Supporting Information

Synthesis of Rocaglamide Derivatives and Evaluation of Wnt Signal Inhibitory Activity

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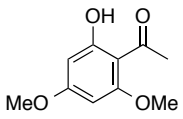
Contents

General experimental procedure

NMR spectra were recorded on JEOL ECP400 and ECP600 spectrometers in a deuterated solvent whose chemical shift was taken as an internal standard. Mass spectra were obtained using AccuTOF LC-plus JMS-T100LP (JEOL). IR spectra were measured on ATR on a JASCO FT-IR 230 spectrophotometer. Column chromatography was performed using silica gel PSQ100B (Fuji Silysia Chemical Ltd., Kasugai, Japan) and silica gel 60N (Kanto Chemical Co., Inc., Tokyo, Japan). Photochemical reactions were carried out using HL-400B-8 (400 W, 33 A; mercury lamp) and HB400P-1 (400 W) (SEN Light Co., Osaka, Japan) with cooling system consists of TRL-117ST and TC-107E (THOMAS, KAGAKU Co., Ltd., Tokyo, Japan). Mercury lamp was cooled using glass container (Pyrex) (USHIO Inc., Tokyo, Japan) with water.

2-hydroxy-4,6-dimethoxyacetophenone (**8**)



The mixture of 2,4,6-trihydroxyacetophenone (4.0 g, 21.4 mmol), K_2CO_3 (16.0 g, 115.6 mmol), and methyl trifluoromethanesulfonate (6.6 mL, 59.9 mmol) in dry acetone (107 mL) was stirred

for 3 h under reflux condition. The reaction mixture was filtered on celite and then filtrate was concentrated. The resulting residue was diluted with H_2O and then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was purified by silicagel column chromatography (hexane:AcOEt = 25:1) to afford **8** (3.61 g, 18.8 mmol, 88%).

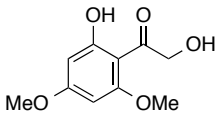
IR (ATR): 3099, 3006, 2945, 2849, 1612, 1593, 1456, 1439, 1422, 1388, 1365, 1322, 1267, 1219, 1204, 1155, 1110, 1080, 1044, 1029, 997, 961, 941, 893, 835, 804 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 14.04 (s, 1H), 6.06 (d, *J* = 2.2 Hz, 1H), 5.92 (d, *J* = 2.2 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.61 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 203.1, 167.5, 166.0, 162.9, 105.9, 93.4, 90.7, 55.5, 55.5, 32.9.

ESI-HRMS $[M-H]^-$: calcd for $C_{10}H_{11}O_4$ 195.0657, found 195.0609.

2-hydroxy-1-(2-hydroxy-4,6-dimethoxyphenyl)ethan-1-one (**9**)



A solution of **8** (400 mg, 2.0 mmol) in CH_2Cl_2 (5.2 mL) was cooled to 0 ºC and added triethylamine (832 µL, 6.0 mmol) and TBSOTf (1.1 mL, 5.6 mmol). The reaction mixture was stirred for 30 min and the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and separated organic layer was dried over Na_2SO_4. After filtration and concentration, the crude product was directly used for next reaction.

The crude product was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 ºC. To the mixture was added $NaHCO_3$ (420 mg, 5.0 mmol) and mCPBA (552 mg, 3.2 mmol) and the reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ and water. The combined organic layer was dried over Na_2SO_4 and filtered. The solvent was concentrated and the crude product was directly used for next reaction.

The crude product was dissolved in THF (10 mL) and H_2O (1 mL) and $TsOH \cdot H_2O$ (37.6 mg, 0.2 mmol) was added to the mixture. Then the mixture was stirred for 9 h under reflux condition and the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was extracted with EtOAc and dried over Na_2SO_4. After filtration and concentration, the resulting residue was purified by silicagel C.C. (hexane:AcOEt = 5:1→2:1) to afford **9** (290.9 mg, 69% in 3 steps).

IR (ATR): 3457, 2980, 2943, 2174, 2141, 1722, 1703, 1688, 1630, 1592, 1546, 1500, 1459, 1422, 1391, 1325, 1279, 1217, 1201, 1151, 1116, 1092, 999, 959, 938, 810 cm^{-1}.

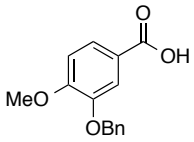
^{1}H-NMR (400 MHz, $CDCl_3$): δ 13.20 (s, 1H), 6.08 (d, *J* = 2.2 Hz, 1H), 5.91 (d, *J* = 2.2 Hz, 1H),

4.69 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.00 (brs, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 201.9, 167.2, 167.1, 163.1, 103.3, 93.7, 90.9, 68.6, 55.7, 55.7.

ESI-HRMS $[M+Na]^+$: calcd for $C_{10}H_{12}NaO_5$ 235.0582, found 235.0590.

3-(benzyloxy)-4-methoxybenzoic acid (**10**)



To a solution of 3-hydroxy-4-methoxybenzoic acid (1.0 g, 6.0 mmol) in MeOH (11 mL) was added H_2SO_4 (36 μL, 0.36 mmol) and the reaction mixture was stirred for 18 h under reflux condition. The reaction mixture was cooled to rt and concentrated *in vacuo*. The resulting mixture was diluted with sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated, and the residue was purified by silicagel flash C.C. (hexane:AcOEt = 5:1) to give methyl 3-hydroxy-4-methoxybenzoate (1.04 g, 95% yield).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.59 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.66 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.8, 150.4, 145.2, 123.4, 122.8, 115.6, 109.8, 56.0, 51.9.

ESI-HRMS $[M-H]^-$: calcd for $C_9H_9O_4$ 181.0501, found 181.0527.

To a solution of methyl 3-hydroxy-4-methoxybenzoate (1.02 g, 5.6 mmol) in MeOH was added DBU (1.3 mL, 8.4 mmol) and benzyl bromide (736 μL, 6.2 mmol) and then the reaction mixture was stirred for 20 h under reflux condition. After removal of solvent, the resulting residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by crystallization to give methyl 3-(benzyloxy)-4-methoxybenzoate (1.21 g, 79% yield).

IR (ATR): 2942, 2184, 1962, 1707, 1584, 1509, 1436, 1384, 1341, 1293, 1261, 1207, 1176, 1127, 1006, 873, 847 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.48-7.30 (m, 5H), 6.90 (d, *J* = 8.6 Hz, 1H), 5.17 (s, 2H), 3.93 (s, 3H), 3.87 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.8, 153.6, 147.7, 136.6, 128.6, 128.0, 127.5, 124.0, 122.5, 114.4, 110.7, 71.0, 56.0, 51.9.

ESI-HRMS $[M+Na]^+$: calcd for $C_{16}H_{16}NaO_4$ 295.0946, found 295.0871.

To a solution of 3-(benzyloxy)-4-methoxybenzoate (844 mg, 3.1 mmol) in THF (3.4 mL) was

added 1*N* NaOH (8.4 mL) and stirred for 3 h under reflux condition. The reaction was quenched with 1*N* HCl and the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. Filtration and concentration afforded **10** (800 mg, 98%).

IR (ATR): 2957, 2039, 1681, 1599, 1517, 1438, 1348, 1301, 1269, 1224, 1135, 1021 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.65 (d, *J* = 2.2 Hz, 1H), 7.48-7.30 (m, 5H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.19 (s, 2H), 3.95 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.2, 154.3, 147.8, 136.5, 128.6, 128.1, 127.5, 124.9, 121.6, 114.7, 110.7, 71.0, 56.1.

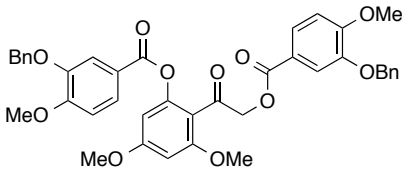
ESI-HRMS $[M+Na]^+$: calcd for $C_{15}H_{14}NaO_4$ 281.0790, found 281.0793.

Compound **11**, **16a-d**

General procedure

To a solution of **9** (300 mg, 1.4 mmol) in CH_2Cl_2 (14 mL) was added **15a** (538 mg, 4.2 mmol), DMAP (59 mg, 0.48 mmol) and EDC·HCl (1.2 g, 6.3 mmol). The reaction mixture was stirred at rt for 8 h and then diluted with water. The mixture was extracted with CH_2Cl_2 and the organic layer was dried over Na_2SO_4. After filtration and concentration, the resulting residue was purified by silicagel chromatography (hexane:AcOEt = 3:1) to afford **16a** (605 mg, 1.4 mmol, quant.).

2-(2-((3-(benzyloxy)-4-methoxybenzoyl)oxy)-4,6-dimethoxyphenyl)-2-oxoethyl 3-(benzyloxy)-4-methoxybenzoate (**11**); 90%



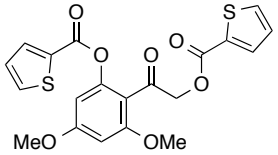
IR (ATR): 2936, 2840, 1718, 1600, 1512, 1455, 1420, 1344, 1290, 1265, 1201, 1175, 1130, 1098, 1019 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.44-7.25 (m, 10H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 2.0 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 5.20 (s, 2H), 5.14 (s, 2H), 5.02 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H).

^{13}C-NMR (100 MHz $CDCl_3$): δ 194.1, 165.5, 164.6, 162.9, 159.7, 154.1, 153.7, 151.2, 147.8, 147.6, 136.5, 136.5, 128.5, 127.9, 127.6, 125.1, 124.3, 122.0, 121.4, 114.8, 114.4, 113.5, 110.7, 110.6, 100.8, 96.3, 70.9, 70.8, 69.4, 56.0, 56.0, 55.9, 55.7.

ESI-HRMS $[M+Na]^+$: calcd for $C_{40}H_{36}NaO_{11}$ 715.2155, found 715.2067.

3,5-dimethoxy-2-(2-((thiophene-2-carbonyl)oxy)acetyl)phenyl thiophene-2-carboxylate (**16a**); quant.



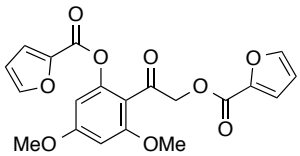
IR (ATR): 3102, 2943, 2841, 1717, 1608, 1573, 1522, 1457, 1412, 1360, 1332, 1248, 1220, 1197, 1152, 1094, 1053, 1022 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 3.9, 1.5 Hz, 1H), 7.77 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.61 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.52 (dd, *J* = 4.8, 1.1 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.9, 1H), 7.05 (dd, *J* = 4.8, 3.7 Hz, 1H), 6.43 (d, *J* = 2.2 Hz, 1H), 6.38 (d, *J* = 2.2 Hz, 1H), 5.22 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 193.2, 163.1, 161.4, 160.2, 159.9, 150.8, 135.1, 133.9, 133.7, 133.1, 132.7, 132.3, 128.0, 127.7, 113.2, 100.9, 96.6, 69.5, 56.0, 55.7.

ESI-HRMS $[M+Na]^+$: calcd for $C_{20}H_{16}NaO_7S_2$ 455.0235, found 455.0203.

2-(2-((furan-2-carbonyl)oxy)-4,6-dimethoxyphenyl)-2-oxoethyl furan-2-carboxylate (**16b**); quant.



IR (ATR): 3141, 2944, 2851, 1734, 1609, 1566, 1470, 1421, 1391, 1361, 1334, 1295, 1228, 1173, 1105, 1013 cm^{-1}.

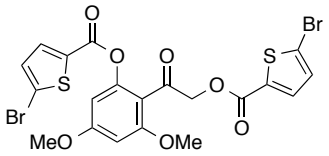
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.55 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.35 (dd, *J* = 3.6, 0.8, 1H), 7.18 (dd, *J* = 3.6, 0.8 Hz, 1H), 6.53 (dd, *J* = 3.6, 1.6 Hz, 1H), 6.47 (dd, *J* = 3.6, 2.0 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 5.26 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.5, 163.3, 160.1, 157.8, 156.5, 150.6, 147.3, 146.5, 144.1,

143.5, 120.1, 118.6, 112.9, 112.2, 111.9, 101.0, 96.7, 69.3, 56.1, 55.8.

ESI-HRMS $[M+Na]^+$: calcd for $C_{20}H_{16}NaO_9$ 423.0692, found 423.0673.

2-(2-((5-bromothiophene-2-carbonyl)oxy)-4,6-dimethoxyphenyl)-2-oxoethyl 5-bromothiophene-2-carboxylate (**16c**); 91%



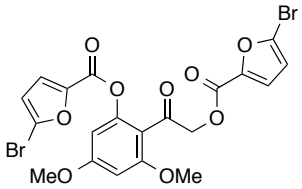
IR (ATR) : 1732, 1608, 1415, 1227, 1100 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 3.9 Hz, 1H), 7.53 (d, *J* = 3.9 Hz, 1H), 7.09 (d, *J* = 3.9 Hz, 1H), 7.04 (d, *J* = 3.9 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.38 (d, *J* = 2.3 Hz, 1H), 5.18 (s, 2H), 3.86 (s, 3H), 3.82 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.5, 163.3, 160.3, 160.0, 159.2, 150.7, 135.3, 134.2, 134.1, 133.4, 131.1, 130.9, 121.8, 120.7, 112.9, 101.1, 96.7, 69.7, 56.1, 55.8.

ESI-MS $[M+Na]^+$: calcd for $C_{20}H_{14}{}^{79}Br^{81}BrO_7S_2$ 612.8425, found 612.8486. $C_{20}H_{14}{}^{79}Br_2O_7S_2$ 610.8445, found 610.8394. $C_{20}H_{14}{}^{81}Br_2O_7S_2$ 614.8405 found 614.8307.

2-(2-((5-bromofuran-2-carbonyl)oxy)-4,6-dimethoxyphenyl)-2-oxoethyl 5-bromofuran-2-carboxylate (**16d**); 95%.



IR (ATR): 3154, 2943, 2845, 1731, 1682, 1608, 1567, 1459, 1421, 1358, 1332, 1286, 1228, 1206, 1142, 1106, 1015 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 3.7 Hz, 1H), 7.12 (d, *J* = 3.7 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 6.42 (d, *J* = 3.3 Hz, 1H), 6.39 (s, 2H), 5.24 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.0, 163.4, 160.2, 156.7, 155.3, 150.5, 145.7, 145.2, 128.8, 127.8, 122.2, 120.8, 114.3, 114.0, 112.6, 101.1, 96.7, 69.4, 56.1, 55.8.

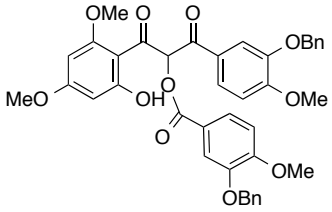
ESI-HRMS $[M+Na]^+$: calcd for $C_{20}H_{14}{}^{79}Br^{81}BrNaO_9$ 582.8882, found 582.8861. $C_{20}H_{14}{}^{79}Br_2NaO_9$ 578.8902, found 578.8956. $C_{20}H_{14}{}^{81}Br_2NaO_9$ 582.8861, found 582.8852.

Compound **12**, **17a-d**

General procedure

To a solution of **16a** (578 mg, 1.3 mmol) in THF (38 mL) was added of LHMDS (1.3 M, 3.1 mL, 4.0 mmol) at -20°C in dropwise manner. The reaction mixture was stirred for 2 h and the reaction was quenched using sat. aq. $NaHCO_3$. The resulting mixture was extracted using EtOAc. The combined organic layers were then washed with brine, dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the resulting residue was purified by silicagel chromatography (hexane:AcOEt = 3:1) to afford **17a** (432 mg, 1.0 mmol, 75 %).

1-(3-(benzyloxy)-4-methoxyphenyl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxopropan-2-yl 3-(benzyloxy)-4-methoxybenzoate (**12**) (used to next step without purification.)



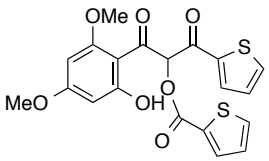
IR (ATR): 2945, 1718, 1681, 1598, 1513, 1426, 1270, 1216, 1159, 1114, 1020 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 13.26 (s, 1H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 1.6 Hz, 1H), 7.64-7.59 (m, 2H), 7.43-7.20 (m, 11H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.08 (d, *J* = 2.0 Hz, 1H), 5.76 (d, *J* = 2.0 Hz, 1H), 5.21-5.09 (m, 4H), 3.94 (s, 3H), 3.90 (s, 3H), 3.79 (s, 3H), 3.15 (s, 3H).

^{13}C-NMR (100 MHz $CDCl_3$): δ 194.3, 189.8, 167.7, 166.9, 165.1, 161.5, 154.4, 154.3, 148.0, 147.8, 136.5, 136.3, 128.6, 128.5, 128.1, 128.0, 127.7, 127.6, 127.5, 124.9, 123.8, 121.1, 114.8, 113.0, 110.8, 104.4, 94.1, 91.0, 71.0, 70.7, 56.1, 56.1, 55.7, 55.1.

ESI-HRMS $[M+Na]^+$: calcd for $C_{40}H_{36}NaO_{11}$ 715.2155, found 715.2067.

1-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxo-3-(thiophen-2-yl)propan-2-yl thiophene-2-carboxylate (**17a**); 85%.



IR (ATR): 3103, 2943, 1715, 1671, 1624, 1577, 1521, 1463, 1414, 1359, 1274, 1244, 1217, 1159, 1114, 1091, 861, 821 cm^{-1}.

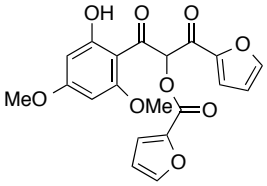
^{1}H-NMR (400 MHz, $CDCl_3$): δ 13.17 (s, 1H), 7.91 (d, *J* = 4.4 Hz, 1H), 7.83 (d, *J* = 4.2 Hz, 1H),

7.72 (d, *J* = 5.3 Hz, 1H), 7.61 (d, *J* = 5.3 Hz, 1H), 7.21 (s, 1H), 7.17 (dd, *J* = 5.3, 4.4 Hz, 1H), 7.11 (dd, *J* = 5.3, 4.2 Hz, 1H), 6.09 (d, *J* = 2.4 Hz, 1H), 5.83 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 3H), 3.41 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.9, 183.7, 167.7, 167.1, 161.5, 160.9, 141.7, 134.9, 133.8, 133.4, 131.9, 128.5, 128.0, 104.4, 94.1, 91.0, 78.1, 55.7, 55.2.

ESI-HRMS $[M+Na]^+$: calcd for $C_{20}H_{16}NaO_7S_2$ 455.0235, found 455.0196.

1-(furan-2-yl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxopropan-2-yl furan-2-carboxylate (**17b**); 70%.



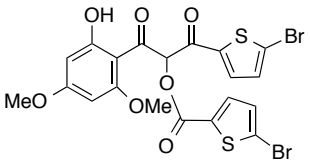
IR (ATR): 3136, 2945, 1728, 1682, 1609, 1567, 1463, 1438, 1420, 1392, 1347, 1296, 1275, 1248, 1215, 1158, 1105, 1048, 1011 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 13.15 (s, 1H), 7.64 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.61 (dd, *J* = 1.8, 0.9, 1H), 7.36 (dd, *J* = 3.7, 0.7 Hz, 1H), 7.29 (dd, 3.7, 0.9 Hz, 1H), 7.19 (s, 1H), 6.60 (dd, 3.7, 1.8 Hz, 1H), 6.51 (dd, 3.7, 1.8 Hz, 1H), 6.09 (d, *J* = 2.6 Hz, 1H), 5.82 (d, *J* = 2.6 Hz, 1H), 3.80 (s, 3H), 3.43 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.7, 179.4, 167.8, 167.2, 161.5, 157.2, 150.9, 147.24, 147.21, 143.3, 119.7, 118.9, 112.8, 112.1, 104.3, 94.1, 91.0, 55.7, 55.3.

ESI-HRMS $[M+Na]^+$: calcd for $C_{20}H_{16}NaO_9$ 423.0692, found 423.0672.

1-(5-bromothiophen-2-yl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxopropan-2-yl 5-bromothiophene-2-carboxylate (**17c**); 86%



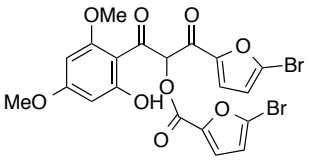
IR (ATR) : 2925, 1720, 1671, 1631, 1412, 1330, 1238, 1217, 1160, 1115, 1090, 896 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 13.1 (s, 1H), 7.65 (d, *J* = 3.9 Hz, 1H), 7.55 (d, *J* = 3.9 Hz, 1H), 7.14 (d, *J* = 4.2 Hz, 1H), 7.08 (d, *J* = 4.2 Hz, 1H), 7.08 (s, 1H), 6.08 (d, *J* = 2.3 Hz, 1H), 5.83 (d, *J* = 2.3 Hz, 1H), 3.79 (s, 3H), 3.47 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.2, 182.4, 167.8, 167.3, 161.4, 159.7, 142.9, 135.3, 133.6, 132.8, 131.2, 131.2, 124.2, 122.1, 104.3, 94.2, 91.2, 77.7, 55.8, 55.3.

ESI-MS $[M+Na]^+$: calcd for $C_{20}H_{14}{}^{79}Br^{81}BrNaO_7S_2$ 612.8425, found 612.8362. $C_{20}H_{14}{}^{79}Br_2NaO_7S_2$ 610.8445, found 610.8397. $C_{20}H_{14}{}^{81}Br_2NaO_7S_2$ 614.8405, found 614.8322.

1-(5-bromofuran-2-yl)-3-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-dioxopropan-2-yl-5-bromofuran-2-carboxylate (**17d**); 65%.



IR (ATR): 3146, 2924, 2850, 2159, 1730, 1683, 1613, 1578, 1451, 1421, 1359, 1275, 1248, 1214, 1159 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 13.06 (s, 1H), 7.29 (d, *J* = 4.0 Hz, 1H), 7.23 (d, *J* = 3.5 Hz, 1H), 7.08 (s, 1H), 6.56 (d, *J* = 4.0 Hz, 1H), 6.47 (d, *J* = 3.5 Hz, 1H), 6.08 (d, *J* = 2.2 Hz, 1H), 5.83 (d, *J* = 2.2 Hz, 1H), 3.79 (s, 3H), 3.50 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 192.0, 177.8, 167.8, 167.3, 161.4, 156.0, 152.3, 144.8, 129.6, 128.9, 121.9, 121.1, 115.0, 114.2, 104.2, 94.1, 91.1, 76.9, 55.7, 55.4.

ESI-HRMS $[M+Na]^+$: calcd for $C_{20}H_{14}{}^{79}Br^{81}BrNaO_9$ 580.8882, found 580.8869. $C_{20}H_{14}{}^{79}Br_2NaO_9$ 578.8902, found 578.8945. $C_{20}H_{14}{}^{81}Br_2NaO_9$ 582.8861, found 582.8855.

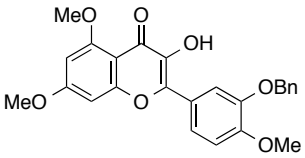
Compound **13**, **19a-d**

General procedure

To a solution of **17a** (404 mg, 0.93 mmol) in 12 mL of glacial acetic acid was added 246 μL of sulfuric acid. The resulting mixture was stirred at rt for 22 h. The reaction was quenched with cool water and filtered. Then resulting residue was added EtOH and stirred for a few hours under reflux condition. The reaction mixture was concentrated and resulting crude product **18a** (307 mg) was used for next reaction without further purification.

To a solution of crude product **18a** (307 mg) in EtOH (3.7 mL) was added 1*N* NaOH (890 μL). The reaction mixture was heated at 80 ºC and stirred for 5 h. The reaction was quenched with 1*N* HCl and filtered by Kiriyama funnel. The residue was washed with cooled EtOH and the solvent was evaporated *in vacuo* to afford **19a** (149 mg, 0.5 mmol, 66% from **17a**).

2-(3-(benzyloxy)-4-methoxyphenyl)-3-hydroxy-5,7-dimethoxy-4*H*-chromen-4-one (**13**); 75% in 3 steps from **11**.



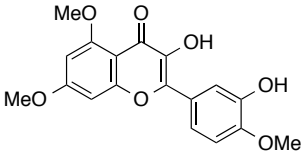
IR (ATR): 2938, 1615, 1514, 1496, 1456, 1437, 1335, 1259, 1213, 1160, 1020 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 2.0 Hz, 1H), 7.80 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.51-7.49 (m, 2H), 7.39-7.28 (m, 3H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 6.32 (d, *J* = 2.0 Hz, 1H), 5.23 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.90 (s, 3H).

^{13}C-NMR (100 MHz $CDCl_3$): δ 171.9, 164.3, 160.5, 158.8, 150.9, 147.9, 142.0, 137.5, 136.9, 128.5, 128.0, 127.6, 123.6, 121.2, 113.0, 111.4, 106.2, 95.6, 92.3, 71.3, 56.4, 56.0, 55.8.

ESI-HRMS $[M+H]^+$: calcd for $C_{15}H_{23}O_7$ 435.1444, found 435.1440.

3-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-5,7-dimethoxy-4*H*-chromen-4-one (**14**)



To a solution of **13** (30 mg, 0.069 mmol) in THF (950 μL) and EtOH (950 μL) was added $Pd(OH)_2$ on activated carbon (3 mg). Under balloon pressure of hydrogen, the reaction mixture was stirred for 2 h. The reaction mixture was filtered through a celite and the solvent was removed *in vacuo* to afford a yellow-white solid **14** (23.8 mg, quant.).

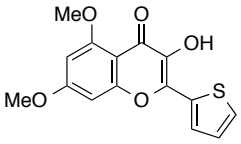
IR (ATR): 3422, 3242, 2952, 2882, 1722, 1614, 1512, 1437, 1334, 1250, 1210, 1159, 1034 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.78 (d, *J* = 2.0 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.35 (d, *J* = 2.4 Hz, 1H), 5.69 (brs, 1H), 3.98 (s, 3H), 3.98 (s, 3H), 3.92 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.9, 164.4, 160.5, 158.9, 147.7, 145.6, 141.9, 137.7, 124.4, 120.5, 113.1, 110.5, 106.2, 95.7, 92.4, 56.4, 56.0, 55.8.

ESI-HRMS $[M+H]^+$: calcd for $C_{18}H_{17}O_7$ 345.0974, found 345.0943.

3-hydroxy-5,7-dimethoxy-2-(thiophen-2-yl)-4*H*-chromen-4-one (**19a**); 66%.



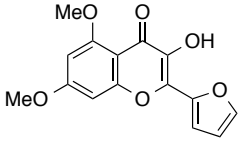
IR (ATR): 1614, 1557, 1436, 1370, 1325, 1237, 1213, 1158, 1107, 1032, 808 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 4.0 Hz, 1H), 7.56 (d, *J* = 5.2 Hz, 1H), 7.21 (dd, *J* = 5.2, 4.0 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.35 (d, *J* = 2.0 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.3, 164.4, 160.6, 158.7, 140.0, 136.6, 133.0, 128.7, 128.2, 128.0, 106.4, 95.8, 92.5, 56.4, 55.8.

ESI-HRMS $[M+Na]^+$: calcd for $C_{15}H_{12}NaO_5S$ 327.0303, found 327.0301.

2-(furan-2-yl)-3-hydroxy-5,7-dimethoxy-4*H*-chromen-4-one (**19b**); 92%.



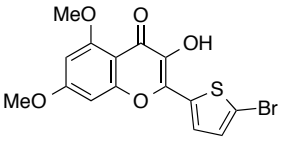
IR (ATR): 3296, 2922, 2850, 1602, 1568, 1490, 1456, 1435, 1363, 1306, 1267, 1240, 1214, 1157, 1133, 1106, 1076, 1055, 997, 977, 938, 915, 885, 846, 820 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.23 (dd, *J* = 3.7, 0.9 Hz, 1H), 6.62 (dd, *J* = 3.7, 1.8 Hz, 1H), 6.58 (d, *J* = 2.2 Hz, 1H), 6.35 (d, *J* = 2.2 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.2, 164.4, 160.6, 158.6, 144.3, 144.1, 136.3, 135.9, 114.1, 112.5, 106.5, 95.9, 92.6, 56.4, 55.8.

ESI-HRMS $[M+Na]^+$: calcd for $C_{15}H_{12}NaO_6$ 311.0532, found 311.0512.

2-(5-bromothiophen-2-yl)-3-hydroxy-5,7-dimethoxy-4*H*-chromen-4-one (**19c**); 55%



IR (ATR) : 2921, 1608, 1439, 1232, 1159, 1130, 1053 cm^{-1}.

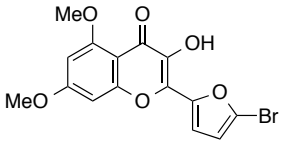
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 3.9 Hz, 1H), 7.14 (d, *J* = 3.9 Hz, 1H), 6.50 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H).

^{13}C-NMR (150 MHz, $CDCl_3$) : δ 171.2, 164.6, 160.6, 158.6, 138.5, 136.1, 134.2, 130.8, 128.1, 116.8, 106.4, 95.9, 92.5, 56.5, 55.9, 53.4.

ESI-MS $[M+Na]^+$: calcd for $C_{15}H_{11}{}^{79}BrNaO_5S$ 404.9408, found 404.9445. $C_{15}H_{11}{}^{81}BrNaO_5S$

406.9388, found 406.9372.

2-(5-bromofuran-2-yl)-3-hydroxy-5,7-dimethoxy-4*H*-chromen-4-one (**19d**); 55%.



IR (ATR): 3414, 1616, 1489, 1455, 1244, 1217, 1163, 1128, 1008, 923, 815 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.14 (brs, 1H), 7.14 (d, *J* = 3.5 Hz, 1H), 6.59 (d, *J* = 2.2 Hz, 1H), 6.52 (d, *J* = 3.5 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.0, 164.5, 160.5, 158.6, 146.0, 136.1, 134.8, 124.7, 116.4, 114.4, 106.5, 96.0, 92.6, 56.4, 55.9.

ESI-HRMS $[M+H]^+$: $C_{15}H_{12}{}^{81}BrO_6$ calcd 368.9797, found for 368.9747.

Compound **5**, **22a-d**

General procedure

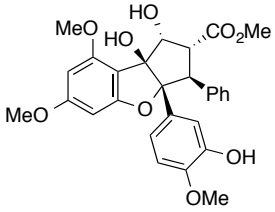
To solution of 3-hydroxychromone (**19a**; 91 mg, 0.30 mmol) in dry acetonitrile (4.7 mL) and dry MeOH (3.2 mL) was added methyl cinnamate (610 μL, 3.9 mmol). The reaction mixture was irradiated (400 W mercury lamp) at 0 °C for 2 h. The solvent was removed *in vacuo* and the resulting residue was purified by silicagel column chromatography (hexane:AcOEt = 10:1→2:1→1:1) to afford a mixture containing **20a** (95.7 mg).

To a mixture containing **20a** (95.7 mg) in dry MeOH (7 mL) was added NaOMe (31 mg, 0.57 mmol). The reaction mixture was stirred for 2 h under reflux condition. The reaction was quenched with sat. aq. NH_4Cl and the mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. After filtration and concentration, the resulting residue was purified by silicagel column chromatography (hexane:AcOEt = 2:1) to afford inseparable keto-enol isomers of **21a** (55.9 mg, 0.12 mmol, 53% in 2 steps from **19a**).

A mixture of tetramethylammonium triacetoxyborohydride (189 mg, 0.72 mmol) and acetic acid (70 μL, 1.2 mmol) in dry acetonitrile (3.1 mL) was stirred at rt for 5 min. The mixture was added to a solution of keto-enol tautomers **21a** (55.9 mg, 0.12 mmol) in dry acetonitrile (2.1 mL) and the mixture was stirred at rt for 2 h. The reaction was quenched with sat. aq. NH_4Cl and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. After filtration and concentration, the resulting residue was purified by silicagel column chromatography (hexane:AcOEt = 3:2) to afford **22a** (45.9 mg, 0.098 mmol,

82%).

methyl (1*R**,2*R**,3*S**,3a*R**,8b*S**)-1,8b-dihydroxy-3a-(3-hydroxy-4-methoxyphenyl)-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**5**); 35% in 3 steps.



IR (ATR): 3490, 2951, 2842, 1740, 1622, 1597, 1512, 1499, 1454, 1437, 1340, 1266, 1216, 1200, 1146, 1120, 1059, 1030 cm^{-1}.

^{1}H-NMR (400 MHz, CD_3OD): δ 7.05-7.00 (m, 3H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.65 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 6.16 (d, *J* = 2.0 Hz, 1H), 4.85 (m, 1H), 4.21 (d, *J* = 14.2 Hz, 1H), 3.97 (dd, *J* = 14.2, 6.0 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H).

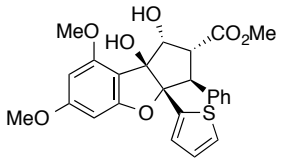
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.10-7.03 (m, 3H), 6.94-6.92 (m, 2H), 6.82 (d, *J* = 2.2 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.28 (d, *J* = 1.8 Hz, 1H), 6.11 (d, *J* = 1.8 Hz, 1H), 5.43 (brs, 1H), 4.99 (d, *J* = 6.6 Hz, 1H), 4.33 (d, *J* = 14.3 Hz, 1H), 3.95 (dd, *J* = 14.3, 6.6 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.65 (s, 3H), 3.58 (brs, 1H), 1.86 (brs, 1H).

^{13}C-NMR (100 MHz, CD_3OD): δ 172.6, 165.2, 162.2, 159.3, 147.7, 146.0, 139.2, 130.0, 129.1, 128.5, 127.2, 120.7, 116.6, 111.2, 109.2, 102.7, 95.1, 93.1, 90.0, 80.6, 56.4, 56.2, 56.1, 56.0, 52.5, 52.2.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.6, 164.1, 160.9, 157.0, 145.7, 144.6, 137.0, 127.8, 127.7, 127.6, 126.5, 119.7, 114.4, 109.5, 107.5, 101.8, 93.7, 92.6, 89.4, 79.5, 55.8, 55.7, 55.7, 55.0, 52.0, 50.5.

ESI-HRMS $[M+Na]^+$: calcd for $C_{28}H_{28}NaO_9$ 531.1631, found 531.1598.

methyl (1*R**,2*R**,3*S**)- 1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-3a-(thiophen-2-yl)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**22a**); 43% in 3 steps.



IR (ATR): 2950, 2844, 1735, 1623, 1597, 1499, 1455, 1436, 1339, 1276, 1216, 1200, 1146, 1116, 1033 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.13-7.09 (m, 4H), 7.02-6.99 (m, 2H), 6.89 (dd, *J* = 3.5, 1.1 Hz, 1H), 6.87 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.28 (d, *J* = 1.8 Hz, 1H), 6.14 (d, *J* = 1.8 Hz, 1H), 4.97 (dd, *J* = 6.2, 1.8 Hz, 1H), 4.33 (d, *J* = 14.3 Hz, 1H), 3.92 (ddd, *J* = 14.3, 6.2, 1.1 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.65 (s, 3H), 3.43 (dd, *J* = 1.8, 1.1 Hz, 1H), 2.01 (s, 1H).

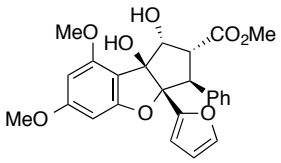
^{1}H-NMR (400 MHz, pyridine-d_5): δ 7.83 (br s, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 3.4 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 5.5 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 4.8 Hz, 1H), 6.90-6.88 (m, 1H), 6.42 (d, *J* = 2.1 Hz, 1H), 6.29 (d, *J* = 2.1 Hz, 1H), 5.63 (t, *J* = 5.5 Hz, 1H), 5.12 (d, *J* = 13.8 Hz, 1H), 4.57 (dd, *J* = 13.8, 5.5 Hz, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 3.60 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.4, 164.2, 160.9, 157.1, 137.4, 136.5, 127.8, 127.7, 126.8, 126.4, 125.9, 125.6, 107.0, 101.6, 93.5, 93.0, 89.4, 79.0, 55.8, 55.7, 55.0, 52.0, 50.1.

^{13}C-NMR (100 MHz, pyridine-d_5) : δ 171.4, 163.9, 161.8, 159.0, 141.1, 139.2, 128.7, 128.0, 126.69, 126.66, 126.62, 124.7, 109.2, 102.5, 94.7, 92.8, 89.4, 80.4, 56.3, 55.6, 55.4, 52.3, 51.5.

ESI-HRMS $[M+Na]^+$: calcd for $C_{25}H_{24}NaO_7S$ 491.1140, found 491.1099.

methyl (1*R**,2*R**,3*S**,3a*S**,8b*S**)-3a-(furan-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**22b**); 13% in 3 steps.



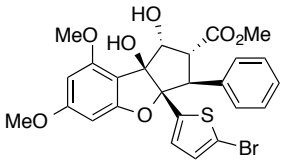
IR(ATR): 3505, 2950, 2844, 1742, 1625, 1600, 1499, 1455, 1437, 1344, 1285, 1216, 1201, 1147, 1122, 1083, 1033, 914, 813 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 0.8, 2.0 Hz, 1H), 7.17-7.08 (m, 5H), 6.26 (d, *J* = 2.0 Hz, 1H), 6.18 (dd, *J* = 0.8, 3.4 Hz, 1H), 6.13 (dd, *J* = 2.0, 3.4 Hz, 1H), 6.12 (d, *J* = 2.0 Hz, 1H), 4.94 (d, *J* = 6.0 Hz, 1H), 4.30 (dd, *J* = 6.0, 14.0 Hz, 1H), 4.17 (d, *J* = 14.0 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H), 3.42 (brs, 1H), 2.01 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.6, 164.2, 161.3, 156.9, 149.4, 142.6, 136.6, 127.8, 127.6, 126.8, 110.1, 109.6, 107.0, 100.2, 94.3, 92.9, 89.6, 79.3, 55.8, 55.7, 54.2, 52.0, 50.1.

ESI-HRMS $[M+Na]^+$: calcd for $C_{25}H_{24}NaO_8$ 475.1369, found 475.1365.

methyl(1*R**,2*R**,3*S**,3a*S**,8b*S**)-3a-(5-bromothiophen-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**22c**); 55% in 3 steps.



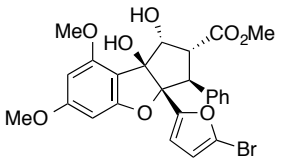
IR (ATR) : 3507, 1743, 1599, 1499, 1437, 1201, 1148, 1117, 885, 811 cm^{-1}.

^{1}H-NMR (400 MHz, pyridine-d_5): δ 7.42 (d, *J* = 7.4 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 3.9 Hz, 1H), 6.87 (d, *J* = 3.9 Hz, 1H), 6.46 (br, 1H), 6.29 (br, 1H), 5.58 (d, *J* = 4.9 Hz, 1H), 5.15 (d, *J* = 14.1 Hz, 1H), 4.53 (dd, *J* = 14.1, 4.9 Hz, 1H), 3.72 (s, 3H), 3.61 (s, 3H), 3.59 (s, 3H).

^{13}C-NMR (100 MHz, pyridine-d_5) : δ 171.3, 163.9, 161.8, 159.0, 143.3, 139.0, 129.9, 128.6, 128.2, 127.5, 126.9, 111.2, 108.7, 102.4, 94.8, 93.0, 89.3, 80.2, 56.1, 55.6, 55.3, 52.4, 51.6.

ESI-MS $[M+Na]^+$: calcd for $C_{25}H_{23}{}^{79}BrNaO_7S$ 567.0246, found 569.0238. $C_{25}H_{23}{}^{81}BrNaO_7S$ 571.0225, found 571.0225.

methyl (1*R**,2*R**,3*S**,3a*S**,8b*S**)-3a-(5-bromofuran-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (**22d**); 32% in 3 steps.



IR (ATR): 3483, 2951, 2842, 1738, 1625, 1600, 1505, 1455, 1437, 1376, 1343, 1284, 1201, 1148, 1116, 1073, 1034, 915, 813 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.20-7.10 (m, 5H), 6.24 (d, *J* = 2.0 Hz, 1H), 6.14 (d, *J* = 3.2 Hz, 1H), 6.12 (d, *J* = 2.0 Hz, 1H), 6.02 (d, *J* = 3.2 Hz, 1H), 4.92 (d, *J* = 6.0 Hz, 1H), 4.26 (dd, *J* = 14.2, 6.0 Hz, 1H), 4.18 (d, *J* = 14.2 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H), 3.31 (brs, 1H).

^{13}C-NMR (100 MHz $CDCl_3$): δ 170.6, 164.3, 161.2, 157.0, 151.2, 136.3, 127.9, 127.7, 127.0, 121.9, 112.0, 111.6, 106.8, 99.9, 94.2, 93.0, 89.6, 79.1, 55.8, 55.7, 54.1, 52.0, 49.9.

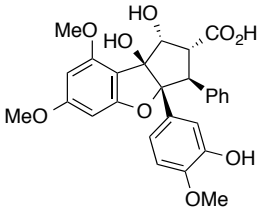
ESI-HRMS $[M+Na]^+$: calcd for $C_{25}H_{23}{}^{79}BrNaO_8$ 553.0474, found 553.0470. calcd for $C_{25}H_{23}{}^{81}BrNaO_8$ 555.0454, found 555.0448.

Compound **4**, **23a-d**

General procedure

Rocaglamide derivative **22a** (10.3 mg, 0.022 mmol) was dissolved in 4.7 mL of a 5:1 mixture of dry THF and distilled water. Lithium hydroxide monohydrate (13.8 mg, 0.33 mmol) was added and the reaction mixture was stirred at rt for 23 h. The mixture was diluted with CH_2Cl_2 and washed with 1*N* HCl and the organic layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and filtered. Concentration *in vacuo* gave rocagloic acid **23a** (9.7 mg, 0.021 mmol, 97%).

(1*R**,2*R**,3*S**,3a*R**,8b*S**)-1,8b-dihydroxy-3a-(3-hydroxy-4-methoxyphenyl)-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**4**); quant.



IR (ATR): 2934, 2842, 1725, 1597, 1499, 1428, 1333, 1268, 1216, 1199, 1146, 1120, 1030 cm^{-1}.

^{1}H-NMR (400 MHz, Py-d_5): δ 7.56 (s, 1H), 7.54 (d, *J* = 4.8 Hz, 2H), 7.17 (d, *J* = 5.8 Hz, 1H), 7.11 (t, *J* = 4.8 Hz, 2H), 6.96 (t, *J* = 4.8 Hz, 1H), 6.70 (d, *J* = 5.8 Hz, 1H), 6.48 (d, *J* = 1.2 Hz, 1H), 6.27 (d, *J* = 1.2 Hz, 1H), 5.82 (d, *J* = 3.2 Hz, 1H), 5.36 (d, *J* = 9.2 Hz, 1H), 4.80 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 3.52 (s, 3H).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09-7.04 (m, 3H), 6.94-6.92 (m, 2H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.63 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.58 (d, *J* = 8.6 Hz, 1H), 6.25 (d, *J* = 2.0 Hz, 1H), 6.09 (d, *J* = 2.0 Hz, 1H), 4.98 (d, *J* = 6.6 Hz, 1H), 4.26 (d, *J* = 14.1 Hz, 1H), 3.92 (dd, *J* = 14.1, 6.6 Hz, 1H), 3.81 (s, 6H), 3.76 (s, 3H).

^{13}C-NMR (100 MHz, Py-d_5): 173.7, 163.7, 162.4, 159.0, 147.1, 146.6, 140.5, 131.3, 129.0, 128.0, 126.2, 120.0, 117.3, 110.9, 109.8, 103.2, 95.3, 92.4, 89.3, 81.0, 56.4, 55.59, 55.56, 55.3,

53.3.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.2, 164.0, 160.8, 157.0, 145.7, 144.5, 136.7, 127.8, 127.7, 127.5, 126.5, 119.6, 114.4, 109.5, 107.3, 101.7, 93.6, 92.6, 89.4, 79.3, 55.7, 55.7, 54.9, 50.2.

ESI-HRMS $[M+Na]^+$: calcd for $C_{27}H_{26}NaO_9$ 517.1475, found 517.1456.

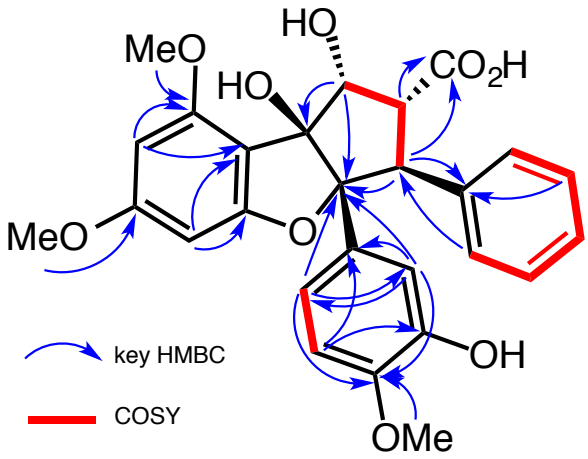
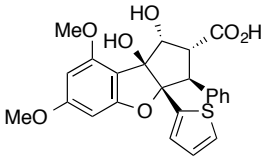


Figure 1. HMBC and COSY of **4**

(1*R**,2*R**,3*S**,3a*S**,8b*S**)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-3a-(thiophen-2-yl)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**23a**); 97%.



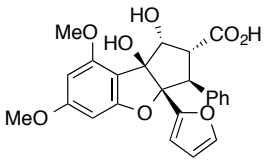
IR (ATR): 3472, 1717, 1599, 1499, 1200, 1148, 1118 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09-7.06 (m, 4H), 6.98-6.96 (m, 2H), 6.85-6.83 (m, 2H), 6.24 (d, *J* = 1.8 Hz, 1H), 6.10 (d, *J* = 1.8 Hz, 1H), 4.94 (dd, *J* = 5.9, 1.8 Hz, 1H), 4.24 (d, *J* = 13.9 Hz, 1H), 3.87 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.1 164.2, 160.8, 157.0, 137.2, 136.2, 127.8, 127.7, 126.9, 126.4, 126.0, 125.6, 106.8, 101.5, 93.4, 93.0, 89.4, 78.8, 55.78, 55.72, 54.9, 49.7.

ESI-HRMS $[M+Na]^+$: calcd for $C_{24}H_{22}NaO_7S$ 477.0984, found 477.0972.

(1*R**,2*R**,3*S**,3a*S**,8b*S**)-3a-(furan-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**23b**); 87%.



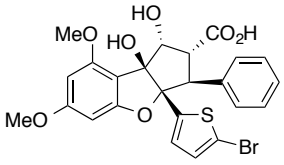
IR (ATR): 3373, 2938, 1716, 1602, 1501, 1454, 1217, 1200, 1148, 1122 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 2.0 Hz, 1H), 7.15-7.09 (m, 5H), 6.24 (d, *J* = 2.0 Hz, 1H), 6.16 (d, *J* = 3.2 Hz, 1H), 6.13 (dd, *J* = 2.0, 3.2 Hz, 1H), 6.10 (d, *J* = 2.0 Hz, 1H), 4.95 (d, *J* = 6.0 Hz, 1H), 4.28 (dd, *J* = 6.0, 14.2 Hz, 1H), 4.12 (d, *J* = 14.2 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.3, 164.3, 161.2, 156.9, 149.2, 142.6, 136.3, 127.9, 127.7, 126.9, 110.1, 109.6, 106.8, 100.1, 94.2, 92.9, 89.6, 79.1, 55.8, 55.7, 54.1, 49.7.

ESI-HRMS $[M+Na]^+$: calcd for $C_{24}H_{22}NaO_8$ 461.1212, found 461.1143.

(1*R**,2*R**,3*S**,3a*S**,8b*S**)-3a-(5-bromothiophen-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (23c); 66%



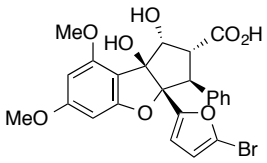
IR (ATR) : 3450, 1725, 1599, 1501, 1217, 1146, 1118 cm^{-1}.

^{1}H-NMR (400 MHz, pyridine-d_5): δ 7.56-7.54 (m, 2H), 7.21-7.17 (m, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 3.9 Hz, 1H), 6.87 (d, *J* = 3.9 Hz, 1H), 6.49 (d, *J* = 1.9 Hz, 1H), 6.31 (d, *J* = 1.9 Hz, 1H), 5.77 (d, *J* = 4.7 Hz, 1H), 5.30 (d, *J* = 14.0 Hz, 1H), 4.68 (dd, *J* = 14.0, 4.7 Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H).

^{13}C-NMR (100 MHz, pyridine-d_5) : δ 173.3, 163.8, 162.0, 159.0, 143.7, 139.6, 129.8, 128.8, 128.1, 127.4, 126.7, 111.0, 109.0, 102.7, 94.9, 92.9, 89.3, 80.4, 56.4, 55.6, 55.3, 52.8.

ESI-MS $[M+Na]^+$: calcd for $C_{24}H_{21}{}^{79}BrNaO_7S$ 555.0089, found 555.0072. $C_{24}H_{21}{}^{81}BrNaO_7S$ 557.0069, found 557.0047.

(1*R**,2*R**,3*S**,3a*S**,8b*S**)-3a-(5-bromofuran-2-yl)-1,8b-dihydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylic acid (**23d**); quant.



IR (ATR): 3477, 2944, 2024, 1717, 1626, 1503, 1455, 1200, 1148, 1117 cm^{-1}.

^{1}H-NMR (400 MHz, CD_3OD): δ 7.20-7.06 (m, 5H), 6.23 (d, *J* = 1.8 Hz, 1H), 6.16 (d, *J* = 1.8 Hz, 1H), 6.09 (d, *J* = 3.4 Hz, 1H), 6.01 (d, *J* = 3.4 Hz, 1H), 4.77 (d, *J* = 5.2 Hz, 1H), 4.17 (dd, *J* = 13.8, 5.2 Hz, 1H), 4.09 (d, *J* = 13.8 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H).

^{13}C-NMR (100 MHz CD_3OD): δ 174.2, 165.4, 162.6, 159.5, 154.3, 138.8, 129.1, 128.6, 127.5, 122.0, 112.3, 112.3, 101.2, 108.2, 95.7, 93.3, 89.8, 79.8, 56.1, 55.9, 55.7, 52.2.

ESI-HRMS $[M+Na]^+$: calcd for $C_{24}H_{21}{}^{79}BrNaO_8$ 539.0318, found 539.0265, $C_{24}H_{21}{}^{81}BrNaO_8$ 541.0297, found 541.0243.

Reporter gene assay and transfection for Wnt signal inhibitory activity

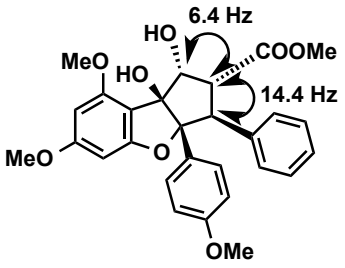
A cell-based assay method was previously described (Li et al., 2009, *Chem. Asian J.* 4, 540–547). This assay was used to evaluate TCF/β-catenin transcriptional activity. Assay cells (STF/293 cells) were seeded into 96- well plates (3 x 10^4 cells/well). After 24 h, the cells were treated with compounds combined with 15 mM LiCl for another 24 h. The cells were then lysed, and luciferase activity was measured using the Luciferase Assay System (Promega) on a Luminoskan Ascent (Thermo). To eliminate the nonspecific inhibition of TOP activity, FOP activity was also evaluated. HEK293 cells were plated on 24-well plates (1 x 10^5 cells/well) and incubated for 24 h. Using Lipofectamine 2000, the cells were transiently transfected with 500 ng/well of the luciferase reporter construct (SuperFOPflash), and 25 ng/well of pRL-CMV (Promega, USA) for normalization. Compounds combined with 15 mM LiCl were then added to the cells 12 h post-transfection. After being incubated for 24 h with the compounds, cells were lysed and luciferase activity was measured using PICAGENE Dual Seapansy (Toyo Ink) with Luminoskan Ascent (Thermo).

Viability assay

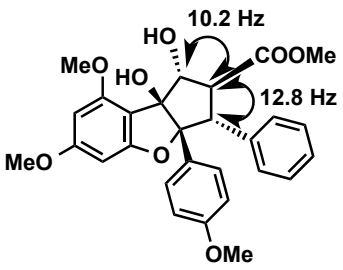
STF/293 (3 x 10^4 cells/well), AGS, HCT116, SW480, DLD1, RKO and HEK293 cells (5 x 10^3 cells/well) were seeded into 96-well plates for 24 h. Compounds were then added and incubated as described. The viability of cells was measured using the fluorometric microculture cytotoxicity assay (FMCA) (Lindhagen et al., 2008, *Nat. Protoc.* 3, 1364–1369). After being

incubated with the compounds, cells were washed with PBS and then added to fluorescein diacetate (Wako, Japan) in PBS. Cells were incubated for 1 h and fluorescence was measured using a Fluoroskan (Ascent).

Figure 2 Comparison of coupling constant of synthetic compound **5** with reported value.

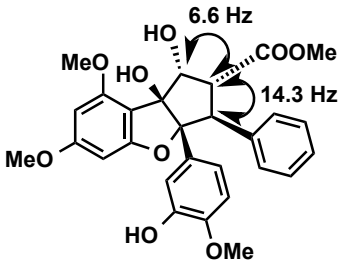


***endo* methyl rocaglate**
determined by X-ray



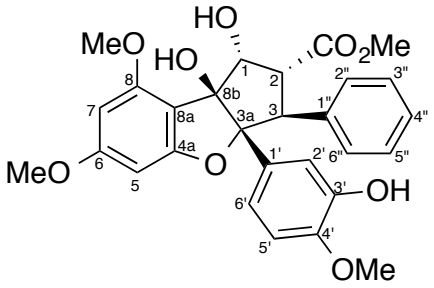
***exo* methyl rocaglate**

Baudouin Gerard; Sheharbano Sangji; Daniel J. O'Leary; John A. Porco, Jr. *J. Am. Chem. Soc.* 2006, *128*, 7754-7755.



Synthetic compound 5

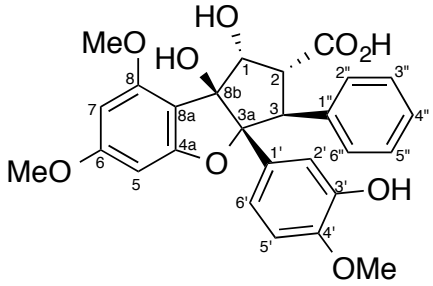
Table 1 Comparison of data of synthetic compound **5** with reported value.



position	^{1}H-NMR δ (*J* in Hz) **5** (400 MHz)	^{1}H-NMR δ (*J* in Hz) ref 10	^{13}C-NMR δ (*J* in Hz) **5** (100 MHz)	^{13}C-NMR δ (*J* in Hz) ref 10
1	overlapped	4.89 (d, 6.2)	80.6	80.7
2	3.96 (dd, 6.3, 14.1)	4.01 (dd, 6.2, 14.2)	52.2	52.2
3	4.22 (d, 14.1)	4.27 (d, 14.2)	56.4	56.4
3a			102.7	102.8
4a			*	**
5	6.27 (d, 2.0)	6.32 (d, 1.9)	90.0	90.0
6			*	**
7	6.16 (d, 2.0)	6.21 (d, 2.0)	93.1	93.1
8			*	**
8a			109.2	109.3
8b			95.1	95.1
1’			130.0	130.1
2’	6.71 (d, 2.2)	6.76 (d, 2.0)	116.6	116.7
3’			146.0	146.0
4’			*	**
5’	6.62 (d, 8.4)	6.67 (d, 8.6)	111.2	111.2
6’	6.65 (dd, 2.2, 8.4)	6.70 (dd, 2.1, 8.5)	120.7	120.7
1”			139.2	139.2
2”/6”	6.91 (m)	6.95 (m)	129.1	129.1
3”/5”	7.01 (m)	7.05 (m)	128.5	128.5
4”	7.01 (m)	7.05 (m)	127.2	127.2
6-OMe	3.81 (s)	3.86 (s)	56.2, 56.1, 56.0	56.2, 56.1, 56.0
8-OMe	3.82 (s)	3.87 (s)		
4’-OMe	3.70 (s)	3.76 (s)		
CO_2Me			172.6	172.6
CO-OMe	3.61 (s)	3.66 (s)	52.5	52.5

*147.7, 159.3, 162.2, 165.2 exchangeable
**147.8, 159.3, 162.2, 165.3 exchangeable
(in CD_3OD)

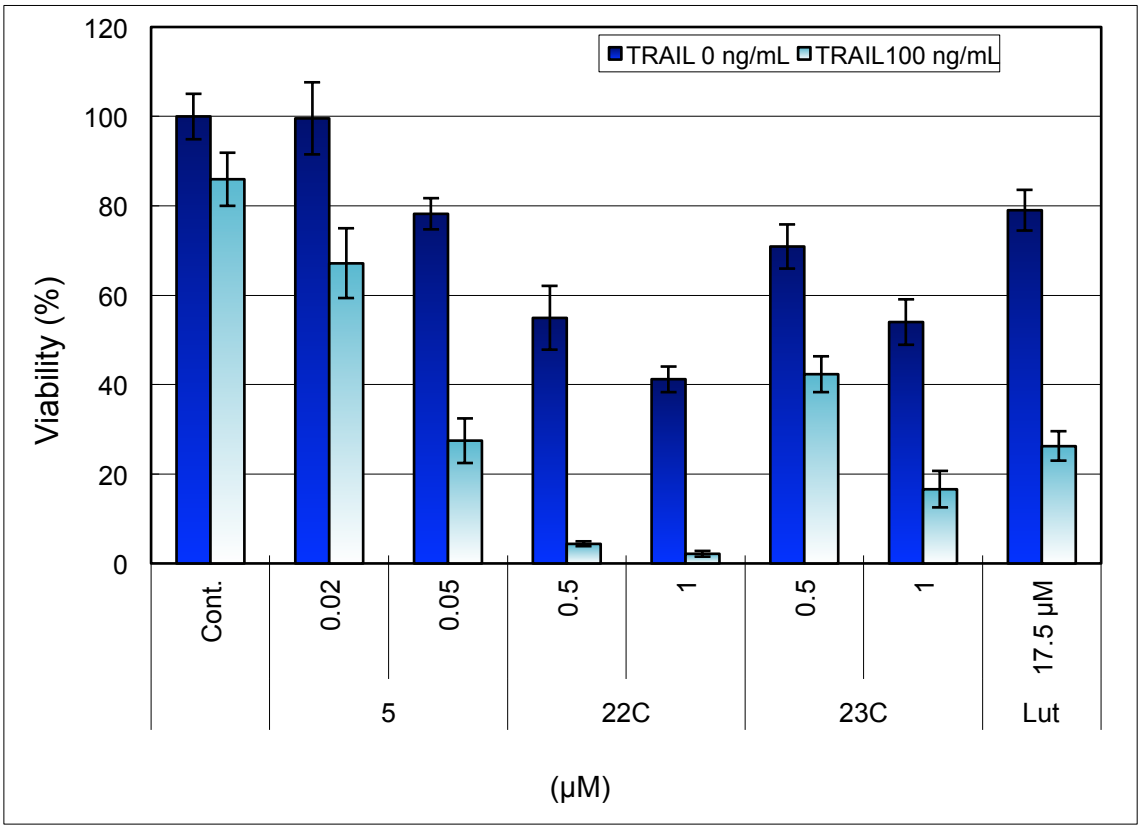
Table 2 Comparison of data of synthetic compound **4** with reported value.



position	^{1}H-NMR δ (*J* in Hz) **4** (400 MHz)	^{1}H-NMR δ (*J* in Hz) ref 5 (400 MHz)	^{13}C-NMR δ (*J* in Hz) **4** (100MHz)	^{13}C-NMR δ (*J* in Hz) ref 5 (100MHz)
1	4.98 (d, 6.6)	4.93 (d, 5.5)	79.3	78.8
2	3.92 (dd, 6.6, 14.1)	3.87 (dd, 5.5, 14.5)	50.2	51.4
3	4.26 (d, 14.1)	4.29 (d, 14.5)	55.7	55.9
3a			101.7	101.7
4a			160.8	161.1
5	6.25 (d, 2.0)	6.28 (d, 2.0)	89.4	88.9
6			164.0	163.9
7	6.09 (d, 2.0)	6.13 (d, 2.0)	92.6	92.4
8			157.0	157.4
8a			107.3	106.9
8b			93.6	93.7
1’			127.5	127.7
2’	6.78 (d, 2.0)	6.84 (d, 2.5)	114.4	114.6
3’			144.5	144.3
4’			145.7	145.8
5’	6.58 (d, 8.6)	6.60 (d, 8.5)	109.5	109.6
6’	6.63 (dd, 2.0, 8.6)	6.71 (dd, 2.5, 8.5)	119.6	119.5
1”			136.7	136.5
2”/6”	7.09-7.04 (m)	7.14-7.06 (m)	127.7	128.2
3”/5”	6.94-6.92 (m)	7.14-7.06 (m)	127.8	128.8
4”	7.09-7.04 (m)	7.14-7.06 (m)	126.5	126.7
Ar-OMe	3.81 (s) 3.81 (s) 3.76 (s)	3.86 (s) 3.84 (s) 3.77 (s)	55.7 55.7 54.9	55.6 55.6 55.6
CO_2H			174.2	173.2

(in $CDCl_3$)

Figure 3 TRAIL resistance overcoming activity of **5**, **22c** and **23c**.



X-ray data for **22a**

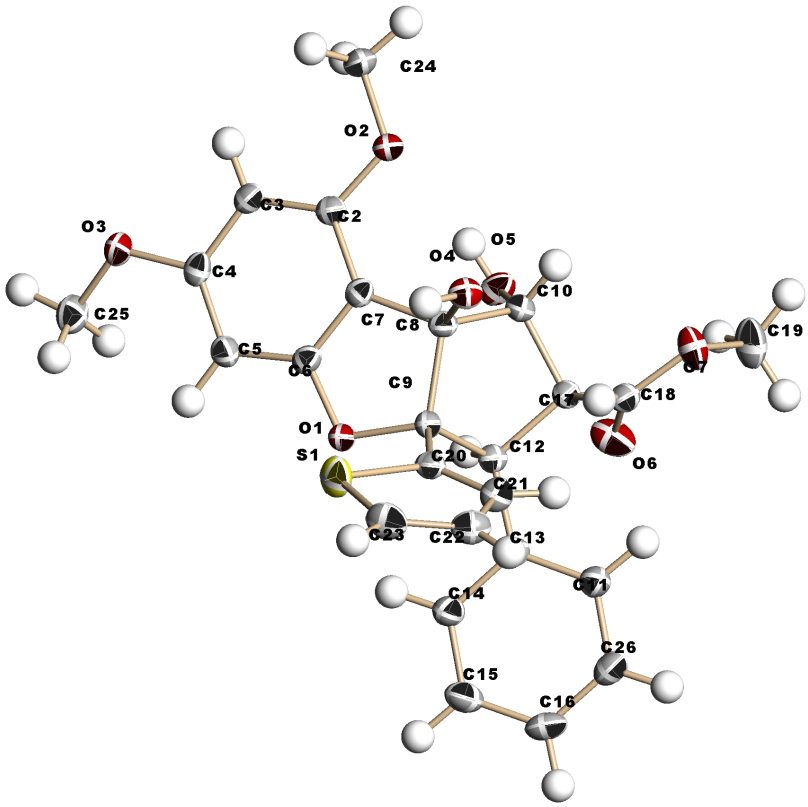


Figure 4. X-ray structure of compound **22a.**

Table 3. Crystal data for **22a**

Chemical formula $C_{25}H_{24}O_7S$

Formula weight 468.50

Wavelength 1.54178 Å

Crystal size 0.200 x 0.200 x 0.800 mm

Crystal system orthorhombic

Space group Pbca

Unit cell dimensions

a = 9.8131(3) Å α = 90°

b = 20.4457(5) Å β = 90°

c = 21.4000(6) Å γ = 90°

Volume 4293.6(2) $Å^3$

Z 8

Density (calculated) 1.450 g/cm^3

Absorption coefficient 1.744 mm^{-1}

F(000) 1968

Table 4. Data collection and structure refinement for 22a

Theta range for data collection 4.13 to 68.11°

Index ranges -11<=h<=9, -24<=k<=23, -25<=l<=23

Reflections collected 14098

Independent reflections 3851 [R(int) = 0.0174]

Coverage of independent

Reflections 98.3%

Absorption correction multi-scan

Max. and min. transmission 0.7217 and 0.3359

Structure solution technique direct methods

Structure solution program SHELXS-97 (Sheldrick, 1997)

Refinement method Full-matrix least-squares on F^2

Refinement program SHELXL-97 (Sheldrick, 1997)

Function minimized $\Sigma w(F_o^2 - F_c^2)^2$

Data / restraints / parameters 3851 / 0 / 355

Goodness-of-fit on F2 1.035

Final R indices 3510 data; $I>2\sigma(I)$ R1 = 0.0374, wR2 = 0.0999

all data R1 = 0.0404, wR2 = 0.1030

Weighting scheme $w=1/[\sigma^2(F_o^2)+(0.0672P)^2+1.5656P]$where $P=(F_o^2+2F_c^2)/3$

Largest diff. peak and hole 0.337 and -0.252 $eÅ^{-3}$

R.M.S. deviation from mean 0.049 $eÅ^{-3}$

X-ray data for **23c**

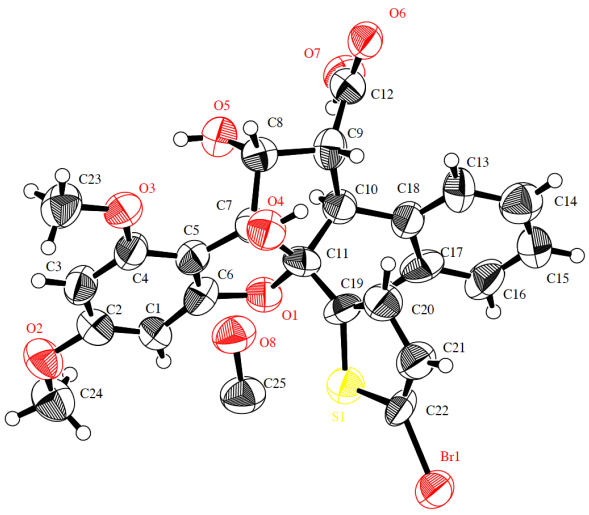


Figure 5. X-ray structure of compound **23c.**

Table 5. Crystal data for **23c**

A. Crystal Data

Empirical Formula	$C_{25}H_{21}BrO_8S$
Formula Weight	561.40
Crystal Color, Habit	colorless, platelet
Crystal Dimensions	0.200 X 0.030 X 0.010 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	a = 11.1283(3) Å
	b = 29.5193(7) Å
	c = 7.7932(2) Å
	b = 108.307(2) ^{o}
	V = 2430.5(1) $Å^3$
Space Group	$P2_1/c$ (#14)

Z value	4
D_{calc}	1.534 g/cm^3
F_{000}	1144.00
m(CuKa)	35.352 cm^{-1}

B. Intensity Measurements

Diffractometer	R-AXIS RAPID
Radiation	CuKa (l = 1.54187 Å)
Voltage, Current	40kV, 30mA
Temperature	-180.0^{o}C
Detector Aperture	460 x 256 mm
Data Images	30 exposures
w oscillation Range (c=54.0, f=0.0)	80.0 - 260.0^o
Exposure Rate	10.0 sec./^{o}
w oscillation Range (c=54.0, f=90.0)	80.0 - 260.0^o
Exposure Rate	10.0 sec./^{o}
w oscillation Range (c=54.0, f=180.0)	80.0 - 260.0^o
Exposure Rate	10.0 sec./^{o}
w oscillation Range (c=54.0, f=270.0)	80.0 - 260.0^o
Exposure Rate	10.0 sec./^{o}
w oscillation Range (c=0.0, f=0.0)	80.0 - 260.0^o
Exposure Rate	10.0 sec./^{o}
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2q_{max}$	136.5^o
No. of Reflections Measured	Total: 26111
	Unique: 4455 (R_{int} = 0.2105)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.564 - 0.965)
	Secondary Extinction
	(coefficient: 1.17000e-003)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function Minimized	$S\ w\ (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\ s^2(Fo^2) + (0.1860 \cdot P)^2 + 0.0000 \cdot P\ ]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2q_{max}$ cutoff	136.5^o
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	4455
No. Variables	317
Reflection/Parameter Ratio	14.05
Residuals: R1 (I>2.00s(I))	0.1210
Residuals: R (All reflections)	0.2434
Residuals: wR2 (All reflections)	0.3993
Goodness of Fit Indicator	1.014
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	$1.07\ e^-/Å^3$
Minimum peak in Final Diff. Map	$-0.94\ e^-/Å^3$

X-ray data for **23d**

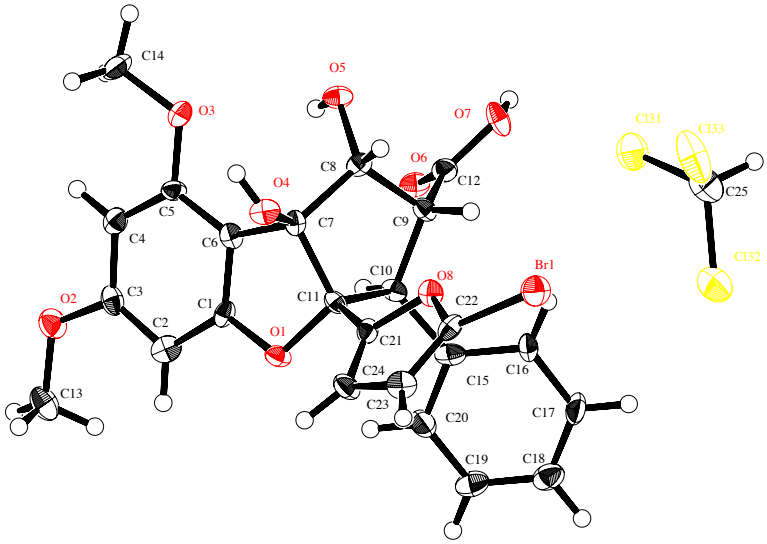


Figure 6. X-ray structure of compound **23d.**

Table 6. Crystal data for **23d**

A. Crystal Data

Empirical Formula	$C_{25}H_{22}BrCl_3O_8$
Formula Weight	636.71
Crystal Color, Habit	colorless, platelet
Crystal Dimensions	0.200 X 0.050 X 0.050 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.7833(3) Å
	b = 10.5843(4) Å
	c = 14.6153(5) Å
	a = 74.063(2)°
	b = 80.510(2)°
	g = 63.284(2)°
	V = 1298.37(8) Å^3
Space Group	P-1 (#2)

Z value	2
D_{calc}	1.629 g/cm^3
F_{000}	644.00
m(CuKa)	54.275 cm^{-1}

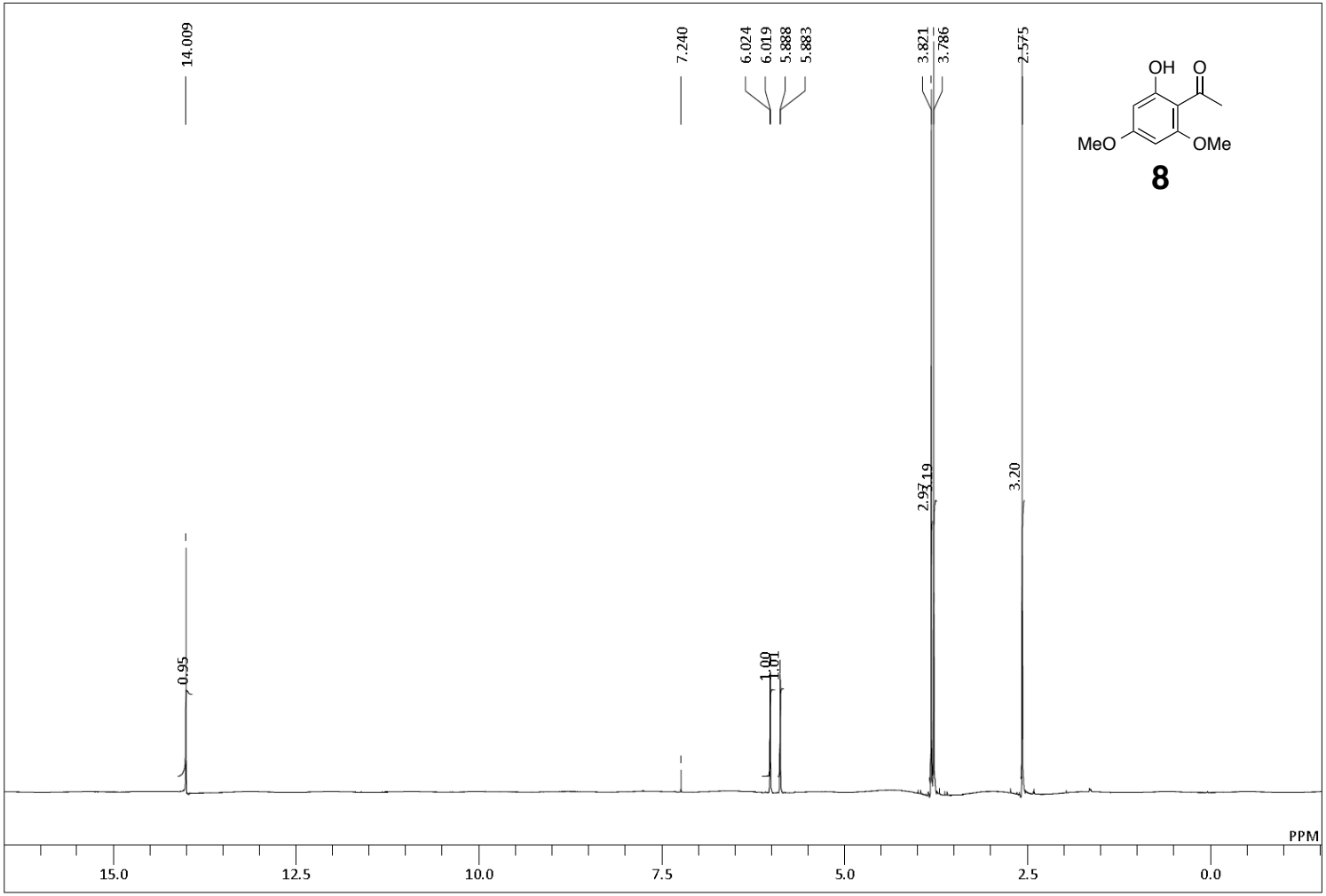
B. Intensity Measurements

Diffractometer	R-AXIS RAPID
Radiation	CuKa (l = 1.54187 Å)
Voltage, Current	40kV, 30mA
Temperature	-180.0°C
Detector Aperture	460 x 256 mm
Data Images	30 exposures
w oscillation Range (c=54.0, f=0.0)	80.0 - 260.0°
Exposure Rate	4.0 sec./°
w oscillation Range (c=54.0, f=90.0)	80.0 - 260.0°
Exposure Rate	4.0 sec./°
w oscillation Range (c=54.0, f=180.0)	80.0 - 260.0°
Exposure Rate	4.0 sec./°
w oscillation Range (c=54.0, f=270.0)	80.0 - 260.0°
Exposure Rate	4.0 sec./°
w oscillation Range (c=0.0, f=0.0)	80.0 - 260.0°
Exposure Rate	4.0 sec./°
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2q_{max}$	136.5°
No. of Reflections Measured	Total: 13987
	Unique: 4644 (R_{int} = 0.0629)
Corrections	Lorentz-polarization
	Absorption
	(trans. factors: 0.617 - 0.762)
	Secondary Extinction
	(coefficient: 2.40000e-004)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function Minimized	$S\ w\ (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\ s^2(Fo^2) + (0.0000 \cdot P)^2 + 8.1150 \cdot P\ ]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
$2q_{max}$ cutoff	136.5^o
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	4644
No. Variables	335
Reflection/Parameter Ratio	13.86
Residuals: R1 (I>2.00s(I))	0.0547
Residuals: R (All reflections)	0.1044
Residuals: wR2 (All reflections)	0.1490
Goodness of Fit Indicator	1.137
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	$0.77\ e^-/Å^3$
Minimum peak in Final Diff. Map	$-0.84\ e^-/Å^3$

Compound **8**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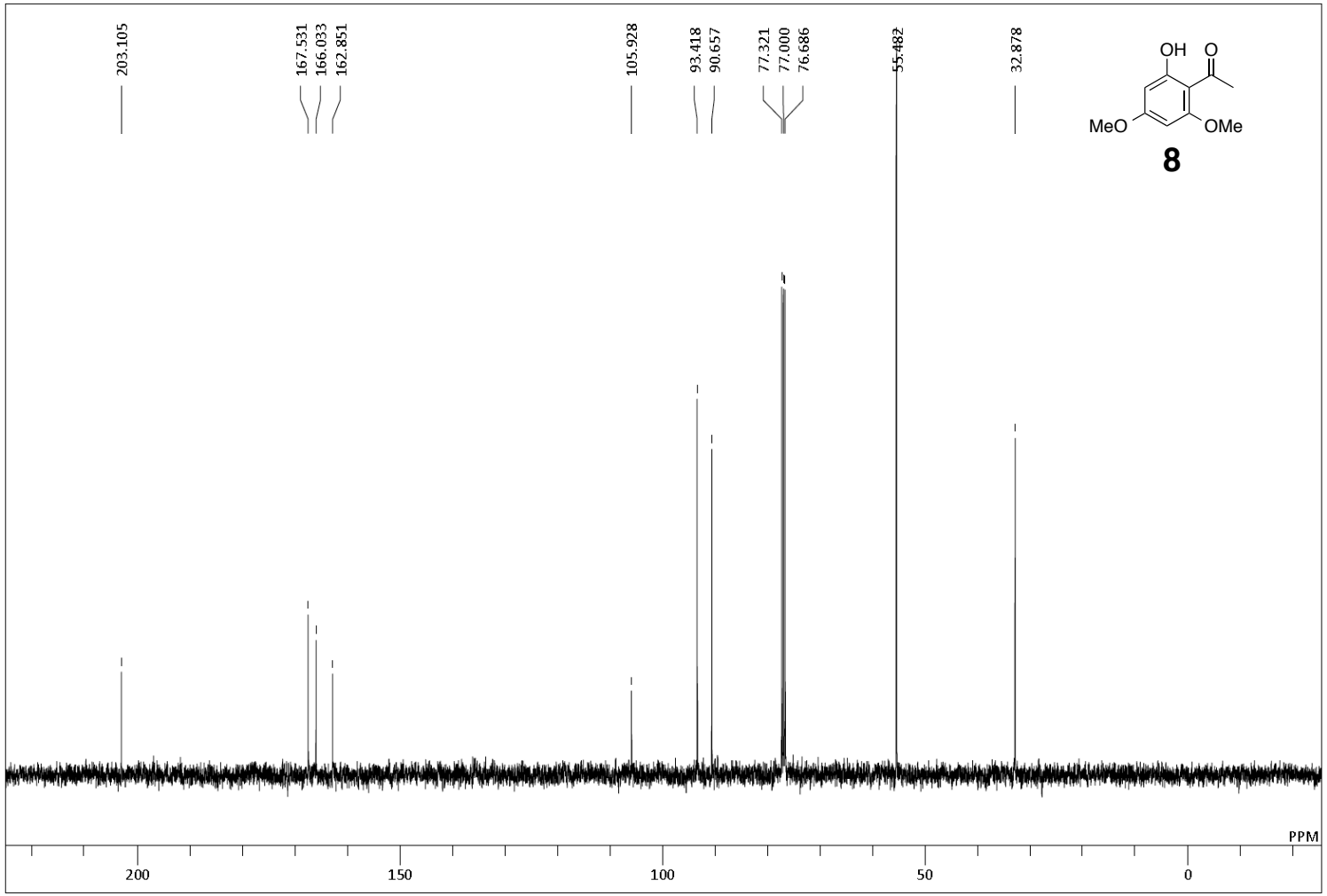
6.019
5.888
5.883
3.821
3.786
2.575
2.97
3.19
3.20
0.95
1.00
1.01
OH
O
MeO
OMe
8
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0

Compound **8**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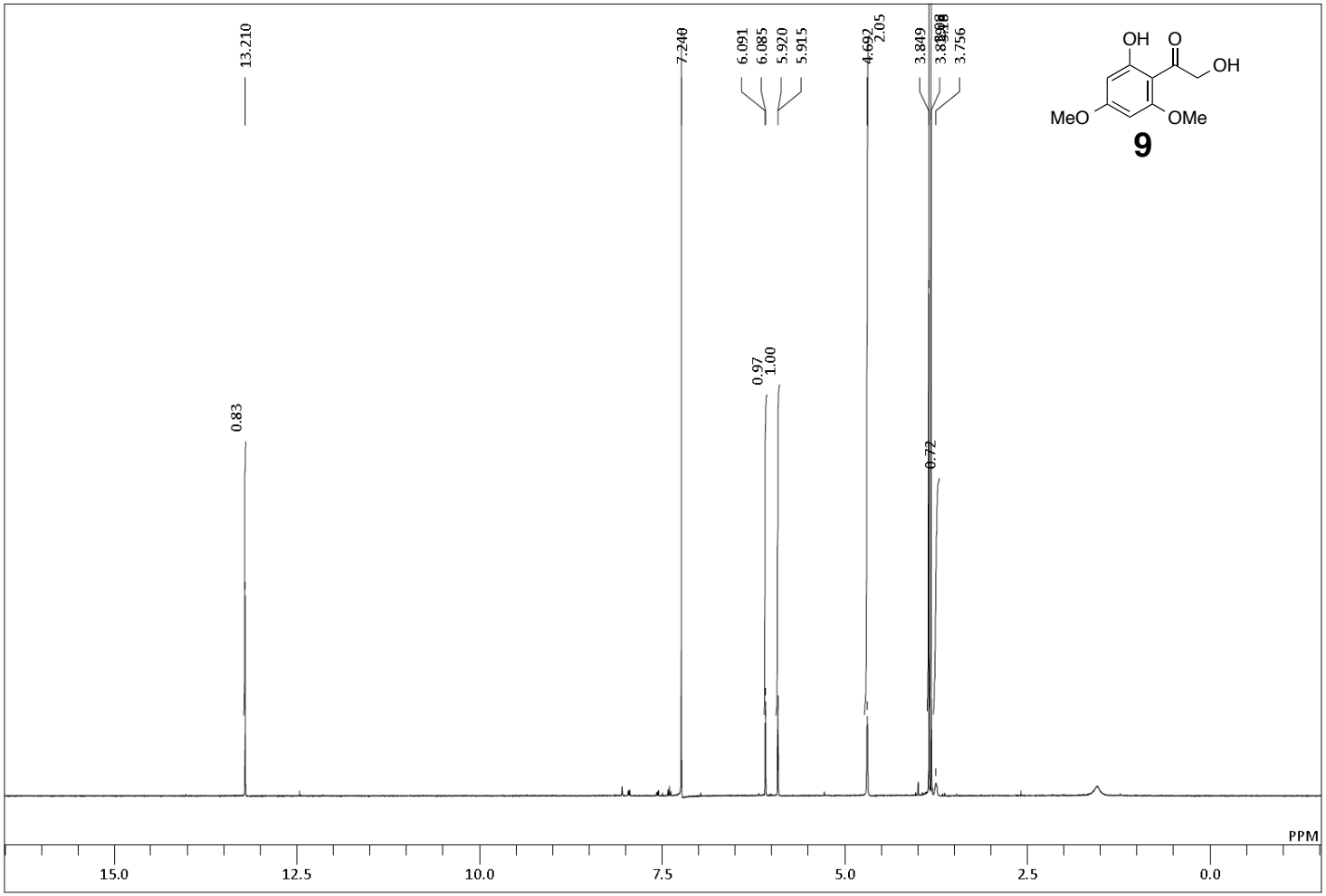
166.033
162.851
105.928
93.418
90.657
77.321
77.000
76.686
55.482
32.878
OH
O
MeO
OMe
8
PPM
200
150
100
50
0

Compound **9**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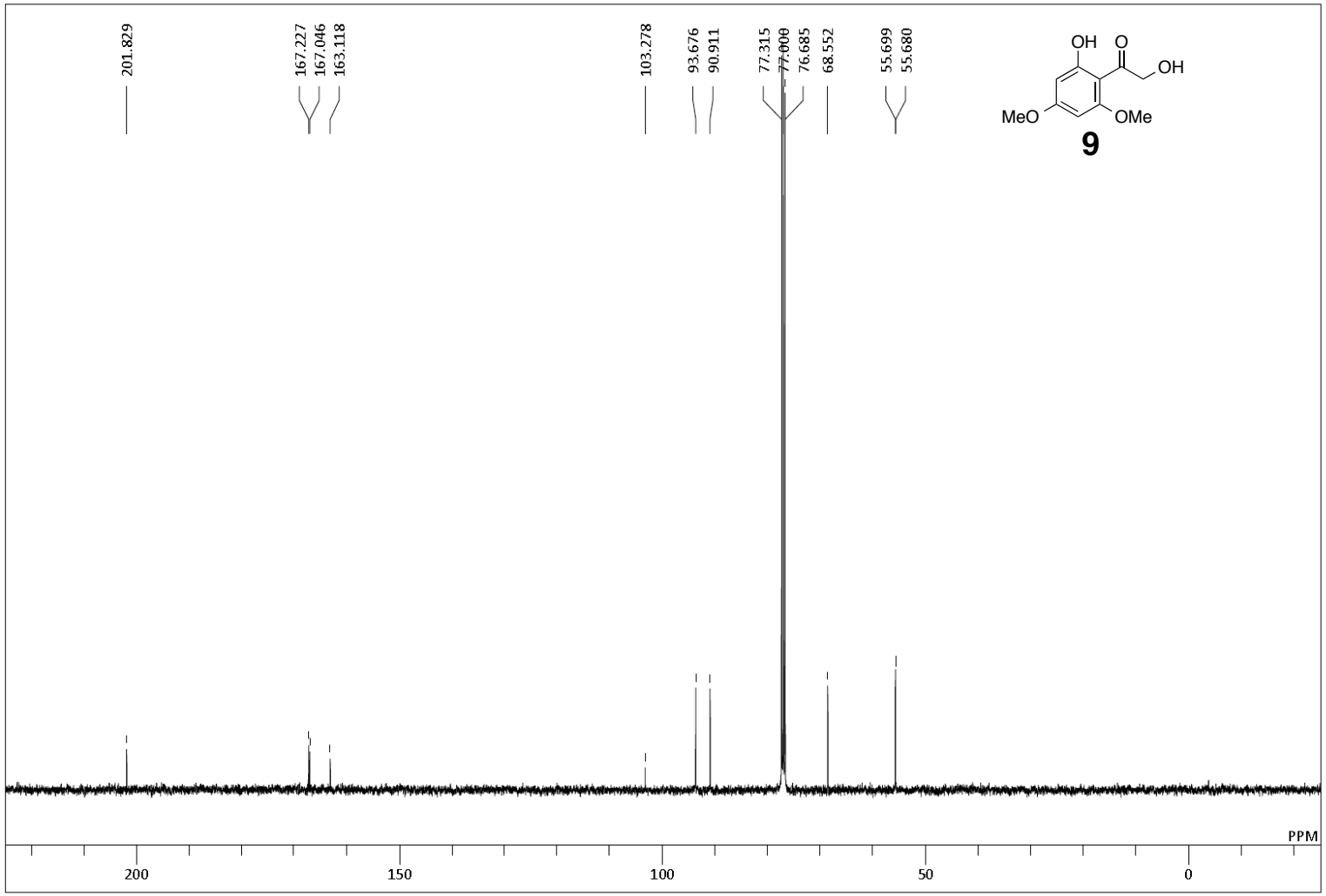
7.240
6.091
6.085
5.920
5.915
4.692
2.05
3.849
3.756
0.83
0.97
1.00
0.72
OH
O
OH
MeO
OMe
9
PPM
15.0
12.5
10.0
7.5
5.0
2.5
0.0

Compound **9**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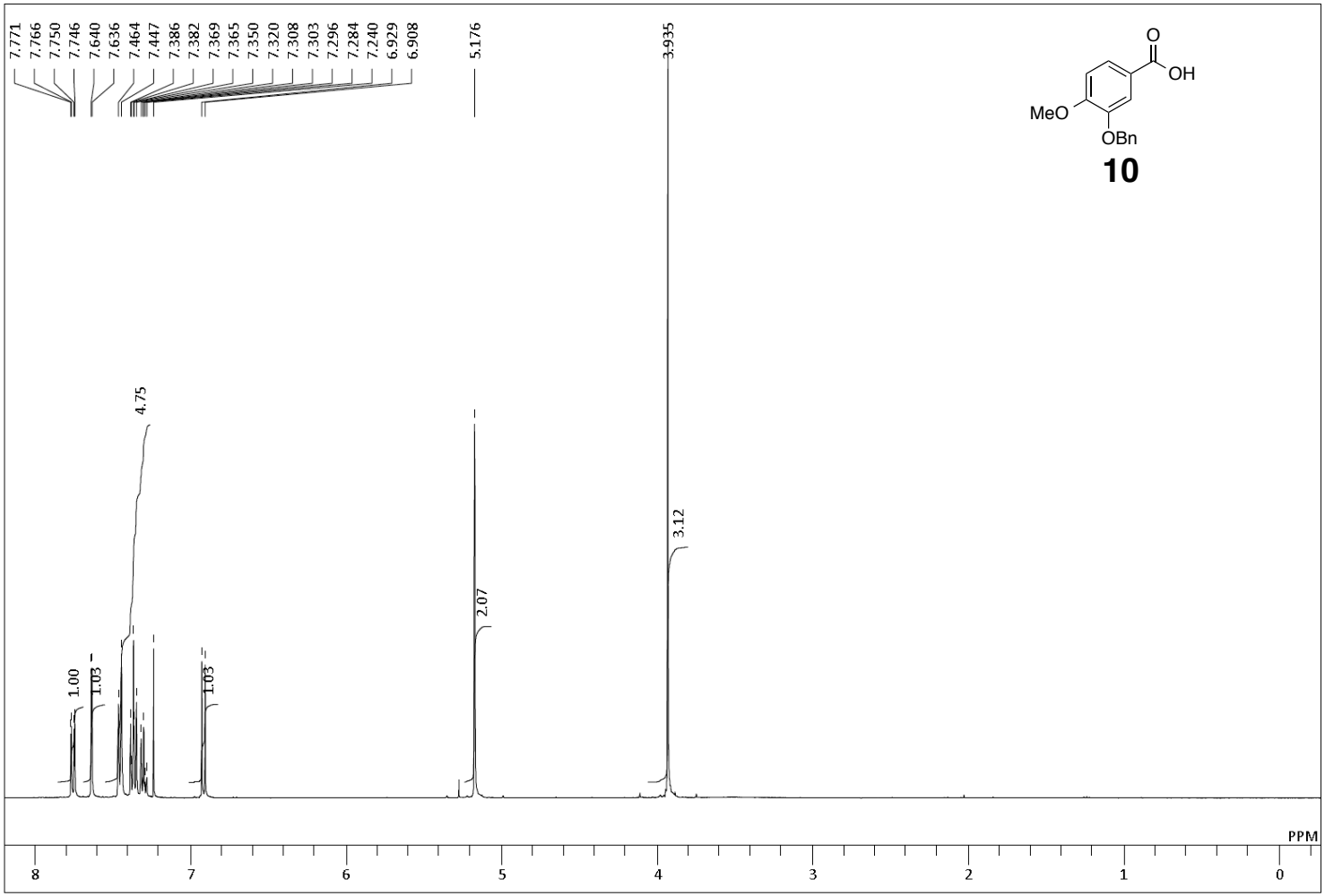
167.046
163.118
103.278
93.676
90.911
77.315
77.000
76.685
68.552
55.699
55.680
OH
O
OH
MeO
OMe
9
PPM
200
150
100
50
0

Compound 10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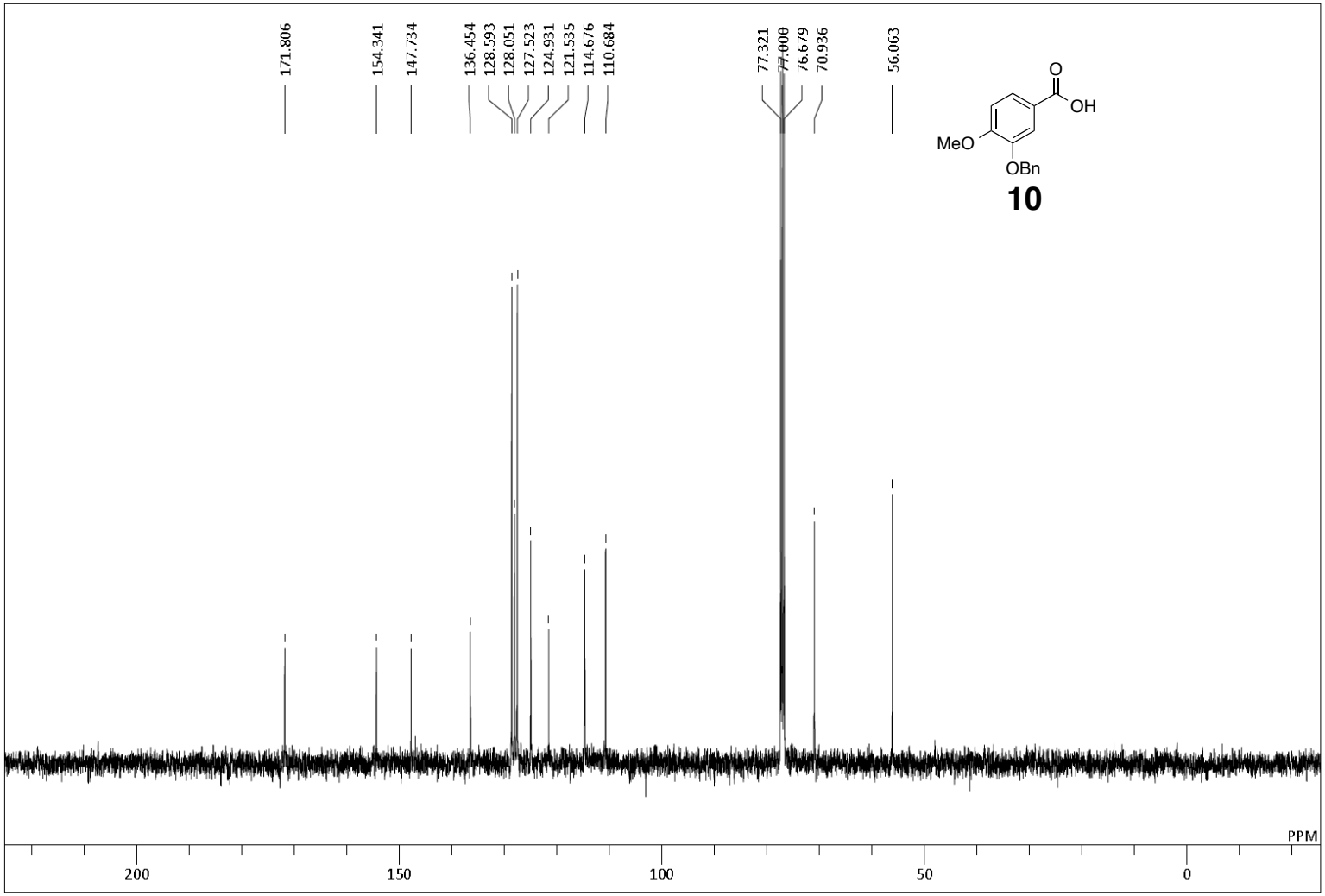
7.766
7.750
7.746
7.640
7.636
7.464
7.447
7.386
7.382
7.369
7.365
7.350
7.320
7.308
7.303
7.296
7.284
7.240
6.929
6.908
5.176
3.935
4.75
3.12
2.07
1.00
1.03
1.03
O
OH
MeO
OBn
10
PPM
8
7
6
5
4
3
2
1
0

Compound 10


171.806
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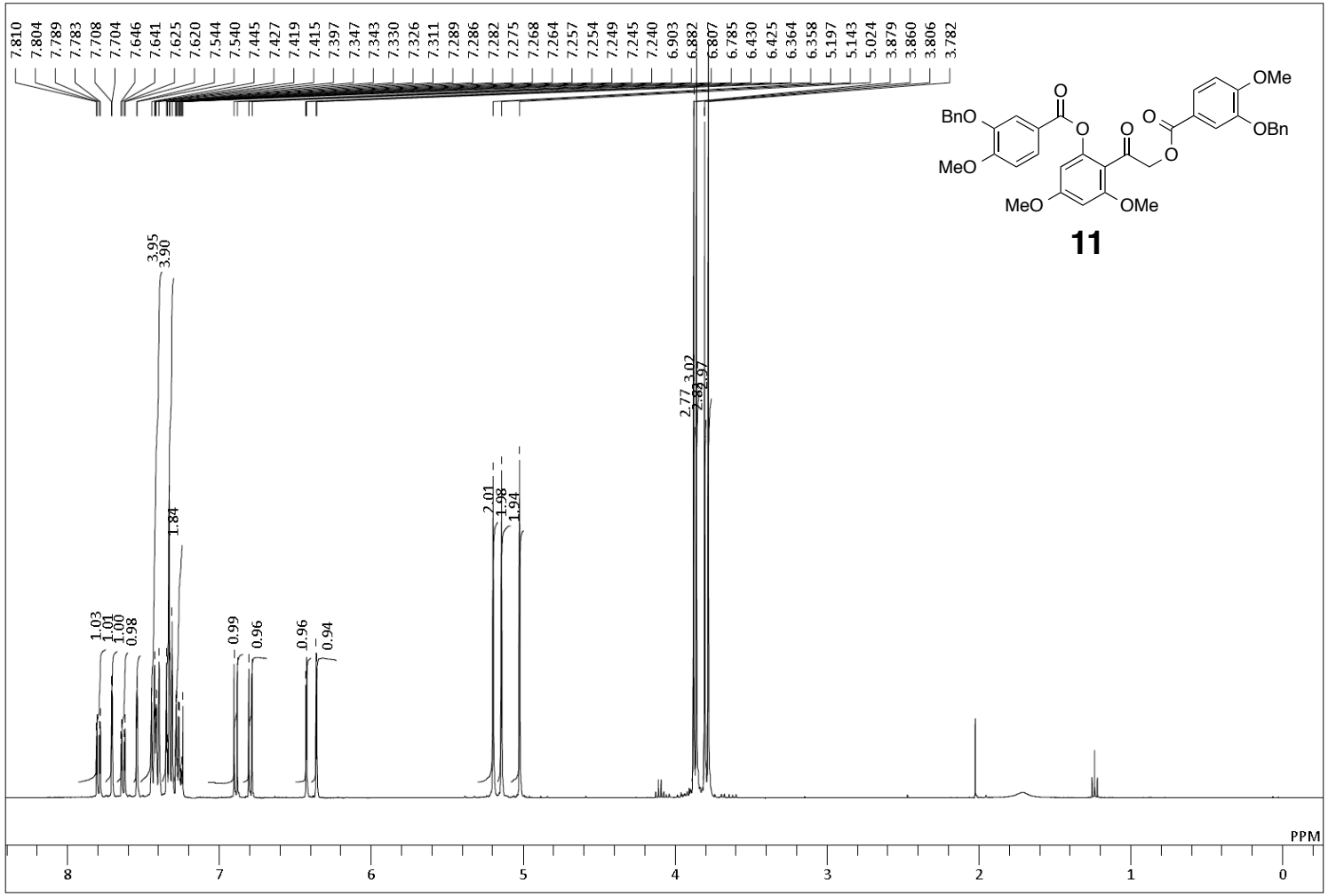
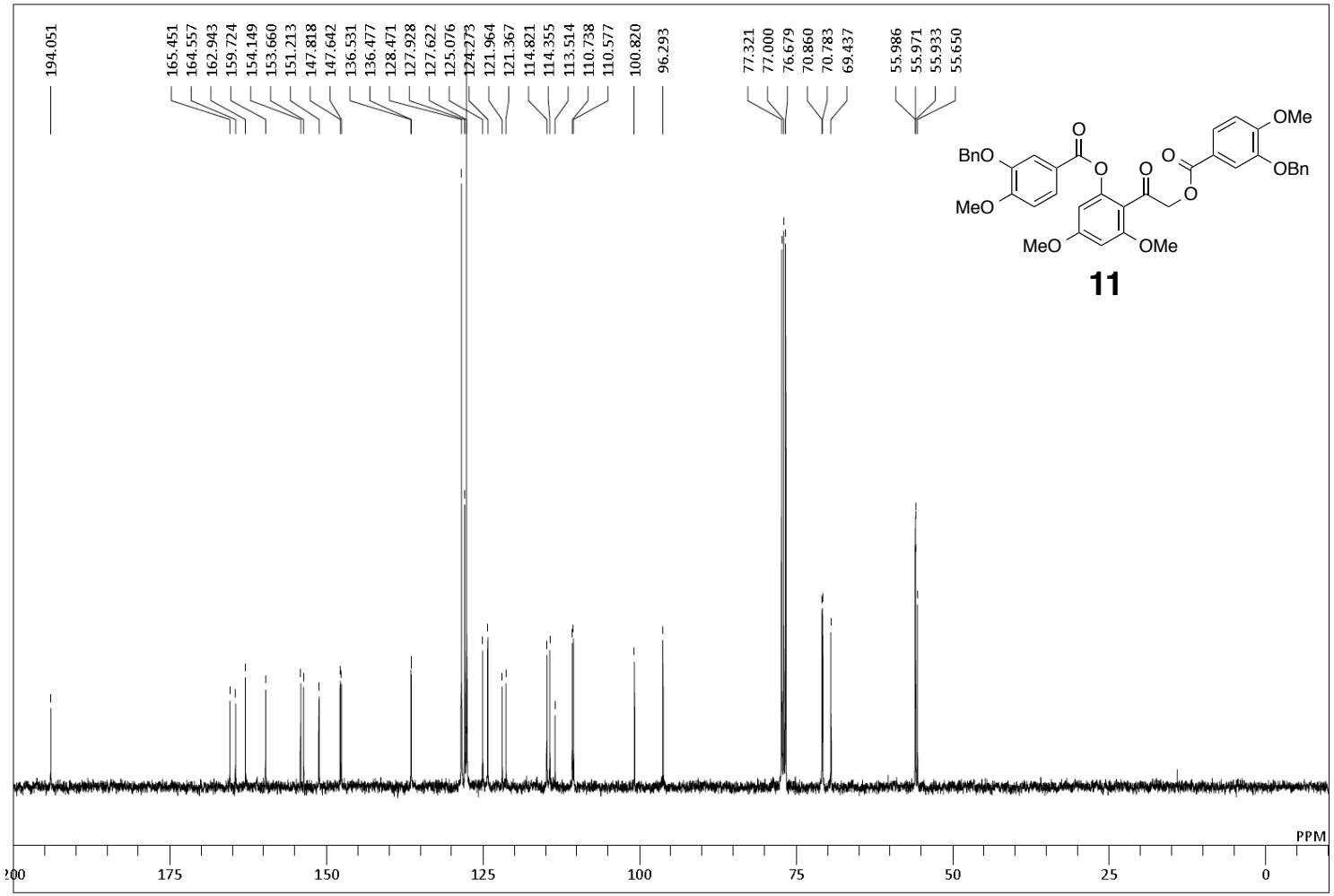
147.734
136.454
128.593
128.051
127.523
124.931
121.535
114.676
110.684
77.321
77.000
76.679
70.936
56.063
O
OH
MeO
OBn
10
PPM
200
150
100
50
0

Compound 11


7.810
7.804
7.789
7.783
7.708
7.704
7.646
7.641
7.625
7.620
7.544
7.540
7.445
7.427
7.419
7.415
7.397
7.347
7.343
7.330
7.326
7.311
7.289
7.286
7.282
7.275
7.268
7.264
7.257
7.254
7.249
7.245
7.240
6.903
6.882
6.807
6.785
6.430
6.425
6.364
6.358
5.197
5.143
5.024
3.879
3.860
3.806
3.782
3.95
3.90
1.84
1.03
1.01
1.00
0.98
0.99
0.96
0.96
0.94
2.01
1.98
1.94
2.77
3.02
2.83
3.97
BnO
MeO
MeO
OMe
OMe
OBn
11
PPM
8
7
6
5
4
3
2
1
0

Compound 11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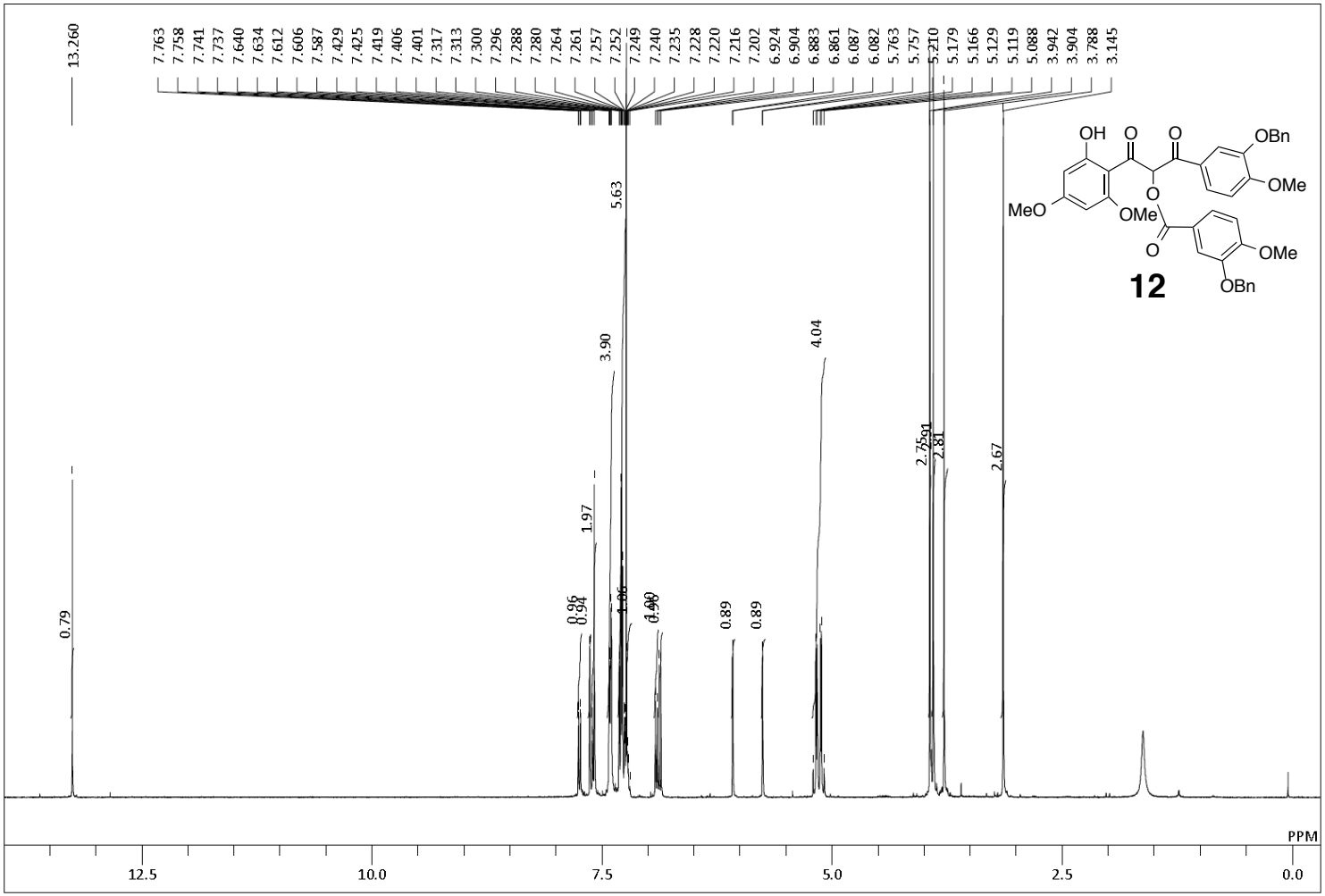
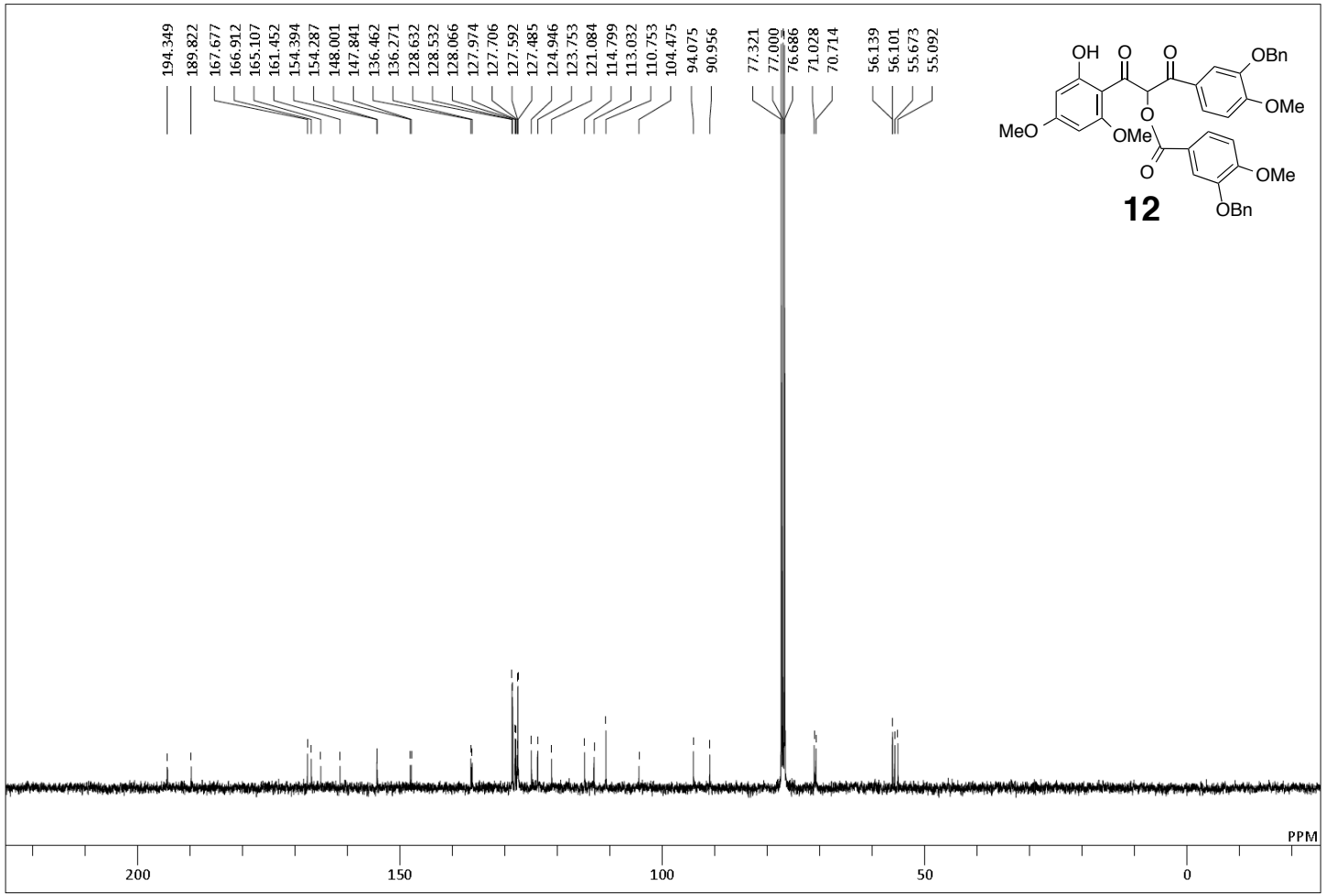
165.451
164.557
162.943
159.724
154.149
153.660
151.213
147.818
147.642
136.531
136.477
128.471
127.928
127.622
125.076
124.273
121.964
121.367
114.821
114.355
113.514
110.738
110.577
100.820
96.293
77.321
77.000
76.679
70.860
70.783
69.437
55.986
55.971
55.933
55.650
BnO
MeO
MeO
OMe
OMe
OBn
11
PPM
200
175
150
125
100
75
50
25
0

Compound 12


13.260
7.763
7.758
7.741
7.737
7.640
7.634
7.612
7.606
7.587
7.429
7.425
7.419
7.406
7.401
7.317
7.313
7.300
7.296
7.288
7.280
7.264
7.261
7.257
7.252
7.249
7.240
7.235
7.228
7.220
7.216
7.202
6.924
6.904
6.883
6.861
6.087
6.082
5.763
5.757
5.210
5.179
5.166
5.129
5.119
5.088
3.942
3.904
3.788
3.145
5.63
3.90
4.04
2.75
2.81
2.67
1.97
0.96
0.94
1.06
0.89
0.89
0.79
OH
O
O
OBn
OMe
MeO
OMe
O
O
OMe
OBn
12
PPM
12.5
10.0
7.5
5.0
2.5
0.0

Compound 12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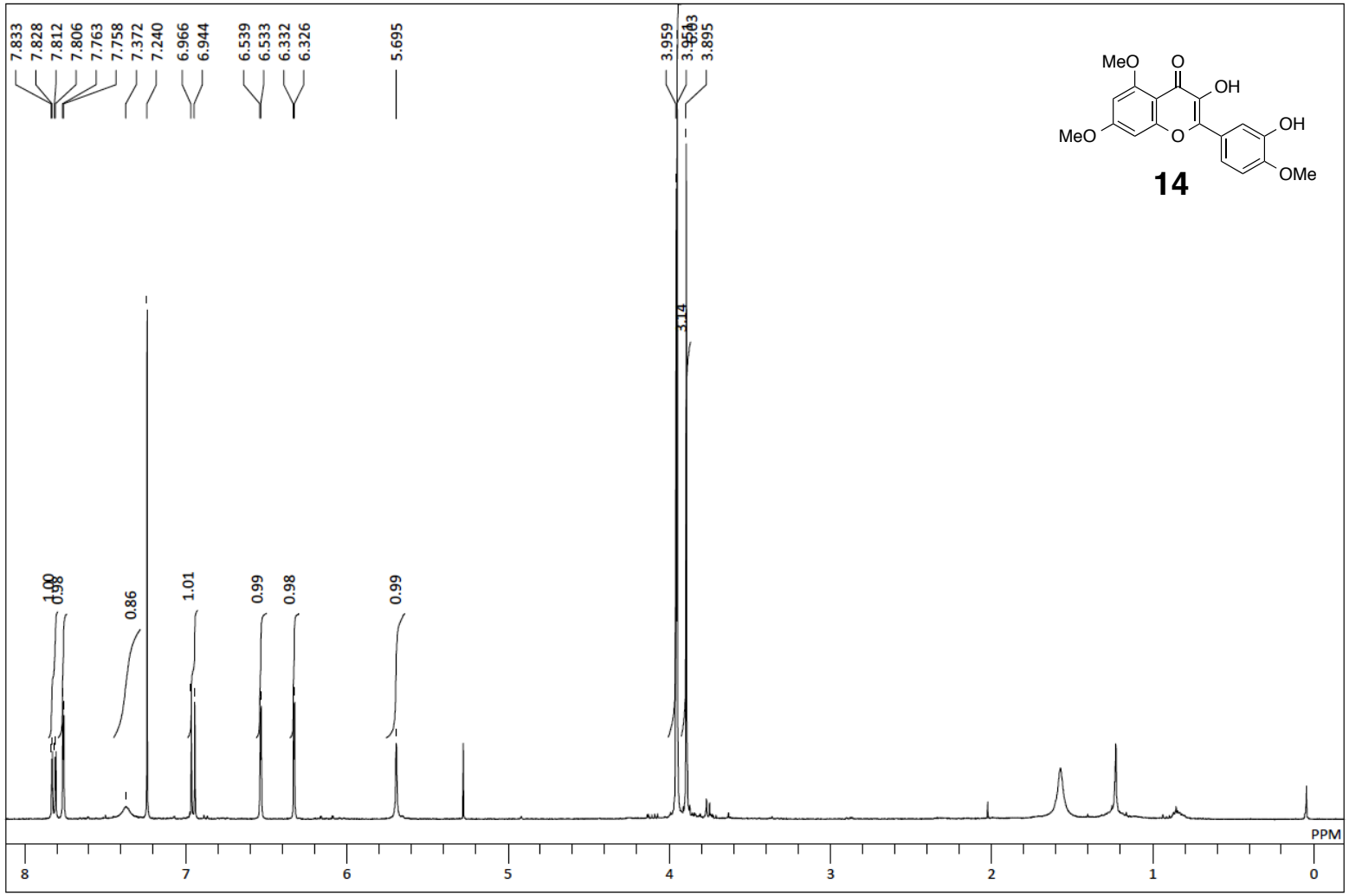
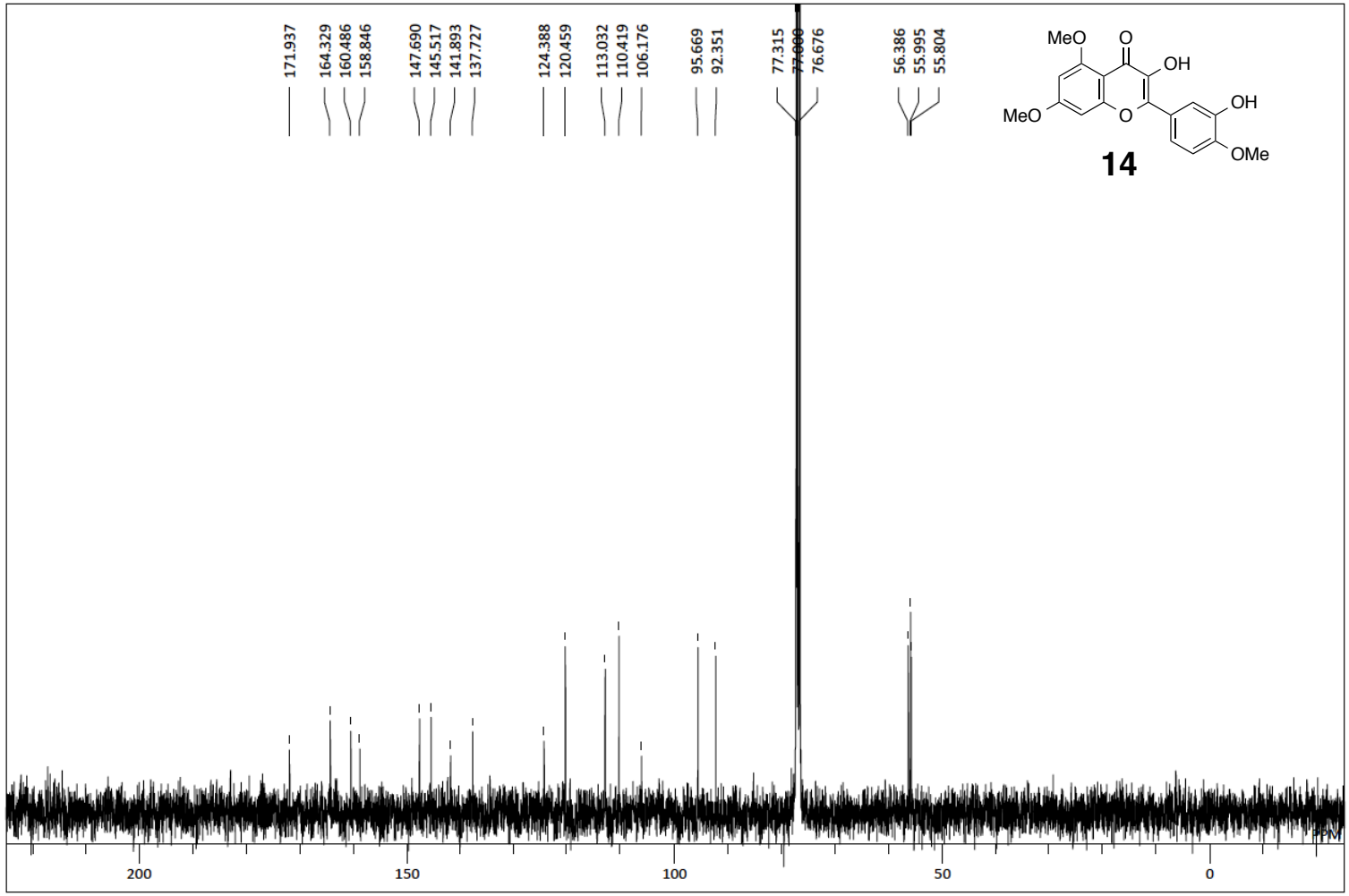
189.822
167.677
166.912
165.107
161.452
154.394
154.287
148.001
147.841
136.462
136.271
128.632
128.532
128.066
127.974
127.706
127.592
127.485
124.946
123.753
121.084
114.799
113.032
110.753
104.475
94.075
90.956
77.321
77.000
76.686
71.028
70.714
56.139
56.101
55.673
55.092
OH
O
O
OBn
OMe
MeO
OMe
O
O
OMe
OBn
12
PPM
200
150
100
50
0

Compound 14


7.833
7.828
7.812
7.806
7.763
7.758
7.372
7.240
6.966
6.944
6.539
6.533
6.332
6.326
5.695
3.959
3.951
3.895
MeO
O
OH
MeO
O
OH
OMe
14
3.14
1.00
0.98
0.86
1.01
0.99
0.98
0.99
PPM
8
7
6
5
4
3
2
1
0

Compound 14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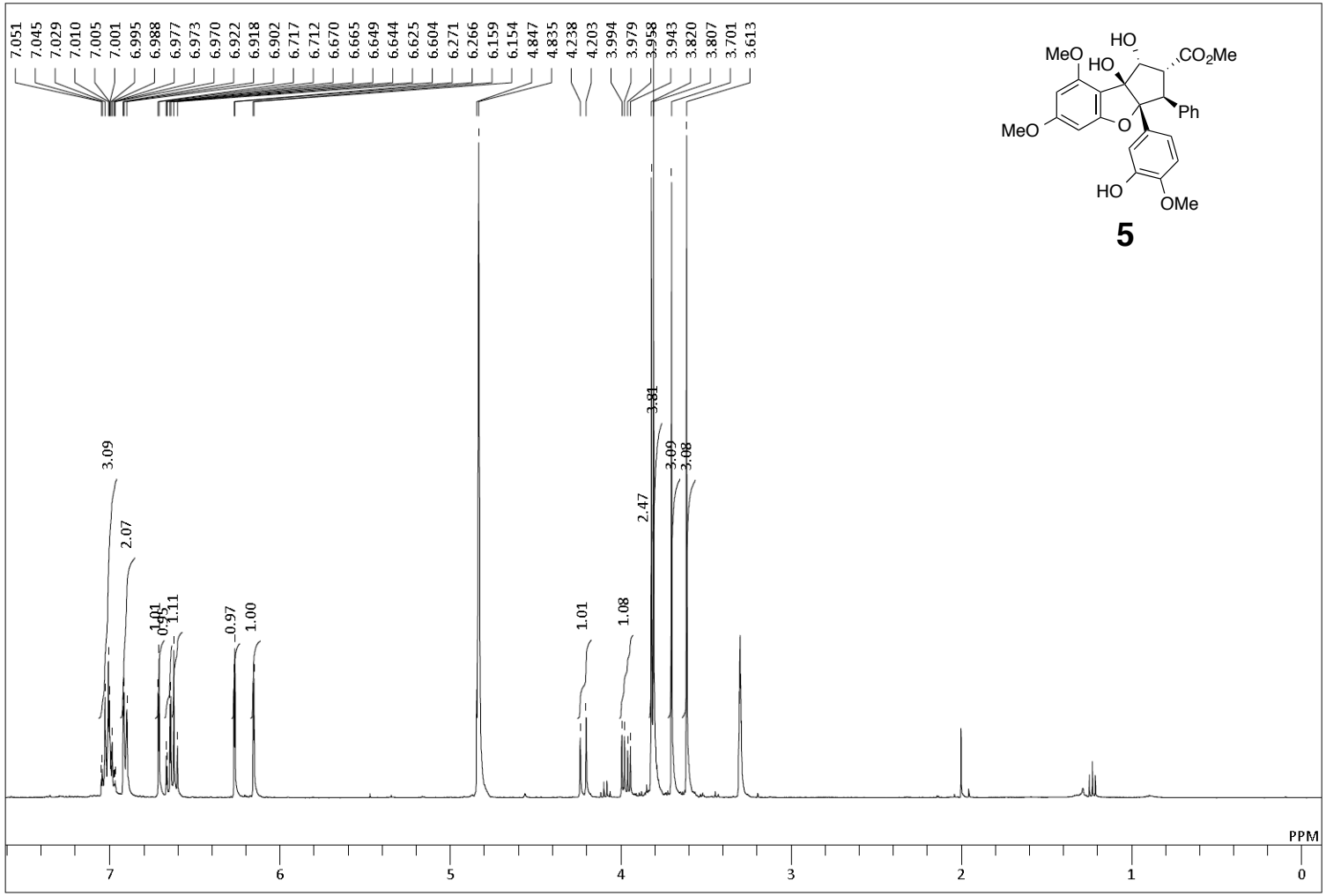
164.329
160.486
158.846
147.690
145.517
141.893
137.727
124.388
120.459
113.032
110.419
106.176
95.669
92.351
77.315
77.000
76.676
56.386
55.995
55.804
MeO
O
OH
MeO
O
OH
OMe
14
200
150
100
50
0

Compound 5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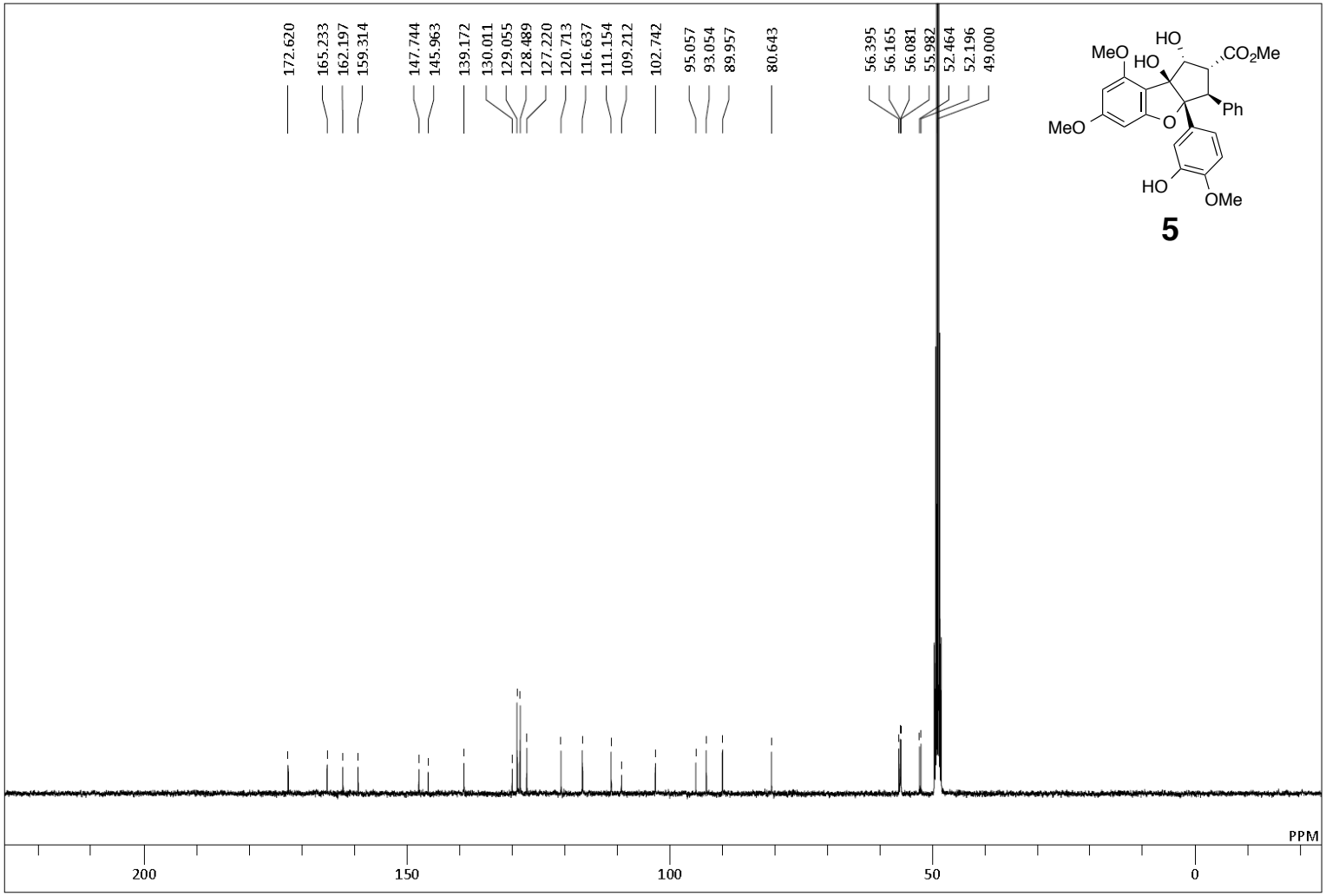
7.045
7.029
7.010
7.005
7.001
6.995
6.988
6.977
6.973
6.970
6.922
6.918
6.902
6.717
6.712
6.670
6.665
6.649
6.644
6.625
6.604
6.271
6.266
6.159
6.154
4.847
4.835
4.238
4.203
3.994
3.979
3.958
3.943
3.820
3.807
3.701
3.613
3.09
2.07
1.01
0.95
1.11
0.97
1.00
1.01
1.08
2.47
3.81
3.09
3.08
MeO
HO
HO
CO2Me
Ph
MeO
O
HO
OMe
5
PPM
7
6
5
4
3
2
1
0

Compound 5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162.197
159.314
147.744
145.963
139.172
130.011
129.055
128.489
127.220
120.713
116.637
111.154
109.212
102.742
95.057
93.054
89.957
80.643
56.395
56.165
56.081
55.982
52.464
52.196
49.000
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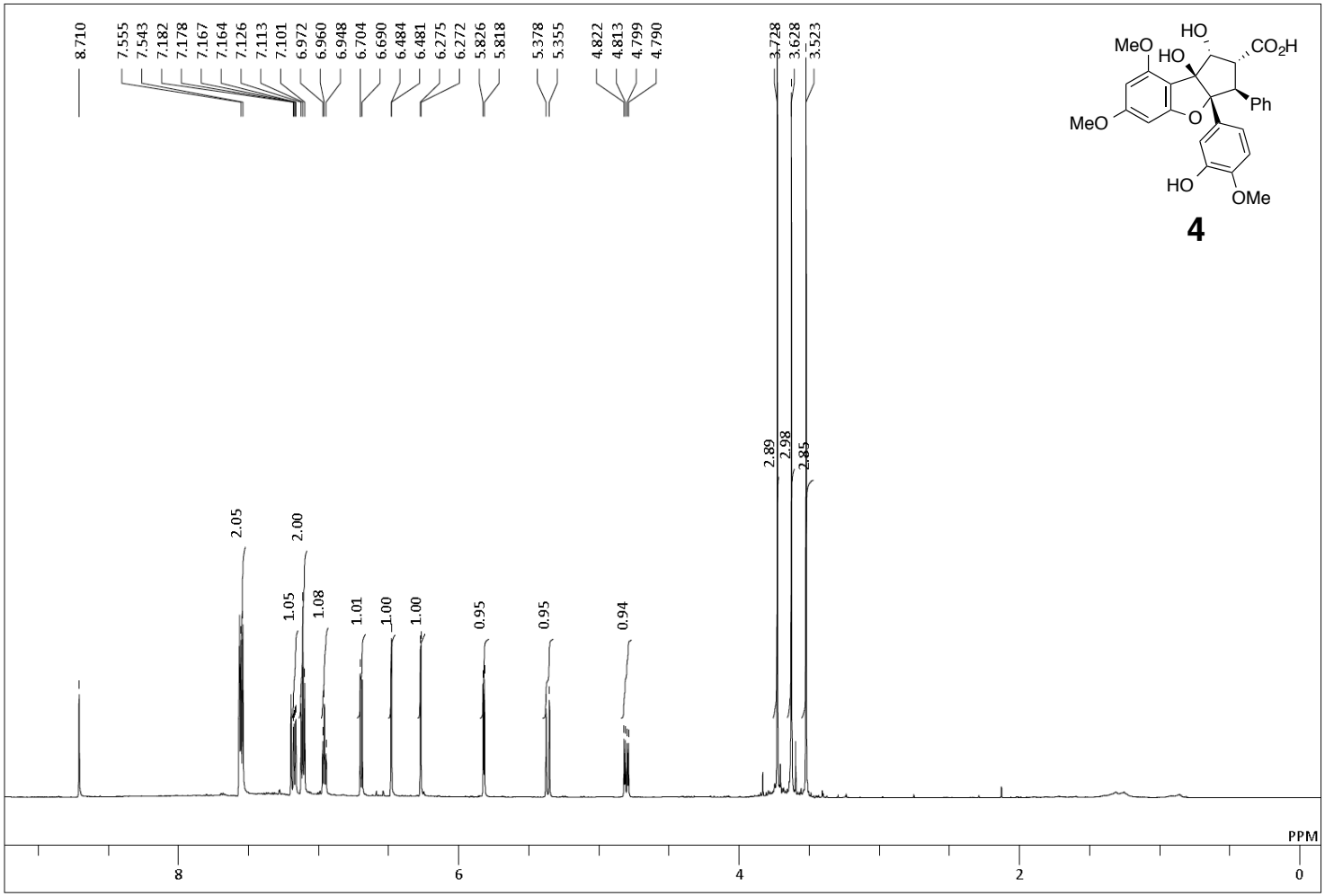
HO
CO2Me
Ph
MeO
O
HO
OMe
5
PPM
200
150
100
50
0

Compound 4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1.01
1.00
1.00
0.95
0.95
0.94
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CO2H
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O
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OMe
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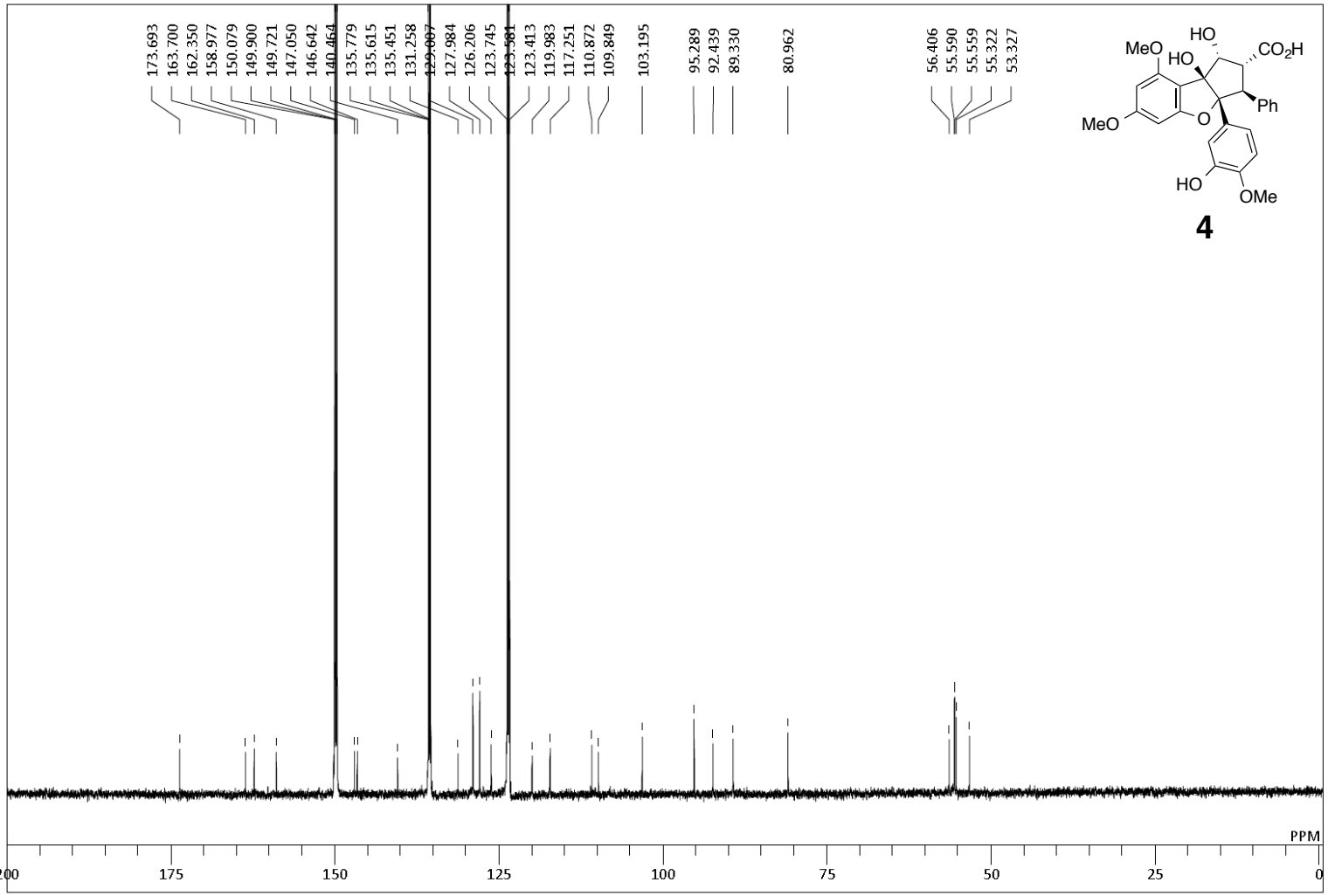
Compound 4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129.007
127.984
126.206
123.745
123.581
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119.983
117.251
110.872
109.849
103.195
95.289
92.439
89.330
80.962
56.406
55.590
55.559
55.322
53.327
HO
MeO
HO
CO2H
Ph
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O
HO
OMe
4
PPM
200
175
150
125
100
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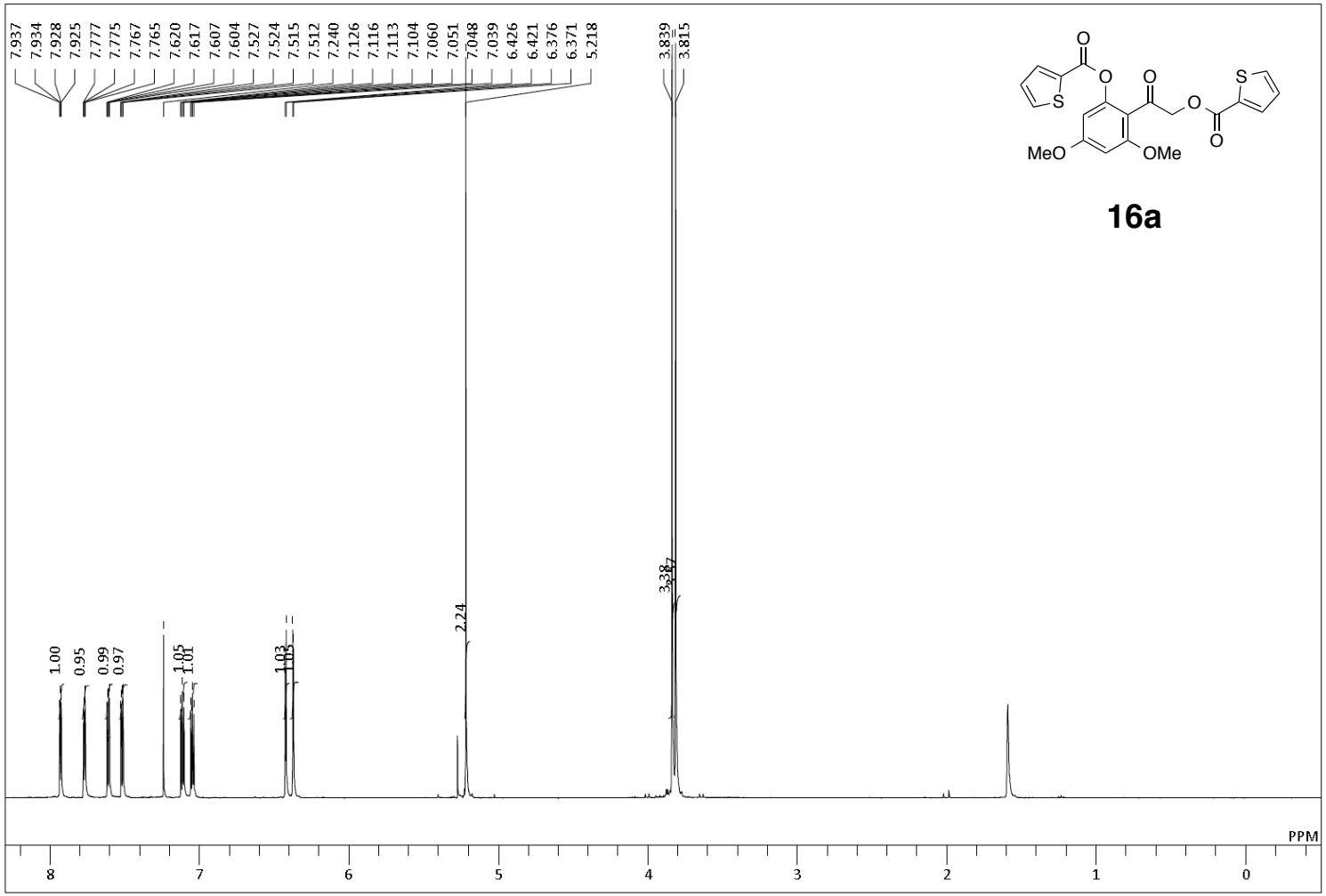
Compound 16a



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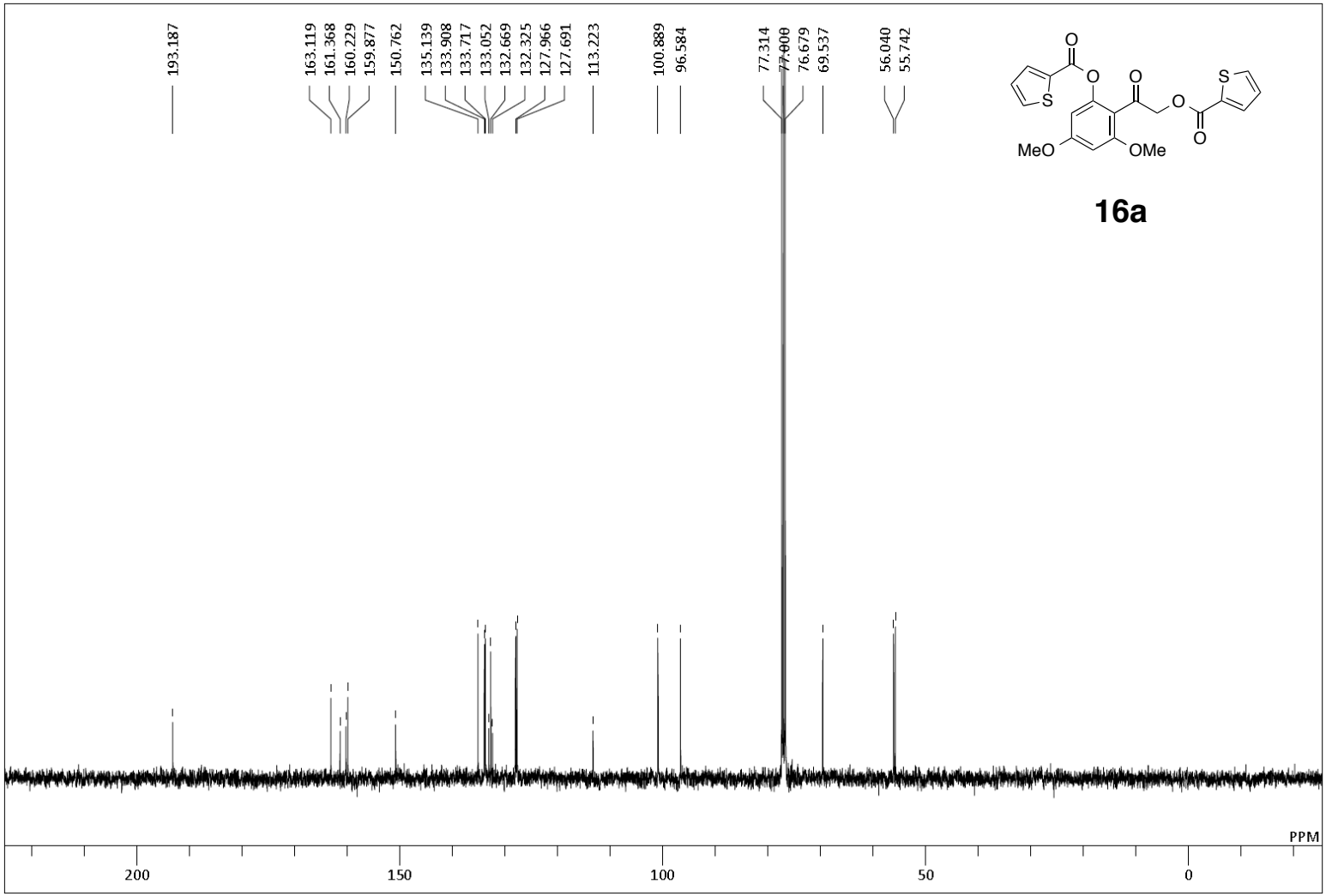

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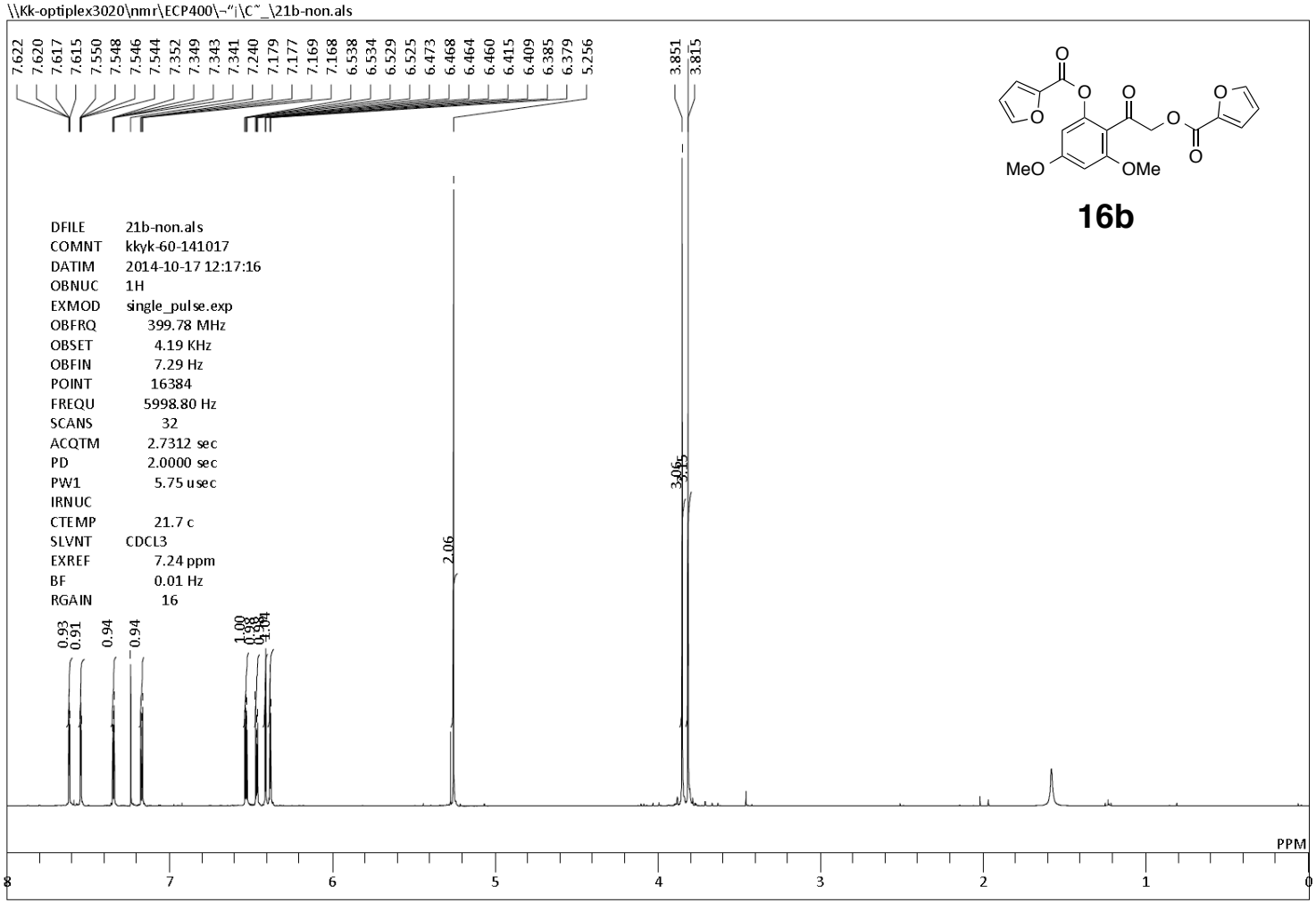

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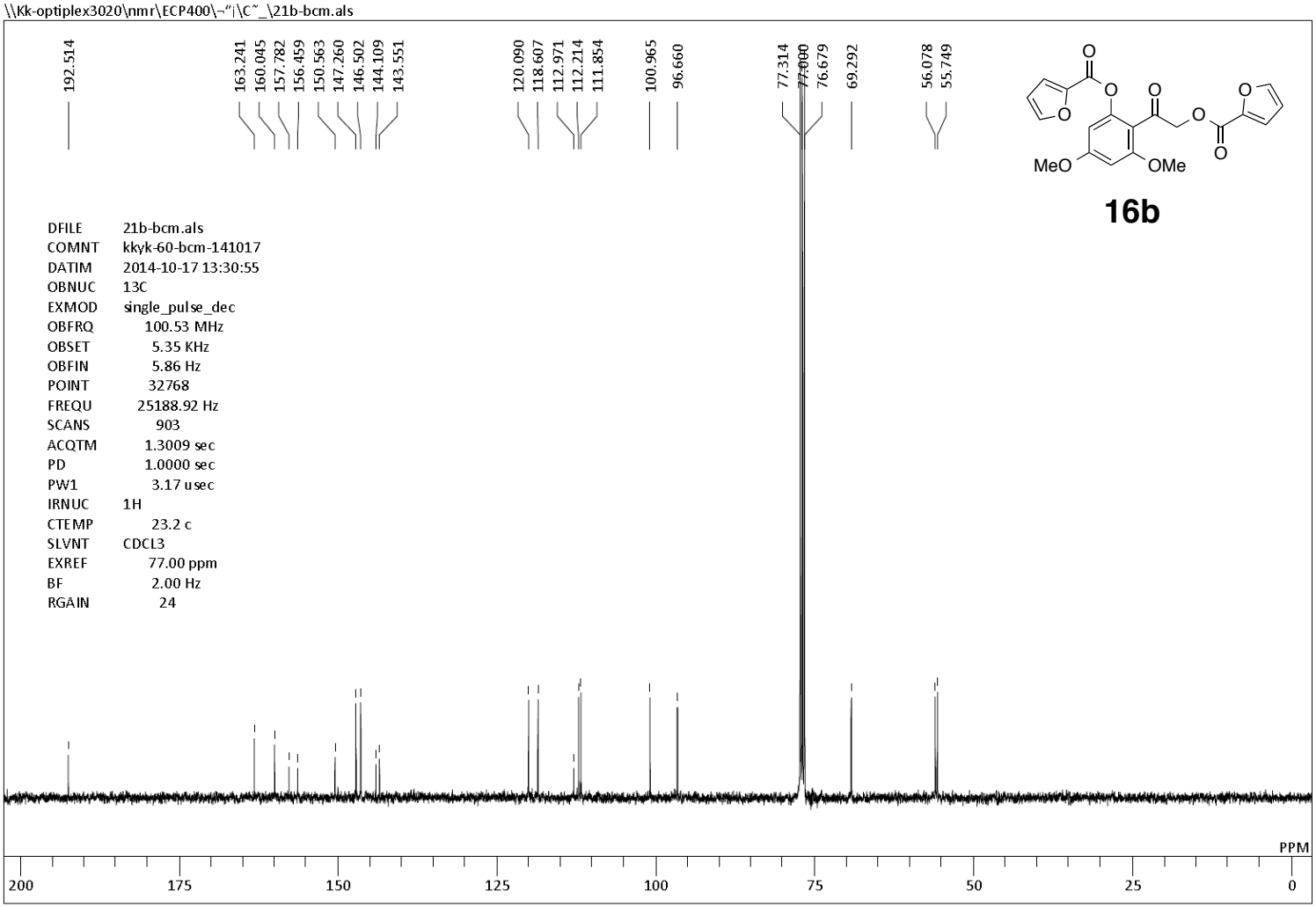

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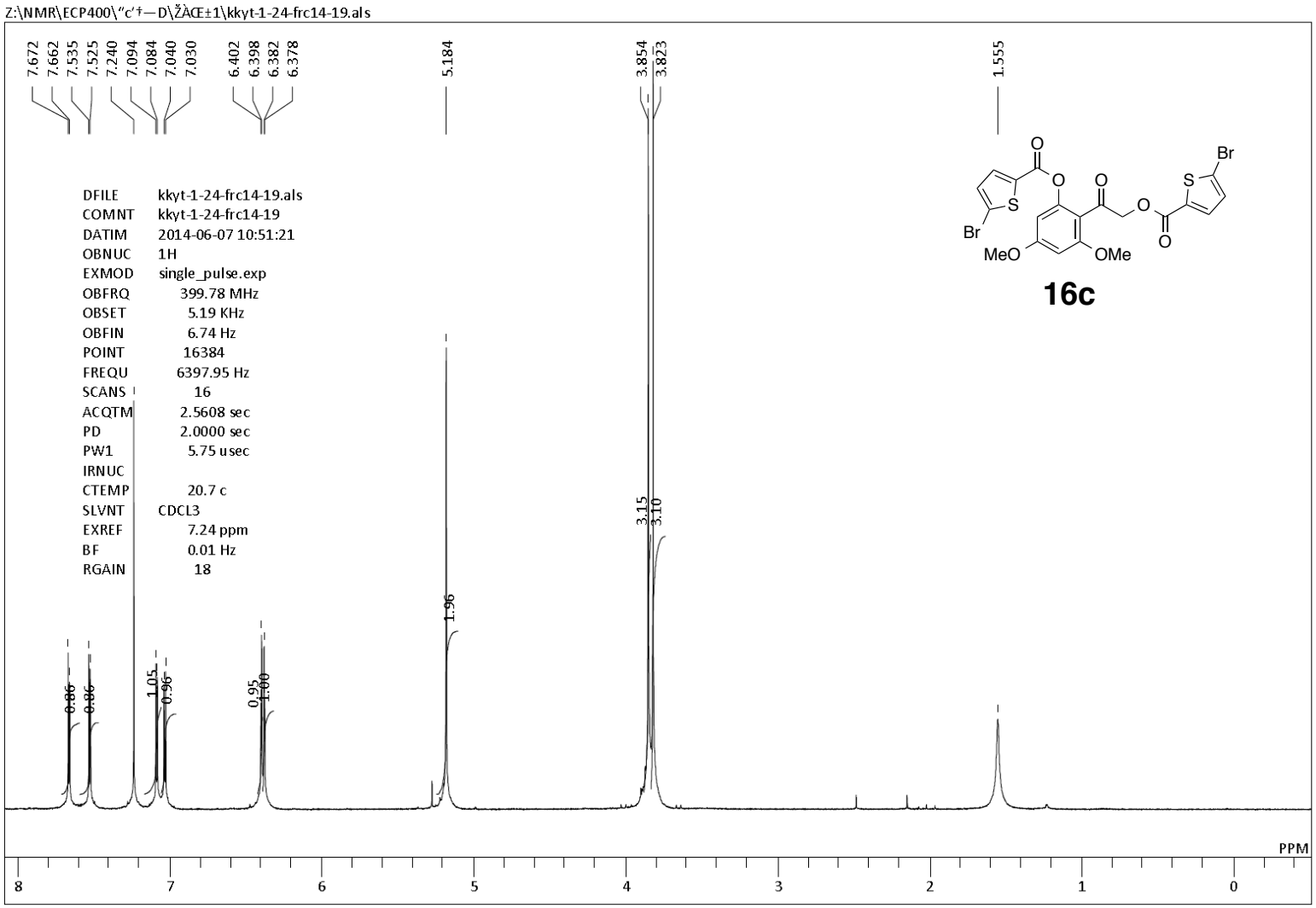

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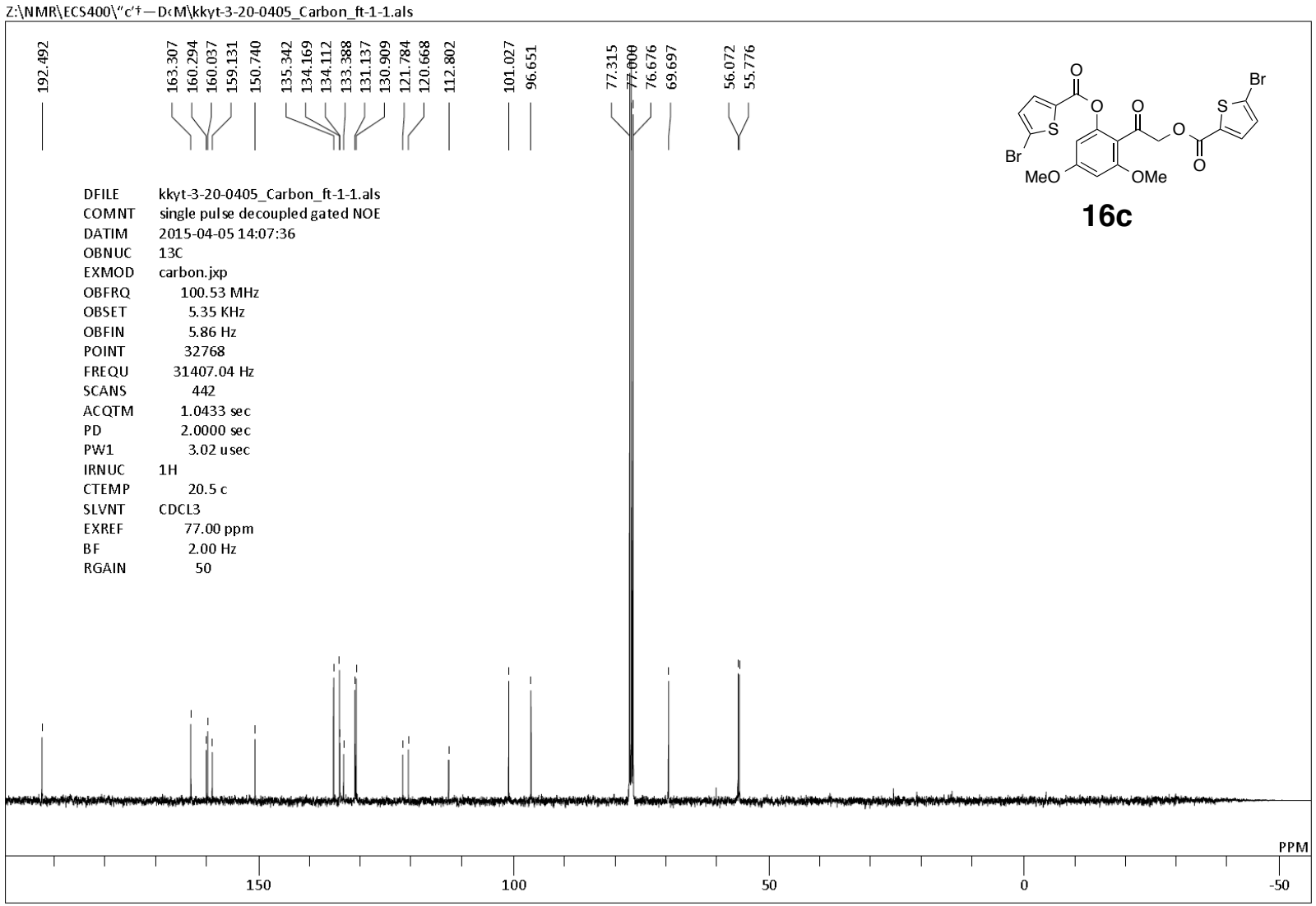

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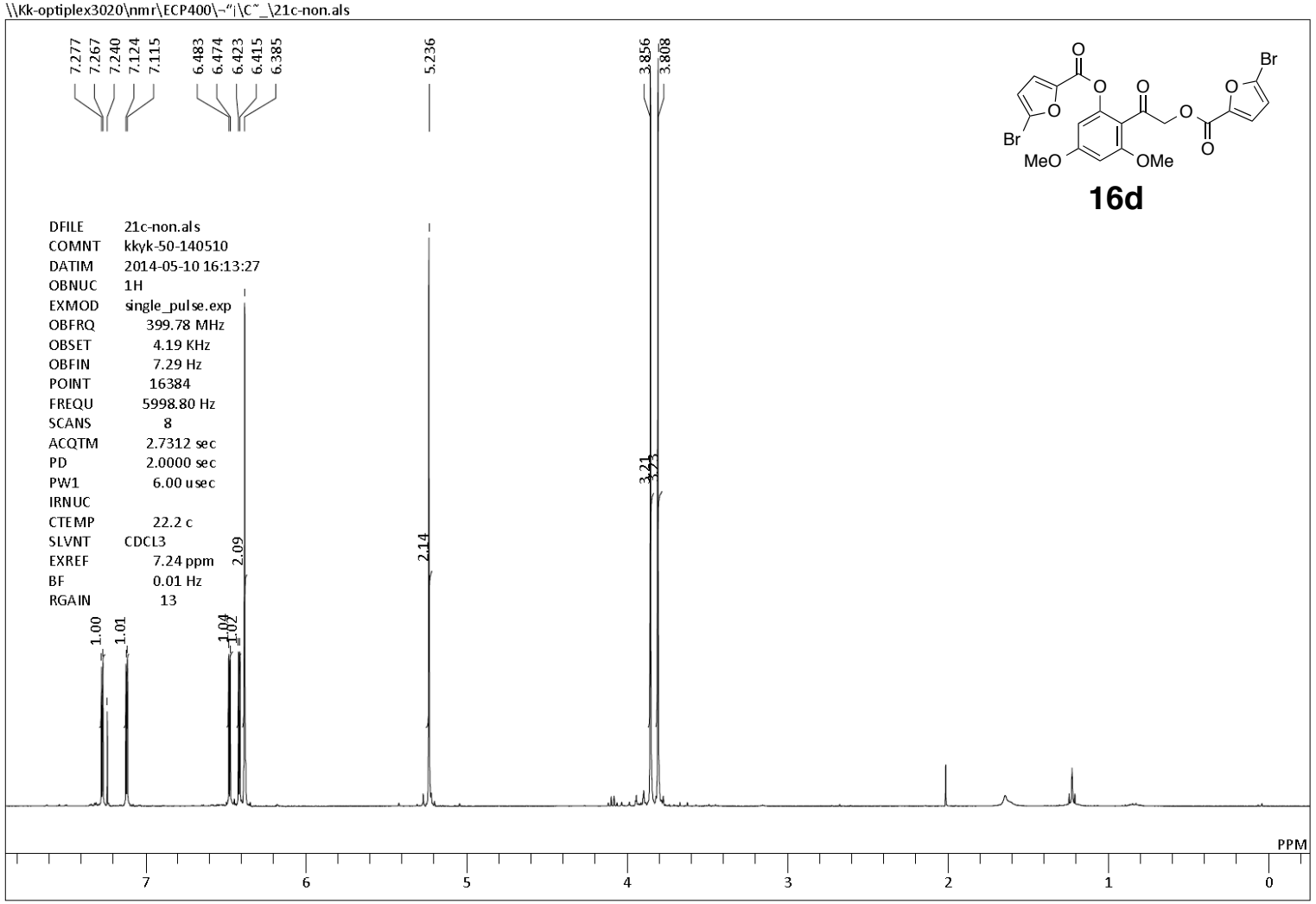

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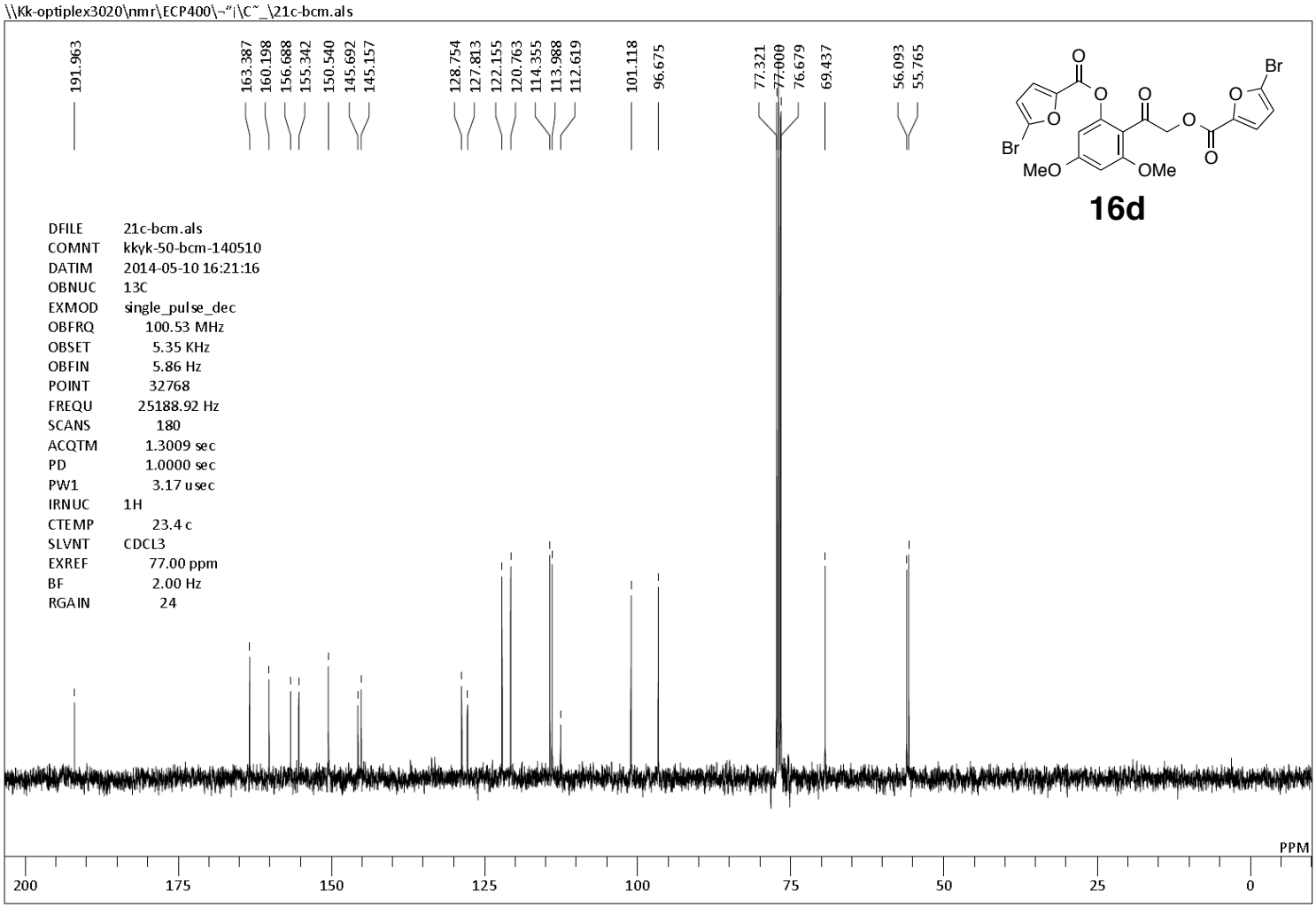

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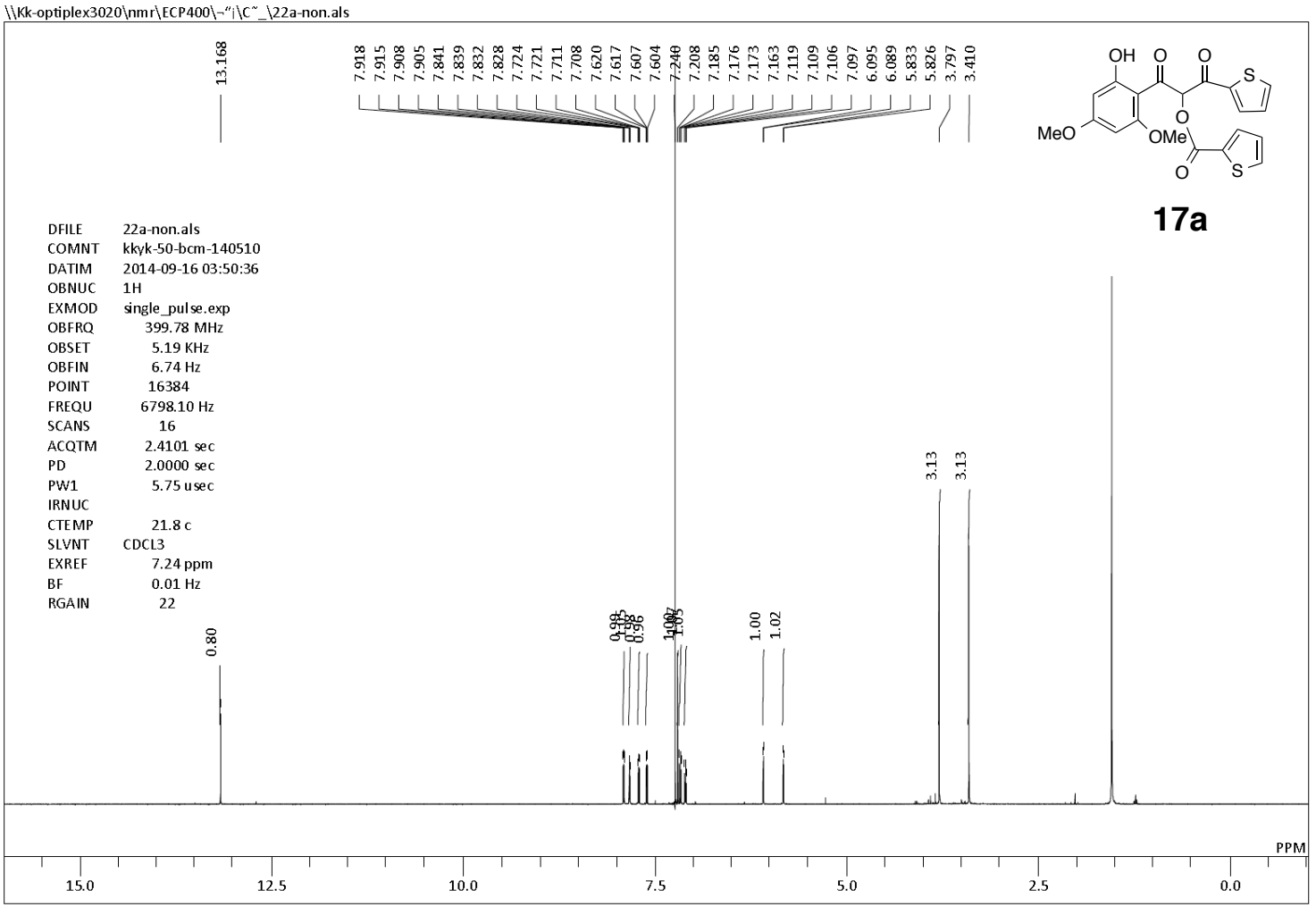

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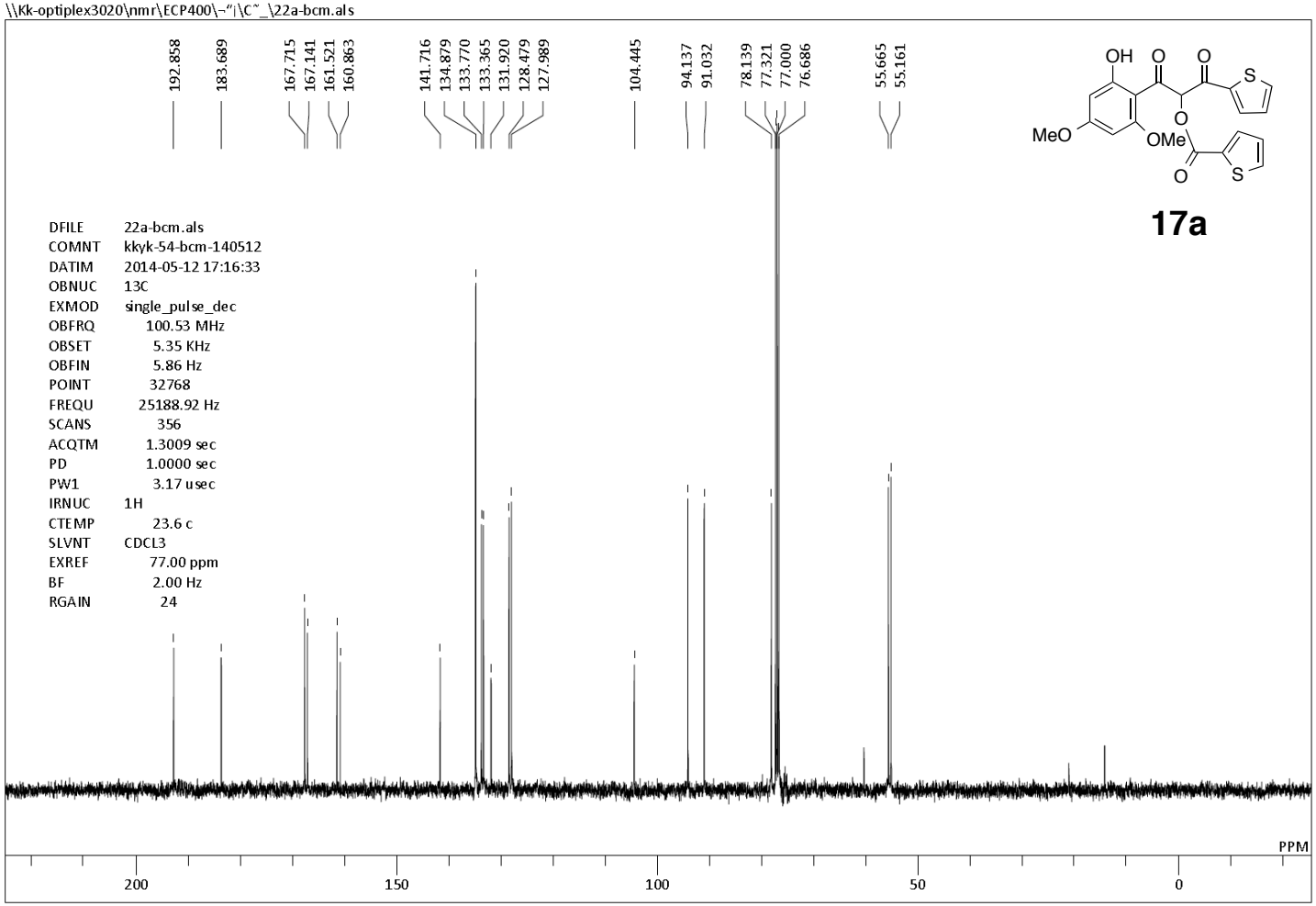

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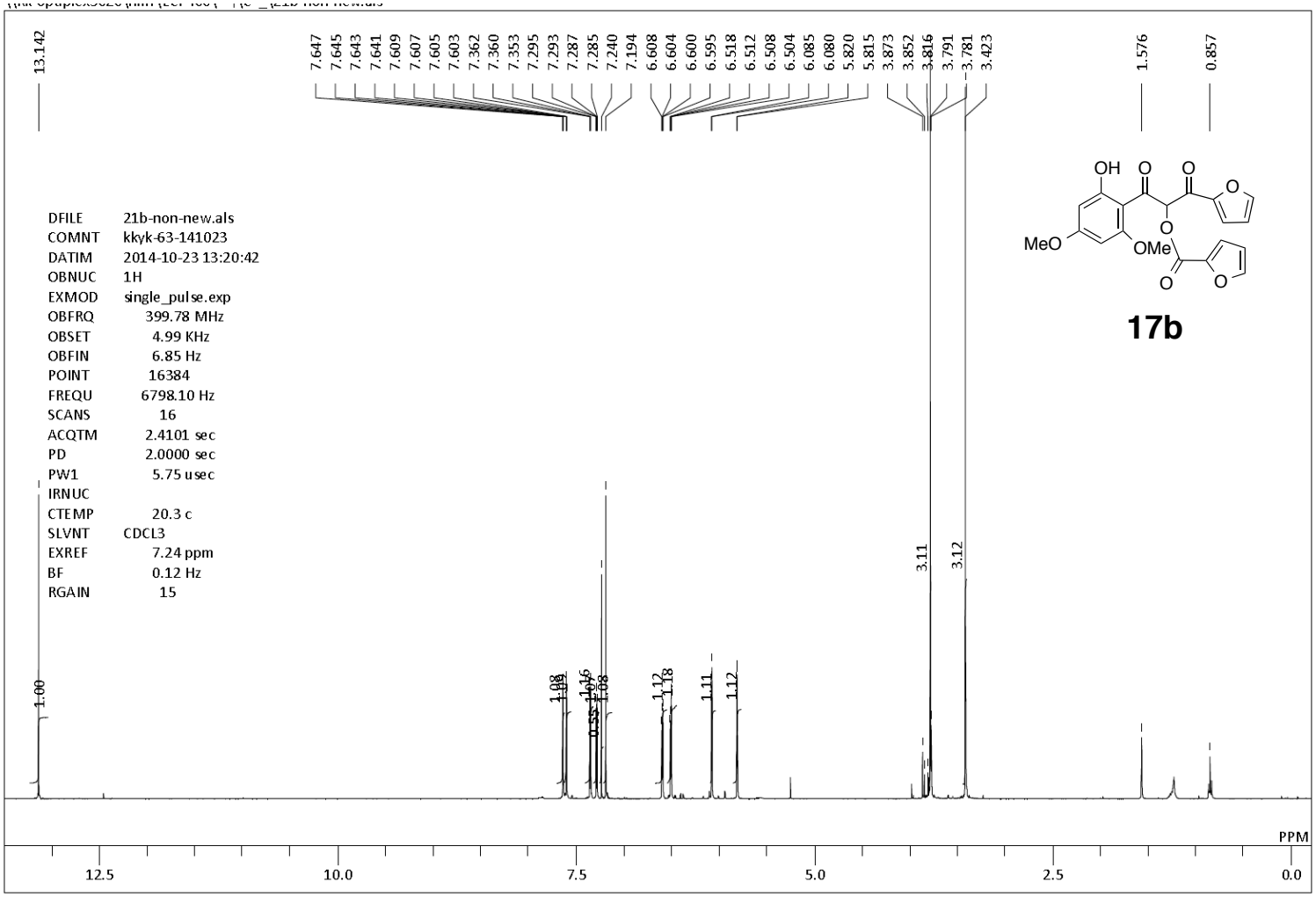

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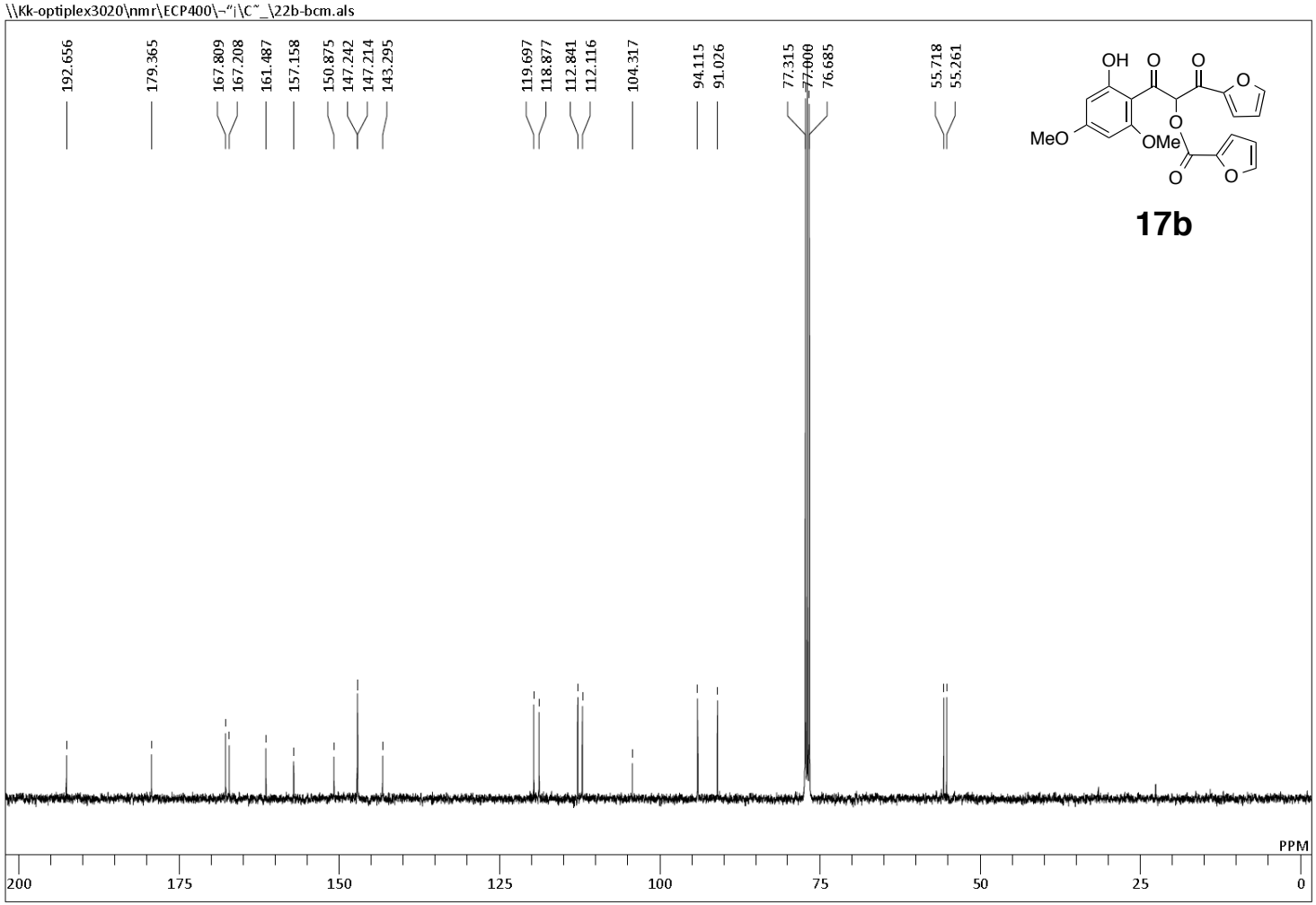

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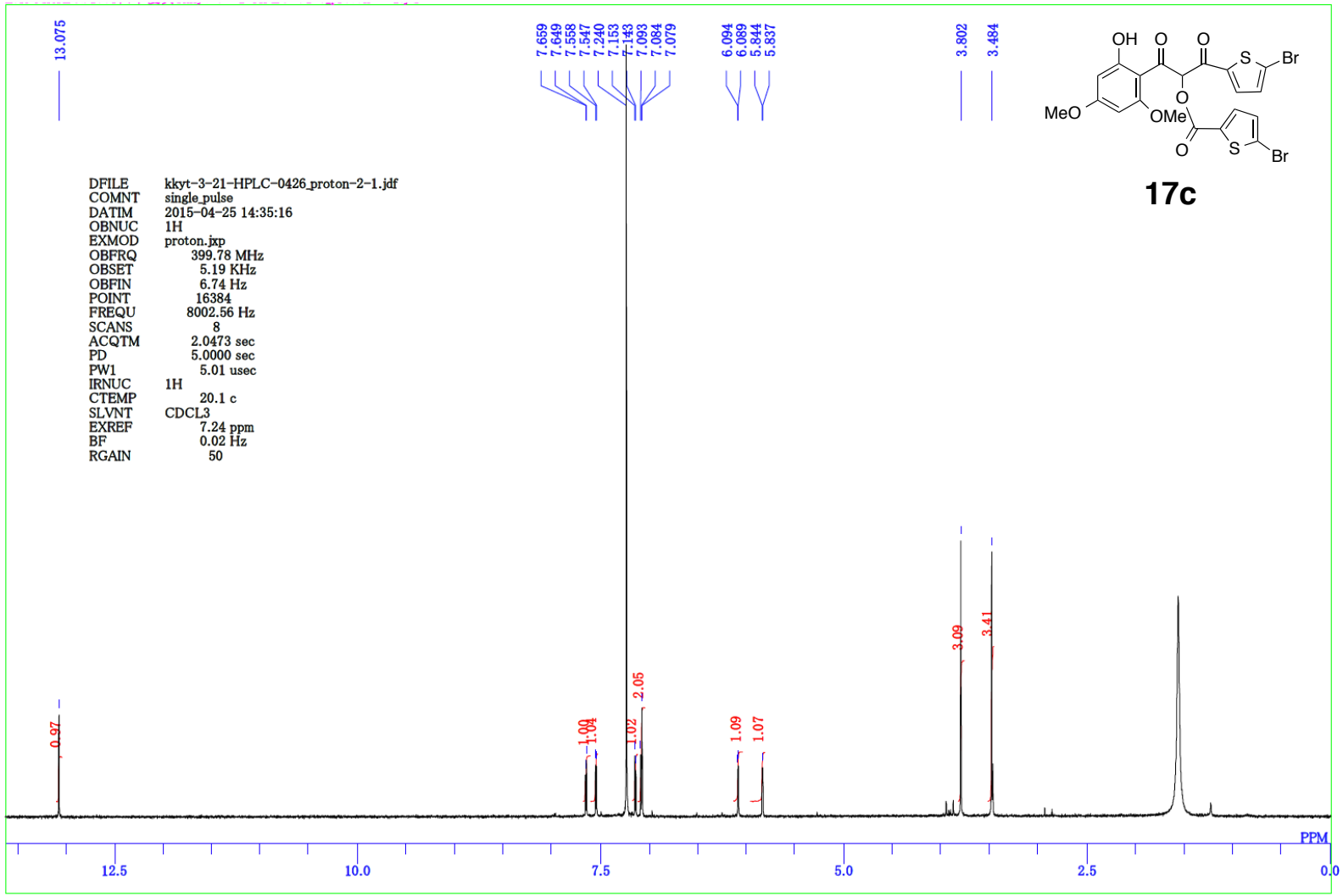

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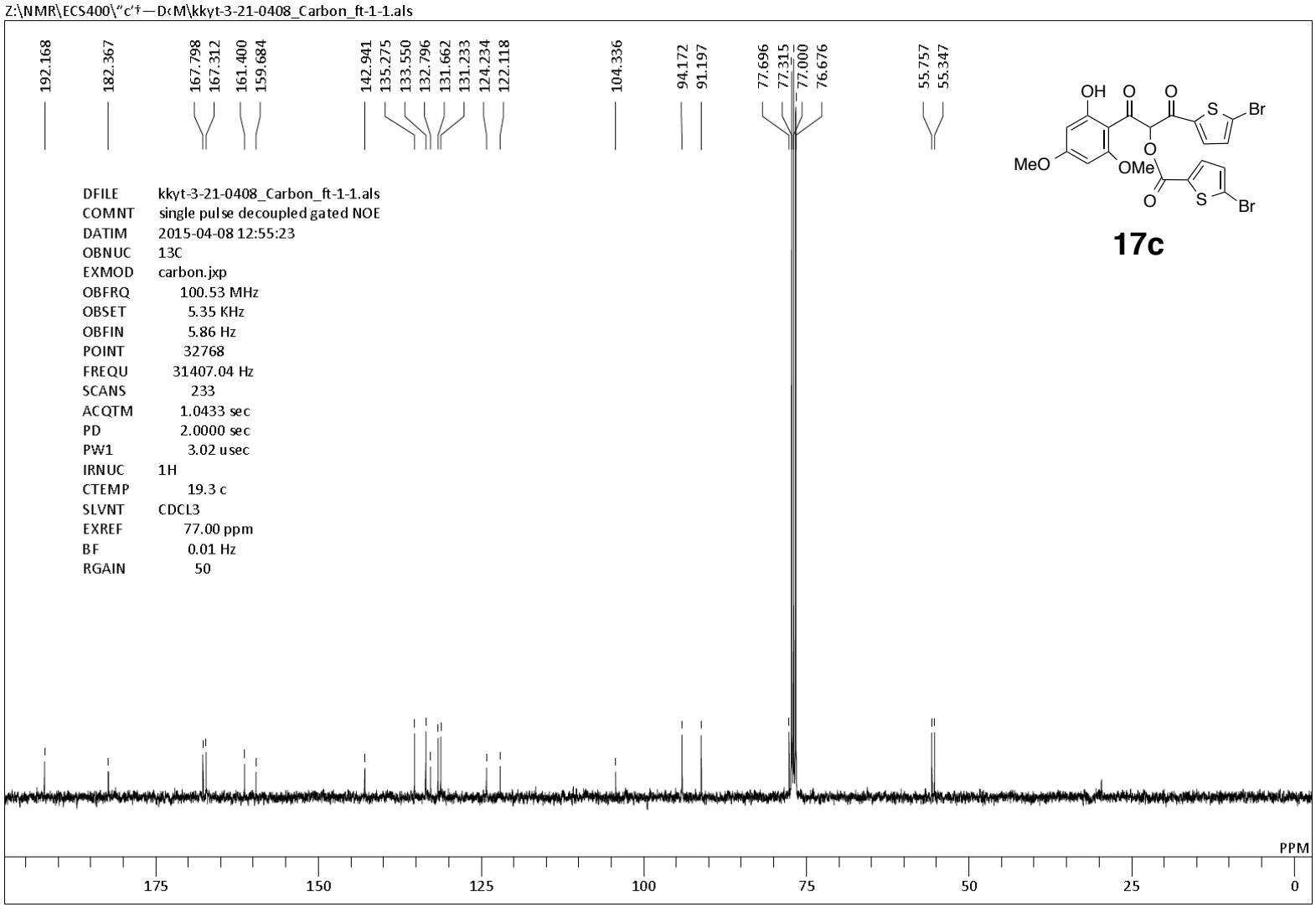

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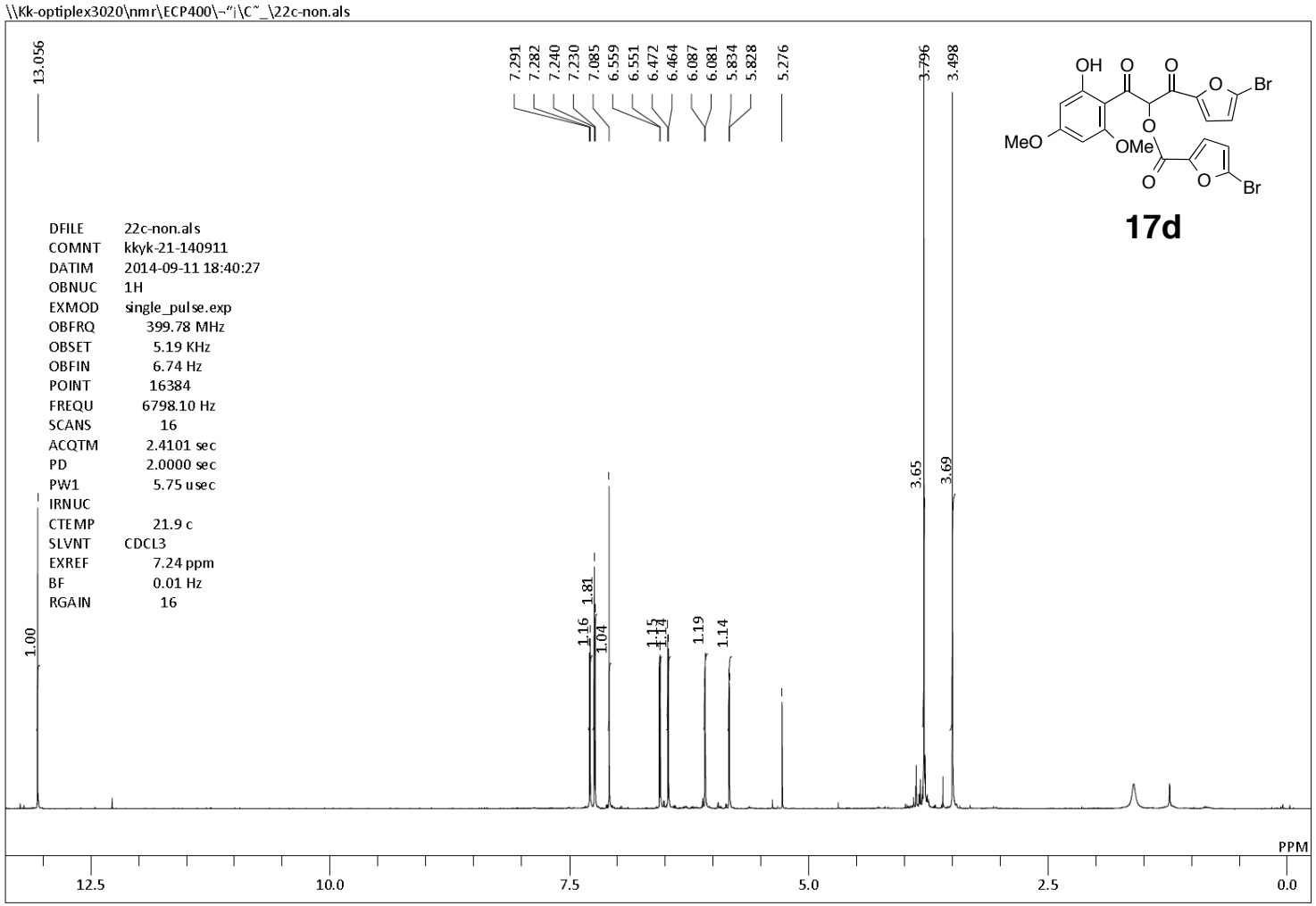

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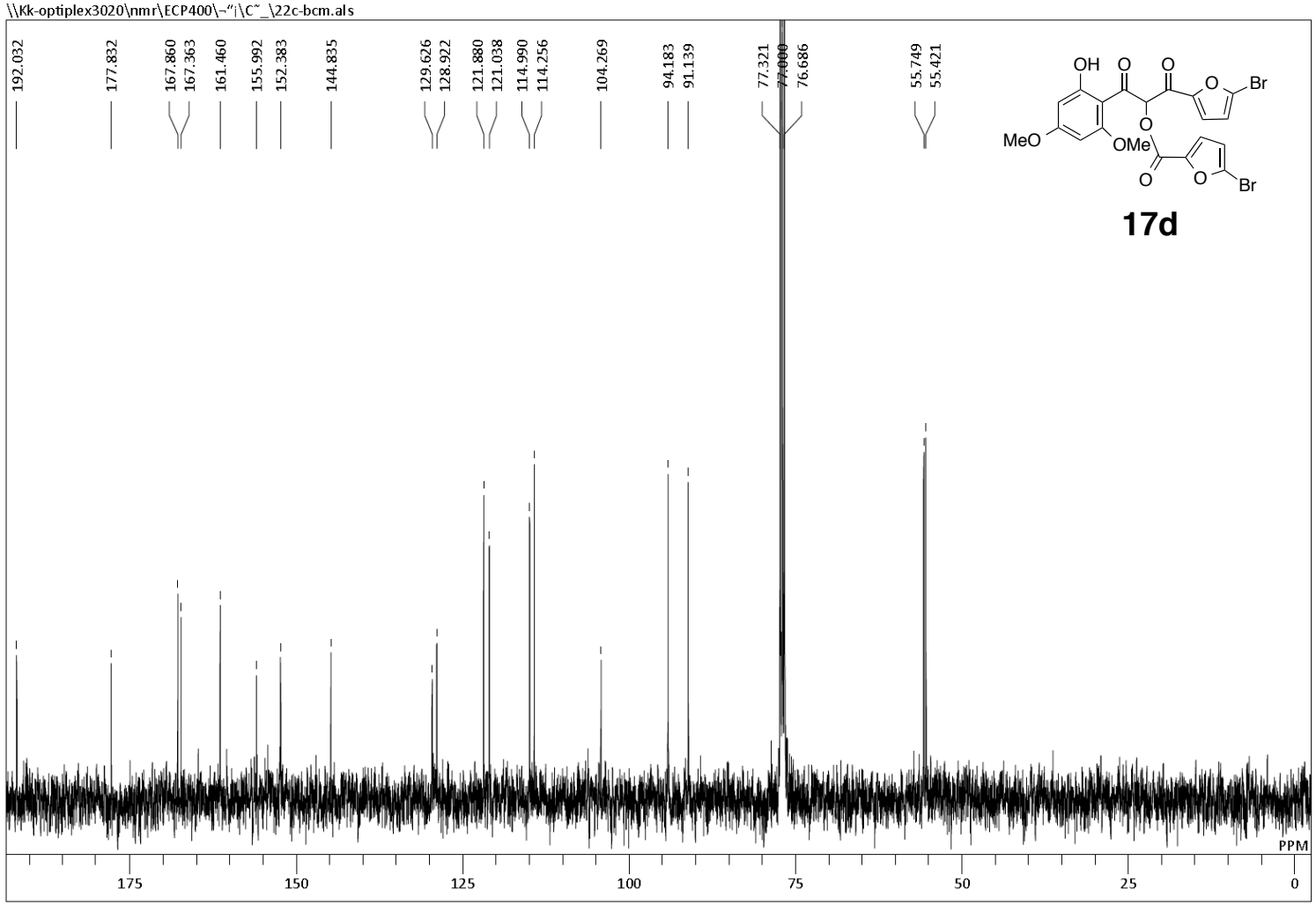

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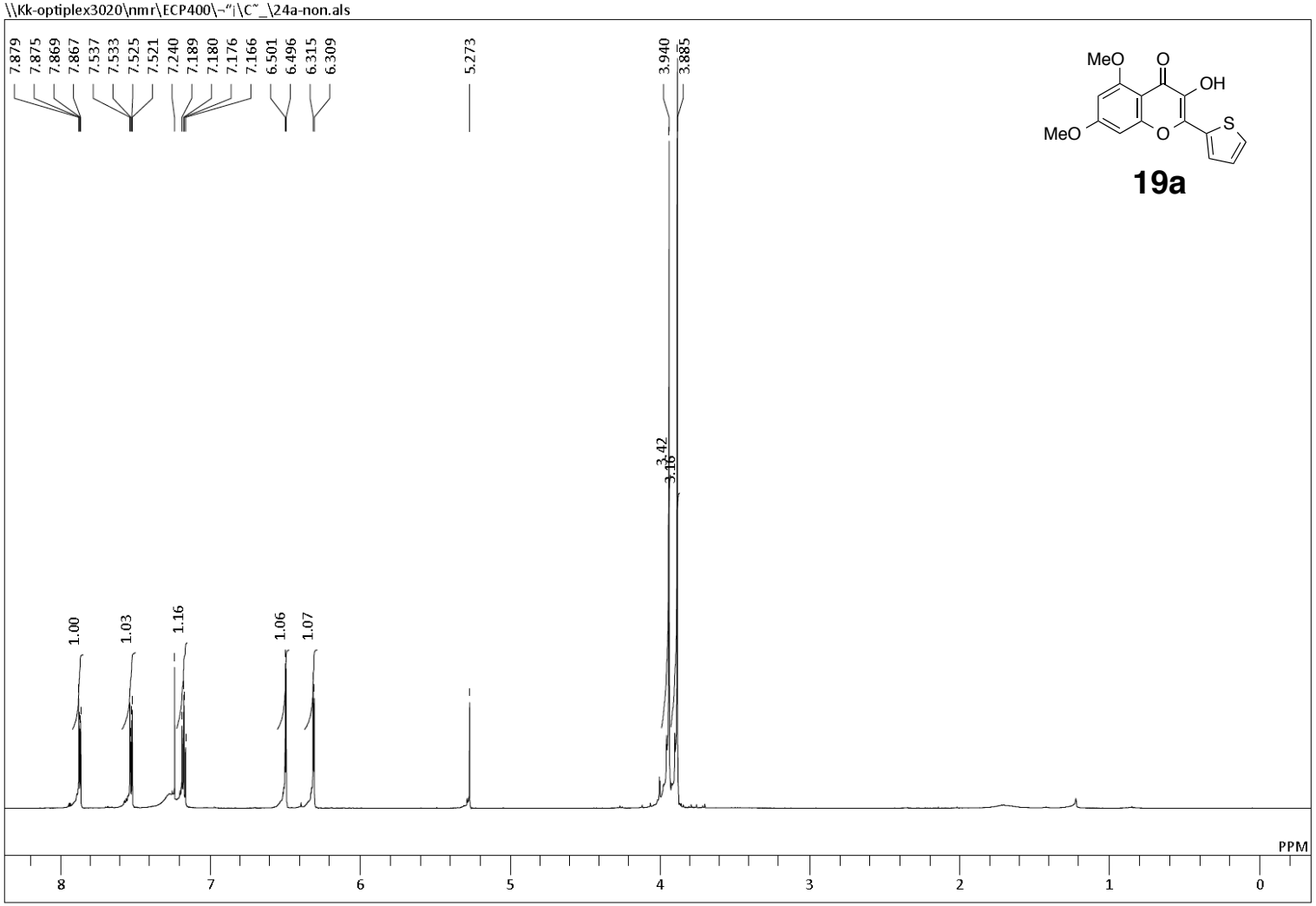

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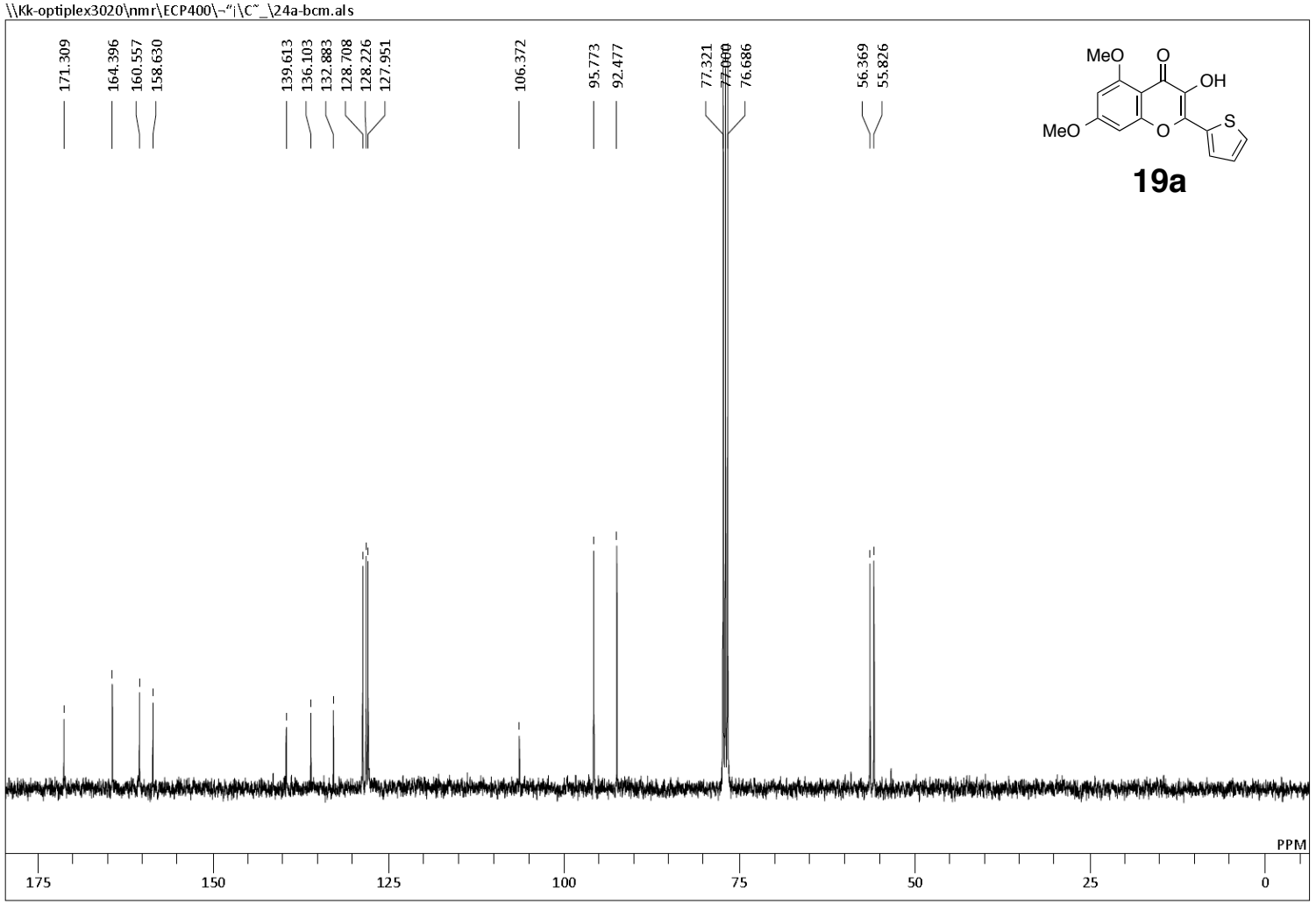

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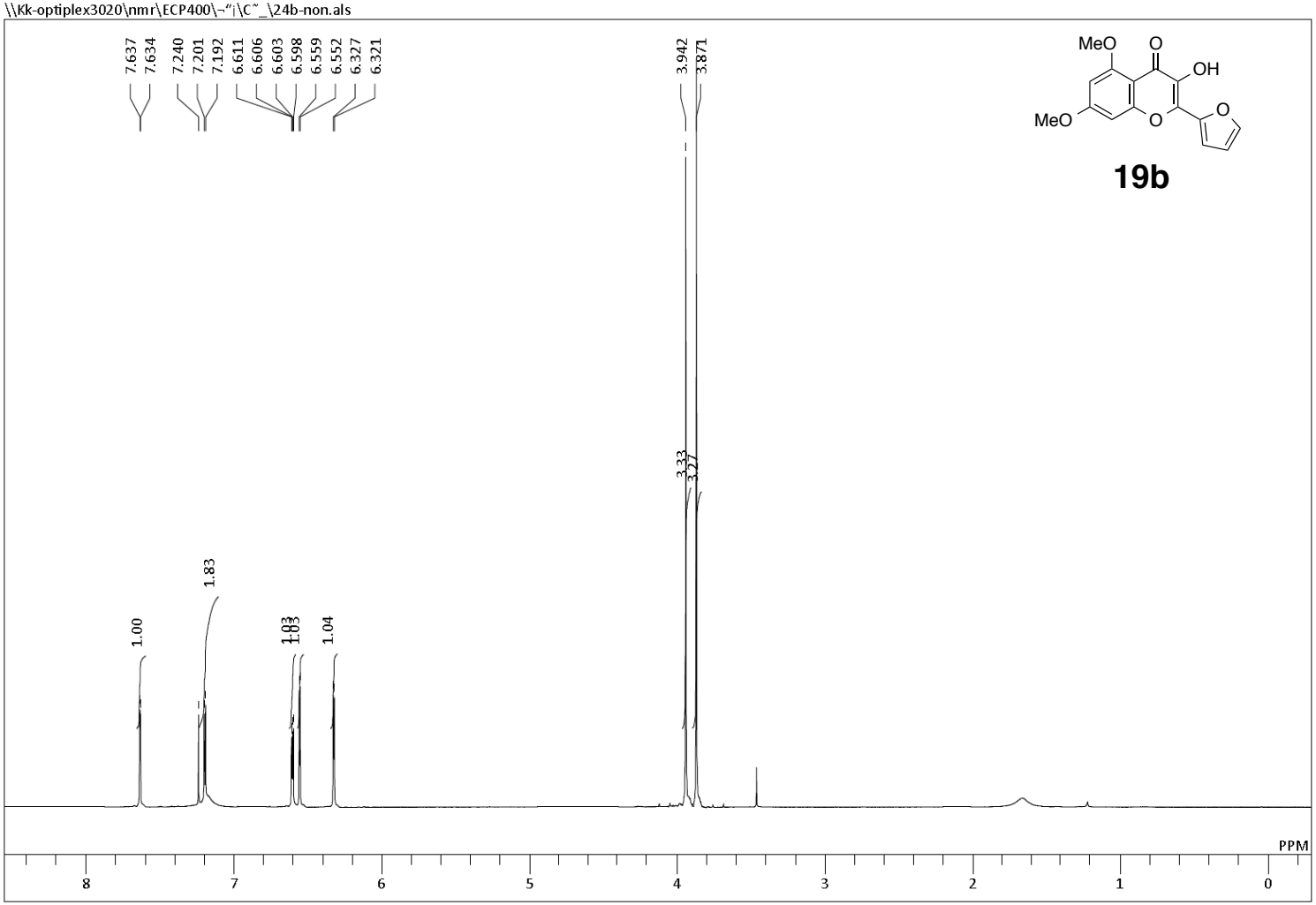

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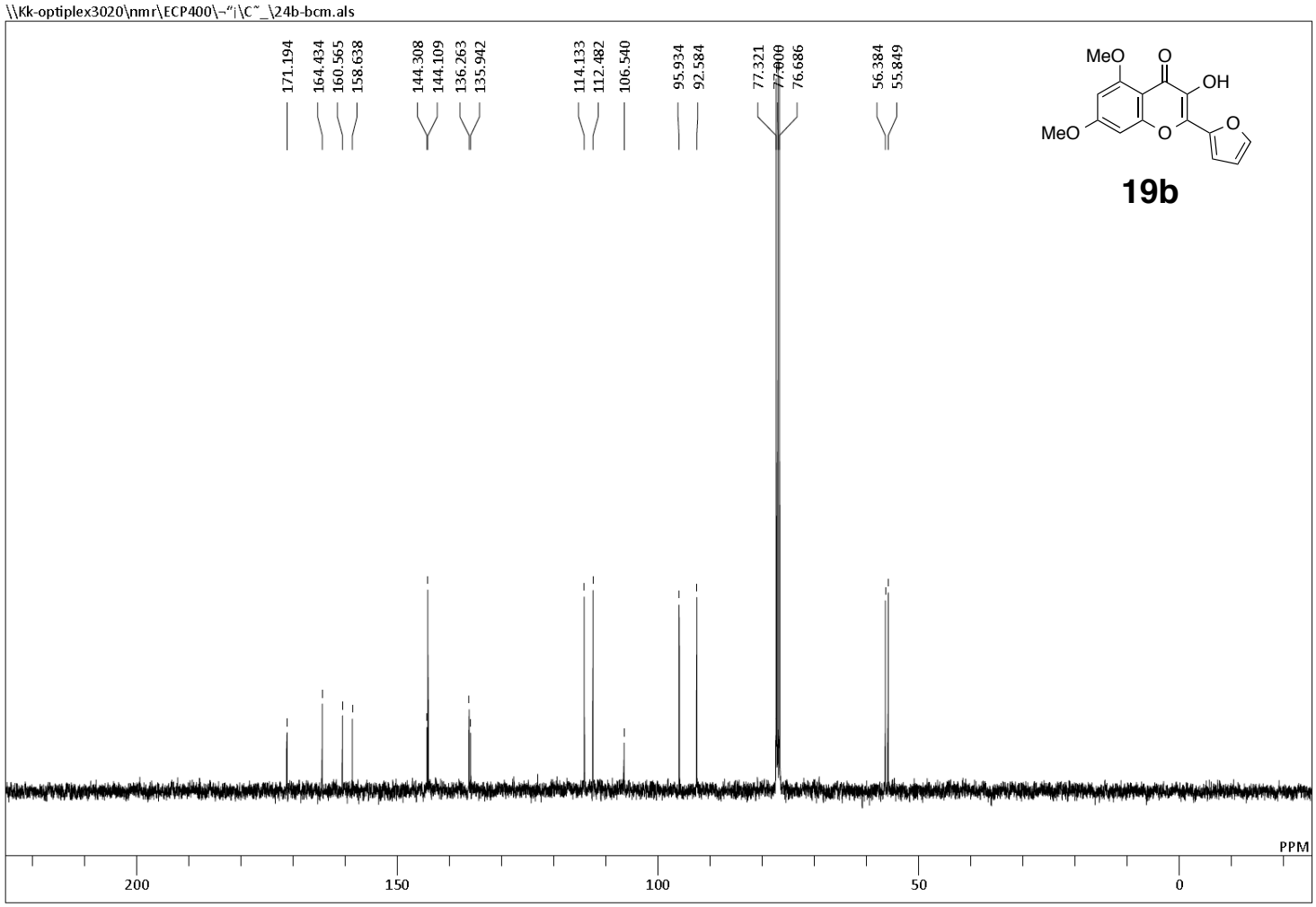

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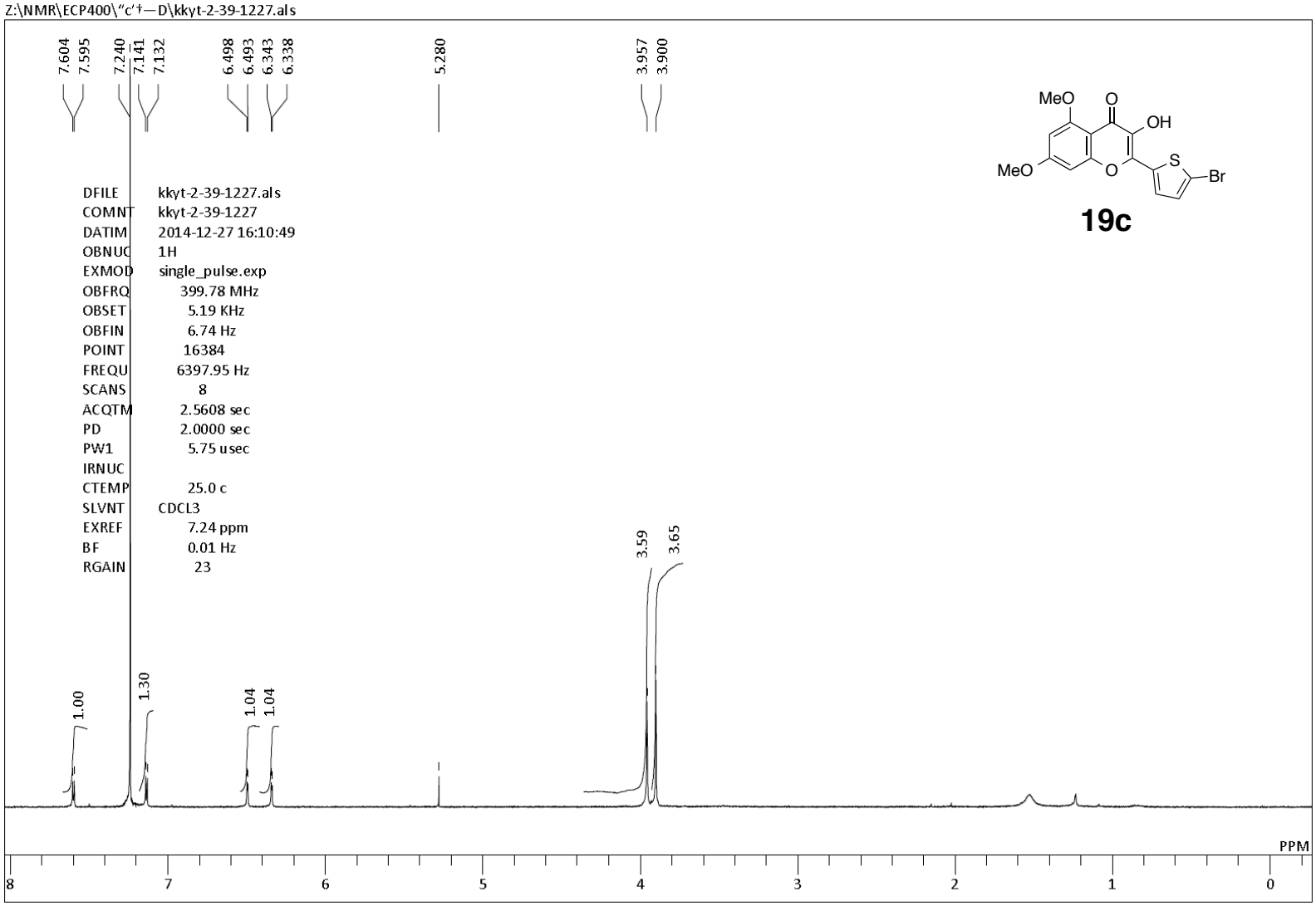

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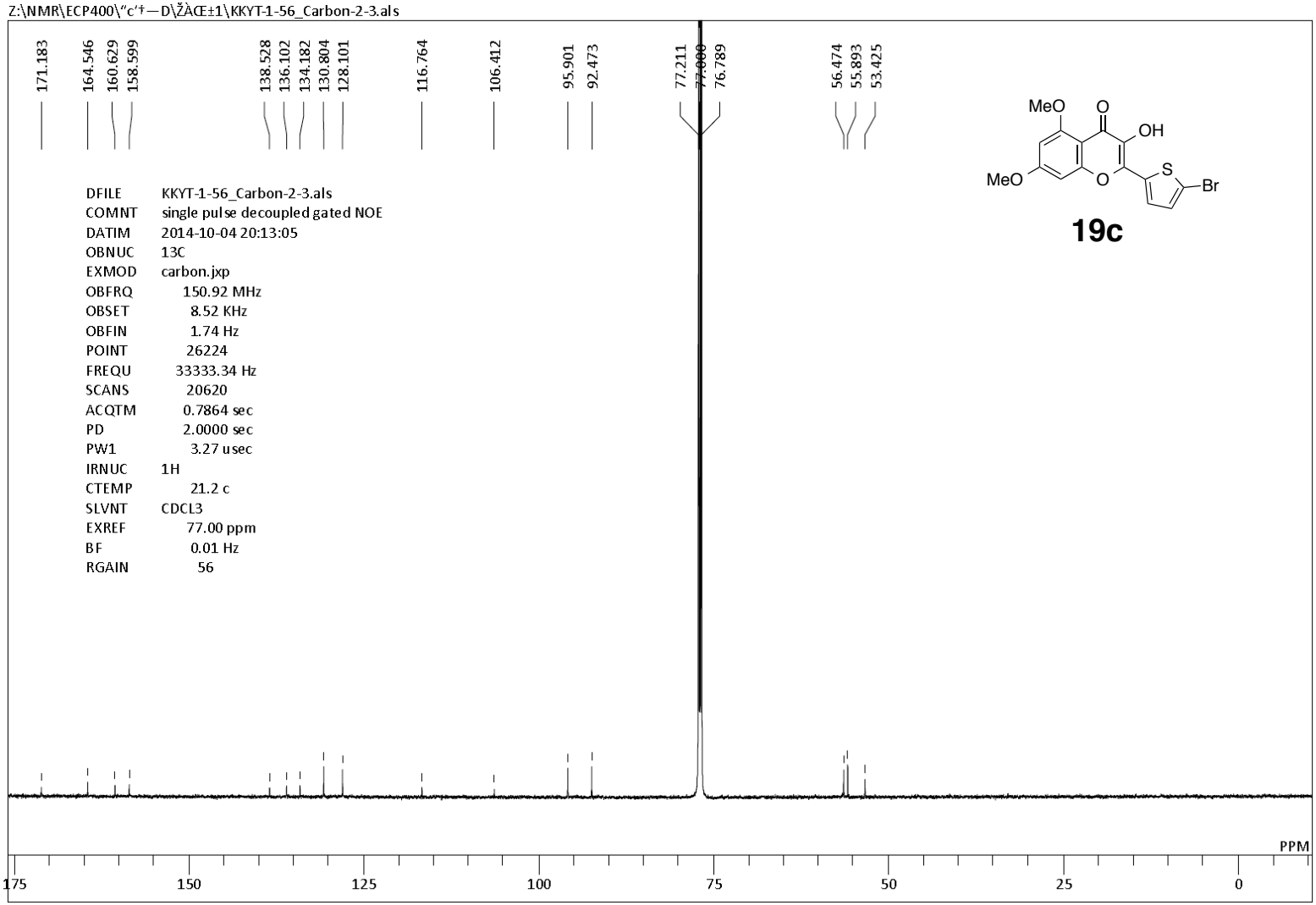

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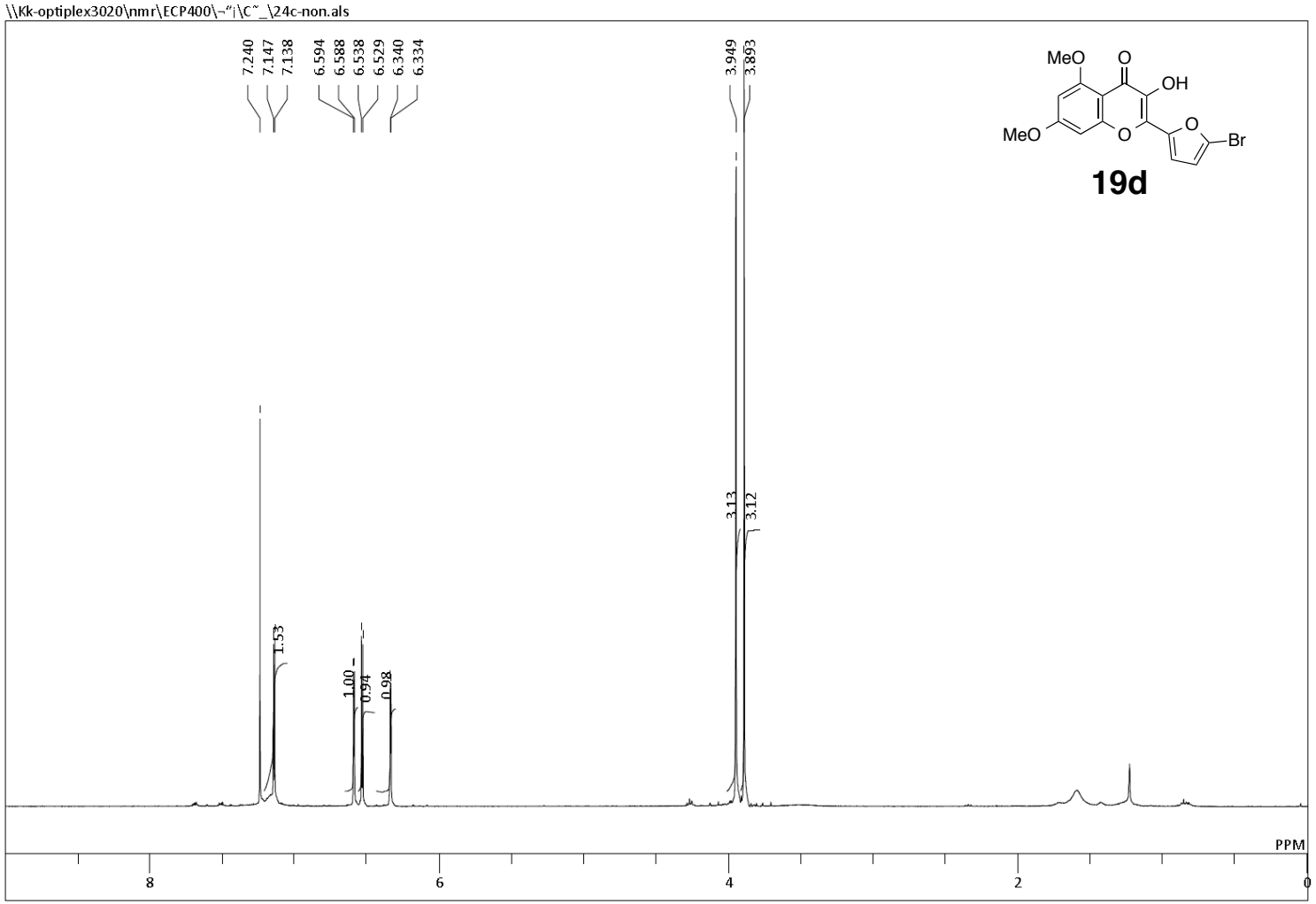

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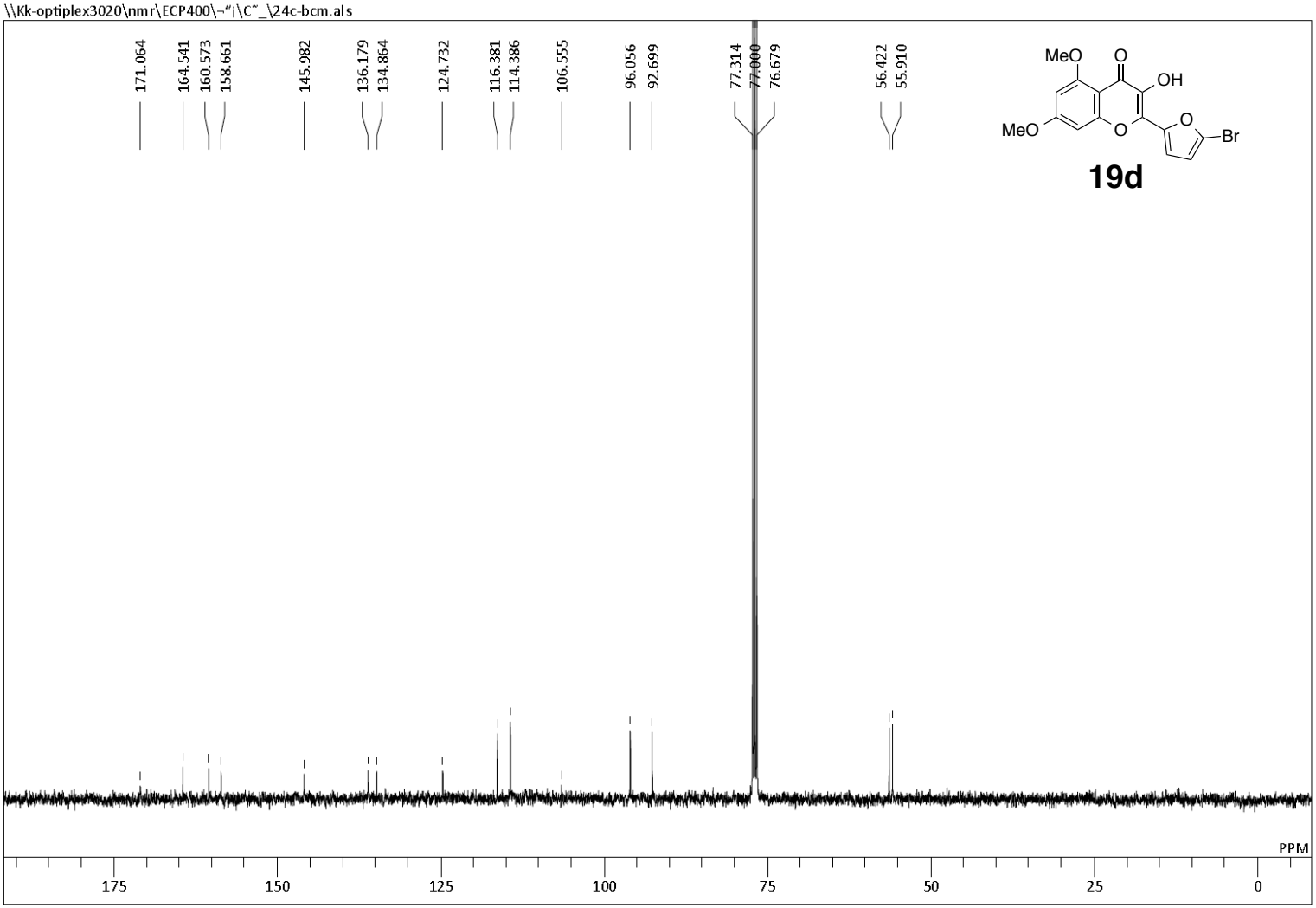

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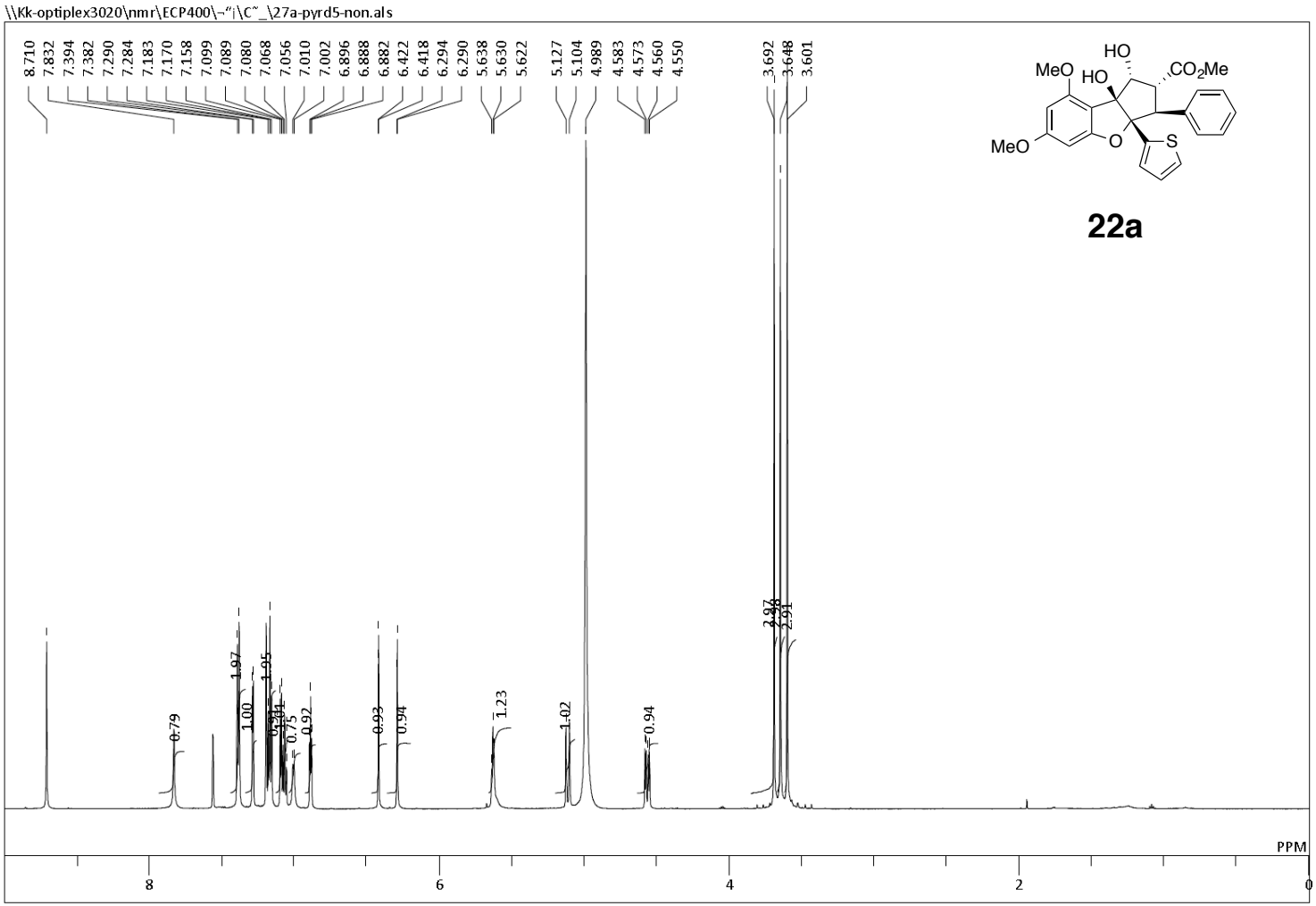

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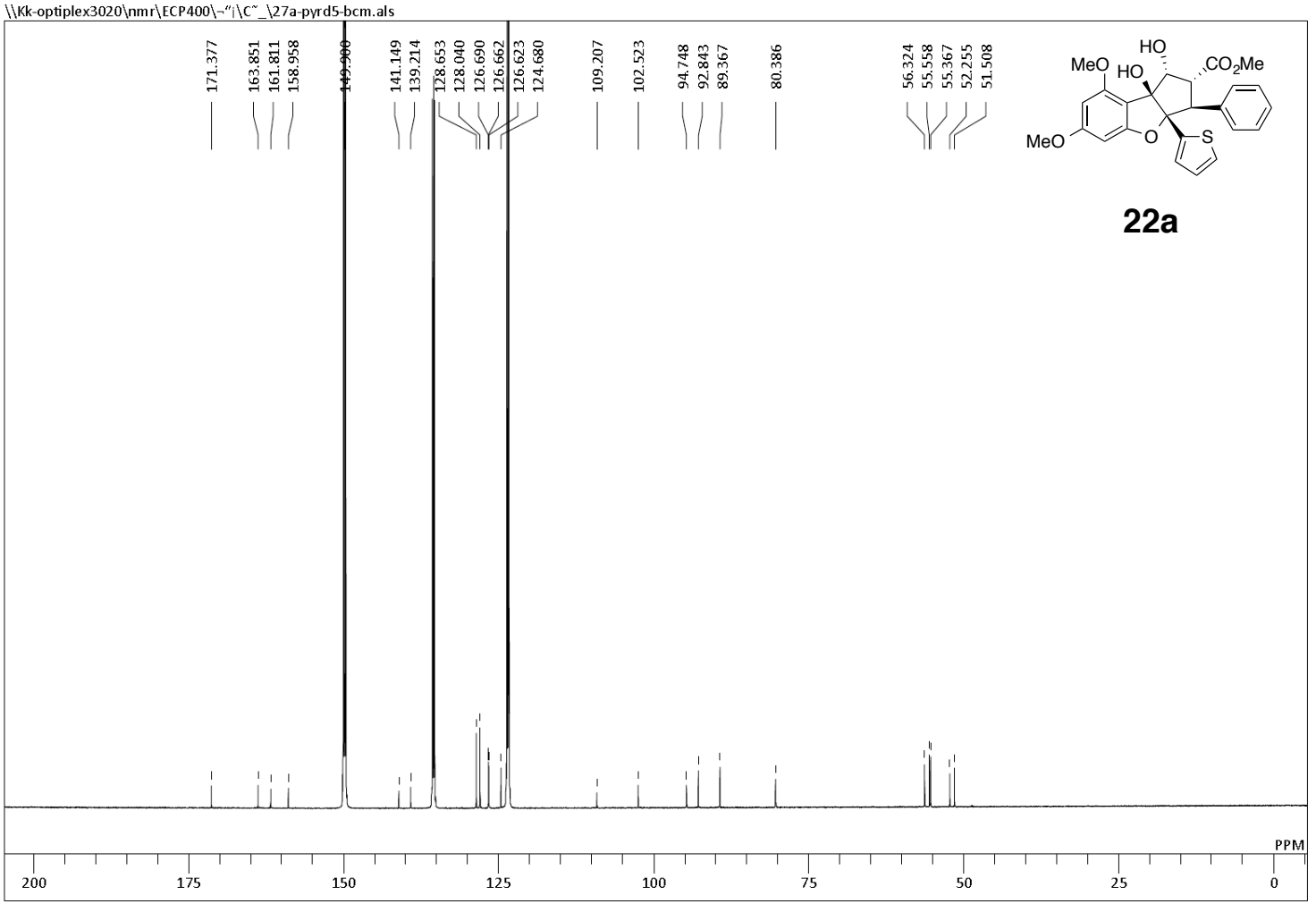

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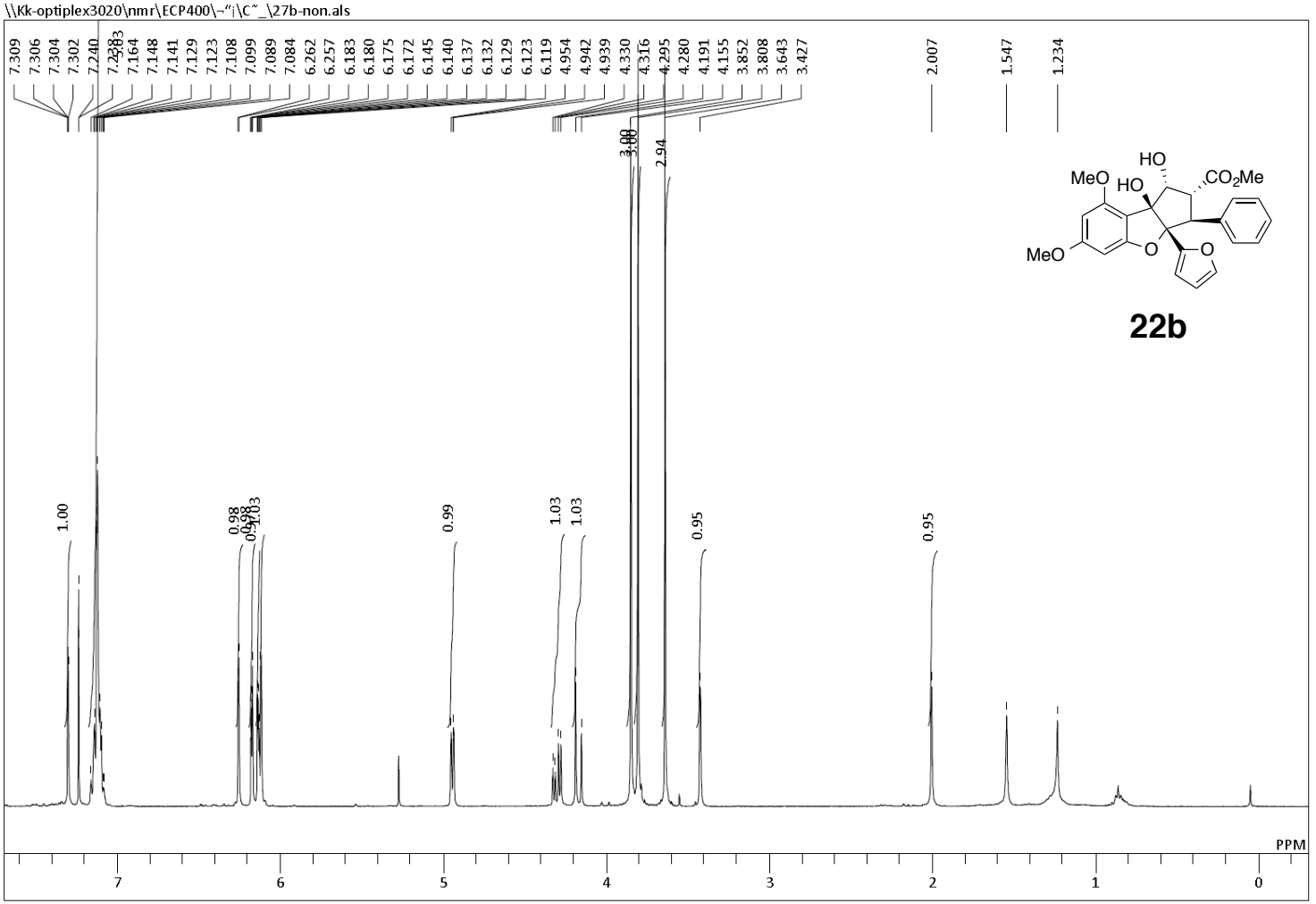

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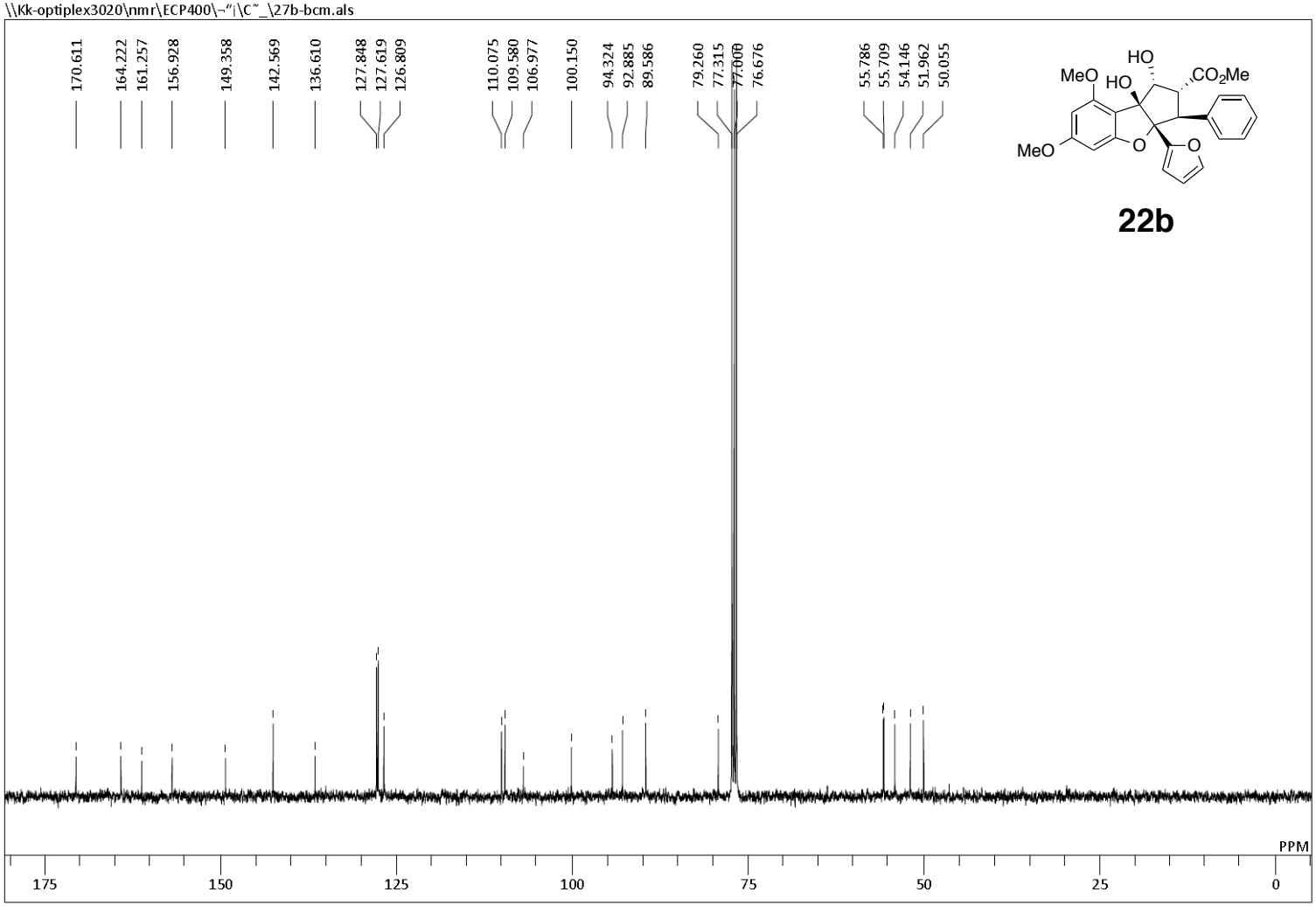

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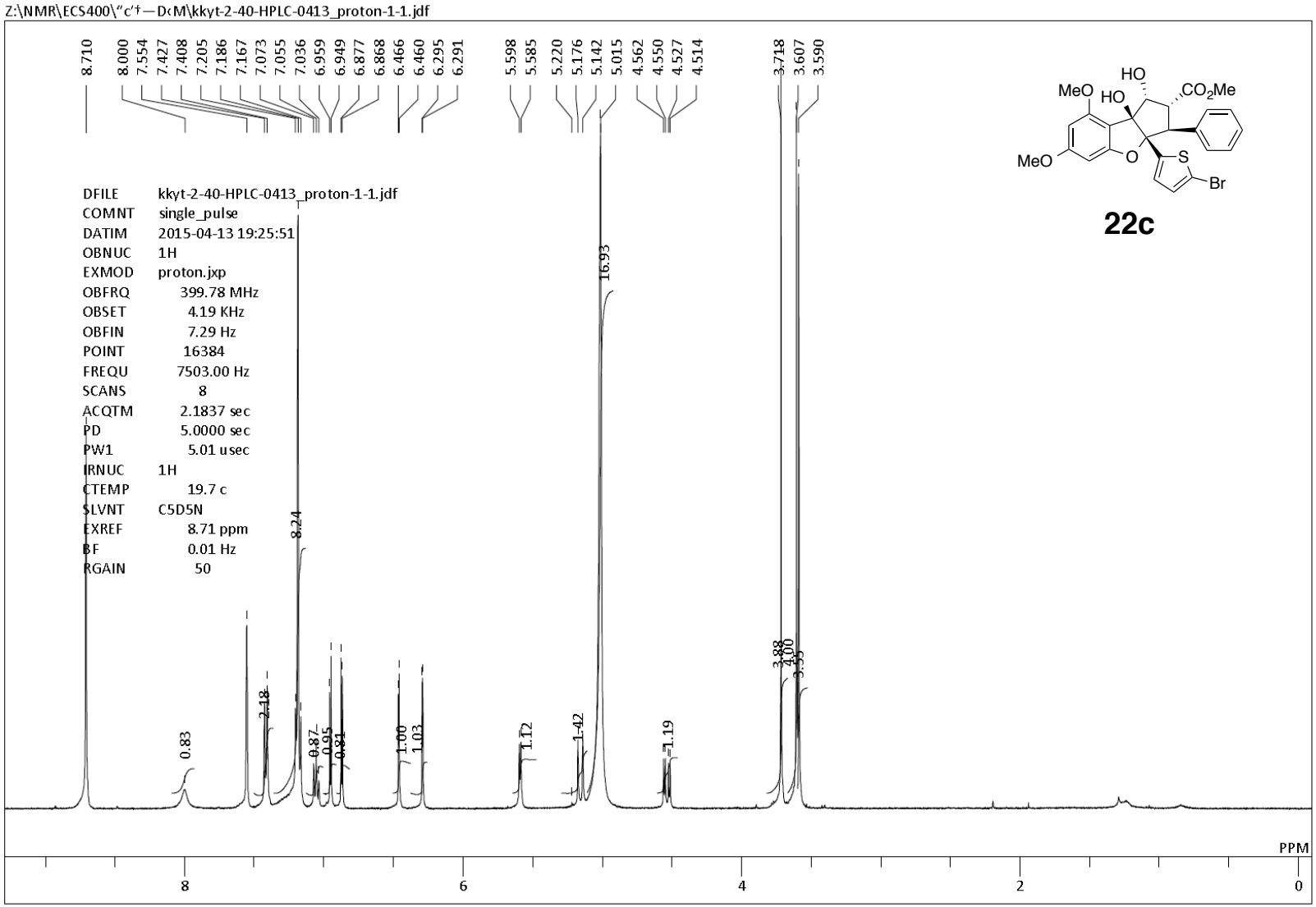

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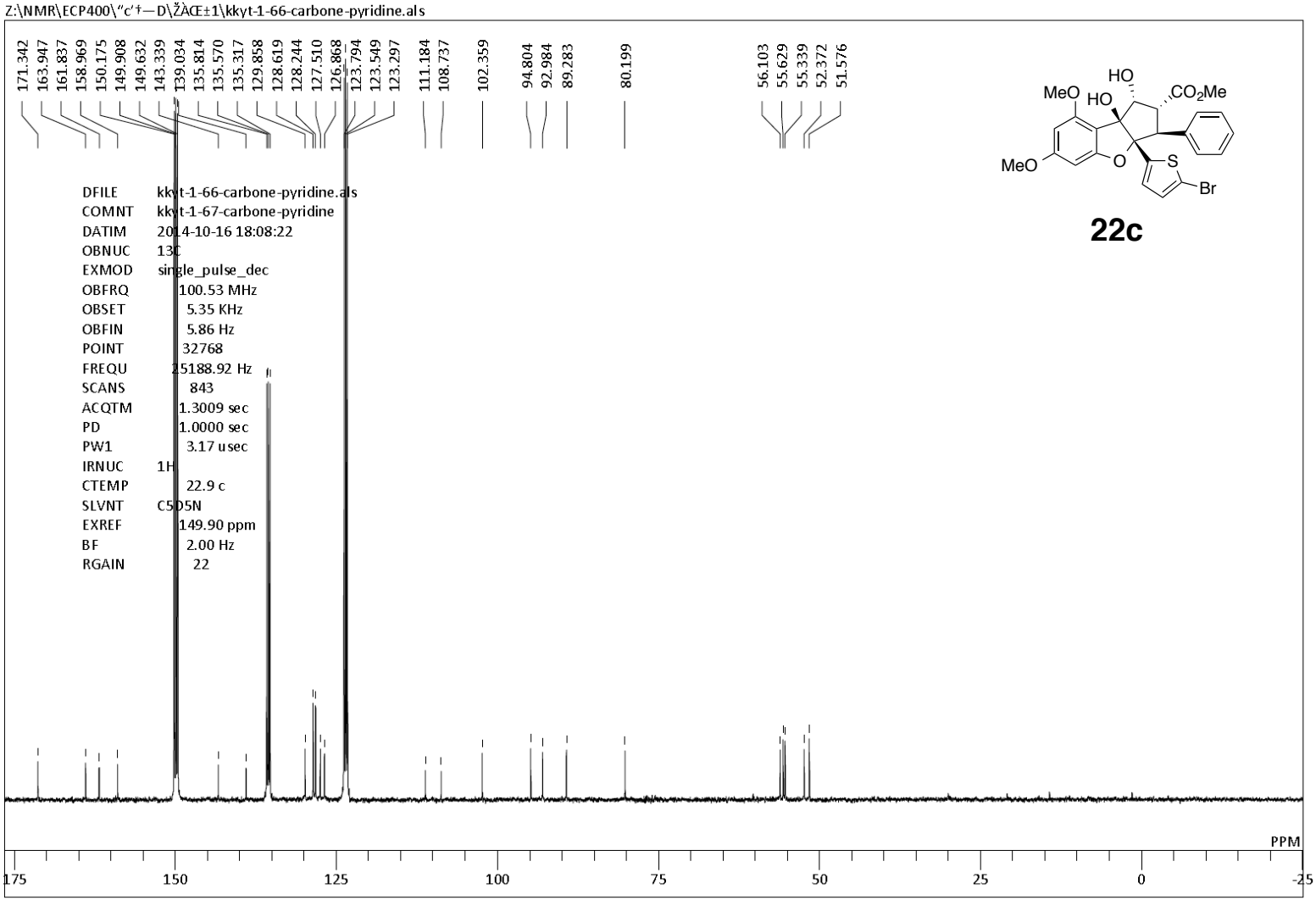

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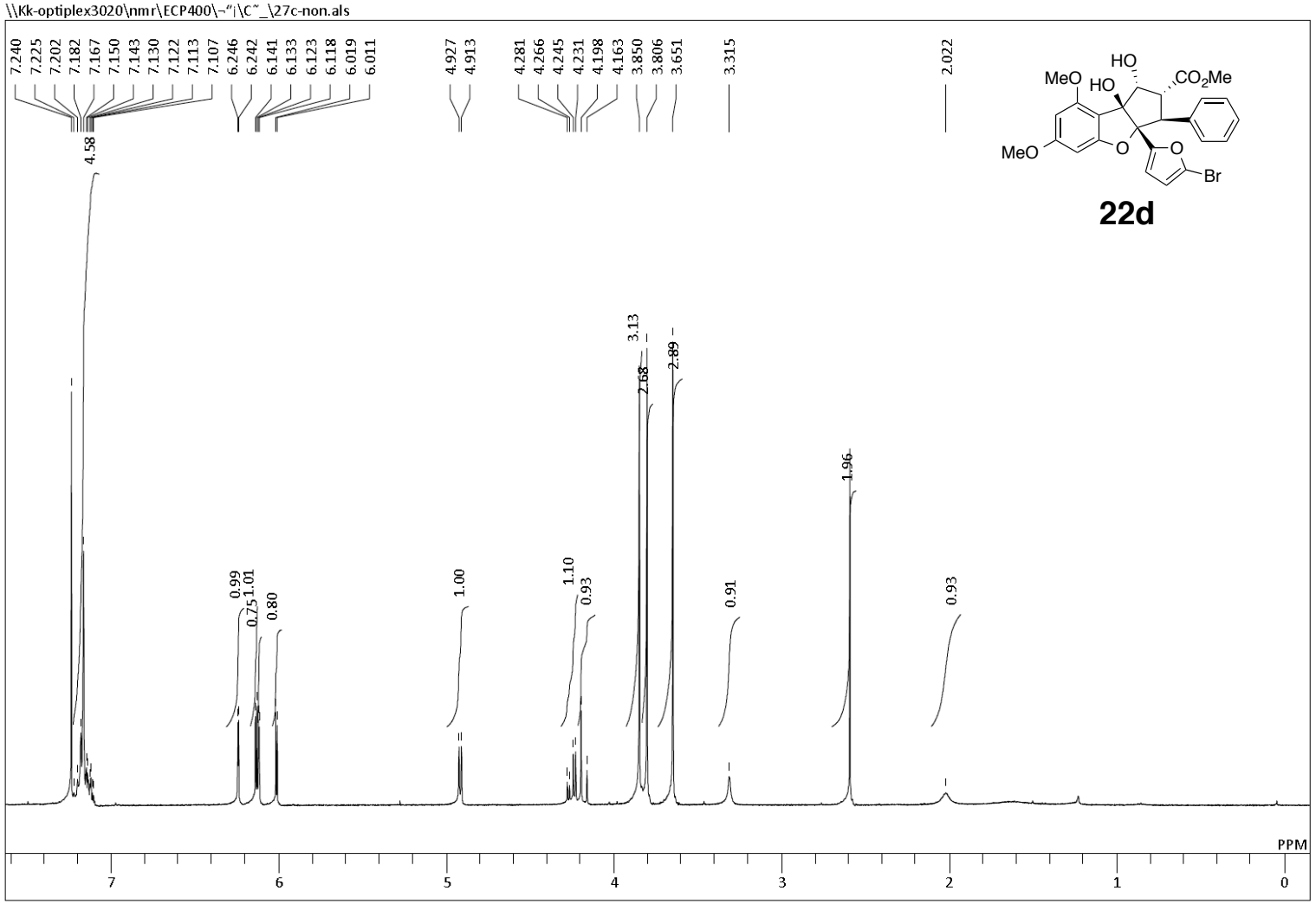

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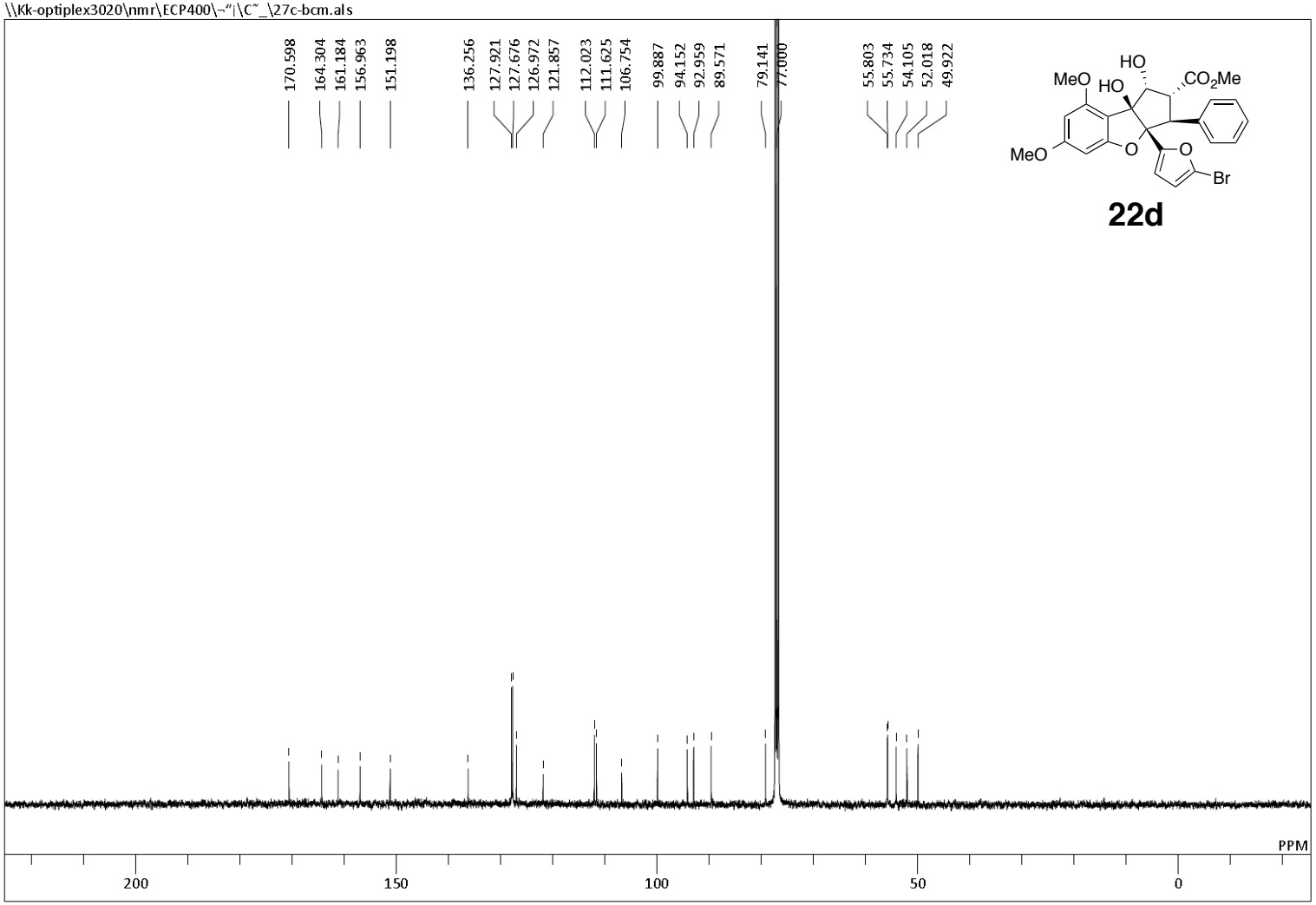

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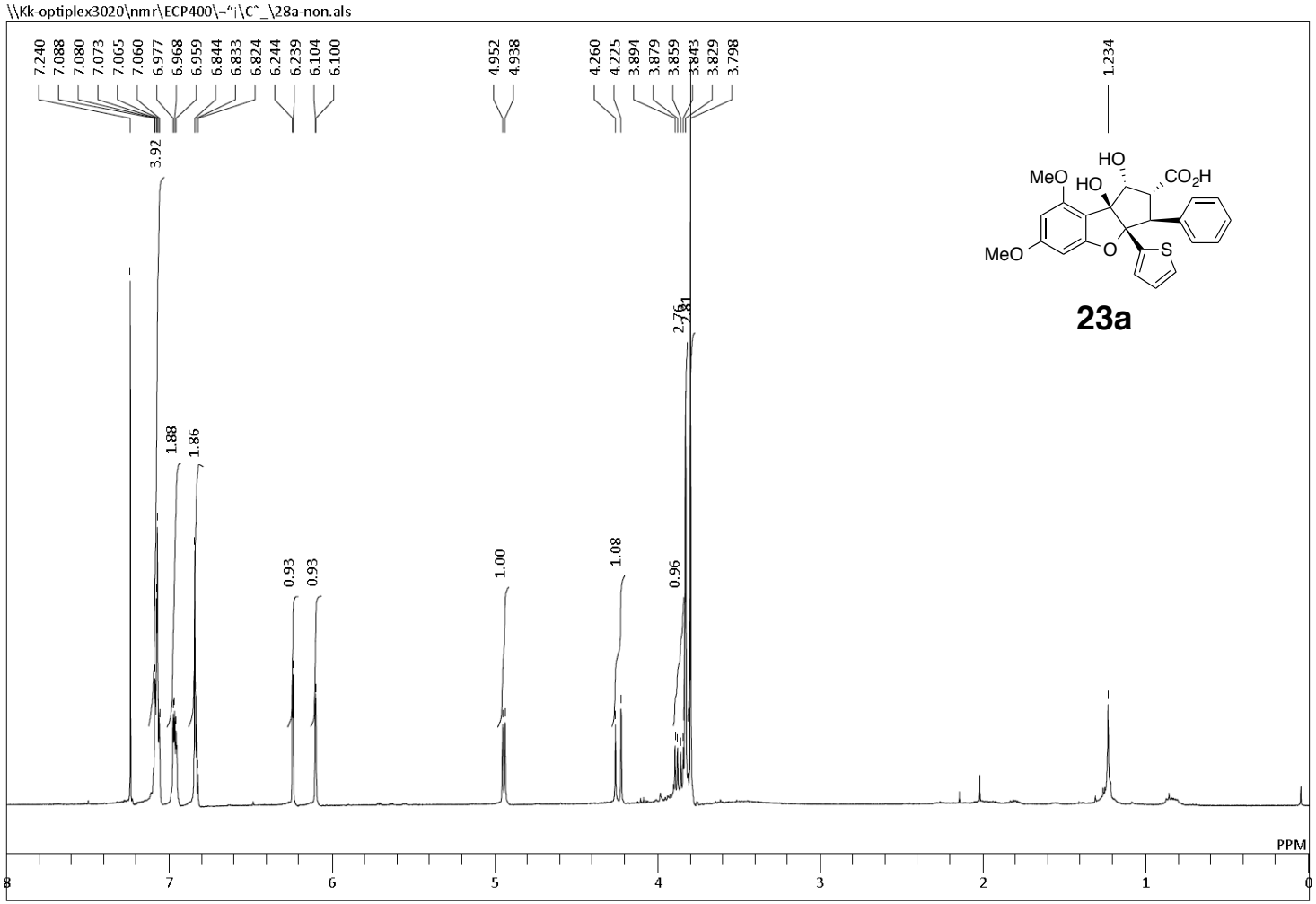

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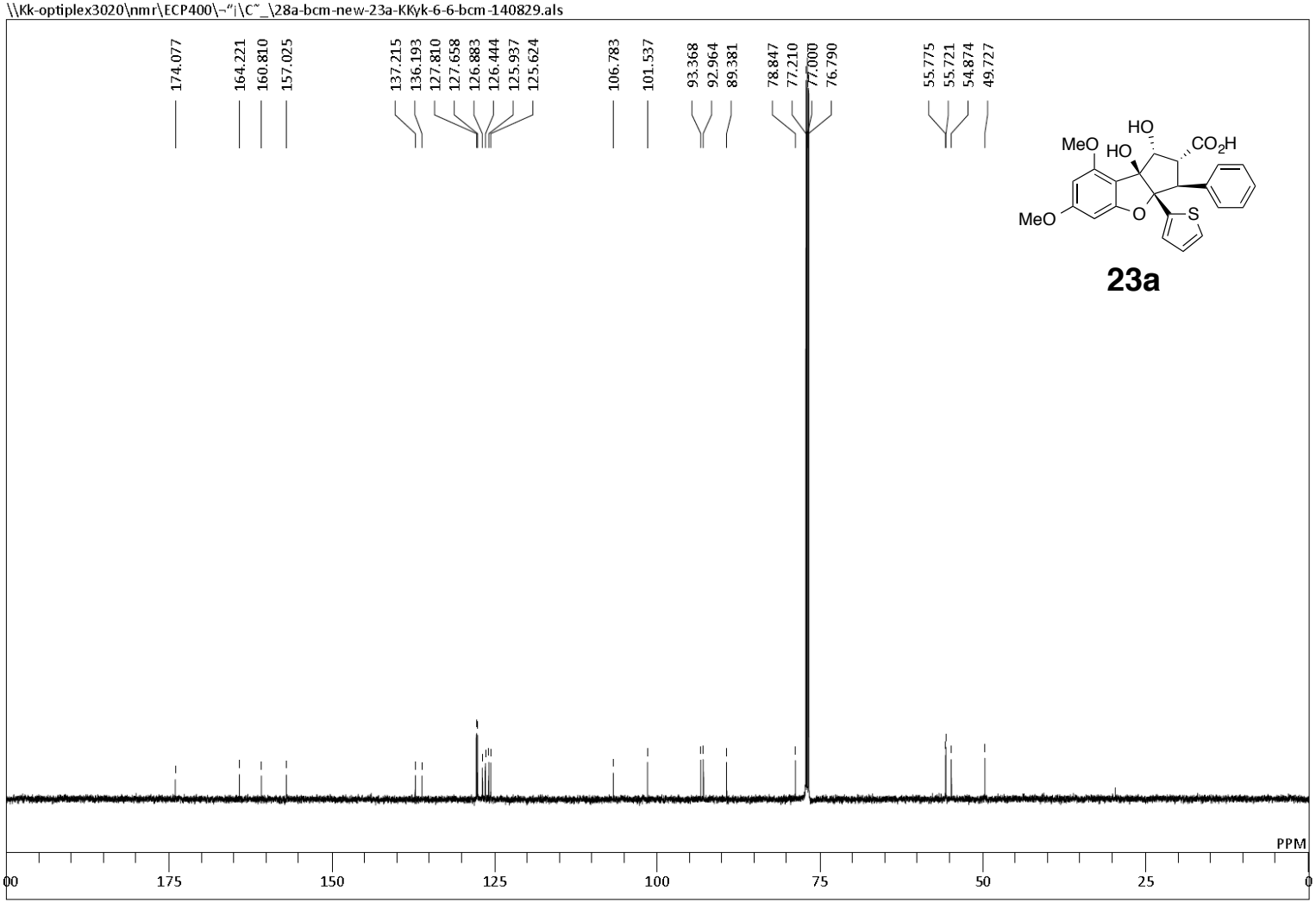

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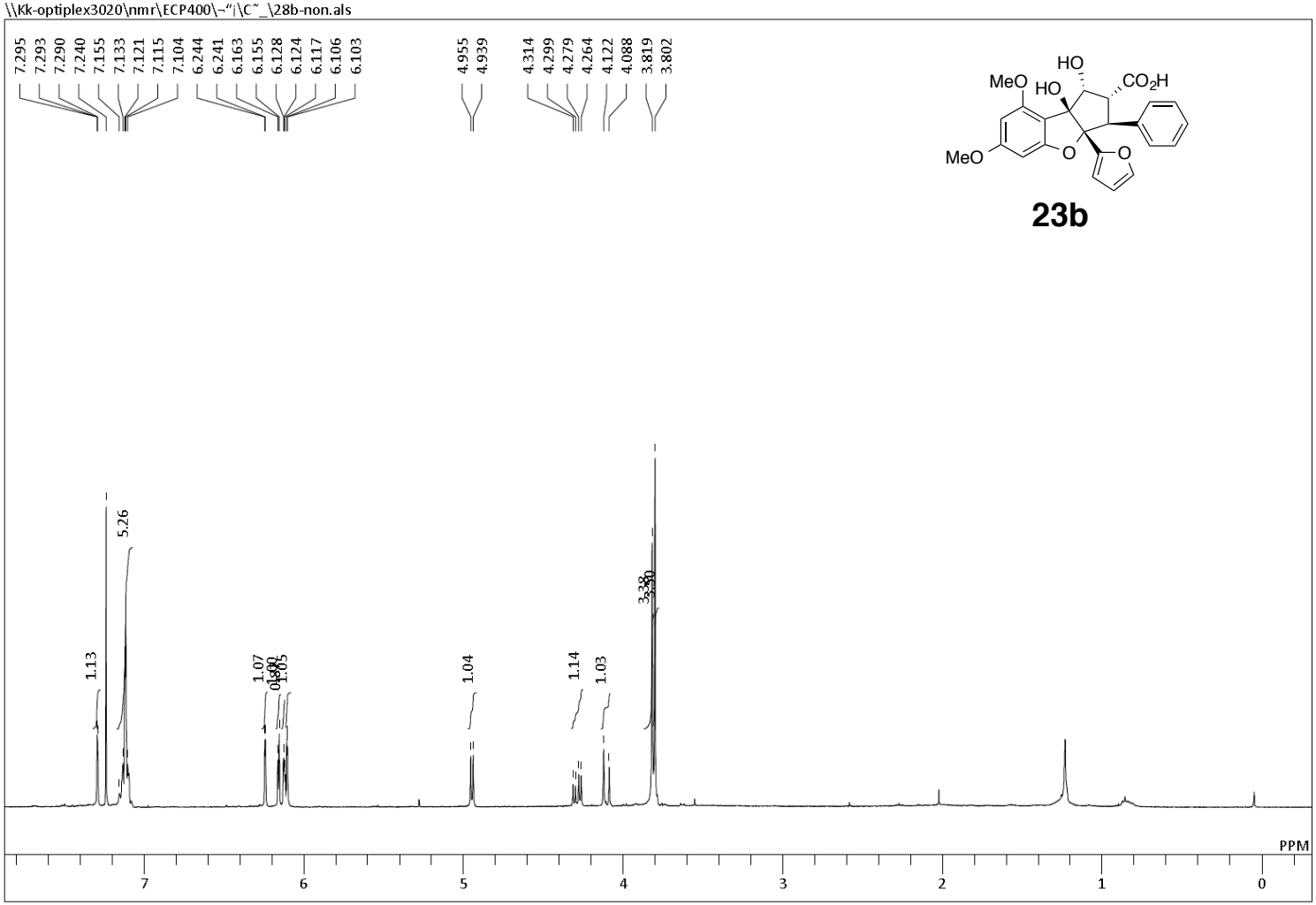

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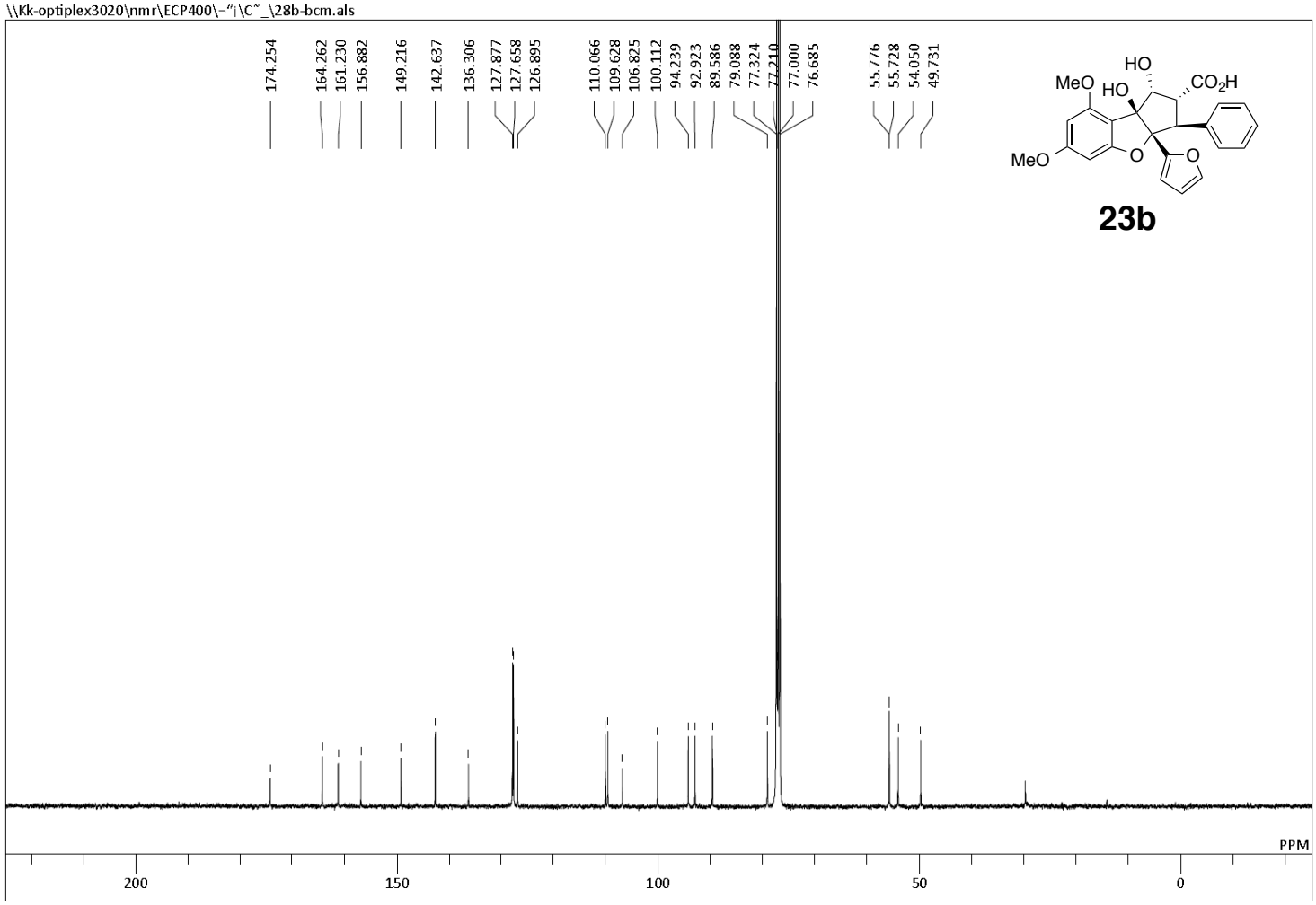

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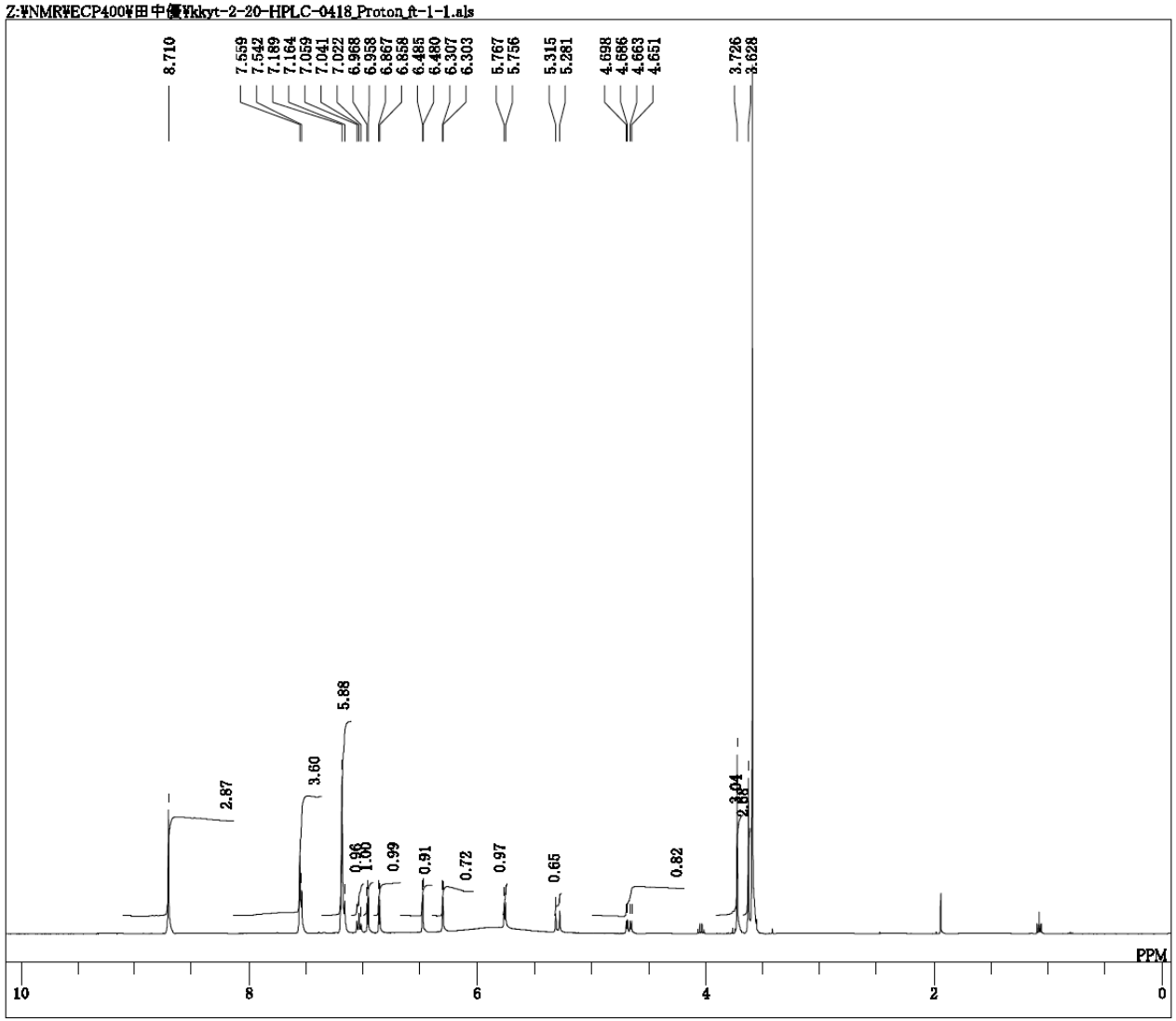
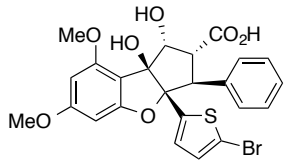
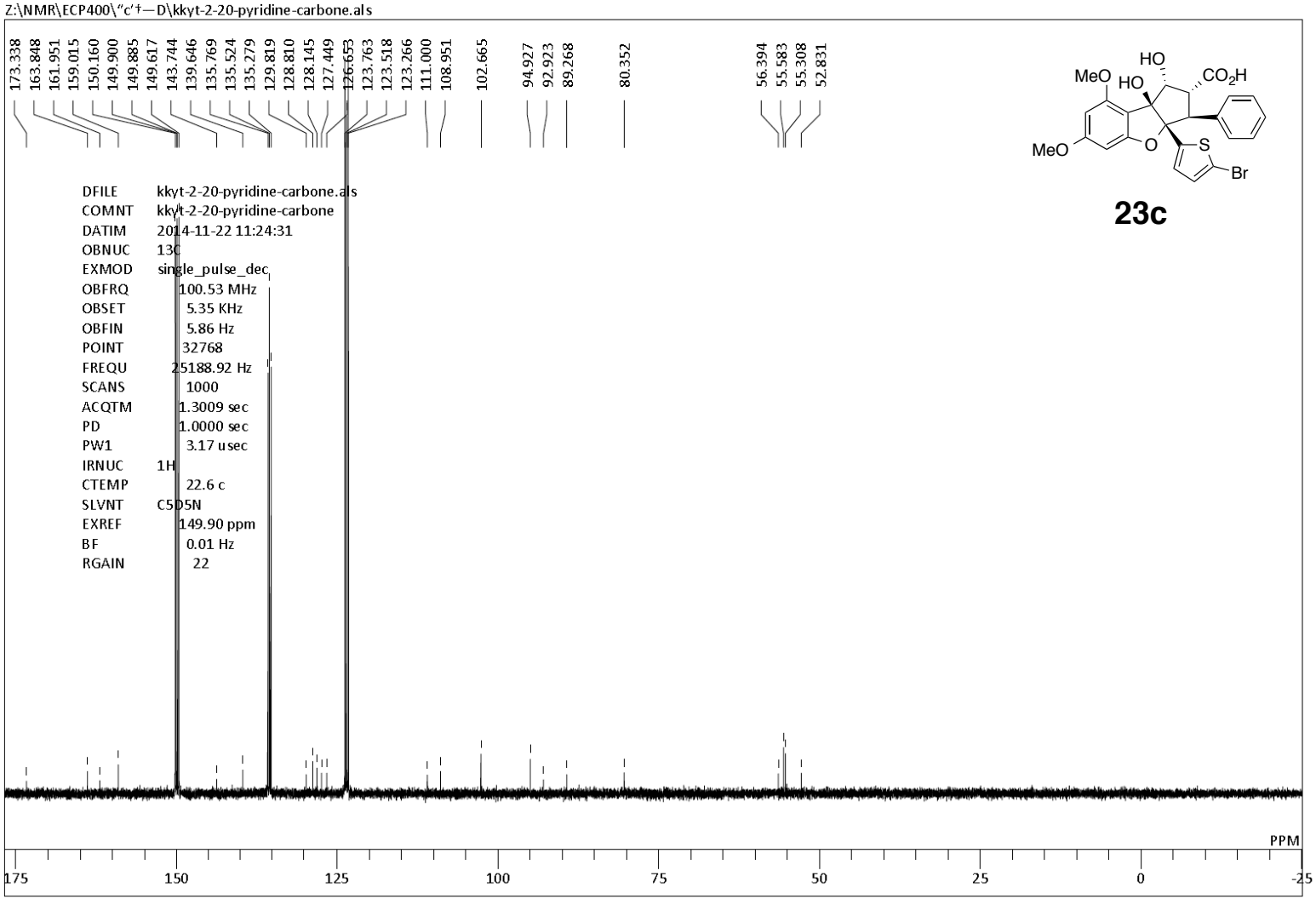




23c

Compound 23c



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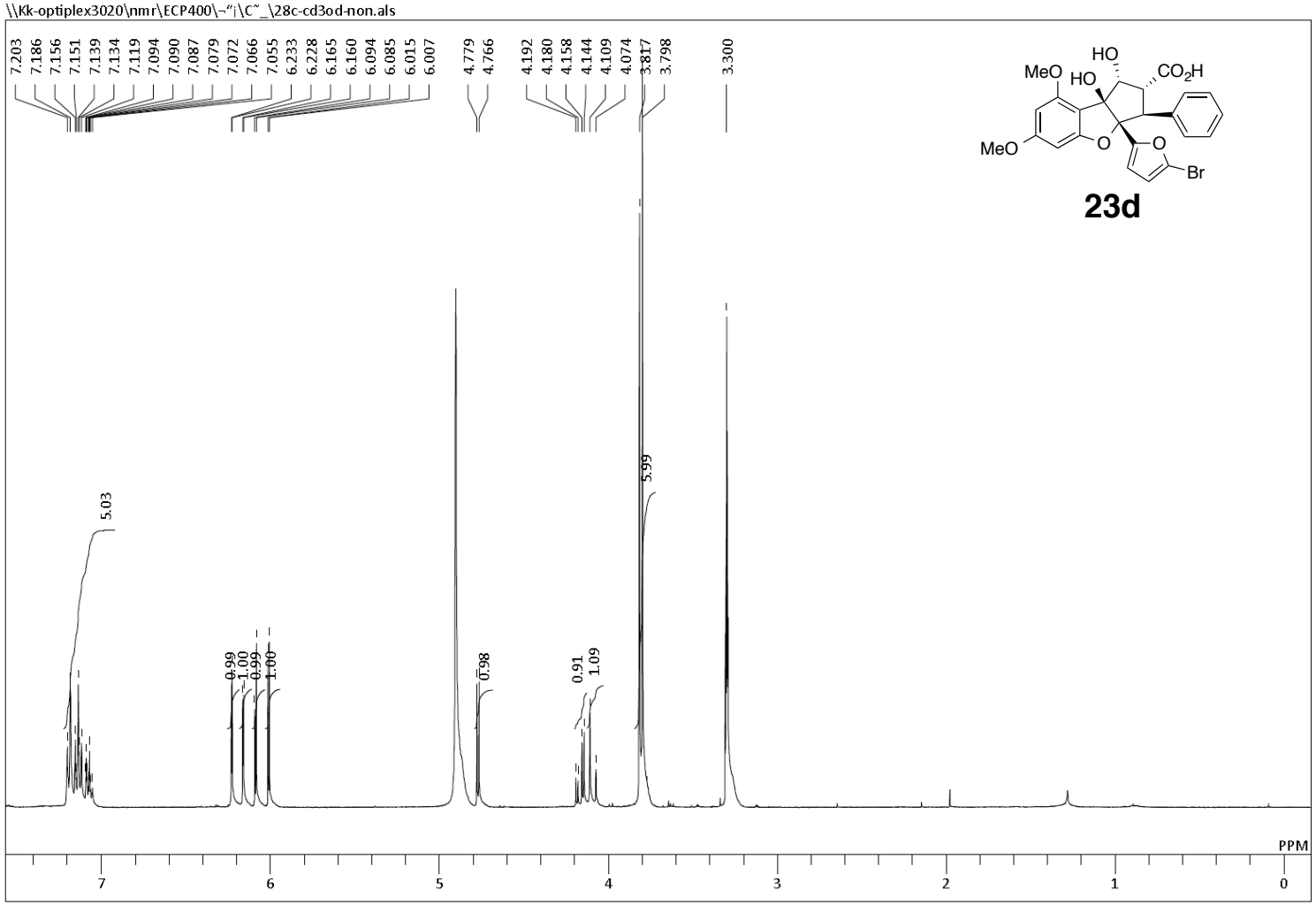

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