Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Practical Synthesis and Divergent Optimization of Halichonine B for the Discovery of Novel Pharmaceutical Leads

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Content

1 General information

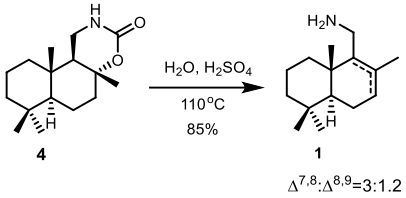
Unless otherwise stated, all solvents and reagents were purchased from commercial sources (Energy or Meryer Chemicals etc.), they were analytically pure and used without further purification. Anhydrous solvents were purchased from commercial sources (Energy Chemicals etc.).

Silica gel GF_{254} and column chromatography silica gel for isolation (200-300 mesh) were both purchased from Qingdao Broadchem Industrial Co., Ltd. Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel GF_{254} with ultraviolet (UV_{254nm} or UV_{365nm}) detection. ^{1}HNMR and ^{13}CNMR spectra were recorded on a Bruker AV 400M or JEOL 500M spectrometers with $CDCl_3$ or CD_3OD as solvent and tetramethylsilane as the internal standard. The chemical shifts (δ) were recorded in parts per million (ppm). Data for ^{1}H NMR are reported as follows: chemical shift (δ: ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet), coupling constant (Hz), integration and assignment (*H*). Data for ^{13}C NMR are reported in terms of chemical shift (δ: ppm). Electrospray ionization high-resolution mass spectrometry (ESI-HRMS) data were also obtained with the Waters XEVO G2-XS Q-TOF mass spectrometer.

The agriculturally important plant pathogens were provided by the College of Plant Protection, Nanjing Agricultural University (Nanjing, China). The *in vitro* antifungal activities were carried out according to the procedures we used previously (Li, D.; Zhang, S.; Song, Z.; Wang, G.; Li, S., Bioactivity-guided mixed synthesis accelerate the serendipity in lead optimization: Discovery of fungicidal homodrimanyl amides. *Eur. J. Med. Chem.* **2017**, 136, 114-121.).

2 Synthesis of drimanyl amine

2.1 Synthesis of amine **1**



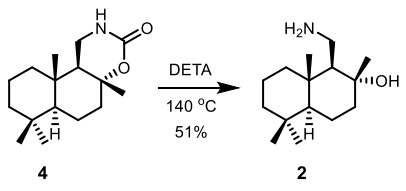
Drimanyl oxazinone **4** was prepared starting from (+)-sclareolide following the previously reported procedure by our group.[1] To a dried flask charged with **4** (776 mg, 3.0 mmol, 1.0 equiv.) was added water (6 mL), concentrated sulfuric acid (20 mL) was then added at 0 °C. The reaction mixture was transferred to a metal bath at 110 °C and stirred for 3 h. The reaction mixture was then adjusted to pH 7-8 with NaOH (50% aqueous solution) and extracted with DCM (50 mL × 3), the combined organic phase was sequentially washed with saturated aqueous NaCl (50 mL × 2), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (200-300 m) with DCM/MeOH (10:1, v/v) as the eluent to give compound **1** (colorless oil, 563.5 mg ($\Delta^{7,8}$: $\Delta^{8,9}$=3:1.2), 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (s, 1H), 3.78 (br, 3.0H), 3.43 (d, J =13.6 Hz, 0.4H), 3.27 (d, J = 13.6 Hz, 0.4H), 2.97 (dd, J = 13.4, 2.4 Hz, 1H), 2.76 (dd, J = 13.5, 6.4 Hz, 1H), 2.07 – 1.95 (m, 2H), 1.93 – 1.89 (m, 1H), 1.87 – 1.82 (m, 2 H), 1.78 (s, 3H), 1.69 (s, 1.2H), 1.68 –1.44 (m, 3.5H), 1.43 – 1.37 (m, 2H), 1.28 – 1.10 (m, 4.8H), 0.95 (s, 1.2H), 0.88 (s, 1.2H), 0.87 (s, 3H), 0.85 (s, 3H), 0.83 (s, 1.2H), 0.78 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 132.6, 132.2, 124.4, 57.0, 51.7, 49.8, 42.2, 41.7, 39.5, 39.4, 38.6, 37.4, 37.1, 36.6, 33.8, 33.4, 33.3, 33.1, 23.8, 22.3, 22.1, 21.7, 20.5, 19.8, 19.0, 18.9, 18.8, 14.4.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{28}N$ 222.22163; Found 222.22113.

2.2 Synthesis of amine **2**



To a dried flask were added oxazinone **4** (2.4 g, 9.0 mmol, 1.0 equiv.) and diethylenetriamine (DETA, 19.3 mL, 180 mmol, 20 equiv.). The reaction mixture was heated to 140 °C, stirred for 24 h and monitored by TLC until the full consumption of oxazinone **4**. The reaction mixture was added water (30 mL), and extracted with the solution of EtOAc/MeOH (30 mL× 3, 10:1, v/v), the combined organic phase was sequentially washed with saturated aqueous NaCl (40 mL × 2), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel (200-300 m) with EtOAc/MeOH (5:1, v/v) as the eluent to give compound **2** (white solid, 1.1 g, 51% yield).

(1*S*,2*R*,4a*S*,8a*S*)-1-(aminomethyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**2**)

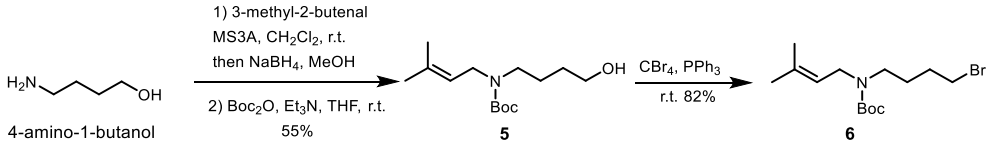
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (br, 3H), 3.18 (dd, J = 12.7, 2.5 Hz, 1H), 2.97 – 2.91 (m, 1H), 1.89 – 1.85 (m, 1H), 1.77 – 1.69 (m, 1H), 1.66 – 1.60 (m, 1H), 1.60 – 1.51 (m, 2H), 1.49 (dd, J = 10.9, 2.5 Hz, 1H), 1.46 – 1.40 (m, 1H), 1.38 – 1.33 (m, 1H), 1.31 (s, 3H), 1.26 – 1.12 (m, 2H), 1.08 – 1.02 (m, 1H), 0.98 (dd, J = 12.2, 2.2 Hz, 1H), 0.86 (s, 3H), 0.77 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 74.3, 59.1, 56.0, 43.8, 41.8, 39.9, 38.3, 37.8, 33.6, 33.4, 24.8, 21.7, 20.1, 18.7, 15.9.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{30}NO$ 240.23219; Found 240.23203.

3 Synthesis of halichonine B (3) and 8-hydroxyl *N*-Boc-halichonine B (11)

tert-butyl (4-bromobutyl)(3-methylbut-2-en-1-yl)carbamate (**6**)



Compound **5** was prepared in an approach according to the previous method.[2] To a stirred solution of 4-amino-1-butanol (1.8 mL, 20 mmol, 1.0 equiv.) in CH_2Cl_2 (110 mL) containing molecular sieves of 3 Å (4 g) was added 3-methyl-2-butenal (2.2 mL, 22 mmol, 1.1 equiv.) at room temperature, and the mixture was stirred at room temperature

for 20 h. The mixture was filtered, and the residue was washed with CH_2Cl_2. Concentration of the filtrate and washings afforded the crude imine intermediate. To a stirred solution of the crude imine intermediate in MeOH (20 mL) was added $NaBH_4$ (1.5 g, 40 mmol, 2.0 equiv.) at 0 °C. After being stirred at room temperature for 30 min, the reaction mixture was diluted with H_2O (80 mL) and extracted with CH_2Cl_2 (60 mL × 3). The combined extracts were washed with brine (60 mL × 2), dried over Na_2SO_4, and filtered. Removal of the solvent afforded the crude amine (2.6 g), which was used for the next reaction without further purification.

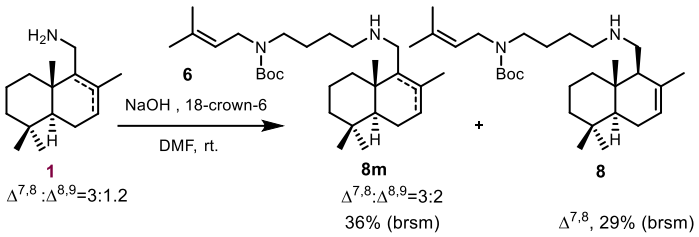
To a stirred solution of the crude amine (2.6 g, 16.5 mmol, 1.0 equiv.) in THF (80 mL) were added Boc_2O (4.2 mL, 18.1 mmol, 1.1 equiv.) and Et_3N (3.6 mL, 26.4 mmol, 1.6 equiv.) at 0 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was diluted with saturated aqueous NH_4Cl (150 mL) and extracted with EtOAc (60 mL × 3). The combined layers were washed with brine (60 mL × 2), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel with petroleum ether /EtOAc (4:1 - 1:1, v/v) to give compound **5** (colorless liquid, 2.8 g, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 – 5.06 (m, 1H), 3.74 (br, 2H), 3.58 (t, J = 6.0 Hz, 2H), 3.14 – 3.10 (m, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.57 – 1.46 (m, 4H), 1.40 (s, 9H).

Compound **5** (343 mg, 1.3 mmol, 1.0 equiv.), triphenylphosphine (682 mg, 2.6 mmol, 2.0 equiv.) and carbon tetrabromide (862 mg, 2.6 mmol, 2.0 equiv.) were dissolved in dry DCM (6 ml) at 0 °C, then allowed to warm to room temperature and stirred overnight. Saturated aqueous $NaHCO_3$ (15 mL) was added and extracted with EtOAc (10 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (200-300 m) with petroleum ether /EtOAc (100:1, v/v) as the eluent to give compound **6** (colorless liquid, 352 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 – 5.12 (m, 1H), 3.79 (d, J = 24.7 Hz, 2H), 3.42 (t, J = 6.7 Hz, 2H), 3.17 (br, 2H), 1.86 – 1.81 (m, 2H), 1.72 (s, 3H), 1.66 (s, 3H), 1.64 – 1.62 (m, 2H), 1.45 (s, 9H).

tert-butyl (3-methylbut-2-en-1-yl)(4-((((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)amino)butyl)carbamate (**8**)



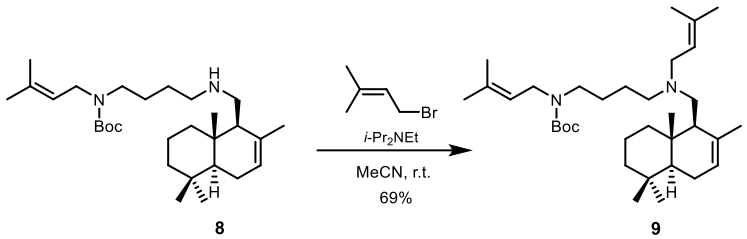
To a stirred solution of amine **1** (176.8 mg, 0.8 mmol, 1.0 equiv.) in anhydrous DMF (4 mL) were added NaOH (32.0 mg, 0.8 mmol, 1.0 equiv.), and 18-crown-6 (105.6 mg, 0.4 mmol, 0.5 eq), and the mixture was stirred at room temperature for 30 min, compound **6** (383.0 mg, 1.2 mmol, 1.5 equiv.) was added at 0 °C. After being stirred at room temperature for 36 h, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (15 mL × 2). The organic layers were washed with brine (15 mL× 2), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (200-300 m) with DCM /EtOAc (3:0-1:1, v/v) as the eluent to give compound **8** (colorless oil, 82 mg), **8m** (colorless oil, 101 mg, $\Delta_{7,8}$:$\Delta_{8,9}$=3:2), and recovery of amine **1** (42 mg, $\Delta_{7,8}$:$\Delta_{8,9}$=3:0.7). The NMR spectra data of compound **8** is in agreement with that in the previous reports.[2]

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 – 5.42 (m, 1H), 5.14 – 5.11 (m, 1H), 3.80 – 3.75 (m, 2H), 3.13 – 3.10 (m, 2H), 2.68 (dd, *J* = 12.2, 2.0 Hz, 1H), 2.65 – 2.60 (m, 1H), 2.55 – 2.50 (m, 1H), 2.46 (dd, *J* = 12.1, 7.3 Hz, 1H), 1.99 – 1.89 (m, 2H), 1.88 – 1.80 (m, 1H), 1.71 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 1.54 – 1.48 (m, 3H), 1.46 – 1.42 (m, 12H (s, 9H)), 1.42 – 1.37 (m, 2H), 1.19 – 1.15 (m, 2H), 1.09 – 1.03 (m, 1H) , 0.86 (s, 3H), , 0.84 (s, 3H), 0.75 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 134.4 (2C), 123.1, 121.3, 79.3, 55.4, 50.2, 50.1, 48.4, 46.2, 44.7, 42.4, 39.5, 36.3, 33.4, 33.1, 28.6 (3C), 27.5, 26.5, 25.9, 23.9, 22.1 (2C), 18.9, 17.9, 14.2.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{53}N_2O_2$ 461.41020; Found 461.40980.

tert-butyl (3-methylbut-2-en-1-yl) (4-((3-methylbut-2-en-1-yl) (((1*S*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)amino)butyl)carbamate (**9**)



8 **9**

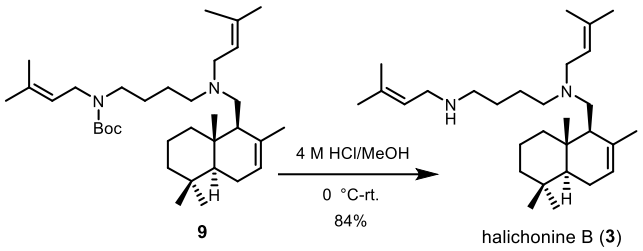
To a stirred solution of amine **8** (152 mg, 0.3 mmol, 1.0 equiv.) in MeCN (3 mL) were added *i*-Pr_2NEt (59 μL, 0.3 mmol, 1.0 equiv.) and 3,3-dimethylallyl bromide (92.6 μL, 0.8 mmol, 2.7 equiv.) at 0 °C. After being stirred at ambient temperature for 15 h, the reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (10 mL × 2). The organic layers were washed with brine (10 mL × 2), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (200-300 m) with DCM /EtOAc (25:1, v/v) as the eluent to give compound **9** (colorless oil, 119.4 mg, 69% yield), the NMR spectra data is in agreement with that in the previous reports.[2]

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 – 5.36 (m, 1H), 5.24 – 5.20 (m, 1H), 5.16 – 5.11 (m, 1H), 3.80 – 3.72 (m, 2H), 3.12 – 3.08 (m, 3H), 2.85 – 2.81 (m, 1H), 2.52 – 2.46 (m, 1H), 2.31 – 2.22 (m, 2H), 2.21 – 2.16 (m, 1H), 2.02 – 1.94 (m, 2H), 1.87 – 1.79 (m, 2H), 1.75 (s, 3H), 1.71 (s, 6H), 1.65 (s, 3H), 1.61 (s, 3H), 1.53 – 1.47 (m, 2H), 1.44 – 1.37 (m, 14H (s, 9H)), 1.21 – 1.13 (m, 2H), 1.02 – 0.96 (m, 1H) , 0.87 (s, 3H) ,0.85 (s, 3H), 0.73 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 136.2, 134.8, 133.9, 122.2, 121.9, 121.2, 79.1, 53.7, 53.3, 51.5, 51.2, 50.2, 46.3, 44.7, 42.3, 39.1, 36.1, 33.3, 33.1, 28.7 (3C), 26.7, 26.0, 25.8, 24.4, 23.7, 22.5, 22.1, 18.9, 18.0, 17.9, 13.7.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{34}H_{61}N_2O_2$ 529.47276; Found 529.47137.

N^1,N^4-bis(3-methylbut-2-en-1-yl)-N^1-(((1*S*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl)butane-1,4-diamine (**3**)



Amine **9** (121 mg, 0.23 mmol) was treated with 4.0 M HCl/MeOH (1 mL) at 0 ℃, and the mixture was stirred at ambient temperature for 2 h. The reaction mixture was concentrated to afford halichonine B HCl salt, The halichonine B HCl salt was purified by column chromatography on Al_2O_3 with DCM/MeOH (10: 1, v/v) as the eluent to give halichonine B (colorless oil, 82 mg, 84% yield).

^{1}H NMR (500 MHz, CD_3OD) δ 5.39 – 5.36 (m, 1H), 5.28 – 5.23 (m, 2H), 3.20 (d, J = 7.0 Hz, 2H), 3.14 (dd, J = 14.2, 6.2 Hz, 1H), 2.89 (dd, J = 14.2, 7.7 Hz, 1H), 2.61 – 2.53 (m, 3H), 2.37 – 2.29 (m, 2H), 2.27 – 2.22 (m, 1H), 2.08 – 2.03 (m, 1H), 2.00 – 1.94 (m, 1H), 1.91 – 1.82 (m, 2H), 1.76 (s, 3H), 1.74 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.60 – 1.56 (m, 1H), 1.55 – 1.51 (m, 1H), 1.51 – 1.44 (m, 4H), 1.44 – 1.40 (m, 1H), 1.24 – 1.17 (m, 2H), 1.07 – 1.00 (m, 1H), 0.90 (s, 3H), 0.87 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 136.9, 136.3, 135.2, 123.1, 123.01, 122.7, 55.0, 54.5, 53.0, 52.3, 51.7, 49.9, 47.6, 43.5, 40.5, 37.4, 34.0, 33.9, 28.4, 26.1, 26.0, 25.8, 24.8, 23.0, 22.5, 19.9, 18.1, 18.0, 14.2.

$[\alpha]_D^5$=+60.0 (c 0.1, MeOH)

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{29}H_{53}N_2$ 429.42030; Found 429.41930.

Comparison tables for halichonine B ^{1}H-NMR and ^{13}C-NMR in CD_3OD

halichonine B 500 MHz	Osamu Ohno's halichonine B[3] 800 MHz	Ichiro Hayakawa's halichonine B[2] 600 MHz
5.39 – 5.36 (m, 1H)	5.34 (s, 1H)	5.36 (m, 1H)
5.28 – 5.23 (m, 2H)	5.22 (m, 1H)	5.28–5.20 (m, 2H)
	5.22 (m, 1H)	

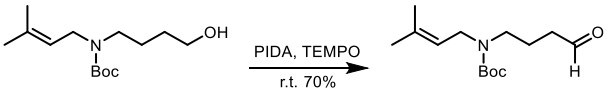
3.20 (d, *J* = 7.0 Hz, 2H)	3.18 (d, *J* = 6.5 Hz, 2H)	3.18 (d, J = 7.0 Hz, 2H)
3.14 (dd, J = 14.2, 6.2 Hz, 1H)	3.11 (dd, *J* = 13.9, 5.7 Hz, 1H)	3.13 (dd, J = 14.1, 6.1 Hz, 1H)
2.89 (dd, J = 14.1, 7.7 Hz, 1H)	2.86 (dd, *J* = 13.9, 7.8 Hz, 1H)	2.88 (dd, J = 14.1, 7.7 Hz, 1H)
2.61 – 2.53 (m, 3H)	2.55-2.52 (m, 3H)	2.59–2.51 (m, 3H)
2.37 – 2.29 (m, 2H)	2.31 (m, 2H)	2.36–2.28 (m, 2H)
2.27 – 2.22 (m, 1H)	2.22 (m, 1H)	2.27–2.20 (m, 1H)
2.08 – 2.03 (m, 1H)	2.03 (m, 1H)	2.04 (br m, 1H)
2.00 – 1.94 (m, 1H)	1.95 (m, 2H)	1.96 (br m, 1H)
1.91 – 1.82 (m, 2H)	1.84 (m, 1H)	1.90–1.80 (m, 2H)
1.76 (s, 3H)	1.74 (s, 3H)	1.75 (s, 3H)
1.74 (s, 3H)	1.74 (s, 3H)	1.73 (s, 3H)
1.72 (s, 3H)	1.70 (s, 3H)	1.71 (s, 3H)
1.67 (s, 3H)	1.68 (s, 3H)	1.66 (s, 3H)
1.65 (s, 3H)	1.63 (s, 3H)	1.64 (s, 3H)
1.60 – 1.56 (m, 1H)	1.55 (m, 1H)	1.61–1.36 (m, 7H)
1.55 – 1.51 (m, 1H)	1.45 (m, 2 H)	
1.51 – 1.44 (m, 4H)	1.43 (m, 2H)	
1.44 – 1.40 (m, 1H)	1.39 (m, 1H)	
	1.38 (m, 1H)	
	1.18 (m, 1H)	
1.24–1.17 (m, 2H)	1.16 (m, 1H)	1.23–1.16 (m, 2H)
1.07–1.00 (m, 1H)	1.01 (m, 1H)	1.03 (ddd, J = 13.1, 13.1, 3.3 Hz, 1H)

0.90 (s, 3H)	0.88 (s, 3H)	0.89 (s, 3H)
0.87 (s, 3H)	0.85 (s, 3H)	0.86 (s, 3H)
0.77 (s, 3H)	0.74 (s, 3H)	0.76 (s, 3H)

halichonine B 126 MHz	Osamu Ohno's halichonine B 100 MHz	Ichiro Hayakawa's halichonine B 150 MHz
14.2	12.8	14.2
18.0	16.7	18.0
18.1	16.7	18.1
19.9	18.5	19.9
22.5	21.1	22.4
23.0	21.6	22.9
24.8	23.5	24.8
25.8	24.3	25.8
26.0	24.6	25.9
26.1	24.7	26.1
28.4	26.2	28.5
33.9	32.5	33.9
34.0	32.6	34.0
37.4	36.1	37.4
40.5	39.2	40.6
43.5	42.2	43.5
47.6	45.8	47.6
49.9	48.0	49.9
51.7	50.4	51.7
52.3	51.0	52.4
53.0	51.7	53.1
54.5	53.0	54.5

55.0	53.6	55.0
122.7	119.0	
123.0	121.5	123.0 (2C)
123.1	121.7	123.1
135.2	134	135.2
136.3	135.4	136.0
136.9	137.4	136.8

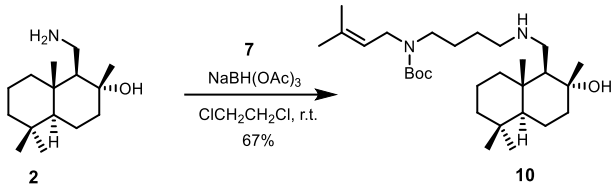
tert-butyl (4-((((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)amino)butyl)(3-methylbut-2-en-1-yl)carbamate (**10**)



5 **7**

To a stirred solution of compound **5** (176 mg, 0.69 mmol, 1.0 equiv.) and 2,2,6,6-tetramethylpiperidinooxy (TEMPO, 11 mg, 0.07 mmol, 0.1 equiv.) in DCM (1 mL) were added (diacetoxyiodo)benzene (PIDA, 243 mg, 0.75 mmol, 1.1 equiv.). The reaction mixture was stirred until the reaction was completely monitored by TLC, and then it was diluted with DCM (15 mL). The mixture was washed with a saturated aqueous solution of $Na_2S_2O_3$ (15 mL) and extracted with DCM (10 mL × 2). The combined organic layers were washed with aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (200-300 m) with petroleum ether /EtOAc (20:1, v/v) as the eluent to give compound **7** (colorless liquid, 123 mg, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 5.11 (s, 1H), 3.84 – 3.69 (m, 2H), 3.15 (s, 2H), 2.42 (t, J = 7.1 Hz, 2H), 1.83 – 1.77 (m, J = 7.2 Hz, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.42 (s, 9H).



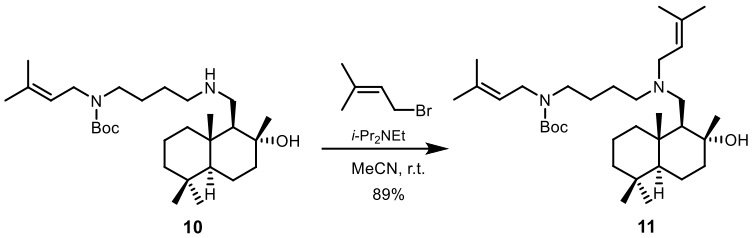
To a schlenk flask containing a stirring bar was charged with amine **2** (741 mg, 3.1 mmol, 1.0 equiv.), aldehyde **7** (794 mg, 3.1 mmol, 1.0 equiv.) and $NaBH(OAc)_3$ (2.6 g, 12.4 mmol, 4.0 equiv.). The flask was evacuated and filled with N_2 (three cycles). Then, anhydrous $ClCH_2CH_2Cl$ (30 mL) was added. The resulting mixture was stirred overnight at room temperature, and quenched with saturated aqueous solution of $NaHCO_3$ (20 mL). The organic layers were separated and the aqueous layers were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (200-300 m) with EtOAc/MeOH (100:1, v/v) as the eluent to give compound **10** (colorless oil, 1.0 g, 67% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (s, 1H), 3.80 – 3.70 (m 2H), 3.15 – 3.08 (m, 2H), 2.93 (dd, J = 12.3, 2.4 Hz, 1H), 2.69 (t, J = 11.9 Hz, 1H), 2.67 – 2.61 (m, 1H), 2.51 – 2.46 (m, 1H), 1.82 – 1.78 (m, 1H), 1.76 – 1.72 (m, 1H), 1.68 (d, J = 1.4 Hz, 3H), 1.62 (s, 3H), 1.61 – 1.53 (m, 2H), 1.50 – 1.47 (m, 2H), 1.47 – 1.45 (m, 1H), 1.41 (s, 11H (s, 9H)), 1.39 – 1.36 (m, 1H), 1.36 – 1.31 (m, 2H), 1.23 (s, 3H), 1.21 – 1.10 (m, 2H), 0.95 – 0.89 (m, 2H), 0.84 (s, 3H), 0.76 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ155.7, 134.4, 121.2, 79.3, 73.5, 58.2, 56.4, 49.7, 46.8, 46.0, 44.7, 43.3, 42.0, 40.2, 37.4, 33.7, 33.5, 28.6 (3C), 27.3, 26.2, 25.9, 25.5, 21.8, 20.0, 18.8, 18.0, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{29}H_{55}N_2O_3$ 479.42070; Found 479.42020.

tert-butyl (4-((((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)(3-methylbut-2-en-1-yl)amino)butyl)(3-methylbut-2-en-1-yl)carbamate (**11**)



Same synthesis procedure as that of compound **9**, the crude product was purified by column chromatography on silica gel column chromatography (200-300 m) with EtOAc as the eluent to give compound **11** (colorless oil, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 – 5.10 (m, 2H), 3.76 (d, J = 27.8 Hz, 2H), 3.24 – 3.17 (m, 1H), 3.17 – 3.05 (m, 2H), 2.83 – 2.78 (m, 1Hz, 1H), 2.72 (t, J = 12.4 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.41 (d, J = 12.9 Hz, 1H), 2.21 – 2.13 (m, 1H), 1.81 – 1.76 (m, 1H), 1.76 – 1.70 (m, 4H (s, 3H)), 1.70 (s, 3H), 1.64 (s, 3H), 1.63 (s, 3H), 1.60 – 1.56 (m, 1H), 1.56 – 1.52 (m, 1H), 1.51 – 1.45 (m, 3H), 1.45 – 1.42 (m, 11H (s, 9H)), 1.41 – 1.33 (m 3H), 1.22 (s, 3H), 1.21 – 1.17 (m, 1H), 1.17 – 1.11 (m, 1H), 0.96 (dd, J = 12.2, 2.1 Hz, 1H), 0.92 – 0.87 (m, 1H), 0.86 (s, 3H), 0.77 (s, 3H), 0.75 (s, 3H).

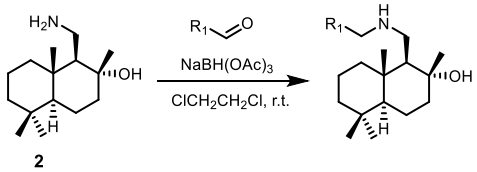
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 135.9, 134.3, 121.2, 120.7, 79.2, 73.4, 56.6, 54.7, 53.9, 51.4 (2C), 46.1, 44.7, 43.4, 42.0, 40.0, 37.3, 33.7, 33.5, 28.6 (3C), 26.6, 26.0, 25.9, 25.3, 24.1, 21.7, 20.0, 18.8, 18.2, 18.0, 15.9.

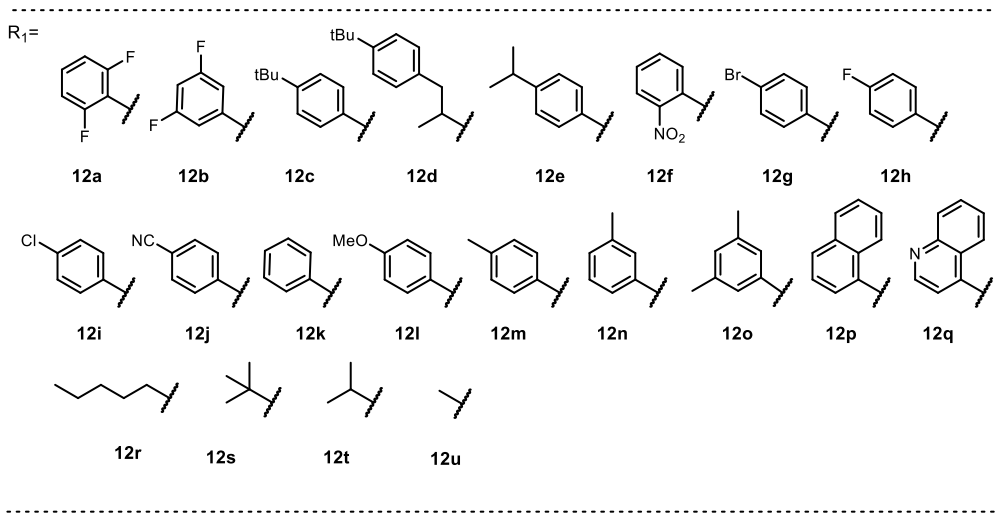
HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{34}H_{63}N_2O_3$ 547.48332; Found 547.48285.

4 Synthesis of halichonine B analogs

4.1 General procedures for the *N*-alkylation of amine **2**

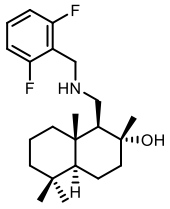
4.1.1 the *N*-mono-alkylation of amine **2**





The analogs **12a**-**12u** can be prepared according to the same synthesis procedure as that of **10**.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((2,6-difluorobenzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12a**)



Yield: 80% **Physical State**: white solid **mp**: 75.5~78.5 ℃

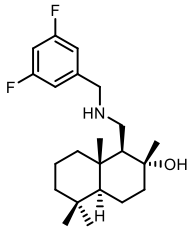
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 1H), 6.90 – 6.84 (m, 2H), 3.86 (s, 2H), 2.95 (dd, *J* = 12.3, 2.5 Hz, 1H), 2.71 (t, *J* = 11.9 Hz, 1H), 1.83 – 1.80 (m, 1H), 1.68 – 1.64 (m, 1H), 1.62– 1.57 (m, 1H), 1.56 – 1.50 (m, 1H), 1.50 – 1.43 (m, 1H), 1.41 – 1.32 (m, 3H), 1.23 – 1.17 (m, 4H (s, 3H)), 1.16 – 1.10 (m, 1H), 0.94 (dd, *J* = 12.1, 2.3 Hz , 2H), 0.86 (s, 3H), 0.77 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8 (d, *J* = 8.2 Hz), 160.9 (d, *J* = 8.4 Hz), 129.3 (t, J = 10.4 Hz), 115.1 (t, J = 19.7 Hz), 111.4 (d, *J* = 6.0 Hz), 111.3 (d, *J* = 6.0 Hz), 73.4, 58.2, 56.3, 45.7, 43.3, 41.9, 40.4, 40.0, 37.5, 33.7, 33.4, 25.4, 21.8, 19.9, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{34}F_2NO$ 366.26030; Found 366.25974.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((3,5-difluorobenzyl)amino)methyl)-2,5,5,8a-

tetramethyldecahydronaphthalen-2-ol (**12b**)



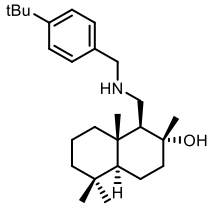
Yield: 69% **Physical State**: white solid **mp**: 92.6~94.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 – 6.80 (m, 2H), 6.71 – 6.67 (m, 1H), 3.83 (d, *J* = 13.7 Hz, 1H), 3.66 (d, *J* = 13.4 Hz, 1H), 2.97 (dd, *J* = 12.1, 2.3 Hz, 1H), 2.74 (t, *J* = 11.9 Hz, 1H), 1.88 – 1.83 (m, 1H), 1.78 – 1.72 (m, 1H), 1.66 – 1.60 (m, 1H), 1.59 – 1.53 (m, 1H), 1.53 – 1.46 (m, 1H), 1.46 – 1.34 (m, 3H), 1.25 – 1.18 (m, 4H (s, 1H)), 1.18 – 1.12 (m, 1H), 0.99 – 0.92 (m, 2H), 0.87 (s, 3H), 0.78 (s, 3H), 0.75 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2 (d, *J* = 12.4 Hz), 162.2 (d, *J* = 12.4 Hz), 143.4 (t, J = 8.5 Hz), 111.1 (d, *J* = 6.0 Hz), 110.9 (d, *J* = 6.0 Hz), 102.8 (t, *J* = 25.3 Hz), 73.7, 58.6, 56.3, 53.4, 46.4, 43.3, 41.9, 40.2, 37.6, 33.7, 33.5, 25.4, 21.7, 20.0, 18.8, 15.9.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{34}F_2NO$ 366.26030; Found 366.25974.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((4-(*tert*-butyl)benzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12c**)



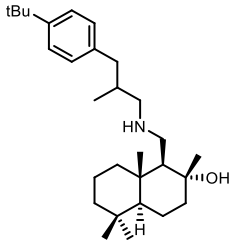
Yield: 80% **Physical State**: colorless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.32 (m, 2H), 7.23 – 7.20 (m, 2H), 3.81 (d, *J* = 12.9 Hz, 1H), 3.64 (d, *J* = 12.8 Hz, 1H), 3.02 (dd, *J* = 12.3, 2.4 Hz, 1H), 2.78 (t, *J* = 11.9 Hz, 1H), 1.86 – 1.83 (m, 1H), 1.79 – 1.75 (m, 1H), 1.65 – 1.60 (m, 1H), 1.60 – 1.54 (m, 1H), 1.53 – 1.46 (m, 1H), 1.44 – 1.40 (m, 2H), 1.40 – 1.34 (m, 1H), 1.30 (s, 9H), 1.22 (s, 3H), 1.21 – 1.19 (m, 1H), 1.18 – 1.13 (m, 1H), 1.00 – 0.93 (m, 2H), 0.88 (s, 3H), 0.79 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 136.3, 128.1, 125.5, 73.6, 58.3, 56.3, 53.7, 46.3, 43.3, 41.9, 40.2, 37.5, 34.6, 33.7, 33.4, 31.5, 25.4, 21.7, 19.9, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{26}H_{44}NO$ 386.34174; Found 386.34082.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((3-(4-(*tert*-butyl)phenyl)-2-methylpropyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12d**)



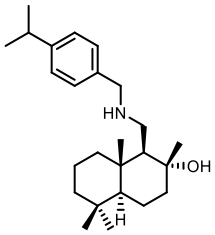
Yield: 55% **Physical State**: colorless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.29 (m, 2H), 7.09 – 7.07 (m, 2H), 7.07 – 7.05 (m, 2H), 7.07 – 7.05 (m, 2H), 2.97 – 2.91 (m, 2H), 2.70 (t, J = 11.8 Hz, 1H), 2.68 – 2.58 (m, 4H), 2.54 – 2.46 (m, 2H), 2.41 – 2.30 (m, 3H), 1.94 – 1.84 (m, 3H), 1.84 – 1.82 (m, 1H), 1.79 – 1.73 (m, 2H), 1.65 – 1.61 (m, 2H), 1.60 – 1.53 (m, 2H), 1.52 – 1.45 (m, 2H), 1.45 – 1.40 (m, 2H), 1.40 – 1.34 (m, 4H), 1.31 (s, 18H), 1.28 (s, 3H), 1.27 (s, 3H), 1.26 – 1.20 (m, 2H), 1.18 – 1.14 (m, 2H), 0.97 – 0.96 (m, 2H), 0.95 – 0.93 (m, 2H), 0.91 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H), 0.87 (s, 6H), 0.79 (s, 6H), 0.77 – 0.76 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 137.6, 137.5, 128.9, 125.2, 73.5, 73.4, 58.5, 58.2, 56.3, 56.1, 47.1, 47.0, 43.3, 41.9, 41.7, 41.0, 40.1, 37.4, 35.3, 35.1, 34.4, 33.7, 33.4, 31.5, 25.5, 25.5, 21.7, 20.0, 18.8, 18.3, 18.2, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{29}H_{50}NO$ 428.38869; Found 428.38831.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((4-isopropylbenzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12e**)



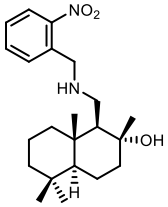
Yield: 67% **Physical State**: colorless oil

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.19 (m, 2H), 7.18 – 7.15 (m, 2H), 3.80 (d, *J* = 12.8 Hz, 1H), 3.64 (d, *J* = 12.8 Hz, 1H), 3.01 (dd, *J* = 12.3, 2.4 Hz, 1H), 2.90 – 2.85 (m, 1H), 2.77 (t, *J* = 11.9 Hz, 1H), 1.86 – 1.82 (m, 1H), 1.79 – 1.74 (m, 1H), 1.65 – 1.59 (m, 1H), 1.59 – 1.52 (m, 1H), 1.52 – 1.46 (m, 1H), 1.45 – 1.40 (m, 2H), 1.40 – 1.34 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H), 1.22 (s, 3H), 1.21 – 1.13 (m, 2H), 0.99 – 0.93 (m, 2H), 0.87 (s, 3H), 0.78 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.0, 136.6, 128.4, 126.6, 73.5, 58.2, 56.3, 53.7, 46.2, 43.3, 41.9, 40.1, 37.4, 33.9, 33.7, 33.4, 25.4, 24.1, 21.7, 19.9, 18.8, 15.9.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{25}H_{42}NO$ 372.32609; Found 372.32553.

(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1-(((2-nitrobenzyl)amino)methyl)decahydronaphthalen-2-ol (**12f**)



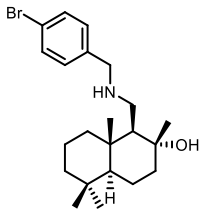
Yield: 48% **Physical State**: yellow solid **mp**: 80.9~83.0 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.42 (m, 1H), 4.02 (d, *J* = 13.6 Hz, 1H), 3.92 (d, *J* = 13.7 Hz, 2H (br, 1H)), 3.03 (dd, *J* = 12.3, 2.4 Hz, 1H), 2.82 (t, *J* = 11.8 Hz, 1H), 1.85 – 1.82 (m, 1H), 1.76 – 1.71 (m, 1H), 1.63 – 1.60 (m, 1H), 1.58 – 1.51 (m, 1H), 1.52 – 1.33 (m, 3H), 1.39 – 1.33 (m, 1H), 1.26 (s, 3H), 1.23 – 1.18 (m, 1H), 1.18 – 1.11 (m, 1H), 1.00 – 0.93 (m, 2H), 0.86 (s, 3H), 0.77 (s, 3H) , 0.76 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 134.2, 133.6, 131.9, 128.6, 125.0, 73.6, 58.3, 56.3, 50.8, 46.6, 43.3, 41.9, 40.1, 37.6, 33.7, 33.4, 25.4, 21.7, 19.9, 18.7, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{35}N_2O_3$ 375.26422; Found 375.26376.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((4-bromobenzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12g**)



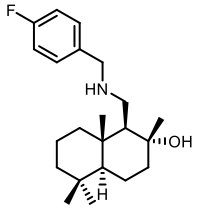
Yield: 68% **Physical State**: white solid **mp**: 123.9~124.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.19 – 7.14 (m, 2H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.61 (d, *J* = 13.2 Hz, 1H), 2.97 (dd, *J* = 12.2, 2.3 Hz, 1H), 2.73 (t, *J* = 11.8 Hz, 1H), 1.86 – 1.82 (m, 1H), 1.77 – 1.73 (m, 1H), 1.65 – 1.59 (m, 1H), 1.60 – 1.52 (m, 1H), 1.52 – 1.45 (m, 1H), 1.45 – 1.34 (m, 3H), 1.24 – 1.18 (m, 4H (s, 3H)), 1.18 – 1.12 (m, 1H), 0.98 – 0.91 (m, 2H), 0.87 (s, 3H), 0.78 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 131.7, 130.1, 121.2, 73.6, 58.5, 56.3, 53.5, 46.3, 43.3, 41.9, 40.2, 37.5, 33.7, 33.5, 25.5, 21.7, 19.9, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{35}BrNO$ 408.18965; Found 408.18912.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((4-fluorobenzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12h**)



Yield: 46% **Physical State**: white solid **mp**: 92.3~93.5 ℃

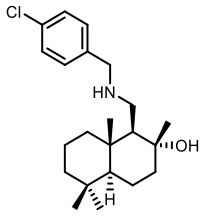
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 2H), 7.00 – 6.95 (m, 2H), 3.81 (d, *J* = 12.9 Hz, 1H), 3.61 (d, *J* = 12.9 Hz, 1H), 2.97 (dd, *J* = 12.2, 2.4 Hz, 1H), 2.73 (t, *J* = 11.8 Hz, 1H), 1.84 – 1.81 (m, 1H), 1.76 – 1.72 (m, 1H), 1.64 – 1.58 (m, 1H), 1.58 – 1.51 (m, 1H), 1.50 – 1.44 (m, 1H), 1.44 – 1.38 (m, 2H), 1.38 – 1.33 (m, 1H), 1.22 –

1.16 (m, 4H (s, 3H)), 1.16 – 1.10 (m, 1H), 0.97 – 0.91 (m, 2H), 0.86 (s, 3H), 0.77 (s, 3H), 0.73 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2 (d, J = 245.3 Hz), 135.0 (d, J = 3.2 Hz), 130.0 (d, J = 7.9 Hz), 115.4 (d, J = 21.5 Hz), 73.6, 58.4, 56.3, 53.3, 46.1, 43.2, 41.9, 40.2, 37.5, 33.7, 33.4, 25.4, 21.7, 19.9, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{35}FNO$ 348.26972; Found 348.26932.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((4-chlorobenzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12i**)



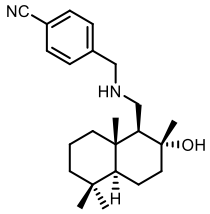
Yield: 68% **Physical State**: white solid **mp**: 127.8~128.6 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 7.24 – 7.21 (m, 2H), 3.82 (d, J = 13.1 Hz, 1H), 3.63 (d, J = 13.1 Hz, 1H), 2.98 (dd, J = 12.3, 2.4 Hz, 1H), 2.73 (t, J = 11.8 Hz, 1H), 1.86 – 1.82 (m, 1H), 1.77 – 1.73 (m, 1H), 1.64 – 1.60 (m, 1H), 1.59 – 1.52 (m, 1H), 1.52 – 1.45 (m, 1H), 1.44 – 1.39 (m, 2H), 1.39 – 1.35 (m, 1H), 1.23 – 1.18 (m, 4H (s, 3H)), 1.18 – 1.12 (m, 1H), 0.98 – 0.92 (m, 2H), 0.87 (s, 3H), 0.78 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 133.1, 129.8, 128.8, 73.6, 58.5, 56.3, 53.4, 46.3, 43.3, 41.9, 40.2, 37.5, 33.7, 33.5, 25.5, 21.7, 20.0, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{35}ClNO$ 364.24017; Found 364.23981.

4-(((((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)amino)methyl)benzonitrile (**12j**)



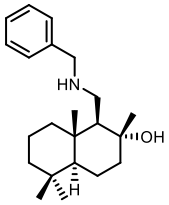
Yield: 66% **Physical State**: white solid **mp**: 146.7~147.1 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.58 (m, 2H), 7.42 – 7.39 (m, 2H), 3.92 (d, *J* = 13.8 Hz, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 2.98 (dd, *J* = 12.2, 2.3 Hz, 1H), 2.73 (t, *J* = 11.7 Hz, 1H), 1.85 – 1.81 (m, 1H), 1.75 – 1.71 (m, 1H), 1.64 – 1.59 (m, 1H), 1.55 (m, 1H), 1.50 – 1.43 (m, 1H), 1.43 – 1.39 (m, 2H), 1.39 – 1.33 (m, 1H), 1.25 – 1.19 (m, 1H), 1.18 (s, 3H), 1.17 – 1.10 (m, 1H), 0.98 – 0.91 (m, 2H), 0.86 (s, 3H), 0.77 (s, 3H), 0.73 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 132.4, 129.0, 118.9, 111.3, 73.7, 58.6, 56.3, 53.7, 46.5, 43.2, 41.8, 40.2, 37.5, 33.6, 33.4, 25.4, 21.7, 19.9, 18.7, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{23}H_{35}N_2O$ 355.27439; Found 355.27390.

(1*S*,2*R*,4a*S*,8a*S*)-1-((benzylamino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12k**)



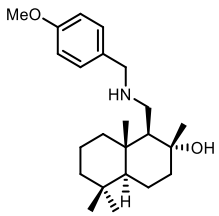
Yield: 61% **Physical State**: white solid **mp**: 154.5~156.5 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.52 (m, 2H), 7.47 – 7.34 (m, 3H), 4.28 (d, *J* = 13.4 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.07 – 2.96 (m, 2H), 1.94 – 1.86 (m, 2H), 1.64 – 1.53 (m, 2H), 1.52 – 1.40 (m, 3H), 1.36 – 1.29 (m, 1H), 1.20 – 1.06 (m, 6H (s, 3H)), 0.96 (dd, *J* = 12.2, 2.0 Hz, 1H), 0.83 (s, 3H), 0.72 (s, 3H), 0.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 131.0, 130.1, 129.5, 129.4, 75.1, 55.8, 55.4, 51.4, 43.9 (2C), 41.4, 39.3, 38.0, 33.4 (2C), 23.8, 21.6, 20.2, 18.5, 16.0.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{36}NO$ 330.27914; Found 330.27869.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((4-methoxybenzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12l**)



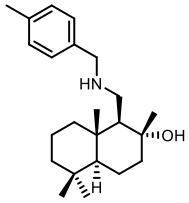
Yield: 50% **Physical State**: white solid **mp**: 240.3~240.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 2H), 6.86 – 6.82 (m, 2H), 3.80 – 3.77 (m, 4H (s, 3H)), 3.59 (d, J = 12.8 Hz, 1H), 2.98 (dd, J = 12.3, 2.4 Hz, 1H), 2.74 (t, J = 11.9 Hz, 1H), 1.85 – 1.81 (m, 1H), 1.77 – 1.72 (m, 1H), 1.63 – 1.59 (m, 1H), 1.58 – 1.45 (m, 2H), 1.42 – 1.39 (m, 2H), 1.38 – 1.33 (m, 1H), 1.24 – 1.17 (m, 4H (s, 3H)), 1.16 – 1.11 (m, 1H), 0.98 – 0.92 (m, 2H), 0.86 (s, 3H), 0.77 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 131.4, 129.6, 113.9, 73.6, 58.2, 56.3, 55.4, 53.4, 46.0, 43.3, 41.9, 40.1, 37.5, 33.7, 33.4, 25.4, 21.7, 19.9, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{23}H_{38}NO_2$ 360.28971; Found 360.28867.

(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1-(((4-methylbenzyl)amino)methyl)decahydronaphthalen-2-ol (**12m**)



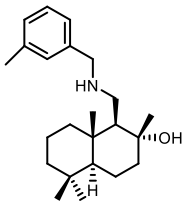
Yield: 77% **Physical State**: white solid **mp**: 75.2~76.5 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 7.7 Hz, 2H), 4.23 (d, J = 13.3 Hz, 1H), 3.94 (d, J = 13.3 Hz, 1H), 2.99 (m, 2H), 2.31 (s, 3H), 1.92 – 1.88 (m, 2H), 1.62 – 1.54 (m, 2H), 1.51 – 1.43 (m, 2H), 1.42 – 1.39 (m, 1H), 1.33 – 1.27 (m, 1H), 1.17 – 1.15 (m, 1H), 1.15 – 1.10 (m, 4H (s, 3H)), 1.10 – 1.06 (m, 1H), 0.96 (dd, J = 12.3, 1.9 Hz, 1H), 0.81 (s, 3H), 0.71 (s, 3H), 0.64 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 130.1, 130.0, 127.6, 75.1, 55.6, 55.4, 50.9, 43.9, 43.6, 41.4, 39.2, 38.0, 33.4 (2C), 23.7, 21.5, 21.4, 20.1, 18.4, 16.0.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{23}H_{38}NO$ 344.29479; Found 344.29425.

(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1-(((3-methylbenzyl)amino)methyl)decahydronaphthalen-2-ol (**12n**)



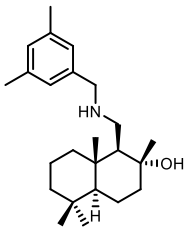
Yield: 45% **Physical State**: white solid **mp**: 235.5~237.2 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, J = 7.5 Hz, 1H), 7.14 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 3.88 (d, J = 13.0 Hz, 1H), 3.68 (d, J = 13.0 Hz, 1H), 3.02 (dd, J = 12.3, 2.3 Hz, 1H), 2.80 (t, J = 11.9 Hz, 1H), 2.33 (s, 3H), 1.87 – 1.83 (m, 1H), 1.74 – 1.70 (m, 1H), 1.65 – 1.60 (m, 1H), 1.59 – 1.53 (m, 1H), 1.52 – 1.47 (m, 2H), 1.44 – 1.40 (m, 1H), 1.38 – 1.34 (m, 1H), 1.25 – 1.18 (m, 4H (s, 3H)), 1.18 – 1.13 (m, 1H), 1.02 – 0.95 (m, 2H), 0.87 (s, 3H), 0.77 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 137.9, 129.4, 128.6, 128.5, 125.7, 73.9, 57.9, 56.2, 53.6, 46.0, 43.4, 41.8, 40.0, 37.6, 33.7, 33.5, 25.2, 21.7, 21.5, 20.0, 18.8, 15.9.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{23}H_{38}NO$ 344.29479; Found 344.29404.

(1*S*,2*R*,4a*S*,8a*S*)-1-(((3,5-dimethylbenzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12o**)



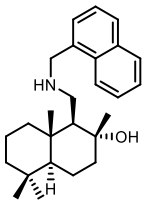
Yield: 41% **Physical State**: white solid **mp**: 163.6~164.5 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (s, 1H), 7.07 (d, J = 1.3 Hz, 2H), 5.62 (br, 2H), 3.90 (d, J = 13.1 Hz, 1H), 3.69 (d, J = 13.1 Hz, 1H), 2.99 (dd, J = 12.5, 2.2 Hz, 1H), 2.81 (t, J = 11.8 Hz, 1H), 2.22 (s, 3H), 2.20 (s, 3H), 1.86 – 1.82 (m, 1H), 1.67 – 1.63 (m, 1H), 1.62 – 1.56 (m, 2H), 1.56 – 1.47 (m, 2H), 1.43 – 1.37 (m, 1H), 1.36 – 1.30 (m, 1H), 1.21 – 1.15 (m, 4H (s, 3H)), 1.15 – 1.10 (m, 1H), 1.03 – 0.97 (m, 1H), 0.95 (dd, J = 12.1, 2.1 Hz, 1H), 0.84 (s, 3H), 0.74 (s, 3H), 0.70 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.0, 136.3, 133.6, 130.1, 130.0, 126.2, 74.0, 57.2, 55.9, 52.6, 45.3, 43.4, 41.7, 39.8, 37.6, 33.5, 33.3, 24.8, 21.6, 19.9, 19.7, 19.5, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{24}H_{40}NO$ 358.31044; Found 358.30988.

(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1-(((naphthalen-1-ylmethyl)amino)methyl)decahydronaphthalen-2-ol (**12p**)



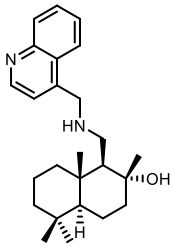
Yield: 66% **Physical State**: white solid **mp**: 163.1~167.6 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.79 (m, 3H), 7.72 (s, 1H), 7.48 – 7.42 (m, 3H), 4.03 (d, J = 12.3 Hz, 1H), 3.84 (d, J = 13.2 Hz, 1H), 3.04 (dd, J = 12.2, 2.4 Hz, 1H), 2.80 (t, J = 11.9 Hz, 1H), 1.88 – 1.84 (m, 1H), 1.78 – 1.74 (m, 1H), 1.65 – 1.60 (m, 1H), 1.60 – 1.54 (m, 1H), 1.53 – 1.45 (m, 2H), 1.45 – 1.34 (m, 2H), 1.26 – 1.19 (m, 4H (s, 3H)), 1.19 – 1.13 (m, 1H), 1.01 – 0.94 (m, 2H), 0.88 (s, 3H), 0.78 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.7, 133.4, 132.9, 128.4, 127.8, 127.8, 126.9, 126.6, 126.2, 125.9, 73.6, 58.4, 56.3, 54.2, 46.3, 43.3, 41.9, 40.2, 37.5, 33.7, 33.4, 25.5, 21.7, 20.0, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{26}H_{38}NO$ 380.29479; Found 380.29416.

(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1-(((quinolin-4-ylmethyl)amino)methyl)decahydronaphthalen-2-ol (**12q**)



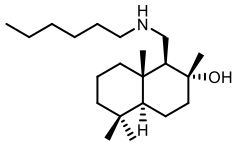
Yield: 32% **Physical State**: white solid **mp**: 125.6~126.0 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 4.4 Hz, 1H), 8.13 (dd, J = 8.5, 1.3 Hz, 1H), 8.02 (dd, J = 8.5, 1.4 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.61 – 7.57 (m, 1H), 7.37 (d, J = 4.4 Hz, 1H), 4.32 (d, J = 14.3 Hz, 1H), 4.18 (d, J = 14.2 Hz, 1H), 3.11 (dd, J = 12.2, 2.4 Hz, 1H), 2.88 (t, J = 11.8 Hz, 1H), 1.87 – 1.82 (m, 1H), 1.81 – 1.75 (m, 1H), 1.66 – 1.55 (m, 2H), 1.54 – 1.48 (m, 1H), 1.49 – 1.44 (m, 2H), 1.41 – 1.35 (m, 1H), 1.22 (s, 3H), 1.21 – 1.12 (m, 2H), 1.02 – 0.94 (m, 2H), 0.87 (s, 3H), 0.79 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 148.4, 144.6, 130.4, 129.5, 127.0, 126.9, 123.1, 120.2, 73.6, 58.8, 56.3, 50.4, 47.1, 43.2, 41.9, 40.3, 37.6, 33.7, 33.5, 25.4, 21.7, 20.0, 18.8, 15.9.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{25}H_{37}N_2O$ 381.29004; Found 381.28953.

(1*S*,2*R*,4a*S*,8a*S*)-1-((hexylamino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12r**)



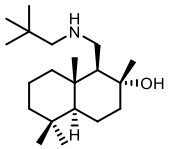
Yield: 37% **Physical State**: white solid **mp**: 166~170.8 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 – 2.06 (m, 2H), 3.04 – 2.95 (m, 1H), 2.88 – 2.81 (m, 1H), 1.96 – 1.89 (m, 2H), 1.86 – 1.79 (m, 2H), 1.70 – 1.60 (m, 3H), 1.60 – 1.52 (m, 1H), 1.52 – 1.43 (m, 1H), 1.39 – 1.35 (m, 1H), 1.34 (m, 5H (s, 3H)), 1.31 – 1.25 (m, 4H), 1.24 – 1.17 (m, 2H), 1.17 – 1.12 (m 1H), 1.01 (dd, J = 12.3, 2.0 Hz, 1H), 0.88 – 0.83 (m, 6H (s, 3H)), 0.75 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 75.0, 55.7, 55.5, 48.5, 45.7, 43.8, 41.4, 39.5, 38.0, 33.4, 33.4, 31.3, 26.5, 26.2, 24.0, 22.6, 21.6, 20.2, 18.5, 16.1, 14.1.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{21}H_{42}NO$ 324.32547; Found 324.32609.

(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1-((neopentylamino)methyl)decahydronaphthalen-2-ol (**12s**)



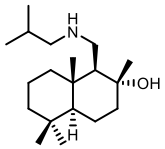
Yield: 73% **Physical State**: white solid **mp**: 89.5~91.5 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.97 (dd, J = 12.3, 2.4 Hz, 1H), 2.70 (t, J = 12.0 Hz, 1H), 2.46 (d, J = 11.2 Hz, 1H), 2.19 (d, J = 11.2 Hz, 1H), 1.84 – 1.80 (m, 1H), 1.78 – 1.74 (m, 1H), 1.63 – 1.58 (m, 1H), 1.58 – 1.52 (m, 1H), 1.51 – 1.44 (m, 1H), 1.44 – 1.33 (m, 3H), 1.25 (s, 3H), 1.23 – 1.17 (m, 1H), 1.17 – 1.11 (m, 1H), 0.99 – 0.92 (m, 2H), 0.88 (s, 9H), 0.86 (s, 3H), 0.77 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 73.4, 62.8, 58.1, 56.3, 47.7, 43.3, 42.0, 40.2, 37.4, 33.7, 33.4, 31.3, 27.9, 25.5, 21.7, 20.0, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{20}H_{40}NO$ 310.31044; Found 310.31003.

(1*S*,2*R*,4a*S*,8a*S*)-1-((isobutylamino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12t**)



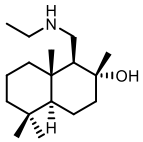
Yield: 37% **Physical State**: white solid **mp**: 163.3~65.2 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.21 – 3.07 (m, 2H), 2.94 – 2.89 (m, 1H), 2.64 – 2.59 (m, 1H), 2.24 – 2.17 (m, 1H), 1.99 – 1.94 (m, 2H), 1.70 – 1.61 (m, 3H), 1.60 – 1.45 (m, 2H), 1.39 – 1.31 (m, 4H (s, 3H), 1.28 – 1.10 (m, 3H), 1.10 – 1.00 (m, 7H), 0.86 (s, 3H), 0.76 (s, 3H), 0.76 (s, 3H).

13C NMR (101 MHz, $CDCl_3$) δ 75.4, 55.5, 55.0, 46.3, 43.8, 41.5, 39.5, 37.9, 33.5, 33.4, 25.9, 24.1, 21.6, 20.5, 20.4, 20.2, 18.5, 16.1.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{19}H_{38}NO$ 296.29479; Found 296.29425.

(1*S*,2*R*,4a*S*,8a*S*)-1-((ethylamino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**12u**)



Yield: 56% **Physical State**: white solid **mp**: 240.3~240.4 ℃

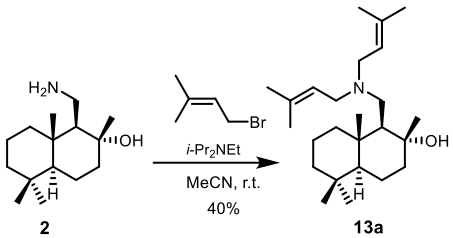
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (br, 1H), 8.70 (br, 1H), 3.15 – 3.05 (m, 3H), 3.02 – 2.96 (m, 1H), 1.95 – 1.91 (m, 1H), 1.89 (dd, J = 9.5, 2.6 Hz, 1H), 1.69 – 1.63 (m, 2H), 1.62 – 1.59 (m, 1H), 1.57 – 1.50 (m, 1H), 1.50 – 1.44 (m, 1H), 1.42 (t, J = 7.2 Hz, 3H), 1.36 – 1.33 (m, 4H (s, 3H)), 1.23 – 1.11 (m, 3H), 0.99 (dd, J = 12.3, 2.0 Hz, 1H), 0.84 (s, 3H), 0.75 (s, 3H), 0.74 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 74.9, 55.8, 55.5, 45.1, 43.8, 43.4, 41.4, 39.5, 38.0, 33.4 (2C), 24.0, 21.5, 20.2, 18.5, 16.1, 11.7.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{17}H_{34}NO$ 268.26349; Found 268.26312.

4.1.2 the *N*-double alkylation of amine **2**

(1*S*,2*R*,4a*S*,8a*S*)-1-((bis(3-methylbut-2-en-1-yl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**13a**)



To a stirred solution of amine **2** (60.0 mg, 0.25 mmol, 1.0 equiv.) in MeCN (2 mL) were added *i*-Pr_2NEt (48.0 μL, 0.27 mmol, 1.1 equiv.) and 3,3-dimethylallyl bromide (70.0 μL, 0.6 mmol, 2.4 equiv.) at 0 °C. After being stirred at ambient temperature for 15 h, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL × 2). The organic layers were washed with brine (10 mL × 2), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel column chromatography (200-300 m) with ether /EtOAc (3:1, v/v) as the eluent to give compound **13a** (colorless oil, 37.5 mg, 40% yield).

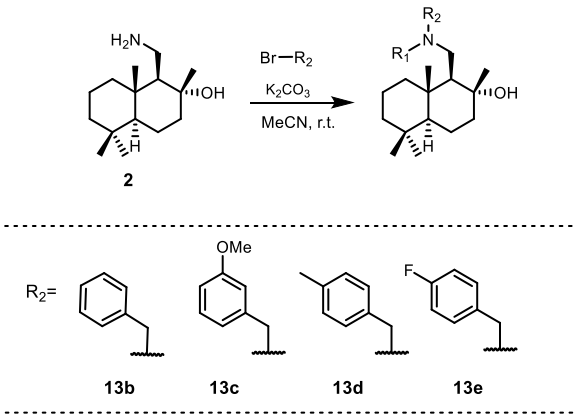
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (s, 2H), 3.22 (d, J = 13.7 Hz, 2H), 2.76 (t, J = 12.3 Hz, 3H), 2.39 (d, J = 12.9 Hz, 1H), 1.82 – 1.78 (m, 1H), 1.77 – 1.75 (m, 1H), 1.72 (s,

6H), 1.62 (s, 6H), 1.61 – 1.52 (m, 3H), 1.49 – 1.46 (m, 1H), 1.45 – 1.39 (m, 1H), 1.38 – 1.33 (m, 1H), 1.22 (s, 3H), 1.21 – 1.16 (m, 1H), 1.16 – 1.12 (m, 1H), 0.97 – 0.94 (m, 1H), 0.90 (dd, *J* = 13.1, 4.1 Hz, 1H), 0.86 (s, 3H), 0.78 (s, 3H), 0.75 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 135.9, 121.2, 73.5, 56.6, 54.7, 51.5, 50.7, 43.4, 42.0, 39.9, 37.3, 33.7, 33.5, 26.0, 25.1, 21.8, 20.0, 18.8, 18.1, 15.9.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{25}H_{46}NO$ 376.35739; Found 376.35687.

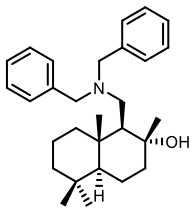
Synthesis of **13b** – **13e**



To a stirred solution of amine **2** (78 mg, 0.3 mmol, 1.0 equiv.) in CH_3CN (1.5 mL) were added K_2CO_3 (45.6 mg, 0.33 mmol, 1.1 equiv.) and added dropwise benzyl bromide (71 μL, 0.6 mmol, 2.0 equiv.) via a syringe. After being stirred at room temperature for 24 h, the reaction mixture was filtered, and concentrated. The crude product was purified by column chromatography on silica gel (200-300 m) with petroleum ether /EtOAc (7:1, v/v) as the eluent to give compound **13b**.

The analogs **13c** – **13e** can be prepared according to the similar treatment described above.

(1*S*,2*R*,4a*S*,8a*S*)-1-((dibenzylamino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**13b**)



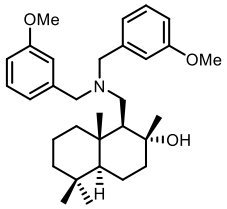
Yield: 46% **Physical State**: white solid **mp**: 109.5~110.9 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.32 (m, 2H), 7.32 – 7.30 (m, 5H), 7.29 (s, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.26 – 7.23 (m, 2H), 4.09 (d, *J* = 12.9 Hz, 2H), 2.94 (d, *J* = 12.9 Hz, 2H), 2.90 (dd, *J* = 13.0, 11.7 Hz, 1H), 2.42 (dd, *J* = 13.0, 2.0 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.76 – 1.71 (m, 2H), 1.61 – 1.56 (m, 2H), 1.55 – 1.48 (m, 1H), 1.46 – 1.42 (m, 1H), 1.39 – 1.34 (m, 1H), 1.20 – 1.08 (m, 2H), 1.02 – 0.95 (m, 2H), 0.86 (s, 3H), 0.76 (s, 3H), 0.67 (s, 3H), 0.59 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 130.0, 128.6, 127.5, 73.6, 59.1, 56.6, 54.7, 51.1, 43.2, 42.0, 40.0, 37.4, 33.7, 33.5, 24.4, 21.7, 20.0, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{29}H_{42}NO$ 420.32609; Found 420.32529.

(1*S*,2*R*,4a*S*,8a*S*)-1-((bis(3-methoxybenzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**13c**)



Yield: 44% **Physical State**: colorless oil

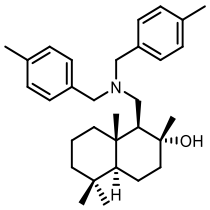
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.8 Hz, 2H), 7.13 (br, 1H), 6.91 (d, *J* = 6.9 Hz, 2H), 6.85 – 6.83 (m, 2H), 6.81 – 6.78 (m, 2H), 4.06 (d, *J* = 13.0 Hz, 2H), 3.79 (s, 6H), 2.94 (d, *J* = 12.9 Hz, 2H), 2.90 – 2.86 (m, 1H), 2.41 (dd, *J* = 13.0, 1.9 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.79 – 1.75 (m, 1H), 1.72 (dd, *J* = 11.6, 1.9 Hz, 1H),1.62 – 1.56 (m, 2H), 1.53 – 1.49 (m, 1H), 1.48 – 1.40 (m, 1H), 1.40 – 1.34 (m, 1H), 1.21 – 1.08 (m, 2H), 1.02 – 0.93 (m, 2H), 0.76 (s, 3H) , 0.79 (s, 3H) , 0.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 139.5, 129.5, 122.0, 115.1, 113.2, 73.7, 59.1, 56.5, 55.3, 54.7, 51.3, 43.2, 41.9, 39.9, 37.4, 33.6, 33.4, 24.5, 21.65, 19.9, 18.7, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{31}H_{46}NO_3$ 480.34722; Found 480.34647.

(1*S*,2*R*,4a*S*,8a*S*)-1-((bis(4-methylbenzyl)amino)methyl)-2,5,5,8a-

tetramethyldecahydronaphthalen-2-ol (**13d**)



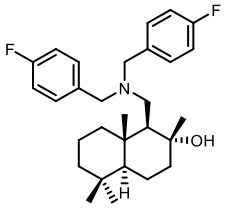
Yield: 50% **Physical State**: colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (br, 1H), 7.18 (d, J = 7.8 Hz, 4H), 7.12 (d, J = 7.8 Hz, 4H), 4.04 (d, J = 12.9 Hz, 2H), 2.90 (t, J = 12.3 Hz, 3H), 2.39 (dd, J = 13.0, 2.0 Hz, 1H), 2.33 (s, 6H), 1.86 – 1.79 (m, 1H), 1.78 – 1.71 (m, 2H), 1.63 – 1.57 (m, 2H), 1.52 (dd, J = 12.4, 3.9 Hz, 1H), 1.48 – 1.43 (m, 1H), 1.41 – 1.34 (m, 1H), 1.20 – 1.10 (m, 2H), 1.03 – 0.95 (m, 2H), 0.87 (s, 3H), 0.77 (s, 3H), 0.68 (s, 3H), 0.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.0, 134.8, 129.7, 129.2, 73.6, 58.6, 56.6, 54.7, 51.0, 43.2, 42.0, 40.0, 37.4, 33.7, 33.5, 24.5, 21.7, 21.2, 19.9, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{31}H_{46}NO$ 448.35739; Found 448.35675.

(1*S*,2*R*,4a*S*,8a*S*)-1-((bis(4-fluorobenzyl)amino)methyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**13e**)



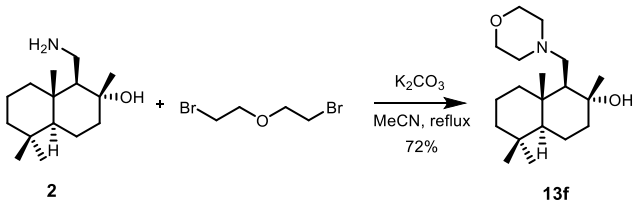
Yield: 57% **Physical State**: white solid **mp**: 126.1~127.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 4H), 7.12 (br, 1H), 7.03 – 6.98 (m, 4H), 4.02 (d, J = 13.0 Hz, 2H), 2.95 – 2.82 (m, 3H), 2.40 (dd, J = 12.8, 1.9 Hz, 1H), 1.83 – 1.79 (m, 1H), 1.76 – 1.72 (m, 1H), 1.71 (dd, J = 11.7, 1.9 Hz, 1H), 1.62 – 1.56 (m, 2H), 1.55 – 1.47 (m, 1H), 1.46 – 1.41 (m, 1H), 1.39 – 1.34 (m, 1H), 1.19 – 1.09 (m, 2H), 1.00 – 0.94 (m, 2H), 0.86 (s, 3H), 0.76 (s, 3H), 0.67 (s, 3H), 0.61 (s,3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4 (d, J = 245.7 Hz), 133.6, 131.4 (d, J = 7.9 Hz), 115.5 (d, J = 21.3 Hz), 73.7, 58.2, 56.6, 54.8, 51.0, 43.1, 41.9, 40.0, 37.4, 33.7, 33.5, 24.5, 21.7, 19.9, 18.8, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{29}H_{40}F_2NO$ 456.30725; Found 456.30646.

(1*S*,2*R*,4a*S*,8a*S*)-2,5,5,8a-tetramethyl-1-(morpholinomethyl)decahydronaphthalen-2-ol (**13f**)



2 **13f**

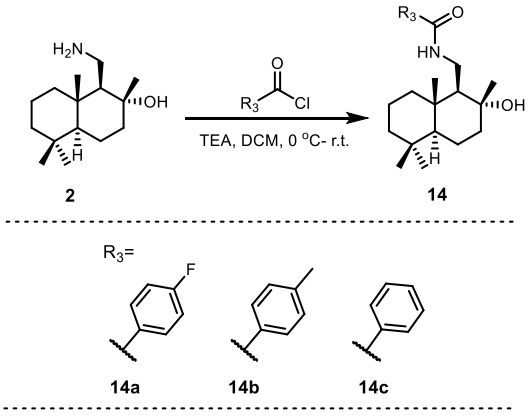
A suspension of amine **2** (287 mg, 1.3 mmol, 1.0 equiv.), 2,2'-dibromodiethyl ether (165.0 μL, 1.3 mmol, 1.0 equiv.), and K_2CO_3 (180 mg, 1.3 mmol, 1.0 equiv.) in CH_3CN (12 ml) was refluxed for 24 h, the reaction mixture was filtered, and concentrated. The crude product was purified by silica gel column chromatography on silica gel (200-300 m) with DCM /MeOH (100:1, v/v) as the eluent to give compound **13f** (colorless oil, 289 mg, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 – 3.66 (m, 4H), 2.78 – 2.59 (m, 3H), 2.48 (dd, J = 12.9, 2.5 Hz, 1H), 2.33 (s, 2H), 1.84 – 1.80 (m, 1H), 1.75 – 1.73 (m, 1H), 1.65 – 1.59 (m, 2H), 1.59 – 1.55 (m, 1H), 1.50 – 1.44 (m, 1H), 1.43 – 1.39 (m, 1H), 1.36 – 1.34 (m, 1H), 1.25 (s, 3H), 1.22 – 1.19 (m, 1H), 1.18 – 1.10 (m, 1H), 0.95 (dd, J = 12.1, 2.2 Hz, 1H), 0.93 – 0.87 (m, 1H), 0.86 (s, 3H), 0.78 (s, 3H), 0.77 (s, 3H),.

^{13}C NMR (126 MHz, $CDCl_3$) δ 73.5, 67.1, 56.5, 56.4, 54.2, 53.9, 43.1, 41.9, 40.1, 37.2, 33.7, 33.5, 25.6, 21.8, 20.0, 18.8, 15.8.

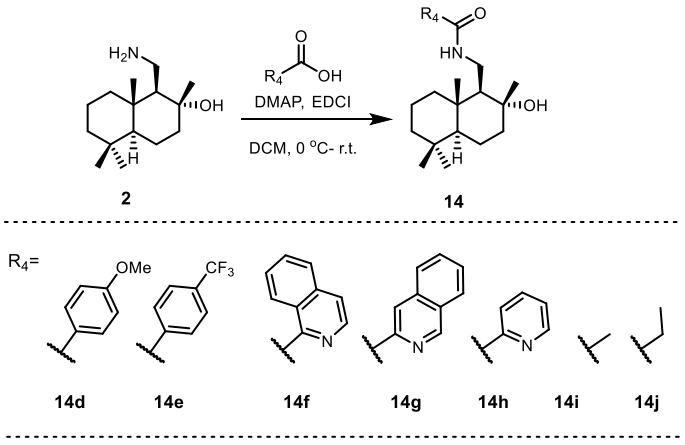
HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{19}H_{36}NO_2$ 310.27406; Found 310.27341.

4.2 General procedures for the synthesis of amide analogs



To a solution of amine **2** (191.2 mg, 0.8 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (10 mL) were added triethylamine (Et_3N) (553.4 μL, 4.0 mmol, 5.0 eq) and 4-fluorobenzoyl chloride (283.5 μL, 2.4 mmol, 3.0 eq) dropwise at 0 ℃. Subsequently, the mixture was stirred at room temperature, and the reaction progress was monitored by TLC until the reaction was complete. The solvent was added a saturated aqueous solution of NH_4Cl (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (15 mL × 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (200-300 m) with petroleum ether/EtOAc (20:1, v/v) as the eluent to give compound **14a**.

The amide analogs **14b** and **14c** were synthesized through similar manipulation.

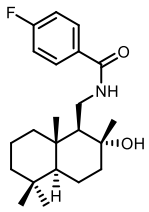


To a stirred solution of 2-picolinic acid (123 mg, 1.0 mmol, 1.2 equiv.) in anhydrous CH_2Cl_2 (8 mL) was added *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI-HCl, 230 mg, 1.2 mmol, 1.5 equiv.) followed by the addition of

amine **2** (191.2 mg, 0.8 mmol, 1.0 equiv.) and 4-dimethylaminopyridine (DMAP, 51 mg, 0.4 mmol, 0.5 equiv.) in an ice bath. The mixture was allowed to gradually warm to room temperature, and it was stirred overnight until full consumption of amine **2** as detected by TLC. The solvent was removed, and the crude product was purified by column chromatography on silica gel (200-300 m) with petroleum ether/EtOAc (3:1-1:1, v/v) as the eluent to give compound **14h**.

The amide analogs **14d** – **14g** and **14i** – **14j** were synthesized through similar manipulation.

4-fluoro-*N*-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)benzamide (**14a**)



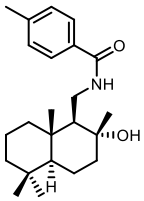
Yield: 74% **Physical State**: white solid **mp**: 163.3~164.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (br, 1H), 7.79 – 7.74 (m, 2H), 7.07 – 7.02 (m, 2H), 3.87 – 3.82 (m, 1H), 3.34 – 3.29 (m, 1H), 2.44 (br, 1H), 1.94 – 1.93 (m, 1H), 1.90 – 1.86 (m, 1H), 1.70 – 1.63 (m, 1H), 1.62 – 1.50 (m, 2H), 1.49 – 1.43 (m, 2H), 1.40 – 1.36 (m, 1H), 1.32 – 1.23 (m, 4H (s, 3H)), 1.17 – 1.10 (m, 1H), 1.05 – 1.00 (m, 1H), 0.94 (dd, *J* = 12.2, 2.2 Hz, 1H), 0.87 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 164.7 (d, *J* = 251.1 Hz), 131.1 (d, *J* = 3.0 Hz), 129.3 (d, *J* = 8.9 Hz), 115.5 (d, *J* = 21.7 Hz), 75.1, 59.6, 56.0, 45.2, 41.8, 40.2, 38.3, 37.5, 33.6, 33.4, 24.5, 21.7, 20.5, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{33}FNO_2$ 362.24898; Found 362.24836.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)-4-methylbenzamide (**14b**)



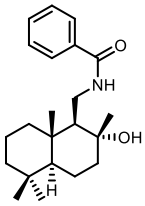
Yield: 75% **Physical State**: white solid **mp**: 141.7~142.2 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 3H (br, 1H)), 7.18 (d, J = 7.9 Hz, 2H), 3.81 – 3.76 (m, 1H), 3.38 – 3.33 (m, 1H), 2.66 (br, 1H), 2.36 (s, 3H), 1.93 – 1.90 (m, 1H), 1.89 – 1.84 (m, 1H), 1.69 – 1.63 (m, 1H), 1.62 – 1.50 (m, 2H), 1.48 – 1.43 (m, 2H), 1.40 – 1.35 (m, 1H), 1.33 – 1.22 (m, 4H (s, 3H)), 1.16 – 1.10 (m, 1H), 1.06 – 1.00 (m, 1H), 0.94 (dd, J = 12.2, 2.3 Hz, 1H), 0.87 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 141.6, 132.0, 129.2, 127.0, 74.7, 60.0, 56.0, 45.1, 41.8, 40.1, 38.3, 37.4, 33.6, 33.4, 24.5, 21.7, 21.5, 20.5, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{23}H_{36}NO_2$ 358.27406; Found 358.27457.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)benzamide (**14c**)



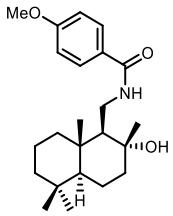
Yield: 56% **Physical State**: white solid **mp**: 172.8~173.7 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.94 (br, 1H), 7.77 – 7.72 (m, 2H), 7.45 – 7.41 (m, 1H), 7.36 – 7.33 (m, 2H), 3.83 – 3.78 (m, 1H), 3.35 – 3.30 (m, 1H), 3.03 (br, 1H), 1.92 – 1.89 (m, 1H), 1.87 – 1.81 (m, 1H), 1.66 – 1.60 (m, 1H), 1.59 – 1.54 (m, 1H), 1.54 – 1.49 (m, 1H), 1.47 (dd, J = 8.4, 3.6 Hz, 1H), 1.45 – 1.40 (m, 1H), 1.38 – 1.34 (m, 1H), 1.30 – 1.21 (m, 4H ((s, 3H))), 1.14 – 1.08 (m, 1H), 1.02 – 0.97 (m, 1H), 0.91 (dd, J = 12.2, 2.2 Hz, 1H), 0.85 (s, 3H), 0.83 (s, 3H), 0.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 134.8, 131.3, 128.5, 127.0, 74.7, 59.7, 55.9, 44.97, 41.7, 40.0, 38.2, 37.5, 33.6, 33.4, 24.4, 21.7, 20.4, 18.6, 15.7.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{34}NO_2$ 344.25841; Found 344.25754.

N-((((1*S*,2*R*,4a*S*,8a*S*))-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)-4-methoxybenzamide (**14d**)



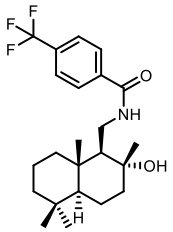
Yield: 80% **Physical State**: white solid **mp**: 142.6~145.2 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br, 1H), 7.73 – 7.68 (m, 2H), 6.83 – 6.78 (m, 2H), 3.77 – 3.73 (m,4H (s, 3H)), 3.31 (dd, *J* = 14.1, 8.1 Hz, 1H), 1.92 – 1.87 (m, 1H), 1.84 – 1.77 (m, 1H), 1.64 – 1.57 (m, 1H), 1.57 – 1.48 (m, 2H), 1.48 – 1.44 (m, 1H), 1.42 – 1.31 (m, 2H), 1.28 – 1.18 (m, 4H (s, 3H)), 1.12 – 1.05 (m, 1H), 1.00 – 0.93z (m, 1H), 0.89 (dd, *J* = 12.1, 2.1 Hz, 1H), 0.83 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 162.0, 128.8, 127.0, 113.6, 74.5, 59.7, 55.9, 55.4, 44.9, 41.7, 40.0, 38.2, 37.4, 33.6, 33.3, 24.3, 21.7, 20.4, 18.6, 15.7.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{23}H_{36}NO_3$ 374.26897; Found 374.26859.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)-4-(trifluoromethyl)benzamide (**14e**)



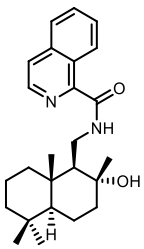
Yield: 65% **Physical State**: yellow solid **mp**: 120.1~121.7 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 5.6 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 3.93 – 3.87 (m, 1H), 3.34 – 3.28 (m, 1H), 2.22 (br, 1H), 1.95 – 1.86 (m, 2H), 1.71 – 1.64 (m, 1H), 1.62 – 1.60 (m, 1H), 1.56 – 1.42 (m, 3H), 1.42 – 1.35 (m, 1H), 1.31 (s, 3H), 1.28 – 1.22 (m, 1H), 1.17 – 1.09 (m, 1H), 1.06 – 0.98 (m, 1H), 0.94 (dd, *J* = 12.1, 2.2 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 138.2, 133.1 (q, J = 32.8 Hz), 127.5, 125.6 (q, J = 3.8 Hz), 123.7 (q, J = 273 Hz), 75.2, 59.2, 56.0, 45.2, 41.7, 40.2, 38.2, 37.7, 33.6, 33.4, 24.5, 21.7, 20.4, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{23}H_{33}F_3NO_2$ 412.24579; Found 412.24528.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)isoquinoline-1-carboxamide (**14f**)



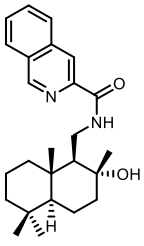
Yield: 42% **Physical State**: white solid **mp**: 131.4~136.0 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 – 9.53 (m, 1H), 8.75 (br, 1H), 8.44 (d, *J* = 5.5 Hz, 1H), 7.86 – 7.79 (m, 1H), 7.76 (dd, *J* = 5.6, 0.9 Hz, 1H), 7.68 (m, 2H), 3.65 – 3.62 (m, 2H), 3.38 (br, 1H), 1.95 – 1.92 (m, 1H), 1.90 – 1.86 (m, 1H), 1.70 – 1.58 (m, 2H), 1.57 – 1.45 (m, 3H), 1.39 – 1.36 (m, 1H), 1.33 – 1.24 (m, 4H (s, 3H)), 1.17 – 1.09 (m, 2H), 0.96 (dd, *J* = 12.2, 2.3 Hz, 1H), 0.90 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 148.8, 140.5, 137.5, 130.6, 128.7, 128.0, 127.1, 126.8, 124.3, 73.5, 62.1, 56.0, 44.5, 41.8, 40.0, 38.6, 36.5, 33.6, 33.4, 24.5, 21.6, 20.5, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{25}H_{35}N_2O_2$ 395.26930; Found 395.26852.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)isoquinoline-3-carboxamide (**14g**)



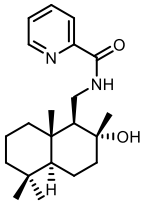
Yield: 56% **Physical State**: white solid **mp**: 160~162.3 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.82 (br, 1H), 8.59 (s, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.77 –z 7.74 (m, 1H), 7.71 – 7.67 (m, 1H), 3.70 – 3.57 (m, 2H), 3.42 (br, 1H), 1.96 – 1.92 (m, 1H), 1.89 – 1.85 (m, 1H), 1.70 – 1.62 (m, 2H), 1.58 – 1.52 (m, 2H), 1.51 – 1.45 (m, 1H), 1.40 – 1.34 (m, 1H), 1.33 – 1.24 (m, 4H (s, 3H)), 1.16 – 1.07 (m, 2H), 0.96 (dd, J = 12.2, 2.3 Hz, 1H), 0.90 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 151.4, 143.7, 136.1, 131.2, 129.7, 128.9, 128.3, 127.8, 120.4, 73.4, 62.2, 56.0, 44.4, 41.8, 40.0, 38.6, 36.6, 33.5, 33.4, 24.6, 21.6, 20.5, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{25}H_{35}N_2O_2$ 395.26930; Found 395.26901.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)picolinamide (**14h**)



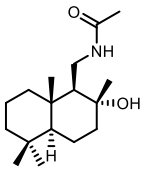
Yield: 45% **Physical State**: white solid **mp**: 165.5~167.1 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (br, 1H), 8.51 – 8.50 (m, 1H), 8.16 – 8.14 (m, 1H), 7.82 – 7.78 (m, 1H), 7.39 – 7.36 (m, 1H), 3.63 – 3.58 (m, 1H), 3.56 – 3.51 (m, 1H), 3.26 (br, 1H), 1.92 – 1.88 (m, 1H), 1.87 – 1.78 (m, 1H), 1.67 – 1.54 (m, 2H), 1.54 – 1.42 (m, 3H), 1.37 – 1.33 (m, 1H), 1.30 – 1.21 (m, 4H (s, 3H)), 1.12 (dd, J = 13.5, 4.1 Hz, 1H), 1.09 – 1.01 (m, 1H), 0.92 (dd, J = 12.2, 2.3 Hz, 1H), 0.86 (s, 3H), 0.84 (s, 3H), 0.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 150.1, 148.4, 137.4, 126.2, 122.3, 73.5, 62.0, 56.0, 44.4, 41.8, 39.9, 38.5, 36.4, 33.6, 33.4, 24.5, 21.6, 20.5, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{21}H_{33}N_2O_2$ 345.25365; Found 345.25421.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)acetamide (**14i**)



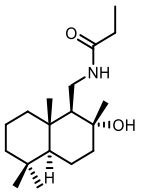
Yield: 70% **Physical State**: white solid **mp**: 139.9~140.9 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (br, 1H), 3.49 – 3.44 (m, 1H), 3.23 – 3.18 (m, 1H), 2.78 (br, 1H), 1.93 (s, 3H), 1.89 – 1.85 (m, 1H), 1.77 – 1.74 (m, 1H), 1.67 – 1.60 (m, 1H), 1.60 – 1.53 (m, 1H), 1.51 – 1.40 (m, 2H), 1.38 – 1.31 (m, 2H), 1.28 – 1.18 (m, 4H (s, 3H)), 1.15 – 1.09 (m, 1H), 1.01 – 0.96 (m, 1H), 0.91 (dd, *J* = 12.2, 2.3 Hz, 1H), 0.85 (s, 3H), 0.80 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 74.1, 60.7, 56.0, 44.7, 41.8, 40.0, 38.4, 36.9, 33.6, 33.3, 24.3, 23.5, 21.6, 20.4, 18.6, 15.7.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{17}H_{32}NO_2$ 282.24276; Found 282.24234.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)propionamide (**14j**)



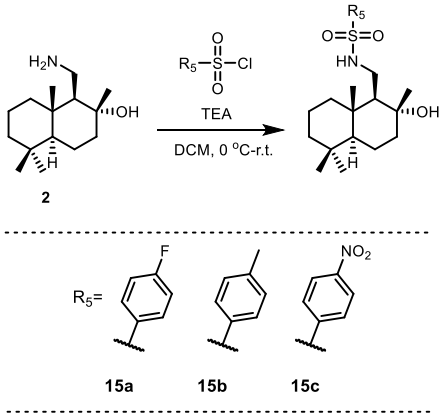
Yield: 73% **Physical State**: white solid **mp**: 150.4~153.5 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (br, 1H), 3.53 – 3.44 (m, 1H), 3.24 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.34 (br, 1H), 2.20 – 2.16 (m, 2H), 1.91 – 1.87 (m, 1H), 1.80 – 1.76 (m, 1H), 1.67 – 1.62 (m, 1H), 1.61 – 1.54 (m, 1H), 1.53 – 1.42 (m, 2H), 1.40 – 1.35 (m, 1H), 1.35 – 1.31 (m, 1H), 1.29 – 1.25 (m, 1H), 1.23 (s, 3H), 1.17 – 1.10 (m, 4H (t, *J* = 7.6 Hz, 1H)), 1.02 – 0.97 (m, 1H), 0.92 (dd, *J* = 12.2, 2.3 Hz, 1H), 0.86 (s, 3H), 0.82 (s, 3H), 0.79 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 74.2, 60.8, 56.0, 44.8, 41.8, 40.1, 38.4, 36.8, 33.6, 33.4, 30.0, 24.5, 21.7, 20.5, 18.6, 15.7, 10.0.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{18}H_{34}NO_2$ 296.25841; Found 296.25842.

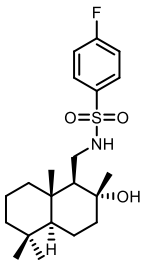
4.3 General procedures for the synthesis of sulfamide analogs



To a stirred solution of **2** (96.0 mg, 0.4 mmol, 1.0 equiv.) in DCM (2.5 mL) were added triethylamine (114.0 μL, 0.8 mmol, 2.0 equiv.) and tosyl chloride (TsCl, 93 mg, 0.5 mmol, 1.2 equiv.) at 0 °C. The mixture was stirred at room temperature for 5 h. The solvent was added a saturated aqueous solution of NH_4Cl (10 mL) and CH_2Cl_2 (5 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography on silica gel (200-300 m) with petroleum ether/EtOAc (5:1, v/v) as the eluent to give compound **15b**.

The sulfonamide analogs were synthesized through similar manipulation.

4-fluoro-*N*-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)benzenesulfonamide (**15a**)



Yield: 80% **Physical State**: white solid **mp**: 139.5~140.0 ℃

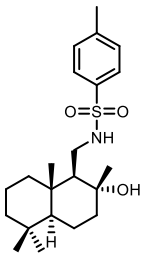
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.87 (m, 2H), 7.22 – 7.15 (m, 2H), 3.21 (dd, J = 12.4, 2.6 Hz, 1H), 2.89 (dd, J = 12.4, 9.4 Hz, 1H), 1.96 (br, 1H), 1.84 – 1.80 (m, 1H), 1.68 – 1.58 (m, 2H), 1.57 – 1.50 (m, 1H), 1.49 – 1.40 (m, 2H), 1.39 – 1.31 (m, 2H),

1.22 – 1.13 (m, 1H), 1.13 – 1.07 (m, 1H), 1.05 (s, 3H), 0.91 – 0.82 (m, 5H (s, 3H)), 0.73 (s, 3H), 0.68 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0 (d, J = 254.0 Hz), 136.0 (d, J = 3.2 Hz), 130.0 (d, J = 9.2 Hz), 116.3 (d, J = 22.5 Hz), 75.2, 58.6, 55.8, 44.9, 41.6, 40.4, 39.8, 38.1, 33.5, 33.4, 24.1, 21.6, 20.3, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{21}H_{33}FNO_3S$ 398.21597; Found 398.21511.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)-4-methylbenzenesulfonamide (**15b**)



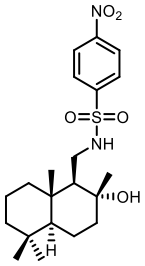
Yield: 90% **Physical State**: white solid **mp**: 158.7~159.1 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 2H), 7.33 – 7.29 (m, 2H), 3.21 (dd, J = 12.5, 2.6 Hz, 1H), 2.89 (dd, J = 12.5, 9.3 Hz, 1H), 2.43 (s, 3H), 1.84 – 1.80 (m, 1H), 1.69 – 1.64 (m, 1H), 1.64 – 1.59 (m, 1H), 1.57 – 1.50 (m, 1H), 1.50 – 1.39 (m, 2H), 1.39 – 1.32 (m, 2H), 1.21 – 1.14 (m, 1H), 1.13 – 1.07 (m, 1H), 1.05 (s, 3H), 0.92 – 0.85 (m, 2H), 0.84 (s, 3H), 0.74 (s, 3H), 0.69 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 137.0, 129.7, 127.4, 75.3, 58.8, 55.8, 45.2, 41.7, 40.4, 39.8, 38.1, 33.6, 33.4, 24.2, 21.7, 21.7, 20.3, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for C22H36NO3S 394.24104; Found 394.24053.

N-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)-4-nitrobenzenesulfonamide (**15c**)



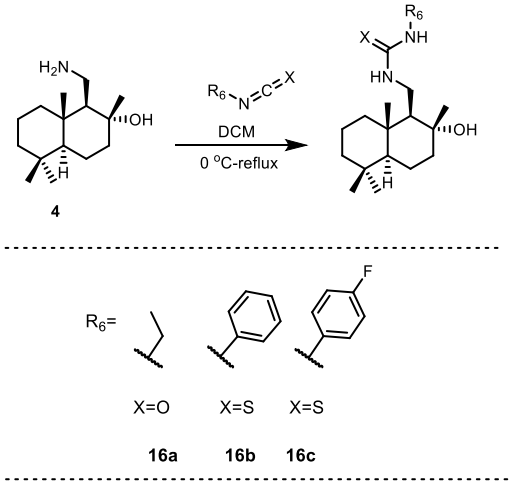
Yield: 56% **Physical State**: white solid **mp**: 176.9~177.4 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 – 8.34 (m, 2H), 8.09 – 8.03 (m, 2H), 6.54 (br, 1H), 3.31 (m, 1H), 2.95 (m, 1H), 1.86 – 1.82 (m, 1H), 1.71 – 1.67 (m, 1H), 1.66 – 1.62 (m, 1H), 1.57 – 1.49 (m, 1H), 1.49 – 1.41 (m, 2H), 1.40 – 1.34 (m, 2H), 1.24 – 1.14 (m, 1H), 1.11 – 1.07 (m, 4H (s, 3H)), 0.92 – 0.84 (m, 5H (s, 3H)), 0.75 (s, 3H), 0.71 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 146.3, 128.5, 124.4, 75.6, 58.6, 55.8, 45.1, 41.6, 40.5, 39.9, 38.1, 33.5, 33.4, 24.4, 21.6, 20.3, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{33}N_2O_5S$ 425.21047; Found 425.21098.

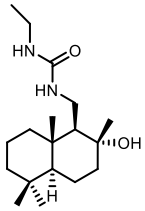
4.4 General procedures for the synthesis of (thio)urea analogs



To a dried flask charged with amine **2** (143 mg, 0.6 mmol, 1.0 equiv.) in anhydrous DCM (6 mL) was added dropwise phenyl isothiocyanate (136 μL, 0.66 mmol, 1.1 equiv.) at 0 °C. the reaction mixture was transferred to a metal bath for reflux overnight until full consumption of **2** as detected by TLC. Evaporate the organic solvent and the crude products were purified by column chromatography on silica gel (200-300 m) with petroleum ether/EtOAc (4:1, v/v) as the eluent to give compound **16b**.

The analogs **16a** and **16c** were synthesized through similar manipulation.

1-ethyl-3-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)urea (**16a**)



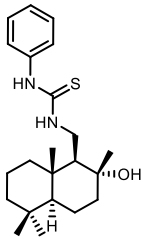
Yield: 72% **Physical State**: white solid **mp**: 173.3~173.8 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.31 (dd, J = 14.6, 4.9 Hz, 1H), 3.22 – 3.14 (m, 3H), 1.88 – 1.84 (m, 1H), 1.68 – 1.63 (m, 2H), 1.61 – 1.54 (m, 1H), 1.53 – 1.41 (m, 2H), 1.40 – 1.34 (m, 2H), 1.29 – 1.22 (m, 1H), 1.20 (s, 3H), 1.15 (dd, J = 13.4, 4.3 Hz, 1H), 1.11 (t, J = 7.2 Hz, 3H), 1.07 (dd, J = 13.0, 3.8 Hz, 1H), 0.93 (dd, J = 12.2, 2.3 Hz, 1H), 0.86 (s, 3H), 0.81 (s, 3H), 0.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 73.5, 62.1, 55.9, 44.3, 41.9, 40.0, 38.4, 37.2, 35.3, 33.5, 33.3, 24.6, 21.6, 20.5, 18.5, 15.7, 15.5.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{18}H_{35}N_2O_2$ 311.26930; Found 311.26855.

1-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)-3-phenylthiourea (**16b**)



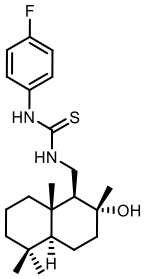
Yield: 52% **Physical State**: white solid **mp**: 173.7~173.9 ℃

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (br, 1H), 7.71 (br, 1H), 7.38 – 7.34 (m, 2H), 7.25 – 7.12 (m, 3H), 4.17 (d, J = 8.4 Hz, 1H), 3.43 (t, J = 12.0 Hz, 1H), 1.84 (dd, J = 42.4, 12.7 Hz, 2H), 1.66 – 1.53 (m, 2H), 1.51 – 1.42 (m, 2H), 1.41 – 1.33 (m, 2H), 1.28 – 1.23 (m, 1H), 1.20 (s, 3H), 1.15 – 1.09 (m, 1H), 1.02 – 0.97 (m, 1H), 0.90 – 0.88 (m, 1H), 0.85 (s, 3H), 0.83 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.4, 136.4, 129.9, 126.8, 125.2, 74.8, 58.5, 55.9, 45.0, 43.6, 41.7, 40.3, 38.1, 33.6, 33.4, 24.6, 21.7, 20.4, 18.6, 15.8.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{35}N_2OS$ 375.24646; Found 375.24601.

1-(4-fluorophenyl)-3-(((1*S*,2*R*,4a*S*,8a*S*)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)methyl)thiourea (**16c**)



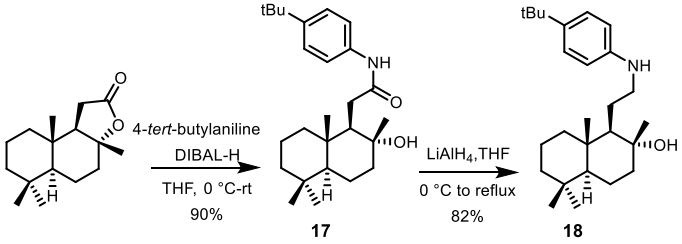
Yield: 65% **Physical State**: white solid **mp**: 189.4~211.2 ℃

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.16 (s, 1H), 7.07 – 7.01 (m, 2H), 3.45 – 3.32 (m, 1H), 3.47 – 3.32 (m, 1H), 1.84 (dd, J = 30.8, 11.4 Hz, 2H), 1.66 – 1.51 (m, 3H), 1.49 – 1.42 (m, 2H), 1.40 – 1.32 (m, 2H), 1.19 (s, 5H (s, 3H)), 1.04 – 0.93 (m, 1H), 0.85 (s, 3H), 0.82 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.8, 162.1, 132.4, 127.7, 116.7 (d, J = 21.8 Hz), 74.9, 58.3, 55.9, 45.0, 43.6, 41.7, 40.2, 38.1, 33.6, 33.4, 24.6, 21.6, 20.3, 18.6, 15.7.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{22}H_{34}FN_2OS$ 393.23704; Found 393.23615.

5 Synthesis of homodrimanyl amine 18



A solution of DIBAL-H (1 M in cyclohexane, 3.0 mL, 3.0 equiv) was added to a cooled (0-5 °C) solution of 4-*tert*-butylaniline (373.0 mg, 2.5 mmol, 2.5 equiv) in anhydrous THF (1.7 mL) under nitrogen atmosphere. The mixture was allowed to warm up and stirred at room temperature for 2 h. To the solution of DIBAL-H-*p*-*tert*-

butylaniline complex was added the sclareolide (0.25 g, 1.0 mmol, 1.0 equiv) in anhydrous THF (2.5 mL) under nitrogen atmosphere at room temperature. The complex was stirred and the reaction progress was monitored by TLC until the reaction was complete (~2 h). The reaction was cooled to 0 ℃ and then quenched with H_2O (1.5 mL) and a 1 M aqueous solution of $KHSO_4$ (4 mL). The resulting mixtures were extracted with CH_2Cl_2 (10 × 3mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (200-300 m) with petroleum ether /EtOAc (4:1, v/v) as eluent to give compound **17** (colorless oil, 359.6 mg, yield 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.44 – 7.40 (m, 2H), 7.32 – 7.28 (m, 2H), 2.58 (dd, *J* = 15.2, 4.4 Hz, 1H), 2.24 (dd, *J* = 15.2, 4.4 Hz, 1H), 1.95 – 1.92 (m, 1H), 1.82 (t, *J* = 4.4 Hz, 1H), 1.69 (m, 2H), 1.58 – 1.47 (m, 2H), 1.37 – 1.32 (m, 1H), 1.30 – 1.25 (m, 11H (s, 9H)), 1.18 (s, 3H), 1.13 – 1.07 (m, 1H), 0.97 (dd, *J* = 12.4, 2.7 Hz, 2H), 0.85 (s, 3H), 0.79 (s, 3H), 0.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 146.8, 136.0, 125.8, 119.5, 73.9, 58.2, 56.1, 44.4, 41.9, 39.4, 38.9, 34.4, 34.3, 33.4, 33.3, 31.5, 24.2, 21.5, 20.6, 18.4, 15.5.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{26}H_{42}NO_2$ 400.32101; Found 400.32050.

To a stirred mixture of $LiAlH_4$ (182.2 mg, 4.8 mmol, 6.0 equiv) in anhydrous THF (5 mL) was added dropwise a THF (5 mL) solution of homodrimanyl amide **17** (320 mg, 0.8 mmol, 1.0 equiv.) at 0 °C. The mixture was warmed to room temperature and then heated to reflux until full consumption of **17** detected by TLC. After the reaction completed, saturated Na_2SO_4 aqueous was added dropwise to quench the reaction at 0 °C. The resulting white precipitation was removed by filtration. The filtrate was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (200-300 m) with petroleum ether /EtOAc (9:1, v/v) as eluent to give (1*R*,2*R*,4a*S*,8a*S*)-1-(2-((4-(*tert*-butyl)phenyl)amino)ethyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (**18**) (colorless oil, 252.9 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 2H), 6.61 – 6.57 (m, 2H), 3.22 – 3.17 (m, 1H), 3.04 – 3.00 (m, 1H), 1.90 – 1.87 (m, 1H), 1.71 – 1.68 (m, 1H), 1.68 – 1.65 (m,

2H), 1.65 – 1.63 (m, 1H), 1.63 – 1.56 (m, 1H), 1.47 – 1.44 (m,1H), 1.43 – 1.40 (m, 1H), 1.40 – 1.36 (m, 1H), 1.29 (m, 10H (s, 9H)), 1.22 (t, J = 4.0 Hz, 1H), 1.17 – 0.11 (m, 4H (s, 3H)), 1.01 – 0.95 (m, 1H), 0.93 (dd, J = 12.2, 2.3 Hz, 1H), 0.88 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 140.1, 126.1, 112.8, 73.5, 59.5, 56.1, 46.7, 44.4, 42.0, 39.6, 39.2, 34.0, 33.5, 33.3, 31.7, 25.3, 24.5, 21.6, 20.7, 18.5, 15.5.

HRMS (ESI) m/z: $[M+H]^+$Calcd for $C_{26}H_{44}NO$ 386.34174; Found 386.34109.

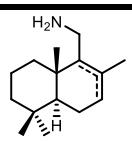
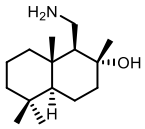
6 Antifungal activity of halichonine B and analogs

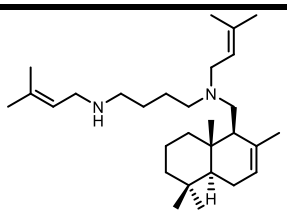
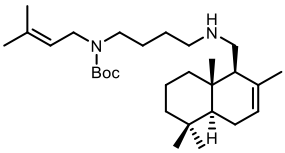
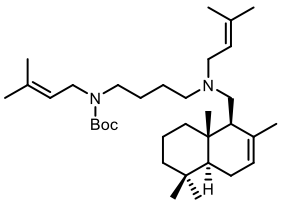
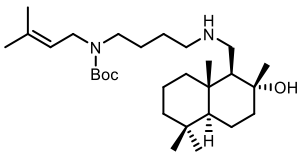
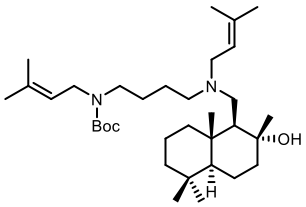
The antifungal activity of the target compounds was tested *in vitro* against the plant pathogenic fungi using the mycelium growth rate test. All the tested compounds were initially dissolved in DMSO. The media containing compounds at a final concentration of 150 μM were then poured into Petri dishes for initial antifungal screening. In the precision antifungal test, the stock solution was diluted to 150, 75, 37.5, 18.75, 9.375, 4.688, 2.344 μM and the above experiments were repeated for three times, the inhibition rates were calculated separately. The statistical analyses were performed by SPSS software version 26.0. The inhibition rate was calculated as follows,

Inhibition rate (%) = (C-T) / (C-5 mm) × 100%

Where C: The average diameter (in mm) of mycelia in the blank test, T: The average diameter (in mm) of mycelia on treated PDA with tested compounds

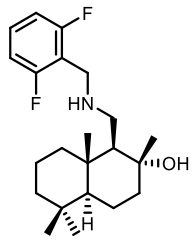
Table S1. The antifungal activity of drimanyl amine, halichonine B, and mimics

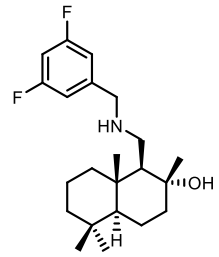
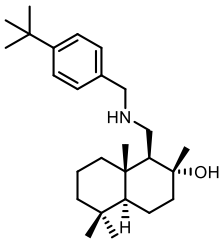
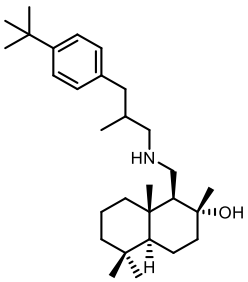
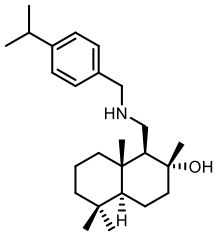
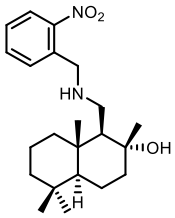
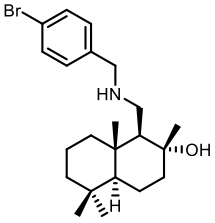
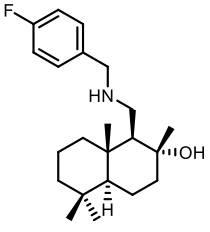
Structure	Compd.	Inhibition rate at 150 μM (%)			
		S. s.	*R. s.*	*F. g.*	*B. c.*
	**1**	66.67	52.83	39.22	45.83
	**2**	15.69	10.00	26.32	40.00

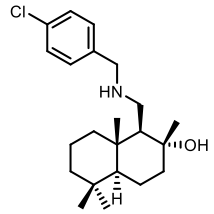
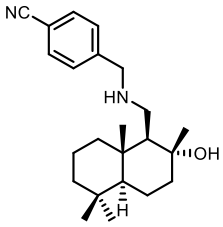
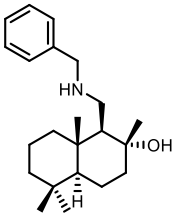
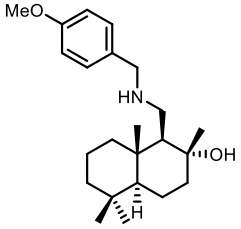
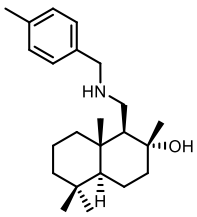
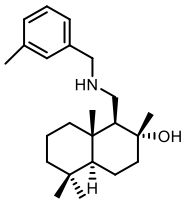
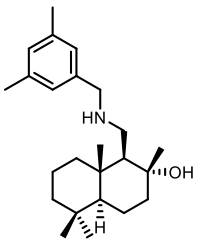
	**3** (halichonine B)	72.00	33.96	35.71	47.83
	**8**	91.11	80.00	45.65	80.00
	**9**	74.00	41.51	19.64	67.39
	**10**	94.00	77.36	82.46	84.78
	**11**	90.00	88.68	67.35	65.22

Note: *S. s.* (*Sclerotinia sclerotiorum*), *R. s.* (*Rhizoctonia solani*), *F. g.* (*Fusarium graminearum*), and *B. c.* (*Botrytis cinerea*)

Table S2 The antifungal activity of halichonine B analogs with unsaturated aliphatic chains

Structure	Compd.	Inhibition rate at 150 μM (%)			
		S. s.	*R. s.*	*F. g.*	*B. c.*
	**12a**	78.00	55.00	25.53	5.00

	**12b**	90.00	70.00	29.79	47.50
	**12c**	92.00	82.50	51.06	77.50
	**12d**	76.00	87.50	59.57	57.50
	**12e**	98.04	86.00	82.46	71.11
	**12f**	76.47	44.00	35.09	35.56
	**12g**	94.00	87.50	44.68	42.50
	**12h**	96.00	72.50	42.55	52.50

	**12i**	82.46	88.24	51.06	47.50
	**12j**	92.00	62.50	34.04	50.00
	**12k**	86.67	47.50	52.17	55.00
	**12l**	88.00	72.50	31.91	50.00
	**12m**	93.33	75.00	50.00	74.00
	**12n**	88.00	85.00	46.81	57.50
	**12o**	76.00	69.81	44.64	86.96

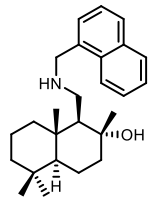
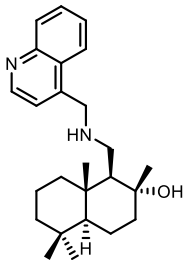
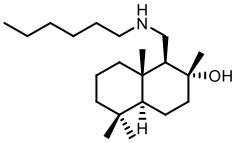
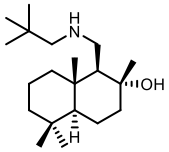
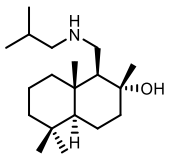
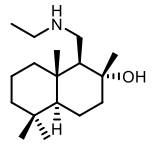
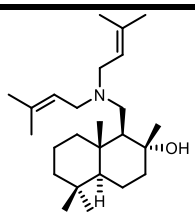
	**12p**	83.33	92.45	83.33	70.59
	**12q**	74.00	57.50	29.79	27.50
	**12r**	68.75	69.81	41.18	68.75
	**12s**	35.29	26.00	24.56	22.22
	**12t**	23.53	24.00	35.09	20.00
	**12u**	13.73	10.00	19.30	11.11

Table S3 The antifungal activity of *N*-double alkylation analogs

Structure	Compd.	Inhibition rate at 150 μM (%)			
		S. s.	*R. s.*	*F. g.*	*B. c.*
	**13a**	57.78	57.50	43.48	66.00

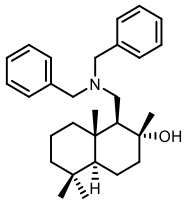
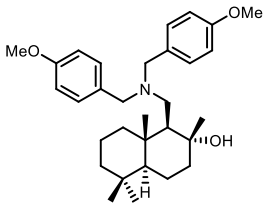
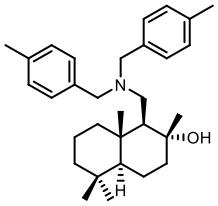
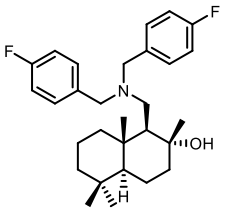
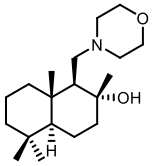
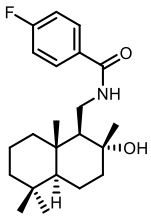
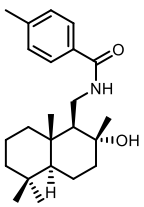
	**13b**	57.41	71.21	51.79	52.17
	**13c**	86.67	50.00	34.78	62.00
	**13d**	84.44	67.50	43.48	64.00
	**13e**	82.22	57.50	41.30	58.00
	**13f**	31.11	7.50	30.43	30.00

Table S4 The antifungal activity of halichonine B analogs (amides)

Structure	Compd.	Inhibition rate at 150 μM (%)			
		S. s.	*R. s.*	*F. g.*	*B. c.*
	**14a**	18.00	37.50	4.26	0
	**14b**	24.00	45.00	31.91	22.50

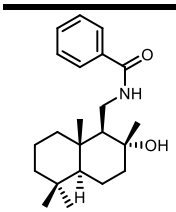
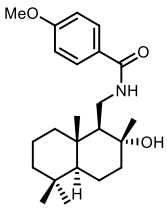
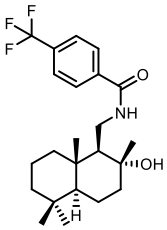
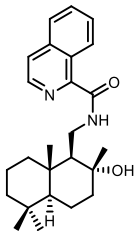
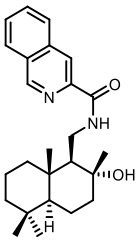
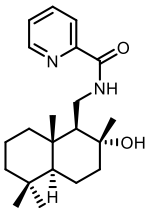
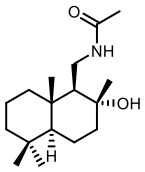
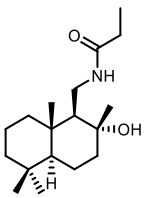
	**14c**	29.41	58.00	38.60	66.67
	**14d**	45.10	52.00	42.11	57.78
	**14e**	7.84	32.00	3.51	24.44
	**14f**	29.41	58.00	36.84	60.00
	**14g**	20.37	33.33	19.64	34.78
	**14h**	7.84	38.00	42.11	42.22
	**14i**	3.92	1.82	17.02	47.92
	**14j**	1.96	27.27	23.40	45.83

Table S5 The antifungal activity of halichonine B analogs (sulfamides)

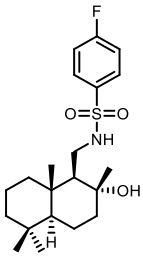
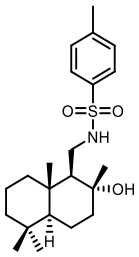
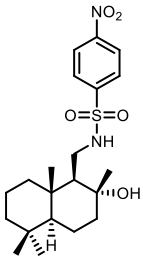
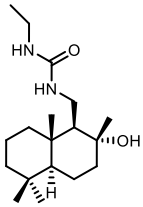
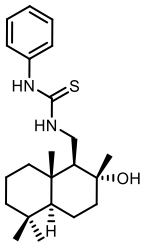
Structure	Compd.	Inhibition rate at 150 μM (%)			
		S. s.	*R. s.*	*F. g.*	*B. c.*
	**15a**	58.82	78.00	47.37	71.11
	**15b**	54.90	70.00	35.09	60.00
	**15c**	2.00	55.00	6.38	0

Table S6 The antifungal activity of halichonine B analogs (ureas and thioureas)

Structure	Compd.	Inhibition rate at 150 μM (%)			
		S. s.	*R. s.*	*F. g.*	*B. c.*
	**16a**	8.00	47.50	29.79	17.50
	**16b**	52.94	62.00	38.60	60.00

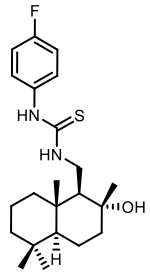
	**16c**	40.00	70.00	23.40	25.00

Table S7 The antifungal activity of homodrimanyl amide **17** and amine **18**

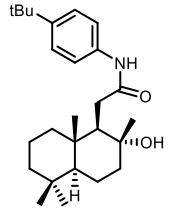
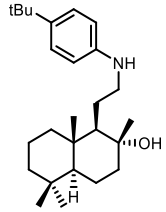
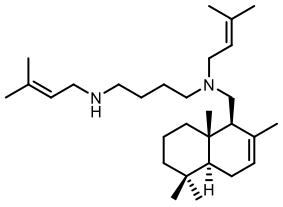
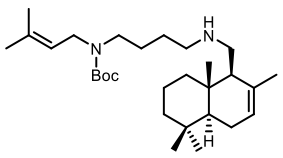
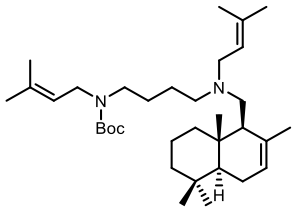
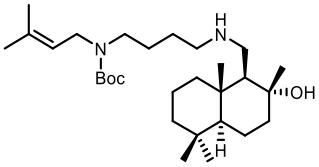
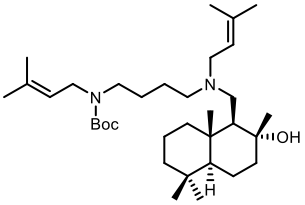
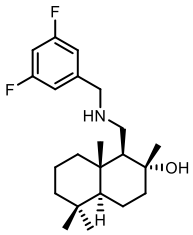
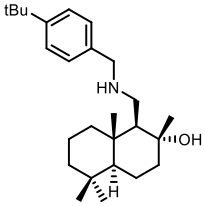
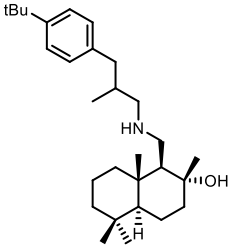
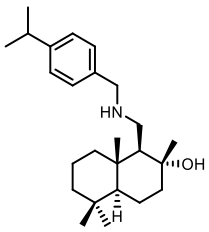
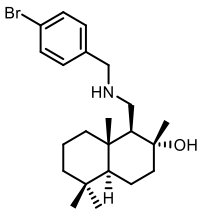
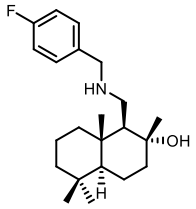
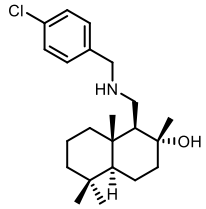
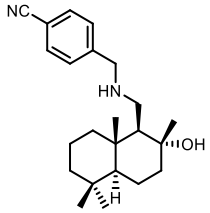
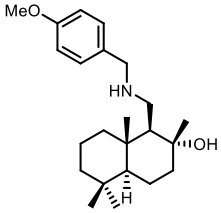
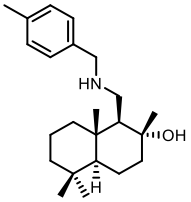
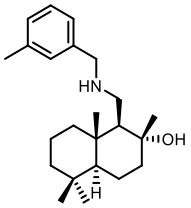
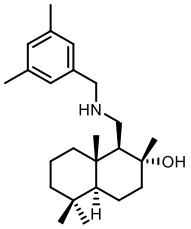
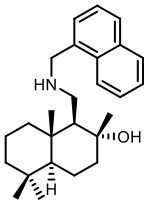
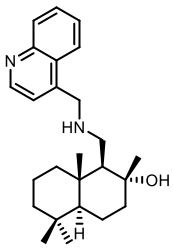
Structure	Compd.	Inhibition rate at 150 μM (%)			
		S. s.	*R. s.*	*F. g.*	*B. c.*
	**17**	9.80	8.00	21.05	33.33
	**18**	13.73	20.00	21.55	55.56

Table S8. EC_{50} against three phytopathogenic fungi *in vitro*

Structure	Compd.	EC_{50} (μM)		
		S. s.	*R. s.*	*B. c.*
	**3**	69.37	＞150	＞150
	**8**	40.35	29.74	27.29

	**9**	55.52	84.13	54.67
	**10**	14.67	23.89	12.63
	**11**	45.18	34.43	20.40
	**12b**	21.97	36.15	＞150
	**12c**	27.75	8.90	12.20
	**12d**	22.49	5.81	＞150
	**12e**	23.77	14.03	23.44
	**12g**	22.87	17.21	＞150

	**12h**	29.04	32.87	＞150
	**12i**	20.14	17.12	＞150
	**12j**	33.98	93.50	＞150
	**12l**	23.48	82.01	＞150
	**12m**	23.89	49.79	62.29
	**12n**	61.90	59.58	＞150
	**12o**	46.63	25.31	35.88
	**12p**	18.47	14.71	50.53

	**12q**	64.93	109.72	＞150

7 Molecular docking

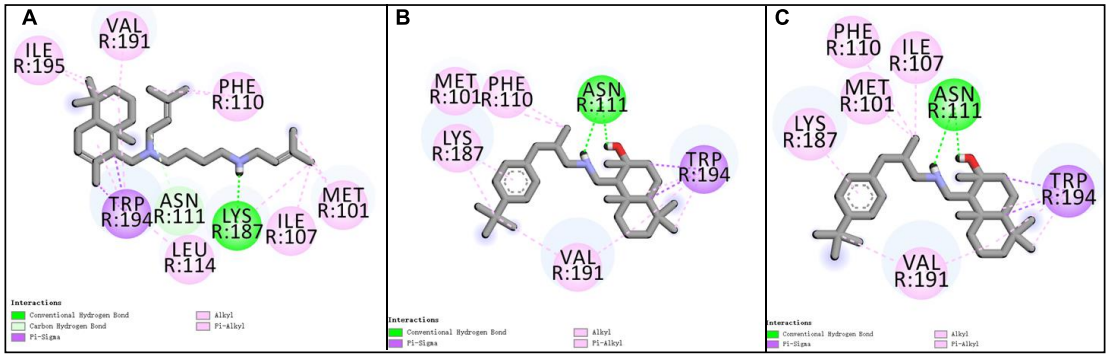
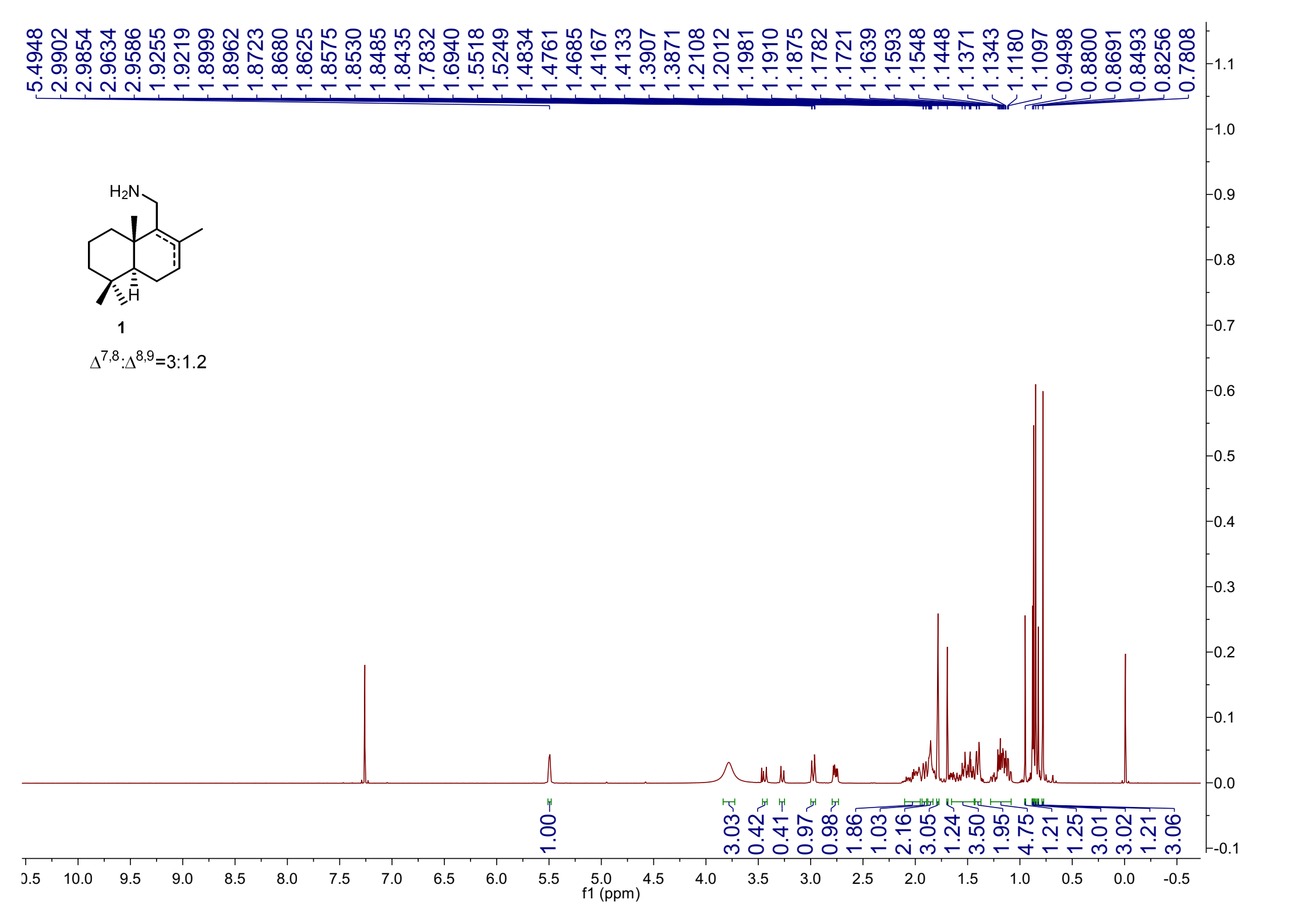


Fig. S1 Binding models of halichonine B and analogs with the predictive protein. halichonine B (**A**), (***R***)-**13d** (**B**), (***S***)-**13d** (**C**)

8 References

1. D. Li, S. Zhang, Z. Song, W. Li, F. Zhu, J. Zhang and S. Li, Synthesis and bio-inspired optimization of drimenal: Discovery of chiral drimane fused oxazinones as promising antifungal and antibacterial candidates, *Eur. J. Med. Chem.*, 2018, **143**, 558-567.
2. I. Hayakawa, T. Nakamura, O. Ohno, K. Suenaga and H. Kigoshi, Synthesis and structure–activity relationships for cytotoxicity and apoptosis-inducing activity of (+)-halichonine B, *Org. Biomol. Chem.*, 2015, **13**, 9969-9976.
3. O. Ohno, T. Chiba, S. Todoroki, H. Yoshimura, N. Maru, K. Maekawa, H. Imagawa, K. Yamada, A. Wakamiya, K. Suenaga and D. Uemura, Halichonines A, B, and C, novel sesquiterpene alkaloids from the marine sponge Halichondria okadai Kadota, *Chem. Commun.*, 2011, **47**, 12453-12455.

9 NMR spectra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0.7808
H2N
H
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Δ7,8:Δ8,9=3:1.2
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3.03
0.42
0.41
0.97
0.98
1.86
1.03
2.16
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1.25
3.01
3.02
1.21
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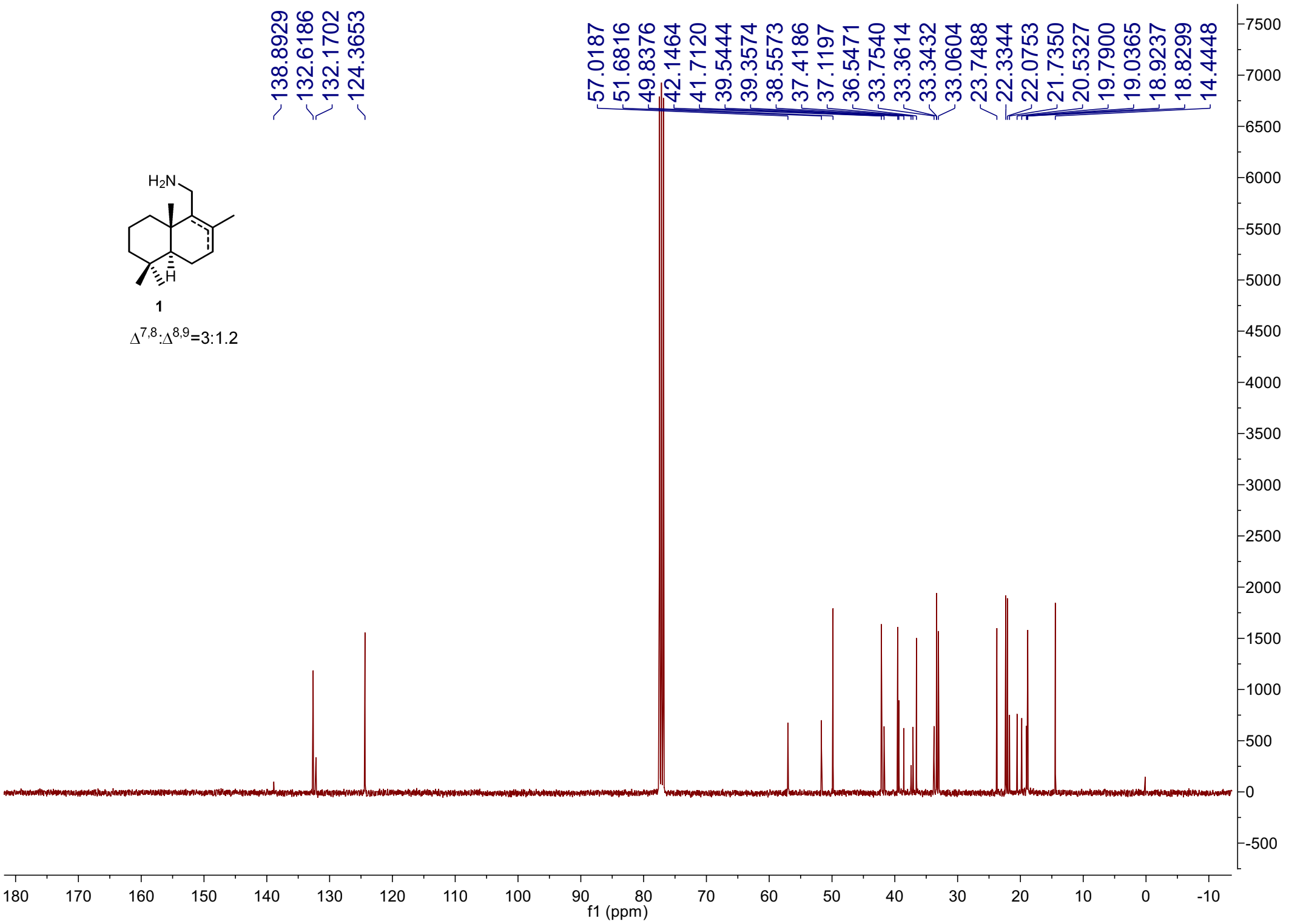
f1 (ppm)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33.0604
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20.5327
19.7900
19.0365
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18.8299
14.4448
H2N
H
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Δ7,8:Δ8,9=3:1.2
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7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
180
170
160
150
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120
110
100
90
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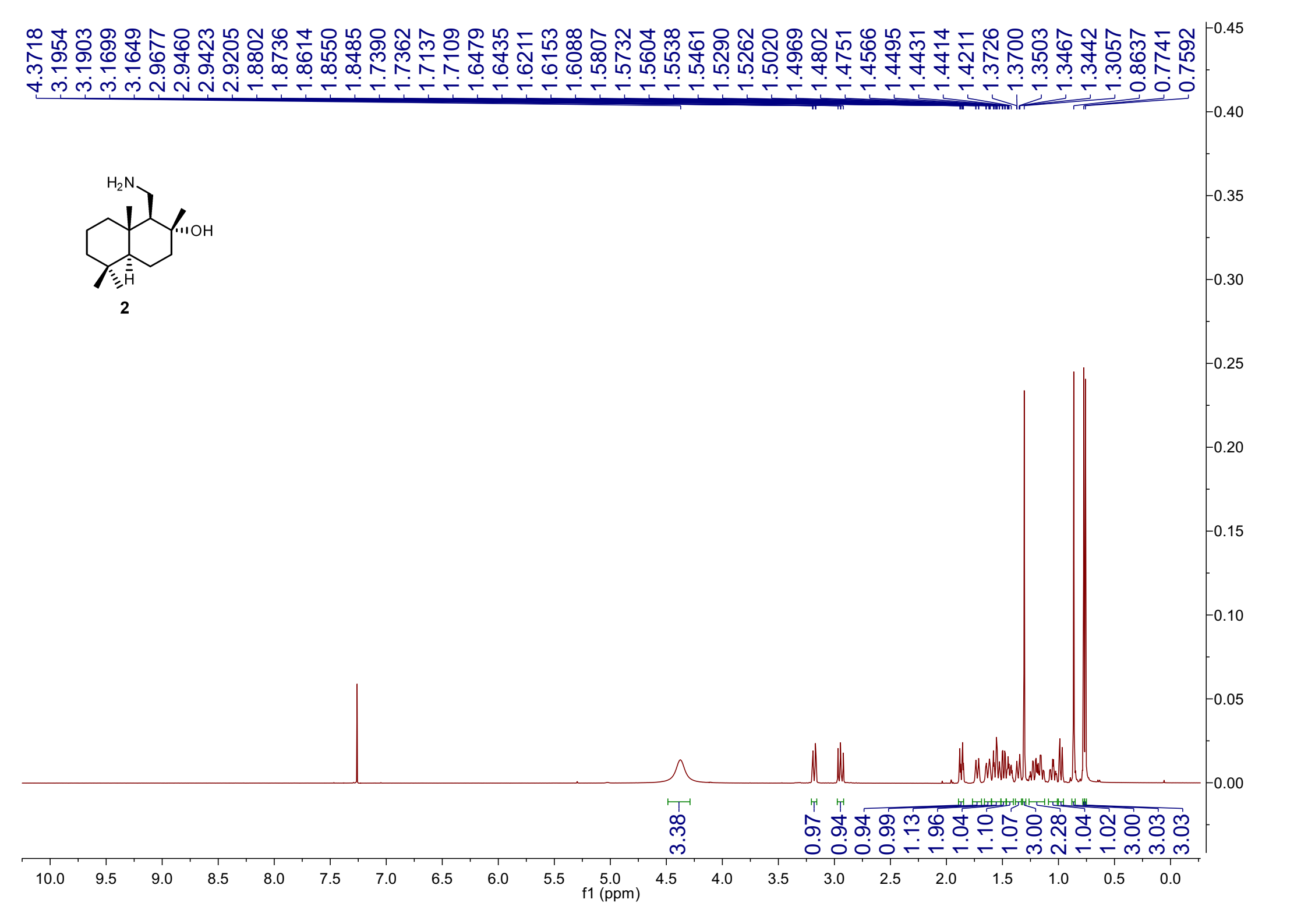
60
50
40
30
20
10
0
-10
f1 (ppm)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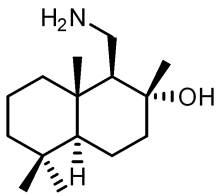
f1 (ppm)



2

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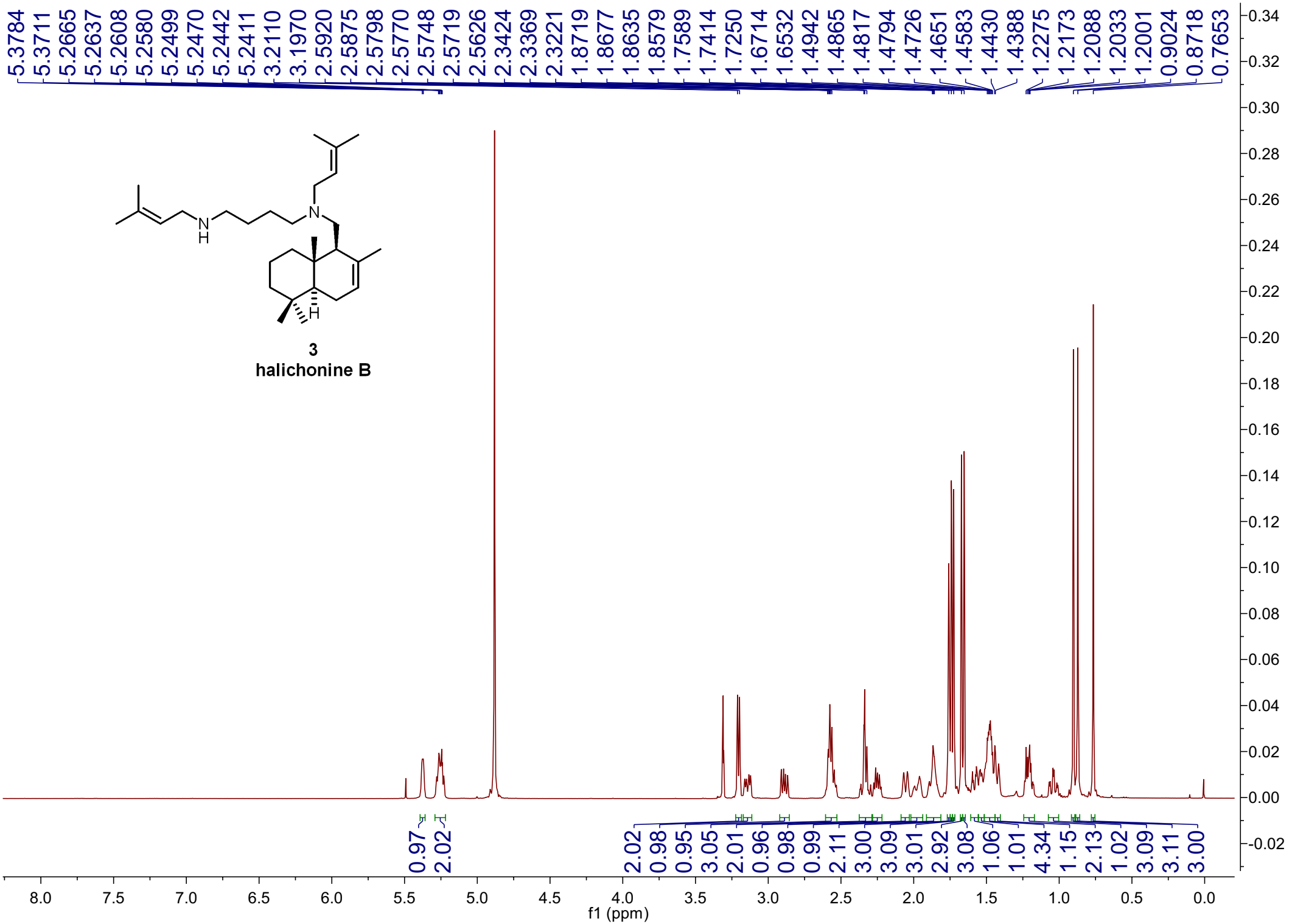
f1 (ppm)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1.06
1.01
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2.13
1.02
3.09
3.11
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0.24
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0.10
0.08
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0.04
0.02
0.00
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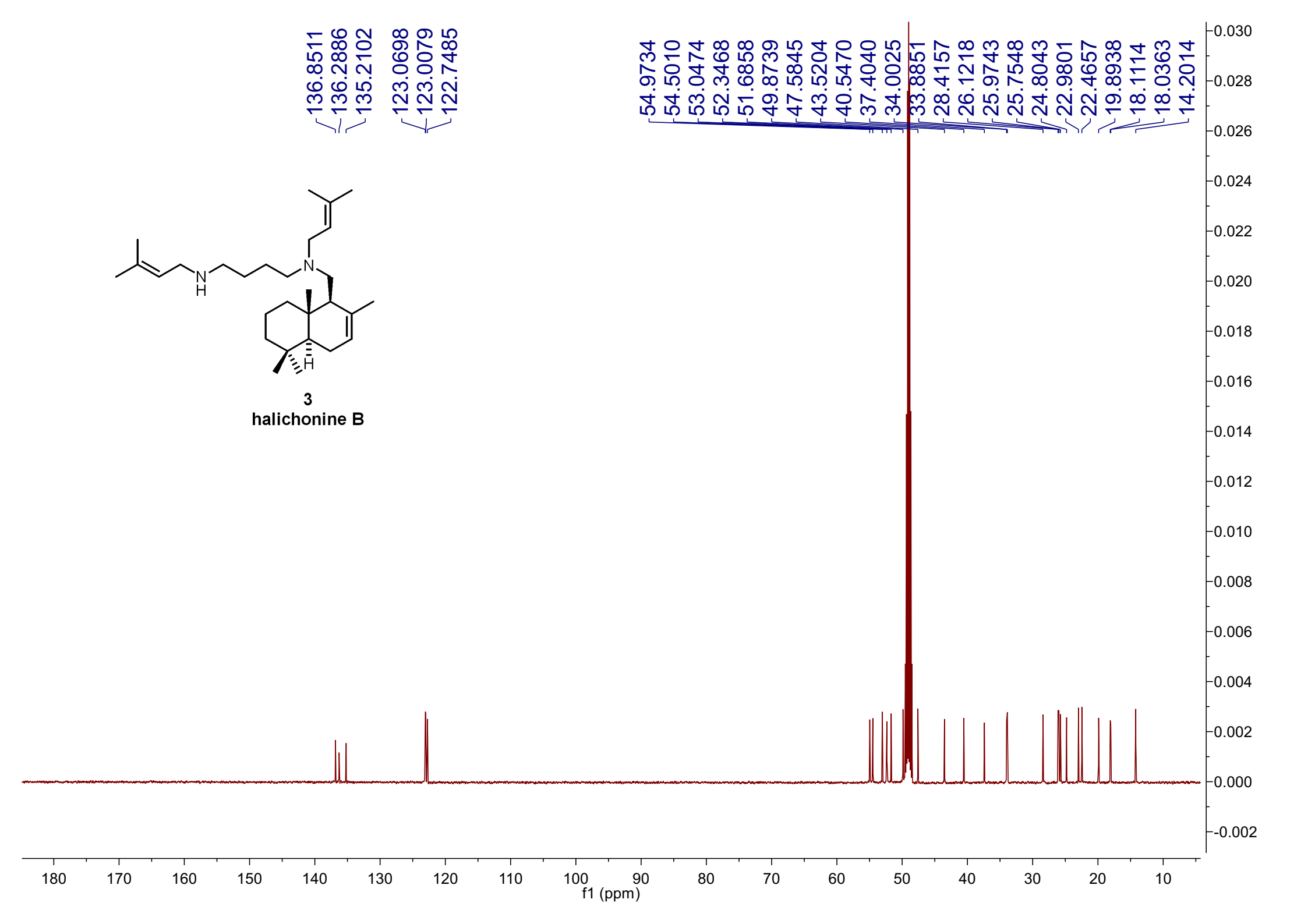
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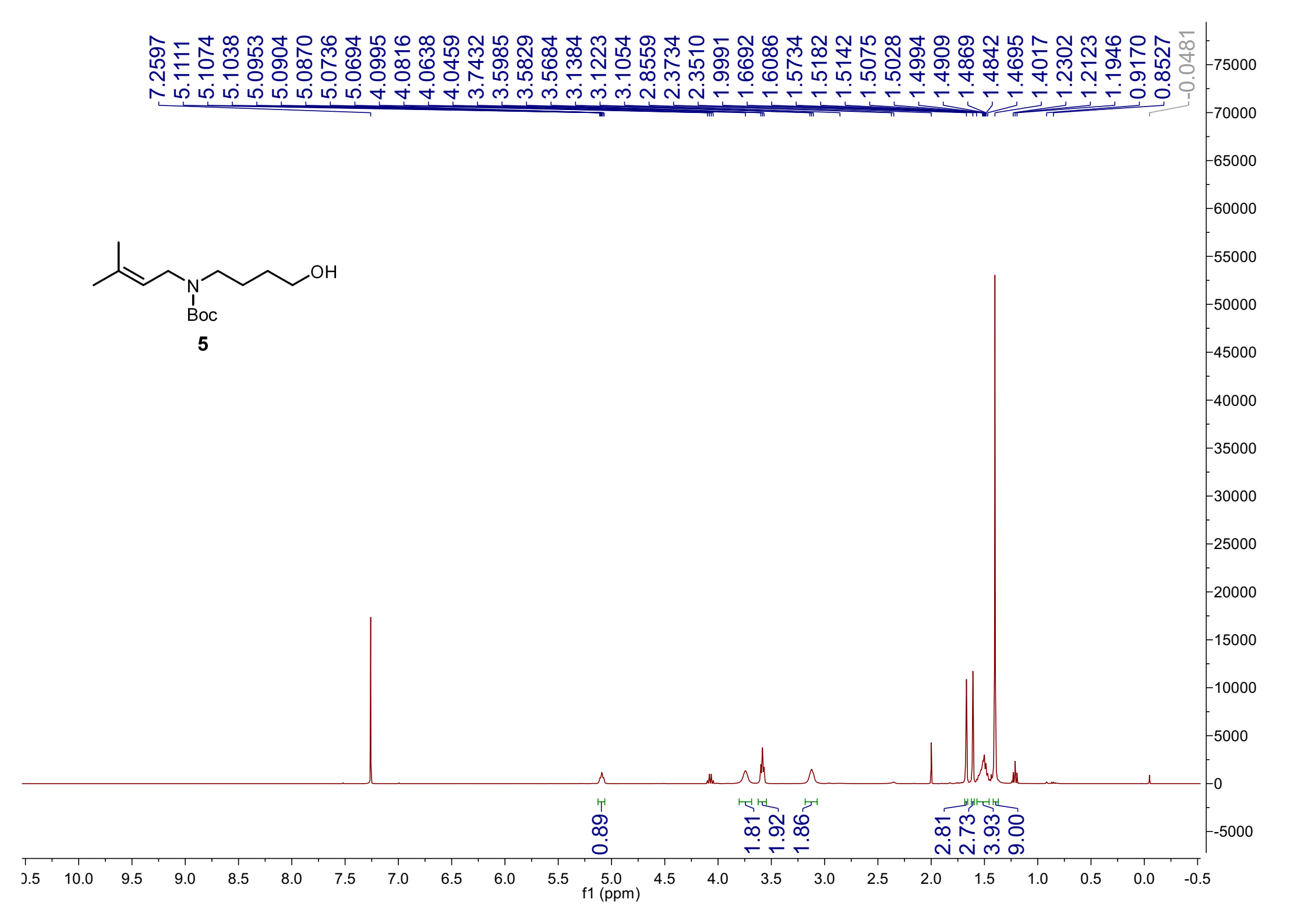
f1 (ppm)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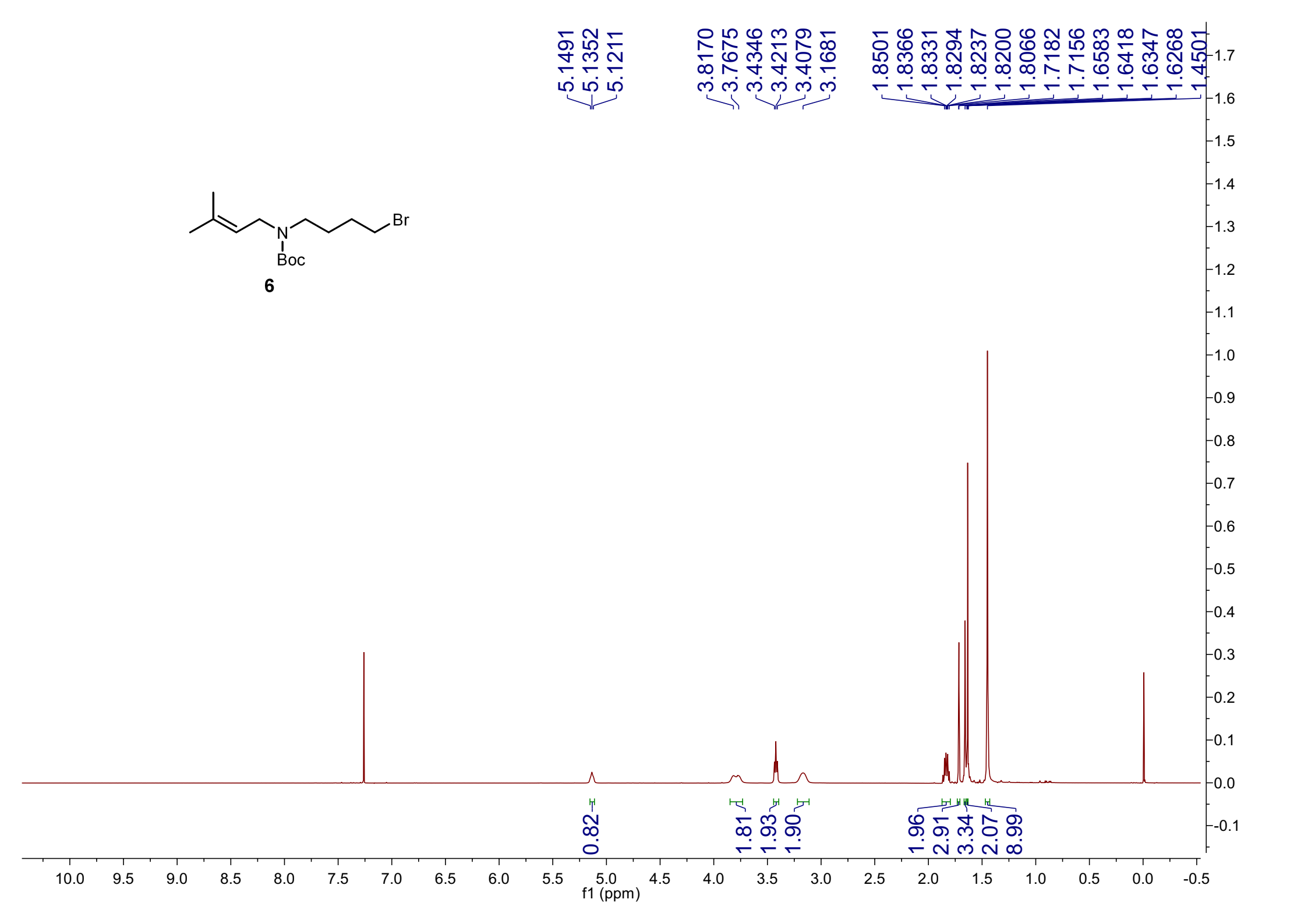
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1.6268
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Br
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Boc
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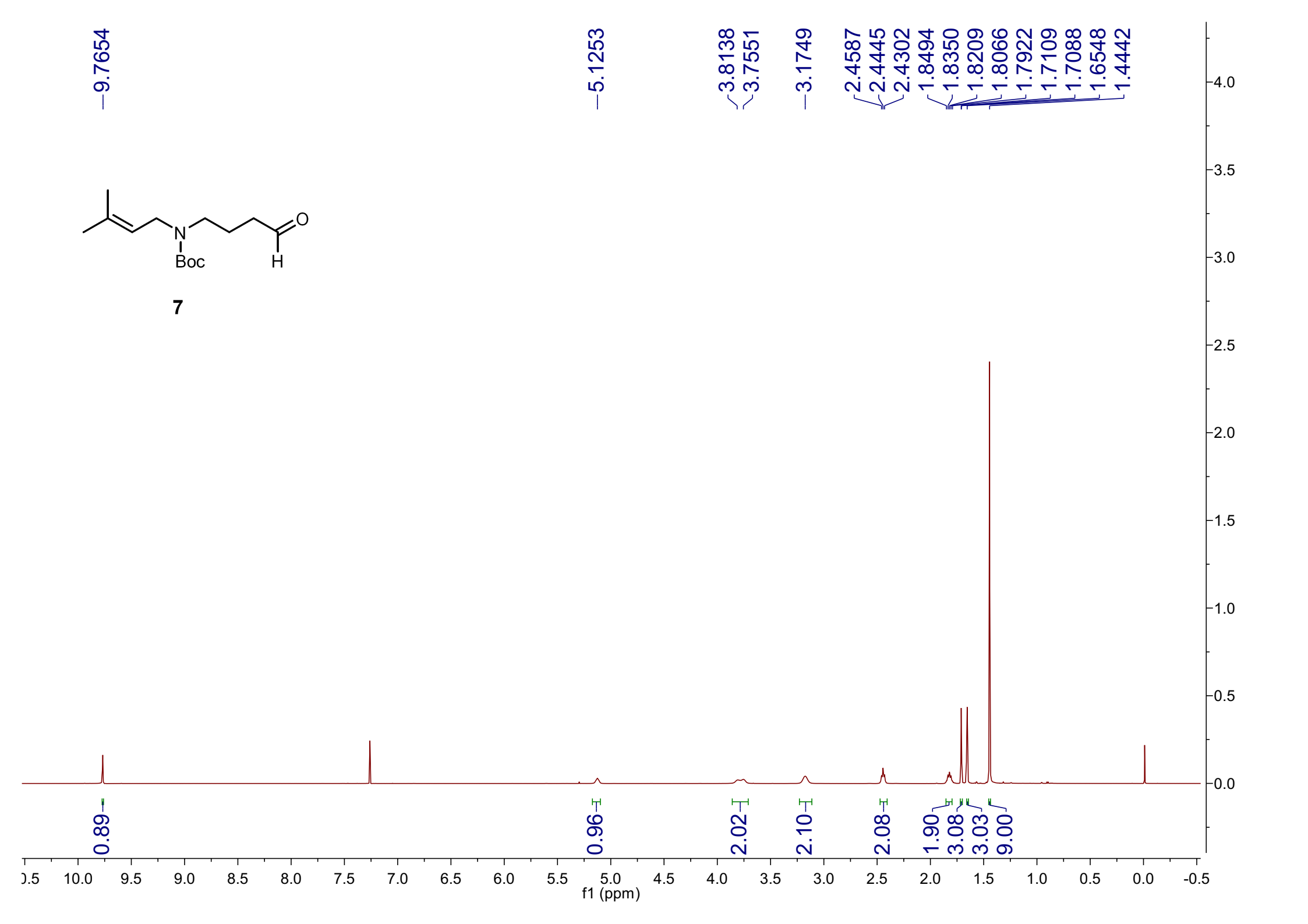
f1 (ppm)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Boc
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3.08
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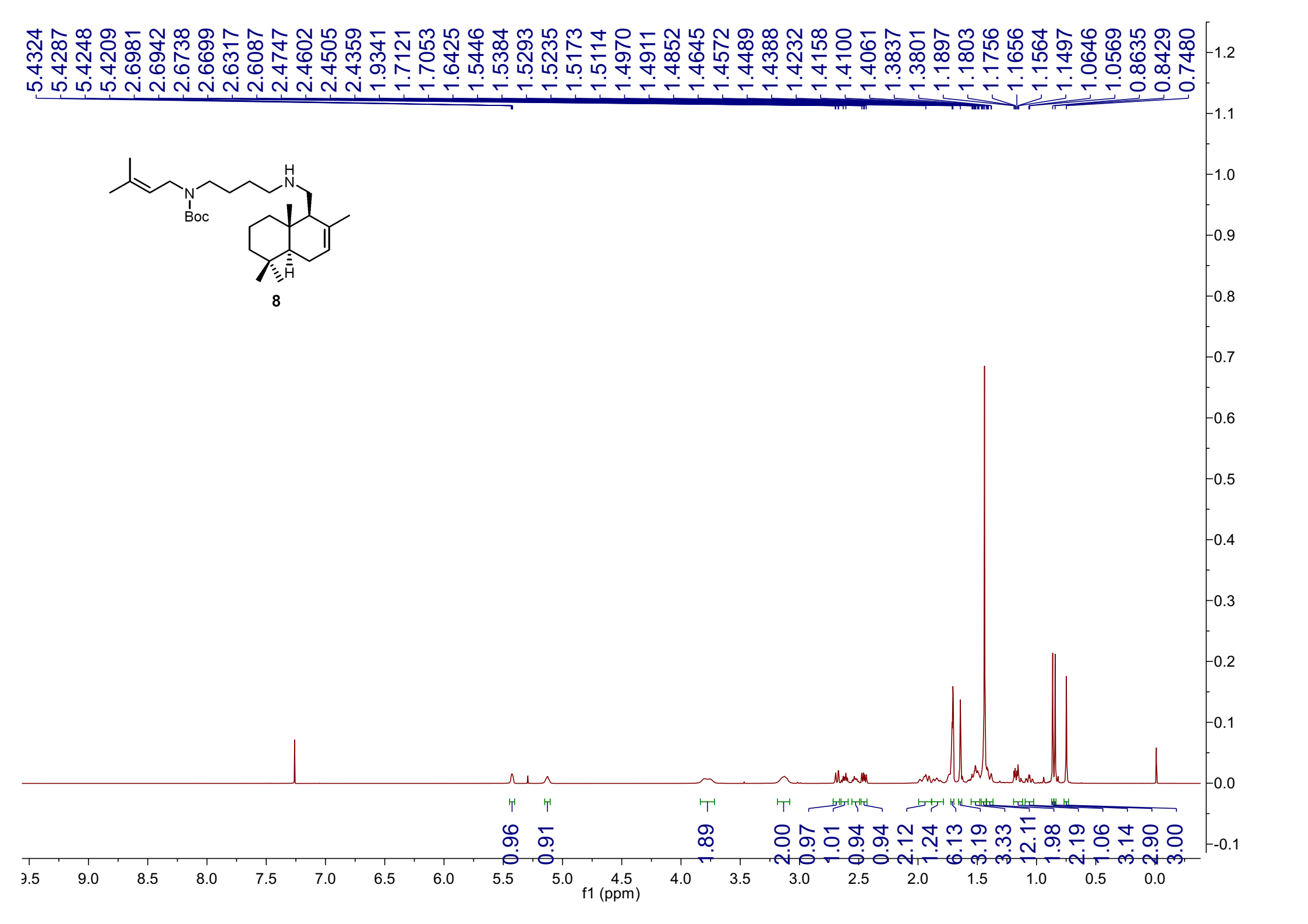
9.00
f1 (ppm)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1.5235
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Boc
H
N
H
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0.97
1.01
0.94
0.94
2.12
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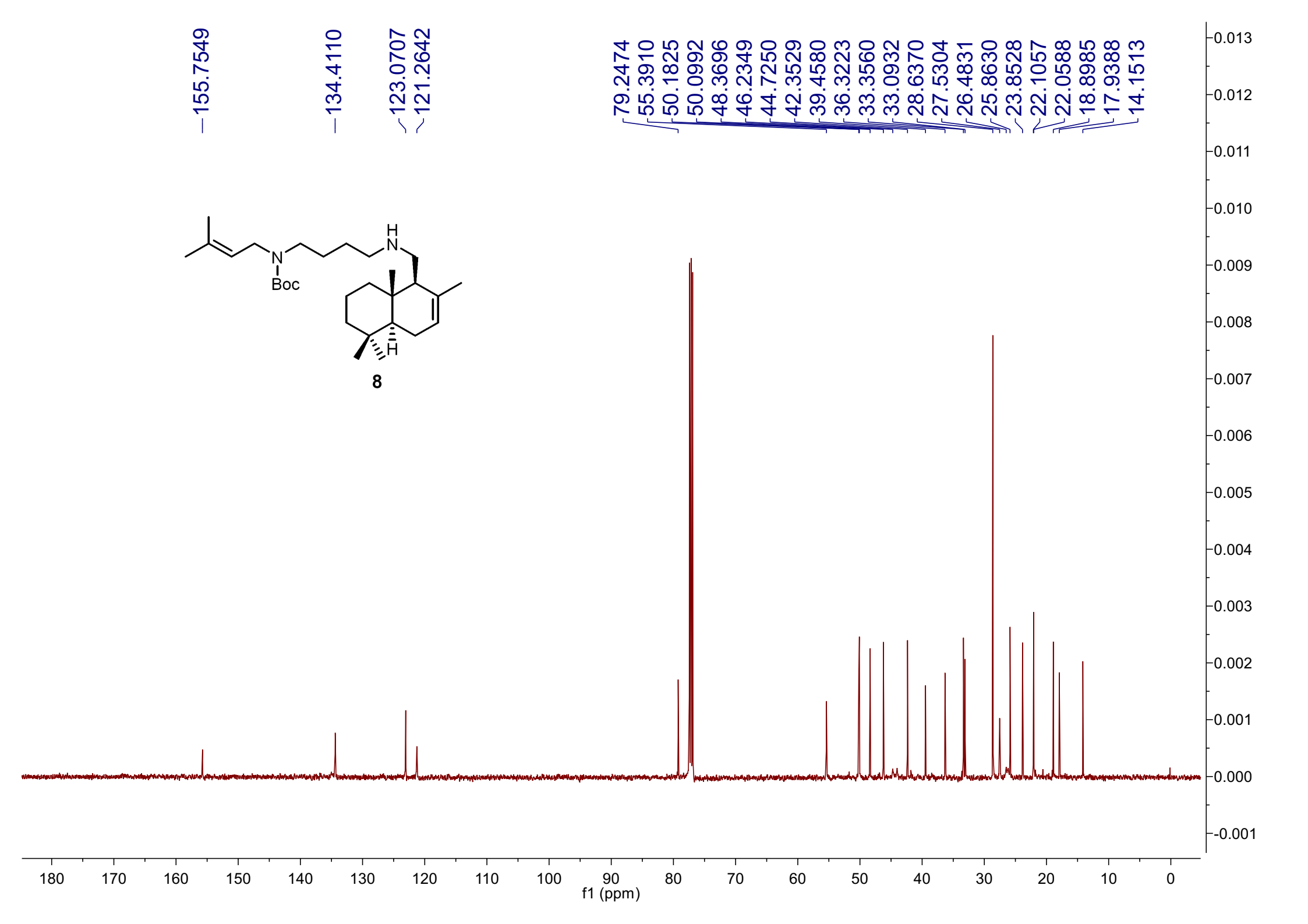
3.00
f1 (ppm)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36.3223
33.3560
33.0932
28.6370
27.5304
26.4831
25.8630
23.8528
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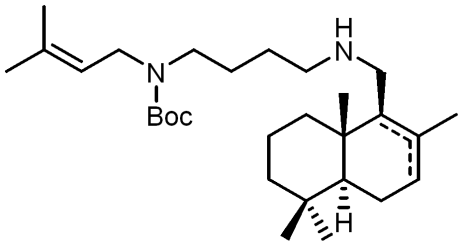
22.0588
18.8985
17.9388
14.1513
N
Boc
H
N
H
8
f1 (ppm)



8m

$\Delta^{7,8}$:$\Delta^{8,9}$=3:2

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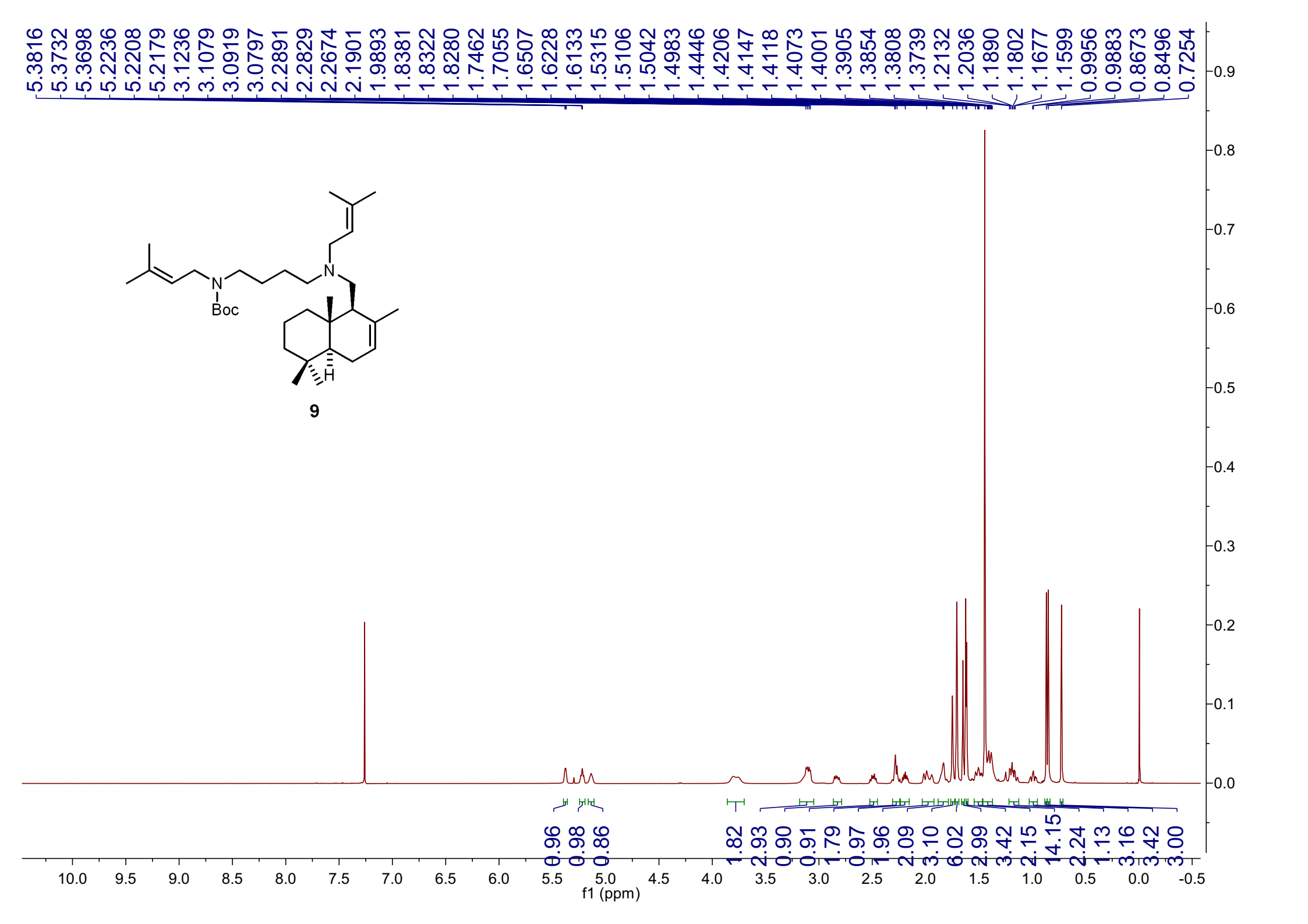
f1 (ppm)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0.8496
0.7254
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N
Boc
H
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0.98
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2.93
0.90
0.91
1.79
0.97
1.96
2.09
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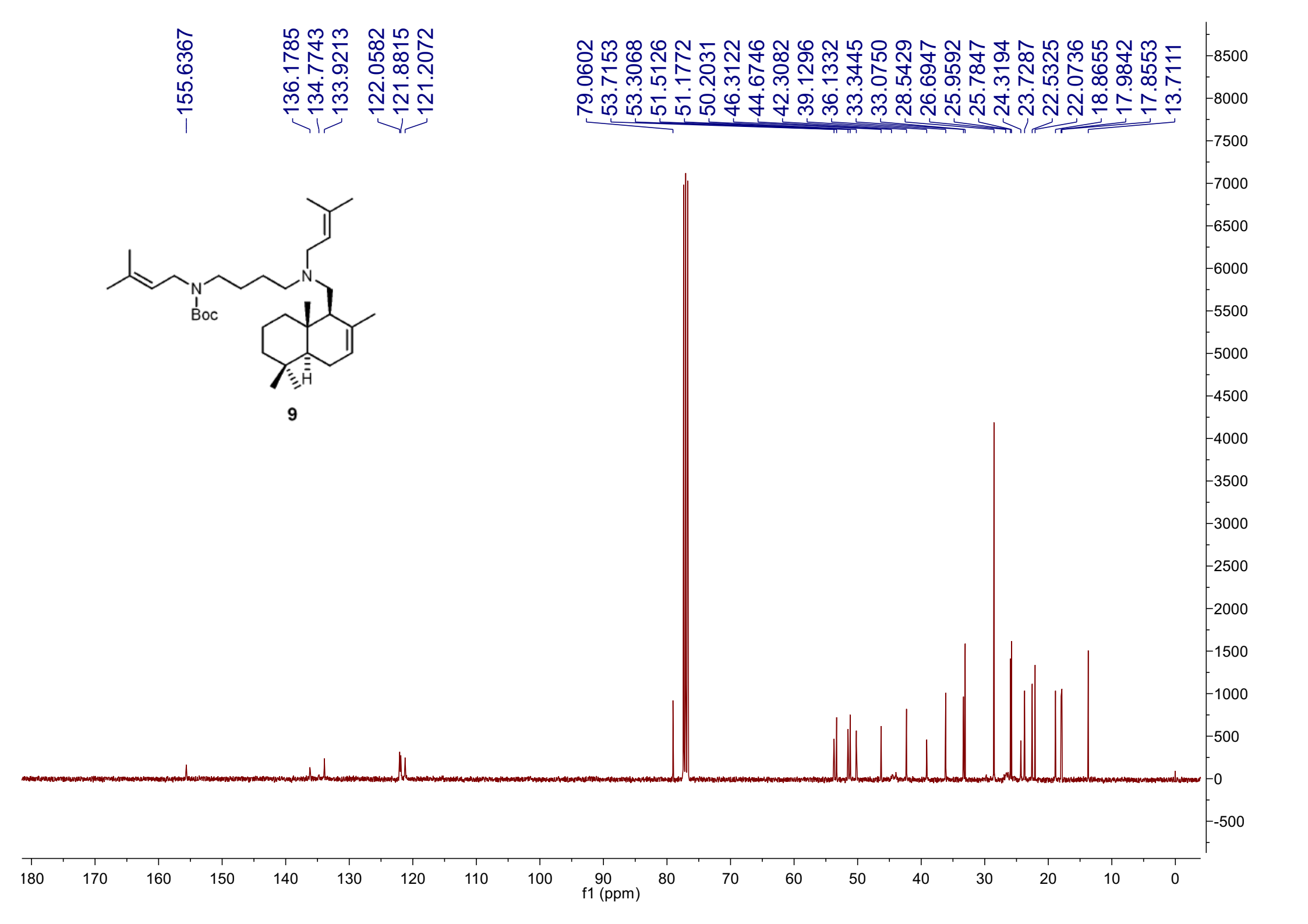
3.16
3.42
3.00
f1 (ppm)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25.9592
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23.7287
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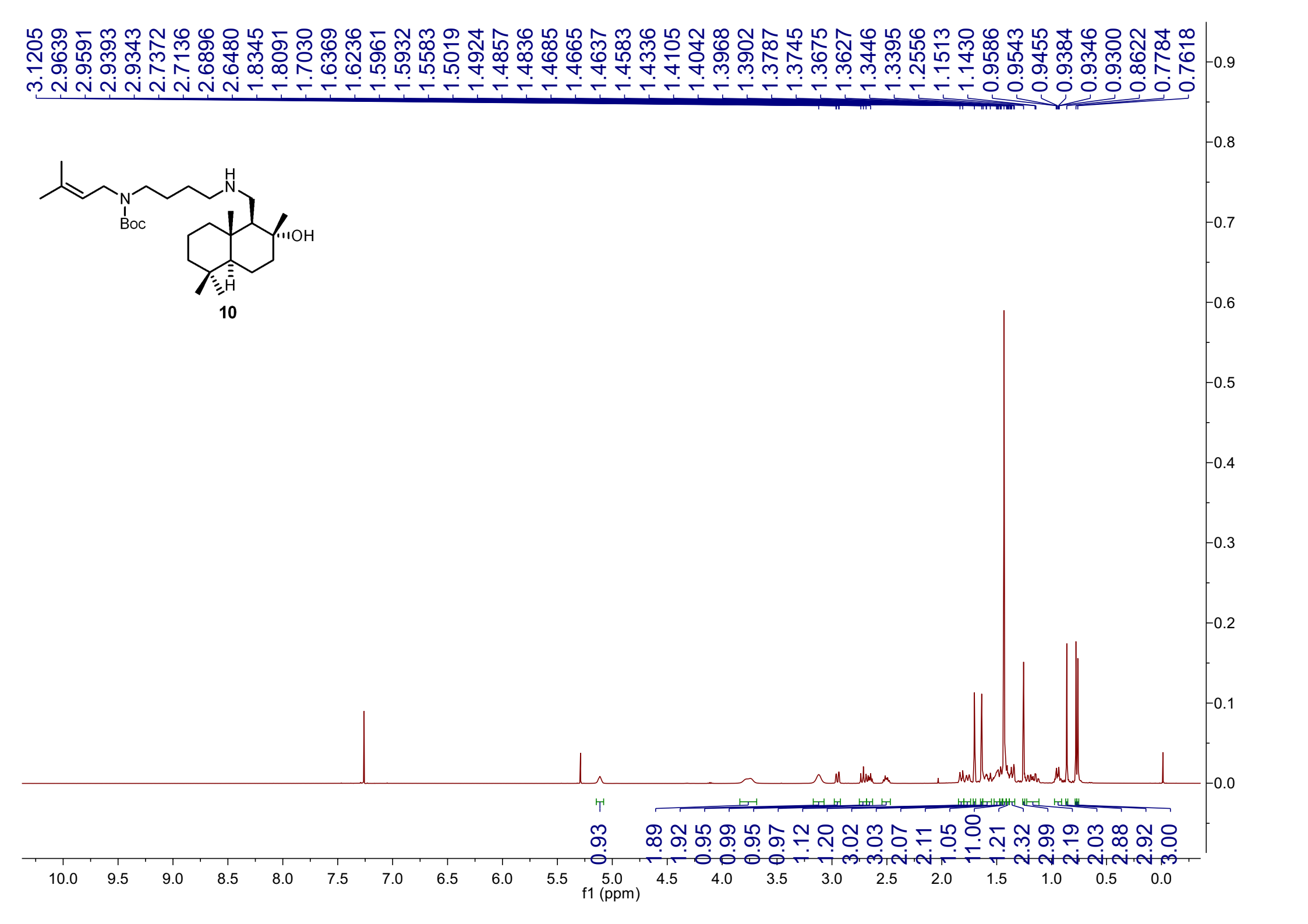
f1 (ppm)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1.5019
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1.4637
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1.1513
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0.9543
0.9455
0.9384
0.9346
0.9300
0.8622
0.7784
0.7618
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N
N
Boc
OH
H
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0.95
0.99
0.95
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3.03
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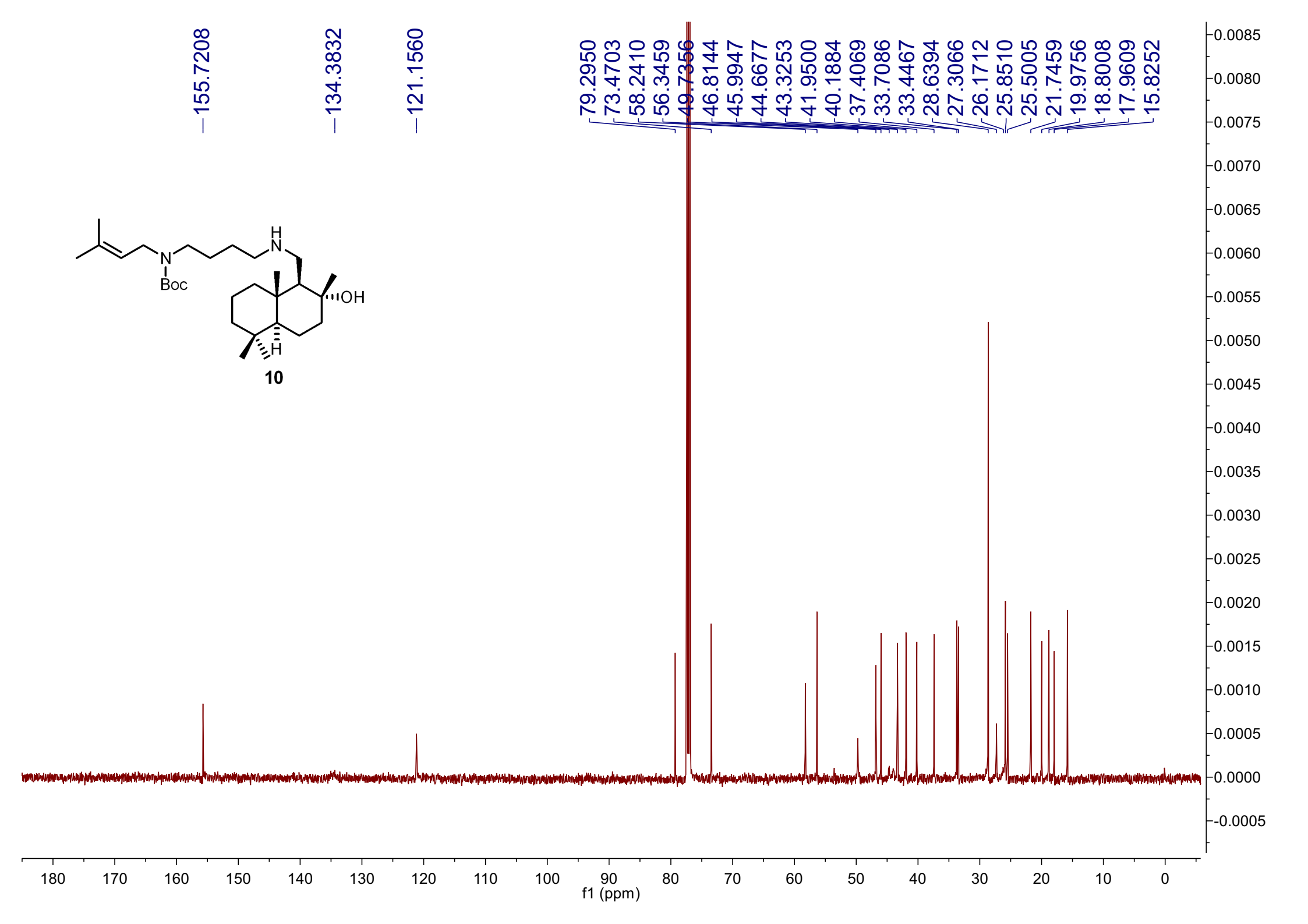
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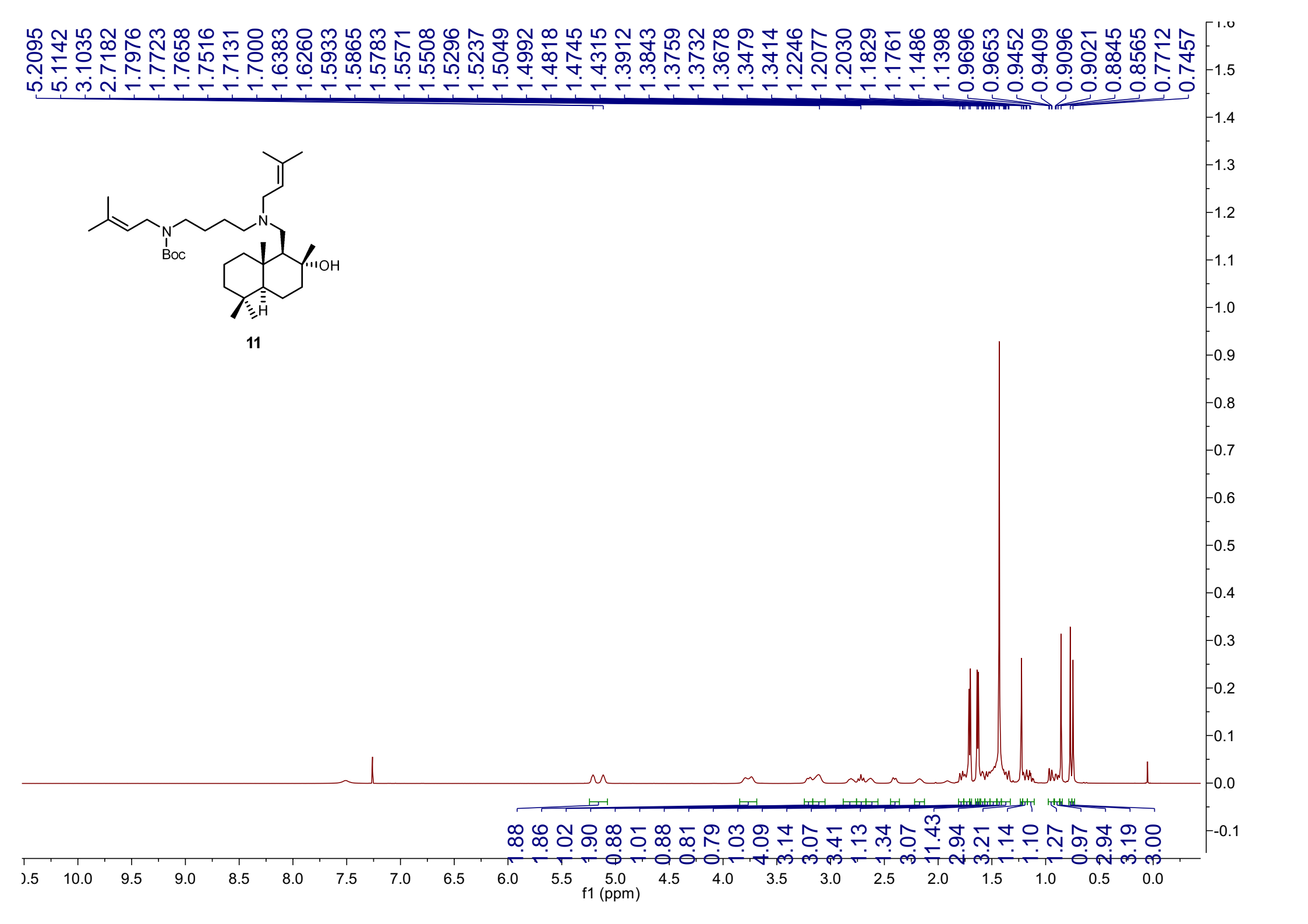
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3.07
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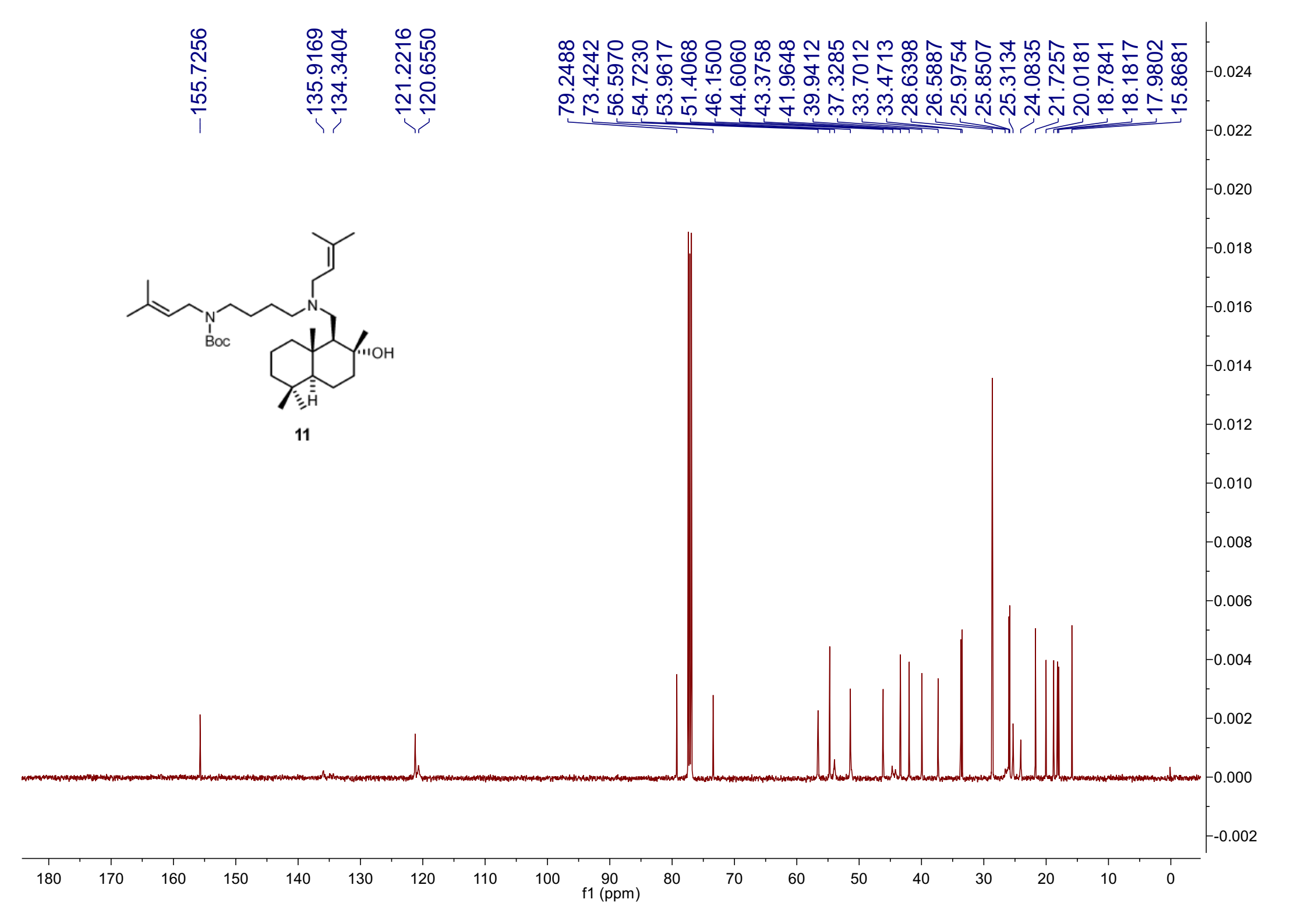
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Boc
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0.008
0.006
0.004
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0.000
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180
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50
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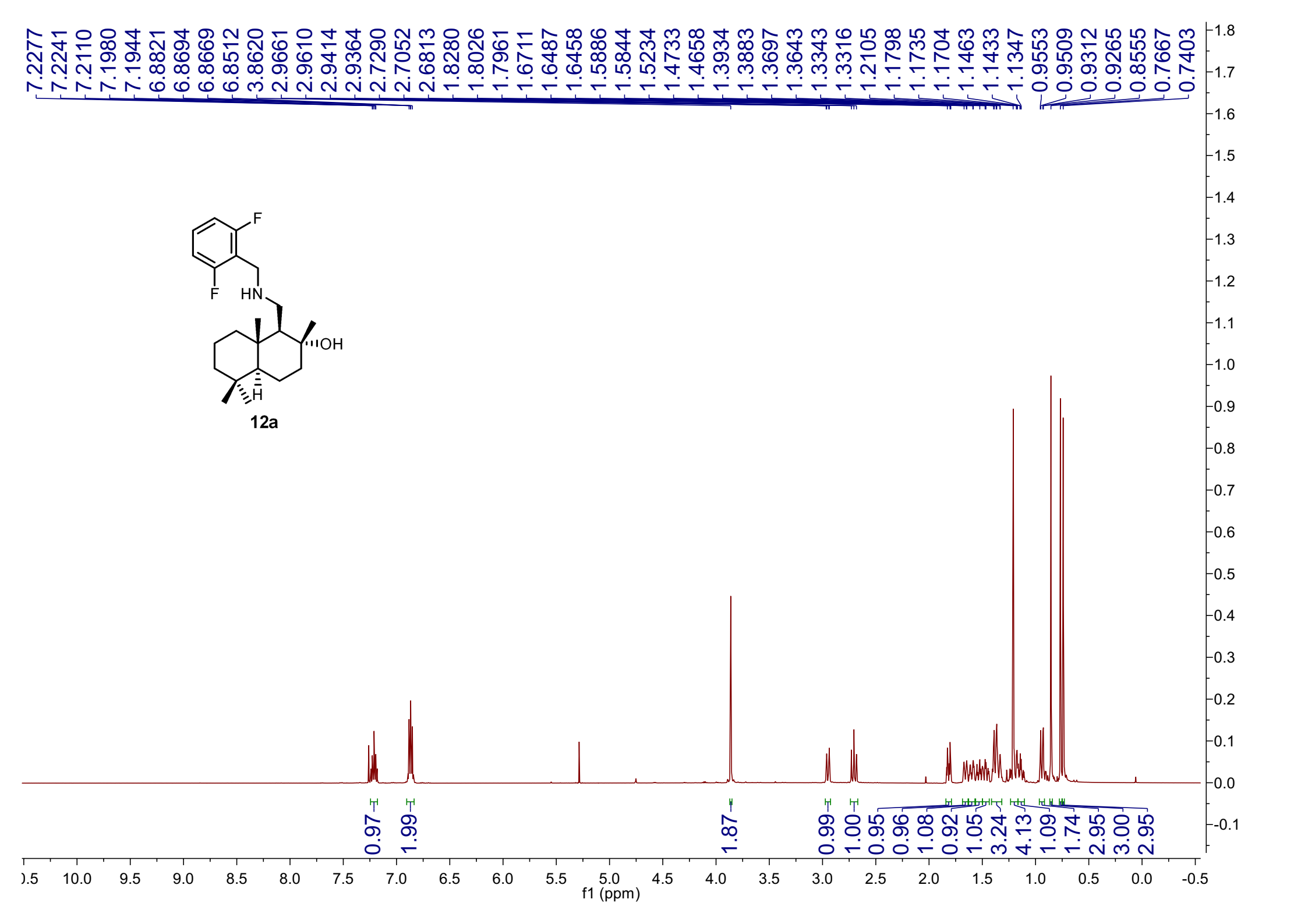
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F
F
HN
OH
H
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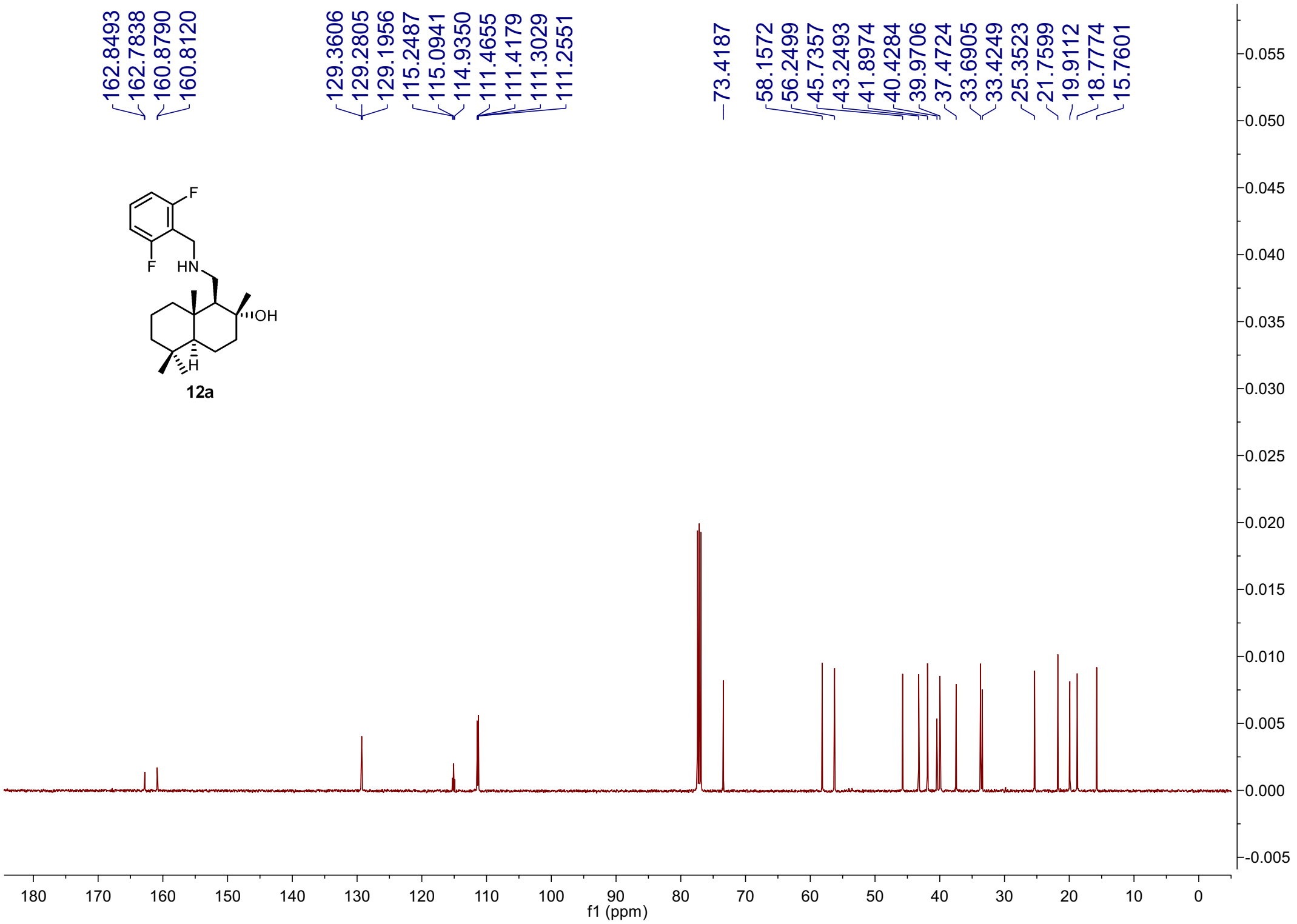
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F
HN
OH
H
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0.025
0.020
0.015
0.010
0.005
0.000
-0.005
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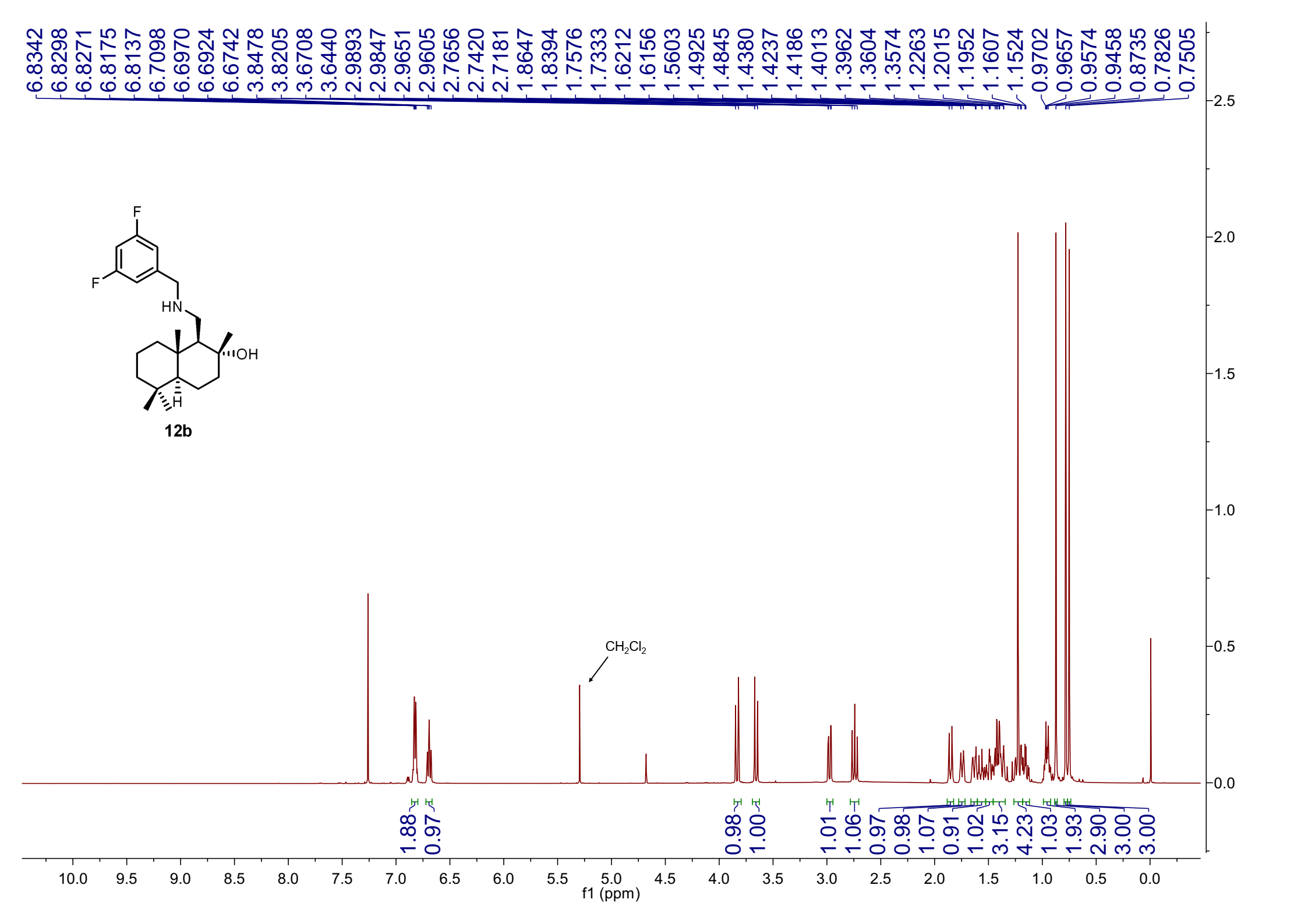
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0.7505
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F
HN
OH
H
12b
CH2Cl2
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0.98
1.00
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1.06
0.97
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2.90
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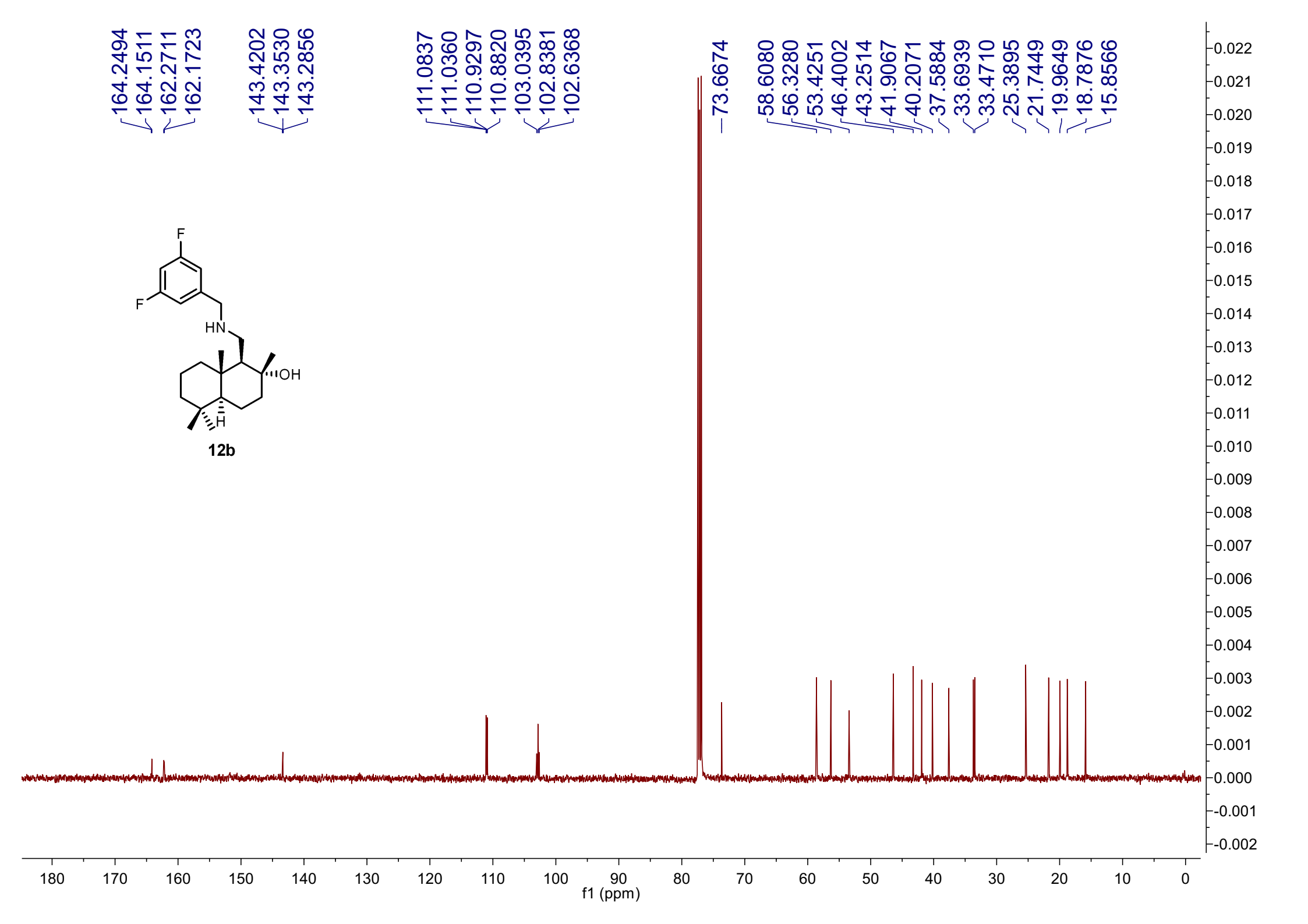
3.00
f1 (ppm)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33.4710
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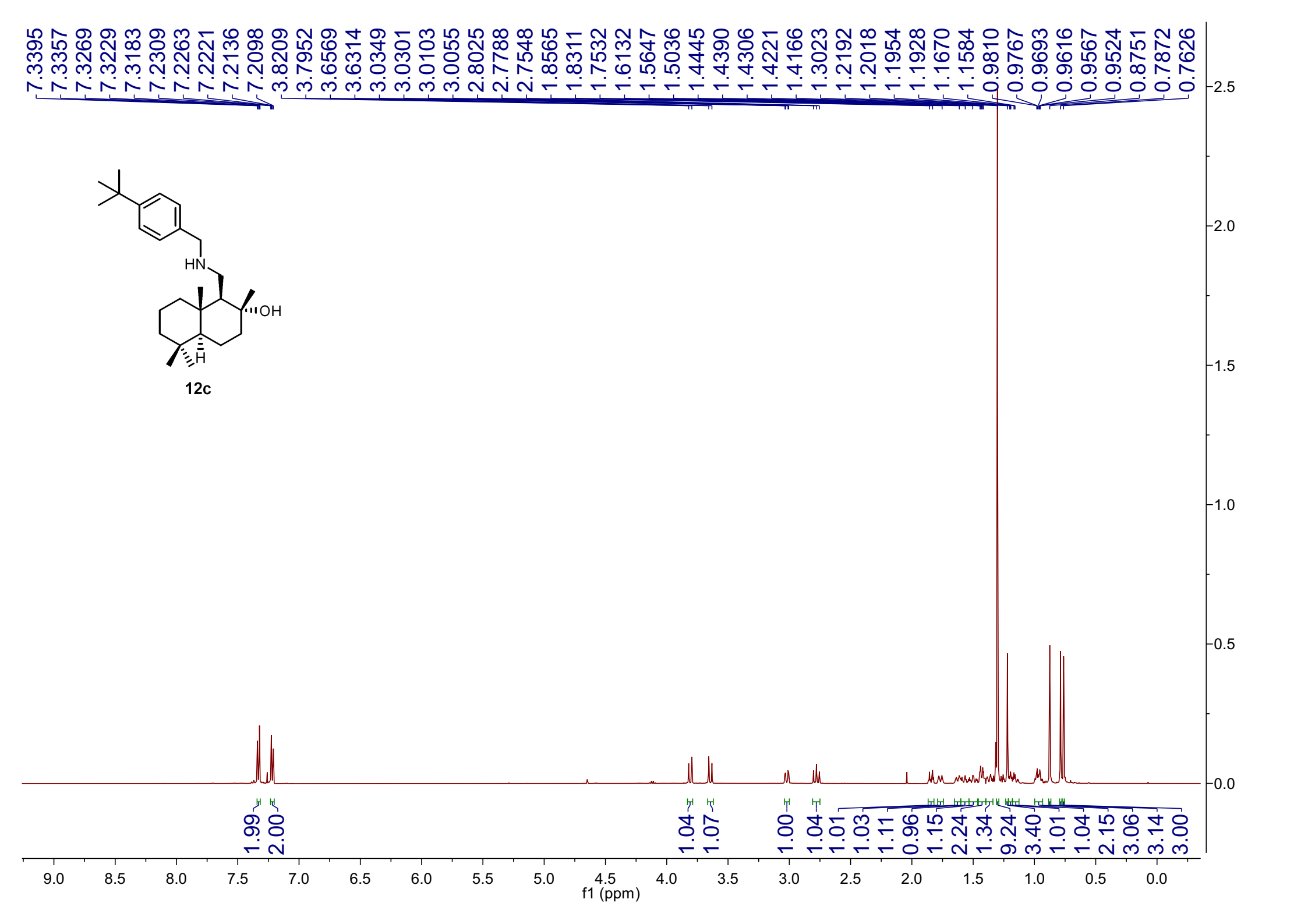
15.8566
F
F
HN
OH
H
12b
f1 (ppm)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OH
H
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2.00
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1.07
1.00
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1.01
1.03
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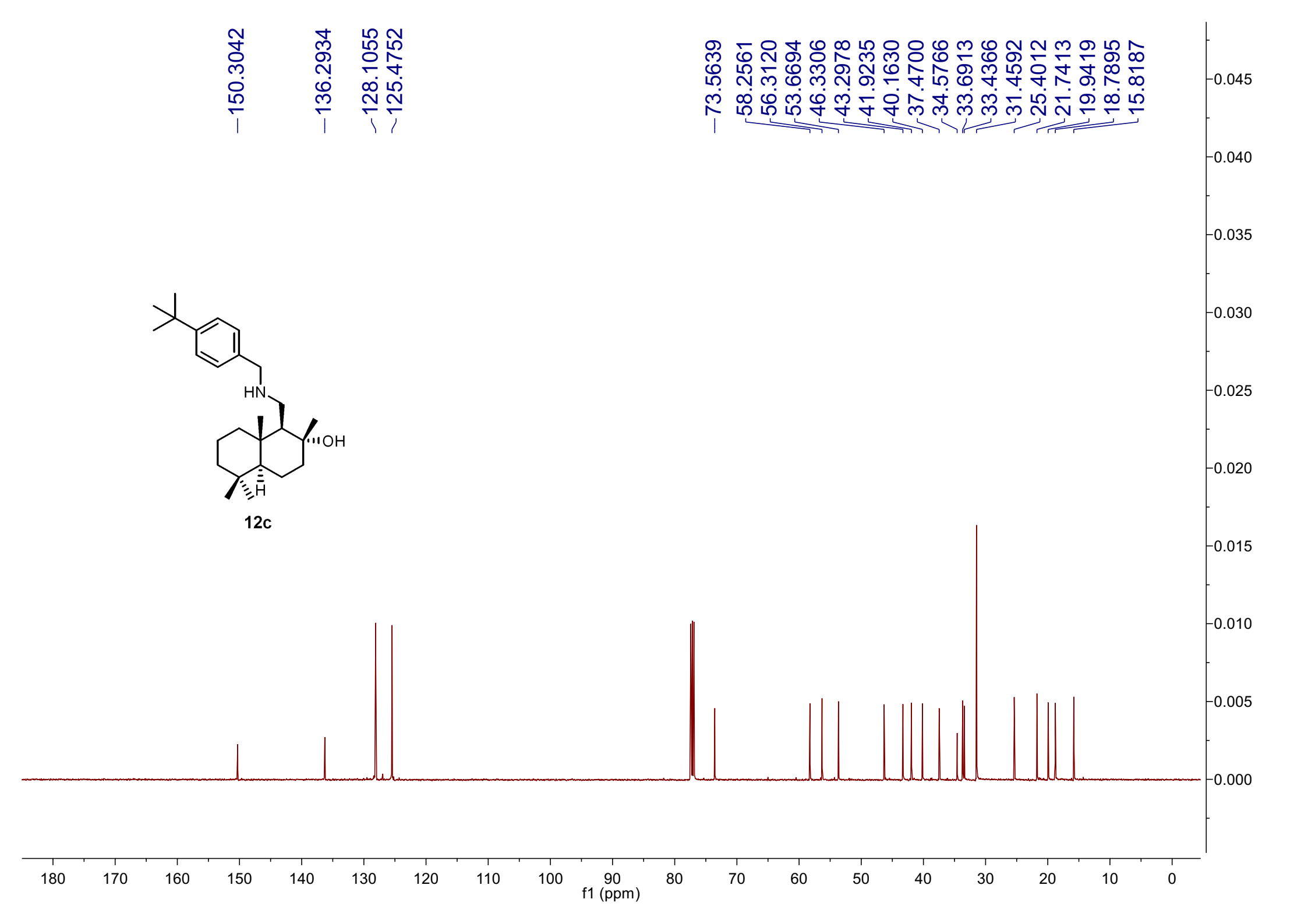
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OH
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0.035
0.030
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0.020
0.015
0.010
0.005
0.000
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170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) 6075

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: 6075

```
Bond precision:   C-C = 0.0076 A          Wavelength=1.54184

Cell:             a=6.9259(3)     b=10.4340(4)     c=34.5744(16)
                  alpha=90        beta=90          gamma=90
Temperature:      150 K
```

	Calculated	Reported
Volume	2498.51(18)	2498.50(18)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C26 H44 N O, Cl	Cl, C26 H44 N O
Sum formula	C26 H44 Cl N O	C26 H44 Cl N O
Mr	422.07	422.07
Dx,g cm-3	1.122	1.122
Z	4	4
Mu (mm-1)	1.454	1.454
F000	928.0	928.0
F000'	931.55	
h,k,lmax	8,13,43	8,12,42
Nref	5075[2931]	4927
Tmin,Tmax	0.828,0.877	0.532,1.000
Tmin'	0.828	

```
Correction method= # Reported T Limits: Tmin=0.532 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.68/0.97        Theta(max)= 74.022

R(reflections)= 0.0689( 4720)                    wR2(reflections)=
                                                 0.1667( 4927)
S = 1.071                  Npar= 273
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

```
PLAT220_ALERT_2_C NonSolvent   Resd 1  C   Ueq(max)/Ueq(min) Range        3.5 Ratio
PLAT222_ALERT_3_C NonSolvent Resd 1  H   Uiso(max)/Uiso(min) Range        4.4 Ratio
PLAT242_ALERT_2_C Low    'MainMol' Ueq as Compared to Neighbors of        C19 Check
PLAT340_ALERT_3_C Low Bond Precision on  C-C Bonds ..............    0.00756 Ang.
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ......      2.665 Check
```

Alert level G

```
PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ..............          2 Report
PLAT042_ALERT_1_G Calc. and Reported Moiety Formula Strings Differ     Please Check
PLAT083_ALERT_2_G SHELXL Second Parameter in WGHT  Unusually Large       5.21 Why ?
PLAT791_ALERT_4_G Model has Chirality at C5          (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C8          (Sohnke SpGr)          R Verify
PLAT791_ALERT_4_G Model has Chirality at C9          (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C10         (Sohnke SpGr)          S Verify
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600         43 Note
PLAT933_ALERT_2_G Number of OMIT Records in Embedded .res File ...          2 Note
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ...........        3.0 Low
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.          6 Info
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   5 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  11 ALERT level G = General information/check it is not something unexpected

   1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   5 ALERT type 2 Indicator that the structure model may be wrong or deficient
   4 ALERT type 3 Indicator that the structure quality may be low
   5 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

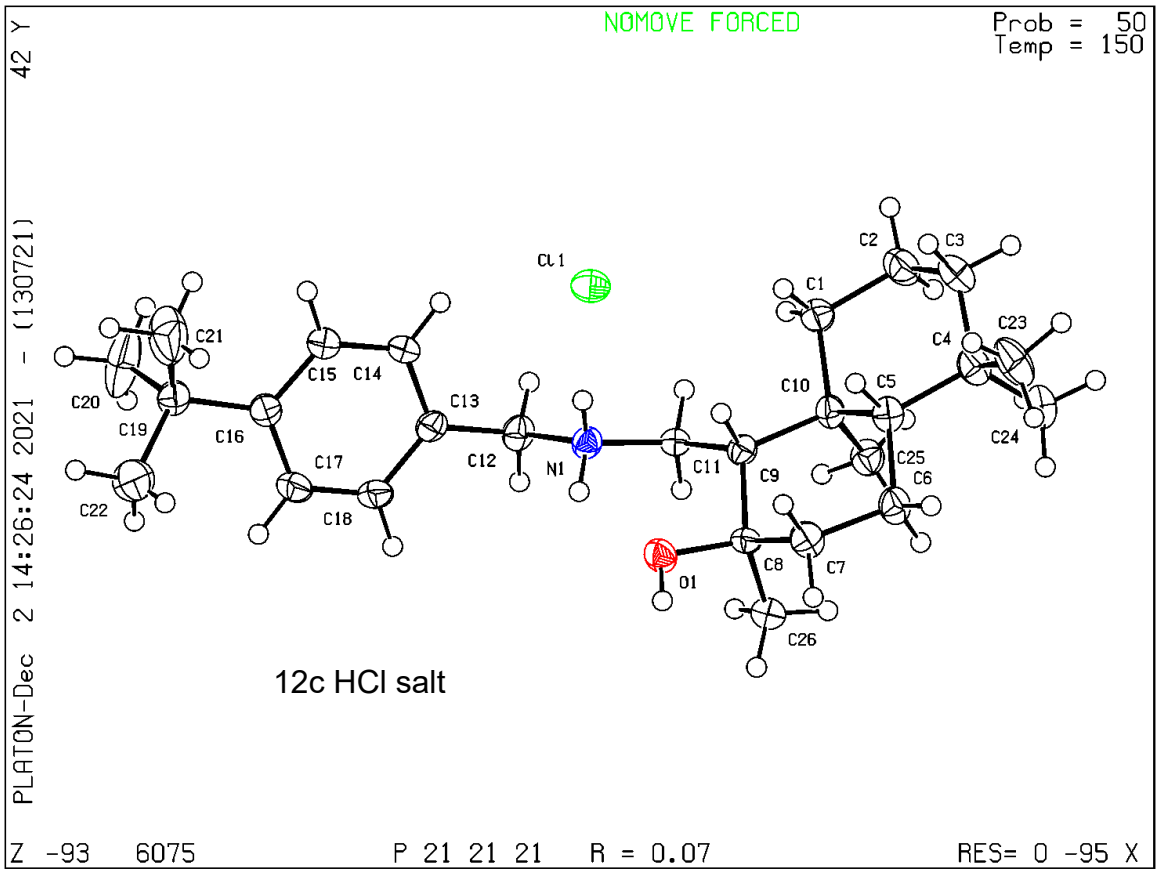
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

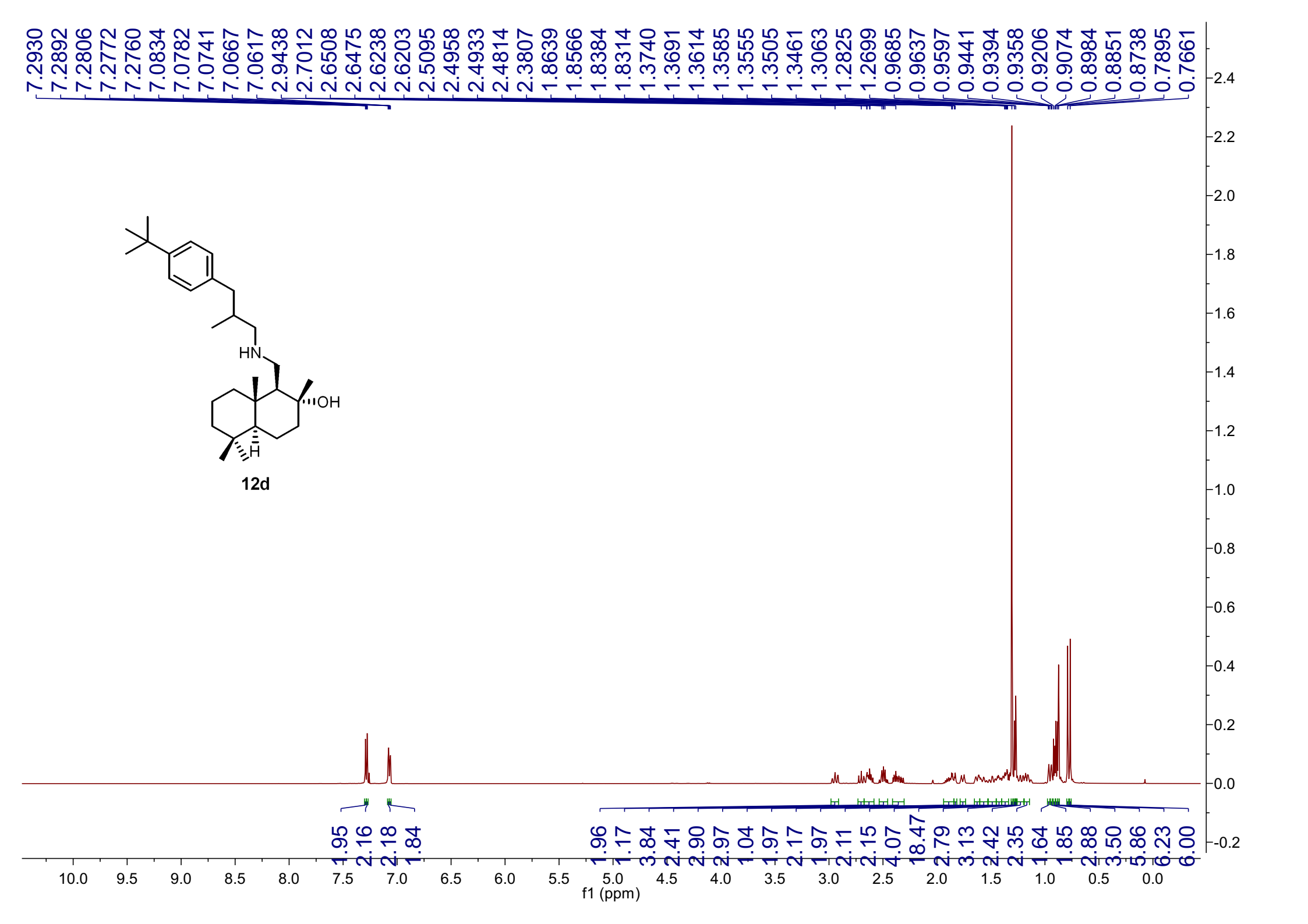
Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 13/07/2021; check.def file version of 13/07/2021

Datablock 6075 - ellipsoid plot

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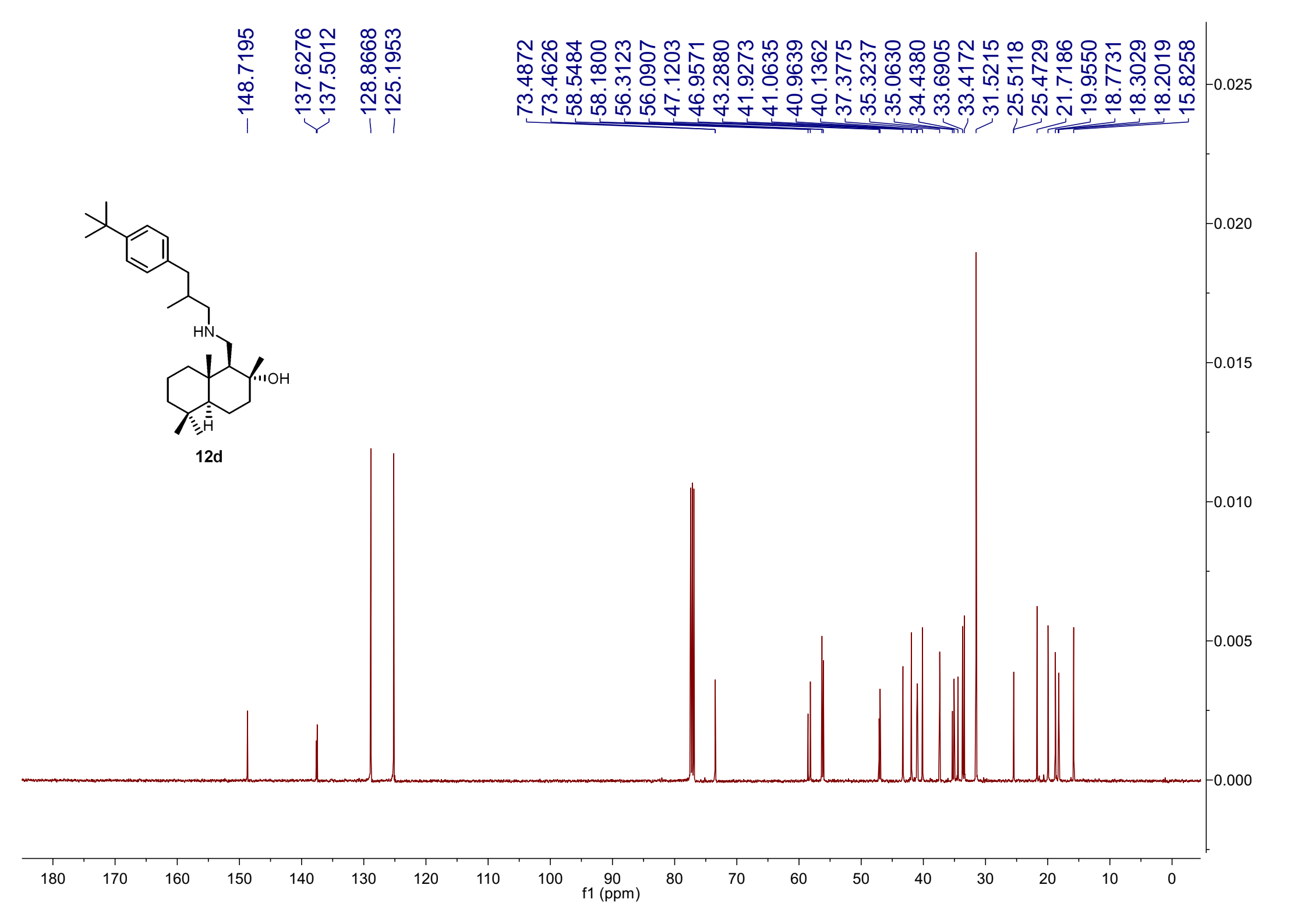
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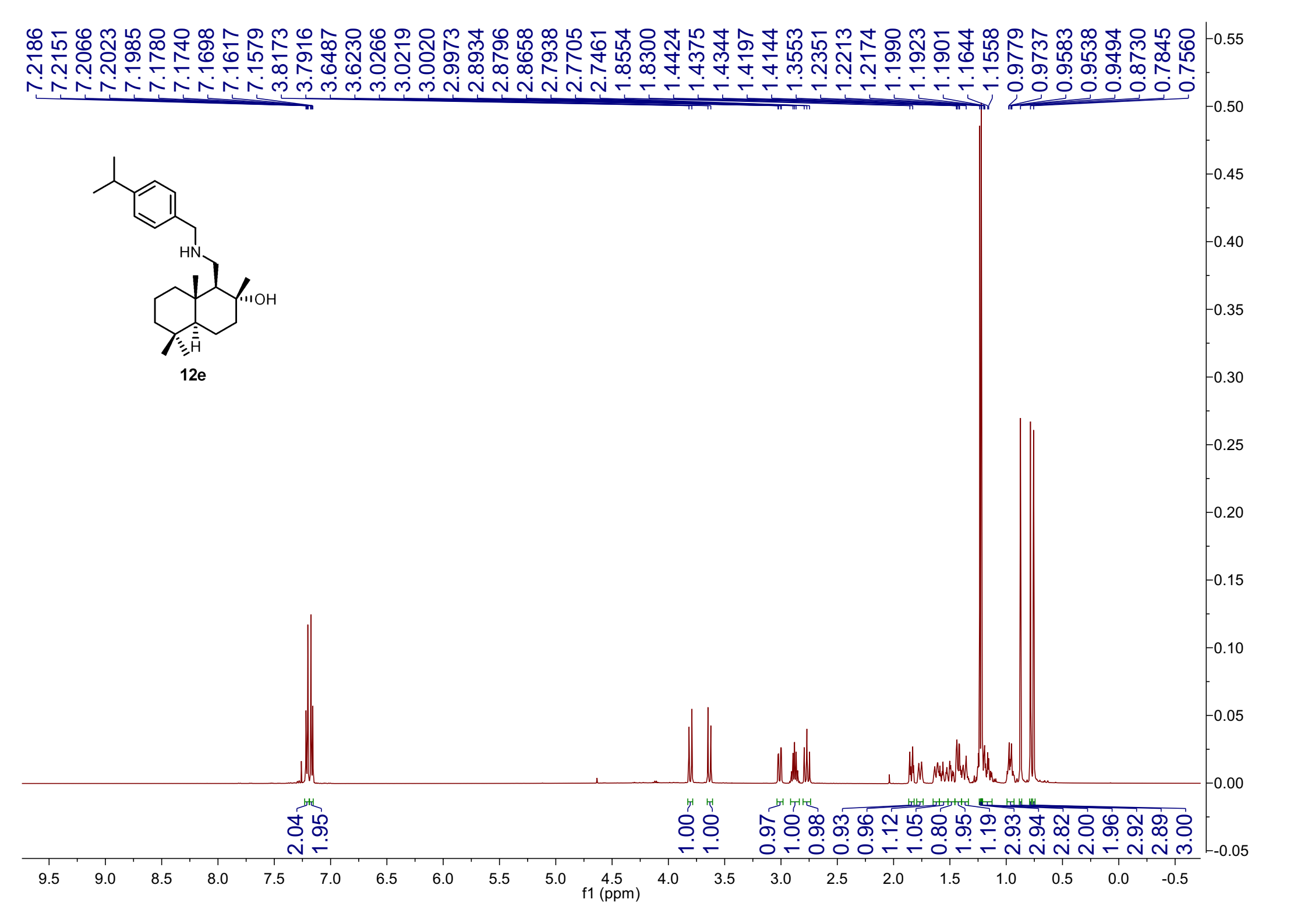
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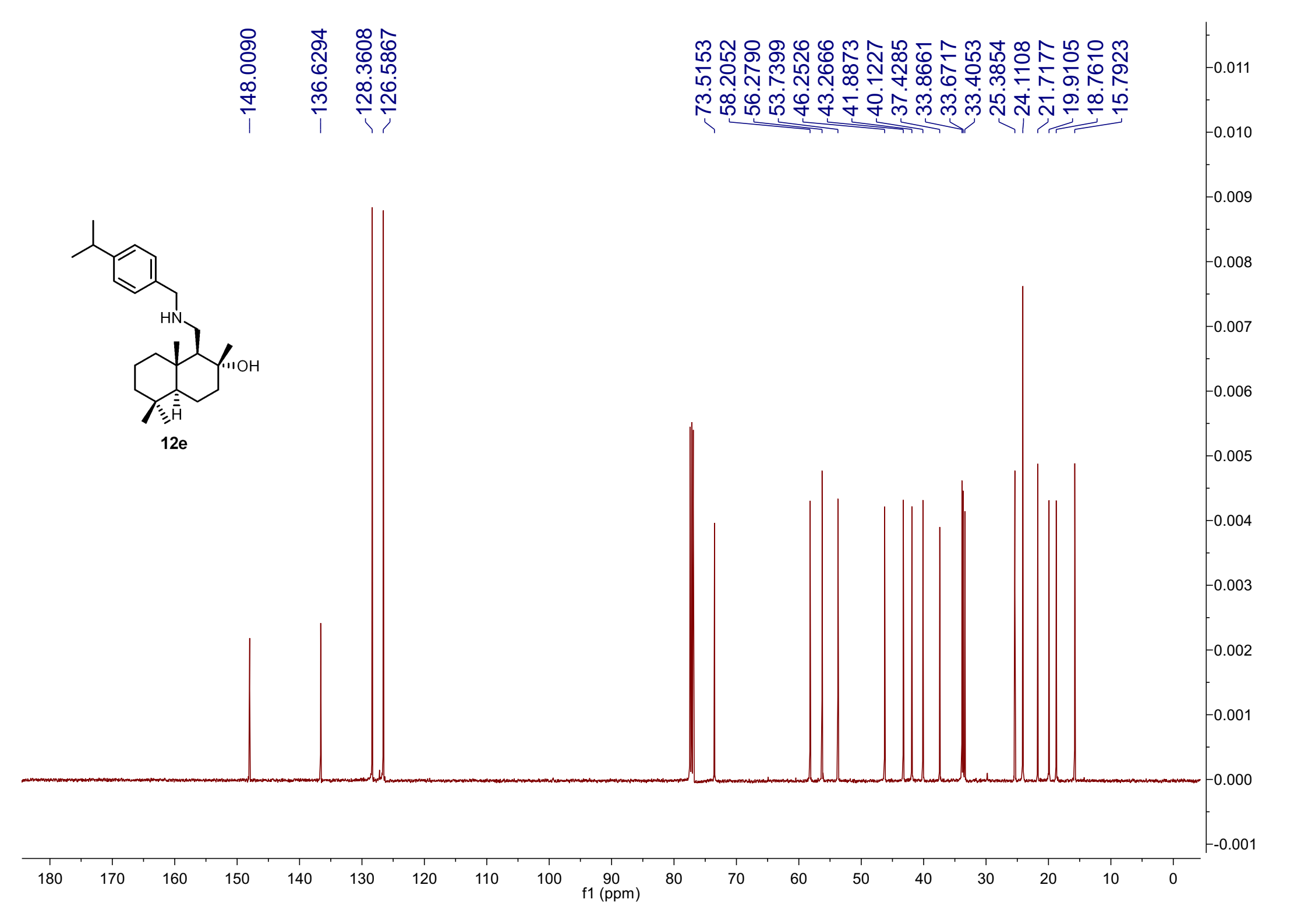
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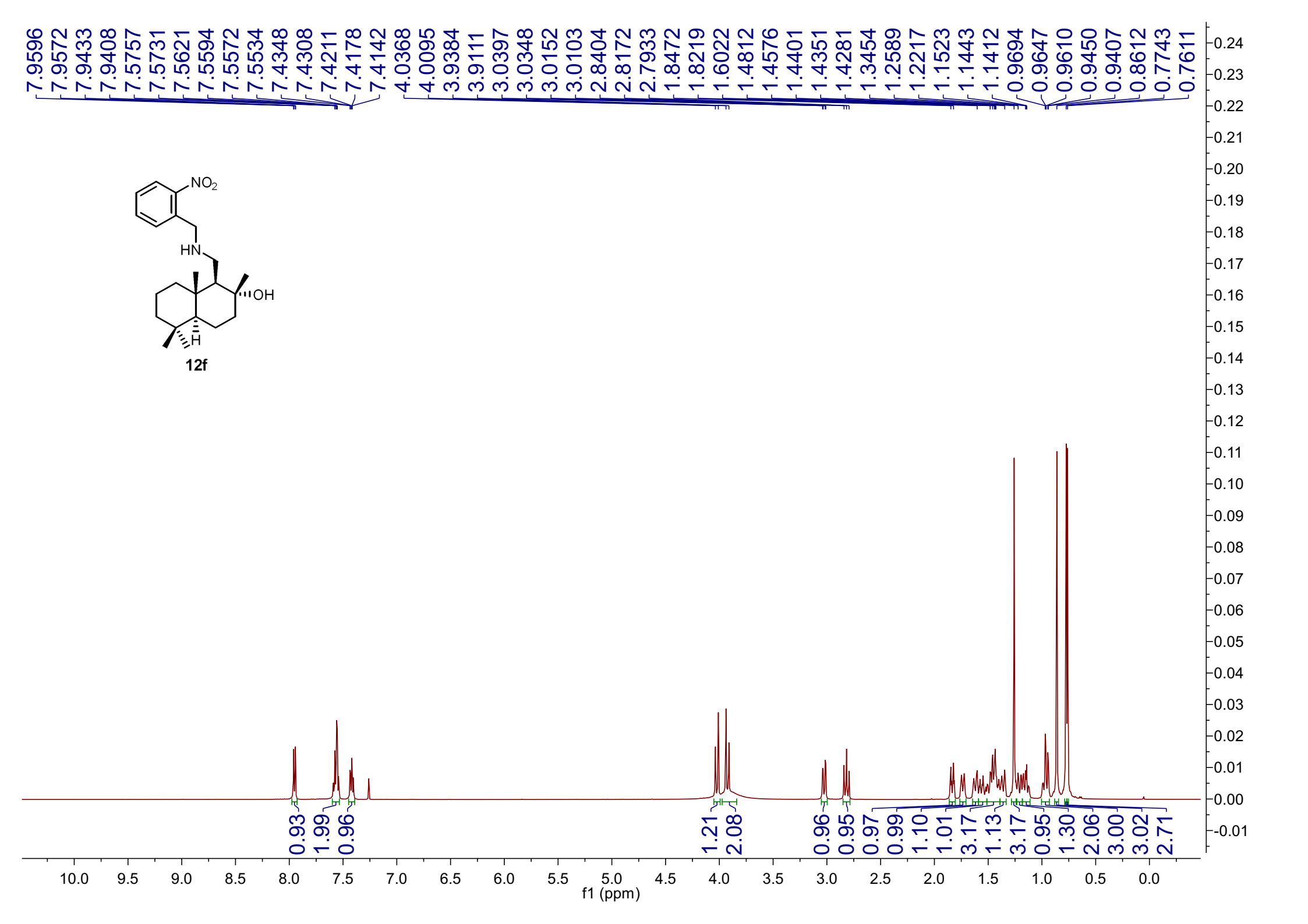
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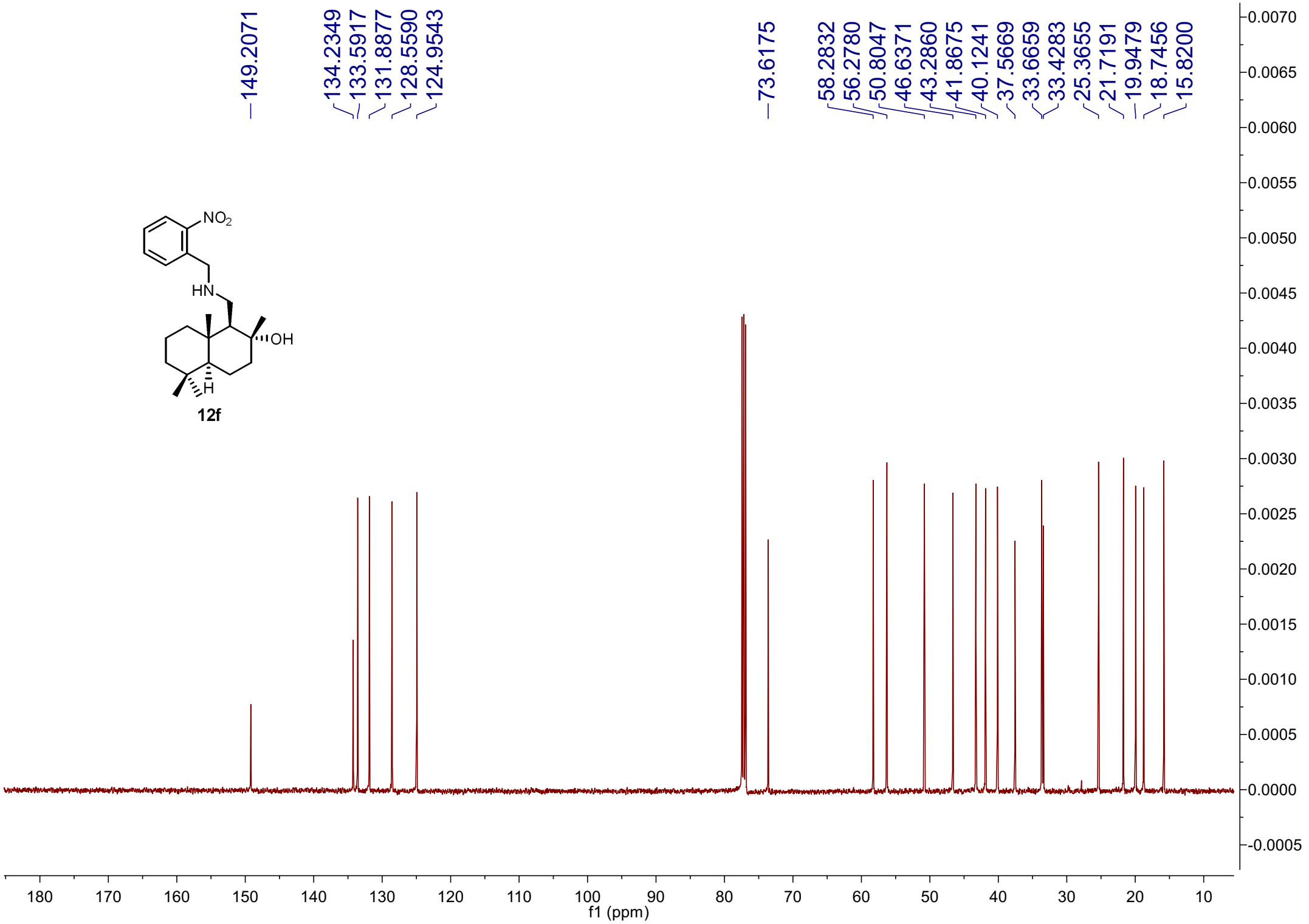
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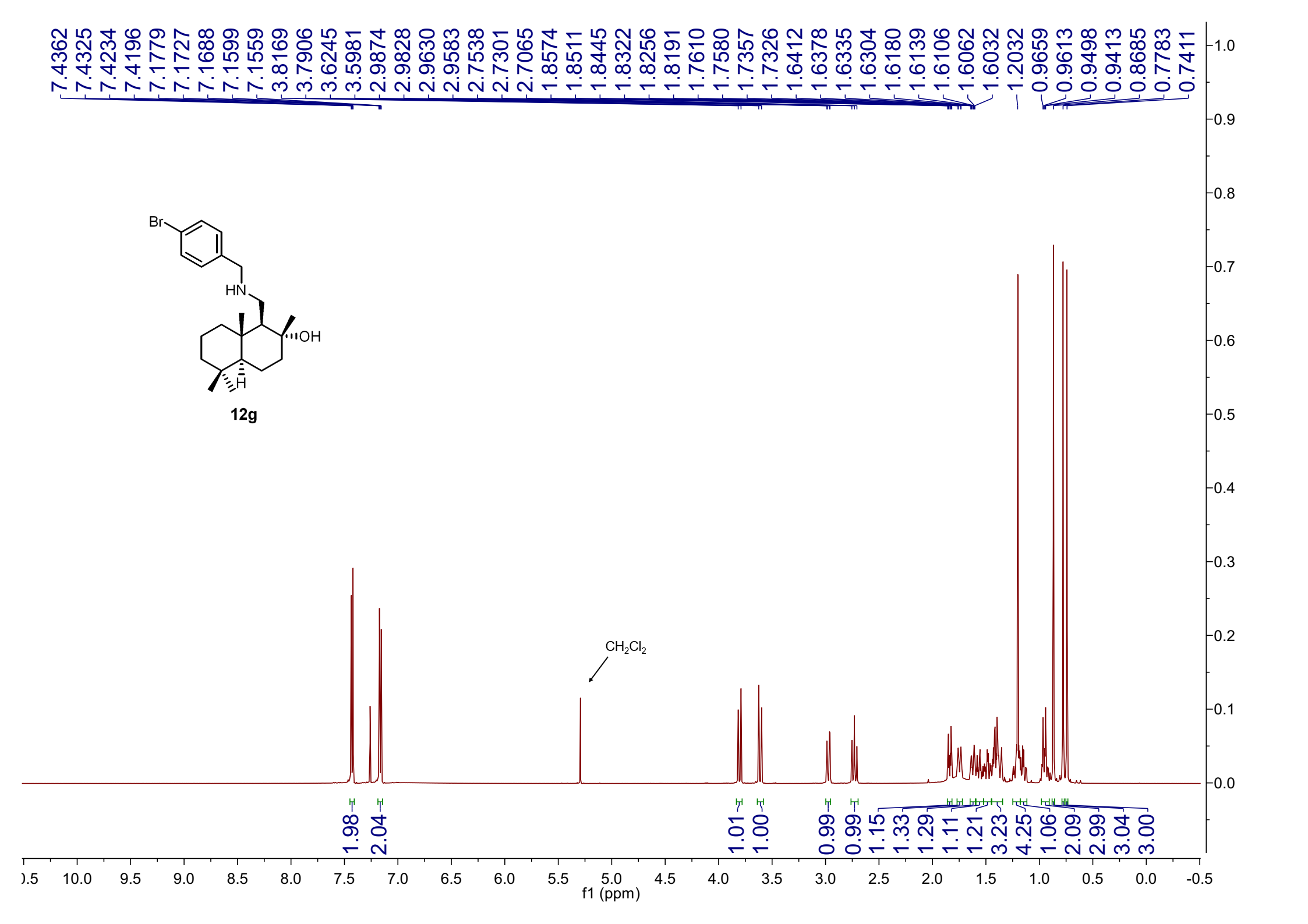
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0.7783
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OH
H
12g
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0.99
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3.00
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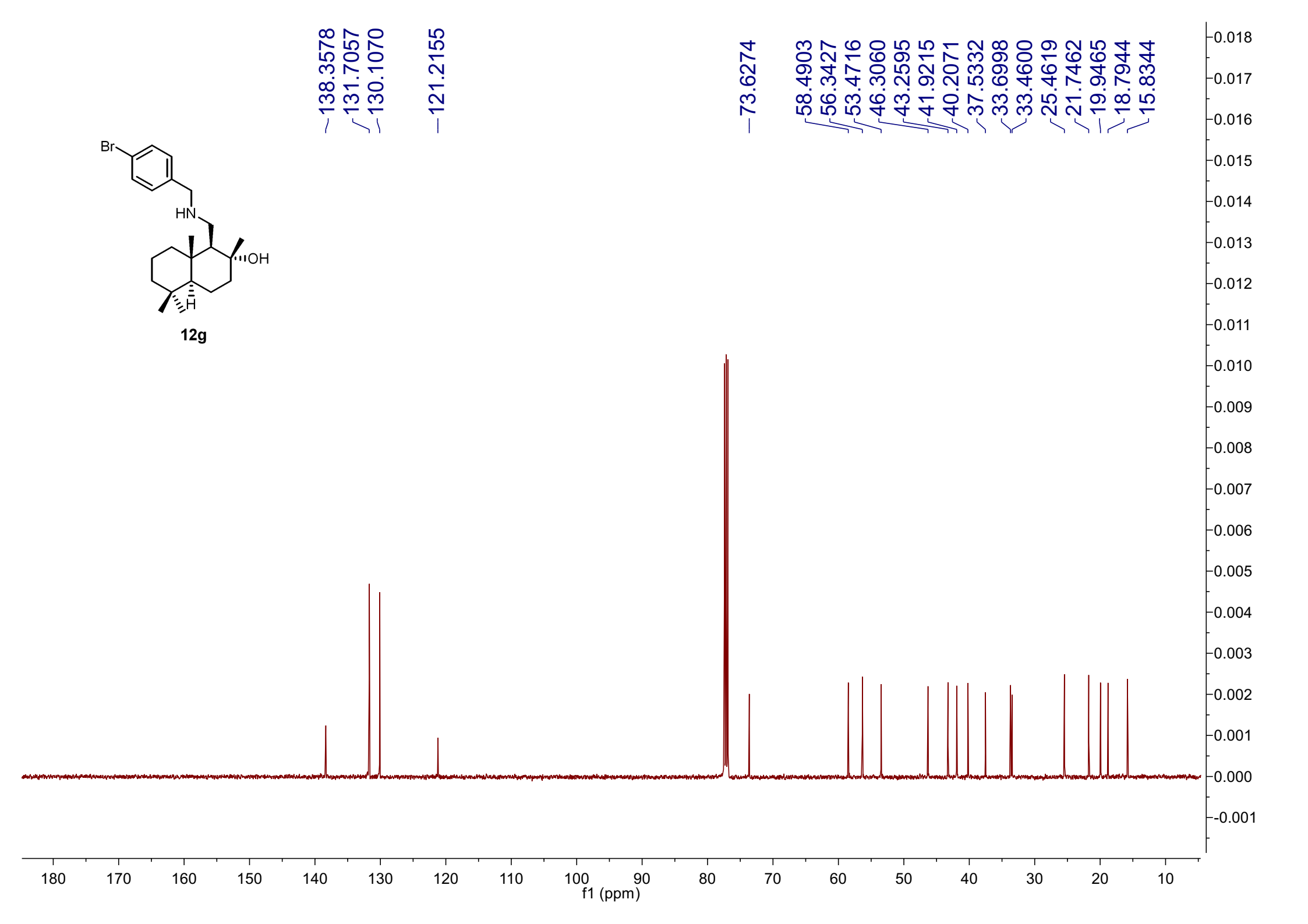
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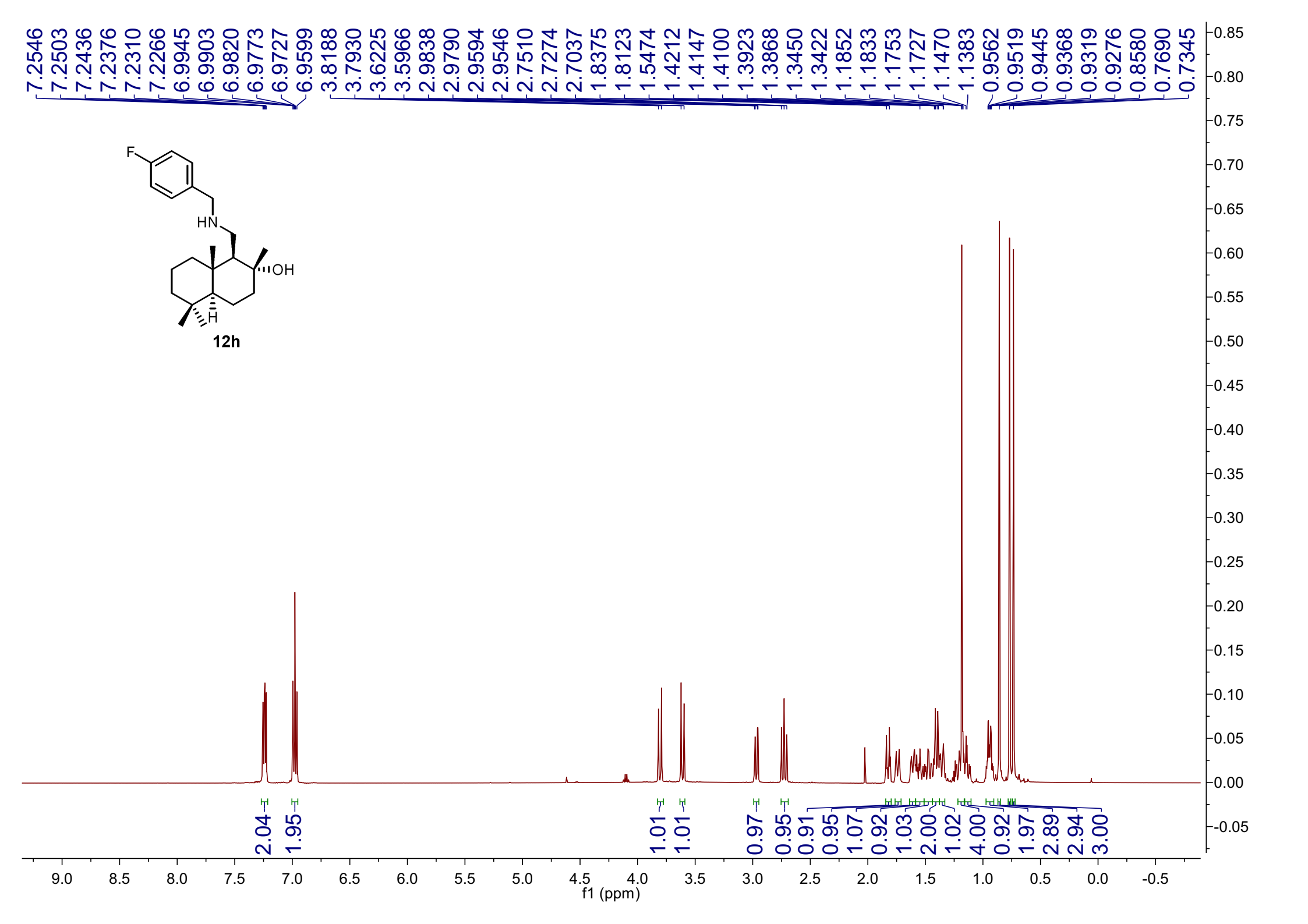
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F
HN
OH
H
12h
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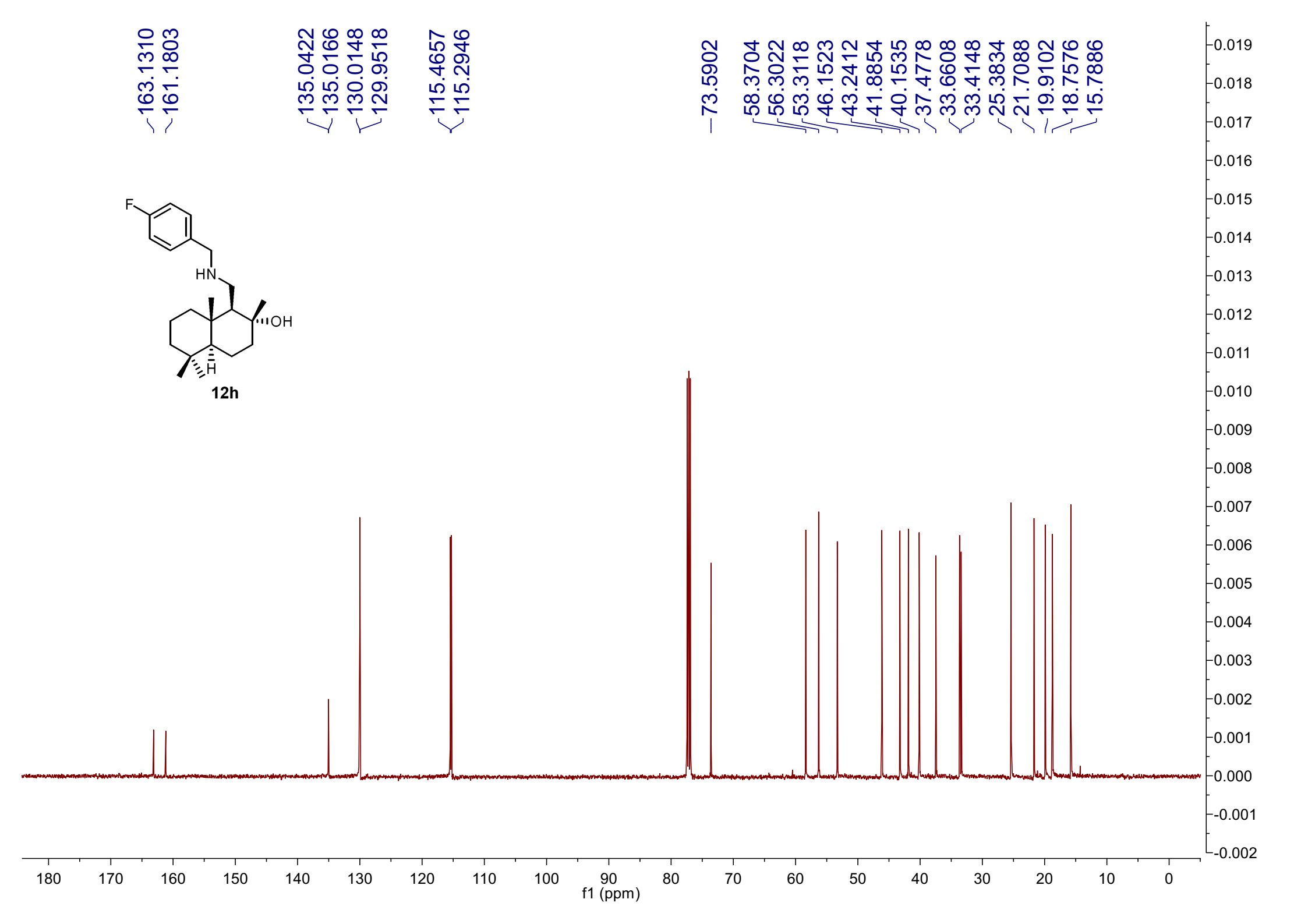
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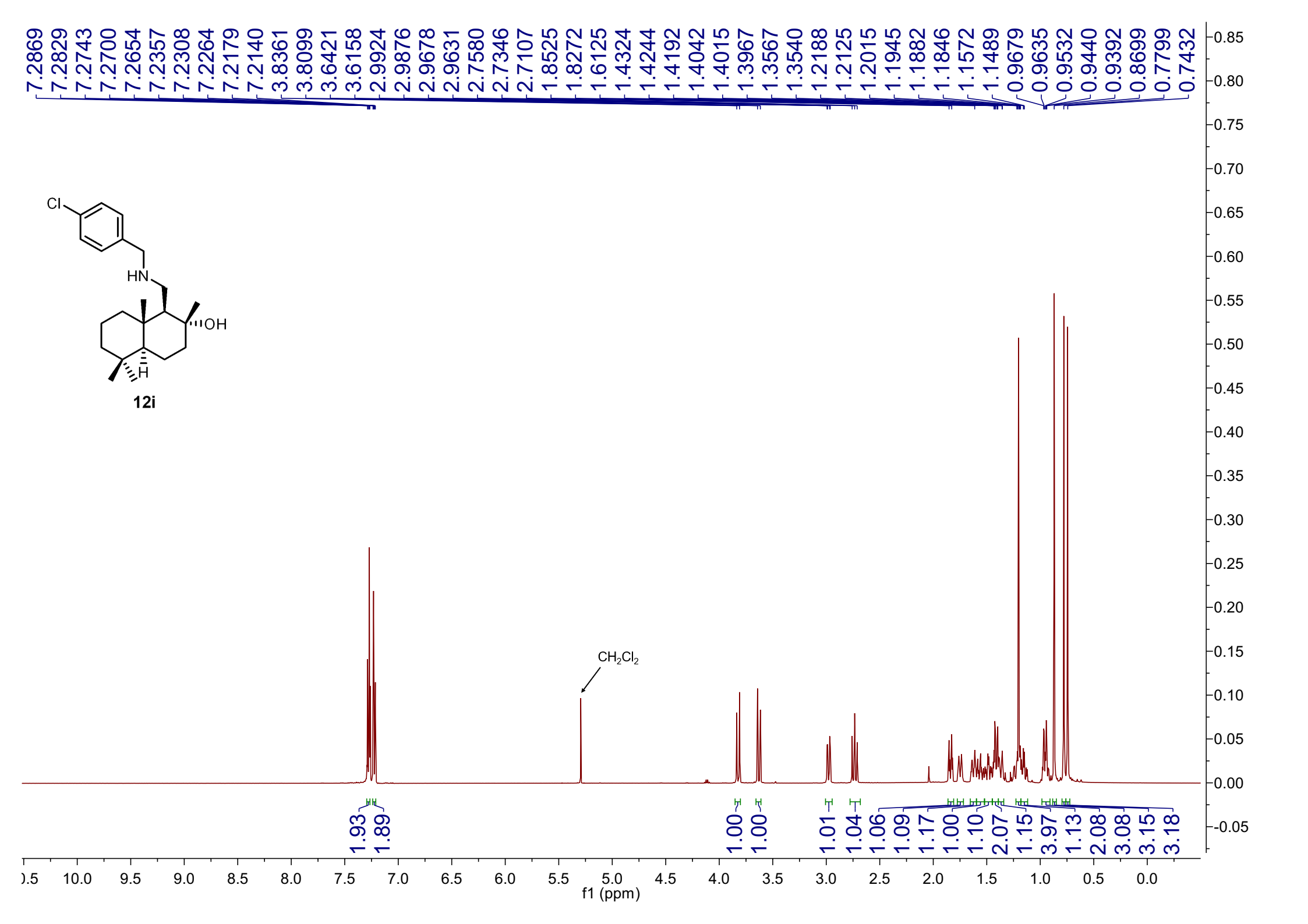
H
12h
f1 (ppm)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Cl
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OH
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12i
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1.01
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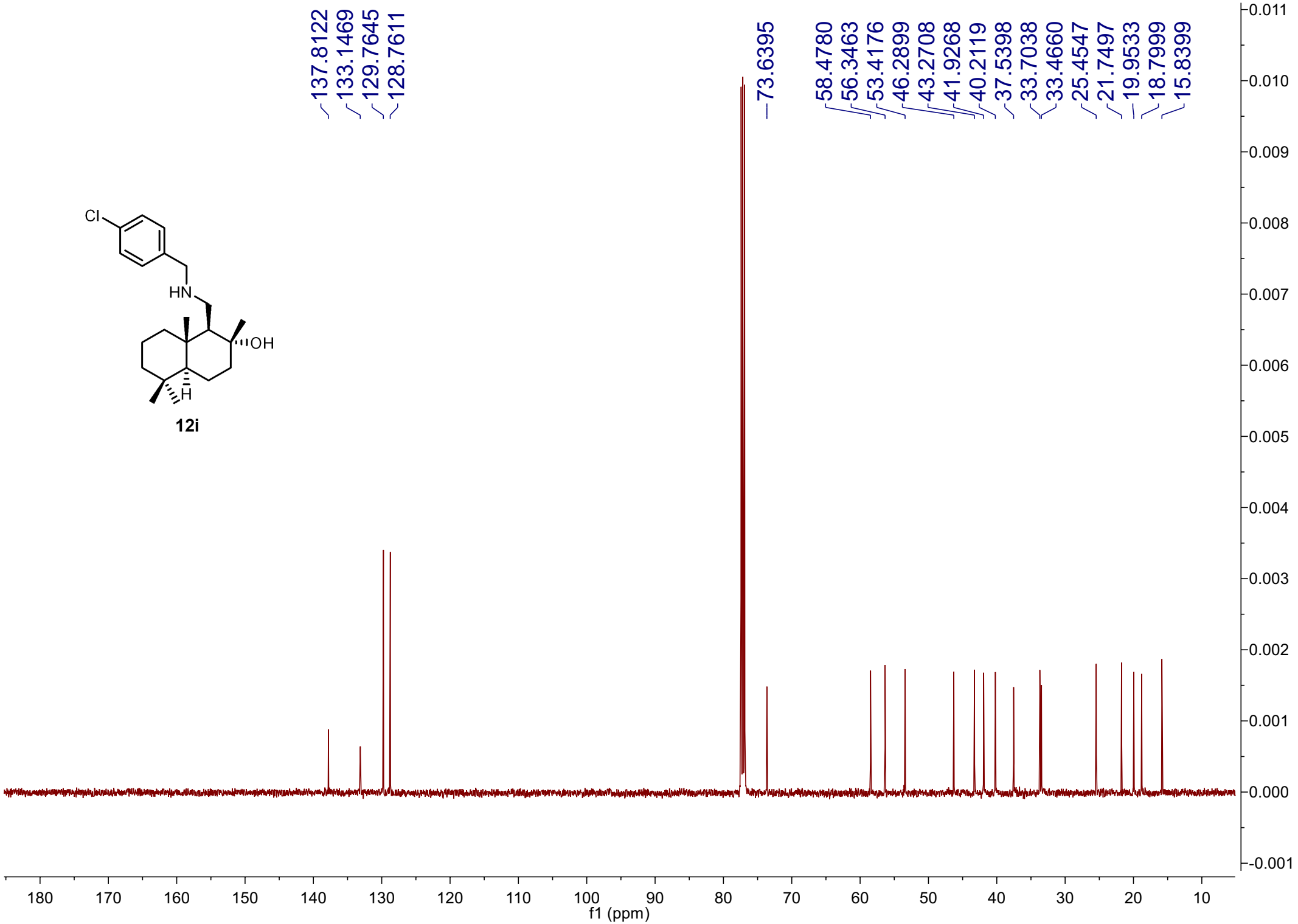
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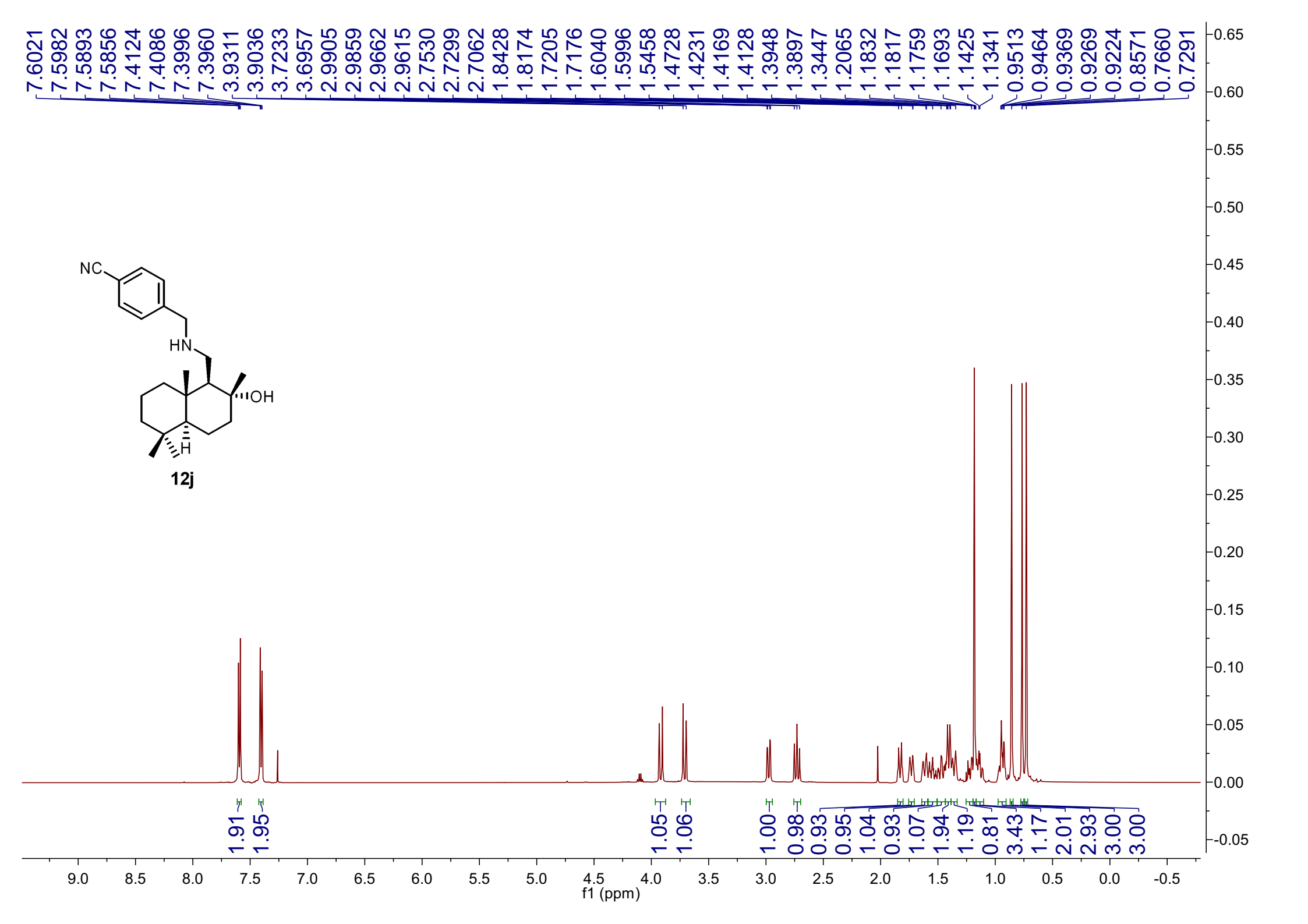
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12j
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1.95
1.05
1.06
1.00
0.98
0.93
0.95
1.04
0.93
1.07
1.94
1.19
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3.43
1.17
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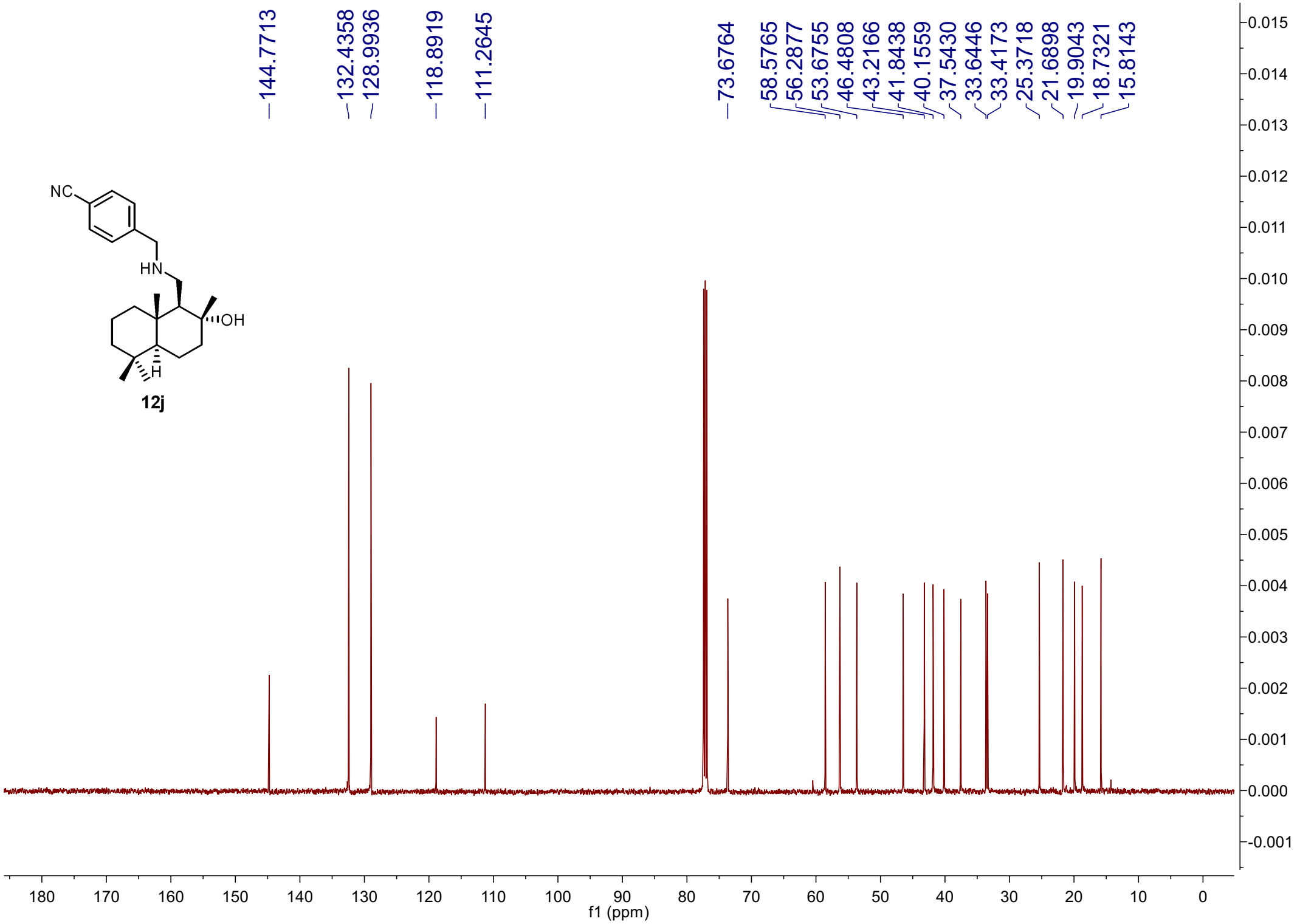
2.93
3.00
3.00
f1 (ppm)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37.5430
33.6446
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18.7321
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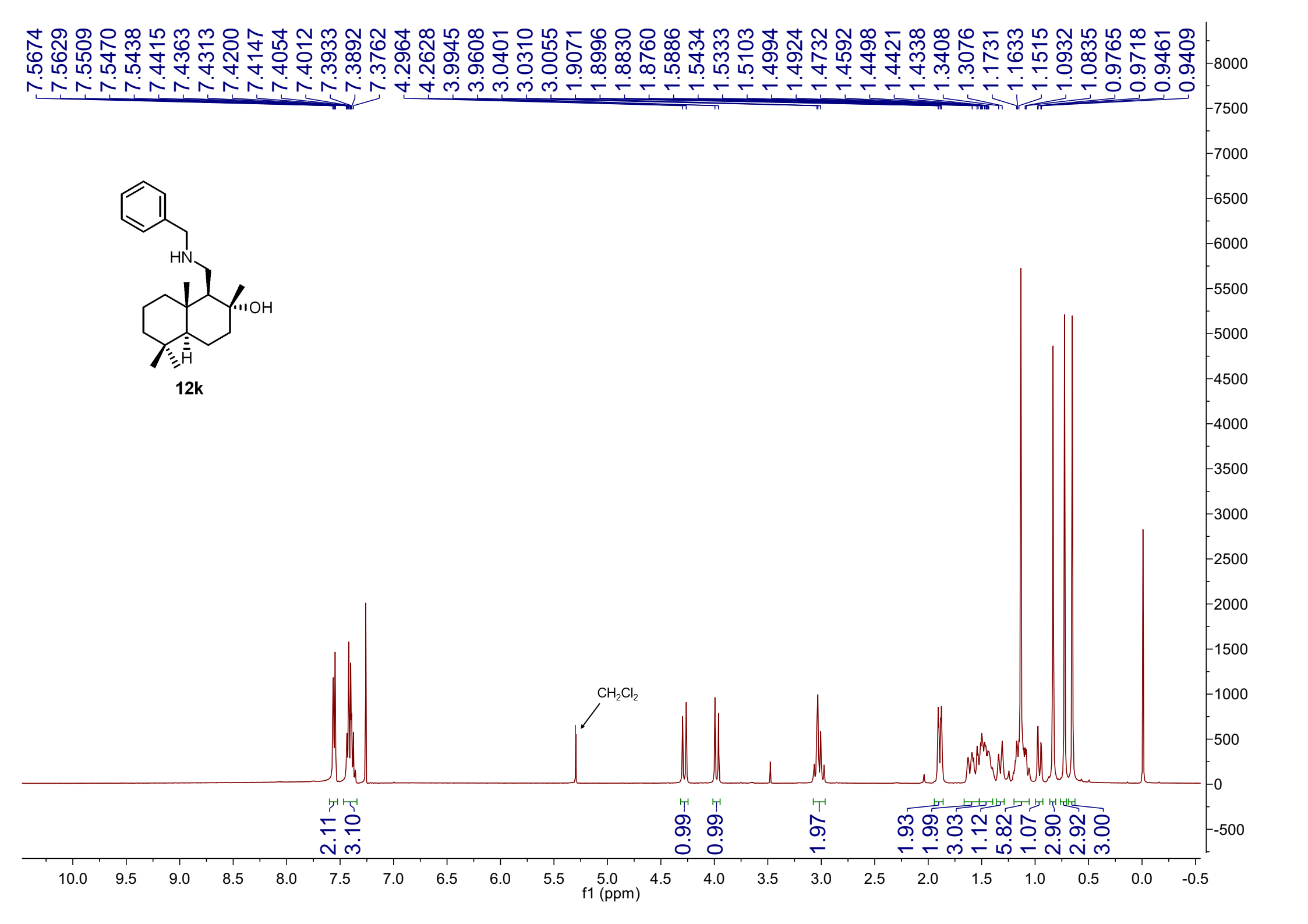
NC
HN
OH
H
12j
f1 (ppm)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7.4012
7.3933
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7.3762
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4.2628
3.9945
3.9608
3.0401
3.0310
3.0055
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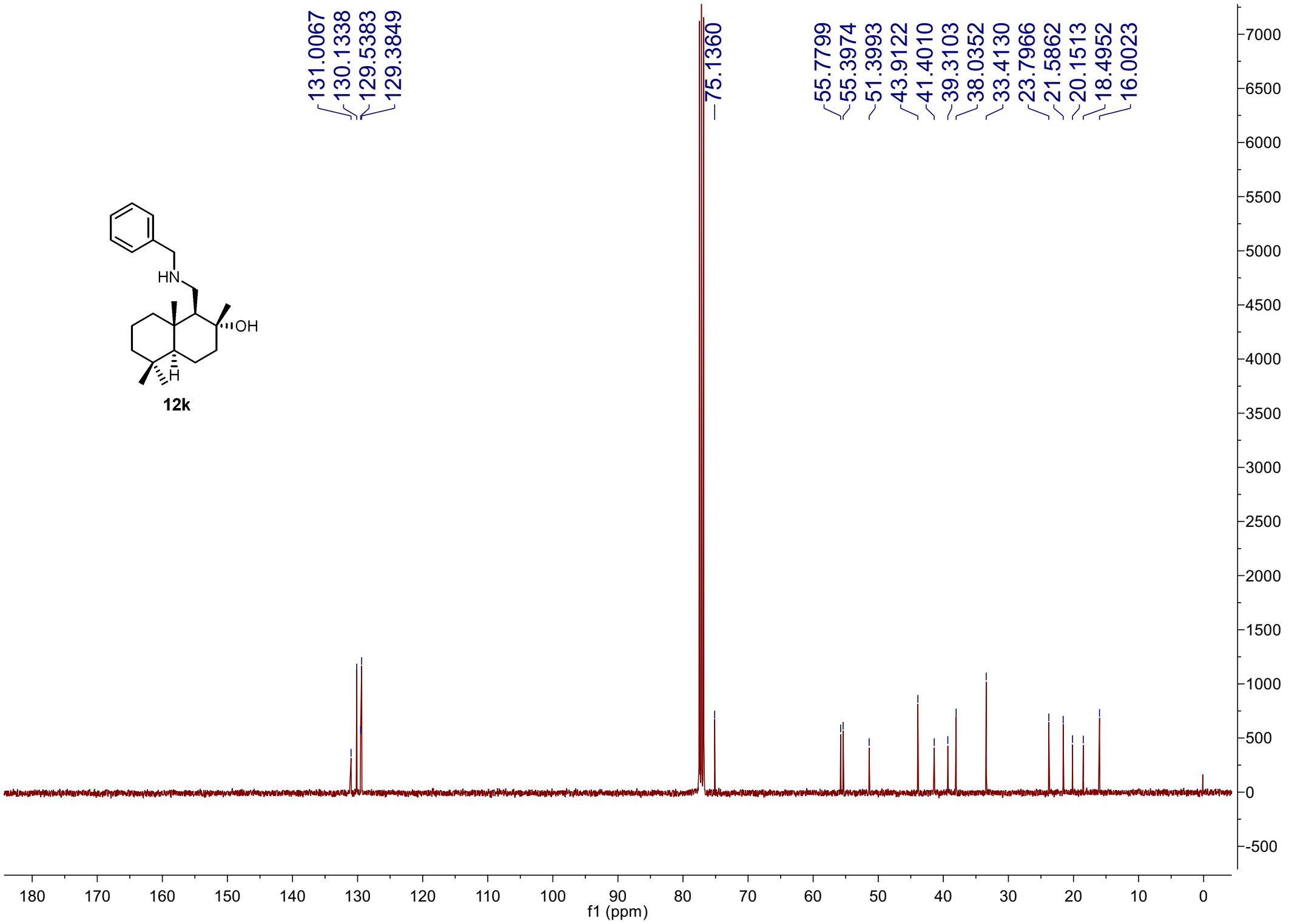
1.5886
1.5434
1.5333
1.5103
1.4994
1.4924
1.4732
1.4592
1.4498
1.4421
1.4338
1.3408
1.3076
1.1731
1.1633
1.1515
1.0932
1.0835
0.9765
0.9718
0.9461
0.9409
HN
OH
H
12k
CH2Cl2
2.11
3.10
0.99
0.99
1.97
1.93
1.99
3.03
1.12
5.82
1.07
2.90
2.92
3.00
f1 (ppm)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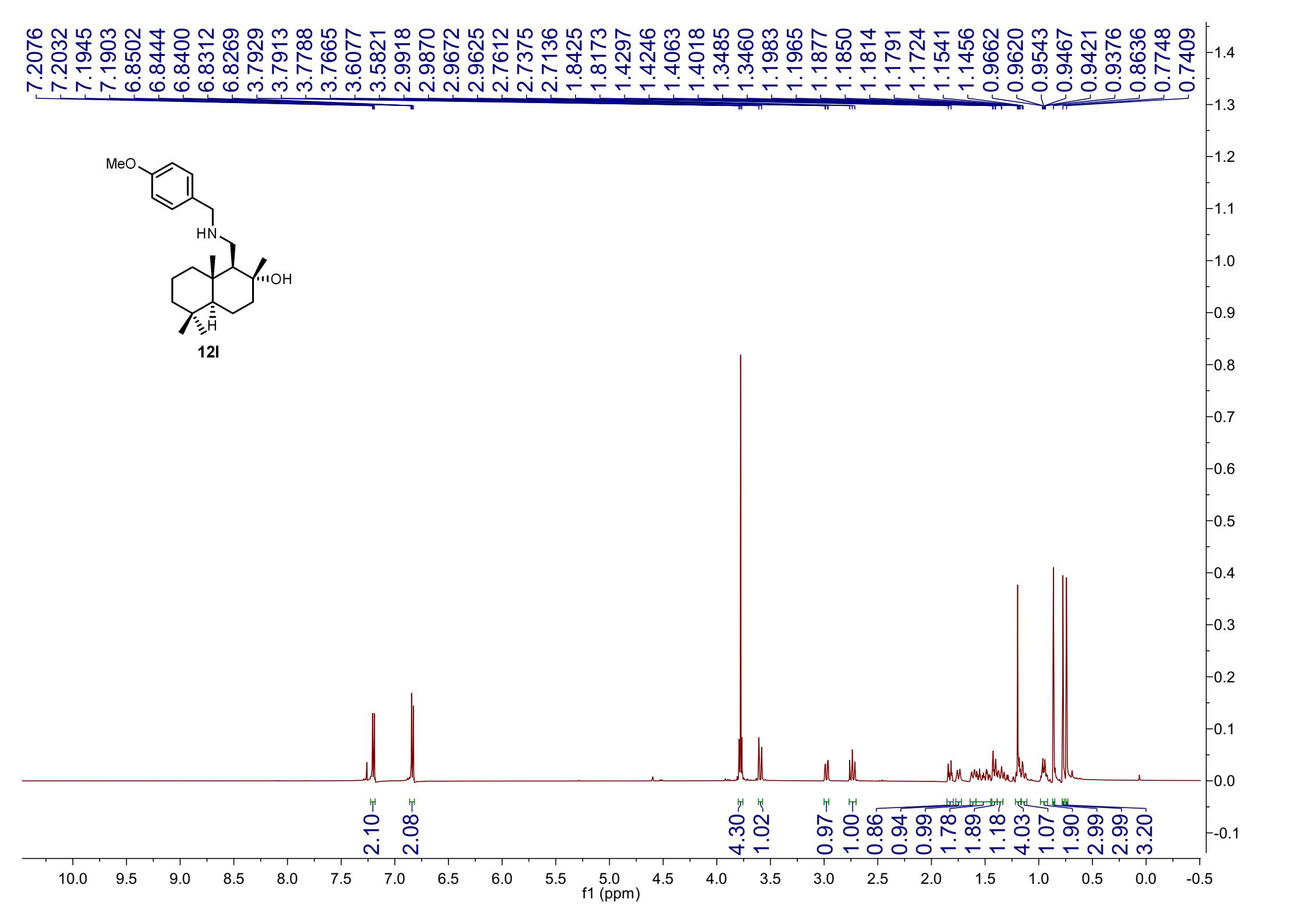
16.0023
HN
OH
H
12k
f1 (ppm)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3.7665
3.6077
3.5821
2.9918
2.9870
2.9672
2.9625
2.7612
2.7375
2.7136
1.8425
1.8173
1.4297
1.4246
1.4063
1.4018
1.3485
1.3460
1.1983
1.1965
1.1877
1.1850
1.1814
1.1791
1.1724
1.1541
1.1456
0.9662
0.9620
0.9543
0.9467
0.9421
0.9376
0.8636
0.7748
0.7409
MeO
HN
OH
H
12l
2.10
2.08
4.30
1.02
0.97
1.00
0.86
0.94
0.99
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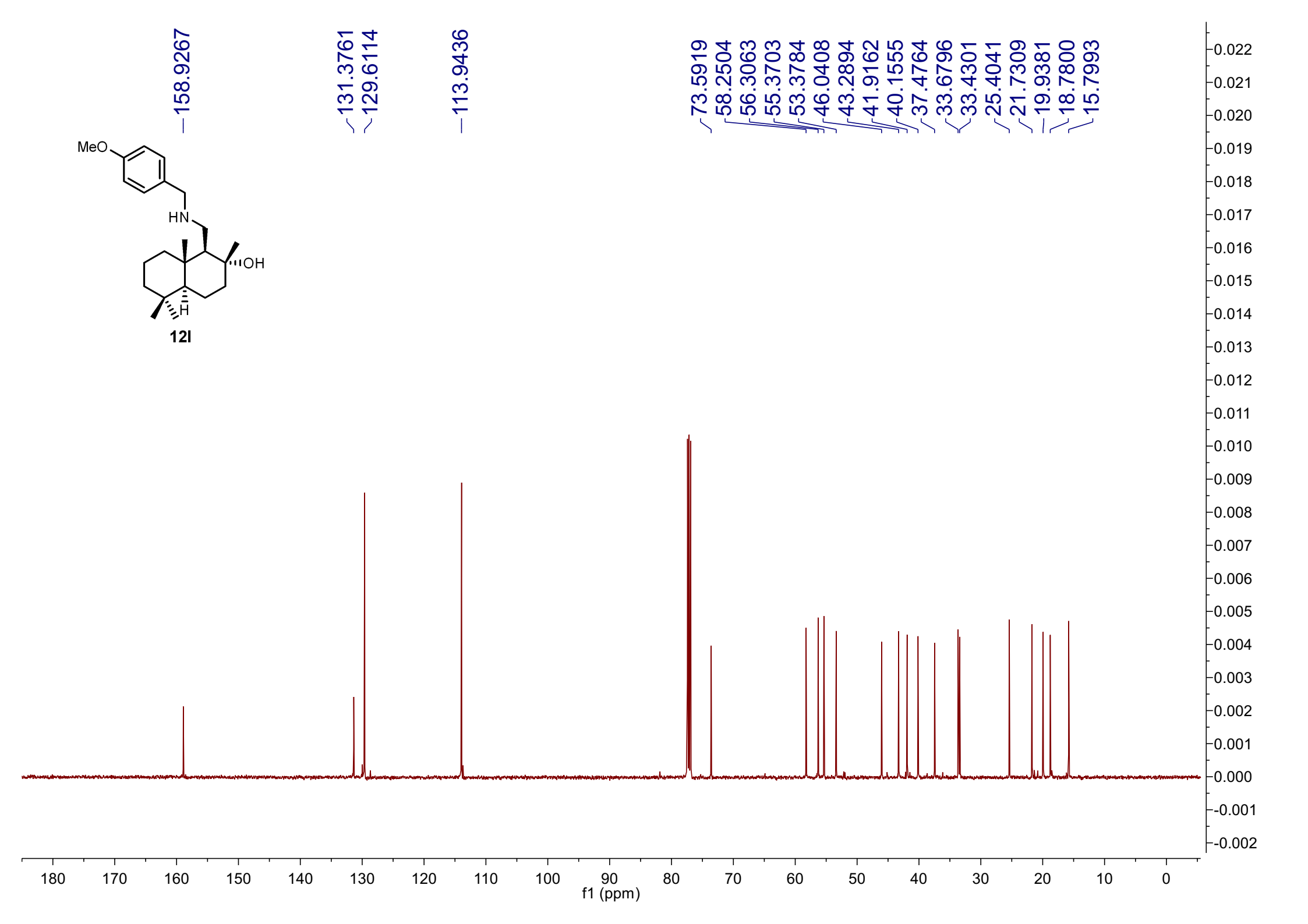
1.89
1.18
4.03
1.07
1.90
2.99
2.99
3.20
f1 (ppm)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33.6796
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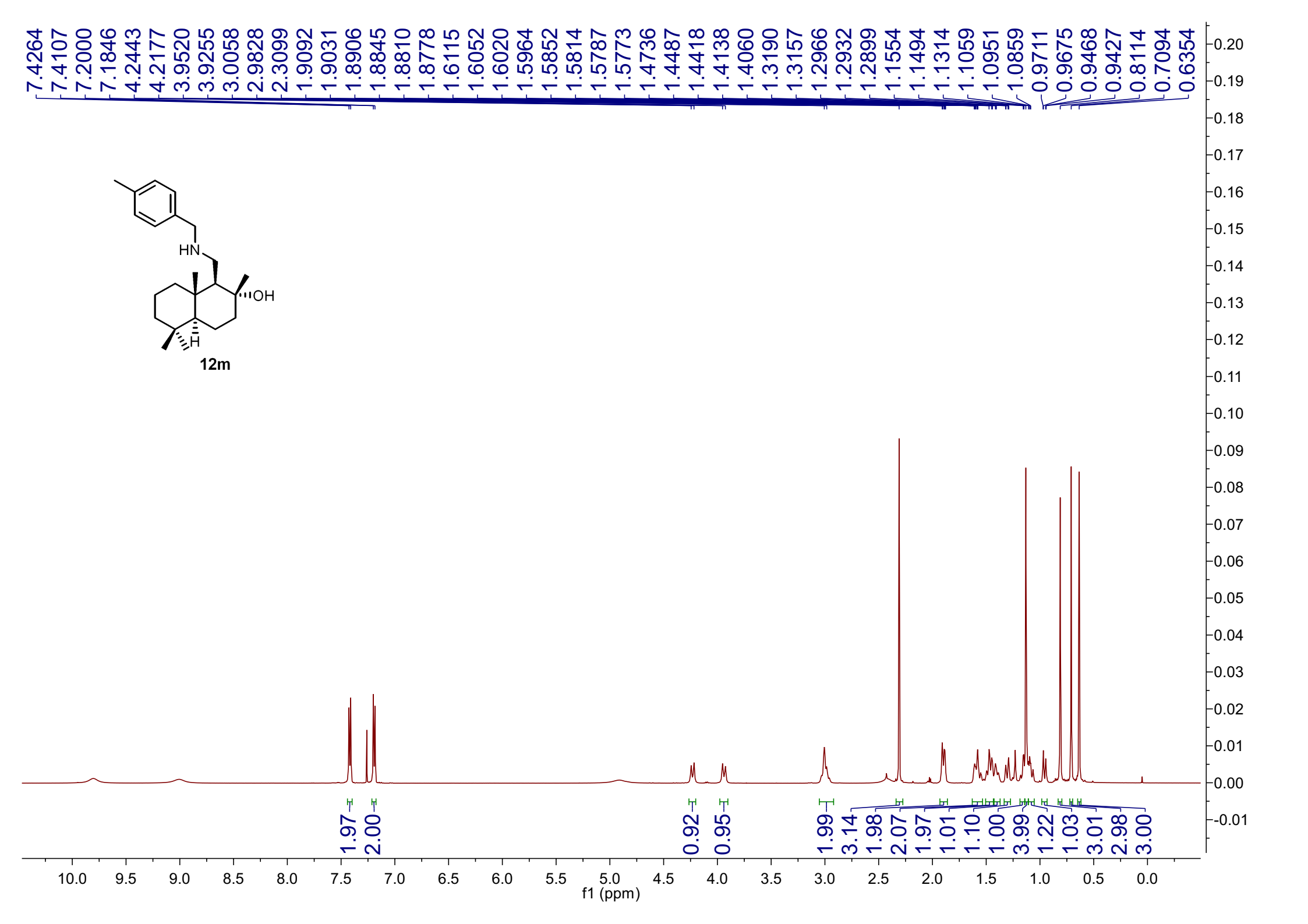
MeO
HN
OH
H
12l
f1 (ppm)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1.6052
1.6020
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1.5852
1.5814
1.5787
1.5773
1.4736
1.4487
1.4418
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1.4060
1.3190
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1.1554
1.1494
1.1314
1.1059
1.0951
1.0859
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0.9468
0.9427
0.8114
0.7094
0.6354
HN
OH
H
12m
1.97
2.00
0.92
0.95
1.99
3.14
1.98
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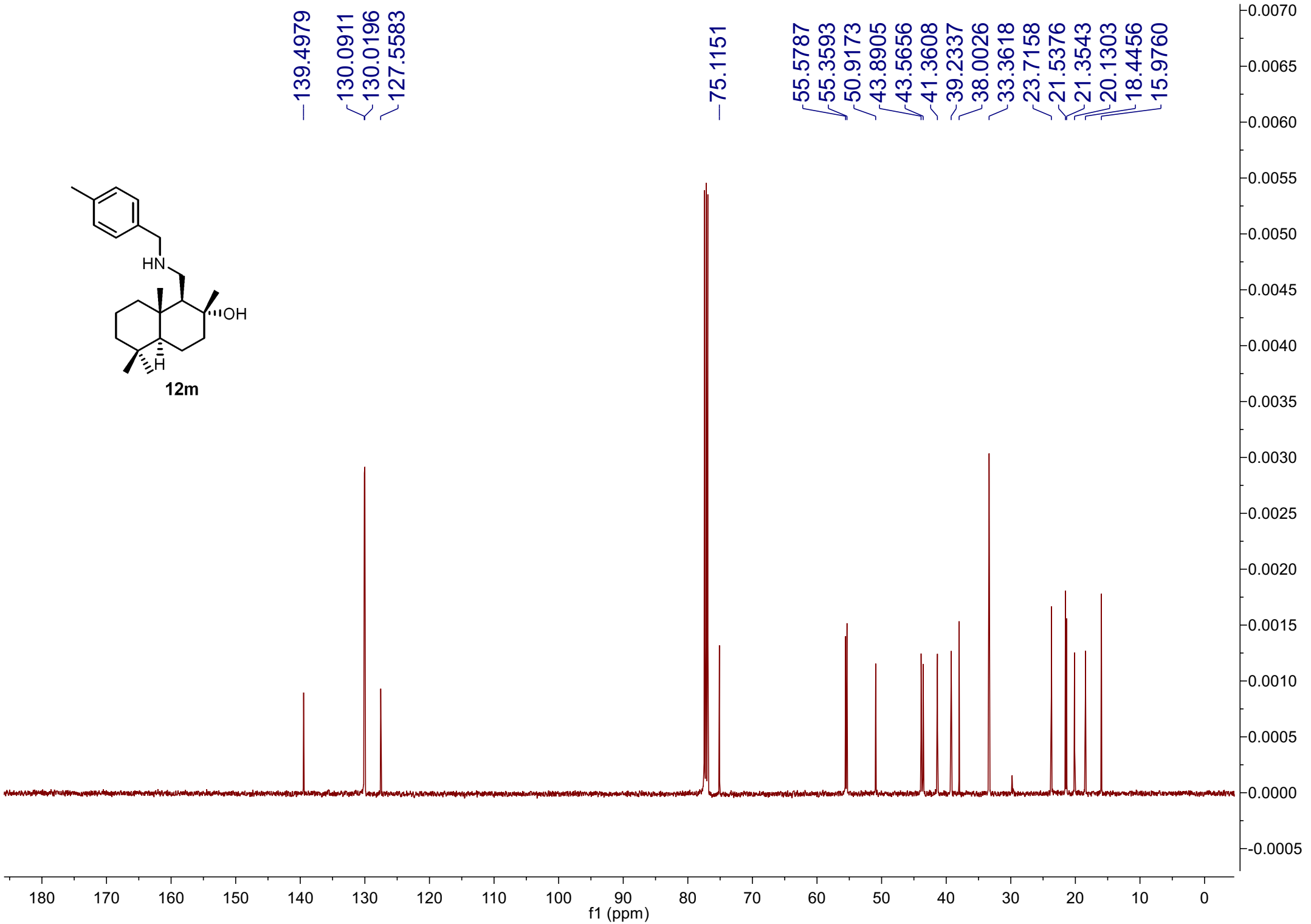
1.01
1.10
1.00
3.99
1.22
1.03
3.01
2.98
3.00
f1 (ppm)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43.5656
41.3608
39.2337
38.0026
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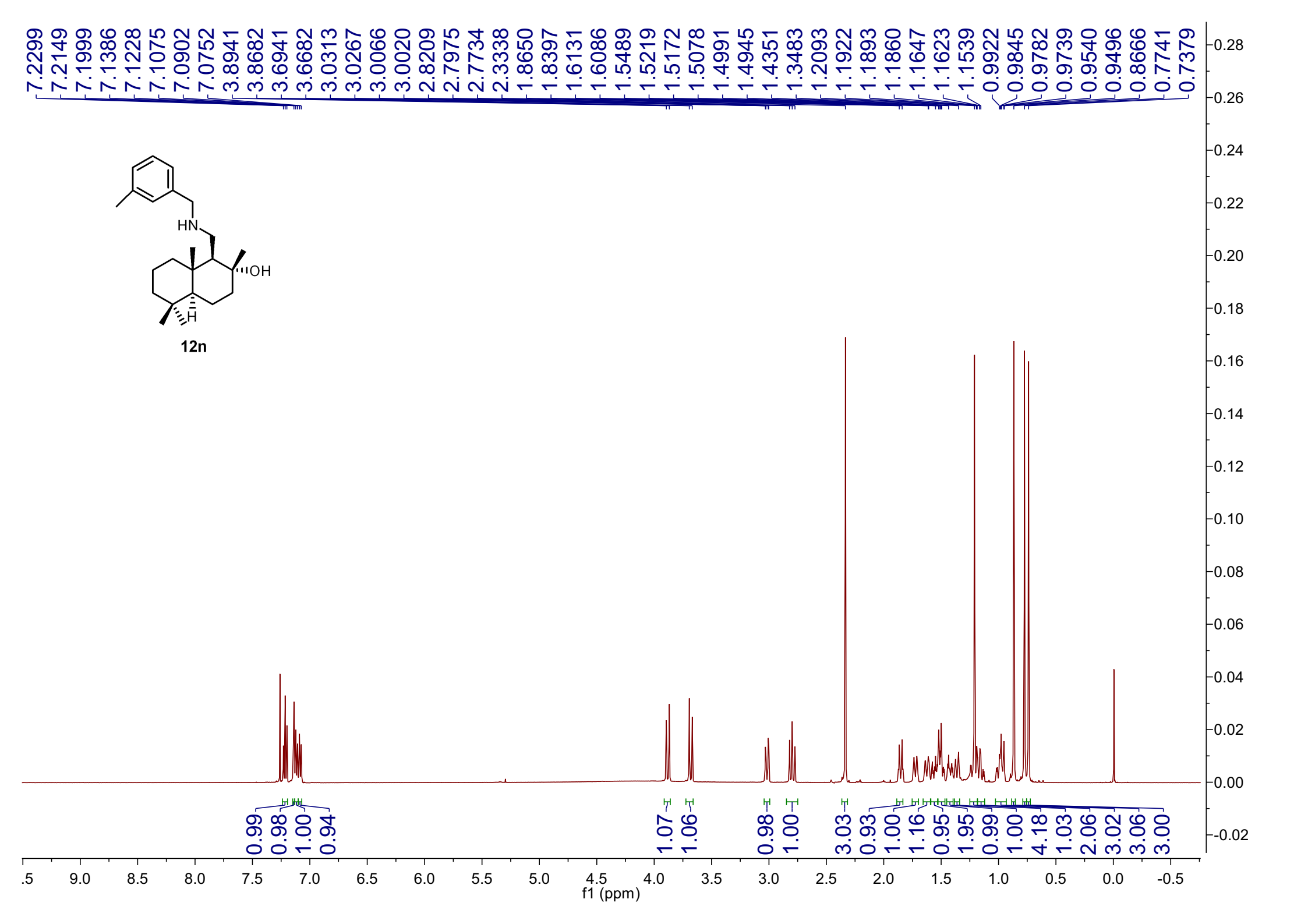
23.7158
21.5376
21.3543
20.1303
18.4456
15.9760
HN
OH
H
12m
f1 (ppm)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3.6941
3.6682
3.0313
3.0267
3.0066
3.0020
2.8209
2.7975
2.7734
2.3338
1.8650
1.8397
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1.5172
1.5078
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1.4945
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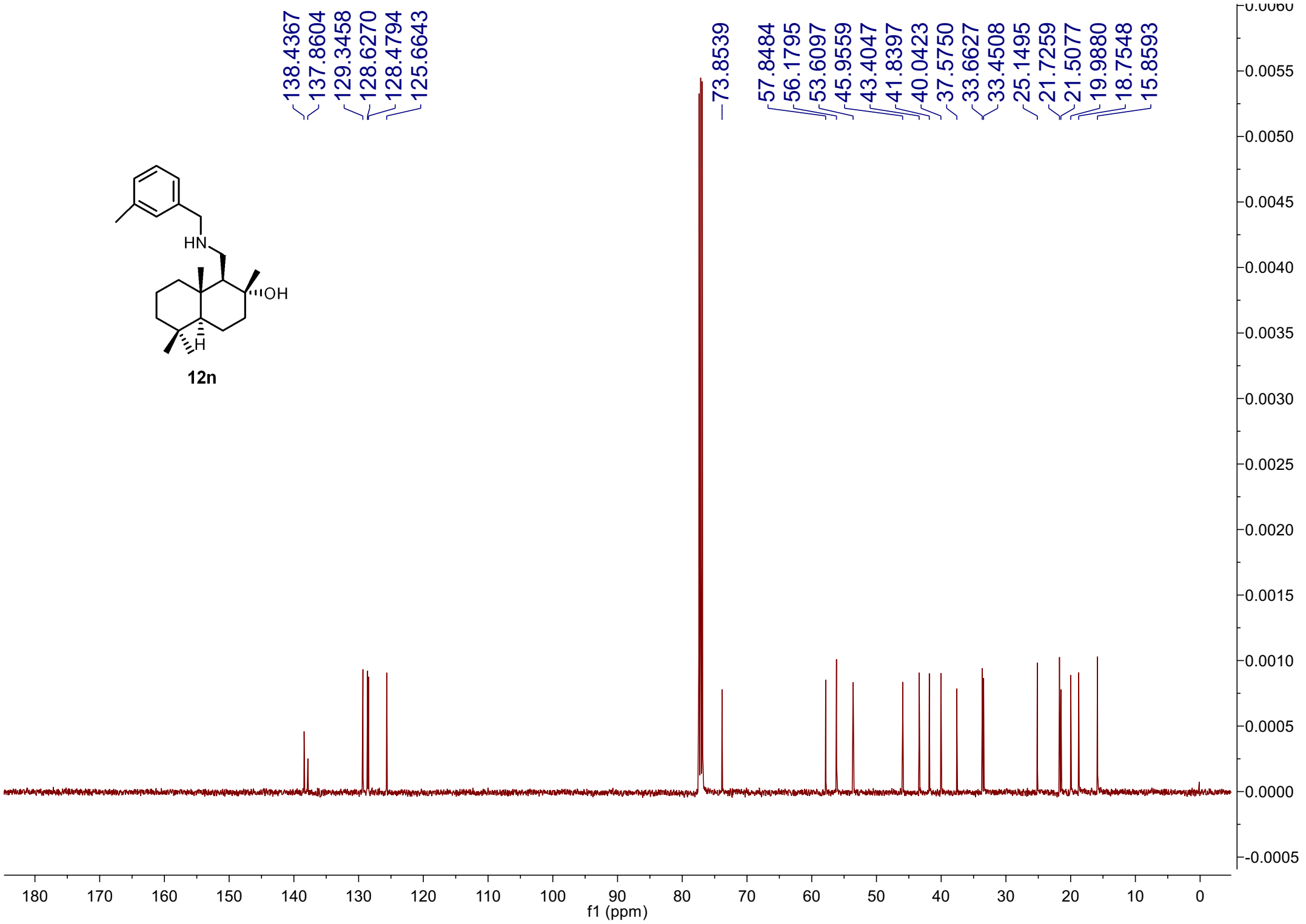
1.2093
1.1922
1.1893
1.1860
1.1647
1.1623
1.1539
0.9922
0.9845
0.9782
0.9739
0.9540
0.9496
0.8666
0.7741
0.7379
HN
OH
H
12n
0.99
0.98
1.00
0.94
1.07
1.06
0.98
1.00
3.03
0.93
1.00
1.16
0.95
1.95
0.99
1.00
4.18
1.03
2.06
3.02
3.06
3.00
f1 (ppm)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45.9559
43.4047
41.8397
40.0423
37.5750
33.6627
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18.7548
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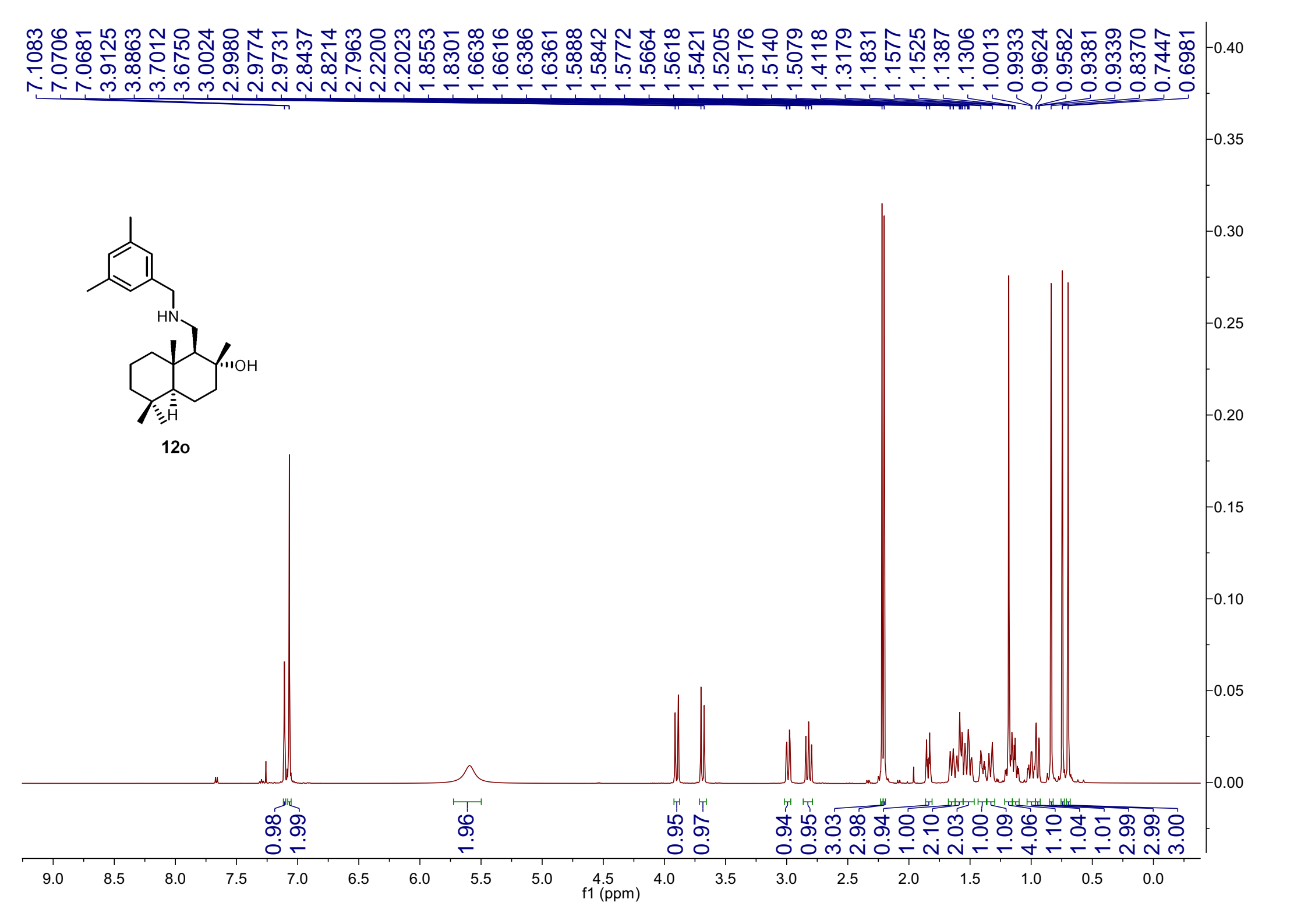
HN
OH
H
12n
f1 (ppm)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2.8437
2.8214
2.7963
2.2200
2.2023
1.8553
1.8301
1.6638
1.6616
1.6386
1.6361
1.5888
1.5842
1.5772
1.5664
1.5618
1.5421
1.5205
1.5176
1.5140
1.5079
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1.1577
1.1525
1.1387
1.1306
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0.9933
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0.9582
0.9381
0.9339
0.8370
0.7447
0.6981
HN
OH
H
12o
0.98
1.99
1.96
0.95
0.97
0.94
0.95
3.03
2.98
0.94
1.00
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2.03
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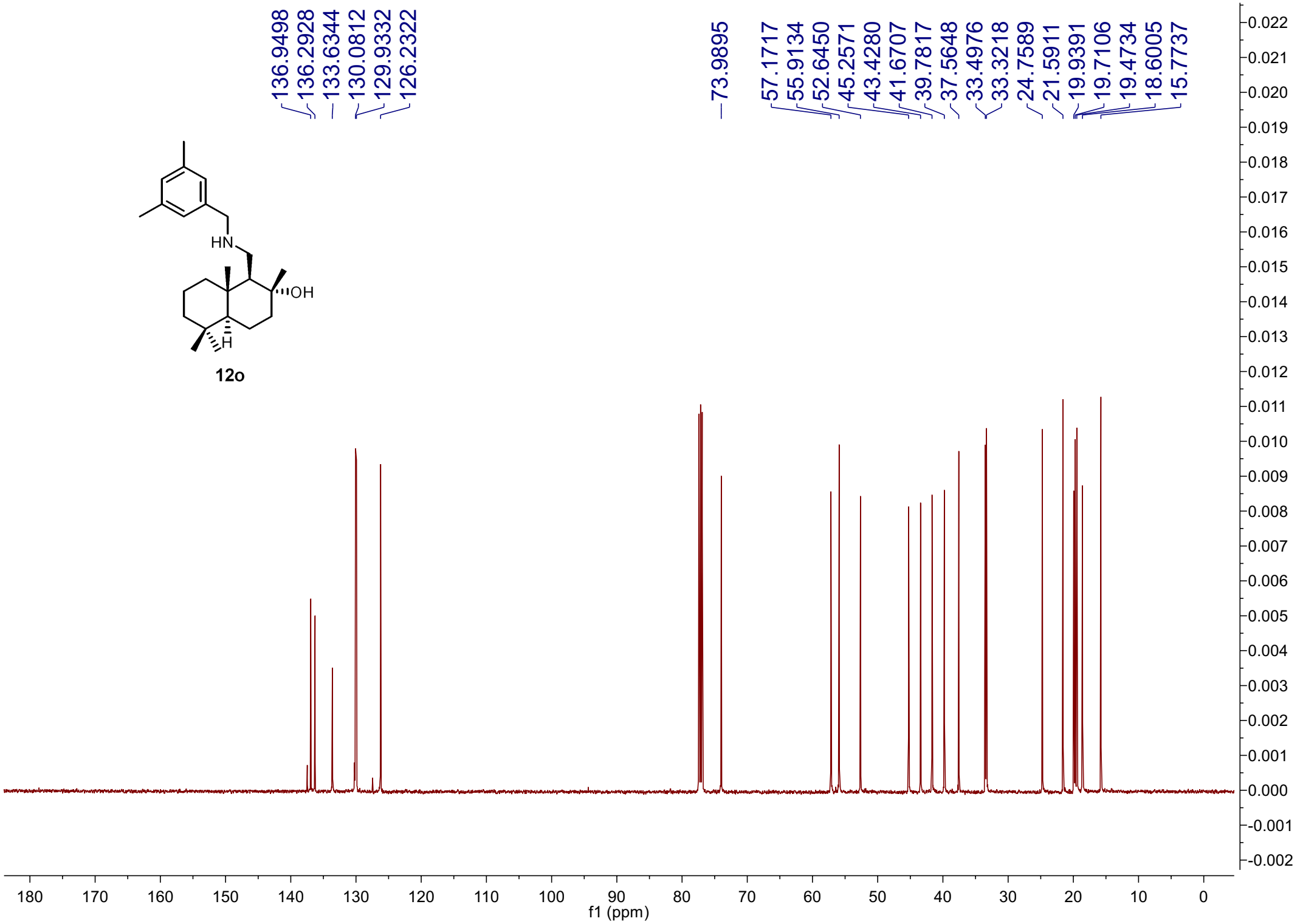
1.09
4.06
1.10
1.04
1.01
2.99
2.99
3.00
f1 (ppm)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52.6450
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41.6707
39.7817
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33.3218
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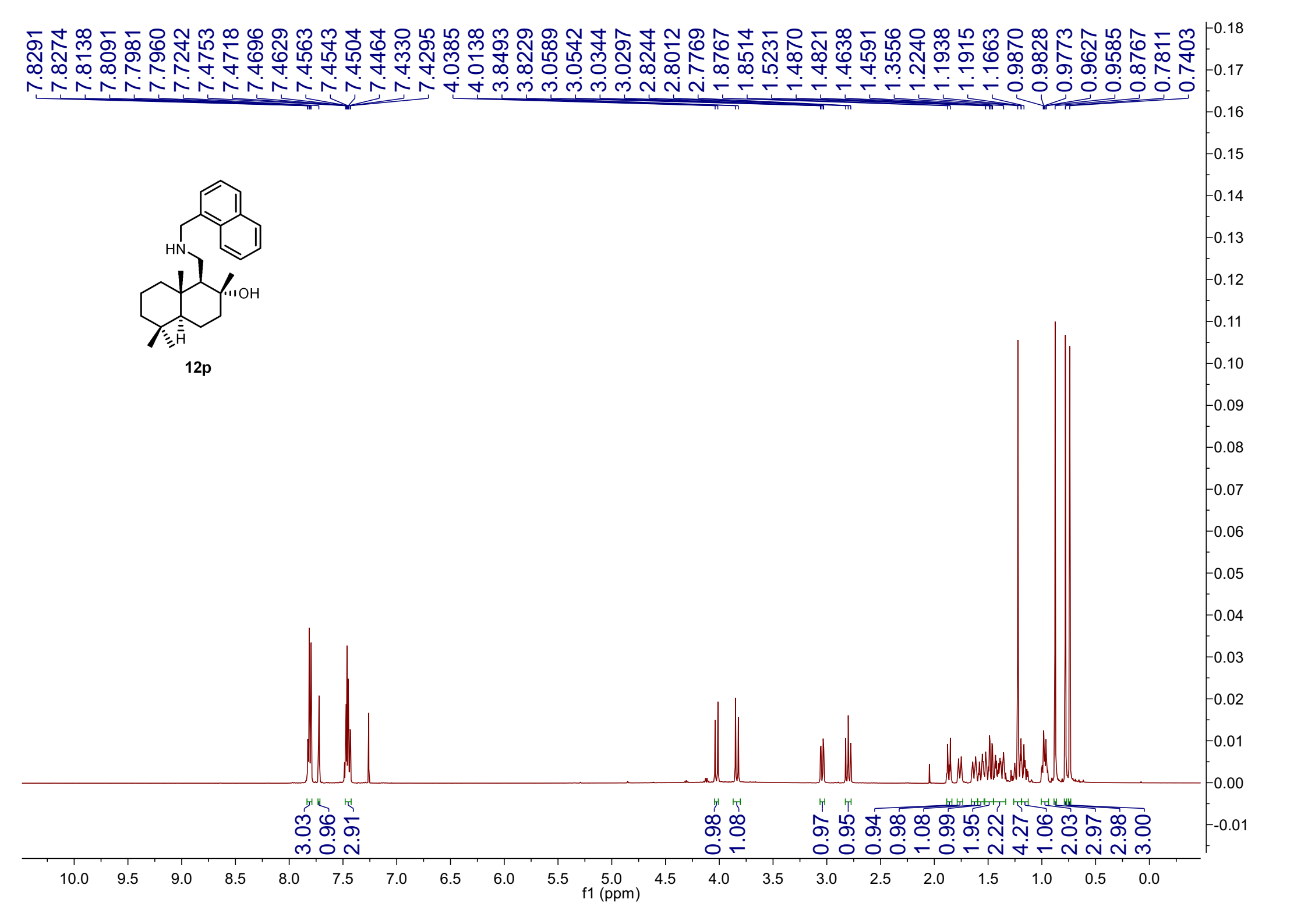
H
12o
f1 (ppm)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7.4563
7.4543
7.4504
7.4464
7.4330
7.4295
4.0385
4.0138
3.8493
3.8229
3.0589
3.0542
3.0344
3.0297
2.8244
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1.8514
1.5231
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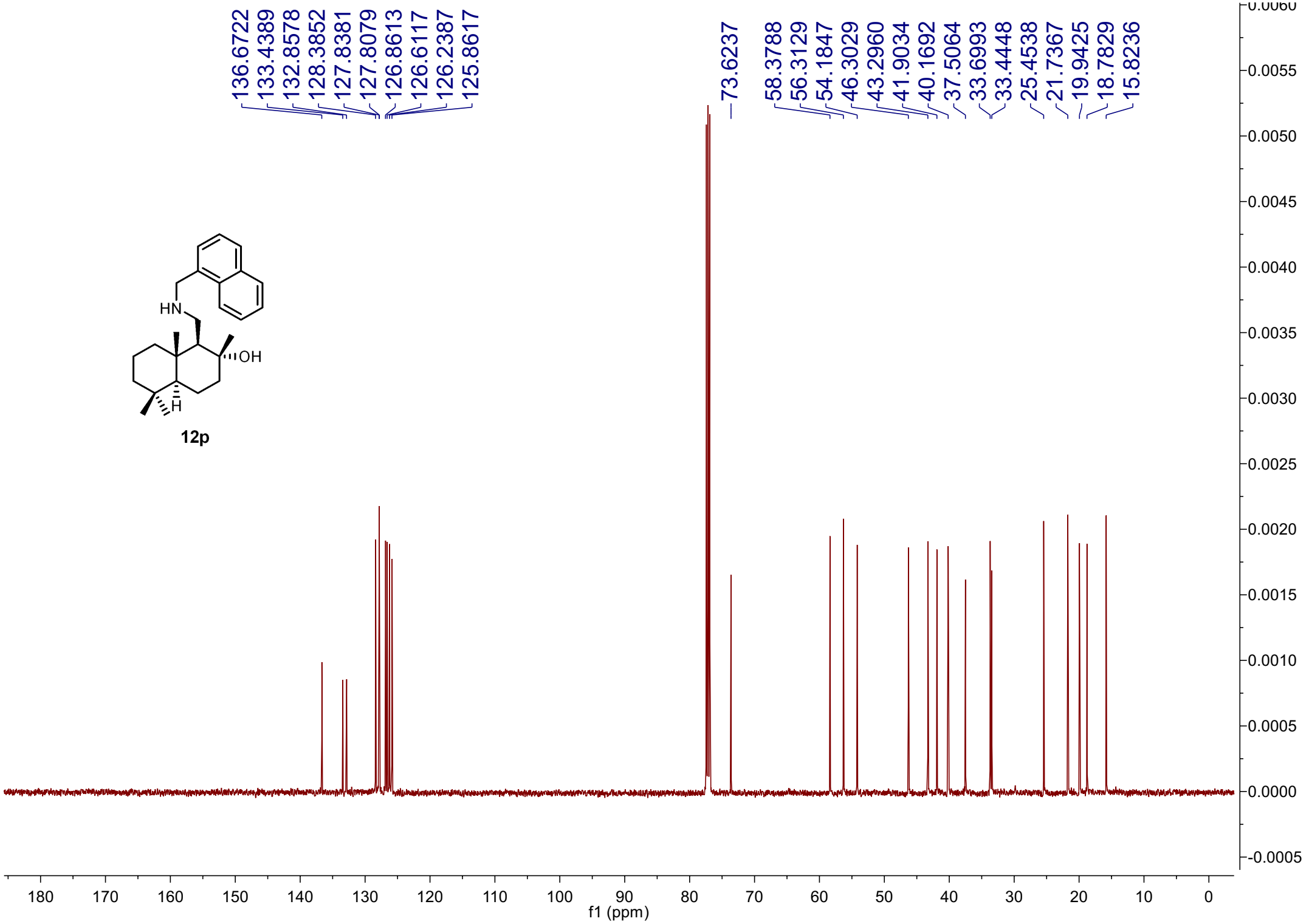
1.4821
1.4638
1.4591
1.3556
1.2240
1.1938
1.1915
1.1663
0.9870
0.9828
0.9773
0.9627
0.9585
0.8767
0.7811
0.7403
HN
OH
H
12p
3.03
0.96
2.91
0.98
1.08
0.97
0.95
0.94
0.98
1.08
0.99
1.95
2.22
4.27
1.06
2.03
2.97
2.98
3.00
f1 (ppm)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54.1847
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H
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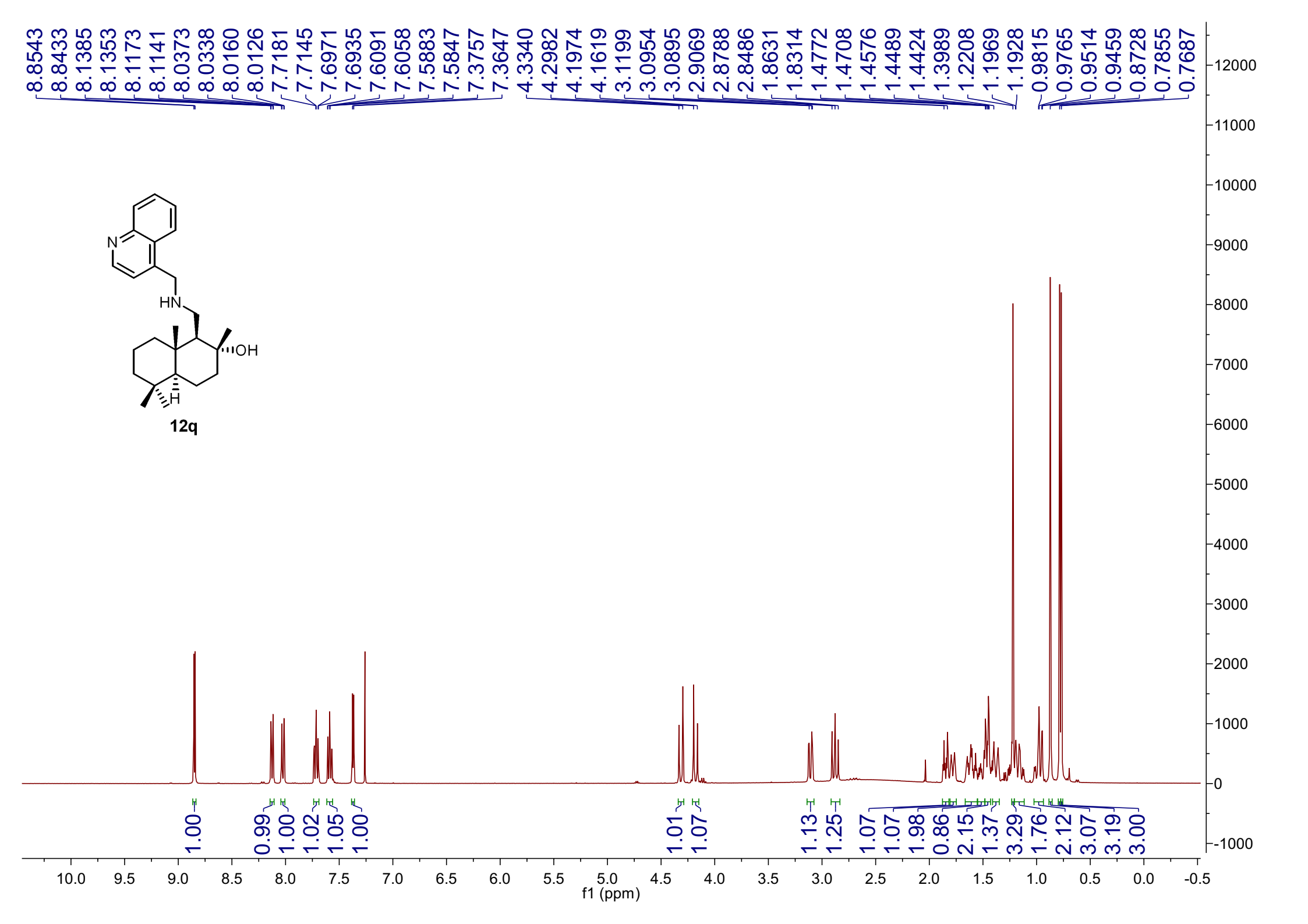
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8.0126
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7.7145
7.6971
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7.6091
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7.5847
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4.1619
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2.8486
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1.4708
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1.4424
1.3989
1.2208
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1.1928
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0.9514
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0.8728
0.7855
0.7687
N
HN
OH
H
12q
1.00
0.99
1.00
1.02
1.05
1.00
1.01
1.07
1.13
1.25
1.07
1.07
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1.76
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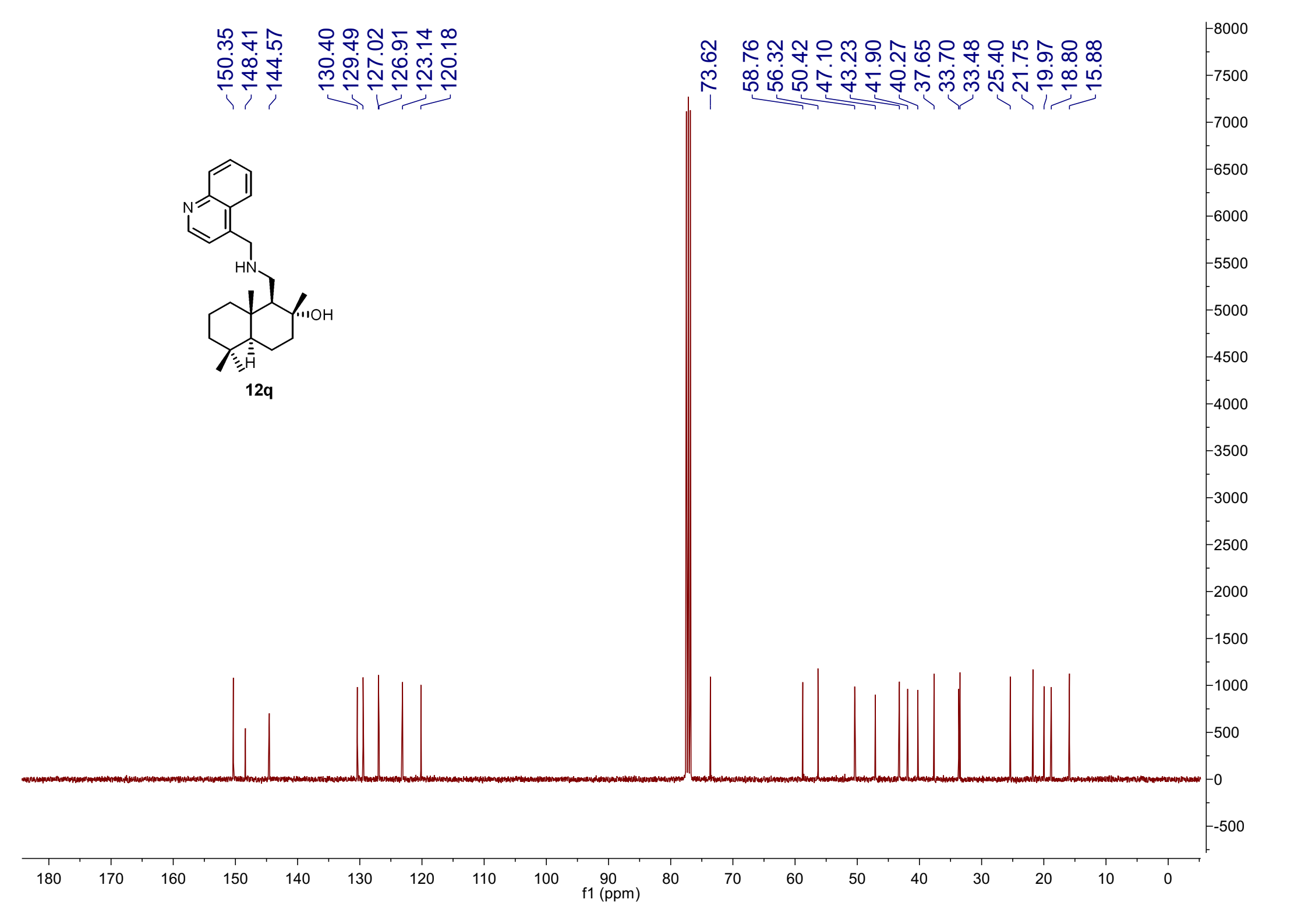
3.19
3.00
f1 (ppm)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58.76
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47.10
43.23
41.90
40.27
37.65
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25.40
21.75
19.97
18.80
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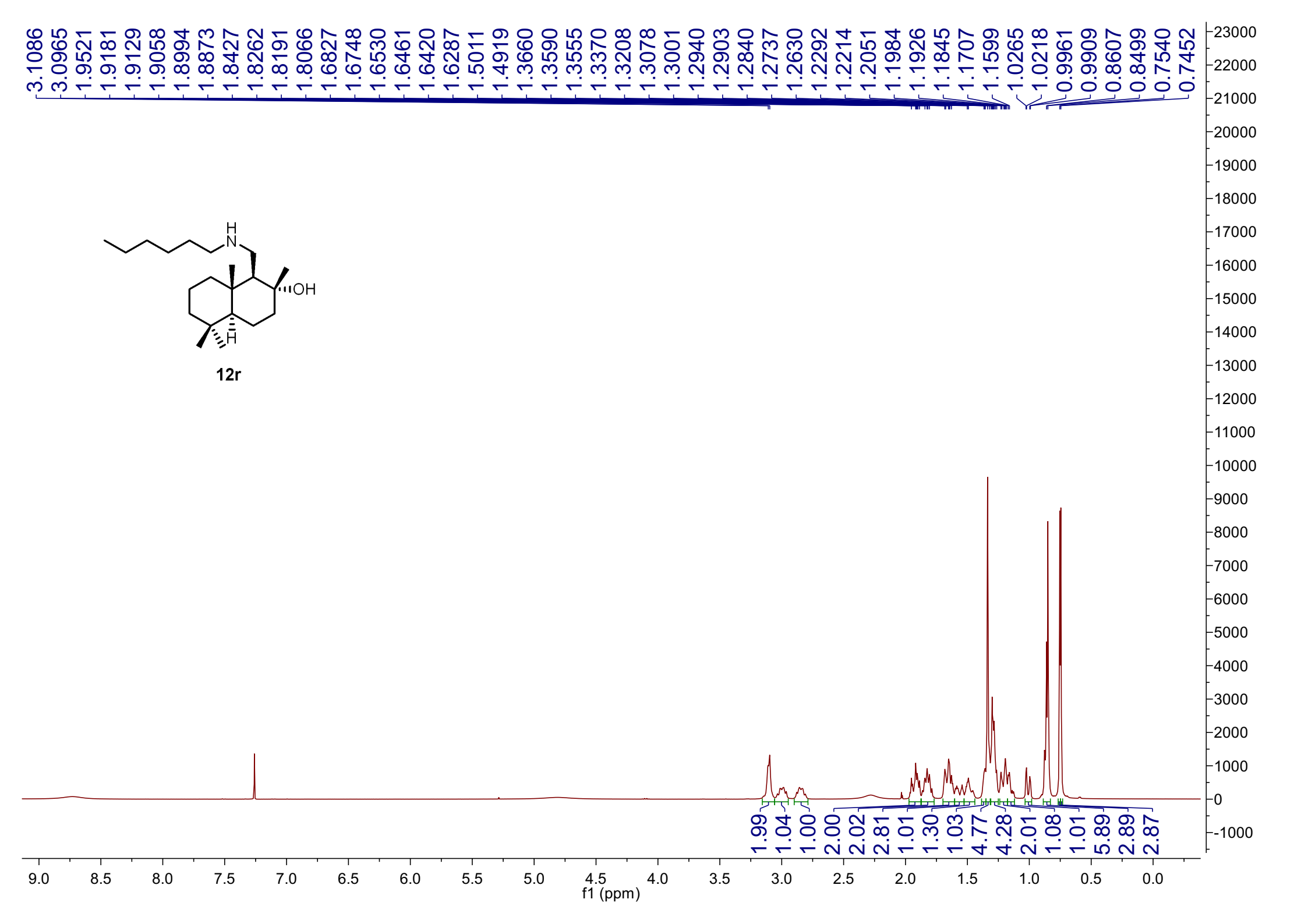
N
HN
OH
H
12q
f1 (ppm)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1.6420
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1.3660
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0.9909
0.8607
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0.7452
H
N
OH
H
12r
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2.00
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5.89
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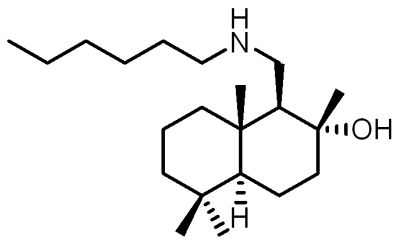
2.87
f1 (ppm)


H
N
OH
H

12r

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26.1965
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22.5801
21.5570
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18.4863
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7000
6500
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5500
5000
4500
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3500
3000
2500
2000
1500
1000
500
0
-500
180
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50
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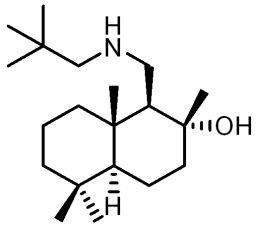
f1 (ppm)


H
N
OH
H

12s

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0.95 0.96 0.93 0.92 0.98 0.99 1.16 0.90 1.03 3.11 2.73 1.03 1.02 2.08 8.77 2.95 2.89 3.00
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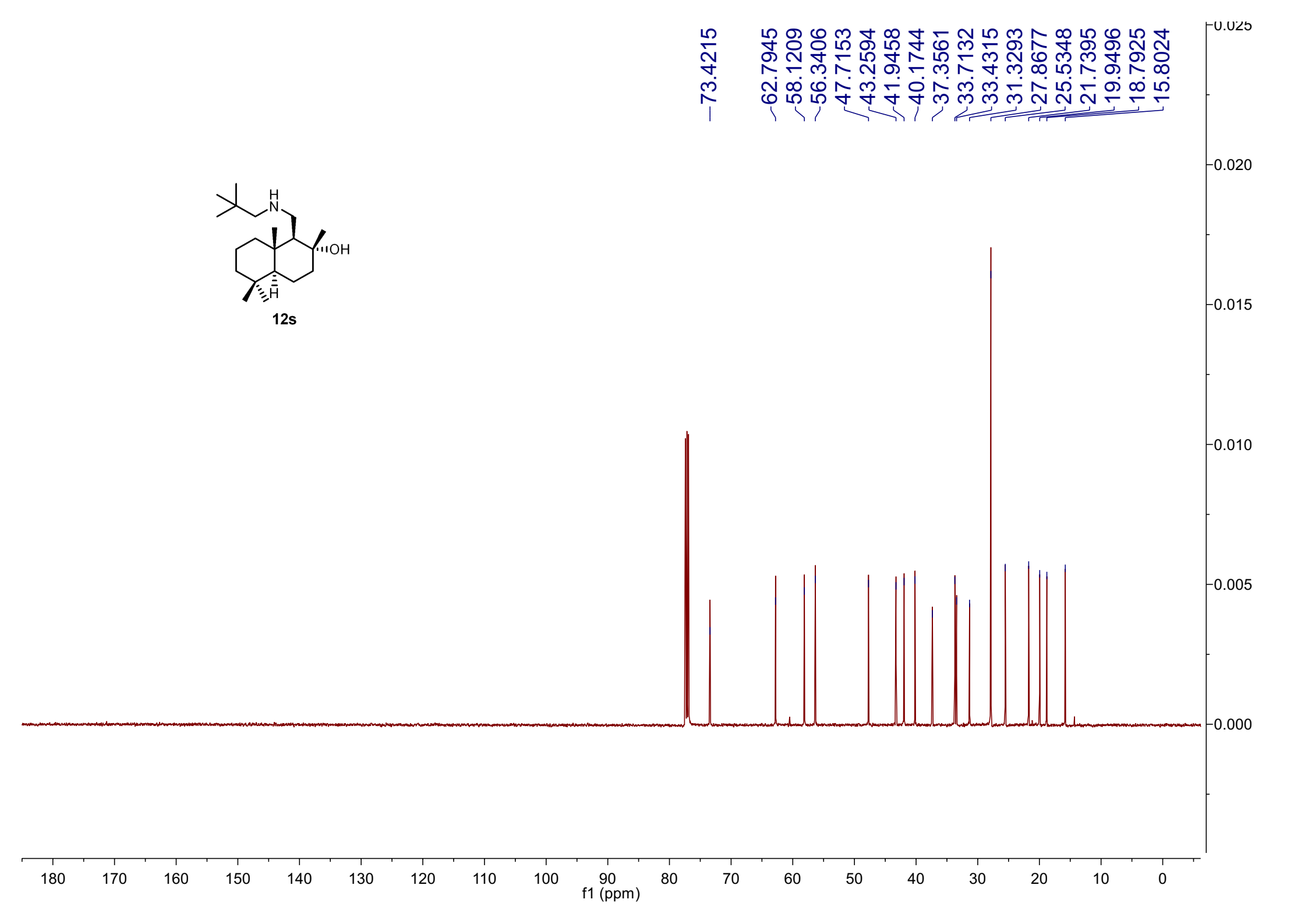
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25.5348
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19.9496
18.7925
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H
N
OH
H
12s
0.025
0.020
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0.005
0.000
180
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150
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50
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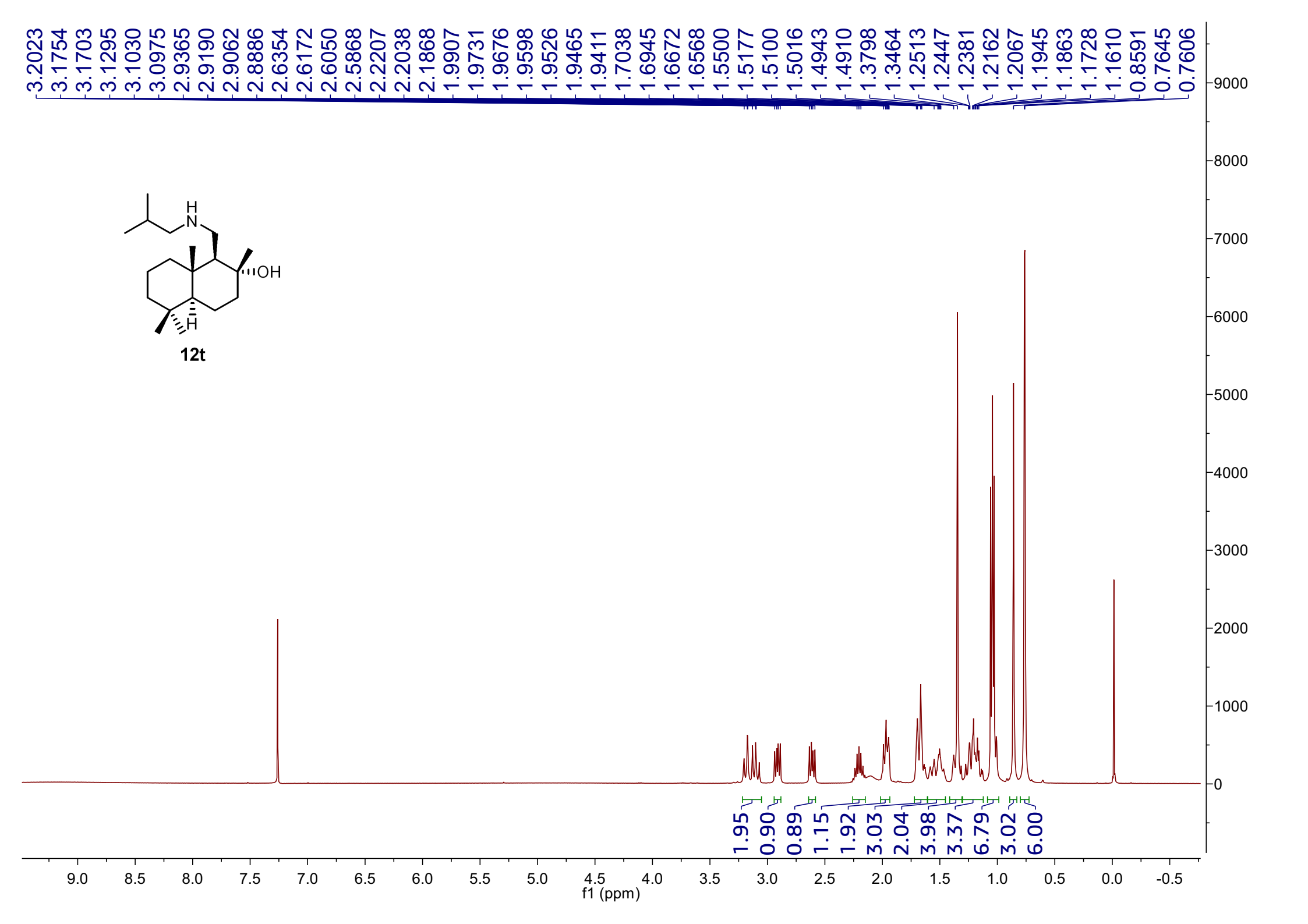
f1 (ppm)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1.9526
1.9465
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1.2447
1.2381
1.2162
1.2067
1.1945
1.1863
1.1728
1.1610
0.8591
0.7645
0.7606
H
N
OH
H
12t
1.95
0.90
0.89
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1.92
3.03
2.04
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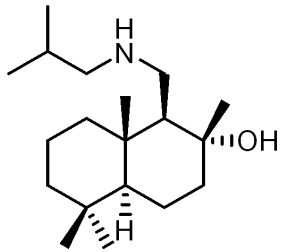
6.79
3.02
6.00
f1 (ppm)


H
N
OH
H

12t

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55.0227
46.3238
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41.4723
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37.8676
33.4645
33.4272
25.9063
24.0621
21.5516
20.4676
20.4384
20.2380
18.4886
16.1342
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
170
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120
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100
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80
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40
30
20
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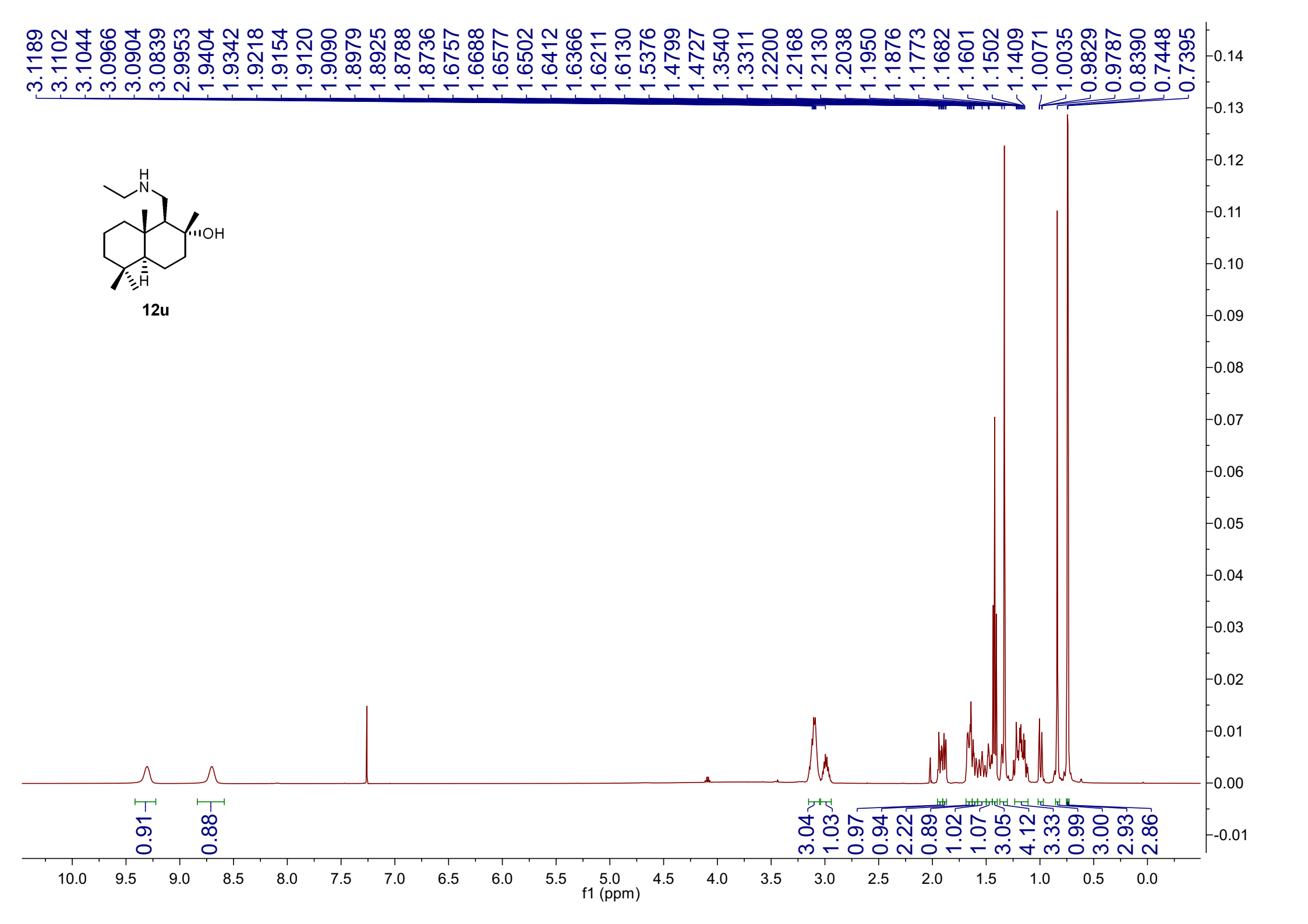
-10
f1 (ppm)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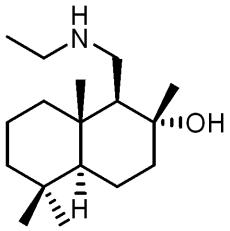
1.9342
1.9218
1.9154
1.9120
1.9090
1.8979
1.8925
1.8788
1.8736
1.6757
1.6688
1.6577
1.6502
1.6412
1.6366
1.6211
1.6130
1.5376
1.4799
1.4727
1.3540
1.3311
1.2200
1.2168
1.2130
1.2038
1.1950
1.1876
1.1773
1.1682
1.1601
1.1502
1.1409
1.0071
1.0035
0.9829
0.9787
0.8390
0.7448
0.7395
H
N
OH
H
12u
0.91
0.88
3.04
1.03
0.97
0.94
2.22
0.89
1.02
1.07
3.05
4.12
3.33
0.99
3.00
2.93
2.86
f1 (ppm)



12u

74.8701
55.7685
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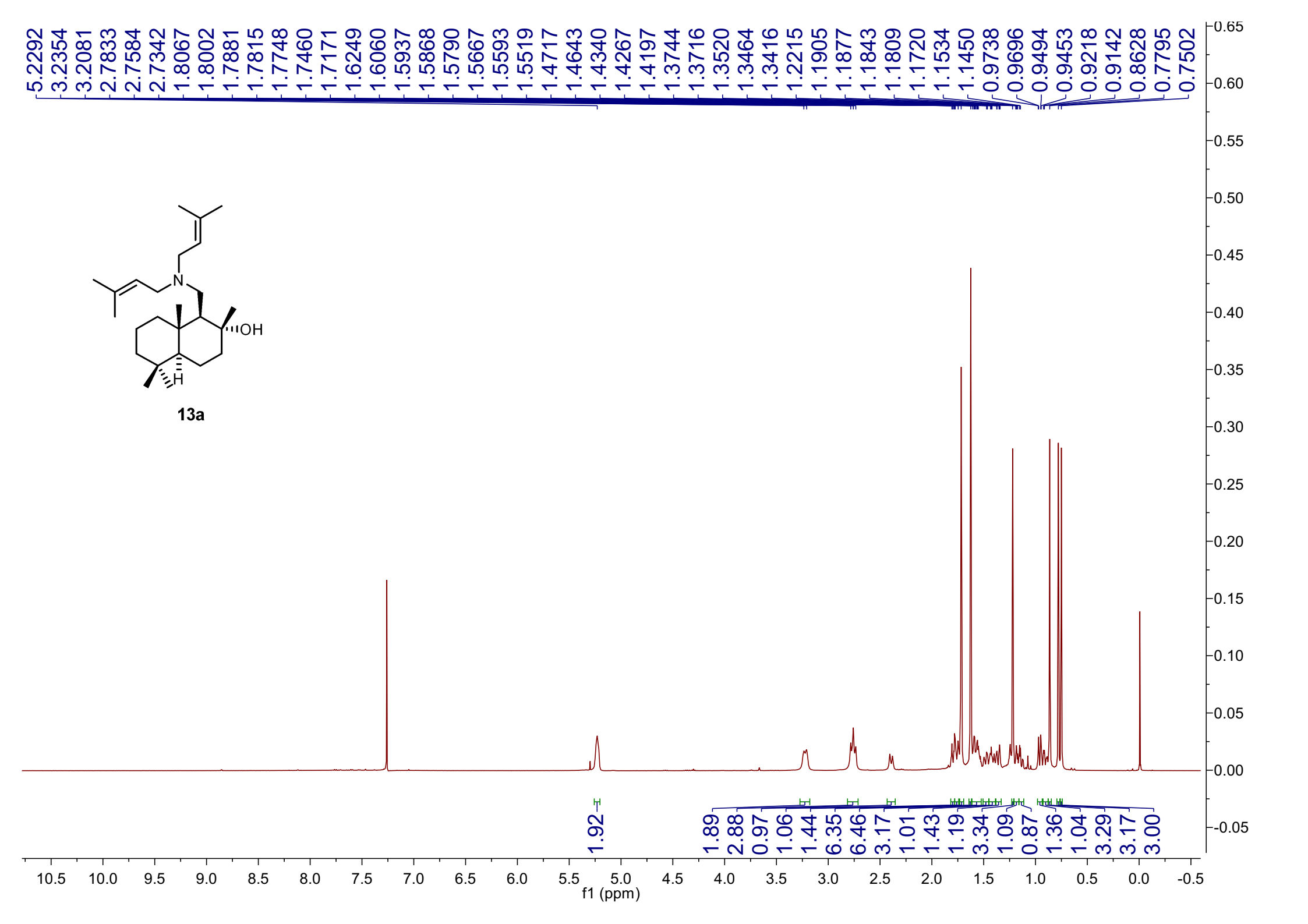
43.7883
43.4082
41.4488
39.5035
37.9666
33.3972
23.9570
21.5041
20.1974
18.4552
16.0778
11.6758

0.0055
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
-0.0005

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

f1 (ppm)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1.8067
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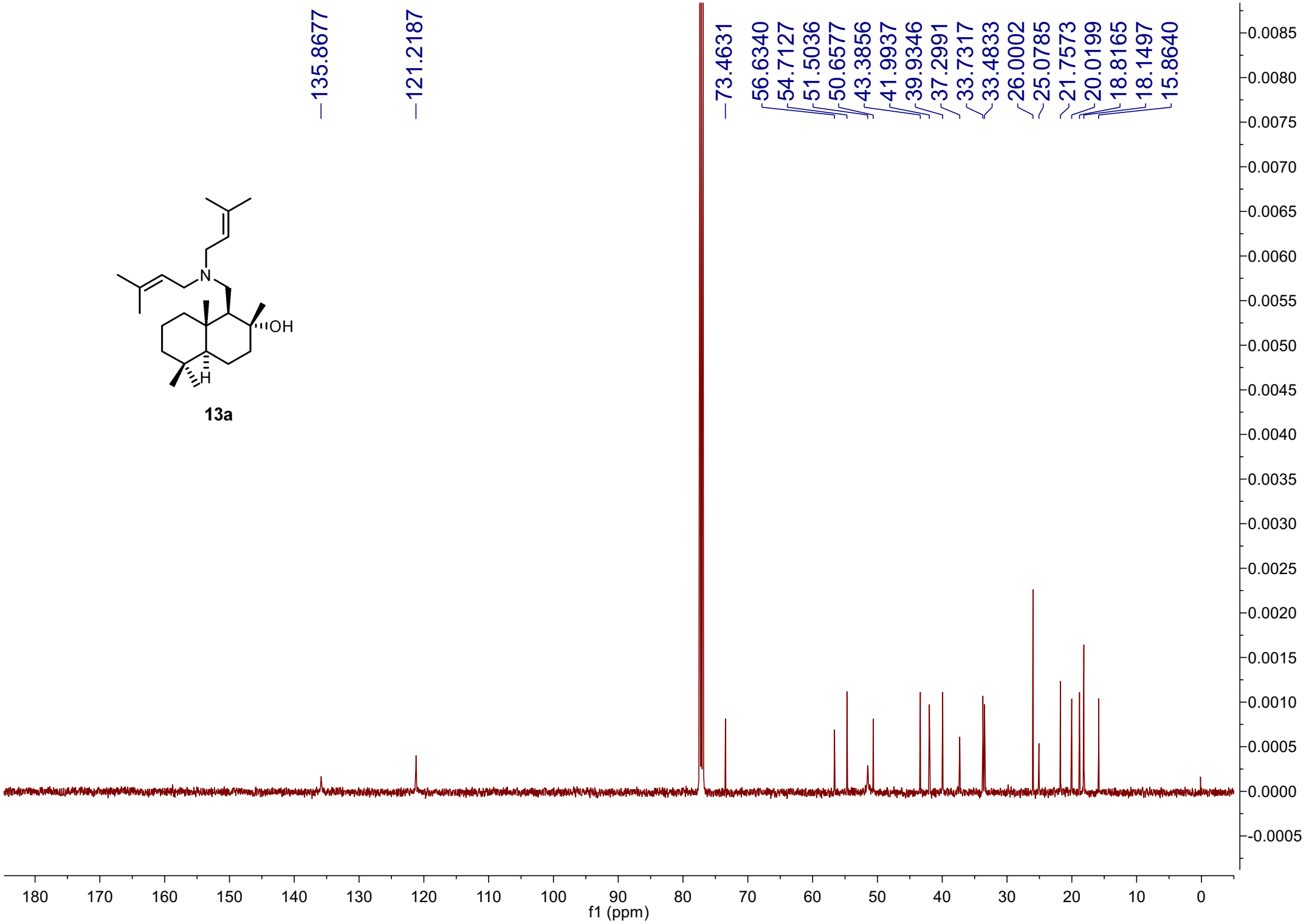
1.7748
1.7460
1.7171
1.6249
1.6060
1.5937
1.5868
1.5790
1.5667
1.5593
1.5519
1.4717
1.4643
1.4340
1.4267
1.4197
1.3744
1.3716
1.3520
1.3464
1.3416
1.2215
1.1905
1.1877
1.1843
1.1809
1.1720
1.1534
1.1450
0.9738
0.9696
0.9494
0.9453
0.9218
0.9142
0.8628
0.7795
0.7502
N
OH
H
13a
1.92
1.89
2.88
0.97
1.06
1.44
6.35
6.46
3.17
1.01
1.43
1.19
3.34
1.09
0.87
1.36
1.04
3.29
3.17
3.00
f1 (ppm)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73.4631
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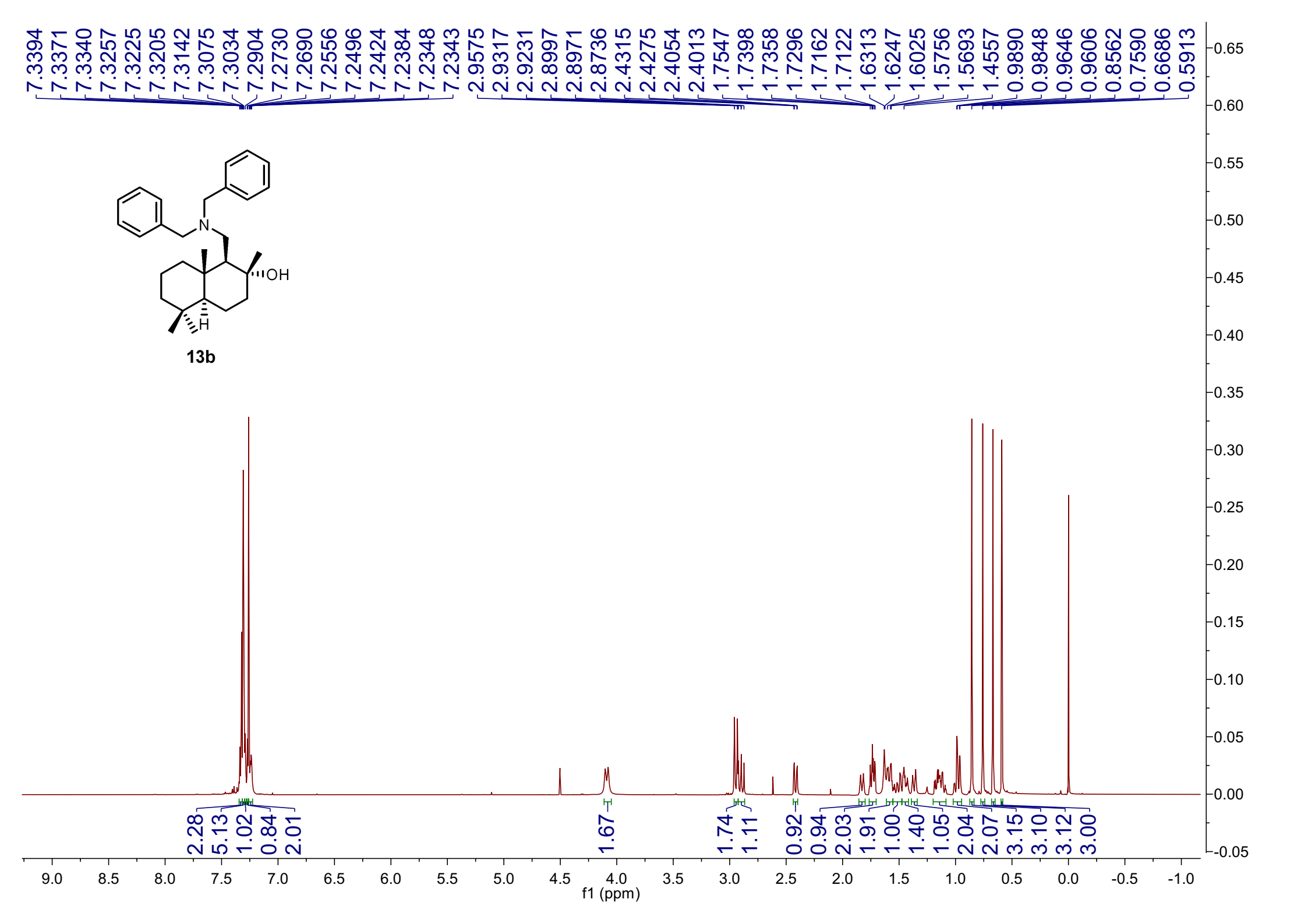
51.5036
50.6577
43.3856
41.9937
39.9346
37.2991
33.7317
33.4833
26.0002
25.0785
21.7573
20.0199
18.8165
18.1497
15.8640
N
OH
H
13a
f1 (ppm)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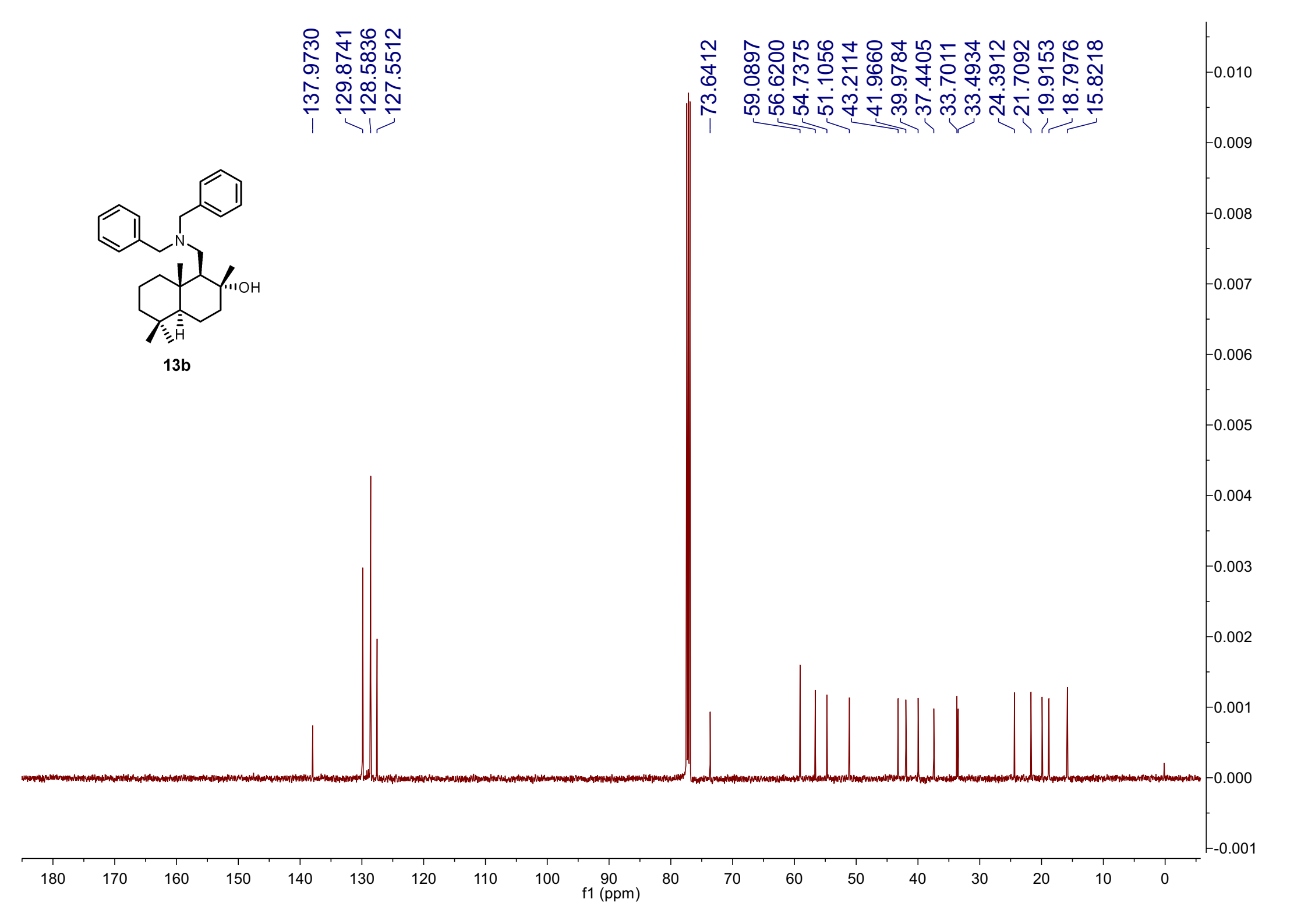
7.3340
7.3257
7.3225
7.3205
7.3142
7.3075
7.3034
7.2904
7.2730
7.2690
7.2556
7.2496
7.2424
7.2384
7.2348
7.2343
2.9575
2.9317
2.9231
2.8997
2.8971
2.8736
2.4315
2.4275
2.4054
2.4013
1.7547
1.7398
1.7358
1.7296
1.7162
1.7122
1.6313
1.6247
1.6025
1.5756
1.5693
1.4557
0.9890
0.9848
0.9646
0.9606
0.8562
0.7590
0.6686
0.5913
N
OH
H
13b
2.28
5.13
1.02
0.84
2.01
1.67
1.74
1.11
0.92
0.94
2.03
1.91
1.00
1.40
1.05
2.04
2.07
3.15
3.10
3.12
3.00
f1 (ppm)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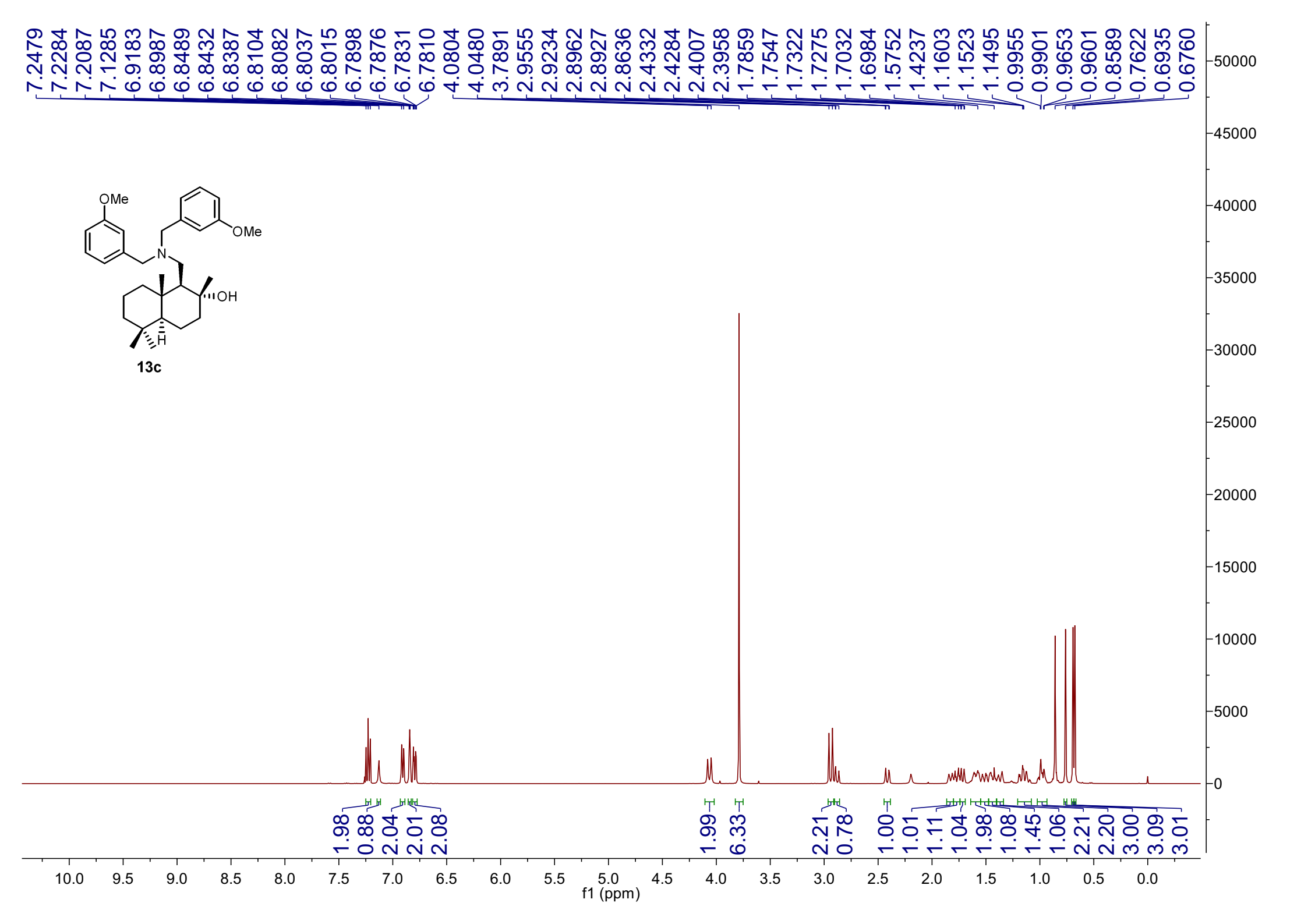
128.5836
127.5512
73.6412
59.0897
56.6200
54.7375
51.1056
43.2114
41.9660
39.9784
37.4405
33.7011
33.4934
24.3912
21.7092
19.9153
18.7976
15.8218
OH
H
N
13b
f1 (ppm)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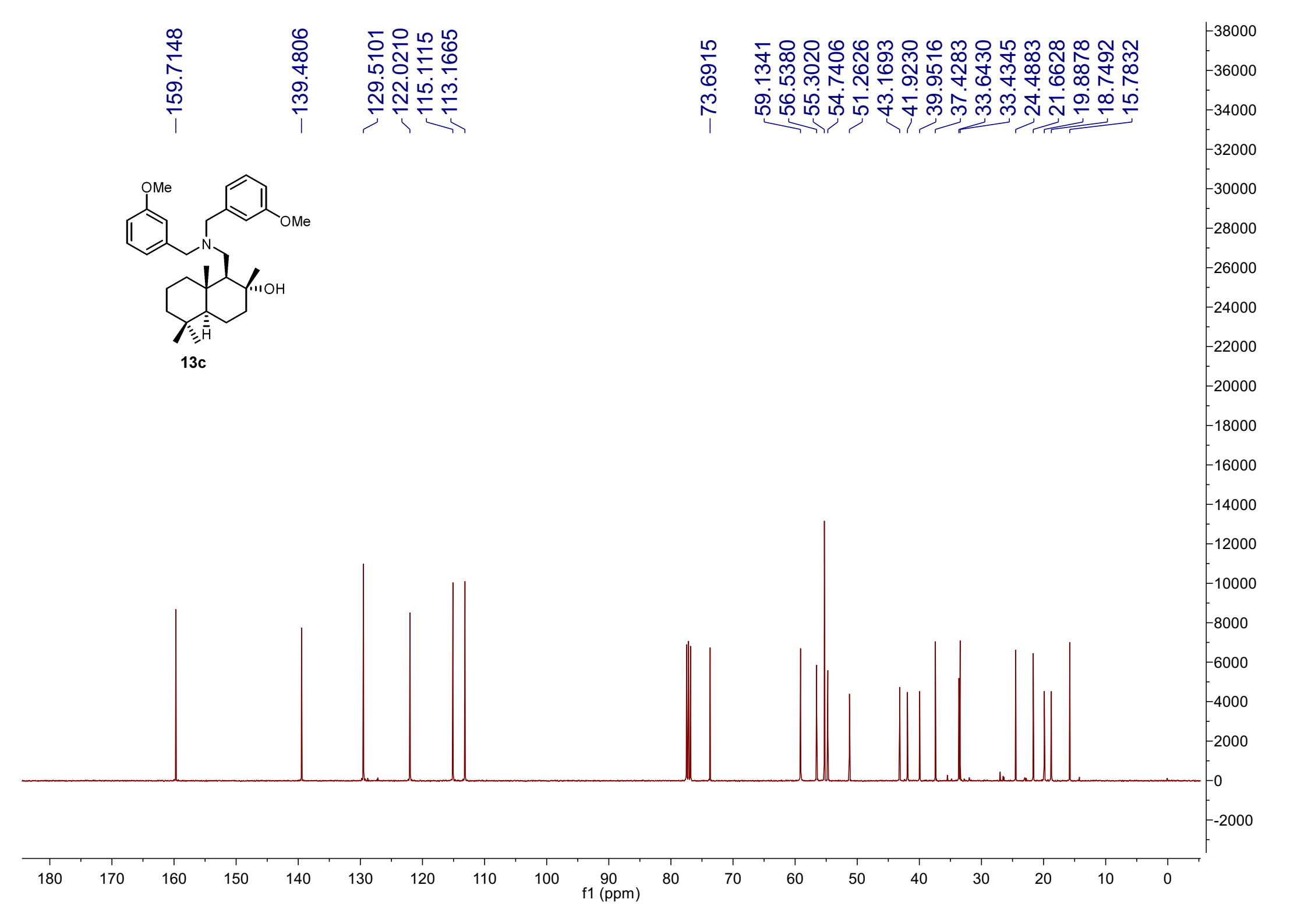
7.2087
7.1285
6.9183
6.8987
6.8489
6.8432
6.8387
6.8104
6.8082
6.8037
6.8015
6.7898
6.7876
6.7831
6.7810
4.0804
4.0480
3.7891
2.9555
2.9234
2.8962
2.8927
2.8636
2.4332
2.4284
2.4007
2.3958
1.7859
1.7547
1.7322
1.7275
1.7032
1.6984
1.5752
1.4237
1.1603
1.1523
1.1495
0.9955
0.9901
0.9653
0.9601
0.8589
0.7622
0.6935
0.6760
OMe
OMe
N
OH
H
13c
1.98
0.88
2.04
2.01
2.08
1.99
6.33
2.21
0.78
1.00
1.01
1.11
1.04
1.98
1.08
1.45
1.06
2.21
2.20
3.00
3.09
3.01
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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113.1665
73.6915
59.1341
56.5380
55.3020
54.7406
51.2626
43.1693
41.9230
39.9516
37.4283
33.6430
33.4345
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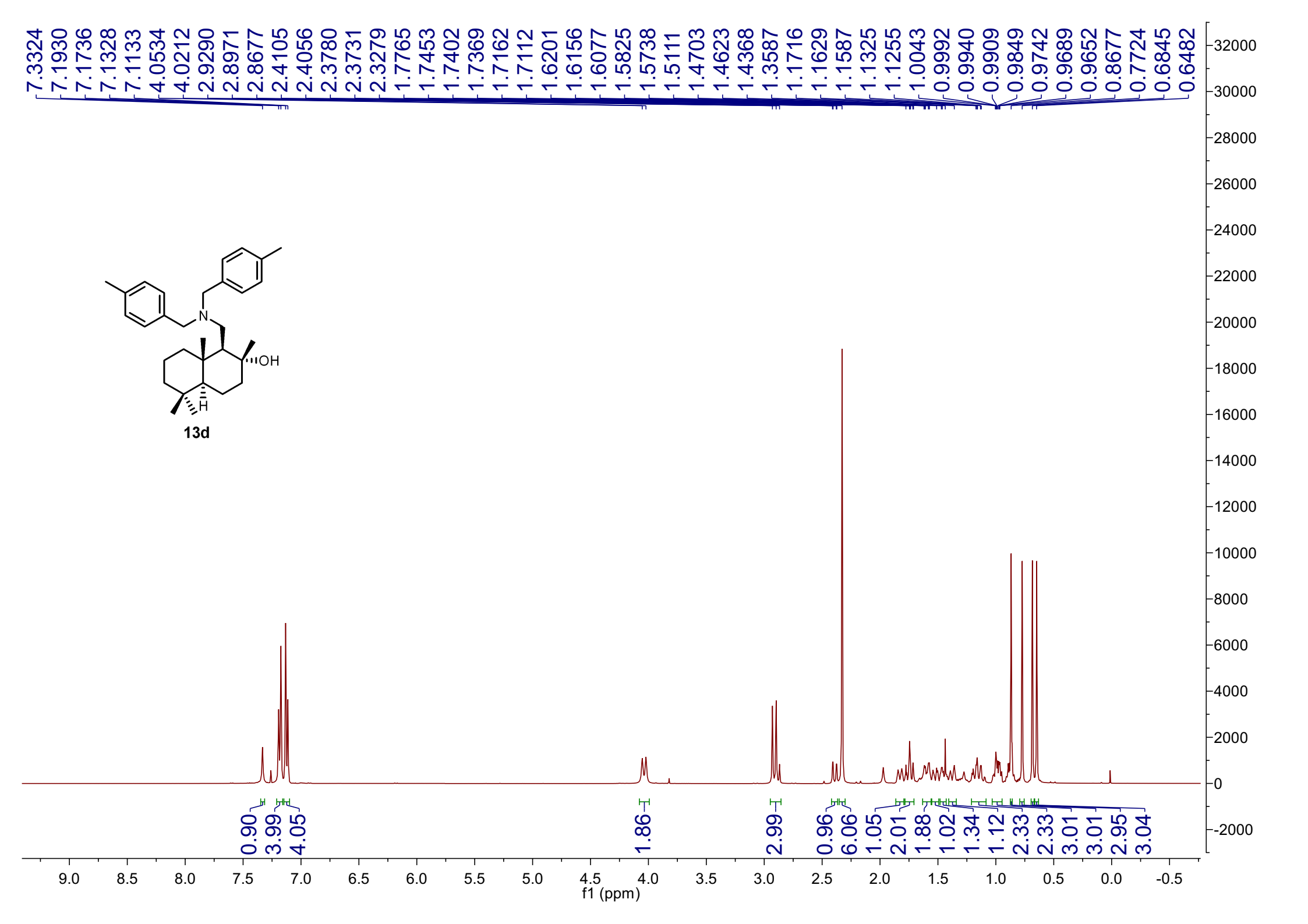
21.6628
19.8878
18.7492
15.7832
OMe
OMe
N
OH
H
13c
f1 (ppm)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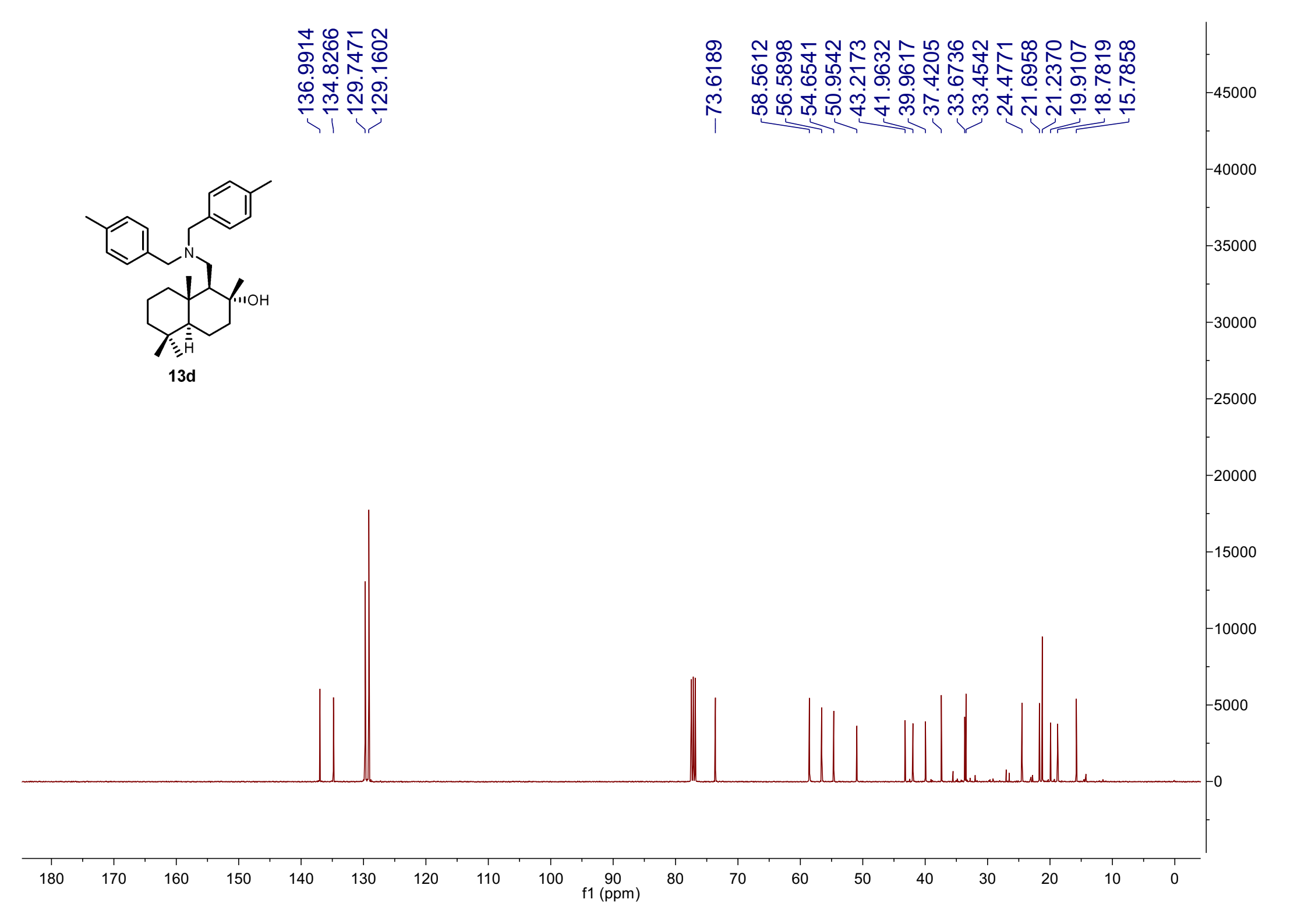
7.1930
7.1736
7.1328
7.1133
4.0534
4.0212
2.9290
2.8971
2.8677
2.4105
2.4056
2.3780
2.3731
2.3279
1.7765
1.7453
1.7402
1.7369
1.7162
1.7112
1.6201
1.6156
1.6077
1.5825
1.5738
1.5111
1.4703
1.4623
1.4368
1.3587
1.1716
1.1629
1.1587
1.1325
1.1255
1.0043
0.9992
0.9940
0.9909
0.9849
0.9742
0.9689
0.9652
0.8677
0.7724
0.6845
0.6482
N
OH
H
13d
0.90
3.99
4.05
1.86
2.99
0.96
6.06
1.05
2.01
1.88
1.02
1.34
1.12
2.33
2.33
3.01
3.01
2.95
3.04
f1 (ppm)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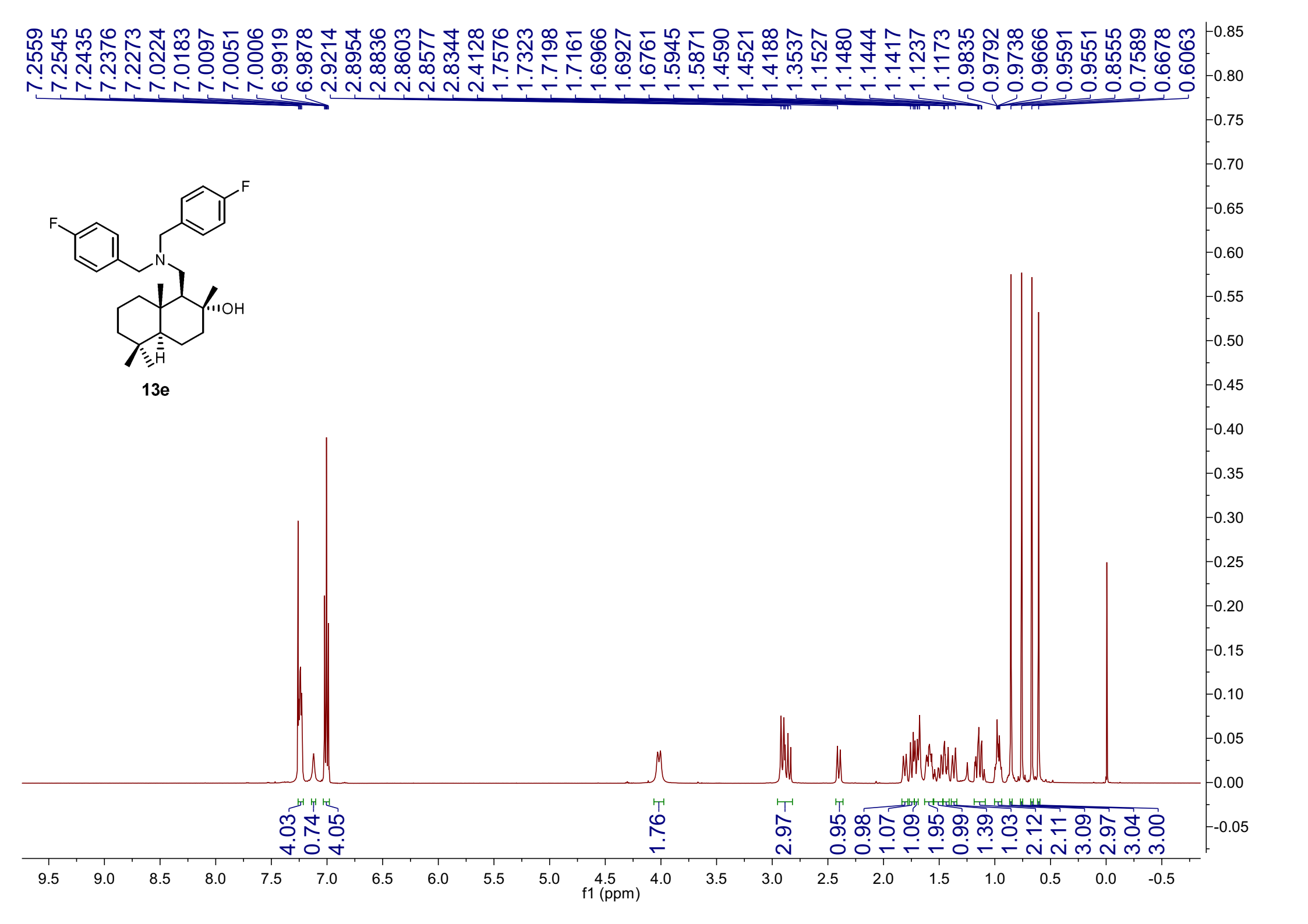
129.1602
73.6189
58.5612
56.5898
54.6541
50.9542
43.2173
41.9632
39.9617
37.4205
33.6736
33.4542
24.4771
21.6958
21.2370
19.9107
18.7819
15.7858
N
OH
H
13d
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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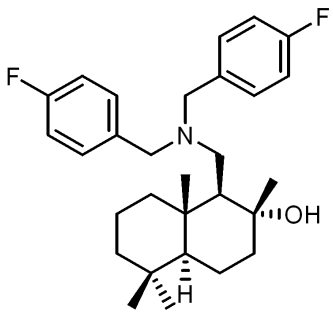
F
F
N
OH
H
13e
4.03 0.74 4.05 1.76 2.97 0.95 0.98 1.07 1.09 1.95 0.99 1.39 1.03 2.12 2.11 3.09 2.97 3.04 3.00
f1 (ppm)


F
F
N
OH
H

13e

163.3349
161.3812
133.5956
131.4223
131.3592
115.5833
115.4139
73.7477
58.2242
56.6109
54.7635
50.9873
43.1380
41.9235
39.9658
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33.6779
33.4859
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19.8883
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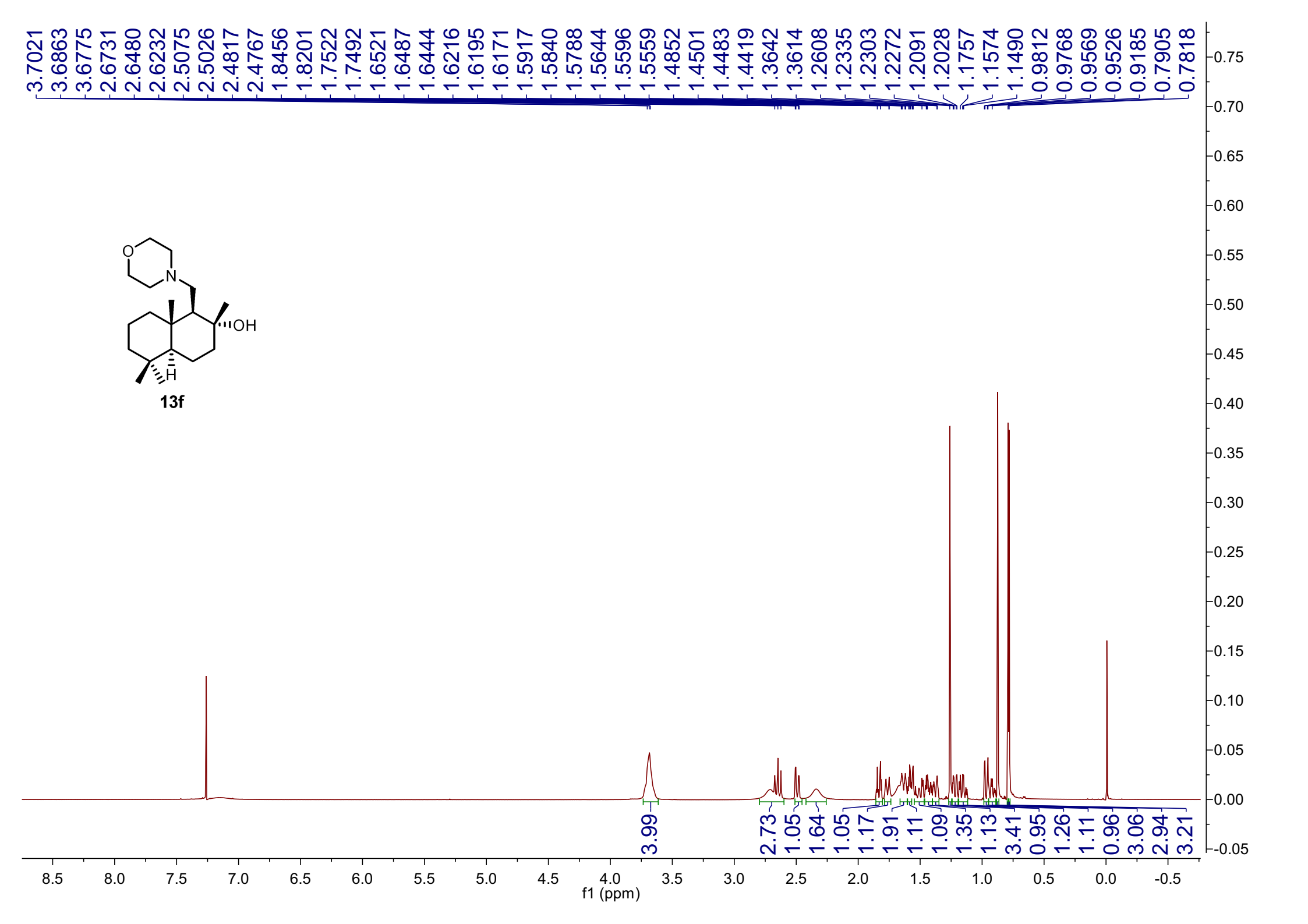
f1 (ppm)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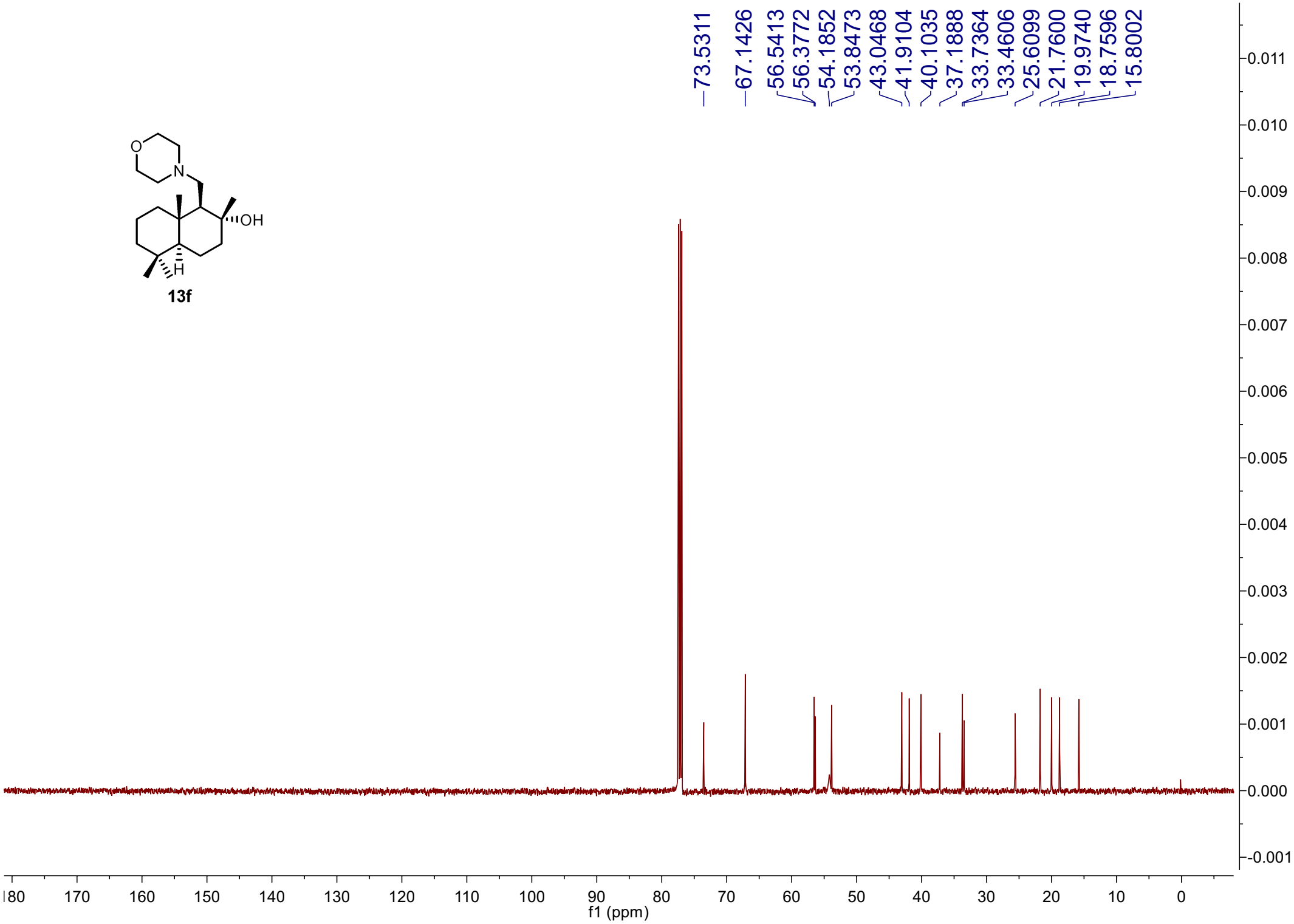
2.4817
2.4767
1.8456
1.8201
1.7522
1.7492
1.6521
1.6487
1.6444
1.6216
1.6195
1.6171
1.5917
1.5840
1.5788
1.5644
1.5596
1.5559
1.4852
1.4501
1.4483
1.4419
1.3642
1.3614
1.2608
1.2335
1.2303
1.2272
1.2091
1.2028
1.1757
1.1574
1.1490
0.9812
0.9768
0.9569
0.9526
0.9185
0.7905
0.7818
O
N
OH
H
13f
3.99
2.73
1.05
1.64
1.05
1.17
1.91
1.11
1.09
1.35
1.13
3.41
0.95
1.26
1.11
0.96
3.06
2.94
3.21
f1 (ppm)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53.8473
43.0468
41.9104
40.1035
37.1888
33.7364
33.4606
25.6099
21.7600
19.9740
18.7596
15.8002
O
N
OH
H
13f
0.011
0.010
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
-0.001
180
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150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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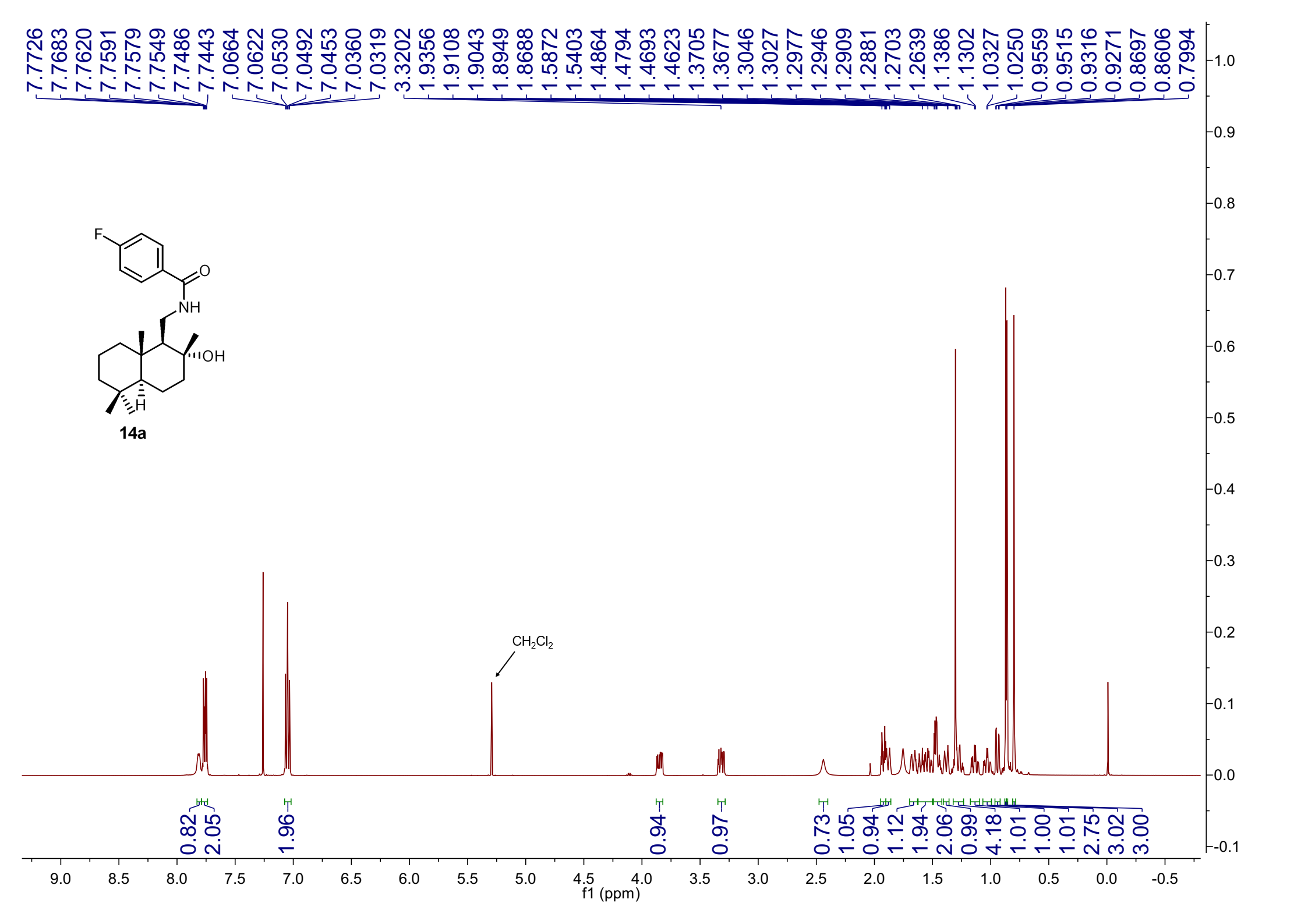
f1 (ppm)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7.7579
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7.7486
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7.0622
7.0530
7.0492
7.0453
7.0360
7.0319
3.3202
1.9356
1.9108
1.9043
1.8949
1.8688
1.5872
1.5403
1.4864
1.4794
1.4693
1.4623
1.3705
1.3677
1.3046
1.3027
1.2977
1.2946
1.2909
1.2881
1.2703
1.2639
1.1386
1.1302
1.0327
1.0250
0.9559
0.9515
0.9316
0.9271
0.8697
0.8606
0.7994
F
O
NH
OH
H
14a
CH2Cl2
0.82
2.05
1.96
0.94
0.97
0.73
1.05
0.94
1.12
1.94
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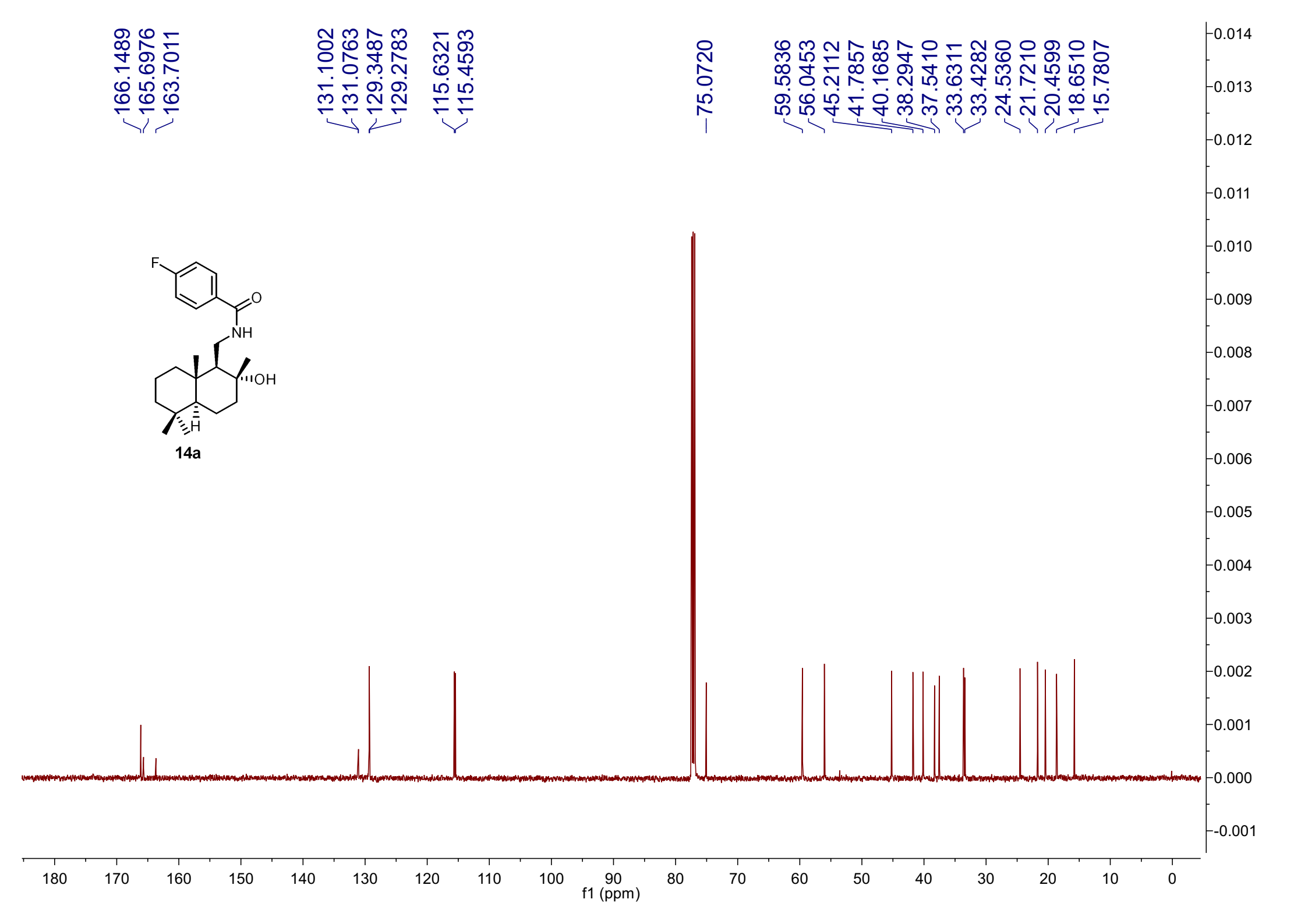
1.00
1.01
2.75
3.02
3.00
f1 (ppm)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59.5836
56.0453
45.2112
41.7857
40.1685
38.2947
37.5410
33.6311
33.4282
24.5360
21.7210
20.4599
18.6510
15.7807
F
O
NH
OH
H
14a
0.014
0.013
0.012
0.011
0.010
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
-0.001
180
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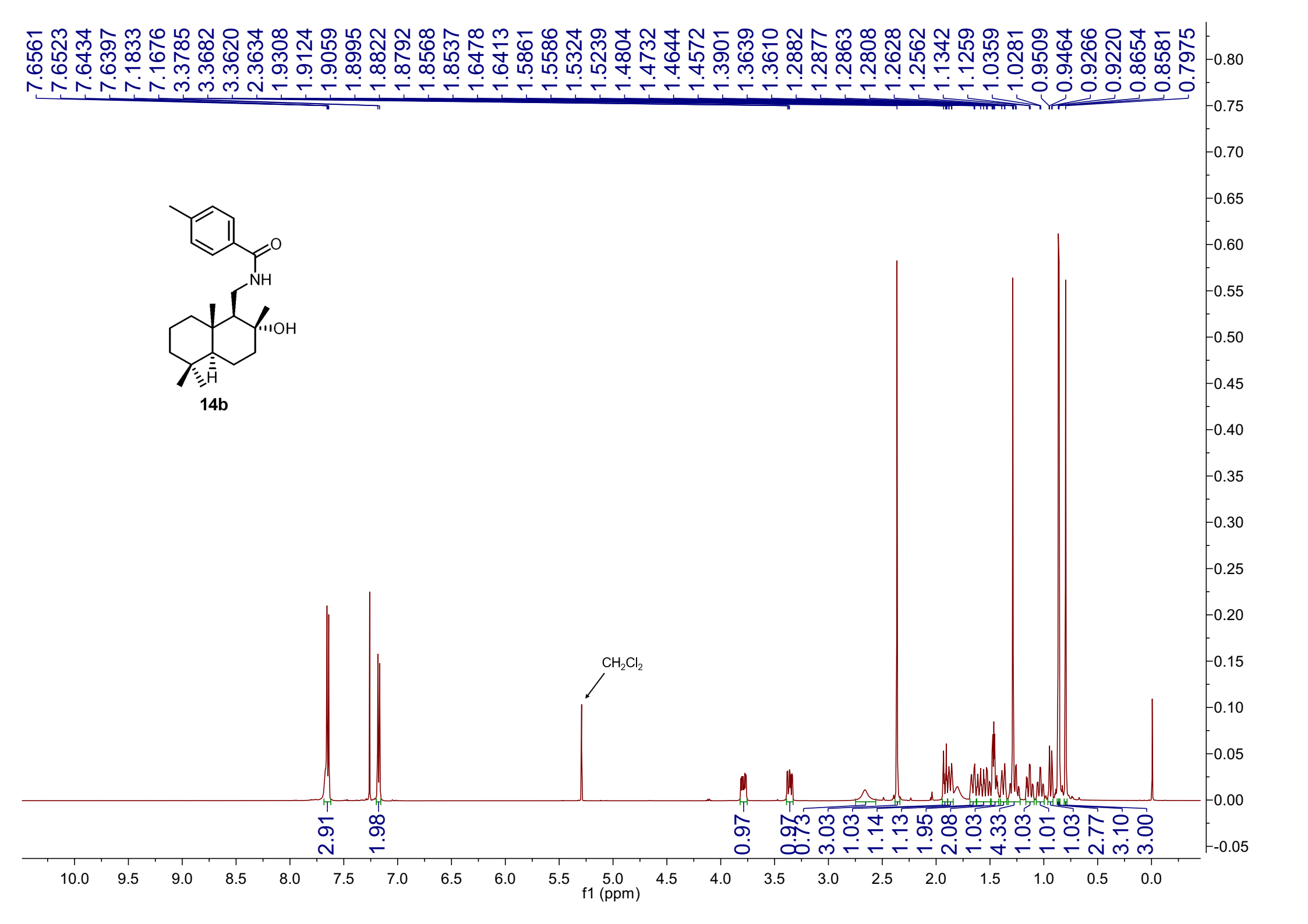
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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3.3785
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3.3620
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1.9308
1.9124
1.9059
1.8995
1.8822
1.8792
1.8568
1.8537
1.6478
1.6413
1.5861
1.5586
1.5324
1.5239
1.4804
1.4732
1.4644
1.4572
1.3901
1.3639
1.3610
1.2882
1.2877
1.2863
1.2808
1.2628
1.2562
1.1342
1.1259
1.0359
1.0281
0.9509
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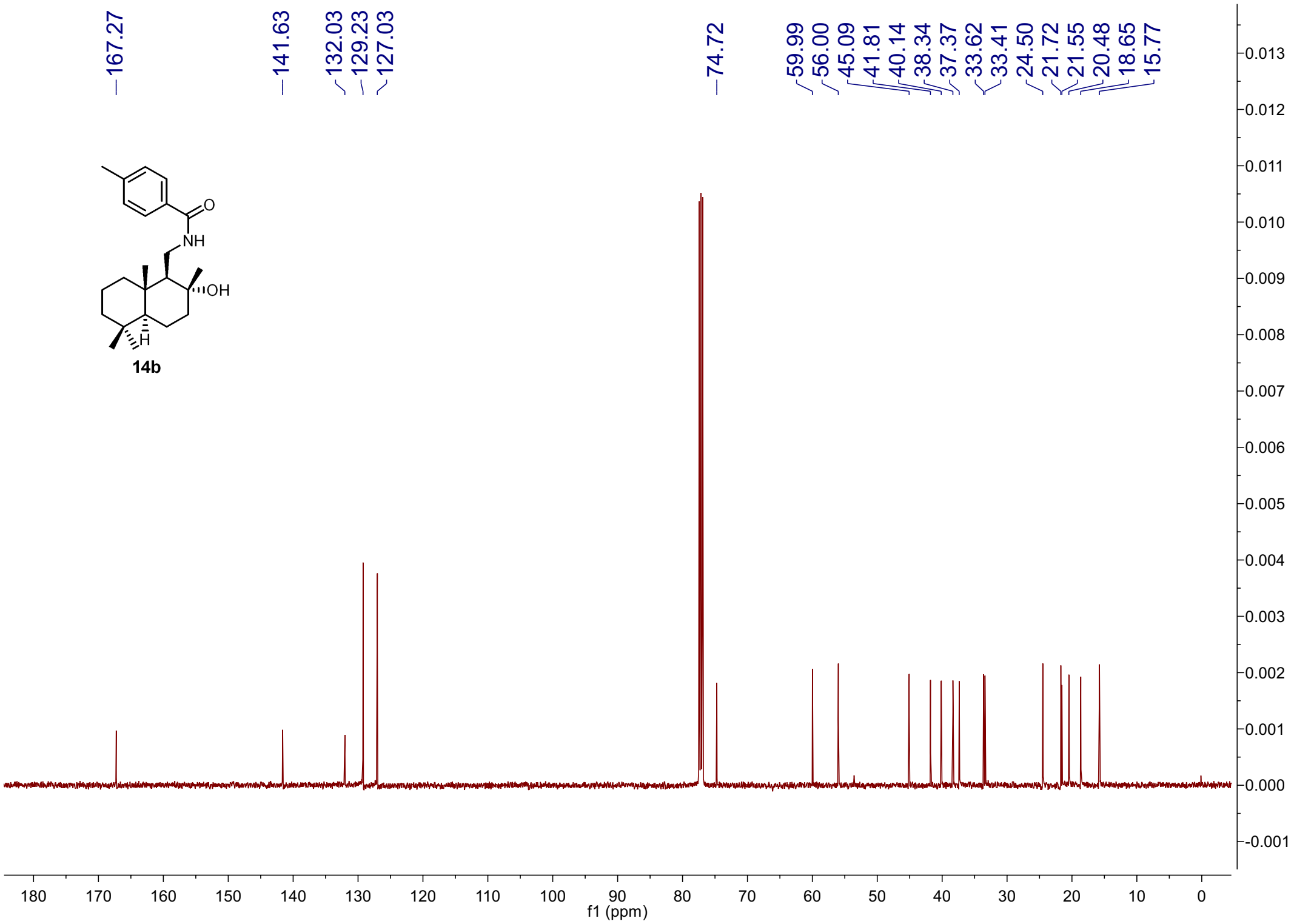
0.9266
0.9220
0.8654
0.8581
0.7975
O
NH
OH
H
14b
CH2Cl2
2.91
1.98
0.97
0.97
0.73
3.03
1.03
1.14
1.13
1.95
2.08
1.03
4.33
1.03
1.01
1.03
2.77
3.10
3.00
f1 (ppm)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132.03
129.23
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56.00
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40.14
38.34
37.37
33.62
33.41
24.50
21.72
21.55
20.48
18.65
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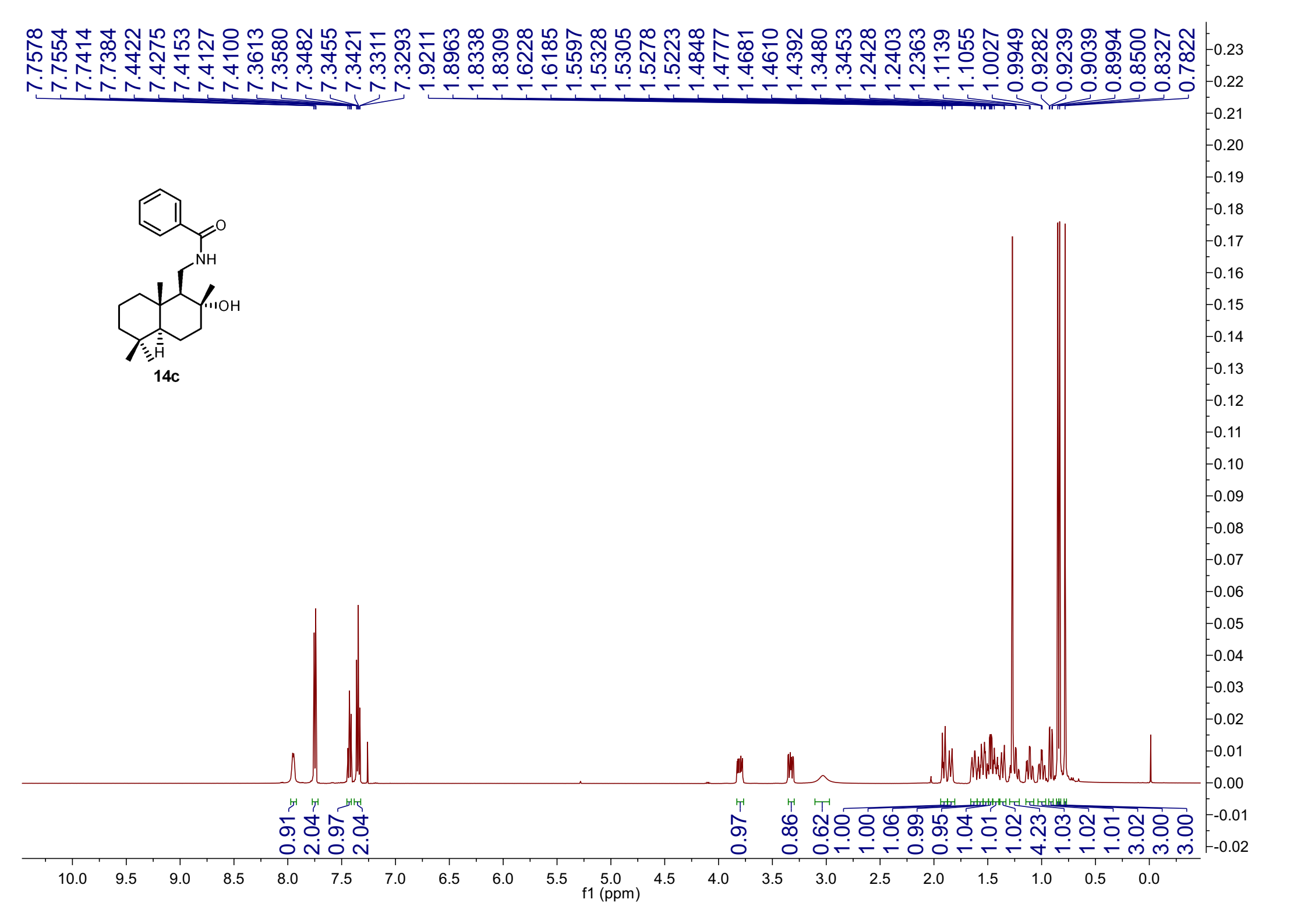
O
NH
OH
H
14b
f1 (ppm)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7.4127
7.4100
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7.3580
7.3482
7.3455
7.3421
7.3311
7.3293
1.9211
1.8963
1.8338
1.8309
1.6228
1.6185
1.5597
1.5328
1.5305
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1.5223
1.4848
1.4777
1.4681
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1.4392
1.3480
1.3453
1.2428
1.2403
1.2363
1.1139
1.1055
1.0027
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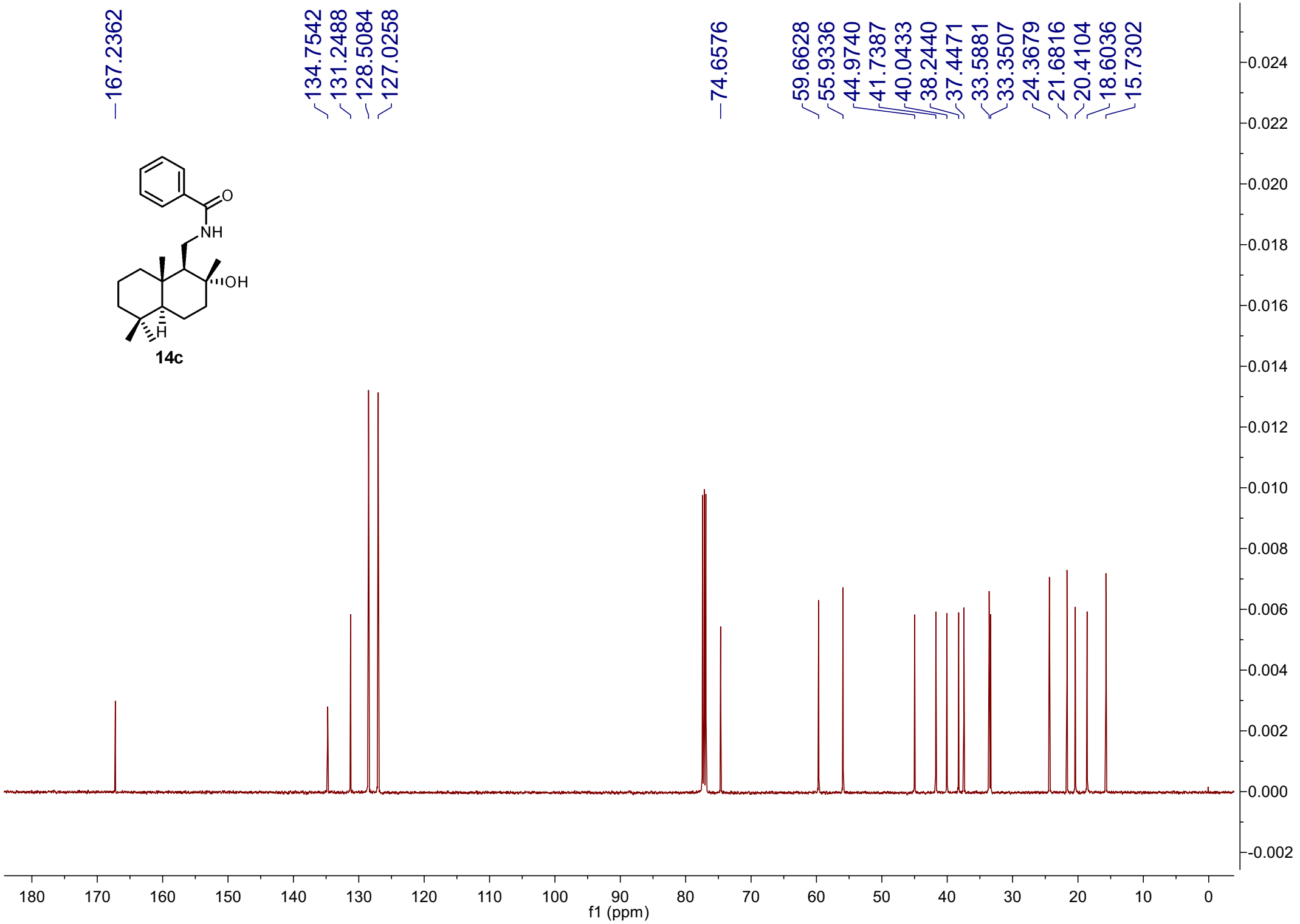
0.9282
0.9239
0.9039
0.8994
0.8500
0.8327
0.7822
O
NH
OH
H
14c
0.91
2.04
0.97
2.04
0.97
0.86
0.62
1.00
1.00
1.06
0.99
0.95
1.04
1.01
1.02
4.23
1.03
1.02
1.01
3.02
3.00
3.00
f1 (ppm)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131.2488
128.5084
127.0258
74.6576
59.6628
55.9336
44.9740
41.7387
40.0433
38.2440
37.4471
33.5881
33.3507
24.3679
21.6816
20.4104
18.6036
15.7302
O
NH
OH
H
14c
0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
-0.002
180
170
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150
140
130
120
110
100
90
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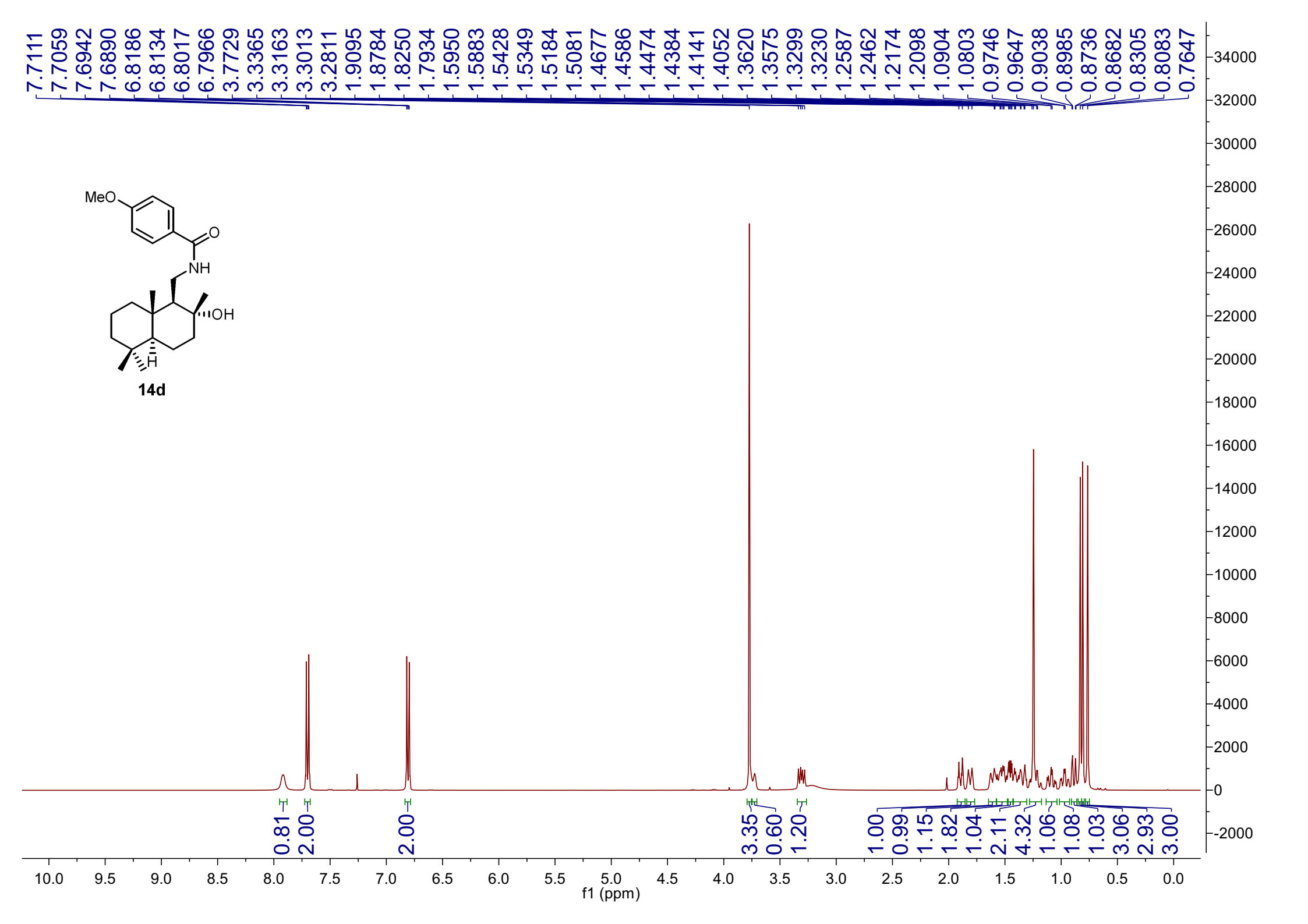
50
40
30
20
10
0
f1 (ppm)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7.7059
7.6942
7.6890
6.8186
6.8134
6.8017
6.7966
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3.3365
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3.3013
3.2811
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1.8784
1.8250
1.7934
1.5950
1.5883
1.5428
1.5349
1.5184
1.5081
1.4677
1.4586
1.4474
1.4384
1.4141
1.4052
1.3620
1.3575
1.3299
1.3230
1.2587
1.2462
1.2174
1.2098
1.0904
1.0803
0.9746
0.9647
0.9038
0.8985
0.8736
0.8682
0.8305
0.8083
0.7647
MeO
O
NH
OH
H
14d
0.81
2.00
2.00
3.35
0.60
1.20
1.00
0.99
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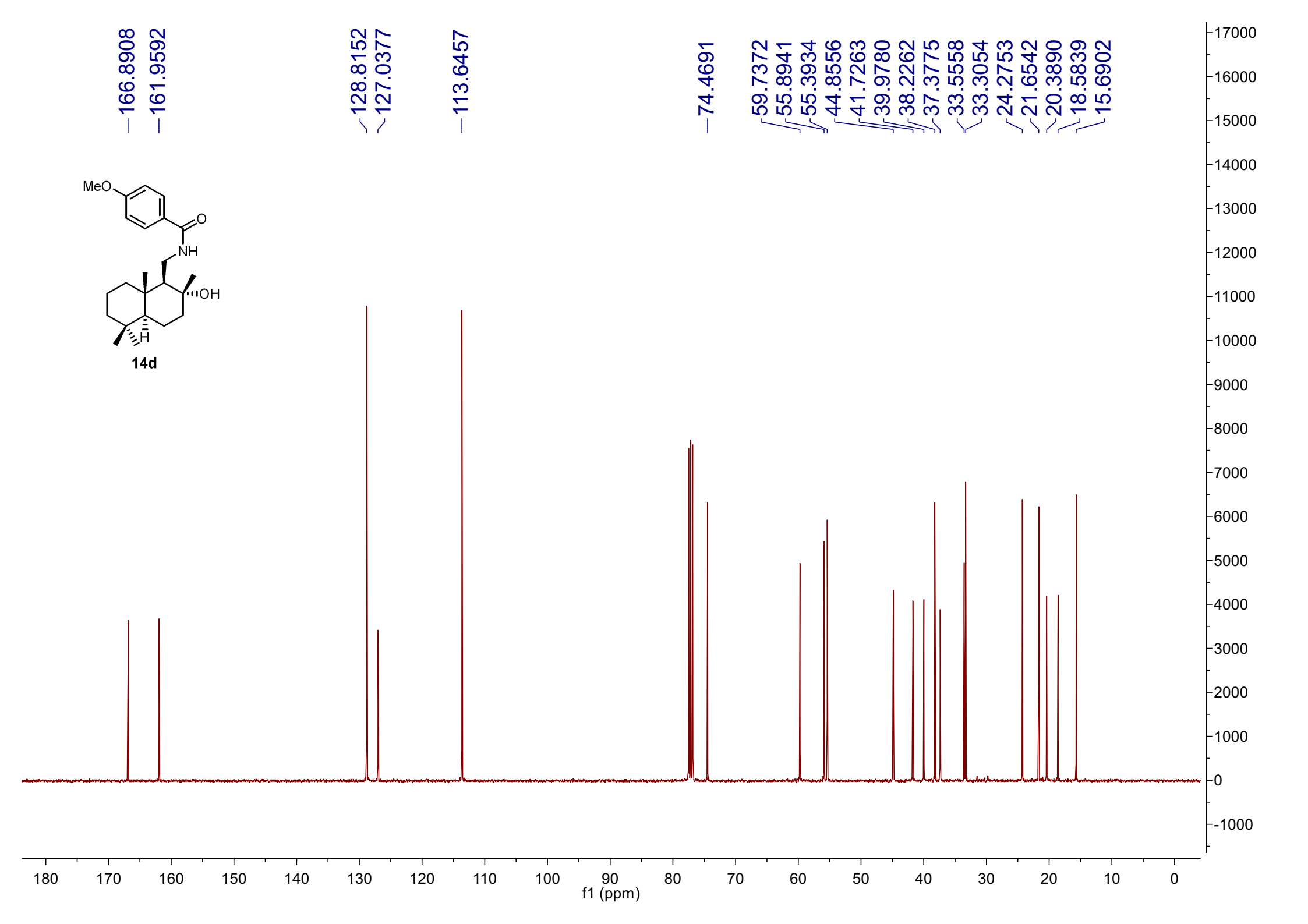
1.08
1.03
3.06
2.93
3.00
f1 (ppm)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38.2262
37.3775
33.5558
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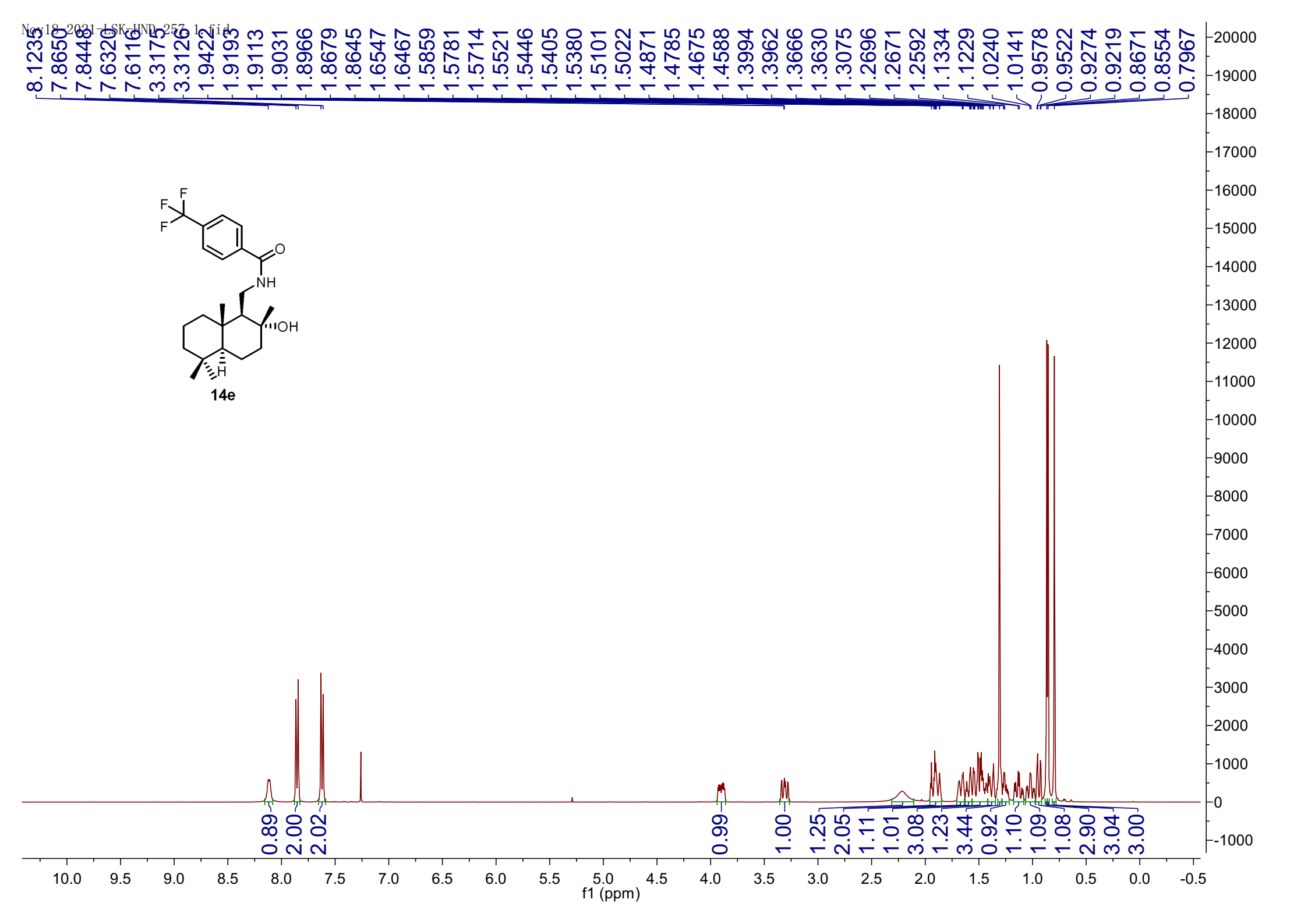
O
NH
OH
H
14d
f1 (ppm)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1.8645
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1.6467
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1.5714
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1.5405
1.5380
1.5101
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1.4675
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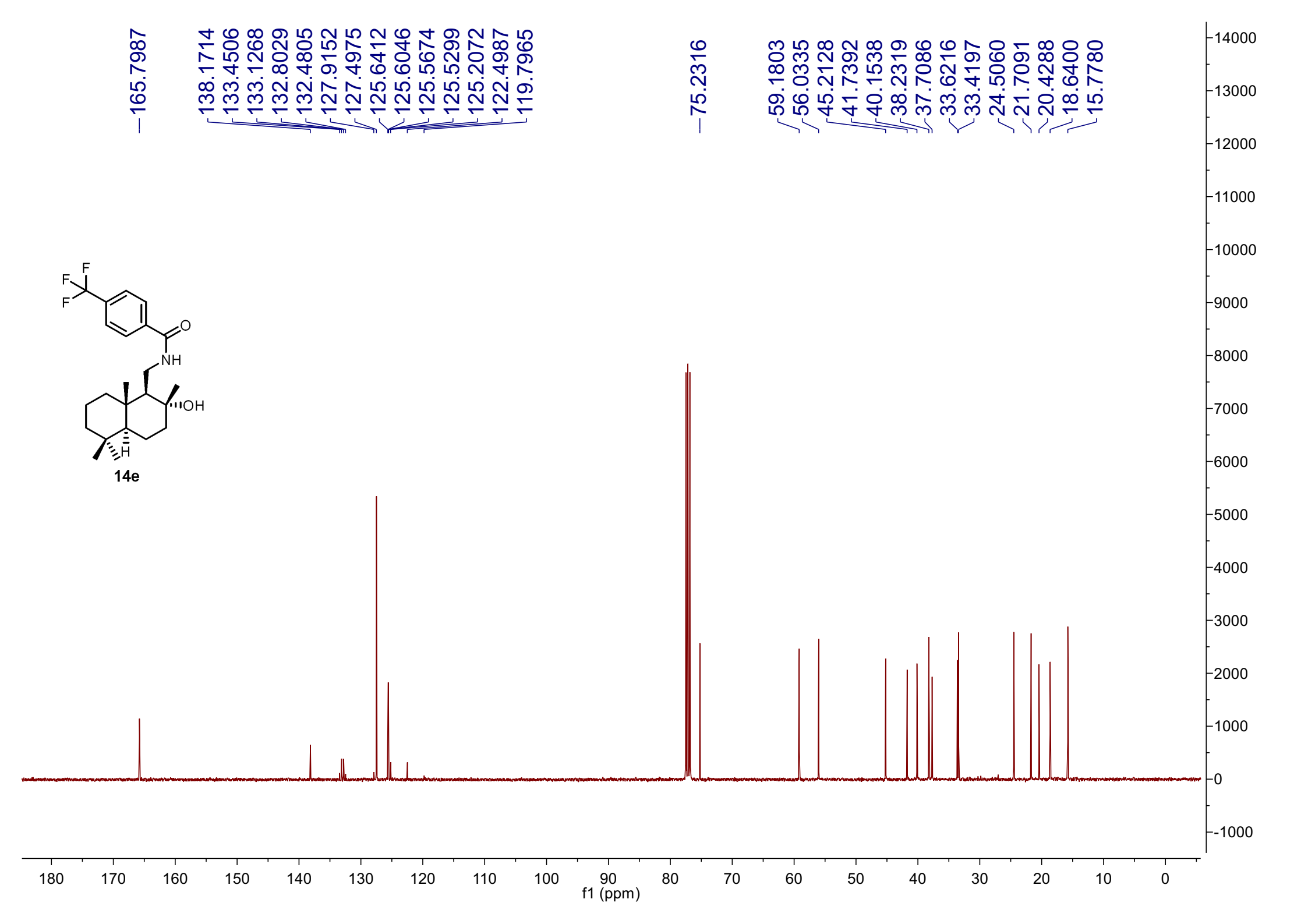
1.3630
1.3075
1.2696
1.2671
1.2592
1.1334
1.1229
1.0240
1.0141
0.9578
0.9522
0.9274
0.9219
0.8671
0.8554
0.7967
F
F
F
O
NH
OH
H
14e
0.89
2.00
2.02
0.99
1.00
1.25
2.05
1.11
1.01
3.08
1.23
3.44
0.92
1.10
1.09
1.08
2.90
3.04
3.00
f1 (ppm)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125.5674
125.5299
125.2072
122.4987
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75.2316
59.1803
56.0335
45.2128
41.7392
40.1538
38.2319
37.7086
33.6216
33.4197
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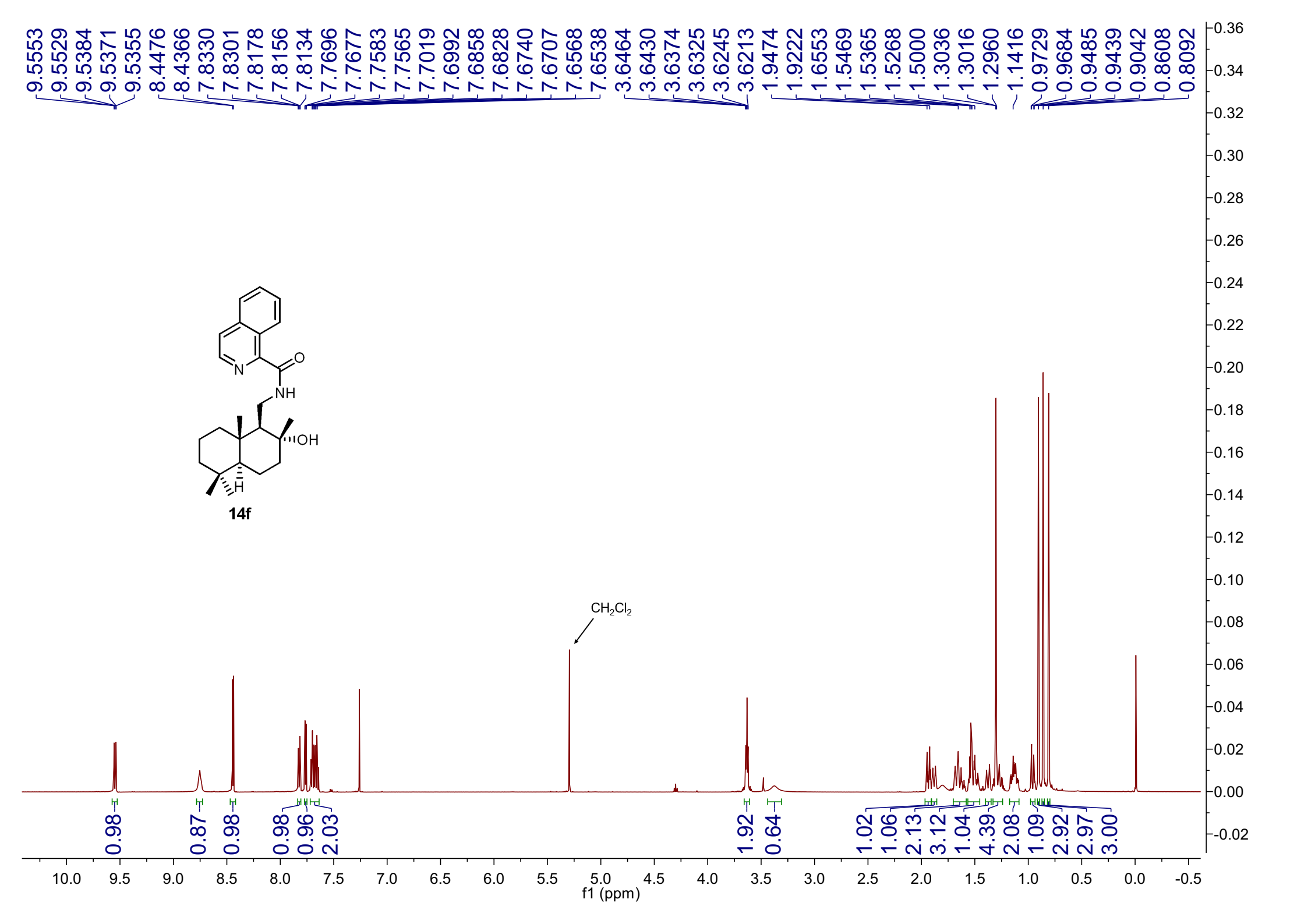
15.7780
F
F
F
O
NH
OH
H
14e
f1 (ppm)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7.8156
7.8134
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7.7677
7.7583
7.7565
7.7019
7.6992
7.6858
7.6828
7.6740
7.6707
7.6568
7.6538
3.6464
3.6430
3.6374
3.6325
3.6245
3.6213
1.9474
1.9222
1.6553
1.5469
1.5365
1.5268
1.5000
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1.3016
1.2960
1.1416
0.9729
0.9684
0.9485
0.9439
0.9042
0.8608
0.8092
O
N
NH
OH
H
14f
CH2Cl2
0.98
0.87
0.98
0.98
0.96
2.03
1.92
0.64
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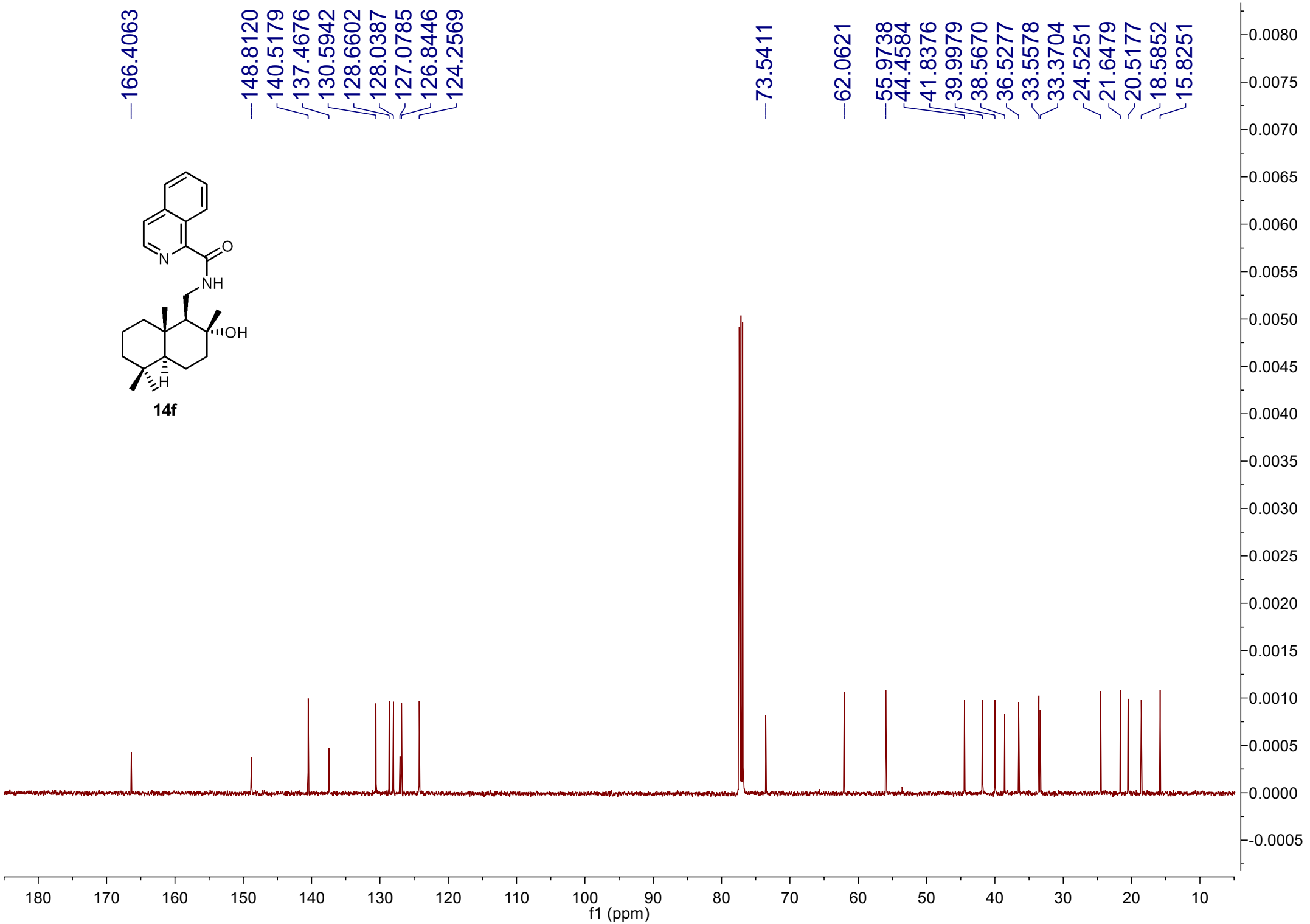
3.12
1.04
4.39
2.08
1.09
2.92
2.97
3.00
f1 (ppm)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124.2569
73.5411
62.0621
55.9738
44.4584
41.8376
39.9979
38.5670
36.5277
33.5578
33.3704
24.5251
21.6479
20.5177
18.5852
15.8251
O
N
NH
OH
H
14f
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0.0075
0.0070
0.0065
0.0060
0.0055
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
-0.0005
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160
150
140
130
120
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100
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80
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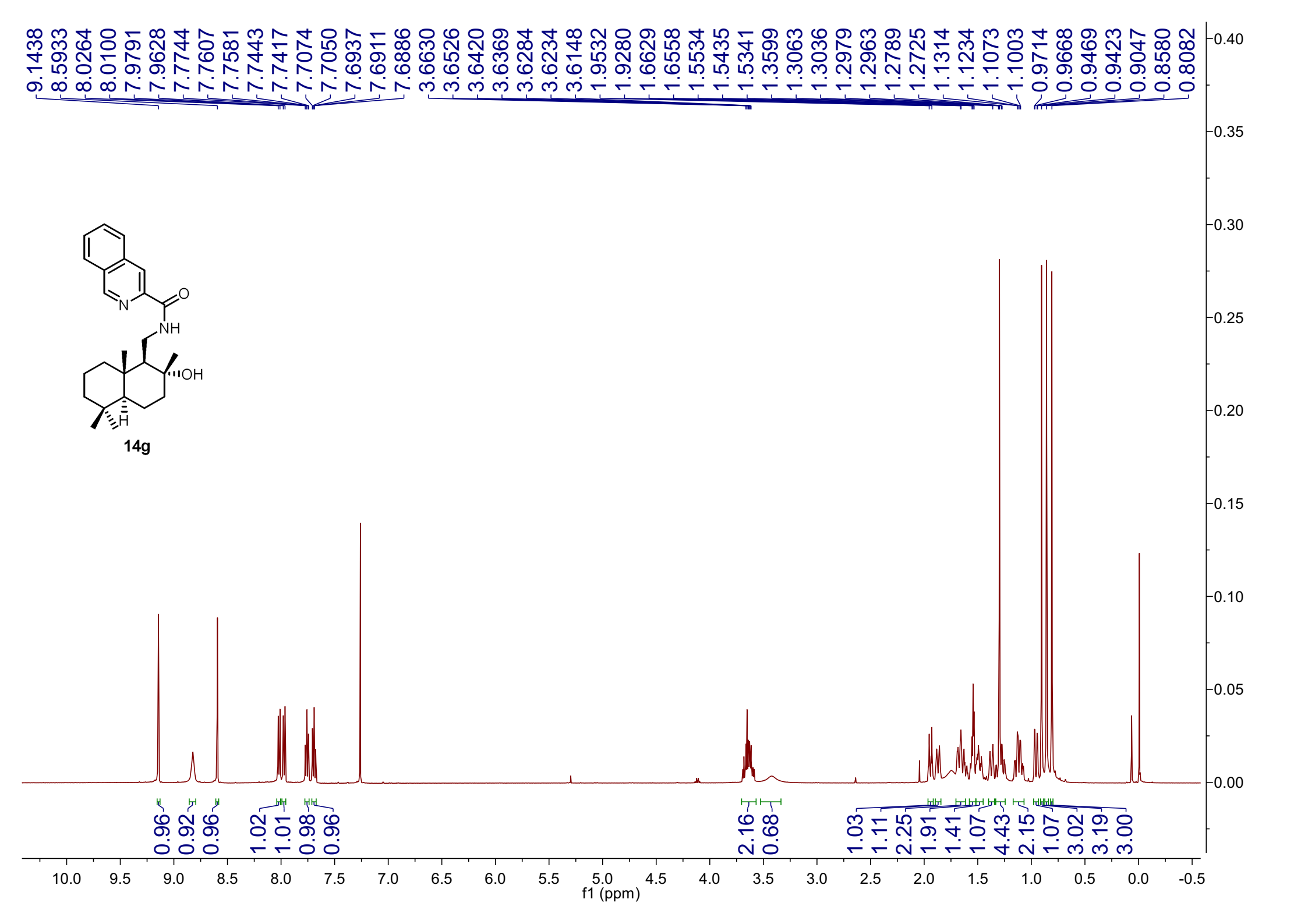
60
50
40
30
20
10
f1 (ppm)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7.7074
7.7050
7.6937
7.6911
7.6886
3.6630
3.6526
3.6420
3.6369
3.6284
3.6234
3.6148
1.9532
1.9280
1.6629
1.6558
1.5534
1.5435
1.5341
1.3599
1.3063
1.3036
1.2979
1.2963
1.2789
1.2725
1.1314
1.1234
1.1073
1.1003
0.9714
0.9668
0.9469
0.9423
0.9047
0.8580
0.8082
O
N
NH
OH
H
14g
0.96
0.92
0.96
1.02
1.01
0.98
0.96
2.16
0.68
1.03
1.11
2.25
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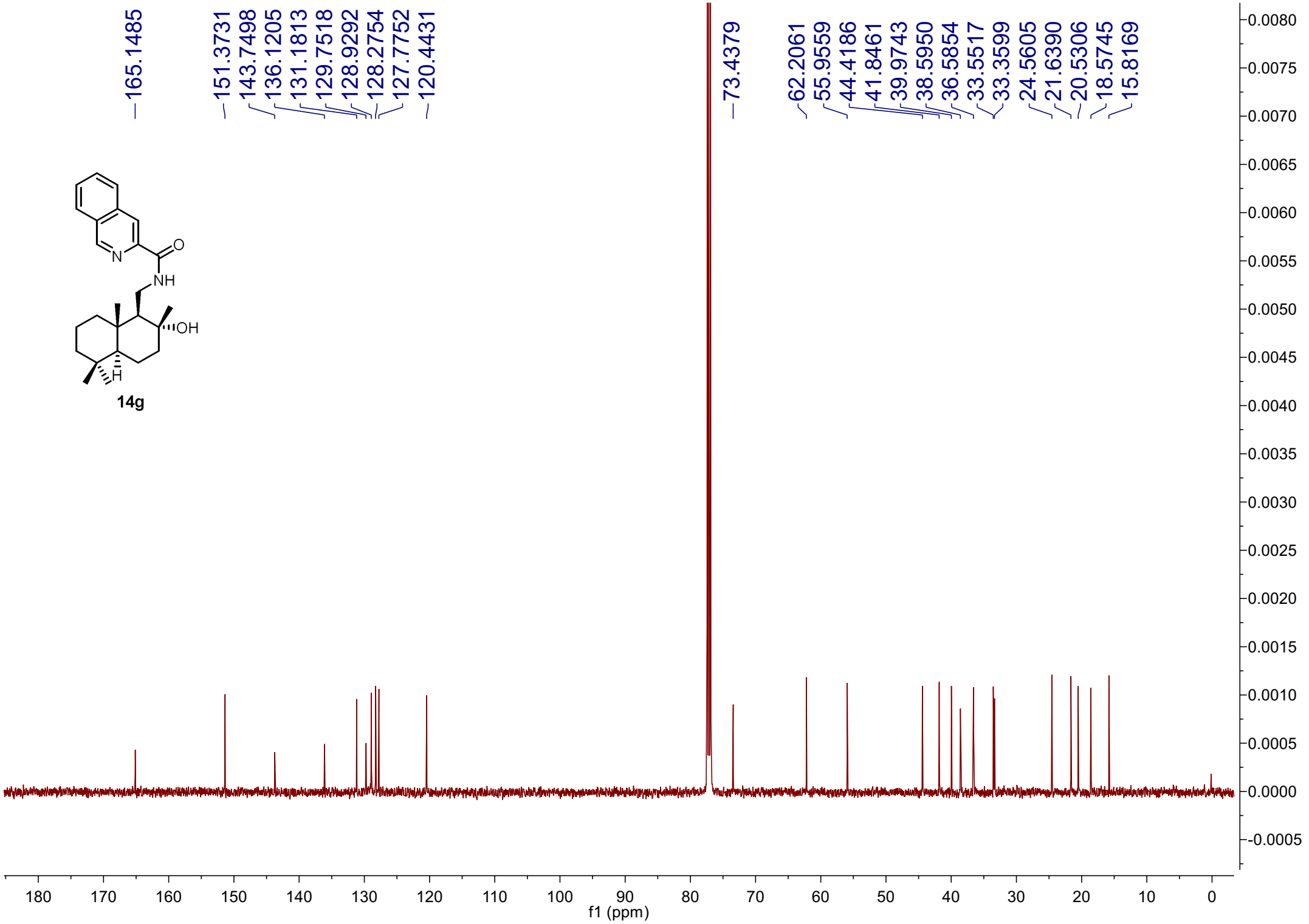
1.41
1.07
4.43
2.15
1.07
3.02
3.19
3.00
f1 (ppm)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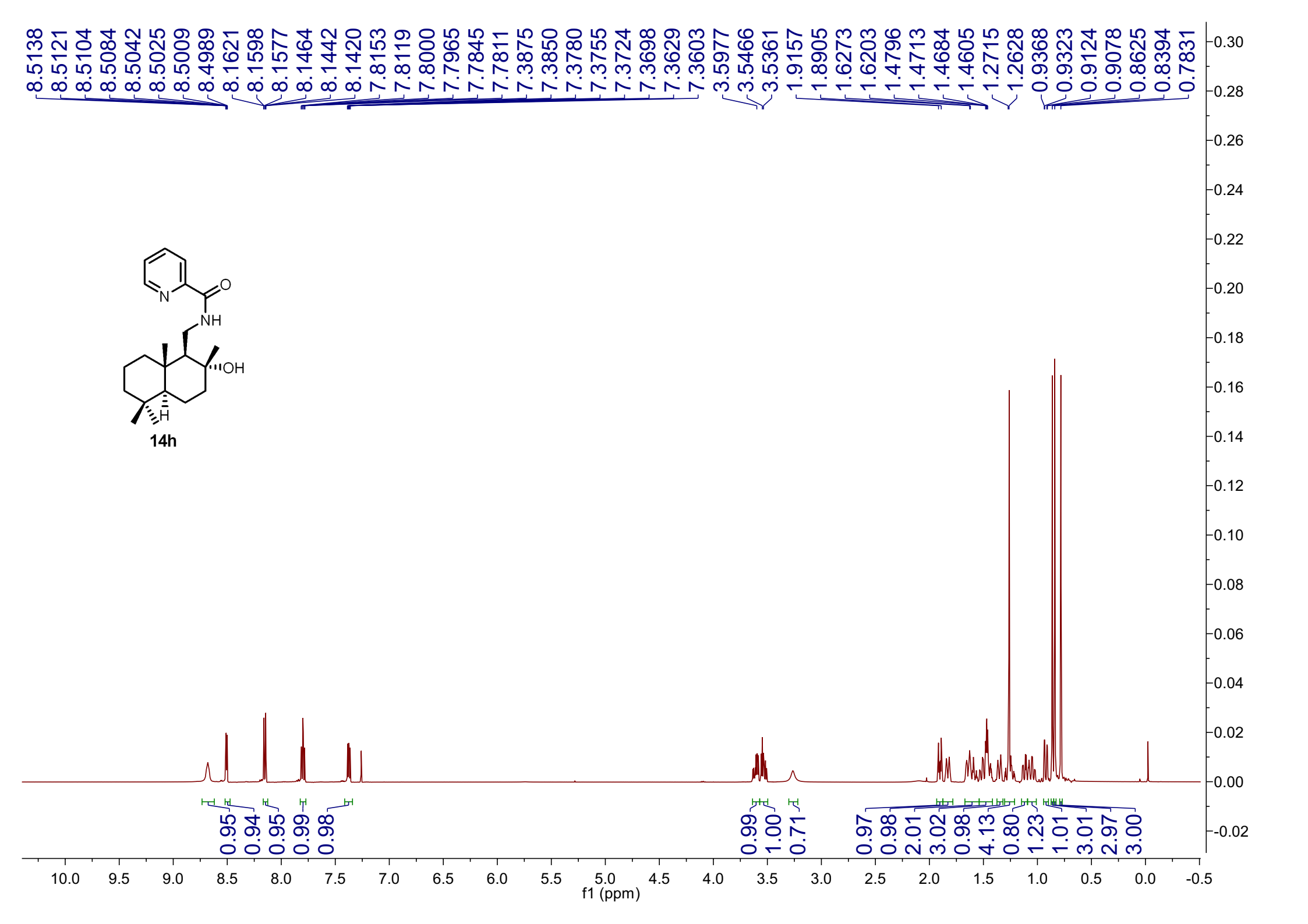
73.4379
62.2061
55.9559
44.4186
41.8461
39.9743
38.5950
36.5854
33.5517
33.3599
24.5605
21.6390
20.5306
18.5745
15.8169
O
N
NH
OH
H
14g
0.0080
0.0075
0.0070
0.0065
0.0060
0.0055
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
-0.0005
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.1464
8.1442
8.1420
7.8153
7.8119
7.8000
7.7965
7.7845
7.7811
7.3875
7.3850
7.3780
7.3755
7.3724
7.3698
7.3629
7.3603
3.5977
3.5466
3.5361
1.9157
1.8905
1.6273
1.6203
1.4796
1.4713
1.4684
1.4605
1.2715
1.2628
0.9368
0.9323
0.9124
0.9078
0.8625
0.8394
0.7831
N
O
NH
OH
H
14h
0.95
0.94
0.95
0.99
0.98
0.99
1.00
0.71
0.97
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3.01
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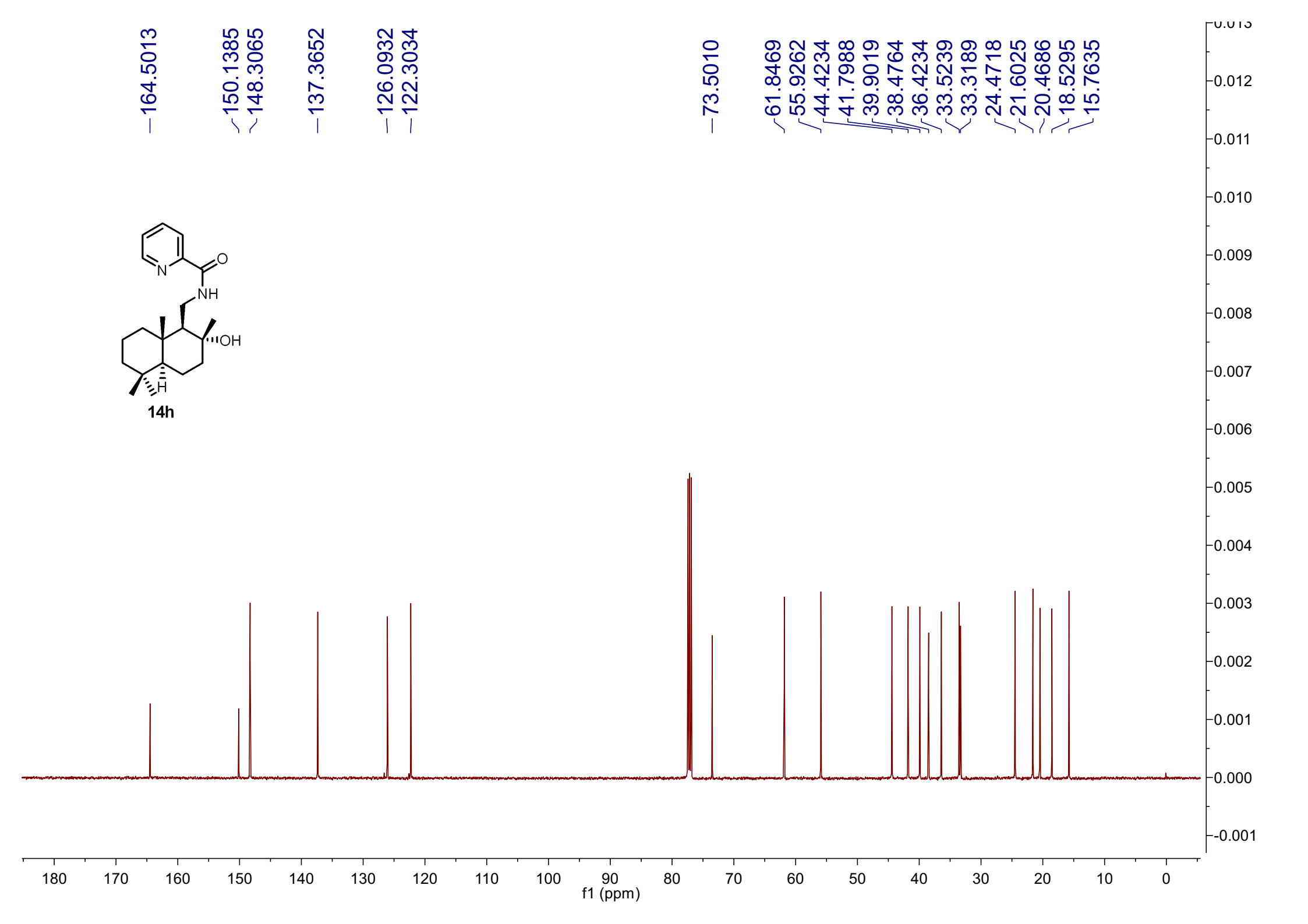
f1 (ppm)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39.9019
38.4764
36.4234
33.5239
33.3189
24.4718
21.6025
20.4686
18.5295
15.7635
N
O
NH
OH
H
14h
f1 (ppm)

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) hno-52

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: hno-52

```
Bond precision:  C-C = 0.0042 A          Wavelength=0.71073

Cell:             a=6.1445(5)      b=7.5145(6)      c=41.152(4)
                  alpha=90         beta=90          gamma=90
Temperature:      150 K
```

	Calculated	Reported
Volume	1900.1(3)	1900.1(3)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C21 H32 N2 O2	C21 H32 N2 O2
Sum formula	C21 H32 N2 O2	C21 H32 N2 O2
Mr	344.49	344.48
Dx,g cm-3	1.204	1.204
Z	4	4
Mu (mm-1)	0.077	0.077
F000	752.0	752.0
F000’	752.29	
h,k,lmax	8,10,56	8,9,56
Nref	5273[3077]	4140
Tmin,Tmax	0.989,0.992	0.883,1.000
Tmin’	0.989	

```
Correction method= # Reported T Limits: Tmin=0.883 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.35/0.79      Theta(max)= 29.410

R(reflections)= 0.0598( 3006)     wR2(reflections)= 0.1207( 4140)

S = 0.975                 Npar= 235
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

```
STRVA01_ALERT_4_C           Flack parameter is too small
           From the CIF: _refine_ls_abs_structure_Flack   -0.600
           From the CIF: _refine_ls_abs_structure_Flack_su    1.000
PLAT340_ALERT_3_C Low Bond Precision on  C-C Bonds ..............    0.00419 Ang.
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ......      2.514 Check
PLAT915_ALERT_3_C No Flack x Check Done: Low Friedel Pair Coverage        68 %
```

Alert level G

```
PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ..............          1 Report
PLAT032_ALERT_4_G Std. Uncertainty on Flack Parameter Value High .      1.000 Report
PLAT791_ALERT_4_G Model has Chirality at C5          (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C8          (Sohnke SpGr)          R Verify
PLAT791_ALERT_4_G Model has Chirality at C9          (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C10         (Sohnke SpGr)          S Verify
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min).          2 Note
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600        390 Note
PLAT916_ALERT_2_G Hooft y and Flack x Parameter Values Differ by .       0.10 Check
PLAT933_ALERT_2_G Number of OMIT Records in Embedded .res File ...          1 Note
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ...........        2.6 Low
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.          3 Info
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   4 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  12 ALERT level G = General information/check it is not something unexpected

   0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   3 ALERT type 2 Indicator that the structure model may be wrong or deficient
   5 ALERT type 3 Indicator that the structure quality may be low
   7 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

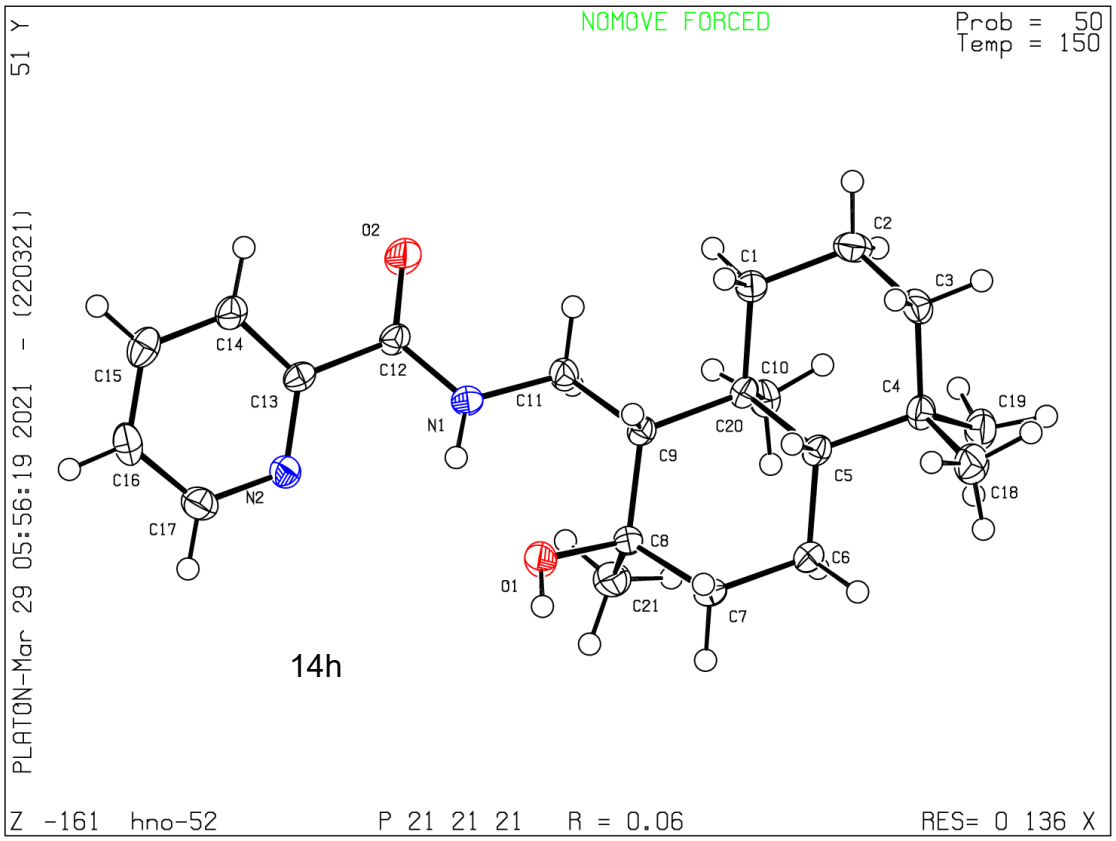
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica, Journal of Applied Crystallography, Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

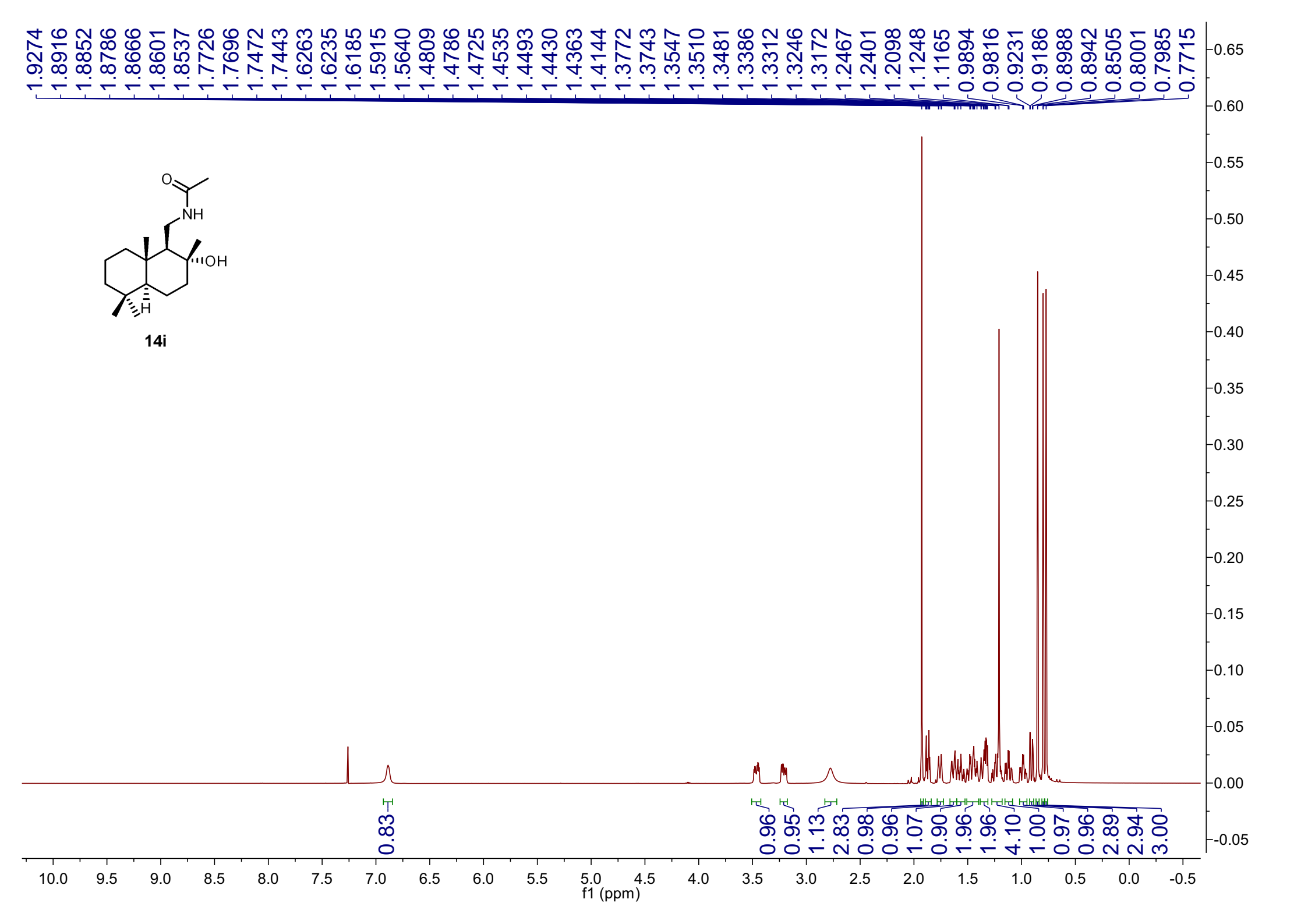
Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 22/03/2021; check.def file version of 19/03/2021

Datablock hno-52 - ellipsoid plot

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1.5915
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1.4809
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1.1248
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0.9231
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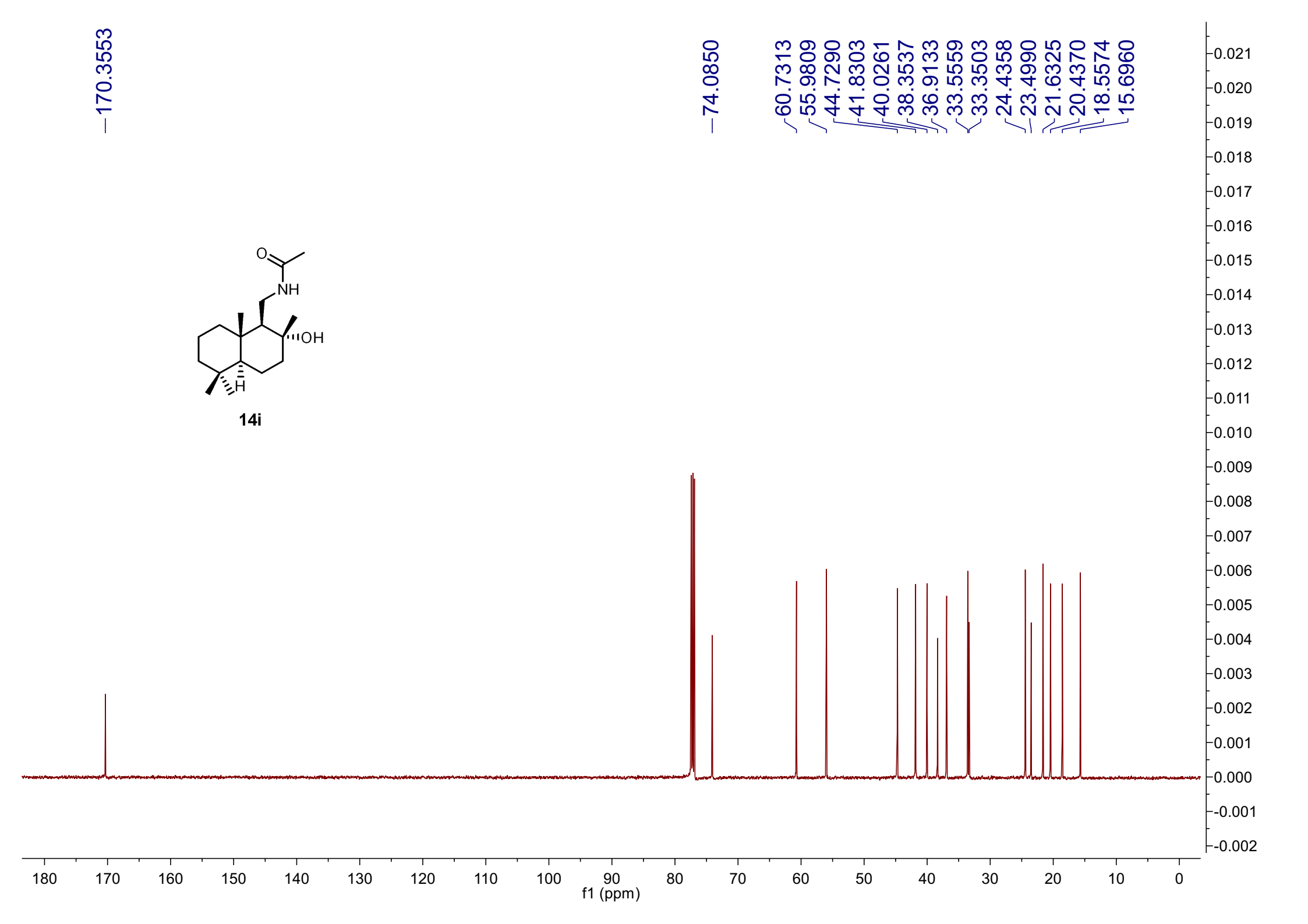
0.8988
0.8942
0.8505
0.8001
0.7985
0.7715
O
NH
OH
H
14i
0.83
0.96
0.95
1.13
2.83
0.98
0.96
1.07
0.90
1.96
1.96
4.10
1.00
0.97
0.96
2.89
2.94
3.00
f1 (ppm)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33.3503
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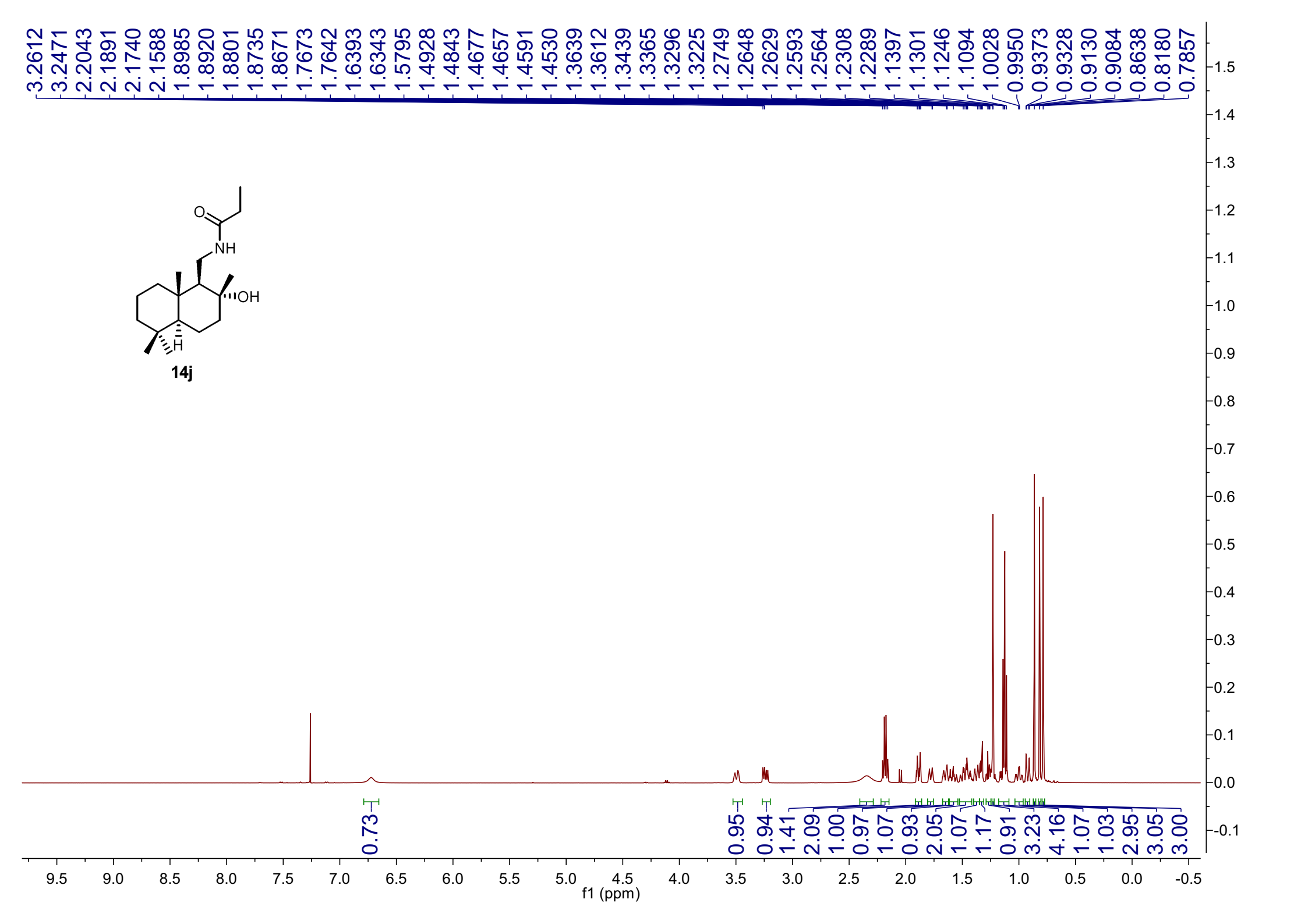
21.6325
20.4370
18.5574
15.6960
O
NH
OH
H
14i
f1 (ppm)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1.8735
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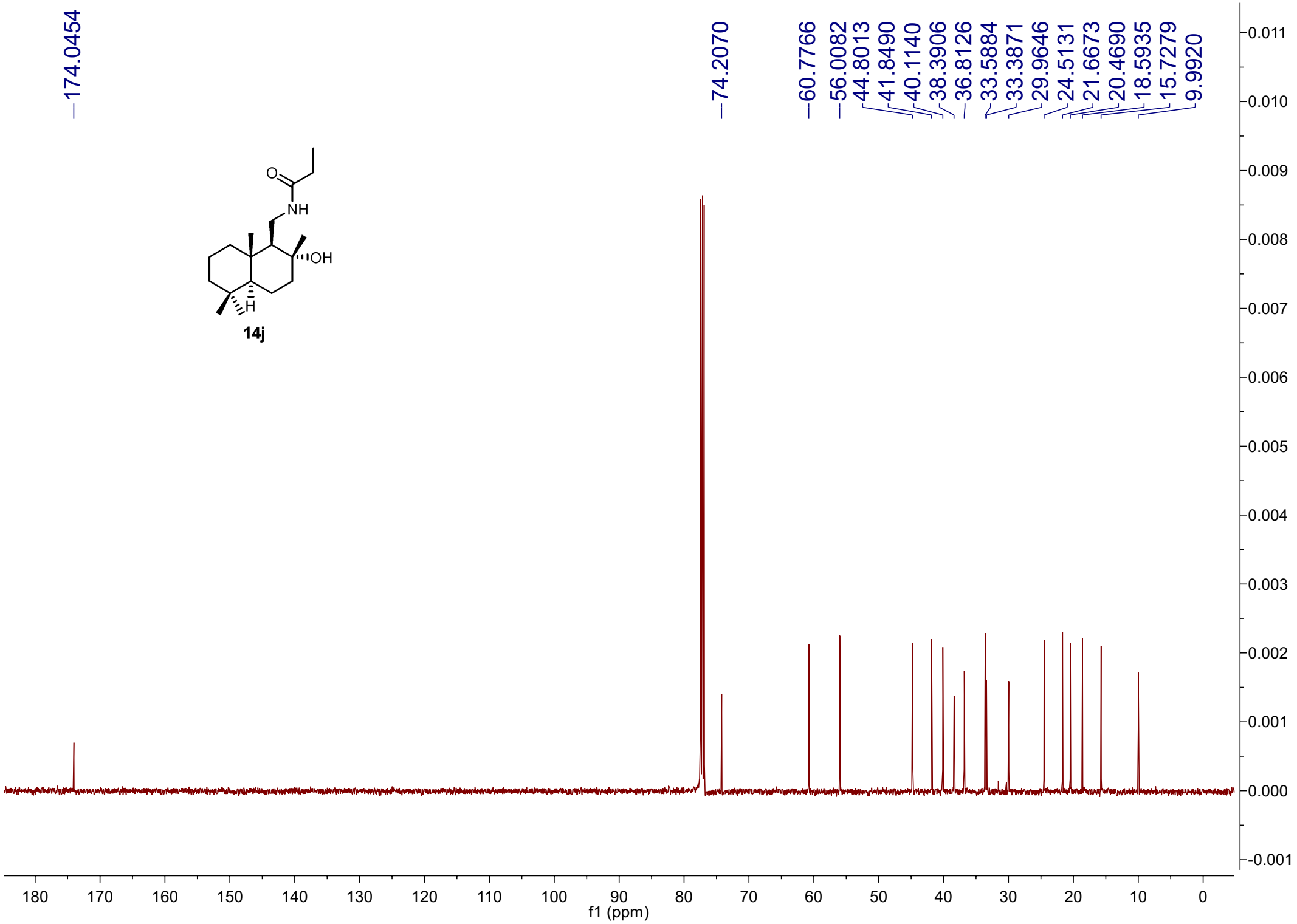
1.7673
1.7642
1.6393
1.6343
1.5795
1.4928
1.4843
1.4677
1.4657
1.4591
1.4530
1.3639
1.3612
1.3439
1.3365
1.3296
1.3225
1.2749
1.2648
1.2629
1.2593
1.2564
1.2308
1.2289
1.1397
1.1301
1.1246
1.1094
1.0028
0.9950
0.9373
0.9328
0.9130
0.9084
0.8638
0.8180
0.7857
O
NH
OH
H
14j
0.73
0.95
0.94
1.41
2.09
1.00
0.97
1.07
0.93
2.05
1.07
1.17
0.91
3.23
4.16
1.07
1.03
2.95
3.05
3.00
f1 (ppm)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29.9646
24.5131
21.6673
20.4690
18.5935
15.7279
9.9920
O
NH
OH
H
14j
0.011
0.010
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
-0.001
180
170
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130
120
110
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90
80
70
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50
40
30
20
10
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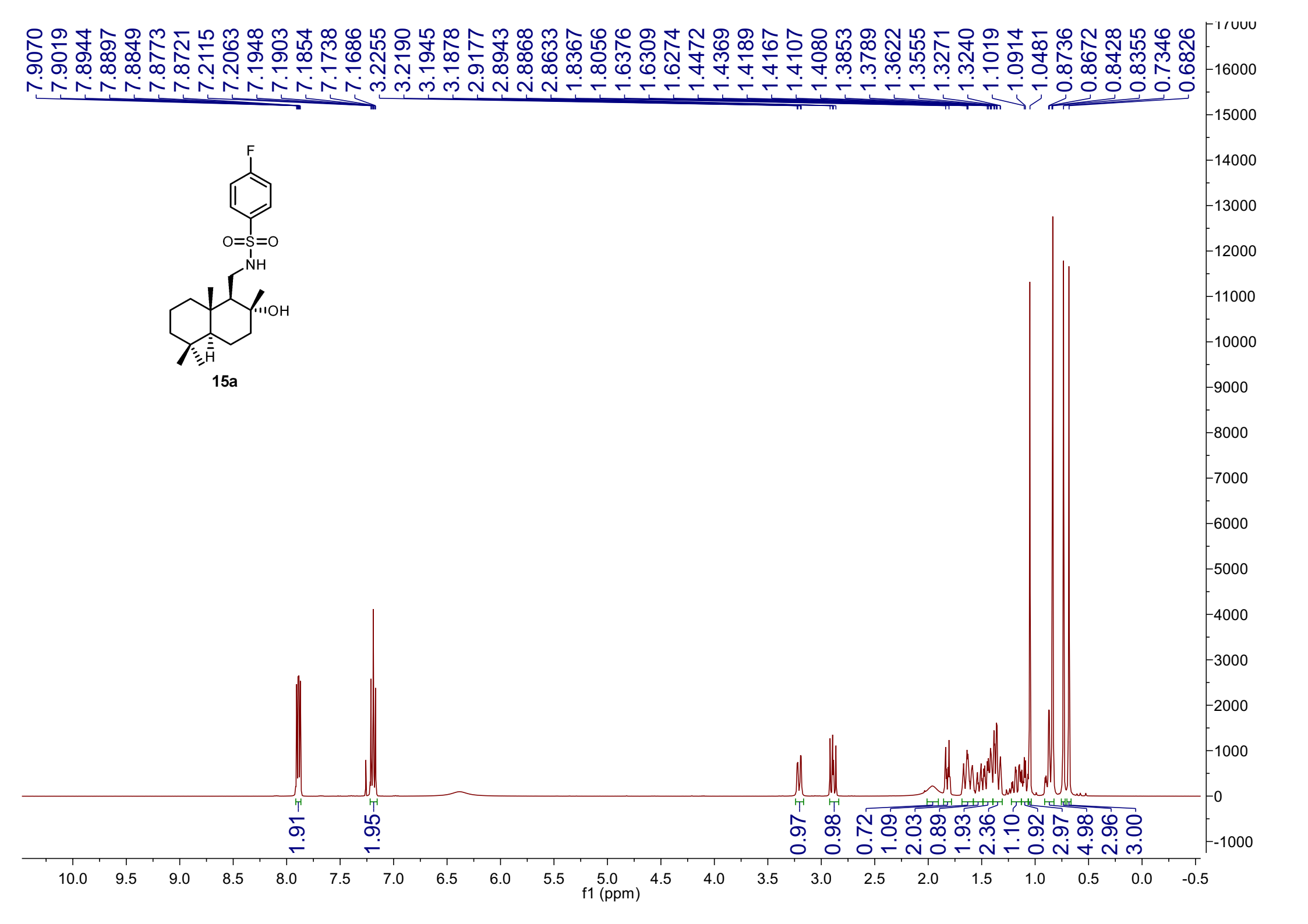
f1 (ppm)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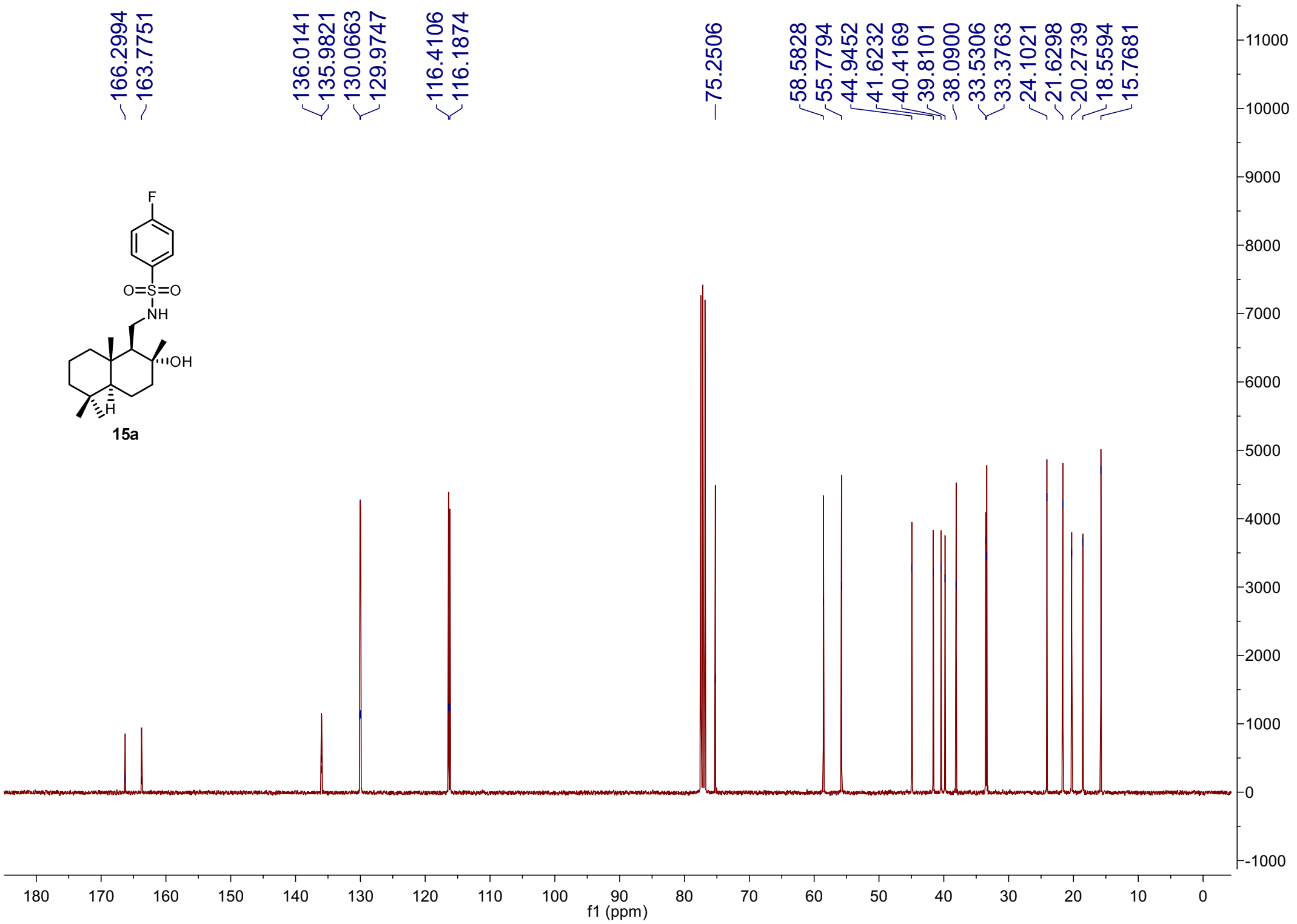
7.1903
7.1854
7.1738
7.1686
3.2255
3.2190
3.1945
3.1878
2.9177
2.8943
2.8868
2.8633
1.8367
1.8056
1.6376
1.6309
1.6274
1.4472
1.4369
1.4189
1.4167
1.4107
1.4080
1.3853
1.3789
1.3622
1.3555
1.3271
1.3240
1.1019
1.0914
1.0481
0.8736
0.8672
0.8428
0.8355
0.7346
0.6826
F
O=S=O
NH
OH
H
15a
1.91
1.95
0.97
0.98
0.72
1.09
2.03
0.89
1.93
2.36
1.10
0.92
2.97
4.98
2.96
3.00
f1 (ppm)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58.5828
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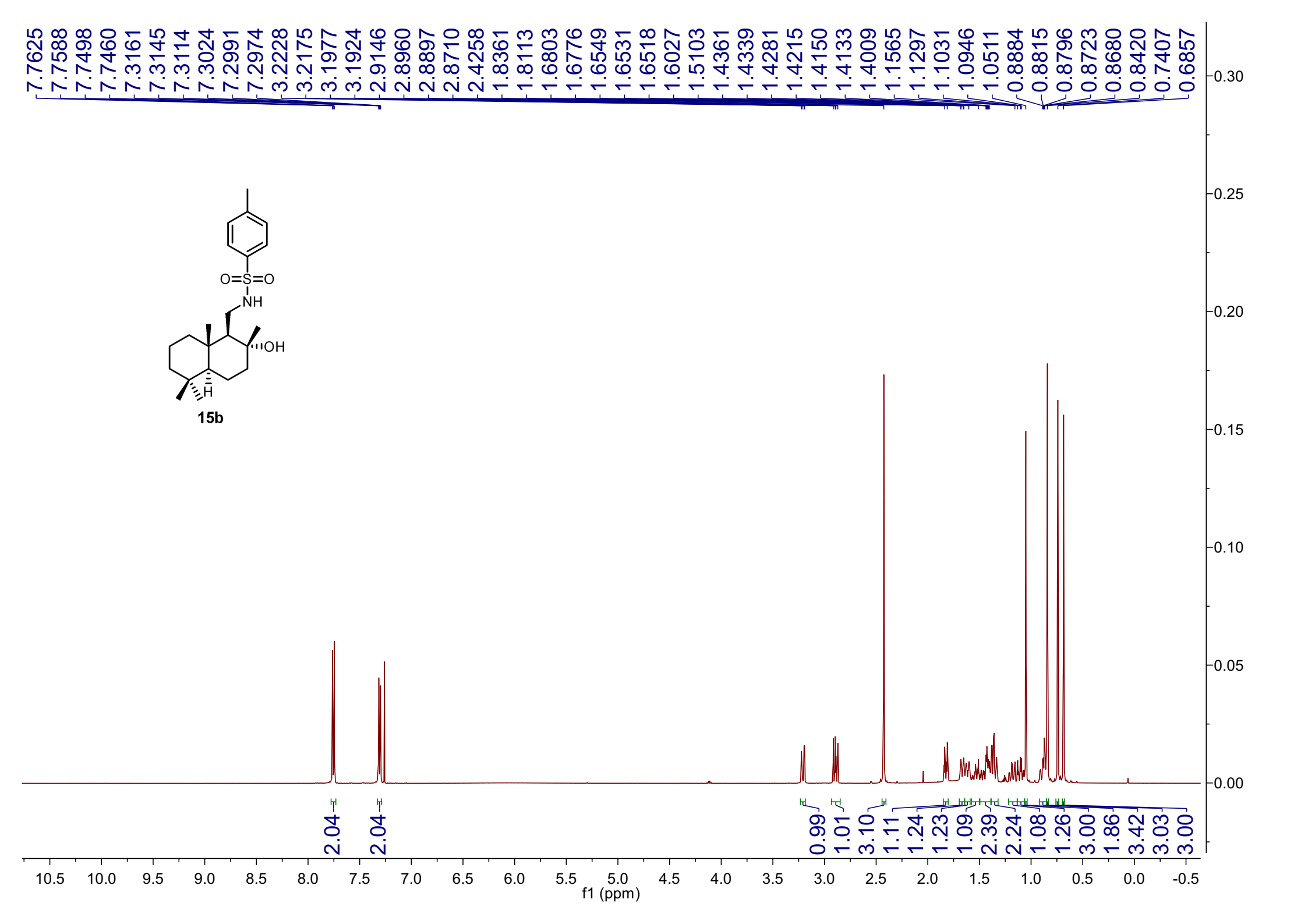
44.9452
41.6232
40.4169
39.8101
38.0900
33.5306
33.3763
24.1021
21.6298
20.2739
18.5594
15.7681
F
O=S=O
NH
OH
H
15a
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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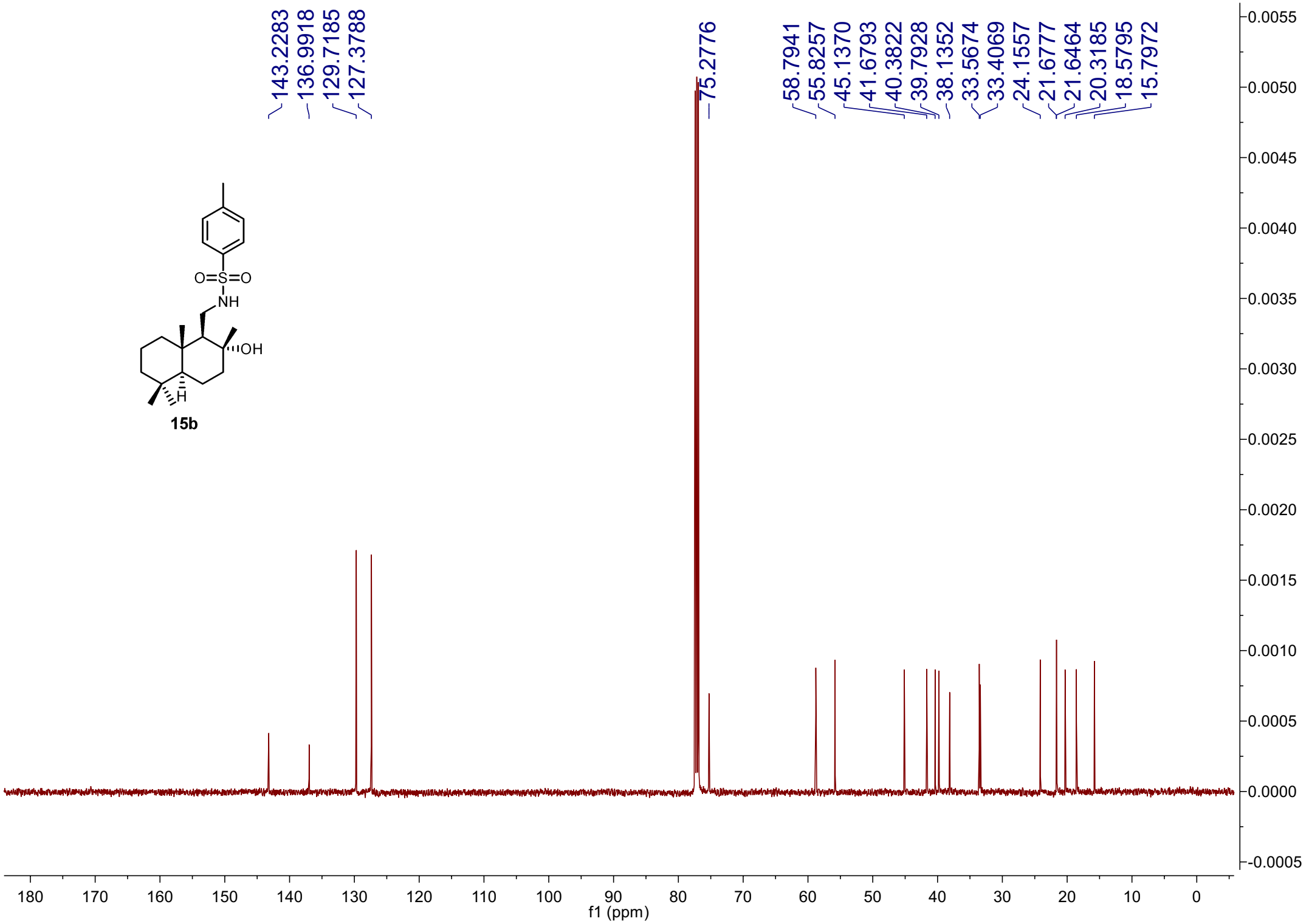
7.7588
7.7498
7.7460
7.3161
7.3145
7.3114
7.3024
7.2991
7.2974
3.2228
3.2175
3.1977
3.1924
2.9146
2.8960
2.8897
2.8710
2.4258
1.8361
1.8113
1.6803
1.6776
1.6549
1.6531
1.6518
1.6027
1.5103
1.4361
1.4339
1.4281
1.4215
1.4150
1.4133
1.4009
1.1565
1.1297
1.1031
1.0946
1.0511
0.8884
0.8815
0.8796
0.8723
0.8680
0.8420
0.7407
0.6857
O=S=O
NH
OH
H
15b
2.04
2.04
0.99
1.01
3.10
1.11
1.24
1.23
1.09
2.39
2.24
1.08
1.26
3.00
1.86
3.42
3.03
3.00
f1 (ppm)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75.2776
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55.8257
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41.6793
40.3822
39.7928
38.1352
33.5674
33.4069
24.1557
21.6777
21.6464
20.3185
18.5795
15.7972
O=S=O
NH
OH
H
15b
0.0055
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
-0.0005
180
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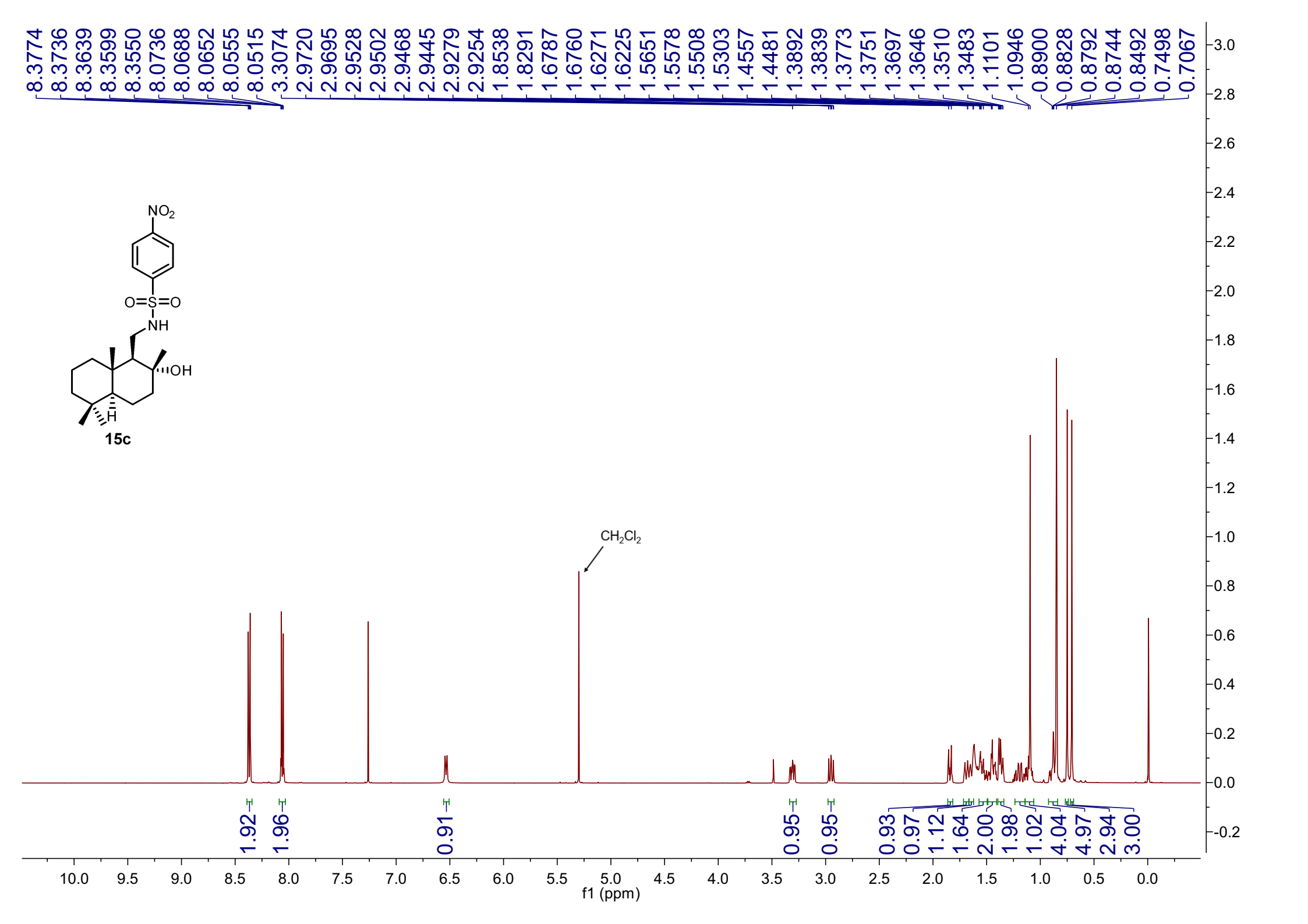
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.3639
8.3599
8.3550
8.0736
8.0688
8.0652
8.0555
8.0515
3.3074
2.9720
2.9695
2.9528
2.9502
2.9468
2.9445
2.9279
2.9254
1.8538
1.8291
1.6787
1.6760
1.6271
1.6225
1.5651
1.5578
1.5508
1.5303
1.4557
1.4481
1.3892
1.3839
1.3773
1.3751
1.3697
1.3646
1.3510
1.3483
1.1101
1.0946
0.8900
0.8828
0.8792
0.8744
0.8492
0.7498
0.7067
NO2
O=S=O
NH
OH
H
15c
CH2Cl2
1.92
1.96
0.91
0.95
0.95
0.93
0.97
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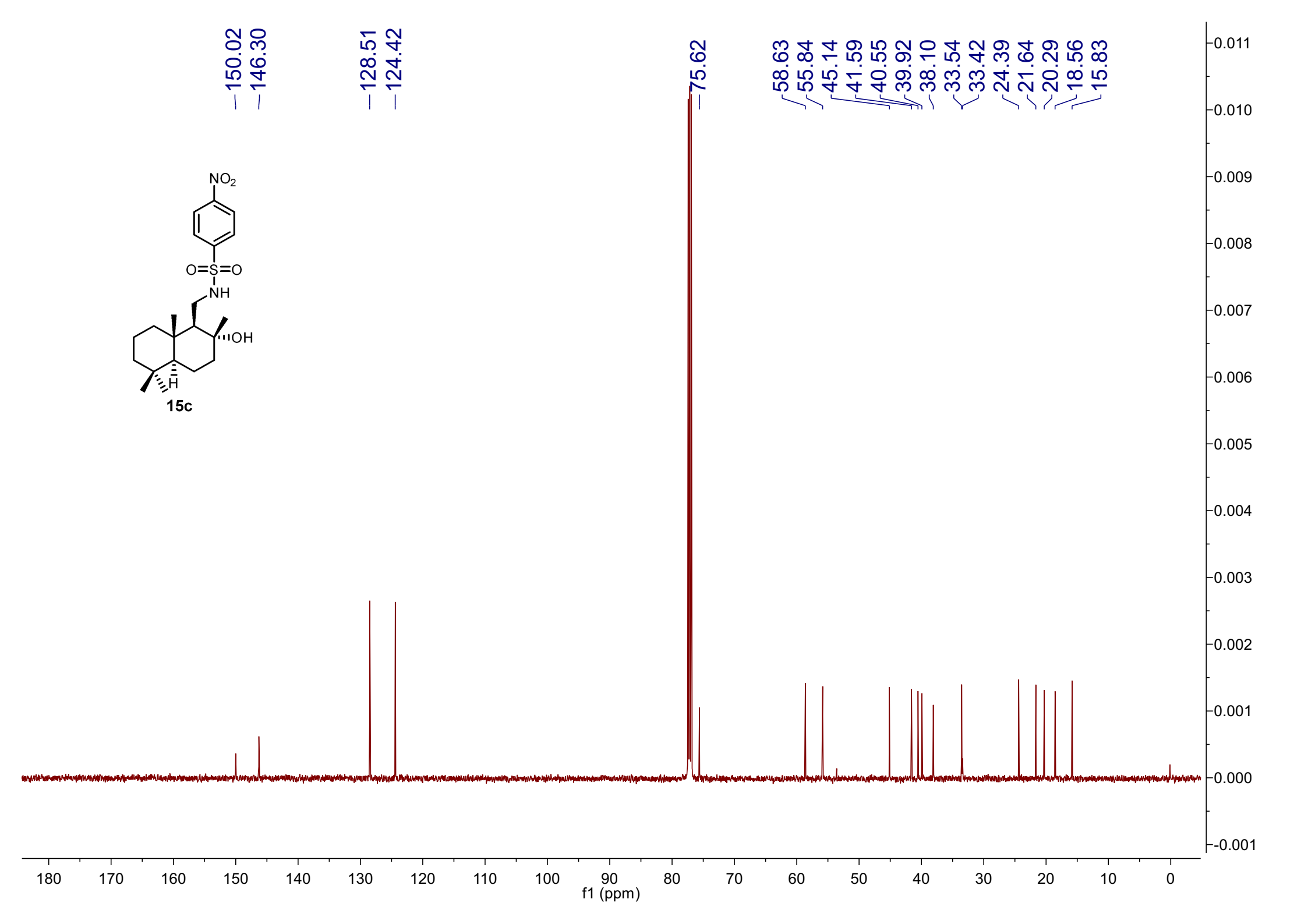
1.64
2.00
1.98
1.02
4.04
4.97
2.94
3.00
f1 (ppm)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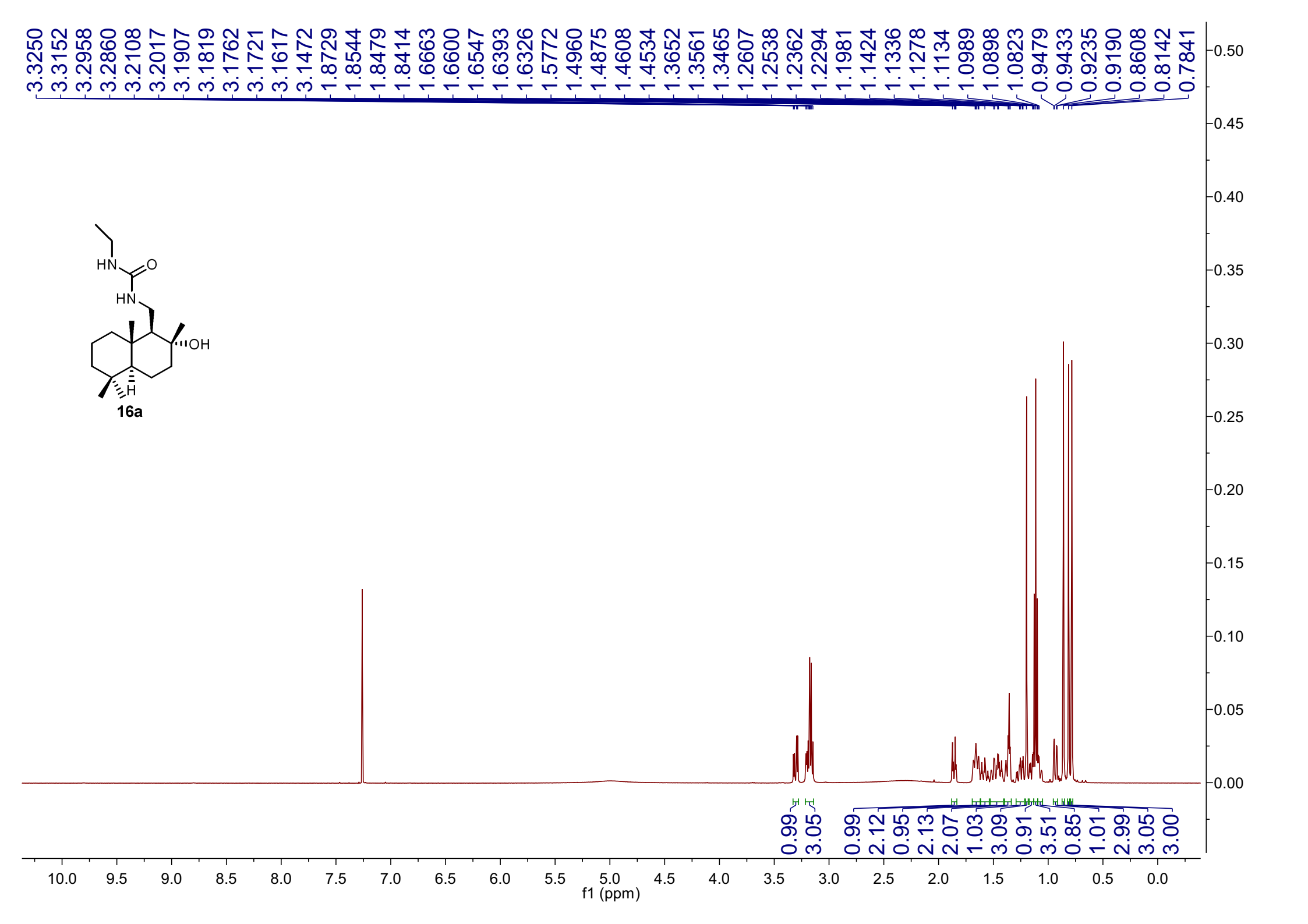
128.51
124.42
75.62
58.63
55.84
45.14
41.59
40.55
39.92
38.10
33.54
33.42
24.39
21.64
20.29
18.56
15.83
NO2
O=S=O
NH
OH
H
15c
f1 (ppm)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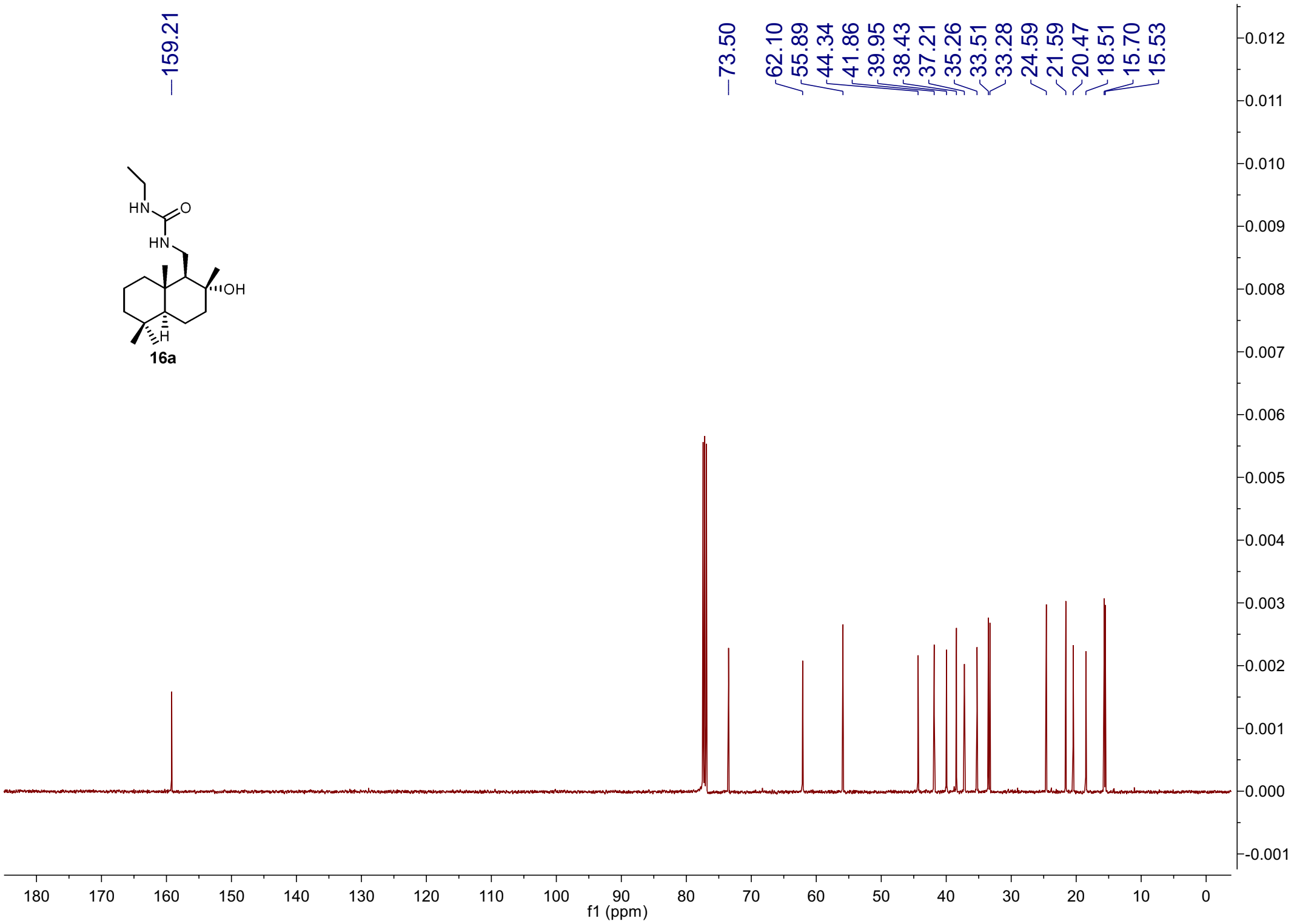
3.2108
3.2017
3.1907
3.1819
3.1762
3.1721
3.1617
3.1472
1.8729
1.8544
1.8479
1.8414
1.6663
1.6600
1.6547
1.6393
1.6326
1.5772
1.4960
1.4875
1.4608
1.4534
1.3652
1.3561
1.3465
1.2607
1.2538
1.2362
1.2294
1.1981
1.1424
1.1336
1.1278
1.1134
1.0989
1.0898
1.0823
0.9479
0.9433
0.9235
0.9190
0.8608
0.8142
0.7841
HN
O
HN
OH
H
16a
0.99
3.05
0.99
2.12
0.95
2.13
2.07
1.03
3.09
0.91
3.51
0.85
1.01
2.99
3.05
3.00
f1 (ppm)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38.43
37.21
35.26
33.51
33.28
24.59
21.59
20.47
18.51
15.70
15.53
HN
O
HN
OH
H
16a
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0.011
0.010
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
-0.001
180
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130
120
110
100
90
80
70
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50
40
30
20
10
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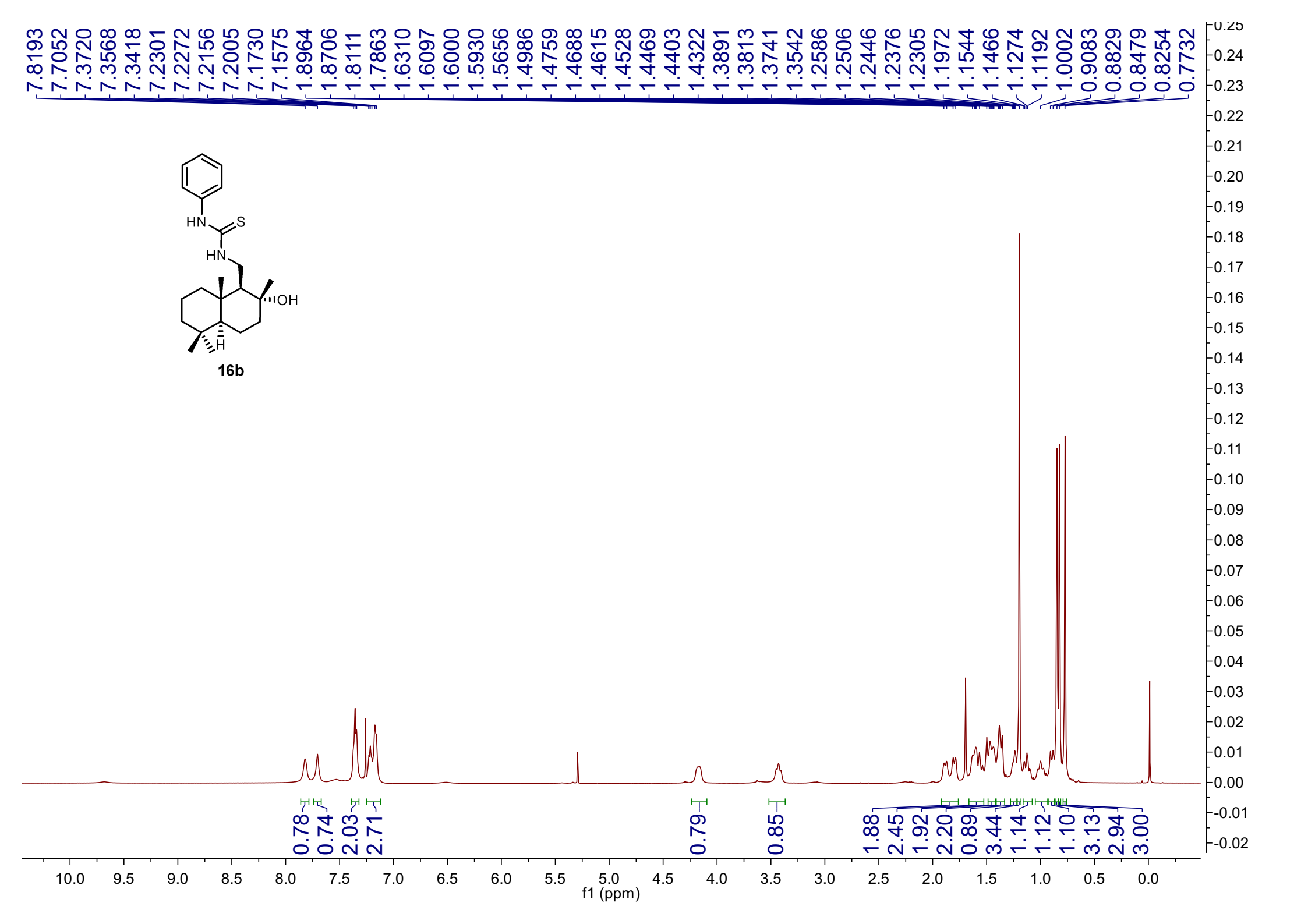
f1 (ppm)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7.1730
7.1575
1.8964
1.8706
1.8111
1.7863
1.6310
1.6097
1.6000
1.5930
1.5656
1.4986
1.4759
1.4688
1.4615
1.4528
1.4469
1.4403
1.4322
1.3891
1.3813
1.3741
1.3542
1.2586
1.2506
1.2446
1.2376
1.2305
1.1972
1.1544
1.1466
1.1274
1.1192
1.0002
0.9083
0.8829
0.8479
0.8254
0.7732
HN
S
HN
OH
H
16b
0.78
0.74
2.03
2.71
0.79
0.85
1.88
2.45
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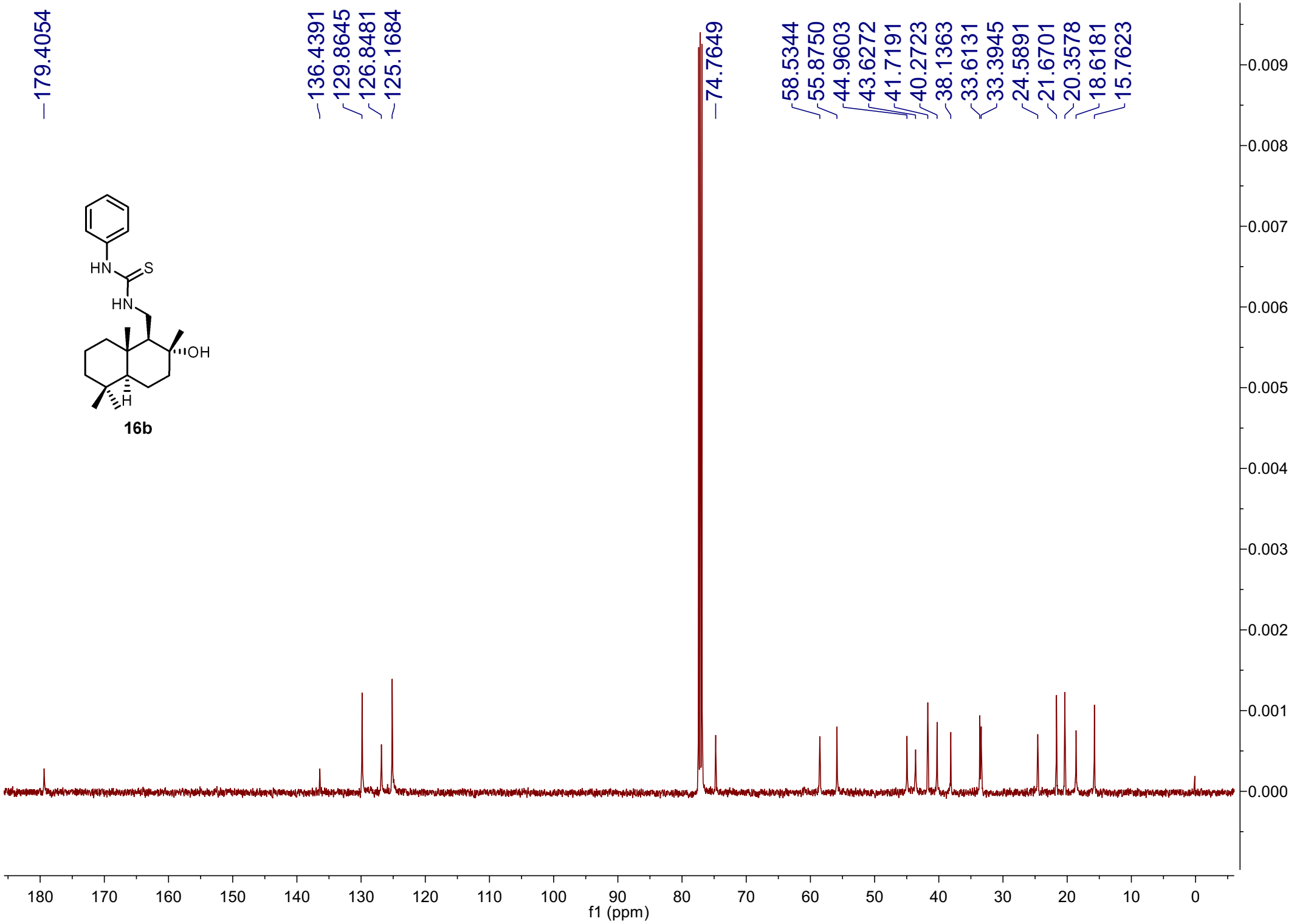
0.89
3.44
1.14
1.12
1.10
3.13
2.94
3.00
f1 (ppm)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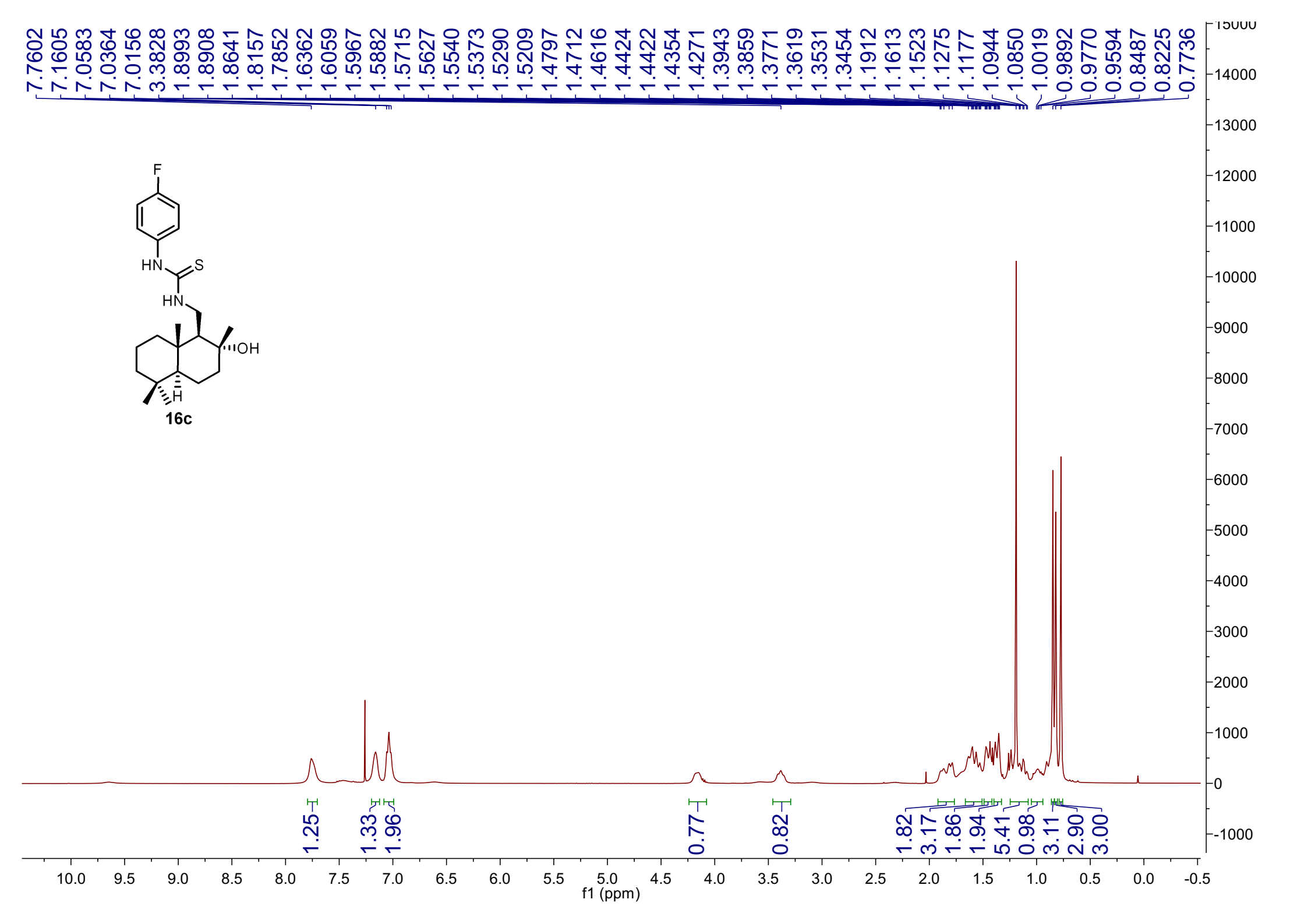
41.7191
40.2723
38.1363
33.6131
33.3945
24.5891
21.6701
20.3578
18.6181
15.7623
HN
S
HN
OH
H
16b
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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1.7852
1.6362
1.6059
1.5967
1.5882
1.5715
1.5627
1.5540
1.5373
1.5290
1.5209
1.4797
1.4712
1.4616
1.4424
1.4422
1.4354
1.4271
1.3943
1.3859
1.3771
1.3619
1.3531
1.3454
1.1912
1.1613
1.1523
1.1275
1.1177
1.0944
1.0850
1.0019
0.9892
0.9770
0.9594
0.8487
0.8225
0.7736
F
HN
S
HN
OH
H
16c
1.25
1.33
1.96
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3.17
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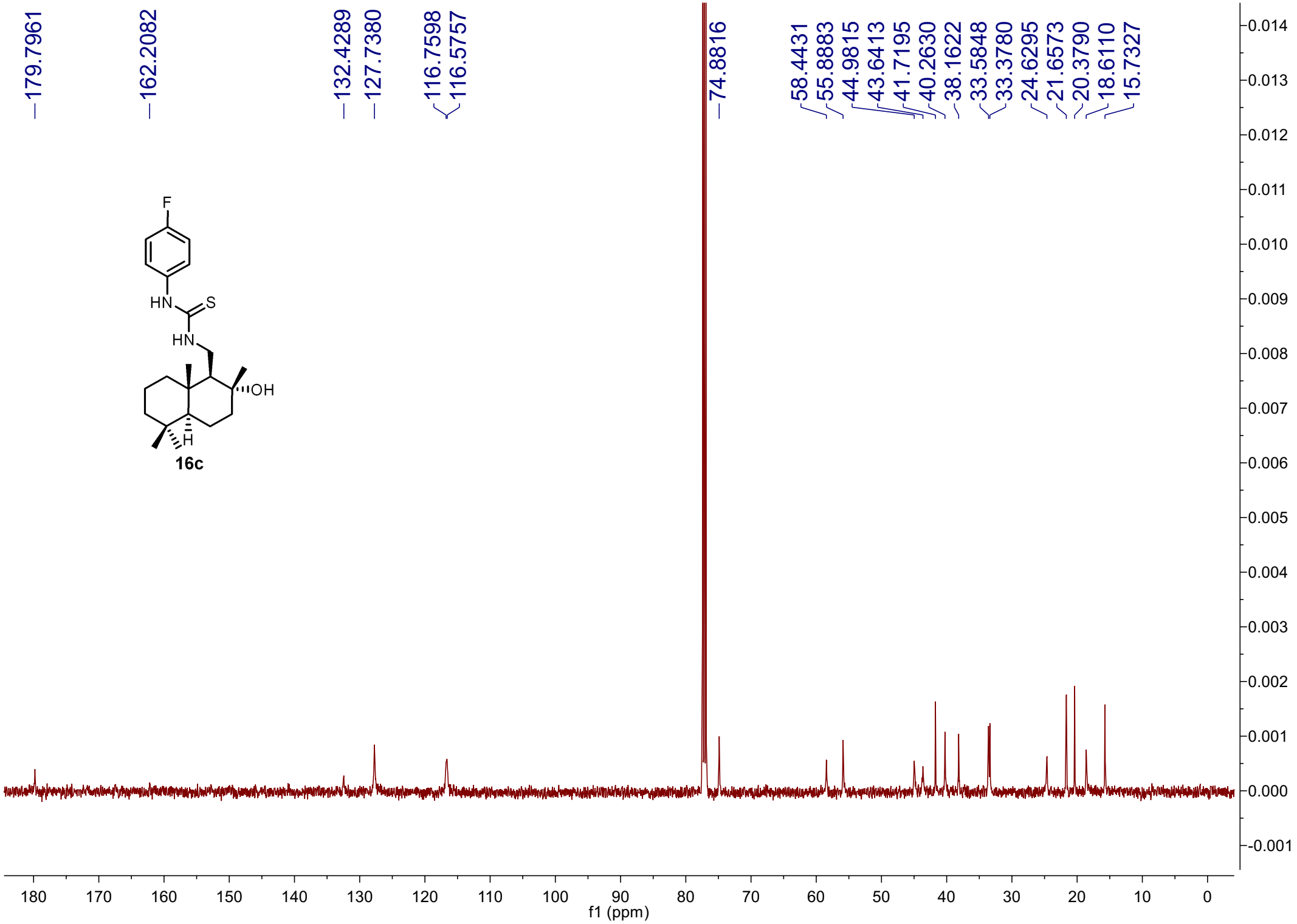
3.11
2.90
3.00
f1 (ppm)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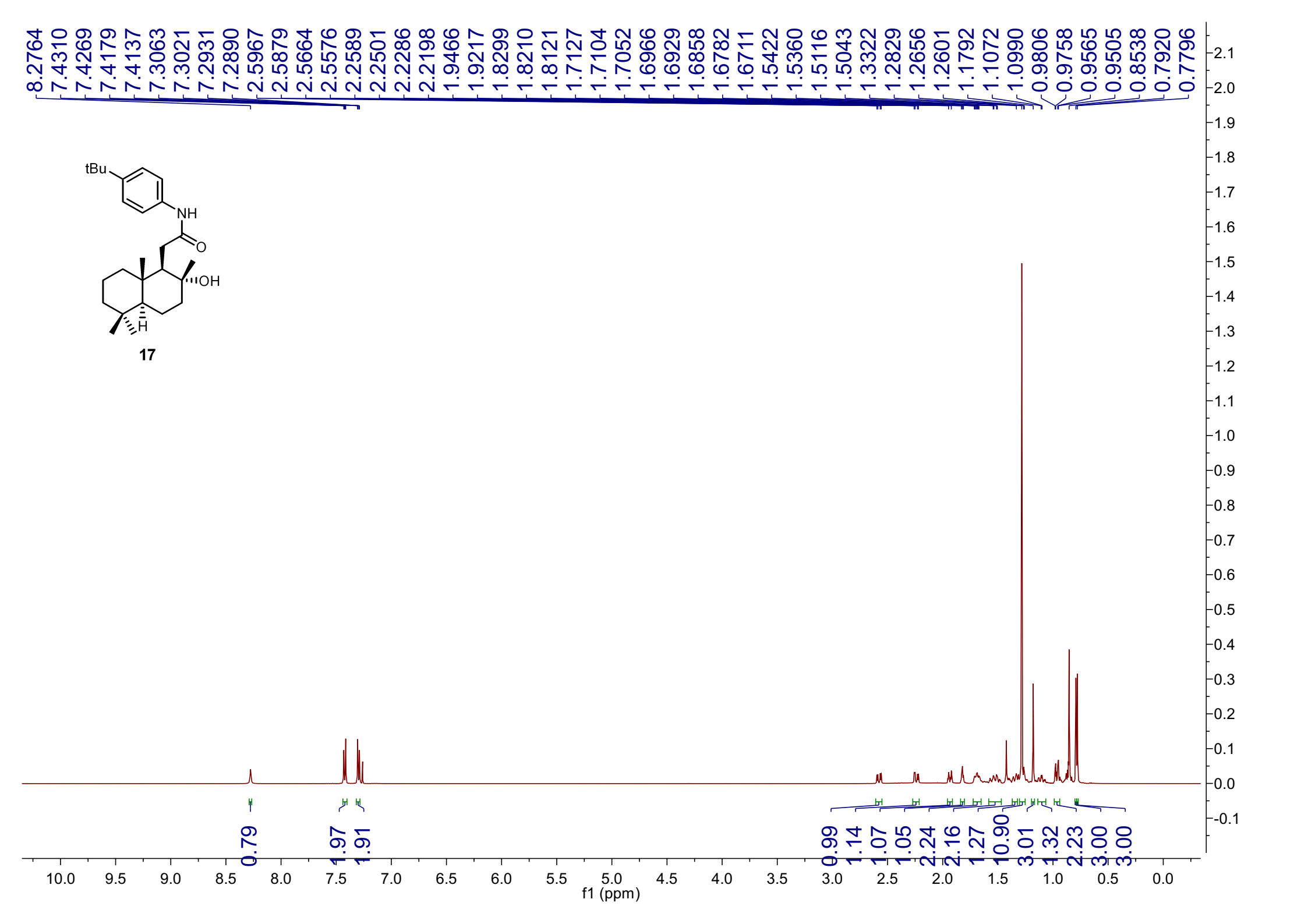
55.8883
44.9815
43.6413
41.7195
40.2630
38.1622
33.5848
33.3780
24.6295
21.6573
20.3790
18.6110
15.7327
F
HN
S
HN
OH
H
16c
0.014
0.013
0.012
0.011
0.010
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
-0.001
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.3021
7.2931
7.2890
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2.5879
2.5664
2.5576
2.2589
2.2501
2.2286
2.2198
1.9466
1.9217
1.8299
1.8210
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1.7127
1.7104
1.7052
1.6966
1.6929
1.6858
1.6782
1.6711
1.5422
1.5360
1.5116
1.5043
1.3322
1.2829
1.2656
1.2601
1.1792
1.1072
1.0990
0.9806
0.9758
0.9565
0.9505
0.8538
0.7920
0.7796
tBu
NH
O
OH
H
17
0.79
1.97
1.91
0.99
1.14
1.07
1.05
2.24
2.16
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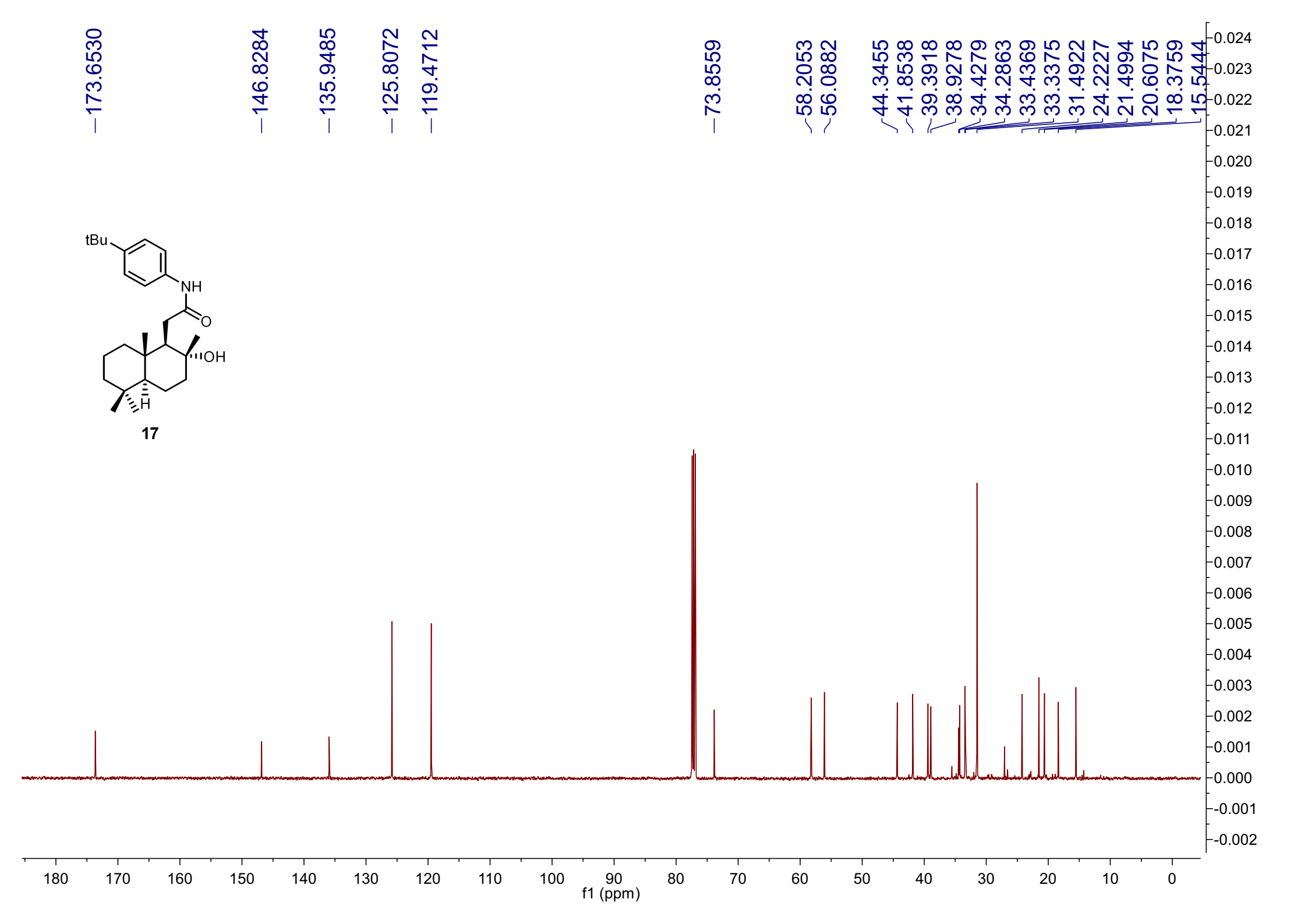
10.90
3.01
1.32
2.23
3.00
3.00
f1 (ppm)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39.3918
38.9278
34.4279
34.2863
33.4369
33.3375
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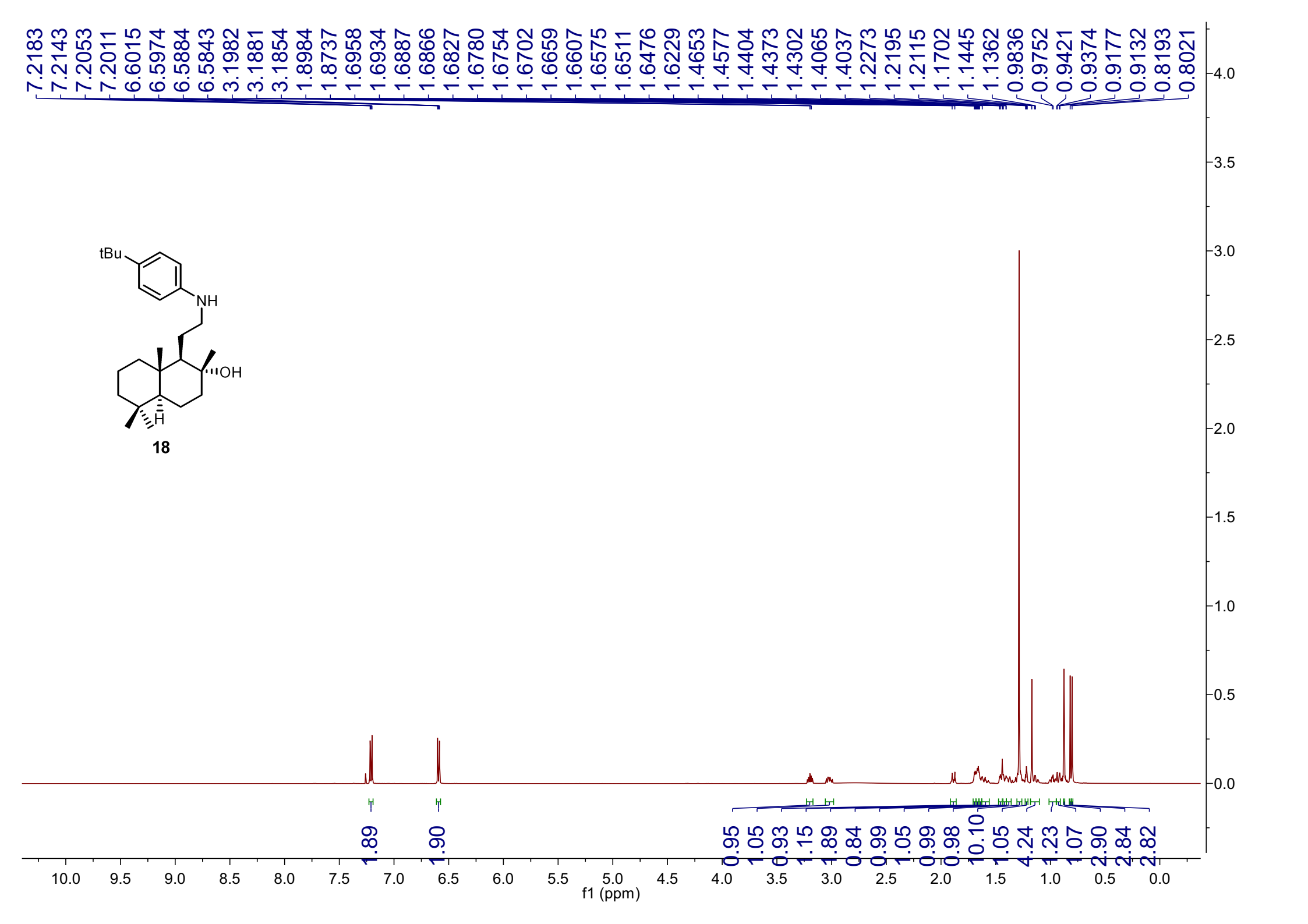
24.2227
21.4994
20.6075
18.3759
15.5444
tBu
NH
O
OH
H
17
f1 (ppm)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3.1854
1.8984
1.8737
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1.6934
1.6887
1.6866
1.6827
1.6780
1.6754
1.6702
1.6659
1.6607
1.6575
1.6511
1.6476
1.6229
1.4653
1.4577
1.4404
1.4373
1.4302
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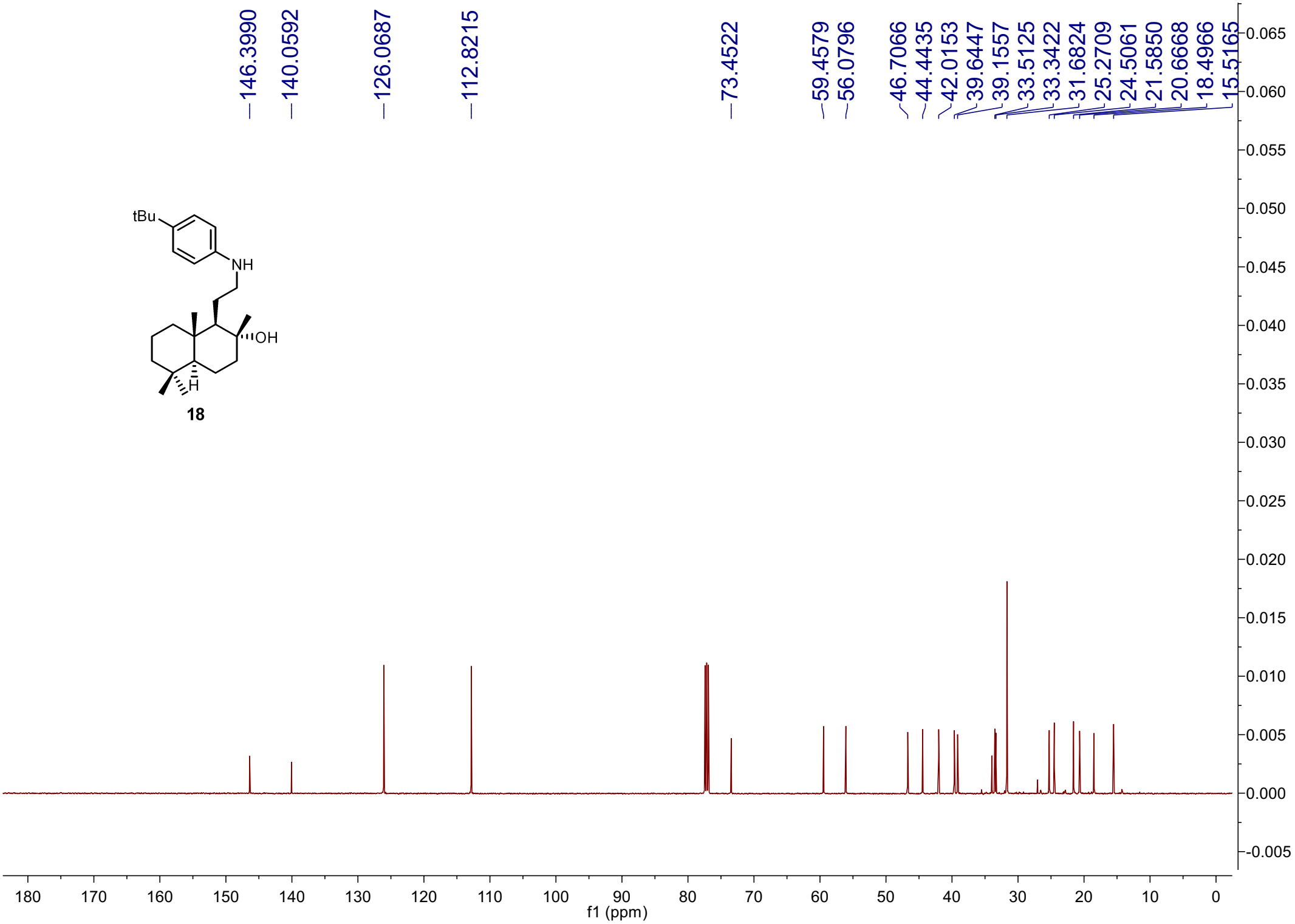
1.1702
1.1445
1.1362
0.9836
0.9752
0.9421
0.9374
0.9177
0.9132
0.8193
0.8021
tBu
NH
OH
H
18
1.89
1.90
0.95
1.05
0.93
1.15
1.89
0.84
0.99
1.05
0.99
0.98
10.10
1.05
4.24
1.23
1.07
2.90
2.84
2.82
f1 (ppm)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39.1557
33.5125
33.3422
31.6824
25.2709
24.5061
21.5850
20.6668
18.4966
15.5165
tBu
NH
OH
H
18
f1 (ppm)