Supporting Information

Base-promoted [4+2] cycloaddition of *para*-quinone methides (*p*-QMs) and 3-cyanochromones: Facile Access to chromeno[2,3-*b*]chromenes

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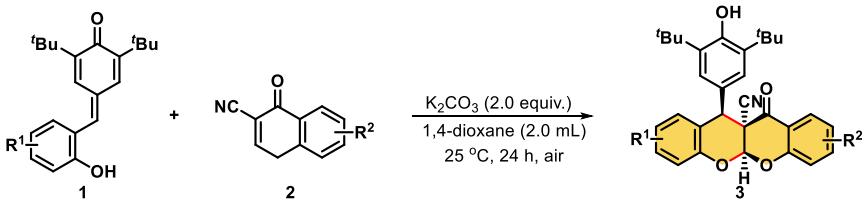
Contents

General Information

PE refers to petroleum ether (b.p. 60-90 °C) and EA refers to ethyl acetate. All other starting materials and solvents were commercially available and were used without further purification unless otherwise stated. All reactions were heated by metal sand bath. ^{1}H NMR (^{13}C NMR) spectra were measured on a Bruker DPX 400 MHz spectrometer in $CDCl_3$ with chemical shift (δ) given in ppm relative to TMS as internal standard [(s = singlet, d = doublet, m = multiplet), coupling constant (Hz)]. HRMS (APCI) was determined by using microTOF-QII HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer. The melting points were measured with digital melting point detector. *ortho*-hydroxyphenyl-substituted *p*-QMs **1** were prepared according to the report[1]. 3-cyanochromones **2** were purchased from Bide Pharmatech Ltd. or Energy Chemical (Shanghai).

General procedure for the synthesis of compounds 3



A dry round-bottom flask was charged with *ortho*-hydroxyphenyl-substituted *p*-QMs **1** (0.2 mmol, 1.0equiv), 3-cyanochromones **2** (0.22 mmol. 1.1 equiv), K_2CO_3 (56 mg, 0.4 mmol, 2.0 equiv) and dry 1,4-dioxane (2.0 mL). The resulting mixture was stirred at room temperature (25 °C) under atmospheric conditions until the reaction was completed (about 24 hours), as monitored by TLC analysis. Then the reaction mixture was diluted with saturated solution of aqueous NH_4Cl (10 mL) and extracted with DCM (3 × 20 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. Following filtration and evaporation, the residue was purified by silica gel chromatography with PE/EA to afford target product **3**.

Crystallographic Data of Compound 3a

Procedure for recrystallization of compounds **3a**: the hexane was slowly added into the solution of **3a** in dichloromethane (with different concentration), then the dichloromethane was evaporated from the mixed solvent system at room temperature under dark and the crystals were obtained after a few days (CCDC number 2386519).

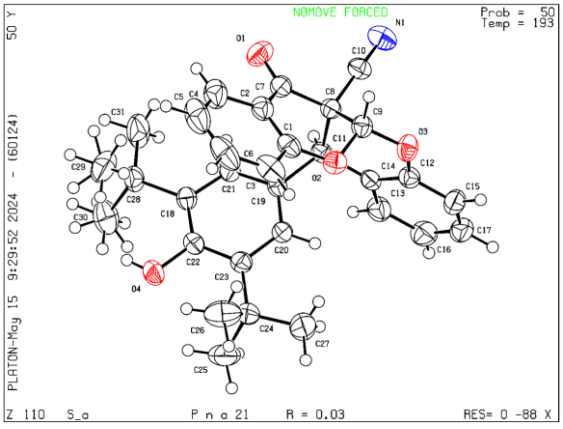
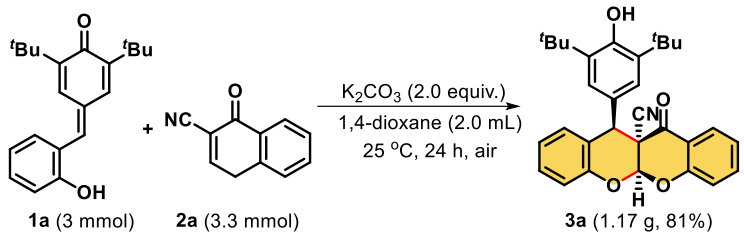


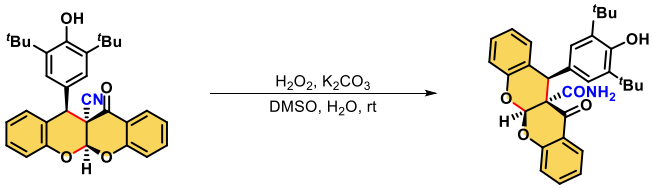
Fig. S1 ORTEP view of X-crystal structure of **3a** (the ellipsoid contour 30% probability levels)

Scale-Up Transformation of 3a



A 50 mL clean and dried round-bottom flask was equipped with a stirring bar and charged with 2,6-di-*tert*-butyl-4-(2-hydroxybenzylidene)cyclohexa-2,5-dien-1-one (**1a**, 931 mg, 3 mmol) and 1-oxo-1,4-dihydronaphthalene-2-carbonitrile (**2a**, 558 mg, 3.3 mmol), K_2CO_3 (834 mg, 6 mmol) and dry 1,4-dioxane (25 mL). Next, the mixture was stirred at 25 °C under air until the reaction completed (about 24 hours). Then, the reaction mixture was diluted with saturated solution of aqueous NH_4Cl (50 mL) and extracted with DCM (3 × 30 mL). The organic layer was washed with water and dried over anhydrous Na_2SO_4. Following filtration and evaporation, purified product **3a** (1.17 g, 81%) was obtained as yellow solid after column chromatography on silica gel (PE/EA= 10/1 v/v).

The hydrolysis of 3a



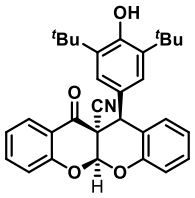
To the solution of **3a** (0.2 mmol 1.0 equiv.) in DMSO (2 mL), cooled in an ice bath, were added 30% H_2O_2 (0.5 mL) and anhydrous K_2CO_3 (0.2 mmol, 2.0 equiv.) The mixture was stirred and allowed to warm up to room temperature (exothermic effect was observed). After 30 min, distilled water (0.5 mL) and DMSO (0.5 mL) were added, cooling applied, and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM and quenched with saturated NH_4Cl. The organic phase was washed twice with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purified product **4** was obtained after recrystallization by using the mixed solvents(*n*-hexane/ether=1: 1, 2 mL), giving 37.9 mg (38%) as yellow solid. m.p:128 °C-129 °C; > 19: 1 dr; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.91 – 7.89 (m, 1H), 7.68 – 7.64 (m, 1H), 7.29 – 7.22 (m, 3H), 7.19 (d, J = 7.2 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.04 (t, J = 7.4 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.87 (s, 2H), 6.13 (s, 1H), 5.27 (s, 1H), 4.79 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (150 MHz, $CDCl_3$) (δ, ppm): 183.0, 156.4, 154.0, 150.8, 137.8, 136.0, 135.9, 129.7, 129.2, 127.9, 126.8, 126.1, 123.6, 122.8, 121.1, 118.7, 118.2, 117.1, 114.3, 95.4, 52.9, 43.5, 34.4, 30.2. HRMS (ESI) m/z calcd for $C_{31}H_{33}NNaO_5$ $[M+Na]^+$ 522.2256, found 522.2238.

Reference

1. J.-P. Tan, P. Yu, J.-H. Wu, Y. Chen, J. Pan, C. Jiang, X. Ren, H.-S. Zhang and T. Wang, *Org. Lett.*, **2019**, *21*, 7298-7302.

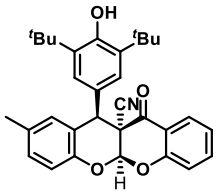
Characterization Data for Compounds 3a-3v

(5aS,11S,11aR)-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3a, major)



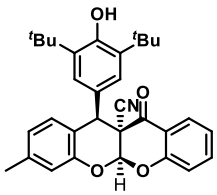
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:196 ºC-197 ºC; 40 mg, 2.5: 1 dr, 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.60 – 7.58 (m, 1H), 7.37 – 7.33 (m, 1H), 7.30 – 7.28 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.12 – 7.10 (m, 1H), 7.07 – 7.05 (m, 1H), 6.89 – 6.85 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.09 (d, *J* = 1.2 Hz, 1H), 4.88 (s, 1H), 4.81 (s, 1H), 1.17 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 185.4, 156.7, 152.9, 149.9, 136.8, 135.9, 131.2, 129.4, 127.4, 126.4, 123.3, 122.8, 120.4, 119.4, 118.1, 117.6, 116.6, 103.2, 95.2, 51.7, 45.7, 34.0, 29.9. HRMS (ESI) m/z calcd for $C_{31}H_{31}NNaO_4$ $[M+Na]^+$ 504.2151 found 504.2147.

(5aR,11aS,12R)-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-methyl-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3b, major)



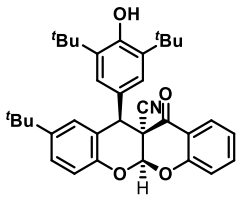
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:184 ºC-185 ºC; 37 mg, >19: 1 dr, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.89 (d, *J* = 8.0 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.20 – 7.14 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.91 – 6.86 (m, 4H), 6.10 (s, 1H), 5.28 (s, 1H), 4.79 (s, 1H), 2.21 (s, 3H), 1.38 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 183.1, 156.5, 153.9, 148.8, 137.8, 135.8, 132.3, 130.0, 129.8, 127.9, 126.8, 126.4, 123.6, 120.4, 118.7, 118.3, 116.8, 114.4, 95.4, 52.7, 43.6, 34.4, 30.3, 20.6. HRMS (ESI) m/z calcd for $C_{32}H_{33}NNaO_4$ $[M+Na]^+$ 518.2307, found 518.2307.

(5aR,11aS,12R)-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-methyl-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3c, major)



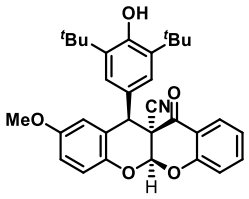
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:177 °C-178 °C; 29 mg, 10: 1 dr, 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.91 – 7.89 (m, 1H), 7.67 – 7.63 (m, 1H), 7.21 – 7.17 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.86 (s, 3H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.12 (s, 1H), 5.27 (s, 1H), 4.72 (s, 1H), 2.32 (s, 3H), 1.37 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 183.3, 156.4, 154.0, 150.5, 139.5, 137.8, 135.8, 129.4, 127.9, 126.8, 126.1, 123.9, 123.6, 118.7, 118.2, 118.1, 117.5, 114.4, 95.5, 53.3, 43.3, 34.4, 30.3, 21.2. HRMS (ESI) m/z calcd for $C_{32}H_{33}NNaO_4$ $[M+Na]^+$ 518.2307, found 518.2305.

(5aR,11aS,12R)-2-(tert-butyl)-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3d, syn isomer)



Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:201 °C-202 °C; 35 mg, 1.5: 1 dr, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.92 (d, *J* = 8.0 Hz, 2H), 7.67 – 7.63 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 3H), 7.38 – 7.35 (m, 3H), 7.31 – 7.28 (m, 5H), 7.23 – 7.19 (m, 2H), 7.15 – 7.12 (m, 6H), 7.04 – 7.00 (m, 7H), 6.88 – 6.84 (m, 6H), 6.67 – 6.62 (m, 9H), 6.12 (s, 2H), 6.06 (s, 3H), 5.27 (s, 2H), 4.86 (s, 3H), 4.80 (s, 3H), 4.71 (s, 2H), 1.37 (s, 36H), 1.24 (s, 27H), 1.20 (s, 18H), 1.16 (s, 54H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 185.6, 183.7, 156.8, 156.3, 153.9, 152.8, 148.4, 147.7, 146.0, 145.5, 137.8, 136.7, 135.7, 134.6, 127.8(3), 127.8(7), 127.4, 127.0, 126.6, 126.5, 126.4, 126.2, 123.7, 122.6, 120.5, 119.7, 119.4, 118.7, 118.0(4), 118.0(8), 117.0, 116.7(0), 116.7(5), 114.3, 95.6, 95.3, 54.0, 52.0, 45.8, 43.5, 34.4, 34.3, 34.0, 31.4, 30.3, 30.0. HRMS (ESI) m/z calcd for $C_{35}H_{39}NNaO_4$ $[M+Na]^+$ 560.2777, found 560.2779.

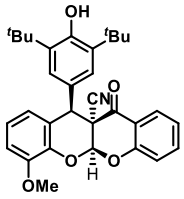
(5aR,11aS,12R)-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-methoxy-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3e, major)



Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:201 °C-202 °C; 30 mg, >19: 1 dr, 59% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.91 – 7.89 (m, 1H), 7.67 – 7.63 (m, 1H), 7.22 – 7.15 (m, 2H), 6.95 – 6.91 (m, 1H), 6.87 (s, br, 3H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.23 (s, 1H), 5.27 (s, 1H), 4.76 (s, 1H), 3.91 (s, 3H), 1.37 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 183.2, 156.3, 154.0, 148.2, 140.3, 137.9, 135.8, 127.8, 126.9, 125.8, 123.7, 122.4, 122.2, 121.1, 118.8, 118.1, 114.2, 111.1, 95.5, 56.1, 53.1, 43.4, 34.4, 30.3. HRMS (ESI) m/z calcd

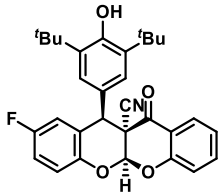
for $C_{32}H_{33}NKO_5$ $[M+Na]^+$ 550.1996, found550.1995.

(5aS,11aS,12R)-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-4-methoxy-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3f, major)



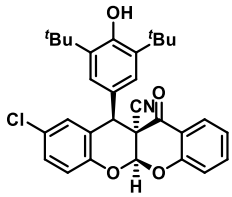
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:185 ºC-186 ºC; 27 mg, 10: 1 dr, 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.90 (d, *J* = 8.0 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.22 – 7.15 (m, 2H), 6.94 – 6.91 (m, 1H), 6.87 (s, br, 3H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.23 (s, 1H), 5.27 (s, 1H), 4.76 (s, 1H), 3.91 (s, 3H), 1.37 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 183.3, 156.3, 154.0, 148.2, 140.3, 137.9, 135.8, 127.8, 126.9, 125.8, 123.7, 122.4, 122.2, 121.1, 118.8, 118.1, 114.2, 111.0, 95.5, 56.1, 53.1, 43.4, 34.4, 30.3. HRMS (ESI) m/z calcd for $C_{32}H_{33}NNaO_5$ $[M+Na]^+$ 534.2256, found 534.2258.

(5aR,11aS,12R)-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-fluoro-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3g, syn isomer)



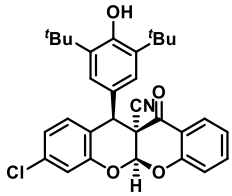
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:196 ºC-197 ºC; 42 mg, 1.5: 1 dr, 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.90 (d, *J* = 8.0 Hz, 3H), 7.69 – 7.65 (m, 3H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.29 (m, 2H), 7.23 – 7.19 (m, 5H), 7.15 (d, *J* = 8.4 Hz, 3H), 7.10 – 7.03 (m, 3H), 7.01 – 6.95 (m, 5H), 6.89 – 6.83 (m, 10H), 6.77 (d, *J* = 8.8 Hz, 3H), 6.71 – 6.67 (m, 6H), 6.12 (s, 3H), 6.08 (s, 2H), 5.31 (s, 3H), 4.92 (s, 2H), 4.77 (s, 2H), 4.74 (s, 3H), 1.38 (s, 54H), 1.18 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 185.0, 182.9, 158.2 ($^1J_{CF}$ = 240.9 Hz), 158.0 ($^1J_{CF}$ = 240.2 Hz), 156.6, 156.2, 154.2, 153.1, 146.8 ($^1J_{CF}$ = 2.2 Hz), 145.9 ($^1J_{CF}$ = 2.1 Hz), 138.0, 136.9, 136.1, 135.0, 127.9, 127.4, 126.7, 125.7, 125.4, 123.8, 122.9, 122.8, 121.8 ($^1J_{CF}$ = 7.6 Hz), 119.3, 119.0 ($^1J_{CF}$ = 8.1 Hz), 118.7, 118.5 ($^1J_{CF}$ = 8.1 Hz), 118.1, 118.0, 116.8 ($^1J_{CF}$ = 23.4 Hz), 116.4 ($^1J_{CF}$ = 22.5 Hz), 115.7 ($^1J_{CF}$ =24.3 Hz), 114.1, 95.5, 95.2, 52.7, 51.4, 45.9, 43.6, 34.4, 34.0, 30.2, 29.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm: -96.26, -97.63. HRMS (ESI) m/z calcd for $C_{31}H_{30}FNNaO_4$ $[M+Na]^+$ 522.2057, found 522.2057.

(5aR,11aS,12R)-2-chloro-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3h, syn isomer)



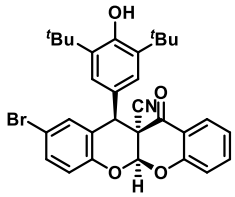
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:203 ºC-204 ºC; 42 mg, 1.5: 1 dr, 81% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.90 (d, *J* = 8.0 Hz, 3H), 7.69 – 7.65 (m, 3H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.30 (m, 5H), 7.22 (d, *J* = 8.0 Hz, 5H), 7.20 – 7.17 (m, 5H), 7.15 – 7.12 (m, 3H), 7.06 (d, *J* = 2.0 Hz, 3H), 6.98 (d, *J* = 8.8 Hz, 3H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.86 (s, 5H), 6.71 – 6.66 (m, 6H), 6.12 (s, 3H), 6.09 (s, 2H), 5.32 (s, 3H), 4.93 (s, 2H), 4.77 (s, 5H), 1.39 (s, 54H), 1.18 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 184.9, 182.6, 156.5, 156.2, 154.2, 153.2, 149.5, 148.5, 138.1, 137.0, 136.1, 130.5, 129.7, 129.4, 129.3, 129.0, 127.9, 127.4, 126.7, 125.6, 123.8, 123.0, 122.0, 119.3, 119.1, 118.7, 118.6, 118.1, 114.0, 95.4, 95.2, 52.4, 51.4, 45.7, 43.4, 34.4, 34.0, 30.2, 29.9. HRMS (ESI) m/z calcd for $C_{31}H_{30}ClNNaO_4$ $[M+Na]^+$ 538.1761, found 538.1757.

(5aR,11aS,12R)-3-chloro-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3i, major)



Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:197 ºC-198 ºC; 27 mg, >19: 1 dr, 44% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.90 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.24 – 7.2.0 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 7.01 – 6.96 (m, 2H), 6.85 (s, 2H), 6.12 (s, 1H), 5.30 (s, 1H), 4.74 (s, 1H), 1.38 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 182.7, 156.2, 154.1, 151.3, 138.0, 136.1, 134.4, 130.7, 127.9, 126.7, 125.6, 123.8, 123.2, 119.9, 118.7, 118.1, 117.4, 114.0, 95.4, 52.7, 43.2, 34.4, 30.2. HRMS (ESI) m/z calcd for $C_{31}H_{30}ClNNaO_4$ $[M+Na]^+$ 538.1761, found 538.1763.

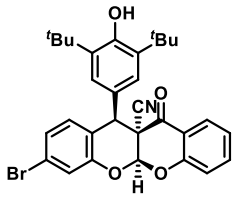
(5aR,11aS,12R)-2-bromo-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3j, major)



Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:234ºC-235 ºC; 34 mg, >19: 1 dr, 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.91 – 7.88 (m, 1H), 7.69 – 7.65 (m, 1H), 7.37 – 7.35 (m, 1H), 7.23 – 7.21 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.85 (s, 2H), 6.12 (s, 1H), 5.32 (s, 1H),

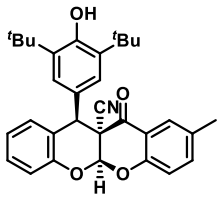
4.77 (s, 1H), 1.39 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 182.6, 156.2, 154.2, 150.0, 138.1, 136.1, 132.3, 132.2, 127.9, 126.7, 125.4, 123.8, 123.2, 118.9, 118.7, 118.1, 115.3, 114.0, 95.3, 52.4, 43.4, 34.4, 30.2. HRMS (ESI) m/z calcd for $C_{31}H_{30}BrNNaO_4$ $[M+Na]^+$ 582.1256, found 582.1254.

(5aR,11aS,12R)-3-bromo-12-(3,5-di-tert-butyl-4-hydroxyphenyl)-11-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3k, major)



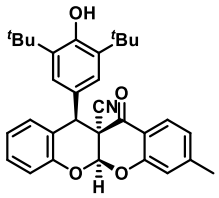
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:214 ºC-215 ºC; 36 mg, >19: 1 dr, 64% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.91 – 7.89 (m, 1H), 7.70 – 7.65 (m, 1H), 7.24 – 7.20 (m, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.13 – 7.10 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.85 (s, 2H), 6.12 (s, 1H), 5.30 (s, 1H), 4.72 (s, 1H), 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 182.4, 156.2, 154.1, 151.4, 138.0, 136.1, 131.0, 127.9, 126.7, 126.1, 124.2, 123.9, 122.1, 120.4, 120.3, 118.7, 118.1, 114.0, 95.4, 52.4, 43.3, 34.4, 30.2. HRMS (ESI) m/z calcd for $C_{31}H_{30}BrNNaO_4$ $[M+Na]^+$ 582.1256, found 582.1255.

(5aR,11R,11aS)-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-methyl-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3l, major)



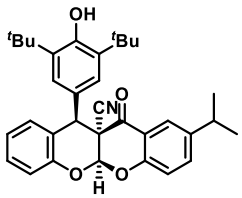
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:215 ºC-216 ºC; 37 mg, >19: 1 dr, 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.67 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.01 – 6.95 (m, 2H), 6.87 (s, 2H), 6.10 (s, 1H), 5.27 (s, 1H), 4.79 (s, 1H), 2.35 (s, 3H), 1.38 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 183.2, 154.4, 153.9, 150.9, 139.0, 135.8, 133.4, 129.7, 129.2, 127.4, 126.8, 126.3, 122.8, 121.1, 118.5, 117.8, 117.1, 114.5, 95.4, 52.7, 43.6, 34.4, 30.2, 20.5. HRMS (ESI) m/z calcd for $C_{32}H_{33}NNaO_4$ $[M+Na]^+$518.2307, found 518.2307.

(5aR,11R,11aS)-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-methyl-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3m, major)



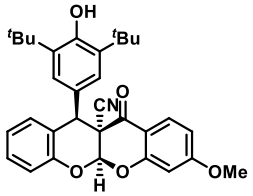
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:177°C-178 °C; 30 mg, >19: 1 dr, 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.78 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 9.6 Hz, 2H), 7.00 (d, *J* = 9.2 Hz, 2H), 6.96 (d, *J* = 7.2 Hz, 2H), 6.87 (s, 2H), 6.10 (s, 1H), 5.26 (s, 1H), 4.79 (s, 1H), 2.43 (s, 3H), 1.37 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 182.5, 156.4, 153.9, 150.9, 149.9, 135.8, 129.7, 129.3, 129.1, 127.8, 126.8, 125.0, 122.8, 121.1, 118.7, 117.0, 115.9, 114.5, 95.4, 52.7, 43.6, 34.4, 30.2, 22.2. HRMS (ESI) m/z calcd for $C_{32}H_{33}NNaO_4$ $[M+Na]^+$518.2307, found 518.2305.

(5aR,11R,11aS)-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-isopropyl-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3n, major)



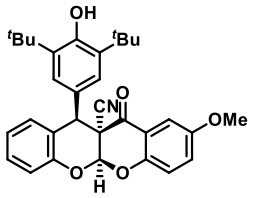
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:218 °C-219 °C; 47 mg, 10: 1 dr, 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.72 (d, *J* = 1.6 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.26 – 7.19 (m, 1H), 7.08 – 7.03 (m, 3H), 6.99 – 6.95 (m, 1H), 6.87 (s, 2H), 6.11 (s, 1H), 5.27 (s, 1H), 4.79 (s, 1H), 2.97 – 2.90 (m, 1H), 1.37 (s, 18H), 1.25 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 183.4, 154.5, 154.0, 150.9, 144.4, 136.7, 135.8, 129.6, 129.2, 126.8, 126.1, 124.9, 122.8, 121.2, 118.5, 117.8, 117.1, 114.5, 95.4, 53.0, 43.6, 34.4, 33.4, 30.2, 24.0, 23.7. HRMS (ESI) m/z calcd for $C_{34}H_{37}NNaO_4$ $[M+Na]^+$ 546.2615, found 546.2616.

(5aR,11R,11aS)-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-methoxy-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3o, major)



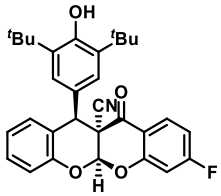
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:210 °C-211 °C; 29 mg, >19: 1 dr, 56% yield; ^{1}H NMR (400 MHz, DMSO + $CDCl_3$) (δ, ppm): 11.62 (d, *J* = 8.4 Hz, 1H), 10.21 (s, 1H), 10.05 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.06 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.90 – 6.83 (m, 2H), 6.51 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 1.33 (s, 18H). ^{13}C NMR (75 MHz, DMSO + $CDCl_3$) (δ, ppm): 188.2, 174.8, 164.3, 163.1, 155.1, 154.9, 153.6, 139.6, 131.8, 129.5, 129.1, 127.2, 126.9, 123.4, 119.8, 116.4, 115.7, 114.0, 101.4, 98.7, 56.6, 56.4, 35.0, 30.7. HRMS (ESI) m/z calcd for $C_{32}H_{32}NNaO_5$ $[M+Na]^+$ 534.2256, found 534.2187.

(5aR,11R,11aS)-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-methoxy-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3p, syn isomer)



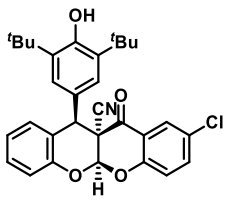
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:183 ºC-184 ºC; 35 mg, 1: 1 dr, 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): δ 7.36 – 7.33 (m, 1H), 7.27 (d, *J* = 5.6 Hz, 2H), 7.24 – 7.19 (m, 2H), 7.11 (d, *J* = 9.2 Hz, 2H), 7.07 – 7.02 (m, 3H), 6.99 – 6.95 (m, 2H), 6.91 – 6.88 (m, 3H), 6.67 – 6.60 (m, 3H), 6.09 (s, 1H), 6.05 (s, 1H), 5.28 (s, 1H), 4.90 (s, 1H), 4.80 (s, 1H), 4.79 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 1.38 (s, 18H), 1.18 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm):185.4, 183.2, 155.6, 154.8, 154.0, 152.9, 151.3, 150.9, 150.8, 149.9, 135.9, 134.8, 131.1, 129.6, 129.4, 129.2, 126.9, 126.8, 126.4, 126.1, 123.2, 122.8, 121.2, 120.5, 120.1, 119.4, 118.1, 117.5, 117.1, 116.6, 114.5, 108.1, 107.2, 95.5, 95.4, 56.0, 55.7, 52.8, 51.6, 45.8, 43.6, 34.4, 34.0, 30.3, 30.0. HRMS (ESI) m/z calcd for $C_{32}H_{32}NNaO_5$ $[M+Na]^+$ 534.2256, found 534.2259.

(5aR,11R,11aS)-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-fluoro-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3q, major)



Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:201 ºC-202 ºC; 42 mg, 4: 1 dr, 84% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.95 – 7.91 (m, 1H), 7.24 – 7.20 (m, 1H), 7.07 – 7.03 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.94 – 6.89 (d, *J* = 8.2 Hz, 1H), 6.86 (d, *J* = 10.0 Hz, 3H), 6.13 (s, 1H), 5.29 (s, 1H), 4.80 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 184.0, 181.6, 168.5 ($^{1}J_{CF}$ = 258.4 Hz), 167.5 ($^{1}J_{CF}$ = 258.2 Hz), 158.3, 158.2, 154.0, 153.0, 150.7, 149.7, 136.0, 131.1, 130.6 ($^{1}J_{CF}$ = 11.6 Hz), 130.1 ($^{1}J_{CF}$ = 11.6 Hz), 129.7, 129.5, 129.3, 126.8, 126.3, 126.1, 123.4, 123.0, 120.9, 120.2, 117.6, 117.0, 116.3, 115.1, 114.2, 112.2 ($^{1}J_{CF}$ = 22.7 Hz), 111.3 ($^{1}J_{CF}$ = 22.7 Hz), 106.1, 105.9, 105.2, 104.9, 95.6, 95.4, 52.4, 51.5, 45.7, 43.6, 34.4, 34.0, 30.2, 29.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ ppm: -119.79, -119.92. HRMS (ESI) m/z calcd for $C_{31}H_{30}NFNaO_4$ $[M+Na]^+$ 522.2057, found 522.2056.

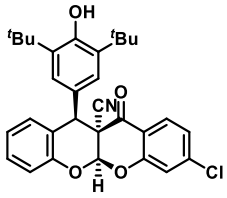
(5aR,11R,11aS)-2-chloro-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3r, major)



Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:182 ºC-183 ºC; 39

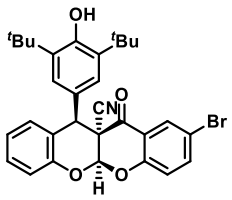
mg, 2: 1 dr, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.84 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.24 – 7.21 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.02 – 6.99 (m, 1H), 6.87 (s, 2H), 6.11 (s, 1H), 5.29 (s, 1H), 4.81 (s, 2H), 1.38 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 182.0, 154.9, 154.1, 150.7, 137.7, 136.0, 131.1, 129.8, 129.4, 127.1, 126.7, 123.1, 120.5, 119.8, 119.1, 117.6, 117.0, 114.0, 95.5, 51.5, 43.6, 34.4, 30.2. HRMS (ESI) m/z calcd for $C_{31}H_{30}NClNaO_4$ $[M+Na]^+$ 538.1761, found 538.1764.

(5aR,11R,11aS)-3-chloro-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3s, major)



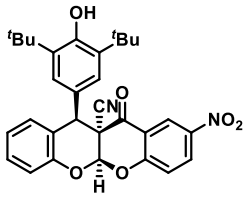
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:212 ºC-213 ºC; 37 mg, 10: 1 dr, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.84 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.07 – 6.99 (m, 3H), 6.87 (s, 2H), 6.12 (s, 1H), 5.28 (s, 1H), 4.80 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 182.0, 156.8, 154.0, 150.7, 144.0, 135.9, 129.7, 129.3, 129.0, 126.8, 126.1, 124.5, 123.1, 120.8, 119.1, 117.0, 116.8, 114.1, 95.5, 52.5, 43.6, 34.4, 30.2. HRMS (ESI) m/z calcd for $C_{31}H_{30}NClNaO_4$ $[M+Na]^+$ 538.1761, found 538.1759.

(5aR,11R,11aS)-2-bromo-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3t, syn isomer)



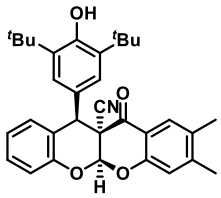
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:167 ºC-168 ºC; 41 mg, 2: 1 dr, 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.99 (d, *J* = 2.4 Hz, 2H), 7.75 – 7.72 (m, 2H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.24 – 7.20 (m, 2H), 7.11 – 7.05 (m, 6H), 7.01 – 6.97 (m, 4H), 6.87 (s, 4H), 6.58 (d, *J* = 8.8 Hz, 1H), 6.11 (s, 2H), 6.08 (s, 1H), 5.29 (s, 2H), 4.96 (s, 1H), 4.81 (s, 3H), 1.38 (s, 36H), 1.19 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): δ 184.5, 181.9, 155.4, 154.0, 153.1, 150.7, 149.7, 147.4, 140.5, 139.2, 136.0, 131.1, 130.2, 129.8, 129.5, 129.4, 126.7, 126.0, 123.4, 123.1, 120.8, 120.0, 119.6, 117.6, 117.0, 116.4, 115.5, 114.0, 95.4, 95.2, 52.3, 51.4, 45.7, 43.6, 34.4, 34.0, 30.2, 30.0. HRMS (ESI) m/z calcd for $C_{31}H_{30}NBrNaO_4$ $[M+Na]^+$ 582.1256, found 582.1242.

(5aR,11R,11aS)-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-2-nitro-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3u, major)

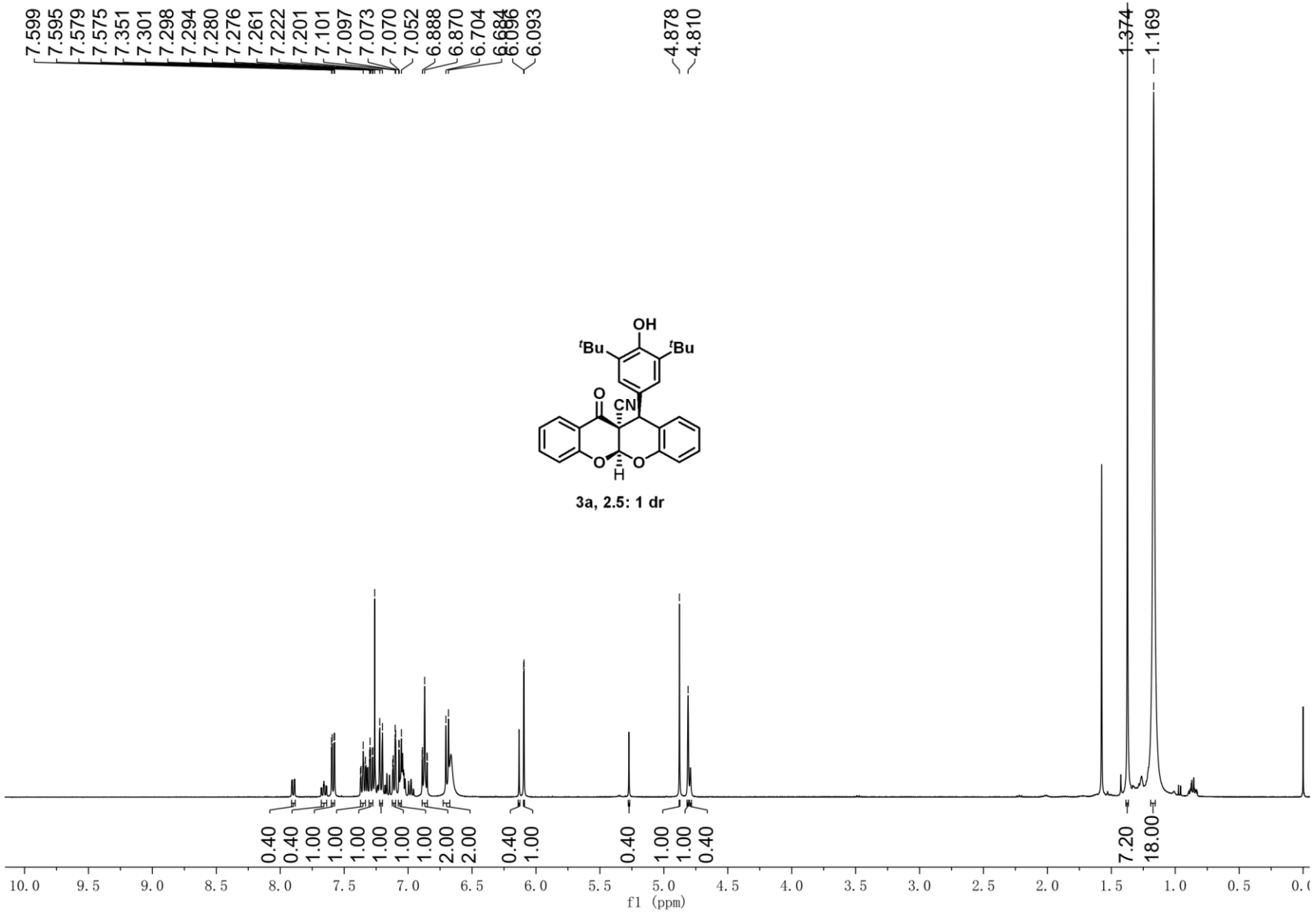


Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:206 ºC-207 ºC; 24 mg, >19: 1 dr, 45% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 9.10 (d, *J* = 2.4 Hz, 1H), 8.51 – 8.48 (m, 1H), 7.60 (d, *J* = 10.8 Hz, 2H), 7.16 – 7.12 (m, 1H), 7.01 (s, 2H), 6.89 – 6.85 (m, 2H), 6.01 (s, 1H), 5.88 (s, 1H), 5.17 (s, 1H), 1.37 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 176.1, 159.1, 155.3, 153.8, 152.8, 144.7, 136.1, 129.3, 129.2, 129.0, 128.3, 127.9, 125.5, 123.7, 123.1, 120.7, 119.9, 117.0, 40.6, 34.4, 30.3. HRMS (ESI) m/z calcd for $C_{31}H_{30}N_2NaO_6$ $[M+Na]^+$ 549.2002, found 549.2314.

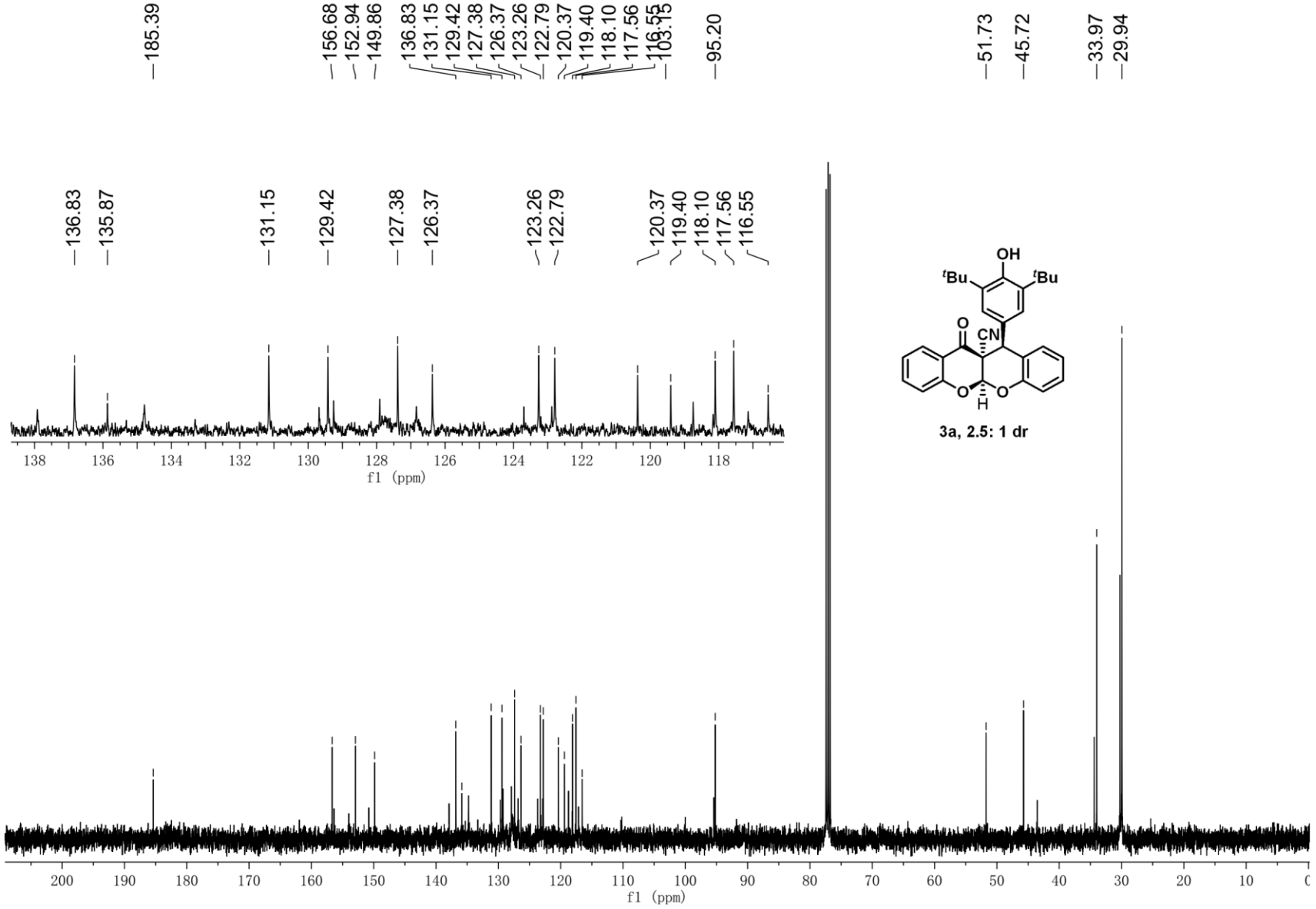
(5aR,11R,11aS)-11-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,3-dimethyl-12-oxo-11H,12H-chromeno[2,3-b]chromene-11a(5aH)-carbonitrile (3v, major)



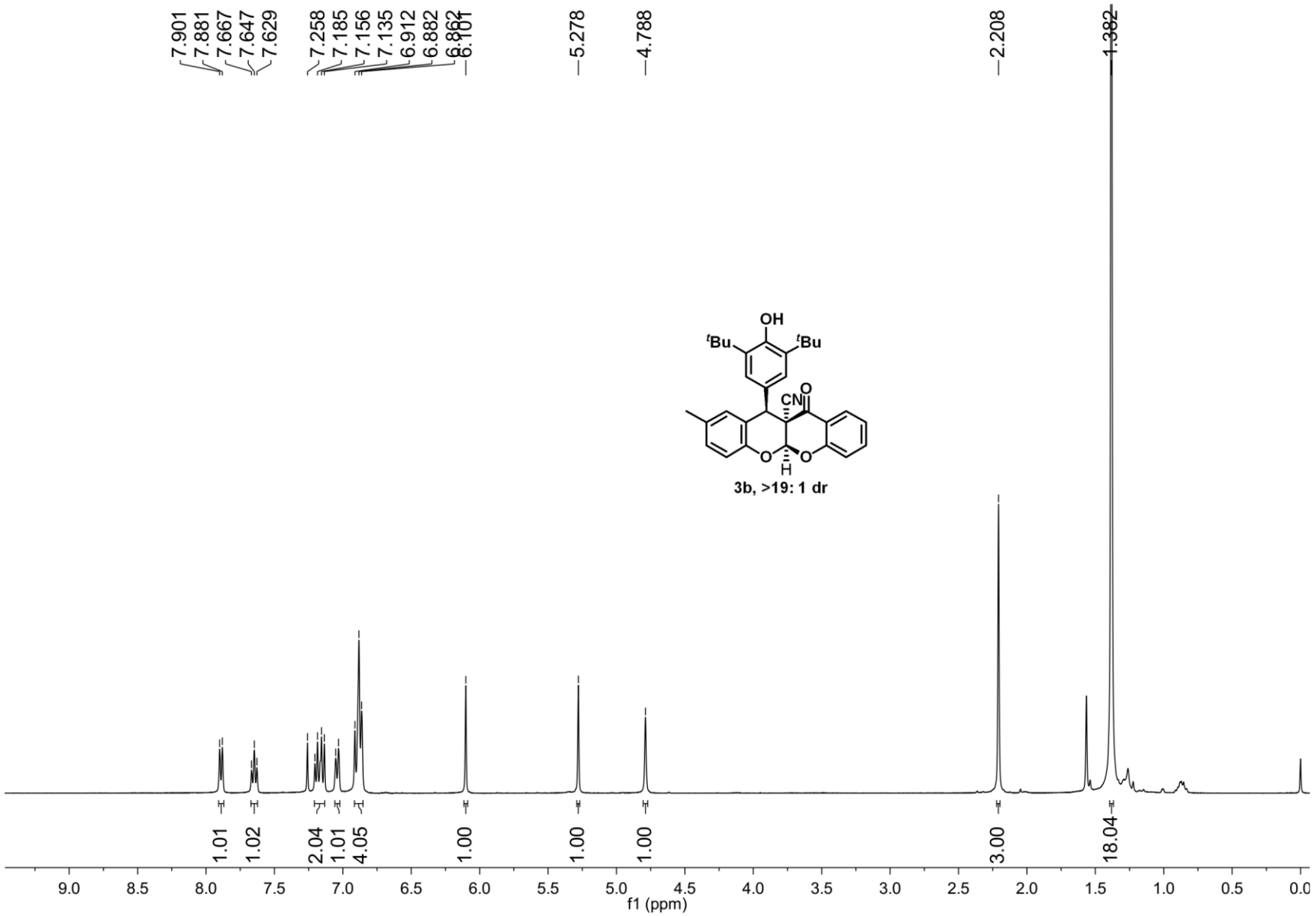
Yellow solid after purification by column chromatography (petroleum ether/ethyl acetate = 10/1); m.p:206 ºC-207 ºC; 24 mg, >19: 1 dr, 48% yield; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.51 (s, 1H), 7.32 (s, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.98 – 6.95 (m, 1H), 6.88 (s, 2H), 6.10 (s, 1H), 5.27 (s, 1H), 4.82 (s, 1H), 2.30 (d, *J* = 4.0 Hz, 6H), 1.38 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): ^{13}C NMR (101 MHz, $CDCl_3$) δ 183.4, 153.9, 152.7, 151.1, 140.1, 135.8, 132.6, 129.7, 129.1, 127.9, 126.8, 125.0, 122.7, 121.1, 117.7, 117.0, 114.7, 95.3, 43.5, 34.4, 30.2, 20.5, 15.6. HRMS (ESI) m/z calcd for $C_{33}H_{35}NNaO_4$ $[M+Na]^+$ 532.2464, found532.2463.



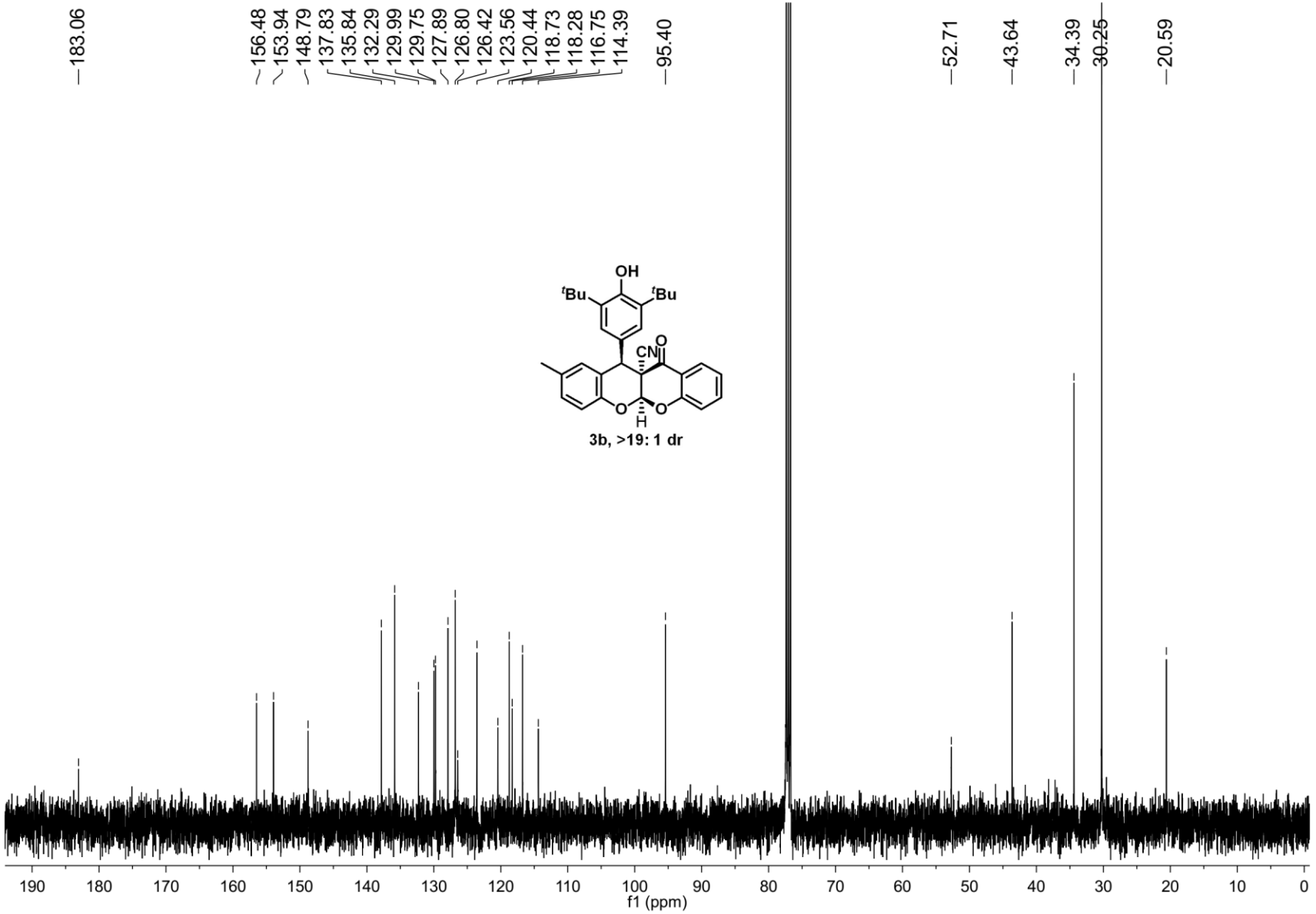
^{1}H NMR Spectrum of Compound 3a



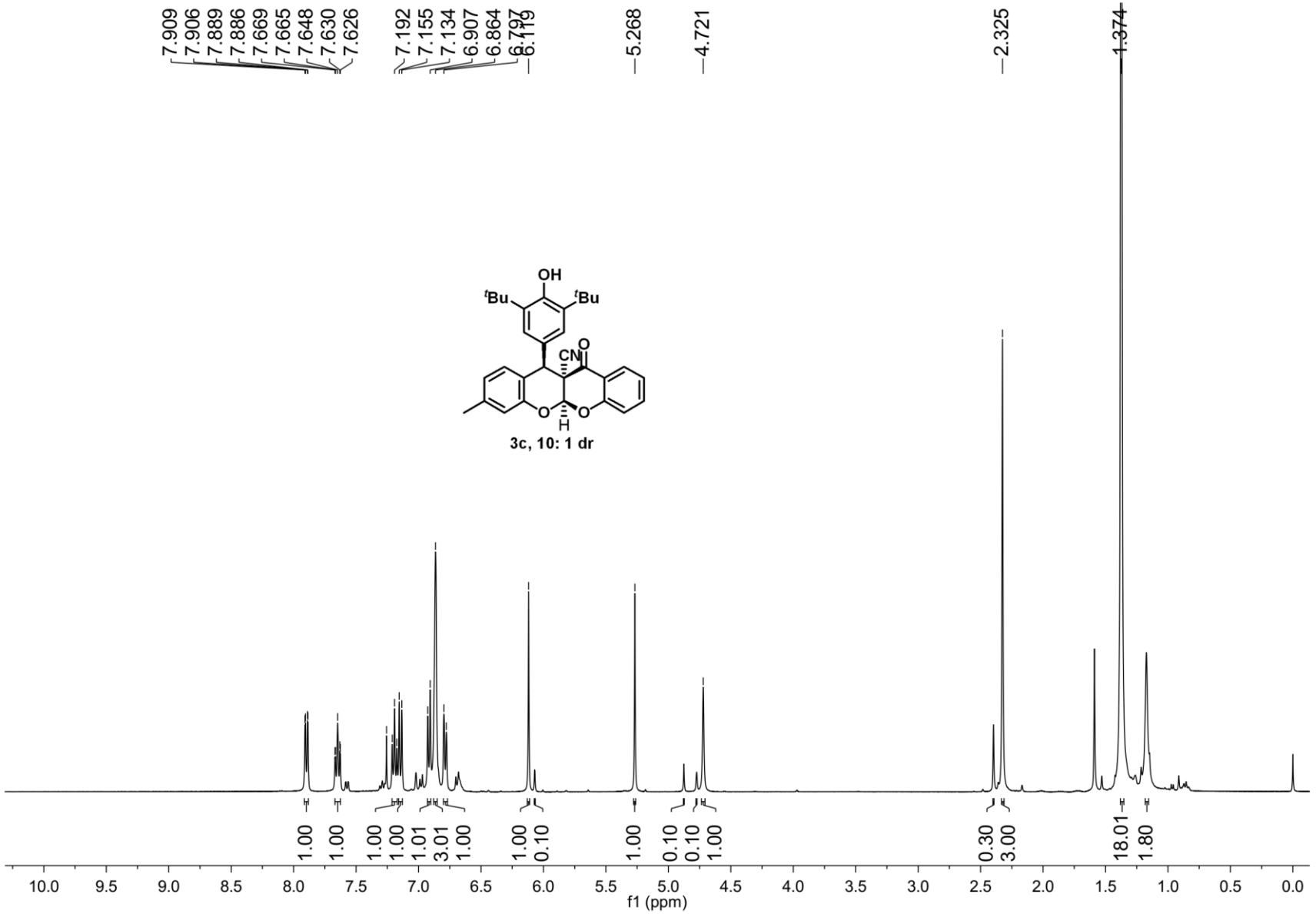
^{13}C NMR Spectrum of Compound 3a



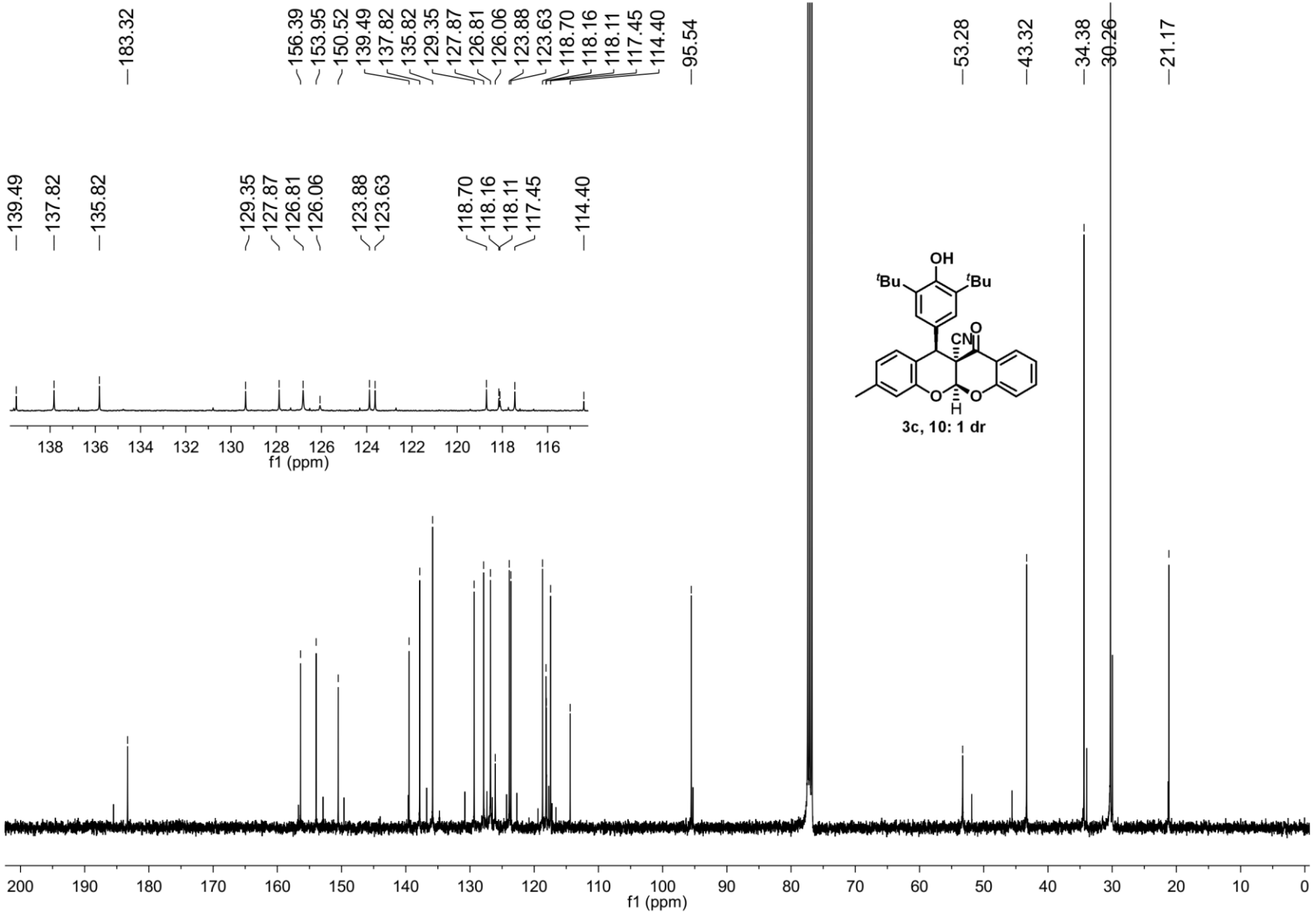
[1]H NMR Spectrum of Compound 3b



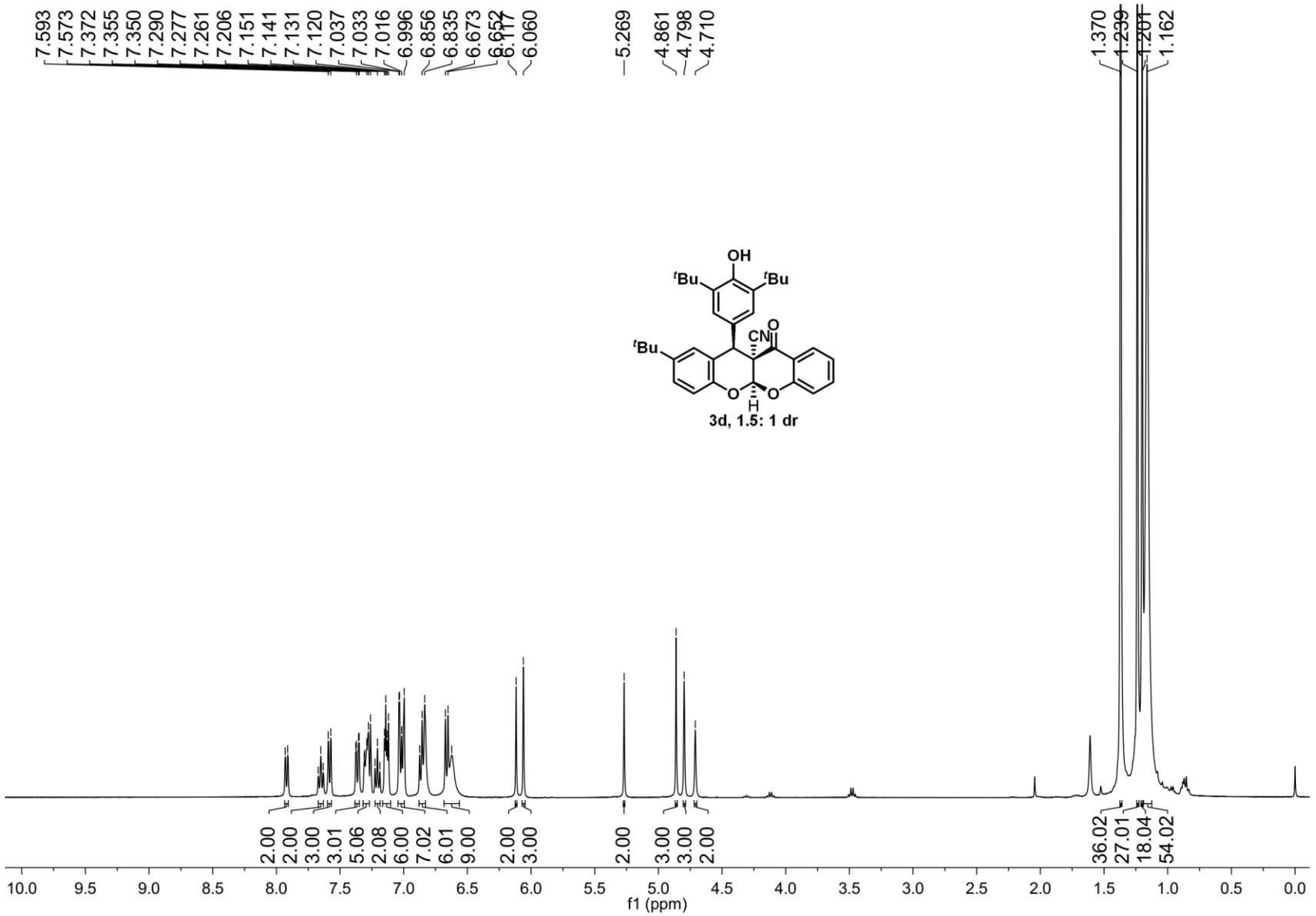
^{13}C NMR Spectrum of Compound 3b



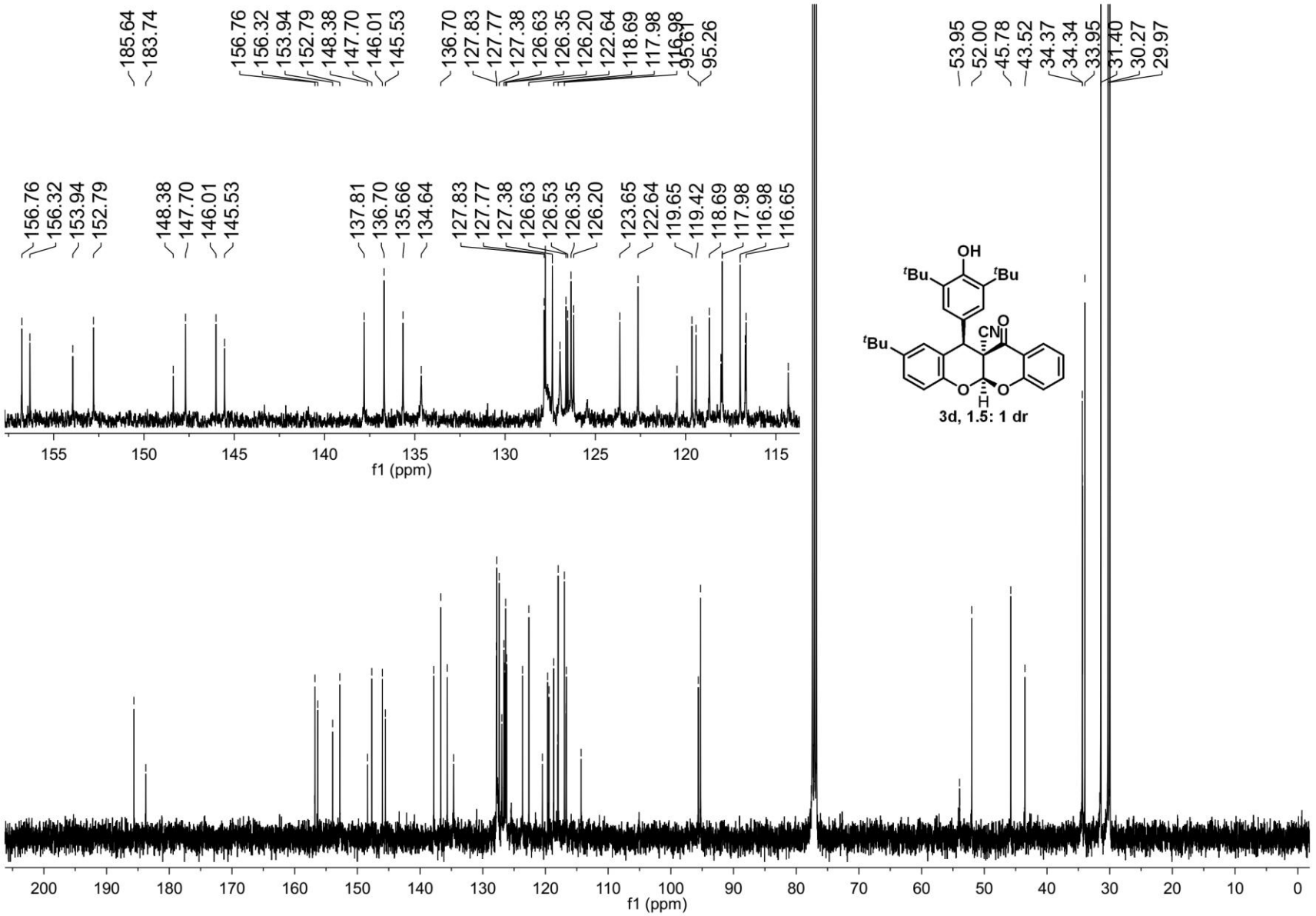
^{1}H NMR Spectrum of Compound 3c



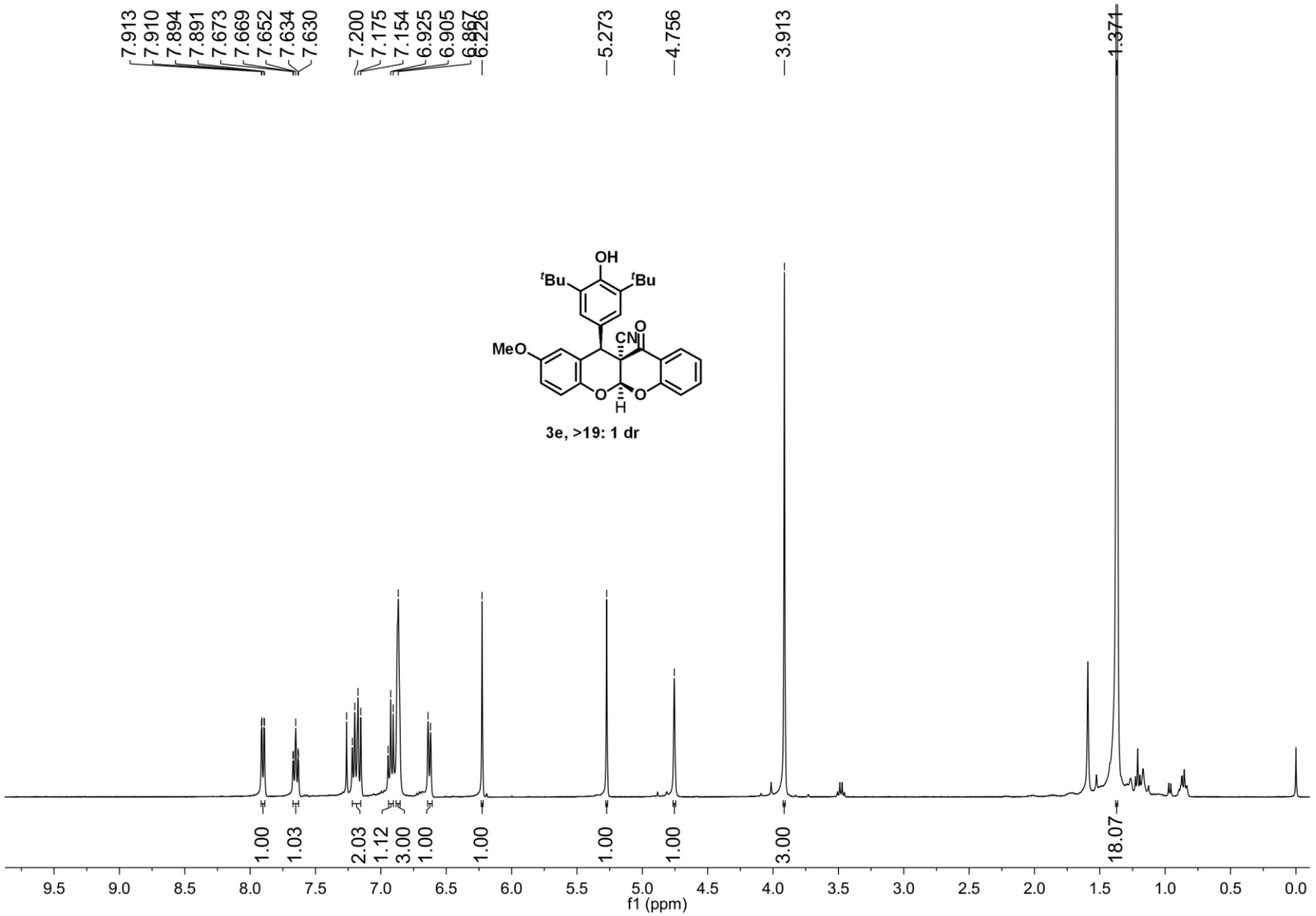
^{13}C NMR Spectrum of Compound 3c



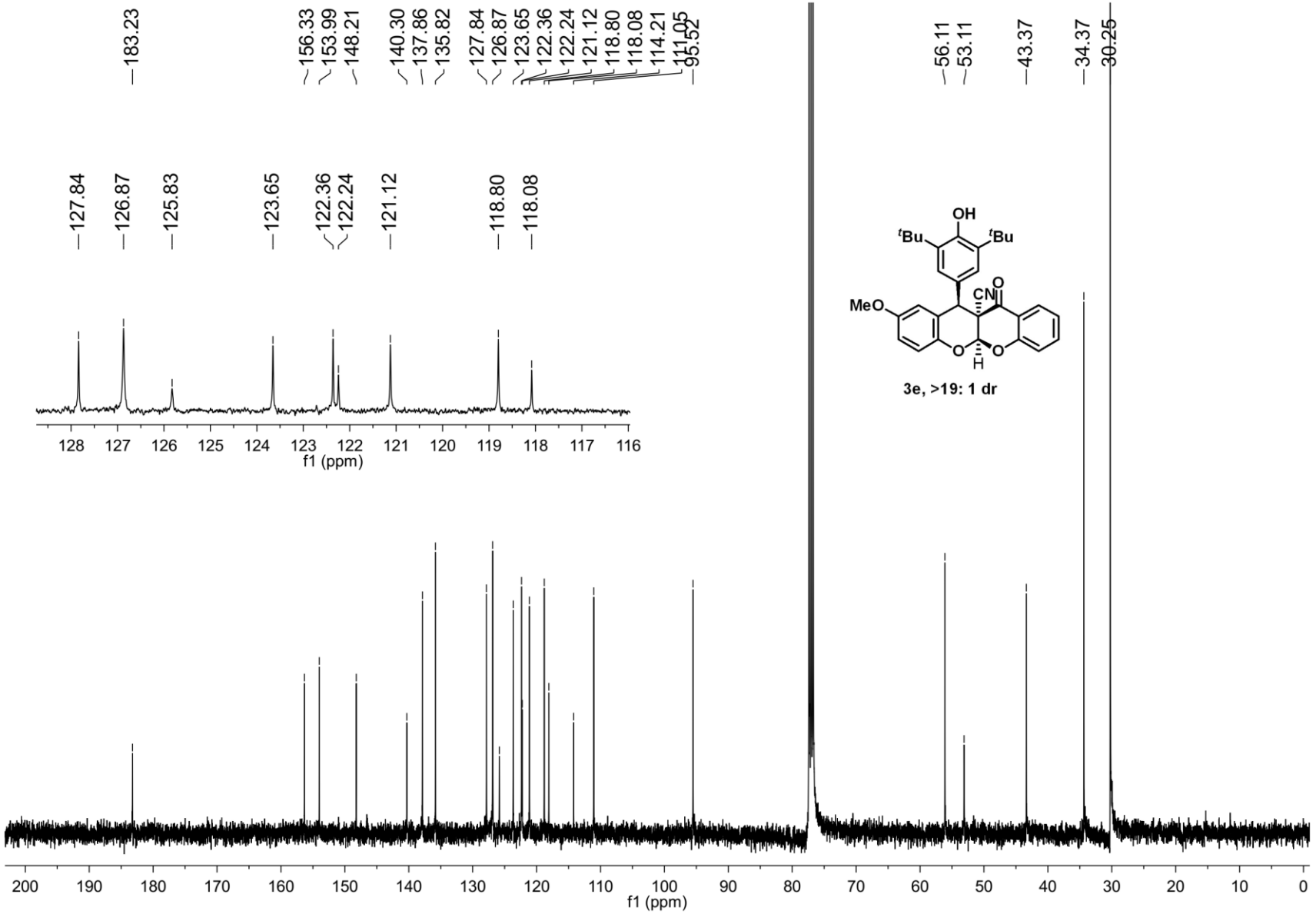
^{1}H NMR Spectrum of Compound 3d



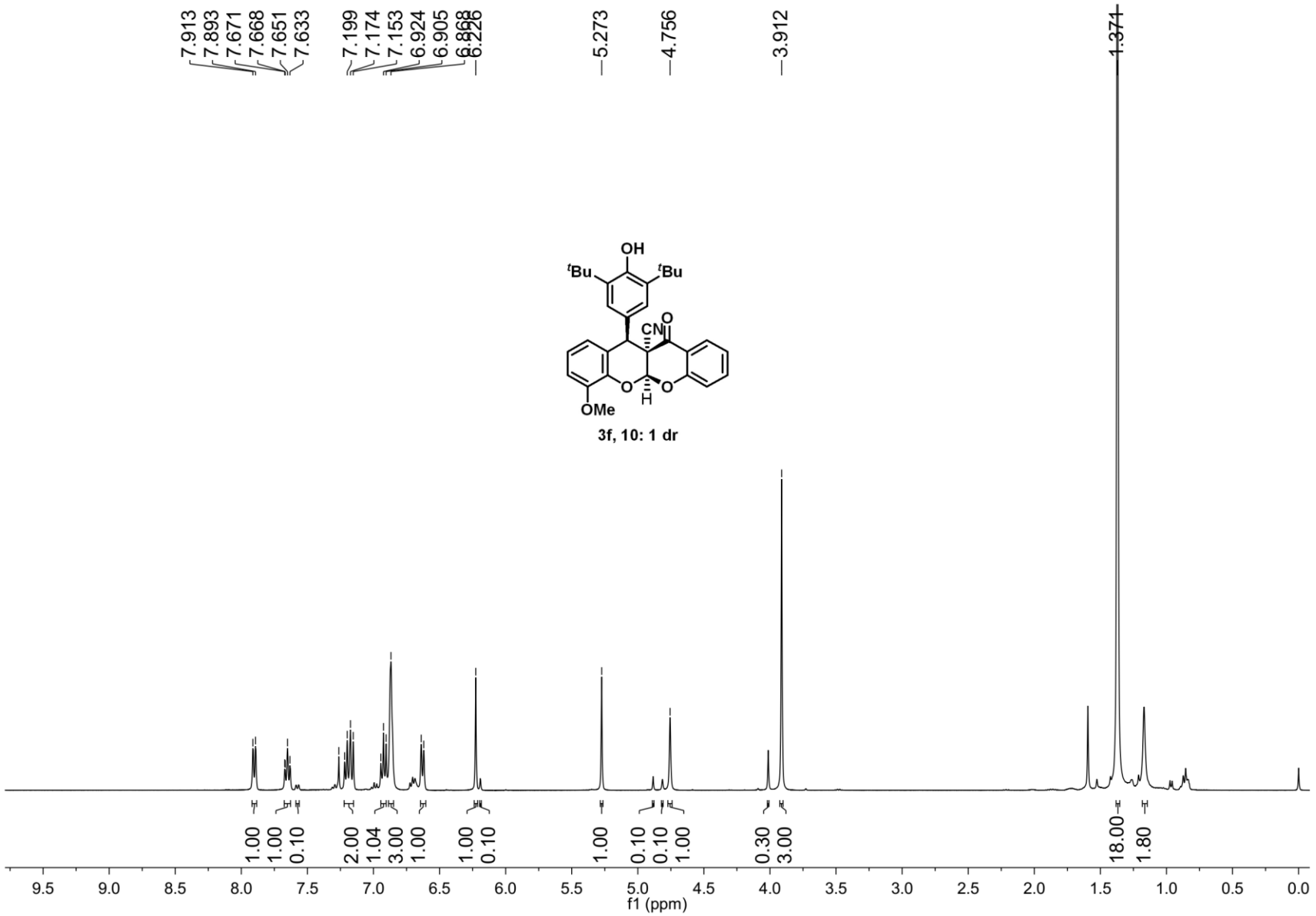
^{13}C NMR Spectrum of Compound 3d



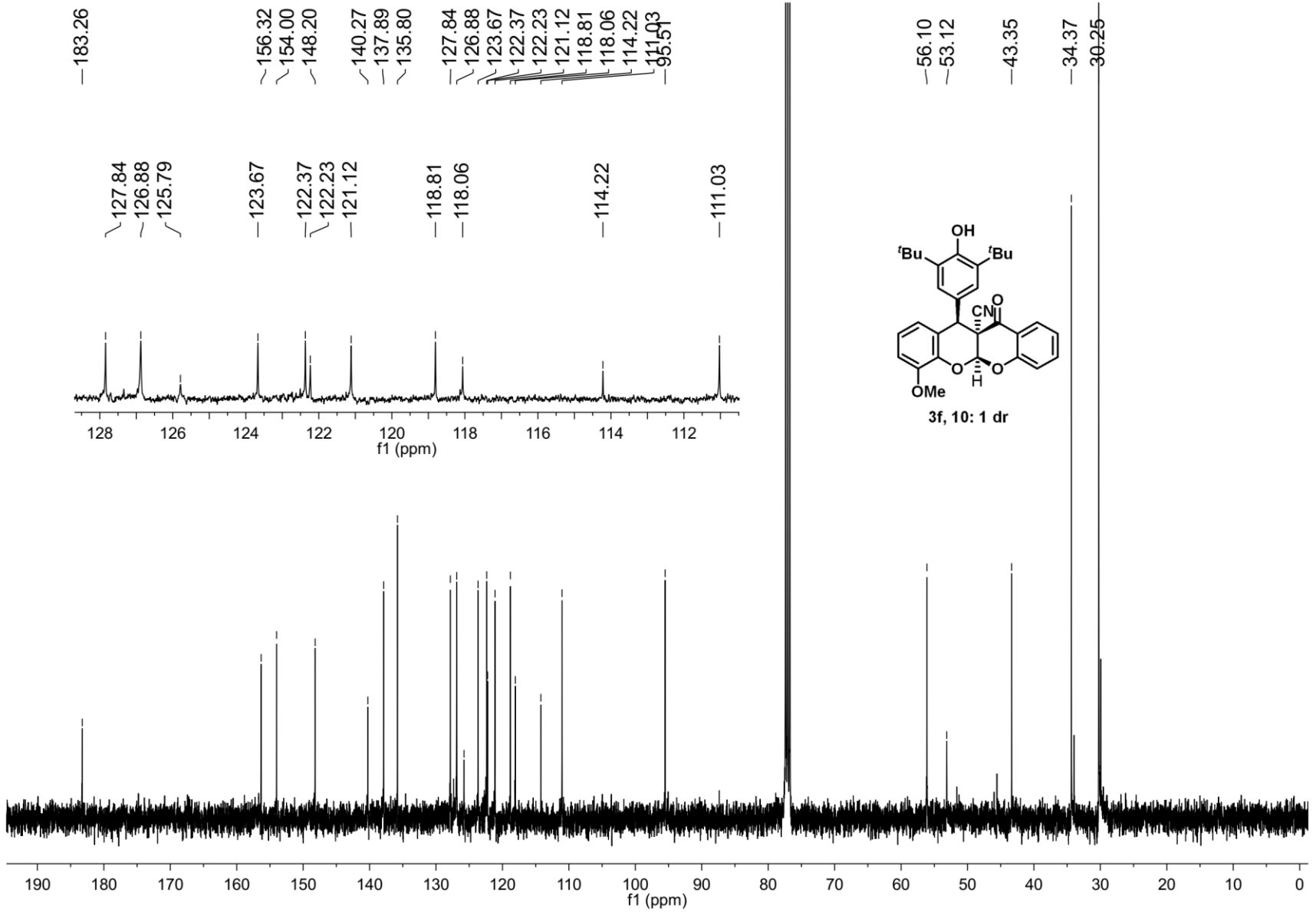
^{1}H NMR Spectrum of Compound 3e



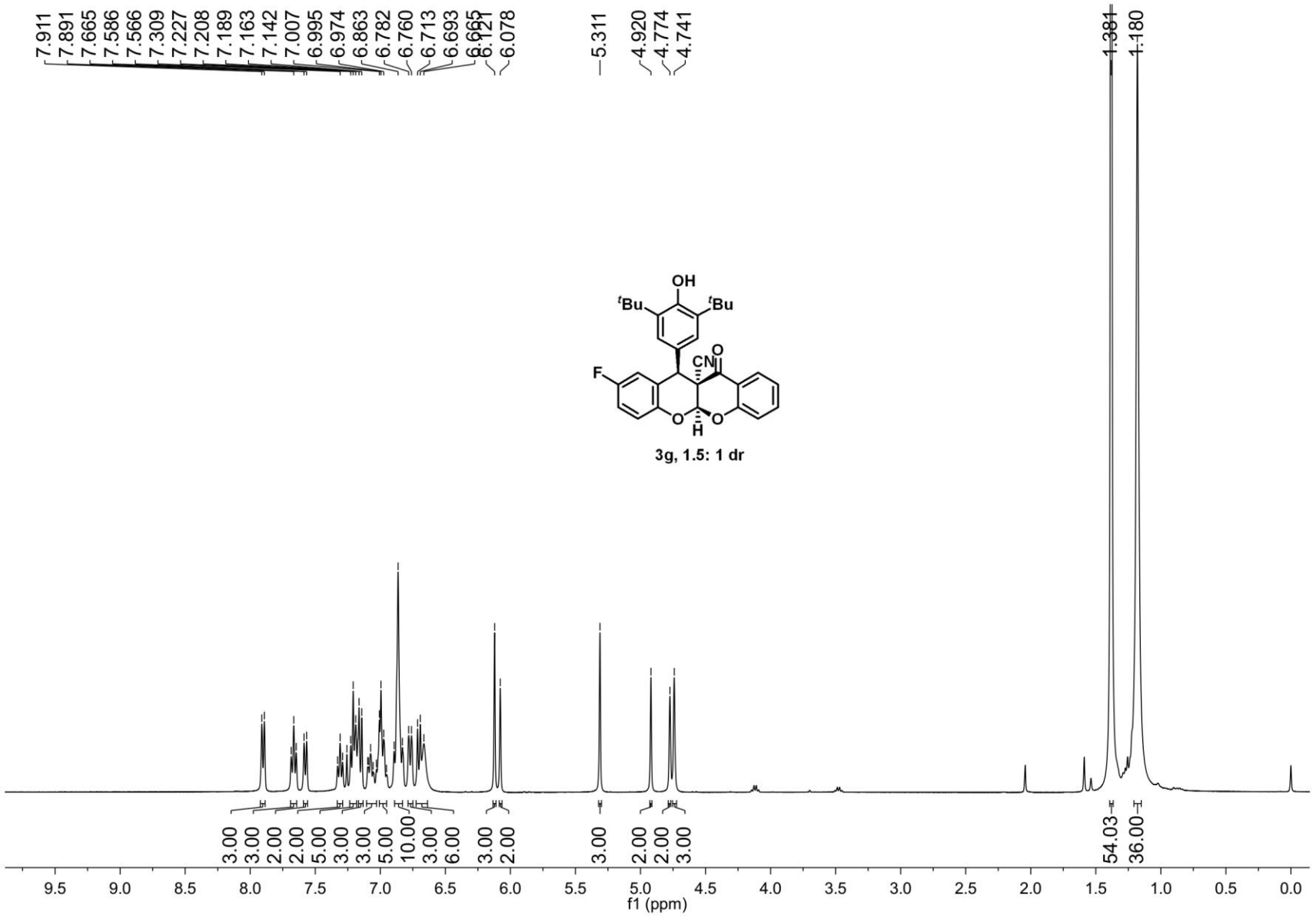
^{13}C NMR Spectrum of Compound 3e



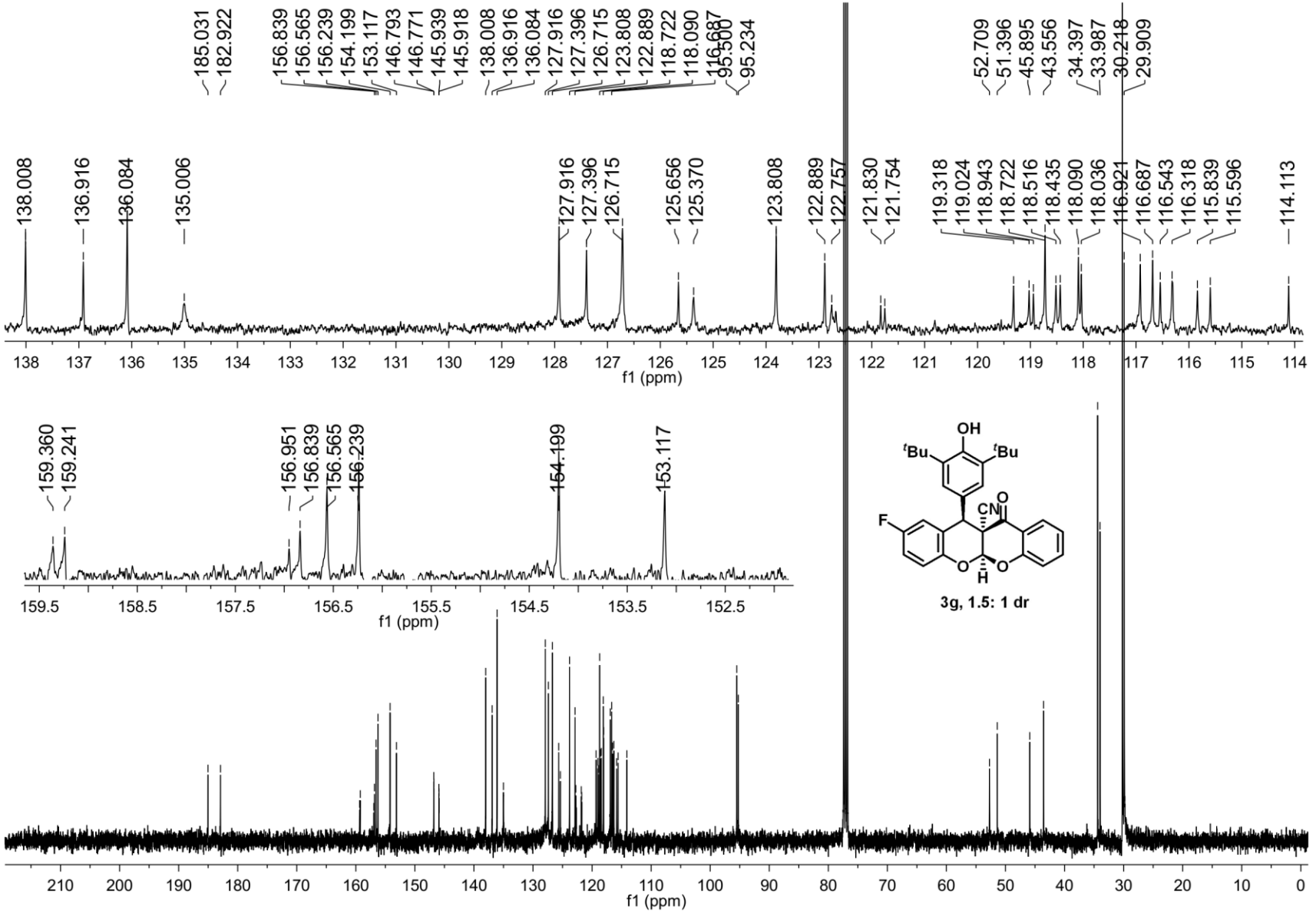
^{1}H NMR Spectrum of Compound 3f



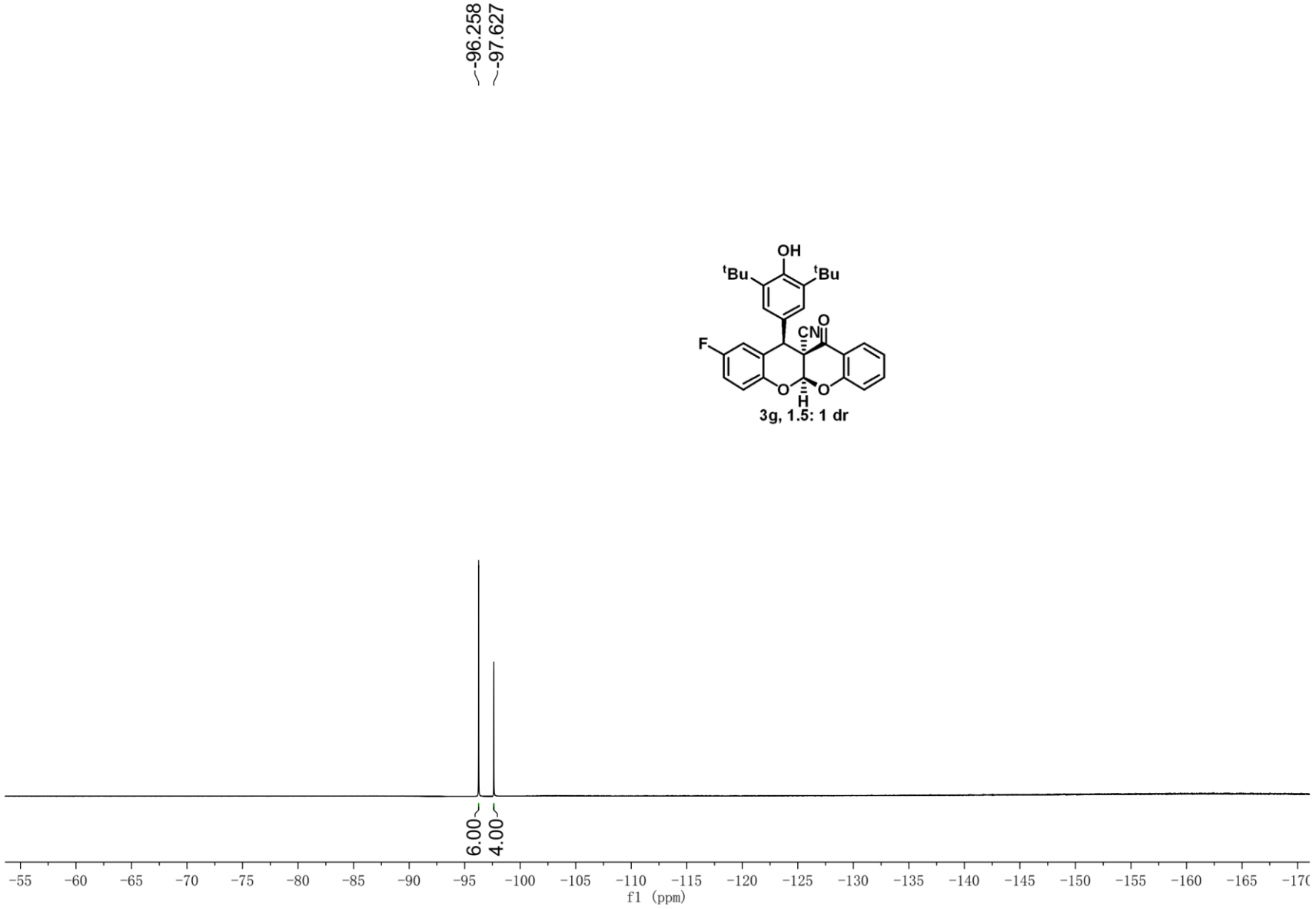
^{13}C NMR Spectrum of Compound 3f



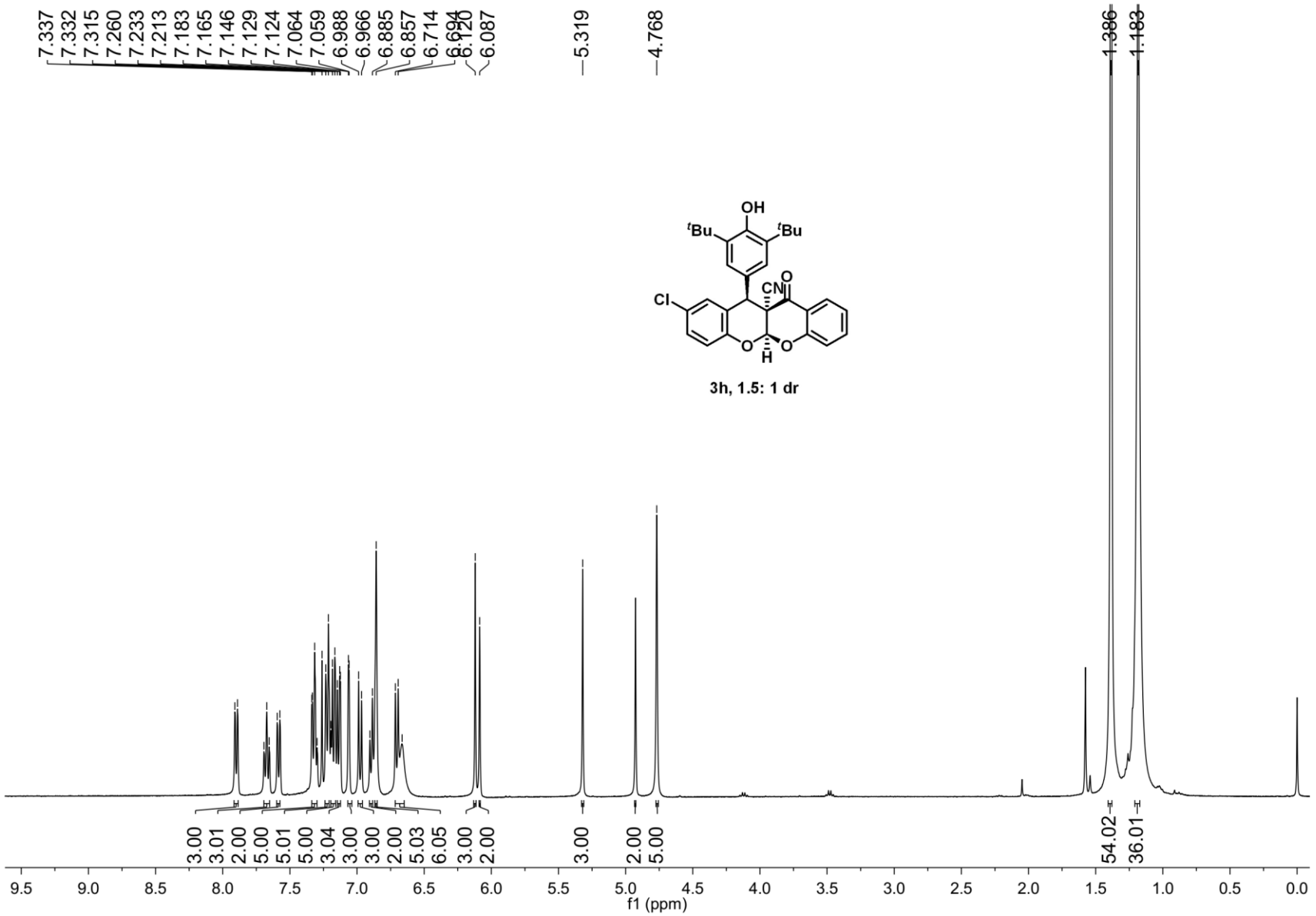
^{1}H NMR Spectrum of Compound 3g



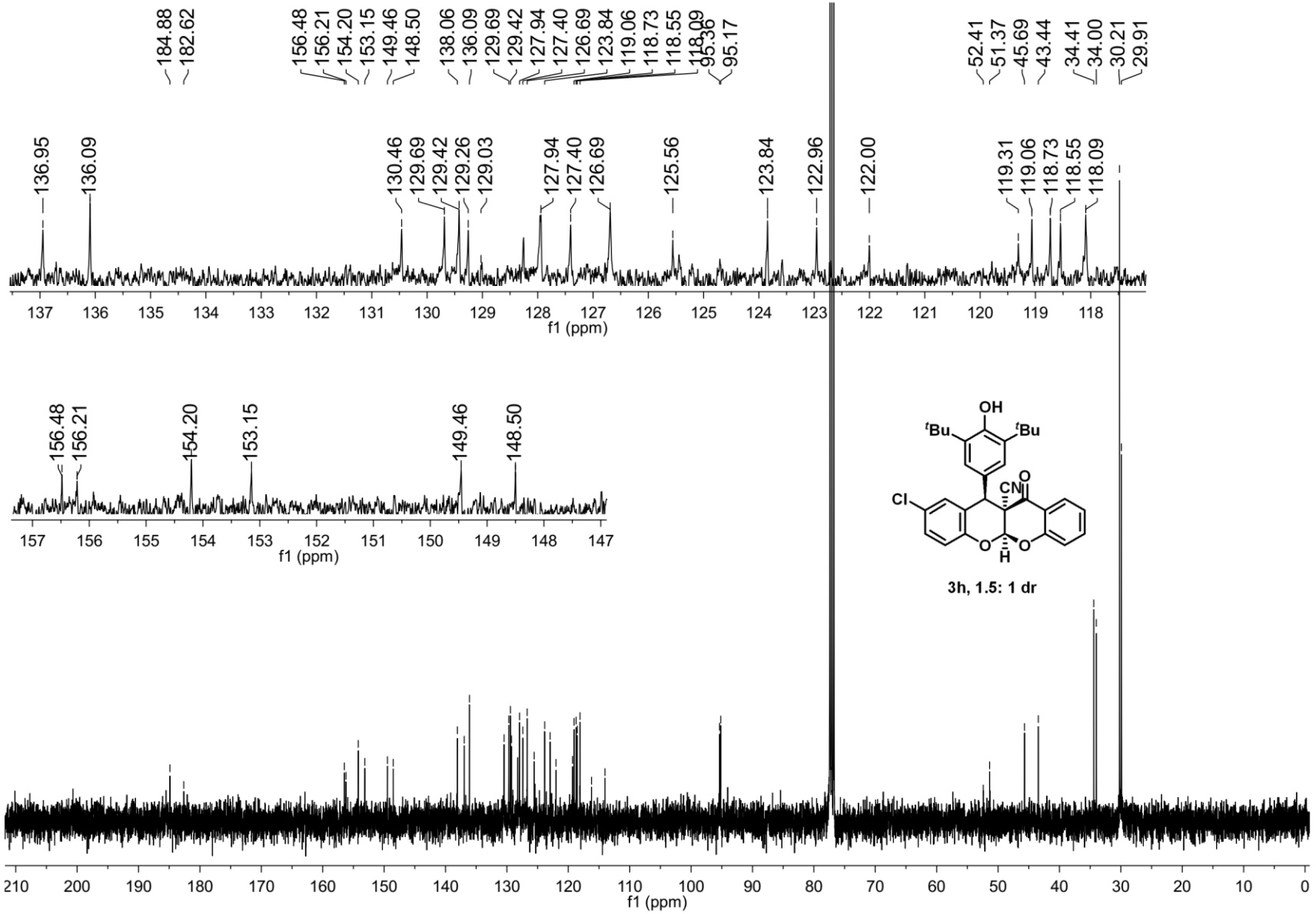
^{13}C NMR Spectrum of Compound 3g



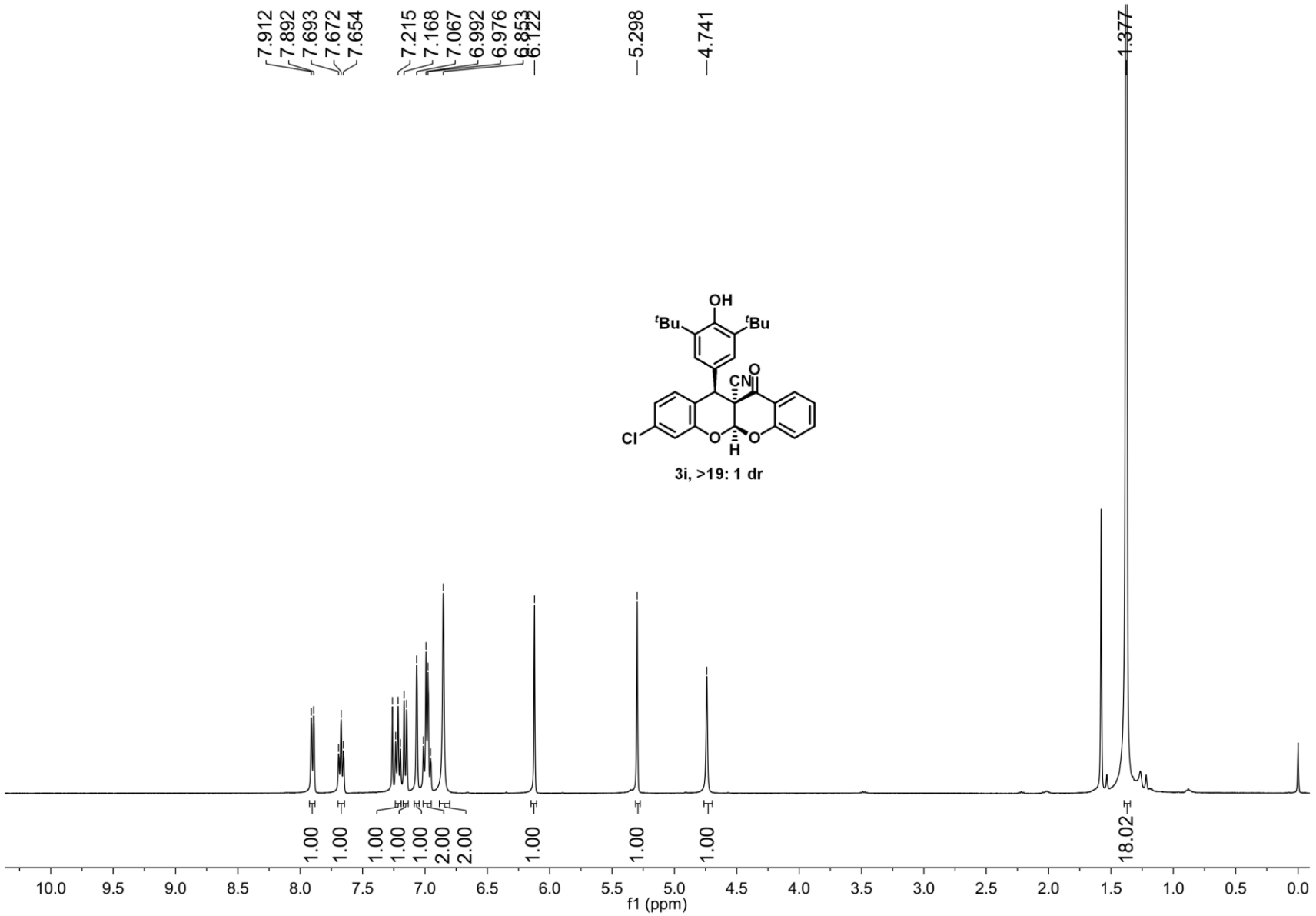
^{19}F NMR Spectrum of Compound 3g



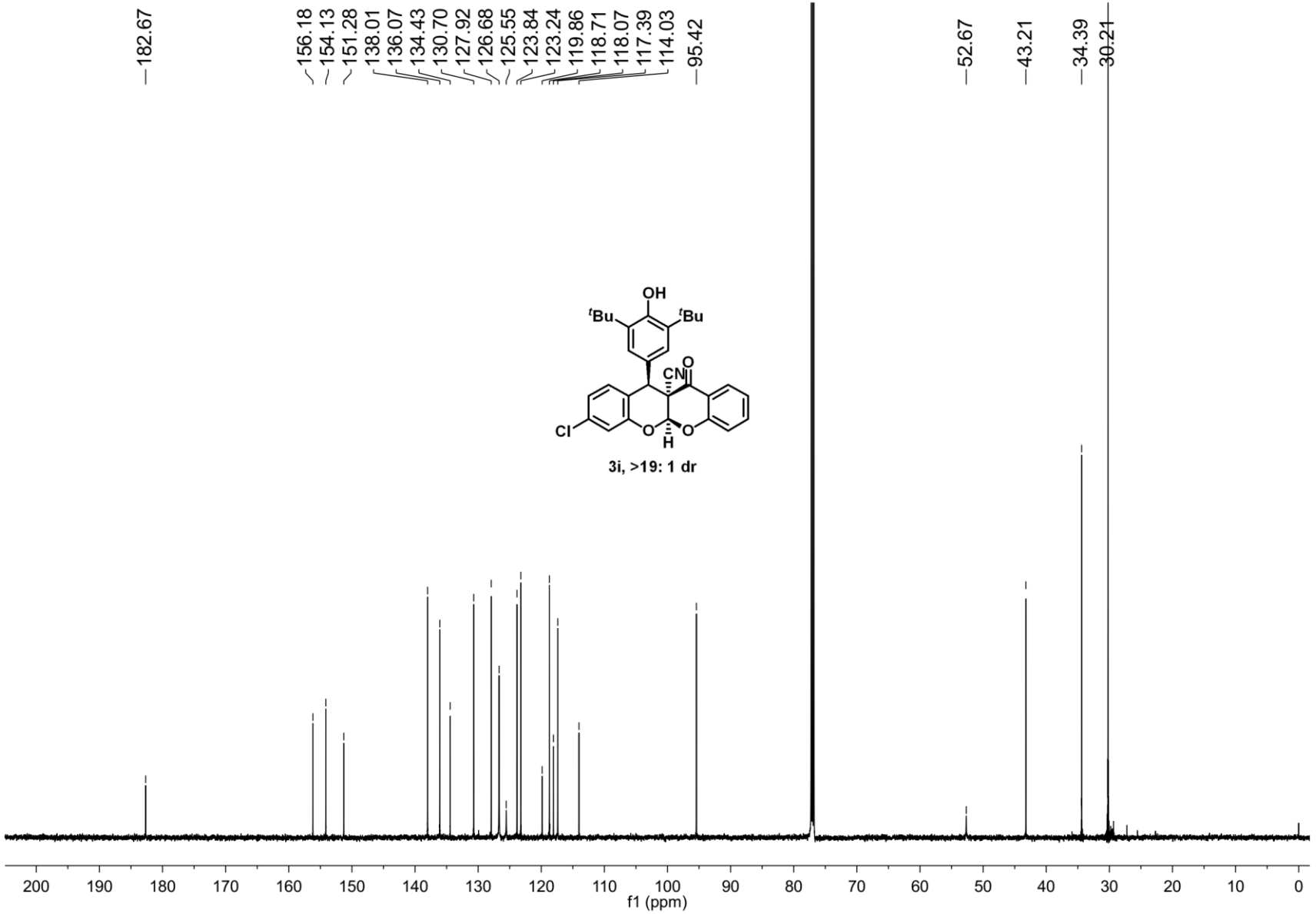
[1]H NMR Spectrum of Compound 3h



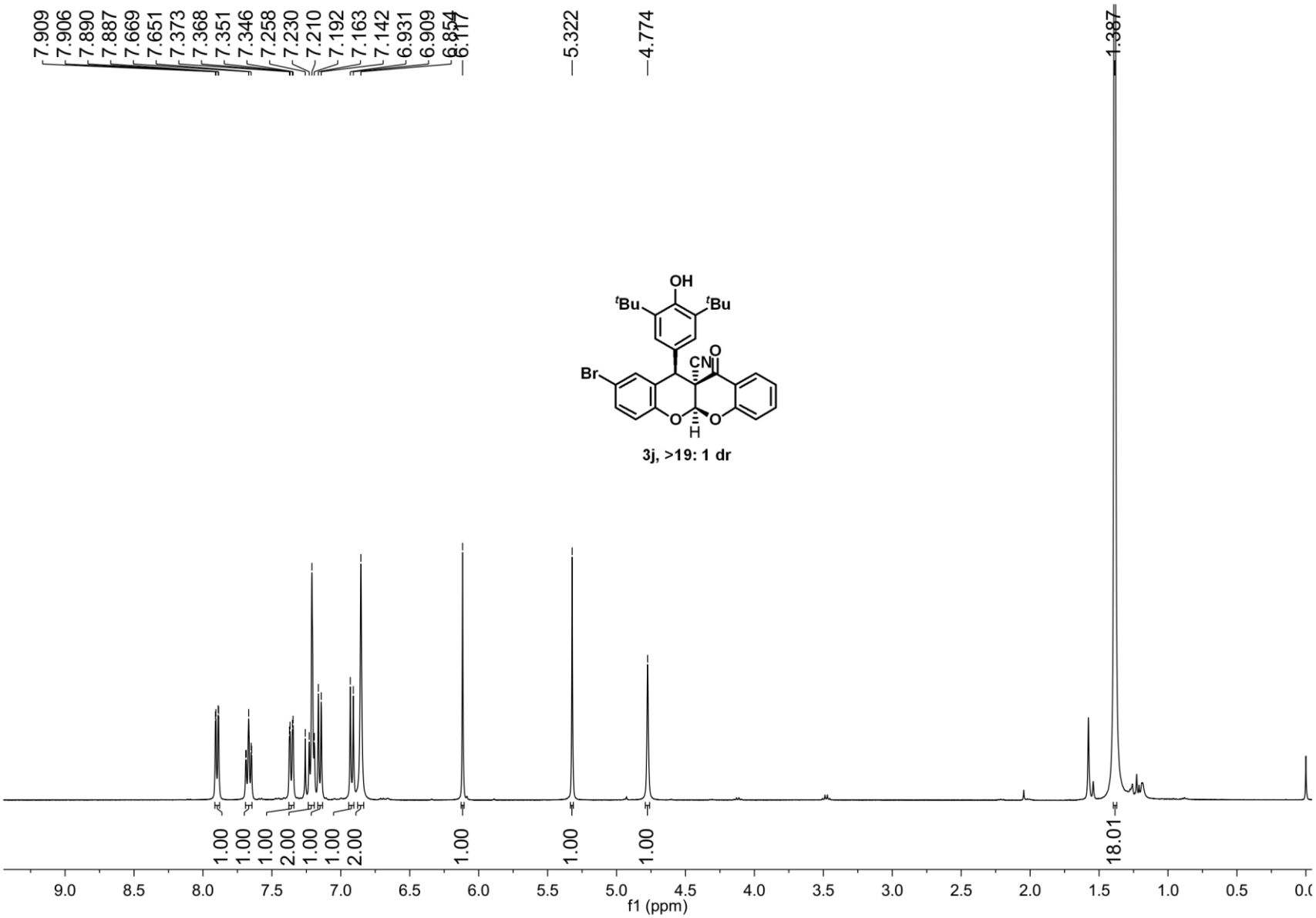
^{13}C NMR Spectrum of Compound 3h



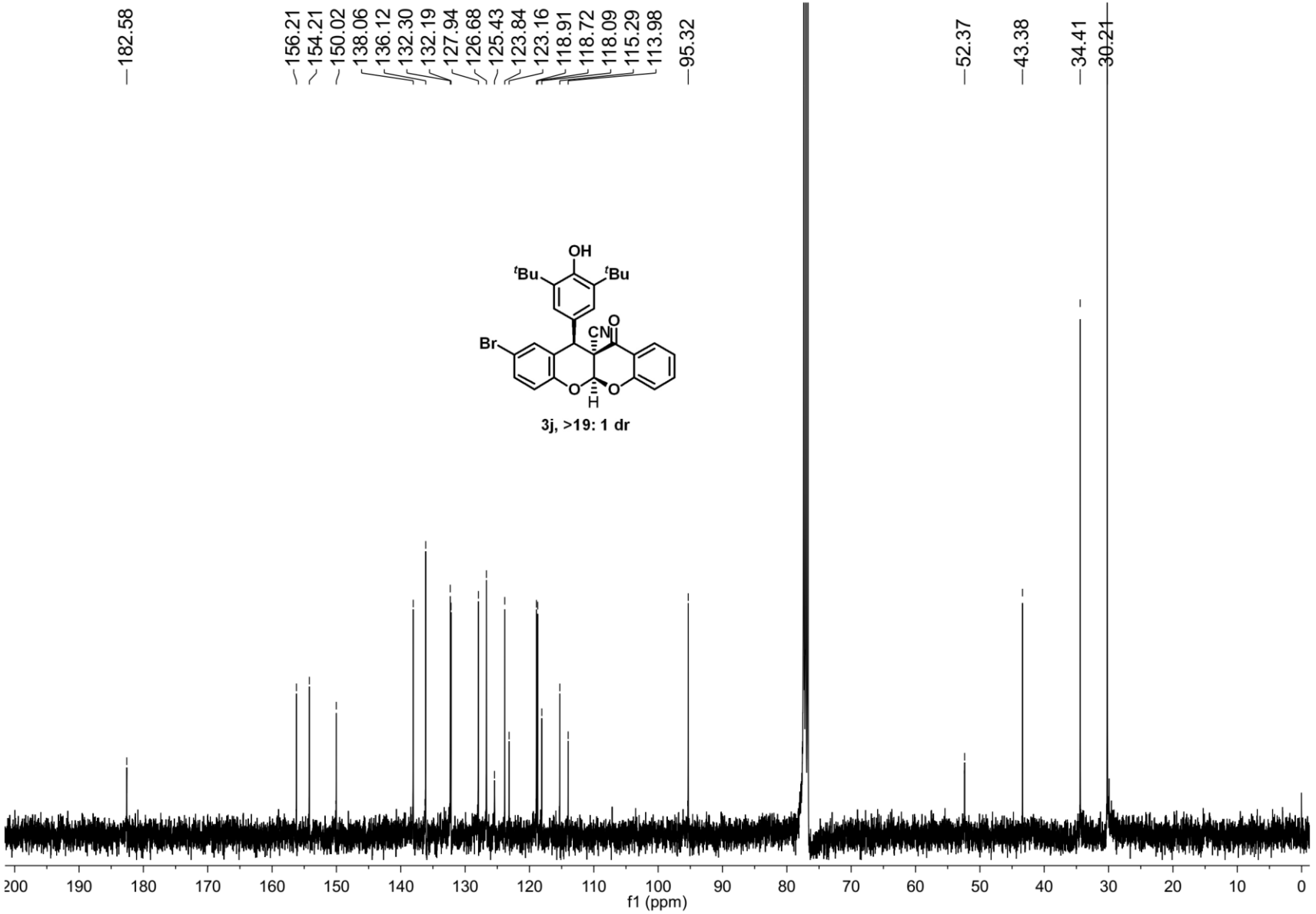
^{1}H NMR Spectrum of Compound 3i



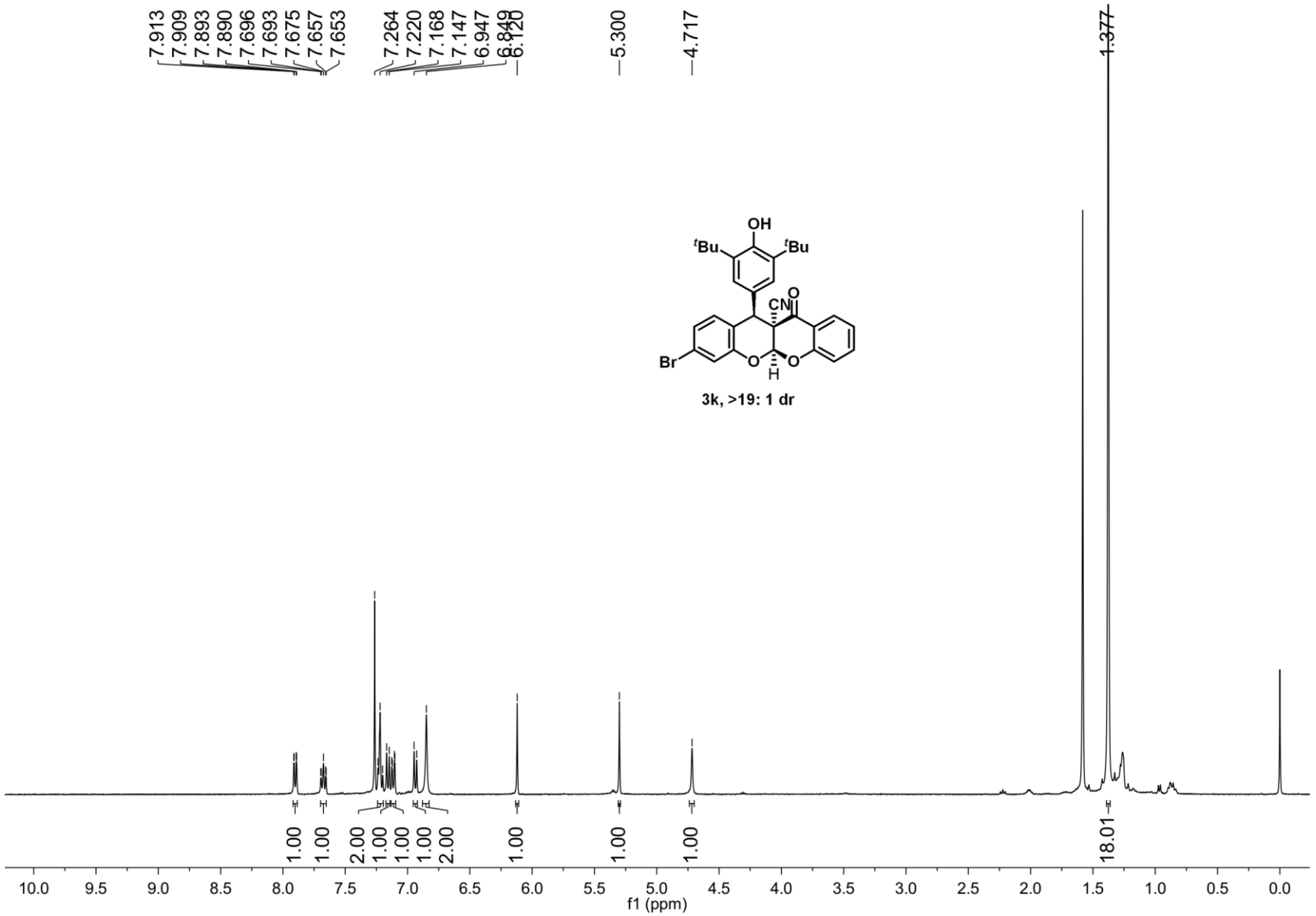
^{13}C NMR Spectrum of Compound 3i



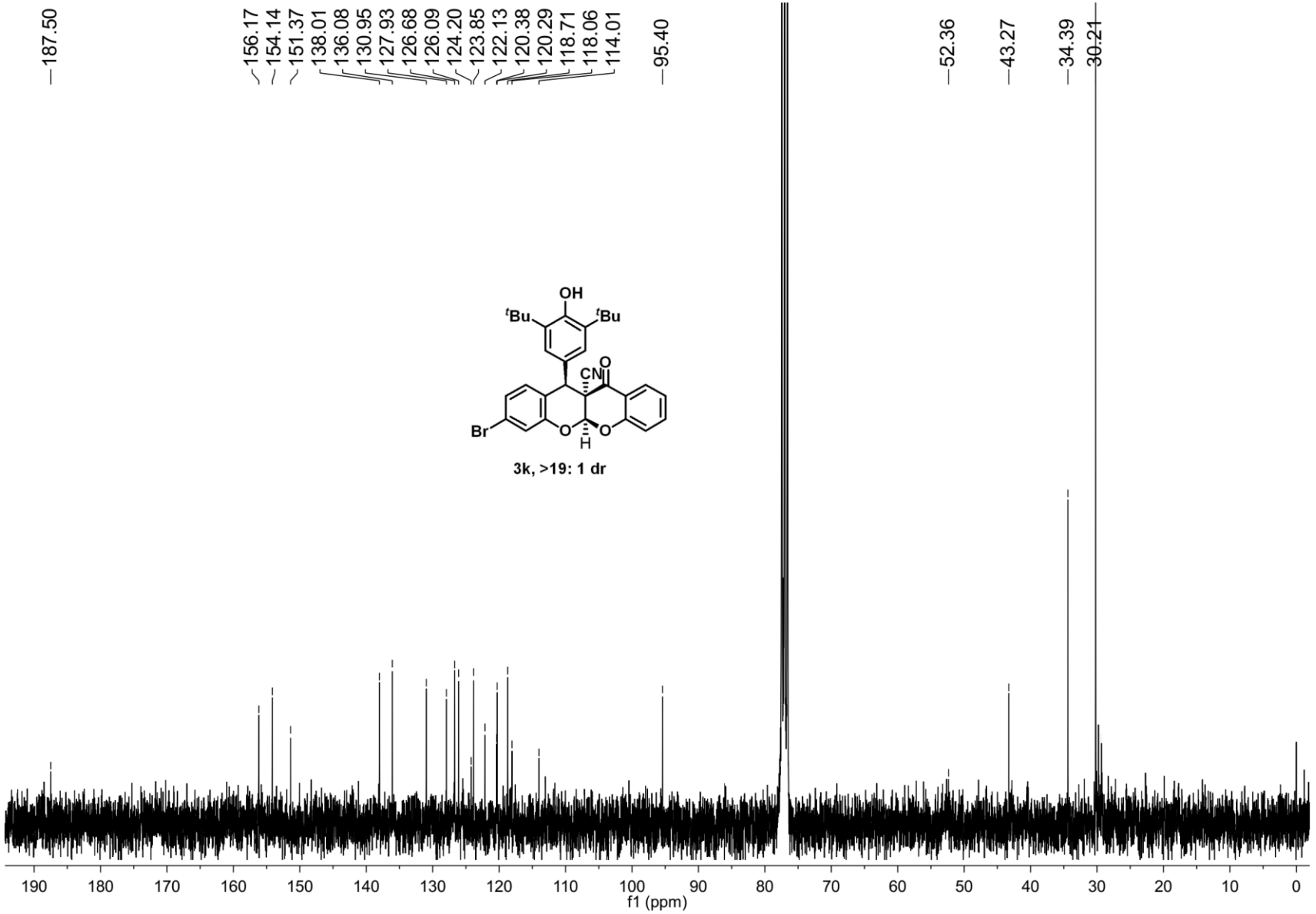
^{1}H NMR Spectrum of Compound 3j



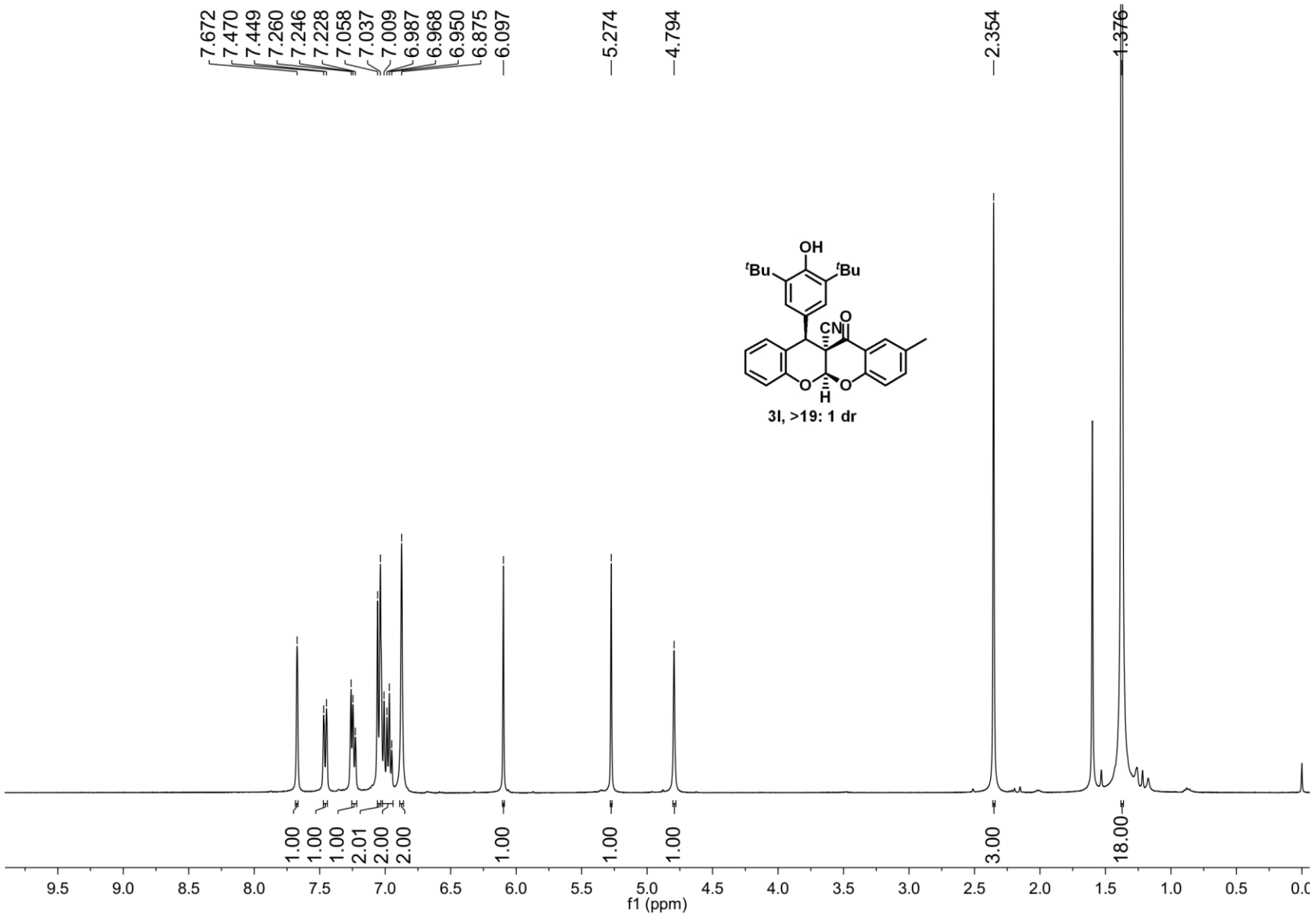
^{13}C NMR Spectrum of Compound 3j



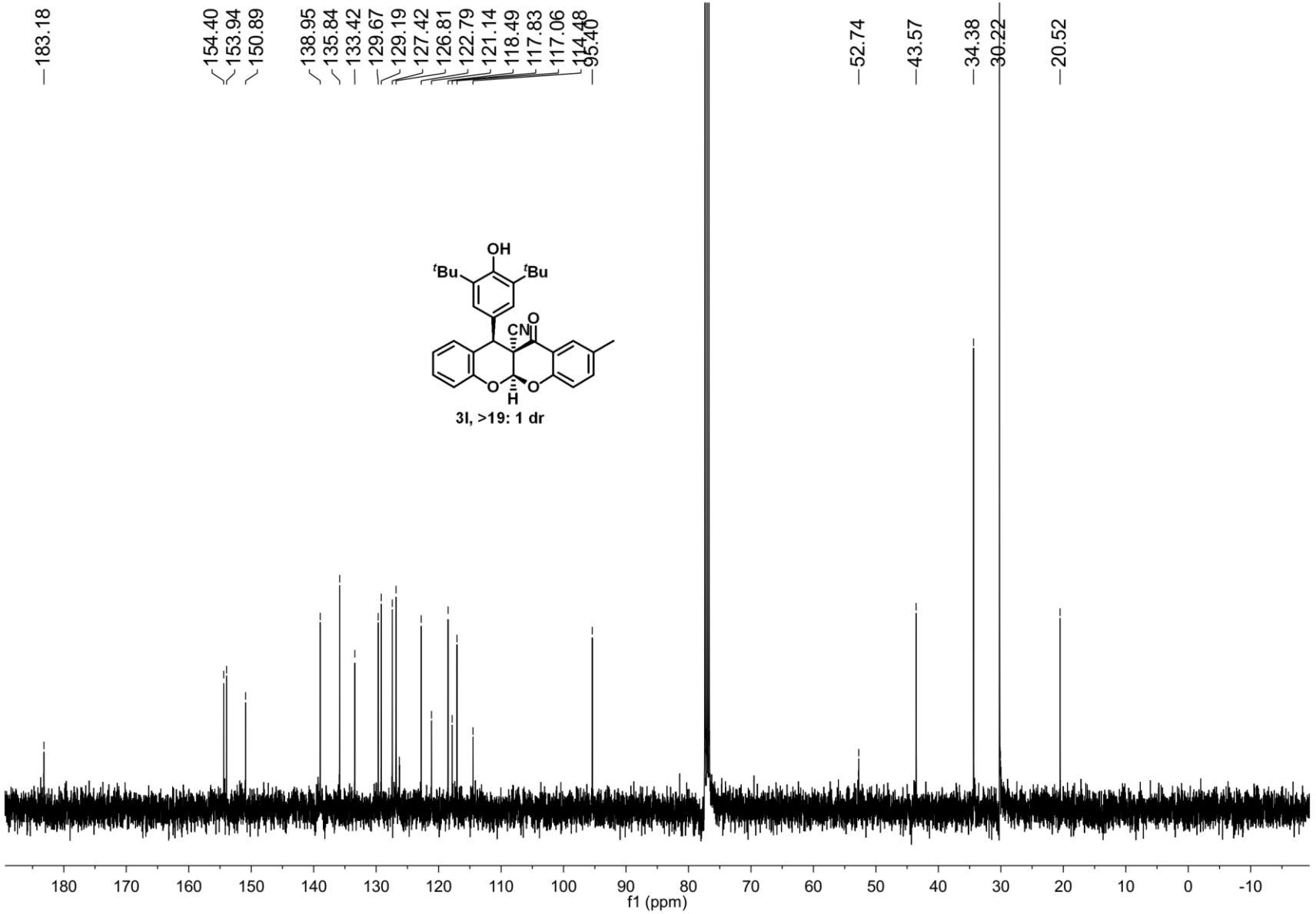
^{1}H NMR Spectrum of Compound 3k



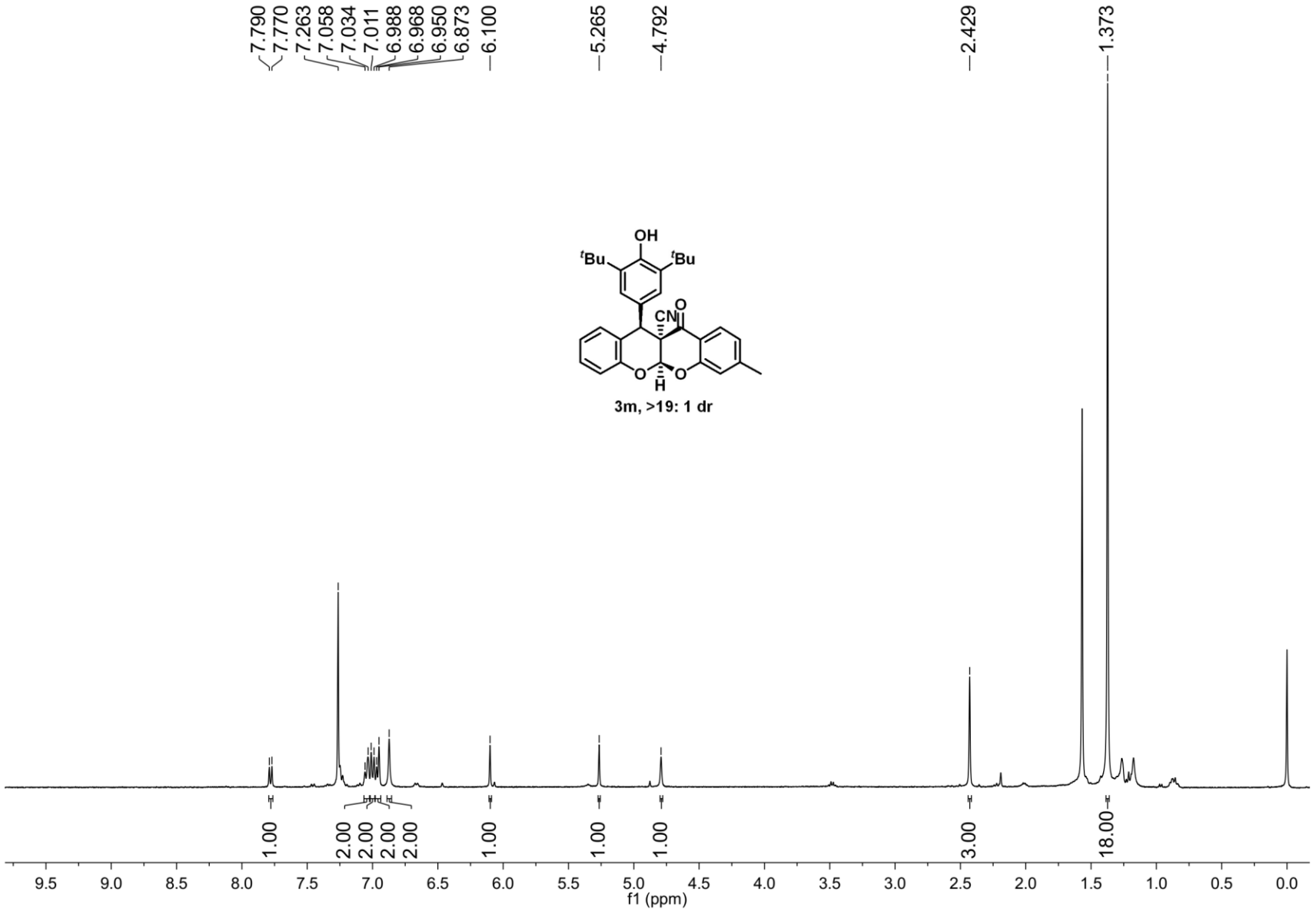
^{13}C NMR Spectrum of Compound 3k



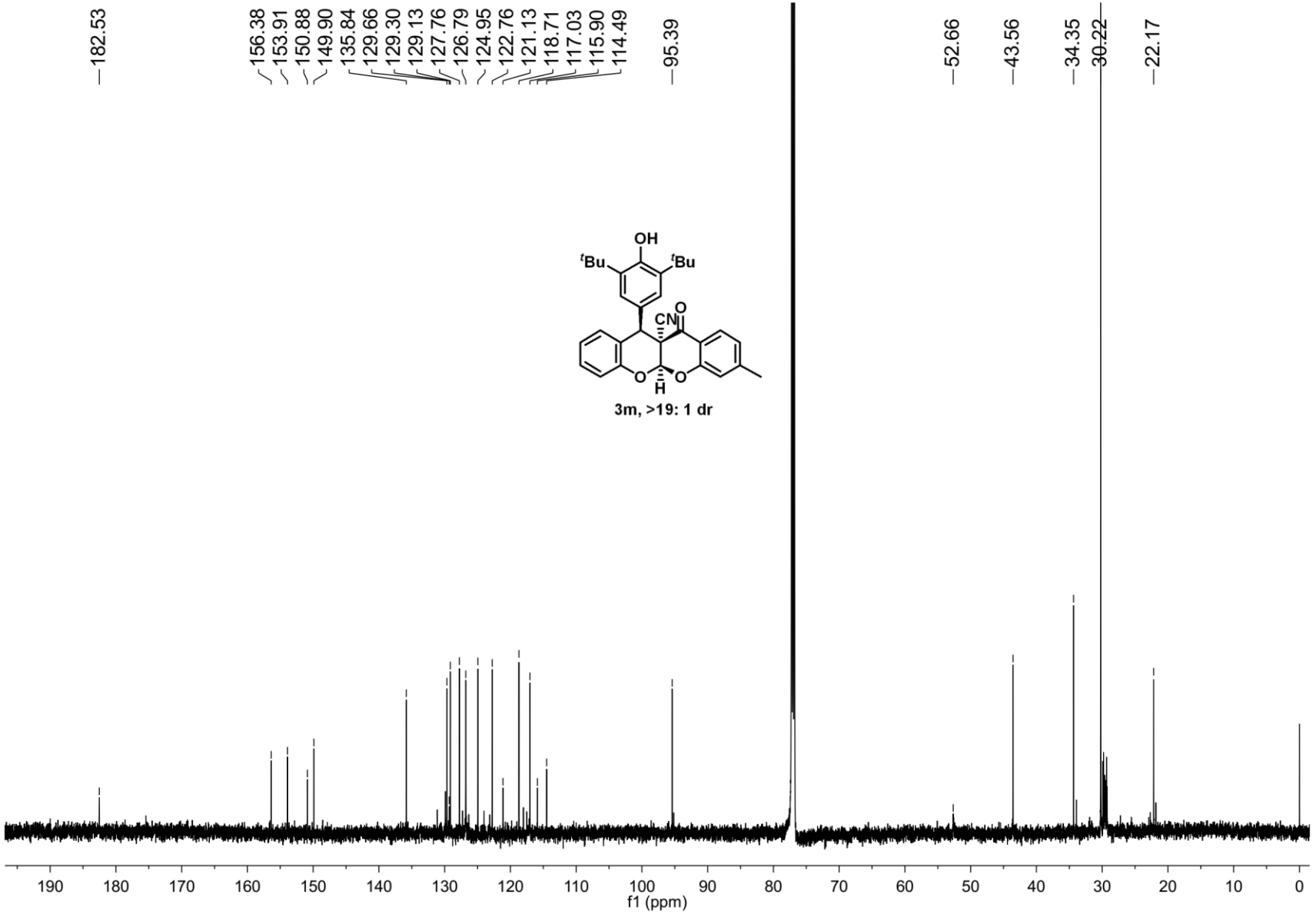
^{1}H NMR Spectrum of Compound 3l



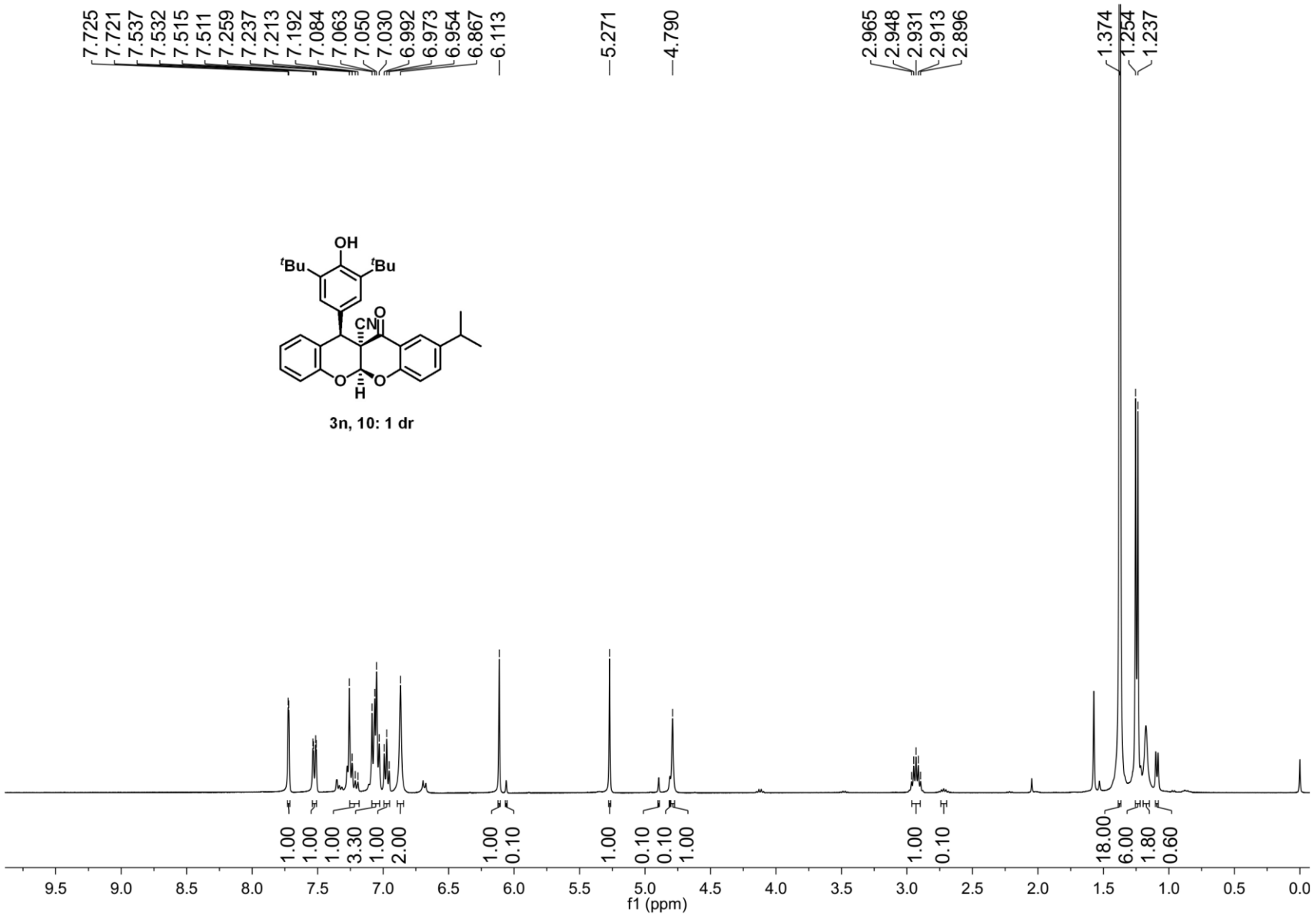
^{13}C NMR Spectrum of Compound 3l



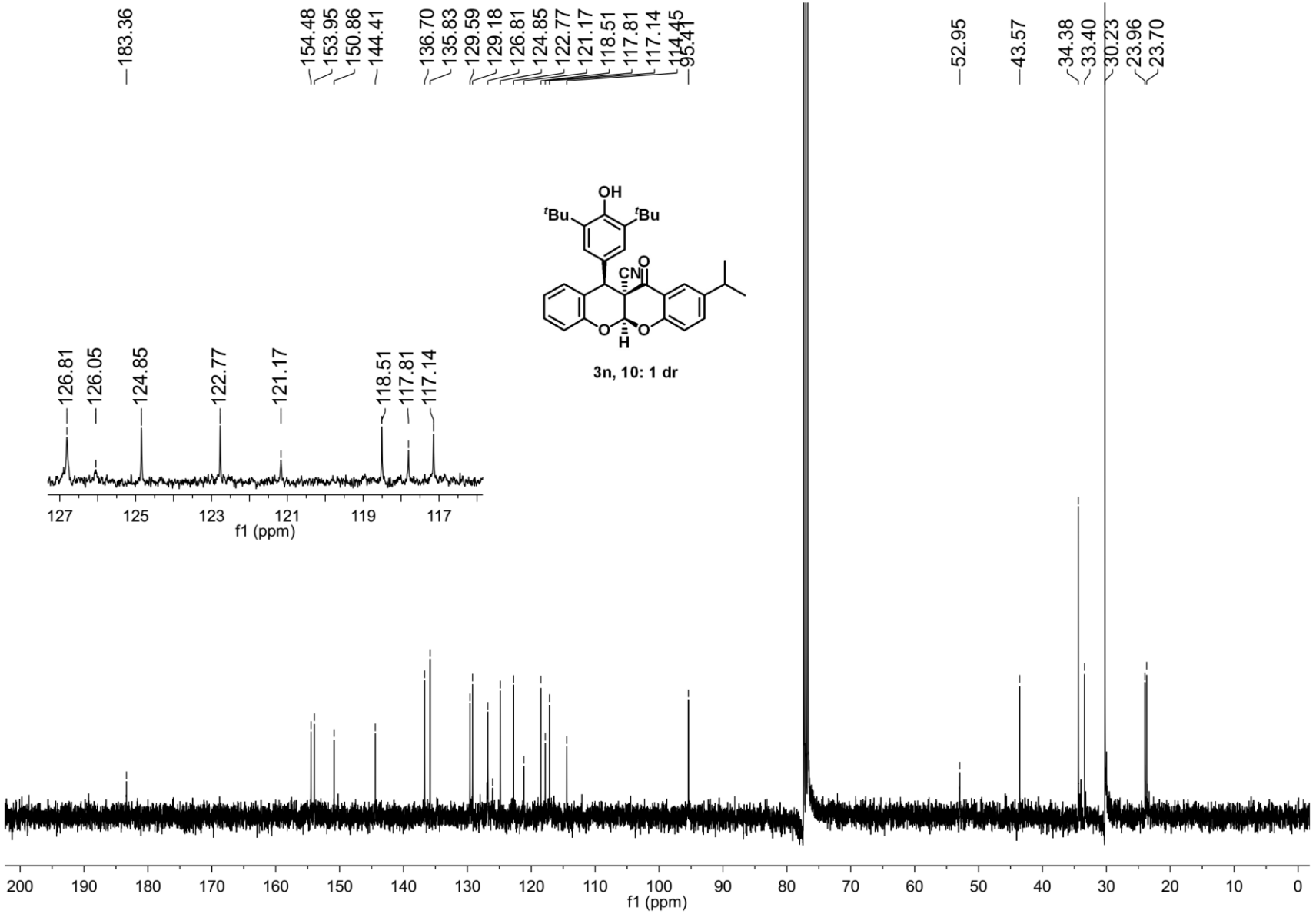
^{1}H NMR Spectrum of Compound 3m



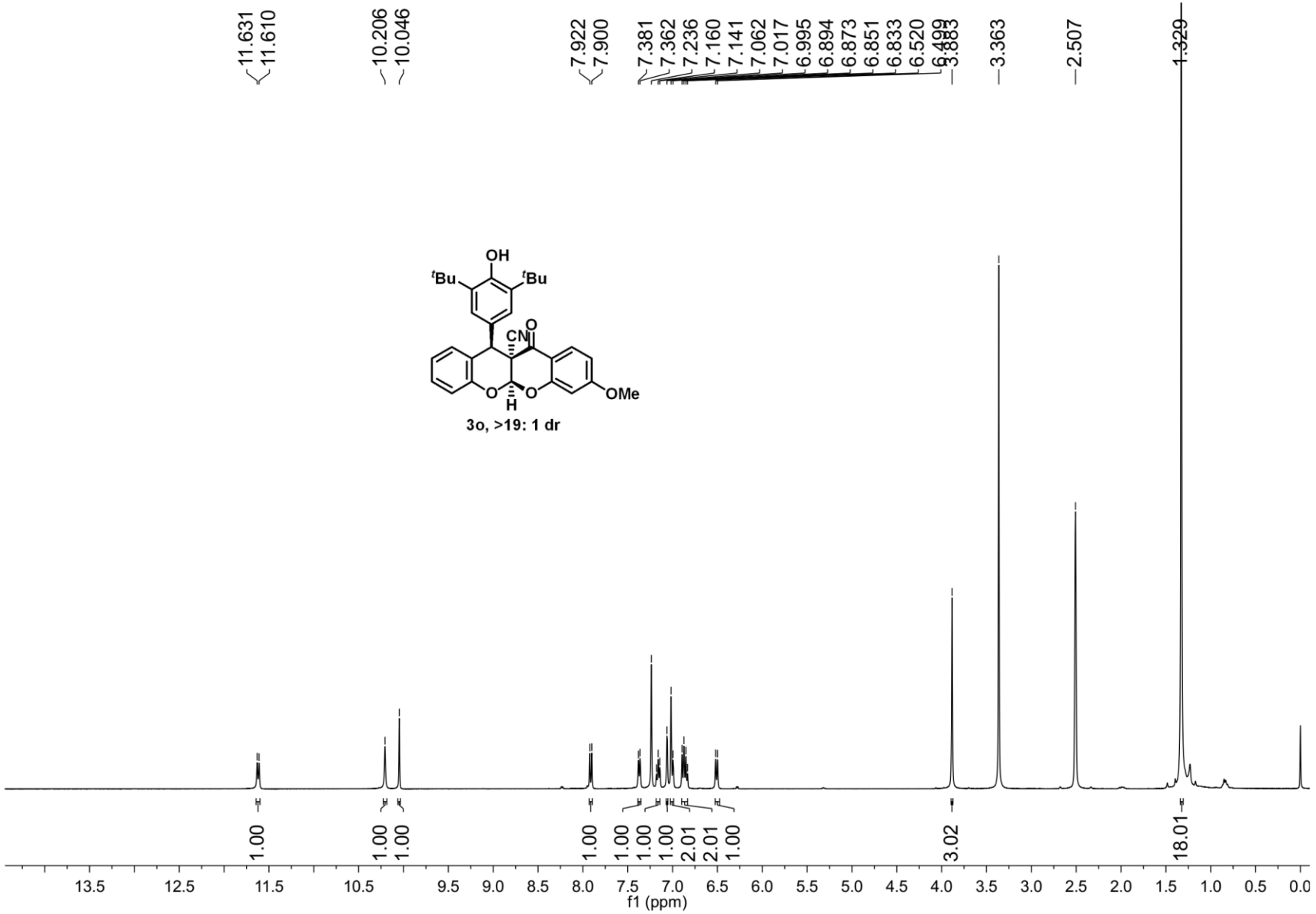
^{13}C NMR Spectrum of Compound 3m



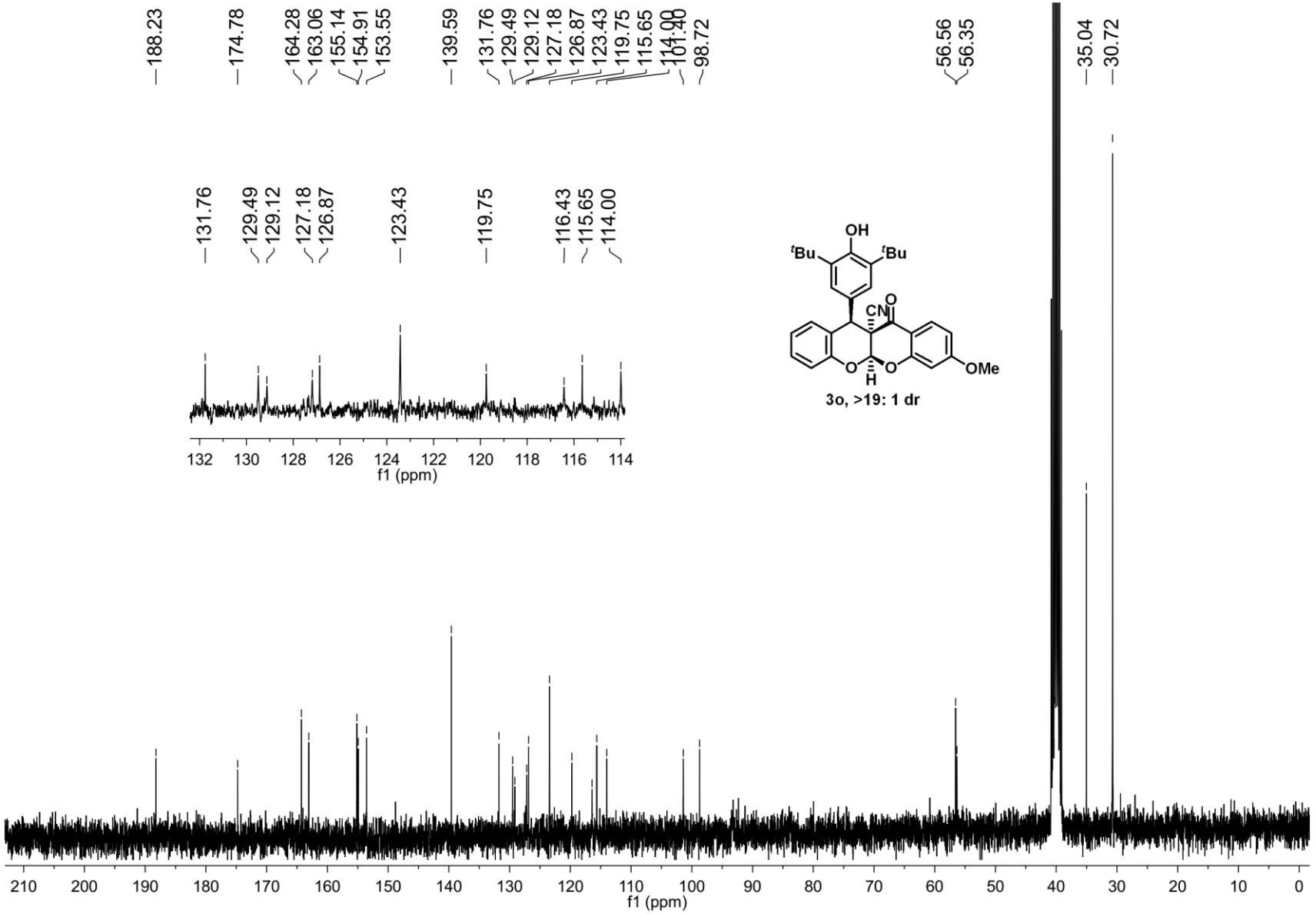
^{1}H NMR Spectrum of Compound 3n



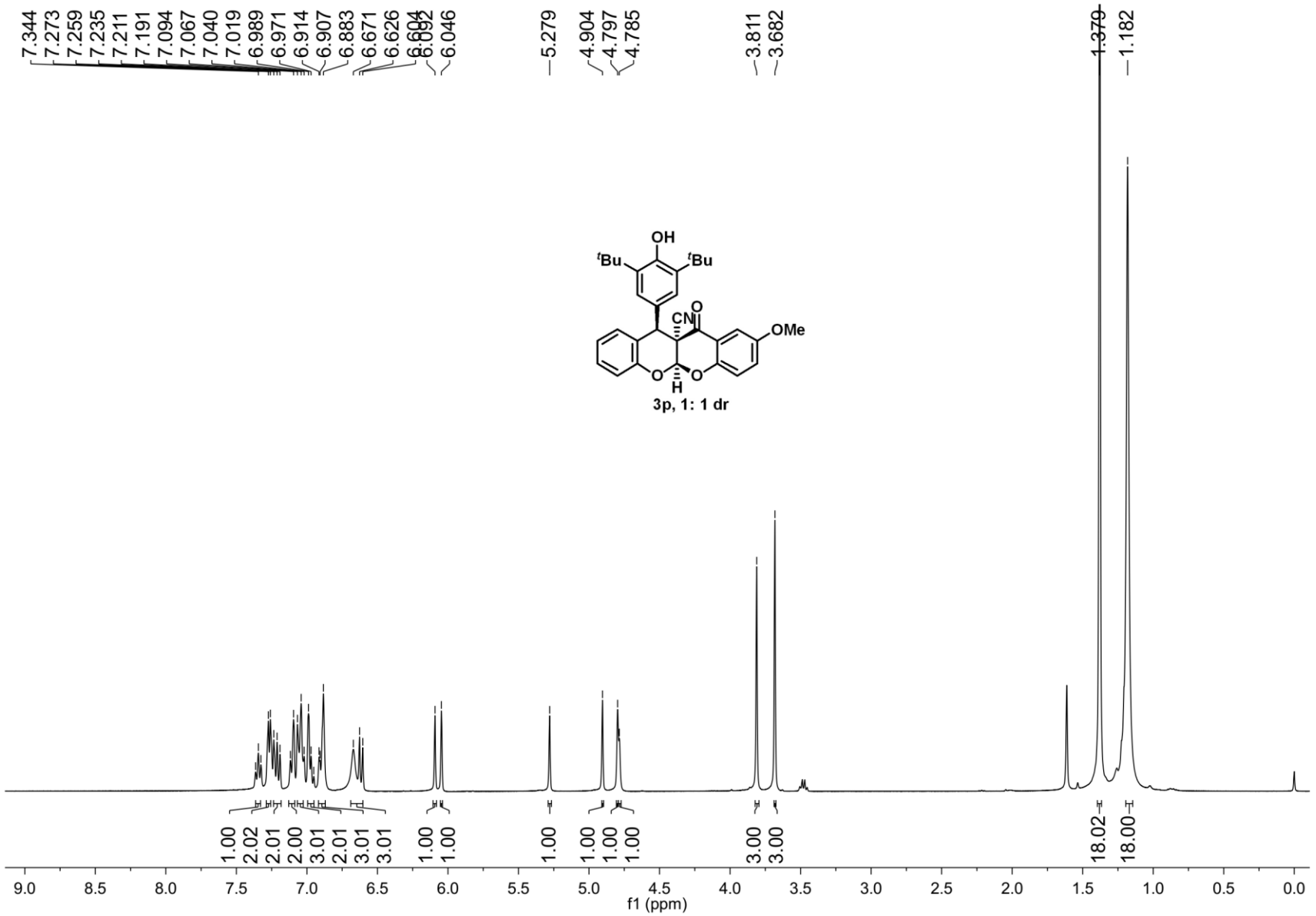
^{13}C NMR Spectrum of Compound 3n



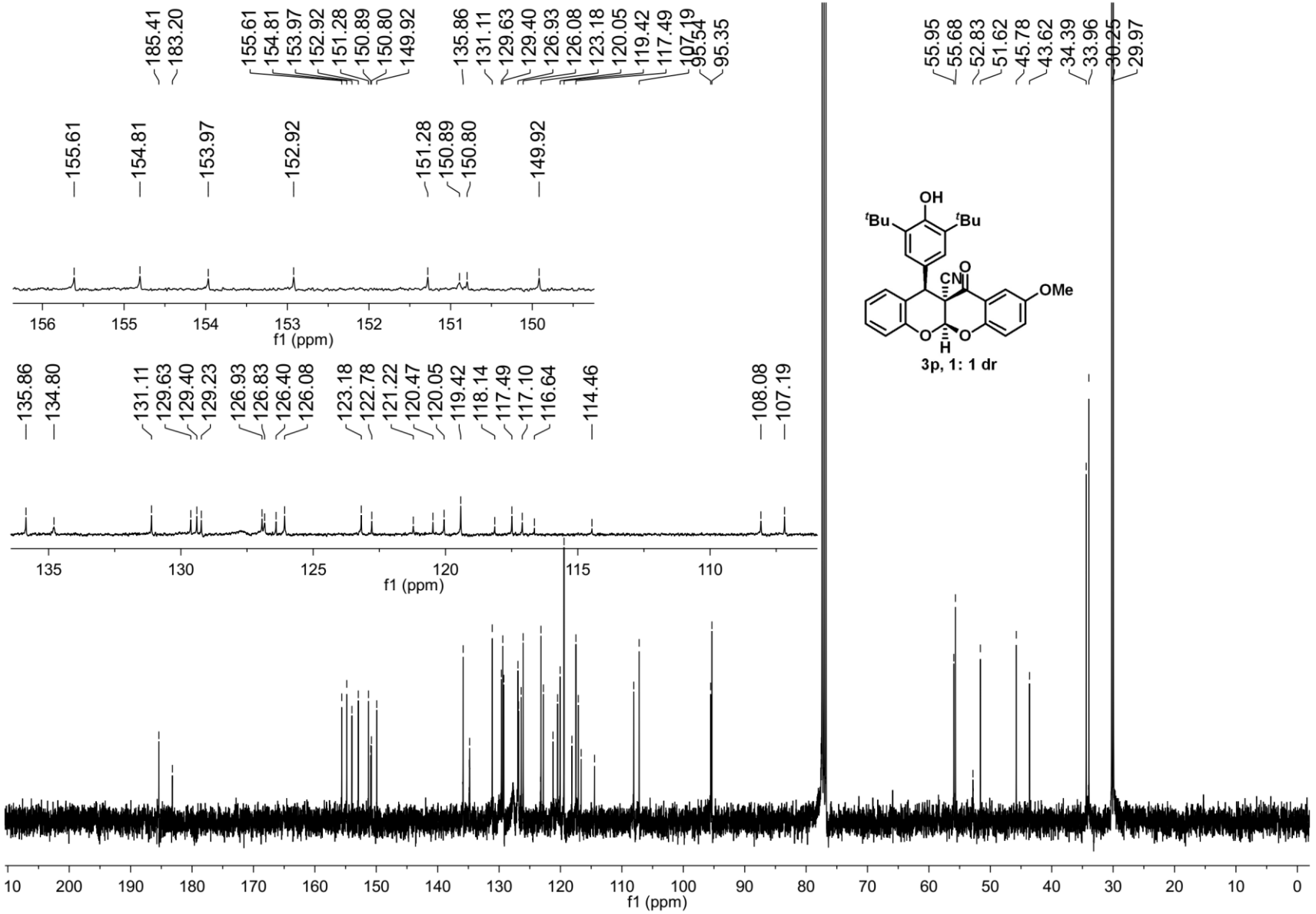
[1]H NMR Spectrum of Compound 3o



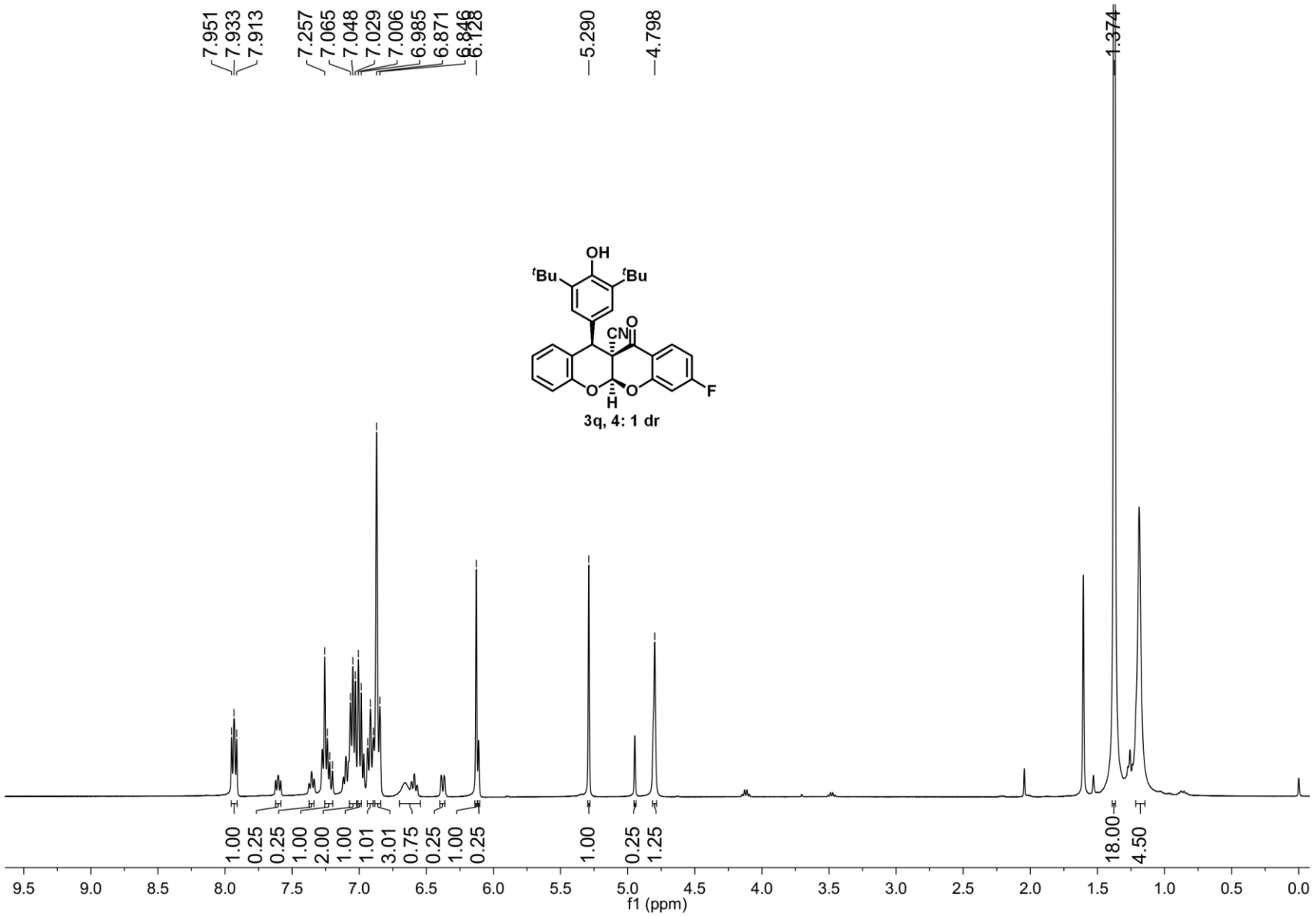
^{13}C NMR Spectrum of Compound 3o



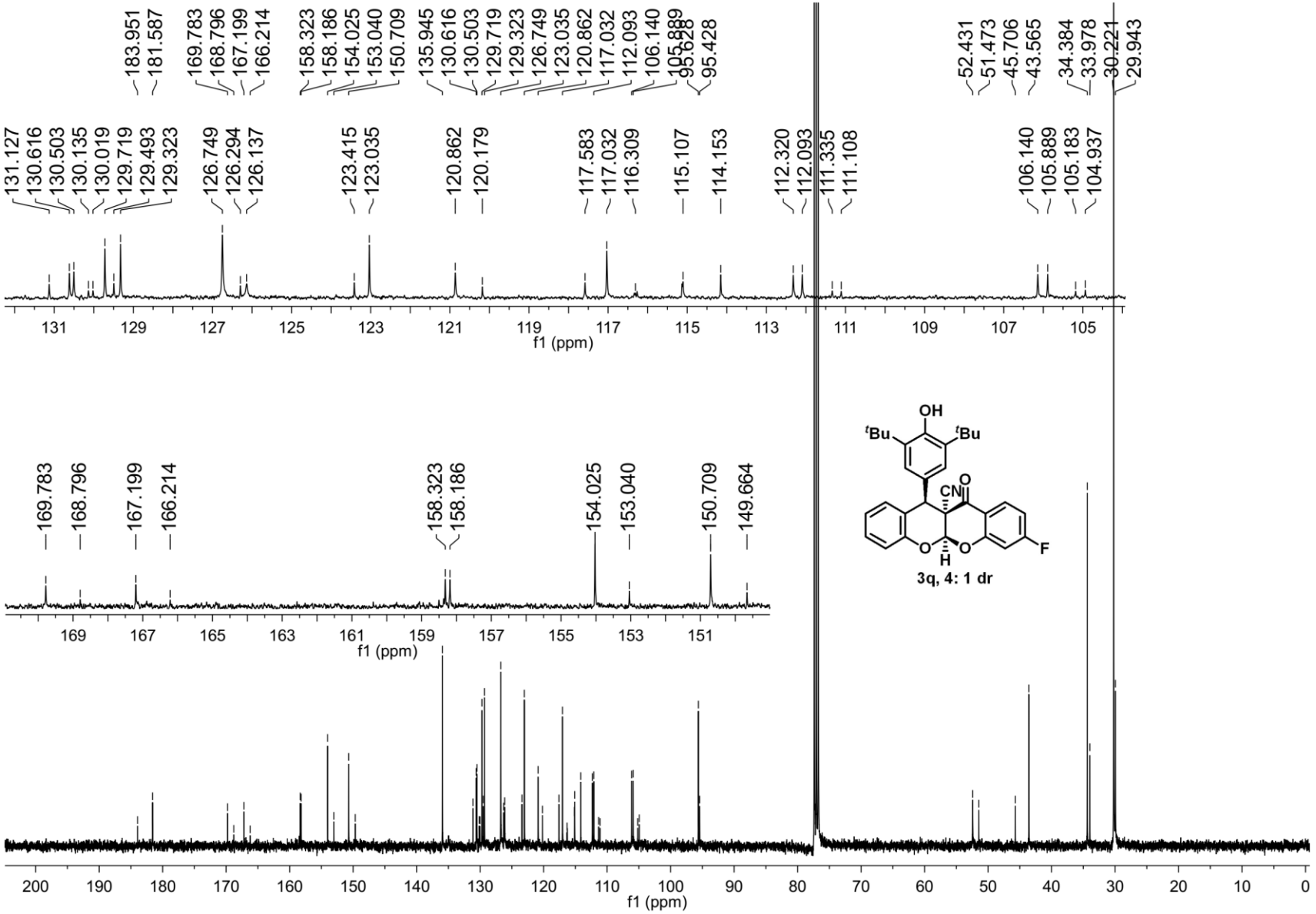
^{1}H NMR Spectrum of Compound 3p



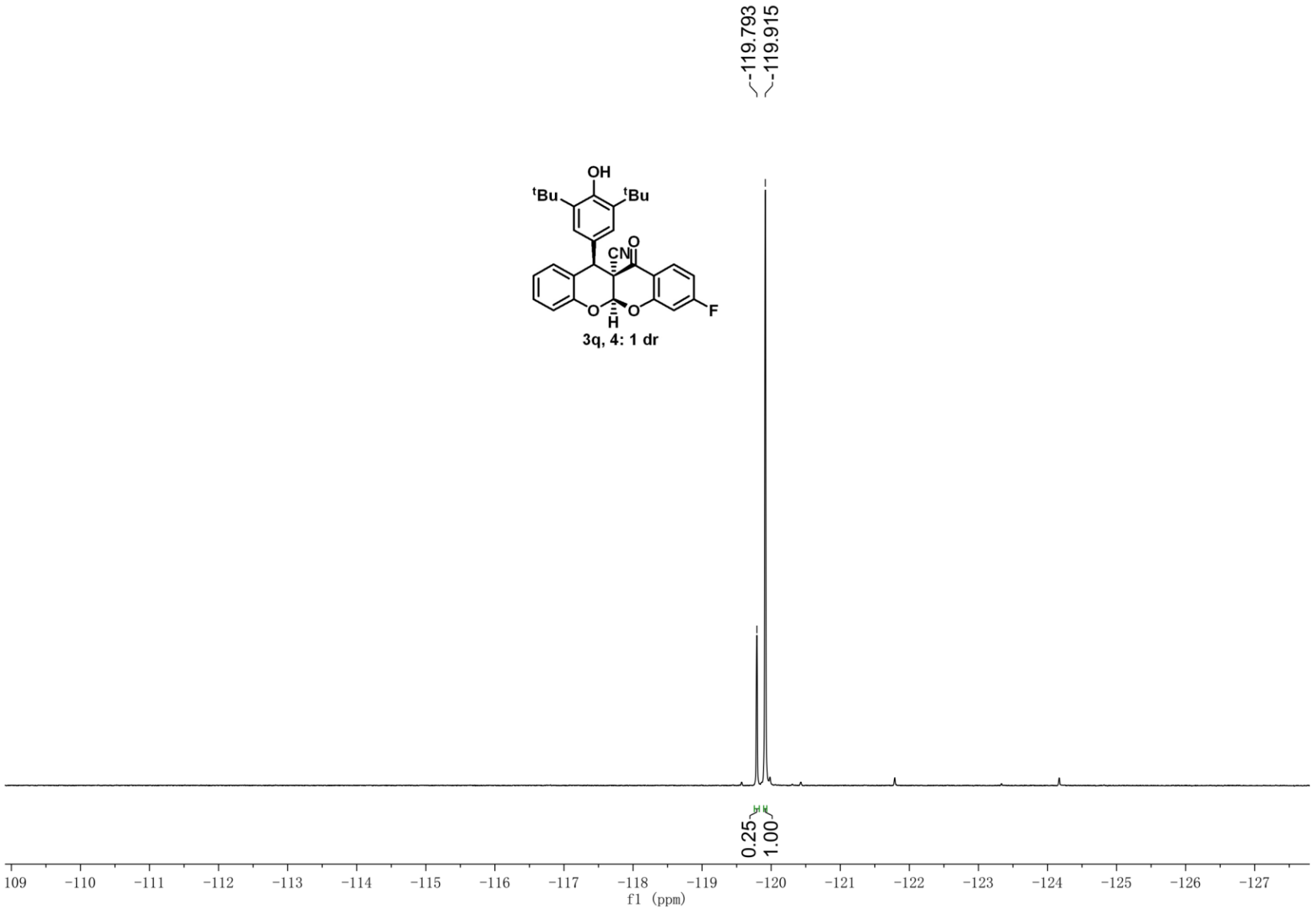
^{13}C NMR Spectrum of Compound 3p



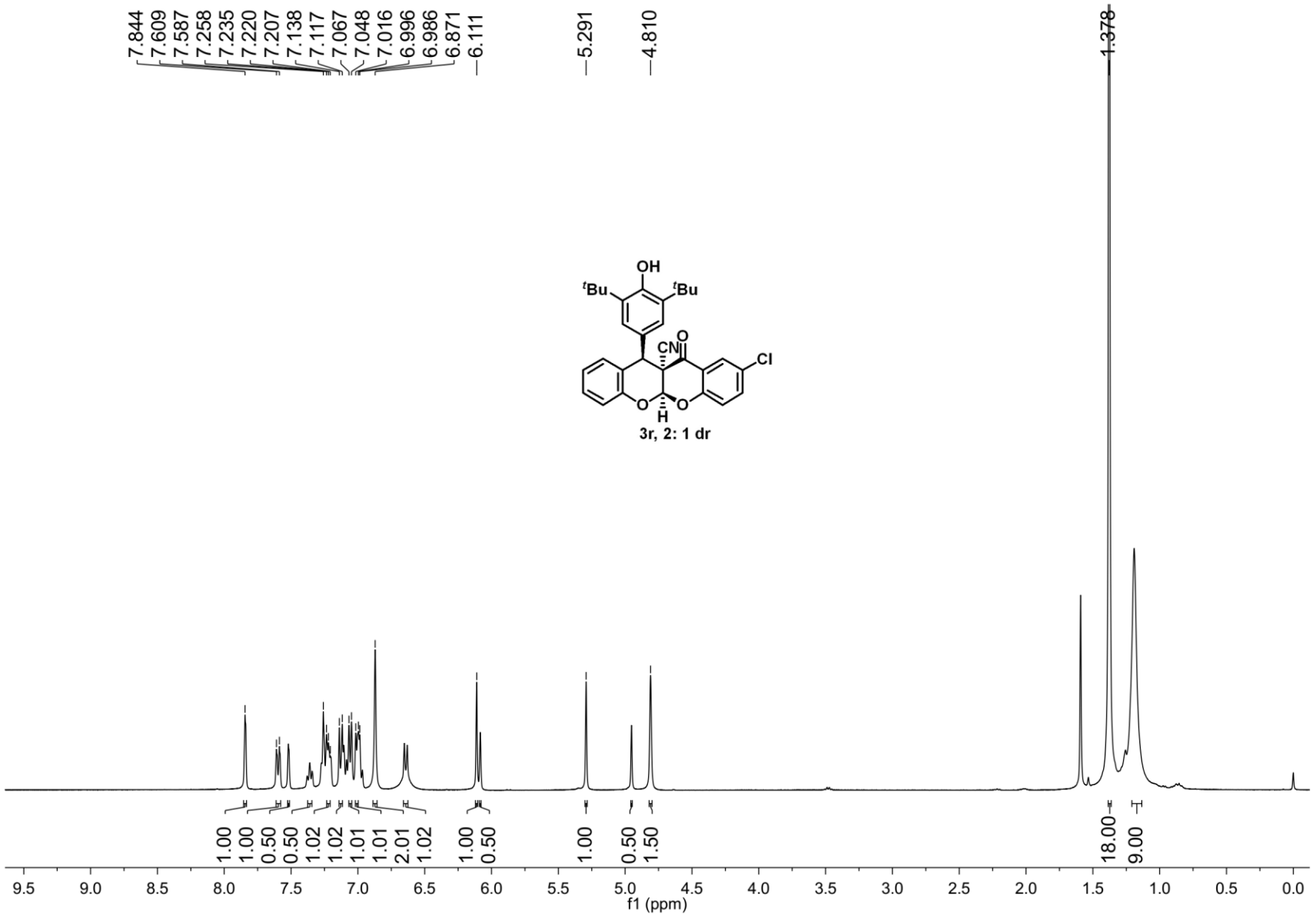
^{1}H NMR Spectrum of Compound 3q



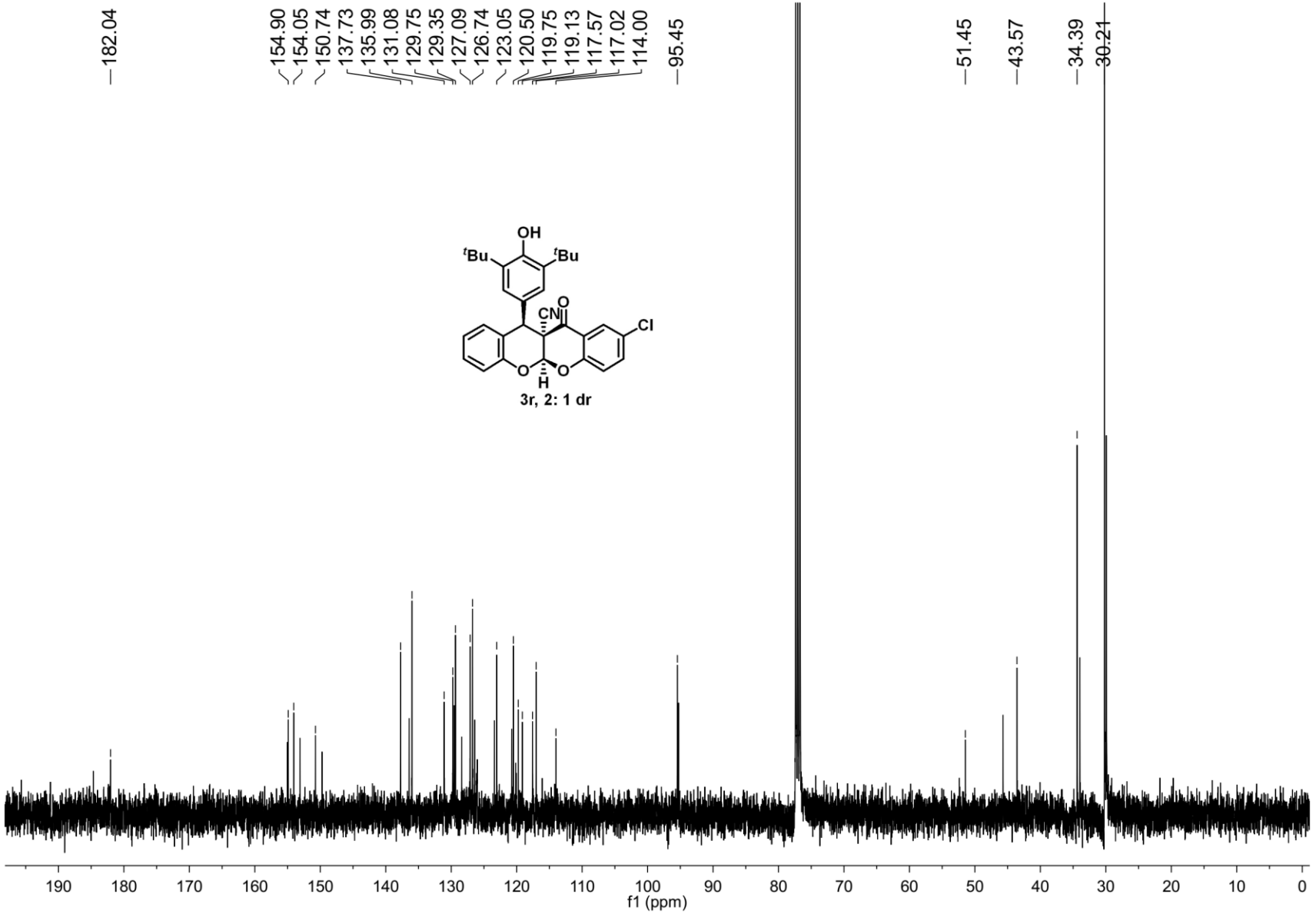
^{13}C NMR Spectrum of Compound 3q



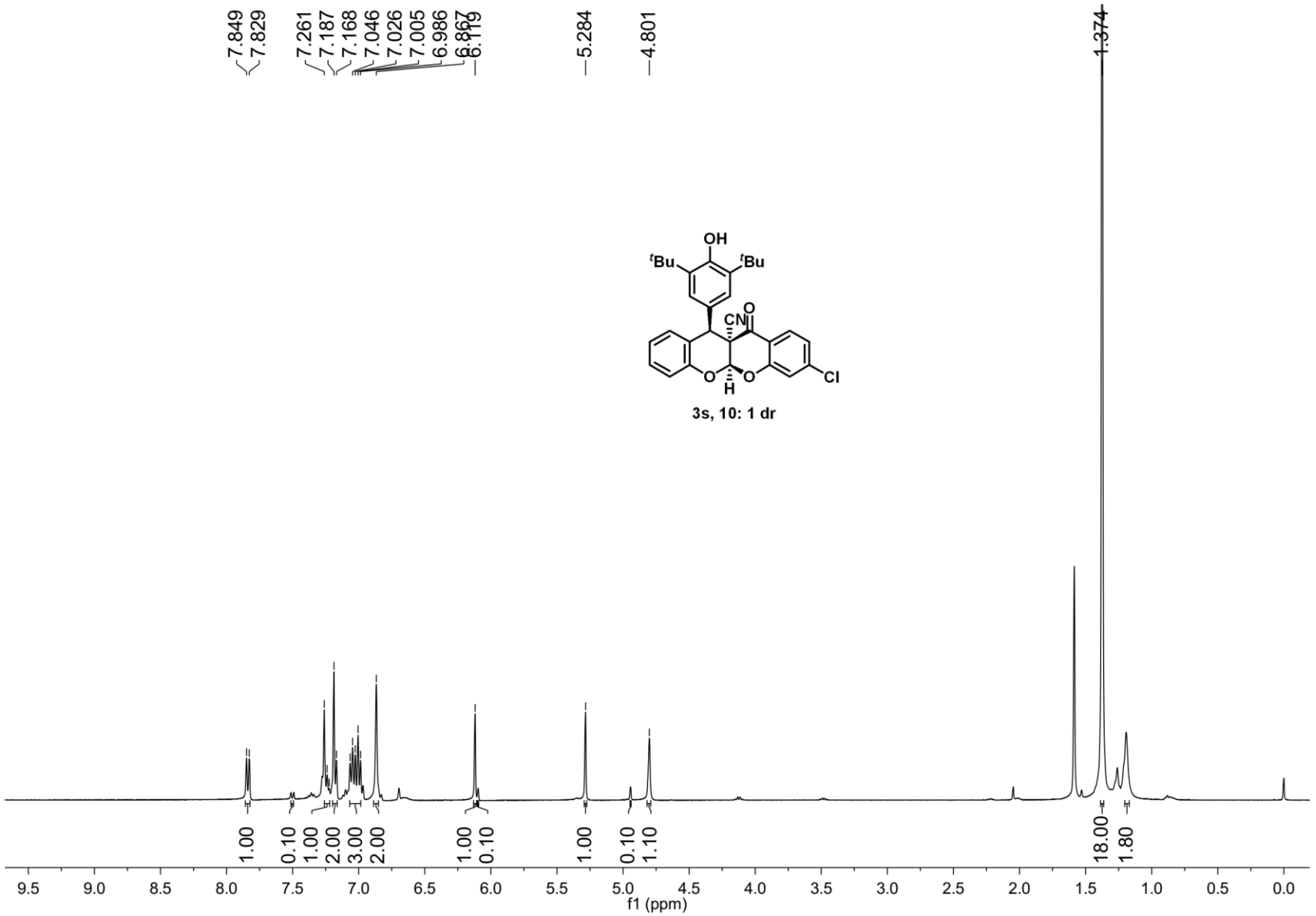
^{19}F NMR Spectrum of Compound 3q



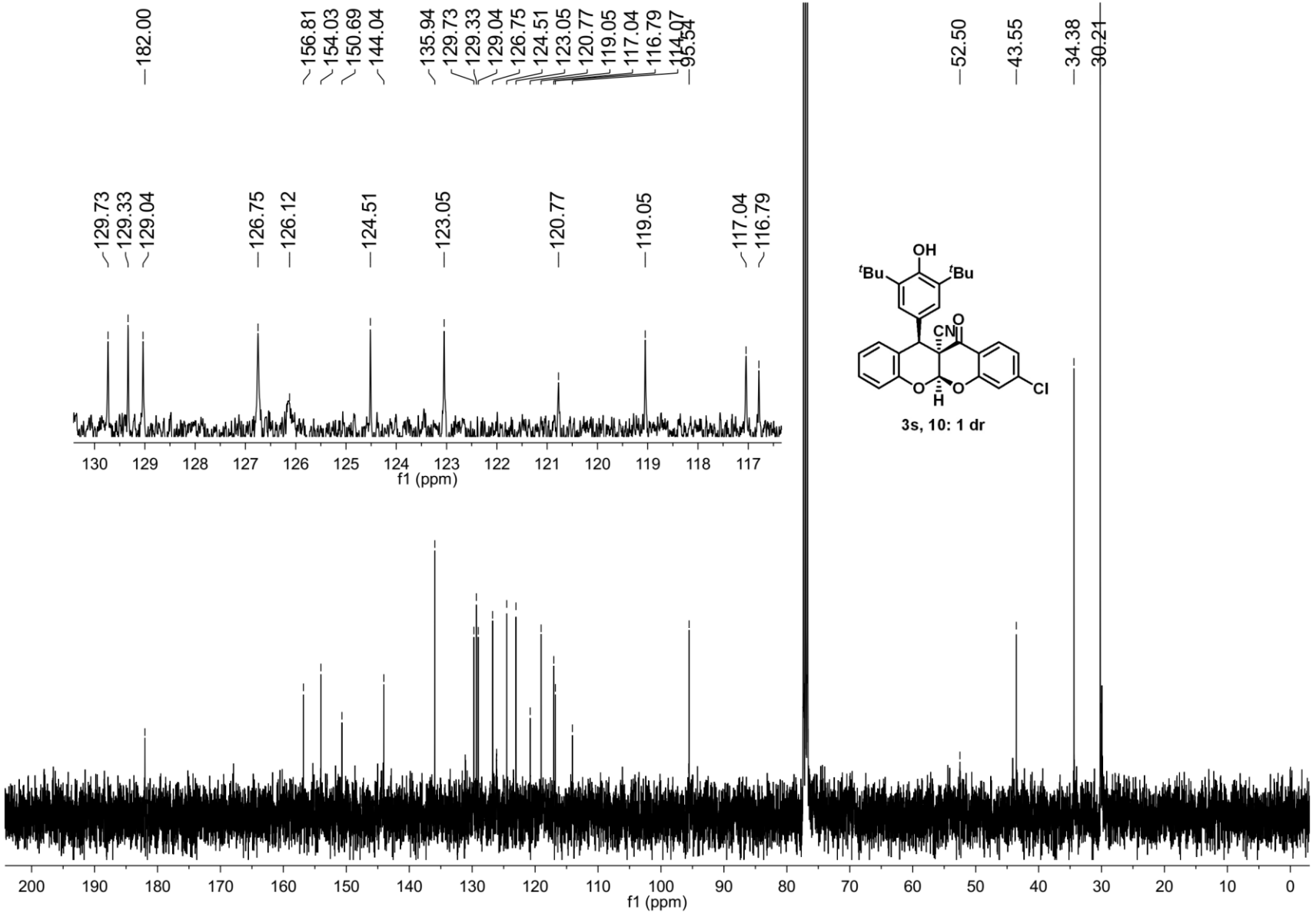
^{1}H NMR Spectrum of Compound 3r



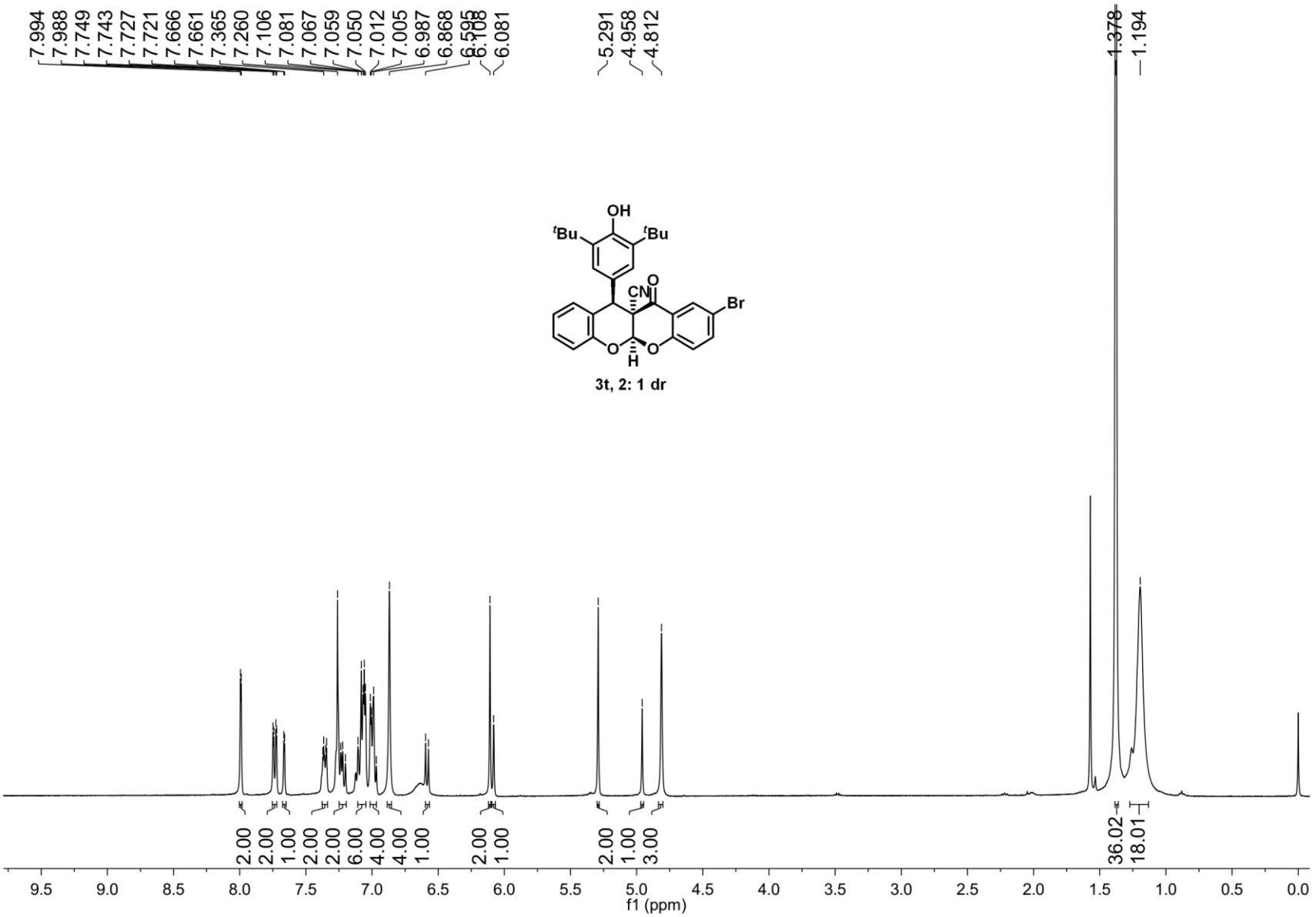
^{13}C NMR Spectrum of Compound 3r



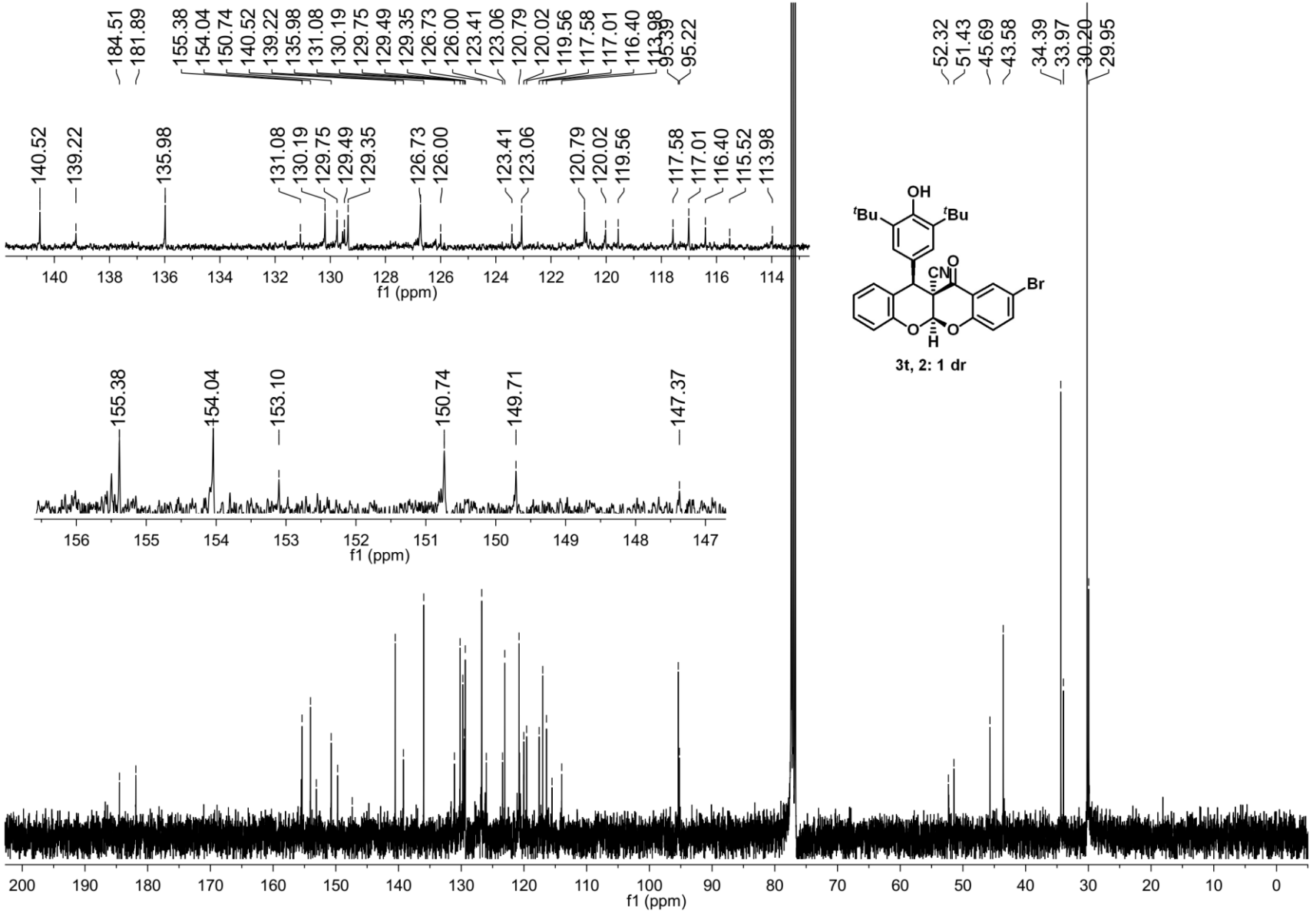
^{1}H NMR Spectrum of Compound 3s



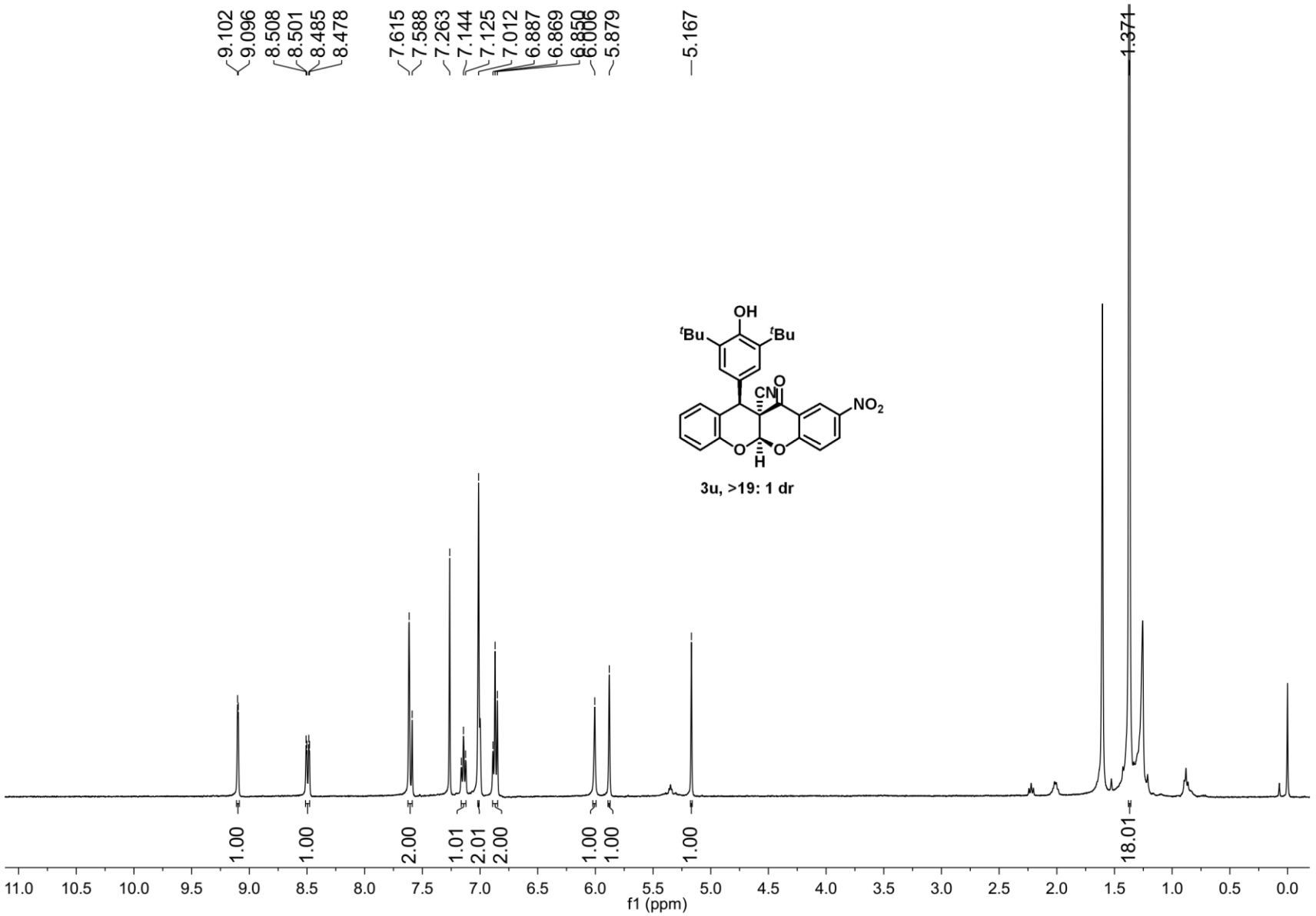
^{13}C NMR Spectrum of Compound 3s



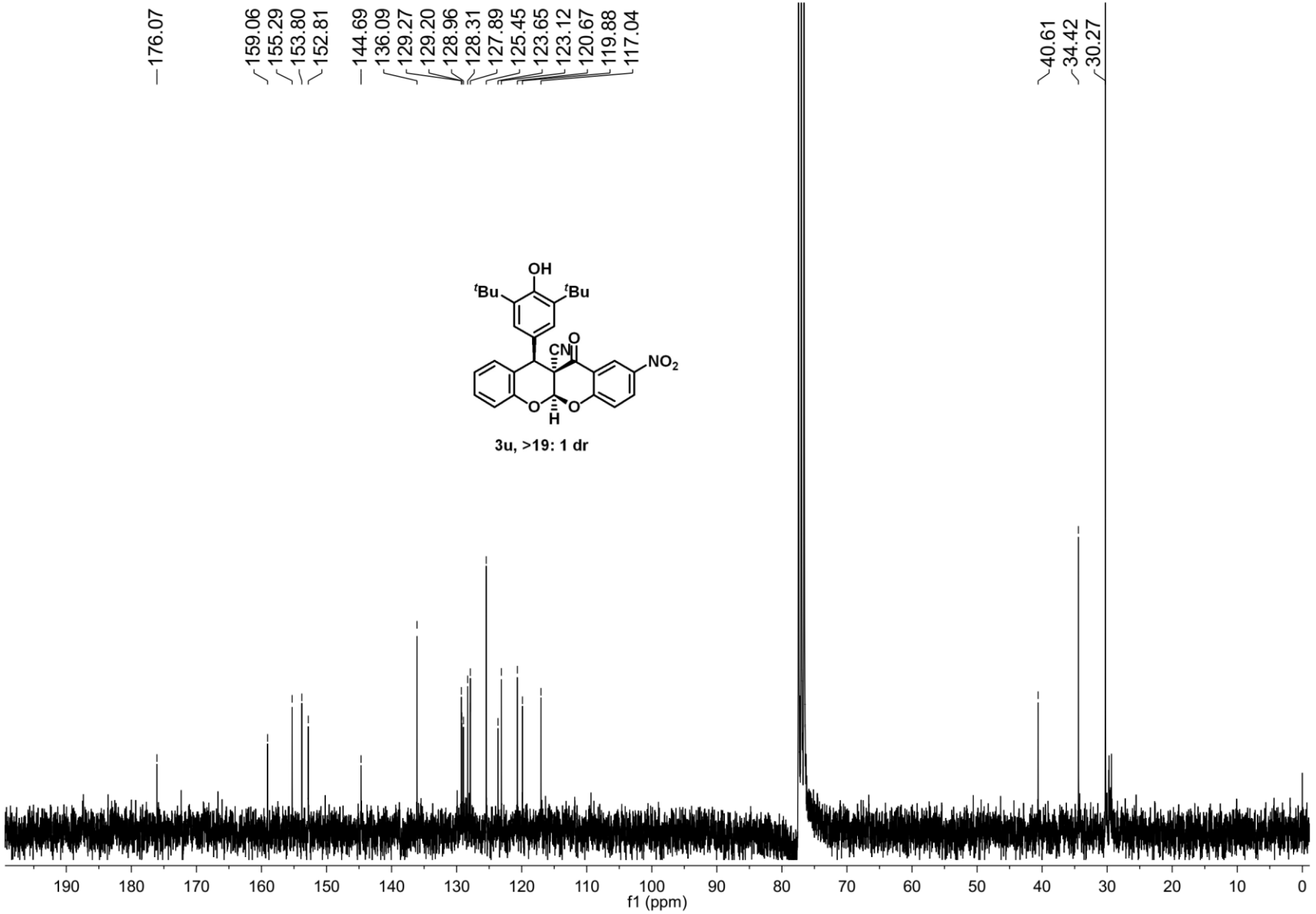
^{1}H NMR Spectrum of Compound 3t



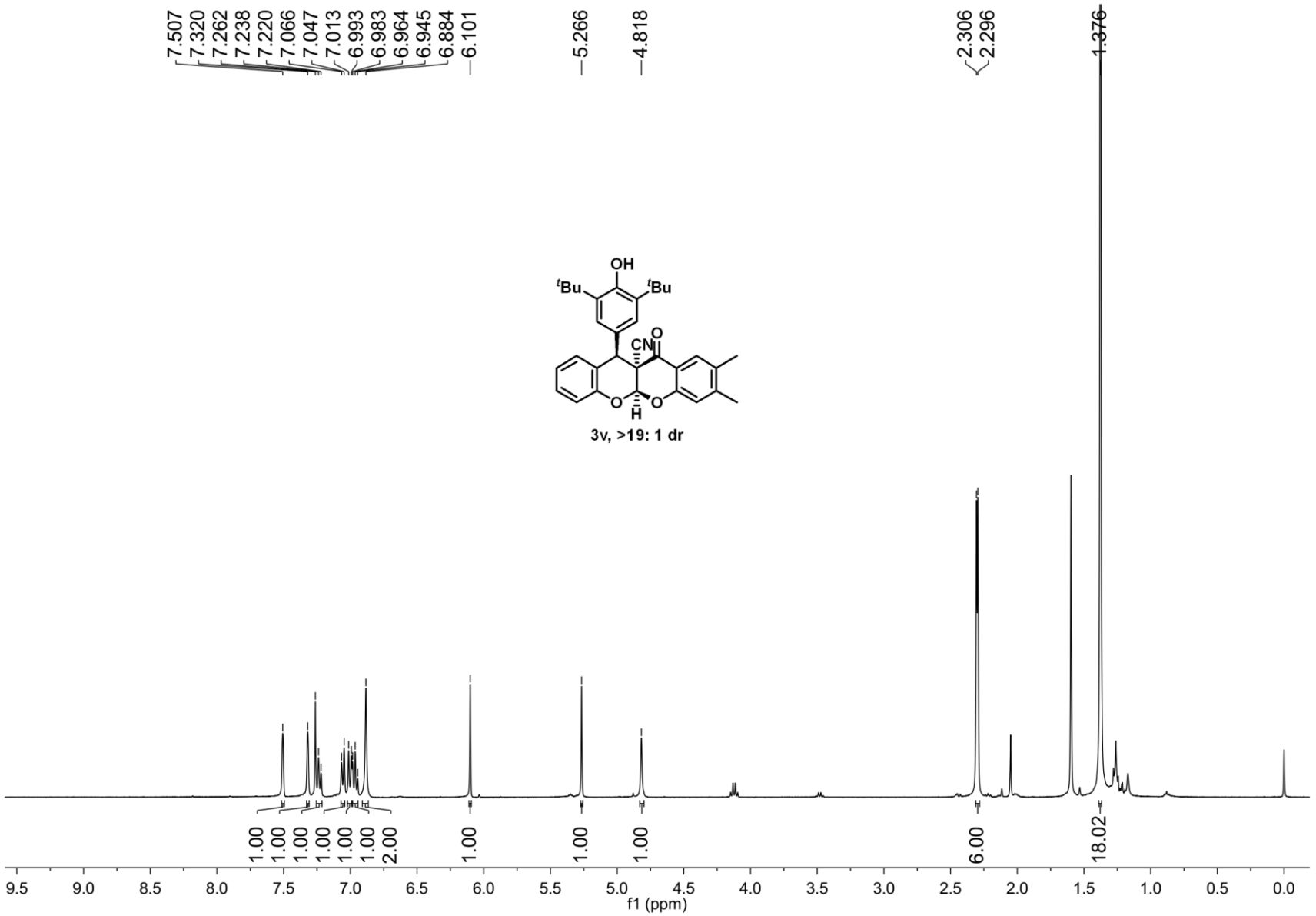
^{13}C NMR Spectrum of Compound 3t



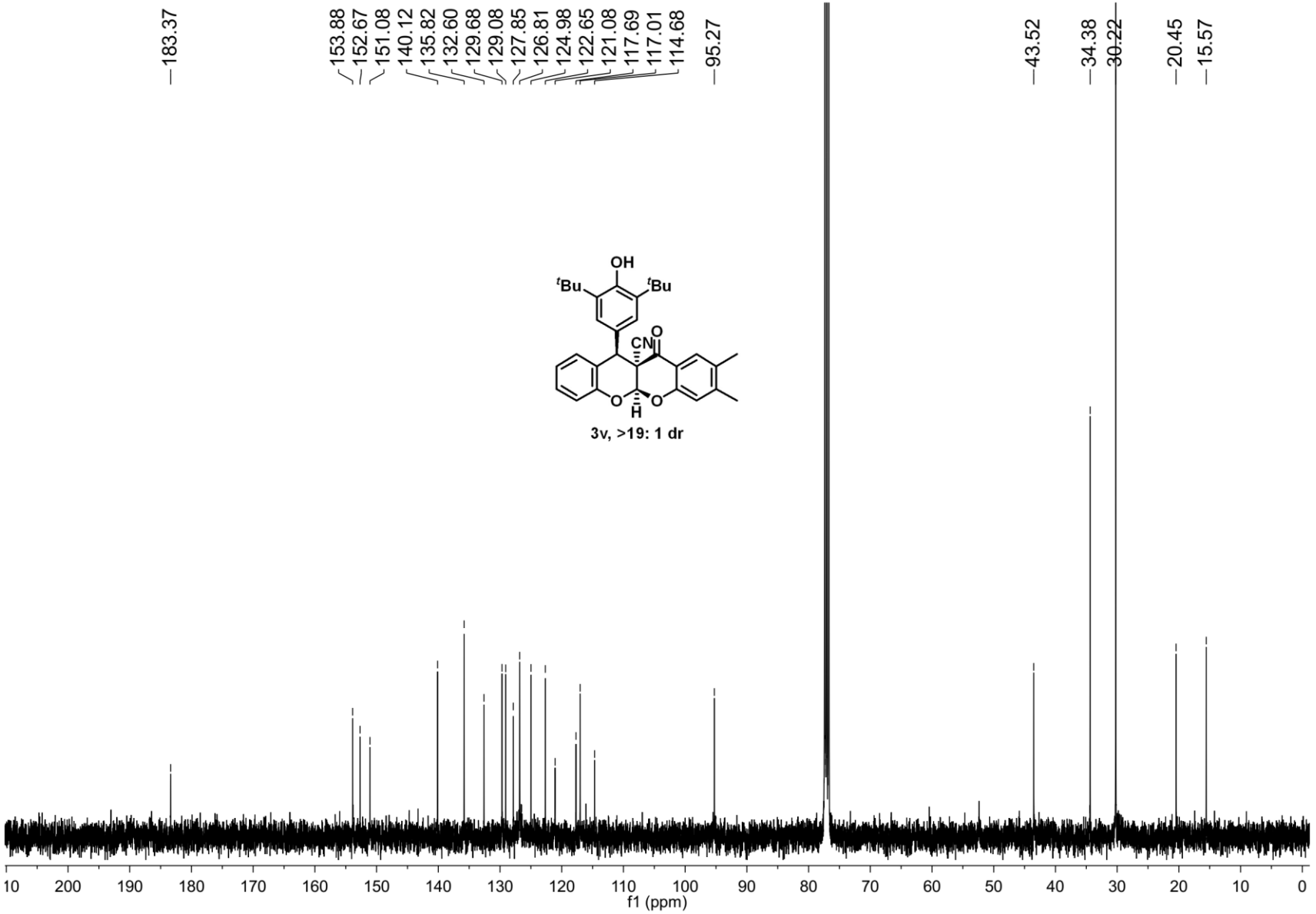
^{1}H NMR Spectrum of Compound 3u



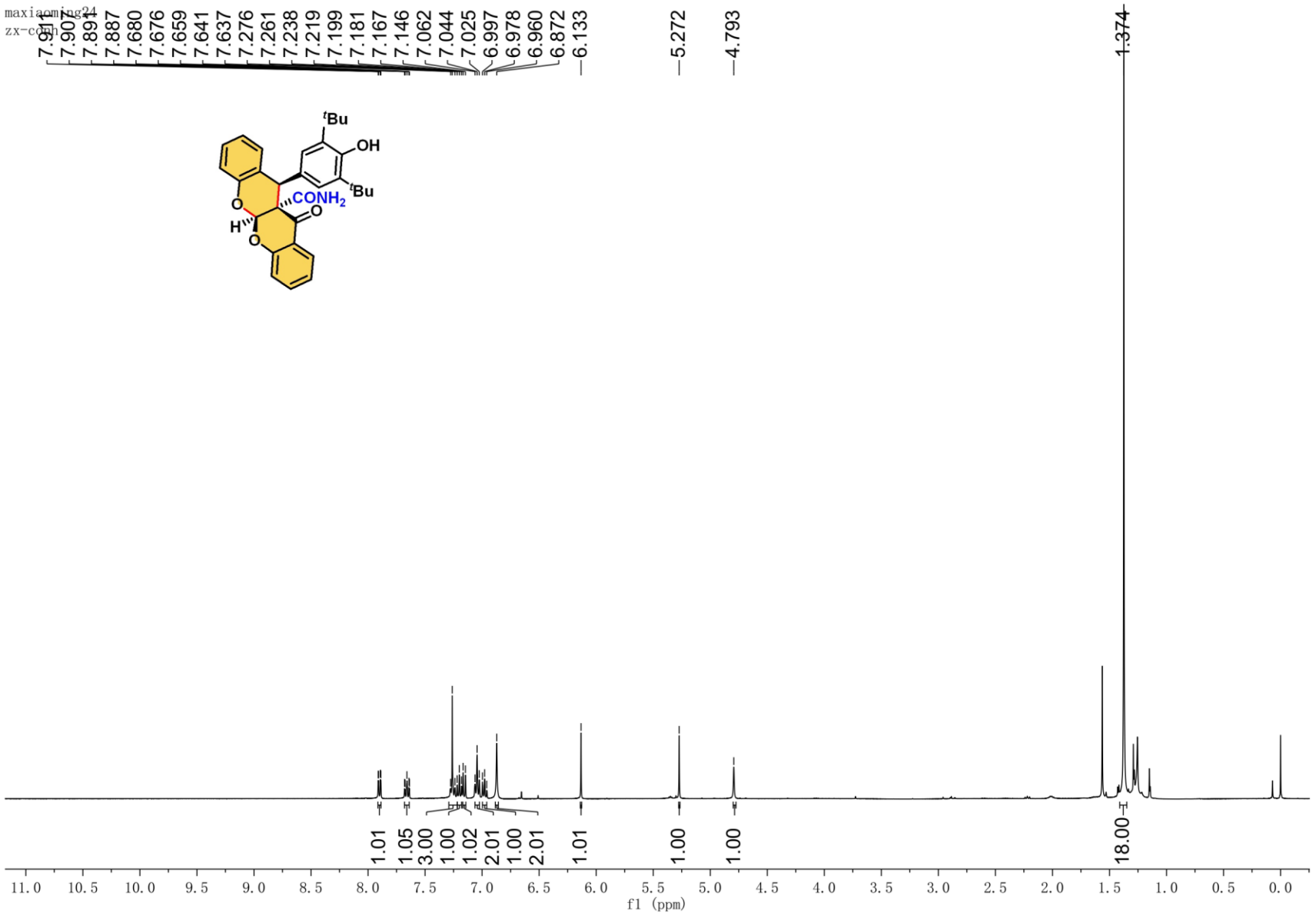
^{13}C NMR Spectrum of Compound 3u



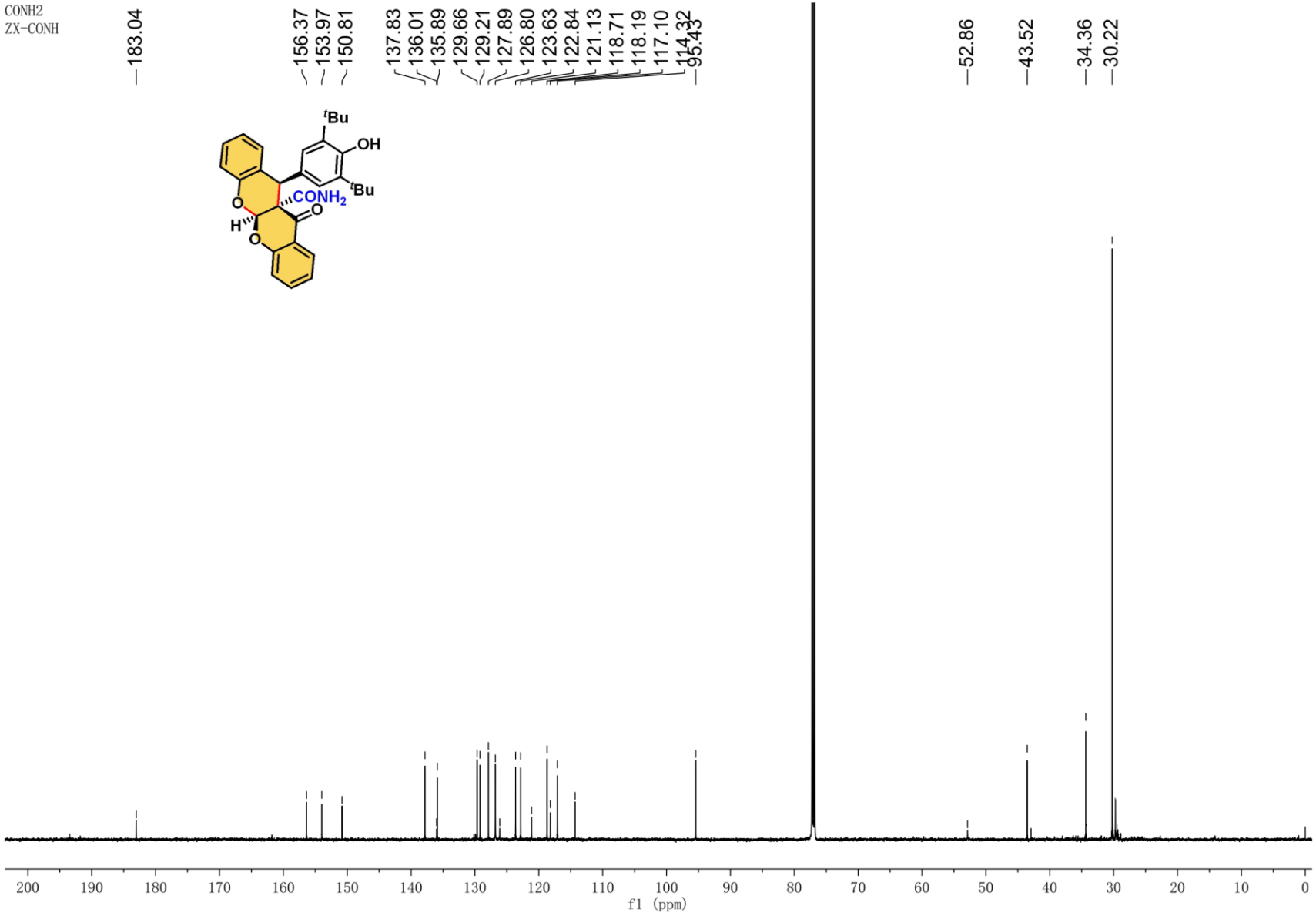
^{1}H NMR Spectrum of Compound 3v



^{13}C NMR Spectrum of Compound 3v



^{1}H NMR Spectrum of Compound 4



^{13}C NMR Spectrum of Compound 4