Diastereoselective Synthesis of 2,8-Dioxabicyclo[3.3.1]nonane Derivatives via I_2-mediated Cascade Reactions

Dong Cheng, XiangZhen Meng*, Yang·Li, XinRun·Ji

School of Chemistry and Material Engineering, Chaohu College, Chaohu, People's Republic of China.

Email:mxzcd79@163.com

Table of Contents General Information and Materials

1. General Information

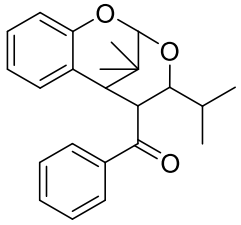
All ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on Brucker spectrometers in $CDCl_3$. Chemical shifts (δ) for NMR were quoted in ppm relative to the solvent peak (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C in CDCl3;). Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Coupling constants *J* are recorded in Hz. Melting points were determined with an X-4 apparatus and are uncorrected. IR spectra were Recorded with a Shimadzu FTIR-8300 spectrophotometer. High-resolution mass spectra (HRMS) were obtained on a waters G2-Xs with an ESI source (Waters, Manchester, UK). Unless otherwise noted, all reactions were carried out under the atmosphere in a sealed tube. Reactions were monitored by thin-layer chromatography (TLC) using pre-coated silica gel plates (GF254). Flash column chromatography was performed on silica gel (particle size 200-300 mesh) and eluted with petroleum ether/ dichloromethane.

2. Typical procedure for the preparation of 2,8-Dioxabicyclo[3.3.1]nonane Derivatives

2-methoxy chalcones **1** (0.5 mmol), aldehydes **2** (5.0 mL), and I_2 (129.5 mg, 0.51 mmol) were loaded into a 10 mL sealed tube. The reaction mixture was stirred at 70℃. After completion, the reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$(15 mL) and extracted with EA (3×10 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (200-300 mesh) using PE/ EA to give the product.

3. Data for all products

(4-Isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(phenyl)methanone (**3a**)



A white solid; Mp: 182 – 186; 76% or 65% yield.

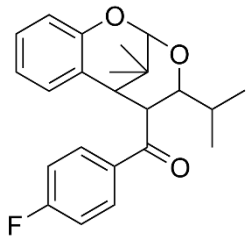
^{1}H NMR (500 MHz, Chloroform-d) δ 8.02 – 7.83 (m, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.10 (m, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.74 (t, *J* = 7.5 Hz, 1H), 6.44 – 6.16 (m, 1H), 5.06 (d, *J* = 2.0 Hz, 1H), 4.27 (dd, *J* = 10.9, 3.2 Hz, 1H), 3.93 (dd, *J* = 10.9, 2.3 Hz, 1H), 2.89 (t, *J* = 2.6 Hz, 1H), 1.72 (qt, *J* = 7.0, 4.5 Hz, 1H), 1.48 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 198.90, 153.75, 136.49, 133.30, 129.66, 129.14, 128.81, 128.12, 121.18, 120.05, 114.46, 99.49, 71.85, 45.22, 44.01, 32.23, 29.40, 24.16, 23.38, 20.41, 15.52.

IR (thin film): 2957, 2873, 1679, 1583, 1527, 1486, 1221, 1076, 976.

HRMS (ESI, m/z): Calculated for $C_{23}H_{26}O_3Na$ (M+Na) 373.1780, Measured 373.1784.

(4-Fluorophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d]-[1,3]dioxocin-5-yl)methanone (**3b**)



A white solid; Mp: 168 – 171; 77% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 – 7.87 (m, 2H), 7.33 – 7.09 (m, 3H), 6.90 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.76 (td, *J* = 7.4, 1.2 Hz, 1H), 6.33 (dd, *J* = 7.5, 1.6 Hz, 1H),

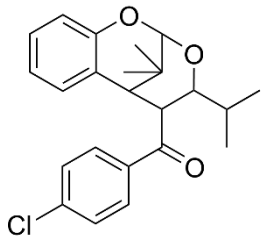
5.09 (d, *J* = 1.9 Hz, 1H), 4.24 (dd, *J* = 10.9, 3.3 Hz, 1H), 3.94 (dd, *J* = 10.9, 2.4 Hz, 1H), 2.89 (dd, *J* = 3.3, 2.0 Hz, 1H), 1.73 (pd, *J* = 6.9, 2.4 Hz, 1H), 1.50 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.28, 167.10 (J_{C-F} = 256.54 Hz), 153.74, 132.88 (J_{C-F} = 3.03 Hz), 130.76 (J_{C-F} = 9.09 Hz), 129.56, 128.88, 121.06, 120.07, 116.39 (J_{C-F} = 22.22 Hz), 114.52, 99.44, 71.78, 45.24, 44.13, 32.22, 29.43, 24.15, 23.39, 20.38, 15.53.

IR (thin film): 2971, 1684, 1599, 1486, 1221, 1095, 1039, 768.

HRMS (ESI, m/z): Calculated for $C_{23}H_{25}FO_3Na$ (M+Na) 391.1685, Measured 391.1688.

(4-Chlorophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d]-[1,3]dioxocin-5-yl)methanone (**3c**)



A white solid; Mp: 163 – 164; 72% yield.

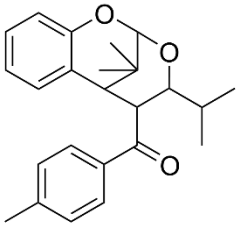
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 7.78 (m, 2H), 7.72 – 7.38 (m, 2H), 7.20 (td, *J* = 7.7, 1.7 Hz, 1H), 6.96 – 6.85 (m, 1H), 6.76 (td, *J* = 7.4, 1.2 Hz, 1H), 6.33 (dd, *J* = 7.5, 1.7 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 4.22 (dd, *J* = 10.9, 3.3 Hz, 1H), 3.94 (dd, *J* = 10.9, 2.4 Hz, 1H), 2.88 (t, *J* = 2.6 Hz, 1H), 1.72 (pd, *J* = 6.9, 2.4 Hz, 1H), 1.49 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.66, 153.76, 139.80, 134.77, 129.53, 129.51, 129.48, 128.90, 120.99, 120.08, 114.54, 99.43, 71.72, 45.35, 44.12, 32.22, 29.45, 24.14, 23.39, 20.37, 15.54.

IR (thin film): 2967, 2875, 1683, 1587, 1486, 1218, 978, 750.

HRMS (ESI, m/z): Calculated for $C_{23}H_{25}ClO_3Na$ (M+Na) 407.1390, Measured 407.1394.

(4-Isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(p-tolyl)methanone (**3d**)



A white solid; Mp: 165 – 170; 61% yield.

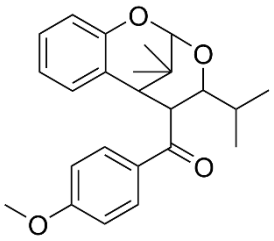
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 – 7.78 (m, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.19 (ddd, *J* = 8.9, 7.4, 1.7 Hz, 1H), 6.89 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.76 (td, *J* = 7.4, 1.2 Hz, 1H), 6.36 (dd, *J* = 7.5, 1.7 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 4.26 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.95 (dd, *J* = 11.0, 2.4 Hz, 1H), 3.02 – 2.72 (m, 1H), 2.91 – 2.90 (m, 1H), 2.49 (s, 3H), 1.75 (pd, *J* = 6.9, 2.4 Hz, 1H), 1.50 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.48, 153.74, 144.09, 134.06, 129.78, 129.69, 128.74, 128.21, 121.29, 120.01, 114.40, 99.52, 71.89, 45.12, 44.14, 32.23, 29.40, 24.16, 23.38, 21.68, 20.38, 15.51.

IR (thin film): 2966, 1678, 1610, 1487, 1221, 1075, 750.

HRMS (ESI, m/z): Calculated for $C_{24}H_{28}O_3Na$ (M+Na) 387.1936, Measured 387.1936.

(4-Isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(4-methoxyphenyl)methanone (**3e**)



A white solid; Mp: 149 – 153; 53% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 – 7.78 (m, 2H), 7.19 (ddd, *J* = 8.8, 7.4, 1.7 Hz, 1H), 7.10 – 6.97 (m, 2H), 6.88 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.75 (td, *J* = 7.4, 1.2 Hz, 1H), 6.36 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 4.23 (dd, *J* = 10.9,

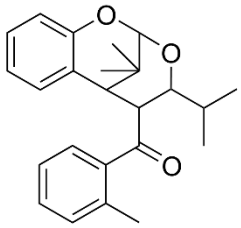
3.3 Hz, 1H), 3.96 – 3.93 (m, 4H), 2.99 – 2.80 (m, 1H), 1.74 (pd, *J* = 6.9, 2.4 Hz, 1H), 1.49 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.32, 163.59, 153.72, 130.31, 129.71, 129.54, 128.72, 121.36, 120.00, 114.38, 114.24, 99.53, 71.95, 55.56, 44.88, 44.27, 32.23, 29.39, 24.17, 23.39, 20.38, 15.51.

IR (thin film): 2967, 2906, 1673, 1601, 1486, 1264, 979, 750.

HRMS (ESI, m/z): Calculated for $C_{24}H_{28}O_4Na$ (M+Na) 403.1885, Measured 403.1882.

(4-Isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(o-tolyl)methanone (**3f**)



A white solid; Mp: 147 – 149; 60% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.50 (td, *J* = 7.5, 1.4 Hz, 1H), 7.45 – 7.33 (m, 2H), 7.20 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 6.90 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.78 (td, *J* = 7.4, 1.2 Hz, 1H), 6.40 (dd, *J* = 7.5, 1.7 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 4.25 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.96 (dd, *J* = 10.8, 2.2 Hz, 1H), 2.94 (dd, *J* = 3.4, 2.0 Hz, 1H), 2.53 (s, 3H), 1.84 (pd, *J* = 6.9, 2.2 Hz, 1H), 1.46 (s, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 3H).

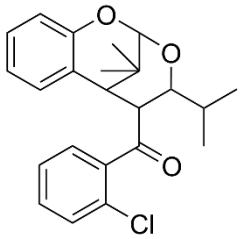
^{13}C NMR (101 MHz, Chloroform-*d*) δ 201.65, 153.91, 140.59, 135.57, 133.29, 132.09, 129.49, 128.87, 128.73, 126.13, 121.36, 120.10, 114.55, 99.52, 71.96, 46.16, 44.04, 32.36, 29.22, 24.03, 23.27, 22.15, 20.54, 15.32.

IR (thin film): 2962, 2906, 1683, 1487, 1222, 1084, 769.

HRMS (ESI, m/z): Calculated for $C_{24}H_{28}O_3Na$ (M+Na) 387.1936, Measured 387.1938.

(2-Chlorophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d]-

[1,3]dioxocin-5-yl)methanone (**3g**)



A white solid; Mp: 120 – 122; 66% yield.

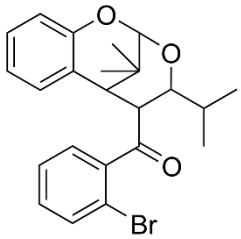
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.57 – 7.39 (m, 3H), 7.22 (td, *J* = 7.7, 1.6 Hz, 1H), 6.96 – 6.87 (m, 1H), 6.83 (td, *J* = 7.4, 1.2 Hz, 1H), 6.60 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.06 (d, *J* = 1.9 Hz, 1H), 4.54 (dd, *J* = 10.9, 3.2 Hz, 1H), 3.92 (dd, *J* = 10.9, 2.0 Hz, 1H), 2.91 (t, *J* = 2.5 Hz, 1H), 1.88 (pd, *J* = 6.9, 1.9 Hz, 1H), 1.41 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 200.54, 154.05, 137.23, 132.76, 131.95, 131.53, 131.50, 129.75, 128.90, 127.35, 121.13, 120.11, 114.53, 99.44, 72.16, 48.64, 43.15, 32.26, 29.13, 24.07, 23.23, 20.60, 15.30.

IR (thin film): 2970, 2873, 1689, 1585, 1486, 1293, 970, 761.

HRMS (ESI, m/z): Calculated for $C_{23}H_{25}ClO_3Na$ (M+Na) 407.1390, Measured 407.1396.

(2-Bromophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo-[d][1,3]dioxocin-5-yl)methanone (**3h**)



A white solid; Mp: 162 – 163; 60% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (t, *J* = 1.8 Hz, 1H), 7.91 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.79 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.21 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H), 6.91 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.79 (td, *J* = 7.4, 1.2 Hz, 1H), 6.35 (dd, *J* = 7.5, 1.6 Hz, 1H), 5.09 (d, *J* = 1.9 Hz, 1H), 4.23 (dd, *J* = 10.9, 3.3 Hz, 1H), 3.94 (dd, *J* = 10.9, 2.5 Hz, 1H), 2.91 (dd, *J* = 3.3, 1.9 Hz, 1H), 1.72 (pd, *J* = 6.9,

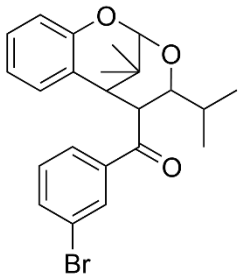
2.5 Hz, 1H), 1.50 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.42, 153.77, 138.17, 136.24, 131.22, 130.75, 129.63, 128.94, 126.58, 123.64, 120.93, 120.16, 114.56, 99.41, 71.72, 45.50, 44.04, 32.24, 29.48, 24.15, 23.40, 20.40, 15.61.

IR (thin film): 2966, 2915, 2875, 1602, 1408, 1206, 970, 762.

HRMS (ESI, m/z): Calculated for $C_{23}H_{25}BrO_3Na$ (M+Na) 451.0885, Measured 451.0881.

(3-Bromophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo-[d][1,3]dioxocin-5-yl)methanone (**3i**)



A white solid; Mp: 142 – 145; 64% yield.

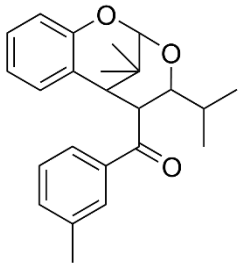
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (q, *J* = 1.6 Hz, 1H), 7.90 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.83 – 7.73 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.26 – 7.14 (m, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.84 – 6.70 (m, 1H), 6.34 (dd, *J* = 7.5, 1.6 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 4.21 (dd, *J* = 10.9, 3.2 Hz, 1H), 3.93 (dd, *J* = 10.9, 2.5 Hz, 1H), 2.89 (t, *J* = 2.6 Hz, 1H), 1.71 (pd, *J* = 6.9, 2.3 Hz, 1H), 1.50 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 197.39, 138.19, 136.20, 131.22, 130.70, 129.60, 128.93, 126.55, 123.61, 120.91, 120.13, 114.55, 99.41, 71.72, 45.50, 44.04, 32.23, 29.47, 24.13, 23.38, 20.35, 15.58.

IR (thin film): 2966, 2915, 1681, 1489, 1206, 978, 762.

HRMS (ESI, m/z): Calculated for $C_{23}H_{25}BrO_3Na$ (M+Na) 451.0885, Measured 451.0890.

(4-Isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(m-tolyl)methanone (**3j**)



A white solid; Mp: 153 – 154; 59% yield.

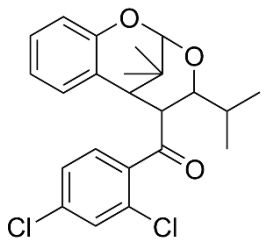
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 2.6 Hz, 2H), 7.48 (dd, *J* = 4.5, 1.8 Hz, 2H), 7.26 – 7.13 (m, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.40 (d, *J* = 7.1 Hz, 1H), 5.10 (d, *J* = 2.0 Hz, 1H), 4.30 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.98 (dd, *J* = 11.0, 2.5 Hz, 1H), 2.94 (t, *J* = 2.5 Hz, 1H), 2.51 (s, 3H), 1.77 (pd, *J* = 6.9, 2.3 Hz, 1H), 1.52 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.00, 153.80, 139.02, 136.59, 134.10, 129.78, 128.97, 128.76, 128.65, 125.28, 121.29, 120.05, 114.42, 99.53, 71.94, 45.29, 44.08, 32.25, 29.45, 24.18, 23.41, 21.57, 20.42, 15.60.

IR (thin film): 2960, 2873, 1673, 1486, 1218, 1075, 749, 891.

HRMS (ESI, m/z): Calculated for $C_{24}H_{28}O_3Na$ (M+Na) 387.1936, Measured 387.1941.

(2,4-Dichlorophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo-[d][1,3]dioxocin-5-yl)methanone (**3k**)



A white solid; Mp: 166 – 167; 72% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.44 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H), 6.90 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.81 (td, *J* = 7.4, 1.2 Hz, 1H), 6.52 (dd, *J* = 7.6, 1.7 Hz, 1H), 5.05 (d,

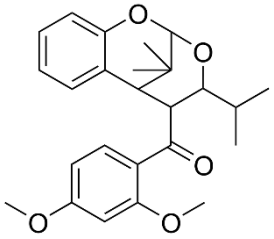
J = 1.9 Hz, 1H), 4.48 (dd, *J* = 10.8, 3.3 Hz, 1H), 3.88 (dd, *J* = 10.8, 2.0 Hz, 1H), 2.90 – 2.81 (m, 1H), 1.83 (pd, *J* = 6.9, 2.0 Hz, 1H)., 1.39 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.41, 154.01, 138.50, 135.47, 132.84, 132.61, 131.27, 129.50, 128.99, 127.82, 120.94, 120.12, 114.64, 99.36, 72.00, 48.66, 43.17, 32.24, 29.12, 24.04, 23.20, 20.54, 15.28.

IR (thin film): 2974, 2906, 1701, 1617, 1585, 1486, 1221, 1093, 756.

HRMS (ESI, m/z): Calculated for $C_{23}H_{24}Cl_2O_3Na$ (M+Na) 441.1000, Measured 441.1099.

(2,4-Dimethoxyphenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobe-nzo[d][1,3]dioxocin-5-yl)methanone (**3l**)



A white solid; Mp: 156 – 159; 67% yield.

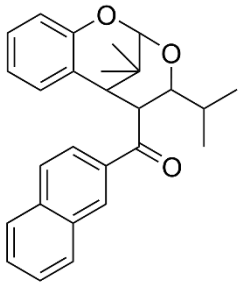
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 (d, *J* = 8.7 Hz, 1H), 7.17 (td, *J* = 7.7, 1.7 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.75 (td, *J* = 7.4, 1.2 Hz, 1H), 6.64 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.43 (dd, *J* = 7.5, 1.7 Hz, 1H), 5.05 (d, *J* = 2.0 Hz, 1H), 4.55 (dd, *J* = 11.1, 3.2 Hz, 1H), 4.01 (s, 3H), 3.92 – 3.88 (m, 4H), 2.89 (t, *J* = 2.6 Hz, 1H), 1.83 (pd, *J* = 6.8, 2.1 Hz, 1H), 1.40 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.65, 164.63, 160.13, 154.00, 134.03, 129.63, 128.44, 121.99, 119.83, 114.27, 105.86, 99.69, 98.46, 72.27, 55.61, 55.50, 49.40, 42.87, 32.20, 29.15, 24.23, 23.23, 20.43, 15.30.

IR (thin film): 2963, 2907, 1657, 1601, 1257, 1214, 1027, 757.

HRMS (ESI, m/z): Calculated for $C_{25}H_{30}O_5Na$ (M+Na) 433.1991, Measured 433.1995.

(4-Isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(naphthalen-2-yl)methanone (**3m**)



A white solid; Mp: 180 – 181; 50% yield.

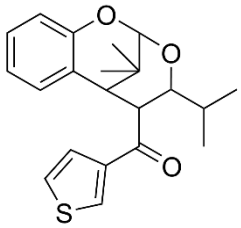
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.52 (s, 1H), 8.12 – 8.00 (m, 3H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.67 (tt, *J* = 8.4, 6.2 Hz, 2H), 7.23 (td, *J* = 7.8, 1.7 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.79 (td, *J* = 7.4, 1.2 Hz, 1H), 6.39 (dd, *J* = 7.5, 1.6 Hz, 1H), 5.14 (d, *J* = 2.0 Hz, 1H), 4.48 (dd, *J* = 11.0, 3.3 Hz, 1H), 4.05 (dd, *J* = 11.0, 2.4 Hz, 1H), 3.03 (t, *J* = 2.6 Hz, 1H), 1.83 (pd, *J* = 6.9, 2.4 Hz, 1H), 1.59 (s, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.94 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.83, 153.82, 133.84, 132.74, 129.78, 129.73, 129.43, 129.16, 128.83, 128.76, 127.92, 127.08, 124.05, 121.28, 120.11, 114.49, 99.56, 71.97, 45.45, 44.33, 32.33, 29.53, 24.19, 23.50, 20.46, 15.66.

IR (thin film): 2958, 2873, 1672, 1486, 1218, 1075, 981, 749.

HRMS (ESI, m/z): Calculated for $C_{27}H_{28}O_3Na$ (M+Na) 423.1936, Measured 423.1930.

(4-Isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(thiophen-3-yl)methanone (**3n**)



A white solid; Mp: 172 – 180; 42% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.58 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.44 (dd, *J* = 5.1, 2.9 Hz, 1H), 7.20 (ddd, *J* = 8.7, 7.4, 1.7 Hz, 1H),

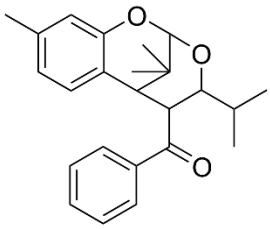
6.89 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.78 (td, *J* = 7.4, 1.2 Hz, 1H), 6.43 (dd, *J* = 7.5, 1.7 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 4.06 (dd, *J* = 11.1, 3.3 Hz, 1H), 3.92 (dd, *J* = 11.0, 2.4 Hz, 1H), 2.97 (t, *J* = 2.7 Hz, 1H), 1.74 (pd, *J* = 6.9, 2.4 Hz, 1H), 1.48 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 193.26, 153.74, 141.86, 131.58, 129.82, 128.80, 127.12, 127.00, 121.20, 120.10, 114.42, 99.46, 71.58, 47.44, 44.43, 32.19, 29.44, 24.17, 23.45, 20.37, 15.54.

IR (thin film): 2966, 2909, 1673, 1487, 1223, 1077, 975, 761.

HRMS (ESI, m/z): Calculated for $C_{21}H_{24}SO_3Na$ (M+Na) 379.1344, Measured 379.1349.

(4-Isopropyl-9,11,11-trimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(phenyl)methanone (**3o**)



A white solid; Mp: 159 – 166; 58% yield.

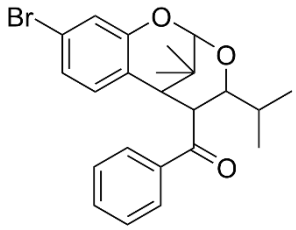
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (dt, *J* = 7.0, 1.4 Hz, 2H), 7.71 – 7.61 (m, 1H), 7.58 (dd, *J* = 8.2, 6.7 Hz, 2H), 6.72 (d, *J* = 1.7 Hz, 1H), 6.58 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.24 (d, *J* = 7.6 Hz, 1H), 5.06 (d, *J* = 1.9 Hz, 1H), 4.28 (dd, *J* = 10.9, 3.2 Hz, 1H), 3.95 (dd, *J* = 11.0, 2.4 Hz, 1H), 2.88 (t, *J* = 2.6 Hz, 1H), 2.31 (s, 3H), 1.75 (pd, *J* = 6.9, 2.4 Hz, 1H), 1.49 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.00, 153.54, 138.74, 136.55, 133.23, 129.33, 129.10, 128.11, 120.97, 118.14, 115.05, 99.48, 71.90, 45.31, 43.74, 32.33, 29.42, 24.17, 23.42, 21.34, 20.38, 15.54.

IR (thin film): 2962, 2872, 1679, 1581, 1449, 1242, 1078, 1027, 785.

HRMS (ESI, m/z): Calculated for $C_{24}H_{28}O_3Na$ (M+Na) 387.1936, Measured 387.1939.

(9-Bromo-4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]-dioxocin-5-yl)(phenyl)methanone (**3p**)



A white solid; Mp: 166 – 167; 62% yield.

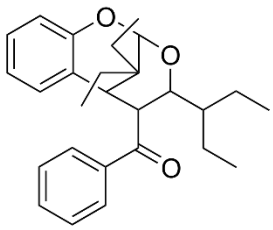
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (dt, *J* = 7.1, 1.4 Hz, 2H), 7.76 – 7.62 (m, 1H), 7.58 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.89 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.22 (d, *J* = 8.0 Hz, 1H), 5.08 (d, *J* = 2.0 Hz, 1H), 4.28 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.91 (dd, *J* = 11.0, 2.4 Hz, 1H), 2.95 – 2.71 (m, 1H), 1.74 (pd, *J* = 6.9, 2.5 Hz, 1H), 1.49 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.65, 154.48, 136.25, 133.48, 130.75, 129.22, 128.08, 123.24, 121.73, 120.40, 117.83, 99.58, 71.88, 44.96, 43.64, 32.10, 29.38, 24.04, 23.28, 20.34, 15.49.

IR (thin film): 2994, 2960, 1682, 1598, 1480, 1214, 977, 710.

HRMS (ESI, m/z): Calculated for $C_{23}H_{25}BrO_3Na$ (M+Na) 451.0885, Measured 451.0889.

(11,11-Diethyl-4-(pentan-3-yl)-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(phenyl)methanone (**3q**)



white liquid; 56% yield.

^{1}H NMR (400 MHz, Chloroform-*d*) δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 – 7.92 (m, 2H), 7.66 (dd, J = 7.4, 1.5 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.21 (t, J = 7.7 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 6.78 (t, J = 7.4 Hz, 1H), 6.40 (dd, J = 7.5, 1.7 Hz, 1H),

5.20 (d, J = 1.9 Hz, 1H), 4.33 (dd, J = 11.0, 3.1 Hz, 1H), 4.22 (dd, J = 10.9, 2.0 Hz, 1H), 3.04 (t, J = 2.5 Hz, 1H), 2.00 (q, J = 7.8 Hz, 2H), 1.68 – 1.58 (m, 1H), 1.50 – 1.33 (m, 4H), 1.24 – 1.13 (m, 2H), 1.13 – 1.07 (m, 3H), 0.95 – 0.87 (m, 6H), 0.80 – 0.71 (m, 3H).

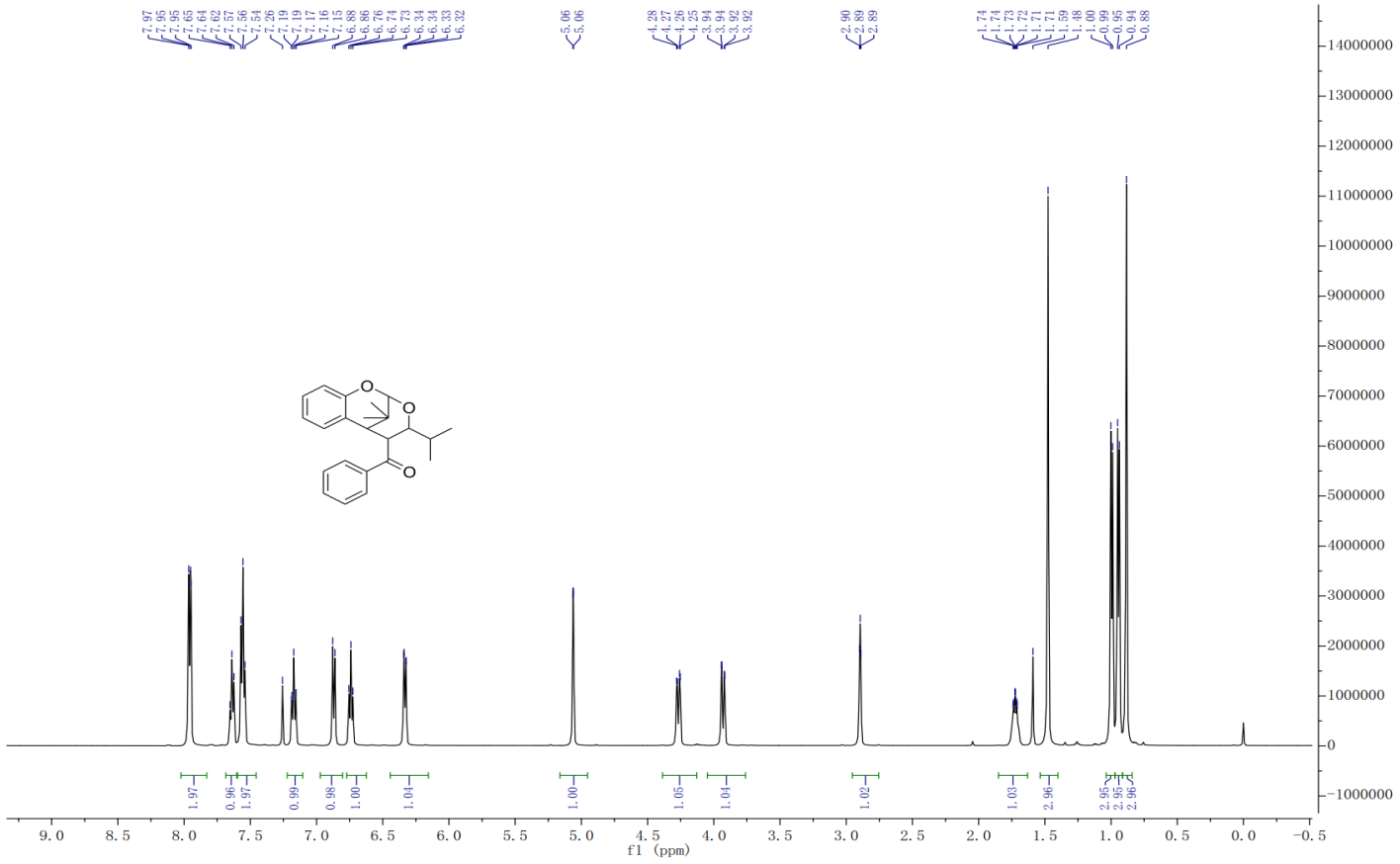
^{13}C NMR (101 MHz, Chloroform-*d*) δ 199.39, 154.69, 136.93, 133.23, 129.68, 129.15, 128.77, 128.02, 121.01, 120.05, 114.13, 97.36, 69.17, 44.03, 42.50, 40.55, 36.93, 23.58, 23.07, 22.28, 21.27, 12.77, 11.78, 7.51, 7.01.

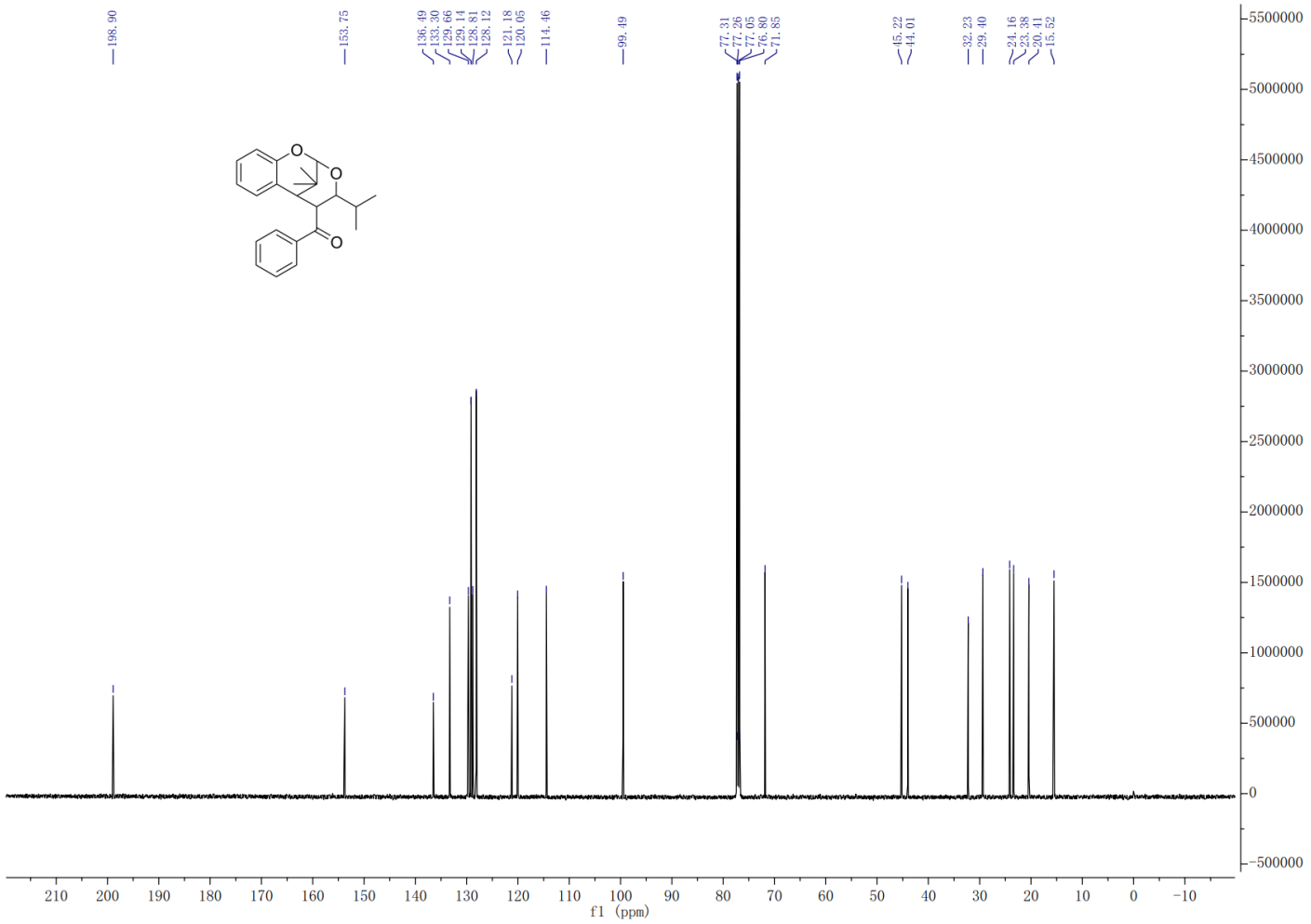
IR (thin film): 2962, 2875, 1679, 1609, 1487, 1223, 1187, 752.

HRMS (ESI, m/z): Calculated for $C_{27}H_{34}O_3Na$ (M+Na) 429.2406, Measured 429.2412.

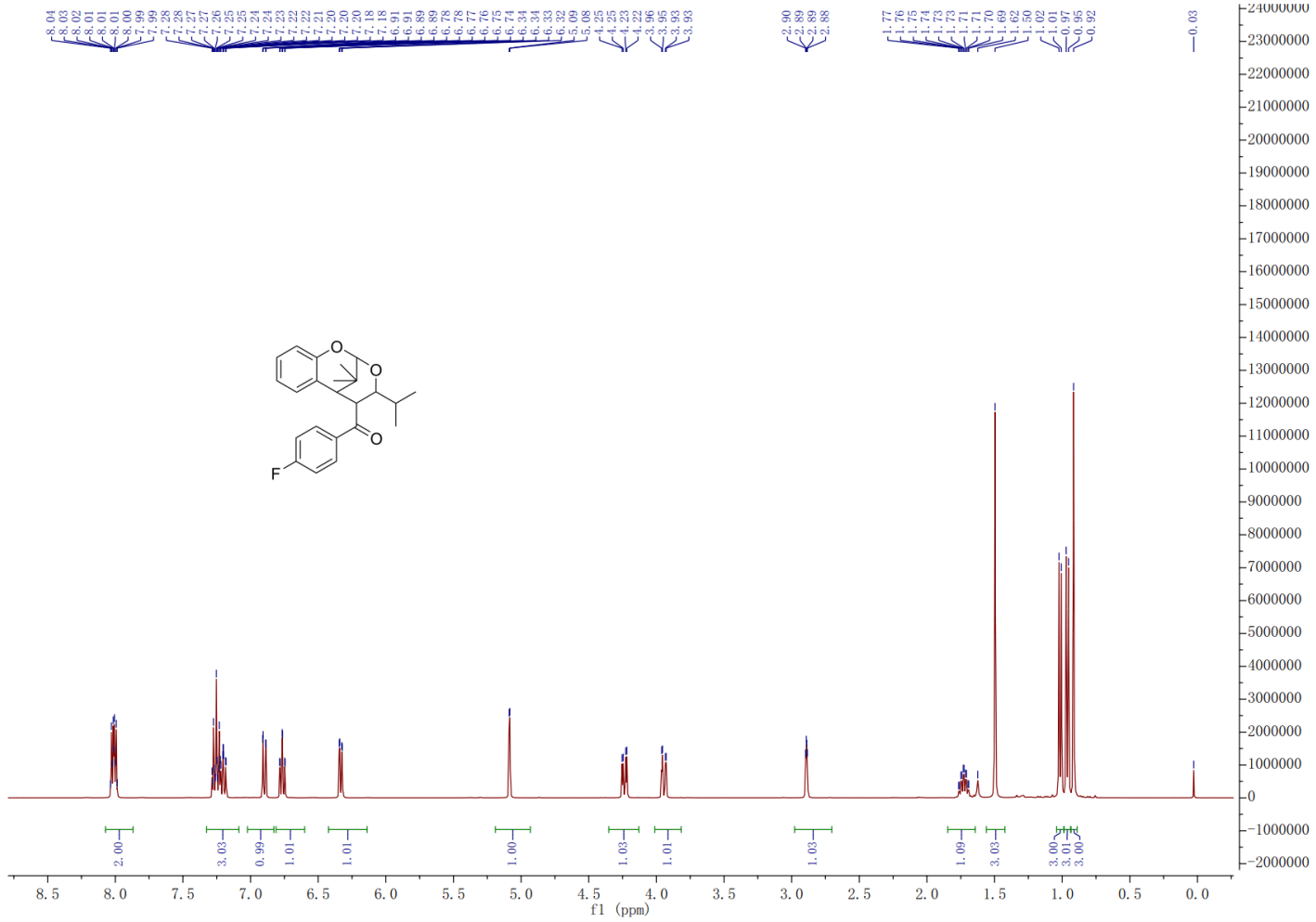
4. Copies of ^{1}H NMR, and ^{13}C NMR spectra

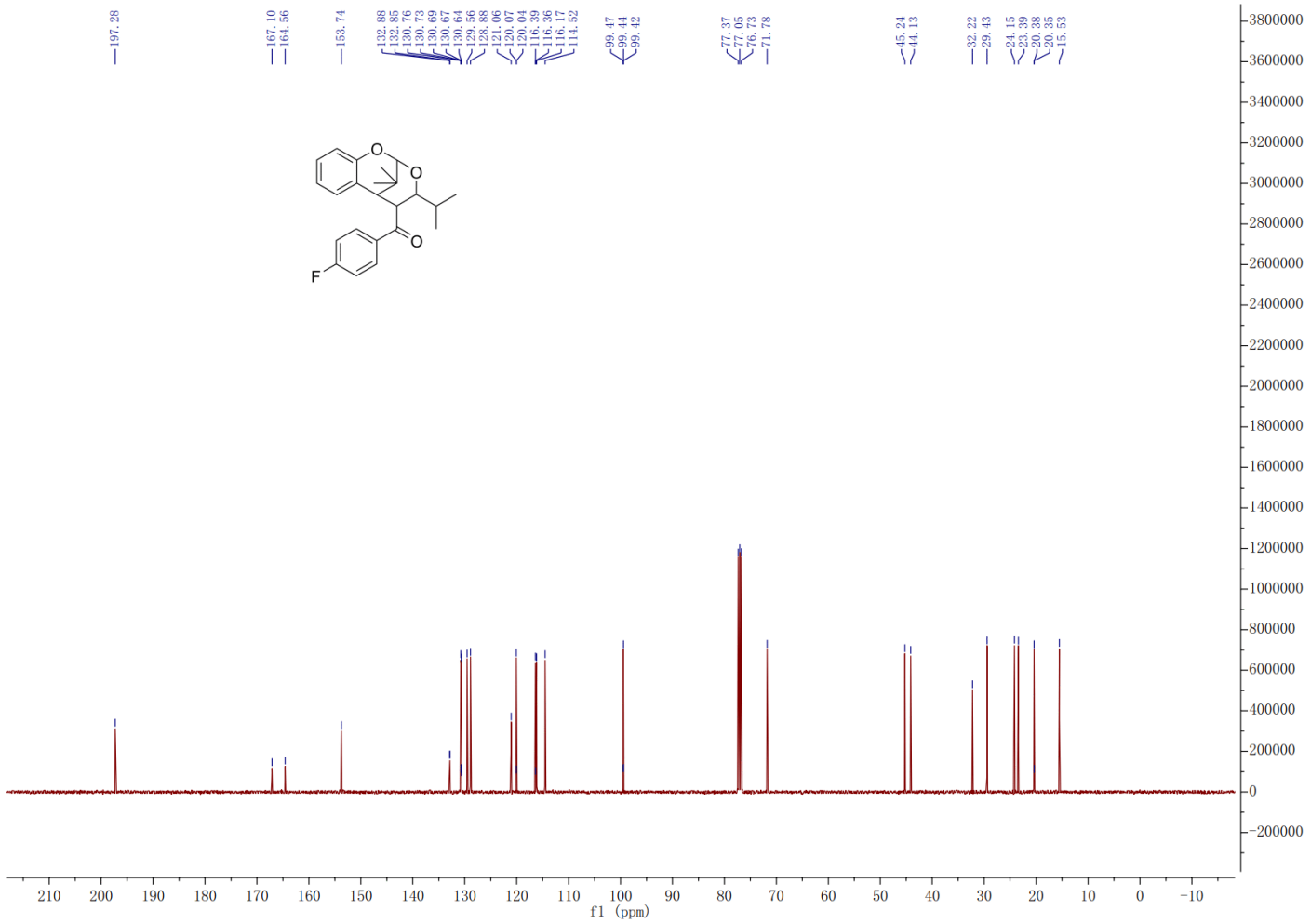
(4-Isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(phenyl)methanone (**3a**)



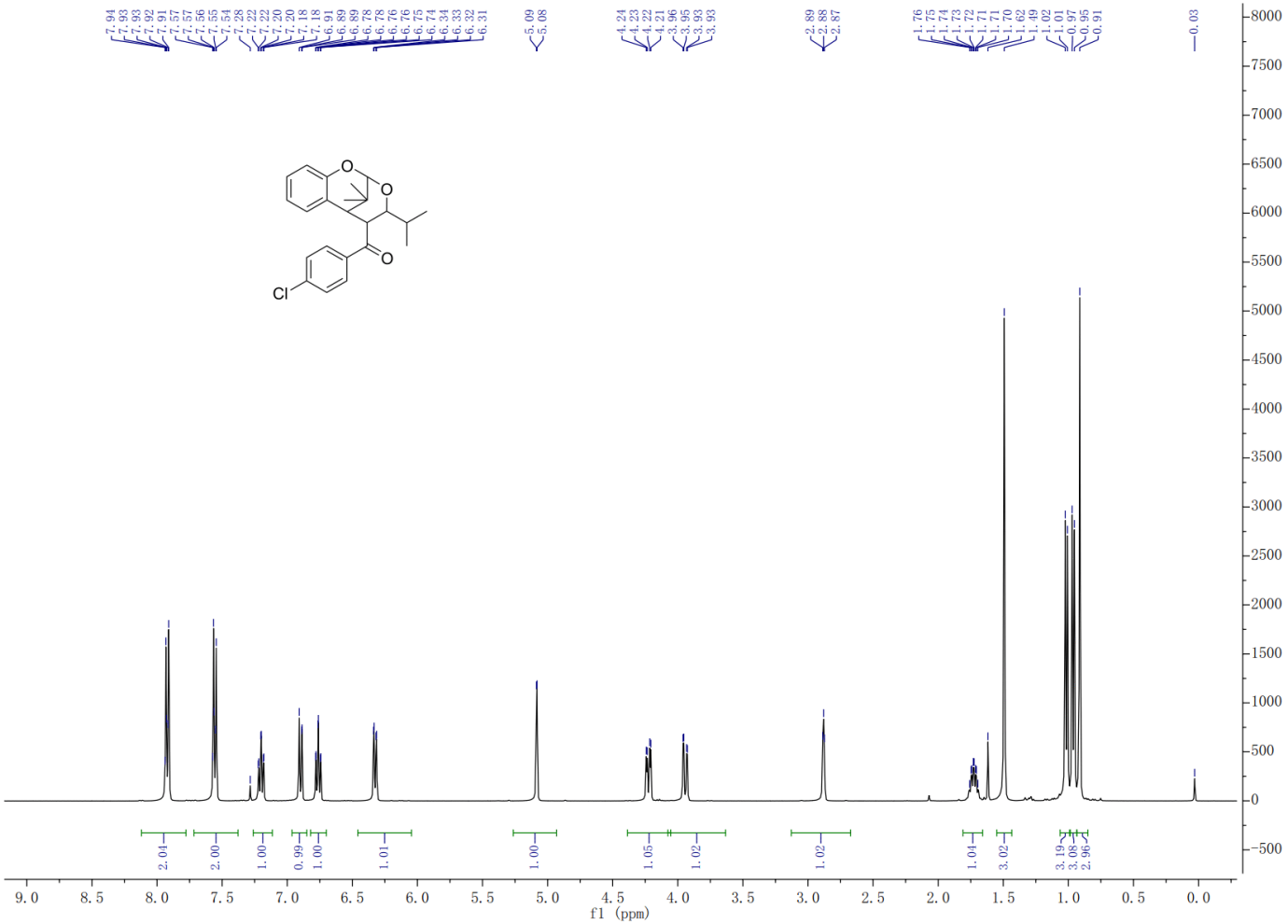

198.90
153.75
136.49
133.30
129.66
129.14
128.81
128.12
121.18
120.05
114.46
99.49
77.31
77.26
77.05
76.80
71.85
45.22
44.01
32.23
29.40
24.16
23.38
20.41
15.52
O
O
O
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
−500000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

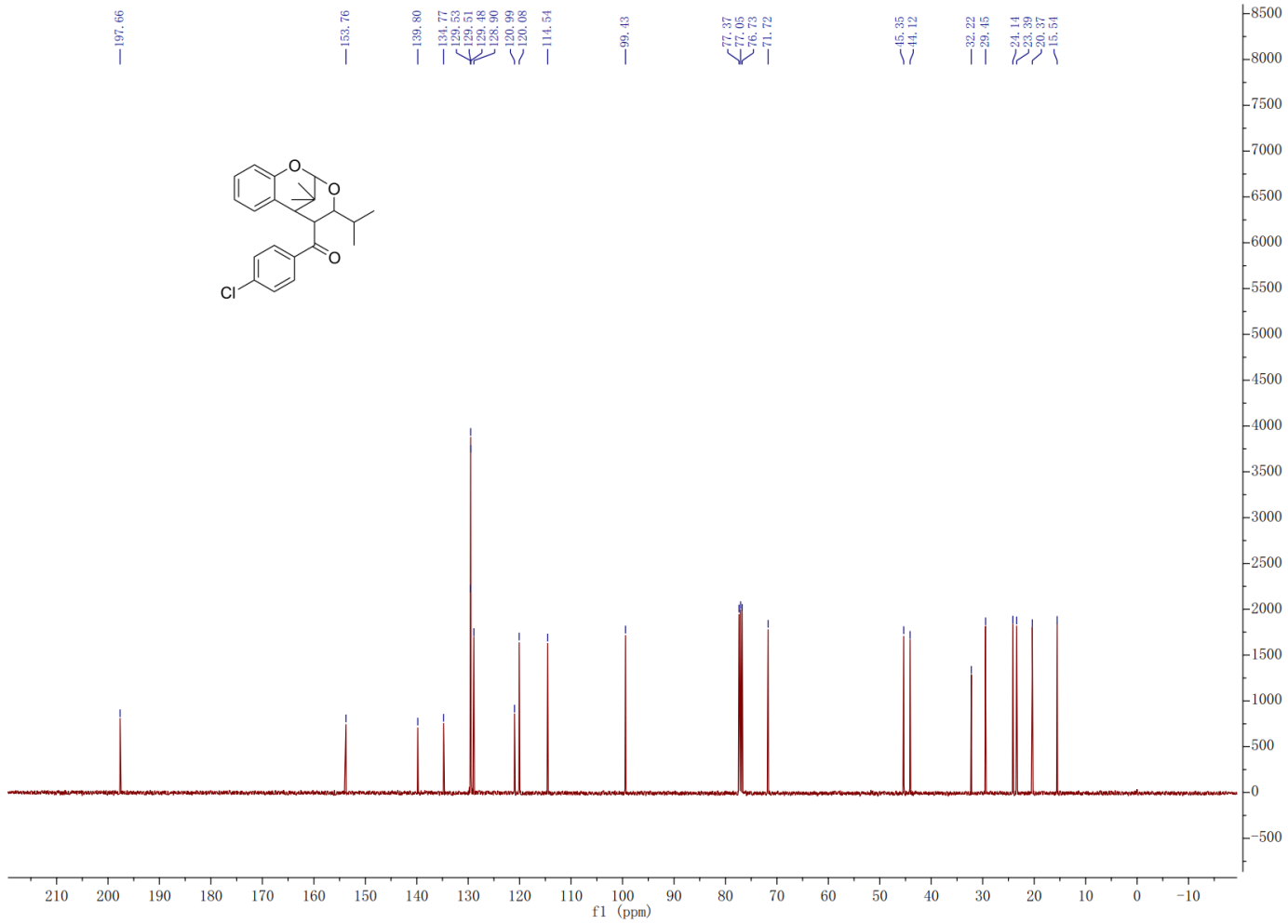
(4-fluorophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)methanone (**3b**)



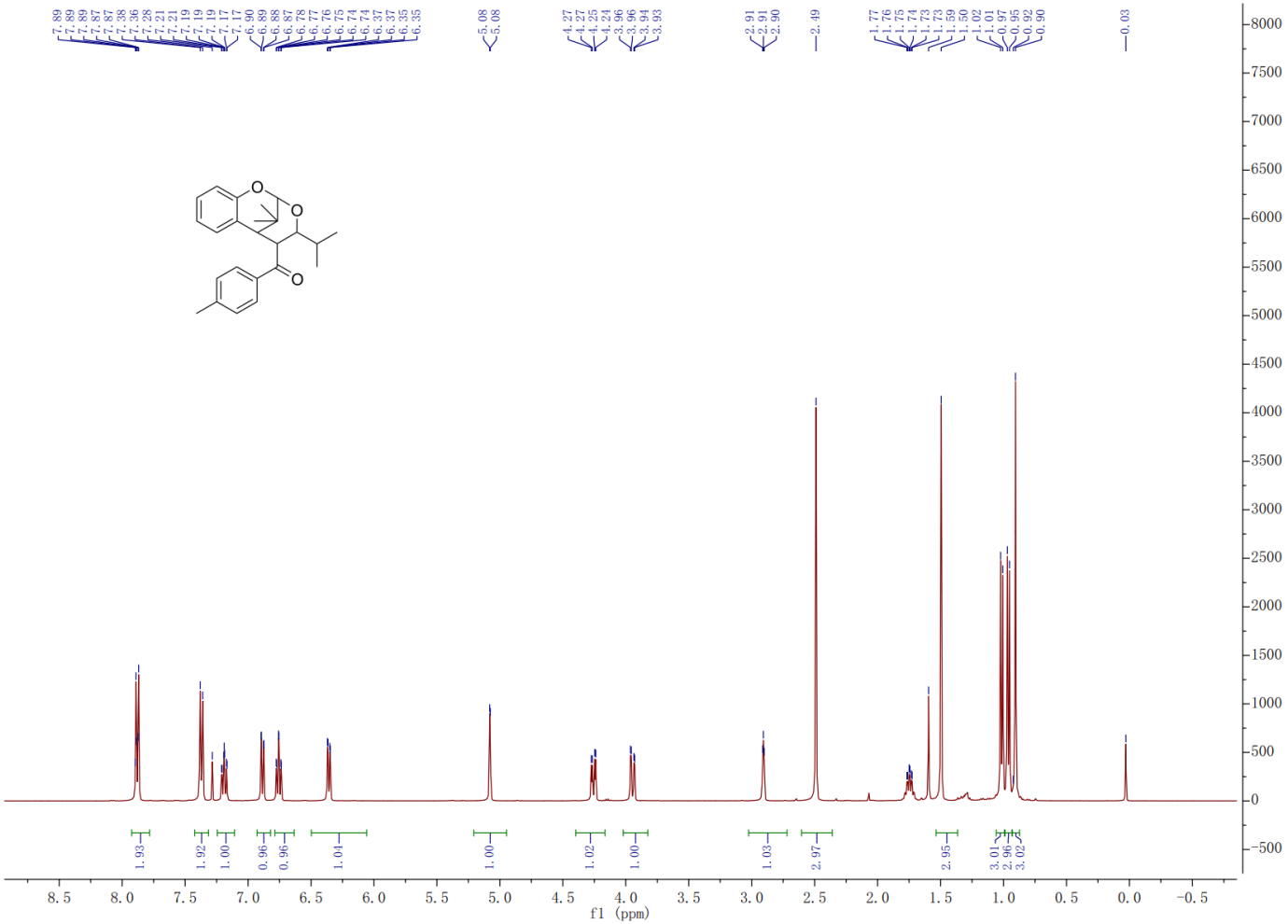

197.28
167.10
164.56
153.74
132.88
132.85
130.76
130.73
130.69
130.67
130.64
129.56
128.88
121.06
120.07
120.04
116.39
116.36
116.17
114.52
99.47
99.44
99.42
77.37
77.05
76.73
71.78
45.24
44.13
32.22
29.43
24.15
23.39
20.38
20.35
15.53
O
O
O
F
f1 (ppm)

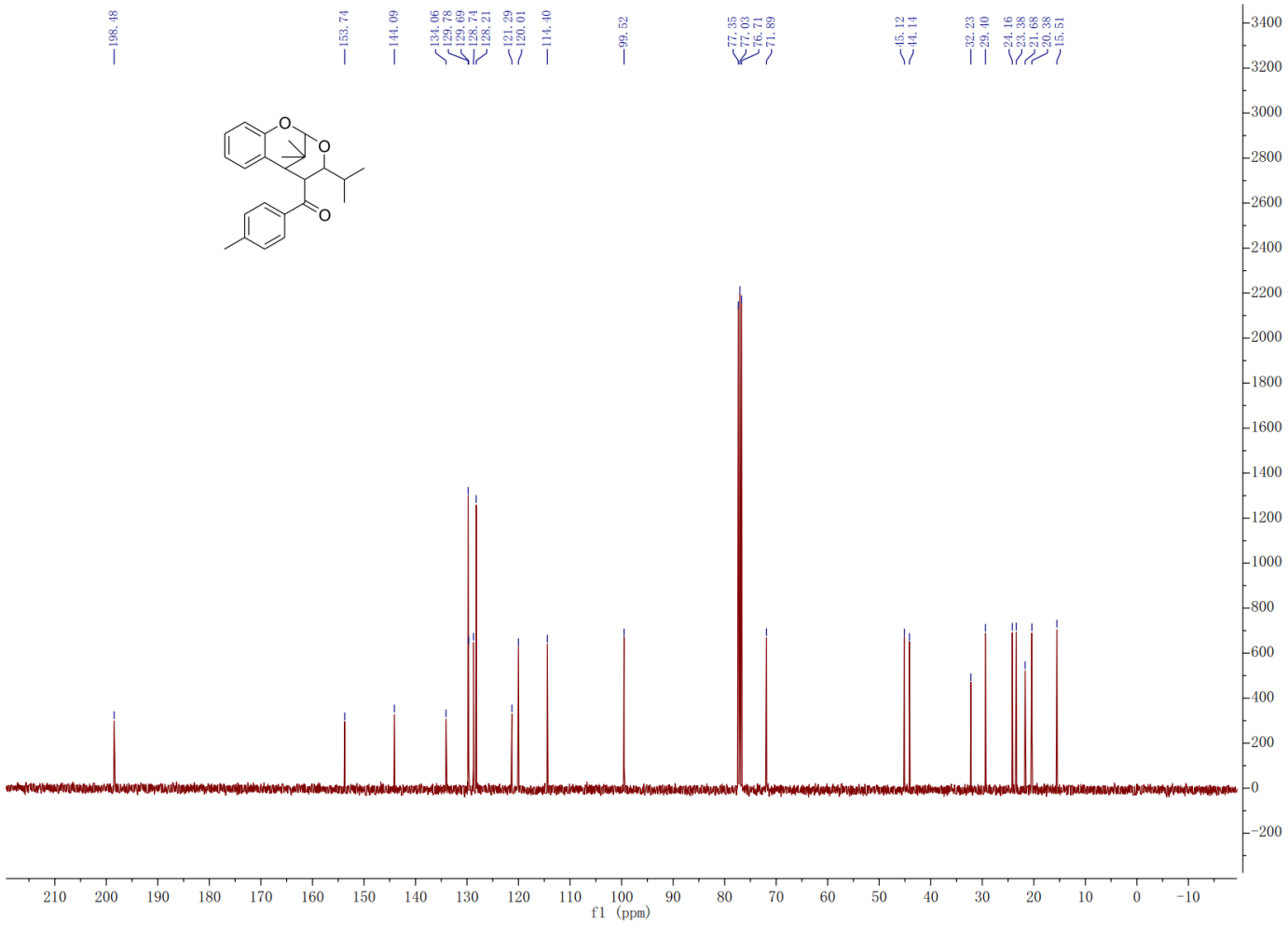
(4-chlorophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)methanone (**3c**)



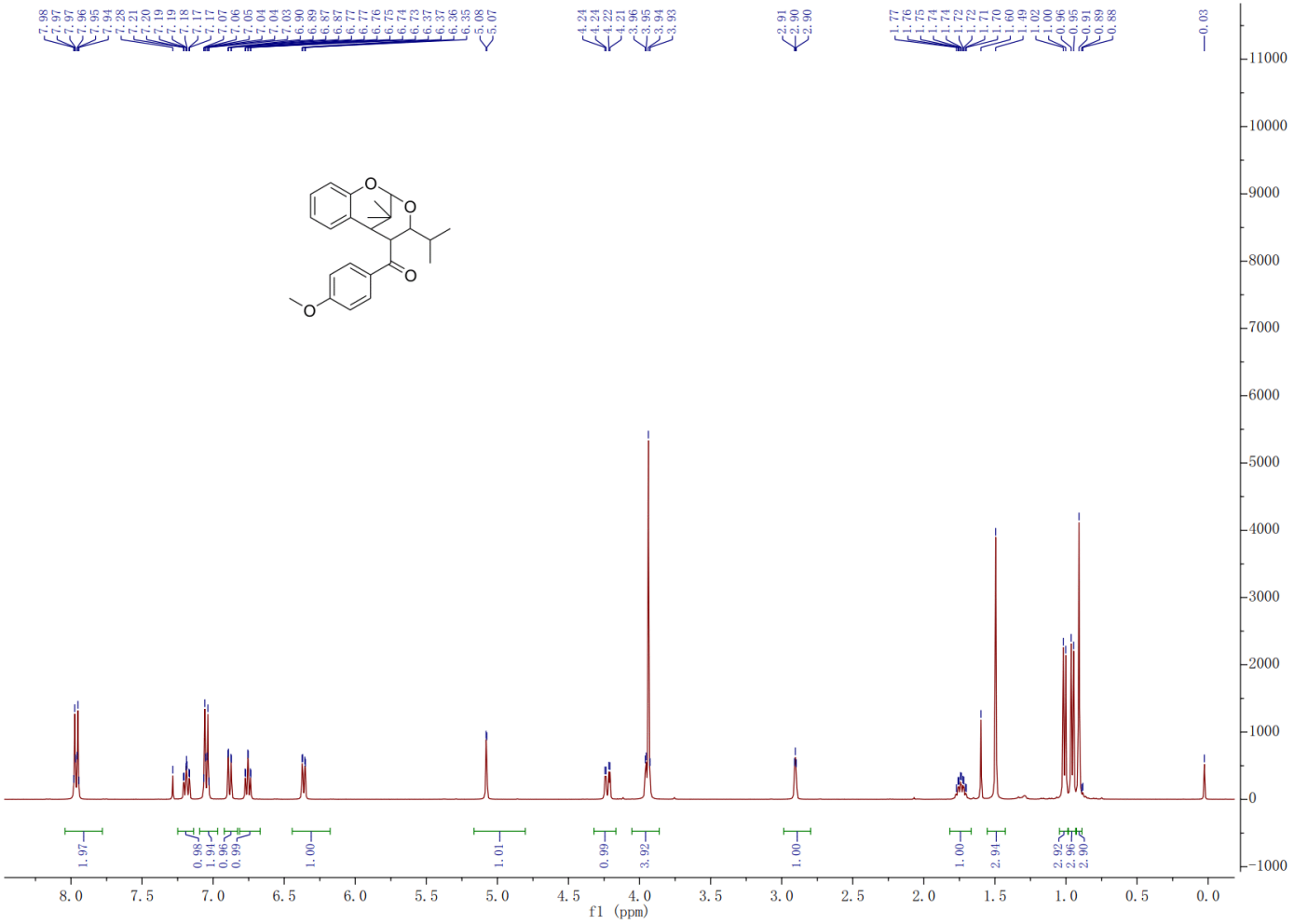

197.66
153.76
139.80
134.77
129.53
129.51
129.48
128.90
120.99
120.08
114.54
99.43
77.37
77.05
76.73
71.72
45.35
44.12
32.22
29.45
24.14
23.39
20.37
15.54
O
O
O
Cl
f1 (ppm)

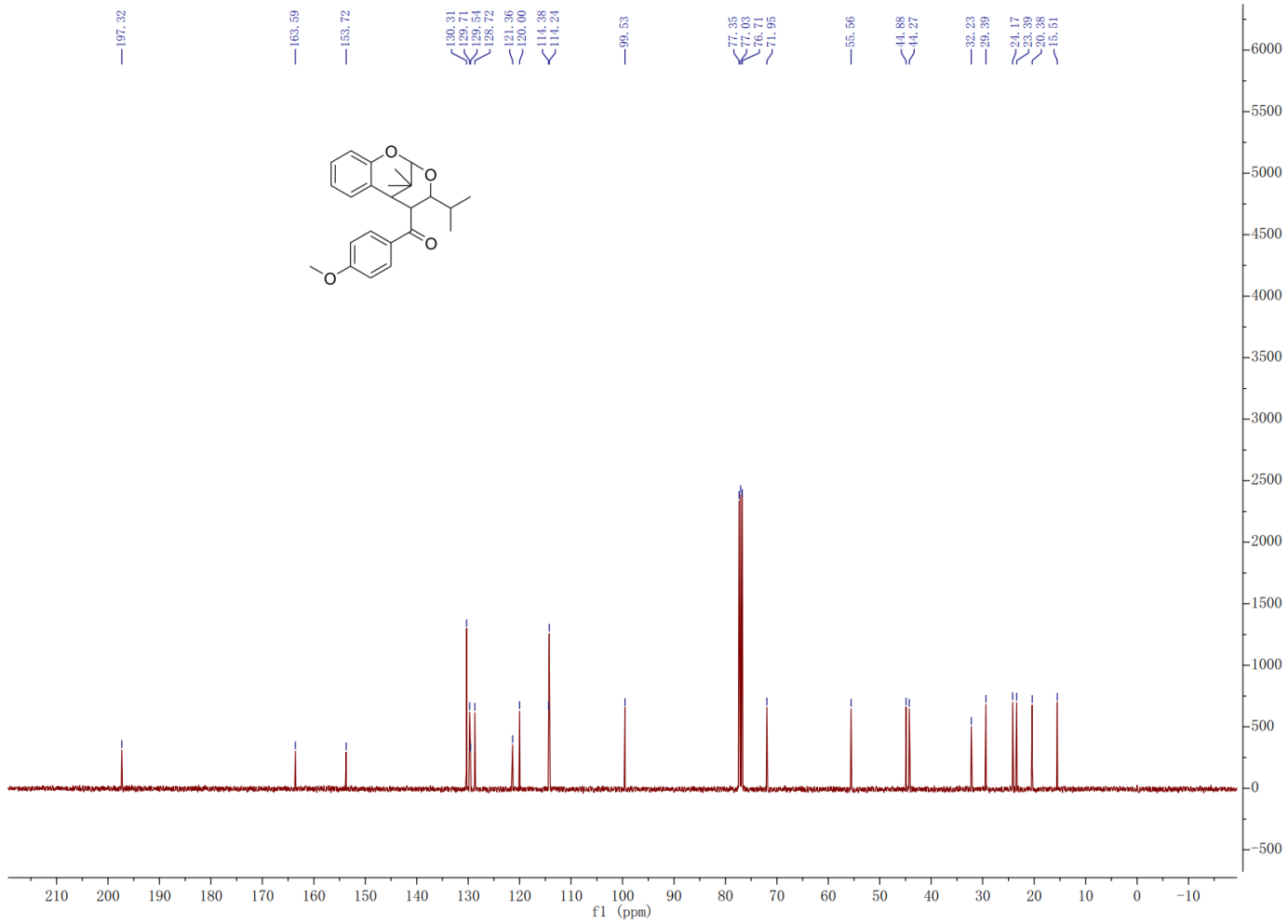
(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(p-tolyl)methanone (**3d**)



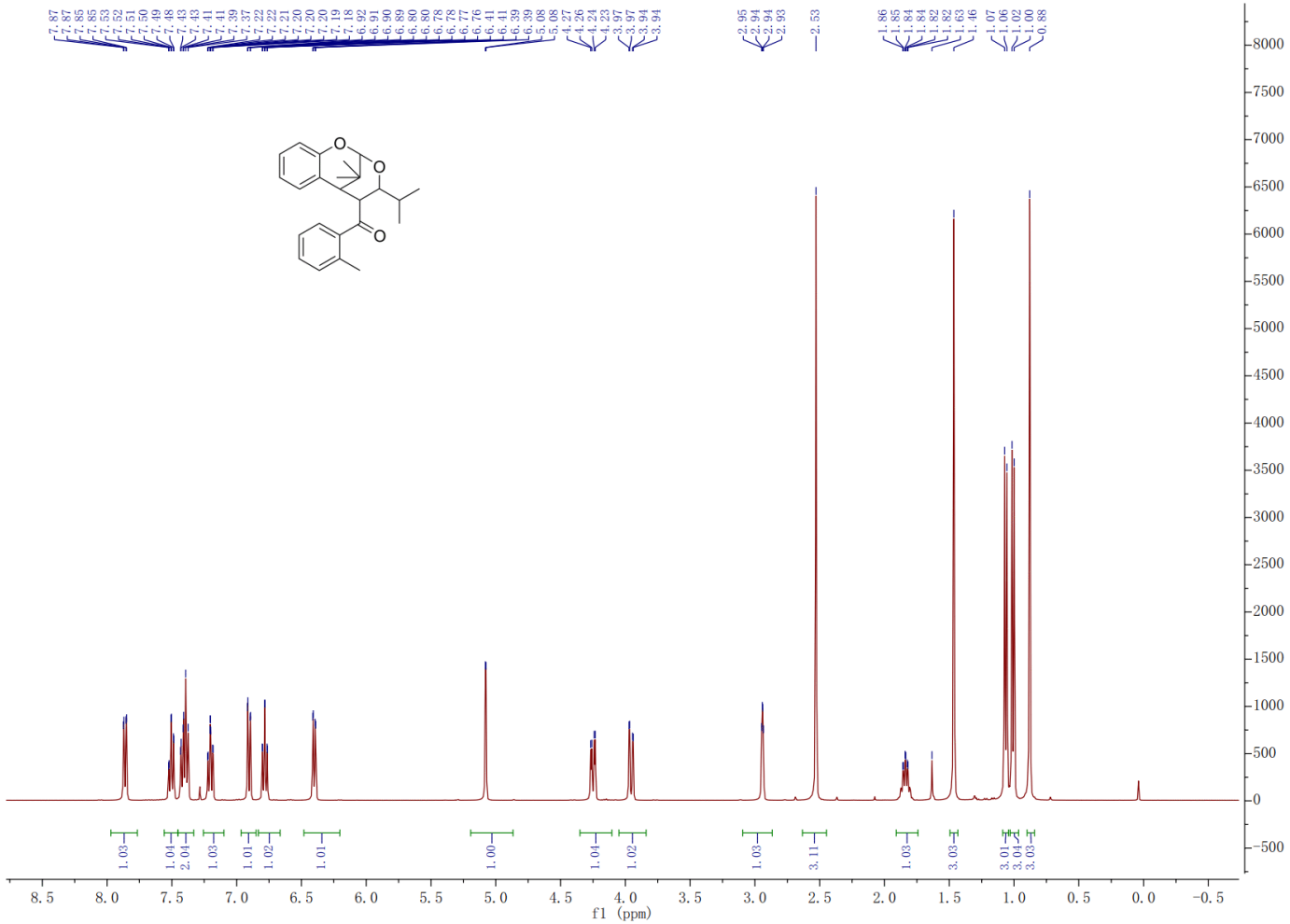

198.48
153.74
144.09
134.06
129.78
129.69
128.74
128.21
121.29
120.01
114.40
99.52
77.35
77.03
76.71
71.89
45.12
44.14
32.23
29.40
24.16
23.38
21.68
20.38
15.51
O
O
O
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

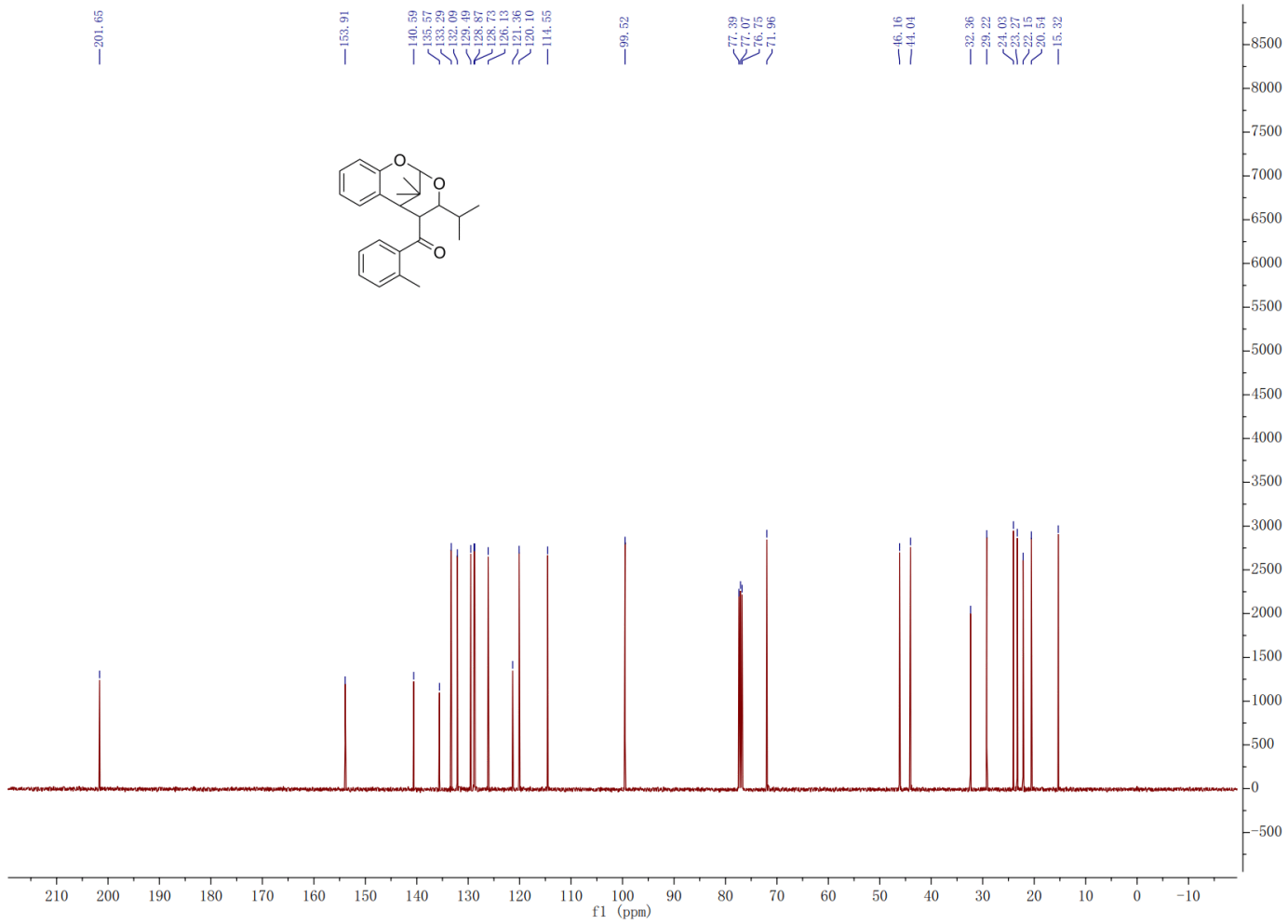
(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(4-methoxyphenyl)methanone (**3e**)



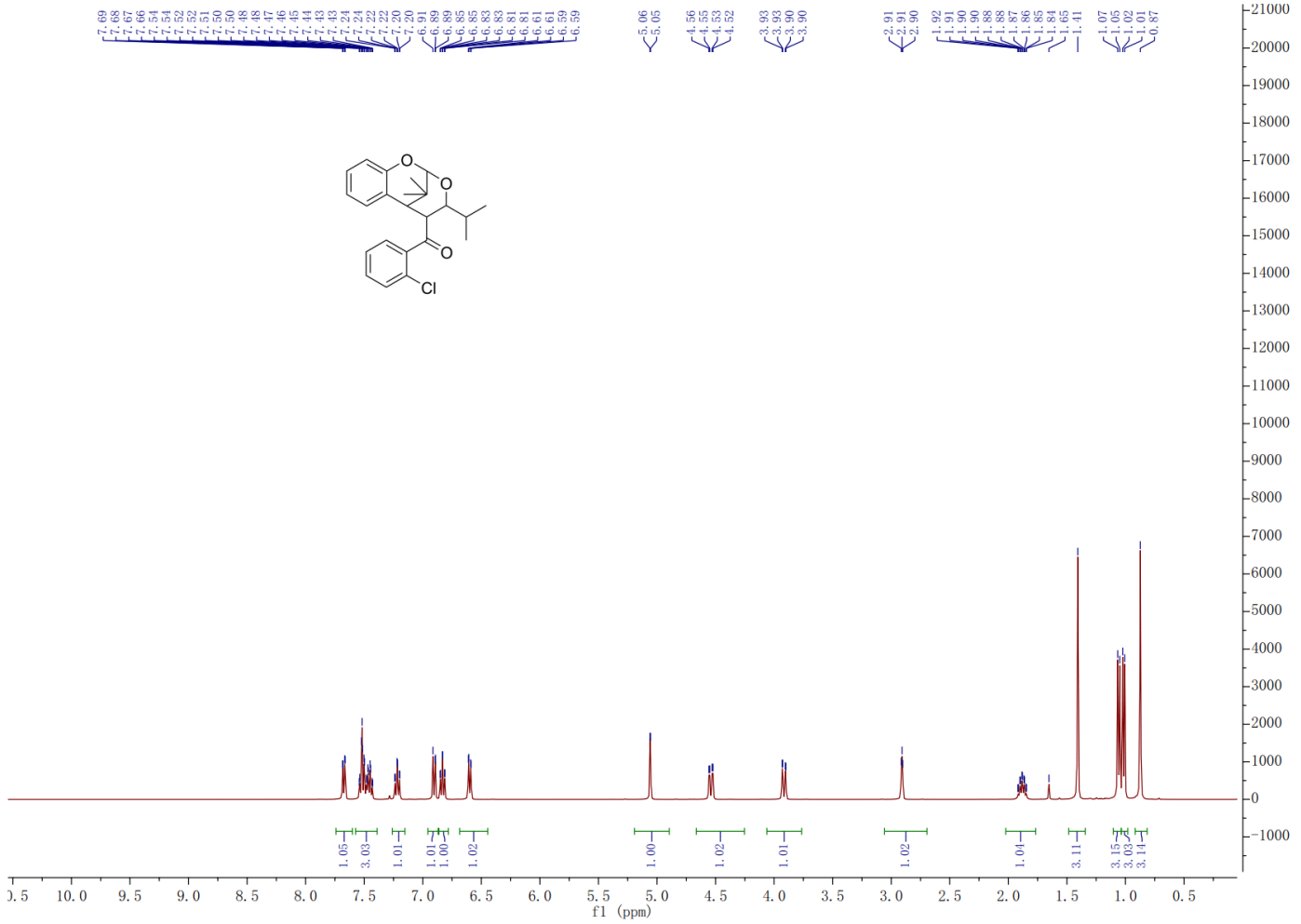

197.32
163.59
153.72
130.31
129.71
129.54
128.72
121.36
120.00
114.38
114.24
99.53
77.35
77.03
76.71
71.95
55.56
44.88
44.27
32.23
29.39
24.17
23.39
20.38
15.51
O
O
O
O
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

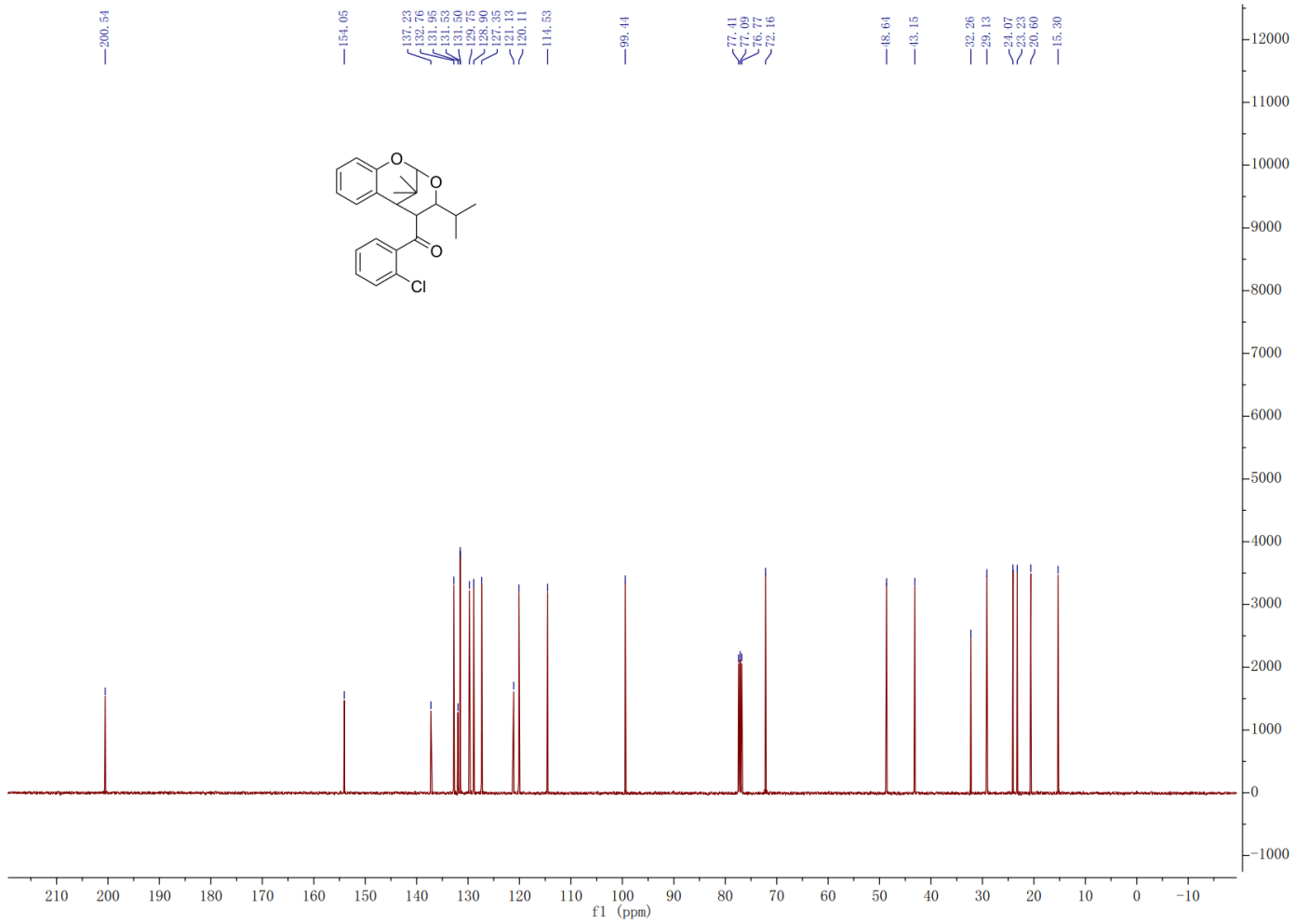
(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(o-tolyl)methanone (**3f**)



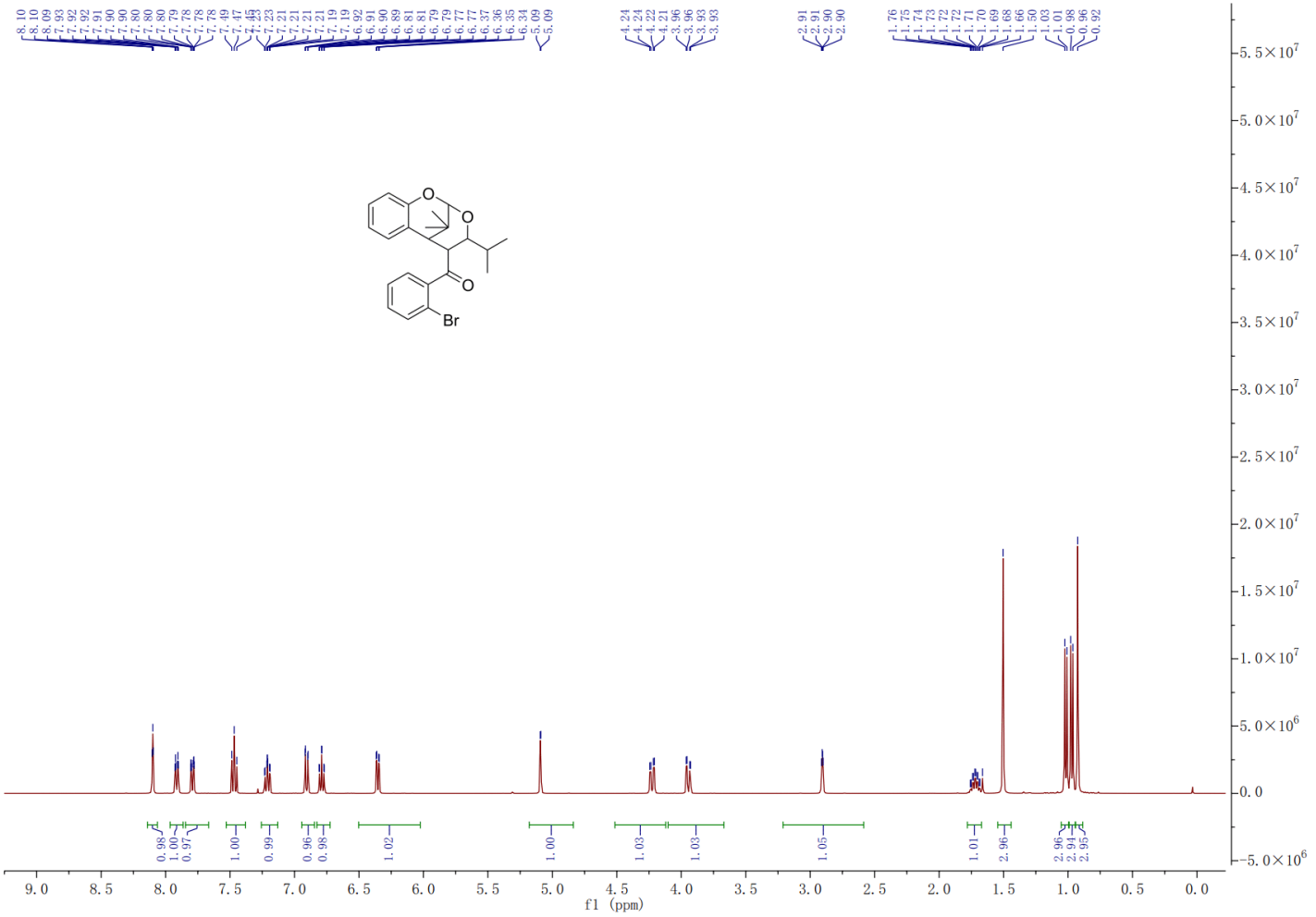

201.65
153.91
140.59
135.57
133.29
132.09
129.49
128.87
128.73
126.13
121.36
120.10
114.55
99.52
77.39
77.07
76.75
71.96
46.16
44.04
32.36
29.22
24.03
23.27
22.15
20.54
15.32
O
O
O
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

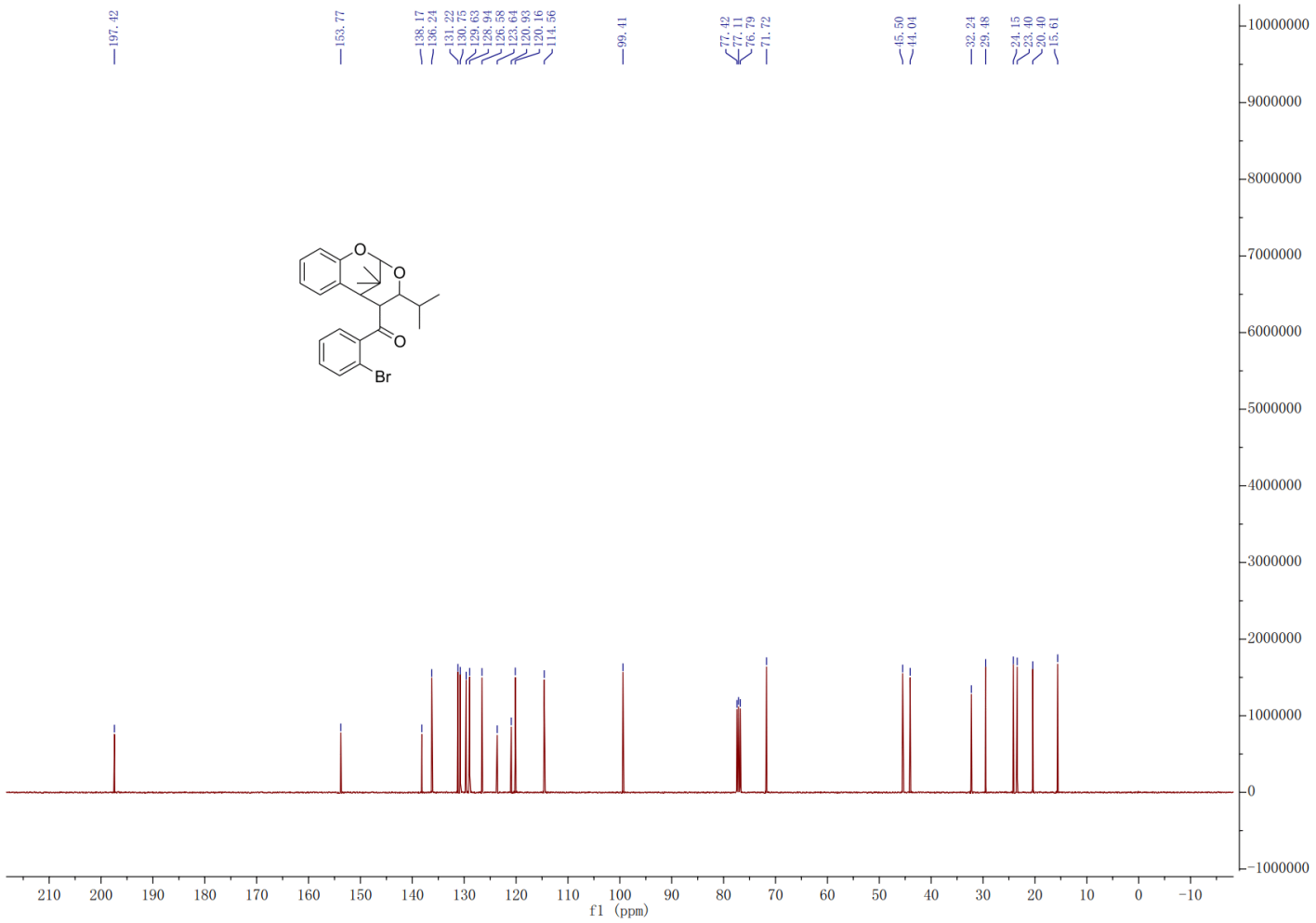
(2-chlorophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)methanone (**3g**)



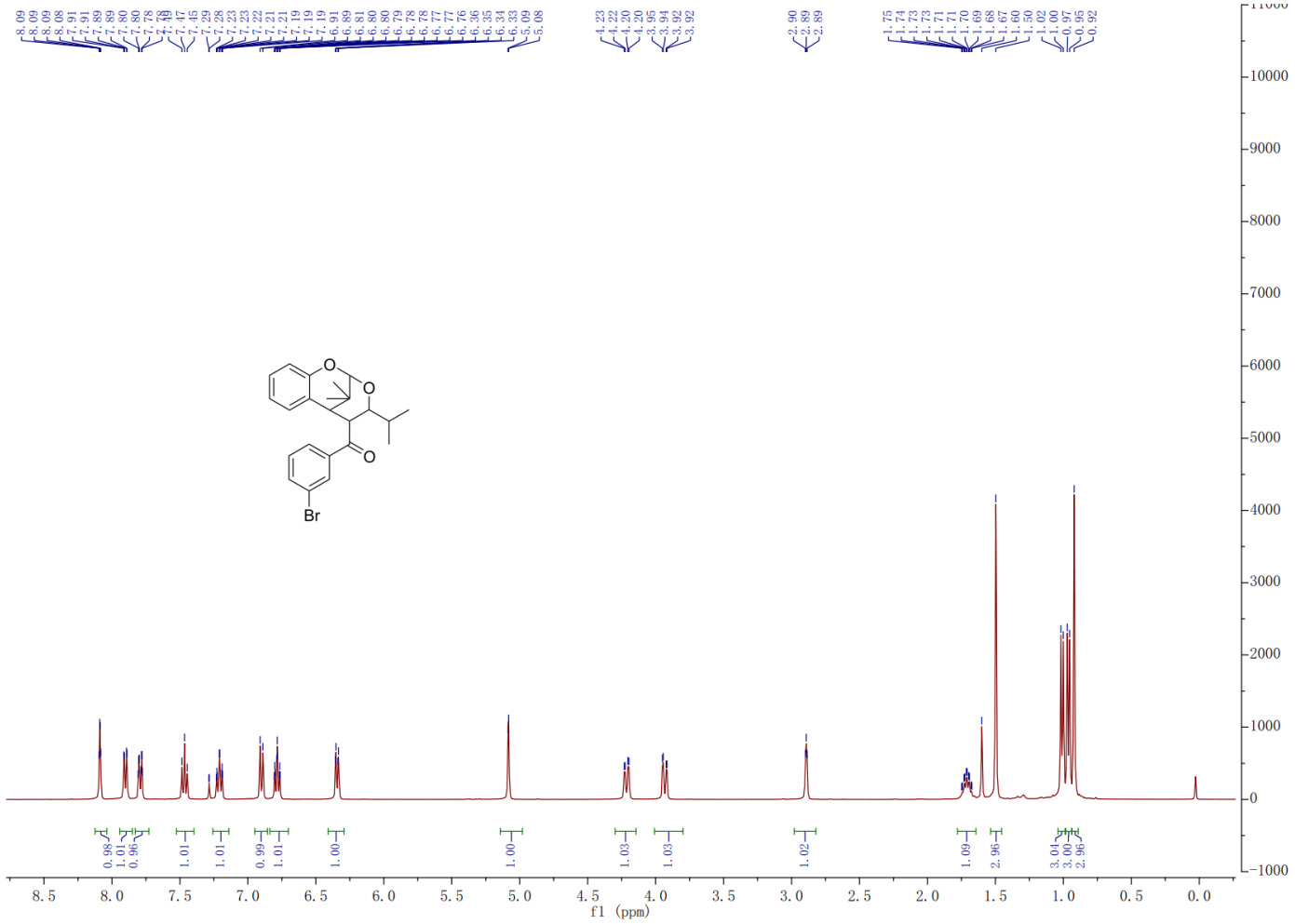

200.54
154.05
137.23
132.76
131.95
131.53
131.50
129.75
128.90
127.35
121.13
120.11
114.53
99.44
77.41
77.09
76.77
72.16
48.64
43.15
32.26
29.13
24.07
23.23
20.60
15.30
O
O
O
Cl
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

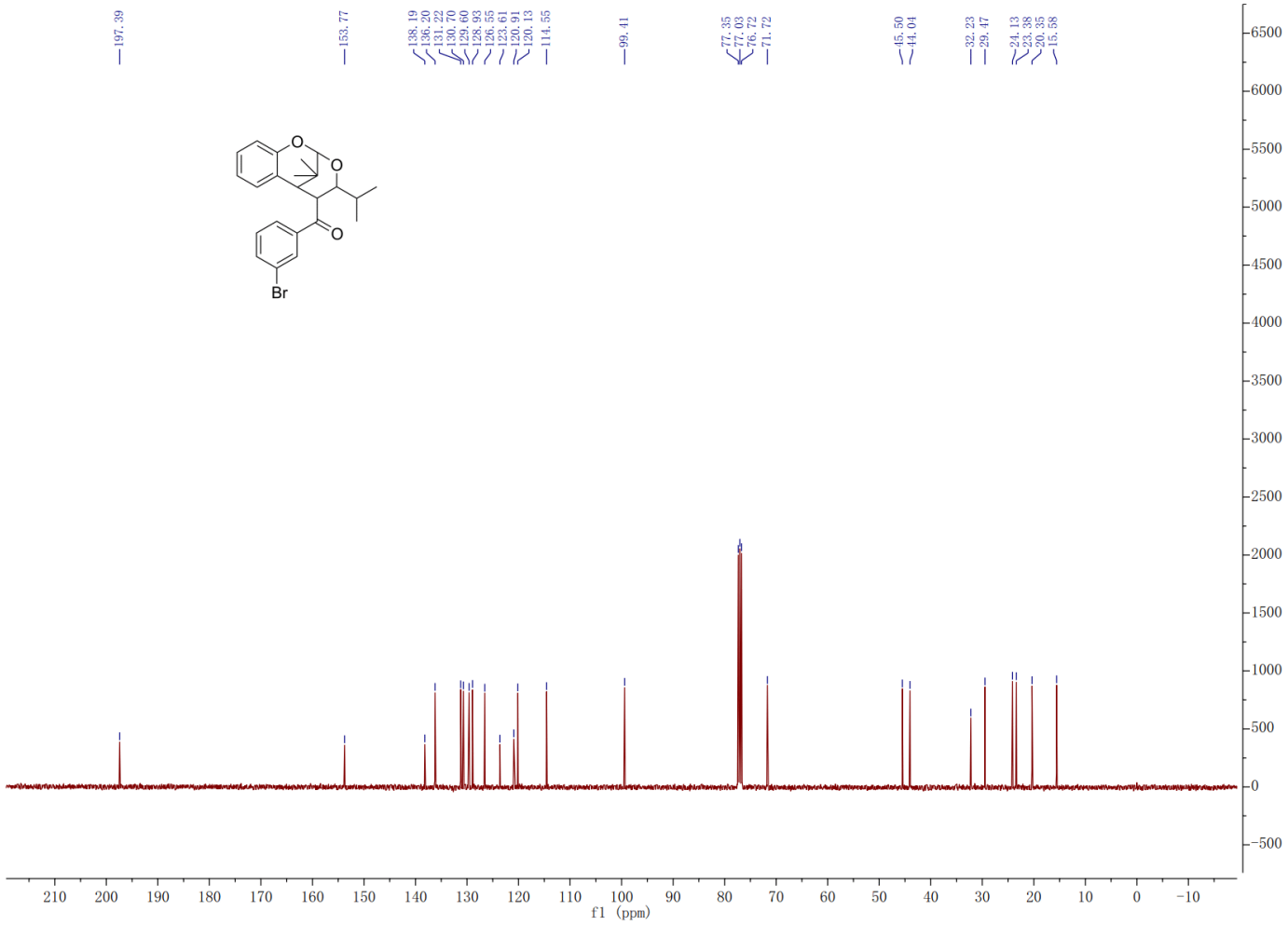
(2-bromophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)methanone (**3h**)



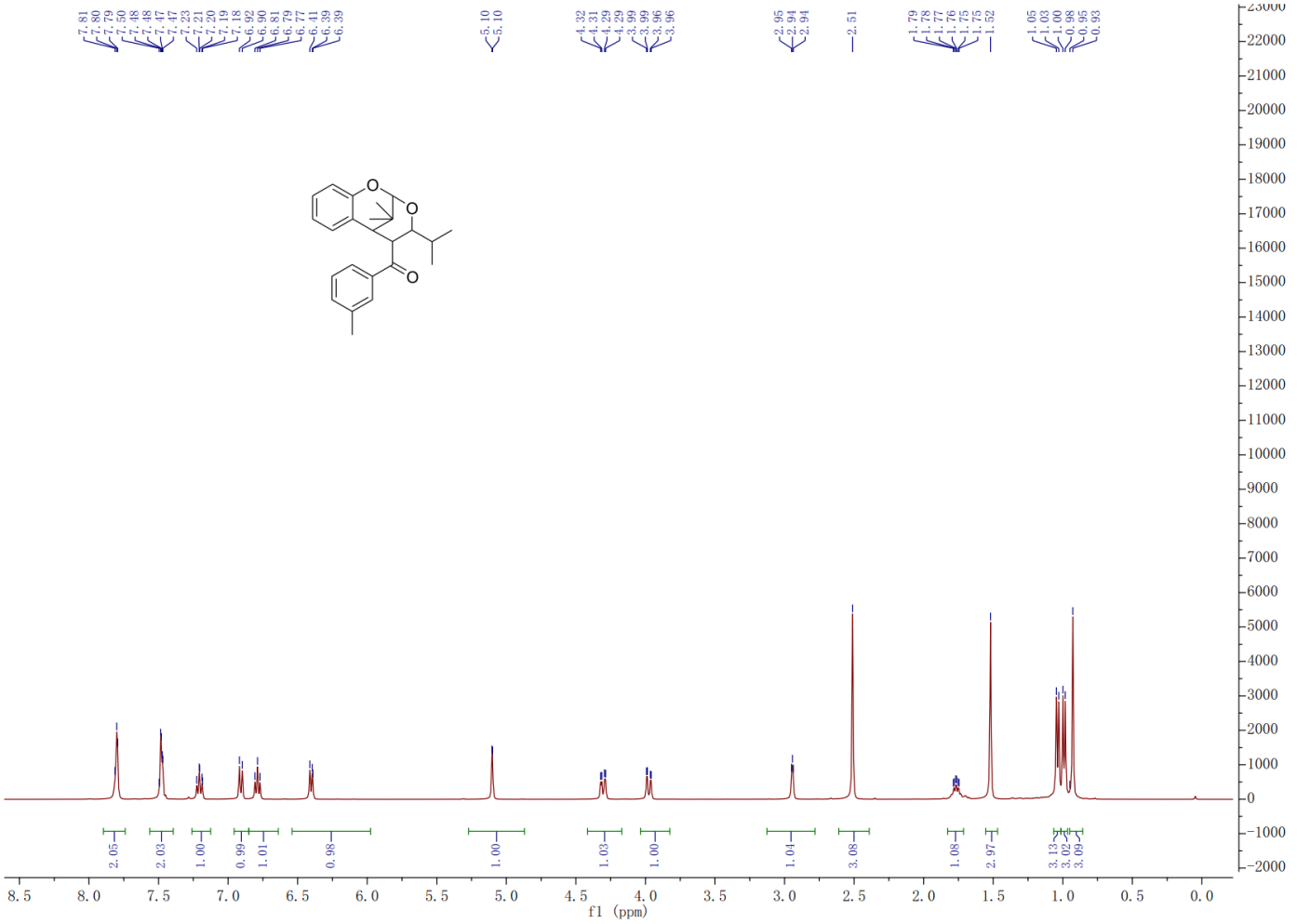

197.42
153.77
138.17
136.24
131.22
130.75
129.63
128.94
126.58
123.64
120.93
120.16
114.56
99.41
77.42
77.11
76.79
71.72
45.50
44.04
32.24
29.48
24.15
23.40
20.40
15.61
O
O
O
Br
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

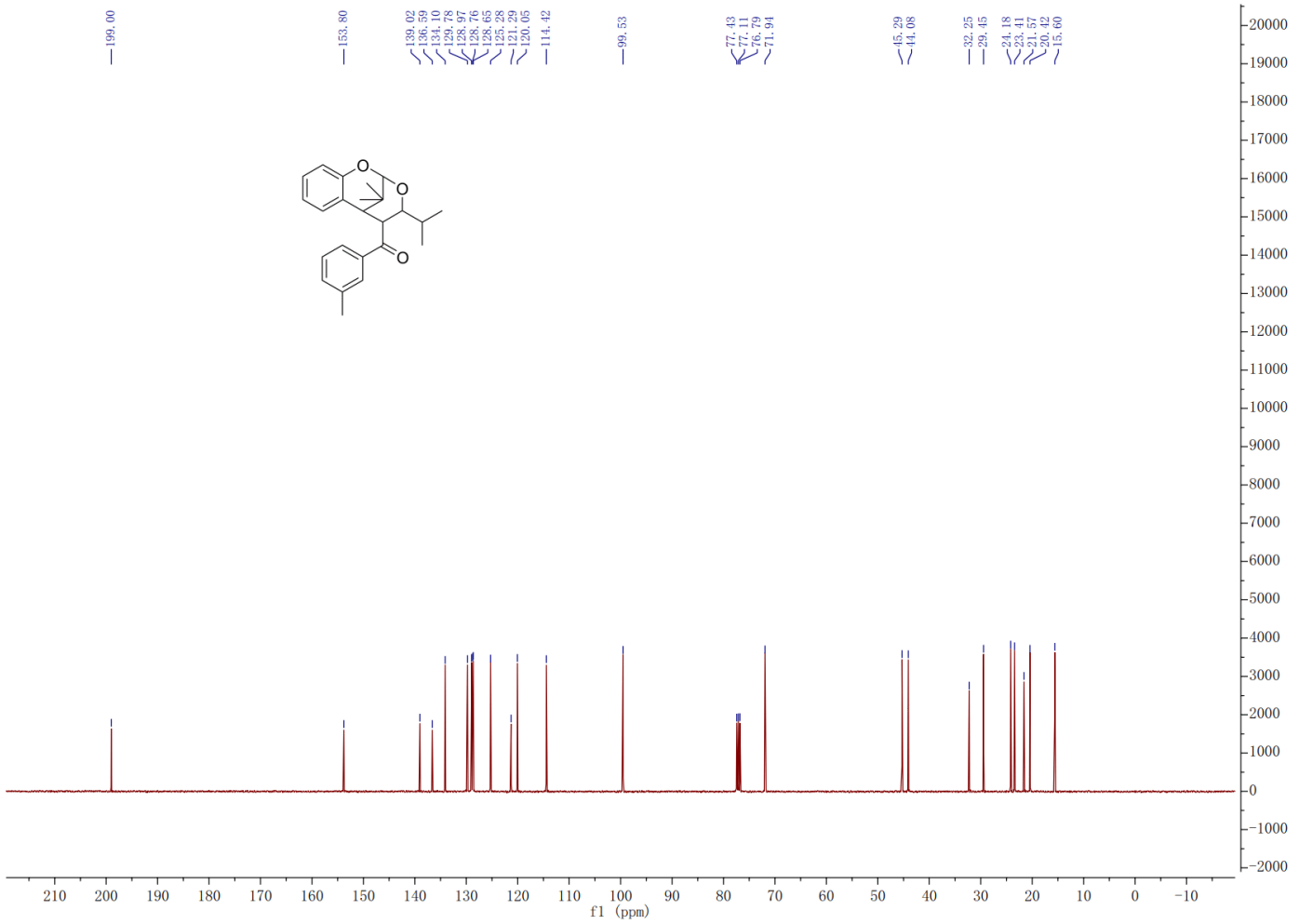
(3-bromophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)methanone (**3i**)



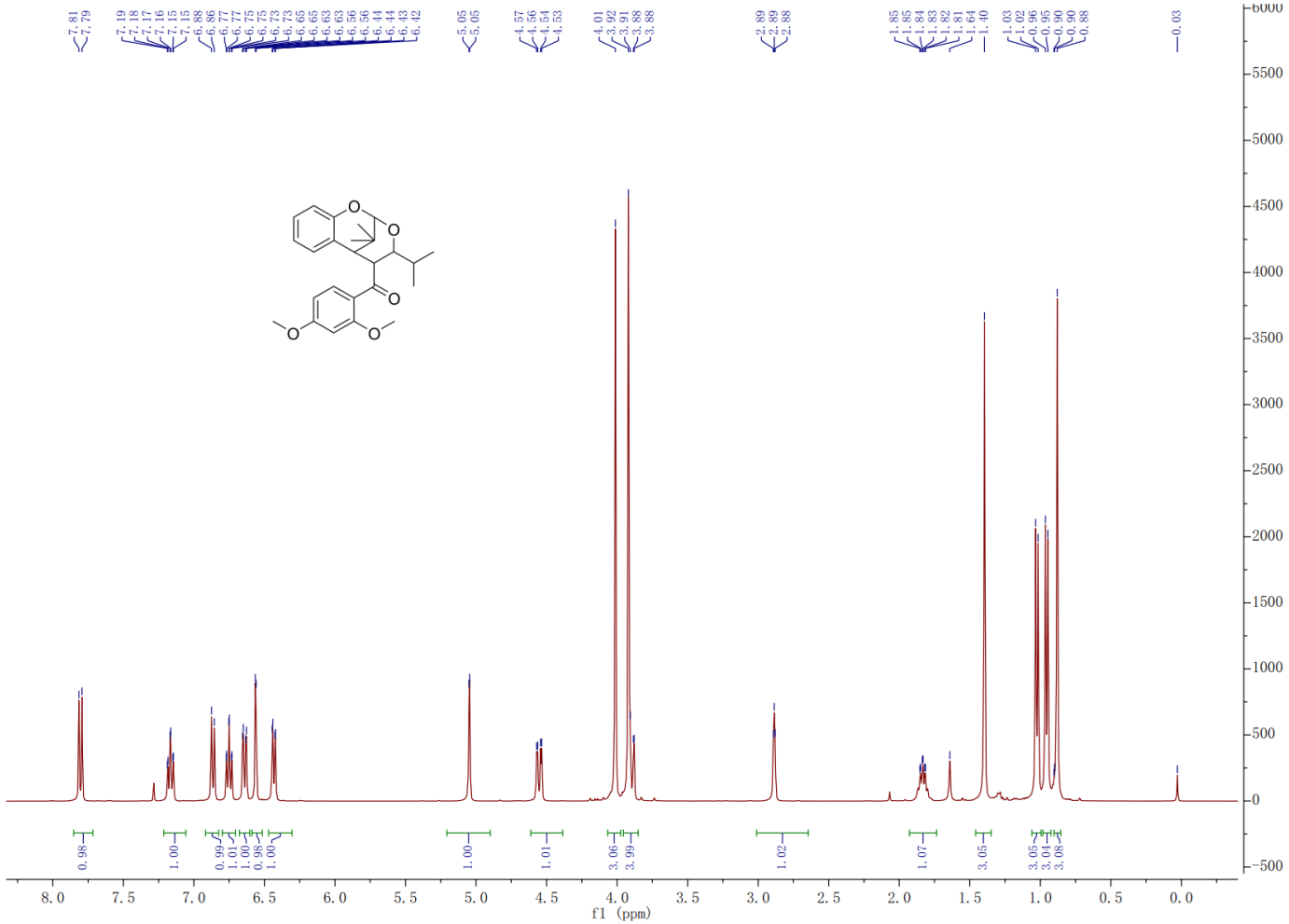

197.39
153.77
138.19
136.20
131.22
130.70
129.60
128.93
126.55
123.61
120.91
120.13
114.55
99.41
77.35
77.03
76.72
71.72
45.50
44.04
32.23
29.47
24.13
23.38
20.35
15.58
O
O
O
Br
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

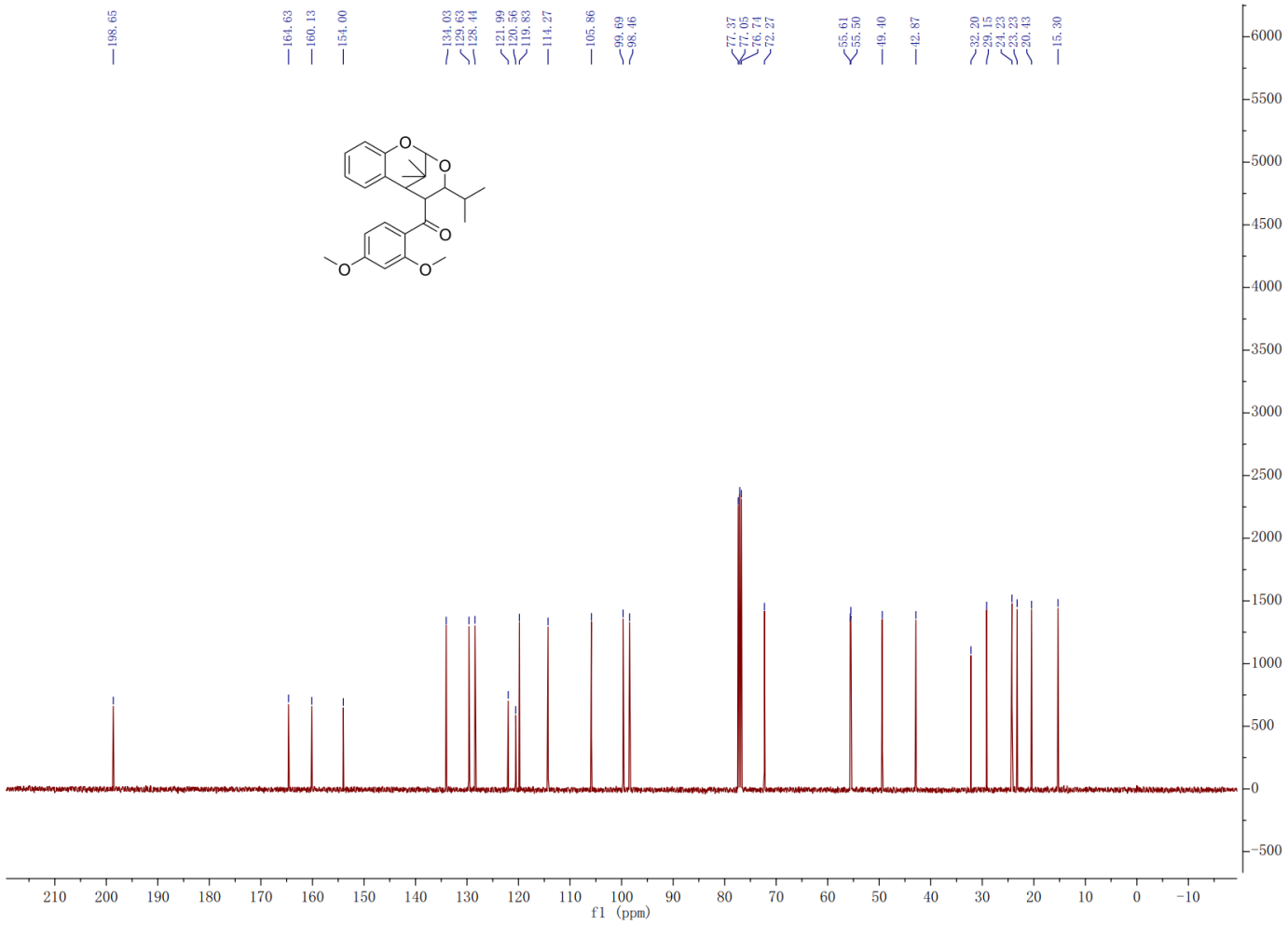
(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(m-tolyl)methanone (**3j**)



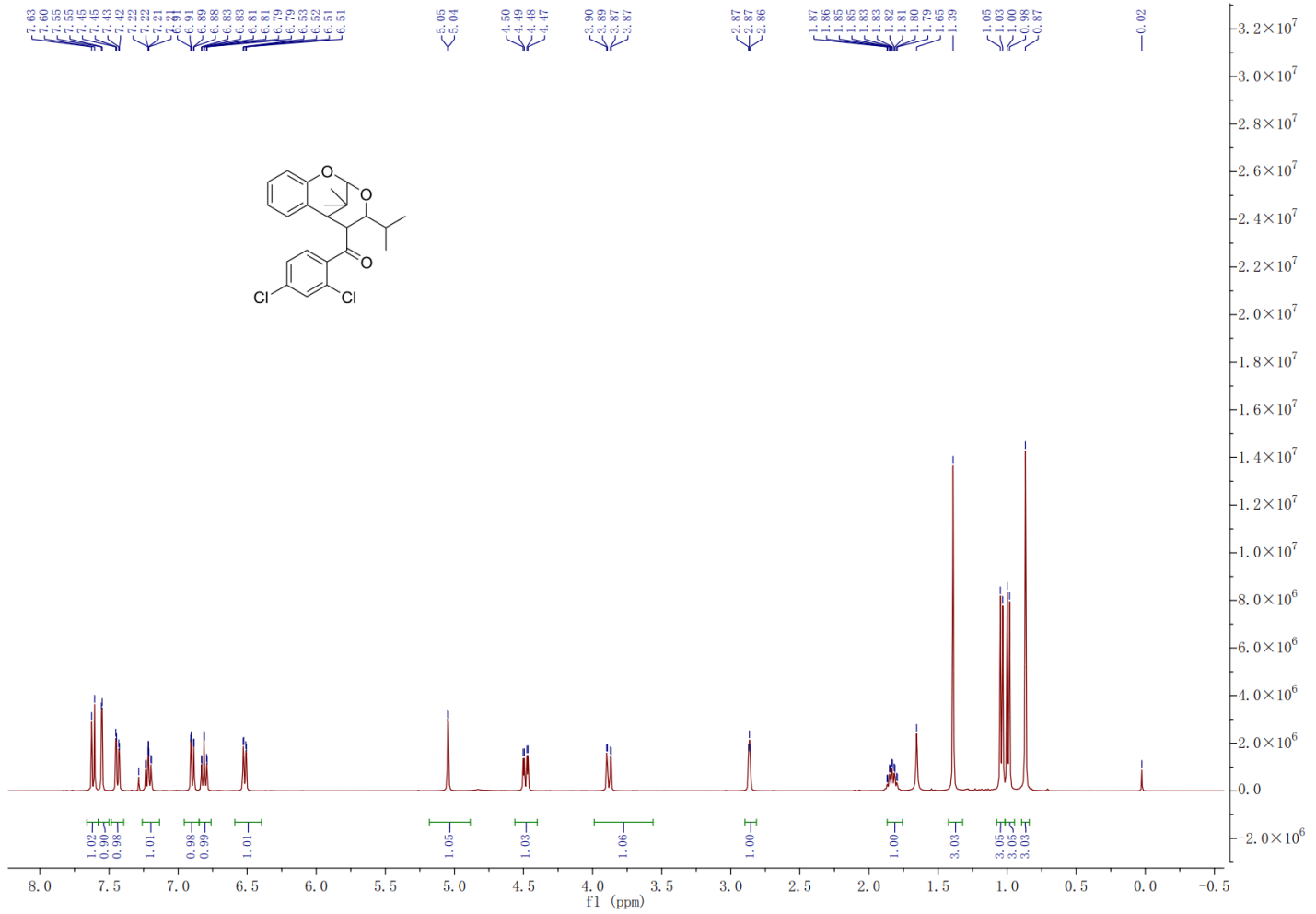

199.00
153.80
139.02
136.59
134.10
129.78
128.97
128.76
128.65
125.28
121.29
120.05
114.42
99.53
77.43
77.11
76.79
71.94
45.29
44.08
32.25
29.45
24.18
23.41
21.57
20.42
15.60
O
O
O
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
−1000
−2000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

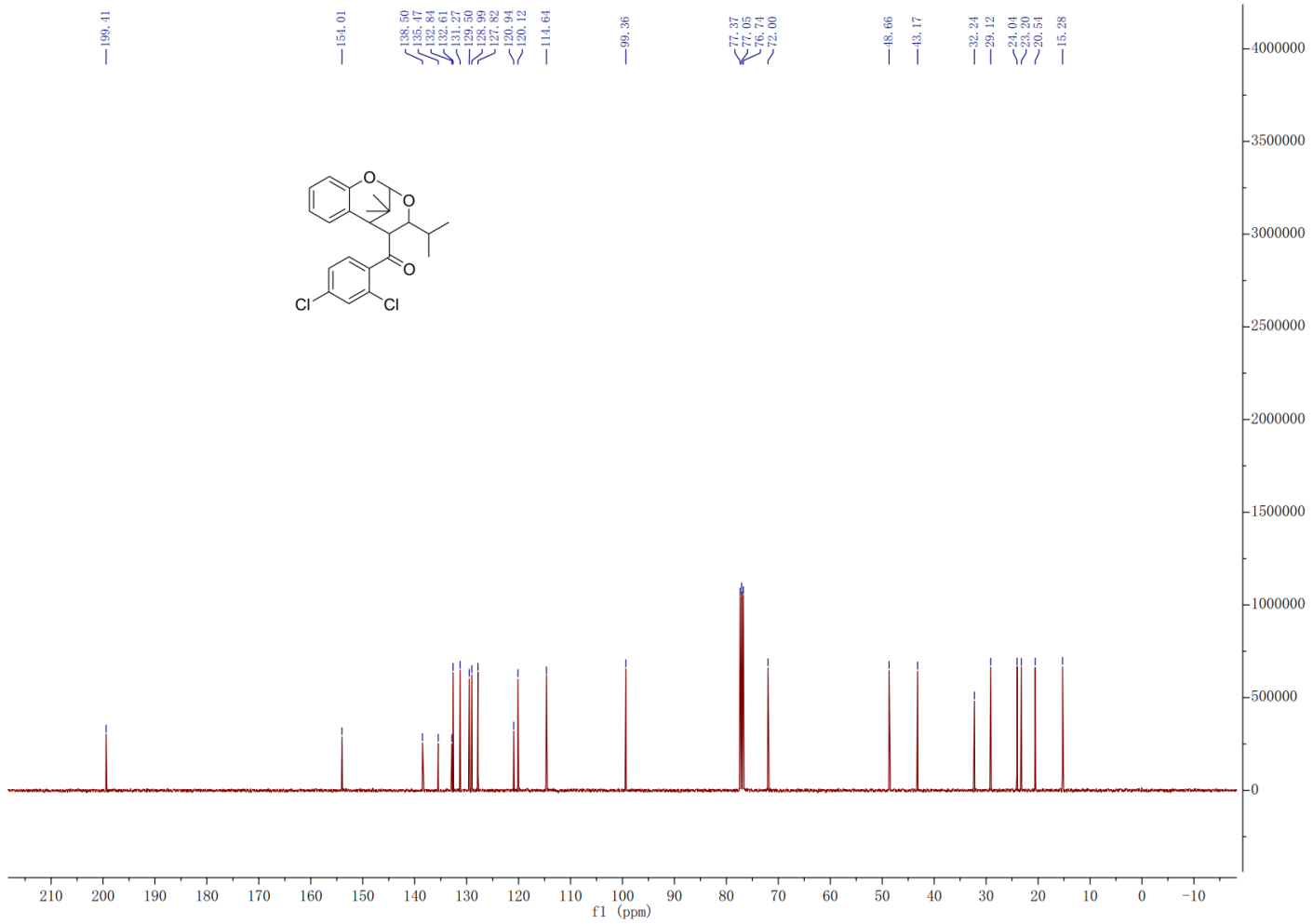
(2,4-dimethoxyphenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)methanone (**3k**)



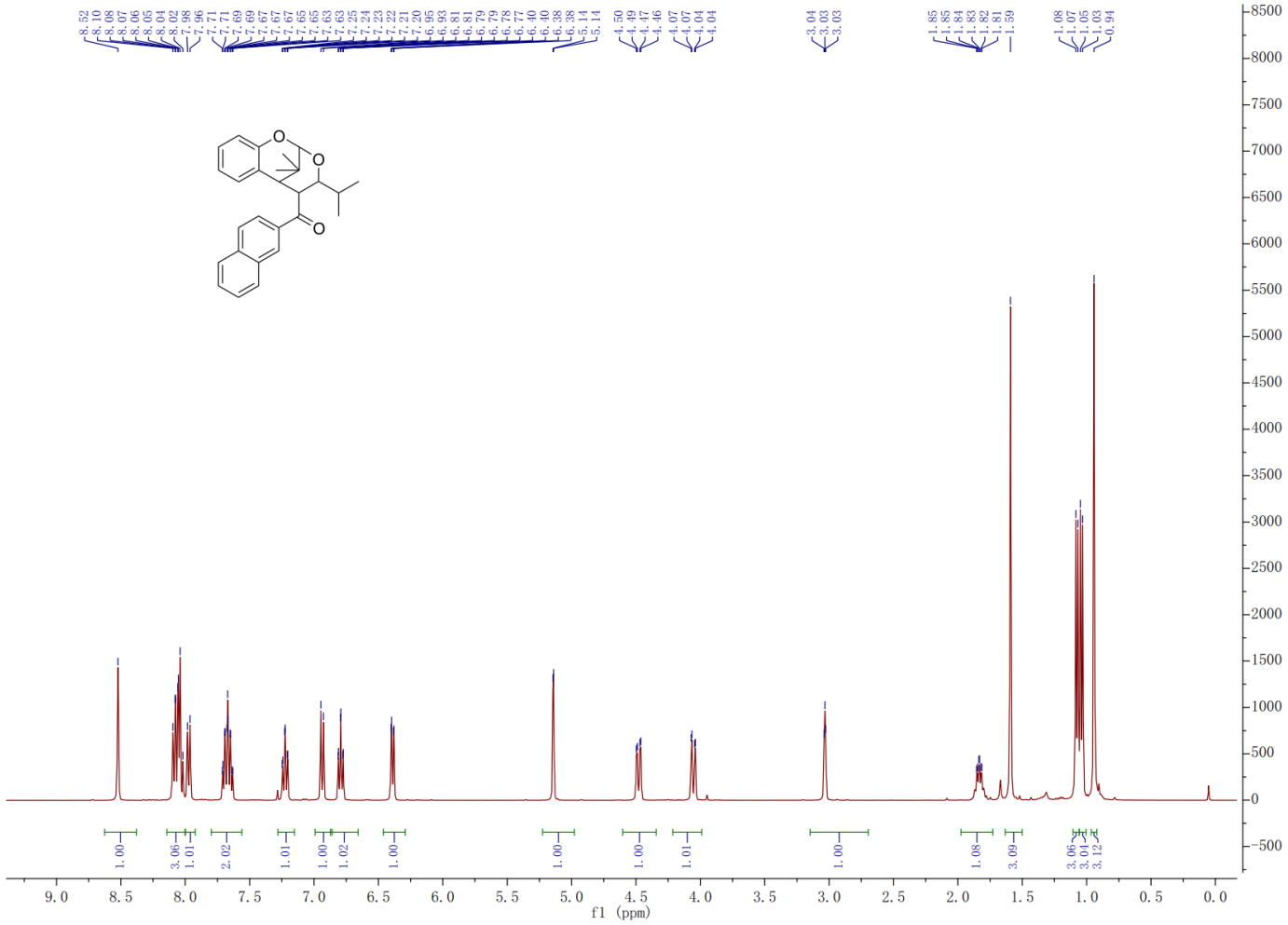

198.65
164.63
160.13
154.00
134.03
129.63
128.44
121.99
120.56
119.83
114.27
105.86
99.69
98.46
77.37
77.05
76.74
72.27
55.61
55.50
49.40
42.87
32.20
29.15
24.23
23.23
20.43
15.30
O
O
O
O
O
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

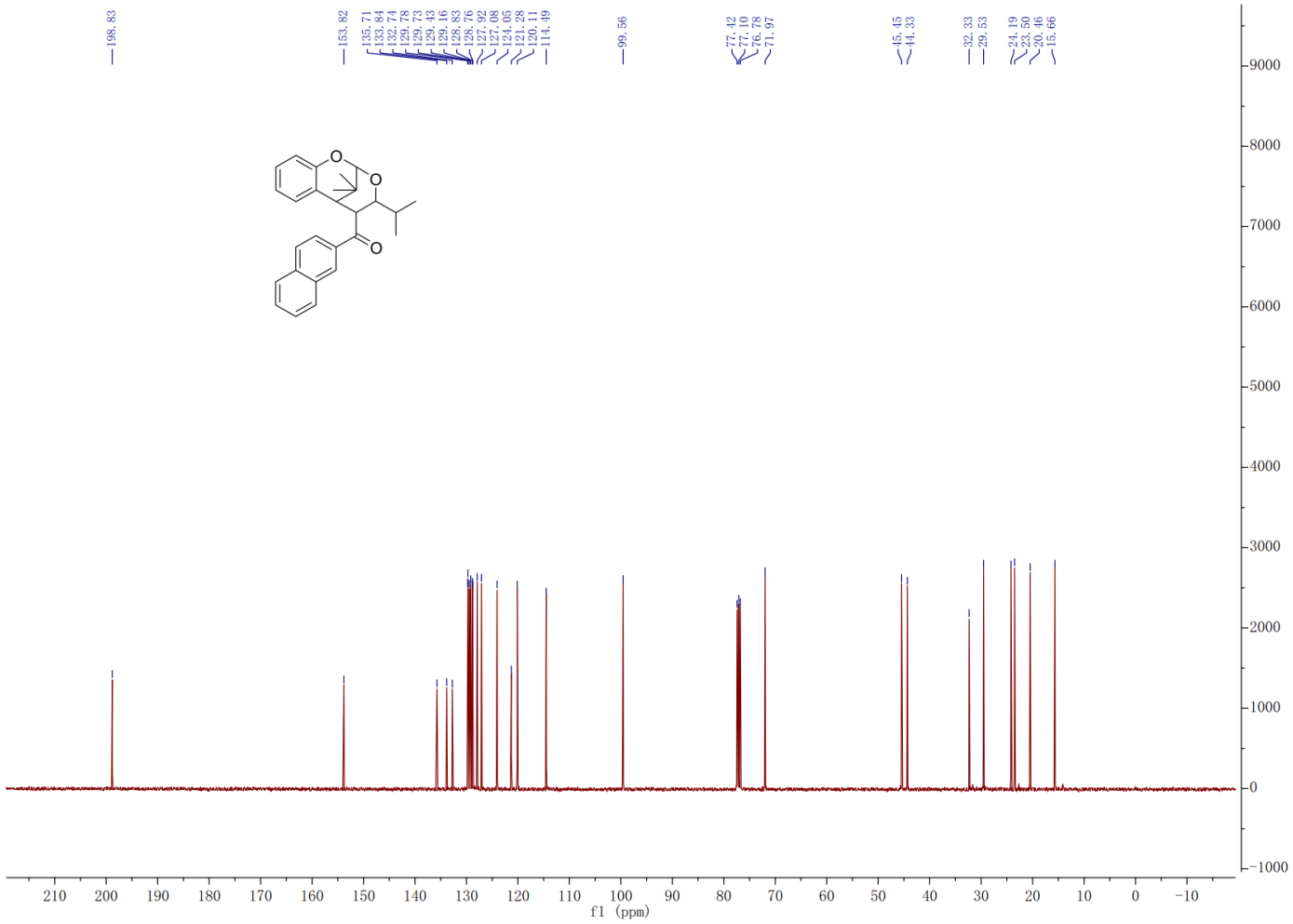
(2,4-dichlorophenyl)(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)methanone (**3l**)



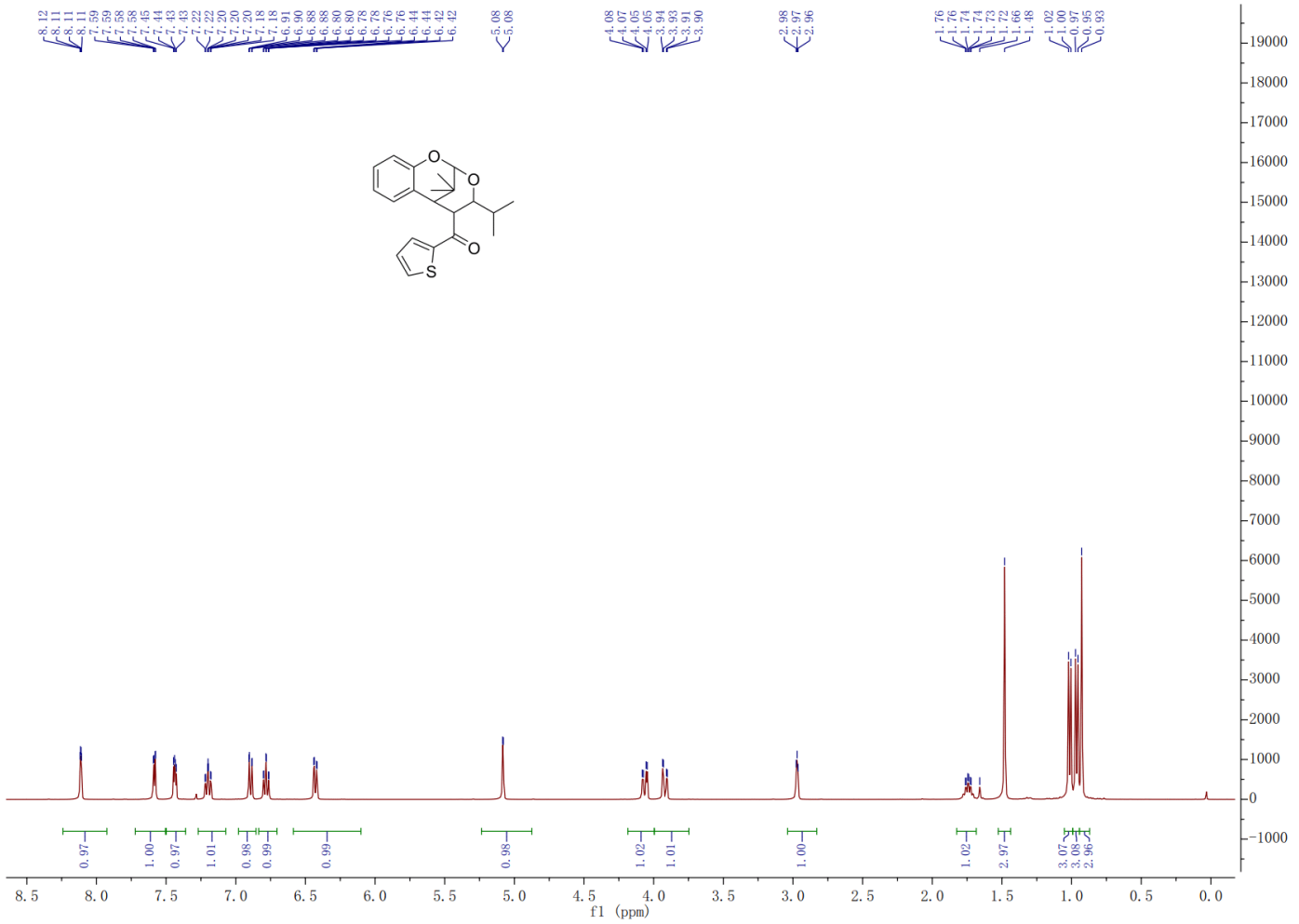

199.41
154.01
138.50
135.47
132.84
132.61
131.77
130.50
128.99
127.82
120.94
120.12
114.64
99.36
77.37
77.05
76.74
72.00
48.66
43.17
32.24
29.12
24.04
23.20
20.54
15.28
O
O
O
Cl
Cl
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

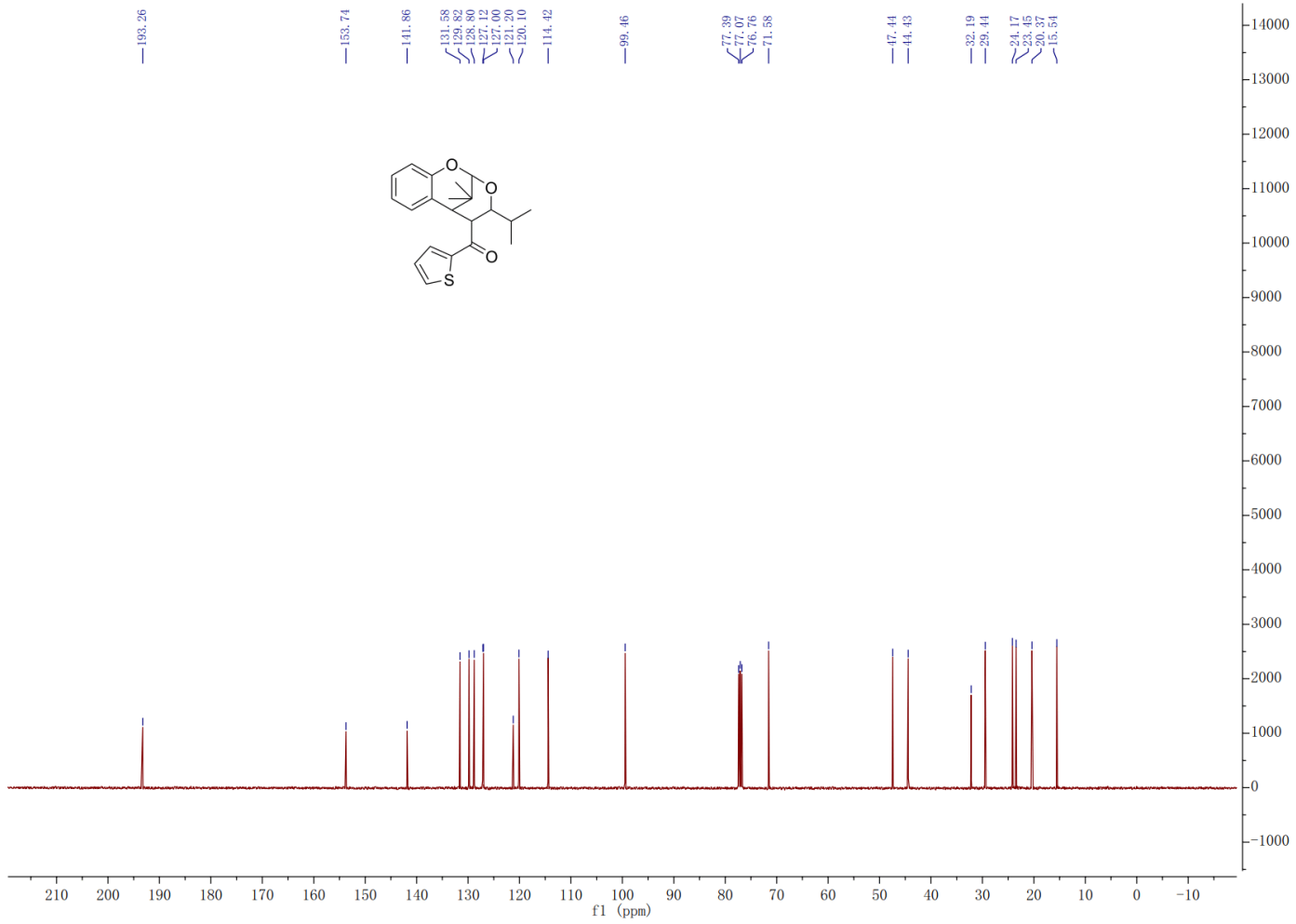
(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(naphthalen-2-yl)methanone (**3m**)



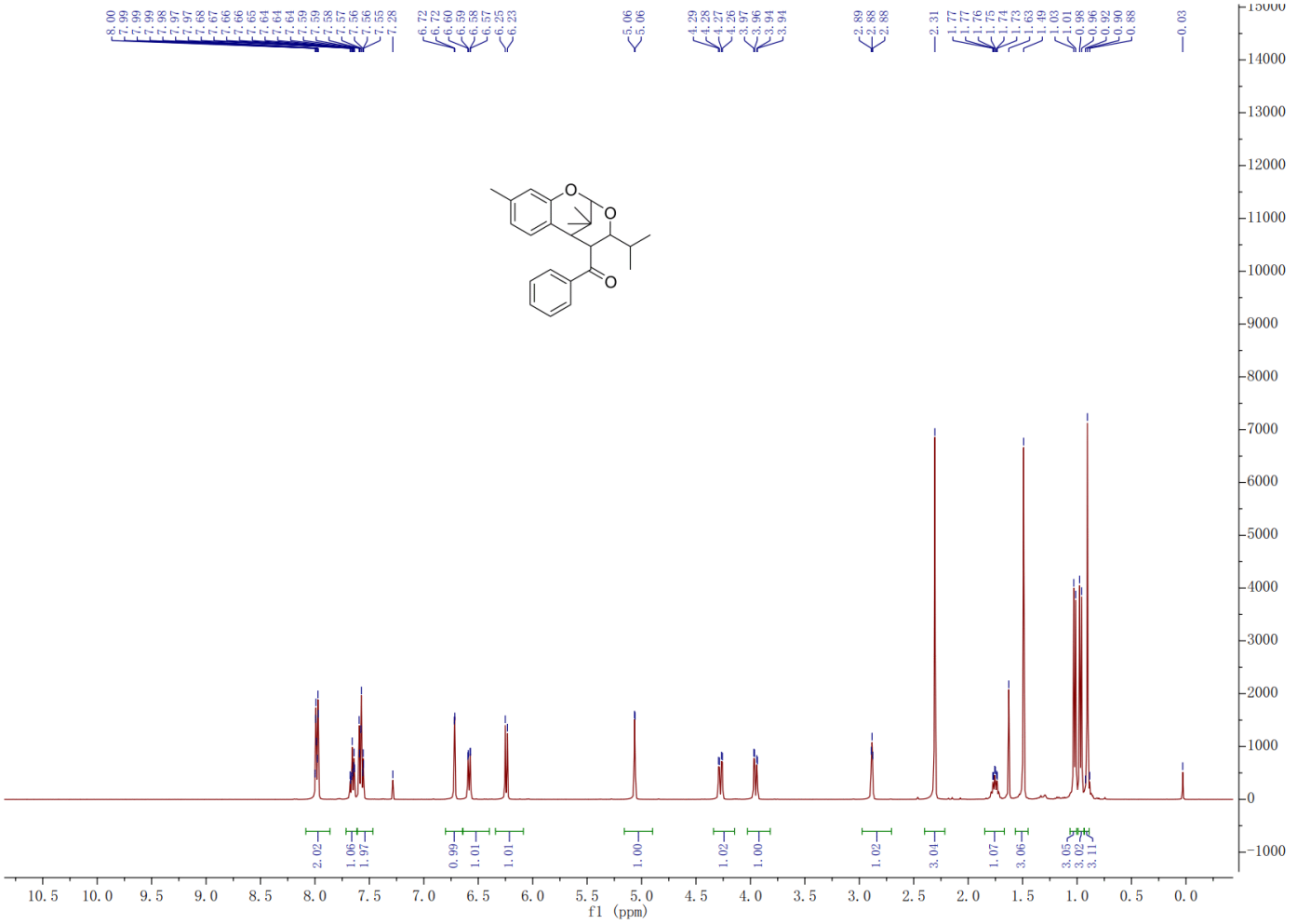

198.83
153.82
135.71
133.84
132.74
129.78
129.73
129.43
129.16
128.83
128.76
127.92
127.08
124.05
121.28
120.11
114.49
99.56
77.42
77.10
76.78
71.97
45.45
44.33
32.33
29.53
24.19
23.50
20.46
15.66
O
O
O
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

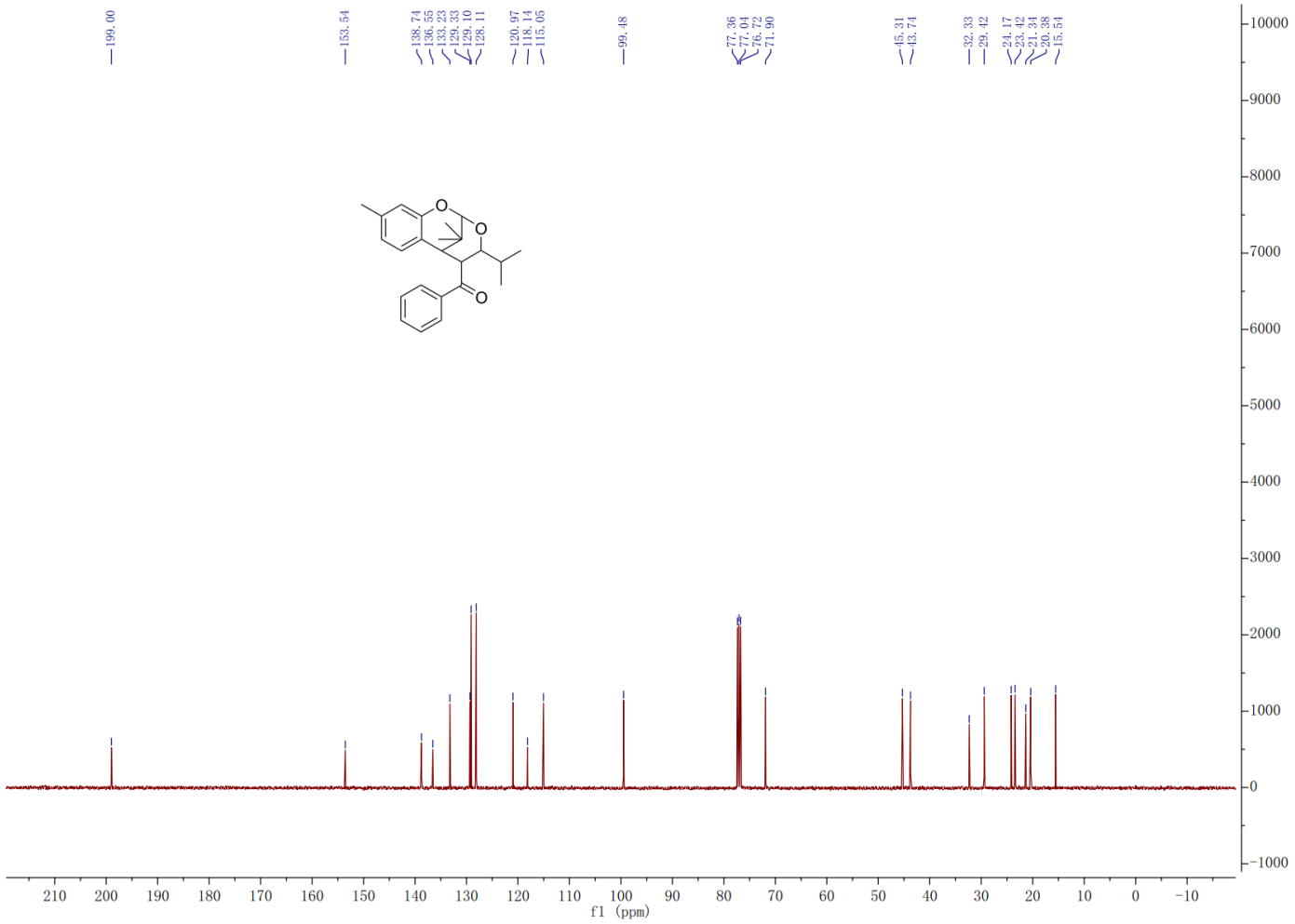
(4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(thiophen-3-yl)methanone (**3n**)



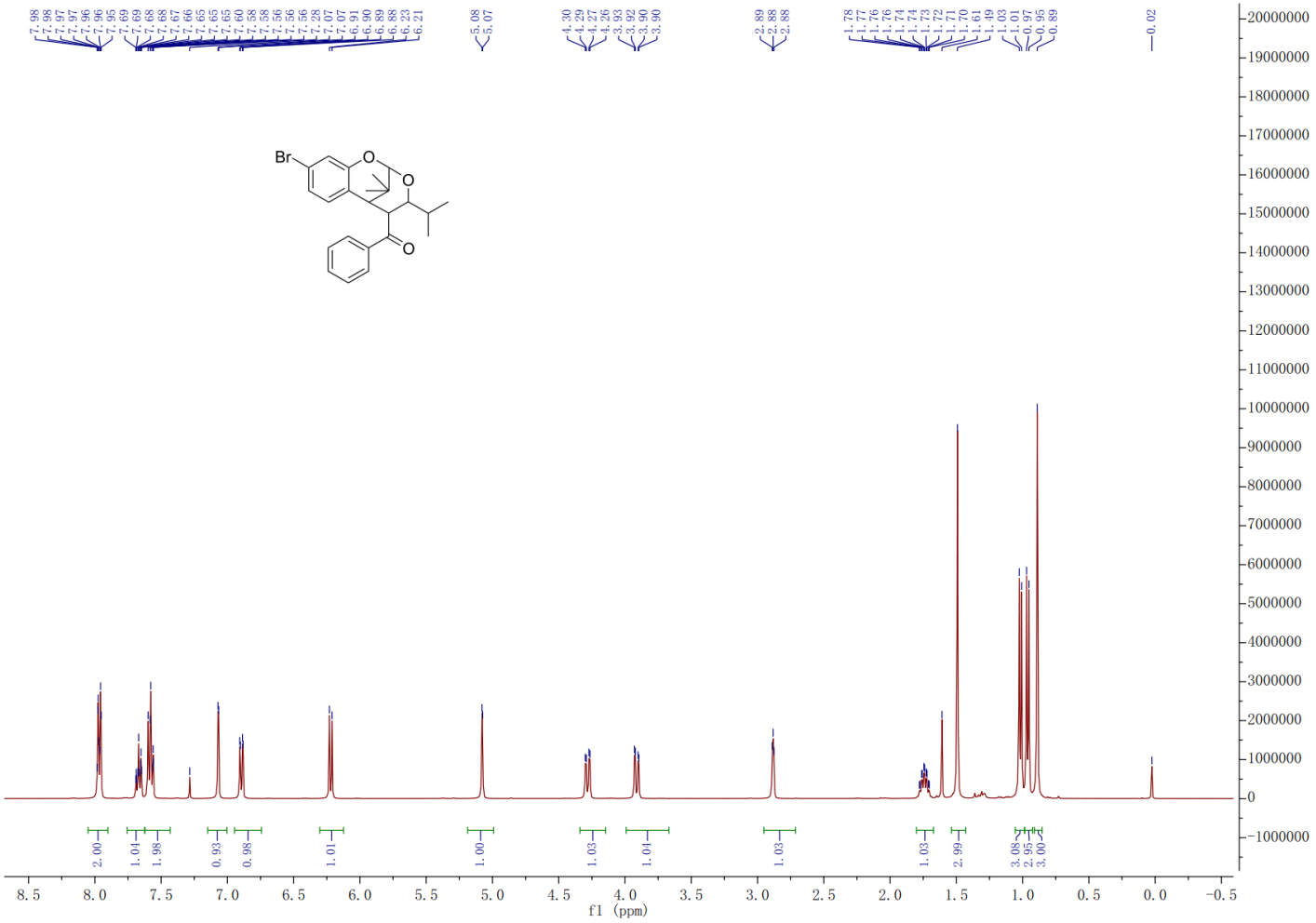

193.26
153.74
141.86
131.58
129.82
128.80
127.12
127.00
121.20
120.10
114.42
99.46
77.39
77.07
76.76
71.58
47.44
44.43
32.19
29.44
24.17
23.45
20.37
15.54
O
O
O
S
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

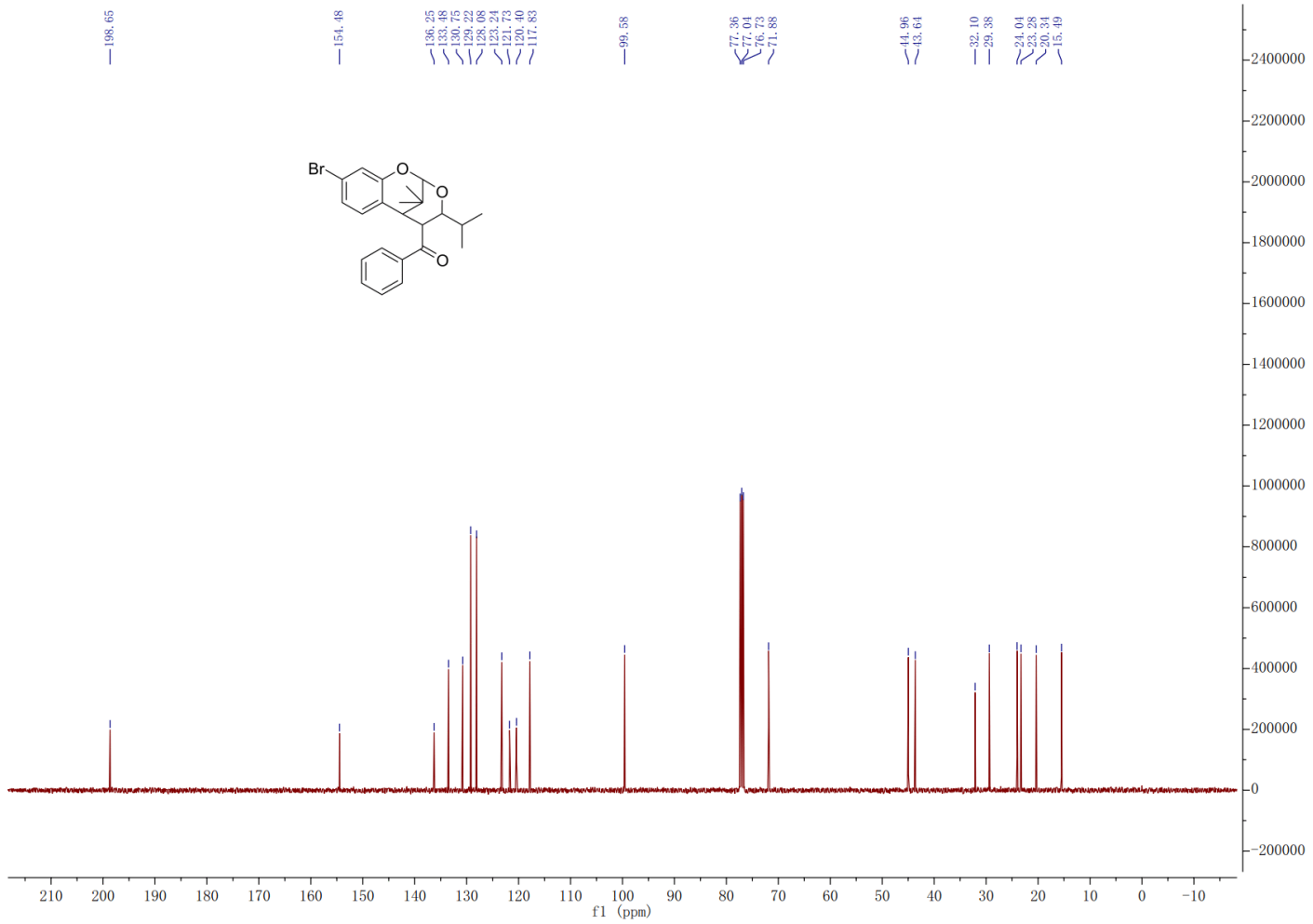
(4-isopropyl-9,11,11-trimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(phenyl)methanone (**3o**)



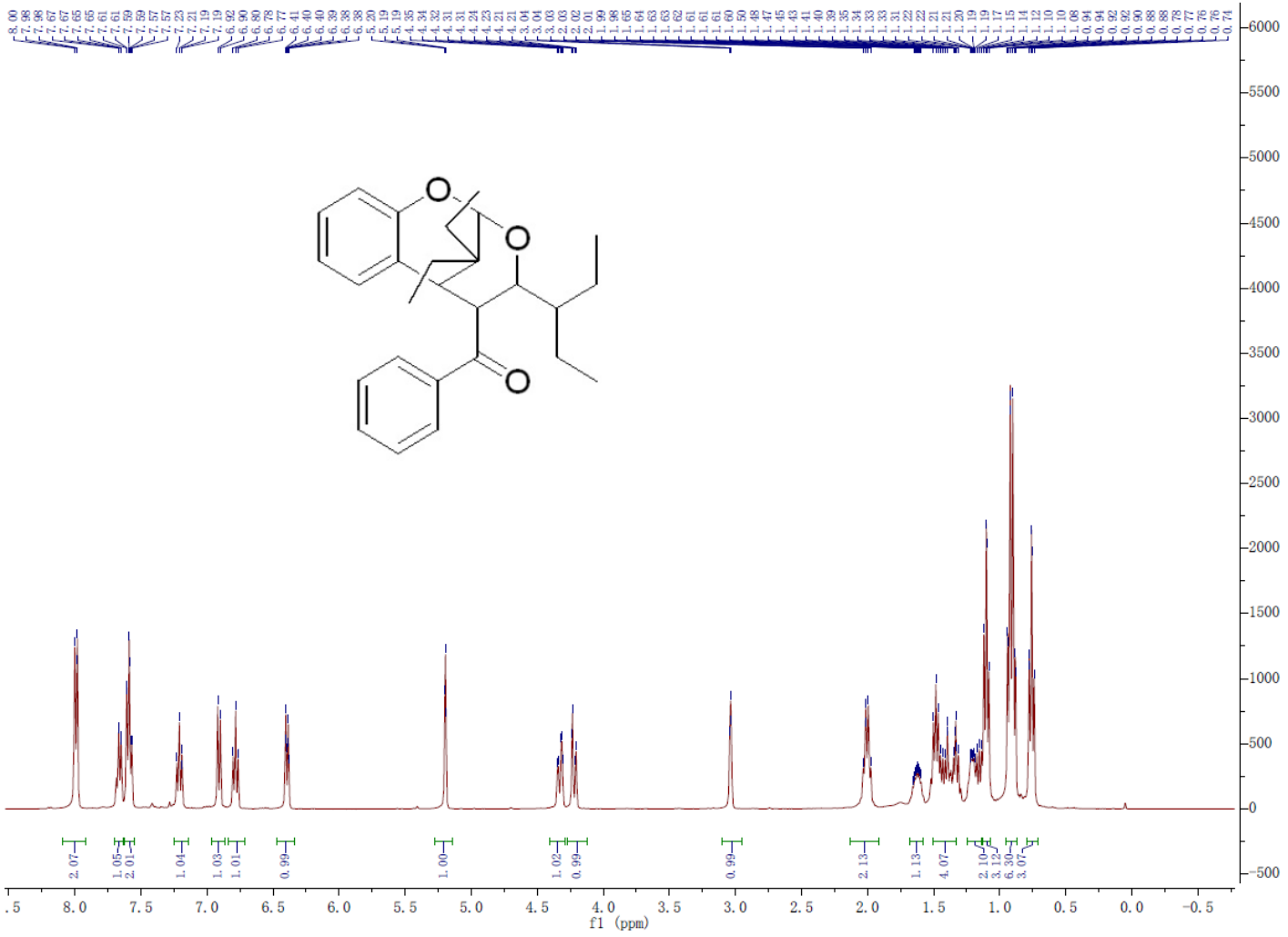

199.00
153.54
138.74
136.55
133.23
129.33
129.10
128.11
120.97
118.14
115.05
99.48
77.36
77.04
76.72
71.90
45.31
43.74
32.33
29.42
24.17
23.42
21.34
20.38
15.54
O
O
O
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

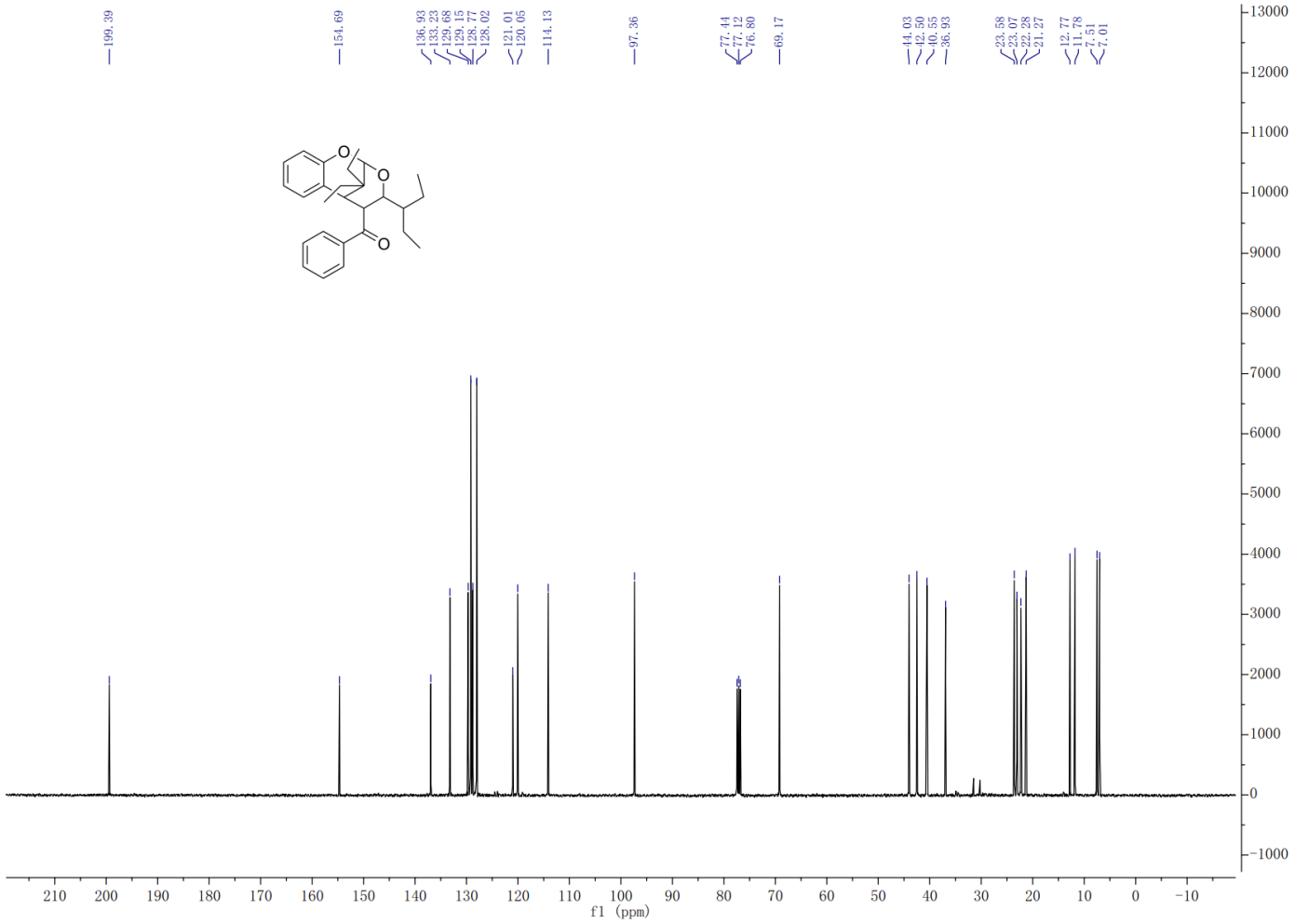
(9-bromo-4-isopropyl-11,11-dimethyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(phenyl)methanone (**3p**)




198.65
154.48
136.25
133.48
130.75
130.22
128.68
123.24
121.73
120.40
117.83
99.58
77.36
77.04
76.73
71.88
44.96
43.64
32.10
29.38
24.04
23.28
20.34
15.49
Br
O
O
O
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(11,11-diethyl-4-isopropyl-5,6-dihydro-4H-2,6-methanobenzo[d][1,3]dioxocin-5-yl)(phenyl)methanone (**3q**)

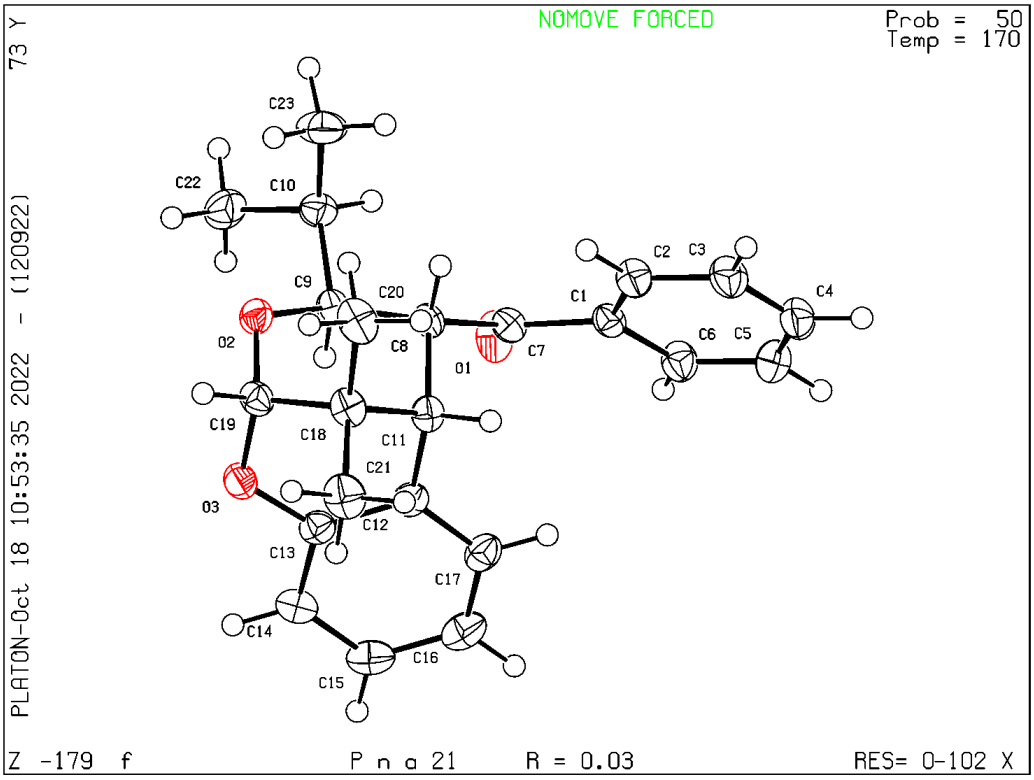



199.39
154.69
136.93
133.23
129.68
129.15
128.77
128.02
121.01
120.05
114.13
97.36
77.44
77.12
76.80
69.17
44.03
42.50
40.55
36.93
23.58
23.07
22.28
21.27
12.77
11.78
7.51
7.01
O
O
O
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

5. X-Ray of **3a**

Table 1Crystal data and structure refinement for 3a

Identification code	**3a**
Empirical formula	$C_{23}H_{26}O_3$
Formula weight	350.44
Temperature/K	169.99(10)
Crystal system	orthorhombic
Space group	$Pna2_1$
a/Å	14.8060(3)
b/Å	10.0952(2)
c/Å	12.6164(2)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1885.77(6)
Z	4
ρ_{calc}g/cm^3	1.234
μ/mm^{-1}	0.636
F(000)	752.0
Crystal size/mm^3	0.13 × 0.1 × 0.08
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	10.606 to 147.72
Index ranges	$-18 \leq h \leq 17$, $-7 \leq k \leq 12$, $-15 \leq l \leq 15$
Reflections collected	6459
Independent reflections	3263 [R_{int}= 0.0252, R_{sigma}= 0.0271]
Data/restraints/parameters	3263/1/239
Goodness-of-fit on F^2	1.040
Final R indexes [I>=2σ (I)]	R_1= 0.0331, wR_2= 0.0841
Final R indexes [all data]	R_1= 0.0343, wR_2= 0.0857
Largest diff. peak/hole / e Å^{-3}	0.13/-0.18
Flack parameter	0.58(12)


NOMOVE FORCED
Prob = 50
Temp = 170
73 Y
PLATON-Oct 18 10:53:35 2022 - (120922)
C23
C22
C10
C9
C20
C2
C3
C1
C4
C6
C5
O2
C8
O1
C7
C19
C18
C11
C21
O3
C12
C13
C17
C14
C16
C15
Z -179 f
P n a 21
R = 0.03
RES= 0-102 X