ELECTRONIC SUPPLEMENTARY INFORMATION

A novel pathway for the thermolysis of *N*-nitrosoanthranilates using flash vacuum pyrolysis leading to 7-aminophthalides

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1. General methods and reagents

Commercially available reagents were used as received from commercial sources. Chromatography solvents (petroleum ether, 40-60 °C and EtOAc) were acquired from VWR. Thin-layer chromatography (TLC) was performed on Merck plates, layer thickness 0.2 mm with silica gel 60 and fluorescence indicator F_{254}. Visualization was accomplished with UV light (254 nm).

^{1}H NMR (300 MHz) and **^{13}C NMR** (75 MHz) spectra were recorded on a Bruker 300 MHz instrument. 2D experiments (HSQC and HMBC) were run on the same instrument with the built-in Bruker pulse sequences. All NMR spectra were measured at ambient temperature in $CDCl_3$. Chemical shifts (δ) are expressed in ppm downfield from TMS as an internal standard. The letters s, d, dd, t, q, and m are used to indicate singlet, doublet, doublet of doublets, triplet, quadruplet, and multiplet. ^{2}H spectra were recorded in $CHCl_3$ and were referenced internally to residual deutero-solvent resonances. Quantitative NMR was performed using 1,3,5-trimethoxybenzene as an internal standard.

GC-MS analysis was performed on a Shimadzu GCMS-QP2010 SE coupled with a DSQ II (EI, 70 eV). A fused silica capillary column Rtx-5MS column (5% diphenyl, 95% dimethylpolysiloxane, 30 m × 0.25 mm × 0.25 µm) was used. The injector temperature was set at 280 °C. After 1 min at 50 °C, the oven temperature was increased by 25 °C/min to 300 °C and kept at 300 °C for 3 min. As a carrier gas, helium at 40 cm s^{-1} linear velocity was used. MS conditions were: ionization voltage of 70 eV, acquisition mass range 50–450 *m*/*z*. AMDIS software was used for chromatogram deconvolution and mass spectral libraries (Wiley Registry of Mass Spectral Data 11th Edition, NIST/EPA/NIH Mass Spectral Library 14) were searched with NIST MS Search software.

GC-FID analysis was performed on a Shimadzu GCFID 2030 with a flame ionization detector, using an RTX -5MS column (30 m × 0.25 mm ID × 0.25 µm) and helium as carrier gas (40 cm/sec linear velocity). The injector temperature was set at 280 °C. Within the GC oven, after 1 min at 50 °C, the temperature was increased by 25 °C/min to 300 °C and kept constant at 300 °C for 4 min. The detector gases used for flame ionization were hydrogen and synthetic air (5.0 quality).

Automated flash column chromatography was performed on a Biotage Isolera system using Biotage SNAP 10 g, 25 g, or 50 g cartridges packed with KP-SIL, 60 Å silica (particle size distribution 32–63 µm).

ATR-FT-IR spectra were recorded on a Bruker Alpha-P instrument.

High resolution mass spectra of novel compounds were recorded on an Agilent 6230 TOF LC/MS instrument. An isocratic gradient of 50:50 H_2O:acetonitrile (with 0.1% 5 M ammonium formate). Ionization was achieved using ESI (Dual AJS ESI), with detection in positive mode. The ionization parameters were set as following: Gas temp. (N_2): 300 °C, drying gas: 5 L min^{-1}, nebulizer: 40 psig, fragmentor: 150 V, skimmer: 65 V, OCT 1 RF Vpp: 750 V, Vcap: 1600 V. The data acquisition window was set to 100-1.600 m/z with 1 spectra/s. The reference masses of 121.050873 and 922.009798 were continuously injected for lock mass calibration. Data was acquired with MassHunter Workstation Rev.B.05.01SP2.

Melting points were determined using a Stuart SMP3 melting point apparatus and are uncorrected.

Microwave irradiation experiments were carried out in an Anton Paar Monowave 400 single-mode microwave reactor using 10 mL Pyrex vials. The reaction temperature was controlled by an external infrared sensor. Reaction times refer to hold times at the temperature indicated. The stirring speed was set to 600 rpm.

Differential scanning calorimetry data were obtained on a Netzsch DSC 204 F1 instrument with the Netzsch Proteus software. The DSC plot was recorded between 20 and 250 °C, with a heating rate of 10 °C/min, using aluminum crucibles.

> ***Caution!*** Most nitrosamines are carcinogens, mutagens, and teratogens and extreme care must be taken during the preparation and handling of these compounds.

2. Flash vacuum pyrolysis set-up

Flash vacuum pyrolysis reactions were performed using the ThalesNano Flash Pyrolysis Platform (Version 1.0). A quartz tube of 60 cm in length and with a 3.5 cm inner diameter was used. The product was collected in a U-tube immersed in acetone/liquid nitrogen (CT1). All joints were lubricated with glisseal HV laboratory grease. The vacuum pump was operated with the ballast valve open.

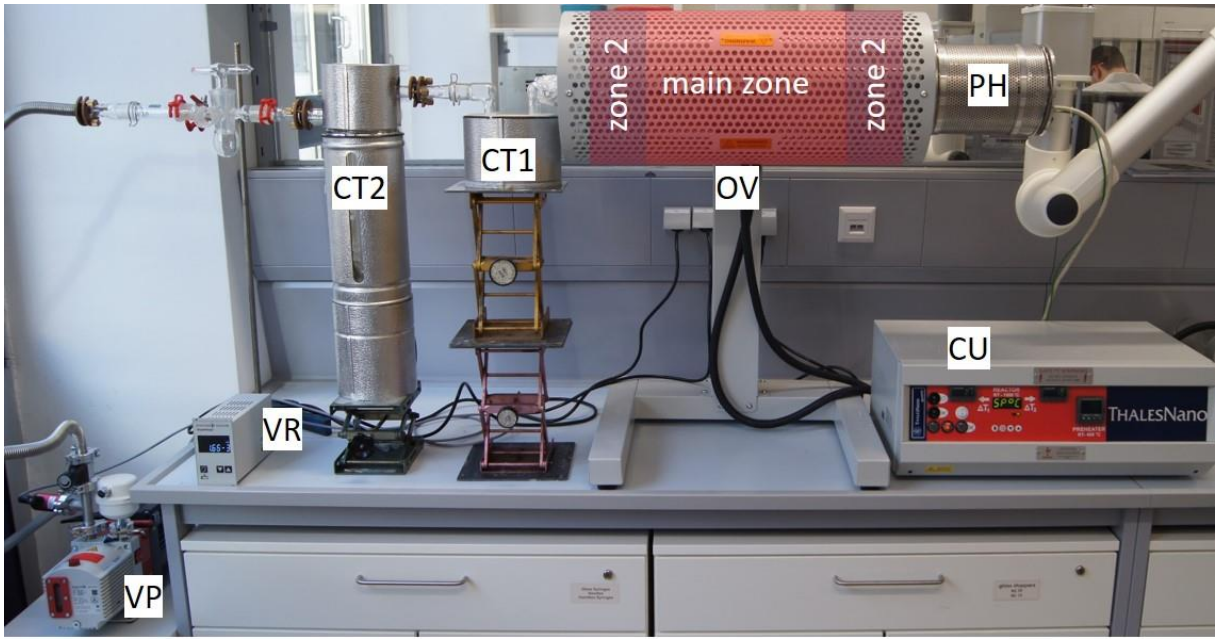


Figure S1. FVP set-up: VP: vacuum pump; VR: vacuum read-out; CT2: cooling trap (liquid N_2); CT1: cooling trap for product collection (U-shaped tube inserted in liquid N_2/acetone); OV: oven; PH: preheater, CU: oven control unit.

Control unit (CU): The preheater temperature can be set from rt−400 °C. The oven temperature can be set from rt−1000 °C. All heating zones can be set separately. The lowest operating pressure is 10^{-3} mbar.

Vacuum Pump (VP): DUO 6 rotary vane pump from Pfeiffer Vacuum. Ultimate pressure: 3 x 10^{-3} mbar. Pumping speed at 50 Hz: 5 m^3/h.

3. GC thermolysis of methyl *N*-methyl-*N*-nitrosoanthranilate (1a)

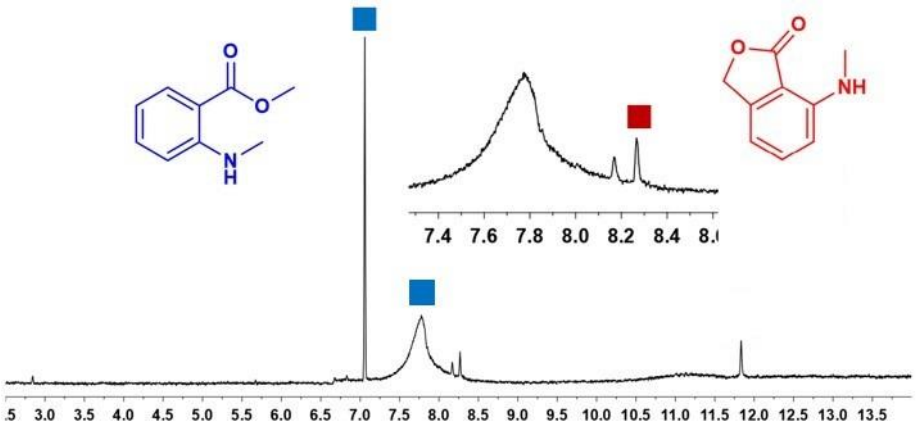


Figure S2. GC-MS chromatogram of the GC thermolysis of methyl *N*-methyl-*N*-nitrosoanthranilate (**1a**). Degradation products marked with blue and red squares were also products of the FVP of **1a.**

4. DSC thermogram of methyl *N*-methyl-*N*-nitrosoanthranilate (1a)

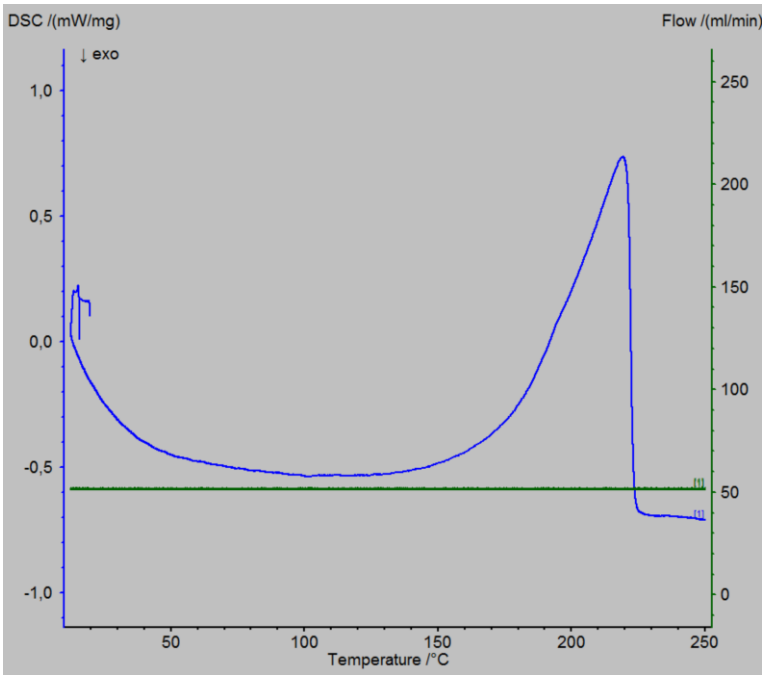


Figure S3. DSC thermogram of methyl *N*-methyl-*N*-nitrosoanthranilate (**1a**). An exothermic peak is observed at 219 °C.

5. Structure elucidation of 7-(methylamino)phthalide (4a)

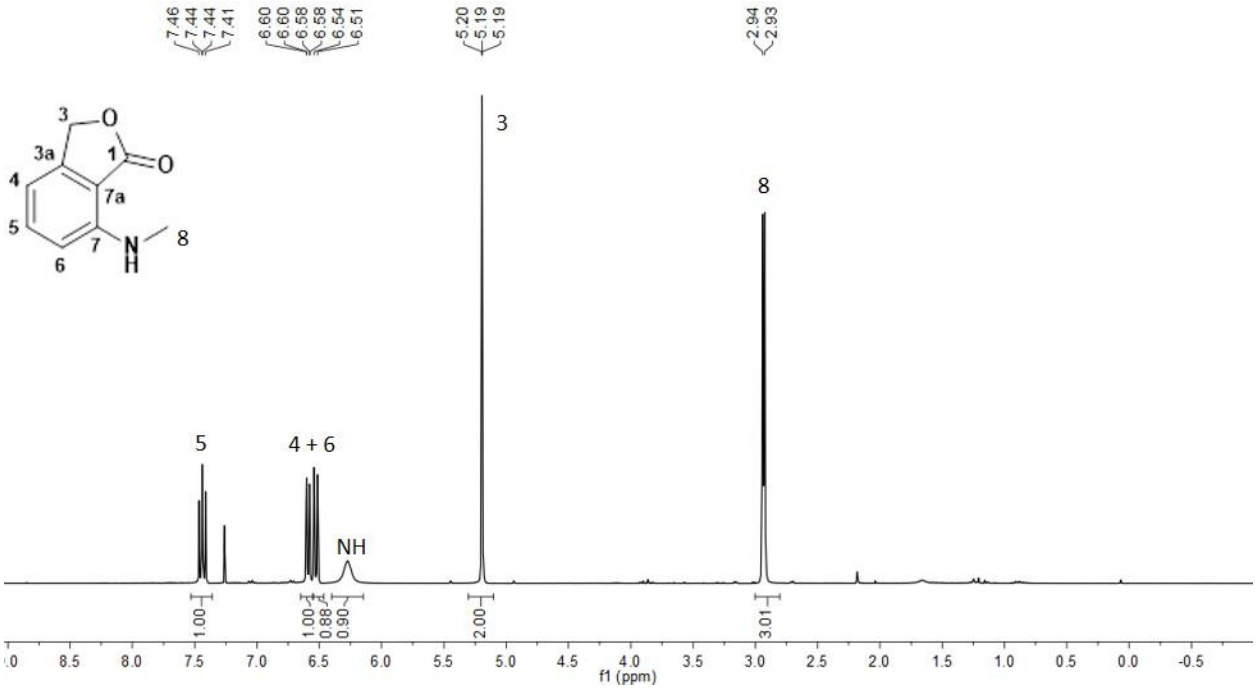


Figure S4. ^{1}H NMR spectrum of **4a** (300 MHz, $CDCl_3$).

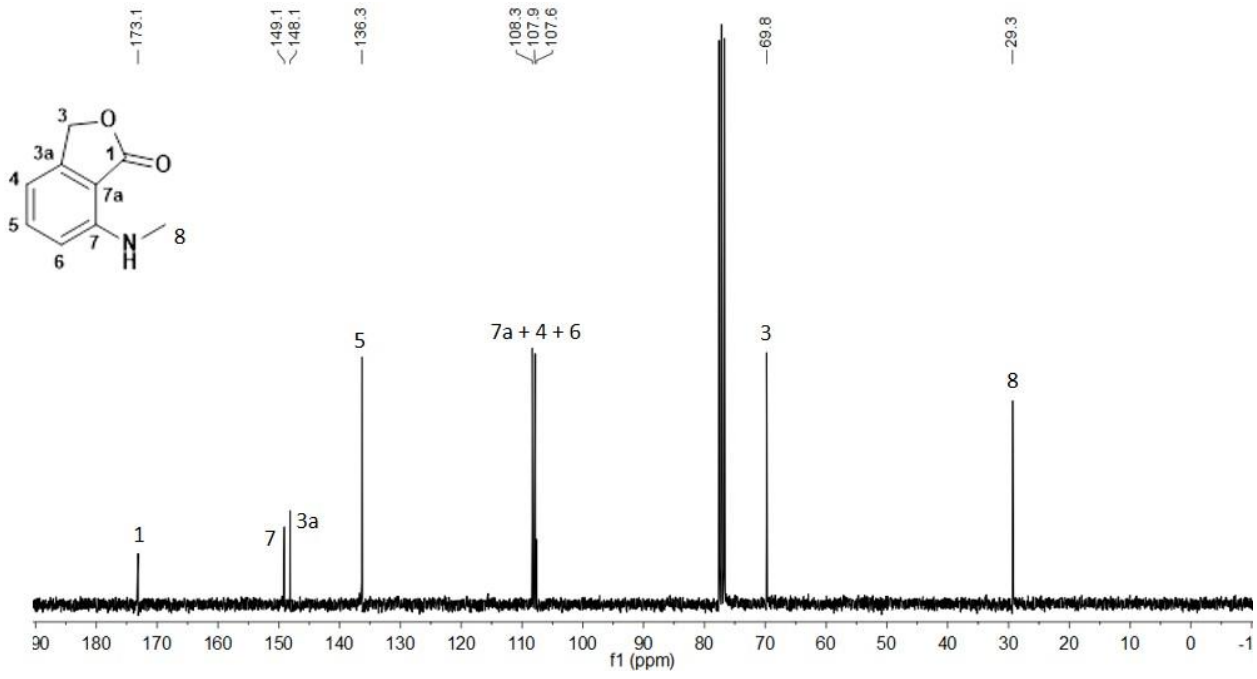


Figure S5. ^{13}C NMR spectrum of **4a** (75 MHz, $CDCl_3$).

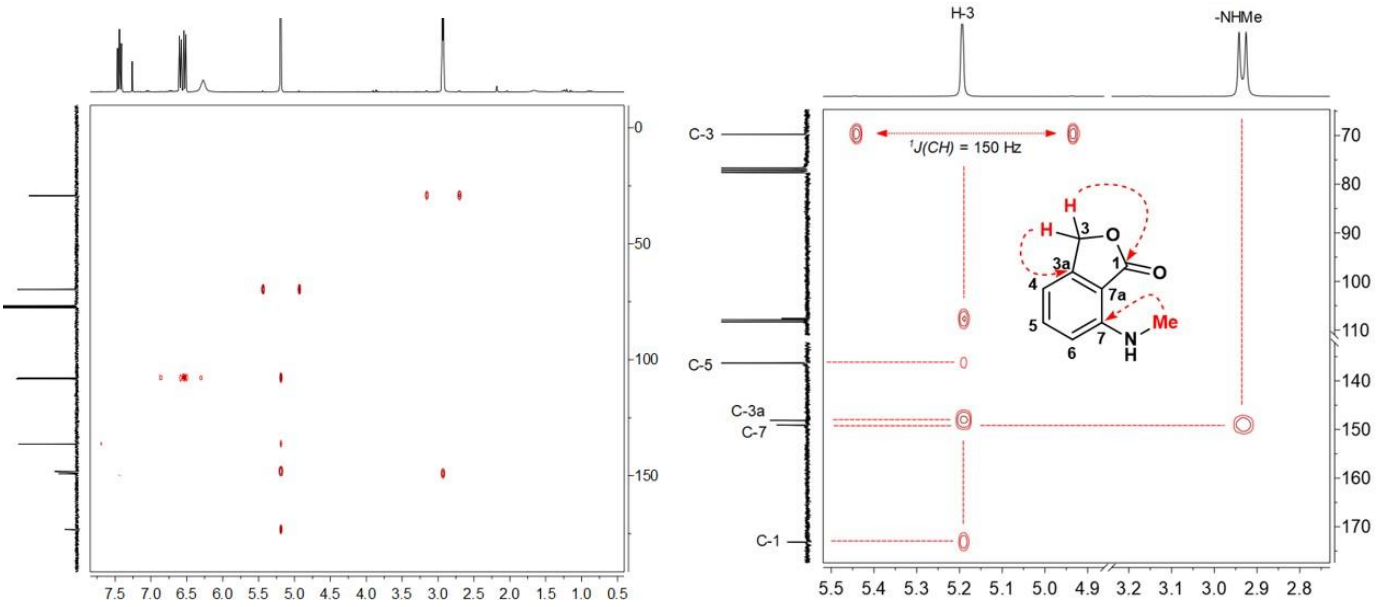


Figure S6. HMBC spectrum of **4a** (300 MHz, $CDCl_3$). Left: full HMBC spectrum; right: zoomed HMBC spectrum showing key correlations.

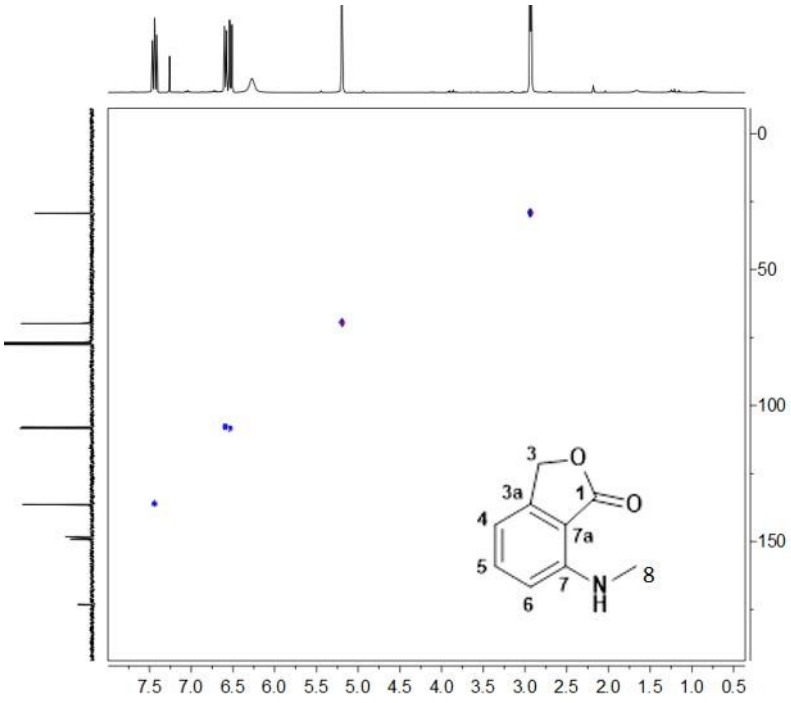


Figure S7. HSQC spectrum of **4a** (300 MHz, $CDCl_3$).

6. Disproportionation mechanism investigations

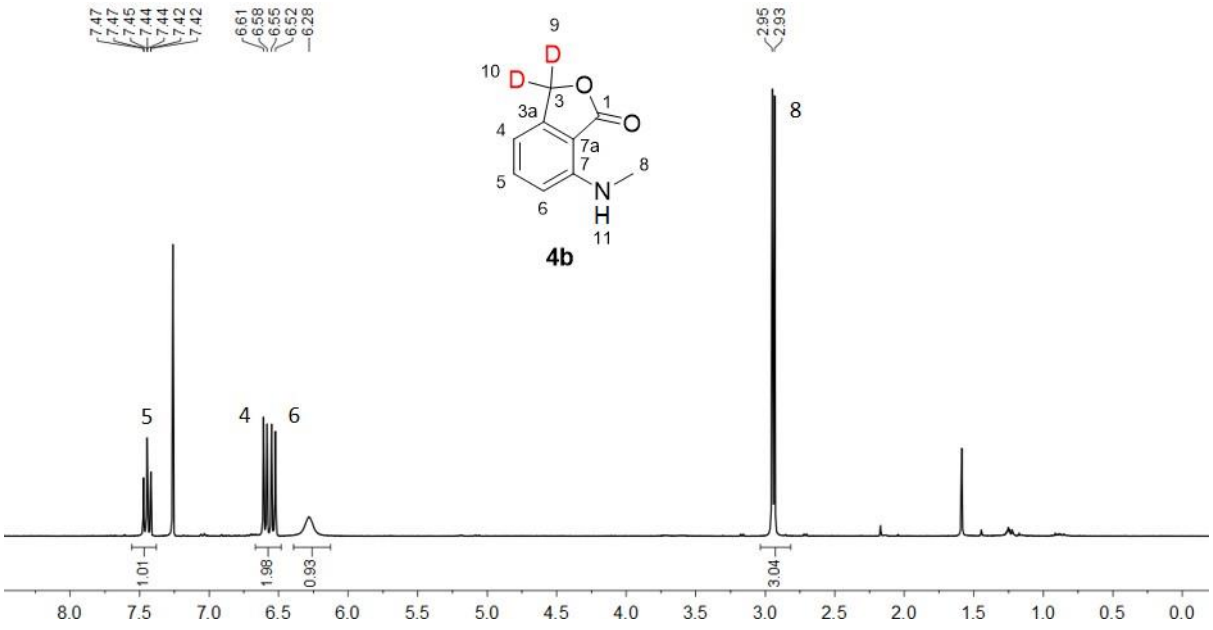


Figure S8. ^{1}H NMR spectrum of **4b** (300 MHz, $CDCl_3$).

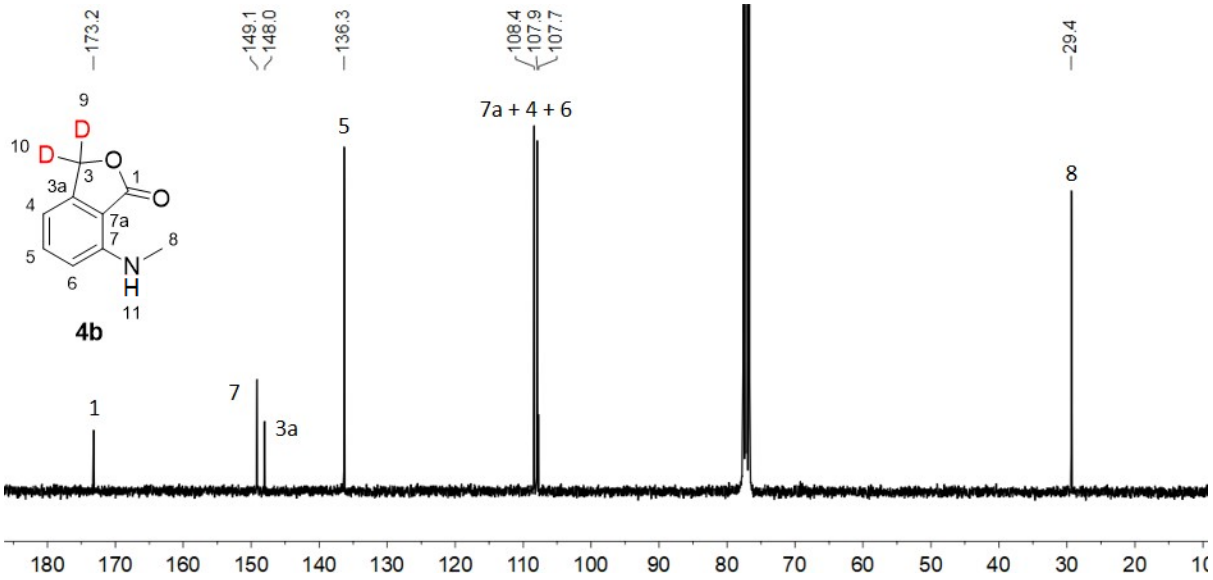


Figure S9. ^{13}C NMR spectrum of **4b** (75 MHz, $CDCl_3$).

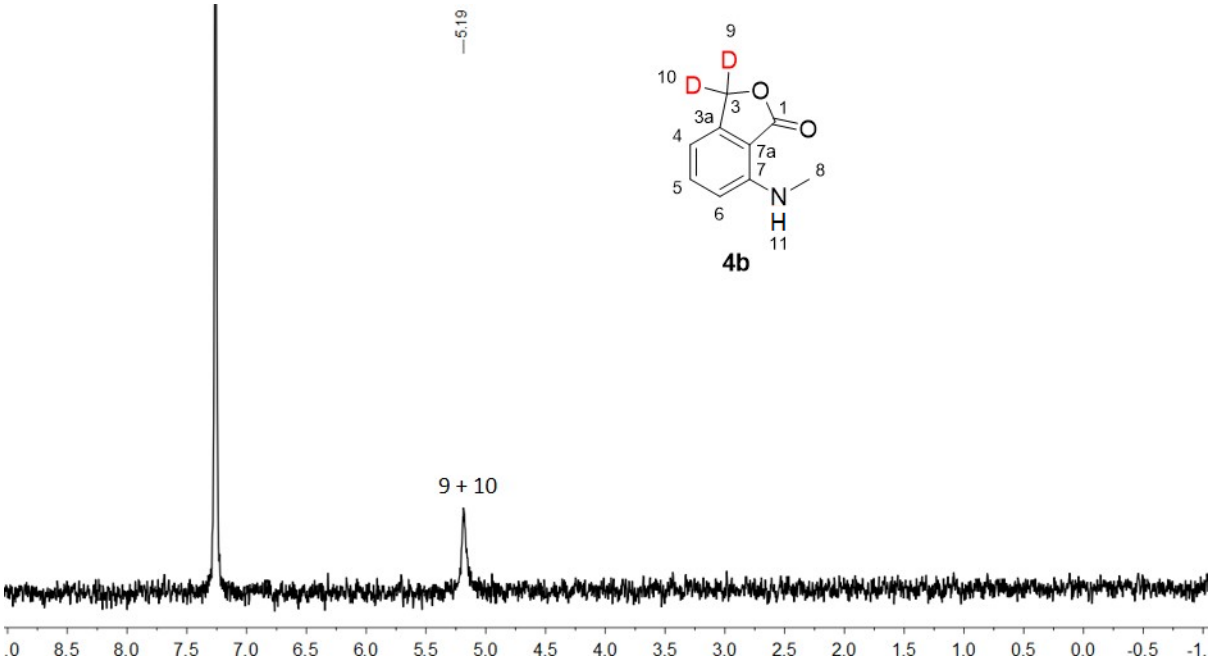


Figure S10. ^{2}H NMR spectrum of **4b** (recorded in $CHCl_3$).

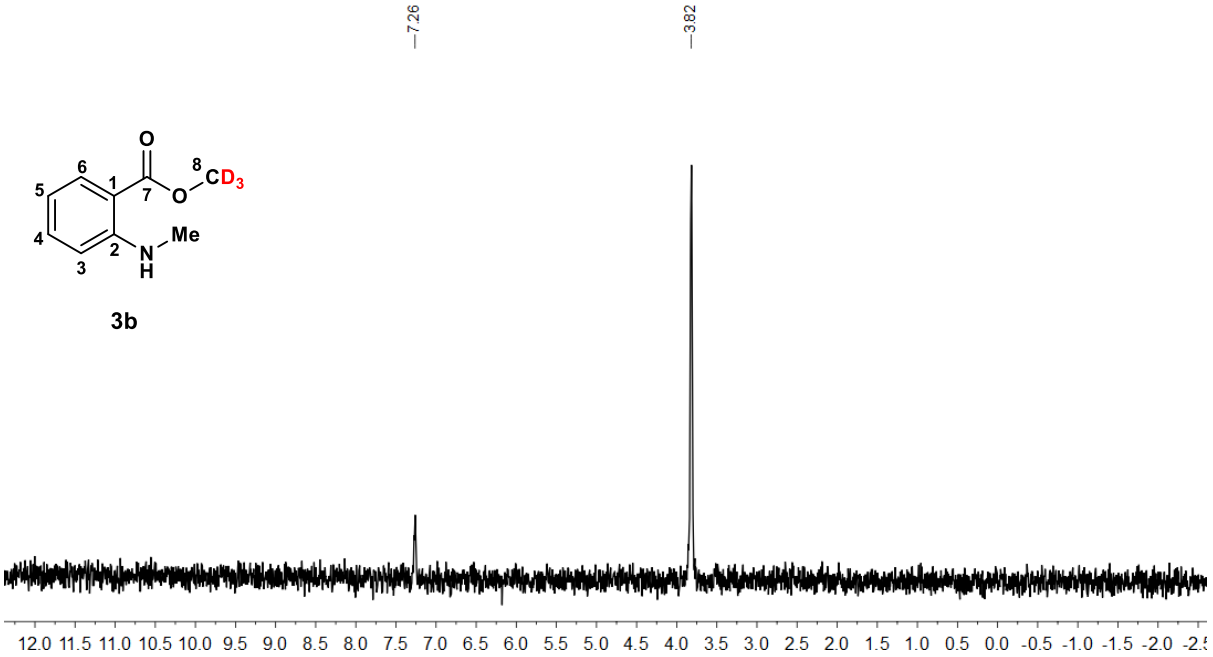
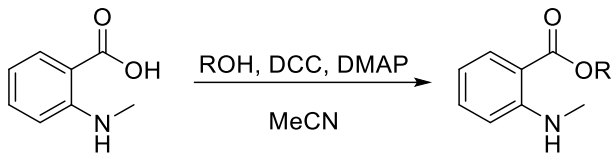


Figure S11. ^{2}H NMR spectrum of **3b** obtained in the FVP of **1b** (recorded in $CHCl_3$).

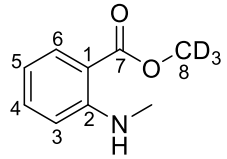
7. Experimental procedure for precursor compounds

7.1. Synthesis of *N*-alkylanthranilates 3b–3j



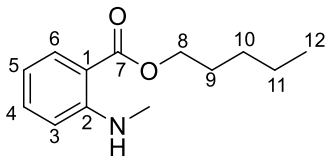
3b, 3g

Alcohol (10 mmol), *N*-methylanthranilic acid (755 mg, 5 mmol), DMAP (200 mg, 1.6 mmol) and DCC (1030 mg, 5 mmol) in dry MeCN (10 mL) were stirred overnight at room temperature. The precipitated urea was filtered off and the filtrate was concentrated in vacuo. The product was purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent.



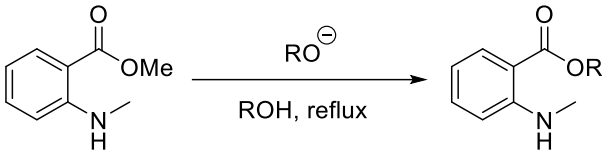
3b

Methyl-*d*$_3$ *N*-methylanthranilate (3b). 23% yield (190 mg); colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.0, 1.7 Hz, 1H, H-6), 7.65 (br s, 1H, NH), 7.41–7.36 (m, 1H, H-4), 6.67 (d, *J* = 8.5 Hz, 1H, H-3), 6.62–6.57 (m, 1H, H-5), 2.91 (d, *J* = 5.1 Hz, 3H, -NMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (C-7), 152.1 (C-2), 134.7 (C-4), 131.6 (C-6), 114.4 (C-5), 110.8 (C-1), 109.9 (C-3), 50.8 (hept, *J* = 22.3 Hz, C-8), 29.6 (-NMe). HRMS *m/z* calcd for $(C_9H_8D_3NO_2 + H)^+$ 169.1051; found 169.1053.



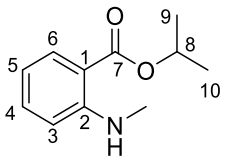
3g

Pentyl *N*-methylanthranilate (3g). 15% yield (170 mg); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.0, 1.6 Hz, 1H, H-6), 7.69 (br s, 1H, NH), 7.39 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H, H-4), 6.69–6.58 (m, 2H, H-3 and H-5), 4.26 (t, *J* = 6.6 Hz, 2H, H-8), 2.92 (s, 3H, -NMe), 1.77 (quint, *J* = 6.9 Hz, 2H, H-9), 1.47–1.39 (m, 4H, H-10 and H-11), 0.95 (t, *J* = 6.6 Hz, 3H, H-12). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (C-7), 152.1 (C-2), 134.6 (C-4), 131.6 (C-6), 114.3 (C-5), 110.7 (C-1), 110.3 (C-3), 64.4 (C-8), 29.6 (-NMe), 28.6 (C-9), 28.4 (C-10), 22.5 (C-11), 14.1 (C-12). HRMS *m/z* calcd for $(C_{13}H_{19}NO_2 + H)^+$ 222.1489; found 222.1488.



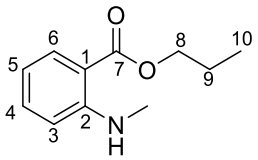
3c, 3d

Isopropyl (**3c**) and **propyl** (**3d**) ***N*-methylanthranilates** were prepared according to a published procedure.[S1]



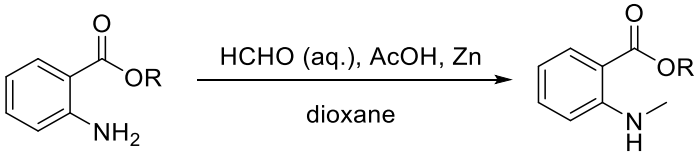
3c

Isopropyl *N*-methylanthranilate (3c). 45% yield; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.0, 1.6 Hz, 1H, H-6), 7.69 (br s, 1H, NH), 7.38 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H, H-4), 6.68–6.56 (m, 2H, H-3 and H-5), 5.20 (sept, *J* = 6.2 Hz, 1H, H-8), 2.91 (d, *J* = 4.9 Hz, 3H, -NMe), 1.36 (d, *J* = 6.3 Hz, 6H, H-9 and H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (C-7), 152.2 (C-2), 134.5 (C-4), 131.7 (C-6), 114.3 (C-5), 110.7 (C-1), 67.6 (C-8), 29.7 (-NMe), 22.1 (C-9 and C-10). The spectral data are in agreement with the previously published values.[S1]



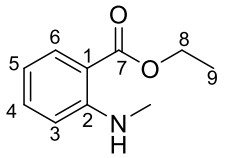
3d

Propyl *N*-methylanthranilate (3d). 52% yield; colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.0, 1.6 Hz, 1H, H-6), 7.67 (br s, 1H, NH), 7.38 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H, H-4), 6.68–6.56 (m, 2H, H-3 and H-5), 4.21 (t, *J* = 6.6 Hz, 2H, H-8), 2.91 (d, *J* = 4.8 Hz, 3H, -NMe), 1.78 (sext, *J* = 7.3 Hz, 2H, H-9), 1.03 (t, *J* = 7.4 Hz, 3H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C-7), 152.2 (C-2), 134.7 (C-4), 131.7 (C-6), 114.4 (C-5), 110.8 (C-1), 110.3 (C-3), 65.9 (C-8), 29.7 (-NMe), 22.3 (C-9), 10.7 (C-10). The spectral data are in agreement with the previously published values.[S1]



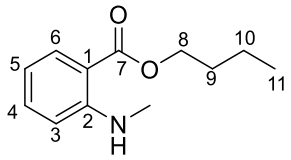
3e, 3f

A mixture of the corresponding anthranilate (5 mmol), 1.20 g of glacial acetic acid (21 mmol), 0.5 mL of 37% aqueous formaldehyde (6.7 mmol), 0.66 g of zinc dust (10 mmol) and 15 mL of dioxane was heated at 50–60 °C for 6 h. The reaction mixture was quenched by the addition of aqueous ammonia solution, extracted with $CHCl_3$, dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The product was purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent.



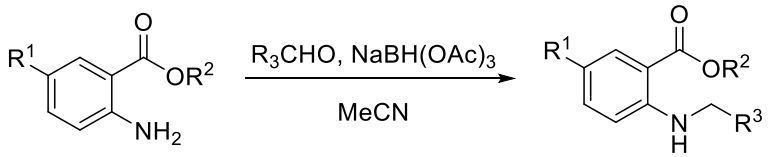
3e

Ethyl *N*-methylanthranilate (3e). 20% yield (180 mg); colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.7 Hz, 1H, H-6), 7.72 (br s, 1H, NH), 7.39 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H, H-4), 6.69–6.59 (m, 2H, H-3 and H-5), 4.34 (q, *J* = 7.1 Hz, 2H, H-8), 2.92 (s, 3H, -NMe), 1.40 (t, *J* = 7.1 Hz, 3H, H-9). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (C-7), 152.0 (C-2), 134.5 (C-4), 131.5 (C-6), 114.2 (C-5), 110.6 (C-1), 110.1 (C-3), 60.1 (C-8), 29.5 (-NMe), 14.4 (C-9). The spectral data are in agreement with the previously published values.[S2]

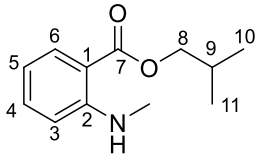


3f

Butyl *N*-methylanthranilate (3f). 23% yield (240 mg); colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.0, 1.7 Hz, 1H, H-6), 7.70 (br s, 1H, NH), 7.39 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H, H-4), 6.69–6.58 (m, 2H, H-3 and H-5), 4.27 (t, *J* = 6.5 Hz, 2H, H-8), 2.91 (s, 3H, -NMe), 1.73 (quint, *J* = 6.5 Hz, 2H, H-9), 1.48 (sext, *J* = 7.3 Hz, 2H, H-10), 0.98 (t, *J* = 7.4 Hz, 3H, H-11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (C-7), 152.1 (C-2), 134.5 (C-4), 131.5 (C-6), 114.4 (C-5), 110.8 (C-1), 110.3 (C-3), 64.1 (C-8), 30.8 (C-9) 29.5 (-NMe), 19.4 (C-10), 13.9 (C-11). The spectral data are in agreement with the previously published values.[S2]



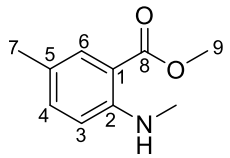
3h-3j



3h

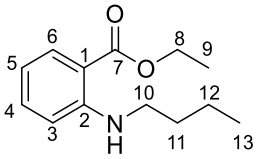
Isobutyl *N*-methylanthranilate (3h). A mixture of isobutyl anthranilate (1 g, 5.18 mmol), 37% aqueous formaldehyde (0.5 mL, 6.7 mmol) and $NaBH(OAc)_3$ (3 g, 14.1 mmol) in MeCN (10 mL) was stirred overnight at room temperature. The reaction mixture was quenched with a saturated solution of Na_2CO_3, extracted with DCM, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The product was purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent. 24% yield (260 mg); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.0, 1.7 Hz, 1H, H-6), 7.70 (br s, 1H, NH), 7.39 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H, H-4), 6.69–6.58 (m, 2H, H-3 and H-5), 4.05 (d, *J* = 6.6 Hz, 2H, H-8), 2.92 (s, 1H, -NMe), 2.08 (nonet, *J* = 6.7 Hz, 1H, H-9), 1.03 (d, *J* = 6.7 Hz, 6H, H-10 and H-11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (C-7), 152.1 (C-2), 134.6 (C-4), 131.6 (C-6), 114.4 (C-5), 110.8 (C-

1), 110.3 (C-3), 70.4 (C-8), 29.6 (-NMe), 28.0 (C-9), 19.4 (C-10 and C-11). HRMS *m/z* calcd for ($C_{12}H_{17}NO_2$ + H)$^+$ 208.1332; found 208.1334.



3i

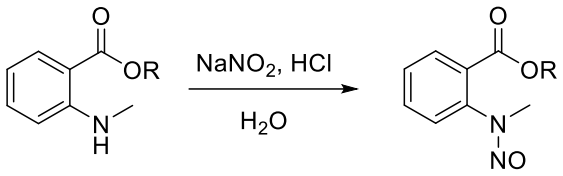
Methyl 5-methyl-2-(methylamino)benzoate (3i). A mixture of methyl 2-amino-5-methylbenzoate (660 mg, 4.0 mmol), 37% aqueous formaldehyde (0.45 mL, 6.0 mmol) and $NaBH(OAc)_3$ (1.6 g, 7.5 mmol) in MeCN (10 mL) was stirred overnight at room temperature. The reaction mixture was quenched with a saturated solution of Na_2CO_3, extracted with DCM, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The product was purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent. 31% yield (220 mg); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.0 Hz, 1H, H-6), 7.46 (br s, 1H, NH), 7.21 (dd, *J* = 8.5, 2.0 Hz, 1H, H-4), 6.60 (d, *J* = 8.6 Hz, 1H, H-3), 3.85 (s, 3H, H-9), 2.90 (s, 3H, -NMe), 2.25 (s, 3H, H-7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C-8), 150.2 (C-2), 135.8 (C-4), 131.4 (C-6), 123.3 (C-5), 110.9 (C-1), 109.7 (C-3), 51.4 (C-9), 29.8 (NMe), 20.2 (C-7). The spectral data are in agreement with the previously published values.[S3]



3j

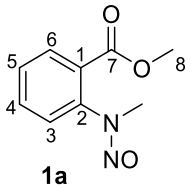
Ethyl *N*-butylanthranilate (3j). A mixture of ethyl anthranilate (825 mg, 5.0 mmol), butanal (360 mg, 5.0 mmol), acetic acid (0.4 mL, 7 mmol) and $NaBH(OAc)_3$ (1.6 g, 7.5 mmol) in MeCN (20 mL) was stirred overnight at room temperature. The reaction mixture was quenched with a saturated solution of Na_2CO_3, extracted with DCM, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The product was purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent. 38% yield (420 mg); colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.0, 1.7 Hz, 1H, H-6), 7.74 (br s, 1H, NH), 7.35 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H, H-4), 6.68 (d, *J* = 8.5 Hz, 1H, H-3), 6.57 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H, H-5), 4.31 (q, *J* = 7.1 Hz, 2H, H-8), 3.19 (t, *J* = 7.0 Hz, 2H, H-10), 1.73–1.63 (m, 2H, H-11), 1.53–1.43 (m, 2H, H-12) 1.38 (t, *J* = 7.1 Hz, 2H, H-9), 0.97 (t, *J* = 7.3 Hz, 3H, H-13). ^{13}C NMR (75 MHz, $CDCl_3$) 168.9 (C-7), 151.3 (C-2), 134.6 (C-4), 131.8 (C-6), 114.3 (C-5), 111.4 (C-1), 110.1 (C-3), 60.3 (C-8), 42.8 (C-10), 31.4 (C-11), 20.5 (C-12), 14.5 (C-9), 14.0 (C-13). HRMS *m/z* calcd for ($C_{13}H_{19}NO_2$ + H)$^+$ 222.1489; found 222.1488.

7.2. Synthesis of *N*-methyl-*N*-nitrosoanthranilates 1a–1f



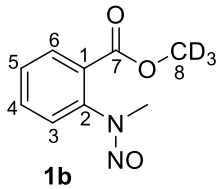
3a-3f **1a-1f**

Compound **1a** was prepared according to a published procedure.[S4] This procedure was slightly modified and used for the preparation of compounds **1b**–**1f**: *N*-methylanthranilate ester **3b**–**3f** (1 mmol) was dissolved by ultrasonication in 3 mL of 4 M HCl, an aqueous solution of $NaNO_2$ (4 M, 1 mL) was added dropwise and the mixture was left stirring for 30 min. The reaction mixture was extracted with Et_2O and the organic phase was washed with HCl (1%, w/w), water, $NaHCO_3$ solution (2%, w/w) and again with water. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The products were pure according to TLC and NMR[S5] and no additional purification was attempted.



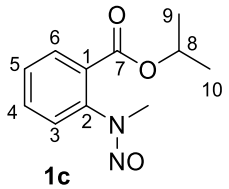
1a

Methyl *N*-methyl-*N*-nitrosoanthranilate (1a). 87% yield (3.37 g), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.8, 1.6 Hz, 1H, H-6), 7.65 (td, *J* = 7.7, 1.6 Hz, 1H, H-4), 7.51 (td, *J* = 7.6, 1.2 Hz, 1H, H-5), 7.37 (dd, *J* = 7.9, 1.1 Hz, 1H, H-3), 3.80 (s, 3H, H-8), 3.40 (s, 3H, -N<u>Me</u>). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (C-7), 141.7 (C-2), 133.1 (C-4), 131.6 (C-6), 129.0 (C-5), 127.1 (C-1), 126.1 (C-3), 52.7 (C-8), 35.4 [-N(NO)<u>Me</u>]. The spectral data are in agreement with the previously published values.[S4]



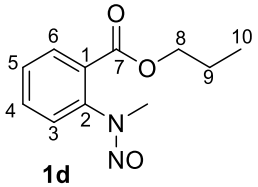
1b

Methyl-*d*$_3$ *N*-methyl-*N*-nitrosoanthranilate (1b). 56% yield (110 mg), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 7.7, 1.6 Hz, 1H, H-6), 7.65 (td, *J* = 7.7, 1.6 Hz, 1H, H-4), 7.52 (td, *J* = 7.6, 1.2 Hz, 1H, H-5), 7.38 (dd, *J* = 7.9, 1.2 Hz, 1H, H-3), 3.40 (s, 3H, -N<u>Me</u>). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2 (C-7), 141.7 (C-2), 133.0 (C-4), 131.6 (C-6), 129.0 (C-5), 127.1 (C-1), 126.1 (C-3), 35.4 [-N(NO)<u>Me</u>].



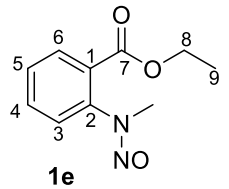
1c

Isopropyl *N*-methyl-*N*-nitrosoanthranilate (1c). 70% yield (155 mg), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.8, 1.7 Hz, 1H, H-6), 7.64 (td, *J* = 7.7, 1.6 Hz, 1H, H-4), 7.52 (td, *J* = 7.6, 1.3 Hz, 1H, H-5), 7.36 (dd, *J* = 7.9, 1.1 Hz, 1H, H-3), 5.13 (sept, *J* = 6.3 Hz, 1H, H-8), 3.41 (s, 3H, -NMe), 1.25 (d, *J* = 6.3 Hz, 6H, H-9 and H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 (C-7), 141.5 (C-2), 132.8 (C-4), 131.6 (C-6), 129.0 (C-5), 128.3 (C-1), 126.0 (C-3), 69.5 (C-8), 35.5 [-N(NO)Me], 21.9 (C-9).



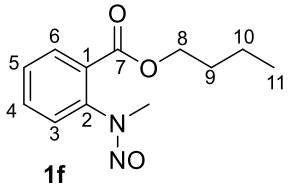
1d

Propyl *N*-methyl-*N*-nitrosoanthranilate (1d). 72% yield (160 mg), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.8, 1.6 Hz, 1H, H-6), 7.65 (td, *J* = 7.7, 1.6 Hz, 1H, H-4), 7.53 (td, *J* = 7.6, 1.2 Hz, 1H, H-5), 7.38 (dd, *J* = 7.9, 1.1 Hz, 1H, H-3), 4.17 (t, *J* = 6.9 Hz, 2H, H-8), 3.41 (s, 3H, -NMe), 1.68 (sext, *J* = 7.3 Hz, 2H, H-9), 0.94 (t, *J* = 7.4 Hz, 3H, H-10). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (C-7), 141.7 (C-2), 132.9 (C-4), 131.6 (C-6), 129.0 (C-5), 127.7 (C-1), 126.1 (C-3), 67.4 (C-8), 35.5 [-N(NO)Me], 22.0 (C-9), 10.5 (C-10).



1e

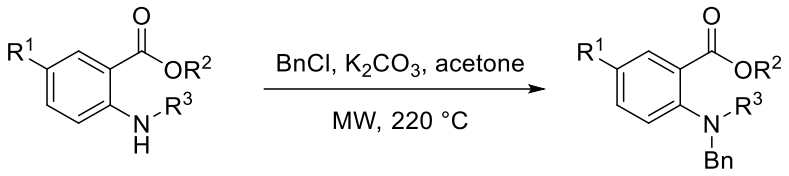
Ethyl *N*-methyl-*N*-nitrosoanthranilate (1e). 78% yield (163 mg), **y**ellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.8, 1.6 Hz, 1H, H-6), 7.66 (td, *J* = 7.7, 1.6 Hz, 1H, H-4), 7.53 (td, *J* = 7.6, 1.3 Hz, 1H, H-5), 7.38 (dd, *J* = 7.9, 1.1 Hz, 1H, H-3), 4.27 (q, *J* = 7.1 Hz, 2H, H-8), 3.42 (s, 3H, -NMe), 1.28 (t, *J* = 7.1 Hz, 3H, H-9). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C-7), 141.7 (C-2), 132.9 (C-4), 131.6 (C-6), 129.0 (C-5), 127.8 (C-1), 126.1 (C-3), 61.8 (C-8), 35.5 [-N(NO)Me], 14.2 (C-9).



1f

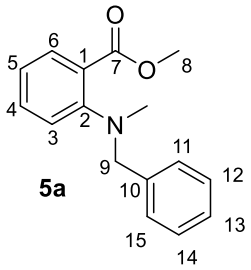
Butyl *N*-methyl-*N*-nitrosoanthranilate (1f). 63% yield (149 mg), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.8, 1.5 Hz, 1H, H-6), 7.64 (td, *J* = 7.7, 1.6 Hz, 1H, H-4), 7.51 (td, *J* = 7.6, 1.3 Hz, 1H, H-5), 7.37 (dd, *J* = 7.9, 1.0 Hz, 1H, H-3), 4.20 (t, *J* = 6.7 Hz, 2H, H-8), 3.40 (s, 3H, -NMe), 1.62 (quint, *J* = 7.3 Hz, 2H, H-9), 1.36 (sext, *J* = 7.3 Hz, 2H, H-10), 0.92 (t, *J* = 7.3 Hz, 3H, H-11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8 (C-7), 141.6 (C-2), 132.9 (C-4), 131.5 (C-6), 129.0 (C-5), 127.6 (C-1), 126.1 (C-3), 65.6 (C-8), 35.4 [-N(NO)Me], 30.6 (C-9), 19.2 (C-10), 13.8 (C-11).

7.3. Synthesis of *N*-alkyl-*N*-benzylanthranilates 5a, 5g–5j



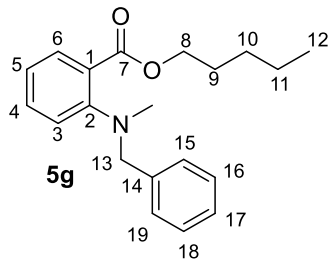
3a, 3g-3j **5a, 5g-5j**

A microwave vial containing the mixture of *N*-alkylanthranilate **3a**, **3g**–**3j (**0.5 mmol), benzyl chloride (0.75 mmol, 85 µL) and K_2CO_3 (600 mg) in 2 mL of acetone was sealed with a snap cap and heated for the required time at 220 °C in the microwave reactor. After cooling to 40 °C by compressed air, the mixture was filtered, concentrated in vacuo and purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent.



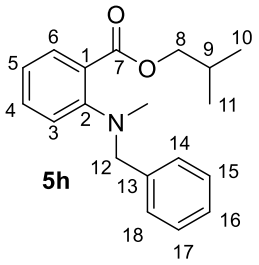
5a

Methyl *N*-benzyl-*N*-methylanthranilate (5a). Reaction time: 1.5 h, 62% yield (80 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.7, 1.7 Hz, 1H, H-6), 7.41–7.28 (m, 6H, H-4 and H-11–H15), 7.03 (dd, *J* = 8.4, 1.0 Hz, 1H, H-3), 6.94 (td, *J* = 7.7, 1.0 Hz, 1H, H-5), 4.36 (s, 2H, H-9), 3.88 (s, 3H, H-8) 2.79 (s, 3H, -NMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (C-7), 151.9 (C-2), 138.2 (C-10), 132.2 (C-4), 131.4 (C-6), 128.4 (C-12 and C-14), 127.9 (C-11 and C-15), 127.1 (C-13), 122.5 (C-1), 119.7 (C-5), 118.6 (C-3), 60.2 (C-9), 52.1 (C-8), 40.7 (-NMe). HRMS *m/z* calcd for $(C_{16}H_{17}NO_2 + H)^+$ 256.1332; found 256.1334.

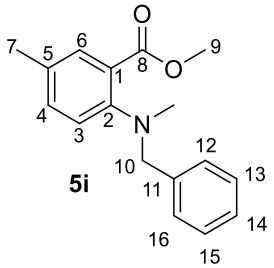


5g

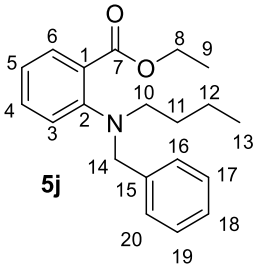
Pentyl *N*-benzyl-*N*-methylanthranilate (5g). Reaction time: 1.5 h, 52% yield (81 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.7, 1.7 Hz, 1H, H-6), 7.39–7.24 (m, 6H, H-4 and H-15–H19), 6.99 (d, *J* = 8.3 Hz, 1H, H-3), 6.91 (td, *J* = 7.7, 1.0 Hz, 1H, H-5), 4.34–4.26 (m, 4H, H-13 and H-8), 2.76 (s, 3H, -NMe), 1.75 (quint, *J* = 7.0 Hz, H-9), 1.44–1.34 (m, 4H, H-10 and H-11), 0.92 (t, *J* = 7.1 Hz, 3H, H-12). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C-7), 151.8 (C-2), 138.3 (C-14), 132.0 (C-4), 131.2 (C-6), 128.5 (C-16 and C-18), 128.0 (C-15 and C-19), 127.2 (C-17), 123.2 (C-1), 119.7 (C-5), 118.8 (C-3), 65.2 (C-8), 59.9 (C-13), 41.0 (-NMe), 28.6 (C-9), 28.3 (C-10), 22.5 (C-11), 14.1 (C-12). HRMS *m/z* calcd for $(C_{20}H_{25}NO_2 + H)^+$ 312.1958; found 312.1962.



Isobutyl *N*-benzyl-*N*-methylanthranilate (5h). Reaction time: 2 h, 56% yield (84 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.7, 1.7 Hz, 1H, H-6), 7.40–7.23 (m, 6H, H-4 and H-14–H18), 6.99 (d, *J* = 8.3 Hz, 1H, H-3), 6.94–6.88 (m, 1H, H-5), 4.34 (s, 2H, H-12), 4.08 (d, *J* = 6.7 Hz, 2H, H-8), 2.77 (s, 3H, -NMe), 2.07 (nonet, *J* = 6.7 Hz, 1H, H-9), 1.01, (d, *J* = 6.7 Hz, 6H, H-10 and H-11). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (C-7), 151.9 (C-2), 138.3 (C-13), 132.0 (C-4), 131.2 (C-6), 128.5 (C-15 and C-17), 128.1 (C-14 and C-18), 127.2 (C-16), 123.1 (C-1), 119.7 (C-5), 118.9 (C-3), 71.2 (C-8), 59.9 (C-12), 41.1 (-NMe), 28.0 (C-9), 19.4 (C-10 and C-11).

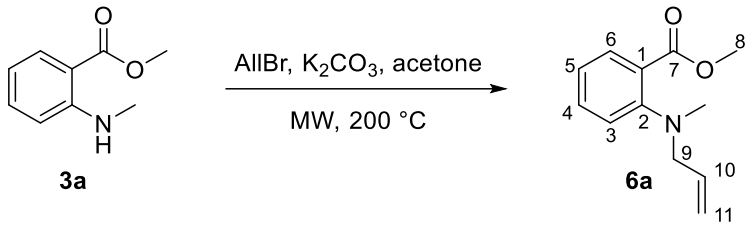


Methyl 2-(benzyl(methyl)amino)-5-methylbenzoate (5i). Reaction time: 2 h, 52% yield (70 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.1 Hz, 1H, H-6), 7.32–7.23 (m, 5H, H-12–H16), 7.17 (dd, *J* = 8.4, 2.3 Hz, 1H, H-4), 6.93 (d, *J* = 8.4, 1H, H-3), 4.25 (s, 2H, H-10), 3.85 (s, 3H, C-9) 2.71 (s, 3H, -NMe), 2.30 (s, 3H, C-7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (C-8), 149.9 (C-2), 138.5 (C-11), 132.9 (C-6), 131.5 (C-4), 129.8 (C-5), 128.4 (C-13 and C-15), 128.1 (C-12 and C-16), 127.1 (C-14), 123.5 (C-1), 119.3 (C-3), 60.8 (C-10), 52.2 (C-9), 40.9 (-NMe), 20.4 (C-7).



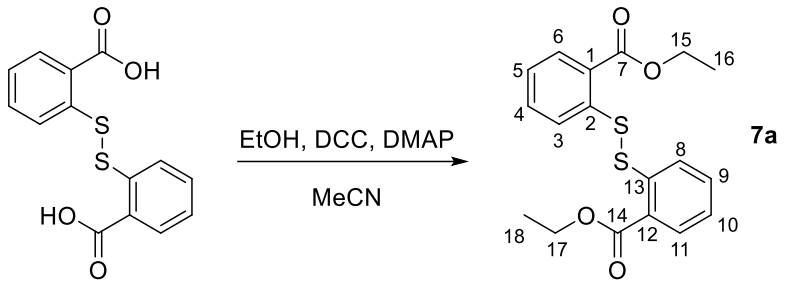
Ethyl *N*-benzyl-*N*-butylanthranilate (5j). Reaction time: 2 h, 58% yield (90 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.7, 1.7 Hz, 1H, H-6), 7.39–7.23 (m, 6H, H-4 and H-16–H-20), 7.04 (dd, *J* = 8.3, 0.8 Hz, 1H, H-3), 6.94 (td, *J* = 7.6, 1.1 Hz, 1H, H-5), 4.40–4.31 (m, 4H, H-8 and H-14), 3.05 (t, *J* = 7.3 Hz, 2H, H-10), 1.52–1.18 (m, 5H, H-9 and H-11), 1.24 (sext, 2H, H-12), 0.83 (t, *J* = 7.3 Hz, 3H, H-13). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (C-7), 150.8 (C-2), 138.9 (C-15), 131.6 (C-4), 130.9 (C-6), 128.3 (C-17 and C-19), 128.3 (C-16 and C-20), 127.0 (C-18), 125.9 (C-1), 121.1 (C-5), 120.6 (C-3), 61.0 (C-8), 57.7 (C-14), 52.3 (C-10), 29.1 (C-11), 20.3 (C-12), 14.4 (C-9), 14.0 (C-13). HRMS *m/z* calcd for $(C_{20}H_{25}NO_2 + H)^+$ 312.1958; found 312.1963.

7.4 Synthesis of methyl *N*-allyl-*N*-methylanthranilate 6a

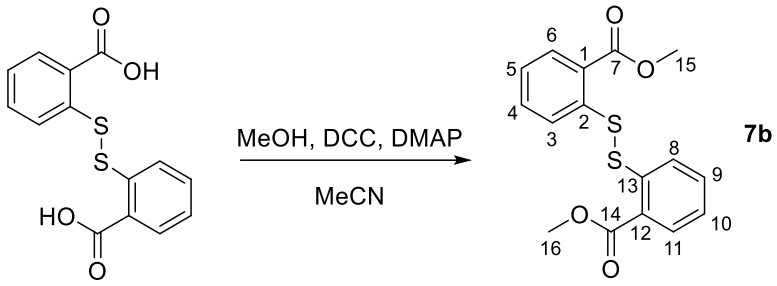


Methyl *N*-methylanthranilate **3a** (338 mg, 2 mmol), allyl bromide (303 mg, 2.5 mmol), K_2CO_3 (700 mg) and 2 mL of acetone were placed in a microwave vial. The vial was sealed with a snap cap and the reaction mixture was heated for 2 h at 220 °C in the microwave reactor. After cooling to 40 °C by compressed air, the mixture was filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent. 39% yield (160 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.8, 1.7 Hz, 1H, H-6), 7.32 (ddd, *J* = 8.9, 7.3, 1.8 Hz, 1H, H-4), 6.97 (dd, *J* = 8.3, 0.7 Hz, 1H, H-3), 6.85 (td, *J* = 7.7, 1.0 Hz, 1H, H-5), 5.97–5.84 (m, 1H, H-10), 5.24–5.16 (m, 2H, H-11), 3.86 (s, 3H, H-8), 3.68 (d, *J* = 5.8 Hz, 2H, H-9), 2.78 (s, 3H, -NMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C-7), 151.7 (C-2), 134.7 (C-10), 132.1 (C-4), 131.4 (C-6), 121.9 (C-1), 119.3 (C-5), 118.1 (C-11), 117.4 (C-3), 59.6 (C-9), 52.0 (C-8), 39.7 (-NMe). HRMS *m/z* calcd for $(C_{12}H_{15}NO_2 + H)^+$ 206.1176; found 206.1178.

7.5 Synthesis of 2,2'-dithiobisbenzoates 7a + 7b

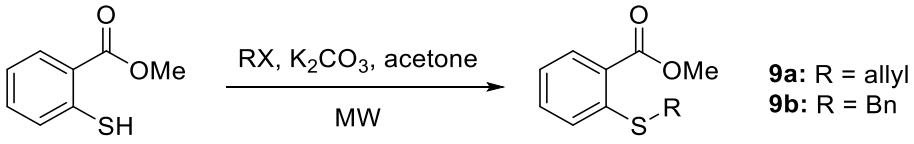


Diethyl 2,2'-disulfanediyldibenzoate (7a). Ethanol (3 mL, 32 mmol), 2,2′-dithiodibenzoic acid (3.0 g, 9.8 mmol), DMAP (300 mg) and DCC (4.2 g, 20.4 mmol) in dry MeCN (20 mL) were stirred overnight at room temperature. The precipitated urea was filtered off and the filtrate was concentrated in vacuo. The product was purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent. 46% yield (1.63 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 7.8, 1.4 Hz, 2H, H-6 and H-11), 7.75 (dd, *J* = 8.2, 0.7 Hz, 2H, H-3 and H-8), 7.43–7.37 (m, 2H, H-4 and H-9), 7.25–7.20 (m, 2H, H-5 and and H-10), 4.45 (q, *J* = 7.1 Hz, 4H, H-15 and H-17), 1.44 (t, *J* = 7.1 Hz, 6H, H-16 and H-18). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C-7 and C-14), 140.4 (C-2 and C-13), 133.1 (C-4 and C-9), 131.5 (C-6 and C-11), 127.7 (C-3 and C-8), 125.9 (C-5 and C-10), 125.6 (C-1 and C-12), 61.6 (C-15 and C-17), 14.5 (C-16 and C-18). The spectral data are in agreement with the previously published values.[S6]

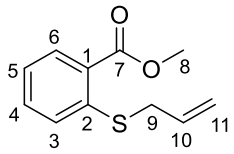


Dimethyl 2,2'-disulfanediyldibenzoate (7b). Methanol, (0.5 mL, 12.4 mmol), 2,2′-dithiodibenzoic acid (612 mg, 2.0 mmol), DMAP (100 mg) and DCC (900 mg, 4.4 mmol) in dry MeCN (20 mL) were stirred overnight at room temperature. The precipitated urea was filtered off and the filtrate was concentrated in vacuo. The product was purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent. 37% yield (250 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.8, 1.5 Hz, 2H, H-6 and H-11), 7.75 (dd, *J* = 8.2, 0.9 Hz, 2H, H-3 and H-8), 7.41 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 2H, H-4 and H-9), 7.23 (td, *J* = 7.7 Hz, 2H, H-5 and and H-10), 3.98 (s, 6H, H-15 and H-16). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C-7 and C-14), 140.5 (C-2 and C-13), 133.2 (C-4 and C-9), 131.6 (C-6 and C-11), 127.4 (C-3 and C-8), 126.0 (C-5 and C-10), 125.6 (C-1 and C-12), 52.5 (C-15 and C-16). The spectral data are in agreement with the previously published values.[S7]

7.6 Synthesis of methyl 2-(alkylthio)benzoates 9a + 9b

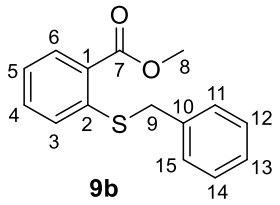


A microwave vial containing the mixture of methyl 2-mercaptobenzoate (300 mg, 1.78 mmol), benzyl chloride or allyl bromide (2 mmol), respectively, and K_2CO_3 (700 mg) in 2 mL of acetone was sealed with a snap cap and heated for 20 min at 100 °C in the microwave reactor. After cooling to 40 °C by compressed air, the mixture was filtered, concentrated in vacuo and purified by flash chromatography on silica gel using EtOAc/petroleum ether as eluent.



9a

Methyl 2-(allylthio)benzoate (9a). 89% yield (330 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.8, 1.5 Hz, 1H, H-6), 7.42 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H, H-4), 7.33–7.30 (m, 1H, H-3), 7.15 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H, H-5), 5.92 (ddt, *J* = 16.7, 10.1, 6.6 Hz, 1H, H-10), 5.32 (dq, *J* = 17.0, 1.4 Hz, 1H, H-11), 5.18 (dq, *J* = 10.1, 1.1 Hz, 1H, H-11), 3.91 (s, 3H, H-8), 3.61 (dt, *J* = 6.6, 1.2 Hz, 2H, H-9). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0 (C-7), 141.3 (C-2), 132.8 (C-10), 132.3 (C-4), 131.3 (C-6), 128.0 (C-3), 126.2 (C-1), 124.1 (C-5), 118.8 (C-11), 52.2 (C-8), 35.5 (C-9). The spectral data are in agreement with the previously published values.[S8]

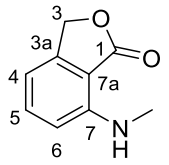


9b

Methyl 2-(benzylthio)benzoate (9b). 85% yield (390 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.8, 1.4 Hz, 1H, H-6), 7.54–7.26 (m, 7H, H-3–H-5, H-11, H-12, H-14 and H-15), 7.16 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H, H-13), 4.17 (s, 2H, H-9), 3.90 (s, 3H, H-8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0 (C-7), 142.1 (C-2), 136.2 (C-10), 132.5 (C-4), 131.4 (C-6), 129.2 (C-11 and C-15), 128.7 (C-12 and C-14), 127.6 (C-1), 127.5 (C-13), 126.0 (C-3), 124.2 (C-5), 52.2 (C-8), 37.4 (C-9).The spectral data are in agreement with the previously published values.[S9]

8. Experimental procedures for the FVP reactions

FVP reactions were carried out in an unpacked quartz tube (60 cm × 3.5 cm ID) with a starting vacuum of 4-5 × 10^{-3} mbar (see Figure S1 for further details). When subjecting *N*-nitroso compounds **1a**–**1i** to FVP, an increase in pressure was observed. The reaction was stopped once the pressure dropped to starting levels. Generally, the reaction time was ≤1 h for all FVP experiments. Pyrolysis products were collected in an acetone/liquid N_2 trap and dissolved in dichloromethane. The solvent was then removed under reduced pressure and the products were isolated by flash column chromatography on silica gel using EtOAc/petroleum ether as eluent.

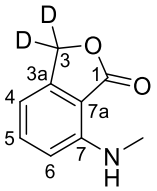


4a

7-(Methylamino)phthalide (4a). ***Method 1*****:** 97 mg (0.5 mmol) of **1a**; oven: 400 °C; preheater: 60-70 °C; T_{zone2} = 400 °C. 35% yield (28.5 mg), colorless solid, mp 92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.5 Hz, 1H, H-5), 6.59 (d, *J* = 7.3 Hz, 1H, H-4), 6.53 (d, *J* = 8.3 Hz, 1H, H-6), 6.27 (br s, 1H, NH), 5.20 (s, 2H, H-3), 2.93 (d, *J* = 4.9 Hz, 3H, -NHMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (C-1), 149.1 (C-7), 148.1 (C-3a), 136.3 (C-5), 108.3 (C-4), 107.9 (C-7a), 107.6 (C-6), 69.8 (C-3), 29.3 (-NMe). FTIR (neat) ν_{max}/cm^{-1}: 3390, 1725; EI-MS *m/z* (relative intensity in %) 163(M^+, 100), 118(91), 90(63), 145(62), 77(49), 117(36), 51(32), 91(28), 119(25), 79(24). HRMS *m/z* calcd for $(C_9H_9NO_2 + H)^+$ 164.0706; found 164.0706.

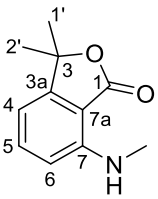
Method 2**:** 50 mg (0.24 mmol) of **6a**; oven: 650 °C; preheater: 70-80 °C; T_{zone2} = 625 °C. 25% ^{1}H NMR yield.

Method 3**:** 120 mg (0.47 mmol) of **5a**; oven: 650 °C; preheater: 100-110 °C; T_{zone2} = 625 °C. 37% ^{1}H NMR yield



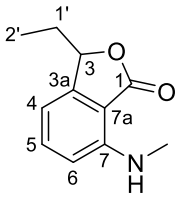
4b

7-(Methylamino)phthalide-3,3-*d*$_2$ (4b). 35 mg (0.18 mmol) of **1b**; oven: 450 °C; preheater: 80-90 °C; T_{zone2} = 470 °C. 27% yield (8.0 mg), colorless solid, mp 92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (t, *J* = 7.8 Hz, 1H, H-5), 6.60 (d, *J* = 7.3 Hz, 1H, H-4), 6.54 (d, *J* = 8.3 Hz, 1H, H-6), 6.28 (br s, 1H, NH), 2.93 (d, *J* = 5.2 Hz, 3H, -NHMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (C-1), 149.1 (C-7), 148.0 (C-3a), 136.3 (C-5), 108.4 (C-4), 107.9 (C-7a), 107.7 (C-6), 29.4 (-NMe). The C-3 signal was not observed; FTIR (neat) ν_{max}/cm^{-1}: 3390, 1725; HRMS *m/z* calcd for $(C_9H_7D_2NO_2 + H)^+$ 166.0834; found 166.0832.



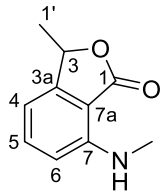
4c

3,3-Dimethyl-7-(methylamino)phthalide (4c). 92 mg (0.41 mmol) of **1c**; oven: 400 °C; preheater: 70-80 °C; T_{zone2} = 420 °C. 28% yield (22.0 mg), yellowish amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.8 Hz, 1H, H-5), 6.53–6.49 (m, 2H, H-6 and H-4), 6.33 (br s, 1H, NH), 2.93 (d, *J* = 5.2 Hz, 3H, -NHMe), 1.60 (s, 6H, H-1'and H-2'). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (C-1), 156.7 (C-7), 149.0 (C-3a), 136.3 (C-5), 108.3 (C-4), 107.0 (C-7a), 106.6 (C-6), 85.3 (C-3), 29.4 (-NMe), 27.4 (C-1' and C-2'). FTIR (neat) ν_{max}/cm^{-1}: 3395, 1720; HRMS *m/z* calcd for $(C_{11}H_{13}NO_2 + H)^+$ 192.1019; found 192.1021.



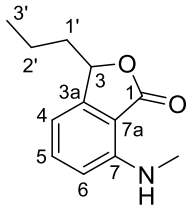
4d

3-Ethyl-7-(methylamino)phthalide (4d). 114 mg (0.51 mmol) of **1d**; oven: 400 °C; preheater: 60-70 °C; T_{zone2} = 420 °C. 34% yield (33.0 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.5 Hz, 1H, H-5), 6.55–6.51 (m, 2H, H-6 and H-4), 6.30 (br s, 1H, NH), 5.33–5.30 (m, 1H, H-3), 2.93 (d, *J* = 5.0 Hz, 3H, -NHMe), 2.12–1.98 (m, 1H, H-1'), 1.84–1.72 (m, 1H, H-1'), 0.99 (t, *J* = 7.4 Hz, 3H, H-2'). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6 (C-1), 151.3 (C-7), 148.9 (C-3a), 136.1 (C-5), 108.3 (C-4), 108.0 (C-7a), 107.5 (C-6), 82.3 (C-3), 29.2 (-NMe), 27.7 (C-1'), 8.8 (C-2'). FTIR (neat) ν_{max}/cm^{-1}: 3400, 1720; HRMS *m/z* calcd for $(C_{11}H_{13}NO_2 + H)^+$ 192.1019; found 192.1021.



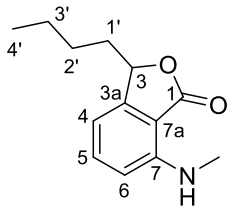
4e

3-Methyl-7-(methylamino)phthalide (4e). 140 mg (0.67 mmol) of **1e**; oven: 400 °C; preheater: 80-90 °C; T_{zone2} = 420 °C. 30% yield (36.0 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.9 Hz, 1H, H-5) 6.55–6.51 (m, 2H, H-4 and H-6), 6.52 (d, *J* = 8.4 Hz, 1H, H-6), 6.30 (br s, 1H, NH), 5.43 (q, *J* = 6.7 Hz, 1H, H-3), 2.93 (d, *J* = 5.2 Hz, 3H, -NHMe), 1.57 (d, *J* = 6.7 Hz, 3H, H-1'). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C-1), 152.8 (C-7), 149.0 (C-3a), 136.3 (C-5), 108.4 (C-4), 107.5 (C-7a), 107.4 (C-6), 77.8 (C-3), 29.3 (-NMe), 20.5 (C-1'). FTIR (neat) ν_{max}/cm^{-1}: 3400, 1725; HRMS *m/z* calcd for $(C_{10}H_{11}NO_2 + H)^+$ 178.0863; found 178.0863.



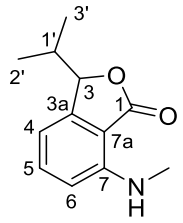
4f

3-Propyl-7-(methylamino)phthalide (4f). 65 mg (0.275 mmol) of **1f**; oven: 400 °C; preheater: 80-90 °C; T_{zone2} = 420 °C. 27% yield (15.0 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.8 Hz, 1H, H-5), 6.55–6.51(m, 2H, H-6 and H-4), 6.31 (br s, 1H, NH), 5.35 (dd, *J* = 7.9, 4.0 Hz, 1H, H-3), 2.93 (d, *J* = 5.2 Hz, 3H, -NHMe), 2.00–1.89 (m, 1H, H-1'), 1.77–1.65 (m, 1H, H-1'), 1.55–1.46 (m, 2H, H-2'), 0.97 (t, *J* = 7.3, 3H, H-3'). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7 (C-1), 151.8 (C-7), 149.0 (C-3a), 136.2 (C-5), 108.4 (C-4), 107.9 (C-7a), 107.6 (C-6), 81.3 (C-3), 37.0 (C-1'), 29.4 (-NMe), 18.3 (C-2'), 14.0 (C-3'). FTIR (neat) ν_{max}/cm^{-1}: 3400, 1720; HRMS *m/z* calcd for $(C_{12}H_{15}NO_2 + H)^+$ 206.1176; found 206.1179.



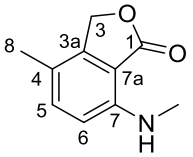
4g

3-Butyl-7-(methylamino)phthalide (4g). 35 mg (0.113 mmol) of **1g**; oven: 650 °C; preheater: 100-120 °C; T_{zone2} = 625 °C. 20% yield (4.9 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.8 Hz, 1H, H-5), 6.55–6.31 (m, 2H, H-6 and H-4), 6.31 (br s, 1H, NH), 5.35 (dd, *J* = 7.8, 4.1 Hz, 1H, H-3), 2.94 (d, *J* = 5.2 Hz, 3H, -NHMe), 2.04–1.92 (m, 1H, H-1'), 1.78–1.66 (m, 1H, H-1'), 1.46–1.32 (m, 4H, H-2' and H-3'), 0.90 (t, *J* = 7.1, 3H, H-4'). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (C-1), 151.7 (C-7), 148.9 (C-3a), 136.1 (C-5), 108.2 (C-4), 107.8 (C-7a), 107.5 (C-6), 81.4 (C-3), 34.5 (C-1'), 29.2 (-NMe), 26.8 (C-2'), 22.5 (C-3'), 13.9 (C-4'). FTIR (neat) ν_{max}/cm^{-1}: 3400, 1730; HRMS *m/z* calcd for $(C_{13}H_{17}NO_2 + H)^+$ 220.1332; found 220.1332.



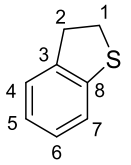
4h

3-Isopropyl-7-(methylamino)phthalide (4h). 52.5 mg (0.18 mmol) of **1h**; oven: 650 °C; preheater: 80-90 °C; T_{zone2} = 625 °C. 21% yield (7.6 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (t, *J* = 7.5 Hz, 1H, H-5), 6.56–6.32 (m, 2H, H-6 and H-4), 6.32 (br s, 1H, NH), 5.24 (d, *J* = 3.6 Hz, 1H, H-3), 2.93 (d, *J* = 5.2 Hz, 3H, -NHMe), 2.26–2.18 (m, 1H, H-1'), 1.11 (d, *J* = 6.9 Hz, 3H, H-3'), 0.81 (d, *J* = 6.9 Hz, 3H, H-2'). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7 (C-1), 150.4 (C-7), 148.9 (C-3a), 136.0 (C-5), 108.4 (C-4), 108.3 (C-7a), 108.0 (C-6), 85.6 (C-3), 32.3 (C-1'), 29.2 (-NMe), 18.7 (C-3'), 15.5 (C-2'). FTIR (neat) ν_{max}/cm^{-1}: 3400, 1730; HRMS *m/z* calcd for $(C_{12}H_{15}NO_2 + H)^+$ 206.1176; found 206.1175.



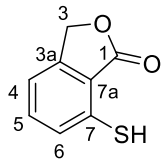
4i

7-(Methylamino)-4-methylphthalide (4i). 60 mg (0.22 mmol) of **1i**; oven: 650 °C; preheater: 90-100 °C; T_{zone2} = 625 °C. 27% yield (10.6 mg), amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.3 Hz, 1H, H-5), 6.48 (d, *J* = 8.3 Hz, 1H, H-6), 6.10 (br s, 1H, NH), 5.14 (s, 2H, H-3), 2.92 (d, *J* =5.2 Hz, 3H, -NHMe), 2.15 (s, 3H, H-8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (C-1), 147.3 (C-7), 146.1 (C-3a), 137.1 (C-5), 117.2 (C-4), 108.6 (C-7a), 107.3 (C-6), 69.1 (C-3), 29.4 (-NMe), 16.3 (C-8); FTIR (neat) ν_{max}/cm^{-1}: 3400, 1725; HRMS *m/z* calcd for $(C_{10}H_{11}NO_2 + H)^+$ 206.1176; found 206.1175.



8

2,3-Dihydrobenzo[*b*]thiophene (8). 100 mg (0.28 mmol) of diester **7a**; oven: 625 °C; preheater: 200 °C; T_{zone2} = 600 °C. 25% yield (19 mg), colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.08 (m, 3H, H-5–H-7), 7.01 (td, *J* = 7.4, 1.2 Hz, 1H, H-4), 3.39–3.25 (m, 4H, H-1 and H-2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6 (C-8), 140.2 (C-3), 127.4 (C-5), 124.5 (C-6), 124.2 (C-4), 122.3 (C-7), 36.3 (C-2), 33.4 (C-1). The spectral data are in agreement with the previously published values.[S10]



10

7-Mercaptophthalide (10). ***Method 1*****:** 100 mg (0.30 mmol) of diester **7b**; oven: 650 °C; preheater: 140 °C; T_{zone2} = 600 °C. 9% yield (9 mg), white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, *J* = 7.7 Hz, 1H, H-5), 7.30 (dd, *J* = 7.9, 0.6 Hz, 1H, H-4), 7.16 (dd, *J* = 7.5, 0.8 Hz, 1H, H-6), 6.27 (s, 1H, SH), 5.25 (s, 2H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C-1), 148.1 (C-3a), 137.2 (C-7), 134.1 (C-5), 128.5 (C-6), 119.9 (C-4), 117.8 (C-7a), 68.9 (C-3). The spectral data are in agreement with the previously published values.[S11]

Method 2**:** 100 mg (0.30 mmol) of **9a**; oven: 650 °C; preheater: 90-100 °C; T_{zone2} = 625 °C. 9% ^{1}H NMR yield.

Method 3**:** 100 mg (0.30 mmol) of diester **9b**; oven: 650 °C; preheater: 80-100 °C; T_{zone2} = 625 °C. 8.5% ^{1}H NMR yield.

9. References and notes

S1 N. S. Radulović, A. B. Miltojević, M. McDermott, S. Waldren, J. A. Parnell, M. M. G. Pinheiro, P. D. Fernandes and F. de Sousa Menezes, *J. Ethnopharmacol.*, 2011, **135**, 610–619.

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S3 W. Li, Z. Duan, R. Jiang and A. Lei, *Org. Lett.*, 2015, **17**, 1397–1400.

S4 A. B. Miltojević and N. S. Radulović, *RSC Adv.*, 2015, **5**, 53569–53585.

S5 Due to the hindered rotation around the N-N bond, NMR spectra of compounds **1b**–**1f** contain two sets of signals of unequal intensities (ca. 10:1), belonging to (*E*) and (*Z*)-isomers. Only the shifts of the more abundant diastereoisomer are listed.

S6 C.-C. Chiang, T.-C. Chang, H.-J. Tsai and L.-Y. Hsu, *Chem. Pharm. Bull. (Tokyo).*, 2008, **56**, 369–373.

S7 D. Dallinger and C. O. Kappe, *Nat. Protoc.*, 2017, **12**, 2138–2147.

S8 Y. Li, K. J. Jardine, R. Tan, D. Song and V. M. Dong, *Angew. Chemie Int. Ed.*, 2009, **48**, 9690–9692.

S9 J.-F. Bonfanti and D. Craig, *Tetrahedron Lett.*, 2005, **46**, 3719–3723.

S10 D. Madec, F. Mingoia, C. Macovei, G. Maitro, G. Giambastiani and G. Poli, *European J. Org. Chem.*, 2005, **2005**, 552–557.

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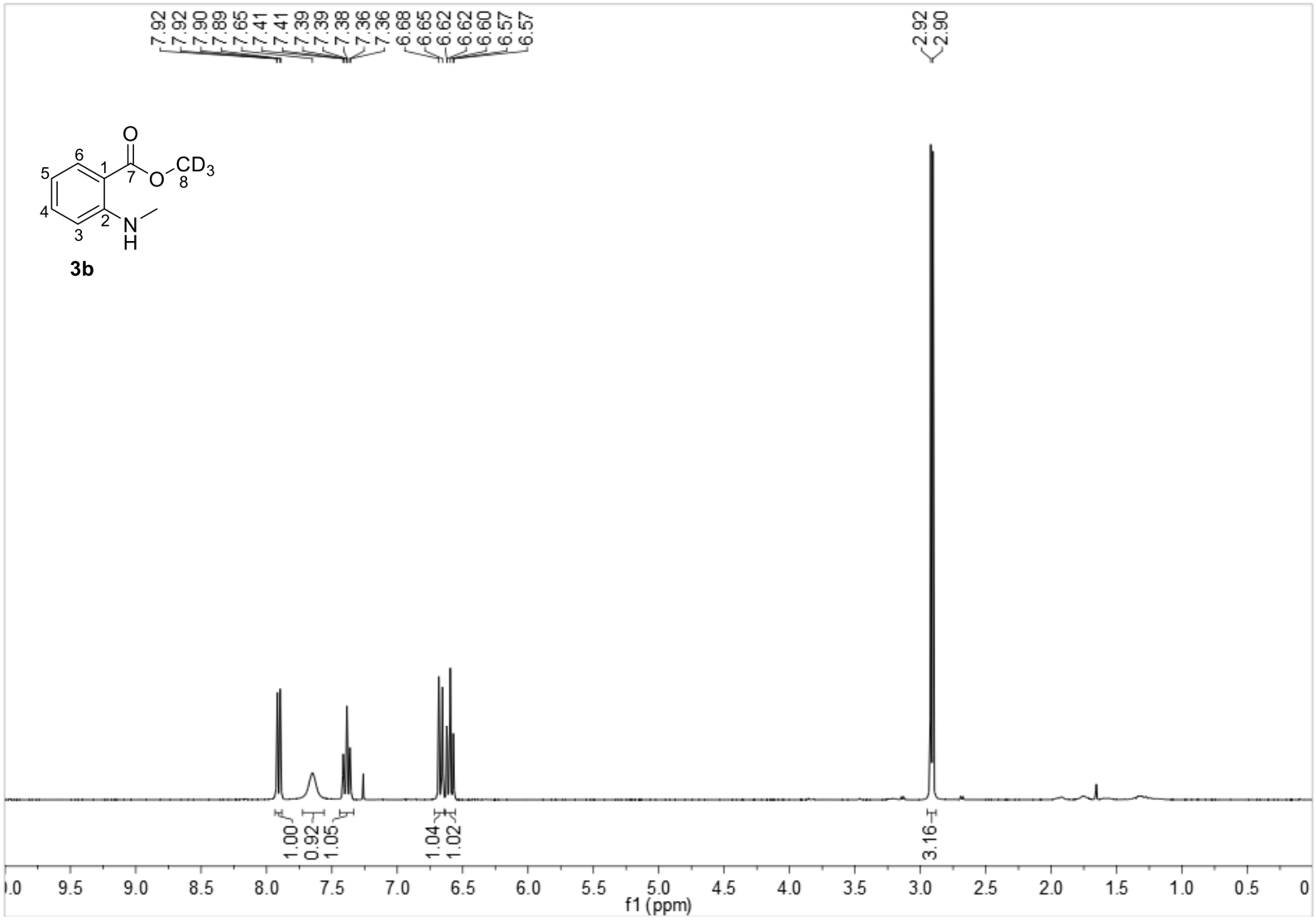
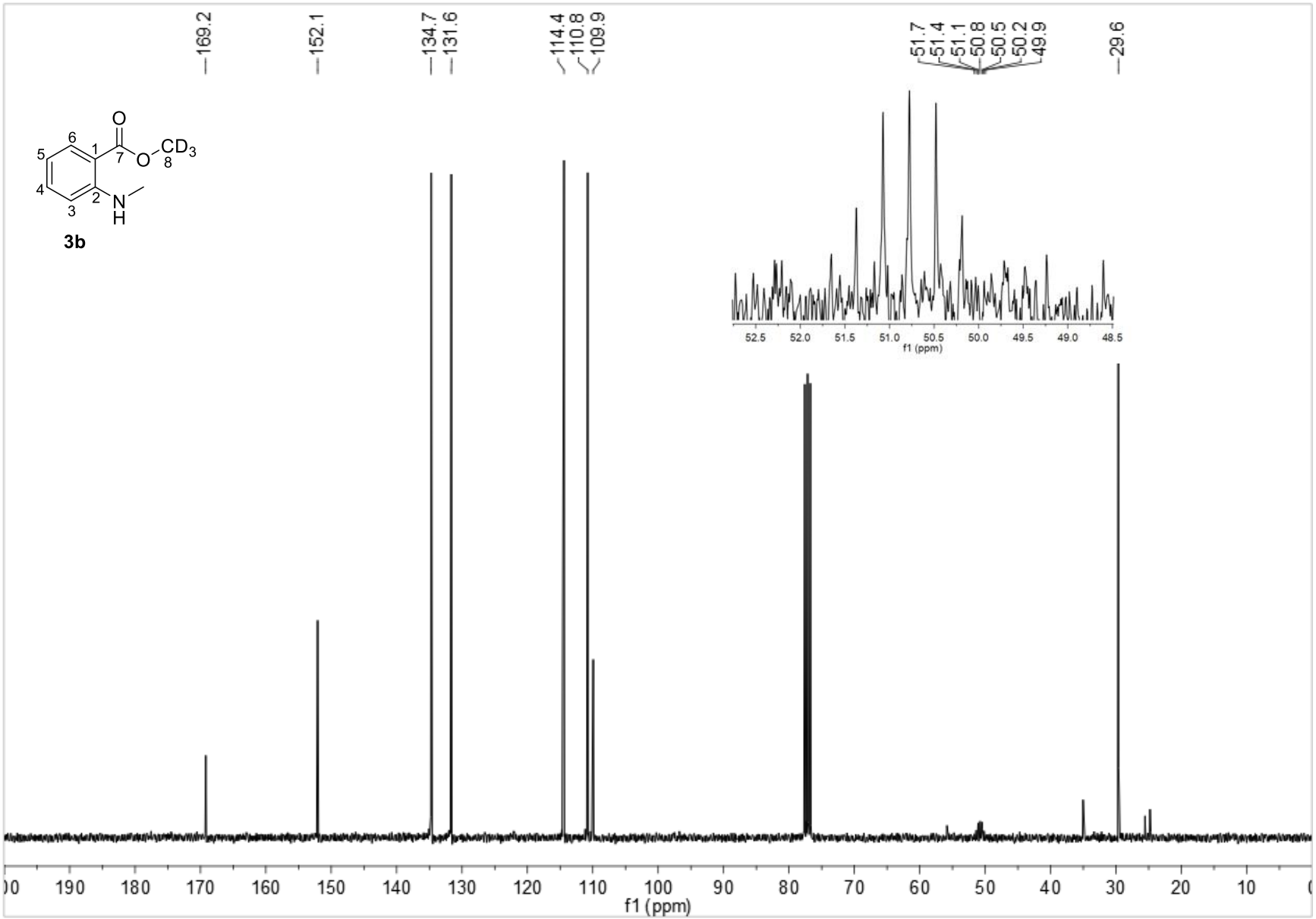
10. ^{1}H / ^{13}C NMR spectra ($CDCl_3$)

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3b
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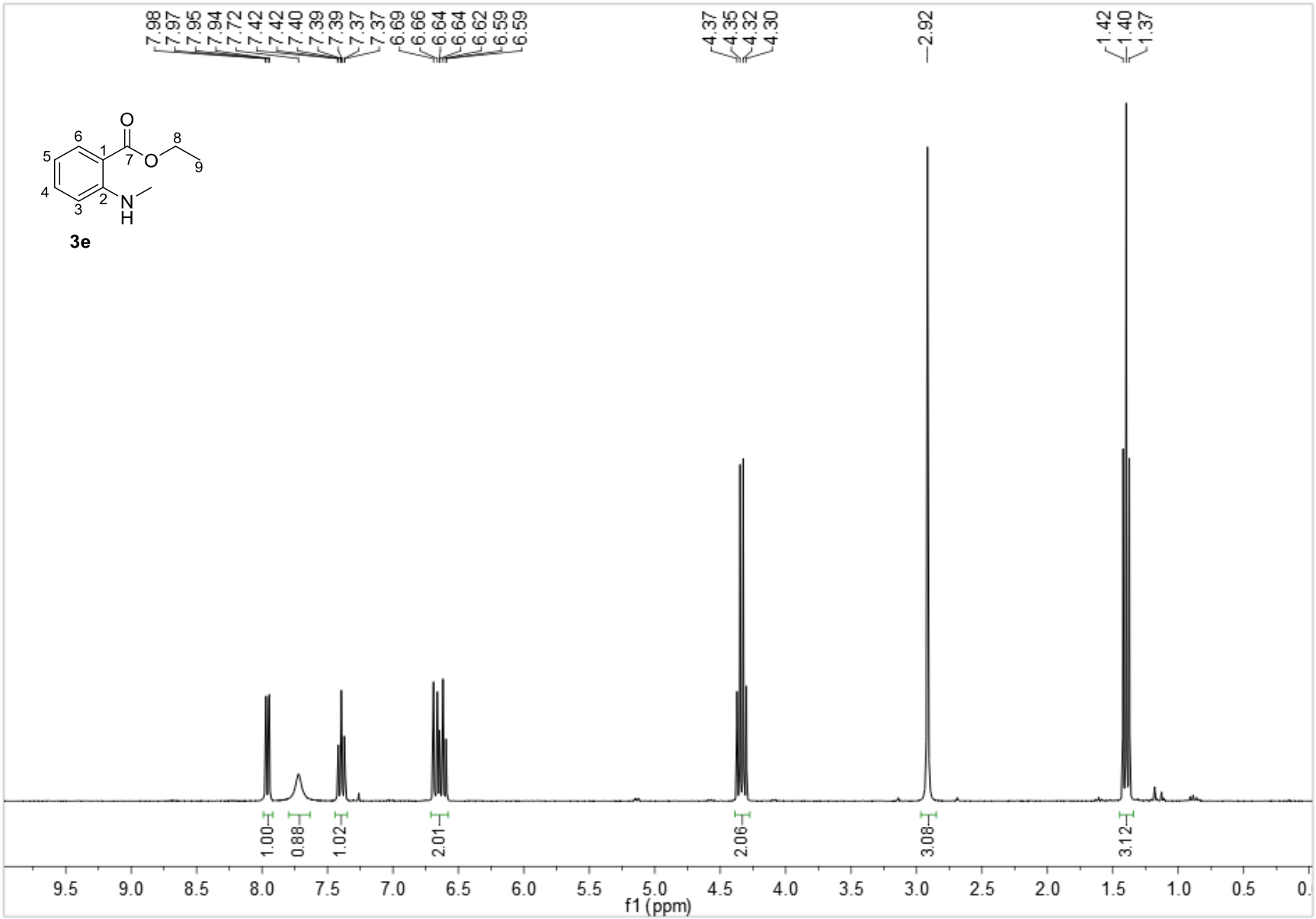
f1 (ppm)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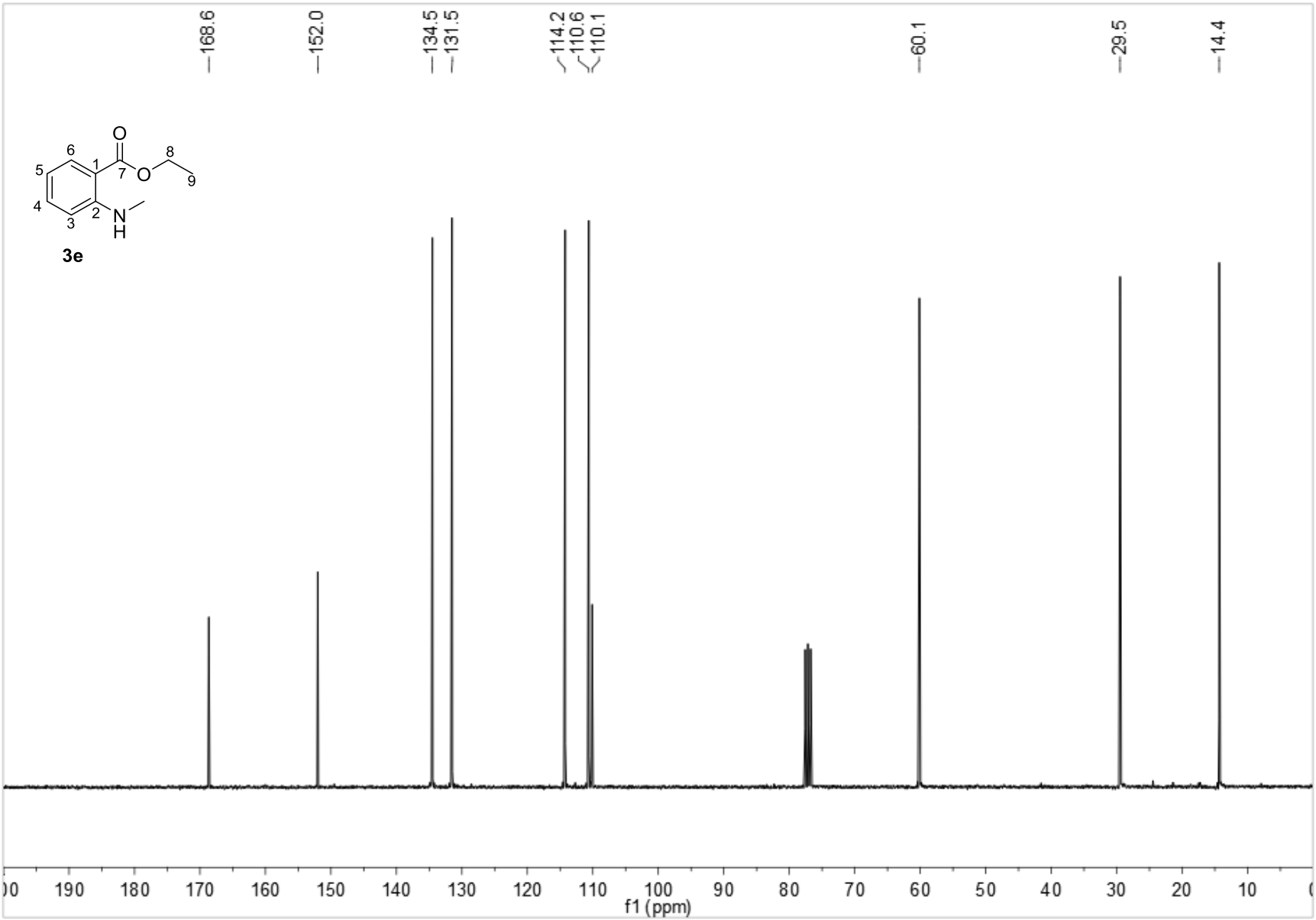
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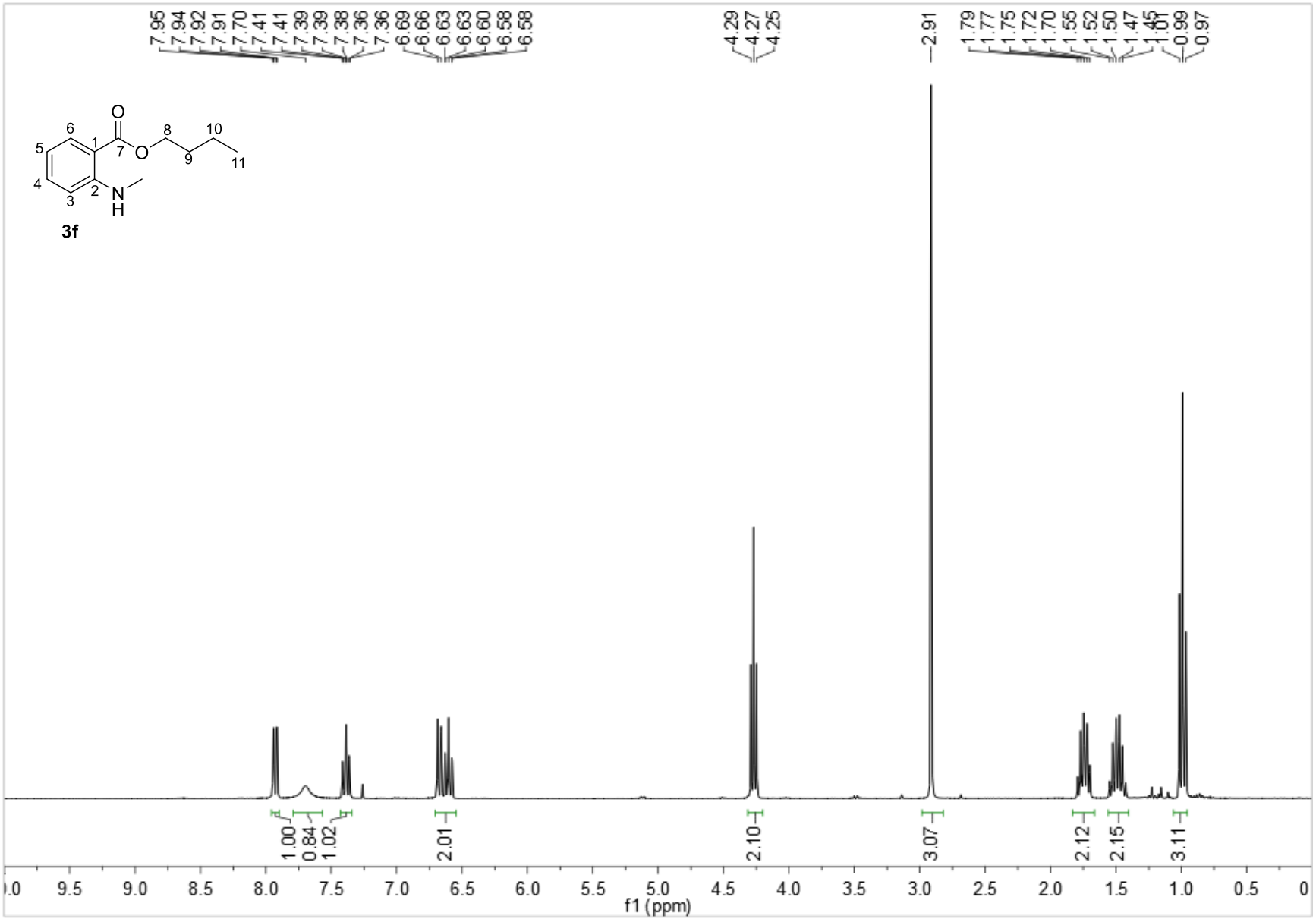
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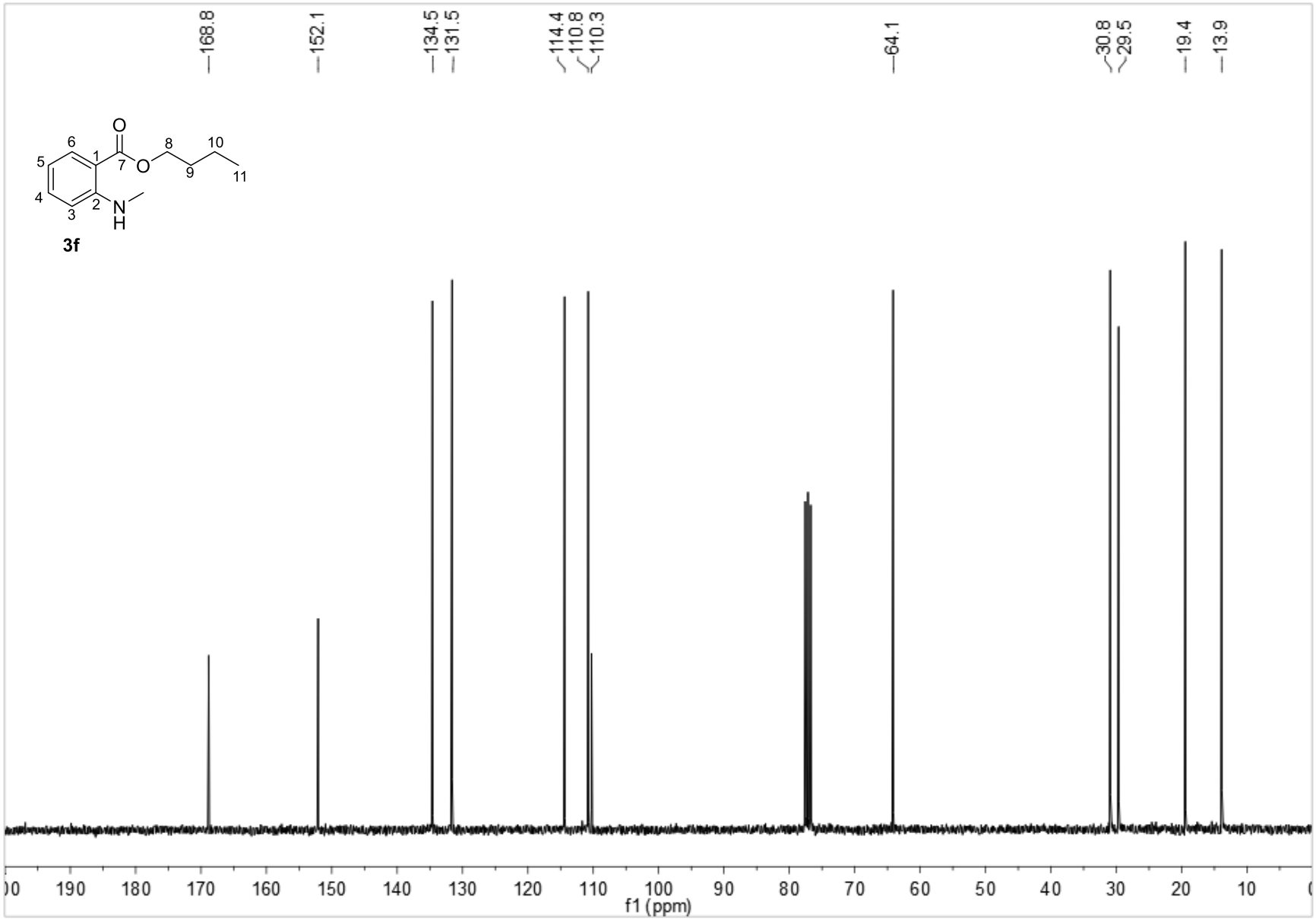
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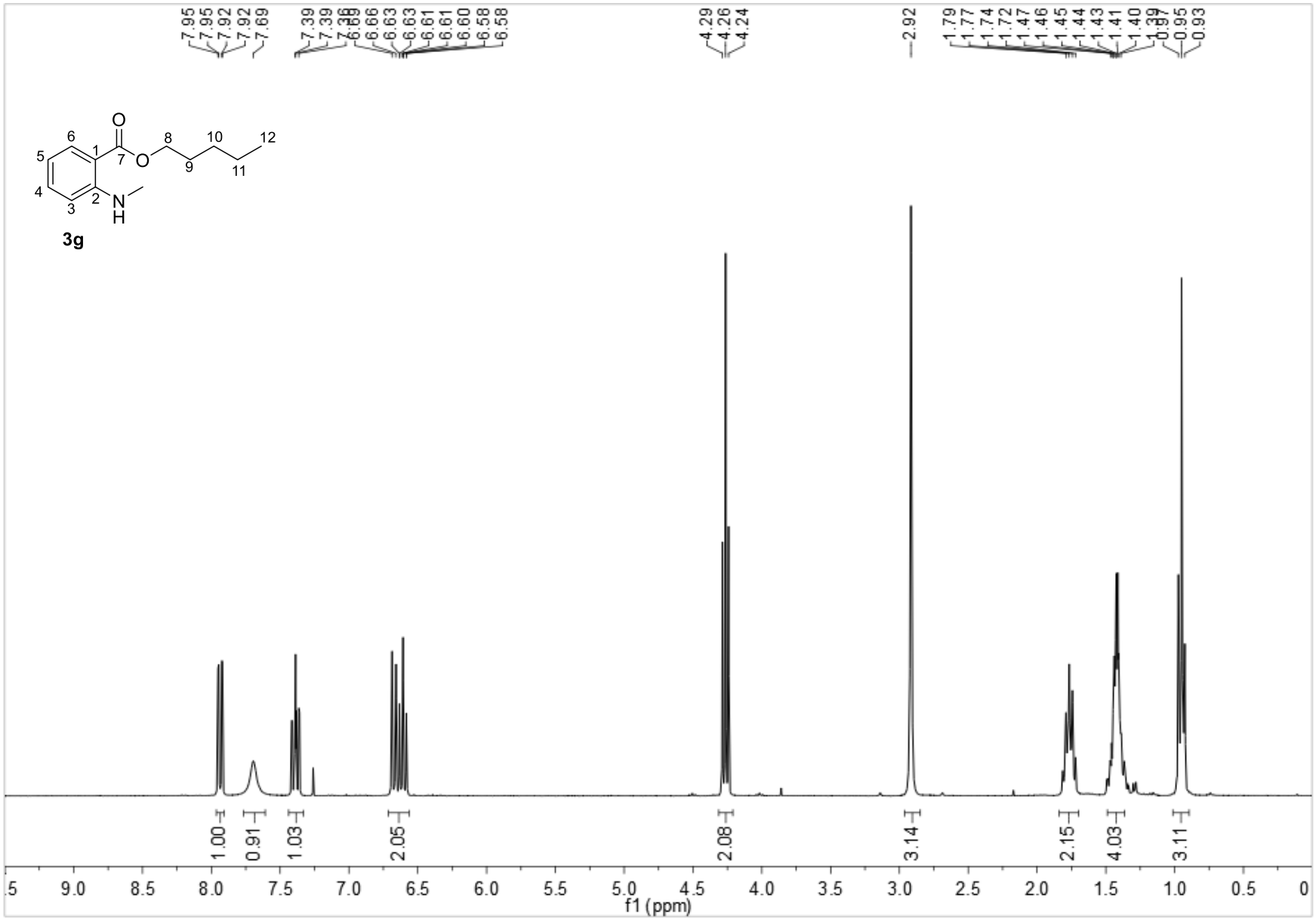
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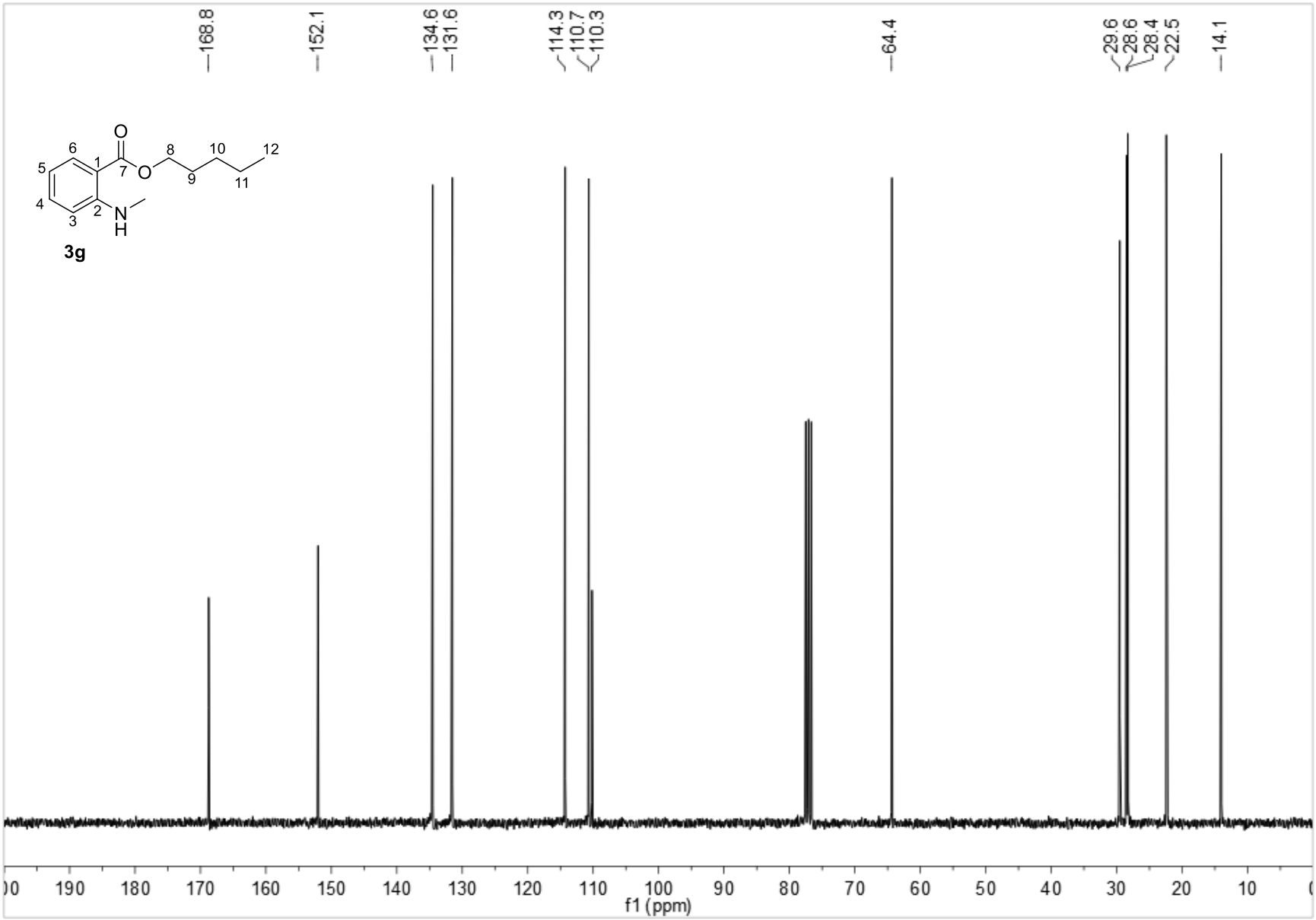
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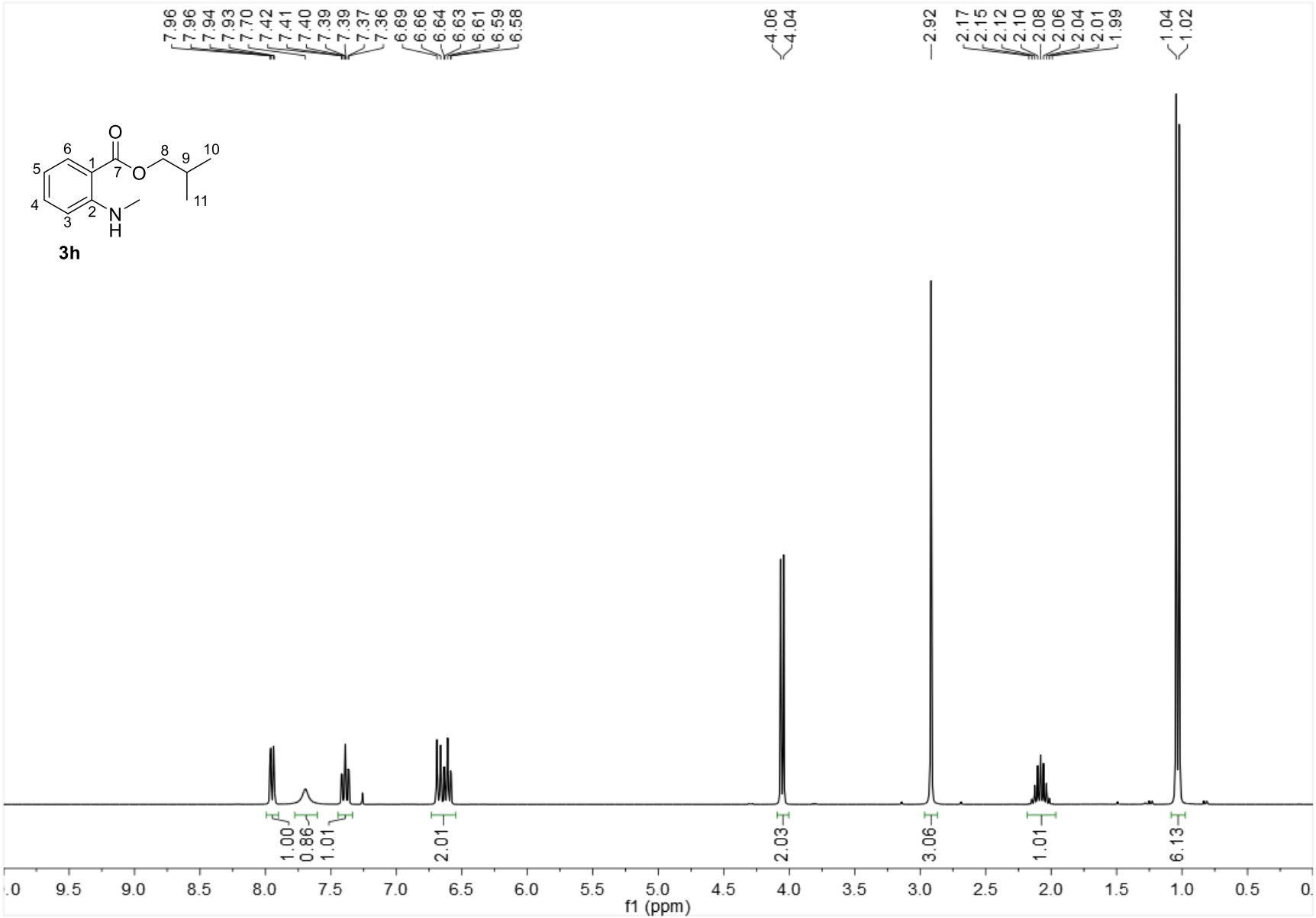
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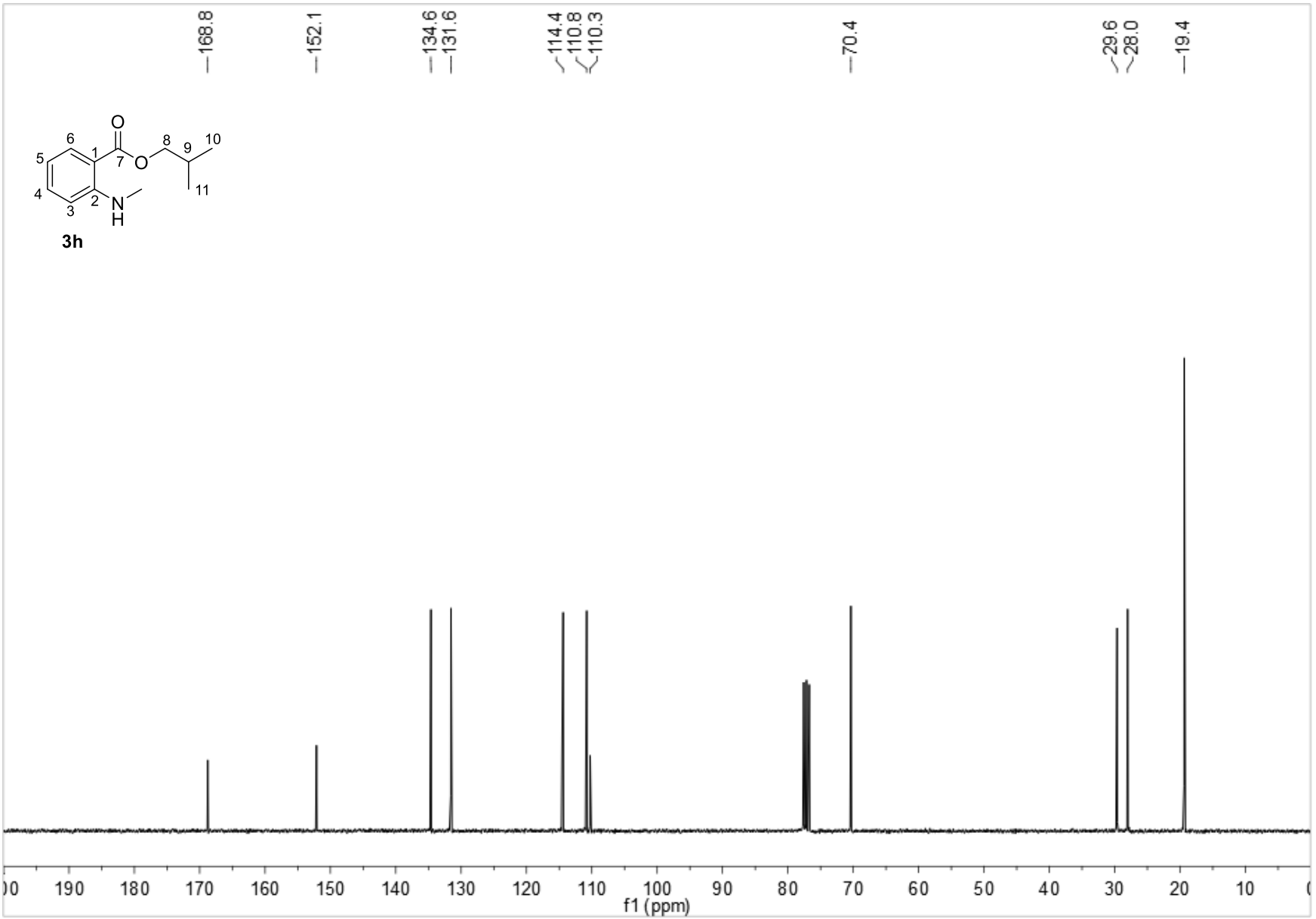
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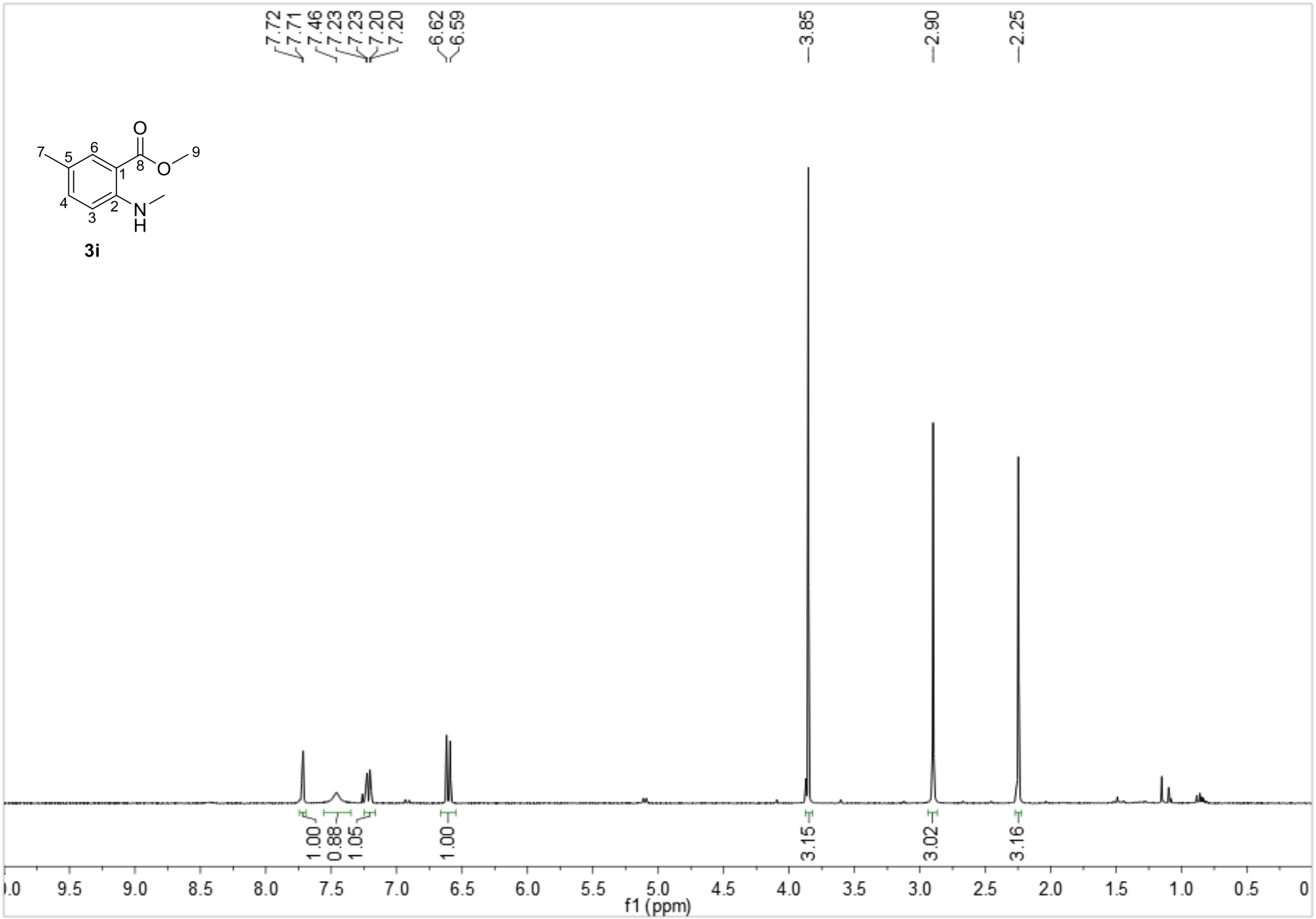
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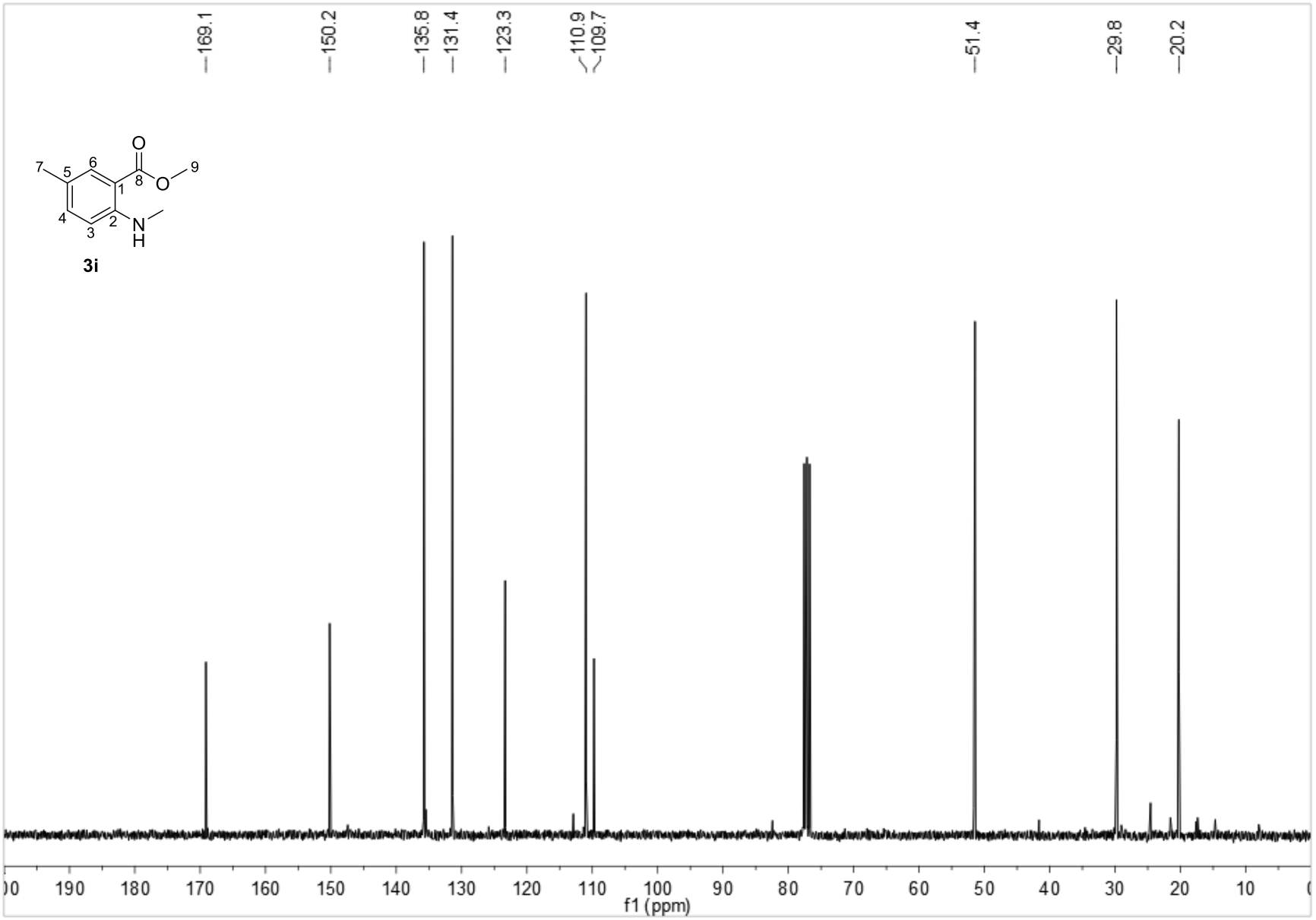
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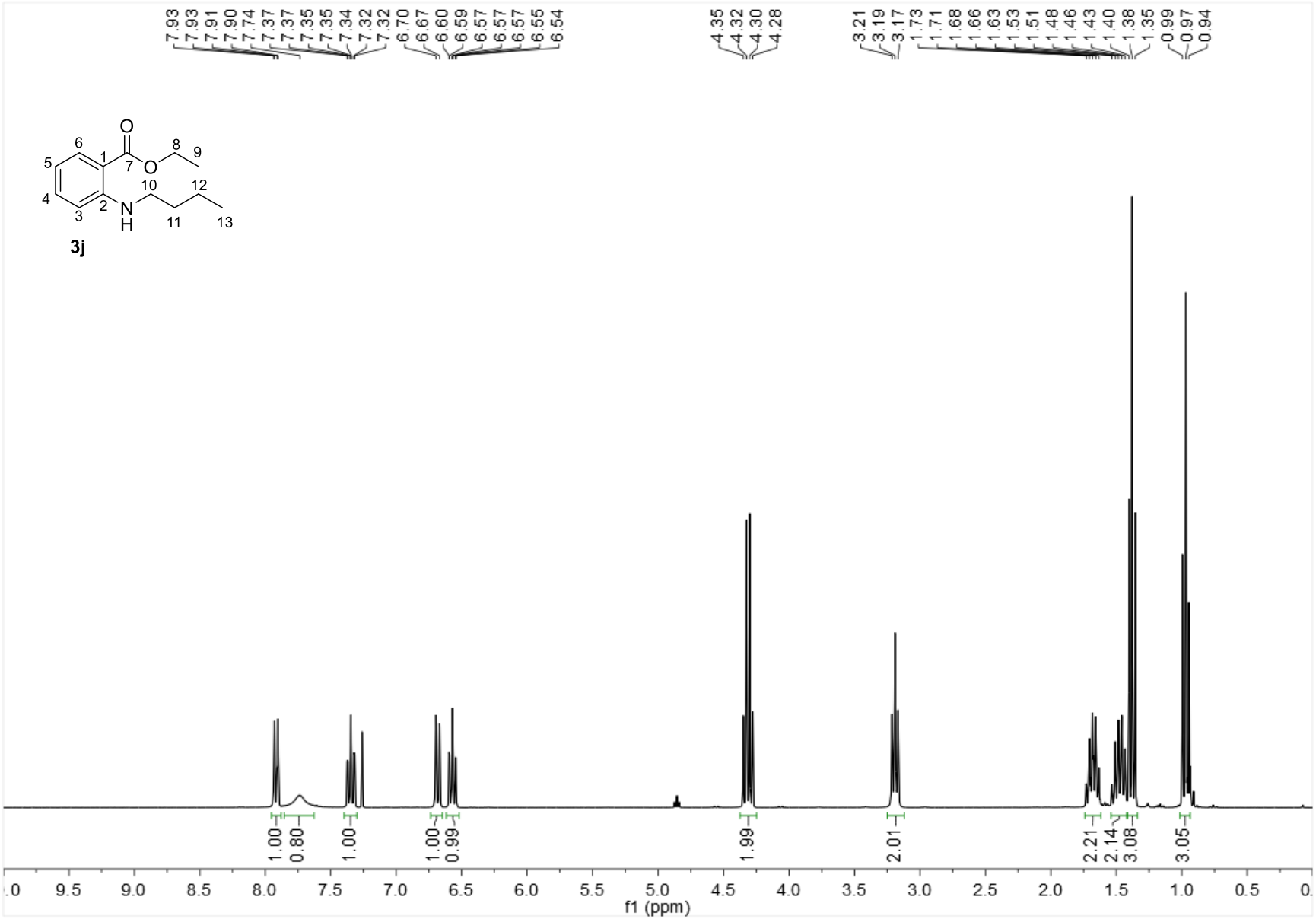
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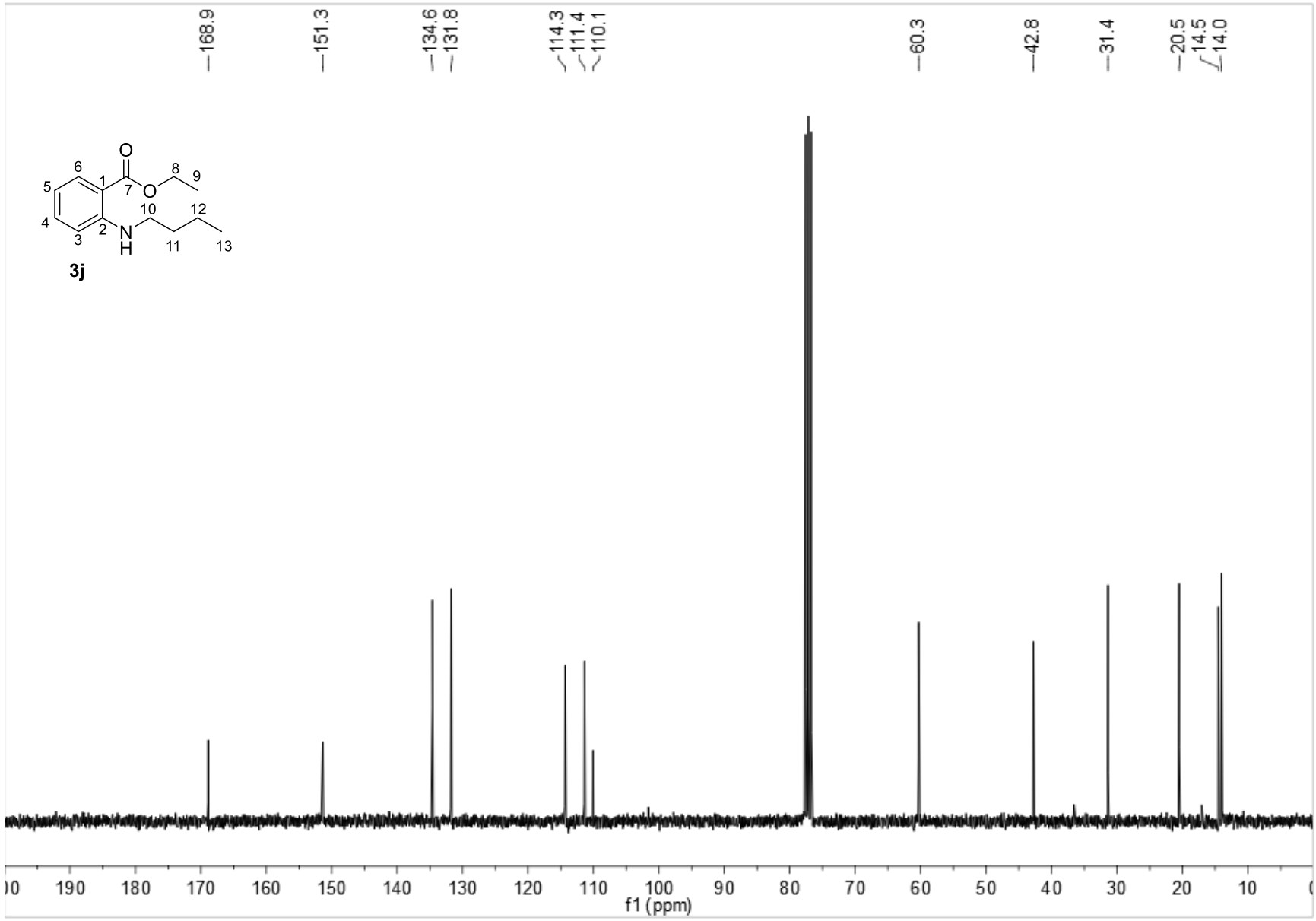
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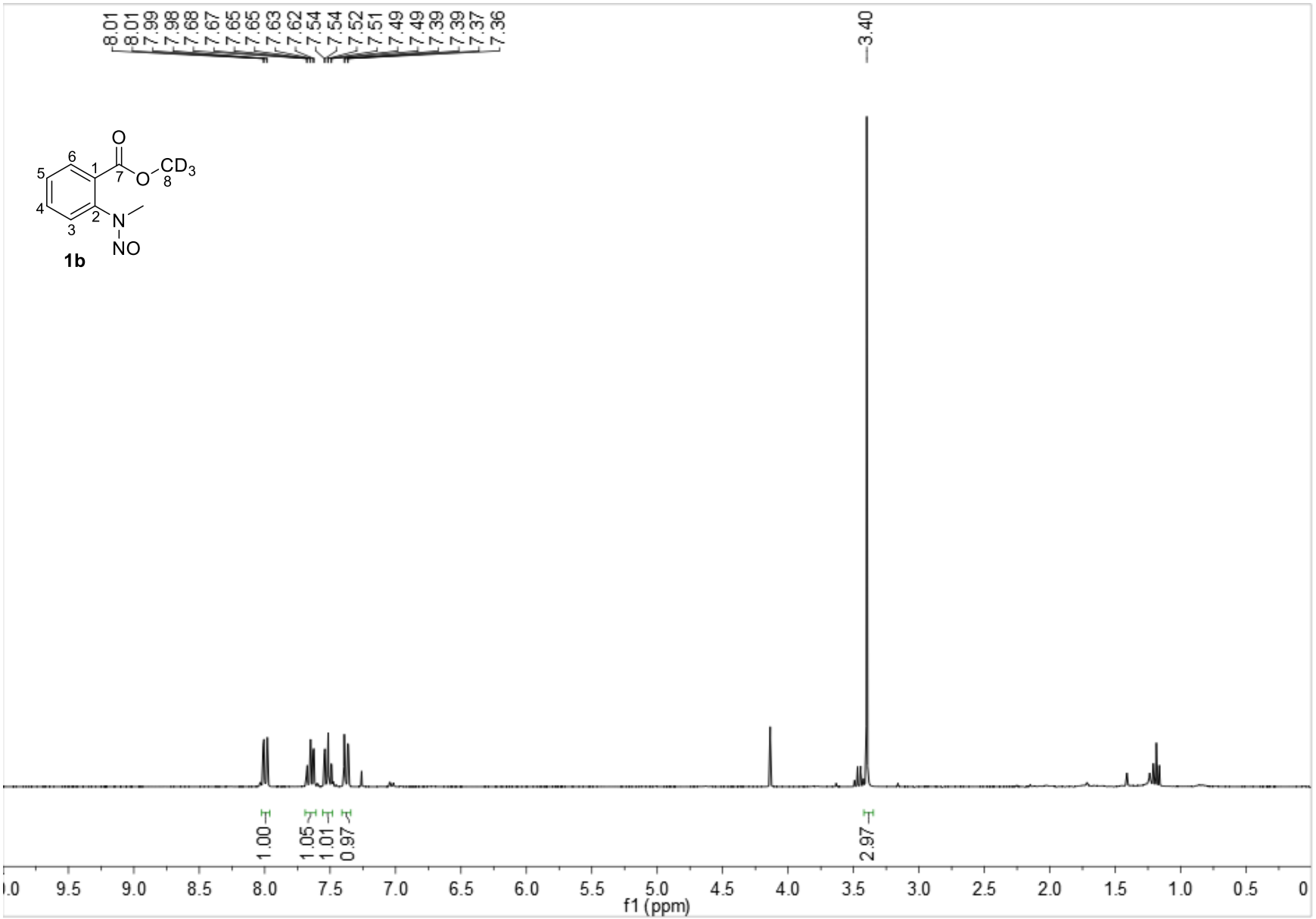
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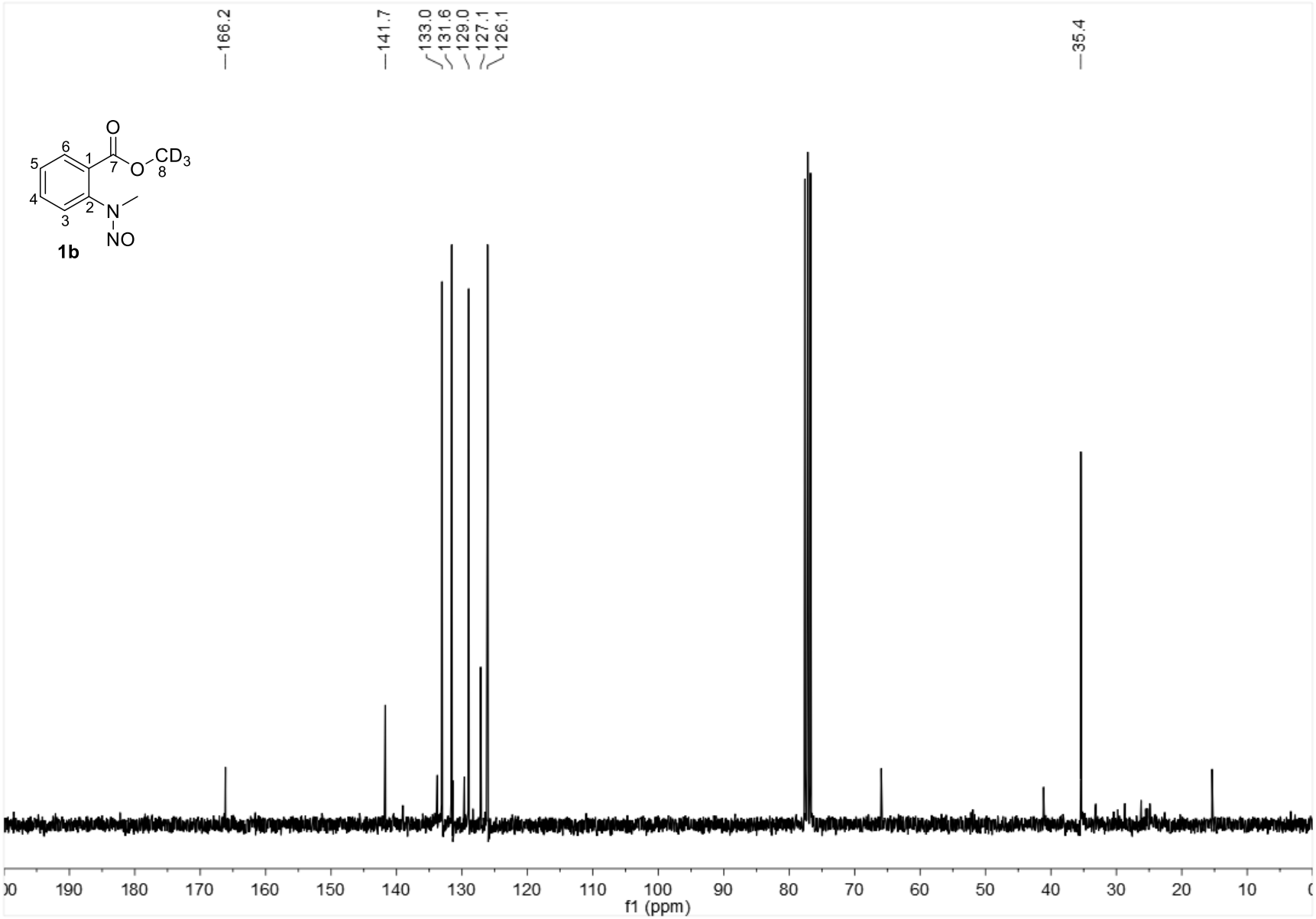
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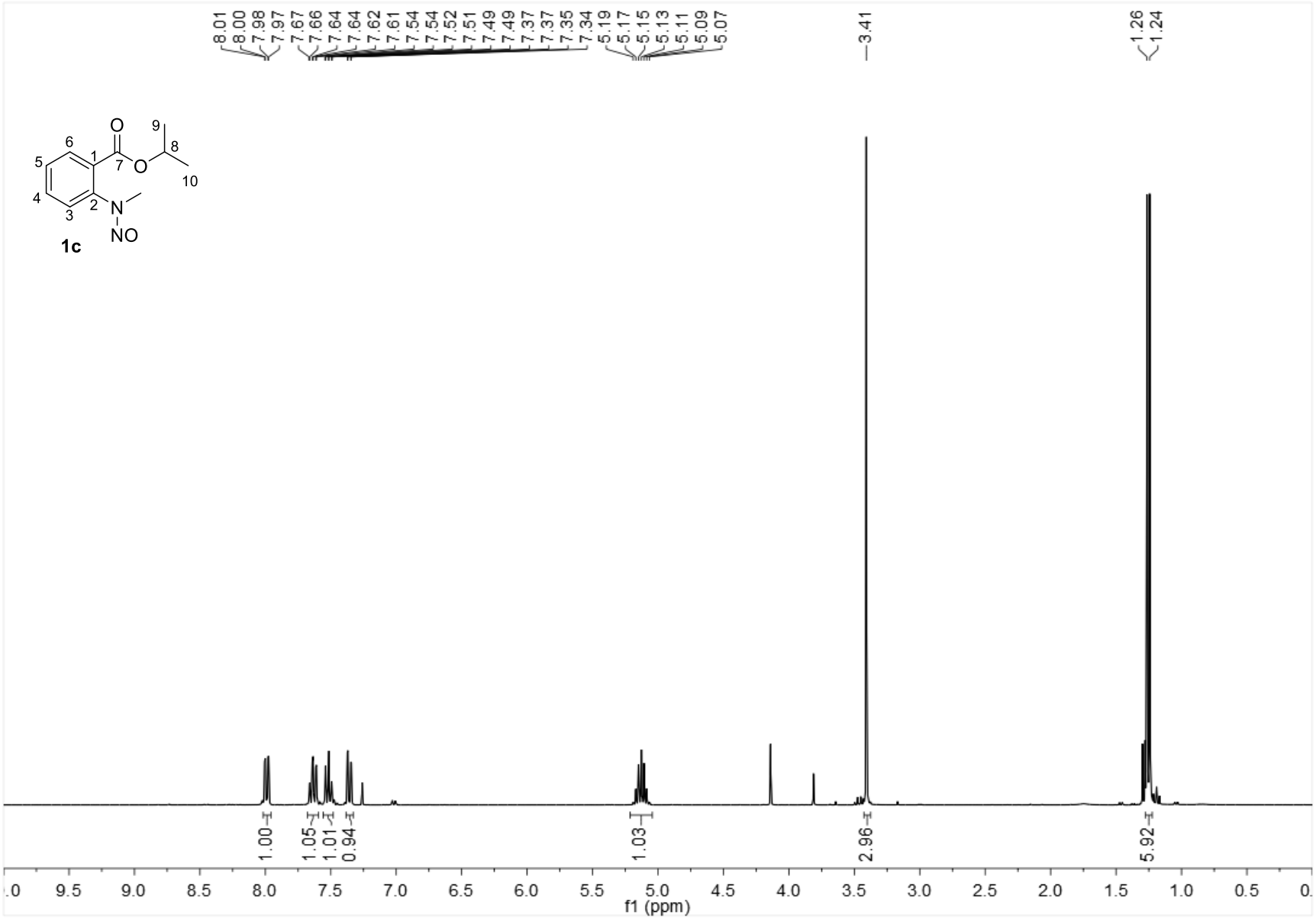
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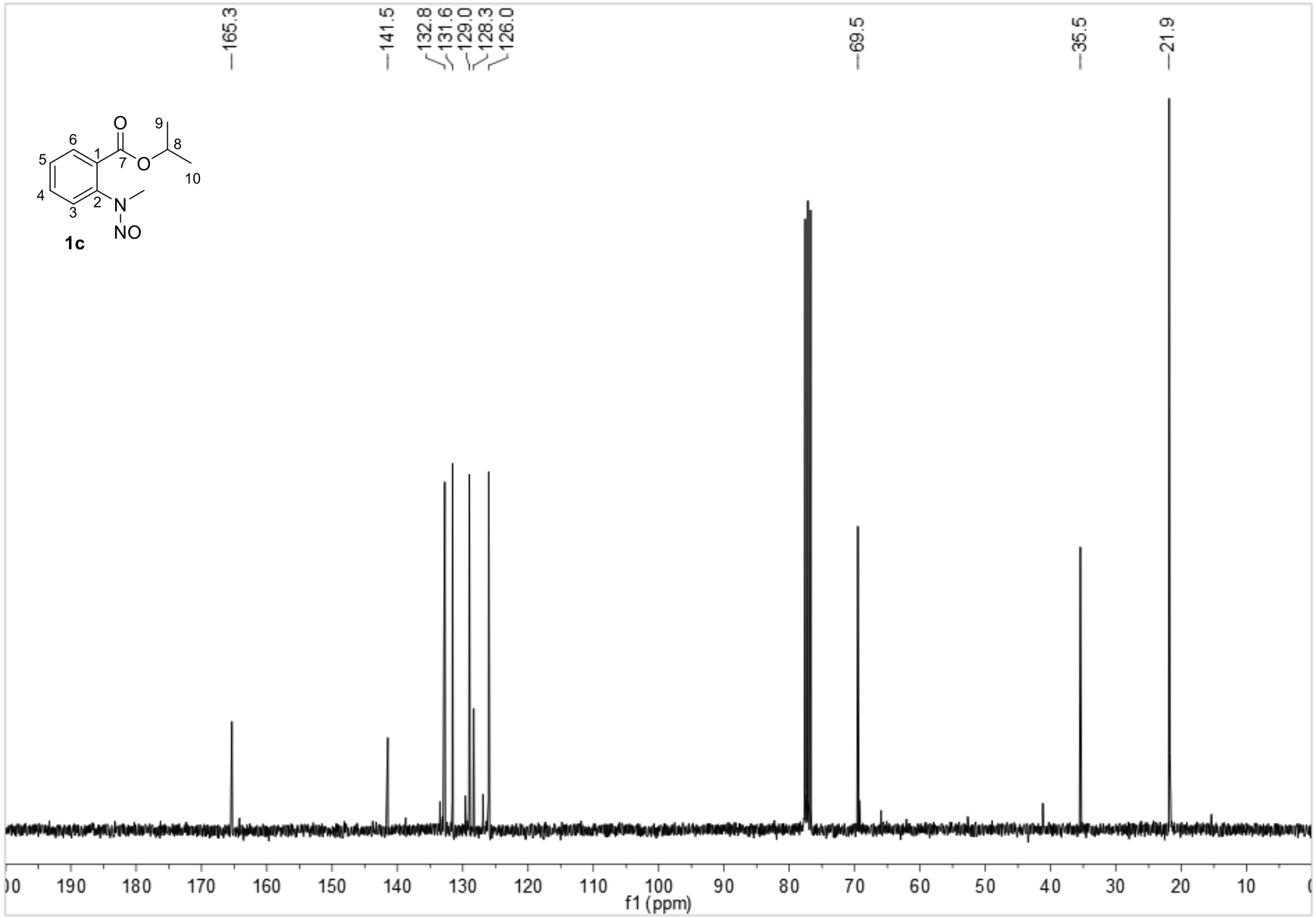
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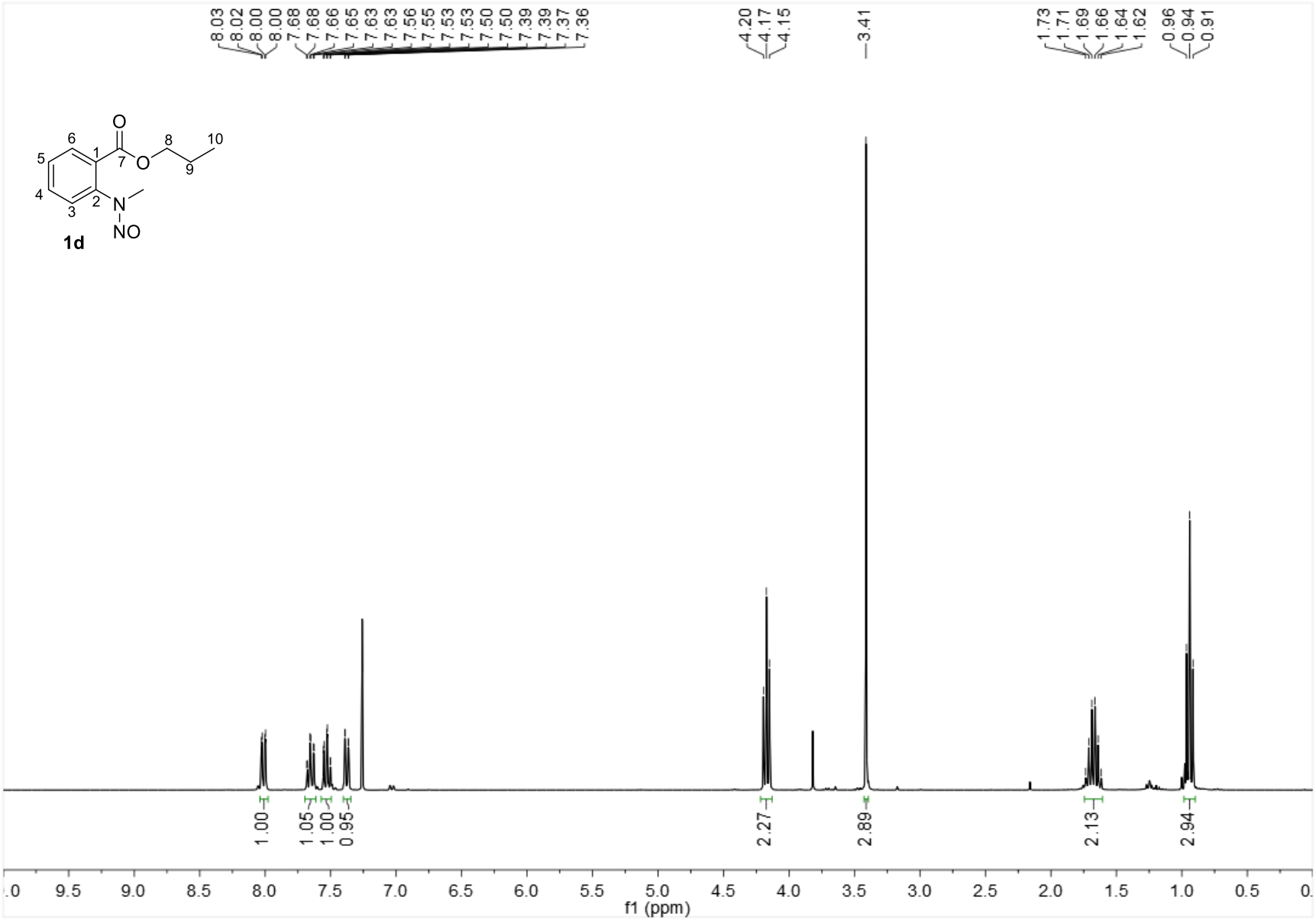
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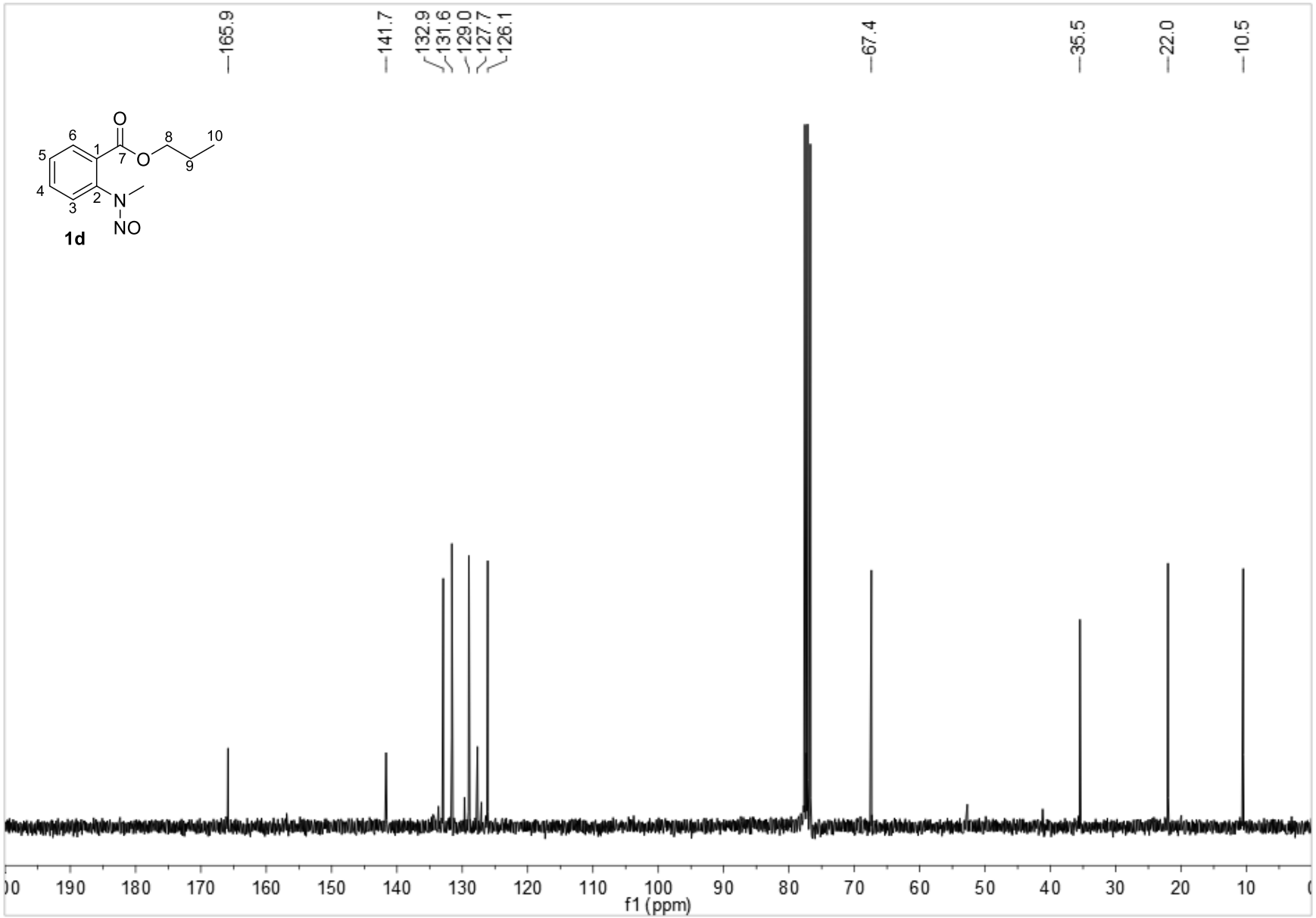
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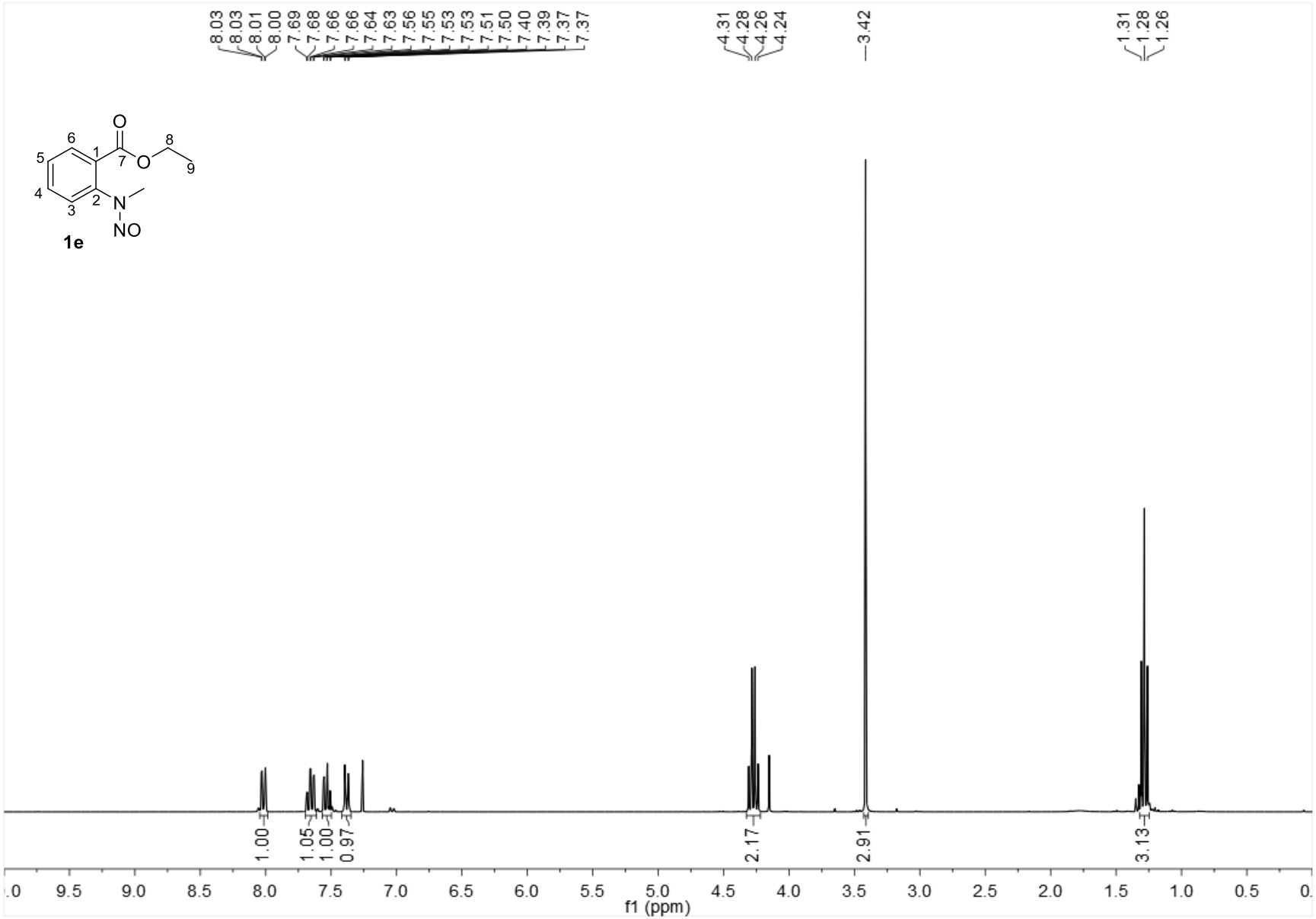
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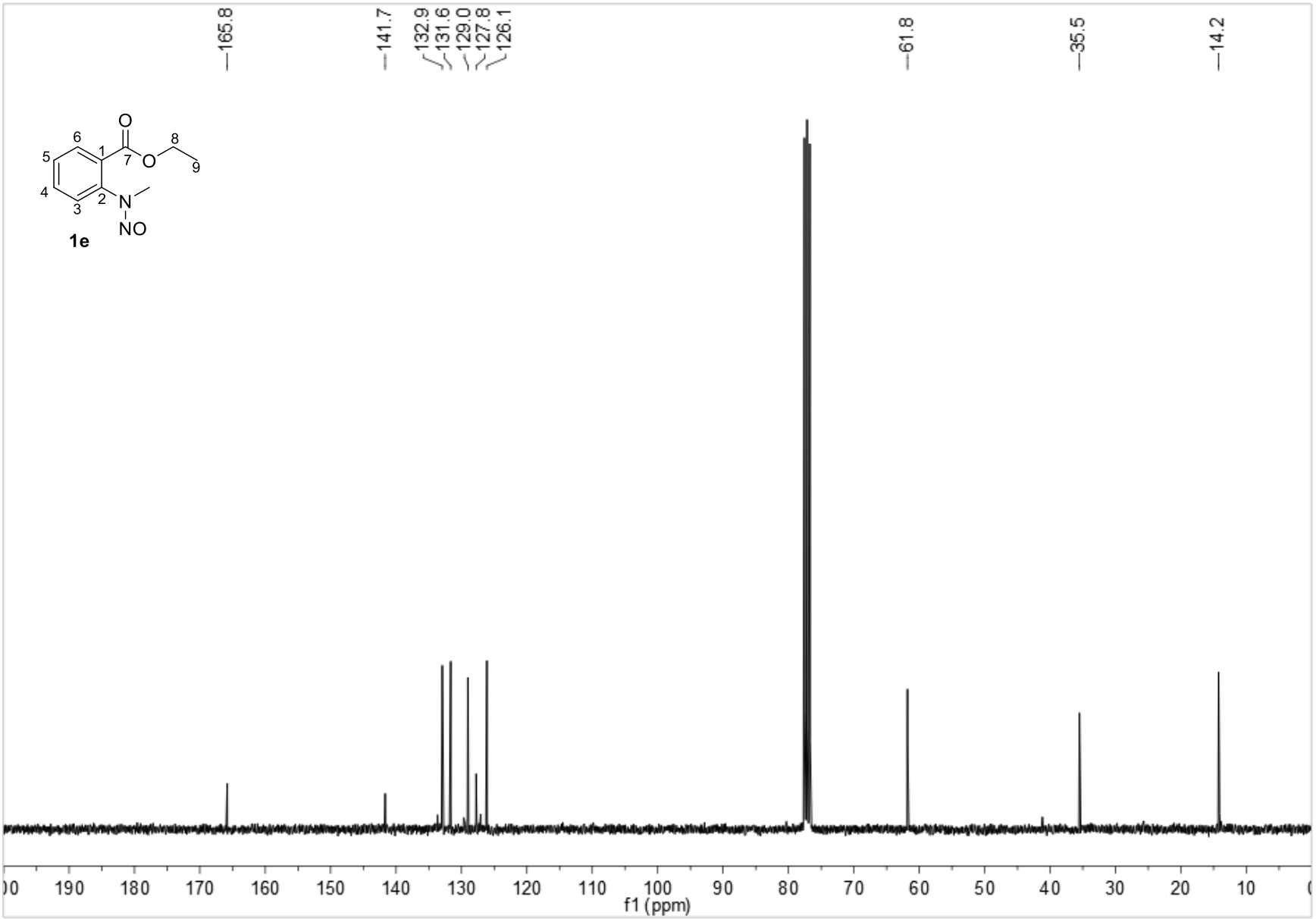
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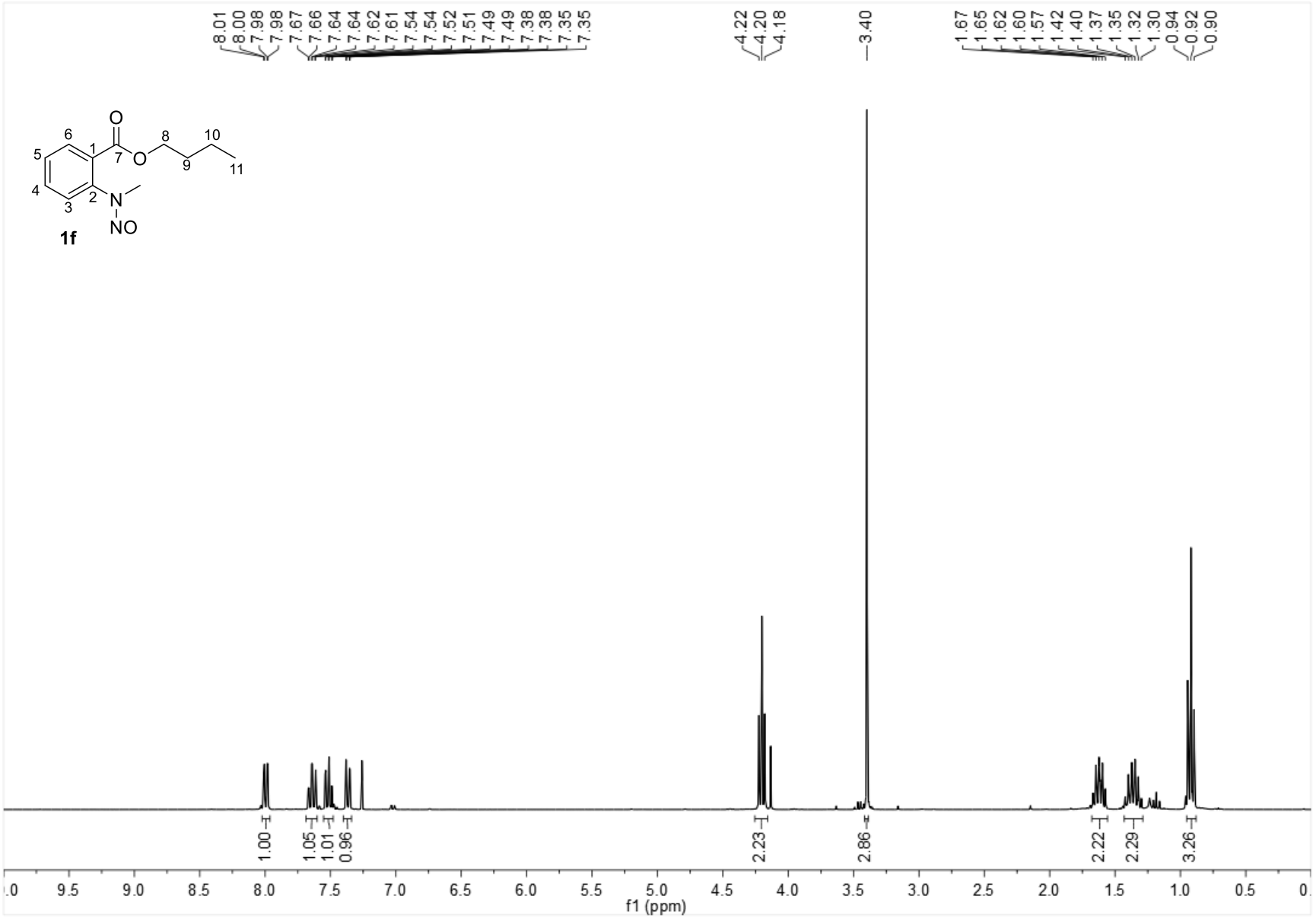
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7.98
7.98
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7.64
7.64
7.62
7.61
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7.54
7.52
7.51
7.49
7.49
7.38
7.38
7.35
7.35
4.22
4.20
4.18
3.40
1.67
1.65
1.62
1.60
1.57
1.42
1.40
1.37
1.35
1.32
1.30
0.94
0.92
0.90
O
6
1
8
10
5
7
O
9
11
4
3
2
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2.22
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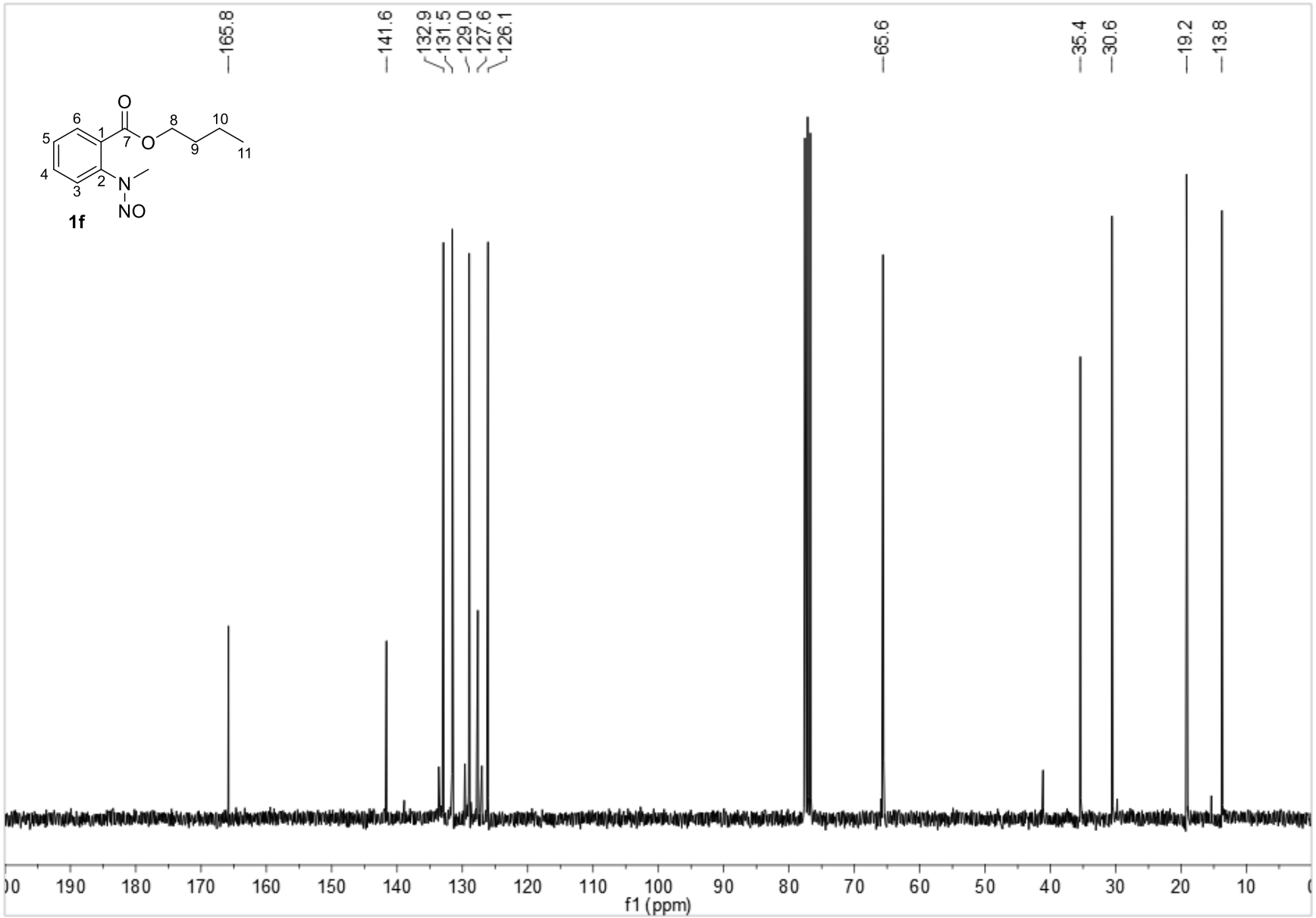
3.26
f1 (ppm)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127.6
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65.6
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19.2
13.8
O
6
1
7
O
8
10
5
9
11
4
2
N
3
NO
1f
190
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120
110
100
90
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60
50
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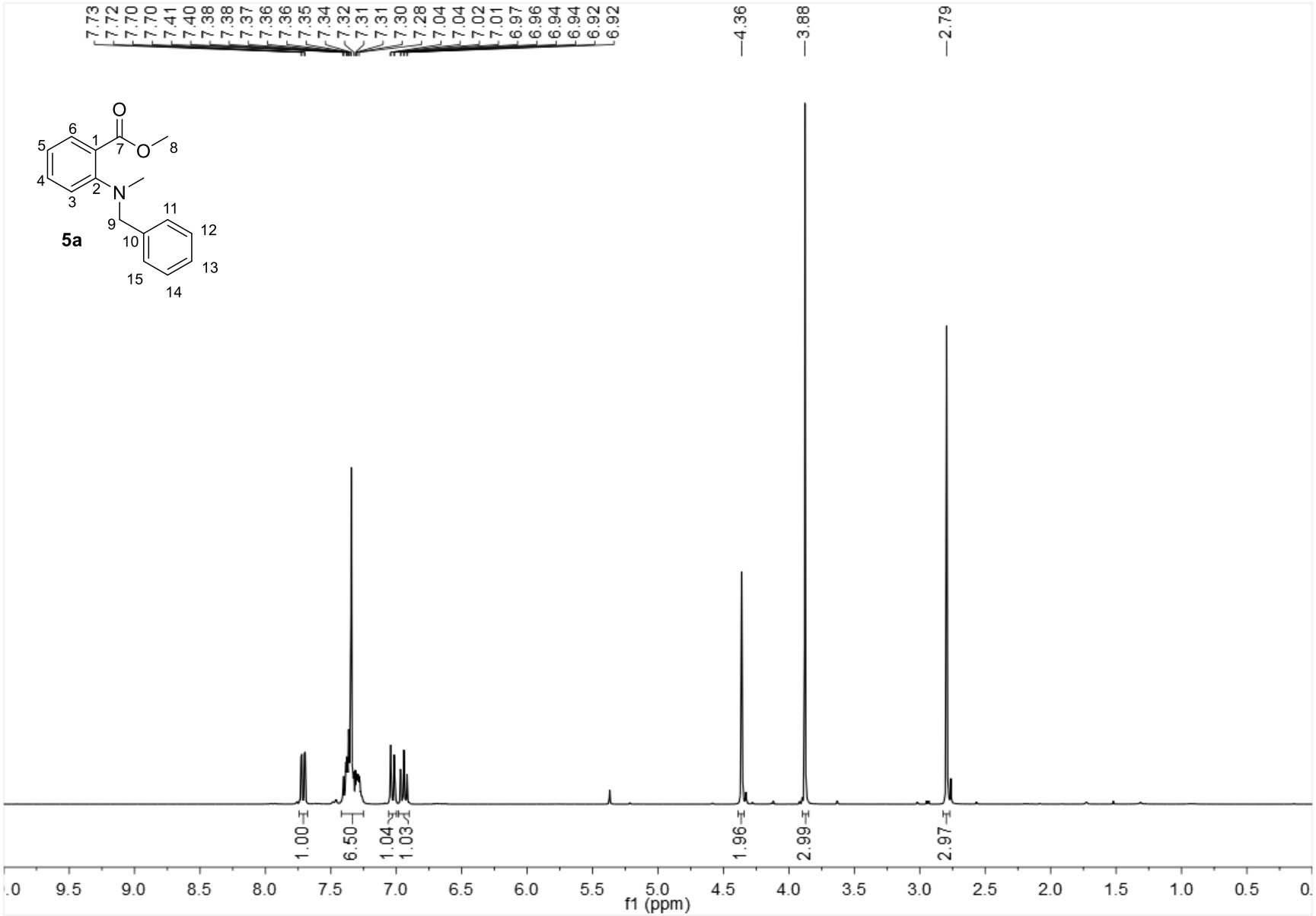
f1 (ppm)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7.32
7.31
7.31
7.30
7.28
7.04
7.04
7.02
7.01
6.97
6.96
6.94
6.94
6.92
6.92
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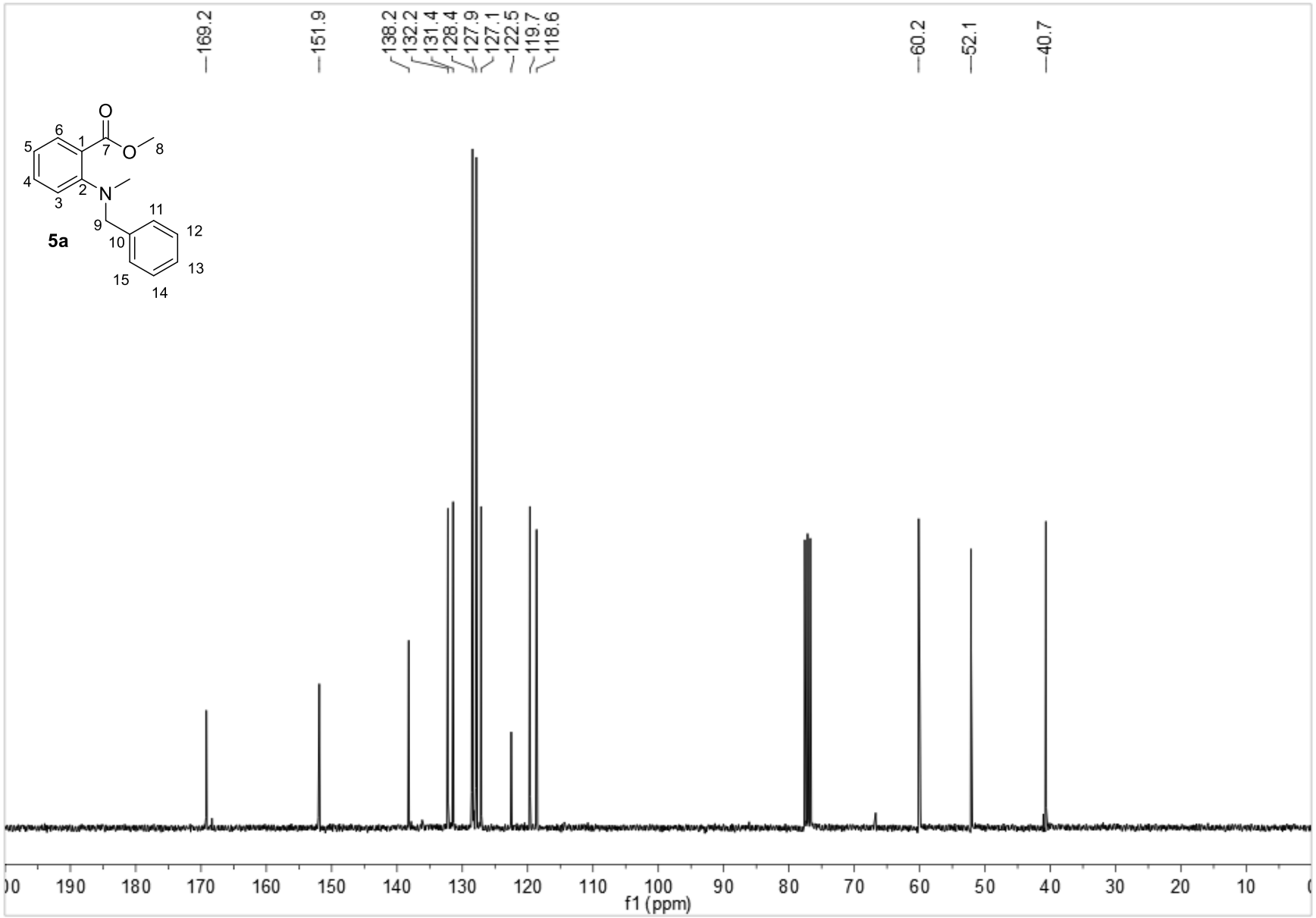
1.03
1.96
2.99
2.97
f1 (ppm)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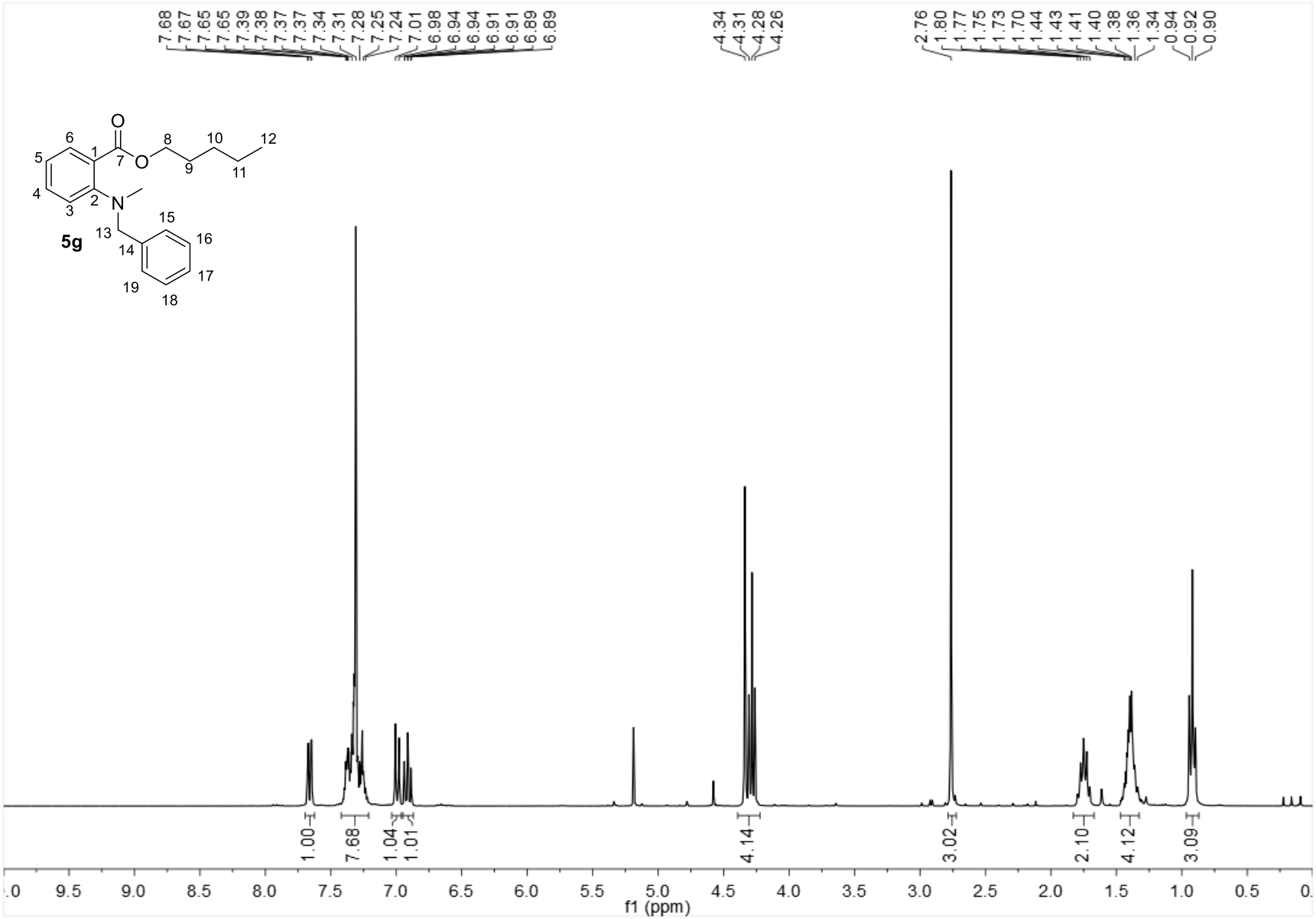
40.7
5a
f1 (ppm)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7.24
7.01
6.98
6.94
6.94
6.91
6.91
6.89
6.89
4.34
4.31
4.28
4.26
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1.77
1.75
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1.70
1.44
1.43
1.41
1.40
1.38
1.36
1.34
0.94
0.92
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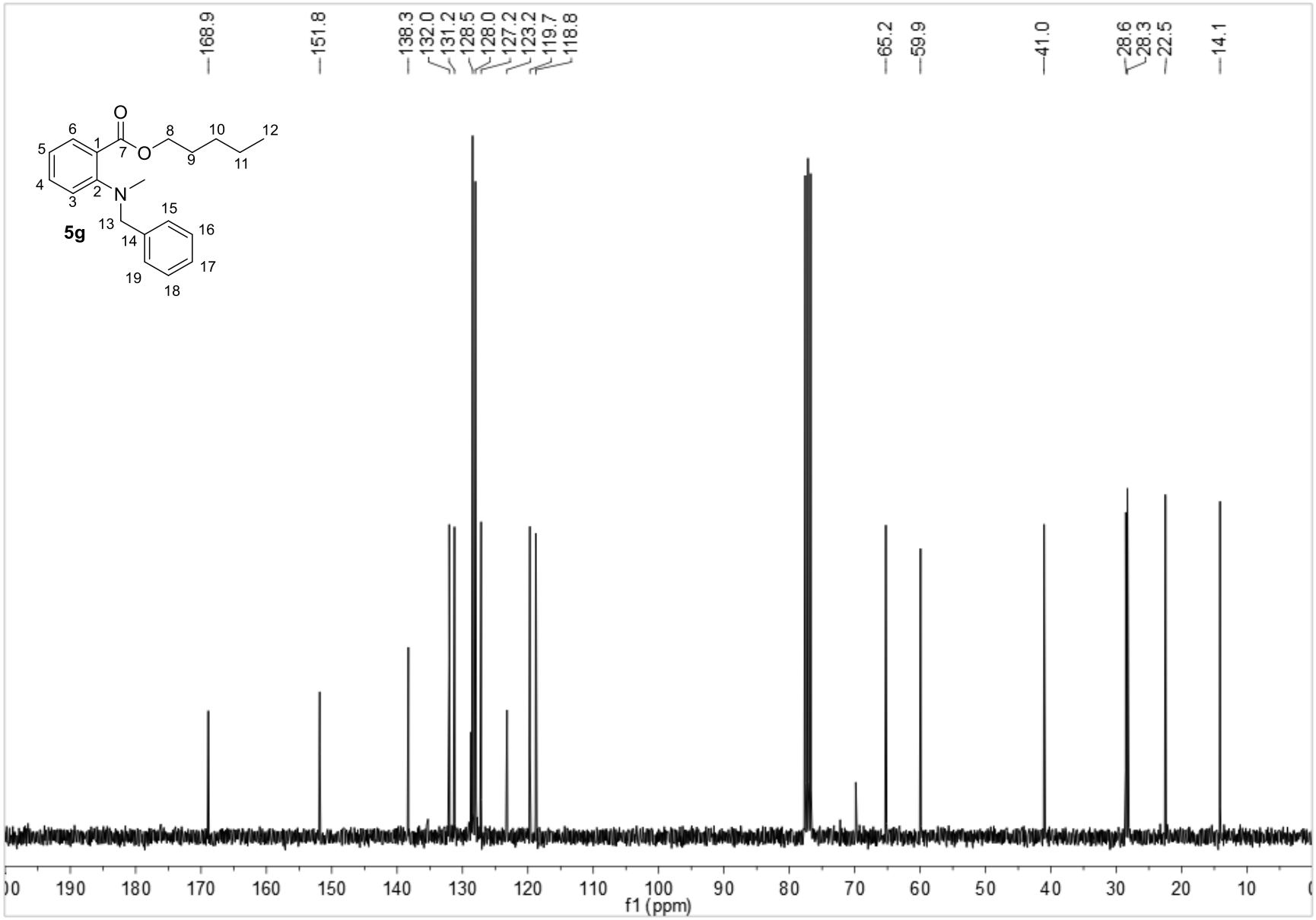
3.09
f1 (ppm)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127.2
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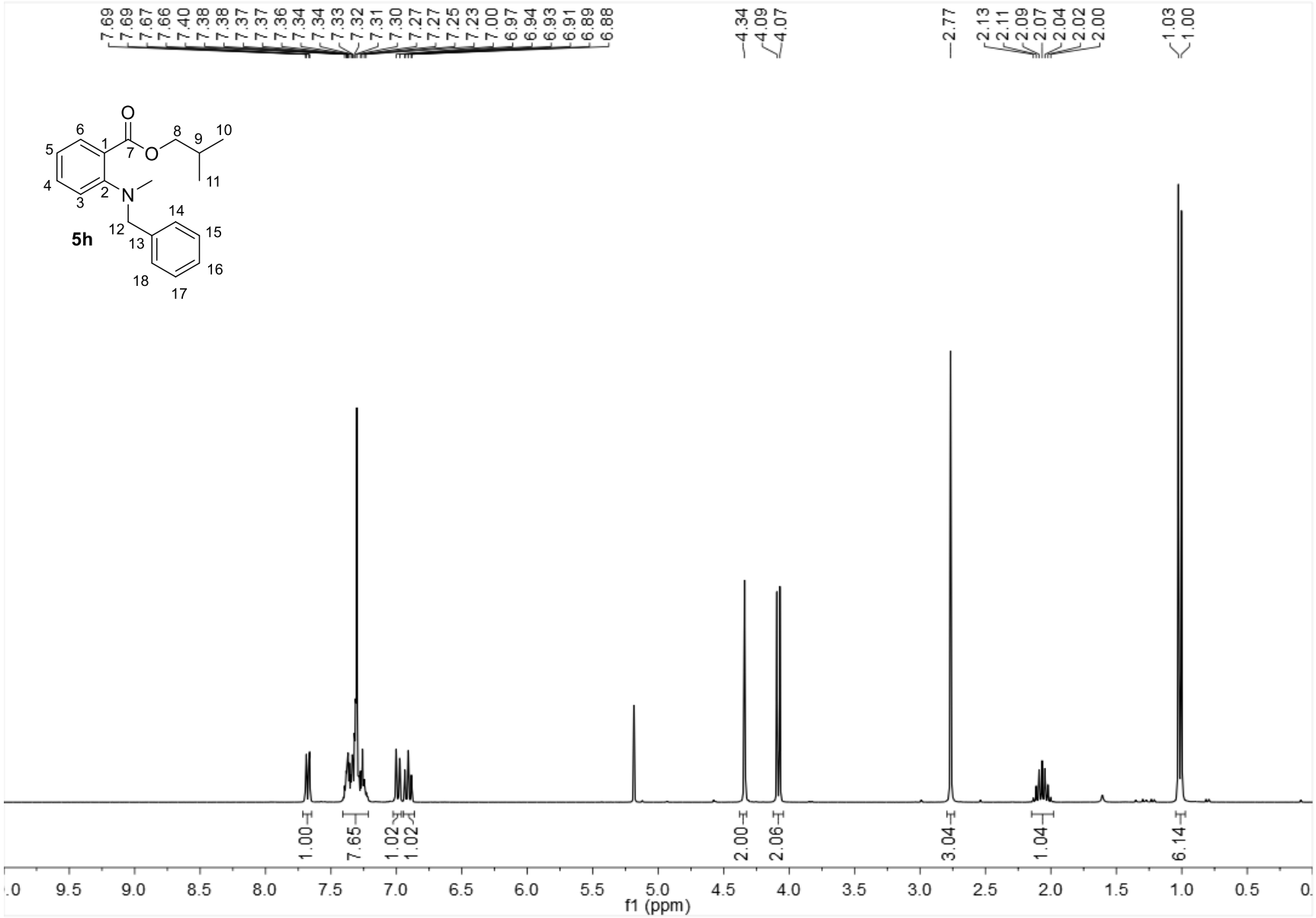
65.2
59.9
41.0
28.6
28.3
22.5
14.1
5g
f1 (ppm)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7.31
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7.23
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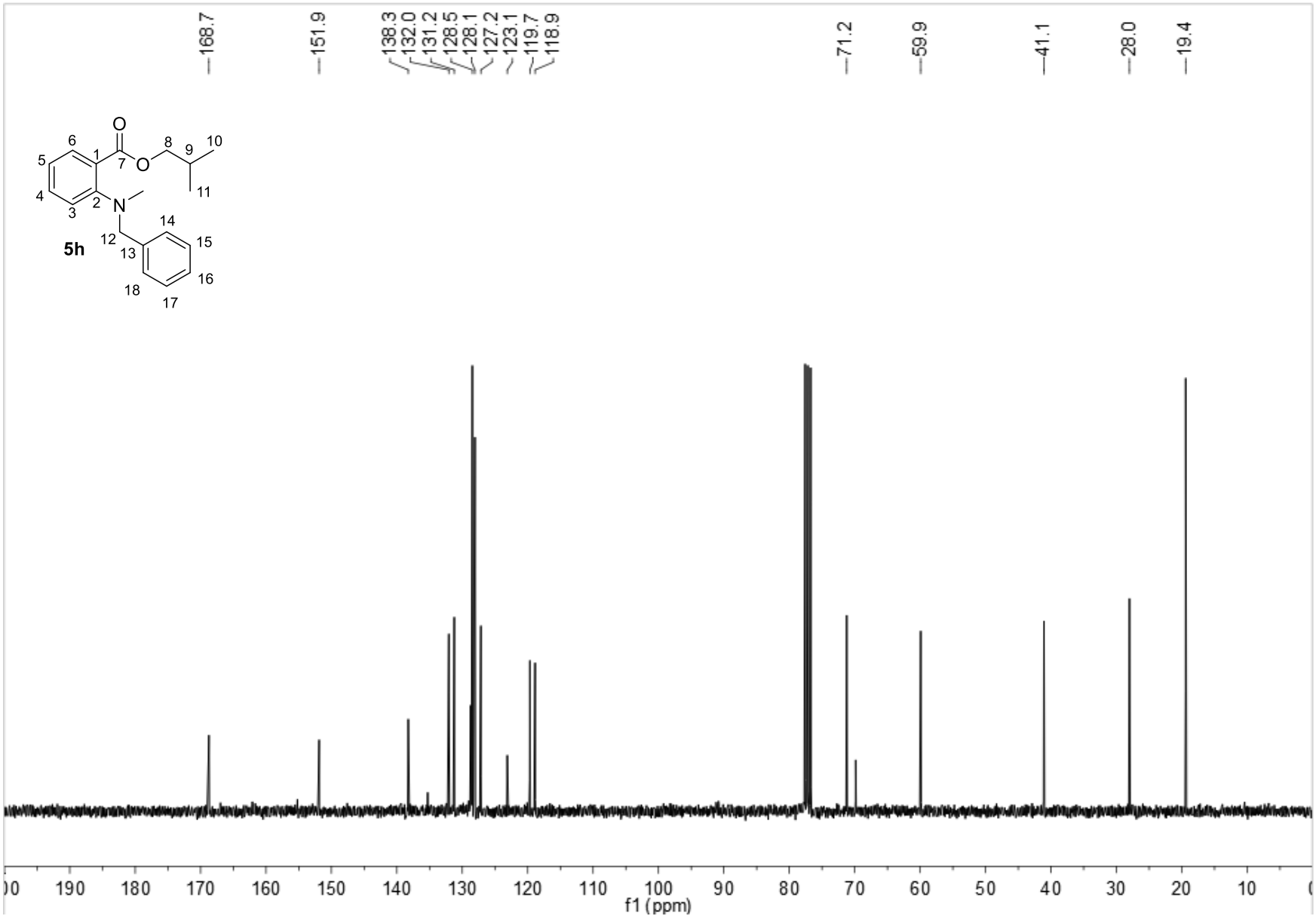
6.94
6.93
6.91
6.89
6.88
4.34
4.09
4.07
2.77
2.13
2.11
2.09
2.07
2.04
2.02
2.00
1.03
1.00
5h
1.00
7.65
1.02
1.02
2.00
2.06
3.04
1.04
6.14
f1 (ppm)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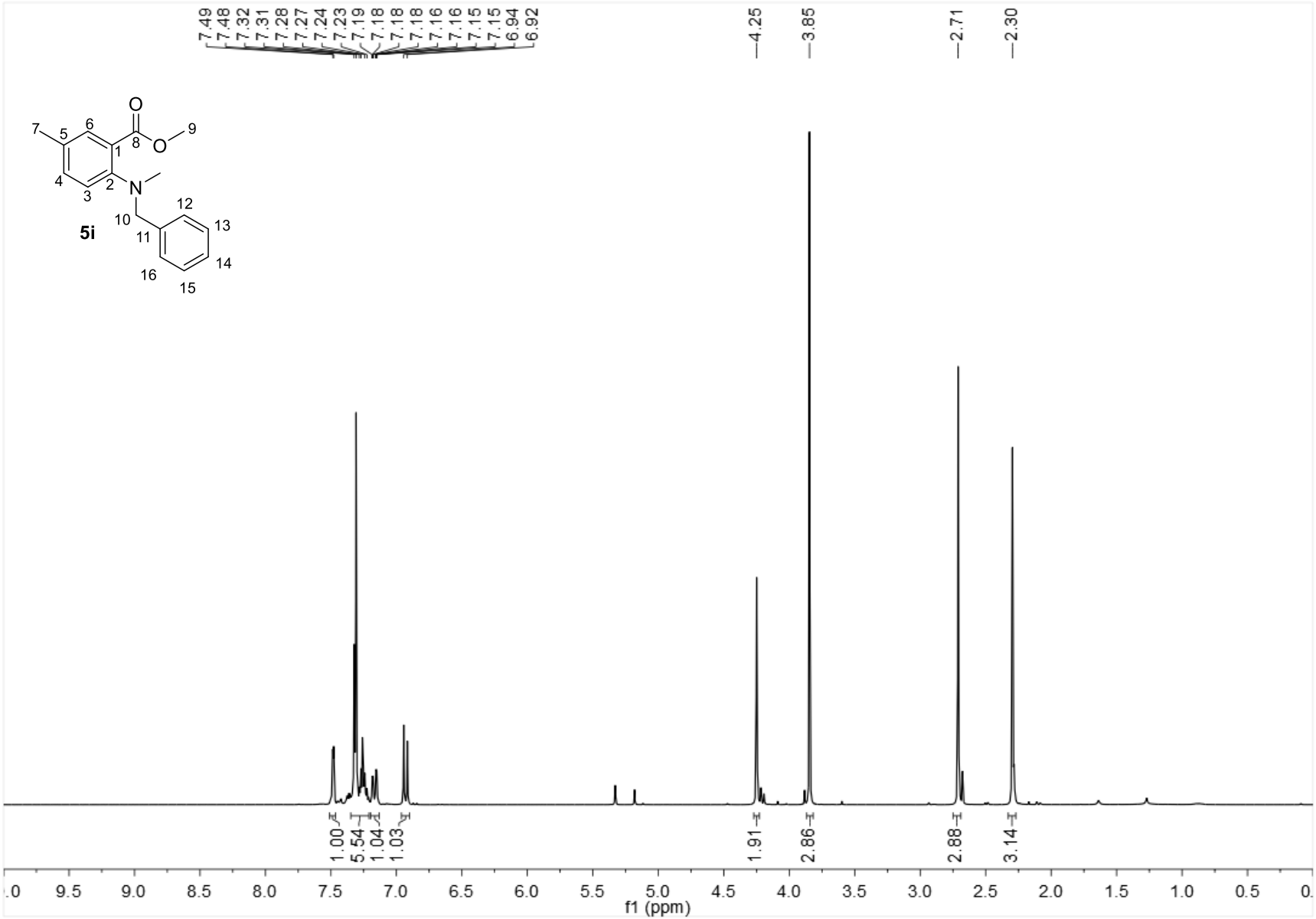
118.9
71.2
59.9
41.1
28.0
19.4
5h
f1 (ppm)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7.19
7.18
7.18
7.18
7.16
7.16
7.15
7.15
6.94
6.92
4.25
3.85
2.71
2.30
O
O
N
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
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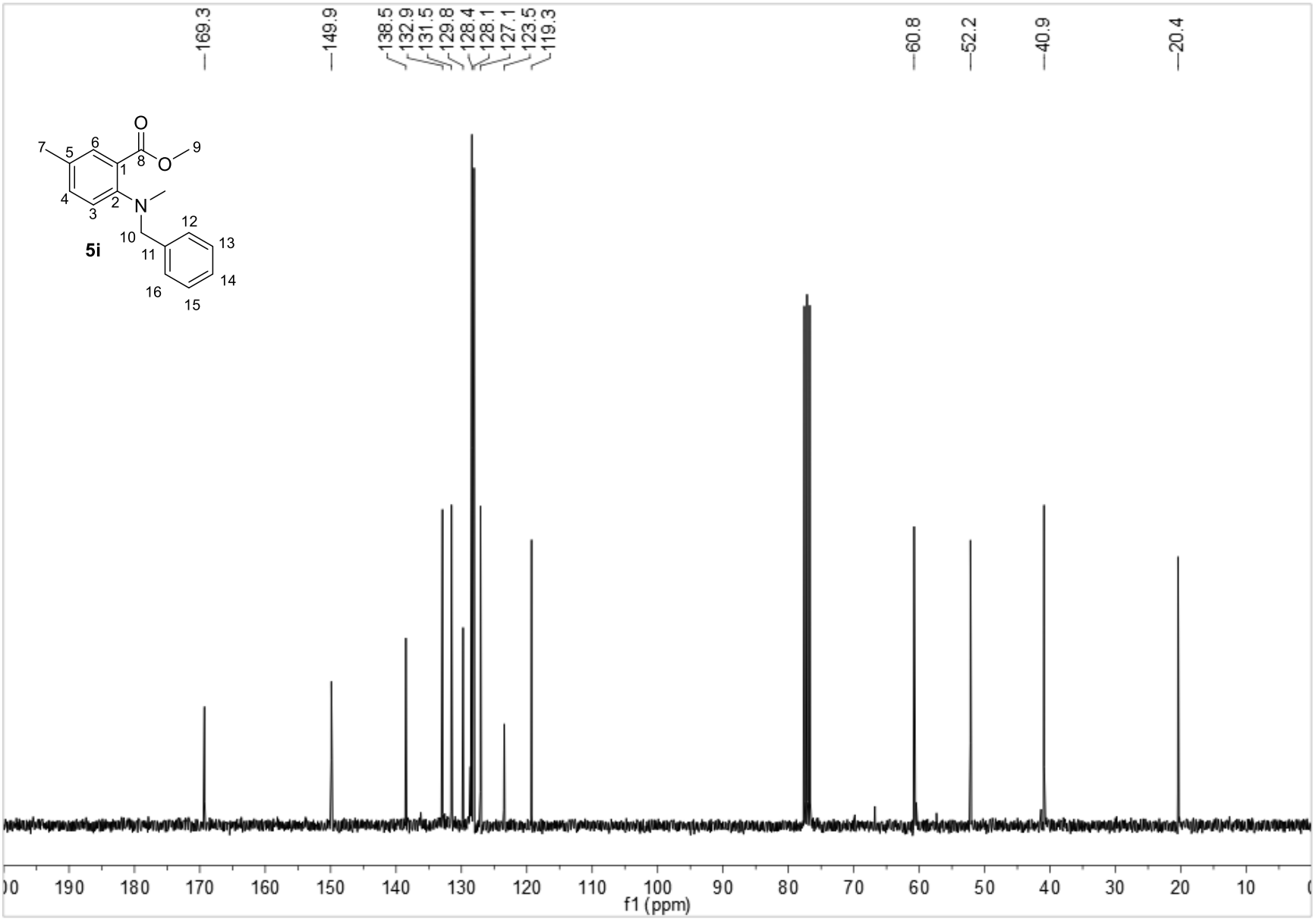
5i
1.00
5.54
1.04
1.03
1.91
2.86
2.88
3.14
f1 (ppm)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132.9
131.5
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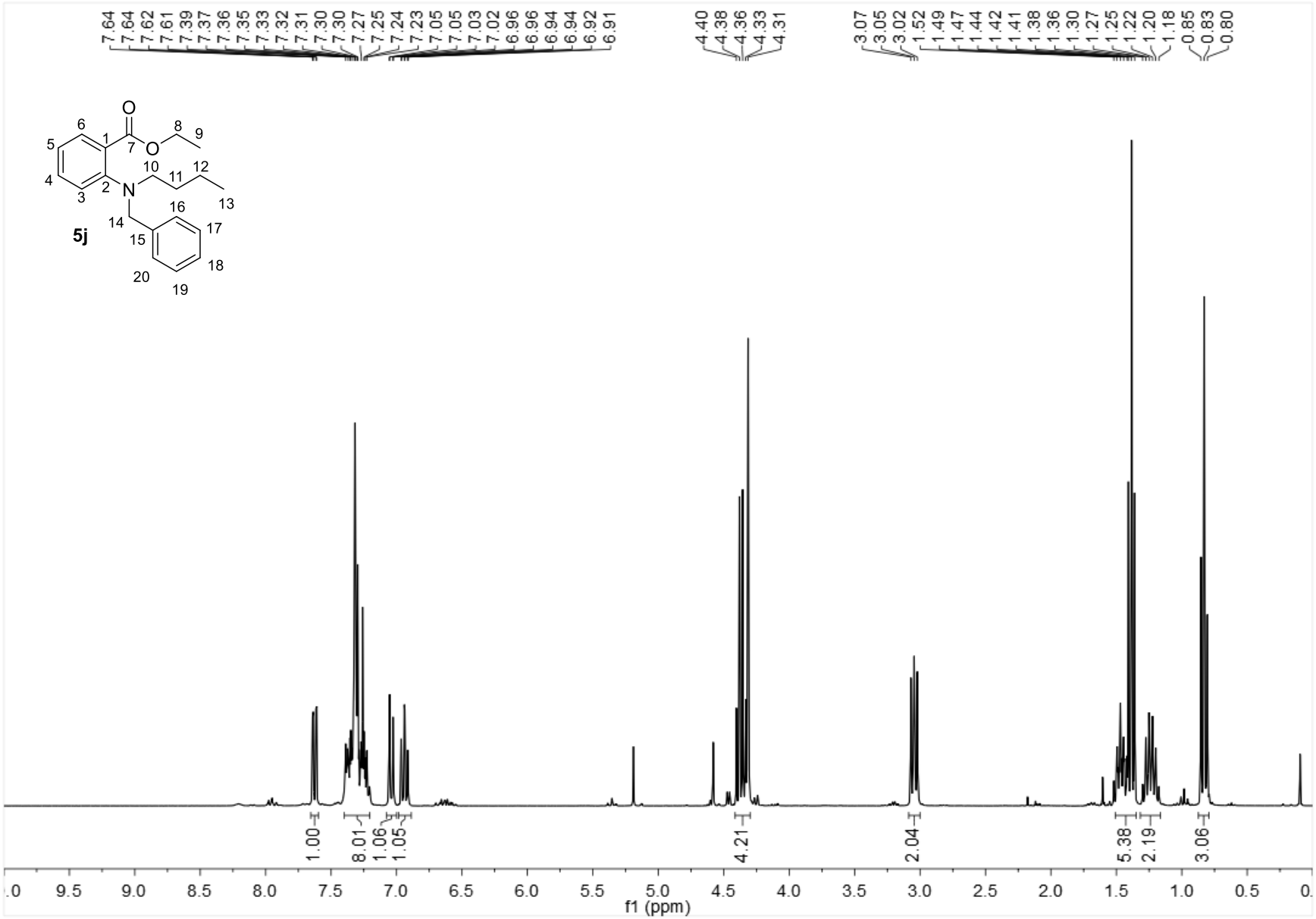
128.4
128.1
127.1
123.5
119.3
60.8
52.2
40.9
20.4
5i
f1 (ppm)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7.31
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7.30
7.27
7.25
7.24
7.23
7.05
7.05
7.03
7.02
6.96
6.96
6.94
6.94
6.92
6.91
4.40
4.38
4.36
4.33
4.31
3.07
3.05
3.02
1.52
1.49
1.47
1.44
1.42
1.41
1.38
1.36
1.30
1.27
1.25
1.22
1.20
1.18
0.85
0.83
0.80
5j
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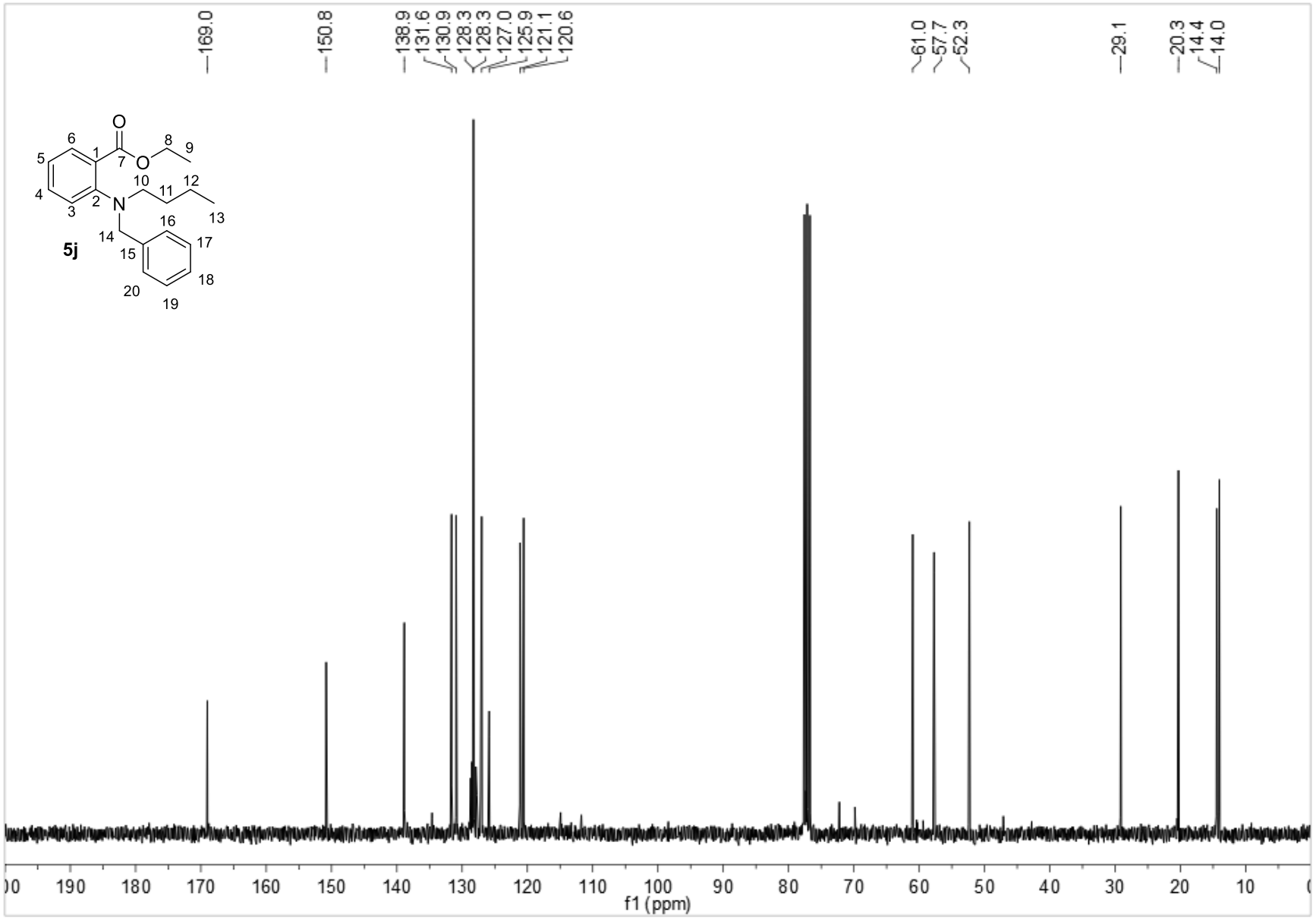
8.01
1.06
1.05
4.21
2.04
5.38
2.19
3.06
f1 (ppm)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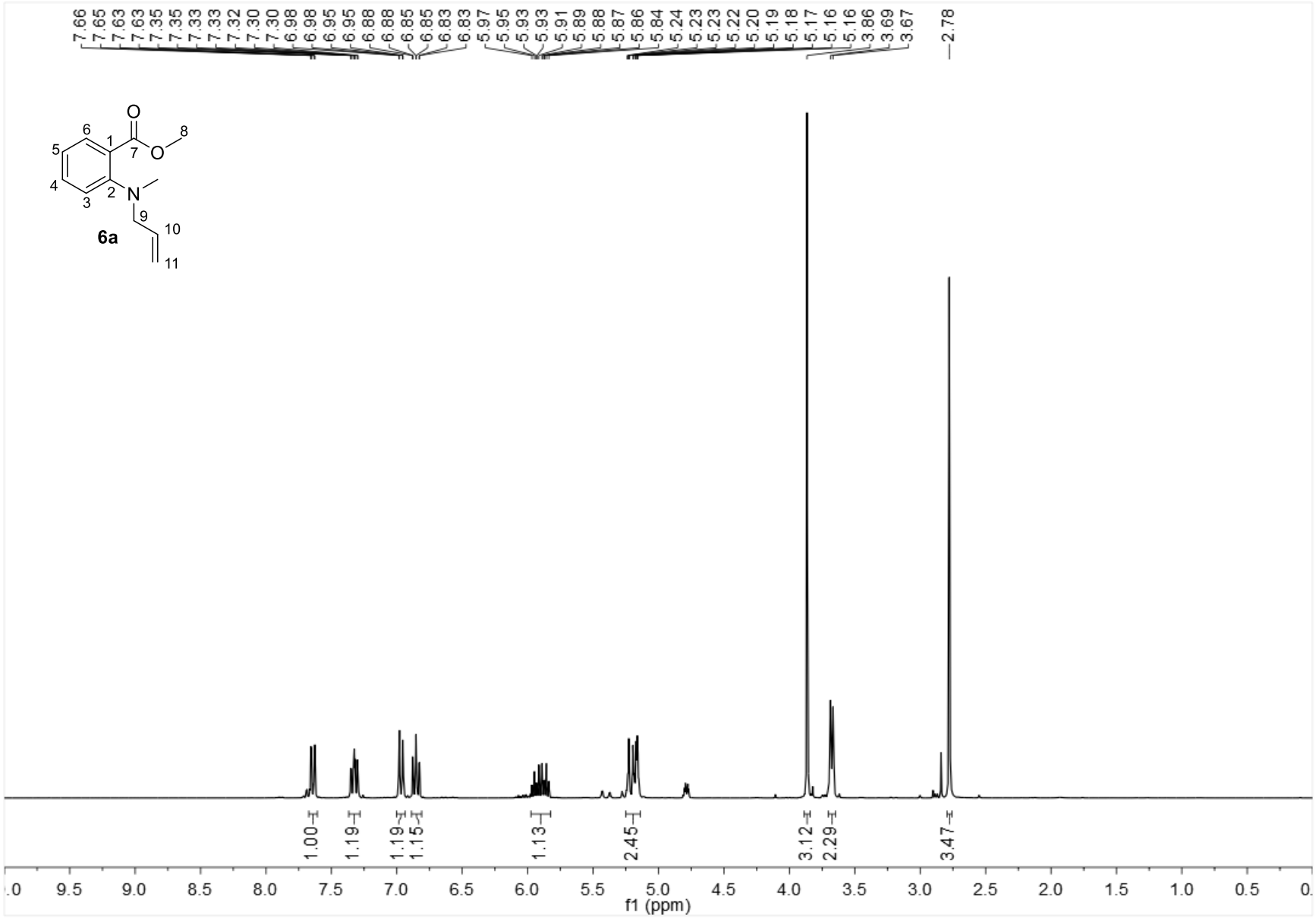
130.9
128.3
128.3
127.0
125.9
121.1
120.6
61.0
57.7
52.3
29.1
20.3
14.4
14.0
5j
f1 (ppm)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6.98
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6.95
6.95
6.88
6.88
6.85
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5.95
5.93
5.93
5.91
5.89
5.88
5.87
5.86
5.84
5.24
5.23
5.23
5.22
5.20
5.19
5.18
5.17
5.16
5.16
3.86
3.69
3.67
2.78
O
O
O
N
1
2
3
4
5
6
7
8
9
10
11
6a
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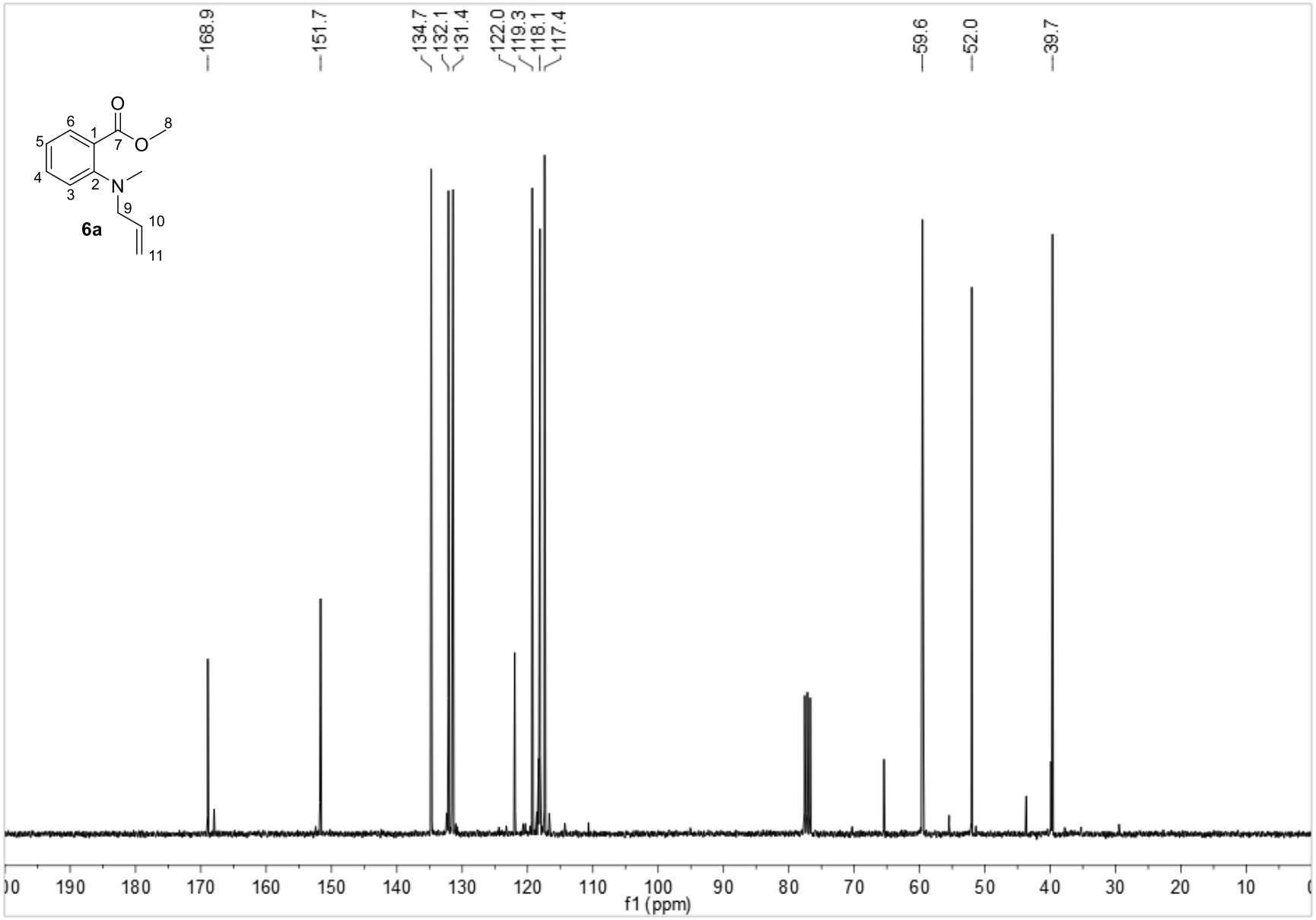
1.19
1.19
1.15
1.13
2.45
3.12
2.29
3.47
f1 (ppm)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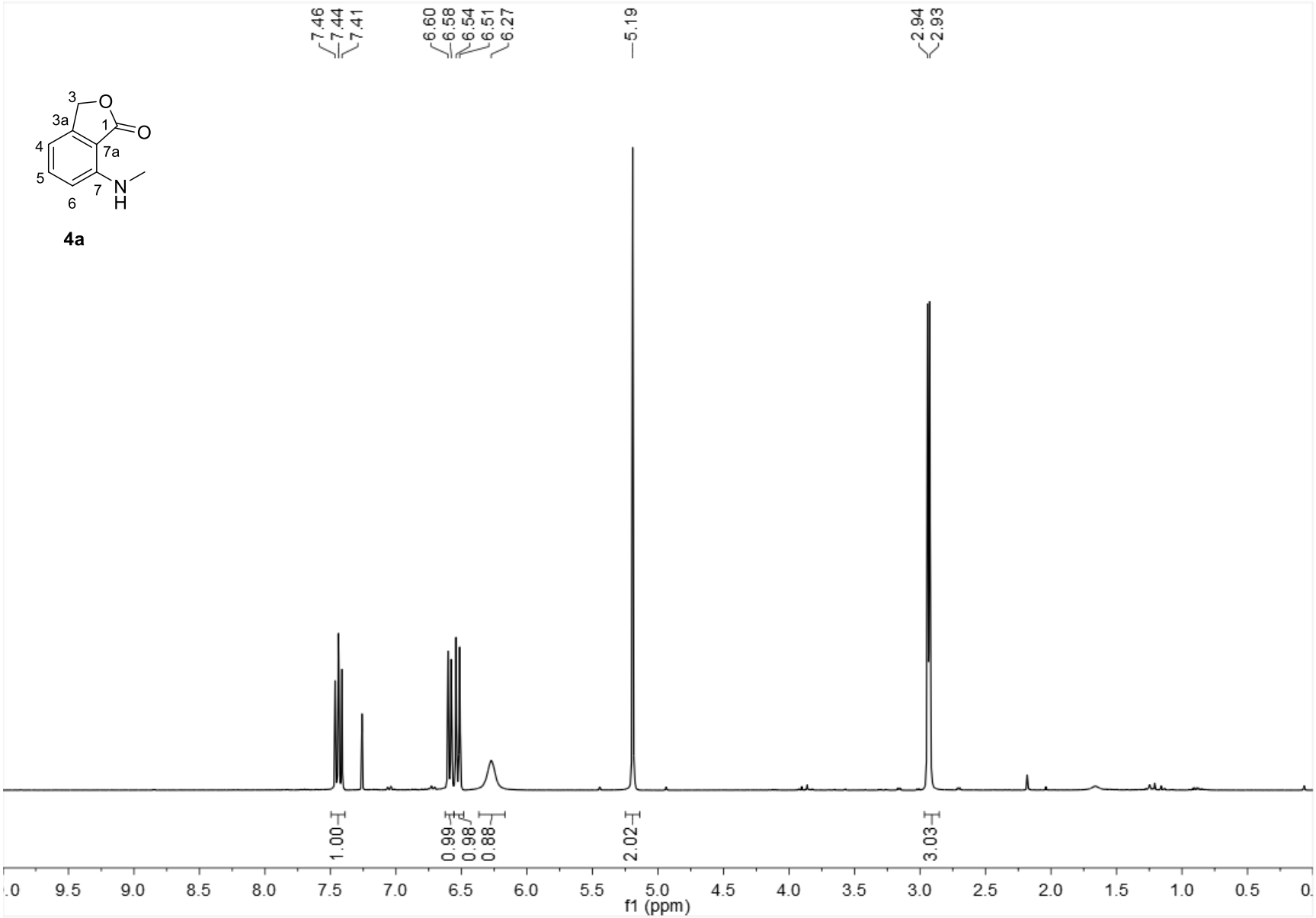
151.7
134.7
132.1
131.4
122.0
119.3
118.1
117.4
59.6
52.0
39.7
6a
f1 (ppm)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7.44
7.41
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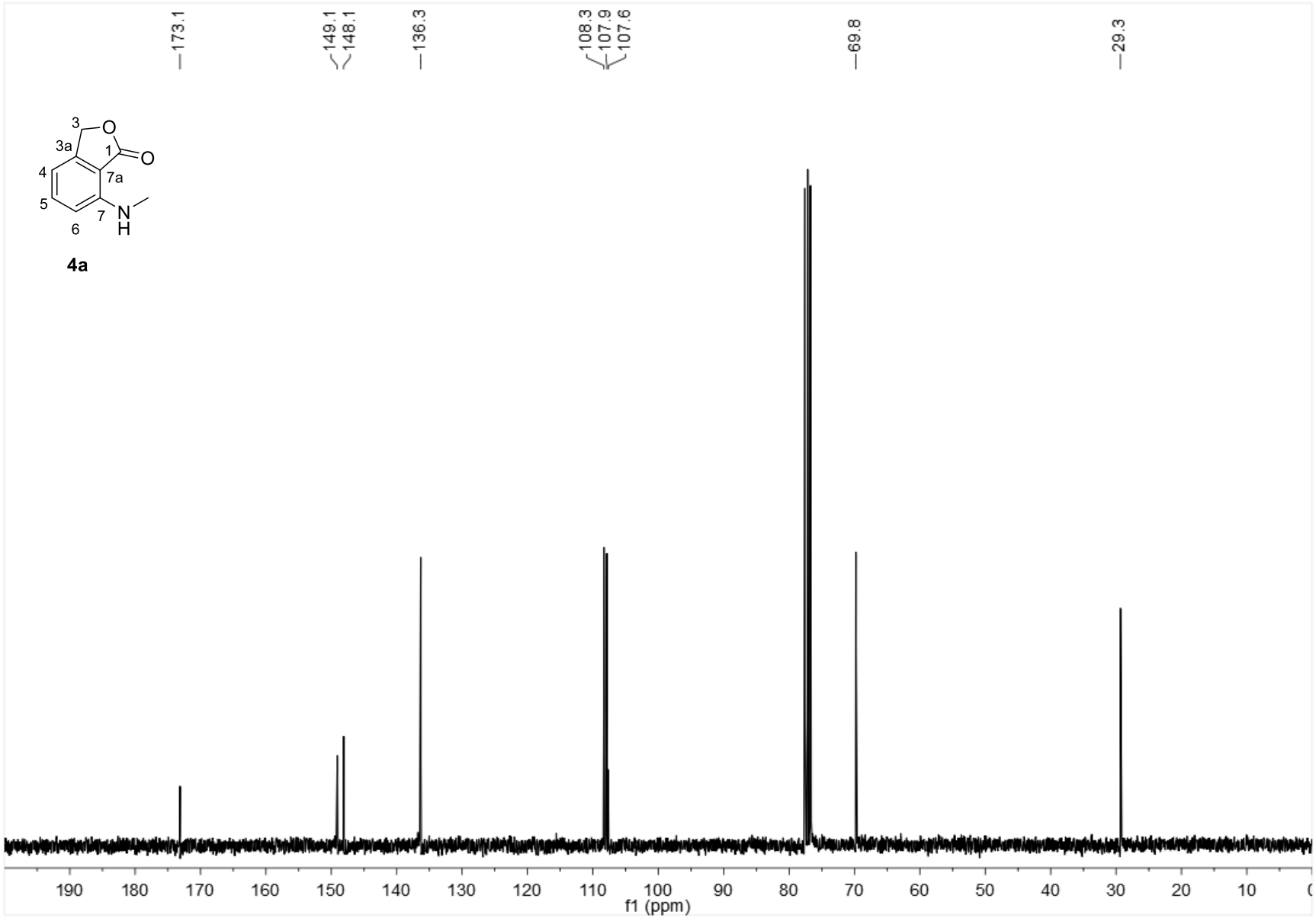
6.58
6.54
6.51
6.27
5.19
2.94
2.93
3
O
1
O
3a
4
7a
5
7
N
H
6
1.00
0.99
0.98
0.88
2.02
3.03
f1 (ppm)

4a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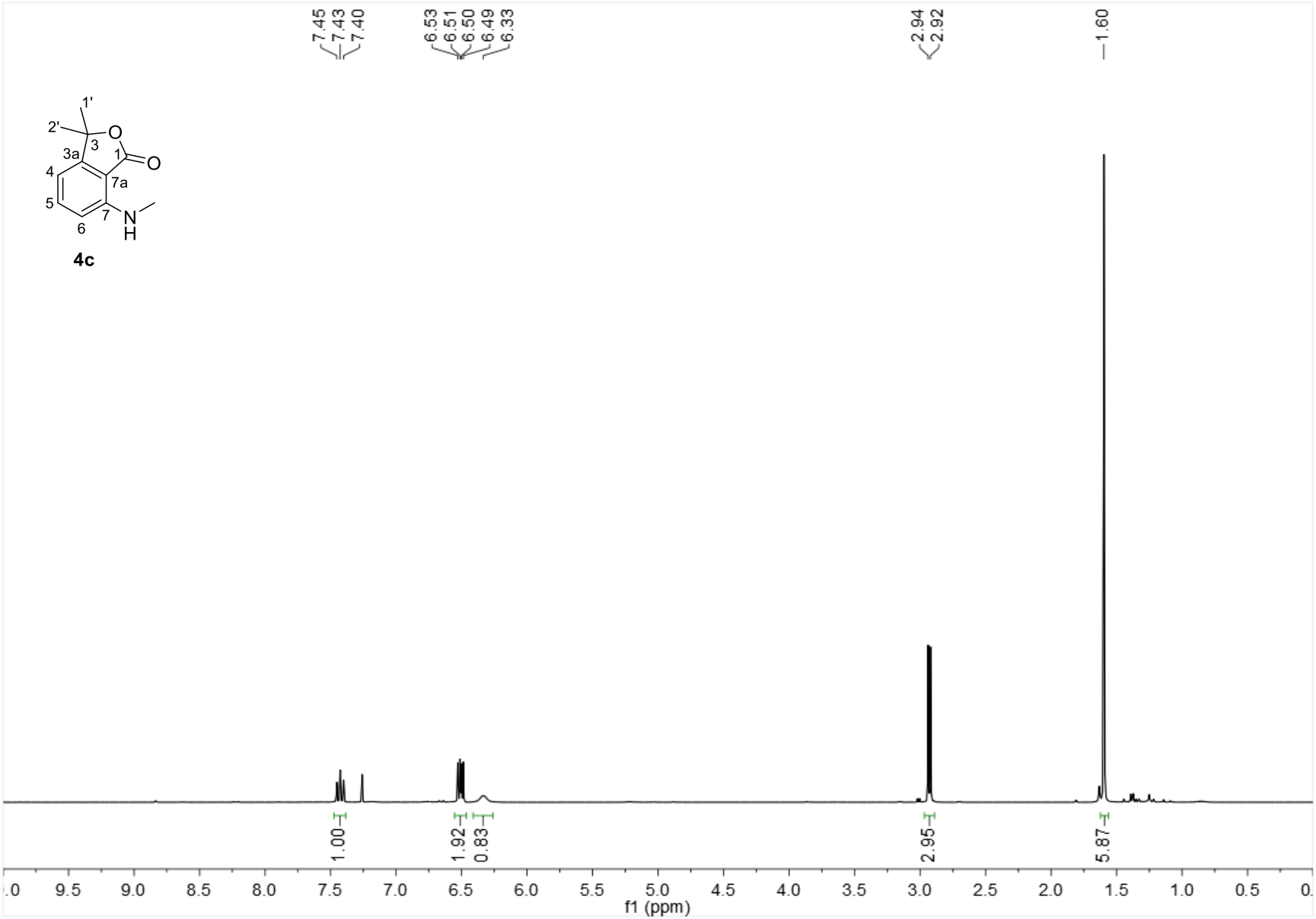
108.3
107.9
107.6
69.8
29.3
3
O
3a
1
O
4
7a
5
7
N
H
6
4a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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7.43
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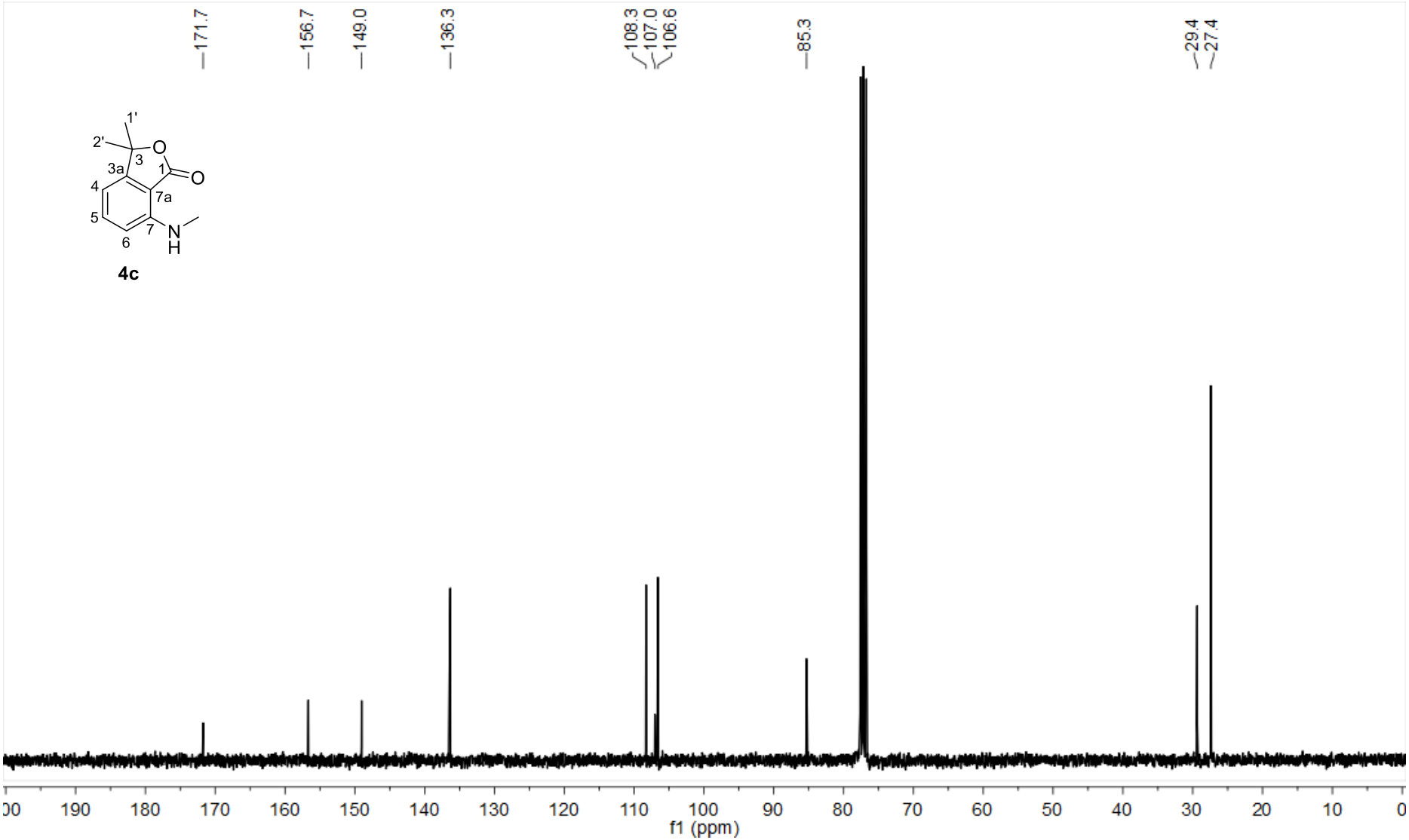
6.53
6.51
6.50
6.49
6.33
2.94
2.92
1.60
1'
2'
3
O
1
O
3a
4
7a
5
7
N
H
6
4c
1.00
1.92
0.83
2.95
5.87
f1 (ppm)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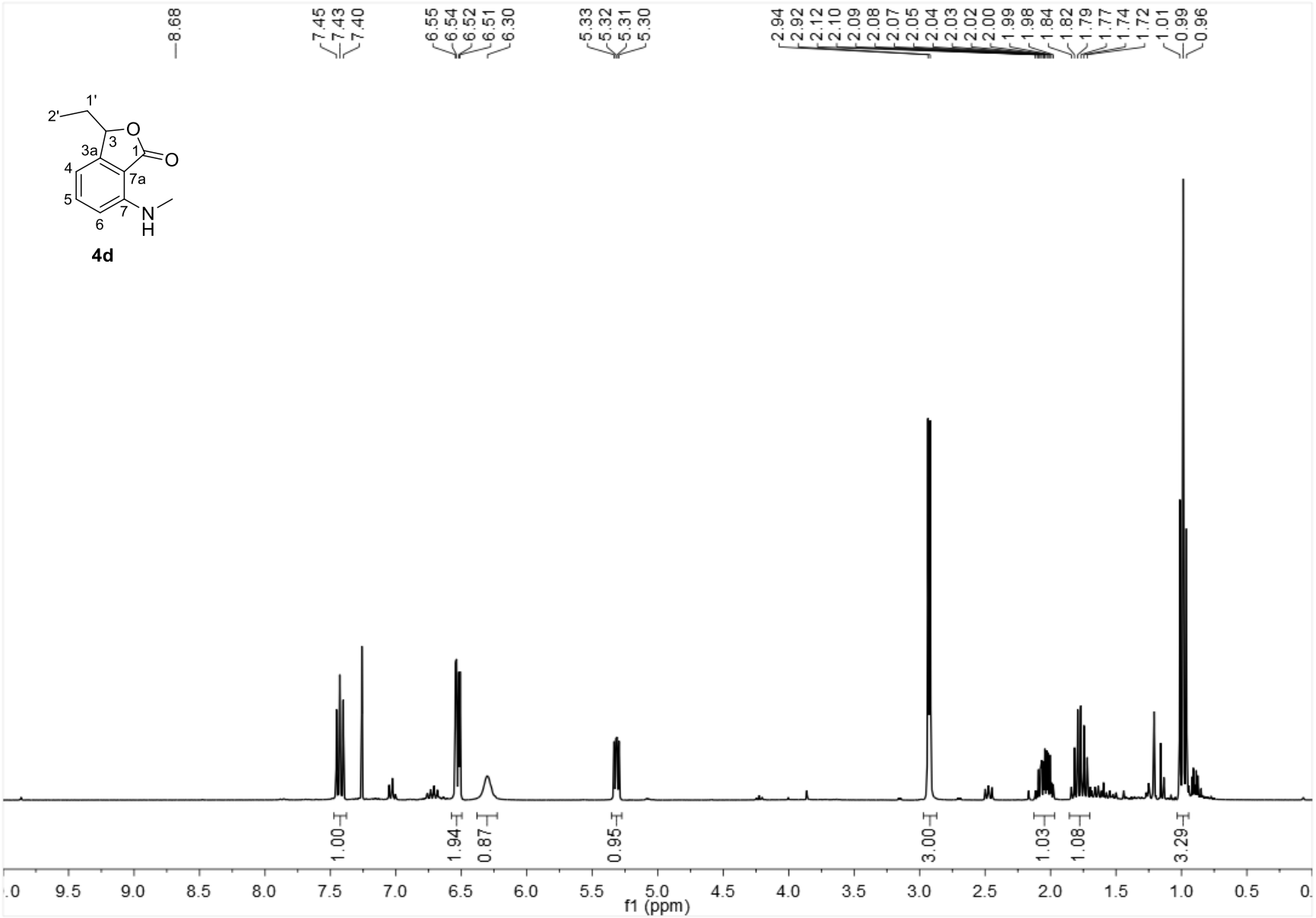
149.0
136.3
108.3
107.0
106.6
85.3
29.4
27.4
1'
2'
O
3
3a
1
O
4
7a
5
7
N
H
6
4c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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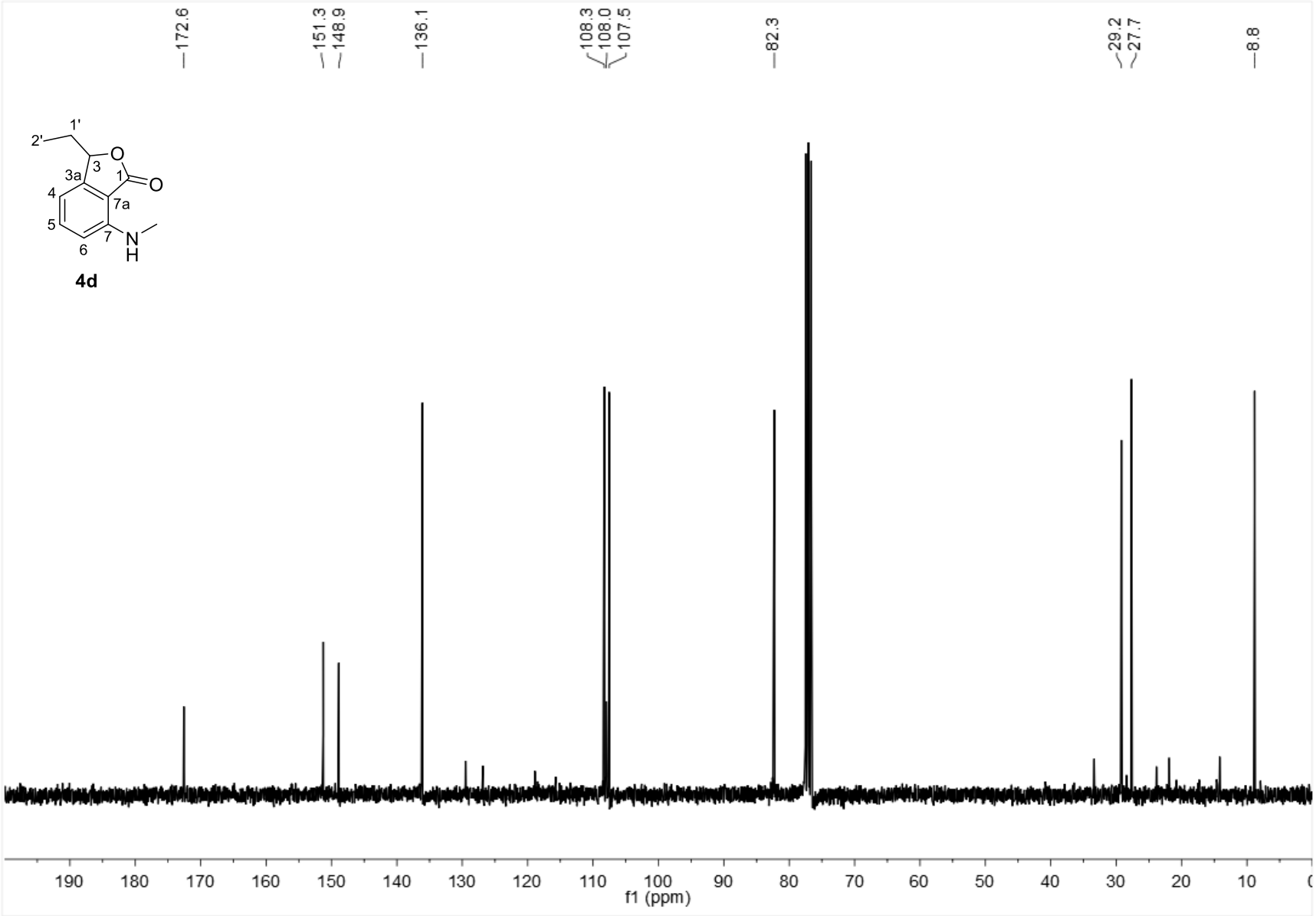
7.43
7.40
6.55
6.54
6.52
6.51
6.30
5.33
5.32
5.31
5.30
2.94
2.92
2.12
2.10
2.09
2.08
2.07
2.05
2.04
2.03
2.02
2.00
1.99
1.98
1.84
1.82
1.79
1.77
1.74
1.72
1.01
0.99
0.96
1'
2'
O
3
3a
1
O
4
7a
5
7
N
H
6
4d
1.00
1.94
0.87
0.95
3.00
1.03
1.08
3.29
f1 (ppm)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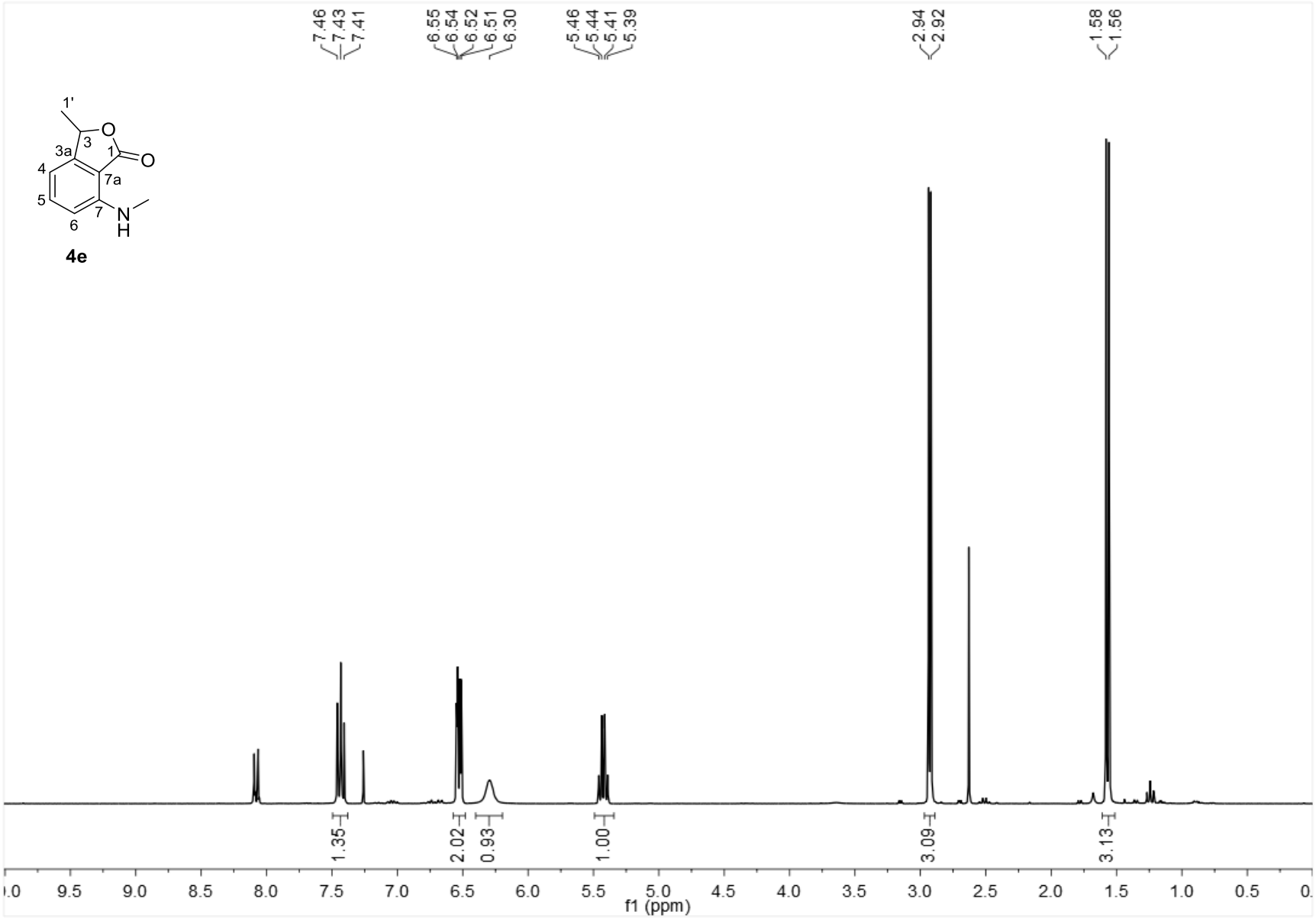
108.3
108.0
107.5
82.3
29.2
27.7
8.8
1'
2'
3
O
1
O
3a
4
7a
5
7
N
H
6
4d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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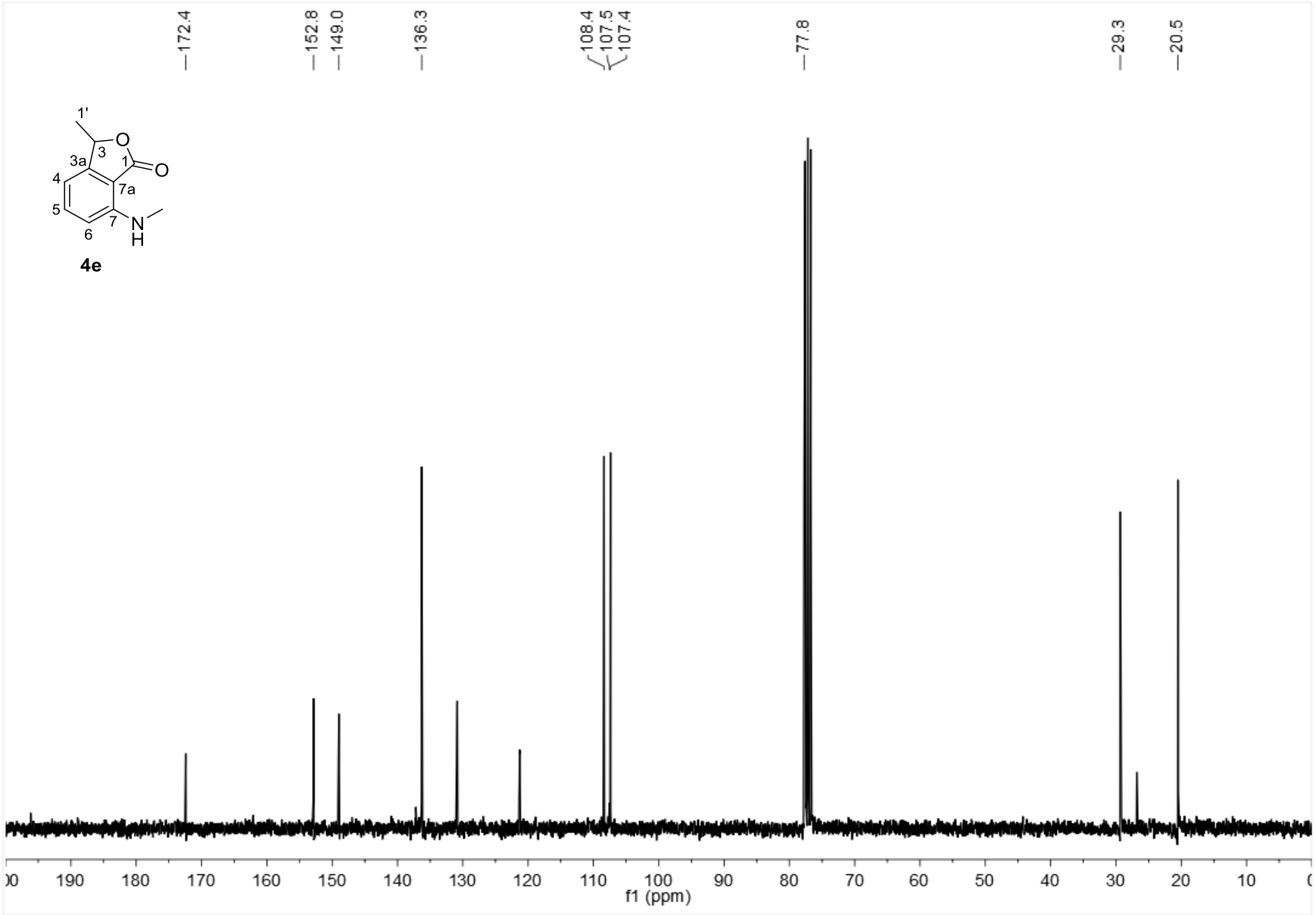
7.41
6.55
6.54
6.52
6.51
6.30
5.46
5.44
5.41
5.39
2.94
2.92
1.58
1.56
1'
O
3
3a
1
O
4
7a
5
7
N
H
6
4e
1.35
2.02
0.93
1.00
3.09
3.13
f1 (ppm)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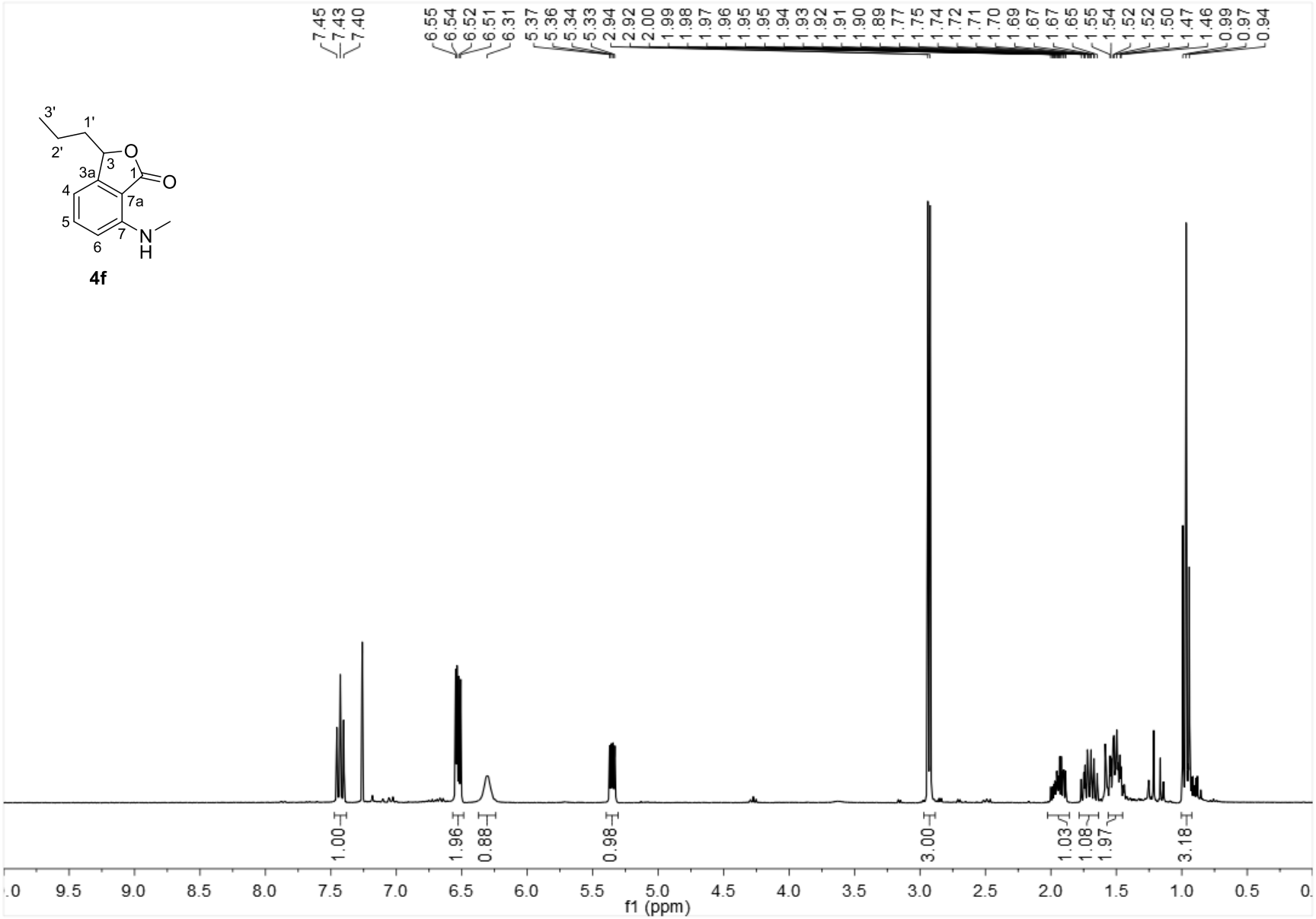
107.5
107.4
77.8
29.3
20.5
1'
O
3
3a
1
O
4
7a
5
7
N
H
6
4e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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7.43
7.40
6.55
6.54
6.52
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6.31
5.37
5.36
5.34
5.33
2.94
2.92
2.00
1.99
1.98
1.97
1.96
1.95
1.94
1.93
1.92
1.91
1.90
1.89
1.77
1.75
1.74
1.72
1.71
1.70
1.69
1.67
1.67
1.65
1.55
1.54
1.52
1.52
1.50
1.47
1.46
0.99
0.97
0.94
3'
1'
2'
O
3
1
O
3a
4
7a
5
7
N
H
6
4f
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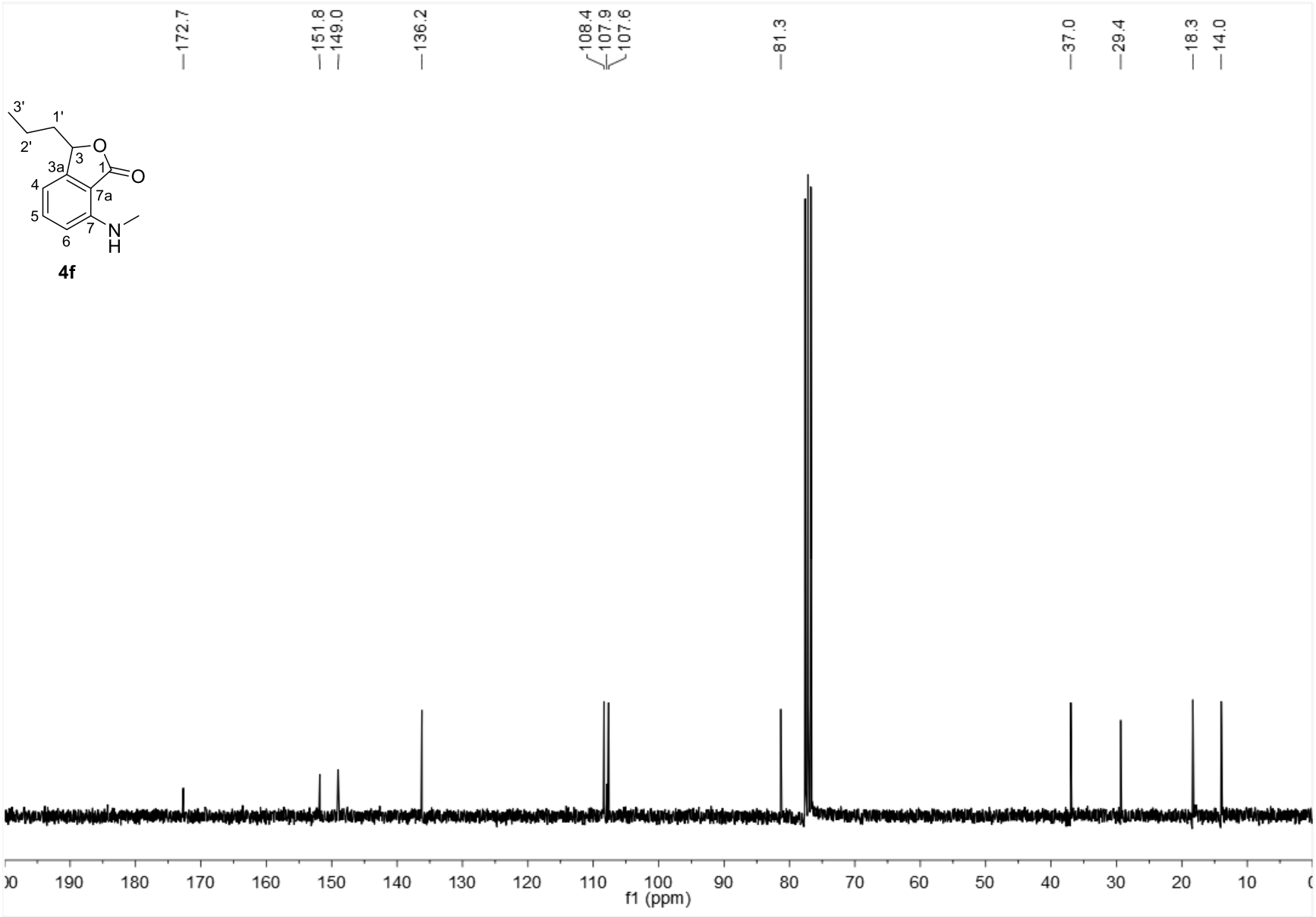
1.96
0.88
0.98
3.00
1.03
1.08
1.97
3.18
f1 (ppm)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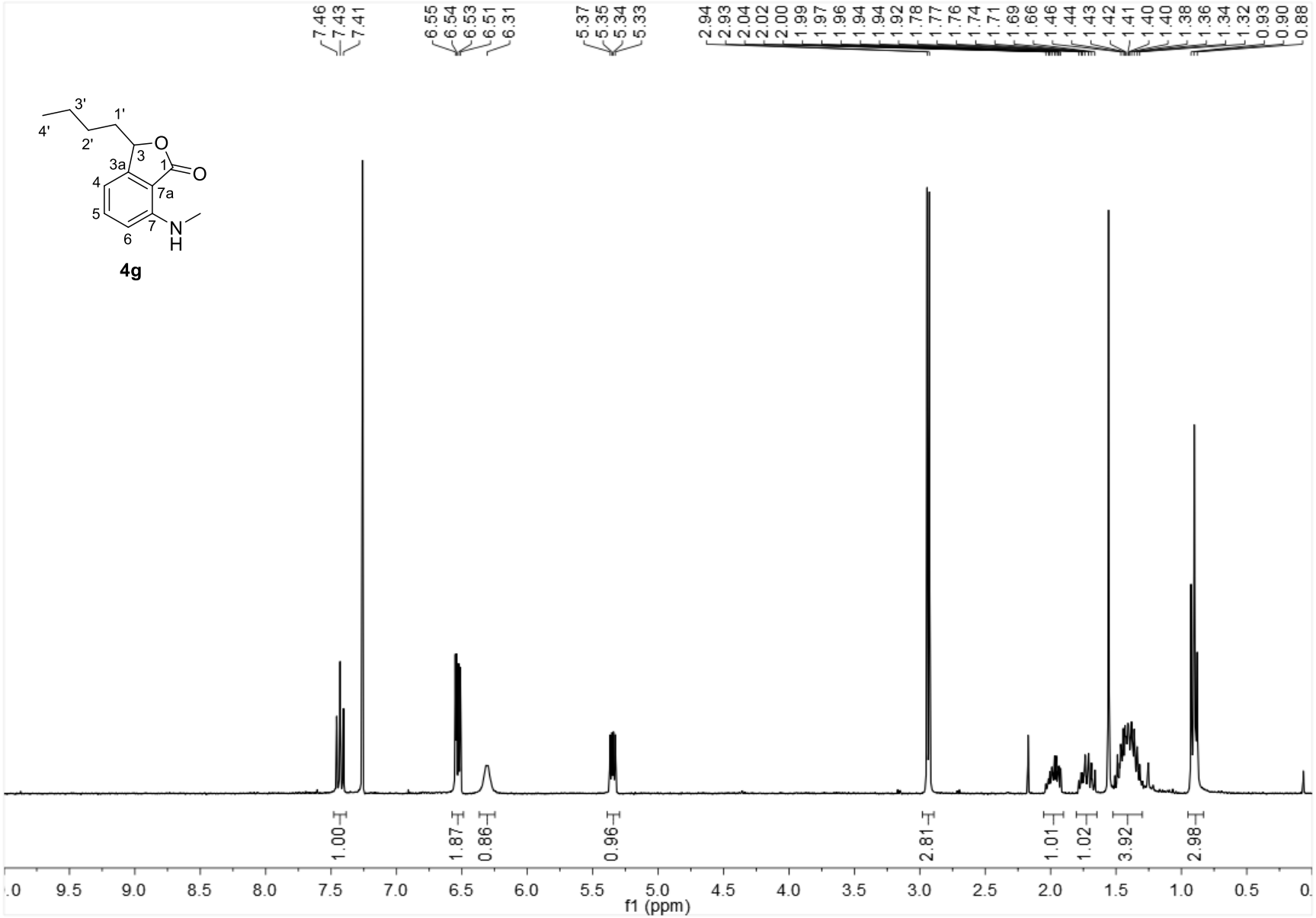
136.2
108.4
107.9
107.6
81.3
37.0
29.4
18.3
14.0
3'
1'
2'
O
3
1
O
3a
4
7a
5
7
N
H
6
4f
f1 (ppm)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7.43
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6.55
6.54
6.53
6.51
6.31
5.37
5.35
5.34
5.33
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2.93
2.04
2.02
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1.96
1.94
1.94
1.92
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1.77
1.76
1.74
1.71
1.69
1.66
1.46
1.44
1.43
1.42
1.41
1.40
1.40
1.38
1.36
1.34
1.32
0.93
0.90
0.88
3'
4'
1'
2'
O
3
3a
1
O
4
7a
5
7
N
H
6
4g
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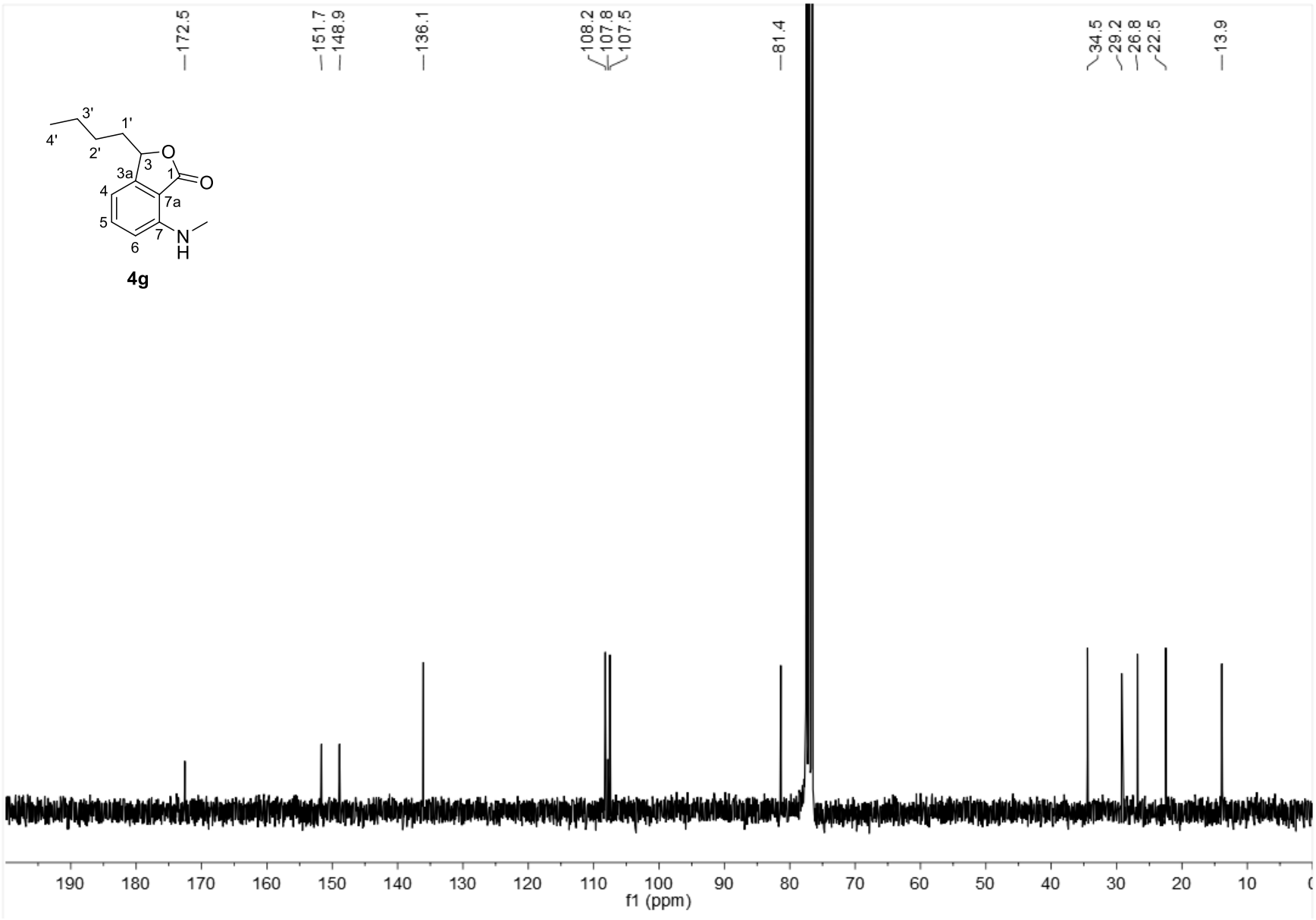
1.87
0.86
0.96
2.81
1.01
1.02
3.92
2.98
f1 (ppm)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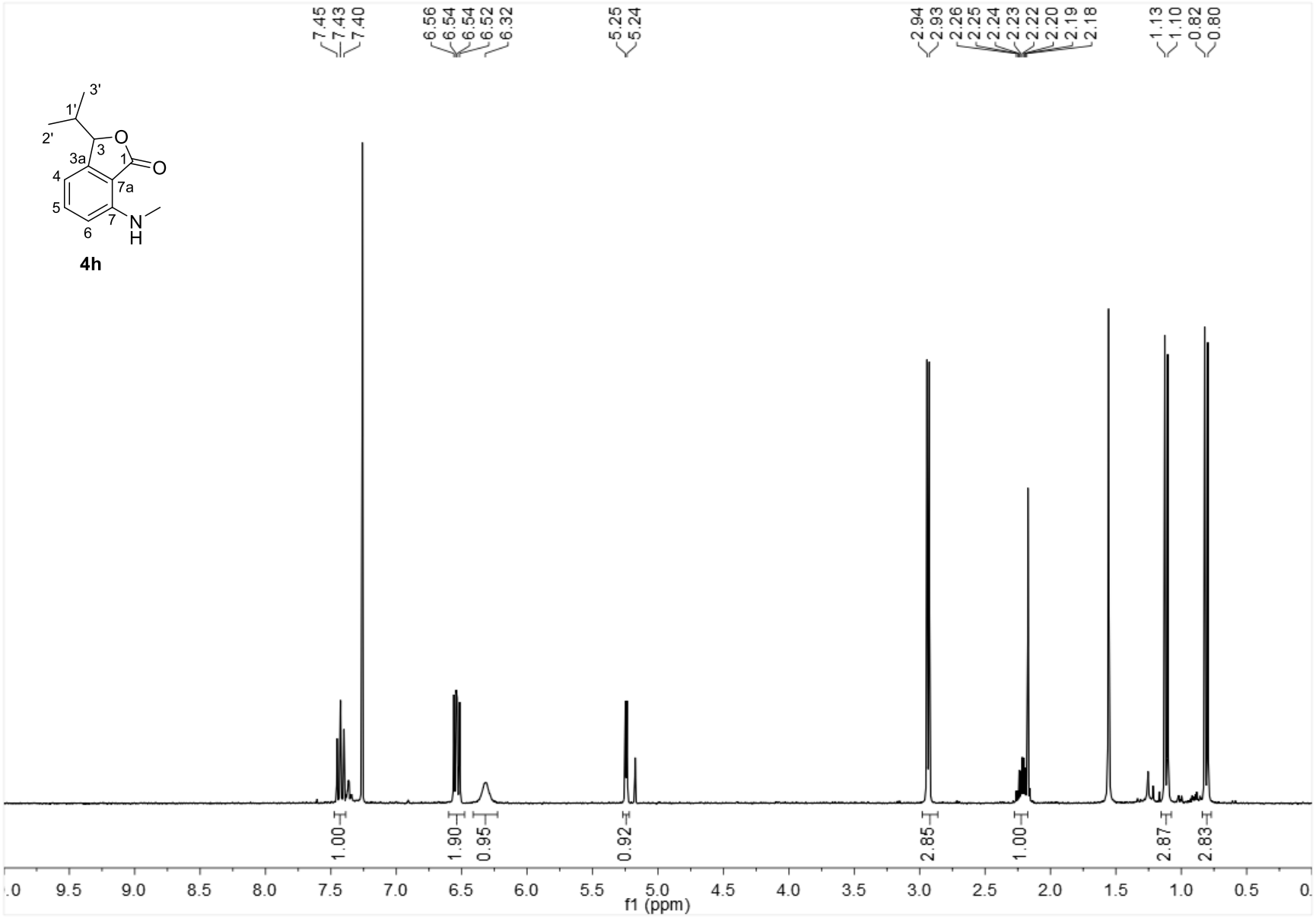
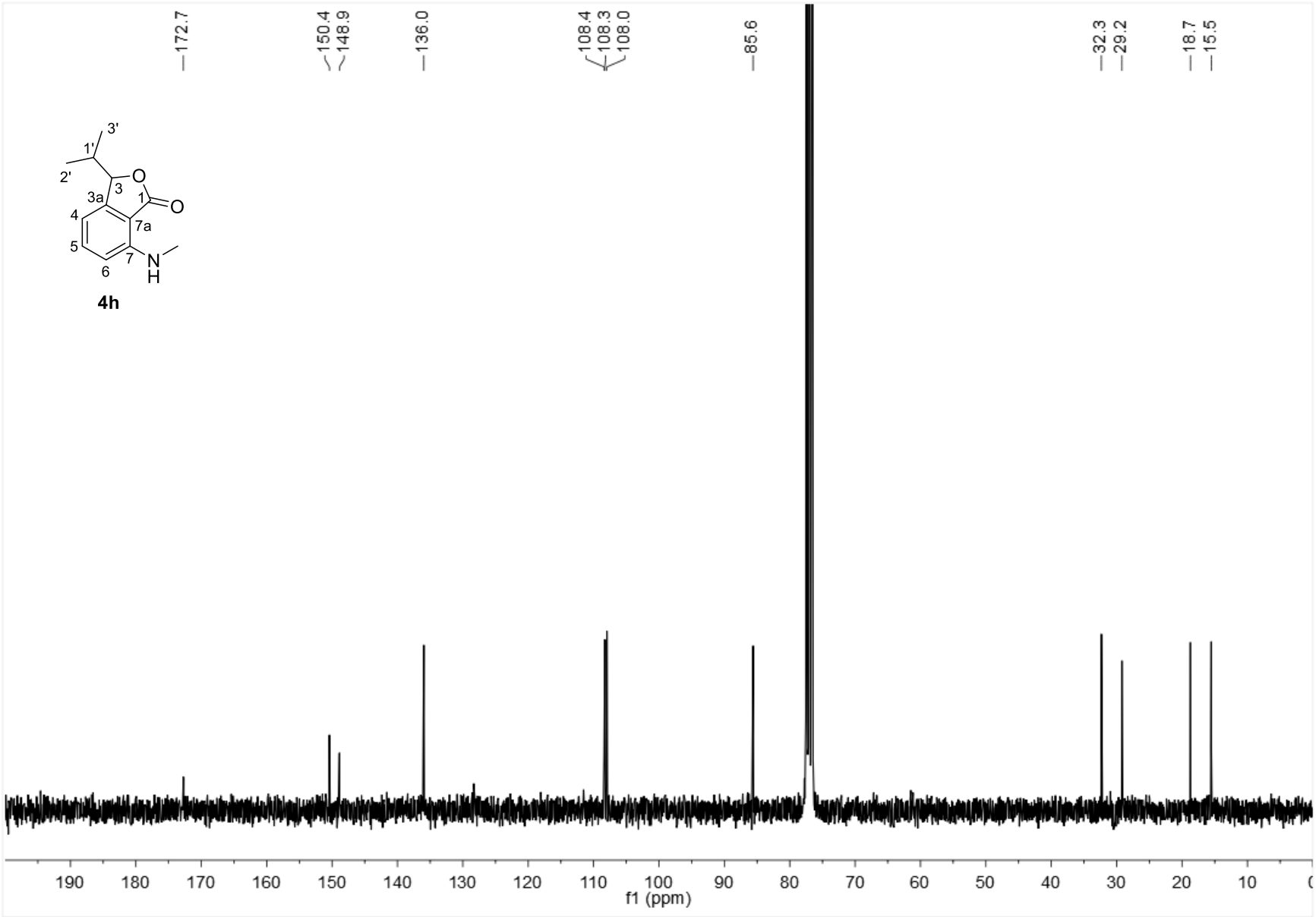
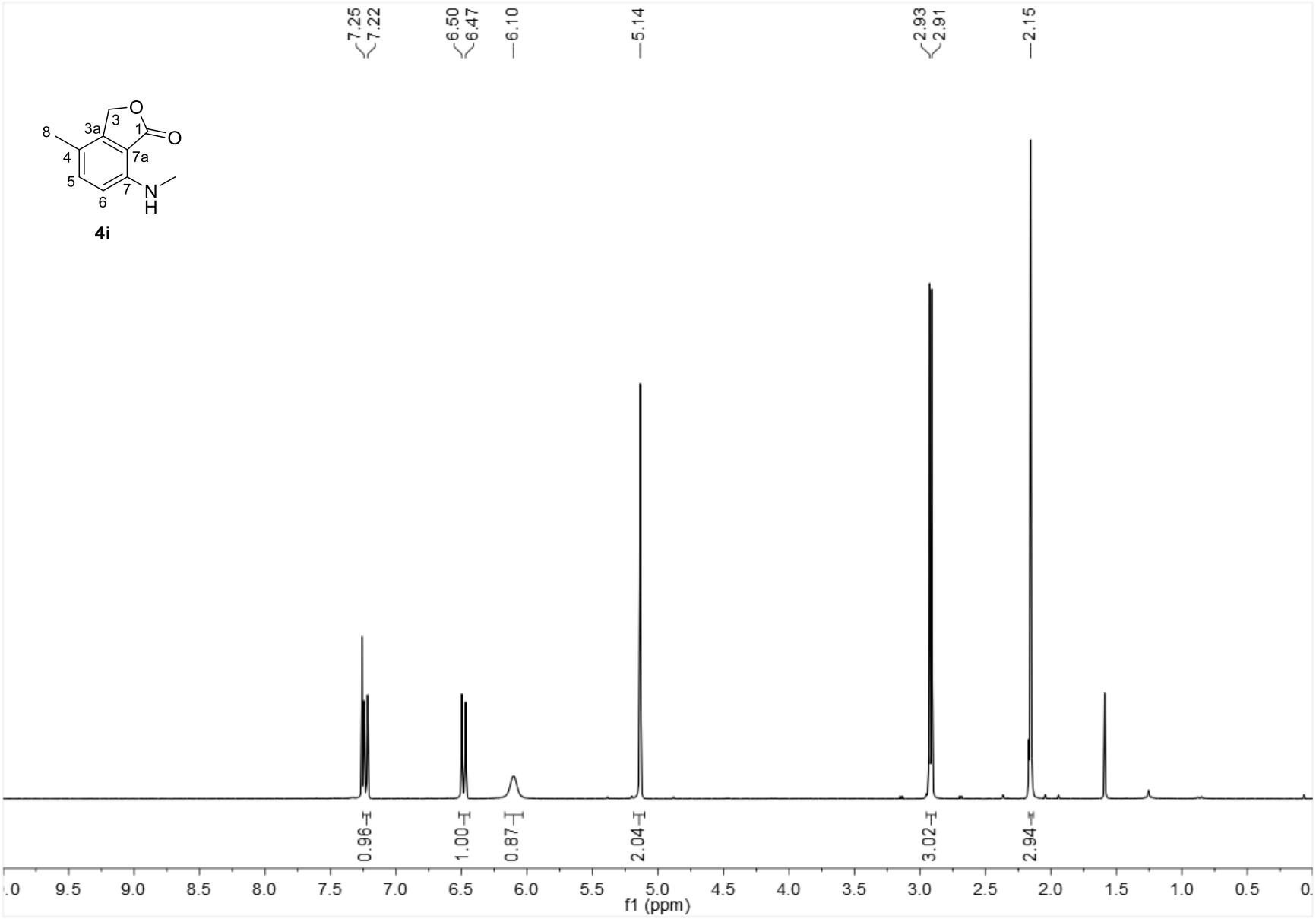
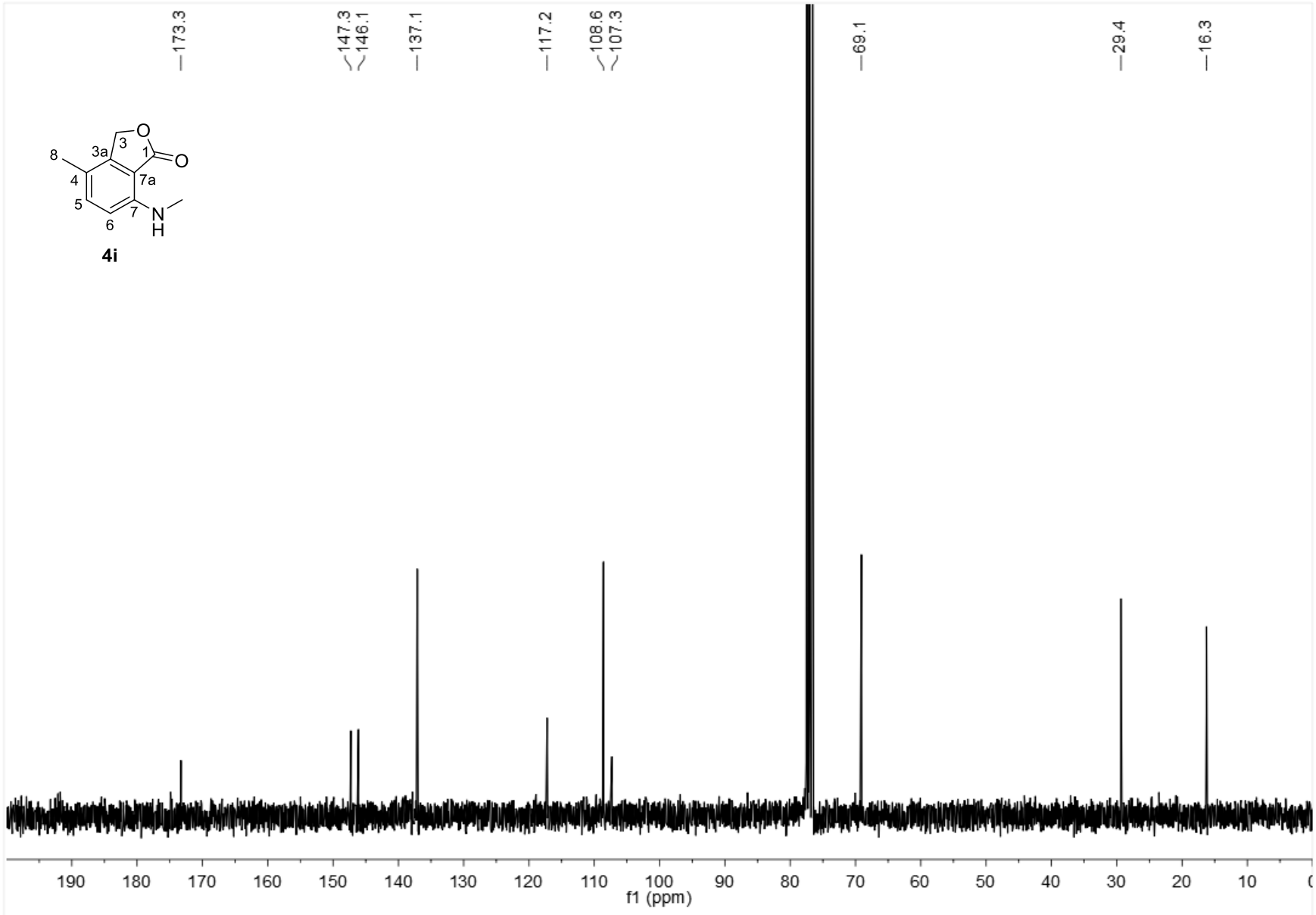
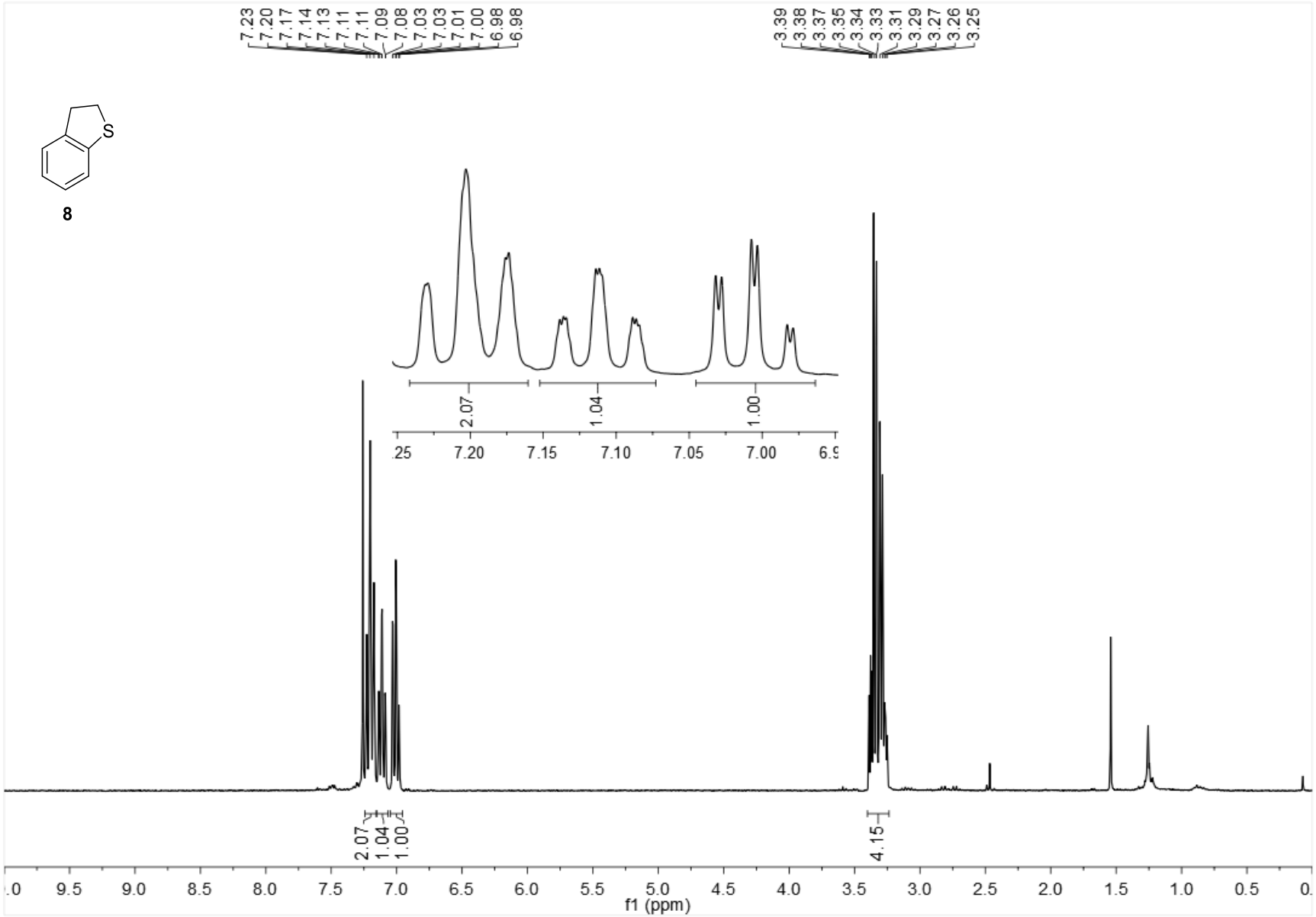
148.9
136.1
108.2
107.8
107.5
81.4
34.5
29.2
26.8
22.5
13.9
3'
1'
4'
2'
3
O
3a
1
O
4
7a
5
7
N
H
6
4g
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

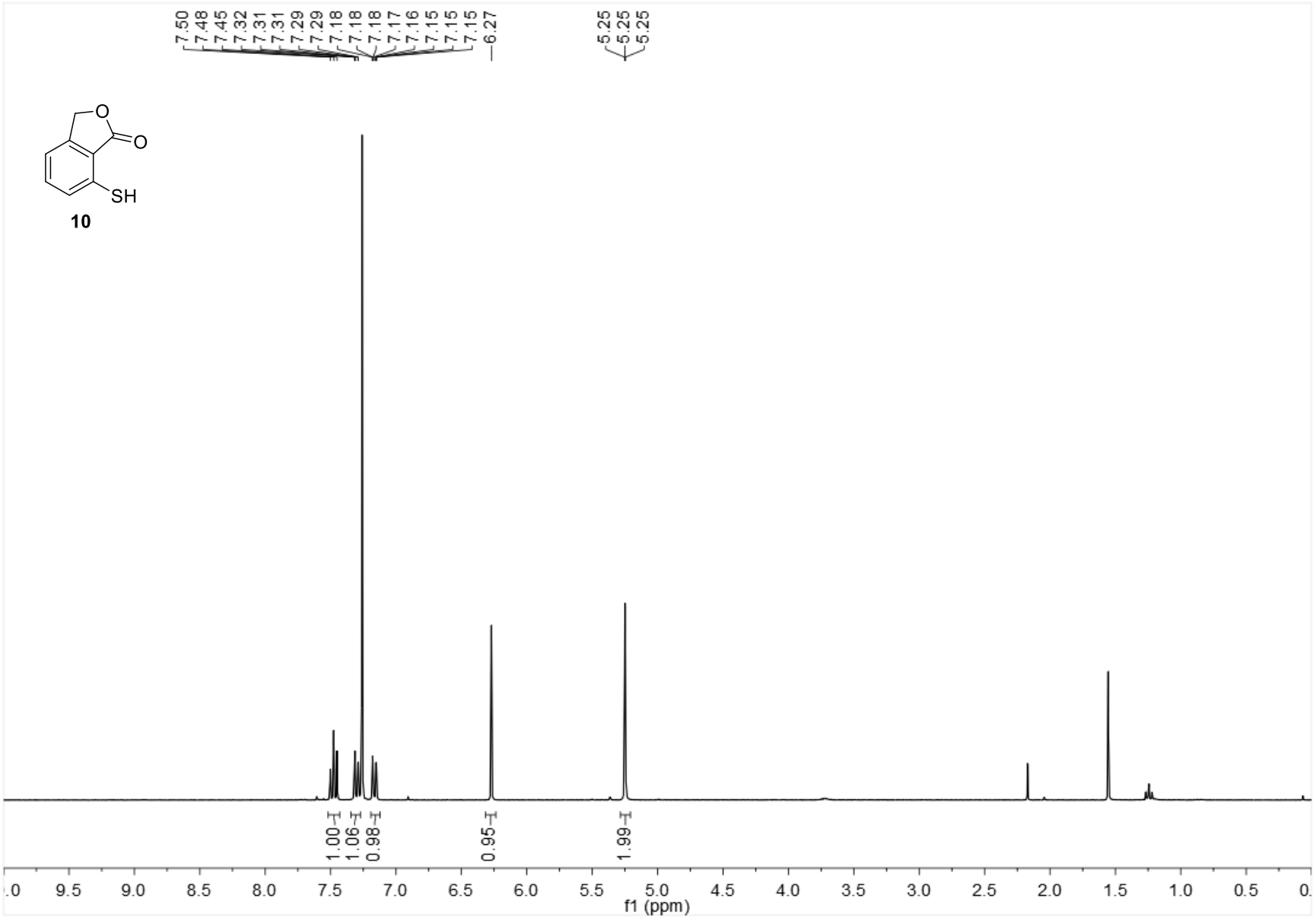

7.45
7.43
7.40
6.56
6.54
6.54
6.52
6.32
5.25
5.24
2.94
2.93
2.26
2.25
2.24
2.23
2.22
2.20
2.19
2.18
1.13
1.10
0.82
0.80
3'
1'
2'
O
3
3a
1
O
4
7a
5
7
N
H
6
4h
1.00
1.90
0.95
0.92
2.85
1.00
2.87
2.83
f1 (ppm)


172.7
150.4
148.9
136.0
108.4
108.3
108.0
85.6
32.3
29.2
18.7
15.5
3'
1'
2'
O
3
1
O
3a
4
7a
5
7
N
H
6
4h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.25
7.22
6.50
6.47
6.10
5.14
2.93
2.91
2.15
O
O
3
3a
1
8
4
7a
5
7
N
H
6
4i
0.96
1.00
0.87
2.04
3.02
2.94
f1 (ppm)


173.3
147.3
146.1
137.1
117.2
108.6
107.3
69.1
29.4
16.3
O
O
3
3a
1
8
4
7a
5
7
6
N
H
4i
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.23
7.20
7.17
7.14
7.13
7.11
7.11
7.09
7.08
7.03
7.03
7.01
7.00
6.98
6.98
3.39
3.38
3.37
3.35
3.34
3.33
3.31
3.29
3.27
3.26
3.25
S
8
2.07
1.04
1.00
4.15
f1 (ppm)


7.50
7.48
7.45
7.32
7.31
7.31
7.29
7.29
7.18
7.18
7.18
7.17
7.16
7.15
7.15
7.15
6.27
5.25
5.25
5.25
O
O
SH
10
1.00
1.06
0.98
0.95
1.99
f1 (ppm)