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Copper-Catalysed Cyanoalkylative Cycloetherification of Alkenes to 1,3-Dihydroisobenzofurans: Development and Application to the Synthesis of Citalopram

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General Information

All reactions were carried out in oven dried glasswares. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used directly unless stated otherwise. CH_3CN, DCM, THF, toluene and DMF were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 30 ppm, Karl-Fischer titration).

Chromatographic purification was conducted with technical grade solvents and silica gel 40-63 μm. TLC was performed on Merck silica gel 60 F_{254} TLC aluminium plates and visualized with UV light (254 nm), permanganate stain, phosphomolyblic acid stain, CAN stain or anisaldehyde stain.

Melting points were measured on a Stuart SMP30 melting point apparatus using open glass capillaries (uncorrected).

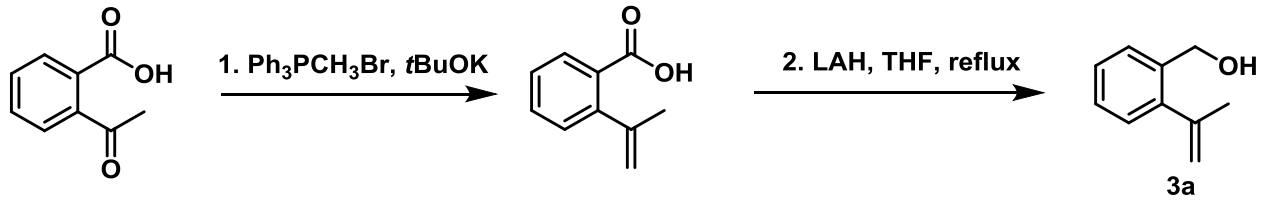
NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 at room temperature, ^{1}H frequency is at 400.13 MHz, ^{13}C frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: $CHCl_3$ [^{1}H: 7.26, ^{13}C: 77.2]; CD_3OD [^{1}H: 3.31, ^{13}C:49.0]). Coupling constants (J) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. When needed, a COSY, HSQC and/or HMBC experiments were carried out to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacle™ ATR accessory as neat films compressed onto a Zinc Selenide window. The spectra were reported in cm^{-1}.

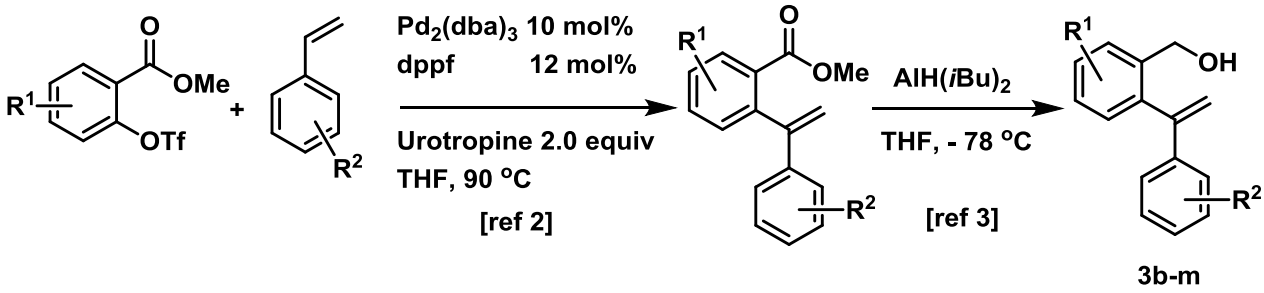
Mass spectra were determined with a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionisation (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI^+). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters or APPI-FT-ICR using a linear ion trap Fourier transform ion cyclotron resonance mass spectrometer from Thermo Scientific.

Synthesis of Compounds 3

Compound **3a** was prepared according to the reported procedure:[1]



Compounds **3b-m** were prepared in 2 steps according to the following general procedure:[2,3]

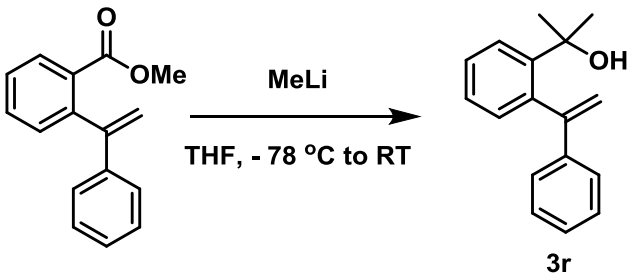


Step 1: In the glovebox, $Pd_2(dba)_3$ and dppf were dissolved in THF (0.2 M) in a sealed tube. After stirring for 10 min at room temperature, phenol triflate (1.0 equiv), styrene (2.0 equiv) and urotropine (2.0 equiv) were successively added. The reaction mixture was heated to 90 °C and stirred overnight. After quenching with water, the reaction mixture was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/30) to give the corresponding 2-vinylbenzoate.

Step 2: To a solution of 2-vinylbenzoate (1.0 equiv) in THF (0.1 M) was added dropwise at – 78 °C a solution of $AlHiBu_2$ in toluene (1.4 M, 2.5 equiv). The reaction mixture was stirred at this temperature for 1 h and then warmed up to 0 °C. After stirring for 3 h, the reaction mixture was quenched with methanol at – 78 °C, then warmed up to room temperature and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/10) to give the corresponding compound **3b-m**.

Compound **3r** was prepared from 2-(1-phenylvinyl)benzoate[2] according to the following procedure:

[1] J. F. M. Hewitt, L. Williams, P. Aggarwal, C. D. Smith, D. J. France, *Chem. Sci.* **2013**, *4*, 3538 – 3543.
[2] L. Qin, X. Ren, Y. Lu, Y. Li, J. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 5915–5919.
[3] L. Wang, G. T. Wang, X. Wang, Y. Tong, G. Sullivan, D. Park, N. M. Leonard, Q. Li, J. Cohen, W.-Z. Gu, et al., *J. Med. Chem.* **2004**, *47*, 612–626.

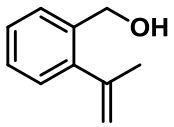


3r

To a solution of methyl 2-(1-phenylvinyl)benzoate (170 mg, 0.71 mmol) in THF (0.1 M) was added dropwise at – 78 °C a solution of MeLi in THF (1.5 M, 1.2 mL). The reaction mixture was stirred at this temperature for 1 h and then slowly warmed up to room temperature. After stirring overnight, the reaction mixture was quenched with an aqueous NH_4Cl solution, extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/50) to give compound **3r** as a colorless oil (121 mg, 71% yield).

Characterization Data of Compounds 3

(2-(prop-1-en-2-yl)phenyl)methanol (3a)



3a

Colorless oil;

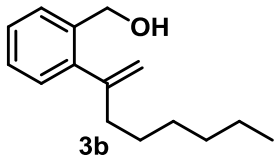
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 1H), 7.30 – 7.23 (m, 2H), 7.19 – 7.10 (m, 1H), 5.26 (p, *J* = 1.7 Hz, 1H), 4.90 (d, *J* = 1.7 Hz, 1H), 4.70 (s, 2H), 2.08 (s, 3H), 1.70 (s, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 143.2, 137.5, 128.3, 128.2, 127.7, 127.4, 115.6, 63.4, 25.2;

ATR-IR *v* 3334 (w), 3316 (w), 3304 (w), 1436 (w), 1195 (w), 1006 (m), 901 (m), 762 (s);

HRMS (ESI) calcd for $C_{10}H_{12}O$ [M+] 148.0883; found 148.0882.

(2-(oct-1-en-2-yl)phenyl)methanol (3b)



Colorless oil;

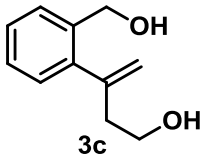
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.33 – 7.23 (m, 2H), 7.12 (dd, *J* = 7.2, 1.8 Hz, 1H), 5.21 (q, *J* = 1.7 Hz, 1H), 4.91 (d, *J* = 2.1 Hz, 1H), 4.68 (s, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 1.43 – 1.19 (m, 8H), 0.87 (t, *J* = 6.7 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 142.6, 137.8, 128.6, 128.3, 127.5, 127.3, 114.4, 63.3, 38.5, 31.8, 29.2, 27.9, 22.8, 14.2;

ATR-IR *v* 3310 (w), 2956 (w), 2927 (m), 2856 (w), 2855 (w), 1458 (w), 1034 (m), 1008 (m), 902 (m), 762 (s), 727 (m);

HRMS (ESI) calcd for $C_{15}H_{22}O$ [M+] 218.1665; found 218.1668.

3-(2-(hydroxymethyl)phenyl)but-3-en-1-ol (3c)



Colorless oil;

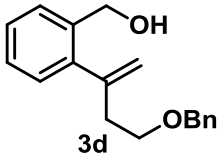
^{1}H NMR (400 MHz, CD_3OD) δ 7.50 – 7.41 (m, 1H), 7.29 – 7.21 (m, 2H), 7.16 – 7.10 (m, 1H), 5.29 (q, *J* = 1.4 Hz, 1H), 4.96 (d, *J* = 1.9 Hz, 1H), 4.63 (s, 2H), 3.55 (t, *J* = 6.7 Hz, 2H), 2.62 (td, *J* = 6.8, 1.4 Hz, 2H);

^{13}C NMR (101 MHz, CD_3OD) δ 146.9, 142.8, 139.3, 129.6, 129.2, 128.2, 128.2, 116.8, 62.8, 60.8, 42.5;

ATR-IR *v* 3319 (w), 2933 (w), 2884 (w), 1446 (w), 1427 (w), 1197 (w), 1042 (m), 1016 (s), 761 (s);

HRMS (ESI) calcd for $C_{11}H_{14}NaO_2^+$ $[M+Na]^+$ 201.0886; found 201.0886.

(2-(4-(benzyloxy)but-1-en-2-yl)phenyl)methanol (3d)



Colorless oil;

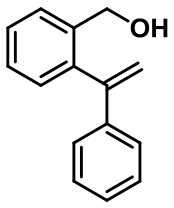
^{1}H NMR (400 MHz, CD_3OD) δ 7.45 – 7.39 (m, 1H), 7.36 – 7.21 (m, 7H), 7.16 – 7.10 (m, 1H), 5.33 (q, *J* = 1.5 Hz, 1H), 5.04 (d, *J* = 1.8 Hz, 1H), 4.68 (s, 2H), 4.43 (s, 2H), 3.50 (t, *J* = 6.1 Hz, 2H), 2.73 (t, *J* = 6.1 Hz, 2H);

^{13}C NMR (101 MHz, CD_3OD) δ 145.4, 141.5, 138.5, 138.0, 129.4, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5, 116.8, 72.8, 67.9, 63.3, 38.6;

ATR-IR *v* 3382 (w), 2914 (w), 2864 (w), 1454 (m), 1362 (w), 1096 (m), 1095 (m), 1078 (m), 1029 (m), 1007 (m), 736 (s), 698 (s);

HRMS (ESI) calcd for $C_{18}H_{20}NaO_2^+$ $[M+Na]^+$ 291.1355; found 291.1355.

(2-(1-phenylvinyl)phenyl)methanol (3e)



3e

Colorless oil;

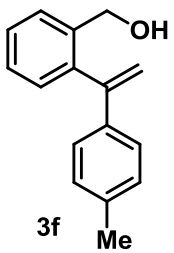
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.40 – 7.24 (m, 8H), 5.80 (d, *J* = 1.3 Hz, 1H), 5.25 (d, *J* = 1.4 Hz, 1H), 4.43 (s, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 140.8, 140.6, 138.8, 130.4, 128.7, 128.24, 128.20, 128.1, 127.8, 126.7, 115.8, 63.4;

ATR-IR *v* 3422 (w), 3416 (w), 3058 (w), 3026 (w), 2924 (w), 1493 (w), 1446 (w), 1026 (m), 757 (s), 700 (s);

HRMS (ESI) calcd for $C_{15}H_{14}O$ [M+] 210.1039; found 210.1042.

(2-(1-(p-tolyl)vinyl)phenyl)methanol (3f)



3f

Colorless oil;

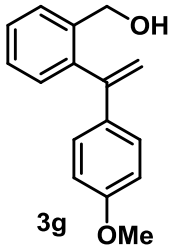
^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.36 (td, *J* = 7.6, 1.4 Hz, 1H), 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 7.17 – 7.08 (m, 5H), 5.76 (d, *J* = 1.4 Hz, 1H), 5.12 (d, *J* = 1.4 Hz, 1H), 4.37 (s, 2H), 2.31 (s, 3H);

^{13}C NMR (101 MHz, CD_3OD) δ 149.8, 141.6, 140.4, 139.1, 138.8, 130.8, 130.1, 128.7, 128.0, 127.9, 127.5, 114.7, 62.6, 21.1;

ATR-IR *v* 3325 (w), 2921 (w), 2886 (w), 2864 (w), 1510 (m), 1035 (m), 1019 (m), 826 (s), 770 (s), 735 (m);

HRMS (ESI) calcd for $C_{16}H_{16}O$ [M+] 224.1196; found 224.1200.

(2-(1-(4-methoxyphenyl)vinyl)phenyl)methanol (3g)



Colorless oil;

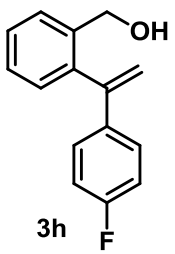
^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.36 (td, *J* = 7.5, 1.5 Hz, 1H), 7.28 (td, *J* = 7.5, 1.4 Hz, 1H), 7.19 – 7.15 (m, 3H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.70 (d, *J* = 1.4 Hz, 1H), 5.06 (d, *J* = 1.5 Hz, 1H), 4.38 (s, 2H), 3.77 (s, 3H);

^{13}C NMR (101 MHz, CD_3OD) δ 161.0, 149.3, 141.7, 140.4, 134.4, 130.8, 128.74, 128.69, 127.98, 127.96, 114.8, 113.6, 62.6, 55.7;

ATR-IR *v* 3364 (w), 2934 (w), 2836 (w), 1509 (s), 1249 (s), 1180 (m), 1033 (s), 837 (s), 773 (m);

HRMS (ESI) calcd for $C_{16}H_{16}NaO_2^+$ $[M+Na]^+$ 263.1042; found 263.1043.

(2-(1-(4-fluorophenyl)vinyl)phenyl)methanol (3h)



Colorless oil;

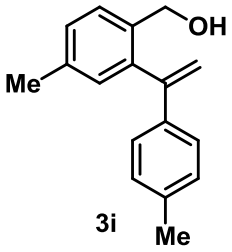
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.38 (td, *J* = 7.5, 1.6 Hz, 1H), 7.32 (td, *J* = 7.4, 1.5 Hz, 1H), 7.25 – 7.21 (m, 3H), 6.97 (t, *J* = 8.7 Hz, 2H), 5.73 (d, *J* = 1.1 Hz, 1H), 5.22 (d, *J* = 1.1 Hz, 1H), 4.43 (s, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 247.7 Hz), 147.4, 140.3, 138.7, 136.8 (d, *J* = 3.3 Hz), 130.3, 128.4 (d, *J* = 8.1 Hz), 128.3, 128.1, 127.8, 115.5 (d, *J* = 21.4 Hz), 115.5, 63.3;

ATR-IR *v* 3335 (w), 2953 (w), 2926 (w), 2898 (w), 2889 (w), 1508 (s), 1225 (m), 1161 (m), 842 (s), 773 (m);

HRMS (ESI) calcd for $C_{15}H_{13}FO$ [M+] 228.0945; found 228.0949.

(4-methyl-2-(1-(p-tolyl)vinyl)phenyl)methanol (3i)



Colorless oil;

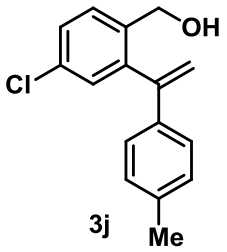
^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.14 – 7.07 (m, 4H), 6.98 (d, *J* = 1.8 Hz, 1H), 5.73 (d, *J* = 1.5 Hz, 1H), 5.10 (d, *J* = 1.5 Hz, 1H), 4.33 (s, 2H), 2.33 (s, 3H), 2.31 (s, 3H);

^{13}C NMR (101 MHz, CD_3OD) δ 149.8, 141.6, 139.2, 138.7, 137.7, 137.3, 131.5, 130.0, 129.3, 128.3, 127.5, 114.5, 62.6, 21.13, 21.10.;

ATR-IR *v* 3383 (w), 2920 (w), 2864 (w), 1510 (w), 1206 (w), 1185 (w), 1035 (m), 1018 (s), 815 (s);

HRMS (ESI) calcd for $C_{17}H_{18}O$ [M+] 238.1352; found 238.1353.

(4-chloro-2-(1-(p-tolyl)vinyl)phenyl)methanol (3j)



Colorless oil;

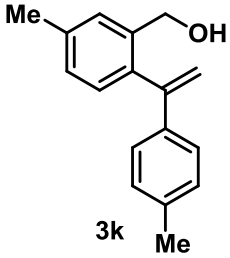
^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (d, *J* = 8.3 Hz, 1H), 7.37 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.18 – 7.08 (m, 5H), 5.79 (d, *J* = 1.1 Hz, 1H), 5.15 (d, *J* = 1.2 Hz, 1H), 4.33 (s, 2H), 2.32 (s, 3H);

^{13}C NMR (101 MHz, CD_3OD) δ 148.5, 143.3, 139.4, 139.2, 138.3, 133.6, 130.5, 130.2, 129.6, 128.7, 127.39, 115.5, 62.0, 21.2;

ATR-IR *v* 3312 (w), 3312 (w), 2921 (w), 2864 (w), 1511 (w), 1039 (m), 879 (m), 825 (s);

HRMS (ESI) calcd for $C_{16}H_{15}ClO$ [M+] 258.0806; found 258.0807.

(5-methyl-2-(1-(p-tolyl)vinyl)phenyl)methanol (3k)



Colorless oil;

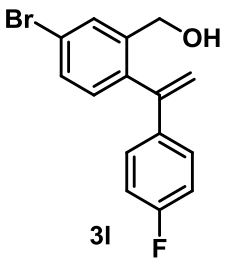
^{1}H NMR (400 MHz, CD_3OD) δ 7.36 (d, *J* = 1.8 Hz, 1H), 7.17 – 7.00 (m, 6H), 5.72 (d, *J* = 1.4 Hz, 1H), 5.10 (d, *J* = 1.4 Hz, 1H), 4.33 (s, 2H), 2.38 (s, 3H), 2.30 (s, 3H);

^{13}C NMR (101 MHz, CD_3OD) δ 149.7, 140.1, 139.3, 138.74, 138.70, 138.4, 130.9, 130.0, 128.7, 128.6, 127.5, 114.6, 62.7, 21.4, 21.1;

ATR-IR *v* 3391 (w), 2920 (w), 2863 (w), 2862 (w), 1511 (w), 1033 (m), 1032 (m), 1018 (s), 818 (s);

HRMS (ESI) calcd for $C_{17}H_{18}O$ [M+] 238.1352; found 238.1354.

(5-bromo-2-(1-(4-fluorophenyl)vinyl)phenyl)methanol (3l)



Colorless oil;

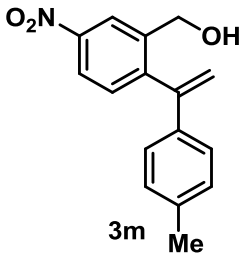
^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, *J* = 2.1 Hz, 1H), 7.45 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.26 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.03 (t, *J* = 8.8 Hz, 2H), 5.79 (d, *J* = 1.0 Hz, 1H), 5.19 (d, *J* = 1.0 Hz, 1H), 4.33 (s, 2H);

^{13}C NMR (101 MHz, CD_3OD) δ 164.0 (d, *J* = 246.4 Hz), 147.7, 143.2, 140.0, 137.7 (d, *J* = 3.3 Hz), 132.6, 131.0, 130.9, 129.5 (d, *J* = 8.2 Hz), 122.9, 116.3 (d, *J* = 22.1 Hz), 116.3, 62.0;

ATR-IR *v* 3309 (w), 2926 (w), 2855 (w), 1507 (s), 1225 (m), 1160 (m), 1037 (m), 1014 (m), 842 (s), 825 (s);

HRMS (ESI) calcd for $C_{15}H_{12}BrFO$ [M+] 306.0050; found 306.0054.

(5-nitro-2-(1-(p-tolyl)vinyl)phenyl)methanol (3m)



Yellow oil;

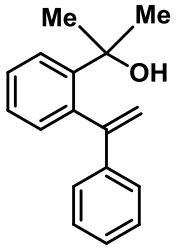
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.15 – 7.08 (m, 4H), 5.84 (d, *J* = 0.8 Hz, 1H), 5.22 (d, *J* = 0.8 Hz, 1H), 4.50 (s, 2H), 2.35 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 147.0, 146.6, 141.0, 138.8, 136.4, 131.1, 129.6, 126.4, 122.6, 122.5, 116.0, 62.2, 21.3;

ATR-IR *v* 3324 (w), 2951 (w), 2924 (w), 2856 (w), 1519 (s), 1344 (s), 1039 (w), 905 (w), 827 (m);

HRMS (ESI) calcd for $C_{16}H_{15}NO_3$ [M+] 269.1046; found 269.1049.

2-(2-(1-phenylvinyl)phenyl)propan-2-ol (3r)



3r

Colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.34 – 7.24 (m, 7H), 7.11 (dd, *J* = 7.5, 1.5 Hz, 1H), 5.87 (d, *J* = 1.3 Hz, 1H), 5.23 (d, *J* = 1.3 Hz, 1H), 1.49 (s, 6H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 146.7, 141.1, 138.5, 132.6, 128.5, 127.9, 127.6, 126.7, 126.6, 126.5, 114.4, 74.4, 32.5;

ATR-IR *v* 3432 (w), 2972 (w), 2929 (w), 1494 (w), 1363 (w), 1166 (w), 902 (m), 783 (m), 761 (s), 712 (s);

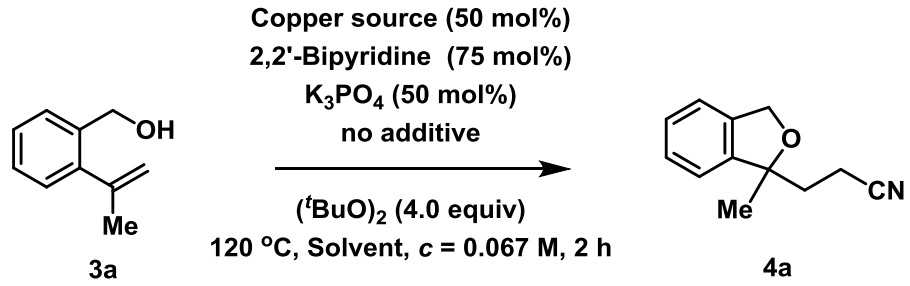
HRMS (ESI) calcd for $C_{17}H_{18}O$ [M+] 238.1352; found 238.1354.

Optimization of The Reaction Conditions

Procedure:

In the glovebox, alkene **3a** (0.1 mmol, 1 equiv), copper catalyst (*x* equiv), ligand (*y* equiv), base (*z* equiv), and additive (*t* equiv) were dissolved in degassed MeCN/MeOH (0.067 M) in a sealed tube. Oxidant (*u* equiv) was then added and the tube was sealed and heated to 100 – 120 °C. After 2 – 24 h, the reaction mixture was cooled down to room temperature, diluted with water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **4a**.

Copper catalyst screening



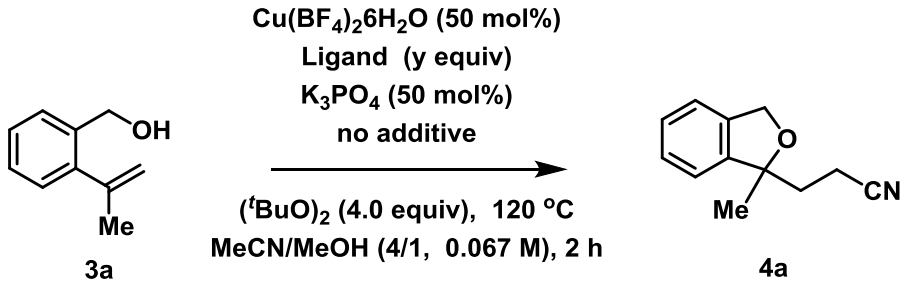
Entry	Cu source (50 mol%)	Solvent	Yield/Conversion[(a)]
1	**$Cu(BF_4)_2.6H_2O$**	MeCN	24% (20%)[(b)] **4a**, 100% conv.
2	**$Cu(OTf)_2$**	MeCN	20% **4a**, 100% conv.
3	**$Cu(OAc)_2$**	MeCN	22% **4a**, 90% conv.
4	**$CuCl_2$**	MeCN	degradation
5	**$CuSO_4$**	MeCN	<10% **4a**, 82% conv.
6	**CuF_2**	MeCN	No reaction
7	**Cu_2O**	MeCN	No reaction
8	**CuCl**	MeCN	22% **4a**, 100% conv.
9	**CuBr**	MeCN	<10% **4a**, 100% conv.
10	**CuI**	MeCN	No reaction
11	**$Cu(acac)_2$**	MeCN	22% **4a**, 73% conv.

12	**$Cu(acac)_2$**	MeCN/MeOH (4/1)	<10% **4a**, 84% conv.
13	**$Cu(BF_4)_2.6H_2O$**	MeCN/MeOH (4/1)	37% (29%)[(b)] **4a**, 100% conv.
14	**$Cu(OTf)_2$**	MeCN/MeOH (4/1)	36% **4a**, 100% conv.
15	**$Cu(OAc)_2$**	MeCN/MeOH (4/1)	25% **4a**, 80% conv.

(a) Yield determined by ^1H NMR spectroscopy with CH_2Br_2 as internal standard

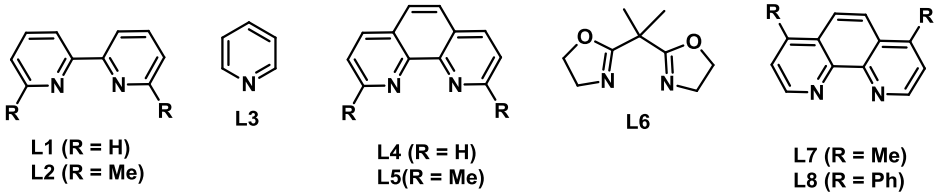
(b) Isolated yield.

Ligand screening



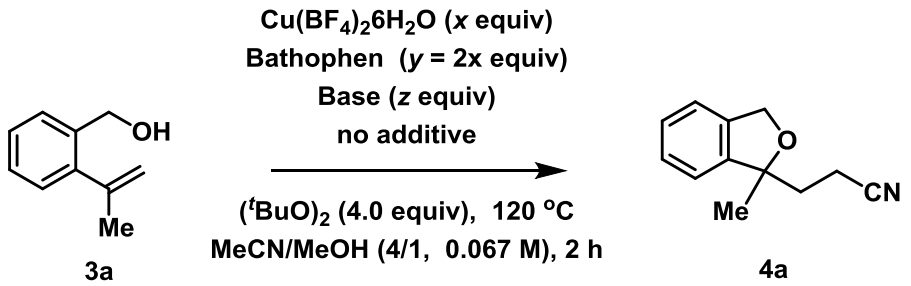
Entry	Ligand (*y* equiv)	Yield/Conversion[(a)]
1	**L1 (0.75)**	37% (29%)[(b)] **4a**, 100% conv.
2	**L2 (0.75)**	0% **4a**, 80% conv.
3	**L3 (1.50)**	<10% **4a**, 84% conv.
4	**L4 (0.75)**	47% (40%)[(b)] **4a**, 100% conv.
5	**L5 (0.75)**	0% **4a**, 63% conv.
6	**L6 (0.75)**	34% **4a**, 100% conv.
7	**L7 (0.75)**	19% **4a**, 76% conv.
8	**L8 (0.75)**	53% (44%)[(b)] **4a**, 100% conv.
9	**L8 (0.25)**	42% **4a**, 100% conv.
10	**L8 (0.50)**	50% **4a**, 100% conv.
11	**L8 (1.00)**	57% (51%)[(b)] **4a**, 100% conv.

(a) Yield determined by ^{1}H NMR spectroscopy with CH_2Br_2 as internal standard
(b) Isolated yield.



Selected ligands used for screening

Base screening

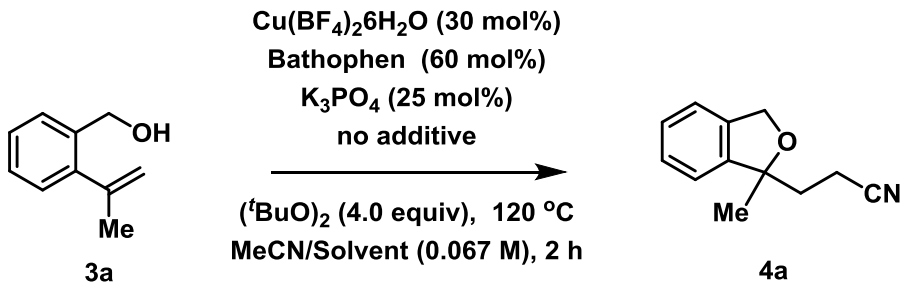


Entry	$Cu(BF_4)_2.6H_2O$ (*x* equiv)	Base (*z* equiv)	Yield/Conversion[(a)]
1	0.5	**K_3PO_4 (0.5)**	57% (51%)[(b)] **4a**, 100% conv.
2	0.5	**Na_3PO_4 (0.5)**	43% **4a**, 100% conv.
3	0.5	**Na_2HPO_4 (0.5)**	13% **4a**, 60% conv.
4	0.5	**K_2CO_3 (0.5)**	45% **4a**, 90% conv.
5	0.5	**CsOPiv (0.5)**	34% **4a**, 83% conv.
6	0.5	**KOH (0.5)**	43% **4a**, 100% conv.
7	0.5	***t*BuOK (0.25)**	54% **4a**, 100% conv.
8	0.5	**none**	20% **4a**, 64% conv.
9	0.3	**K_3PO_4 (0.5)**	50% **4a**, 90% conv.
10	0.2	**K_3PO_4 (0.5)**	30% **4a**, 72% conv.
11	0.1	**K_3PO_4 (0.5)**	26% **4a**, 72% conv.
12	0.3	**K_3PO_4 (0.25)**	52% **4a**, 92% conv.

(a) Yield determined by ^{1}H NMR spectroscopy with CH_2Br_2 as internal standard;

(b) Isolated yield.

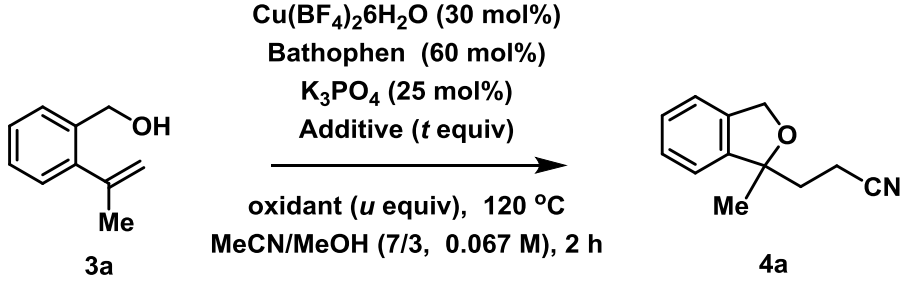
Solvent screening



Entry	Solvents	Yield/Conversion[(a)]
1	**MeCN/MeOH (4/1)**	52% **4a**, 92% conv.
2	**MeCN/EtOH (4/1)**	40% **4a**, 90% conv.
3	**MeCN/*i*PrOH (4/1)**	19% **4a**, 96% conv.
4	**MeCN/*t*BuOH (4/1)**	28% **4a**, 100% conv.
5	**MeCN/CF_3CH_2OH (4/1)**	26% **4a**, 100% conv.
6	**MeCN/H_2O (4/1)**	39% **4a**, 78% conv.
7	**MeCN/MeOH (9/1)**	33% **4a**, 99% conv.
8	**MeCN/MeOH (7/3)**	54% (56%)[(b,c)] **4a**, 90% conv.
9	**MeCN/MeOH (6/4)**	43% **4a**, 83% conv.

(a) Yield determined by ^{1}H NMR spectroscopy with CH_2Br_2 as internal standard
(b) Isolated yield
(c) Reaction time: 3.5 h

Oxidant and Additive screening



Entry	Oxidant (*u* equiv)	Additive (*t* equiv)	Yield/Conversion[(a)]
1	**O1 (4.0)**	none	54% **4a**, 90% conv.
2	**O2 (4.0)**	none	50% **4a**, 100% conv.
3	**O3 (4.0)**	none	50% **4a**, 94% conv.
4	**O4 (4.0)**	none	<10% **4a**, 100% conv.
5	**O1 (3.0)**	none	52% **4a**, 90% conv.
6	**O1 (2.0)**	none	39% **4a**, 80% conv.
7	O4 (4.0)	**BnOH (2.0)**	43% **4a**, 95% conv.
8	O4 (4.0)	**BnOH (1.6)**	58% **4a**, 94% conv.
9	O4 (4.0)	**BnOH (1.2)**	61% (62%)[(b,c)] **4a**, 94% conv.
10	O4 (4.0)	**BnOH (0.7)**	55% **4a**, 95% conv.
11	O4 (4.0)	***p*-$NO_2C_6H_4CH_2OH$ (1.2)**	48% **4a**, 90% conv.
12	O4 (4.0)	***p*-$ClC_6H_4CH_2OH$ (1.2)**	59% **4a**, 93% conv.
13	O4 (4.0)	***p*-$MeOC_6H_4CH_2OH$ (1.2)**	59% **4a**, 91% conv.
14	O4 (4.0)	**Pinacol (1.2)**	25% **4a**, 95% conv.
15	O4 (4.0)	**Benzaldehyde (1.2)**	38% **4a**, 59% conv.
16	O4 (4.0)	**1-Phenylethanol (1.0)**	52% **4a**, 91% conv.
17	O4 (4.0)	**Diphenylcarbinol (1.0)**	60% **4a**, 89% conv.
18	O4 (4.0)	**Diphenylcarbinol (2.0)**	61% **4a**, 93% conv.
19[(d)]	O4 (4.0)	**BnOH (1.2)**	69% (65%)[(b)] **4a**, 100% conv.

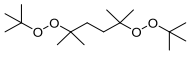
(a) Yield determined by ^{1}H NMR spectroscopy with CH_2Br_2 as internal standard;

(b) Isolated yield

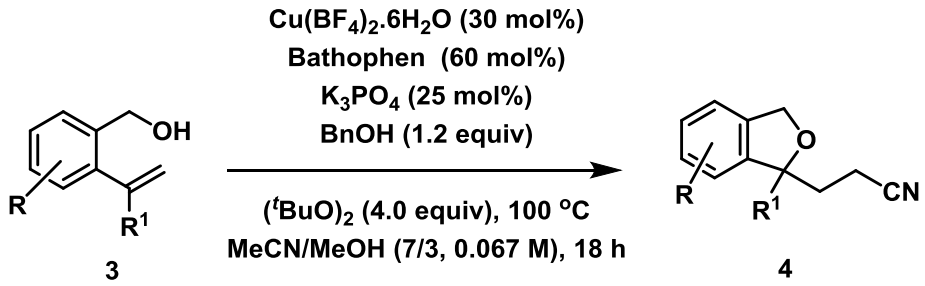
(c) Reaction time : 3 h

(d) Reaction was conducted at 100 ^oC.

O1 = DTBP (di-*tert*-butyl peroxide) **O2 = Dicumyl peroxide**

O3 =  **O4 = *tert*-butyl benzoyl peroxide**

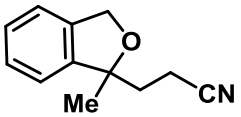
General Procedure for The Synthesis of Dihydroisobenzofurans 4



In the glovebox, alkene **3** (0.1 mmol, 1 equiv), $Cu(BF_4)_2.6H_2O$ (30 mol%), bathophenanthroline (60 mol%), BnOH (120 mol%), and K_3PO_4 (25 mol%) were dissolved in degassed MeCN/MeOH (v/v 7/3, 0.067 M) in a sealed tube. ($^tBuO)_2$ (4 equiv) was then added and the tube was sealed and heated to 100 ^oC. After 18 h, the reaction mixture was cooled down to room temperature, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **4**.

Characterization Data of Compounds 4

3-(1-methyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4a)



4a

Yield: 12.2 mg (65%), colorless oil;

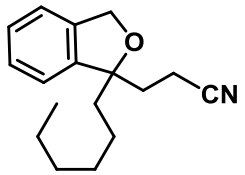
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.10 – 7.06 (m, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.05 (d, *J* = 12.5 Hz, 1H), 2.34 (ddd, *J* = 16.1, 10.0, 5.7 Hz, 1H), 2.24 (ddd, *J* = 13.6, 9.9, 5.7 Hz, 1H), 2.14 (ddd, *J* = 13.7, 9.9, 5.1 Hz, 1H), 2.10 – 1.99 (m, 1H), 1.49 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1, 139.1, 128.3, 128.0, 121.5, 120.9, 120.1, 87.1, 72.0, 37.1, 27.5, 12.4;

ATR-IR *v* 2970 (w), 2928 (w), 2856 (w), 2247 (w), 1454 (w), 1359 (w), 1031 (s), 1019 (s), 763 (s), 726 (s);

HRMS (ESI) calcd for $C_{12}H_{12}NO$ [M+] 186.0913; found 186.0916.

3-(1-hexyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4b)



4b

Yield: 16.1 mg (63%), colorless oil;

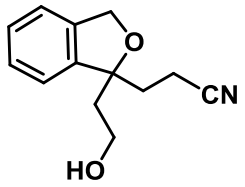
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 2H), 7.13 – 7.07 (m, 1H), 6.99 – 6.91 (m, 1H), 4.99 (s, 2H), 2.26 – 2.09 (m, 2H), 2.07 – 1.96 (m, 1H), 1.86 (ddd, *J* = 17.0, 10.6, 5.1 Hz, 1H), 1.75 – 1.58 (m, 2H), 1.20 – 1.05 (m, 7H), 0.90 – 0.82 (m, 1H), 0.73 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 139.9, 128.2, 128.0, 121.3, 121.2, 120.2, 90.1, 73.2, 41.3, 36.5, 31.8, 29.6, 23.6, 22.7, 14.2, 12.2;

ATR-IR *v* 2929 (m), 2929 (m), 2929 (m), 2856 (w), 2248 (w), 1463 (m), 999 (s), 756 (s), 701 (m);

HRMS (ESI) calcd for $C_{17}H_{23}NNaO^+$ $[M+Na]^+$ 280.1672; found 280.1670.

3-(1-(2-hydroxyethyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4c)



4c

Yield: 10.6 mg (52%), colorless oil;

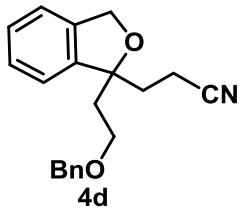
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.27 – 7.25 (m, 1H), 7.09 – 7.04 (m, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 3.67 (ddd, *J* = 11.4, 6.8, 4.8 Hz, 1H), 3.58 (ddd, *J* = 11.4, 6.8, 4.8 Hz, 1H), 2.43 – 2.23 (m, 1H), 2.18 – 1.95 (m, 4H), 1.64 (broad, s, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 139.3, 128.8, 128.4, 121.7, 121.1, 119.8, 90.6, 73.0, 59.3, 42.2, 36.2, 12.1;

ATR-IR *v* 3423 (w), 2952 (w), 2923 (w), 2912 (w), 1028 (s), 1018 (s), 761 (s), 726 (m);

HRMS (ESI) calcd for $C_{13}H_{15}NNaO_2^+$ $[M+Na]^+$ 240.0995; found 240.0994.

3-(1-(2-hydroxyethyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4d)



4d

Yield: 15.3 mg (49%), colorless oil;

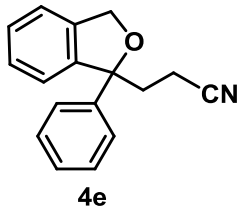
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 5H), 7.23 – 7.17 (m, 3H), 7.12 – 7.03 (m, 1H), 5.08 (d, *J* = 12.5 Hz, 1H), 5.04 (d, *J* = 12.5 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.35 (d, *J* = 11.8 Hz, 1H), 3.53 (ddd, *J* = 9.4, 7.3, 6.1 Hz, 1H), 3.33 (ddd, *J* = 9.4, 7.3, 6.3 Hz, 1H), 2.38 – 2.22 (m, 2H), 2.22 – 2.07 (m, 3H), 1.98 (ddd, *J* = 14.6, 11.0, 4.8 Hz, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 139.5, 138.2, 128.5, 128.4, 128.1, 127.8, 127.7, 121.5, 121.4, 120.0, 88.8, 73.2, 72.9, 66.2, 40.6, 36.6, 12.1;

ATR-IR *v* 2925 (w), 2856 (w), 2246 (w), 1456 (m), 1367 (m), 1366 (m), 1102 (s), 1027 (s), 730 (s), 699 (s);

HRMS (ESI) calcd for $C_{20}H_{21}NNaO_2^+$ $[M+Na]^+$ 330.1464; found 330.1464.

3-(1-phenyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4e)



4e

Yield: 14.6 mg (58%), yellow oil;

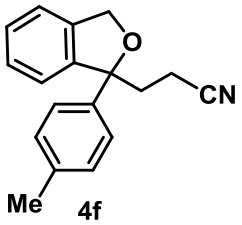
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 2H), 7.39 – 7.15 (m, 7H), 5.20 (d, *J* = 12.5 Hz, 1H), 5.15 (d, *J* = 12.5 Hz, 1H), 2.59 (ddd, *J* = 13.9, 10.2, 5.9 Hz, 1H), 2.47 (ddd, *J* = 14.0, 9.6, 5.7 Hz, 1H), 2.37 – 2.13 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 142.4, 139.2, 128.7, 128.4, 128.0, 127.7, 125.0, 121.9, 121.6, 120.0, 89.9, 72.2, 37.3, 12.7;

ATR-IR *v* 2929 (w), 2928 (w), 2853 (w), 2853 (w), 2247 (w), 1459 (w), 1446 (w), 1018 (m), 753 (s), 753 (s), 725 (s), 700 (s);

HRMS (ESI) calcd for $C_{17}H_{15}NNaO^+$ $[M+Na]^+$ 272.1046; found 272.1048.

3-(1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4f)



4f

Yield: 20.0 mg (76%), colorless oil;

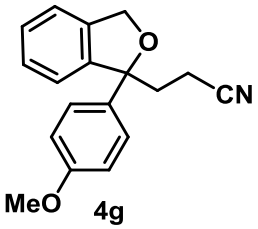
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.24 – 7.19 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.19 (d, *J* = 12.5 Hz, 1H), 5.15 (d, *J* = 12.5 Hz, 1H), 2.58 (ddd, *J* = 13.9, 10.4, 5.7 Hz, 1H), 2.46 (ddd, *J* = 13.9, 9.8, 5.6 Hz, 1H), 2.37 – 2.17 (m, 2H), 2.32 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 140.6, 139.1, 137.4, 129.4, 128.3, 128.0, 124.9, 121.8, 121.6, 120.0, 89.9, 72.2, 37.2, 21.1, 12.7;

ATR-IR *v* 2953 (w), 2945 (w), 2923 (w), 2858 (w), 2247 (w), 1509 (w), 1459 (w), 1017 (s), 817 (s), 758 (s), 732 (s);

HRMS (ESI) calcd for $C_{18}H_{17}NNaO^+$ $[M+Na]^+$ 286.1202; found 286.1205.

3-(1-(4-methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4g)



4g

Yield: 22.9 mg (82%), colorless oil;

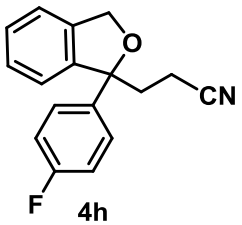
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.8 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.23 – 7.19 (m, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.18 (d, *J* = 12.5 Hz, 1H), 5.13 (d, *J* = 12.5 Hz, 1H), 3.78 (s, 3H), 2.58 (ddd, *J* = 13.8, 10.4, 5.6 Hz, 1H), 2.45 (ddd, *J* = 13.8, 9.9, 5.4 Hz, 1H), 2.37 – 2.14 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 142.6, 139.2, 135.6, 128.3, 128.0, 126.3, 121.8, 121.6, 120.0, 114.1, 89.7, 72.1, 55.4, 37.2, 12.7;

ATR-IR *v* 2952 (w), 2932 (w), 2839 (w), 2246 (w), 1509 (s), 1248 (s), 1029 (s), 830 (s), 760 (s), 735 (s);

HRMS (ESI) calcd for $C_{18}H_{17}NNaO_2^+$ $[M+Na]^+$ 302.1151; found 302.1163.

3-(1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4h)



4h

Yield: 13.9 mg (52%), white solid, mp: 123 – 124 ^oC;

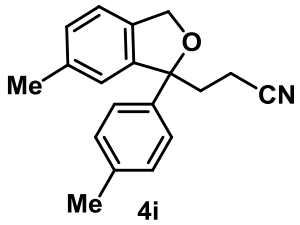
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 2H), 7.36 – 7.28 (m, 3H), 7.25 – 7.22 (m, 1H), 7.09 – 6.92 (m, 2H), 5.19 (d, *J* = 12.5 Hz, 1H), 5.14 (d, *J* = 12.5 Hz, 1H), 2.56 (ddd, *J* = 13.9, 10.2, 5.9 Hz, 1H), 2.46 (ddd, *J* = 14.0, 9.6, 5.6 Hz, 1H), 2.38 – 2.12 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (d, *J* = 246.5 Hz), 142.0, 139.4 (d, *J* = 3.1 Hz), 139.2, 128.5, 128.1, 126.8 (d, *J* = 8.0 Hz), 121.8, 121.7, 119.8, 115.6 (d, *J* = 21.4 Hz), 89.6, 72.2, 37.3, 12.7;

ATR-IR *v* 2934 (w), 2933 (w), 2932 (w), 2916 (w), 2863 (w), 2241 (w), 1506 (s), 1219 (m), 1158 (m), 1009 (s), 832 (s), 767 (s), 738 (s);

HRMS (ESI) calcd for $C_{17}H_{14}FNNaO^+$ $[M+Na]^+$ 290.0952; found 290.0957.

3-(6-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4i)



4i

Yield: 21.0 mg (76%), white solid, mp: 61 – 63 ^oC;

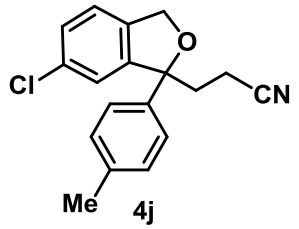
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.10 – 7.08 (m, 3H), 5.16 (d, *J* = 12.5 Hz, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 2.57 (ddd, *J* = 13.8, 10.6, 5.6 Hz, 1H), 2.45 (ddd, *J* = 13.8, 10.1, 5.3 Hz, 1H), 2.38 (s, 3H), 2.37 – 2.18 (m, 2H), 2.32 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 140.8, 137.8, 137.3, 136.2, 129.4, 129.2, 124.9, 122.3, 121.2, 120.1, 89.8, 72.1, 37.1, 21.6, 21.1, 12.7;

ATR-IR *v* 2955 (w), 2954 (w), 2920 (w), 2920 (w), 2853 (w), 2251 (w), 1437 (w), 1356 (w), 1270 (w), 1022 (s), 1011 (s), 821 (s);

HRMS (ESI) calcd for $C_{19}H_{19}NNaO^+$ $[M+Na]^+$ 300.1359; found 300.1365.

3-(6-chloro-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4j)



4j

Yield: 24.0 mg (81%), colorless oil;

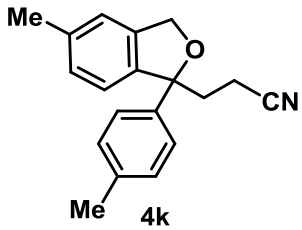
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.14 (dd, *J* = 7.8, 0.9 Hz, 1H), 5.16 (d, *J* = 12.6 Hz, 1H), 5.13 (d, *J* = 12.6 Hz, 1H), 2.56 (ddd, *J* = 13.9, 9.4, 6.6 Hz, 1H), 2.42 (ddd, *J* = 13.9, 8.4, 6.9 Hz, 1H), 2.33 – 2.23 (m, 2H), 2.30 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 139.8, 137.8, 137.5, 133.9, 129.6, 128.6, 124.8, 122.8, 122.1, 119.8, 89.8, 71.8, 37.0, 21.1, 12.7;

ATR-IR *v* 2955 (w), 2926 (w), 2925 (w), 2870 (w), 2245 (w), 1510 (w), 1476 (w), 1030 (s), 817 (s);

HRMS (ESI) calcd for $C_{18}H_{16}ClNNaO^+$ $[M+Na]^+$ 320.0813; found 320.0817.

3-(5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4k)



4k

Yield: 22.1 mg (80%), colorless oil;

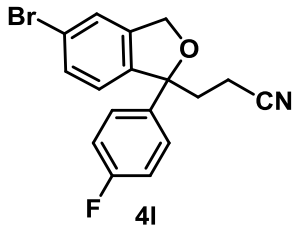
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.13 – 7.10 (m, 1H), 7.02 (s, 1H), 5.16 (d, *J* = 12.5 Hz, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 2.56 (ddd, *J* = 13.8, 10.4, 5.7 Hz, 1H), 2.44 (ddd, *J* = 13.8, 9.9, 5.4 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.33 – 2.19 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 139.7, 139.5, 138.3, 137.3, 129.4, 128.8, 124.9, 122.0, 121.5, 120.1, 89.7, 72.0, 37.2, 21.4, 21.1, 12.7;

ATR-IR *v* 2946 (w), 2945 (w), 2924 (w), 2859 (w), 2247 (w), 1511 (w), 1441 (w), 1028 (s), 1027 (s), 1017 (s), 815 (s);

HRMS (ESI) calcd for $C_{19}H_{19}NNaO^+$ $[M+Na]^+$ 300.1359; found 300.1363.

3-(5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4l)



4l

Yield: 24.4 mg (71%), yellow oil;

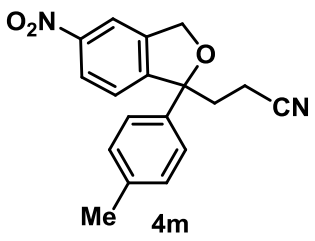
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 1H), 7.43 – 7.37 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.06 – 6.99 (m, 2H), 5.16 (d, *J* = 12.9 Hz, 1H), 5.09 (d, *J* = 12.9 Hz, 1H), 2.54 (ddd, *J* = 13.9, 9.9, 6.0 Hz, 1H), 2.42 (ddd, *J* = 13.9, 9.1, 5.9 Hz, 1H), 2.35 – 2.20 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (d, *J* = 247.0 Hz), 141.5, 141.3, 138.7 (d, *J* = 3.2 Hz), 131.3, 126.7 (d, *J* = 8.1 Hz), 125.1, 123.3, 122.6, 119.6, 115.7 (d, *J* = 21.4 Hz), 89.5, 71.5, 37.1, 12.6;

ATR-IR *v* 2955 (w), 2925 (w), 2862 (w), 2861 (w), 2243 (w), 1506 (s), 1222 (s), 1024 (s), 845 (s), 817 (s), 742 (m);

HRMS (ESI) calcd for $C_{17}H_{13}BrFNNaO^+$ $[M+Na]^+$ 368.0057; found 368.0058.

3-(5-nitro-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4m)



4m

Yield: 24.3 mg (79%), yellow oil;

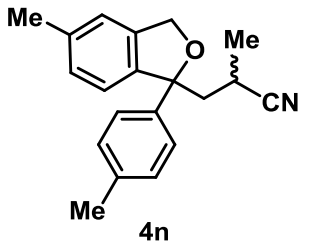
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.09 (d, *J* = 1.8 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.28 (d, *J* = 13.1 Hz, 1H), 5.21(d, *J* = 13.1 Hz, 1H), 2.62 (ddd, *J* = 13.9, 8.6, 7.1 Hz, 1H), 2.47 (ddd, *J* = 14.0, 9.1, 6.3 Hz, 1H), 2.32 (s, 3H), 2.34 – 2.30 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 148.6, 140.9, 138.7, 138.2, 129.8, 124.8, 124.0, 122.6, 119.5, 117.4, 89.8, 71.4, 36.8, 21.1, 12.6;

ATR-IR *v* 2954 (w), 2953 (w), 2925 (w), 2869 (w), 2859 (w), 2858 (w), 2247 (w), 1521 (s), 1345 (s), 1032 (m), 1018 (m), 816 (s), 729 (m);

HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_3^+$ $[M+Na]^+$ 331.1053; found 331.1051.

2-methyl-3-(5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4n)



4n
dr = 1/1

Yield: 21.5 mg (74%), colorless oil;

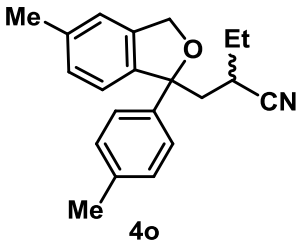
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 0.5H), 7.17 (d, *J* = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.02 (s, 0.5H), 7.01 (s, 0.5H), 5.25 – 5.05 (m, 2H), 2.72 – 2.42 (m, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 2.31 – 2.19 (m, 1H), 1.29 (d, *J* = 7.1 Hz, 1.5H), 1.28 (d, *J* = 7.1 Hz, 1.5H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 141.4, 140.1, 140.0, 139.8, 139.3, 138.2, 138.1, 137.14, 137.09, 129.32, 129.27, 128.63, 128.61, 124.9, 124.8, 123.5, 123.4, 122.2, 122.1, 121.9, 121.5, 90.1, 89.9, 71.9 (2C), 45.6, 45.5, 21.7, 21.4, 21.4, 21.3, 21.1, 21.0, 19.8, 19.5;

ATR-IR *v* 2939 (w), 2938 (w), 2921 (w), 2858 (w), 2857 (w), 2852 (w), 2238 (w), 1510 (w), 1454 (w), 1031 (s), 1018 (s), 819 (s), 813 (s);

HRMS (ESI) calcd for $C_{20}H_{21}NNaO^+$ $[M+Na]^+$ 314.1515; found 314.1514.

2-((5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)methyl)butanenitrile (4o)



4o
dr = 1.1/1.0

Yield: 20.4 mg (67%), colorless oil;

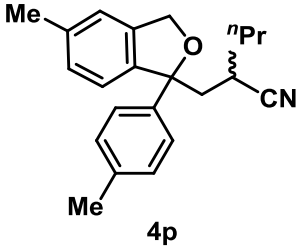
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 7.28 (d, *J* = 7.8 Hz, 0.5H), 7.19 (d, *J* = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.04 (s, 0.53H), 7.02 (s, 0.47H), 5.25 – 5.09 (m, 2H), 2.64 – 2.52 (m, 1.5H), 2.36 (s, 1.5H), 2.35 (s, 1.5H), 2.31 (s, 3H), 2.40 – 2.22 (m, 1.5H), 1.68 – 1.58 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 1.5H), 1.01 (t, *J* = 7.4 Hz, 1.5H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 141.5, 140.1, 140.0, 139.9, 139.3, 138.2, 138.1, 137.1, 137.0, 129.3, 129.2, 128.63, 128.59, 124.9, 124.8, 122.6, 122.5, 122.2, 122.1, 121.9, 121.4, 90.2, 89.9, 72.0, 71.9, 43.7 (2C), 29.0, 28.6, 27.1, 26.6, 21.4, 21.3, 21.1, 21.0, 11.5, 11.4;

ATR-IR *v* 2967 (w), 2926 (w), 2861 (w), 2237 (w), 1510 (w), 1459 (w), 1033 (s), 811 (s);

HRMS (ESI) calcd for $C_{21}H_{23}NNaO^+$ $[M+Na]^+$ 328.1672; found 328.1673.

2-((5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)methyl)pentanenitrile (4p)



4p
dr = 1.1/1.0

Yield: 21.1 mg (66%), colorless oil;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 0.5H), 7.18 (d, *J* = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.04 (s, 0.53H), 7.02 (s, 0.47H), 5.25 – 5.09 (m, 2H), 2.64 – 2.52 (m, 1.5H), 2.45 – 2.38

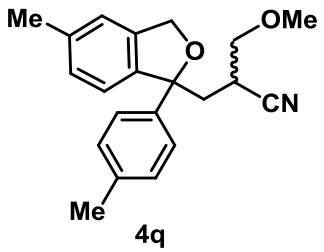
(m, 0.5H), 2.36 (s, 1.5H), 2.35 (s, 1.5H), 2.31 (s, 3H), 2.33 – 2.22 (m, 1H), 1.62 – 1.50 (m, 3H), 1.44 – 1.35 (m, 1H), 0.88 (t, *J* = 7.3 Hz, 1.5H), 0.87 (t, *J* = 7.3 Hz, 1.5H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 141.5, 140.1, 140.0, 139.9, 139.3, 138.2, 138.1, 137.1, 137.0, 129.3, 129.2, 128.62, 128.6, 125.0, 124.8, 122.8, 122.7, 122.2, 122.1, 121.9, 121.4, 90.2, 90.0, 72.0, 71.9, 44.0 (2C), 35.8, 35.4, 27.2, 26.8, 21.4, 21.3, 21.1, 21.0, 20.2, 20.1, 13.66, 13.64;

ATR-IR *v* 2959 (w), 2925 (w), 2865 (w), 2237 (w), 1510 (w), 1465 (w), 1458 (w), 1032 (s), 1018 (s), 820 (s), 813 (s);

HRMS (ESI) calcd for $C_{22}H_{25}NNaO^+$ $[M+Na]^+$ 342.1828; found 342.1830.

3-methoxy-2-((5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)methyl)propanenitrile (4q)



4q
dr = 1.1/1.0

Yield: 21.5 mg (67%), colorless oil;

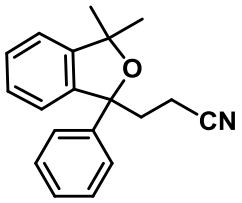
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 0.5H), 7.20 (d, *J* = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.03 (s, 0.53H), 7.02 (s, 0.47H), 5.24 – 5.09 (m, 2H), 3.54 – 3.39 (m, 2H), 3.32 (s, 1.5H), 3.31 (s, 1.5H), 2.83 (dtd, *J* = 7.3, 6.1, 4.6 Hz, 0.5H), 2.69 (dtd, *J* = 8.4, 6.1, 4.5 Hz, 0.5H), 2.62 – 2.40 (m, 2H), 2.35 (s, 3H), 2.31 (s, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.32, 141.29, 140.0, 139.9, 139.8, 139.3, 138.3, 138.2, 137.2, 137.1, 129.3 129.30, 128.69, 128.68, 124.92, 124.88, 122.2, 122.1, 121.9, 121.6, 121.3, 121.1, 90.0, 89.8, 72.7, 72.4, 72.0, 71.9, 59.1 (2C), 40.5, 40.4, 28.3, 28.0, 21.4, 21.3, 21.11, 21.09;

ATR-IR *v* 2924 (w), 2923 (w), 2880 (w), 2865 (w), 2864 (w), 2860 (w), 2242 (w), 1448 (s), 1380 (m), 1379 (m), 1348 (s), 1121 (s), 1030 (s), 1018 (s), 813 (s), 711 (s);

HRMS (ESI) calcd for $C_{21}H_{23}NNaO_2^+$ $[M+Na]^+$ 344.1621; found 344.1628.

3-(3,3-dimethyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (4r)



4r

Yield: 8.3 mg (30%), white solid, mp: 63 – 64 ^{o}C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 2H), 7.40 – 7.30 (m, 5H), 7.26 – 7.22 (m, 1H), 7.15 – 7.09 (m, 1H), 2.62 – 2.48 (m, 1H), 2.38 – 2.19 (m, 3H), 1.61 (s, 3H), 1.42 (s, 3H);

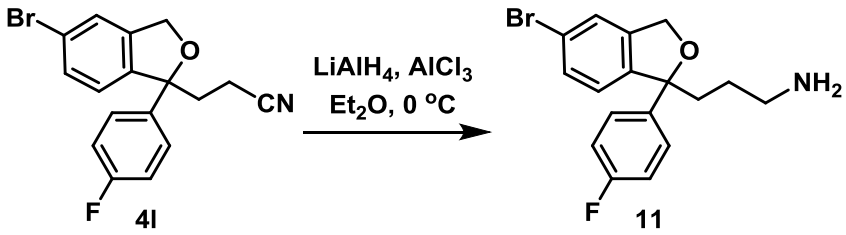
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 144.7, 141.2, 128.7, 128.6, 128.0, 127.5, 125.3, 122.3, 121.2, 120.1, 88.3, 85.7, 39.1, 30.0, 29.9, 12.9;

ATR-IR *v* 974 (w), 2924 (w), 2867 (w), 2853 (w), 2243 (w), 1440 (w), 1052 (m), 975 (m), 765 (s), 704 (s);

HRMS (ESI) calcd for $C_{19}H_{19}NNaO^{+}$ $[M+Na]^{+}$ 300.1359; found 300.1365.

Synthesis of Citalopram (1) from Dihydrobenzofuran 4l

Synthesis of 3-(5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)propan-1-amine (11)



To a suspension of $LiAlH_4$ (14 mg, 1 equiv), and $AlCl_3$ (40 mg, 1 equiv) in diethyl ether (*c* = 0.1 M) was added dropwise a solution of **4l** (102 mg, 1 equiv) in diethyl ether at 0 °C. The stirring was continued at the same temperature until the starting material was consumed. The reaction mixture was then treated by successive dropwise addition of ice-cold water (14 µL), an aqueous 15% NaOH (14 µL), and ice-cold water (42 µL). After stirring for 30 min, the mixture was filtered through a sintered glass frit. The filtrate was then concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (DCM/methanol/Et_3N 20/1/0.02) to give compound **11** as a colourless oil (73.9 mg, 70% yield).

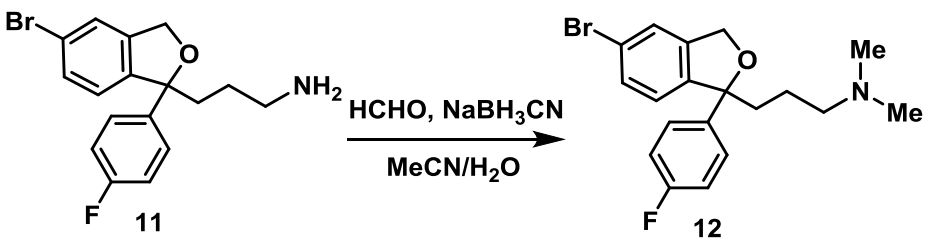
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.34 (m, 3H), 7.31 (s, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 6.97 (t, *J* = 8.5 Hz, 2H), 5.17 (d, *J* = 12.7 Hz, 1H), 5.03 (d, *J* = 12.7 Hz, 1H), 2.89 (broad, s, 2H), 2.39 – 2.27 (m, 1H), 2.22 – 2.15 (m, 1H), 1.75 – 1.71 (m, 1H), 1.62 – 1.56 (m, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 246.3 Hz), 142.7, 141.2, 139.7 (d, *J* = 3.0 Hz), 131.0, 126.9 (d, *J* = 8.1 Hz), 124.8, 123.5, 122.0, 115.5 (d, *J* = 21.4 Hz), 90.7, 71.6, 39.9, 37.8, 22.6;

ATR-IR ν 3355 (w), 2930 (w), 2856 (w), 2253 (w), 1507 (s), 1224 (s), 1031 (s), 1013 (s), 836 (s), 821 (s), 739 (m), 699 (m);

HRMS (ESI) calcd for $C_{17}H_{18}BrFNO^+$ $[M+H]^+$ 350.0550; found 350.0551.

Synthesis of 3-(5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-N,N-dimethylpropan-1-amine (12)



To a solution of **11** (53 mg, 1 equiv) in MeCN (*c* = 0.1 M) at 0 °C was added aqueous formalin (35%, 0.4 mL) and $NaBH_3CN$ (45mg, 5 equiv). The resulting reaction mixture was warmed up to room temperature, occasionally treated with a drop of acetic acid to keep the pH slightly below 7. After stirring for 4 h, the reaction mixture was diluted with ethyl acetate, washed with 1 M NaOH solution, then brine, dried over Na_2SO_4, filtered and concentrated in *vacuo.* The crude product was purified by flash column chromatography on silica gel (chloroform/methanol 30/1 to 20/1) to give compound **12** as a colorless oil (47.0 mg, 83% yield).

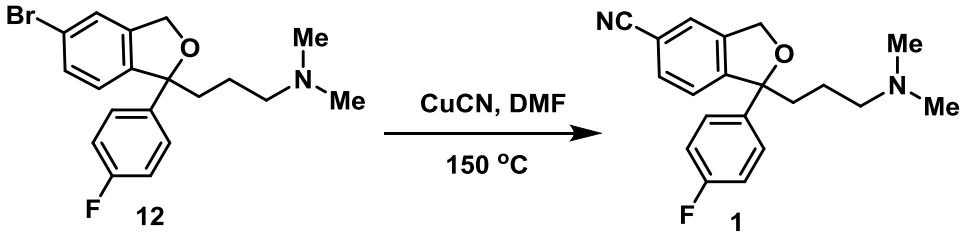
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 3H), 7.34 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.09 – 6.96 (m, 2H), 5.13 (d, *J* = 12.7 Hz, 1H), 5.08 (d, *J* = 12.7 Hz, 1H), 2.37 (t, *J* = 7.4 Hz, 2H), 2.24 (s, 6H), 2.28 – 2.03 (m, 2H), 1.61 – 1.47 (m, 1H), 1.45 – 1.33 (m, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (d, *J* = 245.8 Hz), 143.3, 141.5, 140.4 (d, *J* = 3.2 Hz), 130.8, 126.9 (d, *J* = 7.9 Hz), 124.7, 123.5, 121.7, 115.3 (d, *J* = 21.3 Hz), 90.8, 71.4, 59.4, 45.0, 39.1, 21.8;

ATR-IR ν 2944 (w), 2926 (w), 2854 (w), 2781 (w), 1507 (s), 1468 (m), 1225 (s), 1160 (m), 1033 (s), 834 (s), 820 (s);

HRMS (ESI) calcd for $C_{19}H_{22}BrFNO^+$ $[M+H]^+$ 378.0863; found 378.0865.

Synthesis of 1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile - Citalopram (1)



In a sealed tube, compound **12** (38 mg, 1 equiv) and CuCN (36 mg, 4 equiv) was dissolved in DMF (1 mL). The reaction mixture was evacuated and filled back with N_2 three times. The resultant mixture was then heated to 150 °C for 24 hours. After cooling to room temperature, this solution was partitioned between toluene (5 mL) and aqueous NH_3 25% (5 mL) and stirred vigorously for 10 minutes. The aqueous layer was removed and the organic layer was washed 3 times with aqueous solution of NH_3 25% (3 x 5 mL). The organic phase was then washed with brine (10 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by preparative thin layer chromatography (chloroform/methanol 20/1) to give compound **1** as a colorless oil (23.6 mg, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.50 (s, 1H), 7.45 – 7.40 (m, 3H), 7.03 – 6.99 (m, 2H), 5.20 (d, *J* = 12.9 Hz, 1H), 5.15 (d, *J* = 12.9 Hz, 1H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.30 – 2.11 (m, 2H), 2.22 (s, 6H), 1.57 – 1.45 (m, 1H), 1.42 – 1.35 (m, 1H);

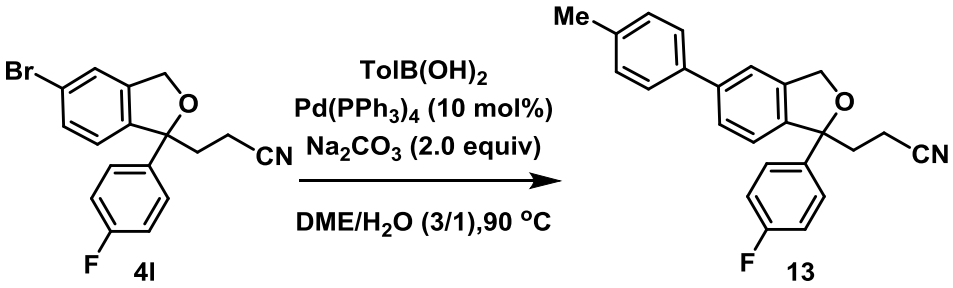
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (d, *J* = 246.3 Hz), 149.5, 140.4, 139.5 (d, *J* = 3.2 Hz), 132.1, 126.9 (d, *J* = 8.1 Hz), 125.4, 122.9, 118.8, 115.5 (d, *J* = 21.4 Hz), 111.9, 91.2, 71.5, 59.3, 45.1 (2C), 38.9, 21.9;

ATR-IR ν 2948 (w), 2858 (w), 2782 (w), 2230 (w), 1508 (s), 1226 (s), 1226 (s), 1035 (s), 835 (s);

HRMS (ESI) calcd for $C_{20}H_{22}FN_2O^+$ $[M+H]^+$ 325.1711; found 325.1714.

Transformation of Dihydrobenzofuran 4l

Synthesis of 3-(1-(4-fluorophenyl)-5-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (13)



To a suspension of 4-tolylboronic acid (10.2 mg, 0.075 mmol, 1.5 equiv), **4l** (17.3 mg, 0.05 mmol, 1.0 equiv) and Na_2CO_3 (10.6 mg, 0.1 mmol, 2.0 equiv) in a mixture of DME/H_2O (3/1, *c* = 0.1 M) was added $Pd(PPh_3)_4$ (5.7 mg, 10 mol%) under N_2. The resulting mixture was heated to 90 °C and stirred for 24 h. The solvent was then removed under reduced pressure, and the residue was diluted with water, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/9 to 2/8) to give compound **13** as a colourless oil (14.5 mg, 82% yield).

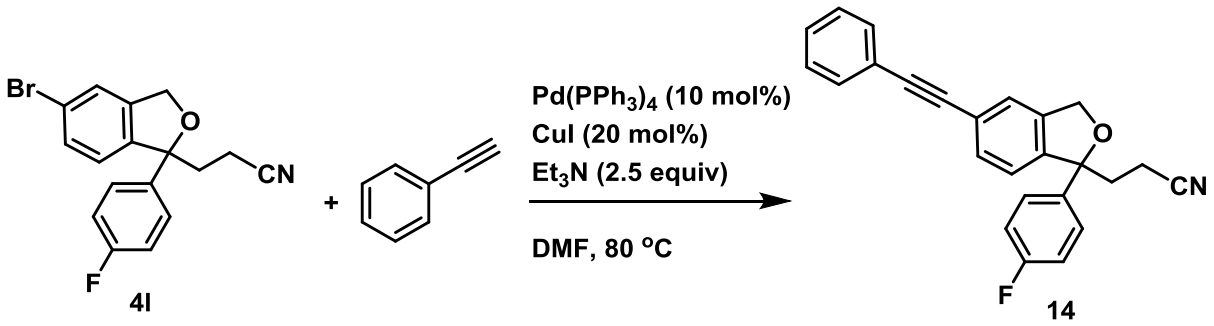
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.38 (m, 6H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.26 – 7.24 (m, 2H), 7.07 – 7.01 (m, 2H), 5.23 (d, *J* = 12.4 Hz, 1H), 5.17 (d, *J* = 12.4 Hz, 1H), 2.59 (ddd, *J* = 13.9, 10.2, 5.9 Hz, 1H), 2.49 (ddd, *J* = 14.0, 9.6, 5.6 Hz, 1H), 2.40 (s, 3H), 2.38 – 2.19 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (d, *J* = 246.4 Hz), 142.0, 140.8, 139.9, 139.4 (d, *J* = 3.2 Hz), 137.68, 137.65, 129.7, 127.2, 126.8 (d, *J* = 8.1 Hz), 122.0, 120.2, 119.9, 115.6 (d, *J* = 21.3 Hz), 89.5, 72.2, 37.3, 21.3, 12.7;

ATR-IR ν 2925 (w), 2856 (w), 2249 (w), 1507 (m), 1225 (m), 908 (m), 835 (m), 813 (s), 730 (s);

HRMS (ESI) calcd for $C_{24}H_{20}FNNaO^+$ $[M+Na]^+$ 380.1421; found 380.1421.

Synthesis of 3-(1-(4-fluorophenyl)-5-(phenylethynyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (14)



To a solution of **4l** (17.3 mg, 0.05 mmol, 1.0 equiv), phenylacetylene (20.4 mg, 0.2 mmol, 4.0 equiv), CuI (1.9 mg, 20 mol%), and Et_3N (18 µL, 0.125 mmol, 2.5 equiv) in DMF (*c* = 0.05 M) was added $Pd(PPh_3)_4$ (5.7 mg, 10 mol%) at room temperature. The resulting mixture was evacuated and filled back with N_2 three times, then warmed up to 80 °C. After stirring for 24 h, the reaction mixture was diluted with water, extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/9 to 2/8) to give compound **14** as a yellow oil (11.5 mg, 62% yield).

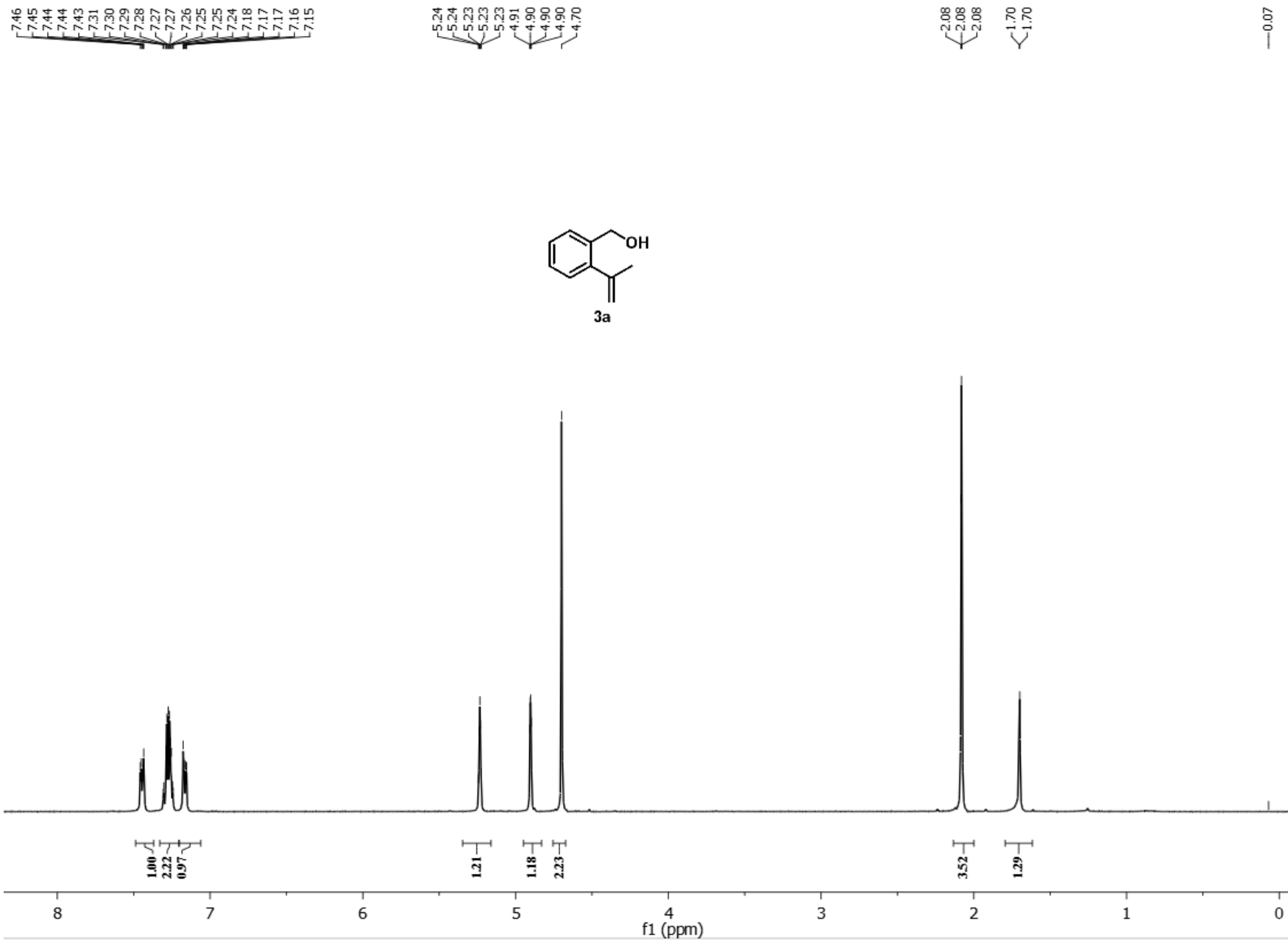
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 3H), 7.45 – 7.42 (m, 3H), 7.37 – 7.34 (m, 3H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.07 – 7.01 (m, 2H), 5.18 (d, *J* = 12.6 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 2.57 (ddd, *J* = 13.9, 10.1, 5.9 Hz, 1H), 2.52 – 2.39 (m, 1H), 2.38 – 2.14 (m, 2H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (d, *J* = 246.6 Hz), 142.2, 139.6, 138.9 (d, *J* = 3.4 Hz), 131.8, 131.7, 128.7, 128.6, 126.8 (d, *J* = 8.1 Hz), 124.8, 123.9, 123.0, 121.8, 119.7, 115.7 (d, *J* = 21.4 Hz), 90.2, 89.6, 88.7, 71.9, 37.1, 12.7;

ATR-IR ν 2955 (w), 2925 (w), 2903 (w), 2855 (w), 2248 (w), 1507 (m), 1225 (m), 836 (s), 835 (s), 757 (s), 691 (s);

HRMS (ESI) calcd for $C_{25}H_{18}FNNaO^+$ $[M+Na]^+$ 390.1265; found 390.1266.

Copies of the ^{1}H and ^{13}C NMR Spectra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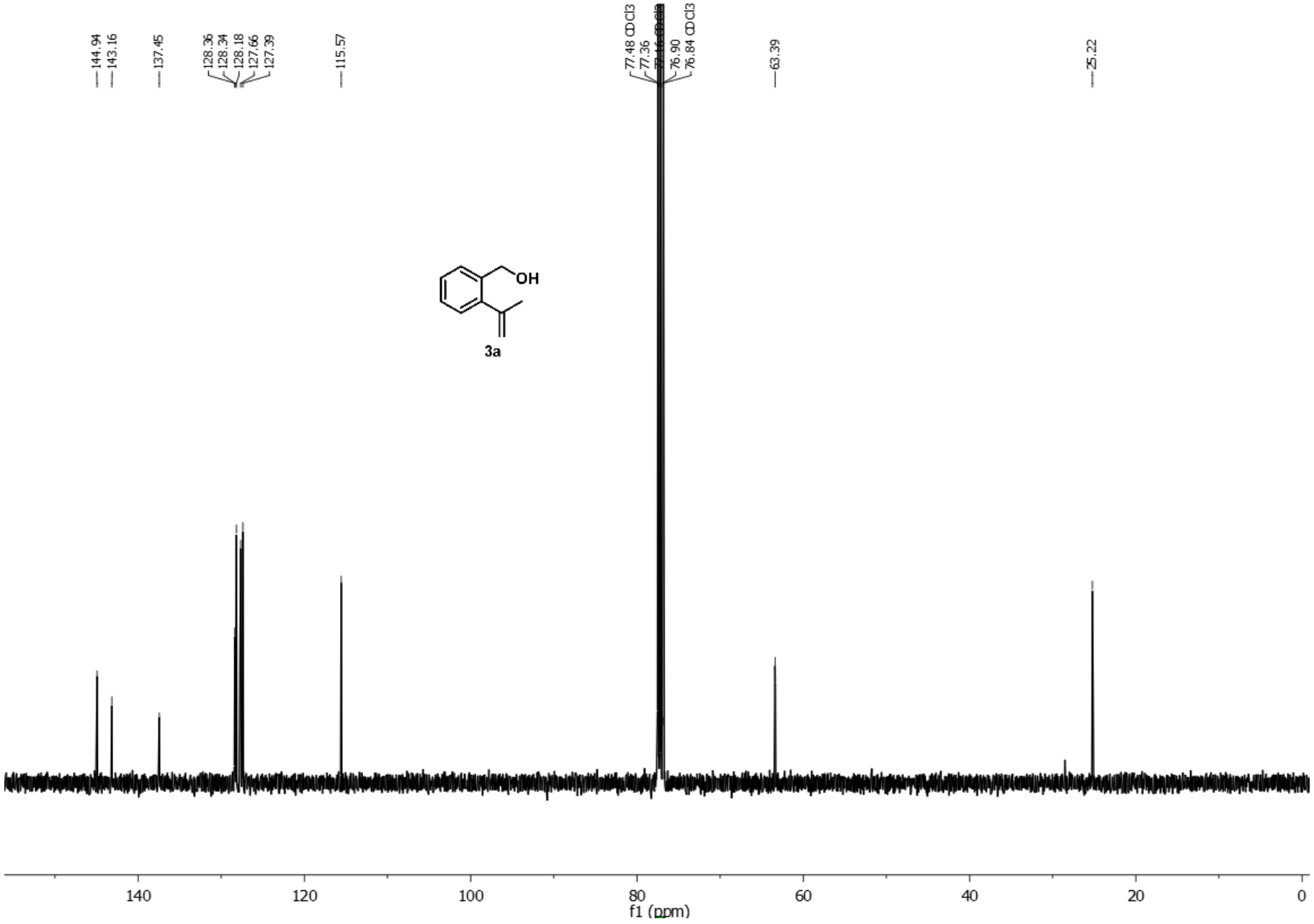
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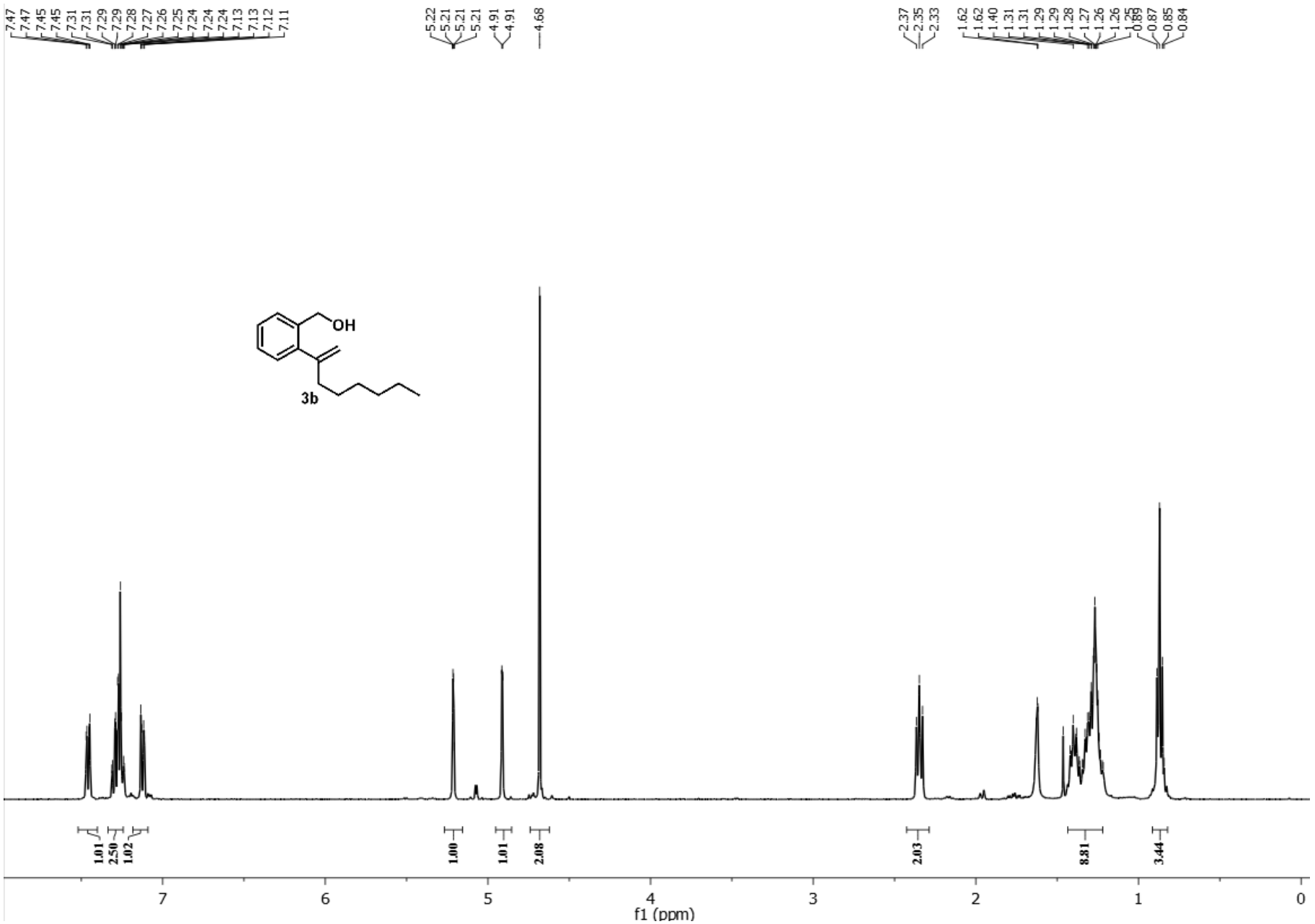
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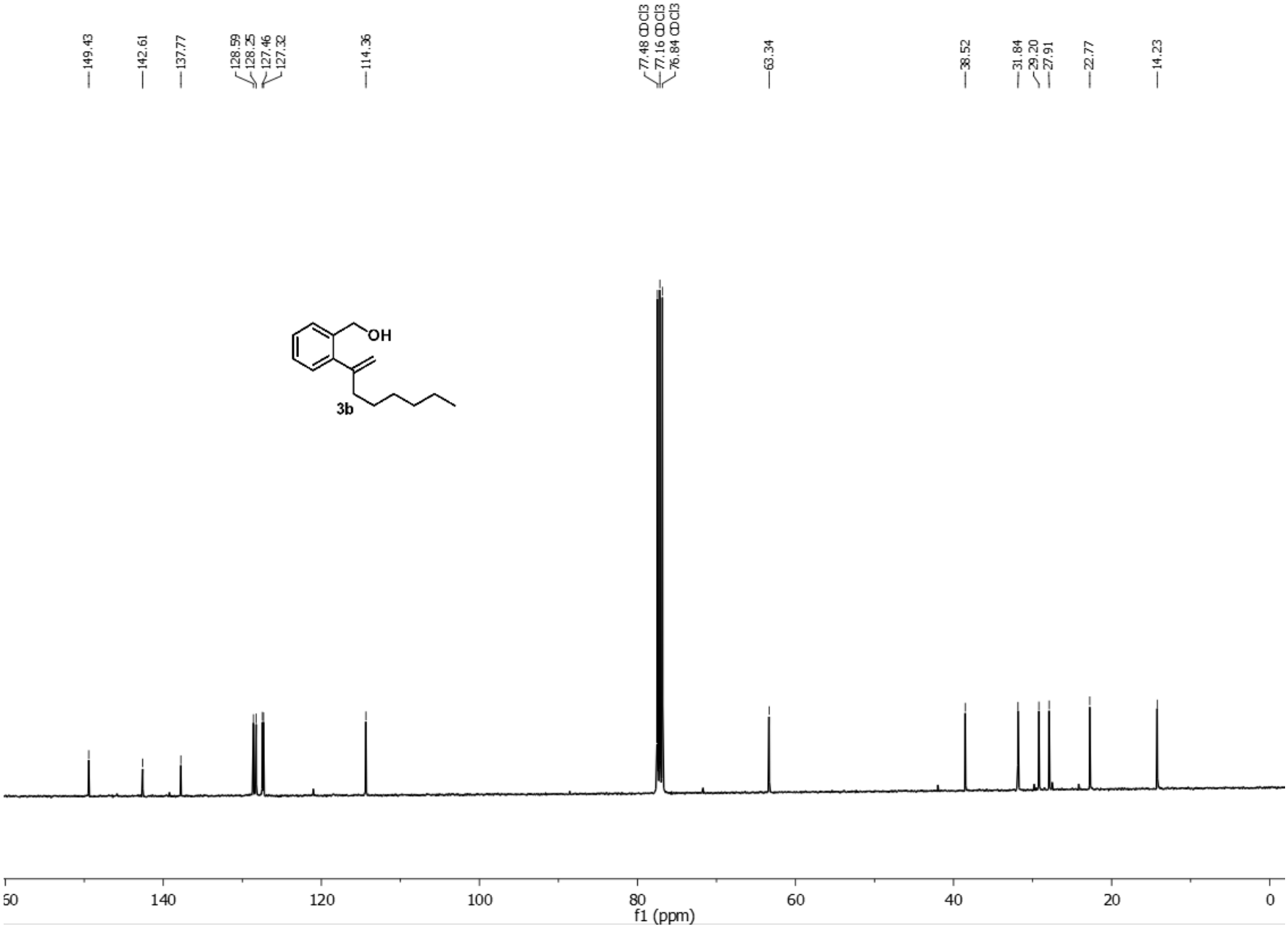
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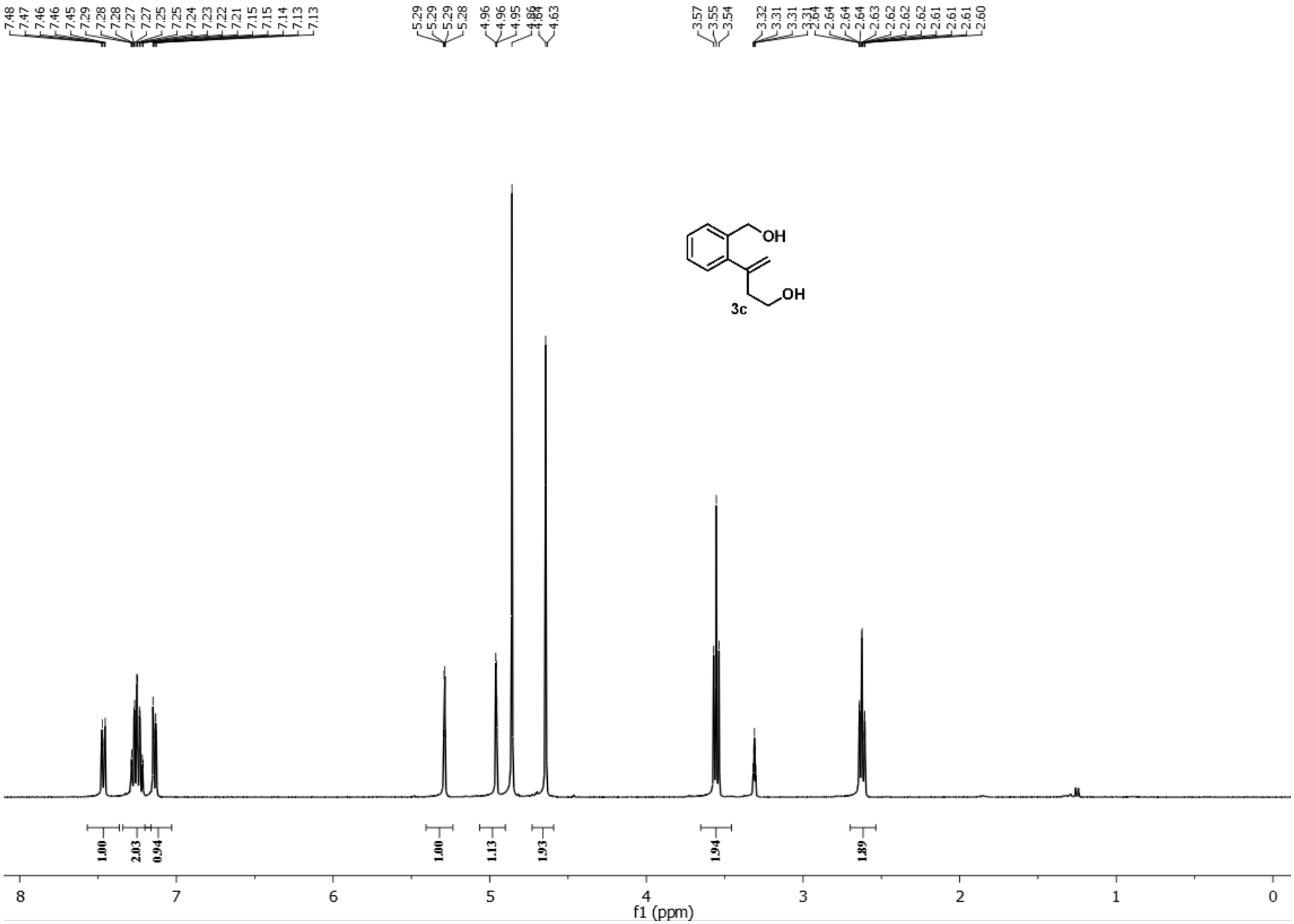
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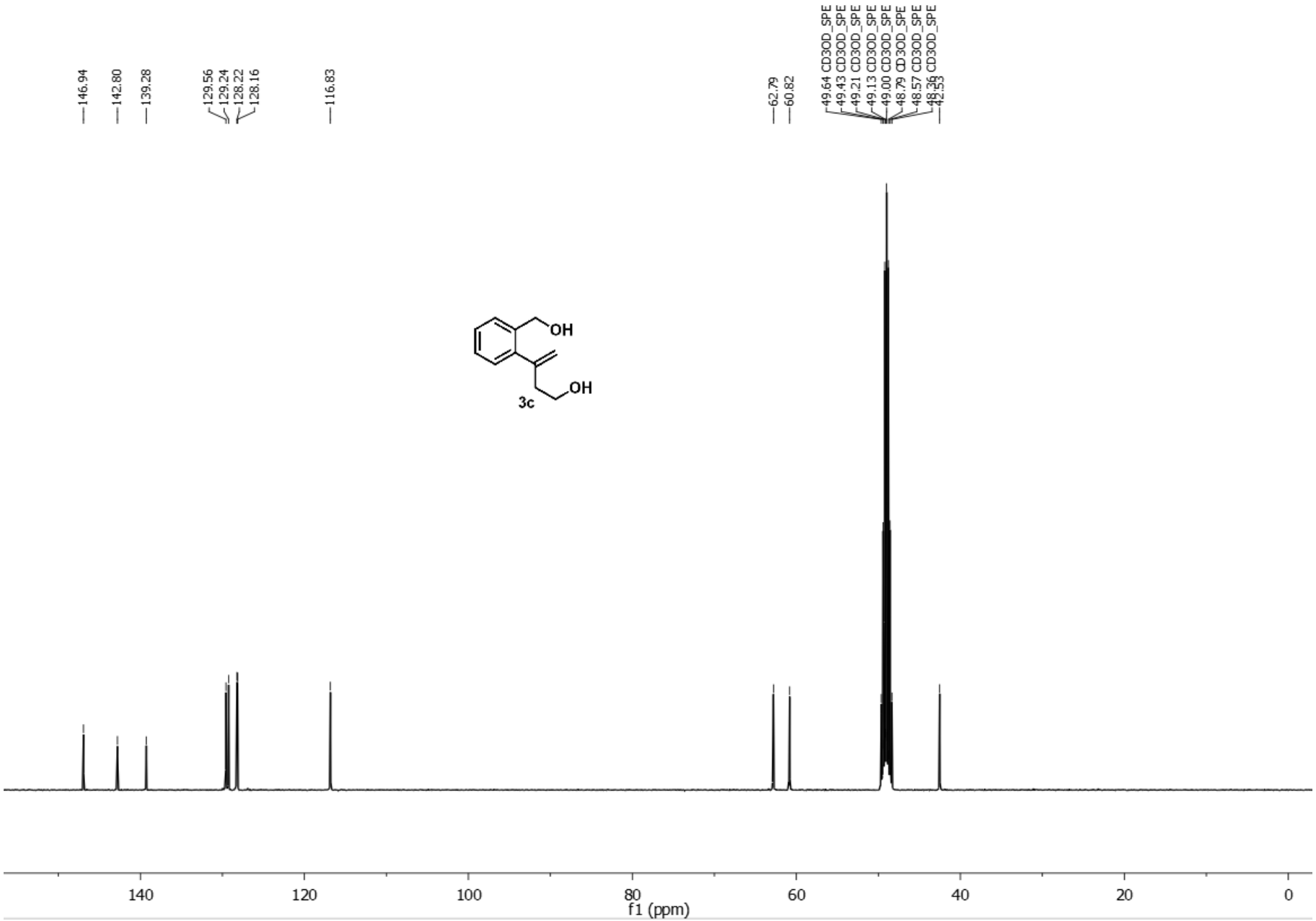
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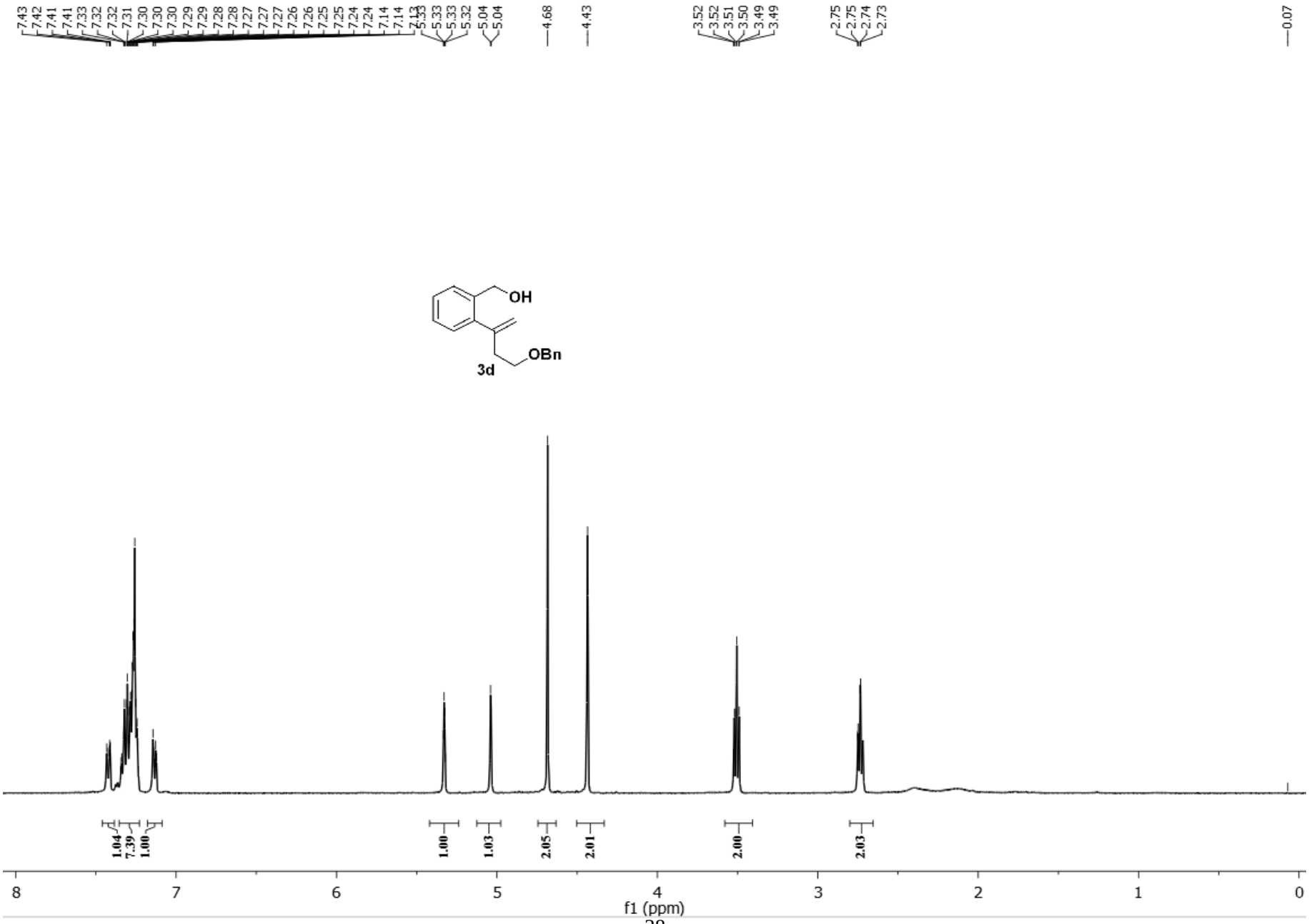
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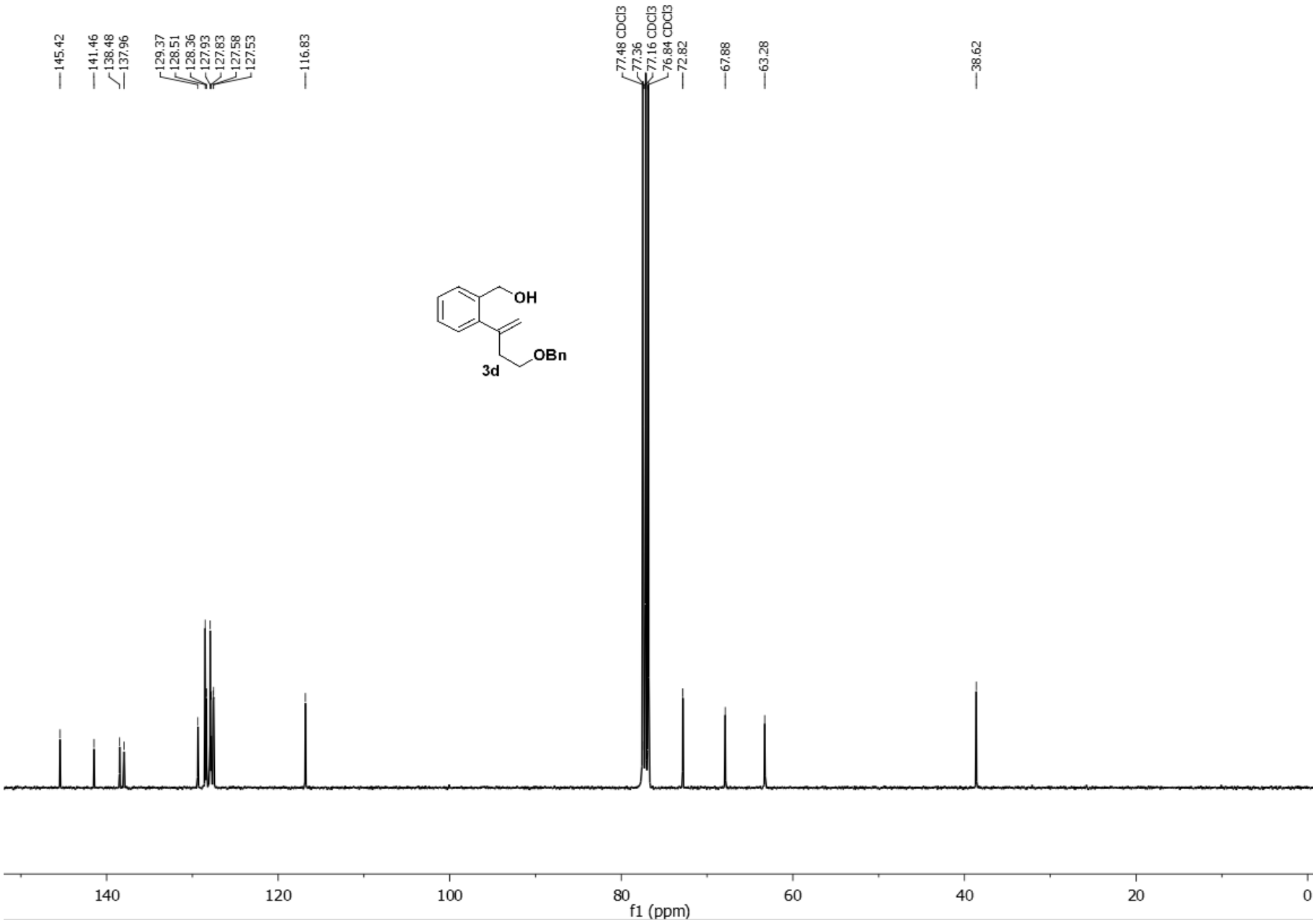
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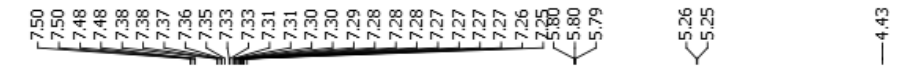
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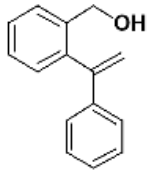
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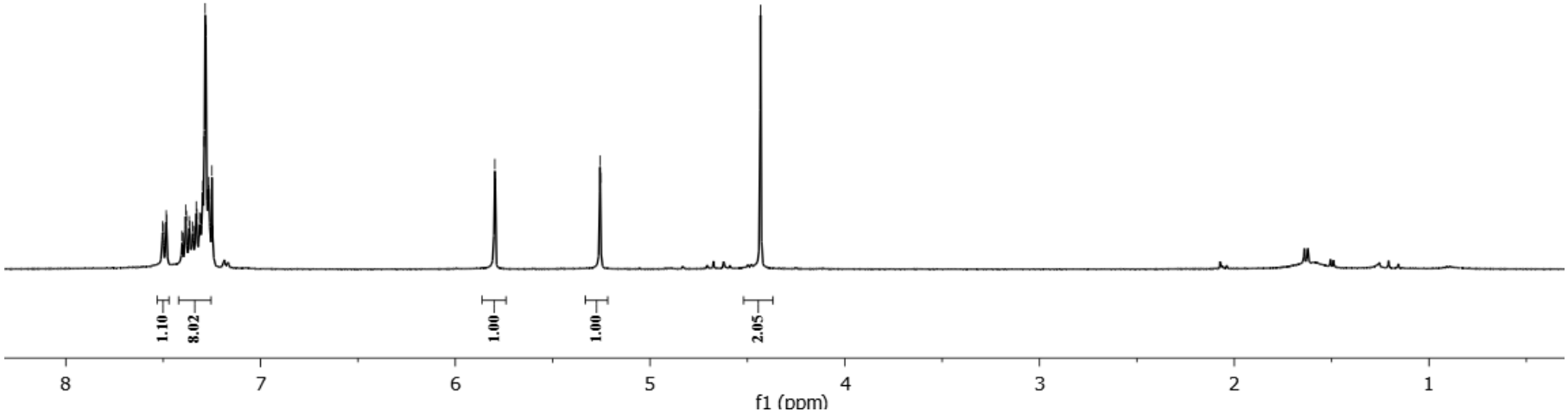
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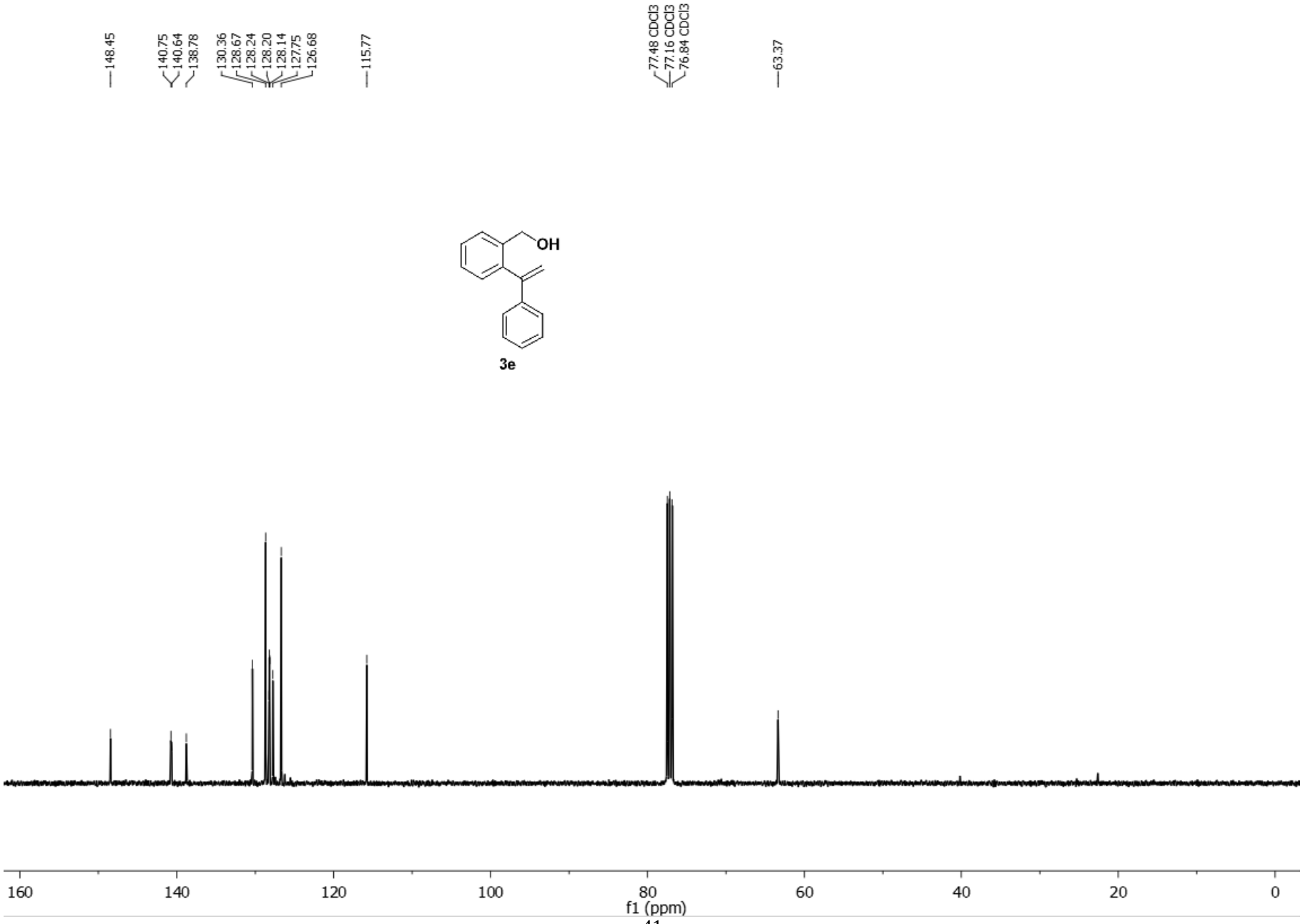
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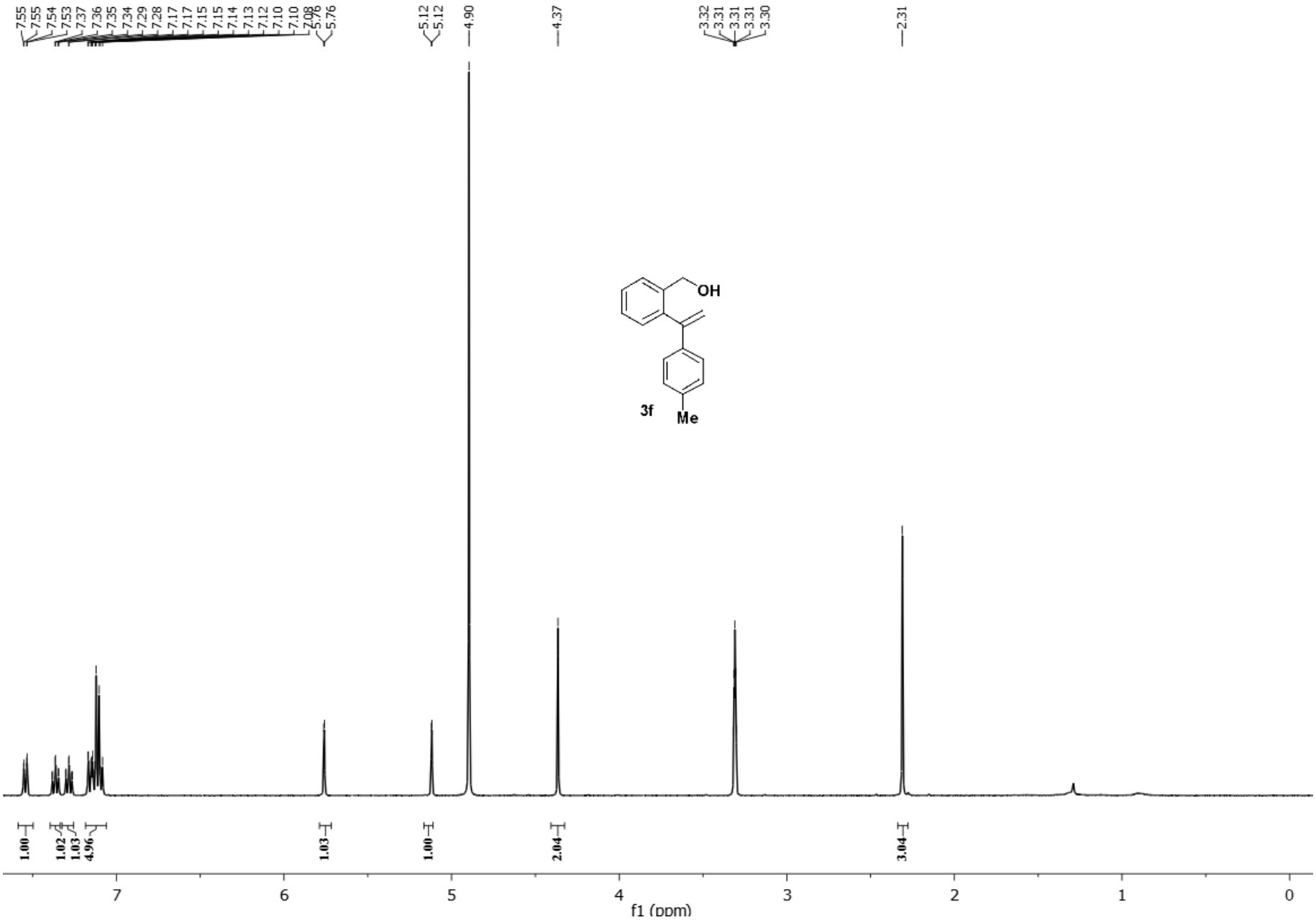
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3.31
3.31
3.31
3.30
2.31
OH
3f
Me
1.00
1.02
1.03
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1.00
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3.04
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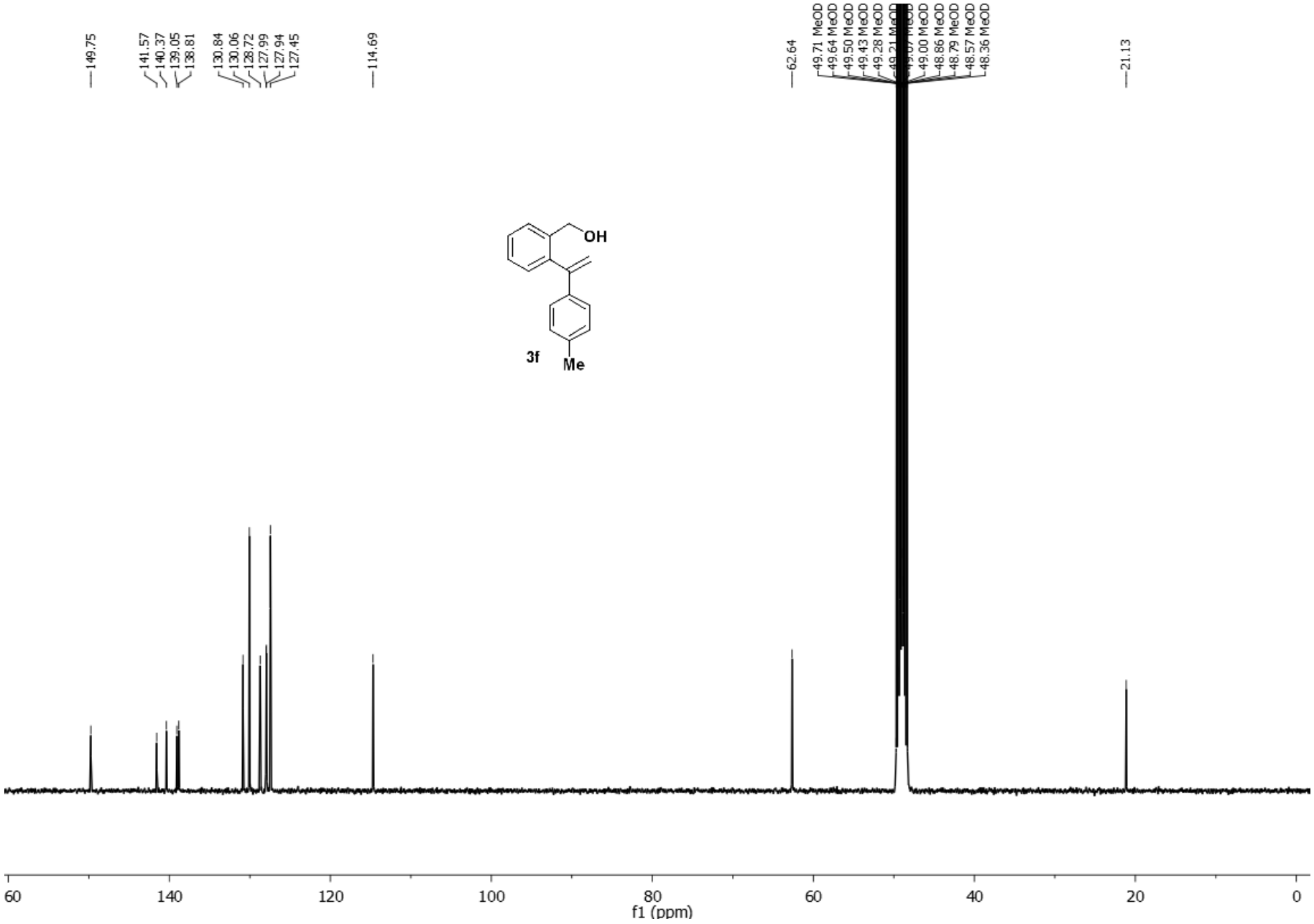
f1 (ppm)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49.71 MeOD
49.64 MeOD
49.50 MeOD
49.43 MeOD
49.28 MeOD
48.86 MeOD
48.79 MeOD
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OH
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Me
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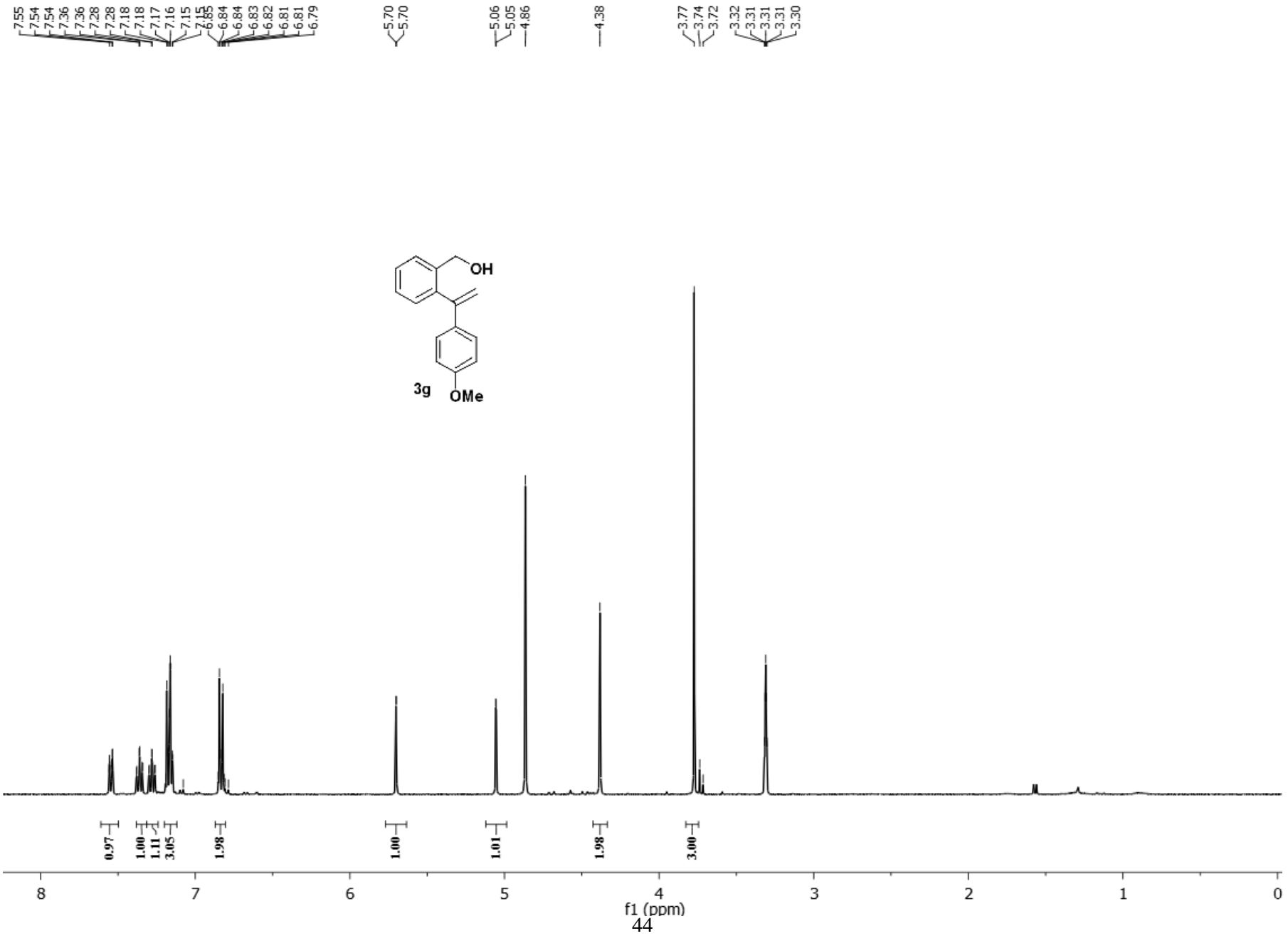
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6.84
6.84
6.83
6.82
6.81
6.81
6.79
5.70
5.70
5.06
5.05
4.86
4.38
3.77
3.74
3.72
3.32
3.31
3.31
3.31
3.30
OH
3g
OMe
0.97
1.00
1.11
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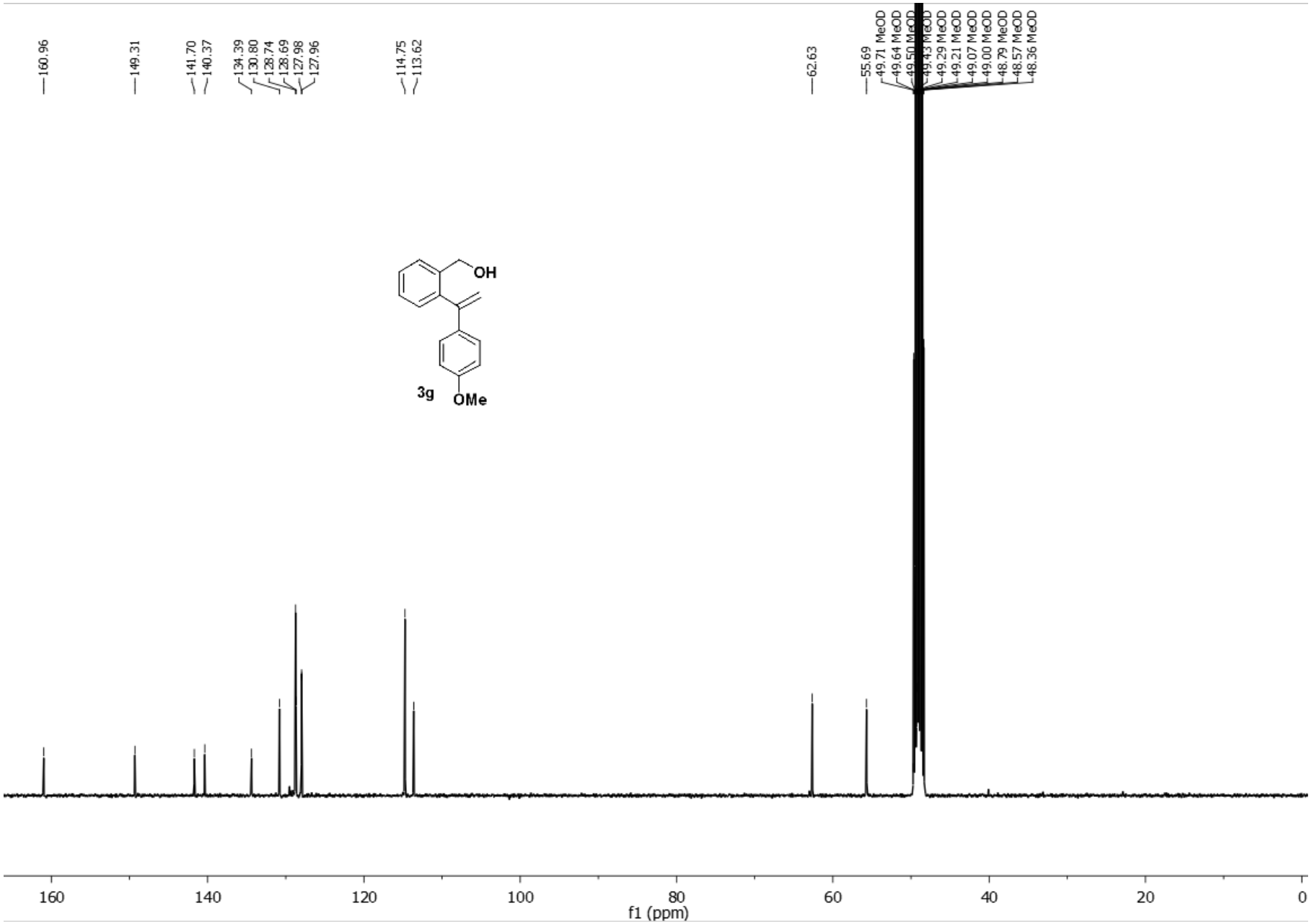
f1 (ppm)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62.63
55.69
49.71 MeOD
49.64 MeOD
49.50 MeOD
49.43 MeOD
49.29 MeOD
49.21 MeOD
49.07 MeOD
49.00 MeOD
48.79 MeOD
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OH
3g
OMe
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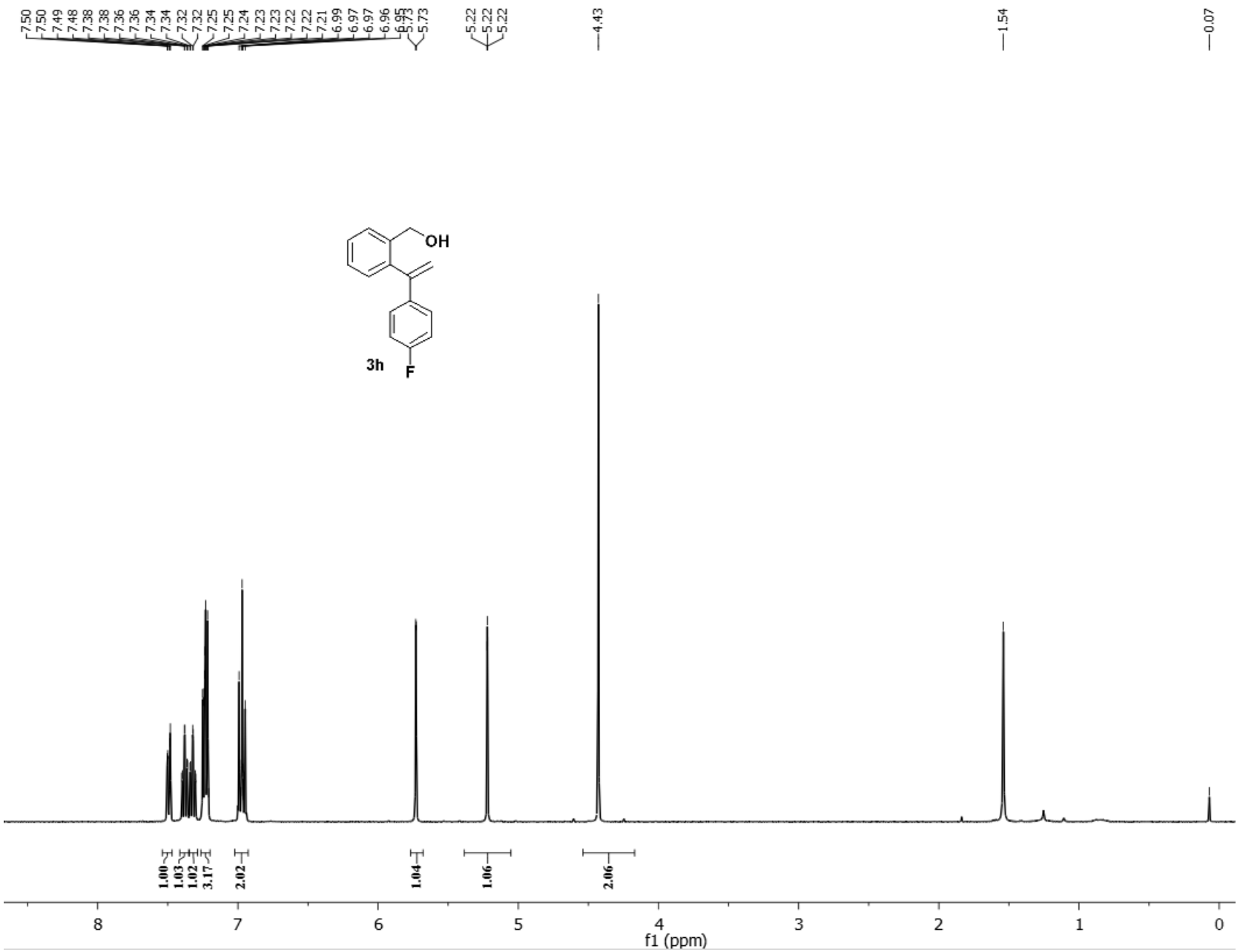
f1 (ppm)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7.23
7.23
7.22
7.22
7.21
6.99
6.97
6.97
6.96
6.95
5.73
5.73
5.22
5.22
5.22
4.43
1.54
0.07
OH
3h
F
1.00
1.03
1.02
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1.06
2.06
8
7
6
5
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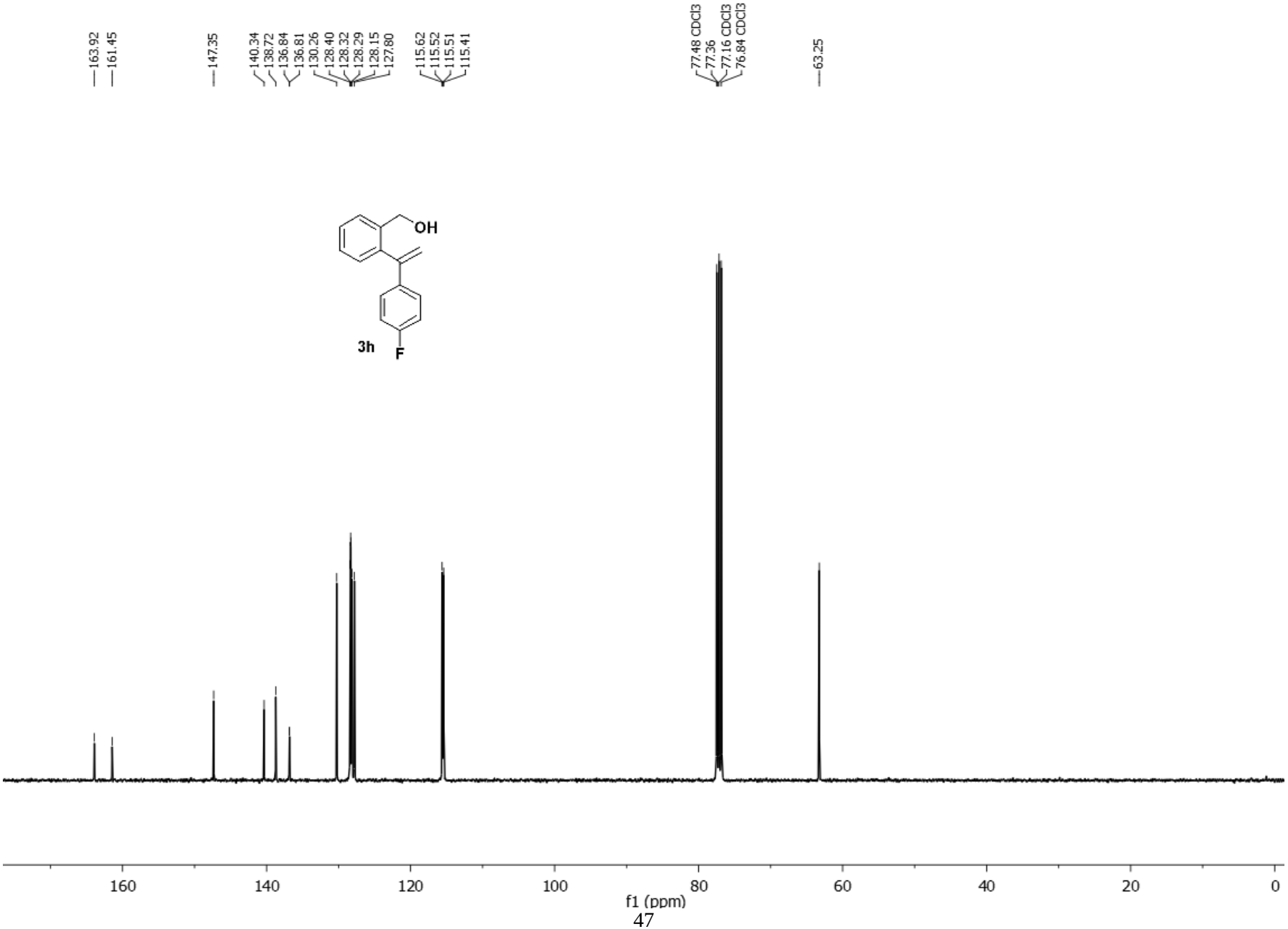
f1 (ppm)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136.81
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128.29
128.15
127.80
115.62
115.52
115.51
115.41
77.48 CDCl3
77.36
77.16 CDCl3
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F
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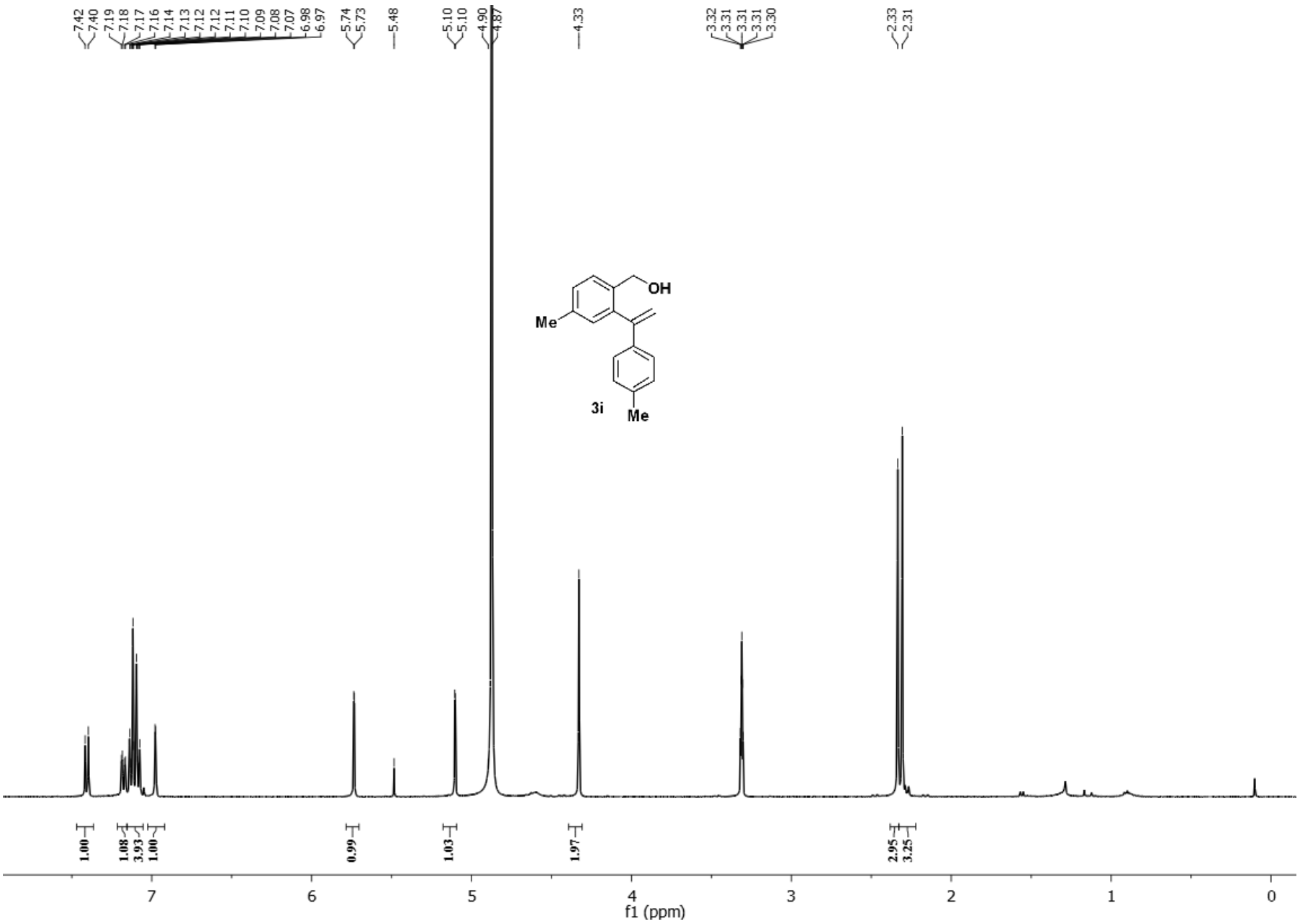
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7.09
7.08
7.07
6.98
6.97
5.74
5.73
5.48
5.10
5.10
4.90
4.87
4.33
3.32
3.31
3.31
3.31
3.30
2.33
2.31
OH
Me
3i
Me
1.00
1.08
3.93
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1.97
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4
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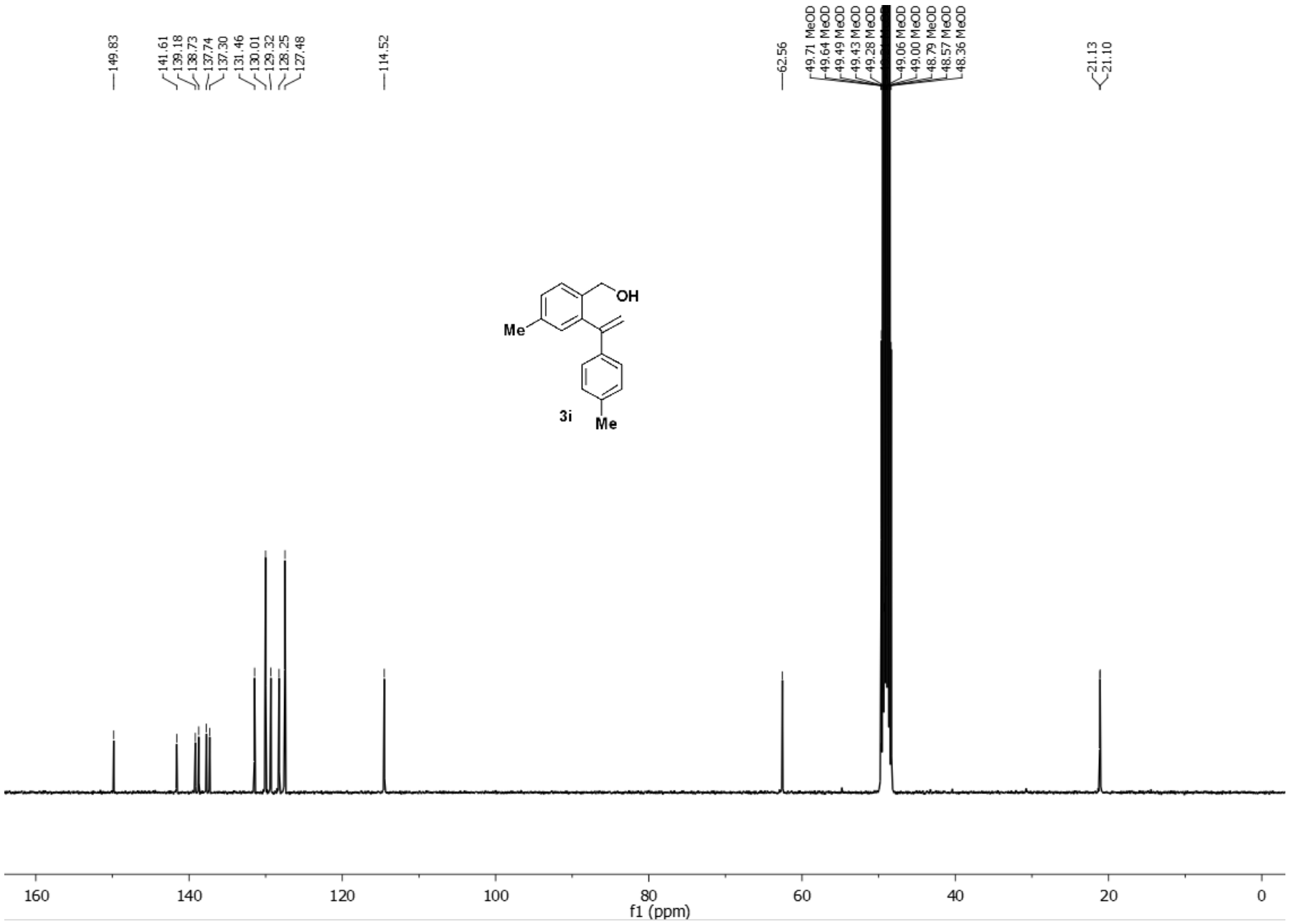
f1 (ppm)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127.48
114.52
62.56
49.71 MeOD
49.64 MeOD
49.49 MeOD
49.43 MeOD
49.28 MeOD
49.06 MeOD
49.00 MeOD
48.79 MeOD
48.57 MeOD
48.36 MeOD
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21.10
OH
Me
3i
Me
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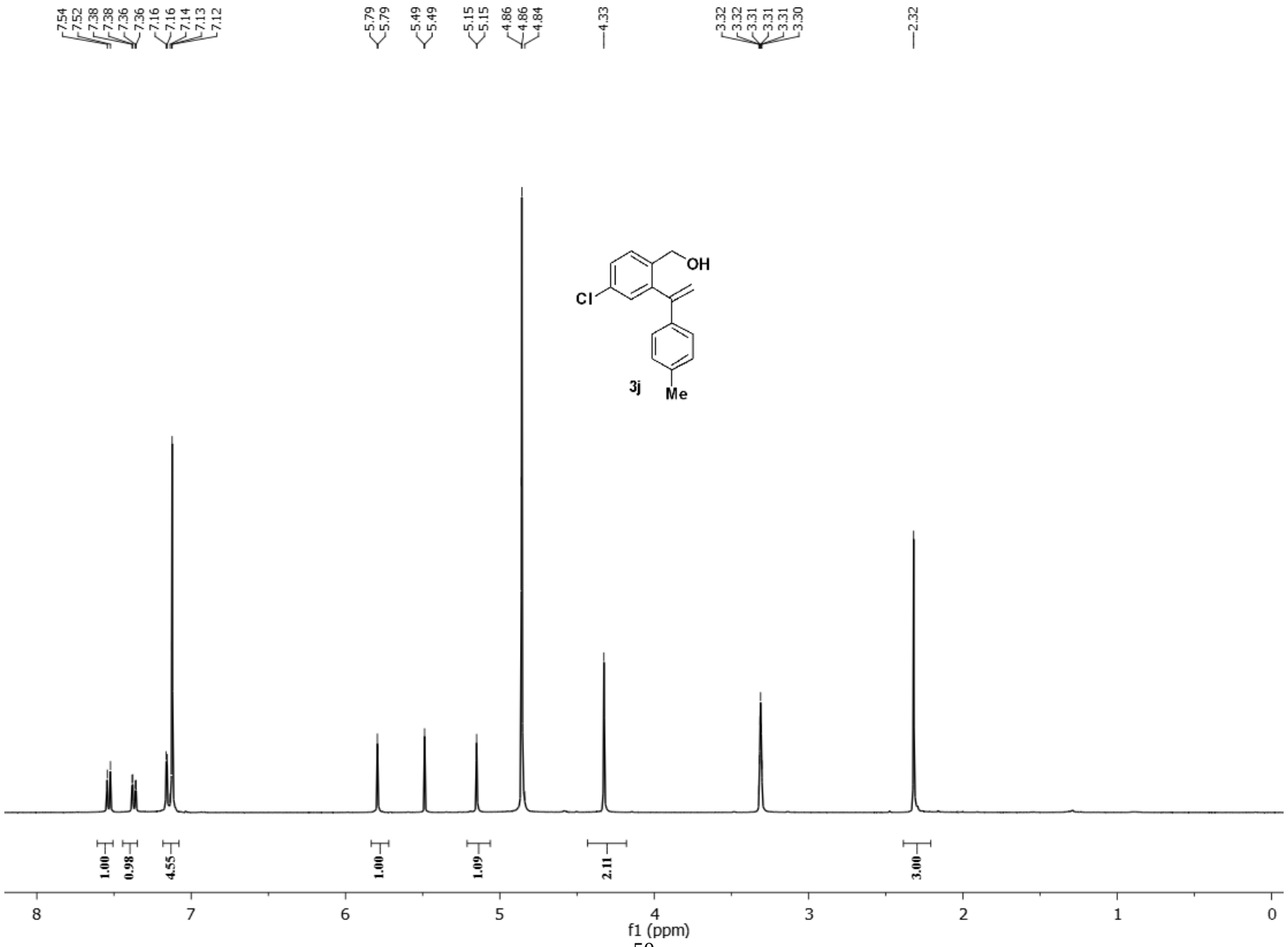
100
80
60
40
20
0
f1 (ppm)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7.12
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5.79
5.49
5.49
5.15
5.15
4.86
4.86
4.84
4.33
3.32
3.32
3.31
3.31
3.31
3.30
2.32
OH
Cl
3j
Me
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0.98
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1.09
2.11
3.00
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4
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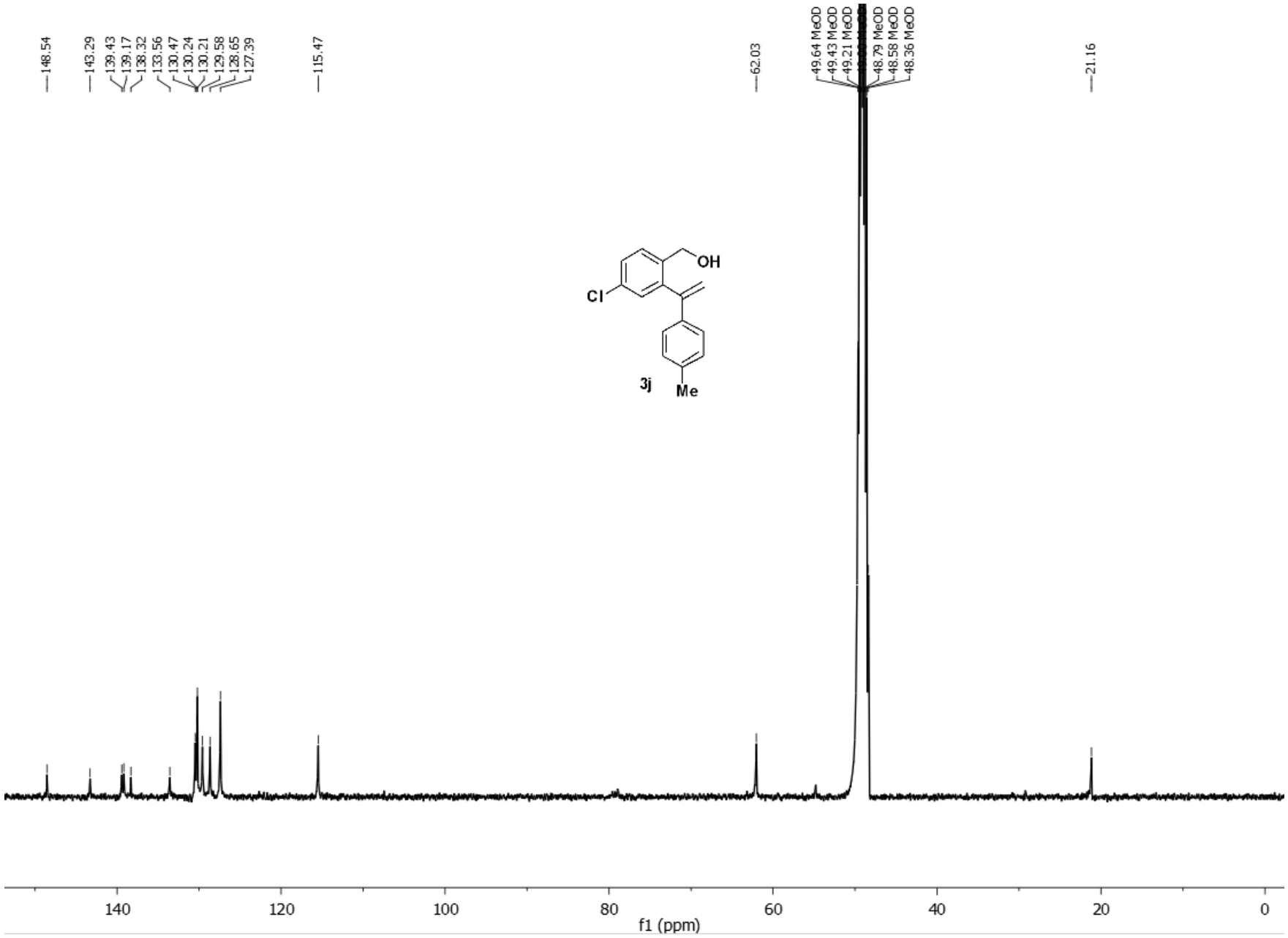
f1 (ppm)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115.47
62.03
49.64 MeOD
49.43 MeOD
49.21 MeOD
48.79 MeOD
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OH
Cl
3j
Me
140
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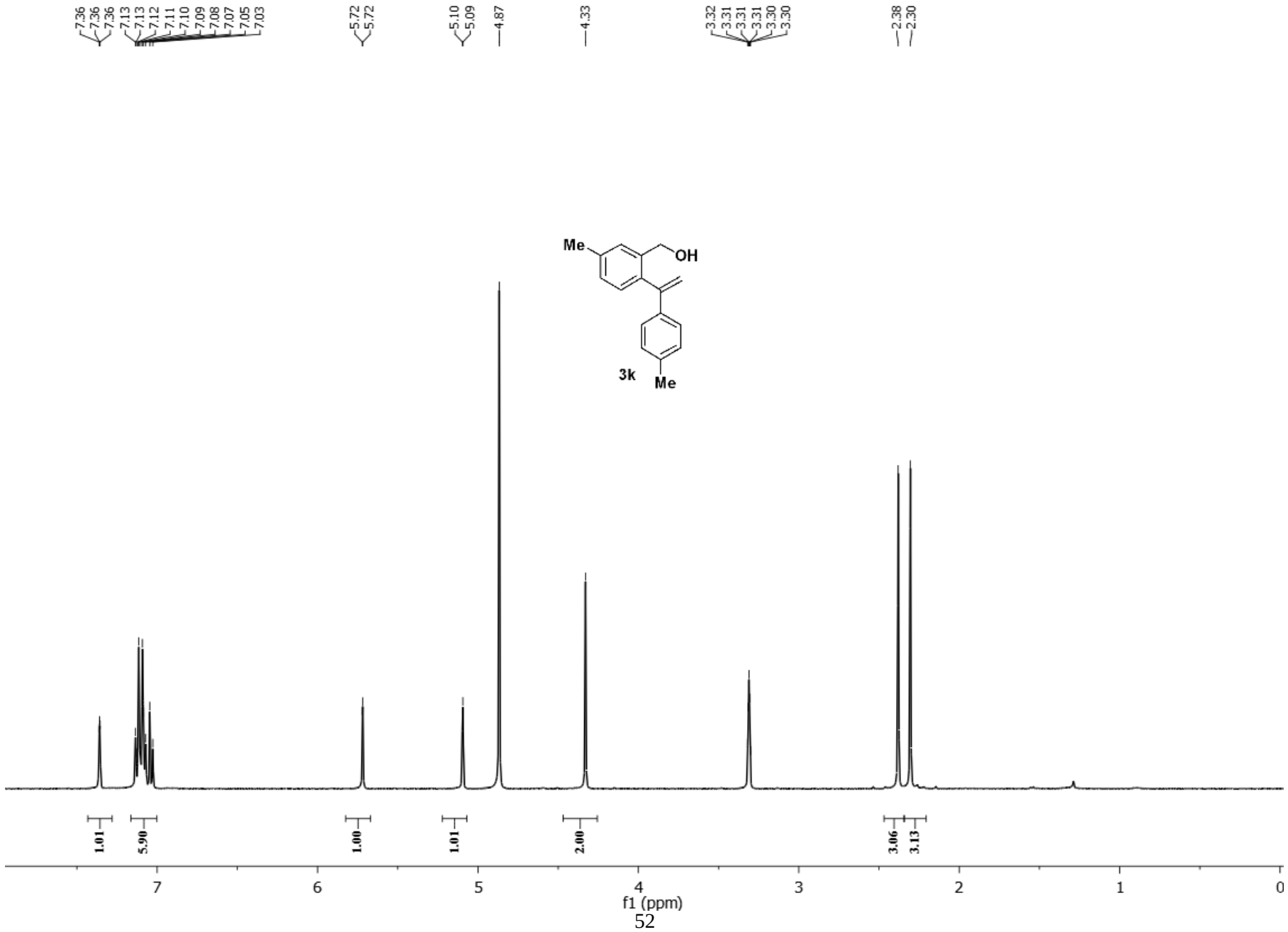
100
80
60
40
20
0
f1 (ppm)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5.72
5.10
5.09
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3.32
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3.31
3.31
3.30
3.30
2.38
2.30
Me
OH
3k
Me
1.01
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2.00
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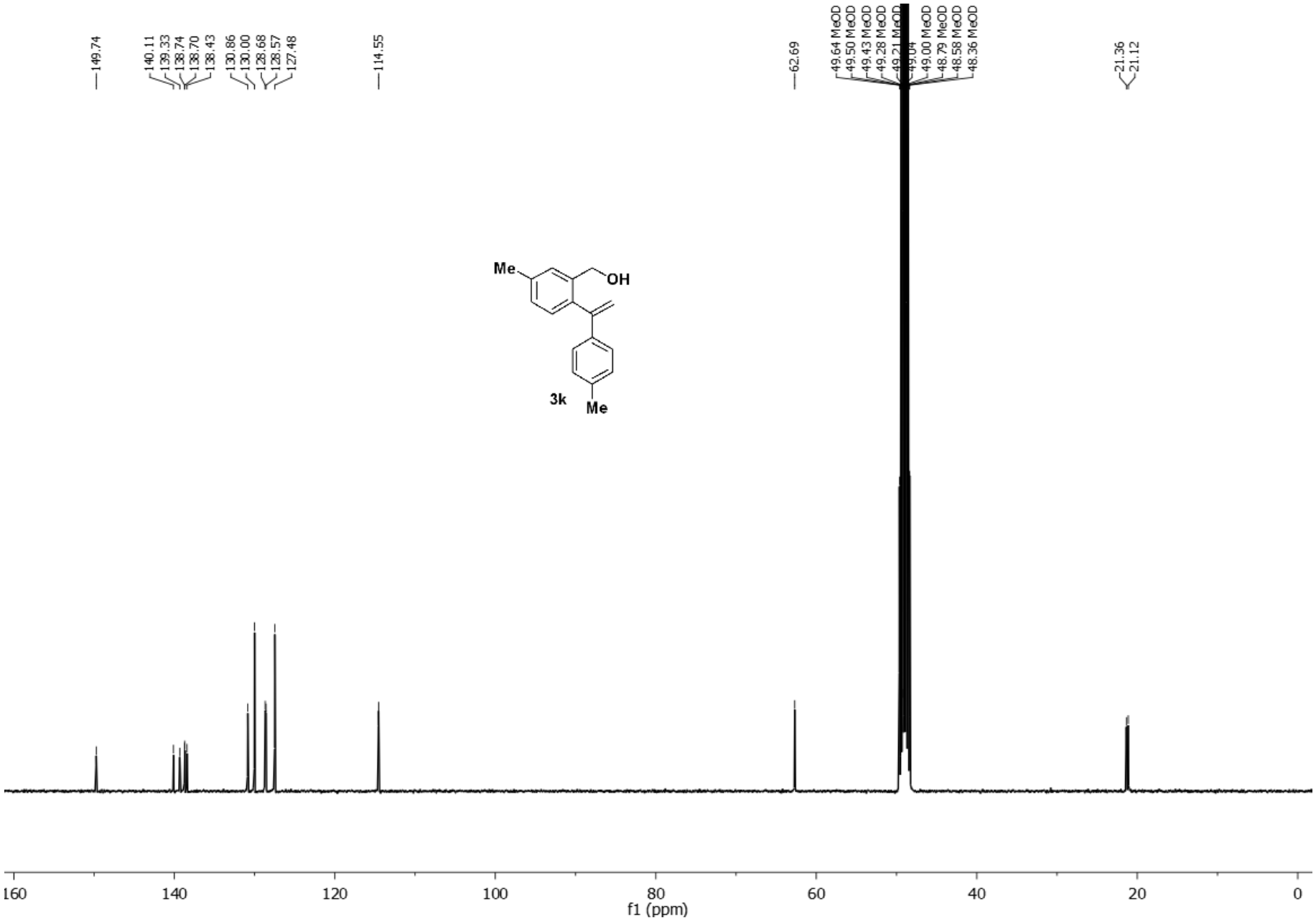
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114.55
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49.50 MeOD
49.43 MeOD
49.28 MeOD
49.21 MeOD
49.04
49.00 MeOD
48.79 MeOD
48.58 MeOD
48.36 MeOD
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Me
OH
3k
Me
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140
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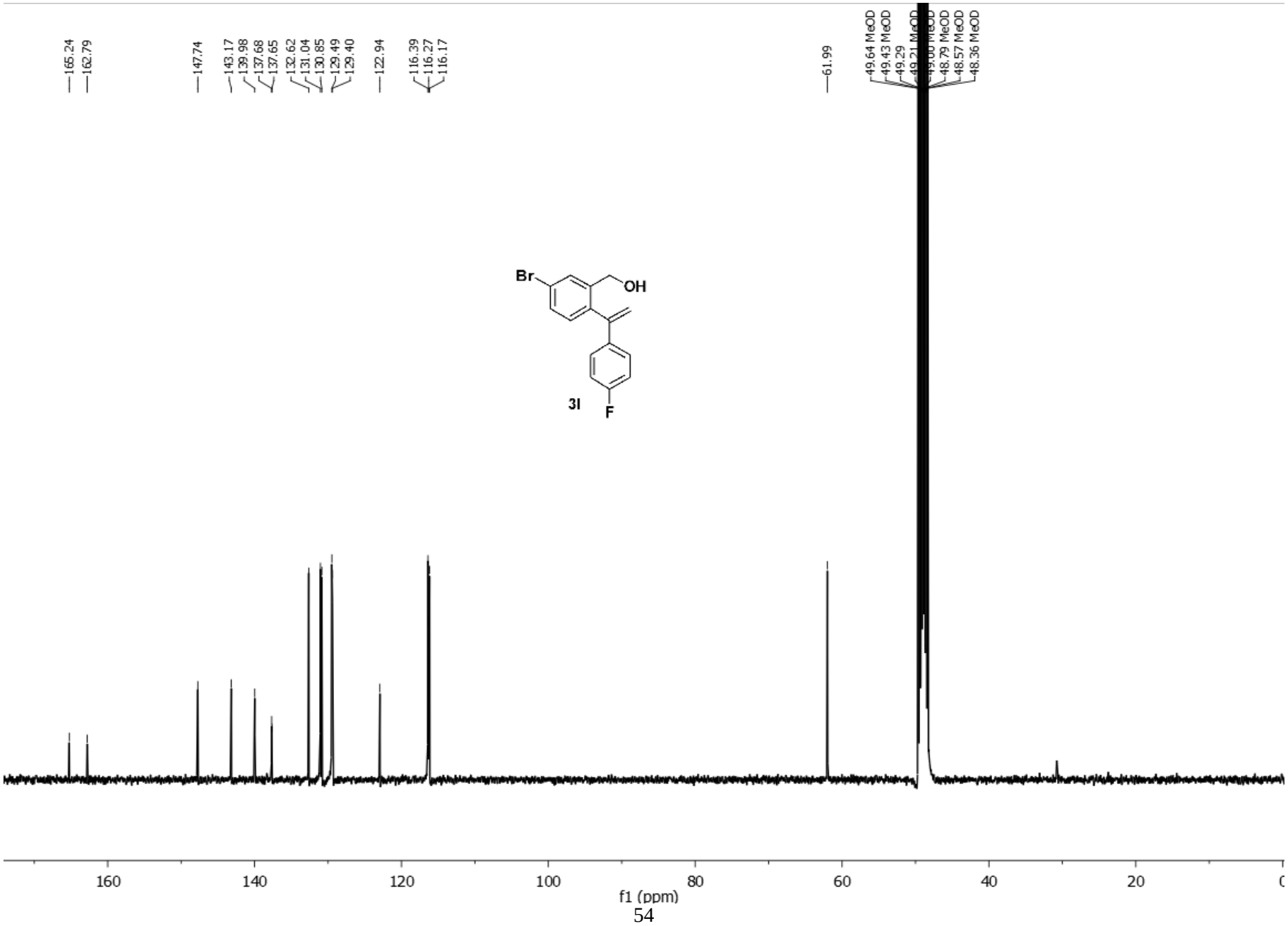
f1 (ppm)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130.85
129.49
129.40
122.94
116.39
116.27
116.17
61.99
49.64 MeOD
49.43 MeOD
49.29
49.21 MeOD
49.00 MeOD
48.79 MeOD
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Br
OH
F
3l
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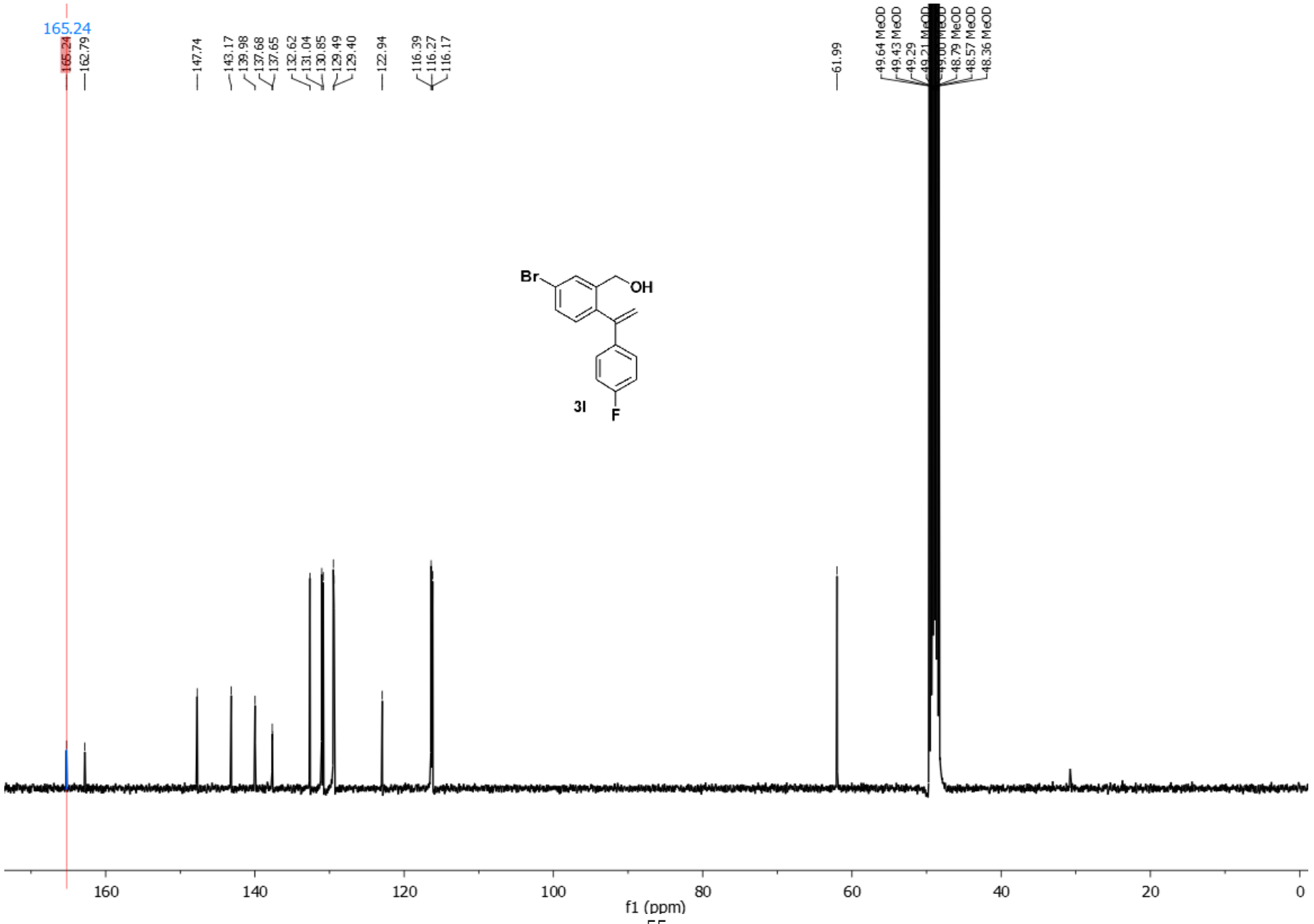
120
100
80
60
40
20
f1 (ppm)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122.94
116.39
116.27
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61.99
49.64 MeOD
49.43 MeOD
49.29
49.21 MeOD
49.00 MeOD
48.79 MeOD
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Br
OH
F
3l
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140
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100
80
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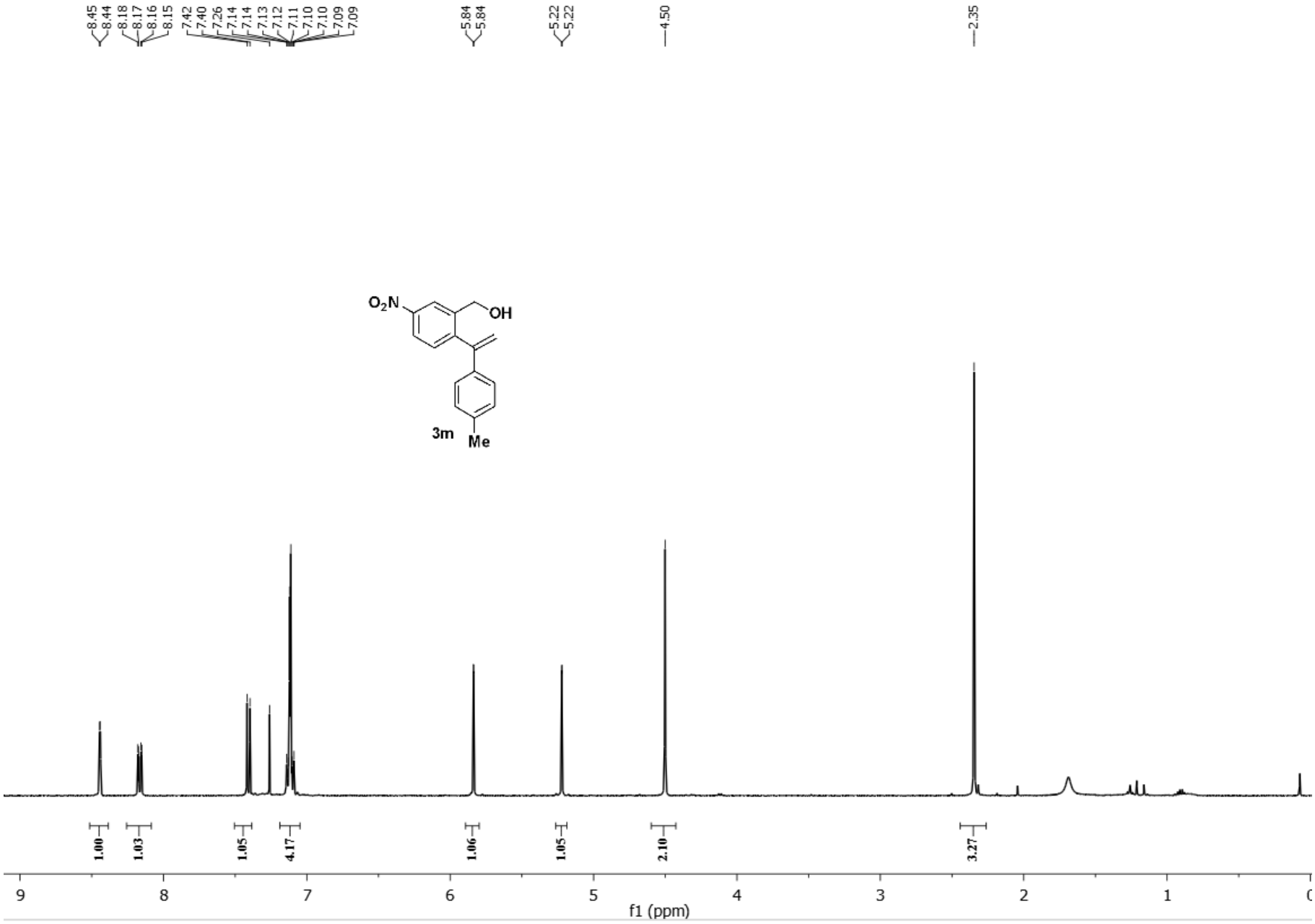
20
0
f1 (ppm)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7.13
7.12
7.11
7.10
7.10
7.09
7.09
5.84
5.84
5.22
5.22
4.50
2.35
O2N
OH
3m
Me
1.00
1.03
1.05
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1.05
2.10
3.27
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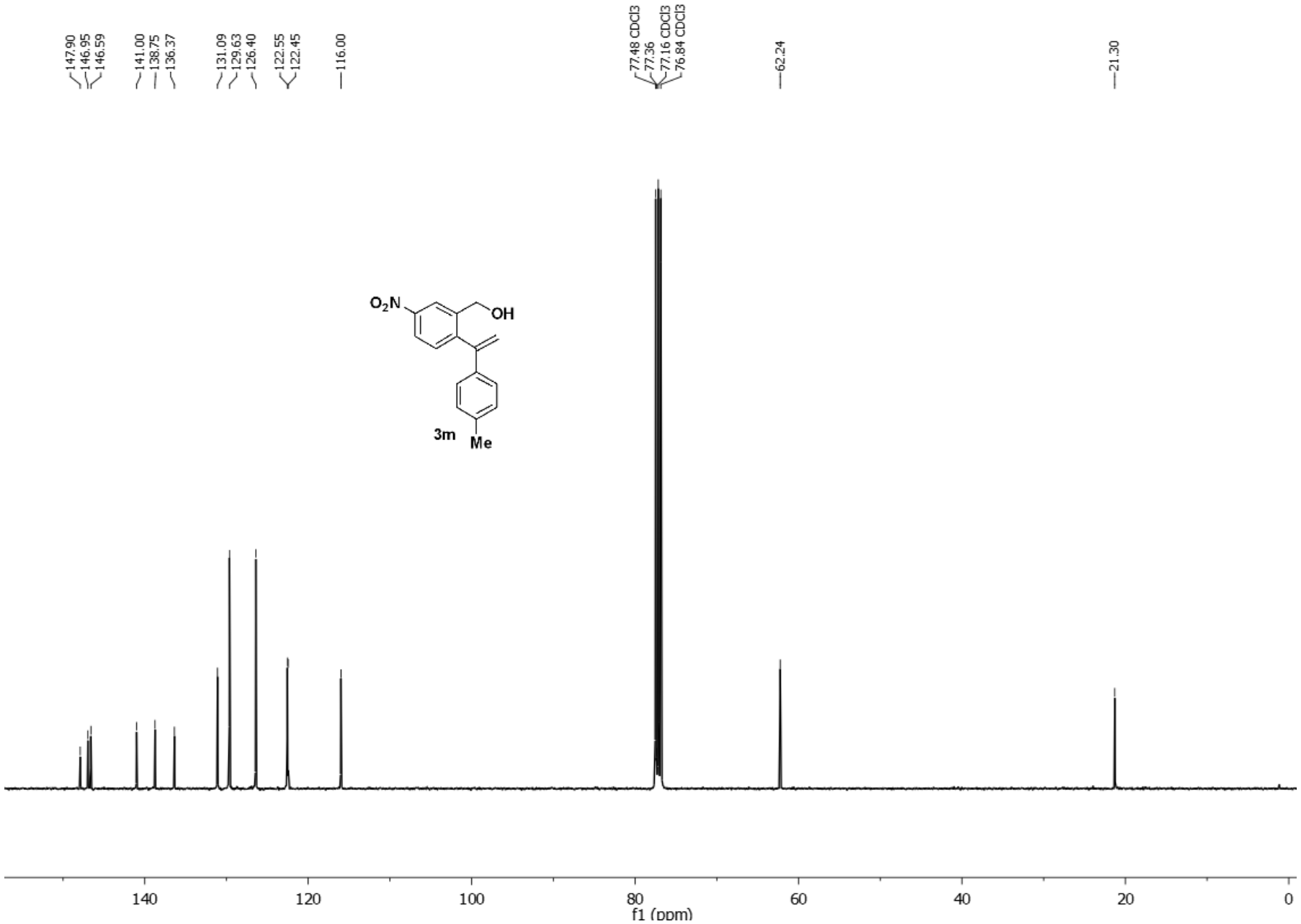
8
7
6
5
4
3
2
1
f1 (ppm)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122.45
116.00
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77.36
77.16 CDCl3
76.84 CDCl3
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O2N
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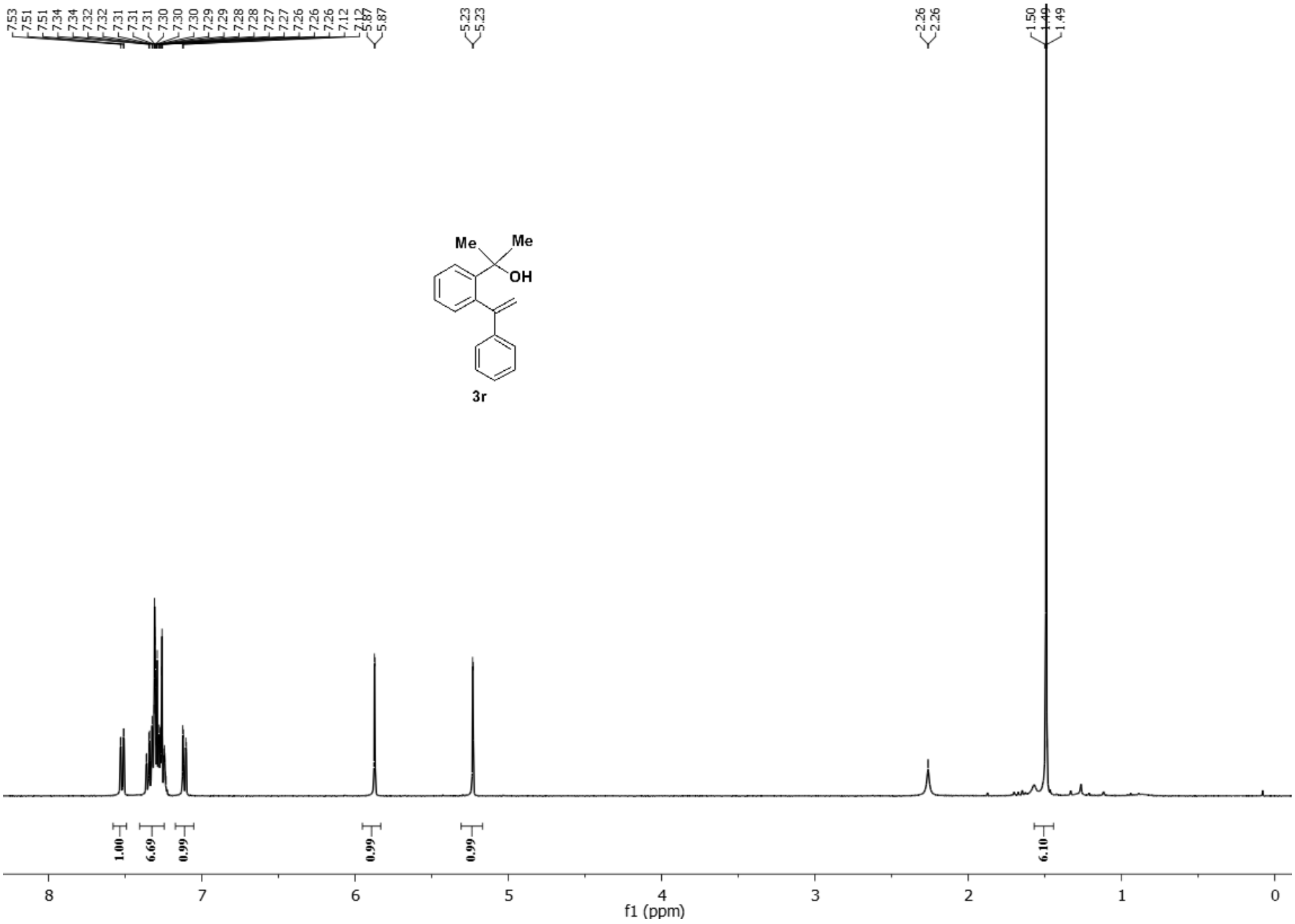
f1 (ppm)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5.23
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2.26
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1.49
Me
Me
OH
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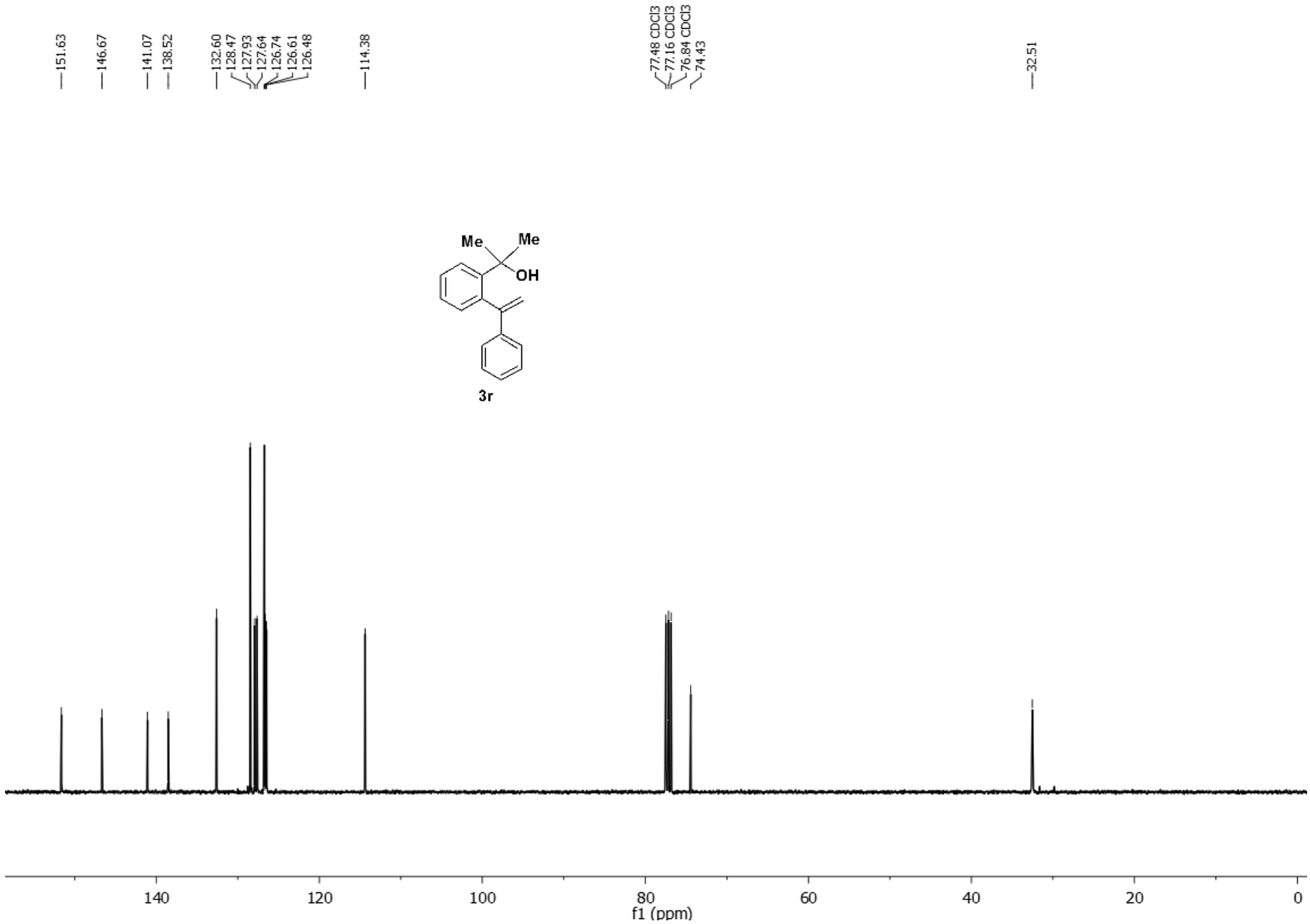
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126.61
126.48
114.38
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77.16 CDCl3
76.84 CDCl3
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32.51
Me
Me
OH
3r
140
120
100
80
60
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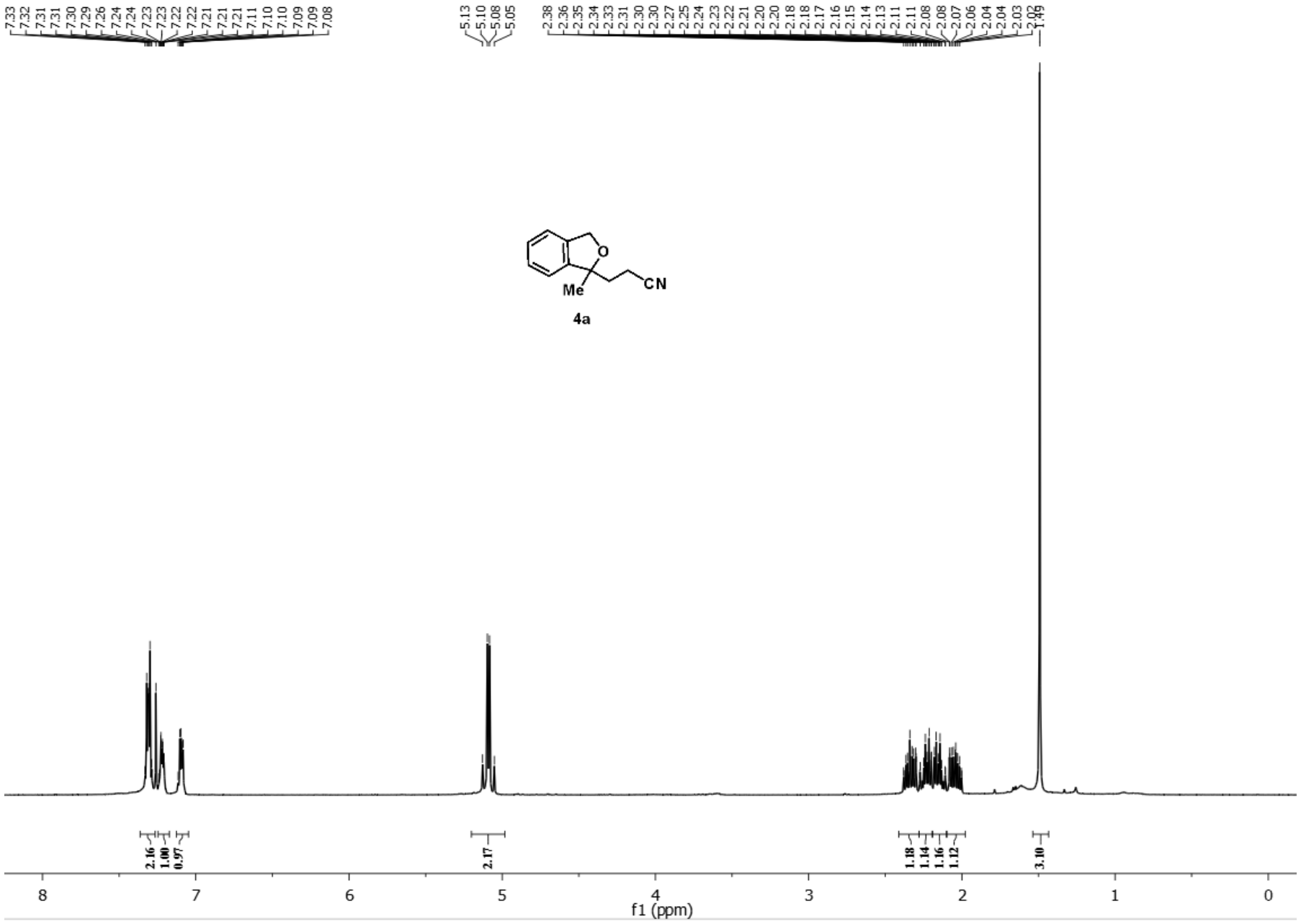
20
0
f1 (ppm)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7.21
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7.10
7.10
7.09
7.09
7.08
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5.10
5.08
5.05
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O
Me
CN
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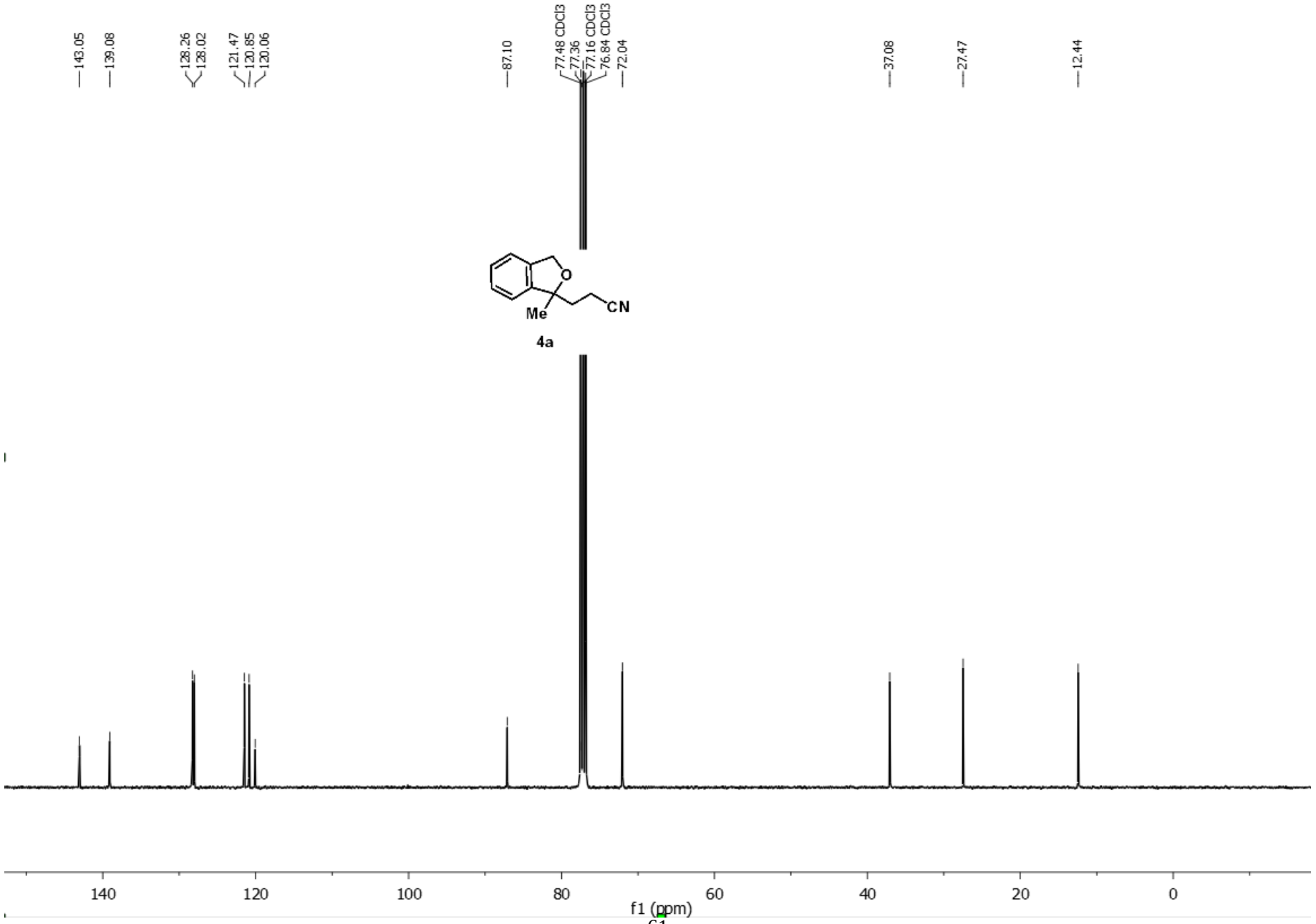
f1 (ppm)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77.36
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76.84 CDCl3
72.04
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O
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CN
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100
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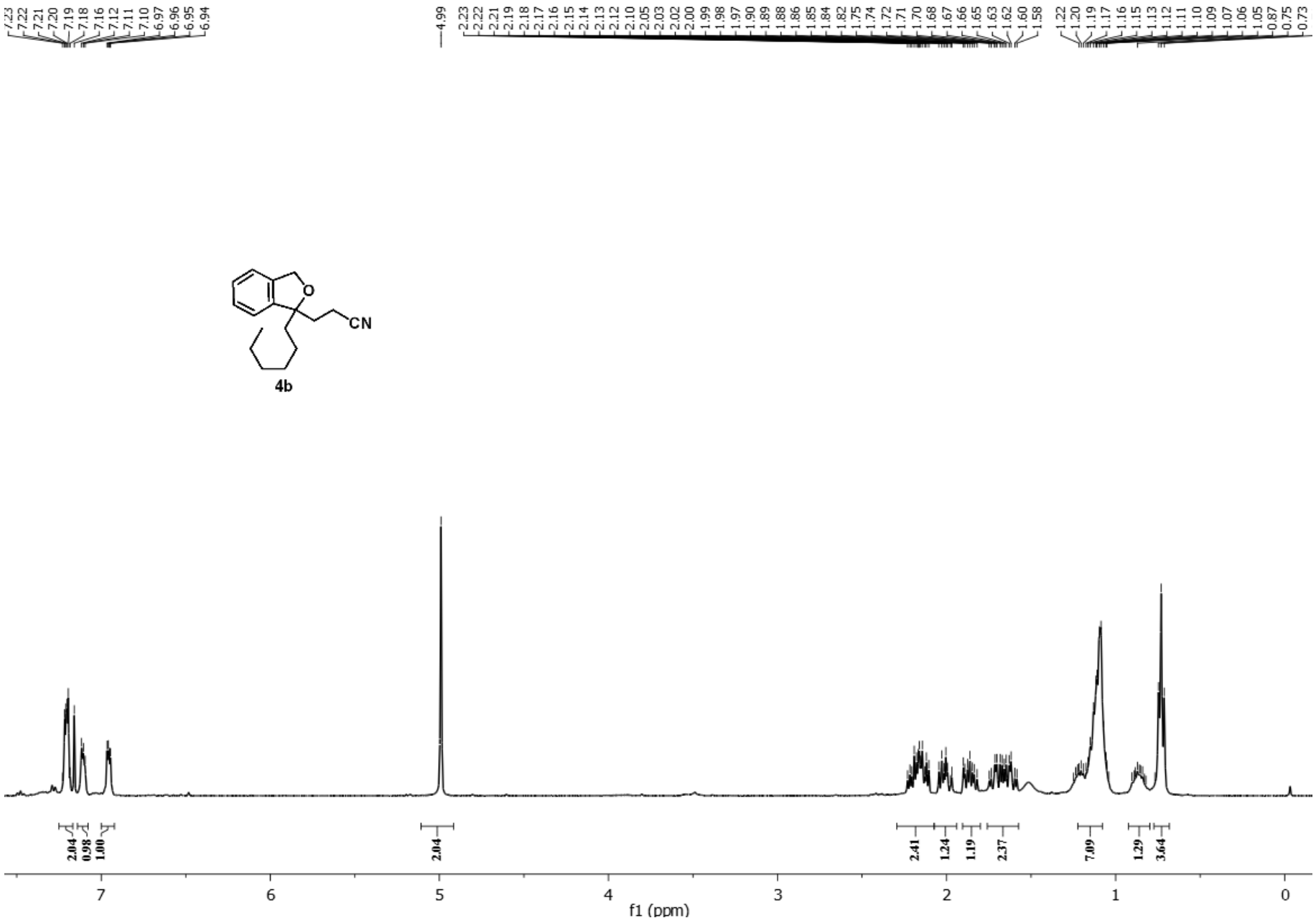
f1 (ppm)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6.94
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2.21
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2.17
2.16
2.15
2.14
2.13
2.12
2.10
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2.02
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1.85
1.84
1.82
1.75
1.74
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1.20
1.19
1.17
1.16
1.15
1.13
1.12
1.11
1.10
1.09
1.07
1.06
1.05
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0.73
O
CN
4b
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1.00
2.04
2.41
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4
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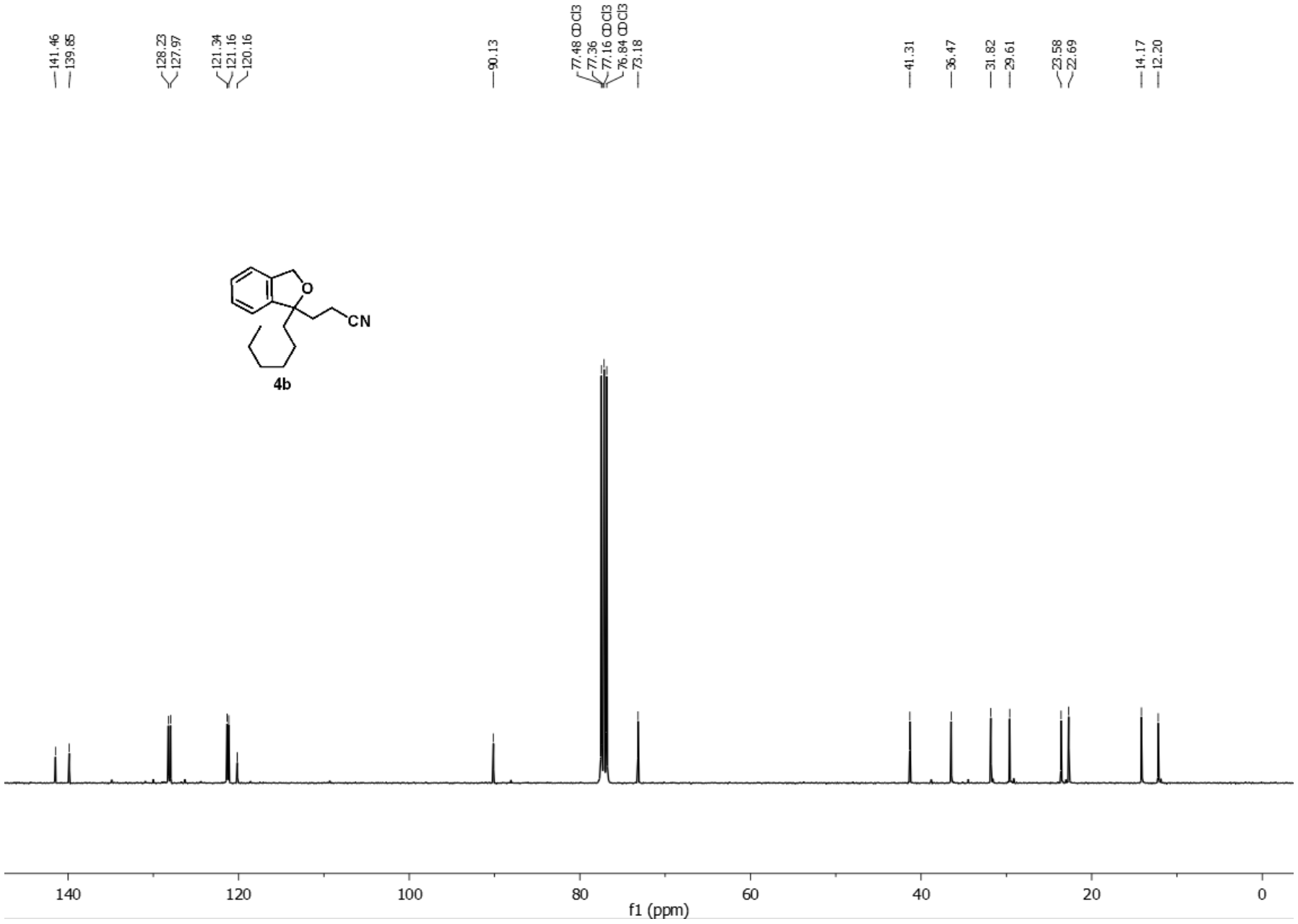
0
f1 (ppm)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77.36
77.16 CDCl3
76.84 CDCl3
73.18
41.31
36.47
31.82
29.61
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12.20
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CN
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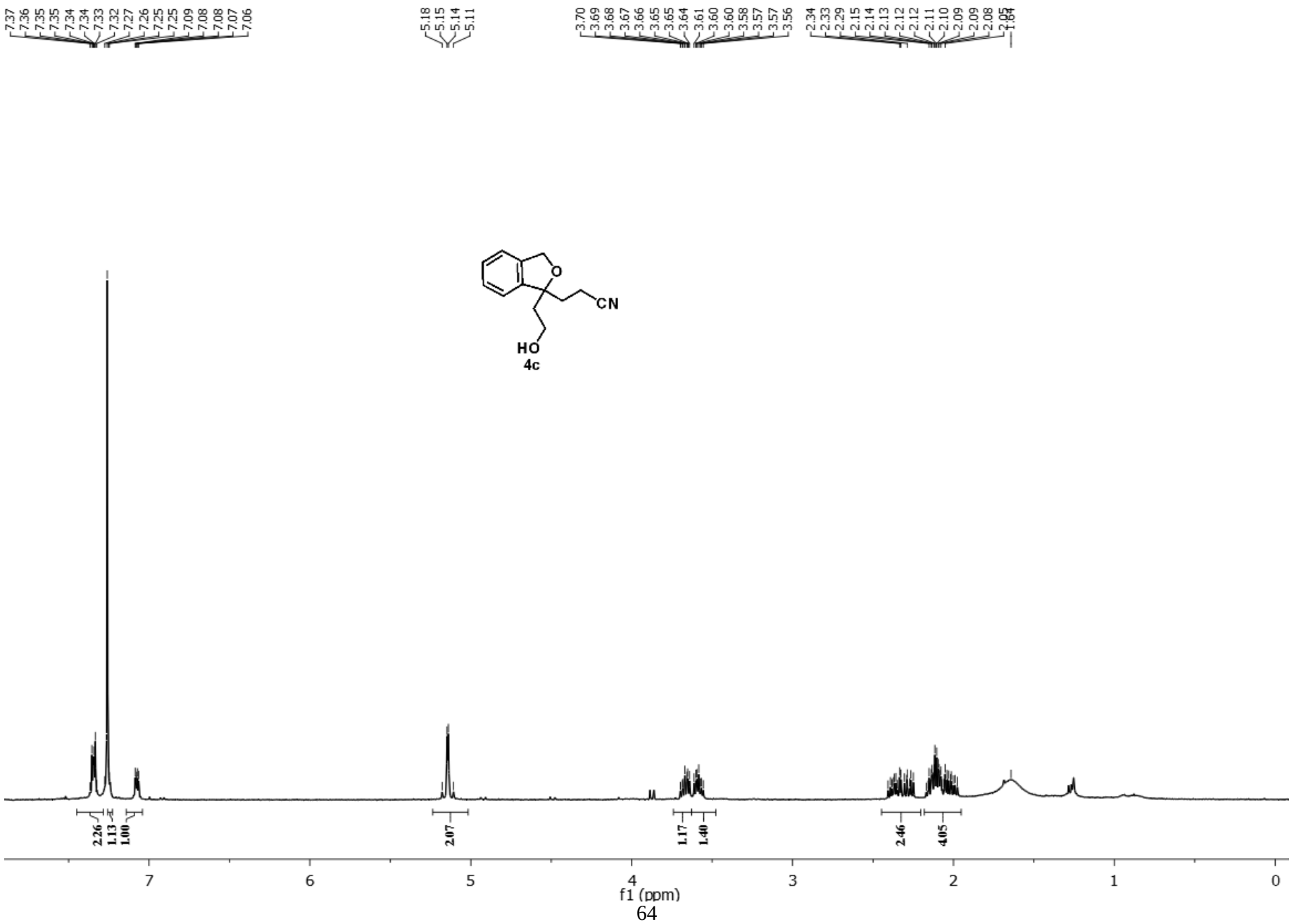
100
80
60
40
20
0
f1 (ppm)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CN
HO
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1.17
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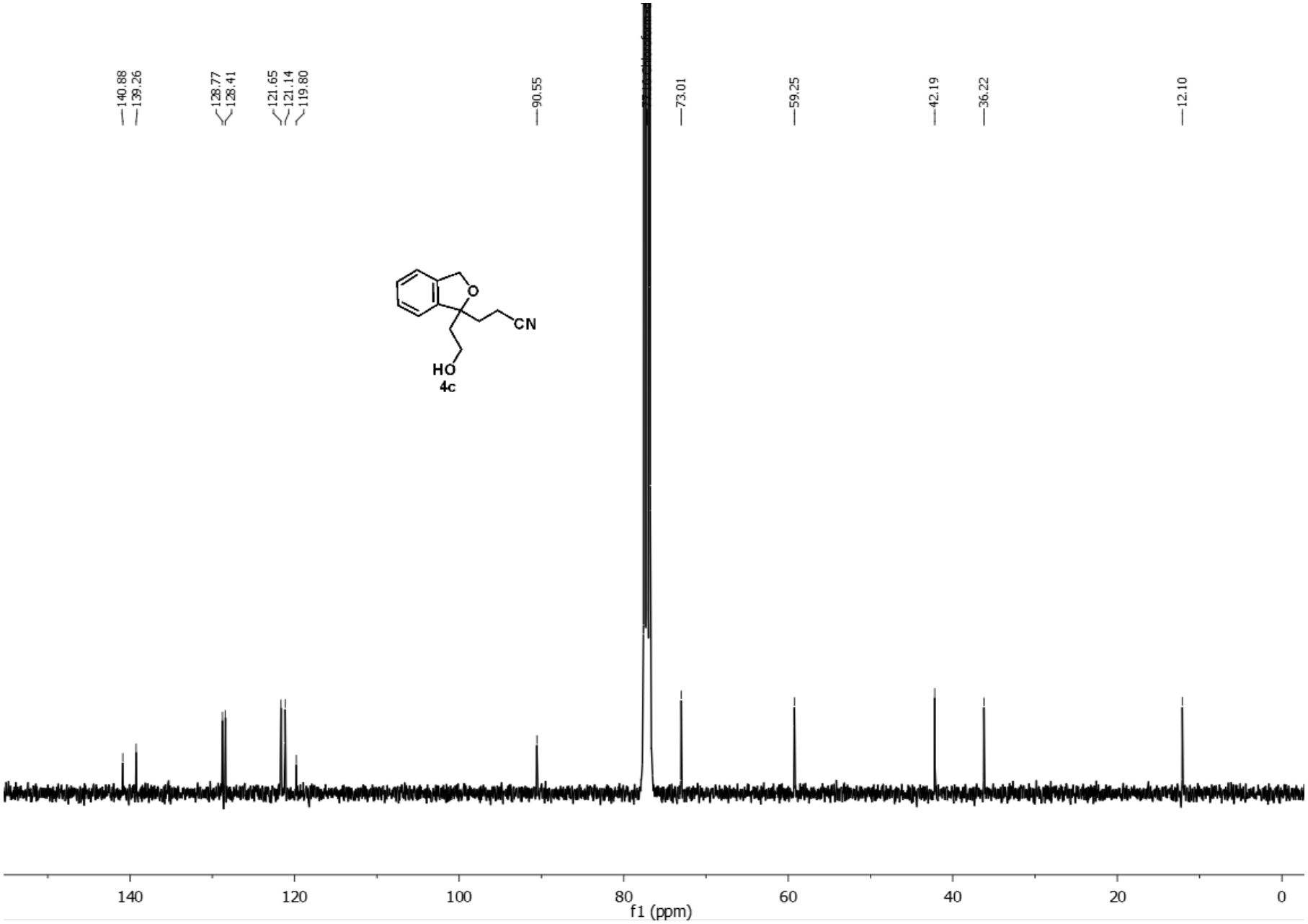
4.05
7
6
5
4
3
2
1
0
f1 (ppm)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90.55
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73.01
59.25
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12.10
O
CN
HO
4c
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20
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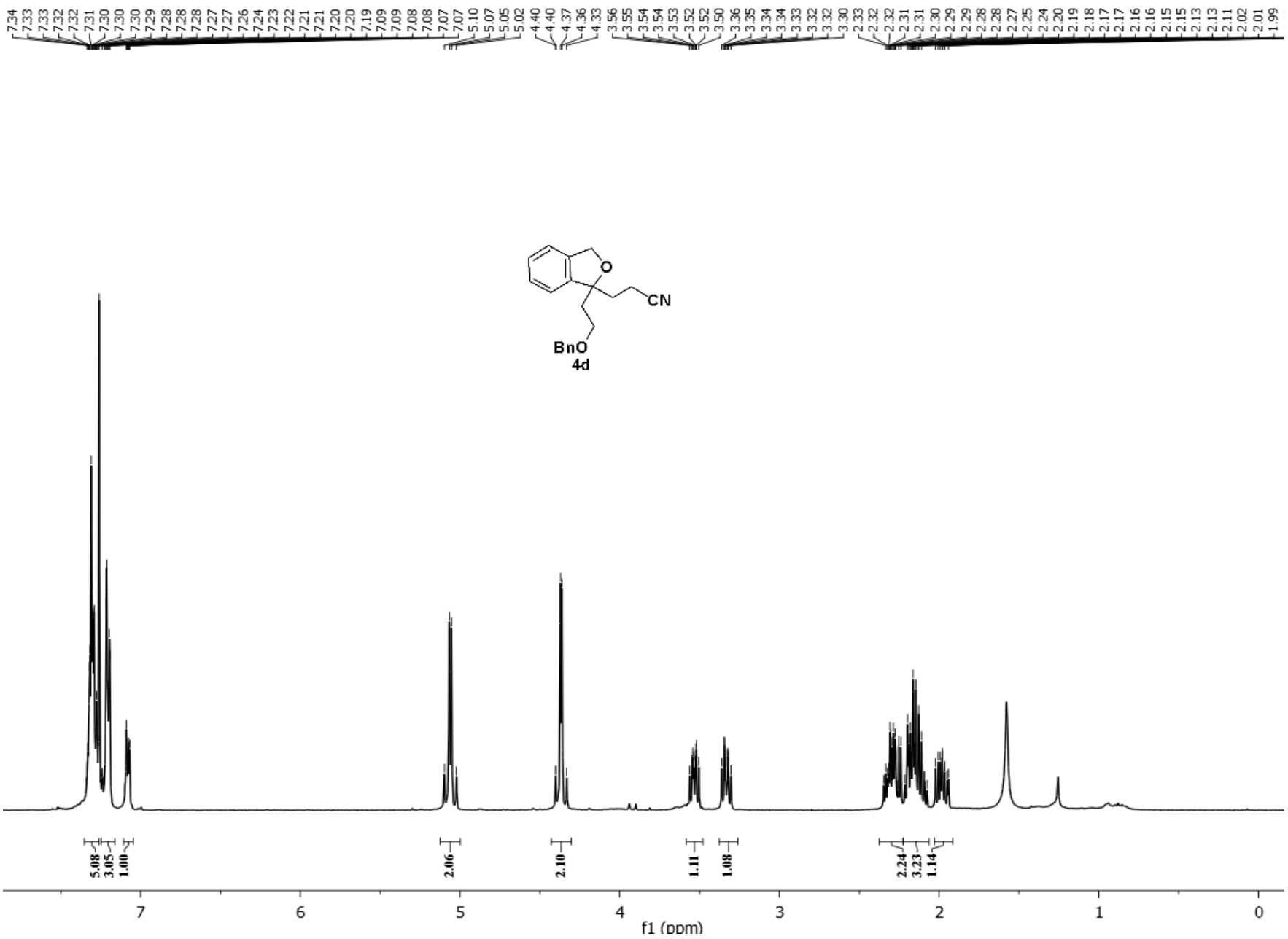
f1 (ppm)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O
CN
BnO
4d
5.08
3.05
1.00
2.06
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2.24
3.23
1.14
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5
4
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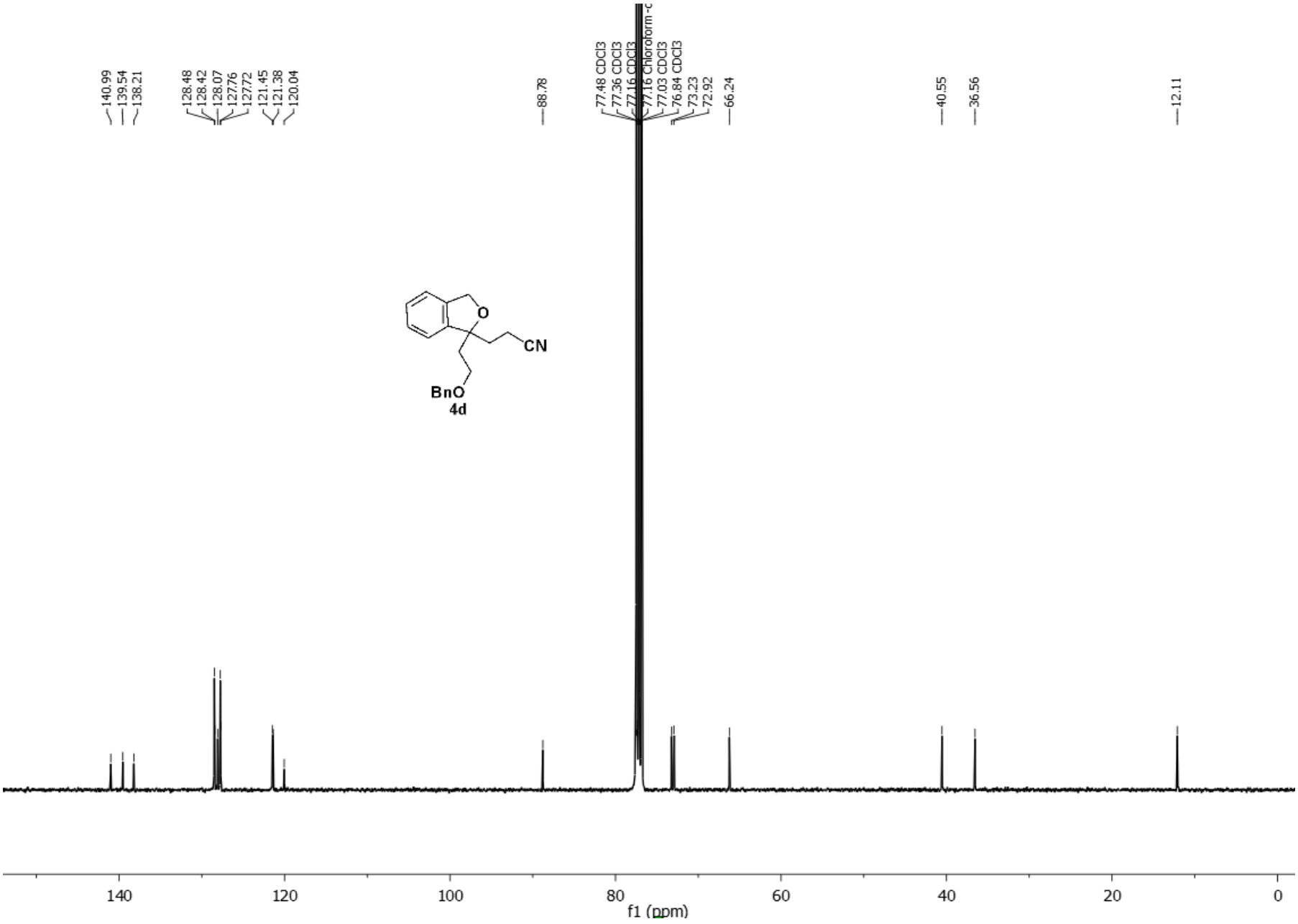
f1 (ppm)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77.16 CDCl3
77.16 Chloroform-d
77.03 CDCl3
76.84 CDCl3
73.23
72.92
66.24
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12.11
O
CN
BnO
4d
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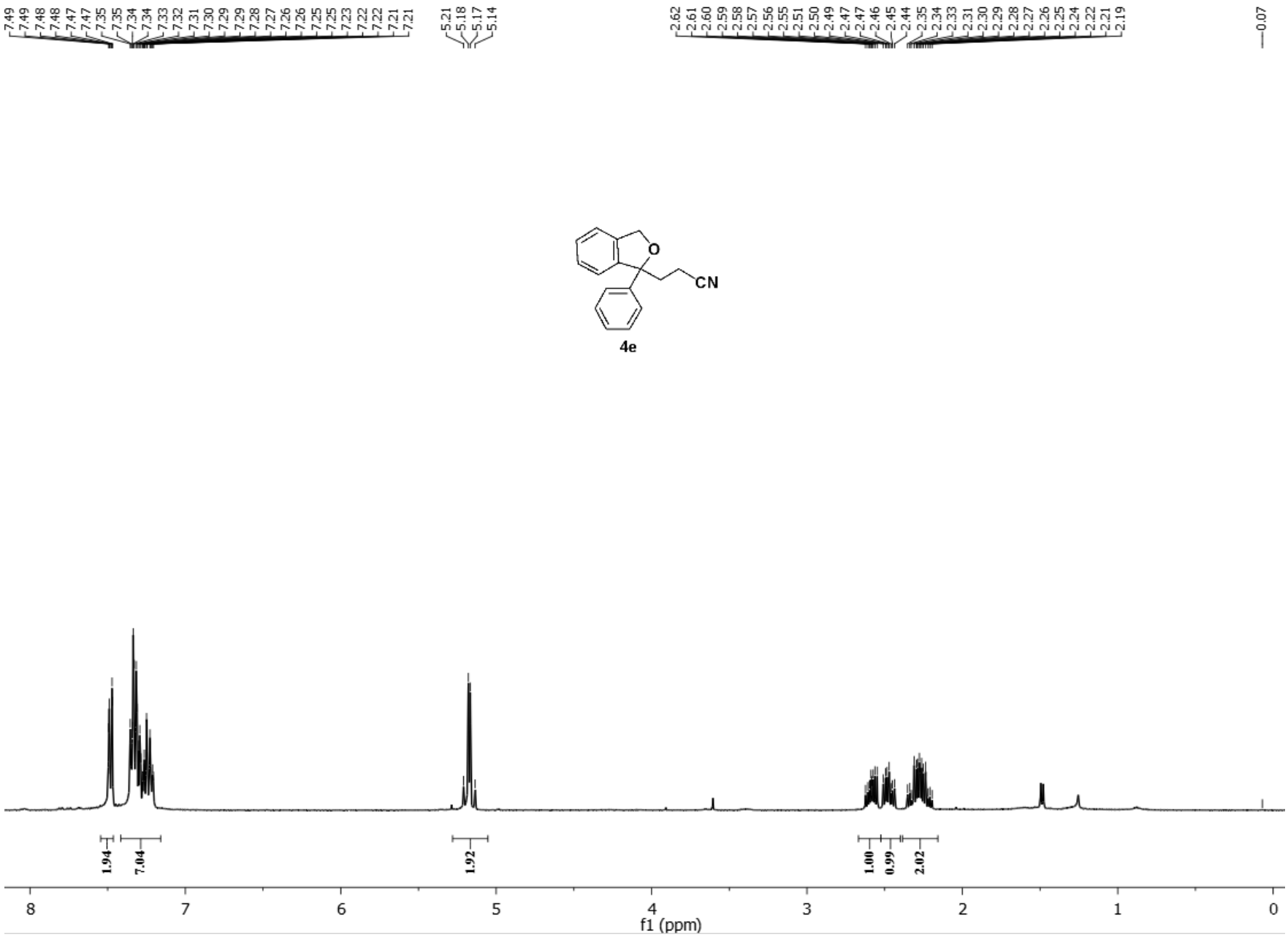
100
80
60
40
20
0
f1 (ppm)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7.22
7.21
7.21
5.21
5.18
5.17
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2.33
2.31
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2.29
2.28
2.27
2.26
2.25
2.24
2.22
2.21
2.19
0.07
O
CN
4e
1.94
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4
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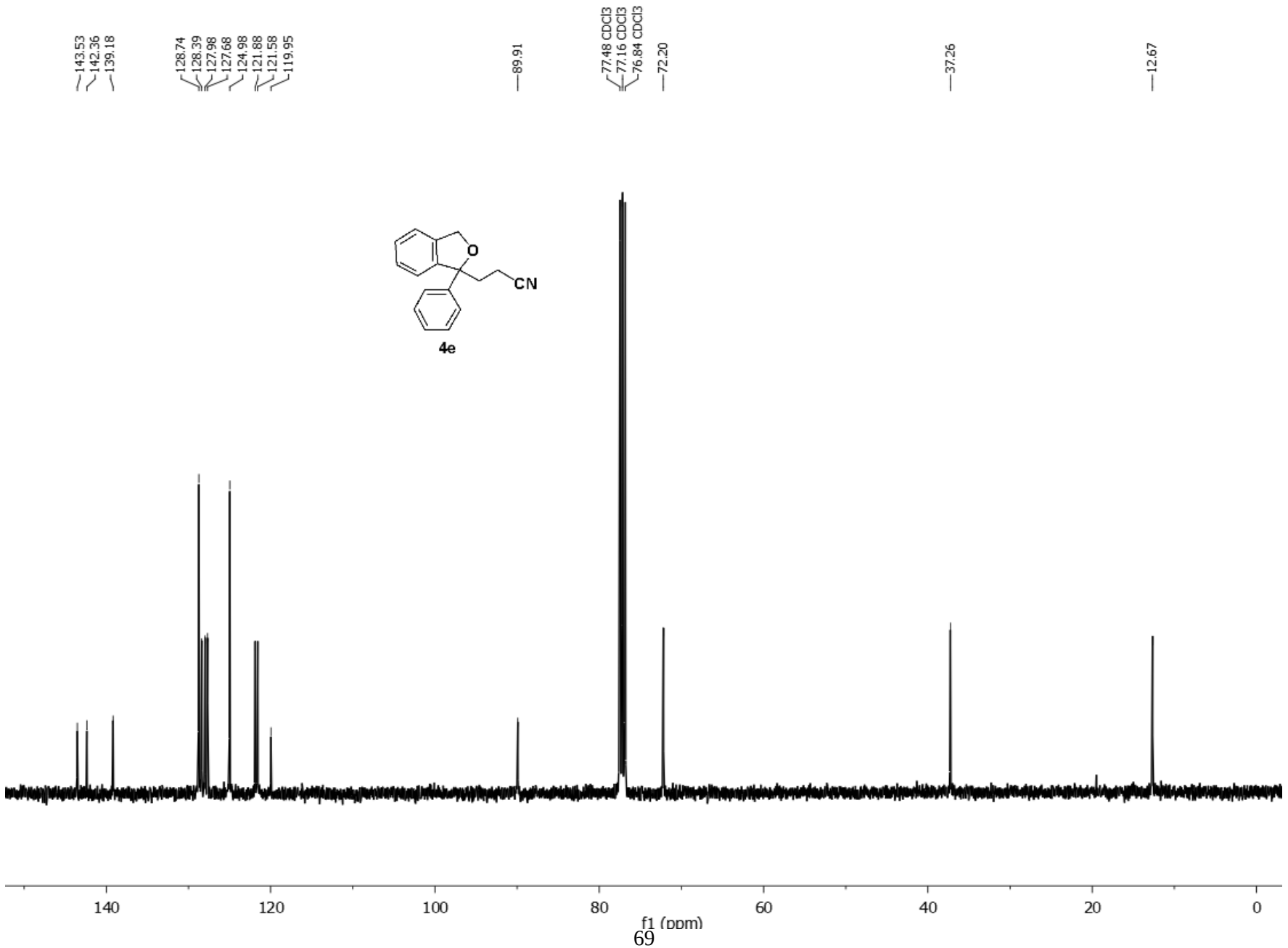
f1 (ppm)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121.58
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89.91
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77.16 CDCl3
76.84 CDCl3
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12.67
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CN
4e
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100
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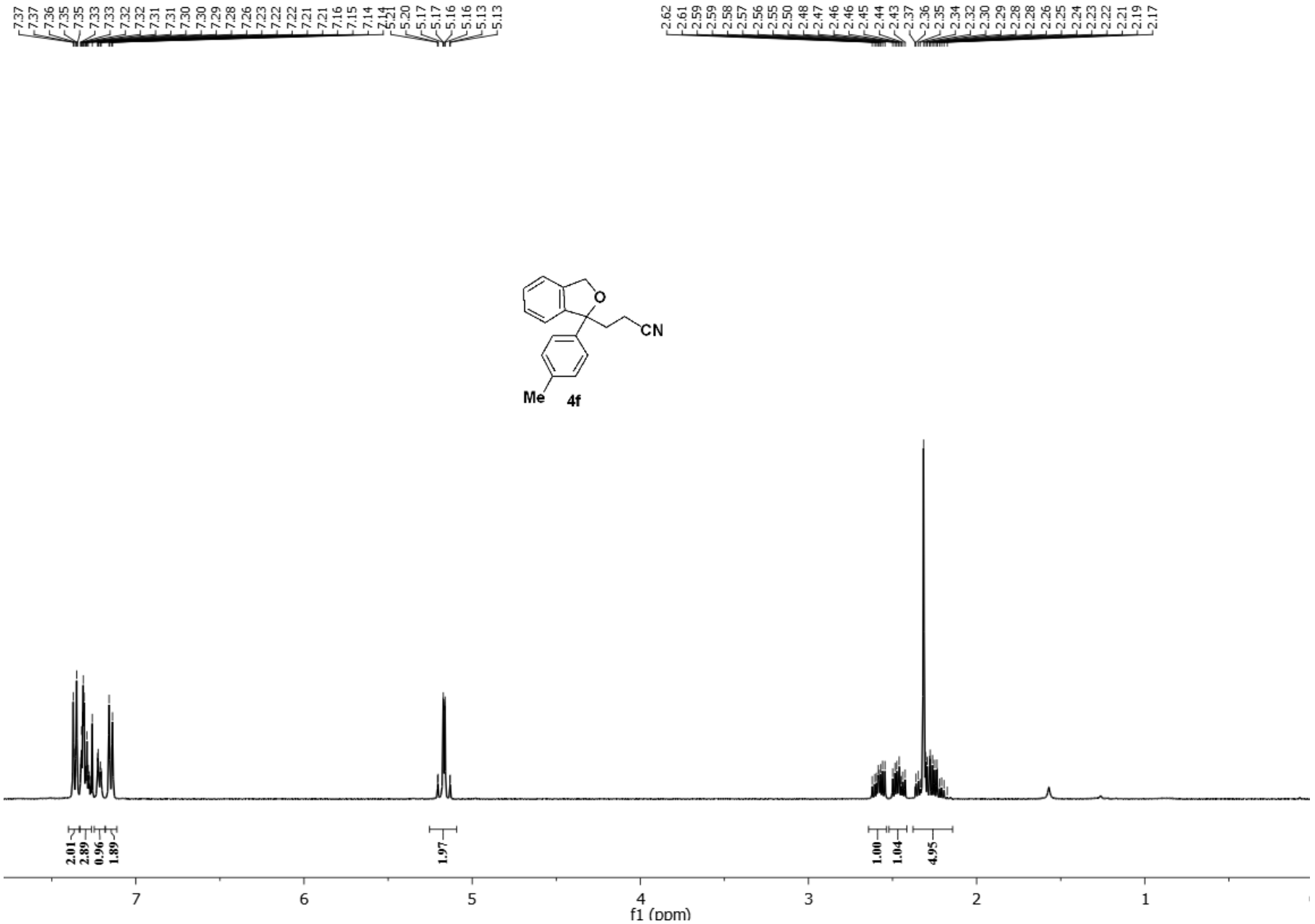
20
0
f1 (ppm)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2.62 2.61 2.59 2.59 2.58 2.57 2.56 2.55 2.50 2.48 2.47 2.46 2.46 2.45 2.44 2.43 2.37 2.36 2.35 2.34 2.32 2.30 2.29 2.28 2.28 2.26 2.25 2.24 2.23 2.22 2.21 2.19 2.17
O
CN
Me
4f
2.01
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1.97
1.00
1.04
4.95
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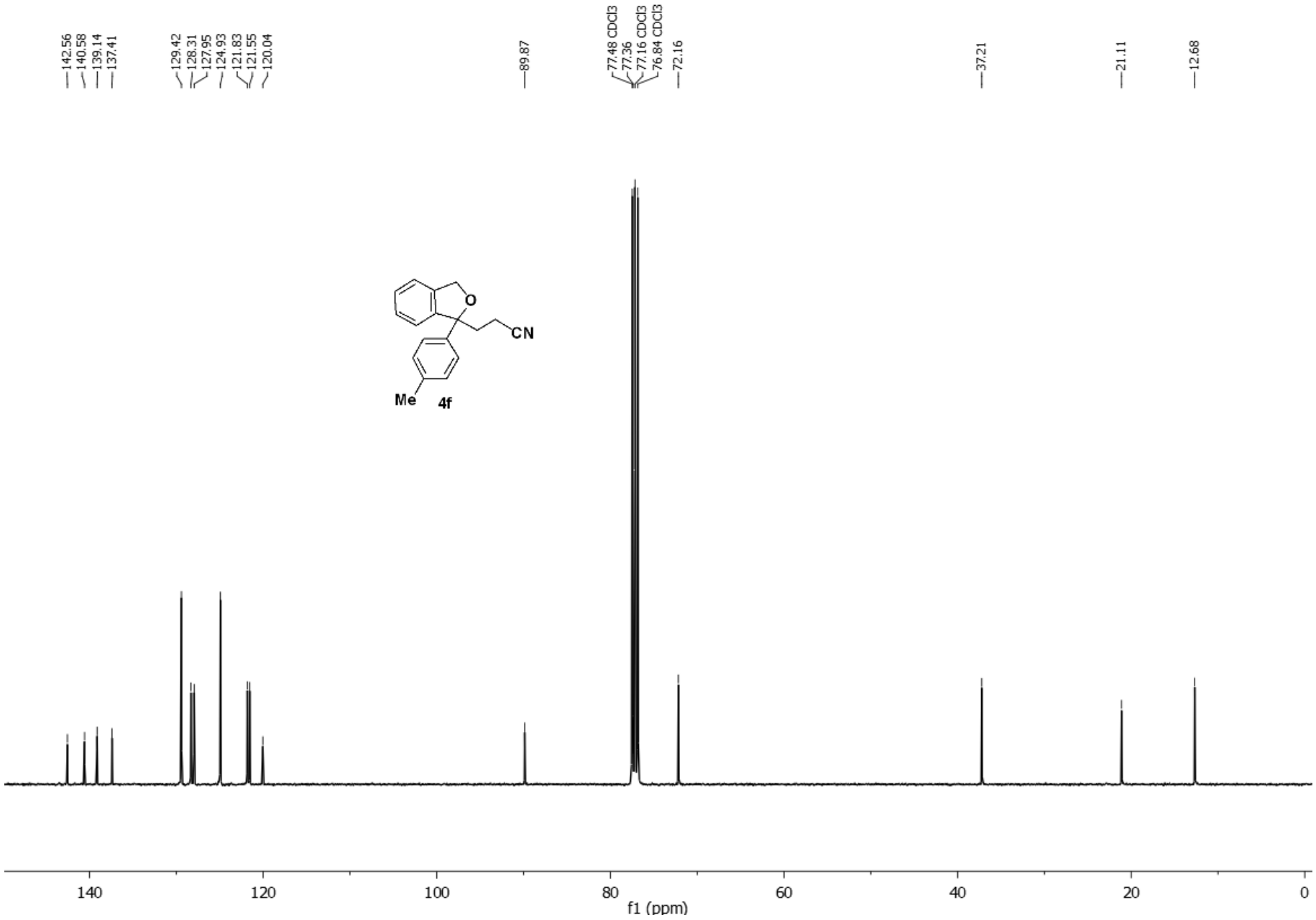
6
5
4
3
2
1
f1 (ppm)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124.93
121.83
121.55
120.04
89.87
77.48 CDCl3
77.36
77.16 CDCl3
76.84 CDCl3
72.16
37.21
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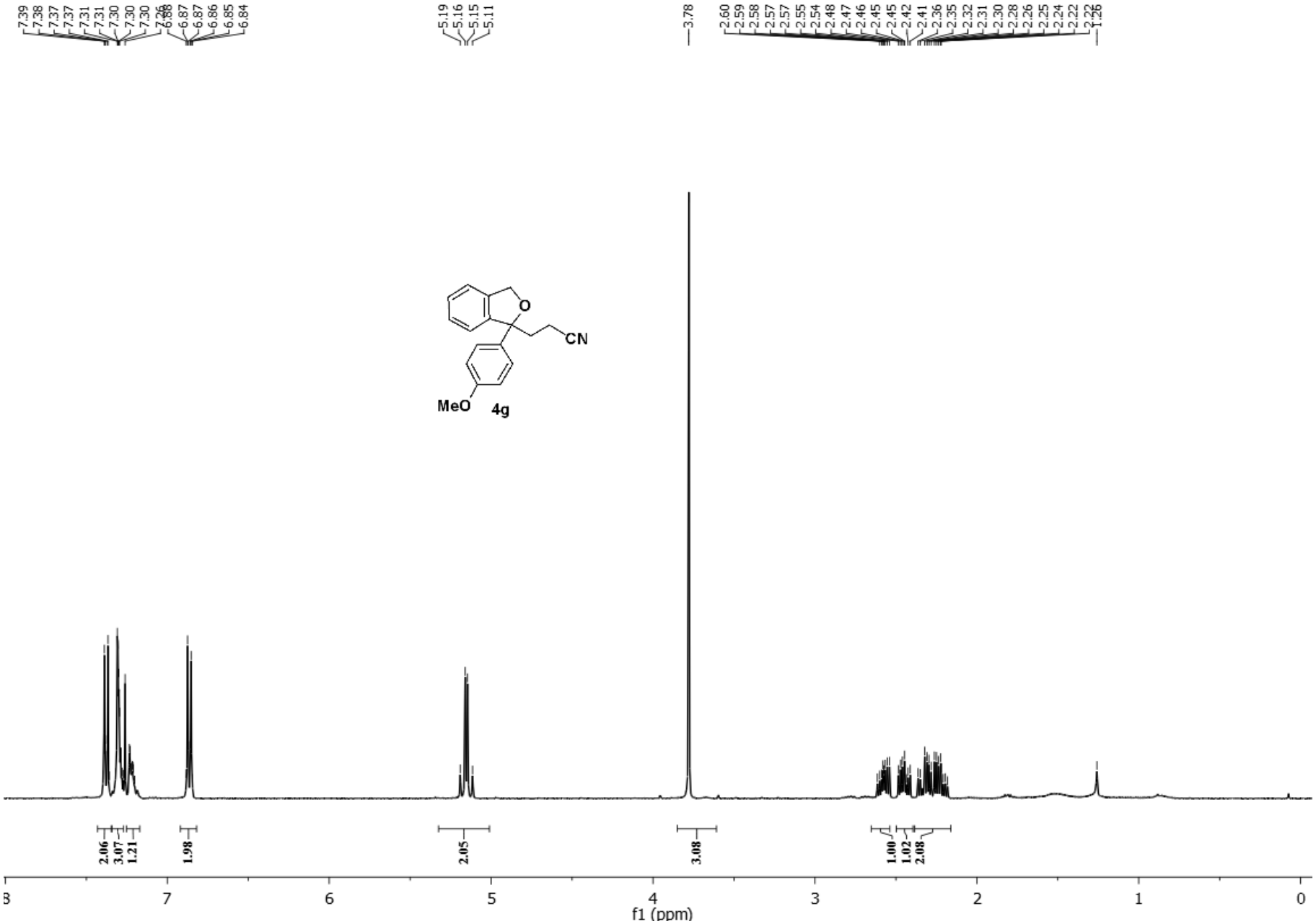
12.68
O
CN
Me
4f
140
120
100
80
60
40
20
0
f1 (ppm)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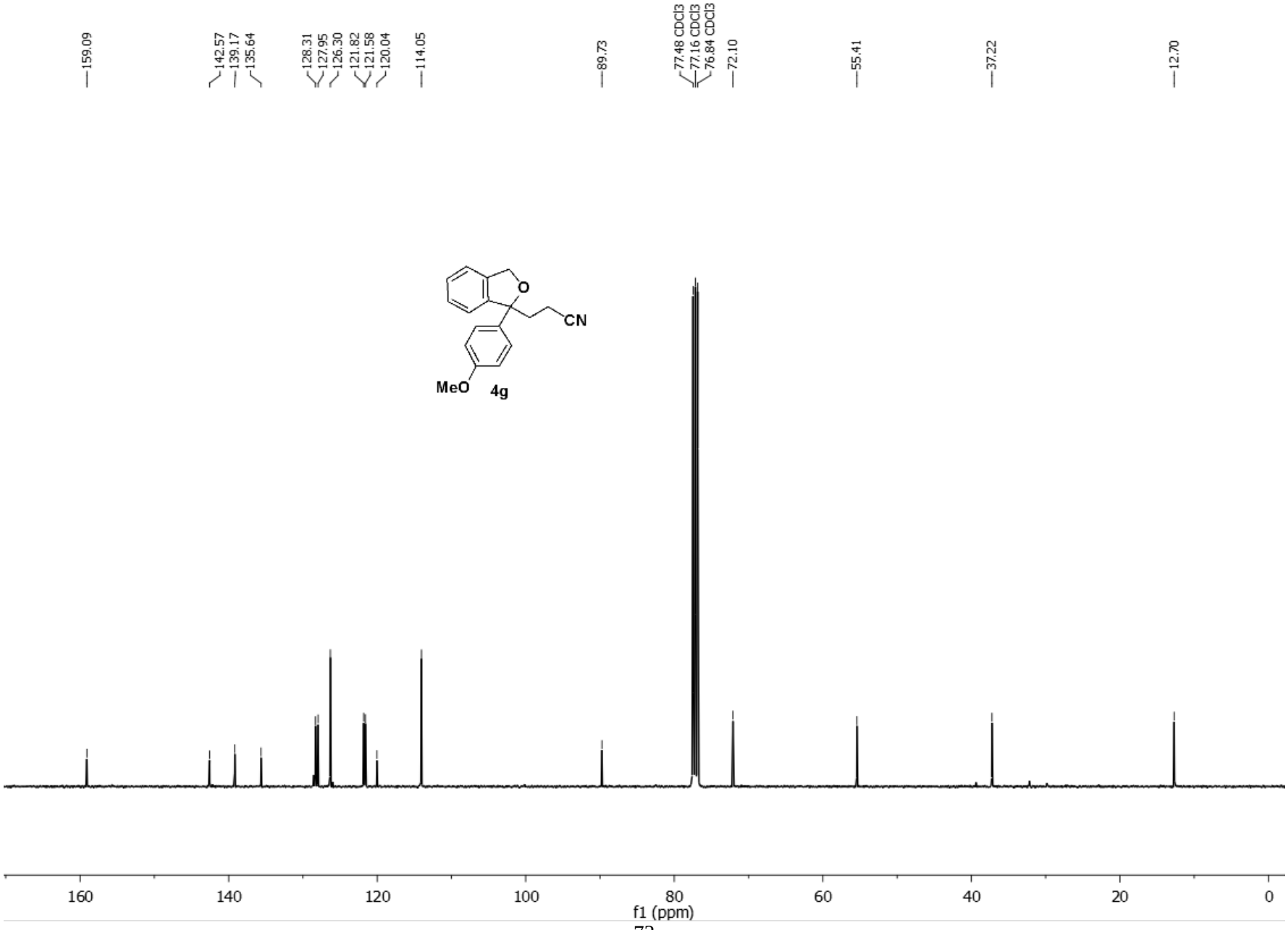
7.26
6.88
6.87
6.87
6.86
6.85
6.84
5.19
5.16
5.15
5.11
3.78
2.60
2.59
2.58
2.57
2.57
2.55
2.54
2.48
2.47
2.46
2.45
2.45
2.42
2.41
2.36
2.35
2.32
2.31
2.30
2.28
2.26
2.25
2.24
2.22
2.22
1.26
O
CN
MeO
4g
2.06
3.07
1.21
1.98
2.05
3.08
1.00
1.02
2.08
8
7
6
5
4
3
2
1
0
f1 (ppm)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127.95
126.30
121.82
121.58
120.04
114.05
89.73
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
72.10
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O
CN
MeO
4g
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100
80
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20
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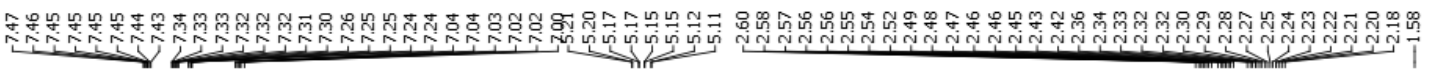
f1 (ppm)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7.30
7.26
7.25
7.25
7.24
7.24
7.04
7.04
7.03
7.02
7.02
7.00
5.21
5.20
5.17
5.17
5.15
5.15
5.12
5.11
2.60
2.58
2.57
2.56
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2.55
2.54
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2.33
2.32
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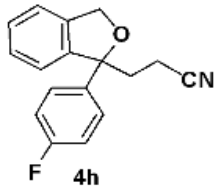
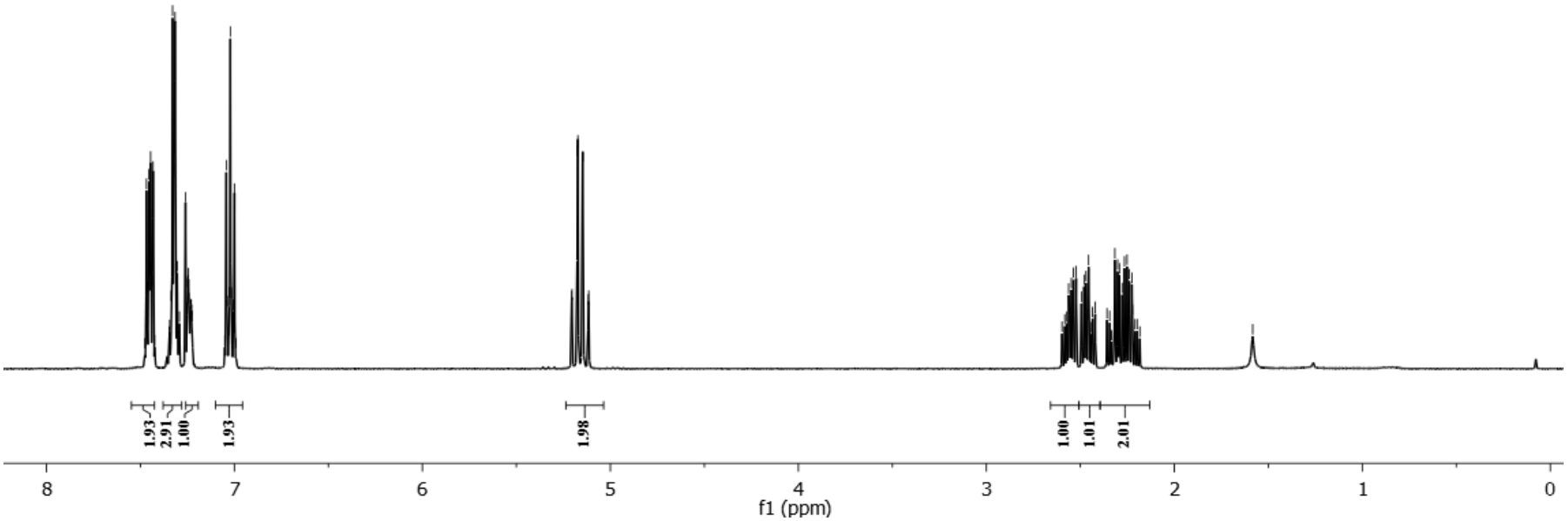
1.58


O
CN
F

4h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2.01
8
7
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5
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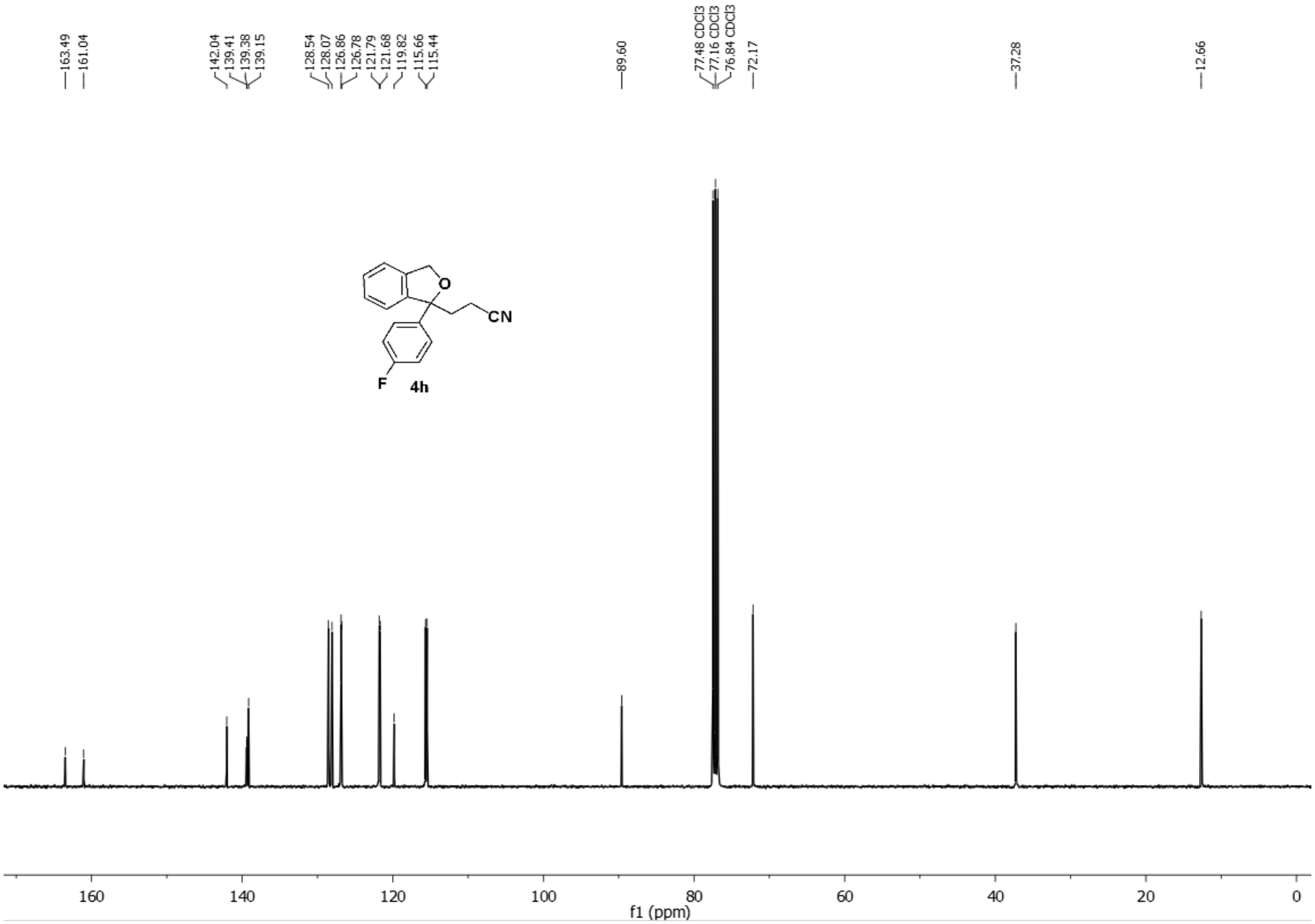
1
0
f1 (ppm)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128.07
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126.78
121.79
121.68
119.82
115.66
115.44
89.60
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
72.17
37.28
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O
CN
F
4h
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100
80
60
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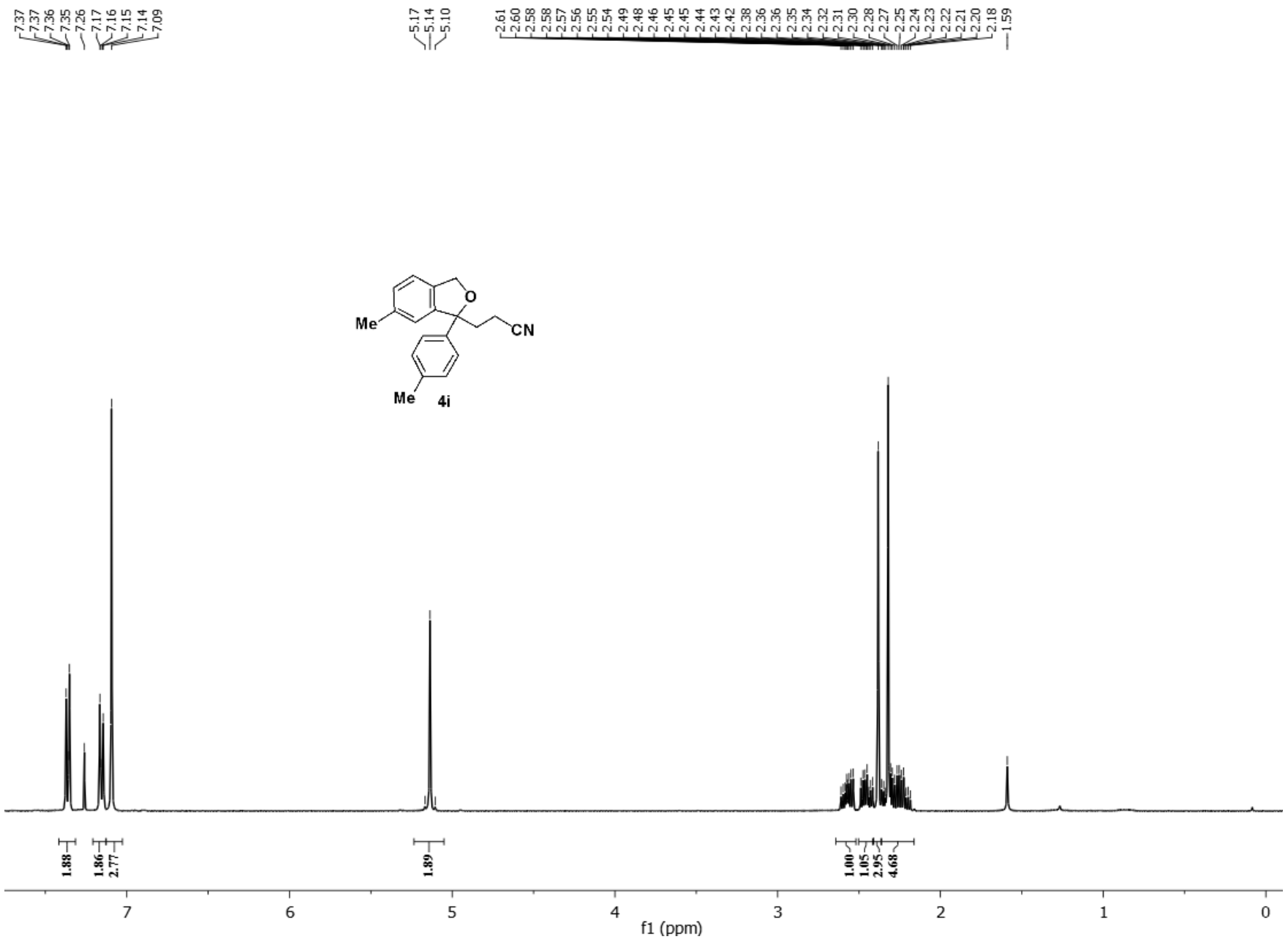
20
0
f1 (ppm)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2.43
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2.23
2.22
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2.20
2.18
1.59
Me
O
CN
Me
4i
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5
4
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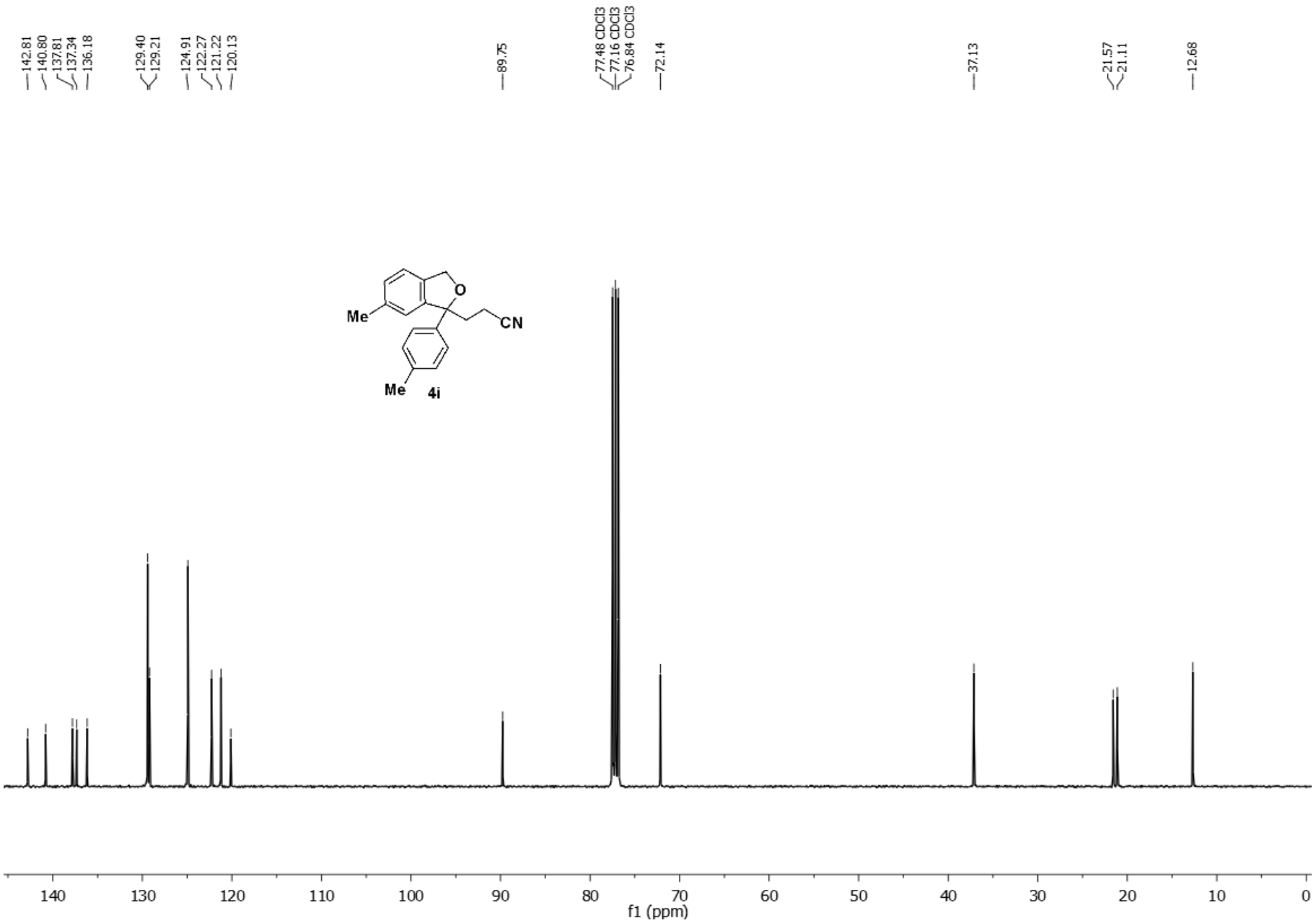
f1 (ppm)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77.16 CDCl3
76.84 CDCl3
72.14
37.13
21.57
21.11
12.68
Me
O
CN
Me
4i
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120
110
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50
40
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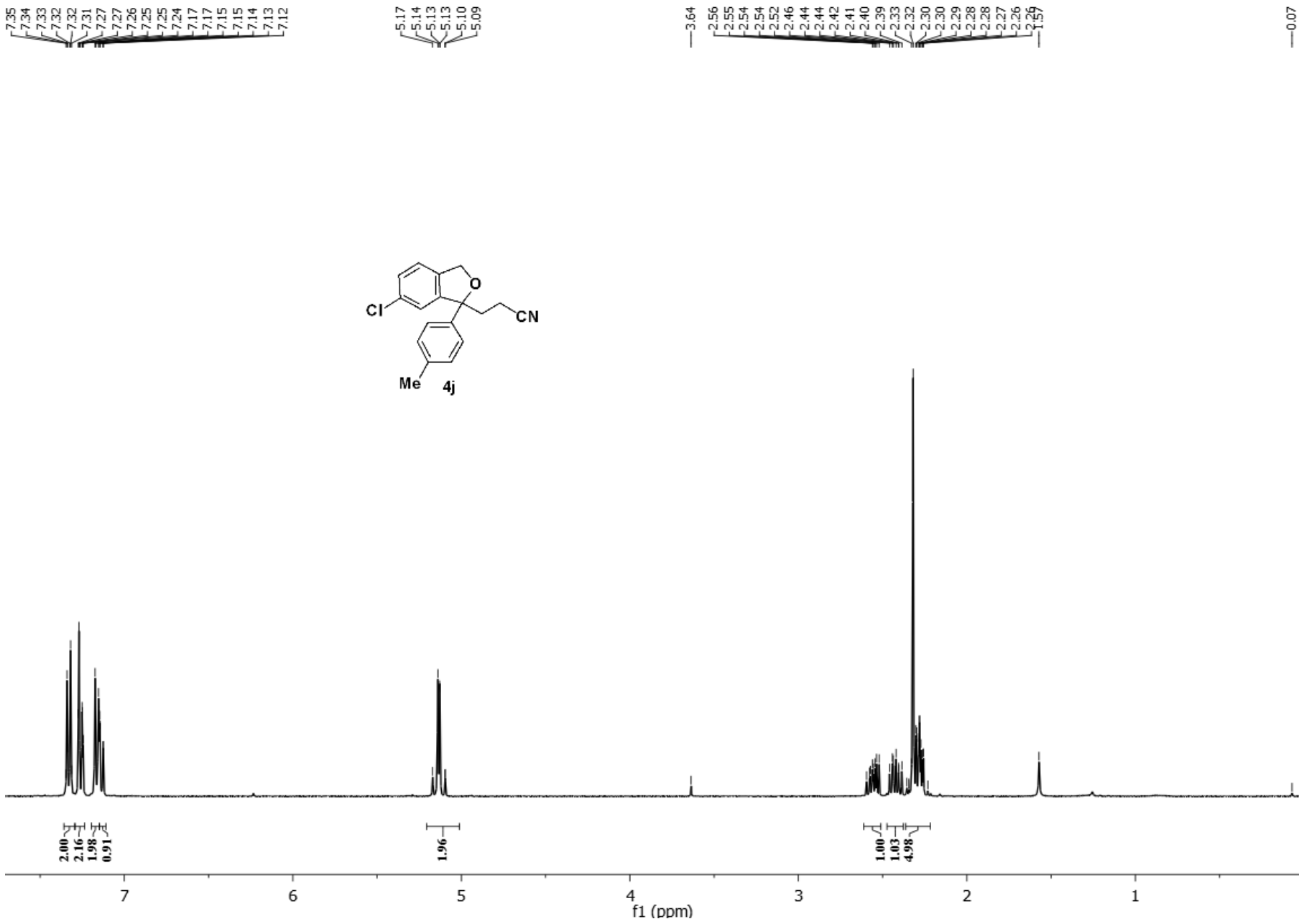
10
0
f1 (ppm)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2.28
2.27
2.26
1.57
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Cl
O
CN
Me
4j
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6
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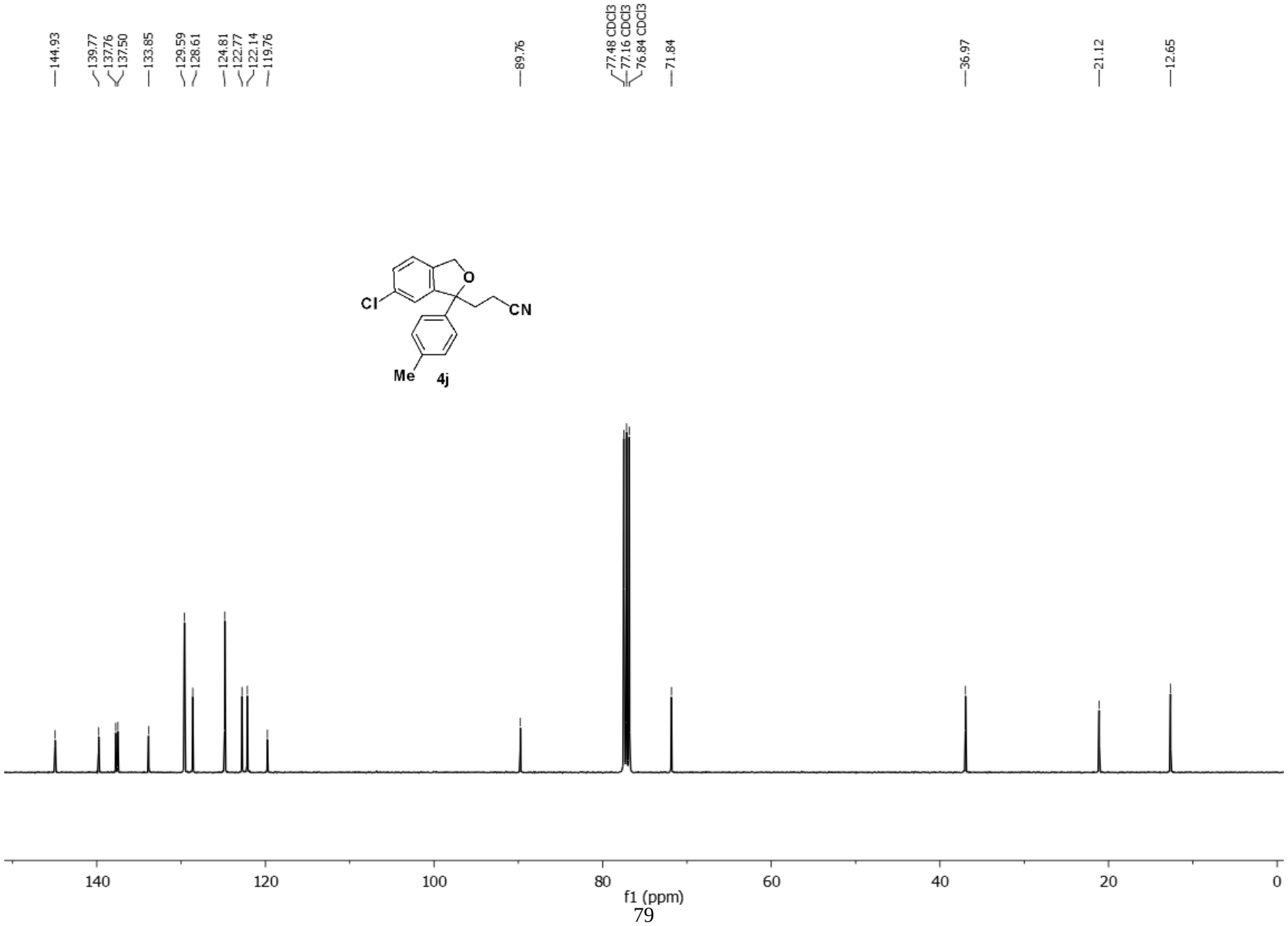
2
1
f1 (ppm)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77.16 CDCl3
76.84 CDCl3
71.84
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Cl
O
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Me
4j
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100
80
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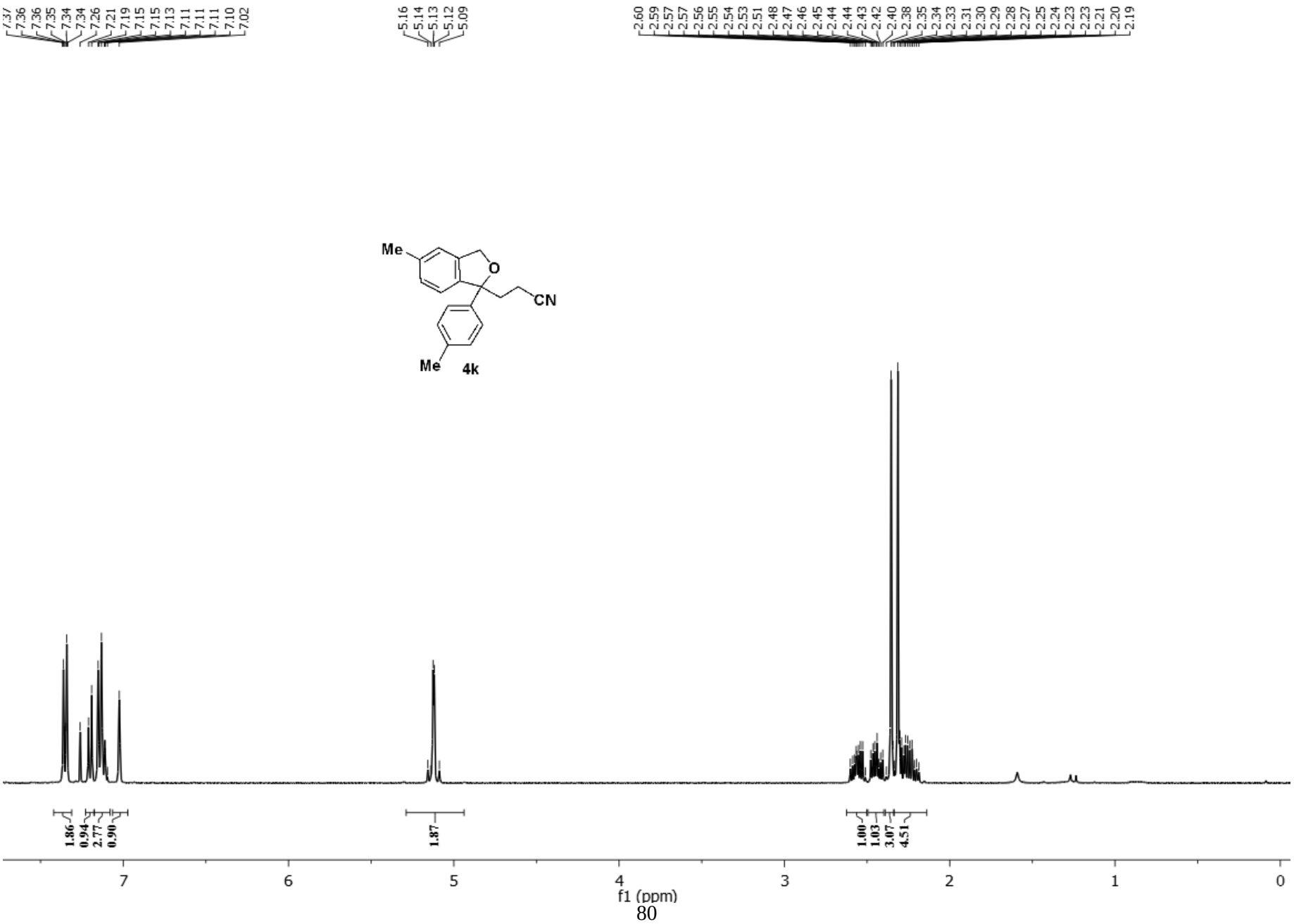
20
0
f1 (ppm)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7.11
7.11
7.10
7.02
5.16
5.14
5.13
5.12
5.09
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2.57
2.57
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2.24
2.23
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2.21
2.20
2.19
Me
O
CN
Me
4k
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0.94
2.77
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7
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5
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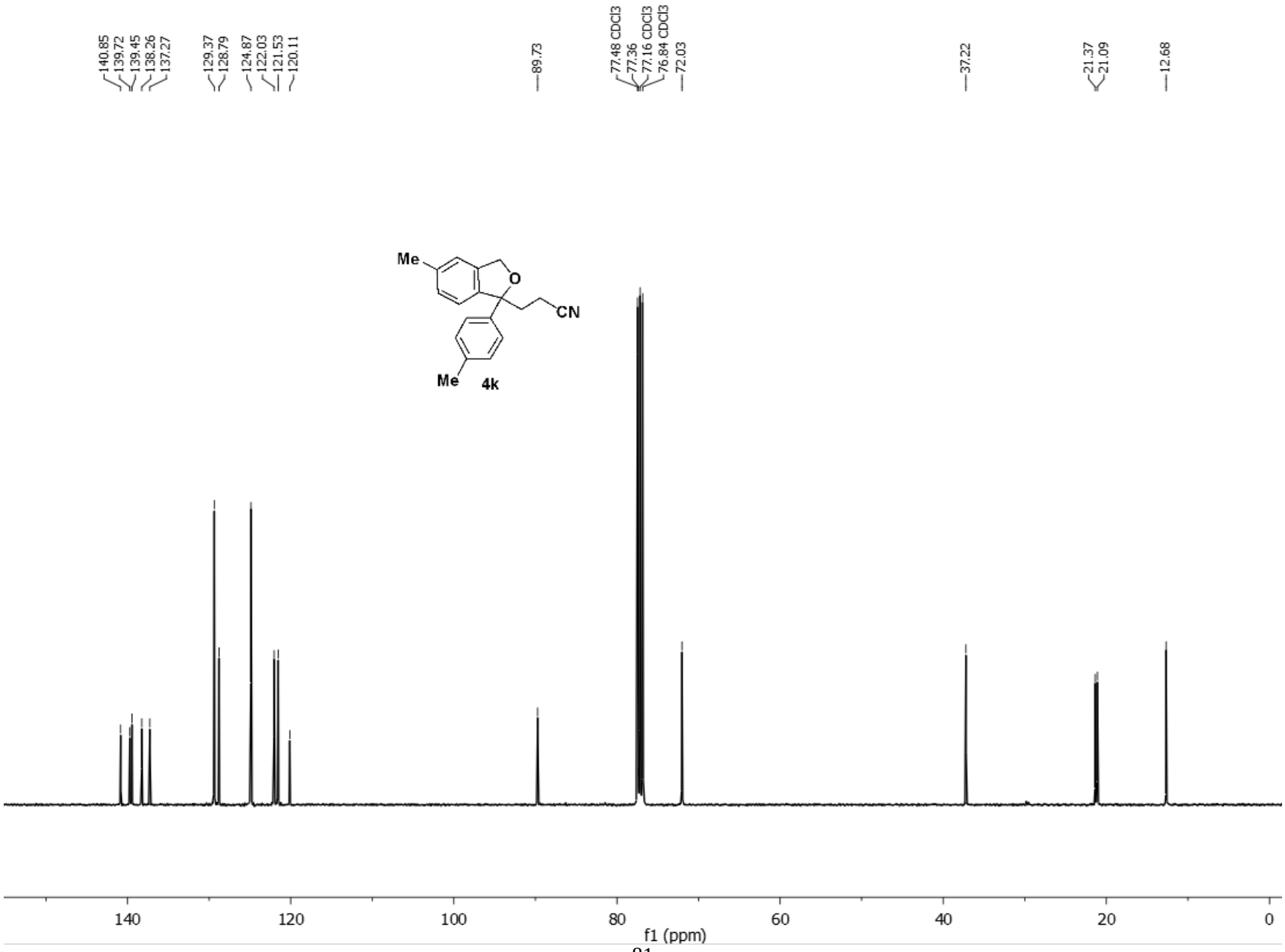
f1 (ppm)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120.11
89.73
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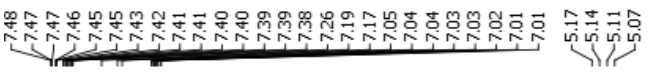
77.36
77.16 CDCl3
76.84 CDCl3
72.03
37.22
21.37
21.09
12.68
Me
O
CN
Me
4k
140
120
100
80
60
40
20
0
f1 (ppm)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7.17
7.05
7.04
7.04
7.03
7.03
7.02
7.01
7.01
5.17
5.14
5.11
5.07

2.58
2.56
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2.54
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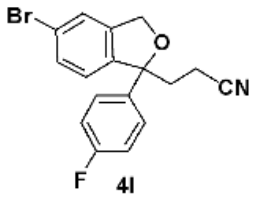
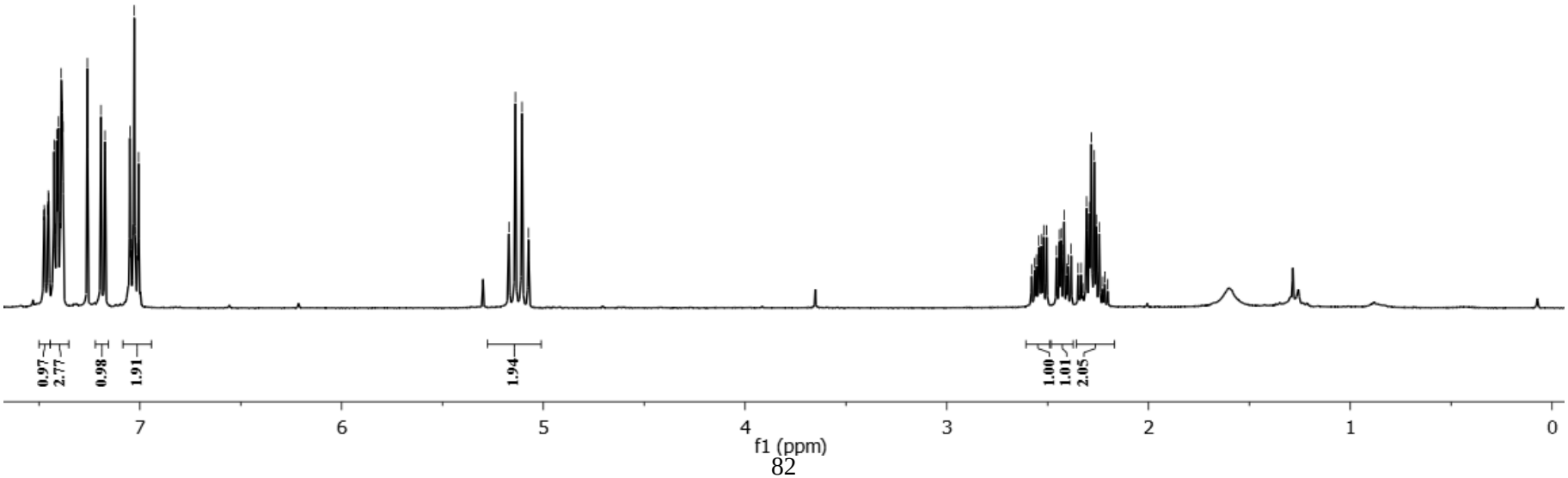
2.20


Br
O
CN
F

4l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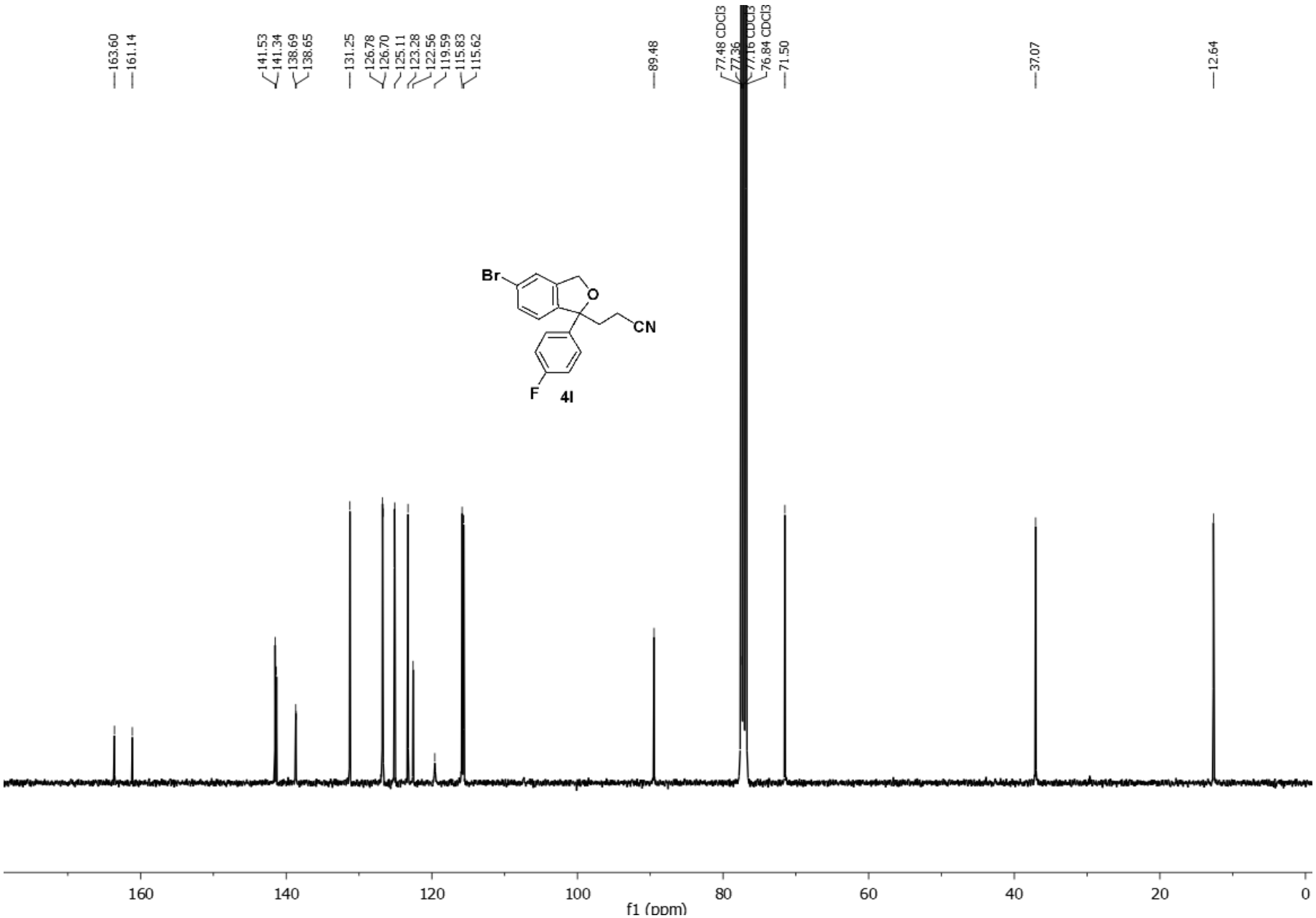
1.01
2.05
7
6
5
4
3
2
1
0
f1 (ppm)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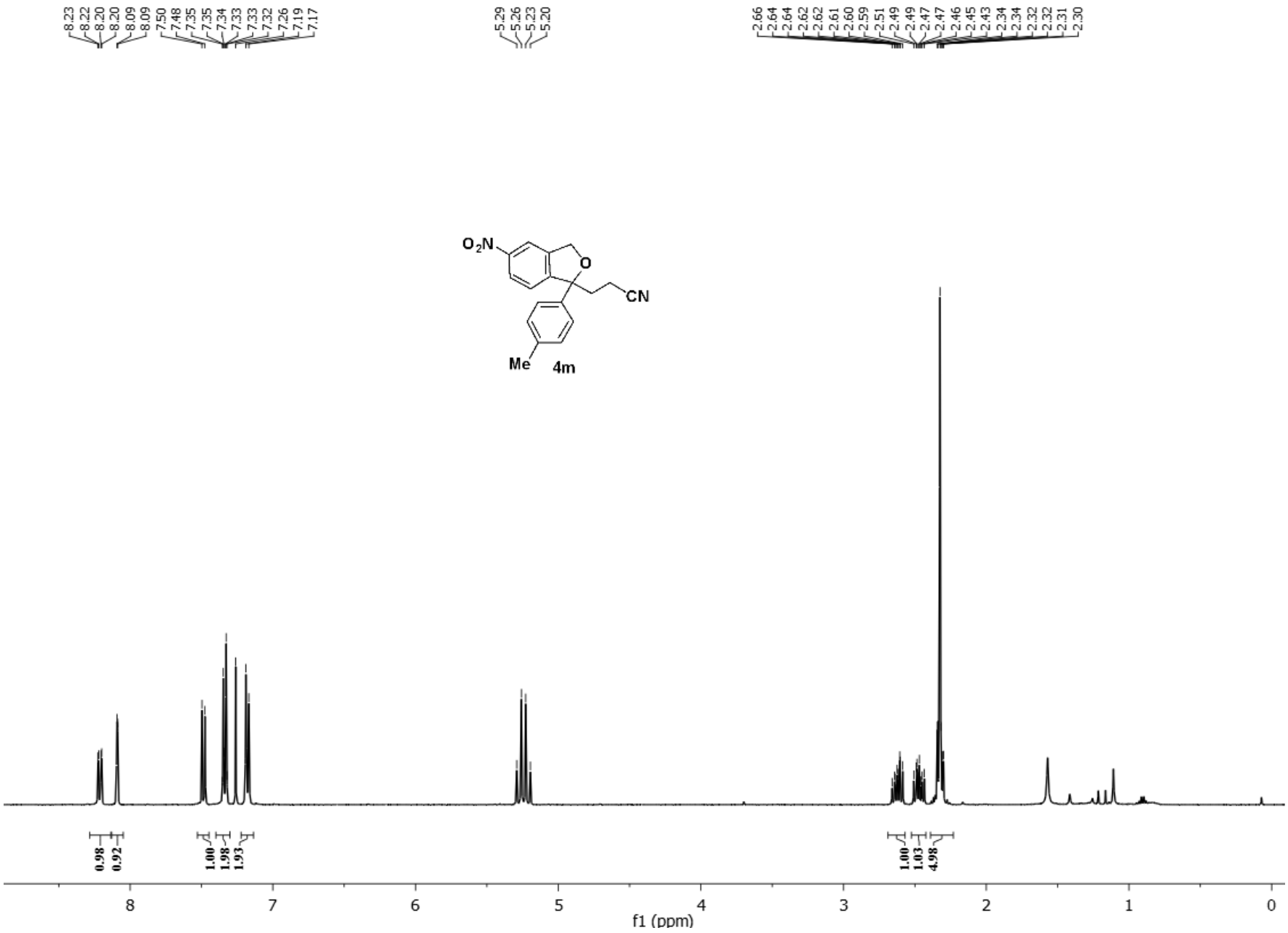
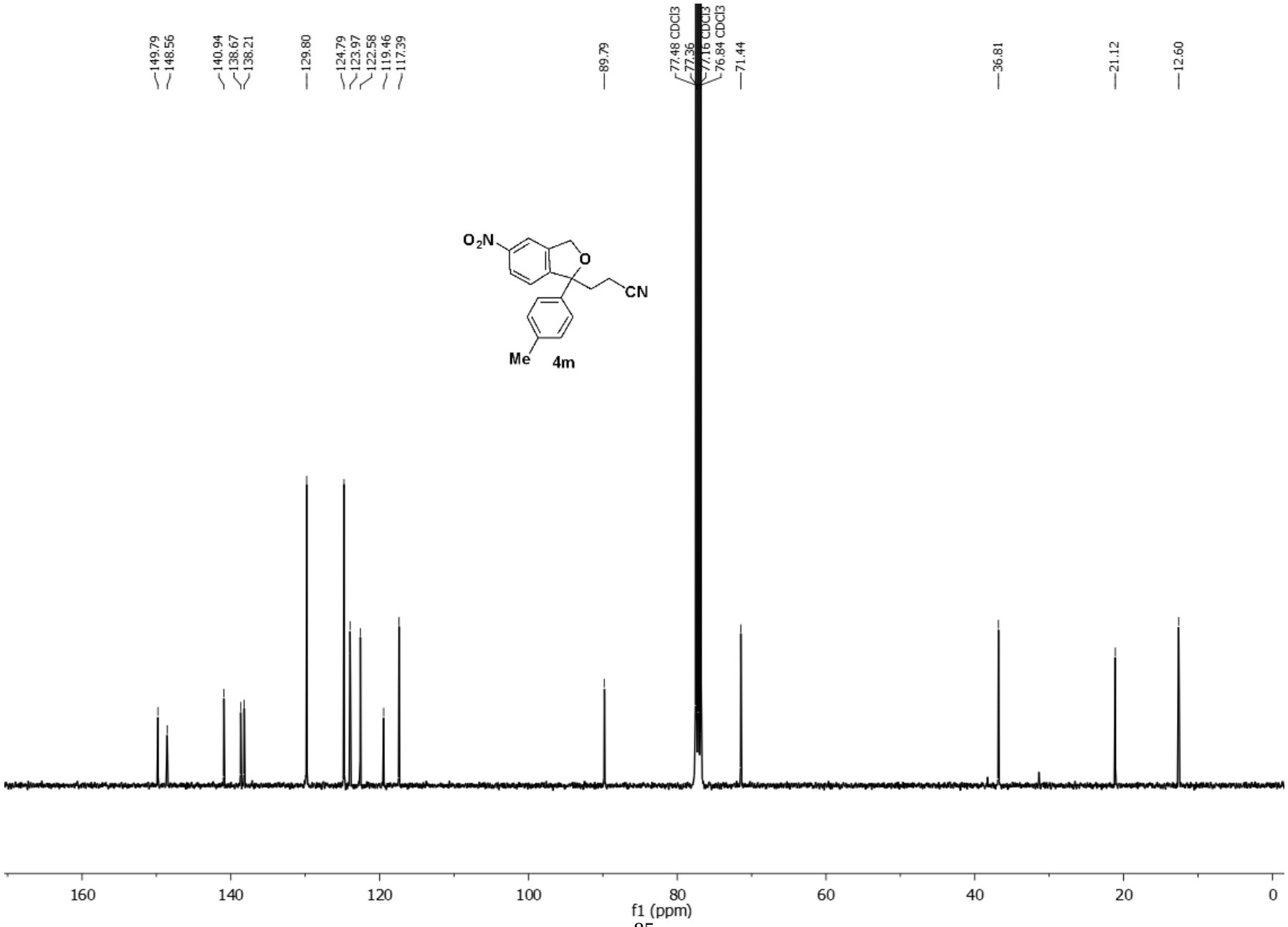
122.56
119.59
115.83
115.62
89.48
77.48 CDCl3
77.36
77.16 CDCl3
76.84 CDCl3
71.50
37.07
12.64
Br
O
CN
F
4l
160
140
120
100
80
60
40
20
0
f1 (ppm)


8.23
8.22
8.20
8.20
8.09
8.09
7.50
7.48
7.35
7.35
7.34
7.33
7.33
7.32
7.26
7.19
7.17
5.29
5.26
5.23
5.20
2.66
2.64
2.64
2.62
2.62
2.61
2.60
2.59
2.51
2.49
2.49
2.47
2.47
2.46
2.45
2.43
2.34
2.34
2.32
2.32
2.31
2.30
O2N
O
CN
Me
4m
0.98
0.92
1.00
1.98
1.93
1.00
1.03
4.98
8
7
6
5
4
3
2
1
0
f1 (ppm)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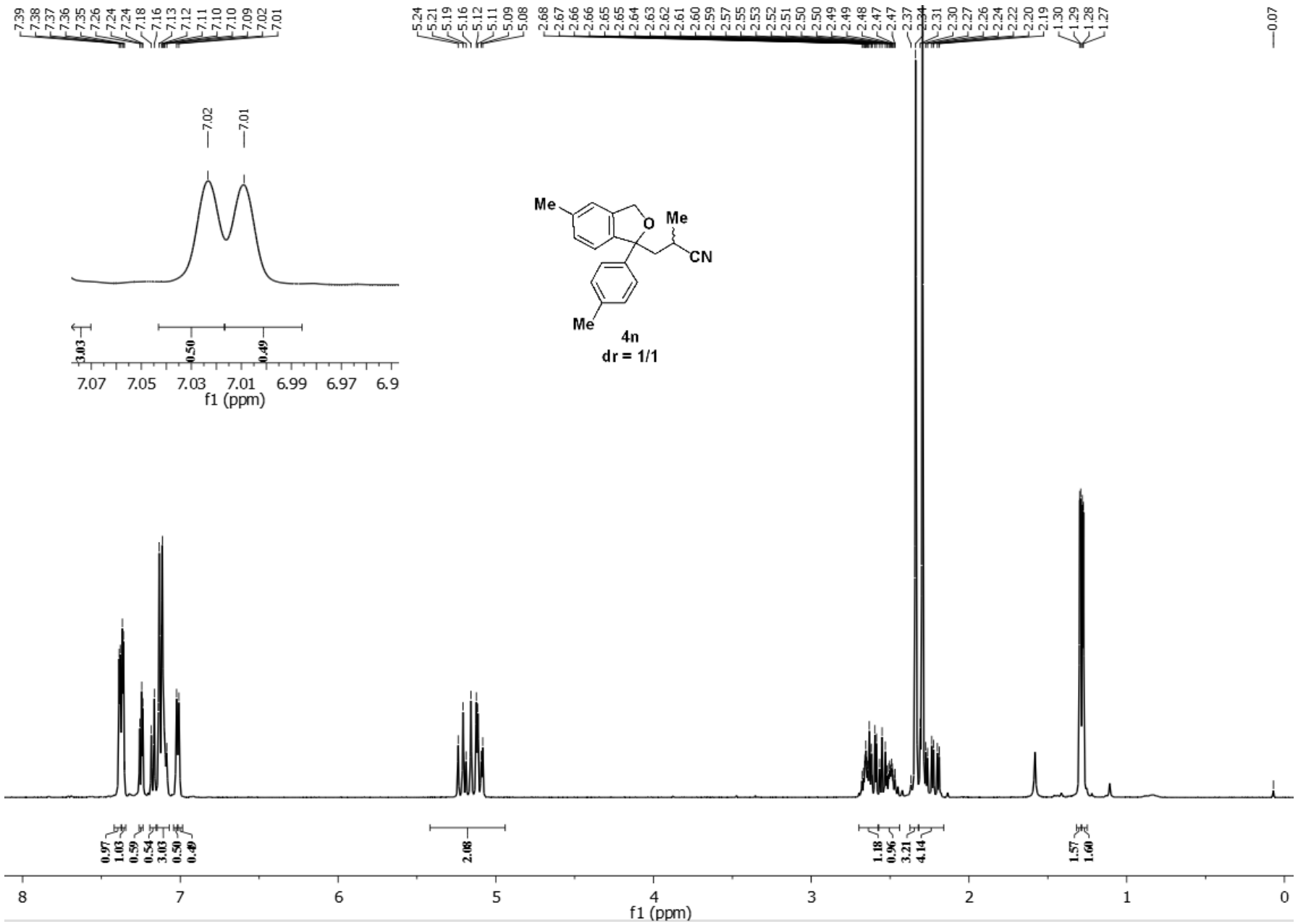
148.56
140.94
138.67
138.21
129.80
124.79
123.97
122.58
119.46
117.39
89.79
77.48 CDCl3
77.36
77.16 CDCl3
76.84 CDCl3
71.44
36.81
21.12
12.60
O2N
O
CN
Me
4m
160
140
120
100
80
60
40
20
0
f1 (ppm)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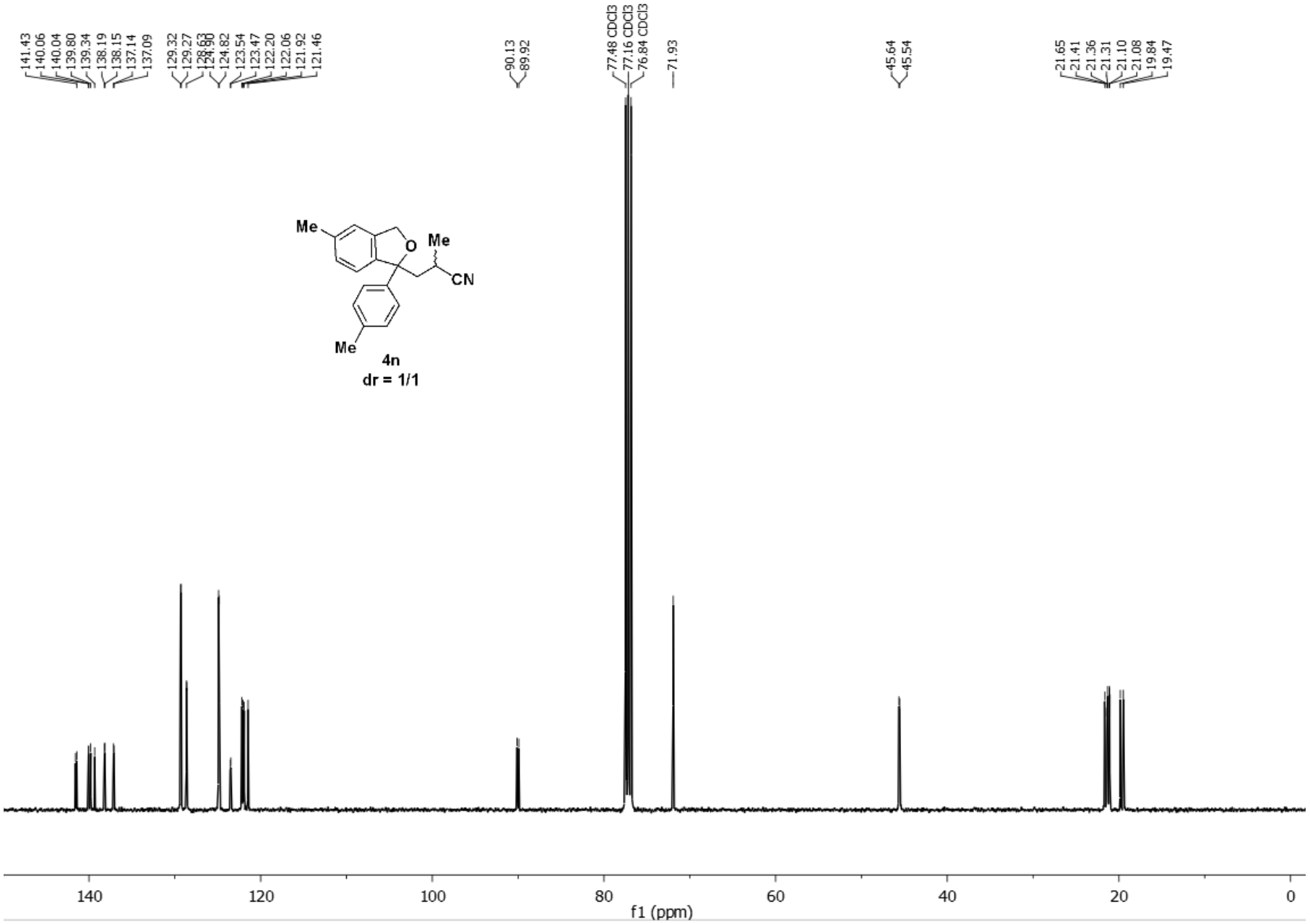
5.24 5.21 5.19 5.16 5.12 5.11 5.09 5.08 2.68 2.67 2.66 2.66 2.65 2.65 2.64 2.63 2.62 2.61 2.60 2.59 2.57 2.55 2.53 2.52 2.51 2.50 2.50 2.49 2.49 2.48 2.47 2.47 2.37 2.34 2.31 2.30 2.27 2.26 2.24 2.22 2.20 2.19 1.30 1.29 1.28 1.27
0.07
7.02
7.01
3.03
0.50
0.49
7.07 7.05 7.03 7.01 6.99 6.97 6.9
f1 (ppm)
Me
O
Me
CN
Me
4n
dr = 1/1
0.97 1.03 0.59 0.54 3.03 0.50 0.49
2.08
1.18 0.96 3.21 4.14
1.57 1.60
8 7 6 5 4 3 2 1 0
f1 (ppm)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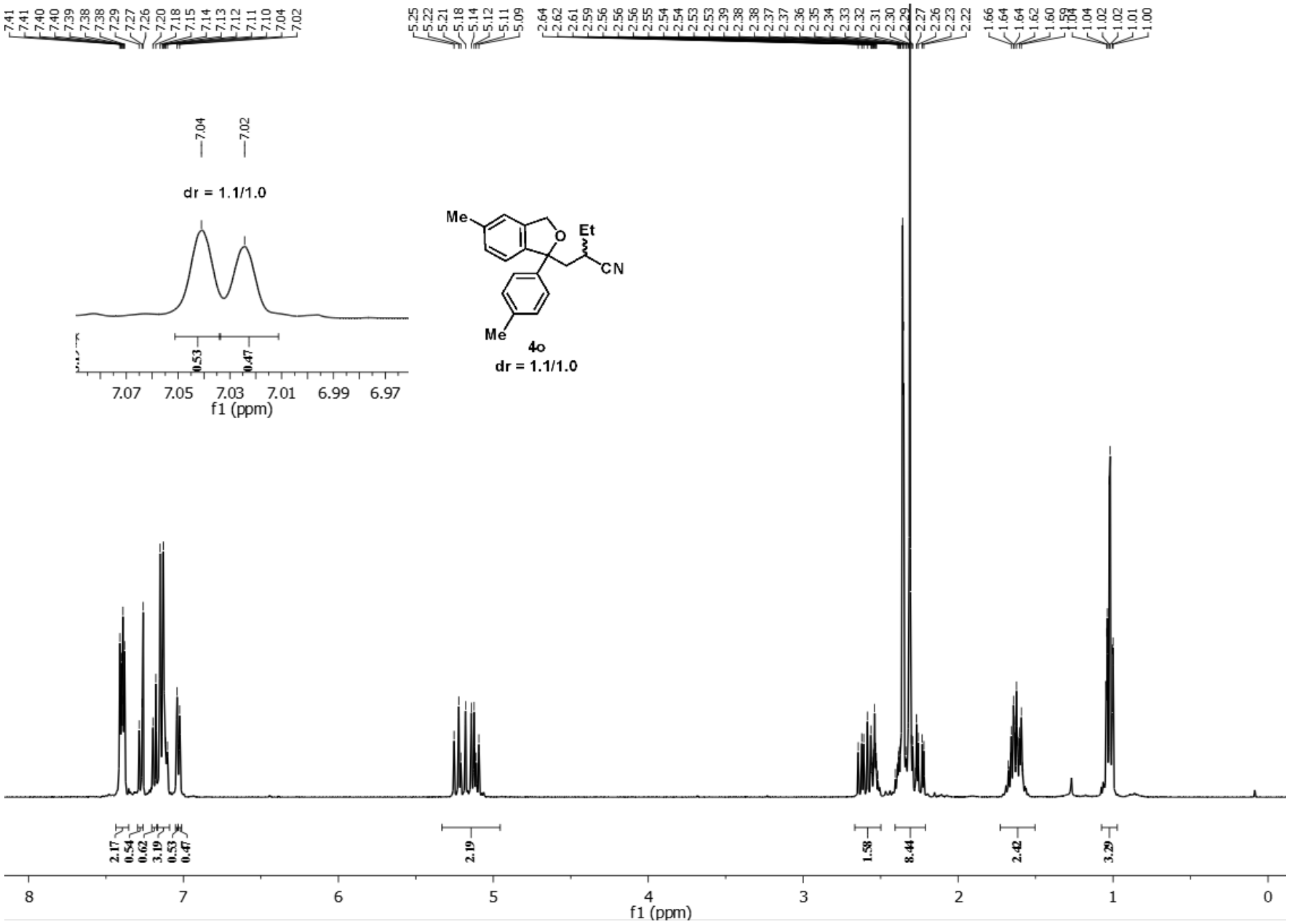
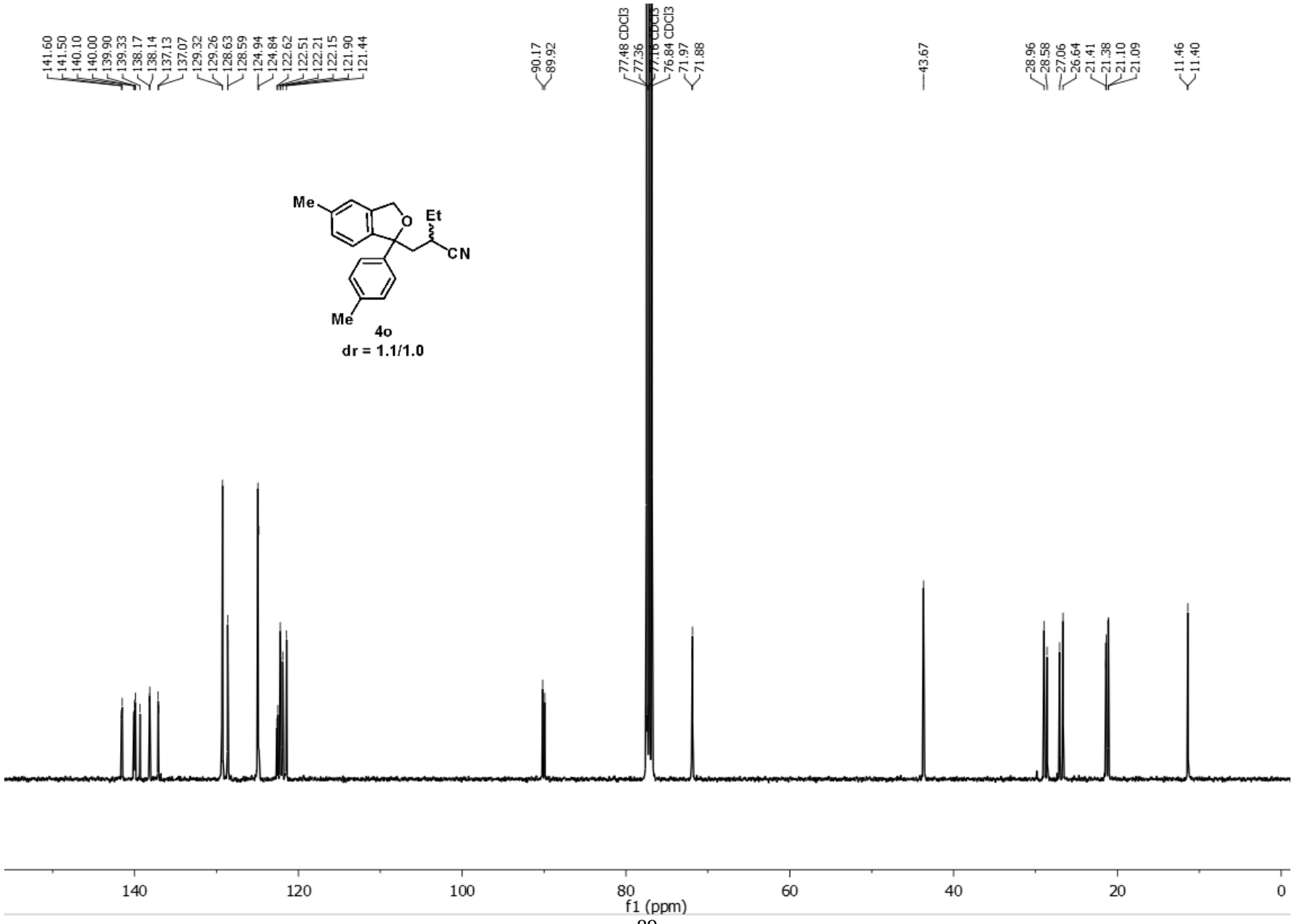
140.06
140.04
139.80
139.34
138.19
138.15
137.14
137.09
129.32
129.27
124.90
124.82
123.54
123.47
122.20
122.06
121.92
121.46
90.13
89.92
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
71.93
45.64
45.54
21.65
21.41
21.36
21.31
21.10
21.08
19.84
19.47
Me
O
Me
CN
Me
4n
dr = 1/1
140
120
100
80
60
40
20
0
f1 (ppm)


7.41 7.41 7.40 7.40 7.39 7.38 7.38 7.29 7.27 7.26 7.20 7.18 7.15 7.14 7.13 7.12 7.11 7.10 7.04 7.02
5.25 5.22 5.21 5.18 5.14 5.12 5.11 5.09
2.64 2.62 2.61 2.59 2.56 2.56 2.56 2.55 2.54 2.54 2.53 2.53 2.39 2.38 2.38 2.37 2.37 2.36 2.35 2.34 2.33 2.32 2.31 2.30 2.29 2.27 2.26 2.23 2.22
1.66 1.64 1.64 1.62 1.60 1.59 1.04 1.02 1.02 1.01 1.00
7.04
7.02
dr = 1.1/1.0
0.53
0.47
7.07 7.05 7.03 7.01 6.99 6.97
f1 (ppm)
Me
O
Et
CN
Me
4o
dr = 1.1/1.0
2.17 0.54 0.62 3.19 0.53 0.47
2.19
1.58
8.44
2.42
3.29
8 7 6 5 4 3 2 1 0
f1 (ppm)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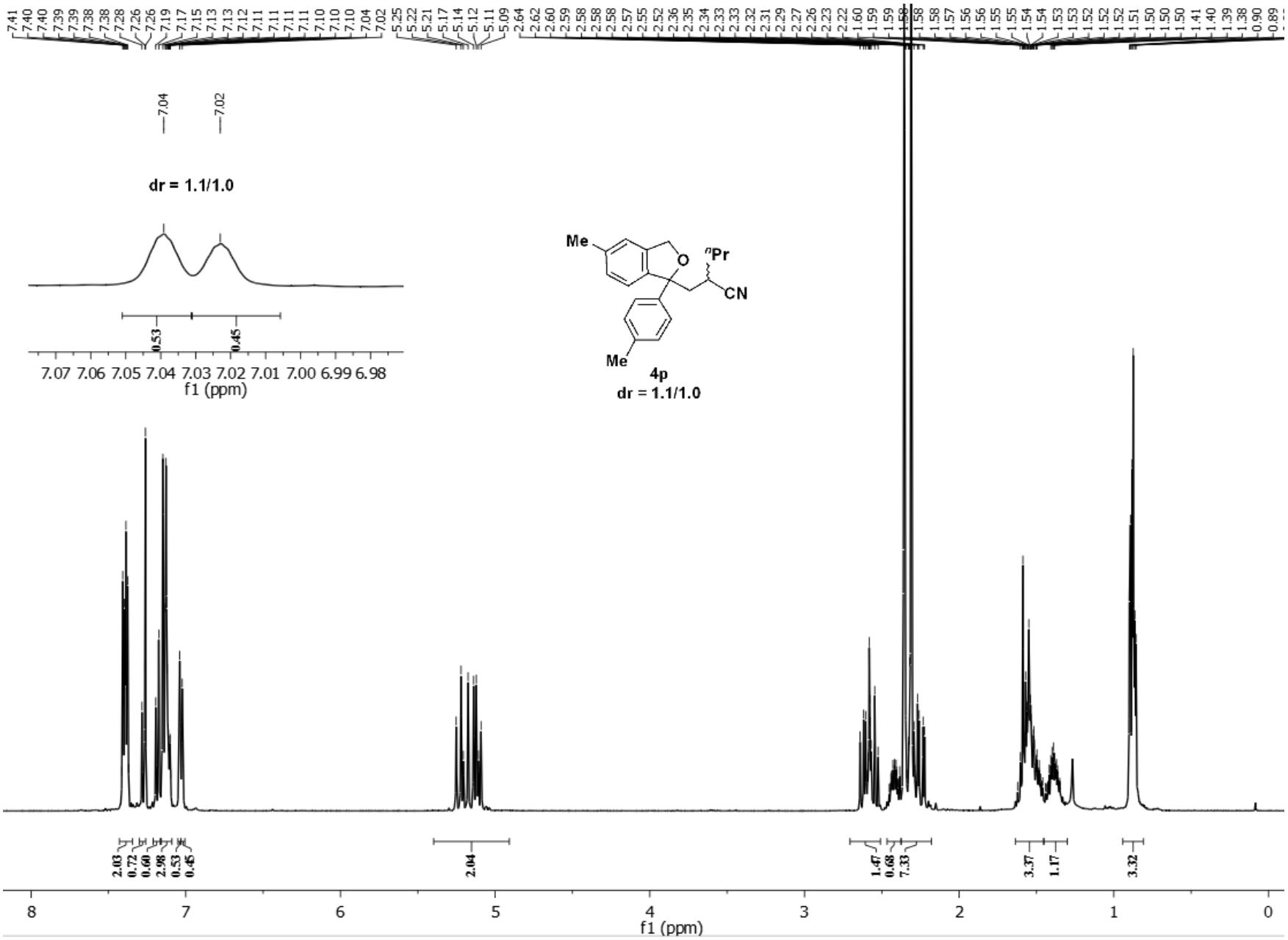
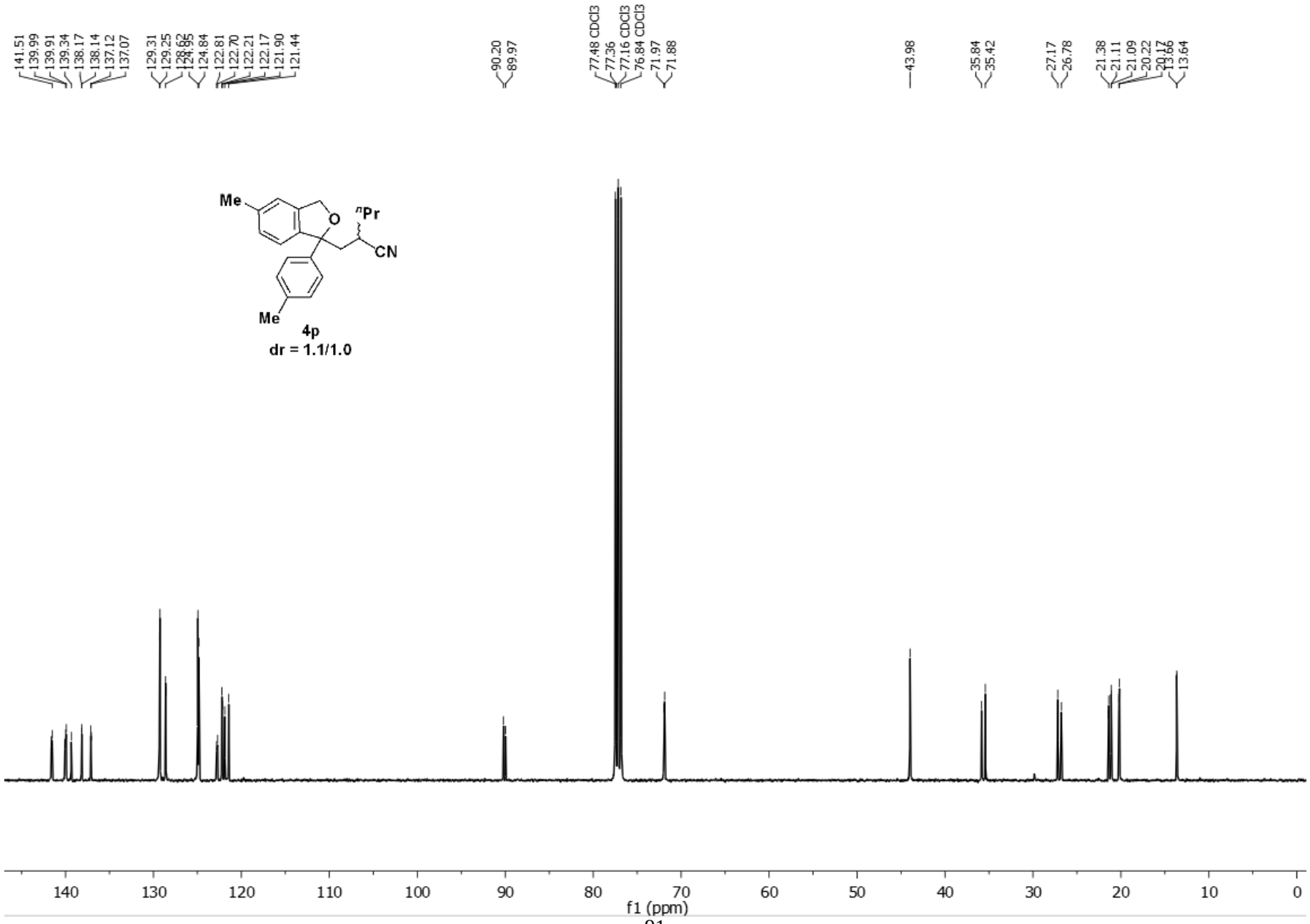
141.50
140.10
140.00
139.90
139.33
138.17
138.14
137.13
137.07
129.32
129.26
128.63
128.59
124.94
124.84
122.62
122.51
122.21
122.15
121.90
121.44
90.17
89.92
77.48 CDCl3
77.36
77.16 CDCl3
76.84 CDCl3
71.97
71.88
43.67
28.96
28.58
27.06
26.64
21.41
21.38
21.10
21.09
11.46
11.40
Me
O
Et
CN
Me
4o
dr = 1.1/1.0
140
120
100
80
60
40
20
0
f1 (ppm)


dr = 1.1/1.0
7.07 7.06 7.05 7.04 7.03 7.02 7.01 7.00 6.99 6.98
f1 (ppm)
Me
O
nPr
CN
Me
4p
dr = 1.1/1.0
8
7
6
5
4
3
2
1
0
f1 (ppm)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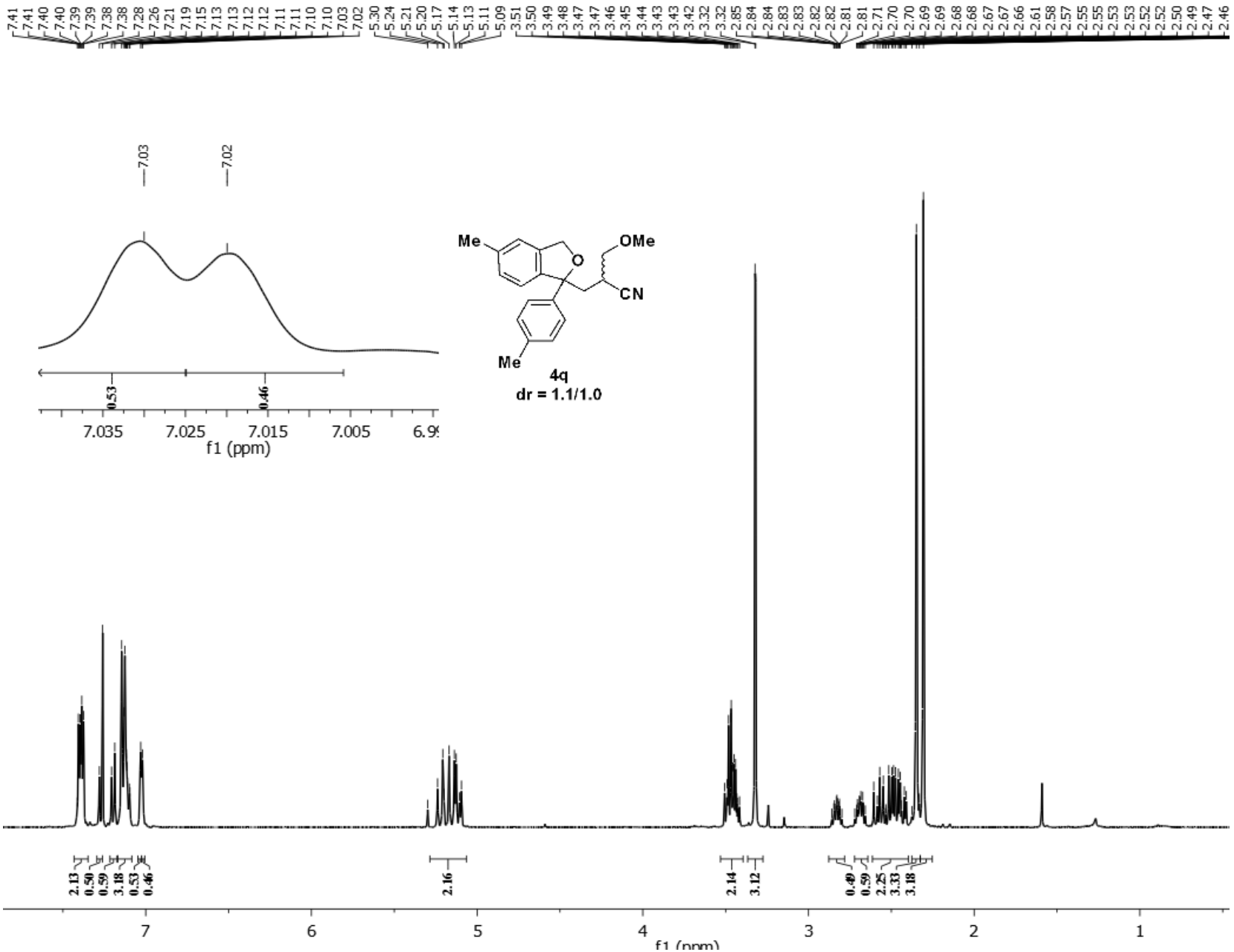
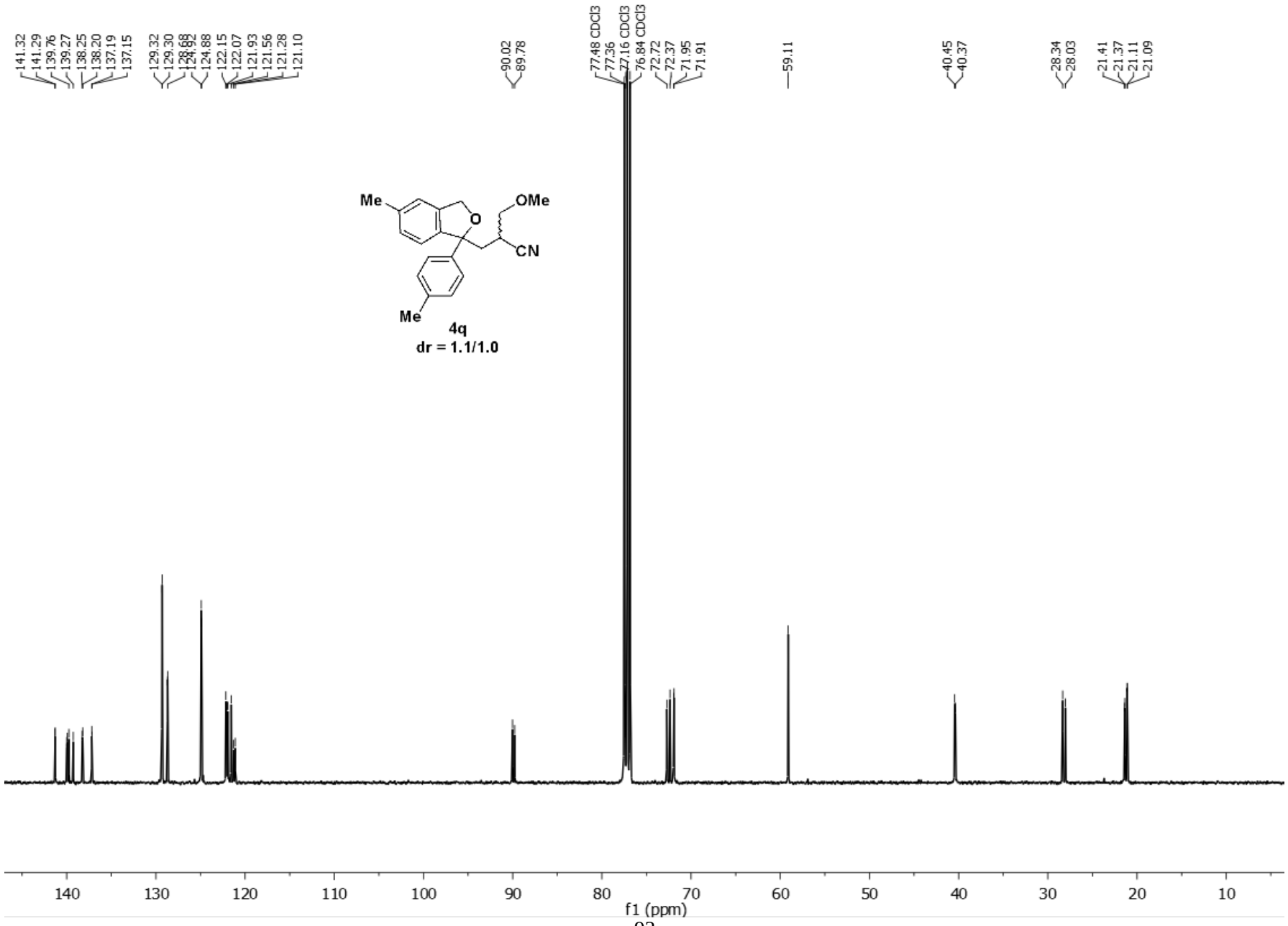
139.99
139.91
139.34
138.17
138.14
137.12
137.07
129.31
129.25
128.62
124.95
124.84
122.81
122.70
122.21
122.17
121.90
121.44
90.20
89.97
77.48 CDCl3
77.36
77.16 CDCl3
76.84 CDCl3
71.97
71.88
43.98
35.84
35.42
27.17
26.78
21.38
21.11
21.09
20.22
20.17
13.66
13.64
Me
O
nPr
CN
Me
4p
dr = 1.1/1.0
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.41 7.41 7.40 7.40 7.39 7.39 7.38 7.38 7.28 7.26 7.21 7.19 7.15 7.13 7.13 7.12 7.12 7.11 7.11 7.10 7.10 7.03 7.02
5.30 5.24 5.21 5.20 5.17 5.14 5.13 5.11 5.09
3.51 3.50 3.49 3.48 3.47 3.47 3.46 3.45 3.44 3.43 3.43 3.42 3.32 3.32
2.85 2.84 2.84 2.83 2.83 2.82 2.82 2.81 2.81 2.71 2.70 2.70 2.69 2.69 2.68 2.68 2.67 2.67 2.66 2.61 2.58 2.57 2.55 2.55 2.53 2.53 2.52 2.52 2.50 2.49 2.47 2.46
7.03
7.02
0.53
0.46
7.035
7.025
7.015
7.005
f1 (ppm)
Me
OMe
O
CN
Me
4q
dr = 1.1/1.0
2.13
0.50
0.59
3.18
0.53
0.46
2.16
2.14
3.12
0.49
0.59
2.25
3.33
3.18
7
6
5
4
3
2
1
f1 (ppm)


141.32
141.29
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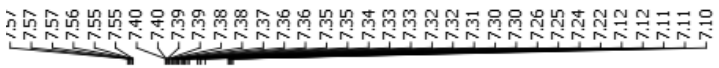
139.27
138.25
138.20
137.19
137.15
129.32
129.30
128.68
124.92
124.88
122.15
122.07
121.93
121.56
121.28
121.10
90.02
89.78
77.48 CDCl3
77.36
77.16 CDCl3
76.84 CDCl3
72.72
72.37
71.95
71.91
59.11
40.45
40.37
28.34
28.03
21.41
21.37
21.11
21.09
Me
OMe
O
CN
Me
4q
dr = 1.1/1.0
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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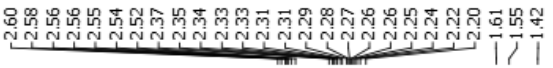
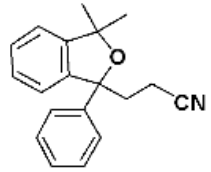
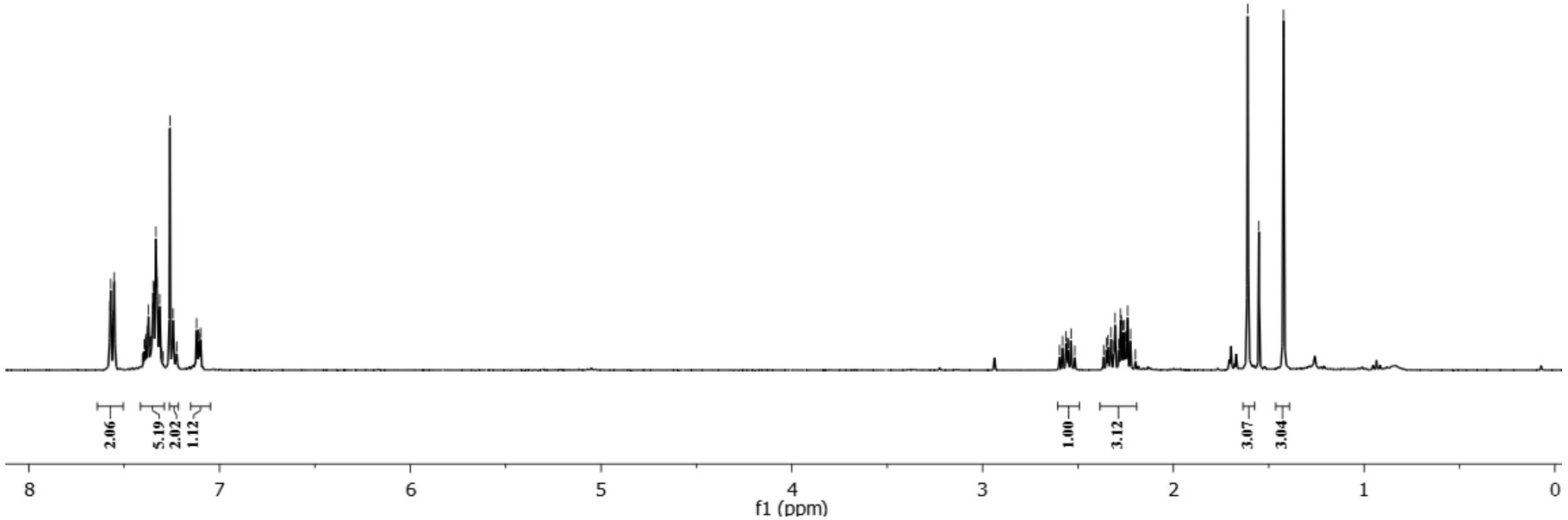
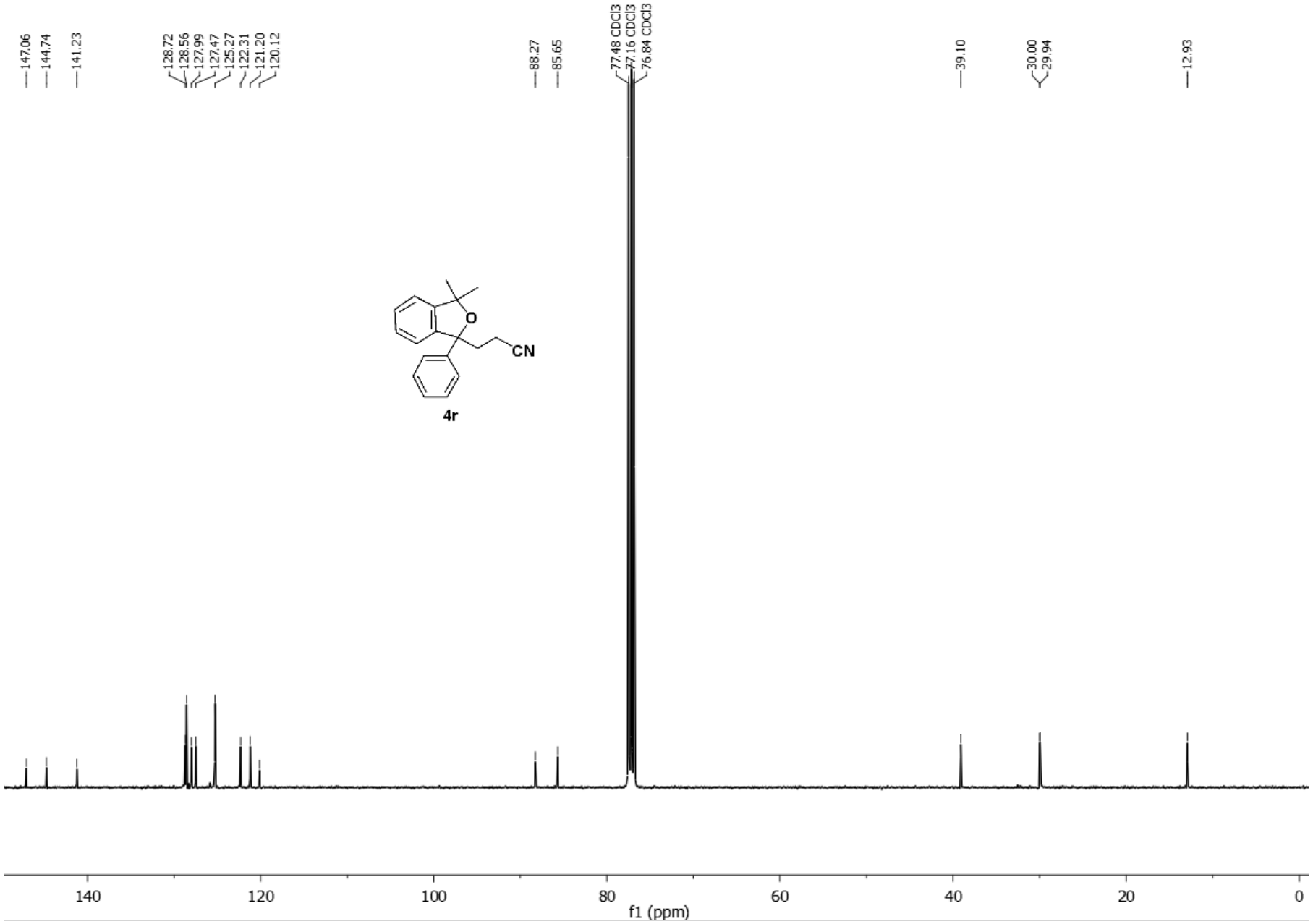
7.57
7.56
7.55
7.55
7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.26
7.25
7.24
7.22
7.12
7.12
7.11
7.11
7.10


2.60
2.58
2.56
2.56
2.55
2.54
2.52
2.37
2.35
2.34
2.33
2.33
2.31
2.31
2.29
2.28
2.27
2.26
2.26
2.25
2.24
2.22
2.20
1.61
1.55
1.42


O
CN

4r


2.06
5.19
2.02
1.12
1.00
3.12
3.07
3.04
8
7
6
5
4
3
2
1
0
f1 (ppm)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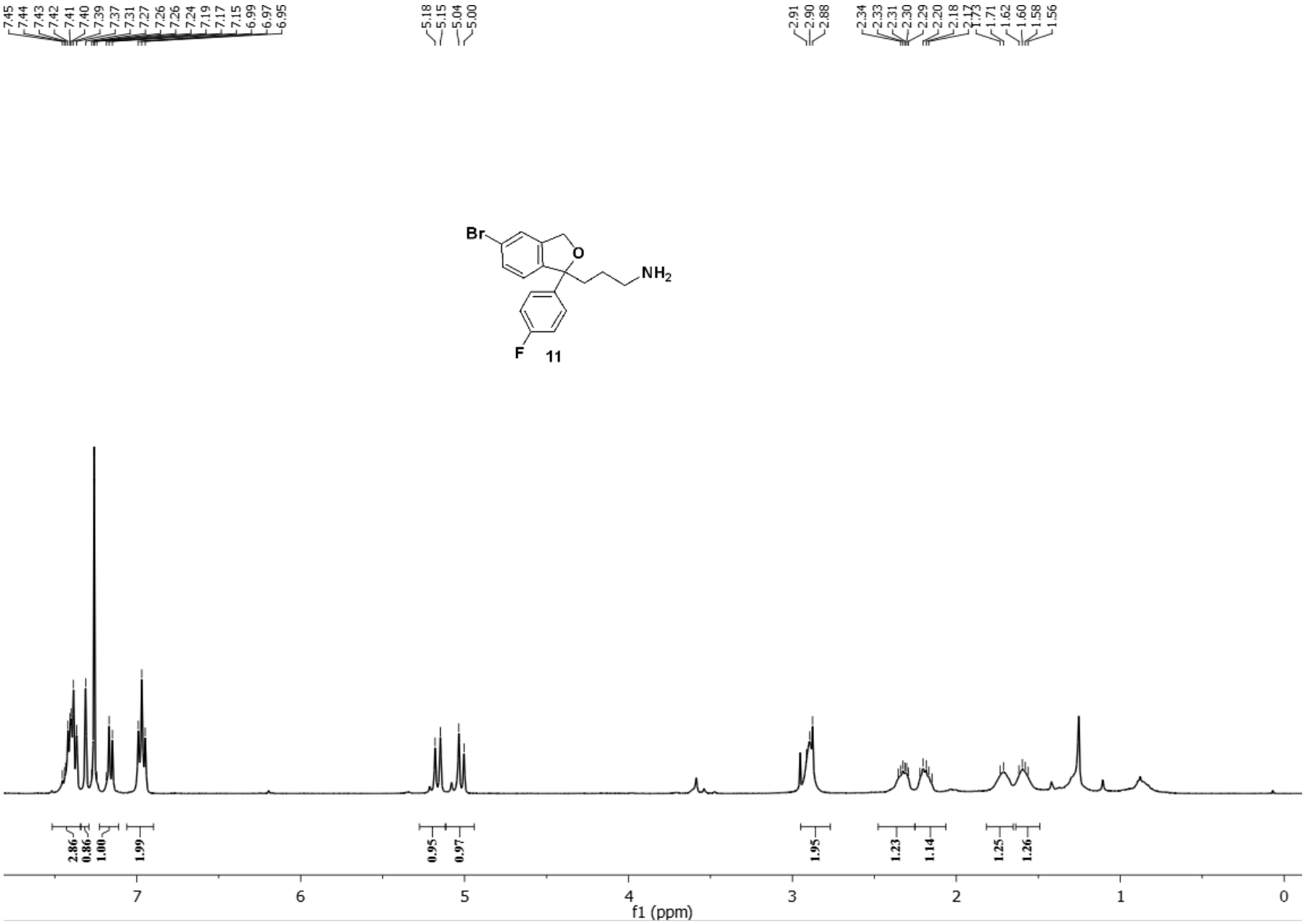
144.74
141.23
128.72
128.56
127.99
127.47
125.27
122.31
121.20
120.12
88.27
85.65
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
39.10
30.00
29.94
12.93
O
CN
4r
140
120
100
80
60
40
20
0
f1 (ppm)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7.44
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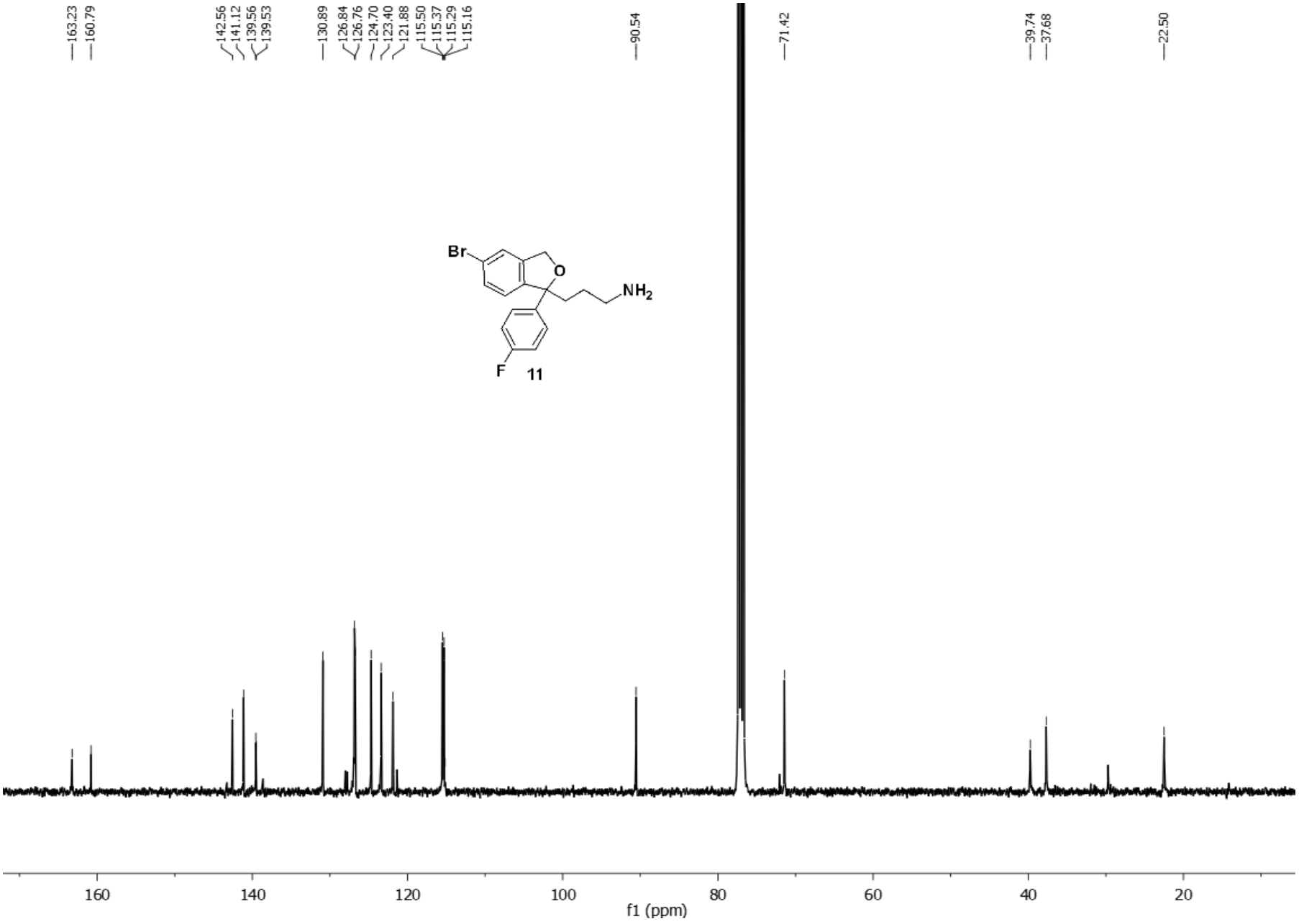
7.40
7.39
7.37
7.31
7.27
7.26
7.26
7.24
7.19
7.17
7.15
6.99
6.97
6.95
5.18
5.15
5.04
5.00
2.91
2.90
2.88
2.34
2.33
2.31
2.30
2.29
2.20
2.18
2.17
1.73
1.71
1.62
1.60
1.58
1.56
Br
O
NH2
F
11
2.86
0.86
1.00
1.99
0.95
0.97
1.95
1.23
1.14
1.25
1.26
7
6
5
4
3
2
1
0
f1 (ppm)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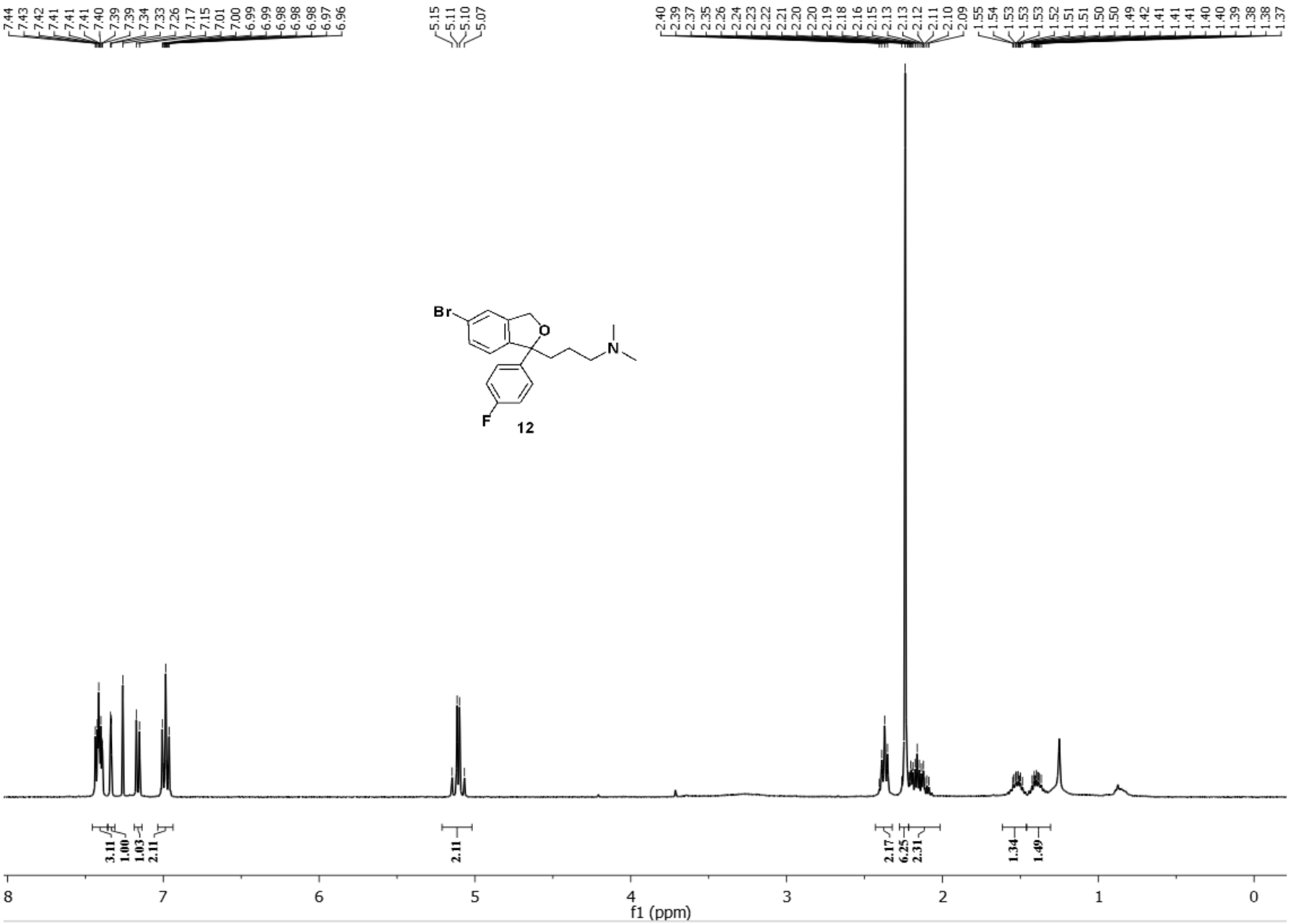
141.12
139.56
139.53
130.89
126.84
126.76
124.70
123.40
121.88
115.50
115.37
115.29
115.16
90.54
71.42
39.74
37.68
22.50
Br
O
NH2
F
11
160
140
120
100
80
60
40
20
f1 (ppm)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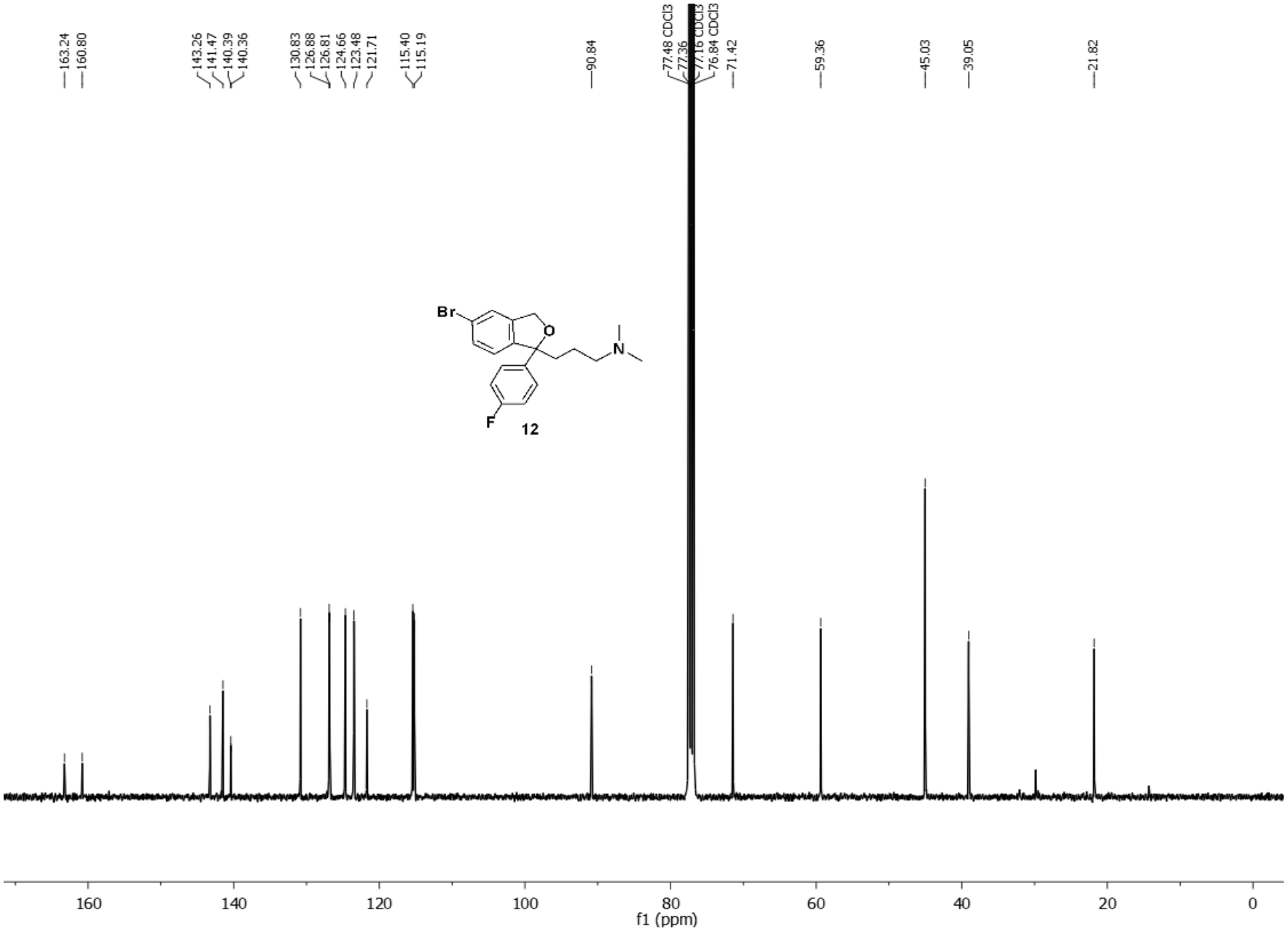
5.15 5.11 5.10 5.07
2.40 2.39 2.37 2.35 2.26 2.24 2.23 2.22 2.21 2.20 2.20 2.19 2.18 2.16 2.15 2.13 2.13 2.12 2.11 2.10 2.09
1.55 1.54 1.53 1.53 1.53 1.52 1.51 1.51 1.50 1.50 1.49 1.42 1.41 1.41 1.41 1.40 1.40 1.39 1.38 1.38 1.37
Br
O
N
F
12
3.11
1.00
1.03
2.11
2.11
2.17
6.25
2.31
1.34
1.49
8
7
6
5
4
3
2
1
0
f1 (ppm)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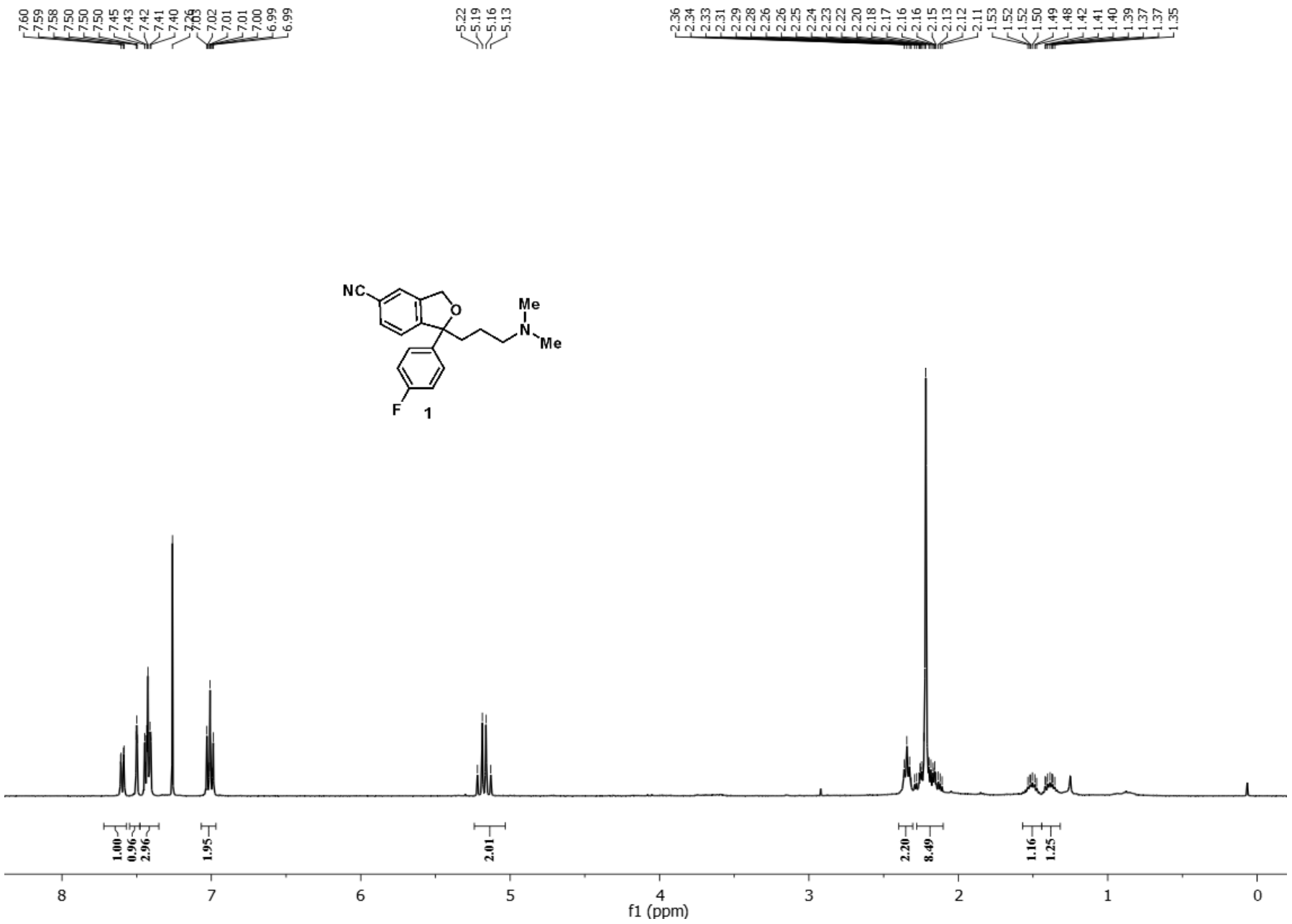
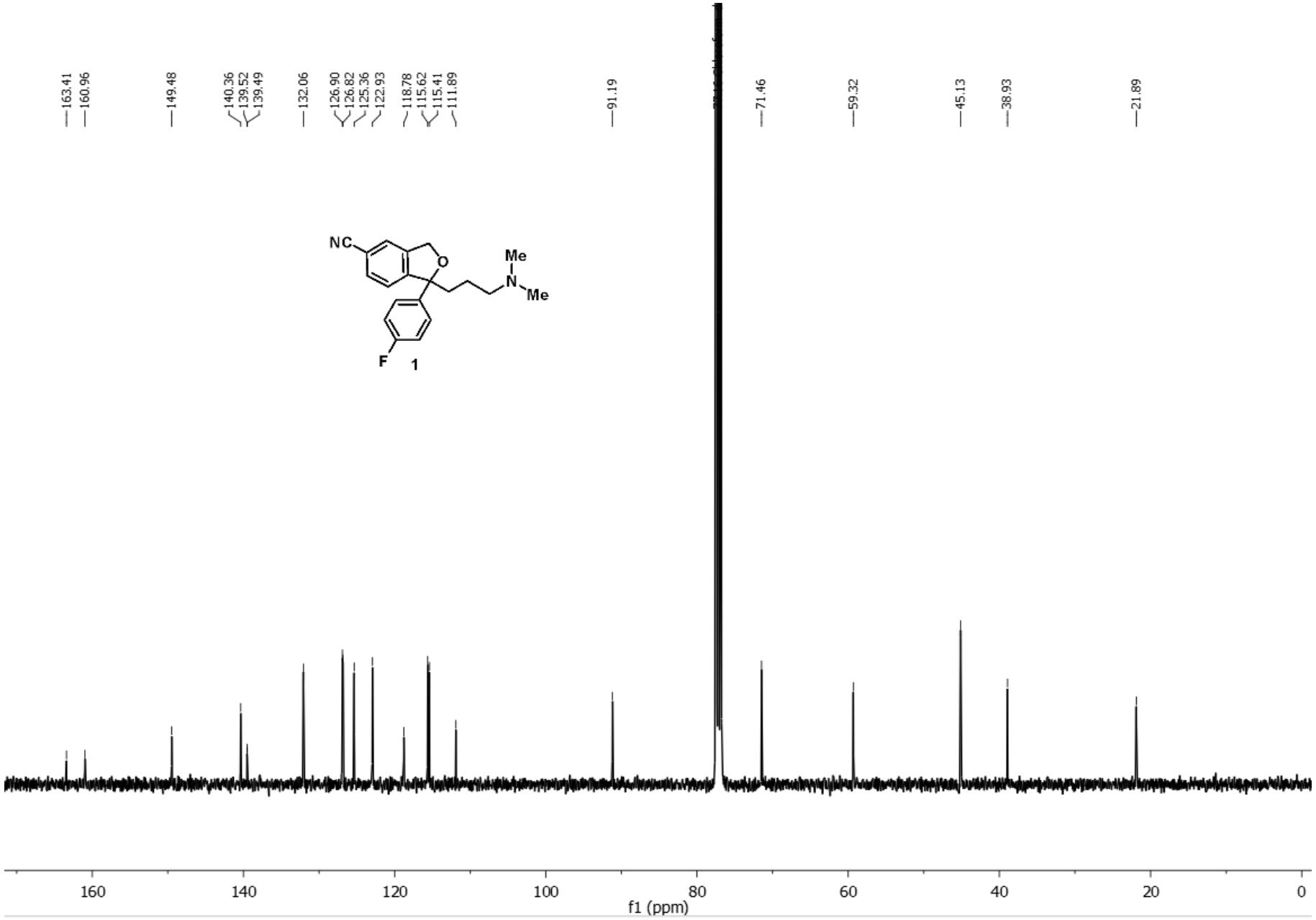
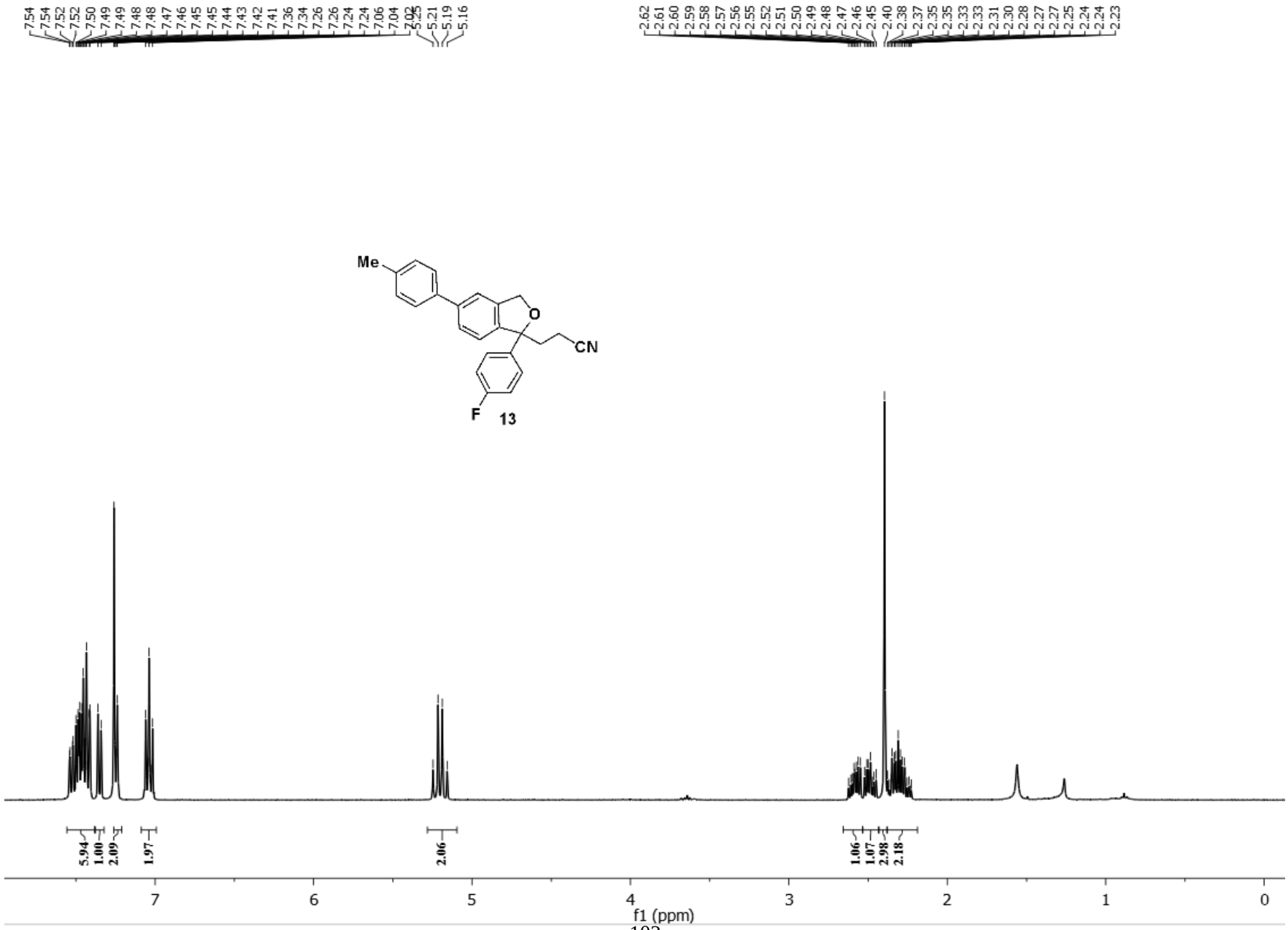
143.26
141.47
140.39
140.36
130.83
126.88
126.81
124.66
123.48
121.71
115.40
115.19
90.84
77.48 CDCl3
77.36
77.16 CDCl3
76.84 CDCl3
71.42
59.36
45.03
39.05
21.82
Br
O
N
F
12
160
140
120
100
80
60
40
20
0
f1 (ppm)


7.60
7.59
7.58
7.50
7.50
7.50
7.45
7.43
7.42
7.41
7.40
7.26
7.03
7.02
7.01
7.01
7.00
6.99
6.99
5.22
5.19
5.16
5.13
2.36
2.34
2.33
2.31
2.29
2.28
2.26
2.26
2.25
2.24
2.23
2.22
2.20
2.18
2.17
2.16
2.16
2.15
2.13
2.12
2.11
1.53
1.52
1.52
1.50
1.49
1.48
1.42
1.41
1.40
1.39
1.37
1.37
1.35
NC
O
Me
N
Me
F
1
1.00
0.96
2.96
1.95
2.01
2.20
8.49
1.16
1.25
8
7
6
5
4
3
2
1
0
f1 (ppm)


163.41
160.96
149.48
140.36
139.52
139.49
132.06
126.90
126.82
125.36
122.93
118.78
115.62
115.41
111.89
91.19
71.46
59.32
45.13
38.93
21.89
NC
O
Me
N
Me
F
1
160
140
120
100
80
60
40
20
0
f1 (ppm)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7.52
7.52
7.50
7.49
7.49
7.48
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7.47
7.46
7.45
7.45
7.44
7.43
7.42
7.41
7.36
7.34
7.26
7.26
7.24
7.24
7.06
7.04
7.02
5.25
5.21
5.19
5.16
2.62
2.61
2.60
2.59
2.58
2.57
2.56
2.55
2.52
2.51
2.50
2.49
2.48
2.47
2.46
2.45
2.40
2.38
2.37
2.35
2.35
2.33
2.33
2.31
2.30
2.28
2.27
2.27
2.25
2.24
2.24
2.23
Me
O
CN
F
13
5.94
1.00
2.09
1.97
2.06
1.06
1.07
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2.18
7
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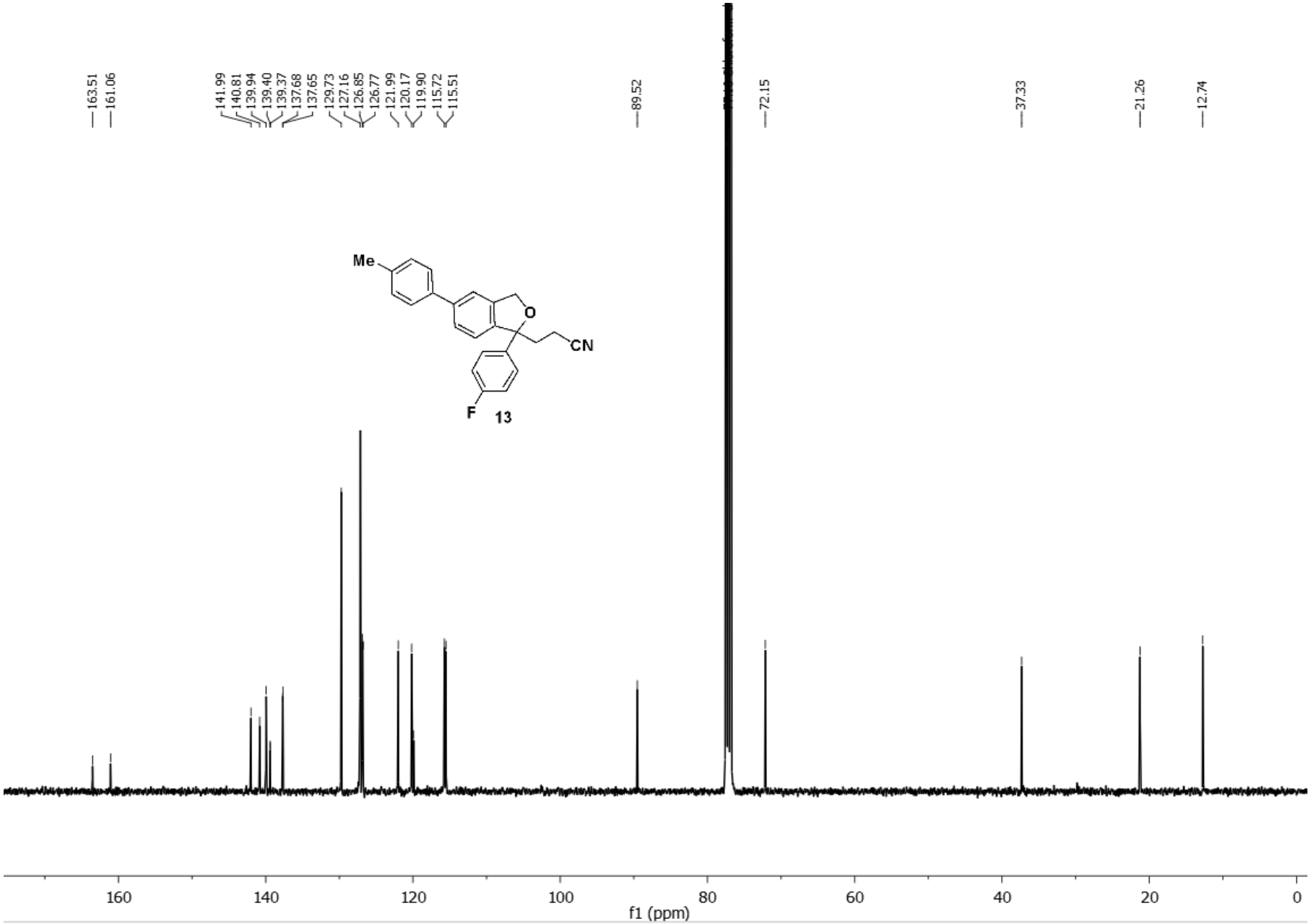
5
4
3
2
1
0
f1 (ppm)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129.73
127.16
126.85
126.77
121.99
120.17
119.90
115.72
115.51
89.52
72.15
37.33
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Me
O
CN
F
13
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140
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80
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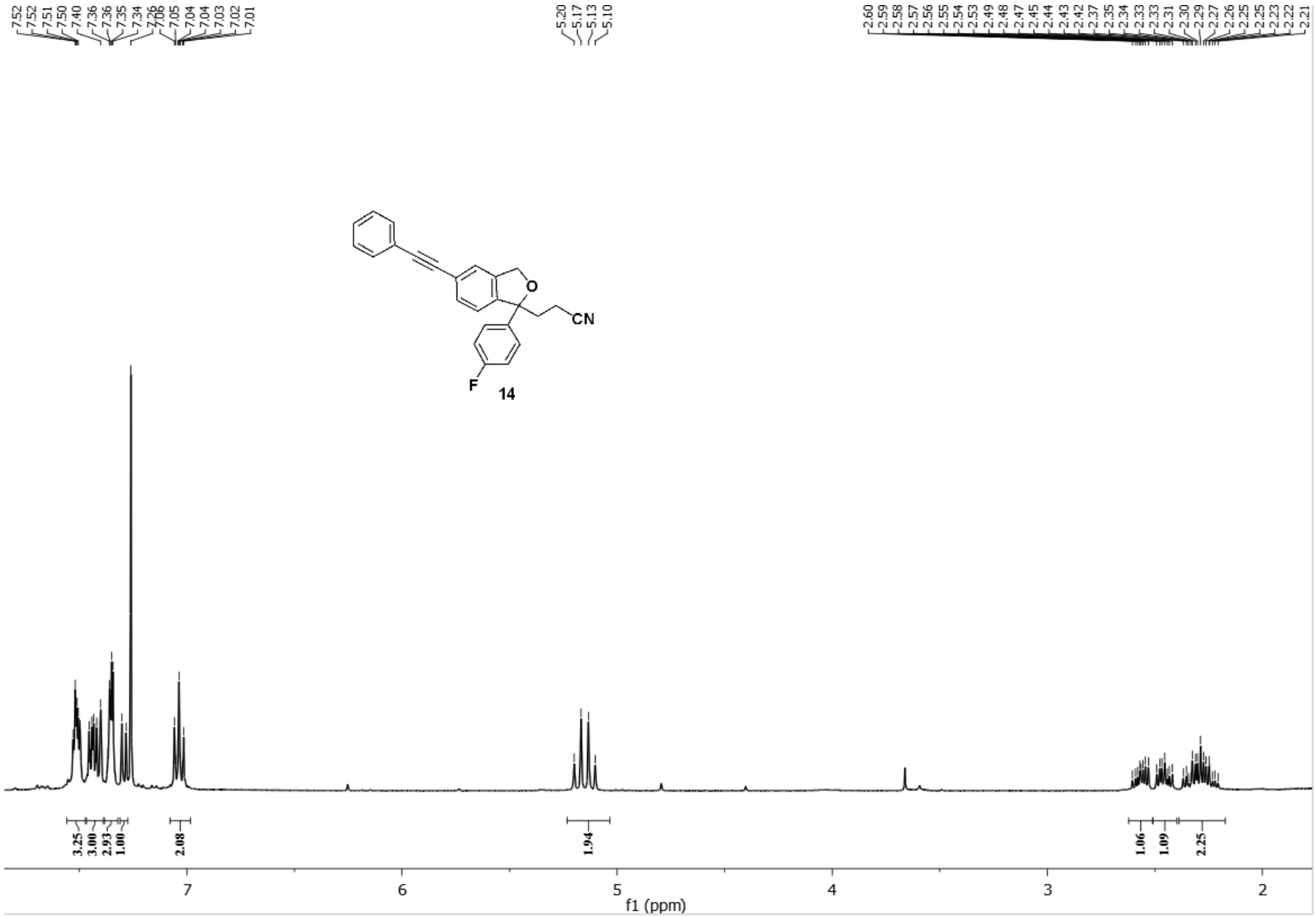
f1 (ppm)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7.04
7.03
7.02
7.01
5.20
5.17
5.13
5.10
2.60
2.59
2.58
2.57
2.56
2.55
2.54
2.53
2.49
2.48
2.47
2.45
2.44
2.43
2.42
2.37
2.35
2.34
2.33
2.33
2.31
2.30
2.29
2.27
2.26
2.25
2.25
2.23
2.22
2.21
O
CN
F
14
3.25
3.00
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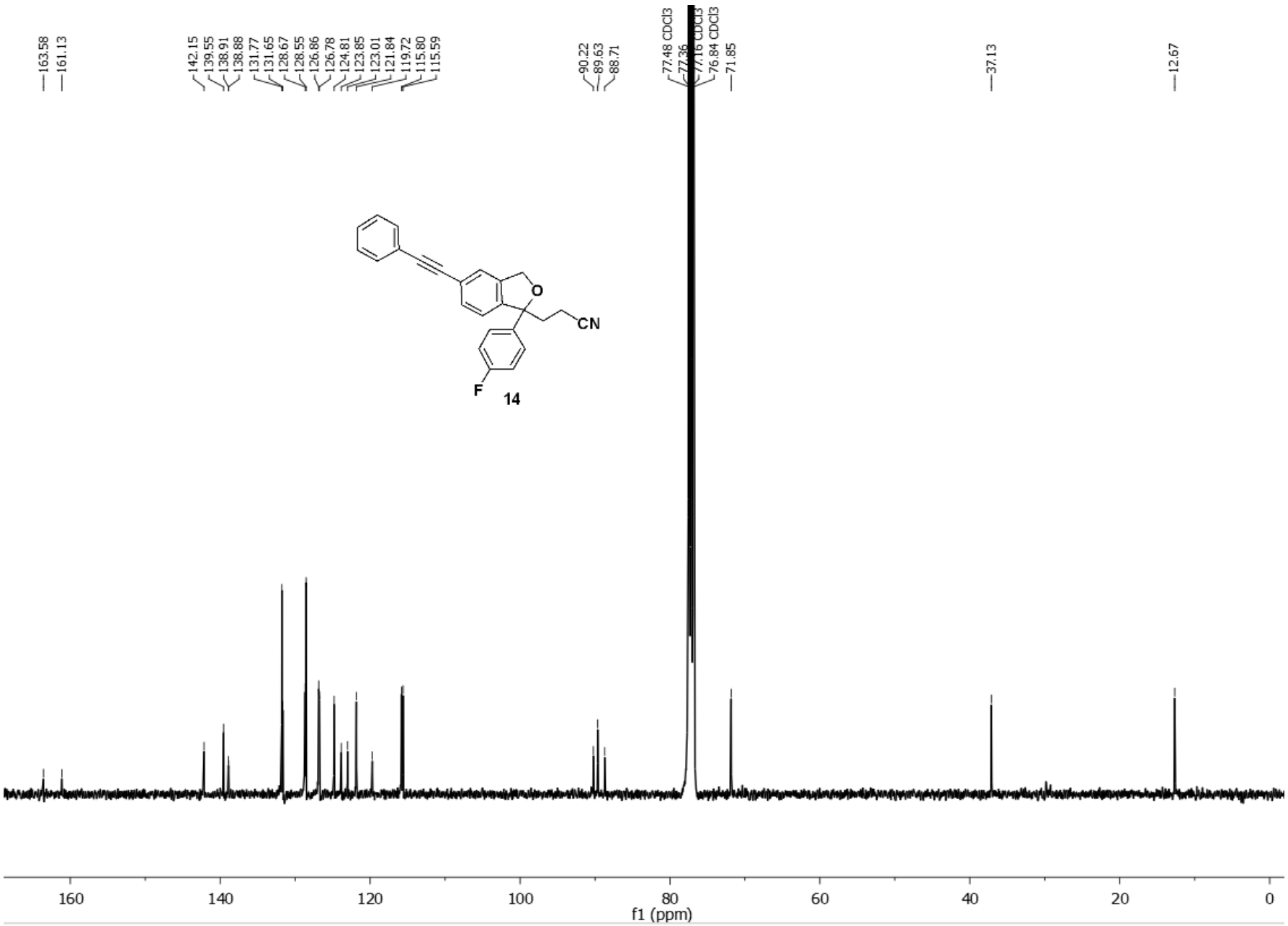
7
6
5
4
3
2
f1 (ppm)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123.01
121.84
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115.80
115.59
90.22
89.63
88.71
77.48 CDCl3
77.36
77.16 CDCl3
76.84 CDCl3
71.85
37.13
12.67
O
CN
F
14
160
140
120
100
80
60
40
20
0
f1 (ppm)