

Supporting Information

Natural Deep Eutectic Solvents as an Efficient and Reusable Catalytic System for the Nazarov Cyclization

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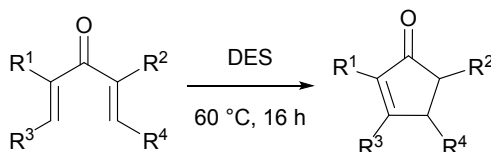
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General information

Flasks and all equipment used for the generation and reaction of moisture-sensitive compounds were dried by electric heat gun under nitrogen. Unless specified, all reagents were used as received without further purifications. Anhydrous THF was obtained by distillation over LiAlH_4 , followed by distillation over Na-benzophenone; benzaldehyde was distilled under vacuum. Flash column chromatography was performed over silica gel (40-63 μm , 230-400 mesh); R_f values refer to TLC carried out on silica gel plates. ^1H NMR and ^{13}C NMR spectra were recorded on a Jeol ECZR600, in CDCl_3 , using residual solvent peak as an internal standard (CHCl_3 , ^1H : 7.26 ppm, ^{13}C : 77.16 ppm). NMR spectra of DESs were recorded in a capillary tube, using D_2O as locking solvent. Multiplicity is reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), m (multiplet), br (broad). GC-MS spectra were recorded at an ionizing voltage of 70 eV.

Synthetic procedures

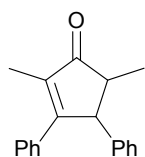
General procedure for the Nazarov cyclization in DES



A vial was charged with the dienone substrate (0.2-0.5 mmol), then the DES (5 g per mmol of substrate) was added and the mixture was stirred at 60 °C for 16 h. Water was added and the mixture was extracted three times with cyclopentyl methyl ether (CPME); the combined organic layers were dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. When required, the crude product was purified by flash column chromatography.

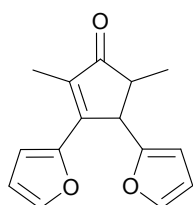
Procedure for DES recycling: a vial was charged with the dienone **1a** (1.0-4.0 mmol), then ChCl/malonic acid 1:1 (5 g or 1 g per mmol of substrate) was added and the mixture was stirred at 60 °C for 16 h. Water was added, causing the precipitation of the product. The solid product was recovered by filtration, while water was evaporated under reduced pressure to afford the eutectic mixture, which was used for the next reaction cycle.

2,5-dimethyl-3,4-diphenylcyclopent-2-en-1-one (**2a**)¹



Synthesized according to the general procedure with ChCl/malonic acid 1:1. White solid, 92% yield, *trans/cis* ratio 83:17. *R_f* 0.25 (PE/Et₂O 9:1). **trans-2a** ¹H NMR (600 MHz) δ (ppm): 7.34-7.24 (m, 5H), 7.23-7.19 (m, 2H), 7.15-7.11 (m, 1H), 7.09-7.06 (m, 2H), 3.98 (quin, 1H, *J* = 2.2 Hz), 2.41 (qd, 1H, *J* = 7.3, 2.8 Hz), 2.03 (d, 3H, *J* = 2.0 Hz), 1.36 (d, 3H, *J* = 7.5 Hz). ¹³C NMR (150 MHz) δ (ppm): 211.1 (Cq), 167.2 (Cq), 142.2 (Cq), 136.9 (Cq), 135.3 (Cq), 129.1 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 126.8 (CH), 56.5 (CH), 51.4 (CH), 15.4 (CH₃), 10.3 (CH₃). **GC-MS** *m/z* (%): 262 [M]⁺ (100), 247 (88), 219 (38), 115 (36). **cis-2a** ¹H NMR (600 MHz) δ (ppm): 7.40-7.37 (m, 2H), 7.34-7.24 (m, 4H), 7.24-7.19 (m, 2H), 7.18-7.16 (m, 1H), 7.00 (br s, 1H), 4.63-4.60 (m, 1H), 2.92 (quin, 1H, *J* = 7.4 Hz), 2.09 (d, 3H, *J* = 1.7 Hz), 0.76 (d, 3H, *J* = 7.5 Hz). ¹³C NMR (150 MHz) δ (ppm): 211.6 (Cq), 166.4 (Cq), 139.3 (Cq), 137.1 (Cq), 135.9 (Cq), 129.1 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.0 (CH), 52.7 (CH), 45.6 (CH), 12.4 (CH₃), 10.4 (CH₃). **GC-MS** *m/z* (%): 262 (100), 247 (92), 219 (40), 115 (40).

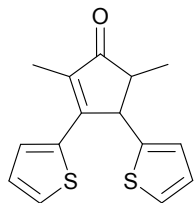
3,4-di(furan-2-yl)-2,5-dimethylcyclopent-2-en-1-one (**2b**)¹



Synthesized according to the general procedure with ChCl/oxalic acid 1:1. Orange solid, 95% yield, *trans/cis* ratio 71/29. *R_f* 0.18 (PE/Et₂O 9:1). **trans-2b** ¹H NMR (600 MHz) δ (ppm): 7.55 (d, 1H, *J* = 1.4 Hz), 7.29-7.28 (m, 1H), 6.56 (d, 1H, *J* = 3.4 Hz), 6.46-6.44 (m, 1H), 6.28 (dd, 1H, *J* = 3.1, 1.7 Hz), 6.10 (d, 1H, *J* = 3.1 Hz), 3.96-3.94 (m, 1H), 2.54 (qd, 1H, *J* = 7.4, 2.8 Hz), 2.15 (d, 3H, *J* = 1.7 Hz), 1.30 (d, 3H, *J* = 7.6 Hz). ¹³C NMR (150 MHz) δ (ppm): 209.6 (Cq), 154.9 (Cq), 151.0 (Cq), 150.6 (Cq), 144.9 (CH), 144.8 (CH), 133.5 (Cq), 114.8 (CH), 112.2 (CH), 110.5 (CH), 106.3 (CH), 47.5 (CH), 47.1 (CH), 16.2 (CH₃), 10.1 (CH₃). **GC-MS** *m/z* (%): 242 [M]⁺ (100), 227 (29). **cis-2b** ¹H NMR (600 MHz) δ (ppm): 7.54 (d, 1H, *J* = 1.4 Hz), 7.28-7.27 (m, 1H), 6.59 (d, 1H, *J* = 3.4 Hz), 6.46-6.44 (m, 1H), 6.36 (dd, 1H, *J* = 3.1, 2.1 Hz), 6.03 (d, 1H, *J* = 3.1 Hz), 4.57 (d, 1H, *J* = 7.2 Hz), 2.83-2.77

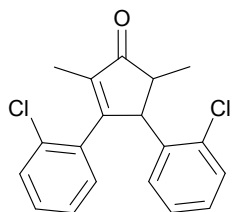
(m, 1H), 2.17 (d, 3H, $J = 1.7$ Hz), 0.88 (d, 3H, $J = 7.6$ Hz). ^{13}C NMR (150 MHz) δ (ppm): 209.8 (Cq), 153.5 (Cq), 151.3 (Cq), 150.5 (Cq), 144.9 (CH), 141.8 (CH), 133.8 (Cq), 114.4 (CH), 112.2 (CH), 110.4 (CH), 107.9 (CH), 44.9 (CH), 43.5 (CH), 11.5 (CH₃), 10.1 (CH₃). **GC-MS** m/z (%): 242 [M]⁺ (100), 227 (29).

2,5-dimethyl-3,4-di(thiophen-2-yl)cyclopent-2-en-1-one (2c)¹



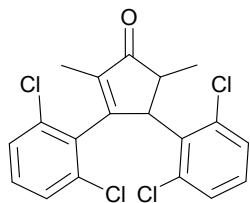
Synthesized according to the general procedure with ChCl/malonic acid 1:1. White solid, 83% yield, *trans/cis* ratio 56/44. R_f 0.20 (PE/Et₂O 9:1). **trans-2c** ^1H NMR (600 MHz) δ (ppm): 7.52-7.49 (m, 1H), 7.29 (d, 1H, $J = 3.8$ Hz), 7.15-7.12 (m, 1H), 7.07-7.04 (m, 1H), 6.92-6.89 (m, 1H), 6.86 (d, 1H, $J = 3.4$ Hz), 4.24 (br s, 1H), 2.49 (qd, 1H, $J = 7.4$ Hz, 2.4 Hz), 2.16 (d, 3H, $J = 1.7$ Hz), 1.34 (d, 3H, $J = 7.6$ Hz). ^{13}C NMR (150 MHz) δ (ppm): 209.3 (Cq), 157.5 (Cq), 146.6 (Cq), 138.1 (Cq), 133.9 (Cq), 130.4 (CH), 130.0 (CH), 127.7 (CH), 127.1 (CH), 124.8 (CH), 124.4 (CH), 51.8 (CH), 51.2 (CH), 16.4 (CH₃), 10.6 (CH₃). **GC-MS** m/z (%): 274 [M]⁺ (100), 259 (57), 231 (37). **cis-2c** ^1H NMR (600 MHz) δ (ppm): 7.52-7.49 (m, 1H), 7.36 (d, 1H, $J = 3.4$ Hz), 7.15-7.12 (m, 1H), 7.07-7.04 (m, 1H), 6.92-6.89 (m, 1H), 6.78 (d, 1H, $J = 3.1$ Hz), 4.85 (d, 1H, $J = 7.2$ Hz), 2.87 (quin, 1H, $J = 7.2$ Hz), 2.18 (d, 3H, $J = 1.4$ Hz), 0.89 (d, 3H, $J = 7.6$ Hz). ^{13}C NMR (150 MHz) δ (ppm): 209.4 (Cq), 157.7 (Cq), 143.6 (Cq), 138.6 (Cq), 133.7 (Cq), 129.9 (CH), 129.9 (CH), 127.7 (CH), 127.1 (CH), 126.2 (CH), 124.4 (CH), 47.4 (CH), 46.0 (CH), 11.3 (CH₃), 10.5 (CH₃). **GC-MS** m/z (%): 274 [M]⁺ (100), 259 (55), 231 (38).

3,4-bis(2-chlorophenyl)-2,5-dimethylcyclopent-2-en-1-one (2d)¹



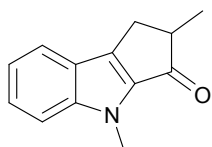
Synthesized according to the general procedure with ChCl/TsOH 1:2. White solid, 89% yield, *trans/cis* ratio 97/3. R_f 0.24 (PE/Et₂O 9:1). **trans-2d** ^1H NMR (600 MHz) δ (ppm): 7.33 (d, 1H, $J = 8.3$ Hz), 7.22 (d, 1H, $J = 7.6$ Hz), 7.18-7.10 (m, 4H), 7.06-7.02 (m, 2H), 4.74 (br s, 1H), 2.53 (br s, 1H), 1.77 (s, 3H), 1.41 (d, 3H, $J = 6.9$ Hz). ^{13}C NMR (150 MHz) δ (ppm): 210.2 (Cq), 165.7 (Cq), 139.8 (Cq), 138.6 (Cq), 134.7 (Cq), 134.3 (Cq), 132.4 (Cq), 130.0 (CH), 129.8 (CH), 129.8 (CH), 129.8 (CH), 129.3 (CH), 128.2 (CH), 127.3 (CH), 126.6 (CH), 53.3 (CH), 50.8 (CH), 15.7 (CH₃), 9.8 (CH₃). **GC-MS** m/z (%): 332 [M+2]⁺ (65), 330 [M]⁺ (98), 317 (66), 315 (100), 297 (23), 295 (65), 269 (27), 267 (79), 232 (30), 202 (31), 115 (56).

3,4-bis(2,6-dichlorophenyl)-2,5-dimethylcyclopent-2-en-1-one (2e)¹



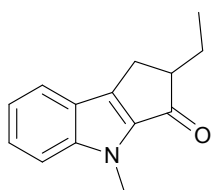
Synthesized according to the general procedure with ChCl/TsOH 1:2. White solid, 84% yield, *trans/cis* ratio 97/3. R_f 0.41 (PE/Et₂O 9:1). **trans-2e** ^1H NMR (600 MHz) δ (ppm): 7.34 (dd, 1H, $J = 7.9, 1.4$ Hz), 7.20-7.12 (m, 4H), 7.04 (t, 1H, $J = 7.9$ Hz), 5.13-5.11 (m, 1H), 3.21 (qd, 1H, $J = 7.4, 1.2$ Hz), 1.68 (d, 3H, $J = 1.7$ Hz), 1.39 (d, 3H, $J = 7.6$ Hz). ^{13}C NMR (150 MHz) δ (ppm): 211.6 (Cq), 160.6 (Cq), 141.0 (Cq), 137.1 (Cq), 136.8 (Cq), 134.4 (Cq), 133.7 (Cq), 133.2 (Cq), 133.1 (Cq), 130.5 (CH), 130.2 (CH), 128.8 (CH), 128.4 (CH), 128.2 (CH), 52.6 (CH), 45.4 (CH), 18.1 (CH₃), 9.3 (CH₃). **GC-MS** m/z (%): 402 [M+4]⁺ (35), 400 [M+2]⁺ (69), 398 [M]⁺ (54), 387 (25), 385 (51), 383 (39), 365 (46), 363 (48), 339 (32), 337 (97), 335 (100), 302 (40), 300 (61), 151 (30), 149 (47), 115 (37), 113 (32).

2,4-dimethyl-1,4-dihydrocyclopenta[b]indol-3(2H)-one (2f)²



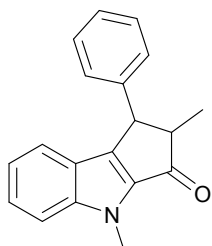
Synthesized according to the general procedure with ChCl/oxalic acid 1:1. Beige solid, 93% yield. **R_f** 0.13 (PE/EtOAc 95:5). **¹H NMR** (600 MHz) δ (ppm): 7.70-7.68 (m, 1H), 7.42 (ddd, 1H, J = 8.3, 6.9, 1.2 Hz), 7.38-7.36 (m, 2H), 7.17 (ddd, 1H, J = 7.9, 6.9, 1.0 Hz), 3.92 (s, 3H), 3.33 (dd, 1H, J = 16.7, 6.4 Hz), 3.07-3.02 (m, 1H), 2.65 (dd, 1H, J = 16.5, 2.4 Hz), 1.37 (d, 3H, J = 7.6 Hz). **¹³C NMR** (150 MHz) δ (ppm): 198.1 (Cq), 145.2 (Cq), 143.1 (Cq), 138.2 (Cq), 126.9 (CH), 123.2 (Cq), 121.9 (CH), 120.3 (CH), 111.1 (CH), 47.6 (CH₃), 30.3 (CH), 28.8 (CH₂), 17.4 (CH₃). **GC-MS** m/z (%): 199 [M]⁺ (94), 184 (100), 171 (34), 170 (43).

2-ethyl-4-methyl-1,4-dihydrocyclopenta[b]indol-3(2H)-one (2g)²



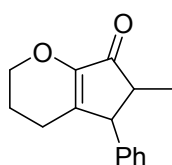
Synthesized according to the general procedure with ChCl/oxalic acid 1:1. White solid, 78% yield. **R_f** 0.21 (PE/EtOAc 95:5). **¹H NMR** (600 MHz) δ (ppm): 7.70 (d, 1H, J = 8.3 Hz), 7.44-7.40 (m, 1H), 7.38-7.36 (m, 1H), 7.18 (ddd, 1H, J = 7.9, 6.9, 1.0 Hz), 3.92 (s, 3H), 3.24 (dd, 1H, J = 16.7, 6.4 Hz), 2.94 (dddd, 1H, J = 9.0, 6.5, 4.1, 2.2 Hz), 2.74 (dd, 1H, J = 16.7, 2.2 Hz), 2.05-1.98 (m, 1H), 1.66-1.58 (m, 1H), 1.03 (t, 3H, J = 7.4 Hz). **¹³C NMR** (150 MHz) δ (ppm): 197.4 (Cq), 145.1 (Cq), 143.5 (Cq), 138.8 (Cq), 126.8 (CH), 123.2 (Cq), 121.9 (CH), 120.3 (CH), 111.1 (CH), 54.3 (CH₃), 30.22 (CH), 26.0 (CH₂), 25.1 (CH₂), 11.6 (CH₃). **GC-MS** m/z (%): 275 [M]⁺ (100), 260 (39), 246 (43), 232 (74).

2,4-dimethyl-1-phenyl-1,4-dihydrocyclopenta[b]indol-3(2H)-one (2h)³



Synthesized according to the general procedure with ChCl/malonic acid 1:1. Pale yellow solid, 80% yield, *trans/cis* ratio 40/60. **R_f** 0.21 (PE/EtOAc 95:5). ***trans*-2h** **¹H NMR** (600 MHz) δ (ppm): 7.43-7.40 (m, 2H), 7.38-7.36 (m, 1H), 7.34-7.22 (m, 4H), 7.10-7.05 (m, 2H), 4.80 (d, 1H, J = 6.5 Hz), 4.00 (s, 3H), 3.42-3.36 (m, 1H), 0.86 (d, 3H, J = 7.6 Hz). **¹³C NMR** (150 MHz) δ (ppm): 197.4 (Cq), 145.3 (Cq), 144.5 (Cq), 139.9 (Cq), 138.7 (Cq), 129.1 (CH), 128.9 (CH), 128.3 (CH), 127.4 (CH), 126.9 (CH), 126.8 (CH), 122.9 (Cq), 122.5 (CH), 120.4 (CH), 111.1 (CH), 52.5 (CH₃), 43.7 (CH), 30.3 (CH), 14.1 (CH₃). **GC-MS** m/z (%): 275 [M]⁺ (100), 260 (37), 246 (46), 232 (78). ***cis*-2h** **¹H NMR** (600 MHz) δ (ppm): 7.43-7.40 (m, 2H), 7.34-7.22 (m, 5H), 7.10-7.05 (m, 2H), 4.14 (d, 1H, J = 3.1 Hz), 3.99 (s, 3H), 2.87 (qd, 1H, J = 7.4, 2.9 Hz), 1.48 (d, 3H, J = 7.6 Hz). **¹³C NMR** (150 MHz) δ (ppm): 196.6 (Cq), 145.2 (Cq), 144.1 (Cq), 142.3 (Cq), 138.3 (Cq), 129.1 (CH), 128.9 (CH), 128.3 (CH), 127.4 (CH), 127.0 (CH), 126.8 (CH), 122.7 (Cq), 122.3 (CH), 120.5 (CH), 111.1 (CH), 58.9 (CH₃), 48.5 (CH), 30.3 (CH), 15.4 (CH₃). **GC-MS** m/z (%): 275 [M]⁺ (100), 260 (39), 246 (43), 232 (74).

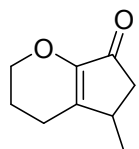
6-methyl-5-phenyl-3,4,5,6-tetrahydrocyclopenta[b]pyran-7(2H)-one (2i)⁴



Synthesized according to the general procedure with ChCl/malonic acid 1:1. White oil, 82% yield, *trans/cis* ratio 77/23. **R_f** 0.28 (PE/EtOAc 8:2). ***trans*-2i** **¹H NMR** (600 MHz) δ (ppm): 7.36-7.32 (m, 2H), 7.27-7.25 (m, 1H), 7.15-7.12 (m, 2H), 4.17-4.14 (m, 2H), 3.35 (q, 1H, J = 1.9 Hz), 2.25 (qd, 1H, J = 7.4, 2.3 Hz), 2.10 (td, 2H, J = 6.6, 1.8 Hz), 2.00-1.88 (m, 2H), 1.27 (t, 3H, J = 7.4 Hz). **¹³C NMR** (150 MHz) δ (ppm): 202.7 (Cq), 150.8 (Cq), 145.4 (Cq), 141.2 (Cq), 129.1 (CH), 127.4 (CH), 127.3 (CH), 67.0 (CH₂), 53.3 (CH), 49.4 (CH), 22.1 (CH₂), 21.6 (CH₂), 15.0 (CH₃). ***cis*-2i** **¹H NMR** (600 MHz) δ (ppm): 7.33-7.30 (m, 2H), 7.27-7.24 (m, 1H), 7.03 (d, 2H, J = 7.2 Hz), 4.22 (ddd, 1H, J = 10.3, 6.5, 3.4 Hz), 4.19-4.15 (m, 1H), 4.02 (d, 1H, J = 6.5 Hz), 2.79-2.73 (m, 1H), 2.19 (t, 2H, J = 6.2 Hz), 2.00-1.88 (m, 2H),

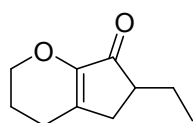
0.69 (d, 3H, $J = 7.6$ Hz). **^{13}C NMR** (150 MHz) δ (ppm): 203.1 (Cq), 151.7 (Cq), 145.0 (Cq), 138.7 (Cq), 129.1 (CH), 128.6 (CH), 127.2 (CH), 67.2 (CH₂), 48.9 (CH), 43.4 (CH), 22.6 (CH₂), 21.8 (CH₂), 12.4 (CH₃).

5-methyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (2j)⁵



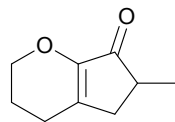
Synthesized according to the general procedure with ChCl/malonic acid 1:1. Pale yellow oil, 84% yield. **^1H NMR** (600 MHz) δ (ppm): 4.13-4.08 (m, 1H), 4.05-4.00 (m, 1H), 2.74-2.68 (m, 1H), 2.59 (dd, $J = 18.6, 6.2$ Hz, 1H), 2.41 (dt, $J = 18.9, 6.9$ Hz, 1H), 2.19 (dt, $J = 18.6, 5.9$ Hz, 1H), 1.96-1.90 (m, 3H), 1.14 (d, $J = 6.9$ Hz, 3H). **^{13}C NMR** (150 MHz) δ (ppm): 200.2 (Cq), 150.6 (Cq), 149.7 (Cq), 66.8 (CH₂), 41.6 (CH₂), 32.1 (CH), 21.9 (CH₂), 21.5 (CH₂), 19.3 (CH₃). **GC-MS** m/z (%): 152 [M]⁺ (97), 137 (100), 124 (25), 109 (31), 81 (44).

6-ethyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (2k)⁴



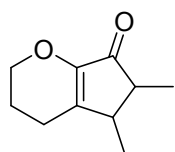
Synthesized according to the general procedure with ChCl/malonic acid 1:1. White oil, 83% yield. **^1H NMR** (600 MHz) δ (ppm): 4.09-4.02 (m, 2H), 2.57 (ddt, $J = 17.4, 6.3, 1.7$ Hz, 1H), 2.31 (t, $J = 6.4$ Hz, 2H), 2.27-2.22 (m, 1H), 2.09 (dq, $J = 17.4, 1.9$ Hz, 1H), 1.94-1.89 (m, 2H), 1.84-1.77 (m, 1H), 1.41-1.33 (m, 1H), 0.90 (t, $J = 7.4$ Hz, 3H). **^{13}C NMR** (150 MHz) δ (ppm): 203.0 (Cq), 150.7 (Cq), 144.4 (Cq), 66.8 (CH₂), 44.8 (CH), 32.8 (CH₂), 24.4 (CH₂), 24.1 (CH₂), 21.7 (CH₂), 11.2 (CH₃). **GC-MS** m/z (%): 166 [M]⁺ (40), 138 (100), 110 (22), 95 (15).

6-methyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (2l)⁴



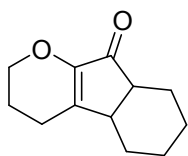
Synthesized according to the general procedure with ChCl/malonic acid 1:1. Pale yellow oil, 94% yield. **^1H NMR** (600 MHz) δ (ppm): 4.11-4.06 (m, 2H), 2.68 (ddt, 1H, $J = 17.4, 6.4, 1.6$ Hz), 2.40-2.34 (m, 1H), 2.33-2.30 (m, 2H), 2.02 (dq, 1H; $J = 17.4, 1.8$ Hz), 1.96-1.91 (m, 2H), 1.17 (d, 3H, $J = 7.5$ Hz). **^{13}C NMR** (150 MHz) δ (ppm): 203.7 (Cq), 150.3 (Cq), 140.1 (Cq), 66.9 (CH₂), 38.1 (CH), 35.0 (CH₂), 24.1 (CH₂), 21.7 (CH₂), 16.6 (CH₃). **GC-MS** m/z (%): 152 [M]⁺ (100), 137 (43), 109 (20), 96 (24), 95 (26), 81 (20), 68 (31), 67 (36).

5,6-dimethyl-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (2m)⁴



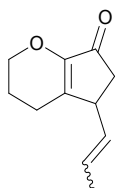
Synthesized according to the general procedure with ChCl/malonic acid 1:1. Pale yellow oil, 95% yield, *trans/cis* ratio 86/14. ***trans*-2m** **^1H NMR** (600 MHz) δ (ppm): 4.11-4.08 (m, 1H), 4.07-4.03 (m, 1H), 2.43-2.36 (m, 1H), 2.27-2.22 (m, 1H), 2.22-2.15 (m, 1H), 1.94 (quin, $J = 5.8$ Hz, 2H), 1.90-1.85 (m, 1H), 1.17 (t, $J = 7.3$ Hz, 3H), 1.16 (d, $J = 7.0$ Hz, 3H). **^{13}C NMR** (150 MHz) δ (ppm): 202.8 (Cq), 149.6 (Cq), 147.6 (Cq), 66.7 (CH₂), 47.4 (CH), 41.4 (CH), 21.7 (CH₂), 21.7 (CH₂), 17.9 (CH₃), 14.8 (CH₃). **GC-MS** m/z (%): 166 [M]⁺ (49), 151 (100), 95 (23) 67 (20). ***cis*-2m** **^1H NMR** (600 MHz) δ (ppm): 4.16-4.12 (m, 1H), 4.03-3.99 (m, 1H), 2.84-2.78 (m, 1H), 2.51-2.46 (m, 1H), 2.43-2.36 (m, 1H), 2.22-2.15 (m, 1H), 1.94 (quin, $J = 5.8$ Hz, 2H), 1.08 (d, $J = 7.6$ Hz, 3H), 1.04 (d, $J = 7.3$ Hz, 3H). **^{13}C NMR** (150 MHz) δ (ppm): 203.4 (Cq), 150.0 (Cq), 148.9 (Cq), 66.9 (CH₂), 42.2 (CH), 36.2 (CH), 22.1 (CH₂), 21.7 (CH₂), 14.9 (CH₃), 11.3 (CH₃). **GC-MS** m/z (%): 166 [M]⁺ (57), 151 (100), 95 (25), 67 (23).

3,4,4b,5,6,7,8,8a-octahydroindeno[2,1-*b*]pyran-9(2*H*)-one (2n)⁴



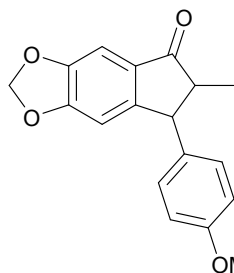
Synthesized according to the general procedure with ChCl/malonic acid 1:1. Pale yellow oil, 83% yield. *R_f* 0.20 (PE/EtOAc 8:2). **¹H NMR** (600 MHz) δ (ppm): 4.12-4.08 (m, 1H), 4.05-4.01 (m, 1H), 2.73-2.69 (m, 1H), 2.40 (q, 1H, *J* = 6.4 Hz), 2.38-2.32 (m, 1H), 2.45-2.19 (m, 1H), 1.98-1.86 (m, 3H), 1.84-1.78 (m, 1H), 1.72-1.64 (m, 1H), 1.51-1.43 (m, 2H), 1.40-1.28 (m, 2H), 1.19-1.14 (m, 1H). **¹³C NMR** (150 MHz) δ (ppm): 203.0 (Cq), 150.4 (Cq), 148.4 (Cq), 67.0 (CH₂), 43.9 (CH), 37.7 (CH), 29.8 (CH₂), 26.8 (CH₂), 22.1 (CH₂), 21.8 (CH₂), 20.6 (CH₂), 20.5 (CH₂). **GC-MS** *m/z* (%): 192 [M]⁺ (100), 164 (68), 149 (25), 138 (24), 136 (24), 135 (42), 79 (33).

5-(prop-1-en-1-yl)-3,4,5,6-tetrahydrocyclopenta[*b*]pyran-7(2*H*)-one (2o)⁴



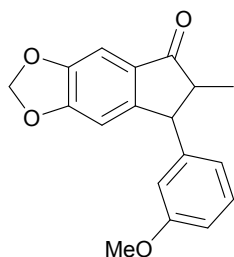
Synthesized according to the general procedure with ChCl/malonic acid 1:1. Pale yellow oil, 91% yield. *R_f* 0.19 (PE/EtOAc 8:2). **(*E*)-2o ¹H NMR** (600 MHz) δ (ppm): 5.63-5.55 (m, 1H), 5.15 (ddq, 1H, *J* = 14.8, 9.0, 1.5 Hz), 4.11-4.04 (m, 2H), 3.20 (t, 1H, *J* = 7.2 Hz), 2.62 (dd, 1H, *J* = 18.8, 6.4 Hz), 2.34 (dt, 1H, *J* = 18.9, 6.4 Hz), 2.16 (dt, 2H, *J* = 19.6, 6.9 Hz), 1.93-1.90 (m, 2H), 1.68 (d, 3H, *J* = 6.5, 1.7 Hz). **¹³C NMR** (150 MHz) δ (ppm): 200.0 (Cq), 151.0 (Cq), 147.5 (Cq), 131.6 (CH), 127.8 (CH), 66.9 (CH₂), 41.3 (CH), 40.4 (CH₂), 22.4 (CH₂), 21.6 (CH₂), 17.9 (CH₃). **GC-MS** *m/z* (%): 178 [M]⁺ (100), 163 (85), 150 (46), 135 (67), 91 (30), 79 (62).

7-(4-methoxyphenyl)-6-methyl-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-one (2p)⁶



Synthesized according to the general procedure with ChCl/TsOH 1:2. Colourless oil, 83% yield, *trans/cis* ratio 89/11. *R_f* 0.26 (PE/EtOAc 9:1). ***trans*-2p ¹H NMR** (600 MHz) δ (ppm): 7.13 (s, 1H), 7.08-7.05 (m, 2H), 6.88-6.85 (m, 2H), 6.54 (s, 1H), 6.03 (s, 2H), 3.84 (d, 1H, *J* = 4.5 Hz), 3.80 (s, 3H), 2.57 (qd, 1H, *J* = 7.3, 4.5 Hz), 1.32 (d, 3H, *J* = 7.3 Hz). **¹³C NMR** (150 MHz) δ (ppm): 206.0 (Cq), 158.8 (Cq), 154.5 (Cq), 154.0 (Cq), 148.7 (Cq), 134.9 (Cq), 120.9 (Cq), 129.0 (CH), 114.4 (CH), 105.8 (CH), 102.3 (CH₂), 102.0 (CH), 55.4 (CH₃), 54.0 (CH), 53.0 (CH), 14.5 (CH₃). **GC-MS** *m/z* (%): 296 [M]⁺ (94), 281 (100),

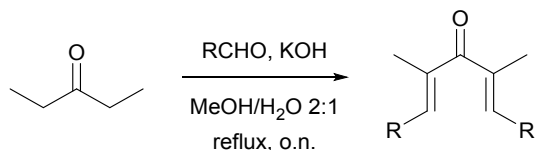
7-(3-methoxyphenyl)-6-methyl-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-one (2q)⁶



Synthesized according to the general procedure with ChCl/TsOH 1:2. Colourless oil, 74% yield, *trans/cis* ratio 96/4. *R_f* 0.28 (PE/EtOAc 9:1). ***trans*-2p ¹H NMR** (600 MHz) δ (ppm): 7.25 (t, 1H, *J* = 8.0 Hz), 7.14 (s, 1H), 6.82 (ddd, 1H, *J* = 8.3, 2.6, 0.8 Hz), 6.74 (br d, 1H, *J* = 7.7 Hz), 6.68-6.67 (m, 1H), 6.58 (s, 1H), 6.05 (s, 2H), 3.87 (d, 1H, *J* = 4.4 Hz), 3.78 (s, 3H), 2.62 (qd, 1H, *J* = 7.3, 4.4 Hz), 1.34 (d, 3H, *J* = 7.3 Hz). **¹³C NMR** (150 MHz) δ (ppm): 205.9 (Cq), 160.2 (Cq), 154.6 (Cq), 153.6 (Cq), 148.8 (Cq), 144.6 (Cq), 131.0 (Cq), 130.0 (CH), 120.4 (CH), 114.0 (CH), 112.2 (CH), 105.9 (CH), 102.4 (CH₂), 102.2 (CH), 55.4 (CH₃), 53.8 (CH), 53.7 (CH), 14.8 (CH₃). **GC-MS** *m/z* (%): 296 [M]⁺ (100), 281 (52).

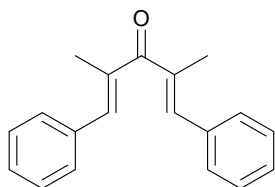
Synthesis of the substrates

General procedure for the aldol condensation of 3-pentanone and aldehydes¹



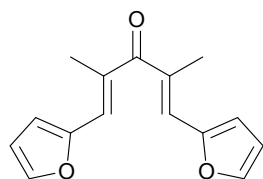
3-pentanone (1.0 eq, 10-20 mmol) was mixed with the aldehyde (2.5 eq) and the mixture was added to a flask already containing KOH (2.5 eq) in 2:1 MeOH/H₂O (1.0 M towards 3-pentanone). The mixture was stirred at reflux overnight, then it was cooled down. A 1.0 M solution of HCl was added until the pH was 7. The mixture was extracted three times with DCM; the combined organic layers were dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude product was recrystallized with MeOH to afford pure dienone.

(1E,4E)-2,4-dimethyl-1,5-diphenylpenta-1,4-dien-3-one (1a)¹



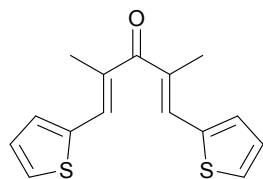
Synthesized according to the general procedure. White solid, 45% yield. ¹H NMR (600 MHz) δ (ppm): 7.45-7.39 (m, 8H), 7.35-7.32 (m, 2H), 7.22-7.20 (m, 2H), 2.21 (d, 6H, *J* = 1.6 Hz). GC-MS *m/z* (%): 262 [M]⁺ (60), 247 (18), 144 (17), 116 (100), 115 (62).

(1E,4E)-1,5-di(furan-2-yl)-2,4-dimethylpenta-1,4-dien-3-one (1b)¹



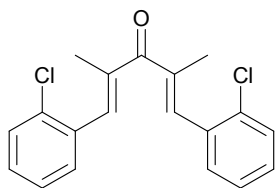
Synthesized according to the general procedure. Yellow solid, 45% yield. ¹H NMR (600 MHz) δ (ppm): 7.54 (d, 2H, *J* = 1.8 Hz), 2.27 (s, 2H), 6.61 (d, 2H, *J* = 3.4 Hz), 6.52 (dd, 2H, *J* = 3.6, 1.8 Hz), 2.25 (d, 6H, *J* = 1.3 Hz). GC-MS *m/z* (%): 242 [M]⁺ (100), 227 (10), 106 (24), 77 (45).

(1E,4E)-2,4-dimethyl-1,5-di(thiophen-2-yl)penta-1,4-dien-3-one (1c)¹



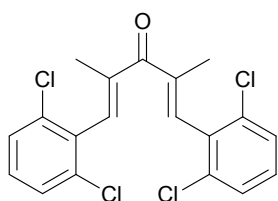
Synthesized according to the general procedure. Yellow solid, 49% yield. ¹H NMR (600 MHz) δ (ppm): 7.52 (d, 2H, *J* = 5.0 Hz), 7.36 (s, 2H), 7.25 (d, 2H, *J* = 3.7 Hz), 7.13 (dd, 2H, *J* = 5.1, 3.6 Hz), 2.28 (d, 6H, *J* = 1.3 Hz). GC-MS *m/z* (%): 274 [M]⁺ (100), 259 (64), 231 (32), 151 (30), 123 (40), 122 (74).

(1E,4E)-1,5-bis(2-chlorophenyl)-2,4-dimethylpenta-1,4-dien-3-one (1d)¹



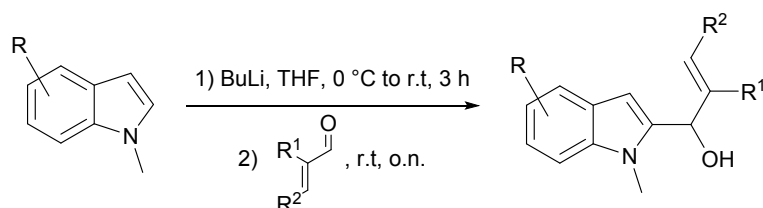
Synthesized according to the general procedure. White solid, 75% yield. ¹H NMR (600 MHz) δ (ppm): 7.44 (dd, 2H, *J* = 7.7, 1.5 Hz), 7.41 (s, 2H), 7.40 (dd, 2H, *J* = 7.6, 1.9 Hz), 7.33-7.36 (m, 4H), 2.07 (d, 6H, *J* = 1.5 Hz). GC-MS *m/z* (%): 294 (22), 236 (45), 234 (100).

(1*E*,4*E*)-1,5-bis(2,6-dichlorophenyl)-2,4-dimethylpenta-1,4-dien-3-one (**1e**)¹



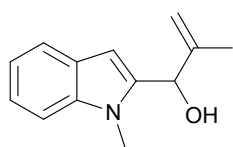
Synthesized according to the general procedure. White solid, 55% yield. **¹H NMR** (600 MHz) δ (ppm): 7.37 (d, 4H, J = 8.2 Hz), 7.27-7.26 (m, 2H), 7.23 (t, 2H, J = 8.1 Hz), 1.86 (d, 6H, J = 1.4 Hz). **GC-MS** m/z (%): 402 [$M+4$]⁺ (9), 400 [$M+2$]⁺ (18), 398 [M]⁺ (14), 367 (33), 365 (95), 363 (100), 177 (58), 150 (44), 149 (82), 115 (80).

General procedure for the synthesis of indole alcohols²



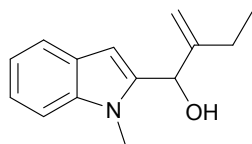
A solution of *N*-methylindole (1.0 eq, 1-5 mmol) in anhydrous THF (0.6 M), in a Schlenk flask under N₂ atmosphere, was cooled down to 0 °C. *n*-BuLi (1.2 eq, 2.5 M solution in hexane) was added and the mixture was stirred at room temperature for 3 h. Then, the α,β -unsaturated aldehyde (1.1 eq) was added and the mixture was stirred at room temperature overnight. After that time, the mixture was cooled down again to 0 °C and a saturated NH₄Cl solution was added. The mixture was extracted three times with Et₂O; the combined organic layers were dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford pure indole alcohol.

2-methyl-1-(1-methyl-1*H*-indol-2-yl)prop-2-en-1-ol²



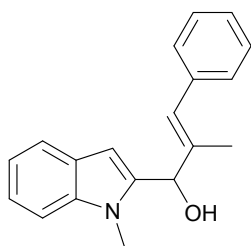
Synthesized according to the general procedure. Pale yellow oil, 74% yield. ***R_f*** 0.23 (PE/EtOAc 9:1). **¹H NMR** (600 MHz) δ (ppm): 7.58 (d, 1H, J = 7.9 Hz), 7.32 (dd, 1H, J = 8.3, 1.0 Hz), 7.24-7.21 (m, 1H), 7.12-7.08 (m, 1H), 6.44 (s, 1H), 5.34 (d, 1H, J = 4.8 Hz), 5.25-5.24 (m, 1H), 5.12 (q, 1H, J = 1.5 Hz), 3.78 (s, 3H), 1.99 (d, 1H, J = 5.0 Hz), 1.77 (s, 3H). **GC-MS** m/z (%): 201 [M]⁺ (54), 184 (100), 183 (46), 168 (35), 132 (40), 117 (28).

1-(1-methyl-1*H*-indol-2-yl)-2-methylenebutan-1-ol²



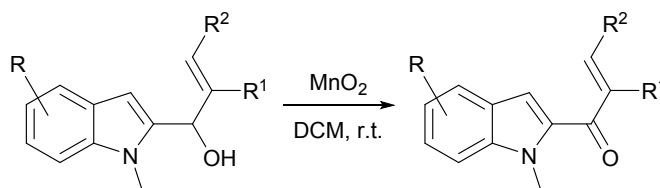
Synthesized according to the general procedure. Yellow oil, 50% yield. ***R_f*** 0.19 (PE/EtOAc 9:1). **¹H NMR** (600 MHz) δ (ppm): 7.58 (d, 1H, J = 7.7 Hz), 7.31 (d, 1H, J = 8.3 Hz), 7.24-7.21 (m, 1H), 7.12-7.09 (m, 1H), 6.43 (s, 1H), 5.38 (d, 1H, J = 4.7 Hz), 5.29-5.28 (m, 1H), 5.14-5.12 (m, 1H), 3.76 (s, 3H), 2.15-2.07 (m, 1H), 2.07-2.00 (m, 1H) superimposed to 2.00 (d, 1H, J = 5.0 Hz), 1.06 (t, 3H, J = 7.3 Hz). **GC-MS** m/z (%): 215 [M]⁺ (67), 198 (100), 182 (41), 144 (40), 132 (62), 117 (34).

(E)-2-methyl-1-(1-methyl-1H-indol-2-yl)-3-phenylprop-2-en-1-ol³



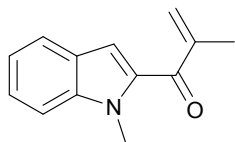
Synthesized according to the general procedure. White solid, 93% yield. R_f 0.32 (PE/EtOAc 85:15). $^1\text{H NMR}$ (600 MHz) δ (ppm): 7.60 (dd, 1H, J = 7.9 Hz, 1.0 Hz), 7.38-7.32 (m, 5H), 7.27-7.21 (m, 2H), 7.12-7.09 (m, 1H), 7.82-7.80 (m, 1H), 6.51 (s, 1H), 5.48 (d, 1H, J = 4.8 Hz), 3.82 (s, 3H), 2.09 (d, 1H, J = 4.9 Hz), 1.90 (d, 3H, J = 1.4 Hz). **GC-MS** m/z (%): 277 $[\text{M}]^+$ (27), 260 (34), 259 (100), 244 (66).

General procedure for the oxidation of indole alcohols to indole dienones⁴



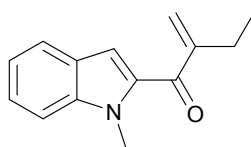
To a solution of indole alcohol (1.0 eq, 1-3 mmol) in DCM (0.1 M towards the substrate), stirring at room temperature, 12 eq of MnO_2 were added portionwise (approximately 2 eq every 10 min). Then, the mixture was filtered through a celite pad and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford pure indole dienone.

2-methyl-1-(1-methyl-1H-indol-2-yl)prop-2-en-1-one (1f)²



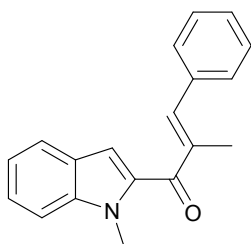
Synthesized according to the general procedure. Pale yellow solid, 73% yield. R_f 0.68 (PE/EtOAc 9:1). $^1\text{H NMR}$ (600 MHz) δ (ppm): 7.69-7.67 (m, 1H), 7.41-7.37 (m, 2H), 7.16 (ddd, 1H, J = 7.9, 6.2, 1.7 Hz), 7.10-7.09 (m, 1H), 4.02 (s, 3H), 2.10-2.09 (m, 3H). **GC-MS** m/z (%): 199 $[\text{M}]^+$ (100), 184 (26), 171 (42), 158 (40), 156 (34), 144 (48), 89 (76).

1-(1-methyl-1H-indol-2-yl)-2-methylenebutan-1-one (1g)²



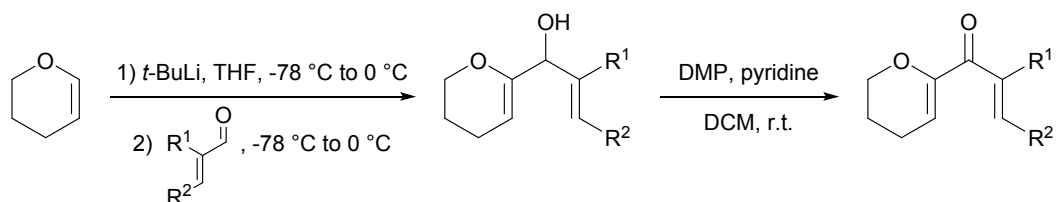
Synthesized according to the general procedure. Yellow oil, 86% yield. R_f 0.77 (PE/EtOAc 9:1). $^1\text{H NMR}$ (600 MHz) δ (ppm): 7.68 (dt, 1H, J = 7.9, 1.1 Hz), 7.41-7.37 (m, 2H), 7.16 (ddd, 1H, J = 7.9, 6.1, 1.7 Hz), 7.10 (s, 1H), 5.80 (d, 1H, J = 1.0 Hz), 5.74 (q, 1H, J = 1.5 Hz), 4.04 (s, 3H), 2.53-2.49 (m, 2H), 1.14 (t, 3H, J = 7.4 Hz). **GC-MS** m/z (%): 213 $[\text{M}]^+$ (100), 198, (46), 184 (26), 170 (55), 159 (42), 144 (60), 131 (34), 89 (67).

(E)-2-methyl-1-(1-methyl-1H-indol-2-yl)-3-phenylprop-2-en-1-one (1h)³



Synthesized according to the general procedure. Yellow solid, 70% yield. R_f 0.66 (PE/EtOAc 9:1). $^1\text{H NMR}$ (600 MHz) δ (ppm): 7.68 (dt, 1H, J = 8.3, 1.1 Hz), 7.50-7.49 (m, 1H), 7.48-7.41 (m, 5H), 7.40-7.37 (m, 1H), 7.37-7.34 (m, 1H), 7.17 (ddd, 1H, J = 8.0, 6.8, 1.3 Hz), 7.08 (d, 1H, J = 0.8 Hz), 4.04 (s, 3H), 2.29 (d, 3H, J = 1.4 Hz). **GC-MS** m/z (%): 275 $[\text{M}]^+$ (100), 260 (29), 232 (30), 89 (35).

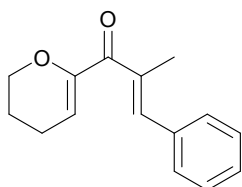
General procedure for the synthesis of dihydropyranyl dienones⁴



A solution of 3,4-dihydropyran (1.0 eq, 5 mmol) in anhydrous THF (1.0 M) was cooled down to -78 °C. *t*-BuLi (1.1 eq, 1.7 M solution in pentane) was added dropwise and the mixture was allowed to warm to 0 °C and stirred for 30 min at that temperature. Then, the mixture was cooled down again to -78 °C and the α,β -unsaturated aldehyde (1.1 eq) was added. The mixture was allowed to warm to 0 °C and it was stirred for 10 min, then H₂O was added and the mixture was extracted three times with EtOAc; the combined organic layers were dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude product was used directly for the subsequent oxidation.

To a solution of Dess-Martin periodinane (1.1 eq) in DCM (0.3 M towards the substrate), pyridine (5.0 eq) was added. The mixture was stirred for 5 min, then the alcohol substrate (1.0 eq) in solution of DCM was added. The mixture was stirred for 30 min, then a 3M NaOH solution was added and the mixture was stirred for 10 min before extracting three times with DCM. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford pure pyranyl dienone.

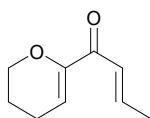
1-(3,4-dihydro-2H-pyran-6-yl)-2-methyl-3-phenylprop-2-en-1-one (1i)⁴



Synthesized according to the general procedure. Colourless oil, 39% yield (2-step). *R_f* 0.36 (PE/EtOAc 9:1). ¹H NMR (600 MHz) δ (ppm): 7.42-7.38 (m, 4H), 7.34-7.31 (m, 1H), 7.25-7.24 (m, 1H), 5.83 (t, 1H, *J* = 4.2 Hz), 4.18-4.16 (m, 2H), 2.26 (td, 2H, *J* = 6.4, 4.2 Hz), 2.14 (d, 3H, *J* = 1.4 Hz), 1.94-1.90 (m, 2H).

GC-MS *m/z* (%): 228 [M]⁺ (79), 227 (34), 213 (38), 200 (84), 199 (39), 129 (30), 117 (62), 115 (100), 91 (37).

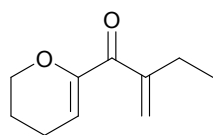
1-(3,4-dihydro-2H-pyran-6-yl)but-2-en-1-one (1j)⁵



Synthesized according to the general procedure. Pale yellow oil, 37% yield (2-step).

¹H NMR (600 MHz) δ (ppm): 7.00 (dq, 1H, *J* = 15.4, 6.9 Hz), 6.67 (dq, 1H, *J* = 15.3, 1.7 Hz), 6.00 (t, 1H, *J* = 4.3 Hz), 4.11-4.08 (m, 2H), 2.23-2.20 (m, 2H), 1.90 (dd, 3H, *J* = 6.9 Hz, 1.7 Hz), 1.87-1.83 (m, 2H). **GC-MS** *m/z* (%): 152 [M]⁺ (33), 137 (31), 124 (25), 83 (13), 68 (100), 55 (22).

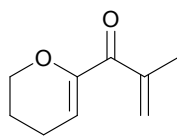
1-(3,4-dihydro-2H-pyran-6-yl)-2-methylenebutan-1-one (1k)⁴



Synthesized according to the general procedure. Pale yellow oil, 35% yield (2-step). ¹H NMR (600 MHz) δ (ppm): 5.86 (t, 1H, *J* = 4.2 Hz), 5.58 (q, 1H, *J* = 1.1 Hz), 5.54 (q, 1H, *J* = 1.5 Hz), 4.13-4.10 (m, 2H), 2.35 (qt, 2H, *J* = 7.6, 1.4 Hz), 2.25-2.21 (m, 2H), 1.89-1.85 (m, 2H), 1.03 (t, 3H, *J* = 7.5 Hz). **GC-MS** *m/z* (%):

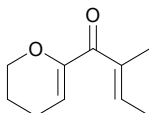
166 [M]⁺ (88), 123 (28), 111 (27), 83 (32), 55 (100).

1-(3,4-dihydro-2H-pyran-6-yl)-2-methylprop-2-en-1-one (1l)⁴



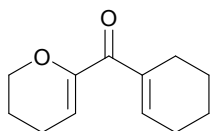
Synthesized according to the general procedure. Colourless oil, 26% yield (2-step). **R_f** 0.45 (PE/EtOAc 8:2). **¹H NMR** (600 MHz) δ (ppm): 5.84 (t, 1H, *J* = 4.2 Hz), 5.65 (quin, 1H, *J* = 1.0 Hz), 5.62 (quin, 1H, *J* = 1.5 Hz), 4.12-4.09 (m, 2H), 2.21 (td, 2H, *J* = 6.4, 4.2 Hz), 1.93 (dd, 3H, *J* = 1.6, 1.0 Hz), 1.88-1.84 (m, 2H). **GC-MS** *m/z* (%): 152 [M]⁺ (100), 137 (10), 124 (35), 111 (24), 83 (24), 69 (73), 68 (24), 55 (80), 41 (72).

1-(3,4-dihydro-2H-pyran-6-yl)-2-methylbut-2-en-1-one (1m)⁴



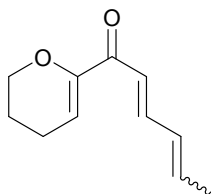
Synthesized according to the general procedure. Colourless oil, 31% yield (2-step). **R_f** 0.50 (PE/EtOAc 8:2). **¹H NMR** (600 MHz) δ (ppm): 6.50-6.45 (m, 1H), 5.61 (t, 1H, *J* = 4.2 Hz), 4.09-4.06 (m, 2H), 2.18 (td, 2H, *J* = 6.4, 4.1 Hz), 1.87-1.82 (m, 2H), 1.81-1.78 (m, 6H). **GC-MS** *m/z* (%): 166 [M]⁺ (37), 151 (100), 138 (28), 123 (22), 83 (47), 55 (88).

cyclohex-1-en-1-yl(3,4-dihydro-2H-pyran-6-yl)methanone (1n)⁴



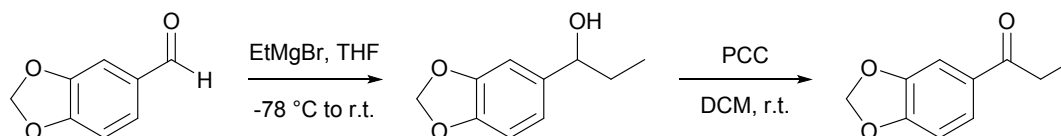
Synthesized according to the general procedure. Colourless oil, 24% yield (2-step). **R_f** 0.20 (PE/EtOAc 8:2). **¹H NMR** (600 MHz) δ (ppm): 6.70-6.67 (m, 1H), 5.66 (t, 1H, *J* = 4.2 Hz), 4.10-4.07 (m, 2H), 2.28-2.24 (m, 2H), 2.23-2.17 (m, 4H), 1.88-1.83 (m, 2H), 1.66-1.57 (m, 4H). **GC-MS** *m/z* (%): 192 [M]⁺ (100), 164 (80), 163 (30), 149 (31), 136 (33), 135 (46), 109 (46), 108 (28), 81 (86), 79 (88), 77 (30), 55 (55), 53 (40).

1-(3,4-dihydro-2H-pyran-6-yl)hexa-2,4-dien-1-one (1o)⁴



Synthesized according to the general procedure. Colourless oil, 28% yield (2-step). **R_f** 0.40 (PE/EtOAc 8:2). **(E)-1o ¹H NMR** (600 MHz) δ (ppm): 7.33-7.28 (m, 1H), 6.62 (d, 1H, *J* = 15.1 Hz), 6.25-6.16 (m, 2H), 5.99 (t, 1H, *J* = 4.3 Hz), 4.10-4.07 (m, 2H), 2.22-2.19 (m, 2H), 1.86-1.82 (m, 5H). **GC-MS** *m/z* (%): 178 [M]⁺ (65), 163 (100), 135 (50), 95 (70), 67 (64).

Synthesis of 1-(benzo[d][1,3]dioxol-5-yl)propan-1-one⁷

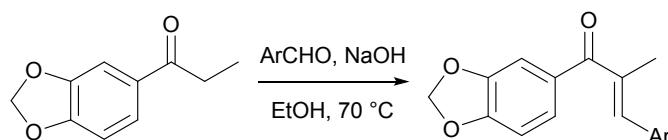


A solution of piperonal (1.0 eq, 15 mmol) in anhydrous THF (0.3 M) was cooled down to -78 °C. EtMgBr (1.5 eq, 3.0 M solution in Et₂O) was added dropwise and the mixture was stirred for 30 min at that temperature. Then, the mixture was allowed to warm to room temperature. A 10% AcOH solution was added and the mixture was extracted three times with Et₂O; the combined organic layers were washed with water, dried over anhydrous Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude product was used directly for the subsequent oxidation.

To a solution of the alcohol (1.0 eq) in DCM (0.25 M), pyridinium chlorochromate (1.3 eq) was added portionwise. The mixture was stirred until complete consumption of the starting material (GC check, 6 h), then it was filtered through a pad of celite and a pad of MgSO₄. The solvent was evaporated

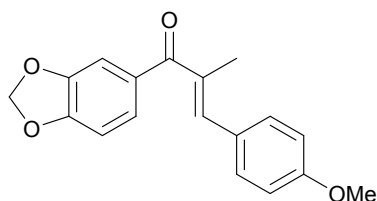
under reduced pressure to afford crude product, which was purified by flash column chromatography to afford pure ketone. White solid, 57% yield (2-steps). R_f 0.46 (PE/EtOAc 9:1) $^1\text{H NMR}$ (600 MHz) δ (ppm): 7.56 (dd, 1H, J = 8.2, 1.7 Hz), 7.44 (d, 1H, J = 1.7 Hz), 6.84 (d, 1H, J = 8.2 Hz), 6.03 (s, 2H), 2.92 (q, 2H, J = 7.2 Hz), 1.20 (t, 3H, J = 7.3 Hz). **GC-MS** m/z (%): 178 $[\text{M}]^+$ (28), 149 (100), 121 (21).

General procedure for the synthesis of aryl vinyl ketones⁶



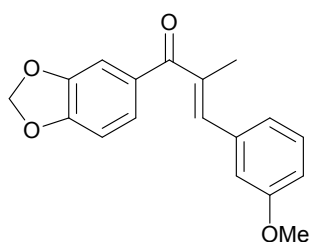
To a solution of NaOH (2.0 eq) in EtOH (0.5 M towards the substrate) the substrate (1.0 eq, 2.0 mmol) and the aldehyde (1.0 eq) were added and the mixture was stirred at 70 °C for 2-3 h. Then, a 1M HCl solution was added and the mixture was extracted three times with EtOAc; the combined organic layers were dried over anhydrous Na_2SO_4 , filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography to afford pure aryl vinyl ketone as the product.

1-(benzo[d][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)-2-methylprop-2-en-1-one (1p)⁶



Synthesized according to the general procedure. White solid, 53% yield. R_f 0.25 (PE/EtOAc 9:1). $^1\text{H NMR}$ (600 MHz) δ (ppm): 7.41-7.39 (m, 2H), 7.24 (dd, 1H, J = 8.0, 1.7 Hz), 7.28 (d, 1H, J = 1.7 Hz), 7.09 (br s, 1H), 6.95-6.92 (m, 2H), 6.85 (d, 1H, J = 8.1 Hz), 6.05 (s, 2H), 3.85 (s, 3H), 2.25 (d, 3H, J = 1.4 Hz). **GC-MS** m/z (%): 296 $[\text{M}]^+$ (100), 295 (28), 281 (39), 188 (38), 149 (55), 121 (28).

1-(benzo[d][1,3]dioxol-5-yl)-3-(3-methoxyphenyl)-2-methylprop-2-en-1-one (1q)⁶



Synthesized according to the general procedure. White solid, 49% yield. R_f 0.29 (PE/EtOAc 9:1). $^1\text{H NMR}$ (600 MHz) δ (ppm): 7.38 (dd, 1H, J = 8.1, 1.7 Hz), 7.34-7.31 (m, 2H), 7.07 (br s, 1H), 7.01 (br d, 1H, J = 7.5 Hz), 6.93 (t, 1H, J = 2.1 Hz), 6.89 (br d, 1H, J = 8.3 Hz), 6.86 (d, 1H, J = 8.1 Hz), 6.05 (s, 2H), 3.83 (s, 3H), 2.24 (d, 3H, J = 1.5 Hz). **GC-MS** m/z (%): 296 $[\text{M}]^+$ (100), 295 (29), 281 (22), 265 (24), 149 (64), 121 (21).

Preparation of the deep eutectic solvents

All the DESs were prepared according to literature procedures. The general procedure involves mixing of the two (or three) components of the mixture and stirring at a certain temperature until a clear homogeneous liquid is formed. Then, the mixture is stirred for another 20-30 min and finally cooled down to room temperature.

DES	mp (lit.)	T of preparation	reference
ChCl/malonic acid 1:1	10 °C	60 °C	8
ChCl/oxalic acid dihydrate 1:1	-40 °C ^a	60 °C	9
ChCl/citric acid 1:1	69 °C	100 °C	8
ChCl/maleic acid 1:1	not reported	100 °C	10
ChCl/L-(+)-lactic acid 1:2	-67 °C ^a	60 °C	11
ChCl/L-(-)-malic acid/H ₂ O 1:1:2	-71 °C ^a	80 °C	12
ChCl/L-(+)-tartaric acid 1:1	47 °C	100 °C	13
ChCl/TsOH monohydrate 1:2	12 °C	60 °C	14
ChCl/R-(-)-mandelic acid 1:1	not reported	60 °C	15
betaine/malonic acid 1:2	not reported	90 °C	16
L-proline/oxalic acid dihydrate 1:1	-14.5 °C	60 °C	13
ChCl/H ₂ O 1:2	not reported	60 °C	17

^a glass transition temperature (T_g)

E-factor calculation

The E-factor for the two-cycles, gram-scale reaction of **1a** in CHCl₃/malonic acid 1:1 was calculated as follows:

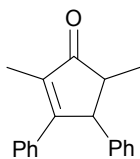
$$e\text{-factor} = \frac{g\text{ DES} + g\text{ H}_2\text{O}}{g\text{ 2a}} = \frac{4\text{ g} + 35\text{ g}}{2\text{ g}} = 19.5$$

25 g of H₂O were employed for dissolving the DES at the end of the reaction and rinsing; 15 g out 25 g of H₂O were recovered from the evaporation and used for the same purpose in the second cycle.

References

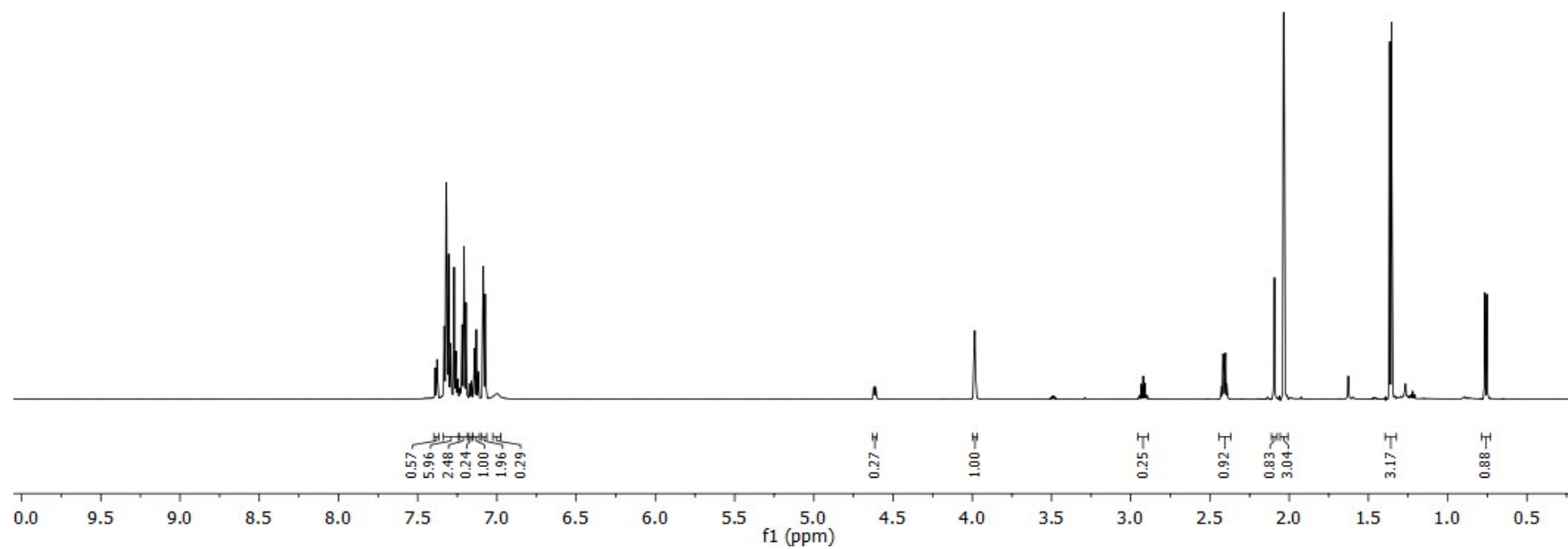
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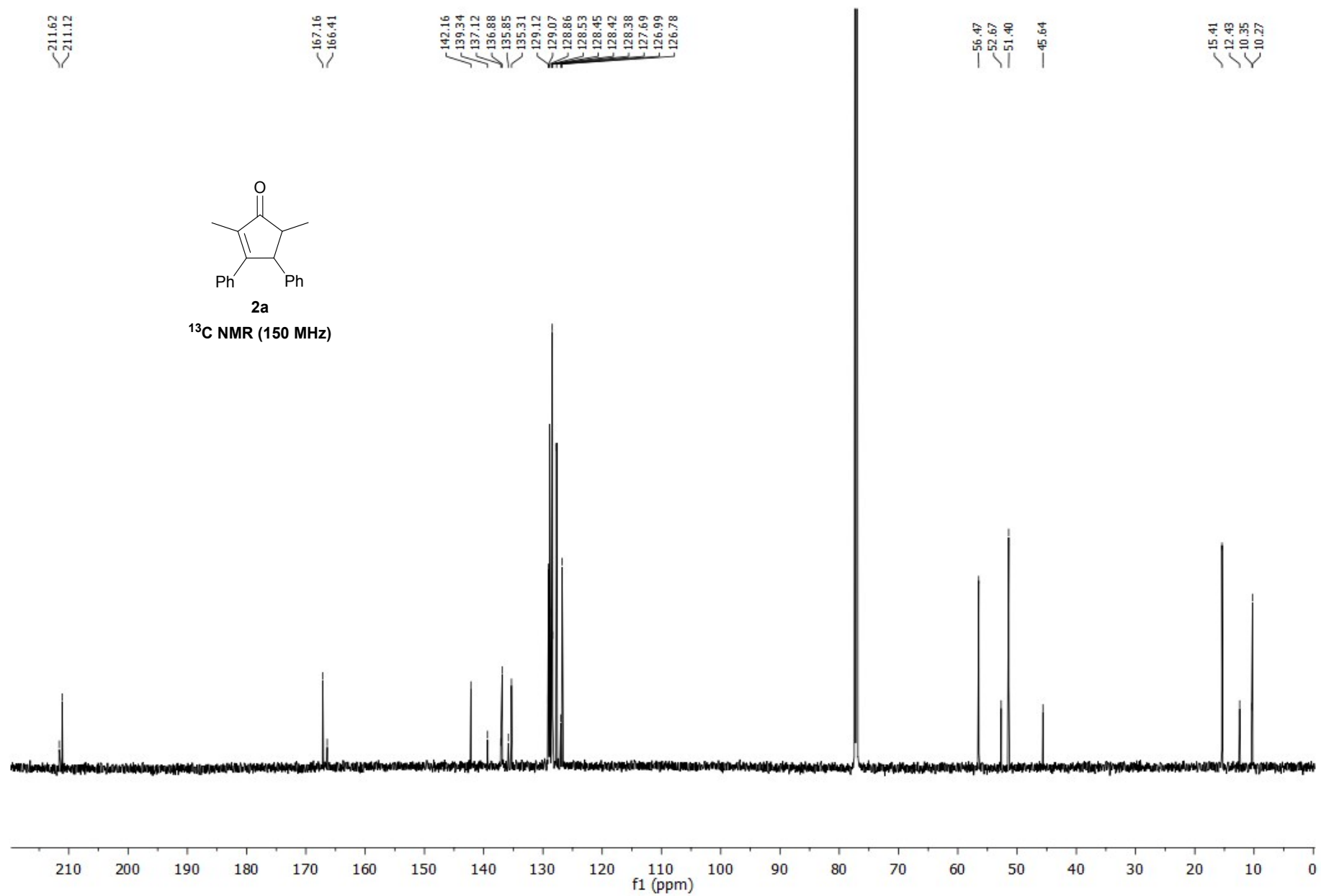
NMR spectra of Nazarov products

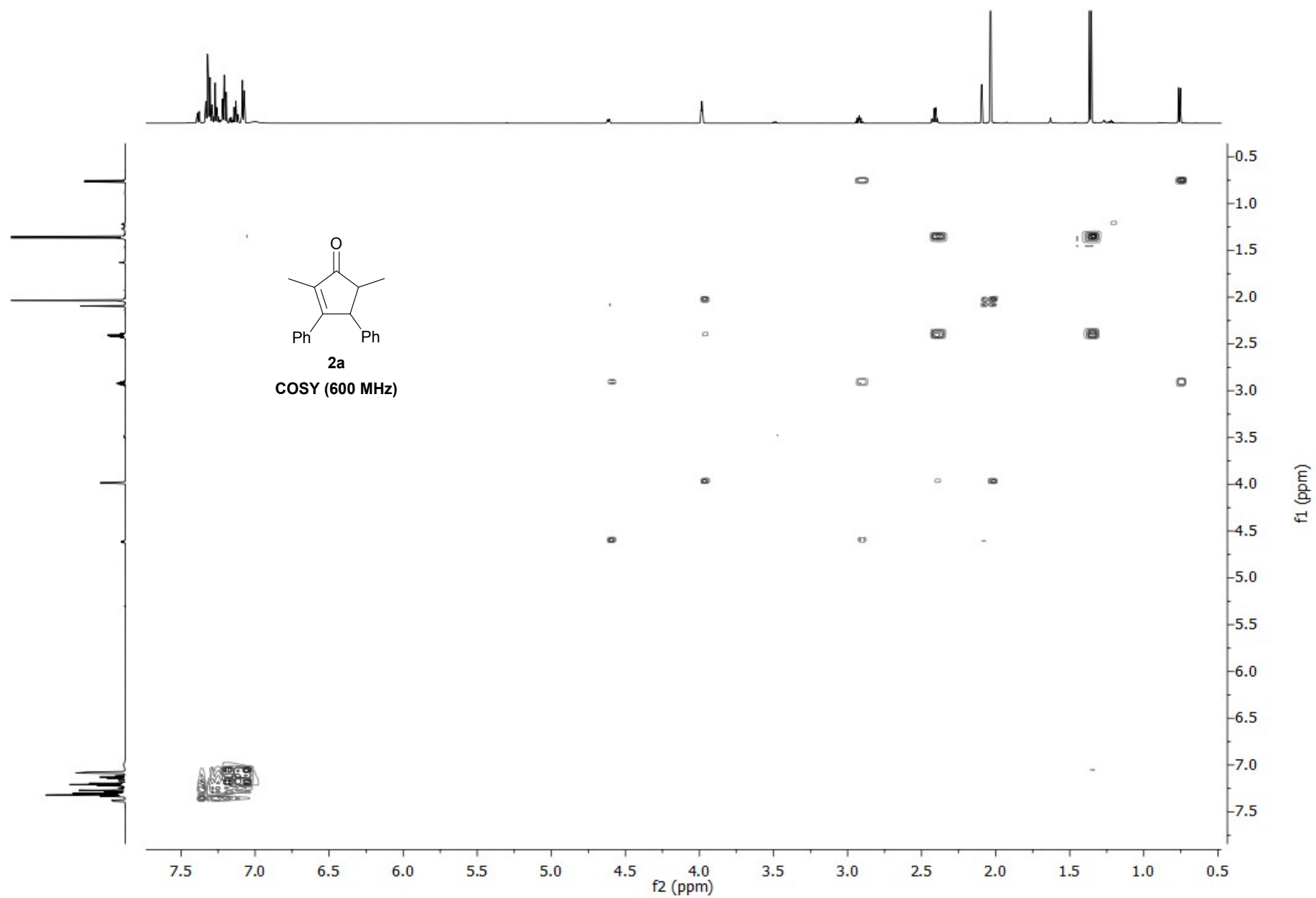


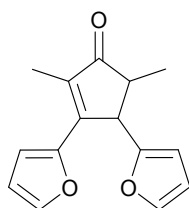
2a

¹H NMR (600 MHz)

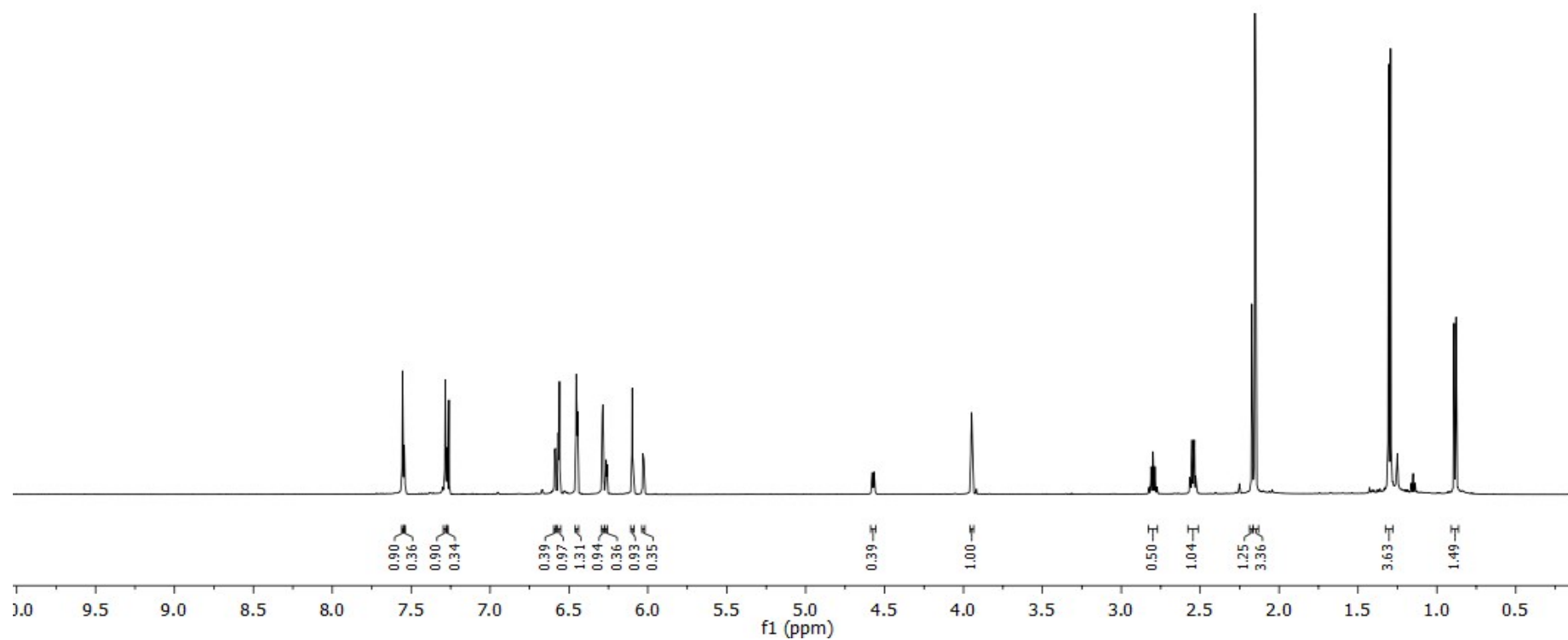


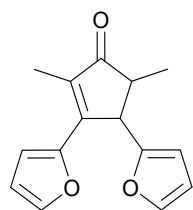






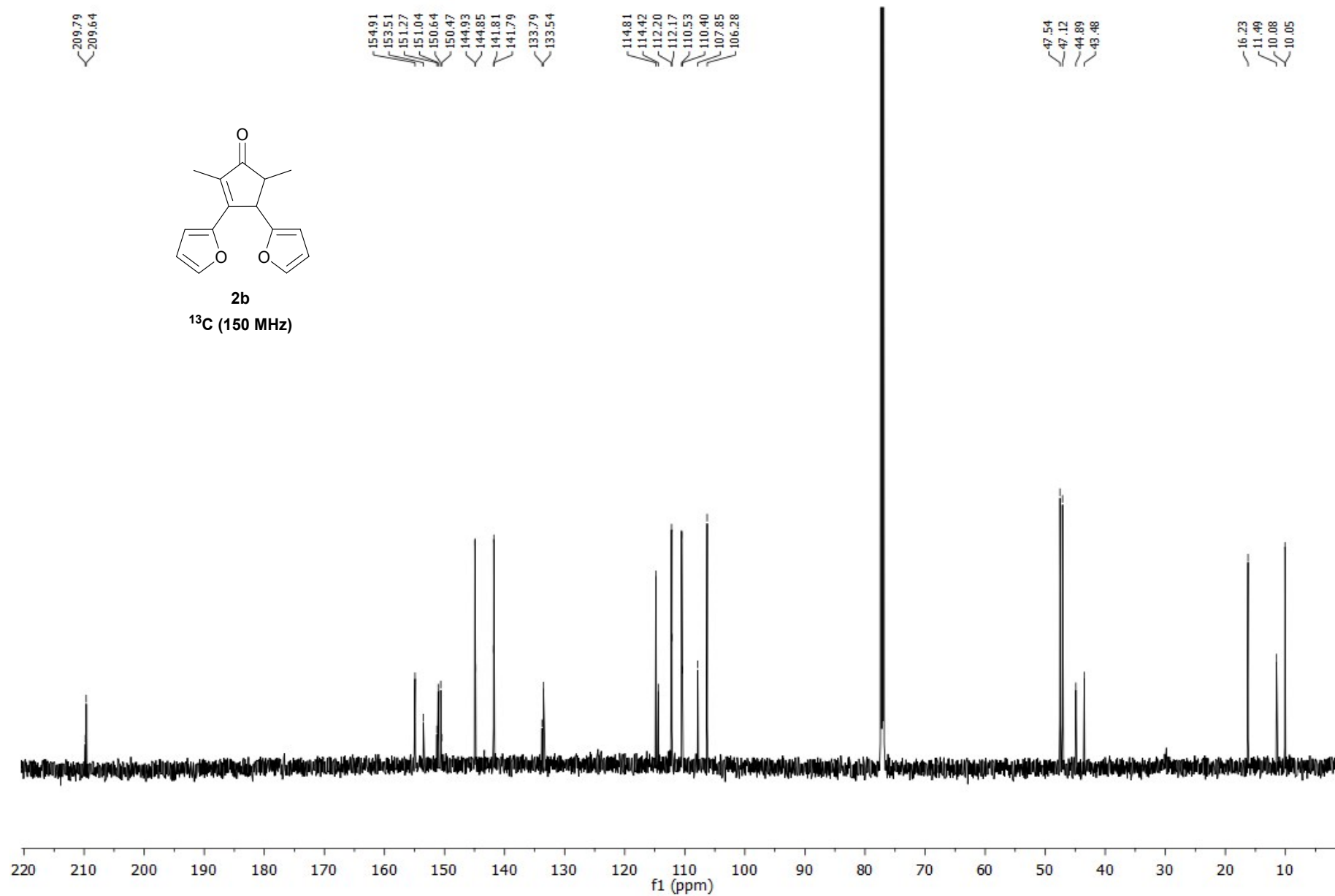
2b
¹H (600 MHz)

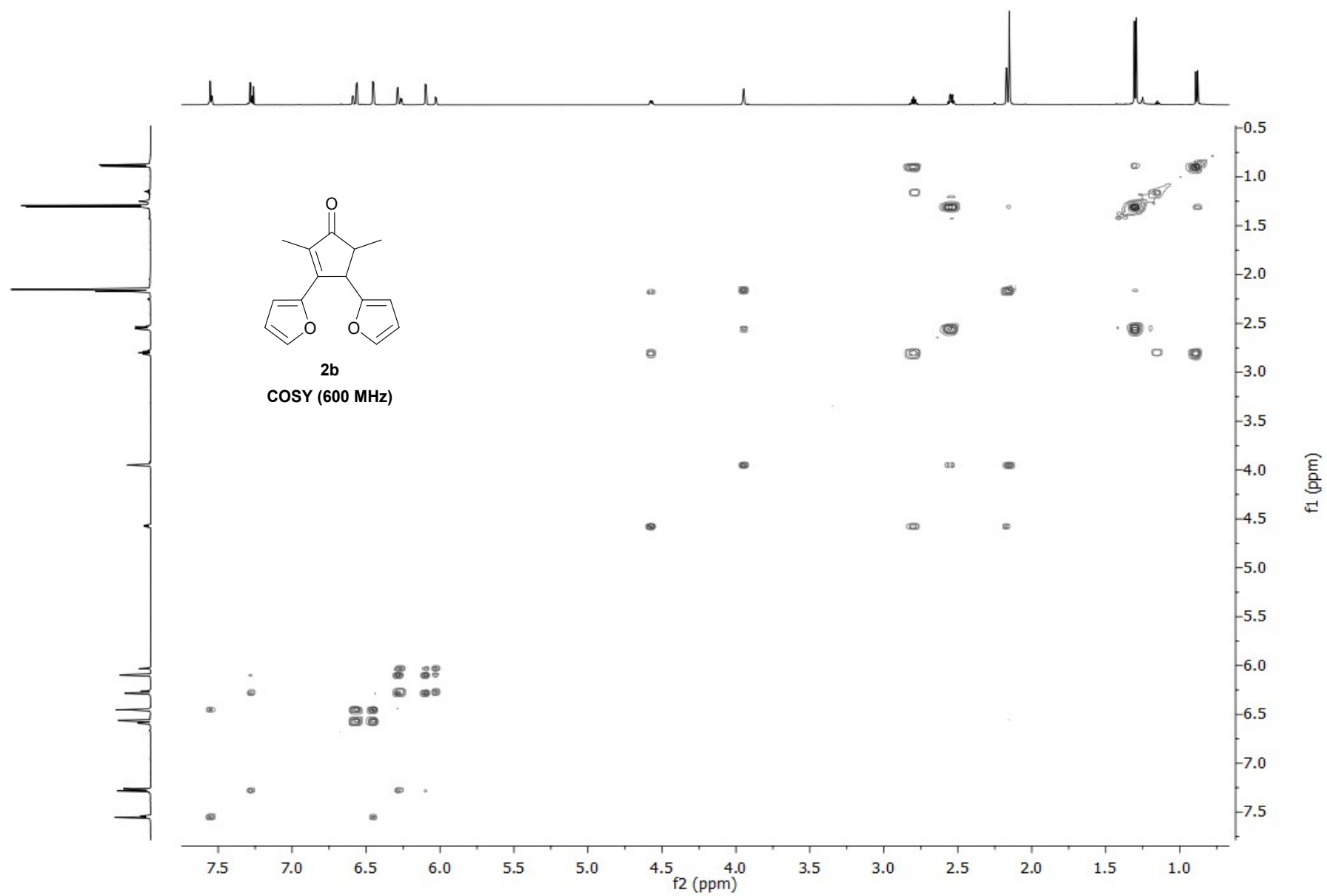


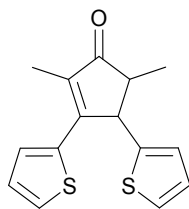


2b

¹³C (150 MHz)

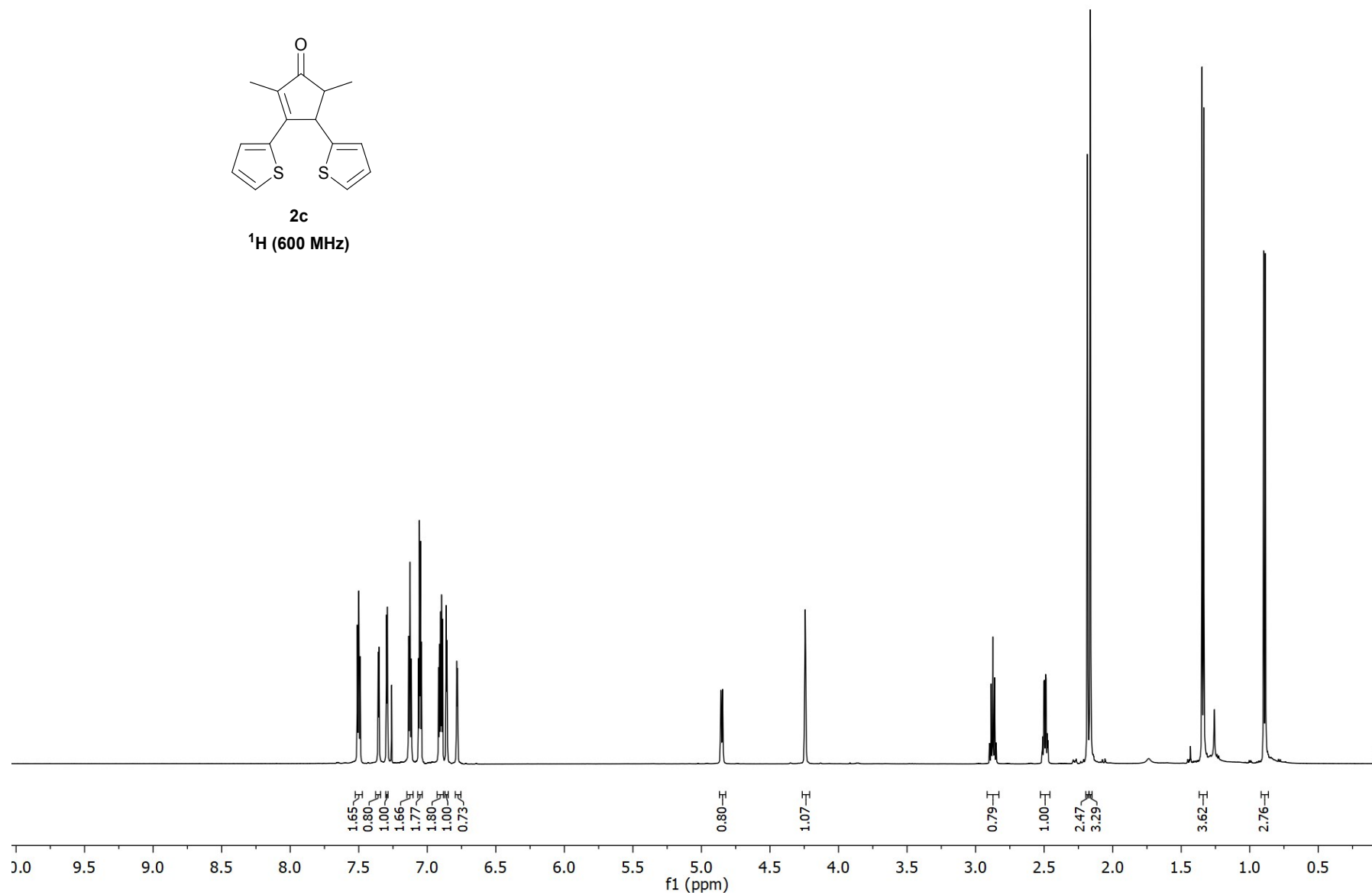


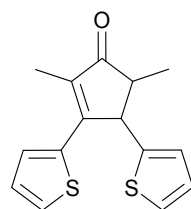




2c

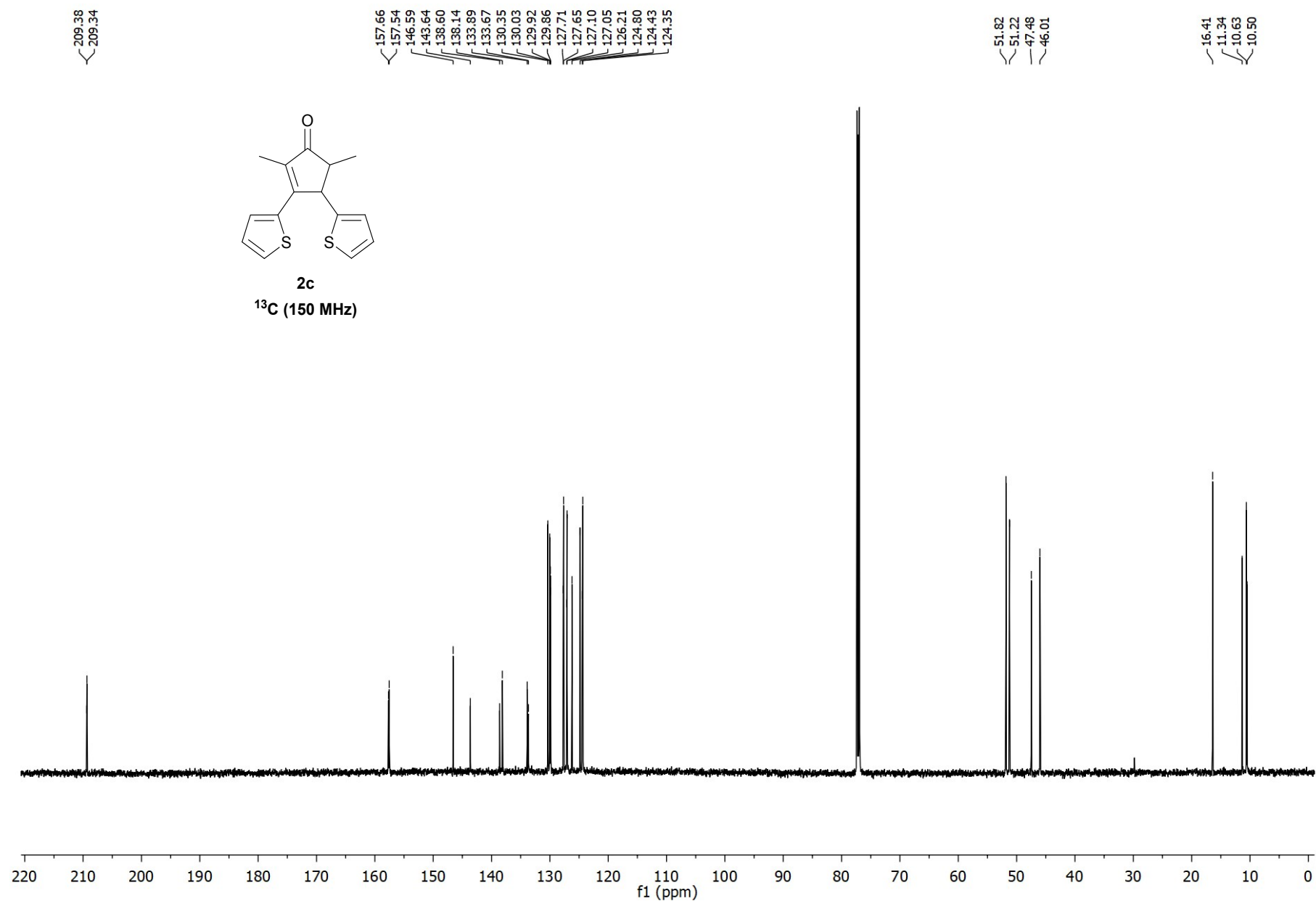
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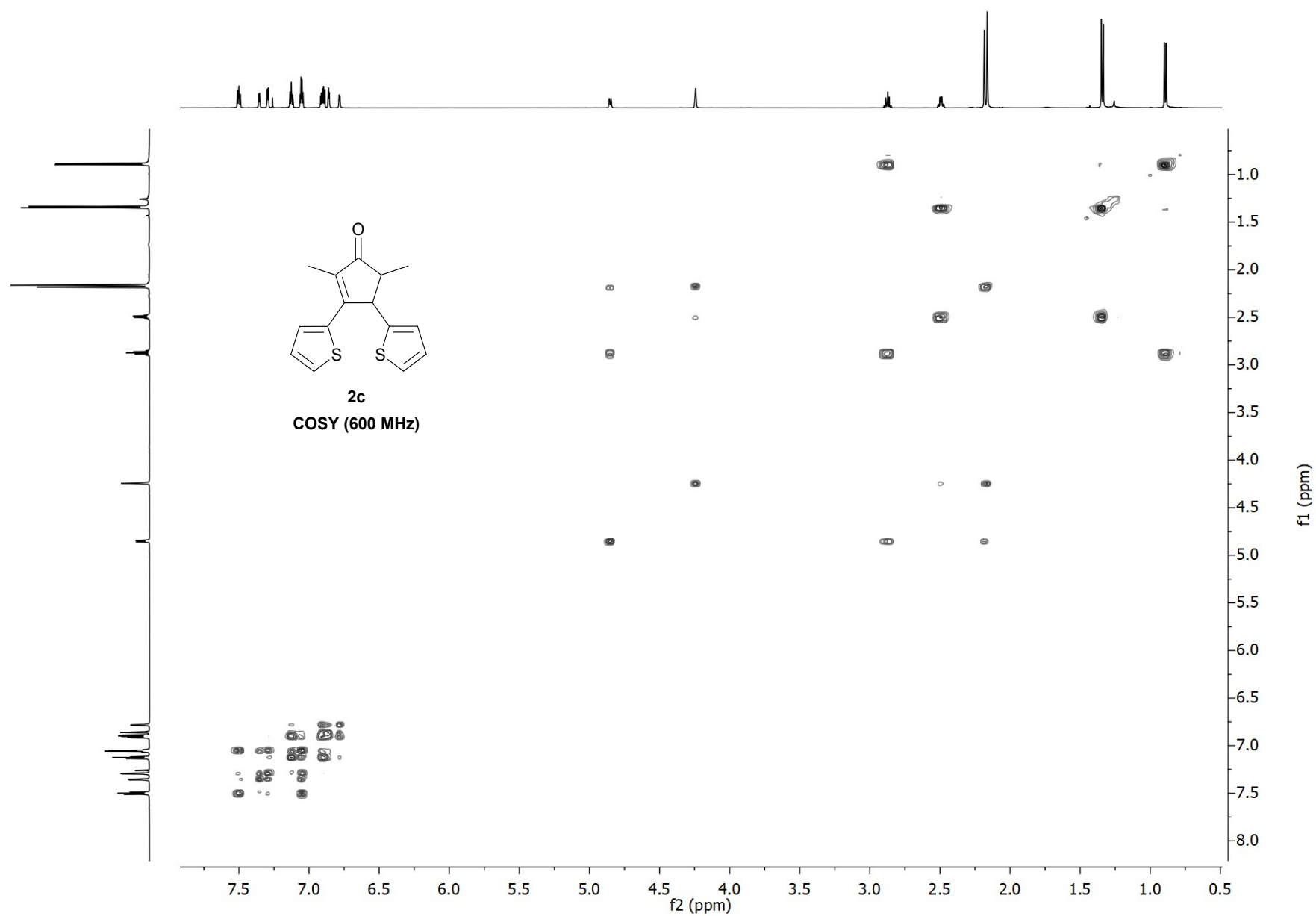




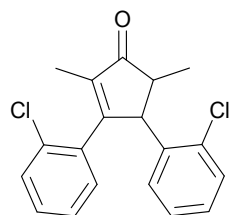
2c

¹³C (150 MHz)



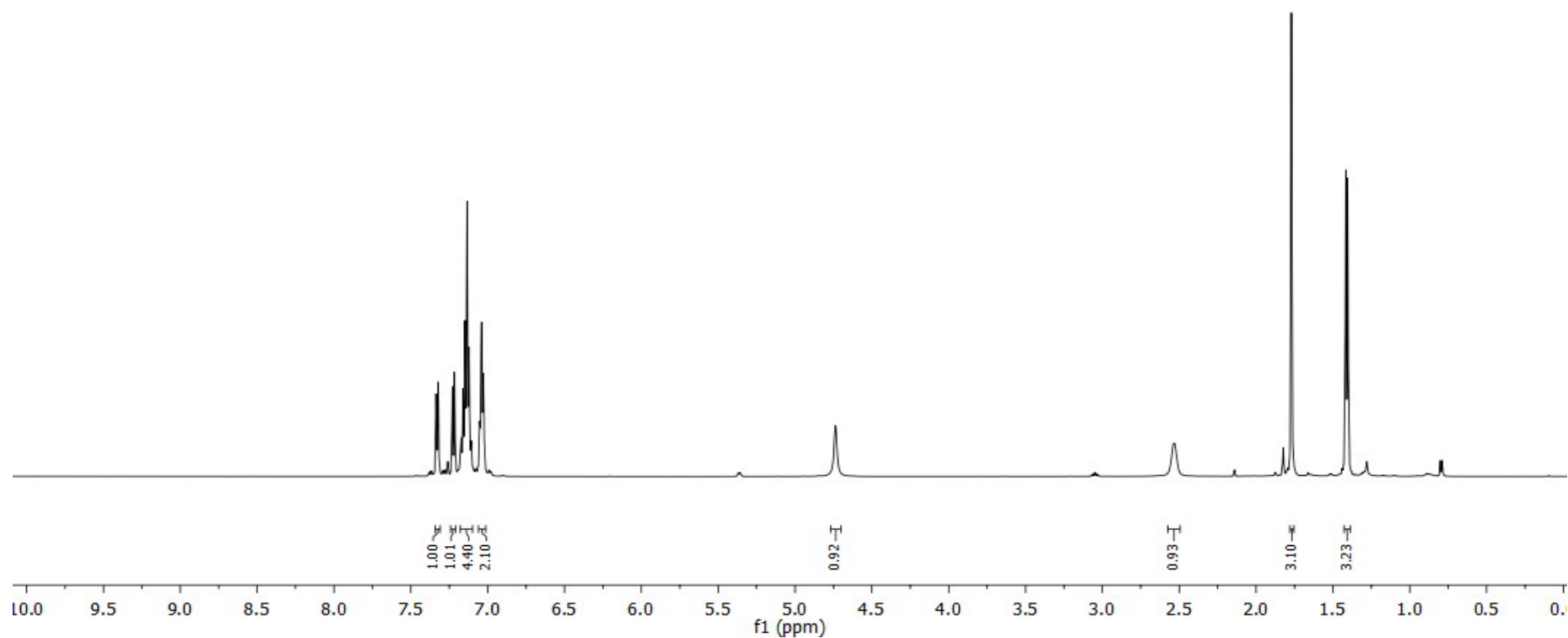


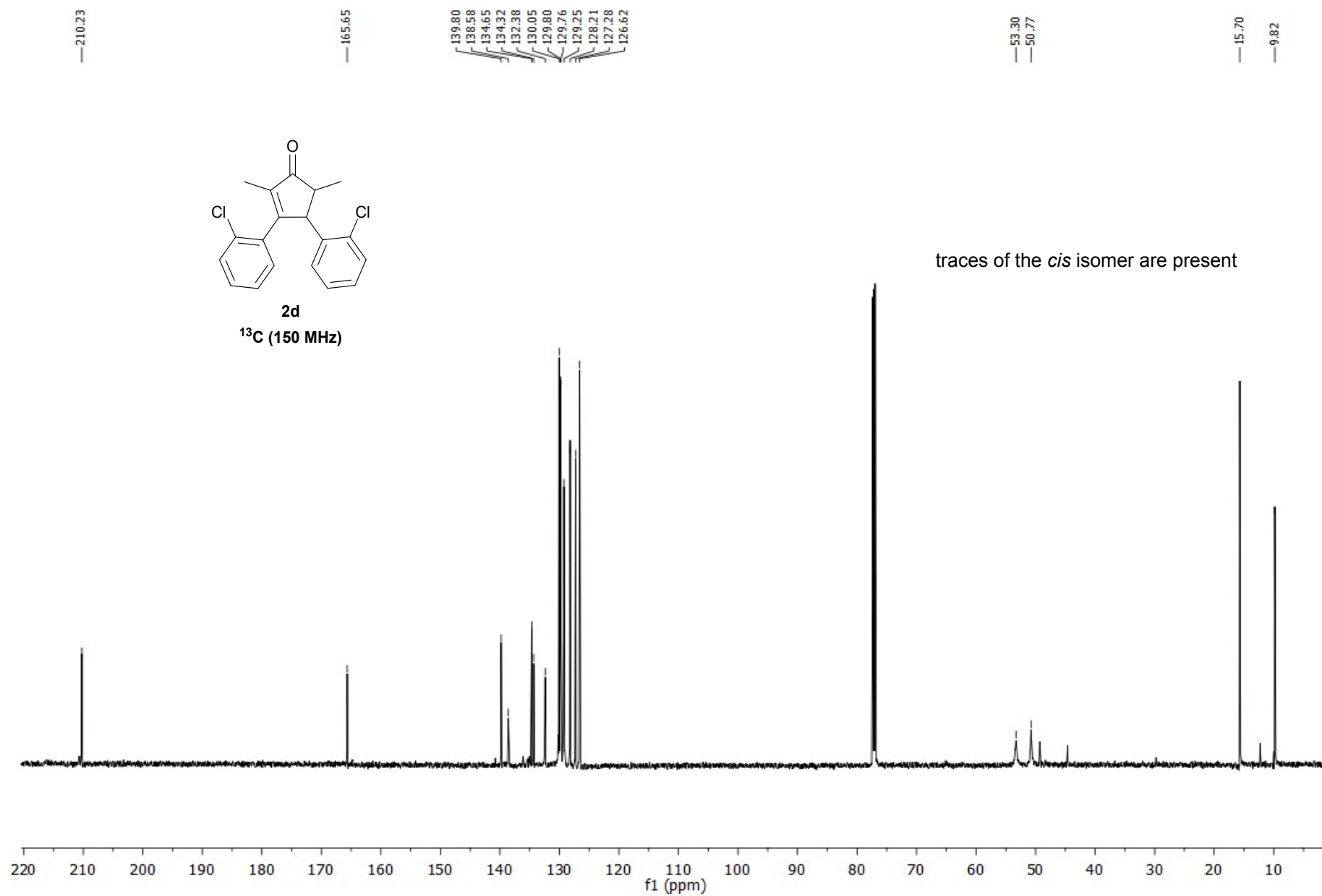
S24

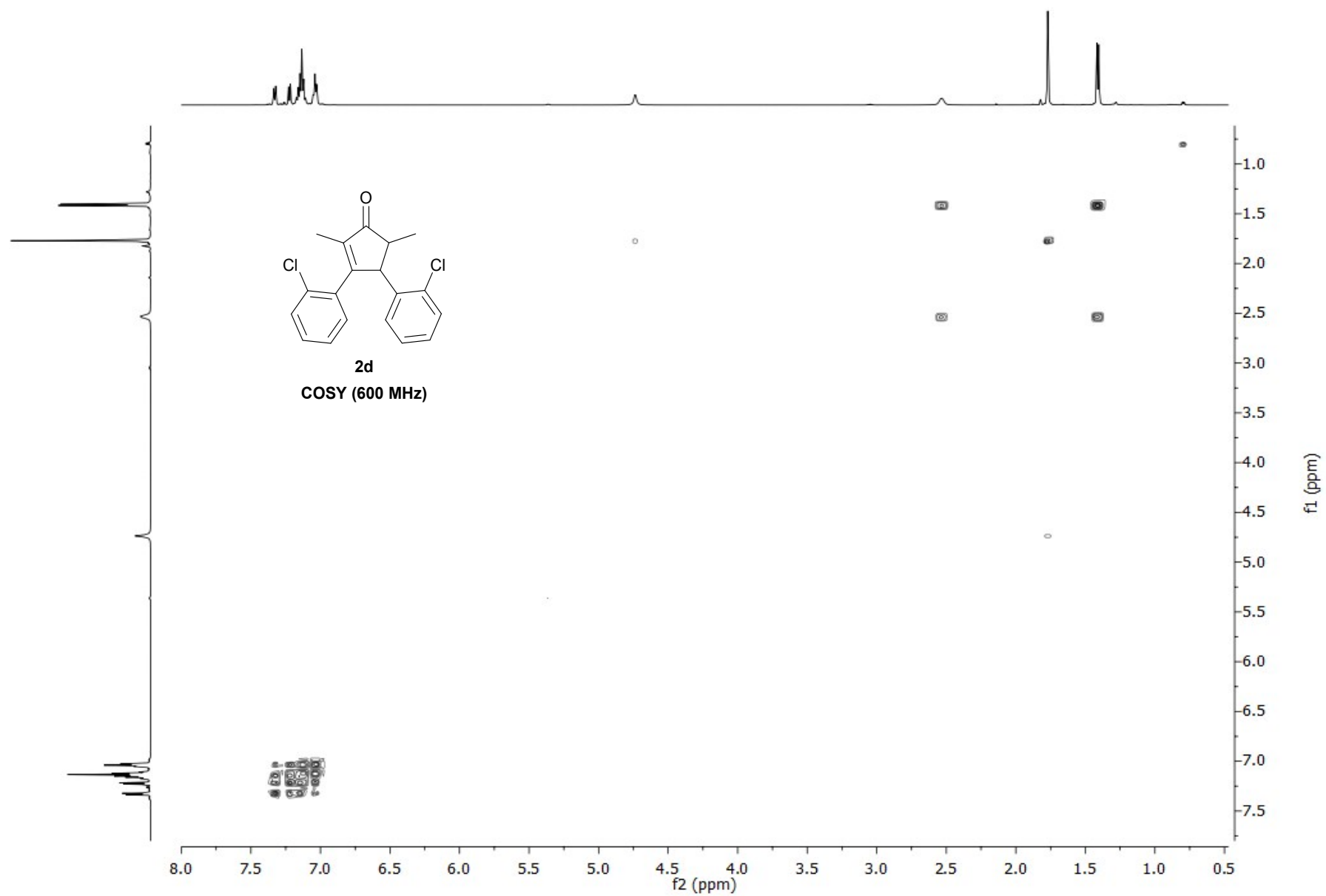


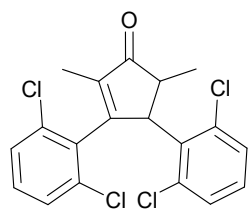
2d
¹H (600 MHz)

traces of the *cis* isomer are present





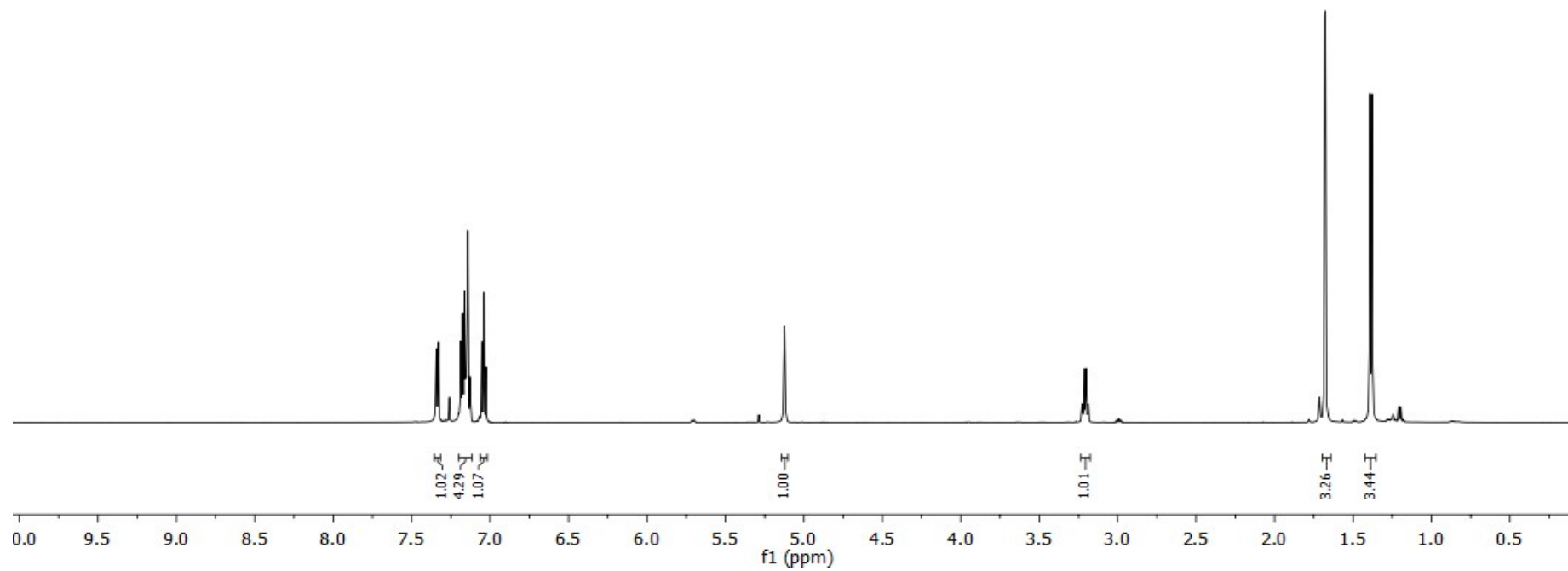


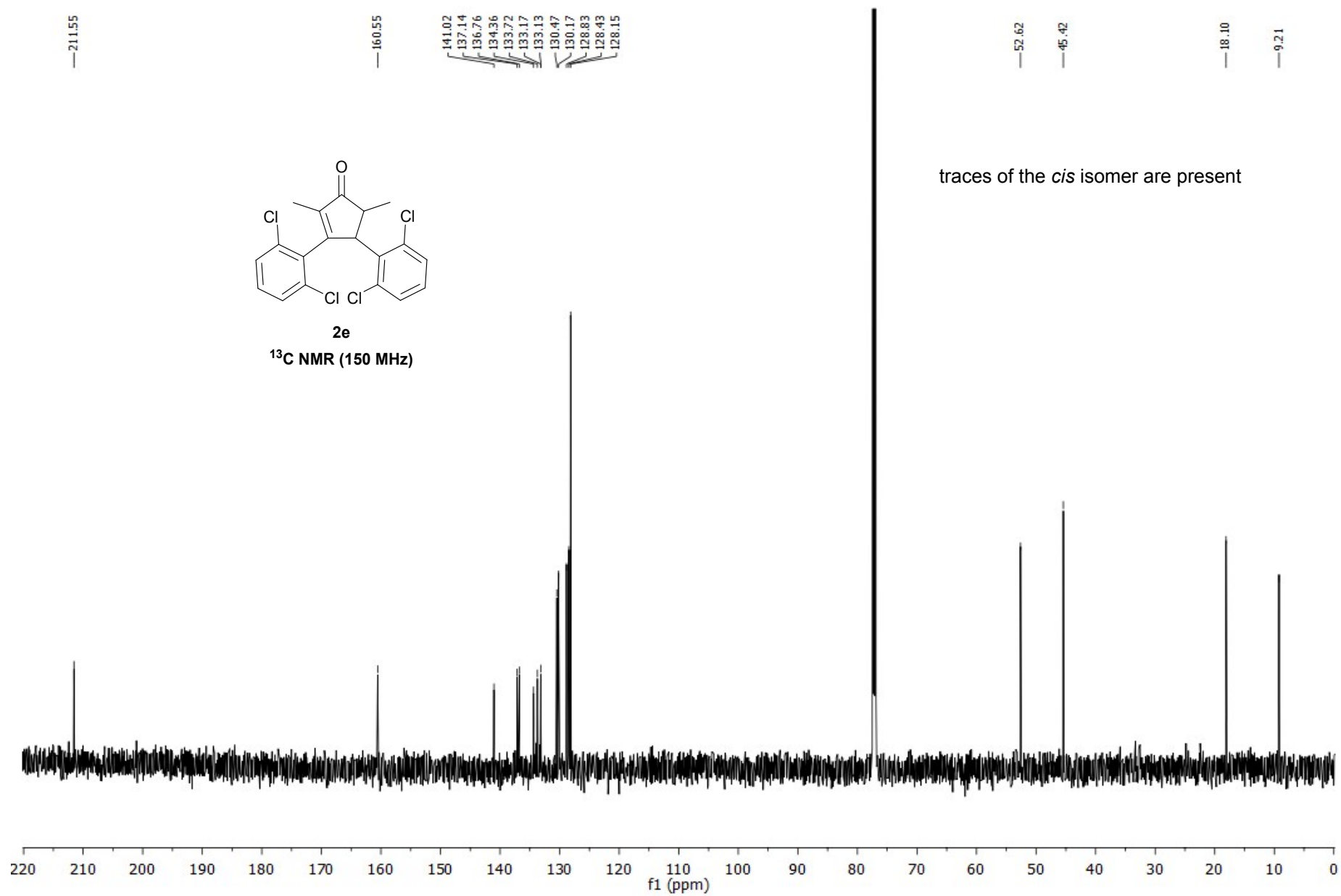


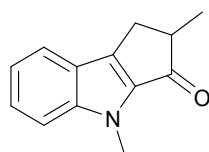
2e

¹H NMR (600 MHz)

traces of the *cis* isomer are present

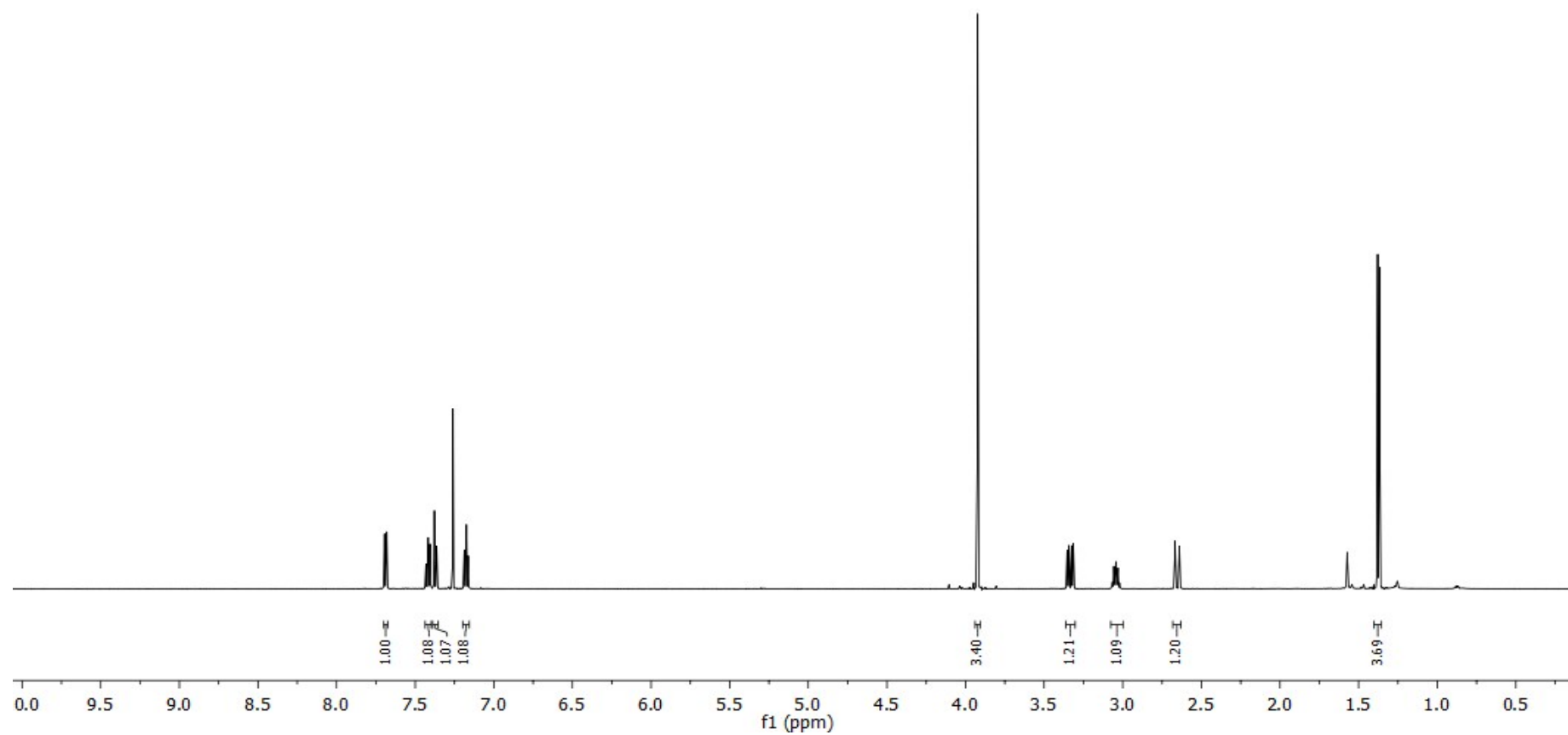


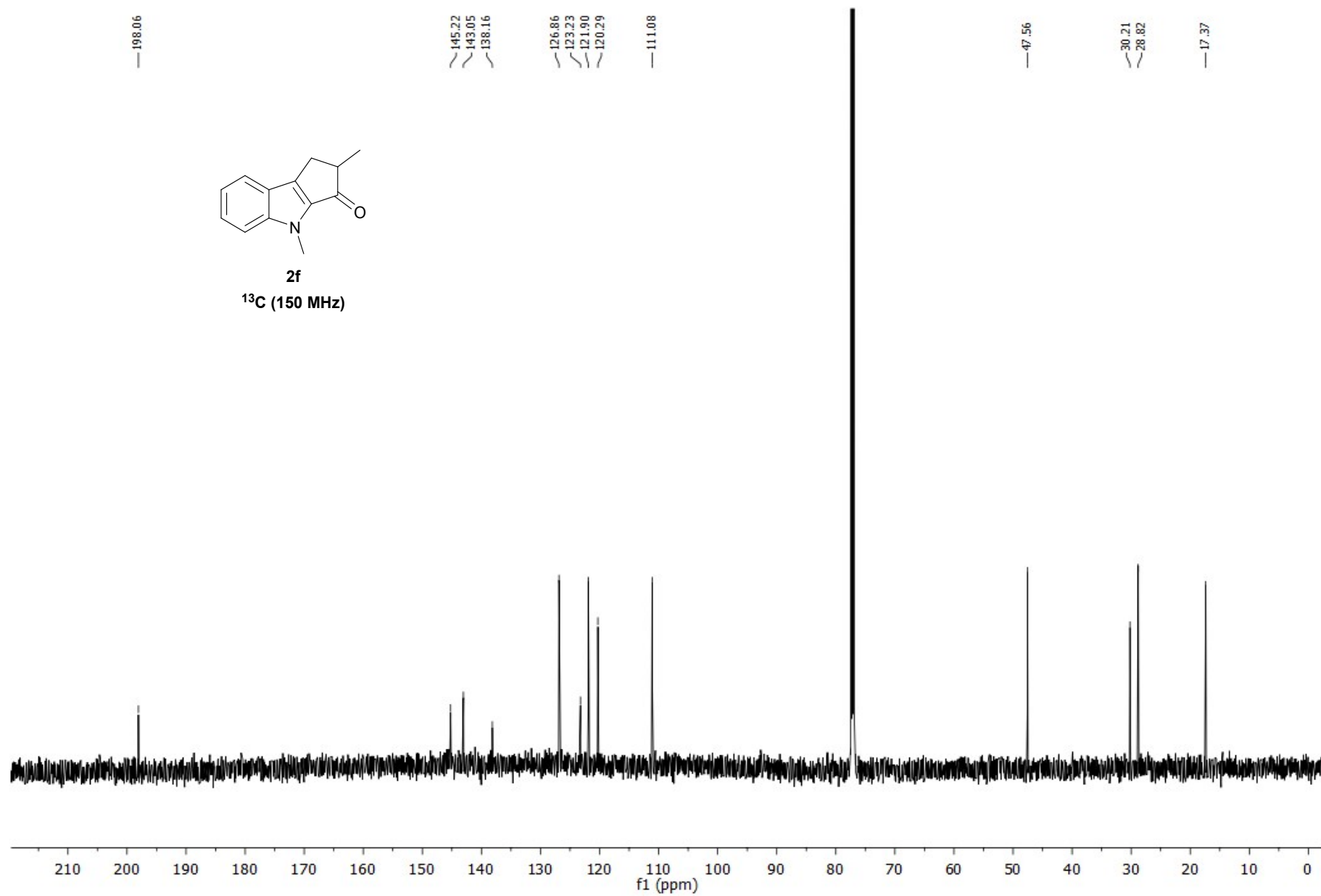


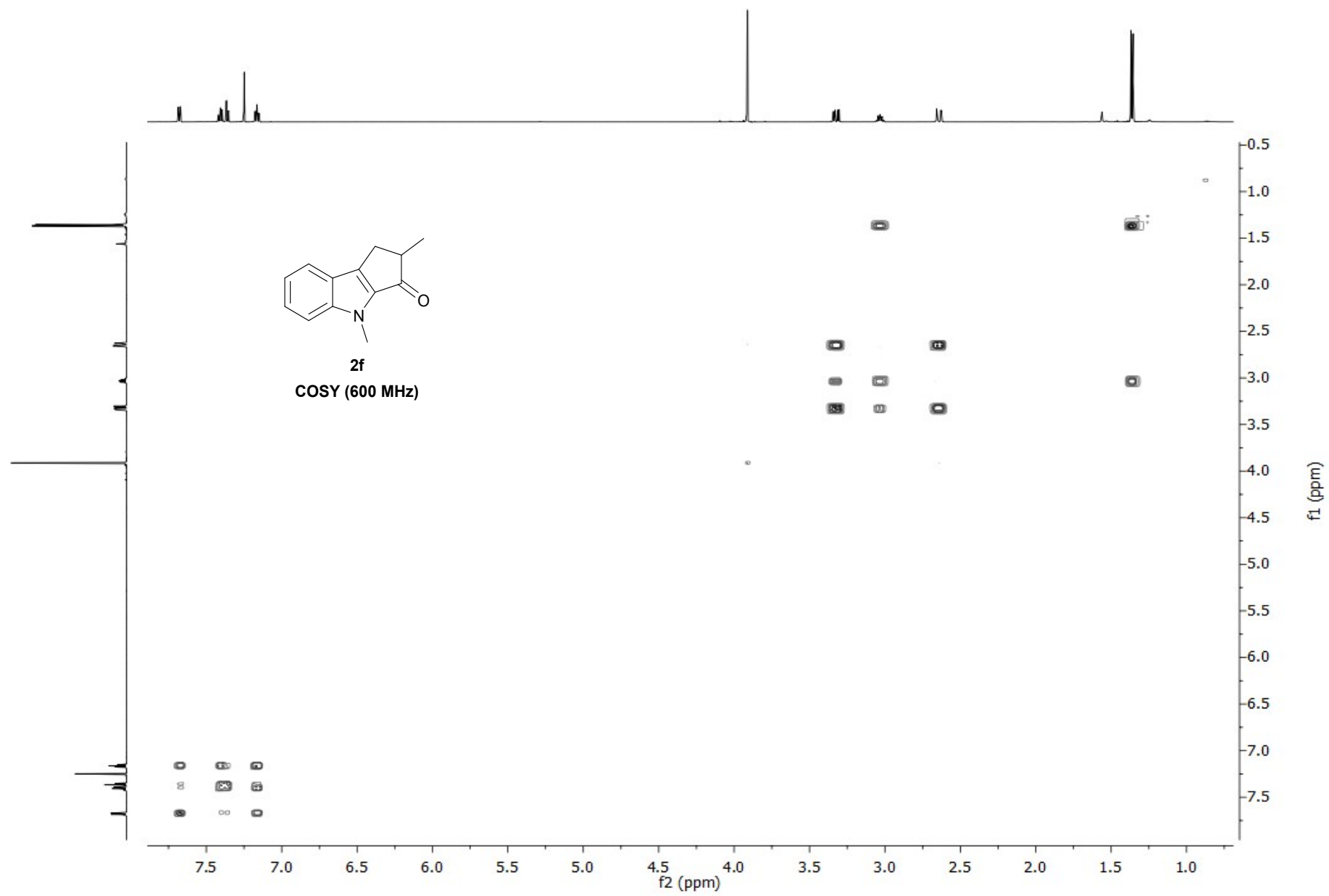


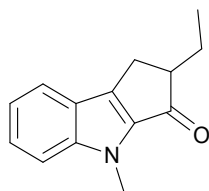
2f

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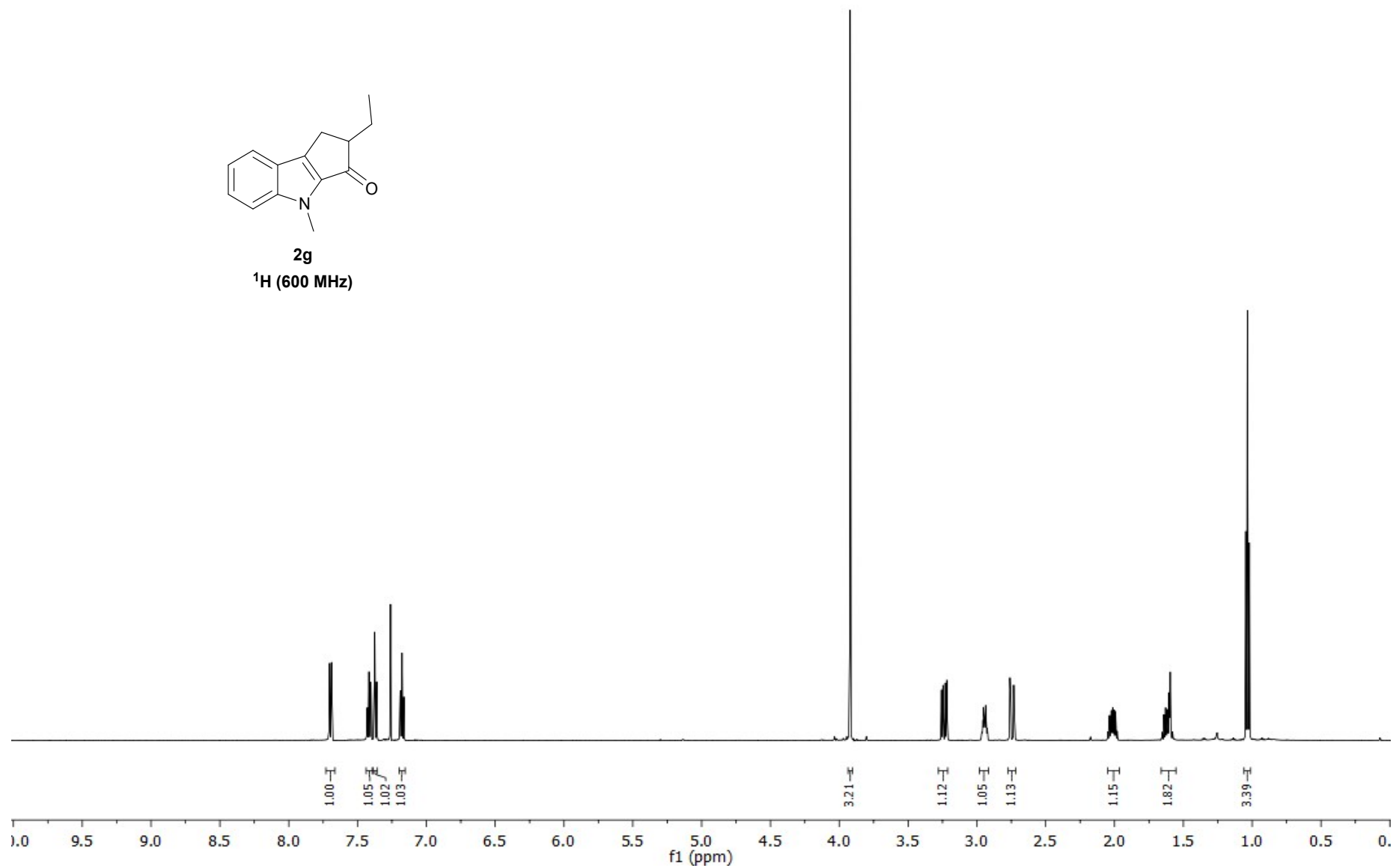


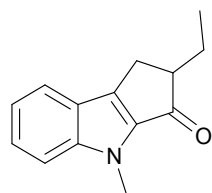






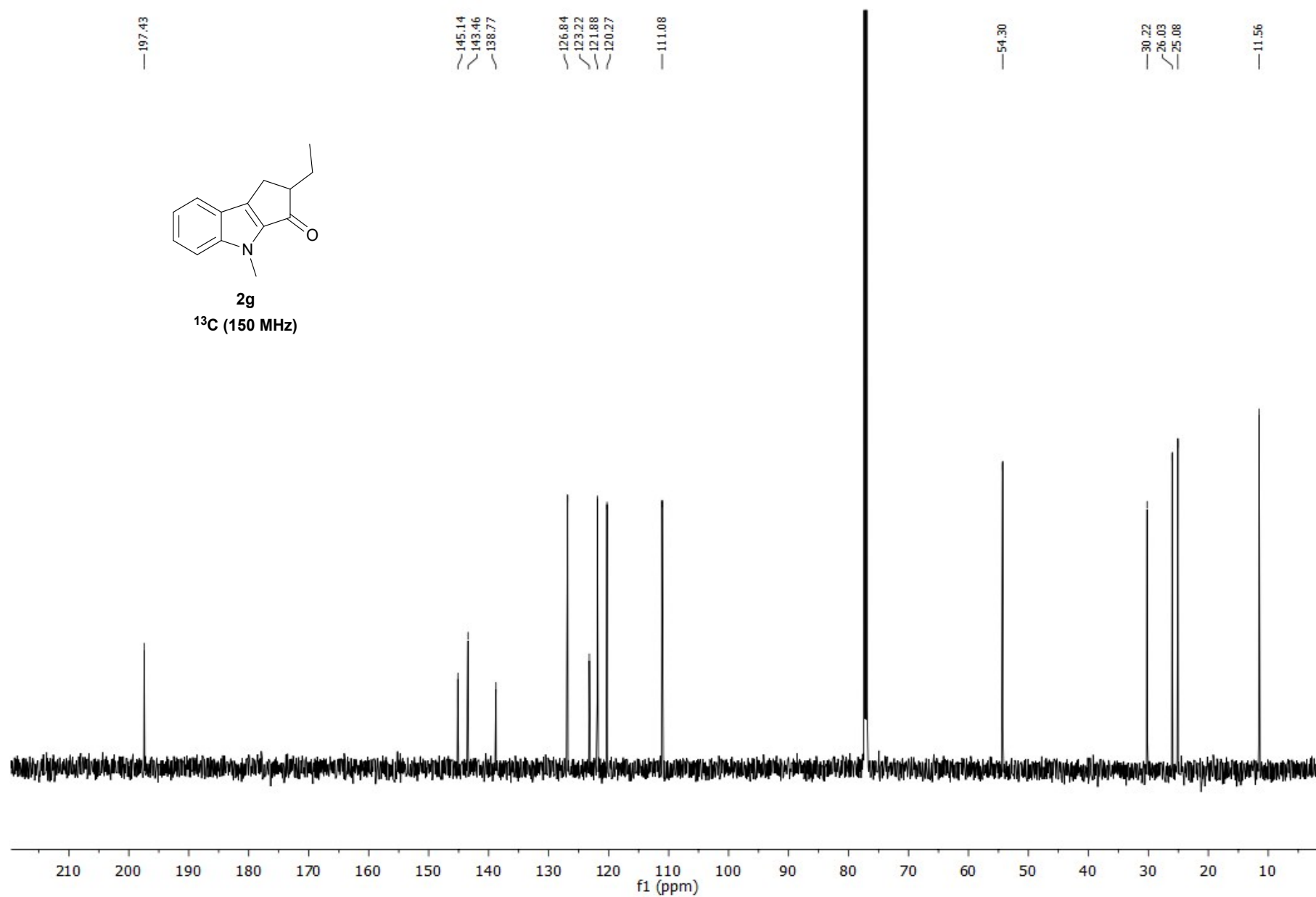
2g
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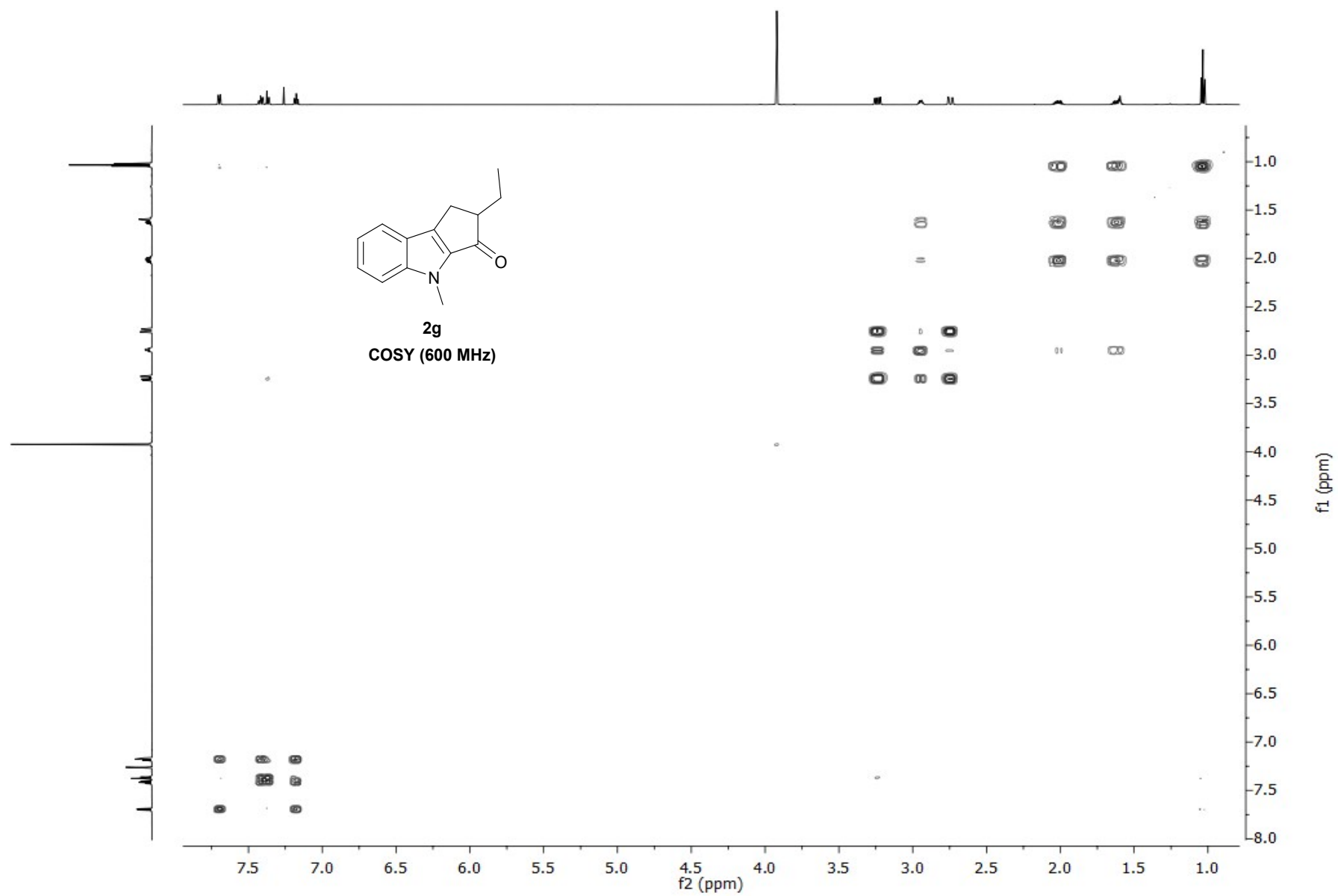


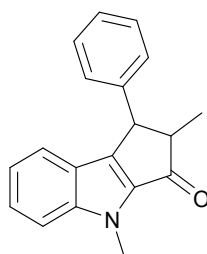


2g

¹³C (150 MHz)

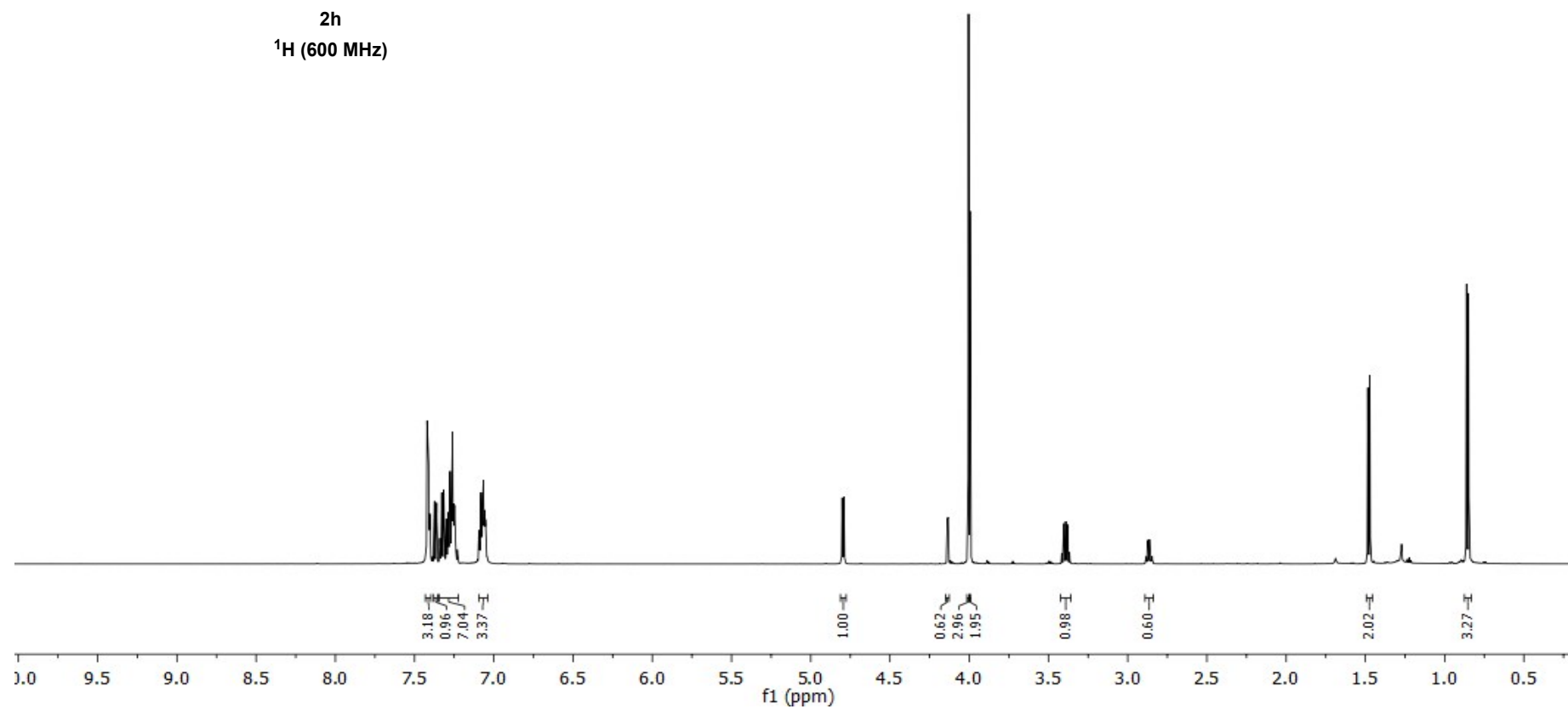




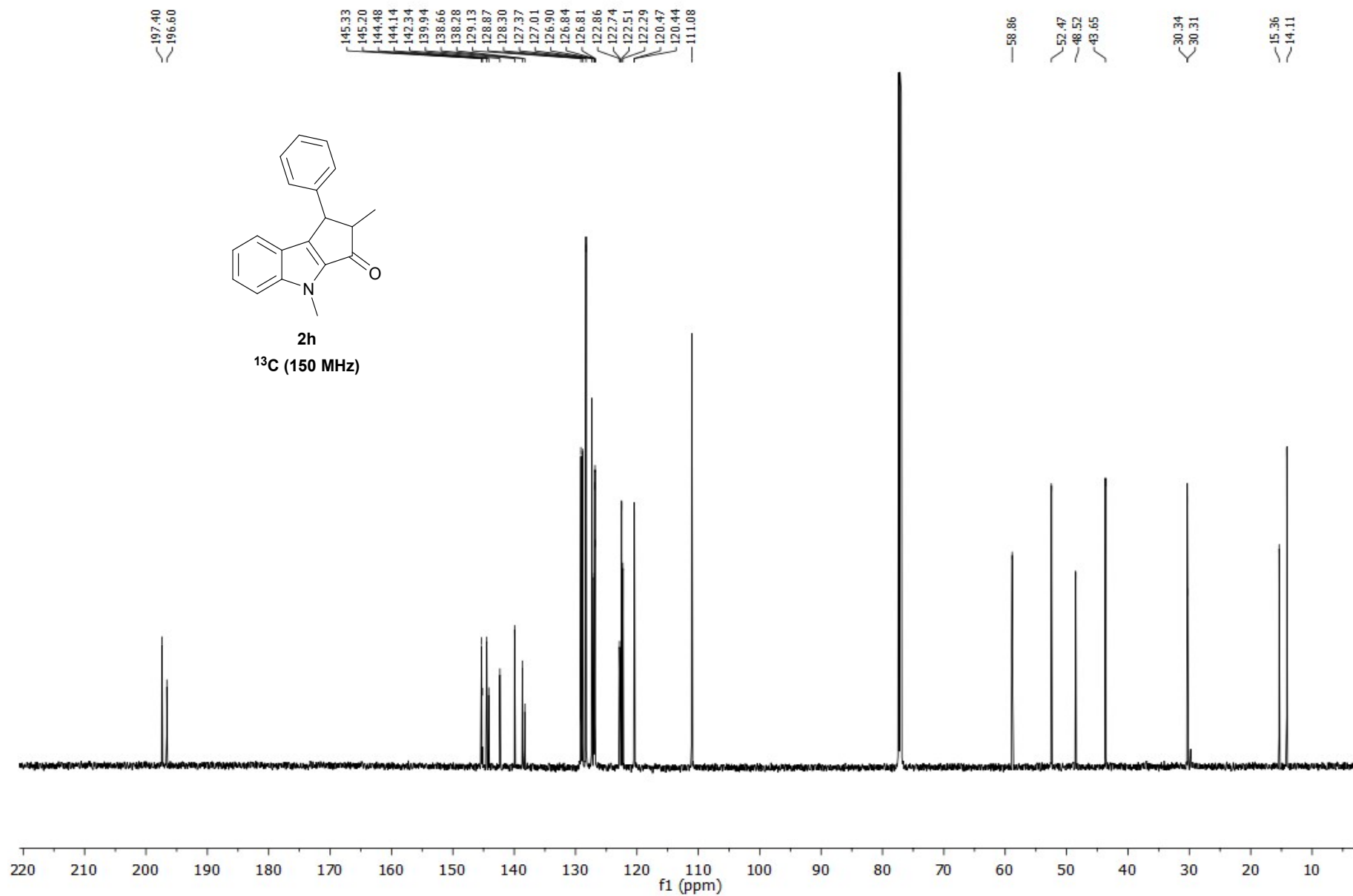


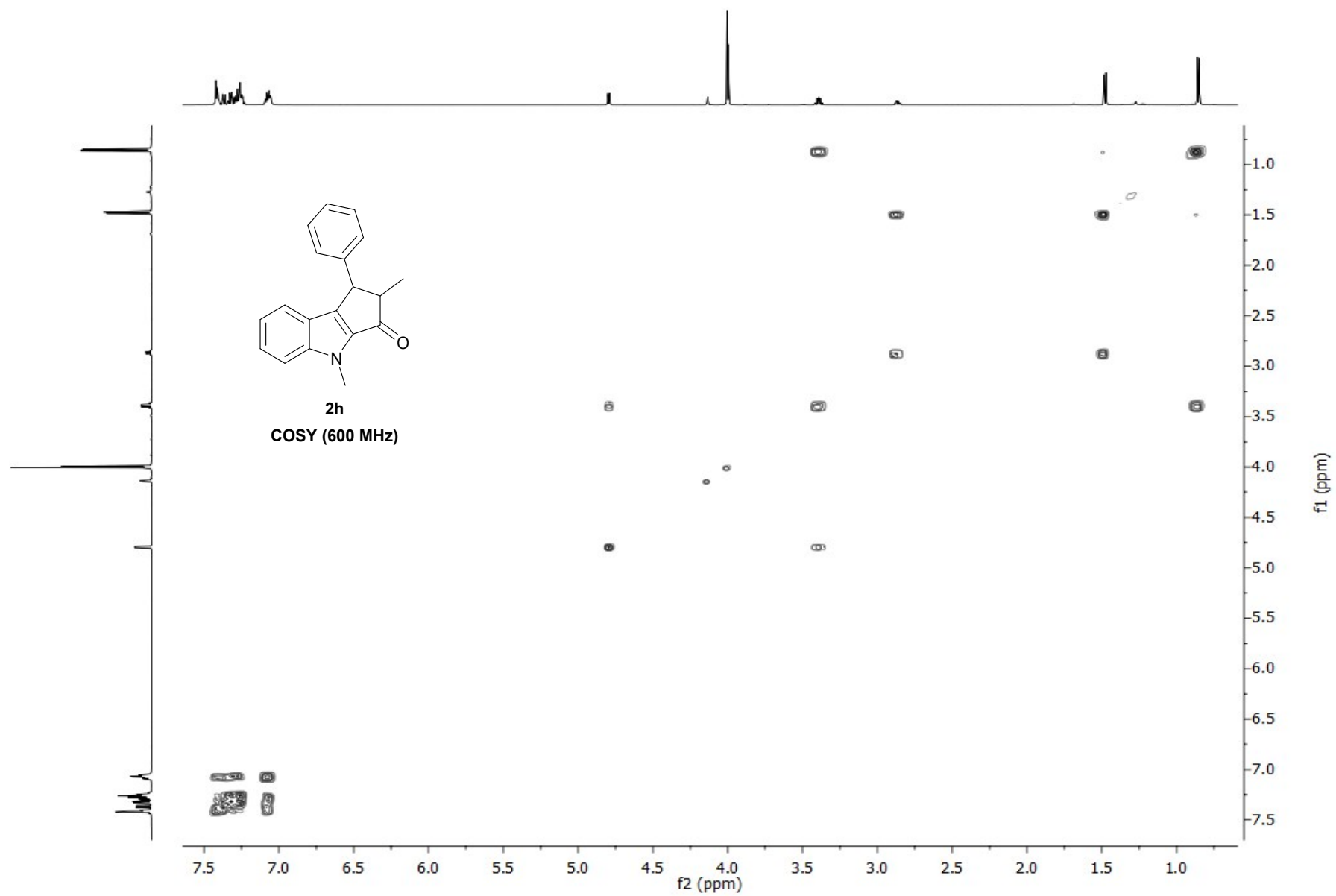
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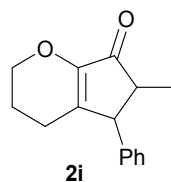
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S37

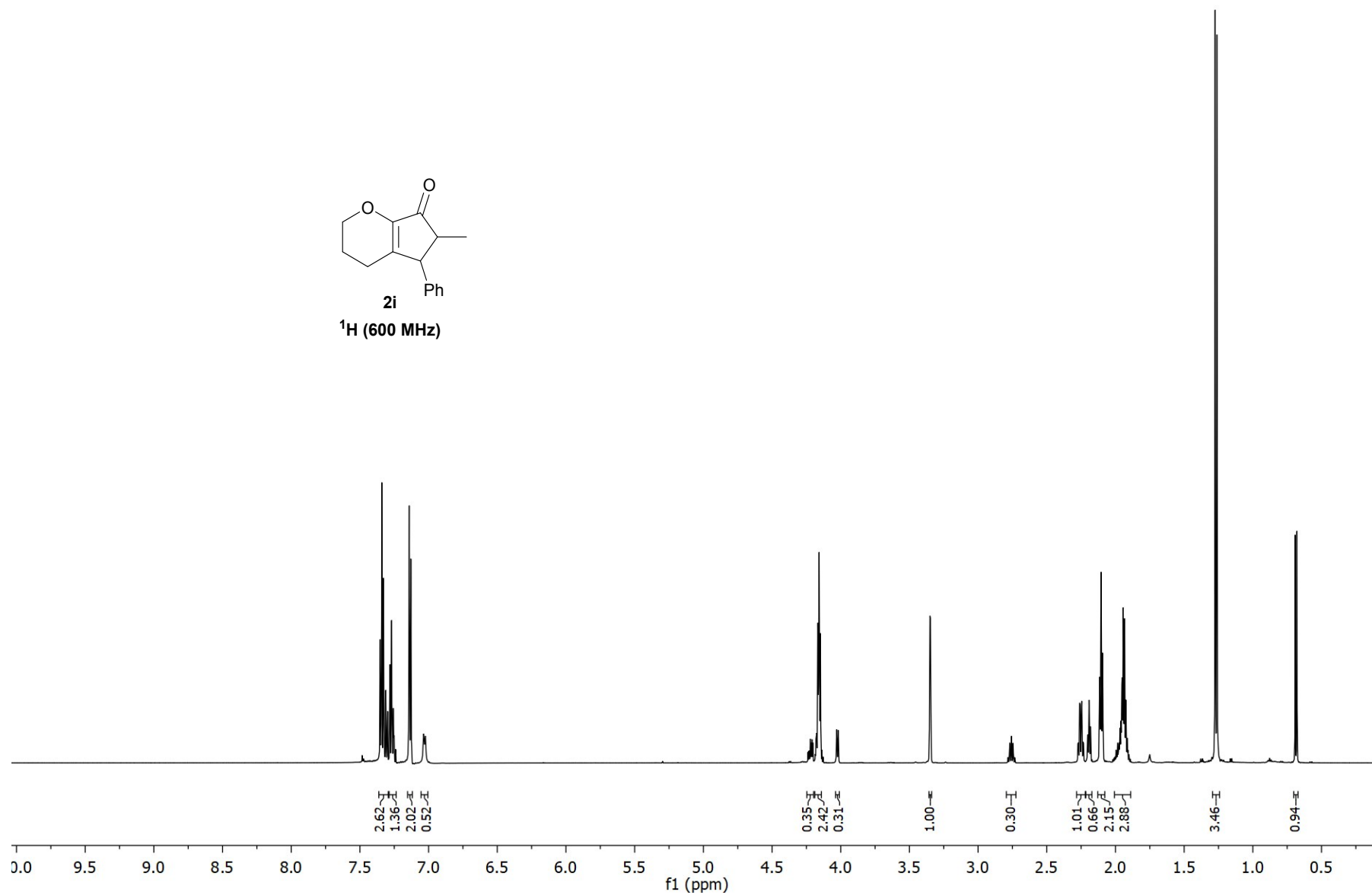




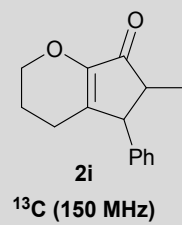


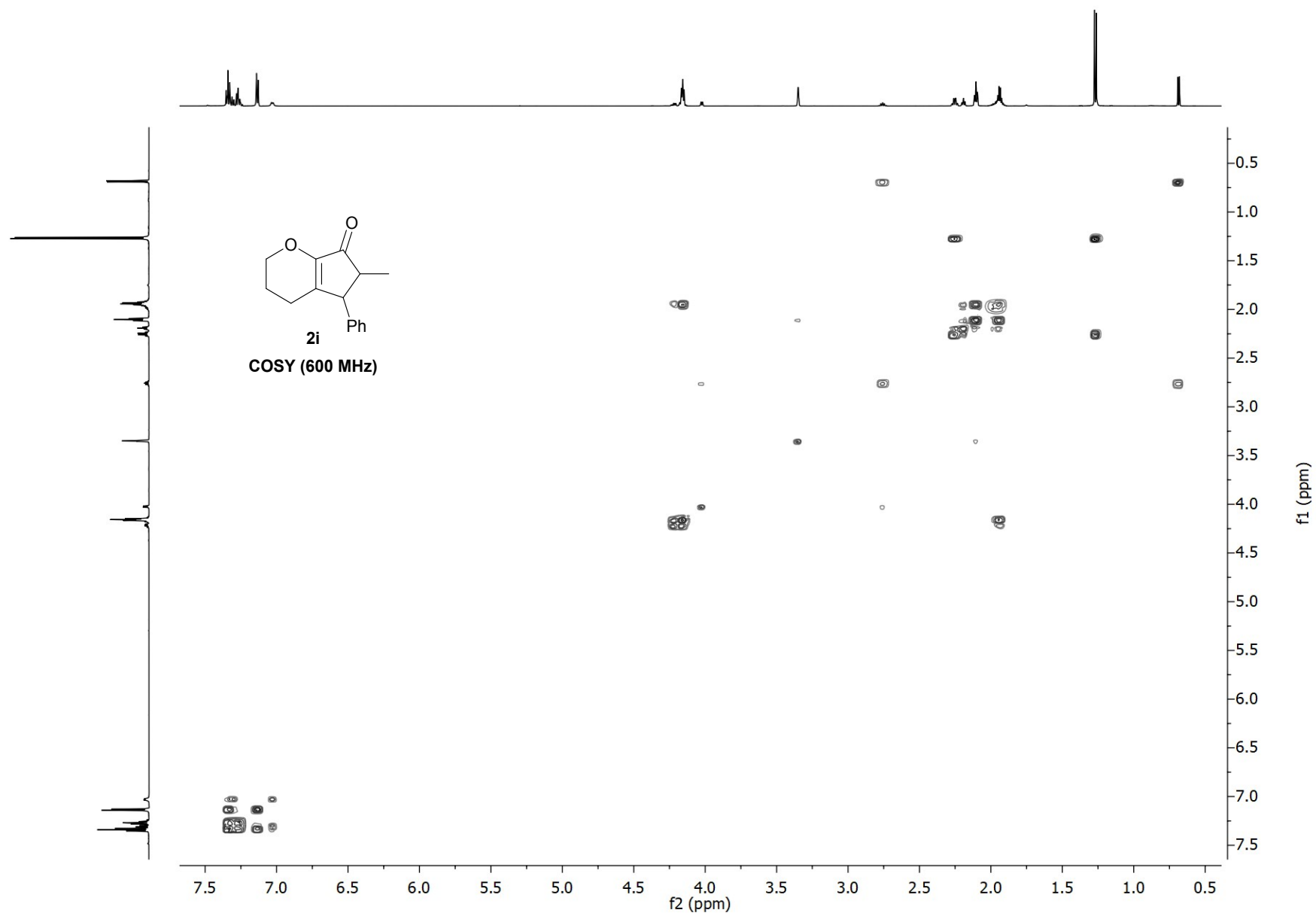
2i

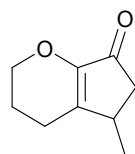
¹H (600 MHz)



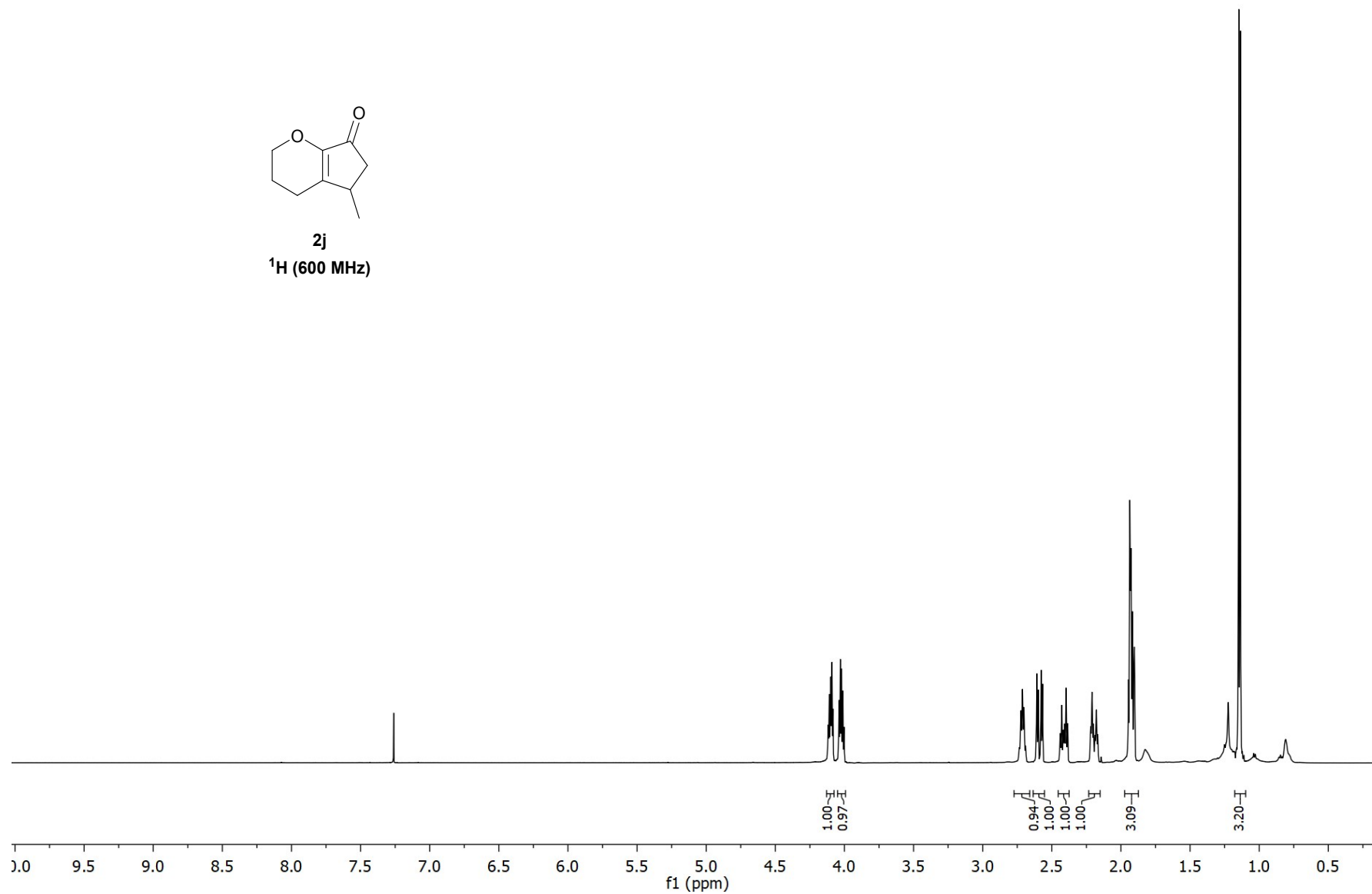
S40

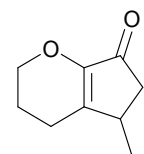




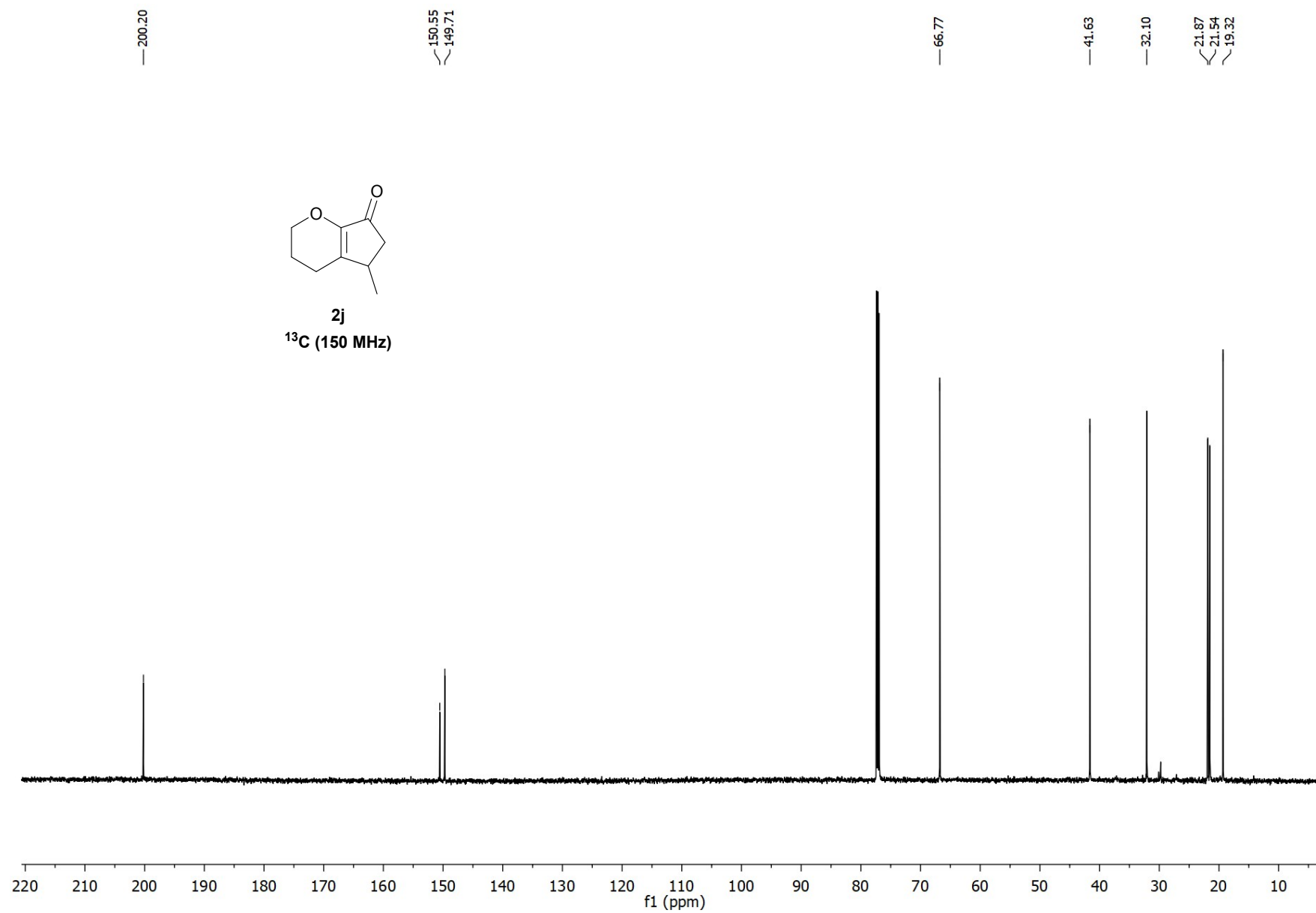


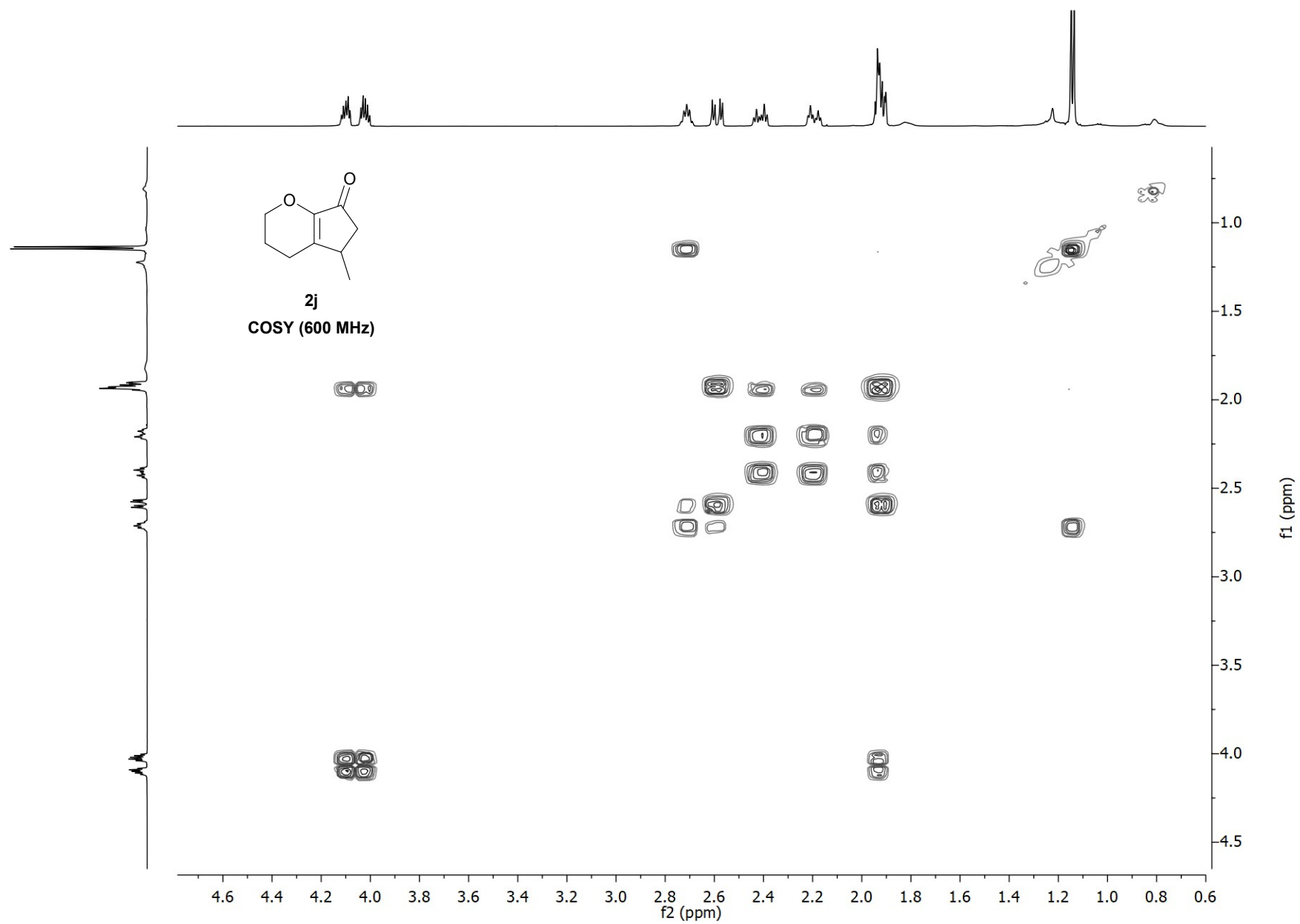
2j
¹H (600 MHz)



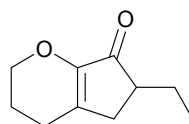


2j
¹³C (150 MHz)

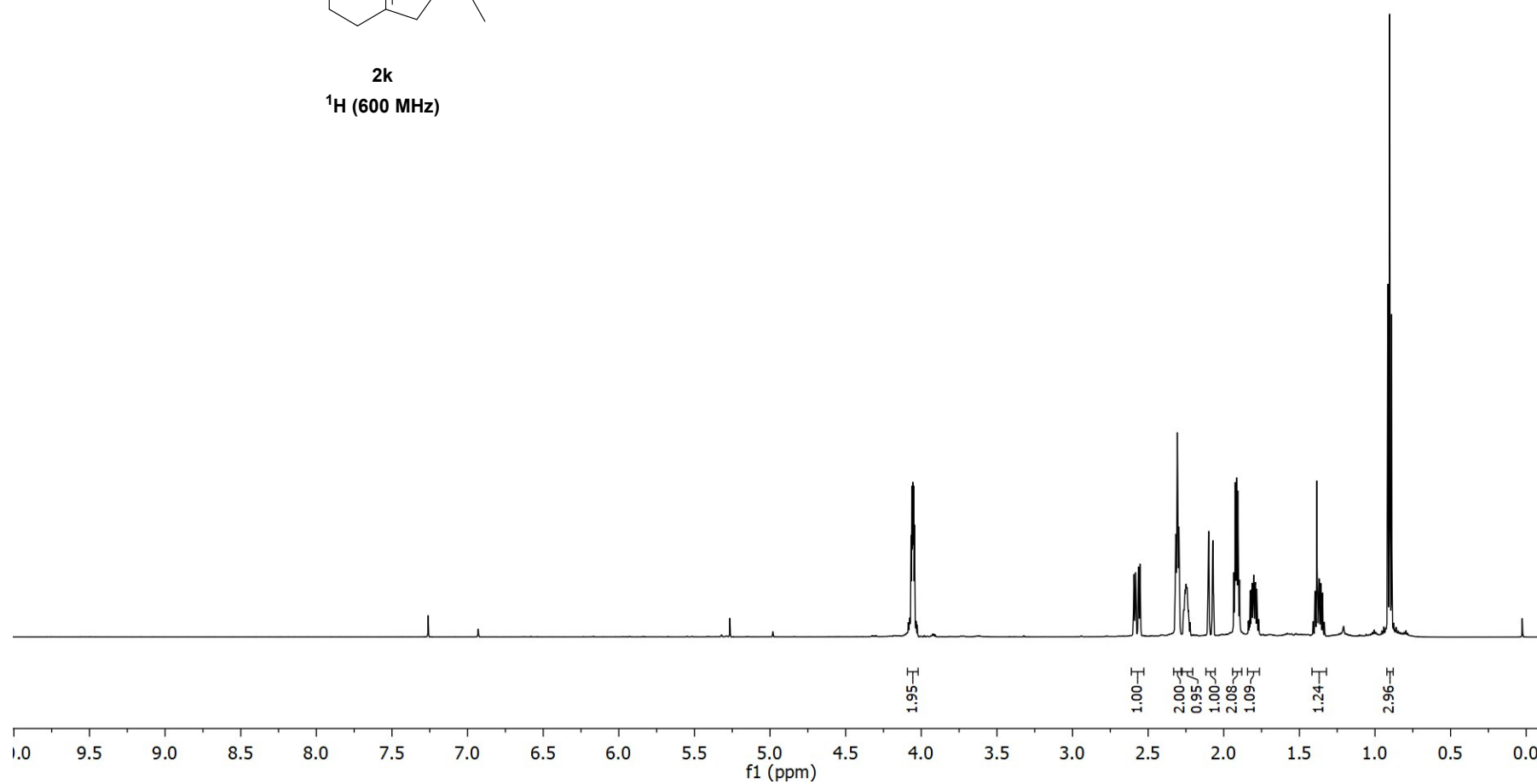


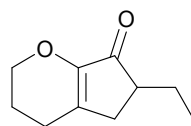


S45

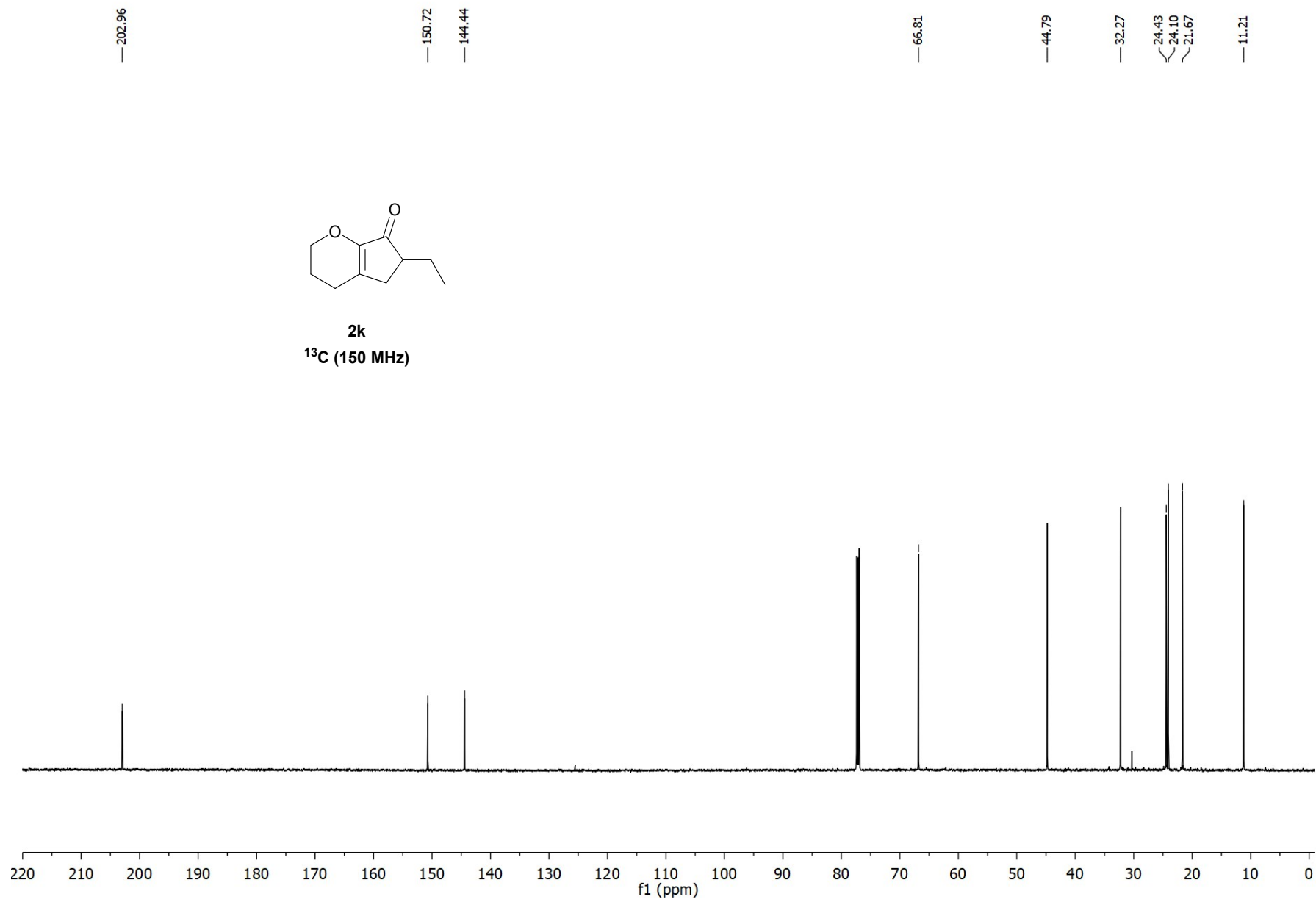


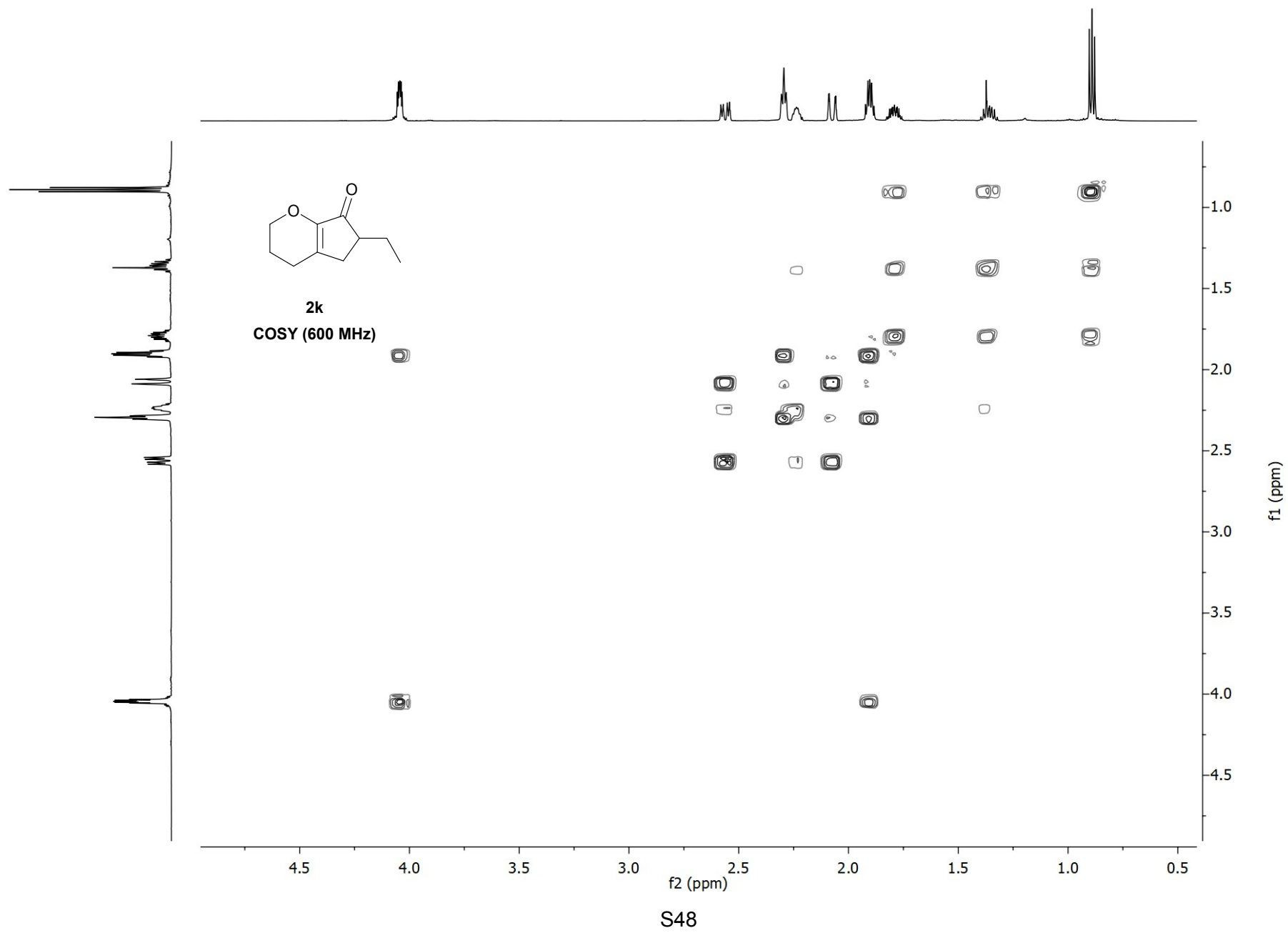
2k
¹H (600 MHz)

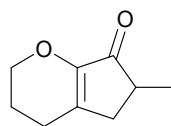




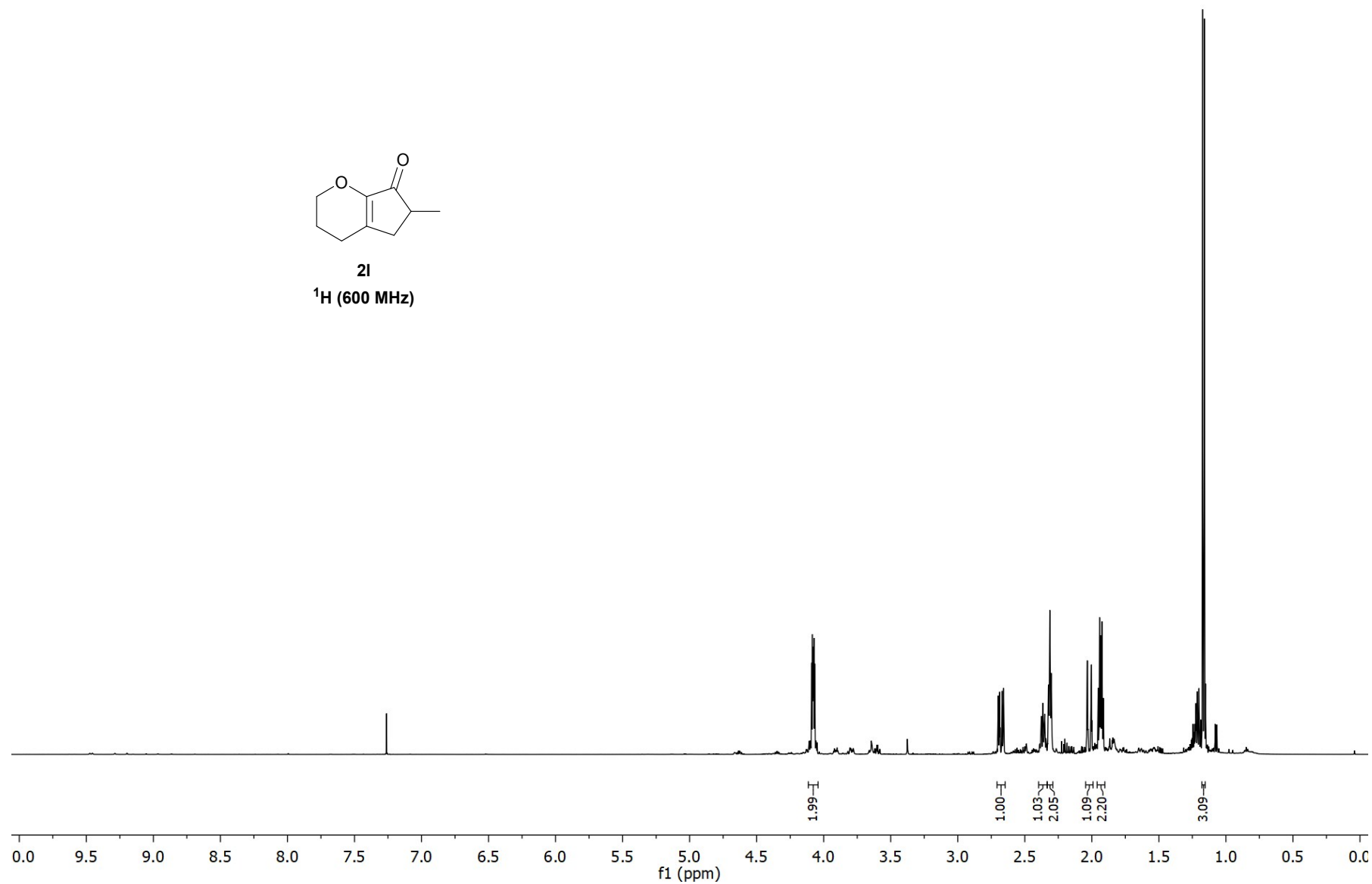
2k
¹³C (150 MHz)

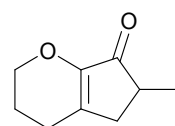




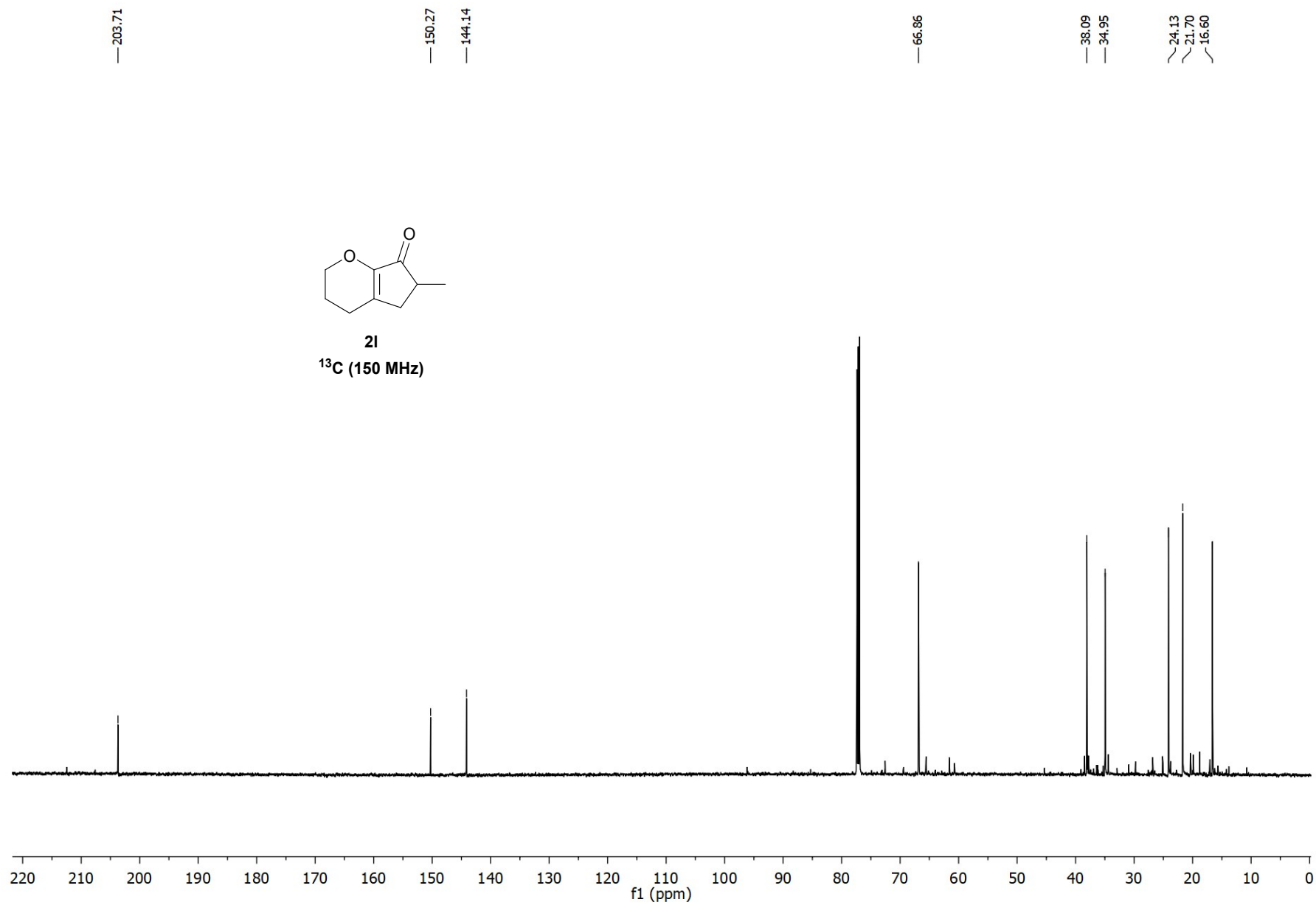


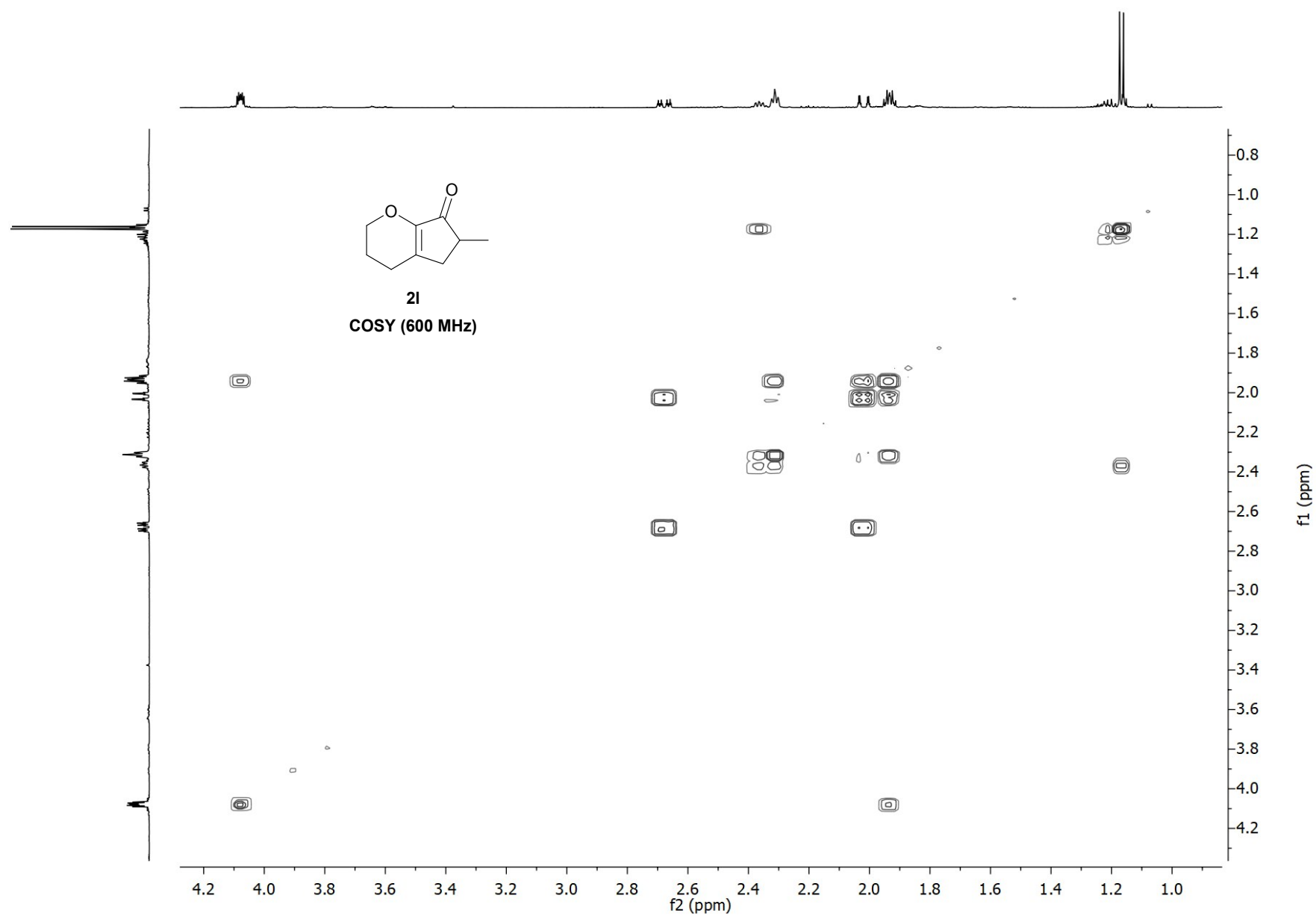
2l
¹H (600 MHz)



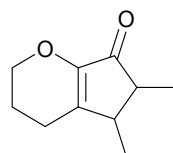


2l
¹³C (150 MHz)



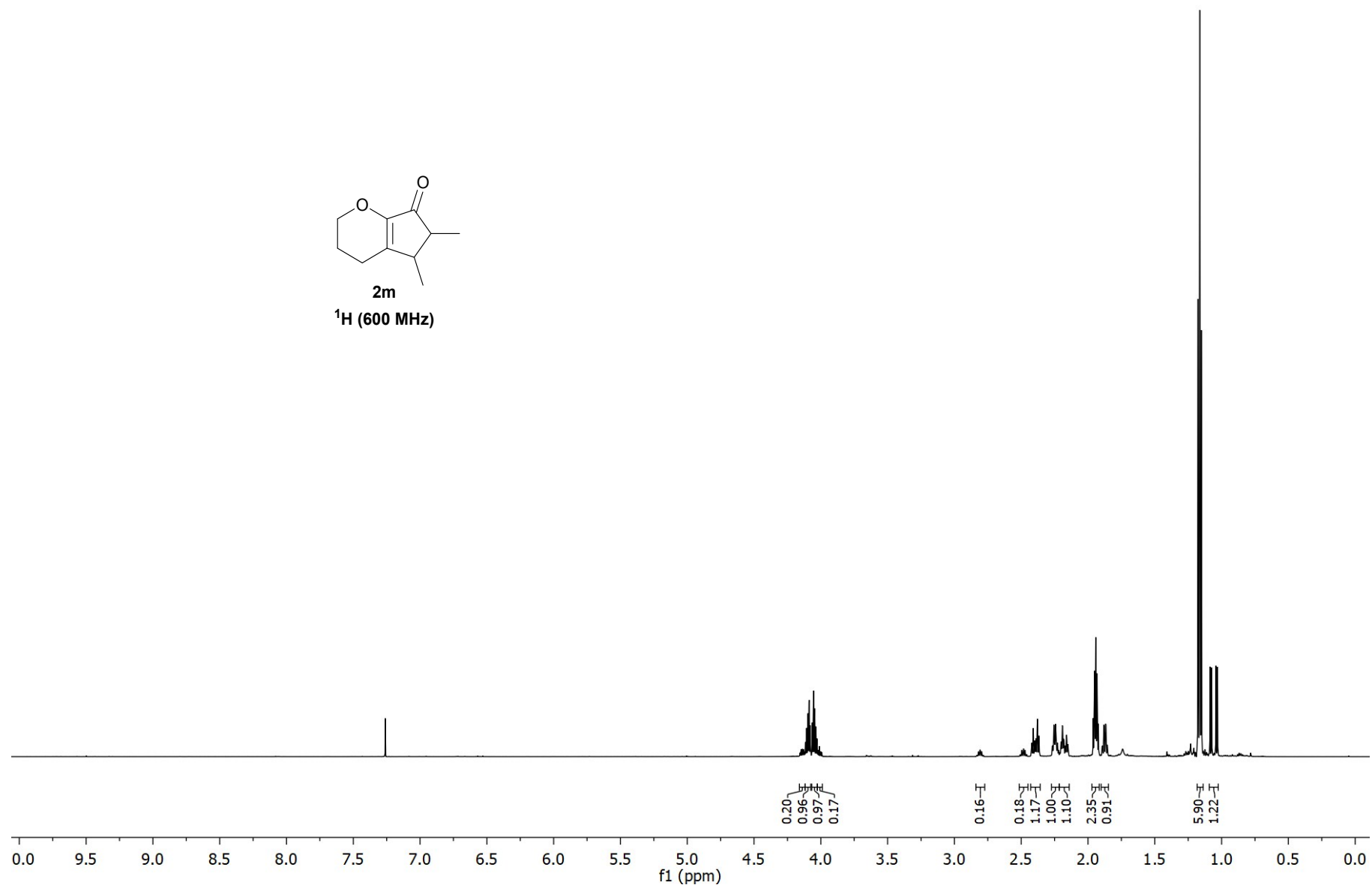


S51

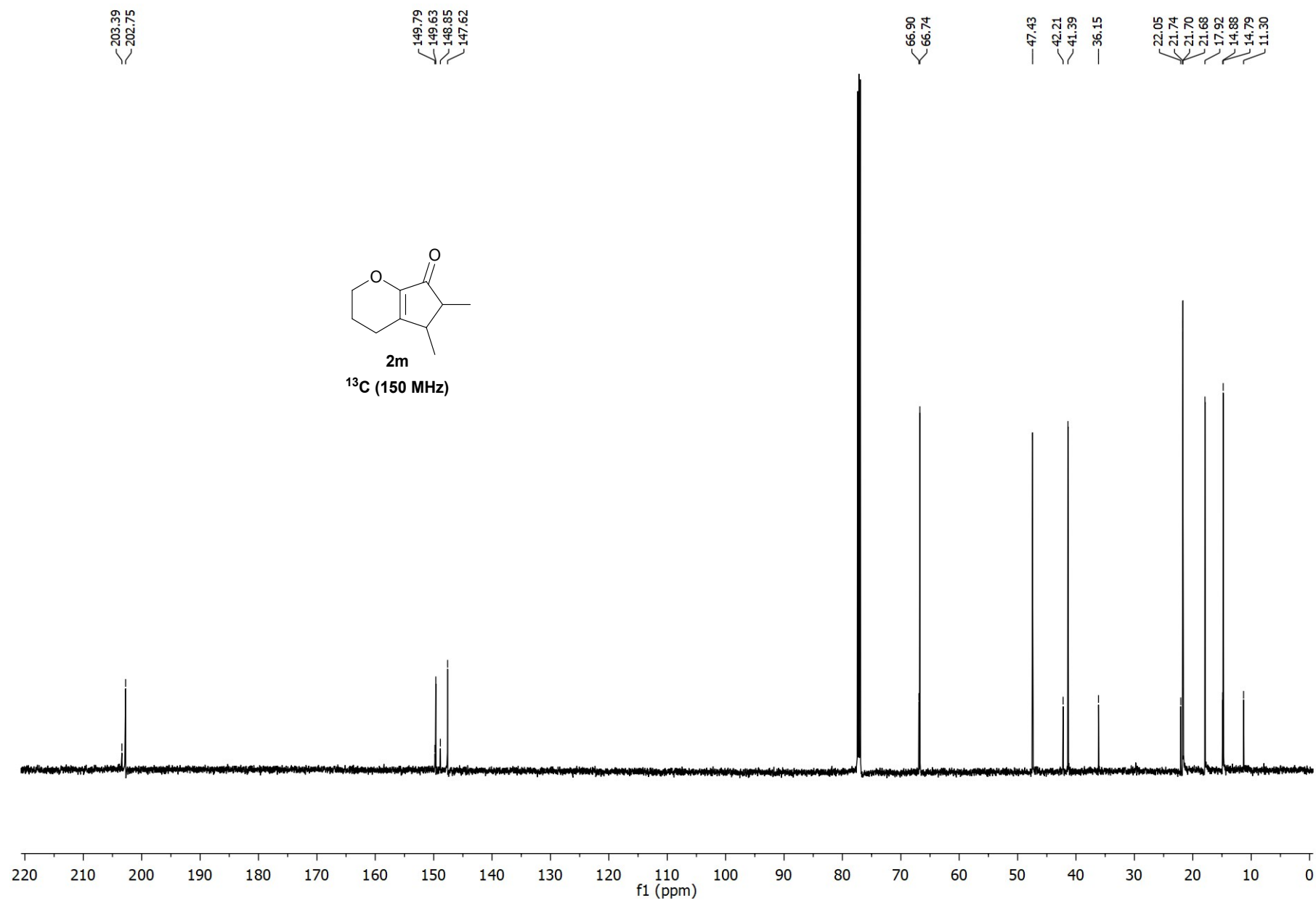


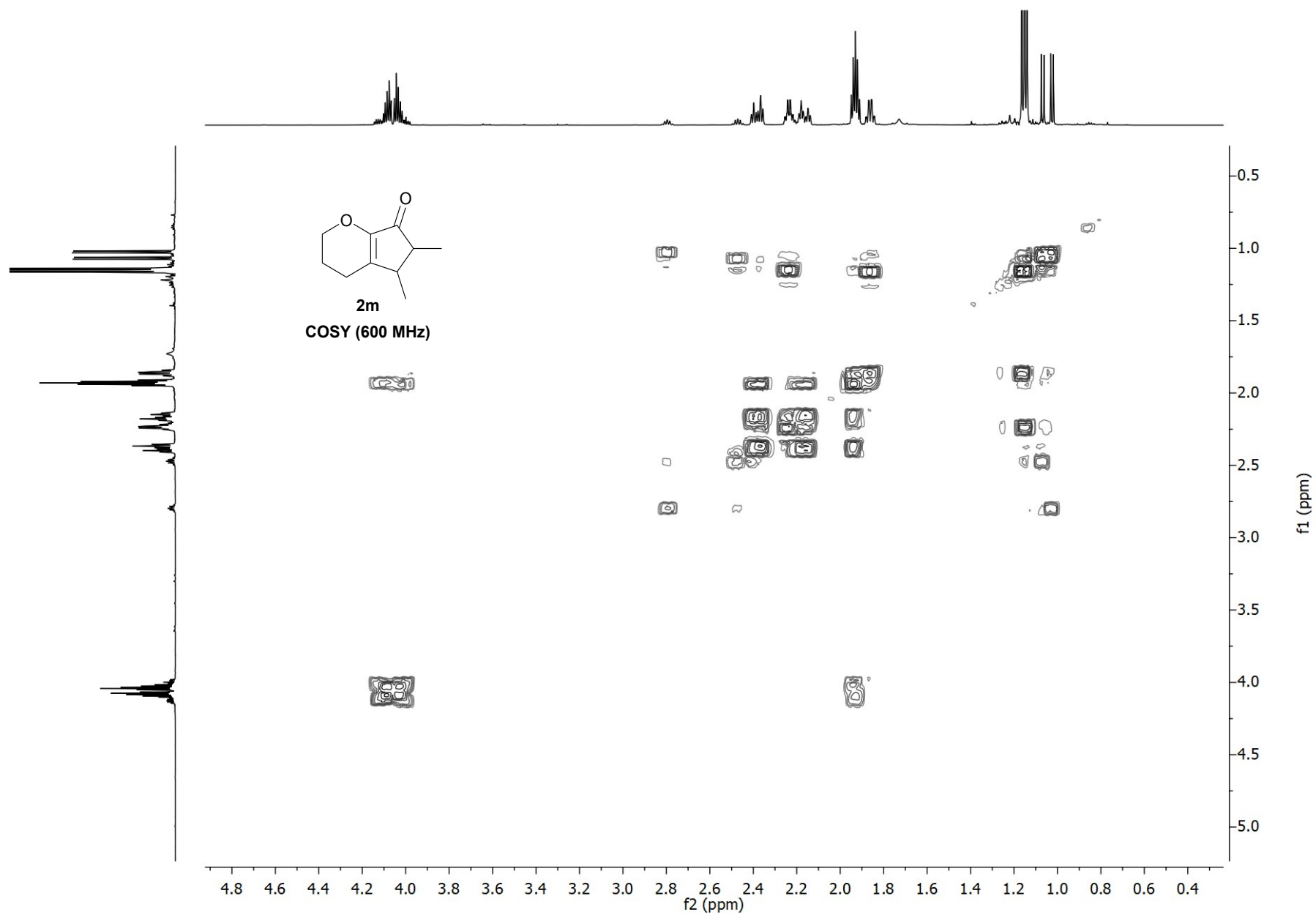
2m

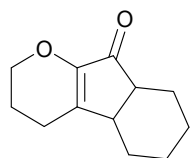
^1H (600 MHz)



S52

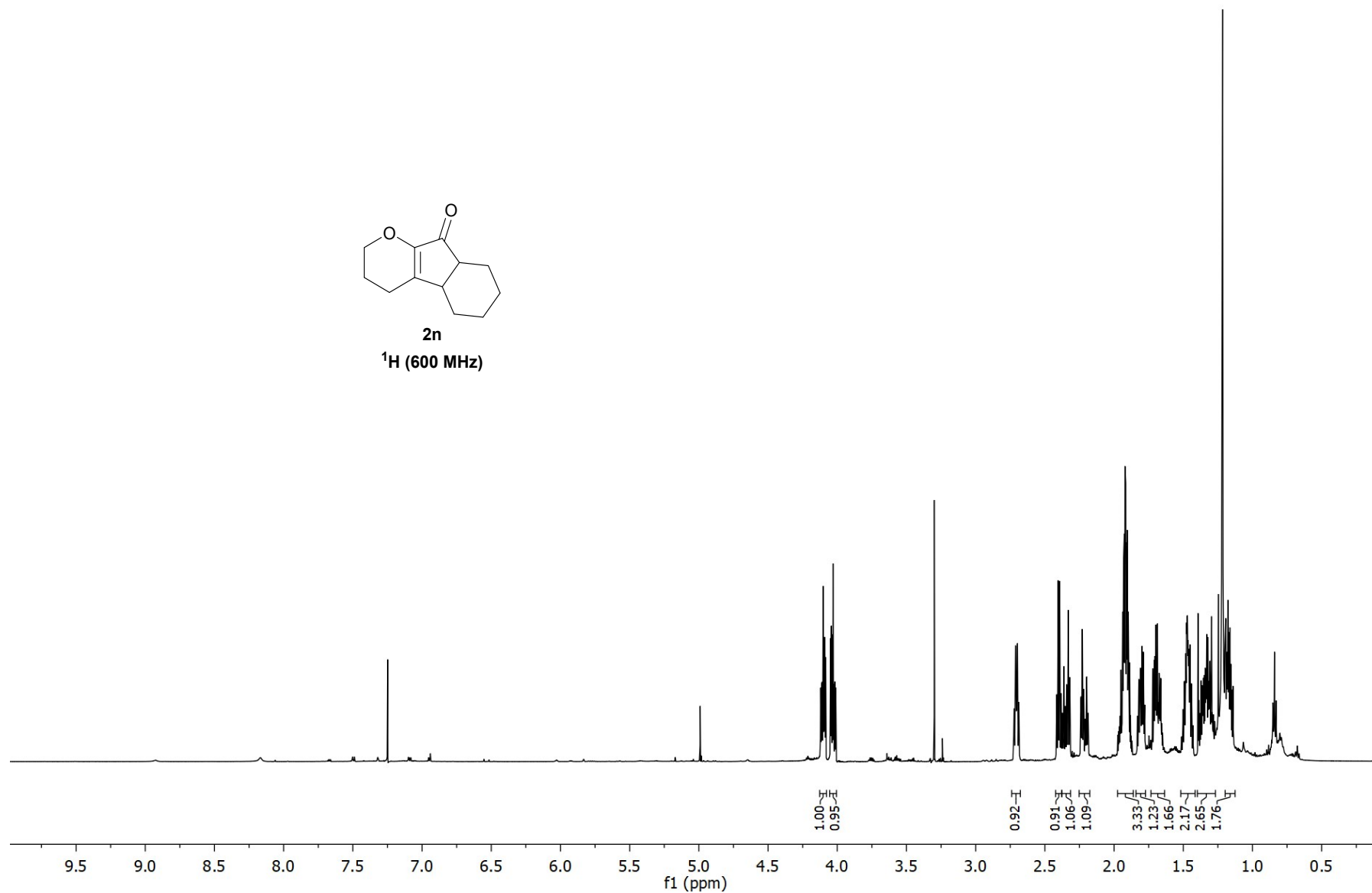




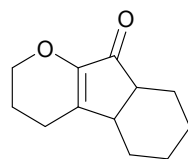


2n

¹H (600 MHz)

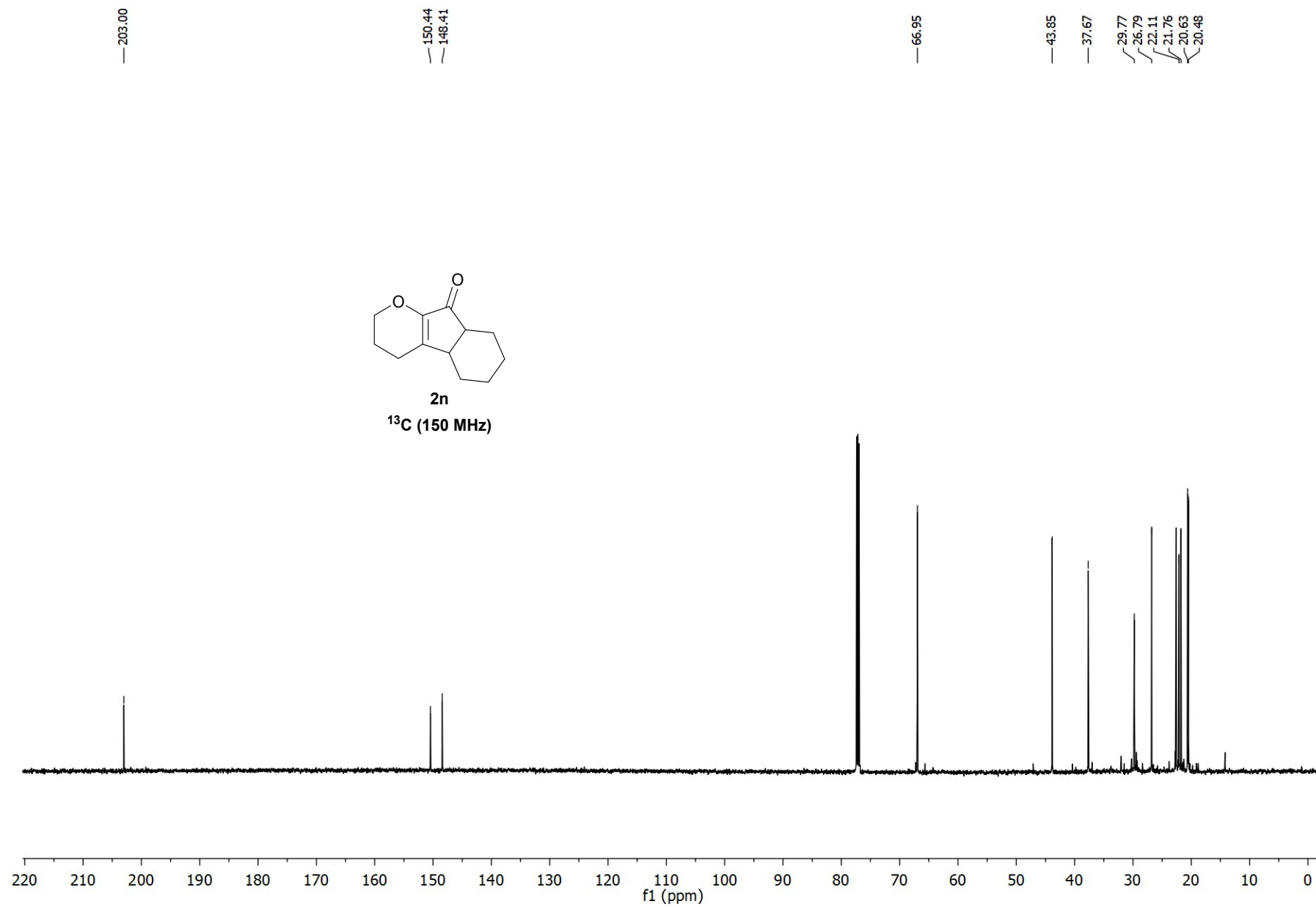


S55

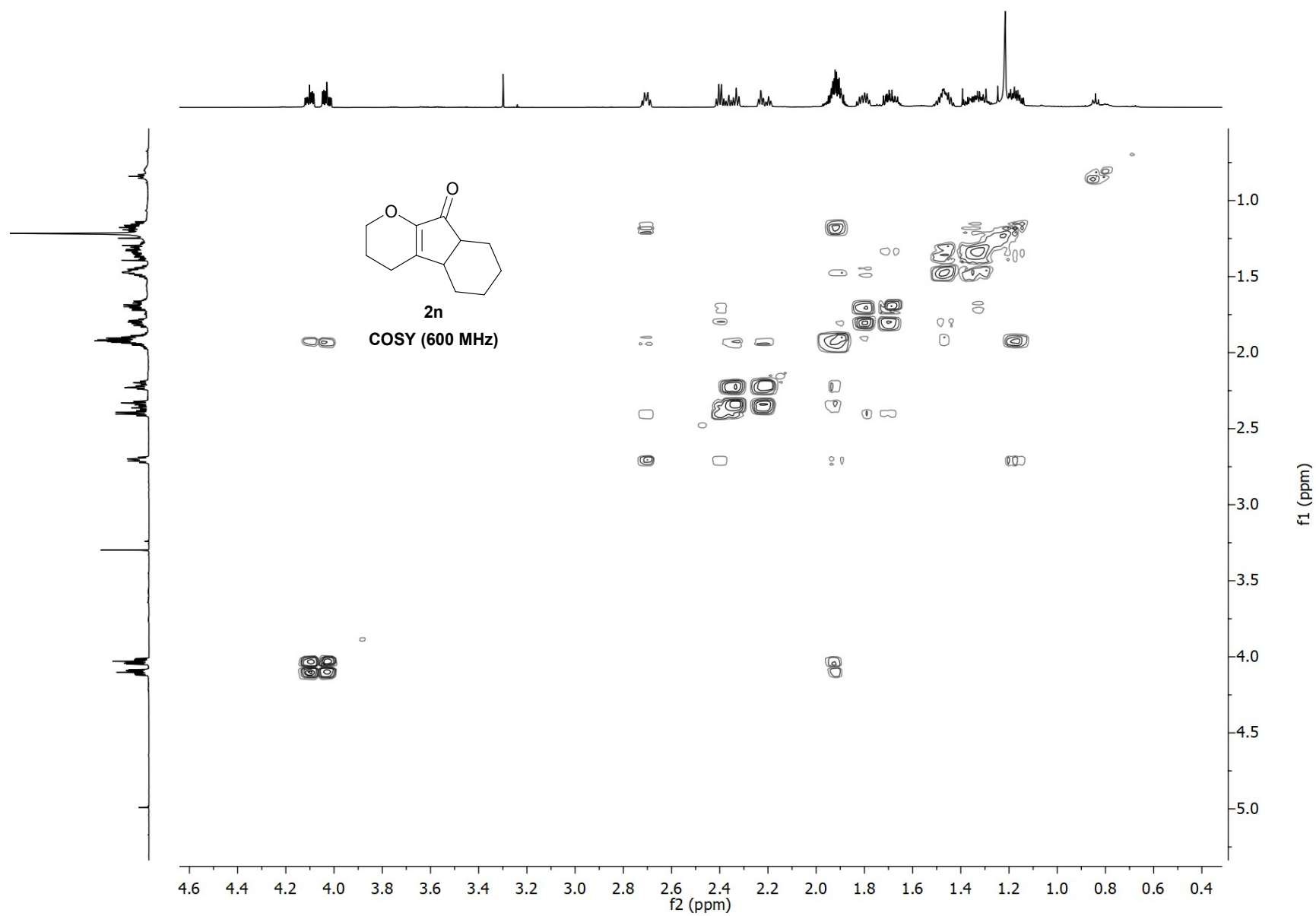


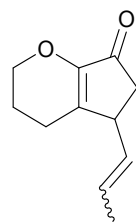
2n

^{13}C (150 MHz)

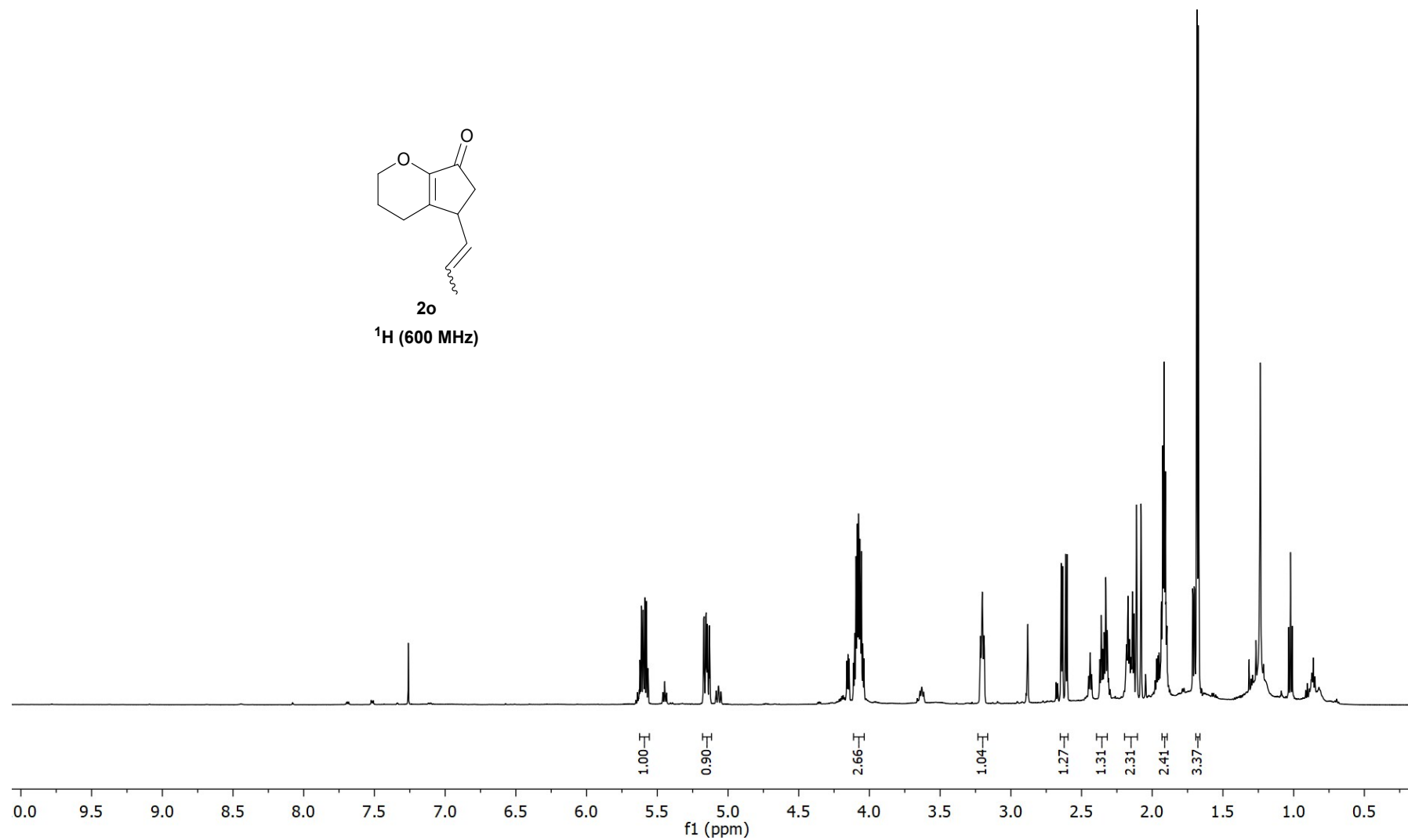


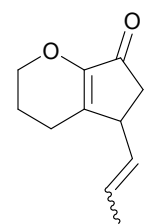
S56





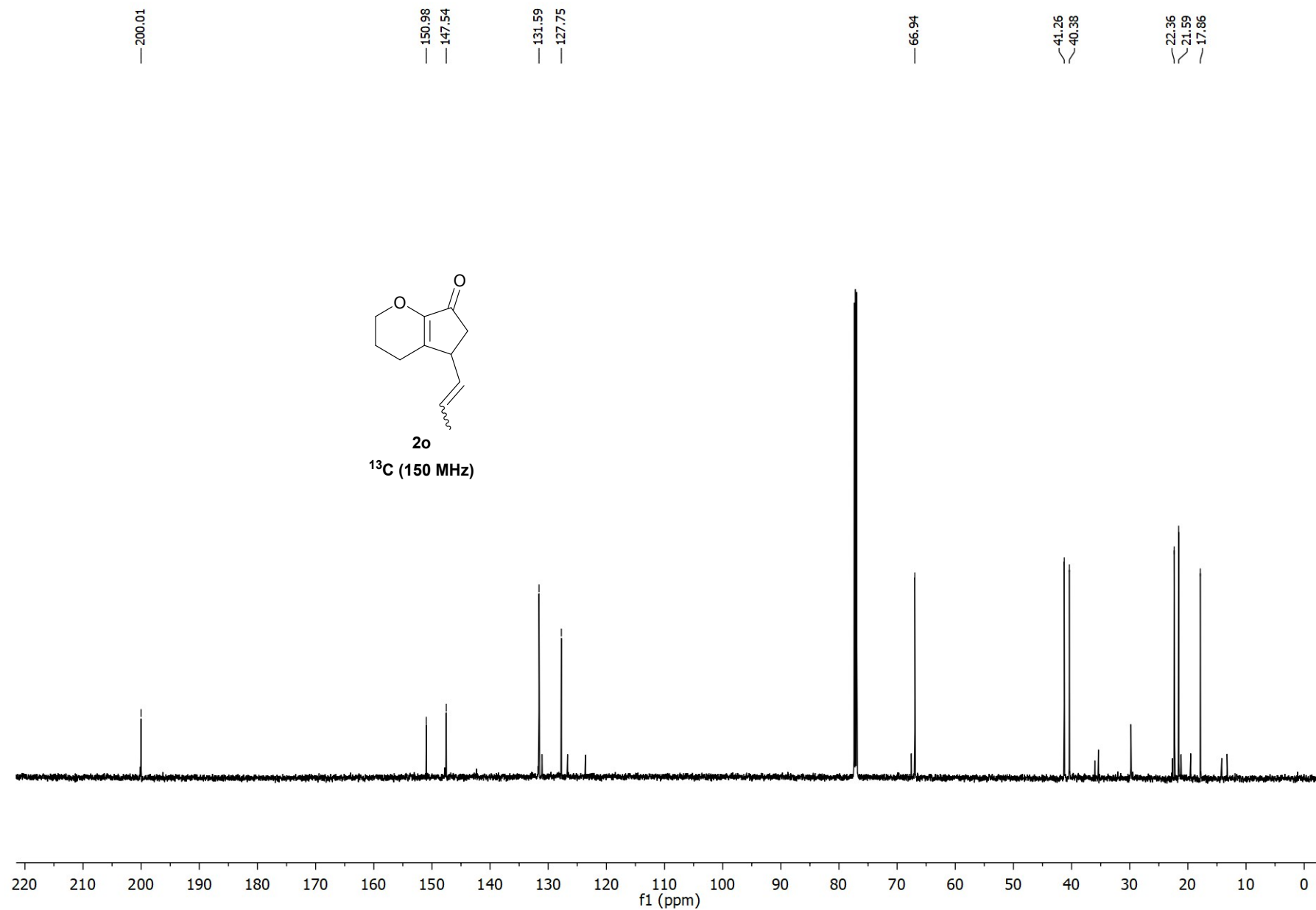
2o
¹H (600 MHz)

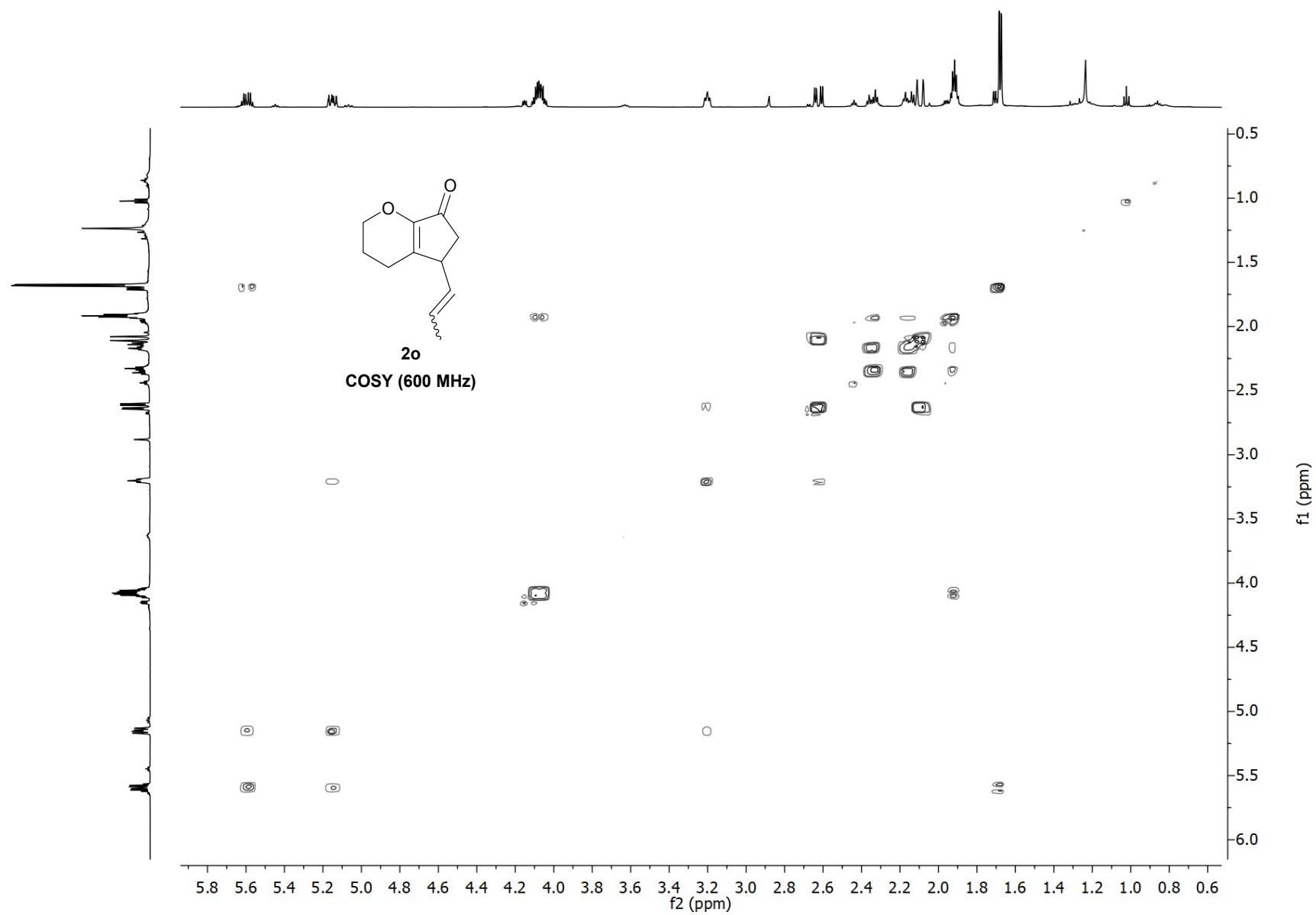


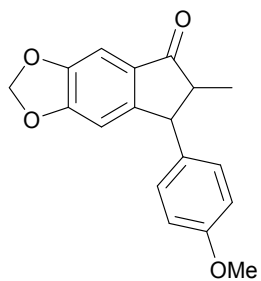


2o

¹³C (150 MHz)

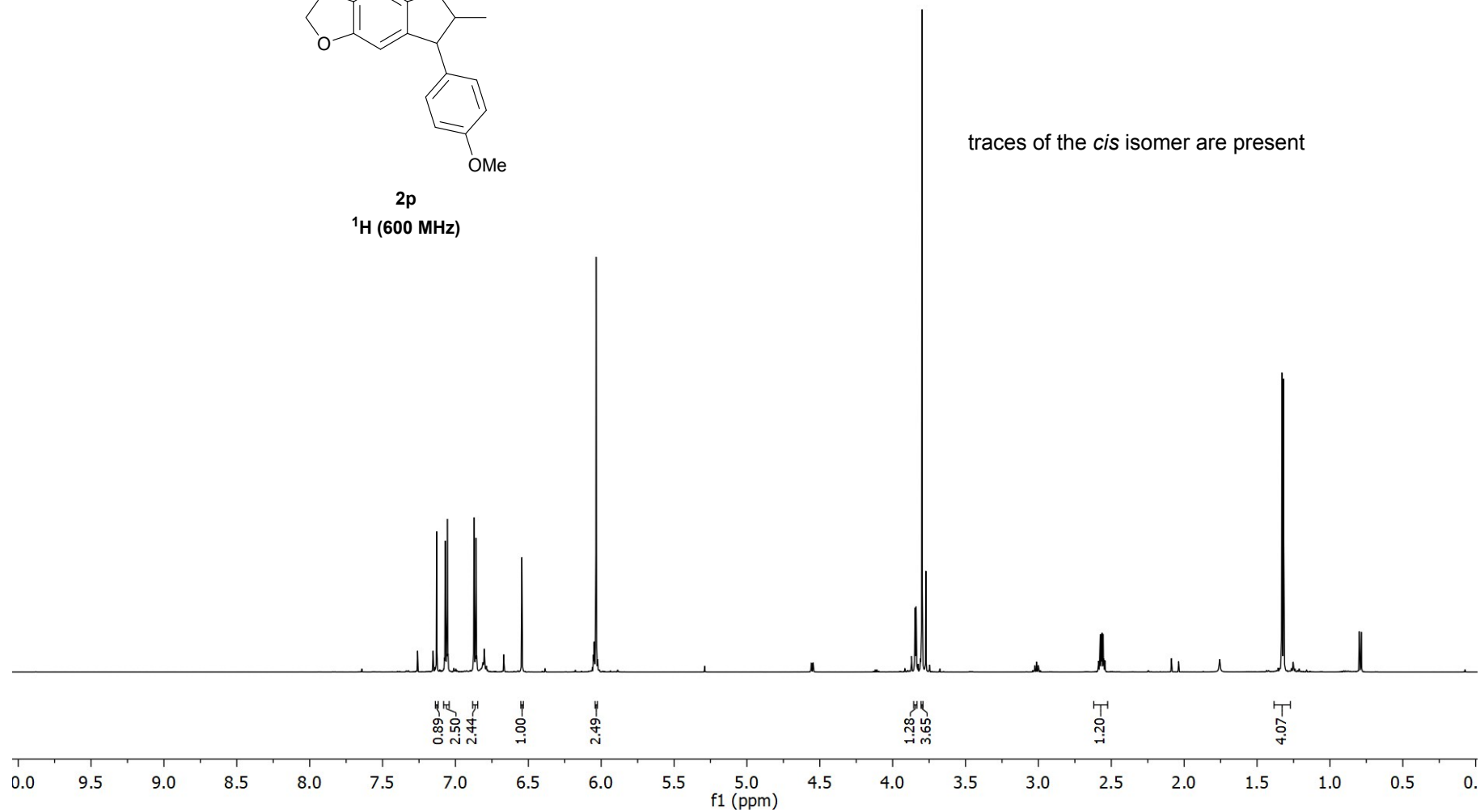


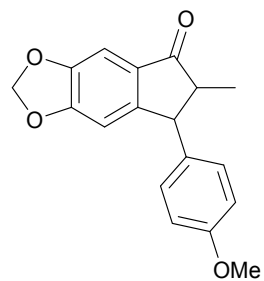




2p
¹H (600 MHz)

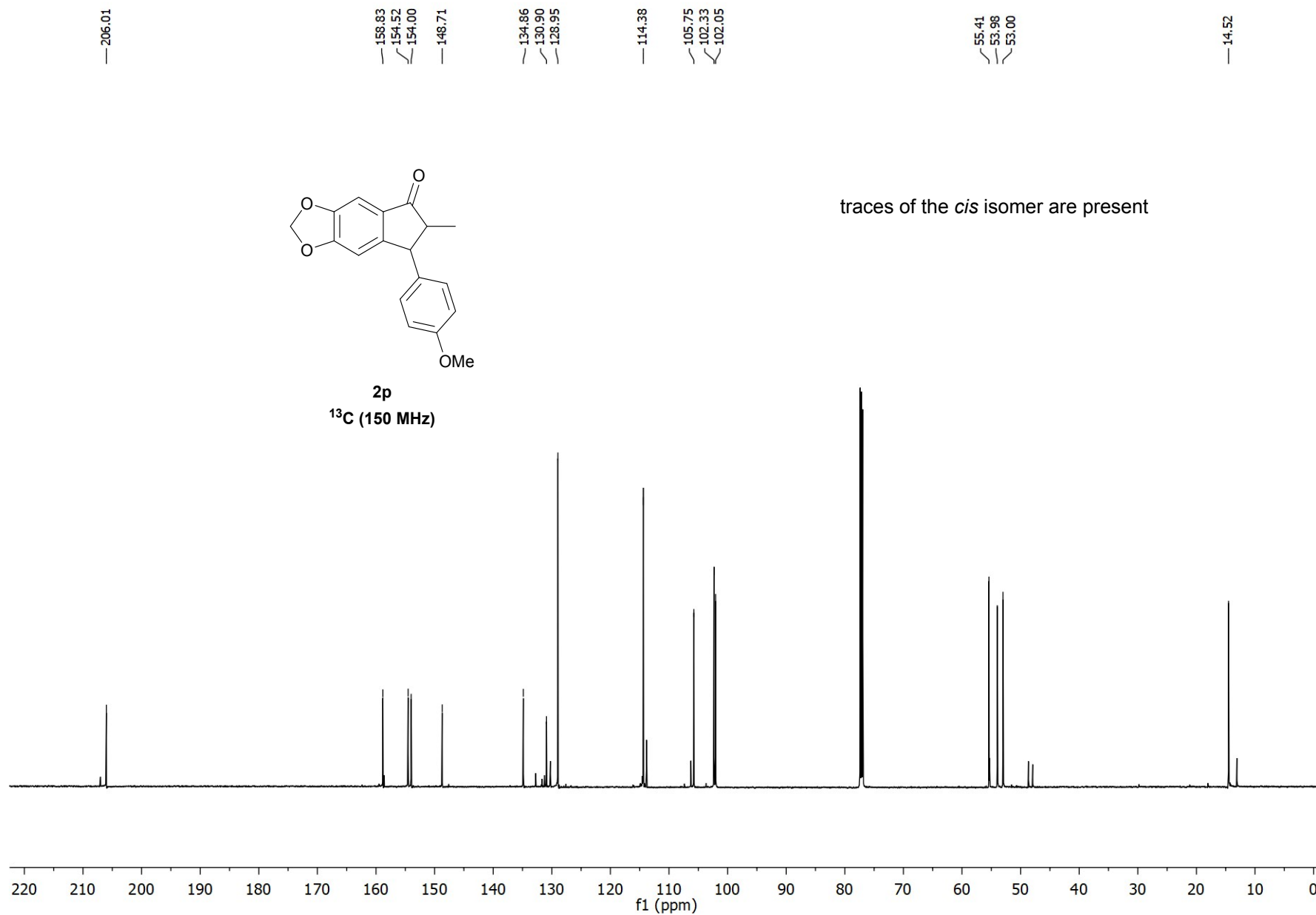
traces of the *cis* isomer are present

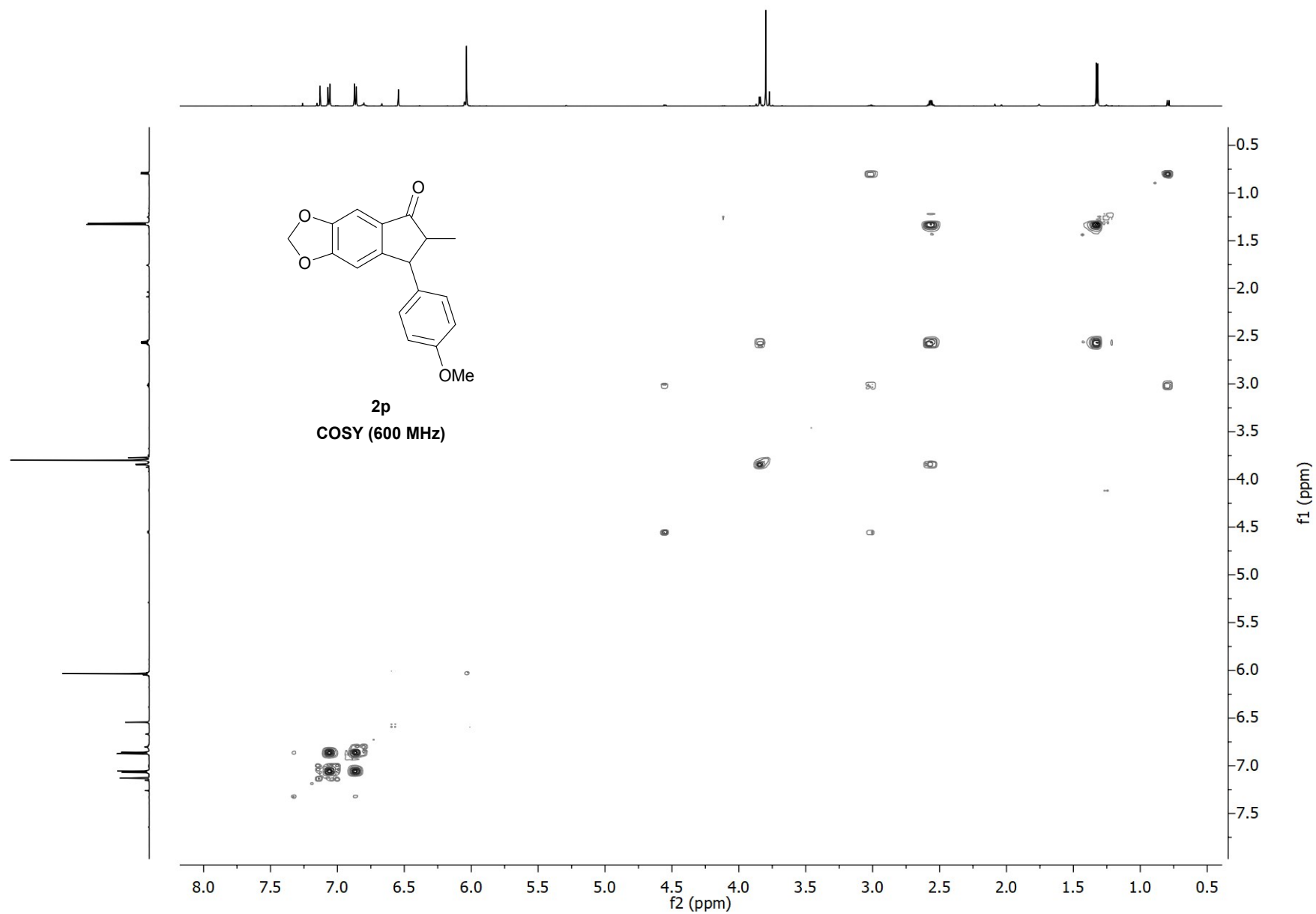




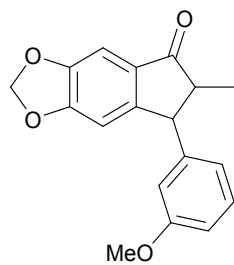
2p
¹³C (150 MHz)

traces of the *cis* isomer are present



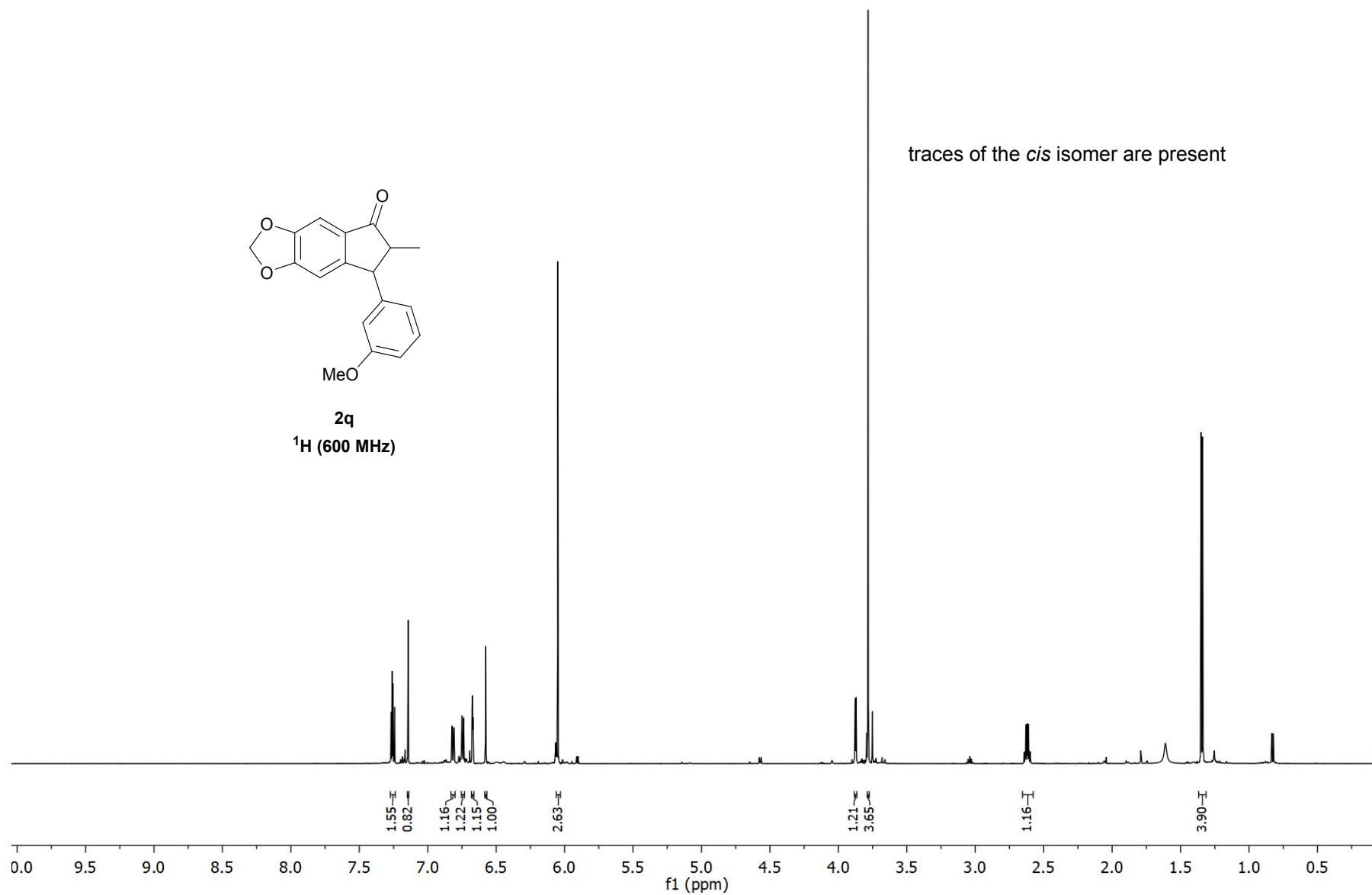


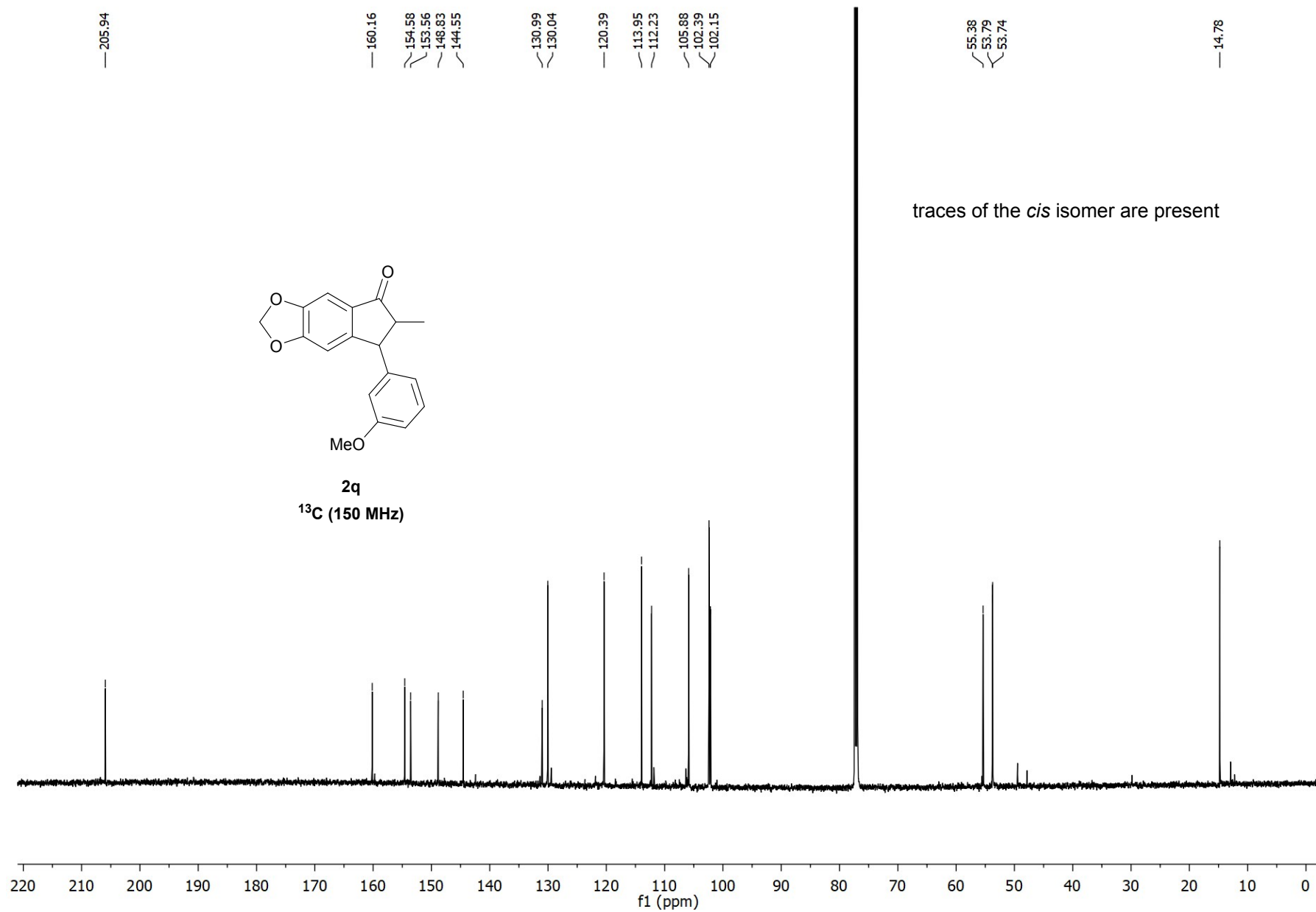
S63

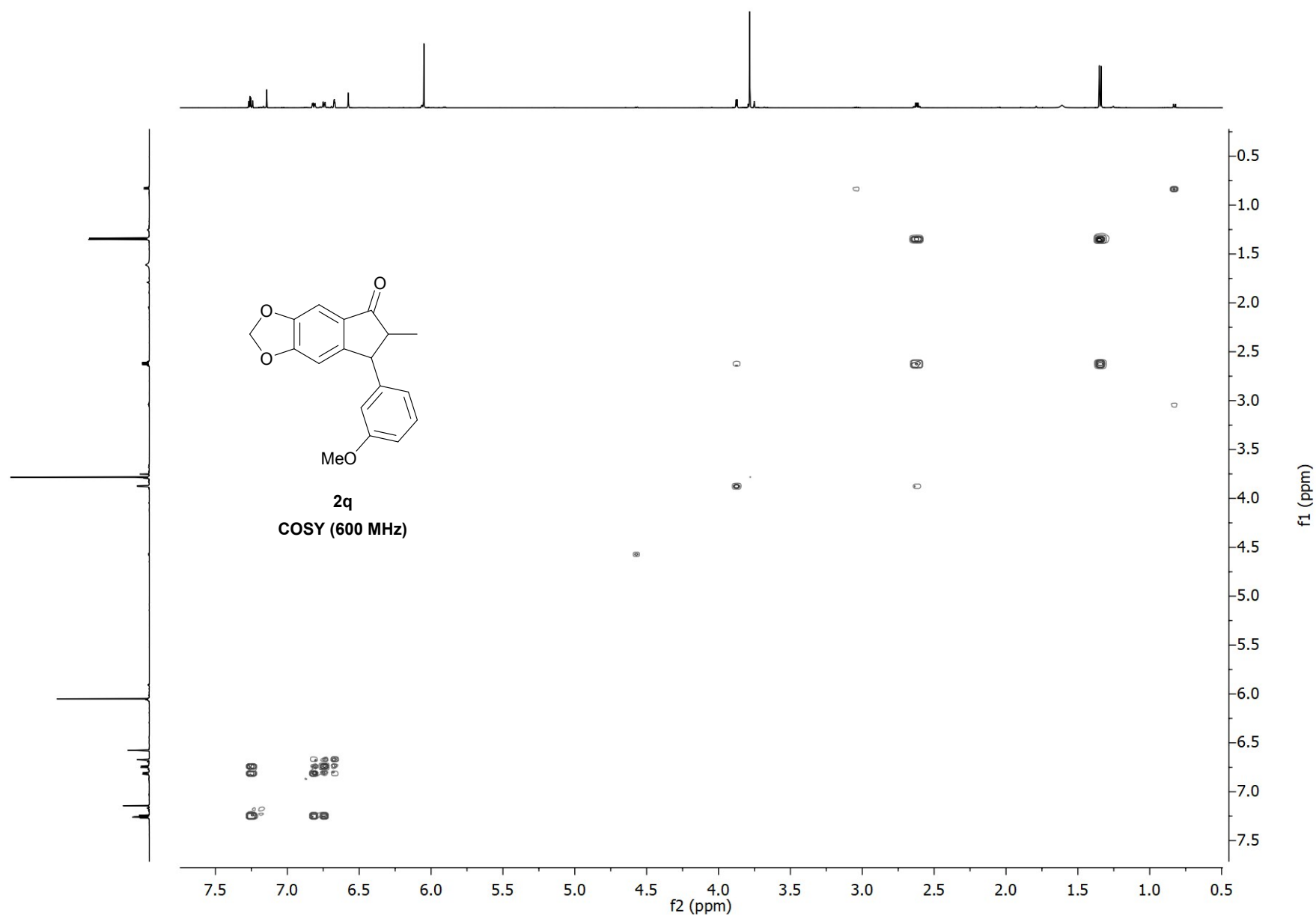


2q
¹H (600 MHz)

traces of the *cis* isomer are present

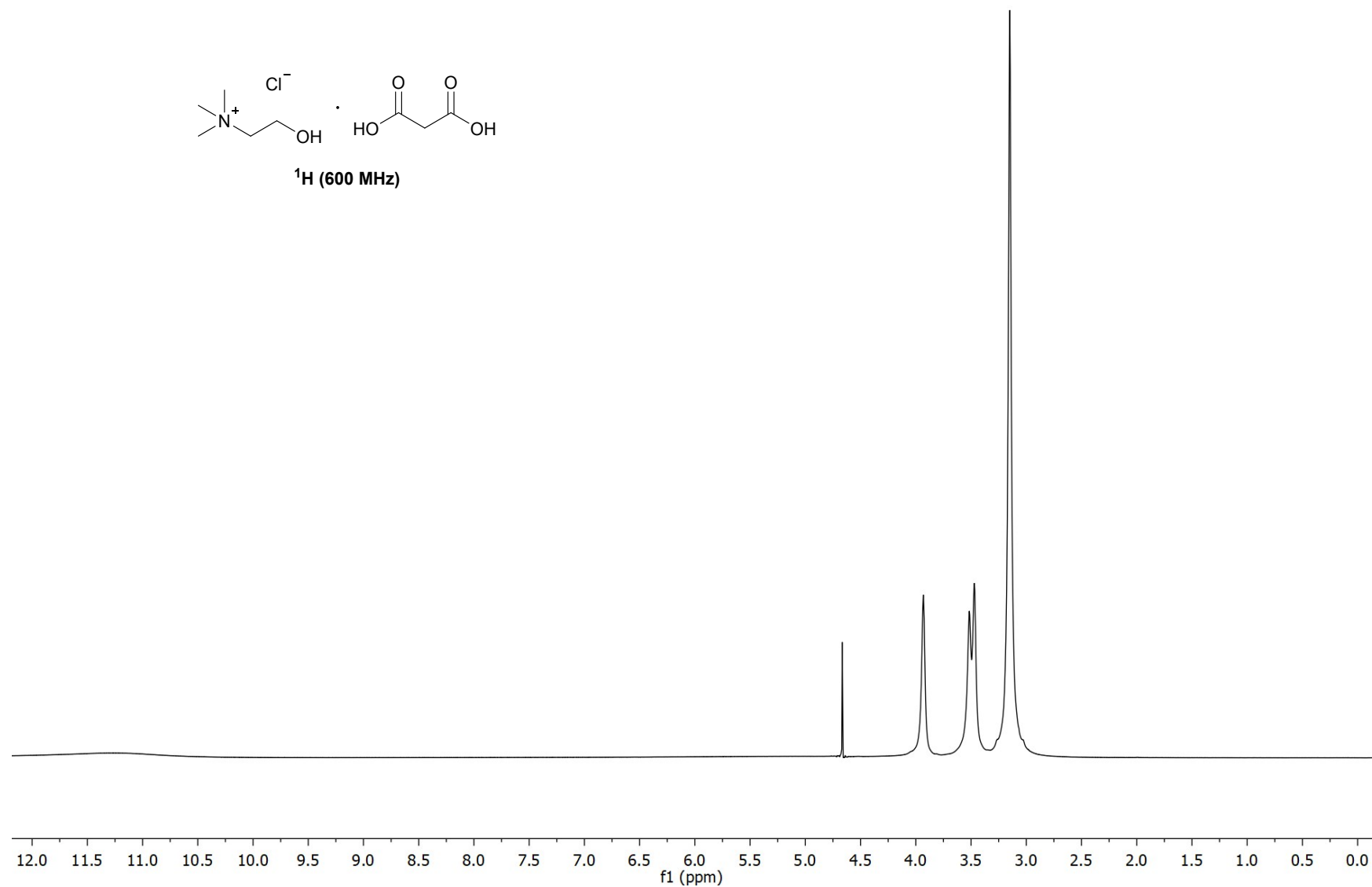
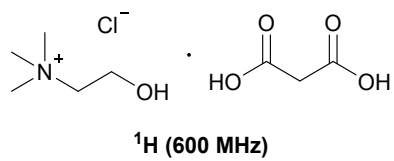




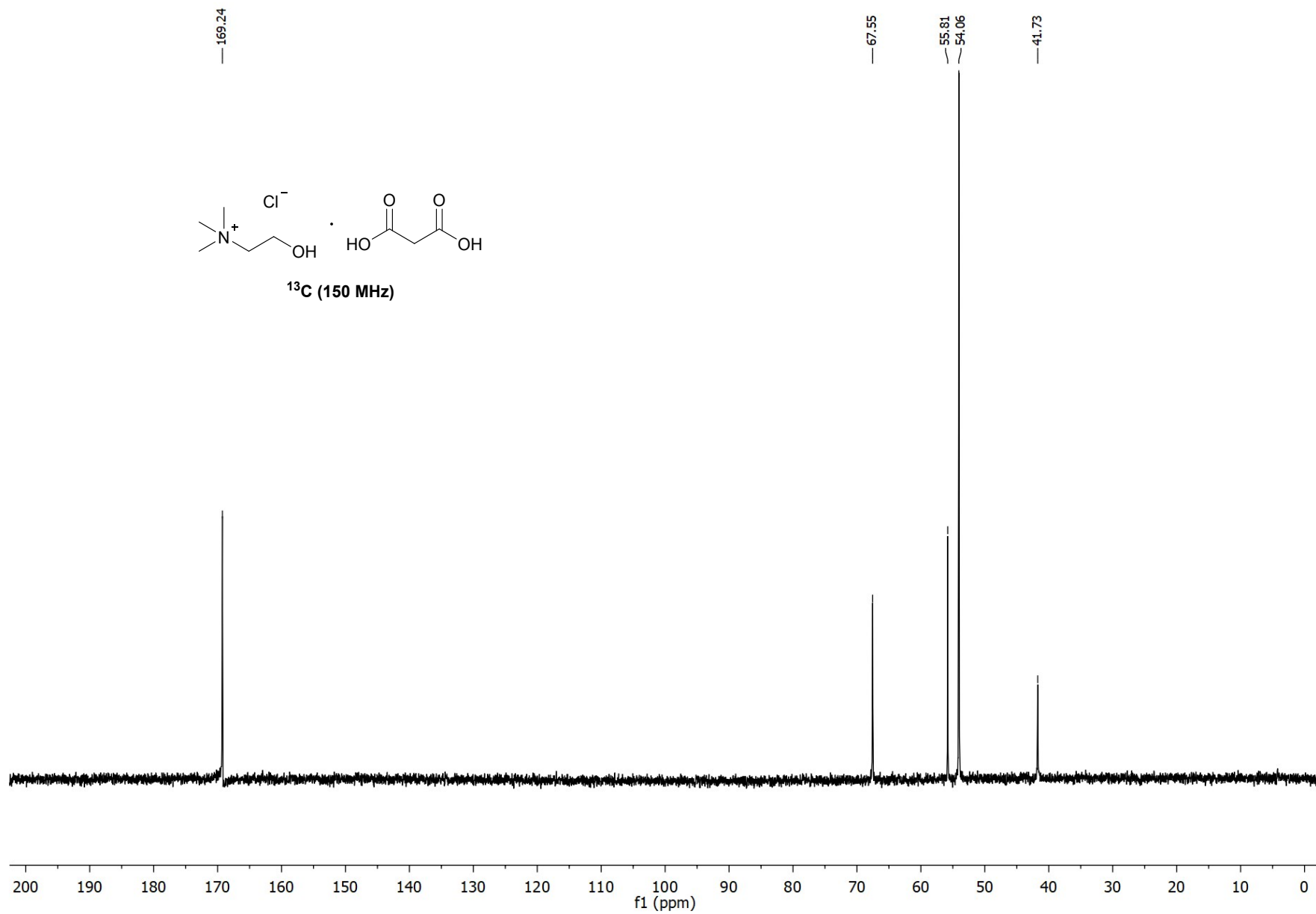
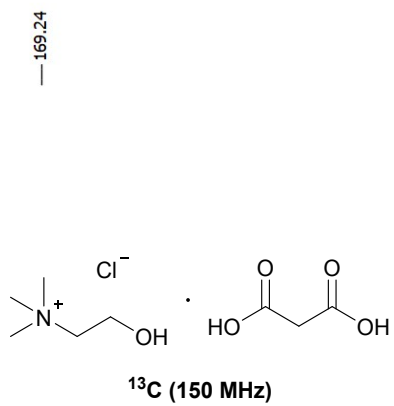


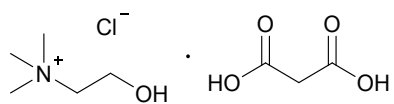
S66

NMR spectra of ChCl/malonic acid 1:1



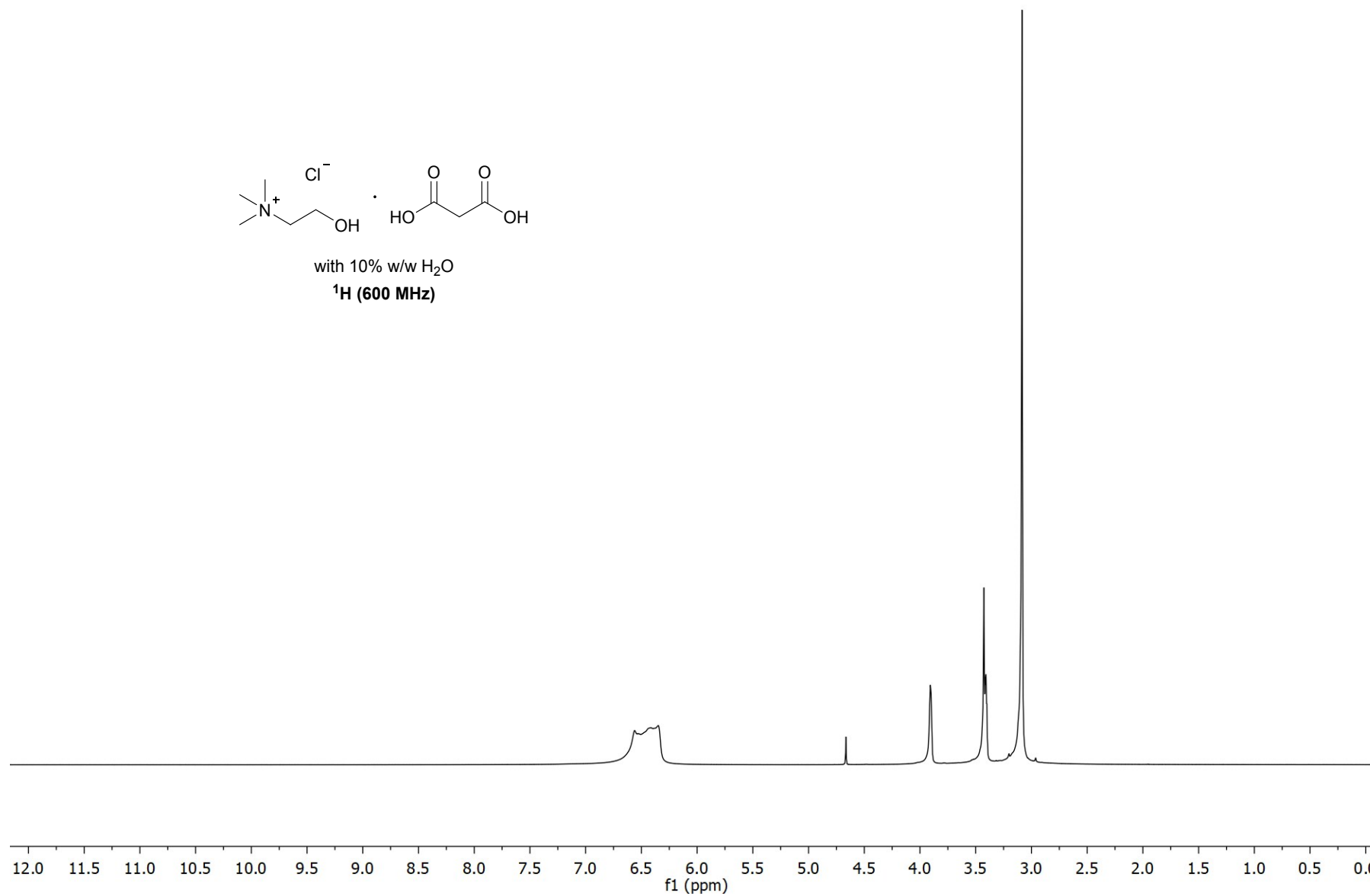
S67



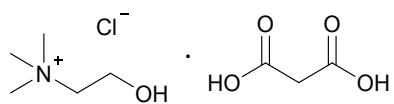


with 10% w/w H₂O

¹H (600 MHz)

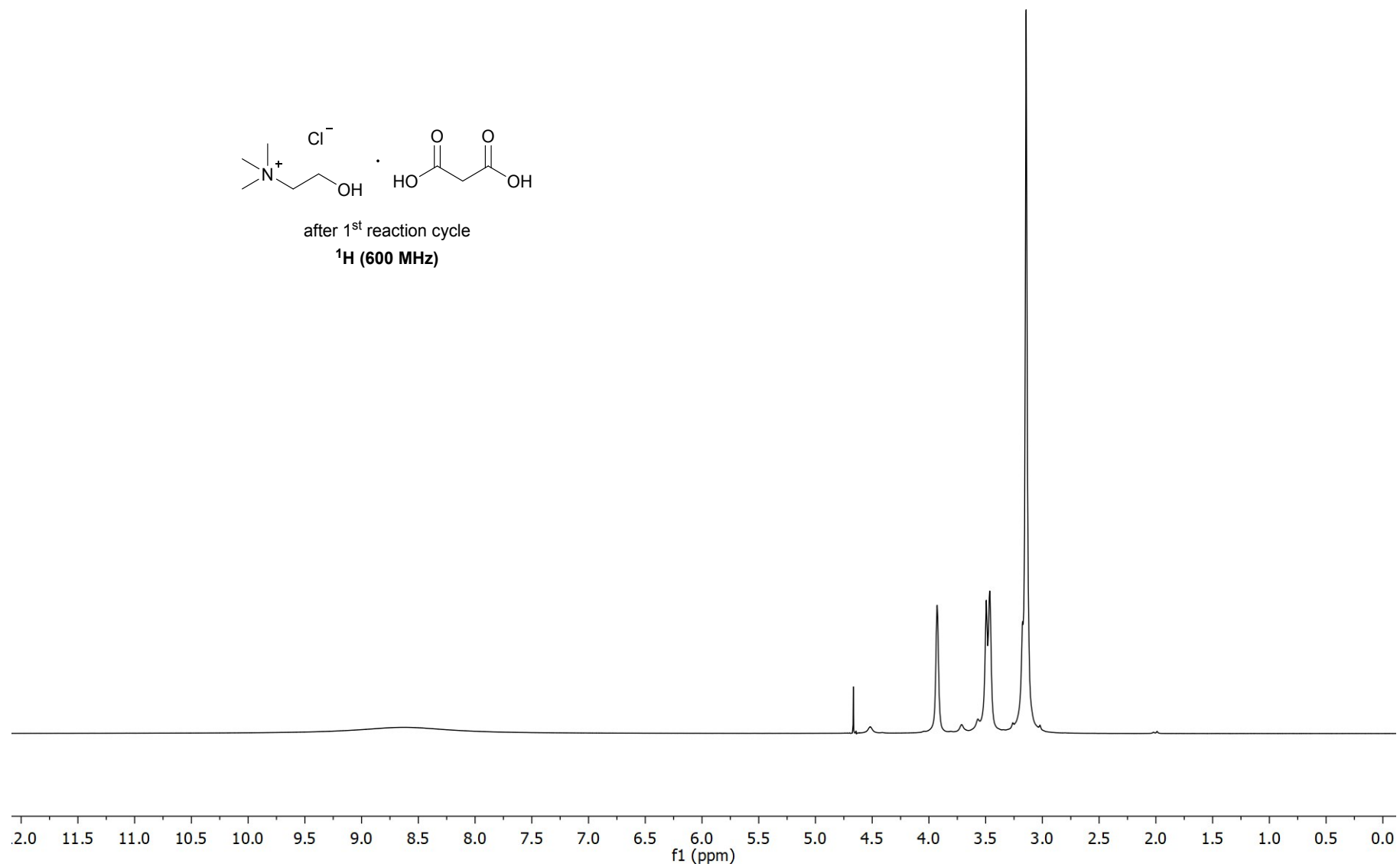


S69

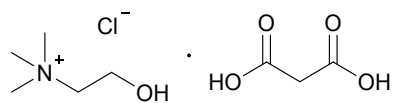


after 1st reaction cycle

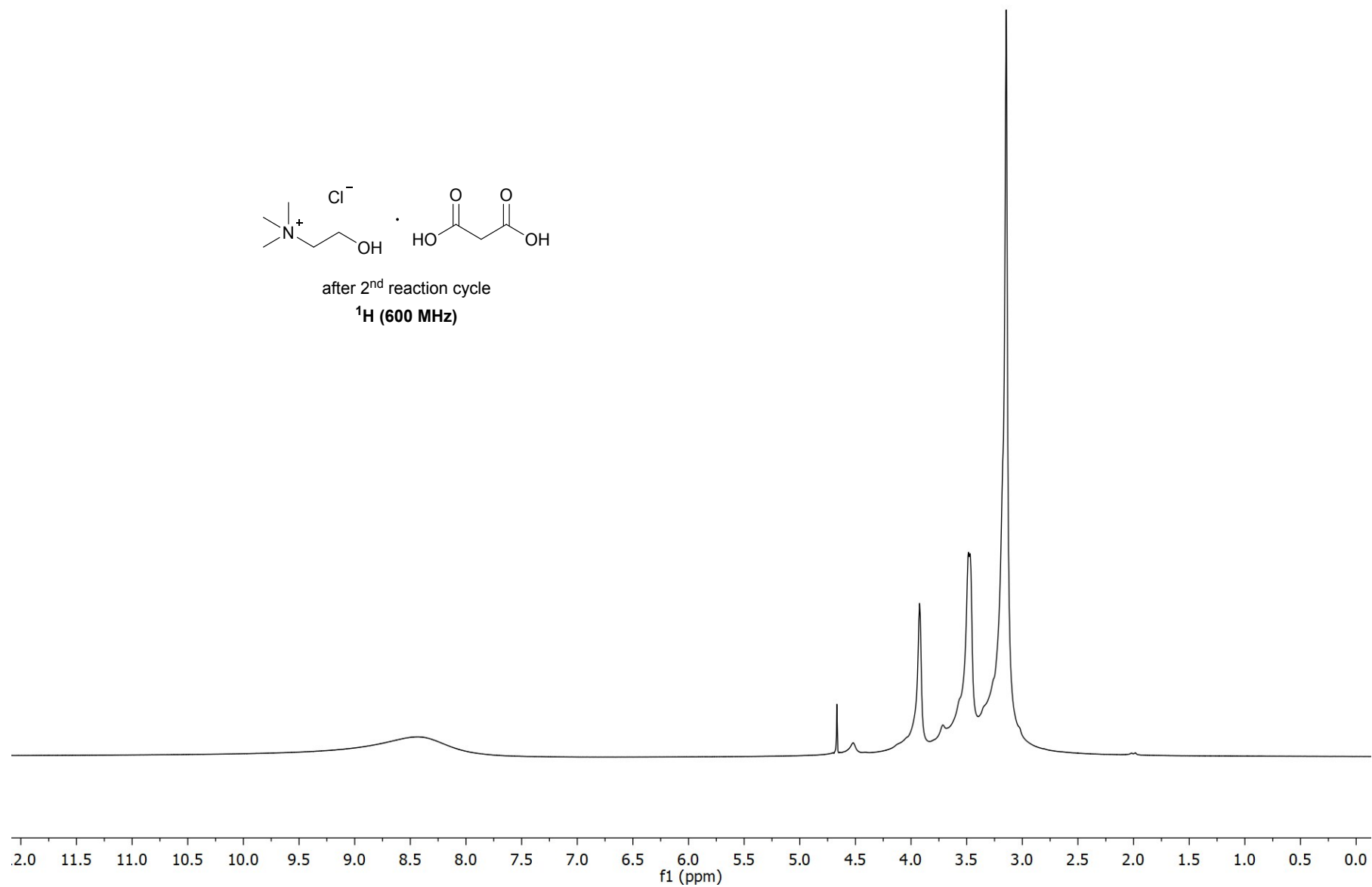
¹H (600 MHz)



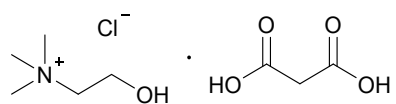
S70



after 2nd reaction cycle
¹H (600 MHz)

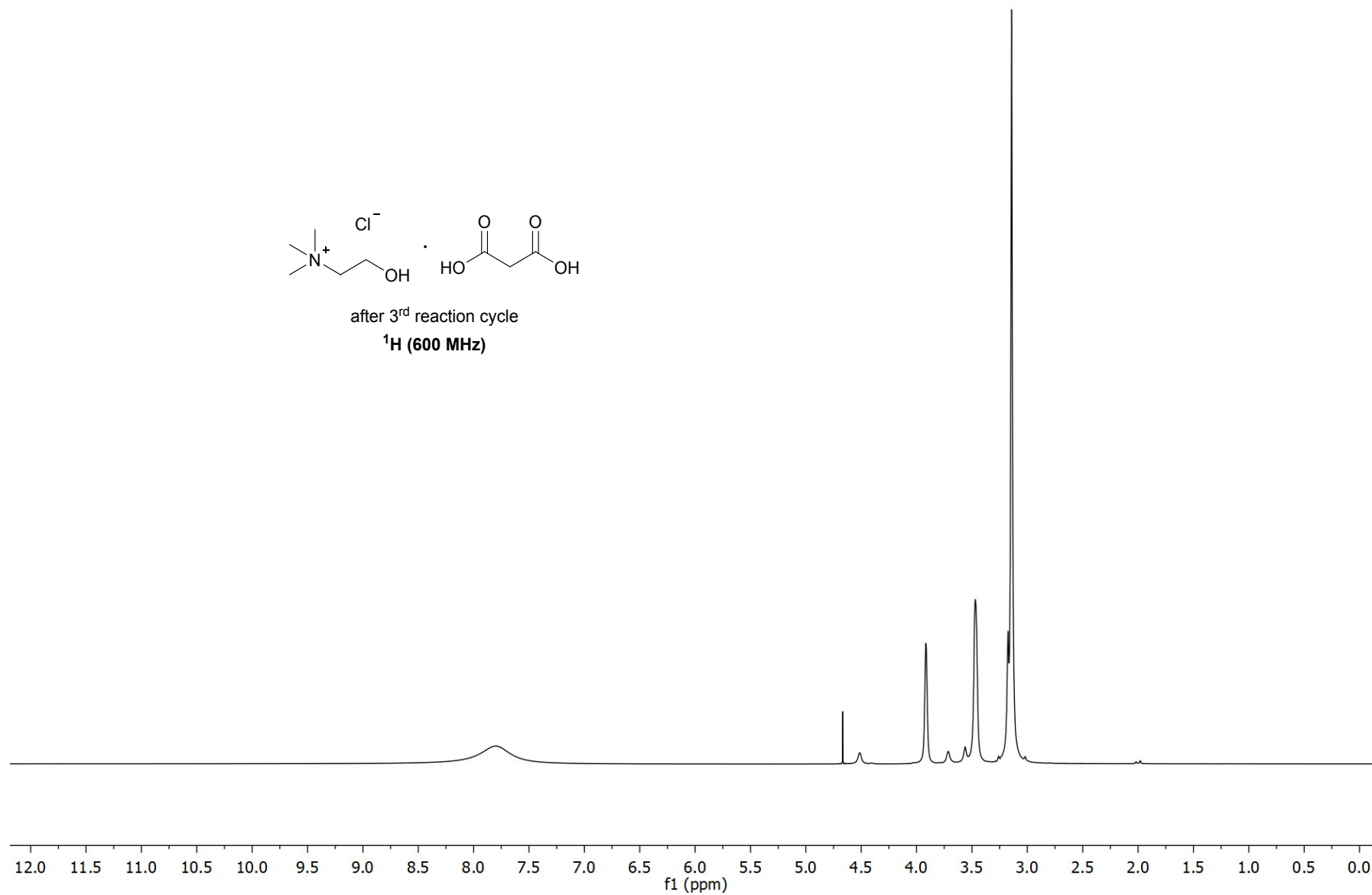


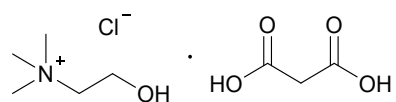
S71



after 3rd reaction cycle

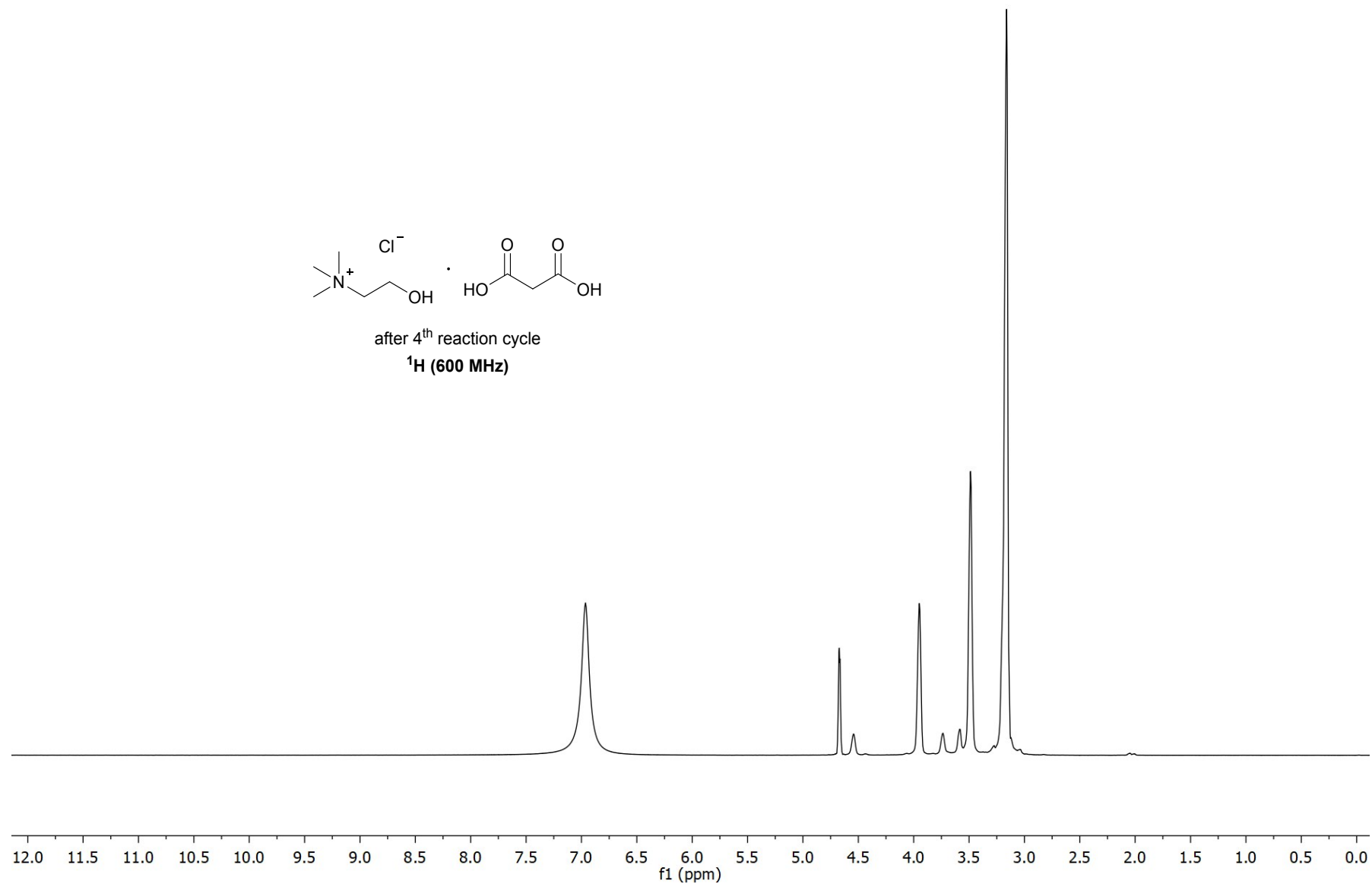
¹H (600 MHz)



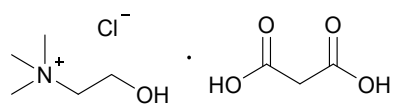


after 4th reaction cycle

¹H (600 MHz)

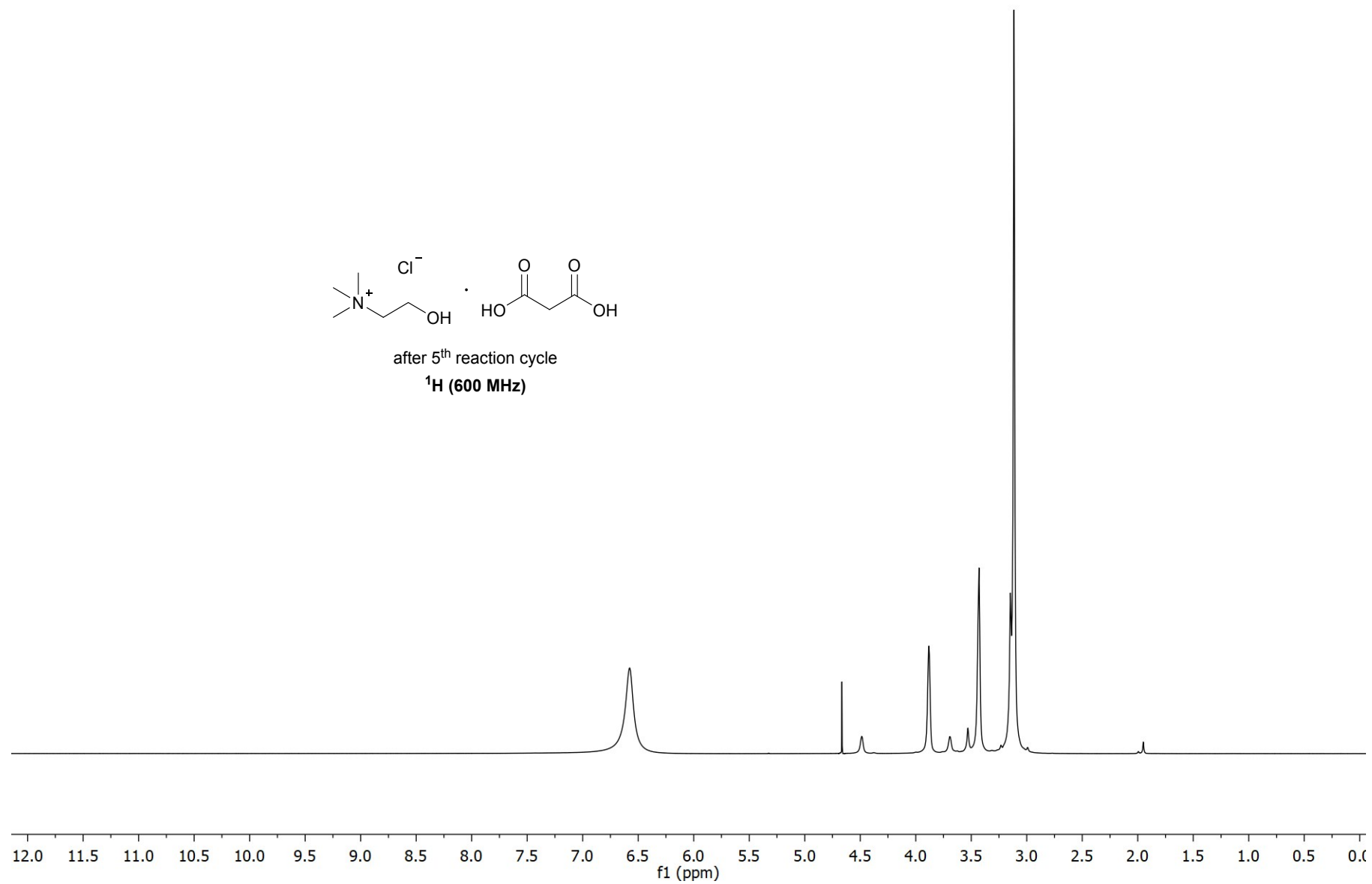


S73



after 5th reaction cycle

¹H (600 MHz)



S74