Electronic Supplementary Material (ESI) for RSC Sustainability.

Supporting Information

Solvent-free synthesis of chalcones using $Mg(HSO_4)_2$

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Table of Contents

General Procedures

All chemicals were purchased from commercial suppliers and used as received, unless otherwise noted. Reaction temperatures correspond to the external temperature of the reaction vessel and reactions were run under an atmosphere of dry nitrogen and in pre-dried reaction vessels unless otherwise noted.

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 aluminum sheets. Visualization was accomplished with UV light and/or potassium permanganate ($KMnO_4$). Retention factor (R_f) values reported were measured using a 5 × 2 cm TLC plate in a developing chamber containing the solvent system described. Silicycle SiliaFlash® P60 (SiO_2, 40–63 μm particle size, 230–400 mesh) and aluminum oxide activated, basic, Brockmann I (Al_2O_3, 58 Å pore size) were used for flash column chromatography.

NMR spectra were recorded using Bruker 300 – 400 MHz spectrometers. ^1H NMR spectra were obtained at either 300 or 400 MHz, $^{13}C\{^1H\}$ NMR were obtained at either 101 or 126 MHz. Chemical shifts are reported in parts per million (ppm) and multiplicities are indicated as: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hertz.

Mass spectrometry (MS) was performed by Thermo scientific LTQ-XL with HESI (Heated Electrospray Ionization source). High resolution QTOF mass spectrometer AB Sciex X500B was used for HRMS spectra, equipped with electrospray ionization (ESI) and using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z.

Infrared (IR) spectra were measured neat on a Perkin-Elmer Spectrum Two FT-IR ATR spectrometer. Peaks are reported in cm^{-1}.

Melting points were measured with Buchi B-540 melting point apparatus.

Abbreviations

THF = tetrahydrofuran, DCM = dichloromethane, MTBE = methyl tert-butyl ether.

Optimization of reaction conditions and setup

First optimization of the solvent-free reaction

The following table summarizes all the first results using as benchmark reaction the one between 4-methylthio acetophenone **1** and aldehyde **2**. In all cases, 2 equivalents of $Mg(HSO_4)_2$ were used:

Entry	Ketone - 1 (equiv.)	Aldehyde - 2 (equiv.)	Heating Mode	Time (min)	Temperature (°C)	Purification mode	Yield (%)
1	1	2	Abderhalden's apparatus	45	60	Solubilization using DCM and filtration	10
2	1	2	None	20	r.t.	Column	10
3	1	1	Abderhalden's apparatus	60	60	Column	75
4	1	1.1	Abderhalden's apparatus	60	60	Column	71
5	1	1.2	Abderhalden's apparatus	45	60	*i*Pr2O Crystallization	n.d.
6	1	1.2	Abderhalden's apparatus	120	60	Basification	n.d.
7	1	1.2	Abderhalden's apparatus	150	50	Column	80
8	1	1.2	Abderhalden's apparatus	180	90	Column	37

Table S1. Results of the first solvent-free reactions.

The synthetical procedure for $Mg(HSO_4)_2$ preparation was directly taken from literature, without any modification.[1] By using a suction flask charged with $MgCl_2$ (1.0 equiv.), H_2SO_4 (2.0 equiv.) was added dropwise at room temperature and after removal of HCl by suction, $Mg(HSO_4)_2$ was obtained as a white solid material.

Solvent-free reactions using different catalyst

The only drawback of the use of **magnesium hydrogensulfate** is that **it is not commercially available**. For this reason, we tried to synthesize our chalcone using other commercially available salts.

We tried to perform the solvent-free reaction without the use of $Mg(HSO_4)_2$: we tested ***other salts***, such as $NaHSO_4$, or KH_2PO_4, or $MgCl_2$ itself. Unfortunately, **any of these salts alone could not replace $Mg(HSO_4)_2$**, given the unreactivity between aldehyde and ketone in the presence of them.

We also tried to use mixtures of salts to perform the solvent-free reaction. At first we mixed $MgCl_2$ with many Cu(II), Fe(II) and K salts; we used small quantities of these salts, and we mixed them with small amounts of ketone and aldehyde, heating for about 20 seconds with a heat gun. We performed a TLC and we noted that for some mixtures we obtained small traces of chalcone:

Mixture of salts	Results
$MgCl_2 + Bu_4NHSO_4$	No traces of chalcone
$MgCl_2 + NaHSO_4$	No traces of chalcone
$MgCl_2 + CuSO_4$	No traces of chalcone
$MgCl_2 + FeSO_4$	Presence of chalcone
$MgCl_2 + K_2HPO_4$	Presence of chalcone
$MgCl_2 + KH_2PO_4$	Presence of chalcone
$MgCl_2 + MgSO_4$	No traces of chalcone
None	No traces of chalcone

Table S2. Mixture of salts used to replace $Mg(HSO_4)_2$.

We focused on the usage of Fe salt, trying to understand which was the active component which catalysed the reaction. Since we didn't obtain any trace of chalcone using $MgSO_4$, we focused our attention on the Fe counterpart:

$$MgCl_2 + FeSO_4 \longrightarrow FeCl_2 + MgSO_4$$

We started thinking that $FeCl_2$ might catalyse the reaction, so the Fe ion might replace Magnesium in the solvent-free reaction.

We thus decided to test the reaction using only a Fe salt: we tried to use $FeCl_3$, performing the reaction on a small scale, and we noted that after only a few seconds of heating we obtained a dark violet colour in the reaction mixture. From the TLC we confirmed the presence of chalcone. The same result was also achieved

using $ZrCl_4$, so we decided to perform a solvent-free reaction on a larger scale using these two salts. We decided to use also sulfamic acid, which is known to catalyse many solvent-free reactions.

All the trials performed with other salts are summarized in the following table. In each case, we used 2 equivalents of salt:

Entry	Ketone - 1 (equiv.)	Aldehyde - 2 (equiv.)	Salt	Heating Mode	Time (h)	Temp (°C)	Yield (%)
9	1	1	Sulfamic Acid	Abderhalden's apparatus	3	80	50
10	1	1	Sulfamic Acid	Abderhalden's apparatus	9	80	60
11	Few mg	Few mg	$MgCl_2 + Bu_4NHSO_4$	Heat gun	/	/	n.d.
12	Few mg	Few mg	$MgCl_2 + NaHSO_4$	Heat gun	/	/	n.d.
13	Few mg	Few mg	$MgCl_2 + CuSO_4$	Heat gun	/	/	n.d.
14	Few mg	Few mg	$MgCl_2 + K_2HPO_4$	Heat gun	/	/	Traces
15	Few mg	Few mg	$MgCl_2 + KH_2PO_4$	Heat gun	/	/	Traces
16	Few mg	Few mg	$MgCl_2 + FeSO_4$	Heat gun	/	/	Traces
17	Few mg	Few mg	$MgCl_2 + MgSO_4$	Heat gun	/	/	n.d.
18	1	1.2	$FeCl_3$	Abderhalden's apparatus	8	60	45
19	1	1.2	$FeCl_3$	Rotavapor	8	60	17
20	1	1.2	$ZrCl_4$	Abderhalden's apparatus	8	60	70
21	1	1.2	$ZrCl_4$	Rotavapor	8	60	40
22	1	1.2	$MgCl_2 + KH_2PO_4$	Abderhalden's apparatus	3	60	n.d.

Table S3. Various trials made with other salts.

As we can see, none of the salts match the results obtained with magnesium hydrogensulfate. The only promising results have been achieved with sulfamic acid and zirconium chloride, but with stronger conditions compared to those used with magnesium hydrogensulfate (8 hours at 60 – 80 °C against 30 minutes at 50 °C).

General Procedures for the Synthesis of reference chalcone 3

Mechanical stirring mode

We performed a mechanical stirring test at 400 rpm using a conical flask in an oil bath at 50°C. We decided to perform the reaction on a gram scale, still using the benchmark reaction between **1** (1.0 equiv.) and **2** (1.2 equiv.) and using $Mg(HSO_4)_2$ (2.0 equiv.) as catalyst. The reaction was monitored every hour with TLC analysis; unfortunately, we noted that after 2 hours the reaction stopped, and it did not reach 100% of conversion.

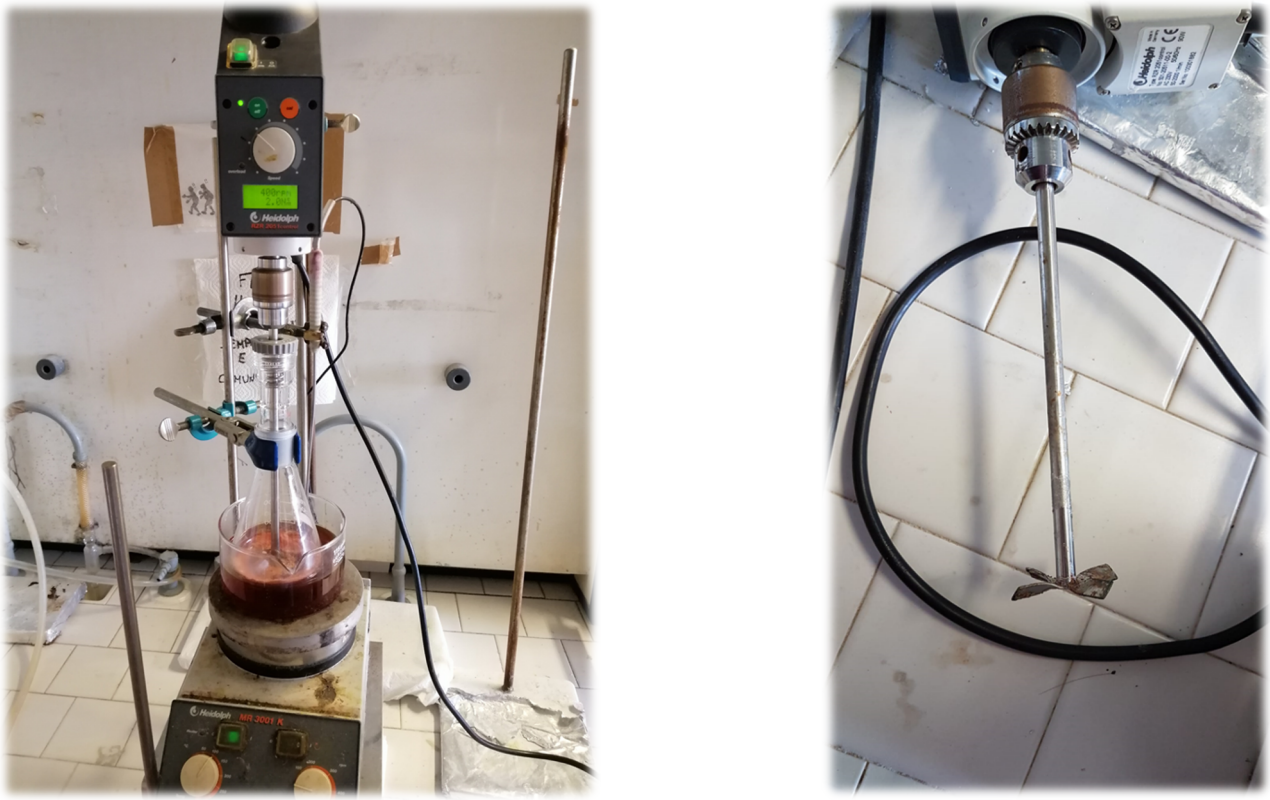


Figure S1. Mechanical stirrers used to optimize the mixing of the reagents.

We decided to change **mechanical stirrer configuration**, to have a better mixing of the reagents. We performed a mechanical stirring test at 200 rpm using a **flask** for a better stirring of the reaction mixture (again, on a gram scale) (Figure S1, Right). This time, the reaction reached **100% of conversion** after only 30 minutes (TLC analysis).

We stopped the stirring and we performed the extraction phase and the purification phase as usually (extractions with AcOEt, purification with activated carbon and recrystallization with toluene), obtaining a **crystallization yield of 82%.**

Ball-mill system

Another stirring-mode we decided to explore was the ball-mill mixing mode, taking advantage from impact and friction between the balls and the mixture of solid reagents. We explored several experimental conditions, such as different configurations, changing the powder to ball ratio, rotation speed, heating times or ramps, and the results are shown in Table S4. Aldehyde **2** (1.2 equiv.), 4-methylthio acetophenone **1** (1.0 equiv.) and catalyst $Mg(HSO_4)_2$ (2.0 equiv.) were ball-milled in a 10 mL stainless steel milling jar (Figure S2). The final product was recovered from the jar and was subjected to the usual work-up procedure, prior to be crystallized from toluene. Unfortunately, in this case we obtained lower yields, so we focused our attention on a different stirring-mode.

Figure S2. Ball-milling system used.

Entry	Ketone - 1 (equiv.)	Aldehyde - 2 (equiv.)	Powder to ball ratio	Heating Time (min)	Rotation speed (rpm)	Yield (%)
23	1	1.2	1:20	60	80	60
24	1	1.2	1:25	60	80	62
25	1	1.2	1:30	60	100	64
26	1	1.2	1:30	90	100	59
27	1	1.2	1:30	60	120	75
28	1	1.2	1:30	60	150	72

Table S4. Various trials made with different ball-milling conditions.

Screw-reactor system

In order to improve the reaction yields and improve the performance of the mechanical reaction, we developed a home-made screw reactor. The system was set up vertically and using a Liebig condenser as a thermostatic jacket, whose inlet and outlet ports were connected to a constant temperature circulation heating bath. Inside of it – 9 mm inner diameter – we introduced a 400 mm long glass rod and with a diameter of 6 mm on which a PTFE spiral screw with 1.5 mm diameter and 10 mm of propeller pitch was wound. The aim was to maximize the corresponding friction by virtually eliminating any interstice between the jacket wall and the screw threads (Figure S3). In order to optimize the reaction conditions, we still used the benchmark reaction between 4-methylthio acetophenone **1** (1.0 equiv.), aldehyde **2** (1.2 equiv.), and $Mg(HSO_4)_2$ (2.0 equiv.). Specifically, the reactants were fed as a solid mixture and the conditions to maximize the yield were obtained by systematically varying temperature, recycles, residence time and screw rotation speed (Table S5).

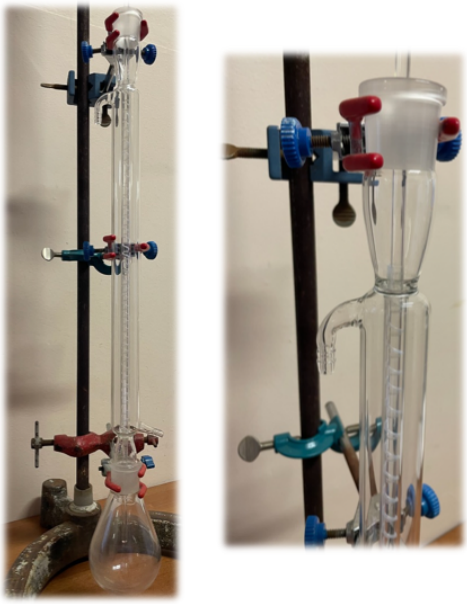
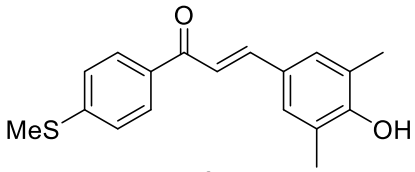


Figure S3. Home-made screw-reactor system used.

Entry	Ketone 1 (equiv.)	Aldehyde 2 (equiv.)	Temperature (°C)	N° of recycles	Residence Time (min)	Screw speed (rpm)	Conversion (%)	Yield (%)
30	1	1.2	80	1	12	20	10	12
31	1	1.2	60	1	12	20	30	27
32	1	1.2	60	1	6	40	35	24
33	1	1.2	50	1	6	40	40	33
34	1	1.2	50	3	18 (total)	40	100	95

Table S5. Various trials made with different screwing conditions.

Characterization data of reference chalcone 3



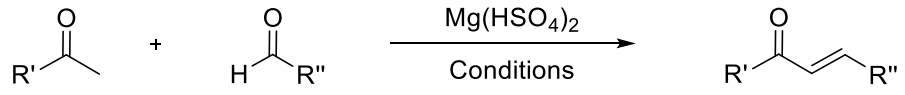
3

(E)-3-(4-hydroxy-3,5-dimethylphenyl)-1-(4-(methylthio)phenyl)prop-2-en-1-one **3** was prepared using all the different mixing modes. Purification by recrystallization afforded desired product as a yellow solid (95%).

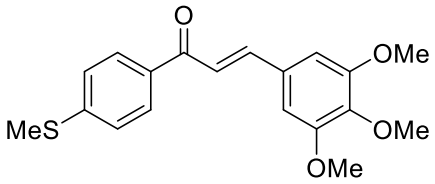
R_f	0.36 (SiO_2, Hex:Et_2O 7:3, UV, Vanillin, $KMnO_4$).
^{1}H NMR	(400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.5 Hz, 2H); 7.75 (d, *J* = 15.6 Hz, 1H); 7.40 (d, *J* = 15.6 Hz, 1H); 7.33 – 7.28 (m ,4H); 2.55 (s, 3H); 2.31 (s, 6H).
^{13}C NMR	(101 MHz, $CDCl_3$) δ 189.6, 155.1, 145.3, 145.3, 134.8, 129.4, 129.0, 127.0, 125.1, 124.0, 118.9, 16.0, 14.9.
HRMS (ESI-TOF)	$[M+H]^+$ calcd. for $C_{18}H_{18}O_2S$ m/z 299.1028 and found m/z 299.1023.
IR	(ATR, neat, cm^{-1}) 3325, 1621, 1597, 1412, 1342, 1250, 1168, 1026, 986, 877, 736. .
m.p.	146 – 149 °C.

Experimental Procedures and Characterization Data 3

General Procedure A for the Synthesis of compounds 6 – 15



All the reactions were performed on a 0.2 mmol scale, using 100 mol% equivalent of ketone, 120 mol% equivalents of aldehyde and 200 mol% equivalents of magnesium catalyst. The procedure involves a premixing of the three components to form either a solid mixture or a paste, depending on whether the ketone or the aldehyde are solid or liquid. After the indicated number of recycles, $Mg(HSO_4)_2$ was removed through a water-EtOAc extraction, addition to organic phase of activated charcoal removed the colored impurity. The solid is generally crystallized from toluene or it is obtained after column chromatography.



6

(E)-1-(4-(methylthio)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **6** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 1:1) afforded desired product as a pale yellow solid (86%).

R_f 0.35 (SiO_2, Hex:Et_2O 1:1, UV, Vanillin).

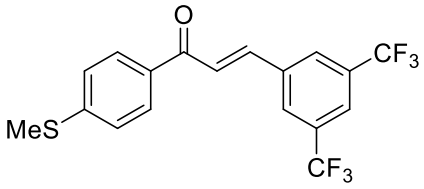
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.01-7.98 (d, *J* = 8.5 Hz, 2H); 7.74 (d, J= 15.6 Hz, 1H); 7.49 (d, J= 15.6 Hz, 1H); 7.37 (d, *J* = 8.5 Hz, 2H); 6.94 (s, 2H); 3.93 (s, 6H); 3.86 (s, 3H); 2.58 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 189.4, 154.4, 146.5, 145.0, 135.3, 131.2, 129.6, 125.8, 121.8, 106.5, 61.3, 56.9, 15.4.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{19}H_{20}O_4S$ m/z 345.1082 and found m/z 345.1086.

IR (ATR, neat, cm^{-1}) 1660, 1609, 1577, 1456, 1339, 1213, 1015, 761.

m.p. 102 – 104 °C.



7

(E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(4-(methylthio)phenyl)prop-2-en-1-one **7** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 95:5) afforded desired product as a pale yellow solid (90%).

R_f 0.37 (SiO_2, Hex:Et_2O 9:1, UV, Vanillin).

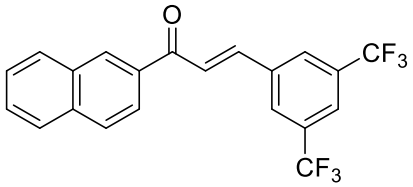
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.14 (s, 2H); 8.02 (d, *J* = 8.5 Hz, 2H); 7.97 (s, 1H); 7.85 (d, *J* = 15.7 Hz, 1H); 7.72 (d, *J* = 15.7 Hz, 1H); 7.39 (d, *J* = 8.5 Hz, 2H); 2.59 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 188.5, 147.5, 140.9, 138.1, 134.4, 133.0 (q, J= 33 Hz), 129.7, 128.9, 128.83, 125.9, 125.8, 124.1 (q, J= 3.8 Hz), 122.2, 15.3.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{18}H_{12}F_6OS$ m/z 391.0513 and found m/z 391.0518.

IR (ATR, neat, cm^{-1}) 1656, 1604, 1579, 1334, 1210, 1012, 757.

m.p. 110 – 112 °C.



8

(E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(naphthalen-2-yl)prop-2-en-1-one **8** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 98:2) afforded desired product as a pale yellow solid (99%).

R_f 0.31 (SiO_2, Hex:Et_2O 98:2, UV, Vanillin).

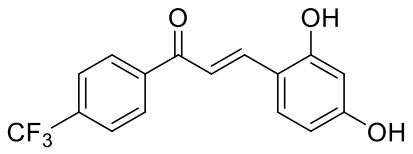
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.45 – 8.41 (m, 1H); 8.12 – 8.09 (m, 3H); 8.01 – 7.96 (m, 2H); 7.90 (dd, *J* = 7.2, 1.3 Hz, 1H); 7.71 (d, *J* = 16.1, 1H); 7.66 – 7.59 (m, 3H); 7.52 (d, *J* = 16.1, 1H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 194.6, 142.0, 137.8, 136.8, 133.6, 133.1, 133.0 (q, J= 33 Hz), 131.2, 130.8, 129.3, 128.9, 128.8, 128.6, 128.5, 127.4, 126.3, 125.7, 125.3, 124.3 (q, J= 3.8 Hz), 122.1.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{21}H_{12}F_6O$ m/z 395.0792 and found m/z 395.0787.

IR (ATR, neat, cm^{-1}) 1635, 1602, 1565, 1439, 1332, 1219, 1011, 758.

m.p. 85 – 87 °C.



9

(E)-3-(2,4-dihydroxyphenyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **9** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 7:3) afforded desired product as an orange solid (73%).

R_f 0.29 (SiO_2, Hex:Et_2O 7:3, UV, Vanillin, $KMnO_4$).

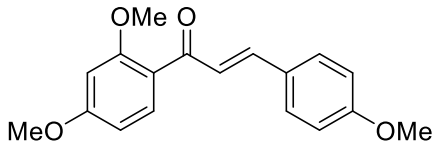
^{1}H NMR (300 MHz, DMSO-*d6*) δ 10.29 (s, 1H); 10.05 (s, 1H); 8.22 (d, *J* = 8.1 Hz, 2H); 8.03 (d, *J* = 15.6 Hz, 1H); 7.91 (d, *J* = 8.1 Hz, 2H); 7.71 (d, *J* = 8.6 Hz, 2H); 7.65 (d, *J* = 15.5 Hz, 1H); 6.40 (d, *J* = 2.3 Hz, 1H); 6.33 (dd, *J* = 8.6, 2.3 Hz, 2H).

^{13}C NMR (75 MHz, DMSO-*d6*) δ 188.6, 161.9, 159.5, 141.8, 141.4, 131.9 (q, J= 32 Hz), 130.7, 128.9, 125.6 (q, J= 3.8 Hz), 116.8, 113.2, 108.1, 102.5.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{16}H_{11}F_3O_3$ m/z 309.0660 and found m/z 309.0665.

IR (ATR, neat, cm^{-1}) 3265, 1653, 1609, 1579, 1436, 1329, 1223, 1025, 752.

m.p. 96 – 98 °C.



10

(E)-1-(2,4-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one **10** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 7:3) afforded desired product as a yellow solid (92%).

R_f 0.35 (SiO_2, Hex:Et_2O 7:3, UV, Vanillin).

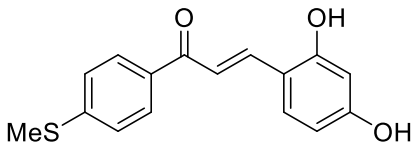
^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.73 (d, *J* = 8.6 Hz, 1H); 7.67 – 7.60 (m, 3H); 7.45 (d, *J* = 15.8 Hz, 1H); 6.99 – 6.94 (m, 2H); 6.63 – 6.56 (m, 2H); 3.94 (s, 3H); 3.90 (s, 3H); 3.87 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 190.8, 164.8, 162.1, 161.1, 142.3, 133.2, 130.7, 128.9, 125.8, 123.1, 115.0, 106.0, 99.2, 56.5, 56.3, 56.1.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{18}H_{18}O_4$ m/z 299.1205 and found m/z 299.1203.

IR (ATR, neat, cm^{-1}) 1640, 1601, 1567, 1452, 1349, 1310, 1215, 1023, 945, 889, 755.

m.p. 96 – 100 °C.



11

(E)-3-(2,4-dihydroxyphenyl)-1-(4-(methylthio)phenyl)prop-2-en-1-one **11** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 7:3) afforded desired product as an orange solid (86%).

R_f 0.30 (SiO_2, Hex:Et_2O 7:3, UV, Vanillin, $KMnO_4$).

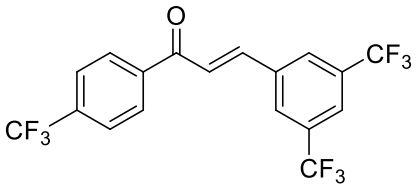
^{1}H NMR (300 MHz, CD_3OD) δ 8.08 (d, *J* = 15.6 Hz, 1H); 7.97 (d, *J* = 8.6 Hz, 2H); 7.66 (d, *J* = 15.6 Hz, 1H); 7.53 (d, *J* = 8.2 Hz, 1H); 7.37 (d, *J* = 8.5 Hz, 1H); 6.40 – 6.36 (m, 2H); 2.56 (s, 3H).

^{13}C NMR (75 MHz, CD_3OD) δ 192.5, 163.3, 161.2, 147.5, 143.4, 136.5, 132.6, 130.2, 126.4, 119.1, 115.8, 109.4, 103.8, 15.0.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{16}H_{14}O_3S$ m/z 287.0664 and found m/z 287.0668.

IR (ATR, neat, cm^{-1}) 3280, 1676, 1605, 1577, 1349, 1218, 1154, 1087, 1021, 915, 890.

m.p. 90 – 92 °C.



12

(E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **12** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 99:1) afforded desired product as a pale-yellow solid (80%).

R_f 0.51 (SiO_2, Hex:Et_2O 9:1, UV, Vanillin).

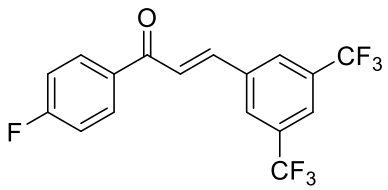
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.20 – 8.15 (m, 4H); 7.99 – 7.84 (m, 4H); 7.69 (d, *J* = 15.8 Hz, 1H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 189.3, 142.5, 141.2, 137.6, 135.0 (q, *J* = 33 Hz), 133.1 (q, *J* = 33 Hz), 129.7, 129.0, 128.9, 126.6 (q, *J* = 3.8 Hz), 125.7, 125.7, 124.6 (q, *J* = 3.8 Hz), 122.7, 122.1.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{18}H_9F_9O$ m/z 413.0510 and found m/z 413.0506.

IR (ATR, neat, cm^{-1}) 1650, 1569, 1510, 1452, 1332, 1290, 1212, 1143, 1011, 956, 805, 756.

m.p. 105 – 108 °C.



13

(E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(4-fluorophenyl)prop-2-en-1-one **13** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 99:1) afforded desired product as a pale-yellow solid (85%).

R_f 0.48 (SiO_2, Hex:Et_2O 9:1, UV, Vanillin).

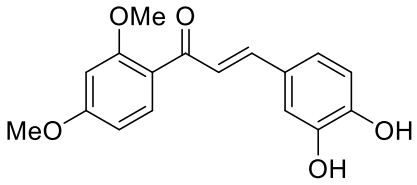
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.15 – 8.11 (m, 4H); 7.97 (s, 1H); 7.86 (d, *J* = 15.7 Hz, 1H); 7.70 (d, *J* = 15.7 Hz, 1H); 7.26 (t, *J* = 8.7 Hz, 2H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 188.3, 168.3, 165.0, 141.5, 137.9, 134.8, 134.7, 133.0 (q, *J* = 33 Hz), 132.1, 132.0, 128.9, 128.8, 125.8,124.3 (q, *J* = 3.8 Hz), 122.1, 116.8, 116.5.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{17}H_9F_7O$ m/z 363.0542 and found m/z 363.0538.

IR (ATR, neat, cm^{-1}) 1665, 1599, 1503, 1341, 1289, 1211, 1175, 1015, 986, 945, 891, 754.

m.p. 115 – 118 °C.



14

(E)-3-(3,4-dihydroxyphenyl)-1-(2,4-dimethoxyphenyl)prop-2-en-1-one **14** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:AcOEt = 8:2) afforded desired product as a yellow solid (85%).

R_f 0.32 (SiO_2, Hex:AcOEt 8:2, UV, Vanillin, $KMnO_4$).

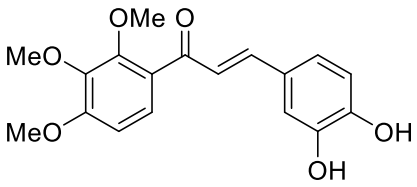
^{1}H NMR (300 MHz, DMSO-*d6*) δ 9.36 (br s, 2H); 7.58 (d, *J* = 8.6 Hz, 1H); 7.41 (d, *J* = 15.7 Hz, 1H); 7.26 (d, *J* = 15.7 Hz, 1H); 7.10 (d, *J* = 2.1 Hz, 1H); 7.01 (dd, *J* = 8.1, 2.1 Hz, 1H); 6.79 (d, *J* = 8.1 Hz, 1H); 6.69 – 6.61 (m, 2H); 3.90 (s, 3H); 3.85 (s, 3H).

^{13}C NMR (75 MHz, DMSO-*d6*) δ 189.2, 163.6, 160.0, 148.4, 145.6, 142.3, 131.9, 126.3, 123.6, 121.8, 121.7, 115.8, 114.5, 105.9, 98.7, 55.9, 55.6.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{17}H_{16}O_5$ m/z 301.0998 and found m/z 301.0996.

IR (ATR, neat, cm^{-1}) 3279, 1636, 1602, 1320, 1219, 1178, 1009, 989, 915, 776.

m.p. 92 – 94 °C.



15

(E)-3-(3,4-dihydroxyphenyl)-1-(2,3,4-trimethoxyphenyl)prop-2-en-1-one **15** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 1:1) afforded desired product as a yellow solid (81%).

R_f 0.34 (SiO_2, Hex: Et_2O 1:1, UV, Vanillin, $KMnO_4$).

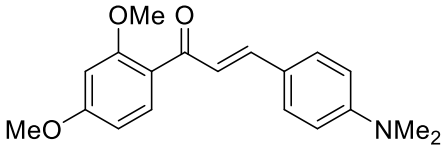
^{1}H NMR (300 MHz, CD_3OD) δ 7.51 (d, *J* = 15.7 Hz, 1H); 7.38 (d, *J* = 8.8 Hz, 1H); 7.25 (d, *J* = 15.7 Hz, 1H); 7.14 (d, *J* = 2.1 Hz, 1H); 7.02 (dd, *J* = 8.2, 2.1 Hz, 1H); 6.89 (d, *J* = 8.9 Hz, 1H); 6.81 (d, *J* = 8.2 Hz, 1H); 3.92 (s, 3H); 3.90 (s, 3H); 3.87 (s, 3H).

^{13}C NMR (75 MHz, CD_3OD) δ 194.0, 158.7, 154.9, 150.2, 147.2, 146.6, 143.8, 128.6, 128.3, 126.8, 124.7, 123.9, 116.9, 115.6, 109.0, 62.8, 61.6, 56.9.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{18}H_{18}O_6$ m/z 331.1103 and found m/z 331.1107.

IR (ATR, neat, cm^{-1}) 3268, 1639, 1570, 1445, 1321, 1295, 1254, 1210, 1168, 1098, 1034, 971, 902, 845.

m.p. 136 – 138 °C.



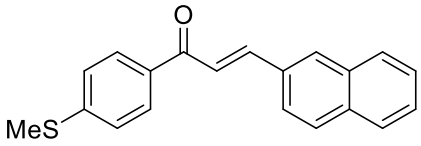
16

(E)-1-(2,4-dimethoxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one **16** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 1:1) afforded desired product as a yellow solid (80%). The obtained spectroscopic data are consistent with those reported in literature.[2]

R_f 0.29 (SiO_2, Hex: Et_2O 1:1, UV, Vanillin).

^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.68 (d, *J* = 8.5 Hz, 1H); 7.61 (d, *J* = 15.7 Hz, 1H); 7.58 – 7.52 (m, 2H); 7.33 (d, *J* = 15.6 Hz, 1H); 6.75 – 6.72 (m, 2H); 6.62 – 6.56 (m, 2H); 3.93 (s, 3H); 3.90 (s, 3H); 3.05 (s, 6H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 191.1, 164.4, 160.8, 152.7, 143.7, 132.9, 130.8, 123.7, 123.6, 123.0, 112.6, 105.9, 99.3, 56.5, 56.3, 40.7.



17

(E)-1-(4-(methylthio)phenyl)-3-(naphthalen-2-yl)prop-2-en-1-one **17** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 6:4) afforded desired product as a pale-yellow solid (55%).

R_f 0.27 (SiO_2, Hex: Et_2O 6:4, UV, Vanillin).

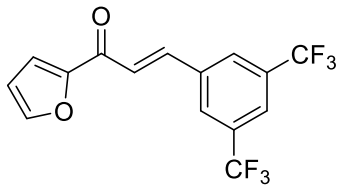
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.12 – 8.10 (m, 1H); 8.06 – 8.02 (m, 2H); 7.97 – 7.86 (m, 5H); 7.72 (d, *J* = 15.7 Hz, 1H); 7.60 – 7.56 (m, 2H); 7.41 – 7.38 (m, 2H); 2.59 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 190.3, 147.5, 145.7, 136.2, 136.1, 135.1, 134.3, 132.1, 130.5, 130.3, 130.2, 129.4, 129.0, 128.4, 126.7, 125.4, 123.7, 16.3.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{20}H_{16}OS$ m/z 305.0922 and found m/z 305.0918.

IR (ATR, neat, cm^{-1}) 1639, 1601, 1549, 1477, 1401, 1312, 1247, 1115, 1019, 980, 798, 763.

m.p. 186 – 189 °C.



18

(E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(furan-2-yl)prop-2-en-1-one **18** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 8:2) afforded desired product as a brown solid (97%).

R_f 0.35 (SiO_2, Hex: Et_2O 8:2, UV, Vanillin).

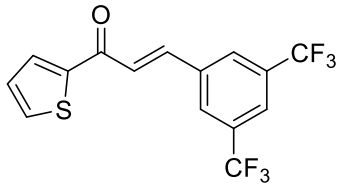
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.14 (s, 2H); 7.96 – 7.87 (m, 2H); 7.76 (d, *J* = 1.8 Hz, 1H); 7.62 (d, *J* = 15.8 Hz, 1H); 7.44 (d, *J* = 3.6 Hz, 1H); 6.69 (dd, *J* = 3.6, 1.8 Hz, 1H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 177.4, 154.2, 148.0, 140.4, 137.8, 133.28, 133.0 (q, J= 33.8 Hz), 129.3, 129.0, 128.9, 125.8, 125.6, 124.3 (q, J= 3.8 Hz), 122.12, 119.0, 113.5.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{15}H_8F_6O_2$ m/z 335.0428 and found m/z 335.0430.

IR (ATR, neat, cm^{-1}) 1632, 1593, 1350, 1229, 1010, 980, 865, 795.

m.p. 106 – 108 °C.



19

(E)-3-(3,5-bis(trifluoromethyl)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one **19** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 8:2) afforded desired product as a pale-orange solid (86%).

R_f 0.32 (SiO_2, Hex: Et_2O 8:2, UV, Vanillin).

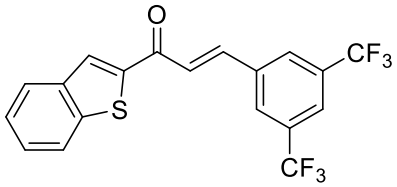
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.14 (s, 2H); 7.98 – 7.96 (m, 2H); 7.88 (d, *J* = 15.7 Hz, 1H); 7.81 (dd, *J* = 4.9, 1.1 Hz, 1H); 7.61 (d, *J* = 15.7 Hz, 1H); 7.28 (dd, *J* = 4.9, 3.8 Hz, 1H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 181.7, 145.8, 140.6, 137.8, 135.6, 133.3, 133.0 (q, J= 33.8 Hz), 129.3, 129.0, 128.9, 125.8, 125.8, 124.3 (q, J= 3.8 Hz), 122.2, 118.6.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{15}H_8F_6OS$ m/z 356.0200 and found m/z 356.0196.

IR (ATR, neat, cm^{-1}) 1634, 1521, 1465, 1399, 1316, 1125, 1013, 988, 855, 792.

m.p. 110 – 112 °C.



20

(E)-1-(benzo[b]thiophen-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)prop-2-en-1-one **20** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 9:1) afforded desired product as a bright-yellow solid (89%).

R_f 0.41 (SiO_2, Hex: Et_2O 8:2, UV, Vanillin).

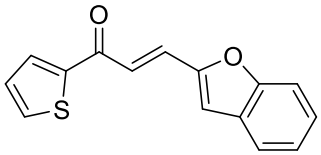
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.23 (s, 1H); 8.17 (s, 2H); 8.03 – 7.88 (m, 4H); 7.72 (d, *J* = 15.7 Hz, 1H); 7.58 – 7.47 (m, 2H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 183.2, 145.4, 143.6, 140.9, 140.1, 137.7, 133.0 (q, J= 33.8 Hz), 130.6, 129.0, 129.0, 128.7, 127.0, 126.0, 125.8, 125.2, 124.4 (q, J= 3.8 Hz), 123.8, 118.6.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{19}H_{10}F_6OS$ m/z 401.0357 and found m/z 401.0354.

IR (ATR, neat, cm^{-1}) 1665, 1612, 1501, 1475, 1405, 1323, 1234, 1115, 1064, 960, 849, 762.

m.p. 163 – 165 °C.



21

(E)-3-(benzofuran-2-yl)-1-(thiophen-2-yl)prop-2-en-1-one **21** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 8:2) afforded desired product as a brown solid (88%).

R_f 0.37 (SiO_2, Hex: Et_2O 8:2, UV, Vanillin).

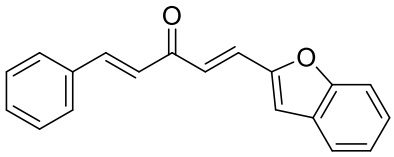
^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.97 (dd, *J* = 3.8, 1.1 Hz, 1H); 7.78 – 7.76 (m, 1H); 7.71 (s, 1H); 7.66 – 7.64 (m, 1H), 7.59 – 7.56 (m, 2H); 7.44 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H); 7.34 – 7.25 (m, 2H); 7.12 (s, 1H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 182.0, 156.4, 153.8, 146.4, 135.0, 132.9, 130.7, 129.4, 129.0, 127.6, 125.0, 122.7, 118.7, 113.3, 112.1.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{15}H_{10}O_2S$ m/z 255.0402 and found m/z 255.0406.

IR (ATR, neat, cm^{-1}) 1647, 1598, 1410, 1202, 1176, 1024, 985, 914, 877, 812, 744.

m.p. 90 – 92 °C.



22

(1E,4E)-1-(benzofuran-2-yl)-5-phenylpenta-1,4-dien-3-one **22** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 8:2) afforded desired product as a yellow solid (94%).

R_f 0.33 (SiO_2, Hex: Et_2O 8:2, UV, Vanillin).

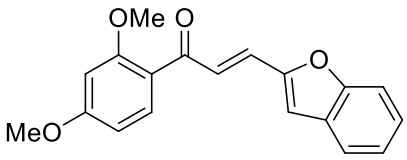
^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.79 (d, *J* = 16.0 Hz, 1H); 7.71 – 7.65 (m, 3H); 7.62 – 7.55 (m, 2H); 7.50 – 7.41 (m, 4H); 7.34 – 7.27 (m, 2H); 7.13 – 7.07 (m, 2H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 188.7, 156.4, 153.9, 144.0, 135.7, 131.3, 130.0, 129.9, 129.8, 129.7, 129.4, 129.2, 127.4, 126.9, 125.9, 124.2, 122.6, 112.9, 112.1.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{19}H_{14}O_2$ m/z 275.0994 and found m/z 275.0990.

IR (ATR, neat, cm^{-1}) 1649, 1594, 1532, 1426, 1324, 1219, 1032, 785.

m.p. 120 – 122 °C.



23

(E)-3-(benzofuran-2-yl)-1-(2,4-dimethoxyphenyl)prop-2-en-1-one **23** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:Et_2O = 8:2) afforded desired product as a pale-yellow solid (85%).

R_f 0.35 (SiO_2, Hex: Et_2O 8:2, UV, Vanillin).

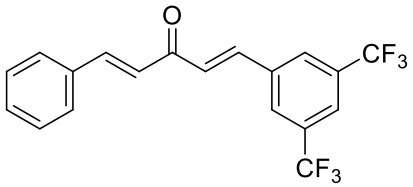
^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.80 (d, *J* = 8.6 Hz, 1H); 7.72 (d, *J* = 15.5 Hz, 1H); 7.68 – 7.53 (m, 3H); 7.43 – 7.38 (m, 1H); 7.32 – 7.26 (m, 1H); 7.05 (s, 1H); 6.64 – 6.57 (m, 2H); 3.98 (s, 3H); 3.91 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 189.9, 165.3, 161.5, 156.3, 154.5, 133.6, 129.5, 128.8, 128.3, 127.0, 124.0, 122.6, 122.4, 112.0, 111.9, 106.3, 99.2, 56.6, 56.4.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{19}H_{16}O_4$ m/z 309.1049 and found m/z 309.1047.

IR (ATR, neat, cm^{-1}) 1665, 1601, 1567, 1471, 1340, 1221, 1002, 751.

m.p. 106 – 107 °C.



24

(1E,4E)-1-(3,5-bis(trifluoromethyl)phenyl)-5-phenylpenta-1,4-dien-3-one **24** was prepared according to the **General Procedure A.** Purification by flash column chromatography (Hex:AcOEt = 95:5) afforded desired product as a bright-yellow solid (95%).

R_f 0.40 (SiO_2, Hex: AcOEt 9:1, UV, Vanillin).

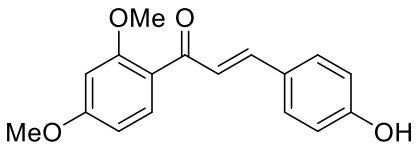
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.12 (s, 2H); 7.96 (s, 1H); 7.83 – 7.68 (m, 4H); 7.50 – 7.47 (m, 3H); 7.29 (d, *J* = 16.0 Hz, 1H); 7.12 (d, *J* = 16.0 Hz, 1H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 189.4, 145.7, 140.7, 138.9, 136.3, 133.9 (q, J= 33.8 Hz), 132.3, 130.7, 130.1, 130.0, 129.7, 129.7, 127.1, 126.7, 125.0 (q, J= 3.8 Hz), 123.1.

HRMS (ESI-TOF) $[M+H]^+$ calcd. for $C_{19}H_{12}F_6O$ m/z 371.0792 and found m/z 371.0796.

IR (ATR, neat, cm^{-1}) 1658, 1599, 1527, 1356, 1226, 1016, 781.

m.p. 112 – 115 °C.



25

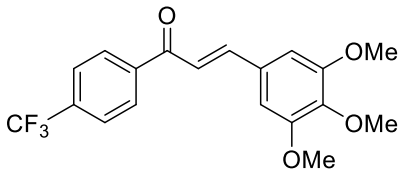
(E)-1-(2,4-dimethoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one **25** was prepared according to the **General Procedure A.** Purification by recrystallization afforded desired product as a bright-yellow solid (95%). The obtained spectroscopic data are consistent with those reported in literature.[3]

R_f 0.30 (SiO_2, Hex: AcOEt 8:2, UV, Vanillin).

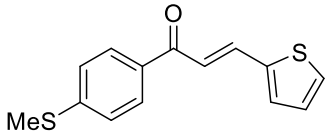
^{1}H NMR (300 MHz, DMSO-*d6*) δ 10.00 (br s, 1H); 7.57 (dd, *J* = 8.5, 5.7 Hz, 3H); 7.48 (d, *J* = 15.7 Hz, 1H); 7.34 (d, *J* = 15.7 Hz, 1H); 6.84 – 6.81 (m, 2H); 6.68 – 6.61 (m, 2H); 3.89 (s, 3H); 3.85 (s, 3H).

^{13}C NMR (75 MHz, DMSO-*d6*) δ 189.4, 163.6, 160.0, 159.7, 141.9, 131.8, 130.3, 125.9, 123.8, 121.8, 115.9, 105.8, 98.7, 55.9, 55.6.

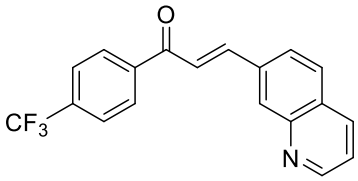
Failed solvent-free synthesis



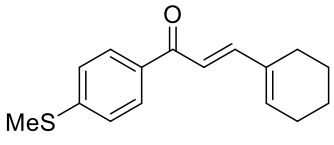
29



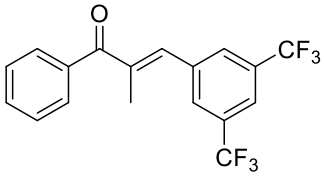
30



31



32



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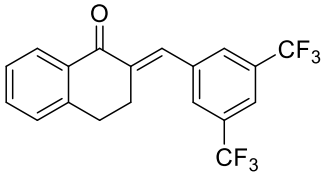
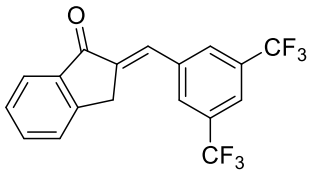


34



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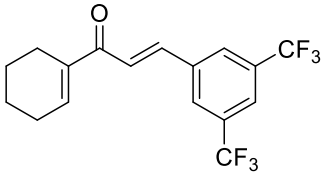
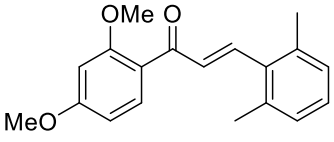
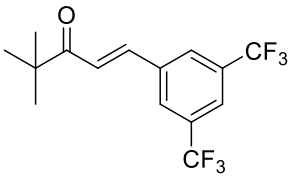


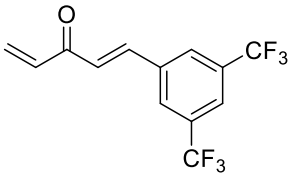
36



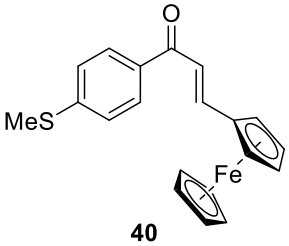
37



38



39

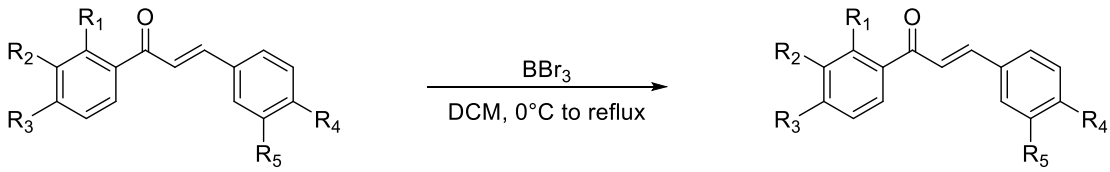


40

We can see that different aliphatic ketones didn't produce the desired chalcones, such as pinacolone (**38**), 3-buten-2-one (**39**), 1-acetylcyclohexene (**36**), as well as other derivatives including tetralone (**34**) or indanone (**35**). The trisubstituted double bond (**33**) was not detected as well.

Various aldehyde derivatives were not tolerated by this protocol, such as cyclohexene carboxaldehyde (**32**), tiophene carboxaldehyde (**30**), quinoline carboxaldehyde (**31**), ferrocene carboxaldehyde (**40**) and 2,6-dimethylbenzaldehyde (**37**). It can be due to both steric and electronic effects. Moreover, the nitrogen-containing heterocycles are not compatible with the use of magnesium hydrogensulfate, due to an acid-base side reaction. As for derivative **37**, the *ortho*-methyl groups can be an obstacle for the aldolic reaction, for their steric repulsion.

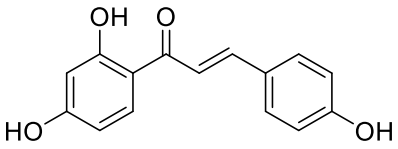
General Procedure B for the Synthesis of Naturally Occurring Chalcones



25, $R_1 = R_3 = OMe$, $R_2 = R_4 = H$, $R_5 = OH$
14, $R_1 = R_3 = OMe$, $R_2 = H$, $R_4 = R_5 = OH$
15, $R_1 = R_2 = R_3 = OMe$, $R_4 = R_5 = OH$

Isoliquiritigenin (26), $R_1 = R_3 = R_5 = OH$, $R_2 = R_4 = H$
Butein (27), $R_1 = R_3 = R_4 = R_5 = OH$, $R_2 = H$
Okanin (28), $R_1 = R_2 = R_3 = R_4 = R_5 = OH$

To a cooled solution (0 °C) of methoxy substituted chalcone (1.0 eq.) in dried DCM (0.05M), a 1 M solution of BBr_3 in DCM (12 equiv) was slowly added under Ar atmosphere. After stirring 0.5 h at room temperature under Ar, the reaction was refluxed and stirred for 4 h. Then it was cooled to rt, H_2O was added to the reaction mixture. A solid precipitate was formed, it was separated by filtration and washed with H_2O and DCM to give the fully deprotected derivative.



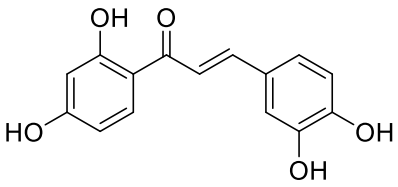
Isoliquiritigenin (26)

(E)-1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one **26** was prepared according to the **General Procedure B,** which afforded desired product as a yellow solid (80%). The obtained spectroscopic data are consistent with those reported in literature.[4]

R_f 0.43 (SiO_2, DCM:MeOH 9:1, UV, Vanillin, $KMnO_4$).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.60 (s, 1H); 10.36 (br s, 2H); 8.16 (d, *J* = 8.9 Hz, 1H); 7.76 – 7.74 (m, 4H); 6.85 (d, *J* = 8.7 Hz, 2H); 6.42 (dd, *J* = 8.9, 2.4 Hz, 1H); 6.30 (d, *J* = 2.4 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-*d6*) δ 192.0, 166.3, 165.4, 160.7, 144.7, 133.3, 131.7, 126.2, 117.90, 116.3, 113.5, 108.6, 103.1.



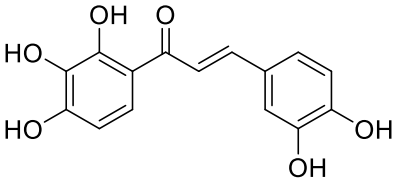
Butein (27)

(E)-1-(2,4-dihydroxyphenyl)-3-(3,4-dihydroxyphenyl)prop-2-en-1-one **27** was prepared according to the **General Procedure B,** cooling the solution at –78 °C, which afforded desired product as an orange solid (71%). The obtained spectroscopic data are consistent with those reported in literature.[4]

R_f 0.29 (SiO_2, DCM:MeOH 9:1, UV, Vanillin, $KMnO_4$).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.59 (s, 1H); 10.69 (br s, 1H); 9.77 (br s, 1H); 9.15 (br s, 1H); 8.13 (d, *J* = 8.9 Hz, 1H); 7.66 (s, 2H); 7.28 (d, *J* = 2.1 Hz, 1H); 7.20 (dd, *J* = 8.2, 2.1 Hz, 1H); 6.82 (d, *J* = 8.2 Hz, 1H); 6.42 (dd, *J* = 8.9, 2.4 Hz, 1H); 6.29 (d, *J* = 2.4 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-*d6*) δ 191.9, 166.2, 165.3, 149.4, 146.1, 145.2, 133.2, 126.7, 122.88, 117.8, 116.2, 116.2, 113.5, 108.6, 103.1.



Okanin (28)

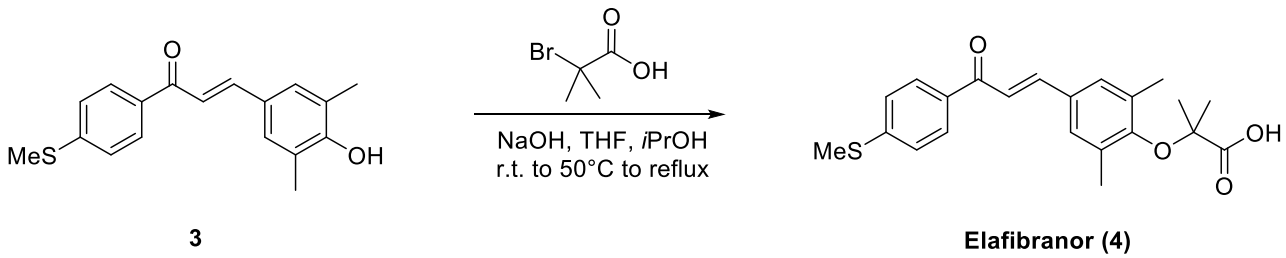
(E)-3-(3,4-dihydroxyphenyl)-1-(2,3,4-trihydroxyphenyl)prop-2-en-1-one **28** was prepared according to the **General Procedure B,** which afforded desired product as an orange solid (52%). The obtained spectroscopic data are consistent with those reported in literature.[5]

R_f 0.10 (SiO_2, DCM:MeOH 9:1, UV, Vanillin, $KMnO_4$).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 13.58 (s, 1H); 10.16 (br s, 1H); 9.81 (br s, 1H); 9.20 (br s, 1H); 8.65 (br s, 1H); 7.67 (d, *J* = 9.0 Hz, 1H); 7.65 (d, *J* = 2.0 Hz, 2H); 7.26 (d, *J* = 2.1 Hz, 1H); 7.20 (dd, *J* = 8.2, 2.1 Hz, 1H); 6.81 (d, *J* = 8.1 Hz, 1H); 6.44 (d, *J* = 8.9, 1H).

^{13}C NMR (101 MHz, DMSO-*d6*) δ 192.5, 154.0, 153.0, 149.3, 146.1, 145.0, 132.9, 126.7, 122.9, 122.8, 117.8, 116.2, 116.2, 113.8, 108.1.

Synthesis of Elafibranor

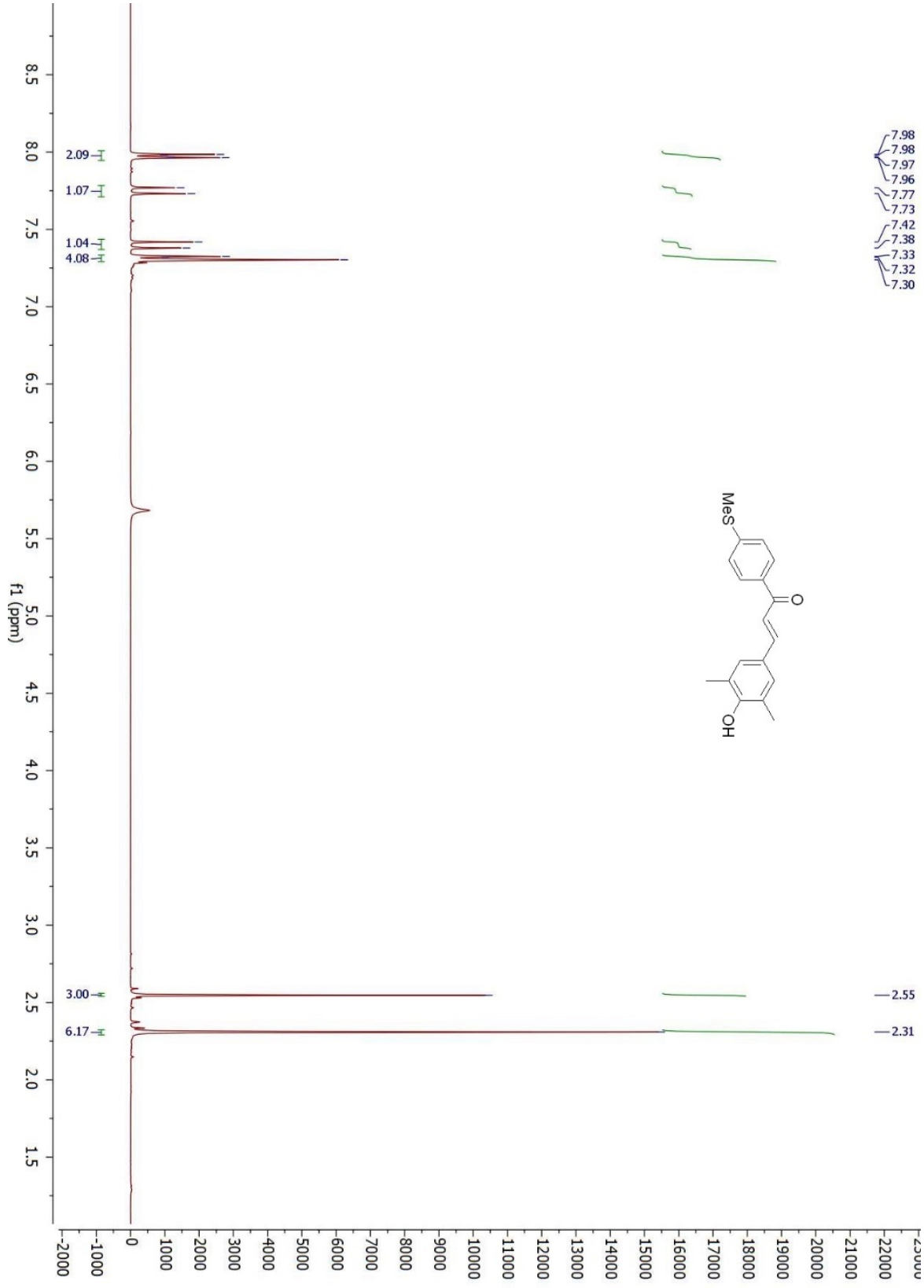


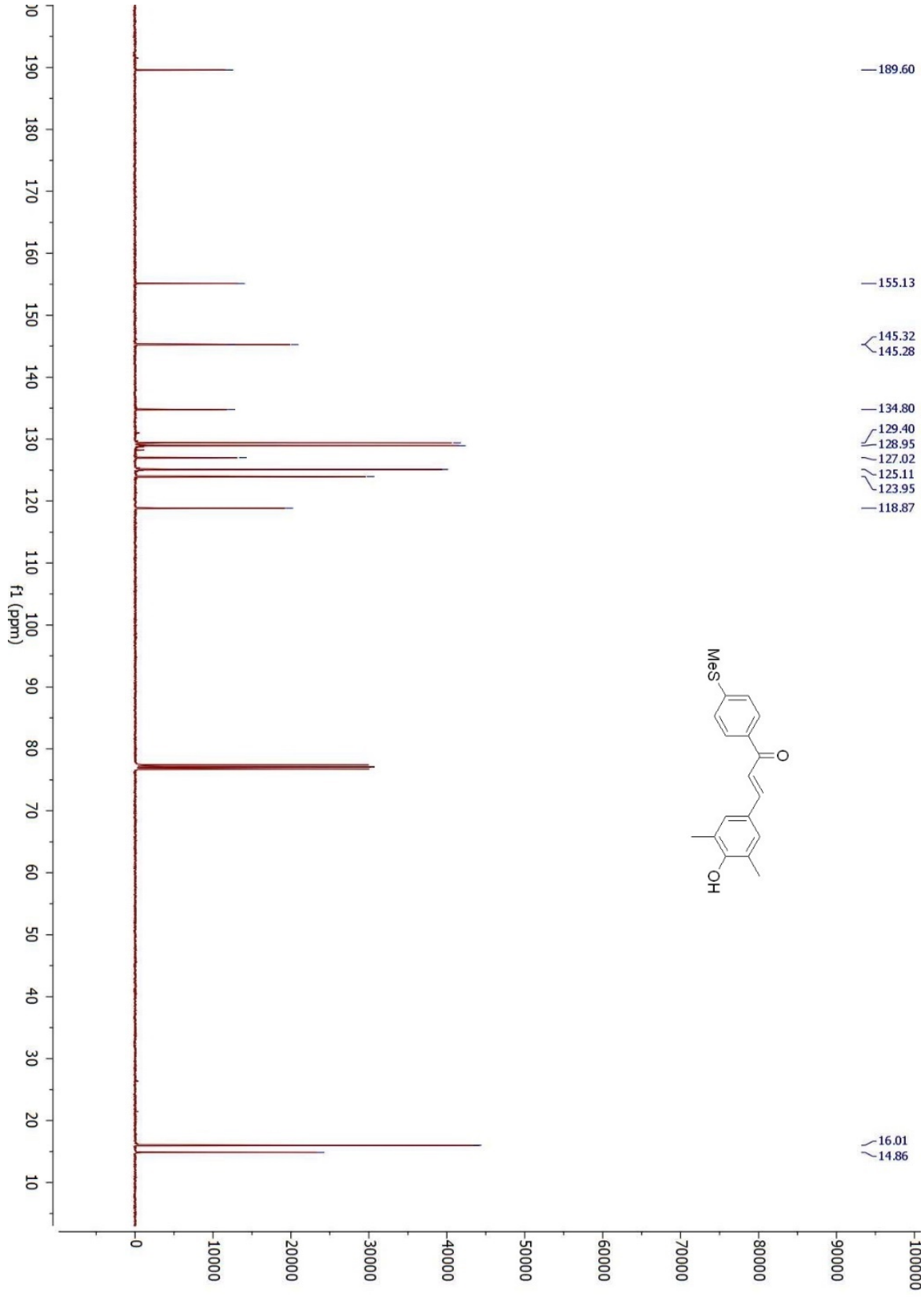
3 **Elafibranor (4)**

(E)-3-(4-hydroxy-3,5-dimethylphenyl)-1-(4-(methylthio)phenyl)prop-2-en-1-one **3** (1 eq.) was dissolved in THF (0.3M), pulverized NaOH (5 eq.) was added and the mixture was stirred for 10 minutes, until the corresponding phenolate was formed as a dark red suspension. *i*PrOH (1M) was added, suspension was heated to 50 °C and a solution of 2-bromo-2-methyl propanoic acid (3 eq.) in THF (0.3M) was added over 20 minutes. After the addition, the mixture was held at 50 °C for 2 hours, then it was heated to reflux for further 2 hours. Once complete, THF was distilled off, and the reaction was quenched using 1M HCl to pH = 3. The mixture was taken up into MTBE, and the aqueous phase was extracted three times. The organic phase was washed with brine, it was dried with Na_2SO_4 and filtered. The crude was purified by column chromatography (Hex:AcOEt 1:1 to 1:2), affording the final carboxylic acid **4** as an orange solid (65%).

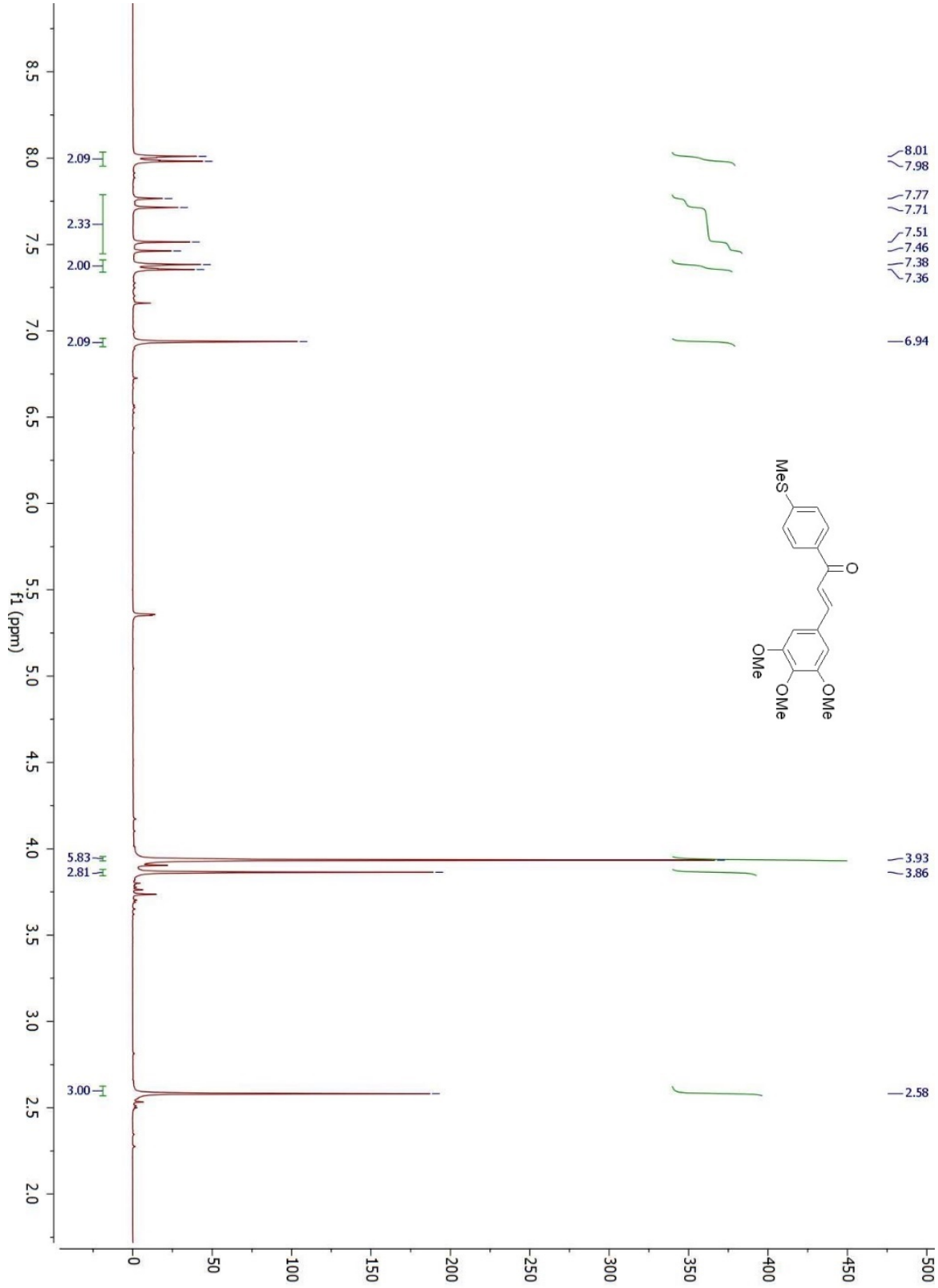
R_f	0.32 (SiO_2, Hex:AcOEt 1:1, UV, Vanillin, $KMnO_4$).
^{1}H NMR	(400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H); 7.64 (d, *J* = 15.6 Hz, 1H); 7.35 (d, *J* = 15.6 Hz, 1H); 7.24 – 7.19 (m, 4H); 2.46 (s, 3H); 2.21 (s, 6H); 1.47 (s, 6H).
^{13}C NMR	(101 MHz, $CDCl_3$) δ 189.3, 177.8, 154.5, 145.7, 144.1, 134.5, 134.0, 133.5, 131.1, 130.6, 129.2, 129.0, 125.1, 121.1, 81.5, 25.2, 18.2, 14.8.
HRMS (ESI-TOF)	$[M+H]^+$ calcd. for $C_{22}H_{24}O_4S$ m/z 385.1395 and found m/z 385.1399.
IR	(ATR, neat, cm^{-1}) 3325, 3076, 1651, 1607, 1423, 1249, 1172, 1055, 969, 873.
m.p.	144 – 146 °C.

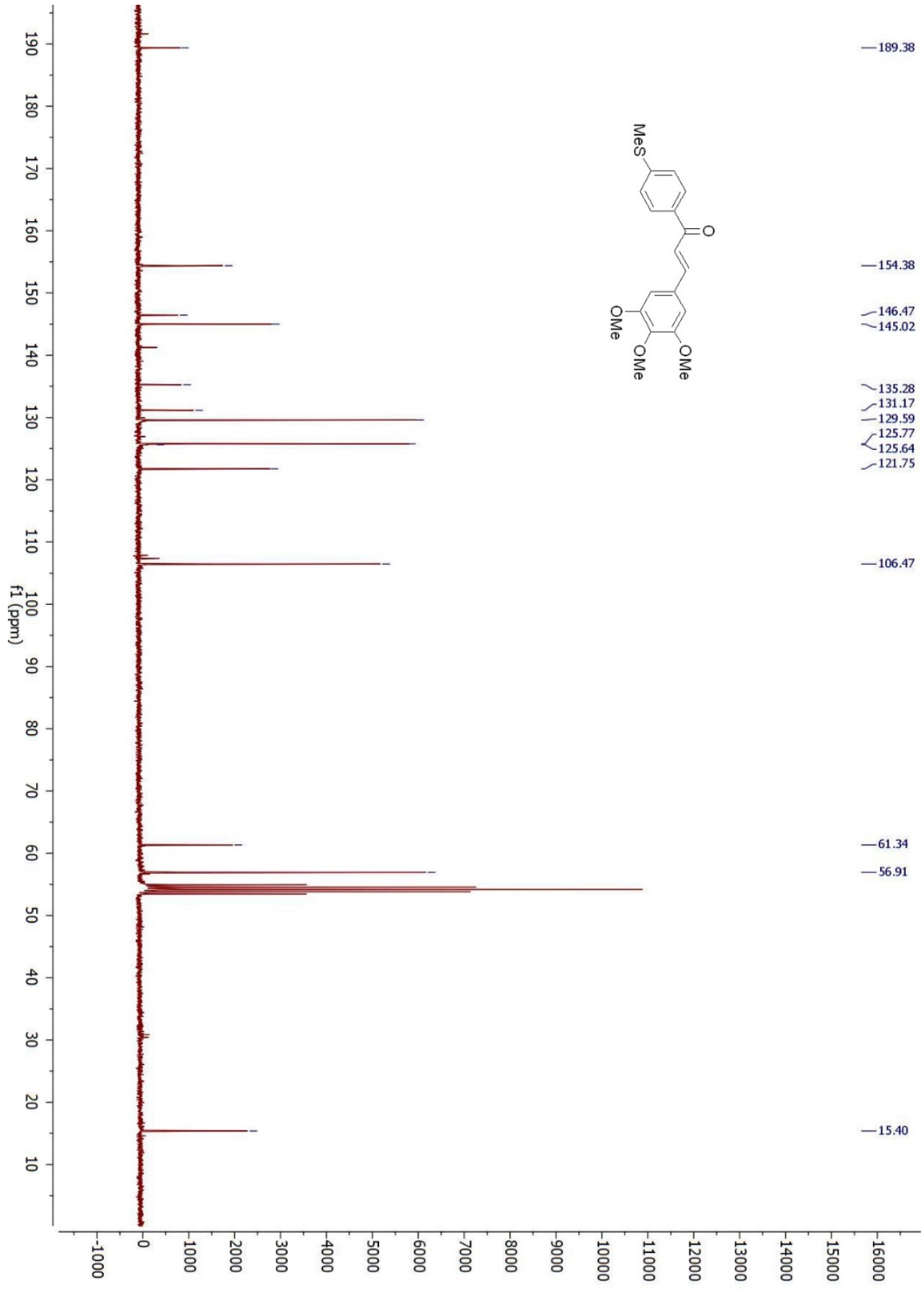
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 3, 400 MHz, $CDCl_3$)



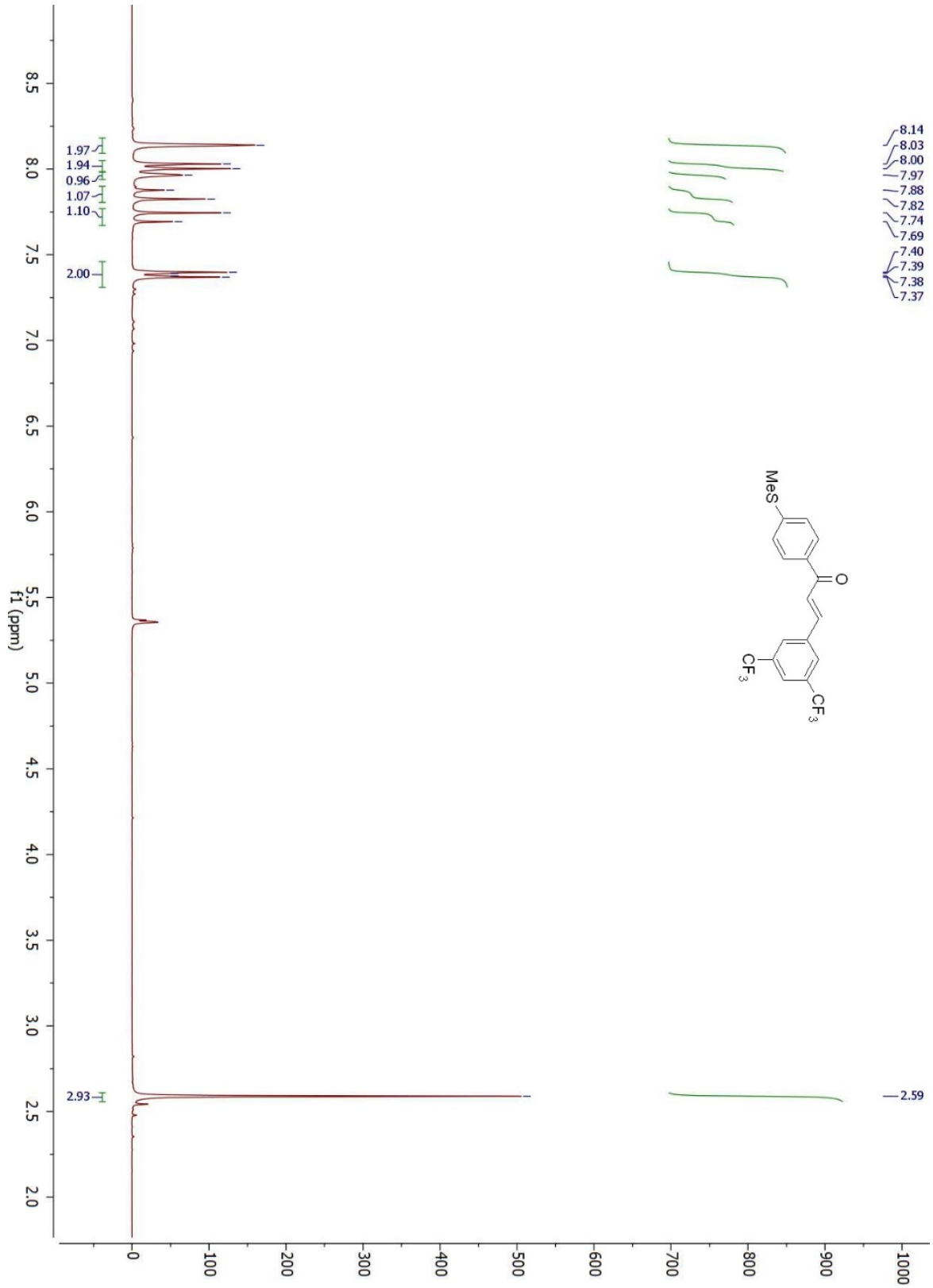

189.60
155.13
145.32
145.28
134.80
129.40
128.95
127.02
125.11
123.95
118.87
16.01
14.86
f1 (ppm)
MeS
O
OH

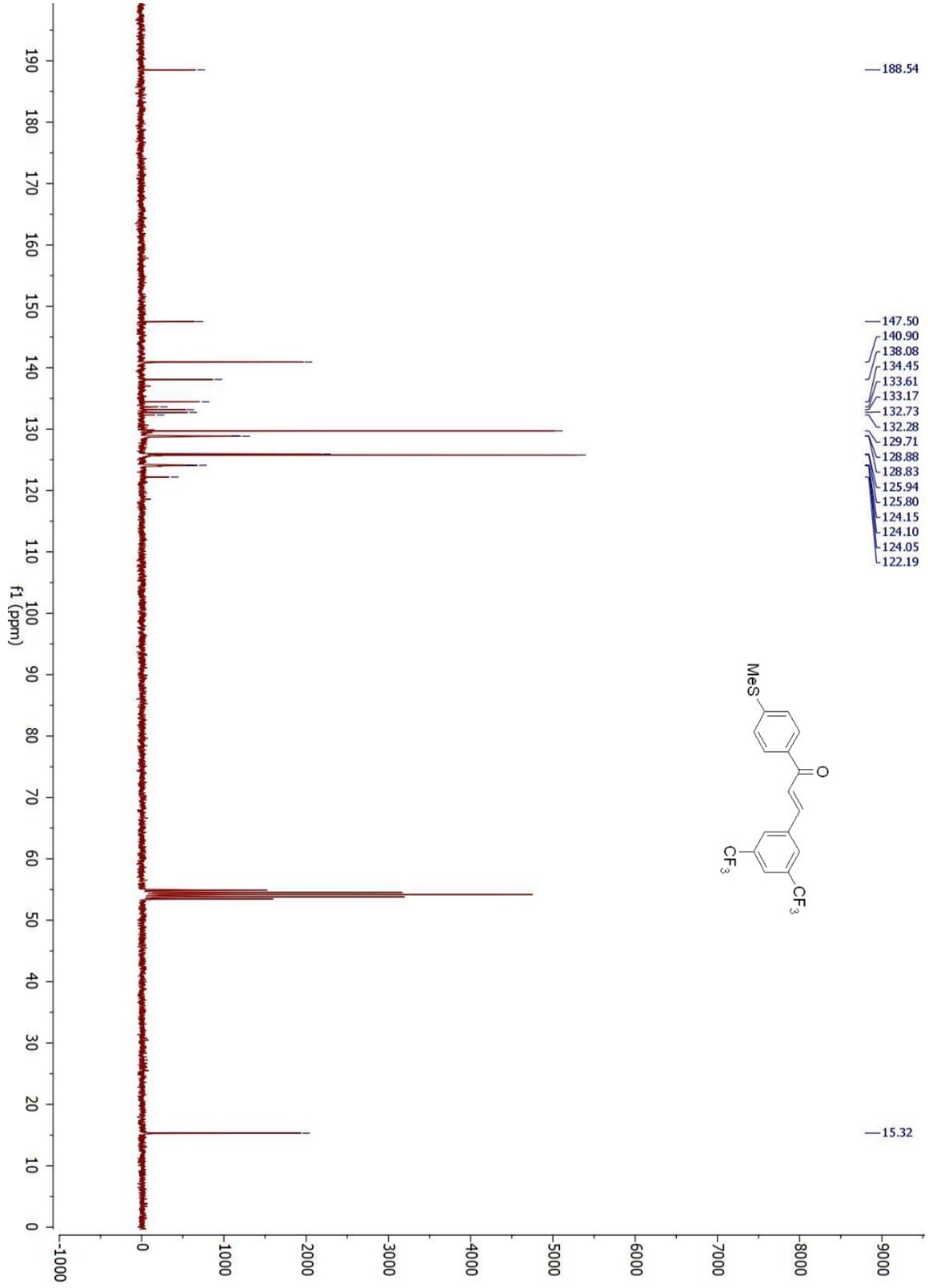
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 6, 300 MHz, CD_2Cl_2)



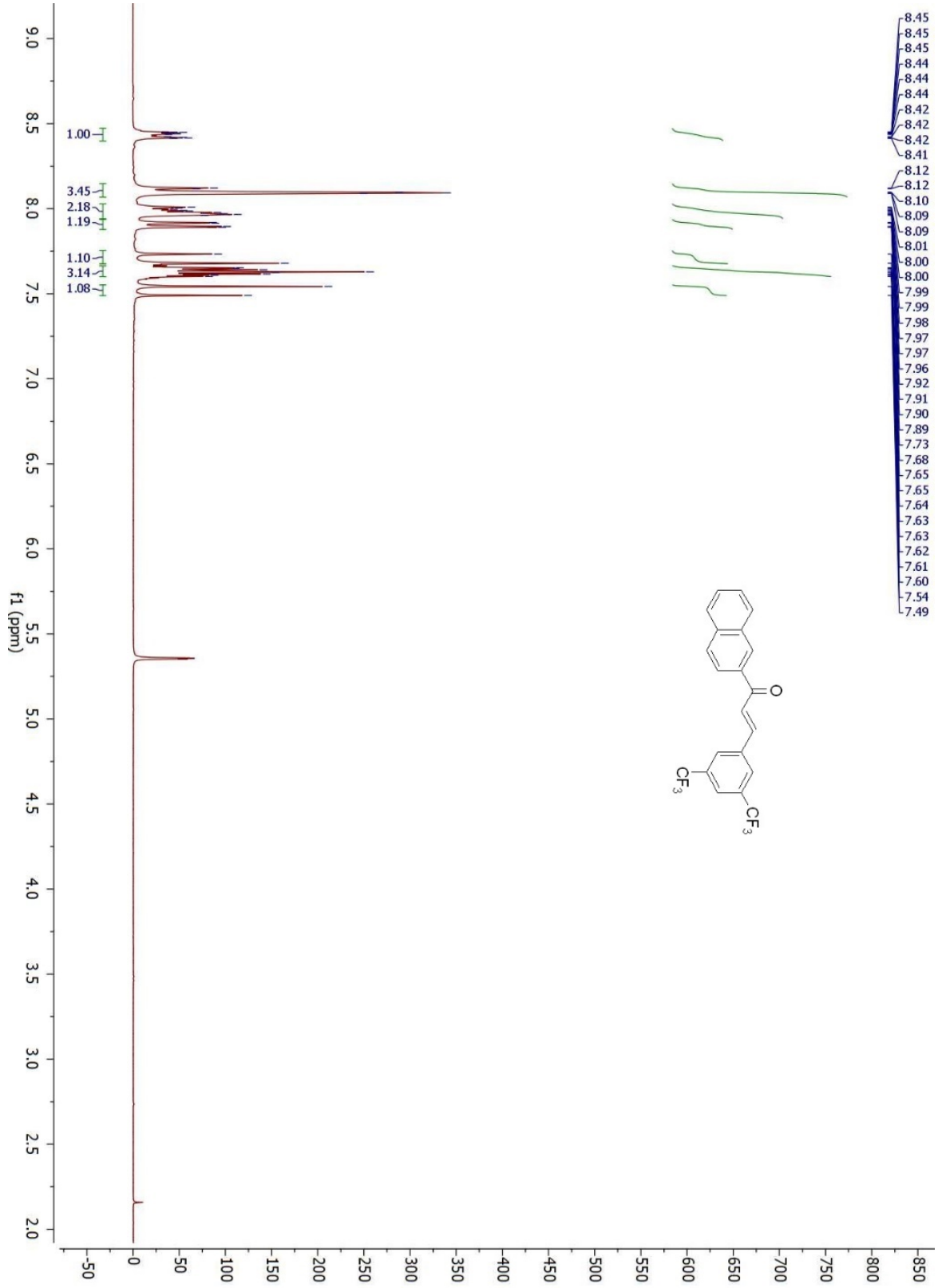

MeS
O
OMe
OMe
OMe
189.38
154.38
146.47
145.02
135.28
131.17
129.59
125.77
125.64
121.75
106.47
61.34
56.91
15.40
f1 (ppm)

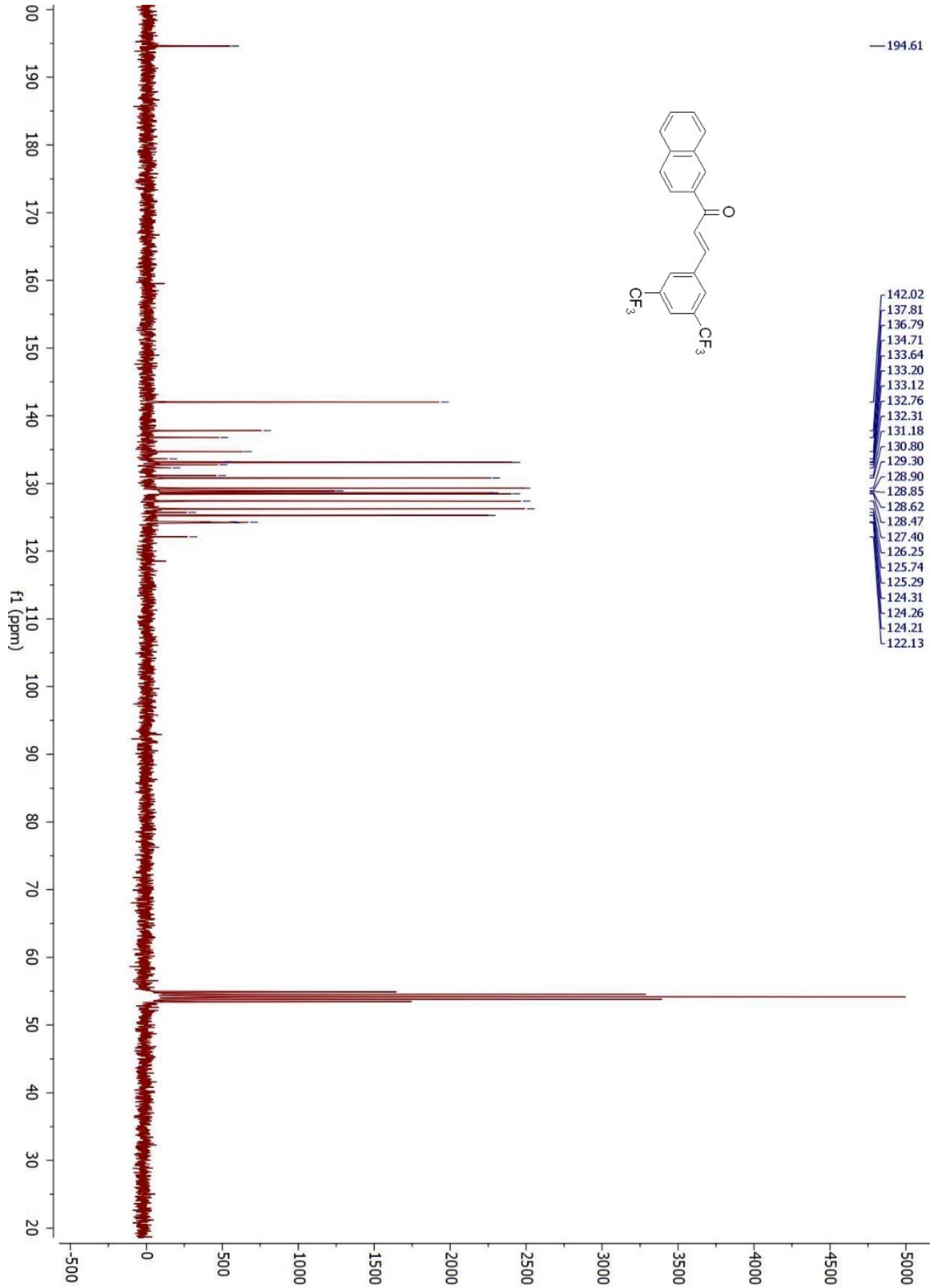
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 7, 300 MHz, CD_2Cl_2)



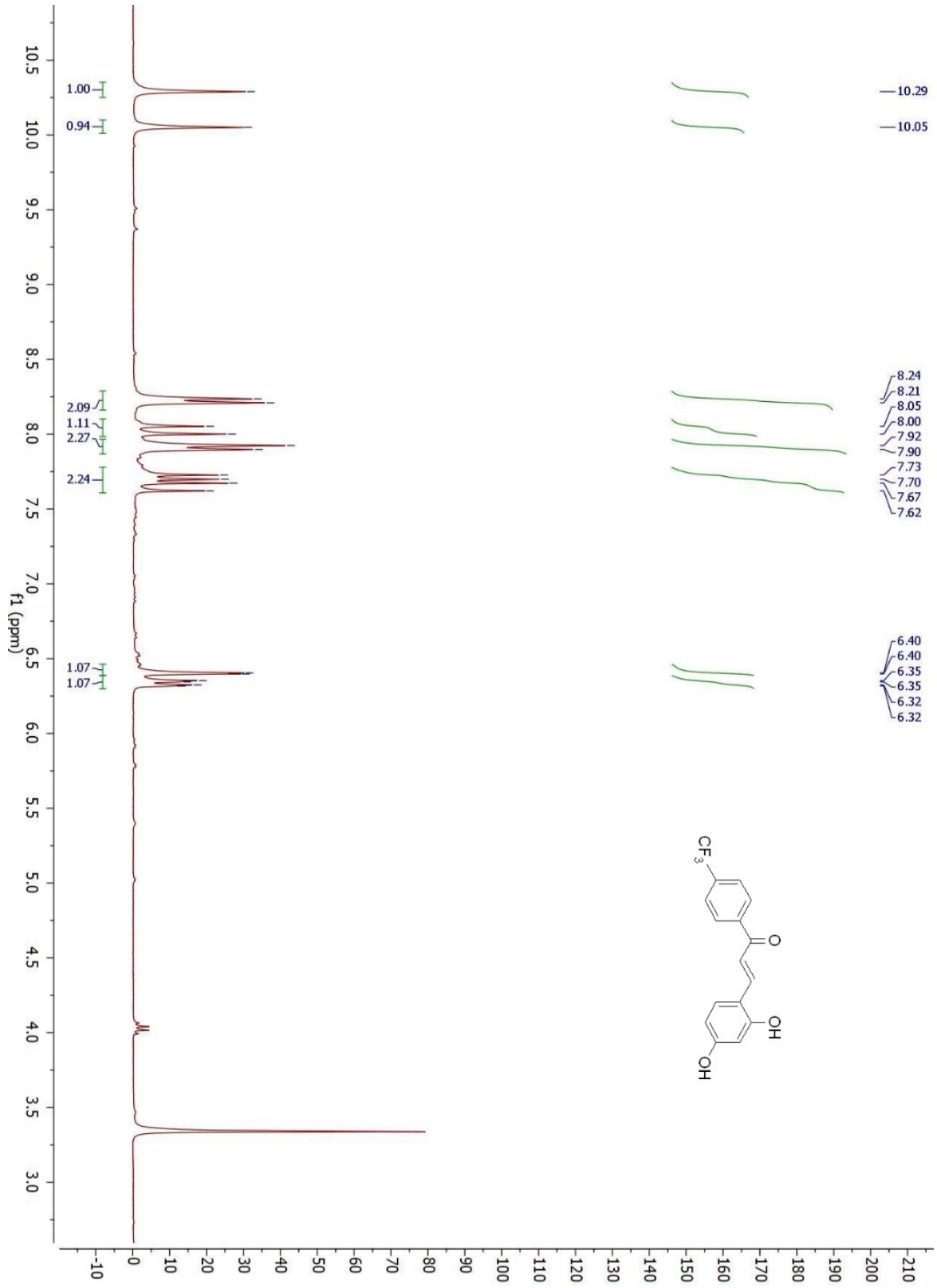

188.54
147.50
140.90
138.08
134.45
133.61
133.17
132.73
132.28
129.71
128.88
128.83
125.94
125.80
124.15
124.10
124.05
122.19
15.32
MeS
O
CF3
CF3
f1 (ppm)

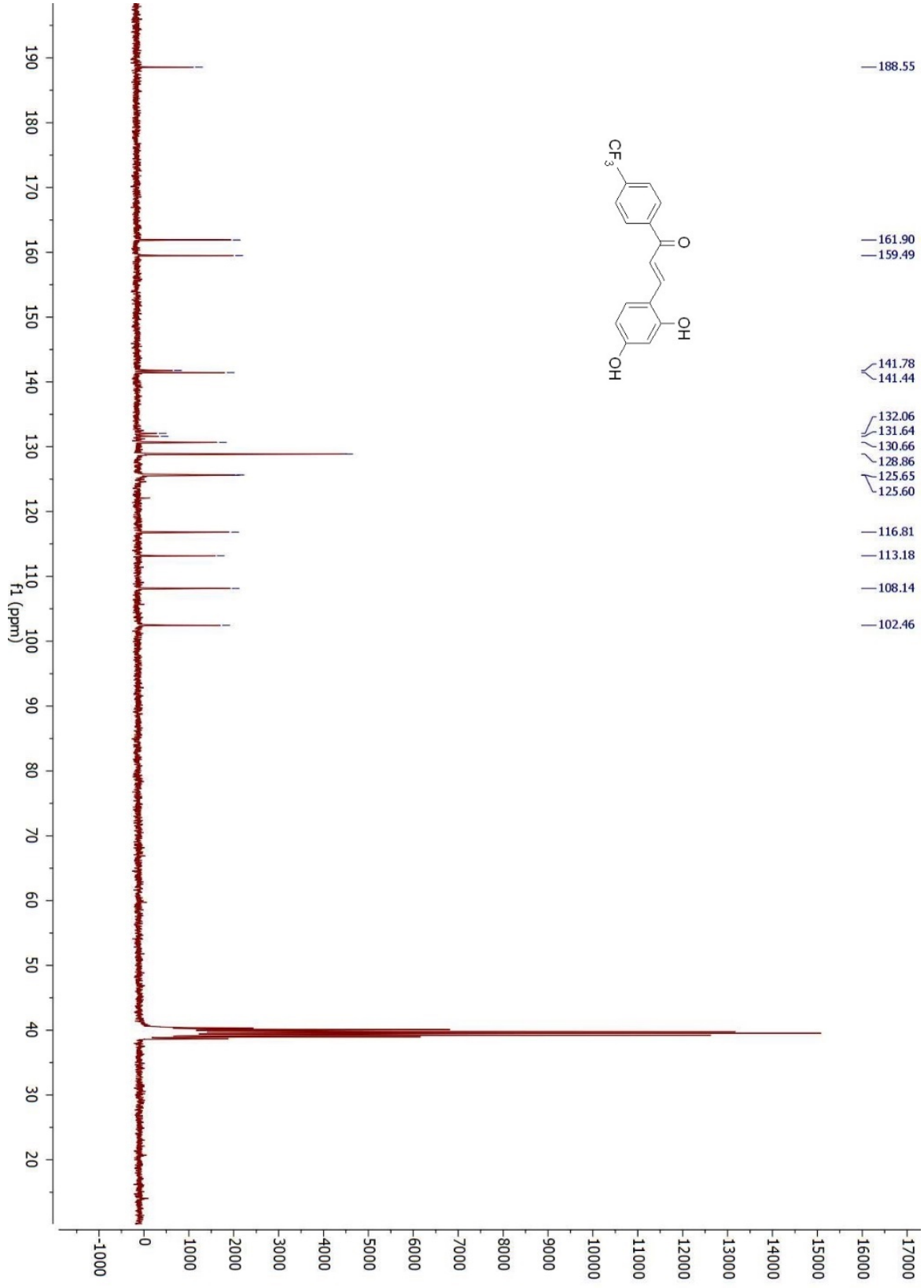
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 8, 300 MHz, CD_2Cl_2)



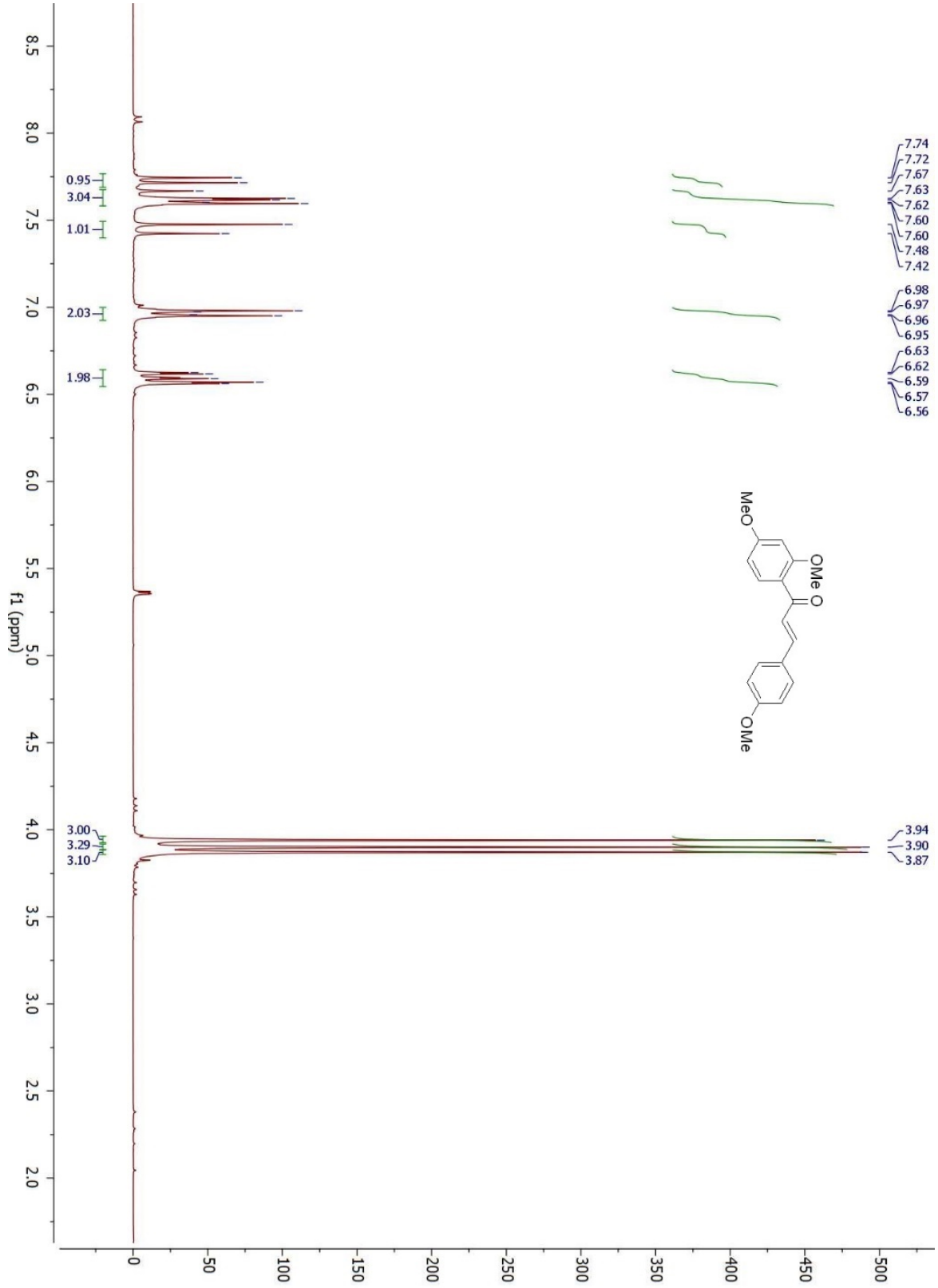

194.61
142.02
137.81
136.79
134.71
133.64
133.20
133.12
132.76
132.31
131.18
130.80
129.30
128.90
128.85
128.62
128.47
127.40
126.25
125.74
125.29
124.31
124.26
124.21
122.13
O
CF3
CF3
f1 (ppm)

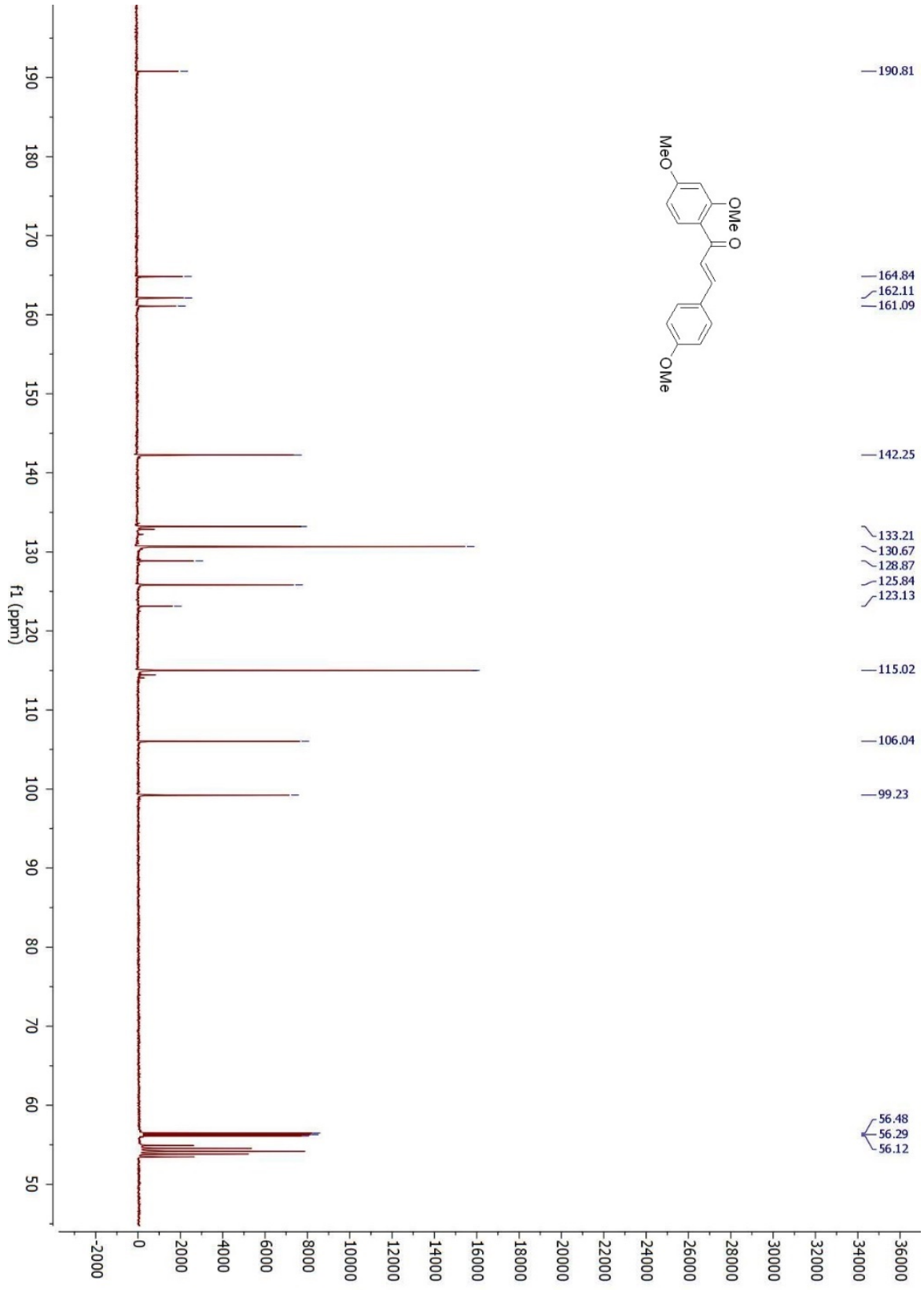
^{1}H-^{13}C{^{1}H} NMR Spectra (Compound 9, 300 MHz, DMSO-*d6*)



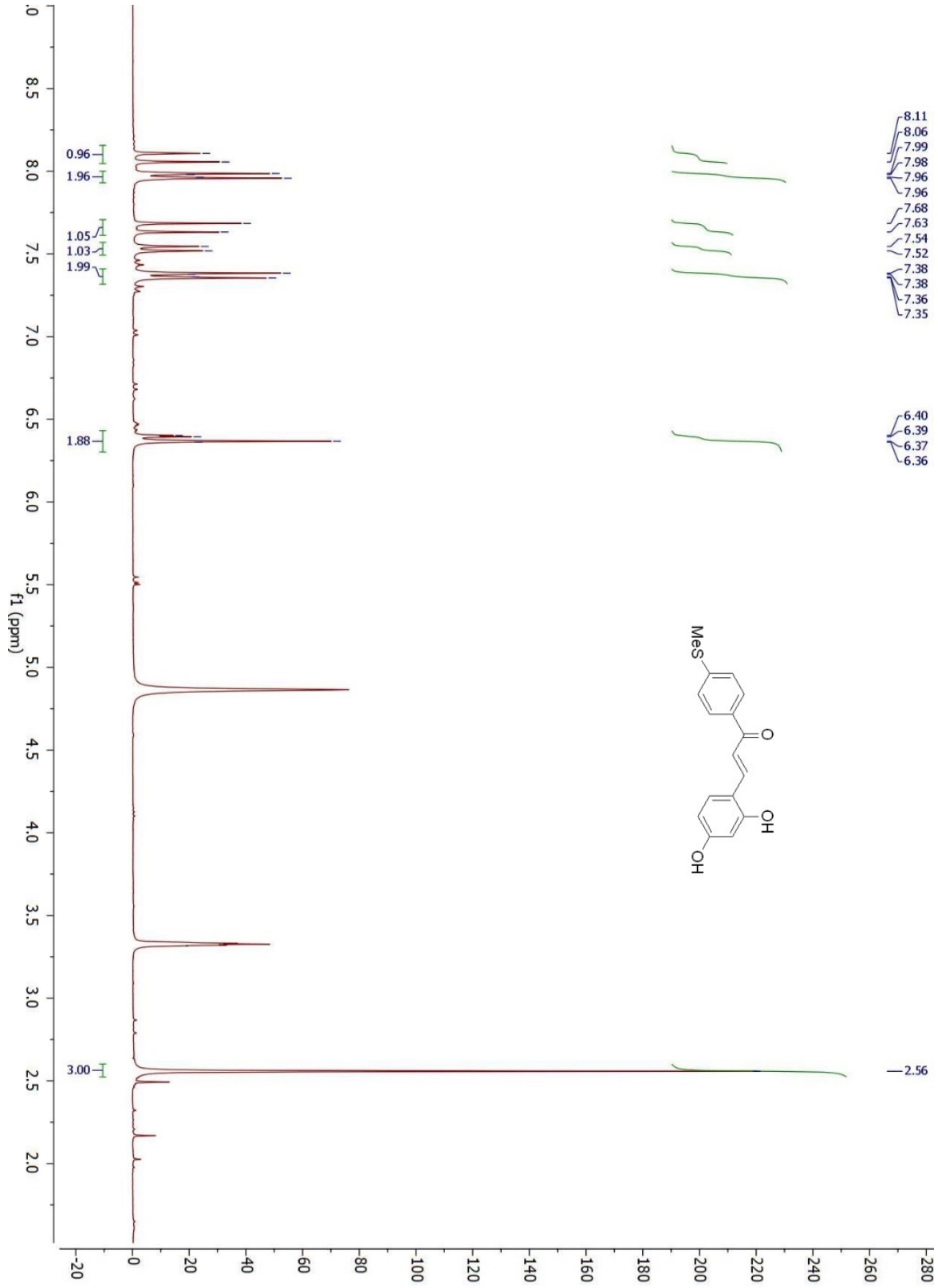

188.55
161.90
159.49
141.78
141.44
132.06
131.64
130.66
128.86
125.65
125.60
116.81
113.18
108.14
102.46
CF3
O
OH
OH
f1 (ppm)

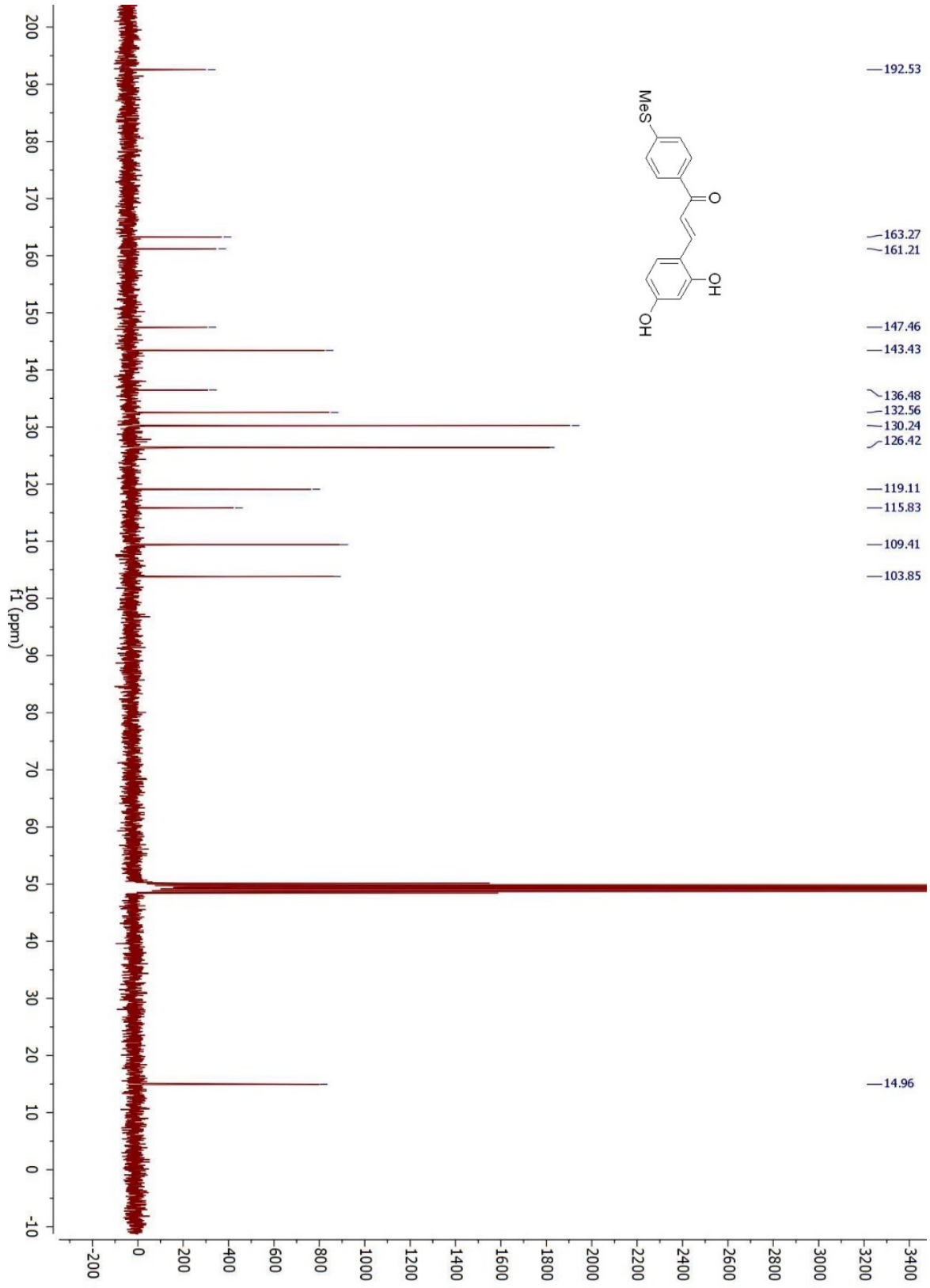
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 10, 300 MHz, CD_2Cl_2)



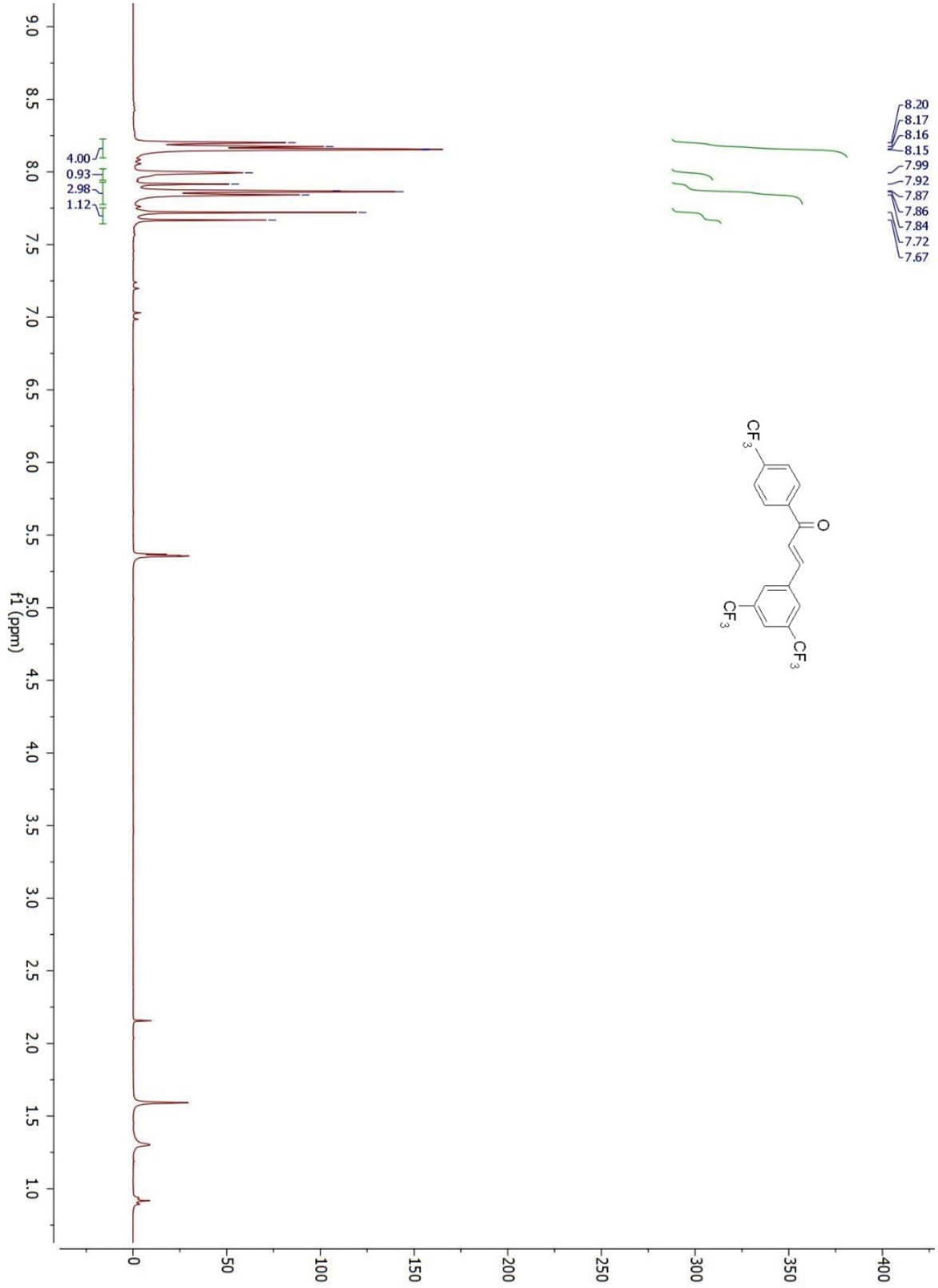

MeO
OMe O
OMe
190.81
164.84
162.11
161.09
142.25
133.21
130.67
128.87
125.84
123.13
115.02
106.04
99.23
56.48
56.29
56.12
f1 (ppm)

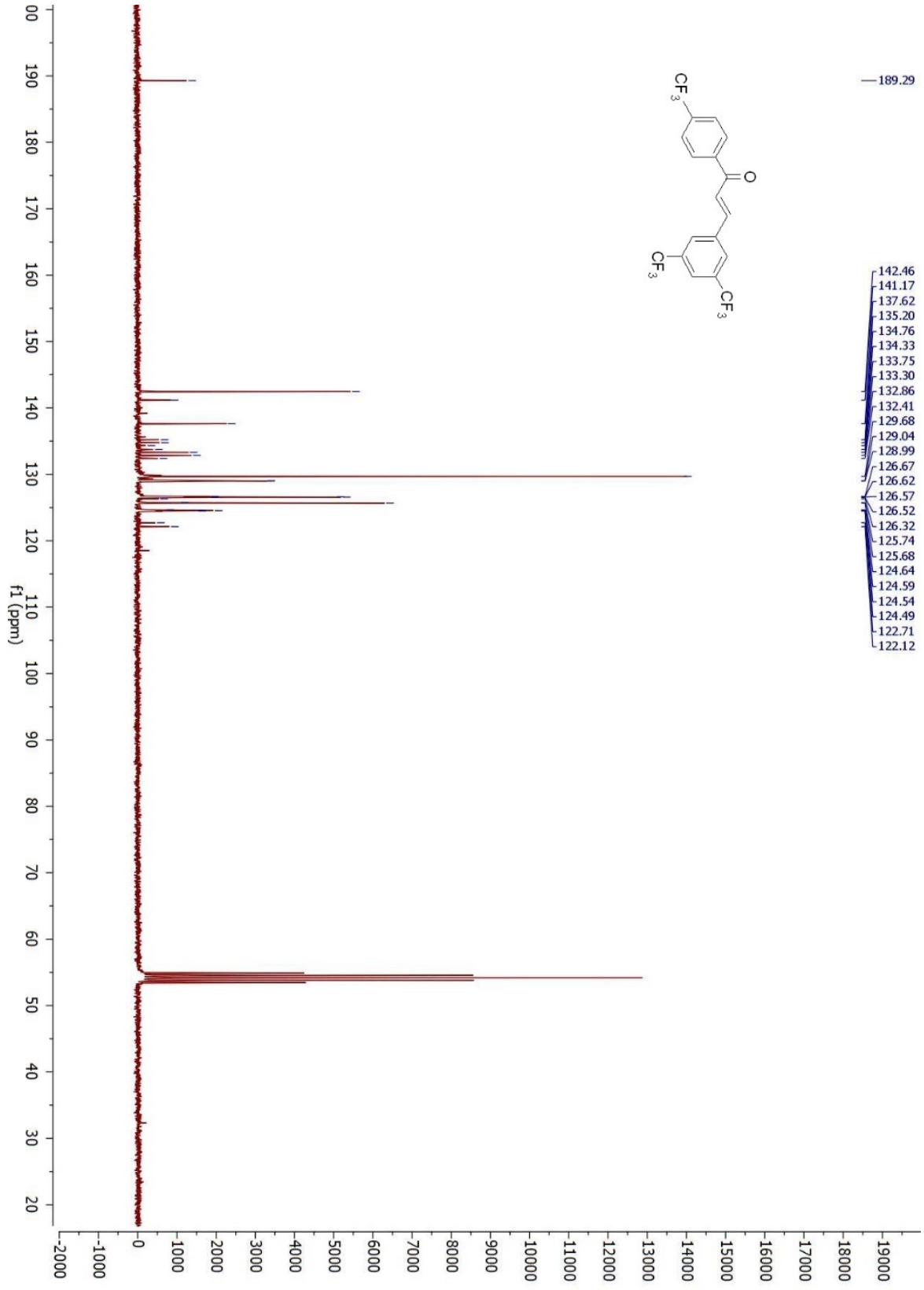
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 11, 300 MHz, CD_3OD)



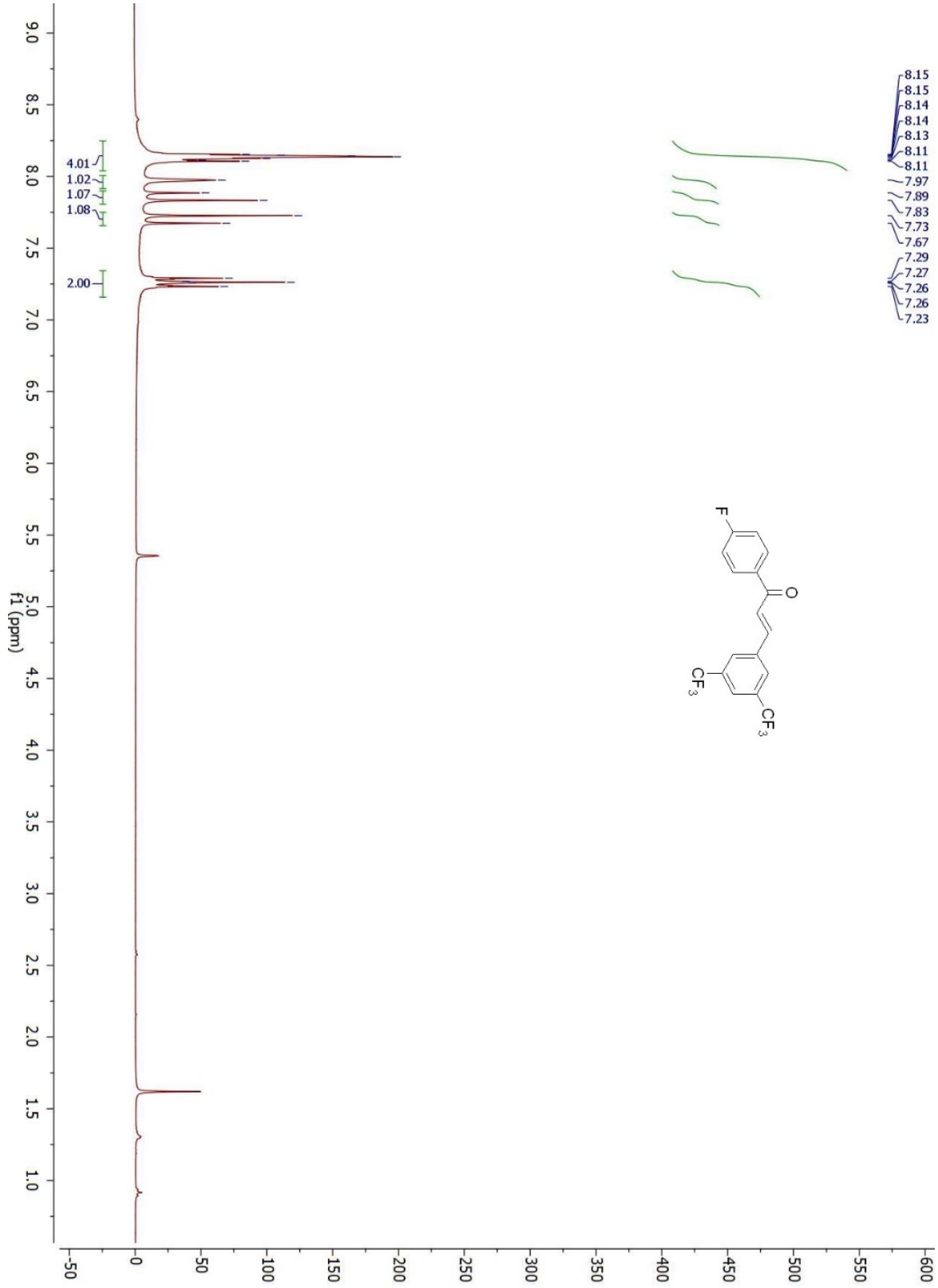

MeS
O
OH
HO
192.53
163.27
161.21
147.46
143.43
136.48
132.56
130.24
126.42
119.11
115.83
109.41
103.85
14.96
f1 (ppm)

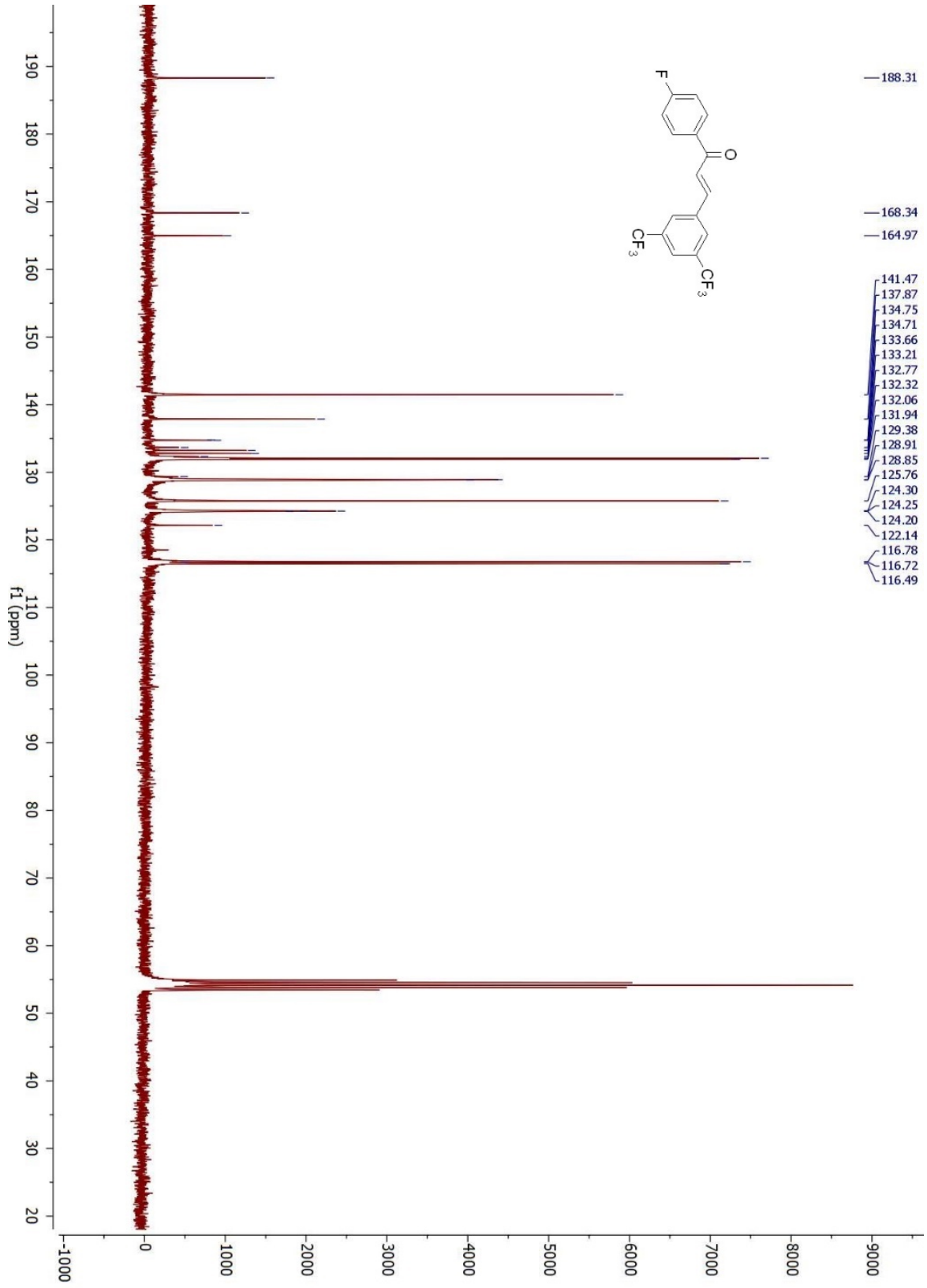
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 12, 300 MHz, CD_2Cl_2)



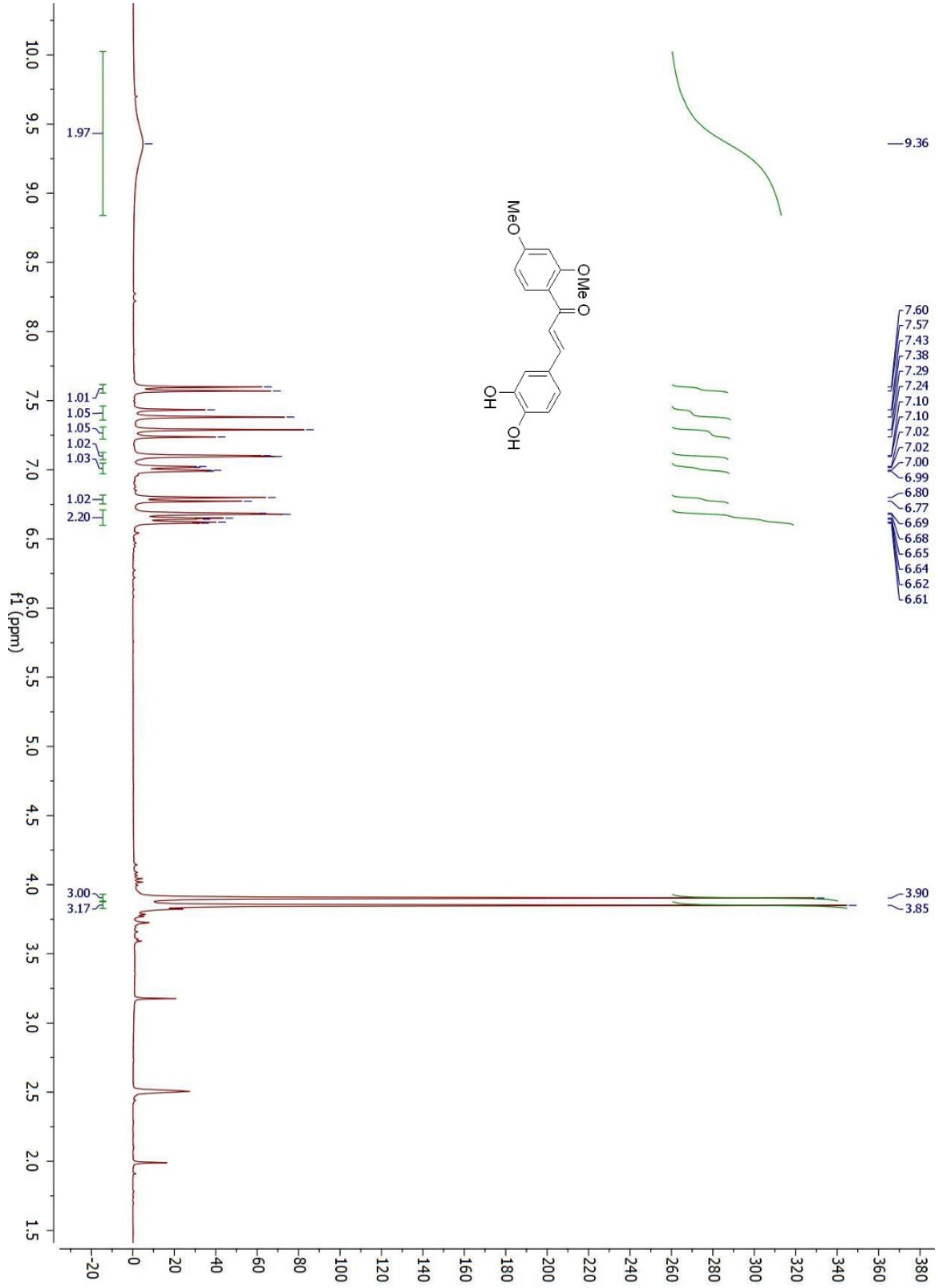

189.29
142.46
141.17
137.62
135.20
134.76
134.33
133.75
133.30
132.86
132.41
129.68
129.04
128.99
126.67
126.62
126.57
126.52
126.32
125.74
125.68
124.64
124.59
124.54
124.49
122.71
122.12
f1 (ppm)

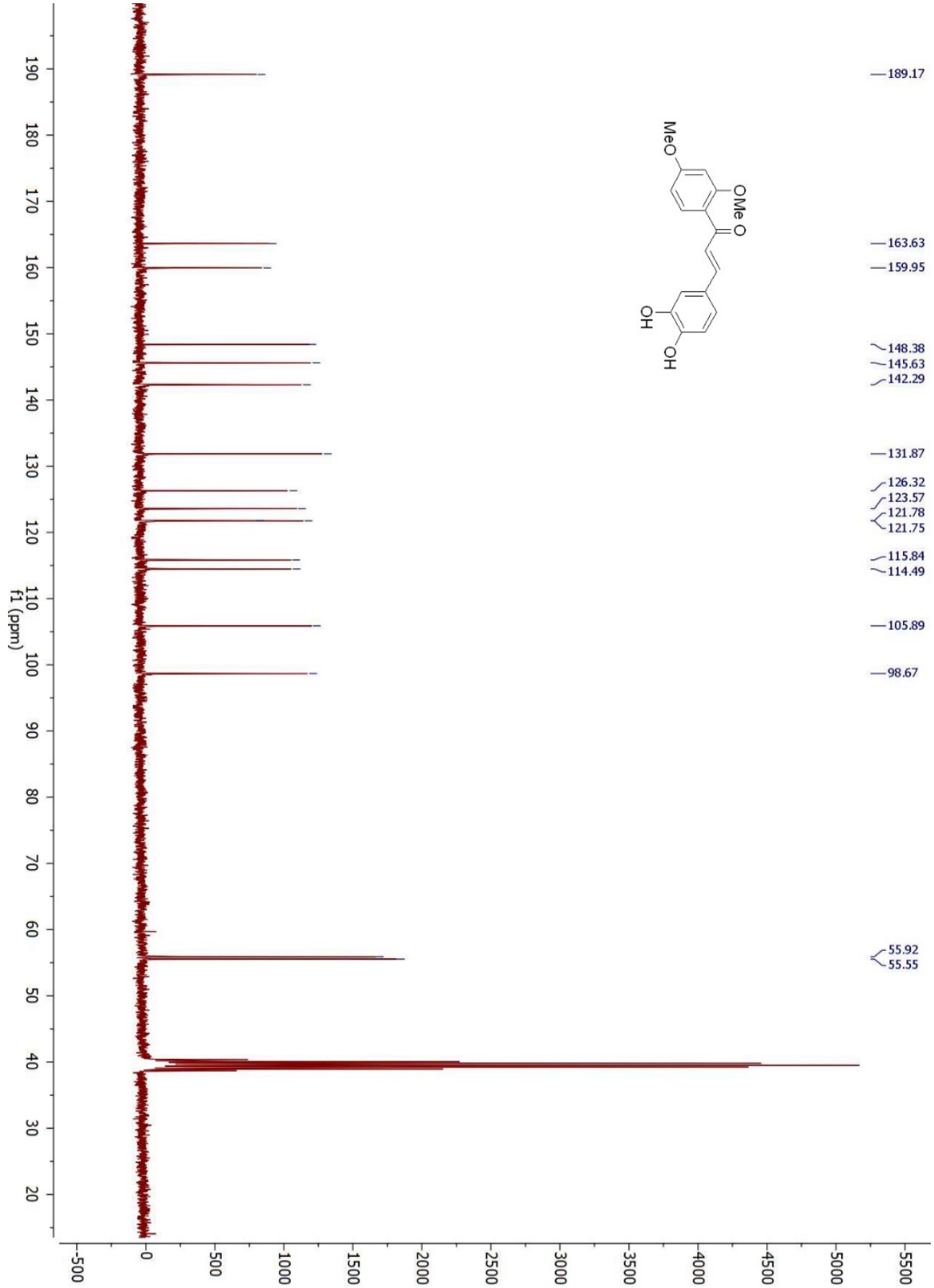
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 13, 300 MHz, CD_2Cl_2)



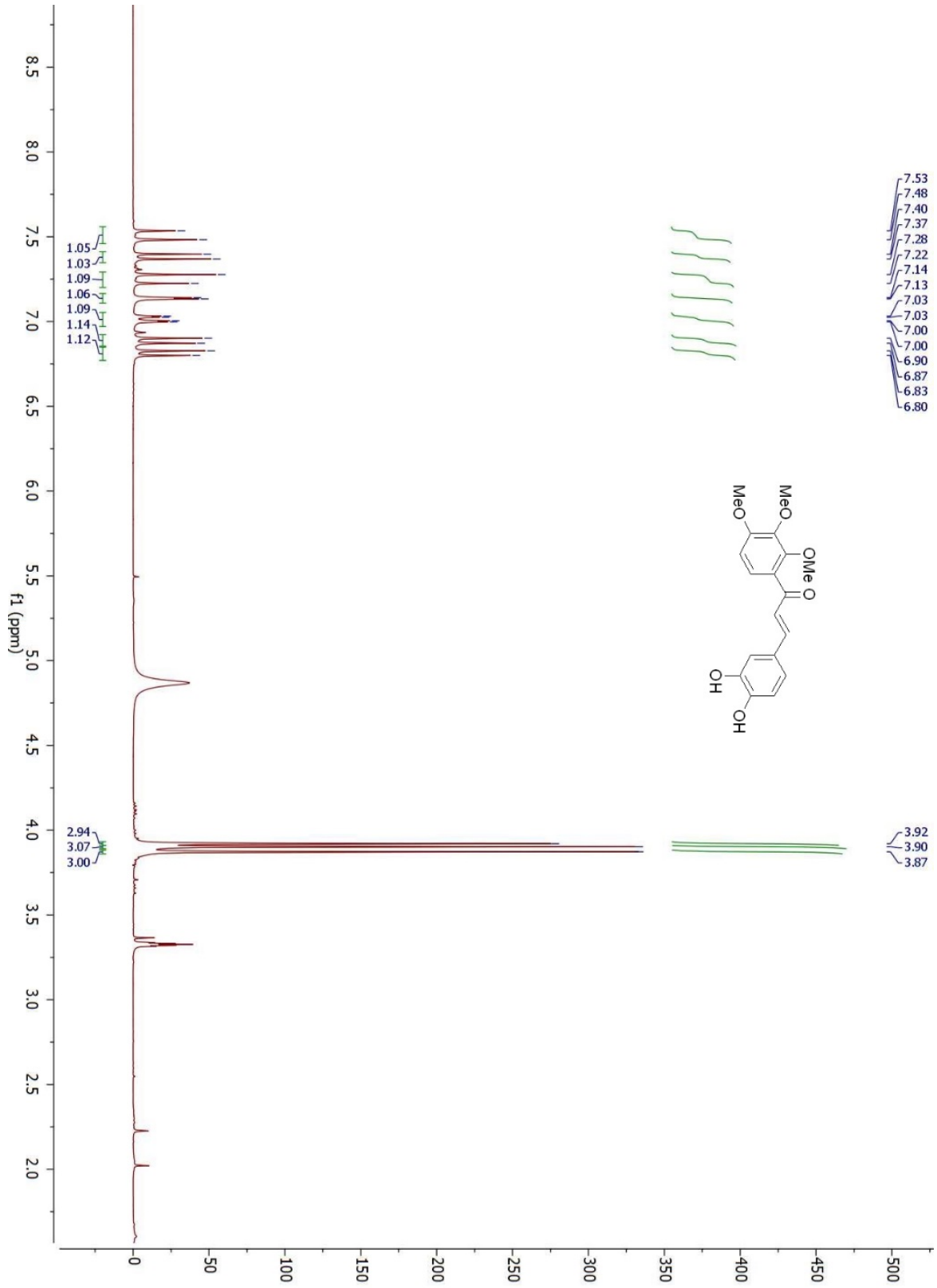

188.31
168.34
164.97
141.47
137.87
134.75
134.71
133.66
133.21
132.77
132.32
132.06
131.94
129.38
128.91
128.85
125.76
124.30
124.25
124.20
122.14
116.78
116.72
116.49
F
O
CF3
CF3
f1 (ppm)

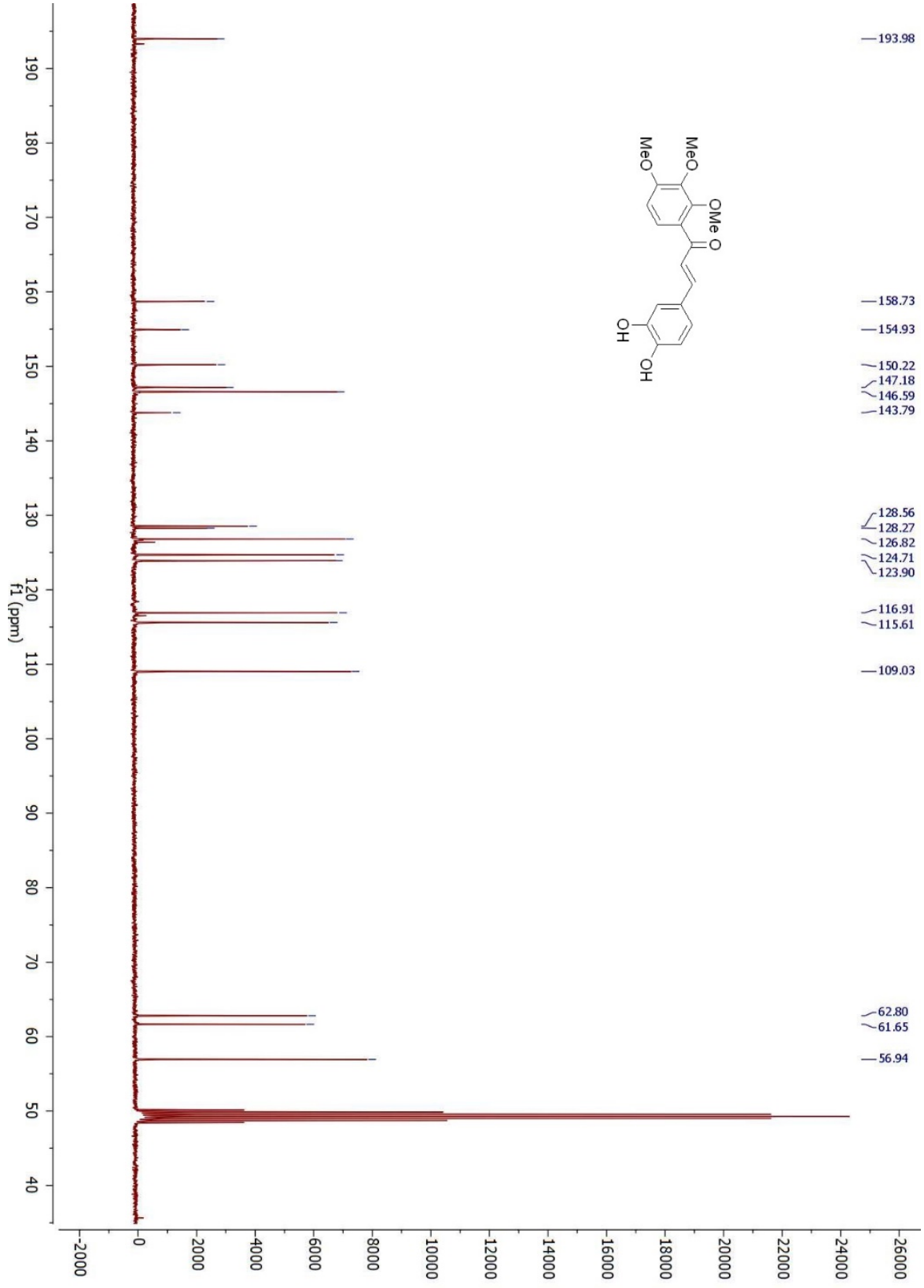
^{1}H-^{13}C{^{1}H} NMR Spectra (Compound 14, 300 MHz, DMSO-*d6*)



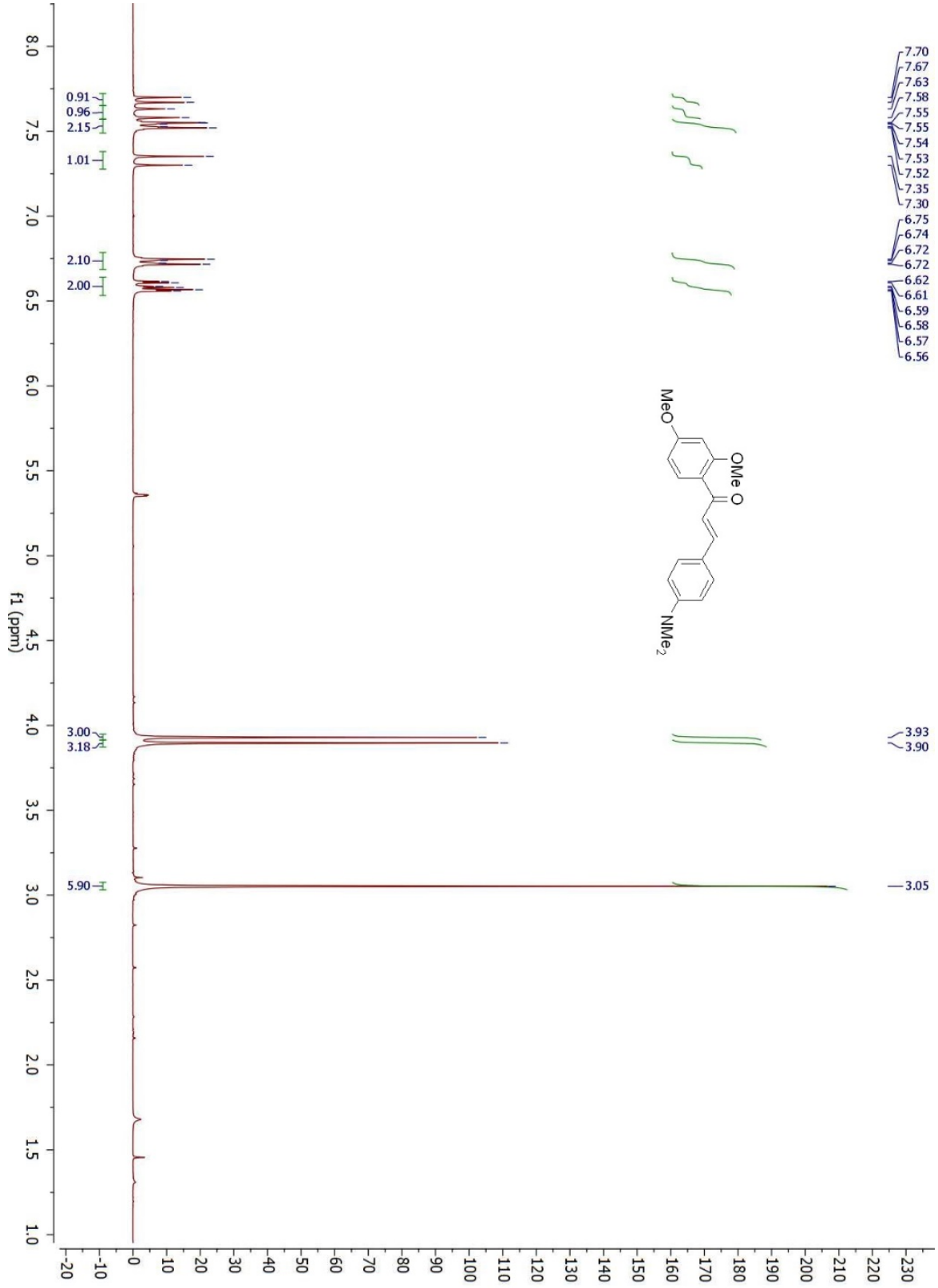

189.17
163.63
159.95
148.38
145.63
142.29
131.87
126.32
123.57
121.78
121.75
115.84
114.49
105.89
98.67
55.92
55.55
MeO
OMe O
OH
OH
f1 (ppm)

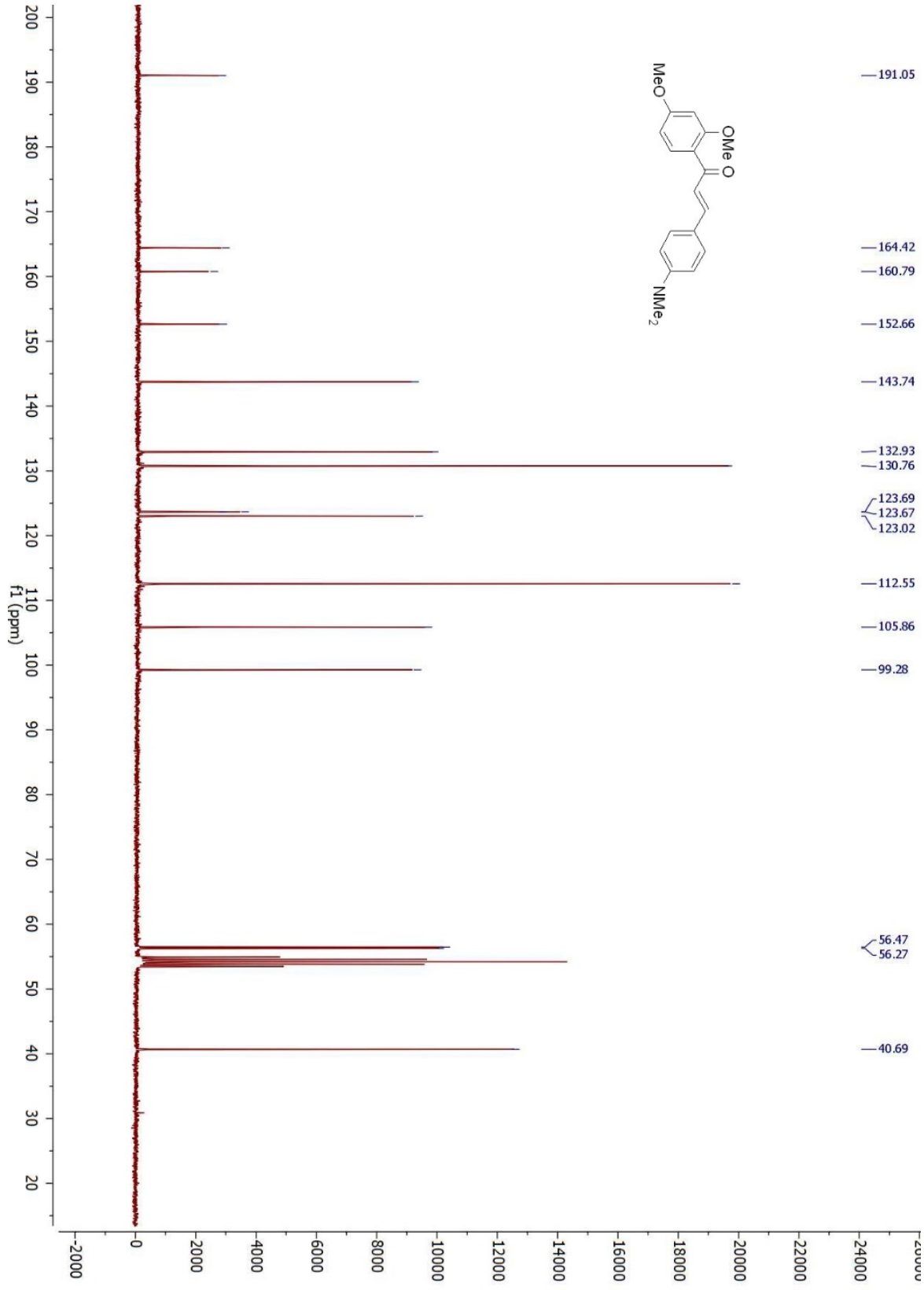
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 15, 300 MHz, CD_3OD)



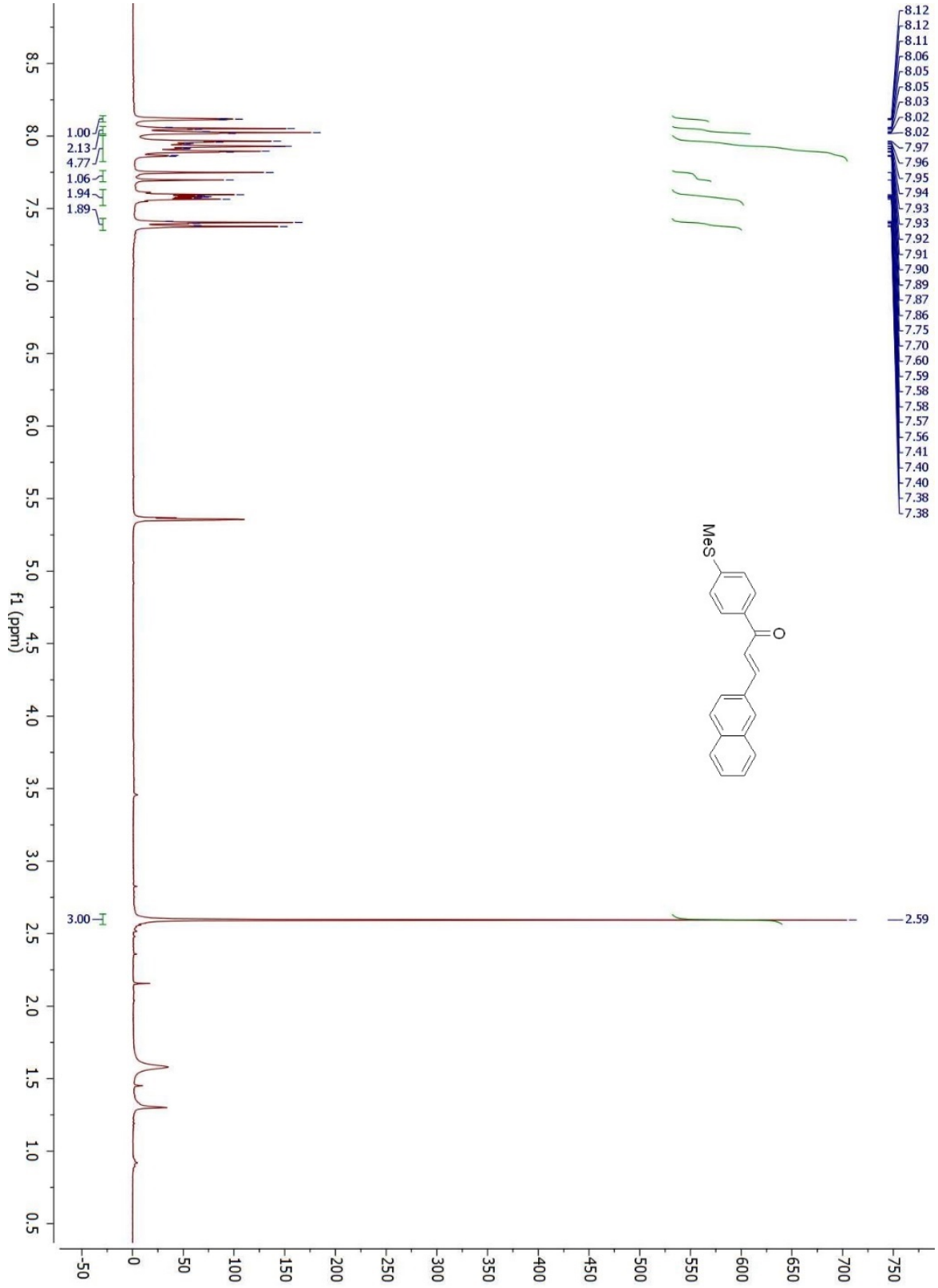

193.98
158.73
154.93
150.22
147.18
146.59
143.79
128.56
128.27
126.82
124.71
123.90
116.91
115.61
109.03
62.80
61.65
56.94
MeO
MeO
OMe
O
OH
OH
f1 (ppm)

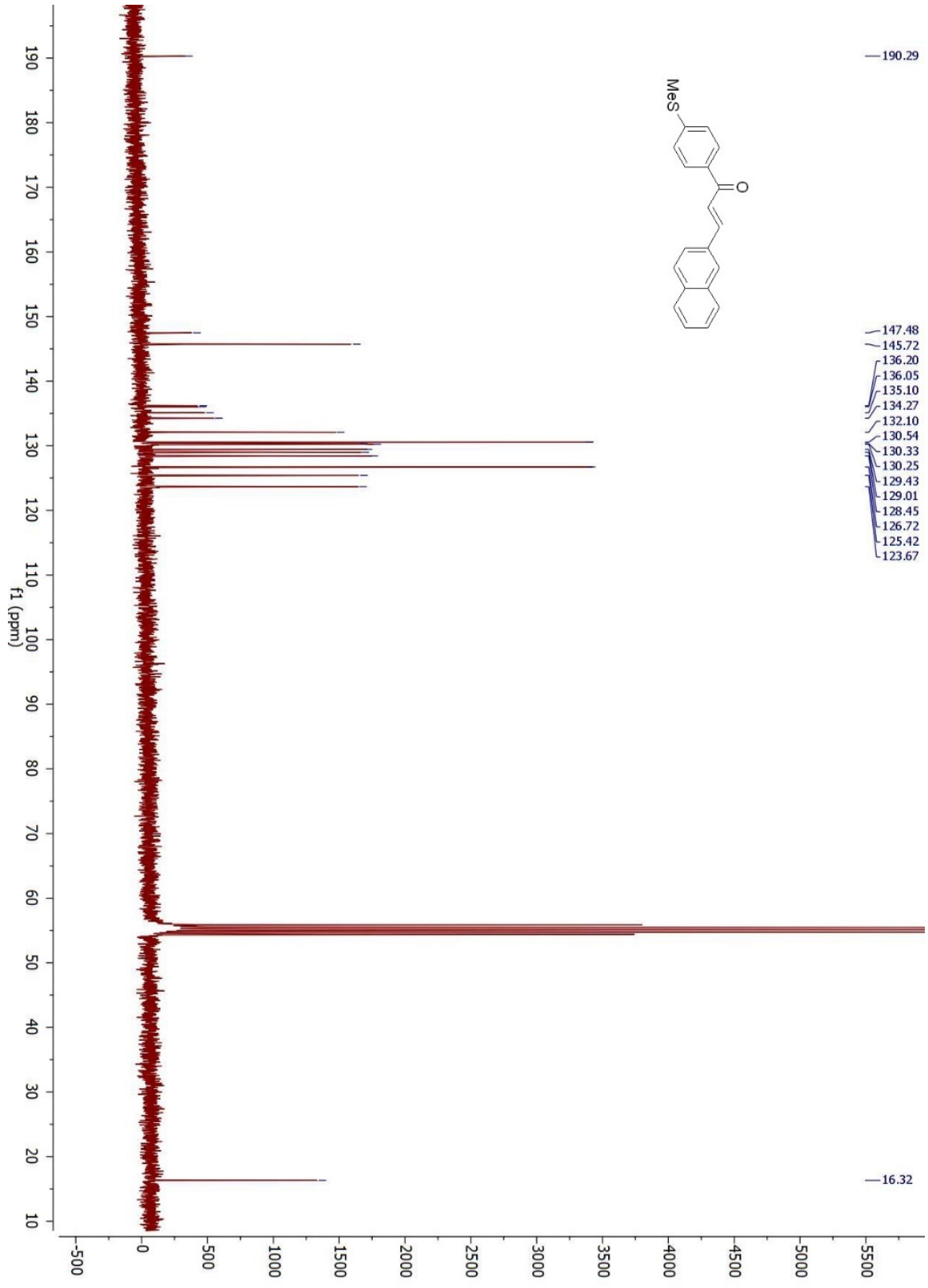
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 16, 300 MHz, CD_2Cl_2)



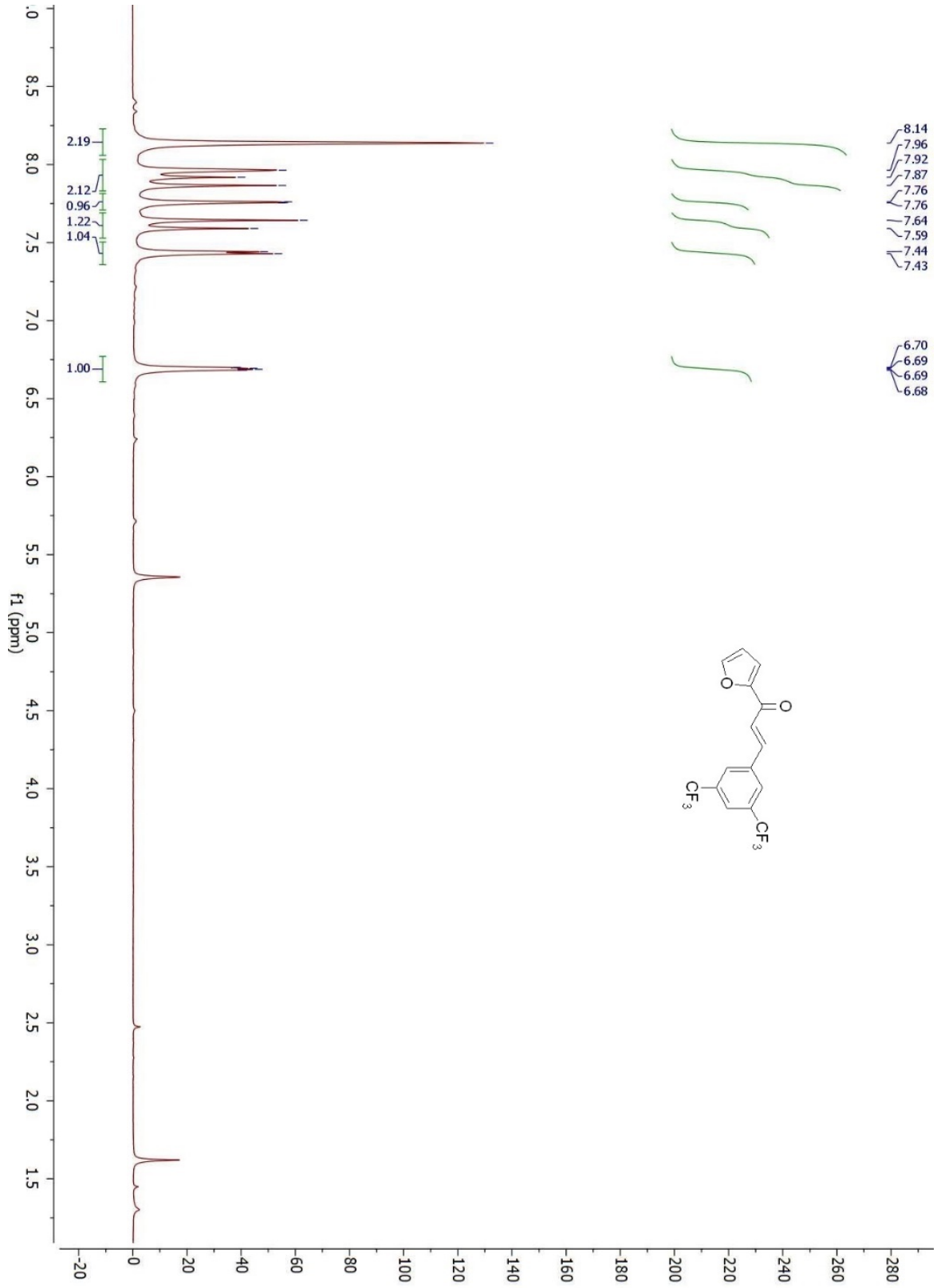

MeO
OMe O
NMe2
191.05
164.42
160.79
152.66
143.74
132.93
130.76
123.69
123.67
123.02
112.55
105.86
99.28
56.47
56.27
40.69
f1 (ppm)

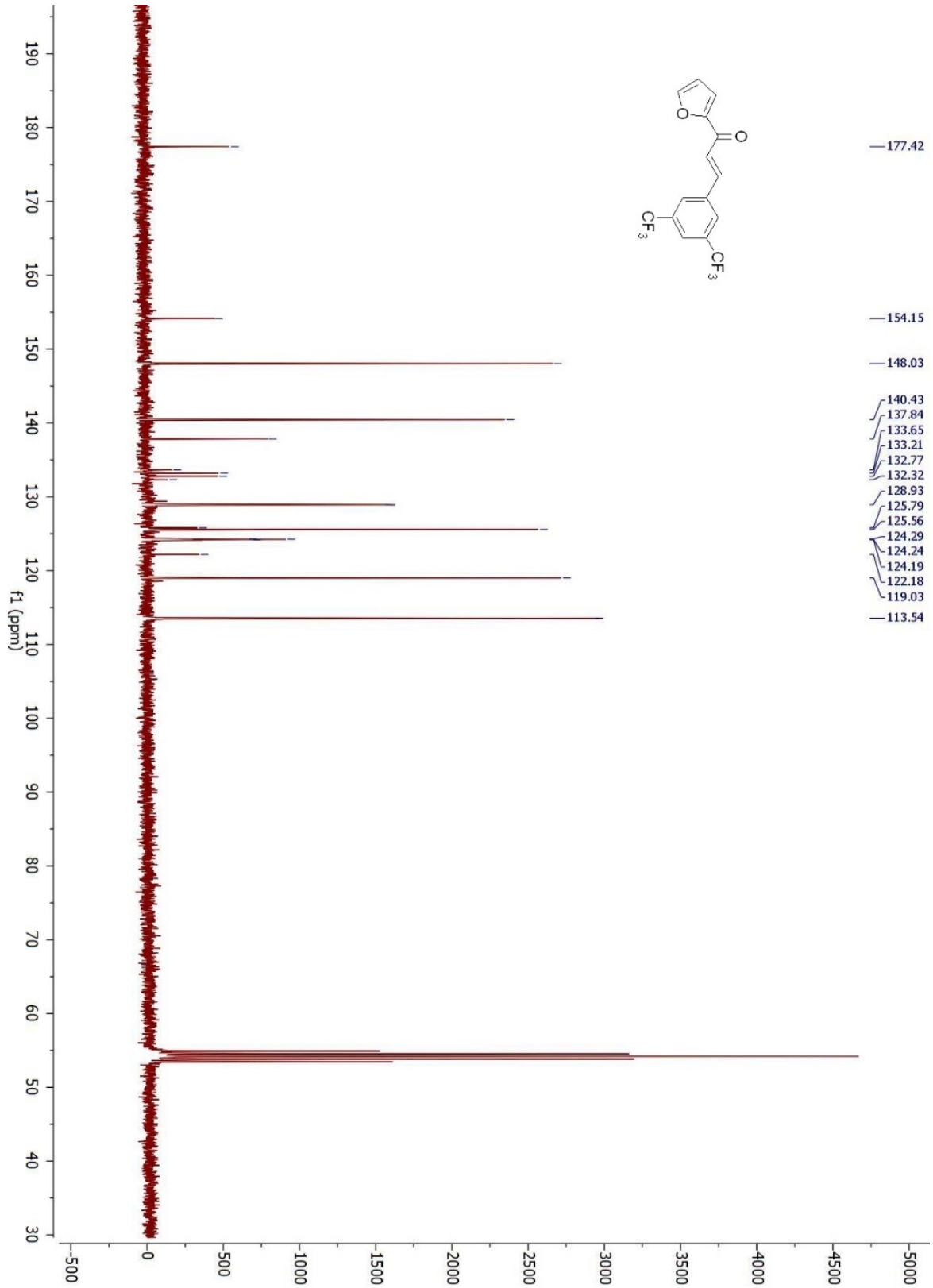
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 17, 300 MHz, CD_2Cl_2)



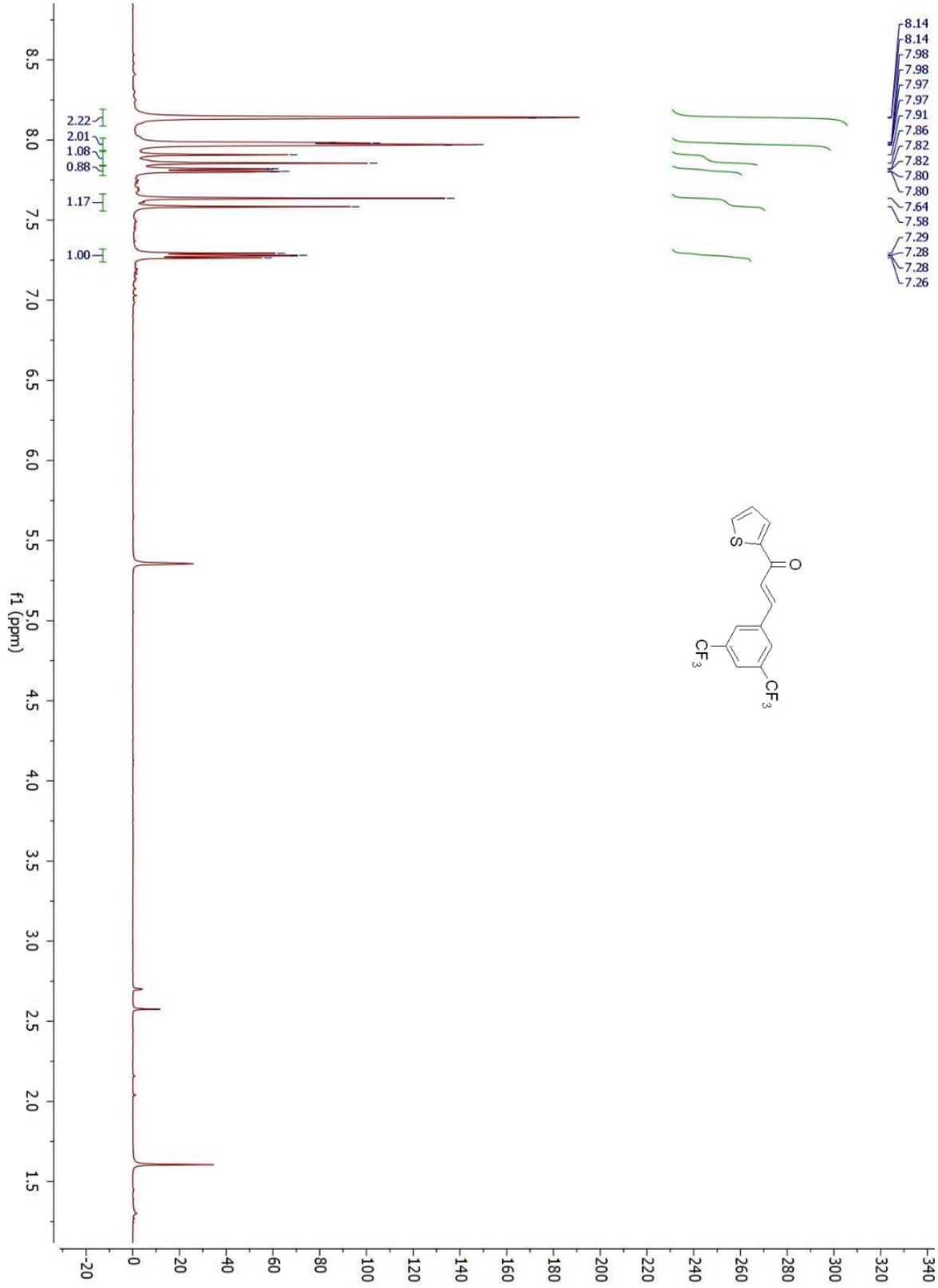

MeS
O
190.29
147.48
145.72
136.20
136.05
135.10
134.27
132.10
130.54
130.33
130.25
129.43
129.01
128.45
126.72
125.42
123.67
16.32
f1 (ppm)

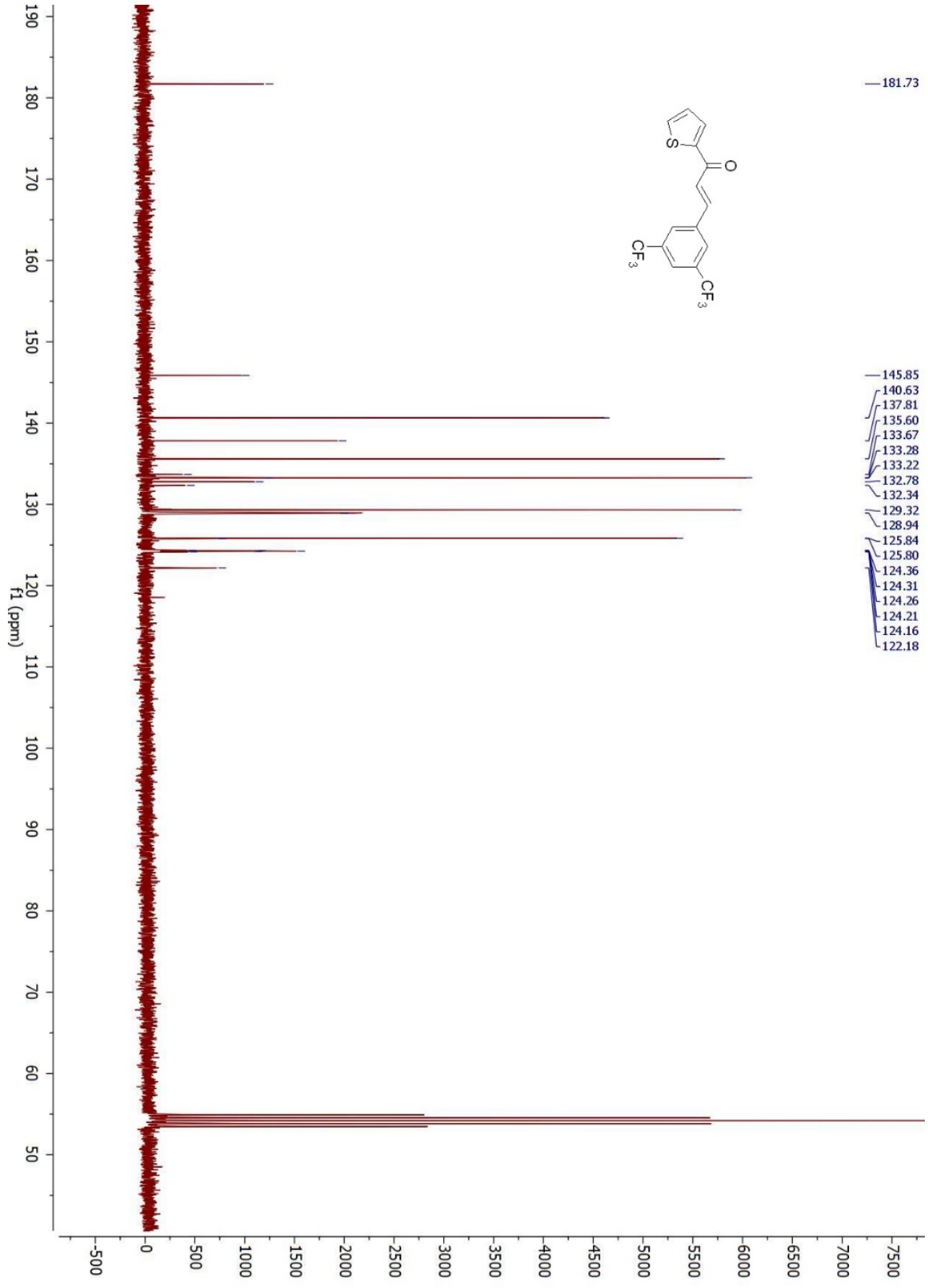
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 18, 300 MHz, CD_2Cl_2)



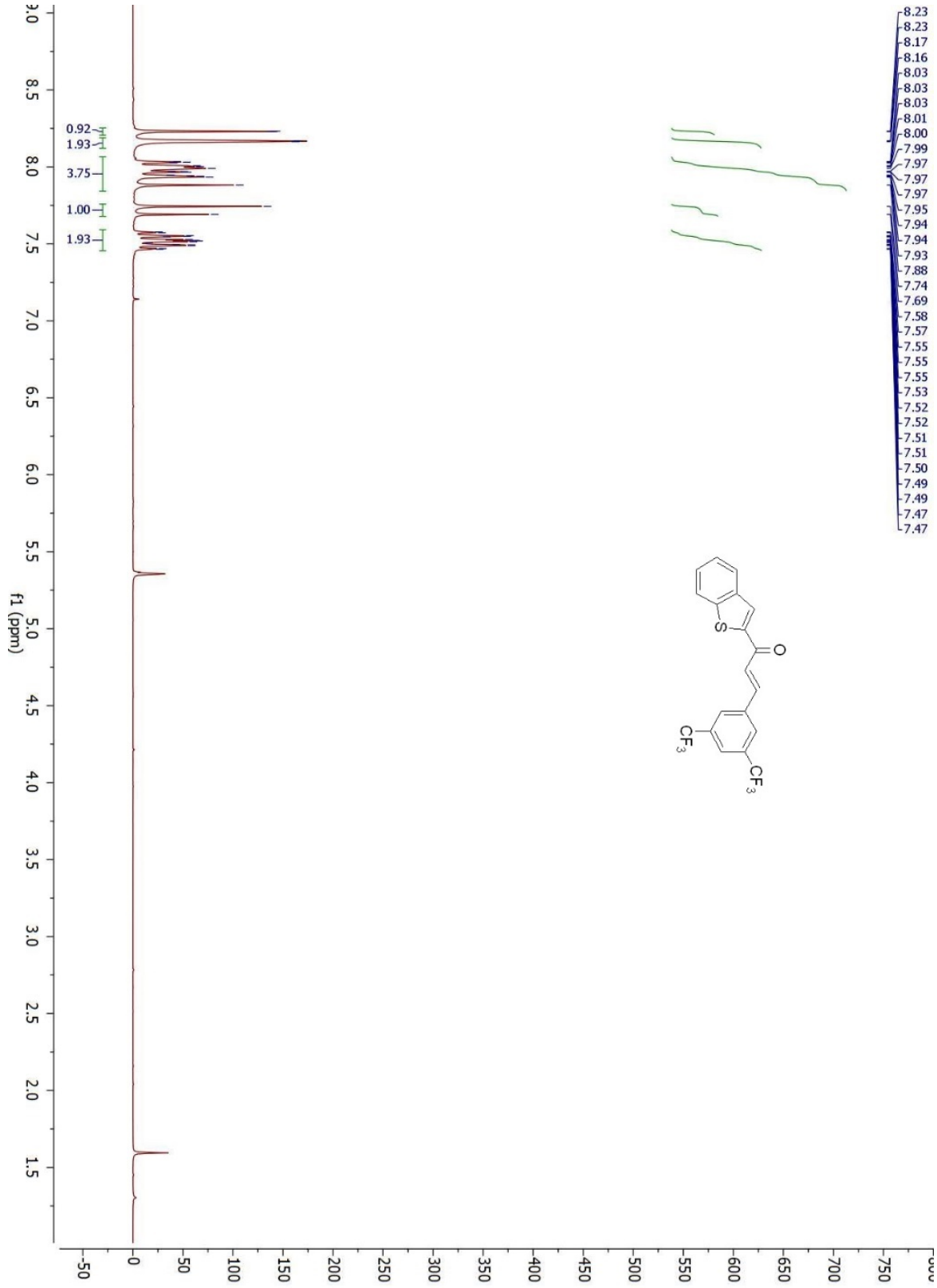

177.42
154.15
148.03
140.43
137.84
133.65
133.21
132.77
132.32
128.93
125.79
125.56
124.29
124.24
124.19
122.18
119.03
113.54
f1 (ppm)

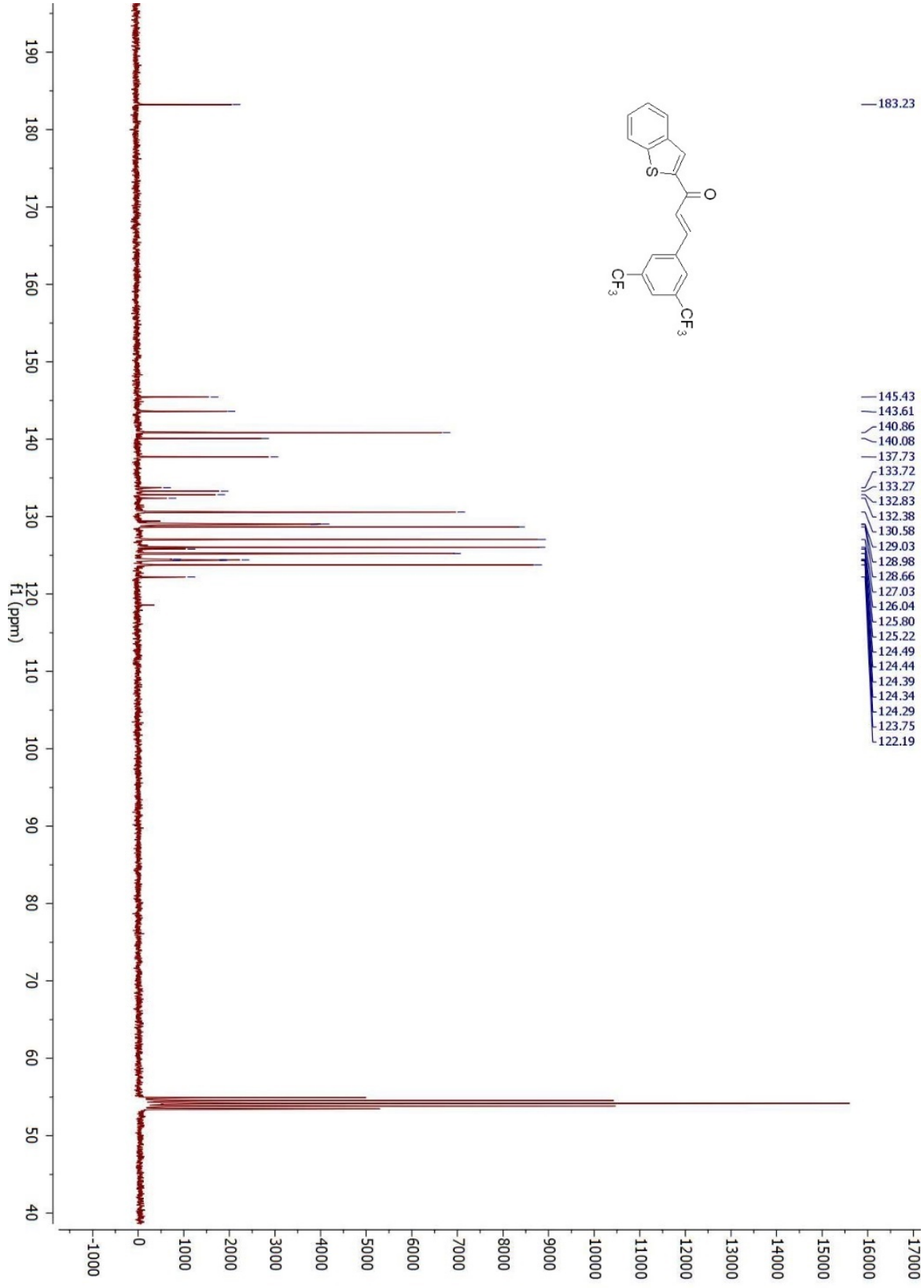
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 19, 300 MHz, CD_2Cl_2)



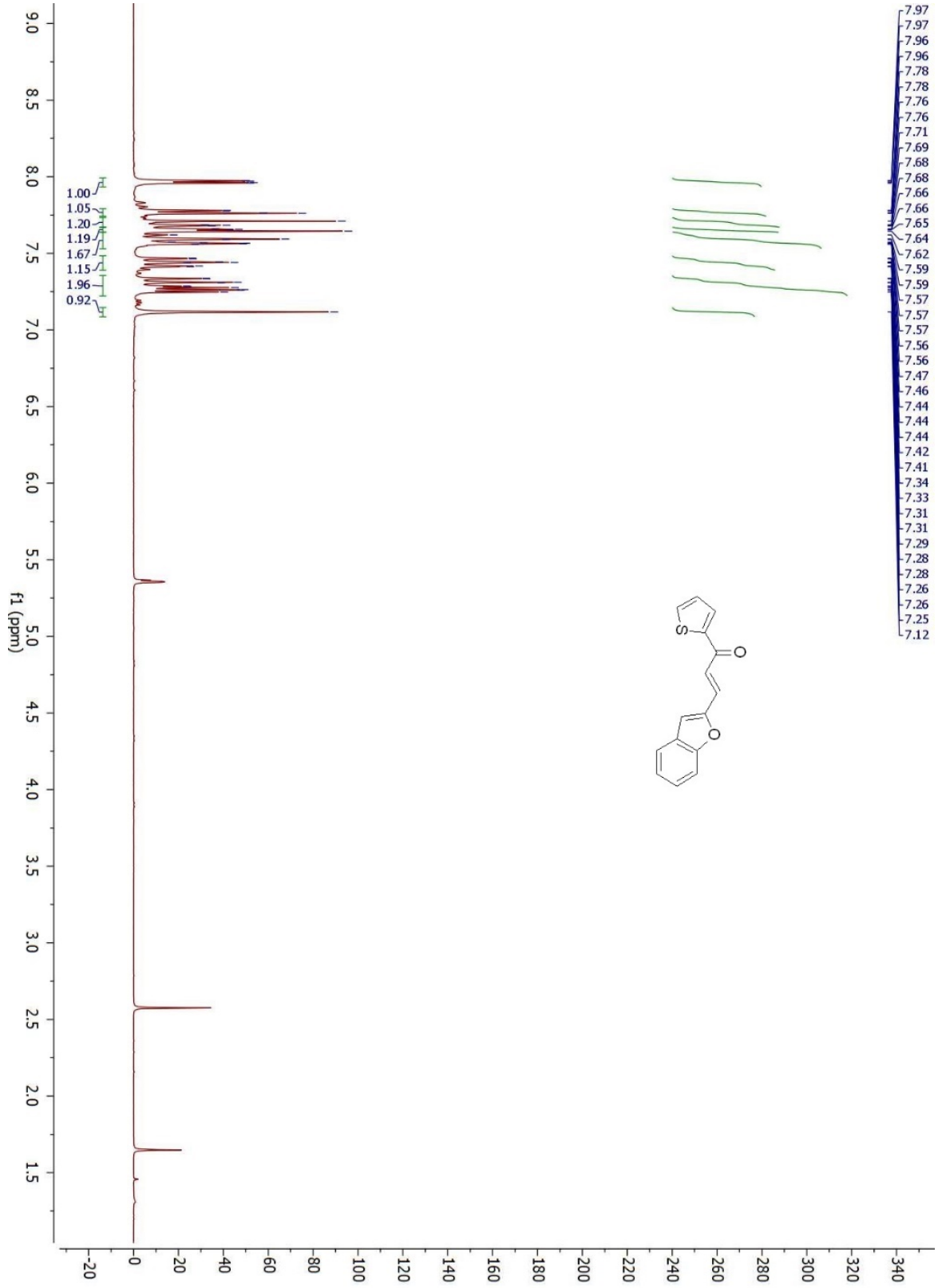

181.73
145.85
140.63
137.81
135.60
133.67
133.28
133.22
132.78
132.34
129.32
128.94
125.84
125.80
124.36
124.31
124.26
124.21
124.16
122.18
S
O
CF3
CF3
f1 (ppm)

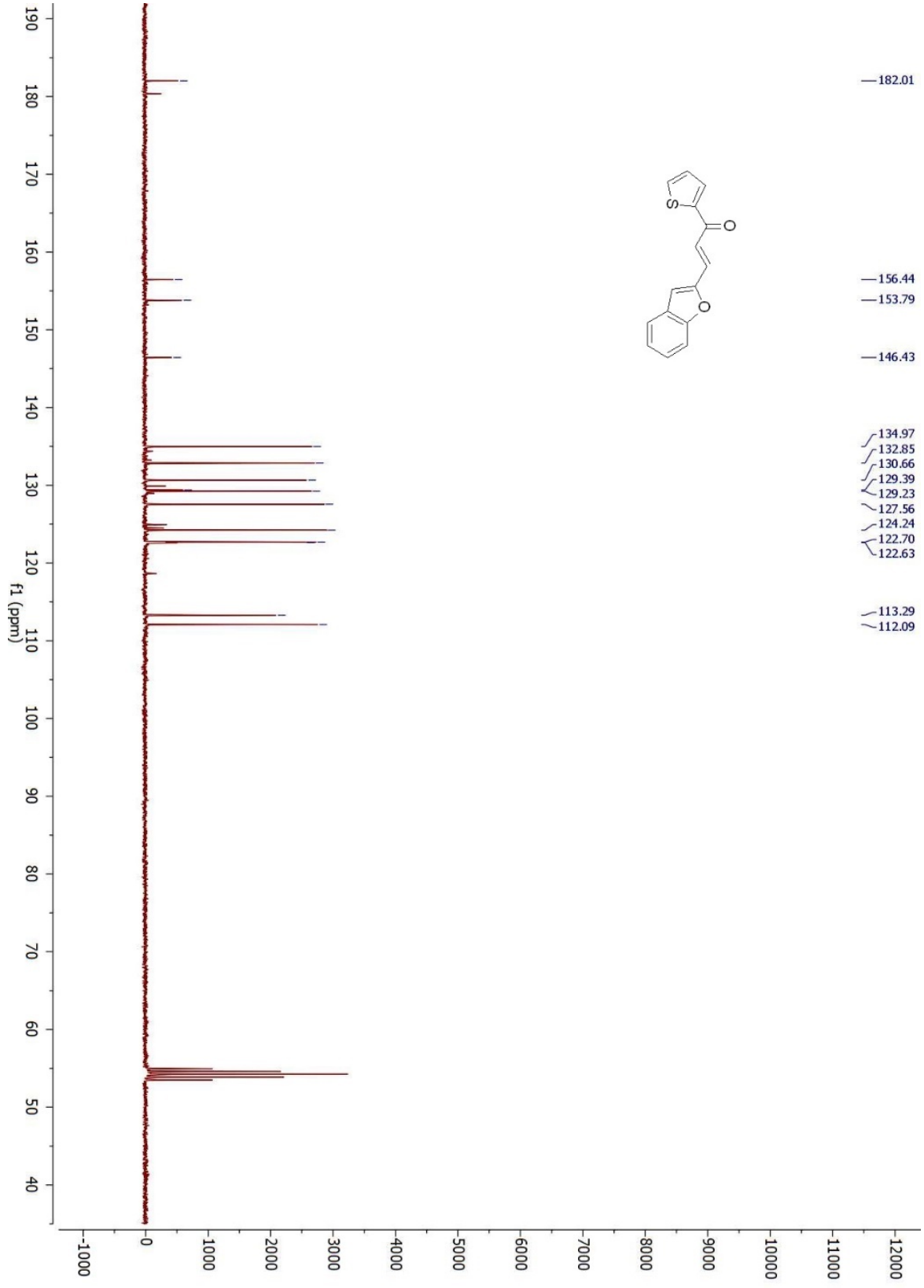
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 20, 300 MHz, CD_2Cl_2)



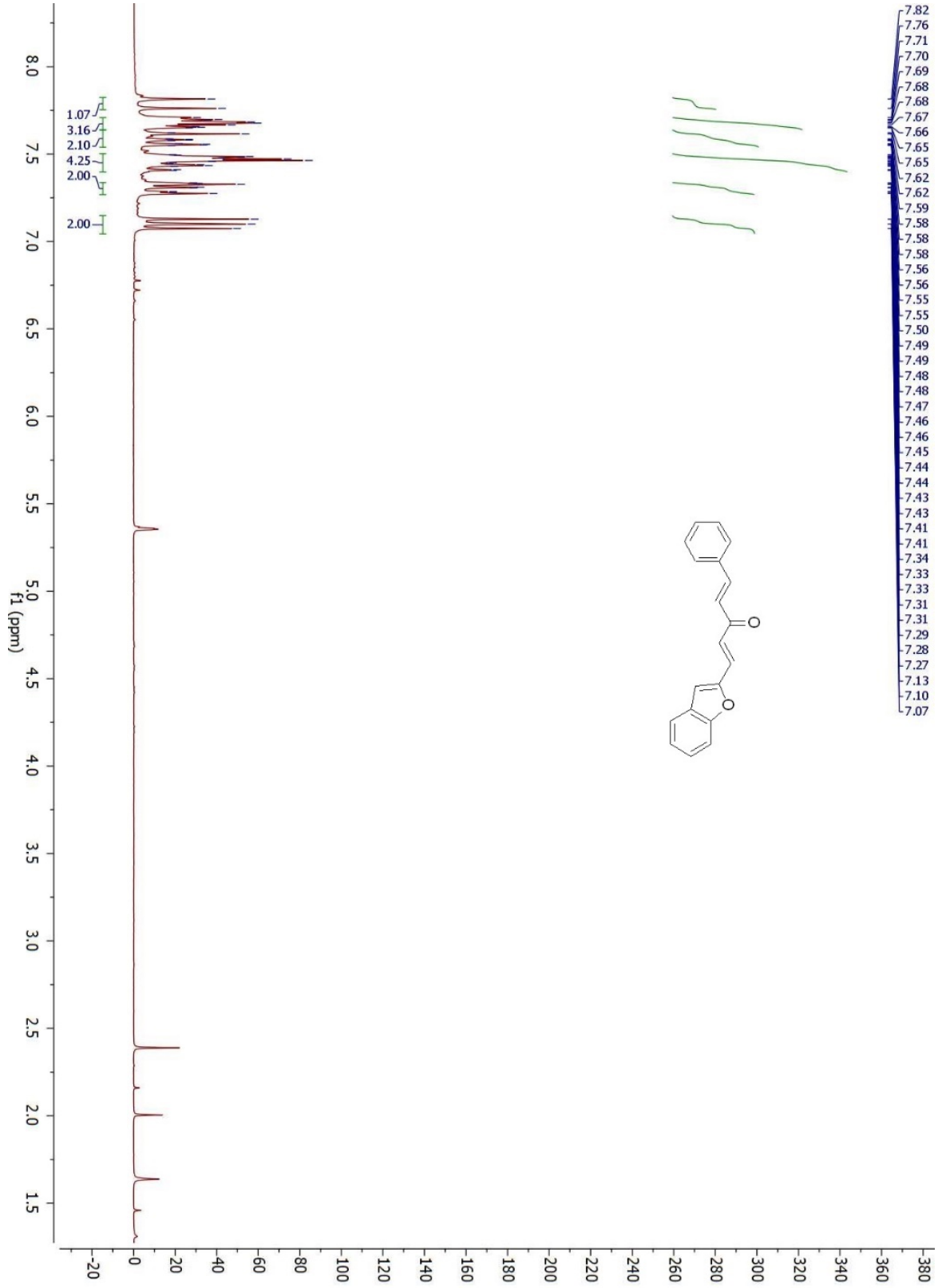

183.23
145.43
143.61
140.86
140.08
137.73
133.72
133.27
132.83
132.38
130.58
129.03
128.98
128.66
127.03
126.04
125.80
125.22
124.49
124.44
124.39
124.34
124.29
123.75
122.19
f1 (ppm)

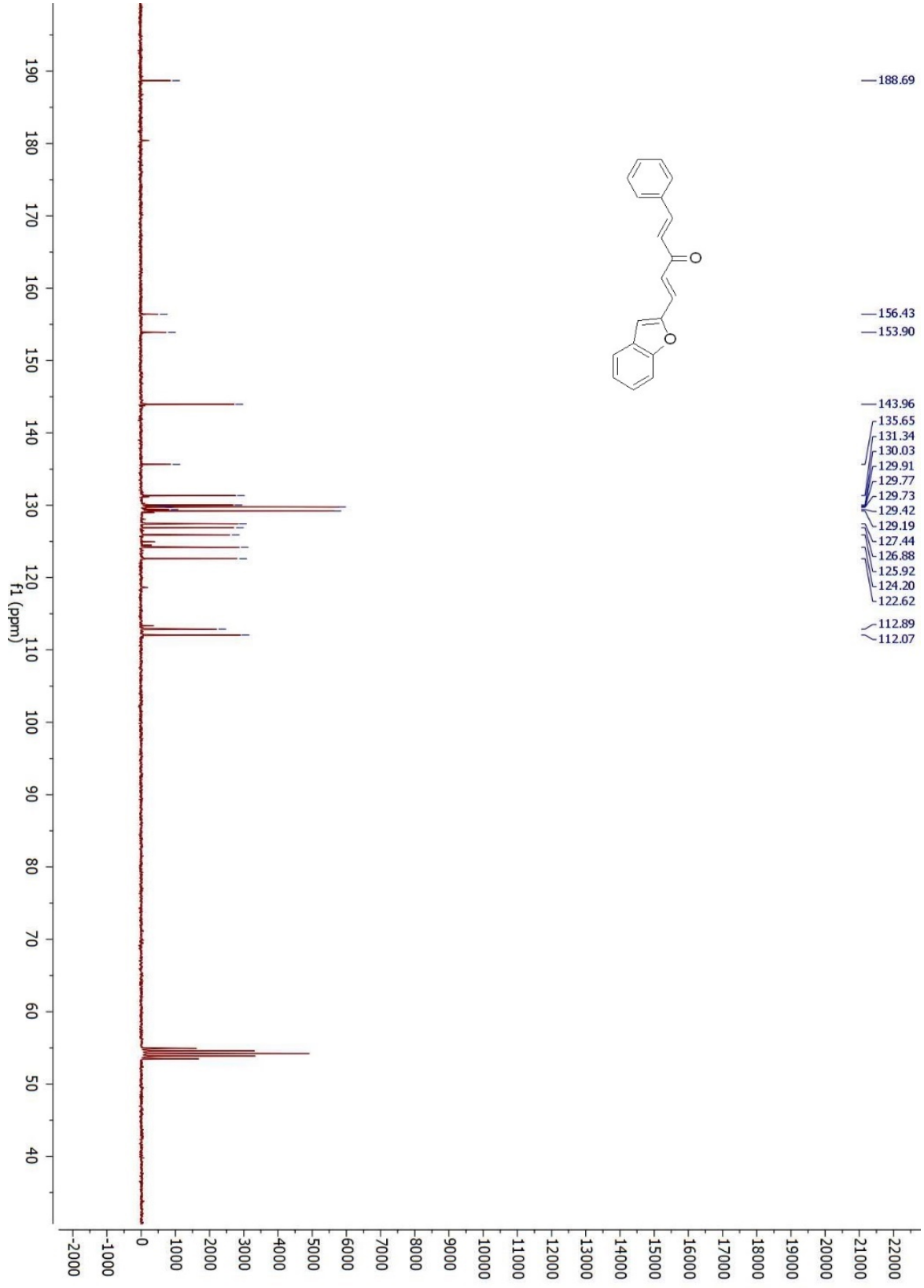
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 21, 300 MHz, CD_2Cl_2)



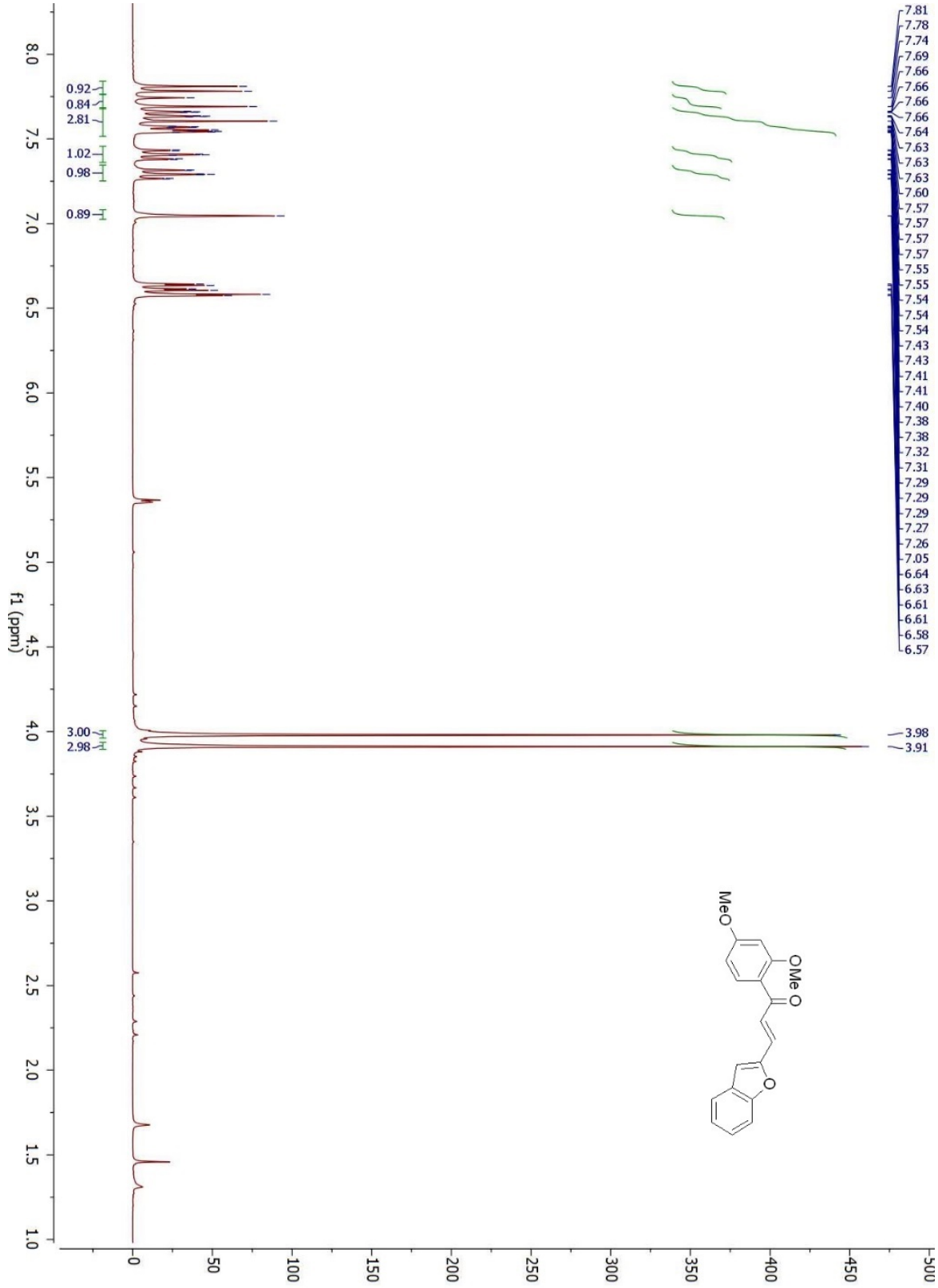

182.01
156.44
153.79
146.43
134.97
132.85
130.66
129.39
129.23
127.56
124.24
122.70
122.63
113.29
112.09
f1 (ppm)

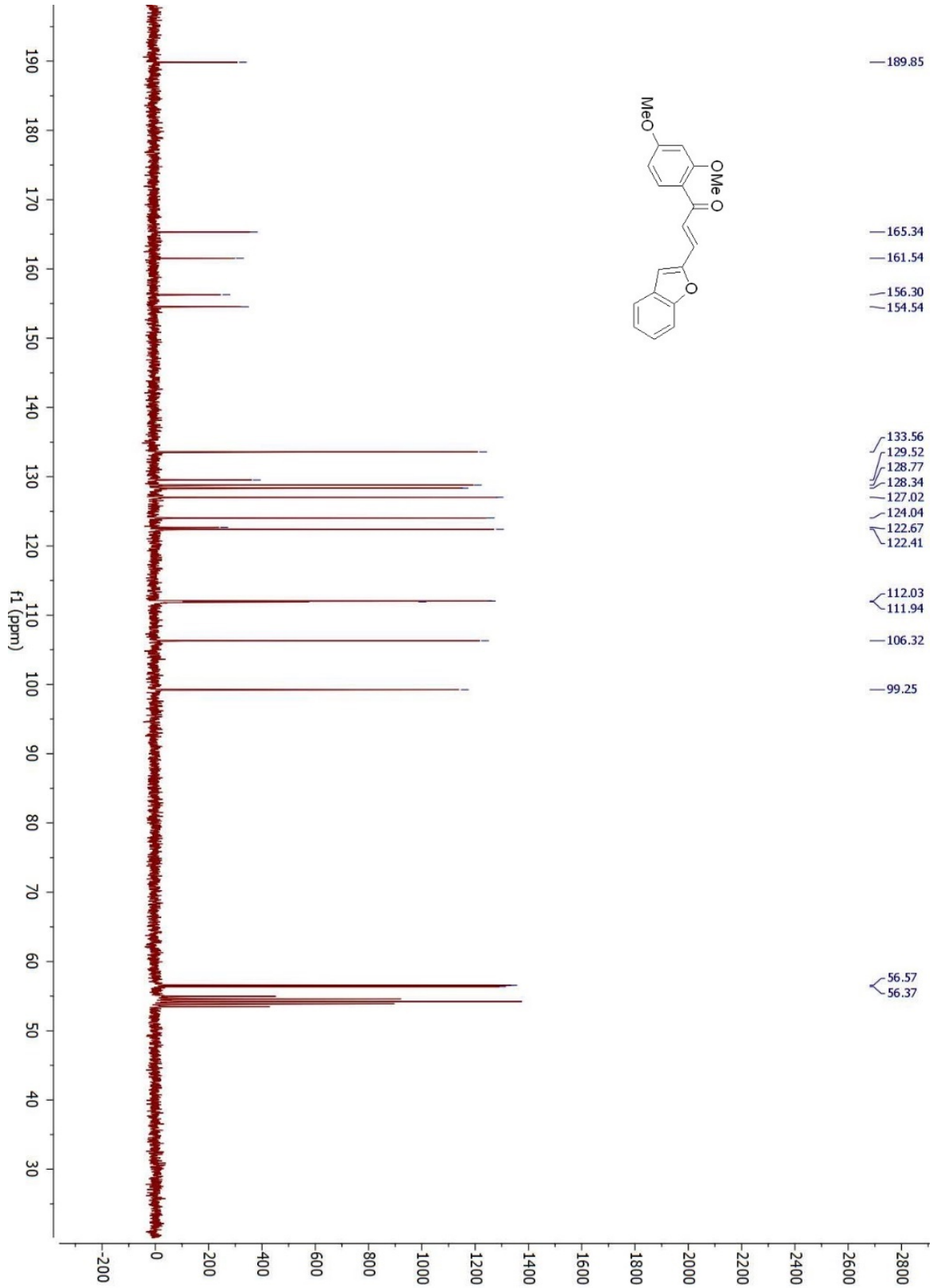
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 22, 300 MHz, CD_2Cl_2)



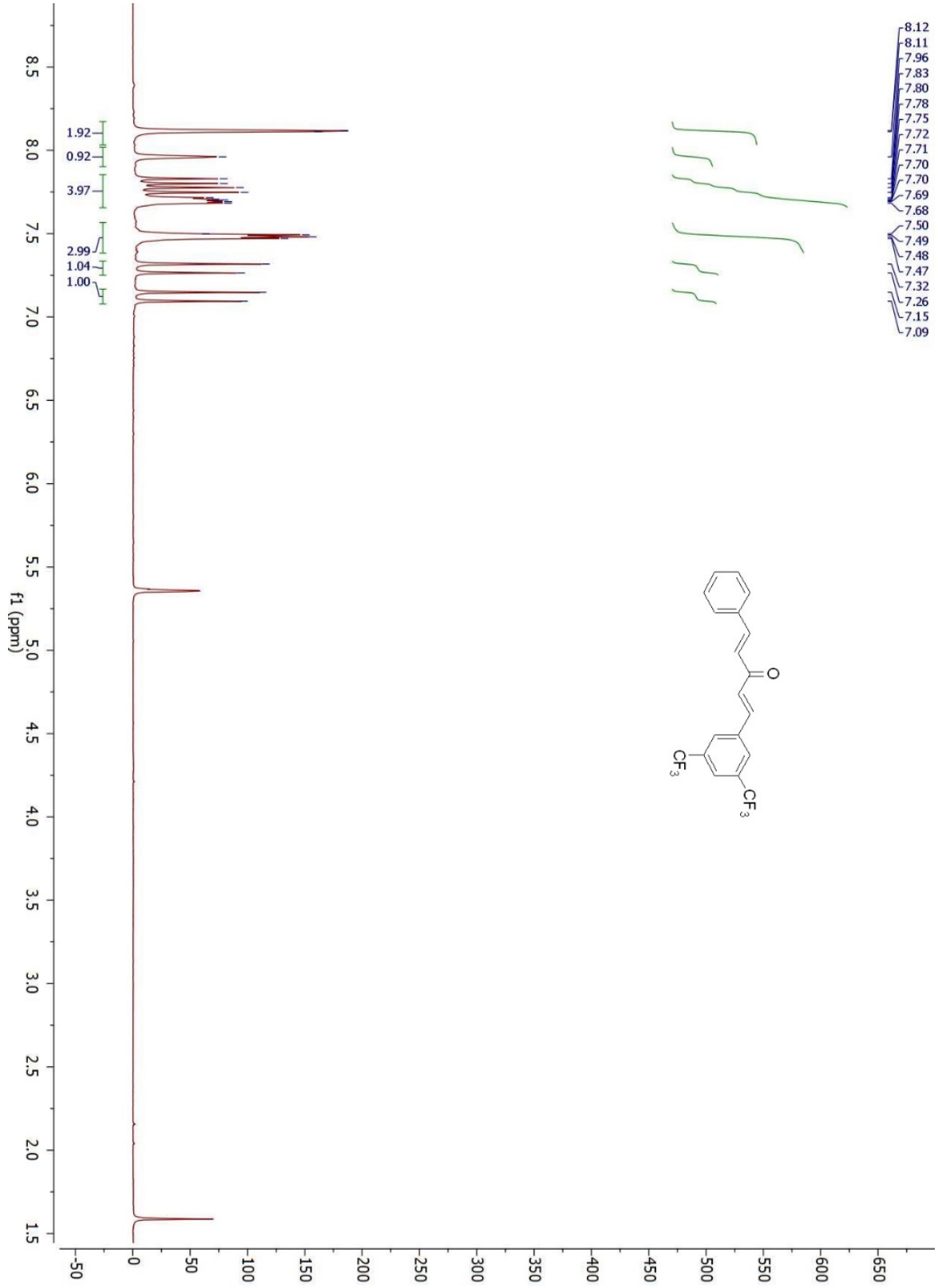

188.69
156.43
153.90
143.96
135.65
131.34
130.03
129.91
129.77
129.73
129.42
129.19
127.44
126.88
125.92
124.20
122.62
112.89
112.07
O
O
f1 (ppm)

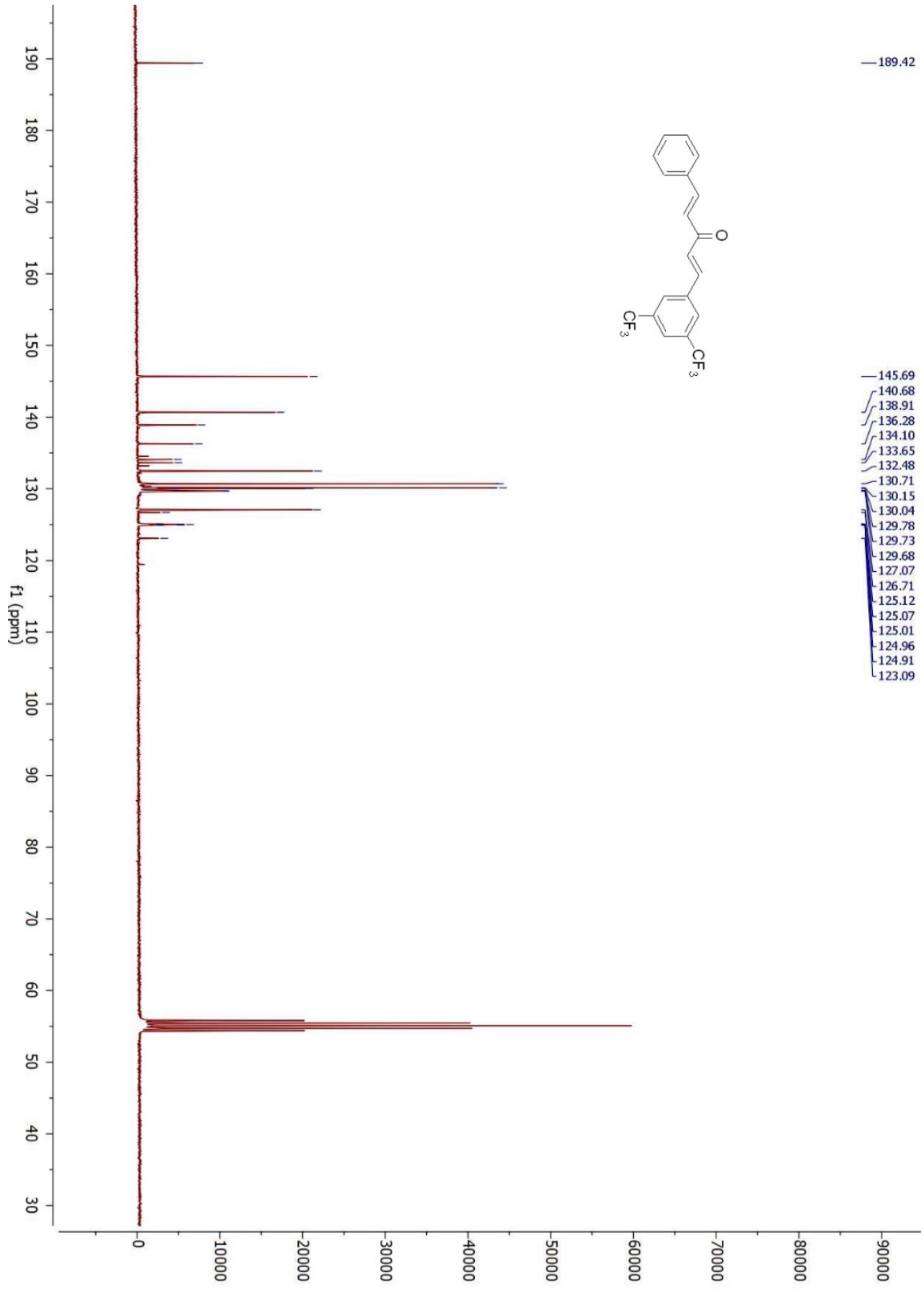
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 23, 300 MHz, CD_2Cl_2)



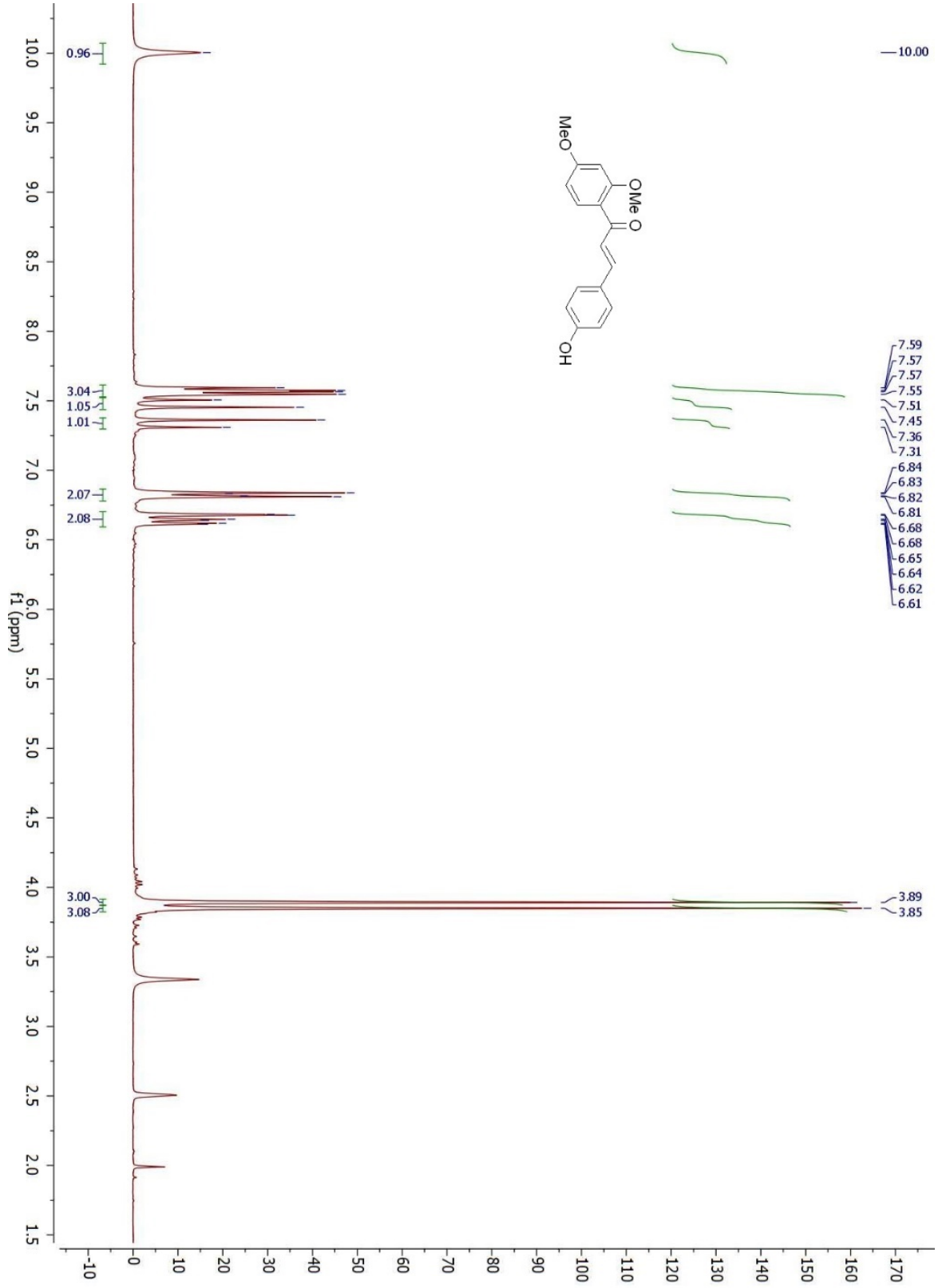

MeO
OMe
O
O
189.85
165.34
161.54
156.30
154.54
133.56
129.52
128.77
128.34
127.02
124.04
122.67
122.41
112.03
111.94
106.32
99.25
56.57
56.37
f1 (ppm)

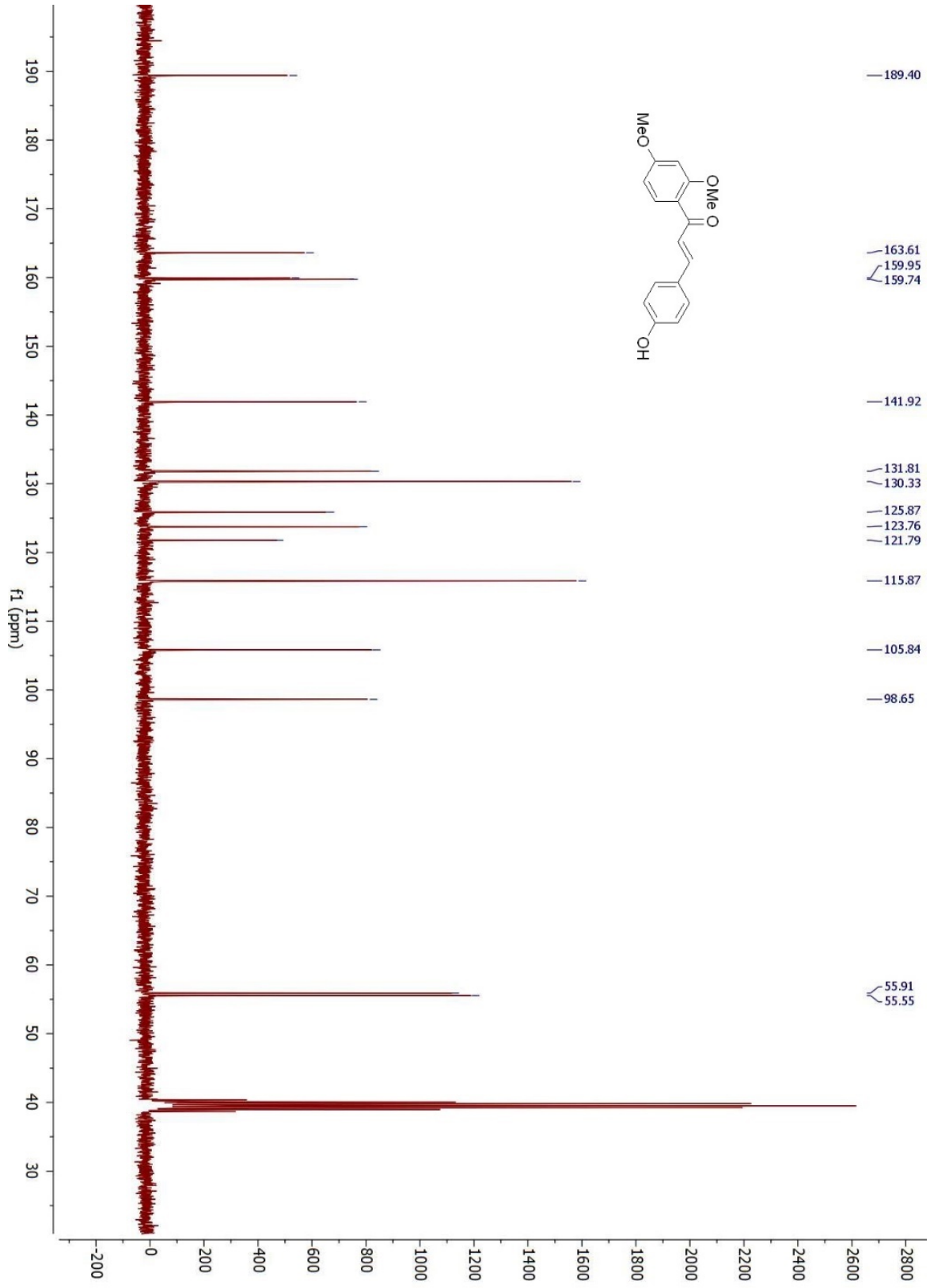
^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 24, 300 MHz, CD_2Cl_2)



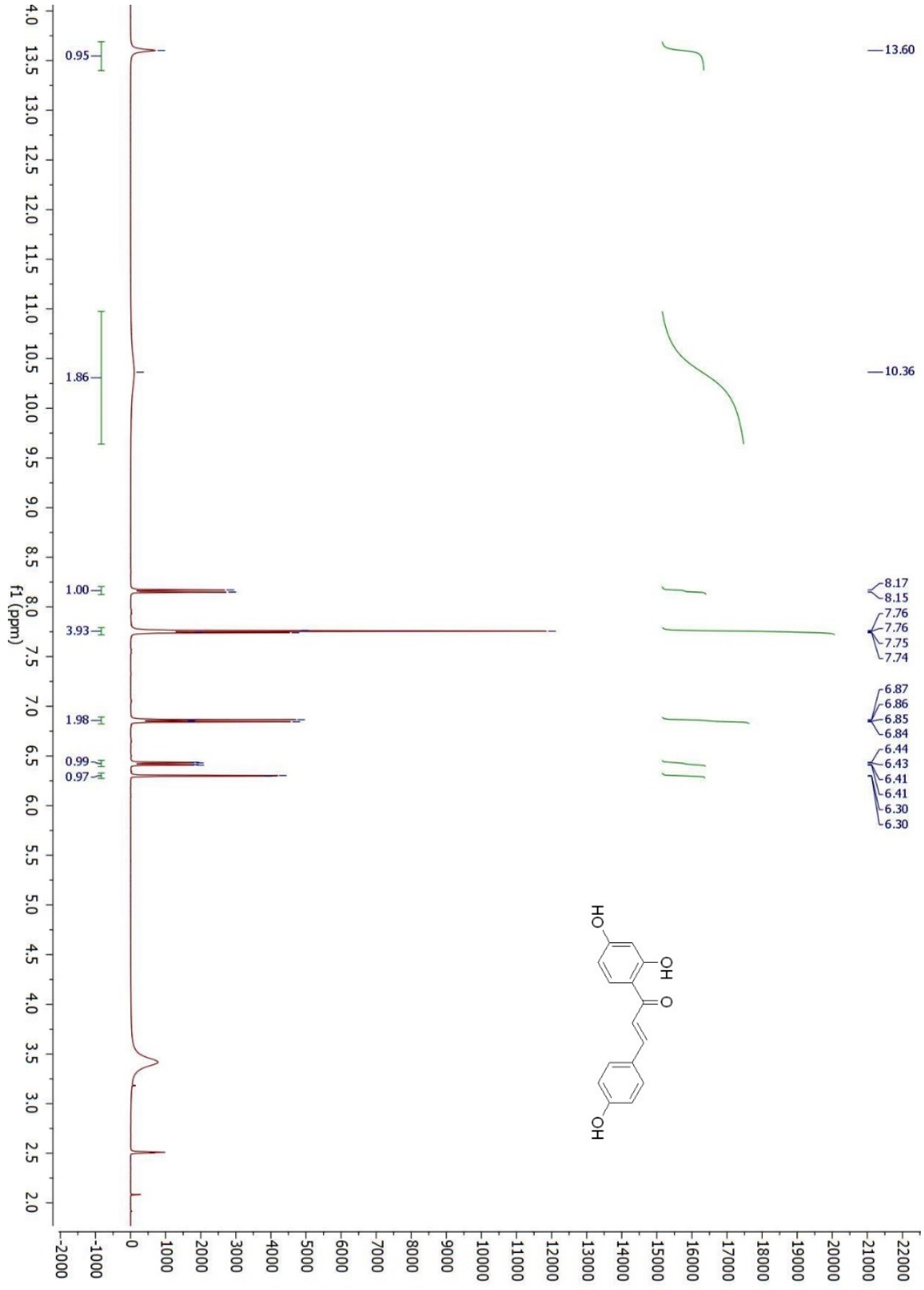

189.42
145.69
140.68
138.91
136.28
134.10
133.65
132.48
130.71
130.15
130.04
129.78
129.73
129.68
127.07
126.71
125.12
125.07
125.01
124.96
124.91
123.09
O
CF3
CF3
f1 (ppm)

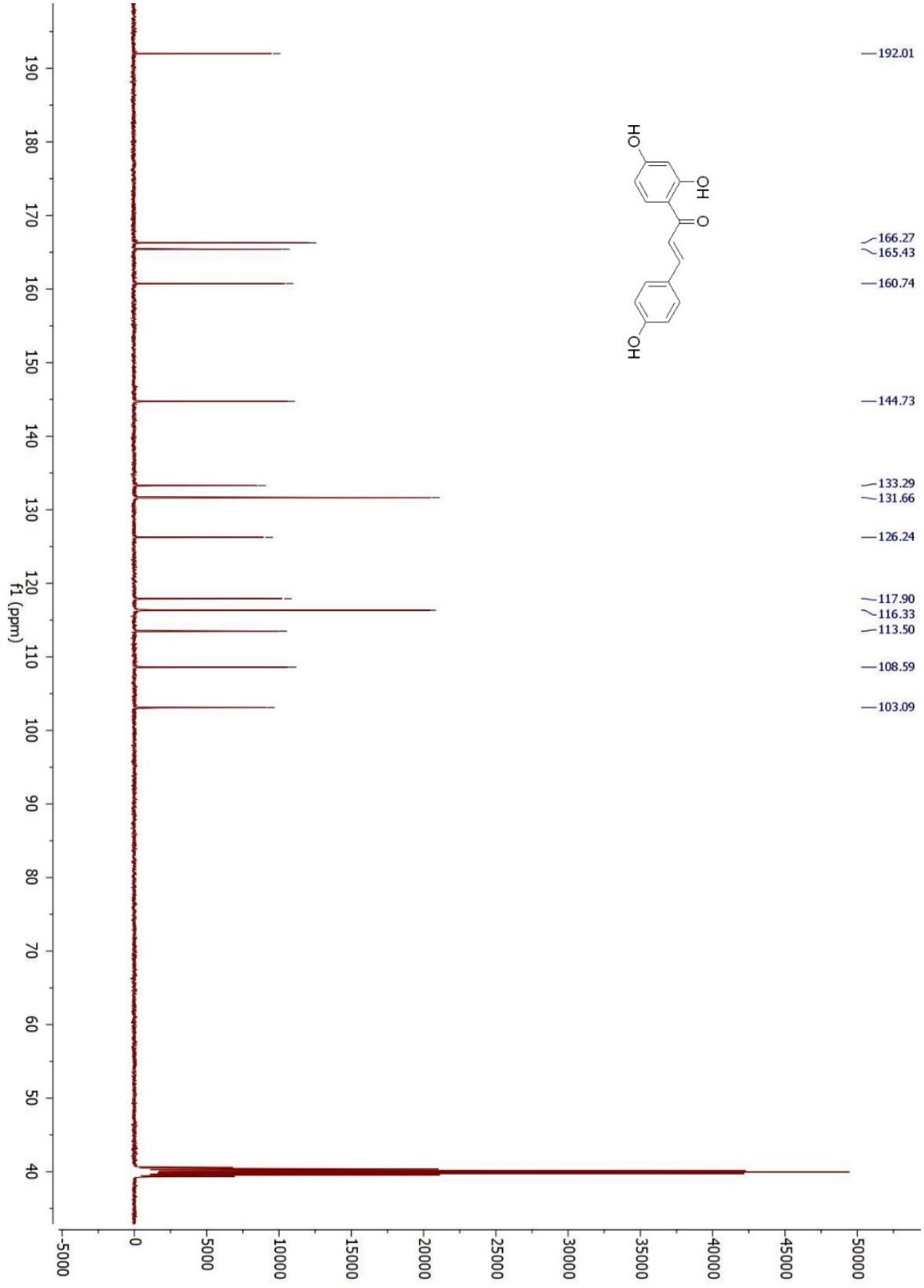
^{1}H-^{13}C{^{1}H} NMR Spectra (Compound 25, 300 MHz, DMSO-*d6*)



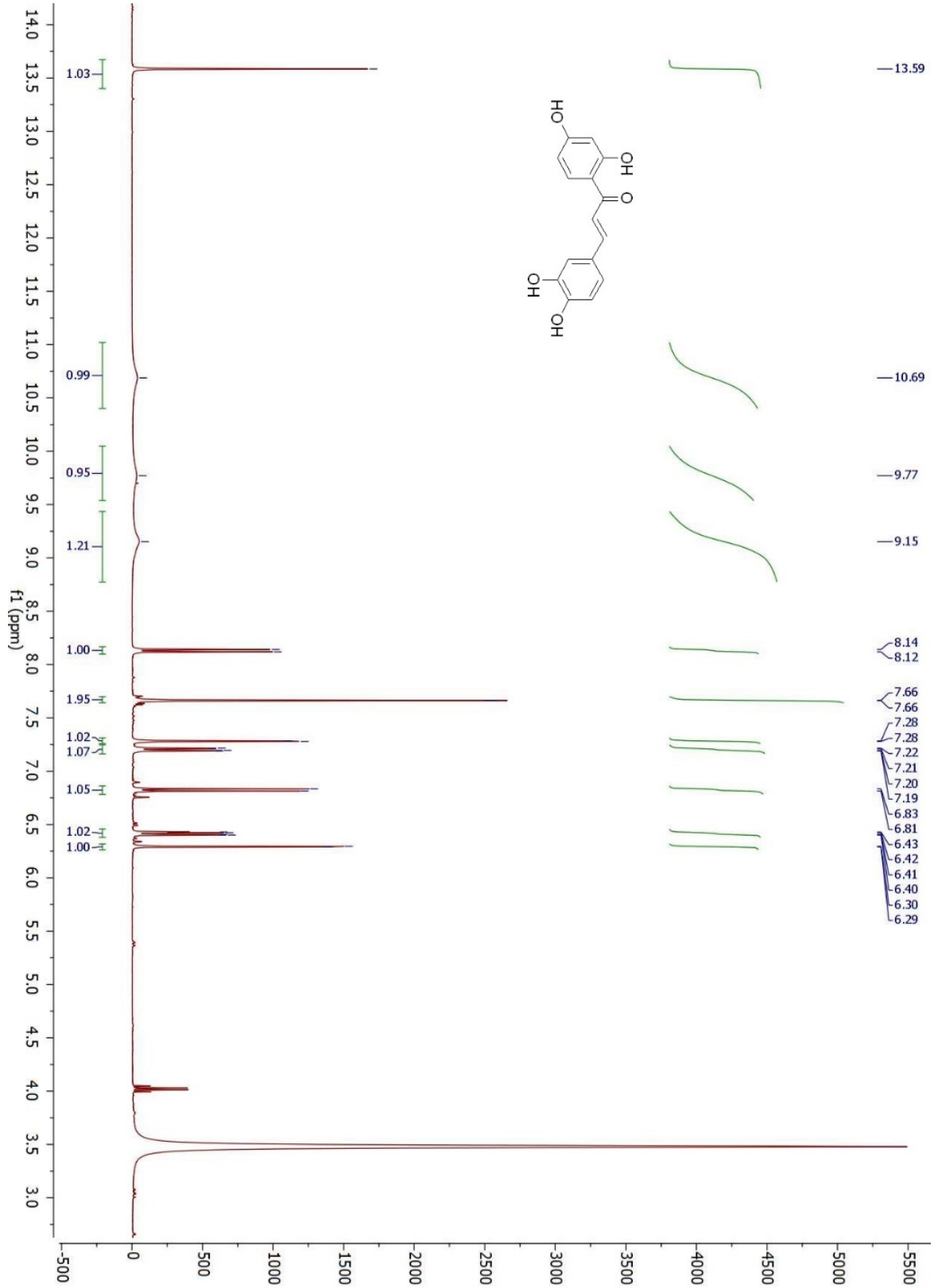

MeO
OMe O
OH
189.40
163.61
159.95
159.74
141.92
131.81
130.33
125.87
123.76
121.79
115.87
105.84
98.65
55.91
55.55
f1 (ppm)

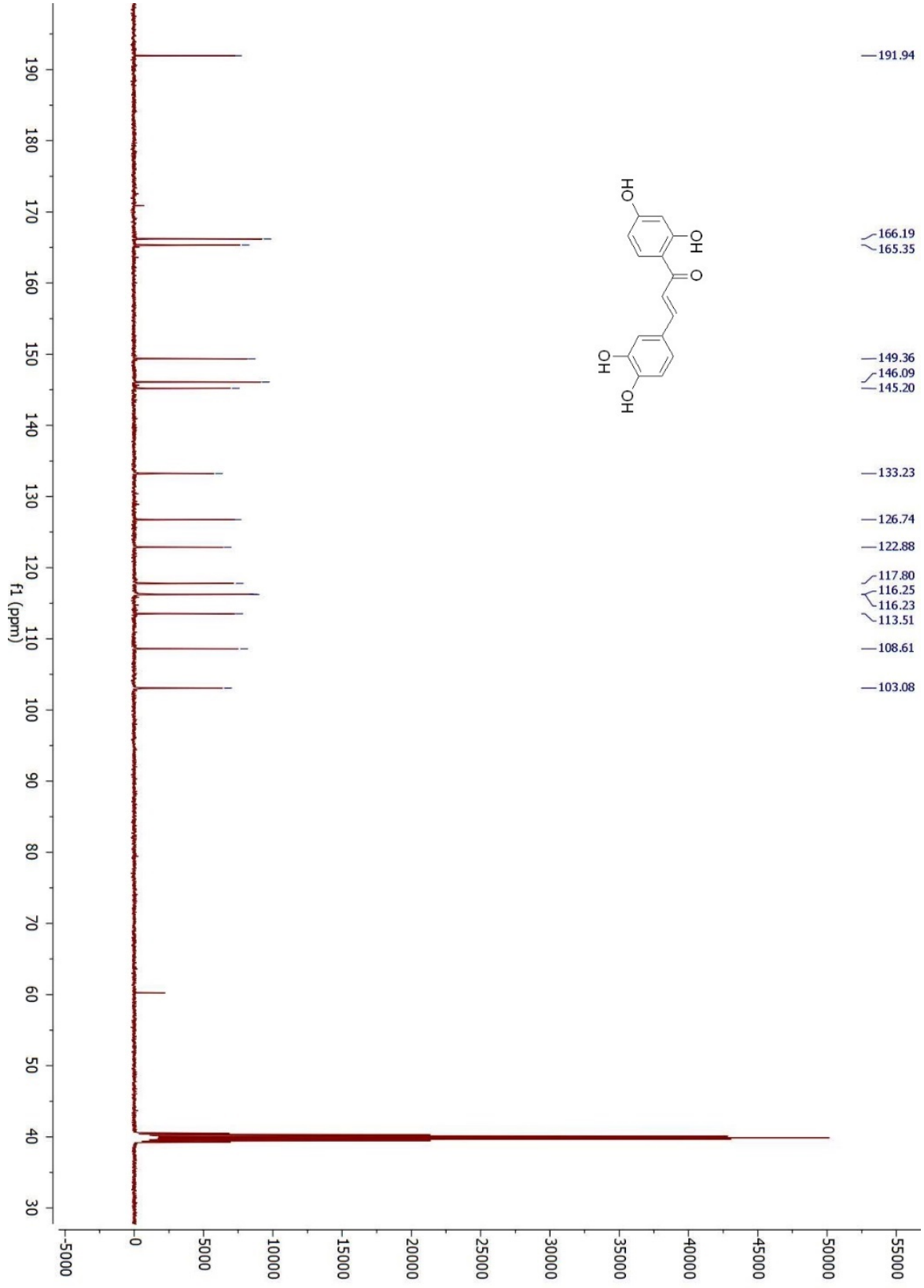
^{1}H-^{13}C{^{1}H} NMR Spectra (Compound 26, 400 MHz, DMSO-*d6*)



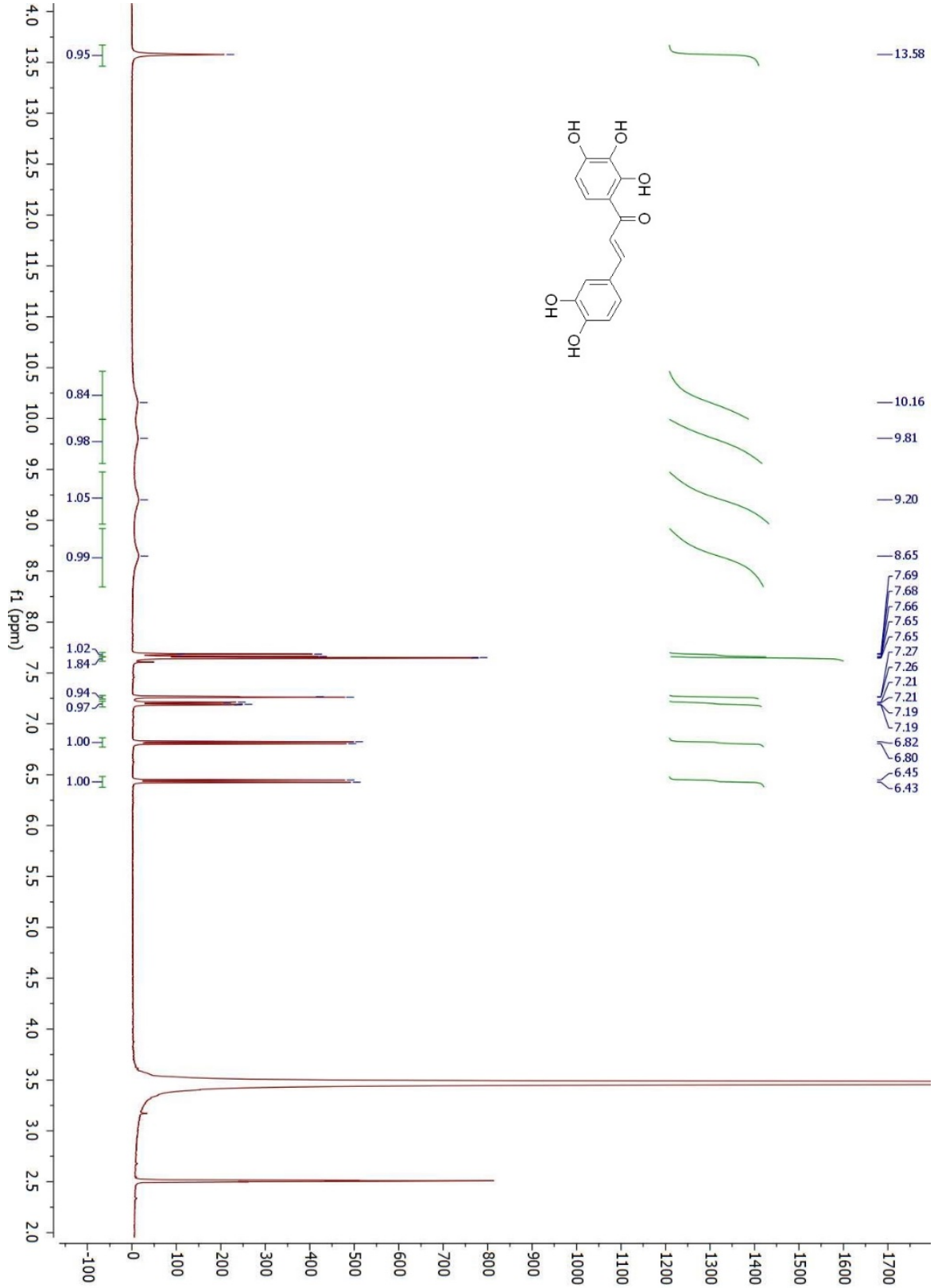

192.01
166.27
165.43
160.74
144.73
133.29
131.66
126.24
117.90
116.33
113.50
108.59
103.09
HO
OH
O
OH
f1 (ppm)

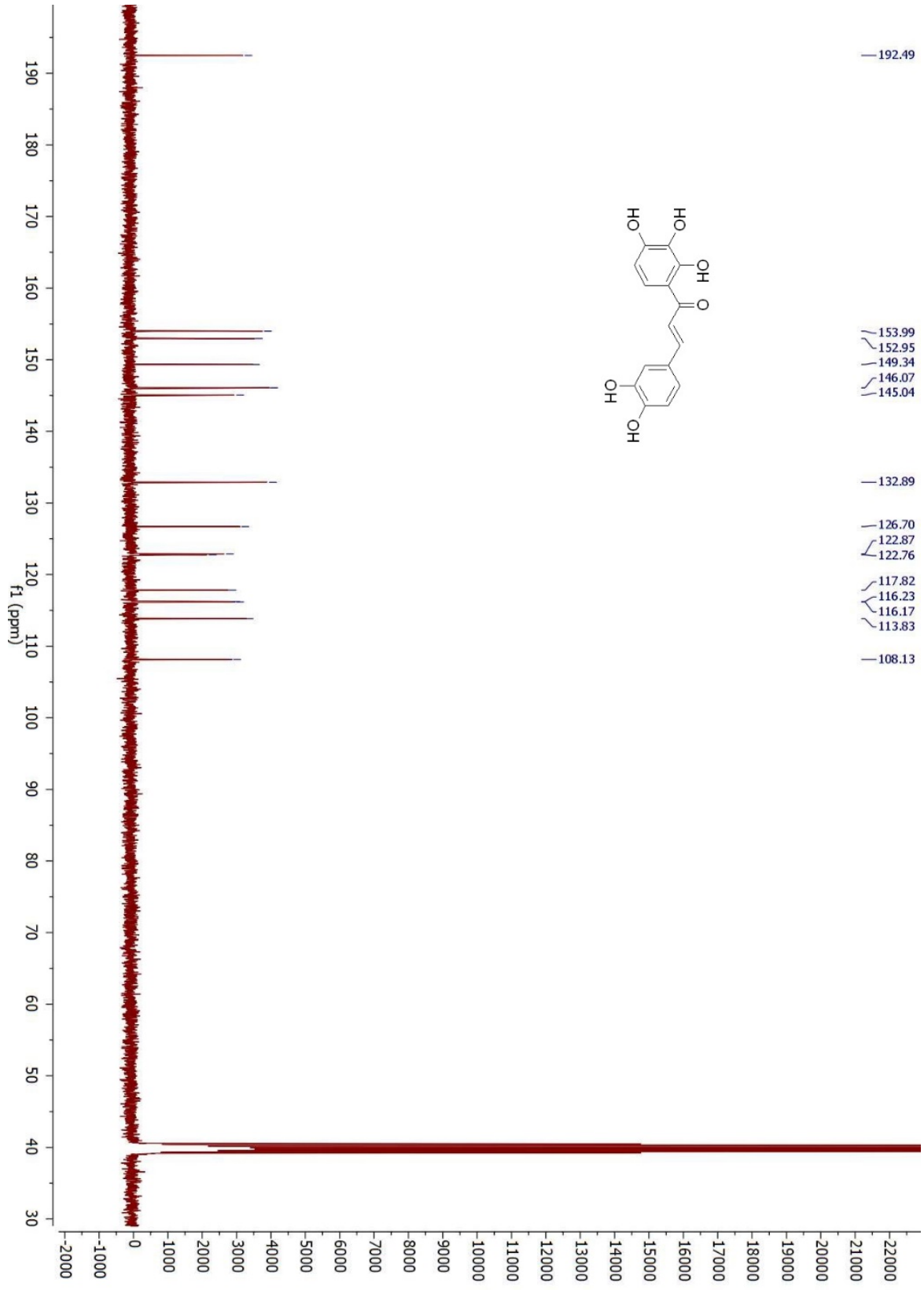
^{1}H-^{13}C{^{1}H} NMR Spectra (Compound 27, 400 MHz, DMSO-*d6*)



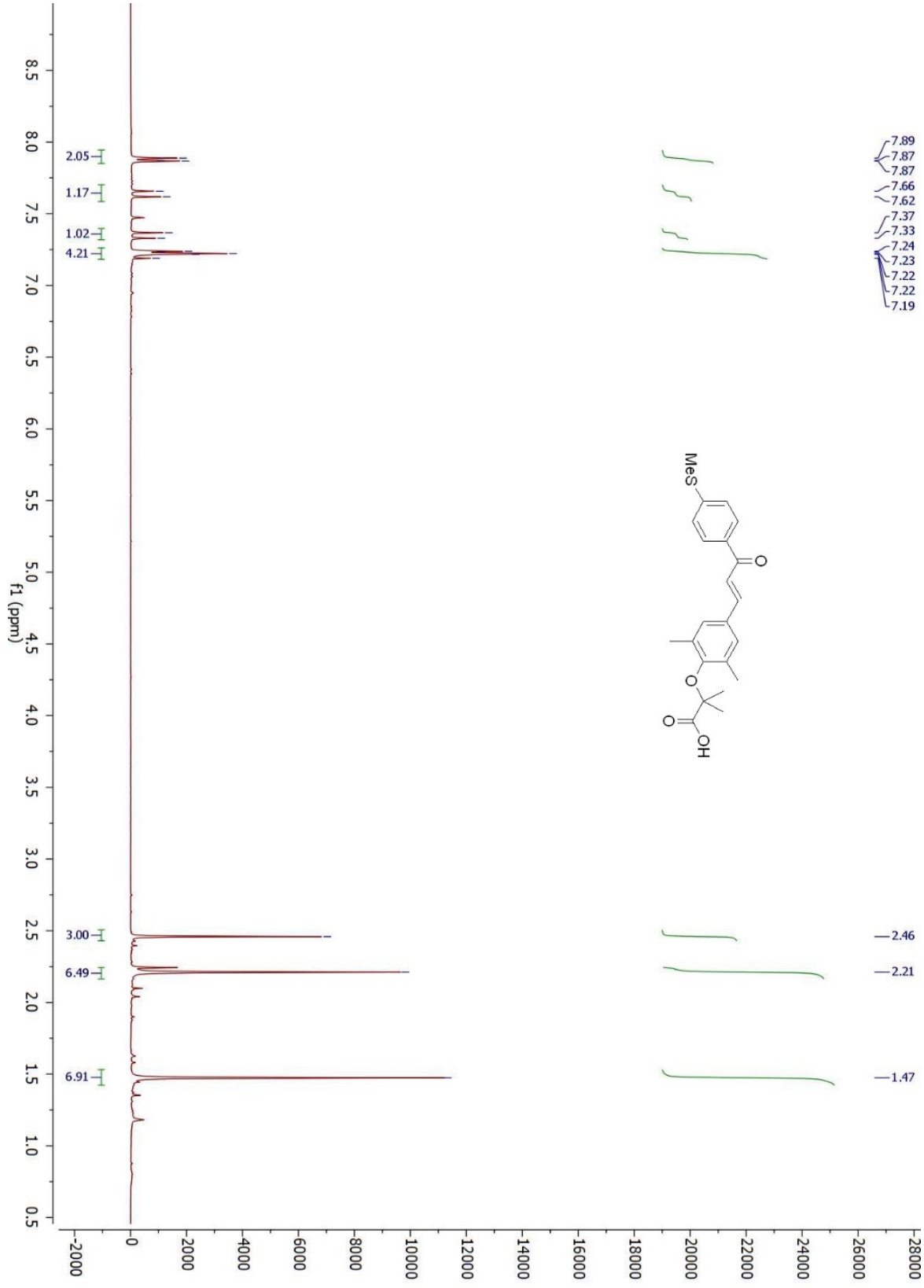

191.94
166.19
165.35
149.36
146.09
145.20
133.23
126.74
122.88
117.80
116.25
116.23
113.51
108.61
103.08
f1 (ppm)

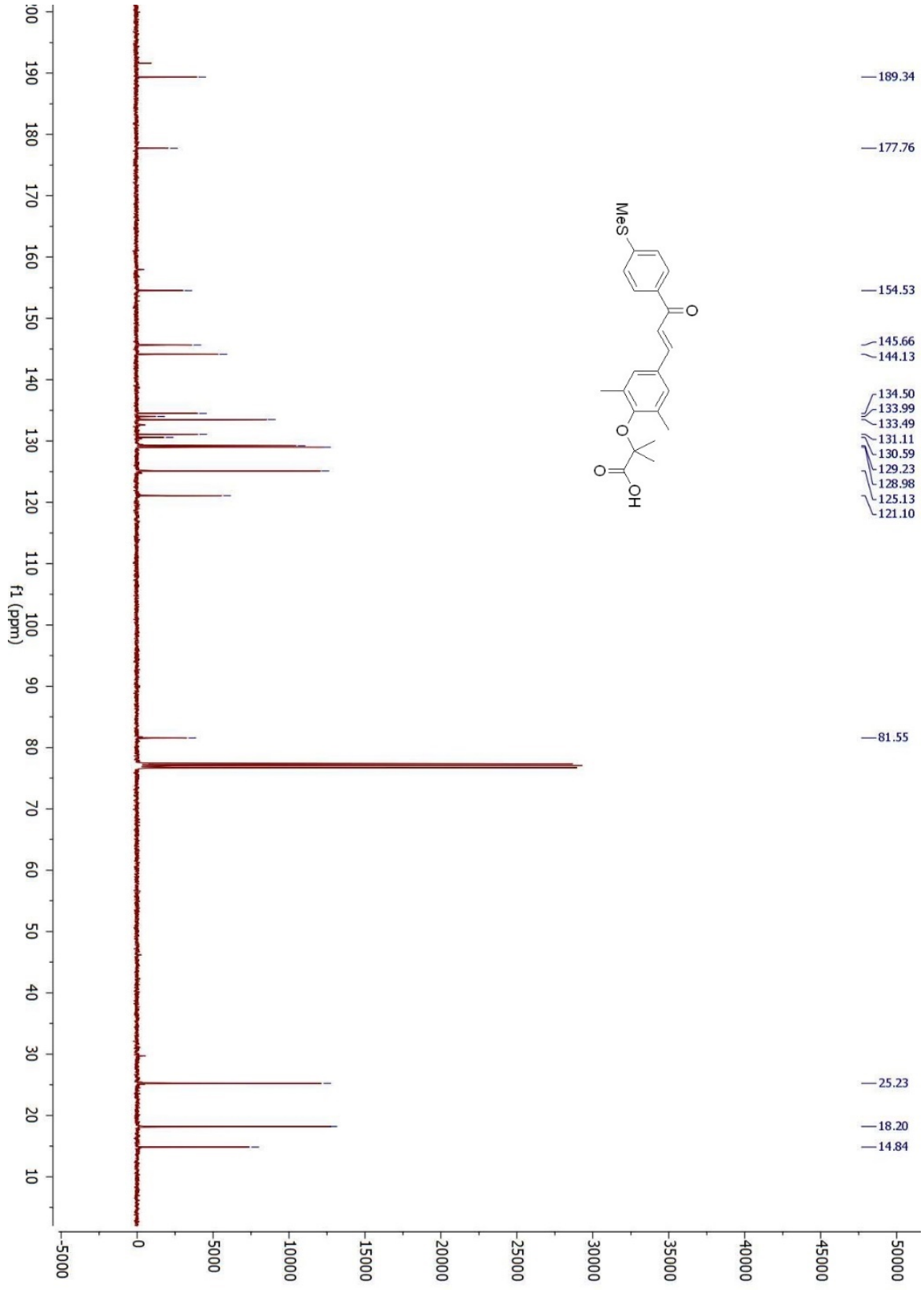
^{1}H-^{13}C{^{1}H} NMR Spectra (Compound 28, 400 MHz, DMSO-*d6*)




192.49
153.99
152.95
149.34
146.07
145.04
132.89
126.70
122.87
122.76
117.82
116.23
116.17
113.83
108.13
f1 (ppm)

^{1}H-$^{13}C\{^{1}H\}$ NMR Spectra (Compound 4 - Elafibranor, 400 MHz, $CDCl_3$)




189.34
177.76
154.53
145.66
144.13
134.50
133.99
133.49
131.11
130.59
129.23
128.98
125.13
121.10
81.55
25.23
18.20
14.84
MeS
O
O
O
OH
f1 (ppm)

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