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Supporting Information

Axially Chiral Cannabinols: A New Platform for Cannabinoid-Inspired Drug Discovery

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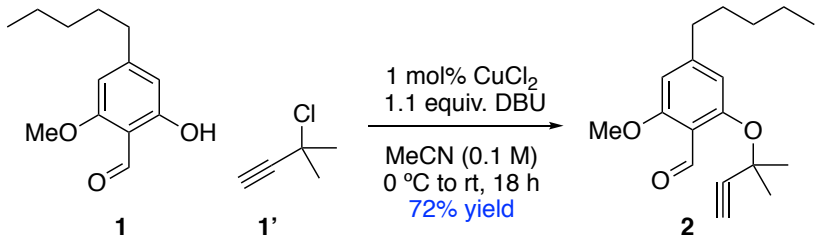
Experimental Section

All commercial materials were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (with $CHCl_3$ residual peak as an internal standard) or toluene-d_8 using a 500 MHz spectrometer. All ^{13}C NMR spectra were recorded with complete proton decoupling. HRMS data were recorded on Agilent Time of Flight 6200 spectrometer. Reaction progress was monitored by thin-layer chromatography (TLC) and visualized by UV light, phosphomolybdic acid stain, and $KMnO_4$ stain. All reactions were carried out using anhydrous solvents obtained dried by passing through activated alumina columns.

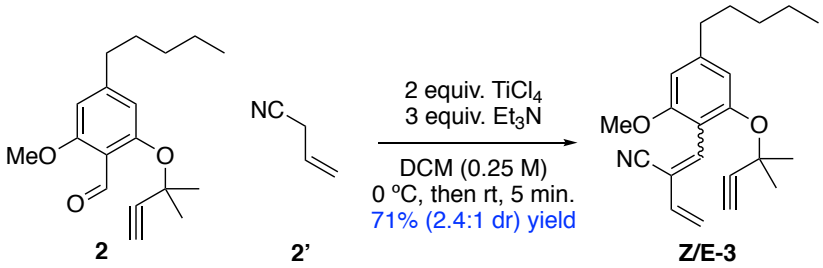
Procedure for Propargylation



To an oven dried Schlenk flask, aldehyde[1] **1** (5 g, 22.5 mmol, 1 equiv.), 1,8-diazabicyclo[5.4.0]undec-7-ene (3.7 ml, 24.7 mmol, 1.1 equiv.), 3-chloro-3-methylbut-1-yne **1'** (2.5 ml, 22.5 mmol, 1 equiv.) and acetonitrile (225 ml, 0.1 M with respect to **1**) was transferred and stirred for 5 minutes at 0 ºC (ice bath) while blanketing with an inert gas. Then, copper(II) chloride dihydrate catalyst (38 mg, 225 µmol, 0.01 equiv.) was transferred at 0 ºC. The ice bath was removed, and the reaction mixture was stirred overnight at room temperature. Upon completion *via* TLC, the reaction mixture was quenched with 100 ml of 1 M NaOH and transferred to a separatory funnel and extracted

with ethyl acetate (2 x 50 ml). The combined organic layers were washed with 1 M HCl (1 x 50 ml), saturated $NaHCO_3$ (1 x 50 ml), brine (1 x 50 ml) and dried over Na_2SO_4. The crude solution was evaporated and purified using column chromatography (hexanes – ethyl acetate 90:10) which gave 2-methoxy-6-((2-methylbut-3-yn-2-yl)oxy)-4-pentylbenzaldehyde (4.7 g, 72%) as a yellow oil.

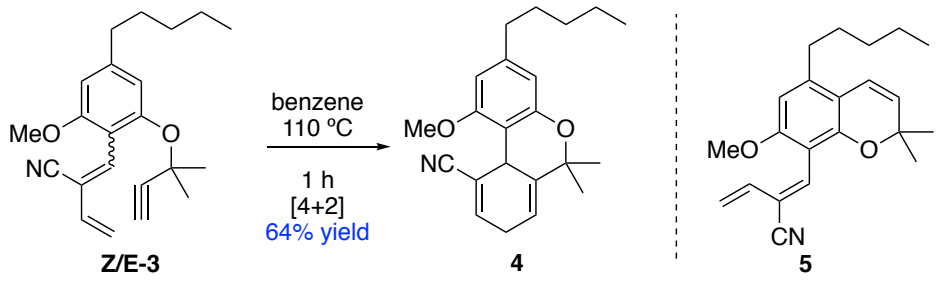
Procedure for the Aldol Condensation



2 **2'** **Z/E-3**

To an oven dried Schlenk flask, aldehyde **2** (4.7 g, 16.3 mmol, 1 equiv.), triethylamine (6.8 ml, 48.9 mmol, 3 equiv.), allyl cyanide **2'** (2.6 ml, 32.6 mmol, 2 equiv.) and dichloromethane (65.2 ml, 0.25 M with respect to **2**) was transferred and stirred for 5 minutes at 0 ºC (ice bath) while blanketing with an inert gas. Then, titanium(IV) tetrachloride (3.6 ml, 32.6 mmol, 2 equiv.) was transferred drop wise over 5 minutes and stirred for another 5 minutes at 0 ºC. Upon completion *via* TLC, the reaction mixture was quenched with 15 ml of water and transferred to a separatory funnel and extracted with dicloromethane (2 x 10 ml). The combined organic layers were washed with brine (1 x 20 ml) and dried over Na_2SO_4. The crude solution was evaporated and purified using column chromatography (hexanes – ethyl acetate 95:5) which gave 2-(2-methoxy-6-((2-methylbut-3-yn-2-yl)oxy)-4-pentylbenzylidene)but-3-enenitrile (3.9 g, 71%, 2.4:1 dr) as a yellow oil.

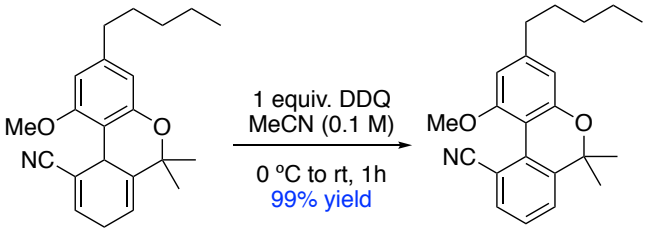
Procedure for the [4+2] Cycloaddition



Z/E-3 **4** **5**

To an oven dried pressure flask, **Z/E-3** (3.9 g, 11.6 mmol, 1 equiv.) and dry toluene (98 ml, 0.1 M with respect to **Z/E-3**) was transferred and heated at 110 ºC for 1 hour. The crude solution was evaporated and purified using column chromatography (hexanes – ethyl acetate 90:10) which gave 1-methoxy-6,6-dimethyl-3-pentyl-8,10a-dihydro-6H-benzo[c]chromene-10-carbonitrile (2.5 g, 64%) as a yellow oil and **5** (1 g, 30%).

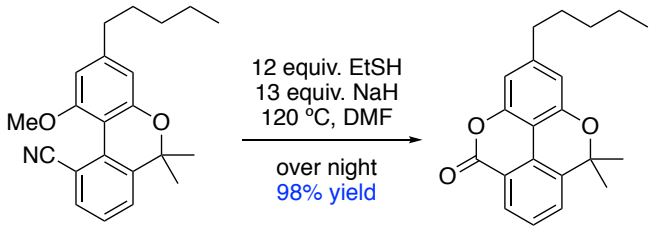
Procedure for Oxidation



4 **(±)-6**

To an oven dried Schlenk flask, **4** (2.5 g, 7.4 mmol, 1 equiv.), 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.7 g, 7.4 mmol, 1 equiv.) and acetonitrile (74 ml, 0.1 M with respect to **4**) was transferred and stirred for 1 hour at 0 ºC (ice bath) while blanketing with an inert gas. Upon completion *via* TLC, the reaction mixture was passed through a short plug of silica. The crude solution was evaporated and purified using column chromatography (hexanes – ethyl acetate 90:10) which gave 1-methoxy-6,6-dimethyl-3-pentyl-6H-benzo[c]chromene-10-carbonitrile (2.5 g, 99%) as a yellow oil.

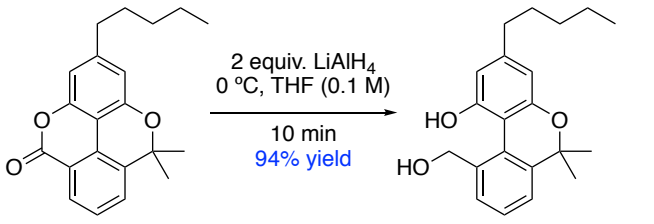
Procedure for Demethylation



(±)-6 **7**

To an oven dried Schlenk flask, NaH (2.3 g, 96.9 mmol, 13 equiv.) and dimethylformamide (19.3 ml, 5 M with respect to NaH) was transferred and cooled to 0 ºC (ice bath) while blanketing with an inert gas. Then, EtSH (6.5 ml, 89.4 mmol, 12 equiv.) was transferred drop wise at 0 ºC and stirred at room temperature for 30 minutes. 1-methoxy-6,6-dimethyl-3-pentyl-6H-benzo[c]chromene-10-carbonitrile (2.5 g, 7.5 mmol, 1 equiv.) was transferred with dimethylformamide (29 ml, 0.26 M with respect to carbonitrile) and stirred over night at 120 ºC. The reaction mixture was quenched with 20 ml of water and transferred to a separatory funnel and extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with brine (1 x 20 ml) and dried over Na_2SO_4. The crude solution was evaporated and purified using column chromatography (hexanes – ethyl acetate 90:10). The imidate was hydrolyzed during the chromatography process and gave lactone **7** (2.4 g, 98%) as yellow oil. *Nb: Excess EtSH can be quenched using 5% bleach (5% NaOCl in water).*

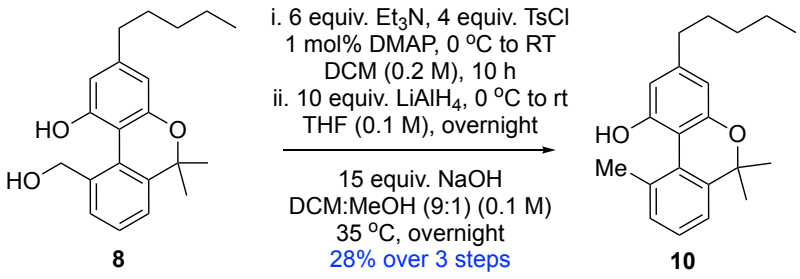
Procedure for Reduction



7 **10-hydroxymethyl-*ax*-CBN, 8**

To an oven dried Schlenk flask, lactone **7** (1.9 g, 5.9 mmol, 1 equiv.) and THF (59 ml, 0.1 M with respect to **7**) was transferred and cooled to 0 ºC (ice bath) while blanketing with an inert gas. Then, $LiAlH_4$ (447 mg, 11.8 mmol, 2 equiv.) was transferred at 0 ºC and stirred for 10 minutes. Upon completion *via* TLC, the reaction mixture was quenched with 25 ml of saturated Rochelle's salt for 1 hour and transferred to a separatory funnel and extracted with ether (3 x 20 ml). The combined organic layers were washed with brine (1 x 20 ml) and dried over Na_2SO_4. The crude solution was evaporated and purified using column chromatography (hexanes – ethyl acetate 80:20) which gave 10-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6H-benzo[c]chromen-1-ol (1.8 g, 94%) as a white solid.

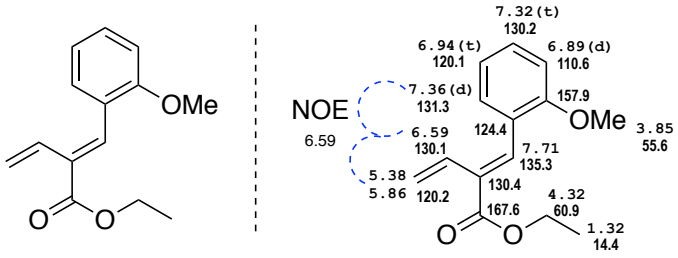
Procedure for the Tosylation/Reduction



To an oven dried Schlenk flask, diol **8** (1.22 g, 3.74 mmol, 1 equiv.), triethylamine (3.13 mL, 22.42 mmol, 6 equiv.), 4-dimethylaminopyridine (5 mg, 37 µmol, 0.01 equiv.) and dichloromethane (8 ml, 0.5 M with respect to **8**) was transferred and stirred for 5 minutes at 0 ºC (ice bath) while blanketing with an inert gas. Then, 4-toluenesulfonyl chloride (2.85 g, 14.95 mmol, 4 equiv.) was transferred at 0 ºC. The ice bath was removed, and the reaction mixture was stirred overnight at room temperature. Upon completion *via* TLC, the reaction mixture was quenched with 20 ml of saturated NH_4Cl and transferred to a separatory funnel and extracted with ethyl acetate (2 x 20 ml). The combined organic

layers were washed with brine (1 x 10 ml) and dried over Na_2SO_4. The crude solution was evaporated and used for the next step. The product was dissolved in anhydrous THF (31 ml, 0.1 M), $LiAlH_4$ (478 mg, 12.6 mmol, 4 equiv.) at 0 ºC. The ice bath was removed, and the reaction mixture was stirred overnight at room temperature. Upon completion *via* TLC, the reaction mixture was quenched with 20 ml of saturated Rochelle's salt for an hour and transferred to a separatory funnel and extracted with ethyl acetate (2 x 20 ml). The combined organic layers were washed with brine (1 x 20 ml) and dried over Na_2SO_4. The crude solution was evaporated and used for the next step. The product was dissolved in a 9:1 solution of DCM:MeOH (0.1 M, 31 mL) and NaOH (1.89 g, 47.14 mmol, 15 equiv.) and heated overnight at 35 ºC. The reaction mixture was transferred to a separatory funnel and extracted with DCM (1 x 20 mL). The organic layers were washed with 2 M HCl (2 x 20 mL) and brine (1 x 20 mL) and dried over Na_2SO_4. The crude solution was evaporated and purified using column chromatography (hexanes – ethyl acetate 95:5) which gave 6,6,10-trimethyl-3-pentyl-6H-benzo[c]chromen-1-ol (361 mg, 28% over three steps) as a yellow oil.

Ethyl (E)-2-(2-methoxybenzylidene)but-3-enoate



Light yellow liquid, 208 mg, 61% (>20:1 dr)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.36 (d, J = 7.2 Hz, 1H), 7.32 (td, J = 8.0, 1.6 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 6.59 (ddd, J = 17.8, 11.6, 1.0

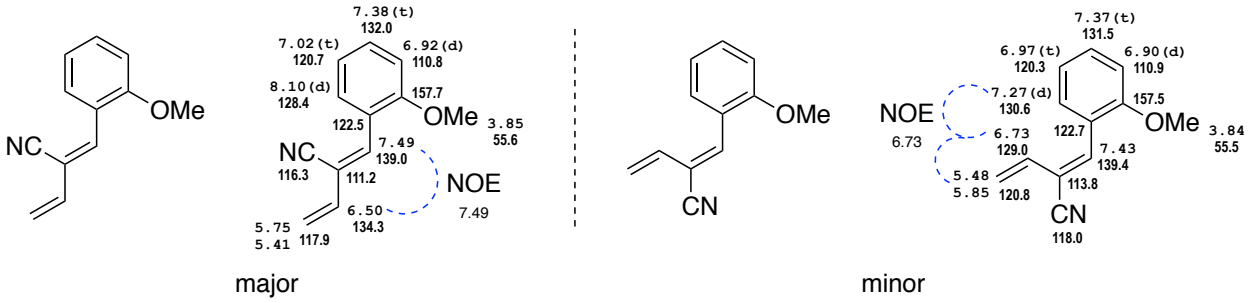
Hz, 1H), 5.86 (dd, J = 17.8, 1.8 Hz, 1H), 5.38 (dt, J = 11.6, 1.6 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 157.9, 135.3, 131.3, 130.4, 130.2, 130.1, 124.4, 120.2, 120.2, 110.7, 60.9, 55.6, 14.4.

HRMS (ESI – TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{16}O_3$ 232.1099; Found 255.0992.

R_f: 0.6 (hexanes – ethyl acetate 95:5)

2-(2-methoxybenzylidene)but-3-enenitrile



Light yellow solid, 107 mg, 79% (4.1:1 dr)

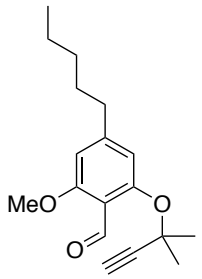
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.8, 1.2 Hz, 4H), 7.49 (s, 4H), 7.43 (s, 1H), 7.41 – 7.35 (m, 6H), 7.27 (dd, J = 7.6, 2.2 Hz, 1H), 7.02 (tq, J = 7.5, 1.0, 0.5, 0.4 Hz, 5H), 6.97 (t, J = 7.4 Hz, 1H), 6.93 – 6.88 (m, 6H), 6.73 (ddd, J = 14.7, 9.8, 0.9 Hz, 1H), 6.50 (ddd, J = 17.1, 10.4, 0.8 Hz, 5H), 5.85 (dd, J = 17.2, 0.9 Hz, 1H), 5.75 (d, J = 17.1 Hz, 5H), 5.48 (dd, J = 10.6, 1.6 Hz, 1H), 5.41 (dd, J = 10.4, 0.8 Hz, 5H), 3.85 (s, 15H), 3.84 (s, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 157.5, 139.4, 139.0, 134.3, 132.0, 131.5, 130.6, 129.0, 128.4, 122.7, 122.5, 120.8, 120.7, 120.3, 118.0, 117.9, 116.3, 113.8, 111.2, 110.9, 110.8, 55.6, 55.5.

HRMS (ESI – TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{11}NO$ 185.0841; Found 186.0913.

R_f: 0.7 (hexanes – ethyl acetate 90:10)

2-methoxy-6-((2-methylbut-3-yn-2-yl)oxy)-4-pentylbenzaldehyde (2)



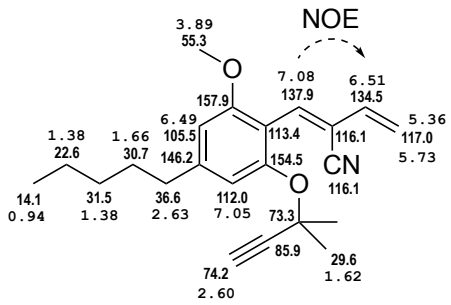
Yellow liquid, 4.7 g, 72%

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.00 (s, 1H), 6.45 (s, 1H), 3.86 (s, 3H), 2.62 – 2.54 (m, 3H), 1.67 (s, 6H), 1.62 – 1.54 (m, 2H), 1.31 (dq, J = 7.6, 3.5 Hz, 4H), 0.89 (t, J = 6.9 Hz, 3H).

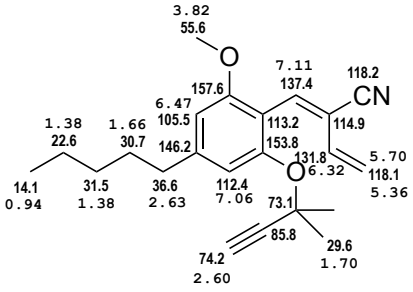
^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 161.0, 159.3, 151.3, 116.1, 112.7, 106.1, 85.5, 74.8, 73.7, 55.9, 36.8, 31.3, 30.3, 29.5, 22.5, 14.0.

R_f: 0.6 (hexanes – ethyl acetate 85:15)

2-(2-methoxy-6-((2-methylbut-3-yn-2-yl)oxy)-4-pentylbenzylidene)but-3-enenitrile (*Z*/*E*-3)



major



minor

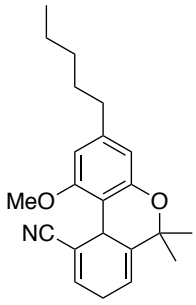
Yellow liquid, 2.2 g, 68% (2.4:1 dr)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 – 7.02 (m, 7H), 6.52 – 6.43 (m, 6H), 6.29 (ddd, J = 17.3, 10.5, 0.9 Hz, 1H), 5.69 (dd, J = 17.1, 12.4 Hz, 3H), 5.36 – 5.31 (m, 3H), 3.86 (s, 7H), 3.79 (s, 3H), 2.60 (t, J = 8.0, 7.4 Hz, 8H), 2.58 (s, 3H), 1.68 (s, 14H), 1.67 – 1.61 (m, 7H), 1.59 (s, 6H), 1.39 – 1.30 (m, 15H), 0.94 – 0.88 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 158.7, 154.5, 153.8, 146.3, 146.2, 138.0, 137.4, 134.5, 131.8, 118.3, 118.1, 117.0, 116.1, 116.1, 114.9, 113.4, 113.2, 112.5, 112.0, 105.5, 85.9, 85.8, 74.2, 73.3, 73.1, 55.6, 55.3, 36.6, 36.6, 31.5, 31.5, 30.8, 30.8, 29.6, 22.6, 14.1.

R_f: 0.75 (hexanes – ethyl acetate 90:10)

1-methoxy-6,6-dimethyl-3-pentyl-8,10a-dihydro-6H-benzo[c]chromene-10-carbonitrile (4)



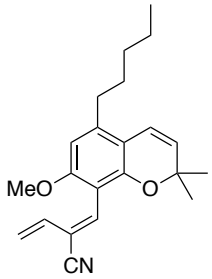
Yellow liquid, 2 g, 68%

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (ddd, J = 5.6, 3.1, 1.0 Hz, 1H), 6.40 (d, J = 1.5 Hz, 1H), 6.37 (d, J = 1.5 Hz, 1H), 5.81 (dt, J = 5.2, 2.4 Hz, 1H), 4.08 (dt, J = 4.1, 2.1, 1.6 Hz, 1H), 3.86 (s, 3H), 2.97 (dtd, J = 21.8, 5.9, 4.2 Hz, 1H), 2.70 (ddt, J = 21.5, 11.8, 2.5 Hz, 1H), 2.54 (td, J = 7.5, 2.6 Hz, 2H), 1.65 – 1.59 (m, 2H), 1.56 (s, 3H), 1.37 – 1.31 (m, 4H), 1.27 (s, 3H), 0.90 (t, J = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 154.4, 145.0, 144.0, 141.2, 118.5, 117.9, 117.2, 110.6, 108.4, 104.1, 76.8, 54.8, 36.1, 32.1, 31.5, 30.7, 27.9, 26.6, 25.4, 22.5, 14.0.

R_f: 0.6 (hexanes – ethyl acetate 90:10)

(Z)-2-((7-methoxy-2,2-dimethyl-5-pentyl-2H-chromen-8-yl)methylene)but-3-enenitrile (5)



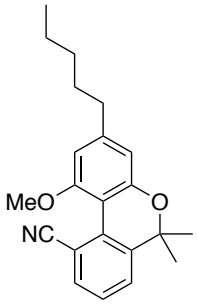
Yellow liquid, 900 mg, 30%

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (d, J = 10.0 Hz, 1H), 6.52 (dd, J = 17.3, 10.5 Hz, 1H), 6.45 (s, 1H), 5.85 (d, J = 17.3 Hz, 1H), 5.74 (d, J = 10.0 Hz, 1H), 5.49 (d, J = 10.2 Hz, 1H), 3.97 (s, 3H), 2.79 (t, J = 8.3 Hz, 2H), 1.79 – 1.71 (m, 2H), 1.56 (s, 6H), 1.56 – 1.52 (m, 4H), 1.10 (t, J = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 157.04, 151.87, 141.73, 136.46, 131.96, 128.33, 118.80, 118.44, 117.72, 114.87, 112.86, 109.24, 103.92, 76.61, 55.50, 33.04, 31.78, 30.95, 27.93, 22.58, 14.10.

R_f: 0.75 (hexanes – ethyl acetate 90:10)

1-methoxy-6,6-dimethyl-3-pentyl-6H-benzo[c]chromene-10-carbonitrile (6)



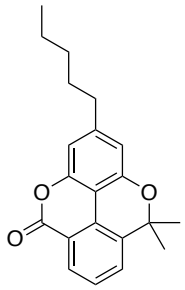
Yellow liquid, 1.9 g, 99%

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.7, 1.3 Hz, 1H), 7.43 (dd, J = 7.8, 1.3 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 6.51 (d, J = 0.9 Hz, 2H), 3.98 (s, 3H), 2.60 (t, J = 7.9 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.57 (s, 6H), 1.36 (dq, J = 7.5, 3.9, 3.5 Hz, 4H), 0.92 (t, J = 6.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 155.3, 147.4, 143.0, 133.7, 130.5, 126.6, 126.5, 119.5, 110.6, 110.3, 108.8, 105.3, 78.0, 54.5, 36.5, 31.7, 30.7, 26.2, 22.7, 14.1.

R_f: 0.65 (hexanes – ethyl acetate 90:10)

9,9-dimethyl-2-pentyl-5H,9H-isochromeno[5,4,3-cde]chromen-5-one (7)



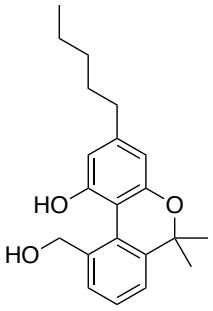
Yellow liquid, 1.9 g, 98%

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (dd, J = 7.5, 1.5 Hz, 1H), 7.58 – 7.42 (m, 2H), 6.72 (s, 1H), 6.61 (s, 1H), 2.62 (dd, J = 8.6, 6.8 Hz, 2H), 1.73 (s, 6H), 1.72 – 1.54 (m, 2H), 1.33 (dq, J = 7.2, 3.6, 3.2 Hz, 4H), 0.89 (t, J = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 151.4, 150.8, 148.1, 135.8, 128.9, 128.7, 128.6, 127.6, 118.0, 111.7, 108.6, 102.4, 79.5, 36.6, 31.5, 30.9, 29.0, 22.6, 14.1.

R_f: 0.7 (hexanes – ethyl acetate 90:10)

10-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6H-benzo[c]chromen-1-ol (8)



White solid, 1.8 g, 94%

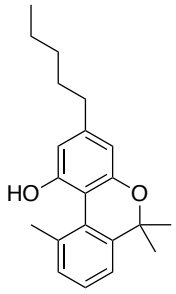
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.51 (dd, J = 7.7, 1.3 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.22 (dd, J = 7.7, 1.4 Hz, 1H), 6.51 (d, J = 1.6 Hz, 1H), 6.47 (d, J = 1.6 Hz, 1H), 4.64 (s, 2H), 3.95 (s, 1H), 2.53 (dd, J = 8.8, 6.8 Hz, 2H), 1.63 (dq, J = 9.4, 7.3 Hz, 2H), 1.55 (s, 6H), 1.35 (dq, J = 7.4, 3.8, 3.3 Hz, 4H), 0.91 (t, J = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 153.0, 145.2, 143.6, 136.4, 130.3, 127.3, 126.4, 122.3, 111.0, 110.6, 109.7, 78.8, 64.6, 35.8, 31.7, 30.6, 26.6, 22.7, 14.1.

HRMS (ESI – TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{26}O_3$ 326.1882; Found 349.1774.

R_f: 0.5 (hexanes – ethyl acetate 85:15)

6,6,10-trimethyl-3-pentyl-6H-benzo[c]chromen-1-ol (10)



Colourless liquid, 110 mg, 74%

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 2H), 7.14 (dd, J = 7.1, 1.8 Hz, 1H), 6.51 (s, 1H), 6.43 (s, 1H), 4.82 (s, 1H), 2.56 (t, J = 8.0 Hz, 2H), 2.41 (s, 3H), 1.69 – 1.48 (m, 8H), 1.34 (p, J = 3.8 Hz, 4H), 0.90 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 152.0, 145.1, 143.8, 134.1, 130.9, 126.9, 126.5, 120.3, 110.7, 110.3, 110.0, 79.0, 35.9, 31.7, 30.6, 26.6, 22.7, 21.7, 14.2.

HRMS (ESI – TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{26}O_2$ 310.1933; Found 311.2006.

R_f: 0.75 (hexanes – ethyl acetate 95:5)

Physical properties of axially-chiral cannabinols

Cartesian coordinates of the optimized geometries 11 – 16 (Figure 5A) at ωB97X/6-31G(d) level with implicit solvation:

Structure 11

O	0.710822	1.916979	-0.506279
C	1.369403	0.745203	-0.282298
C	2.734916	0.762562	-0.591785
C	3.521031	-0.357464	-0.365582
C	2.930750	-1.488395	0.205698
C	1.573177	-1.494511	0.507220
C	0.739571	-0.399920	0.217834
C	-0.754076	-0.394826	0.494845
C	-1.511743	-1.622218	0.018744
C	-2.794430	-1.587096	-0.353068
C	-3.607400	-0.312067	-0.359723
C	-2.875298	0.885789	0.256008
C	-1.400607	0.843353	-0.142790
C	-0.578556	2.107475	0.128005
O	0.998537	-2.571246	1.119859
C	-3.523826	-2.821050	-0.813174
C	-0.360898	2.401480	1.611663
C	-1.155186	3.327945	-0.578096
H	3.161494	1.677088	-0.995221
H	-0.888104	-0.327342	1.587615
H	-4.559494	-0.483817	0.160624
H	-2.960291	0.854211	1.350655
H	1.674661	-3.248731	1.259861

H	-3.936942	-2.678576	-1.820410
H	0.206261	3.330774	1.727134
H	-0.429454	4.146629	-0.543255
H	-1.375949	3.103081	-1.627072
H	3.534909	-2.366216	0.431040
H	-0.979984	-2.569384	0.009893
H	-3.353363	1.813957	-0.075343
H	-1.356181	0.704516	-1.234221
H	-2.866650	-3.696121	-0.832161
H	-4.372911	-3.043256	-0.153822
H	0.194351	1.598973	2.107003
H	-1.322144	2.520755	2.123144
H	-2.073653	3.666203	-0.090113
H	-3.879365	-0.085515	-1.401925
C	4.990461	-0.359997	-0.705114
H	5.595930	-0.637675	0.164667
H	5.207715	-1.086847	-1.496060
H	5.320562	0.623841	-1.051000

Structure 12

C	-0.841152	-0.381388	-0.022135
C	-1.679072	-1.495889	-0.150347
C	-1.421374	0.900070	0.015316
C	-2.806189	1.027296	-0.043601
C	-3.623813	-0.093322	-0.146589
C	-3.067218	-1.370140	-0.204852
H	-4.704068	0.029949	-0.191371
H	-3.264162	2.012217	-0.011270
C	0.638143	-0.466035	-0.002346
C	1.401518	-1.616638	0.272975
C	2.790129	-1.609379	0.160355
C	3.473630	-0.453987	-0.219170
C	1.357652	0.692031	-0.336613
C	2.744533	0.705238	-0.461269
O	0.751332	-2.748940	0.660111
H	3.343689	-2.522647	0.373759
C	4.977988	-0.455725	-0.315441
H	3.235406	1.634577	-0.736663
H	5.430477	-0.333185	0.675640
H	5.335502	0.362688	-0.947097
H	5.348314	-1.398875	-0.729461
H	1.405015	-3.442663	0.826044

O	0.708309	1.860004	-0.594405
C	-0.505079	2.105647	0.155210
C	-0.144774	2.347091	1.623910
C	-1.066943	3.375154	-0.471538
H	-1.364642	3.198112	-1.509355
H	-0.296793	4.151952	-0.453344
H	-1.931476	3.742637	0.087589
H	0.314020	1.458958	2.070135
H	-1.048946	2.586360	2.192708
H	0.556175	3.184777	1.706032
H	-1.239443	-2.484831	-0.211701
C	-3.941891	-2.595684	-0.303579
H	-3.448084	-3.392597	-0.868642
H	-4.170488	-2.994478	0.692083
H	-4.894153	-2.367499	-0.792464

Structure 13

C	-0.938377	0.584912	-0.04373
C	-1.567751	1.815482	-0.32443
C	-1.730901	-0.574755	0.089052
C	-3.117961	-0.482743	0.121171
C	-3.737656	0.754016	-0.02411
C	-2.964360	1.876871	-0.27919
H	-3.449954	2.830367	-0.4784
H	-4.821299	0.830910	0.011363
H	-3.724260	-1.375383	0.245598
C	0.531048	0.382770	-0.00563
C	1.489380	1.277736	0.497856
C	2.855771	1.021845	0.360774
C	3.308683	-0.164642	-0.21195
C	1.017506	-0.858859	-0.44722
C	2.372931	-1.127721	-0.58812
O	1.054947	2.378016	1.167295
H	3.571919	1.752547	0.733448
C	4.783628	-0.418441	-0.39098
H	2.681451	-2.101146	-0.95963
H	5.091538	-0.190810	-1.41837
H	5.030398	-1.467750	-0.20129
H	5.381910	0.204627	0.280403
H	1.819470	2.906960	1.434841
O	0.133827	-1.853656	-0.73919

C	-1.016860	-1.920087	0.144445
C	-1.841807	-3.062599	-0.43435
C	-0.560069	-2.261184	1.565254
H	0.069135	-1.471821	1.987249
H	0.004972	-3.199559	1.563069
H	-1.435551	-2.380460	2.211444
H	-2.206638	-2.812609	-1.43498
H	-2.696388	-3.298096	0.205436
H	-1.212863	-3.955301	-0.5012
C	-0.830434	3.056333	-0.76816
H	-0.585650	3.711441	0.071518
H	0.109583	2.808776	-1.26942
H	-1.454579	3.618830	-1.47004

Structure 14

C	-0.934191	0.222829	-0.084061
C	-1.752239	1.331202	-0.370847
C	-1.540702	-1.040334	0.088139
C	-2.924514	-1.153196	0.155469
C	-3.729867	-0.026933	0.010959
C	-3.140247	1.192192	-0.283288
H	-3.761526	2.063970	-0.479350
H	-4.810853	-0.115720	0.078087
C	-1.242553	2.674732	-0.859962
H	-3.386904	-2.124068	0.309214
C	0.551523	0.246724	-0.047321
C	1.369134	1.277593	0.442800
C	2.758051	1.210984	0.342706
C	3.384705	0.087976	-0.195424
C	1.216394	-0.920361	-0.456992
C	2.599158	-0.999911	-0.569229
O	0.782987	2.343394	1.066806
H	3.357344	2.042466	0.709948
C	4.883890	0.042835	-0.341104
H	3.045735	-1.927788	-0.915634
H	5.183453	0.386414	-1.338271
H	5.264365	-0.975478	-0.216513
H	5.376035	0.688753	0.392161
O	-1.429834	3.716299	0.082871
H	-1.831497	2.960903	-1.737856
H	-0.196458	2.604294	-1.179253

H	1.475271	2.949937	1.366234
O	0.487987	-2.035263	-0.741261
C	-0.635408	-2.264643	0.149909
C	-1.284996	-3.520866	-0.416442
C	-0.125778	-2.520345	1.570473
H	0.372916	-1.638829	1.984439
H	0.579949	-3.357957	1.571228
H	-0.968957	-2.770782	2.222033
H	-1.688868	-3.334357	-1.415862
H	-2.090983	-3.876981	0.230488
H	-0.530161	-4.309925	-0.482348
H	-0.831853	3.491817	0.810958

Structure 15

C	-0.703059	0.391179	-0.100950
C	-1.965188	-0.252073	-0.061162
C	-0.657585	1.802020	-0.180685
C	-1.798154	2.533469	-0.486806
C	-3.002996	1.873268	-0.686384
C	-3.079196	0.512264	-0.434157
H	-4.049683	0.034378	-0.507016
H	-3.893363	2.425393	-0.975210
C	-2.258422	-1.694969	0.446006
H	-1.751331	3.614764	-0.580189
C	0.635933	-0.259208	-0.070430
C	1.010598	-1.415156	-0.768554
C	2.294471	-1.946554	-0.663464
C	3.274378	-1.303435	0.091921
C	1.679597	0.435500	0.557294
C	2.963561	-0.079995	0.681680
O	0.085431	-2.019195	-1.578085
H	2.533834	-2.868221	-1.191268
C	4.649022	-1.902589	0.240298
H	3.716538	0.504550	1.203182
H	4.735215	-2.436289	1.194017
H	5.421562	-1.127549	0.229021
H	4.863132	-2.616485	-0.560447
O	-2.473334	-2.583338	-0.647695
H	0.508749	-2.753837	-2.045588
O	1.433442	1.690031	1.028579
C	0.665454	2.507592	0.107029

C	0.475272	3.812558	0.871952
C	1.471414	2.747645	-1.172004
H	1.653737	1.814271	-1.713423
H	2.434651	3.209320	-0.929681
H	0.915821	3.420566	-1.832813
H	-0.133478	3.651465	1.766466
H	-0.002660	4.574202	0.250937
H	1.456129	4.190227	1.175975
H	-1.644473	-2.566475	-1.153101
C	-1.184893	-2.255600	1.393170
H	-0.257875	-2.516011	0.885097
H	-0.951071	-1.543169	2.192024
H	-1.572360	-3.170530	1.852280
C	-3.575927	-1.722543	1.235667
H	-4.441119	-1.519764	0.601343
H	-3.710624	-2.723107	1.657680
H	-3.561321	-0.997926	2.055778

Structure 16

C	0.601502	-0.989612	-0.268128
C	-0.579806	-1.583713	-0.746994
C	1.690948	-1.834604	0.047282
C	1.542676	-3.215624	0.034054
C	0.335530	-3.793316	-0.348495
C	-0.695288	-2.975886	-0.774810
H	-1.616357	-3.415358	-1.152784
H	0.223881	-4.873940	-0.360649
C	-1.678511	-0.806736	-1.431033
H	2.378527	-3.855608	0.300447
C	0.861342	0.477161	-0.168470
C	-0.033064	1.500393	0.185323
C	0.338913	2.840212	0.206697
C	1.633797	3.226535	-0.137011
C	2.190727	0.892881	-0.371040
C	2.567064	2.230198	-0.403299
O	-1.283974	1.147551	0.665599
H	-0.381954	3.587944	0.527783
C	2.018891	4.682194	-0.169494
H	3.610136	2.469862	-0.590409
H	1.847386	5.101936	-1.167566
H	3.077959	4.818136	0.068000
H	1.425387	5.266483	0.539944
O	-3.013693	-0.849845	-0.884531

H	-1.807931	-1.223378	-2.433808
H	-1.408961	0.240346	-1.556536
O	3.171218	-0.036288	-0.522076
C	3.039048	-1.191951	0.345131
C	4.224632	-2.065084	-0.045691
C	3.154592	-0.762564	1.809824
H	2.335179	-0.100532	2.105424
H	4.104687	-0.243107	1.973953
H	3.123690	-1.648210	2.452246
H	4.128310	-2.415068	-1.077609
H	4.314888	-2.930402	0.615990
H	5.141240	-1.474725	0.042939
C	-2.427989	1.823885	0.355907
C	-3.317818	-1.208495	0.379760
O	-3.355681	1.718373	1.119978
O	-2.522510	-1.528257	1.230258
C	-4.810167	-1.139258	0.574947
H	-5.070727	-1.576993	1.538944
H	-5.117163	-0.089383	0.555667
H	-5.328929	-1.662975	-0.231712
C	-2.522490	2.577530	-0.946436
H	-2.756133	3.624628	-0.736297
H	-1.624651	2.530435	-1.561708
H	-3.368530	2.152737	-1.494222

Cartesian coordinates of the minimum 1, minimum 2 and the transition state structure (Figure 5B) for the atropisomerism at ωB97X/6-31G(d) level with implicit solvation:

Minimum 1

C	0.933797	0.220677	-0.085103
C	1.752918	1.329372	-0.366700
C	1.538736	-1.042978	0.087660
C	2.922279	-1.156314	0.159876
C	3.728403	-0.029846	0.020549
C	3.140484	1.190039	-0.274280
H	3.762764	2.061834	-0.466997
H	4.809083	-0.119096	0.091886
C	1.244008	2.670735	-0.862360
H	3.383978	-2.127490	0.313891
C	-0.551597	0.246983	-0.048739
C	-1.366391	1.279623	0.442371
C	-2.755609	1.214809	0.345116

C	-3.384781	0.092520	-0.191633
C	-1.218548	-0.919049	-0.457496
C	-2.601621	-0.996621	-0.567061
O	-0.776853	2.345102	1.063683
H	-3.353120	2.047273	0.713047
C	-4.884322	0.049470	-0.334564
H	-3.050424	-1.923694	-0.912741
H	-5.374005	0.700379	0.395912
H	-5.266535	-0.967423	-0.203751
H	-5.184874	0.387966	-1.333175
O	1.438570	3.718263	0.072402
H	0.196583	2.600967	-1.176808
H	1.830023	2.949505	-1.744648
H	-1.467538	2.952051	1.365952
O	-0.491611	-2.034545	-0.743661
C	0.632259	-2.266629	0.146255
C	0.123024	-2.525393	1.566401
C	1.281026	-3.521685	-0.423605
H	1.684519	-3.332738	-1.422720
H	0.525917	-4.310350	-0.491168
H	2.087226	-3.879711	0.222011
H	-0.375297	-1.644560	1.982308
H	0.966252	-2.777482	2.217263
H	-0.583005	-3.362752	1.565522
H	0.843215	3.500474	0.804709

Minimum 2

C	0.904105	0.163610	0.104825
C	1.801109	1.242844	-0.035189
C	1.418917	-1.149462	0.136369
C	2.790603	-1.368880	0.199539
C	3.670505	-0.292540	0.183779
C	3.172836	0.993082	0.030374
H	3.863357	1.823830	-0.081121
H	4.742512	-0.461763	0.242595
C	1.359286	2.663746	-0.356172
H	3.183226	-2.380497	0.246363
C	-0.574854	0.286516	0.086332
C	-1.340129	1.320187	0.651374
C	-2.721113	1.383361	0.461972
C	-3.393591	0.382185	-0.236943
C	-1.297239	-0.771919	-0.488555
C	-2.671866	-0.721938	-0.686963
O	-0.704614	2.234497	1.432650

H	-3.277969	2.213985	0.892598
C	-4.879342	0.479843	-0.470344
H	-3.165913	-1.565825	-1.160490
H	-5.375779	1.020880	0.341057
H	-5.334533	-0.511458	-0.555219
H	-5.087542	1.018972	-1.402114
O	2.301854	3.353115	-1.166660
H	1.161324	3.223502	0.561845
H	0.419117	2.633361	-0.917314
H	-1.342821	2.900800	1.723961
O	-0.639000	-1.905388	-0.856979
C	0.427846	-2.303701	0.044227
C	-0.156870	-2.658923	1.413665
C	1.009455	-3.544851	-0.620557
H	1.466313	-3.294977	-1.582654
H	0.204785	-4.266572	-0.789504
H	1.761064	-4.019282	0.015824
H	-0.613100	-1.788904	1.895152
H	0.639965	-3.029617	2.066239
H	-0.915877	-3.441427	1.306747
H	2.888016	3.848244	-0.582457

Transition State

C	0.853639	-0.127135	0.096504
C	1.838466	-1.149274	0.176601
C	1.324122	1.195935	-0.074530
C	2.676510	1.465036	-0.271447
C	3.605832	0.441373	-0.318860
C	3.179751	-0.848297	-0.054872
H	3.902605	-1.651955	0.034111
H	4.655683	0.652707	-0.503253
C	1.552386	-2.643255	0.109765
H	3.009021	2.492463	-0.393226
C	-0.624958	-0.312136	-0.065588
C	-1.343789	-1.526475	-0.162147
C	-2.729586	-1.593116	-0.147901
C	-3.502746	-0.443959	-0.013478
C	-1.447614	0.826762	0.024658
C	-2.843565	0.769919	0.048768
O	-0.660261	-2.703577	-0.074878
H	-3.211594	-2.565730	-0.247846
C	-5.006980	-0.520931	0.006023
H	-3.382928	1.708219	0.138032
H	-5.408712	-0.550071	-1.013803

H	-5.441201	0.349162	0.507330
H	-5.353168	-1.422076	0.522516
O	2.795984	-3.328916	0.225628
H	-1.275375	-3.422548	-0.265346
O	-0.976139	2.086886	0.104844
C	0.418682	2.409702	0.077839
C	0.489852	3.286211	-1.174639
C	0.699945	3.072669	1.433059
H	0.542002	2.352701	2.242042
H	0.020210	3.919244	1.577296
H	1.732226	3.432246	1.487831
H	0.295862	2.690427	-2.071977
H	1.465134	3.768673	-1.279678
H	-0.273286	4.067180	-1.102113
H	2.608858	-4.265900	0.095885
H	0.906393	-2.925203	0.914811
H	1.091921	-2.882855	-0.825898

VT-NMR Studies

The barrier to rotation was measured by selective inversion of one of the methylene protons, followed by monitoring the intensity of its signal and of that of its isochronous partner, as they both relax to equilibrium. These intensities are functions of the exchange rate (k) and of the longitudinal relaxation rates (R1). These rates were determined by iteratively fitting the two R1s in the non-selective inversion-recovery spectra, and the exchange rate k in the selective inversion spectra, using the CIFIT program of Bain and co-workers[2] for four values of temperature in the range -5 to 25 ºC. A plot ln(k/T) *vs.* 1/T (see ESI for details) provided the thermodynamic parameters ΔH = 16.3 kcal/mol, ΔS = 2.85 cal/mol/K and ΔG = 15.5 kcal/mol

^{1}H and ^{1}H-^{13}C gHSQC and gHMBC NMR spectra were obtained on Varian INOVA spectrometer, operating at 500 MHz for proton, equipped with a 5 mm indirect detection probe and z-axis gradients. Chemical shifts, reported in δ (ppm), were referenced on the solvent, on the TMS scale for ^{1}H and ^{13}C. The temperature was calibrated to the neat

methanol standard. The signal of the methylene proton at lower field was inverted. The intensity was monitored over 11 s time intervals, in spectra with an acquisition time of 3.3 s and a relaxation delay of 5 s, taken in 4 transients. The intensities of the two signals in the selective inversion spectra (e1 and e2) and in the non-selective ones (t1 and t2) are given in Table 1.

The rates of exchange could be measured in the temperature interval -5 to 25 ºC, and are given in Table 2. Thermodynamic parameters were calculated from the slope and intercept of the ln(k/T) vs. 1/T, (figure 1) , ΔH = 16.3 kcal/mol, ΔS = 2.85 cal/mol/K and ΔG = 15.5 kcal/mol.

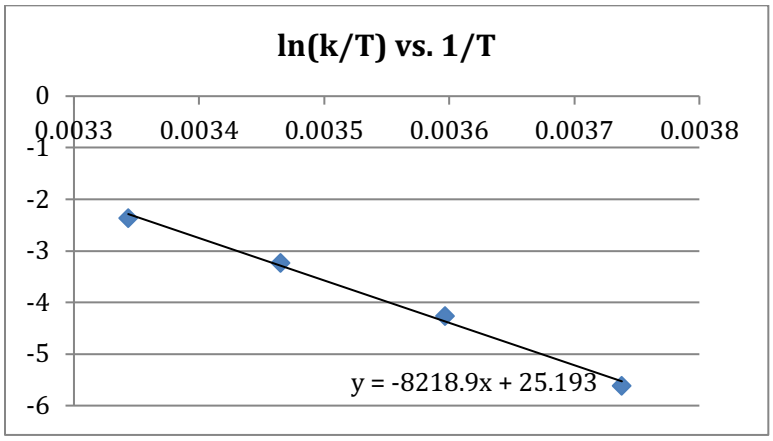


Figure 1. Plot ln(k/T) *vs.* 1/T

Table 1. Intensities of the inverted line (1) and the isochronous one (2), in the selective inversion (e) and the non-selective inversion (t) experiment, as a function of the monitoring time (d2).

temp (oC)			-5				5	
d2 (s)	e1	e2	t1	t2	e1	e2	t1	t2
0.0125	-0.688	0.894	-0.894	-0.902	-0.541	0.698	-0.886	-0.892
0.025	-0.633	0.873	-0.843	-0.851	-0.456	0.651	-0.856	-0.863
0.05	-0.526	0.851	-0.760	-0.777	-0.299	0.564	-0.776	-0.789
0.1	-0.330	0.802	-0.601	-0.627	-0.067	0.462	-0.641	-0.661
0.2	-0.028	0.738	-0.324	-0.360	0.214	0.412	-0.393	-0.415
0.4	0.381	0.720	0.093	0.052	0.478	0.501	0.013	-0.022
0.8	0.740	0.801	0.570	0.537	0.731	0.729	0.479	0.468

1.6	0.942	0.940	0.910	0.896	0.919	0.919	0.879	0.877
3.2	0.980	0.980	1.001	0.995	0.990	0.990	1.004	1.003
6.4	0.995	0.992	1.000	1.000	1.000	0.998	1.004	1.006
12.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

temp (oC)	15				25			
d2 (s)	e1	e2	t1	t2	e1	e2	t1	t2
0.0125	-0.317	0.410	-0.889	-0.894	-0.156	0.184	-0.887	-0.891
0.025	-0.204	0.329	-0.855	-0.863	-0.055	0.110	-0.854	-0.863
0.05	-0.050	0.237	-0.789	-0.796	0.041	0.078	-0.805	-0.806
0.1	0.112	0.196	-0.663	-0.675	0.111	0.114	-0.697	-0.703
0.2	0.256	0.262	-0.449	-0.458	0.212	0.210	-0.503	-0.507
0.4	0.434	0.432	-0.090	-0.098	0.373	0.373	-0.178	-0.178
0.8	0.667	0.664	0.386	0.382	0.611	0.604	0.289	0.285
1.6	0.884	0.882	0.820	0.817	0.845	0.844	0.746	0.745
3.2	0.986	0.987	0.998	0.998	0.977	0.973	0.981	0.983
6.4	0.999	0.999	1.010	1.010	1.003	0.999	1.007	1.006
12.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 2. Rates of exchange (s^{-1}) as a function of temperature

temp	corrected	rate	1/T	ln(k/T)
-5	-5.64	0.974	0.003738	-5.61553
5	4.885	3.925	0.003597	-4.26041
15	15.41	11.42	0.003465	-3.22957
25	25.93	28.13	0.003343	-2.36393

Biological Evaluation

Table 3. The statistical results of one-way ANOVAs examining the dose effects of THC and *ax*-CBN (10) in cannabinoid-related physiological alterations and behavioral alterations in a model of neuropathic pain

Treatment	**Dose**
Cannabinoid-related physiological alterations	
1. Tail-flick Analgesia	
THC	$F(3,35) = 7.22$; $P < 0.0001$
ax-CBN	$F(4,45) = 9.69$; $P < 0.001$
2. Body Temperature	
THC	$F(3,35) = 23.13$; $P < 0.0001$

ax-CBN	$F(4,45) = 17.42$; $P < 0.0001$
3. Locomotion	
THC	$F(3,35) = 35.29$; $P < 0.0001$
ax-CBN	$F(4,45) = 18.36$; $P < 0.0001$
Behavioral alterations in a neuropathic pain model	
1. Mechanical Allodynia	
THC	$F(3,44) = 26.56$; $P < 0.0001$
ax-CBN	$F(4,55) = 20.81$; $P < 0.0001$
2. Thermal Hyperalgesia	
THC	$F(3,22) = 23.44$; $P < 0.0001$
ax-CBN	$F(4,25) = 5.52$; $P < 0.01$

Table 4. The statistical results of two-way ANOVAs examining the interaction of dose and time-related effects of THC and *ax*-CBN (10) in behavioral alterations in a model of neuropathic pain

Drug	**Interaction of treatment and time**
Mechanical Allodynia	
THC	$F(7,98) = 4.81$; $P < 0.0001$
AX-CBN	$F(7,98) = 2.98$; $P < 0.01$
Thermal Hyperalgesia	
THC	$F(7,70) = 10.71$; $P < 0.0001$
AX-CBN	$F(7,70) = 5.99$; $P < 0.0001$

Table 5. The calculated ED_{50} values for *ax*-CBN (10) and THC to reverse allodynia and thermal hyperalgesia, as well as produce acute antinociception, hypothermia, and hypolocomotion. Also shown are selected potency ratios.

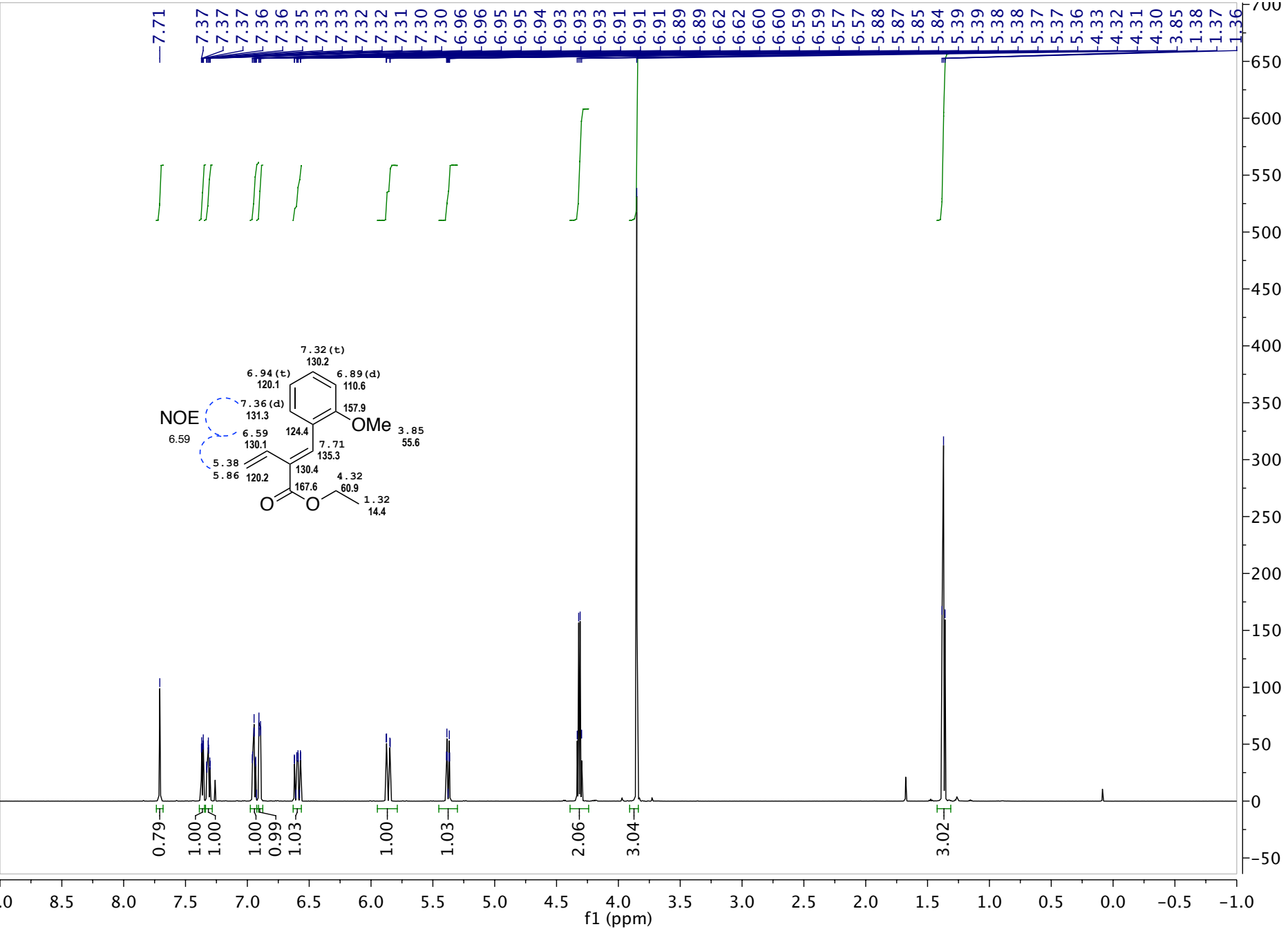
	***ax*-CBN**	**THC**
Allodynia ED_{50} ((95% CL) mg/kg)	153.01 (130.40 – 179.53)	30.32 (26.68 – 34.47)
Thermal Hyperalgesia ED_{50} ((95% CL) mg/kg)	126.01 (95.88 – 165.62)	15.88 (13.58 – 18.56)
Antinociception ED_{50} ((95% CL) mg/kg)	N.A.	N.A.

Body Temp. ED_{50} ((95% CL) mg/kg)	308.98 (201.28 – 471.29)	17.51 (10.98 – 27.93)
Hypolocomotion ED_{50} ((95% CL) mg/kg)	290.20 (233.10 – 319.27)	25.53 (18.14 – 30.54)
Potency Ratio (Thermal Hyperalgesia/ Allodynia)	0.82 (0.53 – 1.27)	0.52 (0.39 – 0.70)
Potency Ratio (Temp/ Allodynia)	2.01 (1.12 – 3.61)	0.58 (0.32 – 1.05)
Potency Ratio (Locomotion/ Allodynia)	1.89 (1.29 – 2.45)	0.84 (0.53 – 1.14)

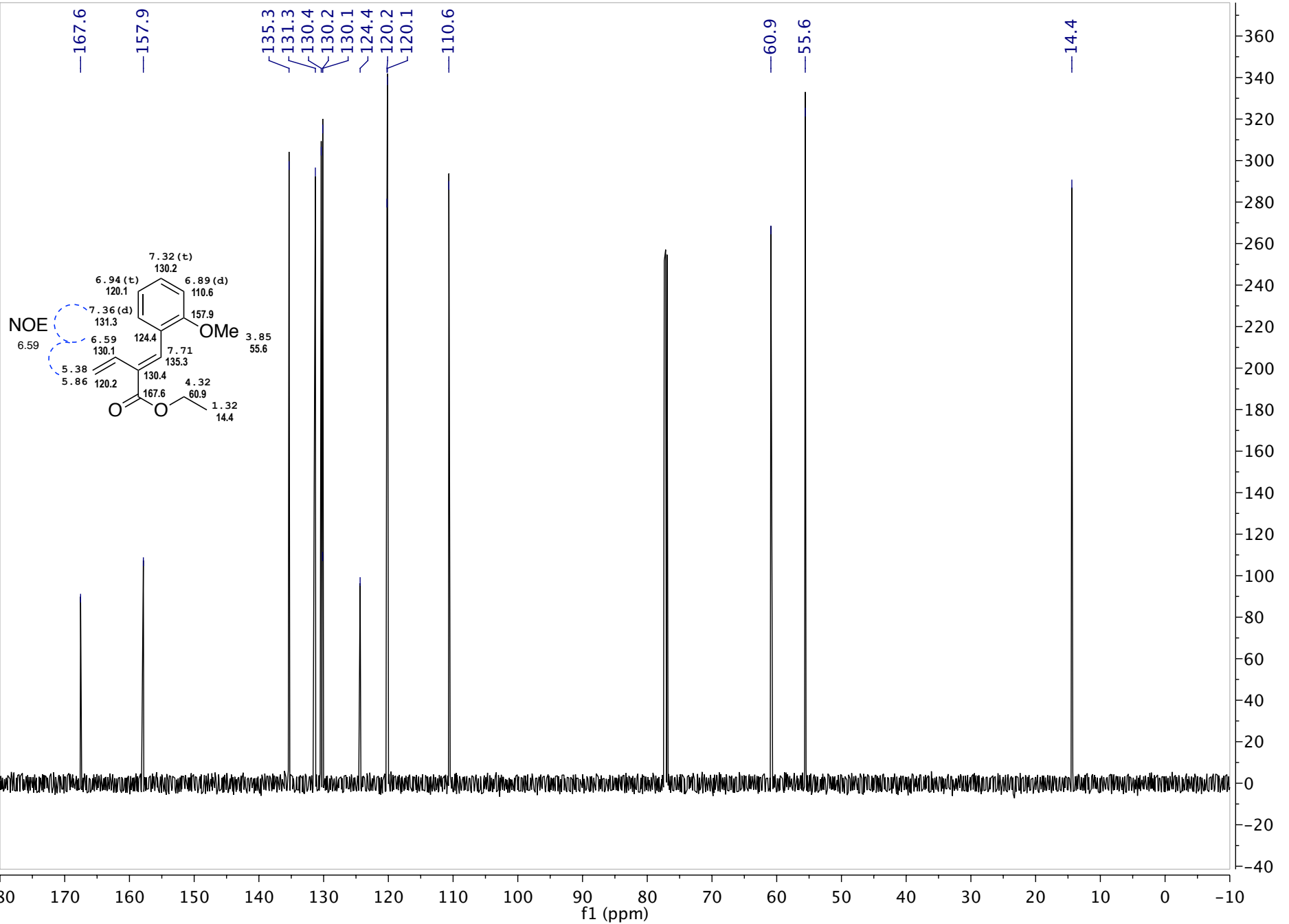
References

1. Lesch, B.; Toräng, J.; Nieger, M.; Bräse, S. *Synthesis*, **2005**, *11*, 1888.
2. Bain, A. D.; Cramer, J. A. *J. Magn. Res. Series* A, **1996**, *118*(1), 21.

^{1}H spectrum of ethyl (E)-2-(2-methoxybenzylidene)but-3-enoate ($CDCl_3$)



^{13}C spectrum of ethyl (E)-2-(2-methoxybenzylidene)but-3-enoate ($CDCl_3$)



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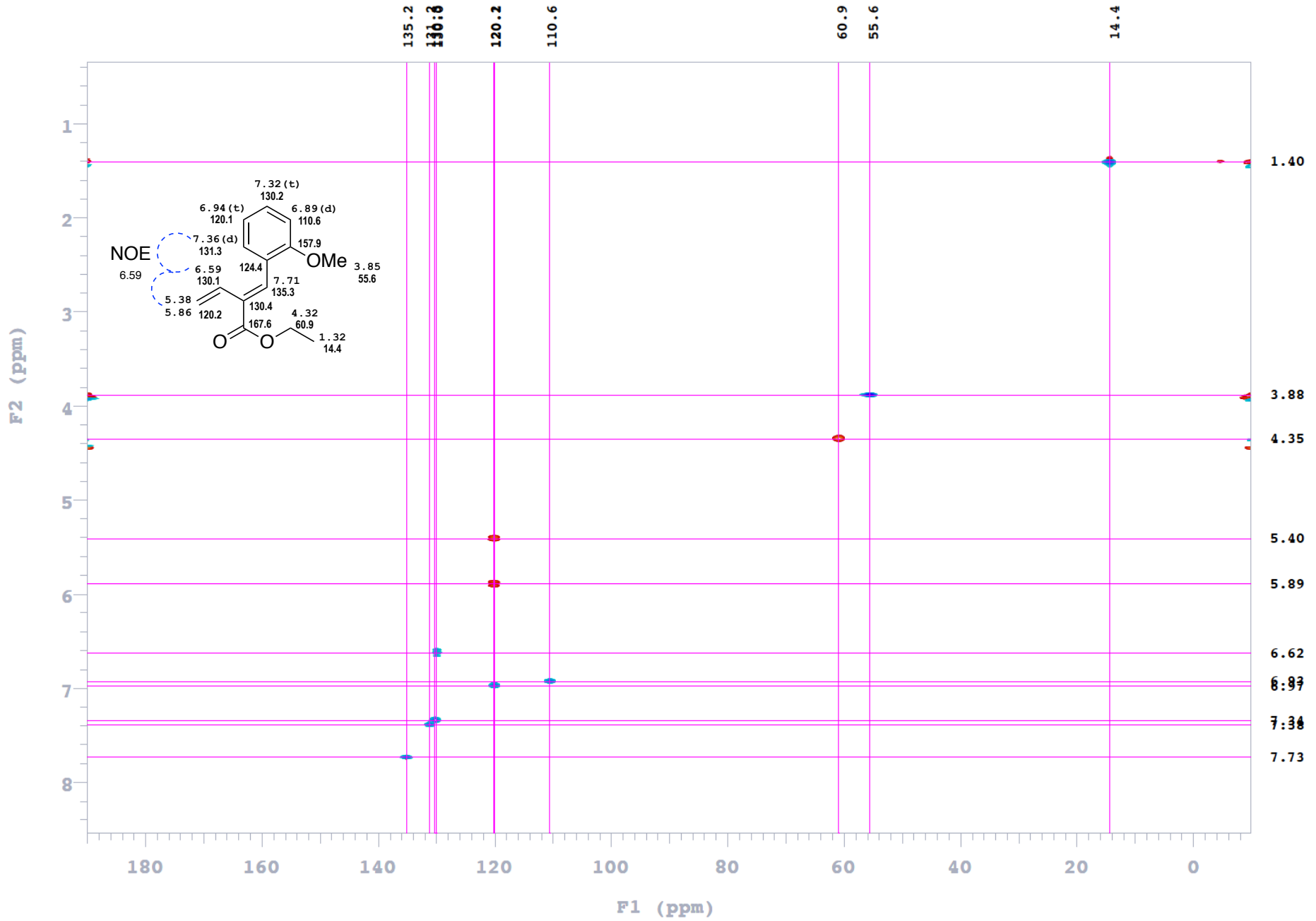

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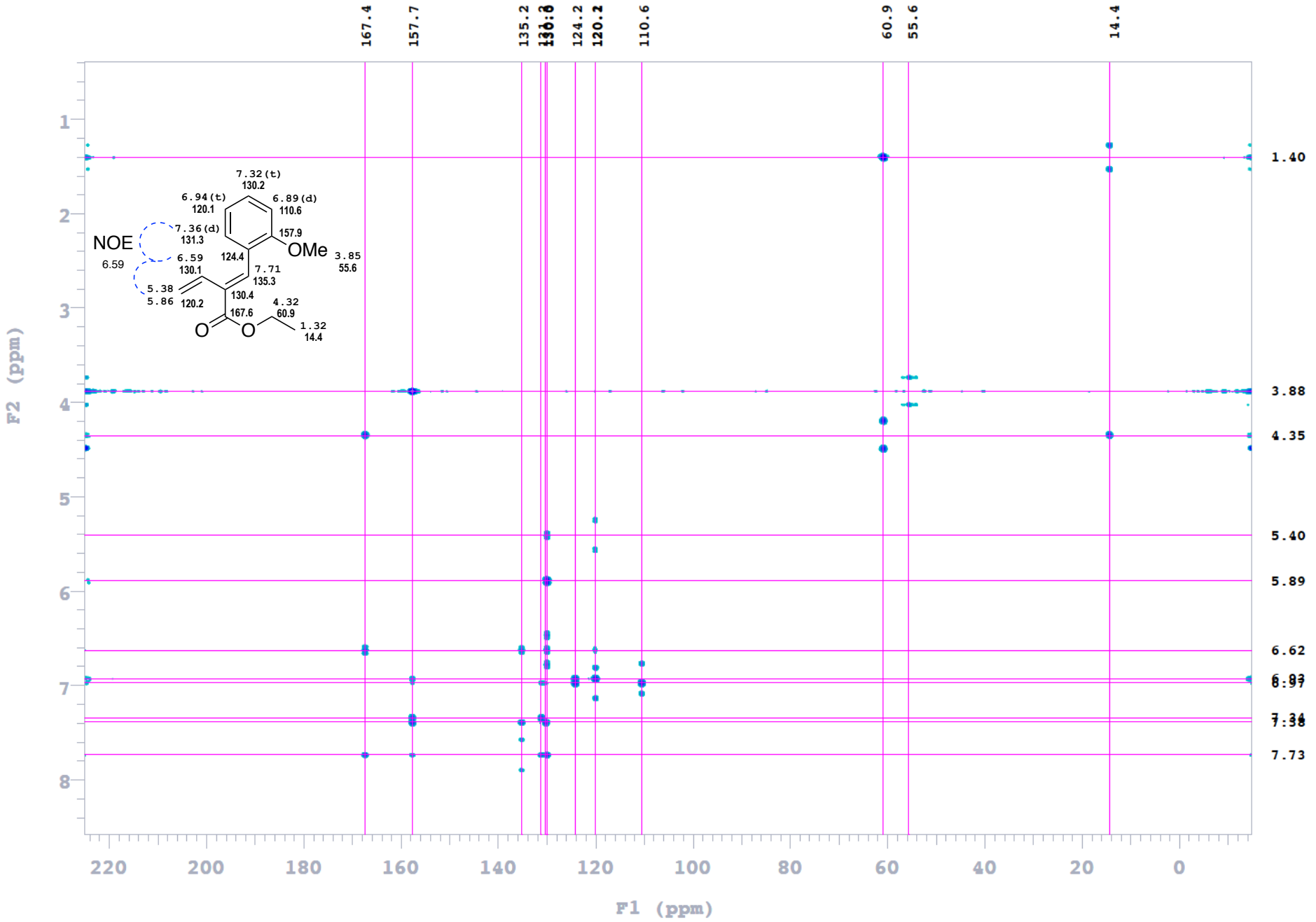
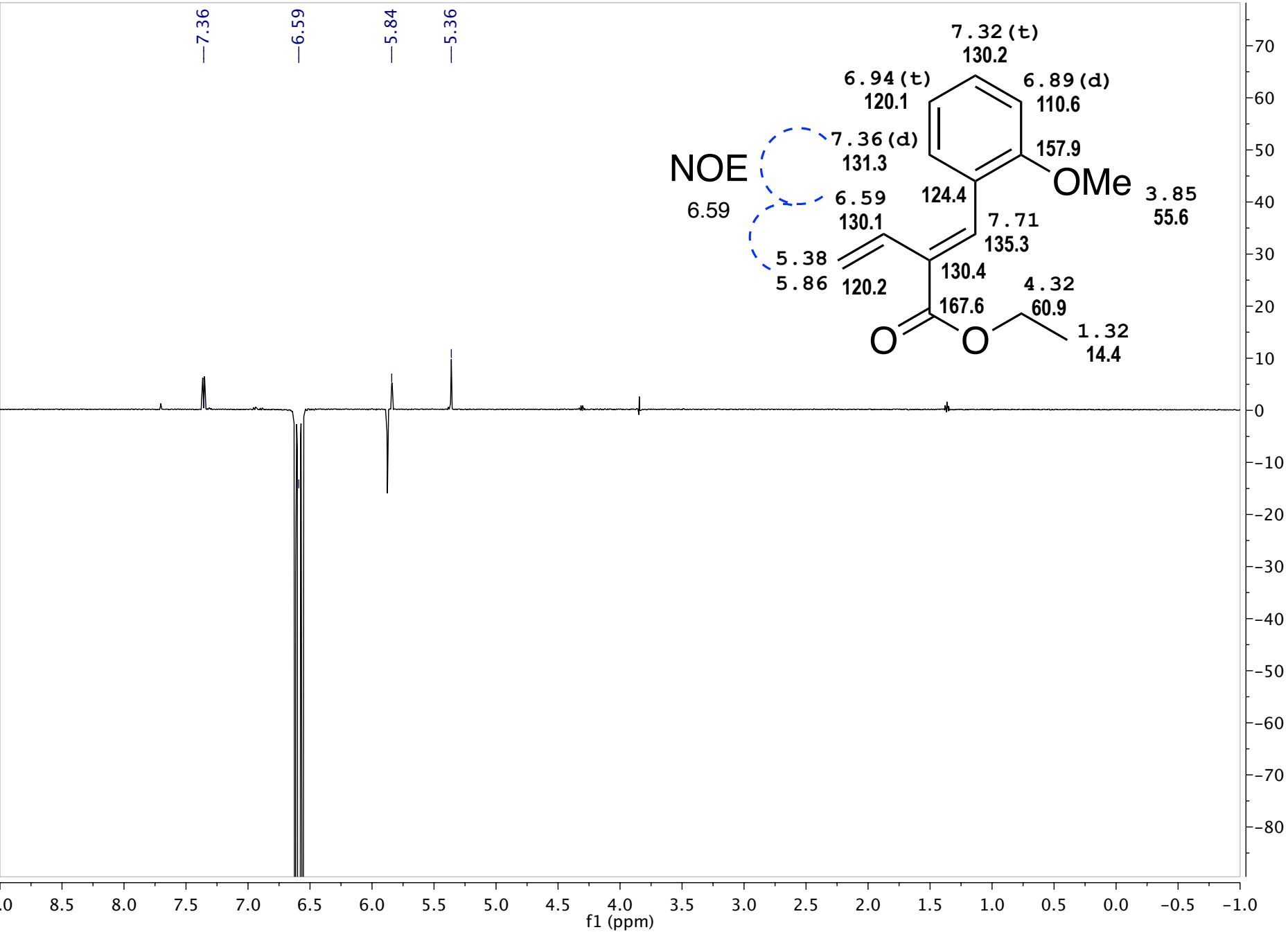


NOE spectrum of ethyl (E)-2-(2-methoxybenzylidene)but-3-enoate at 6.59 δ ($CDCl_3$)



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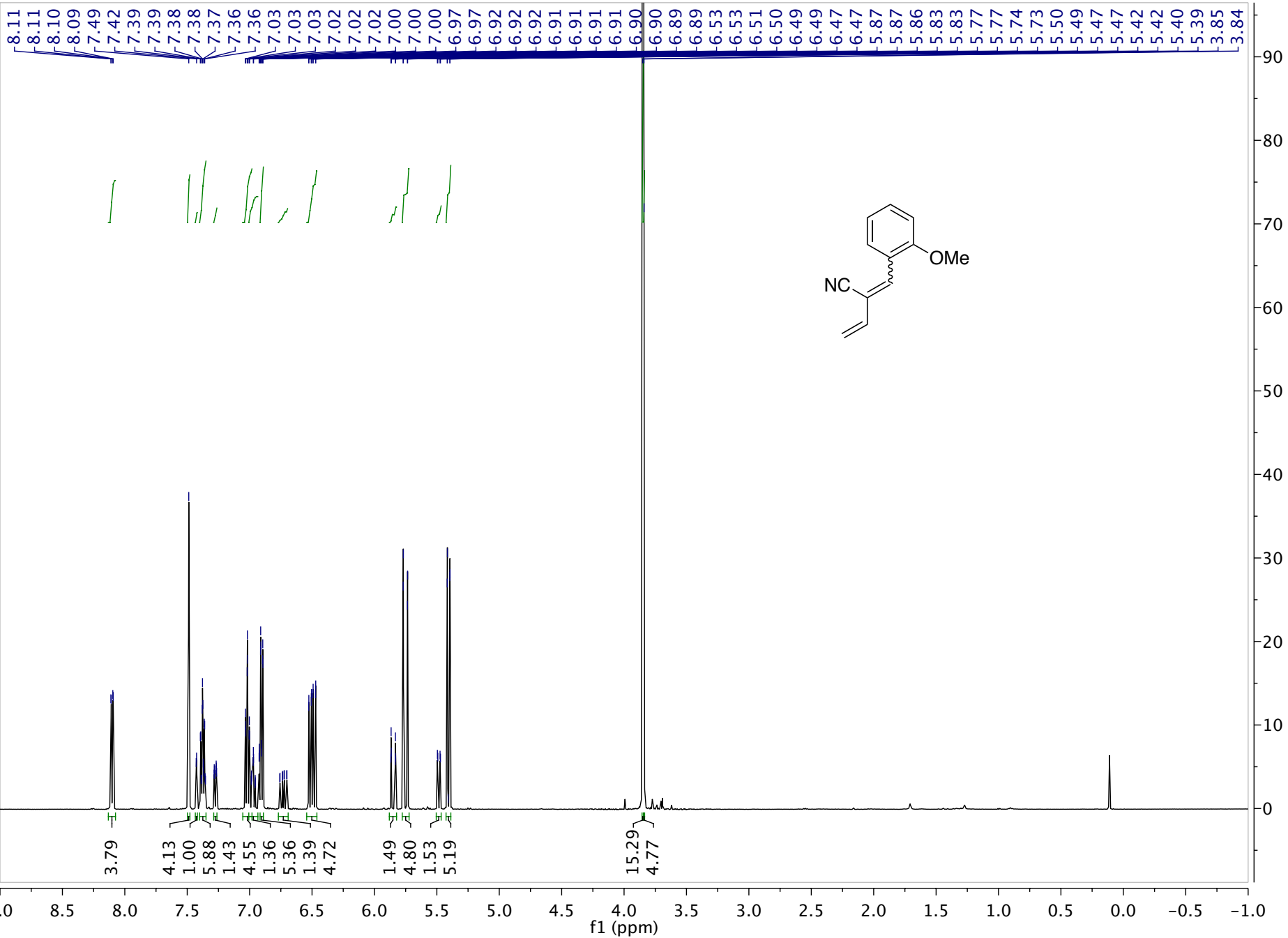

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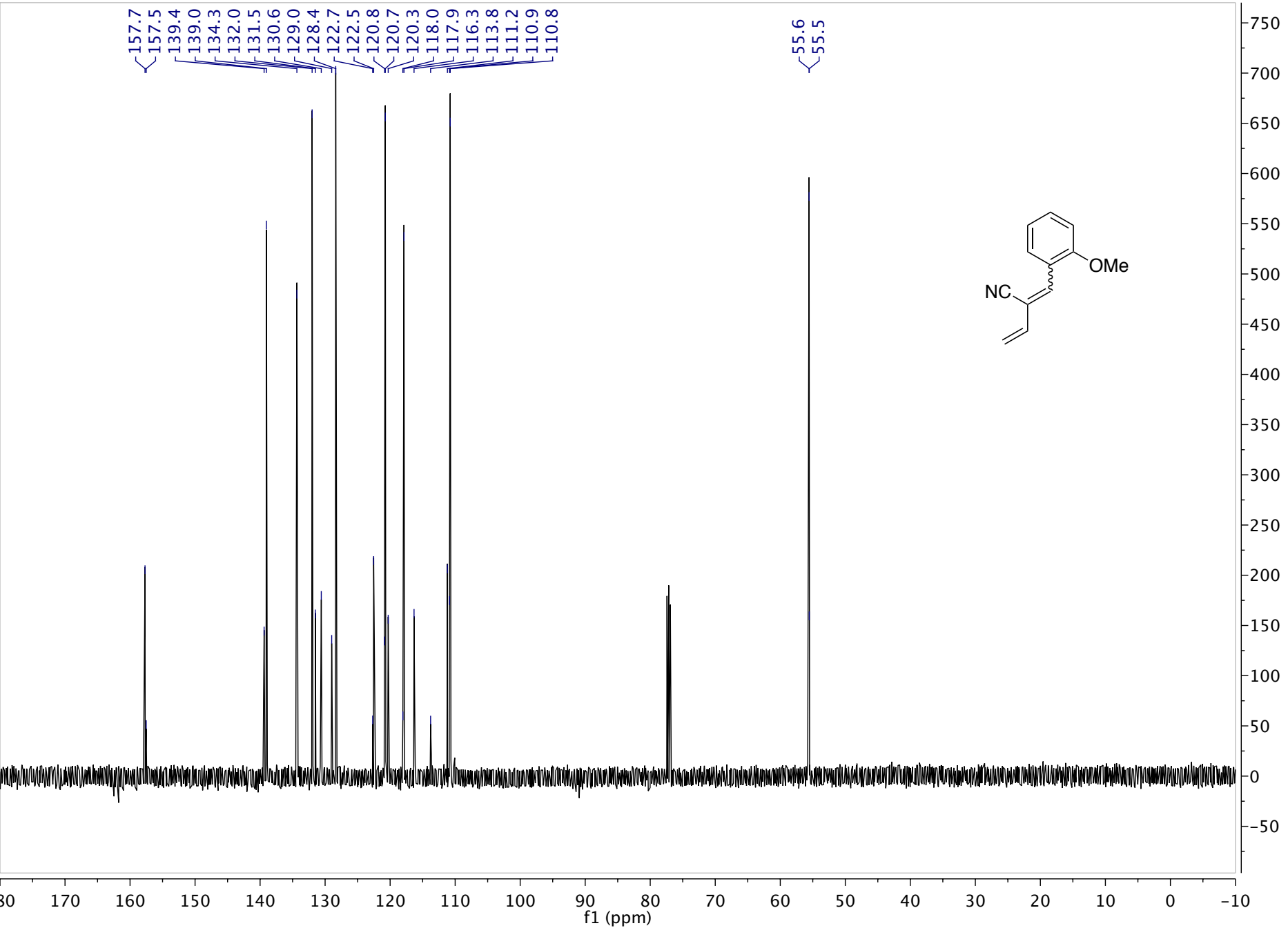

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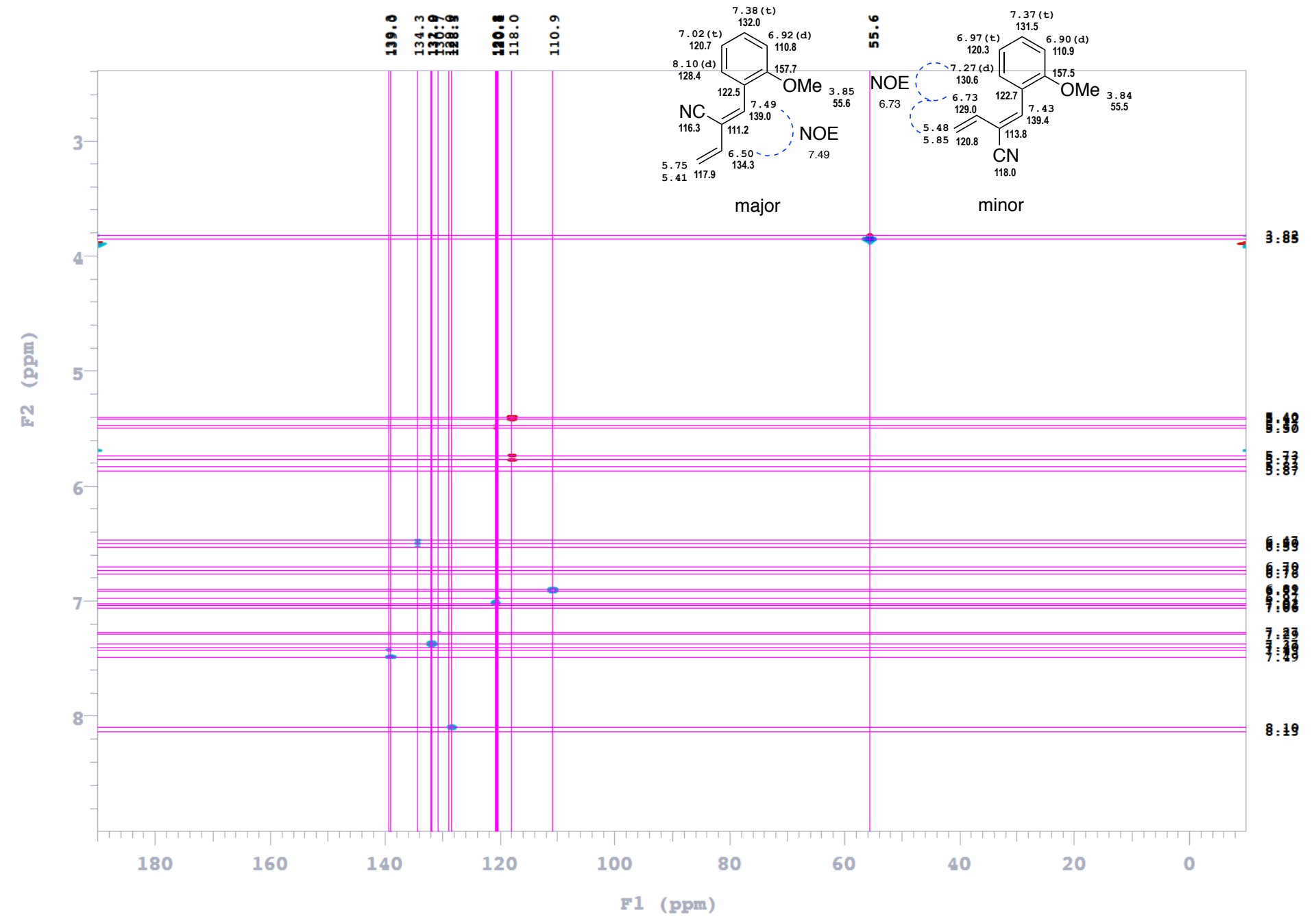

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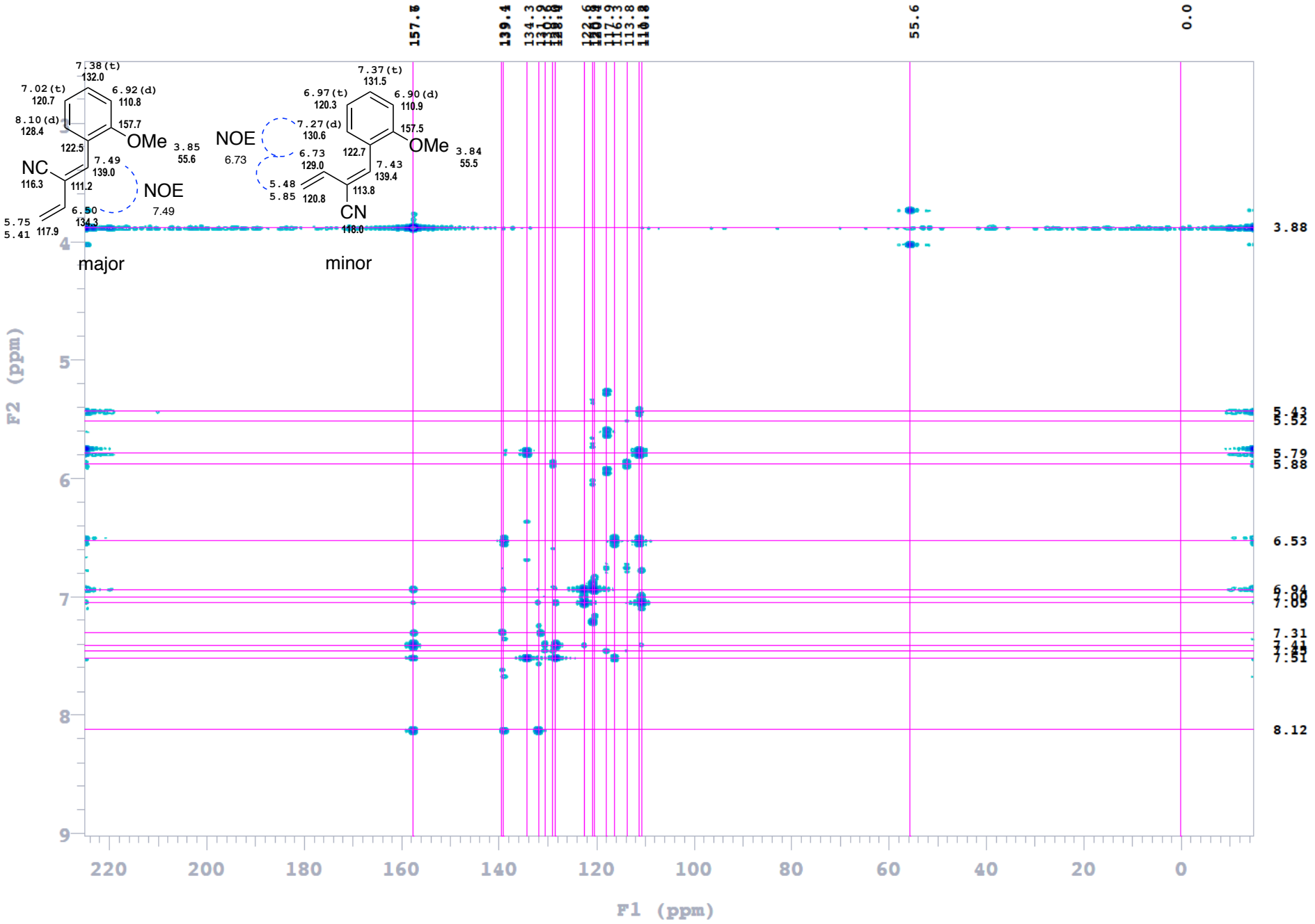
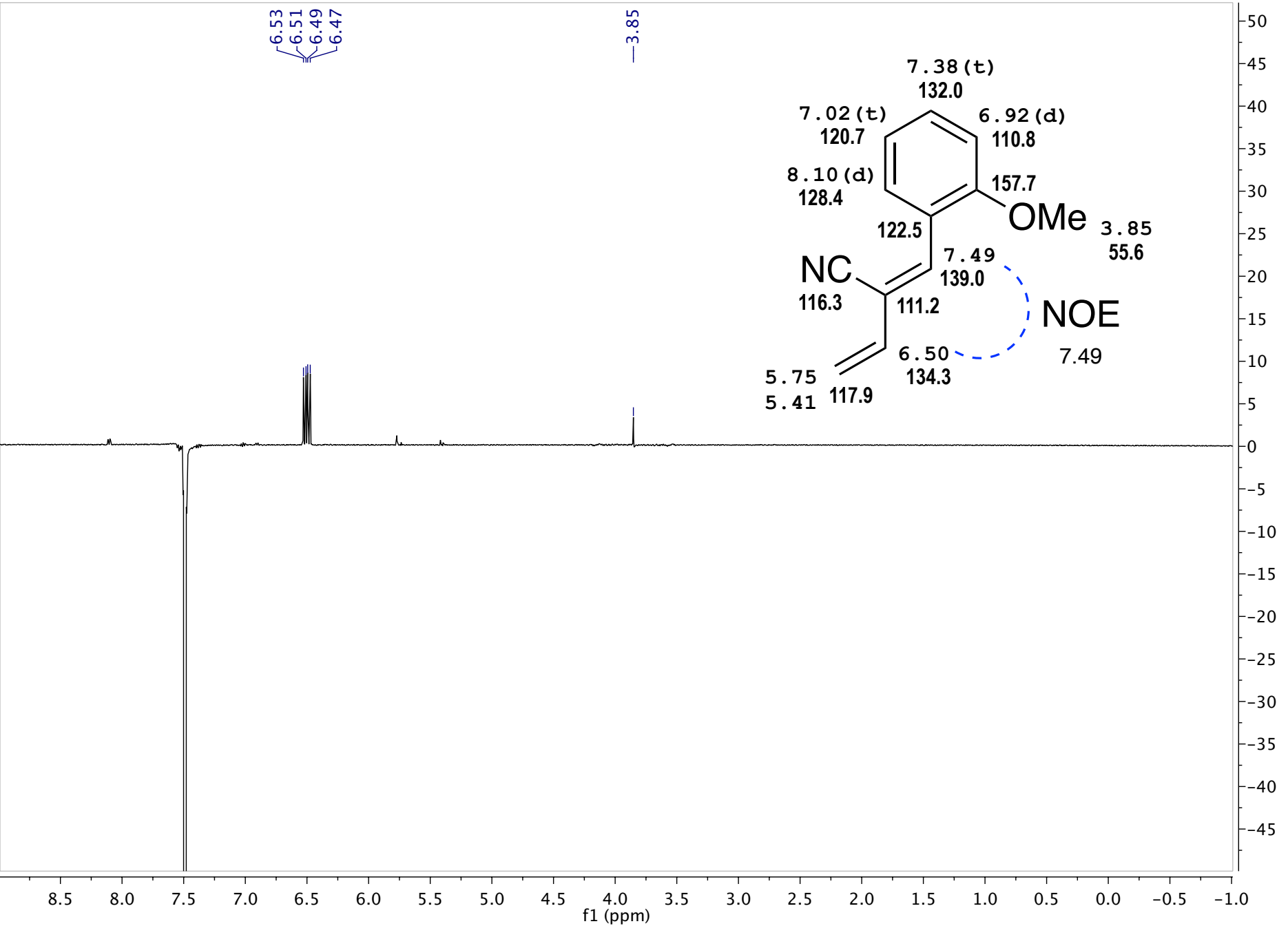
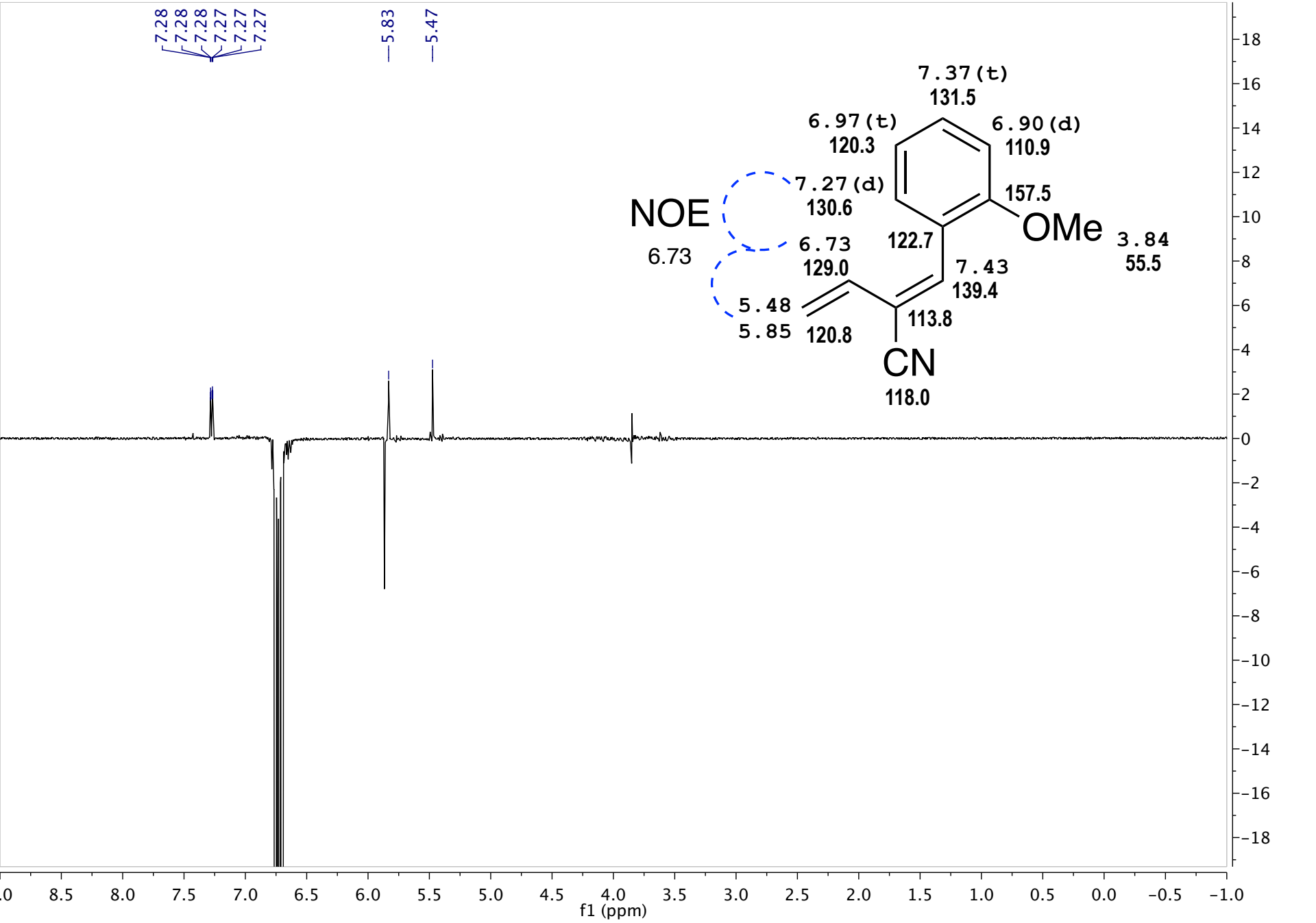


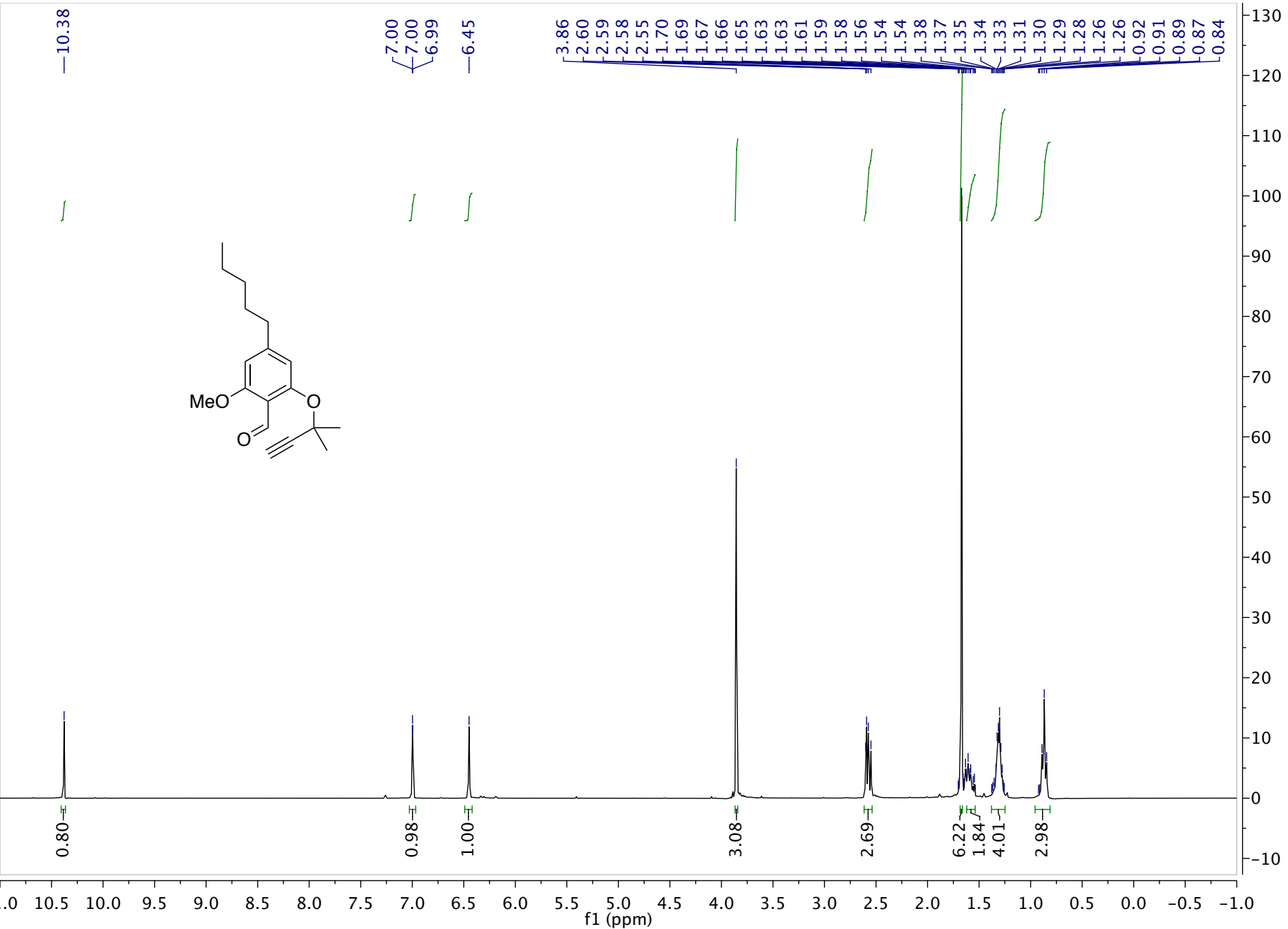
NOE spectrum of (Z)-2-(2-methoxybenzylidene)but-3-enenitrile at 7.49 δ ($CDCl_3$)



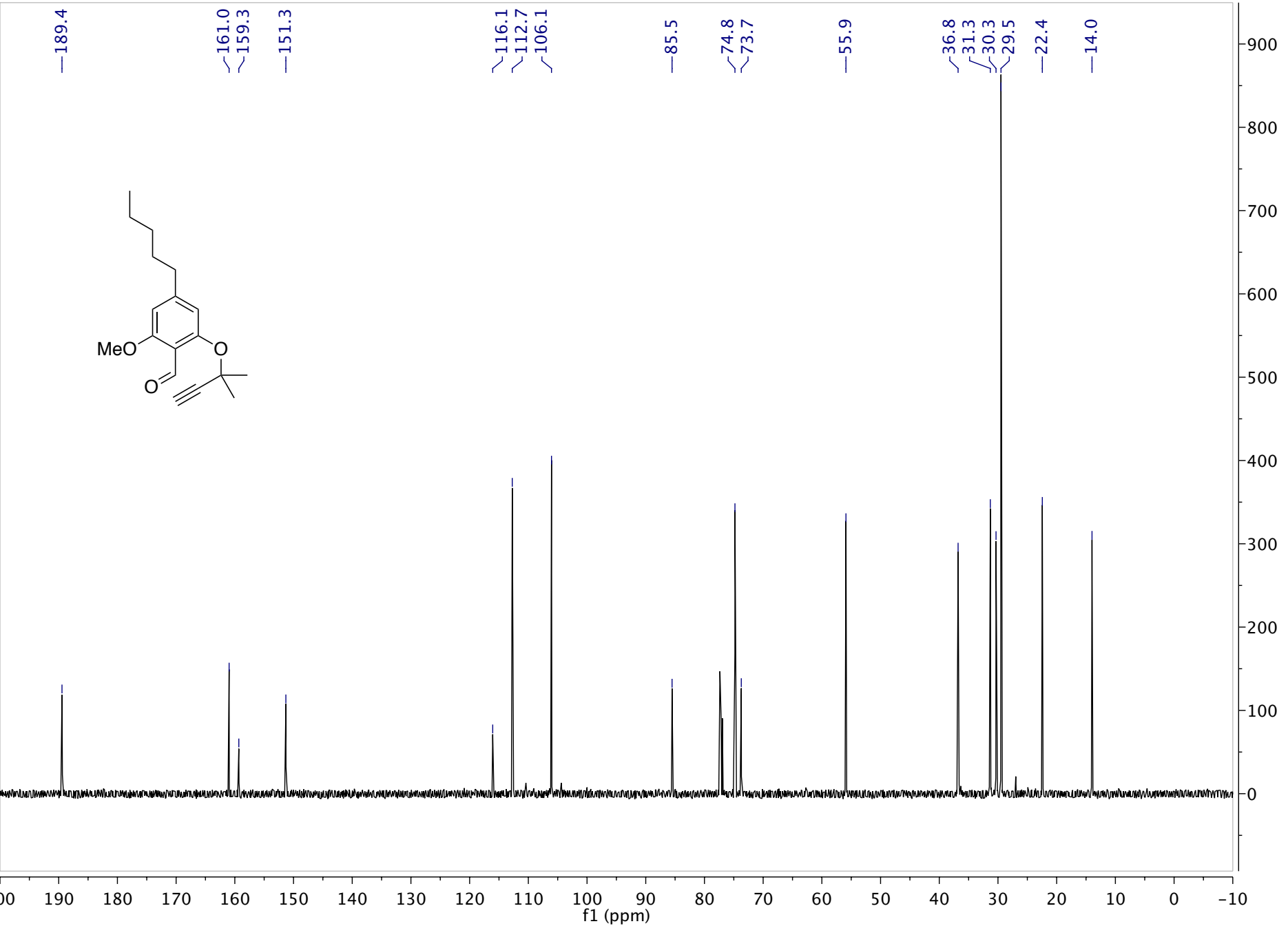
NOE spectrum of (E)-2-(2-methoxybenzylidene)but-3-enenitrile at 7.49 δ ($CDCl_3$)



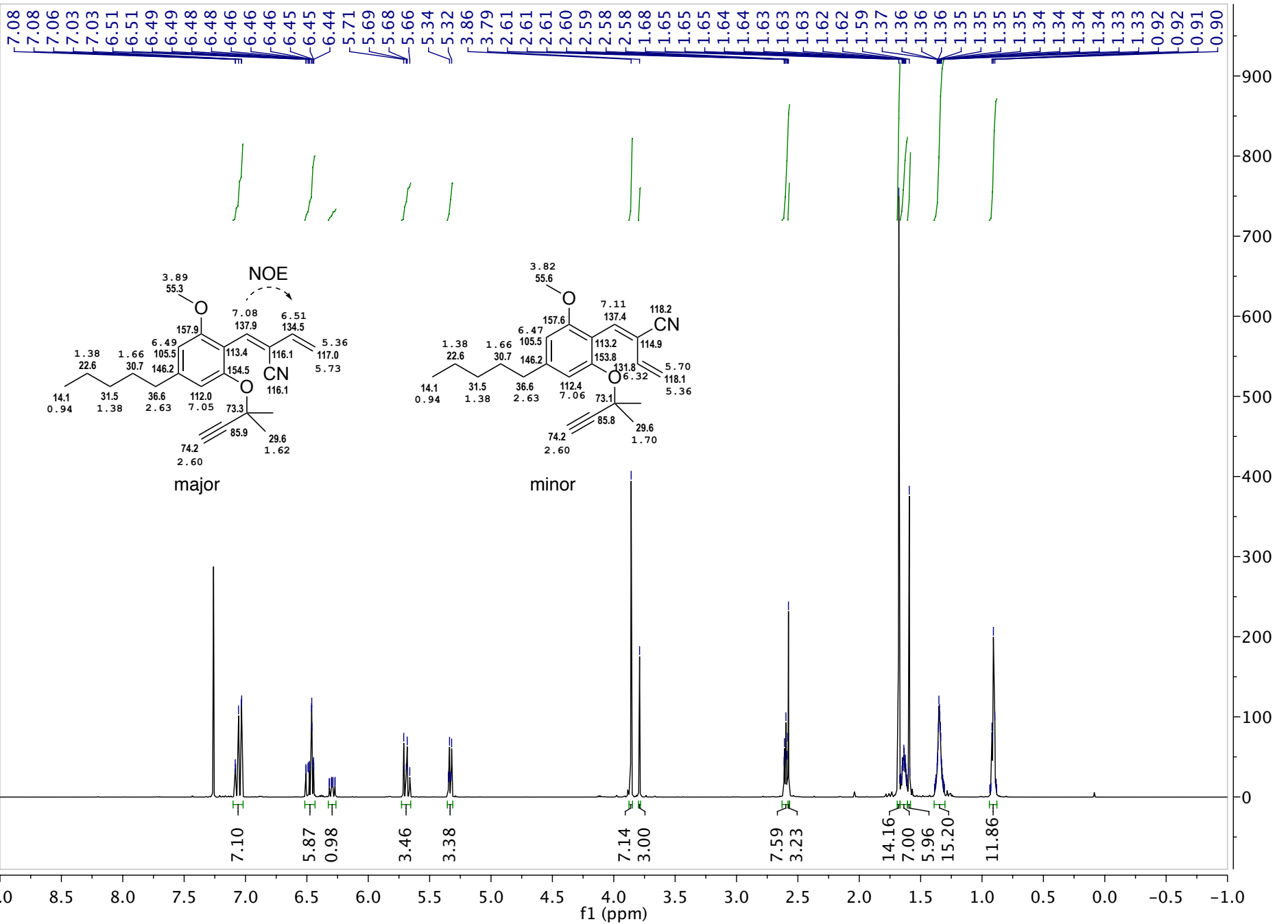
^{1}H spectrum of 2-methoxy-6-((2-methylbut-3-yn-2-yl)oxy)-4-pentylbenzaldehyde (2) ($CDCl_3$)



^{13}C spectrum of 2-methoxy-6-((2-methylbut-3-yn-2-yl)oxy)-4-pentylbenzaldehyde (2) ($CDCl_3$)



^{1}H spectrum of 2-(2-methoxy-6-((2-methylbut-3-yn-2-yl)oxy)-4-pentylbenzylidene)but-3-enenitrile (3) ($CDCl_3$)



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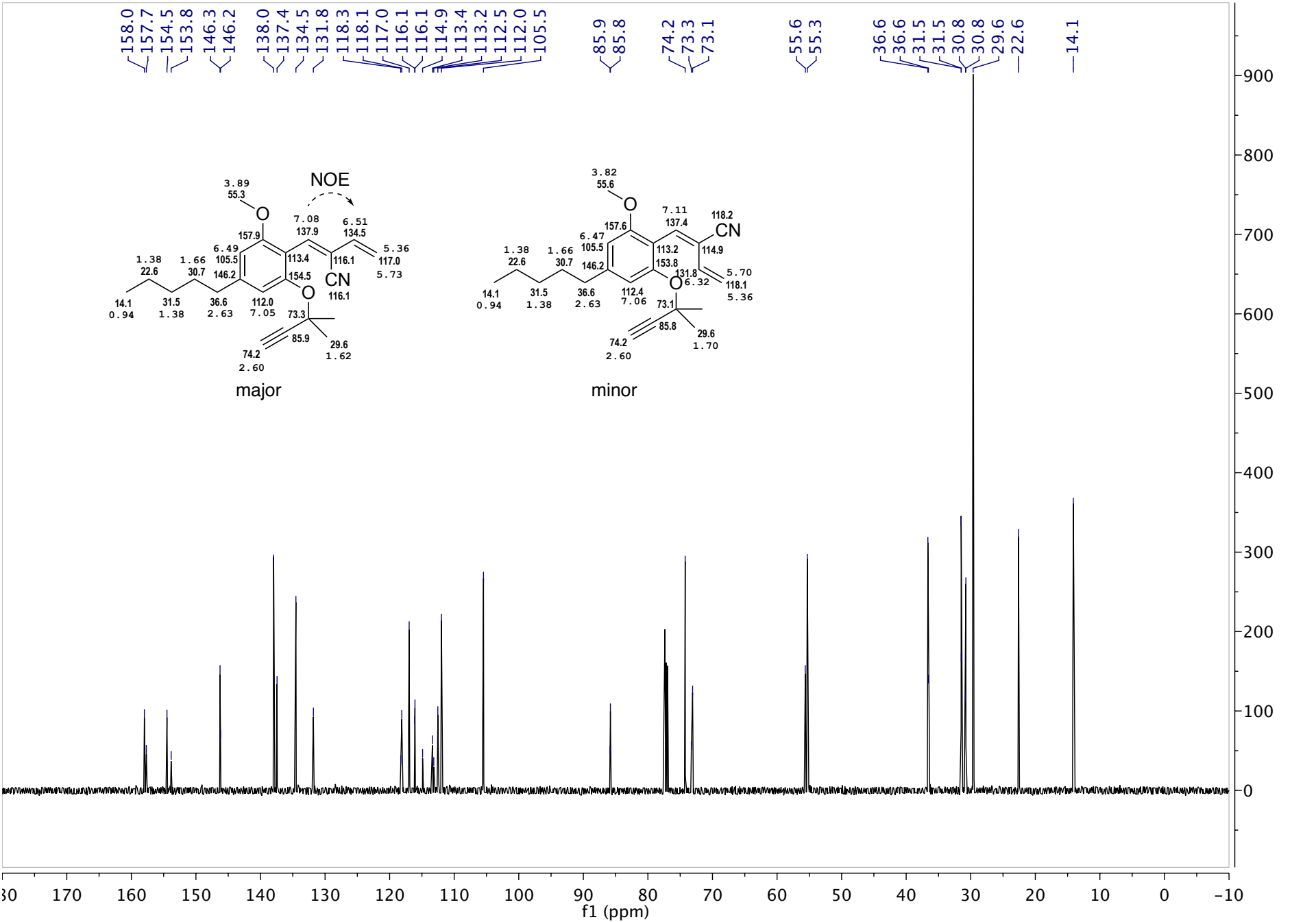

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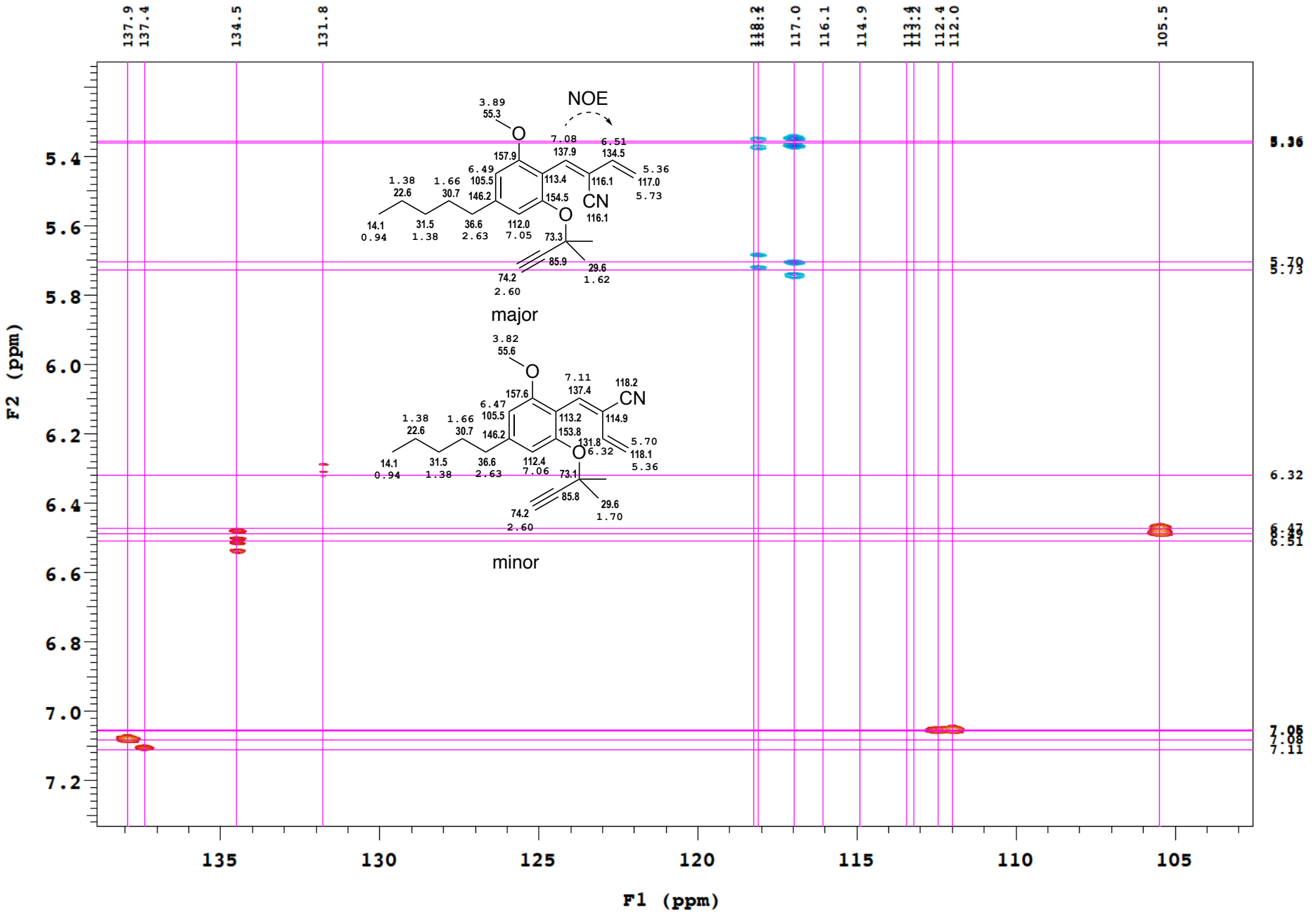

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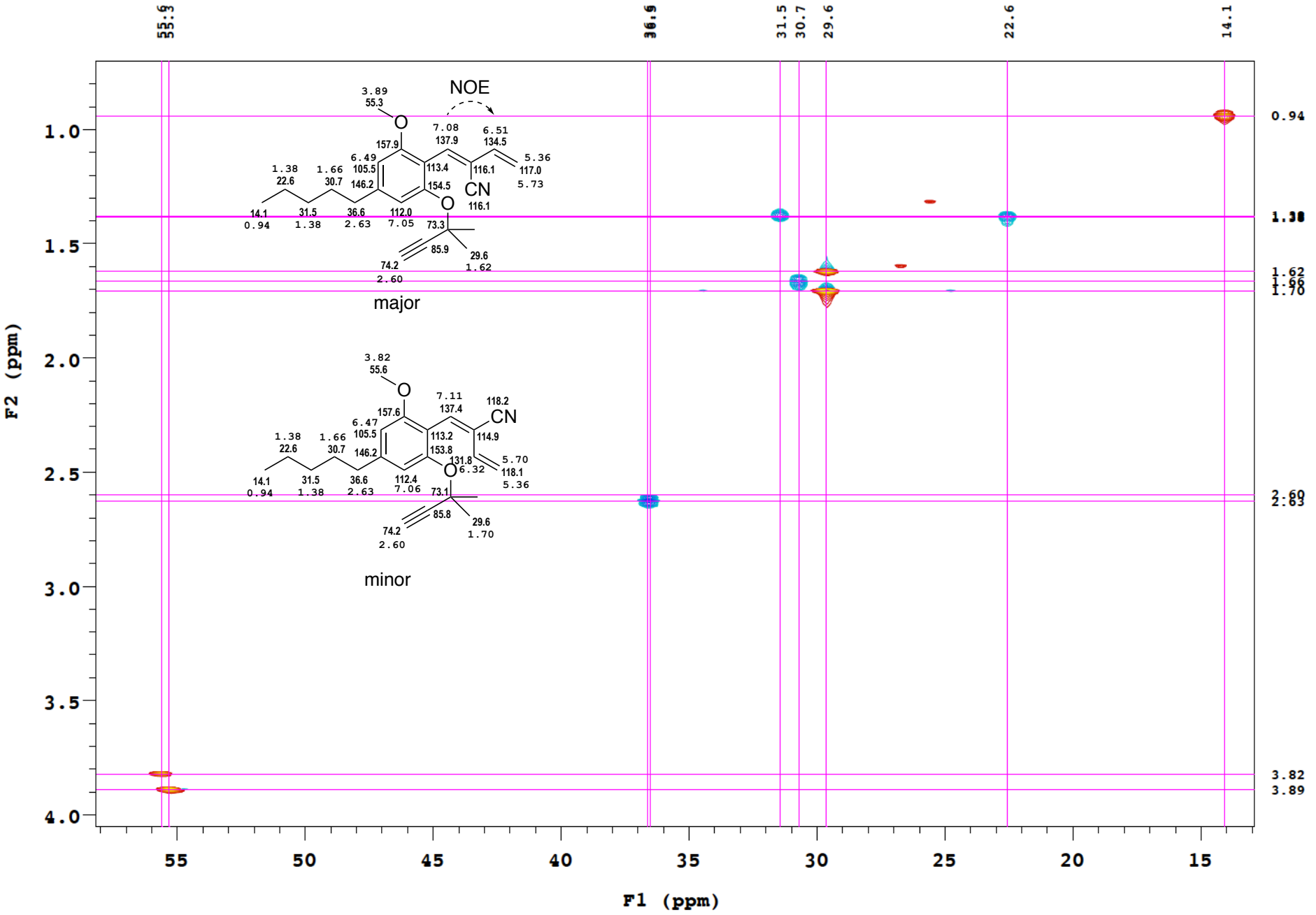

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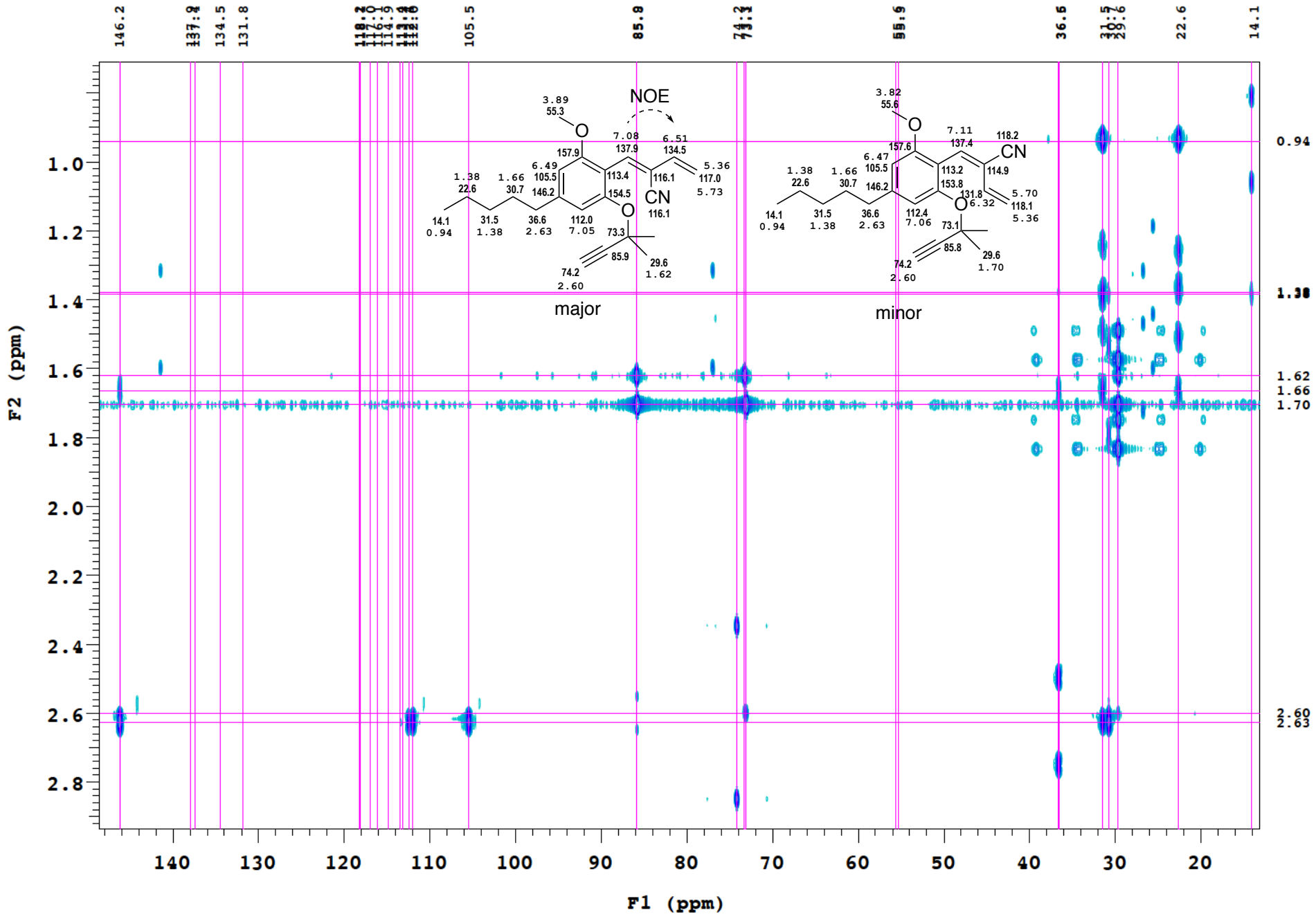

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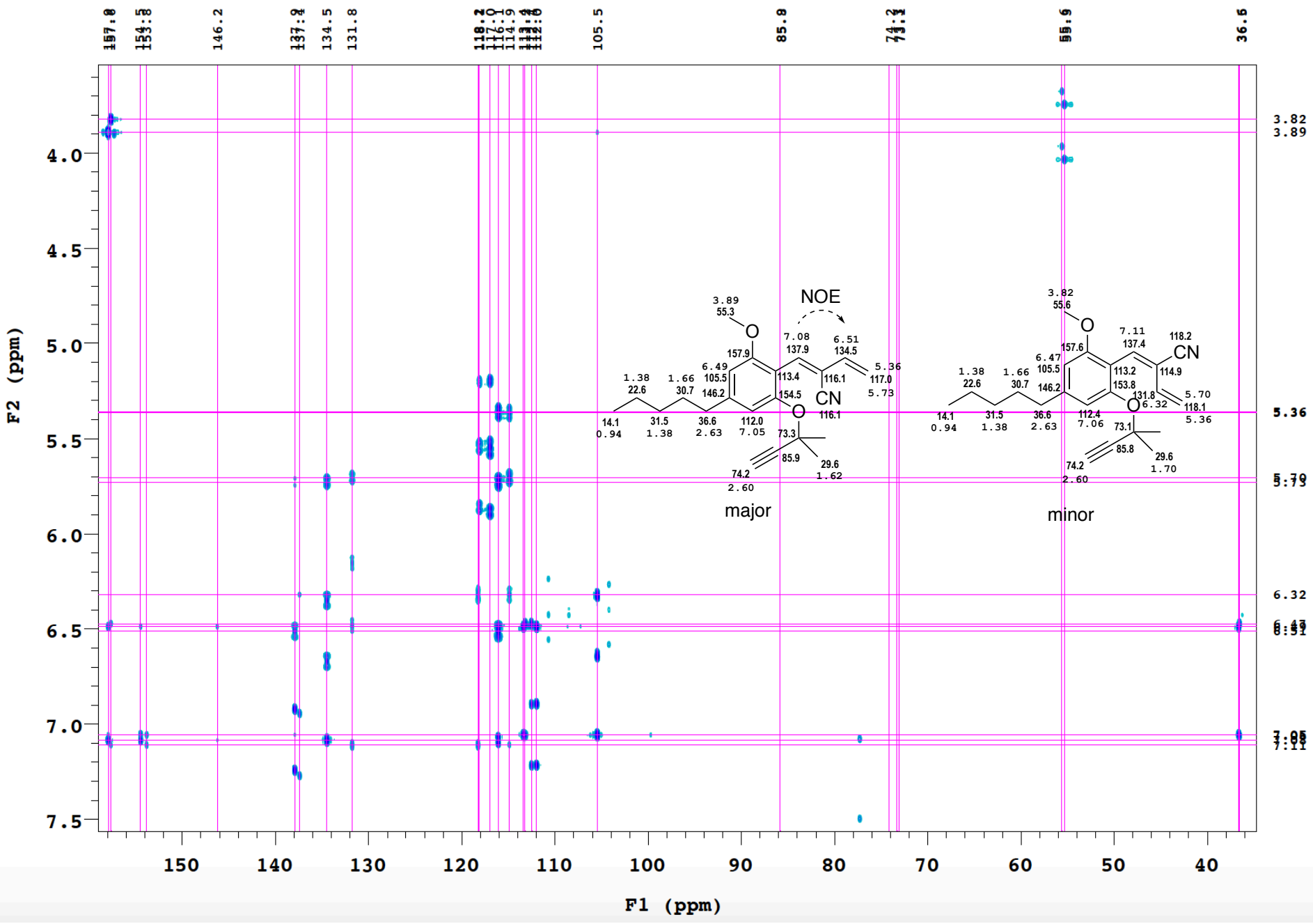

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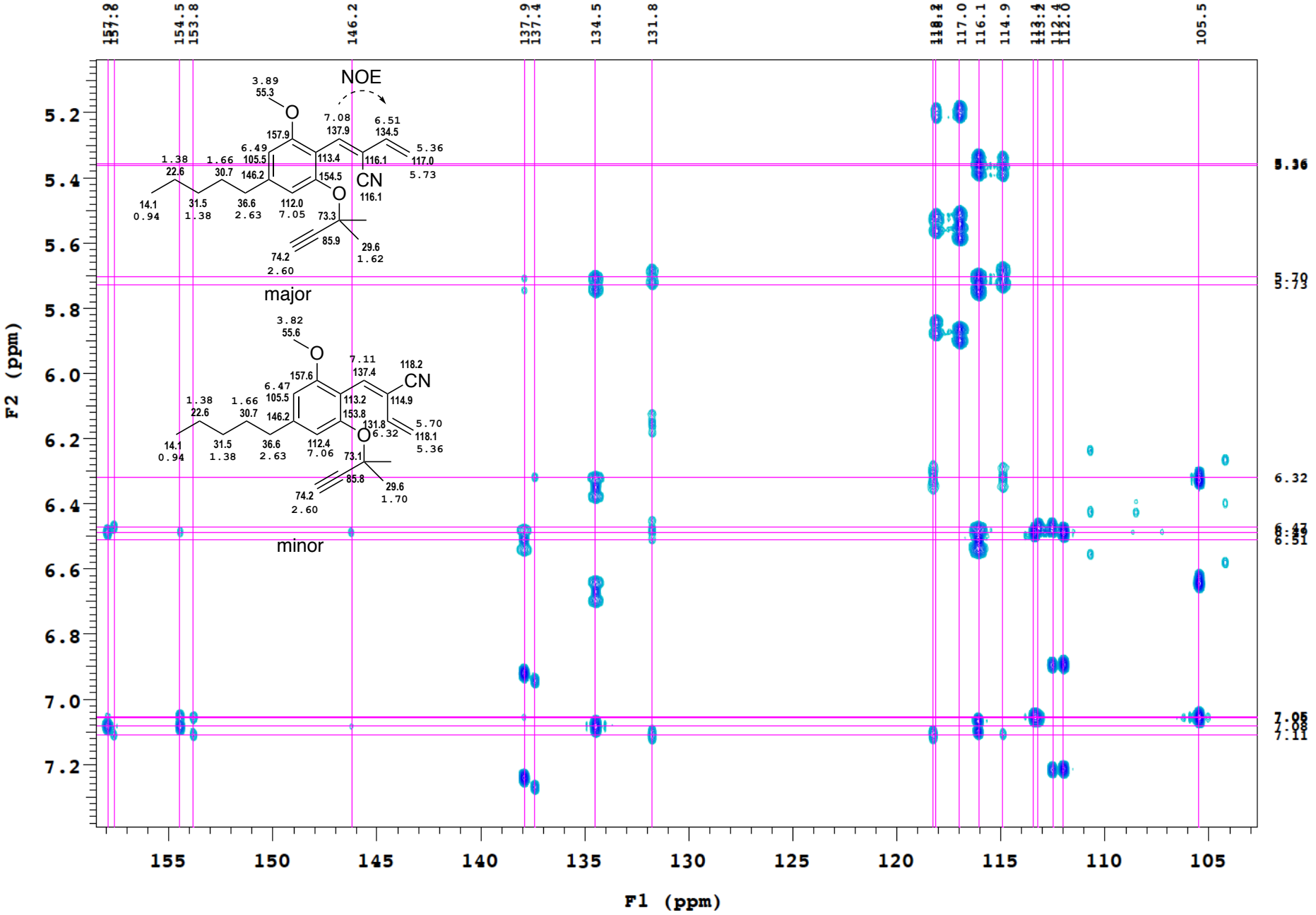
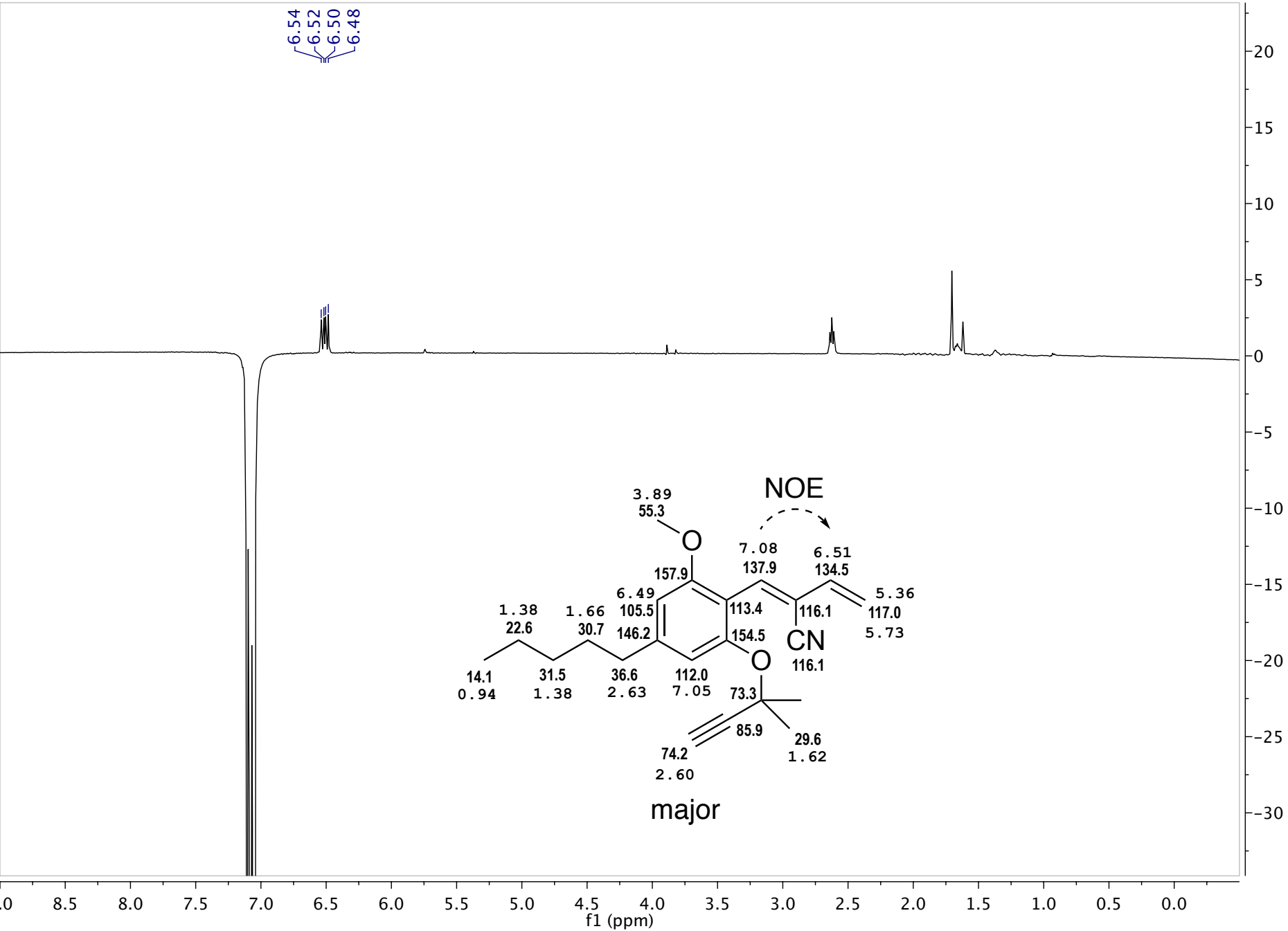
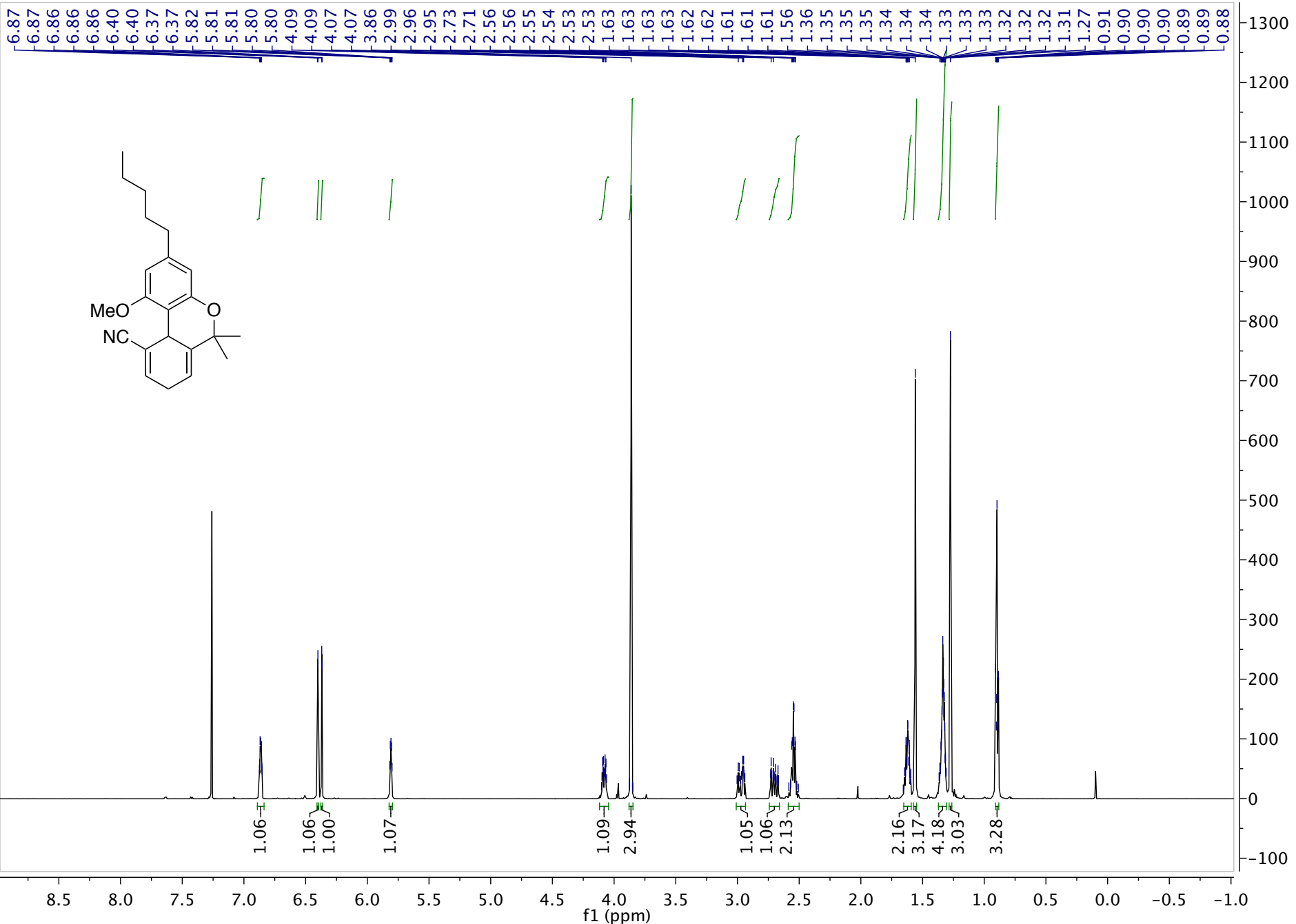


NOE spectrum of (Z)-2-(2-methoxy-6-((2-methylbut-3-yn-2-yl)oxy)-4-pentylbenzylidene)but-3-enenitrile at 7.08 δ (3) ($CDCl_3$)



^{1}H spectrum of 1-methoxy-6,6-dimethyl-3-pentyl-8,10a-dihydro-6H-benzo[c]chromene-10-carbonitrile (4) ($CDCl_3$)



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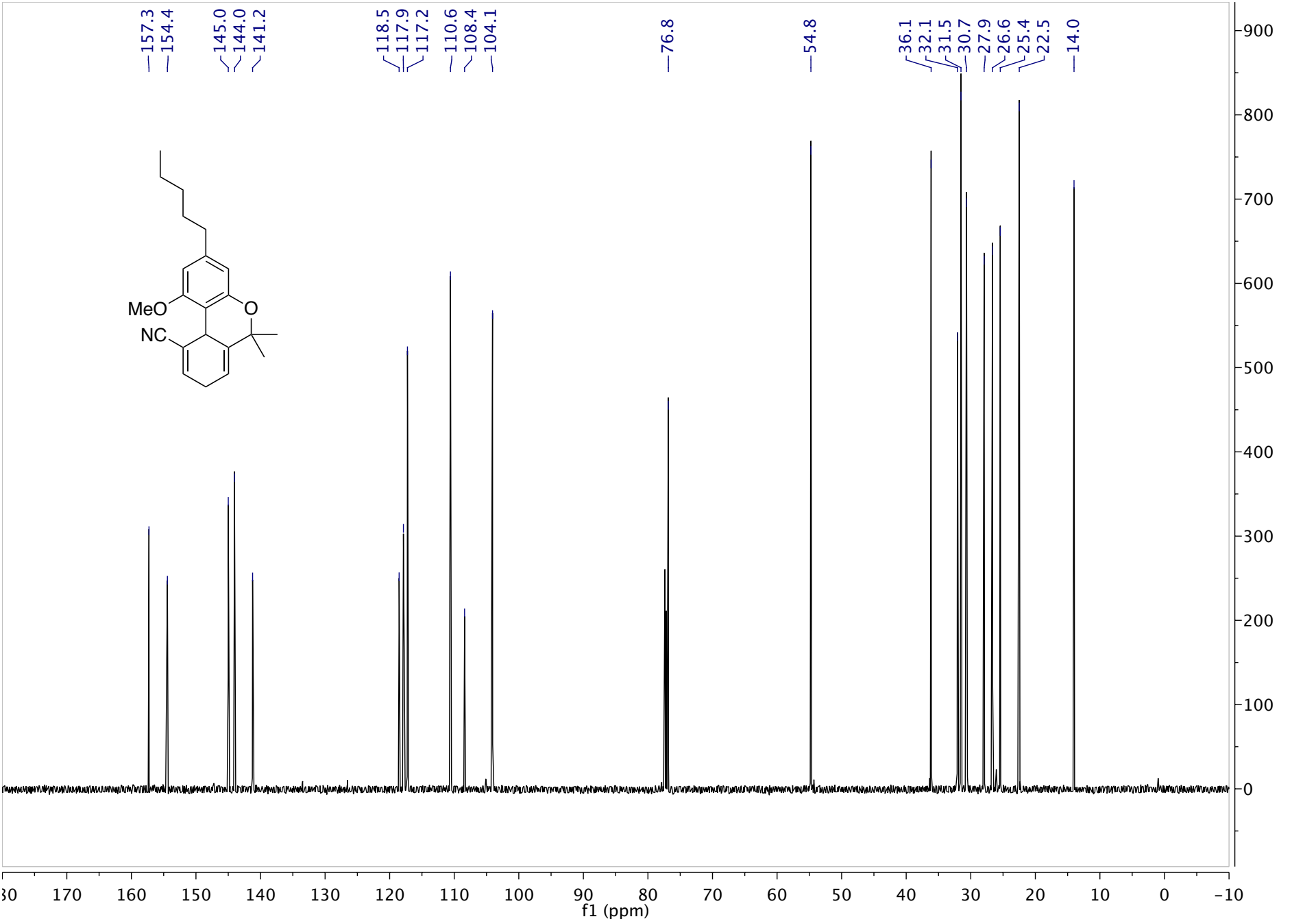
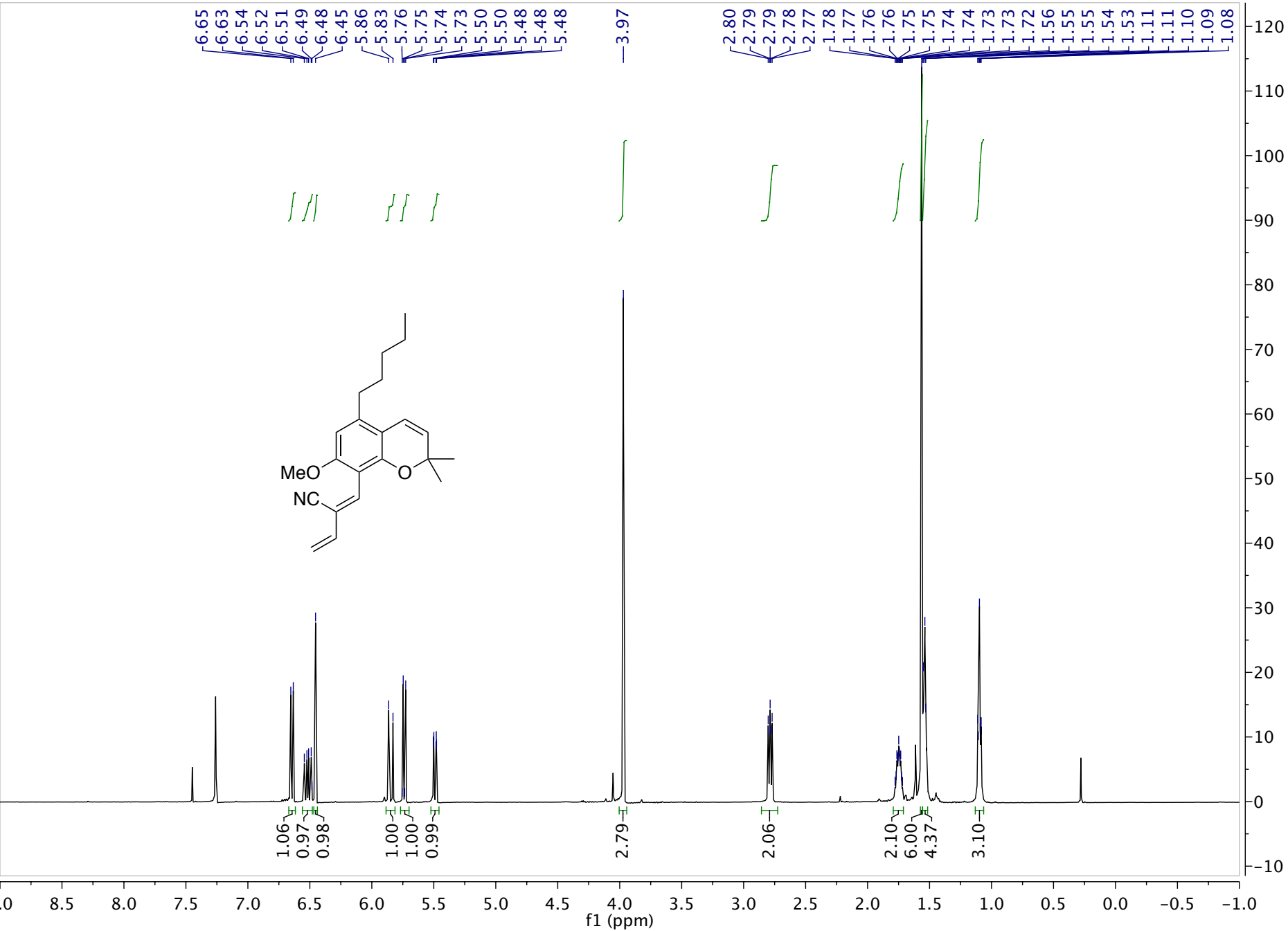


^{1}H spectrum of (Z)-2-((7-methoxy-2,2-dimethyl-5-pentyl-2H-chromen-8-yl)methylene)but-3-enenitrile (5) ($CDCl_3$)



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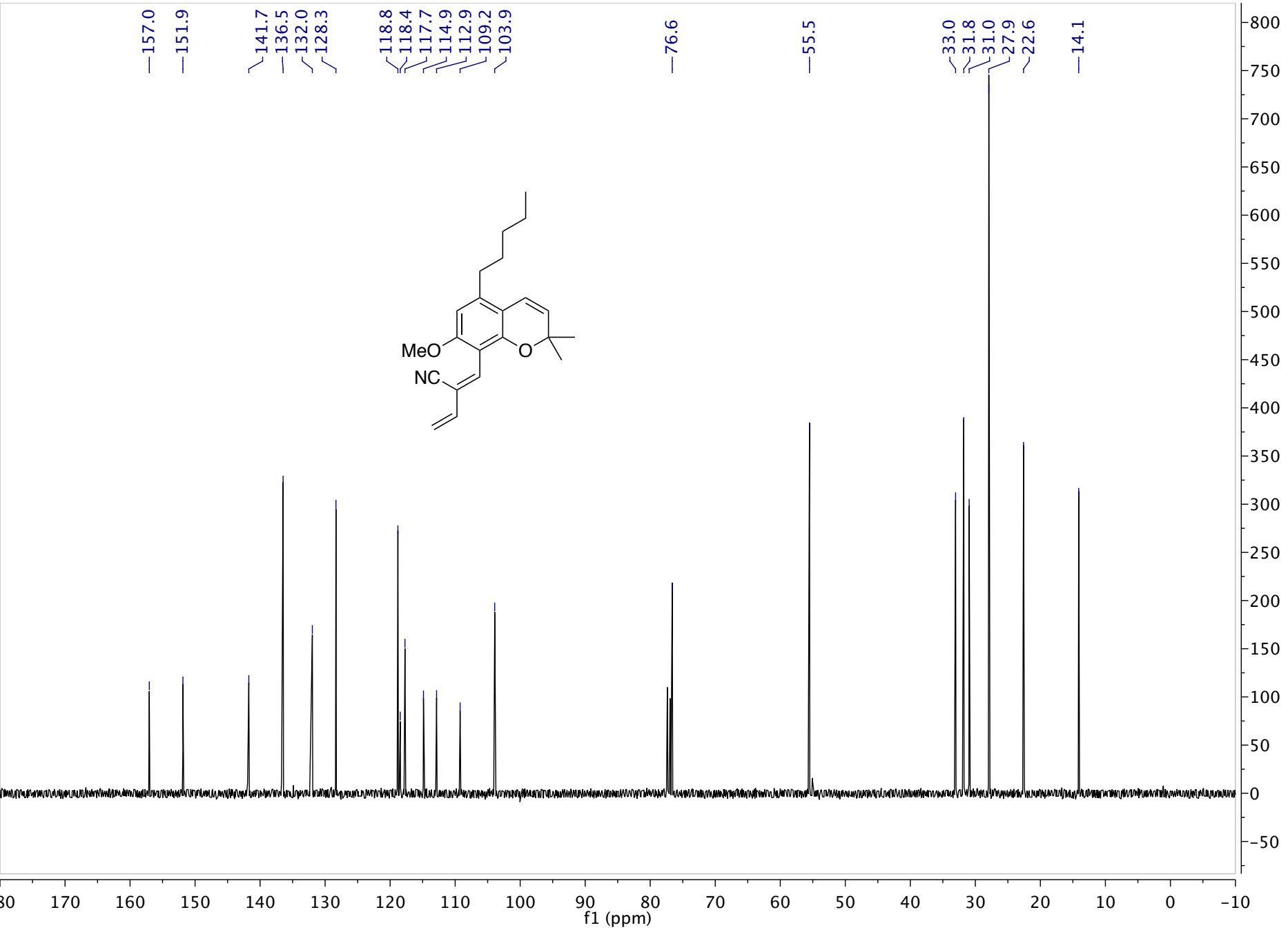

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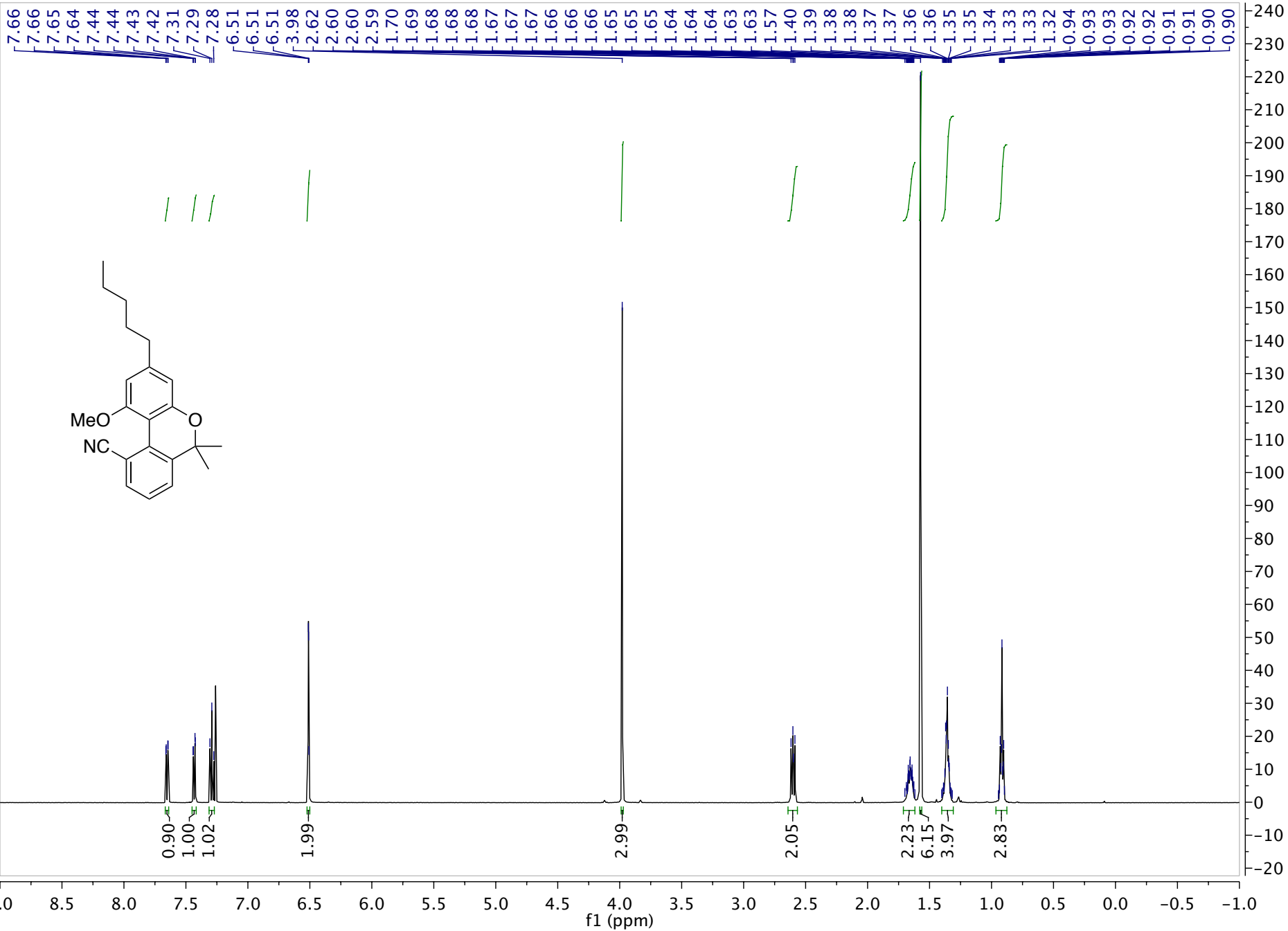
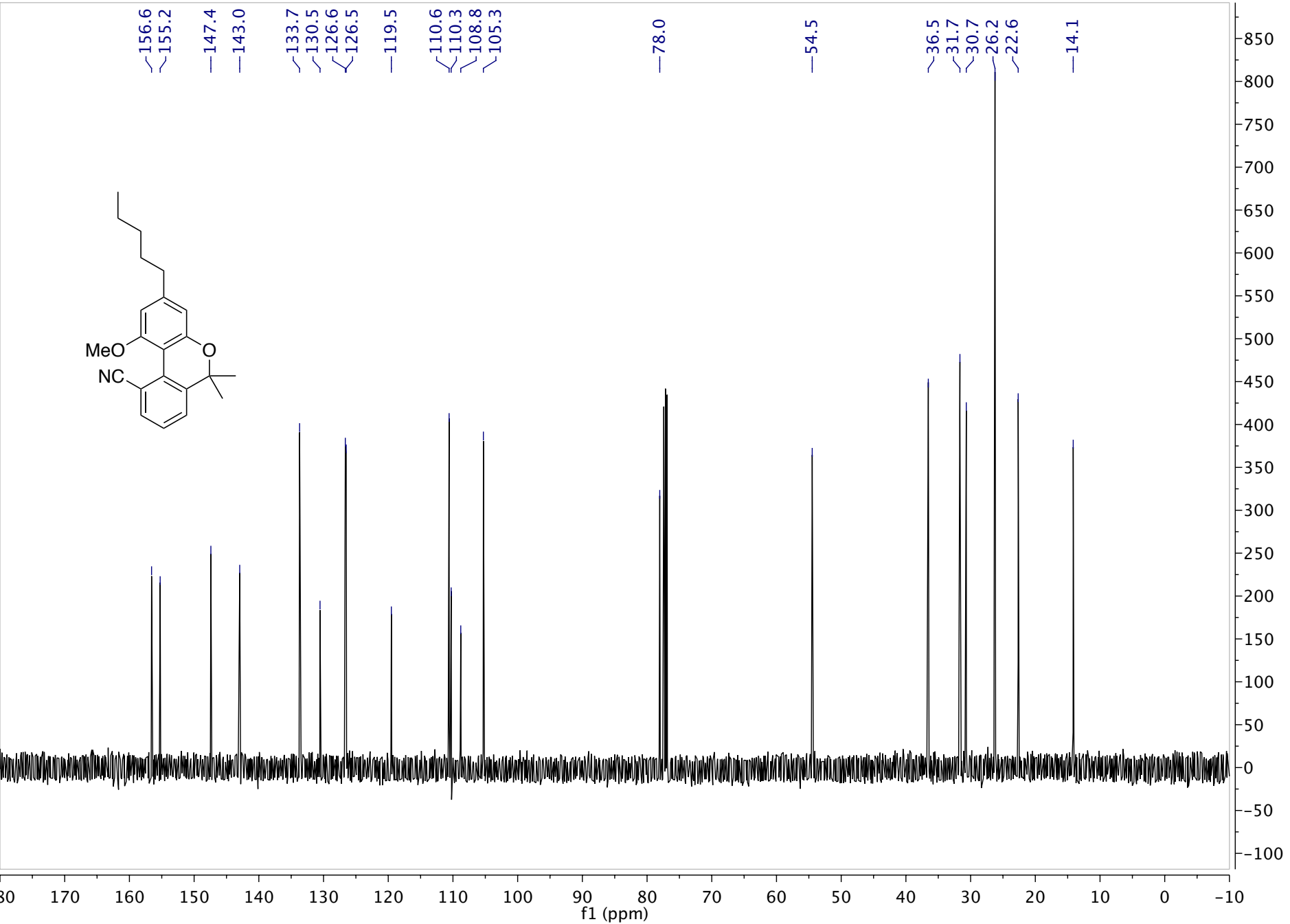
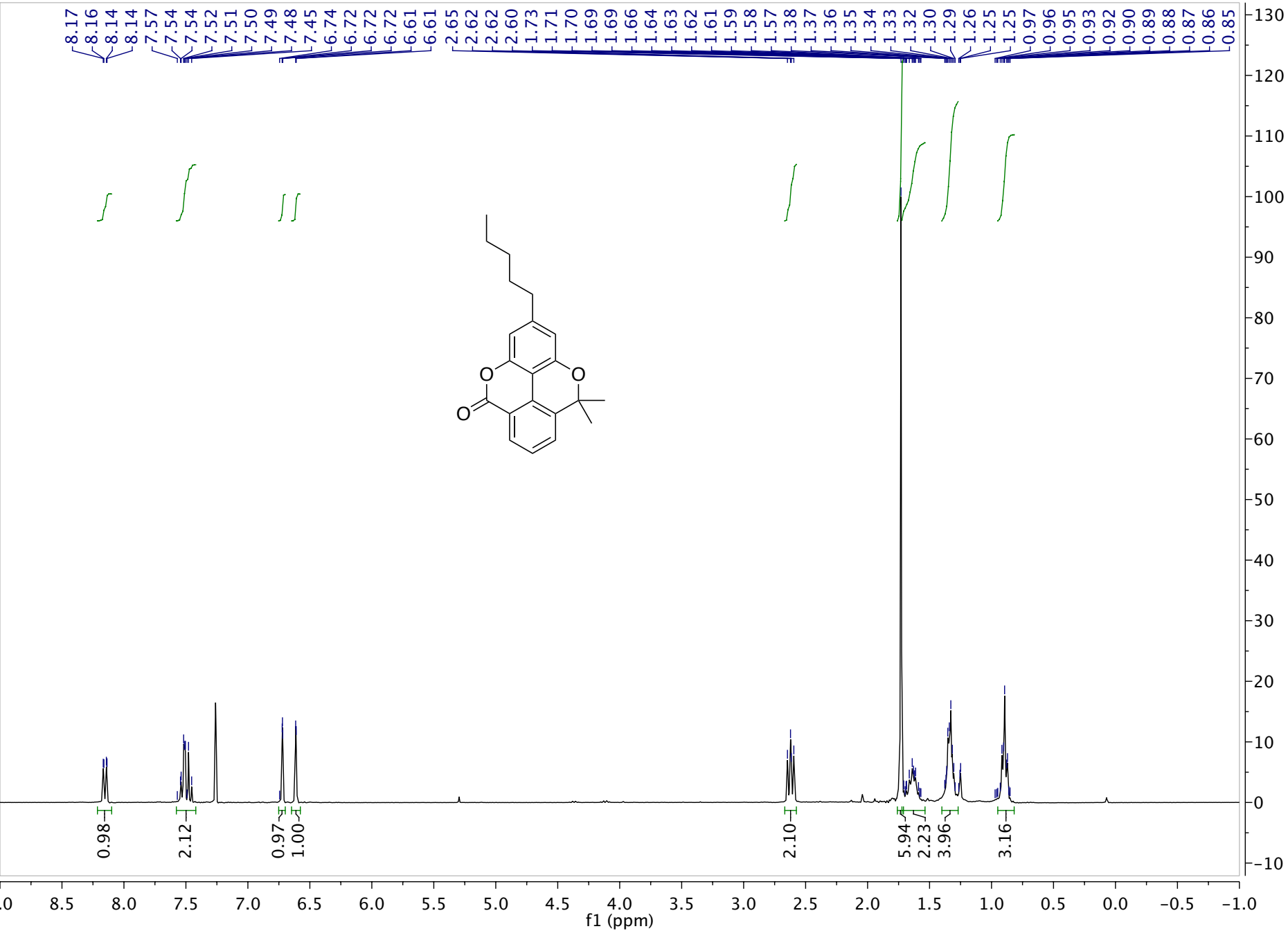


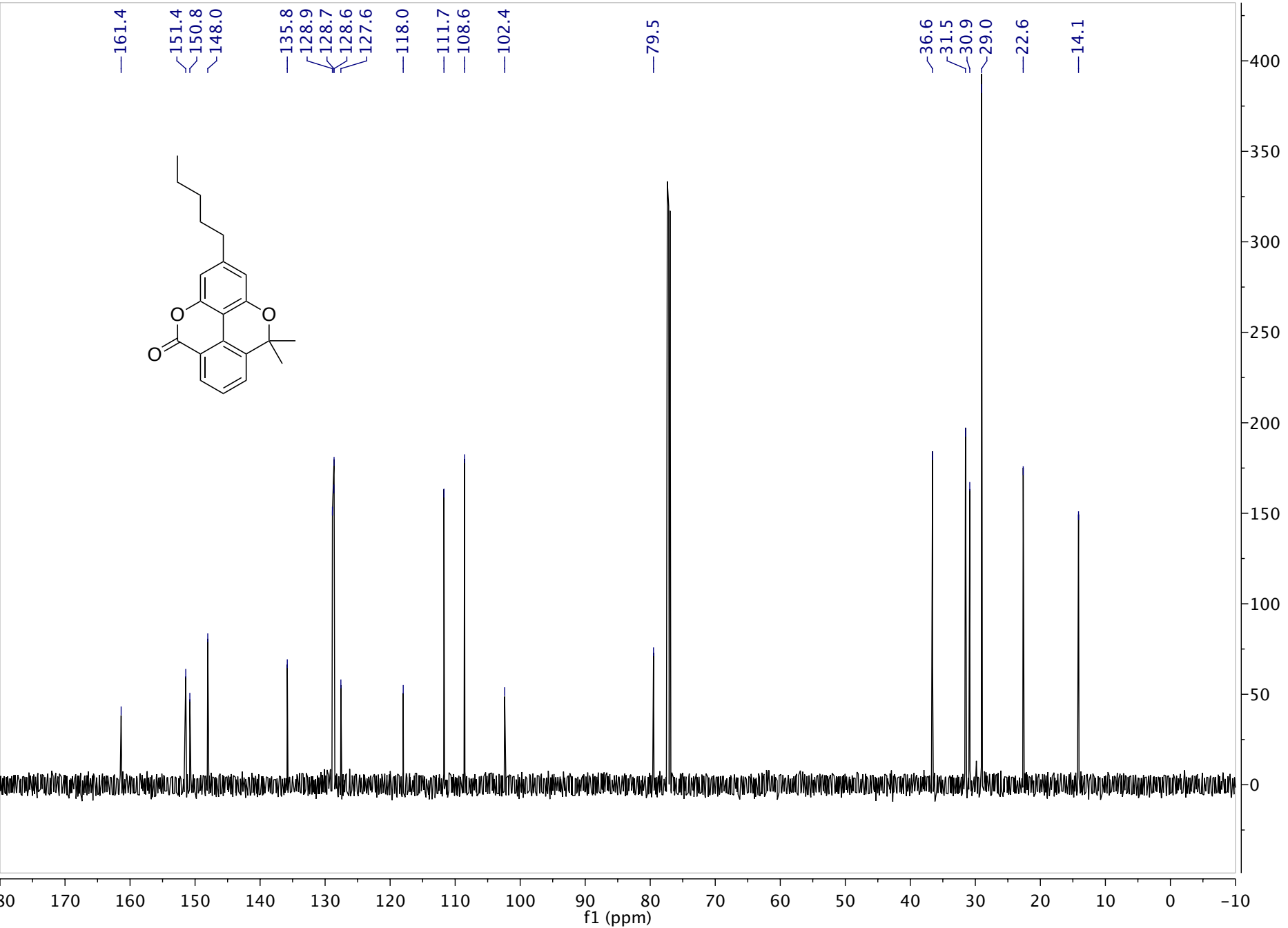
^{13}C spectrum of 1-methoxy-6,6-dimethyl-3-pentyl-6H-benzo[c]chromene-10-carbonitrile (6) ($CDCl_3$)



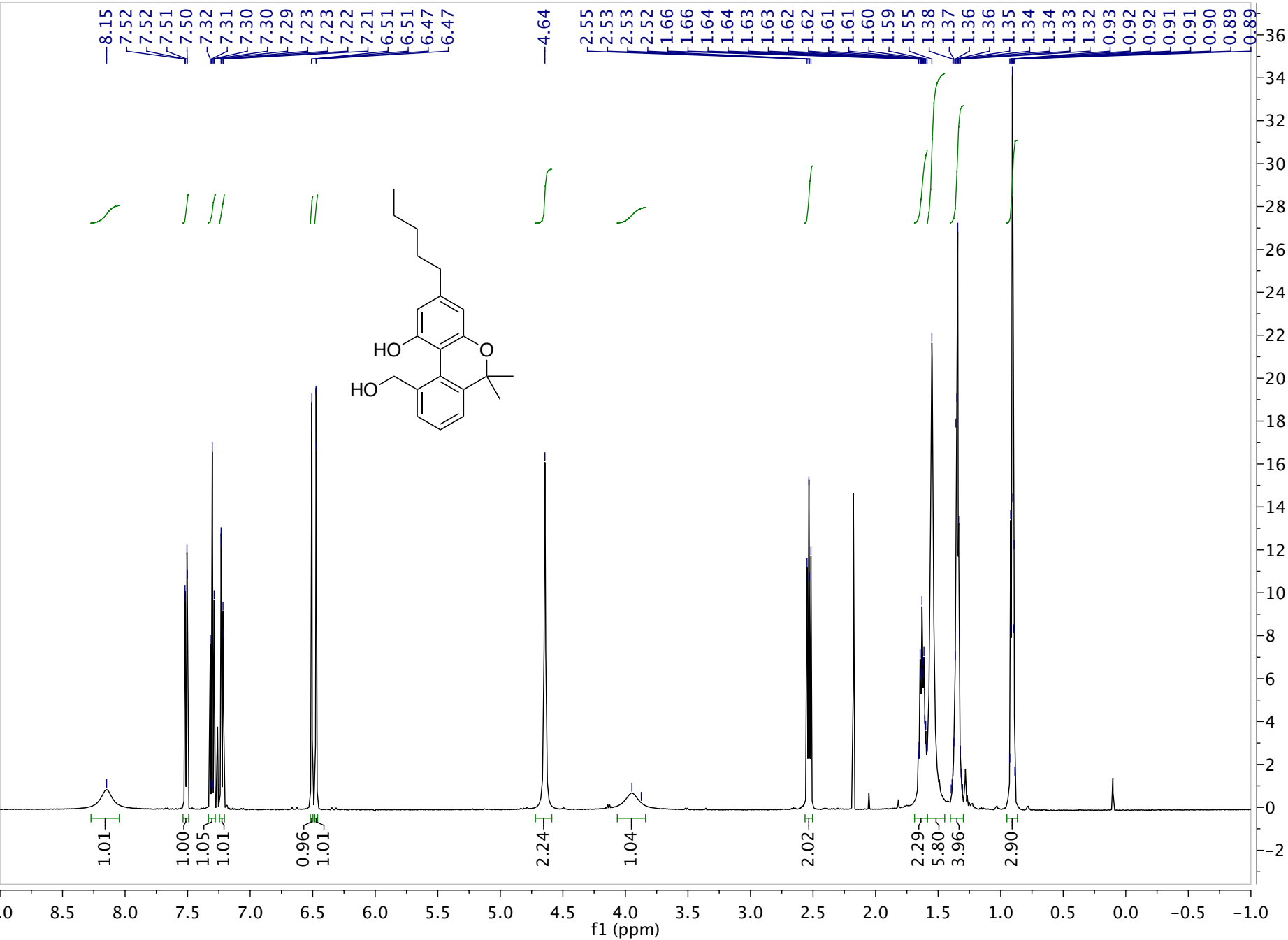
^{1}H spectrum of 9,9-dimethyl-2-pentyl-5H,9H-isochromeno[5,4,3-cde]chromen-5-one (7) ($CDCl_3$)



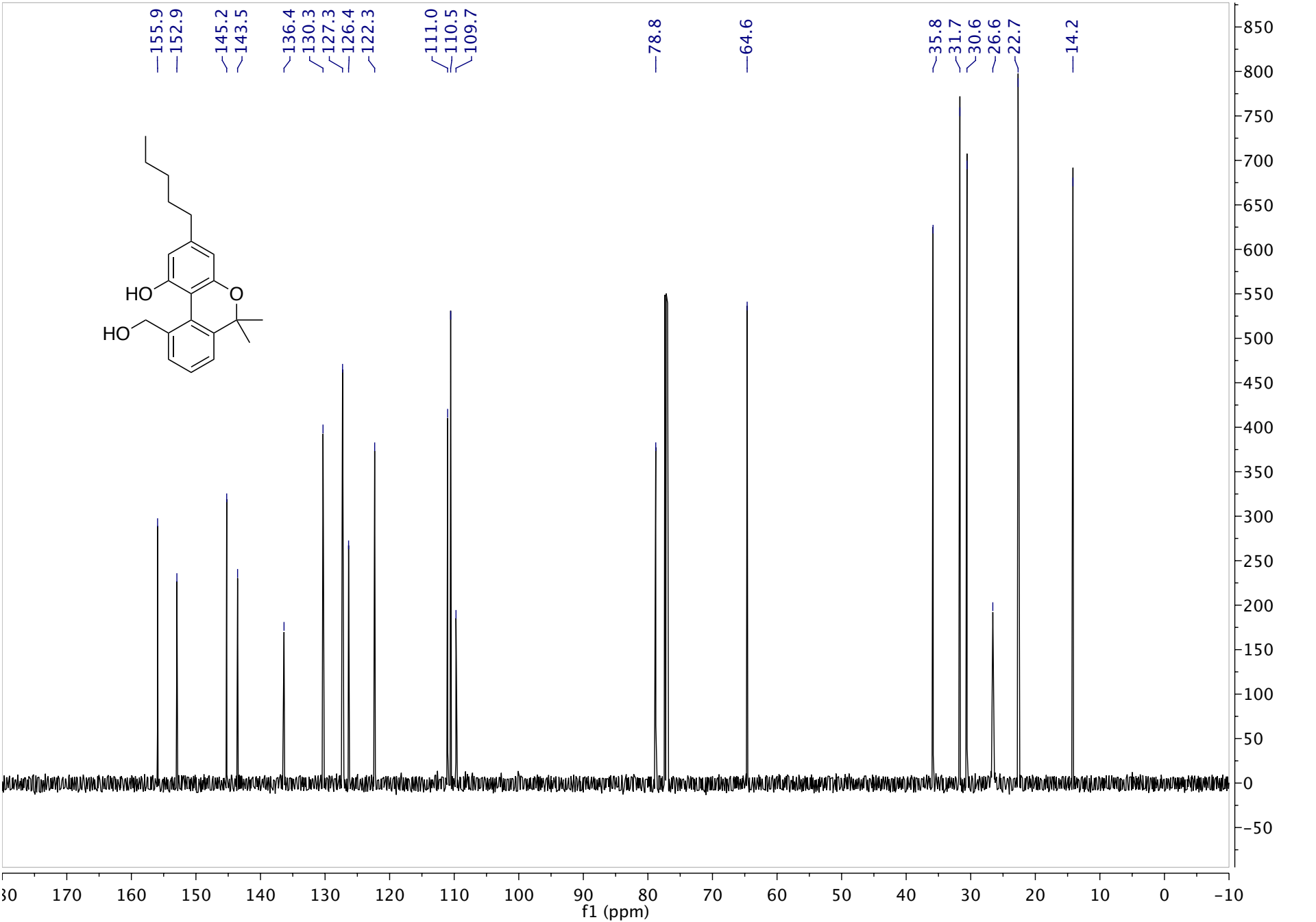
^{13}C spectrum of 9,9-dimethyl-2-pentyl-5H,9H-isochromeno[5,4,3-cde]chromen-5-one (7) ($CDCl_3$)



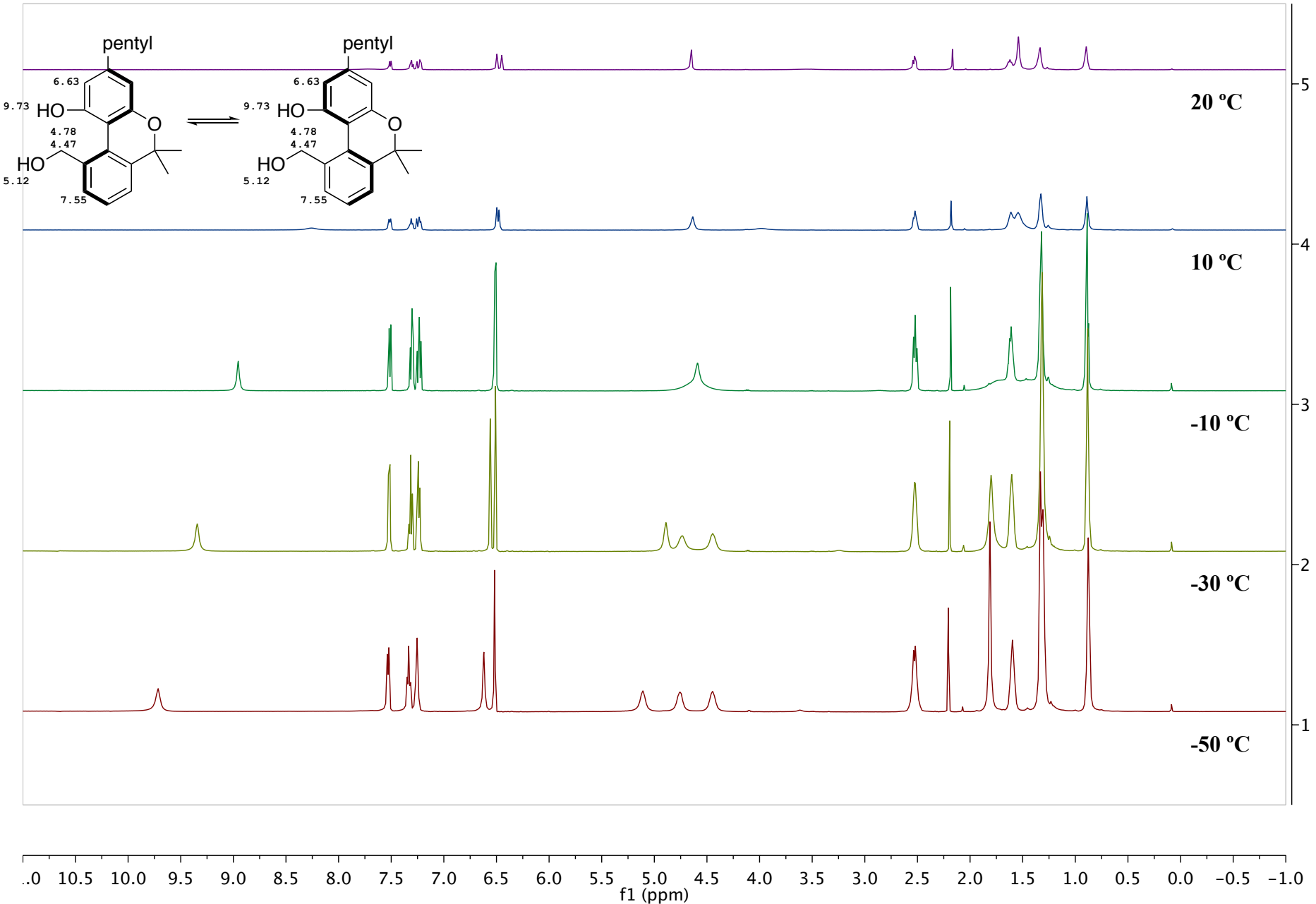
^{1}H spectrum of 10-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6H-benzo[c]chromen-1-ol (8) ($CDCl_3$)



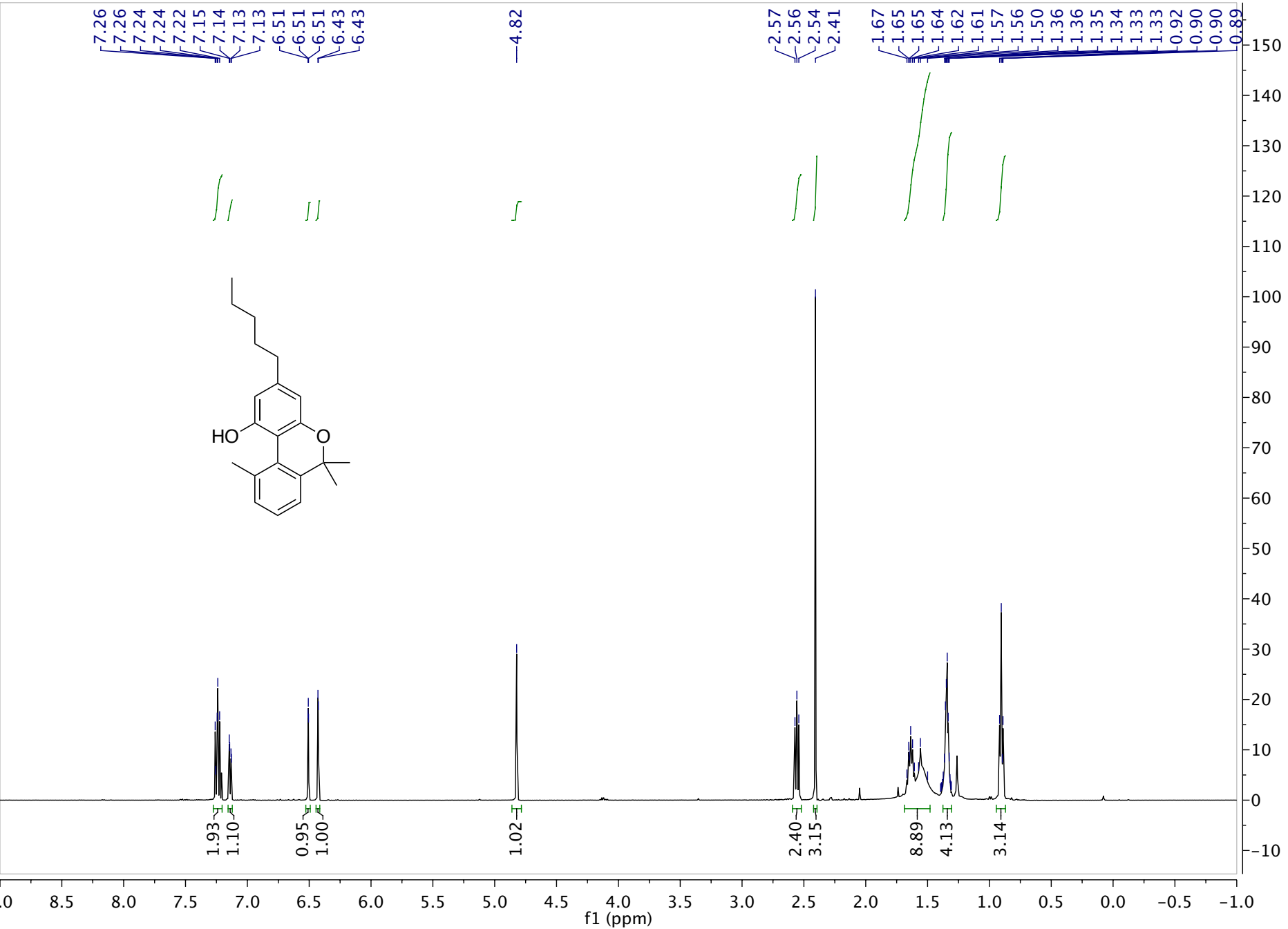
^{13}C spectrum of 10-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6H-benzo[c]chromen-1-ol (8) ($CDCl_3$)



^{1}H spectrum of 10-(hydroxymethyl)-6,6-dimethyl-3-pentyl-6H-benzo[c]chromen-1-ol at variable temperatures (VT) (8) ($CDCl_3$)



^{1}H spectrum of 6,6,10-trimethyl-3-pentyl-6H-benzo[c]chromen-1-ol (10) ($CDCl_3$)



^{13}C spectrum of 6,6,10-trimethyl-3-pentyl-6H-benzo[c]chromen-1-ol (10) ($CDCl_3$)