol (27c)

General procedure F was used. Yield: 13.2 g, 77%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.15 – 4.01 (m, 1H), 3.84 – 3.76 (m, 2H), 3.69 – 3.57 (m, 3H), 3.47 (dd, *J* = 11.4, 5.6 Hz, 1H), 2.12 (br s, 1H), 2.02 – 1.87 (m, 1H), 1.84 – 1.72 (m, 3H), 1.67 – 1.57 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 80.2, 78.6, 65.6, 65.5, 65.4, 38.6, 37.5, 36.7, 26.9 ppm. GCMS (M): 172. HRMS (ESI): calc'd for $C_9H_{17}O_3$ $[M+H]^+$ 173.1178; found 173.1174.



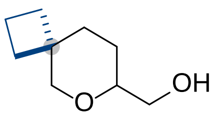
(1-Oxaspiro[4.6]undecan-2-yl)methanol (30c)

General procedure F was used. Yield: 13 g, 71%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.09 – 3.98 (m, 1H), 3.66 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.45 (dd, *J* = 11.4, 5.3 Hz, 1H), 2.14 (br s, 1H), 1.95 – 1.82 (m, 1H), 1.80 – 1.27 (m, 14H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 87.2, 65.3, 41.6, 40.4, 40.1, 38.2, 29.6, 29.5, 27.1, 23.3 ppm. GCMS (M): 184. HRMS (ESI): calc'd for $C_{11}H_{21}O_2$ $[M+H]^+$ 185.1542; found 185.1538.



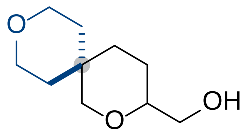
(1-Oxaspiro[4.7]dodecan-2-yl)methanol (31c)

General procedure F was used. Yield: 15 g, 76%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.59 – 4.47 (m, 1H), 4.15 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.95 (dd, *J* = 11.3, 5.2 Hz, 1H), 2.64 (br s, 1H), 2.48 – 2.36 (m, 1H), 2.32 – 1.96 (m, 17H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 87.0, 78.3, 65.3, 37.2, 36.8, 35.5, 28.5, 28.3, 27.4, 24.8, 23.0, 22.8 ppm. GCMS (M): 198. HRMS (ESI): calc'd for $C_{12}H_{23}O_2$ $[M+H]^+$ 199.1698; found 199.1694.



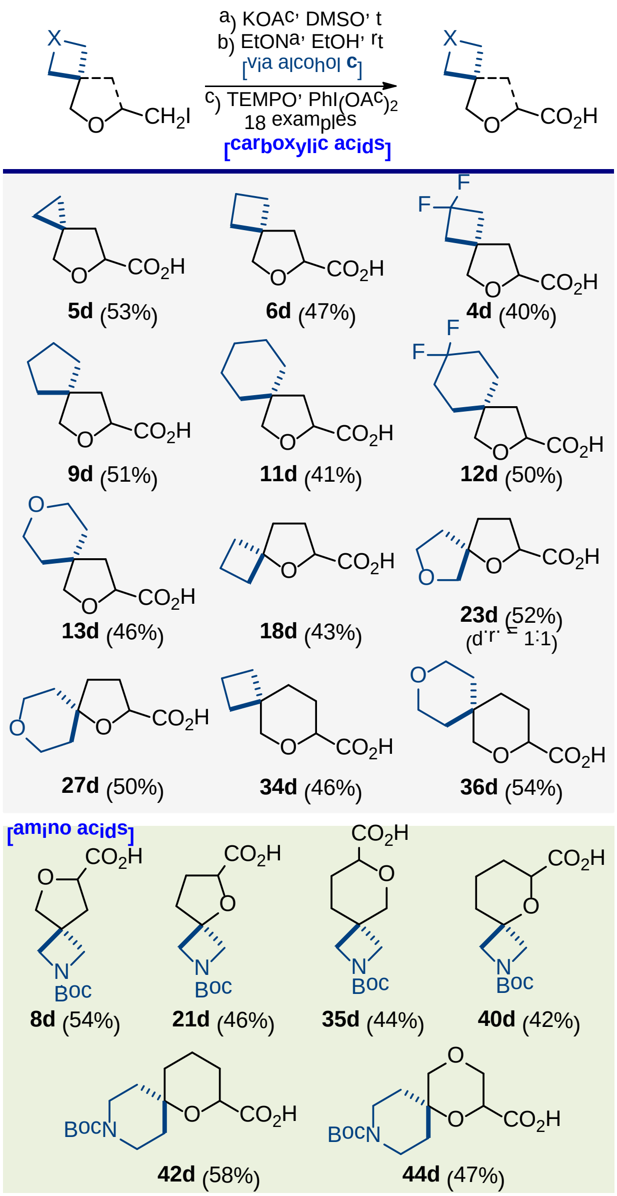
(6-Oxaspiro[3.5]nonan-7-yl)methanol (34c)

General procedure F was used. Yield: 11.4 g, 73%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.85 (dd, *J* = 11.1, 2.2 Hz, 1H), 3.60 – 3.38 (m, 2H), 3.36 – 3.26 (m, 1H), 3.23 (d, *J* = 11.0 Hz, 1H), 2.28 (s, 1H), 2.06 – 1.92 (m, 1H), 1.88 – 1.80 (m, 3H), 1.78 – 1.70 (m, 1H), 1.64-1.53 (m, 2H), 1.45 – 1.21 (m, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 77.9, 76.1, 66.1, 38.1, 35.5, 35.3, 30.3, 29.1, 24.2, 15.4 ppm. GCMS (M): 184. HRMS (ESI): calc'd for $C_9H_{17}O_2$ $[M+H]^+$ 157.1229; found 157.1227.



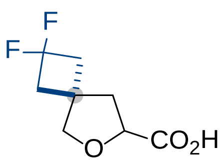
(2,9-Dioxaspiro[5.5]undecan-3-yl)methanol (36c)

General procedure F was used. Yield: 15.6 g, 84%, orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.96 – 3.84 (m, 1H), 3.70 – 3.44 (m, 6H), 3.43 – 3.31 (m, 1H), 3.14 (d, *J* = 11.4 Hz, 1H), 2.31 (s, 1H), 1.90 – 1.81 (m, 1H), 1.78 – 1.67 (m, 1H), 1.62 – 1.54 (m, 1H), 1.54 – 1.40 (m, 1H), 1.40 – 1.16 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 78.8, 75.5, 66.0, 63.9, 63.3, 36.0, 33.6, 31.6, 30.5, 22.9 ppm. GCMS (M): 186. HRMS (ESI): calc'd for $C_{10}H_{19}O_3$ $[M+H]^+$ 187.1334; found 187.1331.



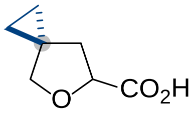
Scheme 4. Synthesis of *oxa*-spirocyclic carboxylic acids and amino acids **4d-6d**, **8d**, **9d**, **11d-13d**, **18d**, **21d**, **23d**, **27d**, **34d-36d**, **40d**, **42d** and **44d**.

General procedure G for synthesis 4d-6d, 8d, 9d, 11d-13d, 18d, 21d, 23d, 27d, 34d-36d, 40d, 42d and **44d** (**4d** as an example. Scale: 0.1 mol for all derivatives).



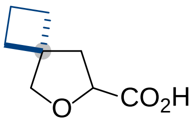
2,2-Difluoro-6-oxaspiro[3.4]octane-7-carboxylic acid (4d)

TEMPO (3.1 g, 0.02 mol, 0.2 equiv) and PhI(OAc)$_2$ (64.4 g, 0.2 mol, 2.0 equiv) were added to a solution of (2,2-difluoro-6-oxaspiro[3.4]octan-7-yl)methanol (17.8 g, 0.1 mol 1.0 equiv) in 2:1 CH_2Cl_2/H_2O (200:100 mL). The mixture was stirred at room temperature for 22 h, and then poured into a sat. aq solution of $Na_2S_2O_3$ (20 mL) and extracted with EtOAc (3 × 200 mL). The organic layers were combined, dried over Mg_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane-EtOAc (4:1)). Yield: 7.7 g, 40%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.85 (br s, 1H), 4.56 (t, *J* = 7.3 Hz, 1H), 4.02 (d, *J* = 8.7 Hz, 1H), 3.92 (d, *J* = 8.7 Hz, 1H), 2.61 (t, *J* = 12.1 Hz, 4H), 2.53 – 2.40 (m, 1H), 2.29 (dd, *J* = 13.0, 6.1 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 177.1, 118.6 (t, *J* = 278.0 Hz), 78.9 (dd, *J* = 5.4, 2.0 Hz), 76.1, 44.6 (t, *J* = 23.2 Hz), 44.0 (t, *J* = 23.3 Hz), 42.3 (d, *J* = 4.4 Hz), 34.8 (t, *J* = 10.1 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -90.9 (d, *J* = 197.0 Hz), -92.5 (d, *J* = 197.0 Hz) ppm. HRMS (ESI): calc'd for: $C_8H_{11}F_2O_3$ [M+H]$^+$ 193.0676; found 193.0678.



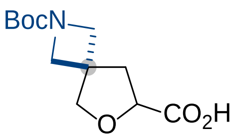
5-Oxaspiro[2.4]heptane-6-carboxylic acid (5d)

General procedure G was used. Yield: 7.5 g, 53%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.98 (br s, 1H), 4.66 (dd, *J* = 8.3, 5.4 Hz, 1H), 3.85 (d, *J* = 8.0 Hz, 1H), 3.79 (d, *J* = 8.0 Hz, 1H), 2.30 (dd, *J* = 12.6, 8.3 Hz, 1H), 2.07 (dd, *J* = 12.6, 5.4 Hz, 1H), 0.84 – 0.56 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 177.3, 77.0, 76.1, 38.8, 21.8, 10.8, 9.4 ppm. LCMS (M+H)$^+$: 143. HRMS (ESI): calc'd for: $C_7H_{11}O_3$ [M+H]$^+$ 143.0708; found 143.0705.



6-Oxaspiro[3.4]octane-7-carboxylic acid (6d)

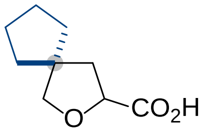
General procedure G was used. Yield: 7.3 g, 47%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.76 (br s, 1H), 4.48 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.93 (d, *J* = 8.4 Hz, 1H), 3.84 (d, *J* = 8.4 Hz, 1H), 2.36 (dd, *J* = 12.7, 8.4 Hz, 1H), 2.16 (dd, *J* = 12.7, 6.4 Hz, 1H), 2.10 – 1.81 (m, 6H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 177.1, 79.9, 76.1, 45.6, 42.9, 31.4, 30.8, 16.4 ppm. HRMS (ESI): calc'd for: $C_8H_{13}O_3$ [M+H]$^+$ 157.0865; found 157.0862.



2-(*Tert*-butoxycarbonyl)-6-oxa-2-azaspiro[3.4]octane-7-carboxylic acid (8d)

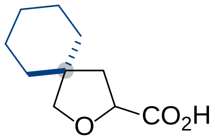
General procedure G was used. Yield: 13.9 g, 54%, white solid, mp = 92-93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.10 (br s, 2H), 4.54 (dd, *J* = 8.4, 5.1 Hz, 1H), 4.16 (d, *J* = 8.9 Hz, 1H), 3.97 (d, *J* = 8.9 Hz, 1H), 3.92 – 3.84 (m, 4H), 2.53 – 2.34 (m, 2H), 1.42 (s, 9H) ppm. ^{13}C NMR (151 MHz,

$CDCl_3$) δ = 175.7, 156.6, 80.6, 78.0, 76.3, 59.0, 58.0, 41.3, 40.2, 28.5 ppm. LCMS $(M-H)^-$: 256. HRMS (ESI): calc'd for $C_{12}H_{20}NO_5$ $[M+H]^+$: 258.1341; found: 258.1343.



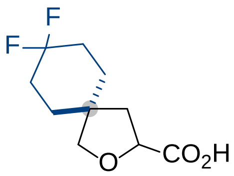
2-Oxaspiro[4.4]nonane-3-carboxylic acid (9d)

General procedure G was used. Yield: 8.7 g, 51%, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 10.24 (br s, 1H), 4.54 (t, J = 7.8 Hz, 1H), 3.78 (d, J = 8.1 Hz, 1H), 3.70 (d, J = 8.0 Hz, 1H), 2.24 (dd, J = 12.6, 8.4 Hz, 1H), 2.02 (dd, J = 12.6, 7.3 Hz, 1H), 1.76 – 1.51 (m, 8H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.9, 79.8, 76.6, 50.7, 43.0, 36.7, 35.5, 25.0, 24.9 ppm. HRMS (ESI): calc'd for: $C_9H_{15}O_3$ $[M+H]^+$ 171.1021; found 171.1025.



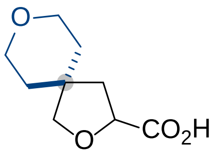
2-Oxaspiro[4.5]decane-3-carboxylic acid (11d)

General procedure G was used. Yield: 7.5 g, 41%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.47 (br s, 1H), 4.52 (t, J = 7.6 Hz, 1H), 3.73 (s, 2H), 2.21 (dd, J = 12.9, 8.7 Hz, 1H), 1.86 (dd, J = 12.9, 7.5 Hz, 1H), 1.49 – 1.41 (m, 8H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 177.5, 79.4, 76.1, 43.9, 35.3, 34.9, 26.0, 24.0, 23.6 ppm. HRMS (ESI): calc'd for: $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1178; found 185.1174.



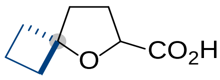
8,8-Difluoro-2-oxaspiro[4.5]decane-3-carboxylic acid (12d)

General procedure G was used. Yield: 11.0 g, 50%, yellow solid, mp = 67-69 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.50 (br s, 1H), 4.58 (t, J = 8.0 Hz, 1H), 3.83 – 3.71 (m, 2H), 2.26 (dd, J = 12.9, 8.9 Hz, 1H), 2.02 – 1.80 (m, 5H), 1.76 – 1.62 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.5, 122.9 (t, J = 241.3 Hz), 78.1, 76.0, 42.7, 40.6, 31.8 (t, J = 24.8 Hz), 31.5 (t, J = 25.5 Hz), 31.2, 30.9 (t, J = 4.9 Hz) ppm. HRMS (ESI): calc'd for: $C_{10}H_{15}F_2O_3$ $[M+H]^+$ 221.0989; found 221.0985.



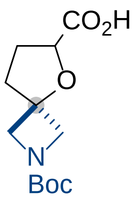
2,8-Dioxaspiro[4.5]decane-3-carboxylic acid (13d)

General procedure G was used. Yield: 8.6 g, 46%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.90 (br s, 1H), 4.56 (dd, *J* = 8.5, 7.4 Hz, 1H), 3.80 (s, 2H), 3.69 (t, *J* = 5.3 Hz, 2H), 3.67 – 3.61 (m, 2H), 2.30 (dd, *J* = 13.0, 8.7 Hz, 1H), 1.96 (dd, *J* = 13.0, 7.2 Hz, 1H), 1.70 – 1.53 (m, 4H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.1, 78.7, 75.9, 65.7, 65.4, 41.5, 41.4, 35.0, 34.9 ppm. LCMS (M-H)$^-$: 185. HRMS (ESI): calc'd for: $C_9H_{15}O_4$ [M+H]$^+$ 187.0970; found 187.0974.



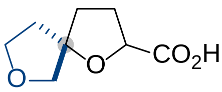
5-Oxaspiro[3.4]octane-6-carboxylic acid (18d)

General procedure G was used. Yield: 6.7 g, 43%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.95 (br s, 1H), 4.47 (dd, *J* = 8.3, 6.0 Hz, 1H), 2.45 – 2.23 (m, 3H), 2.18 – 2.05 (m, 1H), 2.05 – 1.91 (m, 4H), 1.79 – 1.64 (m, 1H), 1.61 – 1.40 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 177.1, 85.8, 76.4, 35.7, 35.3, 29.4, 12.6 ppm. GCMS (M): 156. HRMS (ESI): calc'd for $C_8H_{13}O_3$ [M+H]$^+$ 157.0865; found 157.0862.



2-(*Tert*-butoxycarbonyl)-5-oxa-2-azaspiro[3.4]octane-6-carboxylic acid (21d)

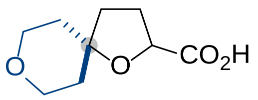
General procedure G was used. Yield: 11.8 g, 46%, beige solid, mp = 118-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.38 (br s, 1H), 4.56 (t, *J* = 5.9 Hz, 1H), 4.20 (d, *J* = 9.3 Hz, 1H), 4.08 (d, *J* = 9.2 Hz, 1H), 3.88 (t, *J* = 8.6 Hz, 2H), 2.42 – 2.25 (m, 1H), 2.25 – 2.01 (m, 3H), 1.42 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.7, 80.3, 80.1, 77.3, 62.4, 61.5, 35.3, 29.7, 28.5 ppm. LCMS (M-H)$^-$: 256. HRMS (ESI): calc'd for: $C_{12}H_{20}NO_5$ [M+H]$^+$ 258.1341; found 258.1344.



1,7-Dioxaspiro[4.4]nonane-2-carboxylic acid (23d)

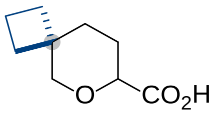
General procedure G was used. Yield: 8.9 g, 52%, yellow oil. Mixture of stereoisomers (d.r. = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.77 (br s, 1H), 4.54 (dd, *J* = 14.1, 8.2 Hz, 1H), 4.07 – 3.79 (m, 3H), 3.66 (dd, *J* = 20.0, 9.4 Hz, 1H), 2.46 – 2.09 (m, 3H), 2.08 – 1.84 (m, 3H) ppm. ^{13}C NMR (126

MHz, $CDCl_3$) δ = 177.0, 176.9, 92.0, 76.8, 76.7, 76.63, 76.57, 68.1, 67.9, 38.7, 38.5, 33.3, 33.2, 30.7, 30.6 ppm. GCMS (M): 172. HRMS (ESI): calc'd for $C_8H_{13}O_4$ $[M+H]^+$ 173.0814; found 173.0811.



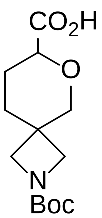
1,8-Dioxaspiro[4.5]decane-2-carboxylic acid (27d)

General procedure G was used. Yield: 9.3 g, 50%, white solid, mp = 86-87 °C. Mixture of stereoisomers (d.r. = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.82 (br s, 1H), 4.55 (dd, *J* = 8.3, 5.9 Hz, 1H), 3.92 – 3.62 (m, 4H), 2.66 – 1.99 (m, 3H), 1.95 – 1.42 (m, 5H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 176.7, 176.4, 83.1, 82.7, 76.2, 65.4, 65.2, 64.3, 37.6, 37.2, 37.1, 36.0, 33.4, 29.6, 28.3 ppm. HRMS (ESI): calc'd for $C_9H_{15}O_4$ $[M+H]^+$ 187.0970; found 187.0966.



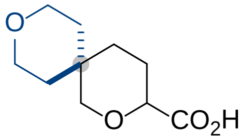
6-Oxaspiro[3.5]nonane-7-carboxylic acid (34d)

General procedure G was used. Yield: 7.8 g, 46%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) = δ 9.46 (br s, 1H), 3.95 (d, *J* = 12.3 Hz, 1H), 3.93 – 3.89 (m, 1H), 3.33 (d, *J* = 11.3 Hz, 1H), 2.07 – 1.82 (m, 5H), 1.80 – 1.70 (m, 1H), 1.69 – 1.56 (m, 3H), 1.55 – 1.43 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.6, 75.9, 75.2, 35.0, 30.1, 28.8, 25.4, 15.3 ppm. LCMS $(M-H)^-$: 169. HRMS (ESI): calc'd for: $C_9H_{15}O_3$ $[M+H]^+$ 171.1021; found 171.1020.



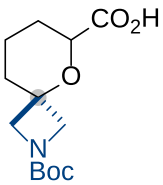
2-(*Tert*-butoxycarbonyl)-6-oxa-2-azaspiro[3.5]nonane-7-carboxylic acid (35d)

General procedure G was used. Yield: 12.5 g, 46%, yellow solid, mp = 126-128 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.62 (br s, 1H), 3.93 – 3.84 (m, 2H), 3.63 – 3.52 (m, 2H), 3.49 – 3.41 (m, 3H), 1.89 (d, *J* = 13.5 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.72 – 1.62 (m, 1H), 1.55 – 1.45 (m, 1H), 1.37 (s, 9H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.0, 155.6, 78.5, 74.1, 72.3, 32.8, 31.4, 28.1, 25.0 ppm. LCMS $(M-H)^-$: 270. HRMS (ESI): calc'd for: $C_{13}H_{22}NO_5$ $[M+H]^+$ 272.1498; found 272.14915.



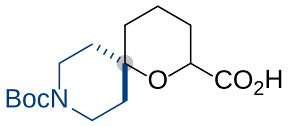
2,9-Dioxaspiro[5.5]undecane-3-carboxylic acid (36d)

General procedure G was used. Yield: 10.8 g, 54%, orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.75 (br s, 1H), 4.06 – 3.92 (m, 2H), 3.76 – 3.53 (m, 4H), 1.99 – 1.72 (m, 4H), 1.68 – 1.30 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.1, 76.1, 75.1, 63.8, 63., 35., 33.8, 31.6, 30.1, 24.1 ppm. LCMS $(M-H)^-$: 199. HRMS (ESI): calc'd for: $C_{10}H_{17}O_4$ $[M+H]^+$ 201.1127; found 201.1125.



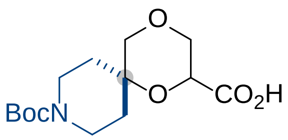
2-(*Tert*-butoxycarbonyl)-5-oxa-2-azaspiro[3.5]nonane-6-carboxylic acid (40d)

General procedure G was used. Yield: 11.4 g, 42%, yellow solid, mp = 122-123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.00 (dd, *J* = 16.7, 9.2 Hz, 2H), 3.88 (d, *J* = 8.9 Hz, 1H), 3.78 (t, *J* = 8.2 Hz, 2H), 2.09 – 1.96 (m, 1H), 1.92 (d, *J* = 11.3 Hz, 2H), 1.70 – 1.32 (m, 3H), 1.44 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.6, 156.6, 80.2, 73.6, 72.1, 32.3, 28.5, 27.7, 19.9 ppm. LCMS $(M-H)^-$: 270. HRMS (ESI): calc'd for: $C_{13}H_{22}NO_5$ $[M+H]^+$ 272.1498; found 272.1495.



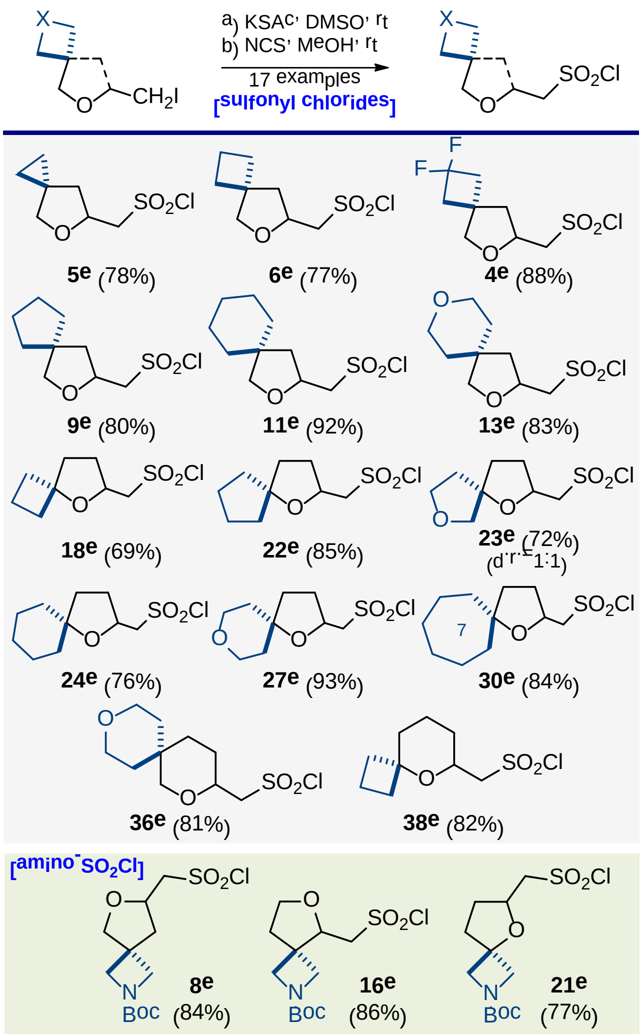
9-(*Tert*-butoxycarbonyl)-1-oxa-9-azaspiro[5.5]undecane-2-carboxylic acid (42d)

General procedure G was used. Yield: 17.3 g, 58%, orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.52 (br s, 1H), 4.14 (d, *J* = 10.3 Hz, 1H), 3.71 (d, *J* = 13.2 Hz, 2H), 3.31 – 3.19 (m, 1H), 3.03 (t, *J* = 11.3 Hz, 1H), 2.07 (t, *J* = 14.8 Hz, 2H), 1.80 – 1.70 (m, 2H), 1.69 – 1.46 (m, 4H), 1.43 (s, 9H), 1.41 – 1.27 (m, 2H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.7, 155.0, 79.8, 73.0, 69.2, 39.4 (br s), 39.3 (br s), 38.9, 34.5, 29.2, 28.6, 28.4, 18.7 ppm. LCMS $(M-H)^-$: 298. HRMS (ESI): calc'd for: $C_{15}H_{26}NO_5$ $[M+H]^+$ 300.1811; found 300.1814.



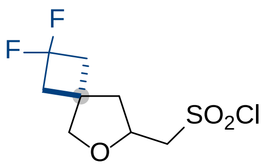
9-(*Tert*-butoxycarbonyl)-1,4-dioxa-9-azaspiro[5.5]undecane-2-carboxylic acid (44d)

General procedure G was used. Yield: 14.1 g, 47%, yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.99 (br s, 1H), 4.47 (dd, *J* = 10.6, 3.1 Hz, 1H), 4.10 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.80 – 3.64 (m, 2H), 3.59 (d, *J* = 11.6 Hz, 1H), 3.45 (t, *J* = 11.1 Hz, 1H), 3.37 – 3.25 (m, 2H), 3.13 (t, *J* = 11.2 Hz, 1H), 2.24 (d, *J* = 14.1 Hz, 1H), 1.65 – 1.20 (m, 12H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 171.4, 155.1, 80.2, 73.6, 71.5, 67.8, 39.3 (br s), 33.6, 28.6, 28.5 ppm. LCMS $(M-H)^-$: 300. HRMS (ESI): calc'd for: $C_{14}H_{24}NO_6$ $[M+H]^+$ 302.1604; found 302.1600.



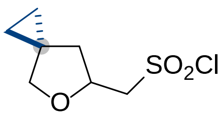
Scheme 5. Synthesis of *oxa*-spirocyclic sulfonyl chlorides **4e-6e**, **8e**, **9e**, **11e**, **13e**, **16e**, **18e**, **21e-24e**, **27e**, **30e**, **36e**, **38e**.

General procedure H for synthesis 4e-6e, 8e, 9e, 11e, 13e, 16e, 18e, 21e-24e, 27e, 30e, 36e and **38e** (**4e** as an example. Scale: 0.1 mol for all derivatives).



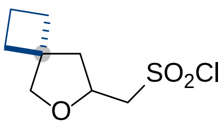
(2,2-Difluoro-6-oxaspiro[3.4]octan-7-yl)methanesulfonyl chloride (4e)

To a solution of **4a** (28.8 g, 0.1 mol, 1.0 equiv) in 150 mL of DMSO was added potassium thioacetate (22.8 g, 0.2 mol, 2.0 equiv). The mixture was stirred at room temperature overnight. The mixture was diluted with water (150 mL) and extracted with MTBE (5 times). The combined organic phases were washed with brine (3 times), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was dissolved in MeCN (500 mL) and 2M HCl (50 mL), and then NCS (58.7 g, 0.44 mol, 4.4 eqiuv) was added in portions at 15-16 °C. The mixture was stirred for 1 h at room temperature and concentrated. The residue was dissolved in MTBE, washed with a saturated solution of $NaHCO_3$ (3 times). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title product. Yield: 22.9 g, 88%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.56 (p, *J* = 6.5 Hz, 1H), 4.01 (dd, *J* = 14.1, 6.6 Hz, 1H), 3.89 (q, *J* = 8.9 Hz, 2H), 3.81 (dd, *J* = 14.1, 5.4 Hz, 1H), 2.63 (q, *J* = 11.9 Hz, 4H), 2.44 (dd, *J* = 12.9, 6.5 Hz, 1H), 1.99 (dd, *J* = 12.9, 8.3 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 118.6 (t, *J* = 278.1 Hz), 78.3 (dd, *J* = 5.3, 2.2 Hz), 73.1, 69.7, 45.8 (t, *J* = 22.8 Hz), 44.1 (d, *J* = 4.1 Hz), 43.6 (t, *J* = 23.5 Hz), 35.1 (t, *J* = 10.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -91.7 (q, *J* = 197.1 Hz) ppm. HRMS (ESI): calc'd for: $C_8H_{12}ClF_2O_3S$ $[M+H]^+$ 261.0164; found 261.0161.



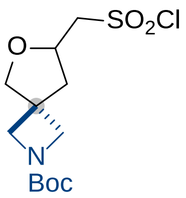
(5-Oxaspiro[2.4]heptan-6-yl)methanesulfonyl chloride (5e)

General procedure H was used. Yield: 16.4 g, 78%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ =4.83 – 4.68 (m, 1H), 4.08 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.88 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.78 (d, *J* = 8.1 Hz, 1H), 3.72 (d, *J* = 8.1 Hz, 1H), 2.18 (dd, *J* = 12.5, 6.6 Hz, 1H), 1.88 (dd, *J* = 12.5, 6.5 Hz, 1H), 0.87 – 0.42 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 75.3, 73.9, 69.9, 40.4, 21.8, 10.7, 10.2 ppm. LCMS $(RSO_3H\text{-}H)^-$: 191. HRMS (ESI): calc'd for: $C_7H_{12}ClO_3S$ $[M+H]^+$ 211.0196; found 211.0194.



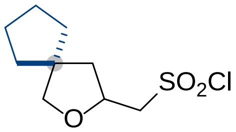
(6-Oxaspiro[3.4]octan-7-yl)methanesulfonyl chloride (6e)

General procedure H was used. Yield: 17.3 g, 77%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.51 (p, *J* = 6.7 Hz, 1H), 3.97 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.84 – 3.74 (m, 3H), 2.34 (dd, *J* = 12.6, 6.5 Hz, 1H), 2.14 – 1.86 (m, 6H), 1.82 (dd, *J* = 12.7, 7.9 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.2, 79.4, 72.9, 70.3, 45.9, 44.7, 32.6, 30.8, 16.5 ppm. HRMS (ESI): calc'd for: $C_8H_{14}ClO_3S$ $[M+H]^+$ 225.0352; found 225.0348.



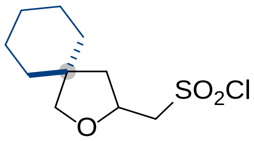
***Tert*-butyl 7-((chlorosulfonyl)methyl)-6-oxa-2-azaspiro[3.4]octane-2-carboxylate (8e)**

General procedure H was used. Yield: 27.3 g, 84%, white solid, mp = 126-127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.62 – 4.47 (m, 1H), 4.04 – 3.89 (m, 7H), 3.79 (dd, *J* = 14.1, 5.4 Hz, 1H), 2.52 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.04 (dd, *J* = 13.0, 8.2 Hz, 1H), 1.43 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.2, 80.1, 77.5, 73.2, 69.6, 59.7, 57.8, 43.1, 40.5, 28.5 ppm. HRMS (ESI): calc'd for $C_{12}H_{21}ClNO_5S$ $[M+H]^+$ 326.0829; found 326.0822.



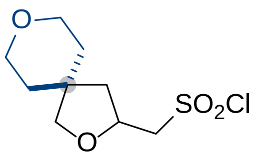
(2-Oxaspiro[4.4]nonan-3-yl)methanesulfonyl chloride (9e)

General procedure H was used. Yield: 19.1 g, 80%, orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.66 – 4.55 (m, 1H), 4.02 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.81 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.69 (d, *J* = 8.2 Hz, 1H), 3.63 (d, *J* = 8.2 Hz, 1H), 2.18 (dd, *J* = 12.5, 6.6 Hz, 1H), 1.73 (dd, *J* = 12.5, 8.6 Hz, 1H), 1.69 – 1.46 (m, 7H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 79.2, 73.4, 70.5, 50.9, 44.9, 37.3, 36.2, 24.9 ppm. HRMS (ESI): calc'd for: $C_9H_{16}ClO_3S$ $[M+H]^+$ 239.0509; found 239.0514.



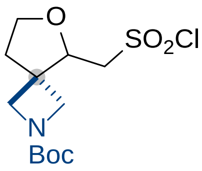
(2-Oxaspiro[4.5]decan-3-yl)methanesulfonyl chloride (11e)

General procedure H was used. Yield: 23.2 g, 92%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.63 – 4.52 (m, 1H), 4.01 (dd, *J* = 14.0, 6.9 Hz, 1H), 3.80 (dd, *J* = 14.0, 4.9 Hz, 1H), 3.65 (s, 2H), 2.15 (dd, *J* = 12.7, 6.8 Hz, 1H), 1.56 – 1.36 (m, 11H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 78.9, 72.9, 70.6, 44.1, 36.6, 35.2, 25.9, 24.2, 23.5 ppm. HRMS (ESI): calc'd for: $C_{10}H_{18}ClO_3S$ $[M+H]^+$ 253.0665; found 253.0662.



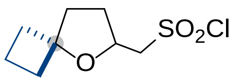
(2,8-Dioxaspiro[4.5]decan-3-yl)methanesulfonyl chloride (13e)

General procedure H was used. Yield: 21.1 g, 83%, beige solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.66 – 4.54 (m, 1H), 4.03 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.82 (dd, *J* = 14.0, 5.1 Hz, 1H), 3.77 – 3.56 (m, 6H), 2.26 (dd, *J* = 12.8, 6.7 Hz, 1H), 1.82 – 1.45 (m, 5H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 78.1, 72.8, 70.2, 65.7, 65.3, 43.7, 41.8, 36.1, 35.2 ppm. LCMS (RSO_3H-H)$^-$: 235. HRMS (ESI): calc'd for: $C_9H_{16}ClO_4S$ $[M+H]^+$ 255.0458; found 255.0454.



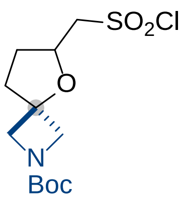
***Tert*-butyl 5-((chlorosulfonyl)methyl)-6-oxa-2-azaspiro[3.4]octane-2-carboxylate (16e)**

General procedure H was used. Yield: 27.7 g, 85%, beige solid, mp = 89-91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.40 (dd, *J* = 8.8, 1.8 Hz, 1H), 4.07 – 3.86 (m, 5H), 3.83 (d, *J* = 8.8 Hz, 2H), 3.76 (d, *J* = 9.3 Hz, 1H), 2.33 – 2.10 (m, 2H), 1.44 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.3, 80.5, 78.2, 67.1, 66.7, 57.0, 55.3, 43.4, 37.0, 28.4 ppm. HRMS (ESI): calc'd for $C_{12}H_{21}ClNO_5S$ $[M+H]^+$ 326.0829; found 326.0832.



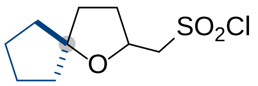
(5-Oxaspiro[3.4]octan-6-yl)methanesulfonyl chloride (18e)

General procedure H was used. Yield: 15.5 g, 69%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.56 (p, *J* = 6.4 Hz, 1H), 3.94 (dd, *J* = 13.9, 6.0 Hz, 1H), 3.73 (dd, *J* = 13.9, 6.2 Hz, 1H), 2.39 – 2.16 (m, 3H), 2.11 – 1.92 (m, 4H), 1.84 (dt, *J* = 14.6, 7.6 Hz, 1H), 1.77 – 1.60 (m, 1H), 1.52 (dq, *J* = 19.5, 9.8 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 143.2, 84.5, 72.9, 70.7, 36.3, 36.0, 35.5, 30.9, 12.7 ppm. LCMS (RSO_3H-H)$^-$: 205. HRMS (ESI): calc'd for $C_8H_{14}ClO_3S$ $[M+H]^+$ 225.0352; found 225.0354.



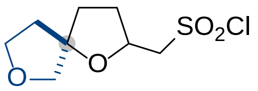
***Tert*-butyl 6-((chlorosulfonyl)methyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (21e)**

General procedure H was used. Yield: 25.1 g, 77%, yellow solid, mp = 85-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.69 – 4.55 (m, 1H), 4.14 – 4.03 (m, 2H), 4.00 (dd, *J* = 14.1, 6.2 Hz, 1H), 3.93 – 3.84 (m, 2H), 3.81 (dd, *J* = 14.1, 5.8 Hz, 1H), 2.41 – 2.28 (m, 1H), 2.28 – 2.15 (m, 2H), 1.88 (dd, *J* = 13.8, 6.3 Hz, 1H), 1.46 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.4, 79.9, 79.3, 73.9, 69.9, 62.1, 61.9, 35.5, 31.0, 28.5 ppm. HRMS (ESI): calc'd for $C_{12}H_{21}ClNO_5S$ $[M+H]^+$ 326.0829; found 326.0821.



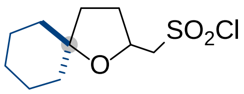
(1-Oxaspiro[4.4]nonan-2-yl)methanesulfonyl chloride (22e)

General procedure H was used. Yield: 20.3 g, 85%, brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.61 – 4.48 (m, 1H), 3.98 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.76 (dd, *J* = 13.9, 6.5 Hz, 1H), 2.41 – 2.17 (m, 1H), 1.99 – 1.84 (m, 3H), 1.85 – 1.66 (m, 4H), 1.68 – 1.43 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 92.9, 72.5, 70.7, 39.2, 38.3, 35.9, 32.0, 24.1, 24.1 ppm. LCMS (RSO_3H-H)$^-$: 219. HRMS (ESI): calc'd for: $C_9H_{16}ClO_3S$ $[M+H]^+$ 239.0509; found 239.0503.



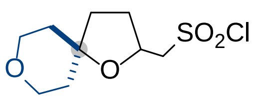
1,7-Dioxaspiro[4.4]nonan-2-yl)methanesulfonyl chloride (23e)

General procedure H was used. Yield: 17.3 g, 72%, black oil. Mixture of stereoisomers (d.r. = 1:1). ^1H NMR (400 MHz, $CDCl_3$) δ = 4.64 – 4.50 (m, 1H), 4.14 – 3.54 (m, 6H), 2.42 – 2.25 (m, 1H), 2.19 – 1.81 (m, 5H). ^1H NMR (400 MHz, $CDCl_3$) δ = 4.64 – 4.50 (m, 1H), 4.14 – 3.54 (m, 6H), 2.42 – 2.25 (m, 1H), 2.19 – 1.81 (m, 5H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 90.8, 90.7, 76.9, 73.2, 73.0, 70.1, 68.1, 68.0, 39.4, 38.7, 33.6, 33.1, 31.9, 31.8 ppm. HRMS (ESI): calc'd for: $C_8H_{14}ClO_4S$ $[M+H]^+$ 241.0301; found 241.303.



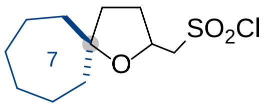
(1-Oxaspiro[4.5]decan-2-yl)methanesulfonyl chloride (24e)

General procedure H was used. Yield: 19.2 g, 76%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.61 – 4.51 (m, 1H), 3.99 (dd, *J* = 13.9, 5.8 Hz, 1H), 3.75 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.35 – 2.23 (m, 1H), 1.94 – 1.74 (m, 3H), 1.72 – 1.61 (m, 2H), 1.61 – 1.52 (m, 2H), 1.47 (dd, *J* = 16.0, 7.7 Hz, 2H), 1.42 – 1.31 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 84.6, 72.3, 70.8, 38.5, 37.3, 35.9, 31.5, 25.6, 23.9, 23.7 ppm. HRMS (ESI): calc'd for: $C_{10}H_{18}ClO_3S$ $[M+H]^+$ 253.0665; found 253.0660.



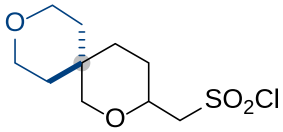
(1,8-Dioxaspiro[4.5]decan-2-yl)methanesulfonyl chloride (27e)

General procedure H was used. Yield: 23.7 g, 93%, yellow solid, mp = 52-53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.57 (p, *J* = 6.2 Hz, 1H), 3.99 (dd, *J* = 14.0, 6.2 Hz, 1H), 3.86 – 3.71 (m, 3H), 3.71 – 3.58 (m, 2H), 2.35 – 2.20 (m, 1H), 1.96 – 1.78 (m, 3H), 1.77 – 1.54 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 81.3, 72.6, 70.5, 65.2, 65.2, 38.6, 37.3, 36.5, 31.1 ppm. HRMS (ESI): calc'd for: $C_9H_{16}ClO_4S$ $[M+H]^+$ 255.0458; found 255.0454.



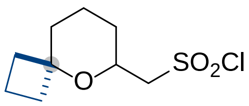
(1-Oxaspiro[4.6]undecan-2-yl)methanesulfonyl chloride (30e)

General procedure H was used. Yield: 22.4 g, 84%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.59 – 4.44 (m, 1H), 3.99 (dd, *J* = 13.9, 5.5 Hz, 1H), 3.75 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.34 – 2.15 (m, 1H), 2.07 – 1.11 (m, 15H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 88.2, 72.4, 70.7, 41.6, 40.4, 37.8, 31.4, 29.3, 23.2, 22.9 ppm. LCMS $(RSO_3H\text{-}H)^-$: 247. HRMS (ESI): calc'd for: $C_{11}H_{20}ClO_3S$ $[M+H]^+$ 267.0822; found 267.0825.



(2,9-Dioxaspiro[5.5]undecan-3-yl)methanesulfonyl chloride (36e)

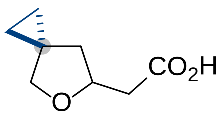
General procedure H was used. Yield: 21.7 g, 81%, white solid, mp = 110-112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.06 – 3.90 (m, 3H), 3.75 (dd, *J* = 13.6, 3.0 Hz, 1H), 3.71 – 3.60 (m, 3H), 3.59 – 3.50 (m, 1H), 3.22 (d, *J* = 11.7 Hz, 1H), 1.96 – 1.87 (m, 1H), 1.83 – 1.71 (m, 1H), 1.71 – 1.54 (m, 3H), 1.45 – 1.26 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 75.7, 73.2, 70.6, 63.8, 63.3, 35.8, 33.8, 31.6, 30.0, 26.6 ppm. HRMS (ESI): calc'd for: $C_{10}H_{18}ClO_4S$ $[M+H]^+$ 269.0614; found 269.0611.



(5-Oxaspiro[3.5]nonan-6-yl)methanesulfonyl chloride (38e)

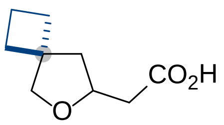
General procedure H was used. Yield: 19.6 g, 82%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.15 – 4.00 (m, 1H), 3.93 (dd, *J* = 14.1, 7.9 Hz, 1H), 3.71 (dd, *J* = 14.1, 3.6 Hz, 1H), 2.23 – 2.08 (m, 1H), 2.08 – 1.98 (m, 2H), 1.98 – 1.86 (m, 1H), 1.87 – 1.72 (m, 3H), 1.74 – 1.50 (m, 3H), 1.50 – 1.22 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 78.0, 71.0, 67.4, 34.7, 32.5, 30.6, 30.4, 20.0, 12.8 ppm. GCMS (M): 238. HRMS (ESI): calc'd for $C_9H_{16}ClO_3S$ $[M+H]^+$ 239.0509; found 239.0514.

General procedure I for synthesis 5f, 6f, 8f, 9f, 13f, 18f, 21f, 29f, 34f-36f, 40f and **44f** (**5f** as an example. Scale: 0.1 mol for all derivatives).



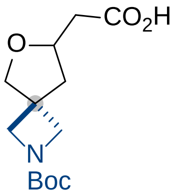
2-(5-Oxaspiro[2.4]heptan-6-yl)acetic acid (5f)

To a solution of **5a** (23.8 g, 0.1 mol, 1.0 equiv) in 150 mL of DMSO was added KCN (26 g, 0.4 mol, 4.0 equiv). The mixture was stirred for 2 d at 90 °C. The mixture was diluted with water (150 mL) and extracted with MTBE (5 times). The combined organic phases were washed with brine (3 times) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. To a solution of nitrile (13.7 g, 0.1 mol, 1 equiv) in ethanol (120 mL) was added potassium hydroxide (0.2 mol, 2.0 equiv), followed by stirring at reflux for 6 h. Then, the reaction mixture was partially concentrated, and water 100 mL was added to the residue. The mixture was partially concentrated under reduced pressure again, and then the residue was washed with CH_2Cl_2. Dilute hydrochloric acid was added to the aqueous layer until the acidic pH was reached. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the desired product. Yield: 11.4 g, 73%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.65 (br s, 1H), 4.57 – 4.42 (m, 1H), 3.75 (d, J = 8.0 Hz, 1H), 3.65 (d, J = 8.0 Hz, 1H), 2.73 (dd, J = 15.6, 7.5 Hz, 1H), 2.60 (dd, J = 15.6, 5.7 Hz, 1H), 1.99 (dd, J = 12.2, 6.4 Hz, 1H), 1.71 (dd, J = 12.2, 7.3 Hz, 1H), 0.72 – 0.48 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 176.7, 75.9, 75.1, 40.7, 40.5, 22.1, 10.9, 10.6 ppm. LCMS $(M-H)^-$: 155. HRMS (ESI): calc'd for: $C_8H_{13}O_3$ $[M+H]^+$ 157.0865; found 157.0862.



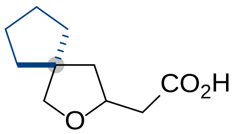
2-(6-Oxaspiro[3.4]octan-7-yl)acetic acid (6f)

General procedure I was used. Yield: 11.9 g, 70%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.55 (br s, 1H), 4.37 – 4.23 (m, 1H), 3.77 (q, J = 8.4 Hz, 2H), 2.61 (dd, J = 15.6, 7.5 Hz, 1H), 2.51 (dd, J = 15.6, 5.6 Hz, 1H), 2.19 (dd, J = 12.4, 6.3 Hz, 1H), 2.09 – 1.92 (m, 4H), 1.95 – 1.72 (m, 2H), 1.64 (dd, J = 12.4, 8.2 Hz, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 176.6, 79.0, 74.7, 46.1, 45.0, 41.2, 40.7, 33.0, 31.2, 16.5 ppm. HRMS (ESI): calc'd for: $C_9H_{15}O_3$ $[M+H]^+$ 171.1021; found 171.1025.



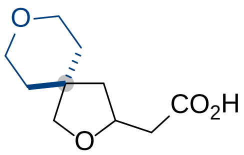
2-(2-(*Tert*-butoxycarbonyl)-6-oxa-2-azaspiro[3.4]octan-7-yl)acetic acid (8f)

General procedure I was used. Yield: 17.9 g, 66%, white solid, mp = 113-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.22 (br s, 1H), 4.35 – 4.22 (m, 1H), 3.99 – 3.81 (m, 6H), 2.62 (dd, *J* = 15.8, 7.3 Hz, 1H), 2.52 (dd, *J* = 15.7, 5.7 Hz, 1H), 2.36 (dd, *J* = 12.8, 6.4 Hz, 1H), 1.85 (dd, *J* = 12.7, 8.3 Hz, 1H), 1.42 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.5, 156.4, 80.1, 77.1, 75.1, 59.7, 58.5, 43.3, 40.7, 40.3, 28.5 ppm. LCMS $(M-H)^-$: 270. HRMS (ESI): calc'd for: $C_{13}H_{22}NO_5$ $[M+H]^+$ 272.1498; found 272.1496.



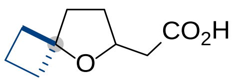
2-(2-Oxaspiro[4.4]nonan-3-yl)acetic acid (9f)

General procedure I was used. Yield: 12.5 g, 68%, orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.59 (br s, 1H), 4.43 – 4.28 (m, 1H), 3.66 (d, *J* = 8.1 Hz, 1H), 3.58 (d, *J* = 8.1 Hz, 1H), 2.65 (dd, *J* = 15.6, 7.5 Hz, 1H), 2.54 (dd, *J* = 15.6, 5.5 Hz, 1H), 2.02 (dd, *J* = 12.3, 6.4 Hz, 1H), 1.82 – 1.30 (m, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 176.7, 78.8, 75.2, 51.0, 45.0, 40.9, 37.5, 36.7, 24.88, 24.87 ppm. HRMS (ESI): calc'd for: $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1178; found 185.1172.



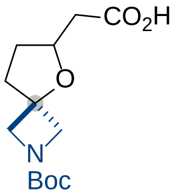
2-(2,8-Dioxaspiro[4.5]decan-3-yl)acetic acid (13f)

General procedure I was used. Yield: 14.4 g, 72%, yellow solid, mp = 103-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.91 (br s, 1H), 4.41 – 4.28 (m, 1H), 3.73 – 3.55 (m, 6H), 2.66 (dd, *J* = 15.7, 7.4 Hz, 1H), 2.54 (dd, *J* = 15.7, 5.7 Hz, 1H), 2.10 (dd, *J* = 12.6, 6.6 Hz, 1H), 1.67 – 1.52 (m, 4H), 1.43 (dd, *J* = 12.6, 8.9 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 176.0, 77.9, 74.6, 65.8, 65.4, 43.7, 41.7, 40.7, 36.6, 35.5 ppm. HRMS (ESI): calc'd for: $C_{10}H_{17}O_4$ $[M+H]^+$ 201.1127; found 201.1122.



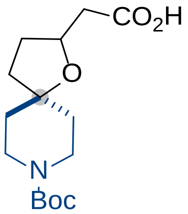
2-(5-Oxaspiro[3.4]octan-6-yl)acetic acid (18f)

General procedure I was used. Yield: 12.8 g, 75%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.85 (br s, 1H), 4.40 – 4.25 (m, 1H), 2.58 (dd, *J* = 15.5, 7.2 Hz, 1H), 2.47 (dd, *J* = 15.5, 6.0 Hz, 1H), 2.30 – 2.17 (m, 2H), 2.17 – 2.07 (m, 1H), 2.04 – 1.83 (m, 4H), 1.74 – 1.55 (m, 2H), 1.57 – 1.44 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 176.4, 83.8, 74.8, 41.4, 36.6, 36.4, 35.8, 30.7, 12.7 ppm. GCMS (M): 170. HRMS (ESI): calc'd for $C_9H_{15}O_3$ $[M+H]^+$ 171.1021; found 171.1024.



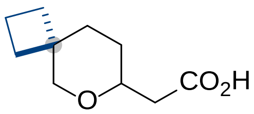
2-(2-(*Tert*-butoxycarbonyl)-5-oxa-2-azaspiro[3.4]octan-6-yl)acetic acid (21f)

General procedure I was used. Yield: 15.2 g, 56%, yellow solid, mp = 109-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.19 (br s, 1H), 4.46 – 4.29 (m, 1H), 4.01 (dd, *J* = 14.0, 9.2 Hz, 2H), 3.84 (dd, *J* = 8.6, 5.5 Hz, 2H), 2.59 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.50 (dd, *J* = 15.6, 5.8 Hz, 1H), 2.20 – 2.01 (m, 3H), 1.70 – 1.53 (m, 1H), 1.41 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.8, 156.6, 79.9, 78.4, 77.2, 75.8, 62.5 (br s), 62.1 (br s), 40.8, 35.9, 30.9, 28.5 ppm. LCMS $(M-H)^-$: 270. HRMS (ESI): calc'd for: $C_{13}H_{22}NO_5$ $[M+H]^+$ 272.1498; found 272.1494.



2-(8-(*Tert*-butoxycarbonyl)-1-oxa-8-azaspiro[4.5]decan-2-yl)acetic acid (29f)

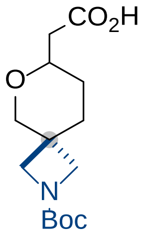
General procedure I was used. Yield: 62%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.40 – 4.28 (m, 1H), 3.59 – 3.48 (m, 2H), 3.40 – 3.27 (m, 2H), 2.62 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.53 (dd, *J* = 15.3, 5.9 Hz, 1H), 2.23 – 2.07 (m, 1H), 1.80 – 1.48 (m, 7H), 1.44 (s, 9H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 155.0, 81.2, 79.6, 74.4, 43.3 – 40.2 (m), 37.8, 36.4, 31.1, 28.6 ppm. LCMS $(M-H)^-$: 298. HRMS (ESI): calc'd for $C_{15}H_{26}NO_5$ $[M+H]^+$ 300.1811; found 300.1808.



2-(6-Oxaspiro[3.5]nonan-7-yl)acetic acid (34f)

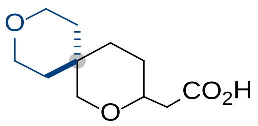
General procedure I was used. Yield: 14.7 g, 80%, yellow solid, mp = 47-49 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.81 (br s, 1H), 3.86 (d, *J* = 11.1 Hz, 1H), 3.73 – 3.60 (m, 1H), 3.26 (d, *J* = 11.1 Hz, 1H), 2.52 (dd, *J* = 15.5, 7.8 Hz, 1H), 2.43 (dd, *J* = 15.5, 4.9 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.91 – 1.81 (m, 3H), 1.75 (dd, *J* = 17.1, 9.3 Hz, 1H), 1.67 – 1.50 (m, 3H), 1.50 – 1.23 (m, 2H) ppm. ^{13}C

NMR (126 MHz, $CDCl_3$) δ = 176.3, 76.4, 73.9, 41.1, 37.7, 35.4, 30.3, 29.0, 28.2, 15.4 ppm. LCMS $(M-H)^-$: 183. HRMS (ESI): calc'd for: $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1178; found 185.1173.



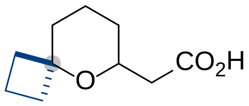
2-(2-(*Tert*-butoxycarbonyl)-6-oxa-2-azaspiro[3.5]nonan-7-yl)acetic acid (35f)

General procedure I was used. Yield: 19.1 g, 67%, white solid, mp = 130-131 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.93 (br s, 1H), 4.01 – 3.90 (m, 1H), 3.82 (d, *J* = 8.5 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.62 (s, 1H), 3.48 (q, *J* = 8.8 Hz, 2H), 3.41 (d, *J* = 11.4 Hz, 1H), 2.52 (dd, *J* = 15.5, 7.8 Hz, 1H), 2.42 (dd, *J* = 15.5, 4.8 Hz, 1H), 2.00 (d, *J* = 13.3 Hz, 1H), 1.71 – 1.58 (m, 2H), 1.41 (s, 9H), 1.35-1.25 (m, 1H) ppm. ^{13}C NMR (151 MHz, $cdcl_3$) δ = 175.8, 156.7, 79.8, 74.4, 73.7, 58.6, 55.7, 40.9, 33.4, 32.9, 28.5, 28.2 ppm. LCMS $(M-H)^-$: 284. HRMS (ESI): calc'd for: $C_{14}H_{24}NO_5$ $[M+H]^+$ 286.1654; found 286.1658.



2-(2,9-Dioxaspiro[5.5]undecan-3-yl)acetic acid (36f)

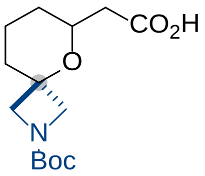
General procedure I was used. Yield: 74%, white solid, mp = 116-118 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 10.34 (br s, 1H), 3.93 – 3.86 (m, 1H), 3.75 – 3.61 (m, 4H), 3.61 – 3.48 (m, 1H), 3.17 (d, *J* = 11.5 Hz, 1H), 2.55 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.46 (dd, *J* = 15.5, 4.8 Hz, 1H), 1.91 – 1.81 (m, 1H), 1.81 – 1.70 (m, 1H), 1.67 – 1.44 (m, 3H), 1.39 – 1.21 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 175.9, 75.7, 74.8, 63.9, 63.3, 41.0, 35.9, 34.0, 31.6, 30.1, 26.9 ppm. LCMS $(M+H)^+$: 215. HRMS (ESI): calc'd for $C_{11}H_{19}O_4$ $[M+H]^+$ 215.1283; found 215.1280.



2-(5-Oxaspiro[3.5]nonan-6-yl)acetic acid (38f)

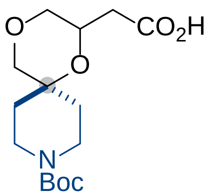
General procedure I was used. Yield: 15.4 g, 84%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 10.78 (br s, 1H), 3.84 – 3.71 (m, 1H), 2.54 (dd, *J* = 15.6, 8.0 Hz, 1H), 2.46 (dd, *J* = 15.6, 5.0 Hz, 1H), 2.11 (dd, *J* = 21.0, 10.2 Hz, 1H), 2.06 – 1.95 (m, 2H), 1.95 – 1.84 (m, 1H), 1.83 – 1.68 (m, 3H), 1.66 – 1.50 (m, 3H), 1.48 – 1.34 (m, 1H), 1.25 (qd, *J* = 13.1, 4.0 Hz, 1H) ppm. ^{13}C NMR (151

MHz, $CDCl_3$) δ = 176.0, 77.7, 68.6, 41.3, 35.0, 33.0, 30.9, 30.8, 20.1, 20.0, 12.8 ppm. GCMS (M):184. HRMS (ESI): calc'd for: $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1178; found 185.1172.



2-(2-(*Tert*-butoxycarbonyl)-5-oxa-2-azaspiro[3.5]nonan-6-yl)acetic acid (40f)

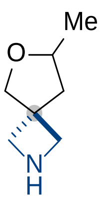
General procedure I was used. Yield: 19.9 g, 70%, beige solid, mp = 169-170 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.92 – 3.64 (m, 5H), 2.56 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.46 (dd, *J* = 15.6, 4.8 Hz, 1H), 1.92 – 1.72 (m, 2H), 1.58 (dt, *J* = 21.2, 11.8 Hz, 3H), 1.43 (s, 9H), 1.34 – 1.17 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 175.5, 156.7, 79.9, 72.9, 70.2, 41.1, 32.6, 30.2, 28.5, 20.1 ppm. LCMS $(M-H)^-$: 284. HRMS (ESI): calc'd for: $C_{14}H_{24}NO_5$ $[M+H]^+$ 286.1654; found 286.1651.



2-(9-(tert-butoxycarbonyl)-1,4-dioxa-9-azaspiro[5.5]undecan-2-yl)acetic acid (44f)

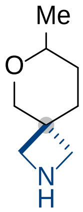
General procedure I was used. Yield: 21.7 g, 69%, yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.59 (br s, 1H), 4.29 – 4.17 (m, 1H), 3.87 – 3.71 (m, 3H), 3.52 (d, *J* = 11.4 Hz, 1H), 3.24 (d, *J* = 11.4 Hz, 1H), 3.21 – 3.10 (m, 2H), 3.08 – 2.99 (m, 1H), 2.48 – 2.31 (m, 3H), 1.43 (s, 9H), 1.42 – 1.31 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 174.8, 155.1, 79.8, 74.2, 70.7, 70.2, 64.9, 39.3, 38.6, 37.1, 33.9, 28.8, 28.6 ppm. HRMS (ESI): calc'd for: $C_{15}H_{26}NO_6$ $[M+H]^+$ 316.1760; found 316.1763.

General procedure J for synthesis 8g and **35g** (**8g** as an example. Scale: 0.1 mol for all derivatives).



7-Methyl-6-oxa-2-azaspiro[3.4]octane hydrochloride (8g)

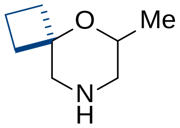
To a solution of **8a** (35.3 g, 0.1 mol, 1.0 equiv) in 150 mL of MeOH was added and Pd/C (5%), (3 g). The mixture was stirred under H_2-ballon at room temperature overnight. After consumption of all starting material, Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in cold EtOAc and 5M HCl in dioxane was added dropwise to achieve a slightly acidic pH. The precipitate was filtered and dried. Yield: 14.4 g, 88%, white solid, mp = 113-114 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.50 (br s, 2H), 3.95 (d, *J* = 9.2 Hz, 1H), 3.93-3.80 (m, 5H), 3.72 (d, *J* = 9.3 Hz, 1H), 2.35 (dd, *J* = 12.8, 6.2 Hz, 1H), 1.66 (dd, *J* = 12.8, 8.3 Hz, 1H), 1.11 (d, *J* = 6.1 Hz, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d$_6$) δ = 75.3, 74.3, 54.5, 54.2, 44.3, 43.6, 20.7 ppm. LCMS $(M+H)^+$: 128. HRMS (ESI): calc'd for $C_7H_{14}NO$ $[M+H]^+$ 128.1075; found 128.1072.



7-Methyl-6-oxa-2-azaspiro[3.5]nonane hydrochloride (35g)

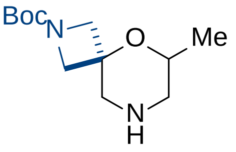
General procedure J was used. Yield: 15.1 g, 85%, yellow solid, mp = 163-165 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.47 (br s, 2H), 4.07 (dd, *J* = 11.3, 2.1 Hz, 1H), 3.70 (t, *J* = 6.2 Hz, 2H), 3.59 – 3.43 (m, 2H), 3.28 (d, *J* = 11.3 Hz, 1H), 2.13 – 1.97 (m, 1H), 1.63 – 1.47 (m, 2H), 1.18 – 1.05 (m, 1H), 1.03 (d, *J* = 6.1 Hz, 3H) ppm. ^{13}C NMR (126 MHz, DMSO-d$_6$) δ = 72.4, 72.0, 53.6, 51.0, 35.8, 31.8, 29.4, 21.3 ppm. LCMS $(M+H)^+$: 142. HRMS (ESI): calc'd for: $C_8H_{16}NO$ $[M+H]^+$ 142.1232; found 142.1235.

General procedure K for synthesis 45g-48g (**45h** as an example. Scale: 0.1 mol for all derivatives).



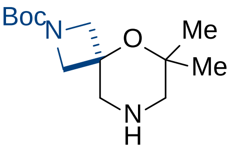
6-Methyl-5-oxa-8-azaspiro[3.5]nonane (45g)

To a solution of **45a** (35.7 g, 0.1 mol, 1.0 equiv) in 200 mL of dry CH_3OH was added Et_3N (15.3 mL, 0.11 mol, 1.1 equiv) and 10% Pd/C (3.5 g). The mixture was stirred under a 25 L rubber ball filled with H_2 for 24 h at room temperature. The mixture was concentrated under reduced pressure. The resulting residue was dissolved in 100 mL of MTBE and filtered through a pad of SiO_2. The filtrate was washed with a 1M solution of $AgNO_3$, filtered through SiO_2 and Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in 150 mL of dry MeOH and 3 g of 10% Pd/C was added to the mixture. The mixture was hydrogenated in autoclave at 50 atm, 8 h at 60 °C and concentrated under reduced pressure to give the desired product. Yield: 12 g, 85%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.58 – 3.43 (m, 1H), 2.87 (d, *J* = 12.4 Hz, 1H), 2.73 (dd, *J* = 12.5, 1.3 Hz, 1H), 2.58 (dd, *J* = 12.4, 1.9 Hz, 1H), 2.38 (dd, *J* = 12.3, 10.5 Hz, 1H), 2.18 – 2.08 (m, 1H), 2.06 – 1.89 (m, 2H), 1.86 – 1.73 (m, 2H), 1.72 (br s, 1H), 1.60 – 1.43 (m, 1H), 1.04 (d, *J* = 6.3 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 75.6, 67.6, 52.2, 32.6, 30.5, 19.1, 12.9 ppm. GCMS (M): 141. HRMS (ESI): calc'd for $C_8H_{16}NO$ $[M+H]^+$ 142.1232; found 142.1227.



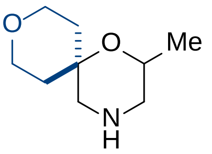
Tert-butyl 6-methyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (46g)

General procedure K was used. Yield: 16.5 g, 68%, grey solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.78 (d, *J* = 7.6 Hz, 1H), 3.70 (d, *J* = 7.6 Hz, 1H), 3.58 (d, *J* = 8.7 Hz, 1H), 3.50 (d, *J* = 8.9 Hz, 1H), 3.49 – 3.42 (m, 1H), 3.02 (br s, 1H), 2.87 (d, *J* = 12.4 Hz, 1H), 2.67 (dd, *J* = 12.2, 1.7 Hz, 1H), 2.19 (dd, *J* = 12.1, 10.4 Hz, 1H), 1.38 (s, 9H), 1.00 (d, *J* = 6.2 Hz, 3H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ = 155.7, 78.6, 70.8, 68.4, 58.7 (br s), 57.7 (br s), 51.1, 51.0, 28.0, 18.7 ppm. LCMS $(M+H)^+$: 243. HRMS (ESI): calc'd for $C_{12}H_{23}N_2O_3$ $[M+H]^+$ 243.1709; found 243.1714.



Tert-butyl 6,6-dimethyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (47g)

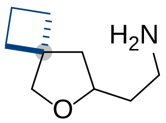
General procedure K was used. Yield: 18.7 g, 73%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.82 (d, *J* = 9.0 Hz, 2H), 3.75 (d, *J* = 9.2 Hz, 2H), 2.93 (s, 2H), 2.63 (s, 2H), 1.82 (s, 1H), 1.43 (s, 9H), 1.18 (s, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 156.8, 79.7, 72.5, 68.8, 60.9 (br s), 55.3, 53.0, 28.5, 26.2 ppm. HRMS (ESI): calc'd for $C_{13}H_{25}N_2O_3$ $[M+H]^+$ 257.1865; found 257.1862.



2-Methyl-1,9-dioxa-4-azaspiro[5.5]undecane (48g)

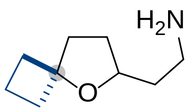
General procedure K was used. Yield: 13.8 g, 81%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.80 (td, *J* = 10.8, 3.1 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.68 – 3.56 (m, 3H), 2.83 (dd, *J* = 12.1, 2.4 Hz, 1H), 2.74 (d, *J* = 12.2 Hz, 1H), 2.52 (d, *J* = 12.2 Hz, 1H), 2.39 – 2.32 (m, 1H), 2.21 (dd, *J* = 14.0, 2.4 Hz, 1H), 1.63 (br s, 1H), 1.61 – 1.48 (m, 2H), 1.49 – 1.38 (m, 1H), 1.05 (d, *J* = 6.2 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 69.2, 65.3, 63.8, 63.3, 54.6, 53.1, 37.5, 30.2, 19.5 ppm. GCMS (M): 171. HRMS (ESI): calc'd for $C_9H_{18}NO_2$ $[M+H]^+$ 172.1338; found 172.1332.

General procedure L for synthesis 6h, 18h and **36h** (**6h** as an example. Scale: 0.1 mol for all derivatives).



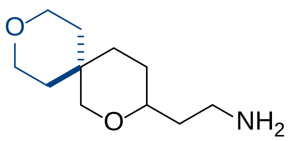
2-(6-Oxaspiro[3.4]octan-7-yl)ethan-1-amine hydrochloride (6h)

To a solution of **6a** (25.2 g, 0.1 mol, 1.0 equiv) in 150 mL of DMSO was added KCN (26 g, 0.4 mol, 4.0 equiv). The mixture was stirred for 2 d at 90 °C. The mixture was diluted with water (150 mL) and extracted with MTBE (5 times). The combined organic phases were washed with brine (3 times) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting nitrile was dissolved in 500 mL of MeOH-NH_3 (17%) and reduced in autoclave with Raney nickel at 50 atm, 8 h. The mixture was filtered and concentrated under reduced pressure. Yield: 12.1 g, 78%, white solid, mp = 89-90 °C. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.15 (s, 3H), 3.90 – 3.77 (m, 1H), 3.70 – 3.60 (m, 1H), 3.58 (d, J = 8.3 Hz, 1H), 2.77 (br s, 2H), 2.09 (dd, J = 12.2, 6.3 Hz, 1H), 2.03 – 1.87 (m, 4H), 1.87 – 1.64 (m, 4H), 1.51 (dd, J = 12.2, 8.2 Hz, 1H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 77.9, 75.5, 45.5, 44.5, 36.4, 33.0, 32.3, 30.9, 15.9 ppm. LCMS $(M+H)^+$: 156. HRMS (ESI): calc'd for $C_9H_{18}NO$ $[M+H]^+$ 156.1388; found 156.1390.



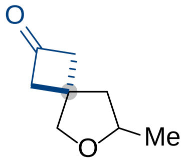
2-(5-Oxaspiro[3.4]octan-6-yl)ethan-1-amine (18h)

General procedure L was used. Yield: 12.4 g, 80%, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.02 – 3.83 (m, 1H), 2.83 – 2.69 (m, 2H), 2.23 – 2.09 (m, 2H), 2.01 – 1.78 (m, 5H), 1.67 – 1.42 (m, 7H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$) δ = 83.0, 77.3, 40.4, 39.7, 36.7, 36.6, 36.0, 31.1, 12.7 ppm. GCMS (M): 155. HRMS (ESI): calc'd for $C_9H_{18}NO$ $[M+H]^+$ 156.1388; found 156.1383.



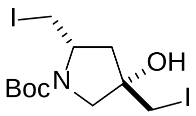
2-(2,9-Dioxaspiro[5.5]undecan-3-yl)ethan-1-amine (36h)

General procedure L was used. Yield: 14.3 g, 72%, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 3.84 (dd, J = 11.4, 2.7 Hz, 1H), 3.64 (t, J = 5.6 Hz, 2H), 3.62 – 3.58 (m, 1H), 3.57 – 3.49 (m, 1H), 3.40 – 3.23 (m, 1H), 3.09 (d, J = 11.4 Hz, 1H), 2.84 – 2.70 (m, 2H), 1.89 – 1.68 (m, 2H), 1.69 – 1.49 (m, 3H), 1.50 – 1.38 (m, 2H), 1.30 (br s, 2H), 1.29 – 1.21 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 76.9, 75.7, 64.0, 63.4, 40.0, 39.0, 36.1, 34.3, 31.8, 30.3, 27.5 ppm. HRMS (ESI): calc'd for $C_{11}H_{22}NO_2$ $[M+H]^+$ 200.1651; found 200.1657.



7-Methyl-6-oxaspiro[3.4]octan-2-one (7i)

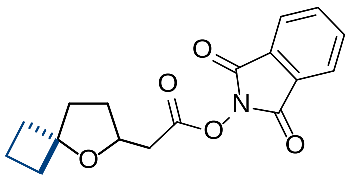
To a solution of **7a** (31.2 g, 0.1 mol, 1.0 equiv) in 150 mL of MeOH was added and Pd/C (5%), (3 g). The mixture was stirred under H_2-ballon at room temperature overnight. After consumption of all starting material, Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in THF (200 mL) and a solution of 2.0 M aqueous solution of HCl (400 mL) was added dropwise at 0 °C, and the resulting mixture was stirred at room temperature overnight. Then the reaction mixture was extracted with CH_2Cl_2 (3 times). The combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$, brine, dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography (hexane/EtOAc, 8:2). Yield: 8.8 g, 63%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.23 – 4.06 (m, 1H), 3.96 (d, J = 8.6 Hz, 1H), 3.84 (d, J = 8.6 Hz, 1H), 3.19 – 2.95 (m, 4H), 2.23 (dd, J = 12.4, 6.3 Hz, 1H), 1.79 (dd, J = 12.4, 8.3 Hz, 1H), 1.27 (d, J = 6.1 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 206.2, 78.2, 75.8, 57.4, 56.1, 46.6, 36.6, 21.3 ppm. GCMS (M): 140. HRMS (ESI): calc'd for $C_8H_{13}O_2$ $[M+H]^+$ 141.0916; found 141.0919.



***Tert*-butyl-4-hydroxy-2,4-bis(iodomethyl)pyrrolidine-1-carboxylate (50)**

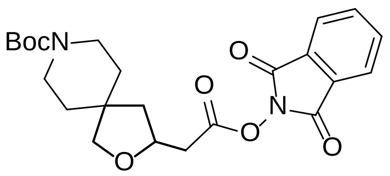
General procedure A was used. Scale 0.01 mol. Yield: 4.3 g, 92%, brown oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ = 5.37 (s, 1H), 4.00 – 3.82 (m, 1H), 3.65 – 3.34 (m, 6H), 2.19 – 2.06 (m, 1H), 2.06 – 1.79 (m, 1H), 1.38 (s, 9H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6) δ 153.6, 153.1, 79.2, 76.1, 75.4, 59.1, 59.0, 58.4, 58.2, 41.8, 41.1, 28.1, 28.0, 18.0, 17.8, 11.6, 11.0 ppm. HRMS (ESI): calc'd for $C_{11}H_{20}I_2NO_3$ $[M+H]^+$ 467.9533; found 467.9538.

General procedure M



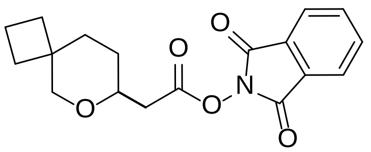
1,3-Dioxoisoindolin-2-yl 2-(5-oxaspiro[3.4]octan-6-yl)acetate

To a solution of **18f** (5.00 g, 0.02937 mol, 1.0 equiv) in CH_2Cl_2 (60 mL) was added *N*-hydroxyphthalimide (4.79 g, 0.02937 mol, 1.0 equiv), DMAP (0.36 g, 0.00293 mol, 0.1 equiv). To the solution was added DIC (4.55 mL, 0.02937 mol, 1.0 equiv) dropwise at room temperature. The mixture was sstirrred at room temperature overnight. The mixture was filtered. The filtrate was washed with water (1 × 60 mL), a sat. aq. solution of Na_2CO_3 (2 × 80 mL), 1M HCl (2 × 80 mL), brine (1 × 60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Yield: 11.96 g, 89%, 70% purity. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.79 (dd, *J* = 5.2, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.3, 3.1 Hz, 2H), 4.34 (p, *J* = 6.7 Hz, 1H), 2.89 (dd, *J* = 15.3, 5.9 Hz, 1H), 2.69 (dd, *J* = 15.3, 7.3 Hz, 1H), 2.23 – 2.13 (m, 3H), 2.00 – 1.95 (m, 1H), 1.94 – 1.89 (m, 3H), 1.75 – 1.66 (m, 1H), 1.66 – 1.58 (m, 1H), 1.48 – 1.37 (m, 1H) ppm.



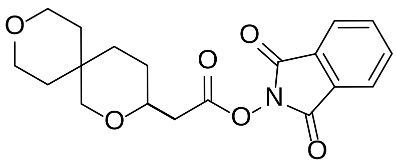
Tert-butyl 3-(2-((1,3-dioxoisoindolin-2-yl)oxy)-2-oxoethyl)-2-oxa-8-azaspiro[4.5]decane-8-carboxylate

General procedure M was used. Yield: 9.36 g, 88%, 70% purity. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.83 – 7.80 (m, 2H), 7.76 – 7.74 (m, 2H), 4.40 (p, *J* = 6.5 Hz, 1H), 3.63 (dd, *J* = 32.9, 8.6 Hz, 2H), 3.42 – 3.30 (m, 4H), 2.96 (dd, *J* = 15.4, 6.2 Hz, 1H), 2.82 (dd, *J* = 15.4, 6.5 Hz, 1H), 1.55 – 1.50 (m, 6H), 1.41 (s, 9H) ppm.



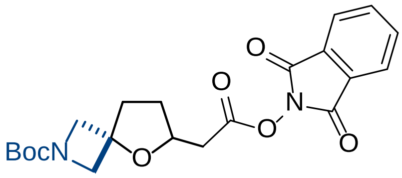
1,3-Dioxoisoindolin-2-yl 2-(6-oxaspiro[3.5]nonan-7-yl)acetate

General procedure M was used. Yield: 3.61 g, 81%, 83% purity. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.86 – 7.79 (m, 2H), 7.78 – 7.70 (m, 2H), 3.85 (dd, *J* = 11.2, 2.2 Hz, 1H), 3.79 – 3.66 (m, 1H), 2.83 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.70 (dd, *J* = 15.2, 5.9 Hz, 1H), 2.06 – 1.93 (m, 1H), 1.90 – 1.35 (m, 10H) ppm.



1,3-Dioxoisoindolin-2-yl 2-(2,9-dioxaspiro[5.5]undecan-3-yl)acetate

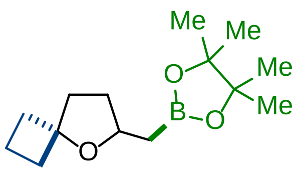
General procedure M was used. Yield: 5.20 g, 79%, 97% purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.3, 3.2 Hz, 2H), 3.89 (dd, *J* = 11.5, 2.2 Hz, 1H), 3.80 – 3.67 (m, 1H), 3.68 – 3.40 (m, 4H), 3.15 (d, *J* = 11.5 Hz, 1H), 2.84 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.72 (dd, *J* = 15.2, 5.7 Hz, 1H), 1.93 – 1.67 (m, 2H), 1.67 – 1.50 (m, 3H), 1.39 – 1.14 (m, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 167.1, 161.8, 134.8, 128.9, 123.9, 75.6, 74.3, 63.8, 63.2, 38.0, 35.8, 33.9, 31.6, 30.0, 26.6 ppm. HRMS (ESI): calc'd for $C_{19}H_{22}NO_6$ $[M+H]^+$ 360.1447; found 360.1440.



Tert-butyl 6-(2-((1,3-dioxoisoindolin-2-yl)oxy)-2-oxoethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate

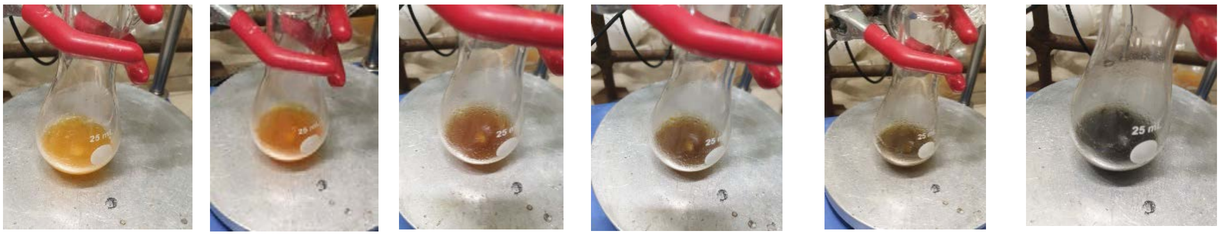
General procedure M was used. Yield: 3.22 g, 71%, 90% purity. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.47 – 4.34 (m, 1H), 4.01 (d, *J* = 8.9 Hz, 2H), 3.83 (dd, *J* = 19.4, 9.1 Hz, 2H), 2.93 (dd, *J* = 15.5, 5.9 Hz, 1H), 2.79 (dd, *J* = 15.5, 6.8 Hz, 1H), 2.24 – 2.03 (m, 3H), 1.84 – 1.72 (m, 1H), 1.39 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.7, 161.8, 156.4, 134.9, 128.9, 124.0, 79.6, 78.6, 75.3, 62.3, 62.0, 37.5, 35.8, 30.5, 28.4 ppm. HRMS (ESI): calc'd for $C_{21}H_{25}N_2O_7$ $[M+H]^+$ 417.1662; found 417.1660.

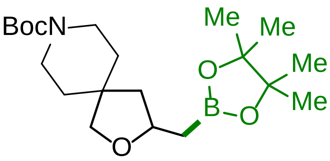
General procedure N for synthesis of 14j, 18j, 34j, 36j and 21j (18j as an example)



2-((5-Oxaspiro[3.4]octan-6-yl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18j)

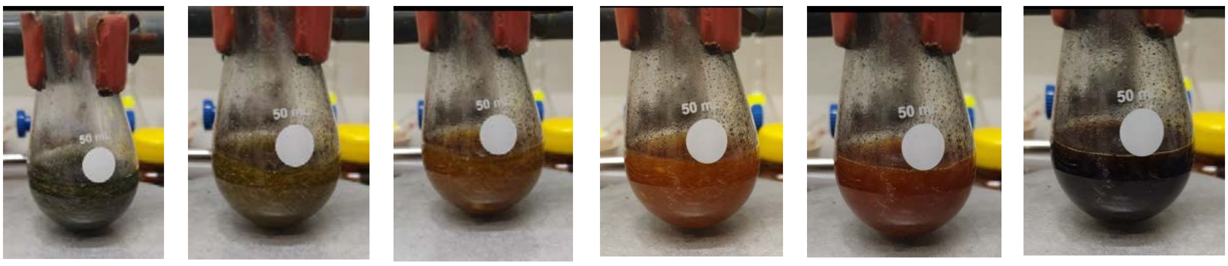
A Schlenk flask was charged with **18f**-NHPI (1.0 g, 0.003171 mol, 1.0 equiv), bis(pinacolato)diboron (2.42 g, 0.0095 mol, 3.0 equiv), ground LiOH▪H_2O (2.0 g, 0.0476 mol, 15.0 equiv), $Cu(acac)_2$ (30 mol%, 0.25 g, 0.00095 mol), $MgBr_2$▪Et_2O (1.22 g, 0.00476 mol, 1.5 equiv) under argon. A degassed mixture of dioxane and DMF (1:4, 23 mL) was added to the mixture. The mixture was stirred at room temperature until the color of the reaction mixture became dark brown (see photos, 10-20 min). The mixture was diluted with MTBE (150 mL), and air was bubbled through the solution (5 min). The mixture was diluted with a sat. aq. solution of NH_4Cl (200 mL), and the organic layer was separated. The organic layer was washed with a 10% aq. solution of K_2CO_3 (2 × 150 mL), brine (1 × 150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The final product was purified by column chromatography (hexane/EtOAc, 100:0 to 50:50). Before chromatography the silica gel in the column was washed with a mixture of hexane/Et_3N (98:2, 400 mL) and 200 mL of pure hexane. Yield: 0.47 g, 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.17 – 4.00 (m, 1H), 2.23 – 2.12 (m, 2H), 2.06 – 1.85 (m, 5H), 1.67 – 1.56 (m, 1H), 1.52 – 1.38 (m, 2H), 1.21 (s, 12H), 1.08 – 0.78 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 83.2, 82.7, 76.1, 37.2, 36.8, 36.3, 32.7, 25.0, 24.8, 12.8 ppm. HRMS (ESI): calc'd for $C_{14}H_{26}BO_3$ $[M+H]^+$ 253.1975; found 253.1971.

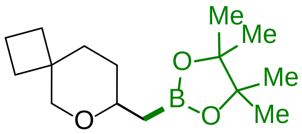




Tert-butyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (14j)

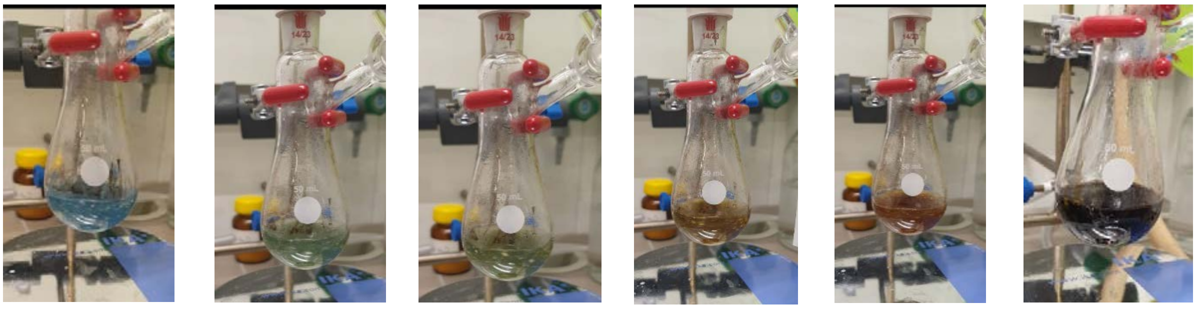
General procedure N was used. Yield: 0.21 g, 24%. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.19 – 4.07 (m, 1H), 3.64 (d, J = 8.6 Hz, 1H), 3.48 (d, J = 8.6 Hz, 1H), 3.41 – 3.23 (m, 4H), 1.94 (dd, J = 12.4, 6.3 Hz, 1H), 1.51 (t, J = 4.8 Hz, 4H), 1.43 (s, 9H), 1.30 – 1.25 (m, 2H), 1.22 (s, 12H), 1.07 (dd, J = 15.1, 8.3 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 155.0, 83.3, 79.5, 77.5, 76.3, 45.3, 42.7, 41.9, 41.6, 36.5, 35.0, 28.6, 25.0, 24.8 ppm. HRMS (ESI): calc'd for $C_{20}H_{37}BNO_5$ $[M+H]^+$ 382.2765; found 382.2761.

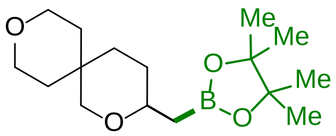




2-((6-Oxaspiro[3.5]nonan-7-yl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (34j)

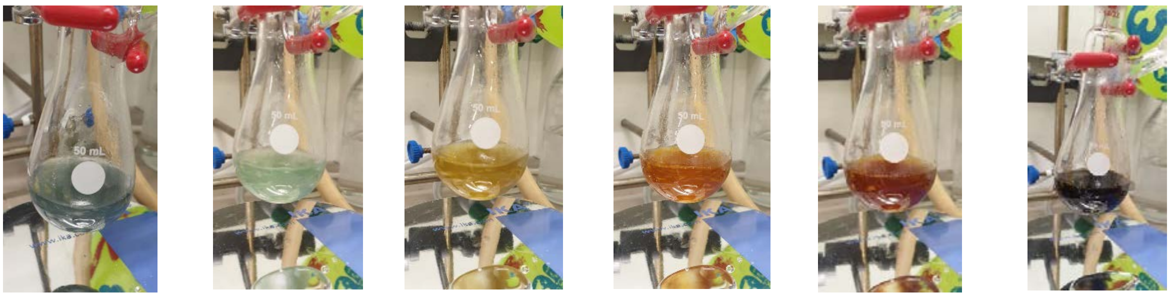
General procedure N was used. Yield: 0.27 g, 39%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.76 (d, J = 10.9 Hz, 1H), 3.46 – 3.28 (m, 1H), 3.18 (d, J = 11.1 Hz, 1H), 2.00 – 1.94 (m, 1H), 1.80 – 1.69 (m, 4H), 1.58 – 1.49 (m, 3H), 1.45 – 1.29 (m, 2H), 1.20 (s, 12H), 1.11 – 0.95 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 83.2, 76.4, 75.2, 37.9, 36.2, 30.5, 30.3, 29.2, 28.4, 24.9, 24.9, 15.4 ppm. HRMS (ESI): calc'd for $C_{15}H_{28}BO_3$ $[M+H]^+$ 267.2132; found 267.2135.

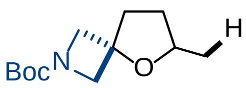




2-((2,9-Dioxaspiro[5.5]undecan-3-yl)methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (36j)

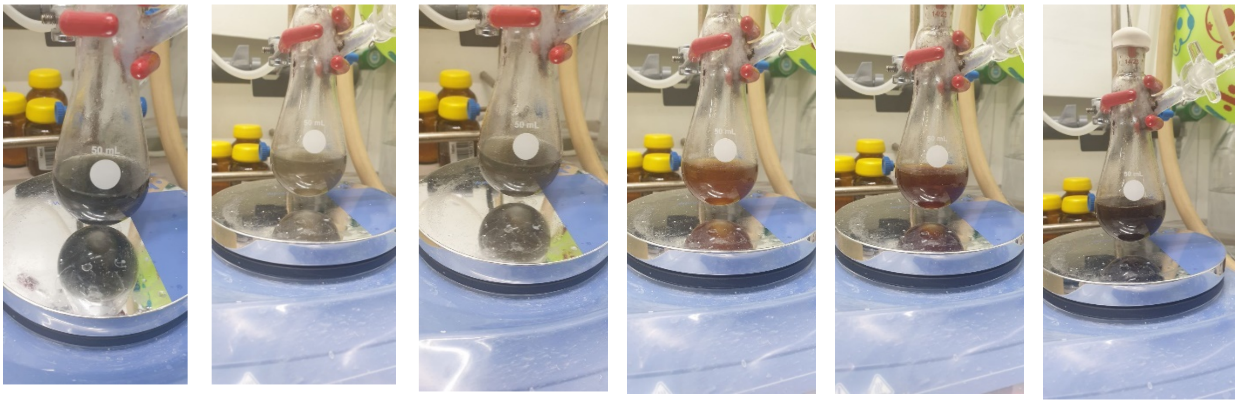
General procedure N was used. Yield: 0.18 g, 22%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.84 (d, J = 11.4 Hz, 1H), 3.70 – 3.44 (m, 5H), 3.13 (d, J = 11.4 Hz, 1H), 1.84 – 1.71 (m, 2H), 1.62 – 1.43 (m, 3H), 1.40 – 1.25 (m, 3H), 1.24 (s, 12H), 1.17 – 0.96 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 83.3, 76.3, 75.7, 64.1, 63.5, 36.2, 34.7, 31.9, 30.1, 29.1, 24.9, 24.9 ppm. HRMS (ESI): calc'd for $C_{16}H_{30}BO_4$ $[M+H]^+$ 297.2237; found 297.2235.





***Tert*-butyl 6-methyl-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (21j)**

Mixture 1. A 50 mL Schlenk flask was charged with **21f**-NHPI (1.0 g, 0.0024 mol, 1.0 equiv) in a mixture of dioxane and DMF (1:4, 24 mL, 0.1 M). The solution was digassed with argon (10 min). Mixture 2. A 25 mL Schlenk flask was charged with bis(pinacolato)diboron (1.83 g, 0.0072 mol, 3.0 equiv), ground $LiOH▪H_2O$ (1.51 g, 0.036 mol, 15.0 equiv), $Cu(acac)_2$ (30 mol%, 0.19 g, 0.00072 mol), $MgBr_2▪Et_2O$ (0.92 g, 0.0036 mol, 1.5 equiv) under argon. The mixture 2 was added to the mixture 1 under argon. The mixture was stirred at room temperature until the color of the reaction mixture became dark brown (see photos, 10-20 min). The mixture was diluted with MTBE (150 mL. The mixture was diluted with a sat. aq. solution of NH_4Cl (200 mL), and the organic layer was separated. The organic layer was washed with a 10% aq. solution of K_2CO_3 (2 × 150 mL), brine (1 × 150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The final product was purified by column chromatography (hexane/EtOAc, 100:0 to 50:50). Before chromatography the silica gel in the column was washed with a mixture of hexane/Et_3N (98:2, 400 mL) and 200 mL of pure hexane. Yield: 0.17 g, 31%. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.13 – 4.03 (m, 1H), 4.00 (d, *J* = 9.1 Hz, 2H), 3.85 (t, *J* = 8.8 Hz, 2H), 2.29 – 1.85 (m, 4H), 1.43 (s, 9H), 1.23 (d, *J* = 6.1 Hz, 3H) ppm. HRMS (ESI): calc'd for $C_{12}H_{22}NO_3$ $[M+H]^+$ 228.1600; found 228.1607.



Experimental pKa values

Equipment

Water purification system NANOpure Diamond D11911 (Thermo Scientific Barnstead, USA) pH-meter, pHi®510 (Beckman Coulter, Canada; Cat# A58734). Multichannel Electronic Pipettes 2-125 µL, 5-250 µL, 15-1250 µL, Matrix (Thermo, USA). Magnetic stirrer standard unit (IKA, USA). Syringe Driver Mdl 100 (KDScientific, USA).

Analytical System

The measurements were done in accordance with Enamine'sinternal Standard Operating Procedure based on the technical protocols for pKa measurement provided by Pion Inc. and Sirius Analytical Inc. Acquisition and analysis of the data were performed usingSmartLoggerII 1.0.14 software (Beckman Coulter). Data analysis was done using GraphPad Prism 5.01 and Excel 2010.
software.

Methods

The tendency of a compound to donate a proton is measured as its acid ionization constant (dissociation constant), or Ka. A more practical scale of representing acidity is pKa which is the negative logarithm of the Ka (pKa = -log Ka). pKa of a test articleisdetermined by pH-metric method based onpotentiometricacid-base titrationat 25 °C.The test and reference compoundsare dissolved in acidified methanol-water (1:4) solution of NaCl (150 mM, pH 2) and slowly titrated with 10 mM sodium hydroxide methanol-water (1:4) solution, while recording pH of the solution as a function of NaOH volume used during the titration (construction of the titration curve). Titration of acidified NaCl solution in absence of any compounds is used for blank plotting. Buffering capacity is calculated in each point of titration curve as the ratio of the NaOH flow (constant) to the pH rise velocity. The pKa value is determined from resulting plot of buffering capacity versus pH as the maximum of buffering capacity.pH-metric method allows to measure pKa sin range between 2.0 and 12.

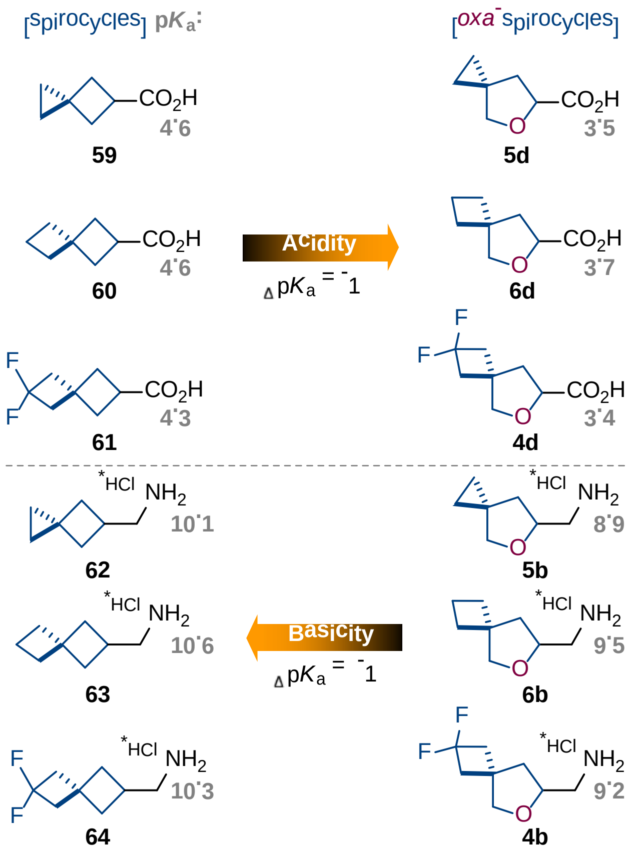


Figure S1. Experimental pK_a values of acids **59-61**, **4d-6d**; and conjugated amines **62·HCl-64·HCl**, **4b·HCl-6b·HCl**.

Data should be considered as approximate due to specific physicochemical properties of the compound, apparently compound forms colloids in the titration media. The pKa values of reference compounds are consistent with published data, thus validating this study.

References

1. http://www.sirius-analytical.com/science/pka/methods-measuring-pka
2. http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con2023944.pdf
3. http://www.chem.wisc.edu/areas/reich/pkatable/pKa_compilation-1-Williams.pdf
4. http://www.jbc.org/content/218/2/961.full.pdf

Determination of Distribution Coefficient (LogD, pH 7.4)

The aim of this study was to determine distribution coefficients for the test articles **66**, **67**, **69**, **70,** **72** and **73** and reference compound (Mebendazole) in *n*-octanol – phosphate buffered saline (PBS), pH 7.4. Distribution coefficient (or LogD) is a logarithm of the ratio of drug concentrations in two immiscible solvents, typically pH-buffered water and *n*-octanol. It is a measure of hydrophobic/hydrophilic properties of a given molecule. The partition of test compounds is determined using shake-flask method, which involves mixing of certain amount of the solute of interest in defined volumes of *n*-octanol and an aqueous buffer of choice followed by equilibration of the mixture by incubation with efficient mixing. Then, the distribution of the compounds in each solvent was analysed by LC-MS/MS.

Reagents and consumables

DMSO Chromasolv Plus, HPLC grade, ≥99.7% (Sigma-Aldrich, USA; Cat #34869)
Acetonitrile Chromasolv, gradient grade, for HPLC, ≥99.9% (Sigma-Aldrich, USA; Cat #34851)
Formic acid for mass spectrometry, ~98% (Fluka, USA; Cat #94318)
Phosphate buffered saline, tablet (Sigma-Aldrich, USA; Cat # P4417)
1-Octanol ACS grade, ≥99% (Sigma-Aldrich, USA; Cat # 472328)
Mebendazole analytical standard, ≥ 98%, HPLC (Sigma-Aldrich, USA; Cat # M2523)
DMSO stock solutions of the test compounds 10mM
Phenomenex Luna® C18 HPLC column, 2.1x50 mm, 5 µm (Cat #5291-126)
1.1 ml microtubes in microracks, pipettor tips (Thermo Scientific, USA).
National Scientific MicroTube™ Rack (Thermo Fisher Scientific, USA; Cat # TN094612R)

Equipment

Gradient HPLC system (Shimadzu, Japan)
Triple quadrapole mass-detector API 3000 with TurboIonSpray Ion Source (AB Sciex, Canada)
VWR Membrane Nitrogen Generators N2-04-L1466, nitrogen purity 99%+ (VWR, USA)
MTR22 Multi Mix Rotator (UNICO, USA)
Laboratory Centrifuge, Sigma 4-15C, Qiagen (SIGMA GmbH, Germany)
Water purification system Millipore Milli-Q Gradient A10 (Millipore, France)
Multichannel Electronic Pipettes 2-125 µL, 5-250 µL, 15-1250 µL, Matrix (Thermo Scientific, USA; Cat ## 2001, 2002, 2004)

Analytical System

All measurements were performed using Shimadzu Prominence HPLC system including vacuum degasser, gradient pumps, reverse phase column, column oven and autosampler. The HPLC system was coupled with tandem mass spectrometer API 3000 (PE Sciex). The both positive and negative ion modes of the TurboIonSpray ion source were used. Acquisition and analysis of the data were performed using Analyst 1.5.2 software (PE Sciex).

Methods

Incubations were carried out in Eppendorf-type polypropylene microtubes in triplicates. 5 µL aliquot of 10 mM DMSO stock of a test compound was added into the previously mutually saturated mixture containing 500 µL of PBS (pH 7.4) and 500 µL of octanol. The solution was allowed to mix in a rotator for 1 hour at 30 rpm. Phase separation was assured by centrifugation for 2 min at 6000 rpm. The octanol phase was diluted 100-fold with 40% acetonitrile, and aqueous phase (PBS buffer) was analyzed without dilution or diluted 10-fold (for Mebendazole). The samples (both phases) were analyzed using HPLC system coupled with tandem mass spectrometer. Mebendazole was used as a reference compound.

Calculations of the partition ratios were carried out using the equation below.

$$D = \frac{d_o \cdot S_O}{d_p \cdot S_P}$$

where: S_O – peak area of the analyte in octanol phase

S_P – peak area of the analyte in PBS buffer

d_o – dilution coefficient for octanol phase

d_p – dilution coefficient for aqueous phase

Results

LogD data for the reference compound (Mebendazole) and test compounds is provided in the table below.

Table S1. Experimental LogD, pH 7.4

Compound ID	Incubation	S_P	S_O	D	LogD, pH 7.4	
Mebendazole	1	9.74E+03	5.26E+05	5.40E+02	2.73	**2.89**
	2	9.93E+03	8.99E+05	9.05E+02	2.96	
	3	1.02E+04	9.61E+05	9.46E+02	2.98	
69	1	5.79E+03	4.46E+06	7.70E+04	4.89	**≥4.5***
	2	5.47E+03	4.73E+06	8.64E+04	4.94	
	3	5.13E+03	4.54E+06	8.84E+04	4.95	
70	1	2.73E+04	2.47E+06	9.03E+03	3.96	**3.97**
	2	2.73E+04	2.52E+06	9.22E+03	3.96	
	3	2.67E+04	2.50E+06	9.40E+03	3.97	
66	1	3.79E+03	1.12E+06	2.95E+04	4.47	**4.46**
	2	3.91E+03	1.12E+06	2.87E+04	4.46	
	3	4.26E+03	1.14E+06	2.66E+04	4.43	
73	1	5.12E+04	1.94E+06	3.79E+03	3.58	**3.58**
	2	5.35E+04	2.00E+06	3.75E+03	3.57	
	3	5.32E+04	2.01E+06	3.78E+03	3.58	
72	1	8.79E+03	2.17E+06	2.46E+04	4.39	**4.40**
	2	9.35E+03	2.29E+06	2.45E+04	4.39	
	3	8.81E+03	2.30E+06	2.61E+04	4.42	
67	1	1.69E+04	7.00E+05	4.14E+03	3.62	**3.64**
	2	1.70E+04	7.21E+05	4.24E+03	3.63	
	3	1.55E+04	7.17E+05	4.64E+03	3.67	

*Reliable measurable range is approximately -1 to 4.5

Analysis of Aqueous Solubility

Study Objective

Six test articles (**66, 67, 69, 70, 72 and 73**) and reference compound (Ondansetron) were assessed for kinetic solubility in phosphate-buffered saline, pH 7.4.

Reagents and consumables

Phosphate buffered saline, pH 7.4 (Sigma-Aldrich, USA; Cat #P3813)

Acetonitrile Chromasolv, gradient grade, for HPLC, ≥99.9% (Sigma-Aldrich, USA; Cat #34851)

Ondansetron base powder (Enamine, Ukraine, Cat # EN300-117273)

DMSO (Sigma-Aldrich, USA; Cat # 34869)

Costar 96 Well Assay Blocks (Corning, USA; Cat # 3958)

MultiScreen HTS 96 Well Filter Plates (Millipore, Ireland; Cat # MSGVS2210)

UV-Star® 96 Well Microplate (Greiner Bio-One, Germany; Cat #655801)

Matrix Disposable pipette tips (ThermoScientific, USA; Cat ## 8041, 7622, 7321)

Flex-Tubes Microcentrifuge Tubes, 1.5ml (Eppendorf, Germany; Cat # 22364111)

Matrix Storage tubes, 1.4 ml (ThermoScientific, USA; Cat # 4247)

Equipment

Water purification system Millipore Milli-Q Gradient A10 (Millipore, France)

Thermomixer R Block, 1.5 ml (Eppendorf, Germany; Cat # 5355)

Matrix Multichannel Electronic Pipette 2-125 µL, 5-250 µL, 15-1250 µL (Thermo Scientific, USA; Cat ## 2011, 2012, 2004)

SpectraMax Plus Microplate Reader (Molecular Devices, USA; Product # 02196)

Multi-Well Plate Vacuum Manifold (Pall Corporation, USA; Product # 5014)

Vacuum pump (Millipore, USA; Model # XX5500000)

Analytical System

The measurements were performed using SpectraMax Plus reader in UV-Vis mode. Acquisition and analysis of the data were performed using SoftMax Pro v.5.4 (Molecular Devices) and Excel 2010 data analysis software.

Methods

Kinetic solubility assay was performed according to the Enamine's aqueous solubility SOP. Briefly, using a 20 mM stock solution of the compounds in 100% DMSO dilutions were prepared to a theoretical concentration of 400 μM in duplicates in phosphate-buffered saline pH 7.4 (138 mM NaCl, 2.7 mM KCl, 10 mM K-phosphate) with 2% final DMSO. The experimental compound dilutions in PBS were further allowed to equilibrate at 25 °C on a thermostatic shaker for two hours and then filtered through HTS filter plates using a vacuum manifold. The filtrates of test compounds were diluted 2-fold with acetonitrile with 2% DMSO before measuring.

In parallel, compound dilutions in 50% acetonitrile/PBS were prepared to theoretical concentrations of 0 μM, 10 μM, 25 μM, 50 μM, 100 μM and 200 μM with 2% final DMSO to generate calibration curves. Ondansetron was used as reference compound to control proper assay performance. 200 μl of each sample was transferred to 96-well plate and measured in 200-550 nm range with 5 nm step.

The concentrations of compounds in PBS filtrate are calculated using a dedicated Microsoft Excel calculation script. Proper absorbance wavelengths for calculations are selected for each compound manually based on absorbance maximums (absolute absorbance unit values for the minimum and maximum concentration points within 0 – 3 OD range). Each of the final datasets is additionally visually evaluated by the operator and goodness of fit (R2) is calculated for each calibration curve. The effective range of this assay is approximately 2-400 μM and the compounds returning values close to the upper limit of the range may have higher actual solubility (e.g. 5'-deoxy-5-fluorouridine). This method is not suitable for liquid (at 25 °C) substances (were not present among the tested compounds).

Results

Table S2. The solubility data of the test and reference compounds are listed in the table below. The calibration curves are shown in the Appendix.

ID	PBS solubility, pH 7.4, µM			SE
	Incubation 1	Incubation 2	Mean	
Ondansetron	104	101	**103****	1.6
EN300-27699318 (**69**)	7	7	**7**	0.1
EN300-27699324 (**70**)	118	118	**118**	0.0
EN300-27721010 (**66**)	3	2	**3**	0.4
EN300-27721011 (**73**)	33	34	**34**	0.5
EN300-27721012 (**72**)	9	9	**9**	0.1
EN300-27721013 (**67**)	361	358	**360**	1.6

*Goodness of fit (R^2) in all titration curves as well as the variations between repeat measurements indicates high quality of the experimental data in the current batch of test articles.

**Ondansetron solubility data are consistent with previously obtained

APPENDIX

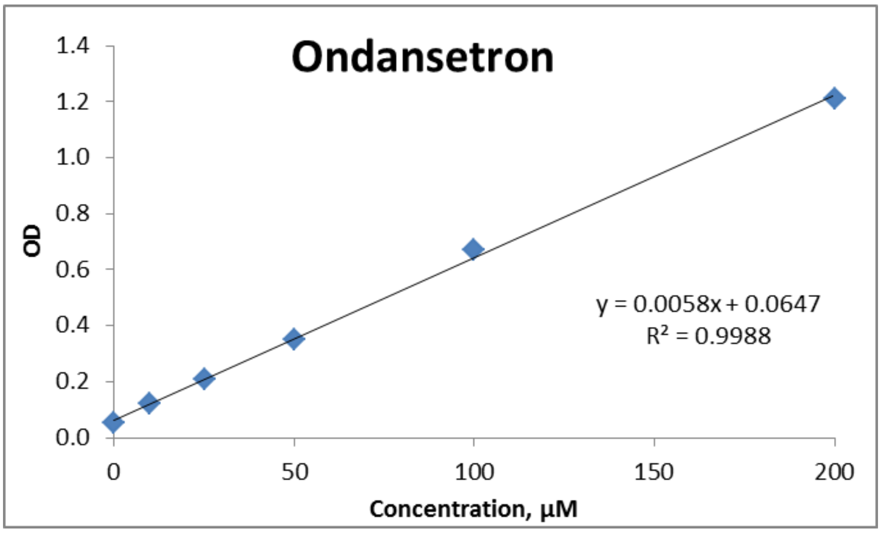


Figure S2. Calibration curve for **Ondansetron**

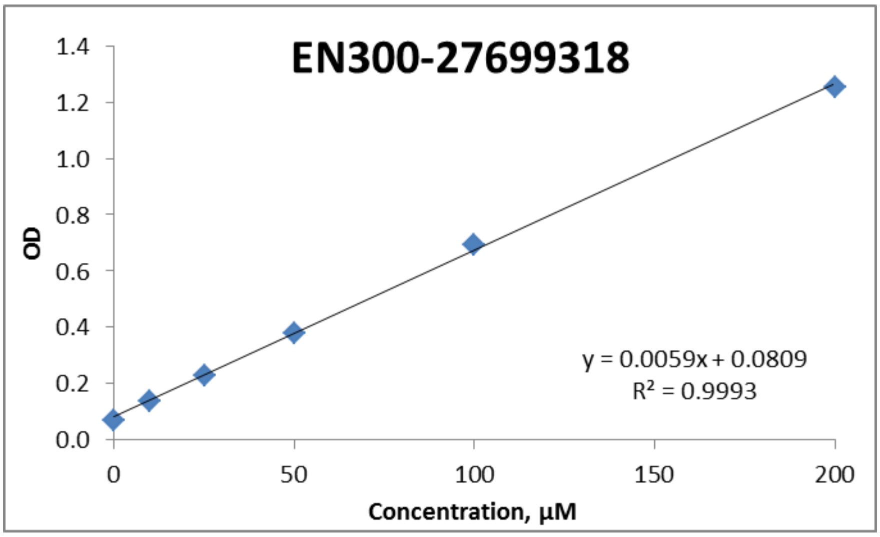


Figure S3. Calibration curve for **EN300-27699318 (69)**

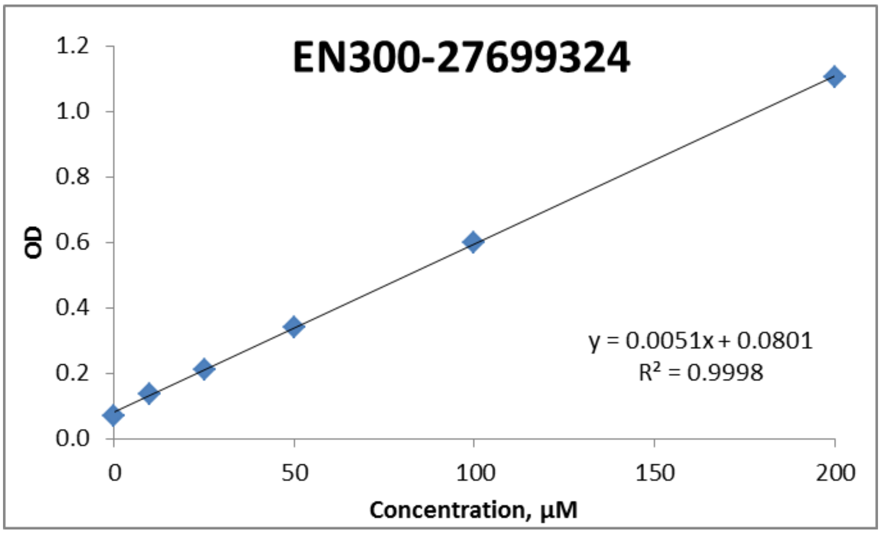


Figure S4. Calibration curve for **EN300-27699324 (70)**

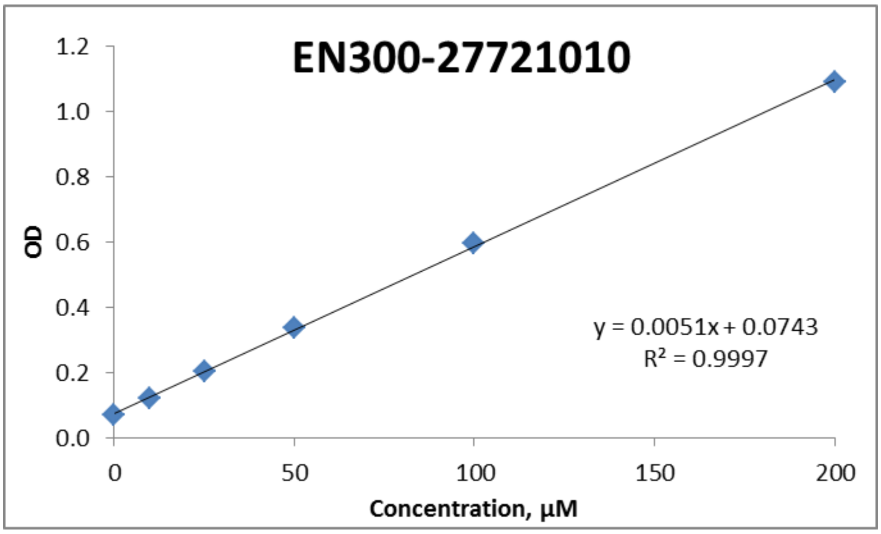


Figure S5. Calibration curve for **EN300-27721010 (66)**

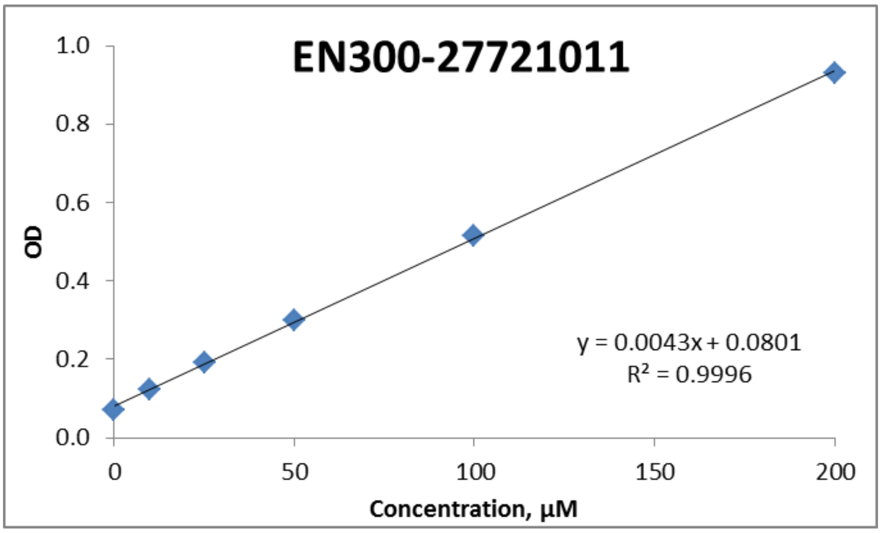


Figure S6. Calibration curve for **EN300-27721011 (73)**

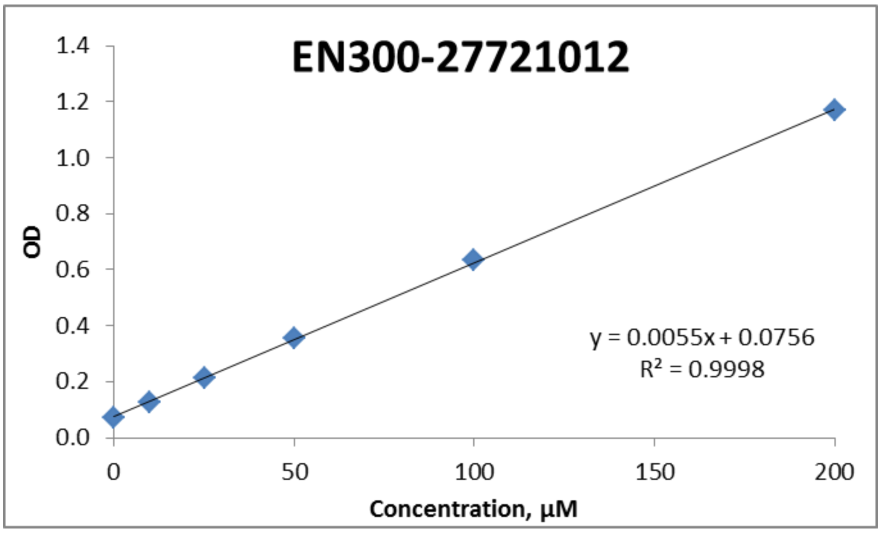


Figure S7. Calibration curve for **EN300-27721012 (72)**

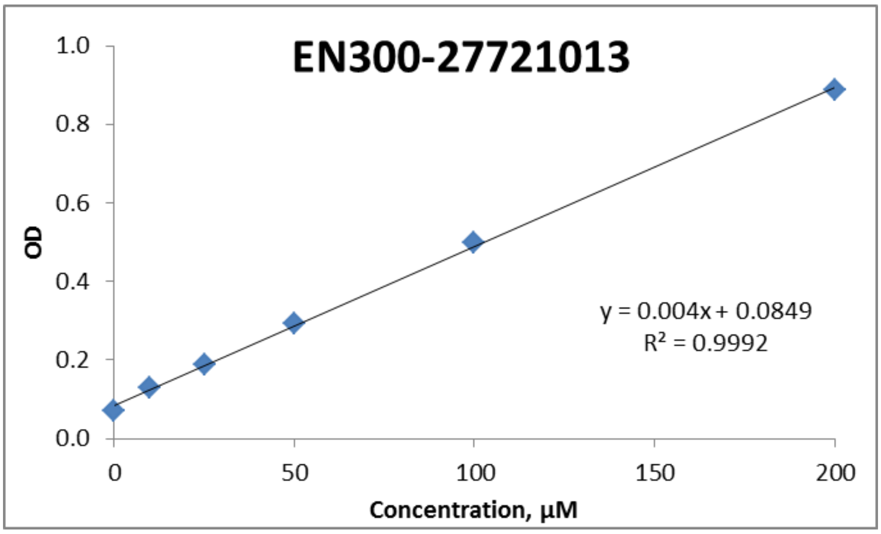


Figure S8. Calibration curve for **EN300-27721013 (67)**

Biological activity (blood pressure tests)

Materials and Methods

Animals

Studies were conducted using 6 month old spontaneously hypertensive (SHR) male rats with the average body weight of 310±6 g and basal systolic blood pressure not less than 185 mmHg, which were in-home breeded in Bienta animal facility. Animals were randomly housed in plastic cages five rats per cage, had free access to water and standard rodent chow *ad libitum* until beginning of the study and maintained at 20-25 °C with a light/dark cycle of 12/12 h. Study design, animal selection, handling and treatment were in accordance with Bienta Animal Care and Use Guidelines, and European Union directive 2010/63/EU.

Blood pressure measurement

The chemicals were dissolved in pure saline (**76**, **77**, **78** and **79**) or in saline containing 4% of captisol (**75**). Animals received 3 mg/kg compound in 5 mL/kg vehicle per os once. Terazosin was used as a reference in the same dosing. Four animals per group were assigned.

Blood pressure (BP) of rats was measured by Tail-Cuff Method using Coda Non-invasive Blood-Pressure System (Kent Scientific Corporation, CT, USA). Rats were placed in plastic holders setting on the warming platform to achieve the tail temperature of 32-35 °C before the testing. Systolic and diastolic BP and heart rate were measured in 15, 60 and 120 min after the dosing, BP lowering values compared to baseline were calculated. To achieve the stable values, the rats were trained before the procedure for 4-5 days.

Statistical analysis

Statistical analysis was performed using two-way ANOVA with Tukey's multiple comparisons test (GraphPad Prism 9.0.1 software for Windows). The difference between groups was considered significant if $p<0.05$.

Results

When analyzing the absolute BP values, we observed that all the tested compounds had no differences in efficacy compared to prototype terazosin. All the chemicals decreased systolic blood pressure at least at one time point. If compared the efficacy in blood pressure decrease, one can see that terazosin, **75**, **76** and **78** decreased both systolic and diastolic blood pressure in 15 and 60 min after the dosing by 48-78 mmHg and by 31-56 mmHg, respectively, compared to basic values. Moreover, both systolic and diastolic blood pressure retained low also in 120 min after the dosing (by 27-34 mmHg compared to basic values) in groups which received **76** and **78**. In group which received compound **75** only diastolic blood pressure remained depressed in 120 min after the dosing (by 28 mmHg compared to basic value).

If compared the BP lowering values, compounds **75**, **76** and **78** demonstrated the same tendency as terazosin does: the maximum BP lowering in 15 min after the dosing with subsequent decrease the BP lowering values. Moreover, **75** decreased systolic BP even more significantly than the reference terazosin did ($p = 0.01$). The BP dynamics of rats received **77** and **79** are different: the first one had the maximum efficacy in 60 min after the dosing, and the second one consequently depressed systolic BP with the maximum depression in 120 min after the dosing, remaining, however at the terazosin's level. Diastolic BP lowering demonstrated the same tendency as systolic one for all tested compounds except terazosin, which depressed BP similarly in all time points.

Conclusion

Compounds **75**, **76** and **78** demonstrated ability to depress both systolic and diastolic BP in SHR rats substantially and similarly to the reference terazosin at least due to 15-120 min after the single dose. Furthermore, systolic BP lowering in 15 min after the dose caused by **75** was more significant compared to that caused by terazosin. Thus, **75** could be a potent antihypertensive therapeutic aimed to fast lowering of increased BP.

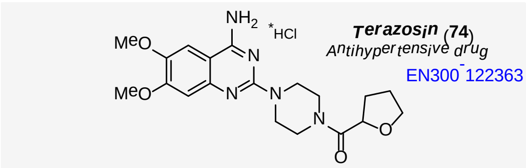
Method

The noninvasive rat blood pressure measurement methodology consists of utilizing a tail-cuff placed on the tail of experimental animal to occlude the blood flow. The following parameters have been tested: systolic and diastolic blood pressure, heart rate, blood flow.

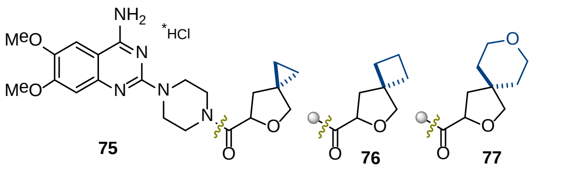
Coda High Throughput System have been used during in vivo experiment.

Numbering of compounds

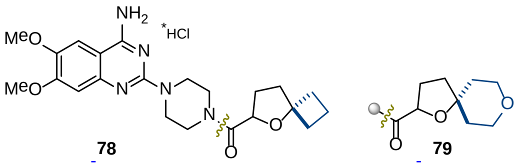
Enamine internal number (EN) – numeration in the manuscript



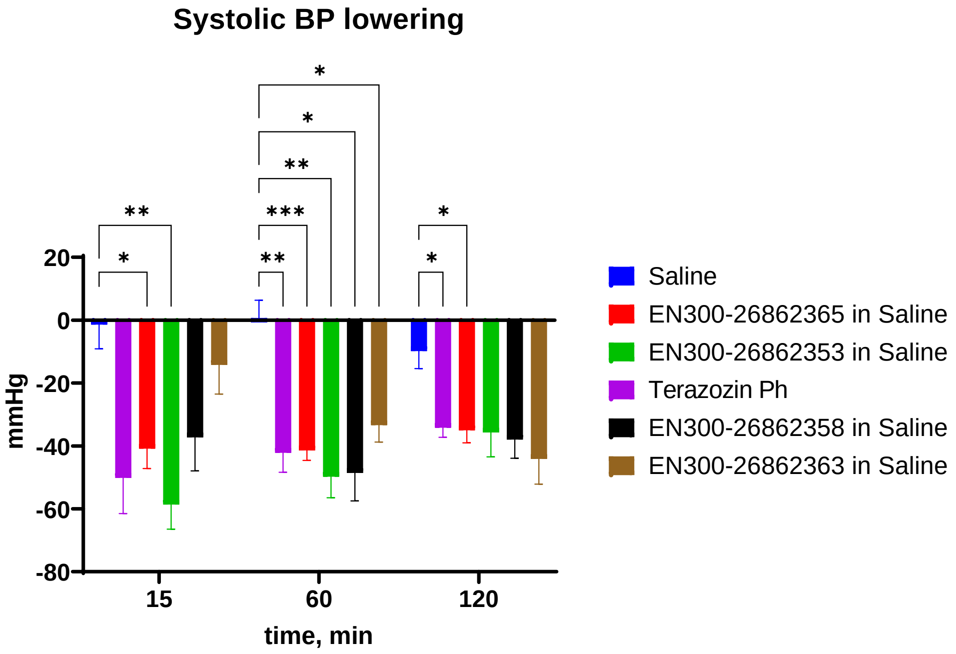
EN300-122363 – compound **74**
EN300-26869300 – compound **75**
EN300-26862353 – compound **76**
EN300-26862358 – compound **77**
EN300-26862365 – compound **78**
EN300-26862363 – compound **79**



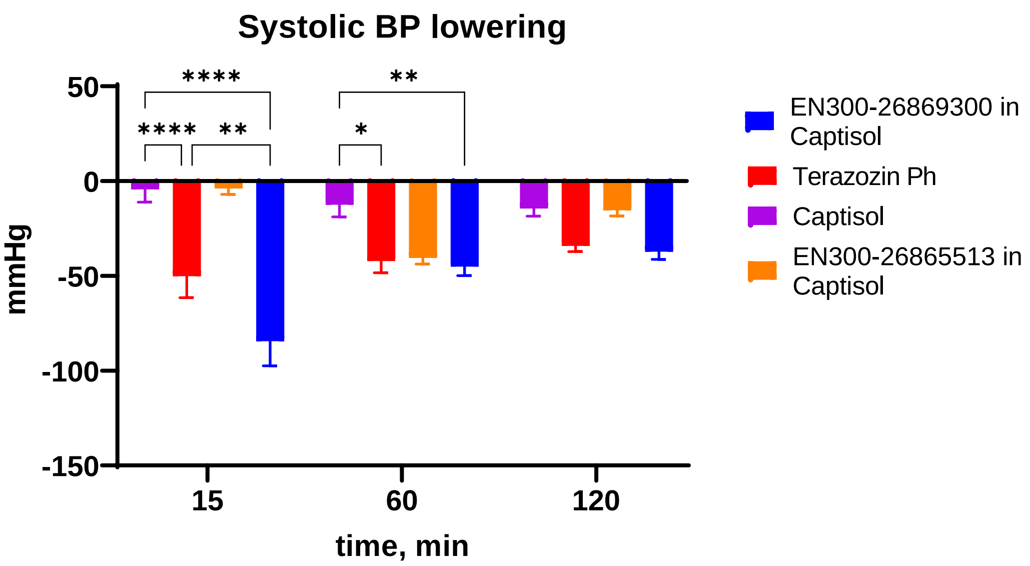
75 EN300-26869300 **76** EN300-26862353 **77** EN300-26862358



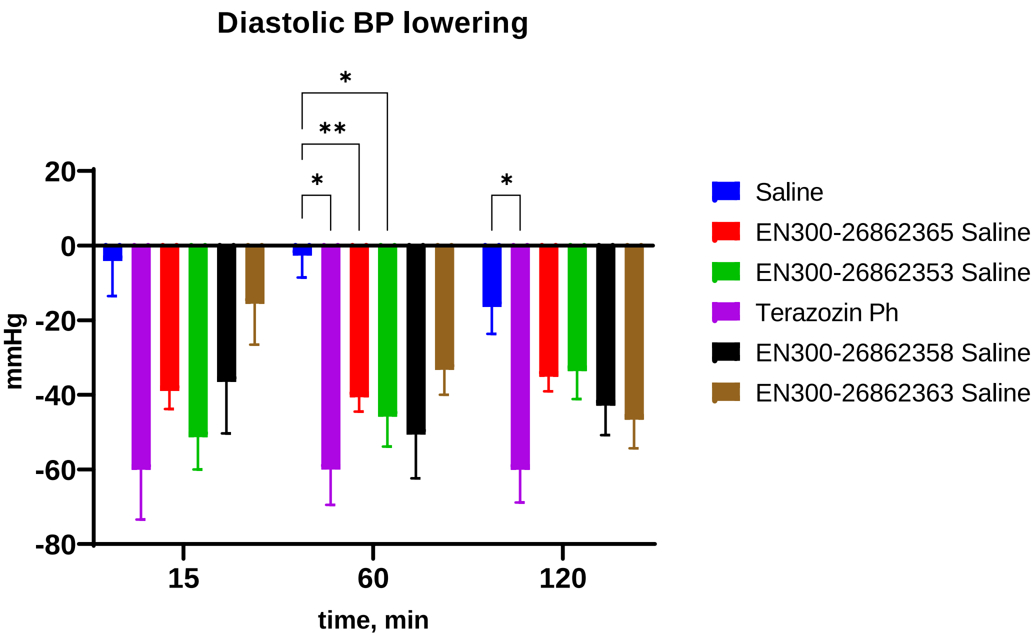
78 EN300-26862365 **79** EN300-26862363



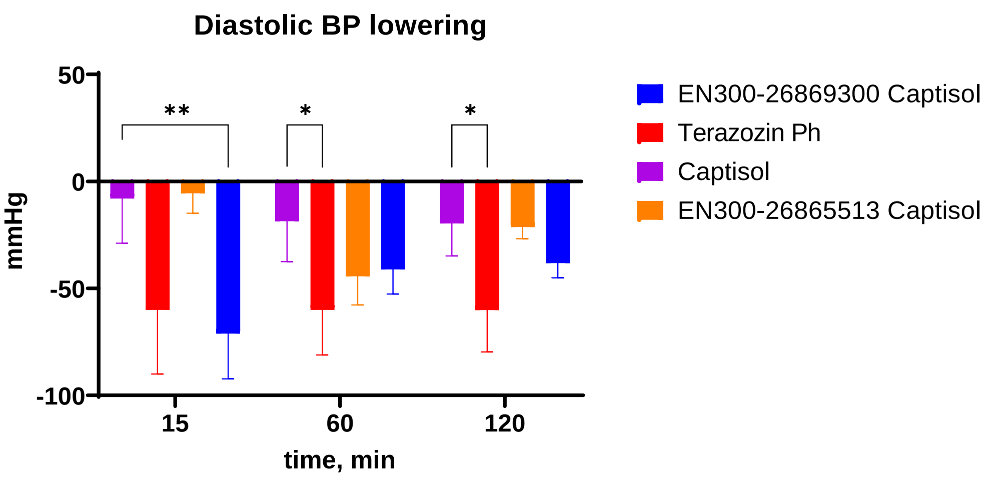
Systolic BP lowering
mmHg
20
0
-20
-40
-60
-80
15
60
120
time, min
*
**
***
Saline
EN300-26862365 in Saline
EN300-26862353 in Saline
Terazozin Ph
EN300-26862358 in Saline
EN300-26862363 in Saline



Systolic BP lowering
mmHg
50
0
-50
-100
-150
15
60
120
time, min
****
**
*
EN300-26869300 in Captisol
Terazozin Ph
Captisol
EN300-26865513 in Captisol



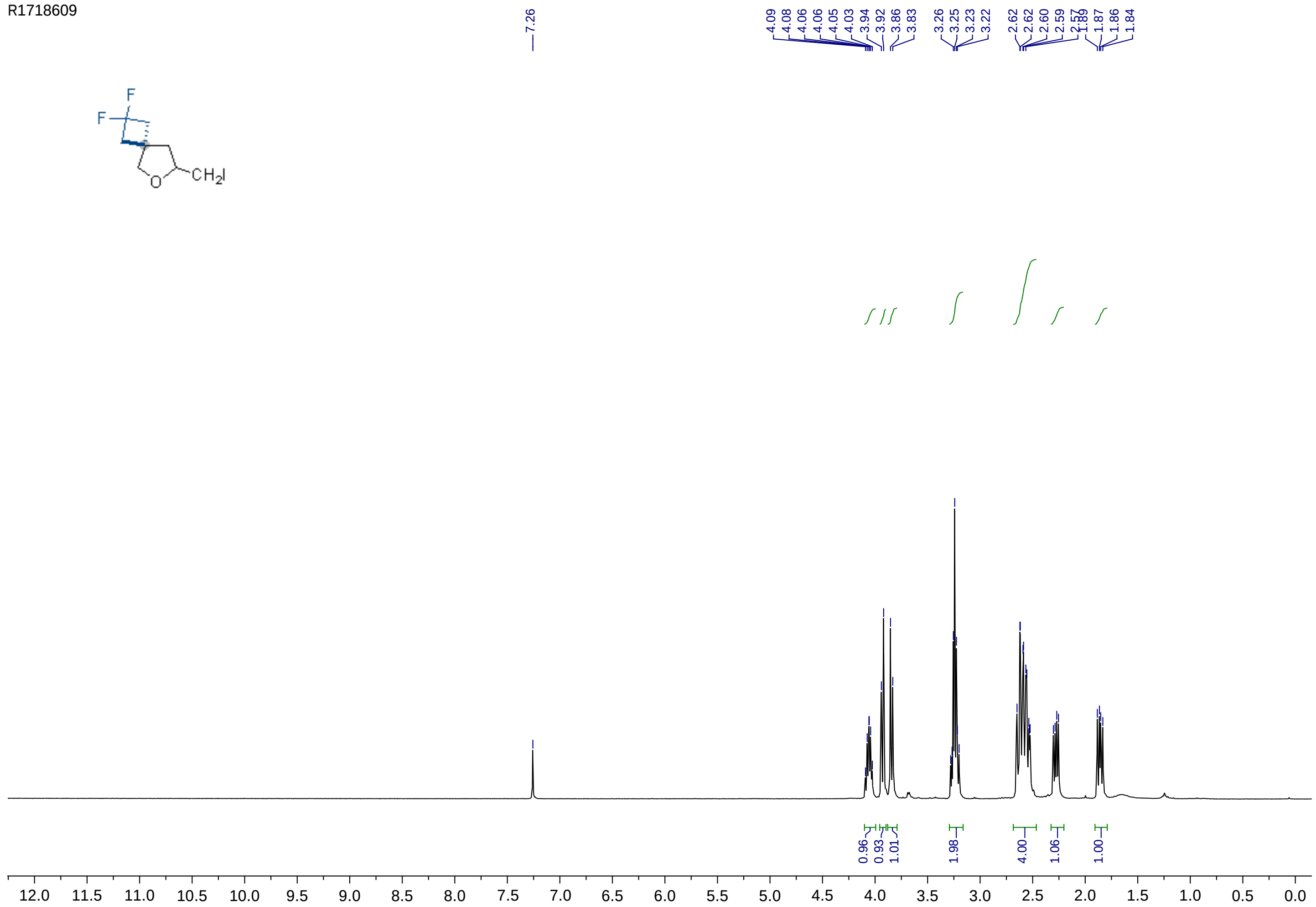
Diastolic BP lowering
*
**
*
*
20
0
-20
-40
-60
-80
mmHg
15
60
120
time, min
Saline
EN300-26862365 Saline
EN300-26862353 Saline
Terazozin Ph
EN300-26862358 Saline
EN300-26862363 Saline

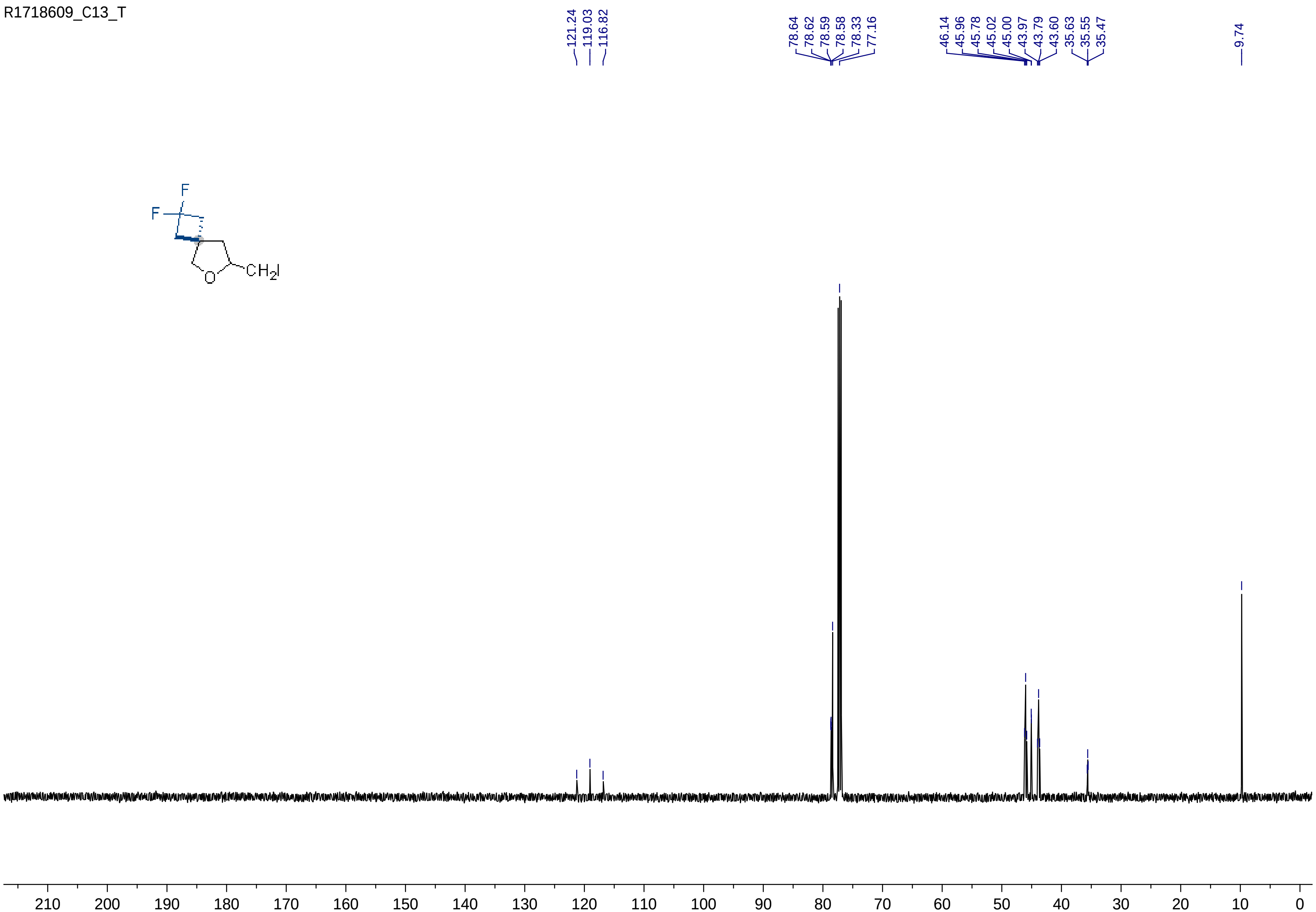


Diastolic BP lowering
**
*
*
50
0
-50
-100
mmHg
15
60
120
time, min
EN300-26869300 Captisol
Terazozin Ph
Captisol
EN300-26865513 Captisol

Copies of ^{1}H, ^{19}F and ^{13}C spectra

Compound 4a

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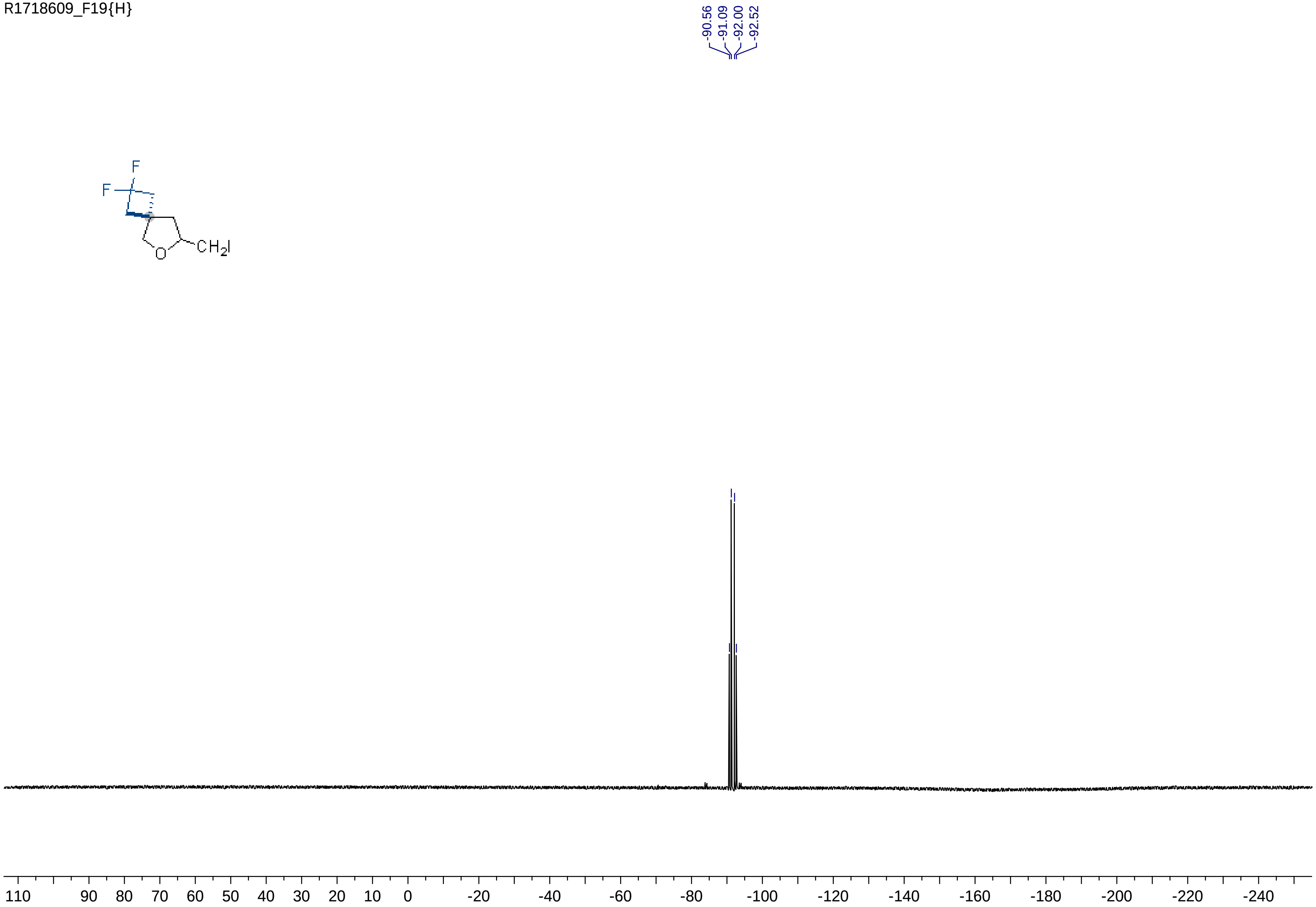
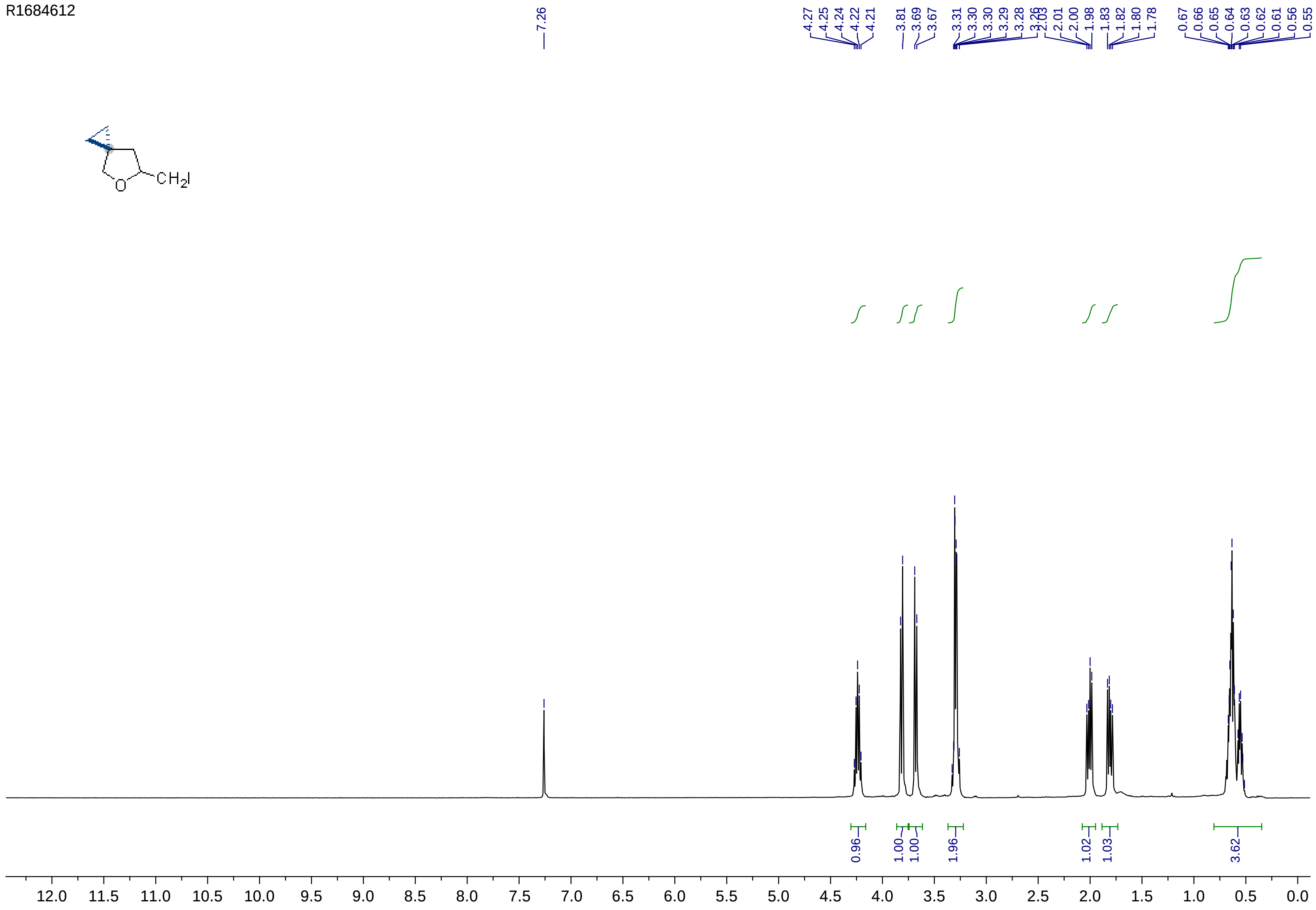
119.03
116.82
78.64
78.62
78.59
78.58
78.33
77.16
46.14
45.96
45.78
45.02
45.00
43.97
43.79
43.60
35.63
35.55
35.47
9.74
F
F
O
CH2I
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

R1718609_F19{H}



Compound 5a


R1684612
CH2I
O
7.26
4.27
4.25
4.24
4.22
4.21
3.81
3.69
3.67
3.31
3.30
3.30
3.29
3.28
3.26
2.03
2.01
2.00
1.98
1.83
1.82
1.80
1.78
0.67
0.66
0.65
0.64
0.63
0.62
0.61
0.56
0.55
0.96
1.00
1.00
1.96
1.02
1.03
3.62
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.0
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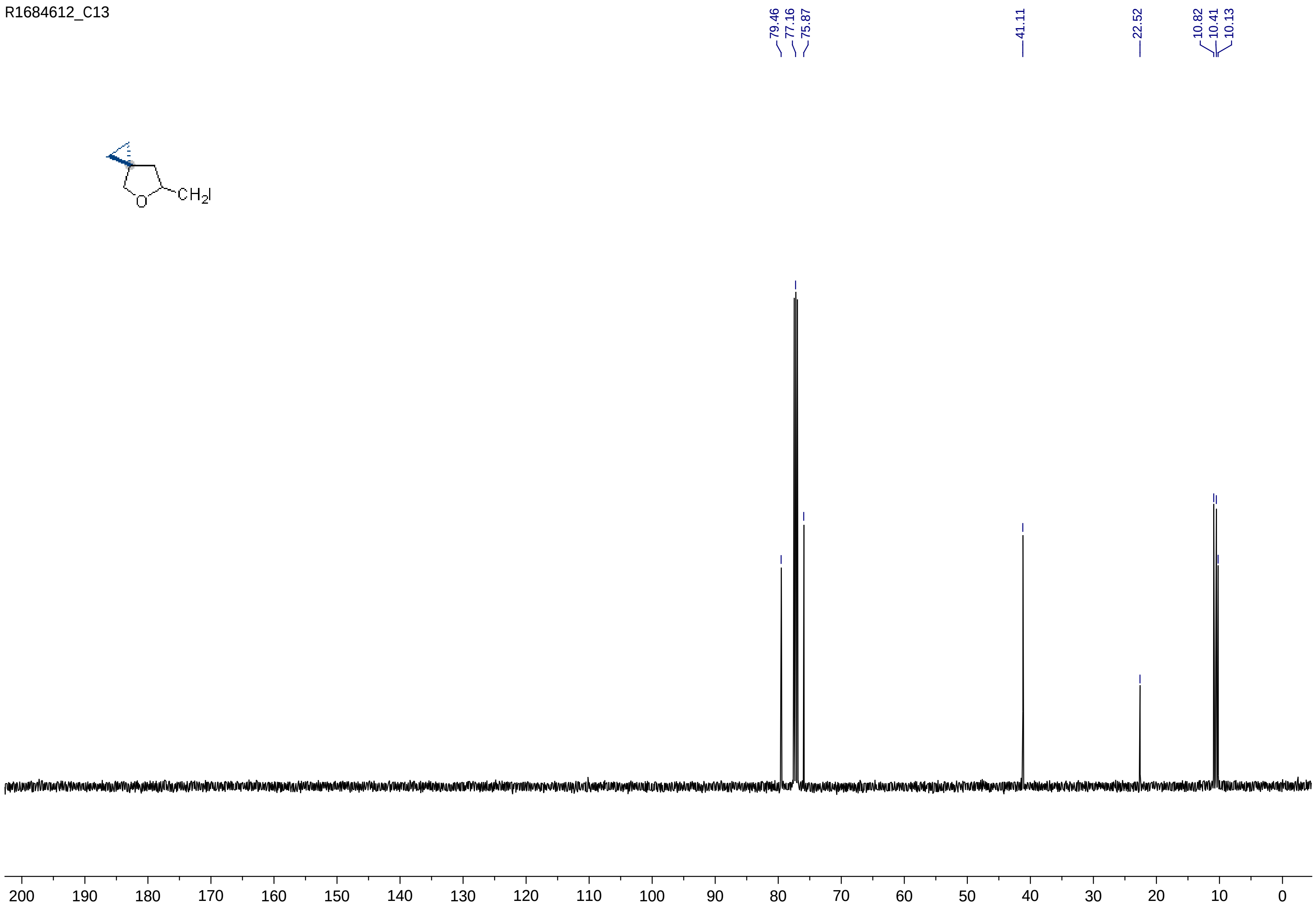
2.0
1.5
1.0
0.5
0.0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77.16
75.87
41.11
22.52
10.82
10.41
10.13
CH2I
O
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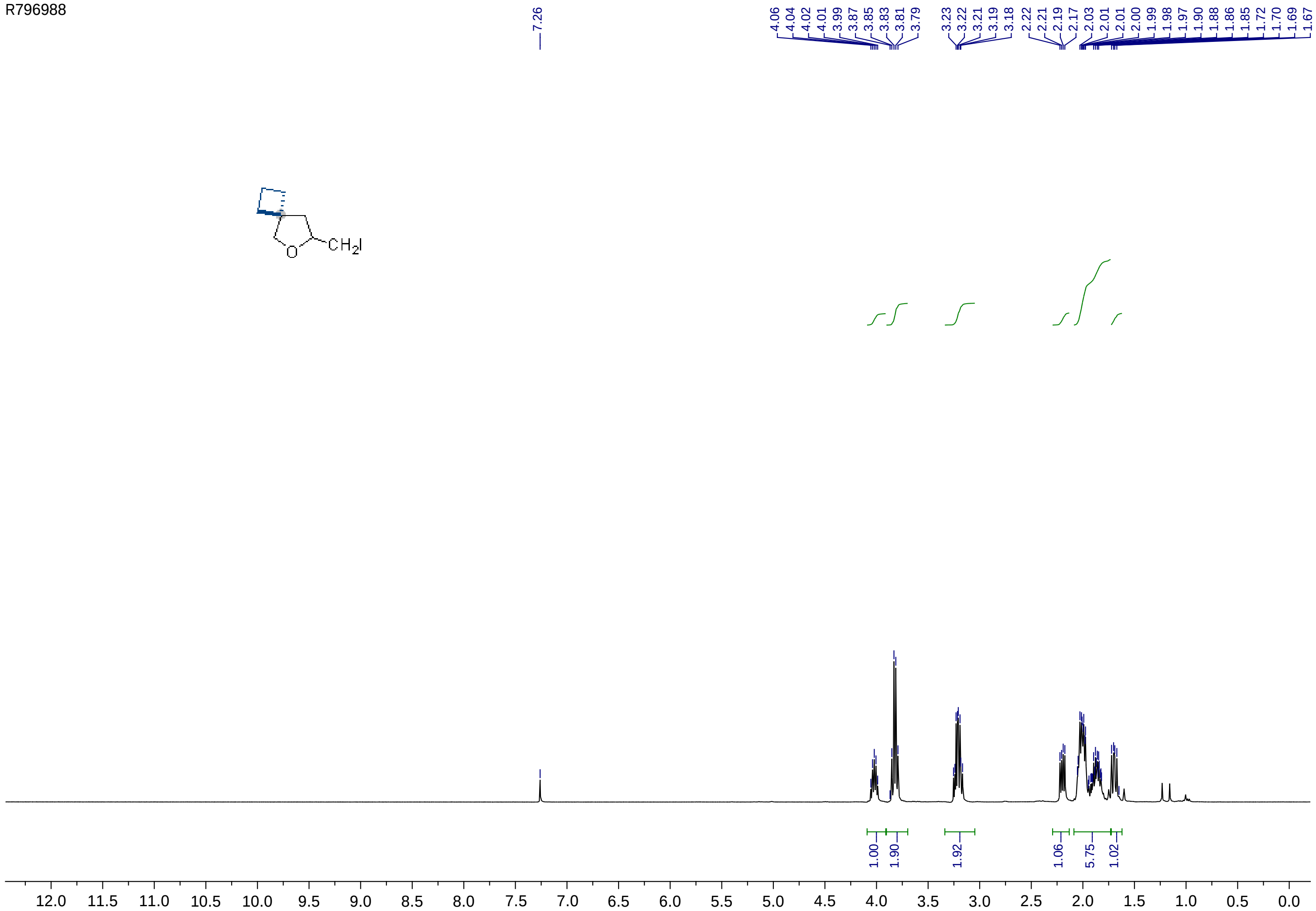
Compound 6a


R796988
7.26
4.06
4.04
4.02
4.01
3.99
3.87
3.85
3.83
3.81
3.79
3.23
3.22
3.21
3.19
3.18
2.22
2.21
2.19
2.17
2.03
2.01
2.01
2.00
1.99
1.98
1.97
1.90
1.88
1.86
1.85
1.72
1.70
1.69
1.67
O
CH2I
1.00
1.90
1.92
1.06
5.75
1.02
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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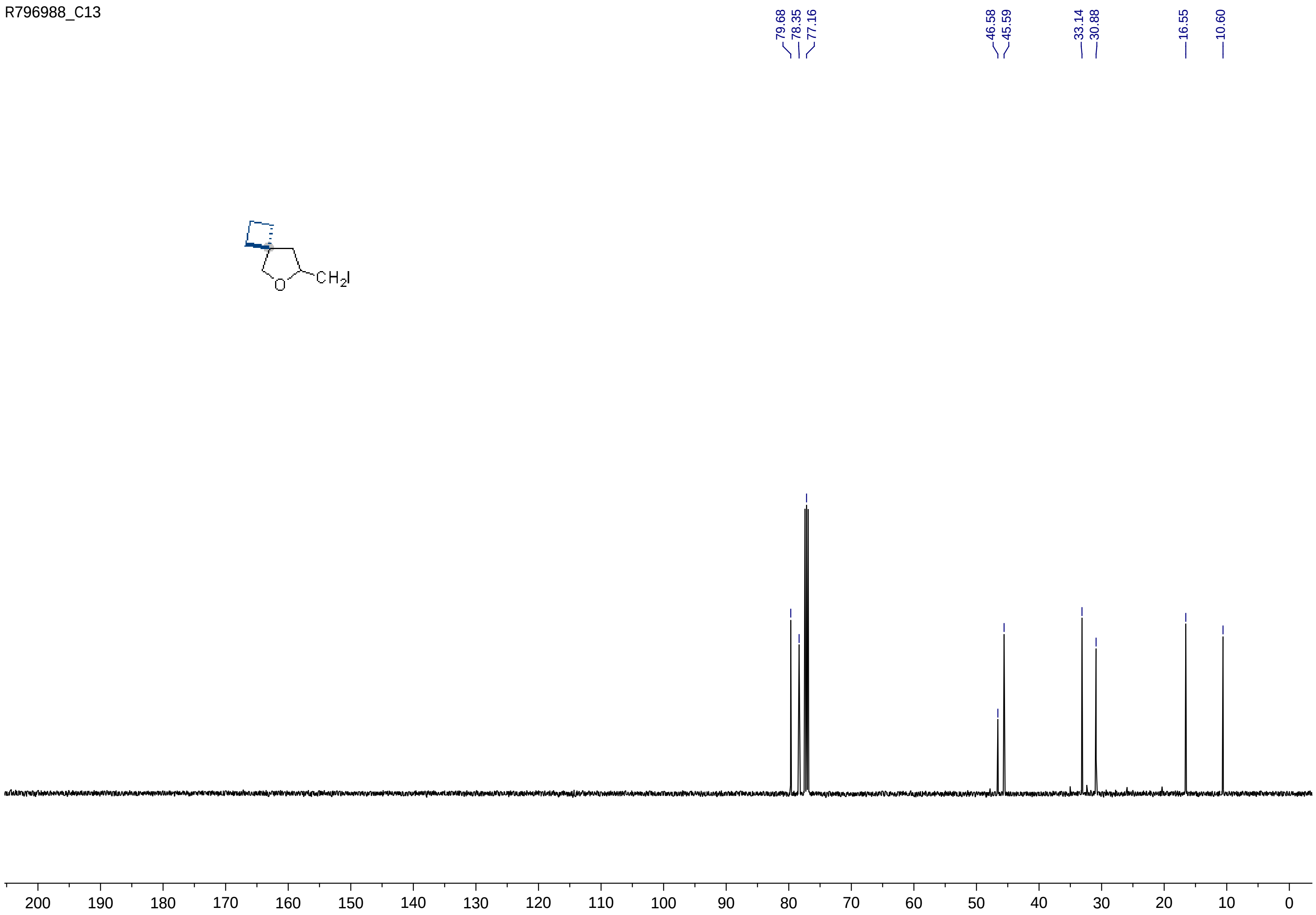
1.0
0.5
0.0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78.35
77.16
46.58
45.59
33.14
30.88
16.55
10.60
O
CH2I
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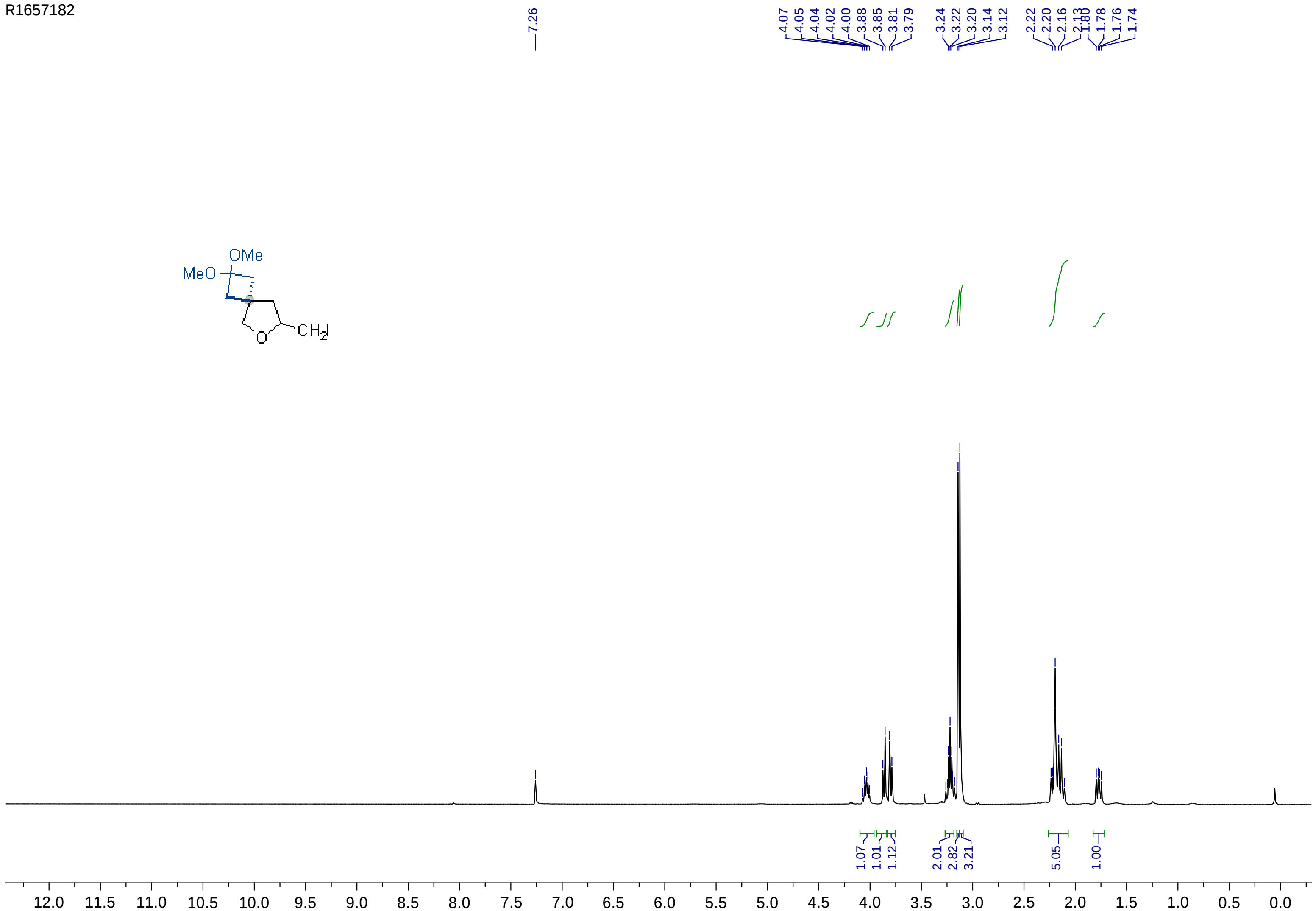
Compound 7a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4.07
4.05
4.04
4.02
4.00
3.88
3.85
3.81
3.79
3.24
3.22
3.20
3.14
3.12
2.22
2.20
2.16
2.13
1.80
1.78
1.76
1.74
OMe
MeO
O
CH2I
1.07
1.01
1.12
2.01
2.82
3.21
5.05
1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

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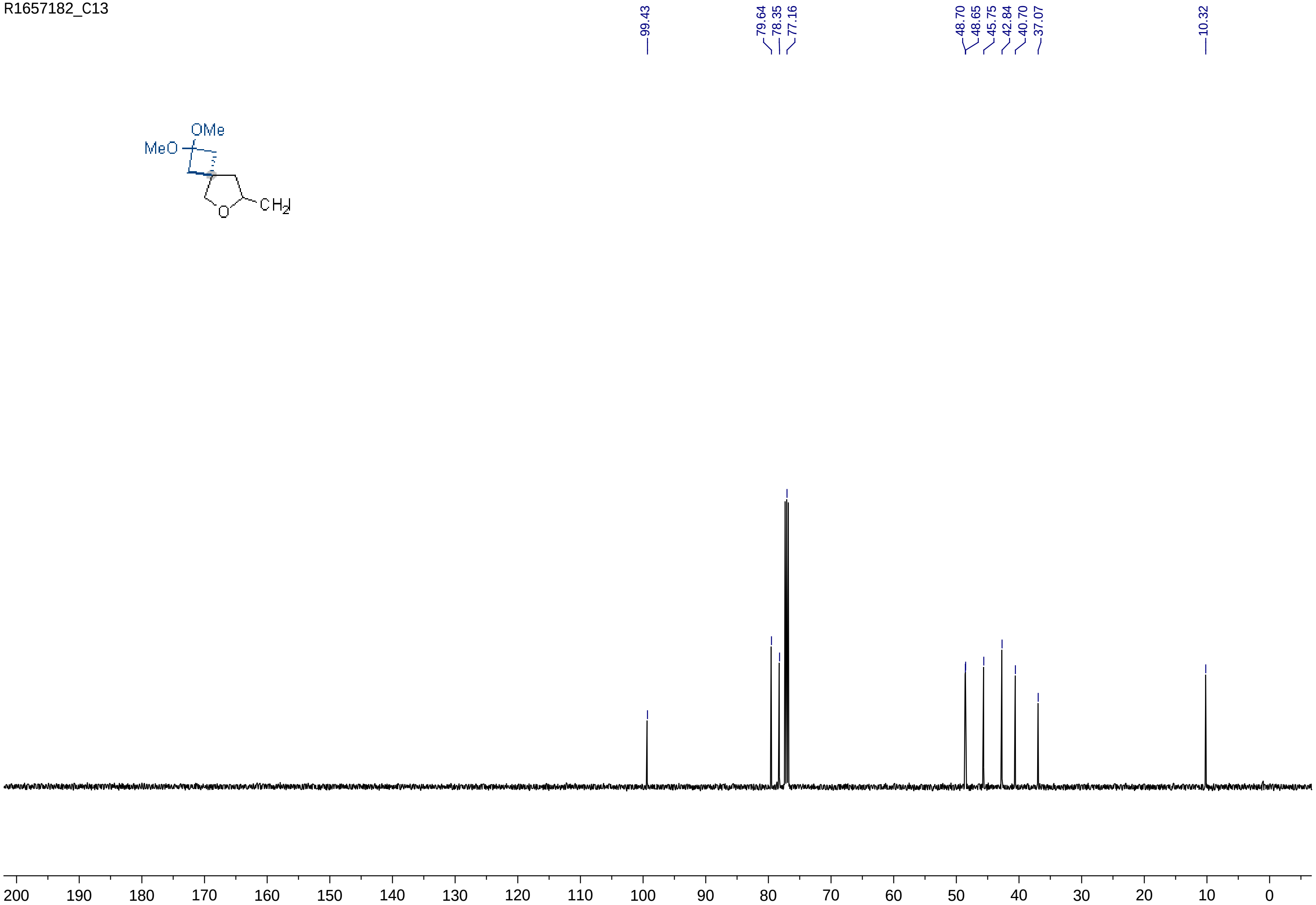
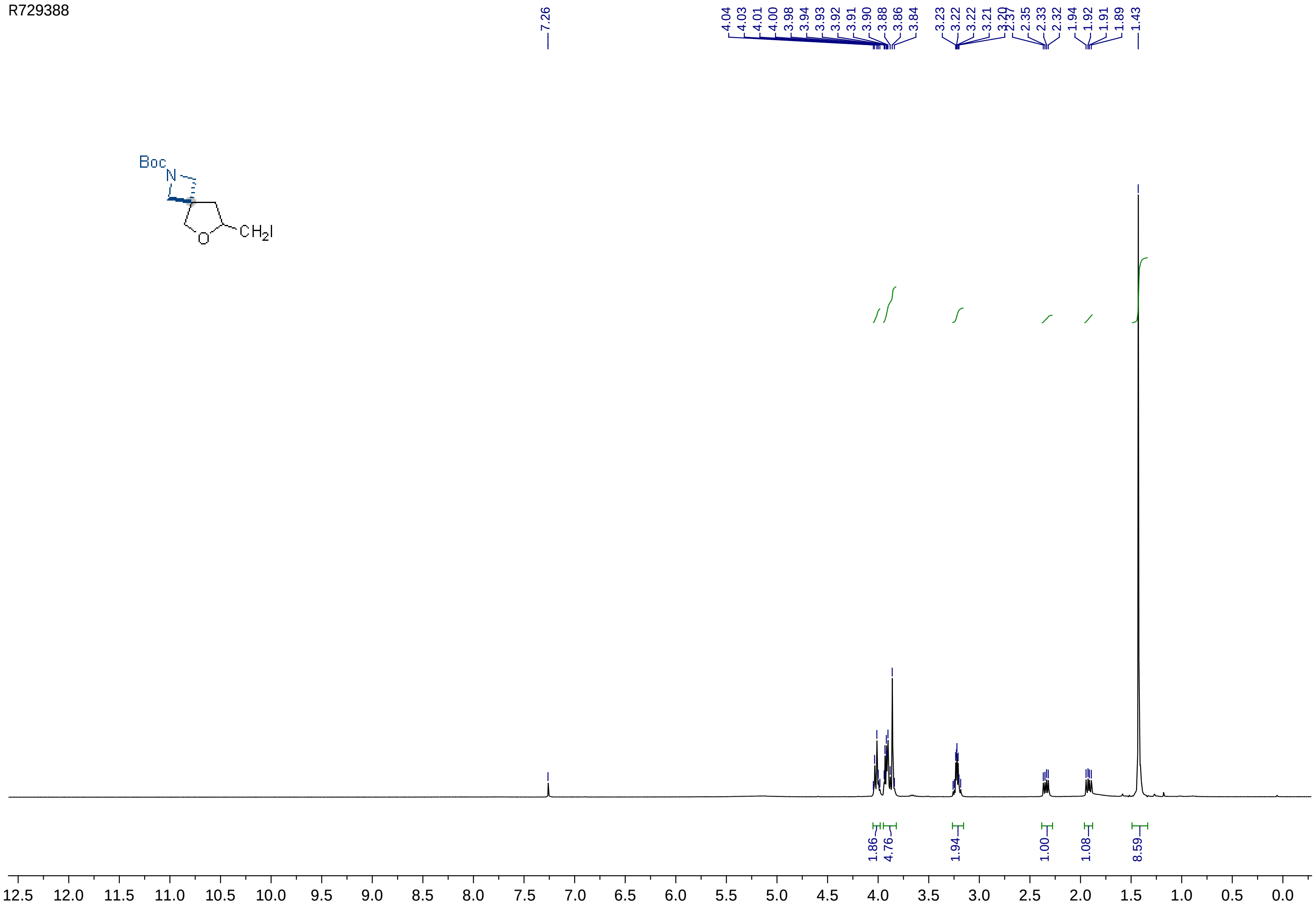
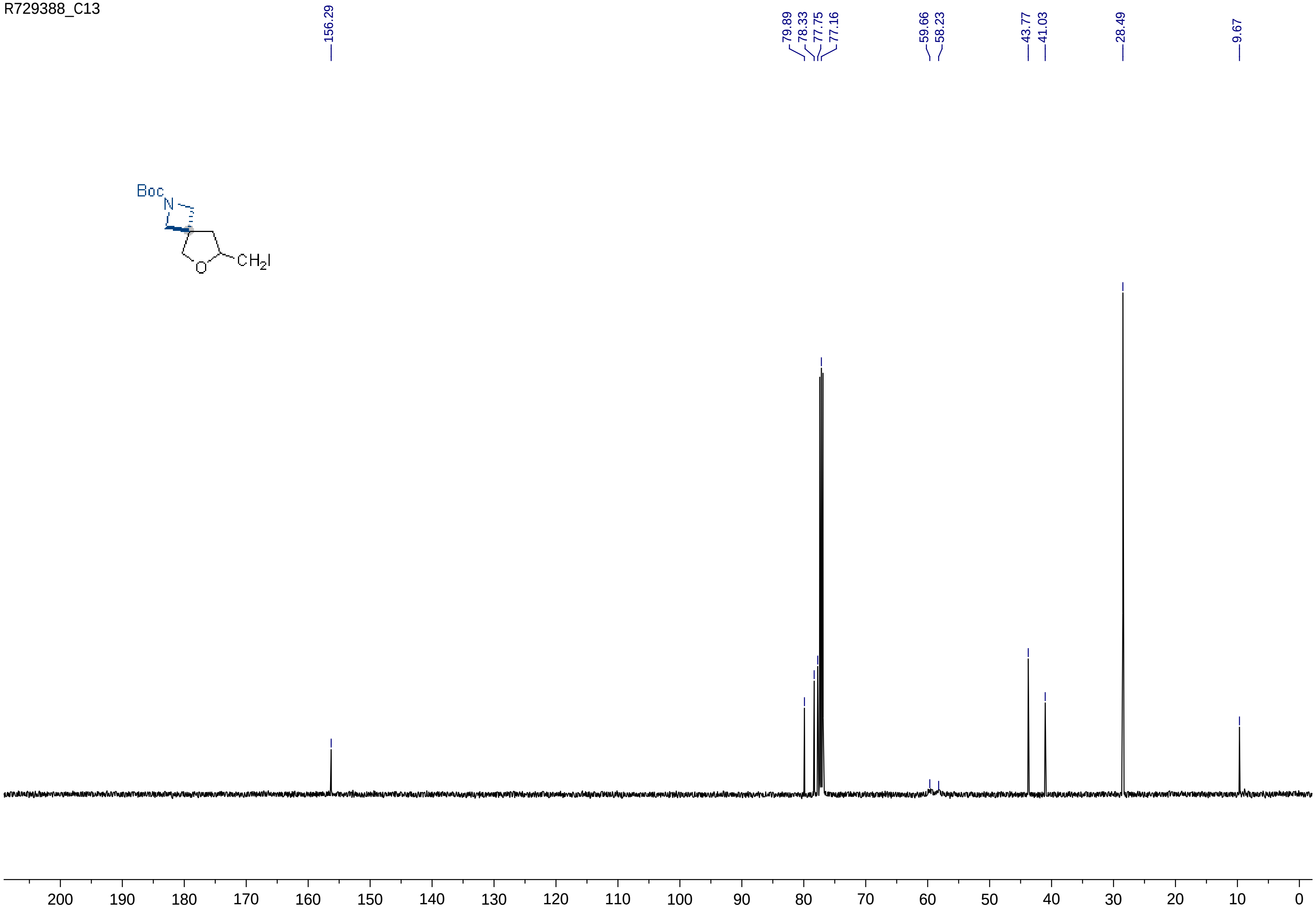


Compound 8a


R729388
7.26
4.04
4.03
4.01
4.00
3.98
3.94
3.93
3.92
3.91
3.90
3.88
3.86
3.84
3.23
3.22
3.22
3.21
3.20
2.37
2.35
2.33
2.32
1.94
1.92
1.91
1.89
1.43
Boc
N
O
CH2I
1.86
4.76
1.94
1.00
1.08
8.59
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

R729388_C13



156.29
79.89
78.33
77.75
77.16
59.66
58.23
43.77
41.03
28.49
9.67
Boc
N
O
CH2I
200
190
180
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130
120
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80
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60
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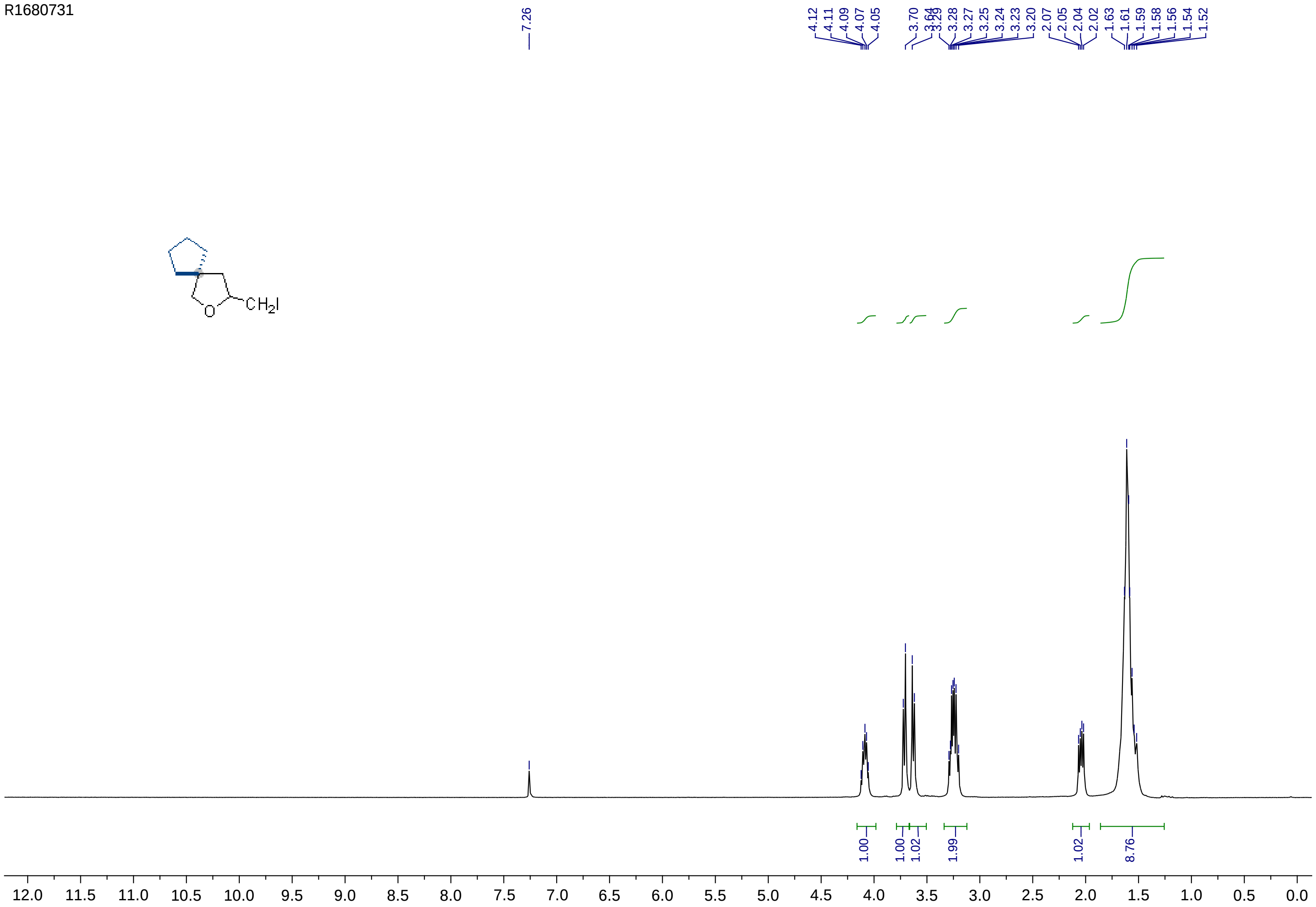
20
10
0

Compound 9a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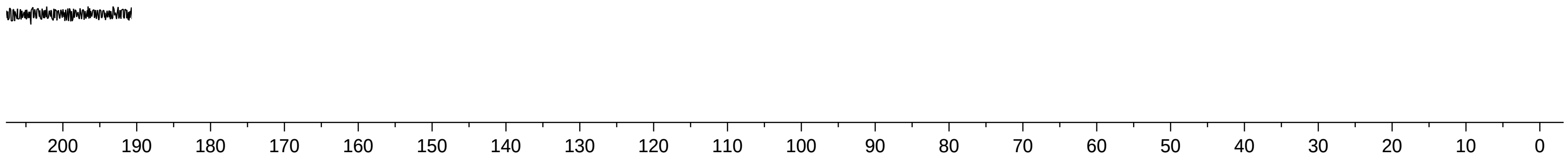
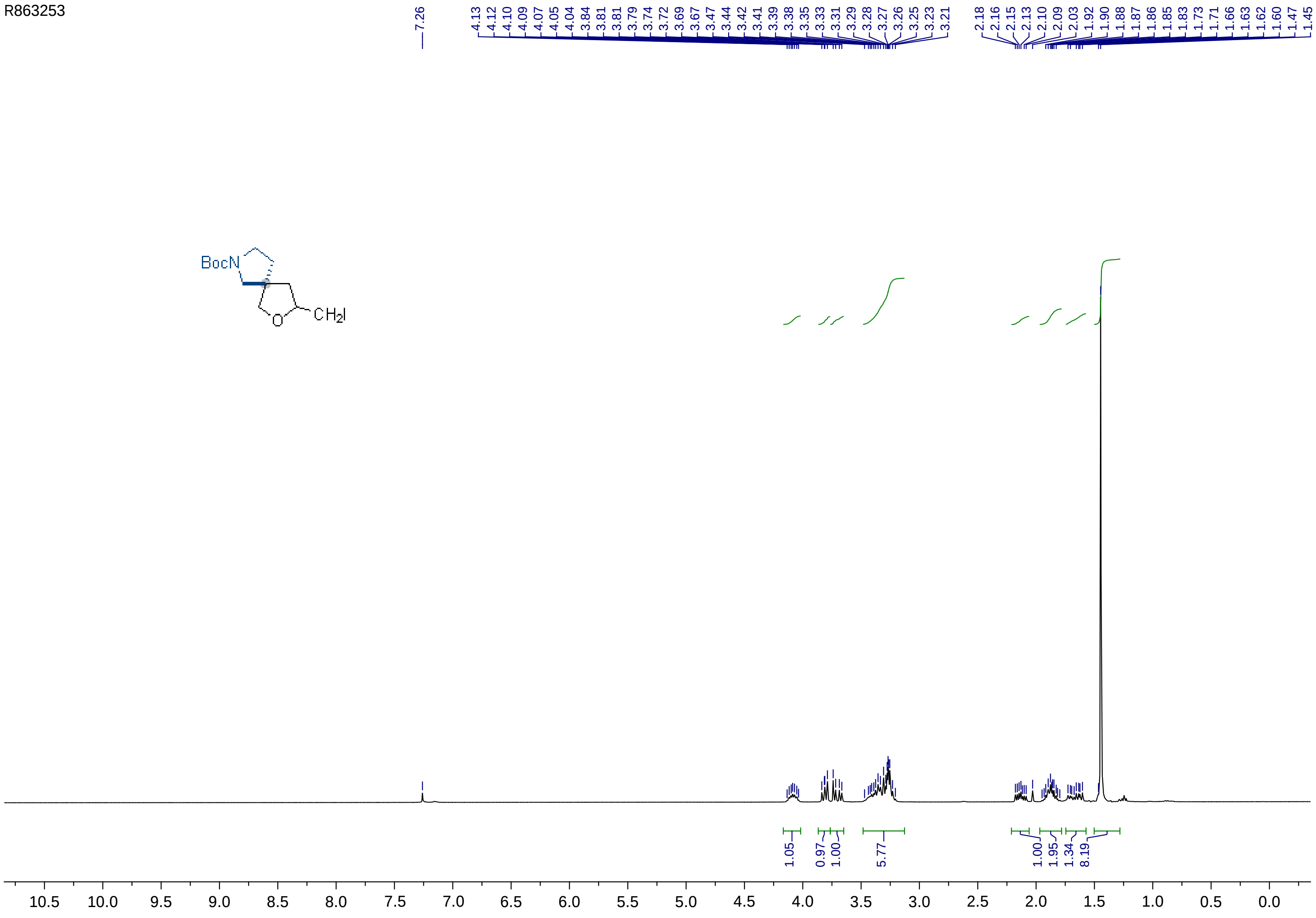
4.12 4.11 4.09 4.07 4.05
3.70 3.64 3.29 3.28 3.27 3.25 3.24 3.23 3.20
2.07 2.05 2.04 2.02
1.63 1.61 1.59 1.58 1.56 1.54 1.52
CH2I
O
1.00 1.00 1.02 1.99 1.02 8.76
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

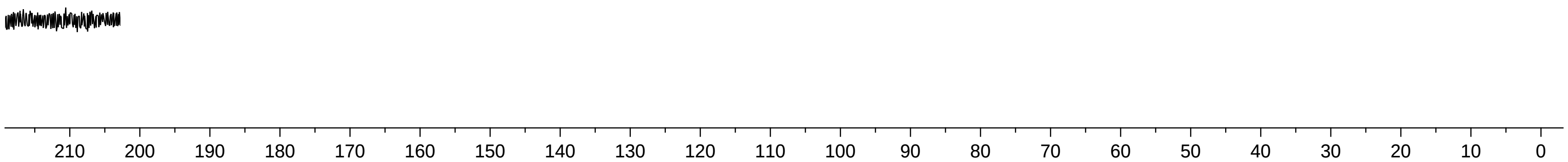
R1680731_13C



Compound 10a



R863253_C13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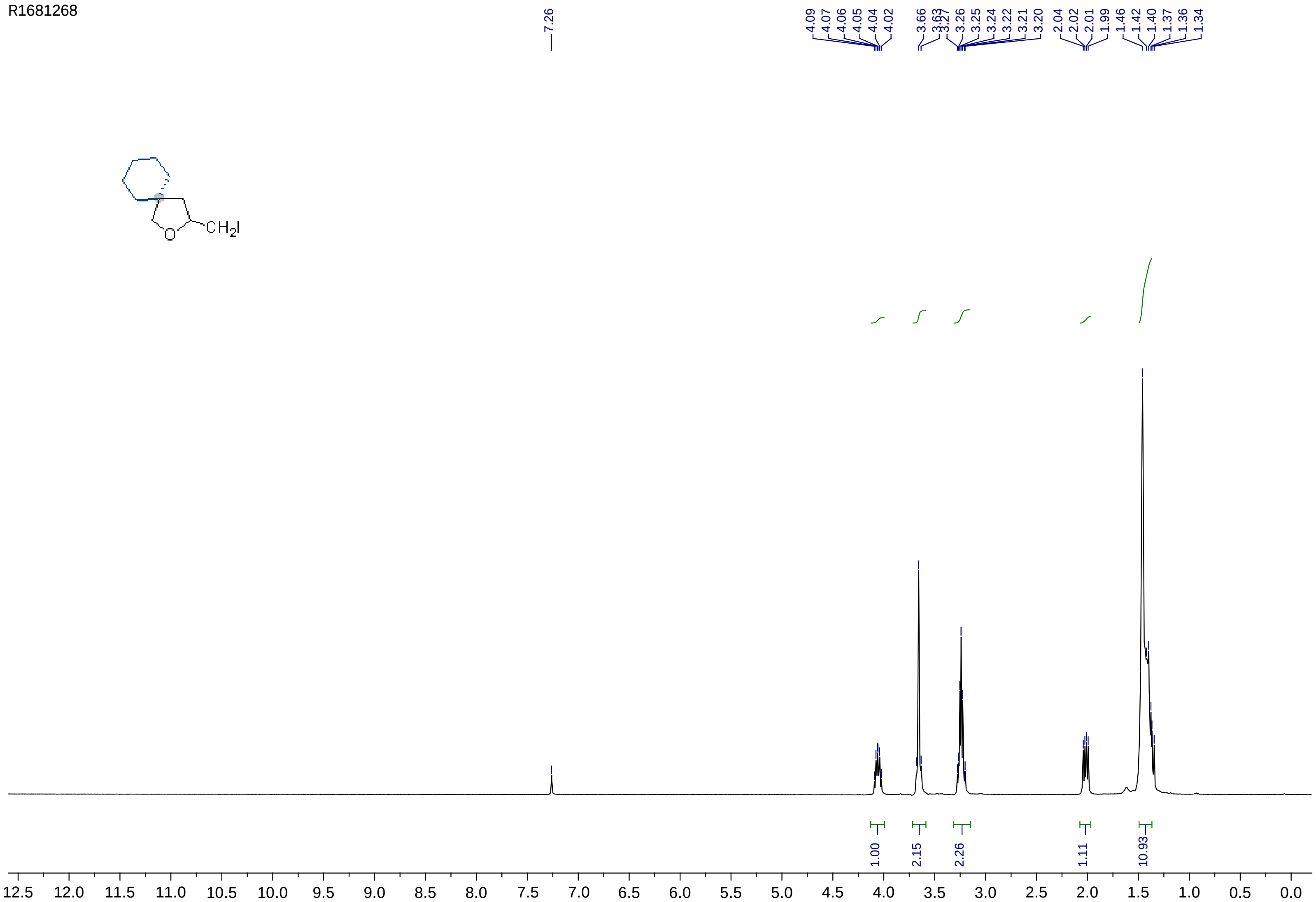
Compound 11a



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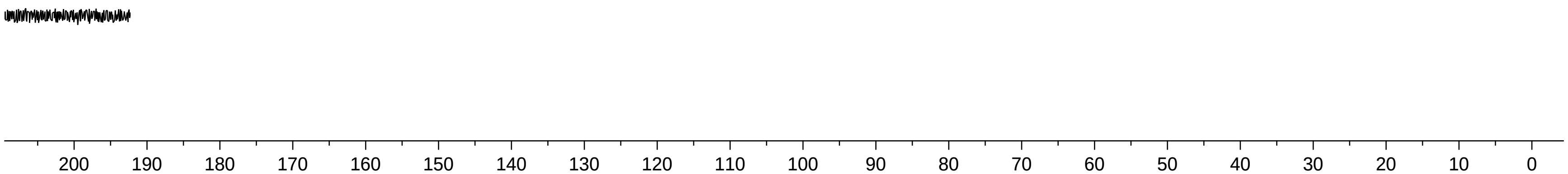
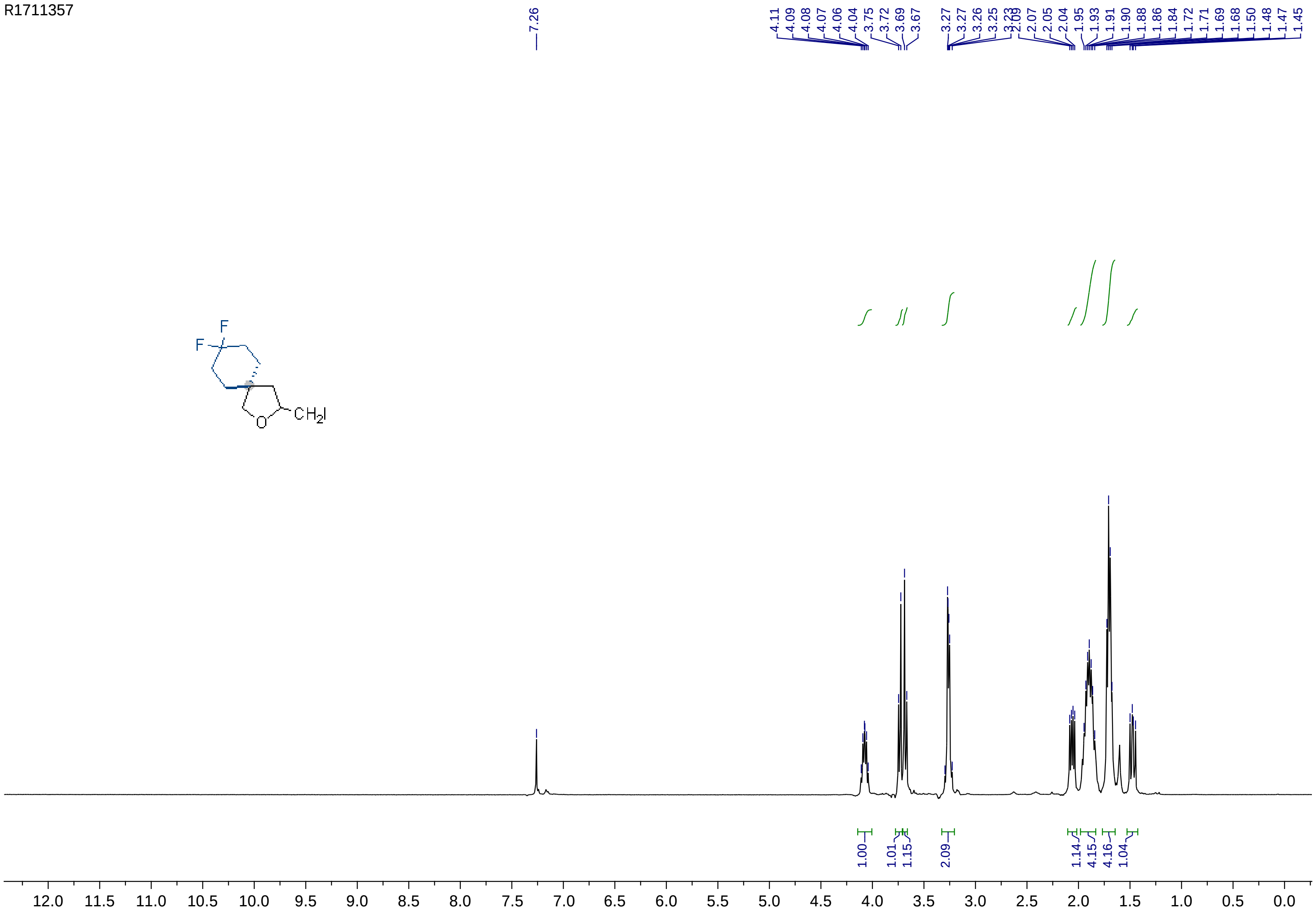
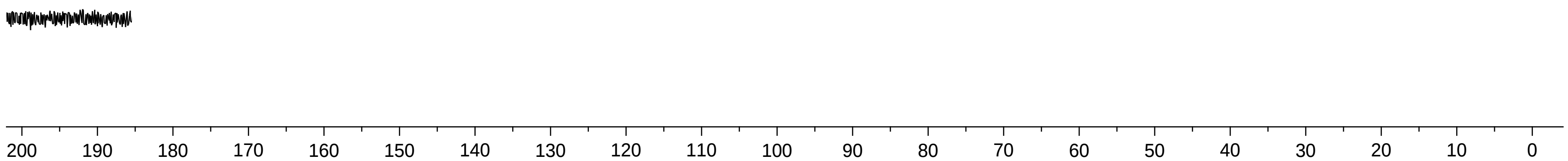
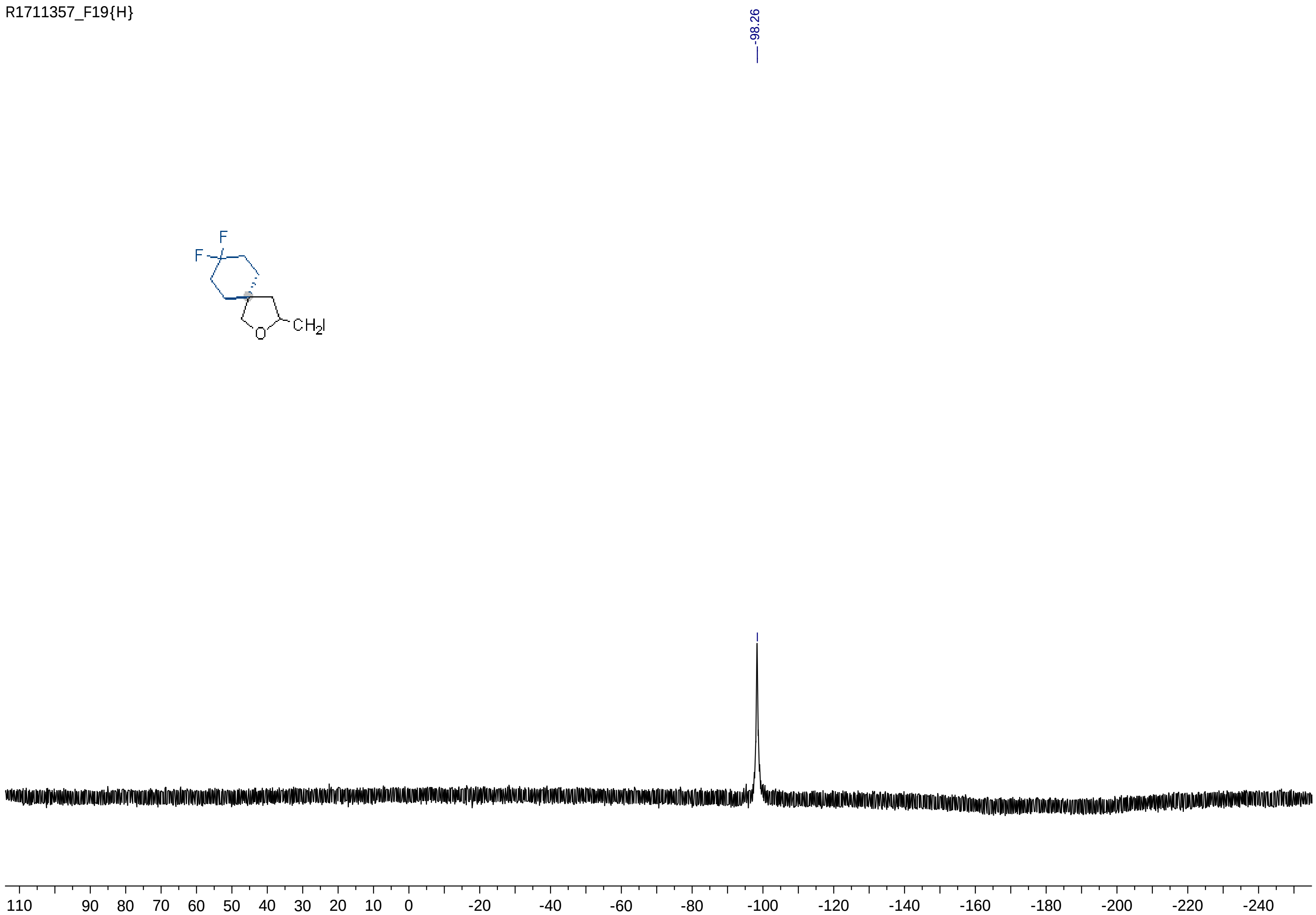


Compound 12a

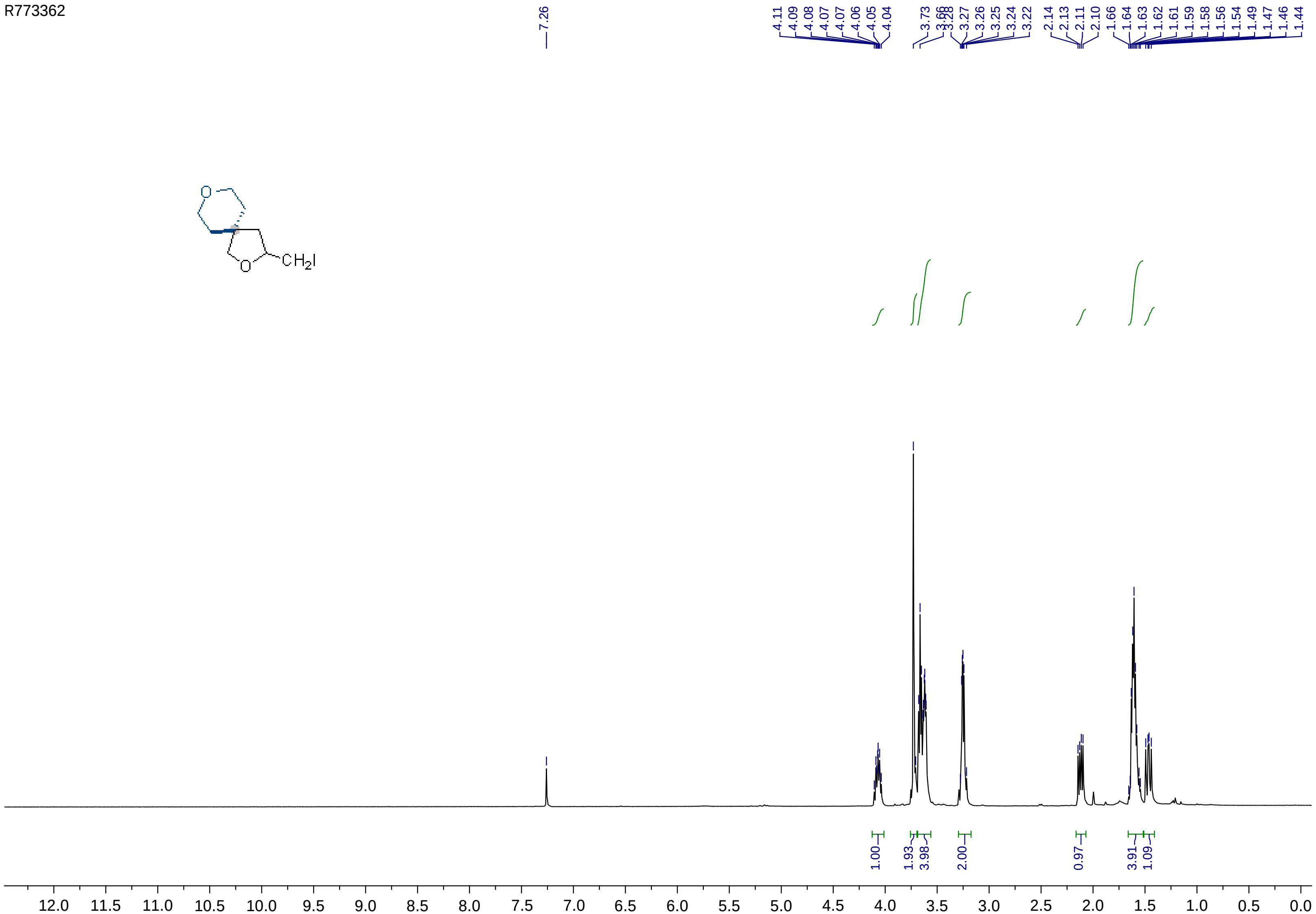


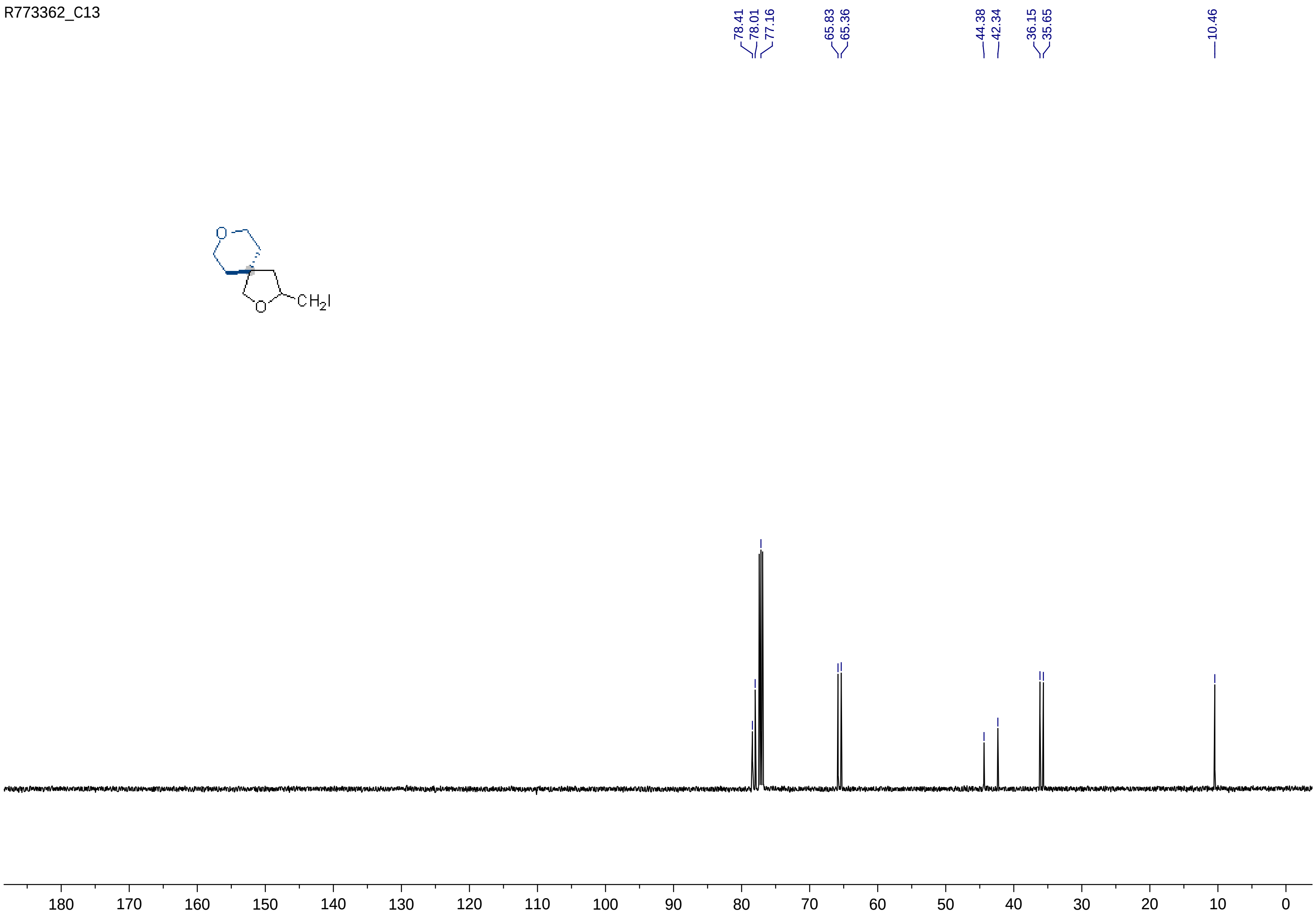
R1711357_C13



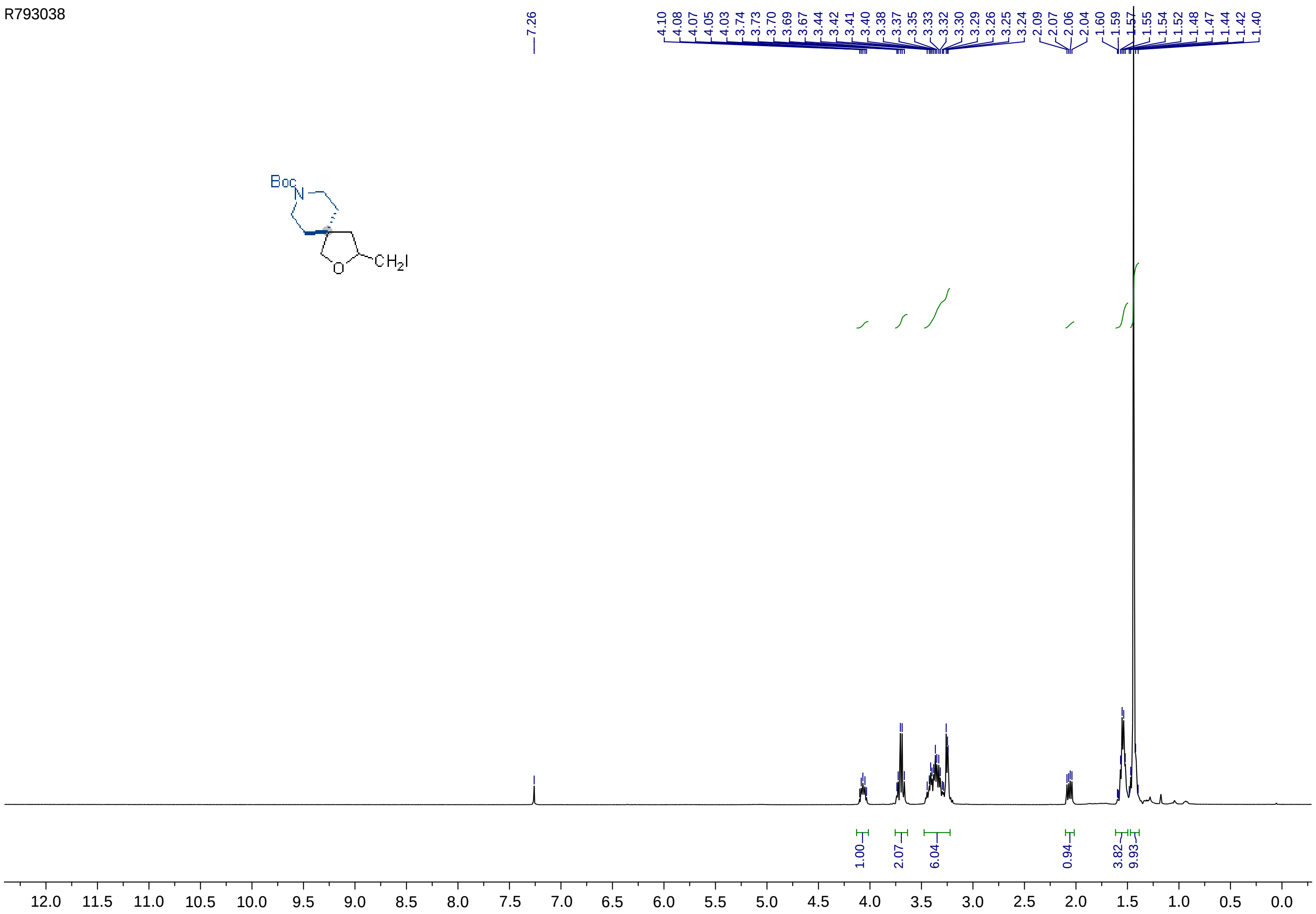

R1711357_F19{H}
-98.26
F
F
O
CH2I
110 90 80 70 60 50 40 30 20 10 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240

Compound 13a

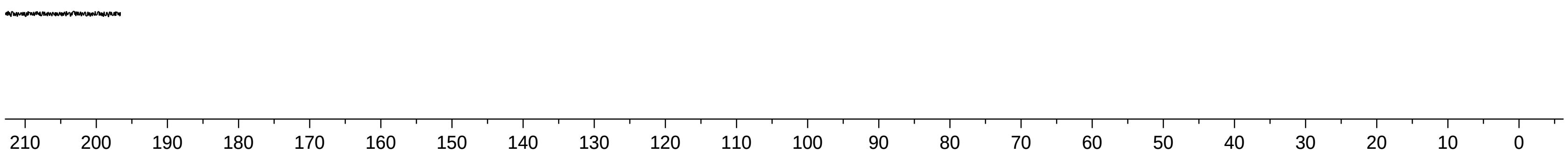



R773362_C13
78.41
78.01
77.16
65.83
65.36
44.38
42.34
36.15
35.65
10.46
O
O
CH2I
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

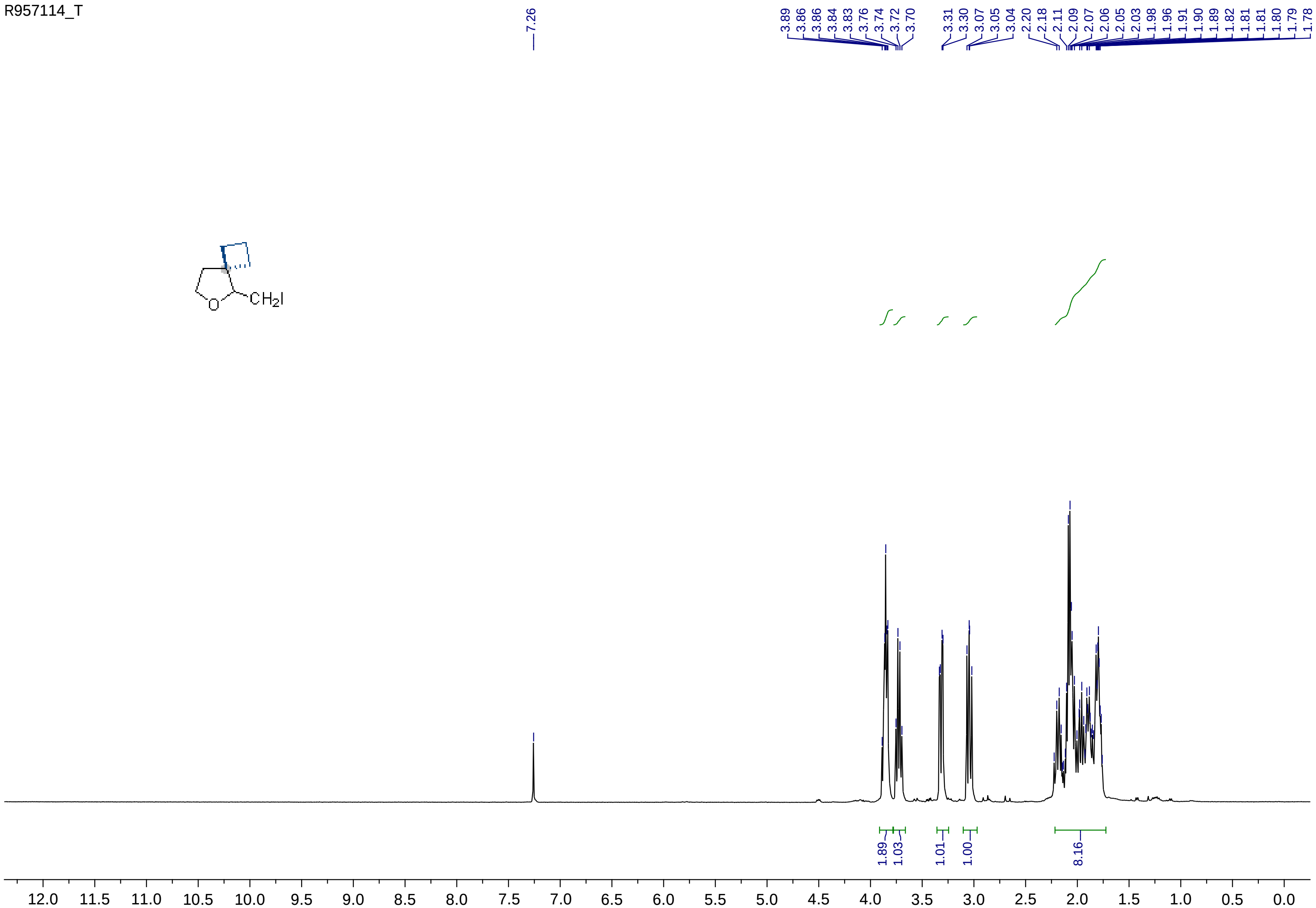
Compound 14a



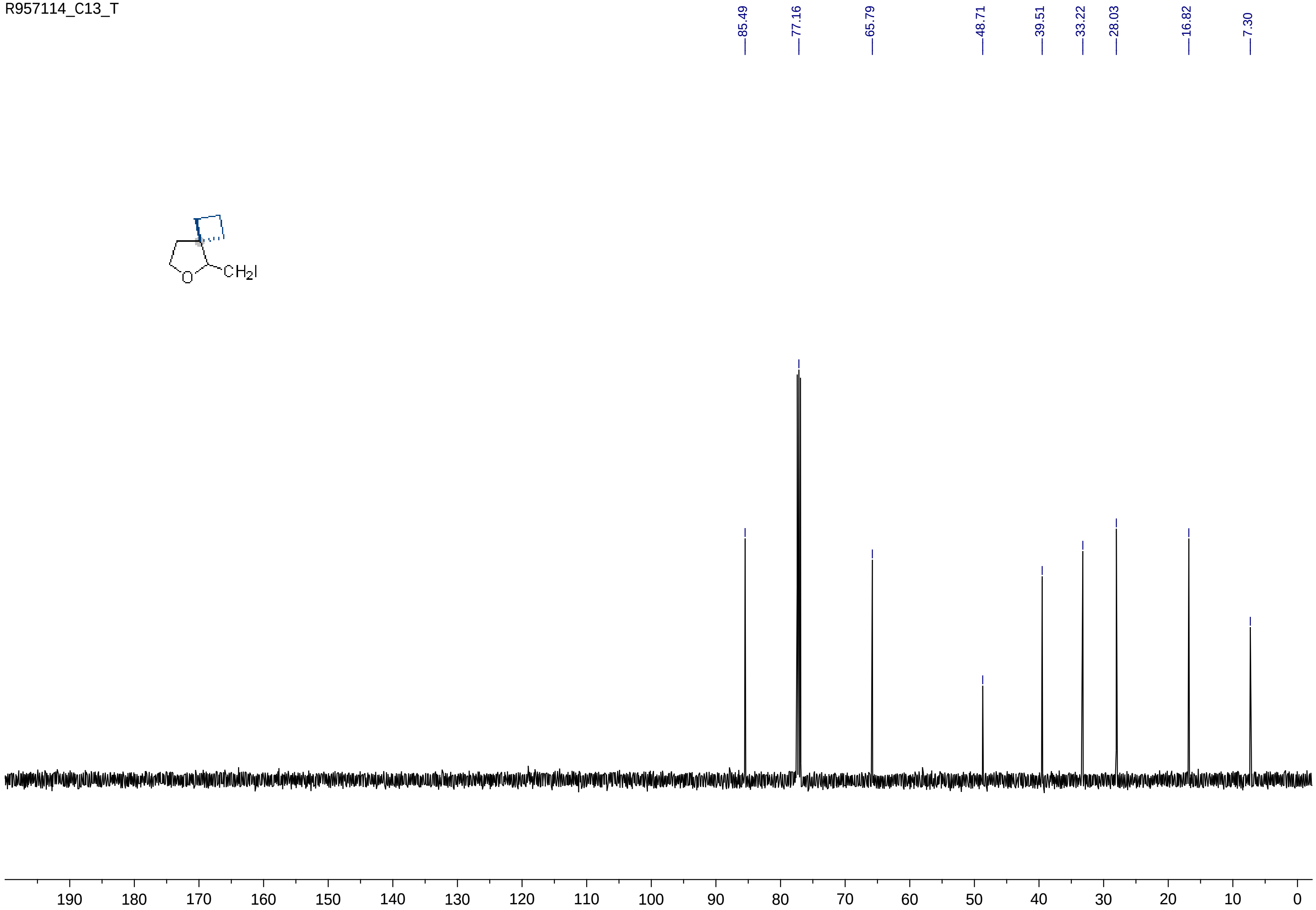
R793038_C13


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

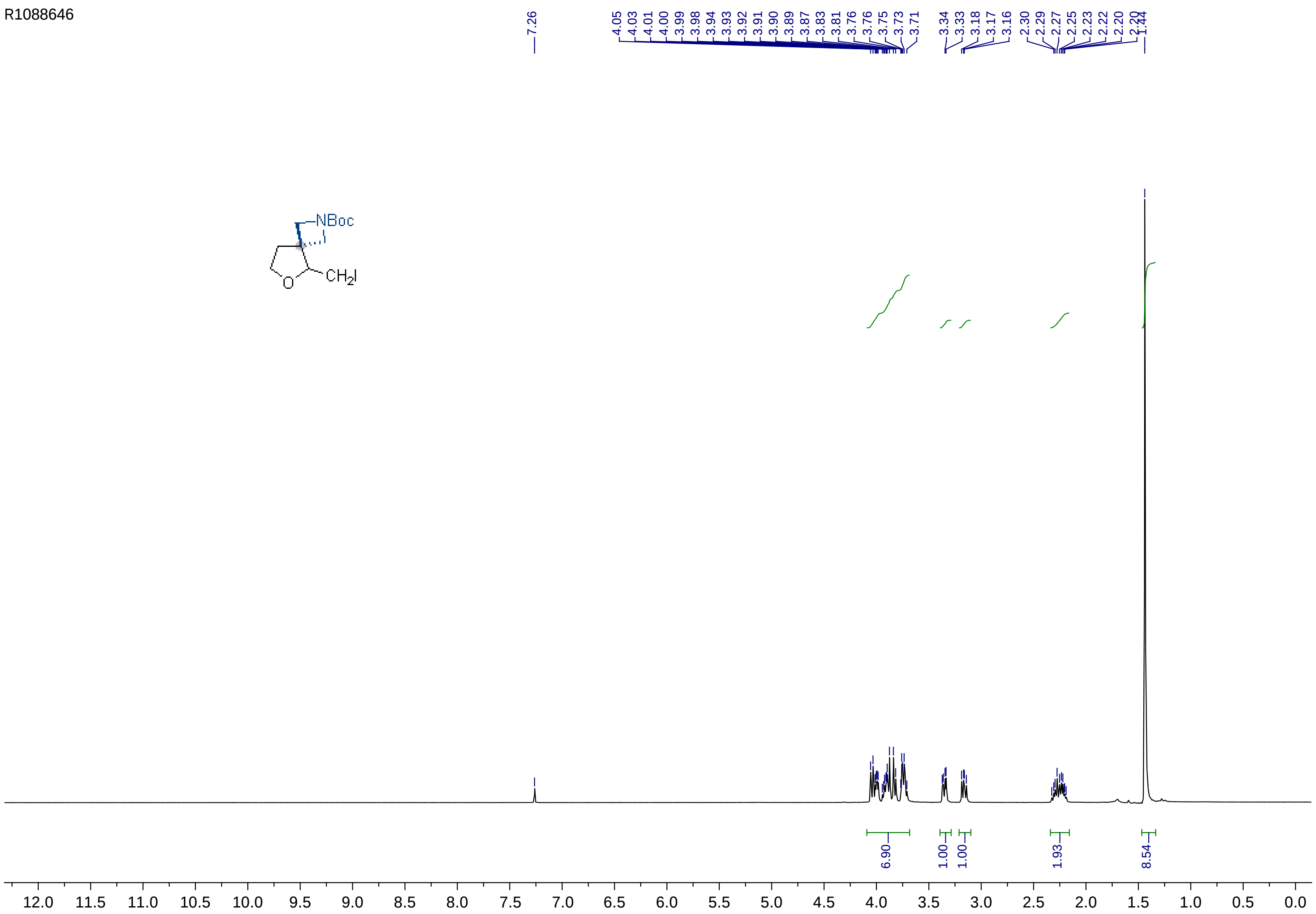
Compound 15a



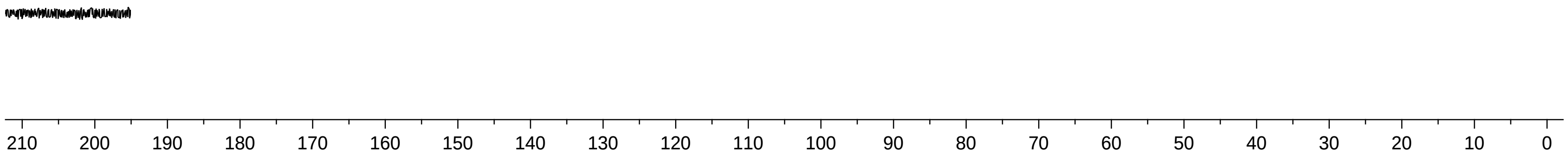
R957114_C13_T



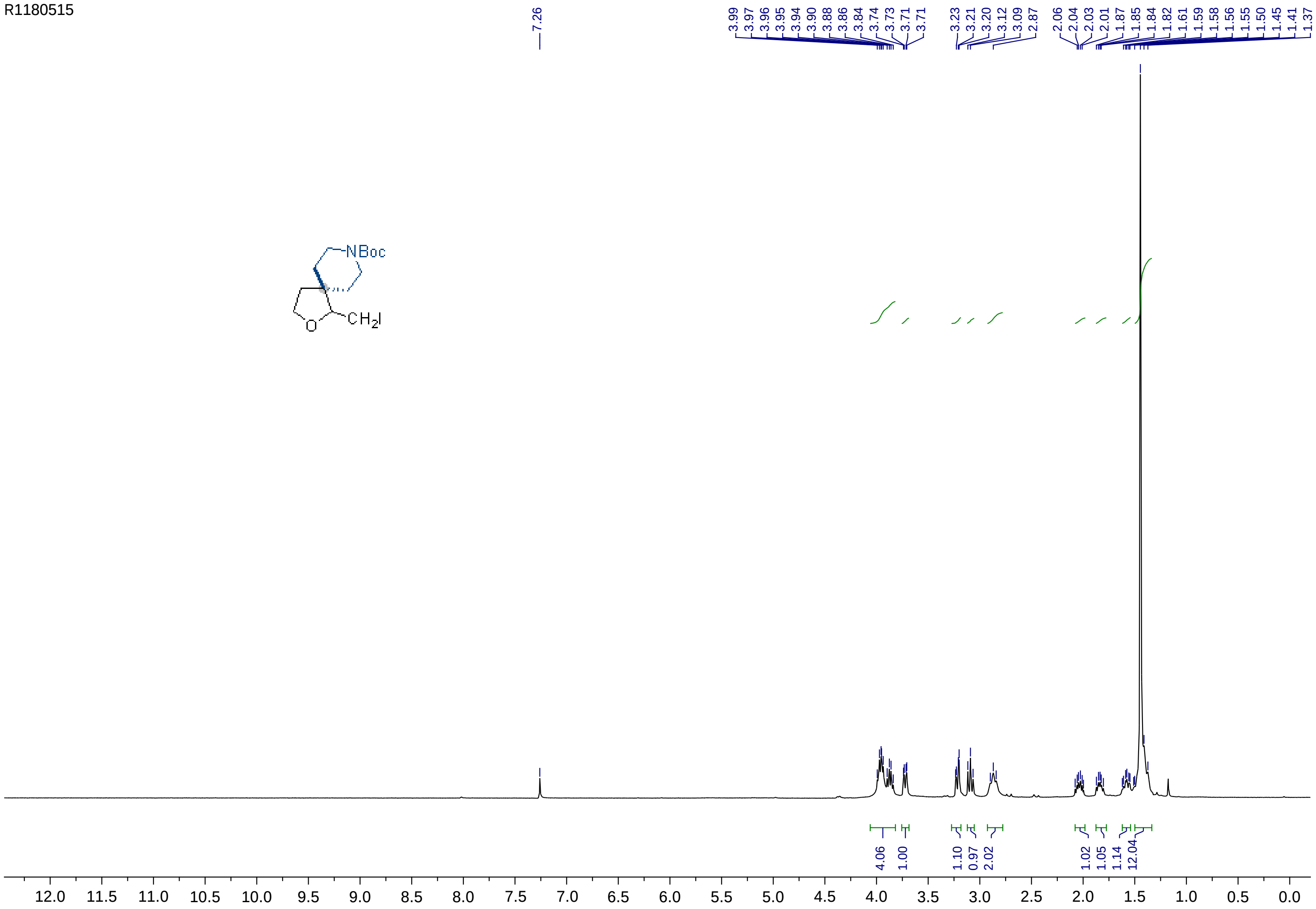
Compound 16a

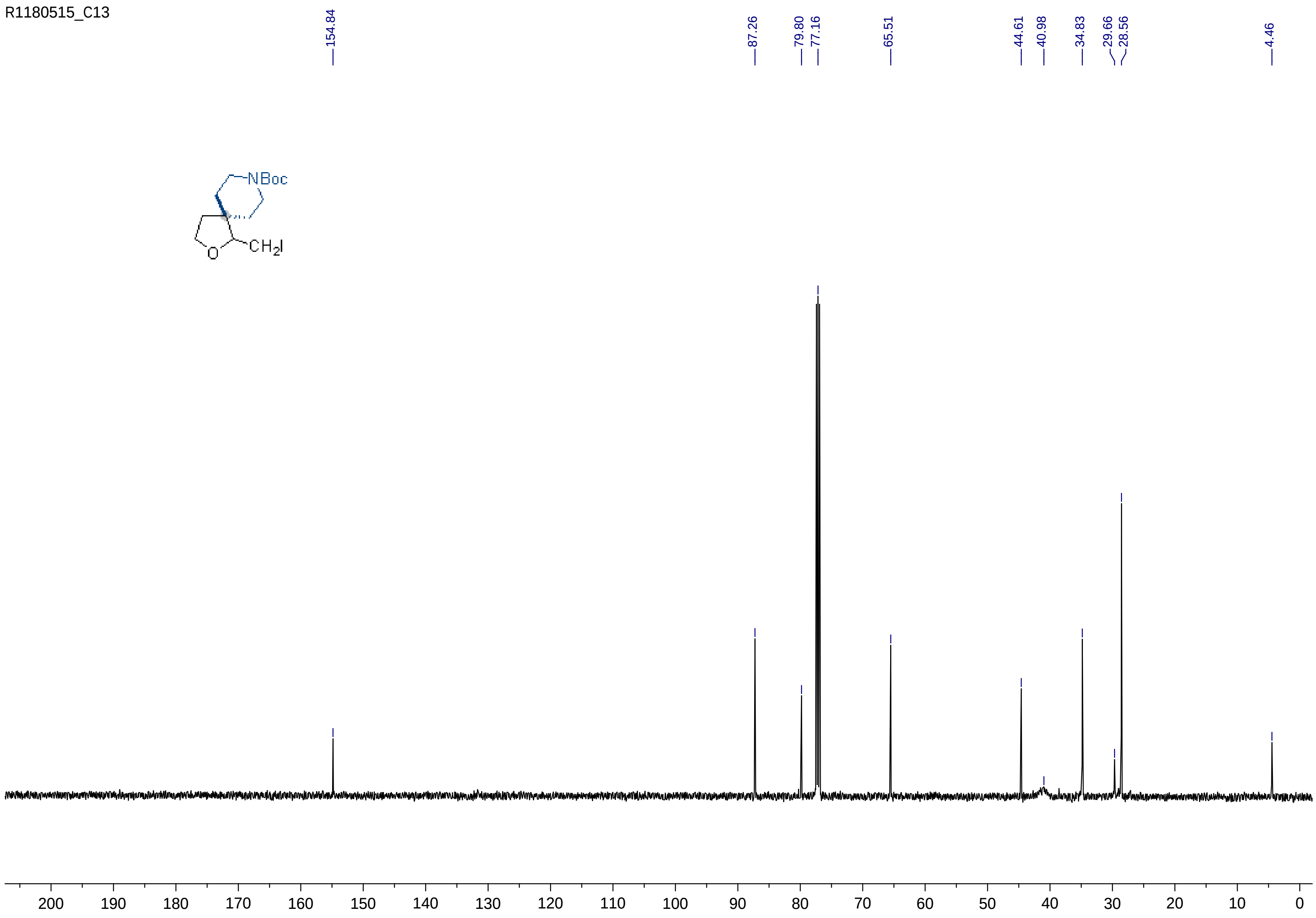


R1088646_C13



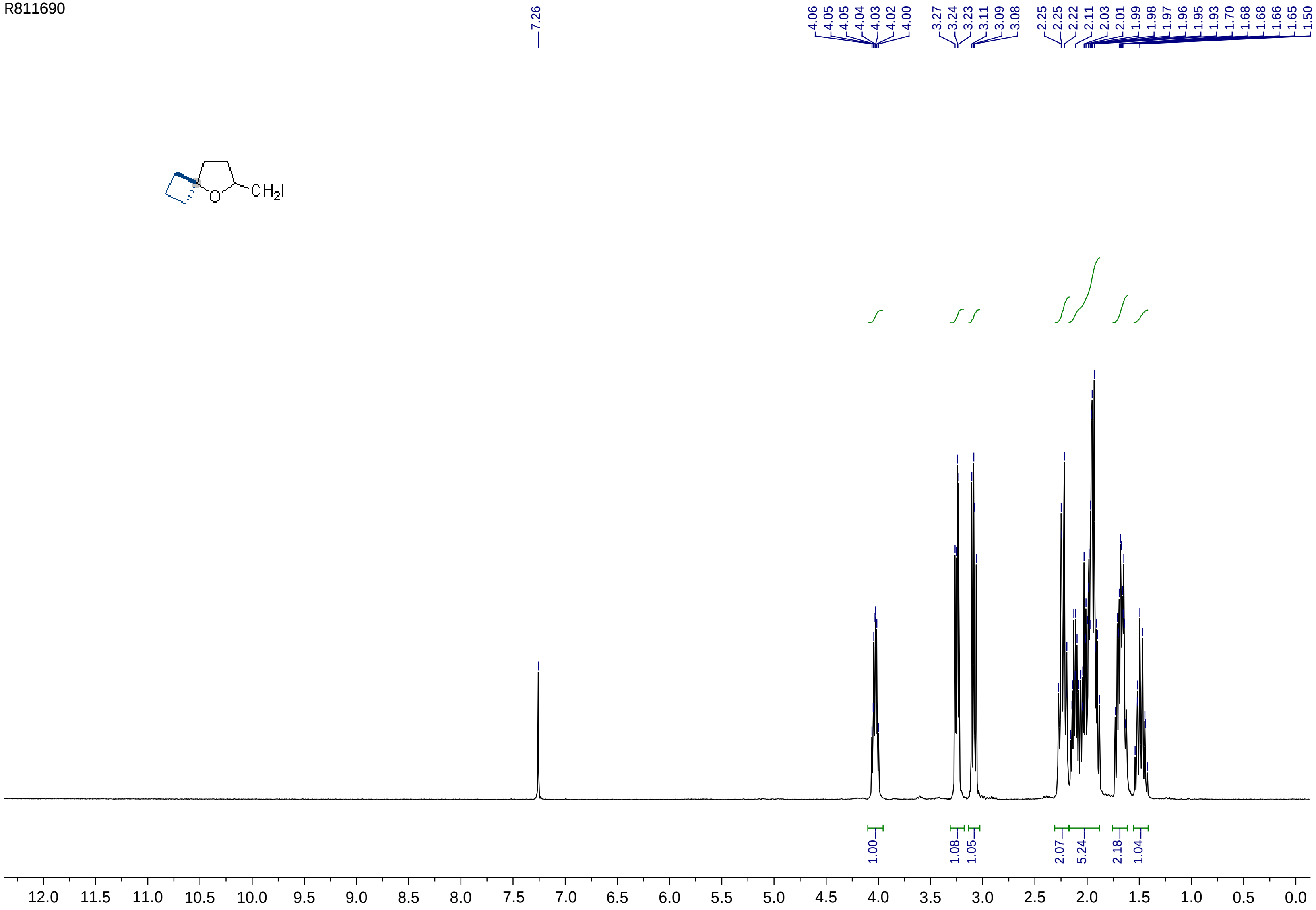
Compound 17a



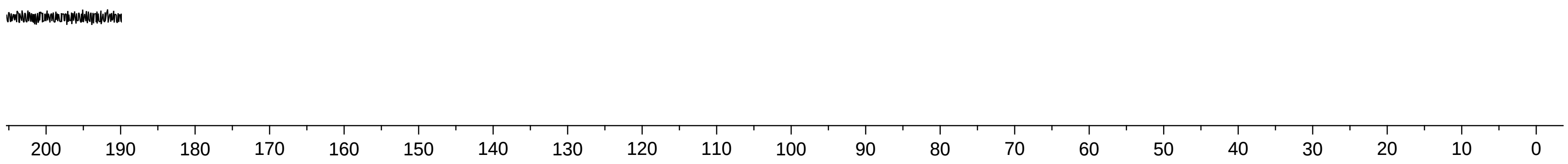


R1180515_C13
154.84
87.26
79.80
77.16
65.51
44.61
40.98
34.83
29.66
28.56
4.46
NBoc
O
CH2I
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

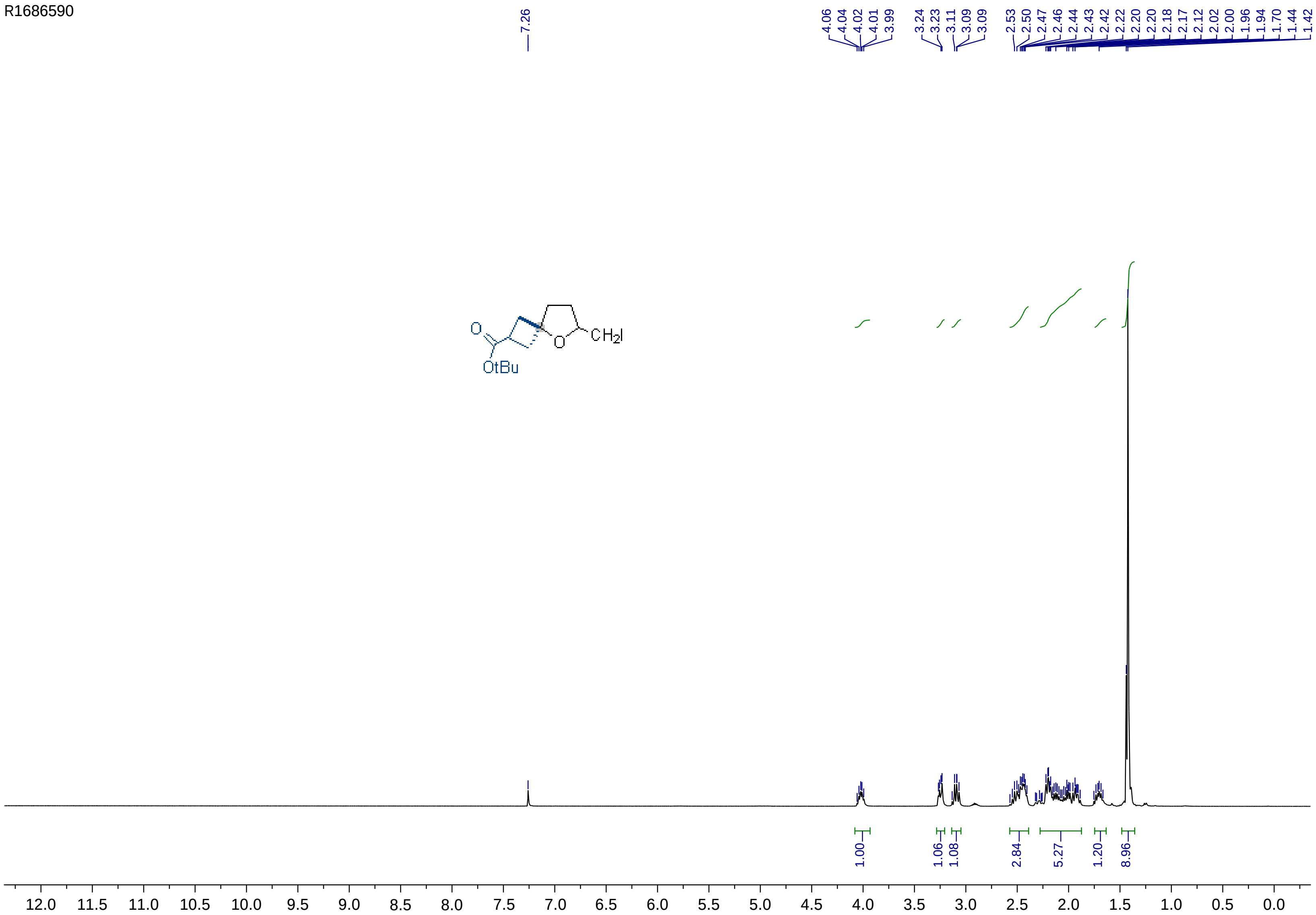
Compound 18a



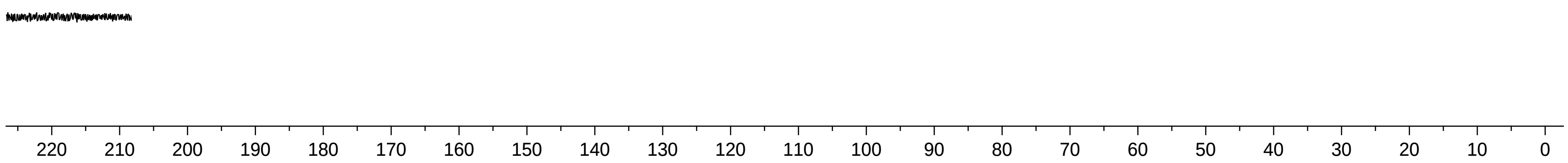
R811690_C13


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

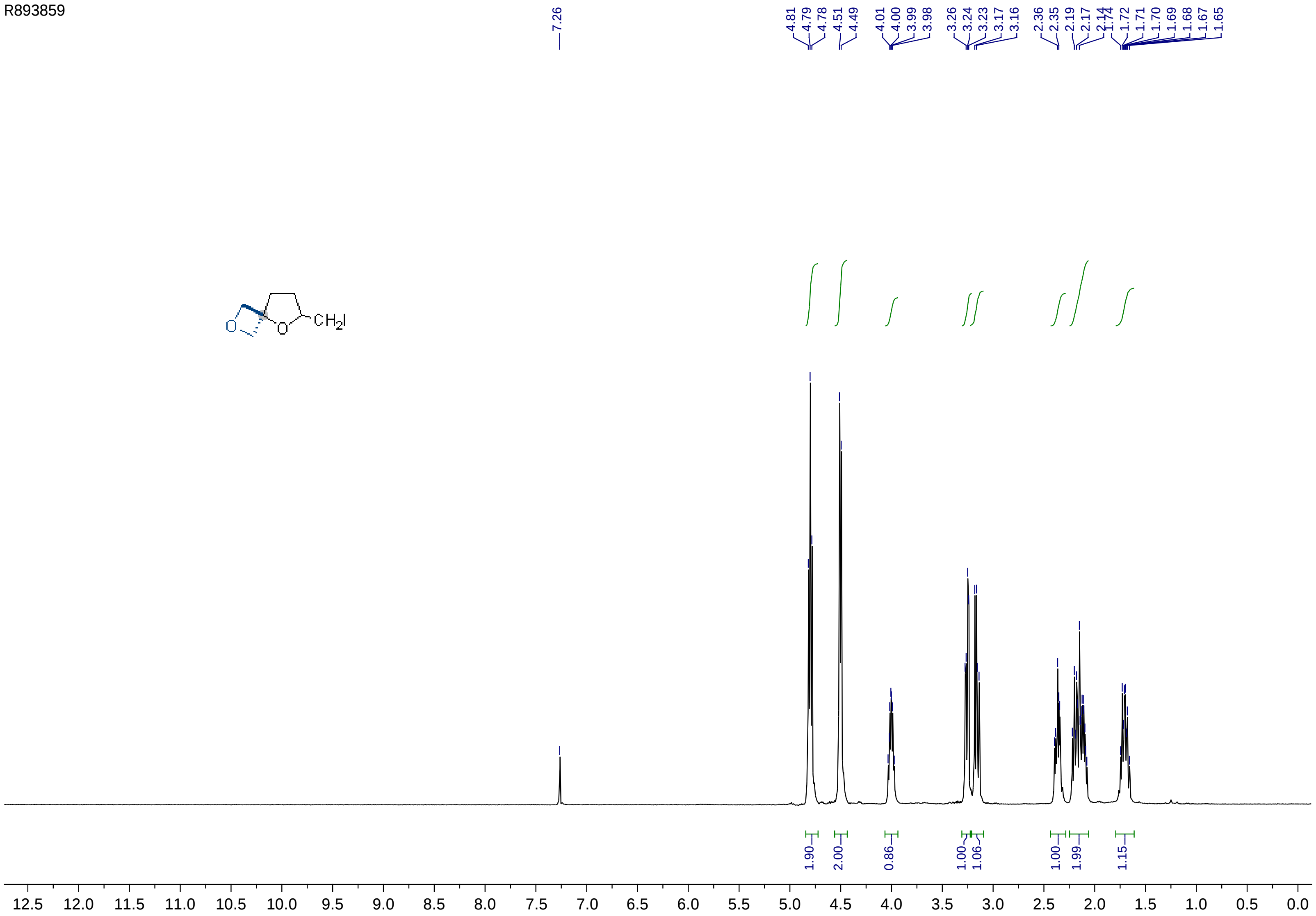
Compound 19a



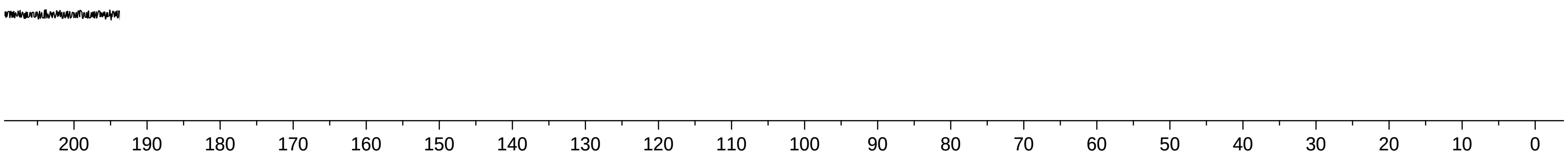
R1686590_C13



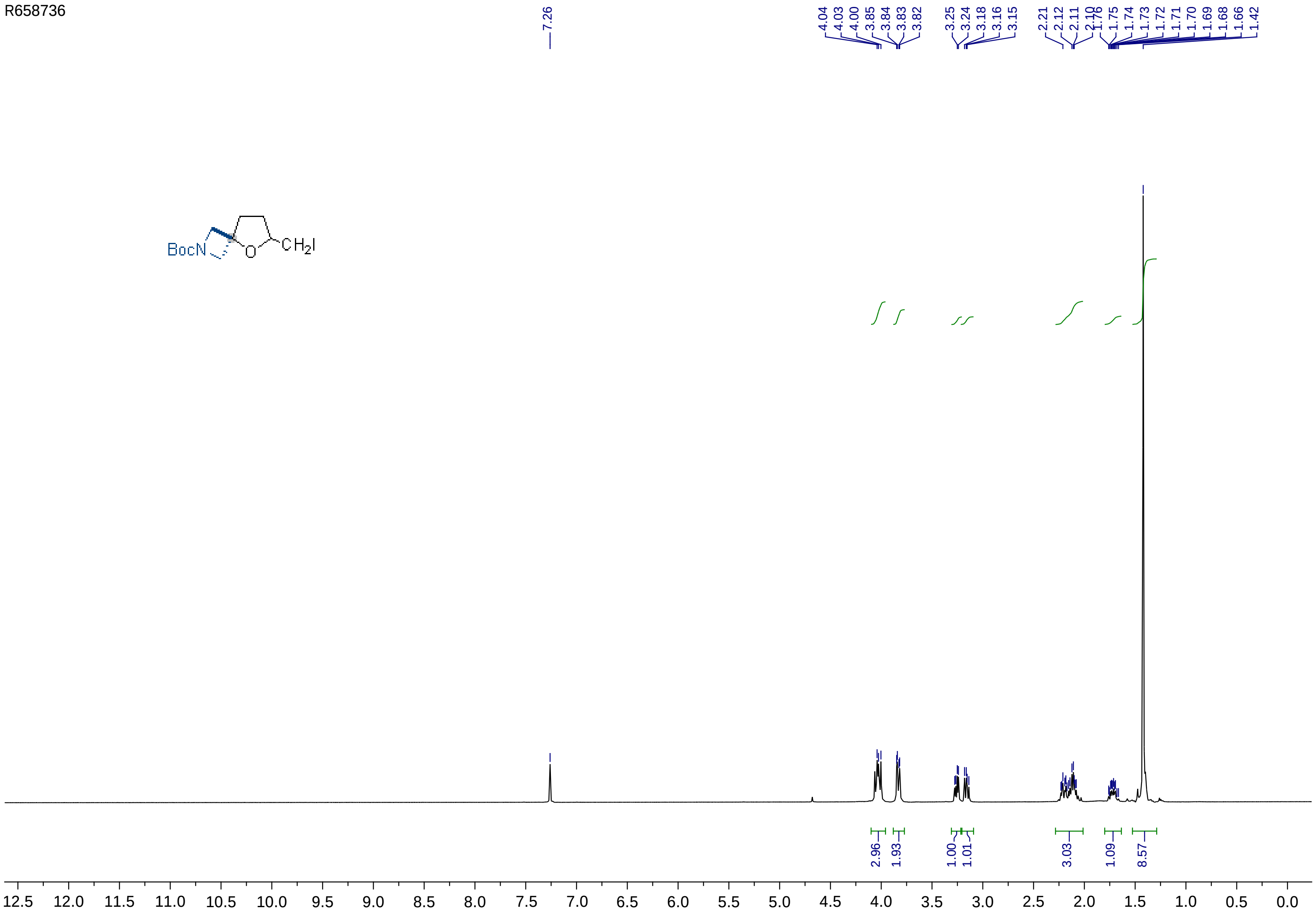
Compound 20a

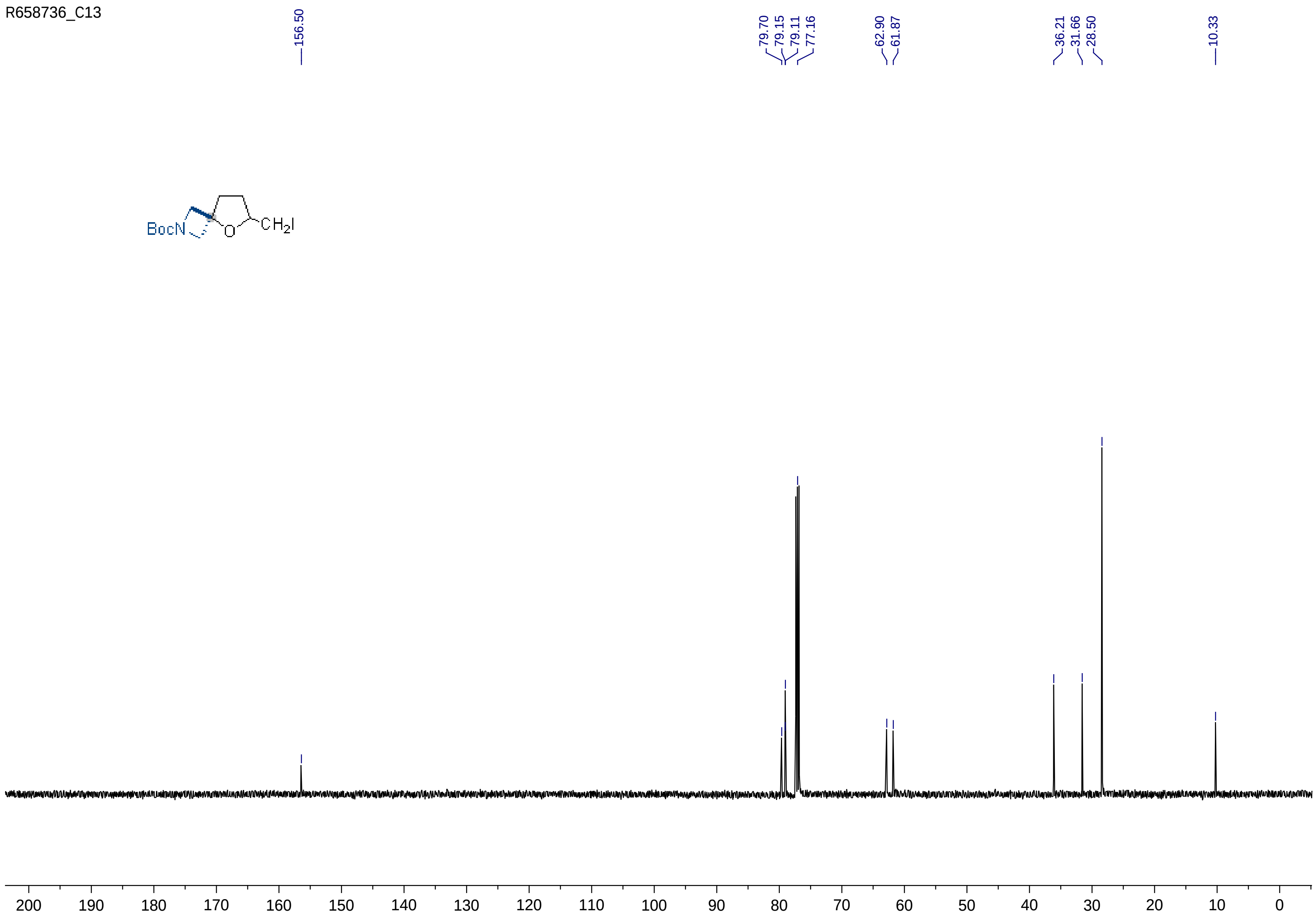


R893859_C13

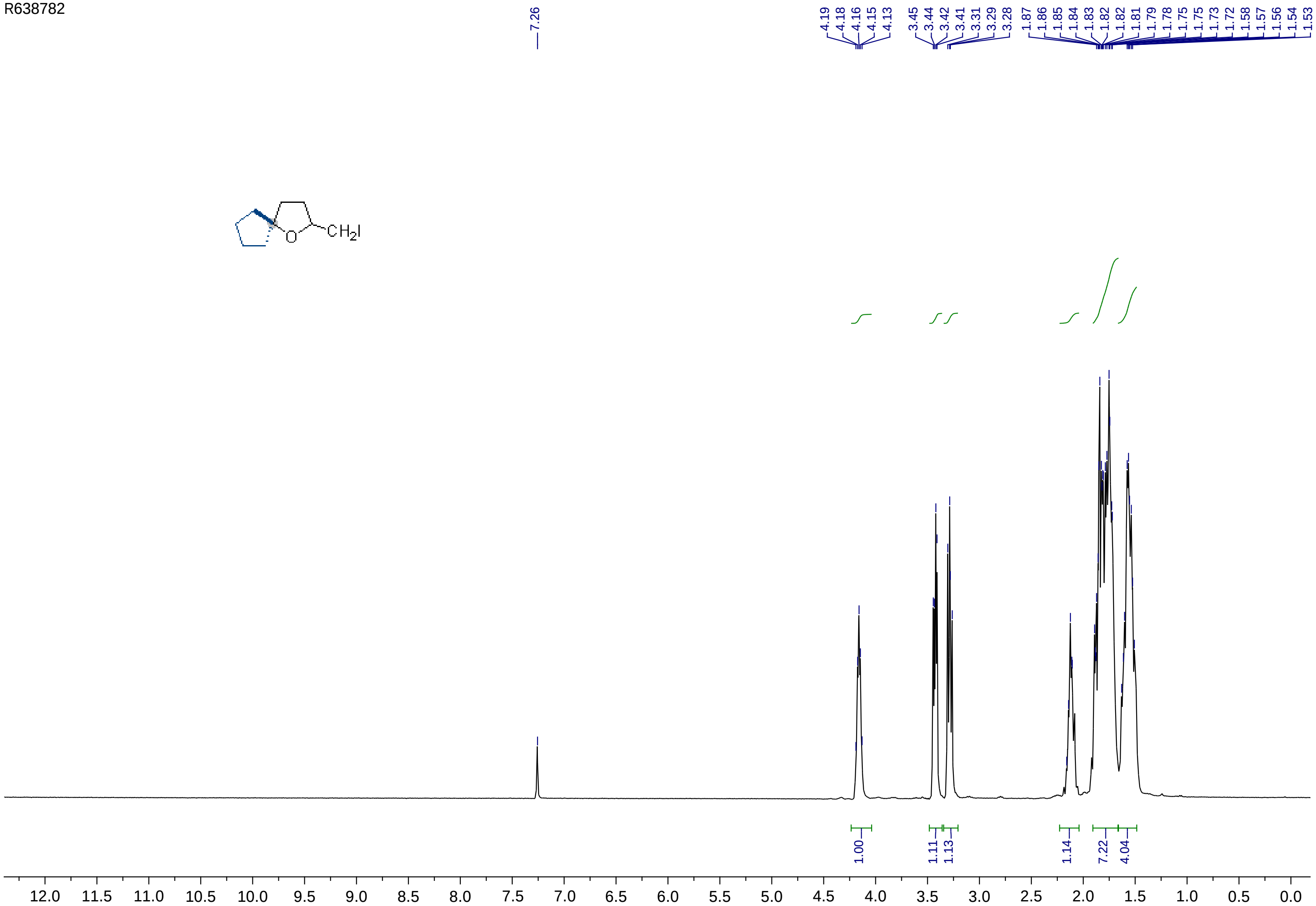

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 21a

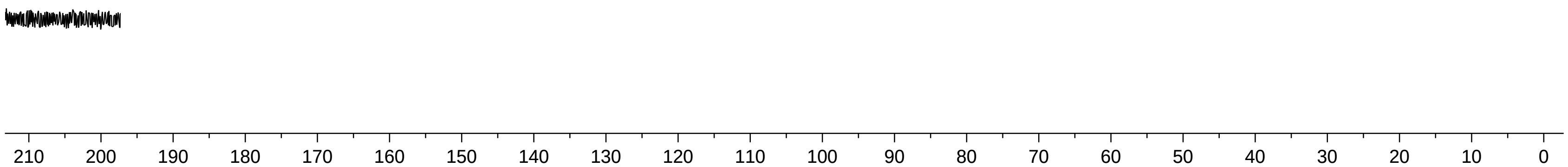



R658736_C13
156.50
79.70
79.15
79.11
77.16
62.90
61.87
36.21
31.66
28.50
10.33
BocN
O
CH2I
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

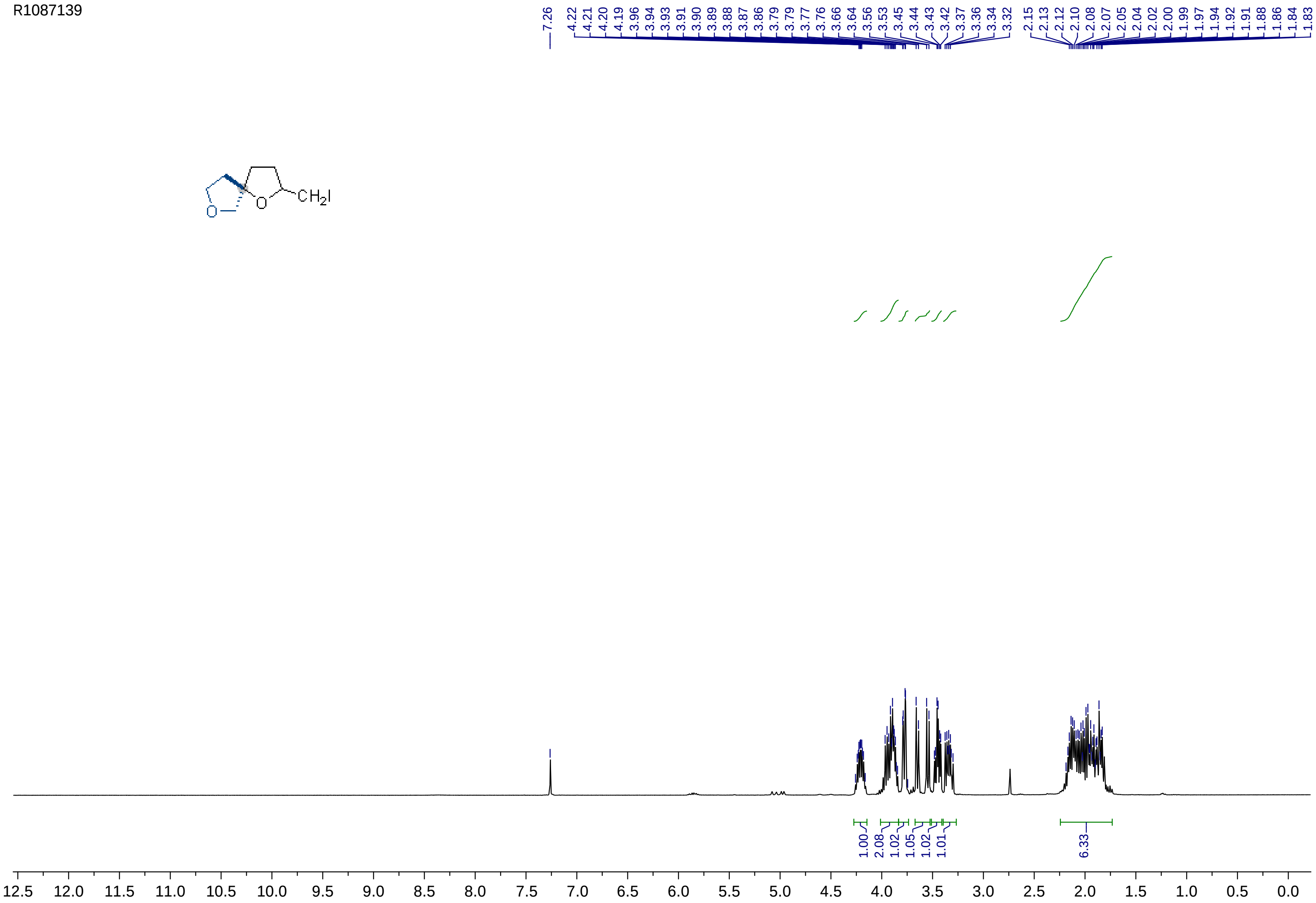
Compound 22a



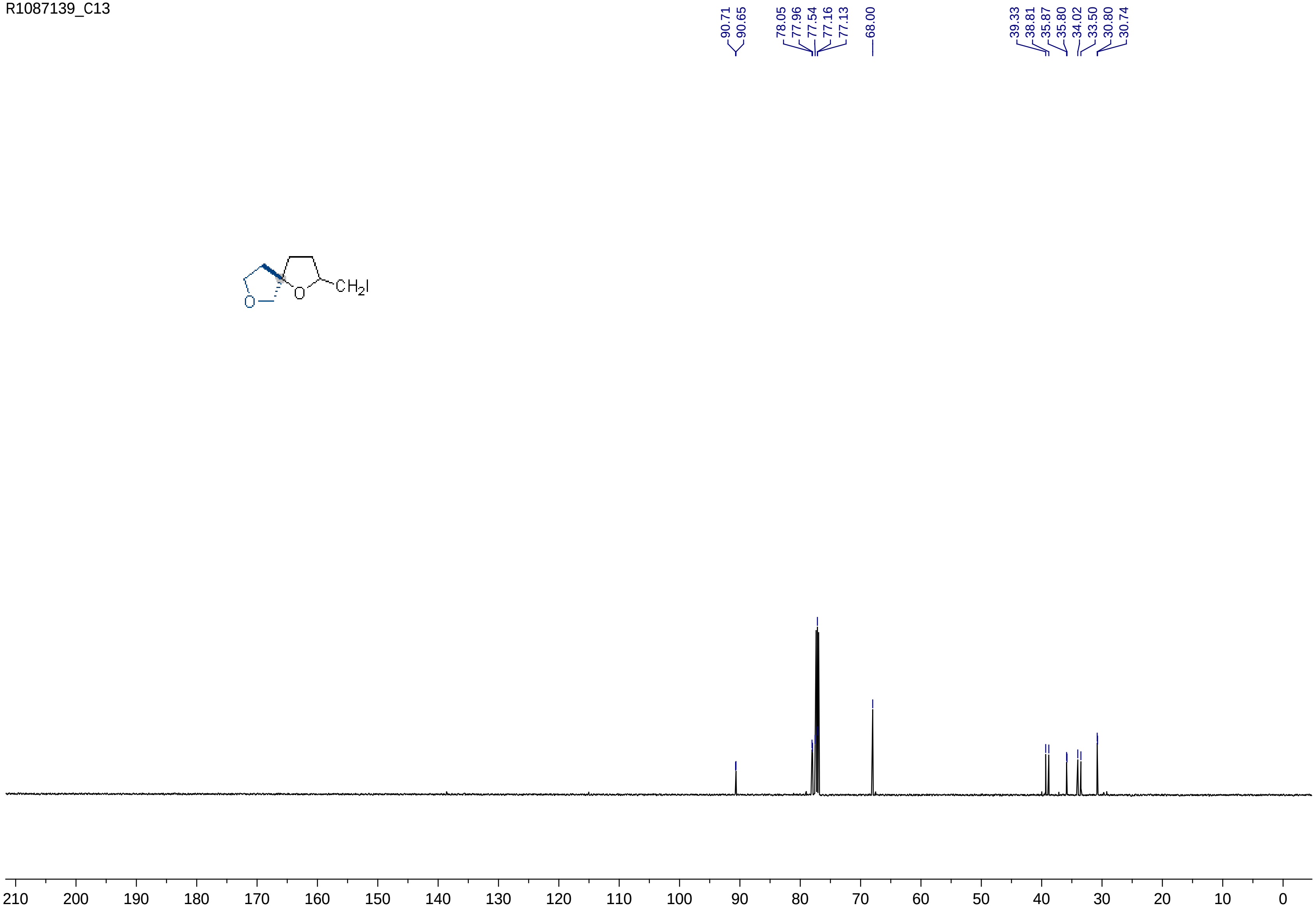
R638782_13C


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

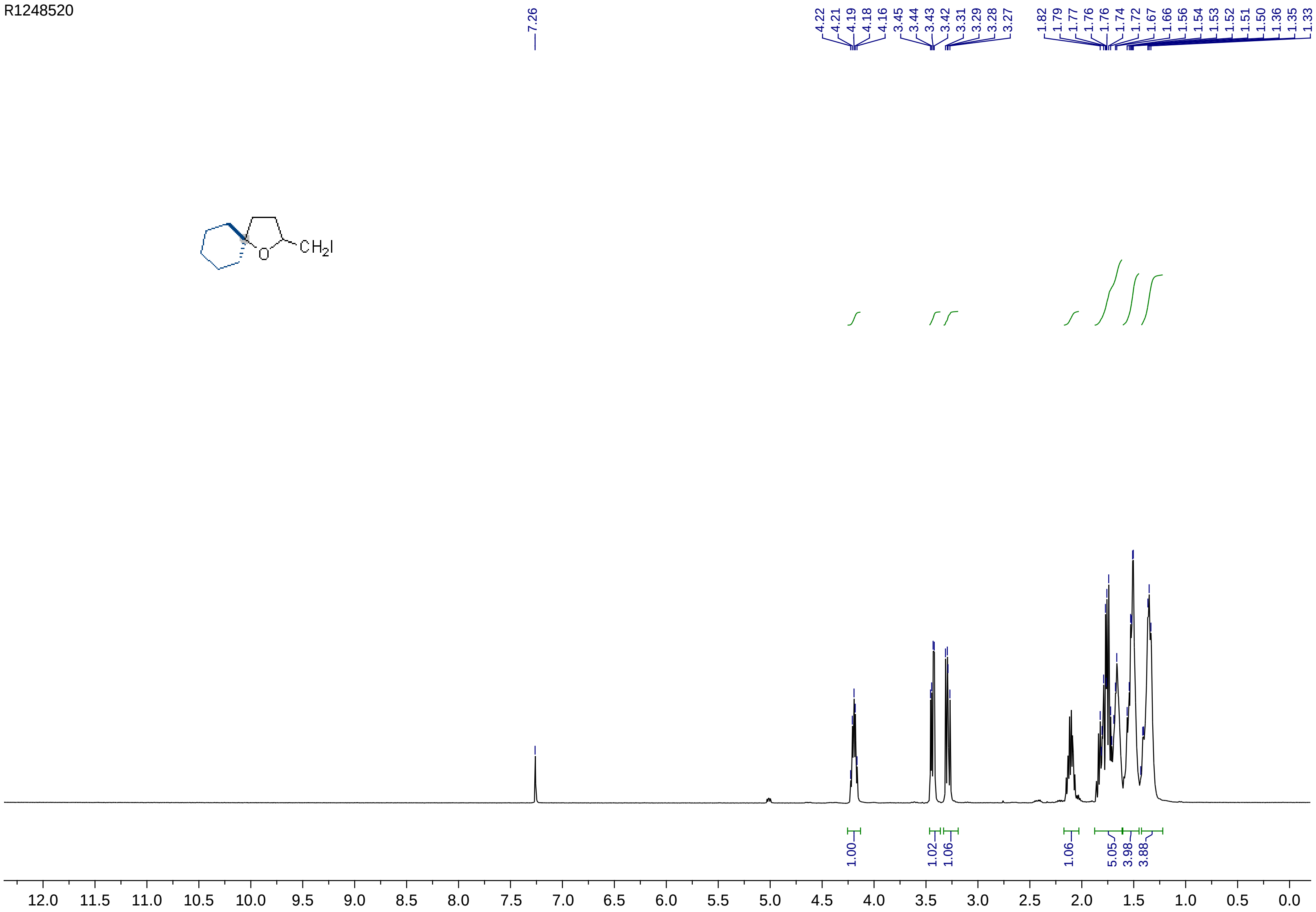
Compound 23a



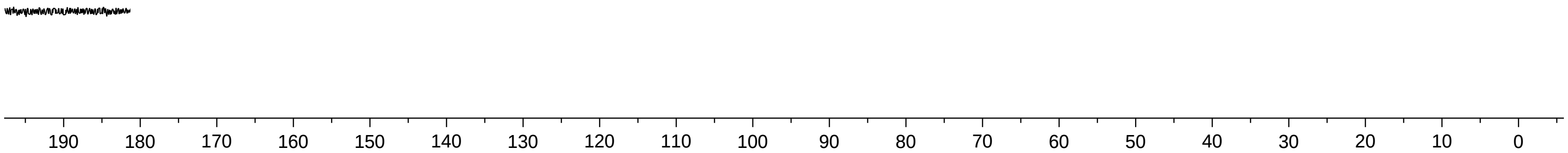
R1087139_C13



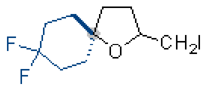
Compound 24a

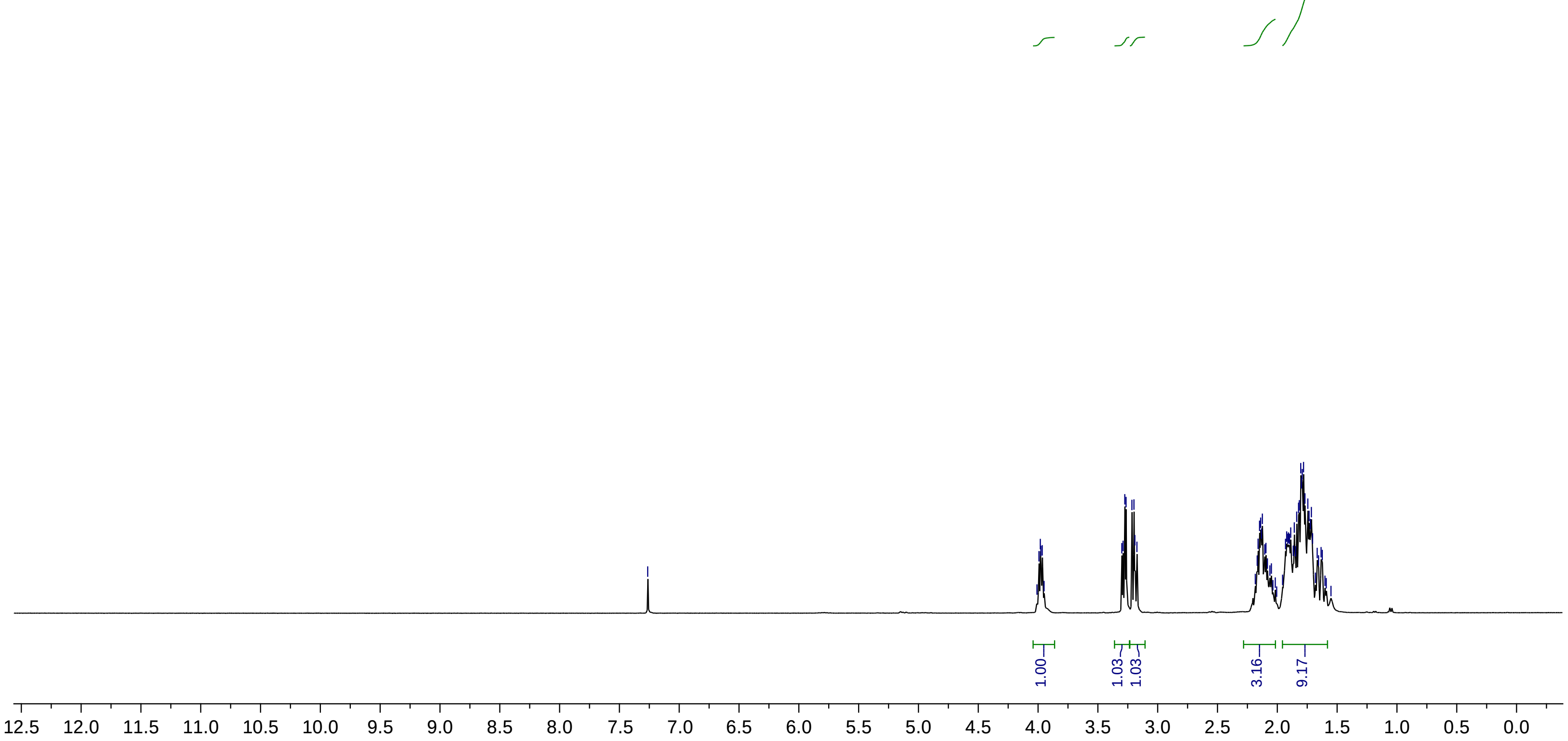


R1248520_13C

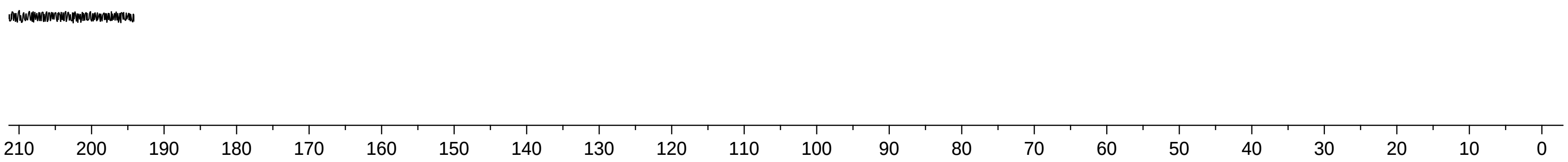


Compound 25a

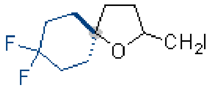


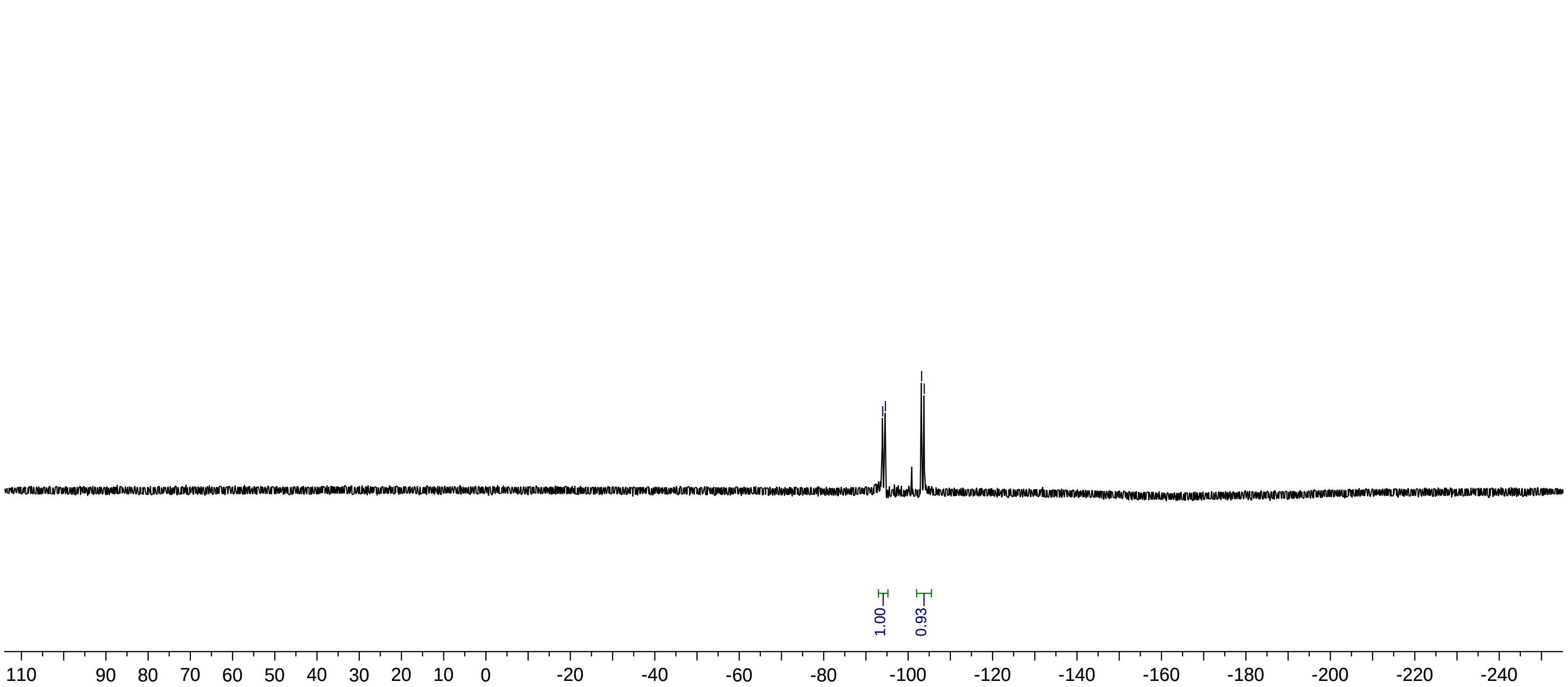


R1691406_C13

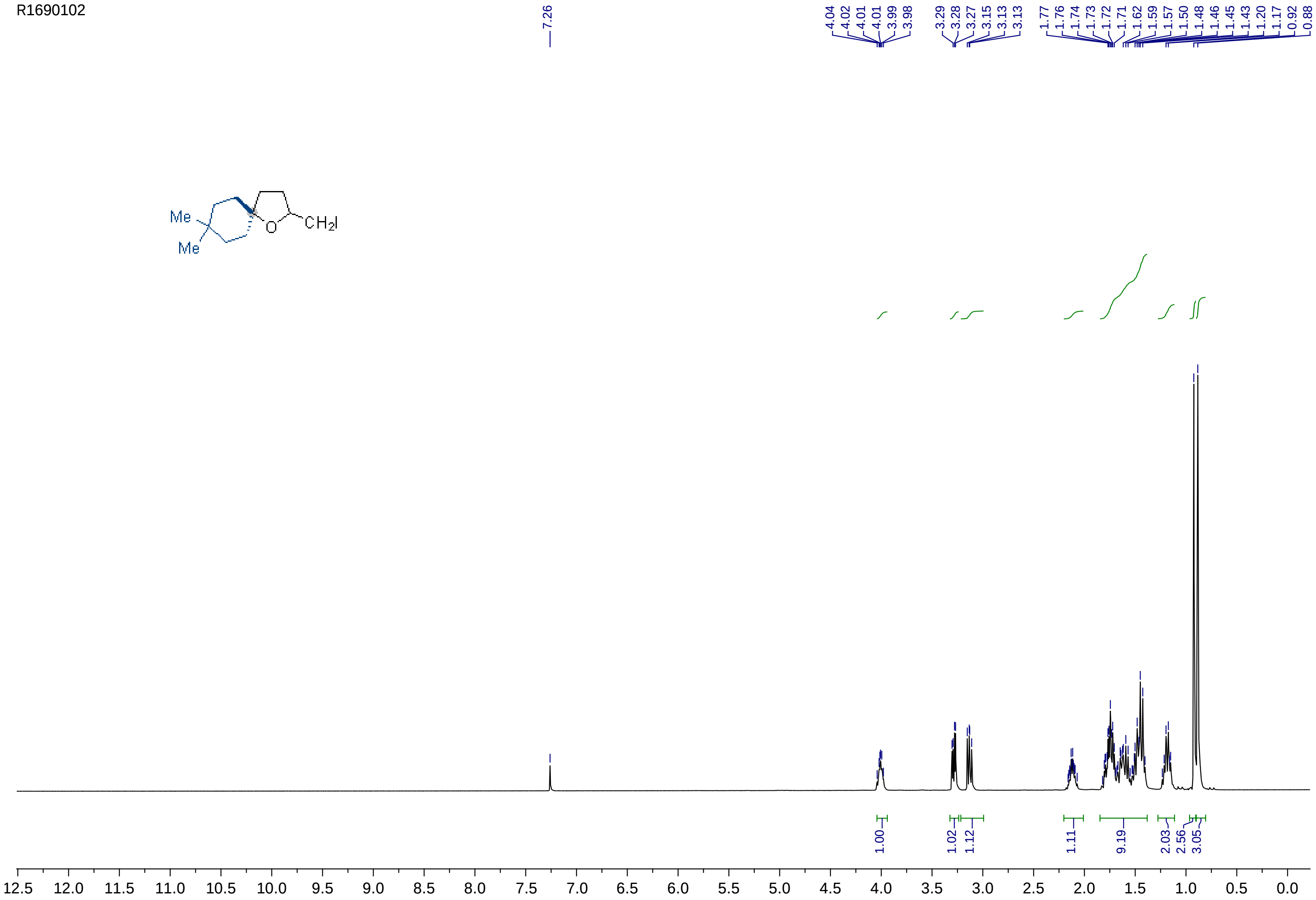


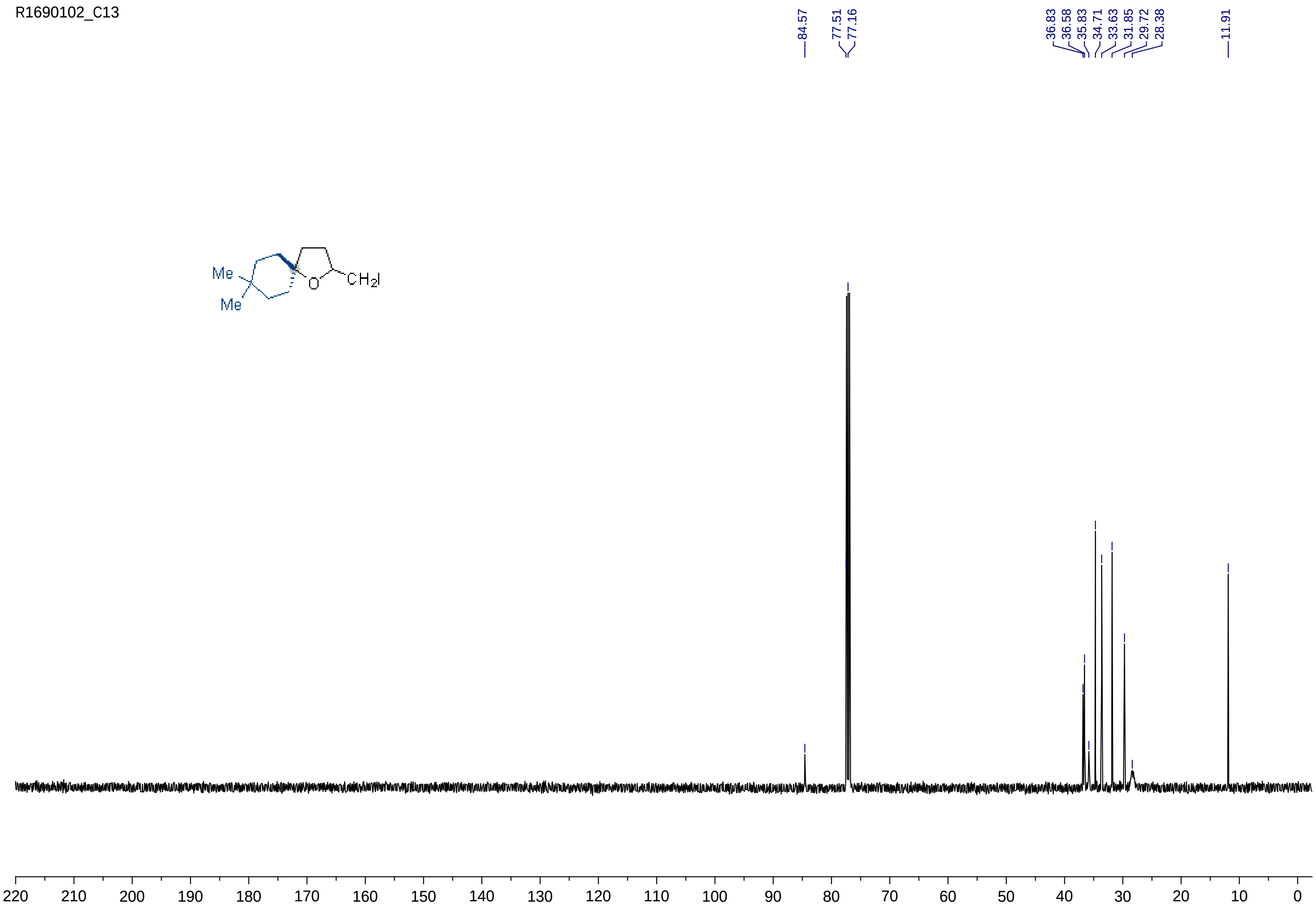
R1691406_F19{H}



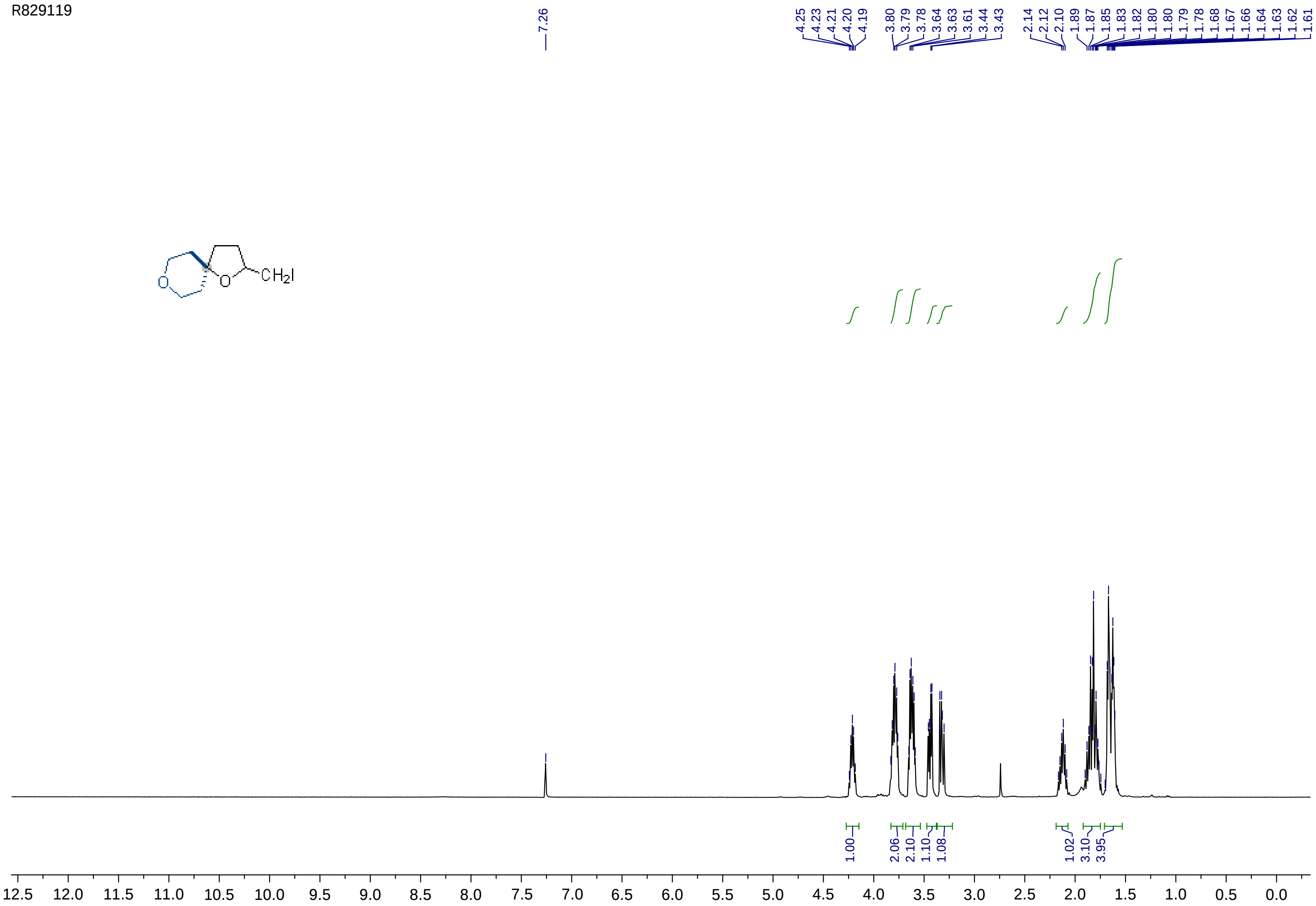


Compound 26a



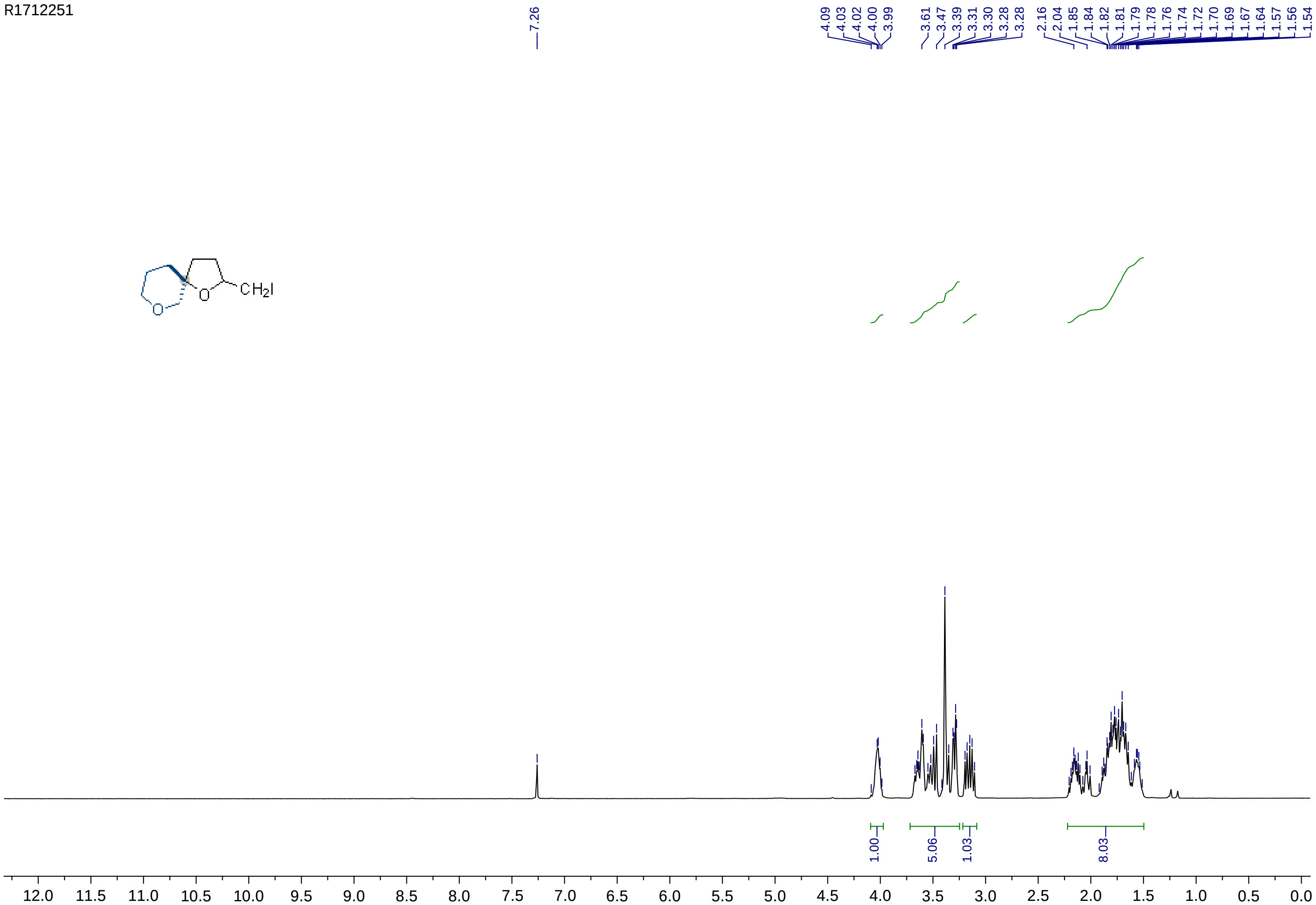

R1690102_C13
84.57
77.51
77.16
36.83
36.58
35.83
34.71
33.63
31.85
29.72
28.38
11.91
Me
Me
O
CH2I
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 27a

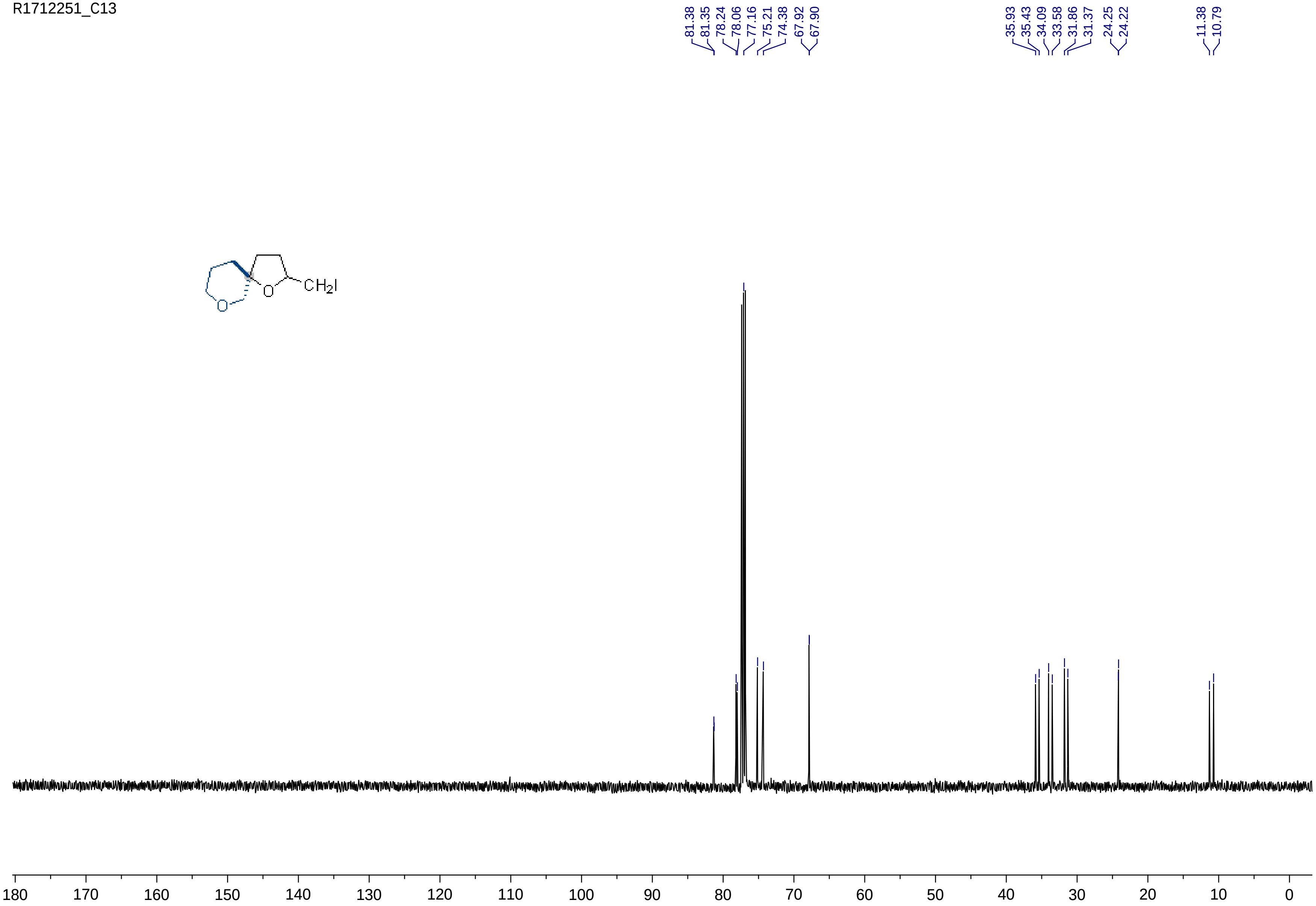



R829119_C13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

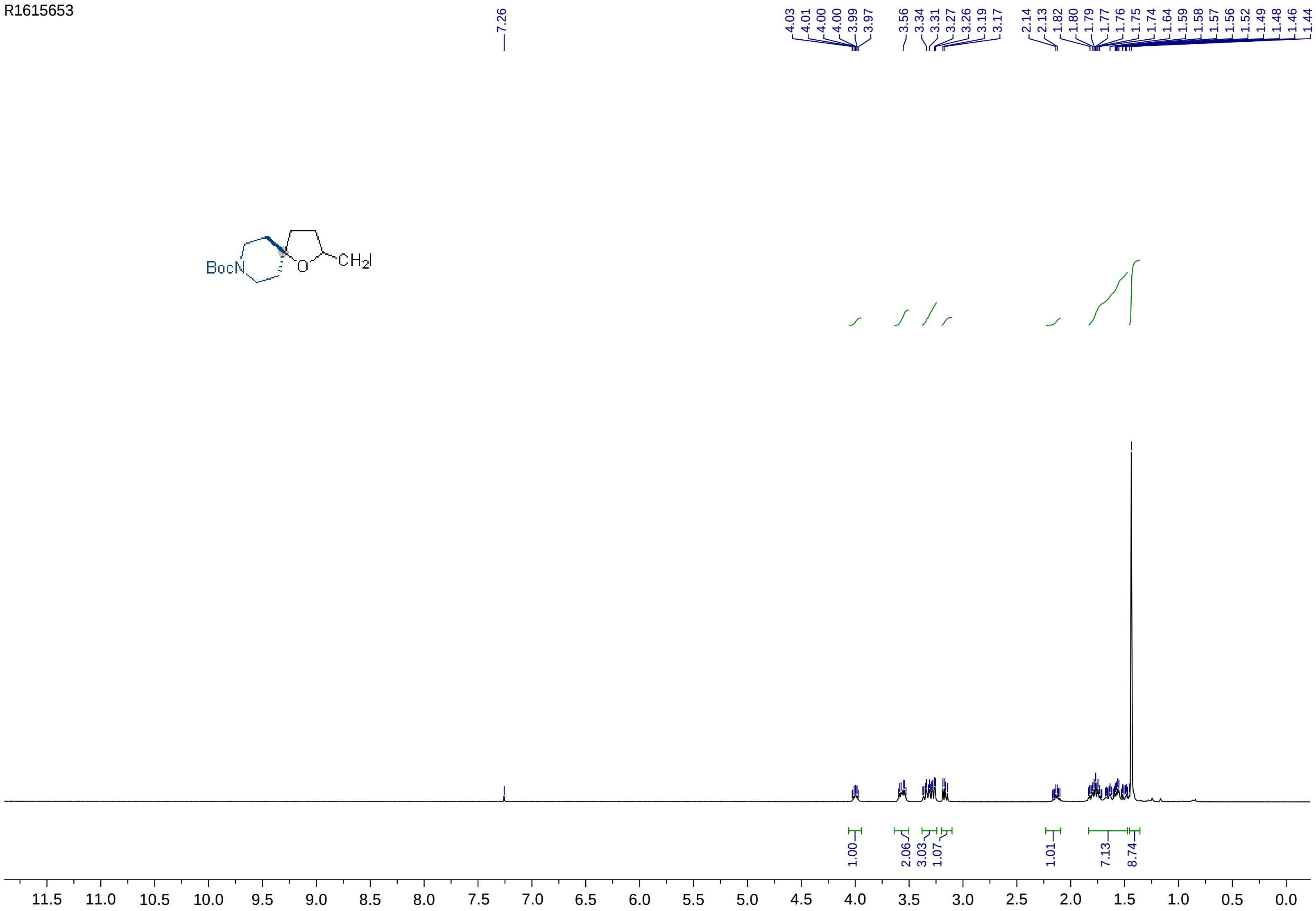
Compound 28a



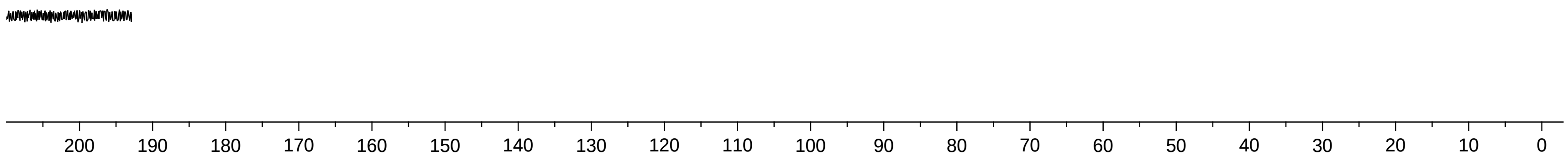
R1712251_C13



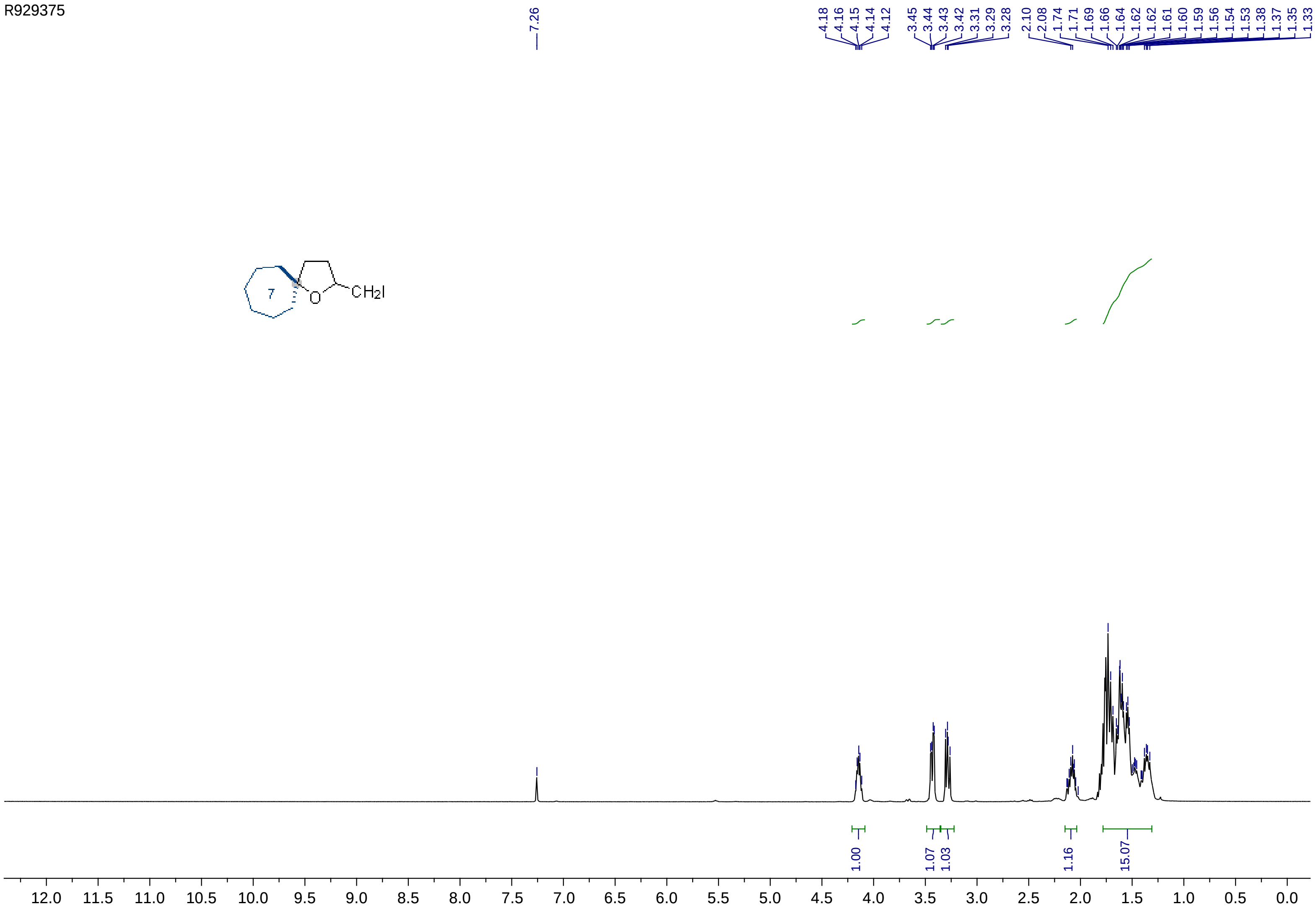
Compound 29a



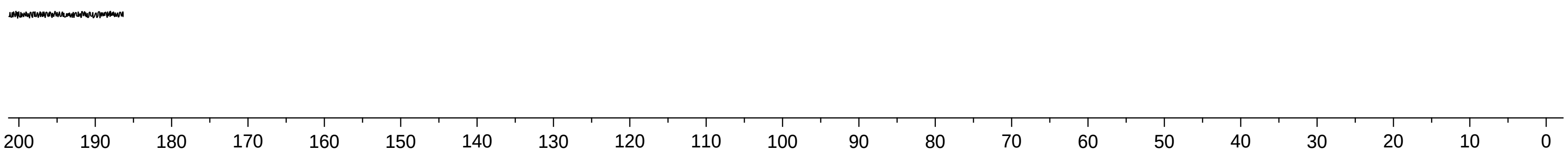
R1615653_C13



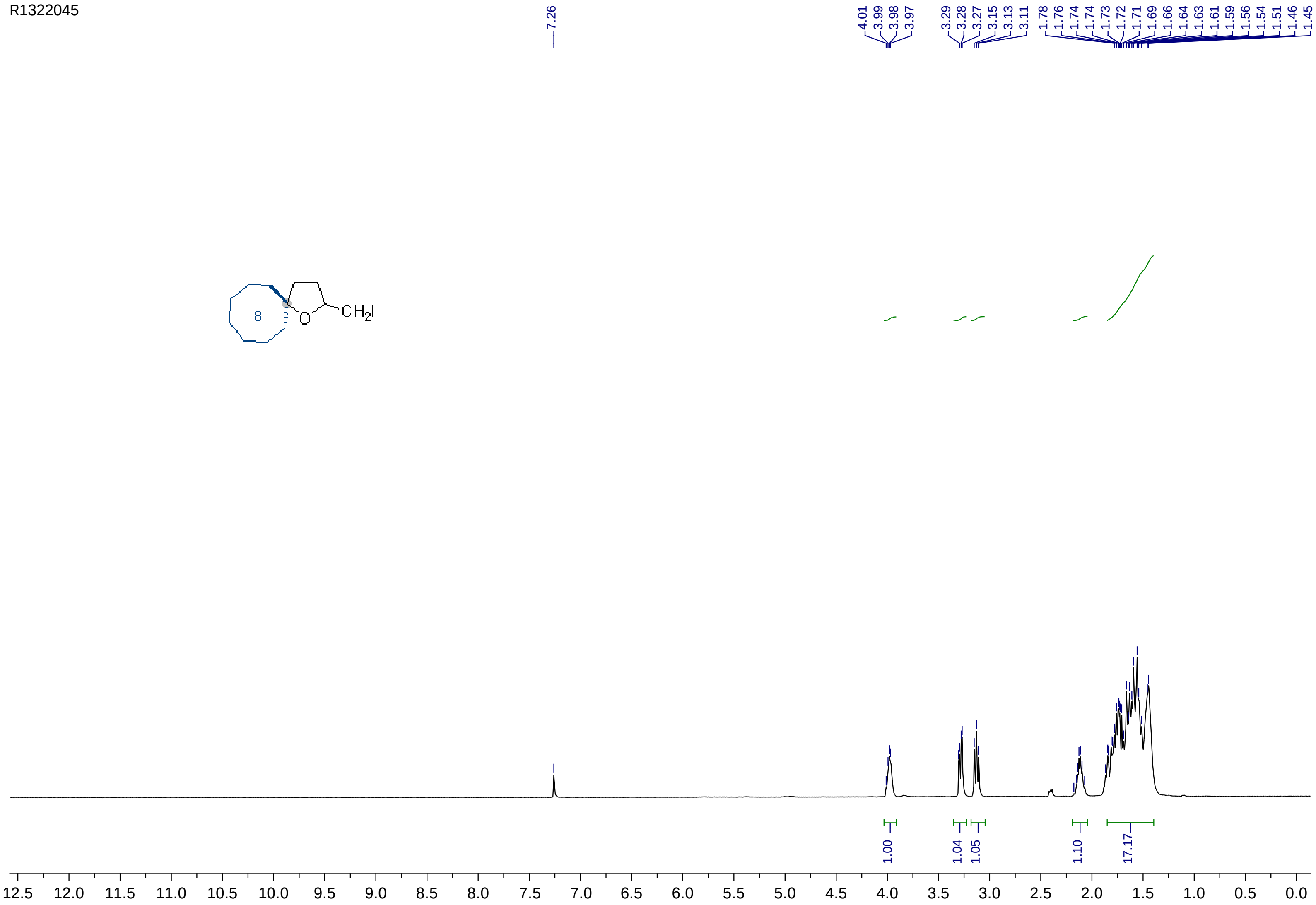
Compound 30a

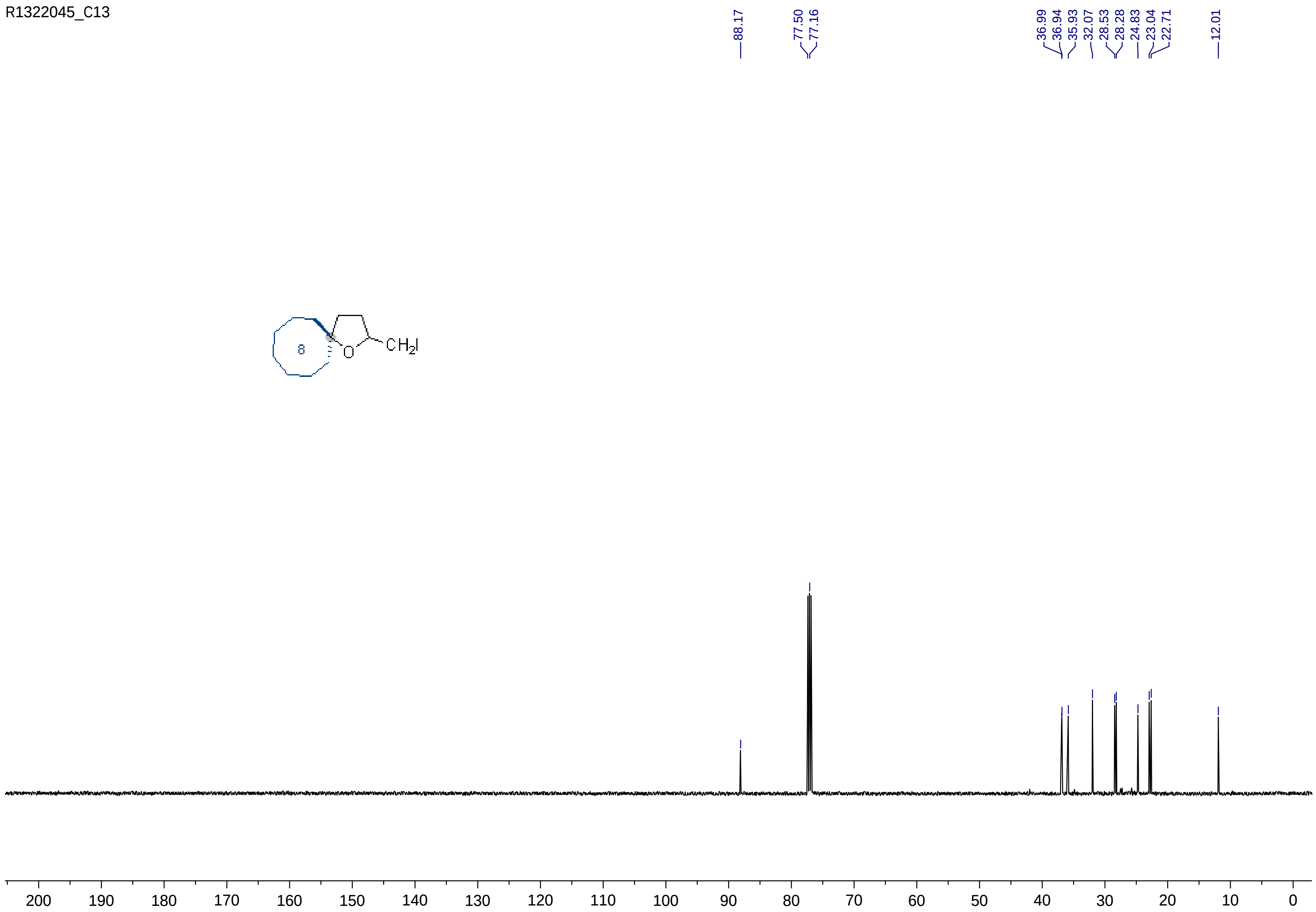


R929375_C13

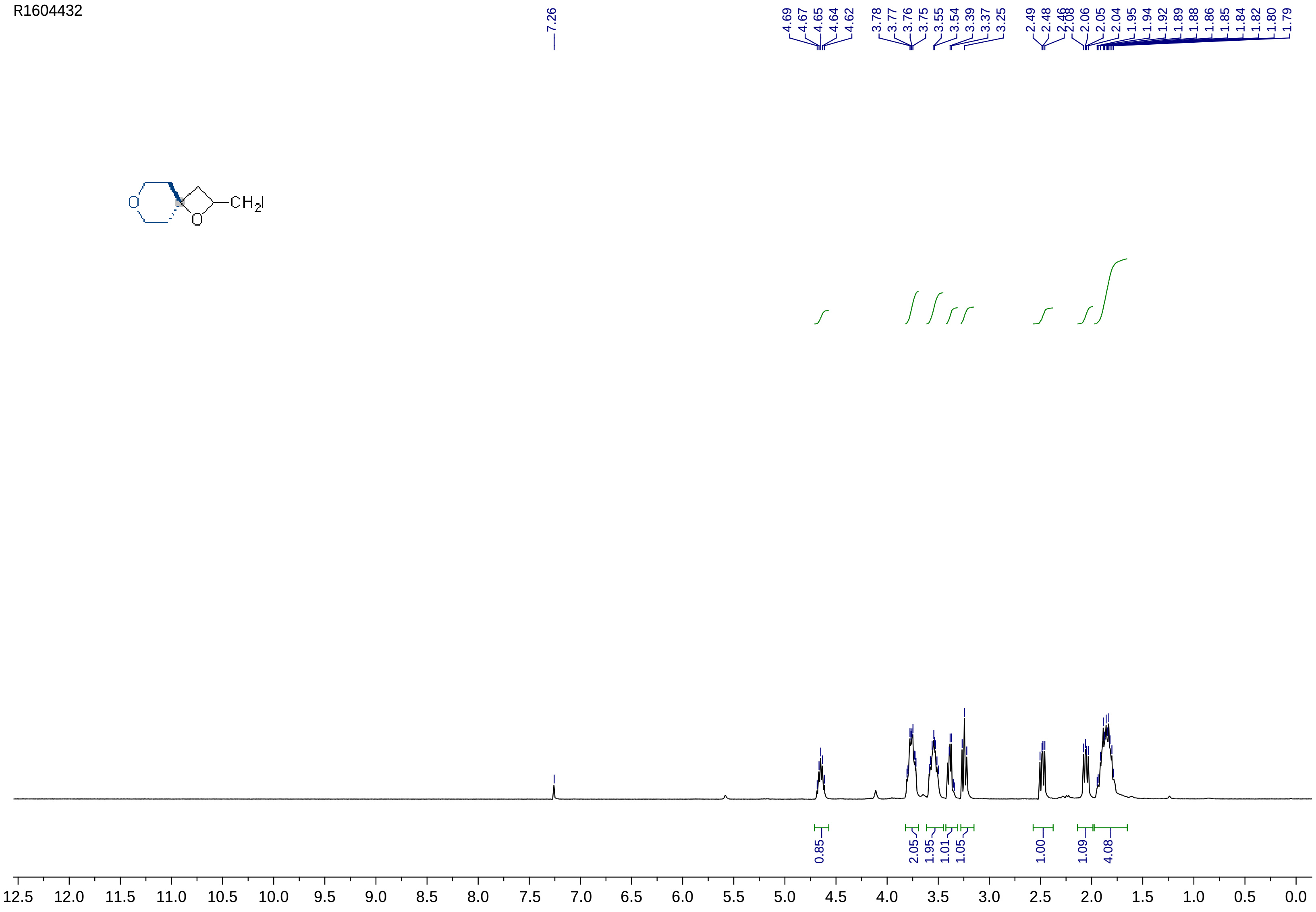

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 31a

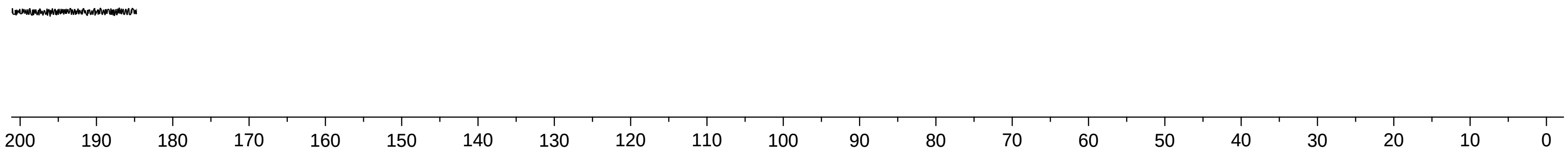



R1322045_C13
88.17
77.50
77.16
36.99
36.94
35.93
32.07
28.53
28.28
24.83
23.04
22.71
12.01
8
O
CH2I
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

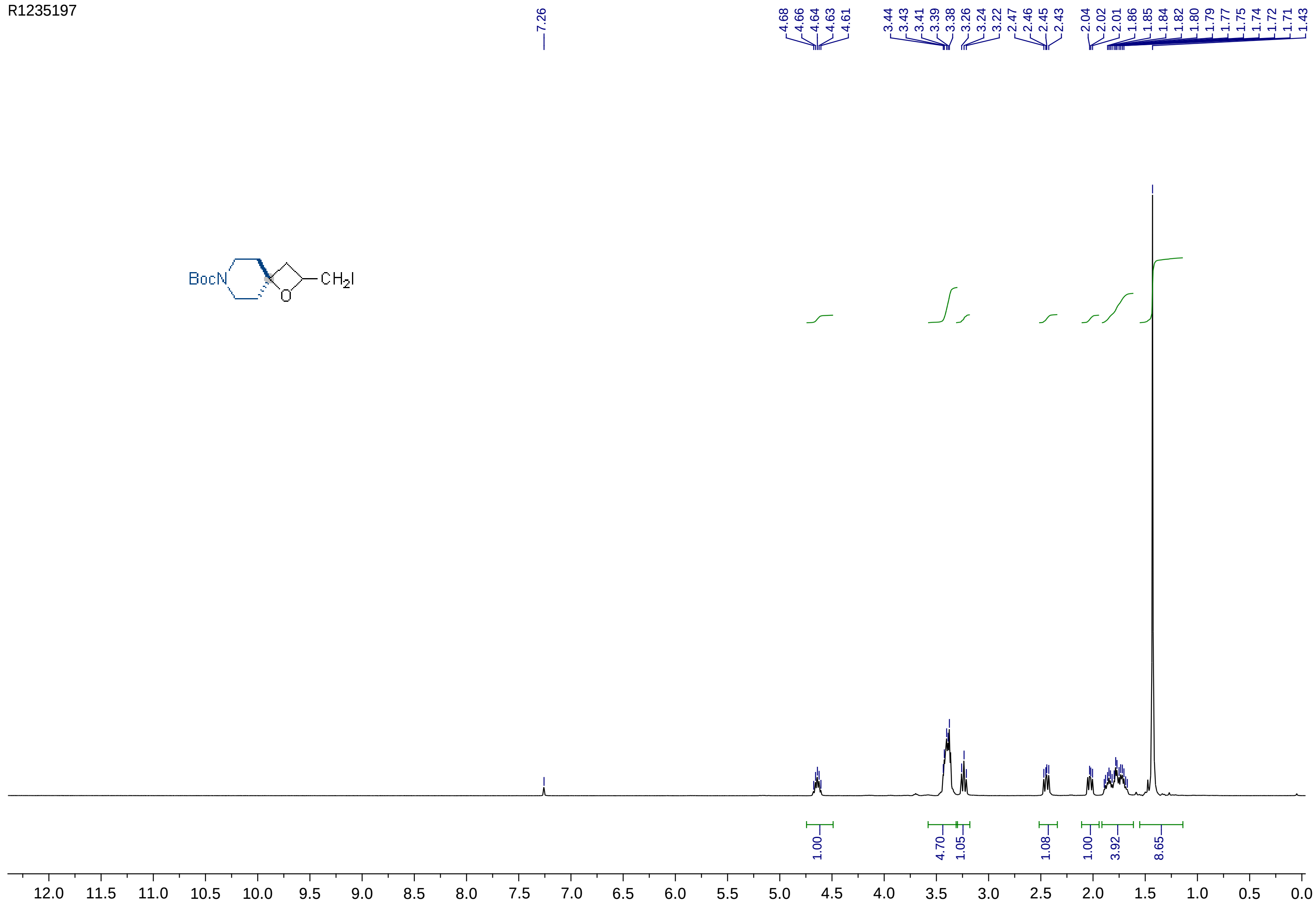
Compound 32a



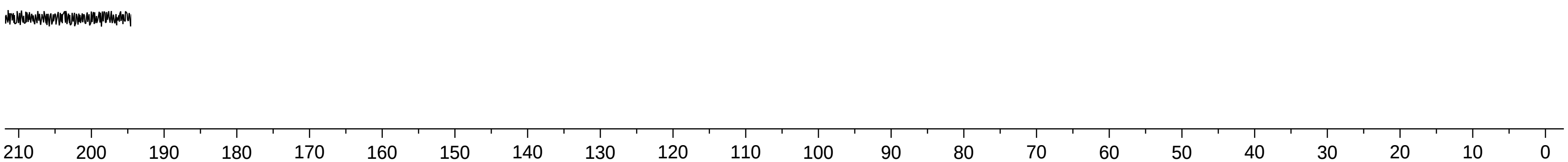
R1604432_C13



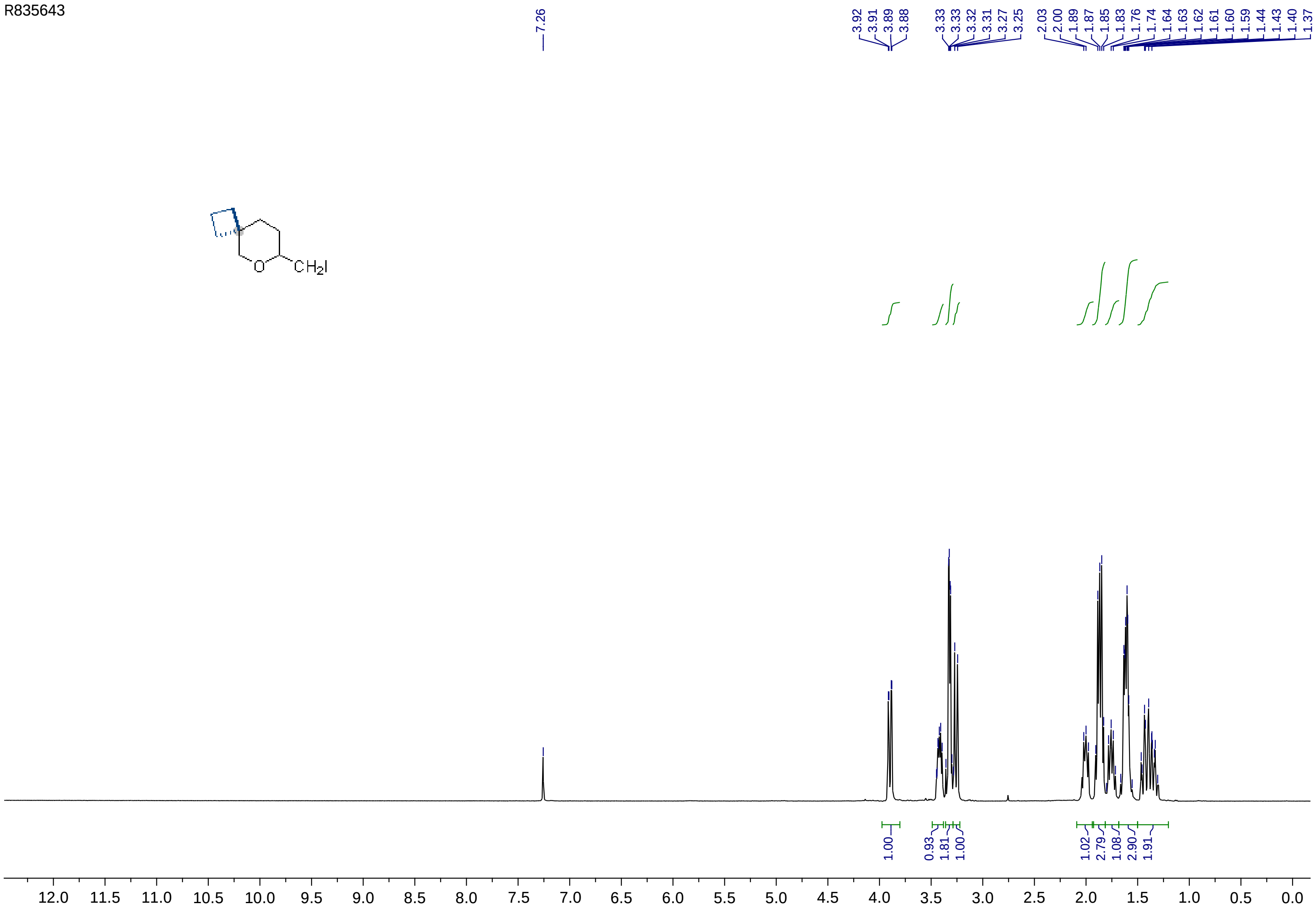
Compound 33a



R1235197_13C

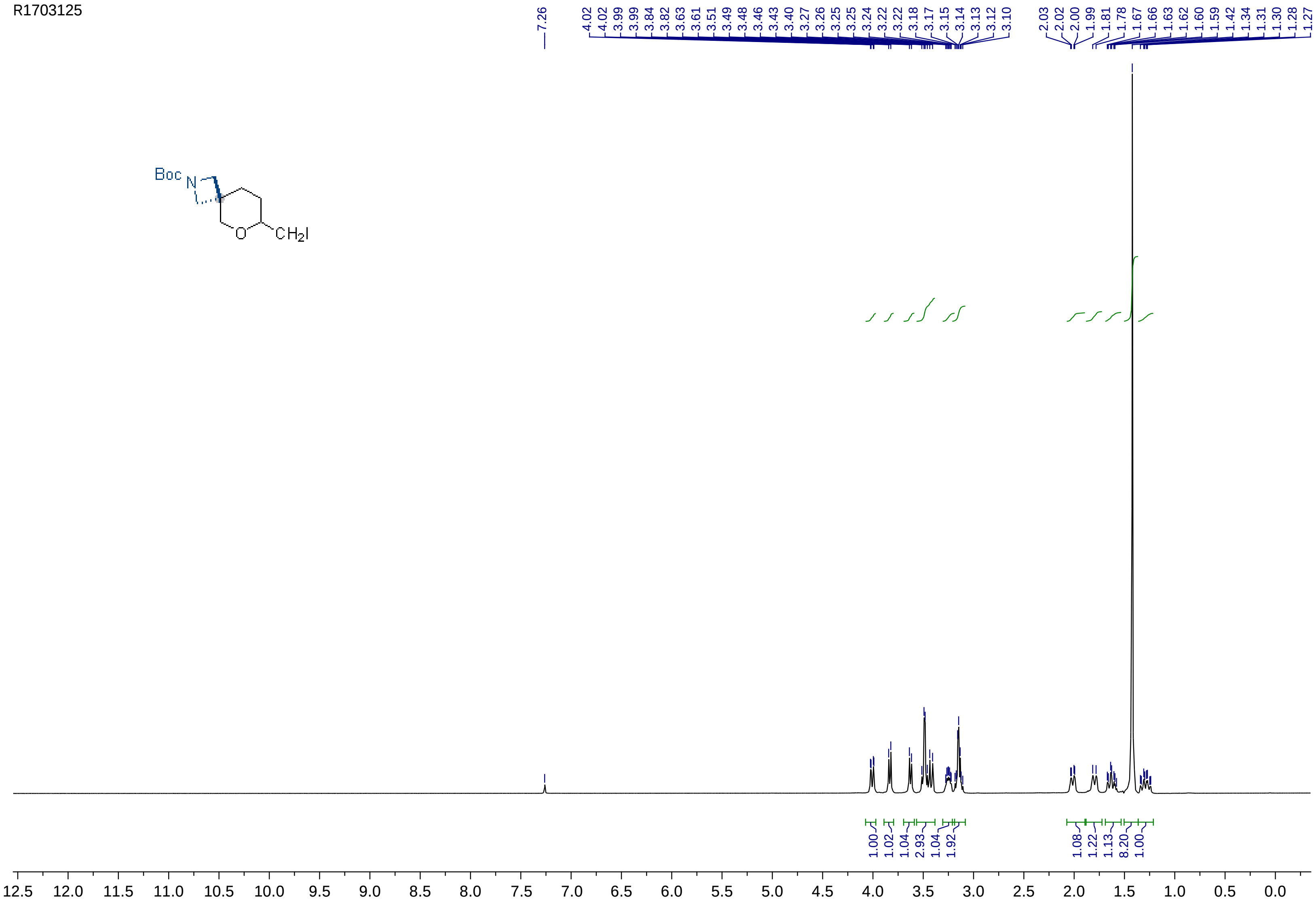


Compound 34a



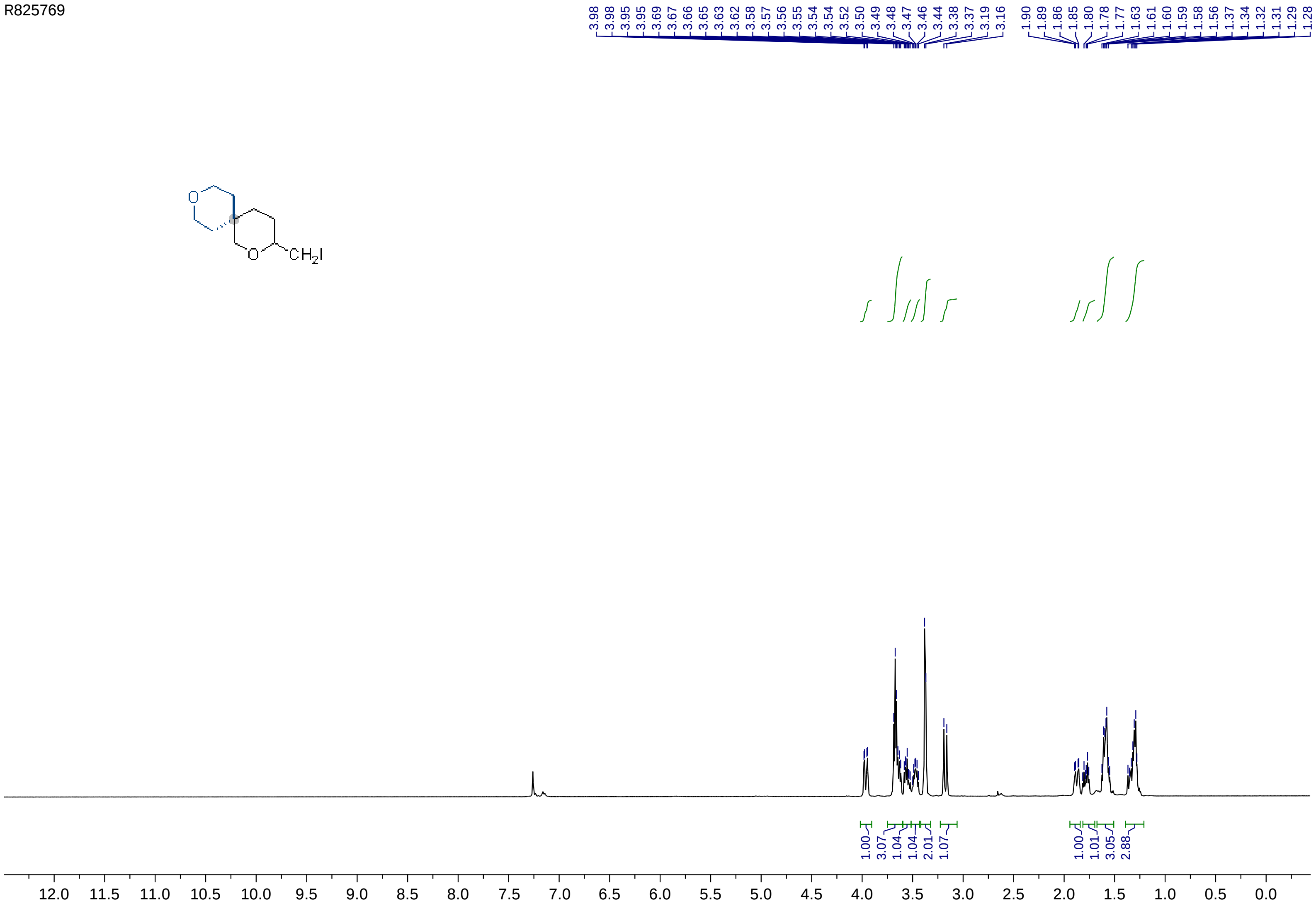

R835643_C13
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

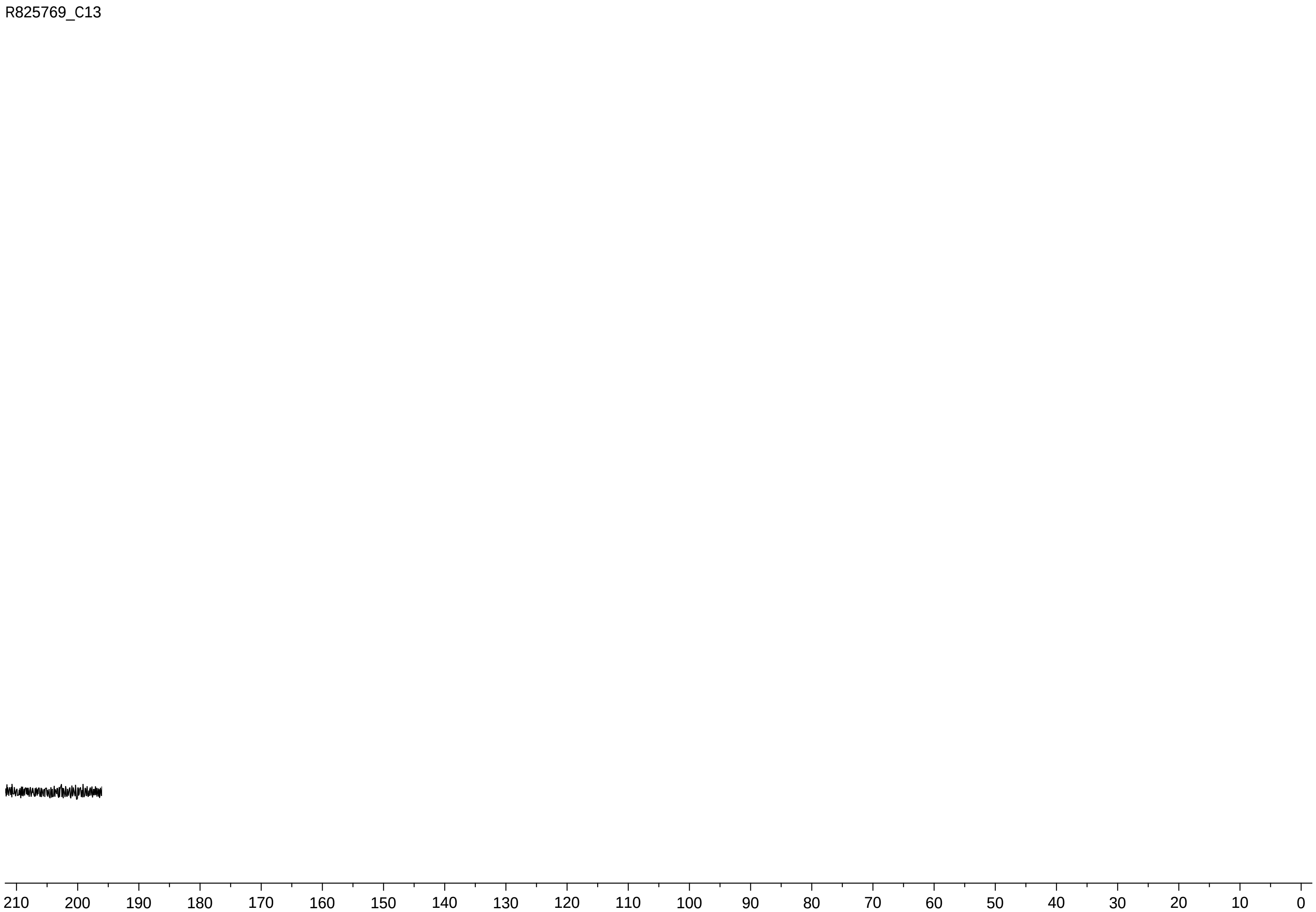
Compound 35a



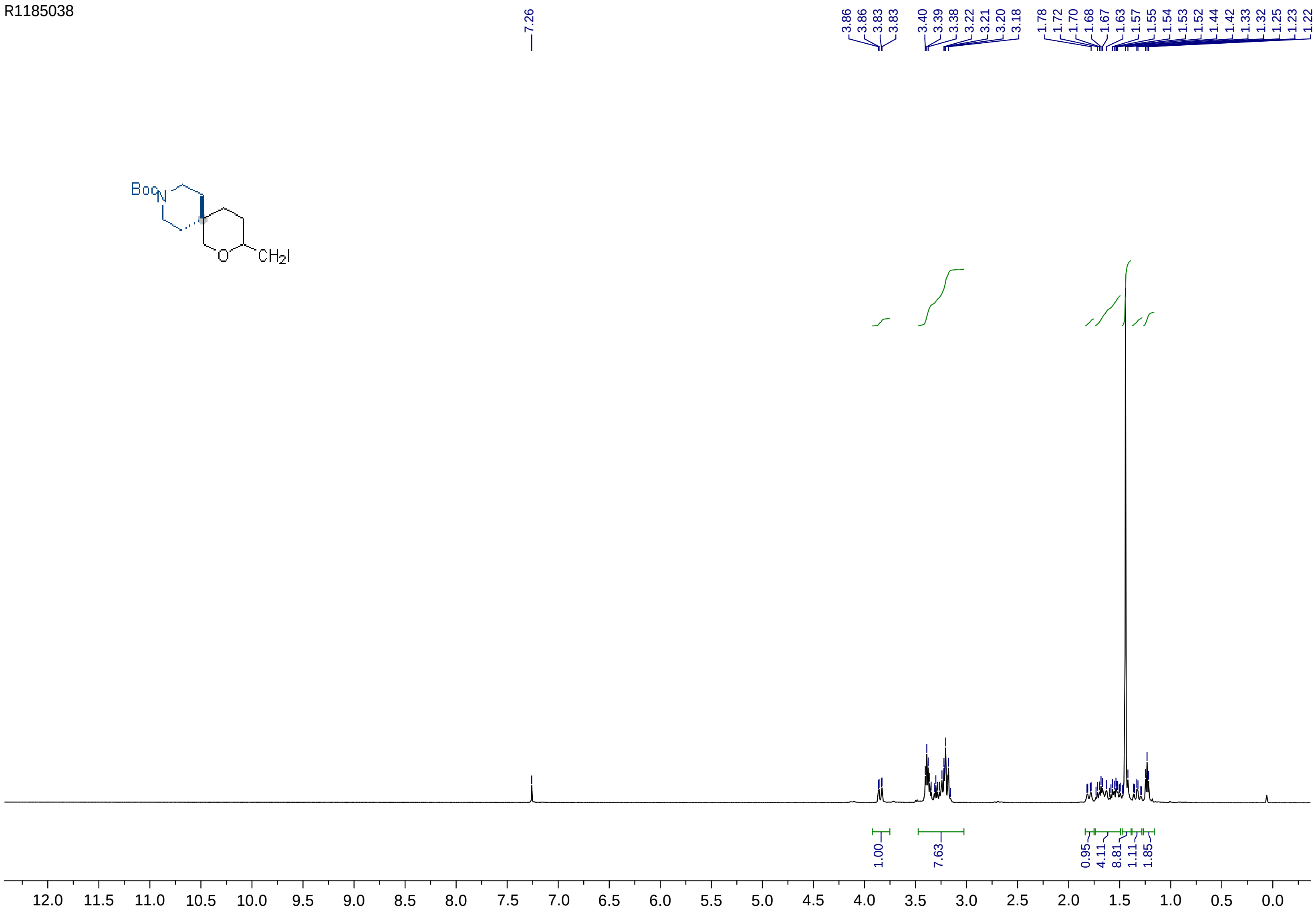

R1703125_13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 36a



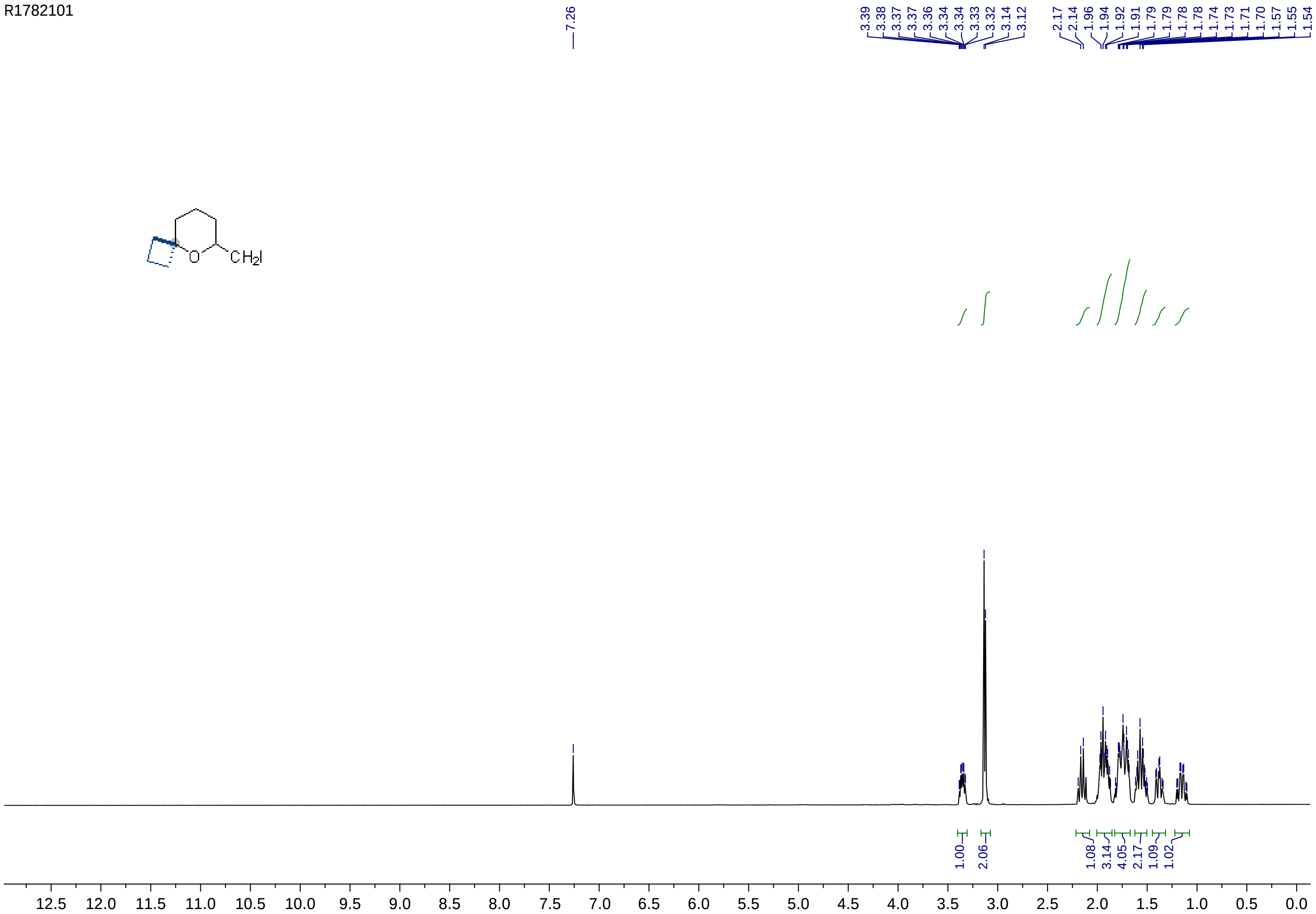

R825769_C13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 37a

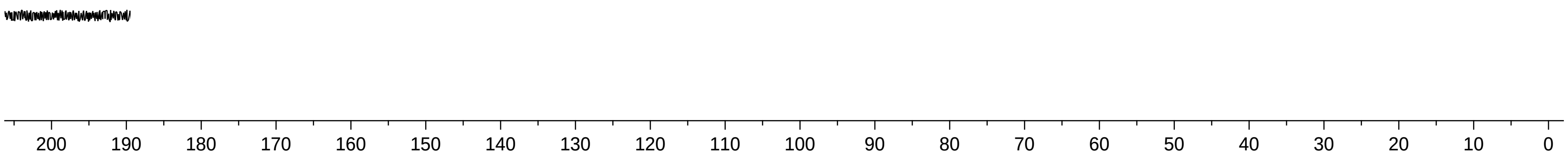



R1185038_C13
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

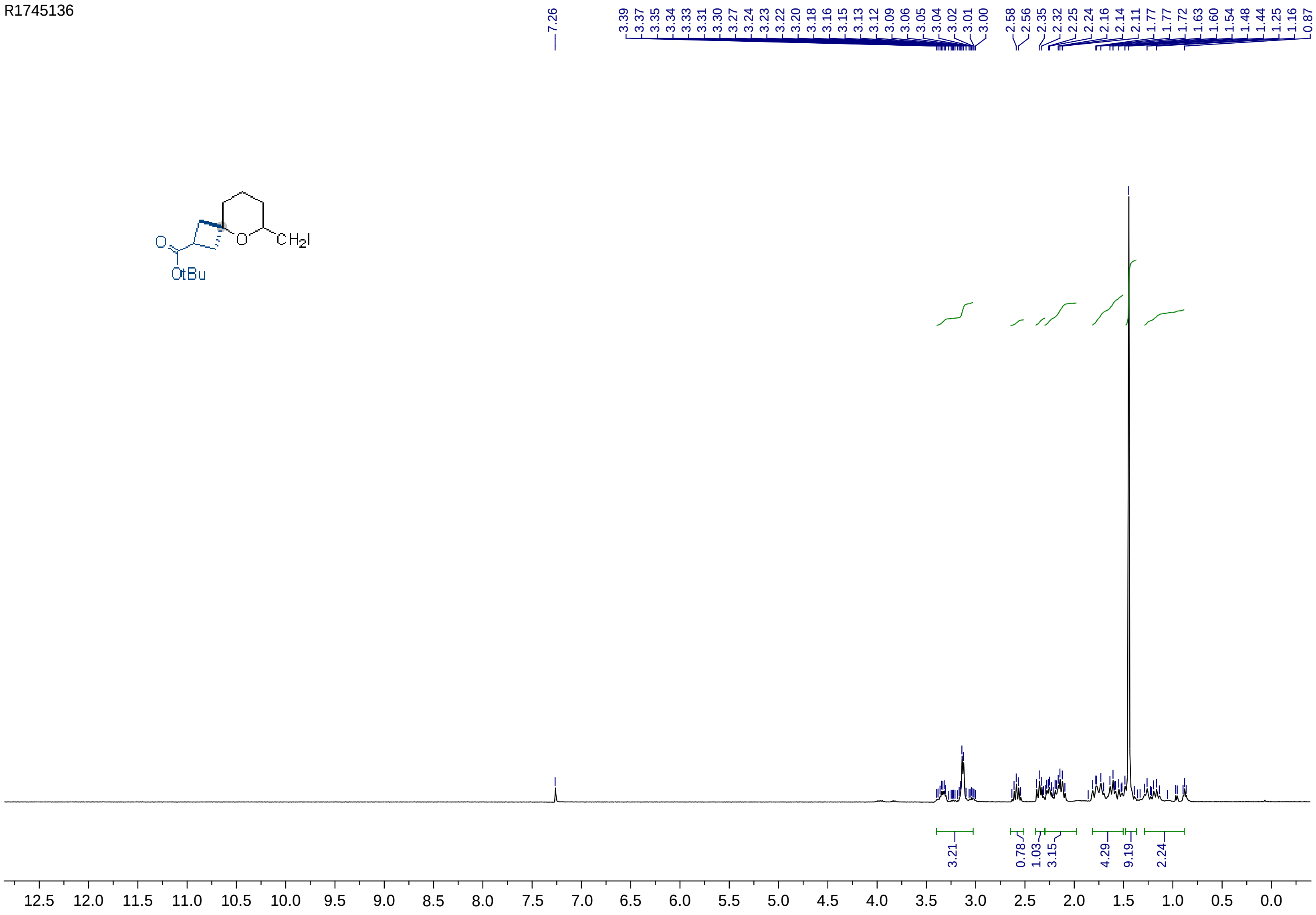
Compound 38a

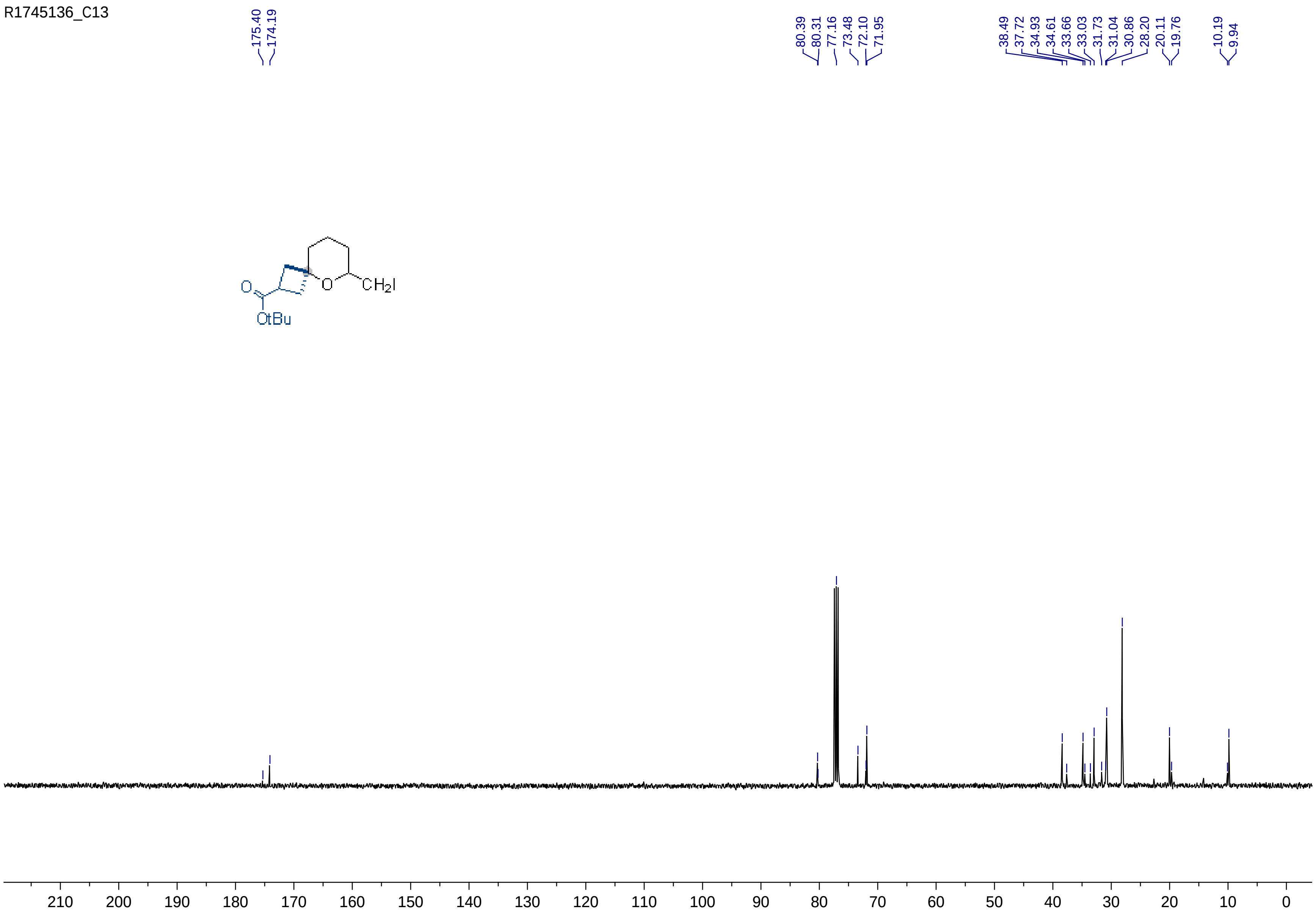


R1782101_C13

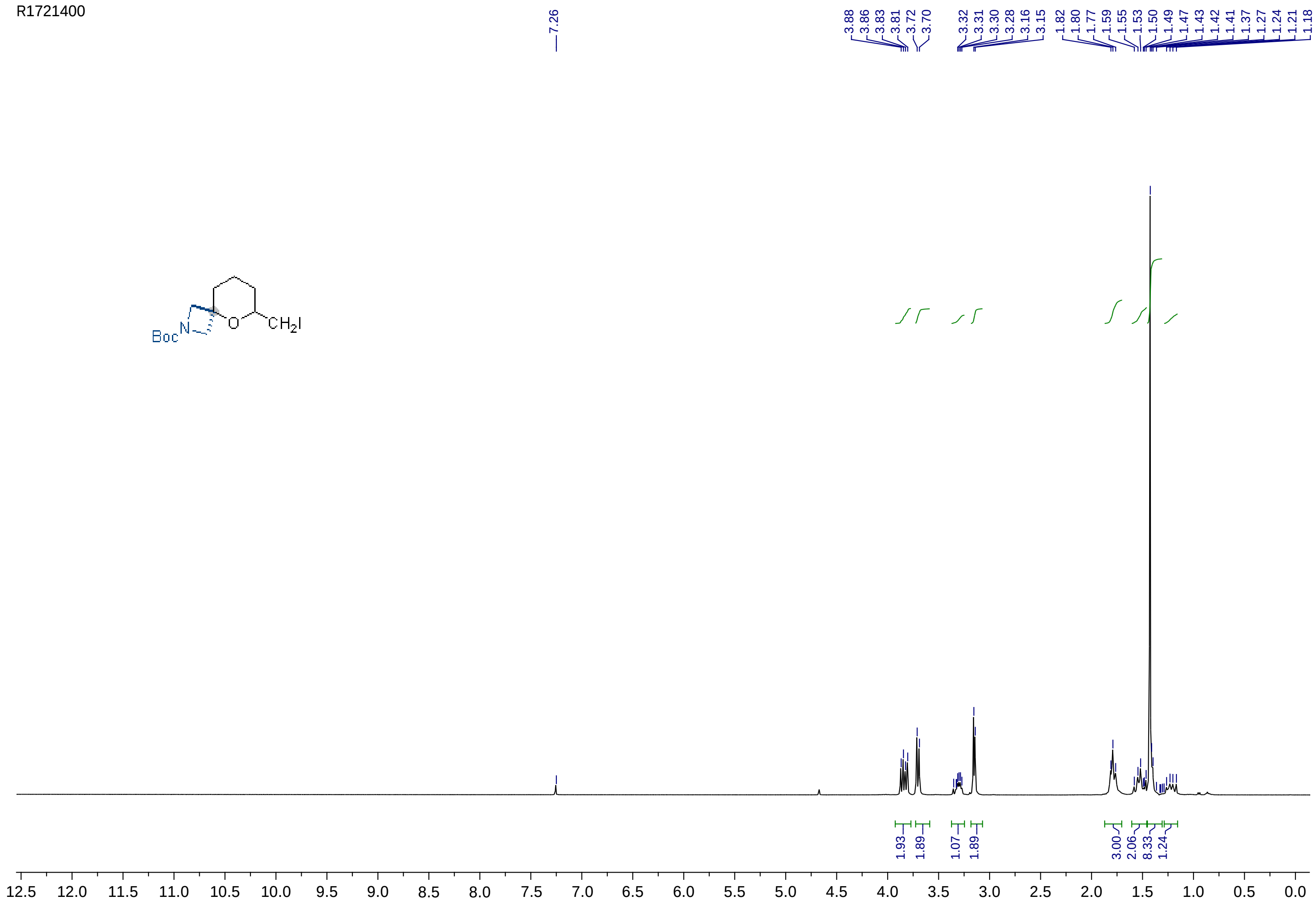


Compound 39a



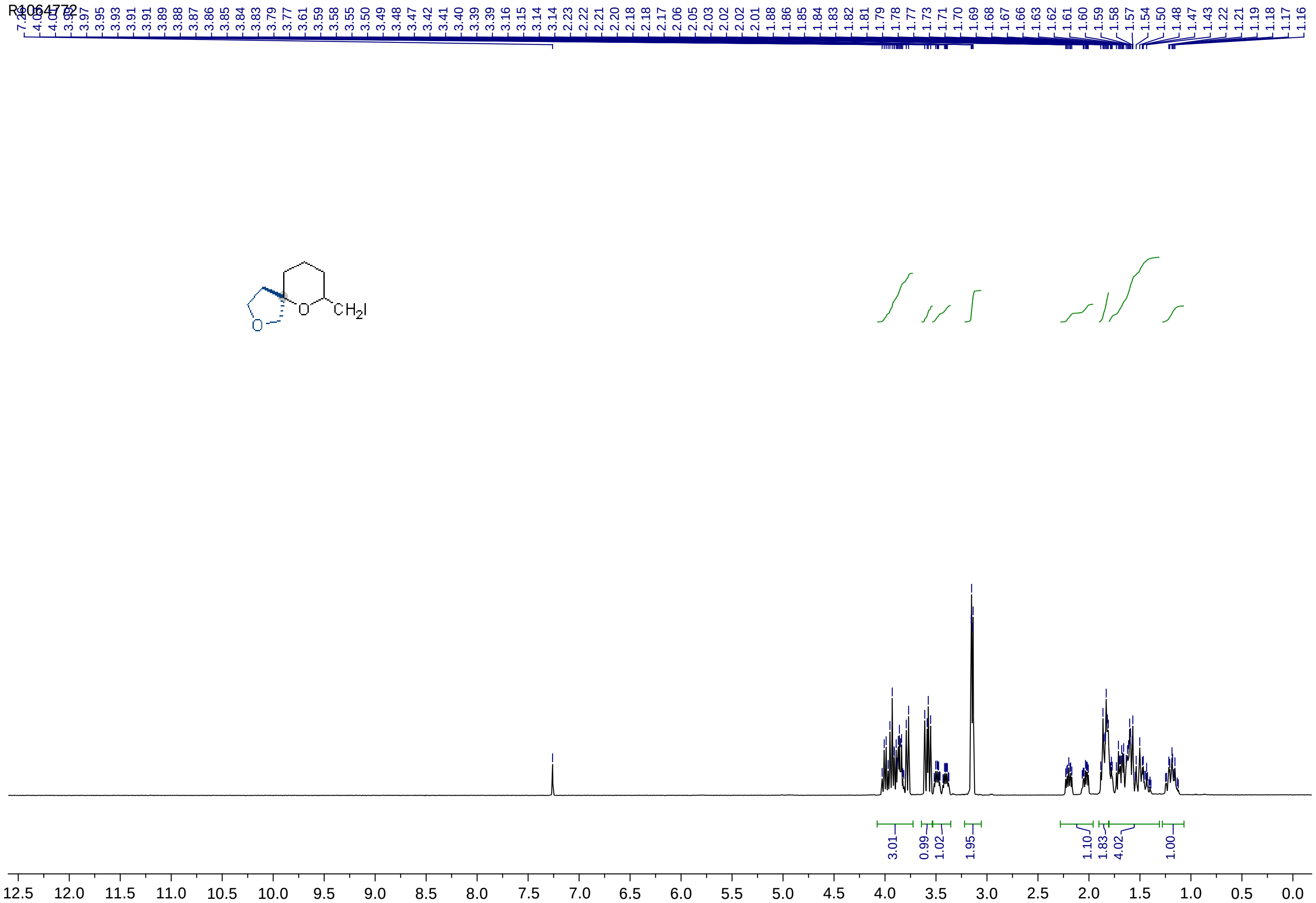

R1745136_C13
175.40
174.19
80.39
80.31
77.16
73.48
72.10
71.95
38.49
37.72
34.93
34.61
33.66
33.03
31.73
31.04
30.86
28.20
20.11
19.76
10.19
9.94
O
OtBu
O
CH2I
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

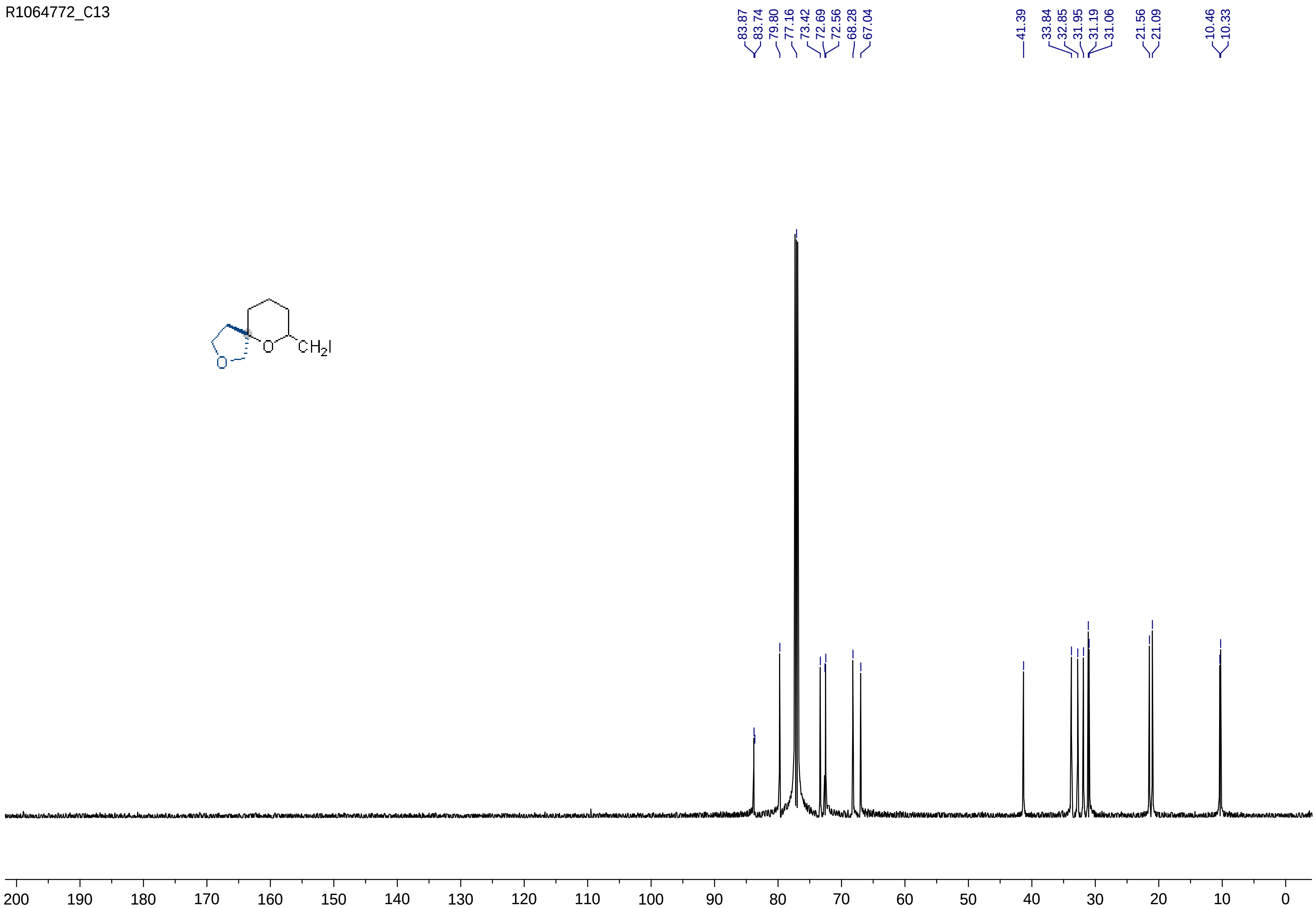
Compound 40a



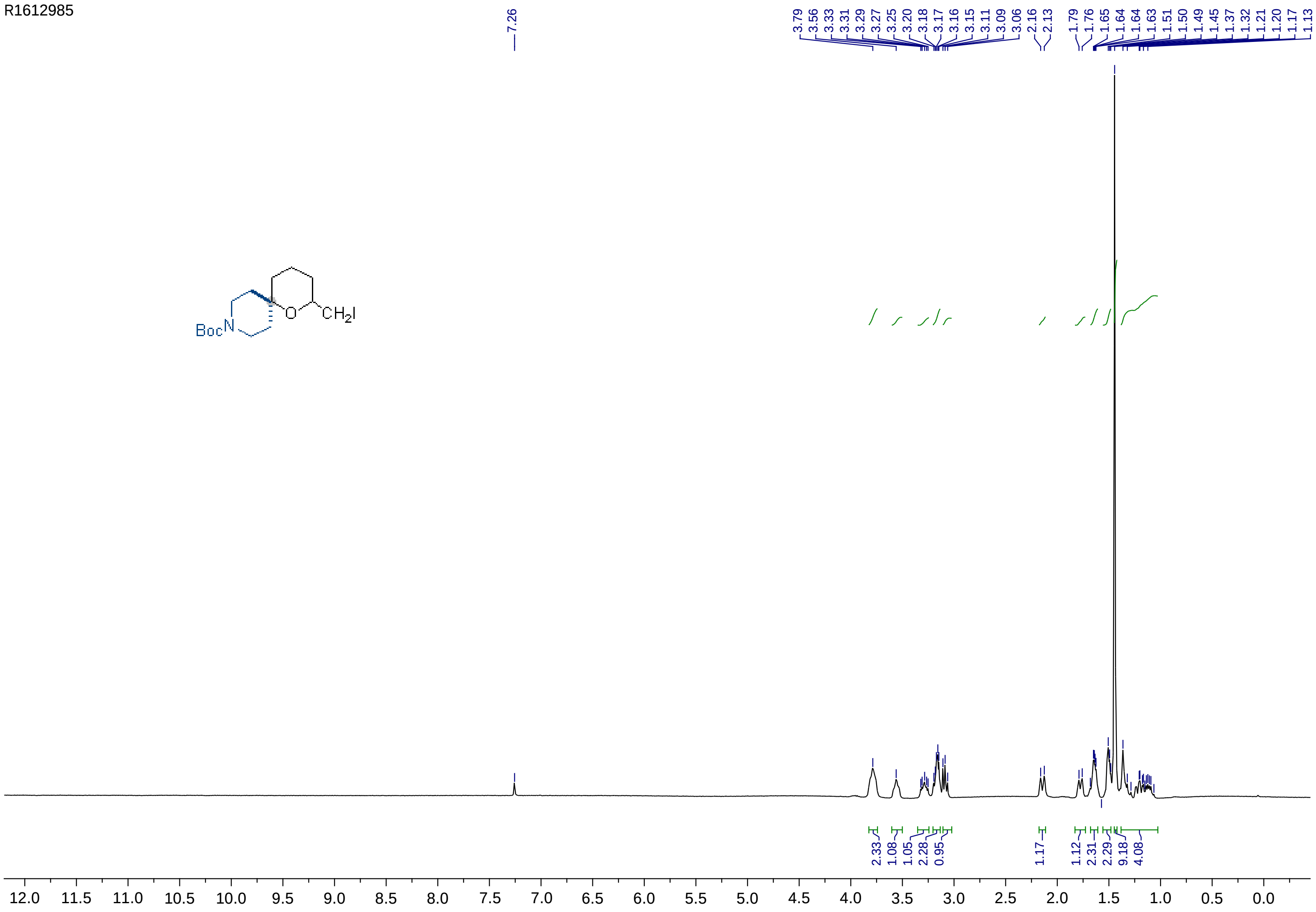

R1721400_C13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 41a



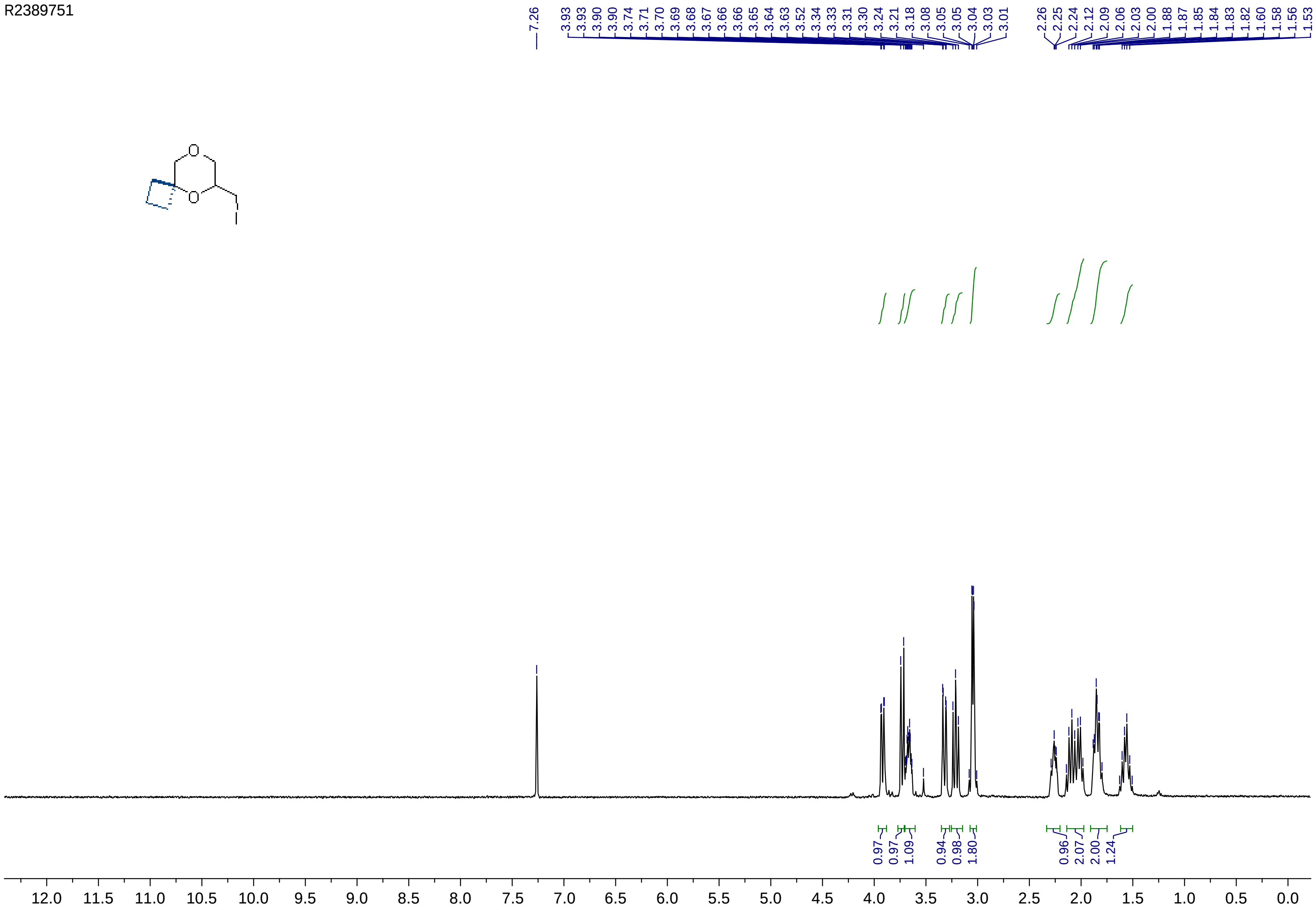

R1064772_C13
83.87
83.74
79.80
77.16
73.42
72.69
72.56
68.28
67.04
41.39
33.84
32.85
31.95
31.19
31.06
21.56
21.09
10.46
10.33
O
O
CH2I
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 42a

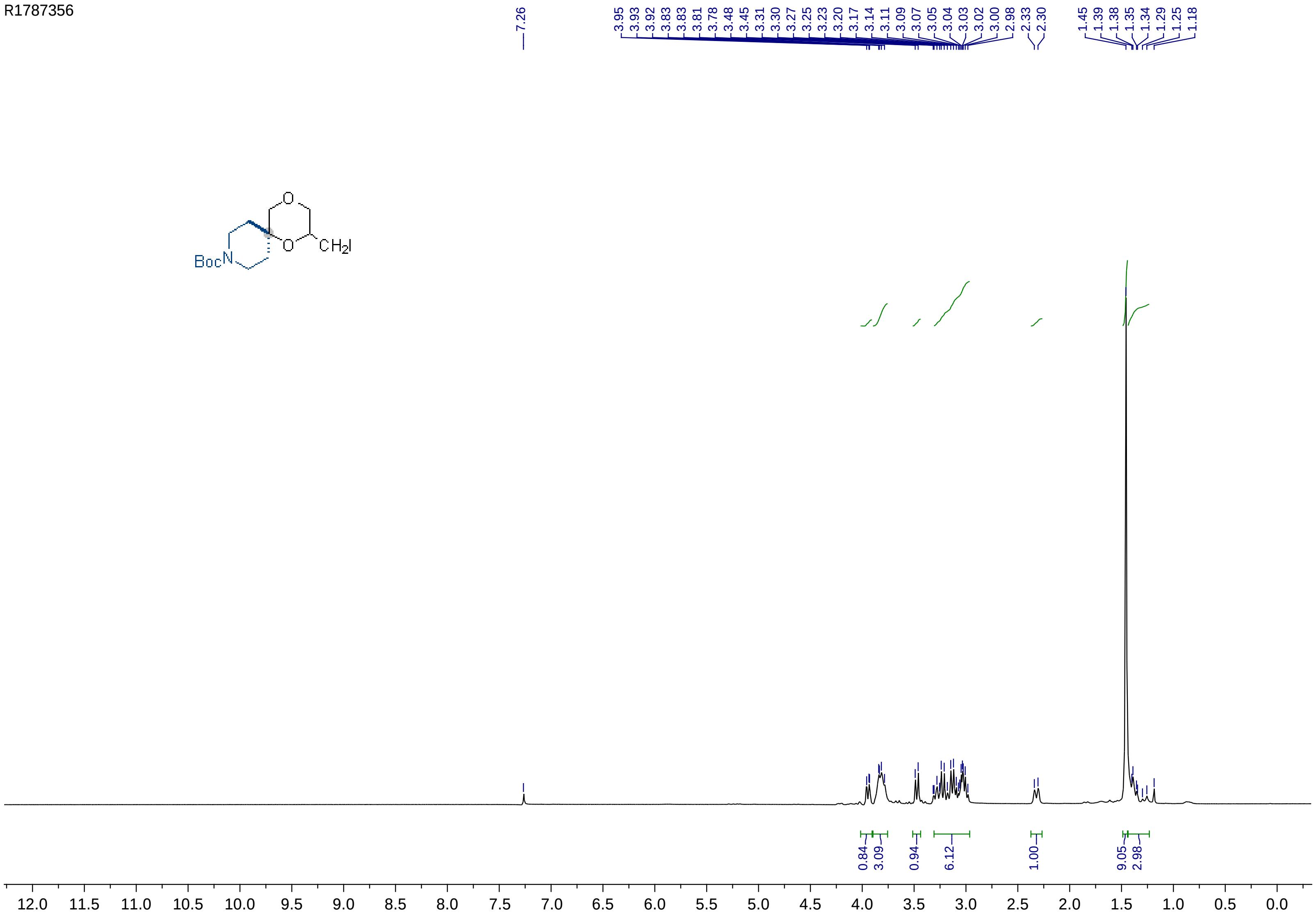



R1612985_C13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

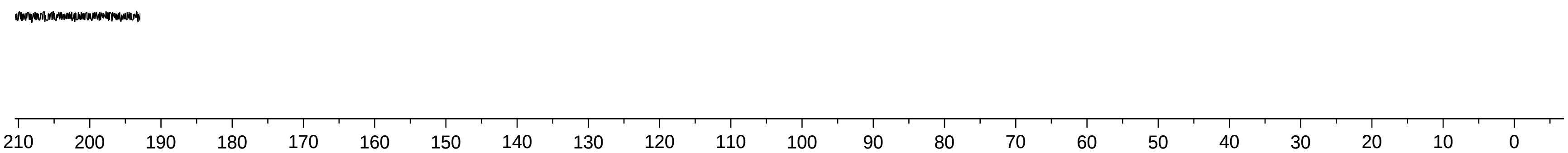
Compound 43a



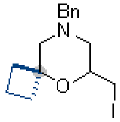
Compound 44a

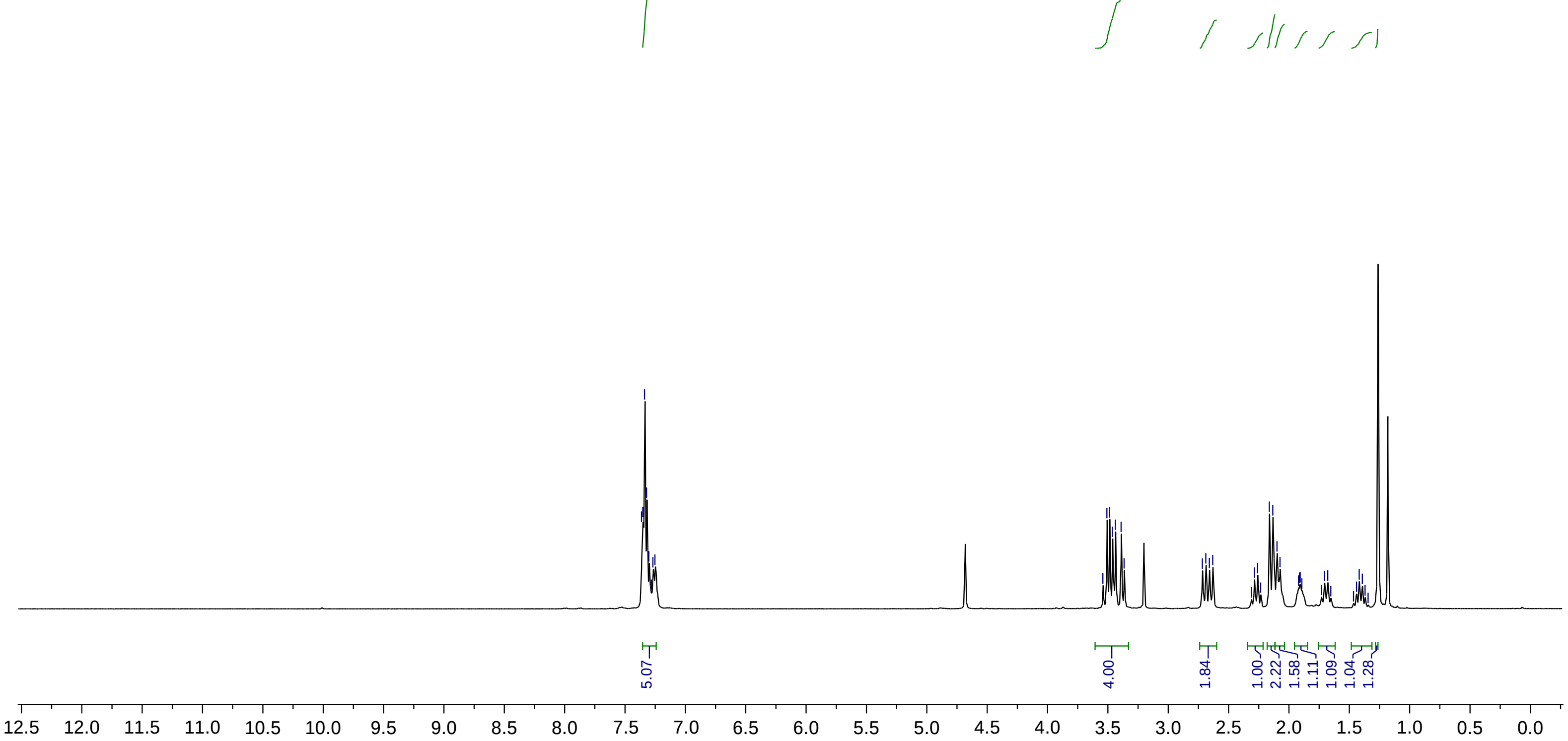


R1787356_C13

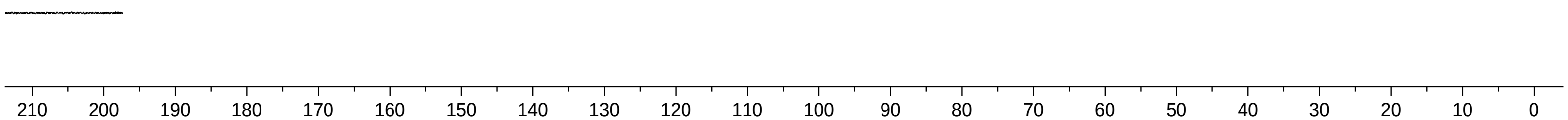


Compound 45a

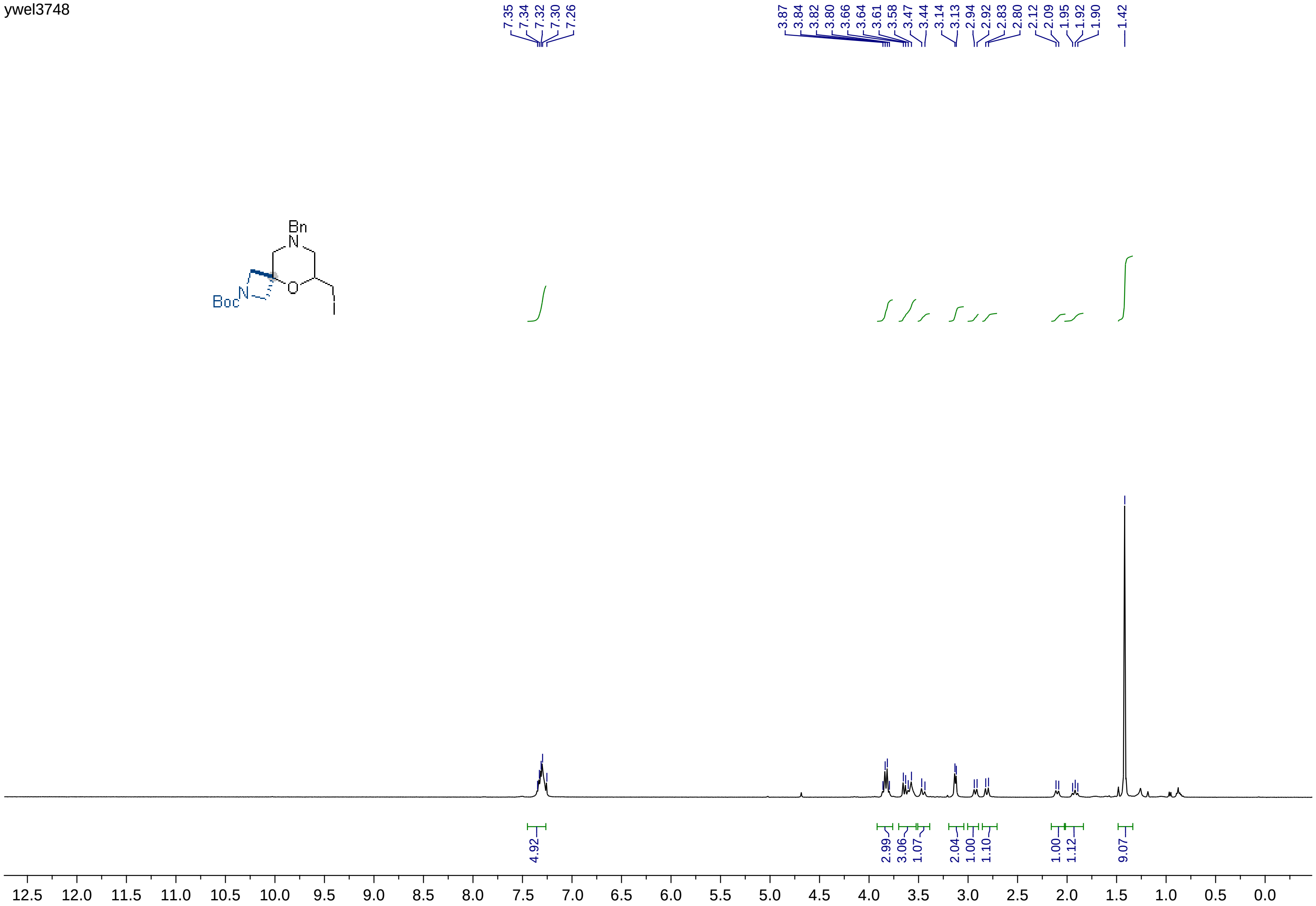




ywel3186-C13

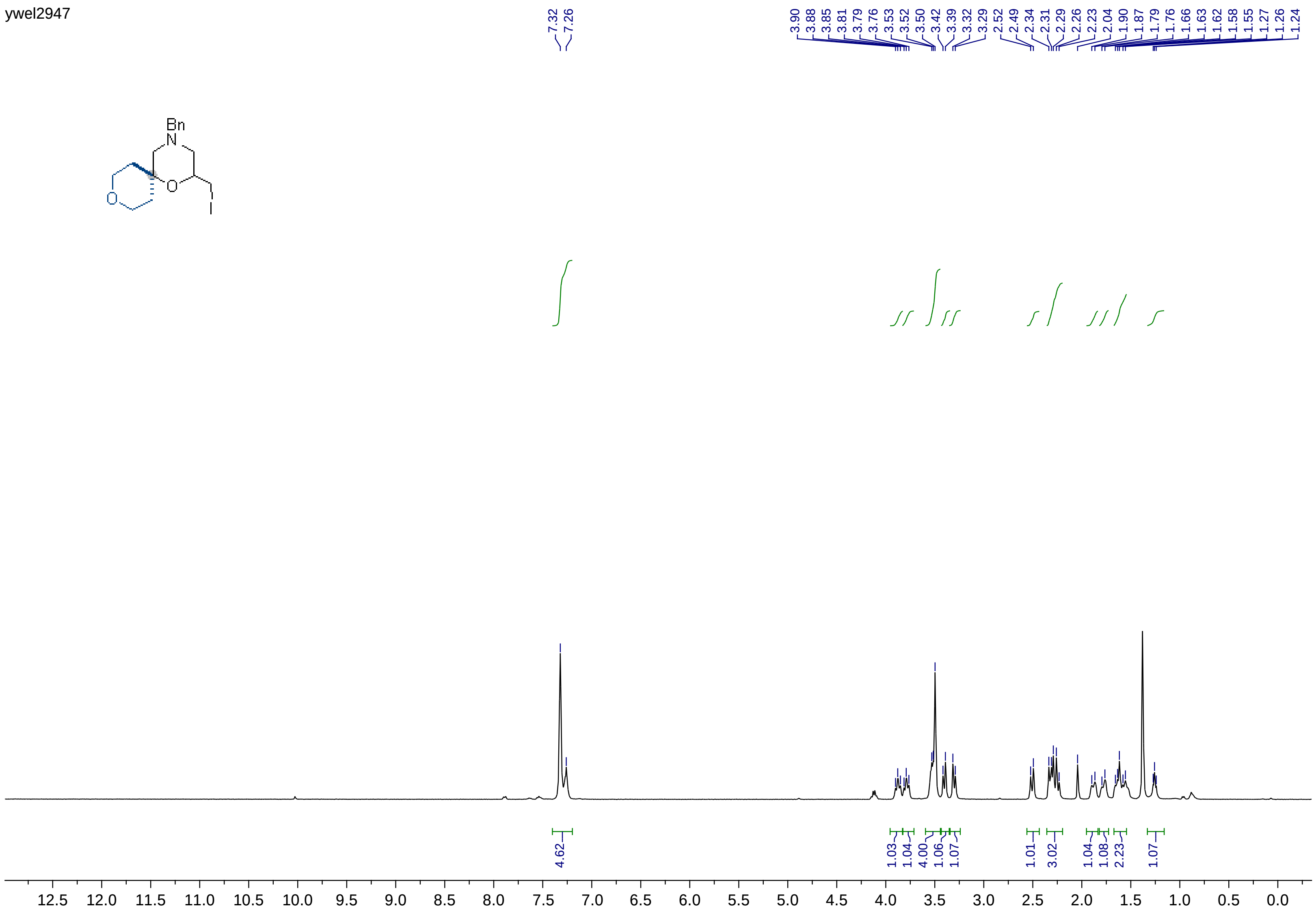


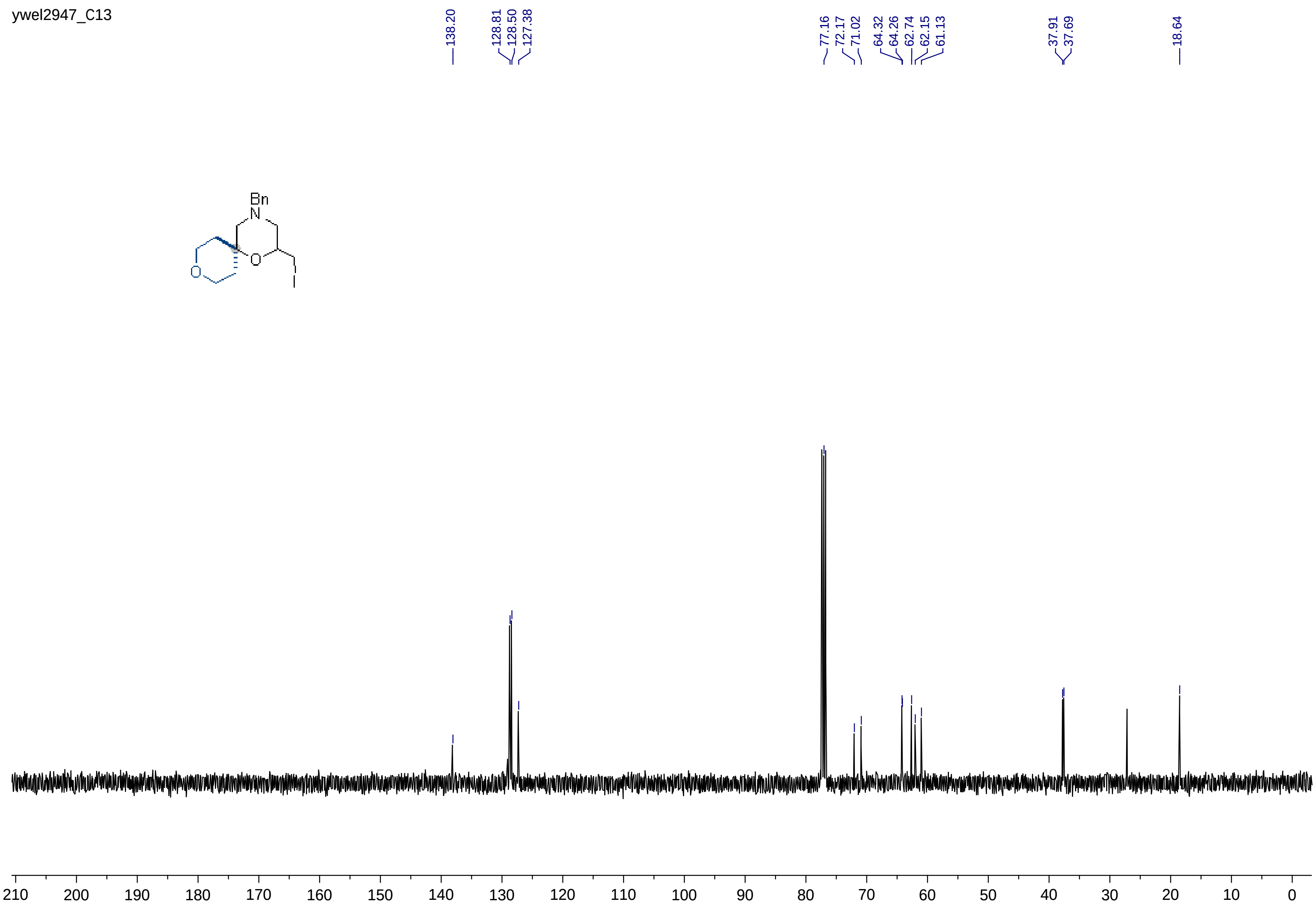
Compound 46a



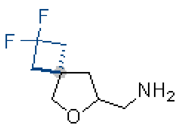

ywel3748_C13
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

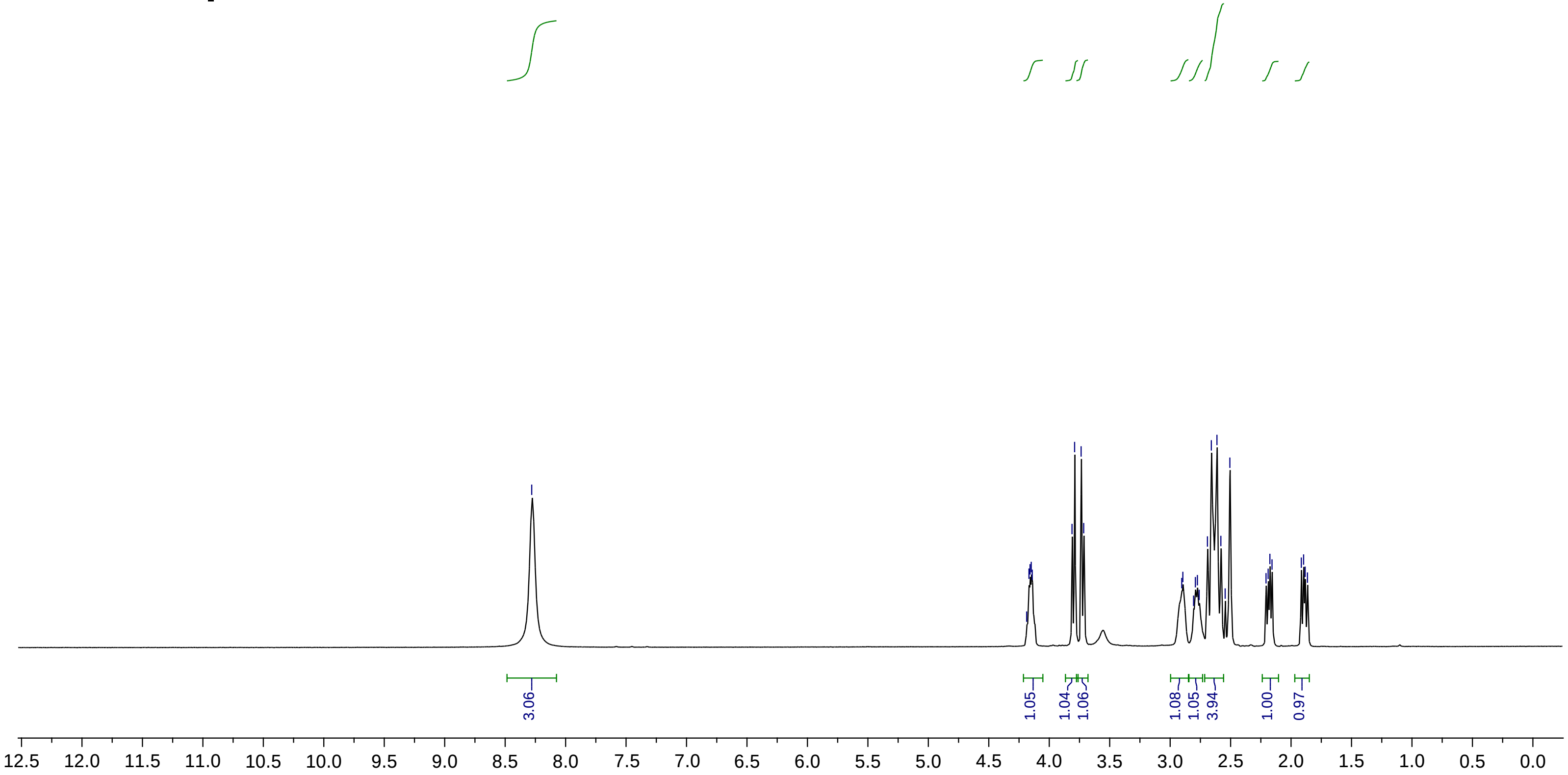
Compound 48a



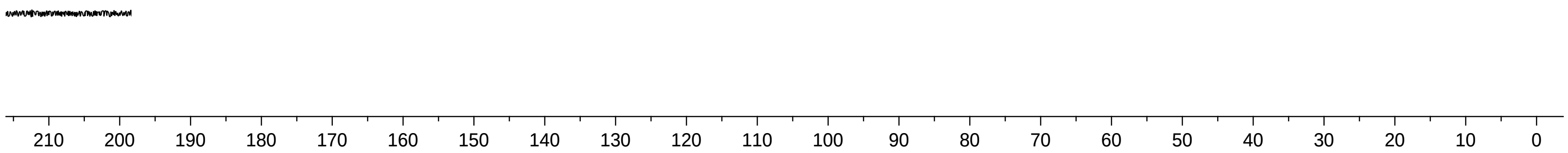

ywel2947_C13
138.20
128.81
128.50
127.38
77.16
72.17
71.02
64.32
64.26
62.74
62.15
61.13
37.91
37.69
18.64
Bn
N
O
O
I
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 4b

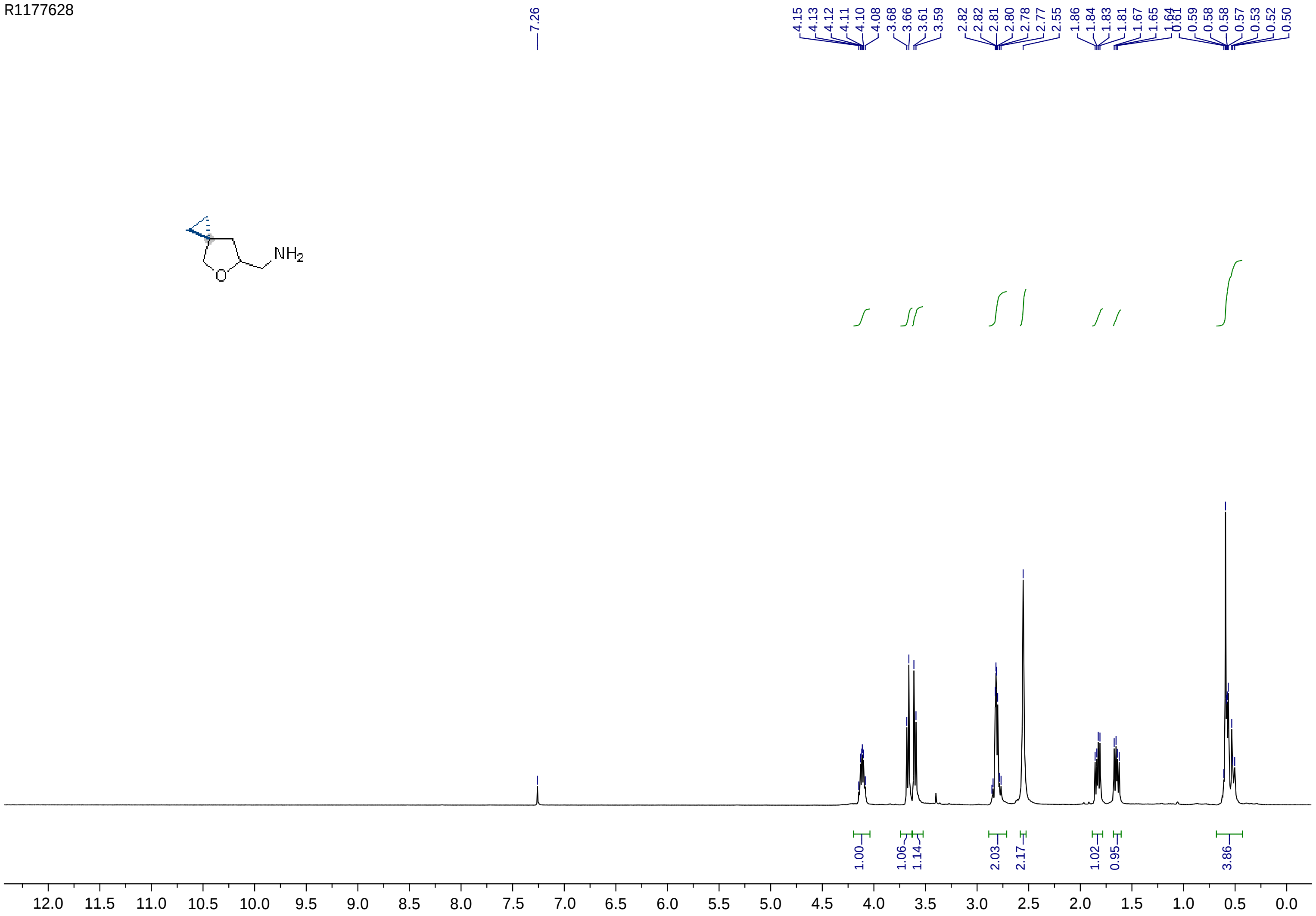



R1726969
8.27
4.18
4.16
4.15
4.14
4.13
3.81
3.78
3.73
3.71
2.90
2.89
2.80
2.79
2.77
2.75
2.69
2.65
2.61
2.57
2.54
2.50
2.20
2.18
2.17
2.15
1.91
1.89
1.88
1.86
3.06
1.05
1.04
1.06
1.08
1.05
3.94
1.00
0.97
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

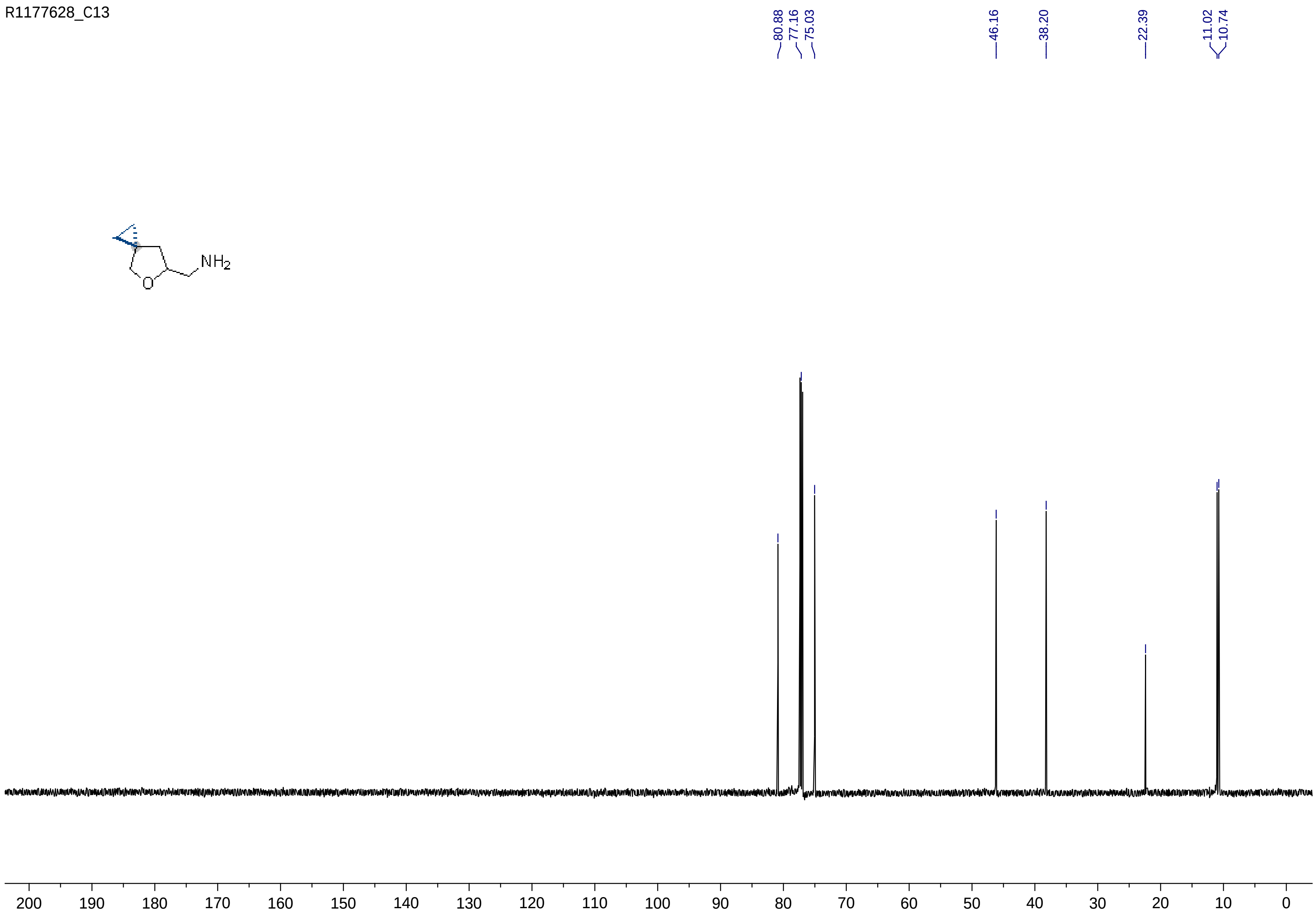
R1726969_C13



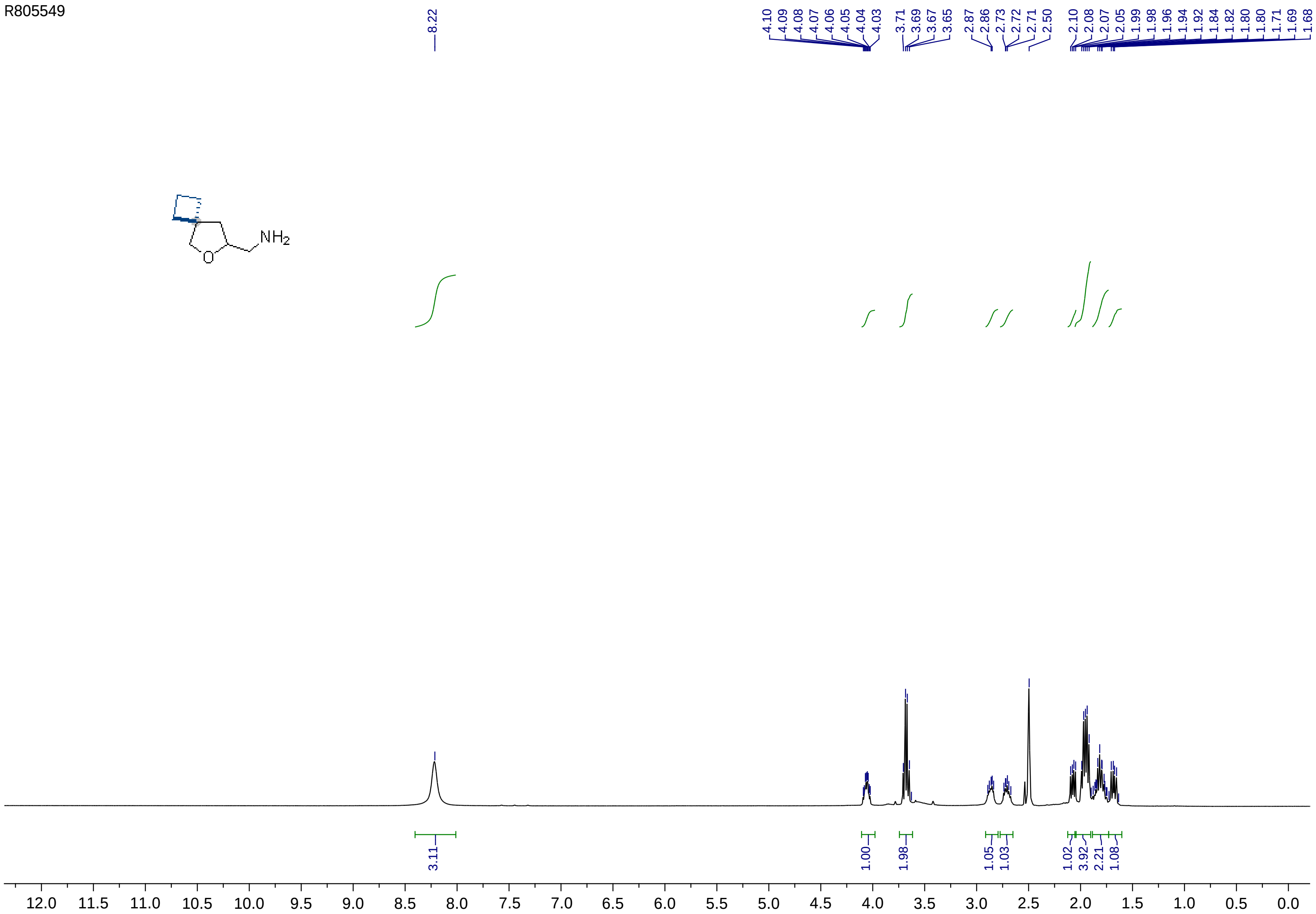
Compound 5b



R1177628
7.26
4.15
4.13
4.12
4.11
4.10
4.08
3.68
3.66
3.61
3.59
2.82
2.82
2.81
2.80
2.78
2.77
2.55
1.86
1.84
1.83
1.81
1.67
1.65
1.64
0.61
0.59
0.58
0.58
0.57
0.53
0.52
0.50
1.00
1.06
1.14
2.03
2.17
1.02
0.95
3.86
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

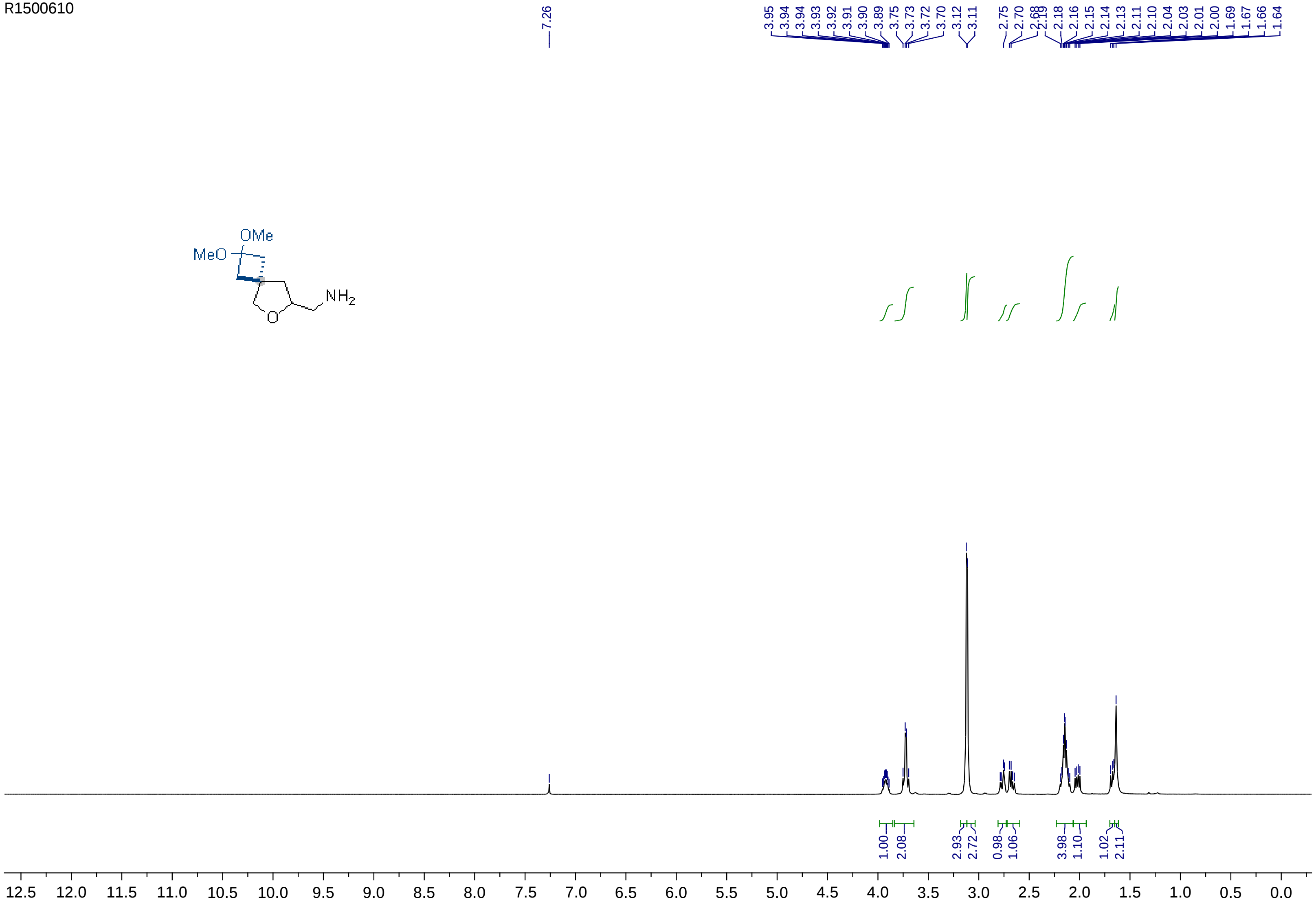

R1177628_C13
80.88
77.16
75.03
46.16
38.20
22.39
11.02
10.74
NH2
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 6b


R805549
NH2
O
8.22
4.10
4.09
4.08
4.07
4.06
4.05
4.04
4.03
3.71
3.69
3.67
3.65
2.87
2.86
2.73
2.72
2.71
2.50
2.10
2.08
2.07
2.05
1.99
1.98
1.96
1.94
1.92
1.84
1.82
1.80
1.80
1.71
1.69
1.68
3.11
1.00
1.98
1.05
1.03
1.02
3.92
2.21
1.08
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

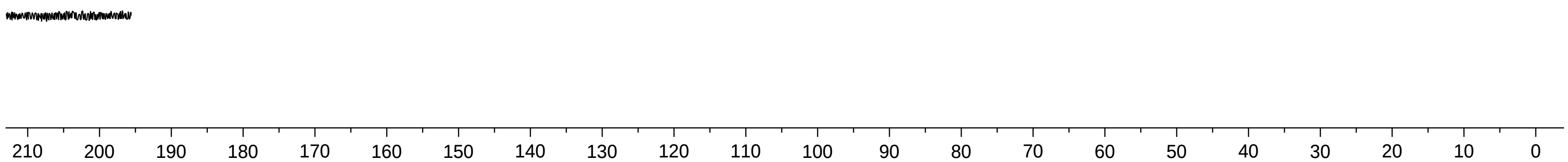

R805549_C13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 7b

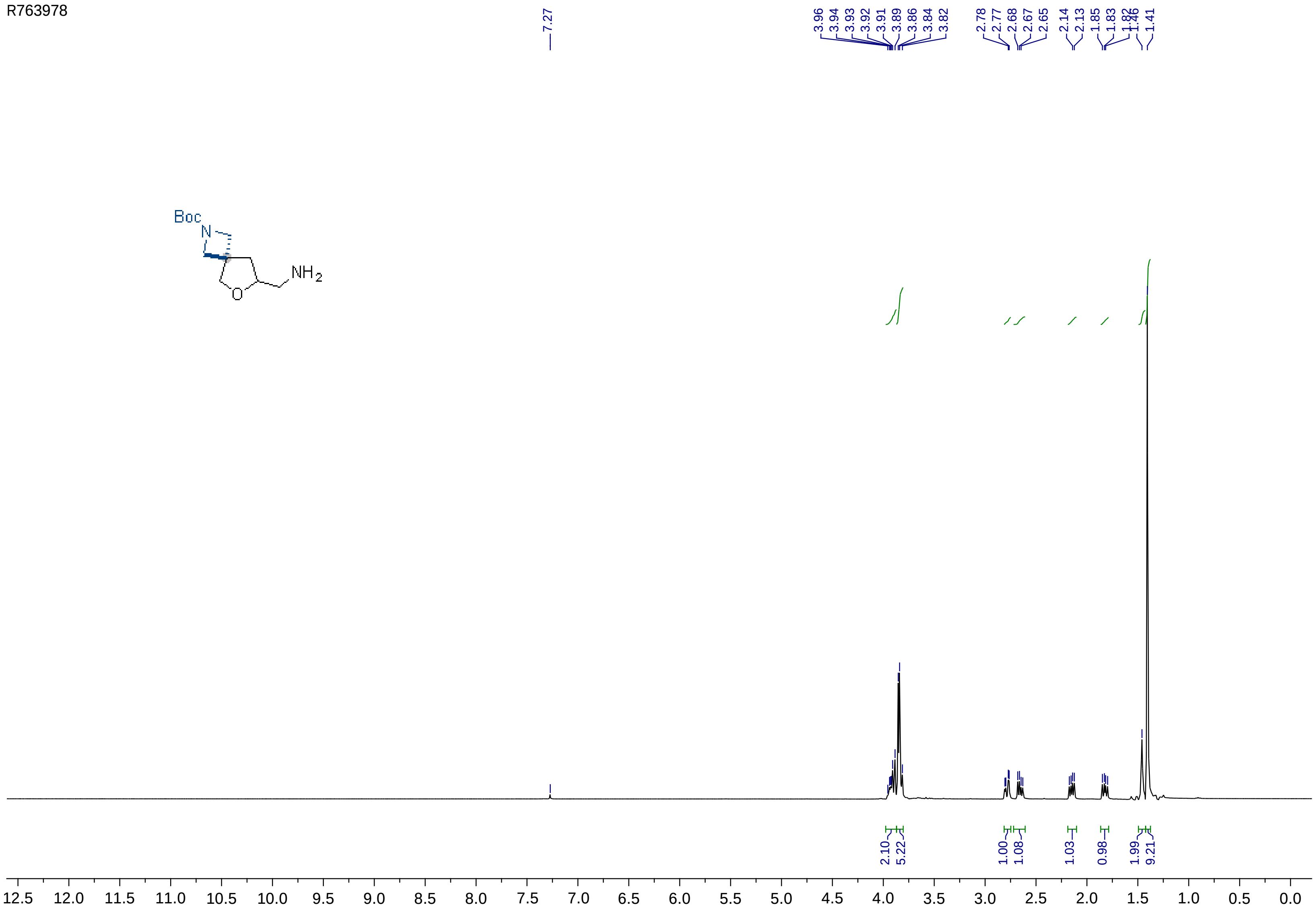


R1500610
OMe
MeO
NH2
O
7.26
3.95
3.94
3.94
3.93
3.92
3.91
3.90
3.89
3.75
3.73
3.72
3.70
3.12
3.11
2.75
2.70
2.68
2.19
2.18
2.16
2.15
2.14
2.13
2.11
2.10
2.04
2.03
2.01
2.00
1.69
1.67
1.66
1.64
1.00
2.08
2.93
2.72
0.98
1.06
3.98
1.10
1.02
2.11
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

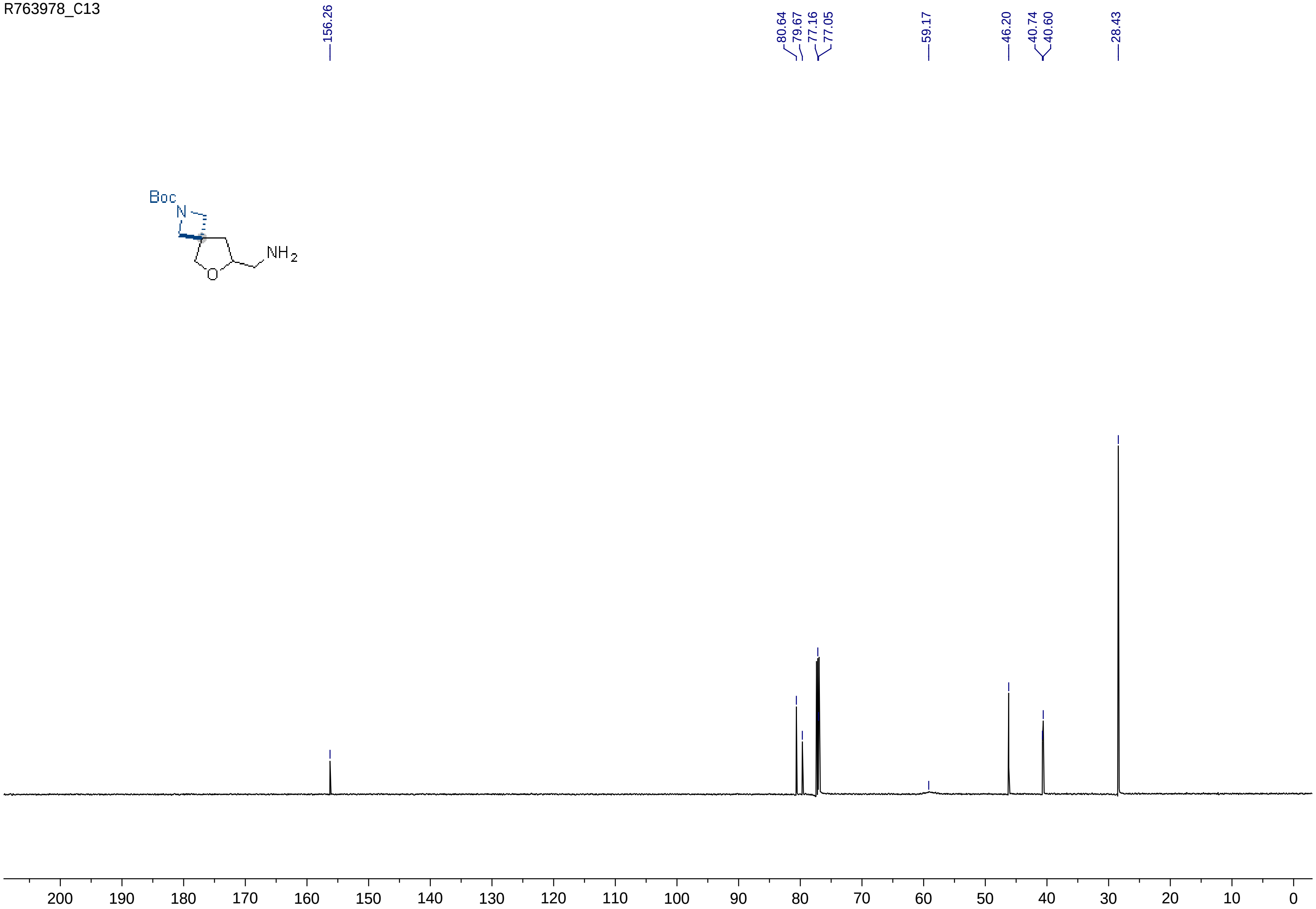
R1500610_C13



Compound 8b

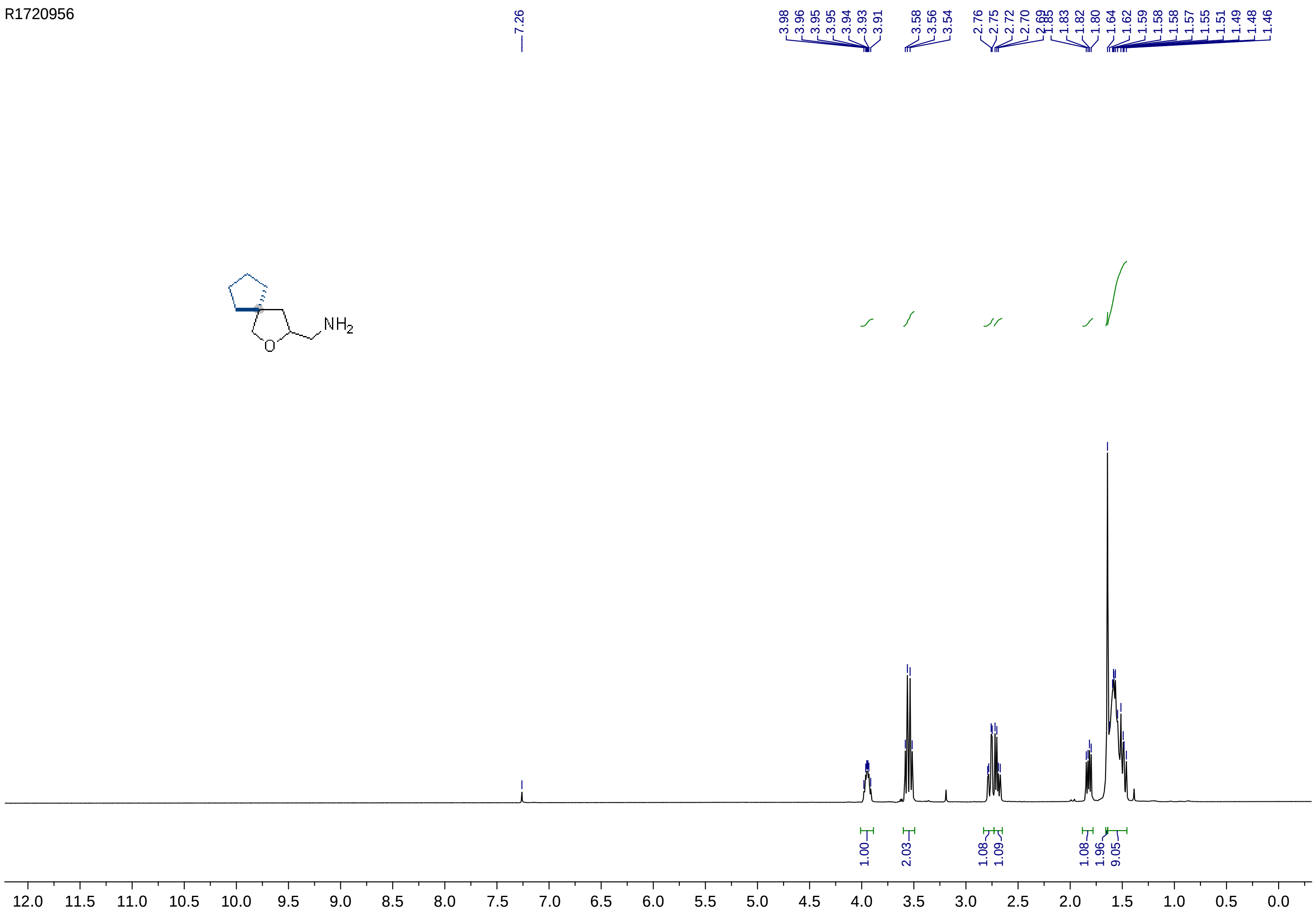

R763978
7.27
3.96 3.94 3.93 3.92 3.91 3.89 3.86 3.84 3.82
2.78 2.77 2.68 2.67 2.65
2.14 2.13
1.85 1.83 1.82 1.46 1.41
Boc
N
O
NH2
2.10 5.22 1.00 1.08 1.03 0.98 1.99 9.21
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

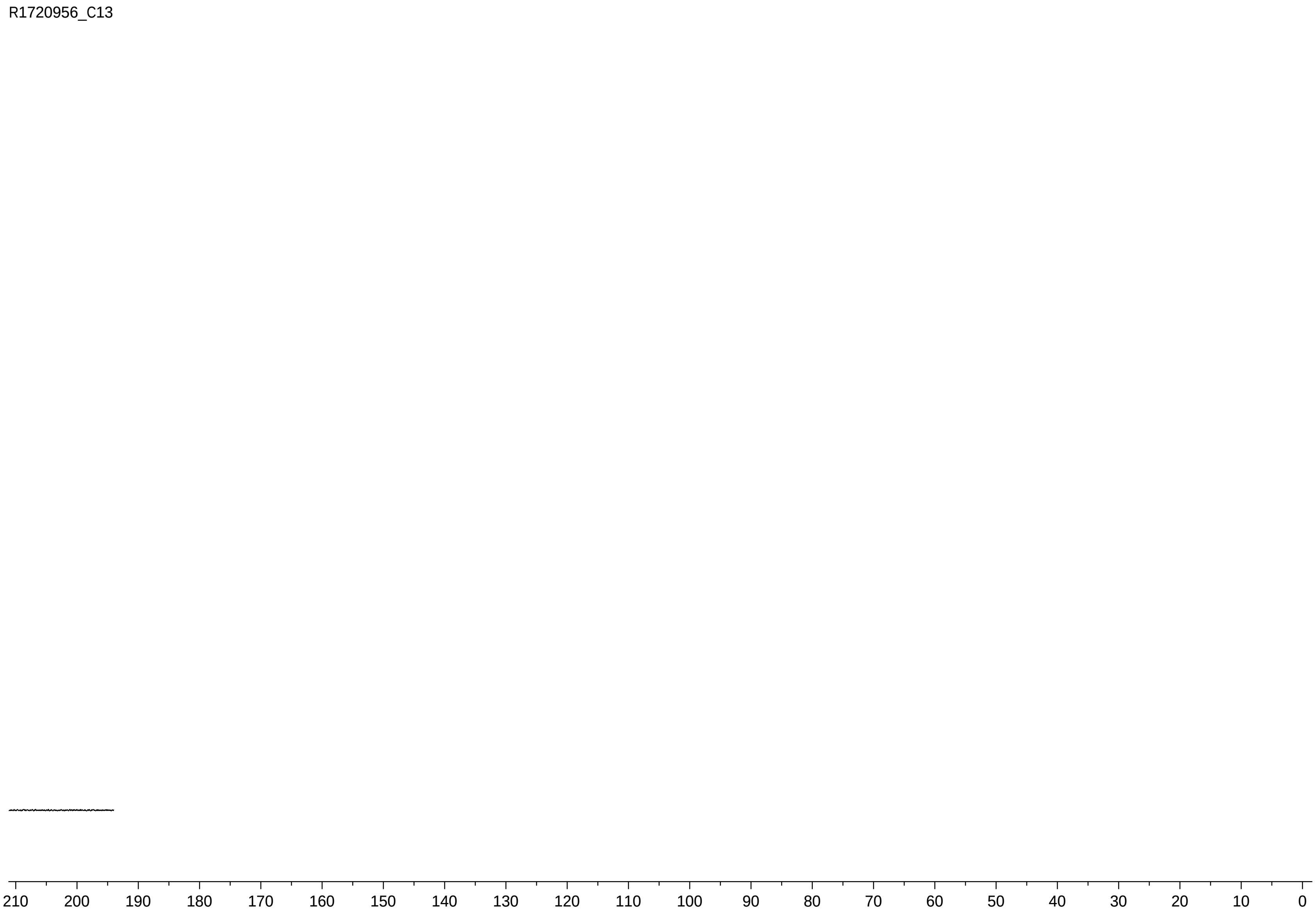
R763978_C13



156.26
80.64
79.67
77.16
77.05
59.17
46.20
40.74
40.60
28.43
Boc
N
O
NH2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 9b




R1720956_C13
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
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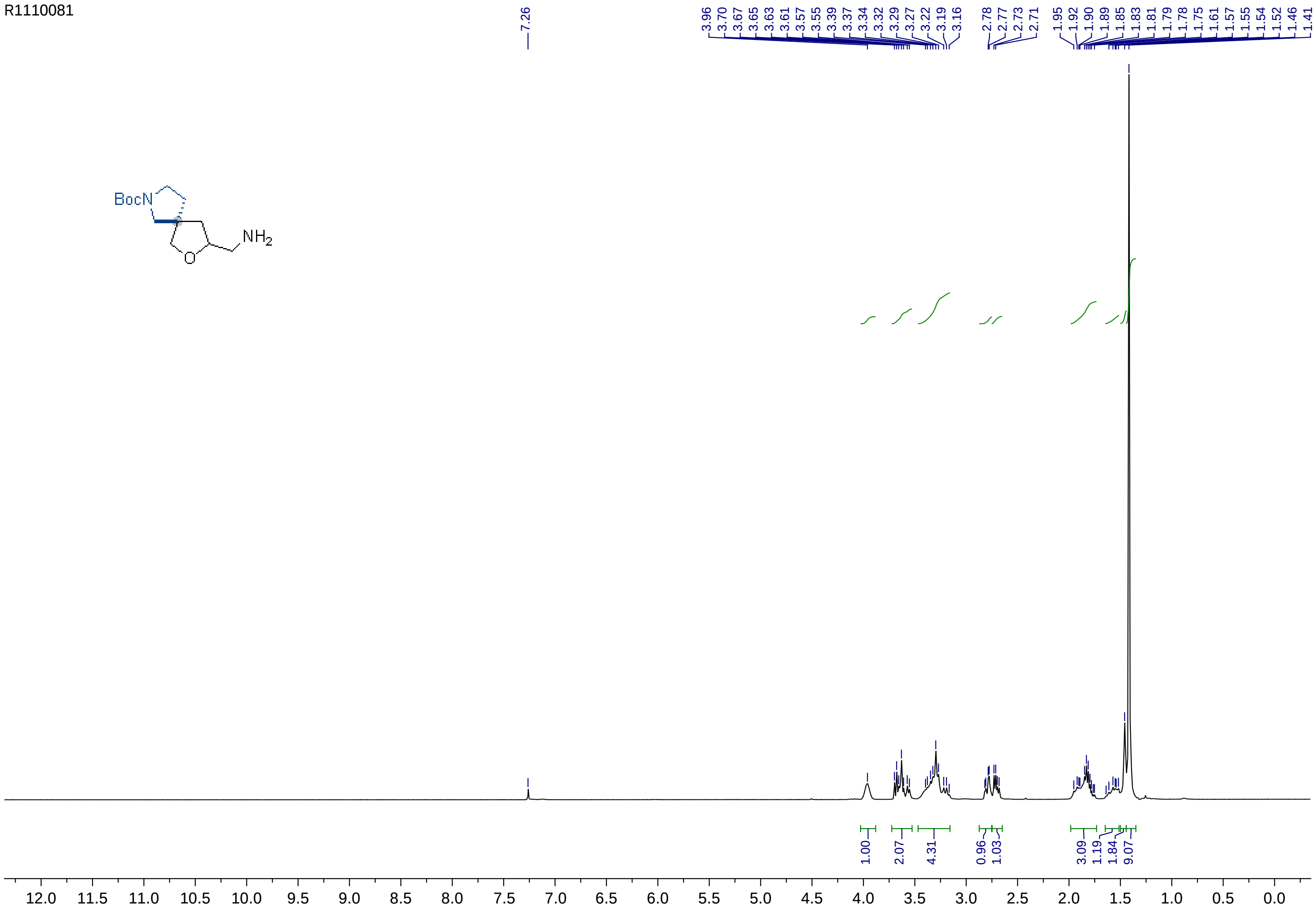
20
10
0

Compound 10b




R1110081_C13
210
200
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180
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160
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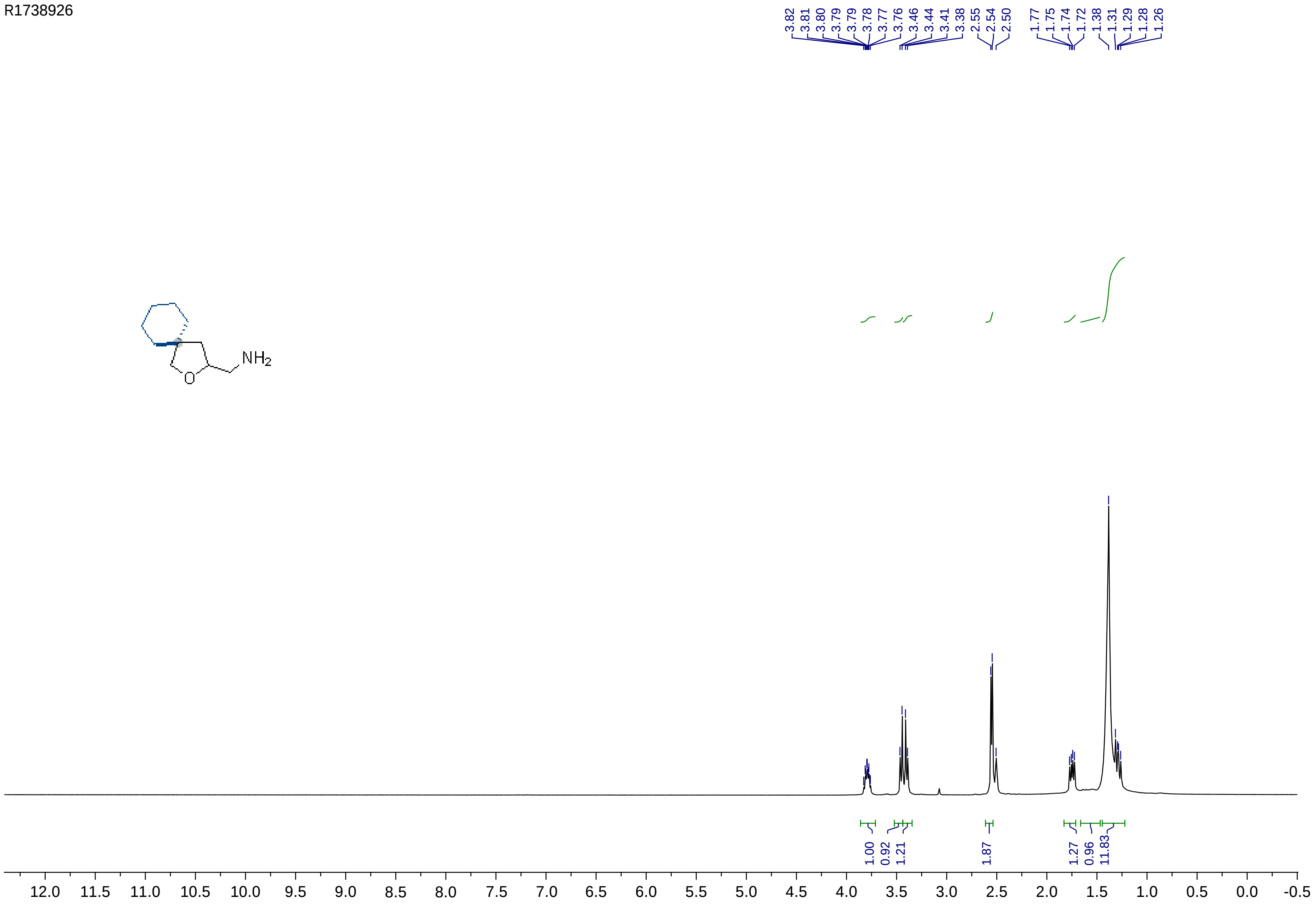
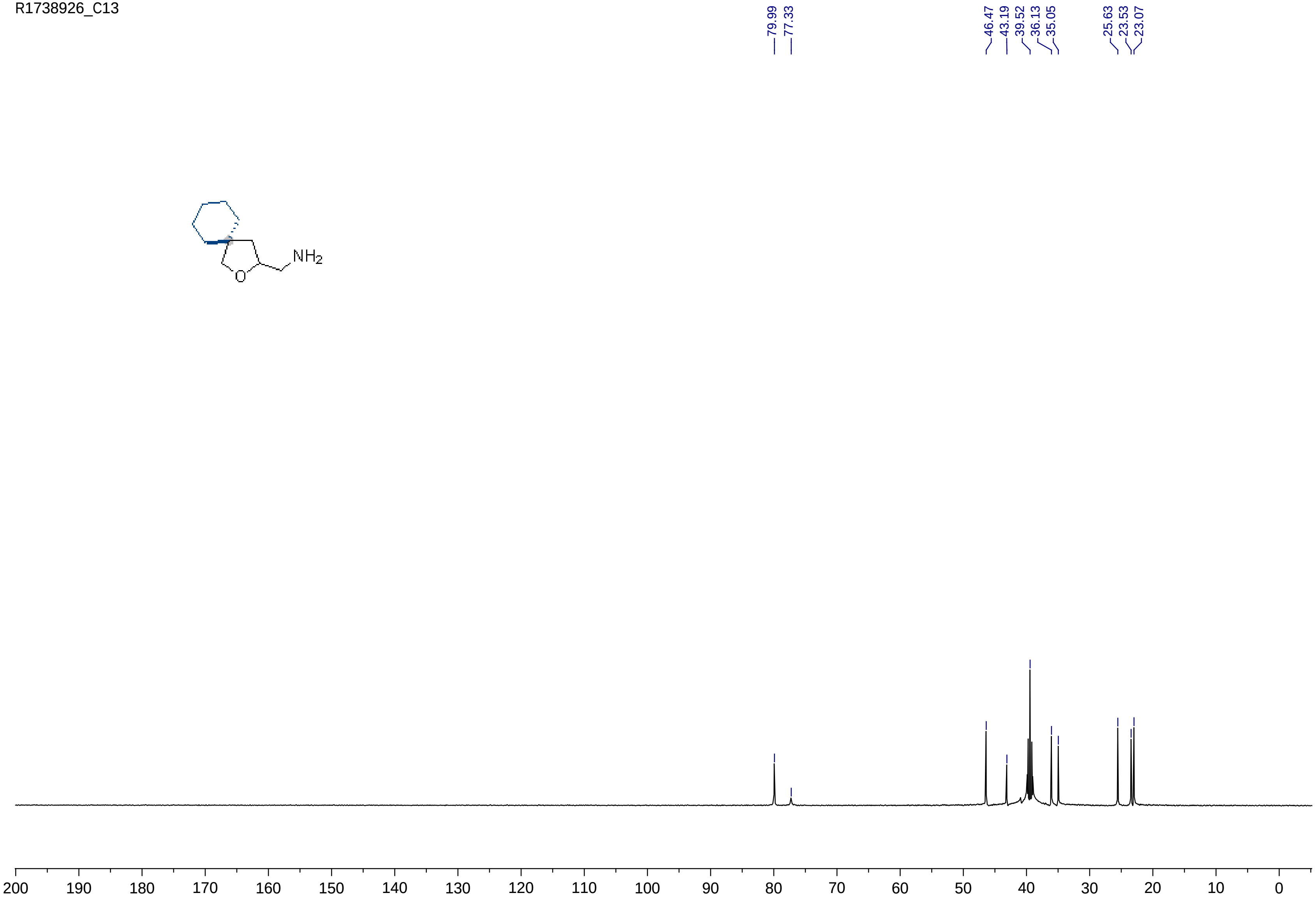
130
120
110
100
90
80
70
60
50
40
30
20
10
0

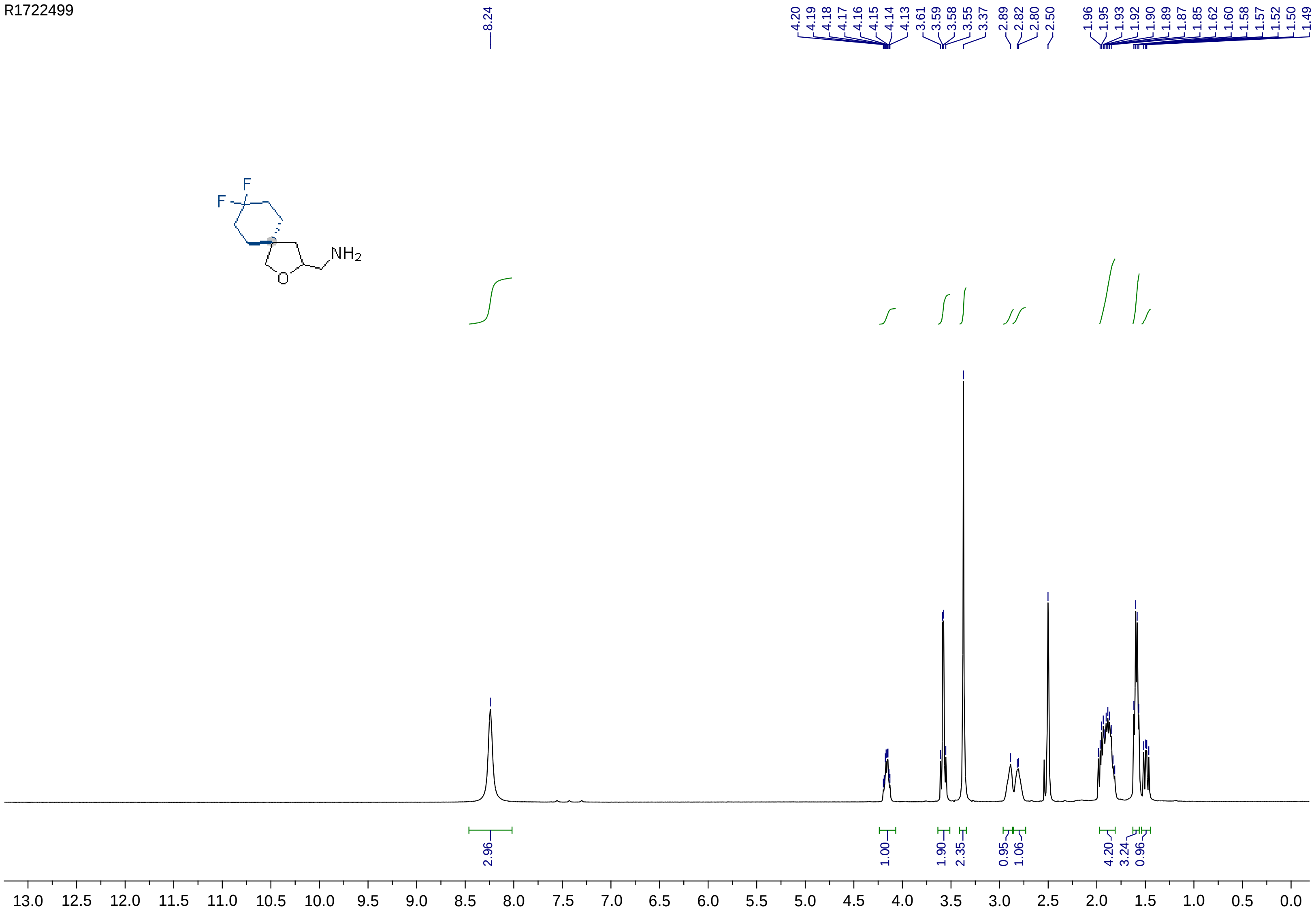
Compound 11b



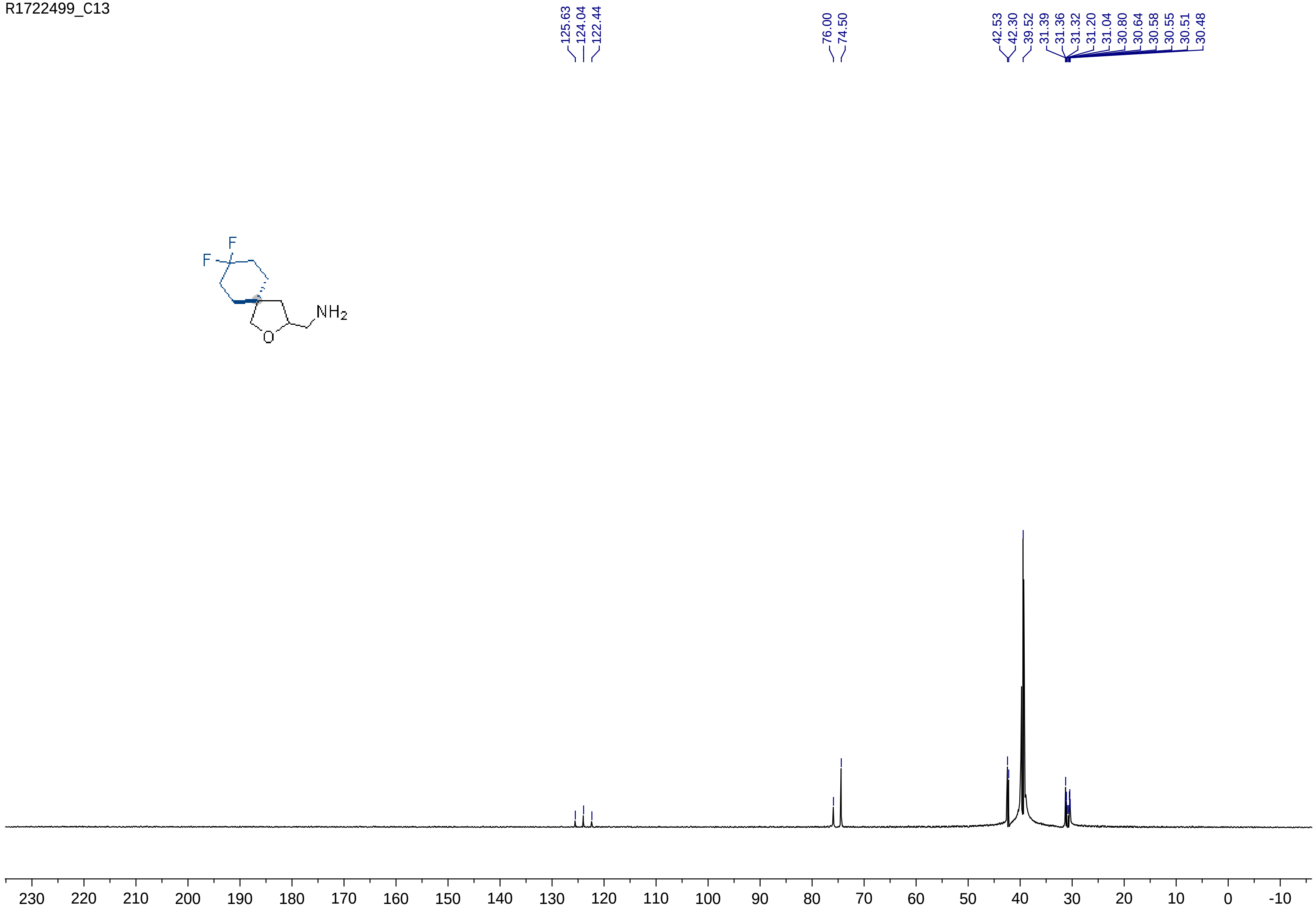
R1738926_C13



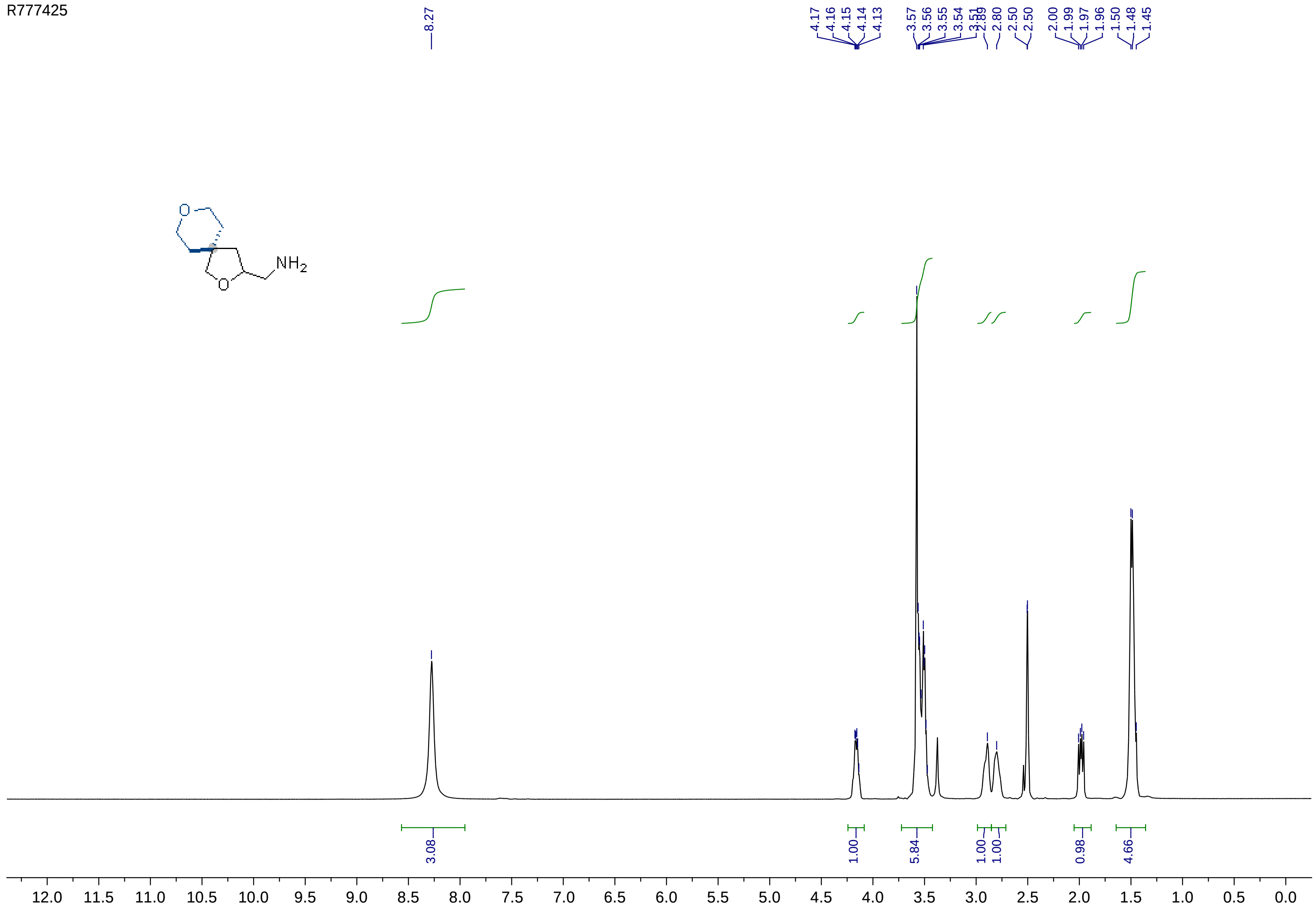
Compound 12b



R1722499_C13

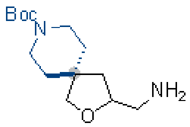


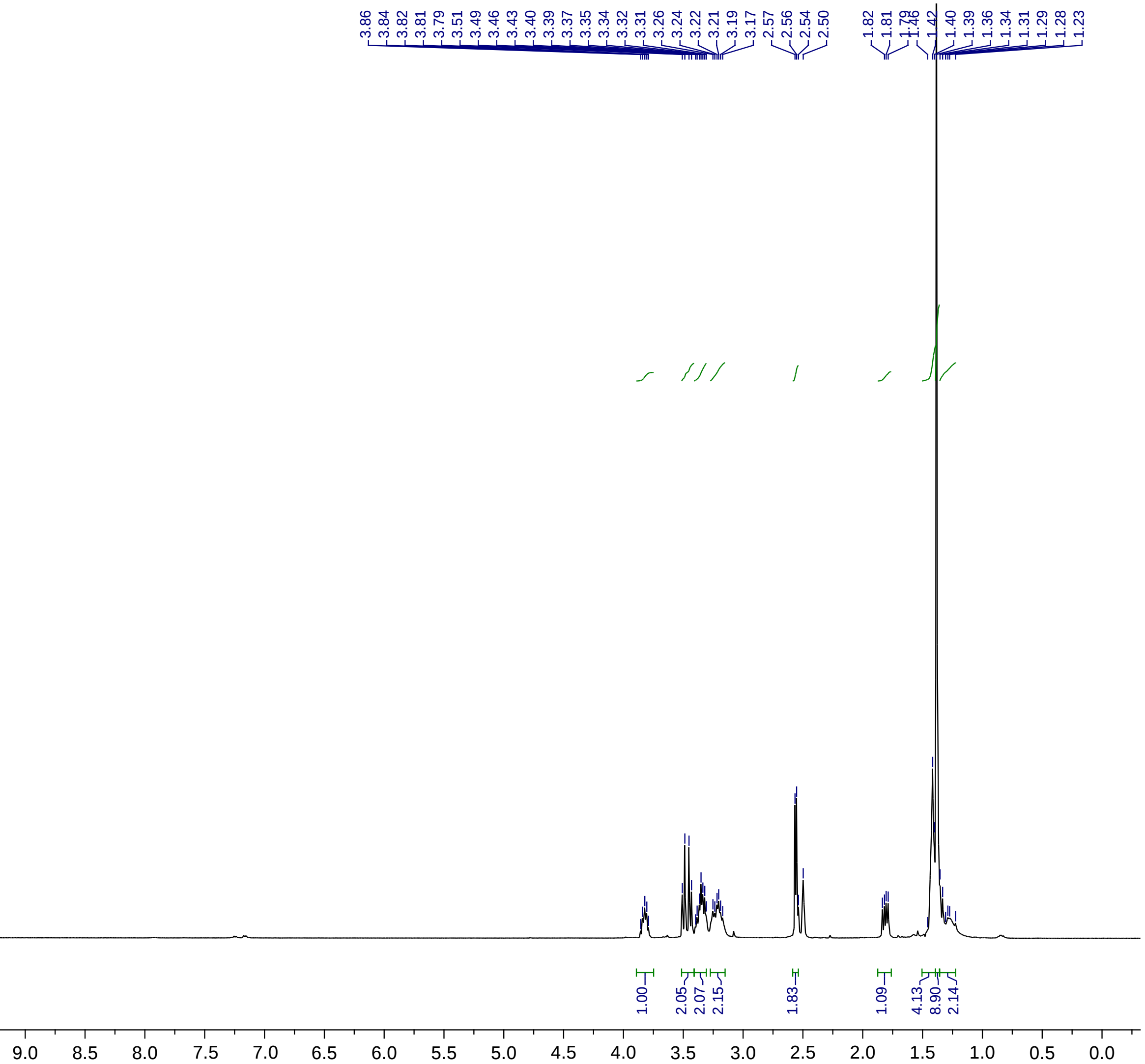
Compound 13b



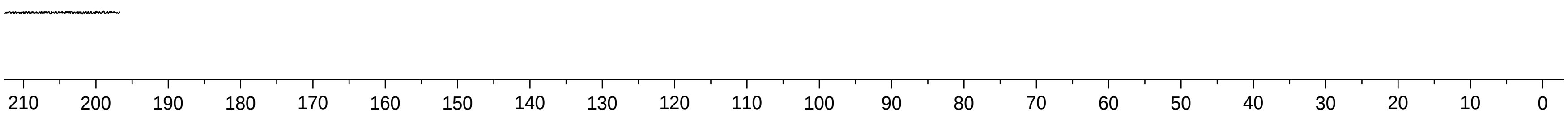

R777425_13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 14b

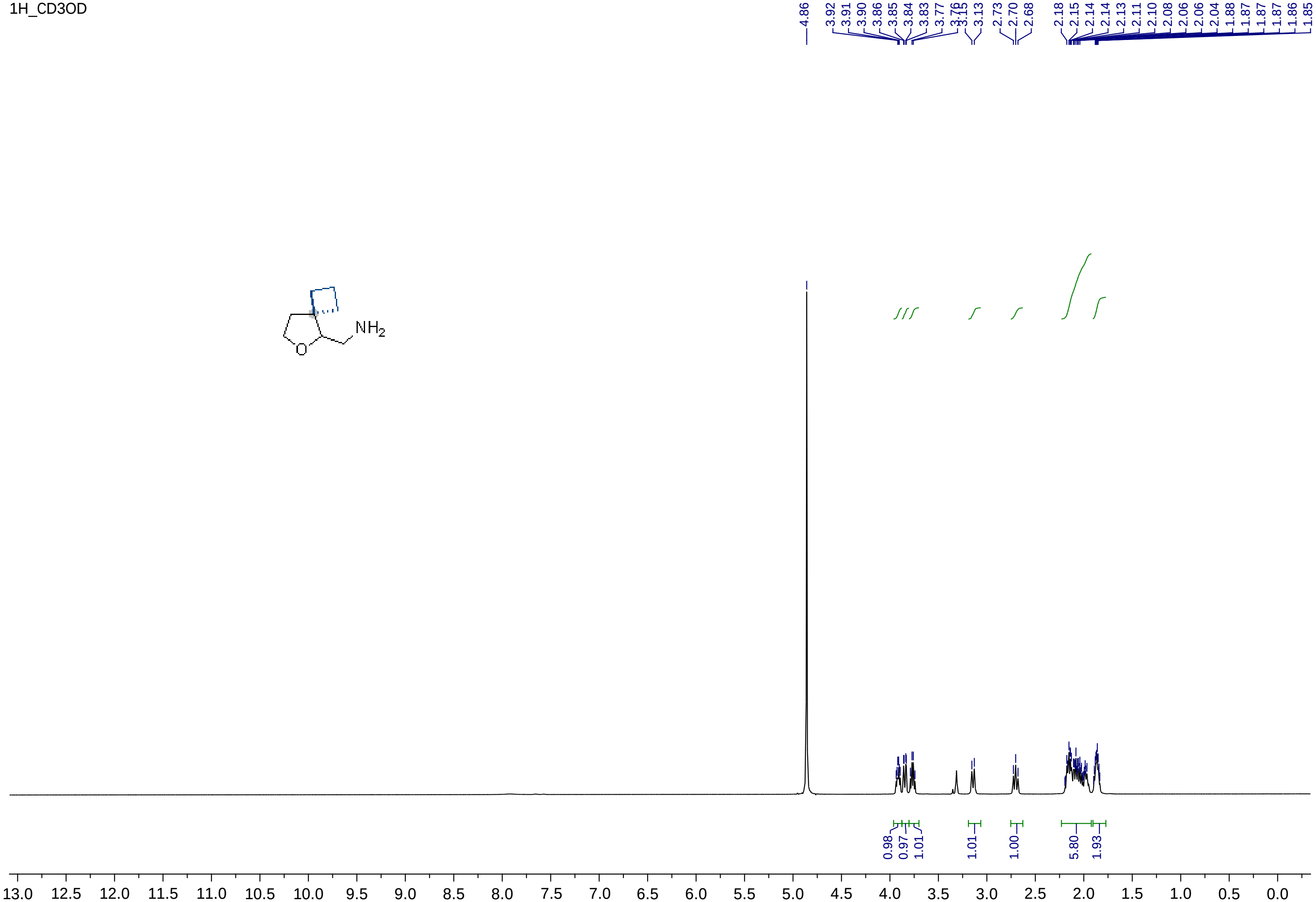


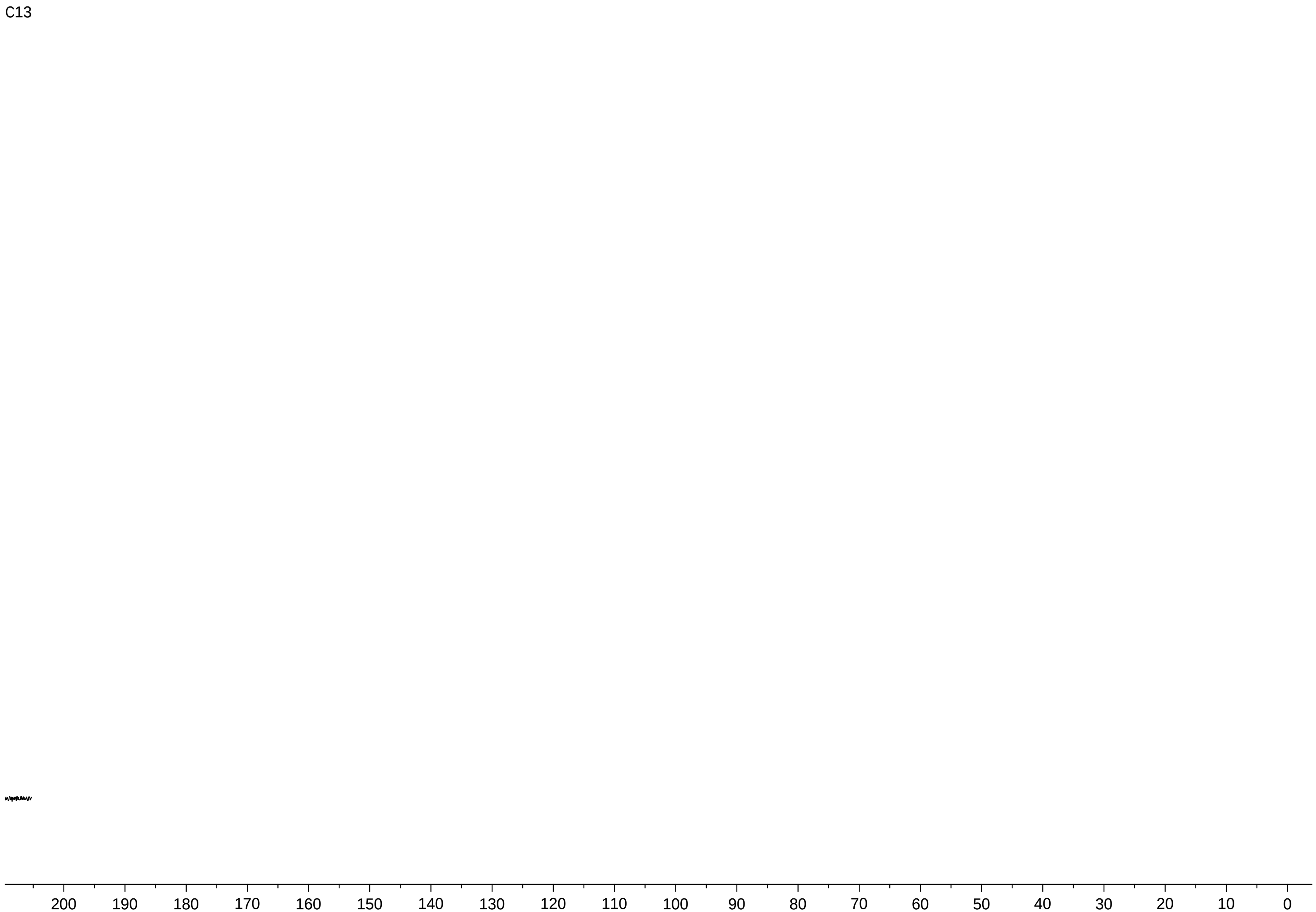


R840260_C13

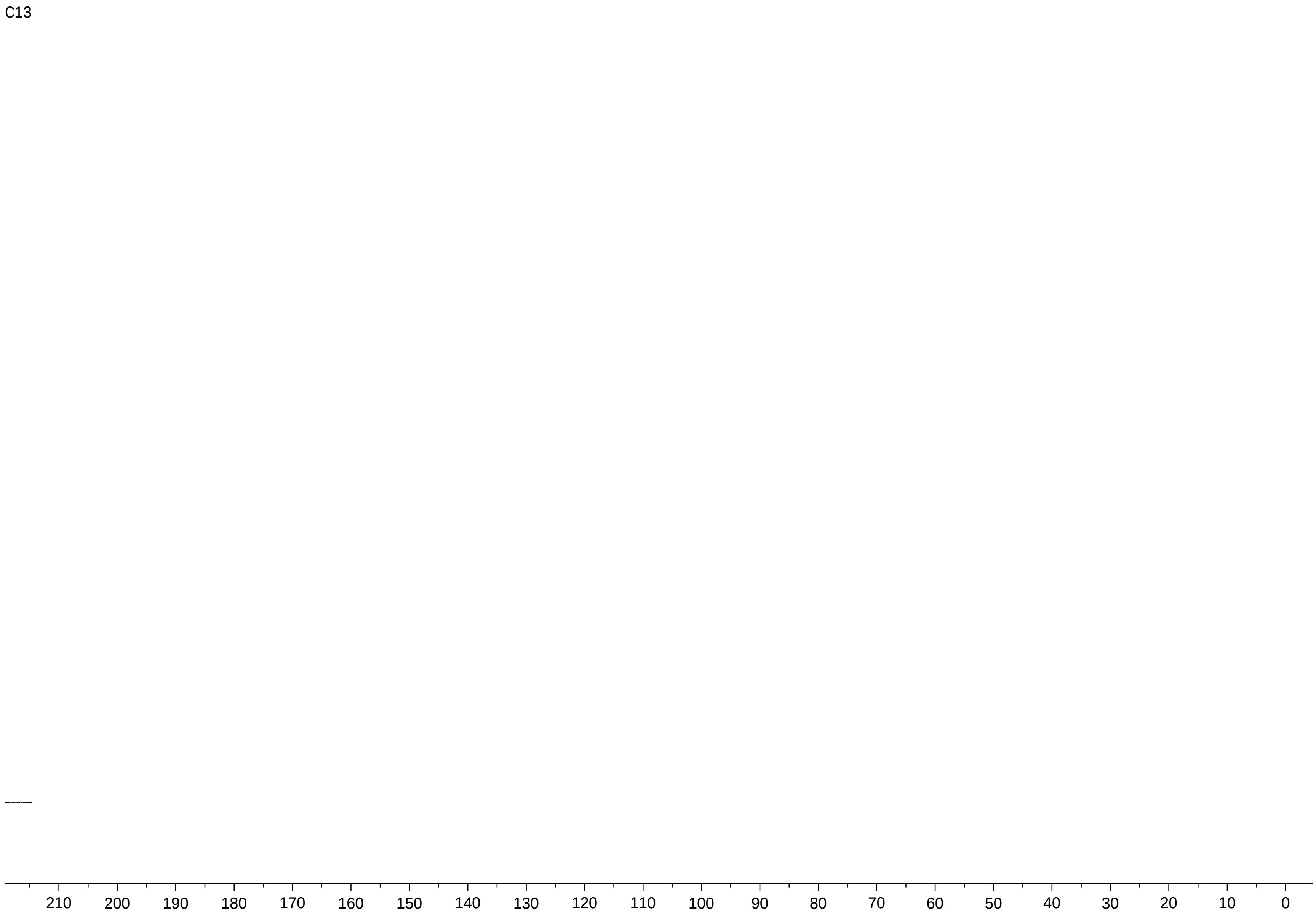

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 15b

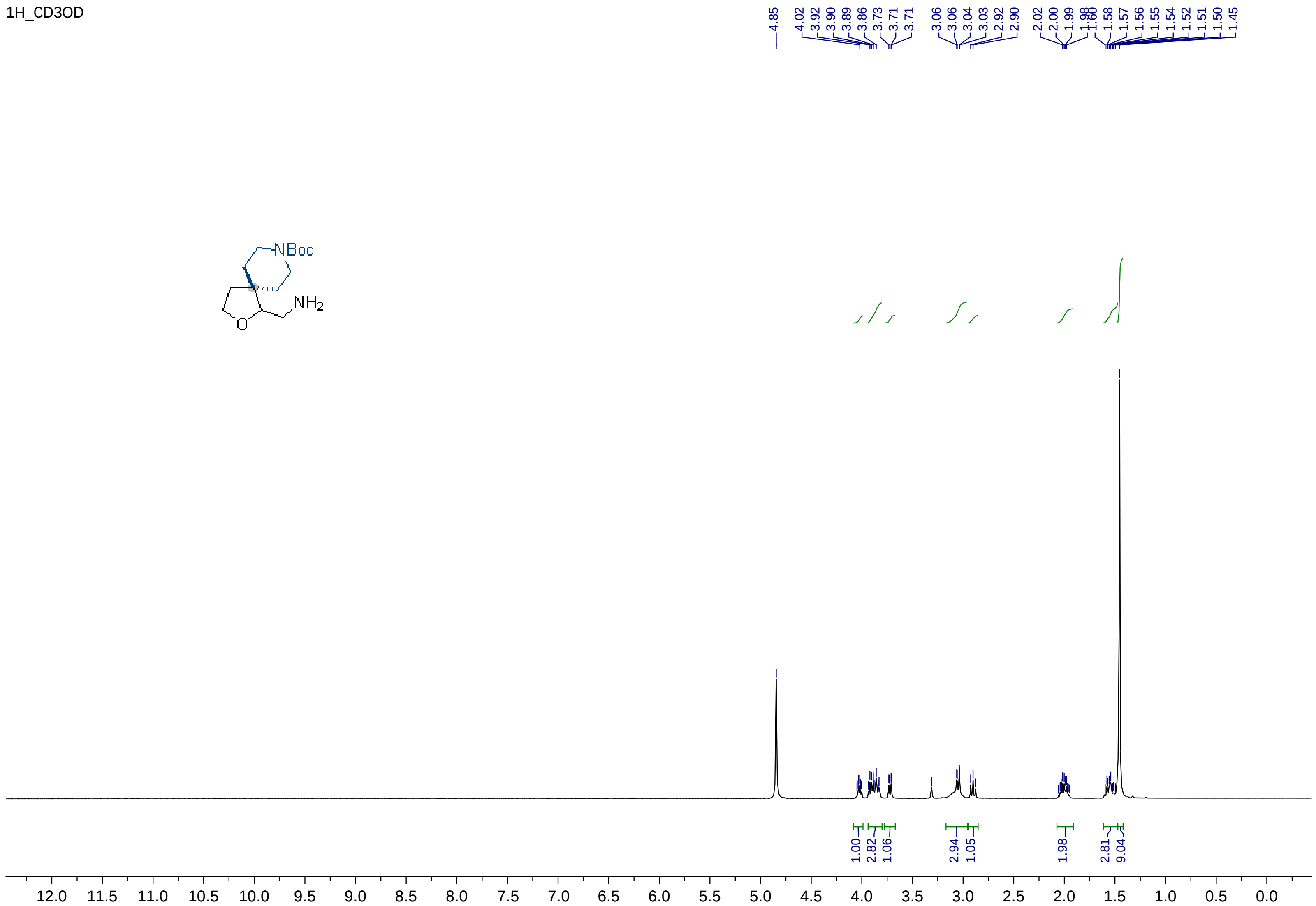



C13
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 16b

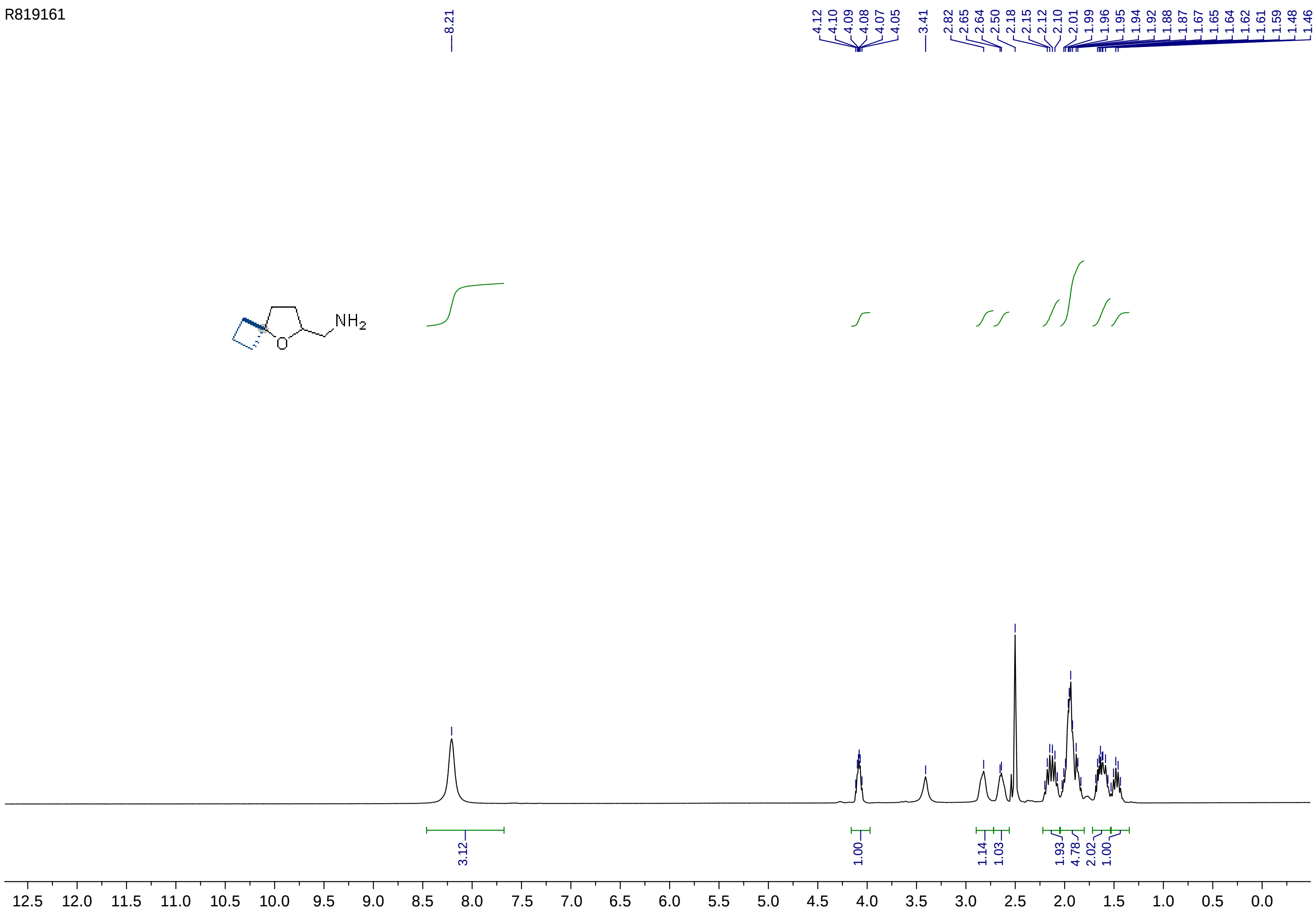

C13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 17b



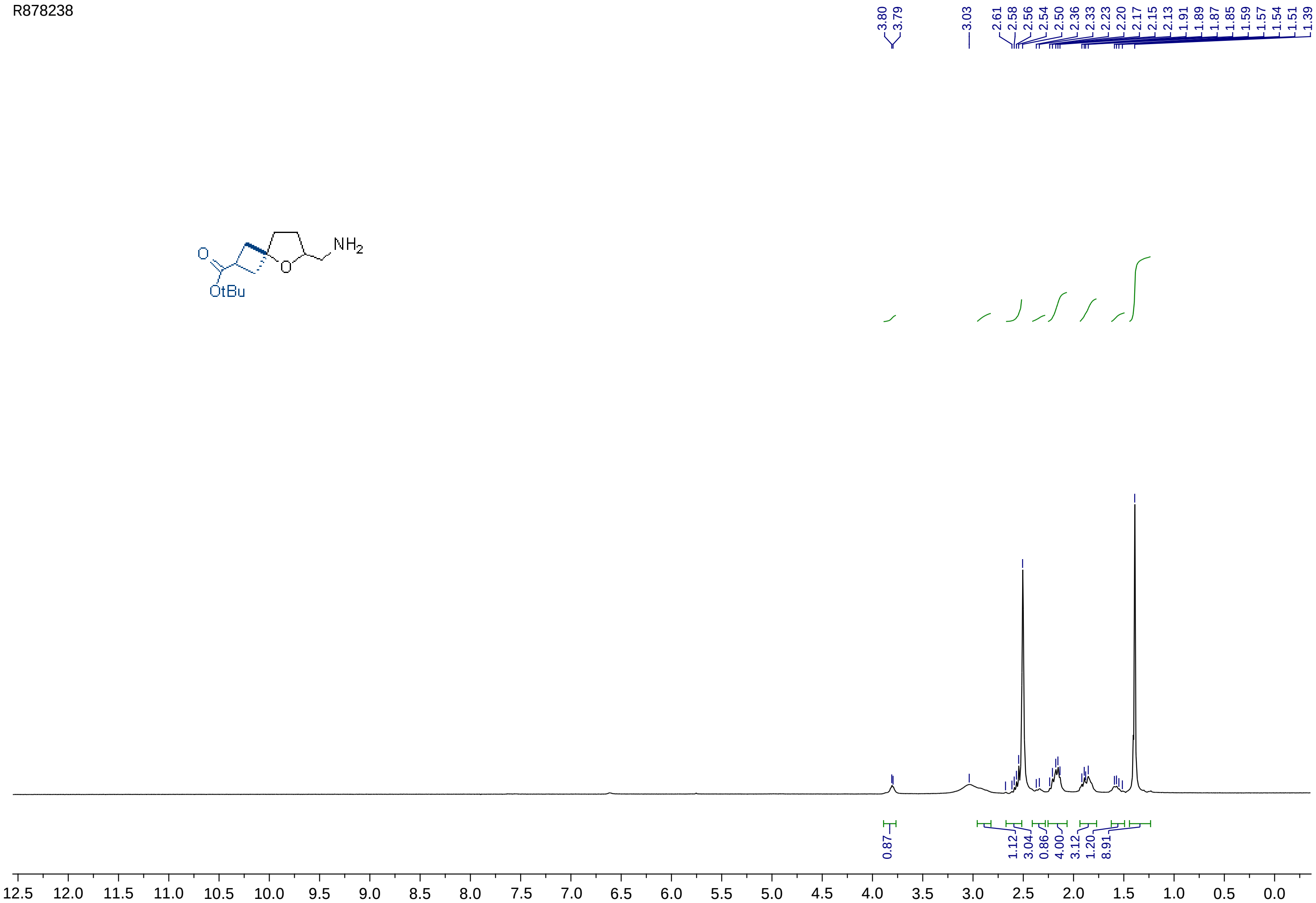

C13
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 18b

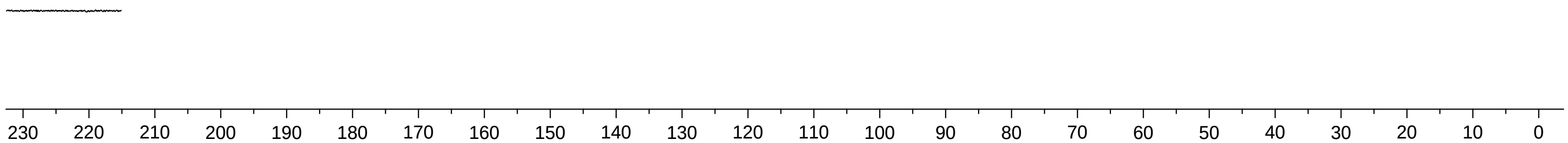



R819161_C13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

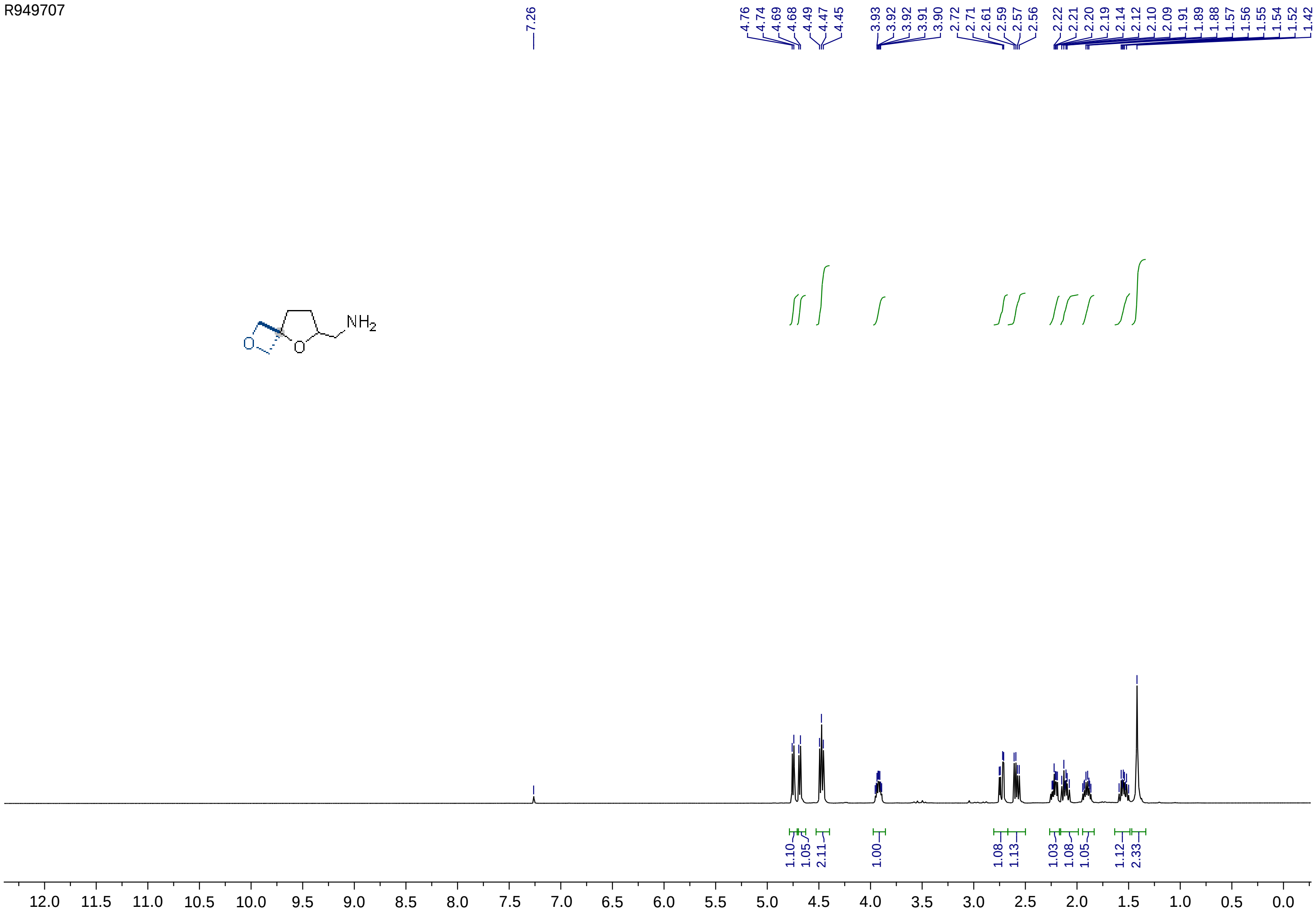
Compound 19b



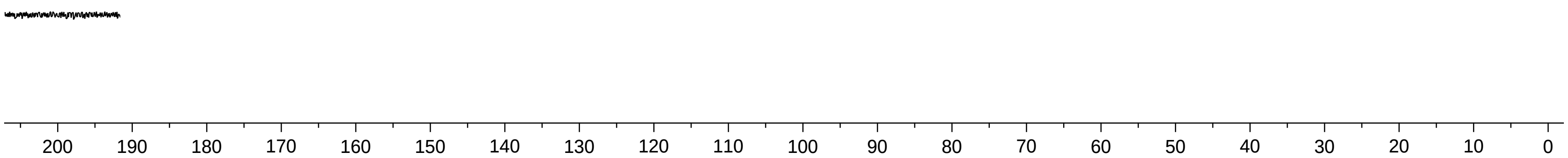
R878238_13C


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

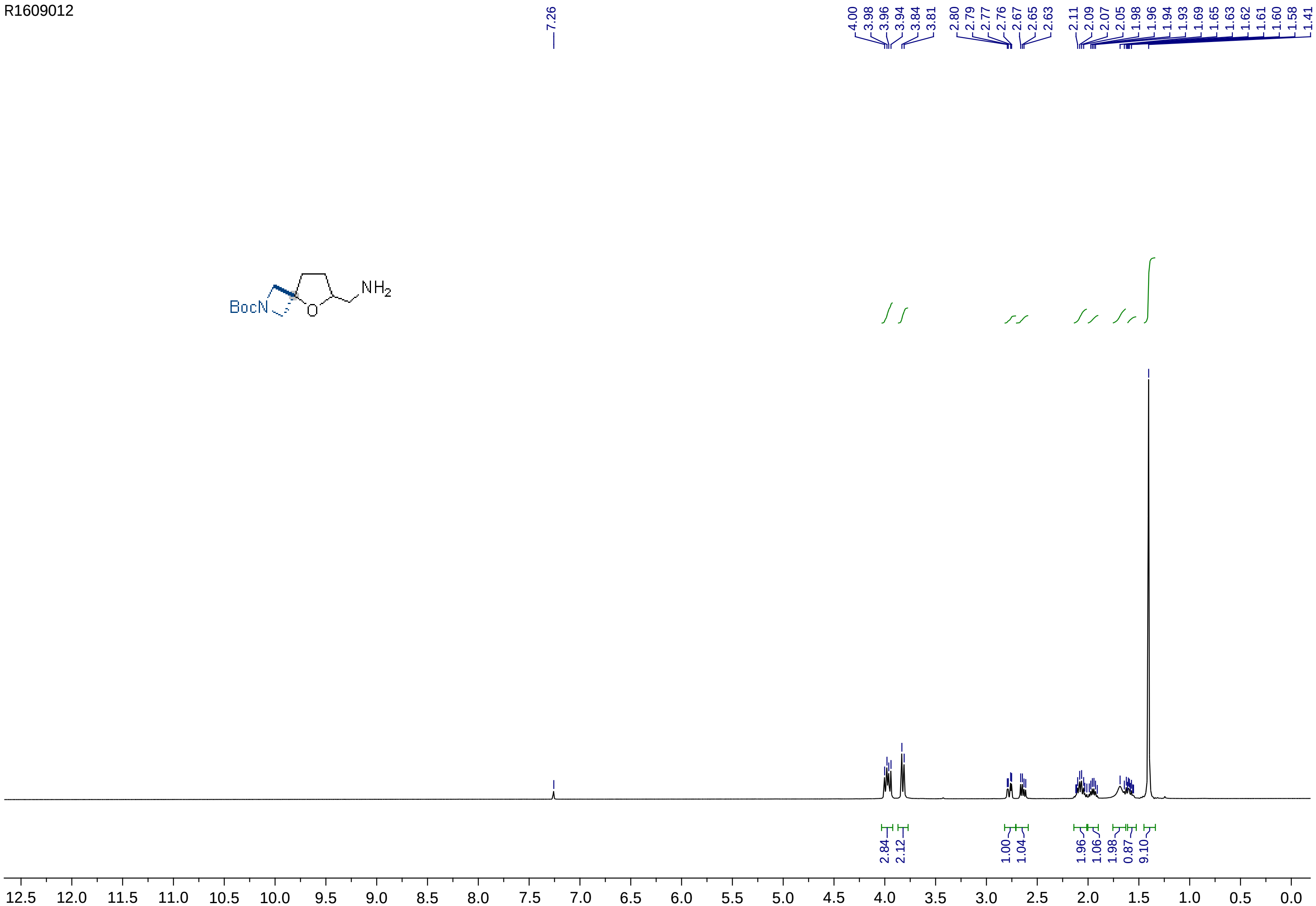
Compound 20b



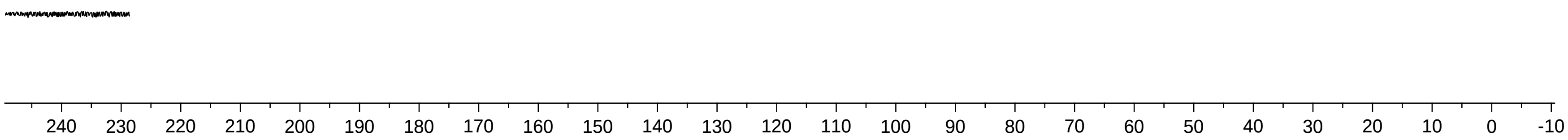
R949707_13C


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

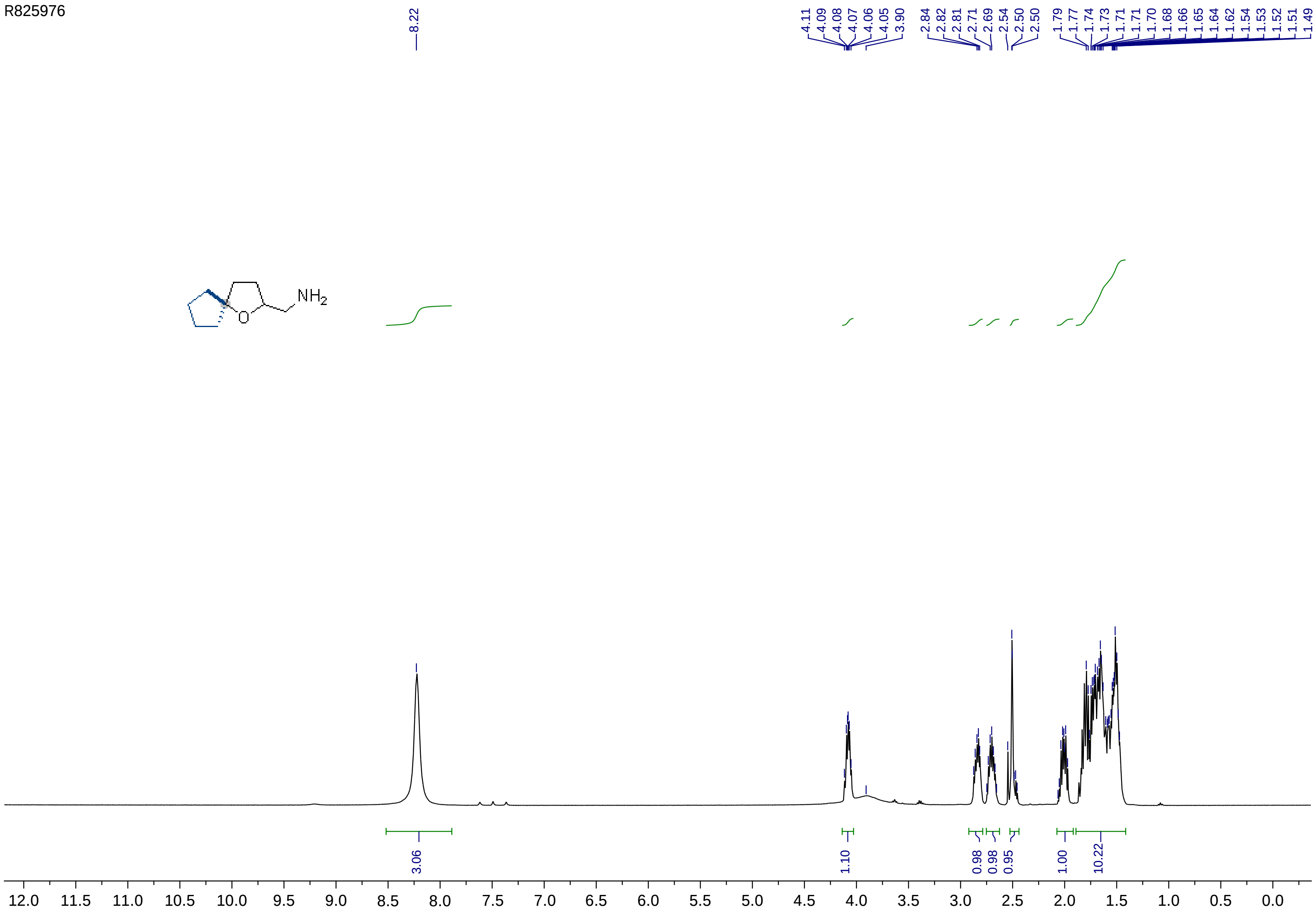
Compound 21b



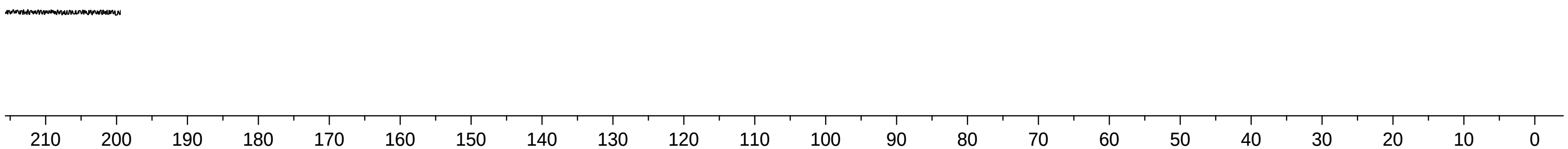
R1609012_C13



Compound 22b



R825976_13C


210
200
190
180
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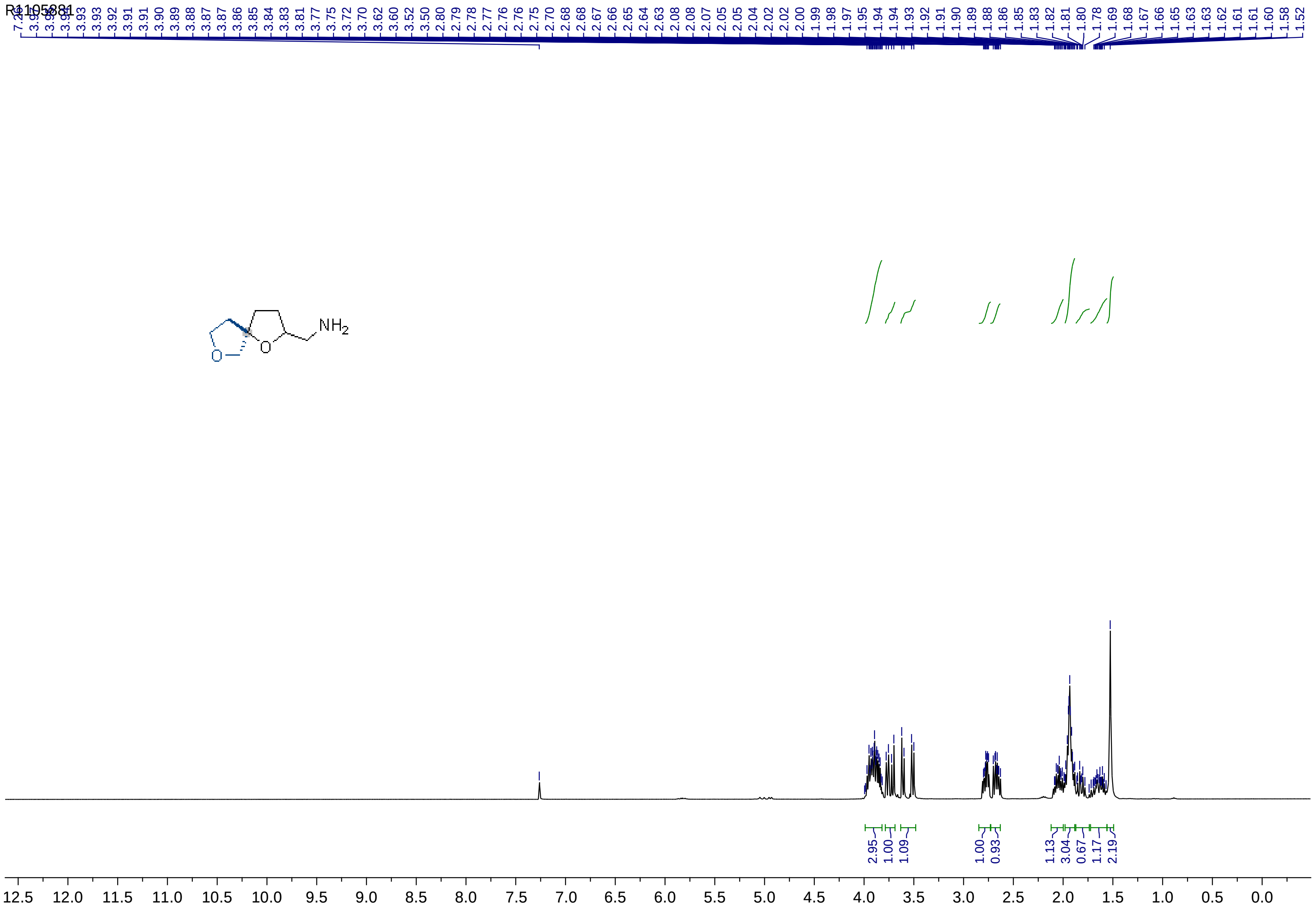
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 23b




R1105881_C13
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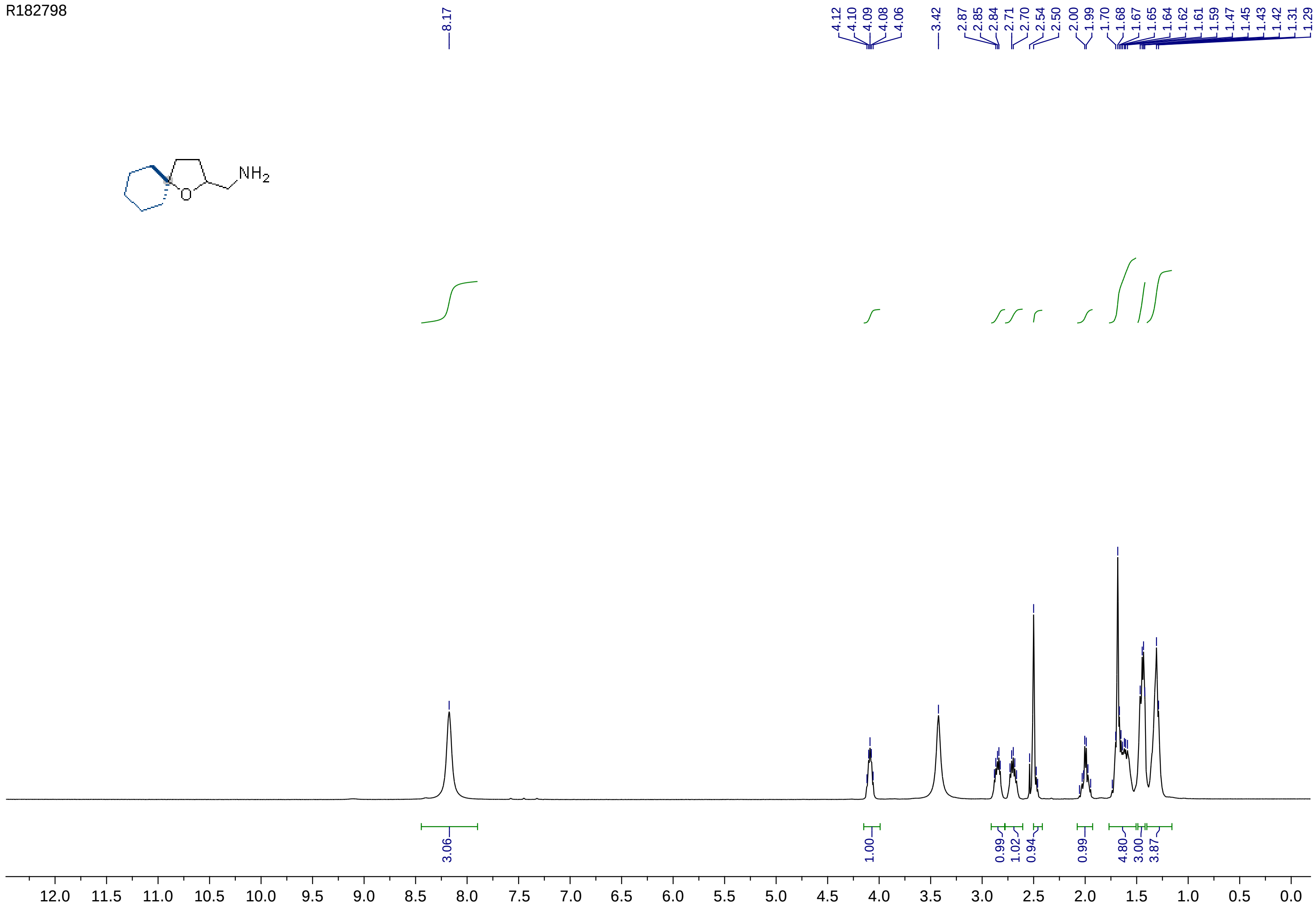
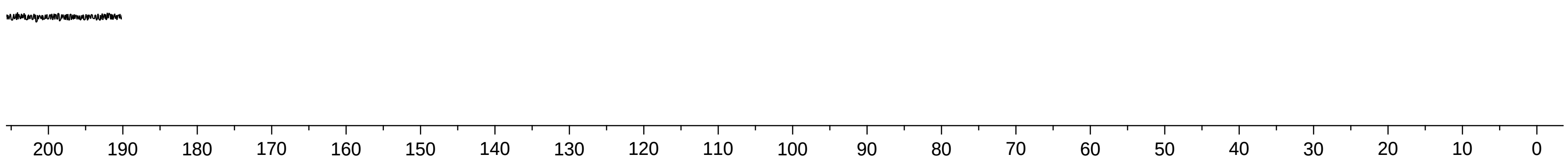
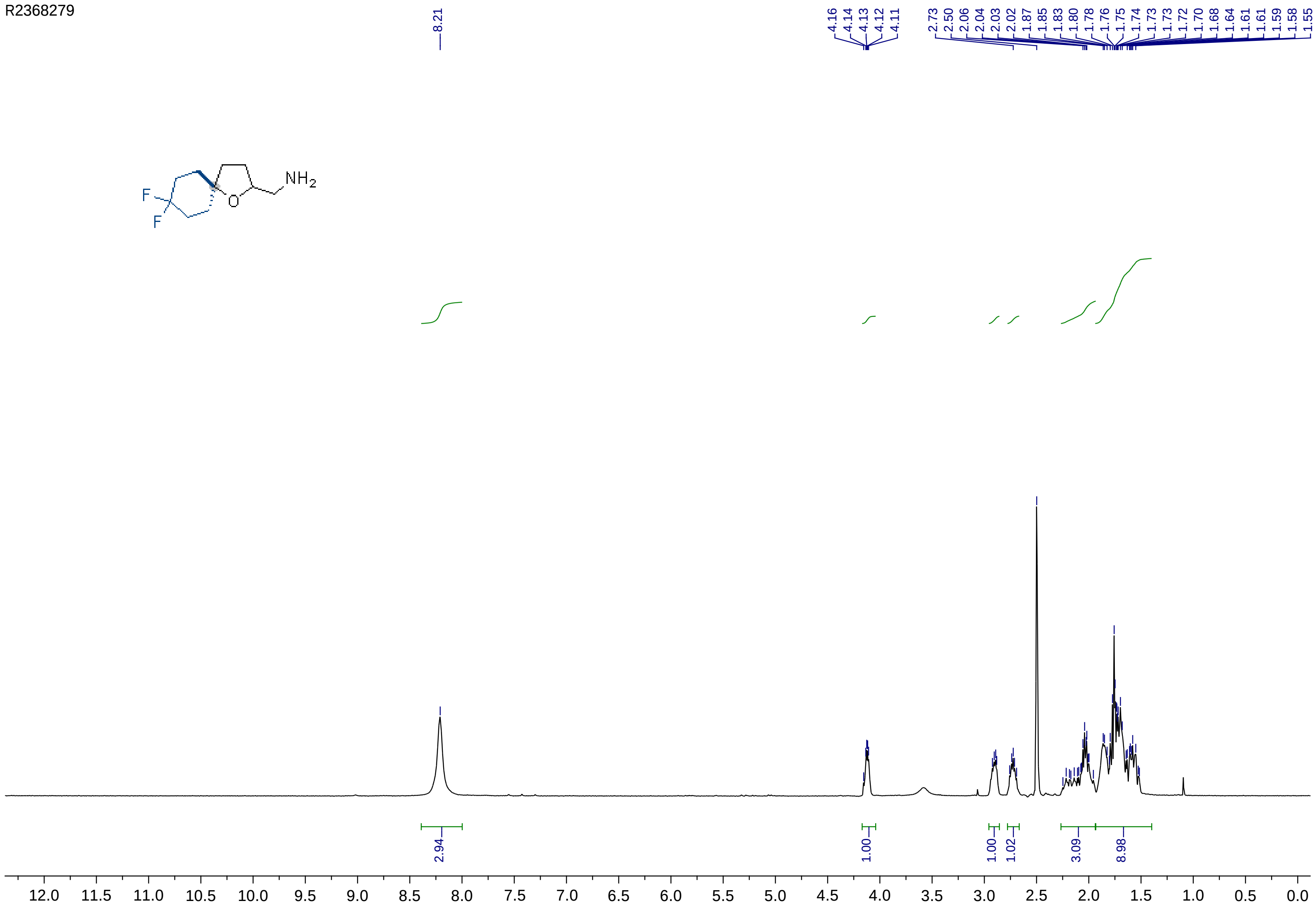
Compound 24b



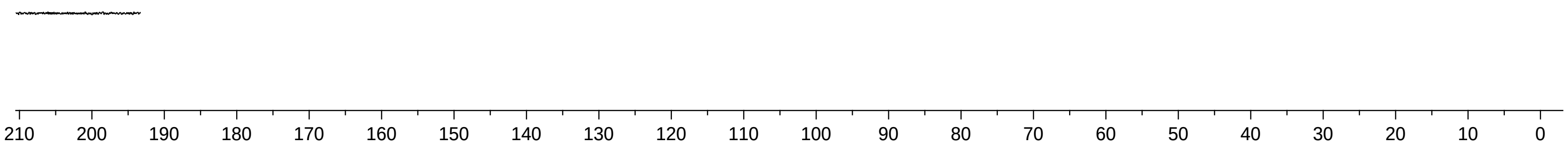
R182798_C13


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

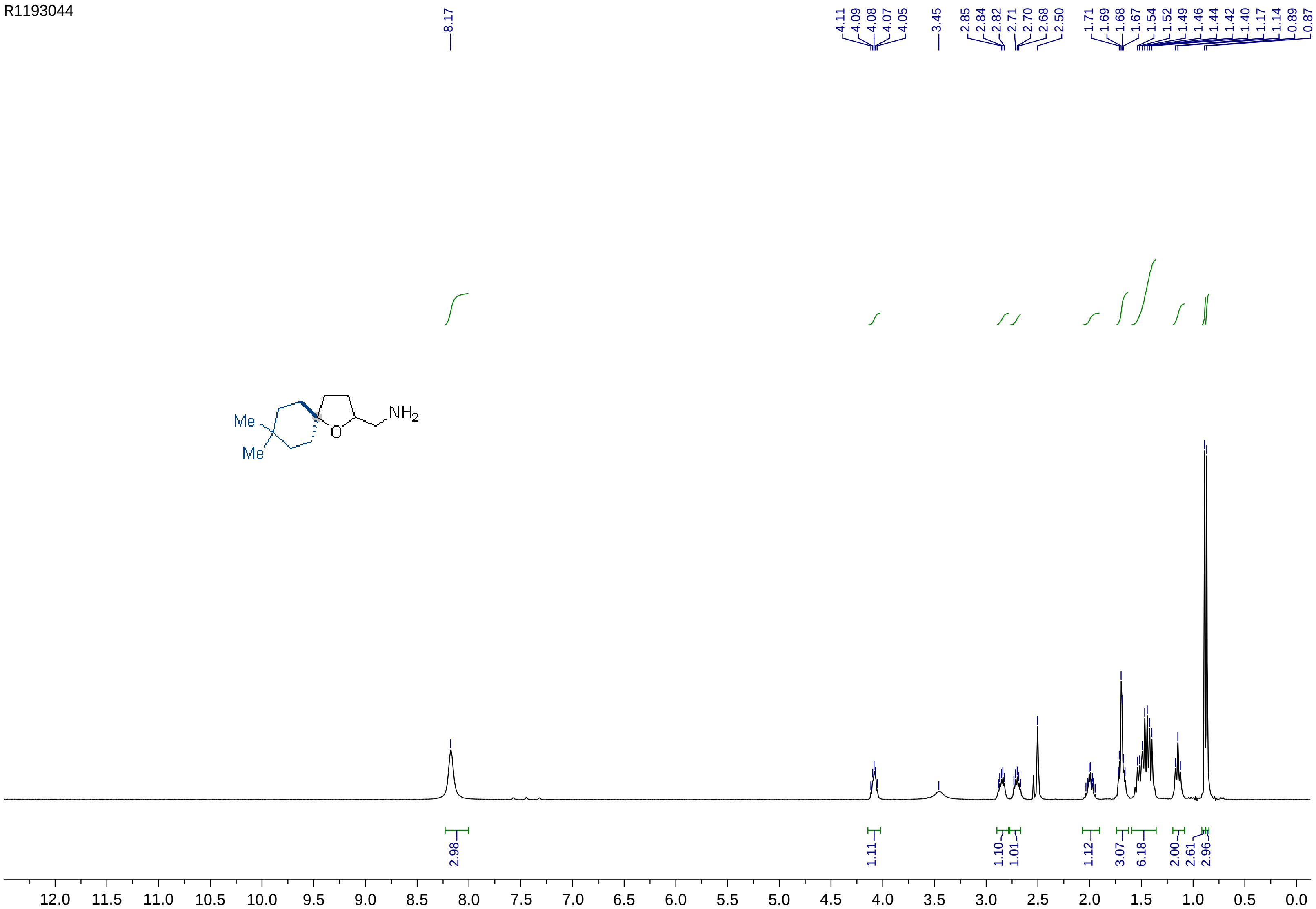
Compound 25b



R2368279_C13

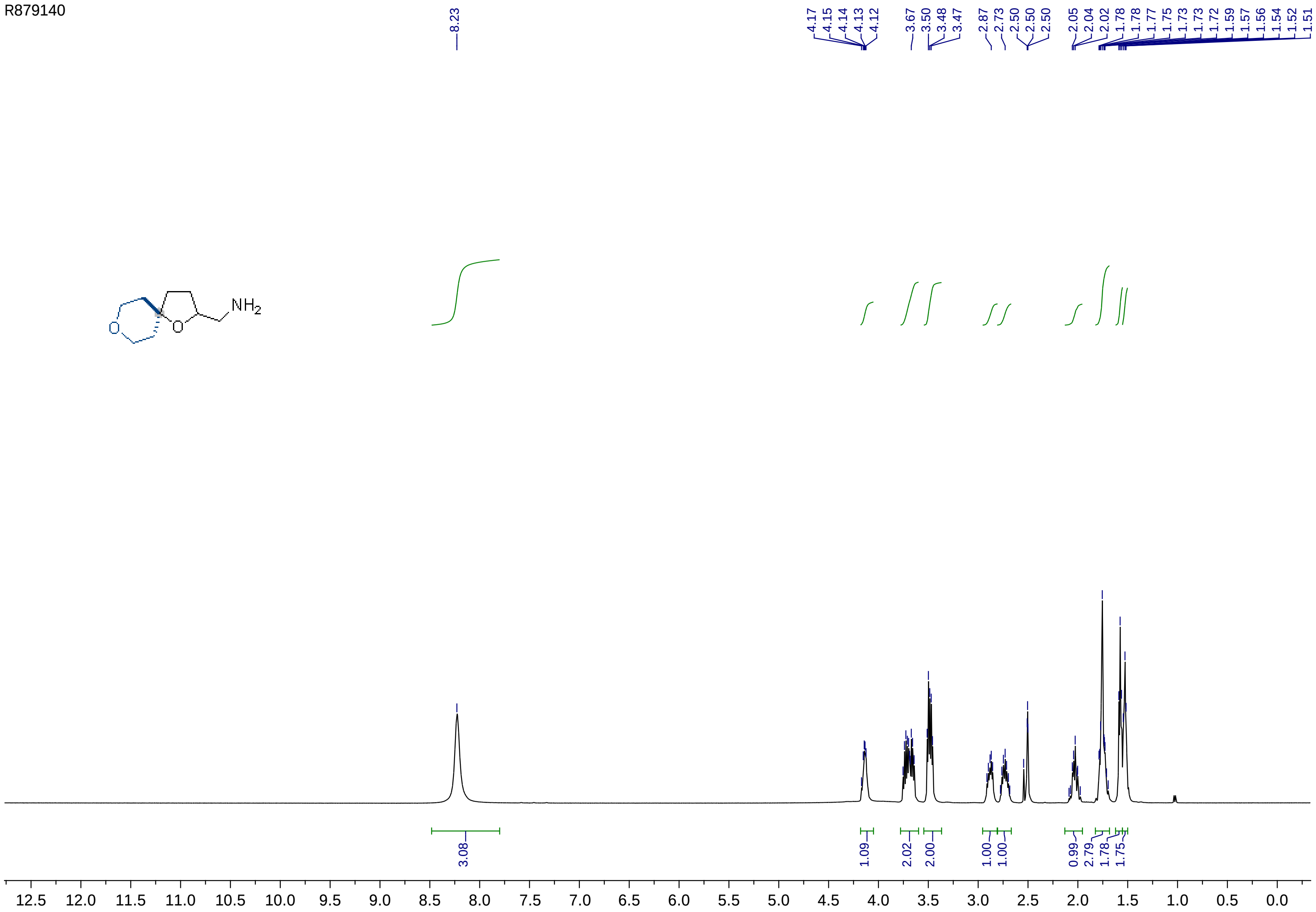


Compound 26b

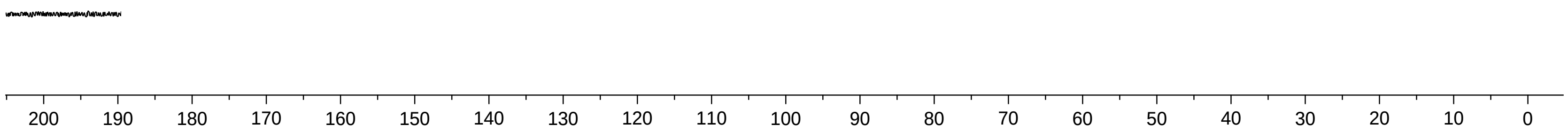



R1193044_13C
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

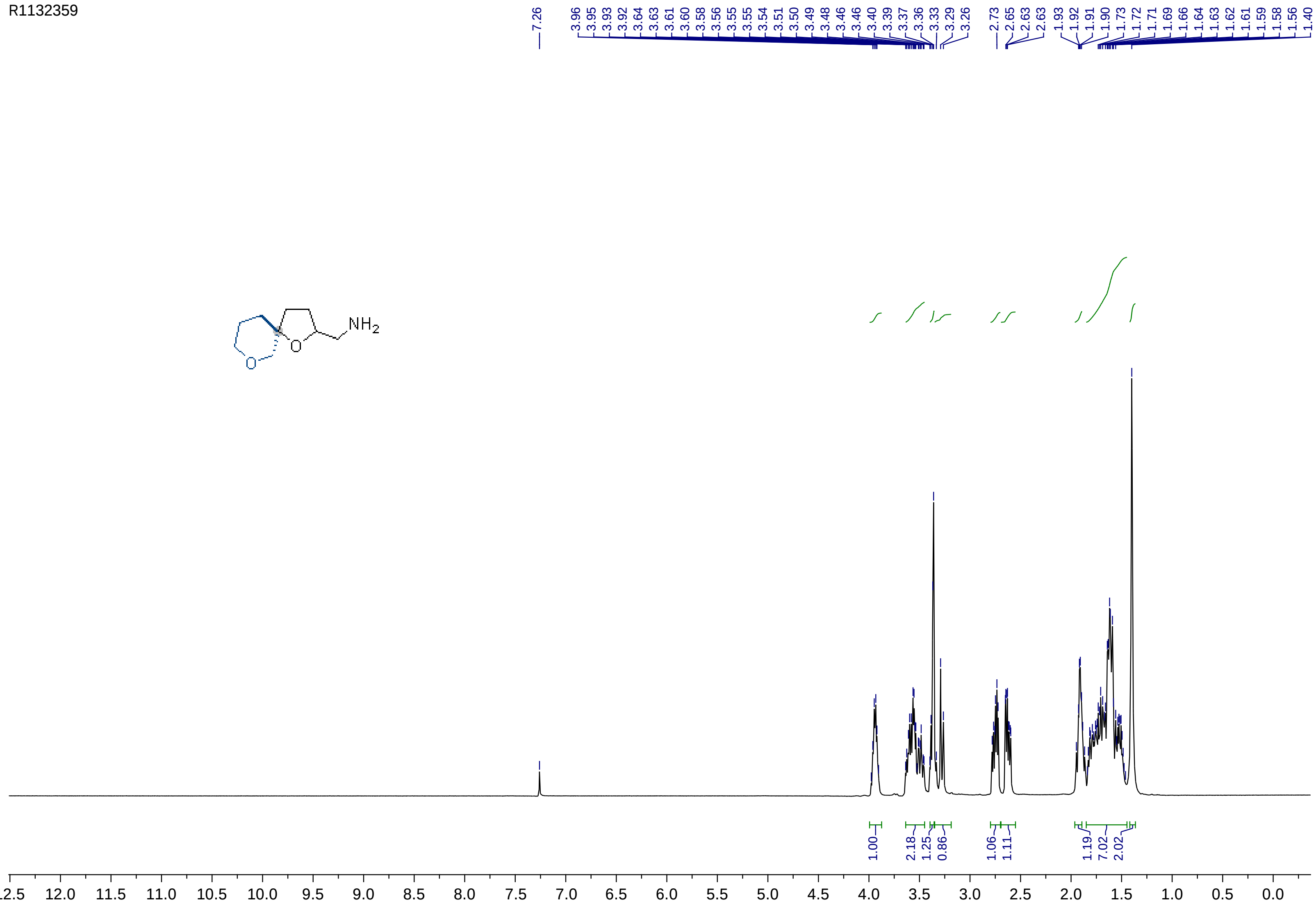
Compound 27b

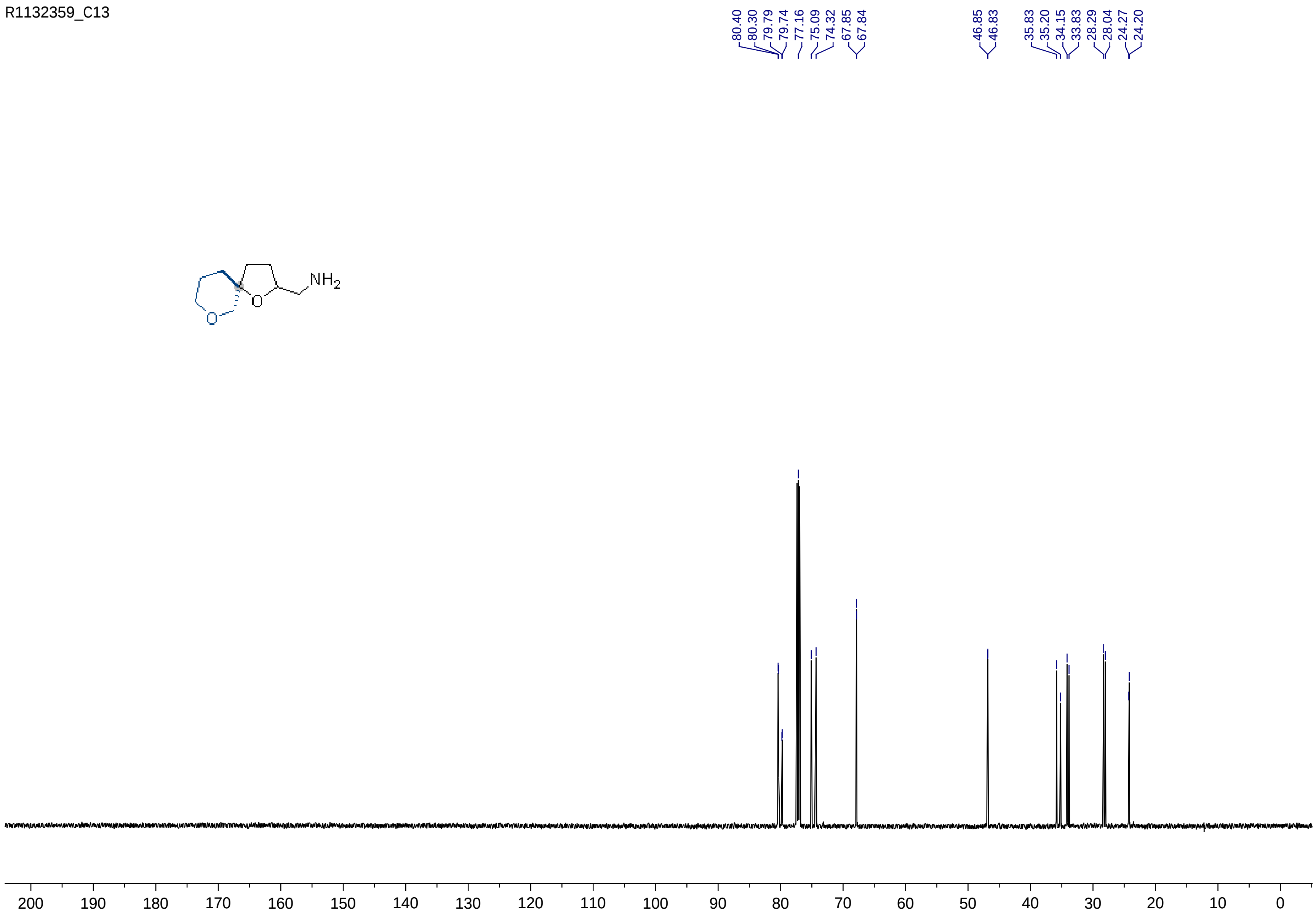


R879140_C13

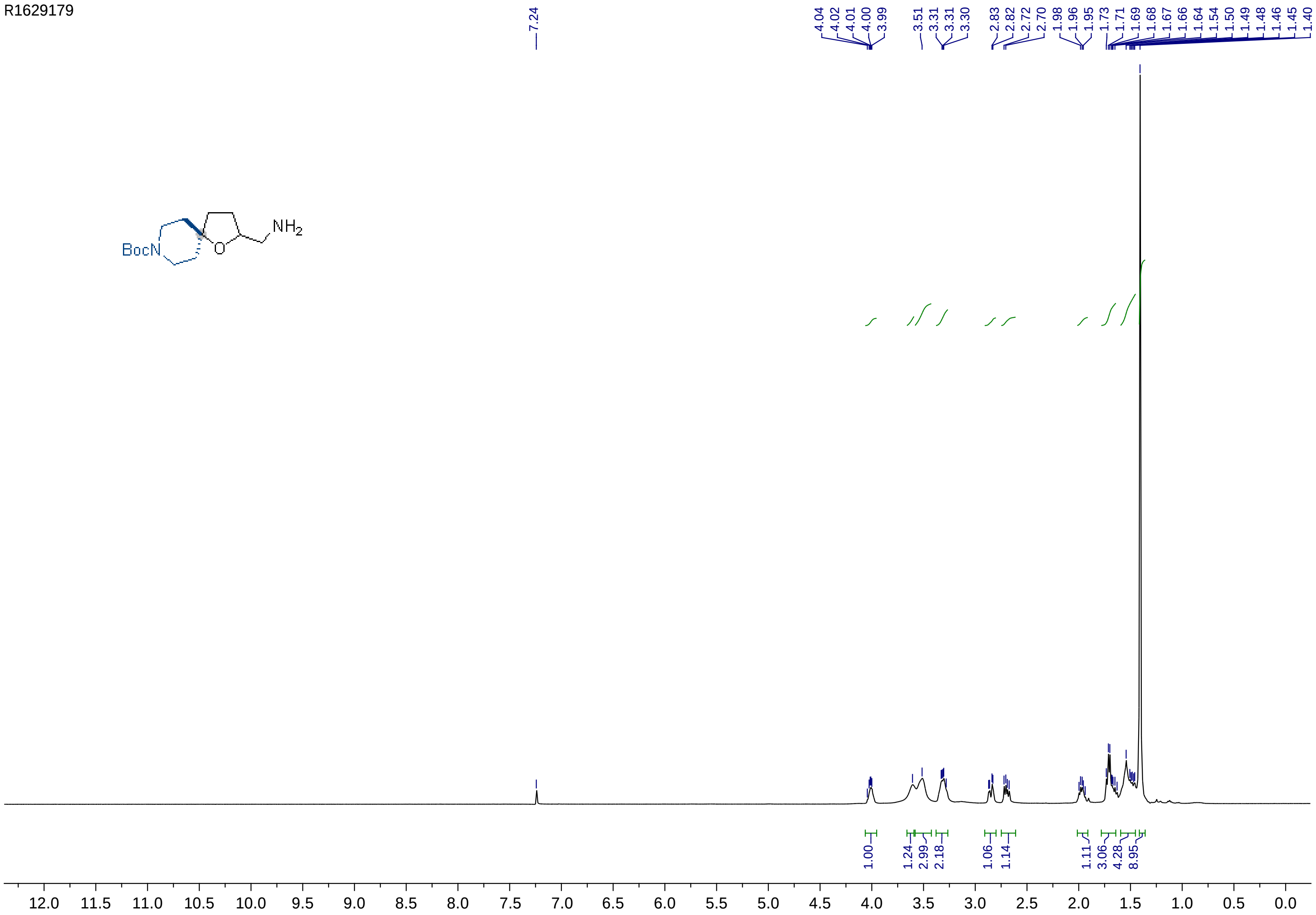

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

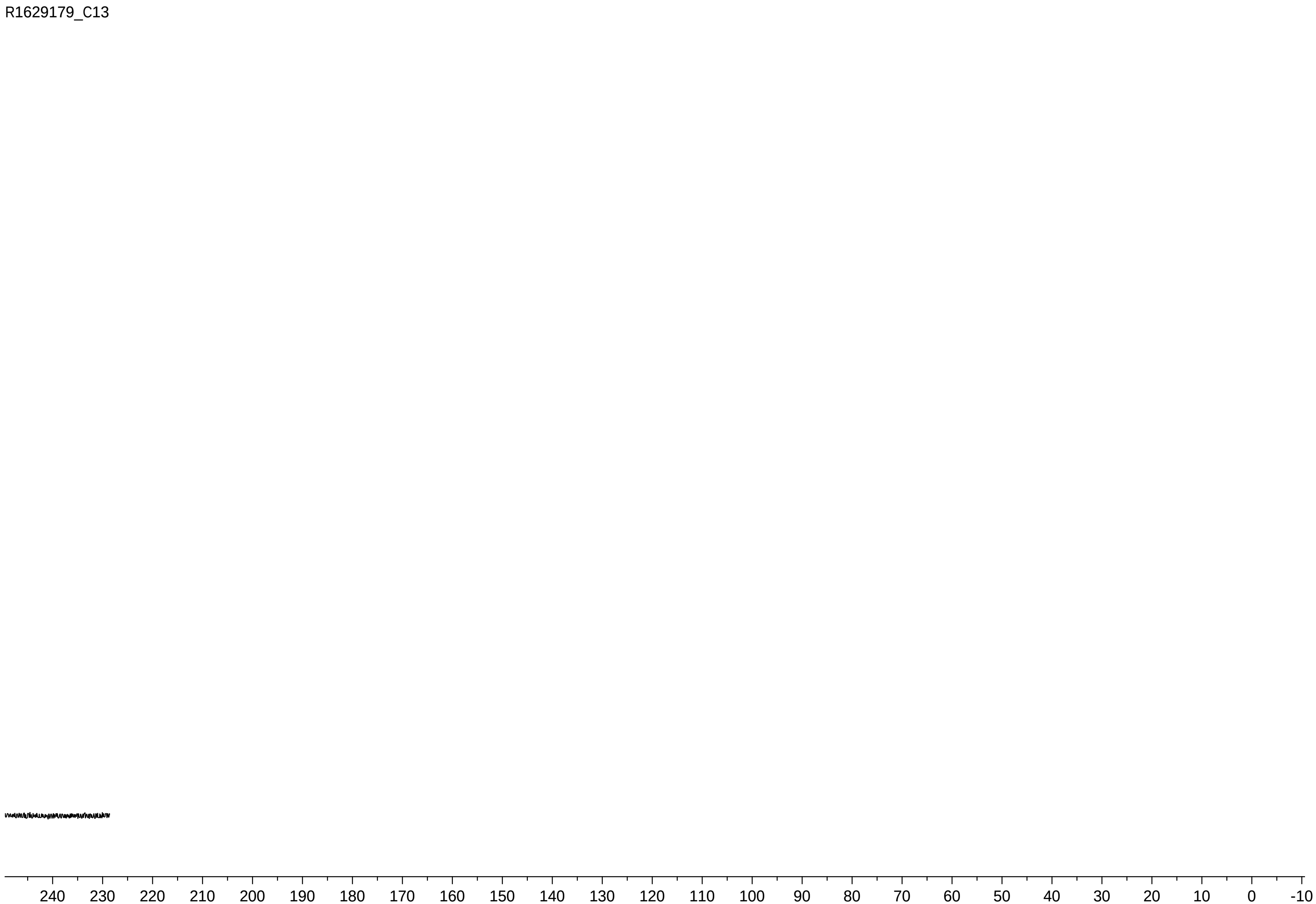
Compound 28b



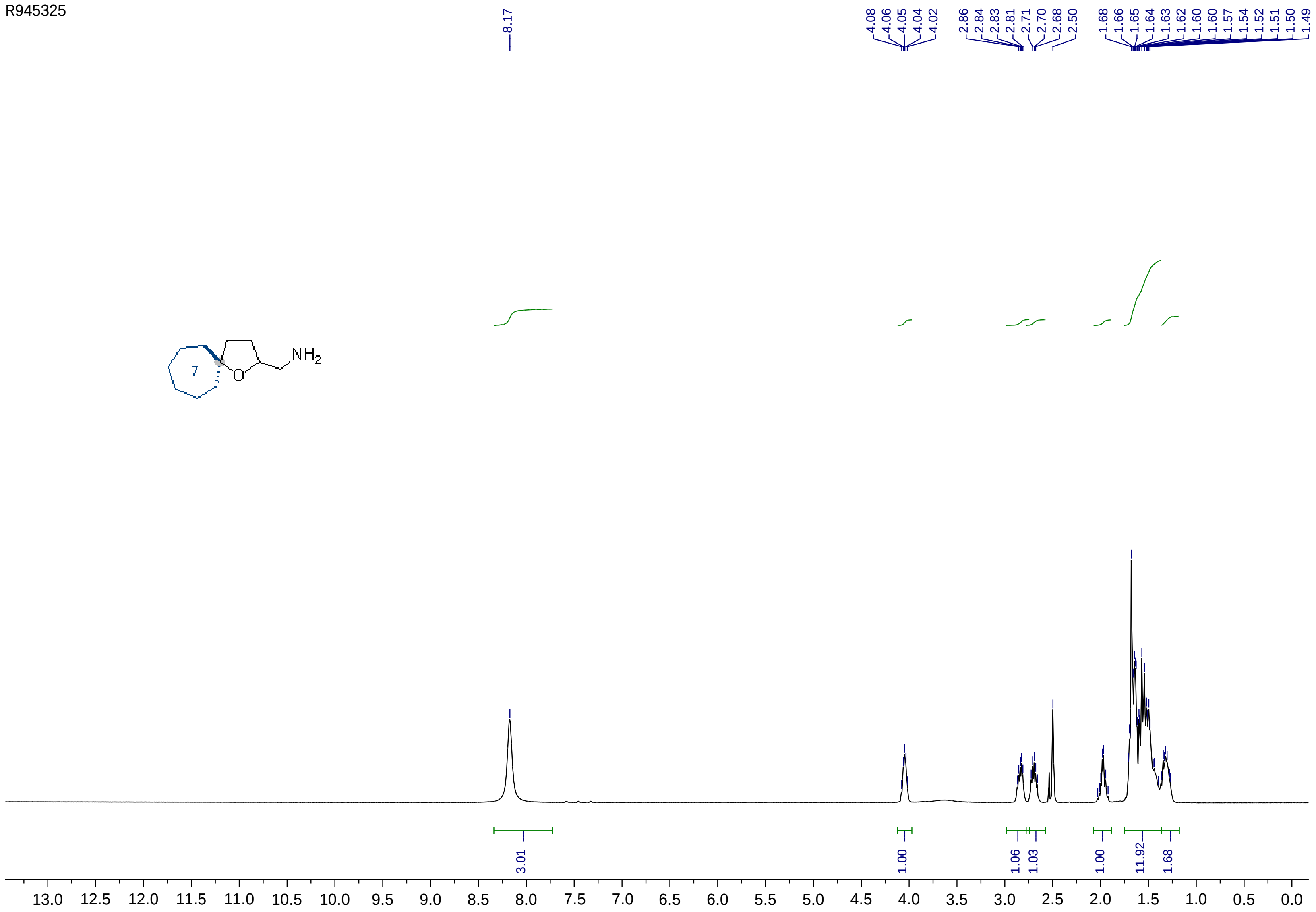

R1132359_C13
80.40
80.30
79.79
79.74
77.16
75.09
74.32
67.85
67.84
46.85
46.83
35.83
35.20
34.15
33.83
28.29
28.04
24.27
24.20
NH2
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 29b



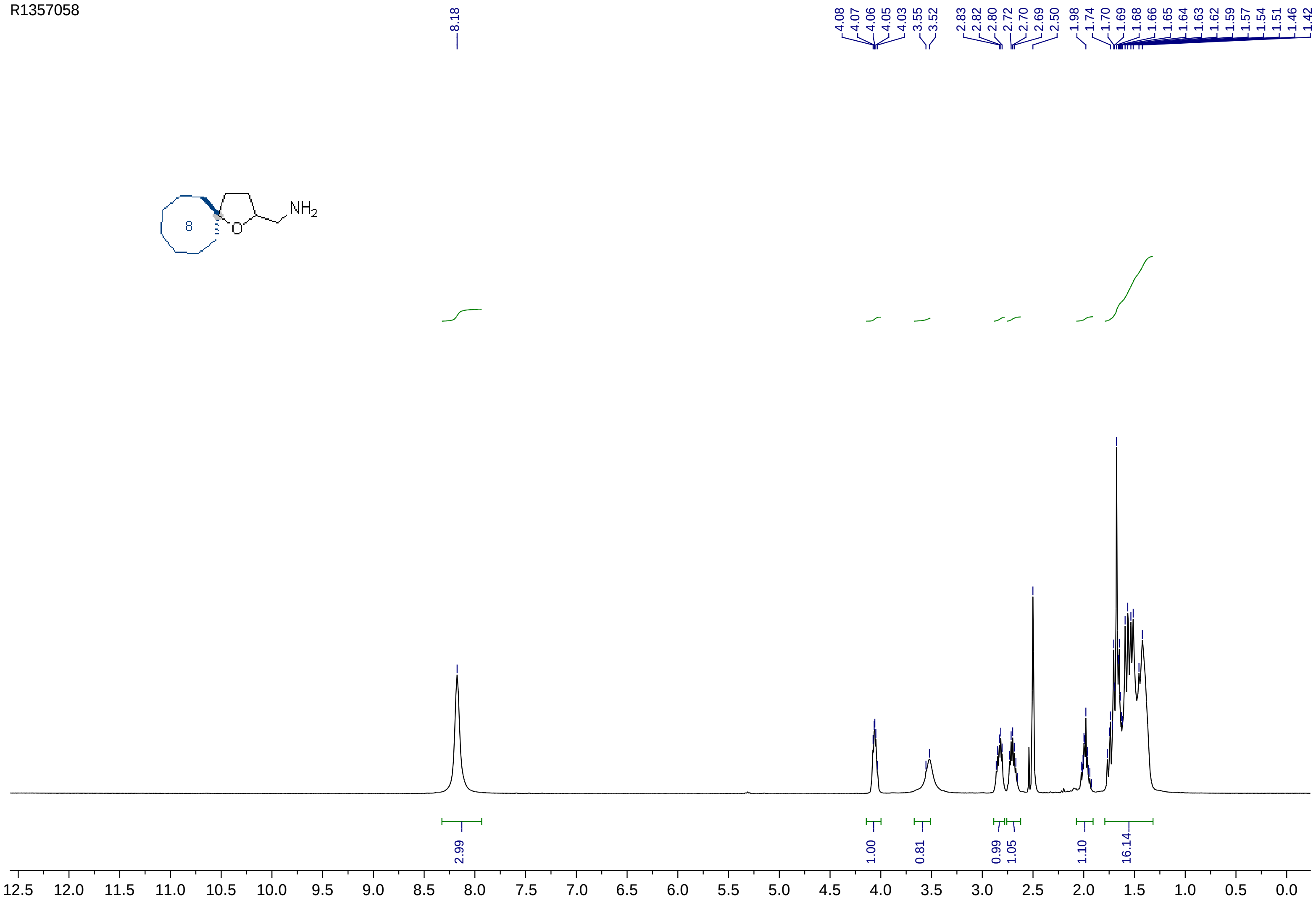

R1629179_C13
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

Compound 30b

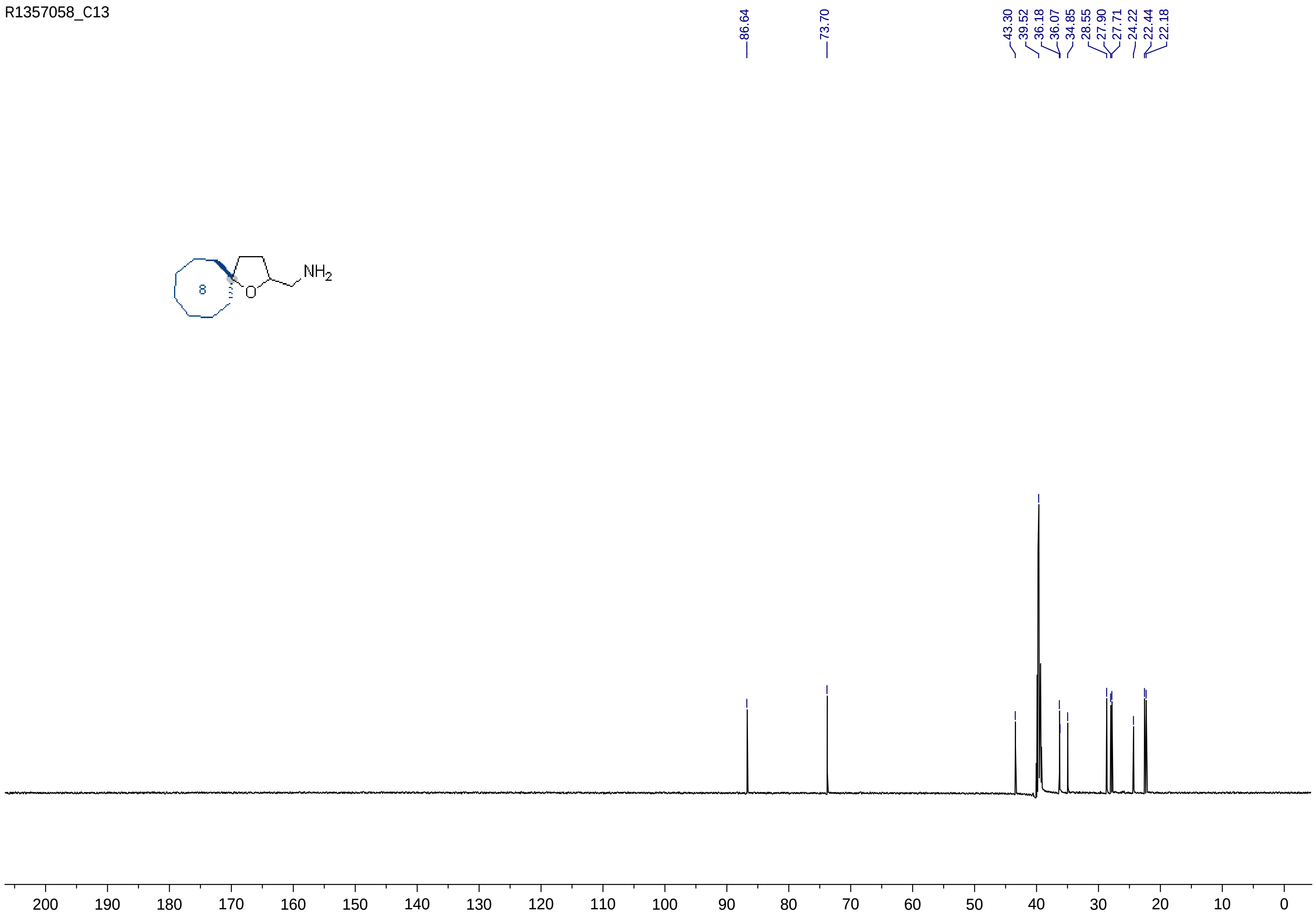



R945325_C13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

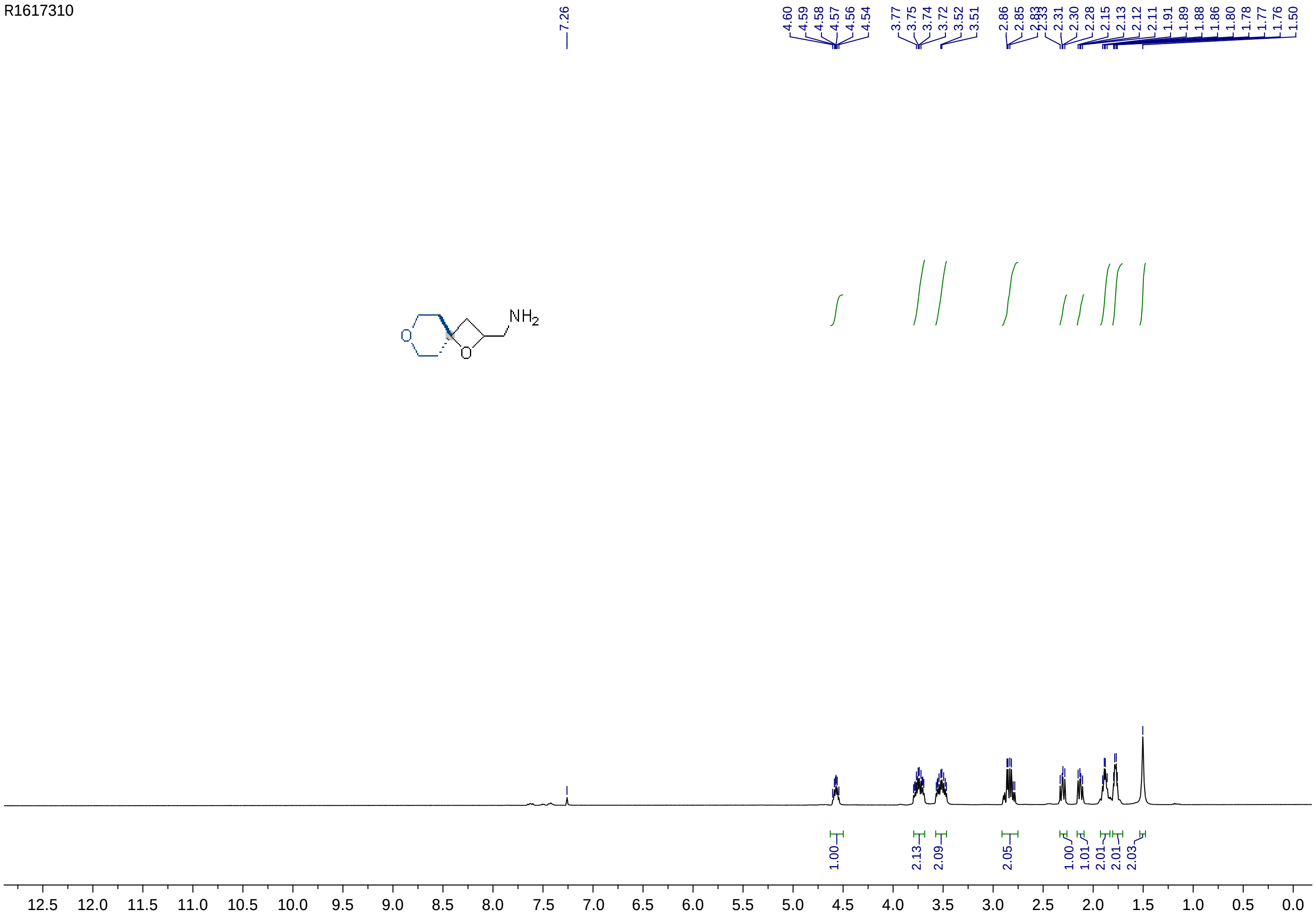
Compound 31b



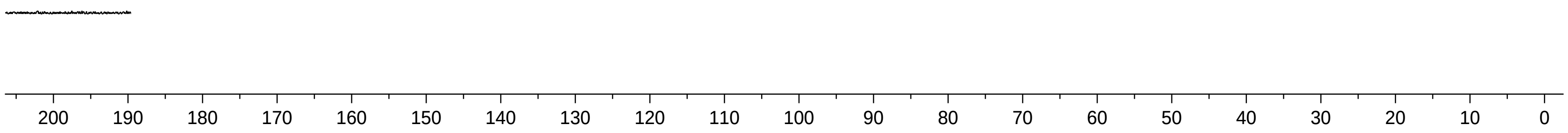
R1357058_C13



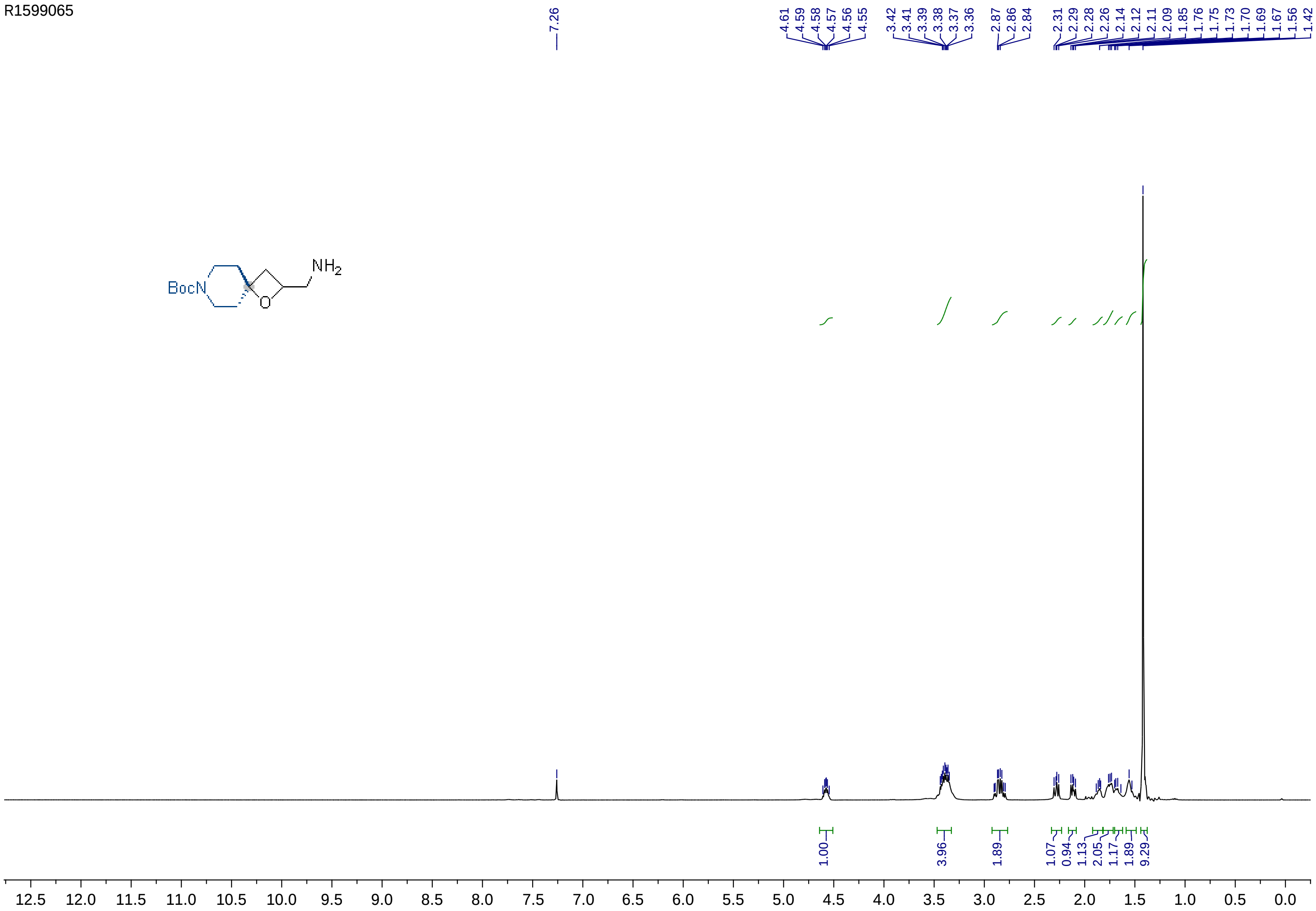
Compound 32b



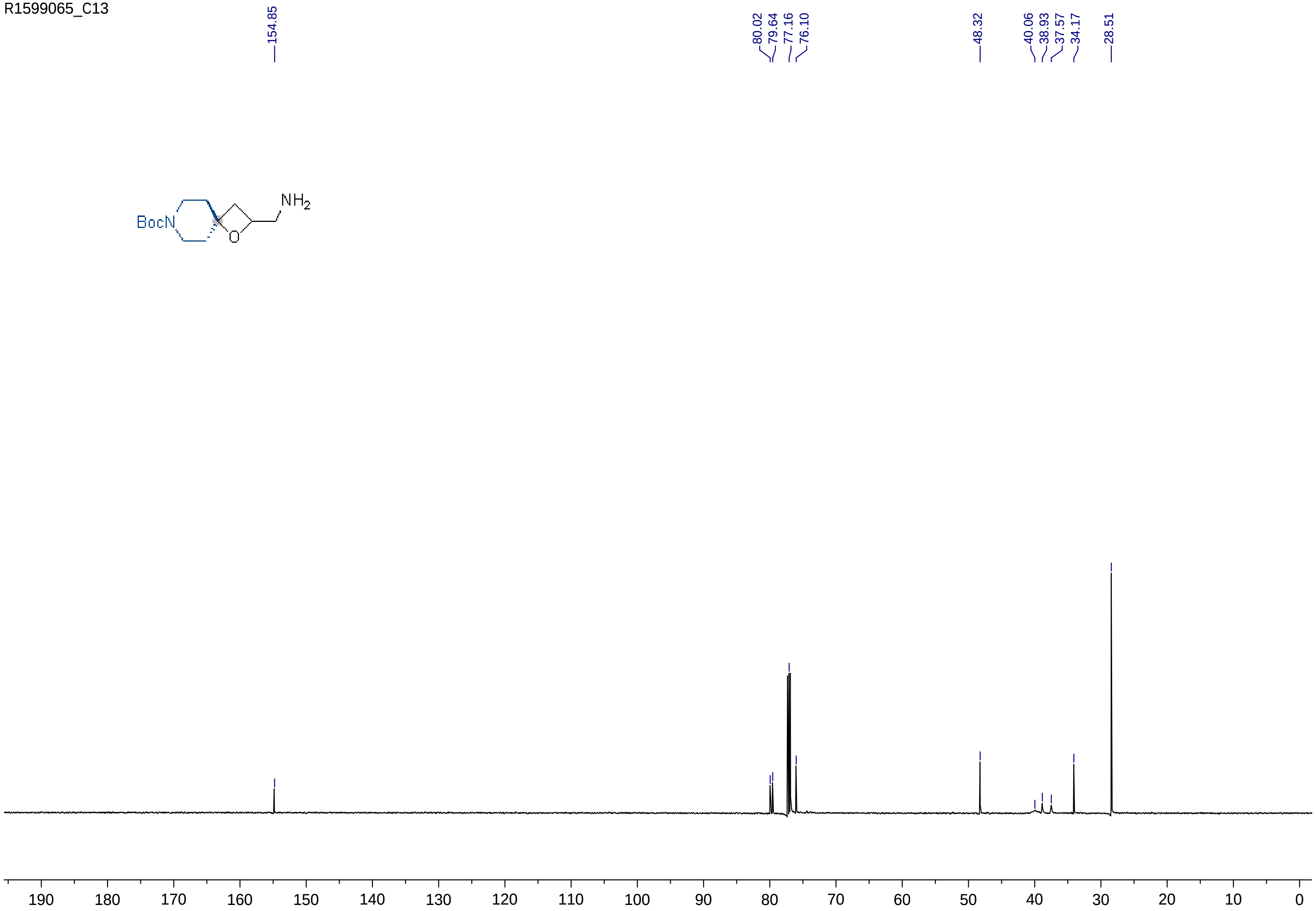
R1617310_C13



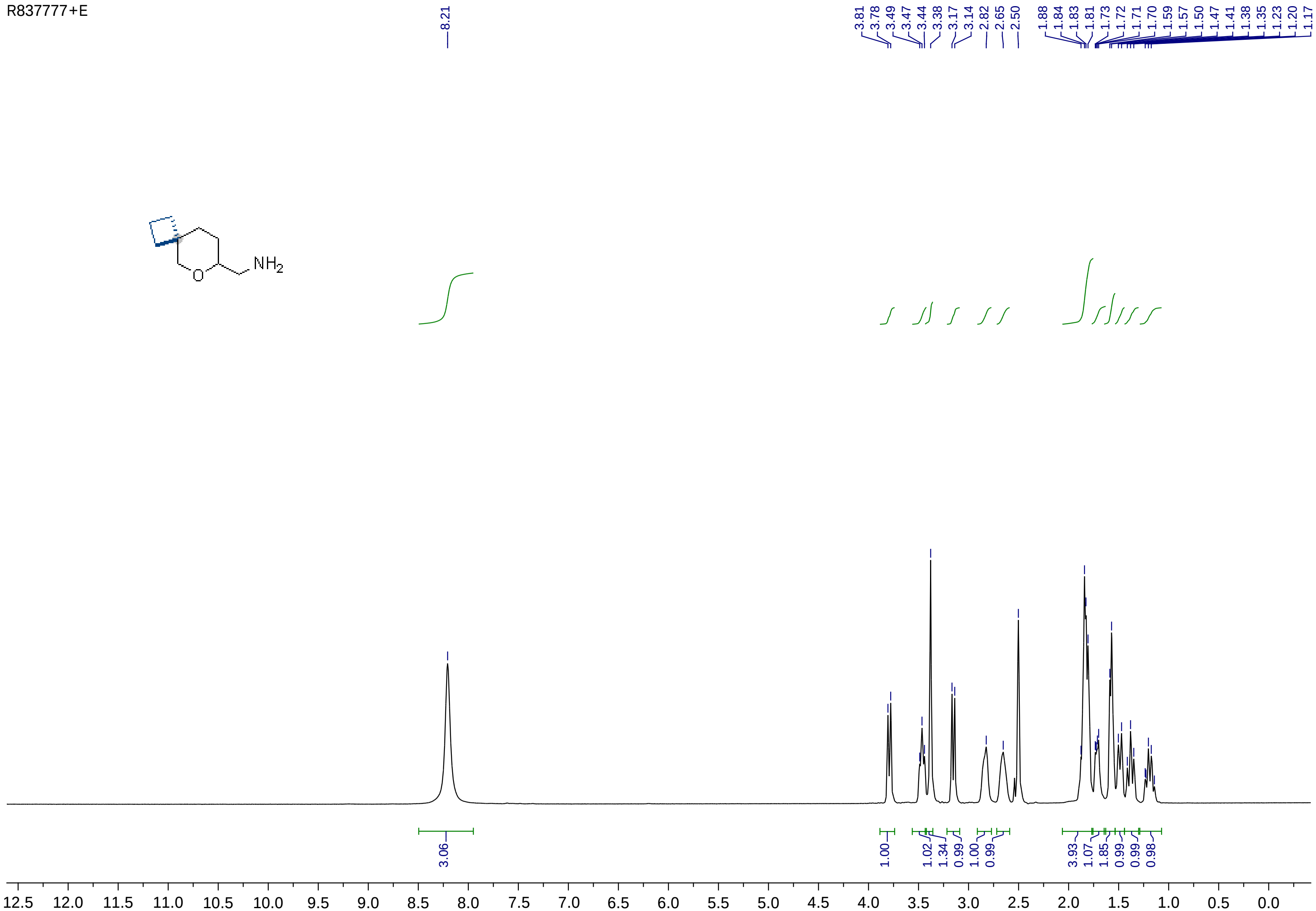
Compound 33b



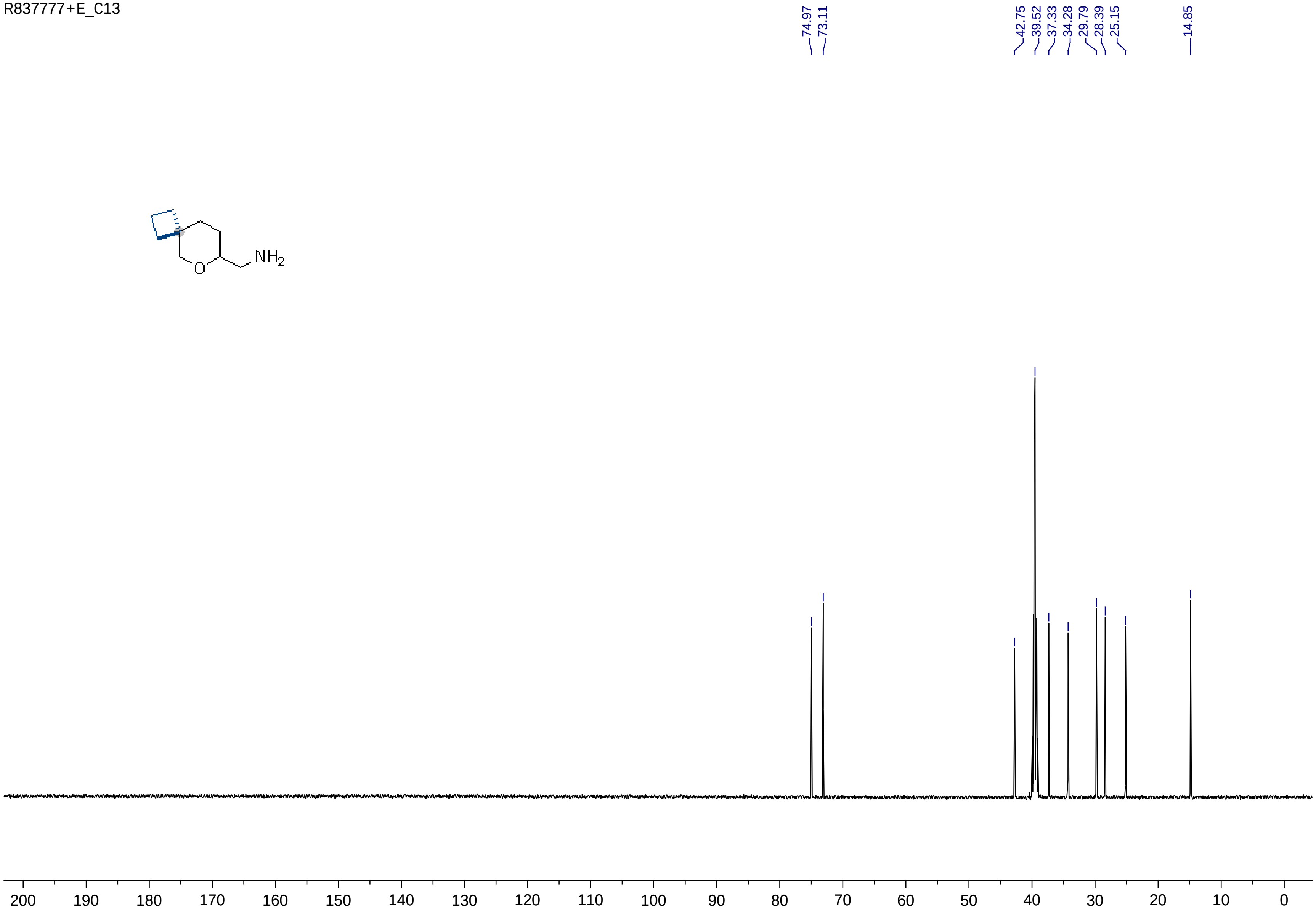
R1599065_C13



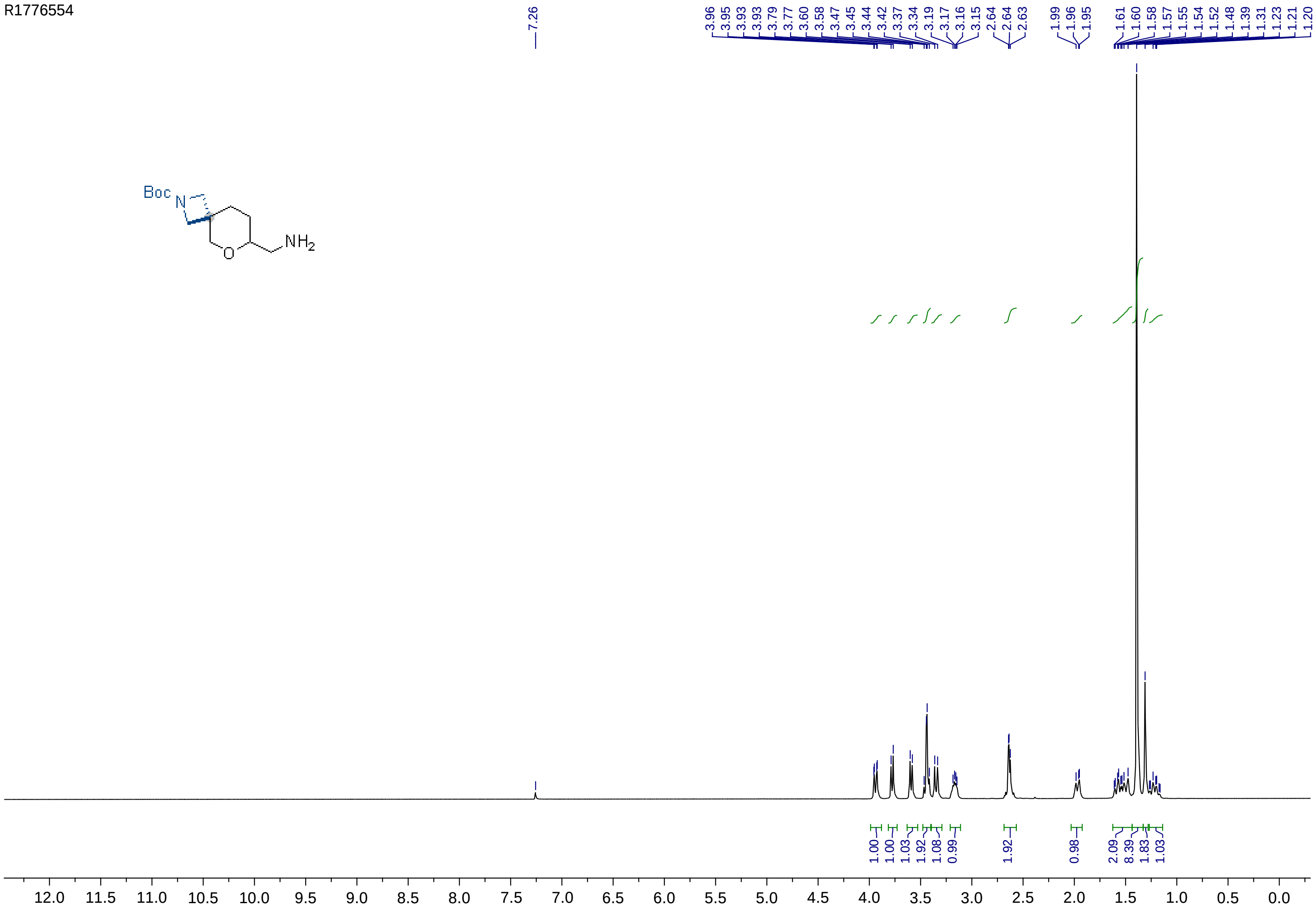
Compound 34b



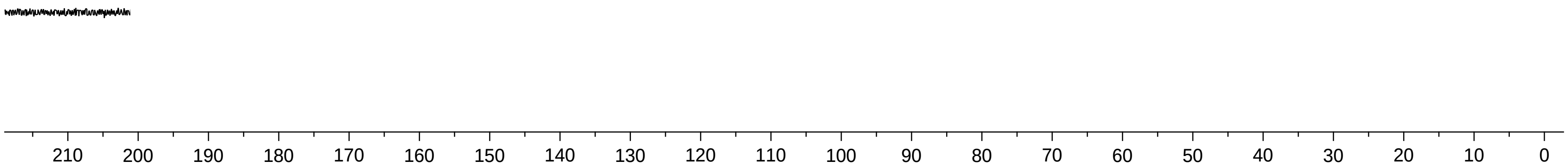
R837777+E_C13



Compound 35b

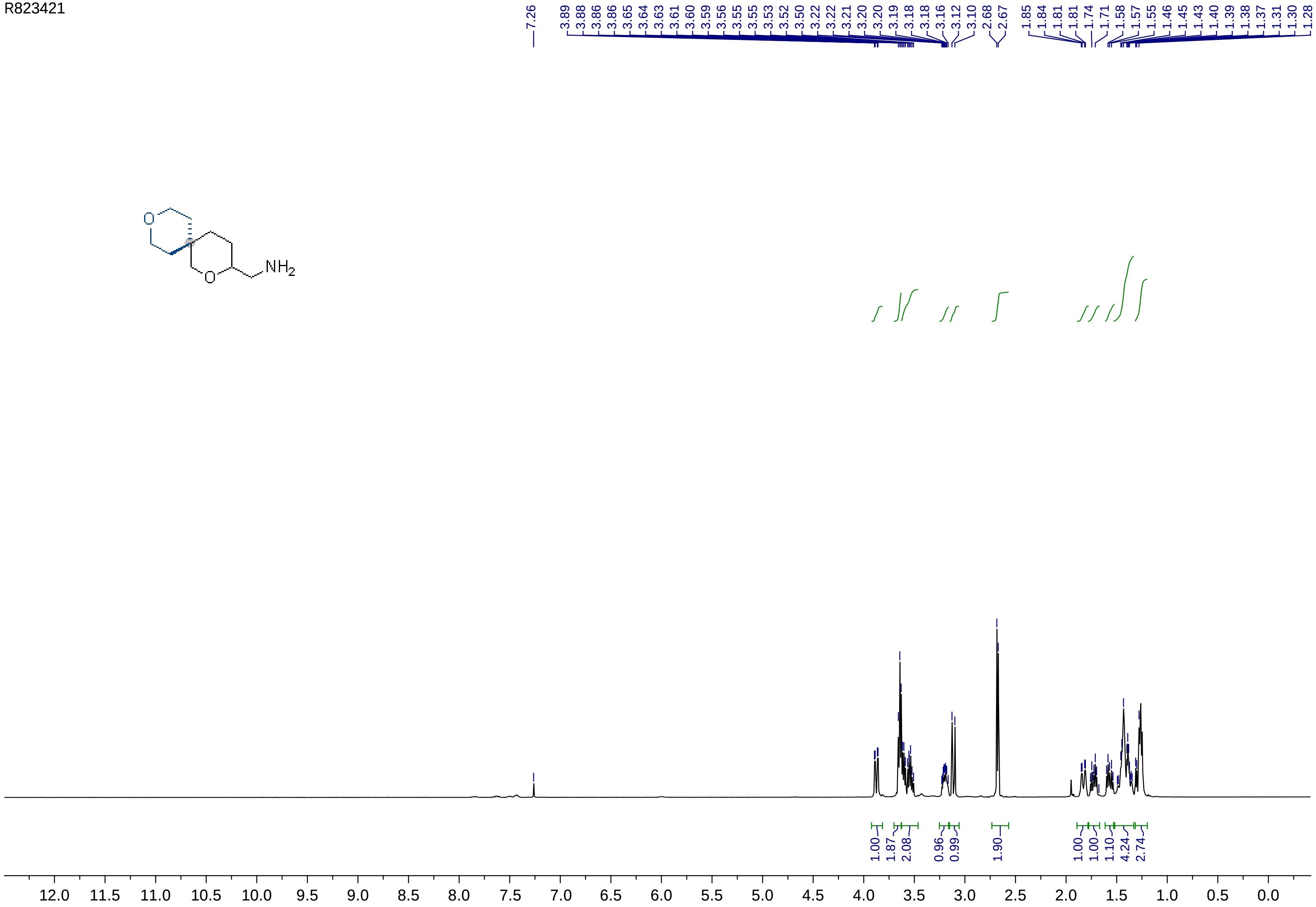


R1776554_C13

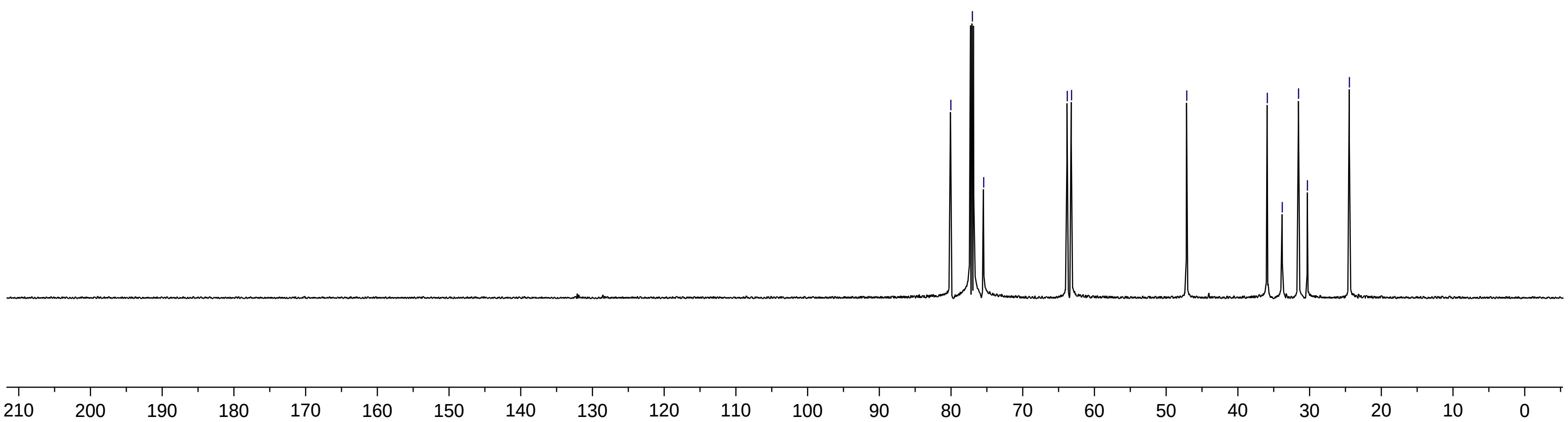


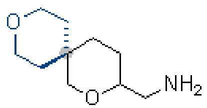
Compound 36b

R823421

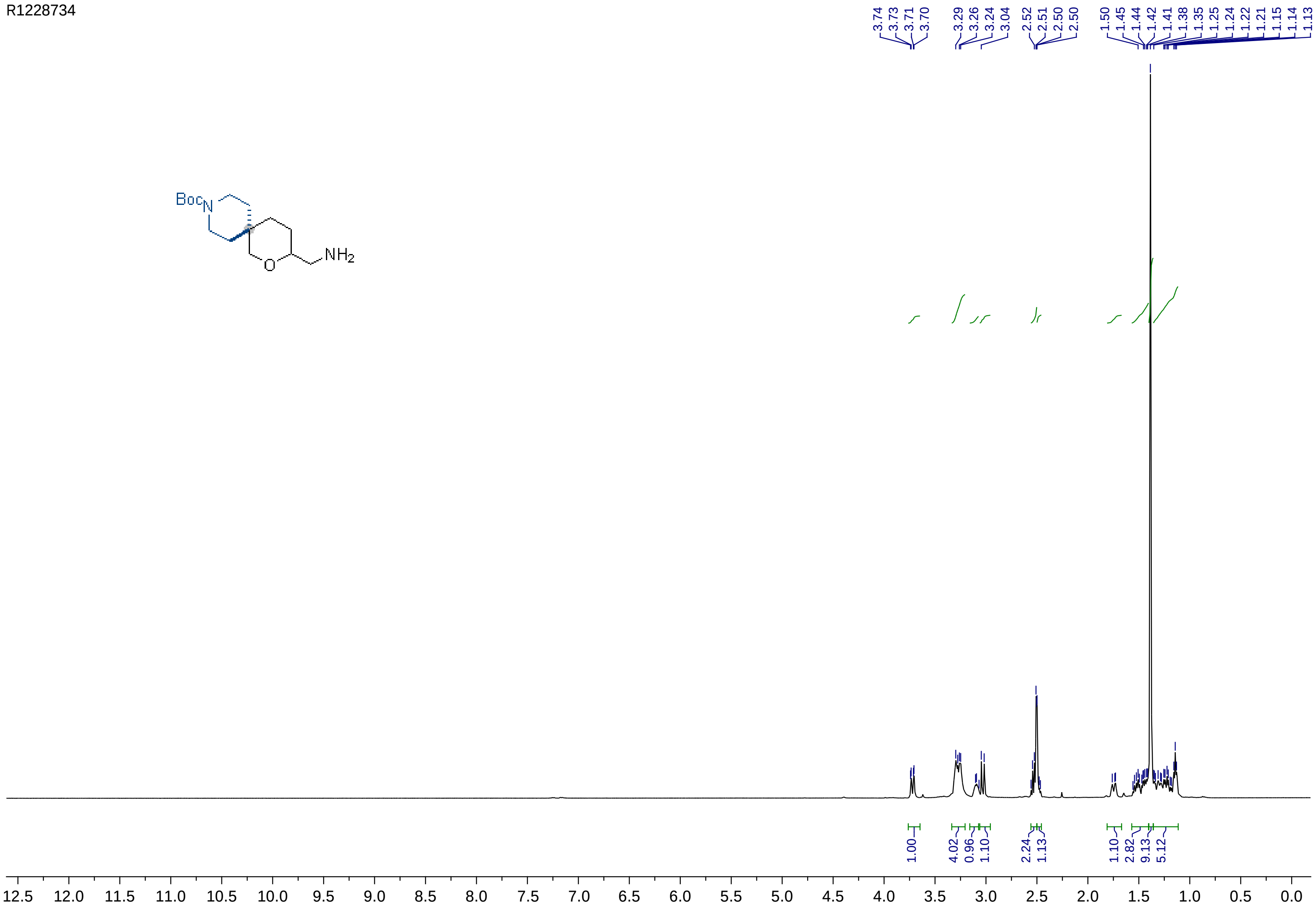


R823421_C13


80.16
77.16
75.58
63.93
63.33
47.26
36.03
33.95
31.67
30.44
24.58
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

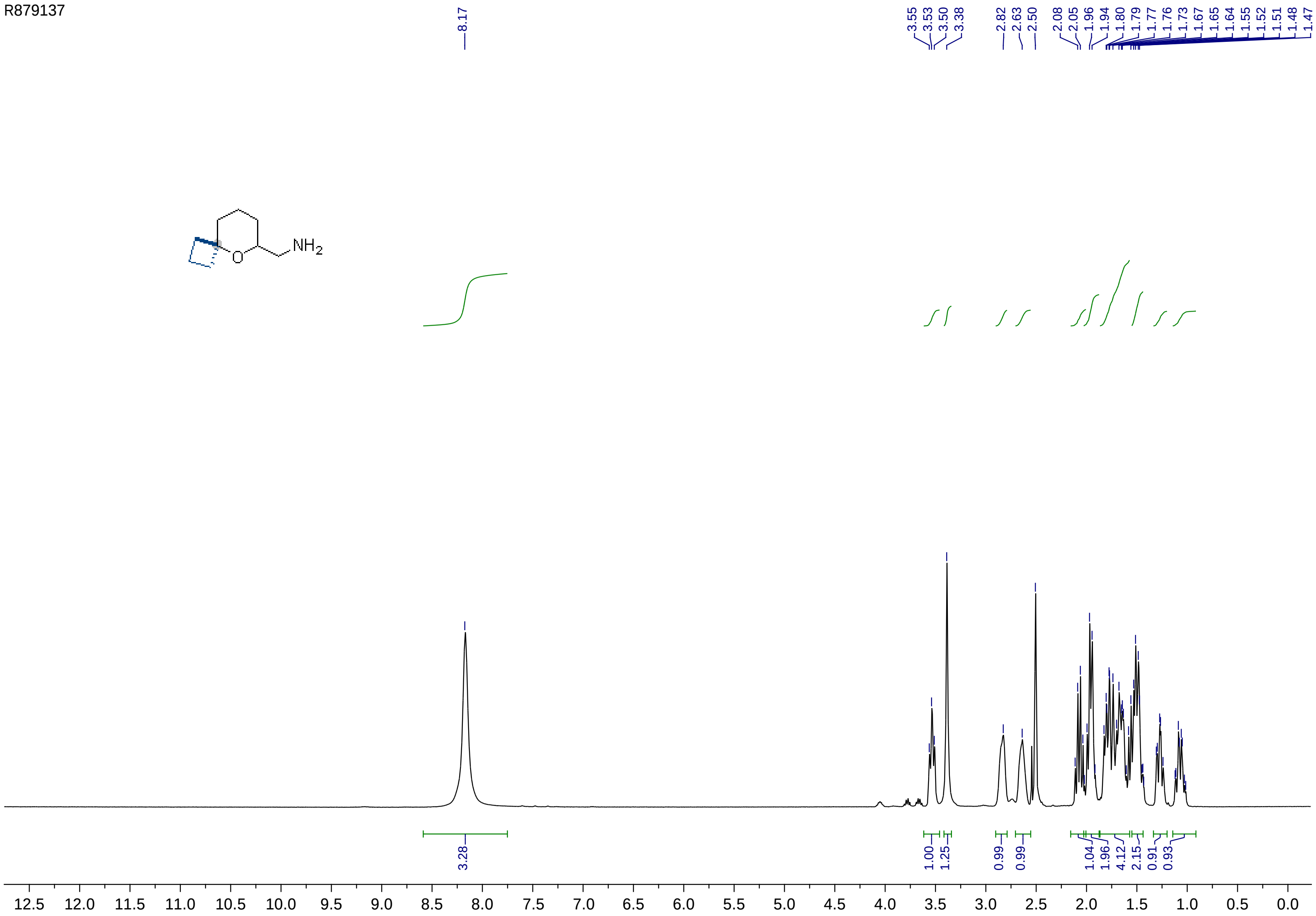

O
O
NH2

Compound 37b

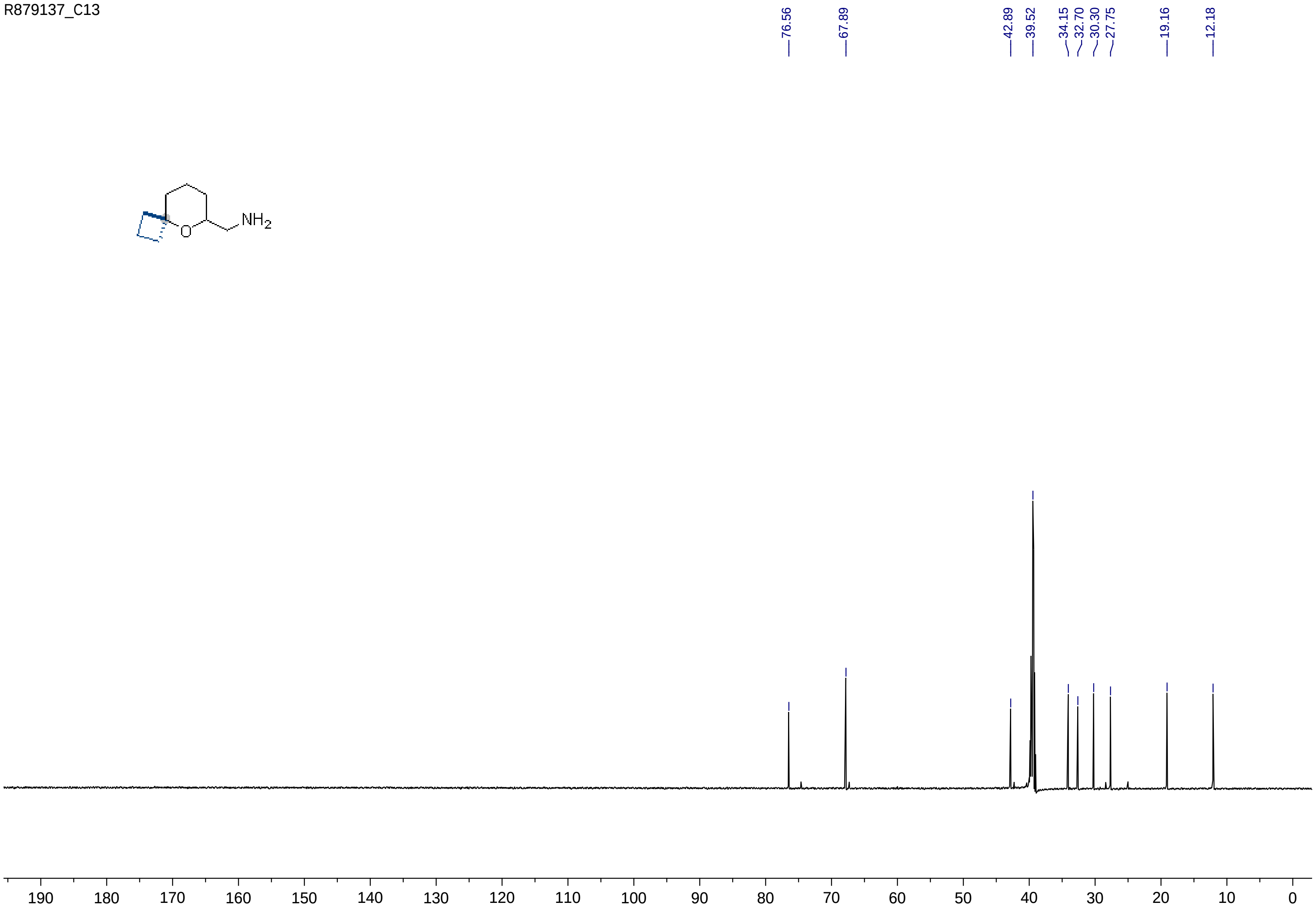



R1228734_C13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 38b

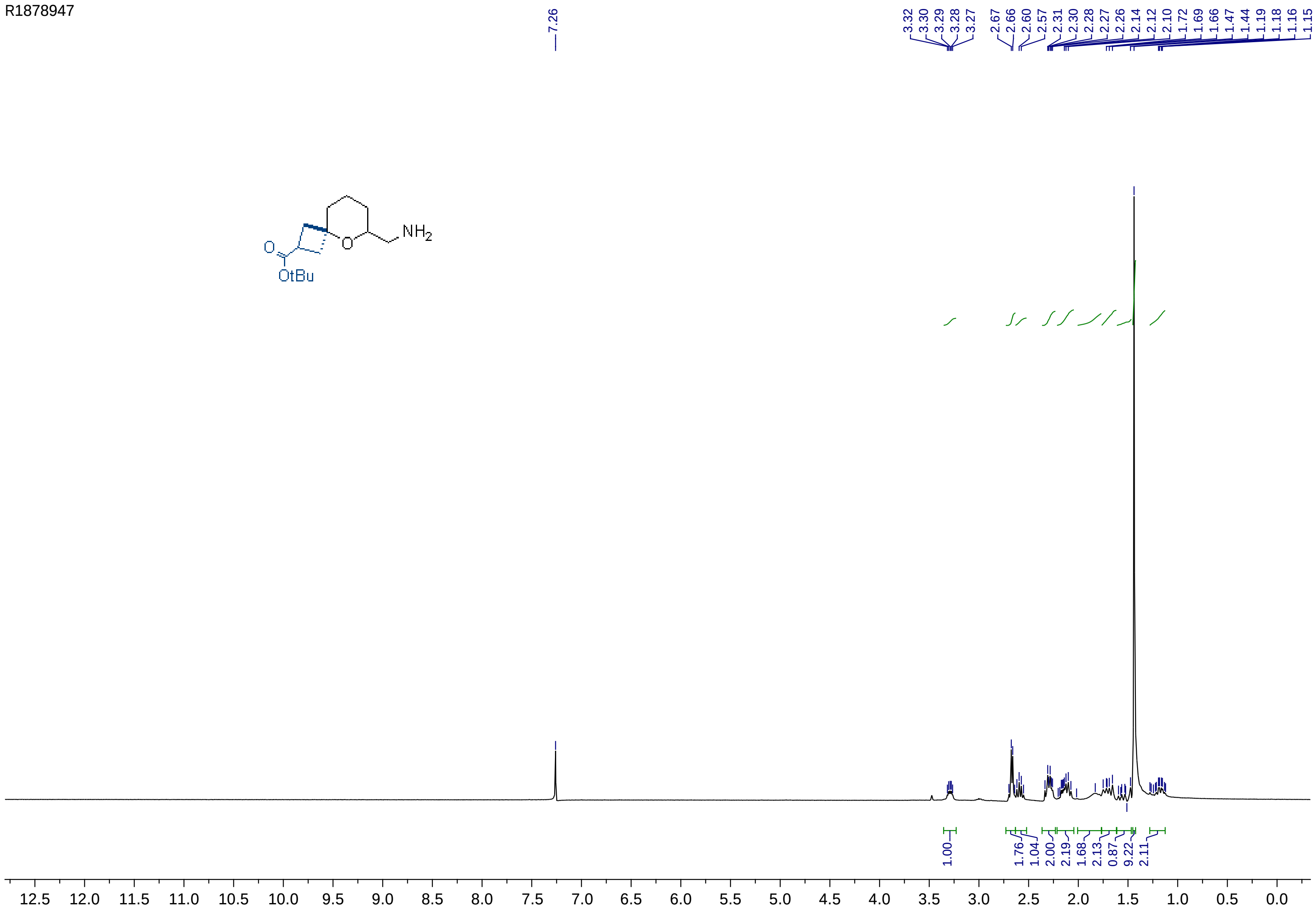


R879137_C13

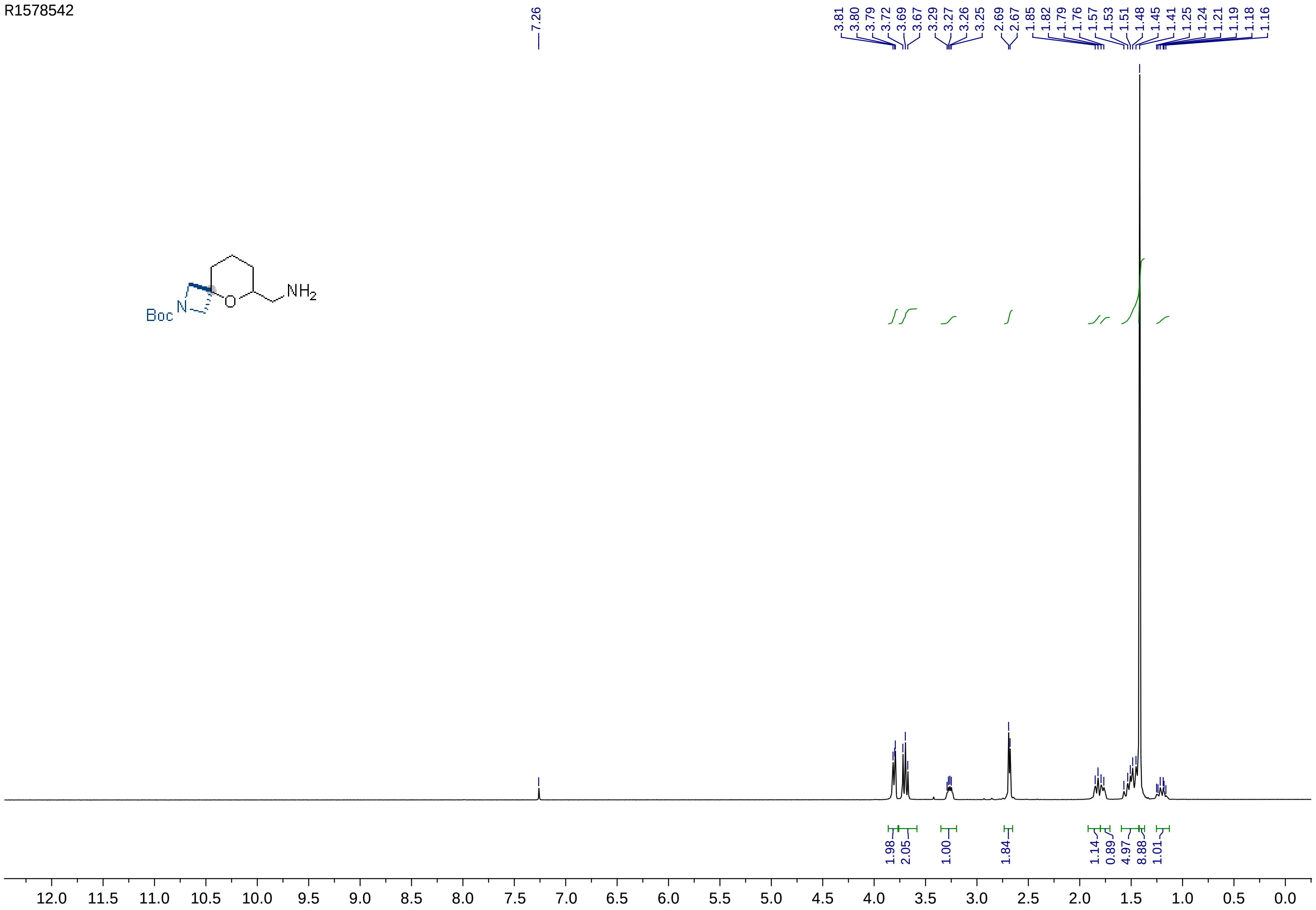


76.56
67.89
42.89
39.52
34.15
32.70
30.30
27.75
19.16
12.18
NH2
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

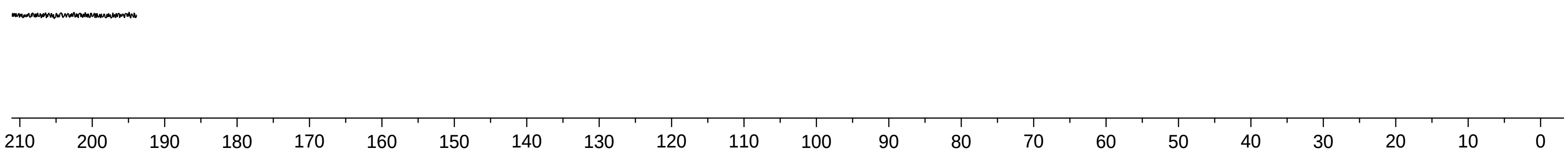
Compound 39b



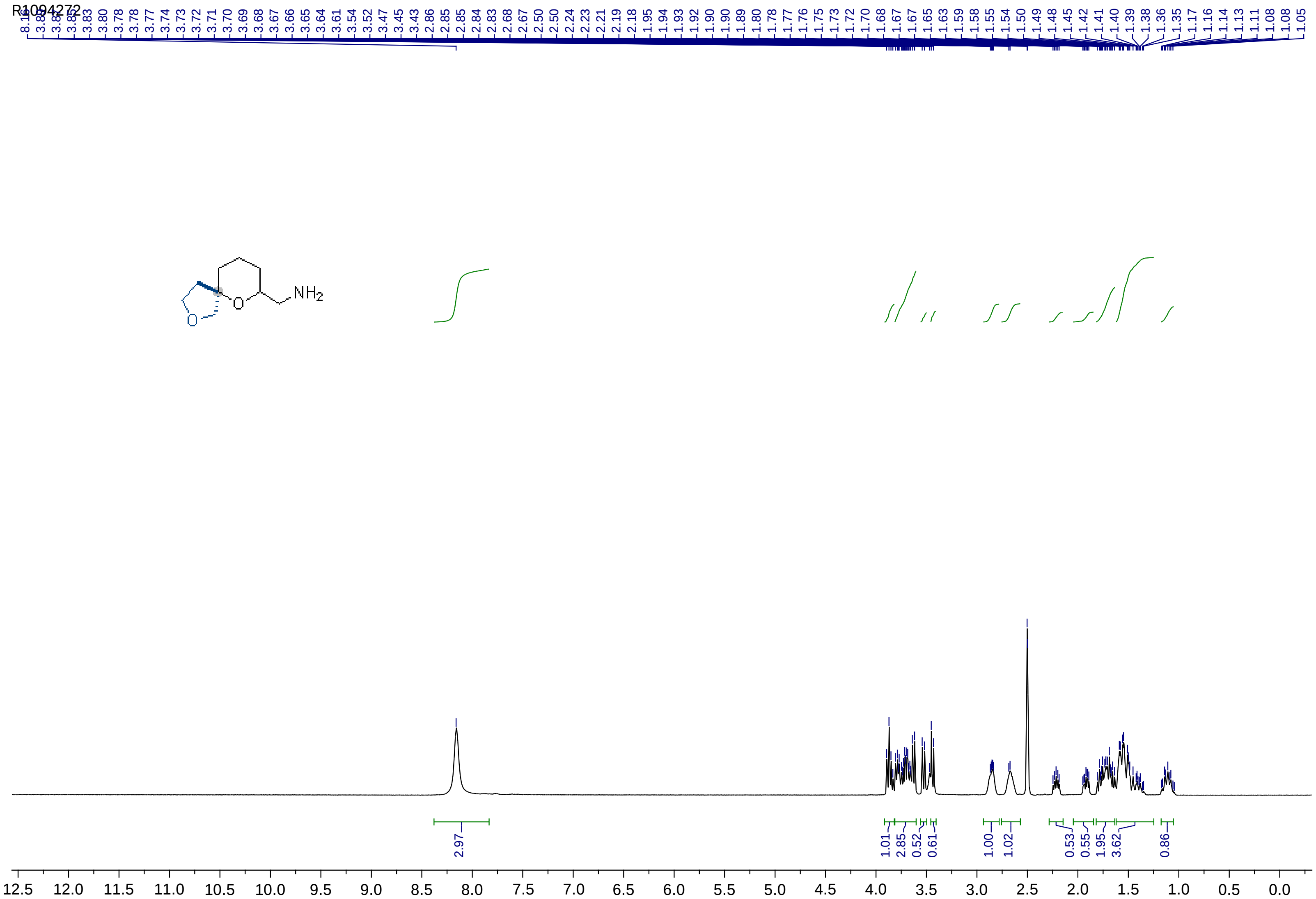
Compound 40b



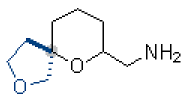
R1578542_C13

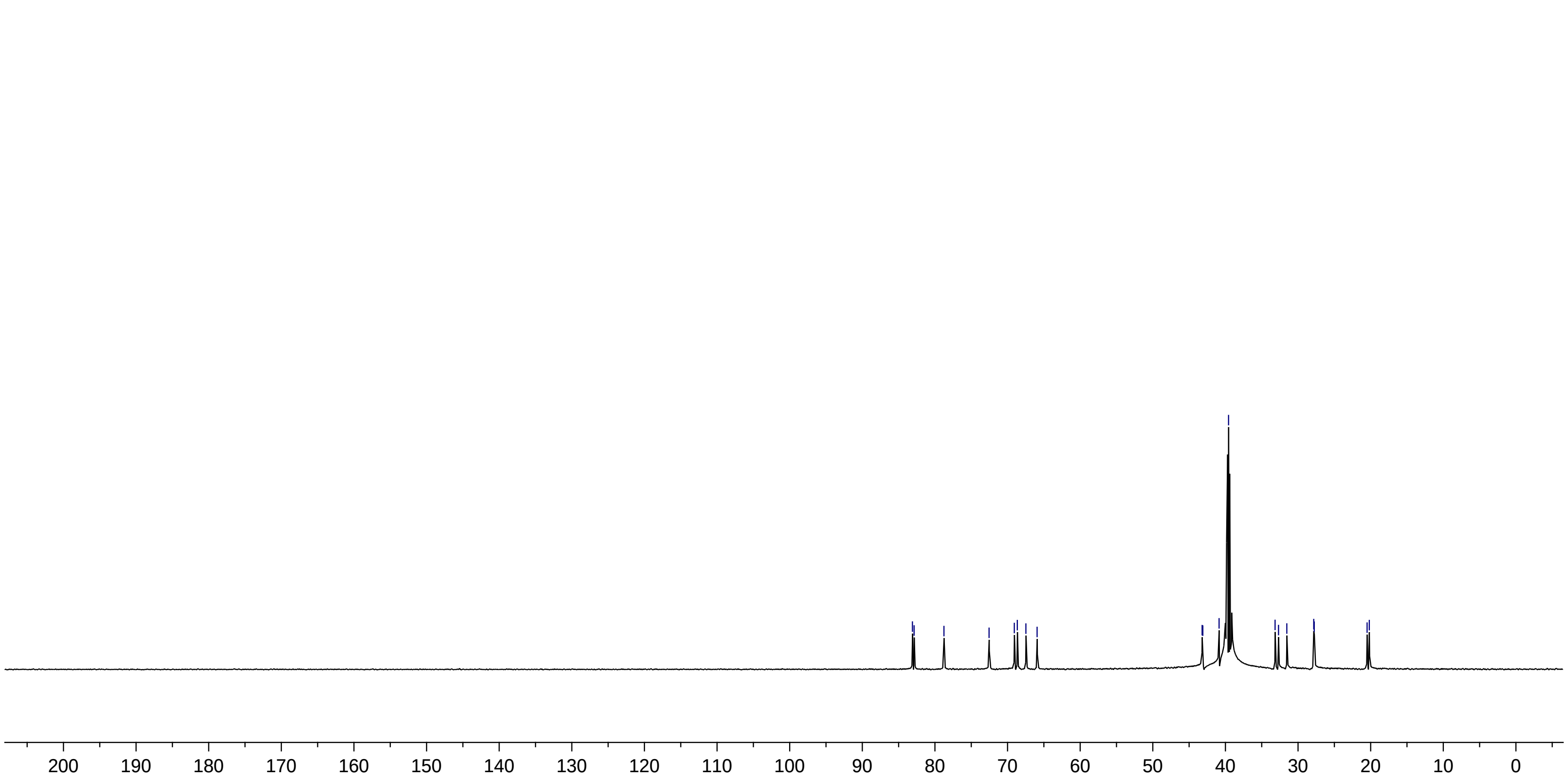


Compound 41b

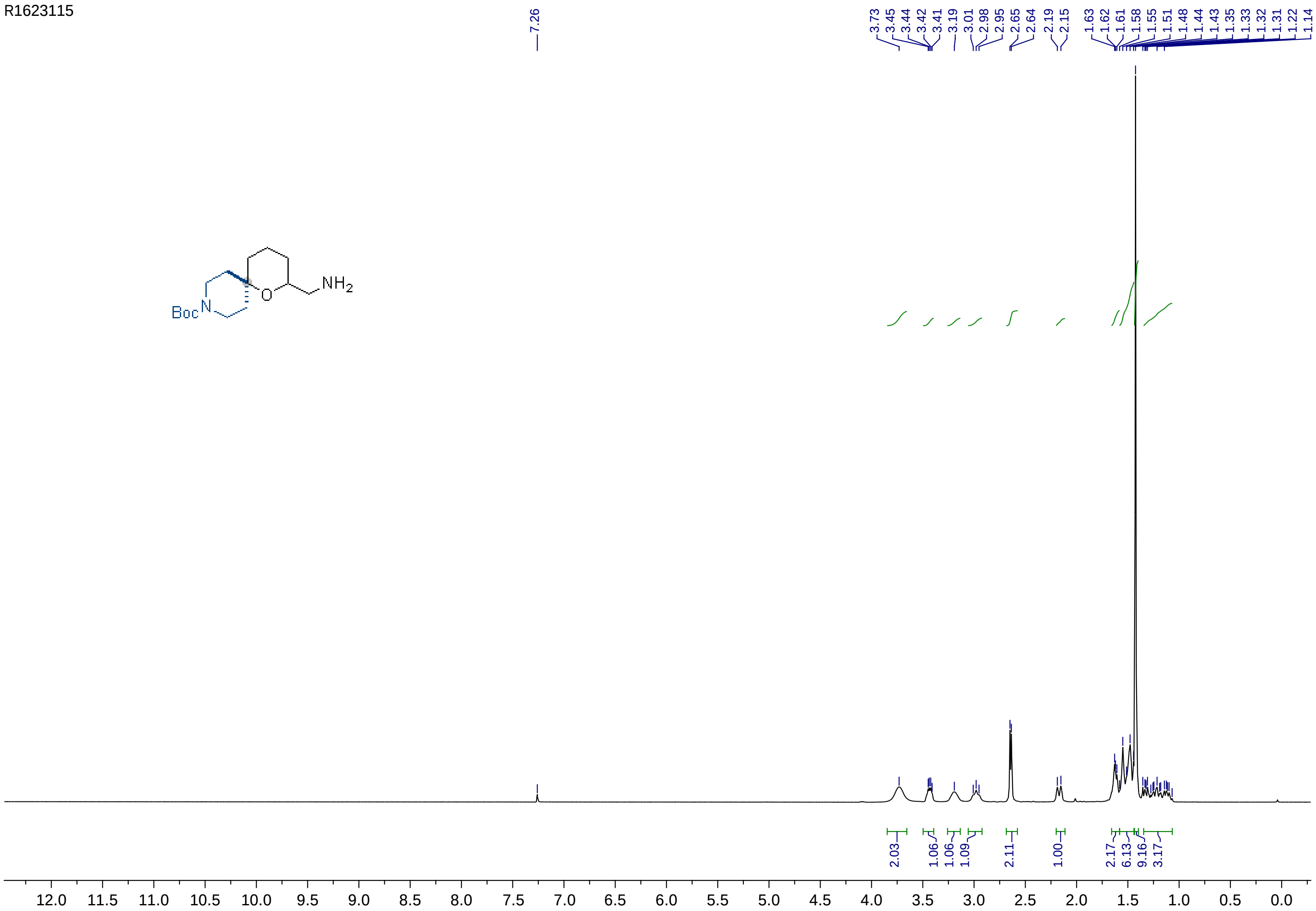


R1094272_C13



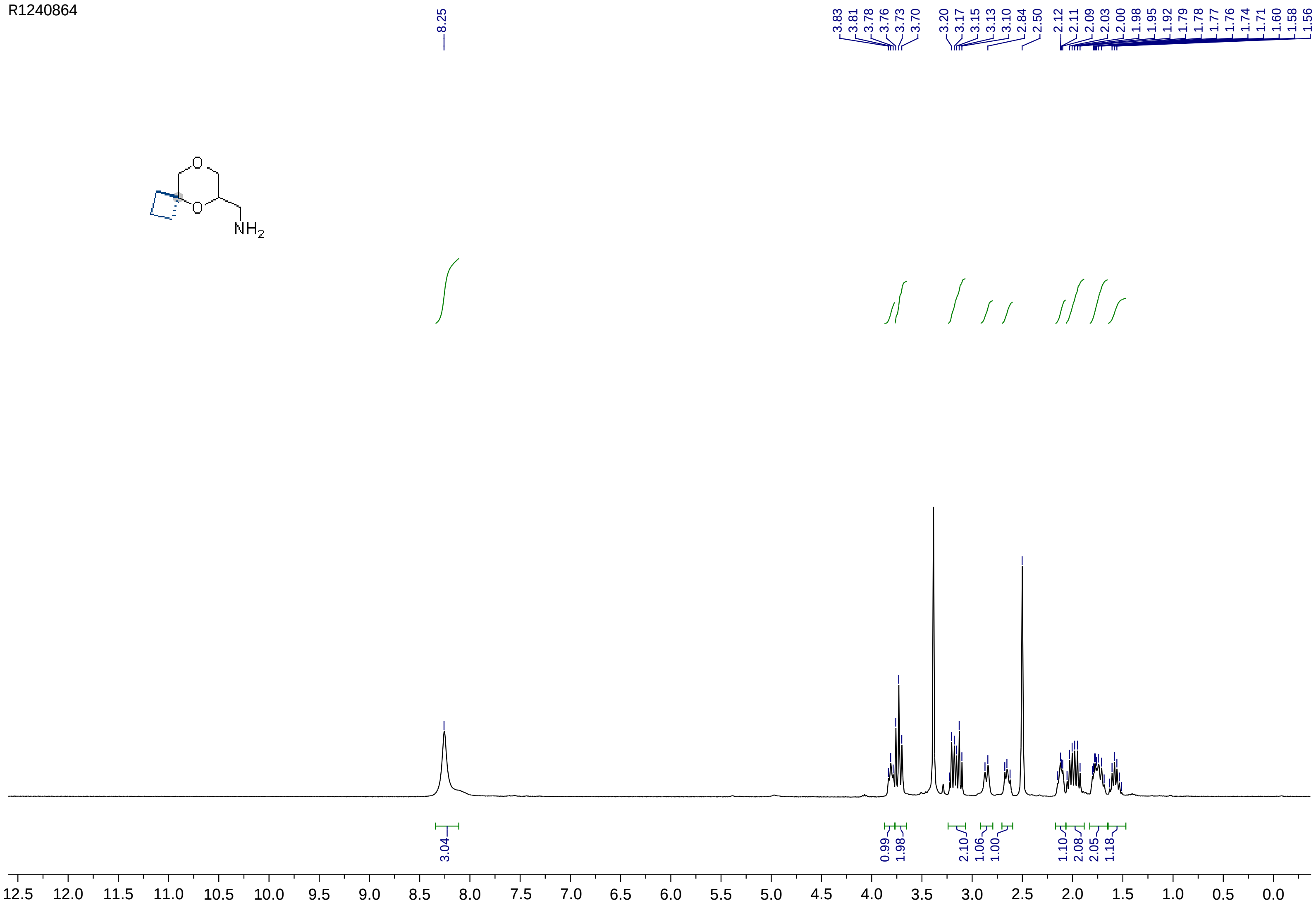


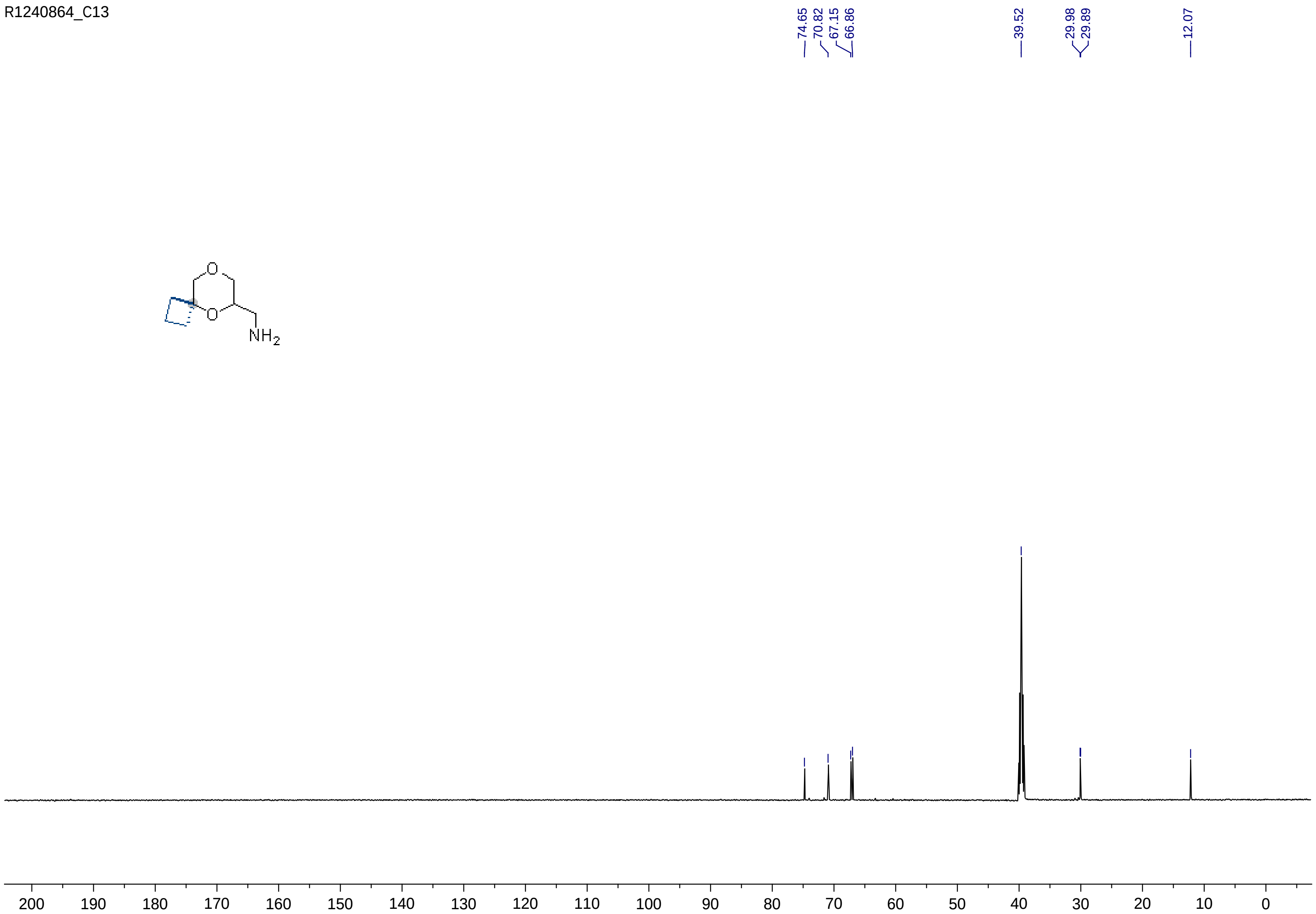
Compound 42b



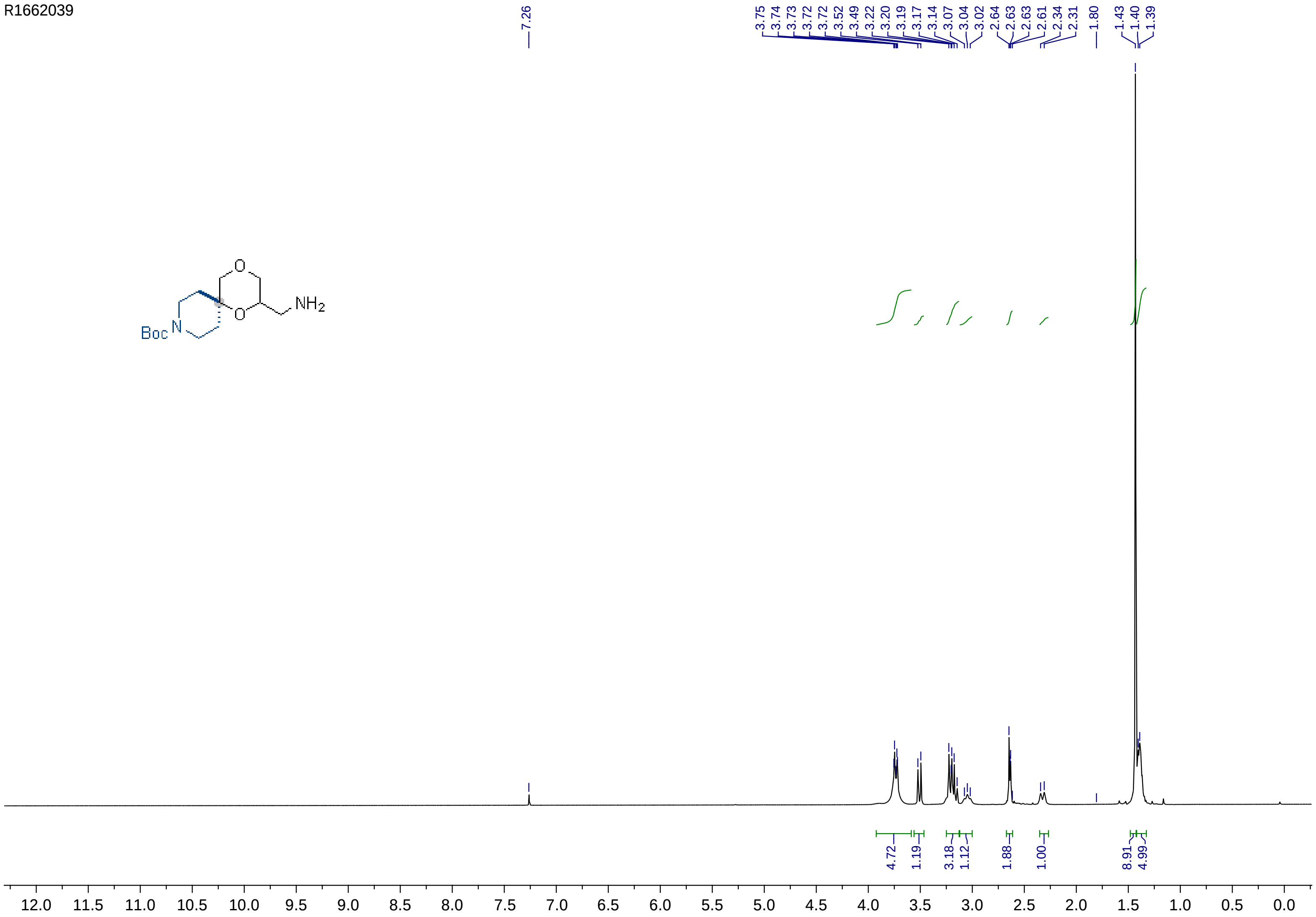

R1623115_C13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 43b

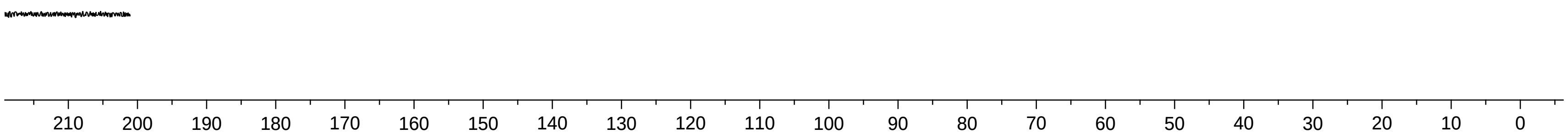



R1240864_C13
74.65
70.82
67.15
66.86
39.52
29.98
29.89
12.07
NH2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

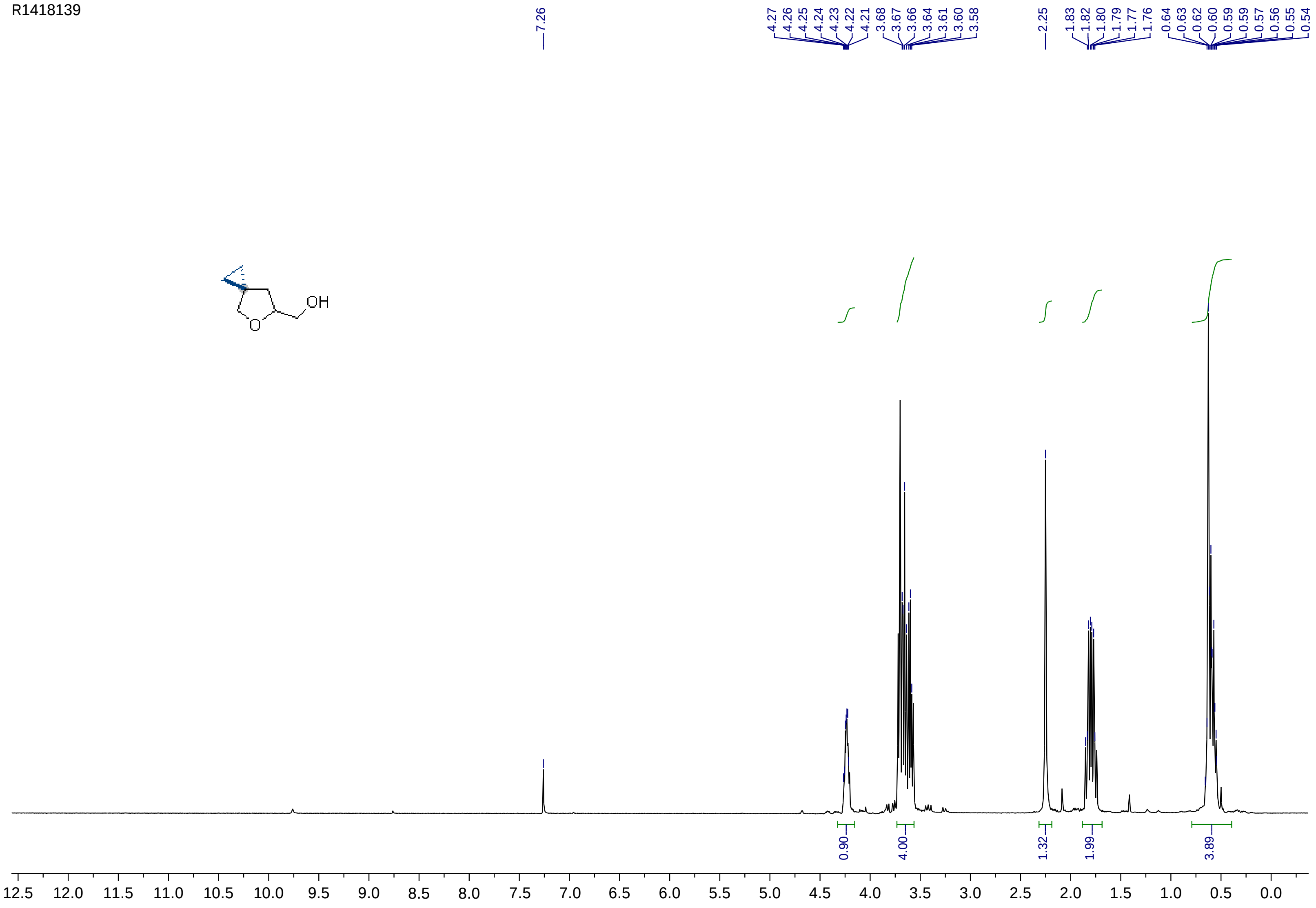
Compound 44b

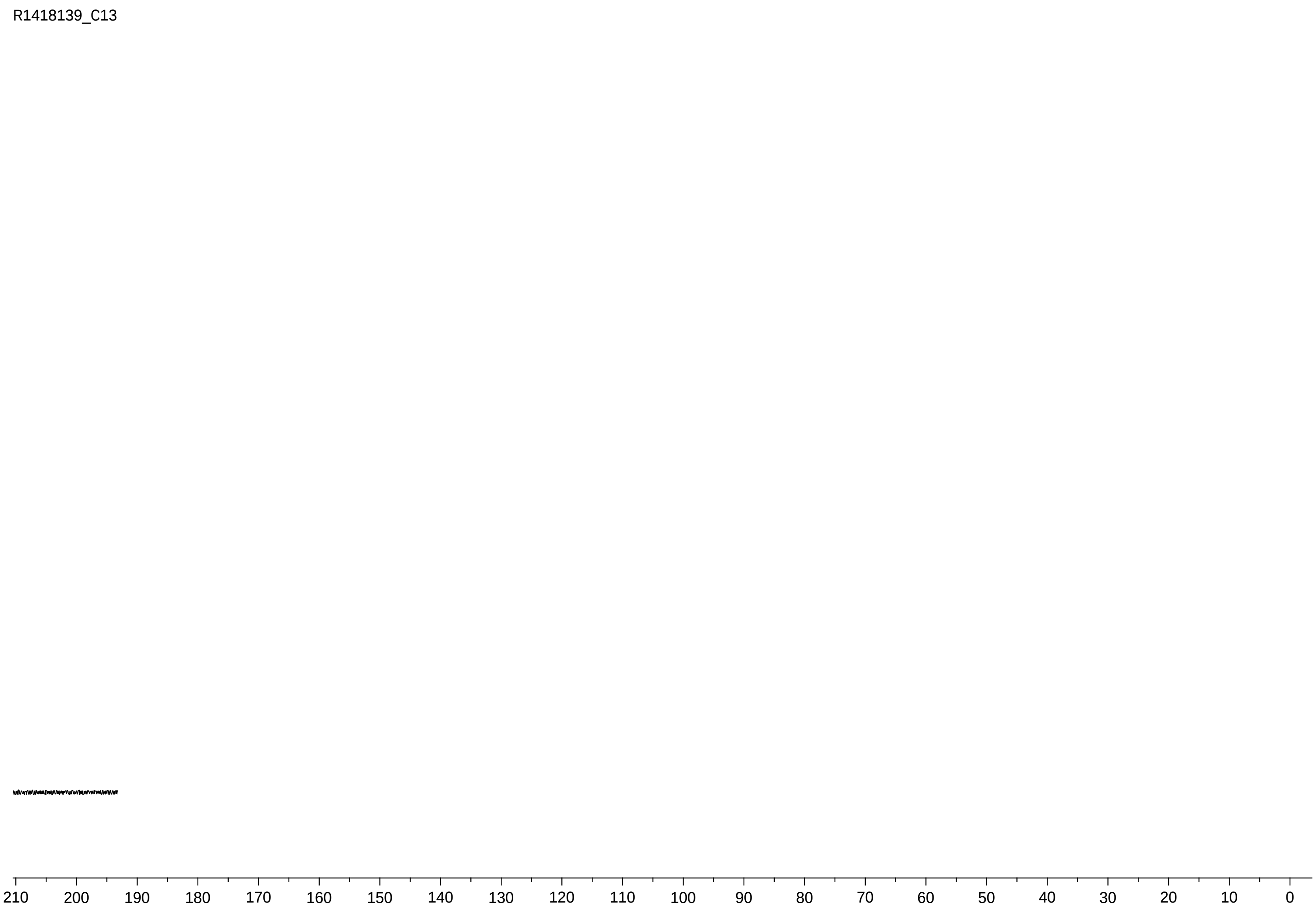


R1662039_C13

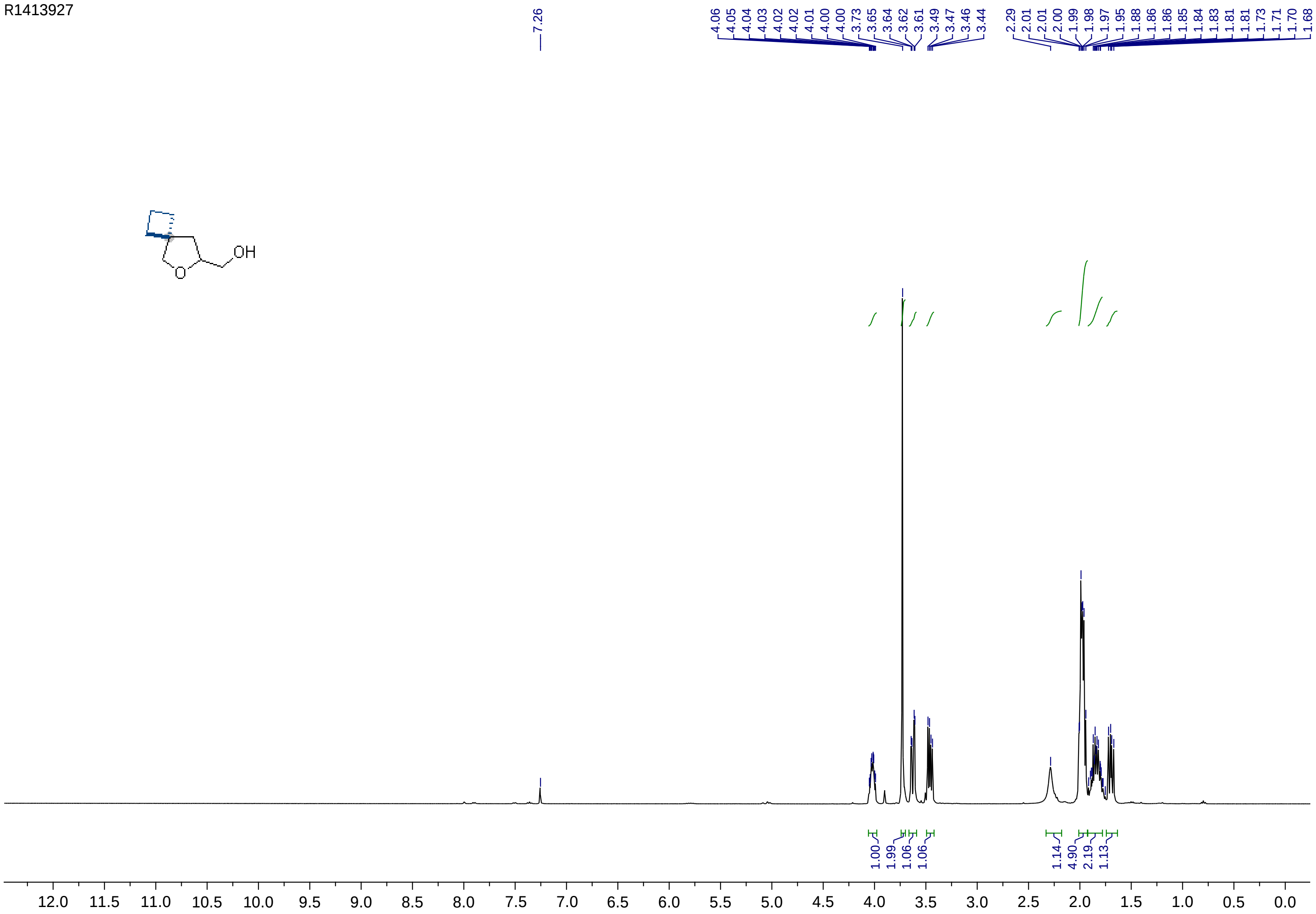


Compound 5c

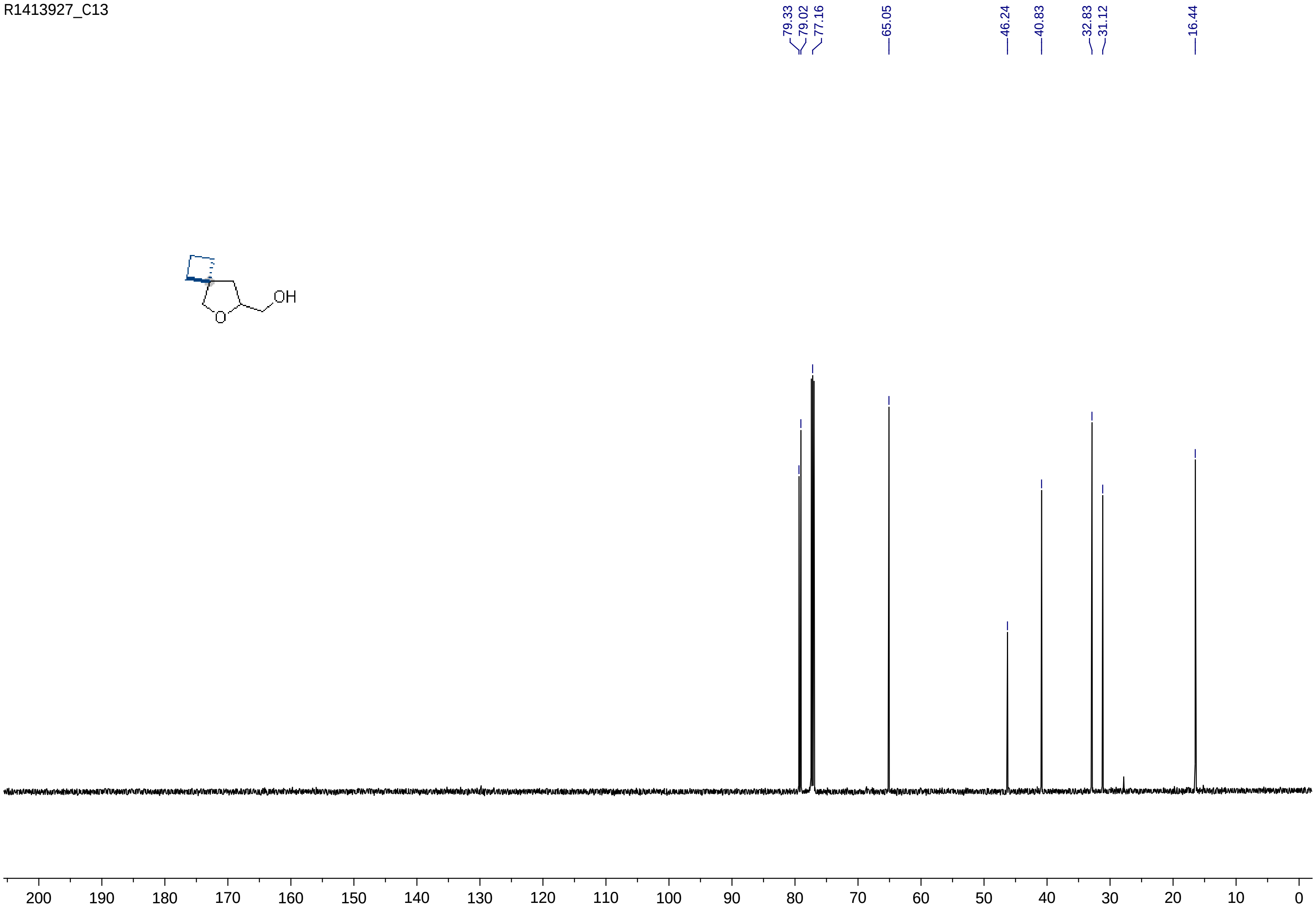

R1418139
7.26
4.27
4.26
4.25
4.24
4.23
4.22
4.21
3.68
3.67
3.66
3.64
3.61
3.60
3.58
2.25
1.83
1.82
1.80
1.79
1.77
1.76
0.64
0.63
0.62
0.60
0.59
0.59
0.57
0.56
0.55
0.54
OH
O
0.90
4.00
1.32
1.99
3.89
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


R1418139_C13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

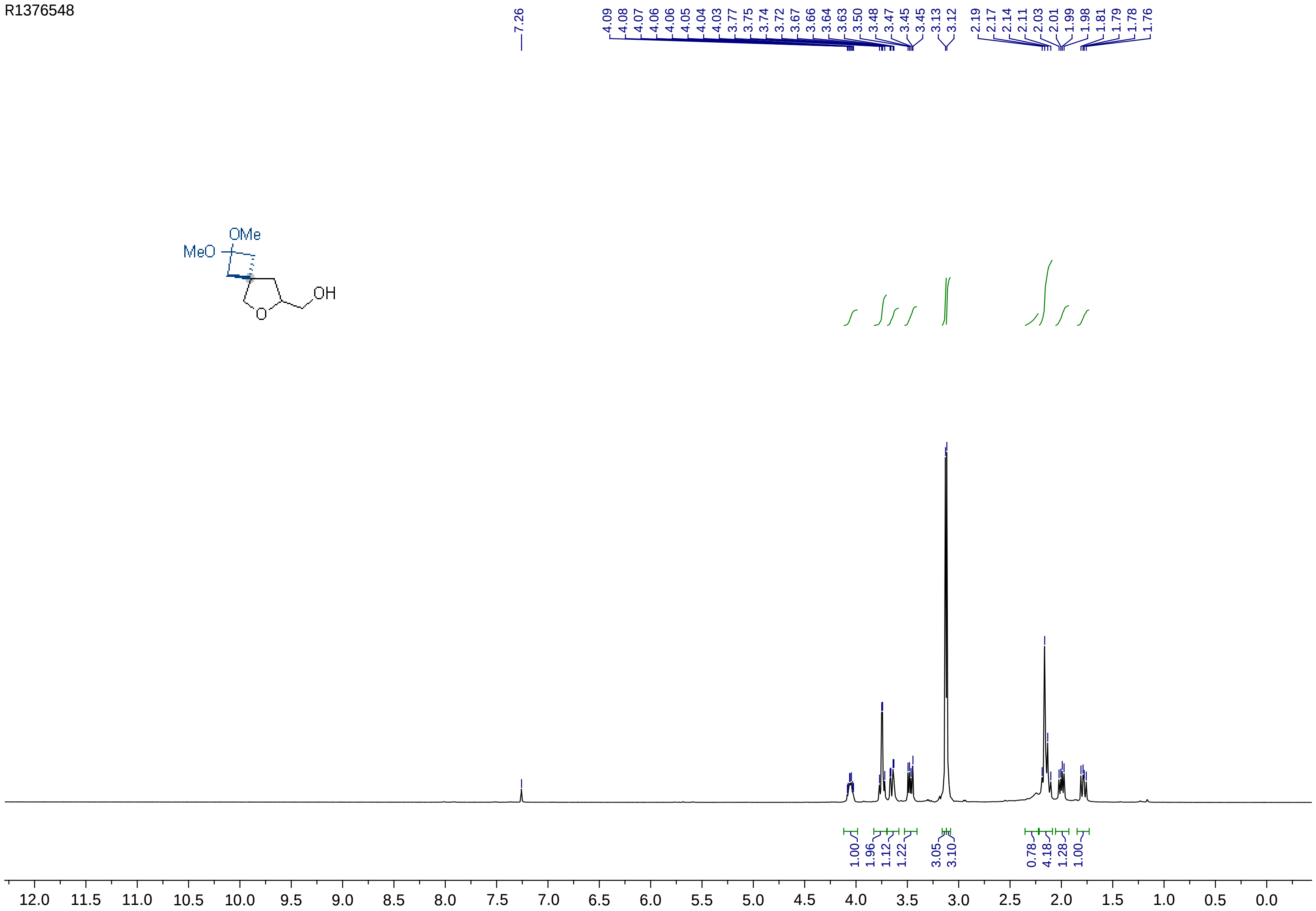
Compound 6c


R1413927
OH
O
7.26
4.06 4.05 4.04 4.03 4.02 4.02 4.01 4.00 4.00 3.73 3.65 3.64 3.62 3.61 3.49 3.47 3.46 3.44
2.29 2.01 2.01 2.00 1.99 1.98 1.97 1.95 1.88 1.86 1.86 1.85 1.84 1.83 1.81 1.81 1.73 1.71 1.70 1.68
1.00 1.99 1.06 1.06
1.14 4.90 2.19 1.13
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

R1413927_C13

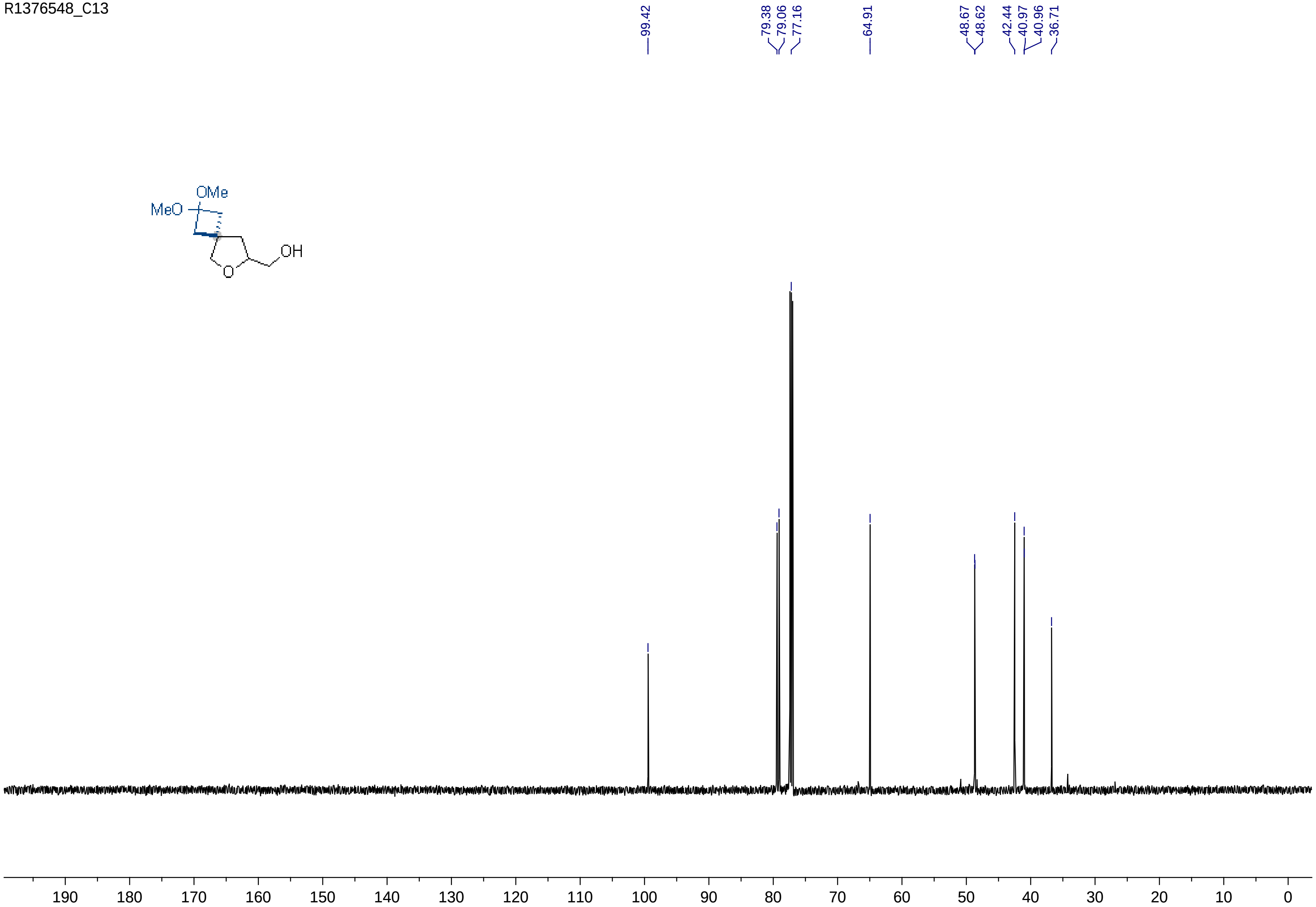


Compound 7c

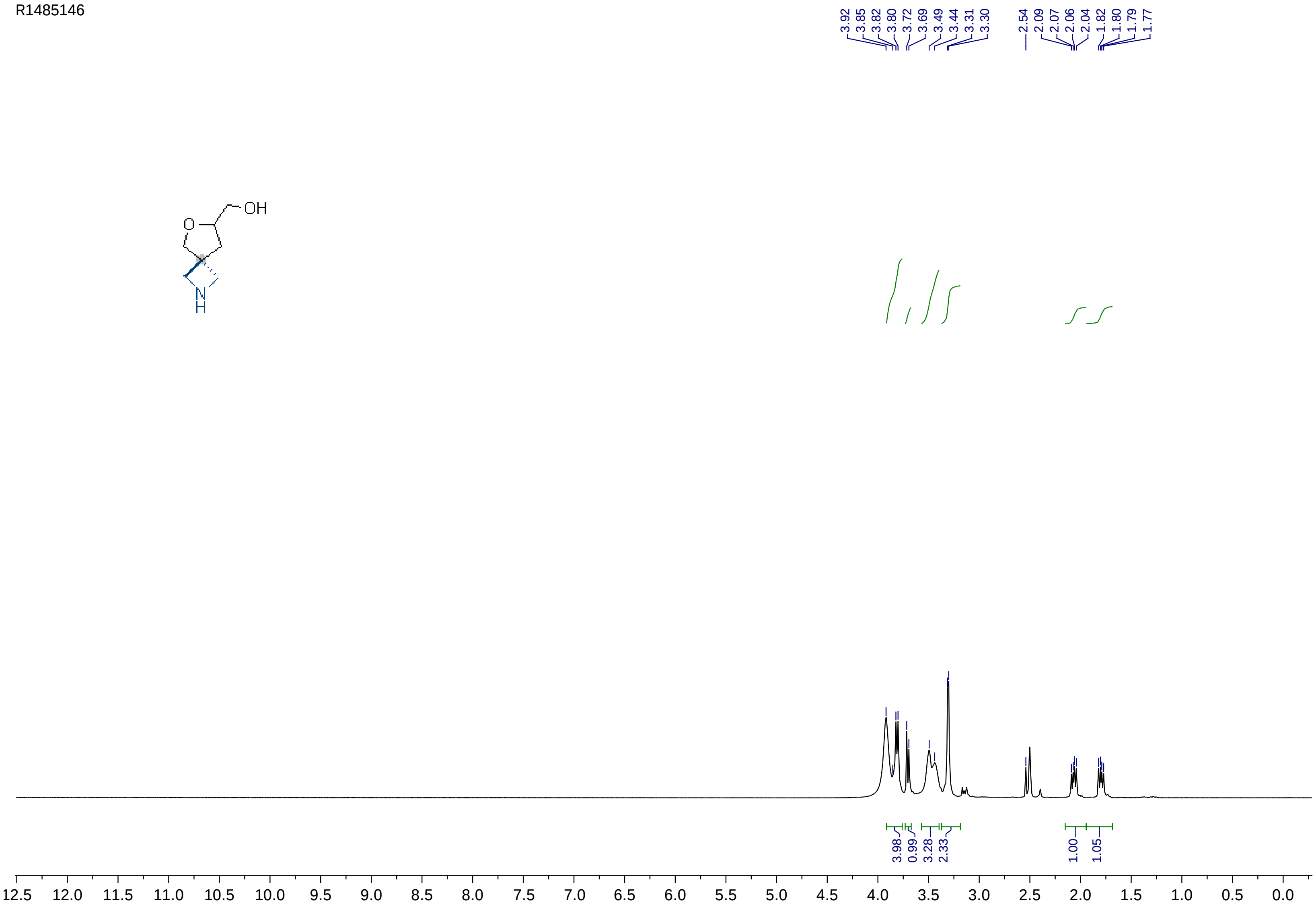


R1376548
OMe
MeO
OH
O
7.26
4.09 4.08 4.07 4.06 4.06 4.05 4.04 4.03 3.77 3.75 3.74 3.72 3.67 3.66 3.64 3.63 3.50 3.48 3.47 3.45 3.45 3.13 3.12
2.19 2.17 2.14 2.11 2.03 2.01 1.99 1.98 1.81 1.79 1.78 1.76
1.00 1.96 1.12 1.22 3.05 3.10 0.78 4.18 1.28 1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

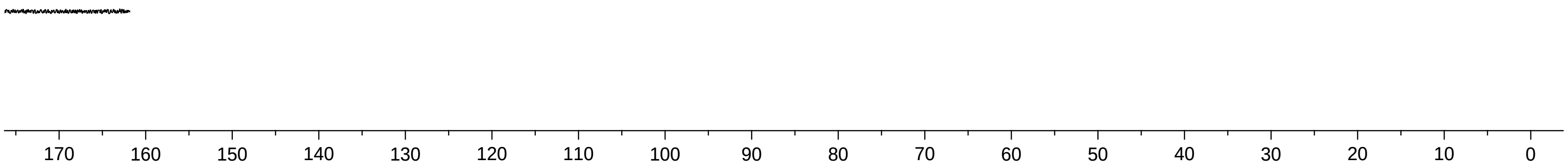
R1376548_C13



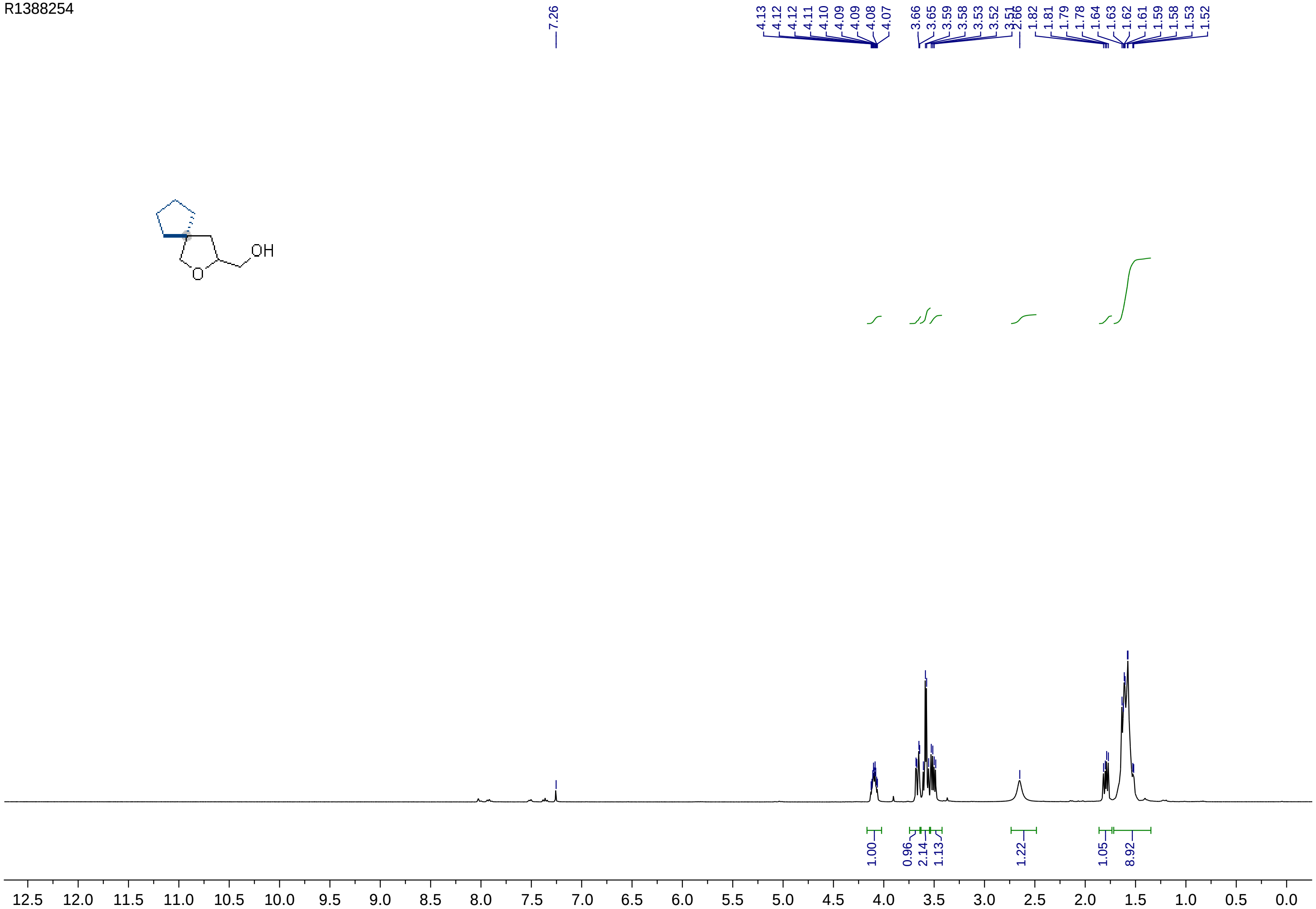
Compound 8c


R1485146
O
OH
N
H
3.92
3.85
3.82
3.80
3.72
3.69
3.49
3.44
3.31
3.30
2.54
2.09
2.07
2.06
2.04
1.82
1.80
1.79
1.77
3.98
0.99
3.28
2.33
1.00
1.05
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

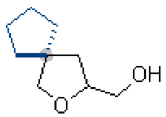
R1485146_C13

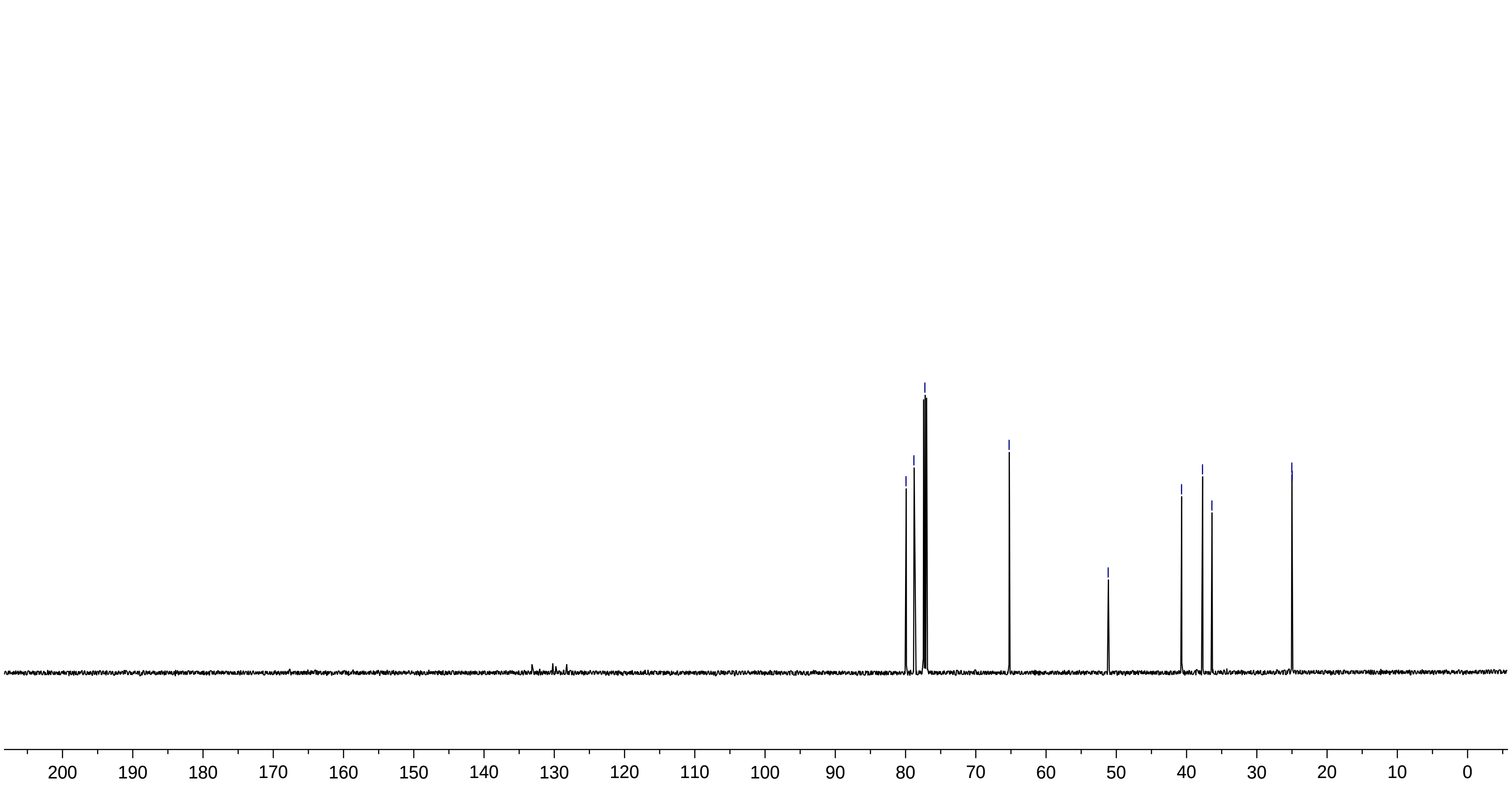


Compound 9c

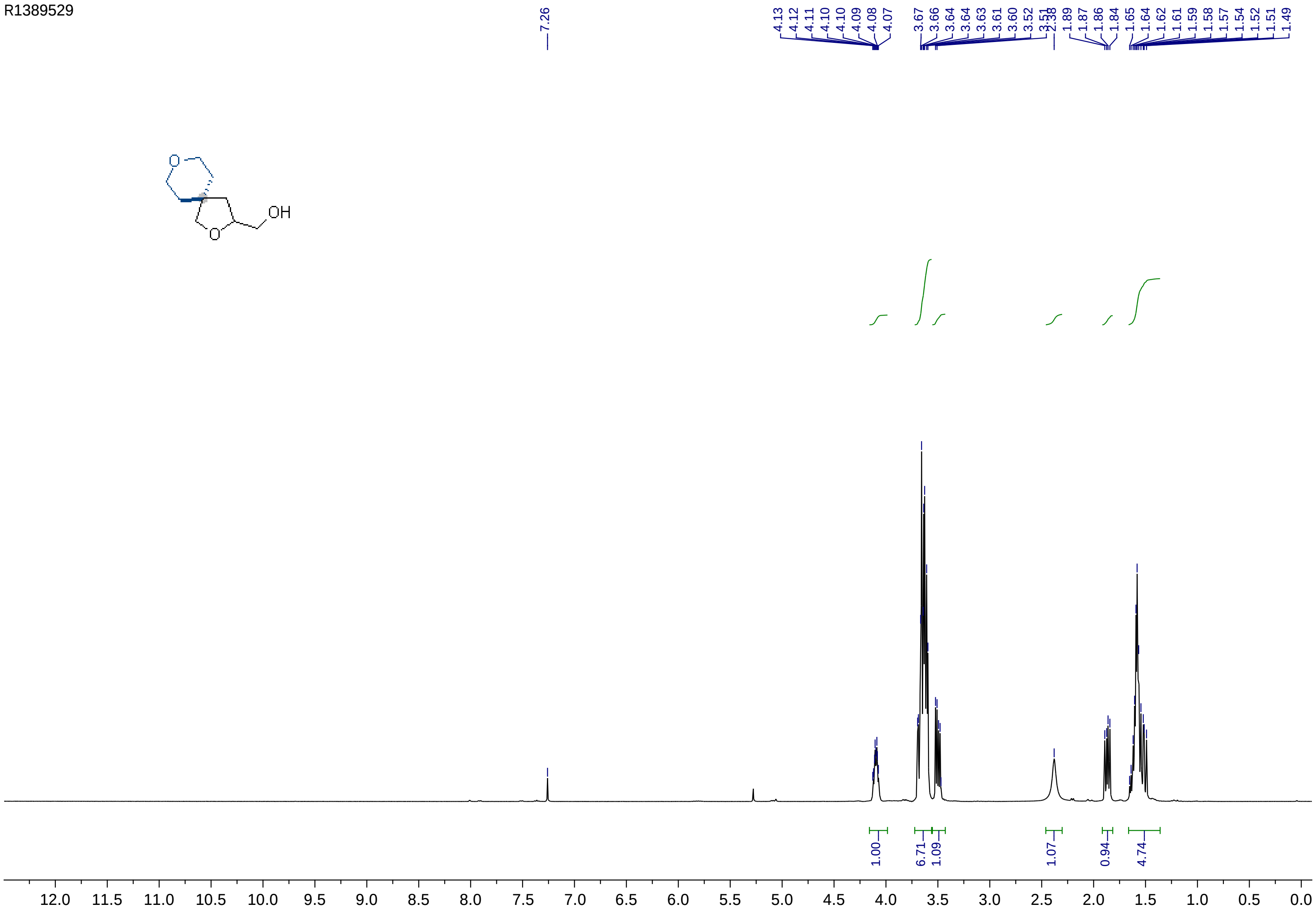

R1388254
OH
O
7.26
4.13 4.12 4.12 4.11 4.10 4.09 4.09 4.08 4.07
3.66 3.65 3.59 3.58 3.53 3.52 3.51
2.66
1.82 1.81 1.79 1.78 1.64 1.63 1.62 1.61 1.59 1.58 1.53 1.52
1.00
0.96
2.14
1.13
1.22
1.05
8.92
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

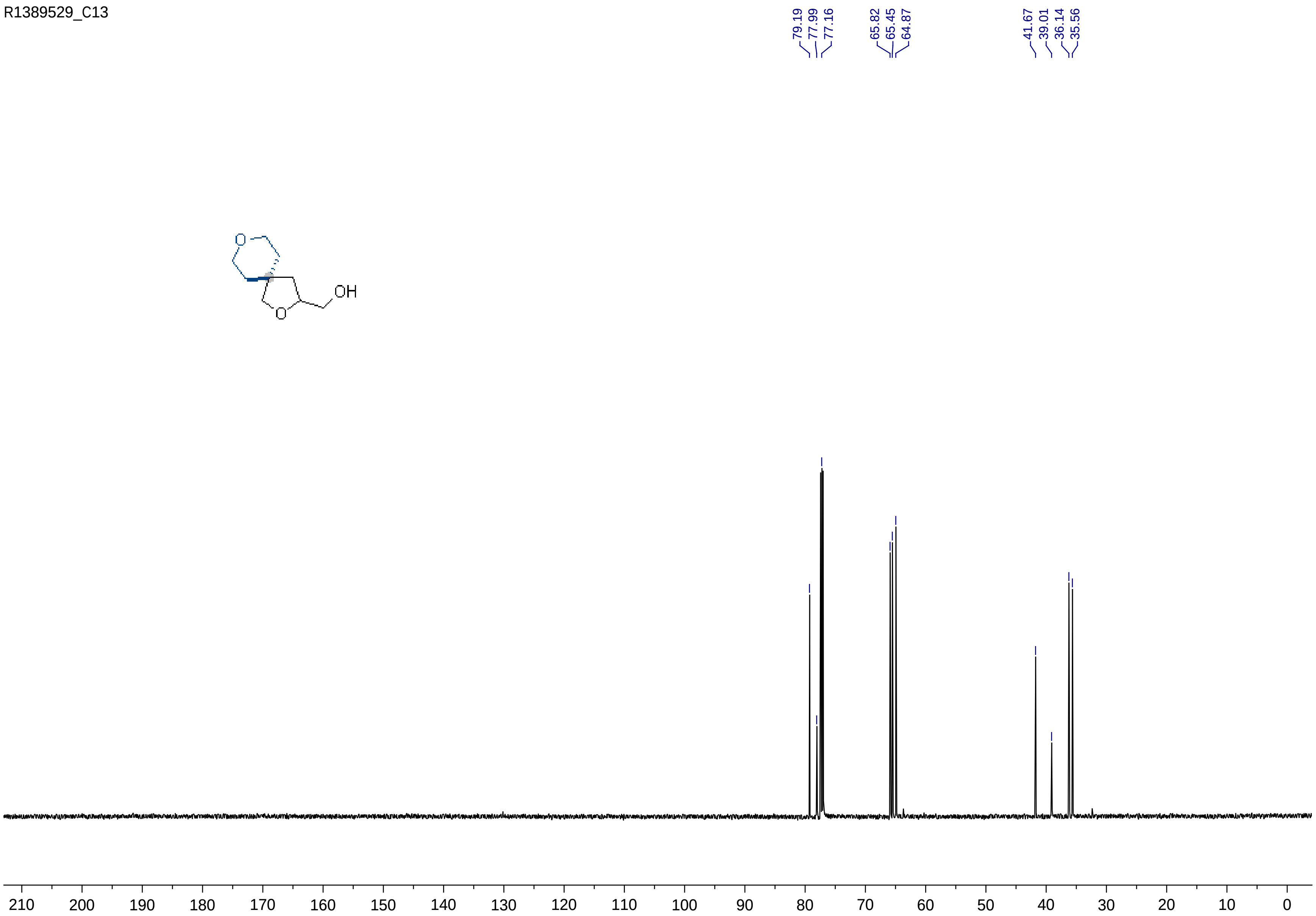
R1388254_C13



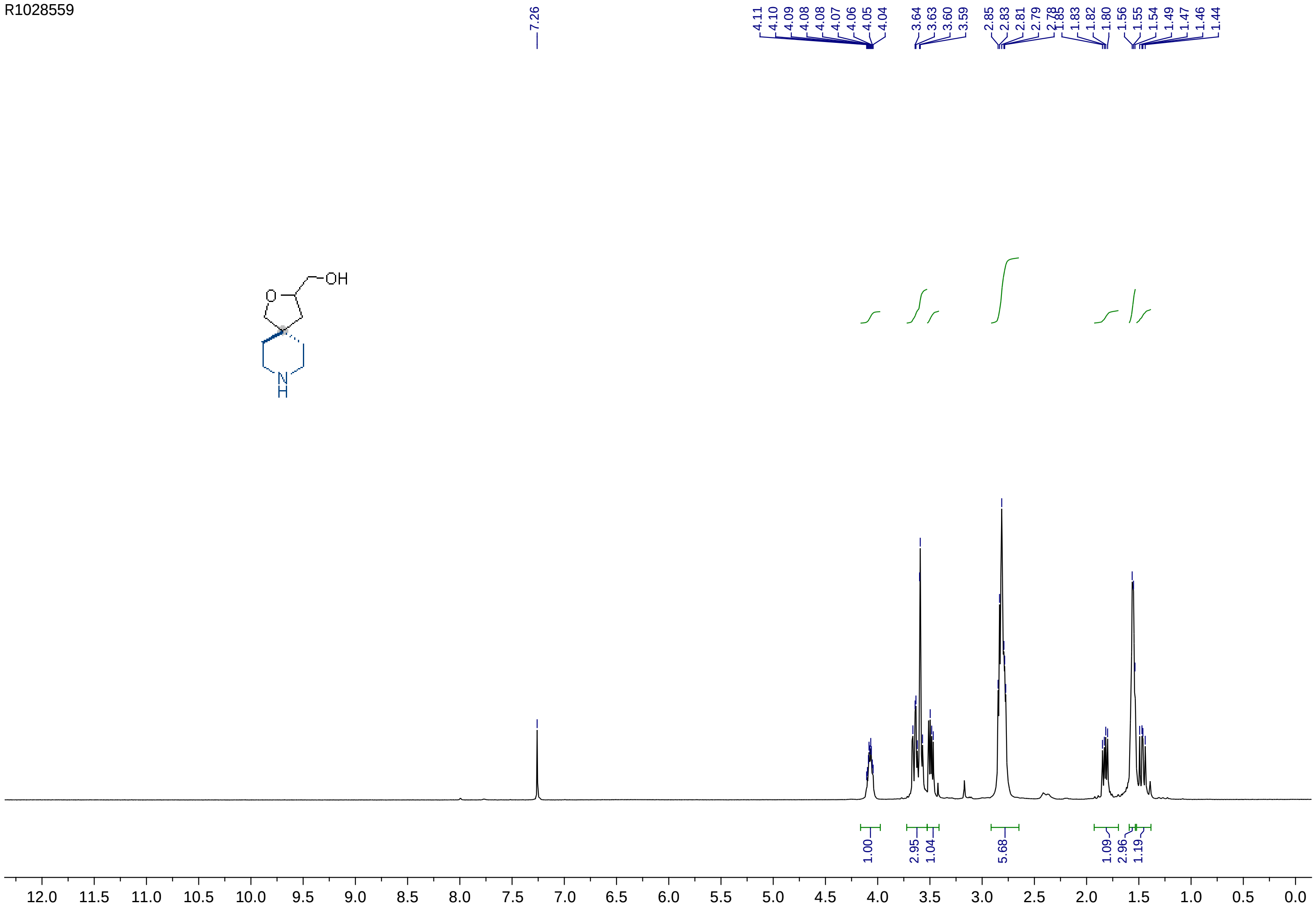


Compound 13c

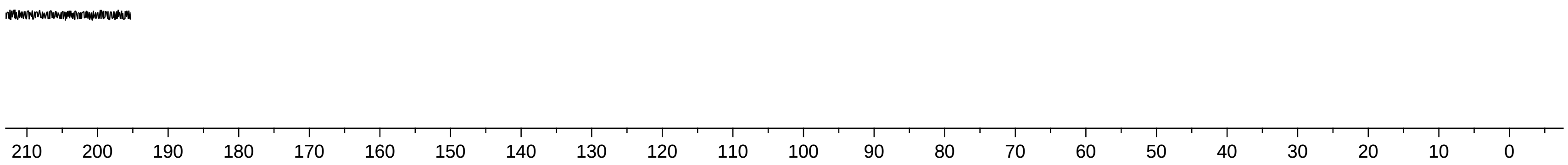



R1389529_C13
79.19
77.99
77.16
65.82
65.45
64.87
41.67
39.01
36.14
35.56
O
O
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

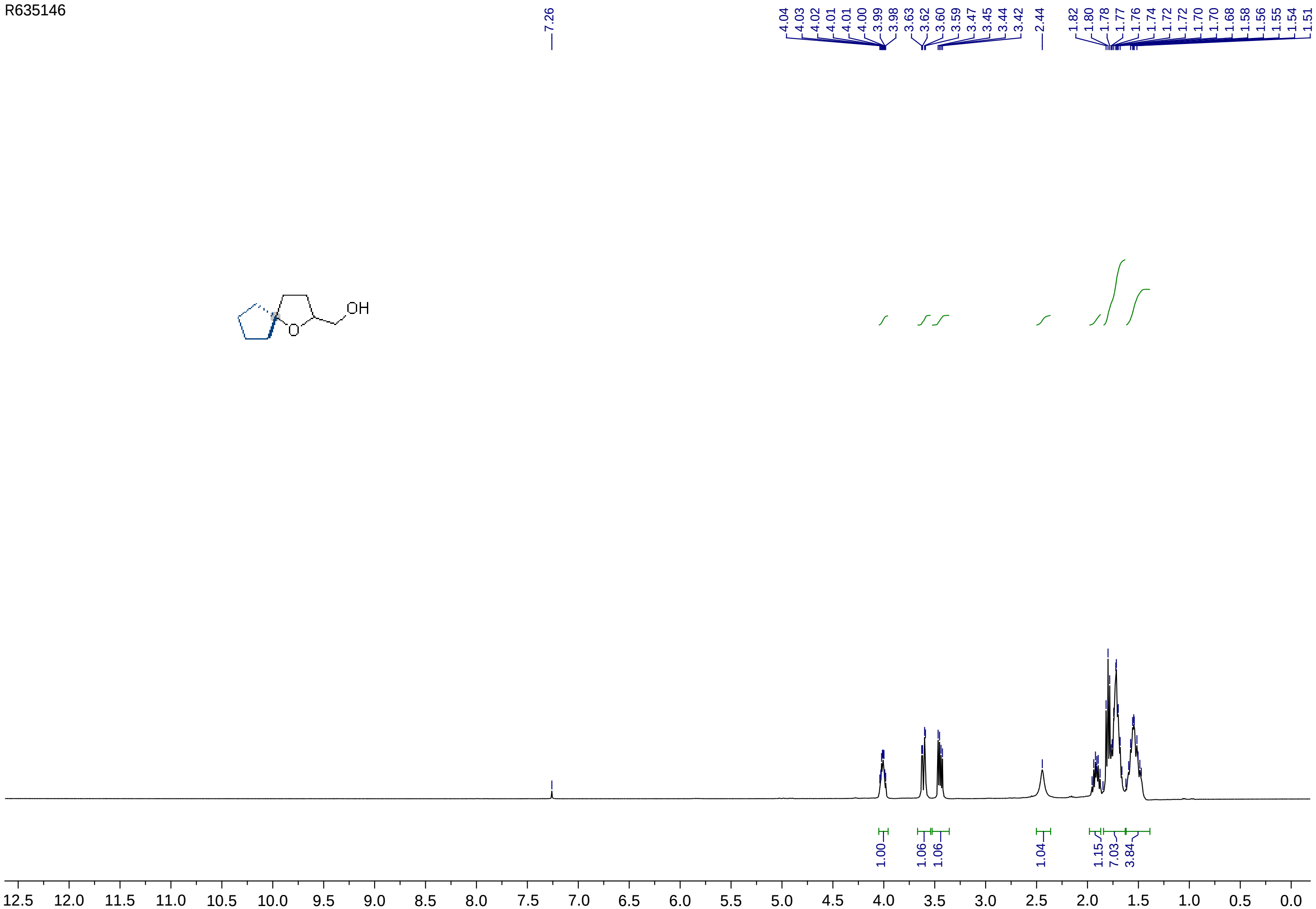
Compound 14c



R1028559_C13

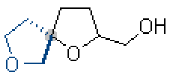


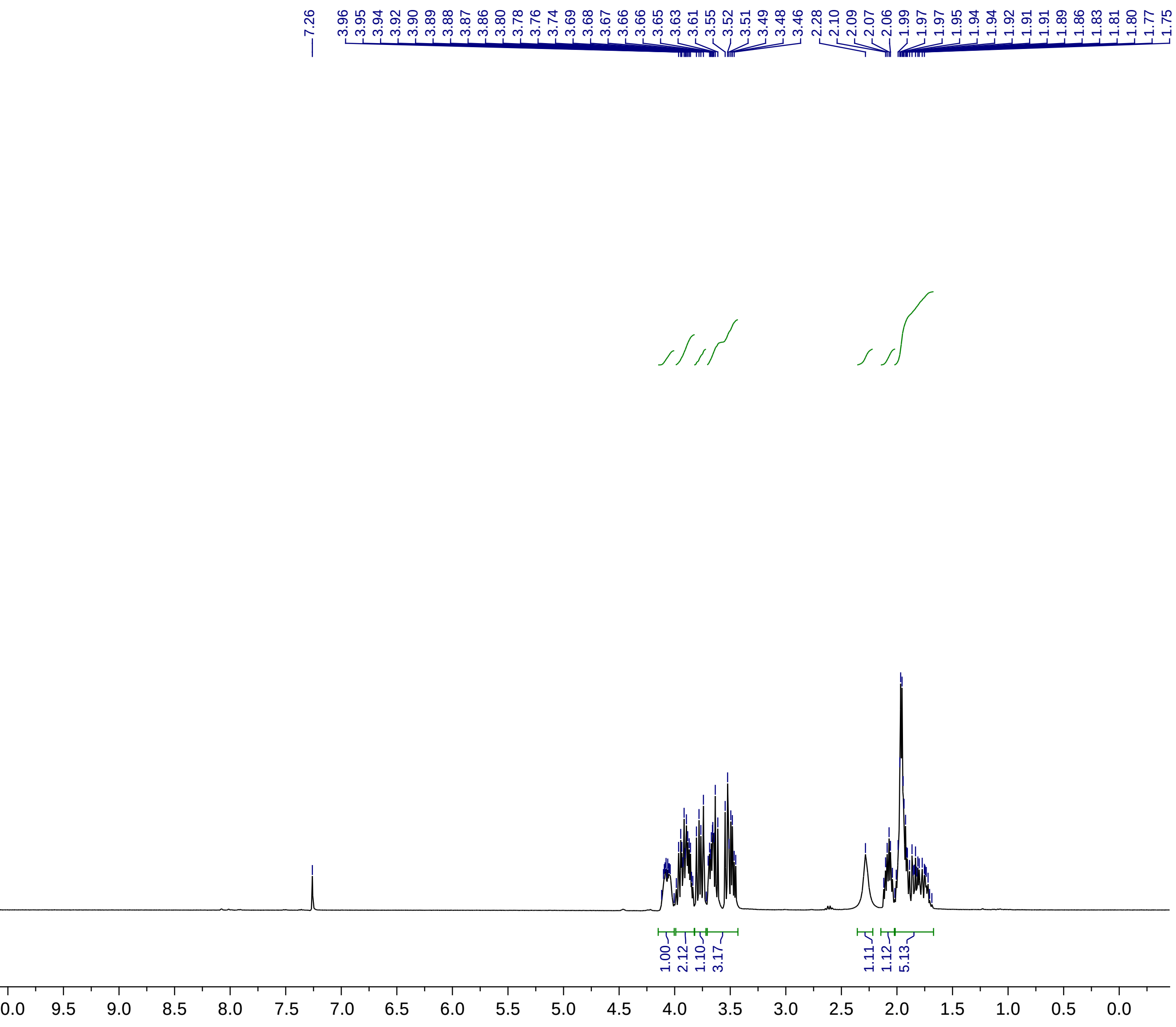
Compound 22c

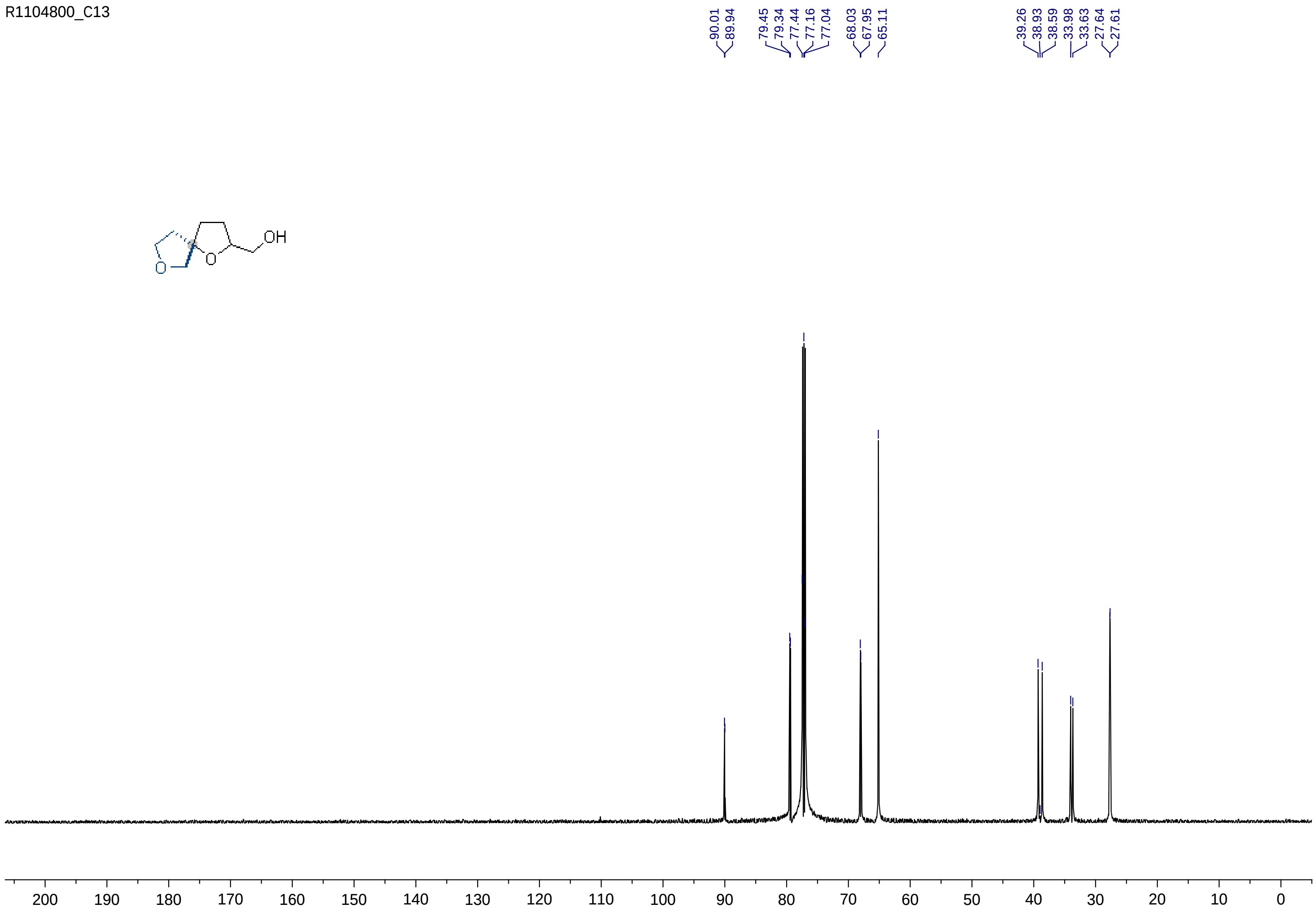



R635146_13C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

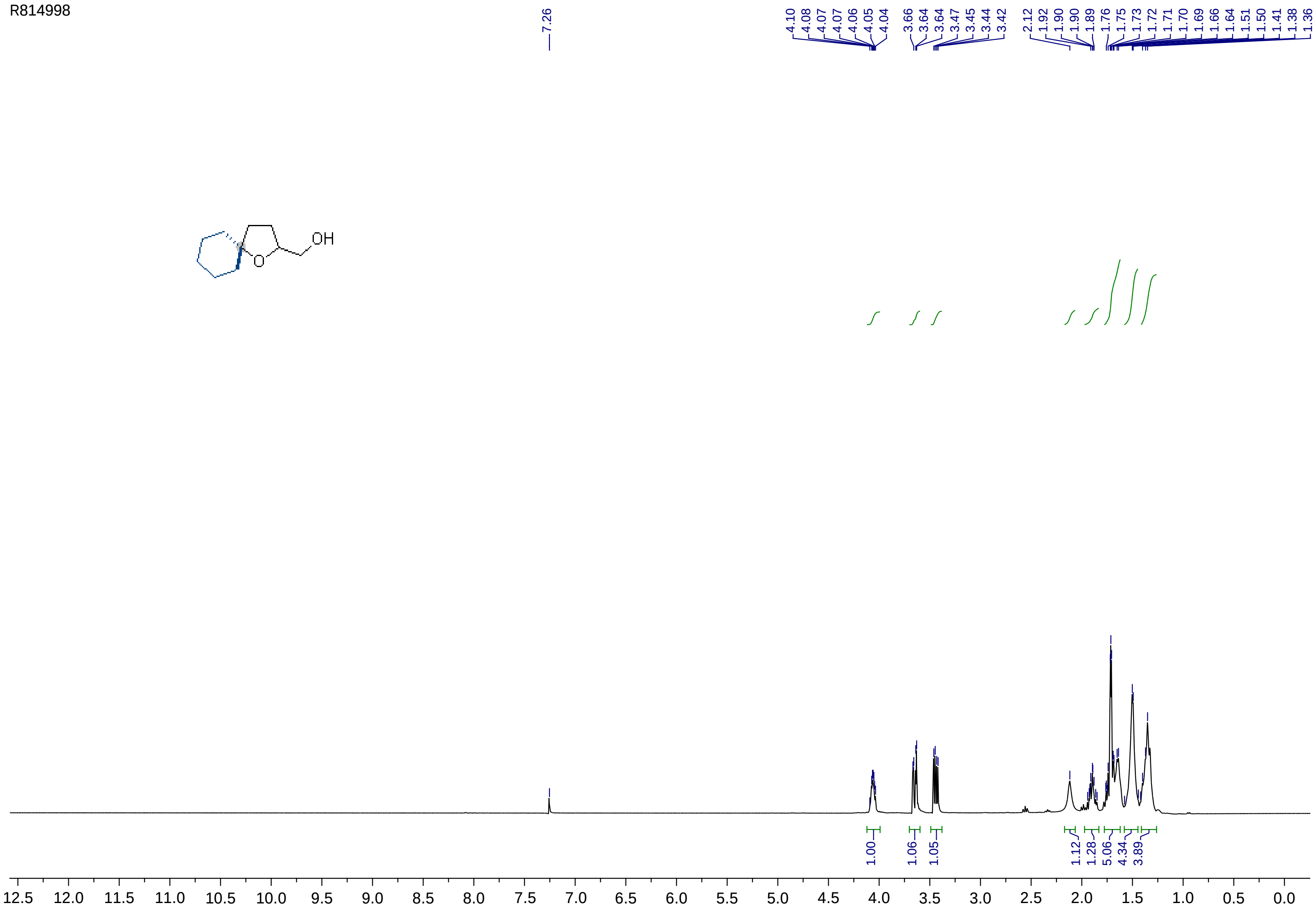
Compound 23c



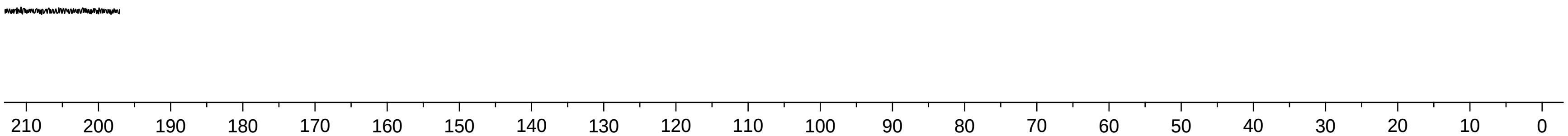



R1104800_C13
90.01
89.94
79.45
79.34
77.44
77.16
77.04
68.03
67.95
65.11
39.26
38.93
38.59
33.98
33.63
27.64
27.61
OH
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

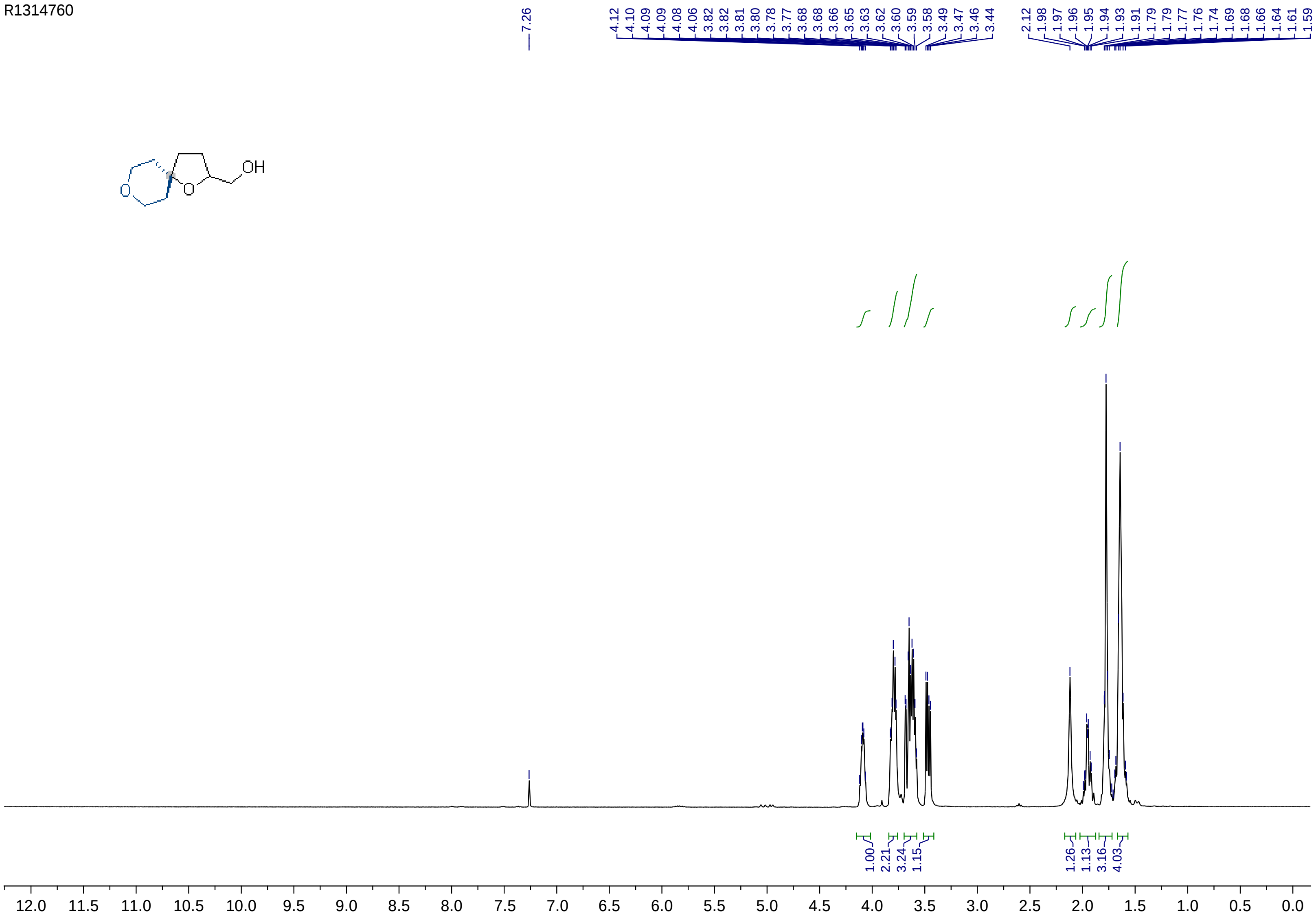
Compound 24c



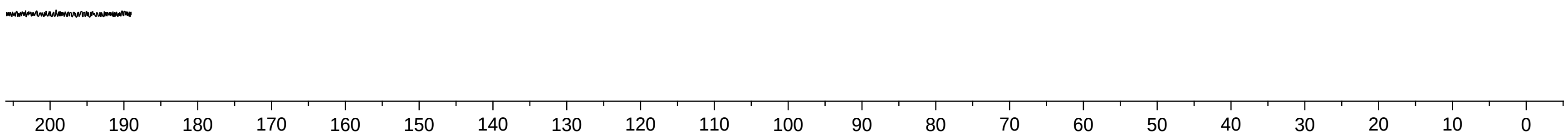
R814998_C13


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

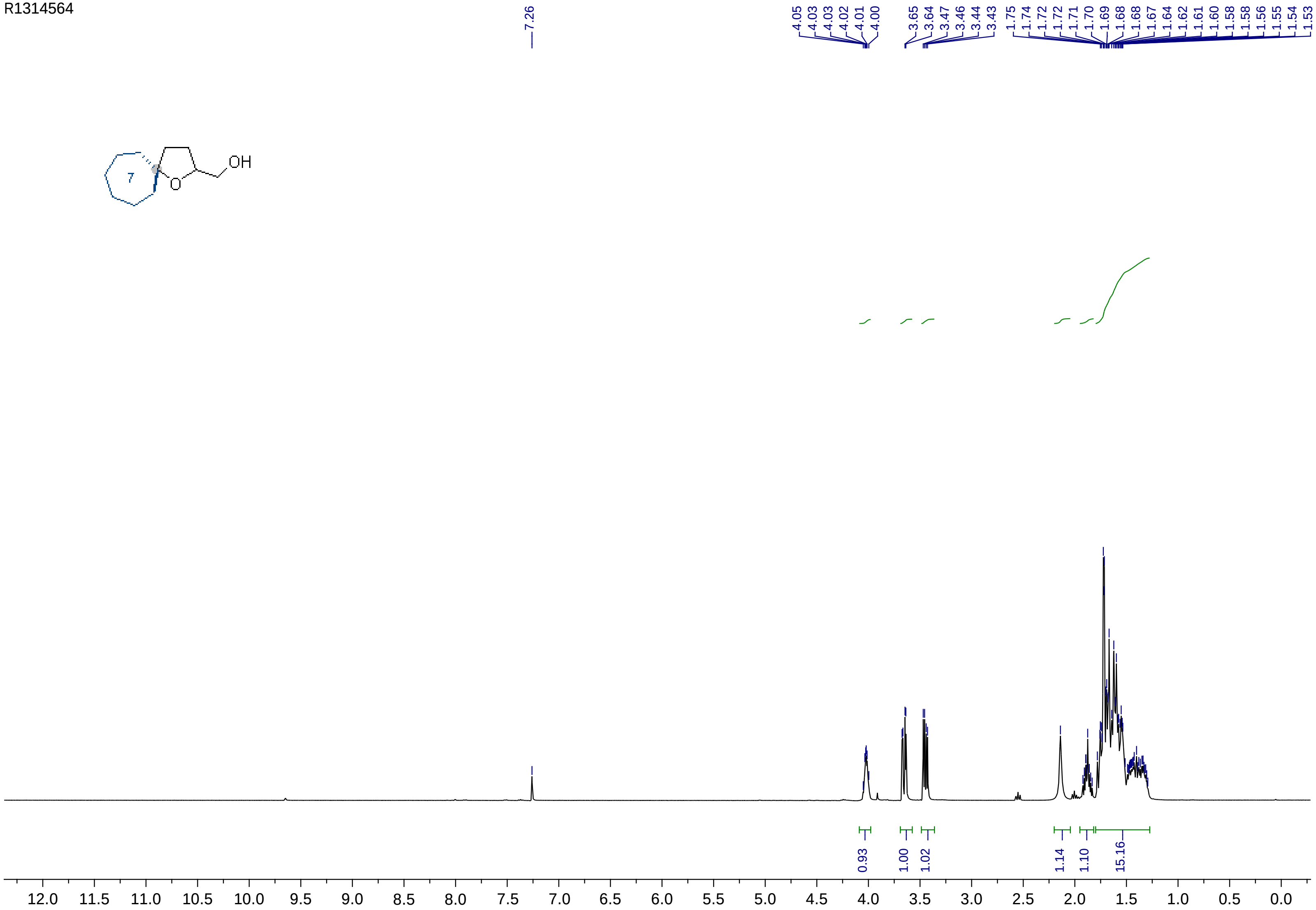
Compound 27c

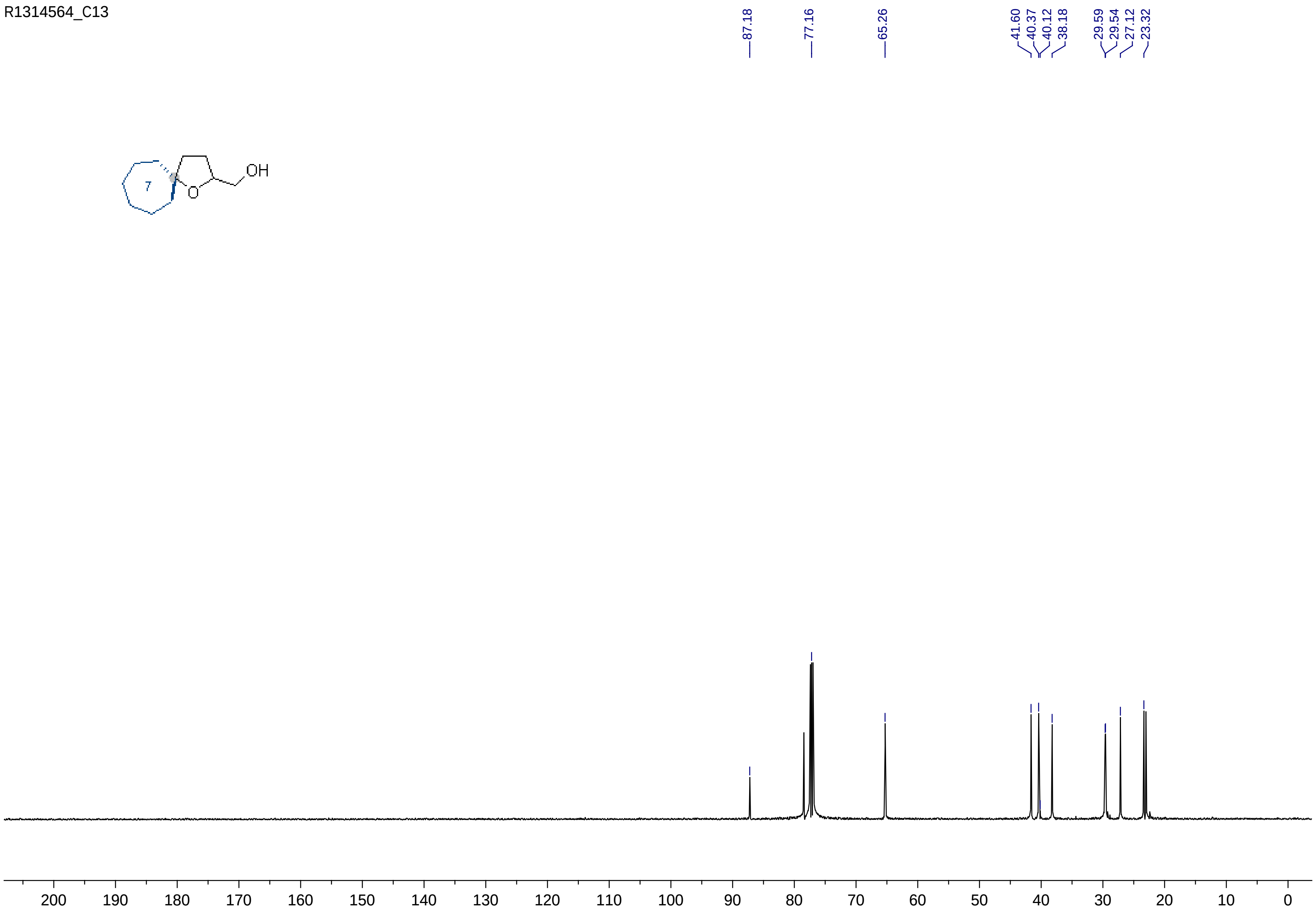


R1314760_C13



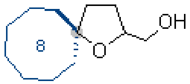
Compound 30c

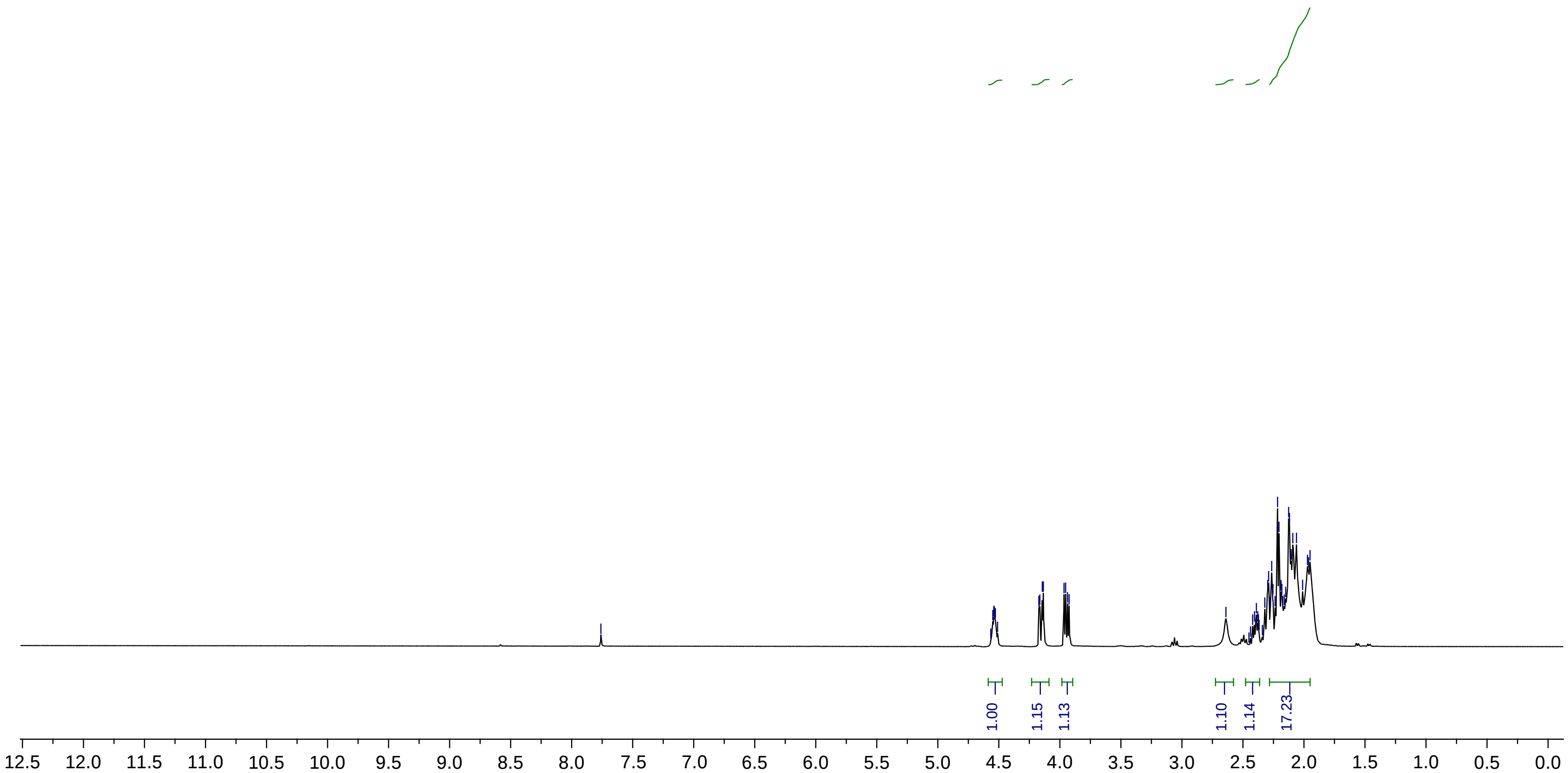



R1314564_C13
87.18
77.16
65.26
41.60
40.37
40.12
38.18
29.59
29.54
27.12
23.32
OH
O
7
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 31c

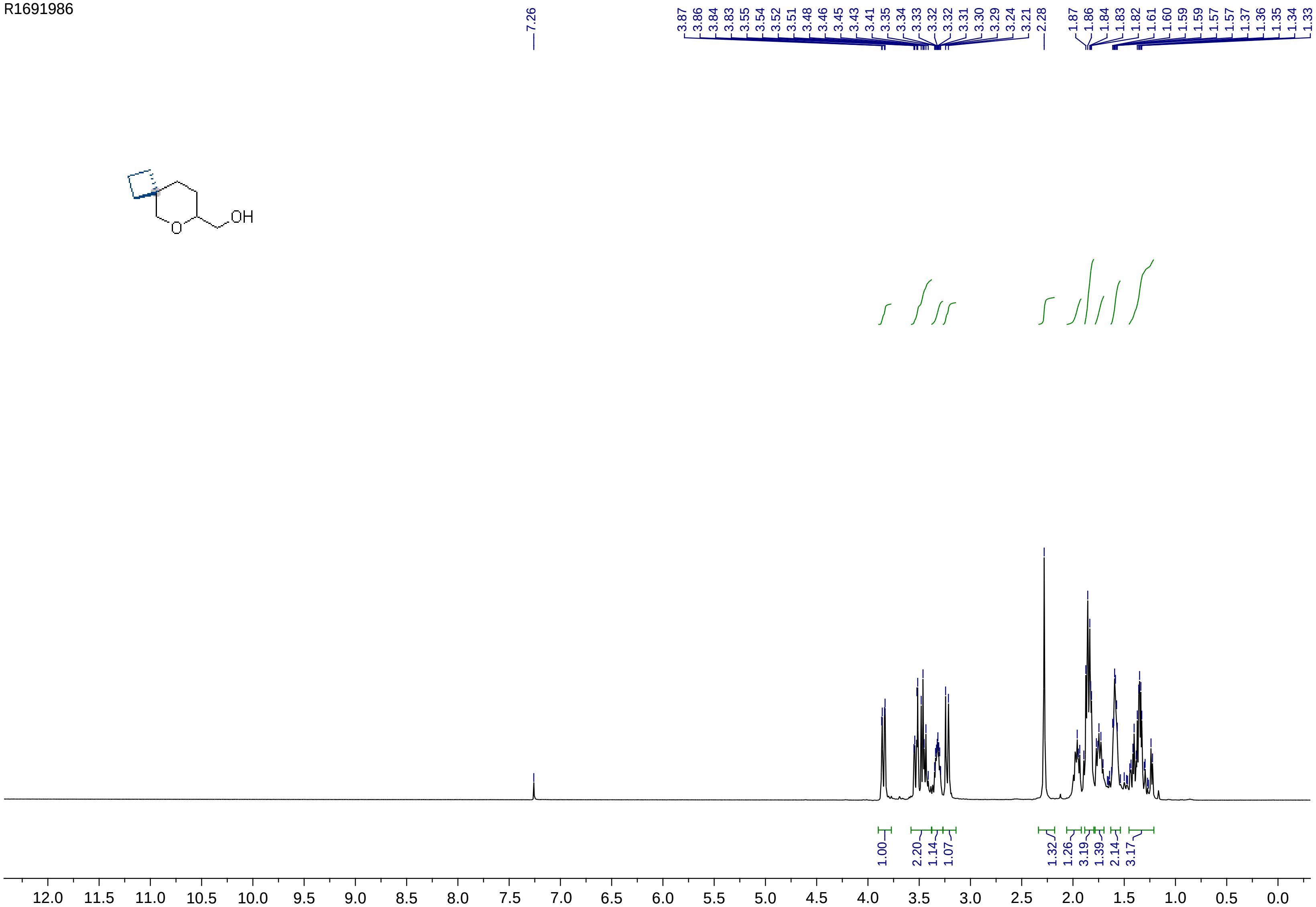
R1416685

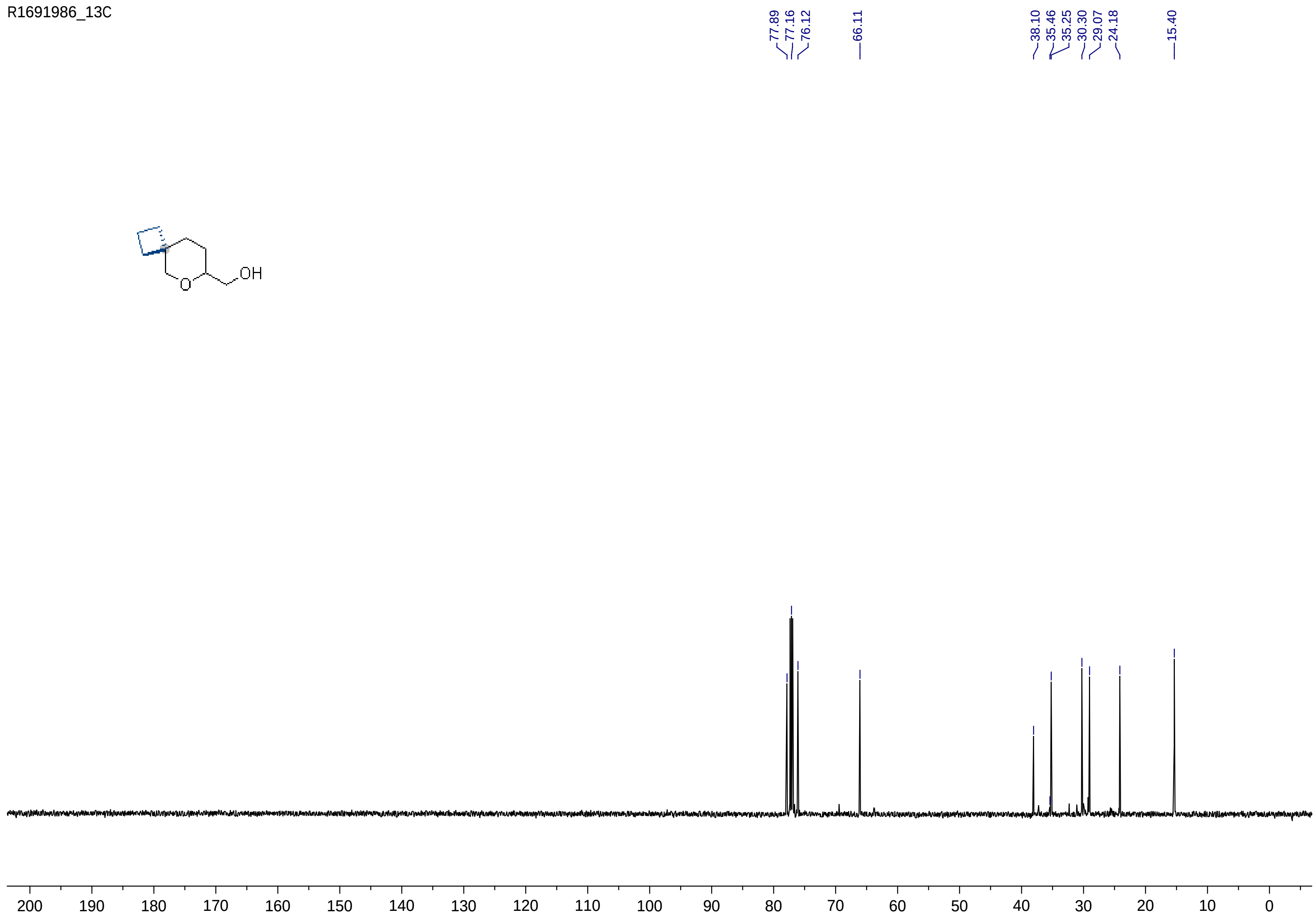




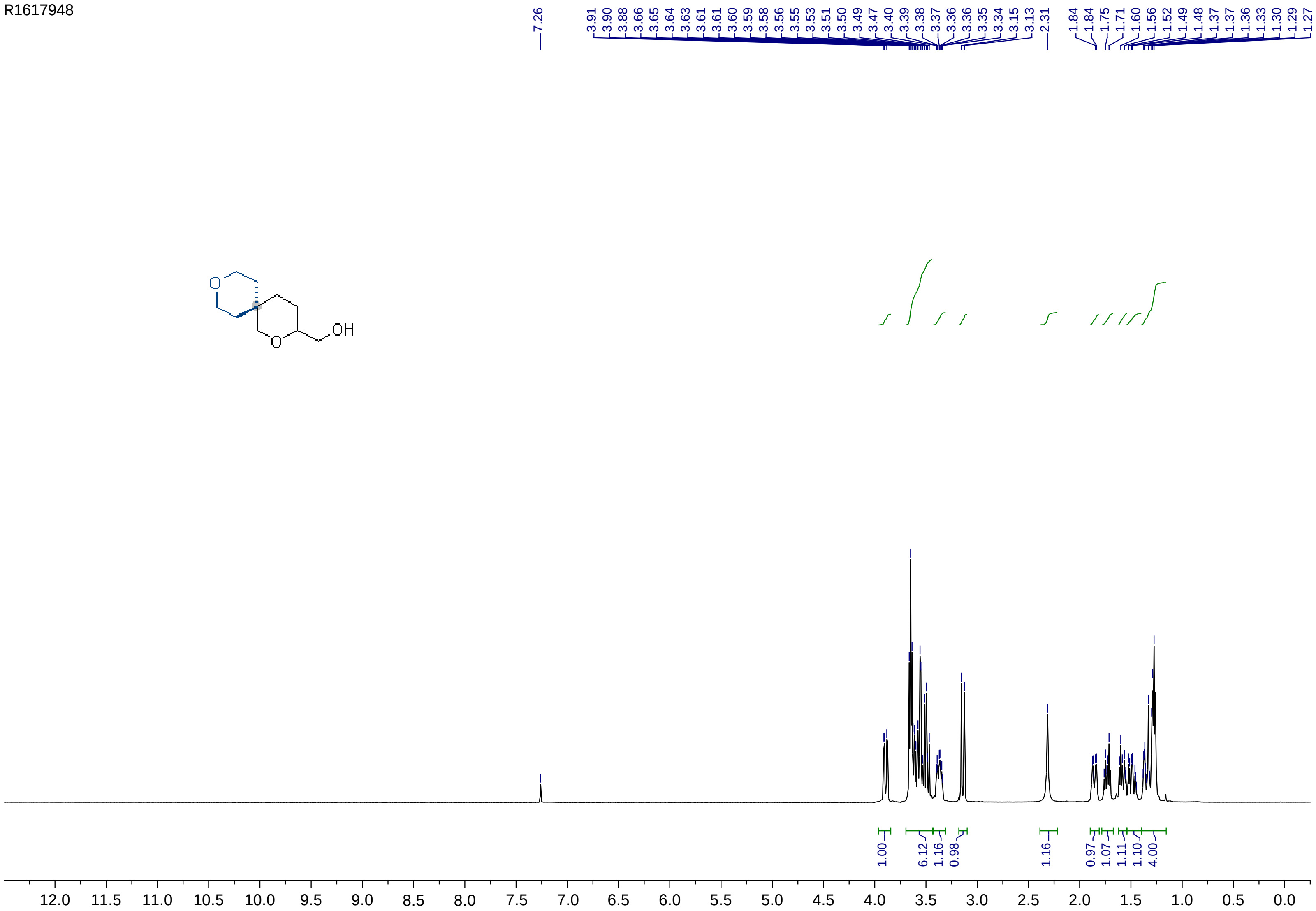

R1416685_C13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 34c

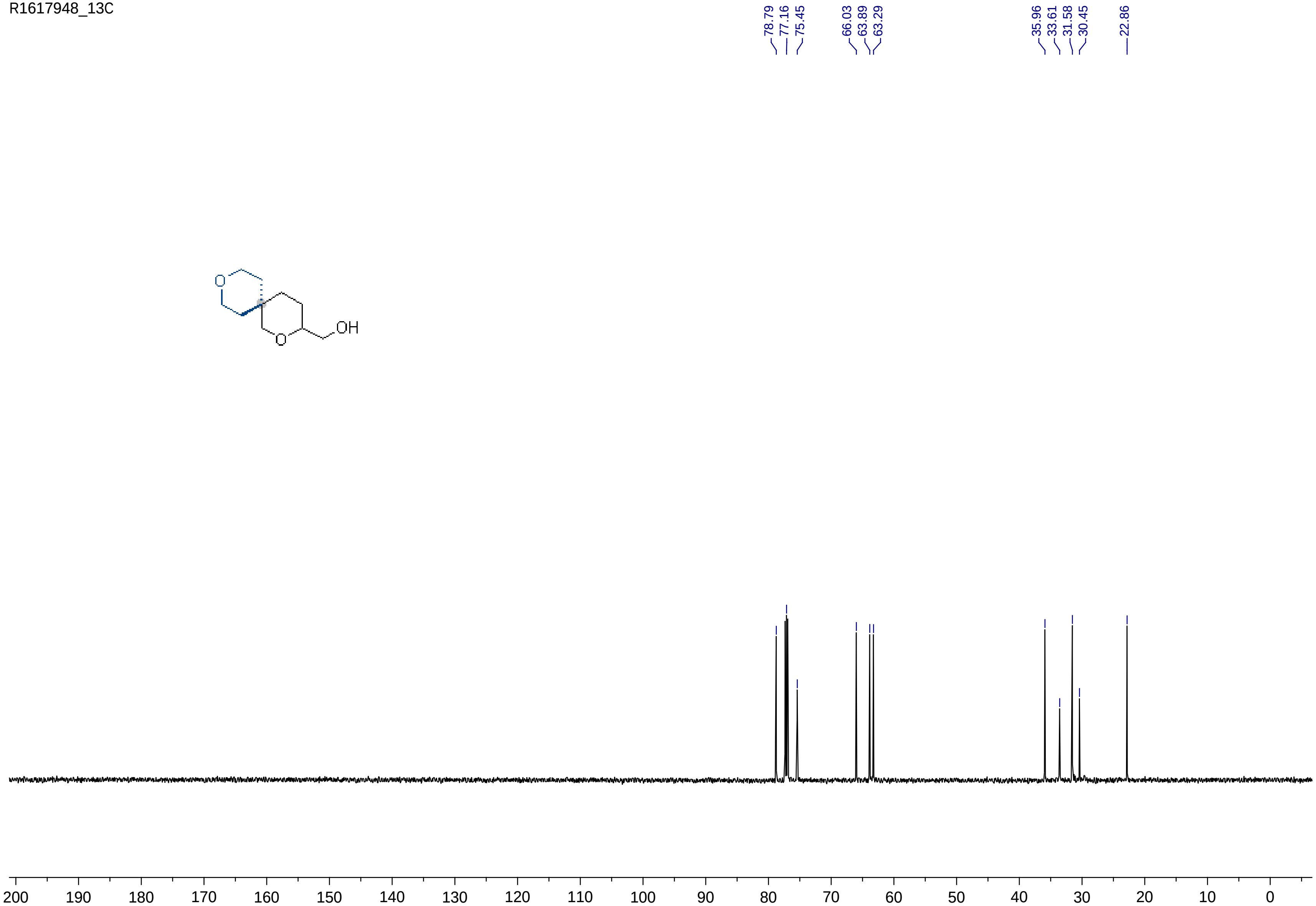



R1691986_13C
77.89
77.16
76.12
66.11
38.10
35.46
35.25
30.30
29.07
24.18
15.40
OH
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

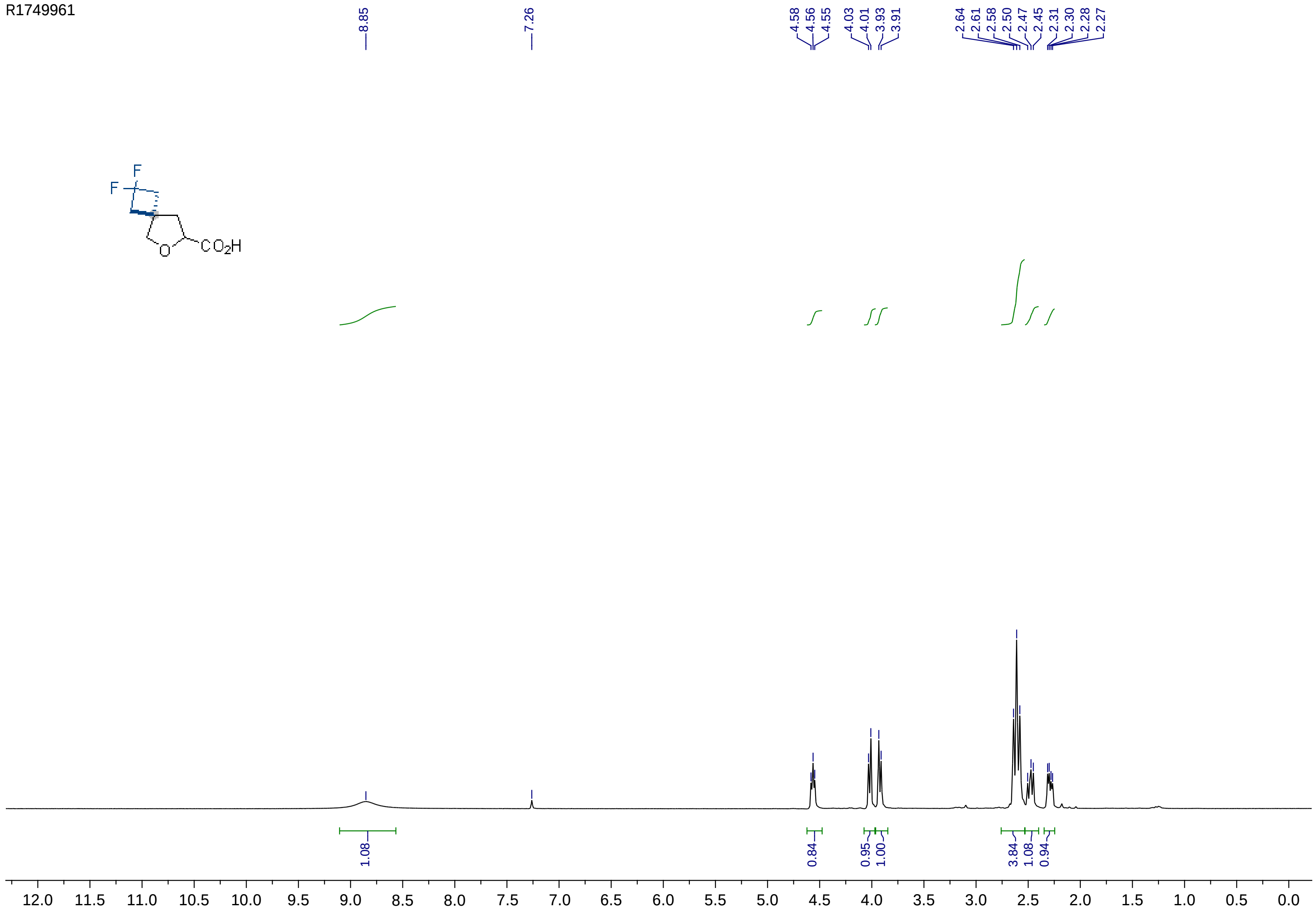
Compound 36c

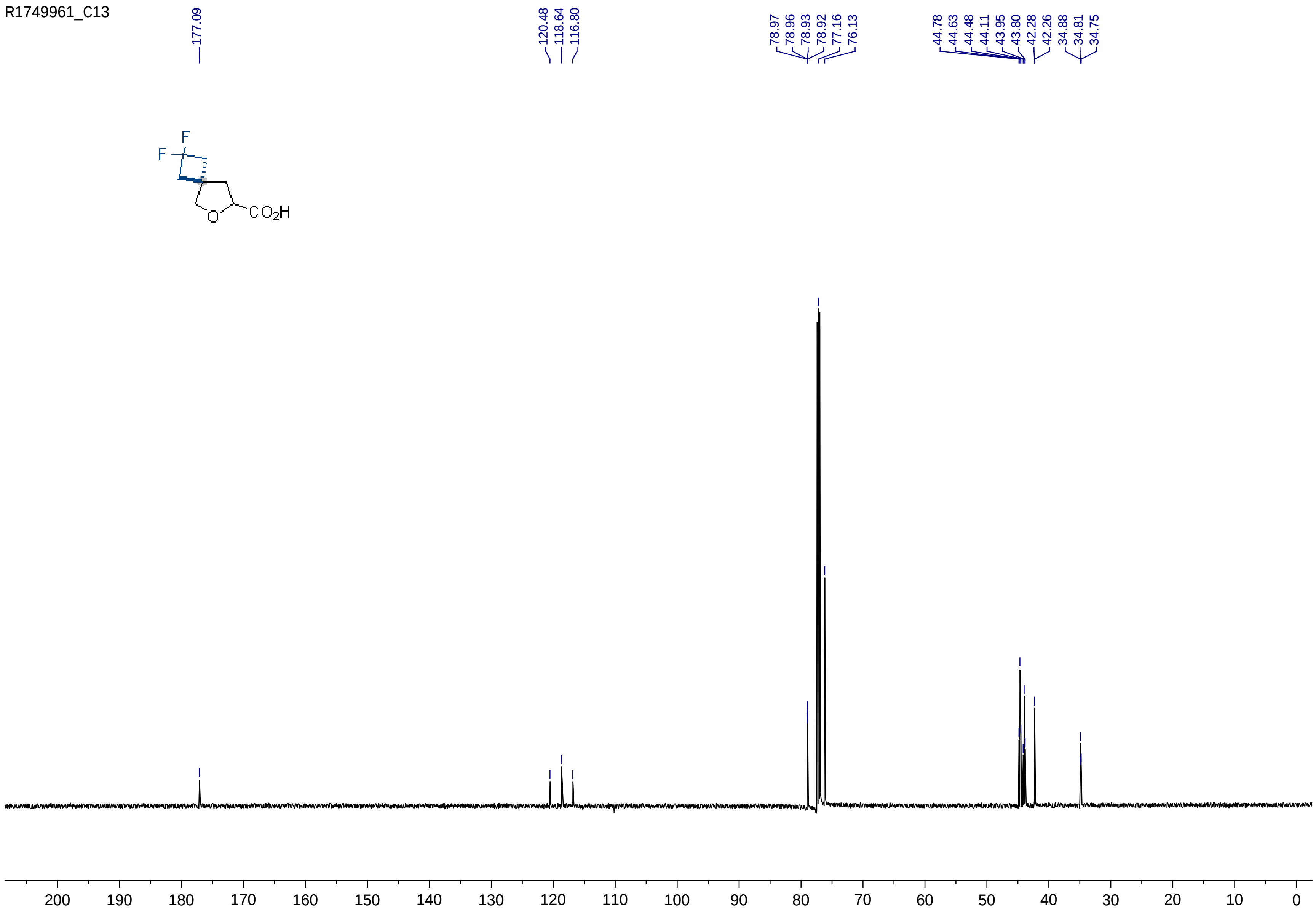


R1617948_13C

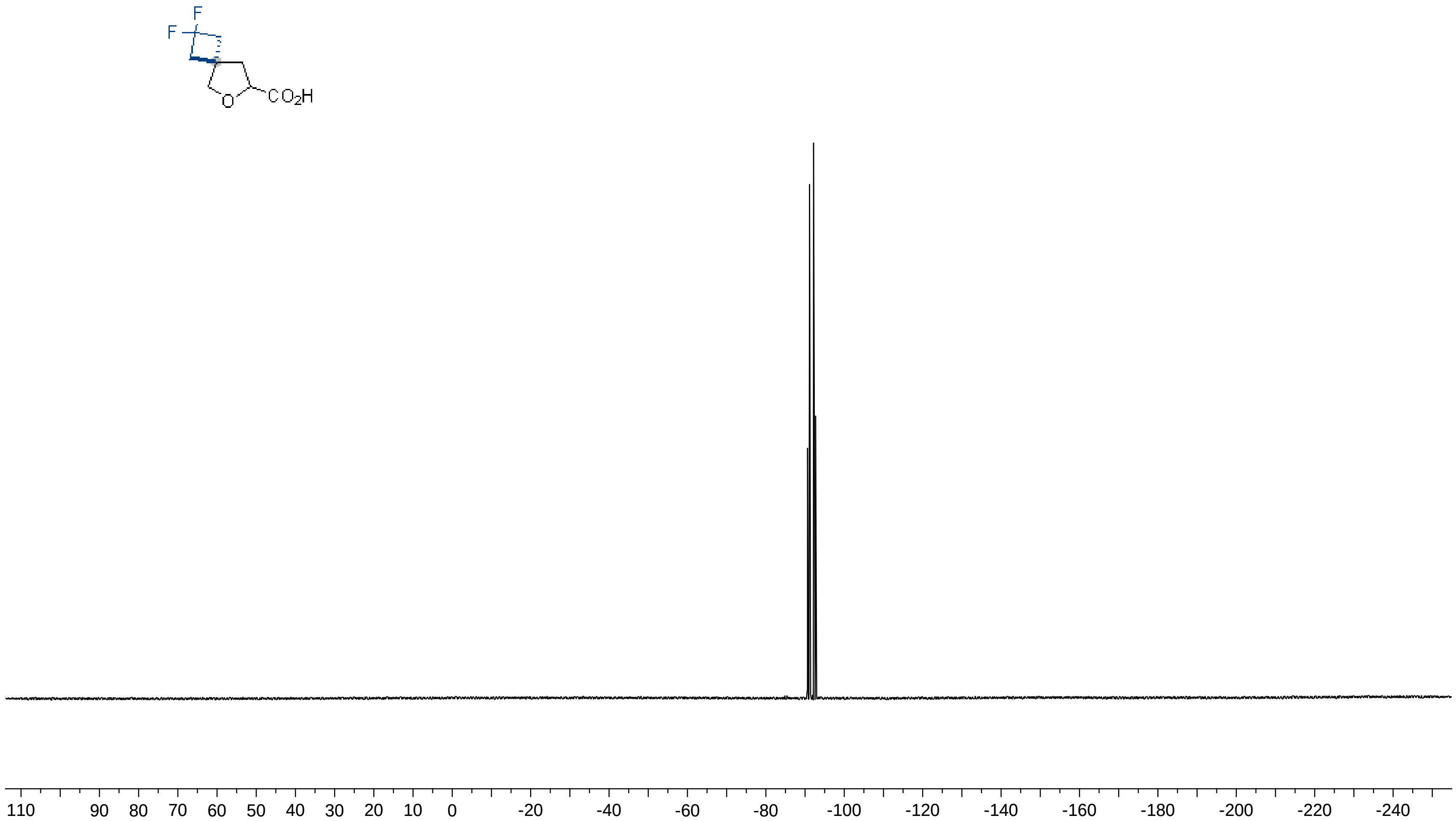


Compound 4d

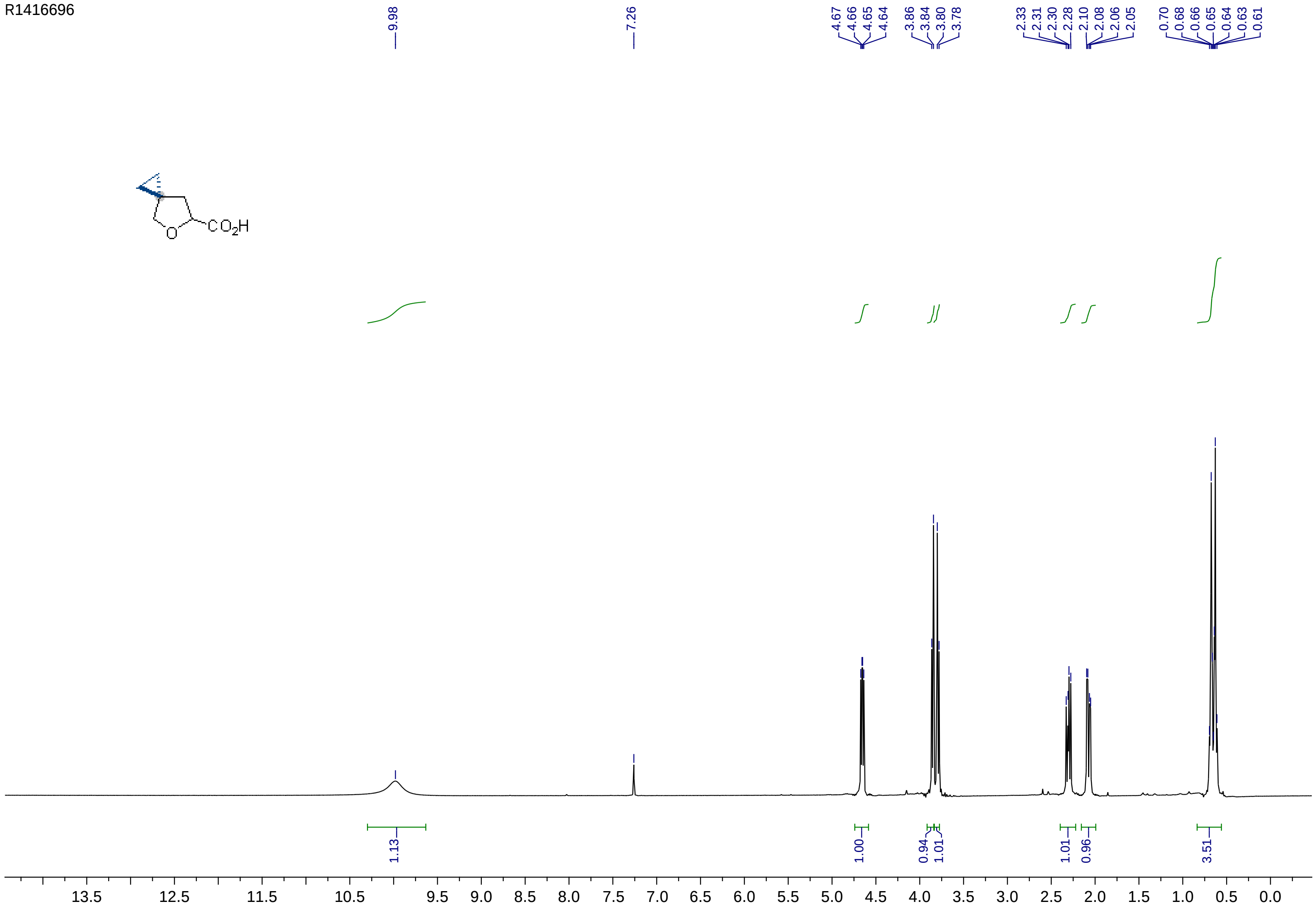

R1749961
8.85
7.26
4.58
4.56
4.55
4.03
4.01
3.93
3.91
2.64
2.61
2.58
2.50
2.47
2.45
2.31
2.30
2.28
2.27
F
F
O
CO2H
1.08
0.84
0.95
1.00
3.84
1.08
0.94
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


R1749961_C13
177.09
120.48
118.64
116.80
78.97
78.96
78.93
78.92
77.16
76.13
44.78
44.63
44.48
44.11
43.95
43.80
42.28
42.26
34.88
34.81
34.75
F
F
O
CO2H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

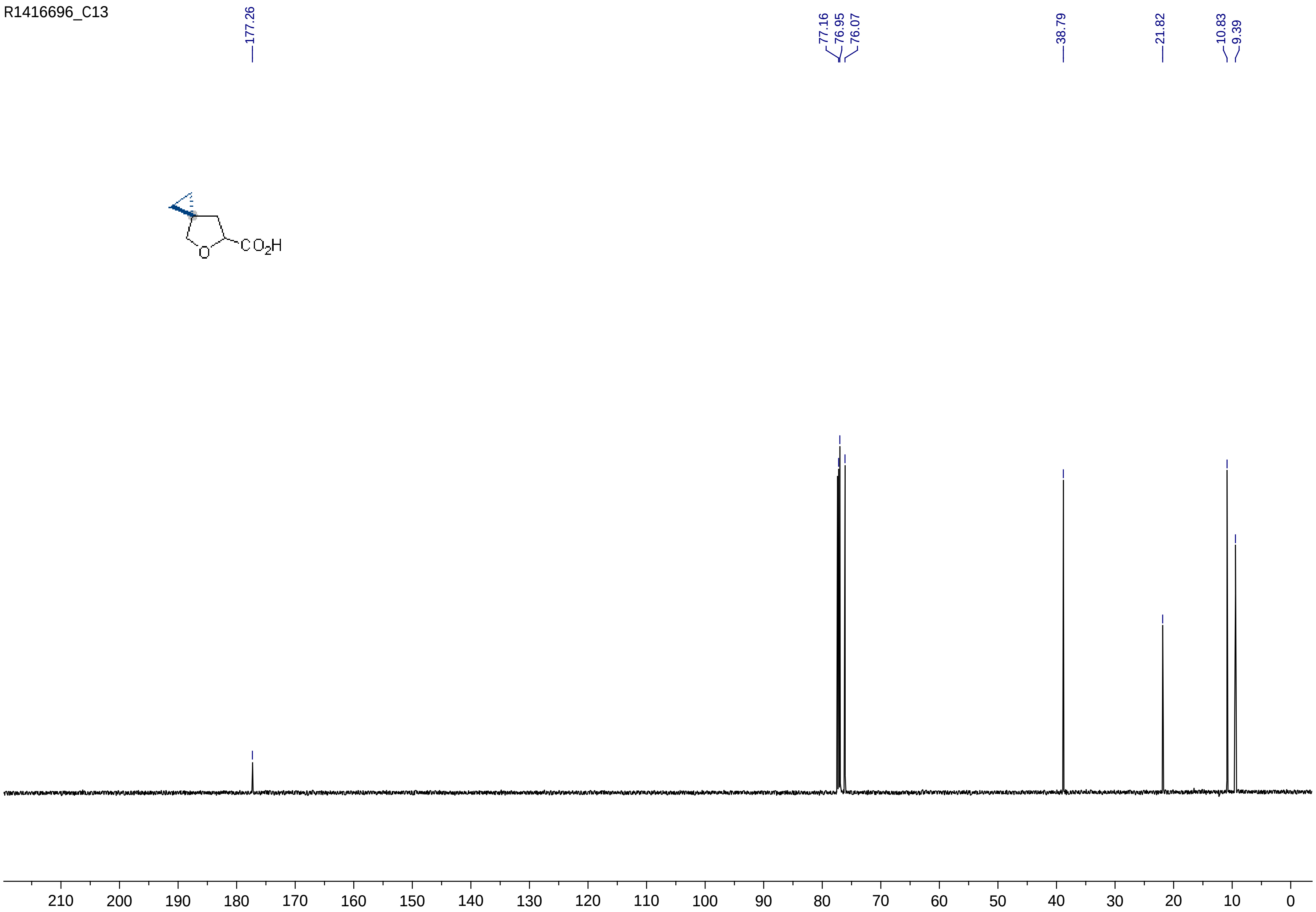
R1749961_F19{H}



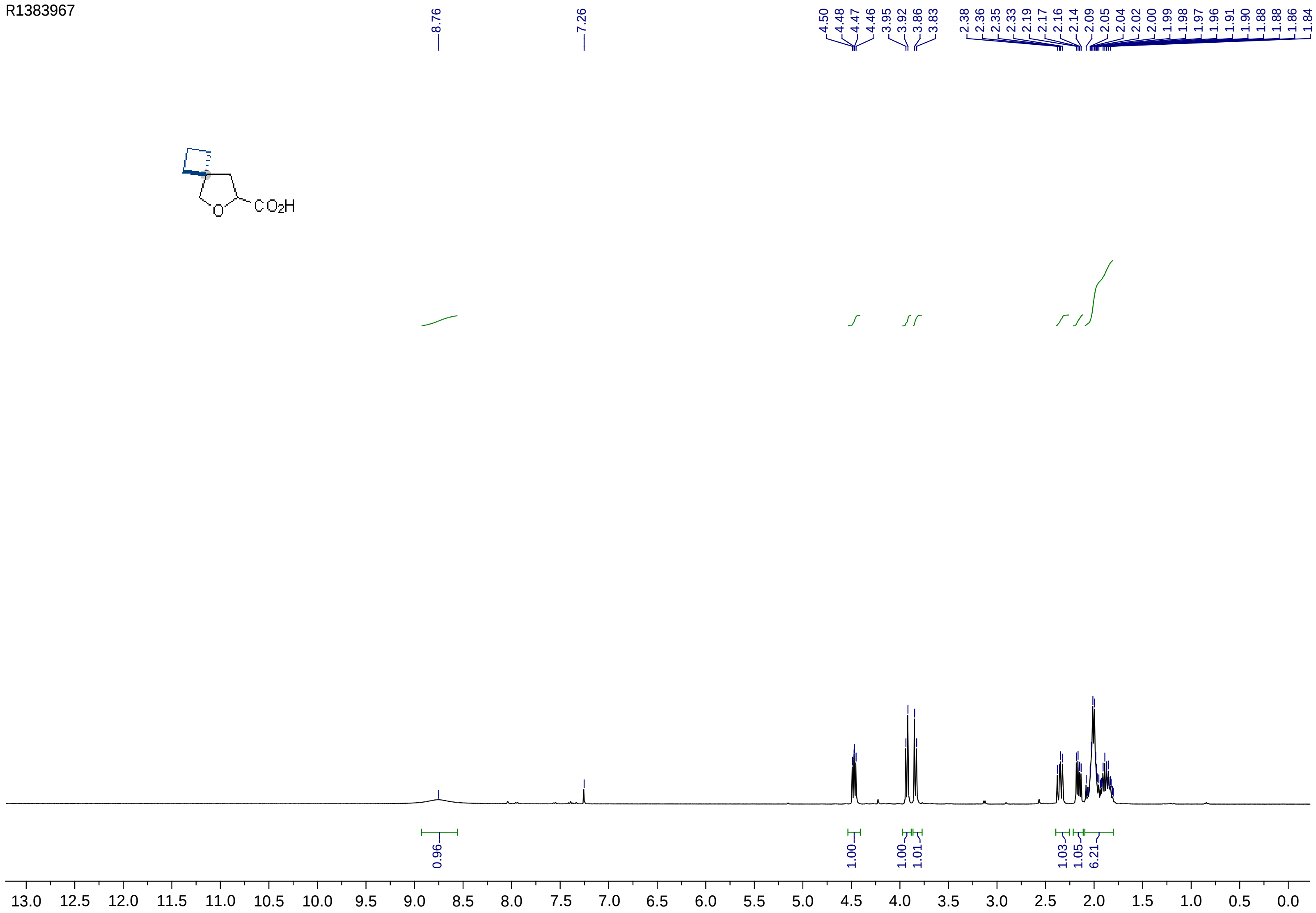
Compound 5d

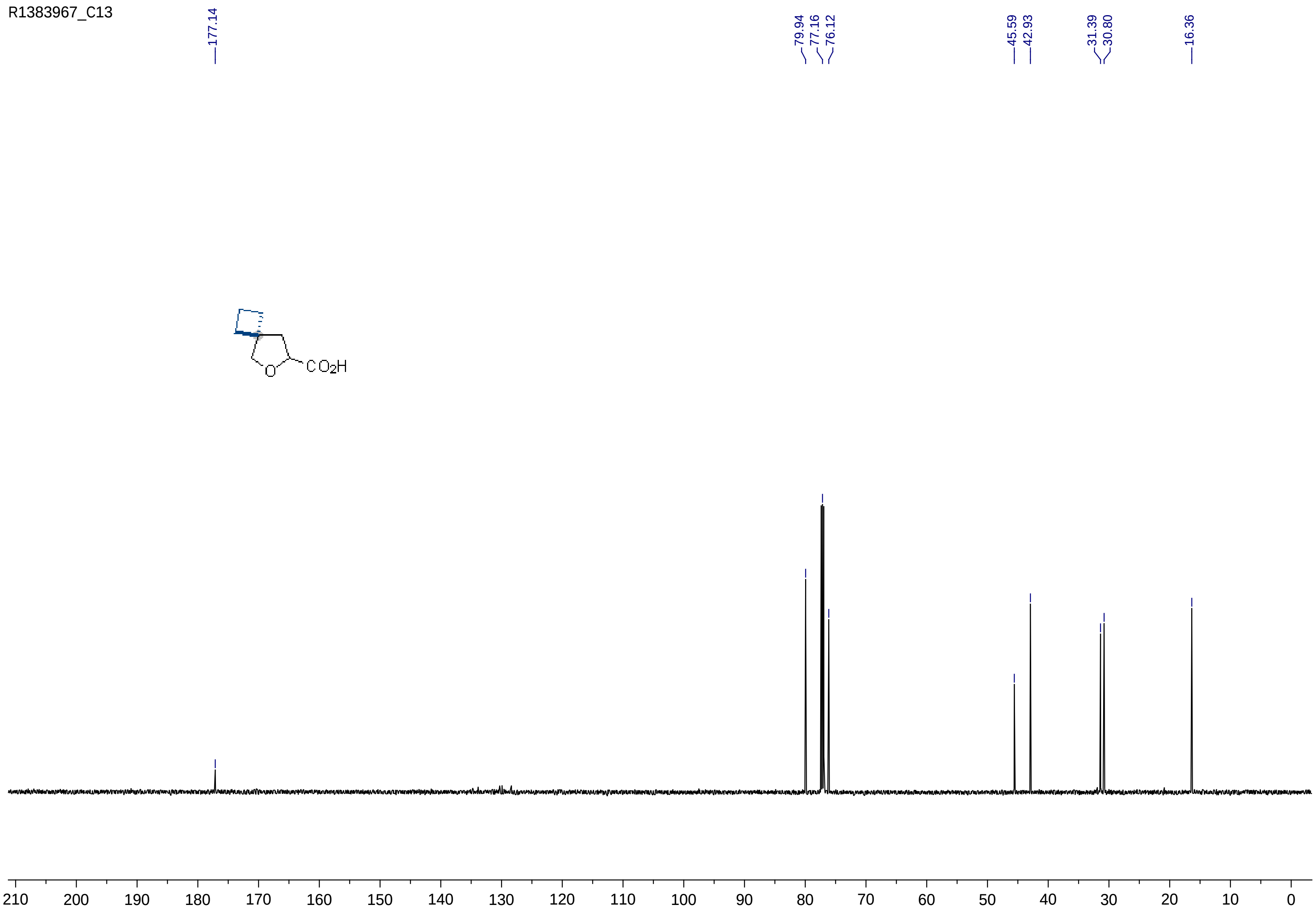

R1416696
9.98
7.26
4.67 4.66 4.65 4.64
3.86 3.84 3.80 3.78
2.33 2.31 2.30 2.28 2.10 2.08 2.06 2.05
0.70 0.68 0.66 0.65 0.64 0.63 0.61
CO2H
O
1.13
1.00
0.94
1.01
1.01
0.96
3.51
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

R1416696_C13

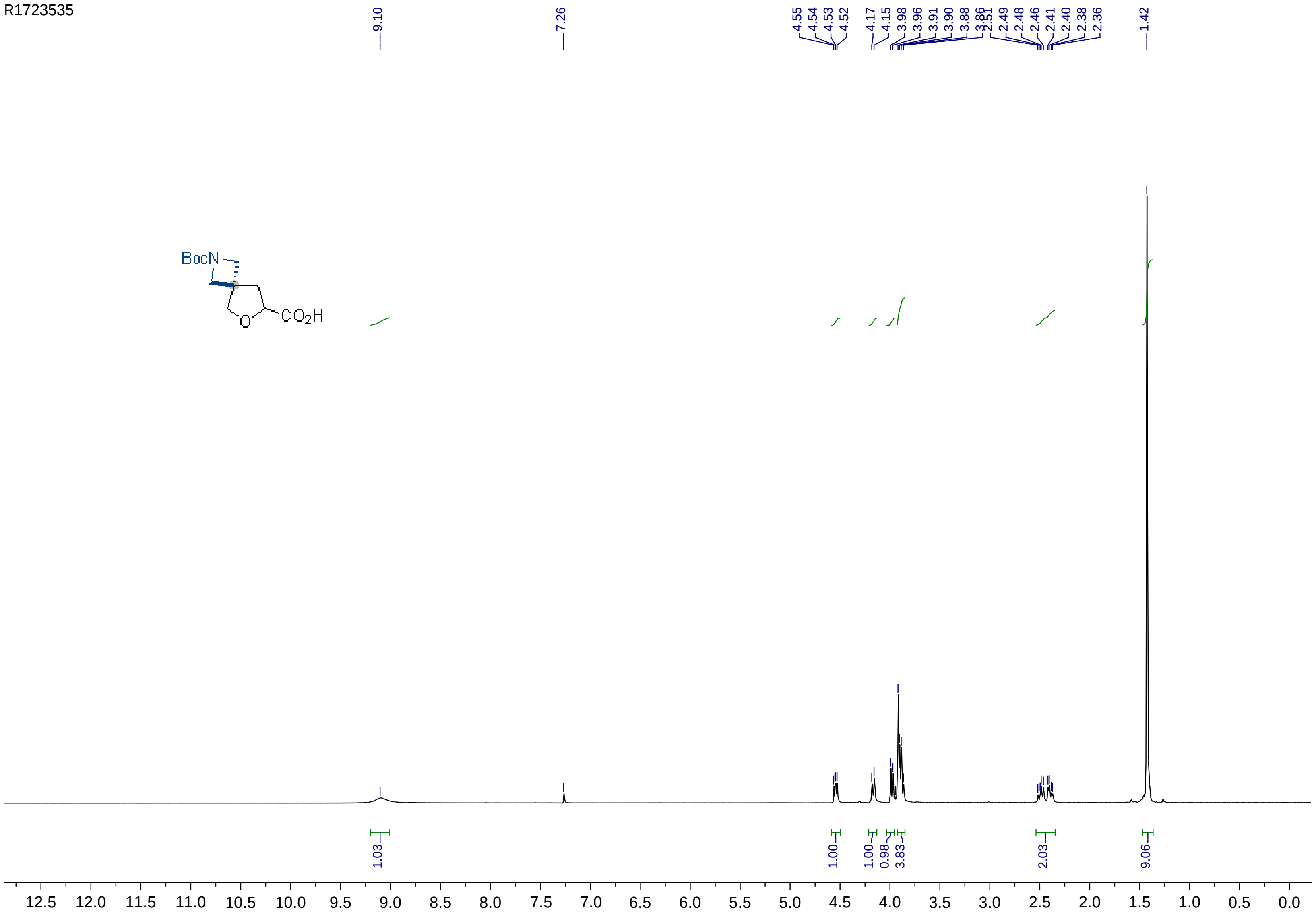


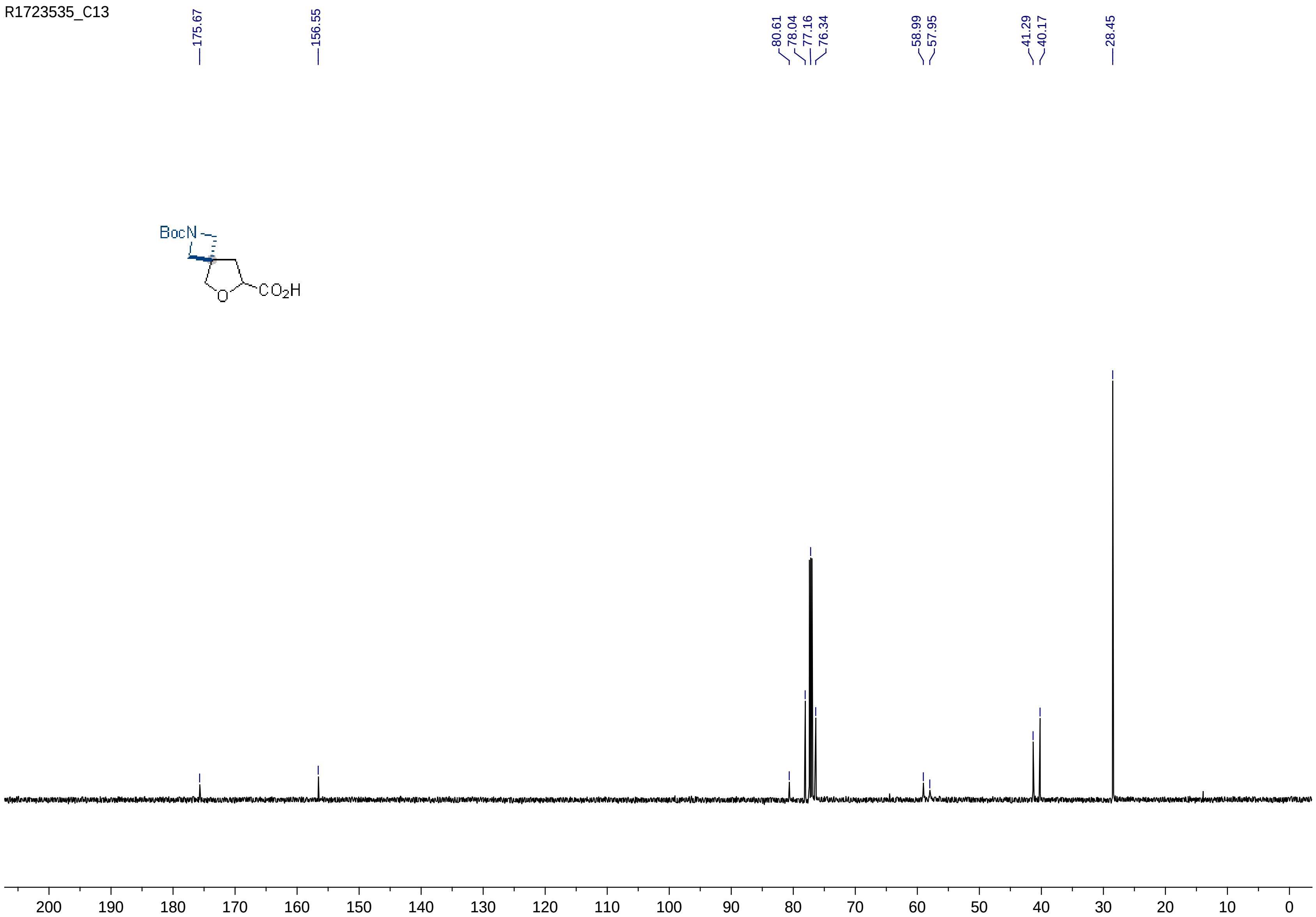
Compound 6d


R1383967
CO2H
8.76
7.26
4.50
4.48
4.47
4.46
3.95
3.92
3.86
3.83
2.38
2.36
2.35
2.33
2.19
2.17
2.16
2.14
2.09
2.05
2.04
2.02
2.00
1.99
1.98
1.97
1.96
1.91
1.90
1.88
1.88
1.86
1.84
0.96
1.00
1.00
1.01
1.03
1.05
6.21
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

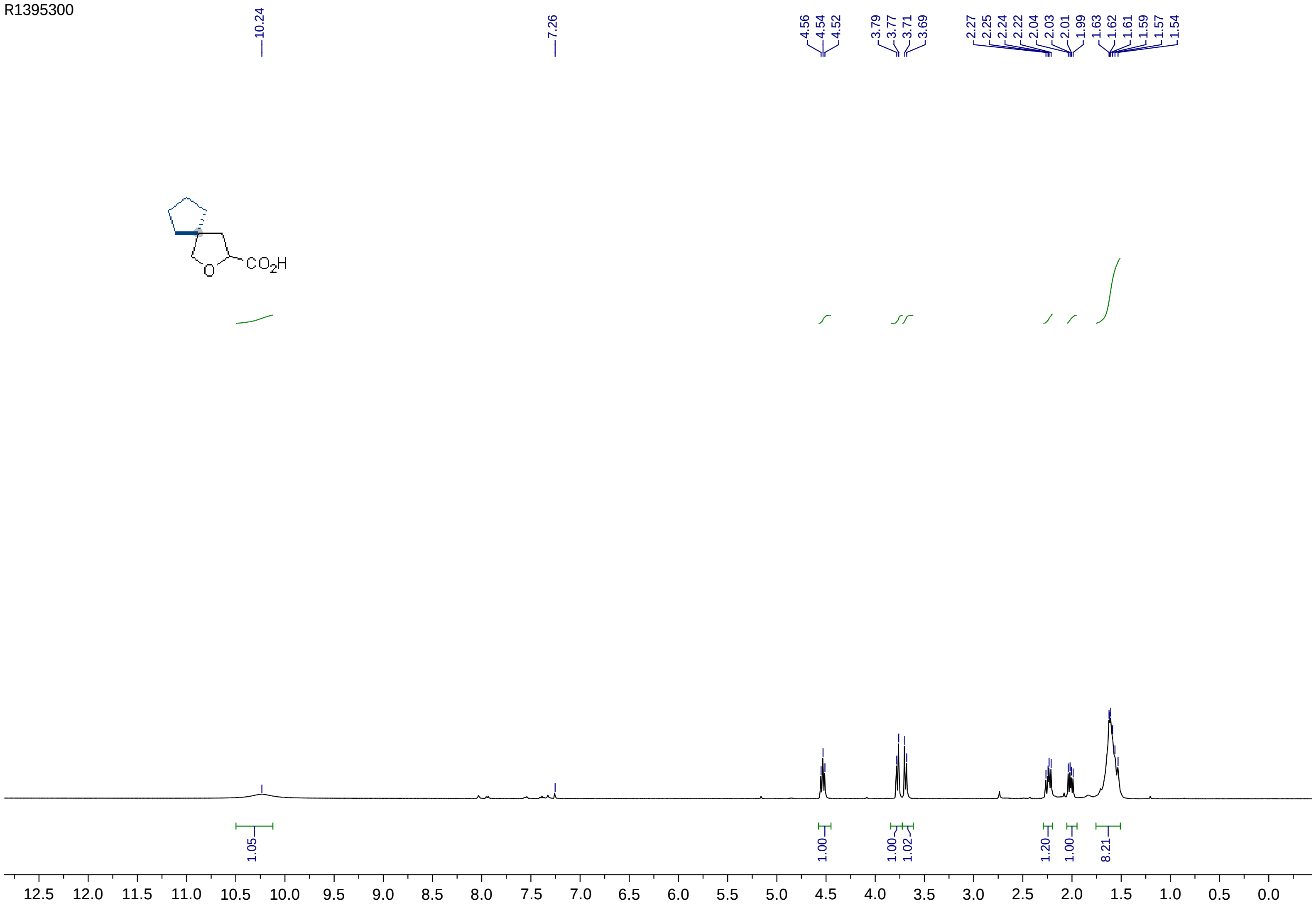

R1383967_C13
177.14
79.94
77.16
76.12
45.59
42.93
31.39
30.80
16.36
CO2H
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 8d


R1723535
9.10
7.26
4.55
4.54
4.53
4.52
4.17
4.15
3.98
3.96
3.91
3.90
3.88
3.86
2.51
2.49
2.48
2.46
2.41
2.40
2.38
2.36
1.42
BocN
O
CO2H
1.03
1.00
1.00
0.98
3.83
2.03
9.06
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

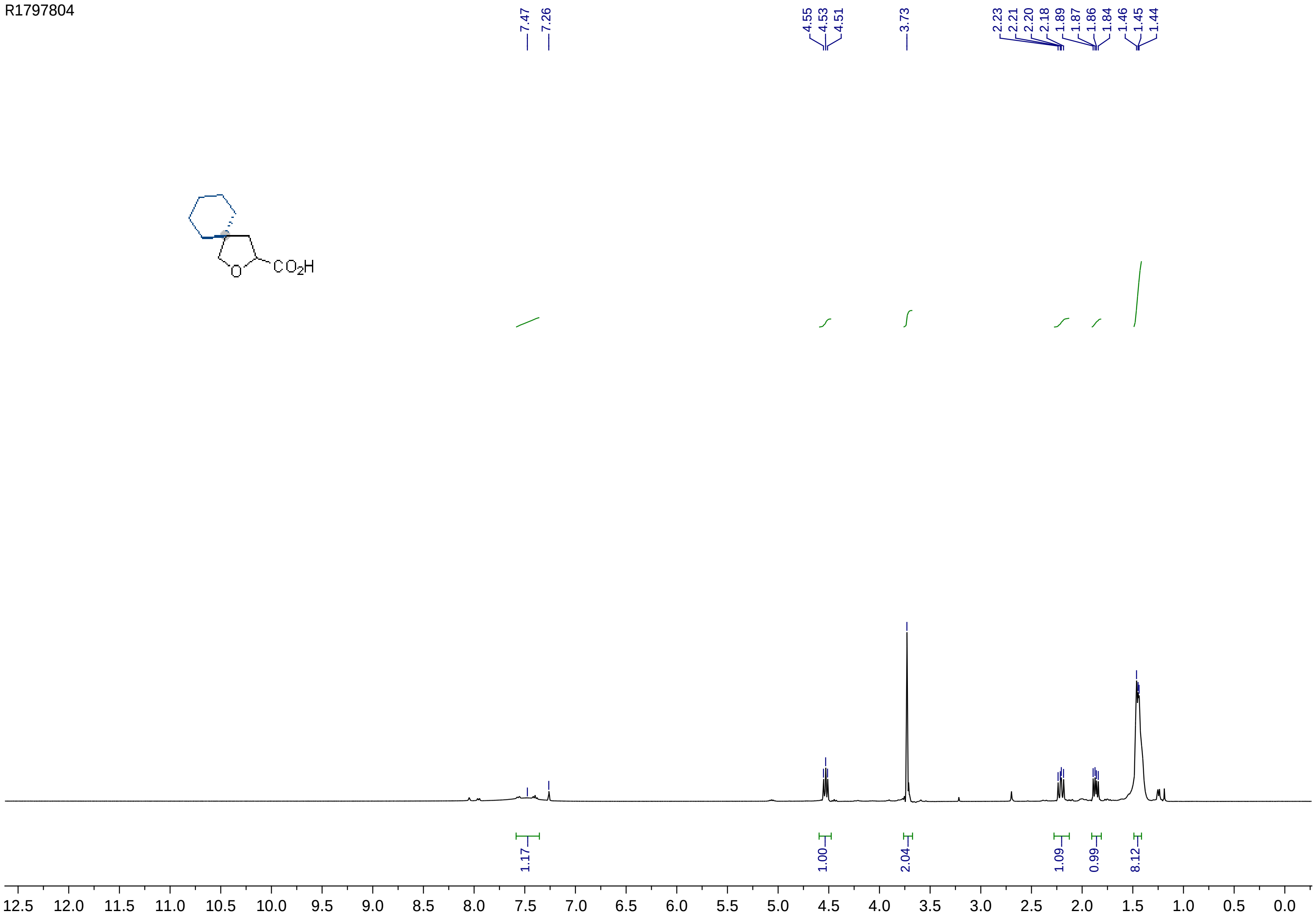

R1723535_C13
175.67
156.55
80.61
78.04
77.16
76.34
58.99
57.95
41.29
40.17
28.45
BocN
O
CO2H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

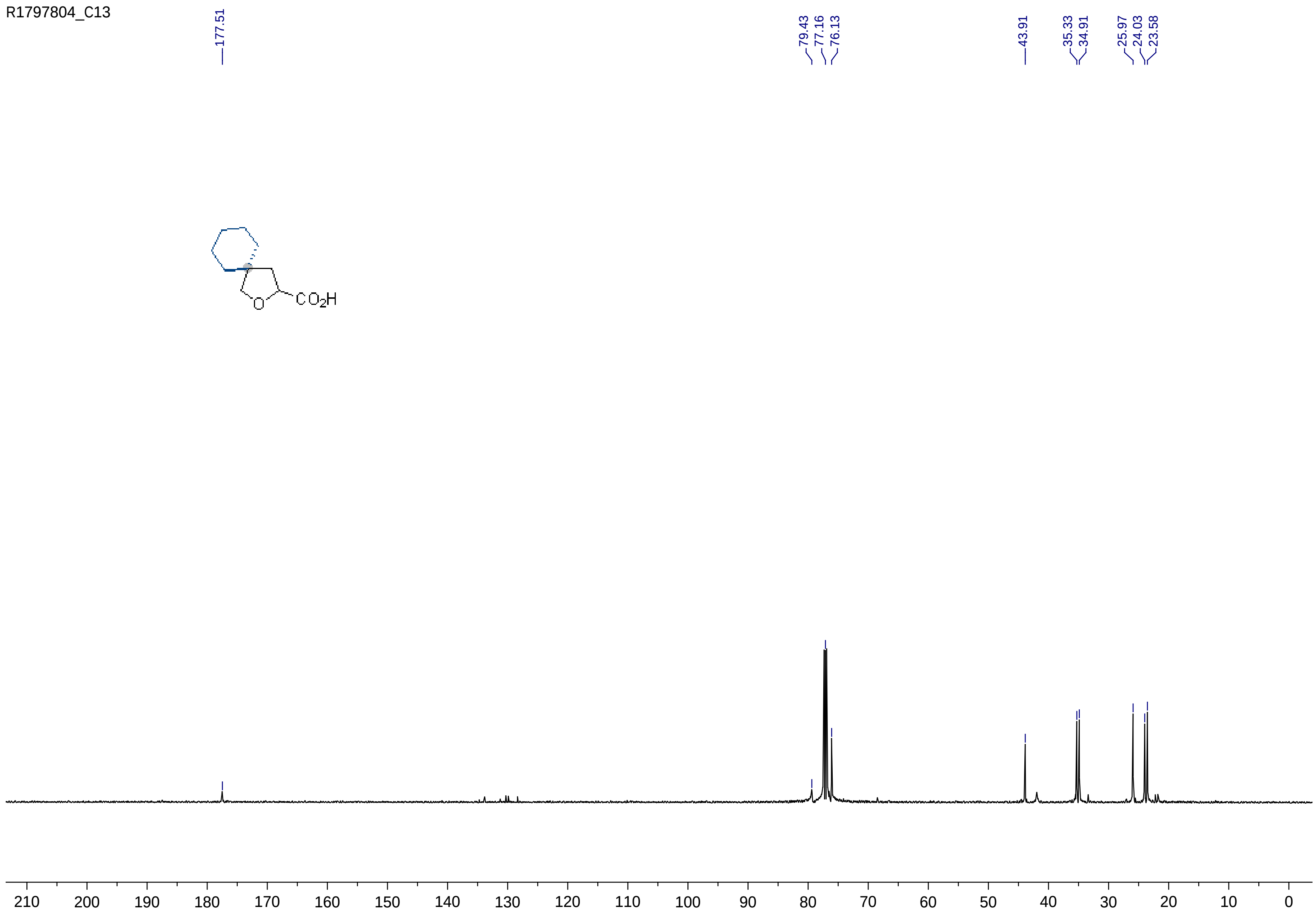
Compound 9d


R1395300
10.24
7.26
4.56
4.54
4.52
3.79
3.77
3.71
3.69
2.27
2.25
2.24
2.22
2.04
2.03
2.01
1.99
1.63
1.62
1.61
1.59
1.57
1.54
CO2H
O
1.05
1.00
1.00
1.02
1.20
1.00
8.21
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

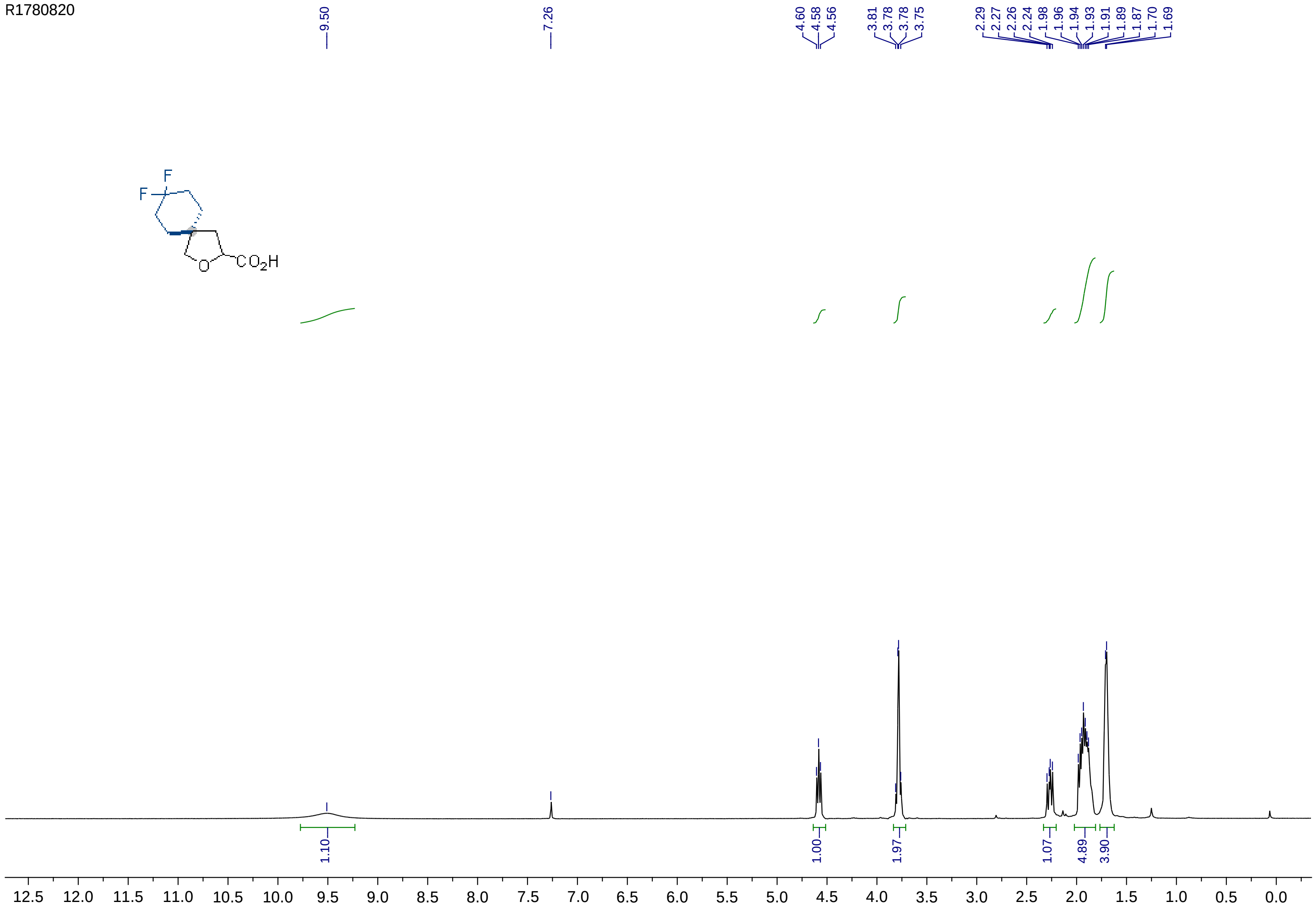

R1395300_13C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 11d

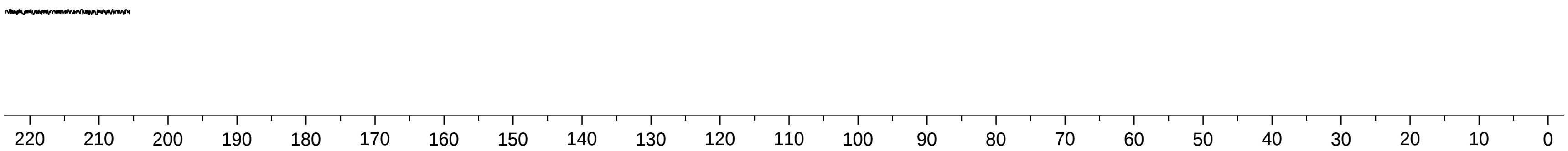



R1797804_C13
177.51
79.43
77.16
76.13
43.91
35.33
34.91
25.97
24.03
23.58
CO2H
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

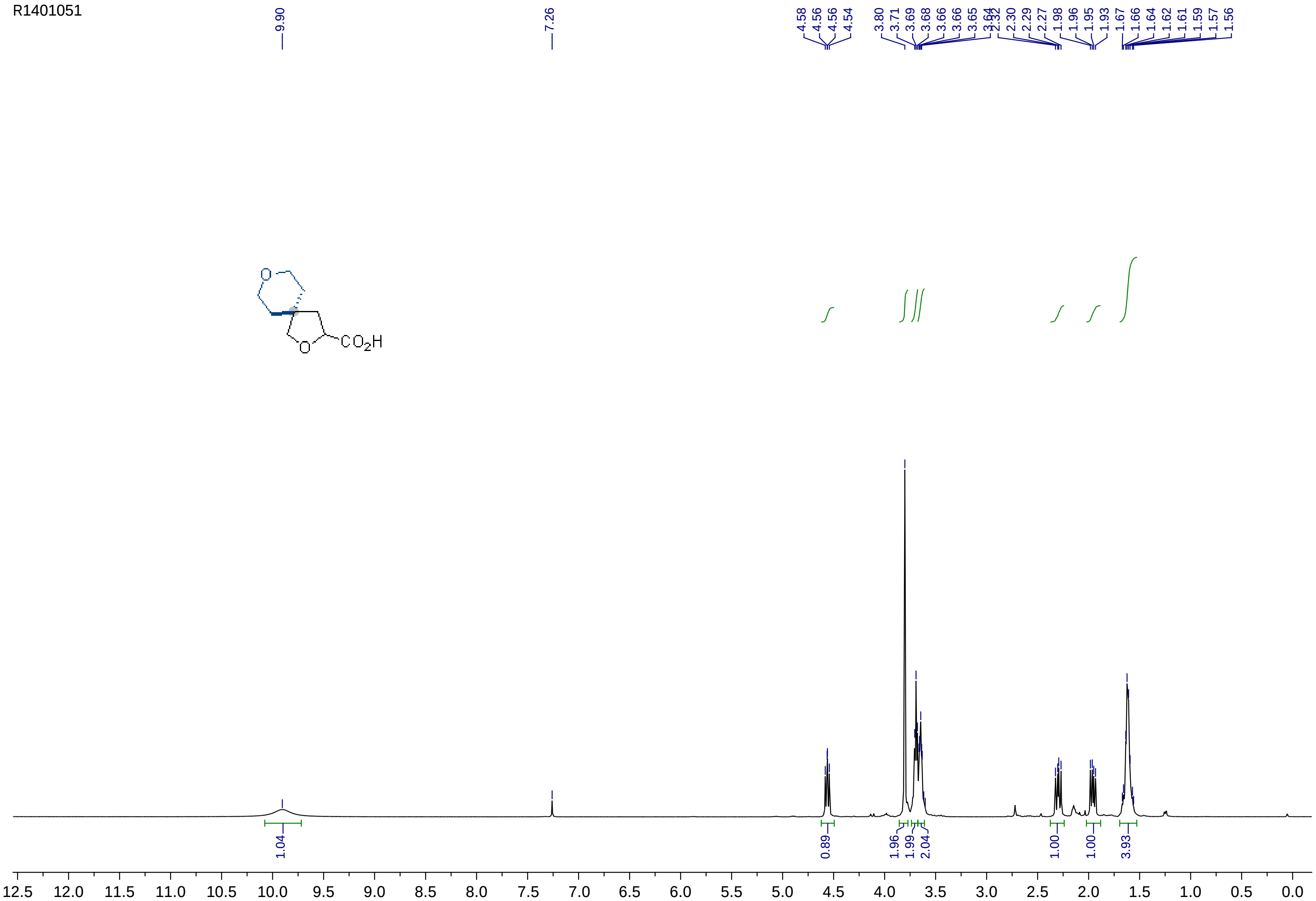
Compound 12d



R1780820_C13

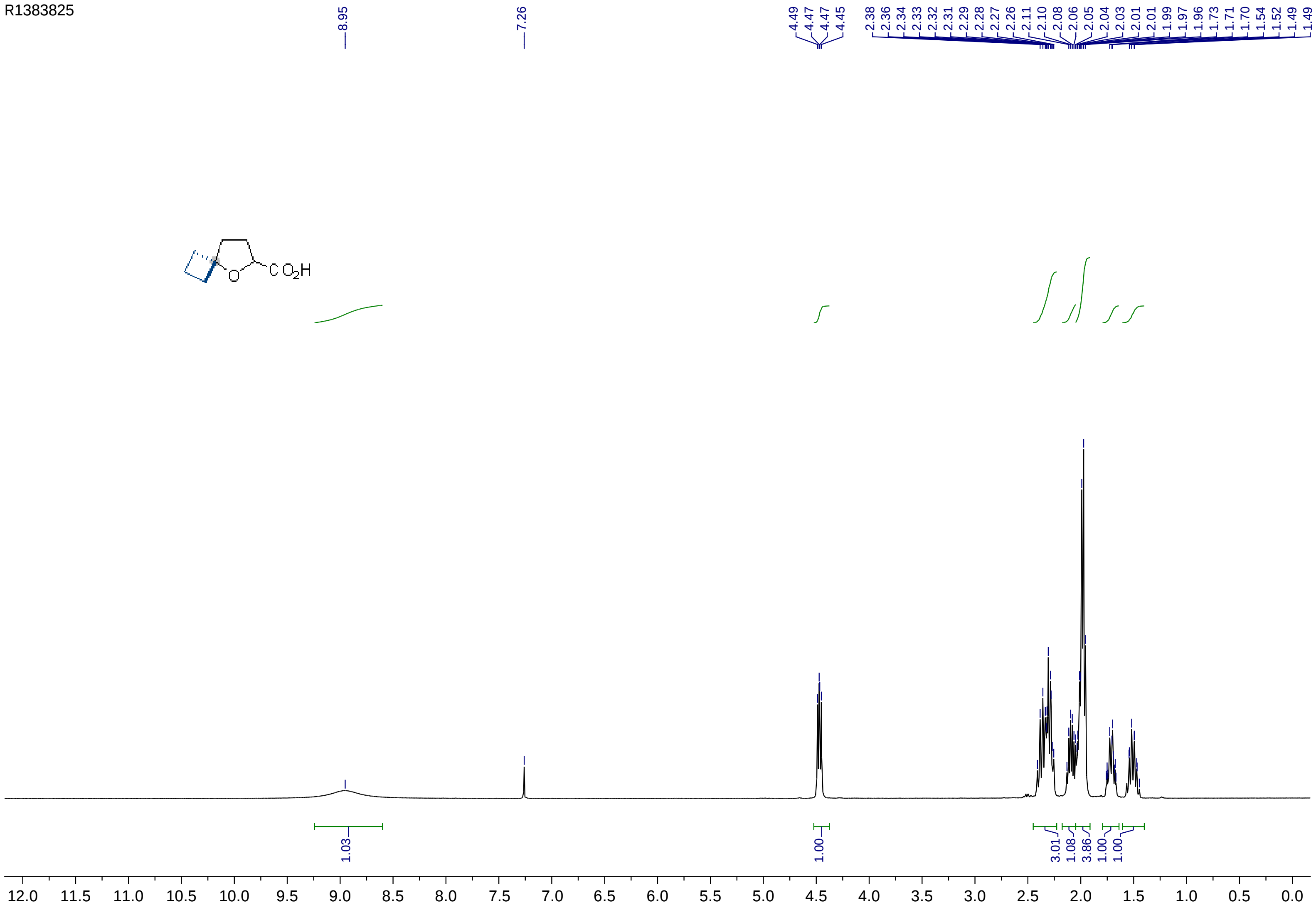


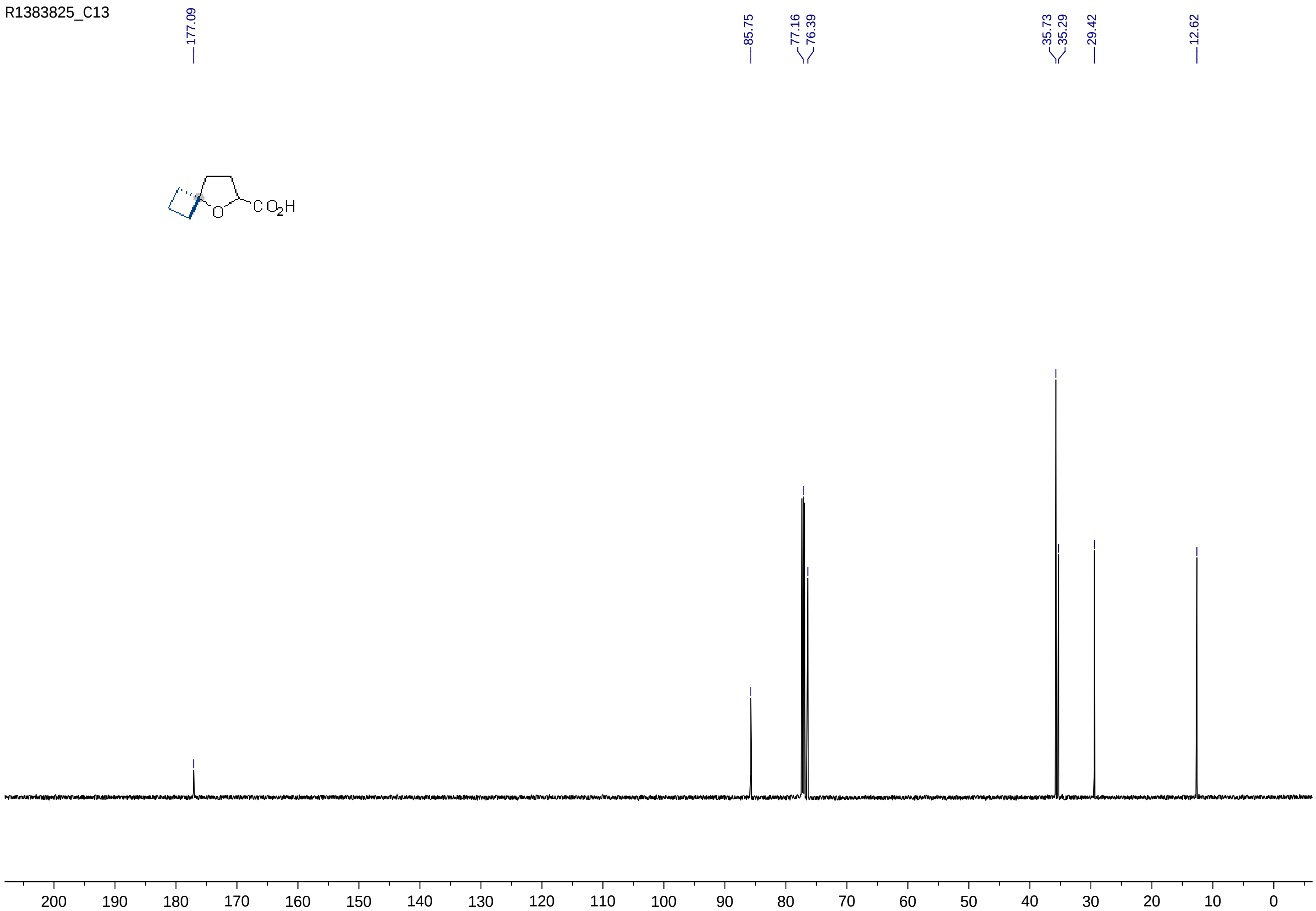
Compound 13d



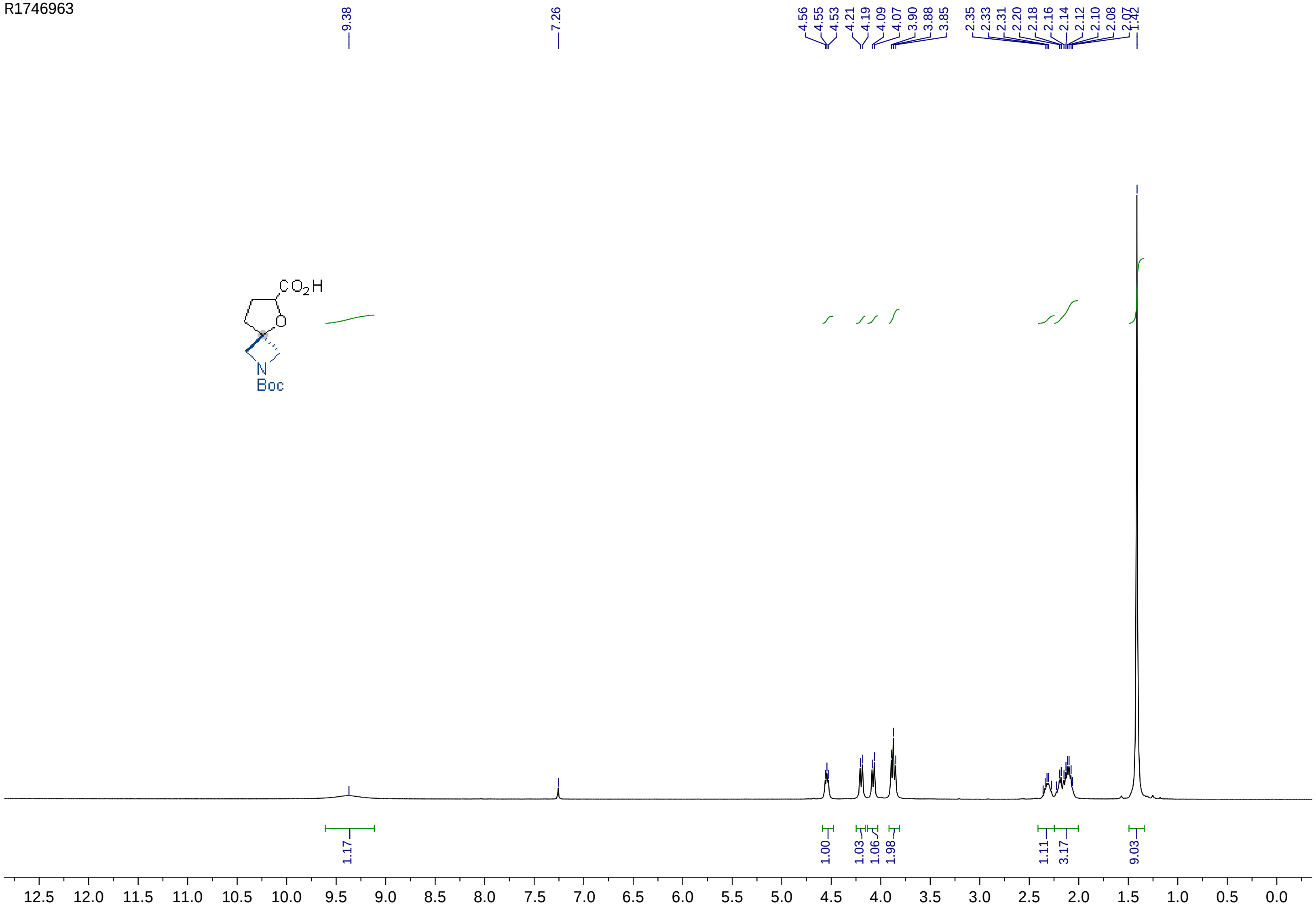

R1401051_C13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

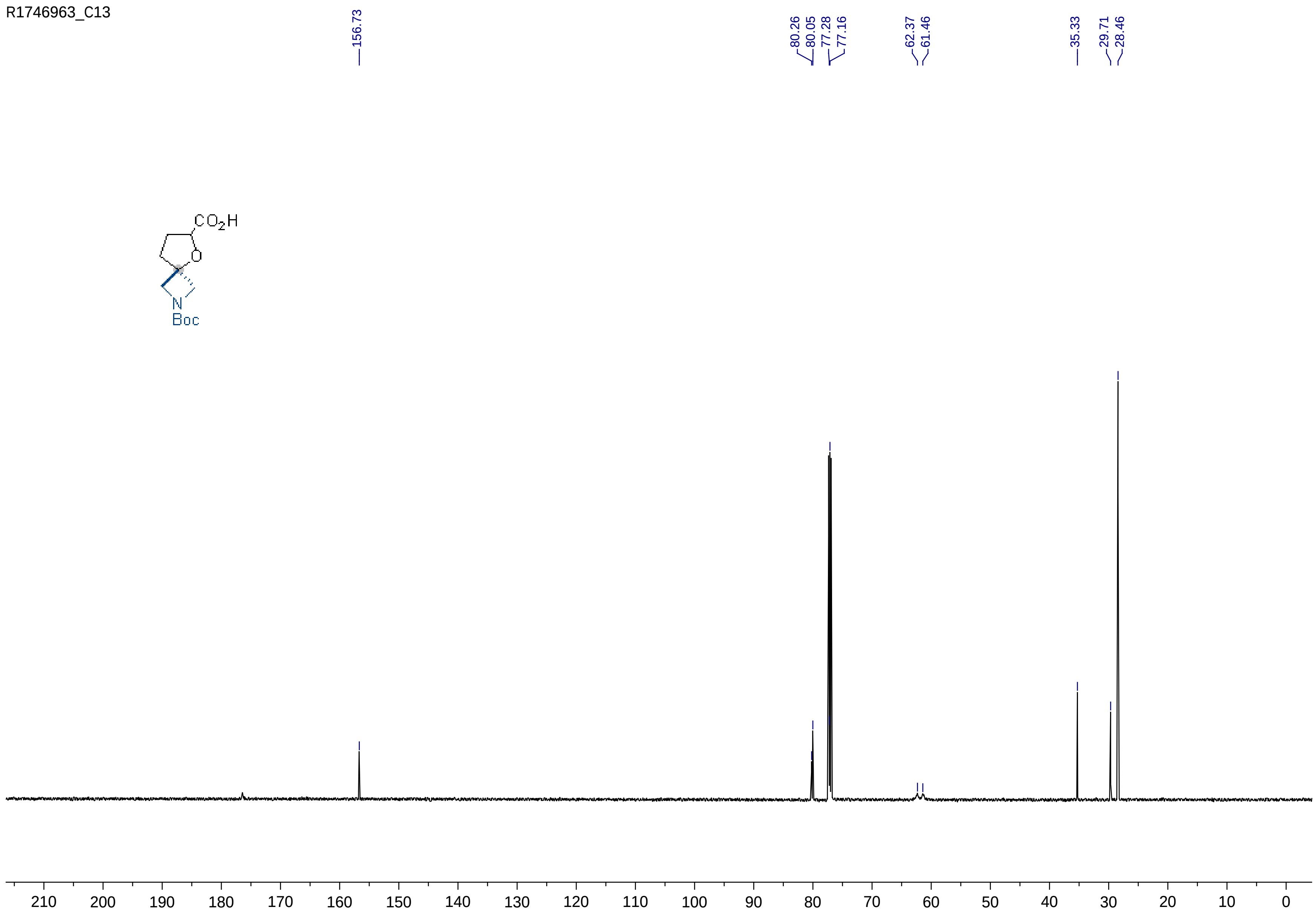
Compound 18d



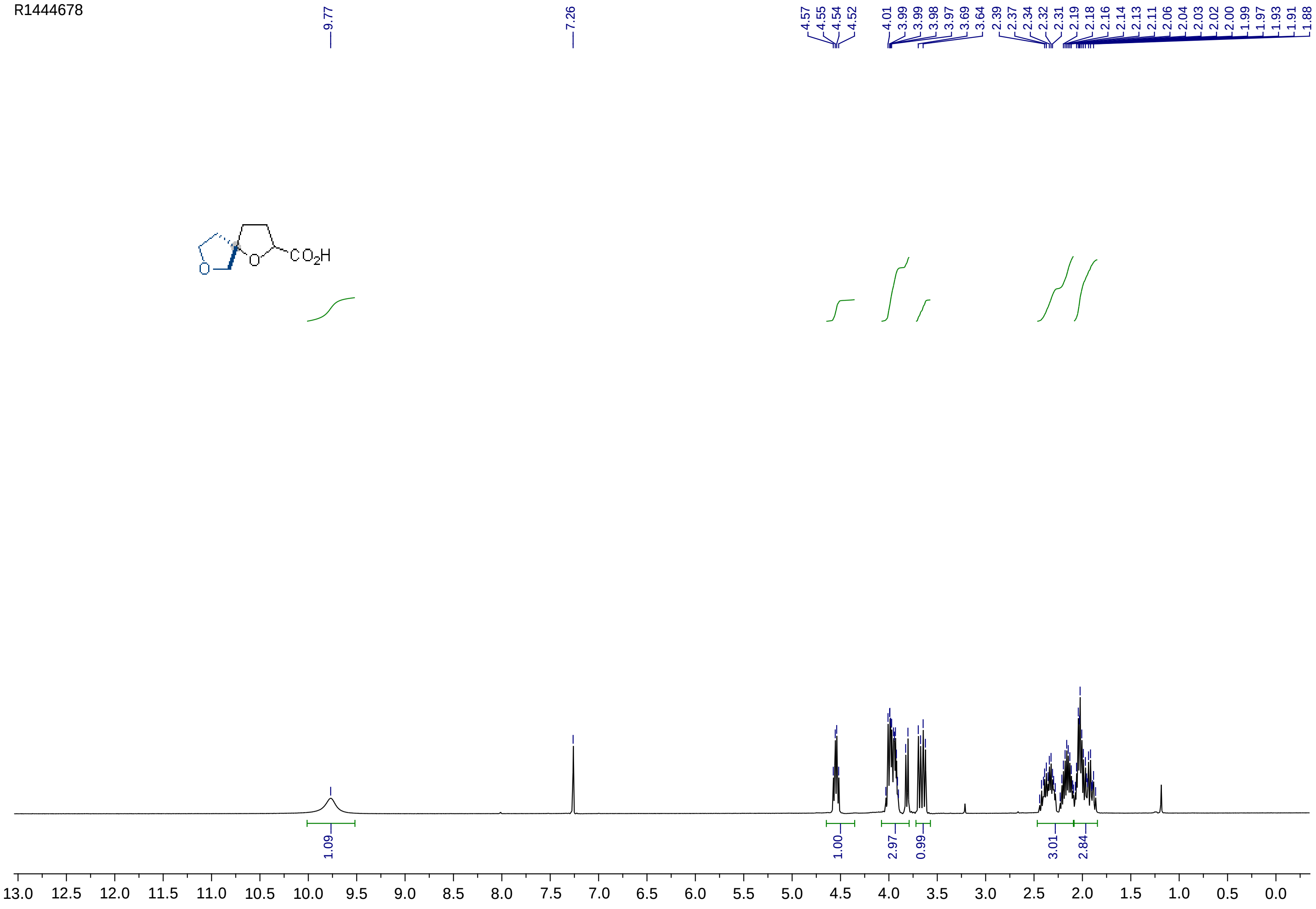

R1383825_C13
177.09
85.75
77.16
76.39
35.73
35.29
29.42
12.62
CO2H
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 21d

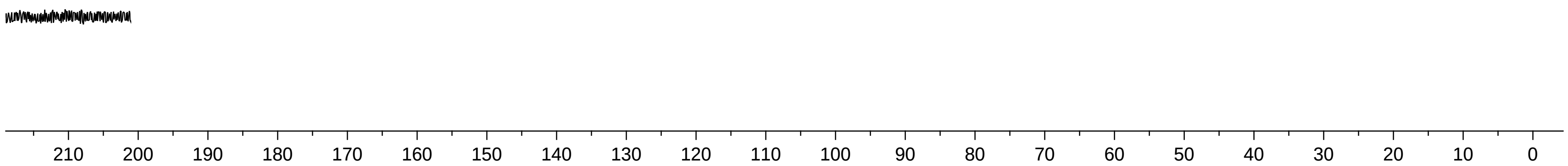



R1746963_C13
156.73
80.26
80.05
77.28
77.16
62.37
61.46
35.33
29.71
28.46
CO2H
O
N
Boc
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

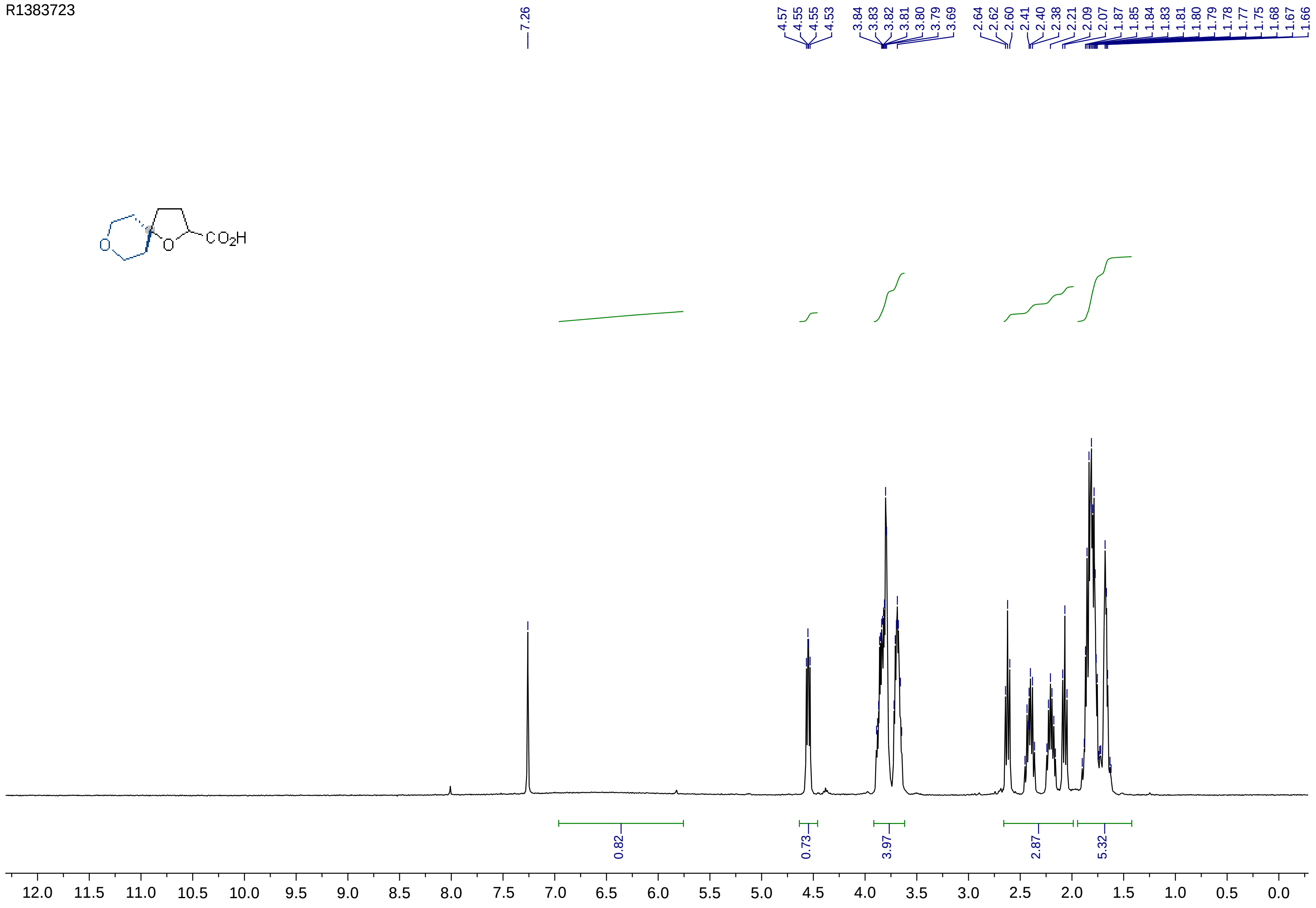
Compound 23d



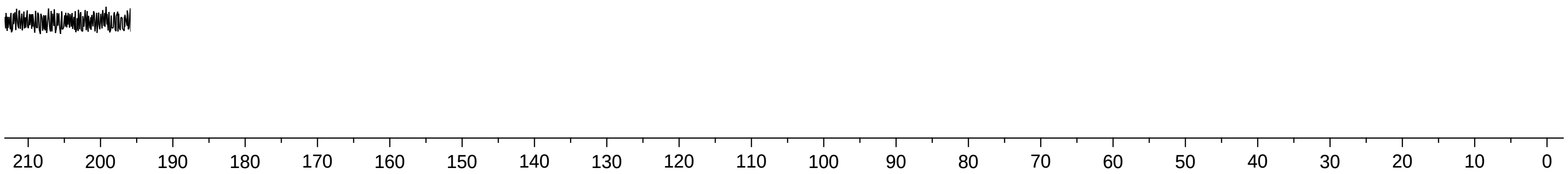
R1444678_C13



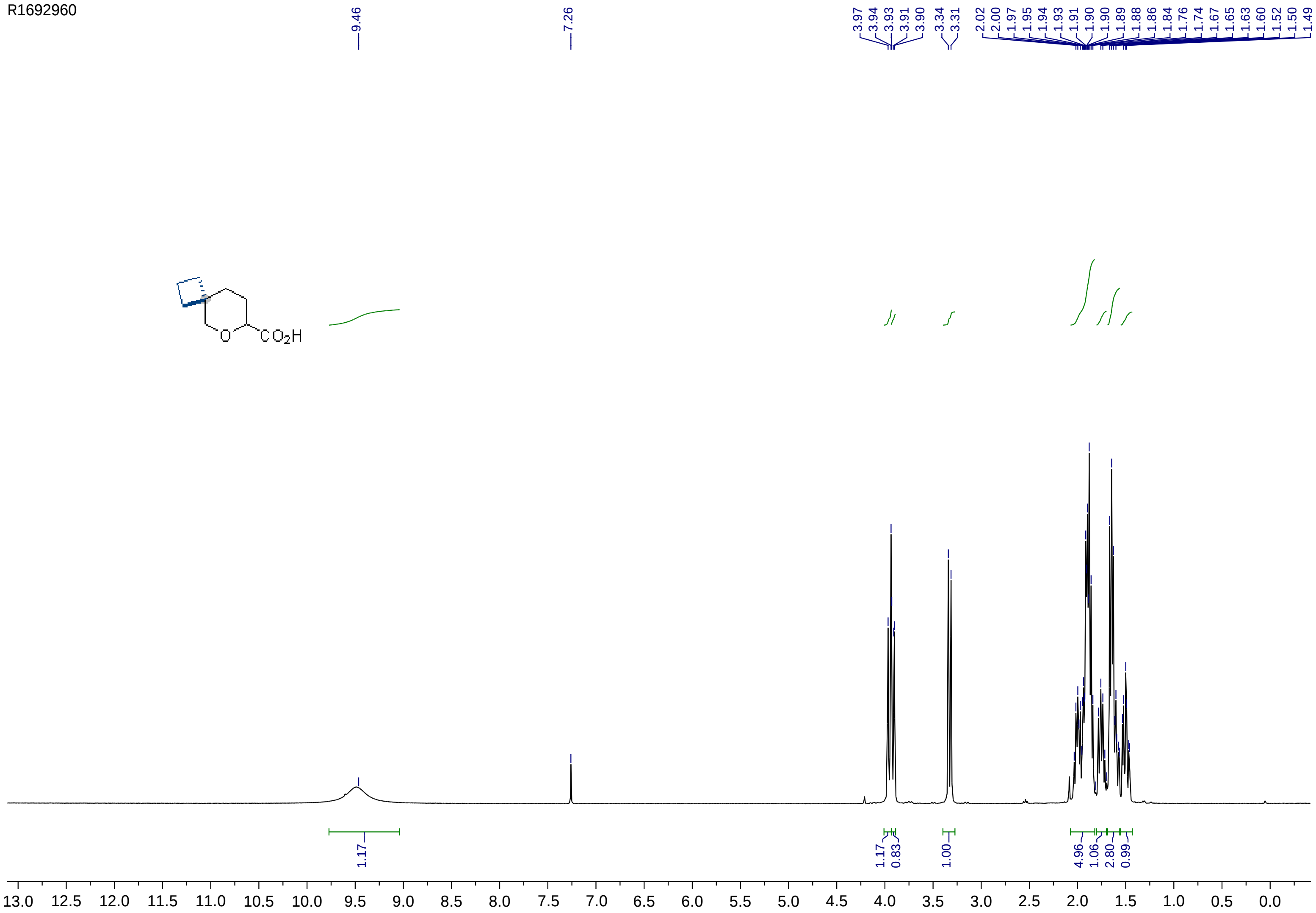
Compound 27d

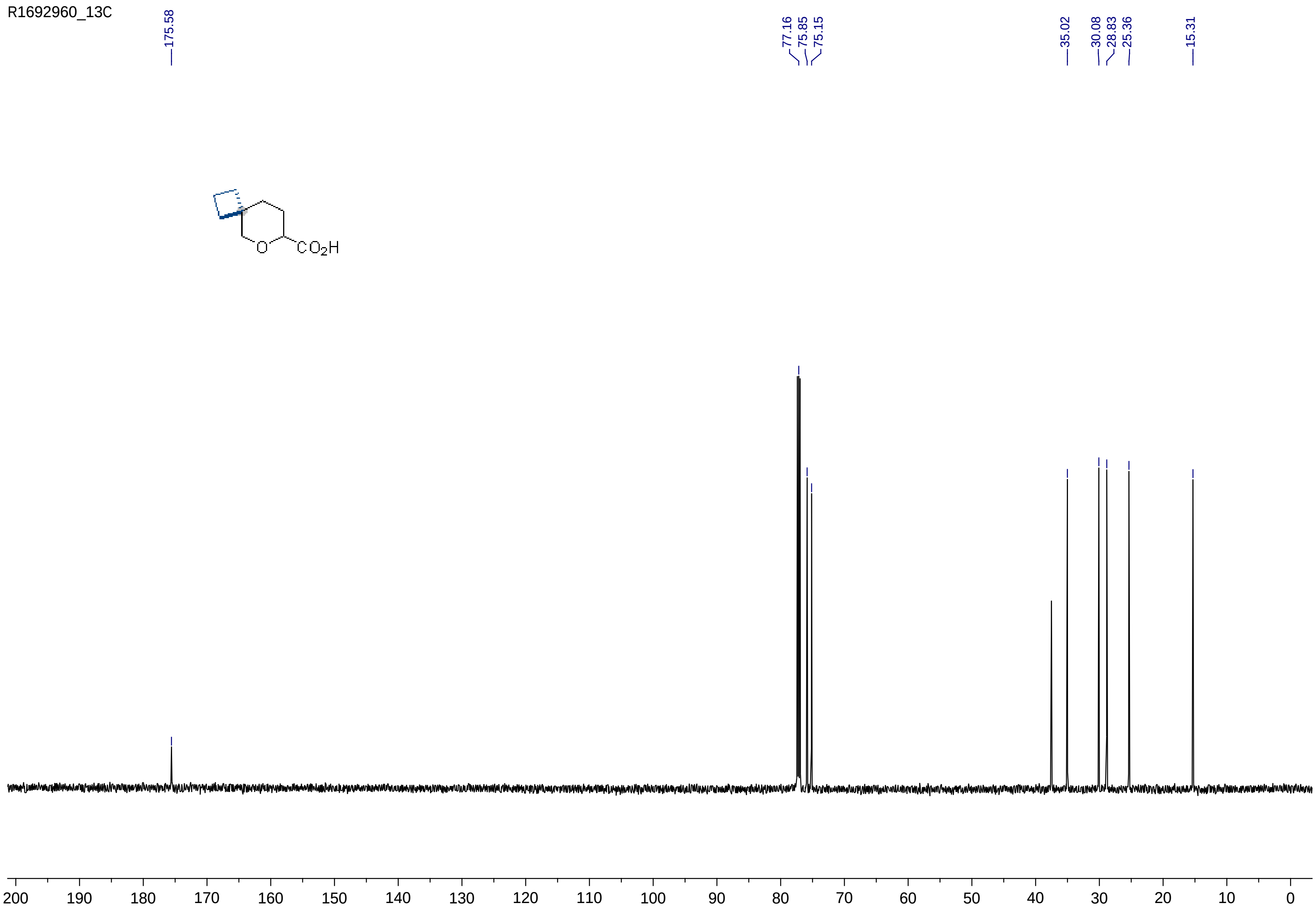


R1383723_C13

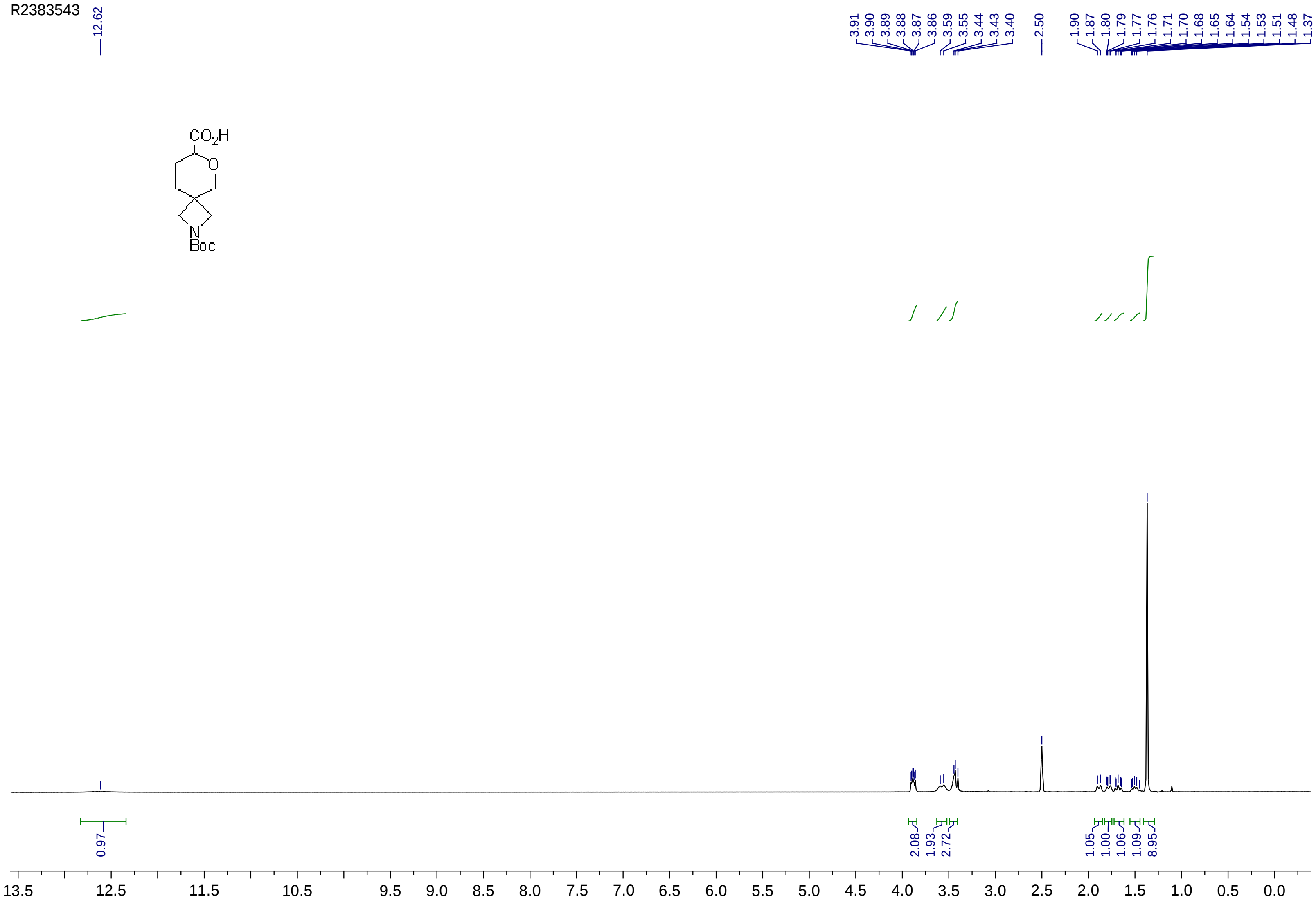


Compound 34d

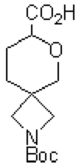


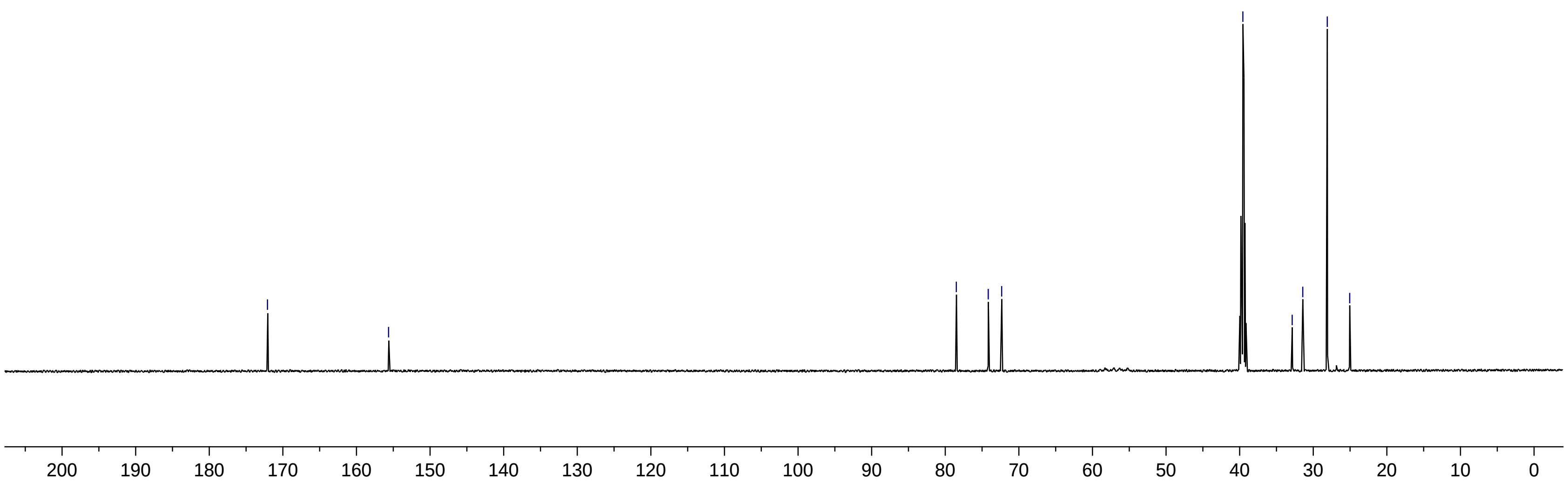

R1692960_13C
175.58
77.16
75.85
75.15
35.02
30.08
28.83
25.36
15.31
CO2H
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 35d

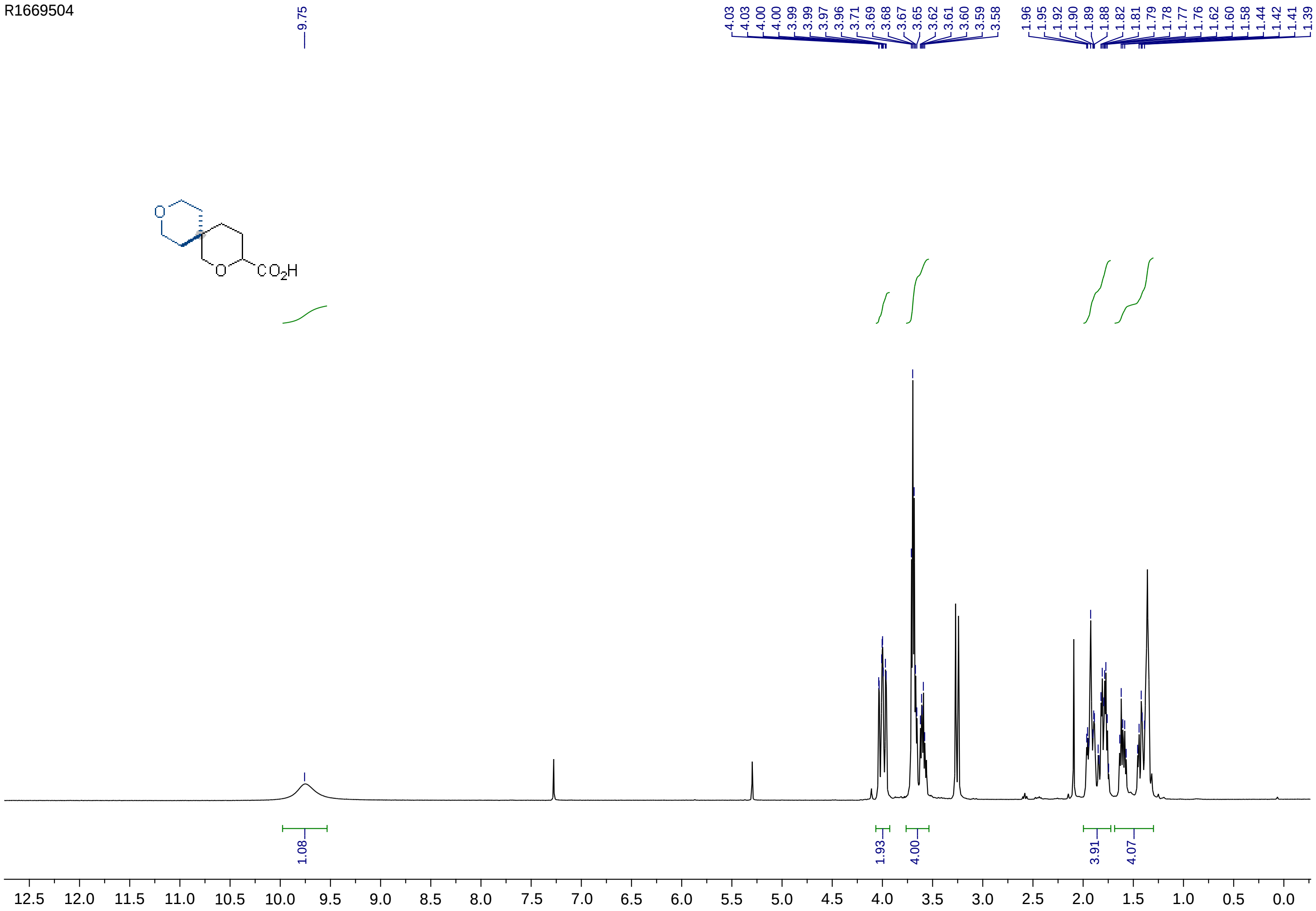


R2383543_C13

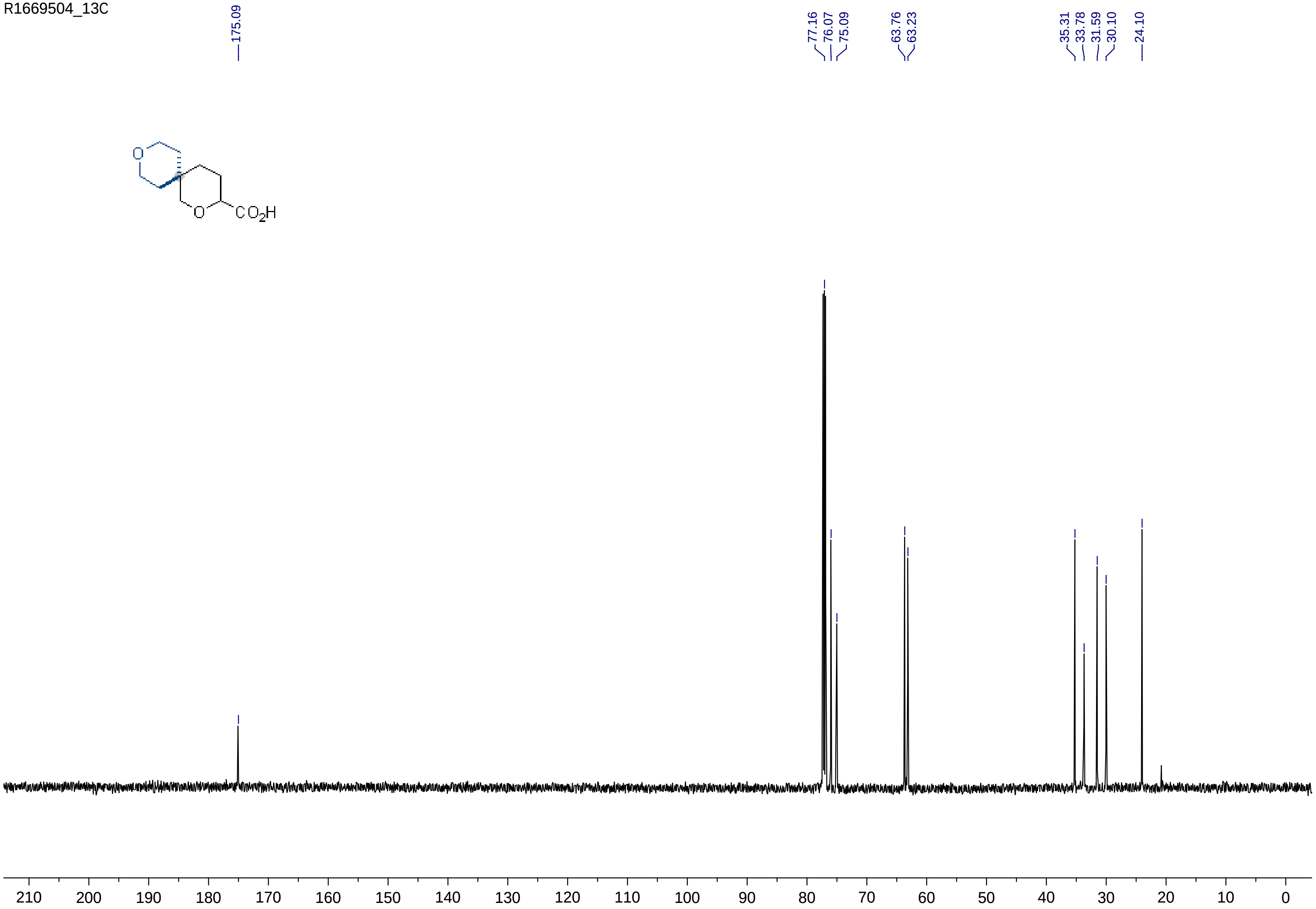




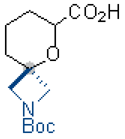
Compound 36d

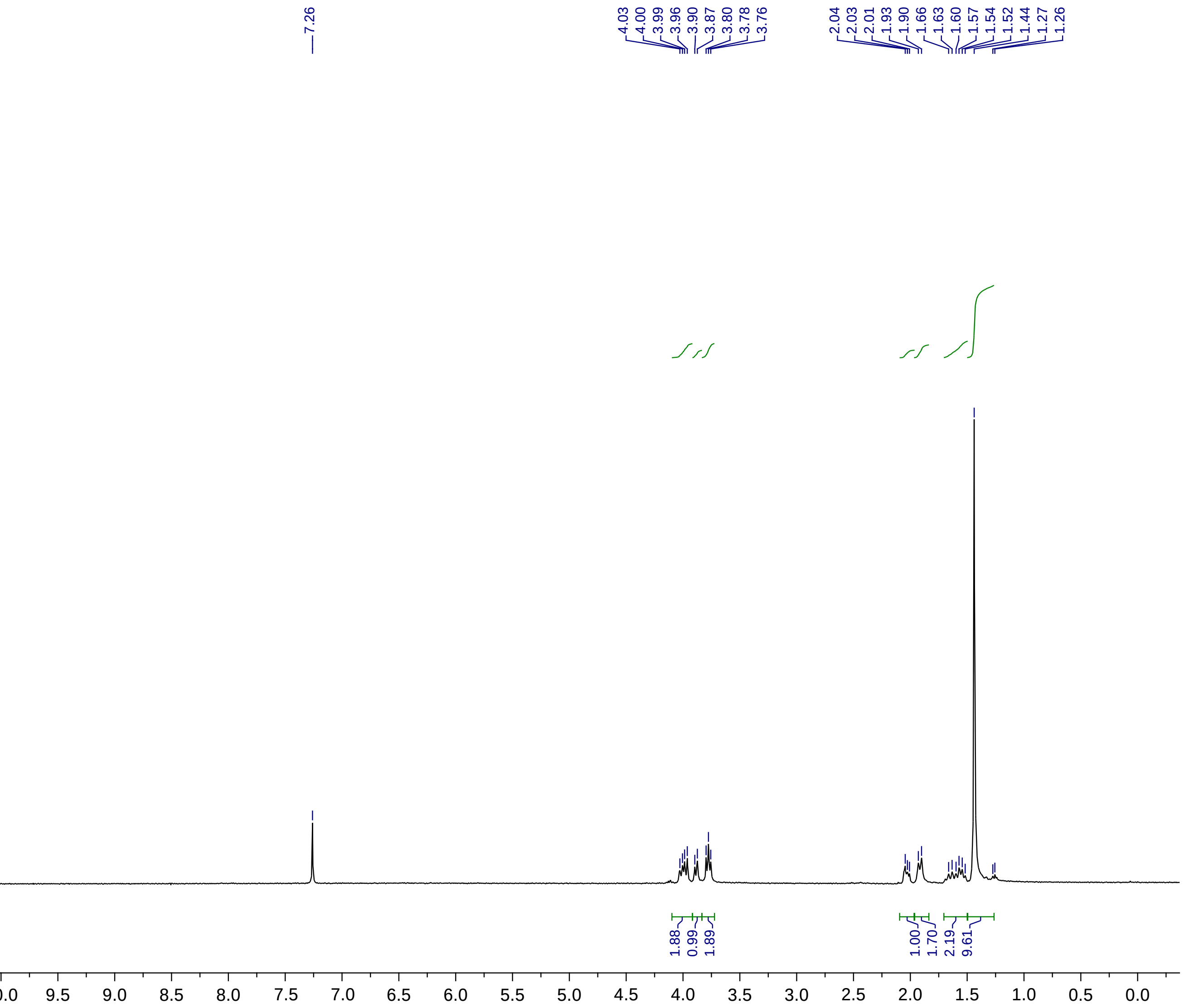


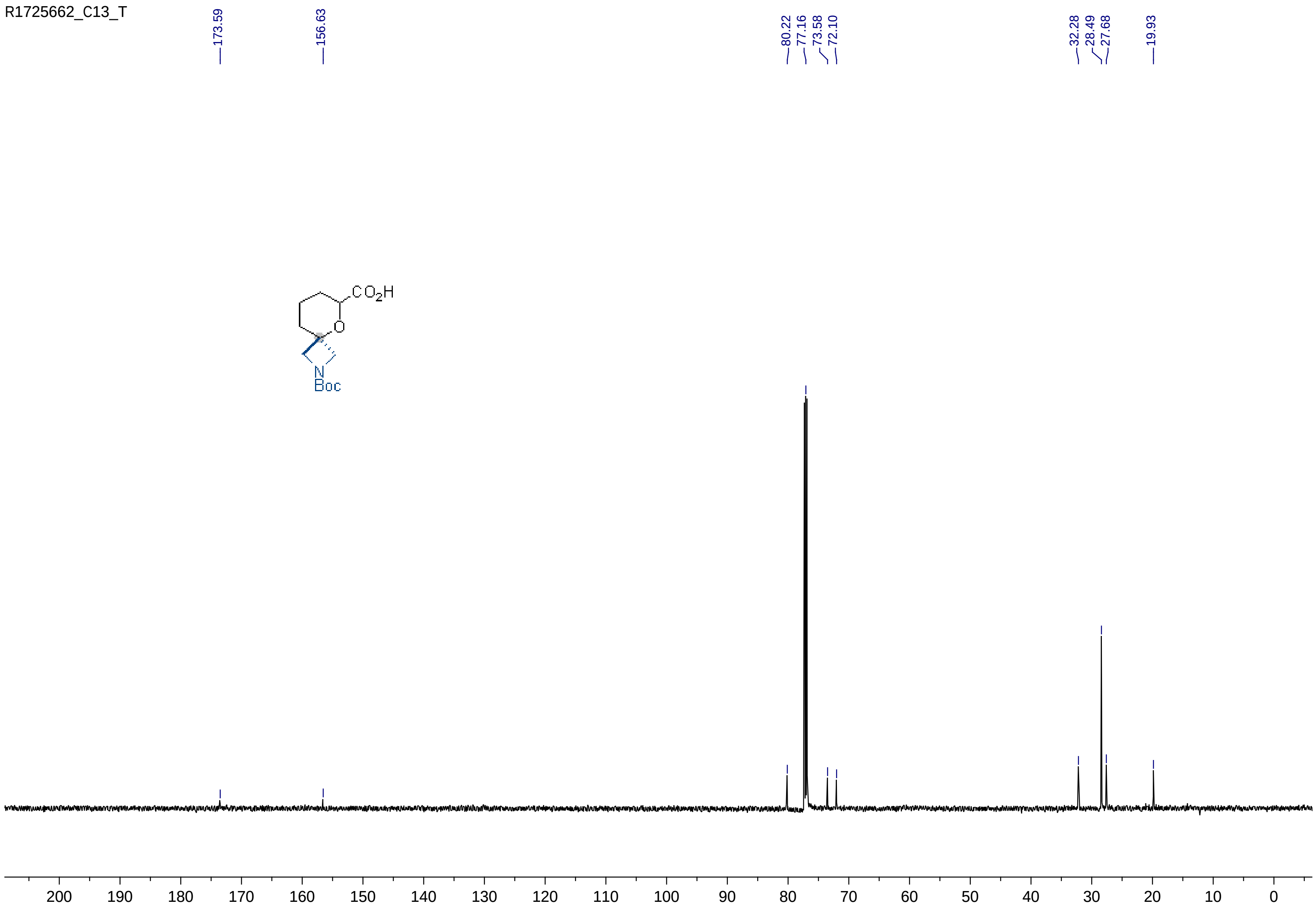
R1669504_13C



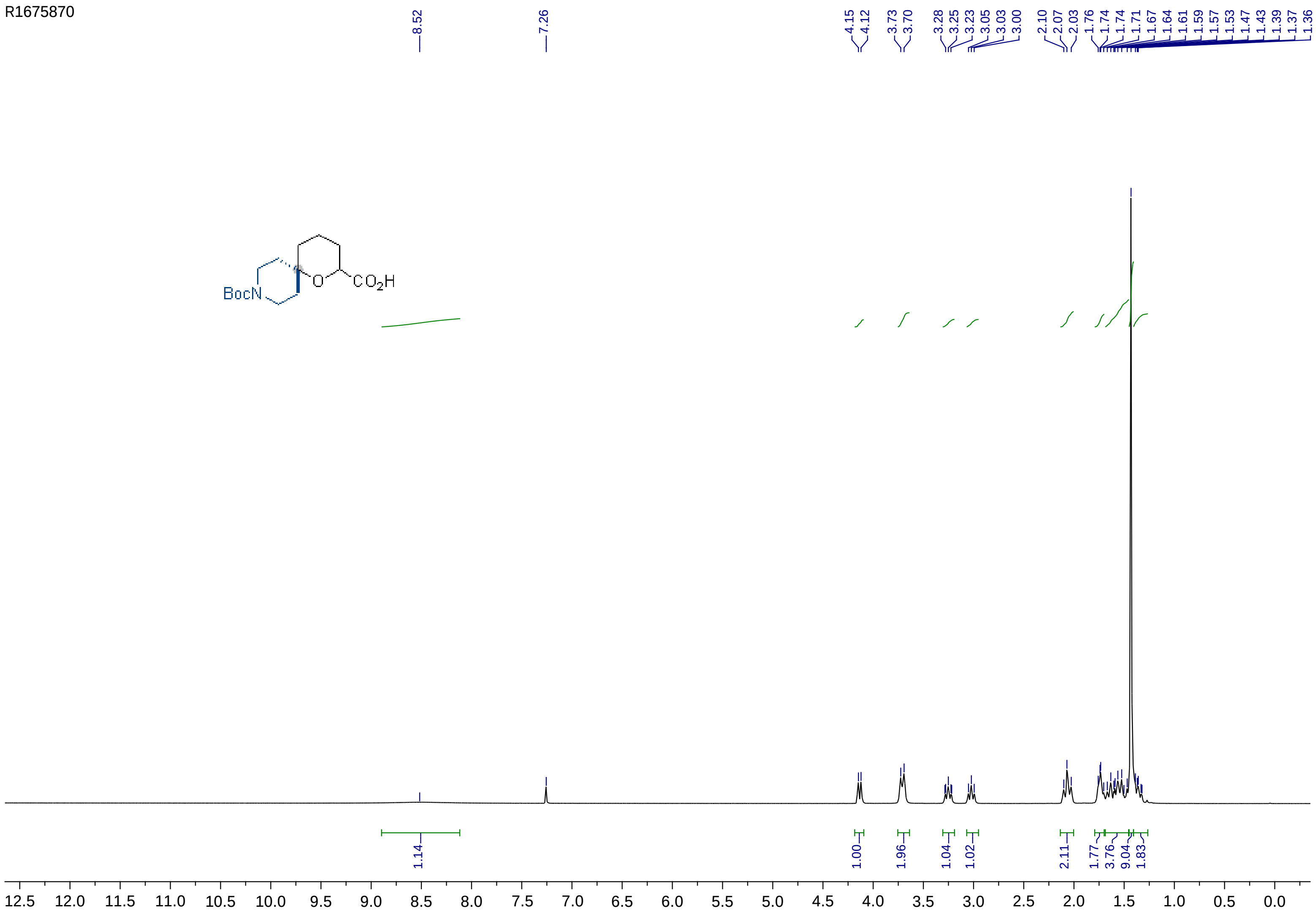
Compound 40d



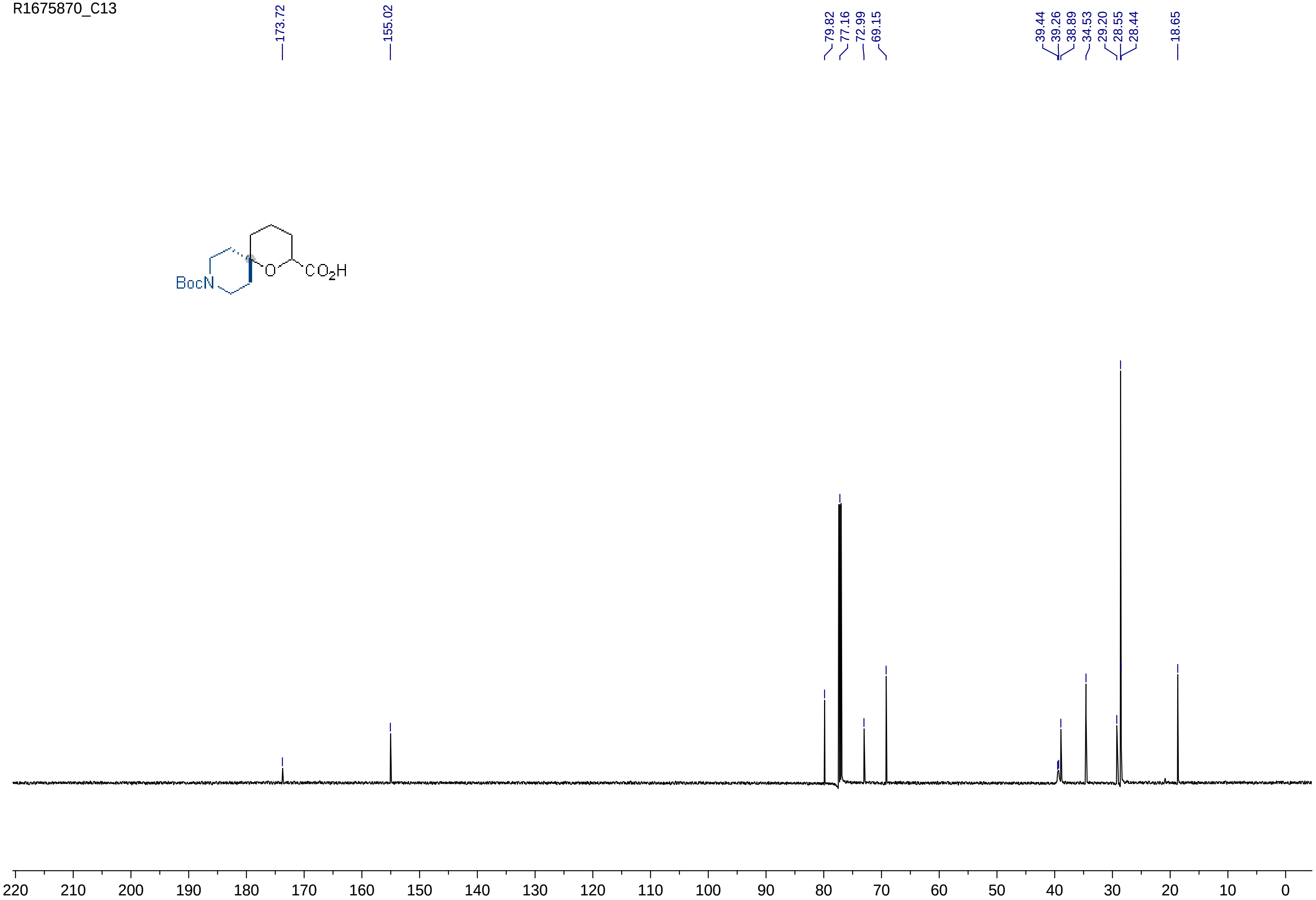



R1725662_C13_T
173.59
156.63
80.22
77.16
73.58
72.10
32.28
28.49
27.68
19.93
CO2H
O
N
Boc
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

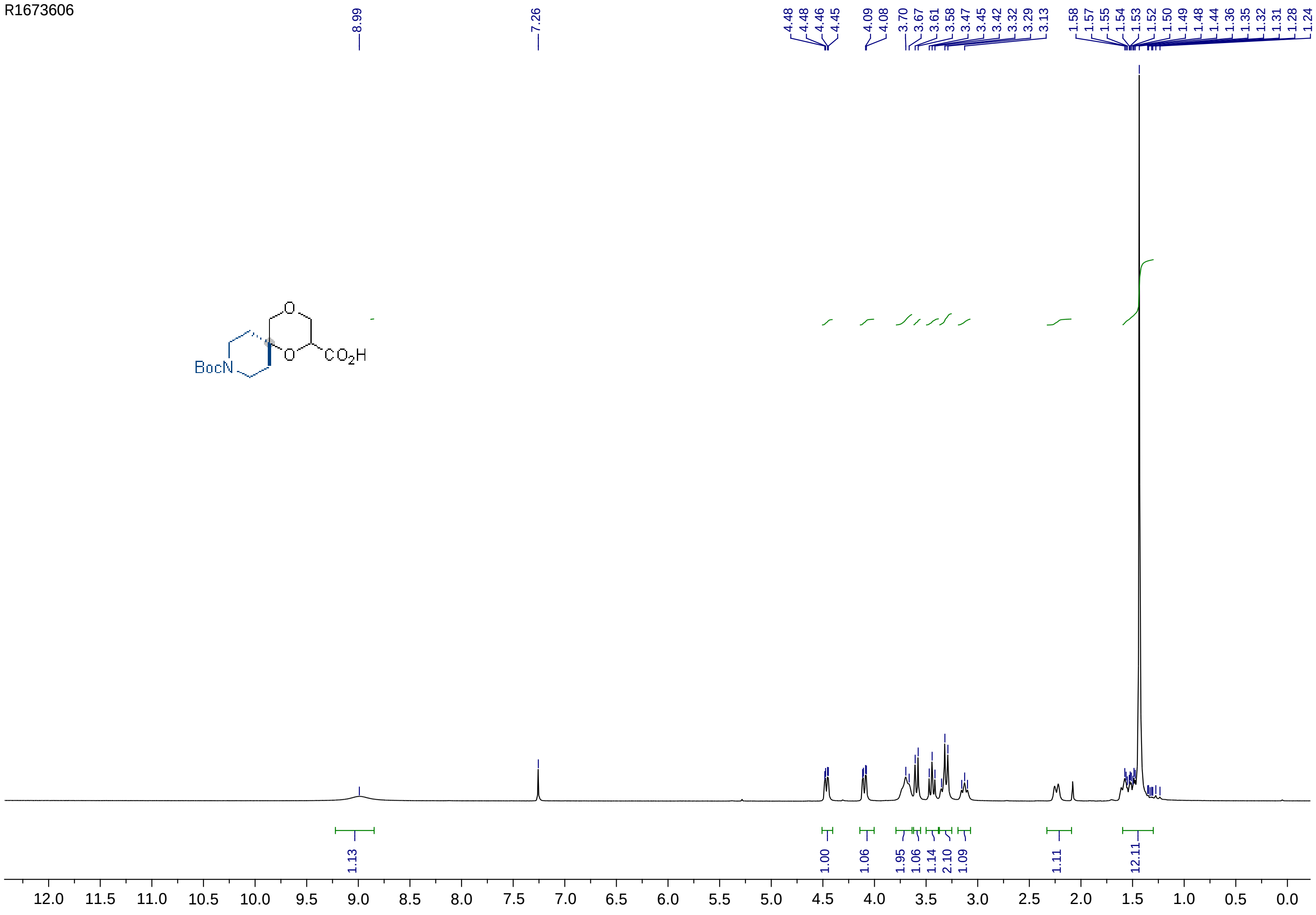
Compound 42d



R1675870_C13

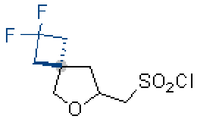


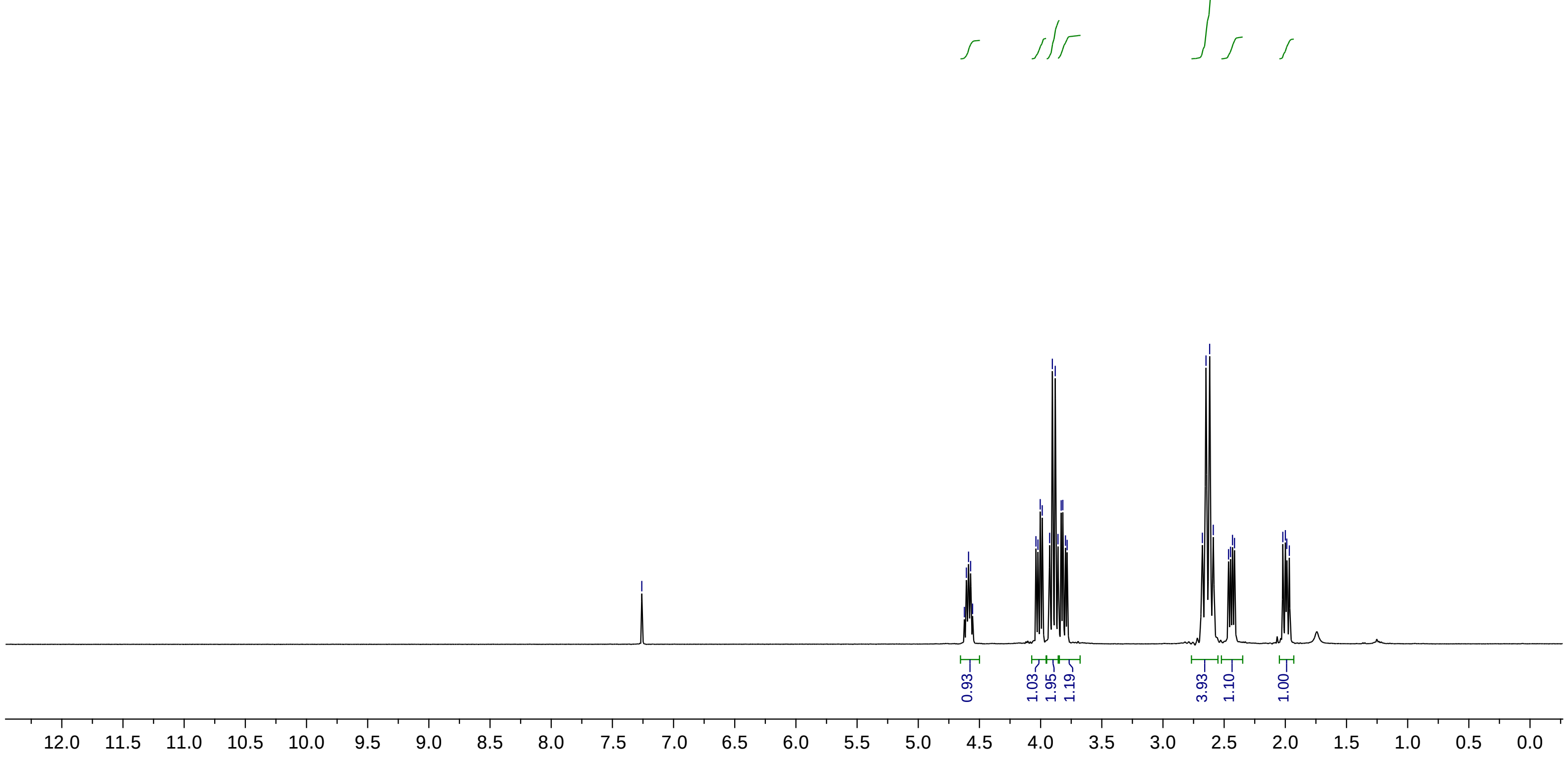
Compound 44d



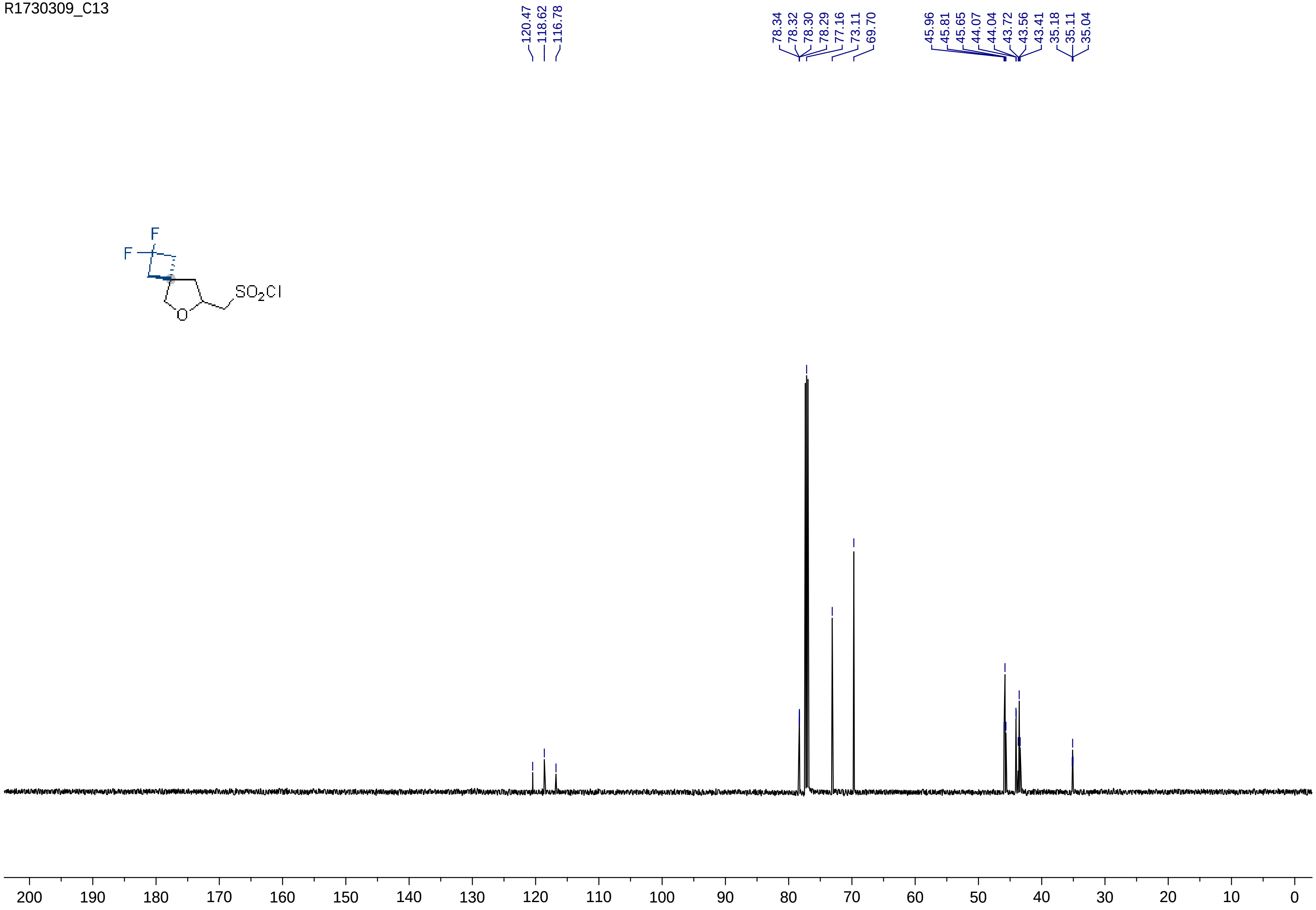

R1673606_C13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

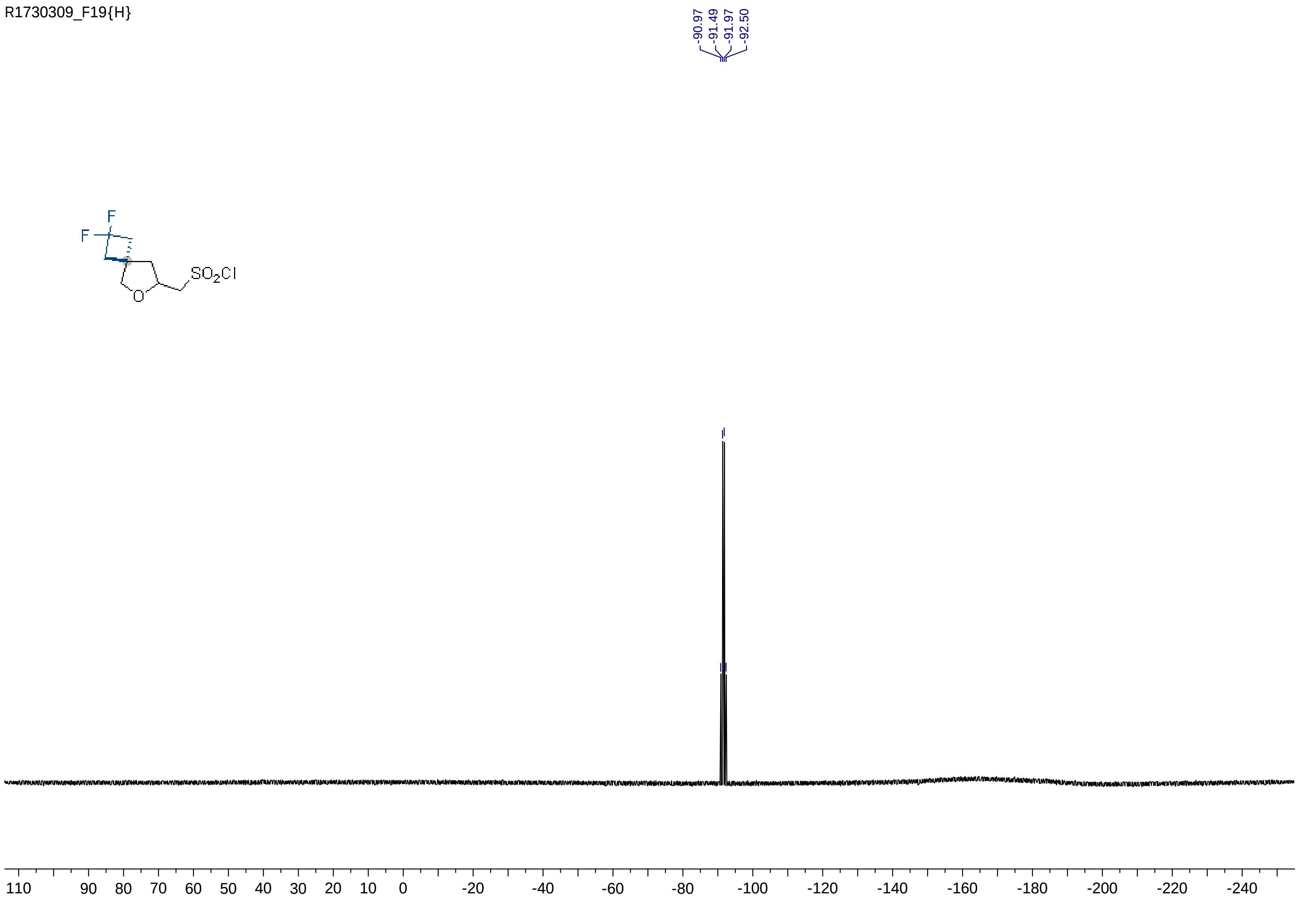
Compound 4e


F
F
SO2Cl
O

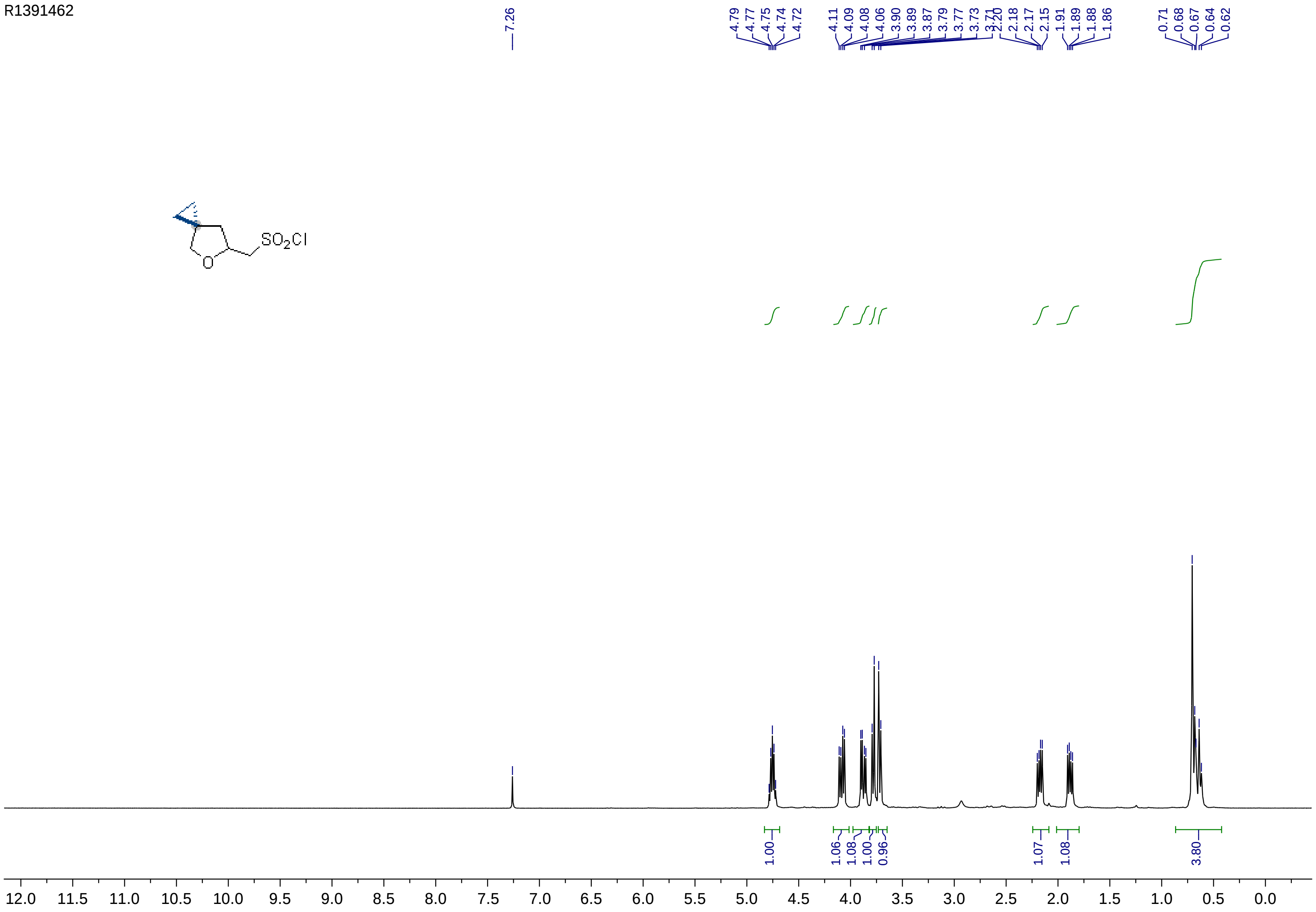

R1730309
7.26
4.62
4.61
4.59
4.57
4.56
4.00
3.99
3.93
3.90
3.88
3.83
3.82
2.68
2.65
2.62
2.59
2.43
2.42
2.02
2.00
1.99
1.97
0.93
1.03
1.95
1.19
3.93
1.10
1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

R1730309_C13



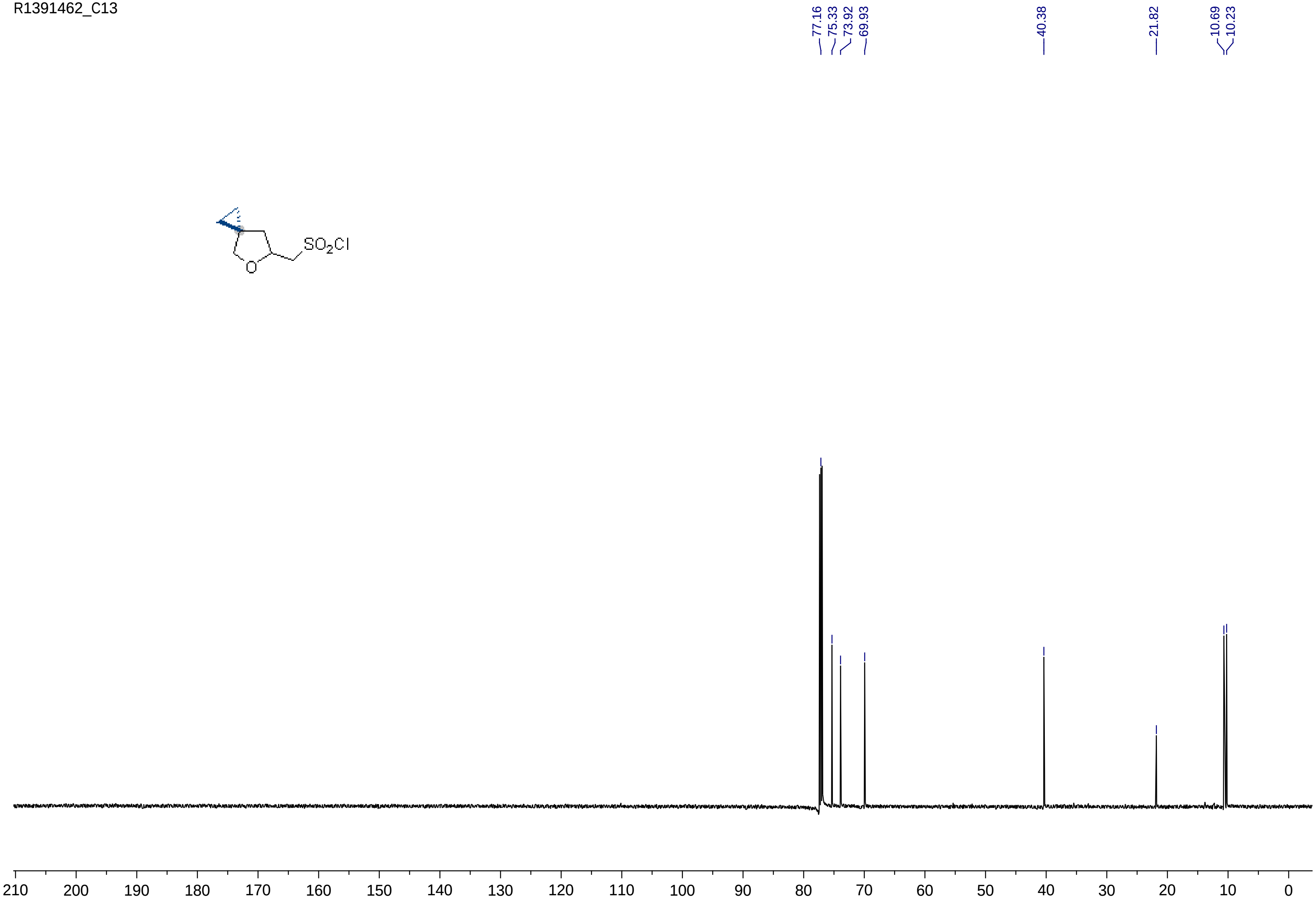

R1730309_F19{H}
-90.97
-91.49
-91.97
-92.50
F
F
SO2Cl
O
110
90
80
70
60
50
40
30
20
10
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240

Compound 5e

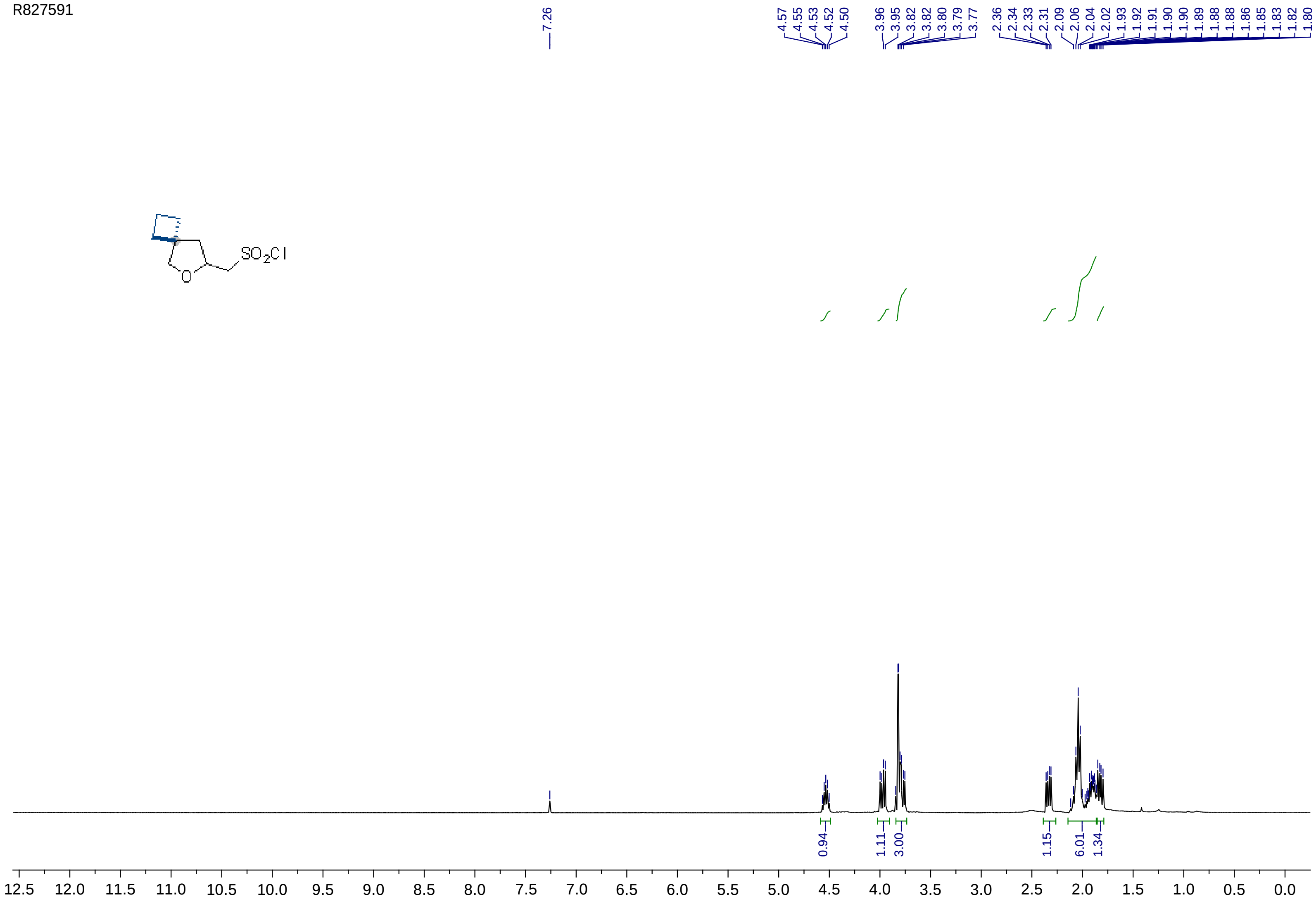


SO2Cl
O
R1391462
7.26
4.79
4.77
4.75
4.74
4.72
4.11
4.09
4.08
4.06
3.90
3.89
3.87
3.79
3.77
3.73
3.71
2.20
2.18
2.17
2.15
1.91
1.89
1.88
1.86
0.71
0.68
0.67
0.64
0.62
1.00
1.06
1.08
1.00
0.96
1.07
1.08
3.80
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

R1391462_C13

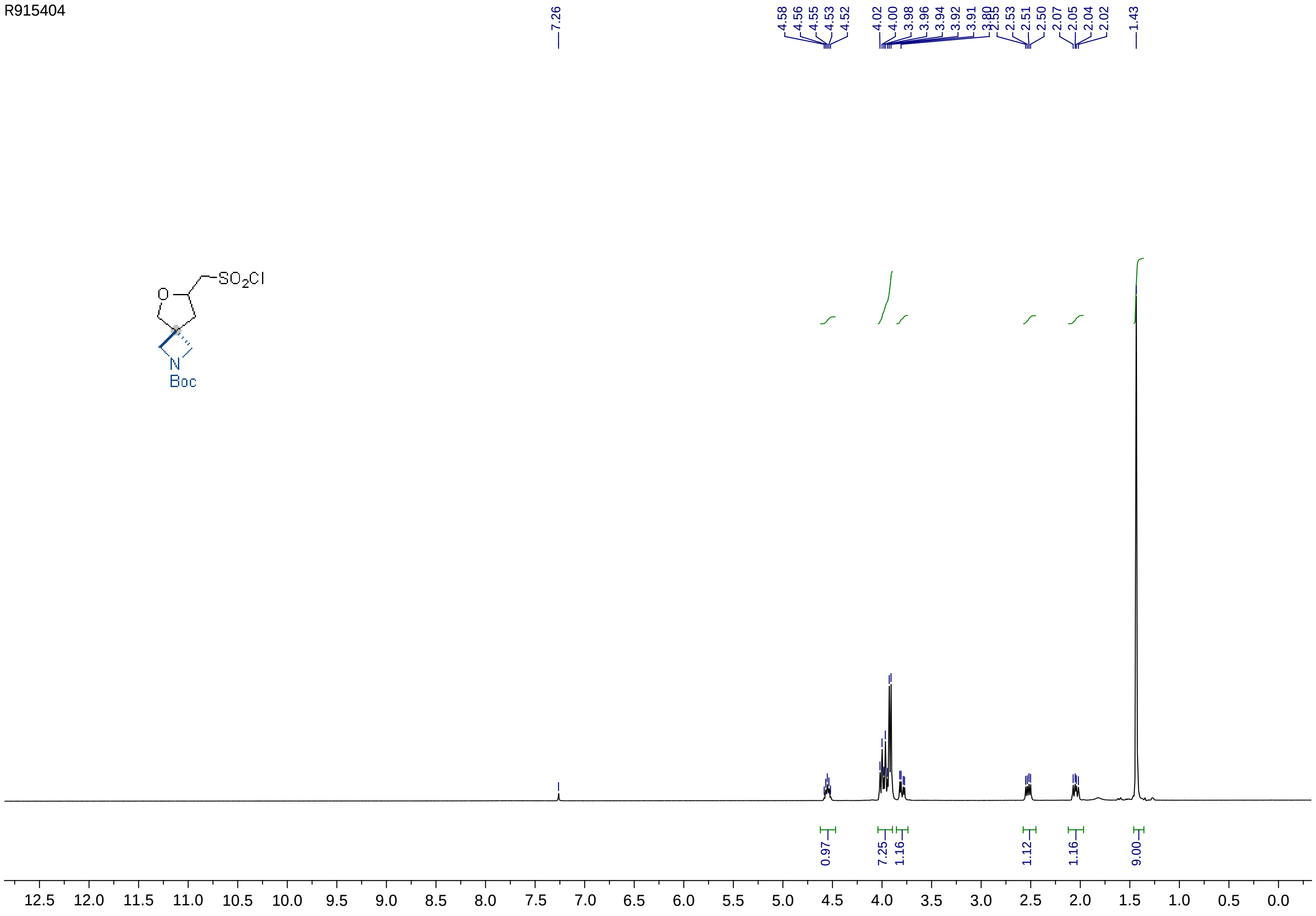


Compound 6e


R827591
SO2Cl
O
7.26
4.57
4.55
4.53
4.52
4.50
3.96
3.95
3.82
3.82
3.80
3.79
3.77
2.36
2.34
2.33
2.31
2.09
2.06
2.04
2.02
1.93
1.92
1.91
1.90
1.89
1.88
1.88
1.86
1.85
1.83
1.82
1.80
0.94
1.11
3.00
1.15
6.01
1.34
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

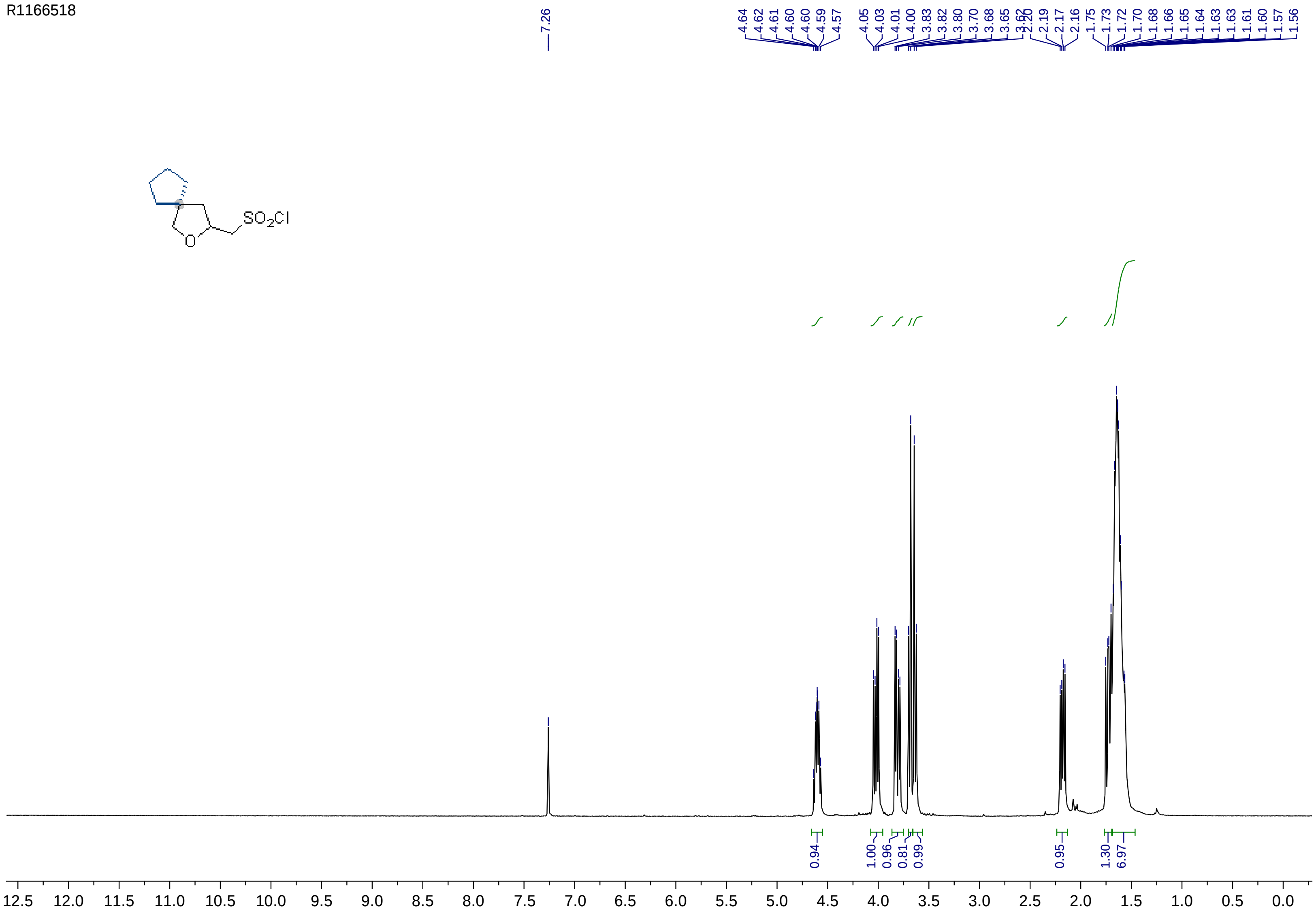

R827591_C13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 8e

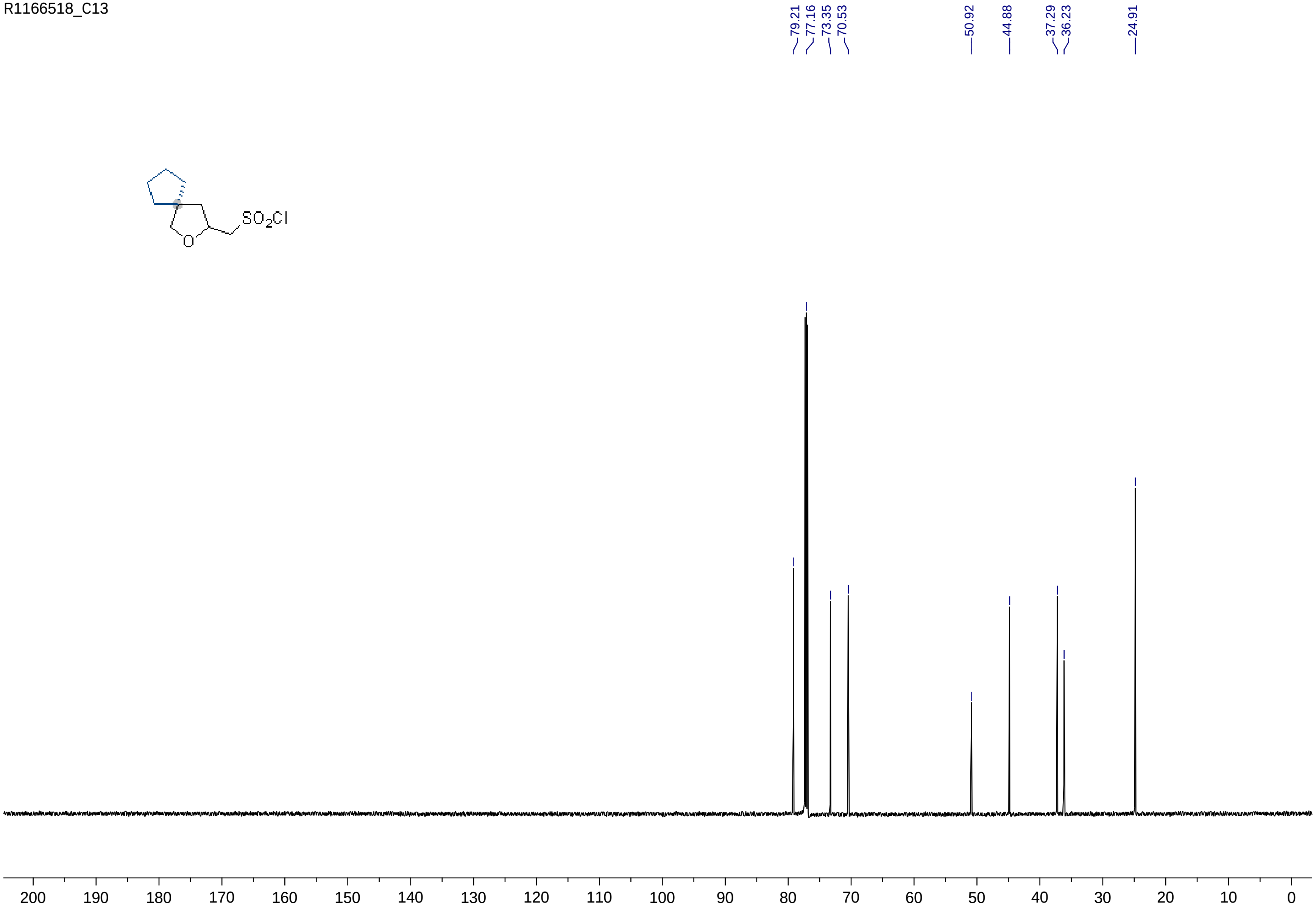

R915404
7.26
4.58
4.56
4.55
4.53
4.52
4.02
4.00
3.98
3.96
3.94
3.92
3.91
3.80
3.55
2.53
2.51
2.50
2.07
2.05
2.04
2.02
1.43
SO2Cl
O
N
Boc
0.97
7.25
1.16
1.12
1.16
9.00
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


R915404_C13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

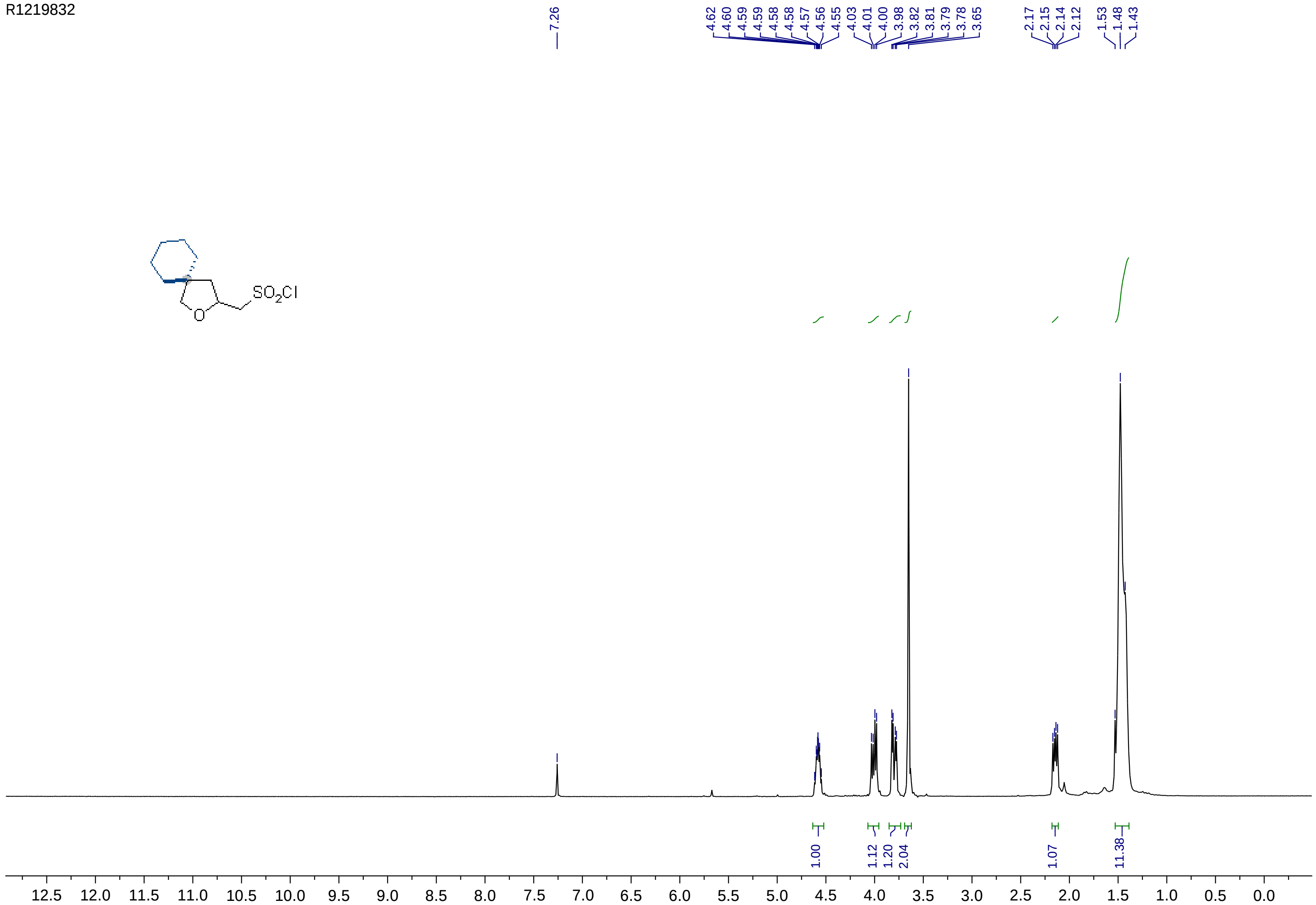
Compound 9e


R1166518
7.26
4.64
4.62
4.61
4.60
4.60
4.59
4.57
4.05
4.03
4.01
4.00
3.83
3.82
3.80
3.70
3.68
3.65
3.62
2.20
2.19
2.17
2.16
1.75
1.73
1.72
1.70
1.68
1.66
1.65
1.64
1.63
1.61
1.60
1.57
1.56
SO2Cl
O
0.94
1.00
0.96
0.81
0.99
0.95
1.30
6.97
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

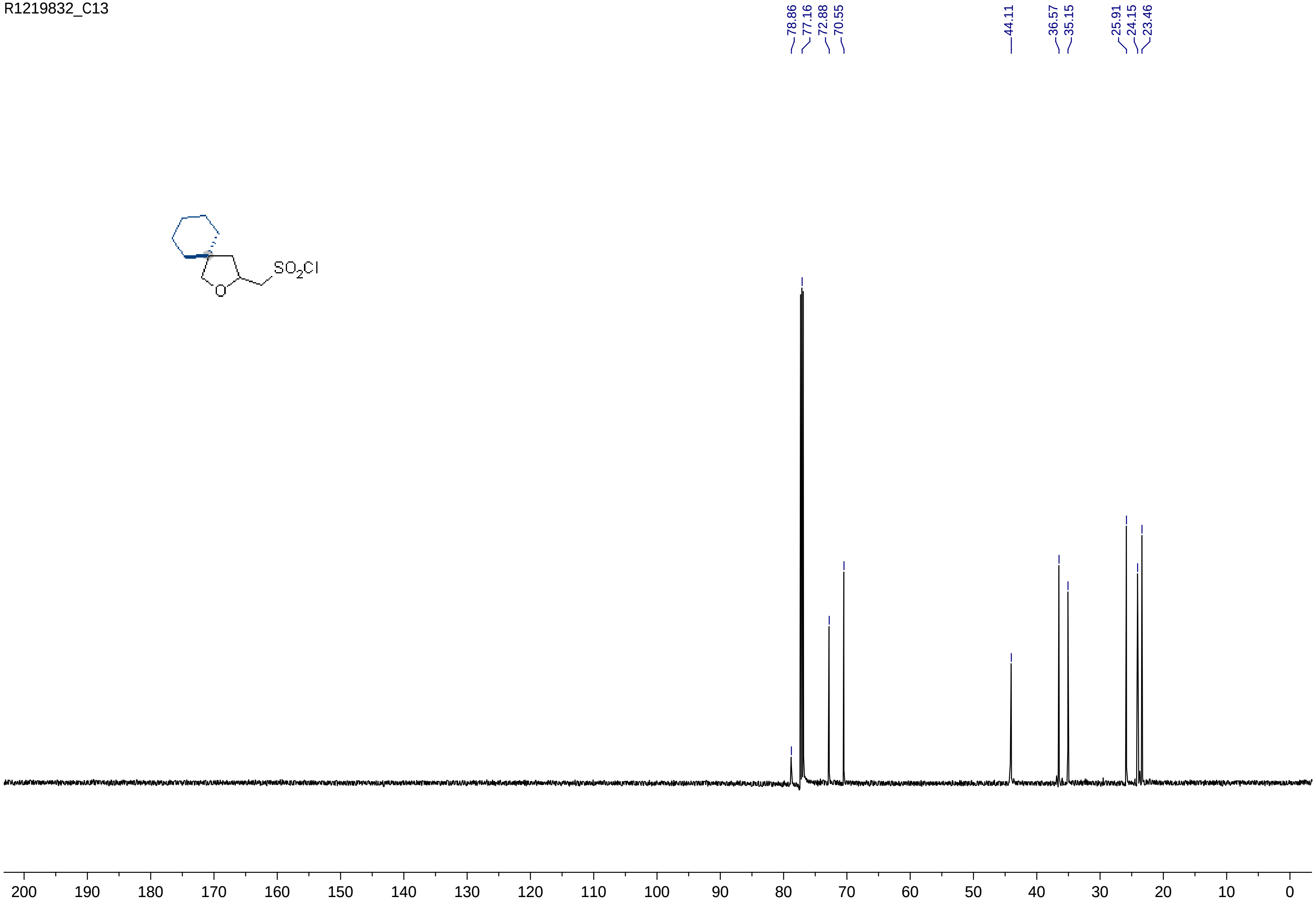
R1166518_C13



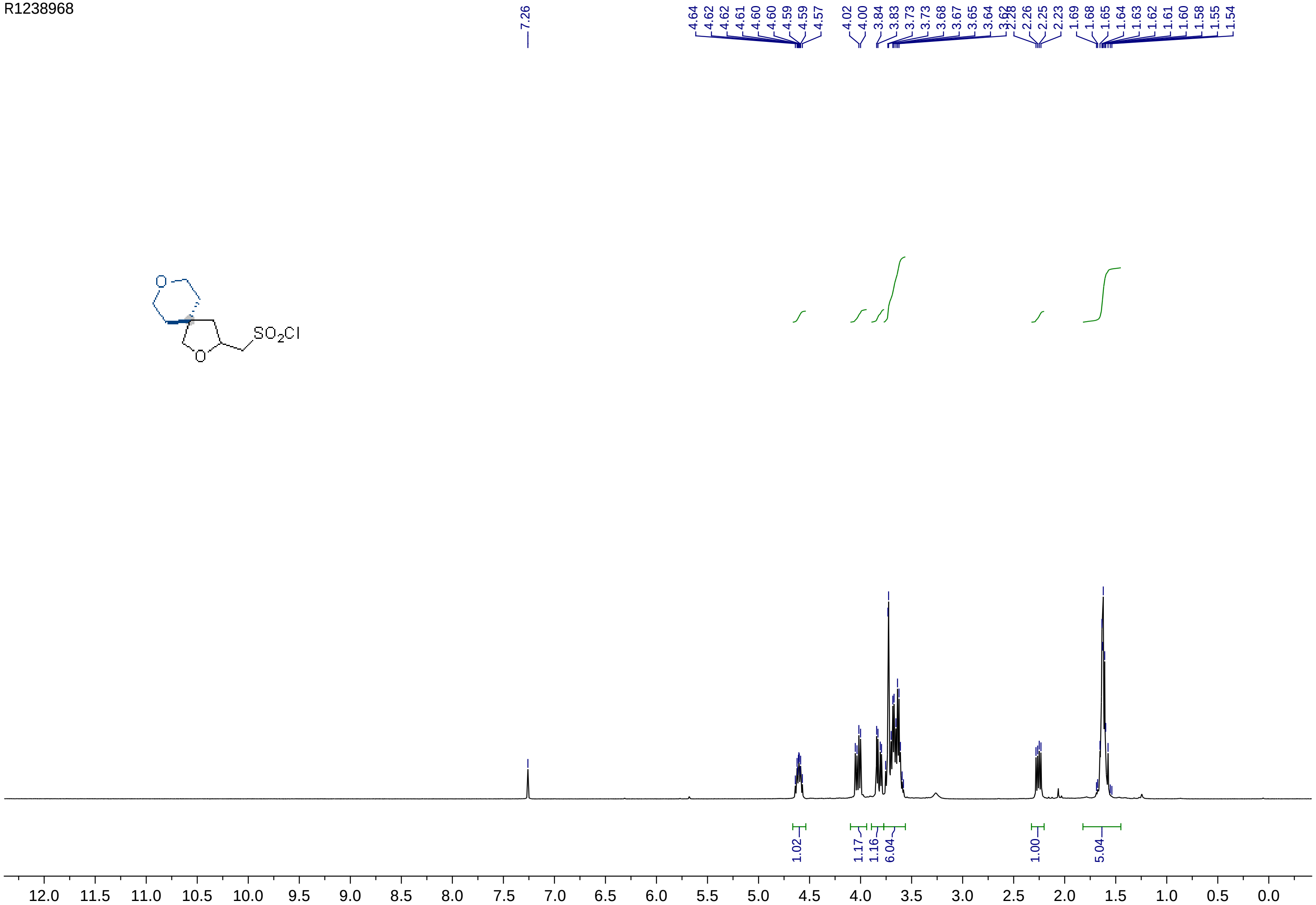
Compound 11e



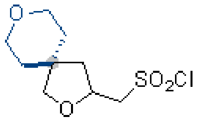
R1219832_C13

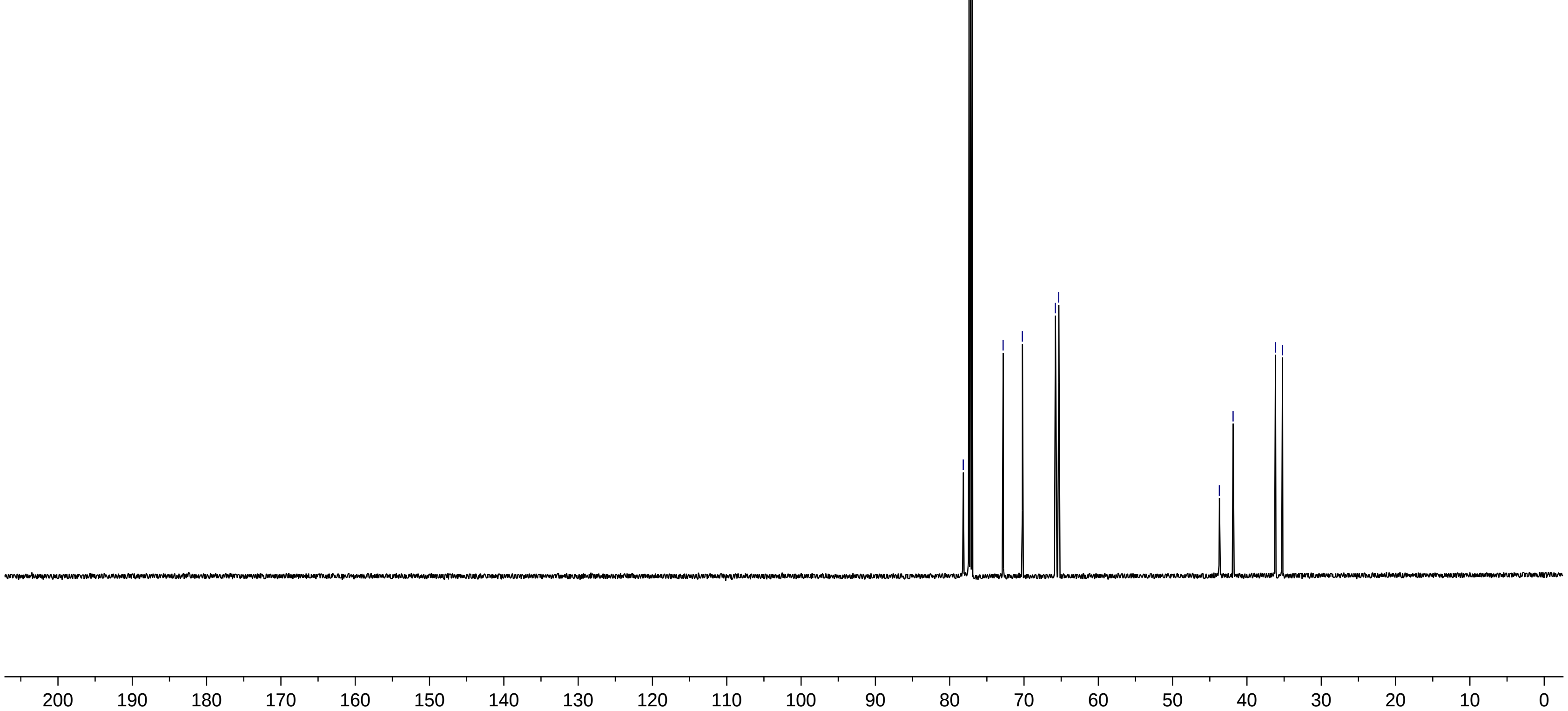


Compound 13e

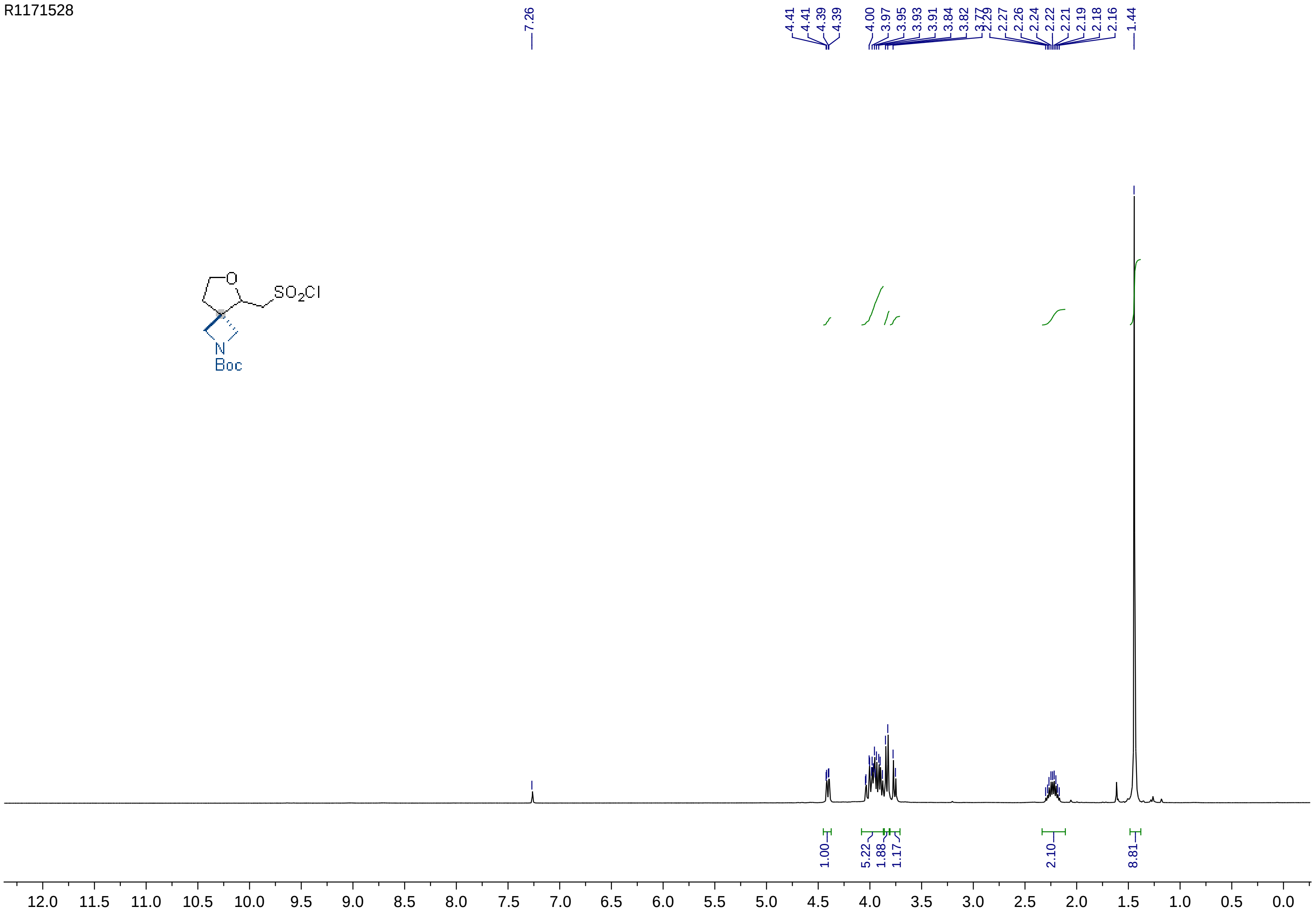


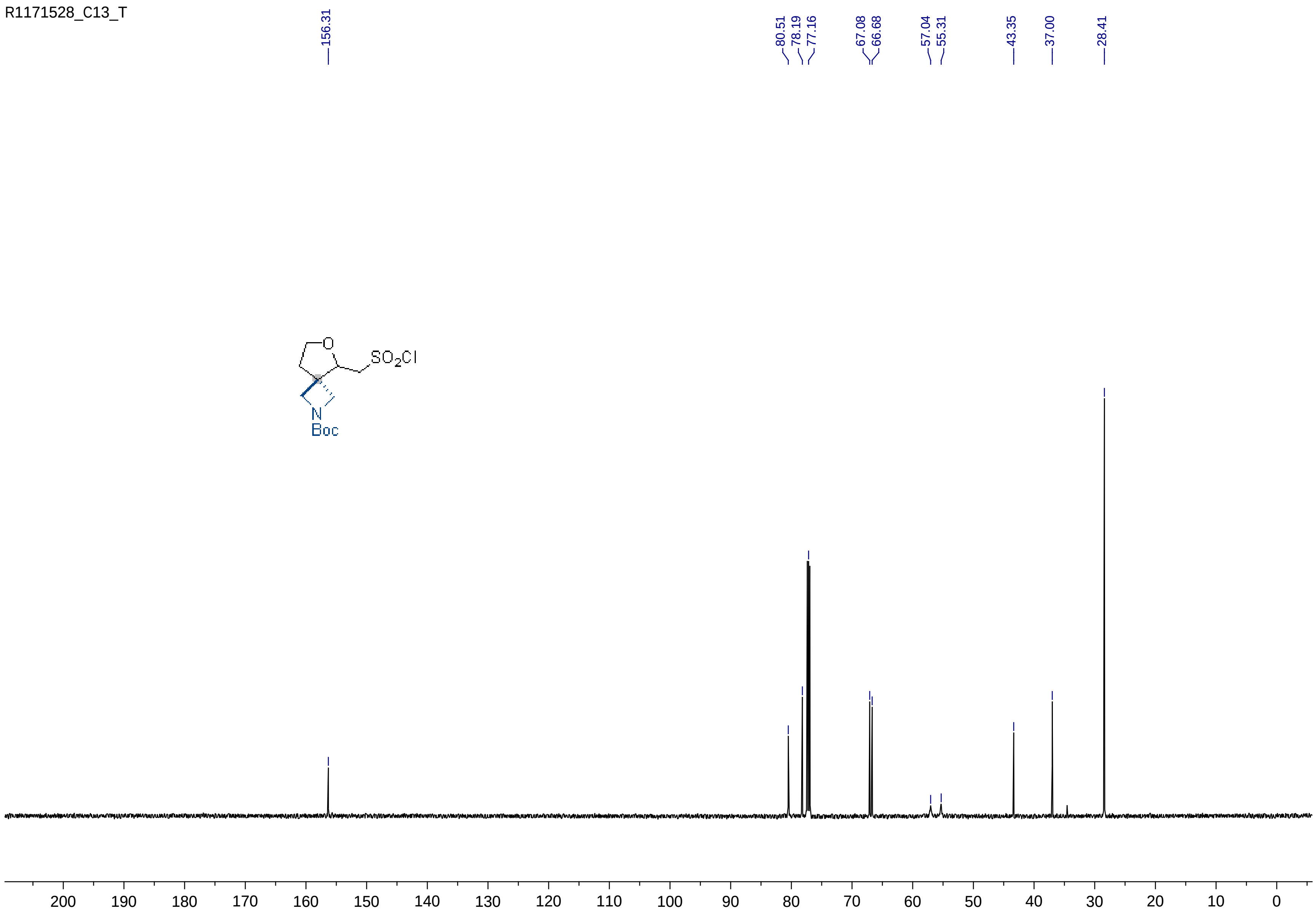
R1238968_C13



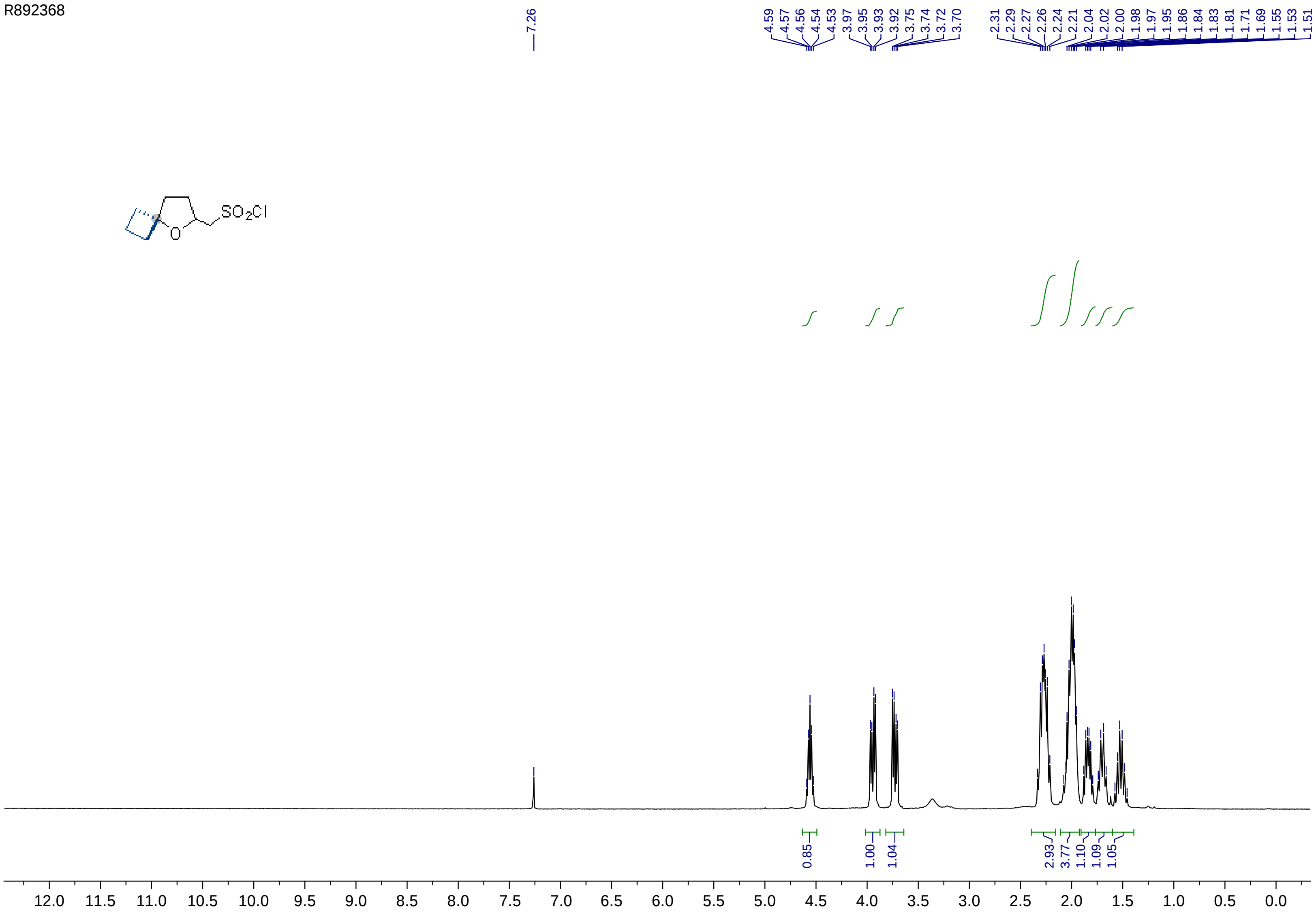


Compound 16e



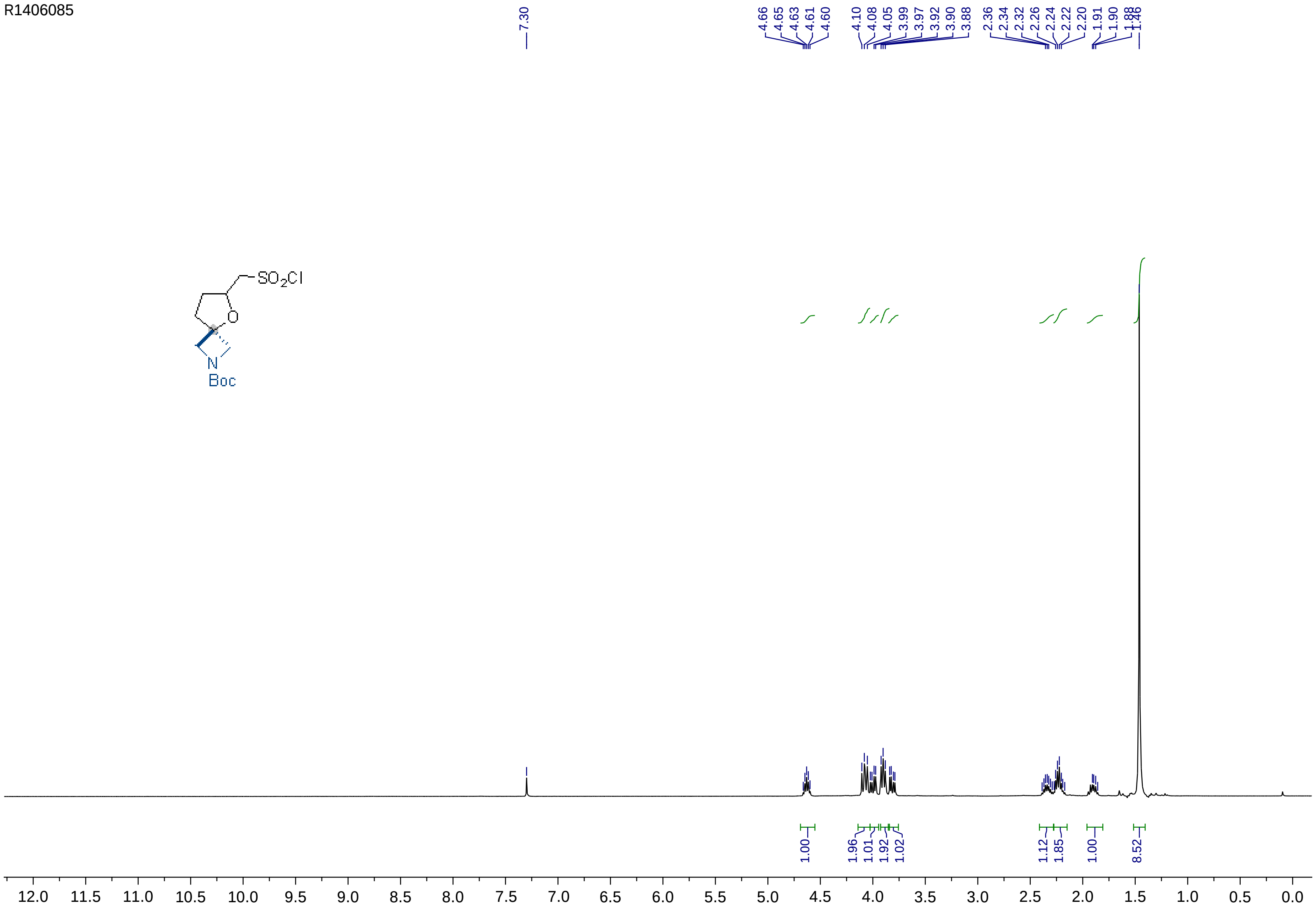

R1171528_C13_T
156.31
80.51
78.19
77.16
67.08
66.68
57.04
55.31
43.35
37.00
28.41
O
SO2Cl
N
Boc
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 18e

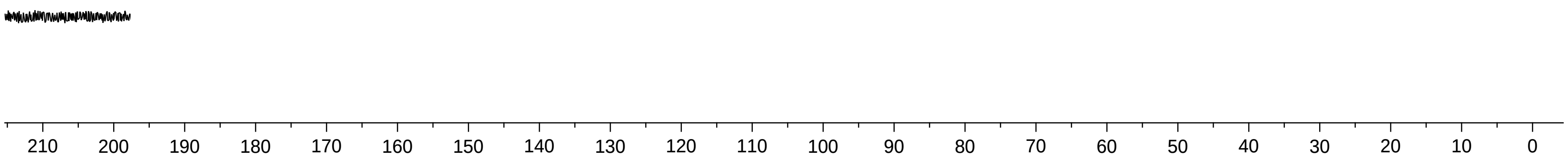



R892368_C13
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

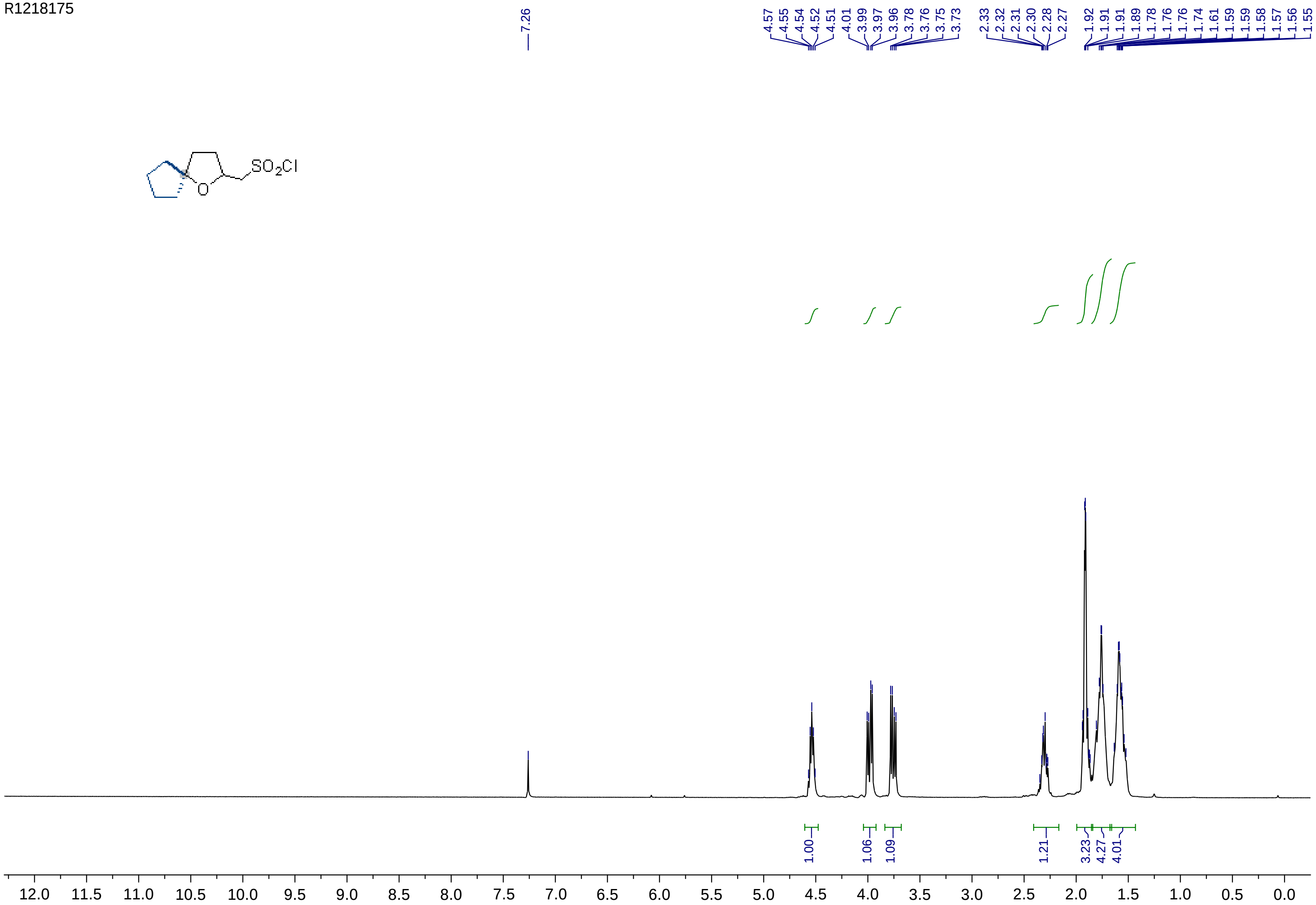
Compound 21e

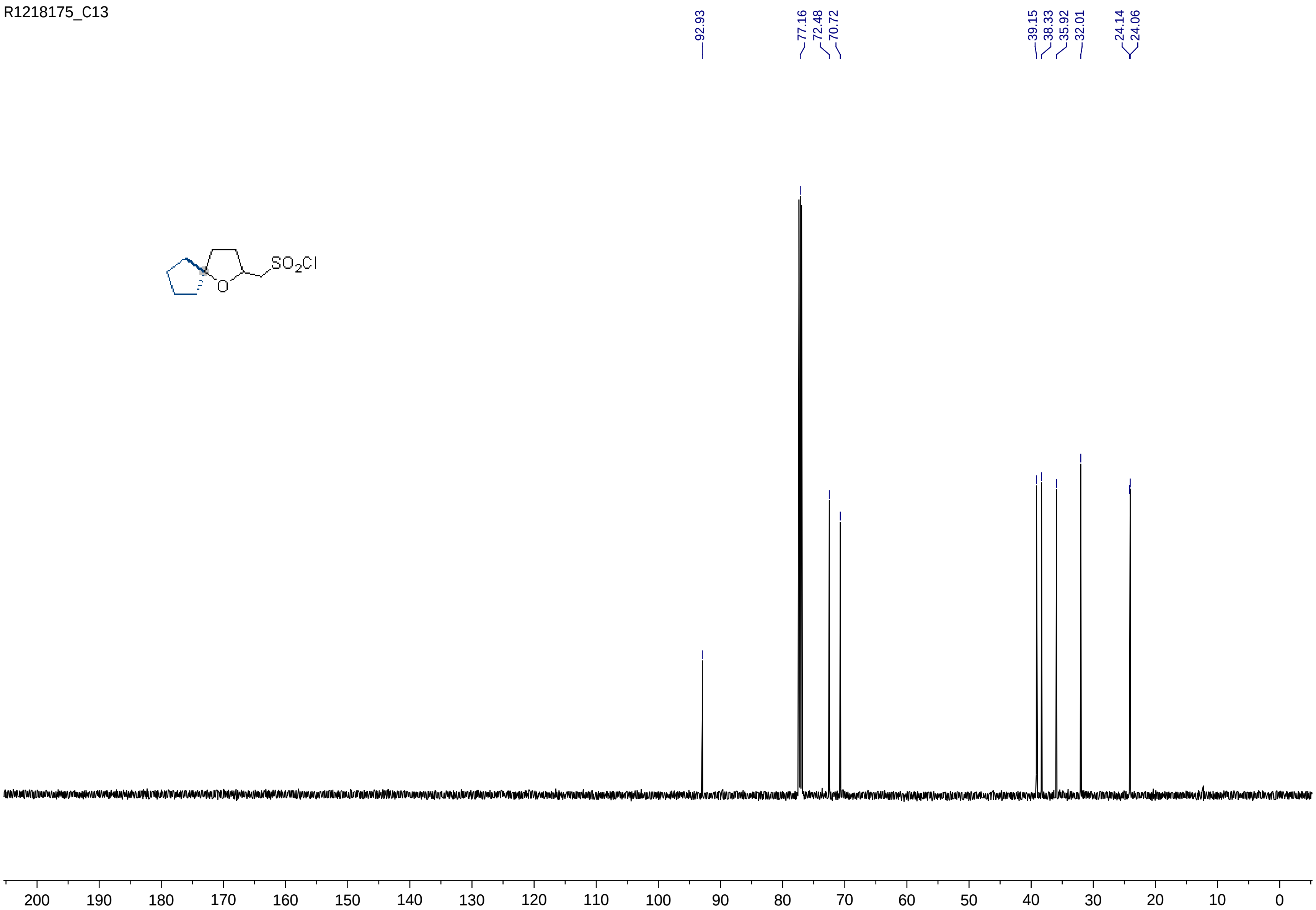


R1406085_C13



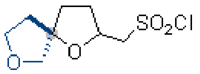
Compound 22e

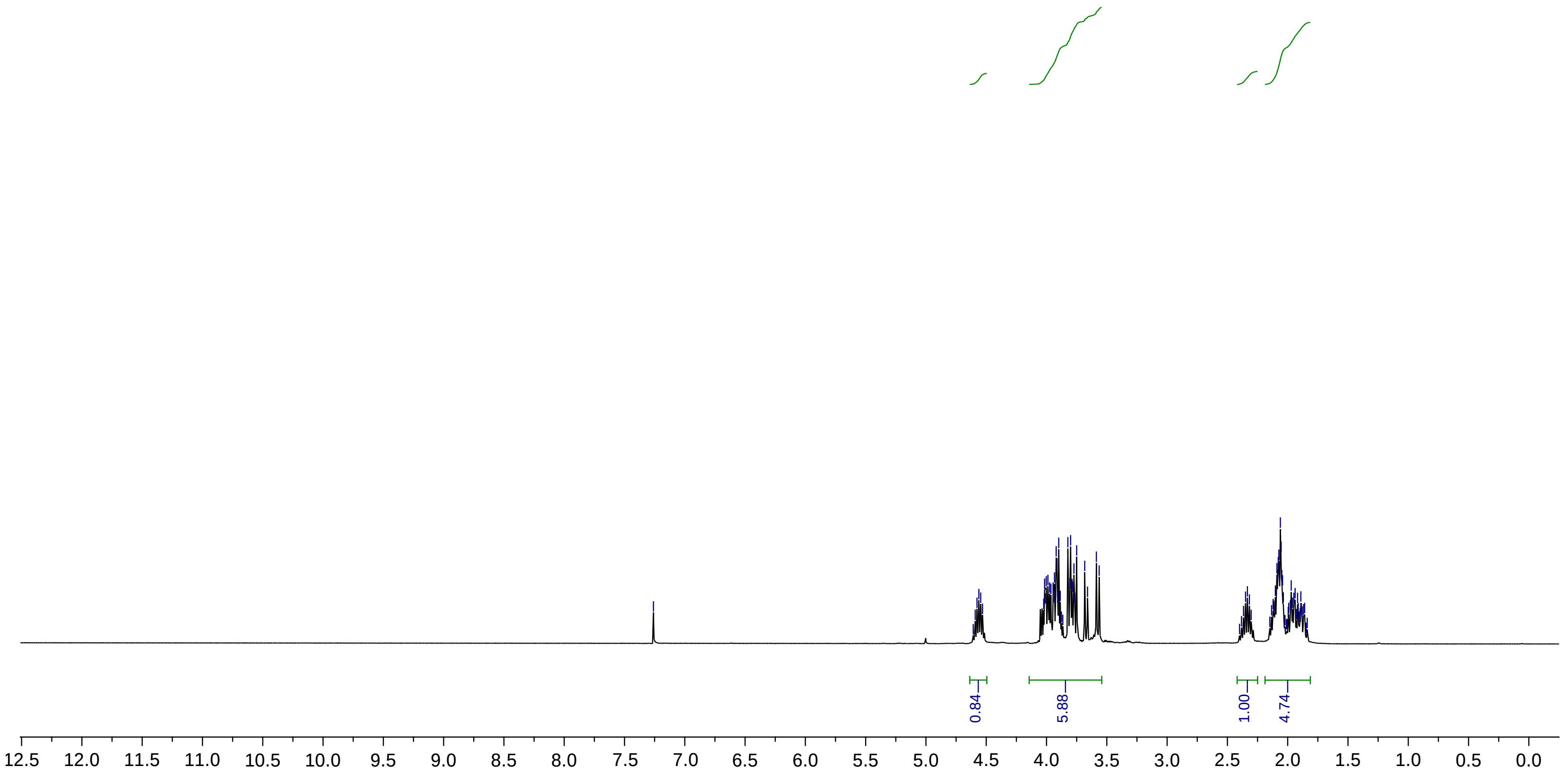


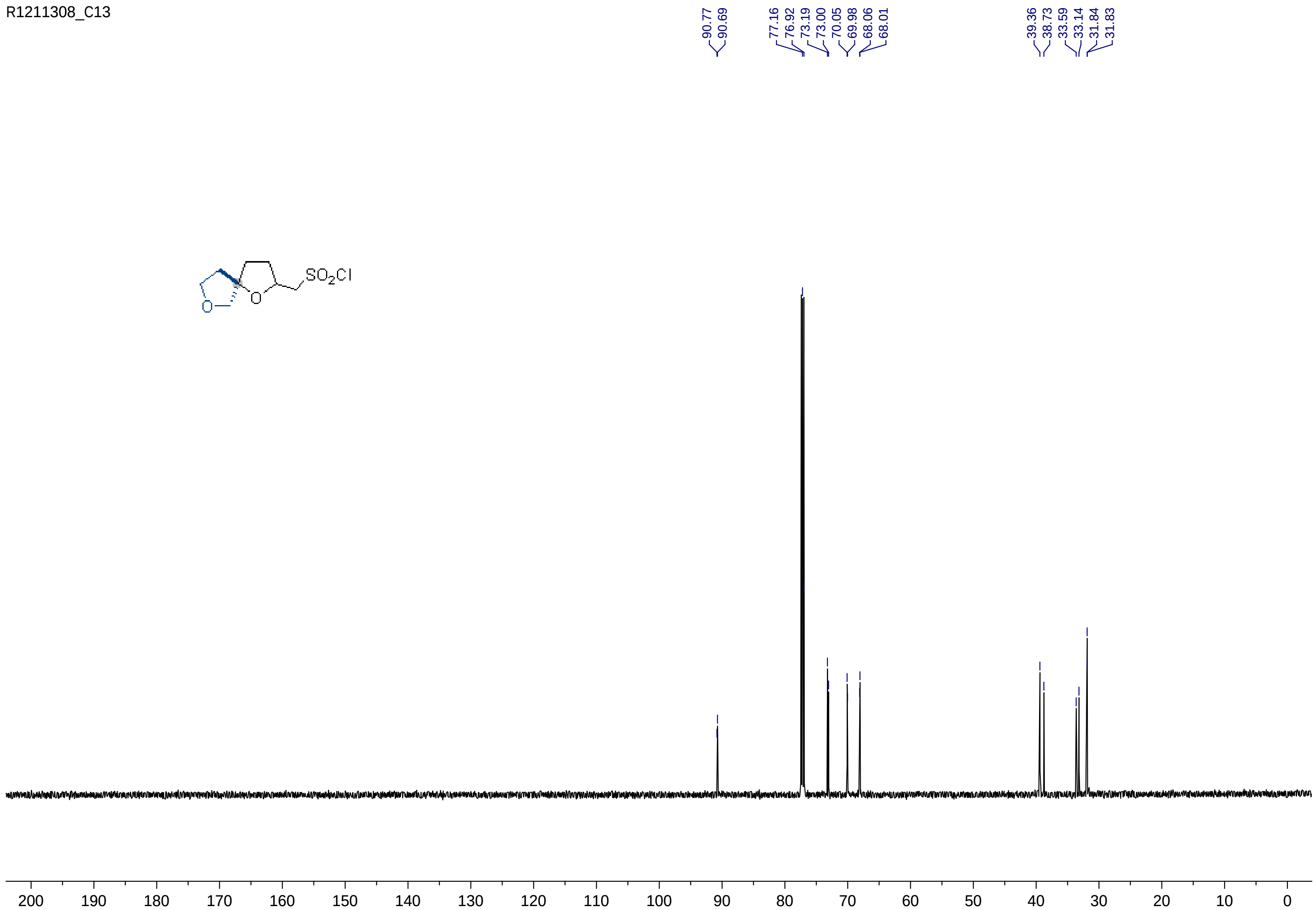

R1218175_C13
92.93
77.16
72.48
70.72
39.15
38.33
35.92
32.01
24.14
24.06
SO2Cl
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 23e

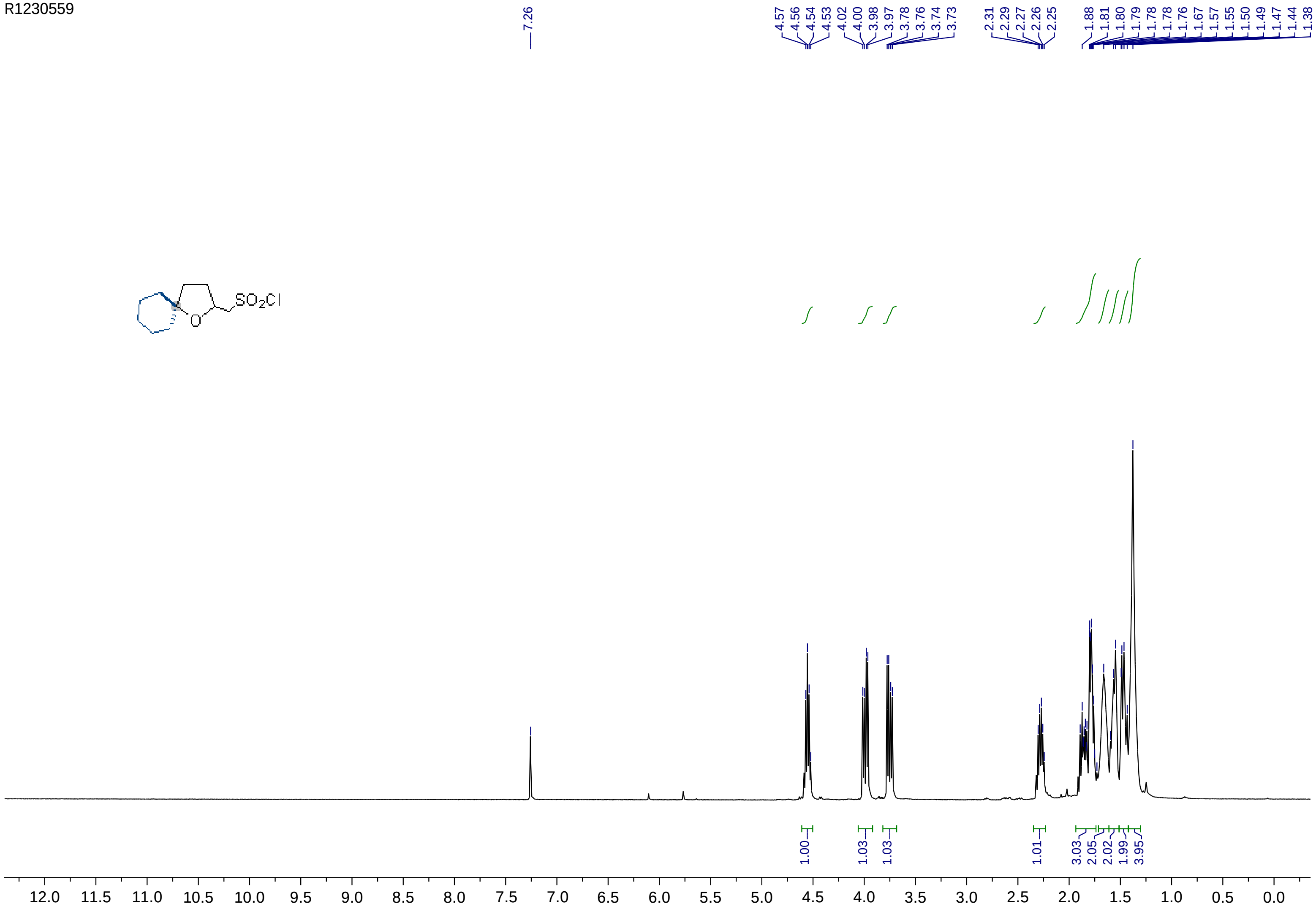
R1211308

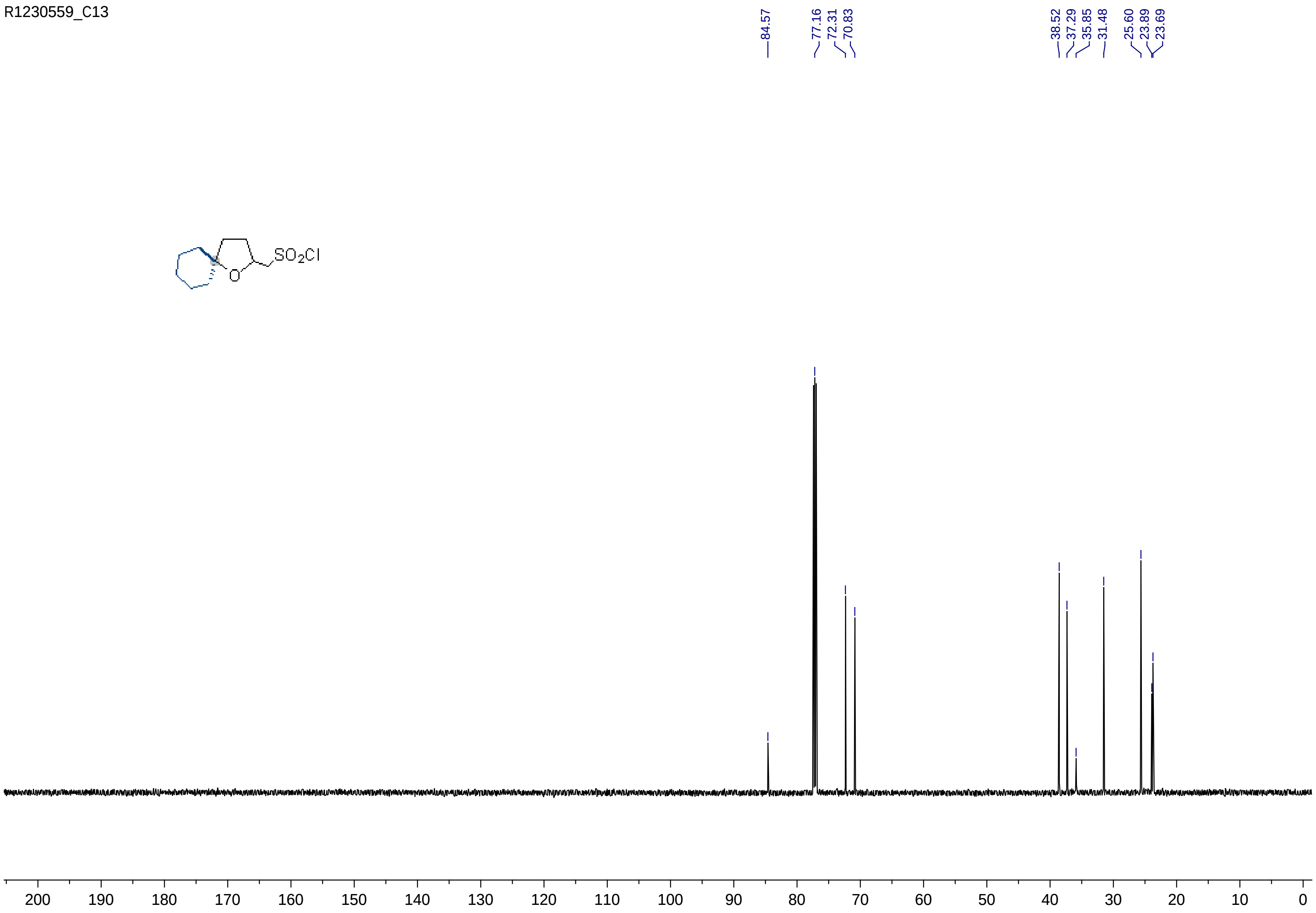




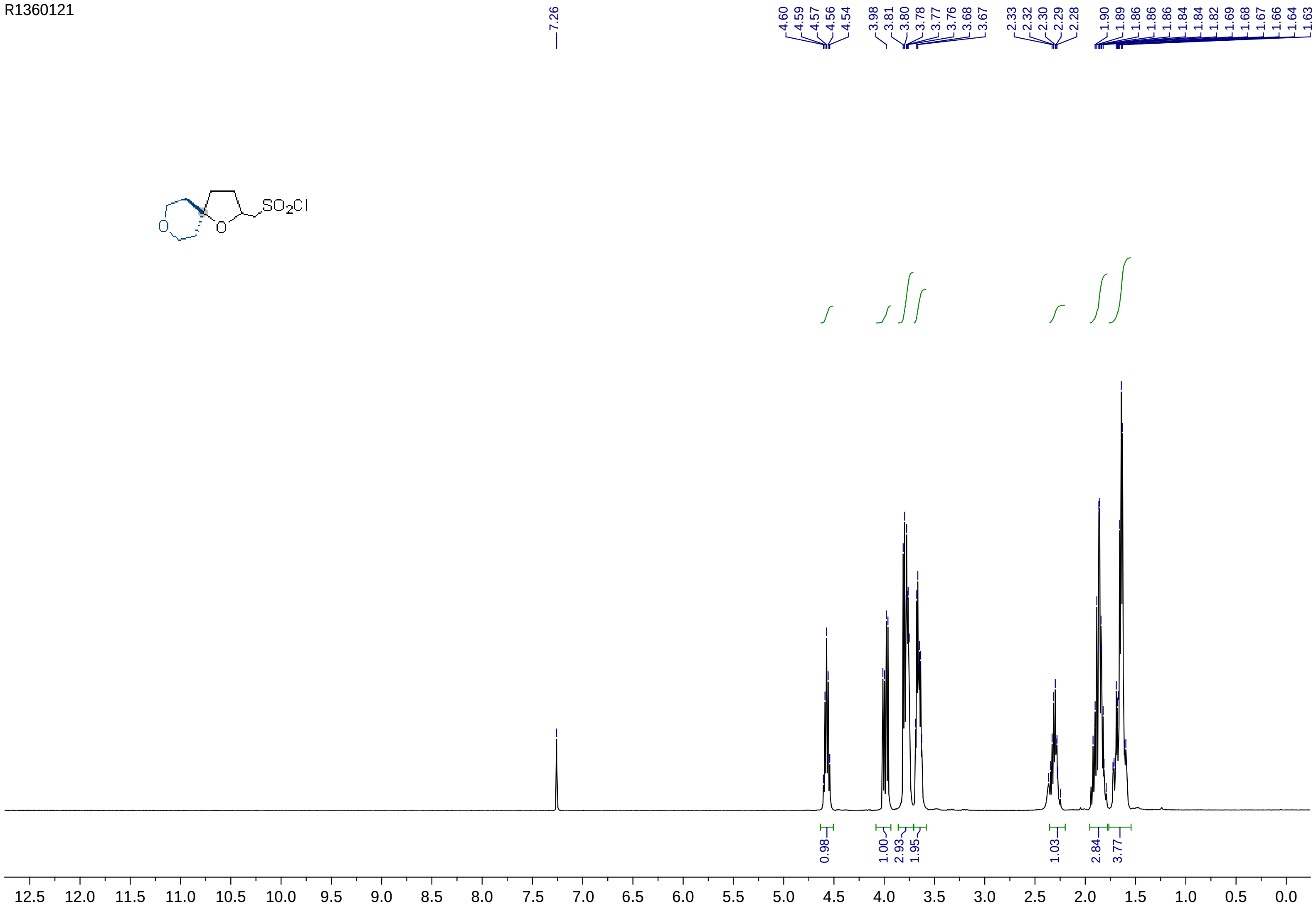

R1211308_C13
90.77
90.69
77.16
76.92
73.19
73.00
70.05
69.98
68.06
68.01
39.36
38.73
33.59
33.14
31.84
31.83
SO2Cl
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

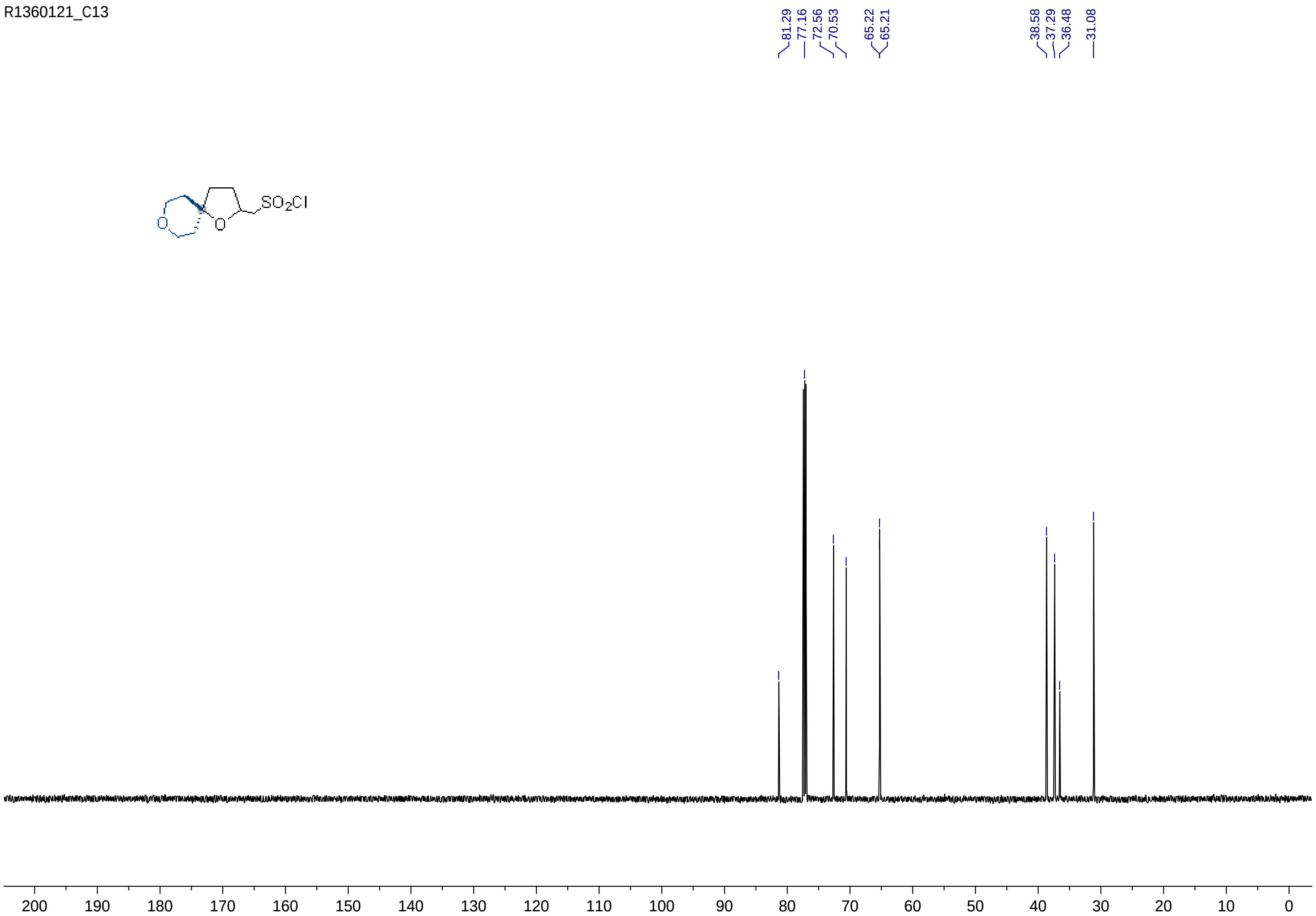
Compound 24e



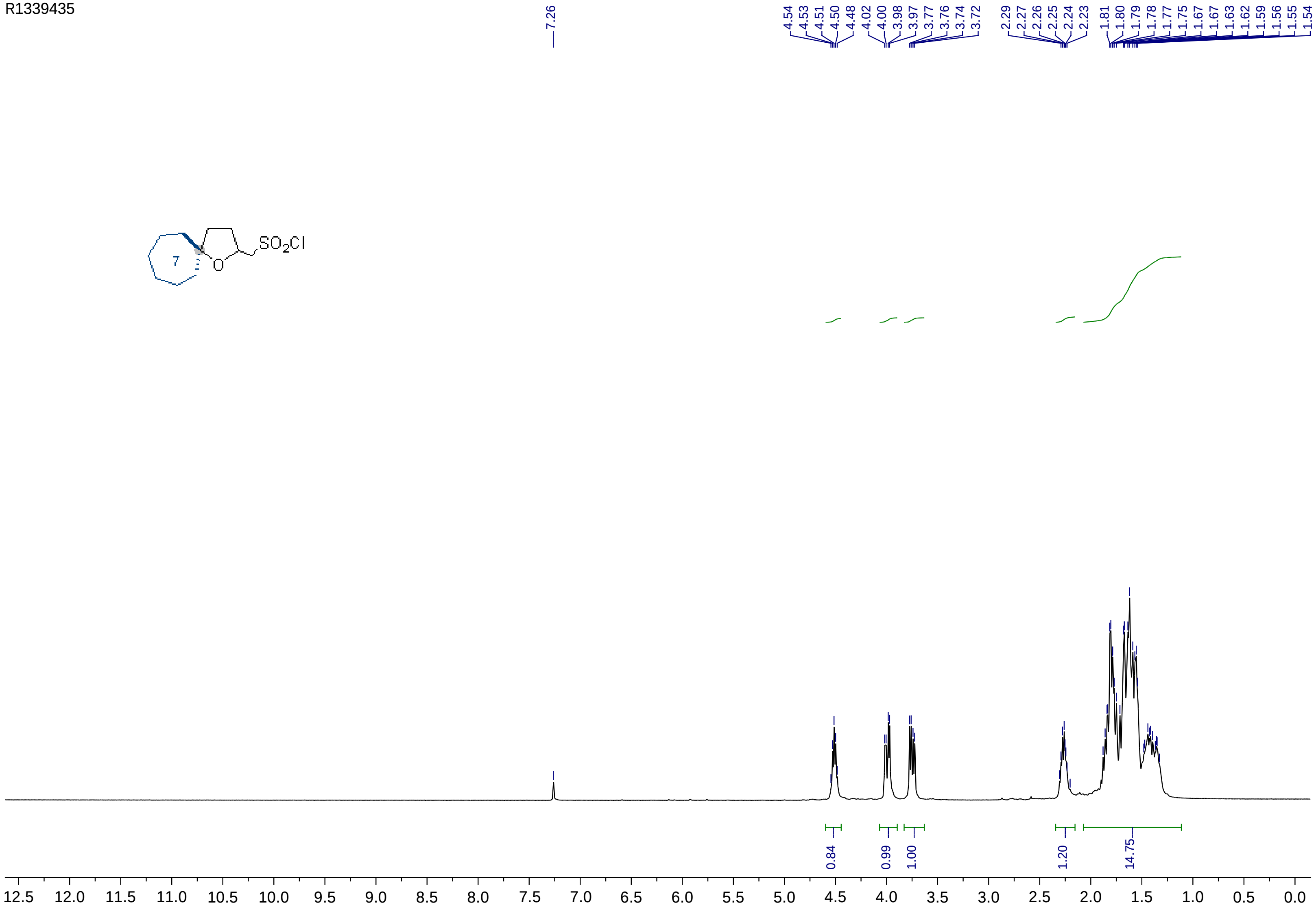

R1230559_C13
84.57
77.16
72.31
70.83
38.52
37.29
35.85
31.48
25.60
23.89
23.69
SO2Cl
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 27e

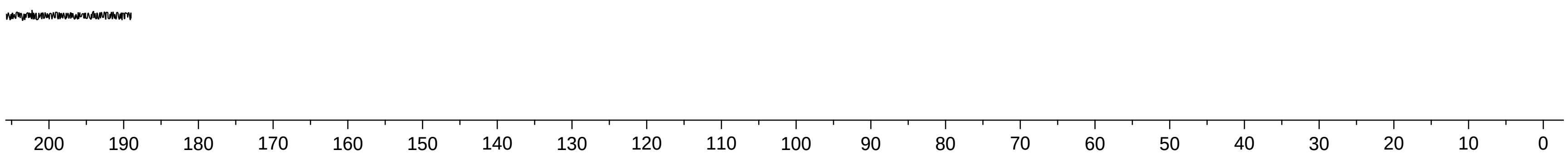



R1360121_C13
81.29
77.16
72.56
70.53
65.22
65.21
38.58
37.29
36.48
31.08
O
O
SO2Cl
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

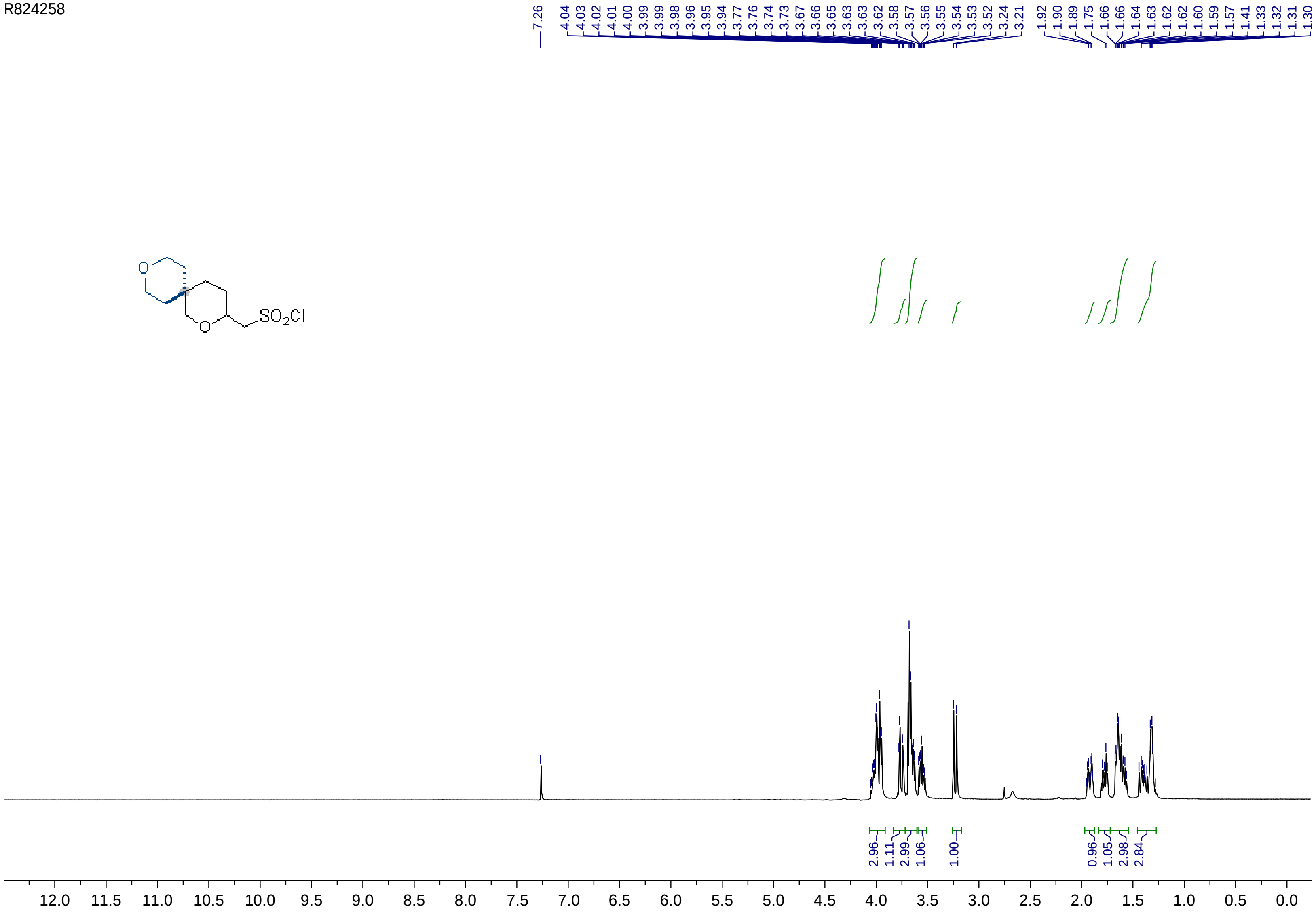
Compound 30e



R1339435_13C

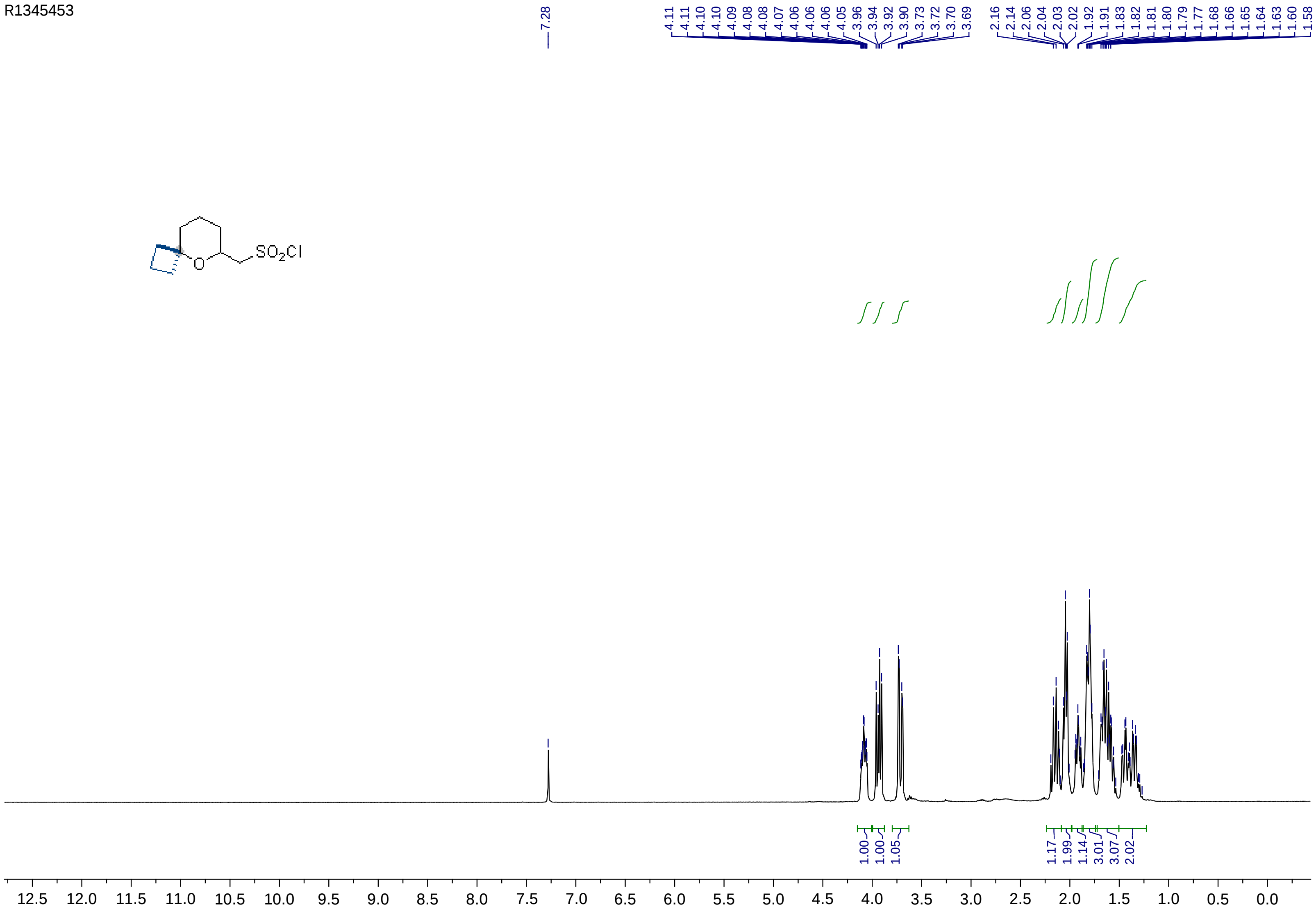


Compound 36e

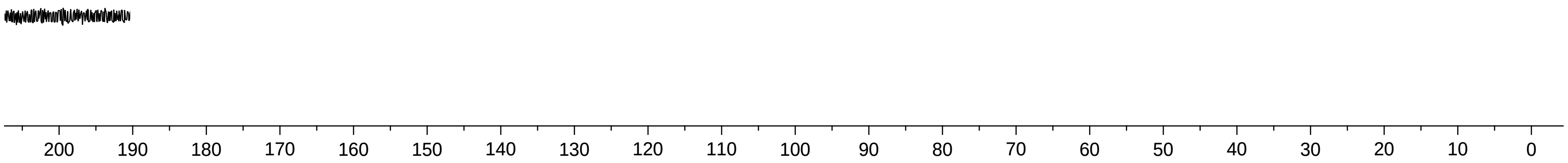



R824258_13C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

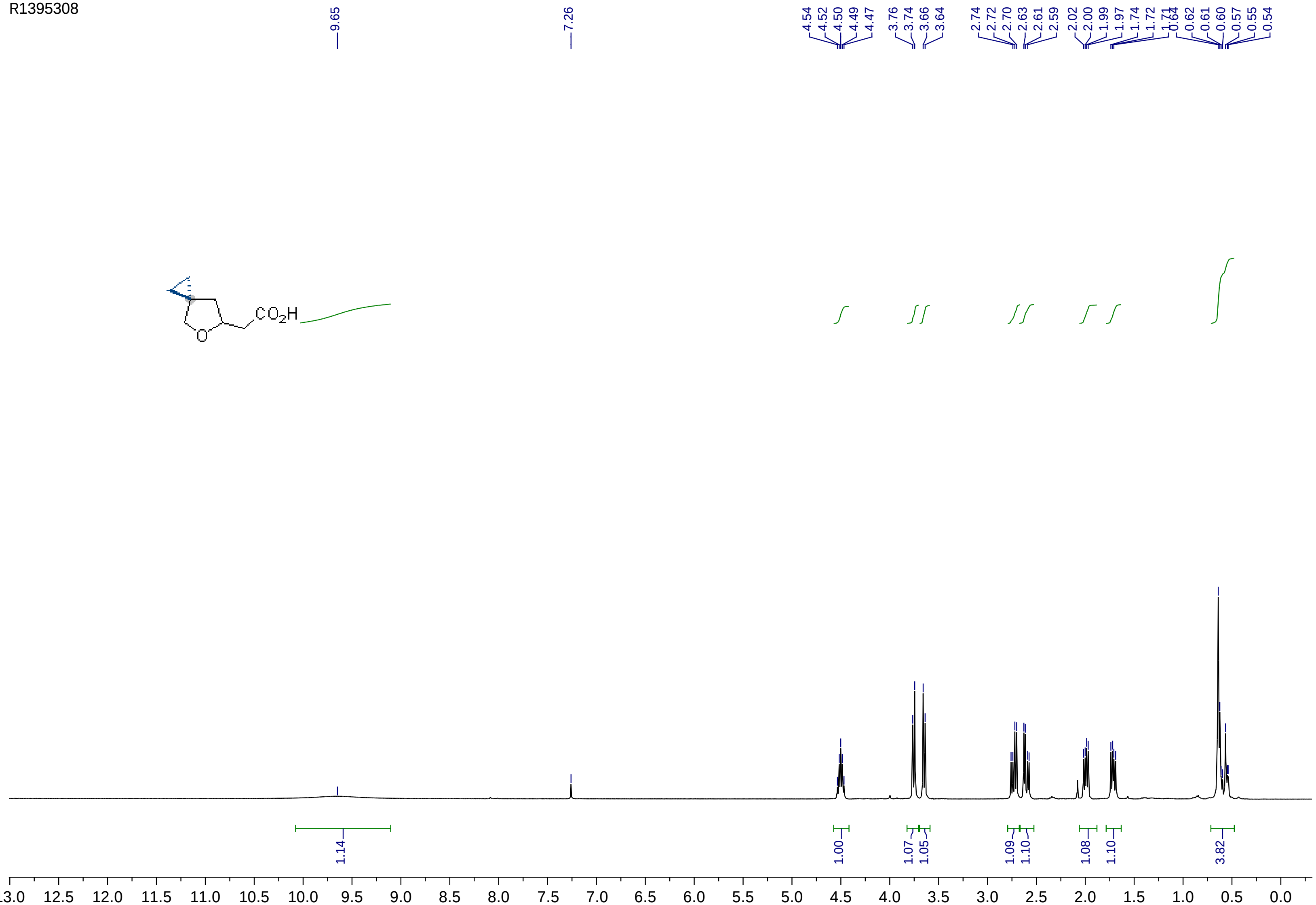
Compound 38e

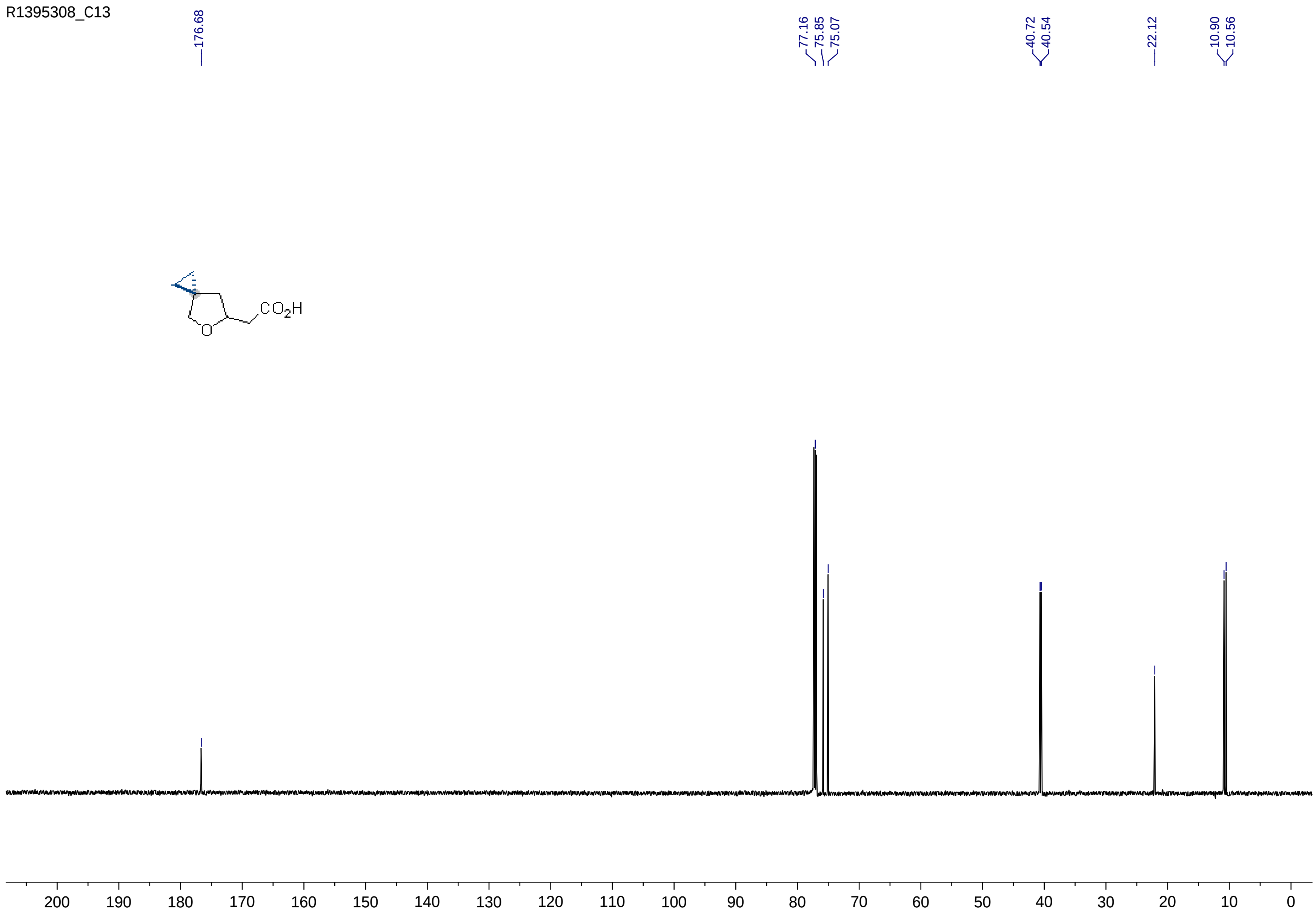


R1345453_C13



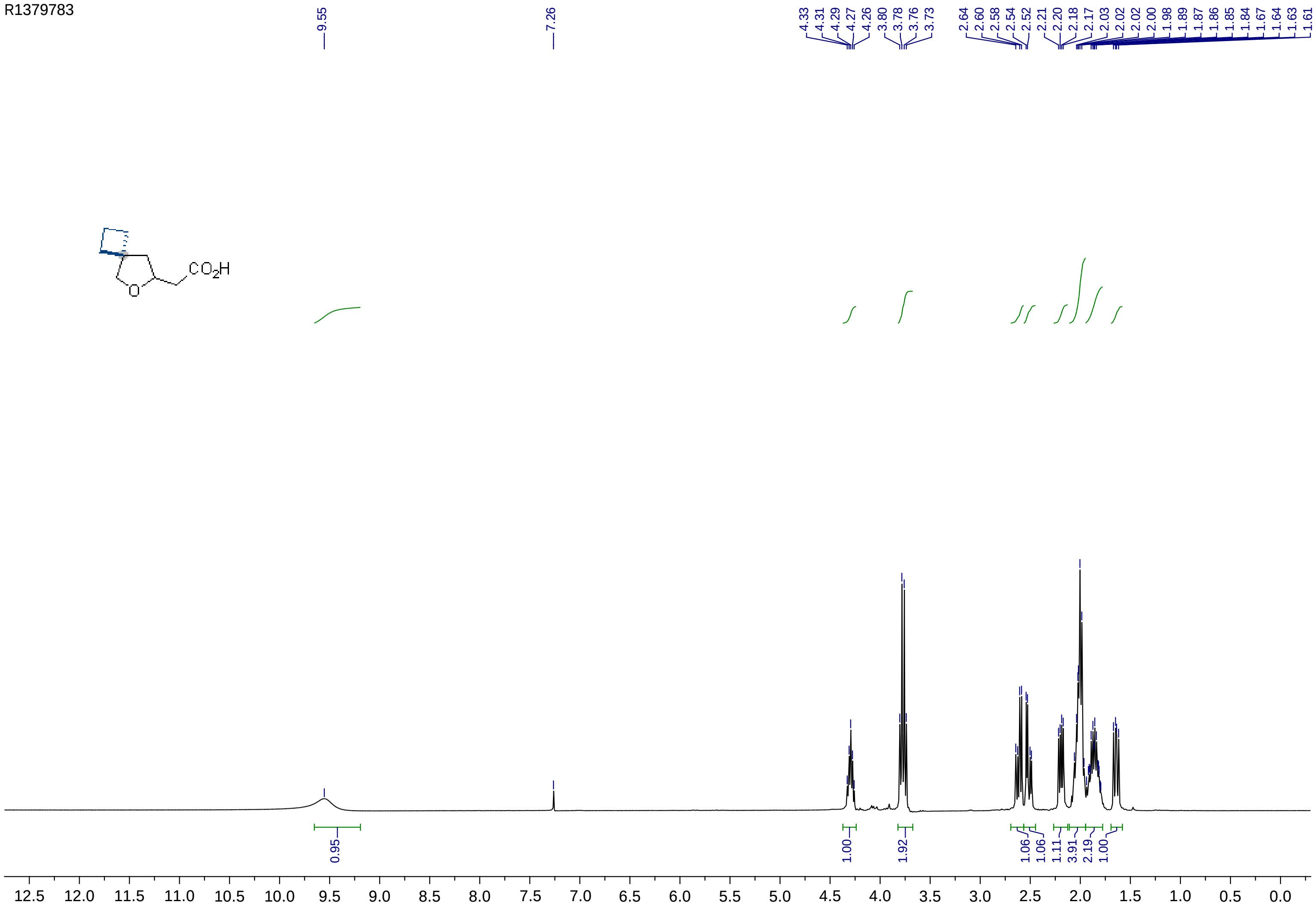
Compound 5f



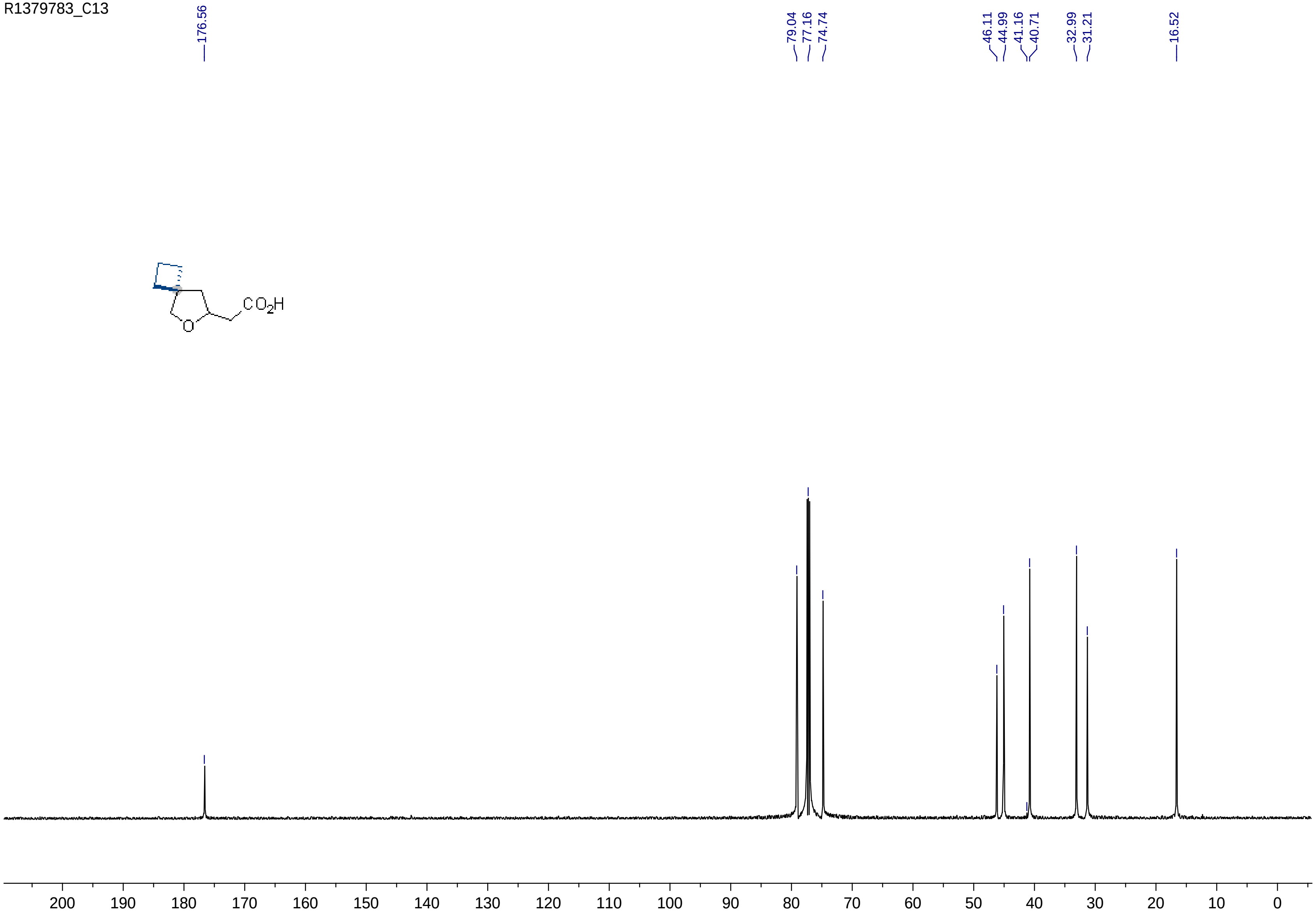


R1395308_C13
176.68
77.16
75.85
75.07
40.72
40.54
22.12
10.90
10.56
CO2H
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

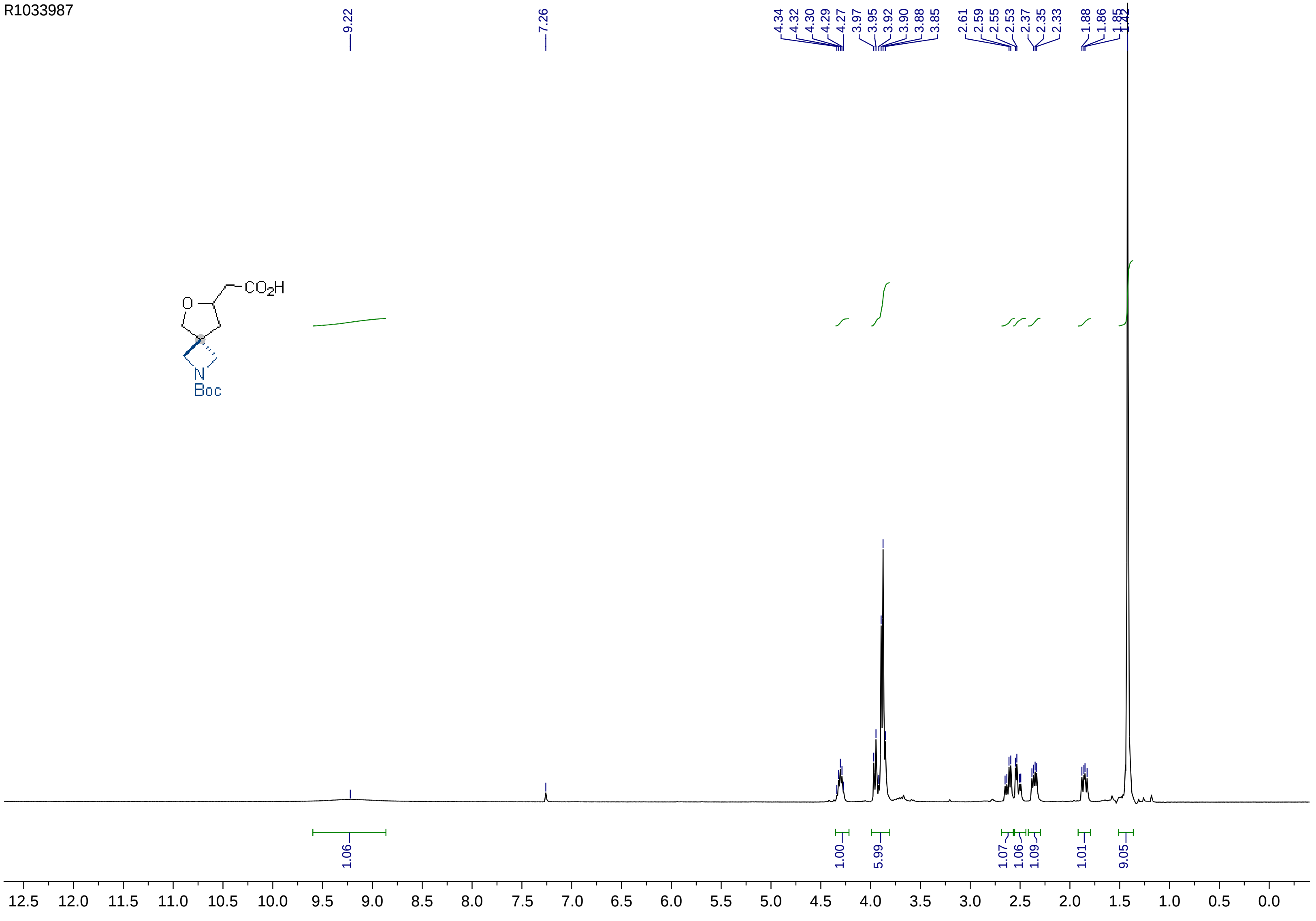
Compound 6f

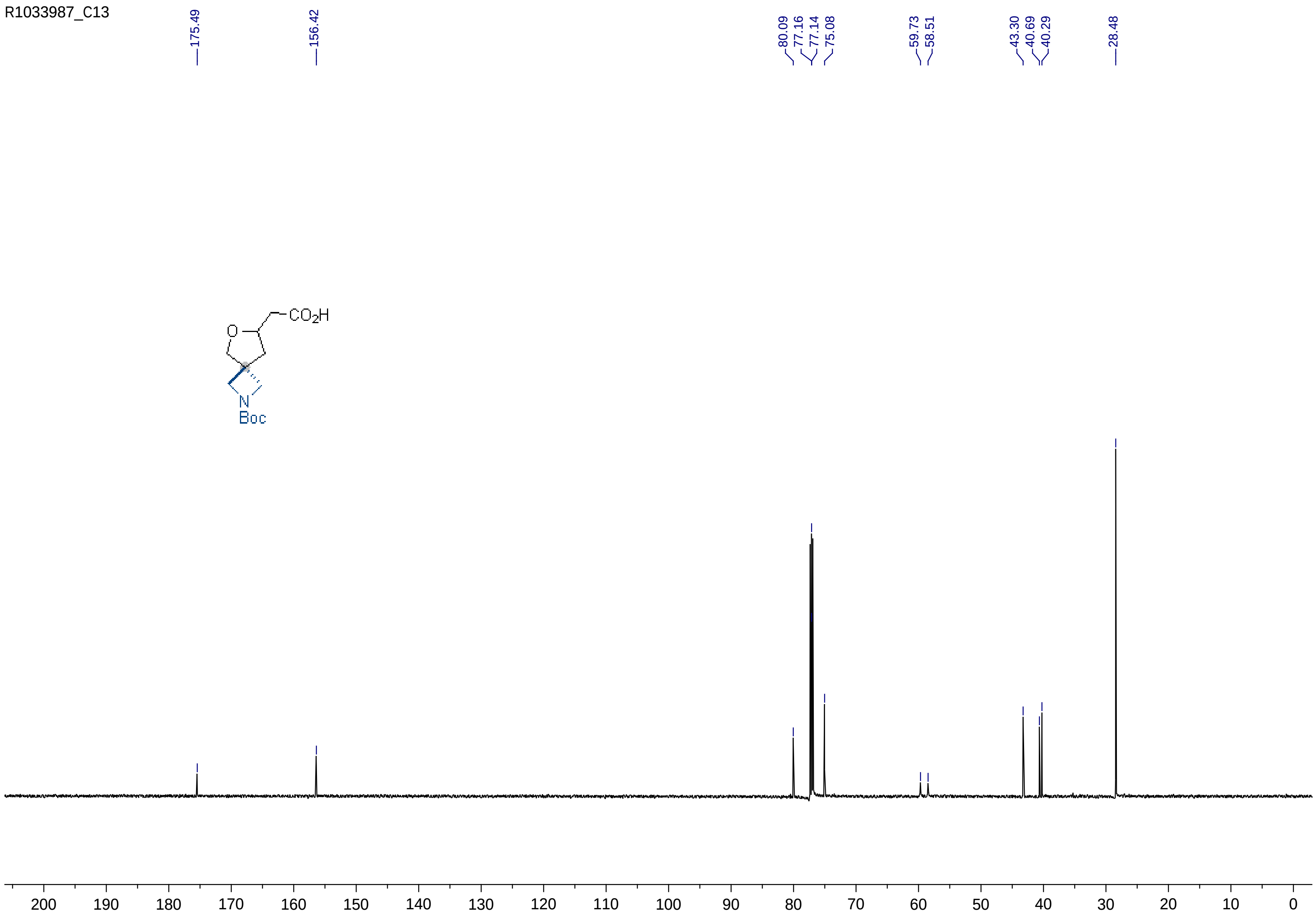

R1379783
9.55
7.26
4.33
4.31
4.29
4.27
4.26
3.80
3.78
3.76
3.73
2.64
2.60
2.58
2.54
2.52
2.21
2.20
2.18
2.17
2.03
2.02
2.02
2.00
1.98
1.89
1.87
1.86
1.85
1.84
1.67
1.64
1.63
1.61
CO2H
O
0.95
1.00
1.92
1.06
1.06
1.11
3.91
2.19
1.00
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

R1379783_C13

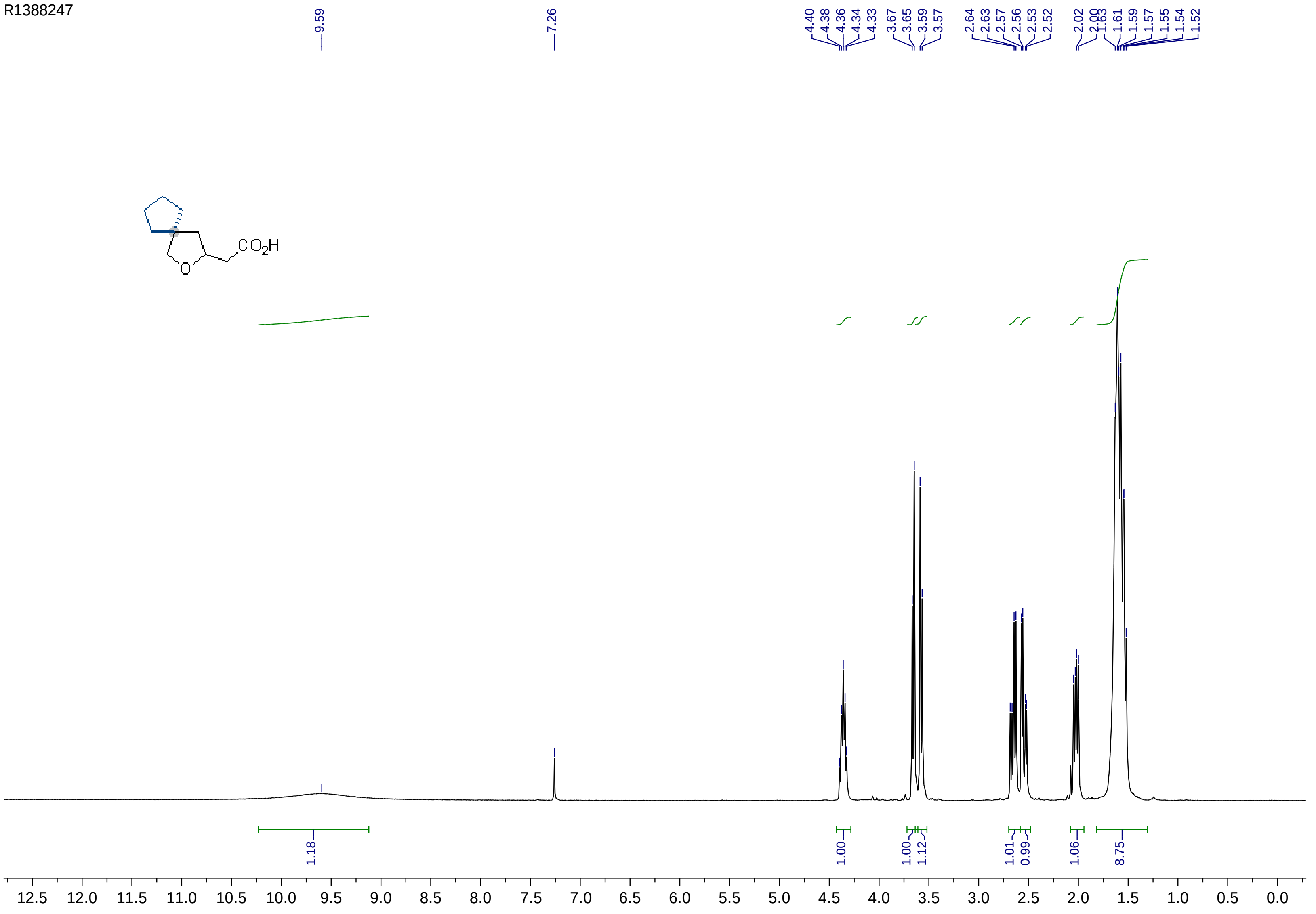


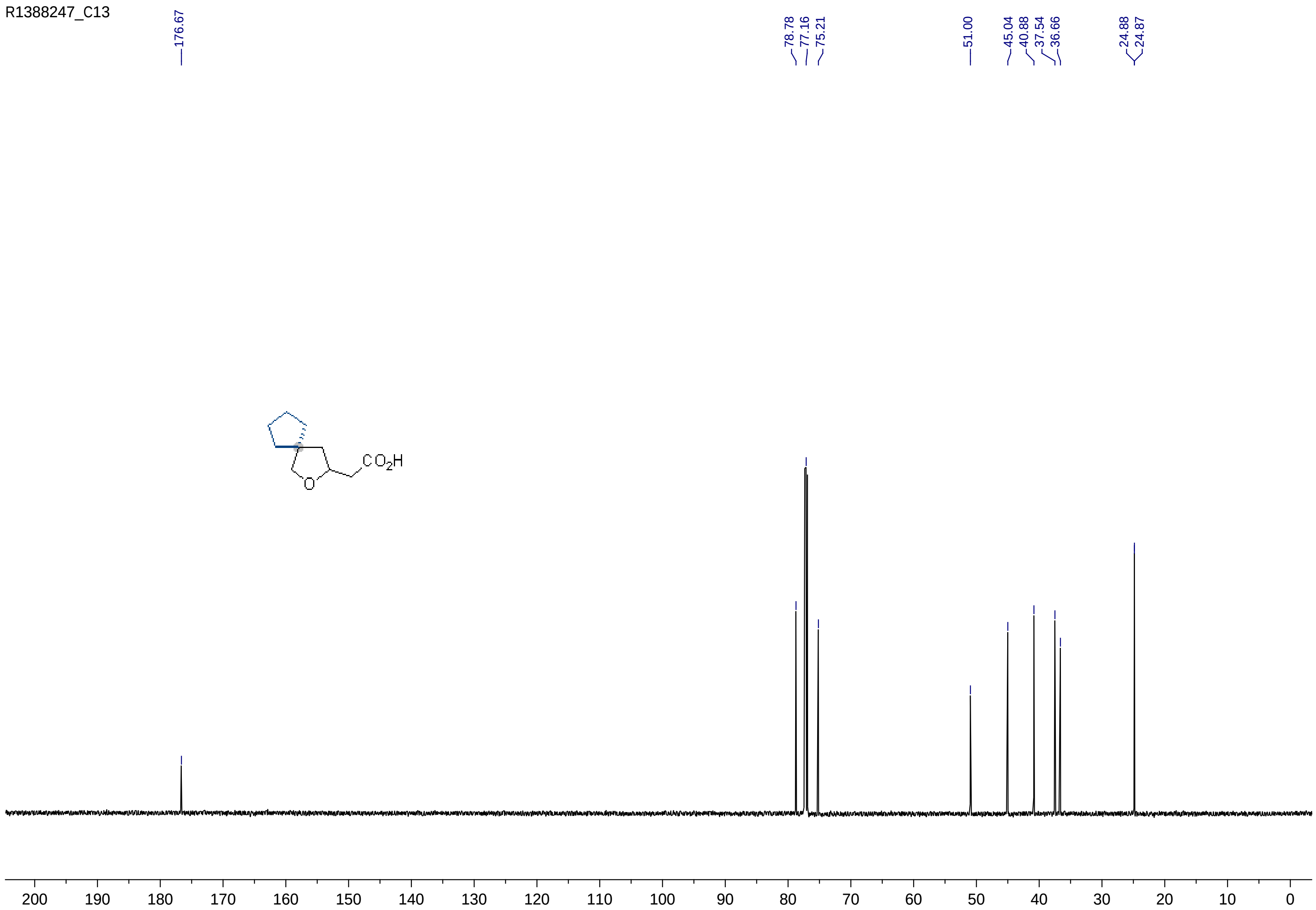
Compound 8f


R1033987
9.22
7.26
4.34
4.32
4.30
4.29
4.27
3.97
3.95
3.92
3.90
3.88
3.85
2.61
2.59
2.55
2.53
2.37
2.35
2.33
1.88
1.86
1.85
1.42
CO2H
O
N
Boc
1.06
1.00
5.99
1.07
1.06
1.09
1.01
9.05
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

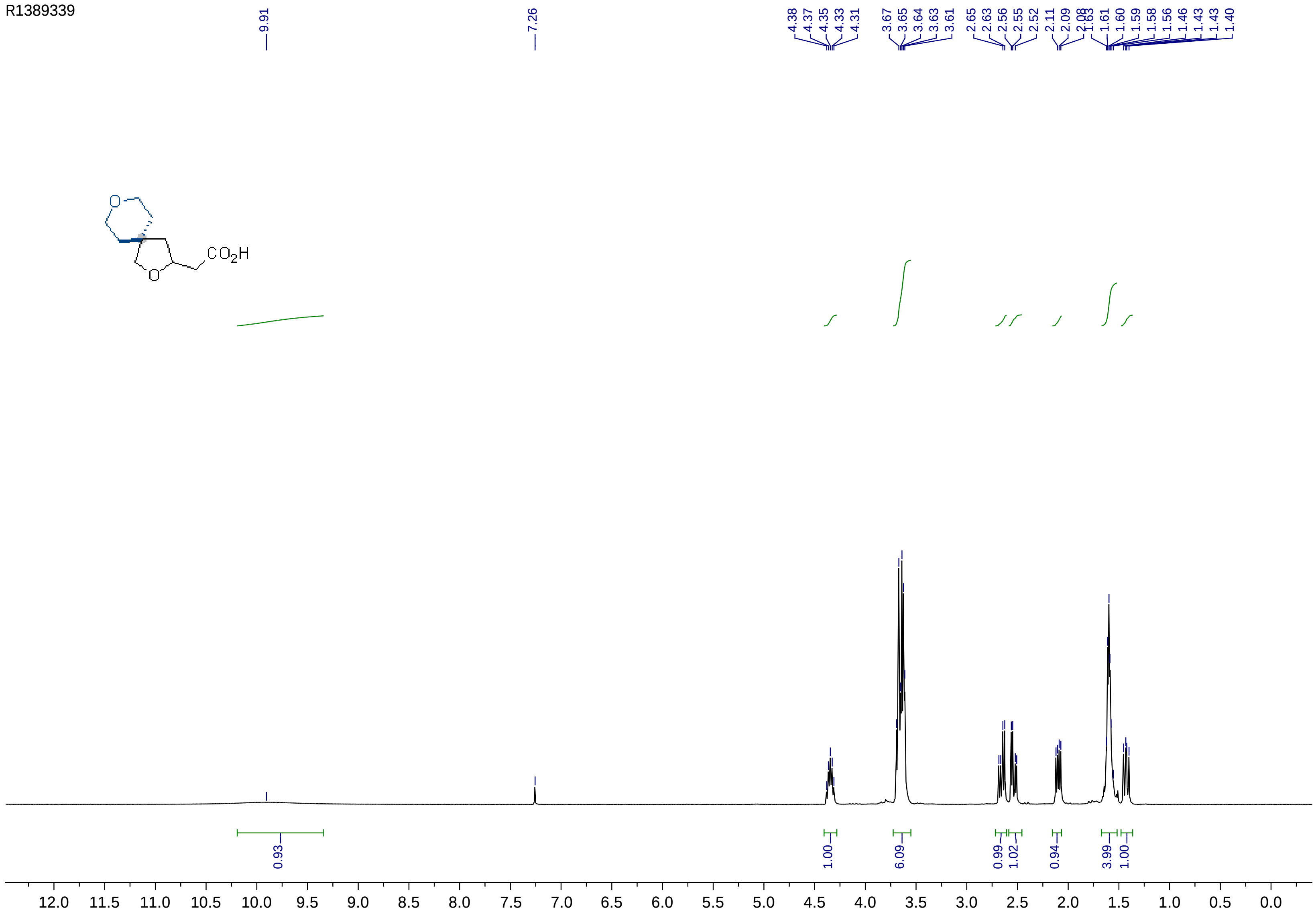

R1033987_C13
175.49
156.42
80.09
77.16
77.14
75.08
59.73
58.51
43.30
40.69
40.29
28.48
CO2H
O
N
Boc
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 9f

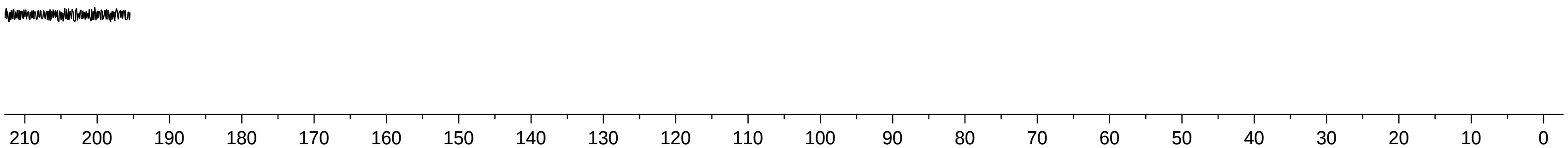



R1388247_C13
176.67
78.78
77.16
75.21
51.00
45.04
40.88
37.54
36.66
24.88
24.87
CO2H
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

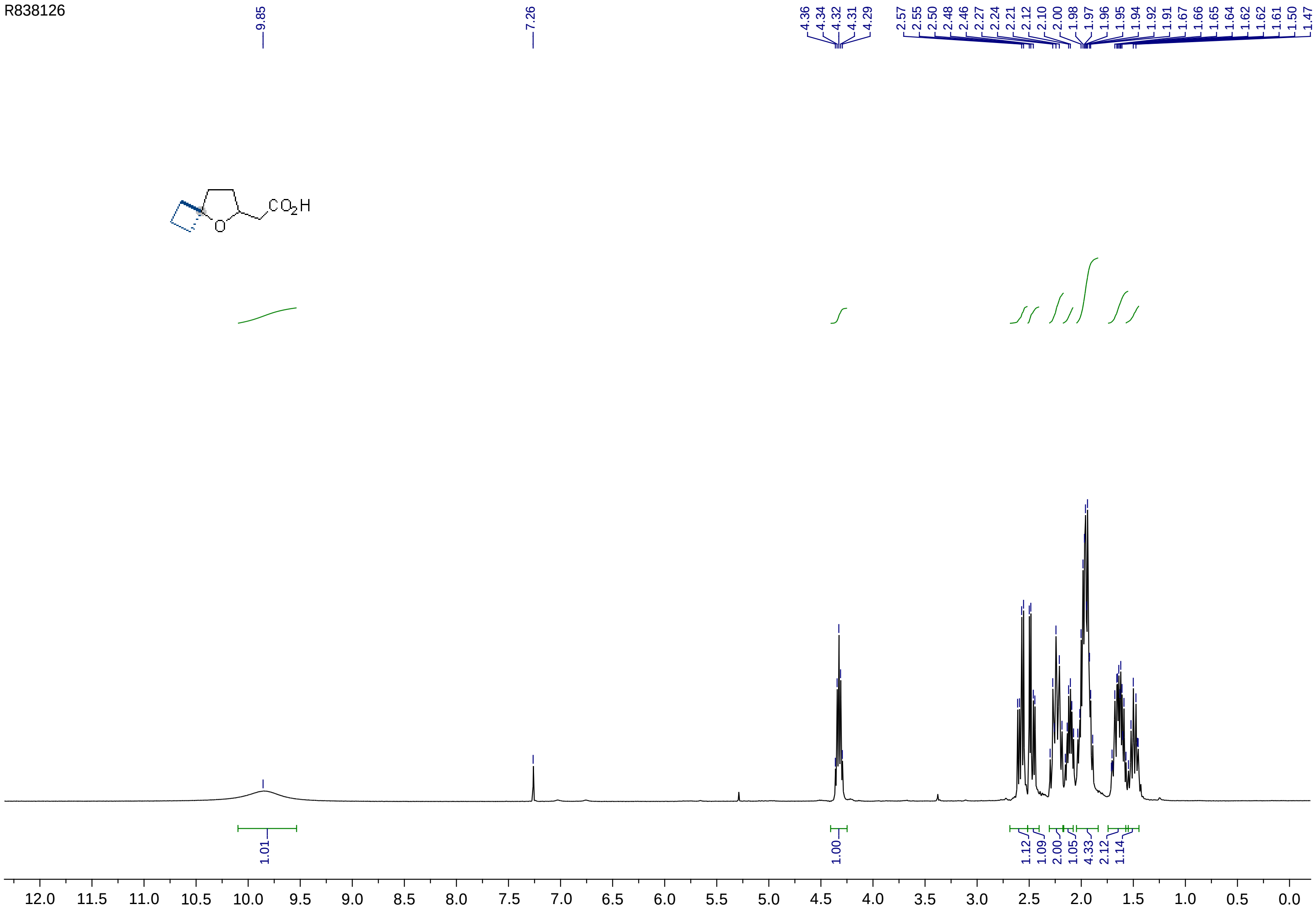
Compound 13f



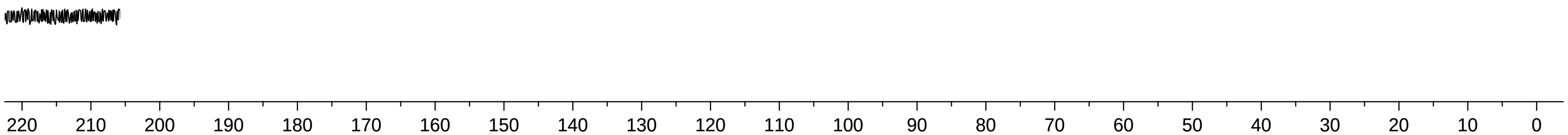
R1389339_C13



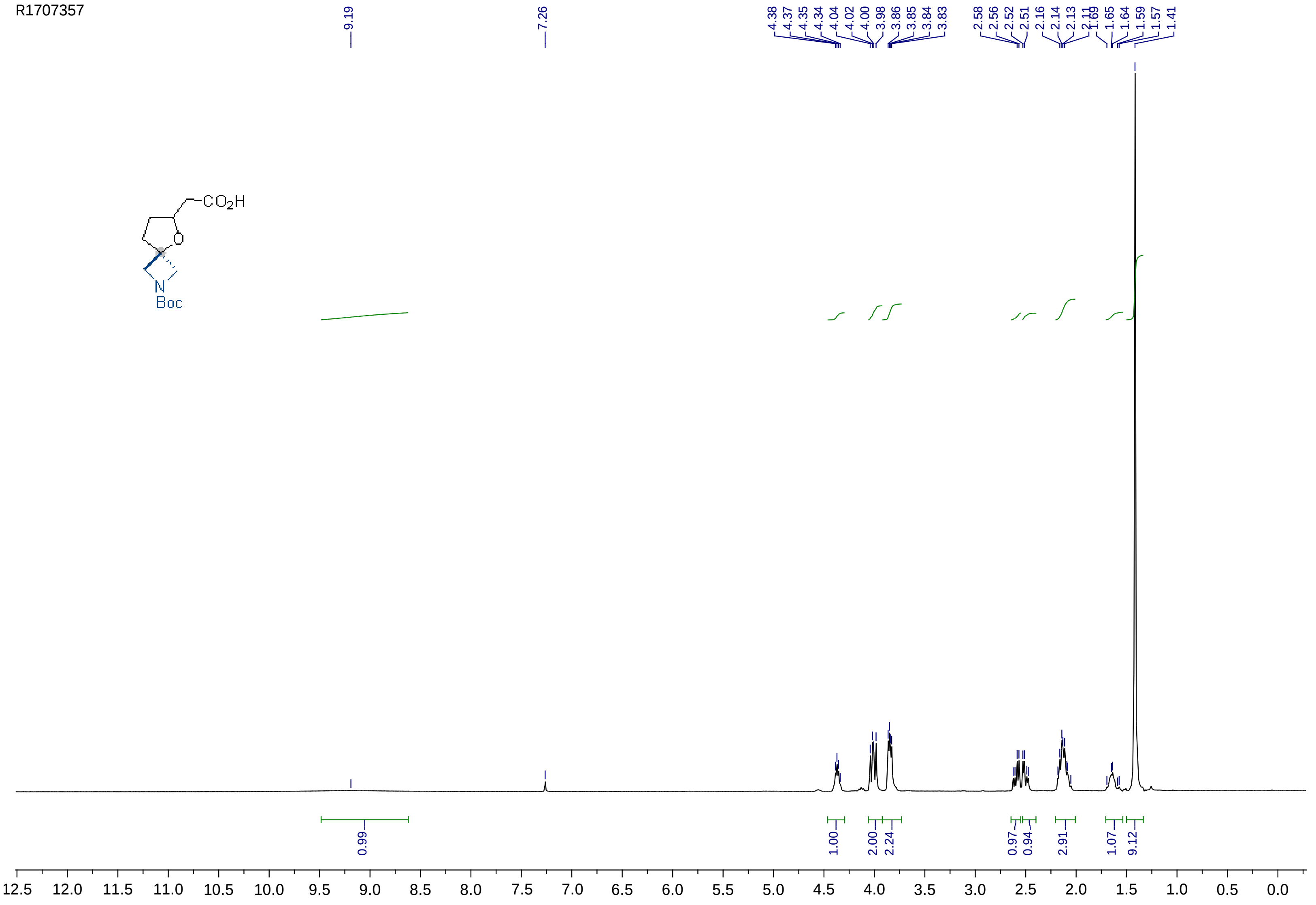
Compound 18f



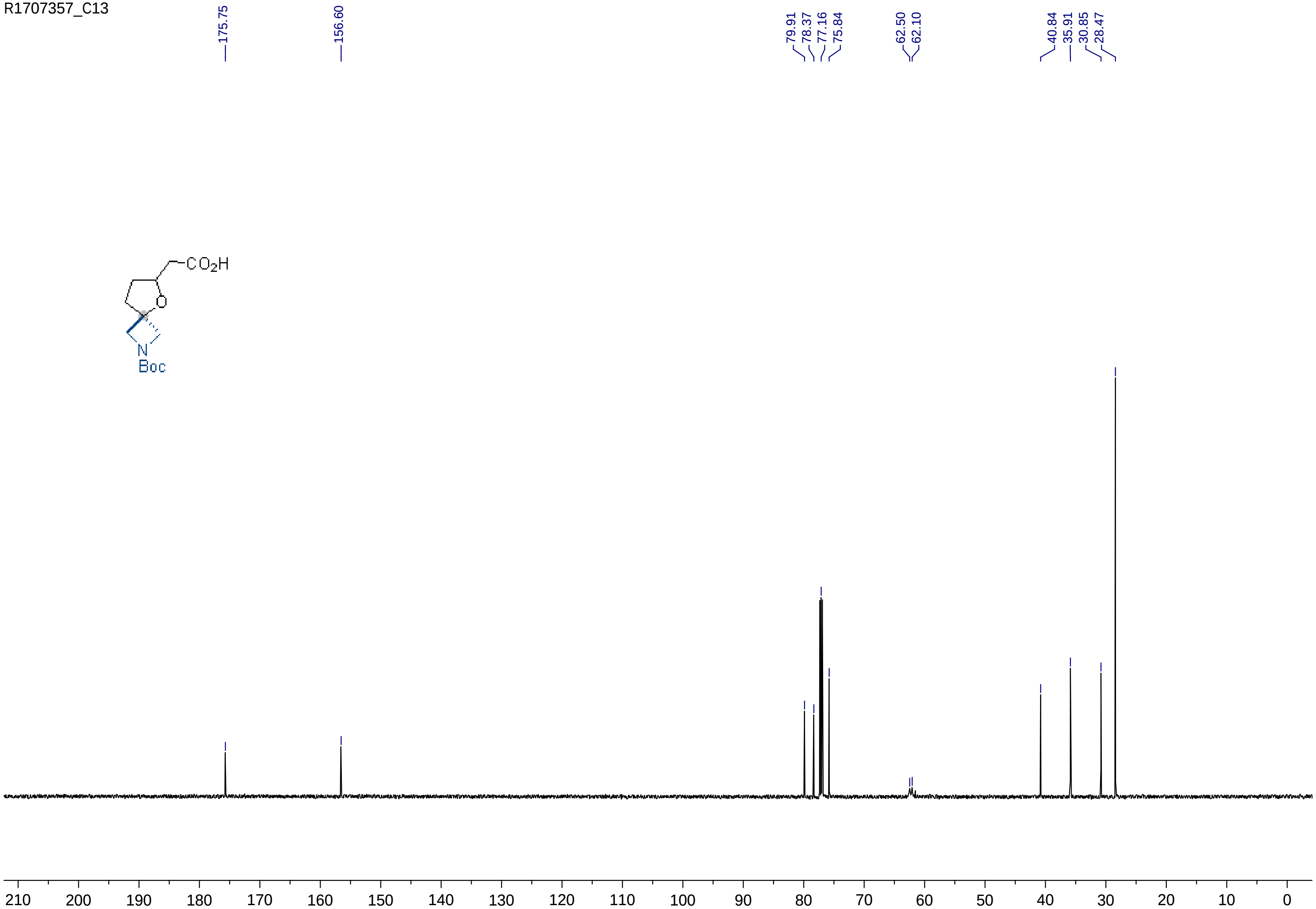
R838126_C13


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

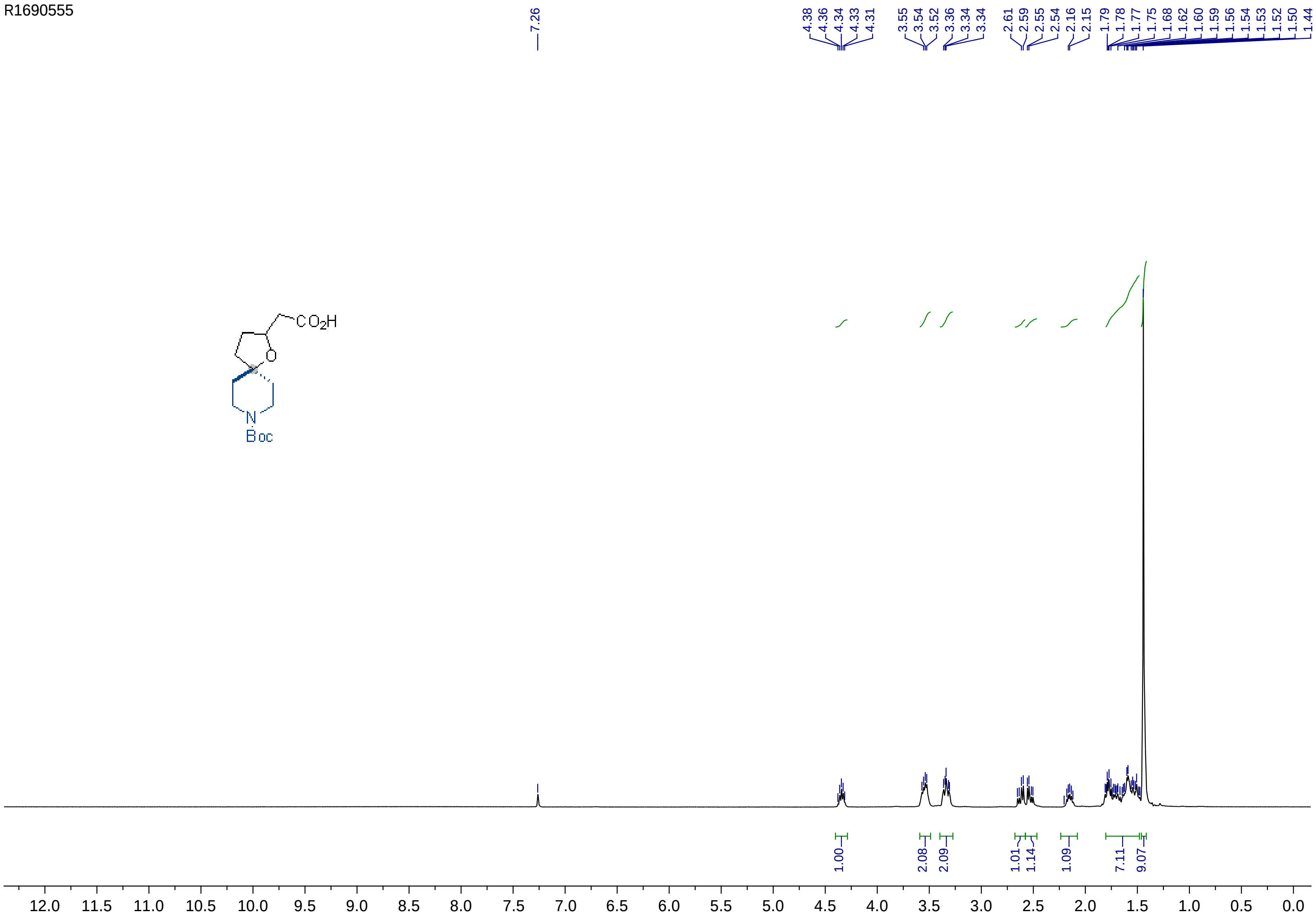
Compound 21f

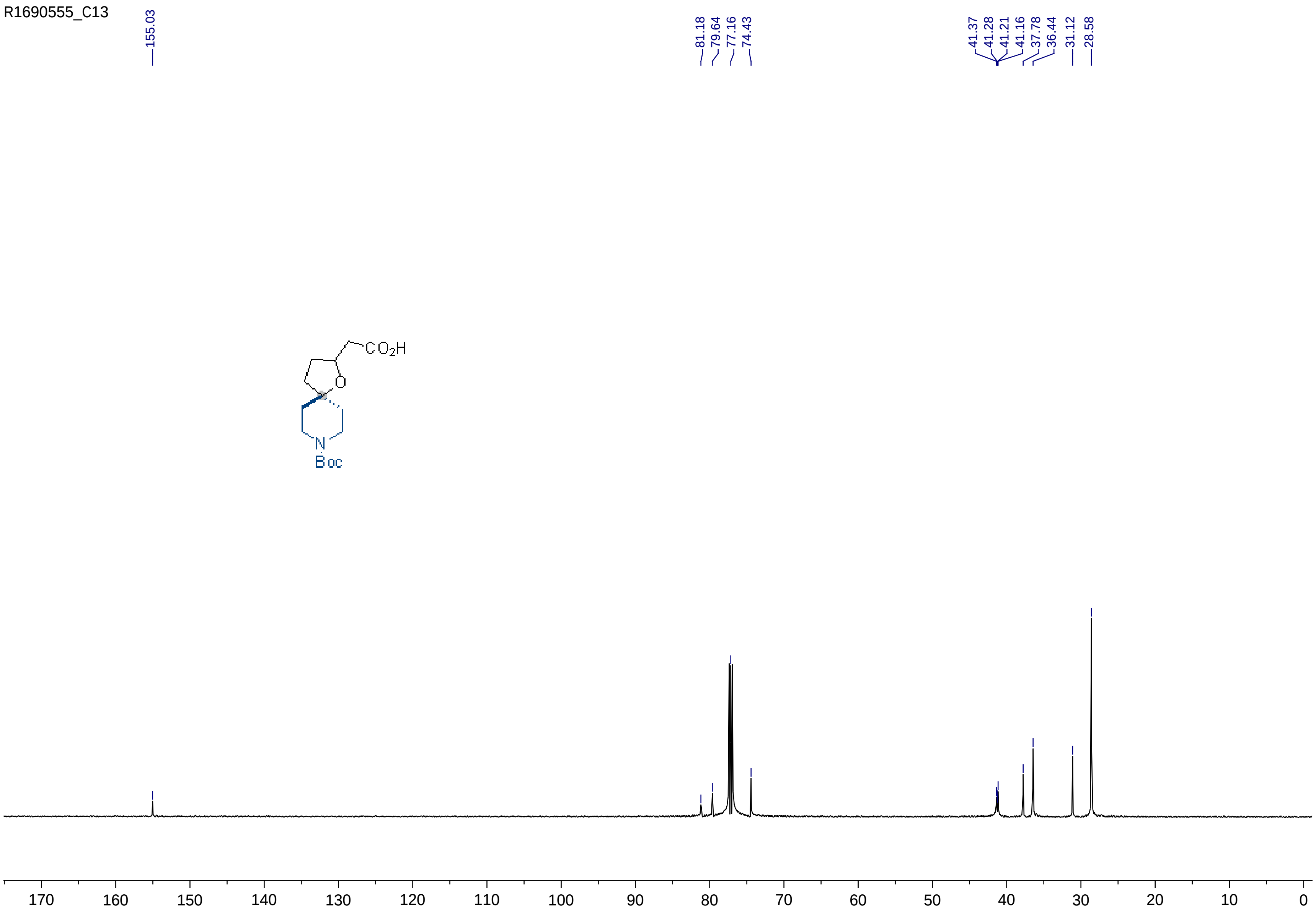


R1707357_C13

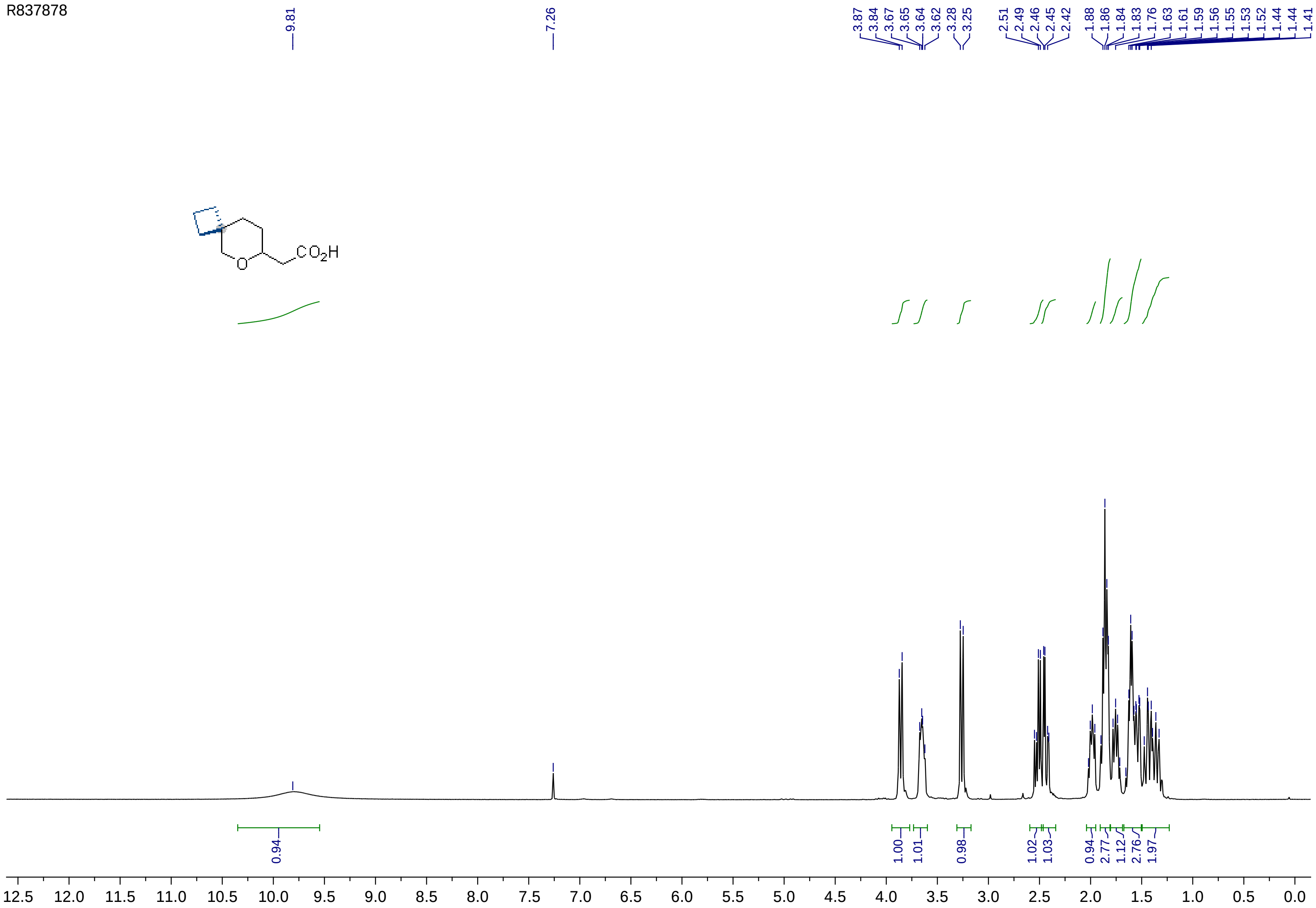


Compound 29f



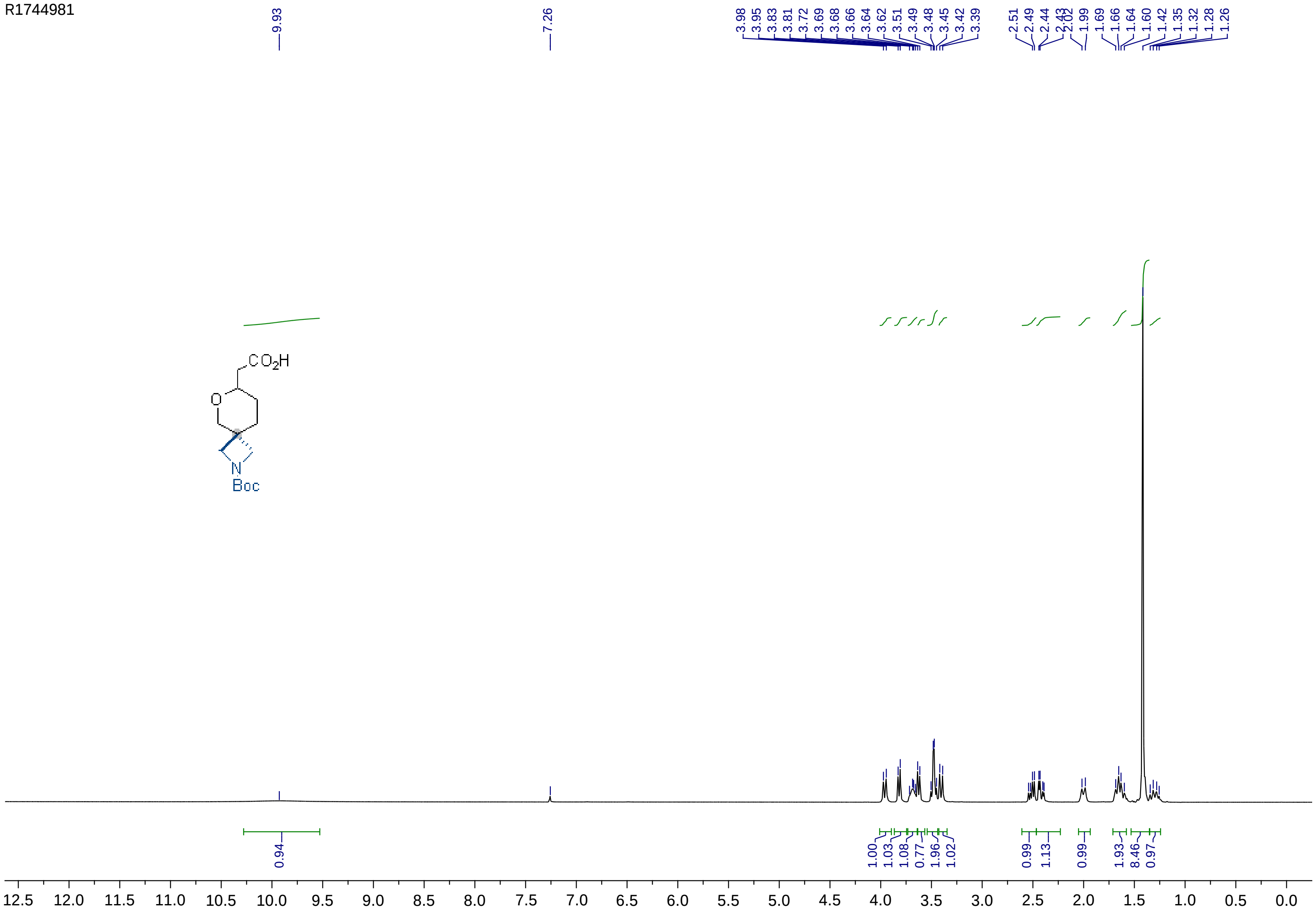

R1690555_C13
155.03
81.18
79.64
77.16
74.43
41.37
41.28
41.21
41.16
37.78
36.44
31.12
28.58
CO2H
O
N
Boc
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

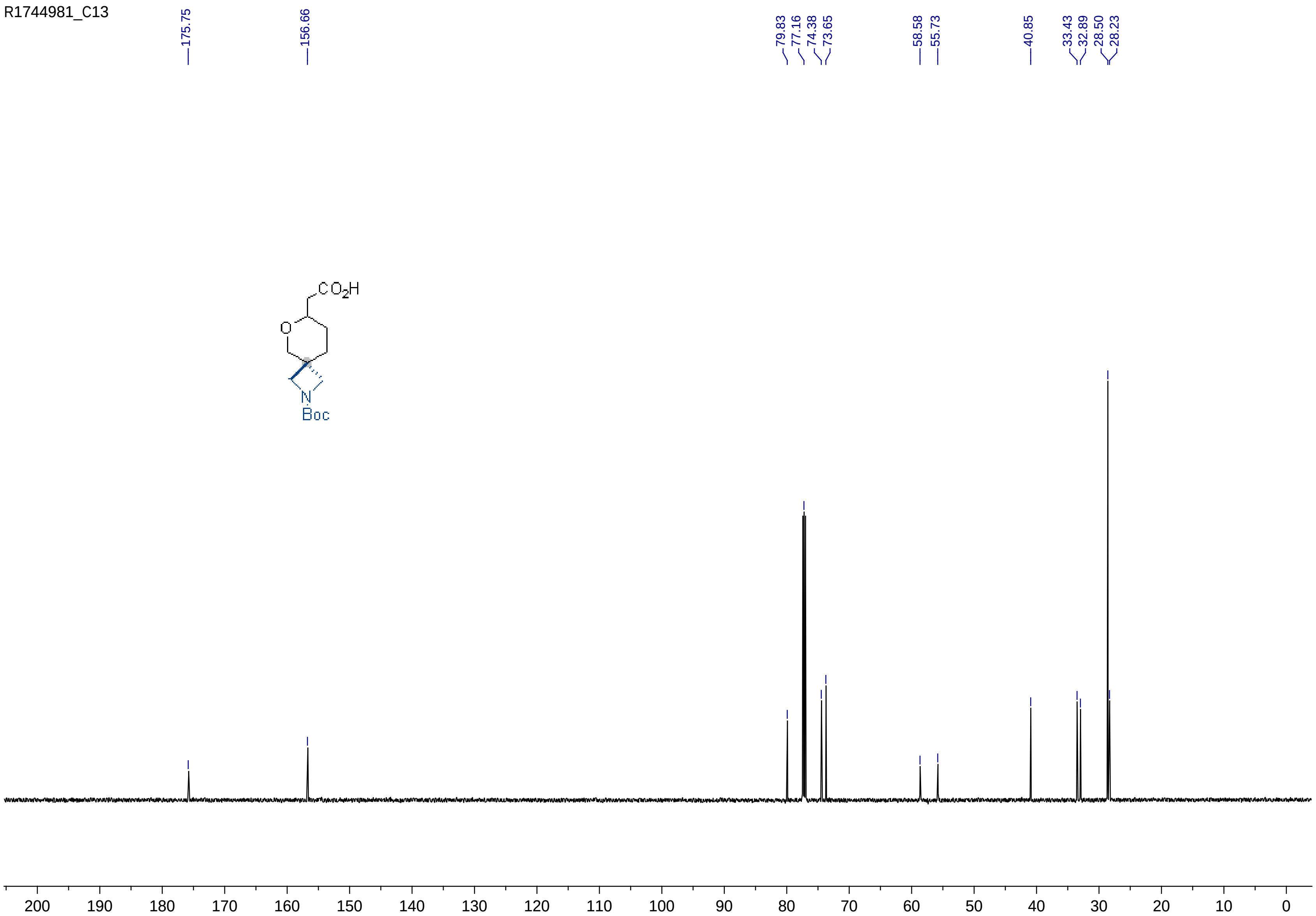
Compound 34f



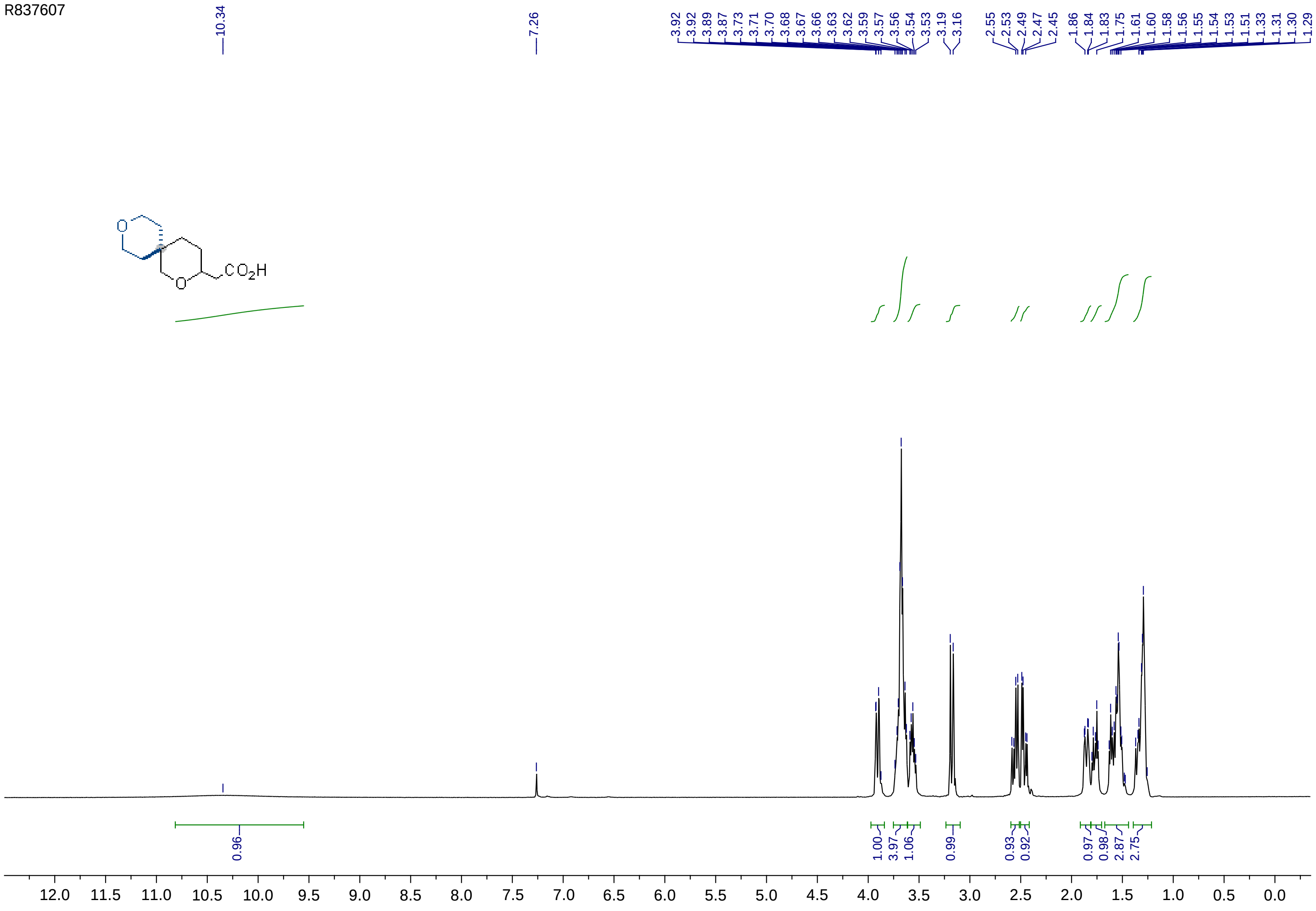

R837878_C13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 35f

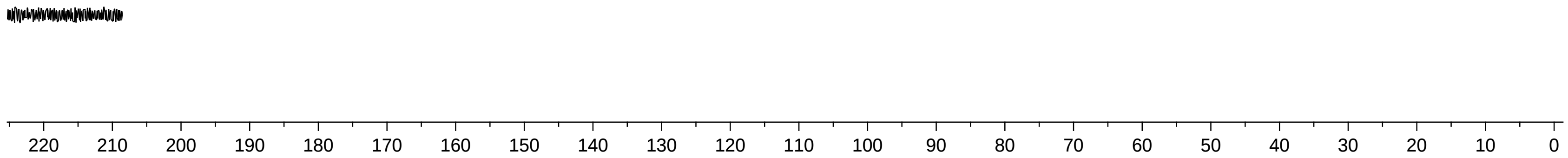



R1744981_C13
175.75
156.66
79.83
77.16
74.38
73.65
58.58
55.73
40.85
33.43
32.89
28.50
28.23
CO2H
O
N
Boc
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

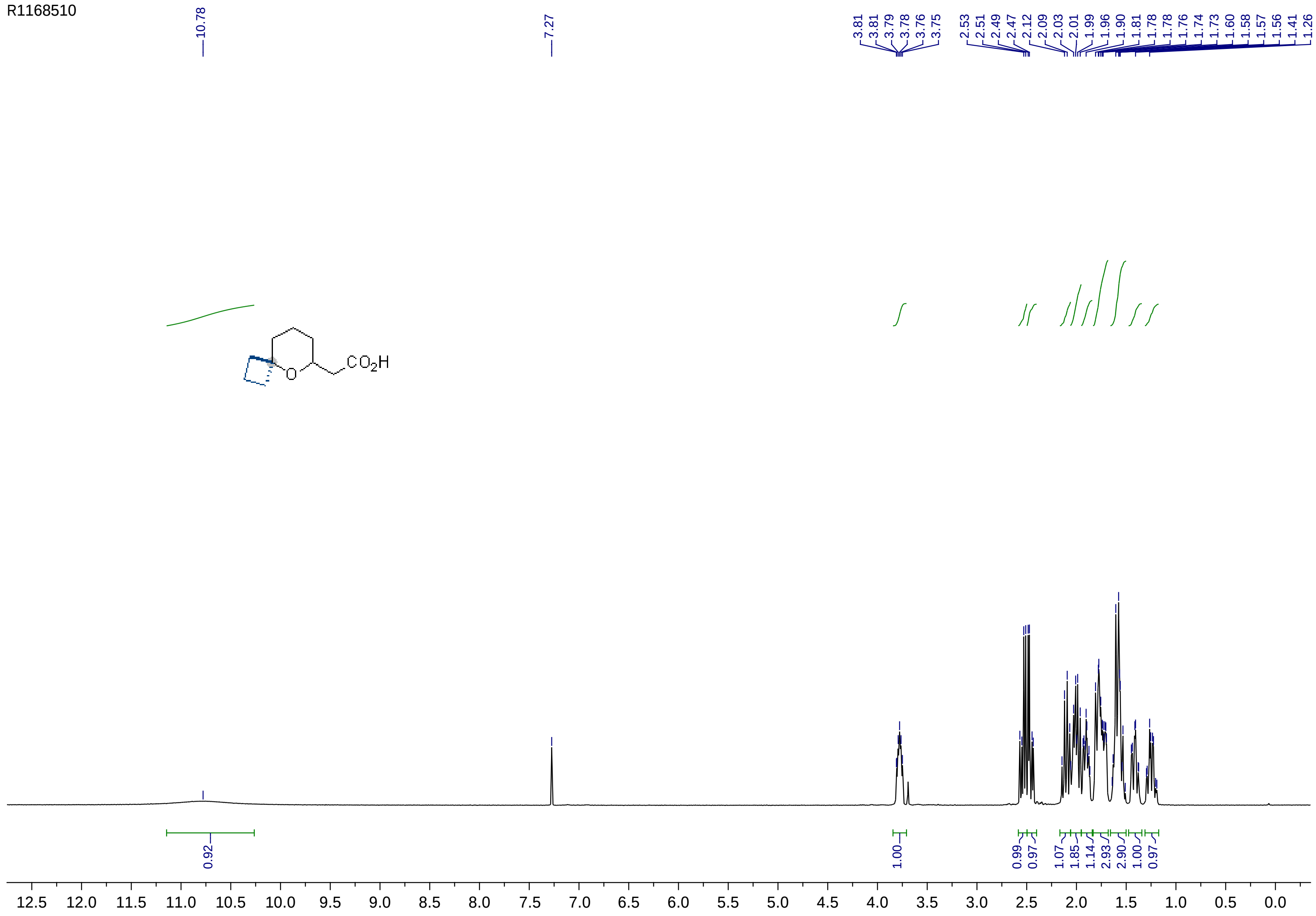
Compound 36f



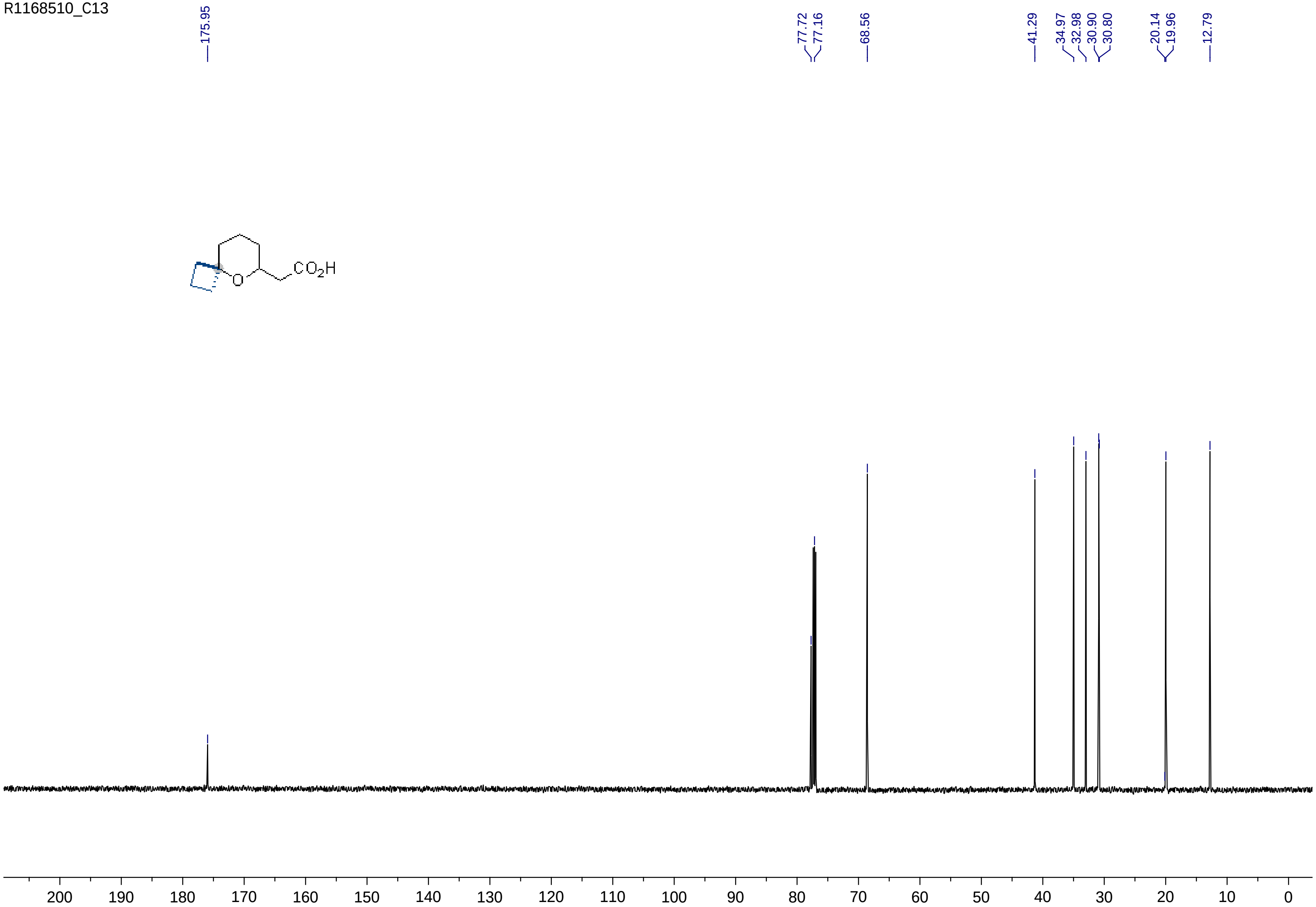
R837607_C13


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

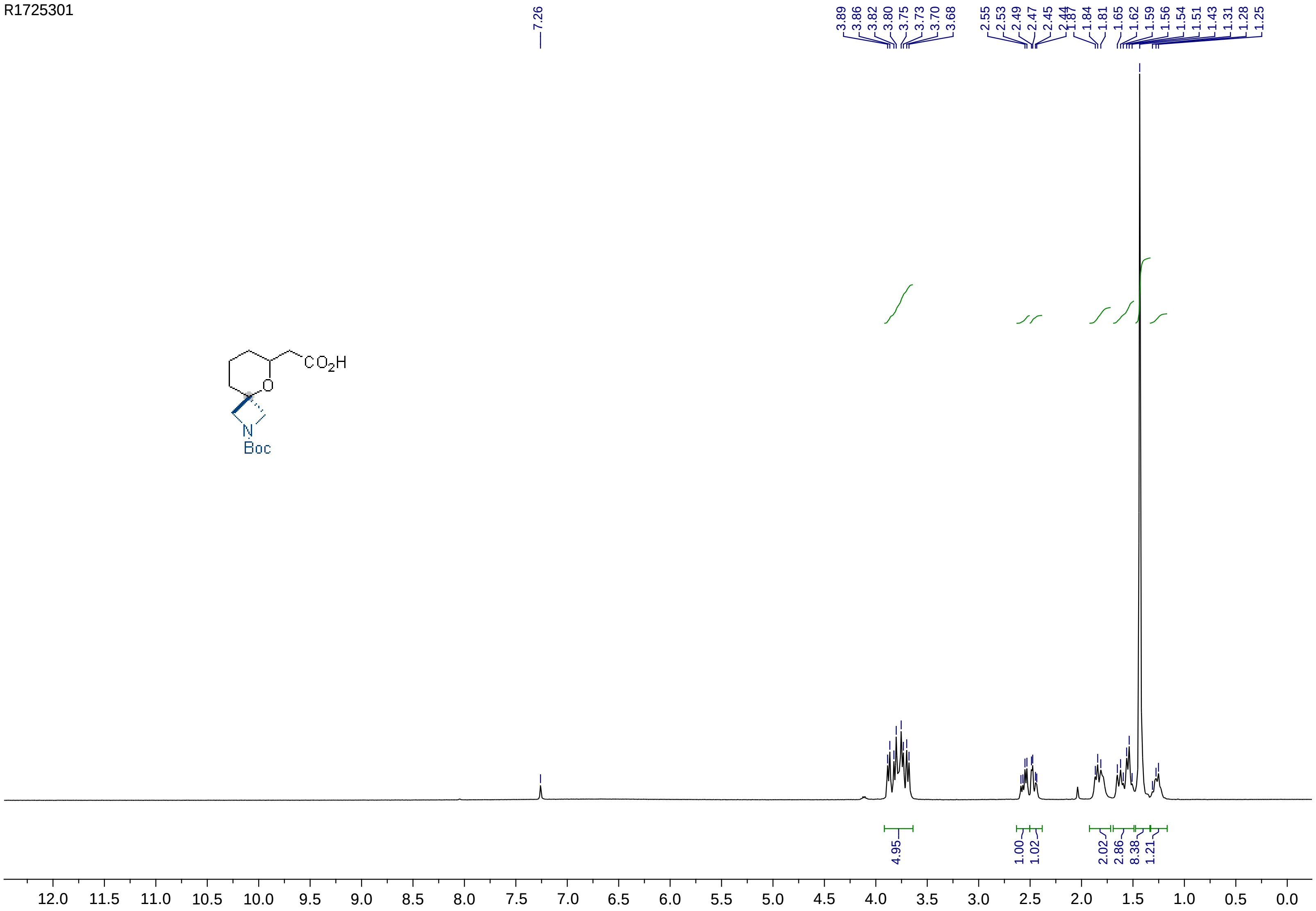
Compound 38f

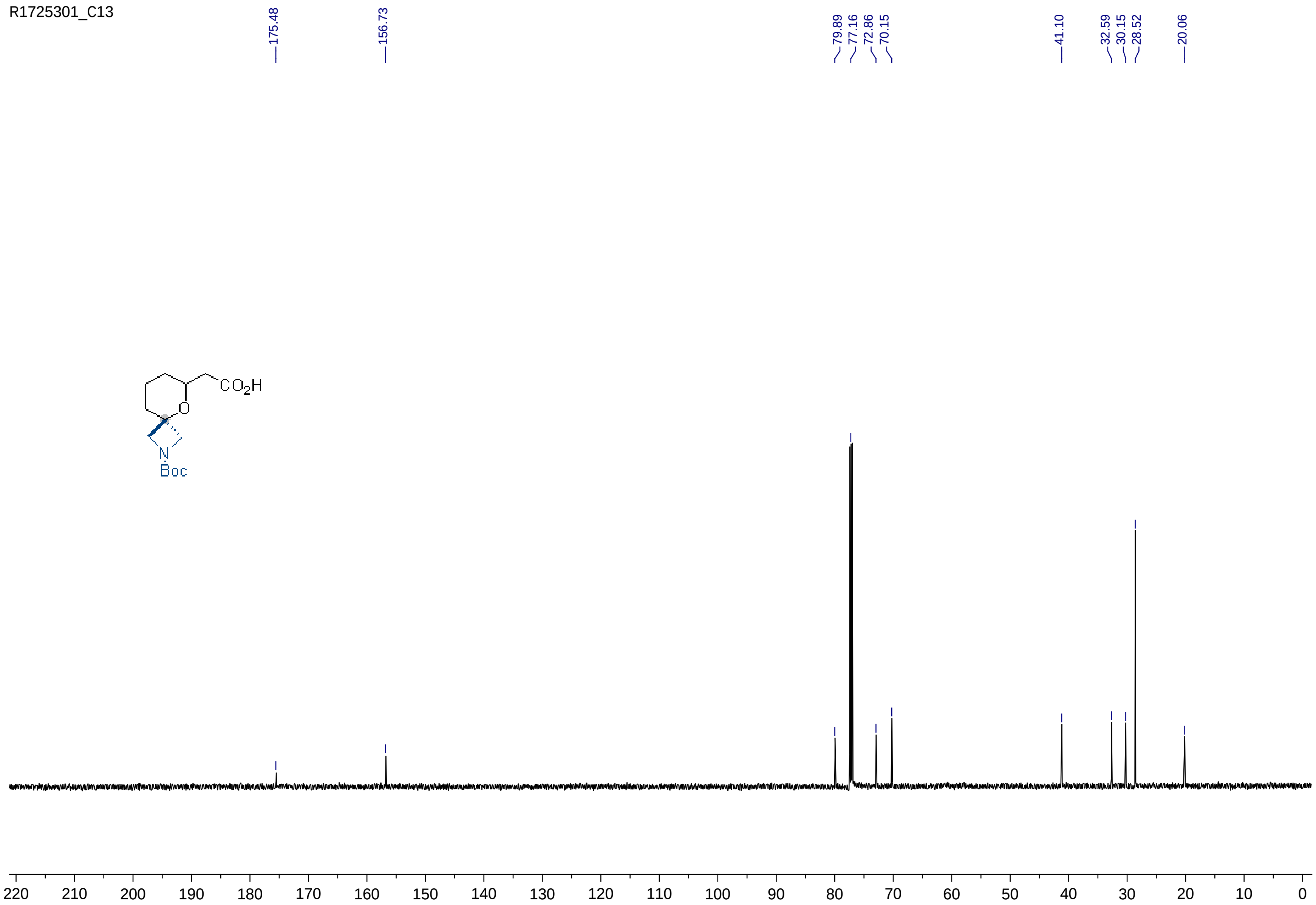


R1168510_C13

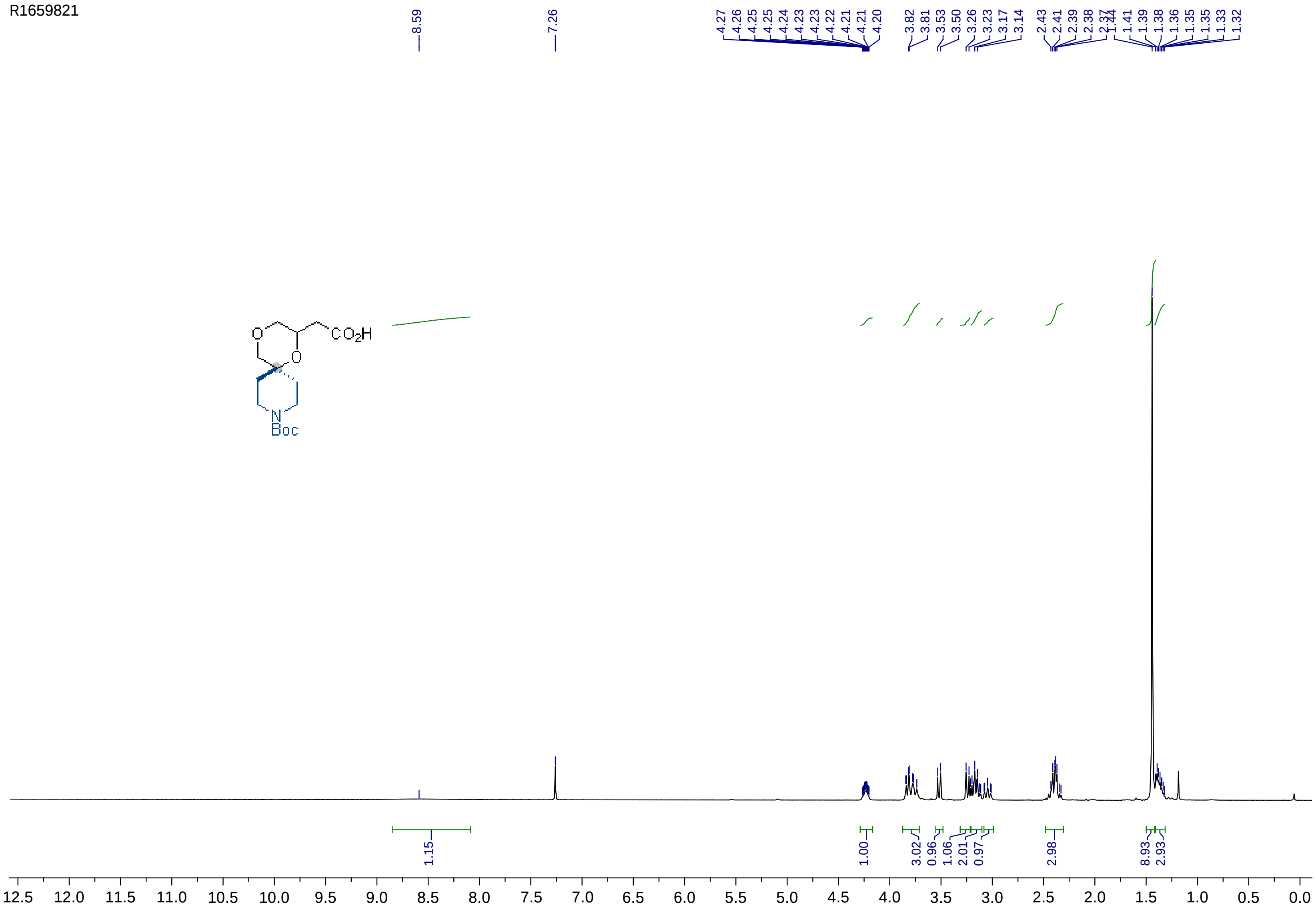


Compound 40f



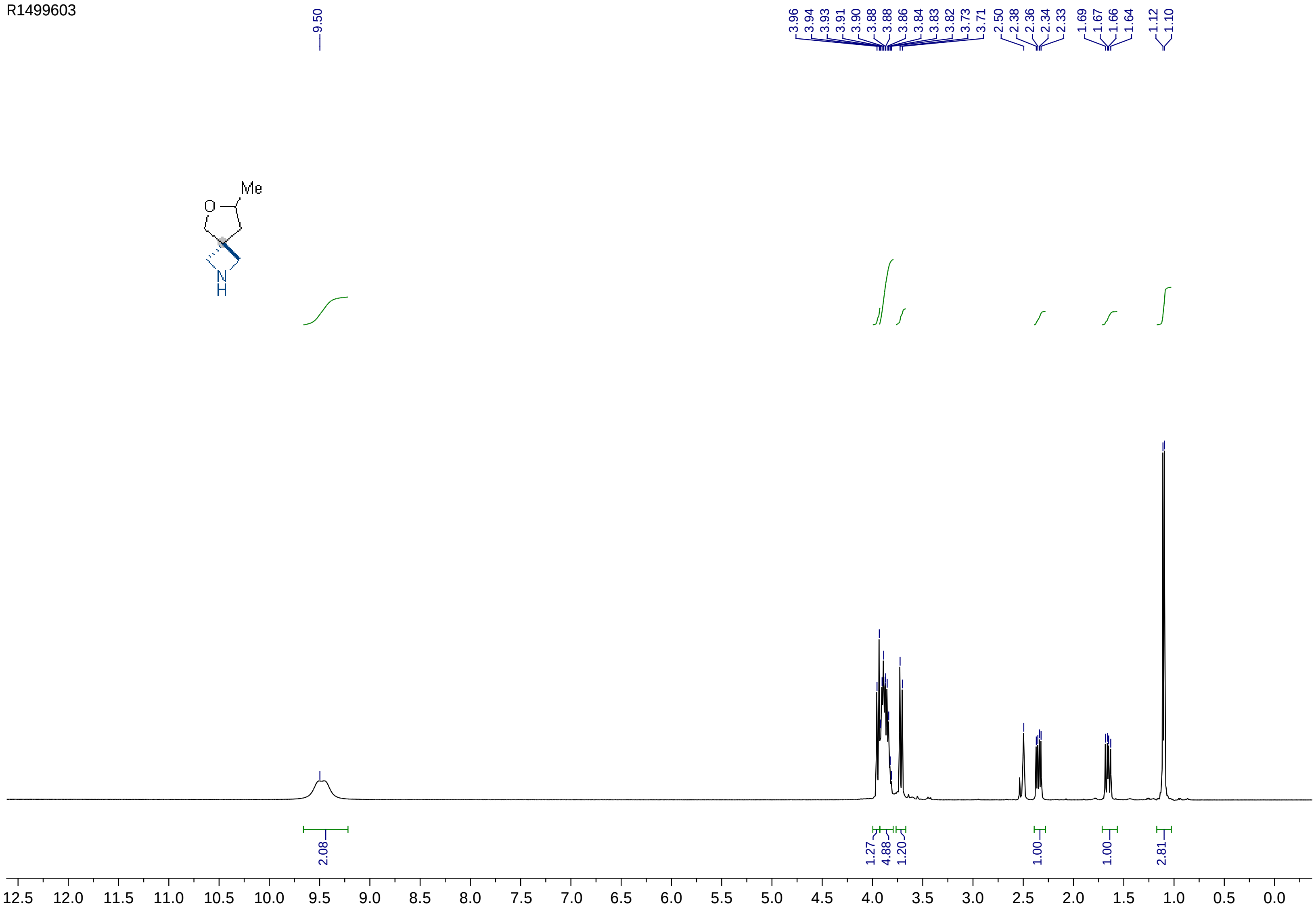

R1725301_C13
175.48
156.73
79.89
77.16
72.86
70.15
41.10
32.59
30.15
28.52
20.06
CO2H
O
N
Boc
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

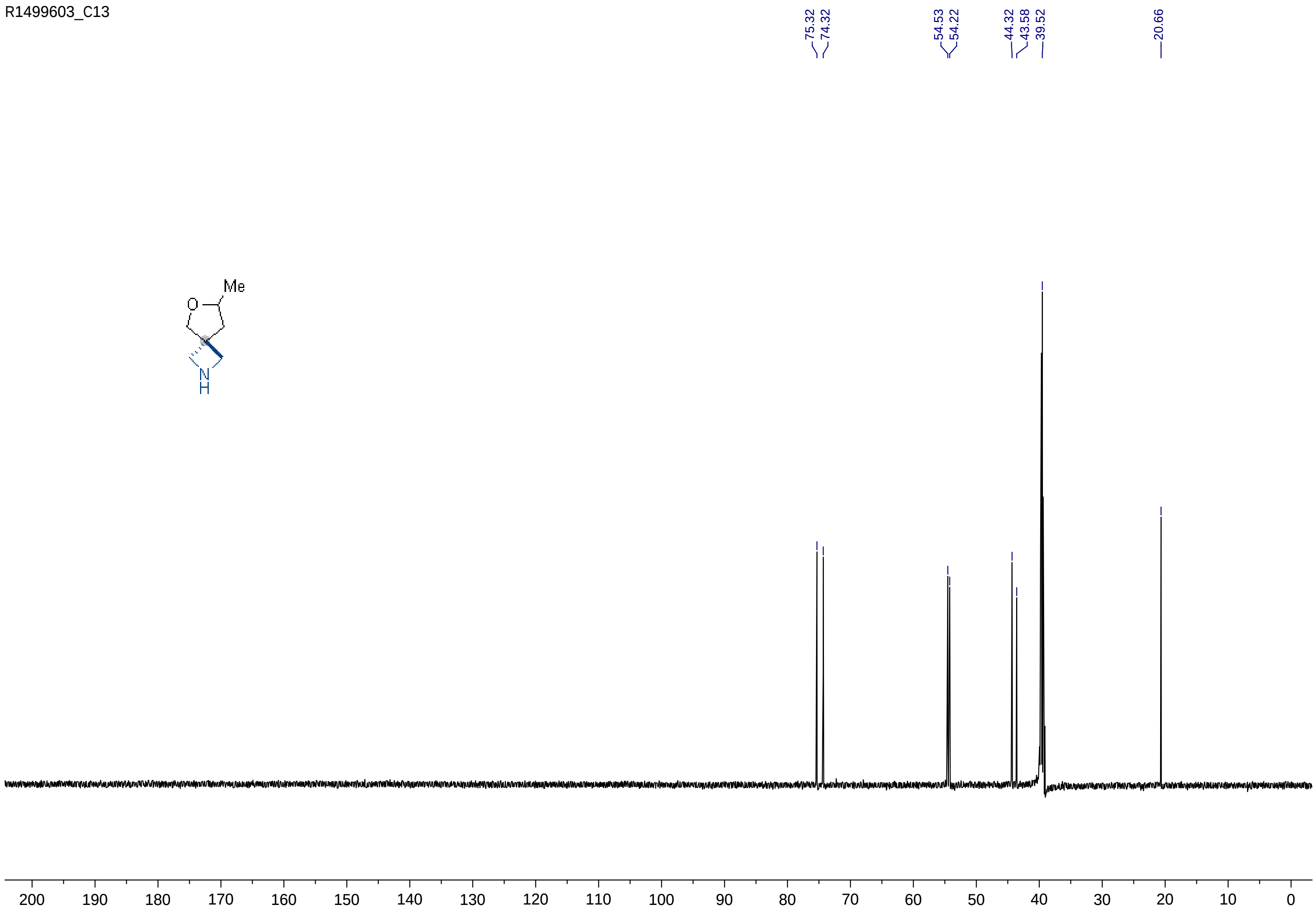
Compound 44f



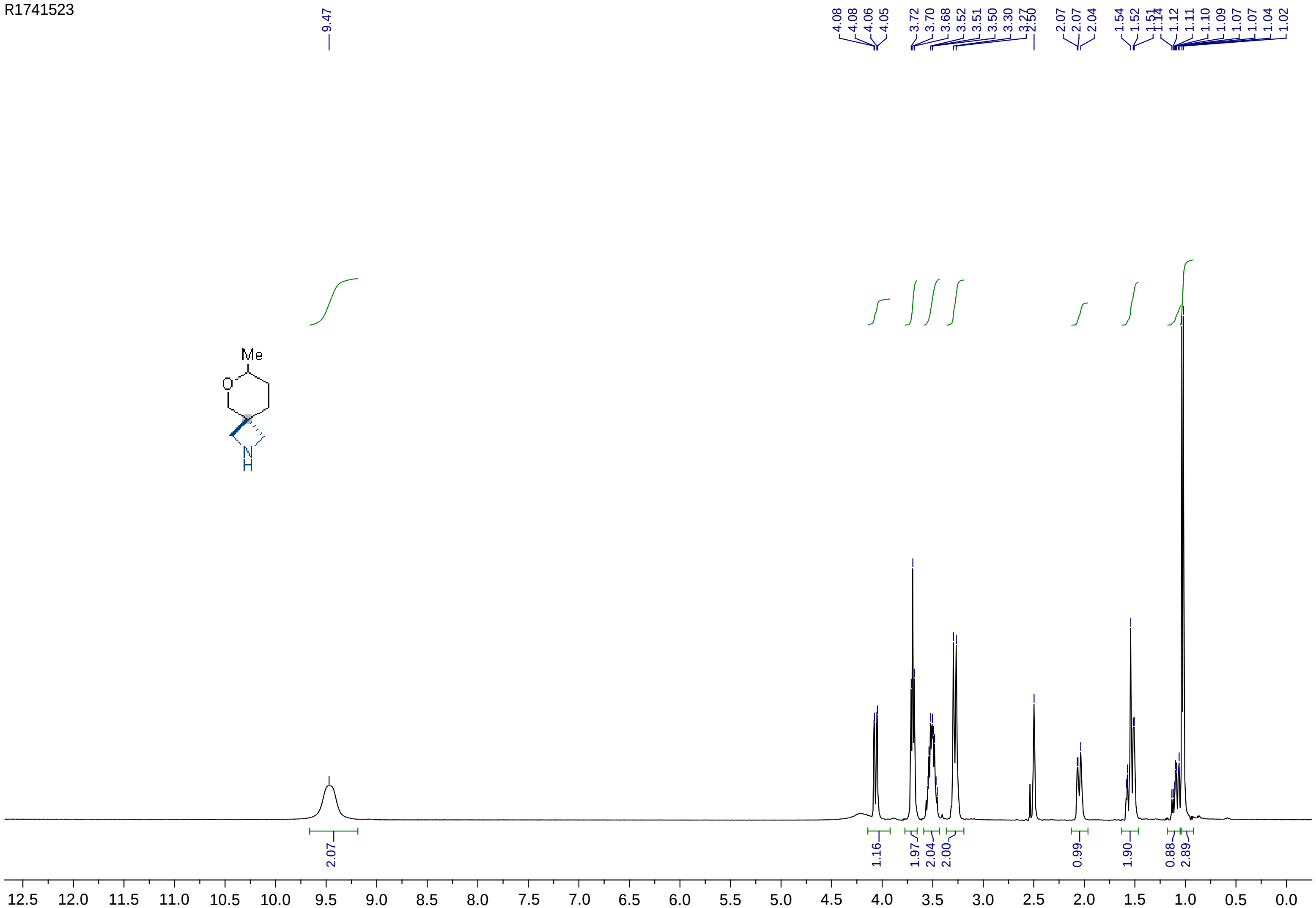

R1659821_C13
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

Compound 8g

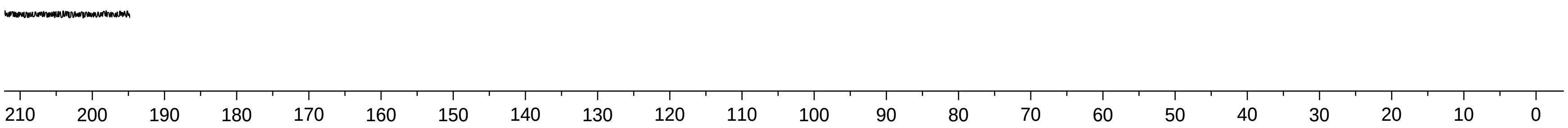

R1499603
Me
O
N
H
9.50
3.96
3.94
3.93
3.91
3.90
3.88
3.88
3.86
3.84
3.83
3.82
3.73
3.71
2.50
2.38
2.36
2.34
2.33
1.69
1.67
1.66
1.64
1.12
1.10
2.08
1.27
4.88
1.20
1.00
1.00
2.81
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


R1499603_C13
75.32
74.32
54.53
54.22
44.32
43.58
39.52
20.66
Me
O
N
H
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

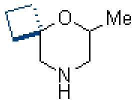
Compound 35g

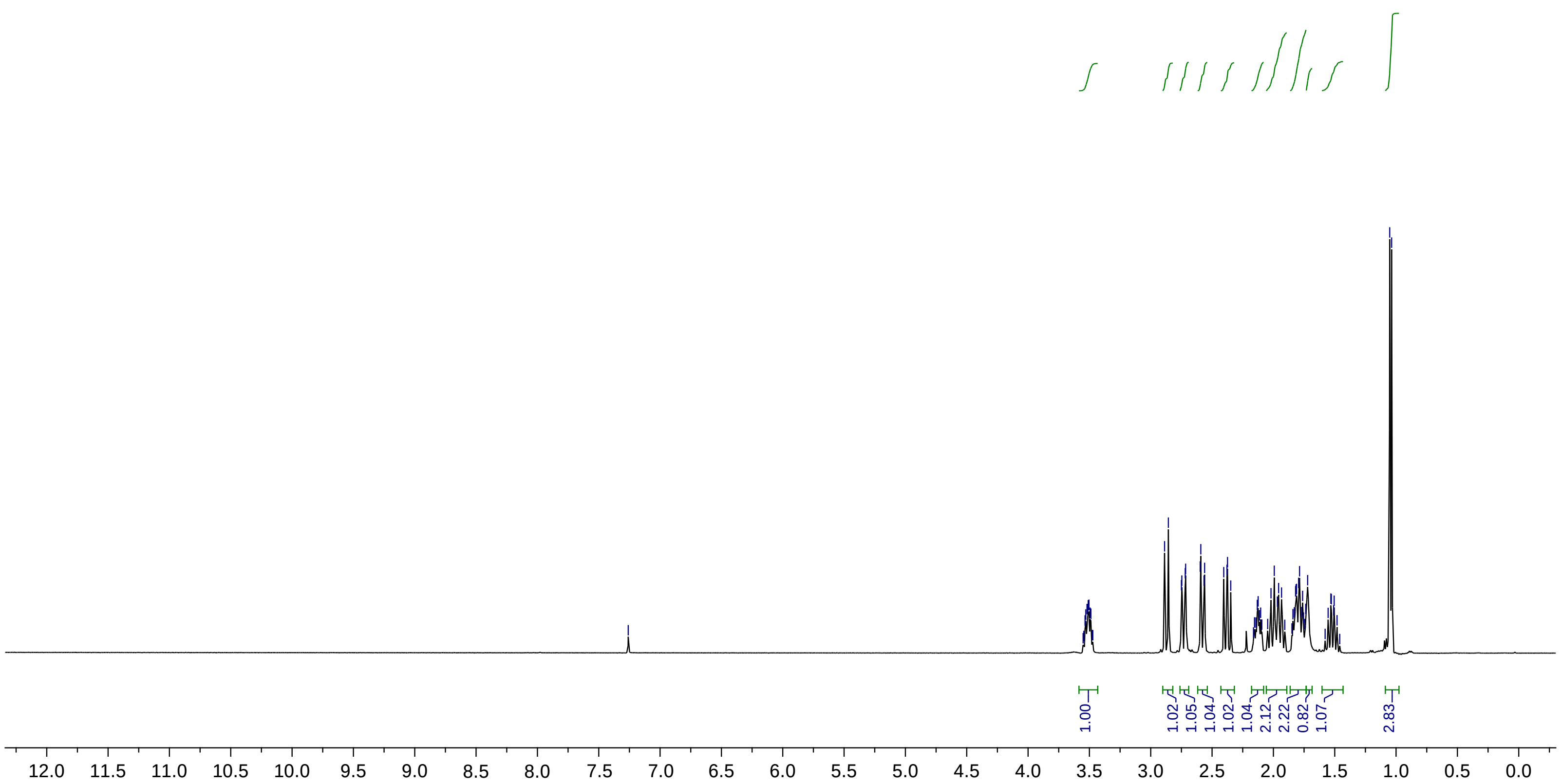


R1741523_C13

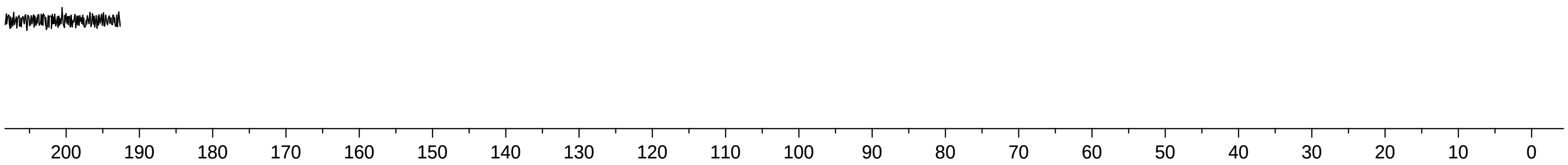


Compound 45g

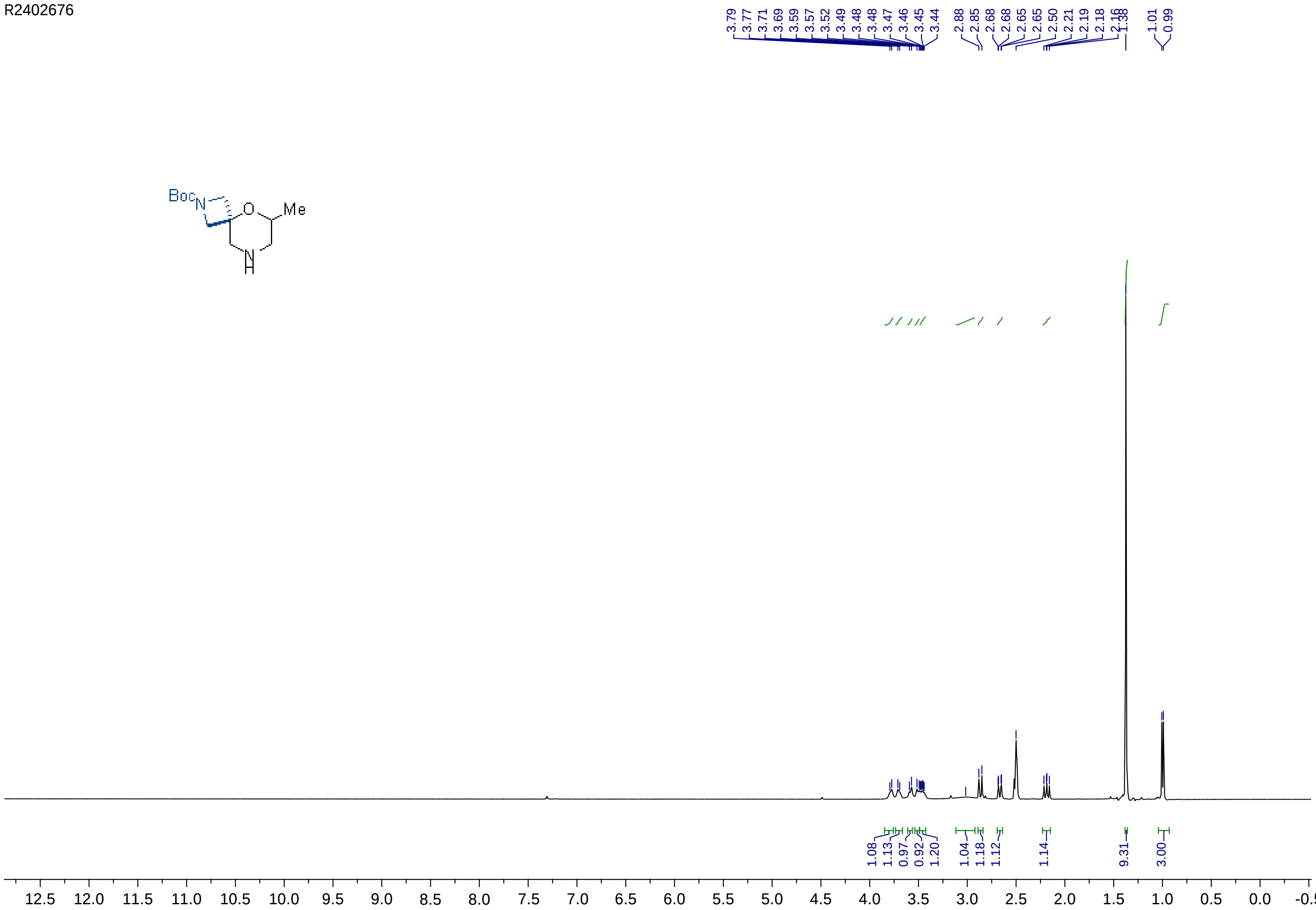


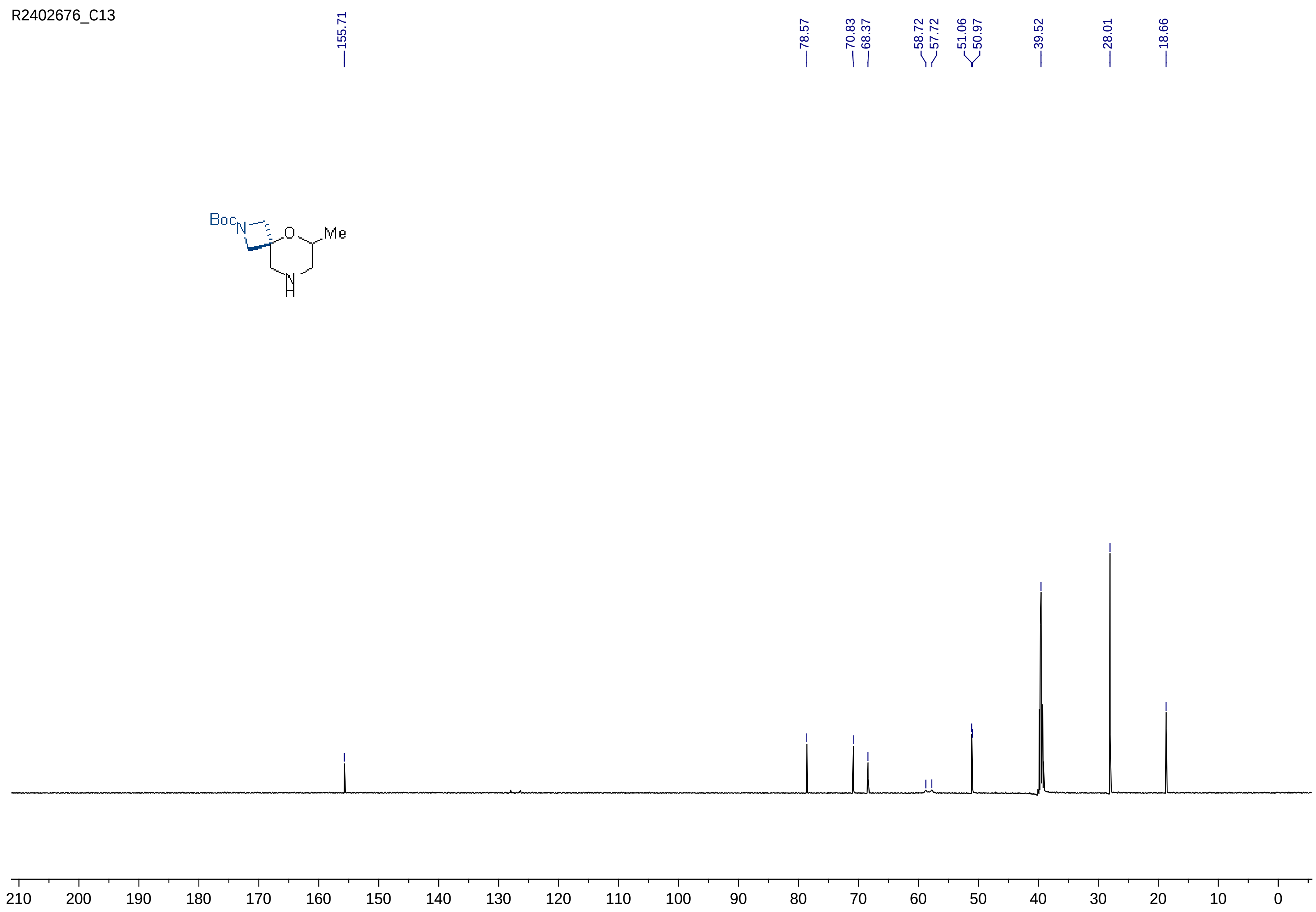


R617136_13C

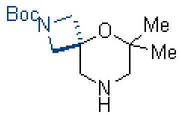

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

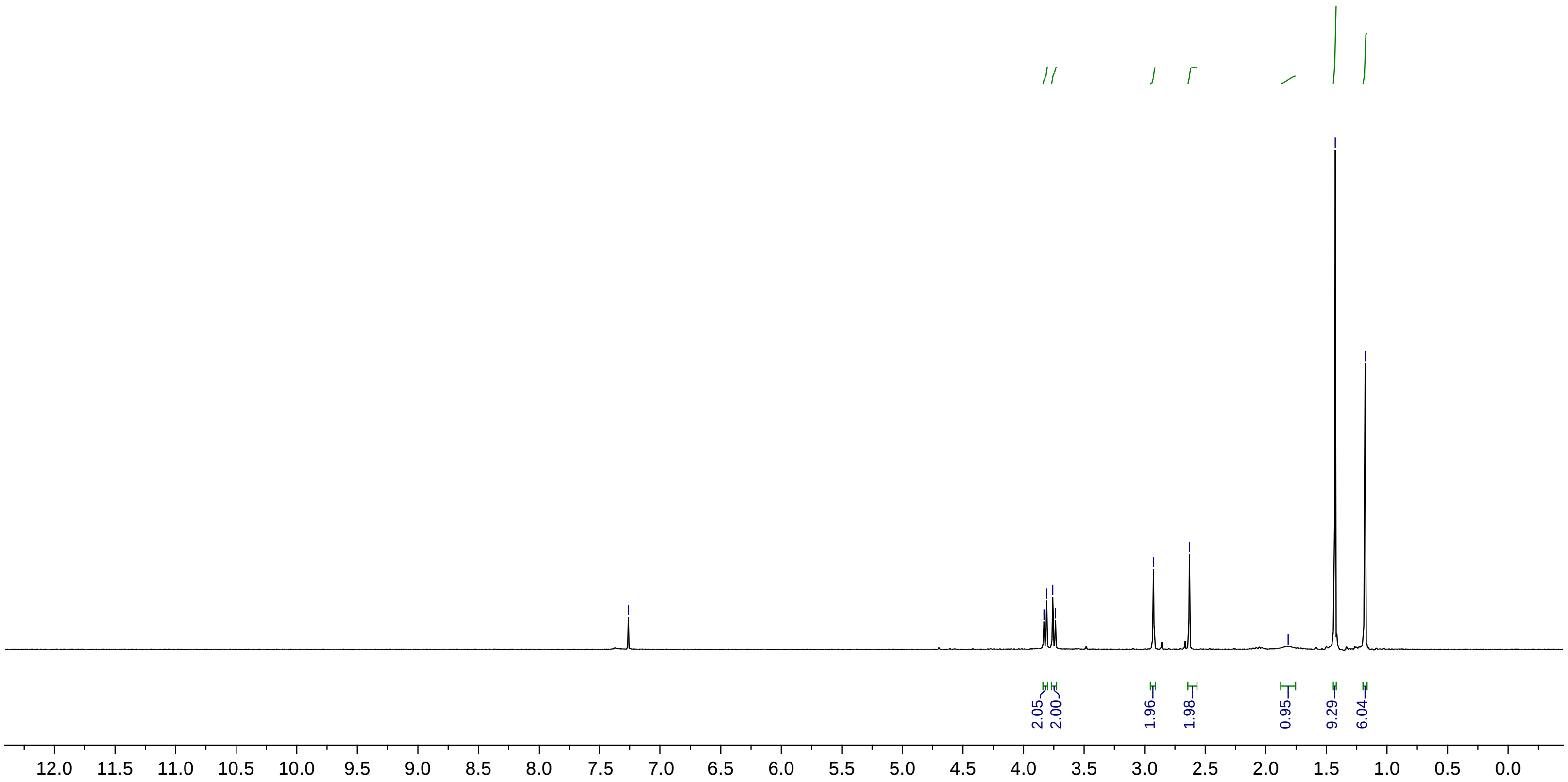
Compound 46g




R2402676_C13
155.71
78.57
70.83
68.37
58.72
57.72
51.06
50.97
39.52
28.01
18.66
Boc
N
O
Me
N
H
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

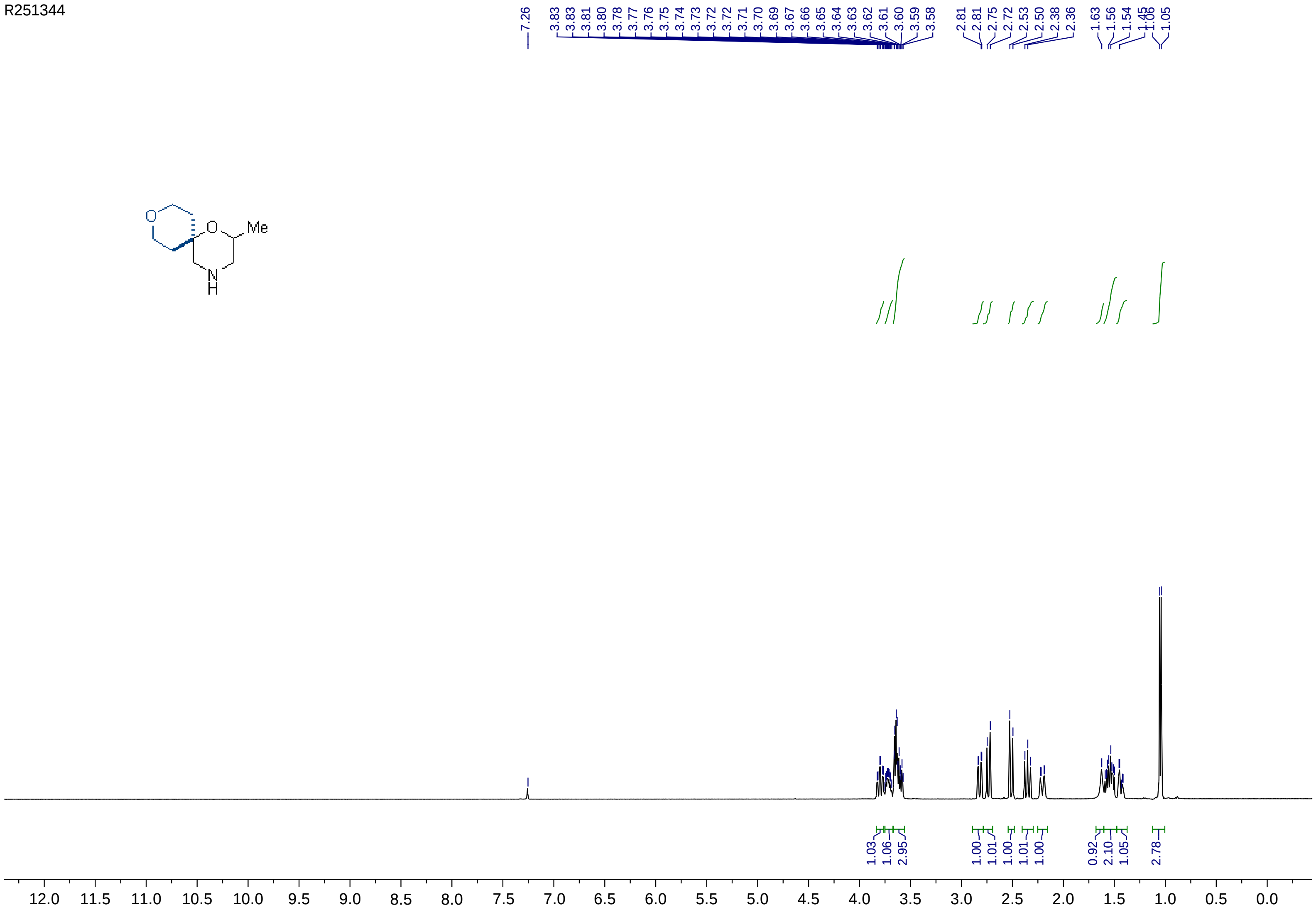
Compound 47g





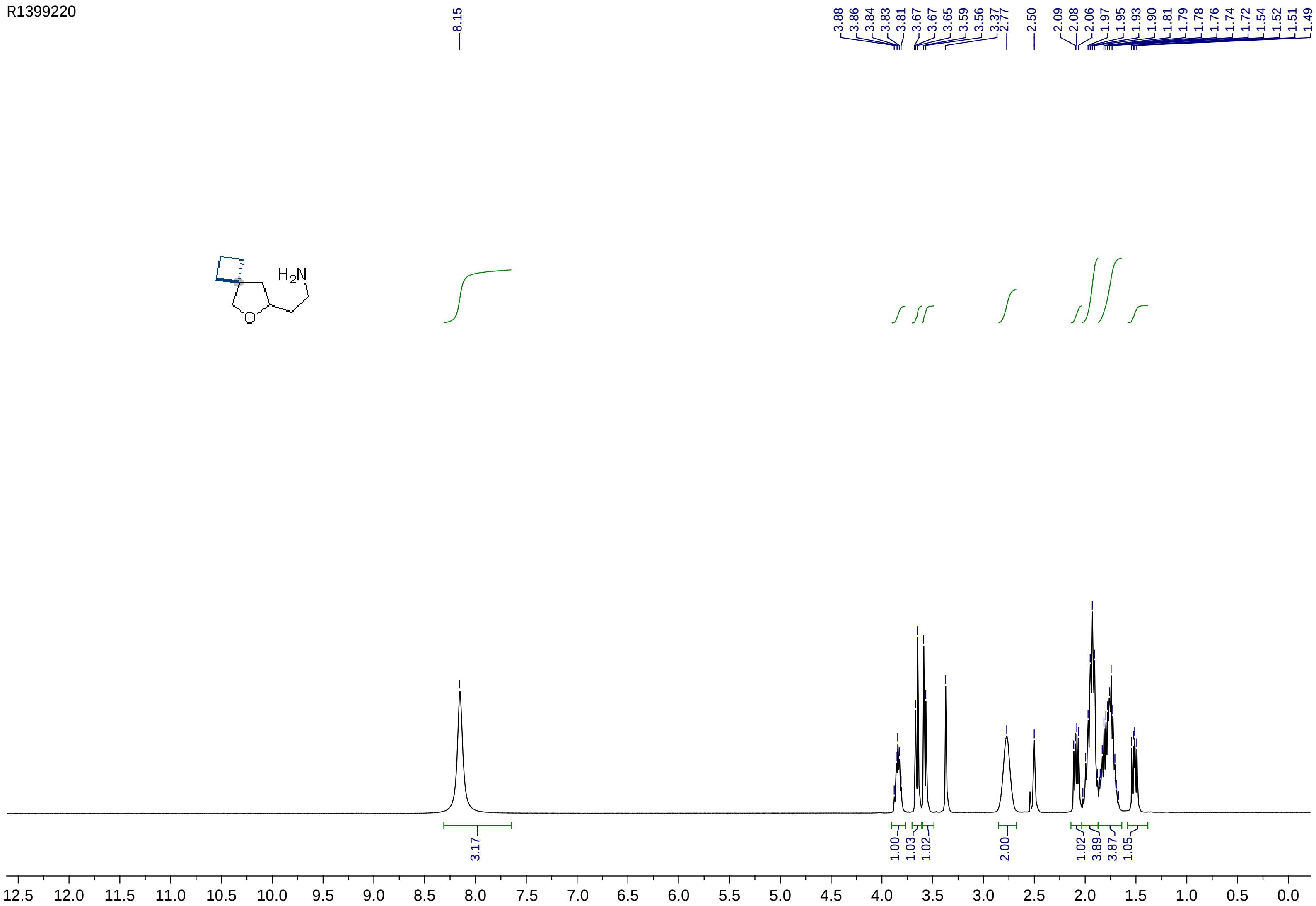

R2401571_C13
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

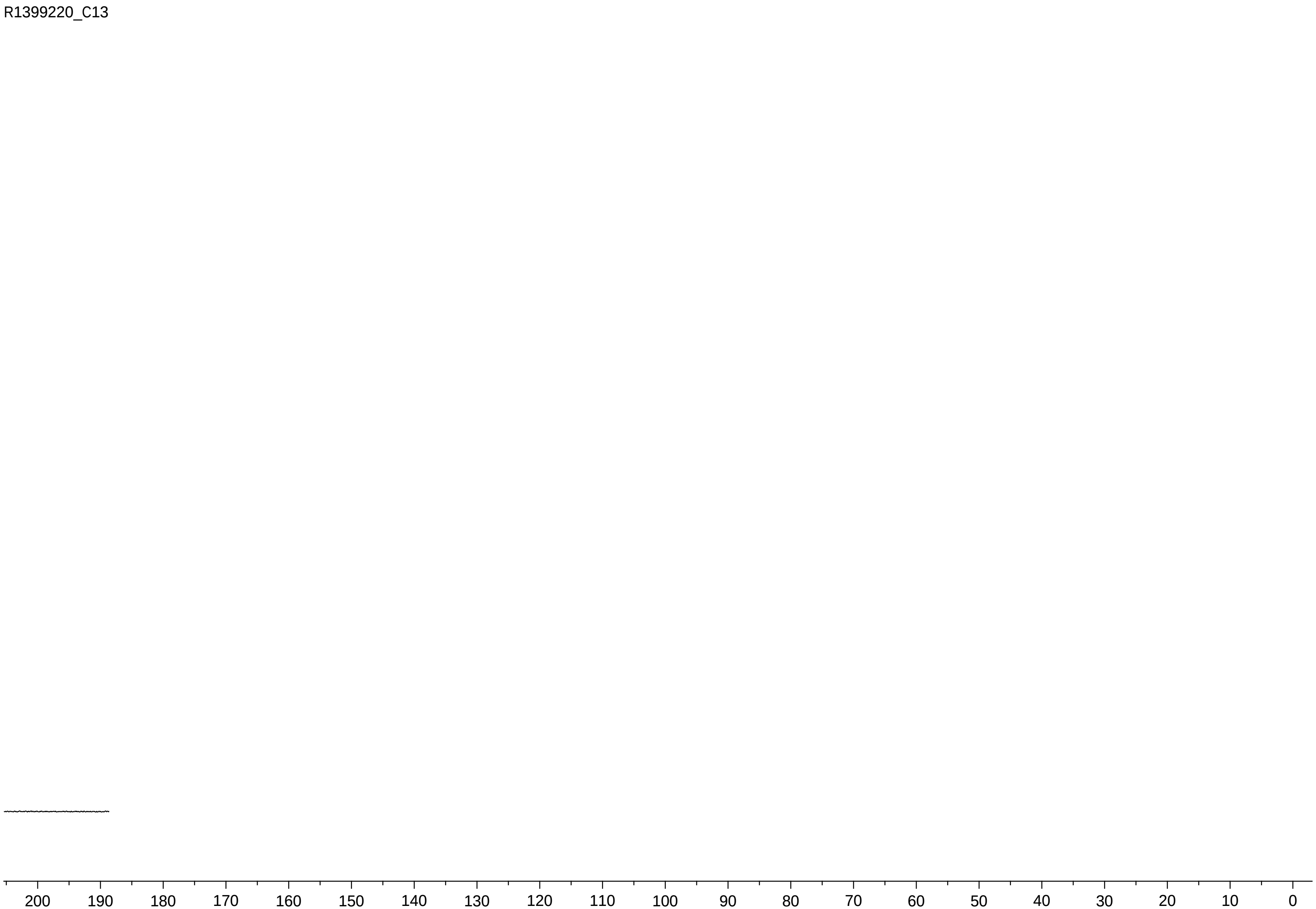
Compound 48g



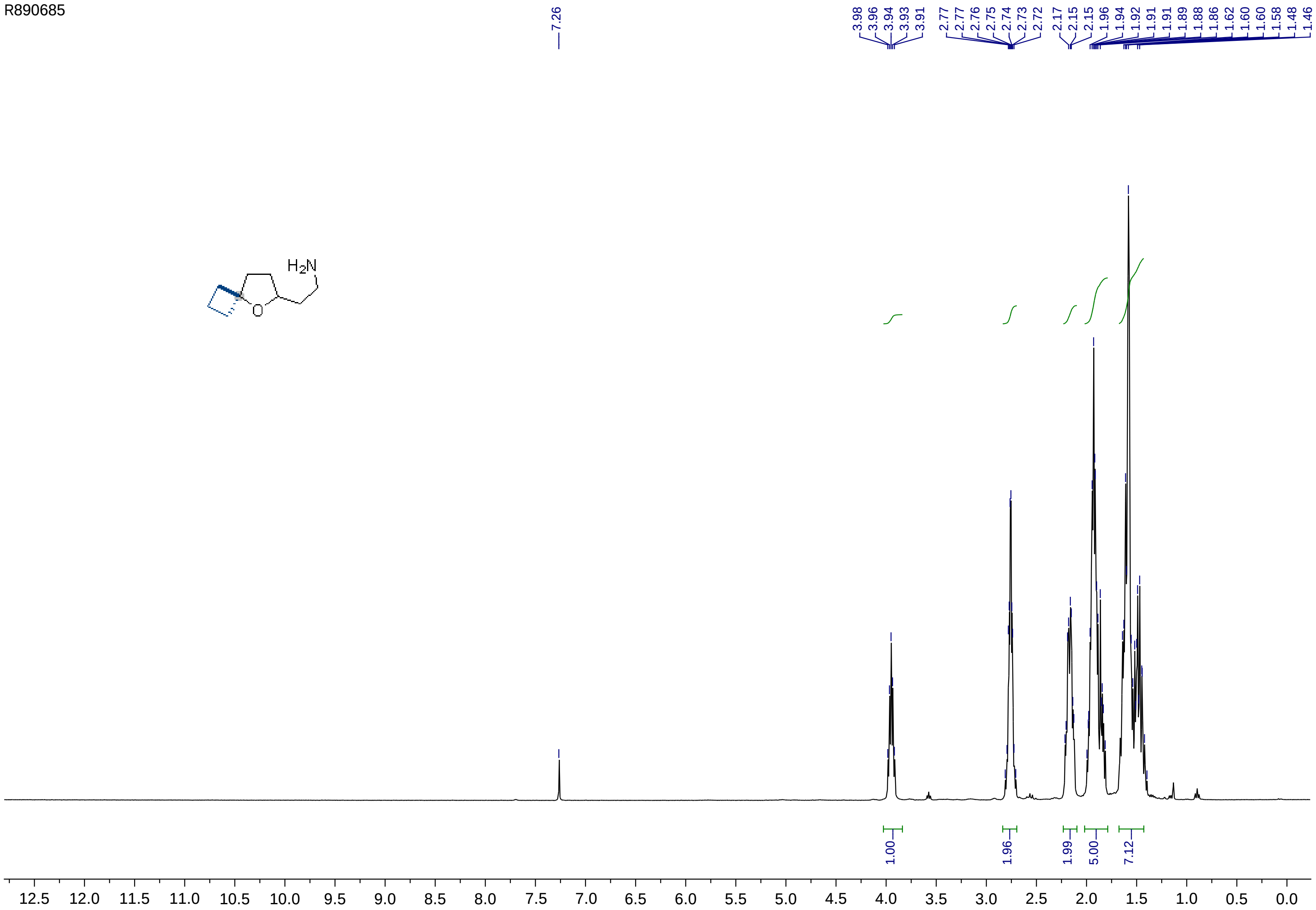

R251344_13C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 6h

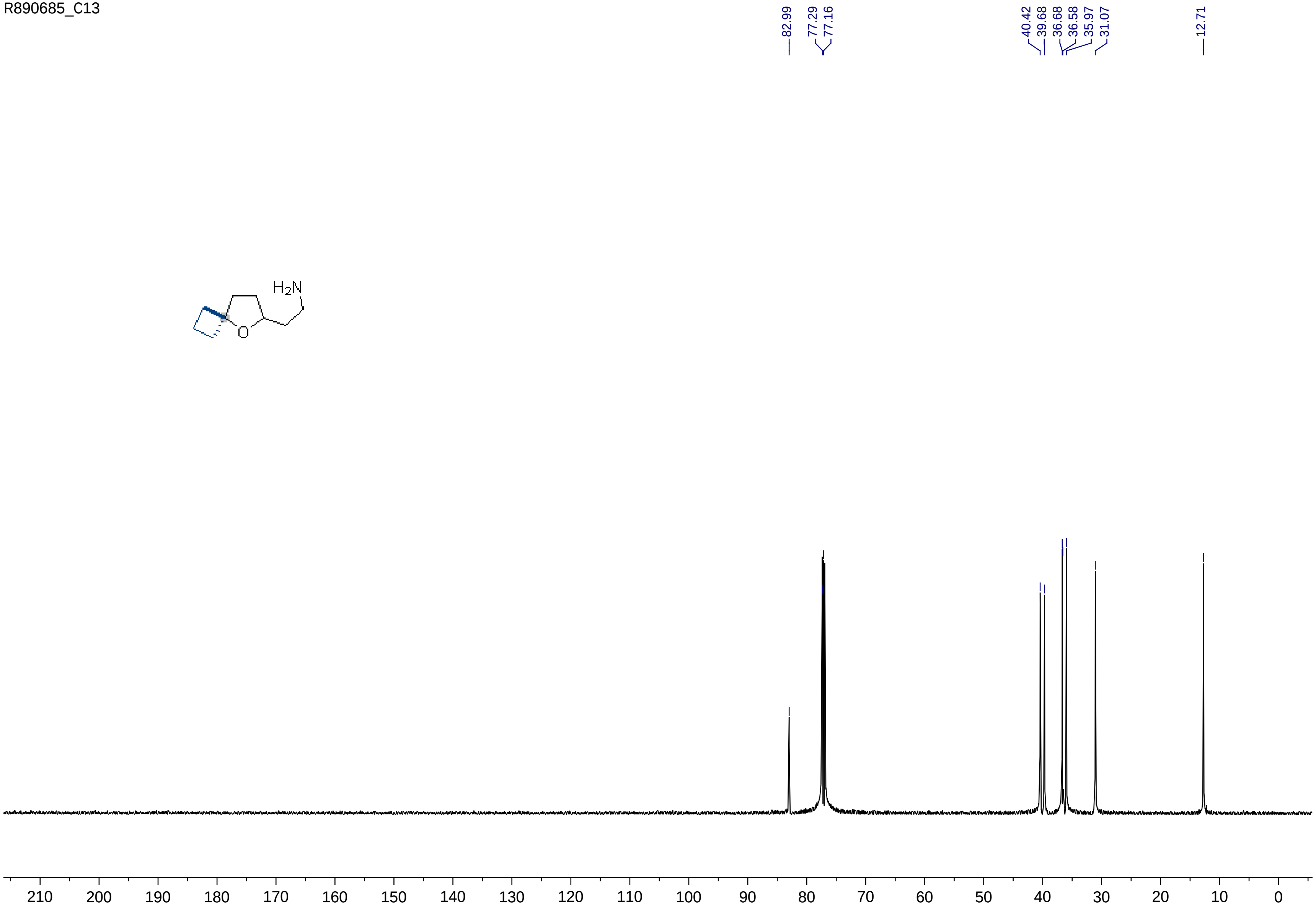

R1399220
8.15
3.88
3.86
3.84
3.83
3.81
3.67
3.67
3.65
3.59
3.56
3.37
2.77
2.50
2.09
2.08
2.06
1.97
1.95
1.93
1.90
1.81
1.79
1.78
1.76
1.74
1.72
1.54
1.52
1.51
1.49
H2N
O
3.17
1.00
1.03
1.02
2.00
1.02
3.89
3.87
1.05
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


R1399220_C13
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

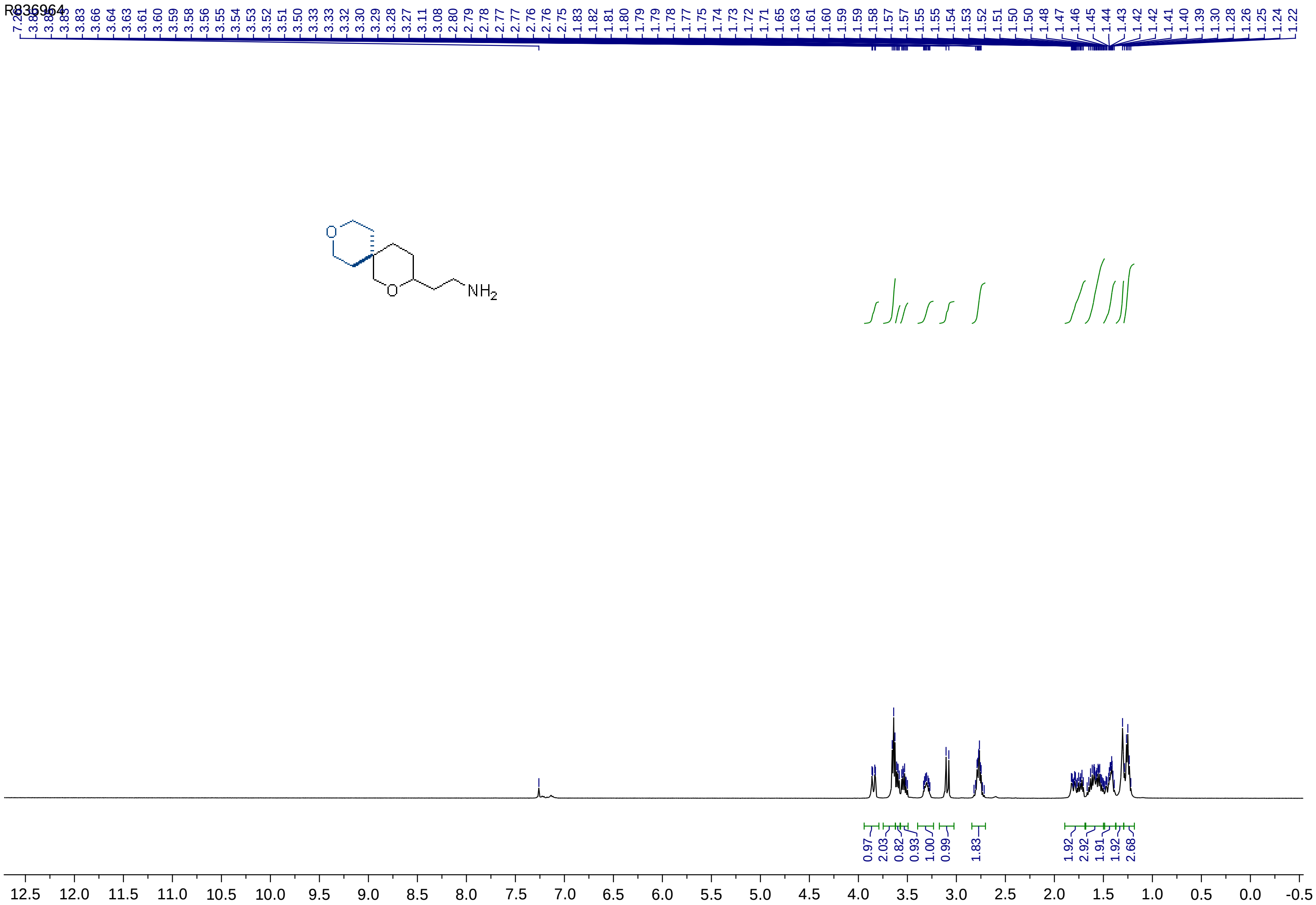
Compound 18h

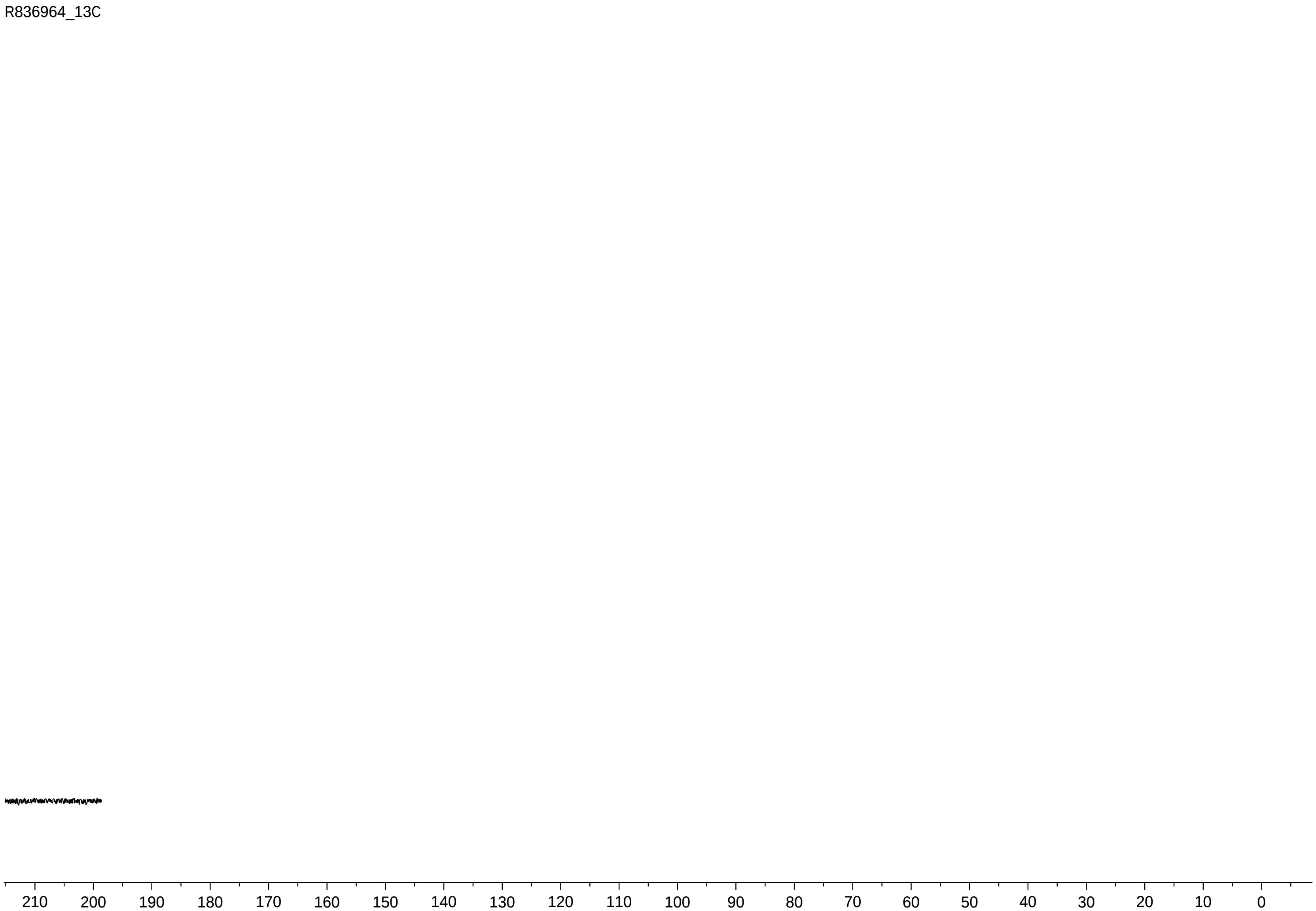


R890685_C13

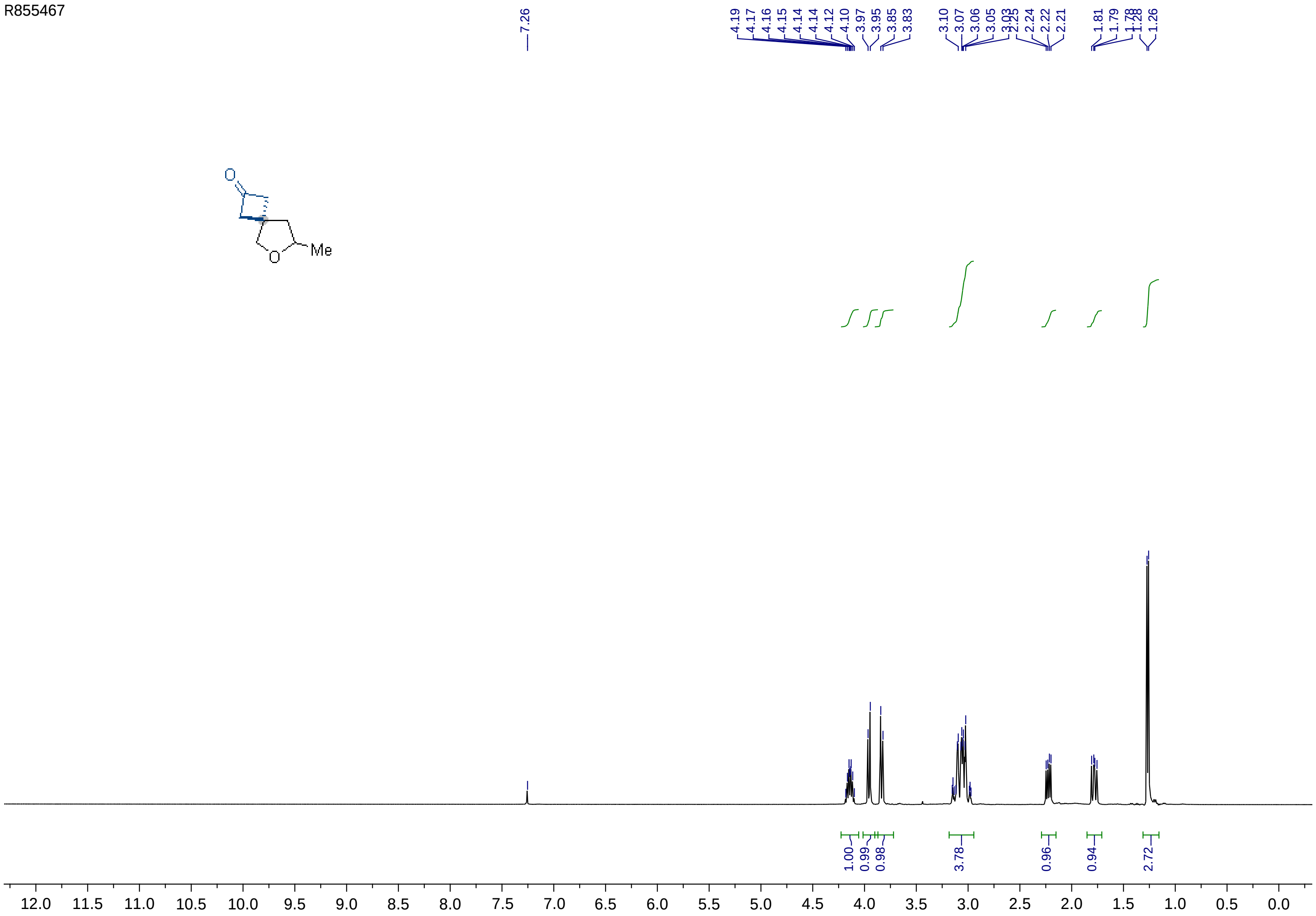

82.99
77.29
77.16
40.42
39.68
36.68
36.58
35.97
31.07
12.71
H2N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 36h

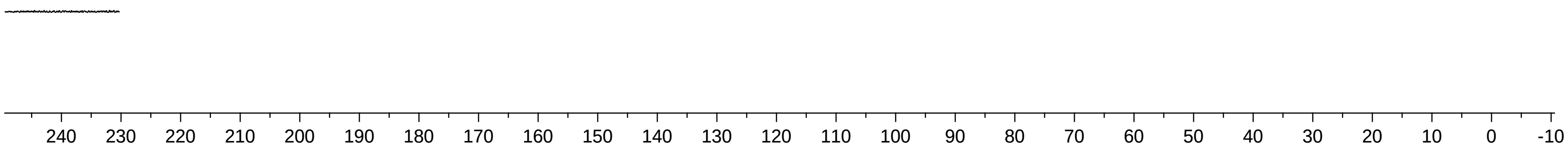



R836964_13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 7i

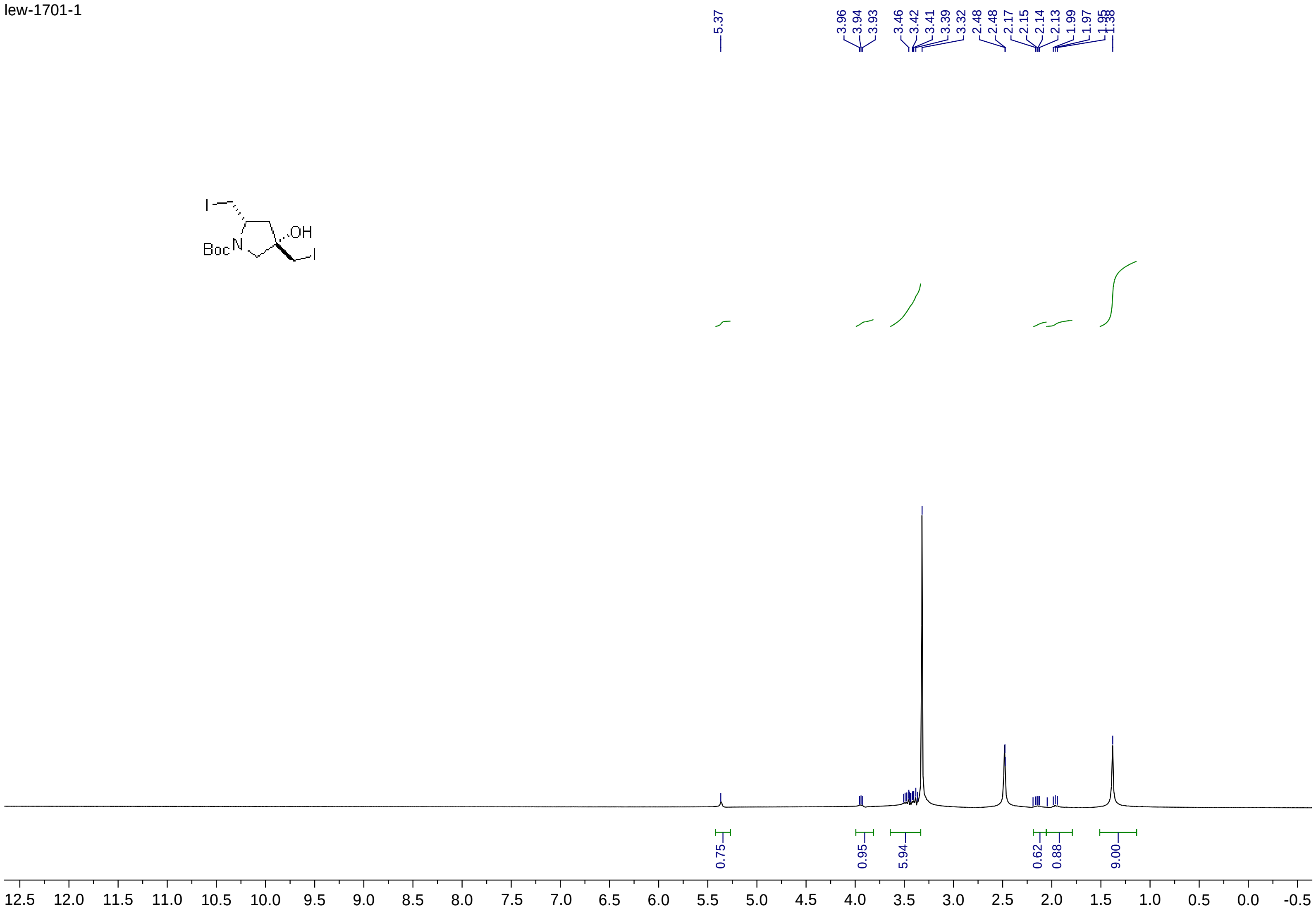

R855467
O
O
Me
7.26
4.19
4.17
4.16
4.15
4.14
4.14
4.12
4.10
3.97
3.95
3.85
3.83
3.10
3.07
3.06
3.05
3.03
2.25
2.24
2.22
2.21
1.81
1.79
1.78
1.28
1.26
1.00
0.99
0.98
3.78
0.96
0.94
2.72
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

R855467_C13

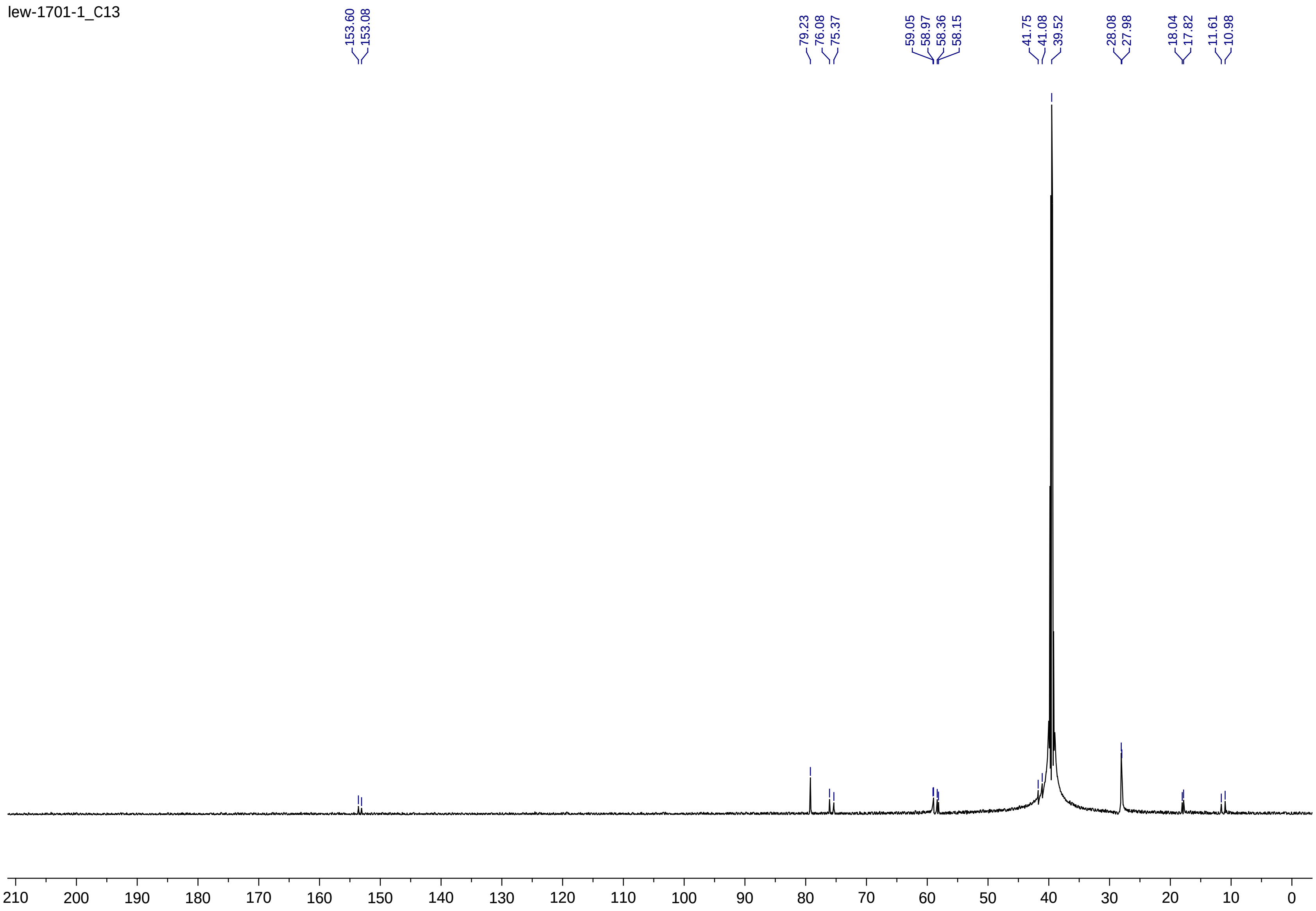


240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

Compound 50



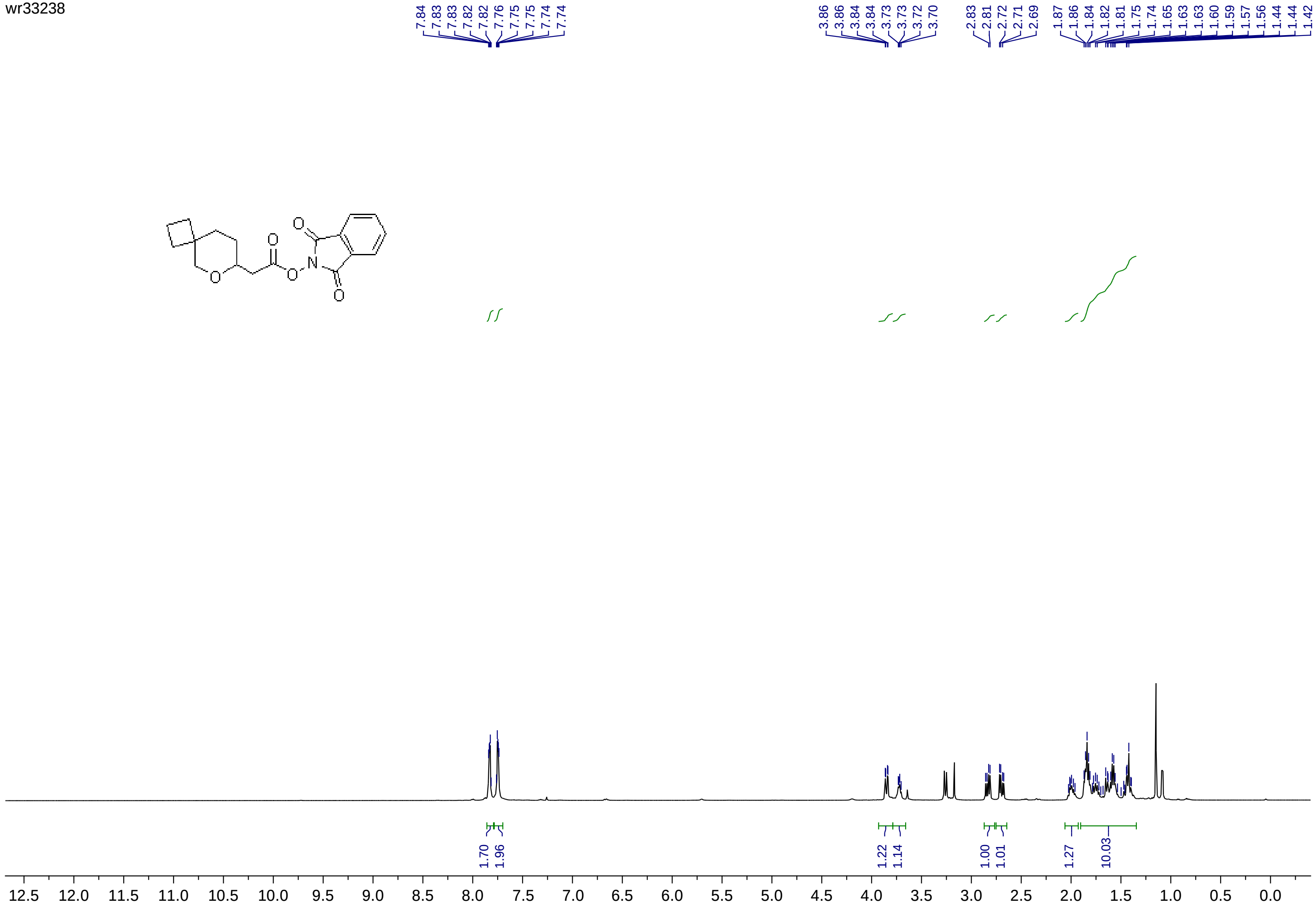
lew-1701-1
Boc
N
OH
I
I
5.37
3.96
3.94
3.93
3.46
3.42
3.41
3.39
3.32
2.48
2.48
2.17
2.15
2.14
2.13
1.99
1.97
1.95
1.38
0.75
0.95
5.94
0.62
0.88
9.00
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


lew-1701-1_C13
153.60
153.08
79.23
76.08
75.37
59.05
58.97
58.36
58.15
41.75
41.08
39.52
28.08
27.98
18.04
17.82
11.61
10.98
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

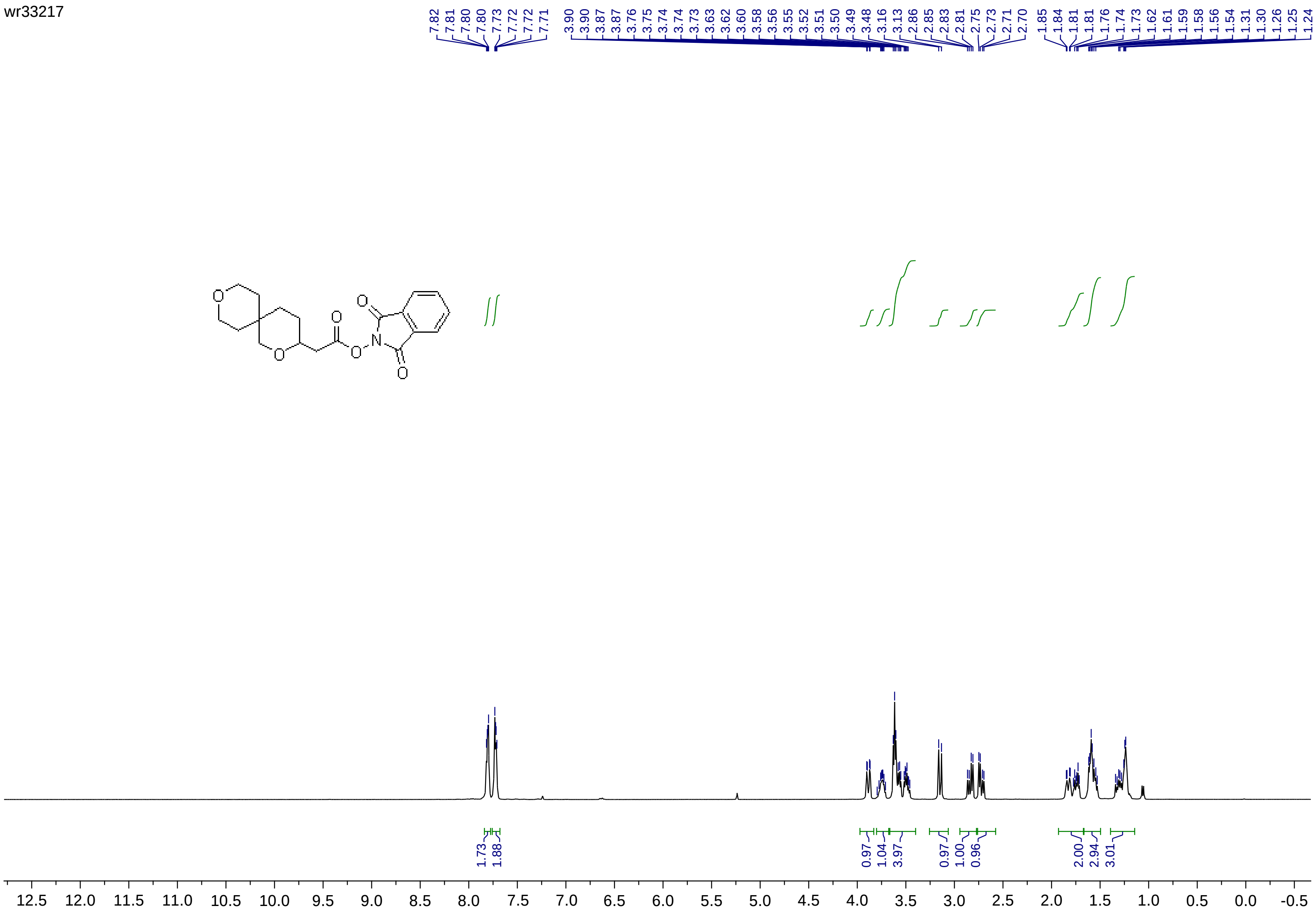
1,3-Dioxoisoindolin-2-yl 2-(5-oxaspiro[3.4]octan-6-yl)acetate (crude)

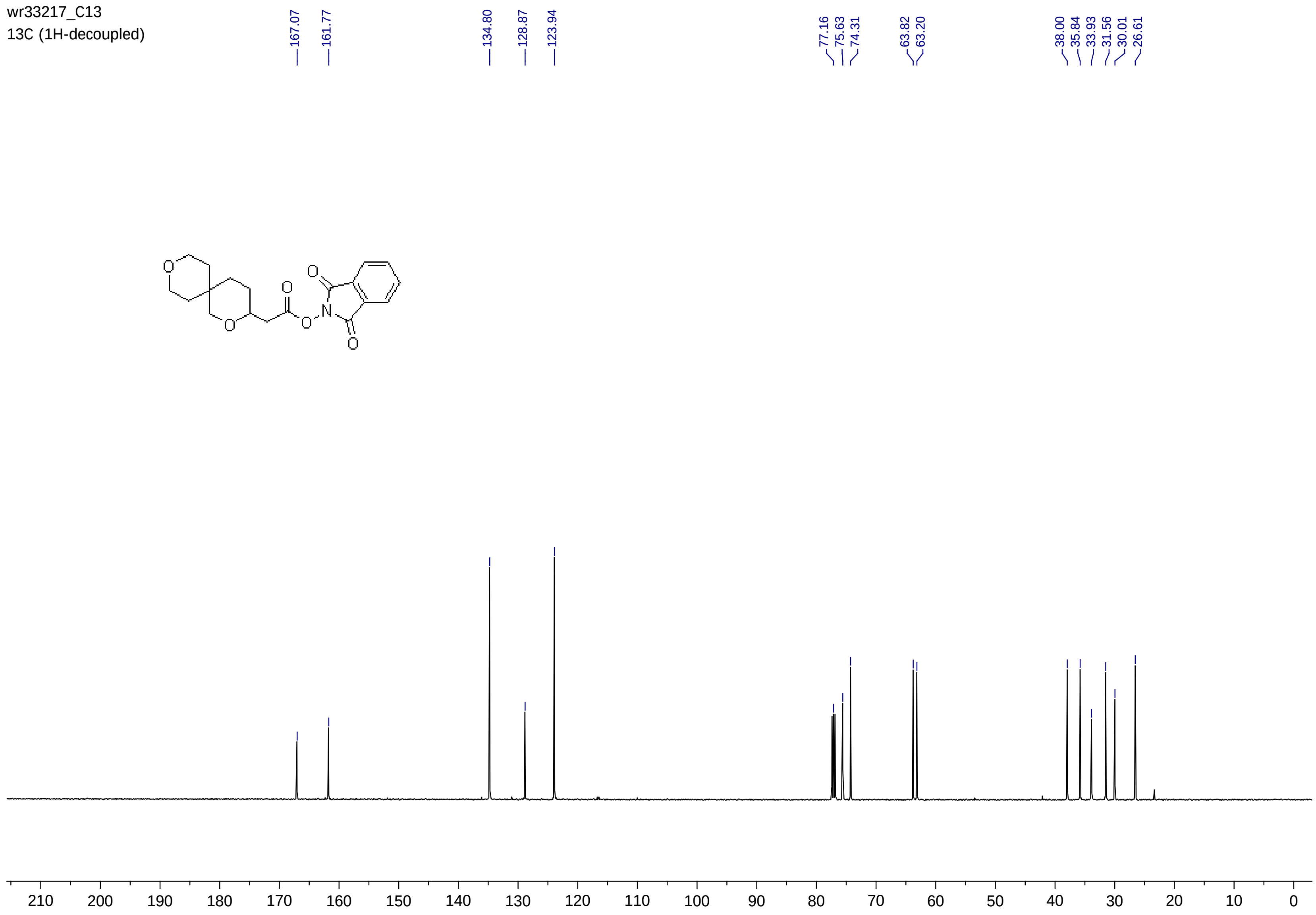
Tert-butyl 3-(2-((1,3-dioxoisoindolin-2-yl)oxy)-2-oxoethyl)-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (crude)

1,3-Dioxoisoindolin-2-yl 2-(6-oxaspiro[3.5]nonan-7-yl)acetate (crude)

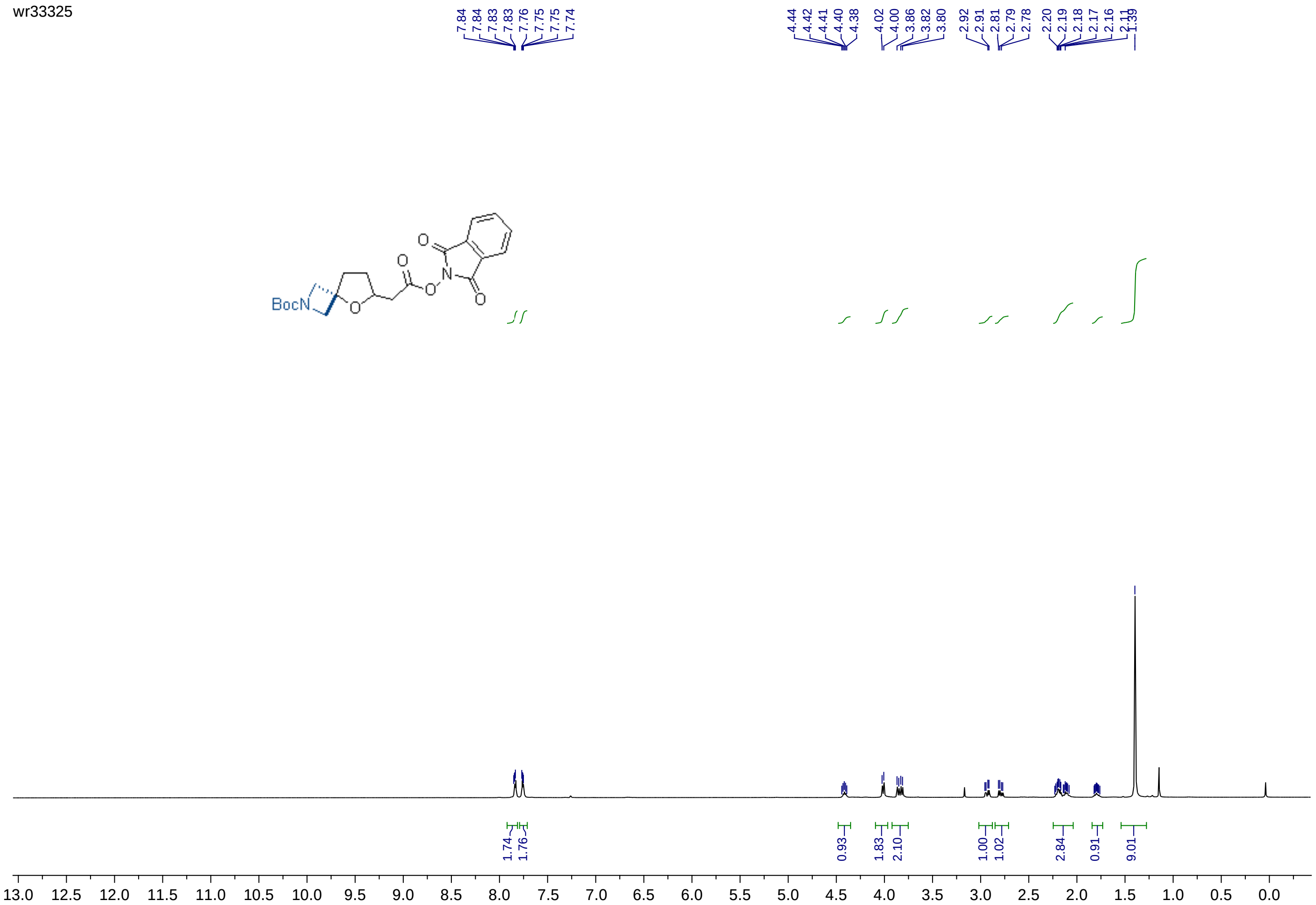


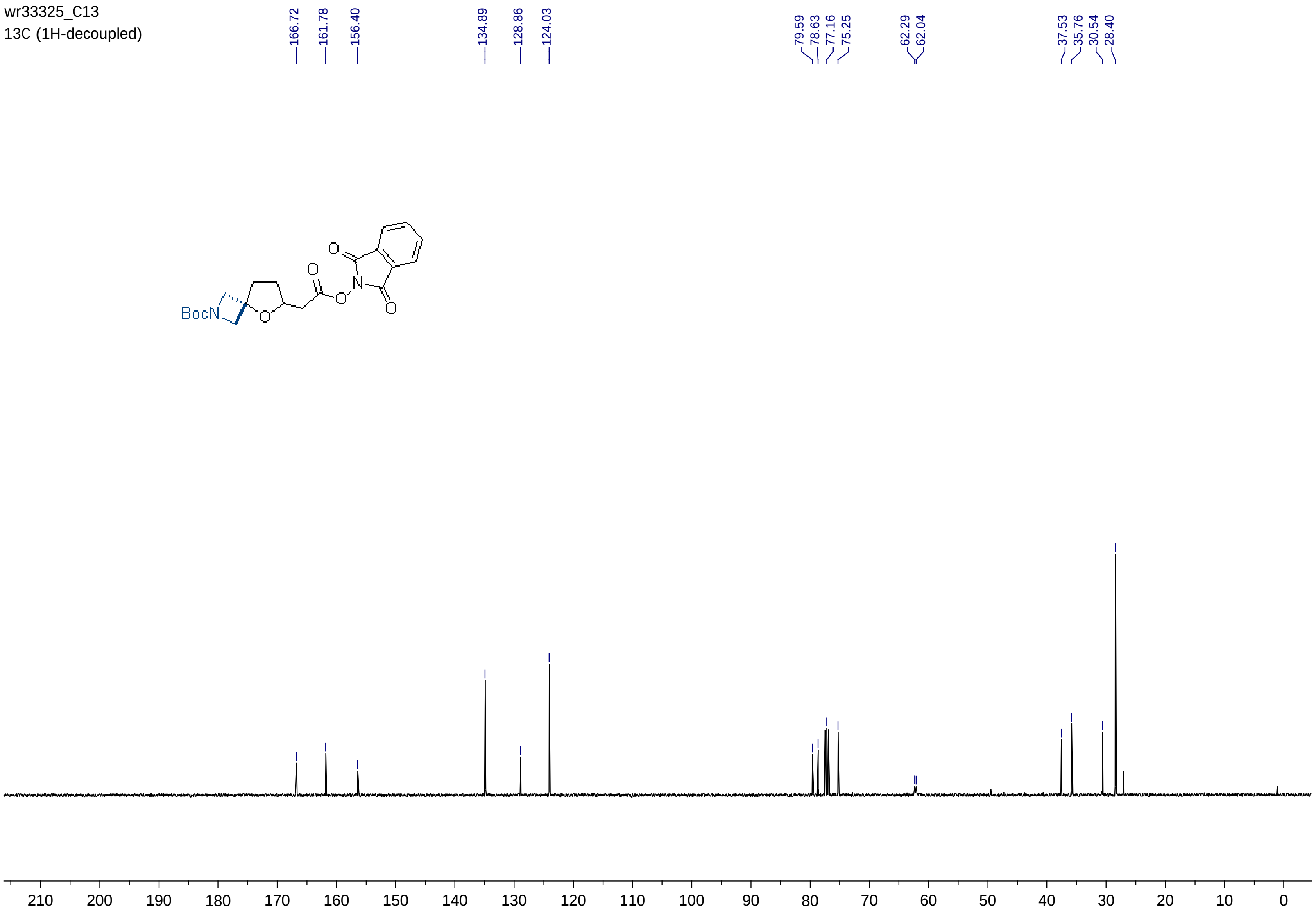
1,3-Dioxoisoindolin-2-yl 2-(2,9-dioxaspiro[5.5]undecan-3-yl)acetate


wr33217
7.82 7.81 7.80 7.80 7.73 7.72 7.72 7.71
3.90 3.90 3.87 3.87 3.76 3.75 3.74 3.74 3.73 3.63 3.62 3.60 3.58 3.56 3.55 3.52 3.51 3.50 3.49 3.48 3.16 3.13 2.86 2.85 2.83 2.81 2.75 2.73 2.71 2.70
1.85 1.84 1.81 1.81 1.76 1.74 1.73 1.62 1.61 1.59 1.58 1.56 1.54 1.31 1.30 1.26 1.25 1.24
O
O
O
O
N
O
O
O
1.73 1.88 0.97 1.04 3.97 0.97 1.00 0.96 2.00 2.94 3.01
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

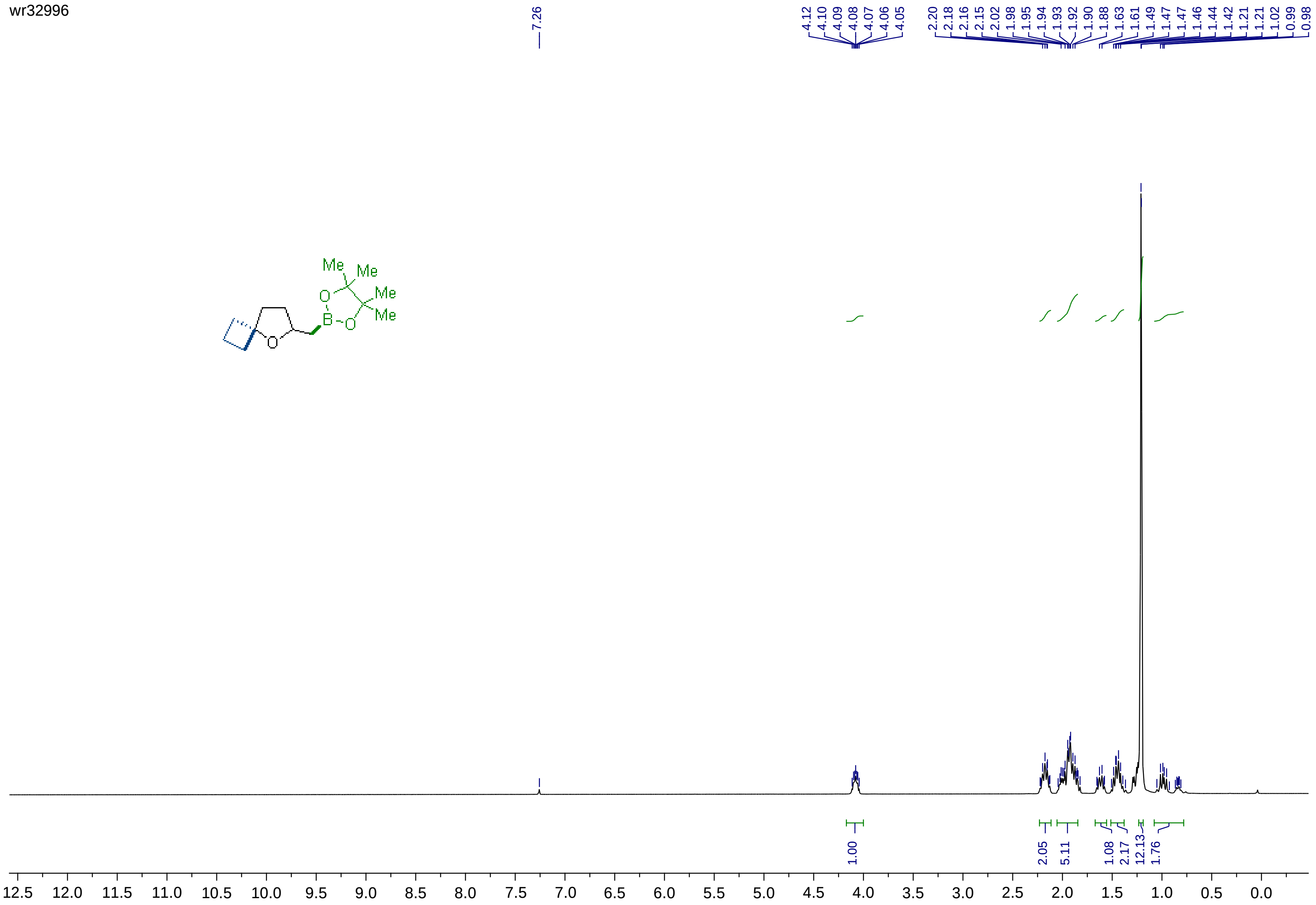

wr33217_C13
13C (1H-decoupled)
167.07
161.77
134.80
128.87
123.94
77.16
75.63
74.31
63.82
63.20
38.00
35.84
33.93
31.56
30.01
26.61
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

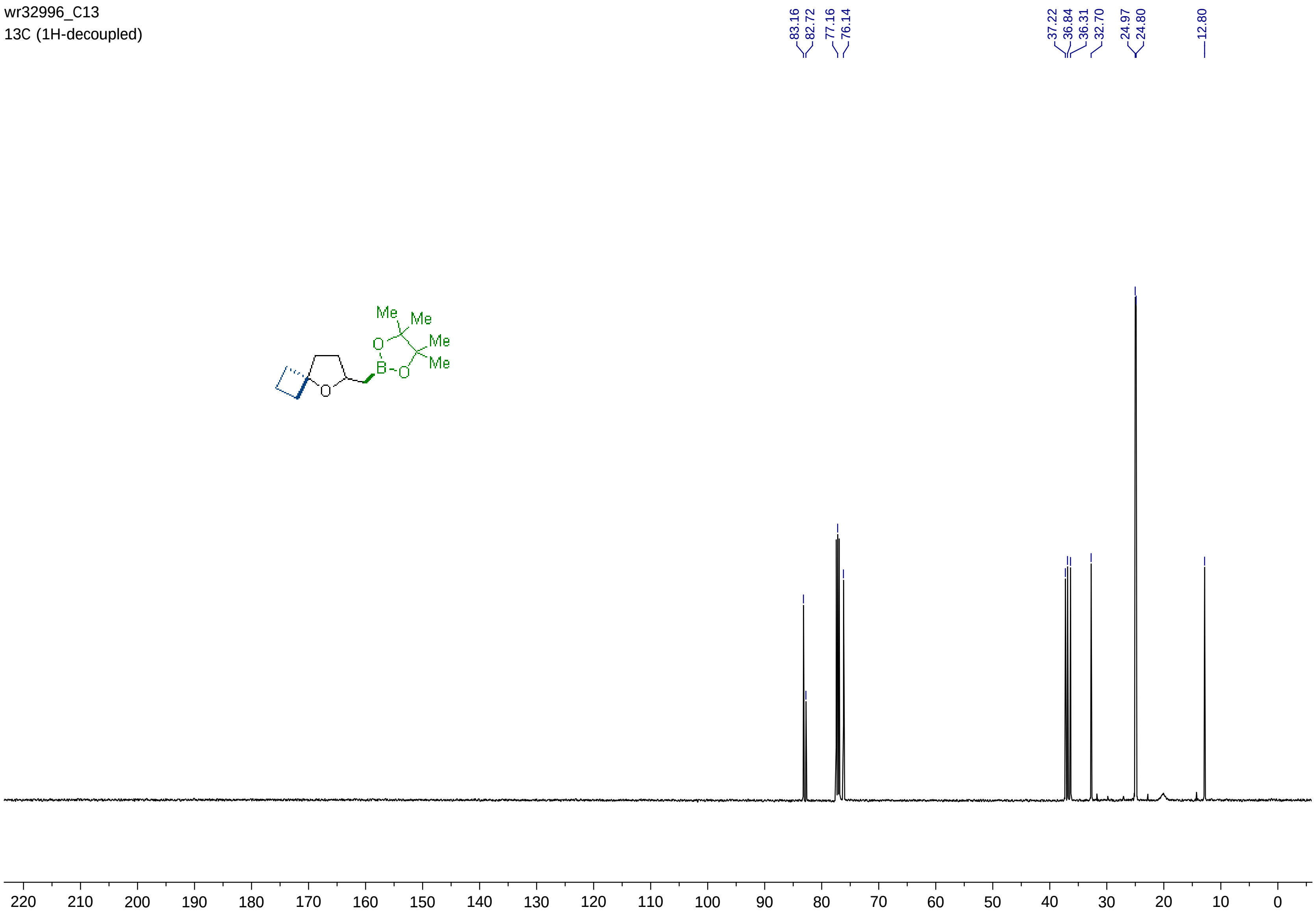
Tert-butyl 6-(2-((1,3-dioxoisoindolin-2-yl)oxy)-2-oxoethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate



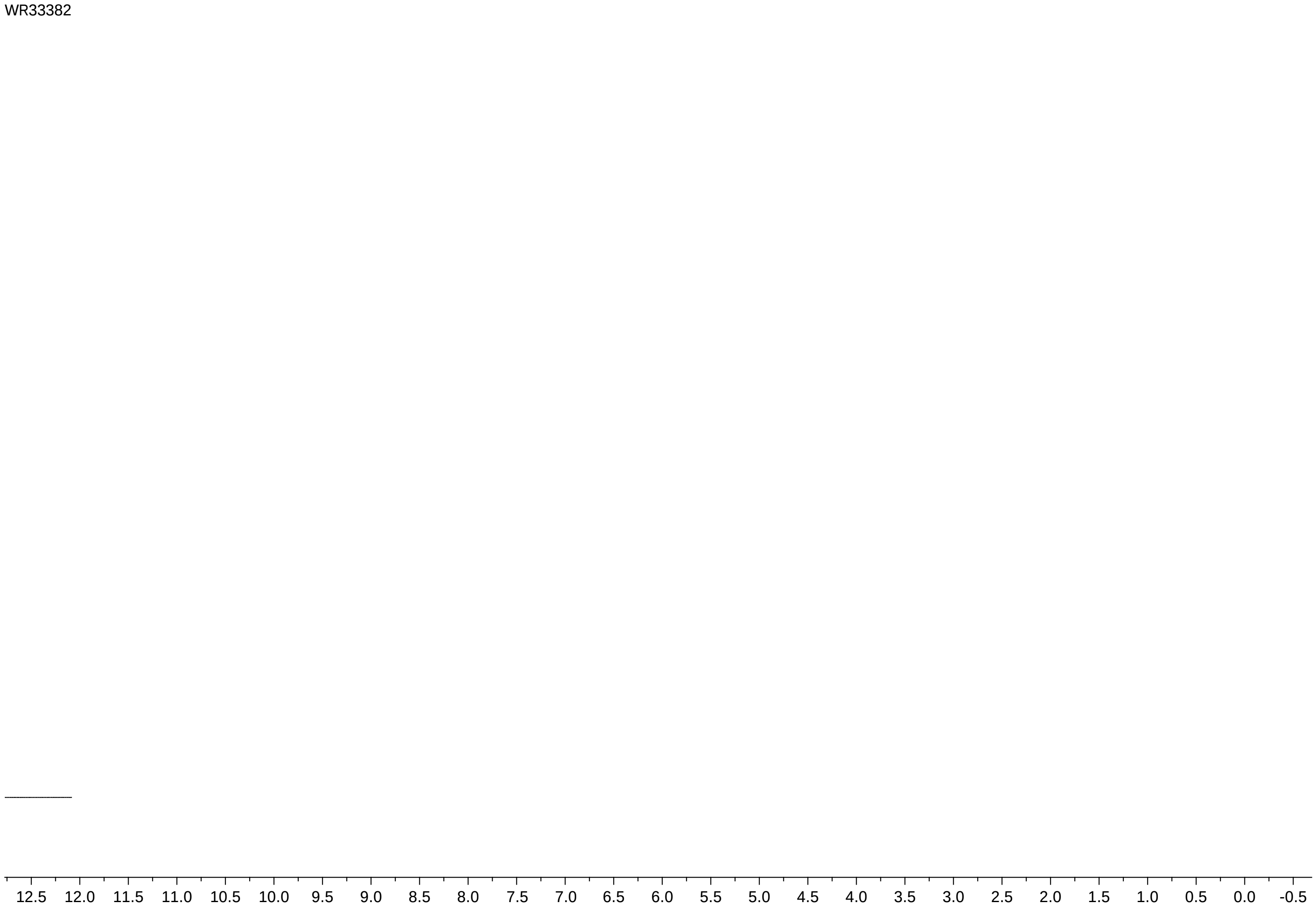

wr33325_C13
13C (1H-decoupled)
166.72
161.78
156.40
134.89
128.86
124.03
79.59
78.63
77.16
75.25
62.29
62.04
37.53
35.76
30.54
28.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 18j

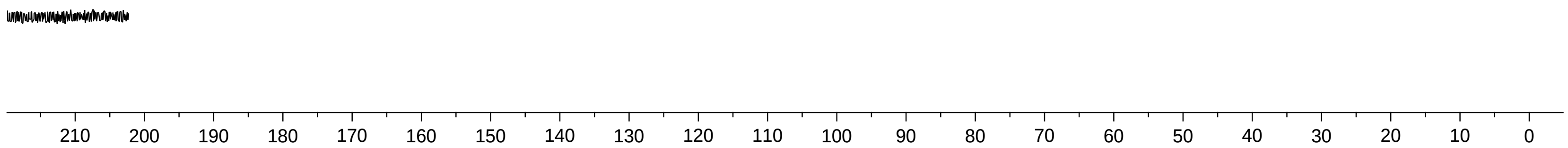



wr32996_C13
13C (1H-decoupled)
83.16
82.72
77.16
76.14
37.22
36.84
36.31
32.70
24.97
24.80
12.80
Me
Me
Me
Me
O
B
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 14j

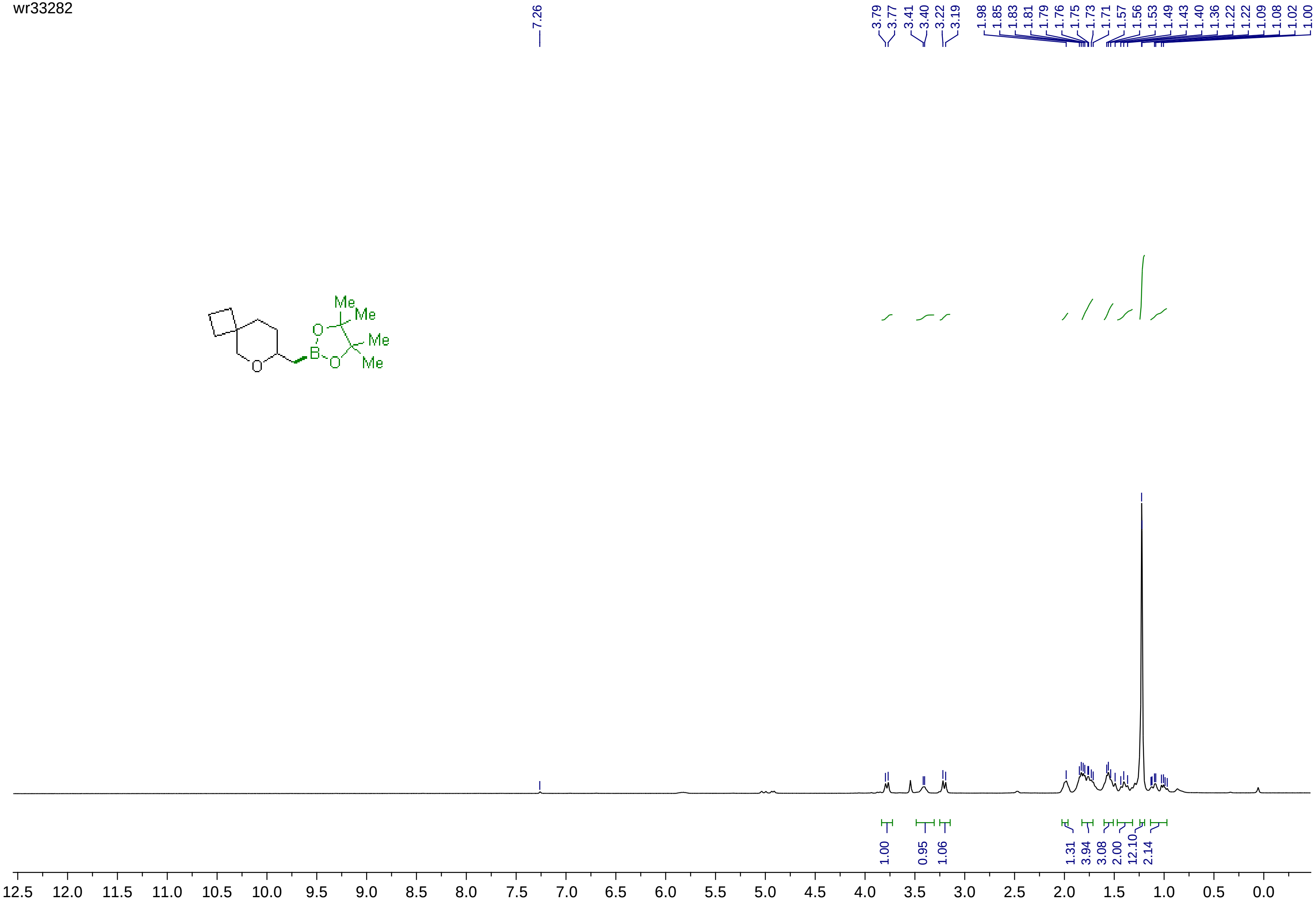


WR33382_C13

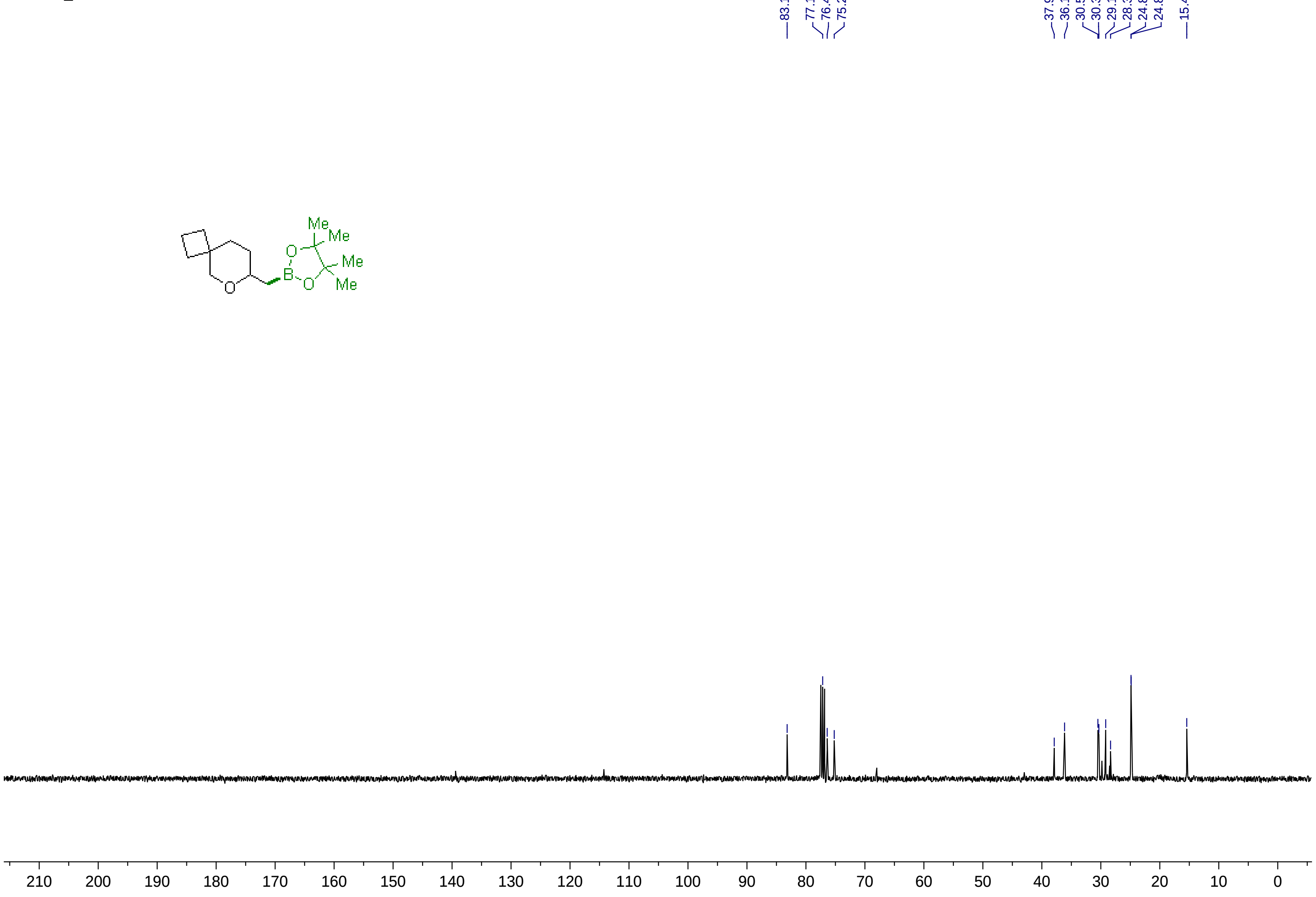

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Compound 34j

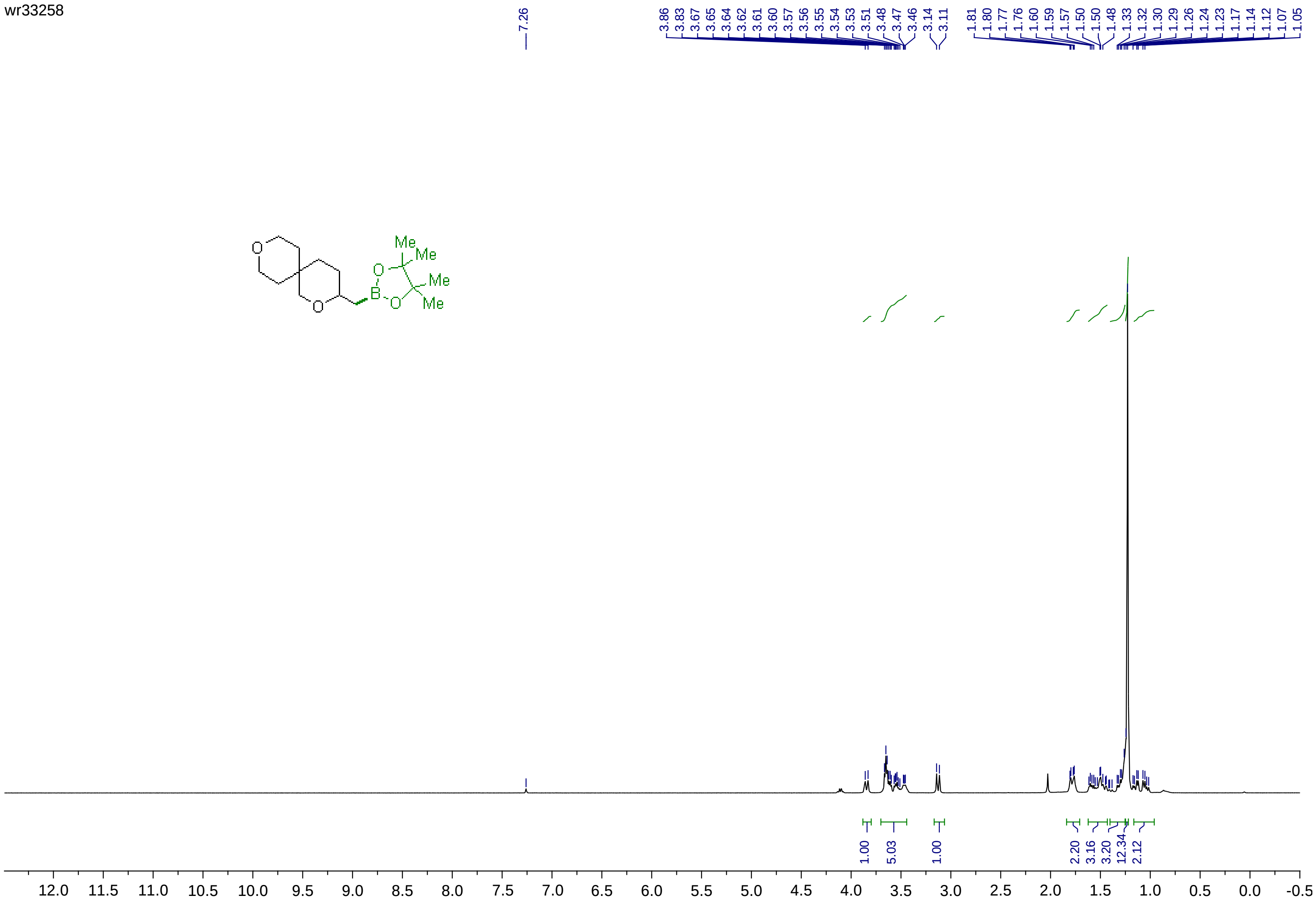
wr33282

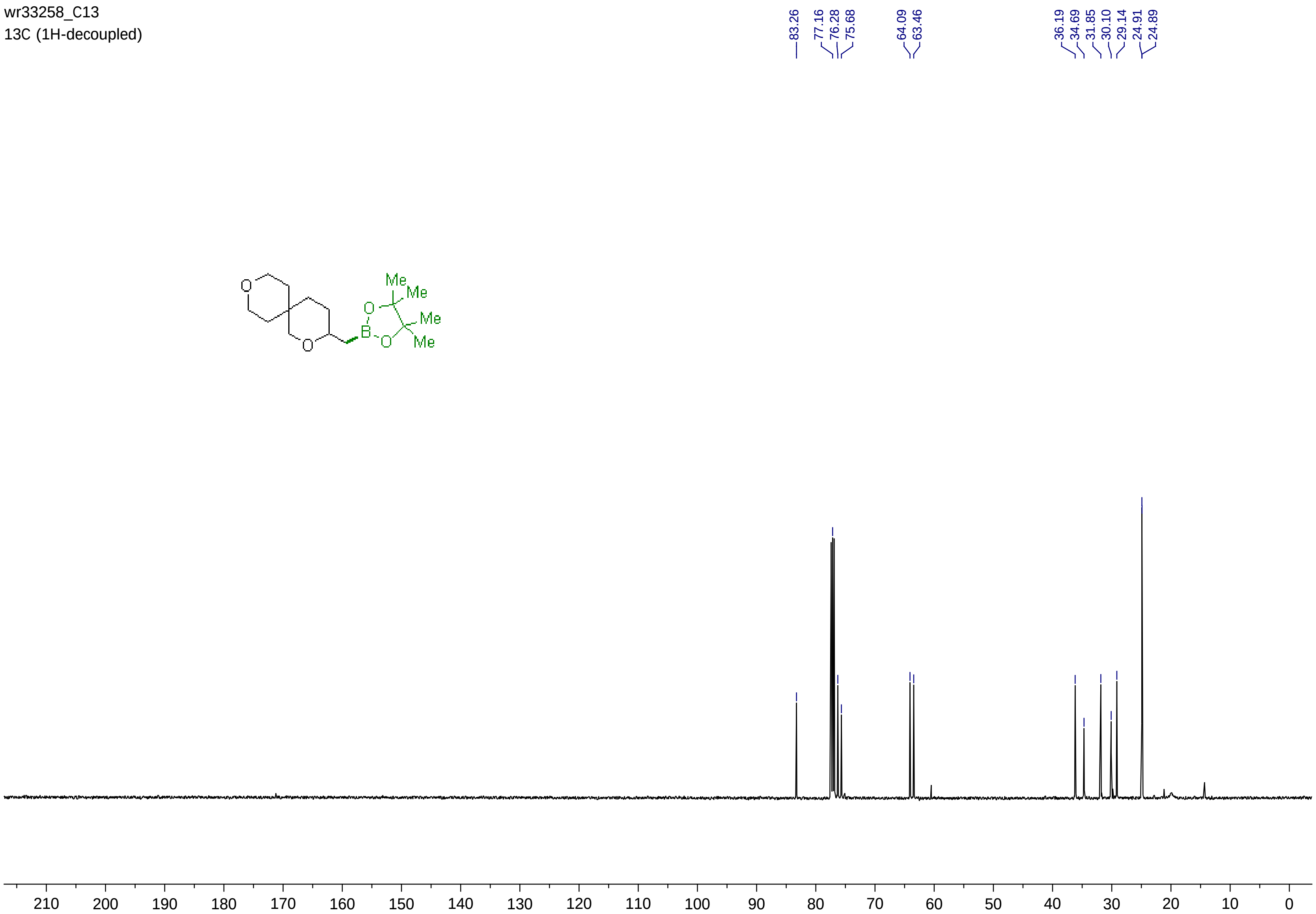


wr33282_C13

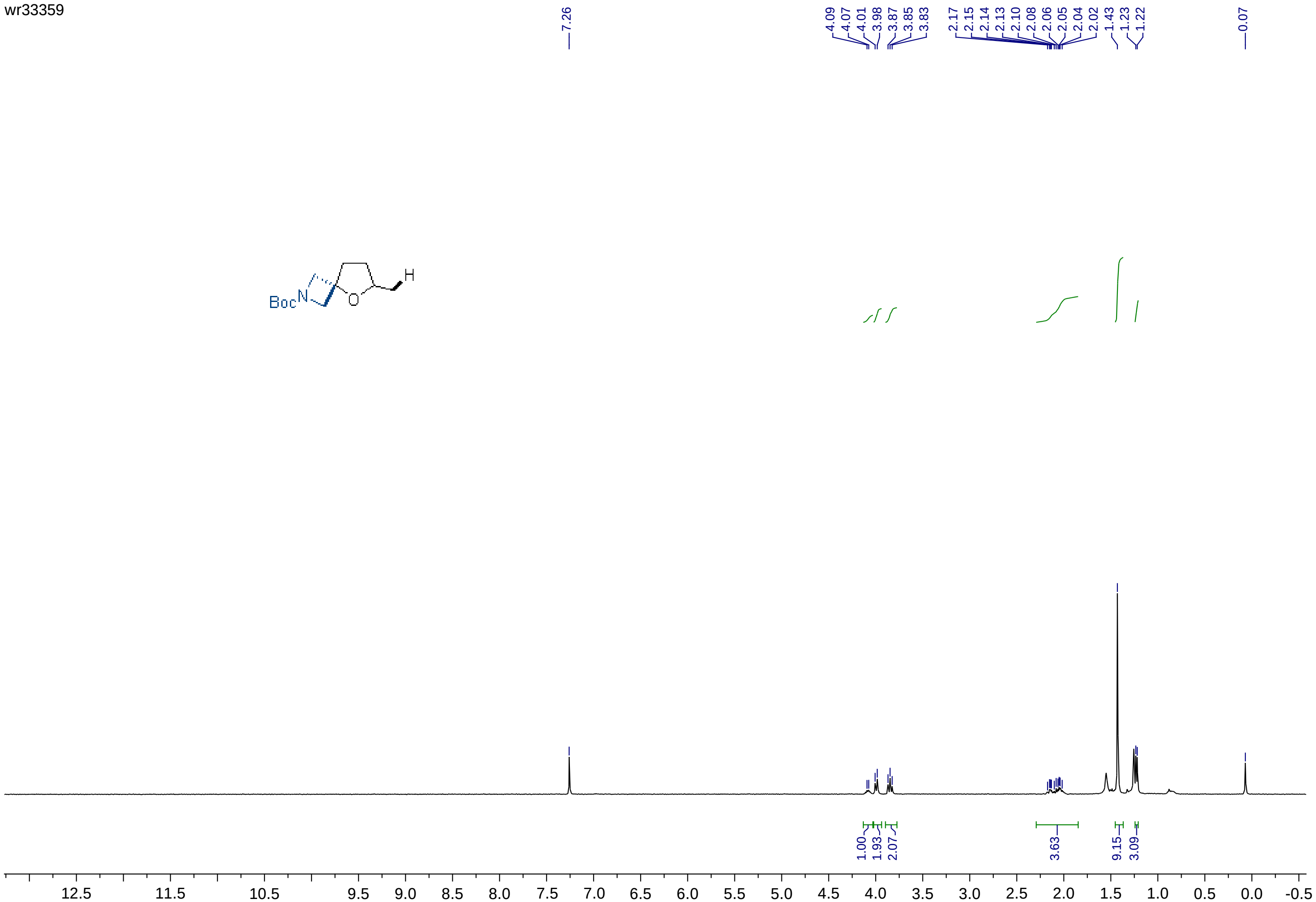

83.19
77.16
76.40
75.20
37.90
36.15
30.50
30.33
29.17
28.35
24.88
24.85
15.43
Me
Me
Me
Me
O
B
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 36j



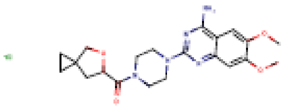

wr33258_C13
13C (1H-decoupled)
83.26
77.16
76.28
75.68
64.09
63.46
36.19
34.69
31.85
30.10
29.14
24.91
24.89
O
O
Me
Me
Me
Me
O
B
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Compound 21j



Compound 75

MaxPeak: 100.00%
Ret_Time: 0.920 min

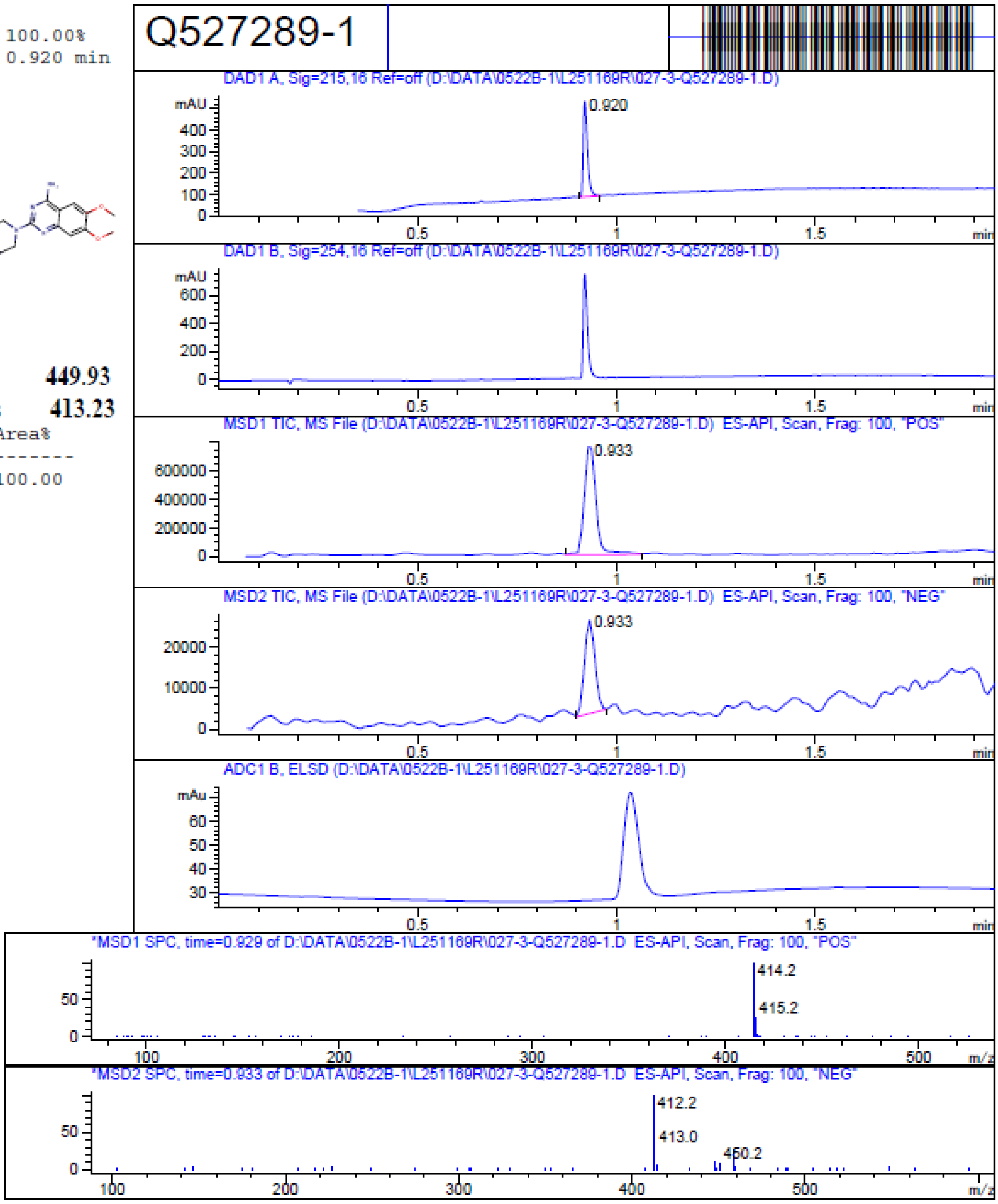


Mol Wt 449.93
Exact Mass 413.23

#	Time	Area%
1	0.920	100.00

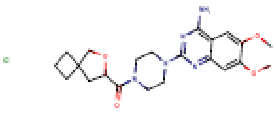
RT 0.933

RT 0.933



Compound 76

MaxPeak: 97.45%
Ret_Time: 0.972 min

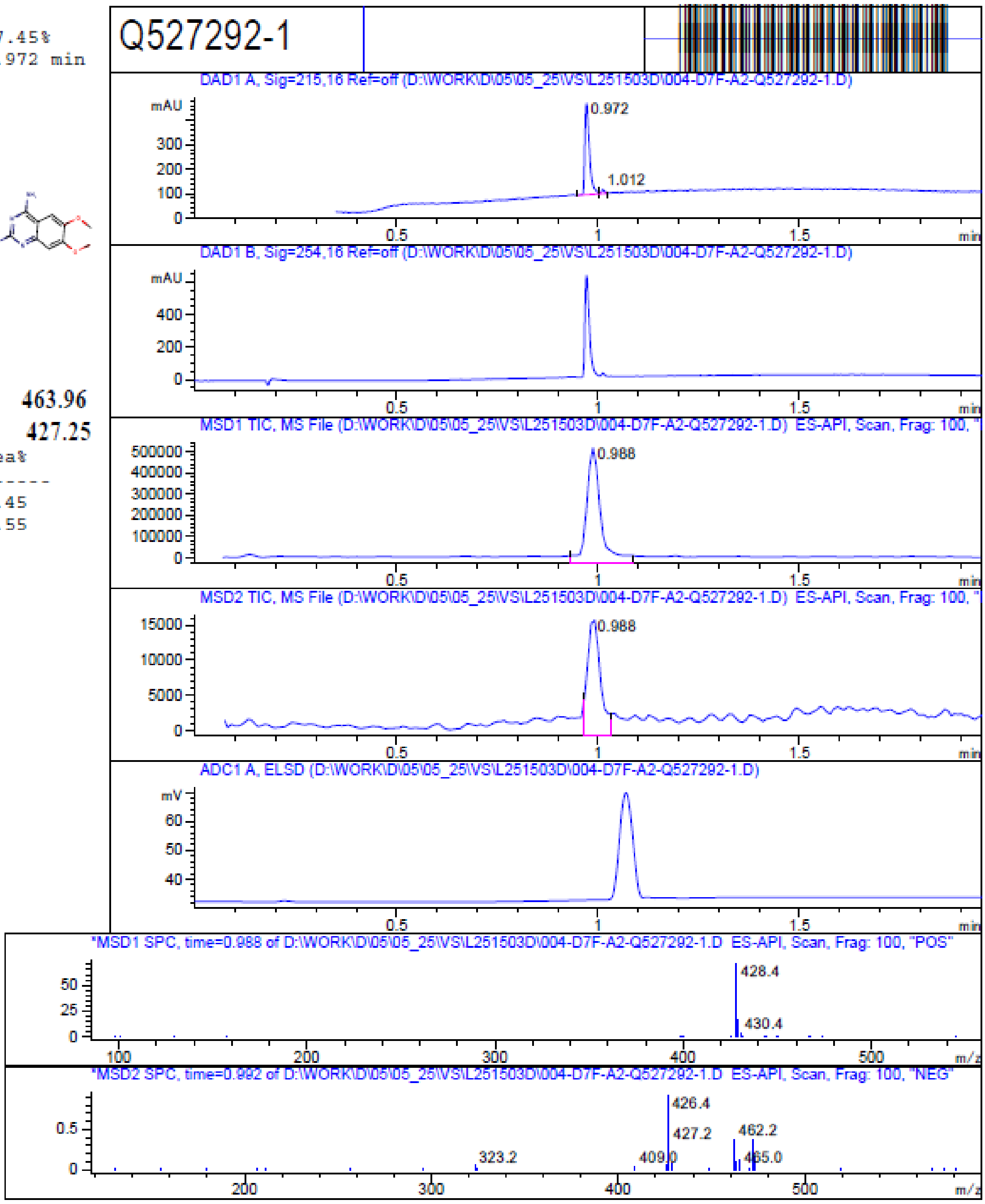


Mol Wt 463.96
Exact Mass 427.25

#	Time	Area%
1	0.972	97.45
2	1.012	2.55

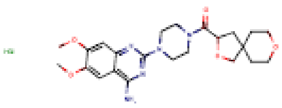
RT 0.988

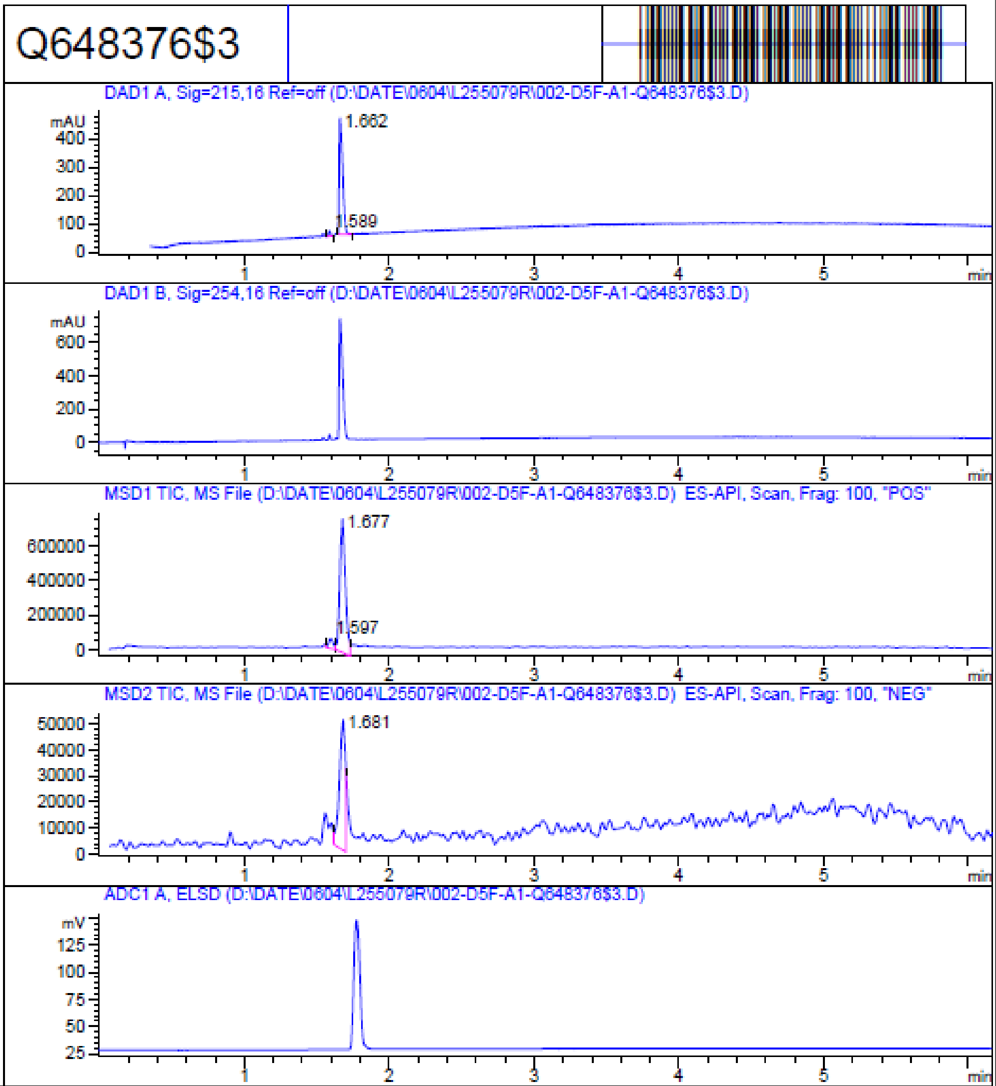
RT 0.988



Compound 77

MaxPeak: 97.58%
Ret_Time: 1.662 min





Mol Wt 493.98

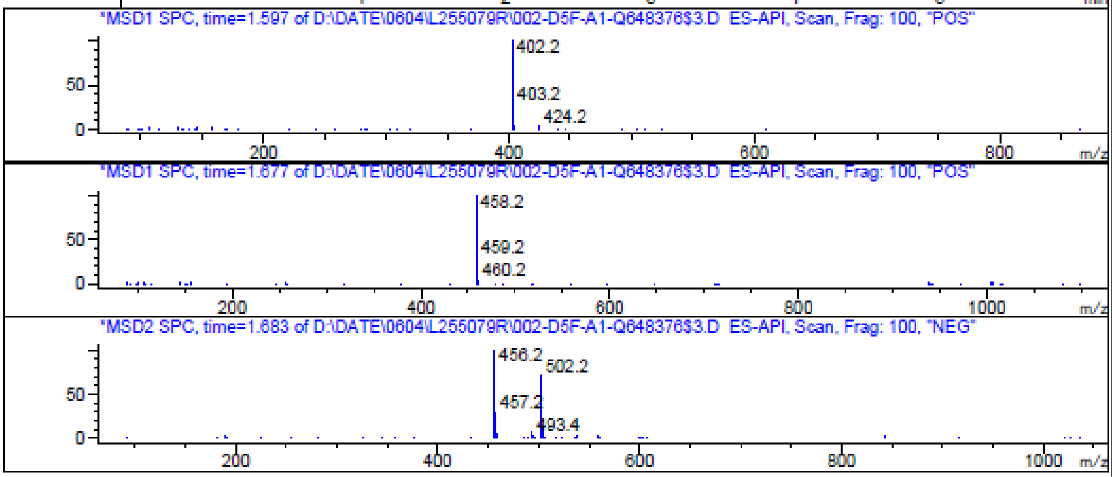
Exact Mass 457.26

#	Time	Area%
1	1.589	2.42
2	1.662	97.58

RT 1.597

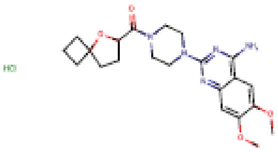
RT 1.677

RT 1.681



Compound 78

MaxPeak: 100.00%
Ret_Time: 0.846 min

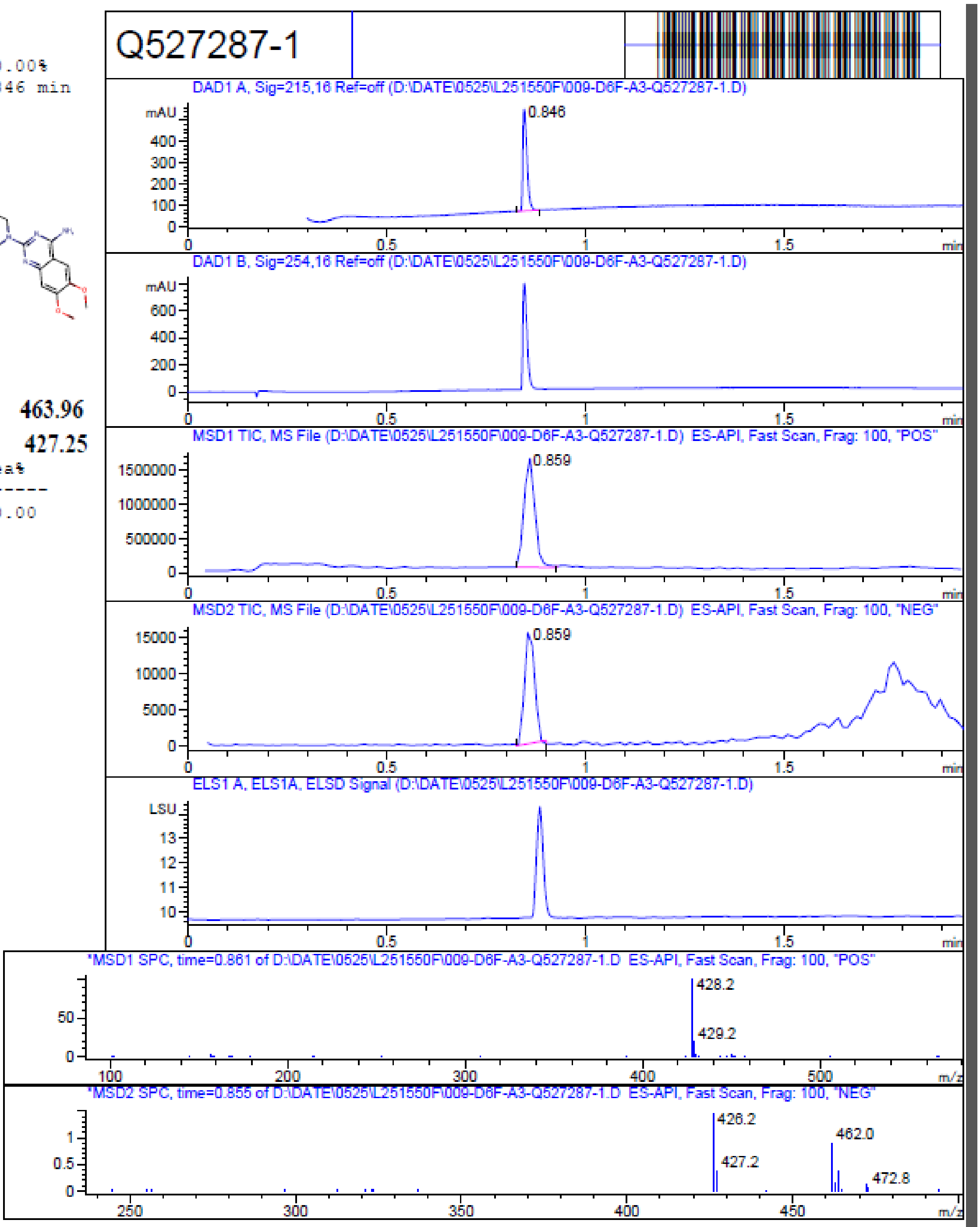


Mol Wt 463.96
Exact Mass 427.25

#	Time	Area%
1	0.846	100.00

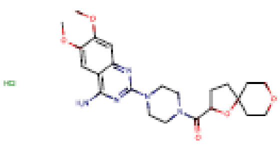
RT 0.859

RT 0.859



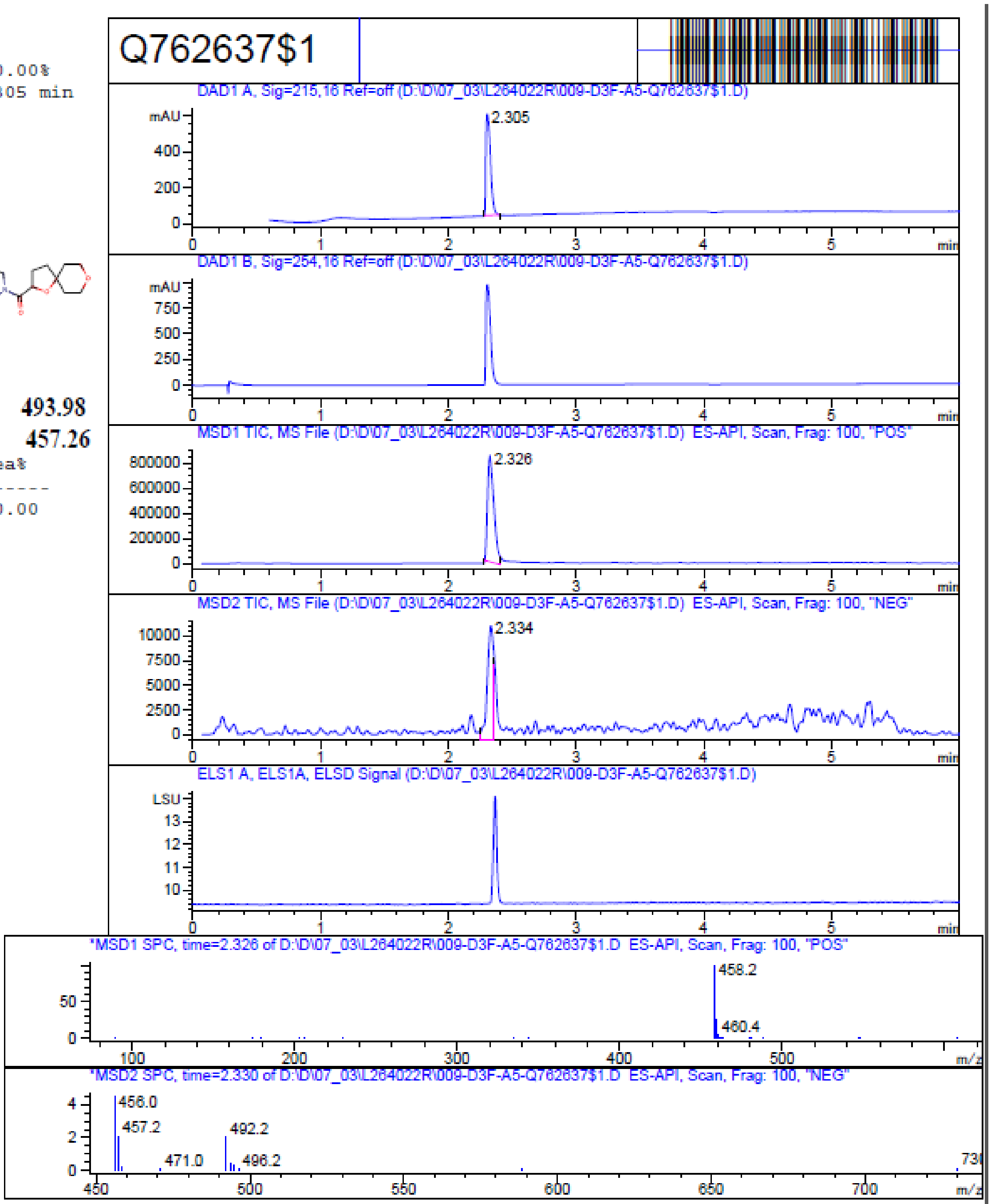
Compound 79

MaxPeak: 100.00%
Ret_Time: 2.305 min



Mol Wt 493.98
Exact Mass 457.26

#	Time	Area%
1	2.305	100.00



RT 2.326

RT 2.334

Crystallographic data (X-Ray)

Crystals of compound **50** suitable for X-Ray diffraction studies were obtained by a low evaporation of a solution in methanol. Diffraction data were collected at room temperature on an Xcallibur-3 diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) operating in the w scans mode. The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the SHELXTL program package. Crystallographic data in this paper have been deposited at Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Structure 50 (CCDC number 2046173)

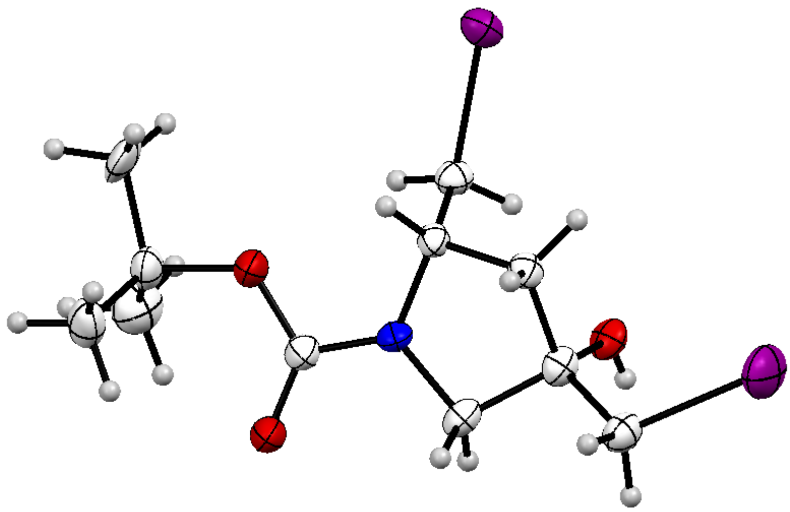


Figure S9. Molecular structure of **50** according to X-ray diffraction data. Thermal ellipsoids are shown at 50% probability level.

Crystal structure determination of 50

data_xr341

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_shelx_SHELXL_version_number '2016/4'

_chemical_formula_moiety 'C11 H19 I2 N O3'

_chemical_formula_sum 'C11 H19 I2 N O3'

_chemical_formula_weight 467.07

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_space_group_IT_number 14

_space_group_name_H-M_alt 'P 21/n'

_space_group_name_Hall '-P 2yn'

_space_group_symop_operation_xyz

_cell_length_a 14.8354(10)

_cell_length_b 5.8785(4)

_cell_length_c 18.7559(12)

_cell_angle_alpha 90

_cell_angle_beta 98.683(4)

_cell_angle_gamma 90

_cell_volume 1616.95(19)

_cell_formula_units_Z 4

_cell_measurement_temperature 173(2)

_cell_measurement_reflns_used 3543

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_cell_measurement_theta_max 24.11

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_exptl_crystal_F_000 888

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_exptl_crystal_size_min 0.040

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_shelx_estimated_absorpt_T_max 0.860

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_exptl_absorpt_correction_T_max 0.7453

_exptl_absorpt_process_details SADABS

_exptl_absorpt_special_details ?

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_diffrn_radiation_wavelength 0.71073

_diffrn_radiation_type MoK\a

_diffrn_source 'sealed tube'

_diffrn_measurement_device_type 'Bruker APEX-II CCD'

_diffrn_measurement_method '\f and \w scans'

_diffrn_reflns_number 10169

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_diffrn_reflns_av_R_equivalents 0.0549

_diffrn_reflns_limit_h_min -18

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_diffrn_reflns_limit_k_min -7

_diffrn_reflns_limit_k_max 6

_diffrn_reflns_limit_l_min -22

_diffrn_reflns_limit_l_max 22

_diffrn_reflns_theta_min 2.197

_diffrn_reflns_theta_max 25.781

_diffrn_reflns_theta_full 25.242

_diffrn_measured_fraction_theta_max 0.993

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_diffrn_reflns_Laue_measured_fraction_full 0.999

_diffrn_reflns_point_group_measured_fraction_max 0.993

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_reflns_number_gt 2443

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_reflns_Friedel_coverage 0.000