

**Structure Activity Relationship Study of 3,4'-Dimethoxyflavone for ArlRS Inhibition in
*Staphylococcus aureus***

Supporting Information

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General biological experimental

Bacterial strains, media, and antibiotics *S. aureus* strains AH1263, AH5929, AH2360, AH2090, AH2087, AH2357, AH2106, AH1292, AH2099, AH2094, AH2084, AH2081, AH2075, AH2072, AH2066, AH2062, AH2216, AH3613, AH3614, AH1677, AH5151, AH5152, AH5380, AH5381, AH1716, AH1717, AH2222 were from our in-house library of *S. aureus* strains at The University of Colorado Anschutz School of Medicine, Aurora. MRSA strains MRSA ATCC BAA-1556 was obtained from the ATCC. Stock cultures were stored in 25% glycerol and maintained at -80 °C. Prior to use, colonies were grown on tryptic soy agar with either chloramphenicol (10 µg/mL strains AH1677, AH5151, AH5152, AH5380, AH5381) or erythromycin (10 µg/mL Strains AH3613, AH3614, AH 1716, AH1717, AH2222) or no antibiotic (all other strains). Cation adjusted mueller hinton broth (CAMHB) (cat# 212322) and tryptic soy broth (TSB) (cat# 211822) was purchased from BD. Oxacillin monosulfate was purchased from TCI (cat # 3LVBA-IK). Chloramphenicol was purchased from Alfa Aesar (cat # 10131638). Erythromycin was purchased from TCI (cat# JRD8F-AT). All assays were run twice from two separate cultures and then repeated at least two separate times (minimum of four biological replicates).

Biological assay protocols

GFP linked reporter strain assay: Bacteria was cultured overnight in fresh TSB (3 mL) along with antibiotic (10 µg/mL) to select for intended plasmid. Overnight cultures were diluted 1:500 in TSB and antibiotic (1:1000 dilution from a 10µg/mL stock) was added. To aliquots (0.5 mL) was added compound from 10 mM stock solutions in DMSO, such that the compound concentration equaled 50 µM. Samples were then dispensed (200 µL) in a black 96 well plate so that each sample occupied two wells. Two wells were filled with only media and two wells were

filled with inoculated media with no compound. Plates were covered with a lid and placed in a BioTek Synergy HTX multi-mode reader plate reader. The plate was continually shaken using the fast orbital setting with an orbital frequency of 807cpm at 37 °C for 24 hours. The OD₆₀₀ and fluorescence intensity with excitation at 485 nm and emission at 528 nm were recorded at the start then subsequently every hour with the gain set 35 and measurements being taken from the bottom of the plate.

Broth microdilution method for the determination of minimum inhibitory concentration (MIC): Bacteria were cultured for 4 to 6 hours in CAMHB and subcultured to 5×10^5 CFU/mL in fresh CAMHB. To aliquots (0.5 mL) was added compound from 10 mM stock solutions in DMSO, such that the compound concentration equaled the highest concentration tested. Samples were then dispensed (200 μ L) into the first row of a 96-well microtiter plate in which all but the final row of subsequent wells were prefilled with 100 μ L of the untreated bacterial subculture. The final row was filled with media to act as a sterility control and blank. Row one wells were mixed 6-7 times, then, 100 μ L was withdrawn and transferred to row two. Row two wells were mixed 6-7 times followed by a 100 μ L transfer from row two to row three. This procedure was used to serially dilute the rest of the rows of the microtiter plate, excluding the last prefilled row, which was used to measure growth in the absence of compound. Plates were then sealed with GLAD Press'n Seal and incubated under stationary conditions at 37 °C. After 16 hours, the plates were removed, and MIC values were measured by recording the OD₆₀₀ of each well. MIC values were determined as the minimum concentration required to achieve 90% growth inhibition compared to growth in untreated wells

Broth microdilution method for measurement of oxacillin potentiation: Bacteria were cultured for 4 to 6 hours in CAMHB and diluted to 5×10^5 CFU/mL in fresh CAMHB. To aliquots (3 mL) was added compound from 10 mM stock solutions in DMSO. One aliquot was not dosed to allow measurement of the antibiotic MIC in the absence of compound. A 500 μ L aliquot of each sample was dosed with oxacillin, and from this 200 μ L was dispensed into the first row of a 96-well microtiter plate in which all but the final row of subsequent wells was prefilled with 100 μ L of the corresponding compound dosed bacterial suspension. The final row was filled with media to act as a sterility control and blank. Row one wells were mixed 6-7 times, then, 100 μ L was withdrawn and transferred to row two. Row two wells were mixed 6-7 times followed by a 100 μ L transfer from row two to row three. This procedure was used to serially dilute the rest of the rows of the microtiter plate, excluding the last prefilled row, which was used to measure growth in the presence of compound alone. Plates were then sealed with GLAD Press'n Seal and incubated under stationary conditions at 37 °C. After 16-18 hours, the plates were removed, and MIC values were measured by recording the OD₆₀₀ of each well. MIC values were determined as the minimum concentration required to achieve 90% growth inhibition compared to growth in untreated wells.

Table S1: Average percent inhibition of fluorescence normalized to growth in *mgrA* P2-GFP, *spx* P2-GFP, *agr* P3-YFP, and P_{hla}-GFP reporter strains when treated with 50 μ M of each compound.

Compound	<i>mgrA</i> P2-GFP reporter	<i>spx</i> P2-GFP reporter	<i>agr</i> P3-YFP reporter	P_{hla}-GFP reporter
1	19	18	21	27
3a	50	35	72	32
3b	37	25	23	-13
3c	42	32	73	10
3d	34	18	0	-44
3e	50	27	17	-62
3f	48	24	12	-88
3g	61	34	12	-46
3h	19	15	-13	-20
3i	17	17	25	38
3j	24	18	24	46
3k	19	3	1	52
3l	19	0	19	3
3m	27	-10	-17	13
3n	21	8	-9	15
3o	11	9	4	3
3p	36	30	32	26
3q	18	12	3	5
3r	11	10	5	-3
3s	14	8	-7	24
3t	25	3	-4	11
3u	6	3	2	-1
3v	23	22	31	5
3w	24	15	20	-29
3x	30	16	5	3
3y	29	28	25	-10
3z	21	12	18	-8
7a	24	11	21	34
7b	30	-4	6	15
10	13	2	-15	12
15	10	3	12	24

16	33	26	52	41
17	61	51	48	-46
18	5	26	-6	0
19	25	24	24	-5
20	13	12	9	-2
21	1	3	-3	12

^aAll values given as percent inhibition compared to untreated samples. ⁿ Negative values denote instances when fluorescence was increased compared to untreated samples.

Table S2: Strains of *S. aureus* used in this study and MIC of oxacillin in all deletion strains and MIC of oxacillin with 60 μ M of compound 17 in strains with lower MICs than parent strain.

Strain number	LOCI	MIC of Oxacillin	MIC of Oxacillin with 60 μ M of compound 17
ATCC BAA-1556	N/A	32	2
AH 1263	USA 300 LAC. CA-MRSA strain LAC, USA300-0114 PFGE type, Erm sensitive	32	1
AH 1292 ²	transduction of <i>agr::tet</i> from RN7208 into AH1263	32	N/A
AH 2216 ³	AH1263 Δ <i>saePQRS</i>	32	N/A
AH 2062 ⁴	AH1263 Δ <i>yesMN</i> LAC*SAUSA300_0217-18 Δ	32	N/A
AH 2066 ⁴	AH1263 Δ <i>lytRS</i> LAC*SAUSA300_0254-55 Δ	32	N/A
AH 2072 ⁴	AH1263 Δ <i>narL</i> LAC*SAUSA300_1219-20 Δ	32	N/A
AH 2075 ⁴	AH1263 Δ <i>arl</i> LAC*SAUSA300_1307-08 Δ	32	N/A
AH 2081 ⁴	AH1263 Δ <i>phoRS</i> LAC*SAUSA300_1638-39 Δ	32	N/A
AH 2084 ⁴	AH1263 Δ <i>airRS</i> LAC*SAUSA300_1798-99 Δ	32	N/A
AH 2087 ⁴	AH1263 Δ <i>vraRS</i> LAC*SAUSA300_1865-66 Δ	8	1
AH 2090 ⁴	AH1263 Δ <i>kdpDE</i> LAC*SAUSA300_2035-36 Δ	8	0.5
AH 2094 ⁴	LAC*SAUSA300_2308-09 Δ	32	N/A
AH 2099 ⁴	AH1263 Δ <i>nsaRS</i> LAC*SAUSA300_2558-59 Δ	32	N/A
AH2106 ⁴	AH1263 Δ <i>nreBC</i> LAC*SAUSA300_2337-38 Δ	64	N/A
AH2357 ⁴	AH1263 Δ <i>srrAB</i> LAC*SAUSA300_1441-42 Δ	64	N/A
AH2360	AH1263 Δ <i>graRS</i> LAC*SAUSA300_0645-46 Δ	2	1
AH 5929 ⁸	AH1263 <i>mecA::Tet</i>	0.25	0.25

AH3613⁵	AH1263 + pHC68 (pCM11_ <i>PmgrA</i> _sGFP, ermR)	N/A	N/A
AH3614⁵	AH1263 Δ arl + pHC68 (pCM11_ <i>PmgrA</i> _sGFP, ermR)	N/A	N/A
AH1677⁶	AH845 / pDB59 (<i>agr</i> type I reporter)	N/A	N/A
AH5151⁷	AH1263 + pHC151 (pCM29_ <i>PsdrD</i> , camR)	N/A	N/A
AH5152⁷	AH1263 Δ arl + pHC151 (pCM29_ <i>PsdrD</i> , camR)	N/A	N/A
AH5380⁷	AH1263 + pHC177 (pCM29_ <i>spxP2</i> , camR)	N/A	N/A
AH5381⁷	AH1263 Δ arl + pHC177 (pCM29_ <i>spxP2</i> , camR)	N/A	N/A
AH1716	AH1263 + pCM27 (<i>P</i> _{hla} _sGFP, ermR)	N/A	N/A
AH1717	AH1263 <i>agr::tet</i> + pCM27 (<i>P</i> _{hla} _sGFP, ermR)	N/A	N/A
AH2222	AH1263 Δ sae <i>PQRS</i> + pCM27 (<i>P</i> _{hla} _sGFP, ermR)	N/A	N/A

General Chemistry Experimental

All reactions were carried out under an atmosphere of nitrogen using anhydrous solvents unless otherwise specified. All chemical reagents for synthesis were used without further purification. Analytical thin layer chromatography (TLC) was performed using 250 μm Silica Gel 60 F254 pre-coated plates (EMD Chemicals Inc.). Flash column chromatography was performed using 230–400 mesh 60Å Silica Gel from Sorbent Technologies. NMR spectra were recorded using broadband probes on a Bruker AVANCE III HD Nanobay (400, 500 or 800 MHz for ^1H and 100 125 or 200 MHz for ^{13}C). All Spectra are presented using MestReNova (Mnova) software and ^1H NMR are typically displayed from 12 to -0.7 ppm without the use of the signal suppression function. Spectra were obtained in the following solvents (reference peaks also included for the ^1H and ^{13}C NMRs): d_6 -DMSO (^1H NMR: 2.50 ppm; ^{13}C NMR: 39.52 ppm), CD_3OD (^1H NMR: 3.31 ppm; ^{13}C NMR: 49.00 ppm) and d_1 - CDCl_3 (^1H NMR: 7.26 ppm; ^{13}C NMR: 77.16 ppm). All NMR experiments were performed at room temperature. Chemical shift values (δ) are reported in parts per million (ppm) for all ^1H and ^{13}C spectra. ^1H NMR multiplicities are reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad hept = heptet. High-resolution mass spectra were obtained for all new compounds from the mass spectrometry and proteomics facility at the University of Notre Dame performed on a Bruker-TOF-ESI spectrometer in positive module using direct infusion in 9:1 acetonitrile: water. The IR spectra analyses were conducted at the Center for Environmental Science and Technology (CEST) at University of Notre Dame using a Bruker Tensor 27, with a diamond lens ATR module, to gather transmission spectra. UV data was taken using a Thermo Scientific, Genesys 10 UV scanning spectrometer.

General procedure for aldol condensation

A mixture of the acetophenone (5-10 mmol, 1 equiv.) and the corresponding aldehyde (1 equiv.) in EtOH (20-40 mL) was stirred at room temperature without a cap and a 50% aqueous solution of NaOH (5-8 mL) was added. The reaction mixture was stirred at room temperature until all of the aldehyde had been consumed. HCl (10%) was then added until neutrality. Precipitated chalcones were generally filtered and crystallized from MeOH although in some cases the product was purified using column chromatography (Hexanes: EtOAc).

General procedure of Algar-Flynn-Oyamada cyclization and alkylation

A solution of the corresponding 2-hydroxychalcone (1-4 mmol) in 3.0 M KOH in MeOH (20-30 mL) was cooled to 0 °C with no cap. An aqueous solution of H₂O₂ (30%) (5-8 mL) was added to the chalcone solution. The resulting mixture was stirred and allowed to warm to room temperature and stirred overnight. The reaction mixture was again cooled to 0 °C and HCl (3 N) was added until the mixture reached pH 2. The precipitate was dissolved in EtOAc and washed with distilled water and brine three times each (20 mL). The organic layer was dried with anhydrous Na₂SO₄. The solvent was evaporated in vacuo and the residue run through a flash silica column. A portion of the resulting residue containing the product (20-100 mg) was added with K₂CO₃ (1.8 equiv.) to a flame dried vial, which was evacuated and placed under argon. The residue and base were then dissolved in CH₃CN (5 mL), and the mixture was heated to 40 °C. The desired alkyl halide (10 equiv.) was subsequently added, and the reaction was allowed to stir until the starting material was totally consumed (as evidenced by TLC). The reaction mixture was then, partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried over Na₂SO₄, filtered and

concentrated. The crude material was purified by column chromatography to yield the final product.

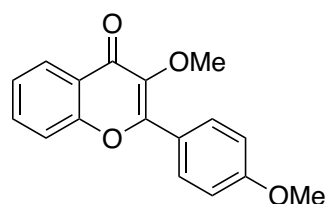
General Procedure for MOM protection

A RBF was charged with DCM (30 mL), aldehyde (1 equiv.) and Hunig's base (1.6 equiv.). MOM-Cl (5.9 M in MeOAc) (1.5 equiv.) was added slowly. Reaction was stirred overnight at rt. The reaction was subsequently diluted with DCM, washed with HCl (2x), sodium bicarbonate (2x), brine (2x), and dried over sodium sulfate before being purified via column chromatography.

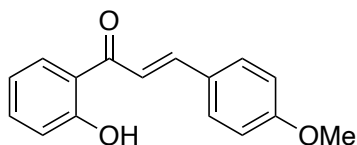
General procedure of MOM deprotection

Compound was added to vial and dissolved in DCM (1.5 mL). TFA (1.5 mL) was then added to the vial and the reaction was allowed to stir until the starting material was consumed (as evidenced by TLC). Following deprotection, compound was purified via column chromatography.

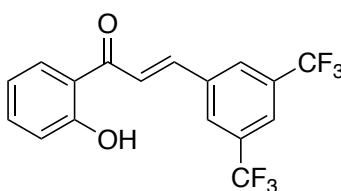
Previously Reported Compounds



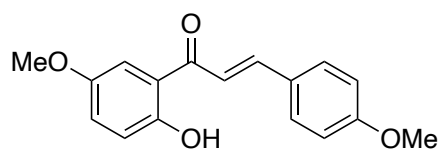
3-Methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (1): was synthesized using the general procedure for Algar-Flynn-Oyamada cyclization and alkylation with **2a** and methyl iodide. Spectral data were consistent with previous reports.⁹



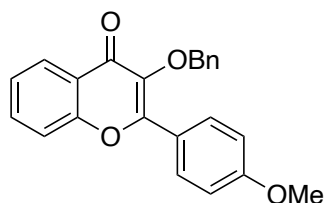
(E)-1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (2a): was synthesized using the general procedure for aldol condensation. Spectral data were consistent with previous reports.¹⁰



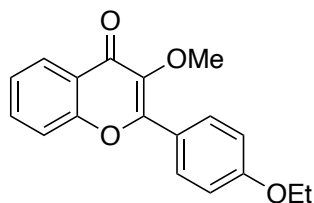
(E)-3-(3,5-Bis(trifluoromethyl)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2k): was synthesized using the general procedure for aldol condensation. Spectral data were consistent with previous reports.¹¹



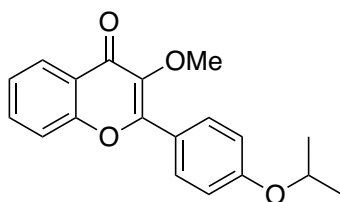
(E)-1-(2-Hydroxy-5-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (2q): was synthesized using the general procedure for aldol condensation. Spectral data were consistent with previous reports.¹²



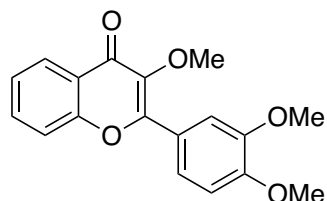
3-(Benzyloxy)-2-(4-methoxyphenyl)-4*H*-chromen-4-one (3b) was synthesized using the general procedure procedure for Algar-Flynn-Oyamada cyclization and alkylation with **2a** and benzyl bromide. Spectral data were consistent with previous reports.⁹



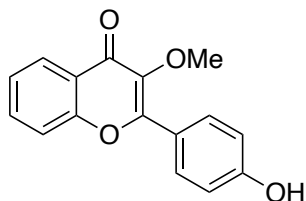
2-(4-Ethoxyphenyl)-3-methoxy-4*H*-chromen-4-one (3j): was synthesized using the general procedure procedure for Algar-Flynn-Oyamada cyclization and alkylation with **2c** and methyl iodide. Spectral data were consistent with previous reports.⁹



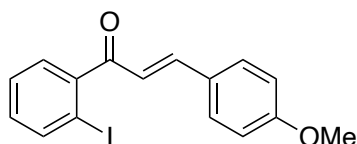
2-(4-Isopropoxyphenyl)-3-methoxy-4*H*-chromen-4-one (3l): was synthesized using the general procedure procedure for Algar-Flynn-Oyamada cyclization and alkylation with **2e** and methyl iodide. Spectral data were consistent with previous reports.⁹



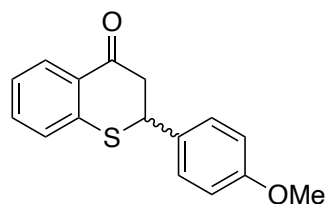
2-(3,4-Dimethoxyphenyl)-3-methoxy-4*H*-chromen-4-one (3n): was synthesized using the general procedure procedure for Algar-Flynn-Oyamada cyclization and alkylation with **2g** and methyl iodide. Spectral data were consistent with previous reports.⁹



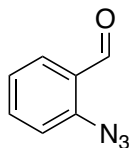
2-(4-Hydroxyphenyl)-3-methoxy-4*H*-chromen-4-one (7a): was synthesized using the general procedure procedure for Algar-Flynn-Oyamada cyclization and alkylation with **6a** and methyl iodide followed by MOM deprotection. Spectral data were consistent with previous reports.¹³



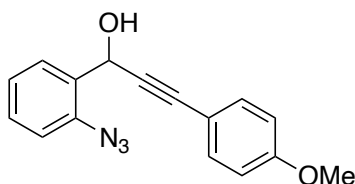
(*E*)-1-(2-Iodophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (8): was synthesized using the general procedure for aldol condensation. Spectral data were consistent with previous reports.¹⁴



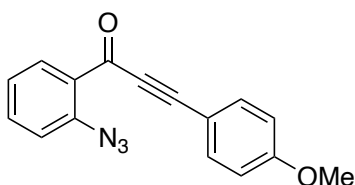
2-(4-Methoxyphenyl)thiochroman-4-one (9): Compound was synthesized using previously reported methods.¹⁵ Spectral data were consistent with previous reports.¹⁵



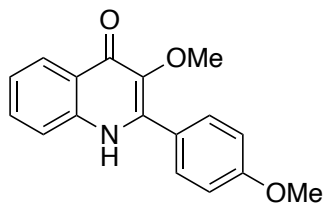
2-Azidobenzaldehyde (12): Compound was synthesized using previously reported methods.¹⁶ Spectral data were consistent with previous reports.¹⁶



1-(2-Azidophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-ol (13): Compound was synthesized using previously reported methods.¹⁶ Spectral data were consistent with previous reports.¹⁶

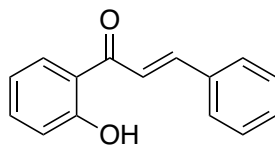


1-(2-Azidophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-one (14): Compound was synthesized using previously reported methods.¹⁶ Spectral data were consistent with previous reports.¹⁶

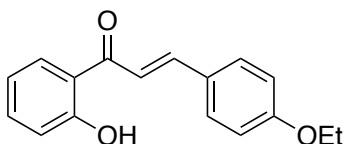


3-Methoxy-2-(4-methoxyphenyl)quinolin-4(1H)-one (15): Compound was synthesized using previously reported methods.¹⁶ Spectral data were consistent with previous reports.¹⁶

Novel Compound Characterization

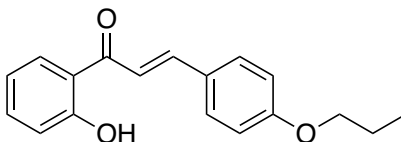


(E)-1-(2-Hydroxyphenyl)-3-phenylprop-2-en-1-one (2b): The general procedure for aldol condensation afforded **2g** as a yellow solid. Yield 39% (436 mg, 1.94 mmol). ^1H NMR (400 MHz, CDCl_3) δ 12.82 (s, 1H), 7.94 (dd, $J = 8.1, 1.7$ Hz, 1H), 7.94 (d, $J = 15.5$ Hz, 1H), 7.71 – 7.66 (m, 3H), 7.51 (ddd, $J = 8.6, 7.2, 1.6$ Hz, 1H), 7.47 – 7.42 (m, 3H), 7.04 (dd, $J = 8.3, 1.2$ Hz, 1H), 6.96 (ddd, $J = 8.2, 7.1, 1.2$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 193.9, 163.7, 145.6, 136.6, 134.7, 131.1, 129.8, 129.2, 128.8, 120.23, 120.1, 119.0, 118.8. UV (λ_{max} nm): 314; IR ν_{max} (cm^{-1}): 3080, 2360, 2342, 1638, 1571; HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{13}\text{O}_2$ $[\text{M}+\text{H}]^+$: 225.0910, found: 225.0919

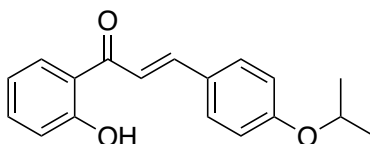


(E)-3-(4-Ethoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2c): The general procedure for aldol condensation afforded **2c** as a yellow solid. Yield 64% (862 mg, 3.21 mmol). ^1H NMR (400 MHz, CDCl_3) δ 12.96 (s, 1H), 7.93 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.91 (d, $J = 15.5$ Hz, 1H), 7.68 – 7.59 (m, 2H), 7.55 (d, $J = 15.4$ Hz, 1H), 7.49 (ddd, $J = 8.6, 7.1, 1.6$ Hz, 1H), 7.03 (dd, $J = 8.4, 1.2$ Hz, 1H), 6.97 – 6.91 (m, 3H), 4.10 (q, $J = 7.0$ Hz, 2H), 1.45 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 193.6, 163.6, 161.5, 145.4, 136.1, 130.6, 129.6, 127.1, 120.1, 118.8,

118.5, 117.3, 115.0, 63.7, 14.7. UV (λ_{max} nm): 364; IR ν_{max} (cm $^{-1}$): 2980, 2359, 2331, 1633, 1603; HRMS (ESI): calcd. for C₁₇H₁₇O₃ [M+H]⁺: 269.1172 found: 269.1179

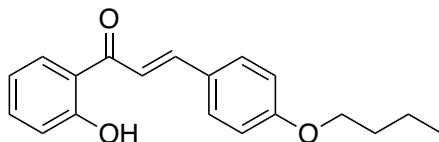


(E)-1-(2-Hydroxyphenyl)-3-(4-propoxyphenyl)prop-2-en-1-one (2d): The general procedure for aldol condensation afforded **2d** as an orange solid. Yield 81% (1.71 g, 6.05mmol). ¹H NMR (400 MHz, CDCl₃) δ 12.96 (s, 1H), 7.93 (dd, J = 8.1, 1.7 Hz, 1H), 7.91 (d, J = 15.4 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.55 (d, J = 15.4 Hz, 1H), 7.49 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H), 7.03 (dd, J = 8.4, 1.2 Hz, 1H), 6.98 – 6.91 (m, 3H), 3.98 (t, J = 6.6 Hz, 2H), 1.91 – 1.78 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 193.7, 163.6, 161.8, 145.6, 136.2, 130.7, 129.6, 127.1, 120.2, 118.8, 118.6, 117.4, 115.1, 69.8, 22.6, 10.6. UV (λ_{max} nm): 360; IR ν_{max} (cm $^{-1}$): 3038, 1693, 1558, 758; HRMS (ESI): calcd. for C₁₈H₁₉O₃ [M+H]⁺: 283.1329 found: 283.1334

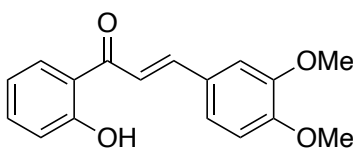


(E)-1-(2-Hydroxyphenyl)-3-(4-isopropoxyphenyl)prop-2-en-1-one (2e): The general procedure for aldol condensation afforded **2e** as a yellow solid. Yield 2% (65 mg, 0.23 mmol). ¹H NMR (400 MHz, CDCl₃) δ 12.97 (s, 1H), 7.93 (dd, J = 8.2, 1.8 Hz, 1H), 7.91 (d, J = 15.4 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.54 (d, J = 15.4 Hz, 1H), 7.49 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 7.02 (dd, J = 8.3, 1.2 Hz, 1H), 6.97 – 6.90 (m, 3H), 4.64 (hept, J = 6.0 Hz, 1H), 1.37 (d, J = 6.0 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 193.8, 163.7, 160.7, 145.6, 136.3, 130.8, 129.7, 127.1, 120.3, 118.9,

118.7, 117.5, 116.1, 70.2, 22.1. UV (λ_{max} nm): 364; IR ν_{max} (cm $^{-1}$): 2974, 2360, 2342, 1636, 1562; HRMS (ESI): calcd. for C₁₈H₁₉O₃ [M+H] $^{+}$: 283.1329, found: 283.1336.



(E)-3-(4-Butoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2f): The general procedure for aldol condensation afforded **2f** as a yellow solid. Yield 81% (1.79 g, 6.05 mmol). ^1H NMR (400 MHz, CDCl₃) δ 12.96 (s, 1H), 7.93 (dd, J = 8.1, 1.7 Hz, 1H), 7.91 (d, J = 15.3 Hz, 1H), 7.64 – 7.61 (m, 2H), 7.54 (d, J = 15.4 Hz, 1H), 7.49 (ddd, J = 8.6, 7.1, 1.6 Hz, 1H), 7.02 (dd, J = 8.4, 1.2 Hz, 1H), 6.98 – 6.90 (m, 3H), 4.02 (t, J = 6.5 Hz, 2H), 1.85 – 1.74 (m, 2H), 1.55 – 1.46 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl₃) δ 193.6, 163.6, 161.7, 145.5, 136.1, 130.6, 129.6, 127.0, 120.1, 118.8, 118.5, 117.2, 114.9, 67.9, 31.2, 19.2, 13.9. UV (λ_{max} nm): 362; IR ν_{max} (cm $^{-1}$): 2951, 2358. 2326, 1634, 1557; HRMS (ESI): calcd. for C₁₉H₂₁O₃ [M+H] $^{+}$: 297.1485 found: 297.1485

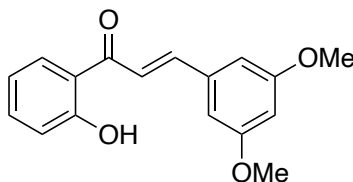


(E)-3-(3,4-Dimethoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2g): The general procedure for aldol condensation afforded **2g** as an orange solid. Yield 37% (532 mg, 1.87 mmol). ^1H NMR (400 MHz, CDCl₃) δ 12.93 (s, 1H), 7.94 (dd, J = 8.1, 1.6 Hz, 1H), 7.90 (d, J = 15.4 Hz, 1H), 7.53 (d, J = 15.4 Hz, 1H), 7.50 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 7.28 (dd, J = 8.4, 2.1 Hz, 1H), 7.18 (d, J = 2.1 Hz, 1H), 7.03 (dd, J = 8.4, 1.1 Hz, 1H), 6.98 – 6.94 (m, 1H), 6.92 (d, J = 8.3 Hz,

1H), 3.98 (s, 3H), 3.95 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 193.7, 163.7, 152.0, 149.4, 145.8, 136.3, 129.7, 127.7, 123.8, 120.2, 118.9, 118.8, 117.9, 111.3, 110.4, 56.2, 56.2. UV (λ_{max} nm): 360; IR_{vmax} (cm⁻¹): 3017, 2360, 2342, 1638, 1566; HRMS (ESI): calcd. for C₁₇H₁₇O₄ [M+H]⁺: 285.1121, found: 285.1129.

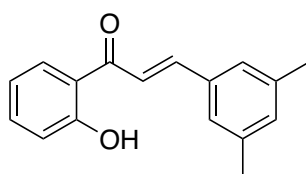


(E)-3-(3,4-Diethoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2h): The general procedure for aldol condensation afforded **2h** as an orange solid. Yield 68% (1.06 g, 3.40 mmol). ¹H NMR (400 MHz, CDCl₃) δ 12.95 (s, 1H), 7.93 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.88 (d, *J* = 15.4 Hz, 1H), 7.51 (d, *J* = 15.3 Hz, 1H), 7.49 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.22 (dd, *J* = 19.0, 2.1 Hz, 2H), 7.03 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.95 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.49 (t, 3H), 1.50 (t, *J* = 7.0 Hz, 3H), 1.49 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 193.7, 163.6, 151.8, 148.9, 145.9, 136.2, 129.6, 127.5, 123.7, 120.2, 118.8, 118.6, 117.6, 112.7, 112.6, 64.8, 64.6, 14.9, 14.8. UV (λ_{max} nm): 376; IR_{vmax} (cm⁻¹): 2982, 1631, 1506, 1139, 1038; HRMS (ESI): calcd. for C₁₉H₂₁O₄ [M+H]⁺: 313.1434, found: 313.1440.

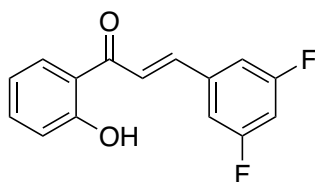


(E)-3-(3,5-Dimethoxyphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2i): The general procedure for aldol condensation afforded **2i** as a yellow orange solid. Yield 38 % (534 mg, 1.88

mmol). ^1H NMR (400 MHz, CDCl_3) δ 12.79 (s, 1H), 7.92 (dd, $J = 8.2, 1.7$ Hz, 1H), 7.84 (d, $J = 15.4$ Hz, 1H), 7.61 (d, $J = 15.4$ Hz, 1H), 7.51 (ddd, $J = 8.6, 7.2, 1.6$ Hz, 1H), 7.04 (dd, $J = 8.4, 1.2$ Hz, 1H), 6.96 (ddd, $J = 8.2, 7.1, 1.2$ Hz, 1H), 6.80 (d, $J = 2.2$ Hz, 2H), 6.55 (t, $J = 2.2$ Hz, 1H), 3.86 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 193.8, 163.7, 161.2, 145.6, 136.6, 136.5, 129.8, 120.7, 120.1, 119.0, 118.7, 106.7, 103.2, 55.6. UV (λ_{max} nm): 214; IR_{vmax} (cm^{-1}): 3015, 2360, 2342, 1637, 1574; HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$: 285.1121, found: 285.112.

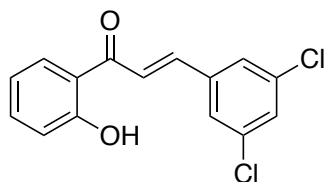


(E)-3-(3,5-Dimethylphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2j): The general procedure for aldol condensation afforded **2j** as an orange brown solid. Yield 49% (622 mg, 2.47 mmol). ^1H NMR (400 MHz, CDCl_3) δ 12.87 (s, 1H), 7.95 (dd, $J = 8.1, 1.6$ Hz, 1H), 7.88 (d, $J = 15.5$ Hz, 1H), 7.65 (d, $J = 15.4$ Hz, 1H), 7.50 (ddd, $J = 8.6, 7.1, 1.6$ Hz, 1H), 7.29 (s, 2H), 7.09 (s, 1H), 7.03 (dd, $J = 8.4, 1.2$ Hz, 1H), 6.95 (ddd, $J = 8.2, 7.1, 1.2$ Hz, 1H), 2.37 (s, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 193.8, 163.7, 145.9, 138.6, 136.3, 134.5, 132.9, 129.7, 126.6, 120.1, 119.6, 118.9, 118.6, 21.3. UV (λ_{max} nm): 210; IR_{vmax} (cm^{-1}): 2915, 1639, 1484, 1201, 1155; HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{17}\text{O}_2$ $[\text{M}+\text{H}]^+$: 253.1223, found: 253.1231.

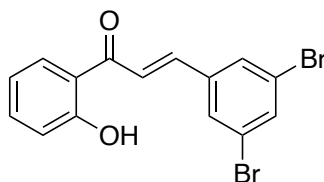


(E)-3-(3,5-Difluorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2l): The general procedure for aldol condensation afforded **2l** as a yellow solid. Yield 5% (67 mg, 0.26 mmol). ^1H

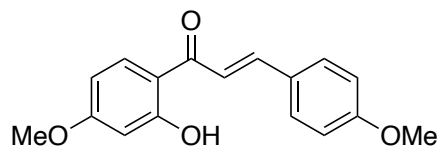
NMR (400 MHz, CDCl₃) δ 12.63 (s, 1H), 7.90 (dd, J = 8.1, 1.7 Hz, 1H), 7.79 (d, J = 15.5 Hz, 1H), 7.63 (d, J = 15.5 Hz, 1H), 7.53 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H), 7.17 (dt, J = 6.4, 2.1 Hz, 2H), 7.05 (dd, J = 8.4, 1.2 Hz, 1H), 6.97 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 6.89 (m, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 193.3, 163.8, 163.4 (dd, J = 249.6, 12.8 Hz), 142.7 (t, J = 3.0 Hz), 138.0 (t, J = 9.5 Hz), 137.0, 129.8, 122.7, 119.9, 119.2, 118.9, 111.3 (dd, J = 19.7, 5.9 Hz), 106.1 (t, J = 25.5 Hz). UV (λ_{max} nm): 202; IR ν_{max} (cm⁻¹): 3098, 2950, 2361, 2342, 1649; HRMS (ESI): calcd. for C₁₅H₁₁F₂O₂ [M+H]⁺: 261.0722, found: 261.0729.



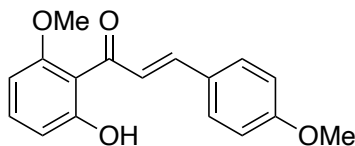
(E)-3-(3,5-Dichlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2m): The general procedure of aldol condensation afforded **2m** as an orange solid. Yield 15% (225 mg, 0.77 mmol). ¹H NMR (500 MHz, CDCl₃) δ 12.62 (d, J = 0.3 Hz, 1H), 7.91 (dd, J = 8.1, 1.6 Hz, 1H), 7.76 (dd, J = 15.5, 0.6 Hz, 1H), 7.65 (d, J = 15.3 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.42 (t, J = 1.8 Hz, 1H), 7.05 (dd, J = 8.4, 1.2 Hz, 1H), 6.97 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 193.1, 163.8, 142.2, 137.7, 137.0, 135.9, 130.5, 129.8, 126.8, 122.8, 119.9, 119.2, 118.9. UV (λ_{max} nm): 208; IR ν_{max} (cm⁻¹): 3061, 2921, 2361, 2342, 1643; HRMS (ESI): calcd. for C₁₅H₁₁Cl₂O₂ [M+H]⁺: 293.0131, found: 293.0129.



(E)-3-(3,5-Dibromophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one (2n): The general procedure for aldol condensation afforded **2n** as a yellow solid. Yield 16% (178 mg, 0.47 mmol). ¹H NMR (400 MHz, CDCl₃) δ 12.62 (s, 1H), 7.91 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.79 – 7.70 (m, 4H), 7.63 (d, *J* = 15.5 Hz, 1H), 7.53 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.05 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.97 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 193.1, 163.8, 142.0, 138.2, 137.0, 135.9, 130.1, 129.8, 123.7, 122.8, 119.9, 119.2, 118.9. UV (λ_{max} nm): 208; IR_{vmax} (cm⁻¹): 3054, 1642, 1567, 1484, 592; HRMS (ESI): calcd. for C₁₅H₁₁Br₂O₂ [M+H]⁺: 380.9120, found: 380.9119.

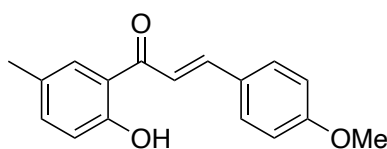


(E)-1-(2-Hydroxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (2o): The general procedure for aldol condensation afforded **2o** as a yellow solid. Yield 54% (764 mg, 2.69 mmol). ¹H NMR (400 MHz, CDCl₃) δ 13.56 (s, 1H), 7.90 – 7.79 (m, 2H), 7.67 – 7.58 (m, 2H), 7.46 (d, *J* = 15.4 Hz, 1H), 7.00 – 6.89 (m, 2H), 6.48 (m, 2H), 3.86 (s, 3H), 3.86 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 191.9, 166.7, 166.1, 161.9, 144.3, 132.4, 131.2, 130.5, 127.6, 117.8, 114.5, 107.7, 101.1, 55.6, 55.5. UV (λ_{max} nm): 362; IR_{vmax} (cm⁻¹): 3079, 1626, 1570, 1361, 1213; HRMS (ESI): calcd. for C₁₇H₁₇O₄ [M+H]⁺: 285.1121 found: 285.1120

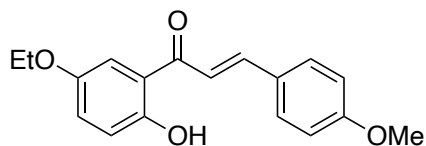


(E)-1-(2-Hydroxy-6-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (2p): The general procedure for aldol condensation afforded **2p** as an orange solid. Yield 48% (686 mg, 2.41

mmol). ^1H NMR (400 MHz, CDCl_3) δ 13.24 (s, 1H), 7.82 (d, $J = 24.5$ Hz, 1H), 7.78 (d, $J = 24.5$ Hz, 1H), 7.62 – 7.55 (m, 2H), 7.35 (t, $J = 8.3$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 1H), 6.62 (dd, $J = 8.4$, 1.0 Hz, 1H), 6.43 (dd, $J = 8.3$, 1.1 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 194.2, 164.8, 161.6, 160.9, 143.1, 135.7, 130.2, 127.9, 125.1, 114.4, 111.9, 110.8, 101.5, 55.8, 55.3. UV (λ_{max} nm): 202; IR_{vmax} (cm^{-1}): 3019, 1626, 1556, 1236, 1170; HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$: 299.1278 found: 299.1282.

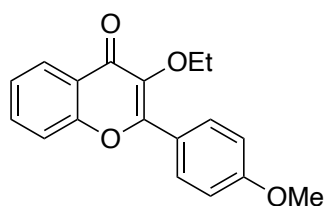


(E)-1-(2-Hydroxy-5-methylphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (2r): The general procedure for aldol condensation afforded **2r** as an orange solid. Yield 49% (983 mg, 3.66 mmol). ^1H NMR (400 MHz, CDCl_3) δ 12.79 (s, 1H), 7.92 (d, $J = 15.4$ Hz, 1H), 7.72 (d, $J = 2.1$ Hz, 1H), 7.70 – 7.65 (m, 2H), 7.57 (d, $J = 15.4$ Hz, 1H), 7.33 (dd, $J = 8.4$, 2.1 Hz, 1H), 6.99 (d, $J = 8.7$ Hz, 2H), 6.96 (d, $J = 8.5$ Hz, 1H), 3.90 (d, $J = 0.8$ Hz, 3H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 193.4, 161.9, 161.4, 145.0, 137.1, 130.5, 129.2, 127.7, 127.2, 119.6, 118.1, 117.4, 114.4, 55.3, 20.5. UV (λ_{max} nm): 356; IR_{vmax} (cm^{-1}): 2999, 1632, 1602, 1574, 1165; HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 269.1172 found: 269.1180

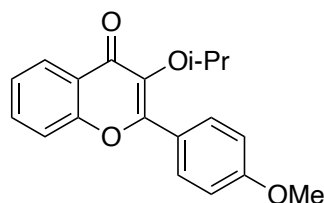


(E)-1-(5-Ethoxy-2-hydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (2s): The general procedure for aldol condensation afforded **2s** as an orange solid. Yield 73% (1.31 mg, 4.38

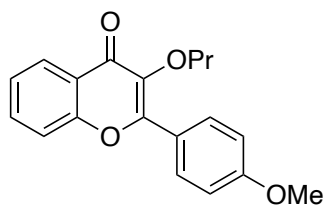
mmol). ^1H NMR (400 MHz, CDCl_3) δ 12.47 (s, 1H), 7.90 (d, $J = 15.4$ Hz, 1H), 7.63 (d, $J = 8.8$ Hz, 2H), 7.48 (d, $J = 15.3$ Hz, 1H), 7.38 (d, $J = 3.0$ Hz, 1H), 7.13 (dd, $J = 9.0, 3.0$ Hz, 1H), 6.98 – 6.93 (m, 3H), 4.05 (q, $J = 7.0$ Hz, 2H), 3.87 (s, 3H), 1.44 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 193.3, 162.0, 157.8, 151.0, 145.4, 130.6, 127.3, 124.1, 119.8, 119.1, 117.5, 114.5, 114.0, 64.5, 55.4, 15.0. UV (λ_{max} nm): 202; IR_{vmax} (cm^{-1}): 2978, 2359, 2342, 1634, 1551; HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$: 299.1278 found: 299.1278.



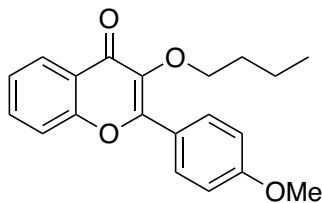
3-Ethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3a): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2a** and ethyl iodide afforded **3a** as a pale-yellow solid. Yield 66% (94 mg, 0.32 mmol). ^1H NMR (500 MHz, CDCl_3) δ 8.29 (dd, $J = 8.0, 1.7$ Hz, 1H), 8.05 (d, $J = 9.0$ Hz, 2H), 7.66 (ddt, $J = 8.5, 7.1, 1.5$ Hz, 1H), 7.51 (dd, $J = 8.5, 1.2$ Hz, 1H), 7.43 – 7.36 (m, 3H), 7.28 (dd, $J = 5.1, 2.1$ Hz, 3H), 6.97 (d, $J = 9.0$ Hz, 2H), 5.12 (s, 2H), 3.89 (s, 3H), 1.33 (t, 3H) ^{13}C NMR (126 MHz, CDCl_3) δ 175.1, 161.6, 156.5, 155.3, 139.4, 136.9, 133.4, 130.7, 129.0, 128.3, 128.2, 125.9, 124.7, 124.3, 123.4, 118.0, 113.9, 74.1, 55.5. UV (λ_{max} nm): 226; IR_{vmax} (cm^{-1}): 2974, 2360, 2341, 1638, 1601; HRMS (ESI): calcd. for $\text{C}_{23}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$: 359.1278, found: 359.1283.



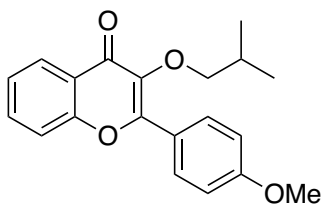
3-Isopropoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one (3c): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2a** and 2-iodopropane afforded **3c** as a pale-yellow solid. Yield 35% (52 mg, 0.17 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.17 (d, *J* = 9.0 Hz, 2H), 7.66 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.52 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.39 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.01 (d, *J* = 9.1 Hz, 2H), 4.68 (sep, *J* = 6.2 Hz, 1H), 3.90 (s, 3H), 1.20 (d, *J* = 6.2 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 175.5, 161.4, 156.4, 155.3, 138.7, 133.2, 130.8, 125.9, 124.6, 124.2, 124.0, 118.0, 113.7, 74.8, 55.5, 22.6. UV (λ_{max} nm): 330; IR_{vmax} (cm⁻¹): 2981, 2360, 2342, 1632, 1601; HRMS (ESI): calcd. for C₁₉H₁₉O₄ [M+H]⁺: 311.1278, found: 311.1280.



2-(4-Methoxyphenyl)-3-propoxy-4*H*-chromen-4-one (3d): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2a** and 1-iodopropane afforded **3d** as an egg-shell white solid. Yield 56% (82 mg, 0.26 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.13 (d, *J* = 8.9 Hz, 2H), 7.65 (ddd, *J* = 8.7, 7.0, 1.7 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 4.00 (t, *J* = 6.8 Hz, 2H), 3.89 (s, 3H), 1.75 (h, *J* = 7.2 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 175.1, 161.4, 155.8, 155.2, 140.0, 133.2, 130.4, 125.7, 124.5, 124.2, 123.5, 117.9, 113.8, 74.2, 55.4, 23.4, 10.5. UV (λ_{max} nm): 202; IR_{vmax} (cm⁻¹): 2968, 2360, 2341, 1635, 1601; HRMS (ESI): calcd. for C₁₉H₁₉O₄ [M+H]⁺: 311.1278, found: 311.1292.

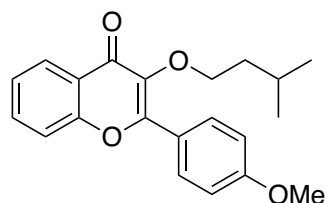


3-Butoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3e): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2a** and 1-iodobutane afforded **3e** as a cream colored solid. Yield 67% (103 mg, 0.32 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.12 (d, *J* = 9.0 Hz, 2H), 7.65 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.51 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.37 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 2H), 4.03 (t, *J* = 6.7 Hz, 2H), 3.89 (s, 3H), 1.77 – 1.65 (m, 2H), 1.47 – 1.33 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 175.2, 161.5, 155.9, 155.3, 140.2, 133.3, 130.5, 125.9, 124.6, 124.3, 123.6, 118.0, 113.9, 72.4, 55.5, 32.3, 19.2, 14.0. UV (λ_{\max} nm): 204; IR_{vmax} (cm⁻¹): 2936, 2362, 2332, 1638, 1602; HRMS (ESI): calcd. for C₂₀H₂₁O₄ [M+H]⁺: 325.1434, found: 325.143.

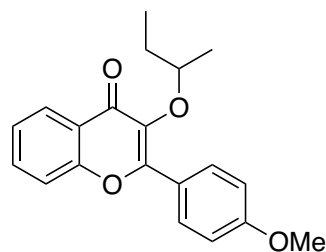


3-Isobutoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3f): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2a** and 2-iodo-2-methylpropane afforded **3f** as an orange oil. Yield 32% (50 mg, 0.15 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.14 – 8.08 (m, 2H), 7.66 (ddt, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.39 (tt, *J* = 8.0, 1.0 Hz, 1H), 7.05 – 7.00 (m, 2H), 3.90 (d, *J* = 0.9 Hz, 3H), 3.79 (d, *J* = 6.6 Hz, 2H), 2.06 (hept, *J* = 6.7 Hz, 1H), 0.96 (dd, *J* = 6.7, 0.9 Hz, 6H). ¹³C NMR (126 MHz,

CDCl₃) δ 175.2, 161.6, 156.0, 155.3, 140.3, 133.3, 130.6, 125.9, 124.7, 124.4, 123.5, 118.0, 113.9, 79.1, 55.5, 29.2, 19.4. UV (λ_{\max} nm): 328; IR ν_{\max} (cm⁻¹): 2947, 2361, 2342, 1637, 1600; HRMS (ESI): calcd. for C₂₀H₂₁O₄ [M+H]⁺: 325.1434, found: 325.1431.

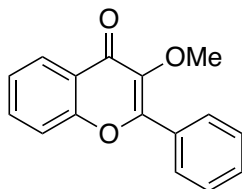


3-(Isopentyloxy)-2-(4-methoxyphenyl)-4H-chromen-4-one (3g): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2a** and 1-iodo-3-methylbutane afforded **3g** as an orange oil. Yield 35% (56 mg, 0.17 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.26 (dd, J = 8.0, 1.7 Hz, 1H), 8.17 – 8.09 (m, 2H), 7.67 (ddd, J = 8.6, 7.0, 1.7 Hz, 1H), 7.53 (dd, J = 8.5, 1.1 Hz, 1H), 7.40 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 7.07 – 6.99 (m, 2H), 4.05 (t, J = 6.8 Hz, 2H), 3.90 (s, 3H), 1.77 (dp, J = 13.3, 6.7 Hz, 1H), 1.62 (m, 2H), 0.88 (d, J = 6.6 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 175.3, 161.5, 156.0, 155.3, 140.2, 133.3, 130.5, 125.9, 124.6, 124.3, 123.6, 118.0, 113.9, 71.2, 55.5, 39.0, 25.0, 22.7. UV (λ_{\max} nm): 324; IR ν_{\max} (cm⁻¹): 2955, 2361, 2342, 1637, 1602; HRMS (ESI): calcd. for C₂₁H₂₃O₄ [M+H]⁺: 339.1591 found: 339.1601.

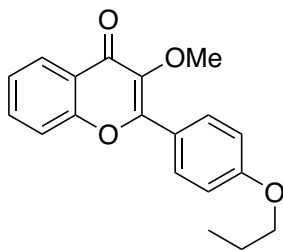


3-(Sec-butoxy)-2-(4-methoxyphenyl)-4H-chromen-4-one (3h): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2a** and 2-bromobutane afforded

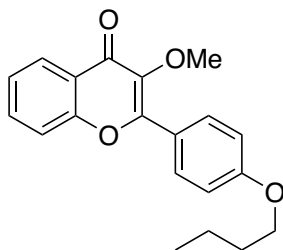
3h as an orange oil. Yield 20% (30 mg, 0.09mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.22 – 8.14 (m, 2H), 8.07 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.58 (td, $J = 7.8, 1.7$ Hz, 1H), 7.35 (td, $J = 7.6, 1.2$ Hz, 1H), 7.20 (dd, $J = 8.1, 1.2$ Hz, 1H), 7.03 – 6.94 (m, 2H), 4.98 (h, $J = 6.3$ Hz, 1H), 3.91 (s, 3H), 1.51 – 1.31 (m, 2H), 1.10 (d, $J = 6.3$ Hz, 3H), 0.82 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.6, 161.4, 156.5, 155.3, 138.7, 133.3, 130.9, 125.9, 124.6, 124.2, 124.0, 118.0, 113.7, 79.3, 55.5, 29.6, 19.2, 9.8. UV (λ_{max} nm): 202; $\text{IR}_{\nu_{\text{max}}}$ (cm^{-1}): 2968, 2361, 2342, 1635, 1602; HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}]^+$: 325.1434 found: 325.1435.



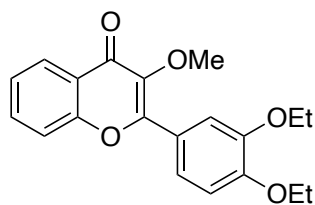
3-Methoxy-2-phenyl-4H-chromen-4-one (3i): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2b** and methyl iodide afforded **3i** as a rusty orange solid. Yield 9% (10 mg, 0.04 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.28 (dd, $J = 7.9, 1.7$ Hz, 1H), 8.13 – 8.09 (m, 2H), 7.69 (ddd, $J = 8.7, 7.1, 1.7$ Hz, 1H), 7.57 – 7.50 (m, 4H), 7.41 (ddd, $J = 8.1, 7.1, 1.1$ Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.3, 155.8, 155.4, 141.7, 133.6, 131.1, 130.9, 128.7, 128.6, 126.0, 124.8, 124.4, 118.1, 60.3. UV (λ_{max} nm): 202; $\text{IR}_{\nu_{\text{max}}}$ (cm^{-1}): 2924, 2360, 2342, 1638, 1607; HRMS (ESI): calcd. for $\text{C}_{16}\text{H}_{13}\text{O}_3$ $[\text{M}+\text{H}]^+$: 253.0859, found: 253.0868.



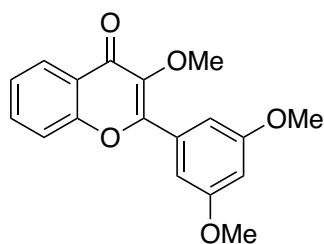
3-Methoxy-2-(4-propoxyphenyl)-4H-chromen-4-one (3k): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2d** and methyl iodide afforded **3k** as a pale-yellow solid. Yield 23% (54 mg, 0.17 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (dd, $J = 8.0, 1.7$ Hz, 1H), 8.15 – 8.07 (m, 2H), 7.67 (ddd, $J = 8.7, 7.0, 1.7$ Hz, 1H), 7.53 (d, $J = 8.3$ Hz, 1H), 7.44 – 7.35 (m, 1H), 7.07 – 6.98 (m, 2H), 4.02 (t, $J = 6.6$ Hz, 2H), 3.89 (s, 3H), 1.86 (m, 2H), 1.07 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.1, 161.3, 155.8, 155.3, 140.9, 133.4, 130.4, 125.9, 124.7, 124.3, 123.1, 118.0, 114.6, 77.5, 77.2, 76.8, 69.8, 60.0, 22.6, 10.6. UV (λ_{max} nm): 202; IR_{vmax} (cm^{-1}): 2958, 2360, 2342, 1628, 1601; HRMS (ESI): calcd. for $\text{C}_{19}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$: 311.1278, found: 311.1273.



2-(4-Butoxyphenyl)-3-methoxy-4H-chromen-4-one (3m) Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2f** and methyl iodide afforded **3m** as a pale-yellow solid. Yield 26% (78 mg, 0.24 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (dd, $J = 8.0, 1.7$ Hz, 1H), 8.15 – 8.07 (m, 2H), 7.67 (ddd, $J = 8.7, 7.1, 1.7$ Hz, 1H), 7.53 (dd, $J = 8.5, 1.1$ Hz, 1H), 7.39 (ddd, $J = 8.1, 7.0, 1.1$ Hz, 1H), 7.06 – 6.98 (m, 2H), 4.06 (t, $J = 6.5$ Hz, 2H), 3.89 (s, 3H), 1.82 (dq, $J = 7.9, 6.4$ Hz, 2H), 1.52 (h, $J = 7.7$ Hz, 2H), 1.00 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.0, 161.2, 155.7, 155.2, 140.8, 133.3, 130.2, 125.8, 124.6, 124.2, 123.0, 117.9, 114.5, 67.9, 59.9, 31.2, 19.25, 13.9. UV (λ_{max} nm): 202; IR_{vmax} (cm^{-1}): 2960, 2360, 2342, 1627, 1601; HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}]^+$: 325.1434, found: 325.1434.

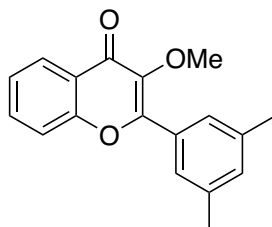


2-(3,4-Diethoxyphenyl)-3-methoxy-4H-chromen-4-one (3o): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2h** and methyl iodide afforded **3o** as a pale-yellow solid. Yield 5% (16 mg, 0.05 mmol). ^1H NMR (800 MHz, CDCl_3) δ 8.27 (dd, $J = 7.9, 1.6$ Hz, 1H), 7.76 (d, $J = 2.1$ Hz, 1H), 7.75 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.67 (ddd, $J = 8.6, 7.0, 1.6$ Hz, 1H), 7.54 (dd, $J = 8.4, 0.9$ Hz, 1H), 7.40 (ddd, $J = 8.1, 7.0, 1.0$ Hz, 1H), 7.00 (d, $J = 8.5$ Hz, 1H), 4.20 (q, $J = 6.9$ Hz, 2H), 4.19 (q, $J = 7.0$ Hz, 2H), 3.88 (s, 3H), 1.51 (t, $J = 7.0$ Hz, 3H), 1.51 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (201 MHz, CDCl_3) δ 175.2, 156.0, 155.3, 151.3, 148.3, 141.0, 133.5, 126.0, 124.8, 124.3, 123.3, 122.4, 118.0, 113.8, 112.5, 64.9, 64.6, 60.1, 14.9, 14.9. UV (λ_{max} nm): 244; IR_{vmax} (cm^{-1}): 2980, 2361, 2342, 1634, 1600; HRMS (ESI): calcd. for $\text{C}_{20}\text{H}_{21}\text{O}_5$ $[\text{M}+\text{H}]^+$: 341.1384, found: 341.1376.

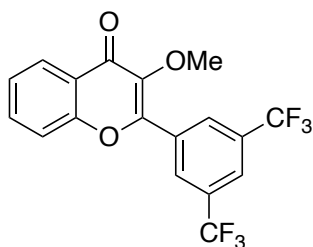


2-(3,5-Dimethoxyphenyl)-3-methoxy-4H-chromen-4-one (3p): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2i** and methyl iodide afforded **3p** as a tan solid. Yield 21% (32 mg, 0.10 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (dd, $J = 8.0, 1.7$ Hz, 1H), 7.69 (ddd, $J = 8.7, 7.1, 1.7$ Hz, 1H), 7.54 (dd, $J = 8.5, 1.1$ Hz, 1H), 7.41 (ddd, $J = 8.0, 7.1, 1.1$ Hz, 1H), 7.29 (d, $J = 2.3$ Hz, 2H), 6.62 (t, $J = 2.3$ Hz, 1H), 3.90 (s, 3H), 3.88 (s, 6H). ^{13}C

NMR (101 MHz, CDCl₃) δ 175.3, 160.8, 155.4, 155.3, 141.8, 133.7, 132.7, 125.9, 124.8, 124.3, 118.2, 106.8, 103.0, 60.3, 55.7. UV (λ_{max} nm): 204; IR ν_{max} (cm⁻¹): 2925, 2360, 2342, 1632, 1602; HRMS (ESI): calcd. for C₁₈H₁₇O₅ [M+H]⁺: 313.1071, found: 313.1079.

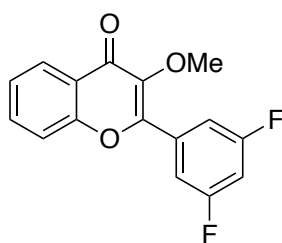


2-(3,5-Dimethylphenyl)-3-methoxy-4H-chromen-4-one (3q): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2j**, and methyl iodide afforded **3q** as an off-white solid. Yield 4% (12 mg, 0.04 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.28 (dd, J = 8.0, 1.6 Hz, 1H), 7.70 – 7.66 (m, 3H), 7.55 (dd, J = 8.6, 1.1 Hz, 1H), 7.40 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 7.16 (t, J = 1.8 Hz, 1H), 3.89 (s, 3H), 2.43 – 2.41 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 175.3, 156.4, 155.5, 141.6, 138.2, 133.5, 132.6, 130.9, 126.4, 126.0, 124.8, 124.4, 118.2, 60.3, 21.6. UV (λ_{max} nm): 208; IR ν_{max} (cm⁻¹): 2917, 2361, 2342, 1632, 1608; HRMS (ESI): calcd. for C₁₈H₁₇O₃ [M+H]⁺: 281.1172, found: 281.1166.

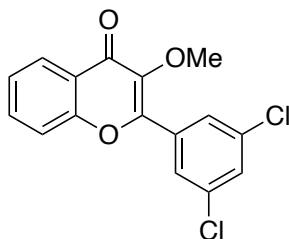


2-(3,5-Bis(trifluoromethyl)phenyl)-3-methoxy-4H-chromen-4-one (3r): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2k** and methyl iodide afforded **3r** as an off-white solid. Yield 8% (14 mg, 0.04 mmol). ¹H NMR (400 MHz, CDCl₃) δ

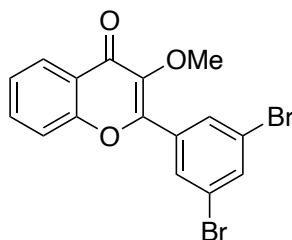
8.60 (d, $J = 1.6$ Hz, 2H), 8.28 (dd, $J = 8.0, 1.7$ Hz, 1H), 8.01 (s, 1H), 7.75 (ddd, $J = 8.7, 7.1, 1.7$ Hz, 1H), 7.65 – 7.58 (m, 1H), 7.55 – 7.36 (m, 1H), 4.00 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.03, 155.24, 151.65, 142.53, 134.29, 133.22, 132.27 (q, $J = 33.8$ Hz), 128.60 (d, $J = 4.1$ Hz), 126.13, 125.40, 124.25, 124.19 – 123.95 (m), 123.21 (q, $J = 272.9$ Hz), 118.22, 60.51. UV (λ_{max} nm): 204; IR_{vmax} (cm^{-1}): 1957, 2361, 2342, 1638, 1134; HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{11}\text{F}_6\text{O}_3$ $[\text{M}+\text{H}]^+$: 389.0607, found: 389.0624.



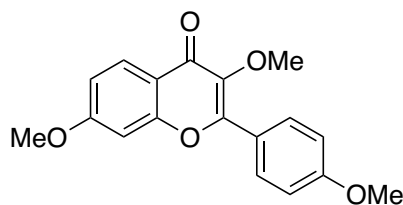
2-(3,5-Difluorophenyl)-3-methoxy-4H-chromen-4-one (3s): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2l** and methyl iodide afforded **3s** as an off-white solid. Yield 16% (15 mg, 0.05 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (dd, $J = 8.1, 1.7$ Hz, 1H), 7.72 (m 3H), 7.55 (dd, $J = 8.5, 1.2$ Hz, 1H), 7.43 (ddd, $J = 8.1, 7.1, 1.0$ Hz, 1H), 6.97 (tt, $J = 8.6, 2.4$ Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.2, 163.1 (dd, $J = 248.3, 12.7$ Hz), 155.2, 152.5, 142.4, 134.1, 133.9 (t, $J = 10.3$ Hz), 126.1, 125.2, 124.2, 118.1, 111.7 (dd, $J = 21.7, 6.8$ Hz), 106.2 (t, $J = 25.3$ Hz), 60.4. UV (λ_{max} nm): 202; IR_{vmax} (cm^{-1}): 2950, 2361, 2342, 1649, 751; HRMS (ESI): calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 289.0671, found: 289.0677.



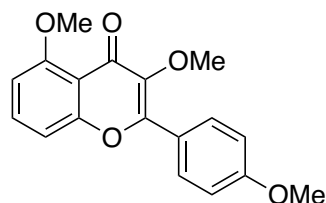
2-(3,5-Dichlorophenyl)-3-methoxy-4H-chromen-4-one (3t): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2m** and methyl iodide afforded **3t** as a white solid. Yield 31% (46 mg, 0.14 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.27 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.02 (d, *J* = 2.0 Hz, 2H), 7.72 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 1.9 Hz, 1H), 7.43 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 3.96 (s, 3H). ¹³C NMR (201 MHz, CDCl₃) δ 175.1, 155.3, 152.4, 142.3, 135.5, 134.1, 133.8, 130.6, 126.9, 126.1, 125.2, 124.2, 118.2, 60.5. UV (λ_{max} nm): 202; IR_vmax (cm⁻¹): 2947, 2360, 2342, 1649, 1135; HRMS (ESI): calcd. for C₁₆H₁₁Cl₂O₃ [M+H]⁺: 321.0080, found: 321.0073.



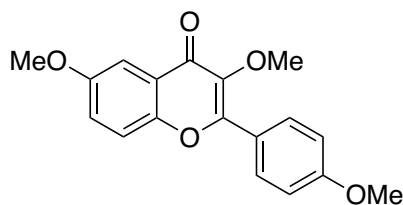
2-(3,5-Dibromophenyl)-3-methoxy-4H-chromen-4-one (3u): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2n** and methyl iodide afforded **3u** as a pale-yellow solid. Yield 3% (7 mg, 0.02 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.26 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.21 (d, *J* = 1.8 Hz, 2H), 7.80 (t, *J* = 1.8 Hz, 1H), 7.72 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.57 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.43 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 3.96 (s, 3H). ¹³C NMR (201 MHz, CDCl₃) δ 175.1, 155.3, 152.2, 142.3, 136.0, 134.3, 134.1, 130.2, 126.1, 125.2, 124.2, 123.2, 118.2, 60.5. UV (λ_{max} nm): 202; IR_vmax (cm⁻¹): 2919, 2360, 2342, 1652, 1023; HRMS (ESI): calcd. for C₁₆H₁₁Br₂O₃ [M+H]⁺: 408.9069, found: 408.9060.



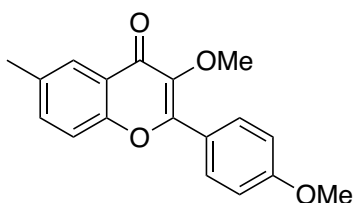
3,7-Dimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3v): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2o** and methyl iodide afforded **3v** as an off-white solid. Yield 12% (20 mg, 0.06 mmol). ^1H NMR (400 MHz, CD_3OD) δ 8.17 – 8.11 (m, 2H), 8.07 (d, $J = 9.0$ Hz, 1H), 7.17 (d, $J = 2.4$ Hz, 1H), 7.13 – 7.08 (m, 2H), 7.06 (dd, $J = 9.0, 2.4$ Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.7, 164.1, 161.5, 157.1, 155.4, 140.8, 130.2, 127.3, 123.5, 118.2, 114.4, 114.1, 100.0, 60.1, 56.0, 55.6. UV (λ_{max} nm): 202; IR_{vmax} (cm^{-1}): 2915, 2361, 2342, 1606, 1258; HRMS (ESI): calcd. for $\text{C}_{19}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}]^+$: 313.1071, found: 313.1074.



3,5-Dimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3w) Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2p** and methyl iodide afforded **3w** as a pale-yellow solid. Yield 4% (18 mg, 0.06 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.14 – 8.07 (m, 2H), 7.54 (t, $J = 8.4$ Hz, 1H), 7.06 – 6.99 (m, 2H), 6.79 (d, $J = 8.2$ Hz, 1H), 4.01 (s, 3H), 3.89 (d, $J = 3.9$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.0, 161.5, 160.1, 157.4, 153.4, 141.5, 133.5, 130.2, 123.3, 114.9, 114.1, 110.2, 105.7, 60.0, 56.6, 55.6. UV (λ_{max} nm): 202; IR_{vmax} (cm^{-1}): 2917, 2361, 2342, 1637, 1600; HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_5$ $[\text{M}+\text{H}]^+$: 313.1071, found: 313.1078.

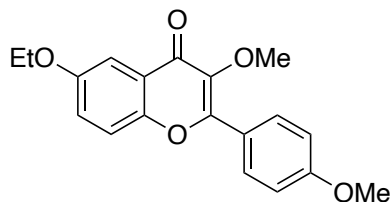


3,6-Dimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3x): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2q** and methyl iodide afforded **3x** as a tan solid. Yield 37% (72 mg, 0.23 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.15 – 8.07 (m, 2H), 7.61 (d, $J = 3.1$ Hz, 1H), 7.46 (d, $J = 9.2$ Hz, 1H), 7.26 (dd, $J = 9.2, 3.0$ Hz, 1H), 7.06 – 7.00 (m, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 174.8, 161.5, 156.6, 155.5, 150.2, 140.6, 130.3, 124.9, 123.7, 123.4, 119.4, 114.1, 104.6, 60.0, 56.0, 55.5. UV (λ_{max} nm): 330; IR_{vmax} (cm^{-1}): 2926, 2360, 2342, 1158, 1611; HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{17}\text{O}_5$ $[\text{M}+\text{H}]^+$: 313.1071, found: 313.1075.

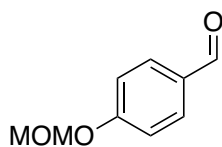


3-Methoxy-2-(4-methoxyphenyl)-6-methyl-4H-chromen-4-one (3y): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2r** and methyl iodide afforded **3y** as a tan solid. Yield 47% (90 mg, 0.30 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.16 – 8.08 (m, 2H), 8.05 (d, $J = 2.6$ Hz, 1H), 7.48 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.42 (d, $J = 8.6$ Hz, 1H), 7.07 – 6.99 (m, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 175.0, 161.5, 155.5, 153.5, 140.8, 134.7, 134.5, 130.3, 125.0, 123.9, 123.4, 117.7, 114.0, 60.0, 55.5, 21.0.

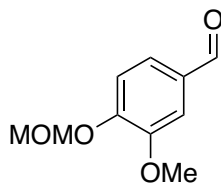
UV (λ_{\max} nm): 202; IR ν_{\max} (cm⁻¹): 2918, 2360, 2342, 1604, 1024; HRMS (ESI): calcd. for C₁₈H₁₇O₄ [M+H]⁺: 297.1121, found: 297.1124.



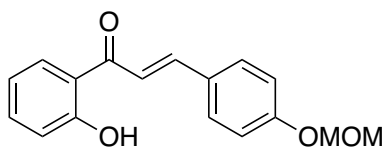
6-Ethoxy-3-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (3z): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2s** and methyl iodide afforded **3z** as an off-white solid. Yield 8% (19 mg, 0.06 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, J = 9.1 Hz, 2H), 7.59 (d, J = 3.1 Hz, 1H), 7.45 (d, J = 9.1 Hz, 1H), 7.25 (d, J = 12.2 Hz, 1H), 7.03 (d, J = 9.0 Hz, 2H), 4.15 (q, J = 7.0 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 174.9, 161.6, 156.0, 155.6, 150.1, 140.6, 130.4, 124.9, 124.1, 123.5, 119.4, 114.1, 105.3, 64.3, 60.1, 55.6, 14.9. UV (λ_{\max} nm): 202; IR ν_{\max} (cm⁻¹): 2937, 2361, 2342, 1634, 1606; HRMS (ESI): calcd. for C₁₉H₁₉O₅ [M+H]⁺: 327.1227, found: 327.1237.



4-(Methoxymethoxy)benzaldehyde (5a): Following the general procedure for MOM protection with 4-hydroxybenzaldehyde afforded **5a** as an egg white colored oil. Yield 95% (1.30 g, 7.82 mmol). ¹H NMR (400 MHz, CDCl₃) δ 9.90 (s, 1H), 7.88 – 7.79 (m, 2H), 7.19 – 7.10 (m, 2H), 5.25 (s, 2H), 3.49 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 190.9, 162.2, 131.9, 130.8, 116.3, 94.1, 77.4, 77.2, 76.9, 56.4. UV (λ_{\max} nm): 266; IR ν_{\max} (cm⁻¹): 2829, 2361, 2342, 1683, 975; HRMS (ESI): calcd. for C₉H₁₁O₃ [M+H]⁺: 167.0703, found: 167.0710.

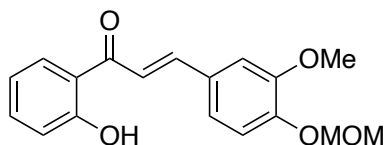


3-Methoxy-4-(methoxymethoxy)benzaldehyde (5b): Following the general procedure for MOM protection with 4-hydroxy-3-methoxybenzaldehyde afforded **5b** as a white solid. Yield 98% (128 mg, 0.65 mmol). ^1H NMR (400 MHz, CDCl_3) δ 9.84 (s, 1H), 7.40 (dd, $J = 7.2, 1.7$ Hz, 2H), 7.27 – 7.22 (m, 1H), 5.30 (s, 2H), 3.93 (s, 3H), 3.50 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 191.1, 152.1, 150.2, 131.2, 126.6, 114.8, 109.6, 95.1, 56.7, 56.2. UV (λ_{max} nm): 224; IR_{vmax} (cm^{-1}): 2931, 2361, 2342, 1681, 970; HRMS (ESI): calcd. for $\text{C}_{10}\text{H}_{13}\text{O}_4$ $[\text{M}+\text{H}]^+$: 197.0808, found: 197.0805.



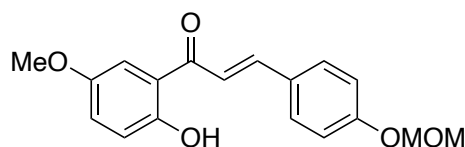
(E)-1-(2-Hydroxyphenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one (6a):

Following the general procedure for aldol condensation using **5a** afforded **6a** as an orange oil. Yield 13% (283 mg, 1.00 mmol). ^1H NMR (400 MHz, CDCl_3) δ 12.92 (s, 1H), 7.95 – 7.87 (m, 2H), 7.66 – 7.60 (m, 2H), 7.56 (d, $J = 15.4$ Hz, 1H), 7.50 (ddd, $J = 8.6, 7.1, 1.6$ Hz, 1H), 7.12 – 7.07 (m, 2H), 7.03 (dd, $J = 8.3, 1.2$ Hz, 1H), 6.95 (ddd, $J = 8.3, 7.2, 1.2$ Hz, 1H), 5.24 (s, 2H), 3.50 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 193.8, 163.7, 159.7, 145.4, 136.4, 130.6, 129.7, 128.5, 120.2, 118.9, 118.8, 118.2, 116.7, 94.3, 56.4. UV (λ_{max} nm): 358; IR_{vmax} (cm^{-1}): 2924, 2361, 2342, 1563, 1148; HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$: 285.1121, found: 285.1120.



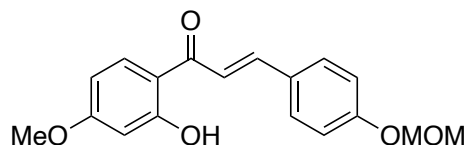
(E)-1-(2-Hydroxyphenyl)-3-(3-methoxy-4-(methoxymethoxy)phenyl)prop-2-en-1-one

(6b): Following the general procedure for aldol condensation using **5b** afforded **6b** as a yellow solid. Yield 17% (370 mg, 1.18 mmol). ¹H NMR (400 MHz, CDCl₃) δ 12.90 (s, 1H), 7.94 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.89 (d, *J* = 15.4 Hz, 1H), 7.54 (d, *J* = 15.4 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.26 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 1.9 Hz, 1H), 7.03 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.00 – 6.91 (m, 1H), 5.30 (s, 2H), 3.97 (s, 3H), 3.53 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 193.8, 163.7, 150.0, 149.4, 145.6, 136.4, 129.7, 129.1, 123.1, 120.2, 118.9, 118.8, 118.5, 115.9, 111.3, 95.3, 56.6, 56.2. UV (λ_{max} nm): 368; IR_{vmax} (cm⁻¹): 2961, 2360, 2342, 1635, 996; HRMS (ESI): calcd. for C₁₈H₁₉O₅ [M+H]⁺: 315.1227, found: 315.1223.



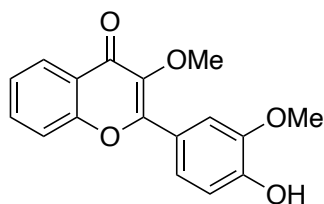
(E)-1-(2-Hydroxy-5-methoxyphenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one

(6c): Following the general procedure for aldol condensation using **5a** afforded **6c** as an orange solid. Yield 40% (952 mg, 3.03 mmol). ¹H NMR (400 MHz, CDCl₃) δ 12.46 (s, 1H), 7.90 (d, *J* = 15.4 Hz, 1H), 7.68 – 7.58 (m, 2H), 7.49 (d, *J* = 15.4 Hz, 1H), 7.36 (d, *J* = 3.1 Hz, 1H), 7.14 (dd, *J* = 9.1, 3.0 Hz, 1H), 7.11 – 7.07 (m, 2H), 6.98 (d, *J* = 9.0 Hz, 1H), 5.24 (s, 2H), 3.85 (s, 3H), 3.50 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 193.2, 159.6, 157.9, 151.7, 145.3, 130.5, 128.3, 123.6, 119.7, 119.2, 118.0, 116.6, 112.8, 94.1, 56.2, 56.0. UV (λ_{max} nm): 202; IR_{vmax} (cm⁻¹): 2899, 1643, 1568, 1148, 999; HRMS (ESI): calcd. for C₁₈H₁₉O₅ [M+H]⁺: 315.1227 found: 315.1234.



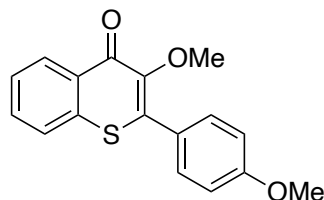
(E)-1-(2-Hydroxy-4-methoxyphenyl)-3-(4-(methoxymethoxy)phenyl)prop-2-en-1-one

(6d): Following the general procedure for aldol condensation using **5a** afforded **6d** as an orange solid. Yield 49% (1.16 g, 3.68 mmol). ^1H NMR (400 MHz, CDCl_3) δ 13.53 (s, 1H), 7.90 – 7.79 (m, 2H), 7.65 – 7.57 (m, 2H), 7.47 (d, $J = 15.4$ Hz, 1H), 7.14 – 7.03 (m, 2H), 6.49 (d, $J = 8.4$ Hz, 2H), 5.23 (s, 2H), 3.86 (s, 3H), 3.50 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 191.6, 166.5, 165.9, 159.2, 143.9, 131.1, 130.2, 128.3, 118.0, 116.4, 114.0, 107.4, 101.0, 94.0, 56.0, 55.3. UV (λ_{max} nm): 358; IR_{vmax} (cm^{-1}): 2977, 1798, 1739, 1364, 1148; HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{19}\text{O}_5$ $[\text{M}+\text{H}]^+$: 315.1227 found: 315.1227.



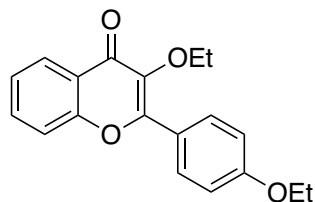
2-(4-Hydroxy-3-methoxyphenyl)-3-methoxy-4H-chromen-4-one (7b): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation with **6b** and methyl iodide, followed by MOM deprotection afforded **7b** as a light pink solid. Yield 10% (16 mg, 0.05 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (dd, $J = 8.0, 1.7$ Hz, 1H), 7.77 (d, $J = 2.0$ Hz, 1H), 7.73 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.68 (ddd, $J = 8.7, 7.1, 1.7$ Hz, 1H), 7.54 (dd, $J = 8.0, 0.9$ Hz, 1H), 7.41 (ddd, $J = 8.1, 7.1, 1.1$ Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 1H), 5.97 (s, 1H), 3.99 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (201 MHz, CDCl_3) δ 175.1, 155.8, 155.3, 148.3, 146.4, 141.0, 133.5, 126.0, 124.8, 124.3,

123.1, 122.9, 118.0, 114.7, 111.2, 60.1, 56.3. UV (λ_{max} nm): 202; IR ν_{max} (cm $^{-1}$): 3290, 2360, 2342, 1633, 1207; HRMS (ESI): calcd. for C $_{17}$ H $_{15}$ O $_5$ [M+H] $^{+}$: 299.0914, found: 299.0919.

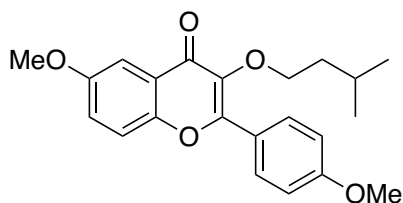


3-Methoxy-2-(4-methoxyphenyl)-4H-thiophen-4-one (10): Compound was synthesized using previously reported methods.¹⁵ Compound **9** (1.1 mmol) was dissolved in 1,4-dioxane (5 mL). Selenium dioxide (1.1 equiv.) was dissolved in water (150 μ L) and added to the reaction mixture which was heated to 40 $^{\circ}$ C and allowed to stir for 3 hours. The reaction was allowed to cool to room temperature diluted with EtOAc, washed with brine three times and dried over sodium sulfate. The solvent was evaporated in vacuo and the residue was roughly purified using a flash column. Following rough purification, resulting residue (14 mg) was added with K $_2$ CO $_3$ (1.8 equiv.) to a flame dried vial, which was evacuated and placed under argon. The residue and base were then dissolved in acetone (2 mL), and the mixture was heated to 40 $^{\circ}$ C. The desired alkyl halide (10 equiv.) was subsequently added, and the reaction was allowed to stir until the starting material was totally consumed (as evidenced by TLC). The reaction mixture was then, partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried over Na $_2$ SO $_4$, filtered and concentrated. The crude material was purified by column chromatography to yield the final product **10** as a white solid. Yield 1% (3 mg, 0.01 mmol). 1 H NMR (400 MHz, CDCl $_3$) δ 8.56 (dt, J = 8.1, 1.1 Hz, 1H), 7.66 – 7.58 (m, 4H), 7.53 (ddd, J = 8.3, 5.3, 3.1 Hz, 1H), 7.05 – 6.96 (m, 2H), 3.88 (s, 3H), 3.71 (s, 3H). 13 C NMR (101 MHz, CDCl $_3$) δ 176.9, 160.9, 147.3, 140.5, 137.1, 133.0, 131.3, 130.8, 129.2, 127.1, 126.0, 125.8, 114.2, 60.2,

55.6. UV (λ_{\max} nm): 202; IR ν_{\max} (cm⁻¹): 2918, 2360, 2342, 1647, 1044; HRMS (ESI): calcd. for C₁₇H₁₅O₃S [M+H]⁺: 299.0736 found: 299.0729.

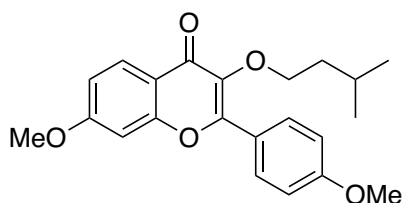


3-Ethoxy-2-(4-ethoxyphenyl)-4H-chromen-4-one (16): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2c** and ethyl iodide afforded **16** as a pale-yellow solid. Yield 10% (43 mg, 0.14 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.25 (dd, $J = 7.9, 1.7$ Hz, 1H), 8.17 – 8.09 (m, 2H), 7.65 (ddd, $J = 8.6, 7.0, 1.7$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.37 (t, $J = 7.5$ Hz, 1H), 7.04 – 6.96 (m, 2H), 4.12 (q, $J = 7.0$ Hz, 4H), 1.46 (t, $J = 7.0$ Hz, 3H), 1.33 (t, $J = 7.1$ Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 175.3, 161.0, 156.0, 155.3, 139.9, 133.3, 130.5, 125.9, 124.6, 124.3, 123.4, 118.0, 114.4, 68.3, 63.8, 15.7, 14.9. UV (λ_{\max} nm): 330; IR ν_{\max} (cm⁻¹): 2986, 2361, 2342, 1636, 1601; HRMS (ESI): calcd. for C₁₉H₁₉O₄ [M+H]⁺: 311.1278 found: 311.1279.

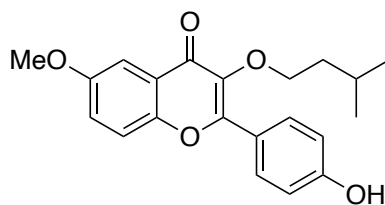


3-(Isopentyloxy)-6-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (17): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2q** and 1-iodo-3-methylbutane afforded **17** as a pale-yellow solid. Yield 12% (27 mg, 0.07 mmol). ¹H NMR (400 MHz, CDCl₃) δ 8.16 – 8.06 (m, 2H), 7.61 (d, $J = 3.1$ Hz, 1H), 7.45 (d, $J = 9.1$ Hz, 1H), 7.25 (dd,

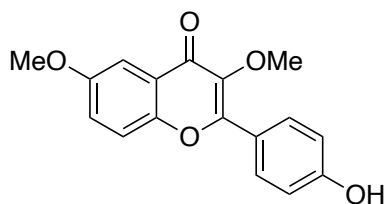
$J = 9.1, 3.0$ Hz, 1H), 7.04 – 6.99 (m, 2H), 4.05 (t, $J = 6.8$ Hz, 2H), 3.91 (s, 3H), 3.90 (s, 4H), 1.77 (dh, $J = 13.2, 6.7$ Hz, 1H), 1.62 (q, $J = 6.8$ Hz, 2H), 0.89 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.0, 161.5, 156.7, 155.8, 150.3, 139.9, 130.5, 125.0, 123.8, 123.7, 119.5, 114.0, 104.7, 71.2, 56.1, 55.6, 39.1, 25.0, 22.7. UV (λ_{max} nm): 202; IR_{vmax} (cm^{-1}): 2943, 2360, 2342, 1614, 1164; HRMS (ESI): calcd. for $\text{C}_{22}\text{H}_{25}\text{O}_5$ $[\text{M}+\text{H}]^+$: 369.1697 found: 369.1694.



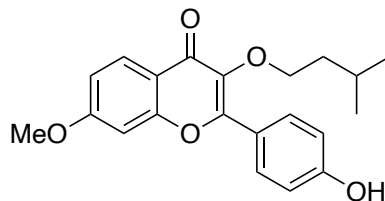
3-(Isopentyloxy)-7-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (18): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation, **2o** and 1-iodo-3-methylbutane afforded **18** as an orange oil. Yield 9% (19 mg, 0.05 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, $J = 8.9$ Hz, 1H), 8.13 – 8.08 (m, 2H), 7.03 – 7.00 (m, 2H), 6.99 (dd, $J = 8.9, 2.4$ Hz, 1H), 6.92 (d, $J = 2.4$ Hz, 1H), 3.99 (t, $J = 6.9$ Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 1.73 (dh, $J = 13.3, 6.7$ Hz, 1H), 1.61 (q, $J = 6.9$ Hz, 2H), 0.86 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 176.4, 166.0, 163.2, 158.5, 157.9, 140.7, 131.4, 127.5, 124.3, 118.6, 116.0, 114.9, 101.1, 72.1, 56.6, 55.9, 40.0, 26.0, 22.9. UV (λ_{max} nm): 210; IR_{vmax} (cm^{-1}): 2954, 2360, 2342, 1601, 1254; HRMS (ESI): calcd. for $\text{C}_{22}\text{H}_{25}\text{O}_5$ $[\text{M}+\text{H}]^+$: 369.1697 found: 369.1702.



2-(4-Hydroxyphenyl)-3-(isopentyloxy)-6-methoxy-4H-chromen-4-one (19): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation with **6c** and 1-iodo-3-methylbutane, followed by MOM deprotection afforded **19** as a pale-yellow solid. Yield 28% (45 mg, 0.13 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.13 – 8.03 (m, 2H), 7.62 (d, $J = 3.1$ Hz, 1H), 7.50 (d, $J = 9.2$ Hz, 1H), 7.32 (dd, $J = 9.2, 3.0$ Hz, 1H), 7.04 – 6.96 (m, 2H), 6.73 (s, 3H), 3.94 (t, $J = 6.9$ Hz, 2H), 3.91 (s, 3H), 1.71 (dp, $J = 13.0, 6.5$ Hz, 1H), 1.61 (q, $J = 6.9$ Hz, 2H), 0.84 (d, $J = 6.5$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 175.5, 159.1, 156.9, 156.8, 150.4, 139.7, 130.8, 124.7, 124.0, 122.9, 119.5, 115.8, 104.6, 77.4, 71.5, 56.0, 39.0, 25.0, 22.7. UV (λ_{max} nm): 202; IR_{Vmax} (cm^{-1}): 3101, 3025, 2362, 2342, 1585; HRMS (ESI): calcd. for $\text{C}_{21}\text{H}_{23}\text{O}_5$ $[\text{M}+\text{H}]^+$: 355.1540 found: 355.1542.

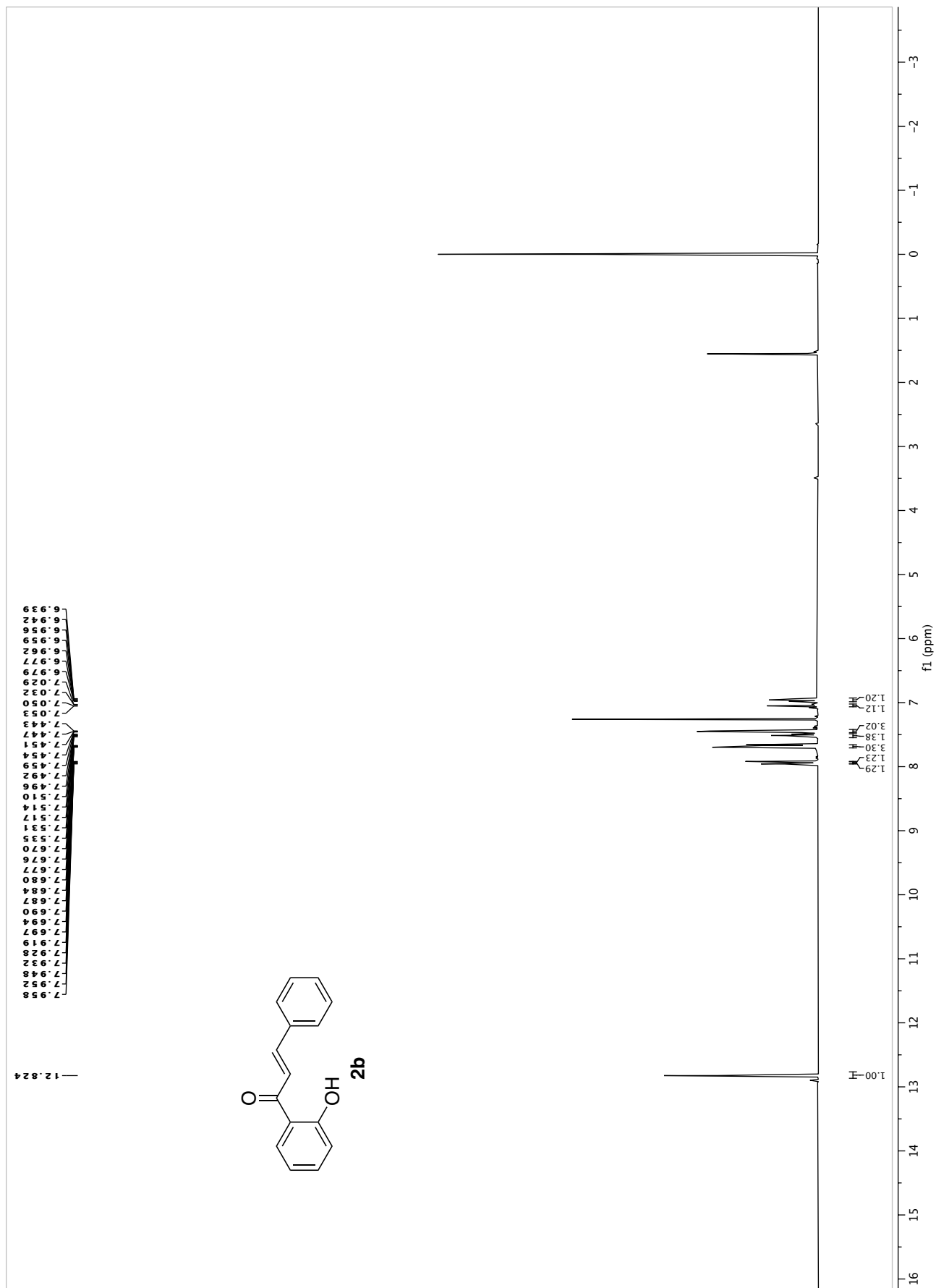


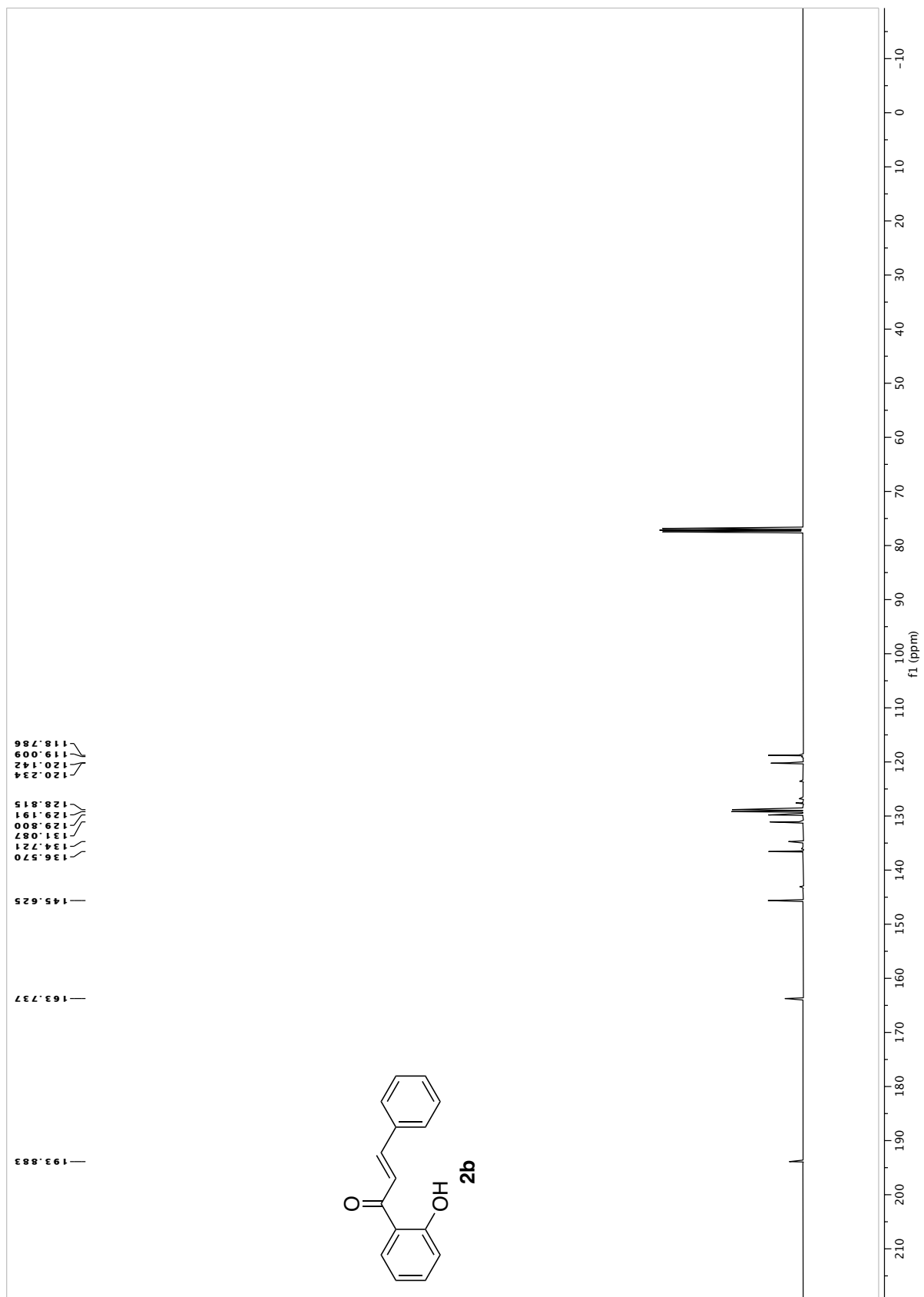
2-(4-Hydroxyphenyl)-3,6-dimethoxy-4H-chromen-4-one (20): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation with **6c** and iodomethane followed, by MOM deprotection afforded **20** as a light brown solid. Yield 28% (57 mg, 0.19 mmol). ^1H NMR (400 MHz, CDCl_3) δ 8.12 – 8.03 (m, 2H), 7.62 (d, $J = 3.1$ Hz, 1H), 7.46 (d, $J = 9.1$ Hz, 1H), 7.28 (dd, $J = 9.1, 3.1$ Hz, 1H), 7.03 – 6.95 (m, 2H), 3.92 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.2, 159.9, 156.2, 155.1, 149.4, 139.4, 130.1, 124.2, 123.1, 121.1, 119.9, 115.6, 104.4, 59.3, 55.7. UV (λ_{max} nm): 202; IR_{Vmax} (cm^{-1}): 3234, 2939, 2361, 2342, 1599; HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{15}\text{O}_5$ $[\text{M}+\text{H}]^+$: 299.0914 found: 299.0915.

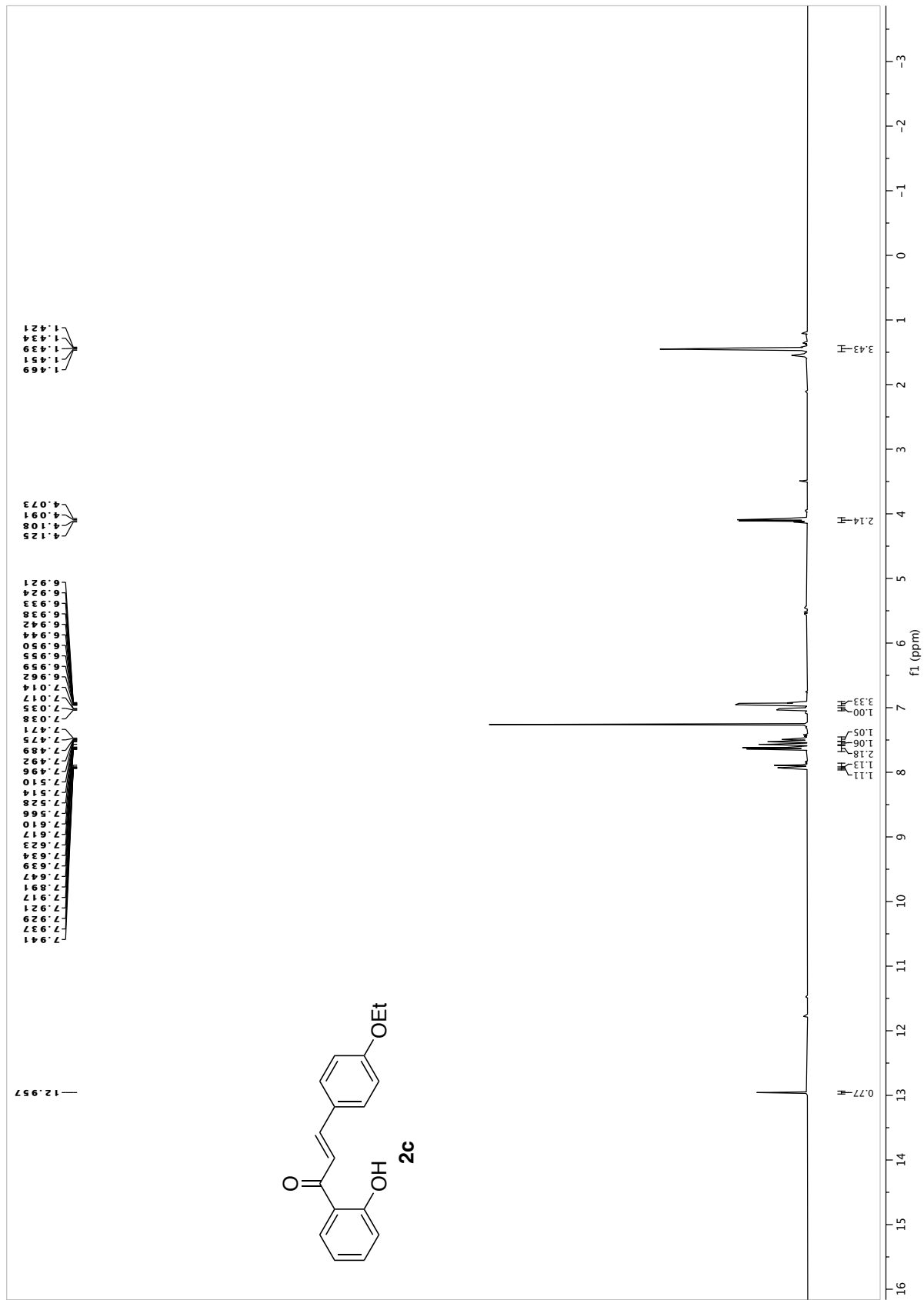


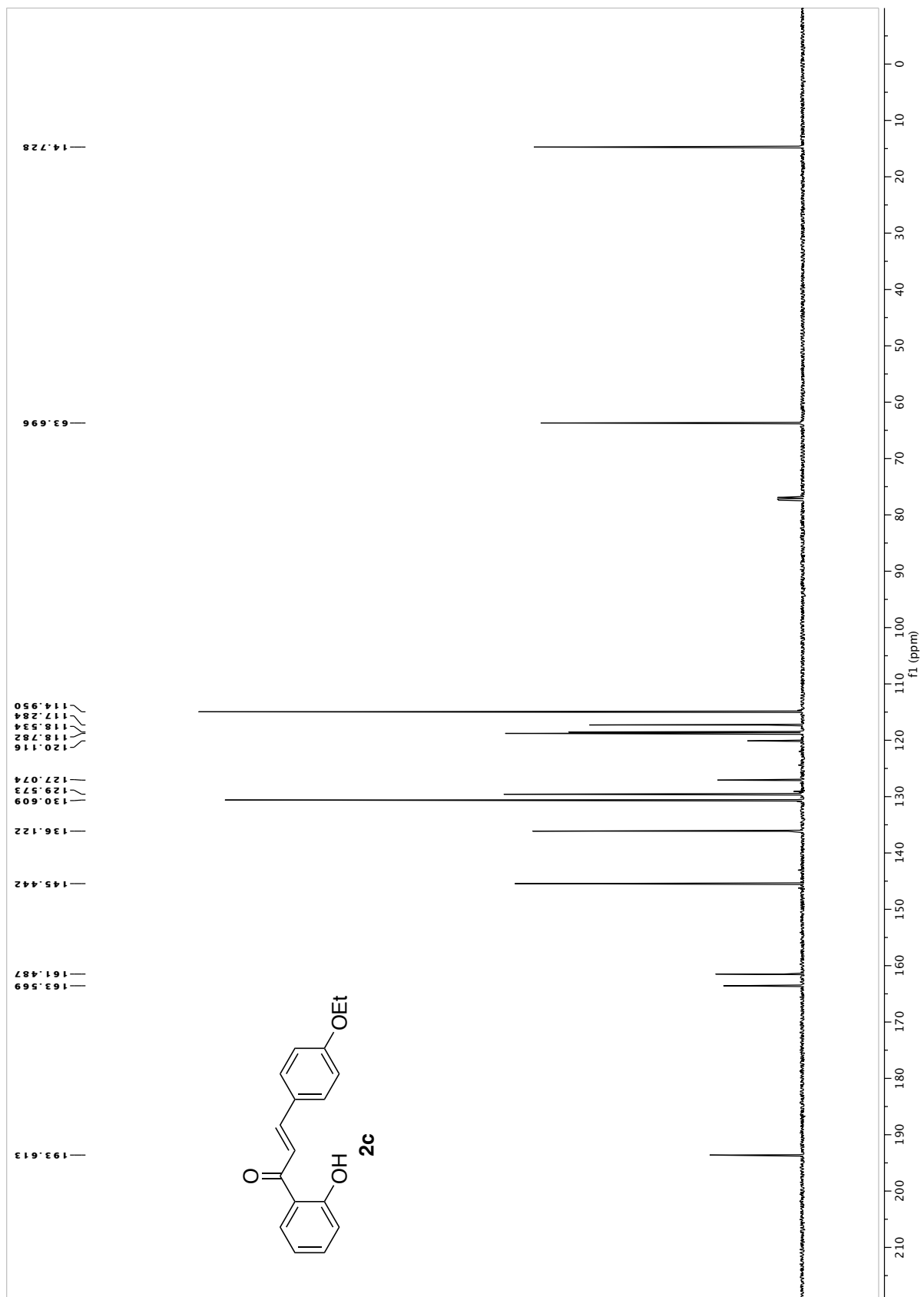
2-(4-Hydroxyphenyl)-3-(isopentyloxy)-7-methoxy-4H-chromen-4-one (21): Following the general procedure for Algar-Flynn-Oyamada cyclization and alkylation with **6d** and 1-iodo-3-methylbutane, followed by MOM deprotection afforded **21** as a light brown solid. Yield 7% (35 mg, 0.10 mmol). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.16 (d, $J = 8.9$ Hz, 1H), 8.10 – 8.01 (m, 2H), 7.02 – 6.94 (m, 2H), 6.97 (dd, $J = 9.0, 2.4$ Hz, 1H), 6.91 (d, $J = 2.4$ Hz, 1H), 4.03 (t, $J = 6.8$ Hz, 2H), 3.92 (s, 3H), 1.75 (dp, $J = 13.3, 6.6$ Hz, 1H), 1.61 (q, $J = 6.8$ Hz, 2H), 0.87 (d, $J = 6.6$ Hz, 6H). $^{13}\text{C NMR}$ (126 MHz, CD_3OD) δ 176.5, 166.0, 161.5, 158.6, 158.5, 140.5, 131.6, 127.5, 123.1, 118.6, 116.4, 116.0, 101.1, 72.2, 56.6, 40.0, 26.0, 22.9. UV (λ_{max} nm): 202; $\text{IR}_{\nu_{\text{max}}}$ (cm^{-1}): 2959, 2360, 2341, 1580, 1173; HRMS (ESI): calcd. for $\text{C}_{21}\text{H}_{23}\text{O}_5$ $[\text{M}+\text{H}]^+$: 355.1540 found: 355.1547.

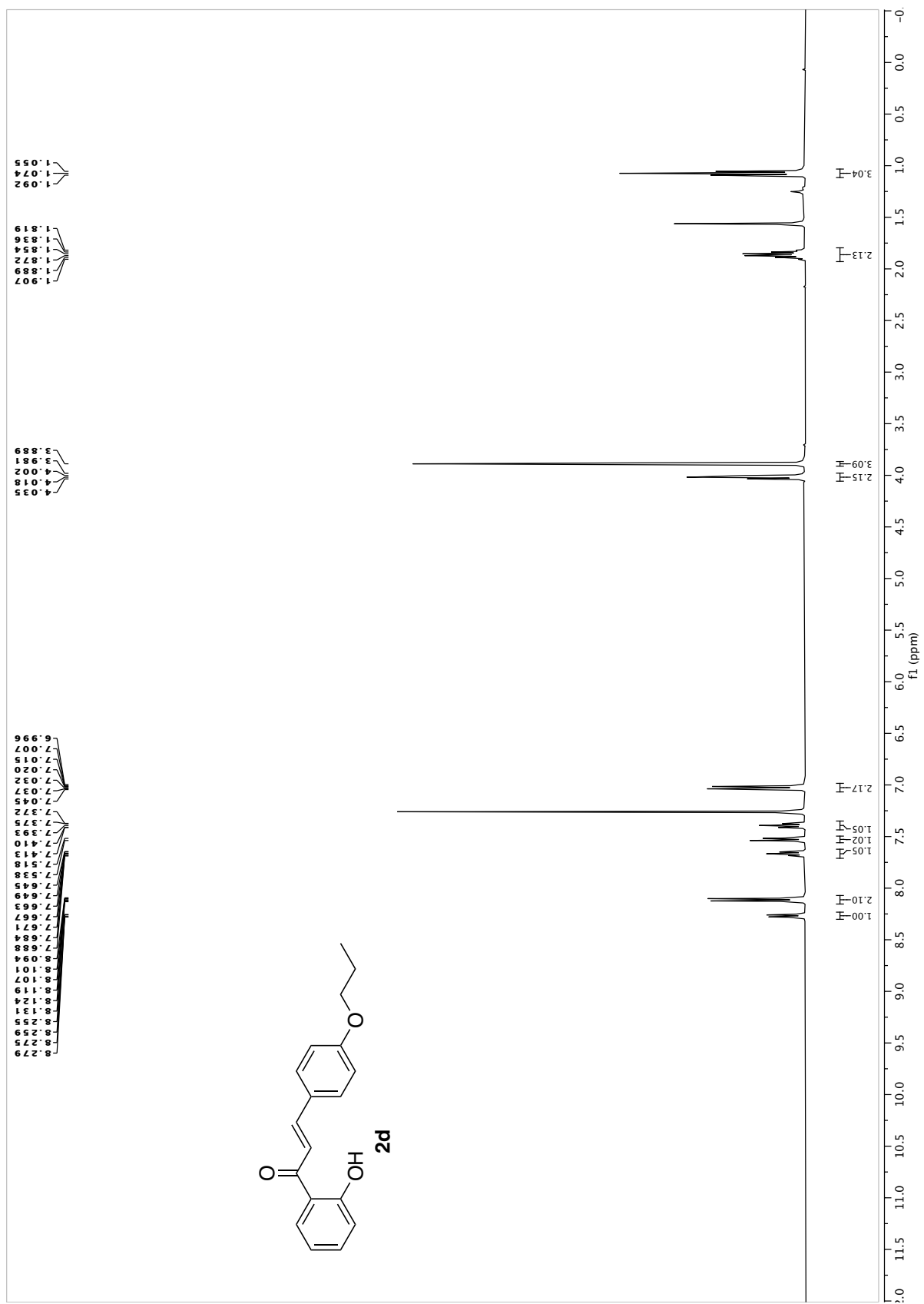
^1H and ^{13}C NMR spectra of novel compounds

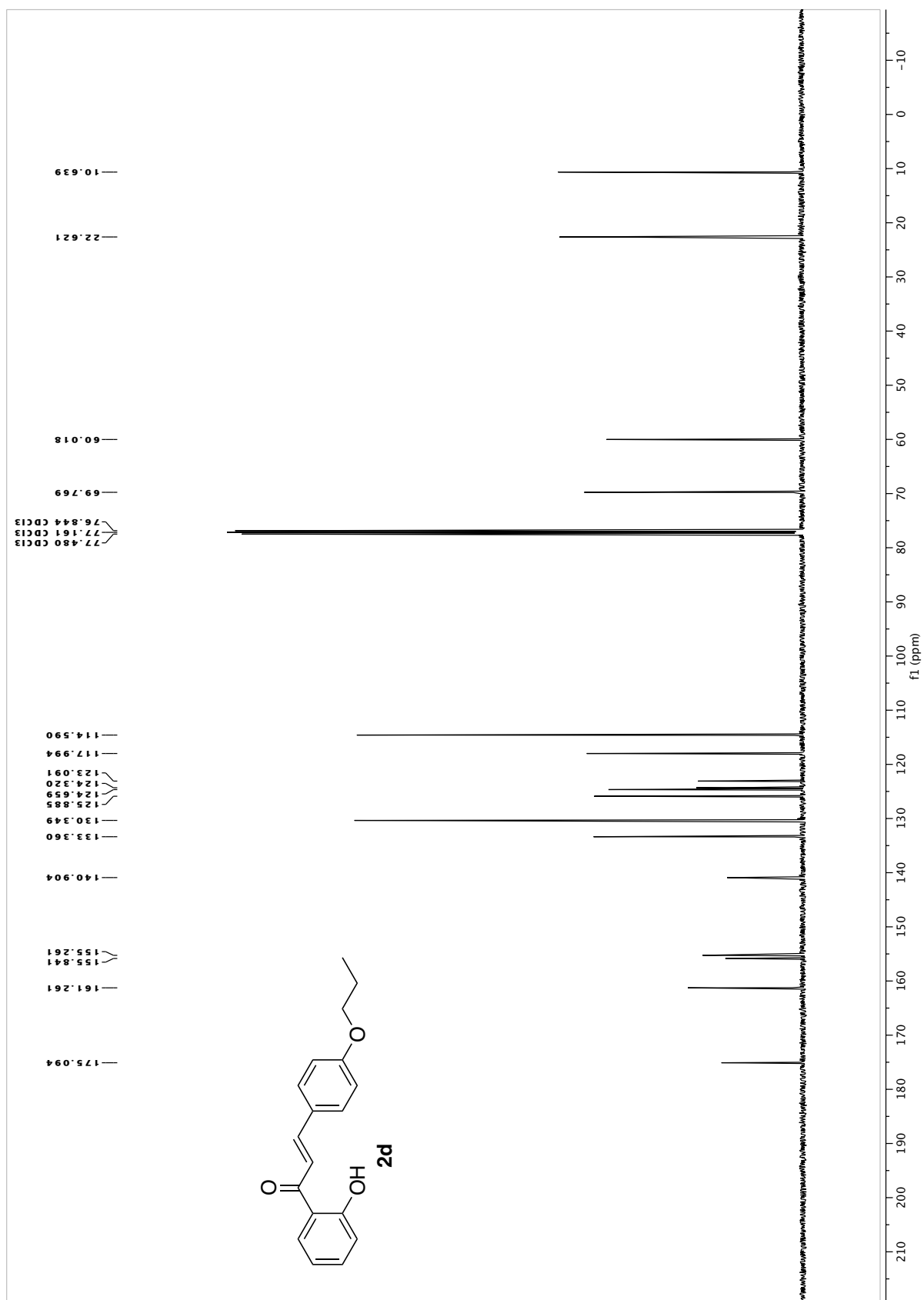


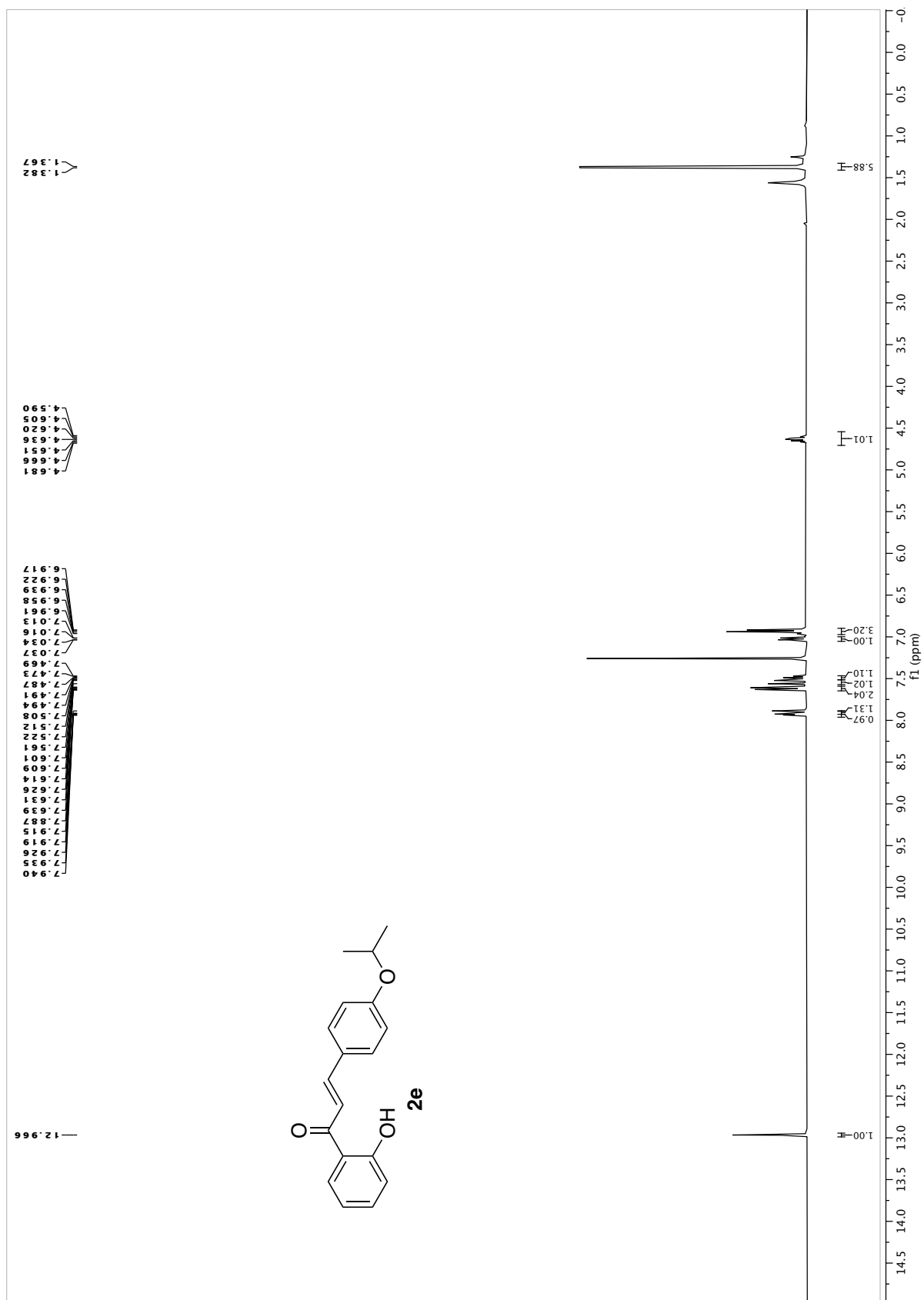


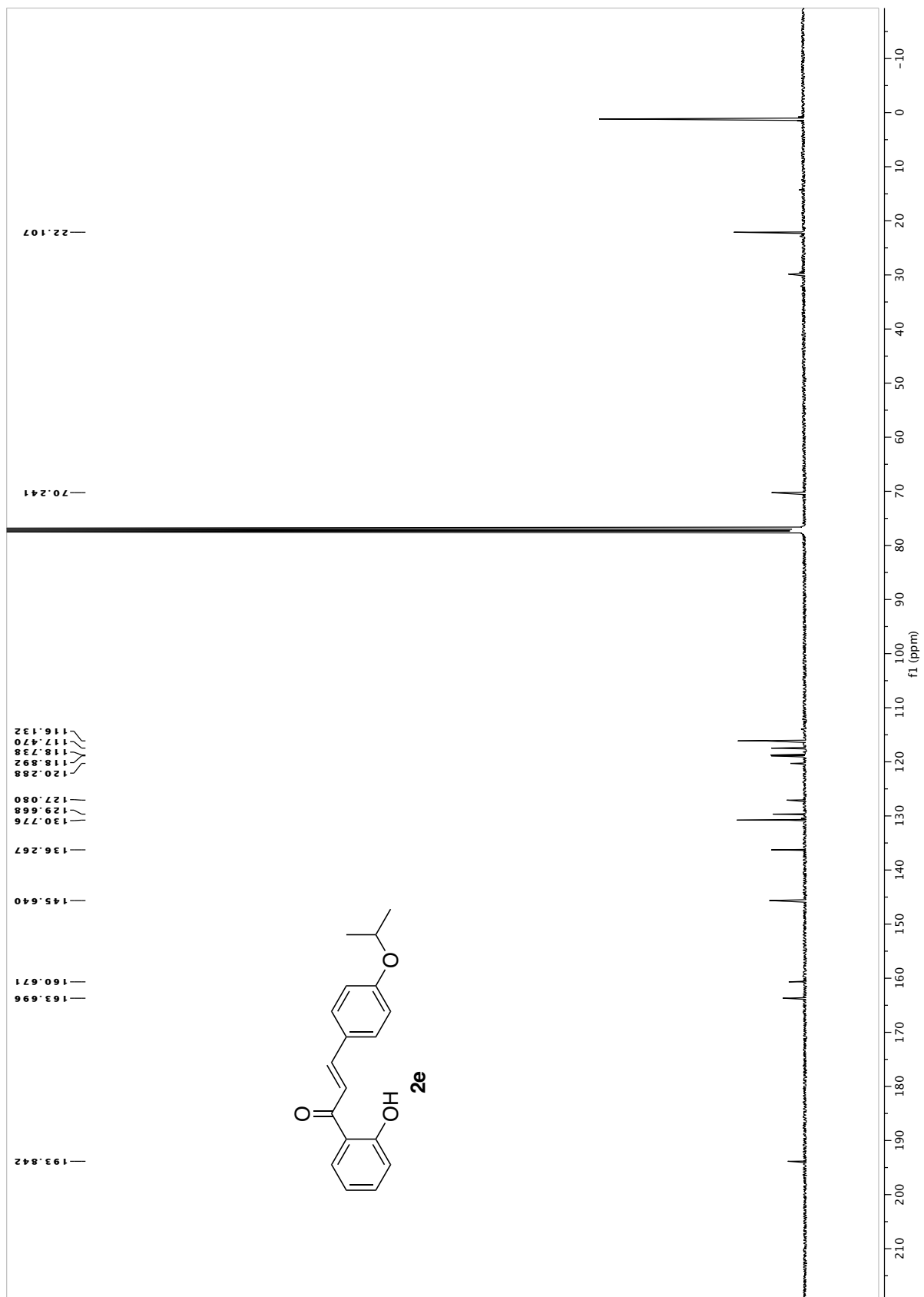


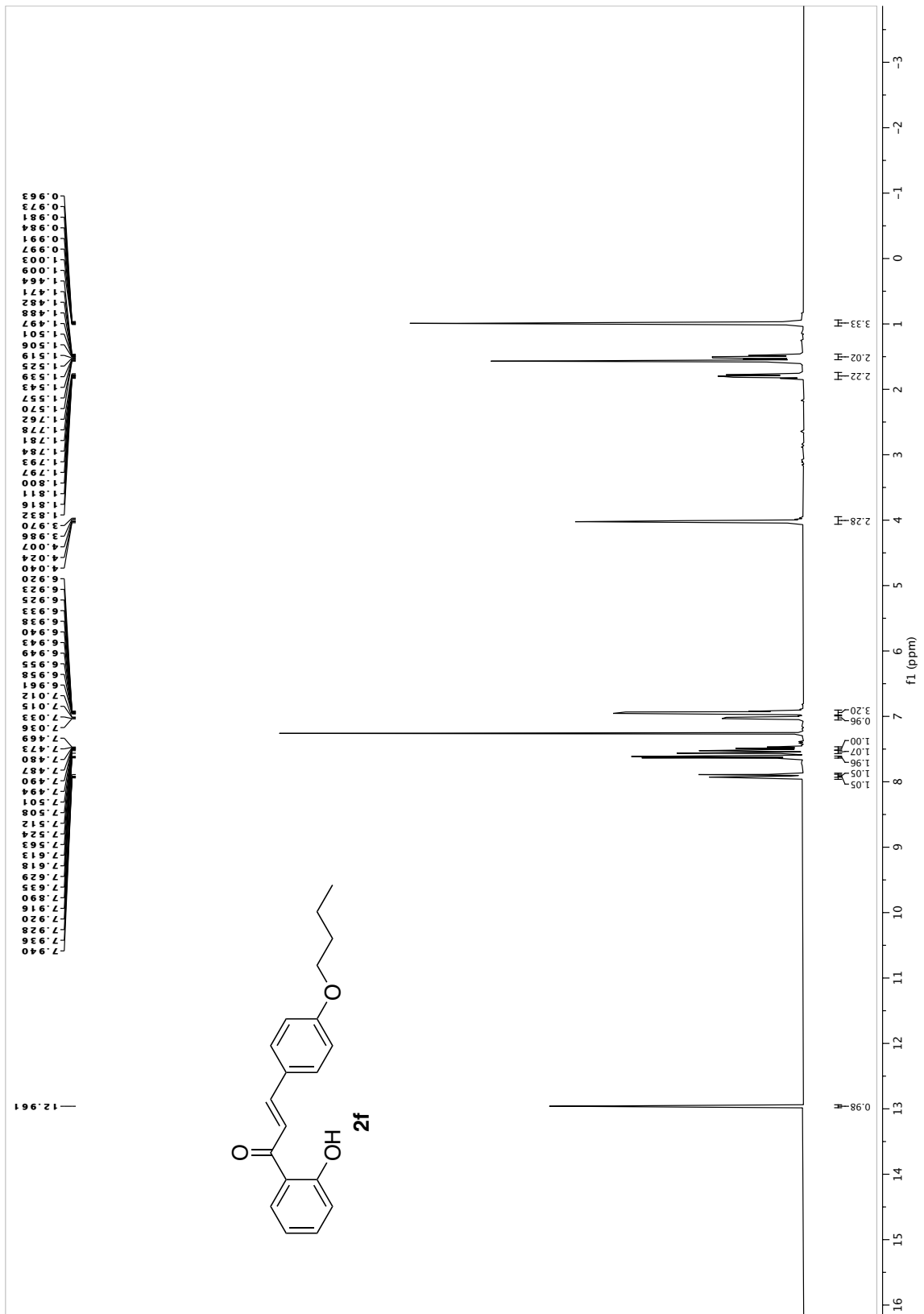


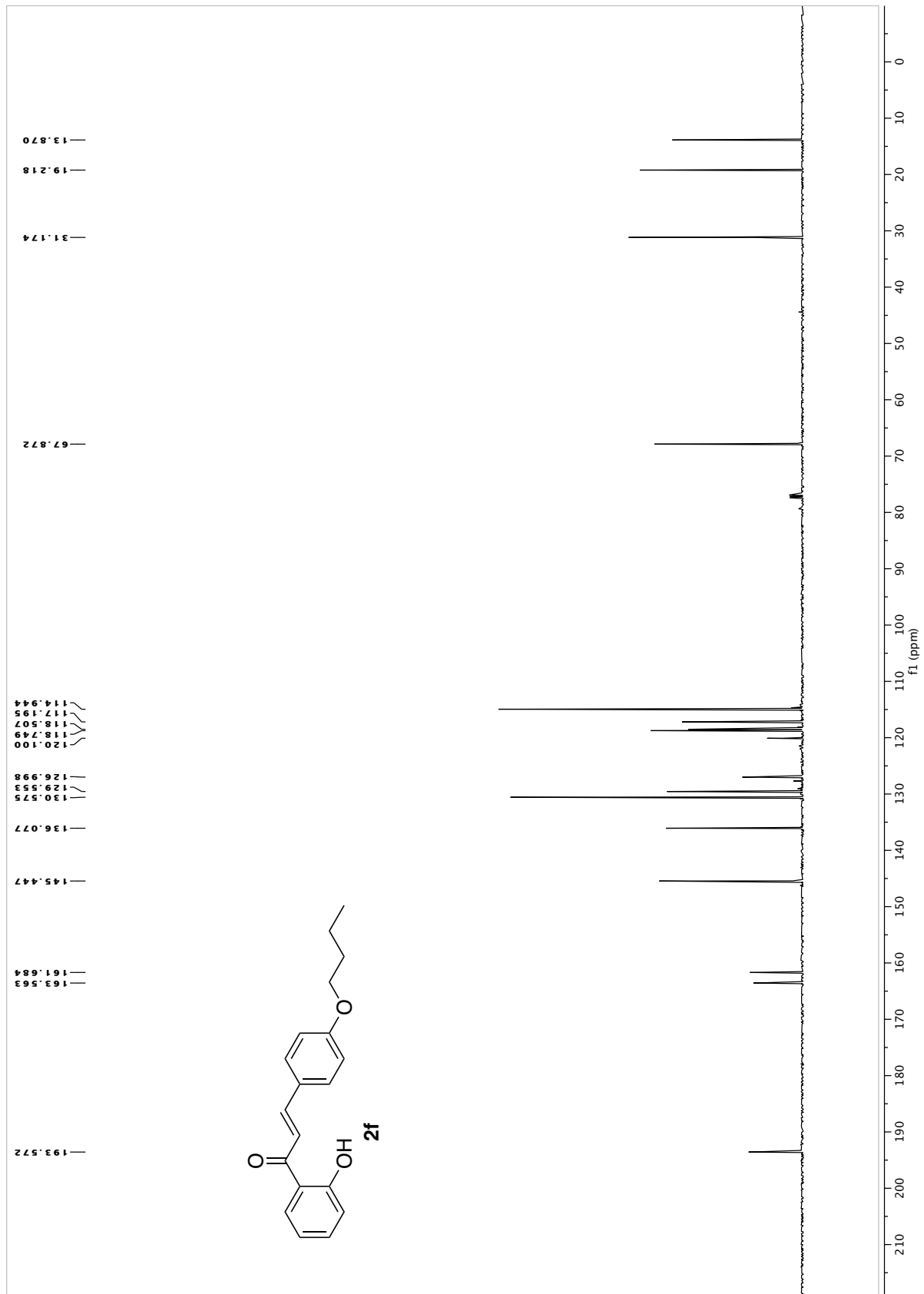


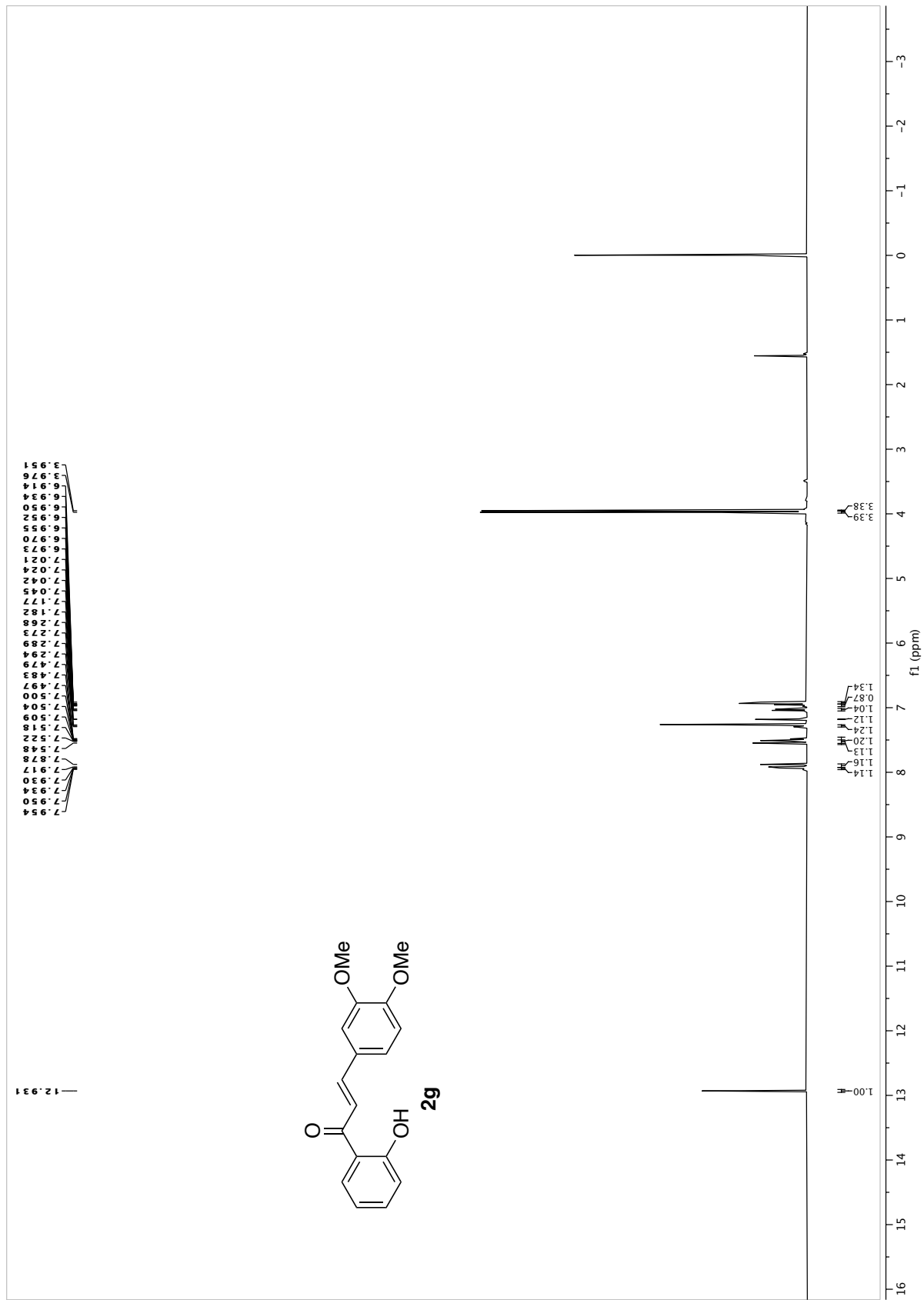


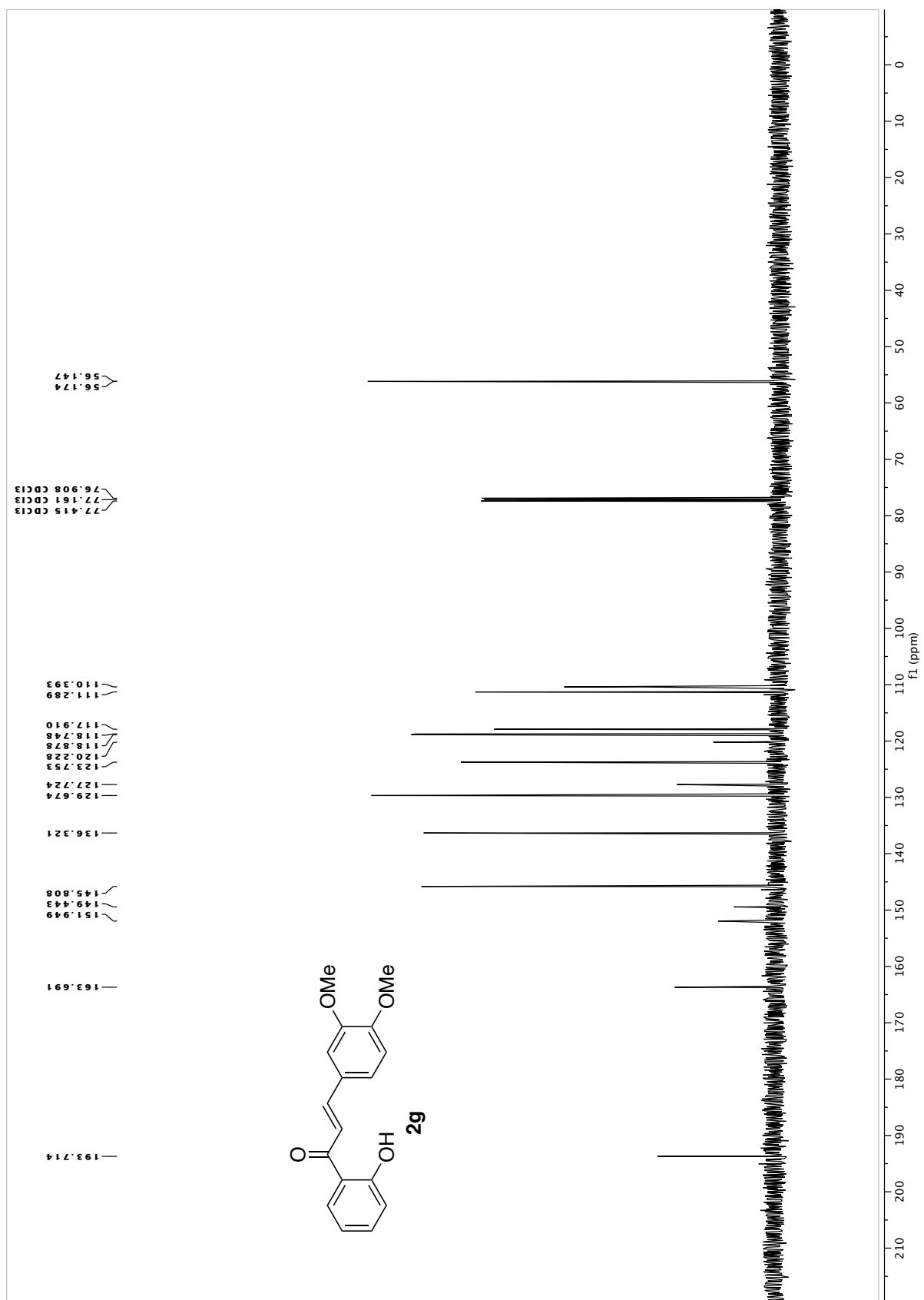


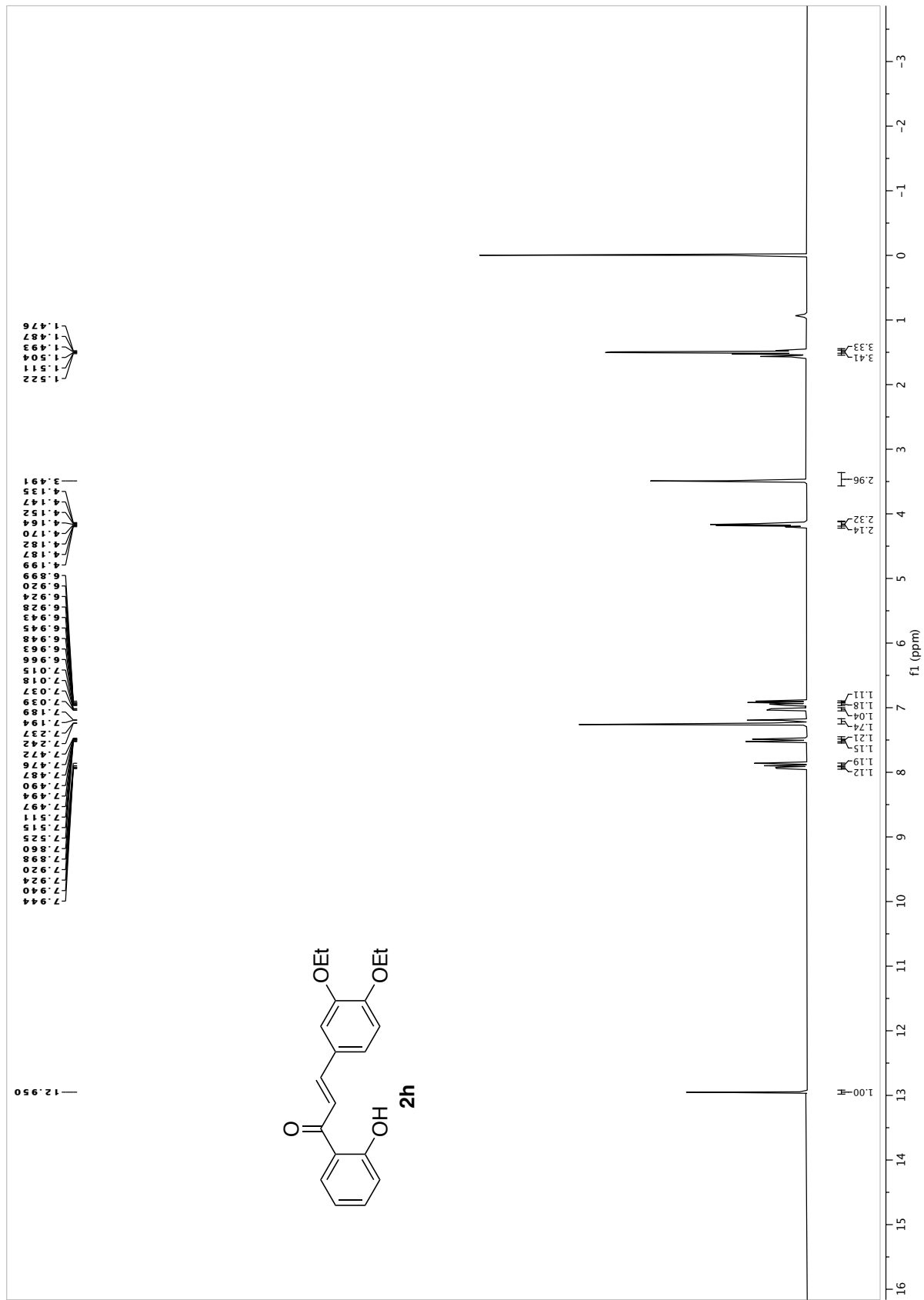


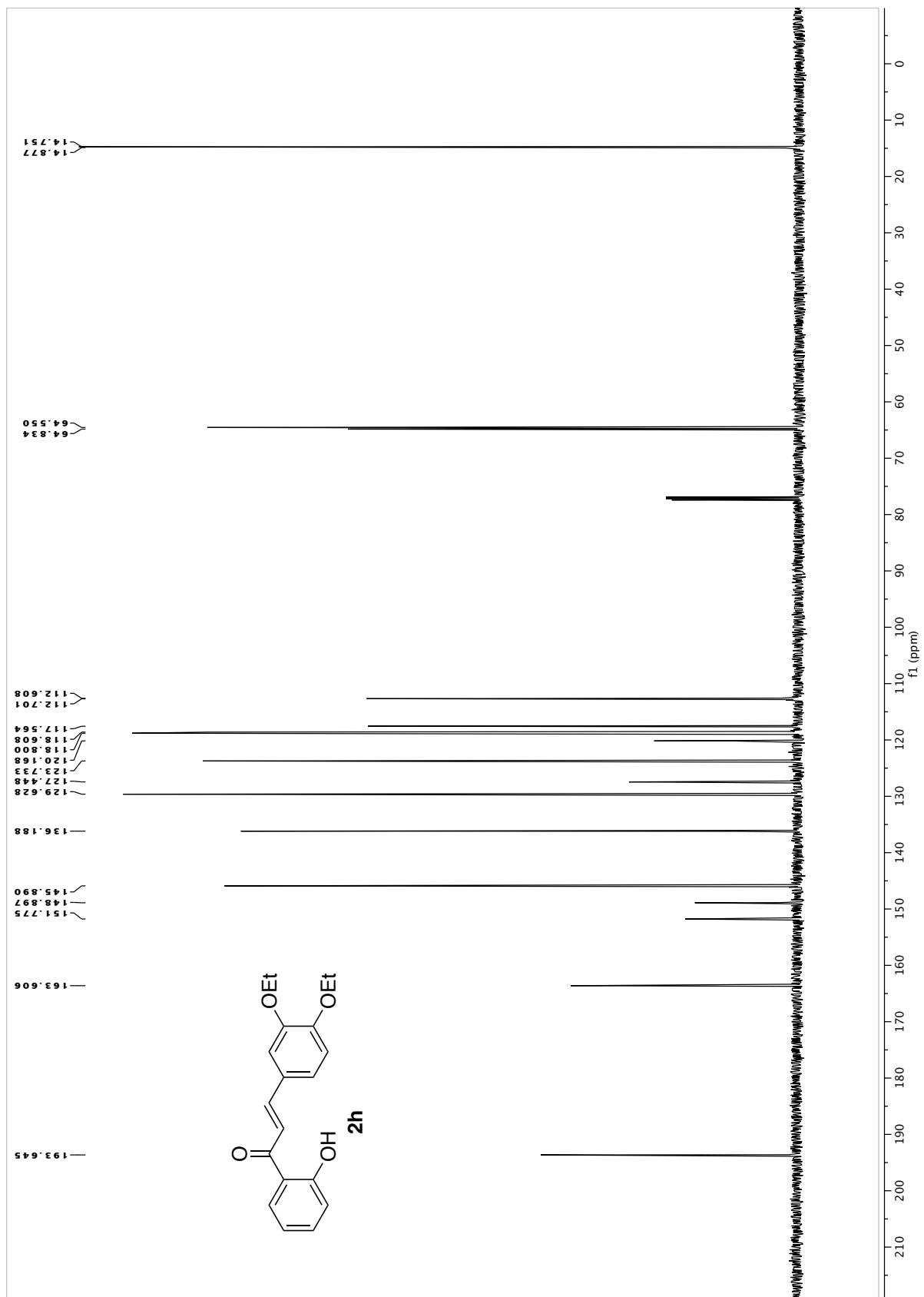


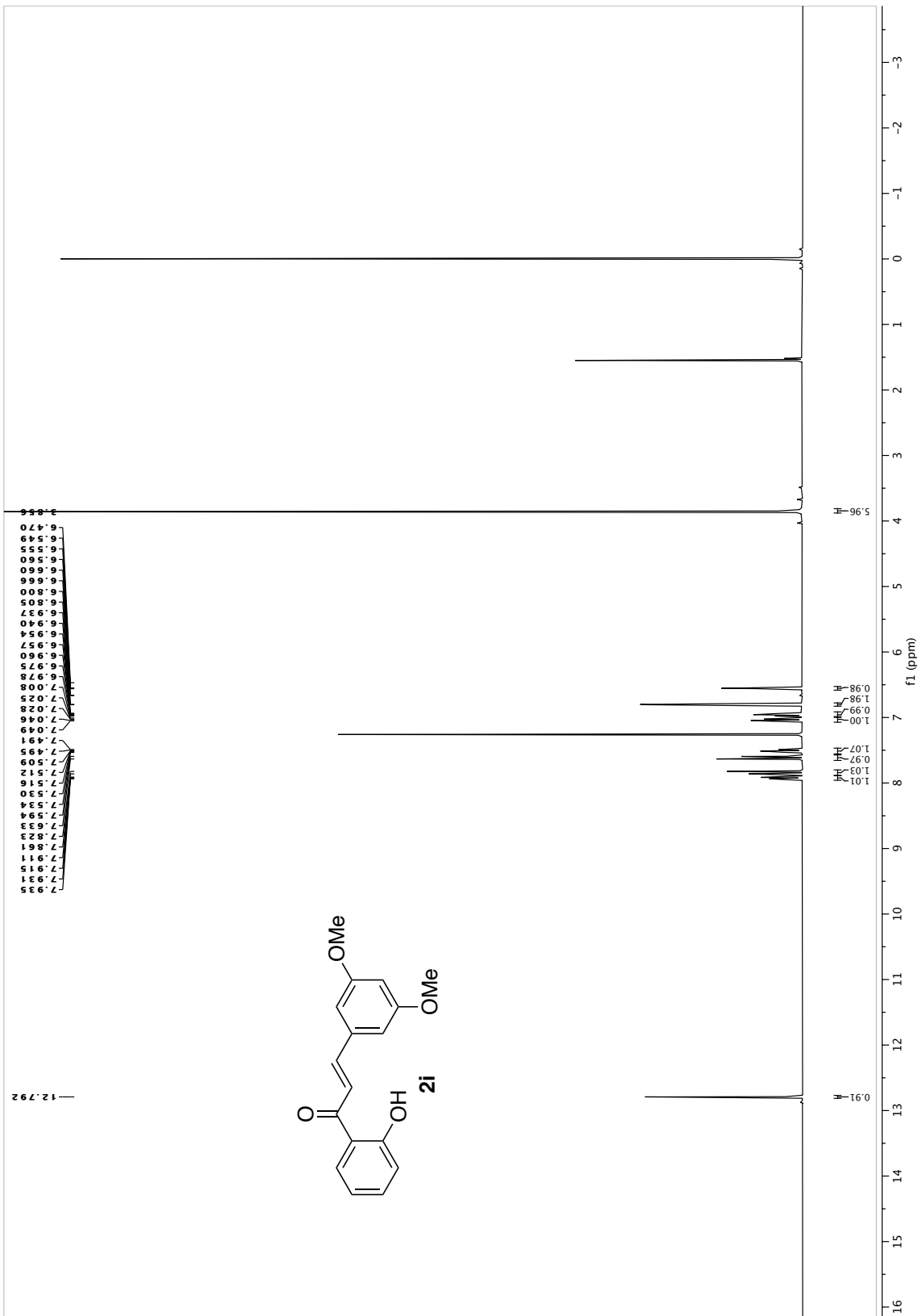


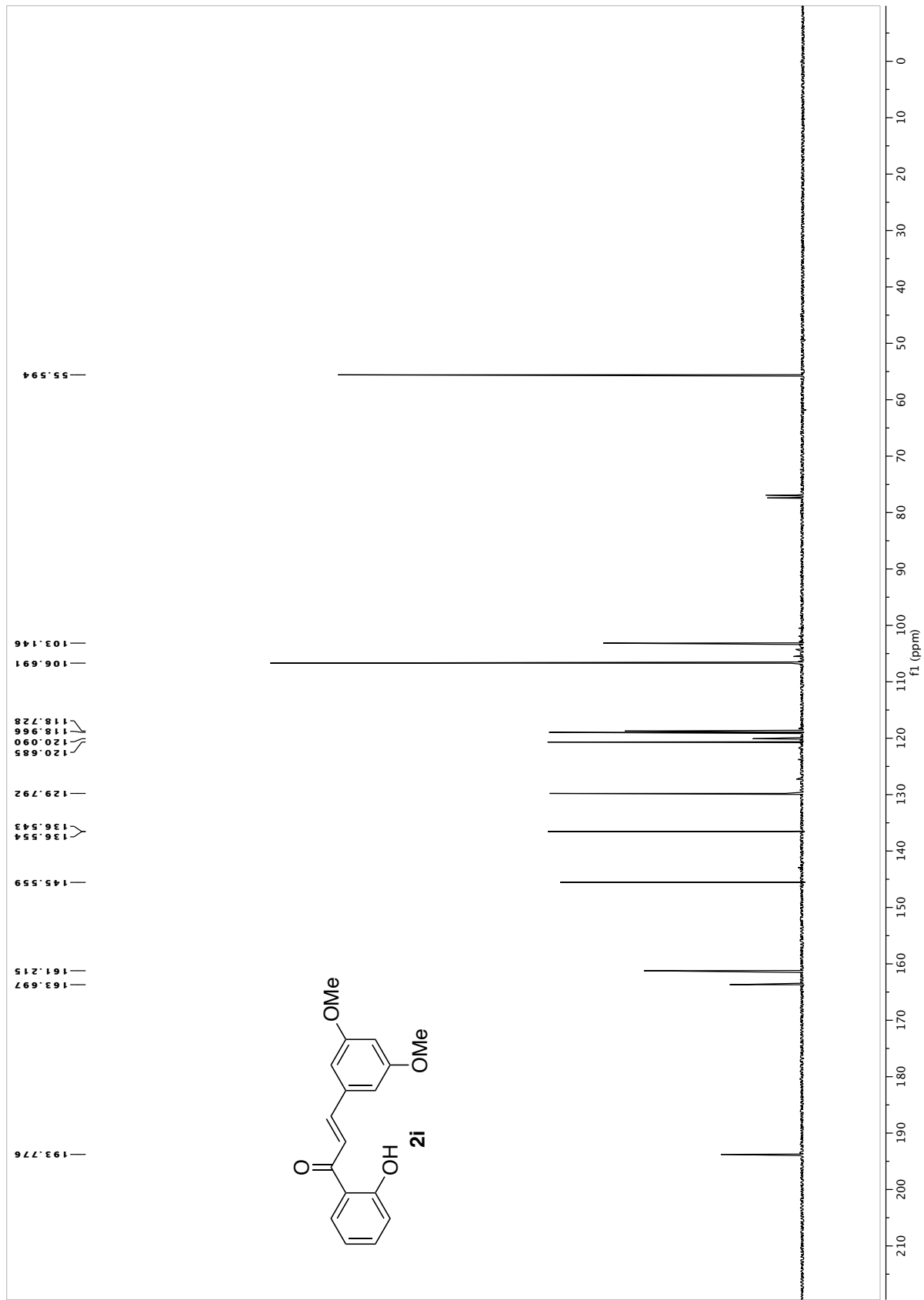


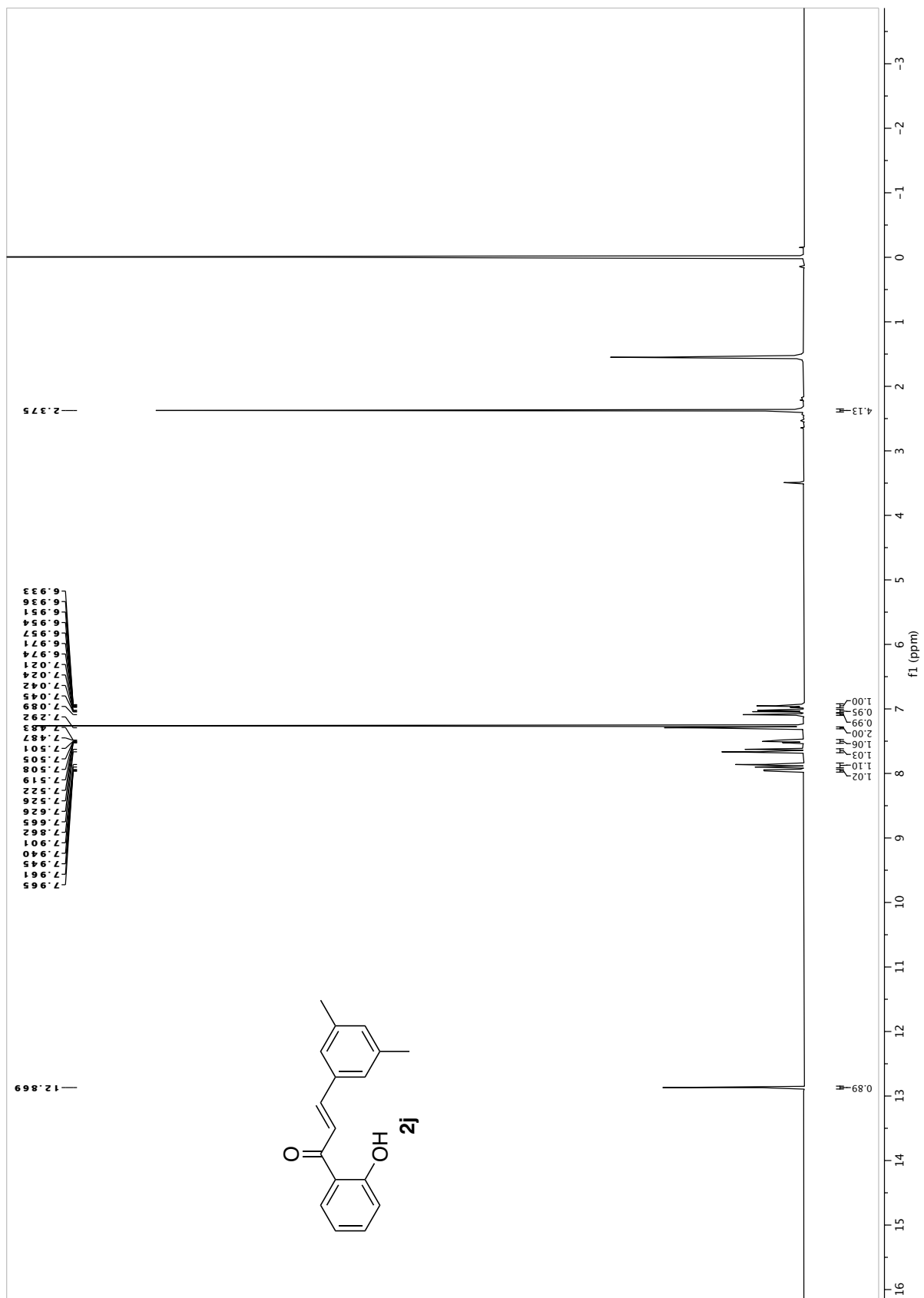


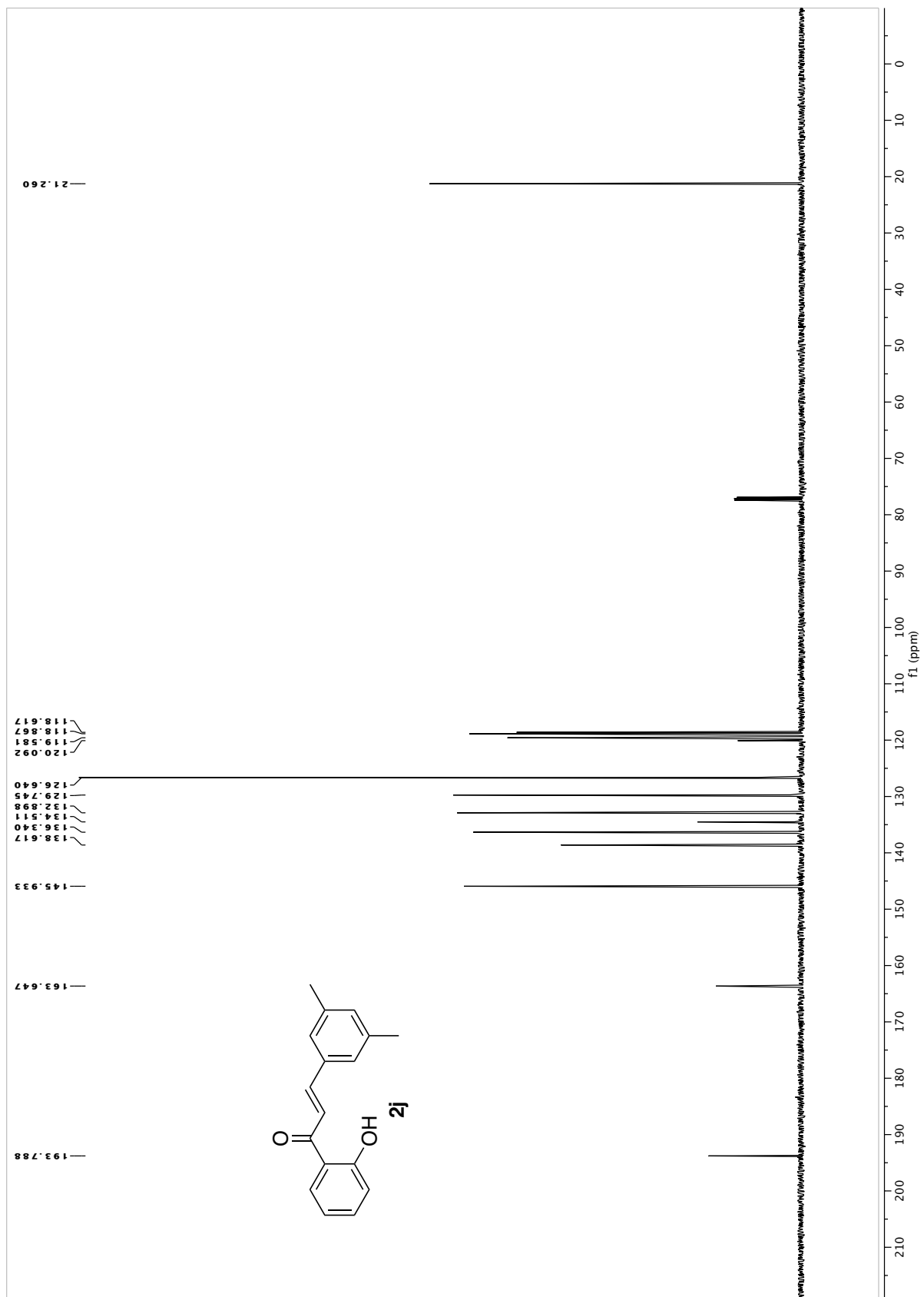


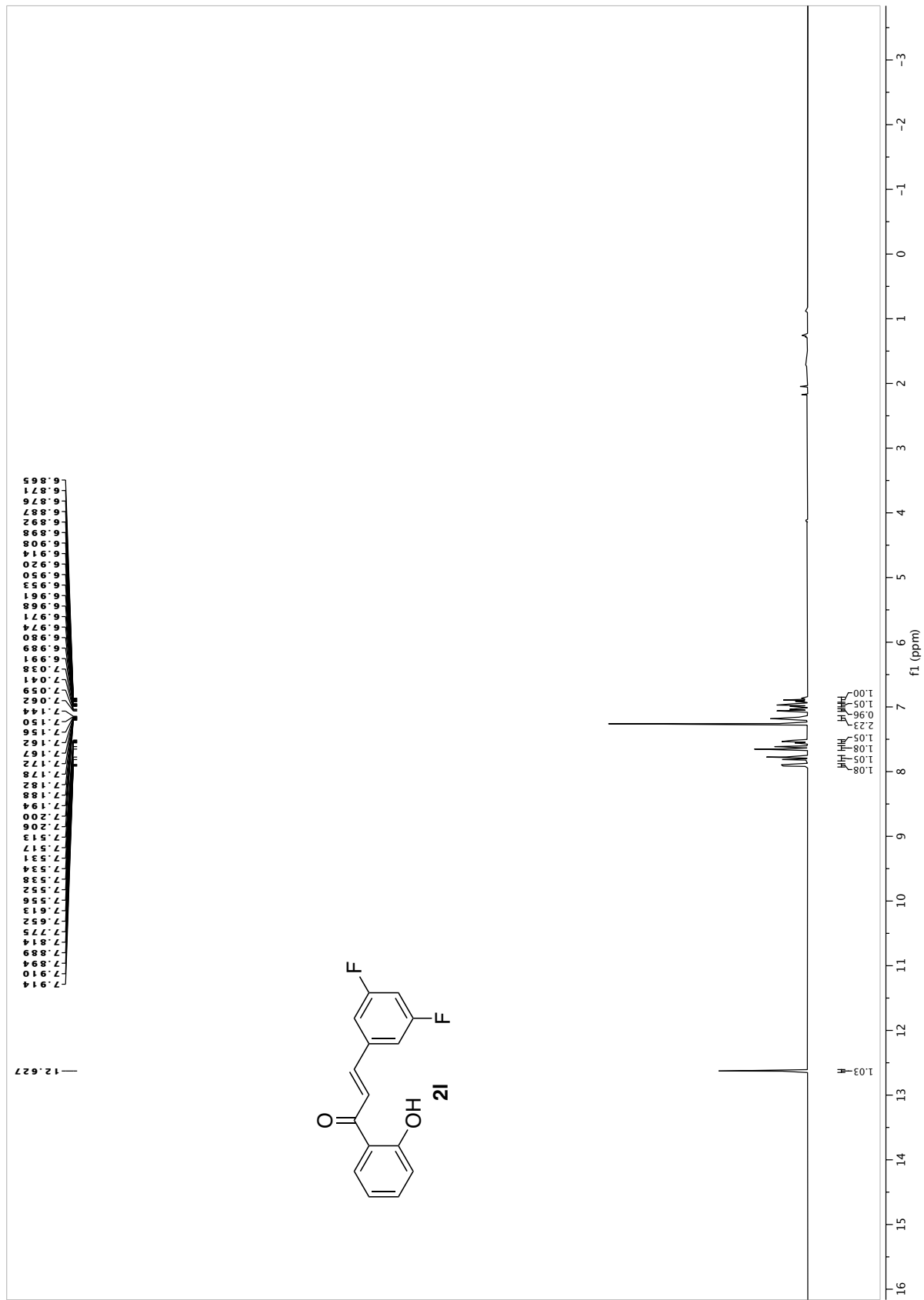


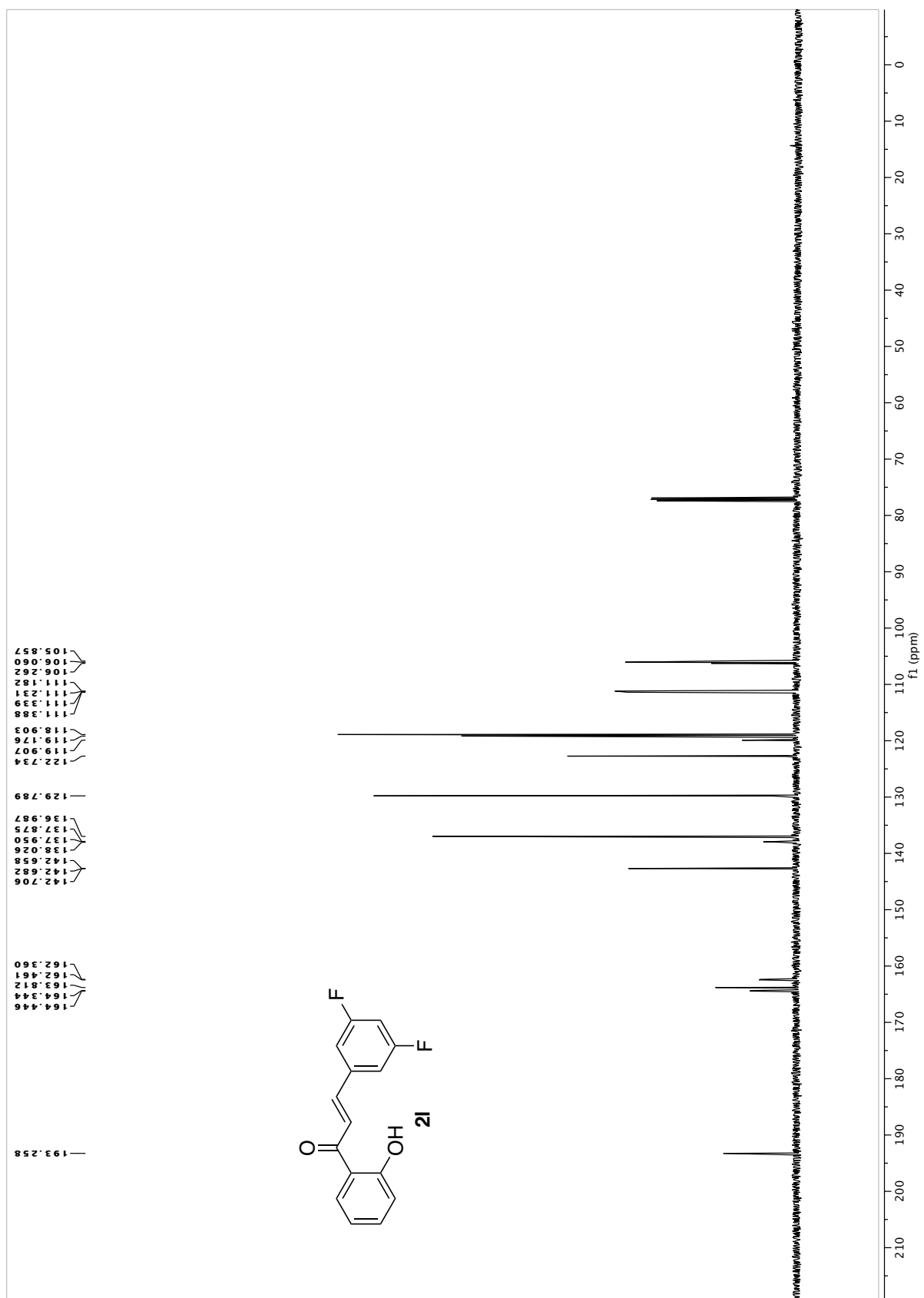


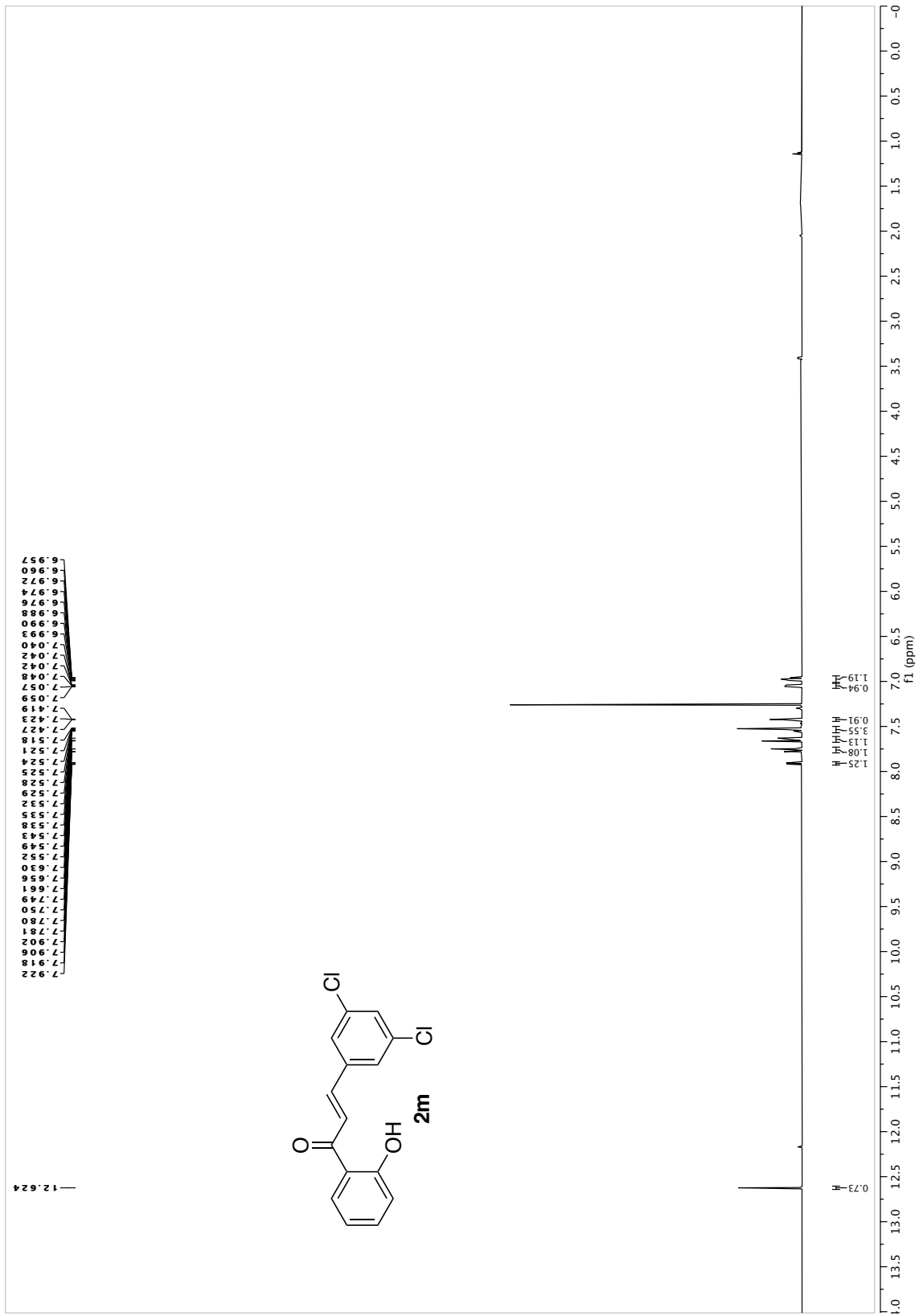


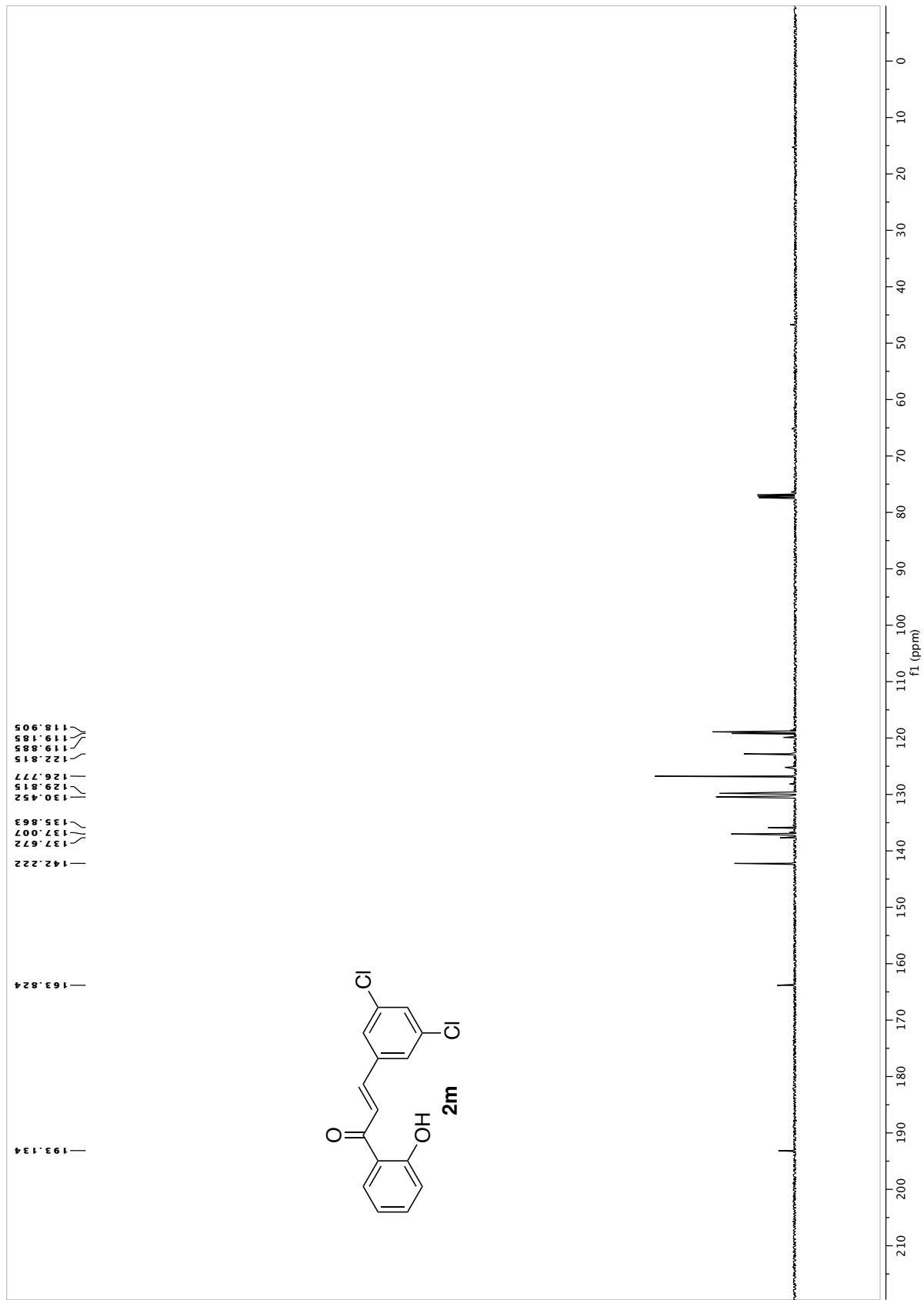


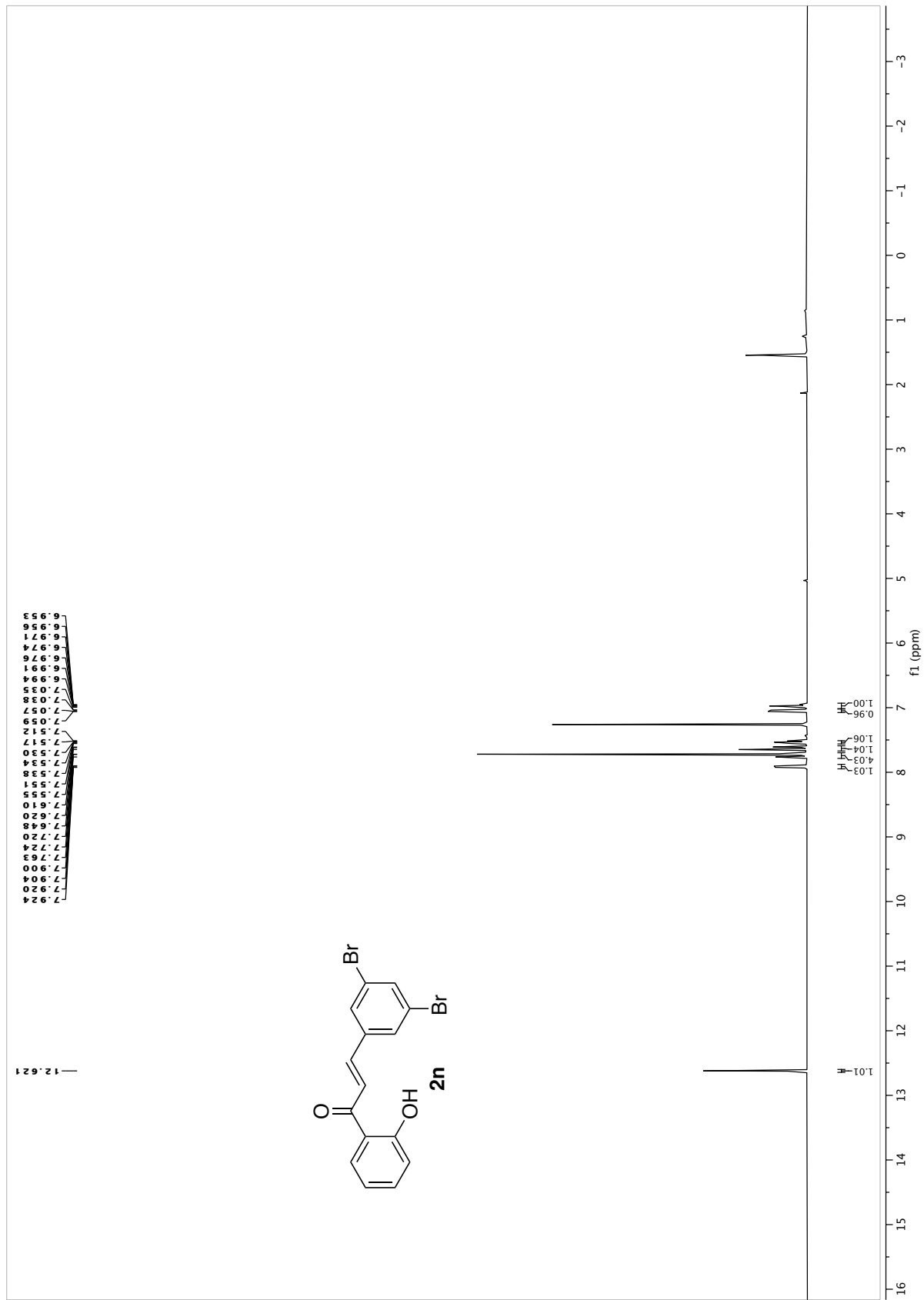


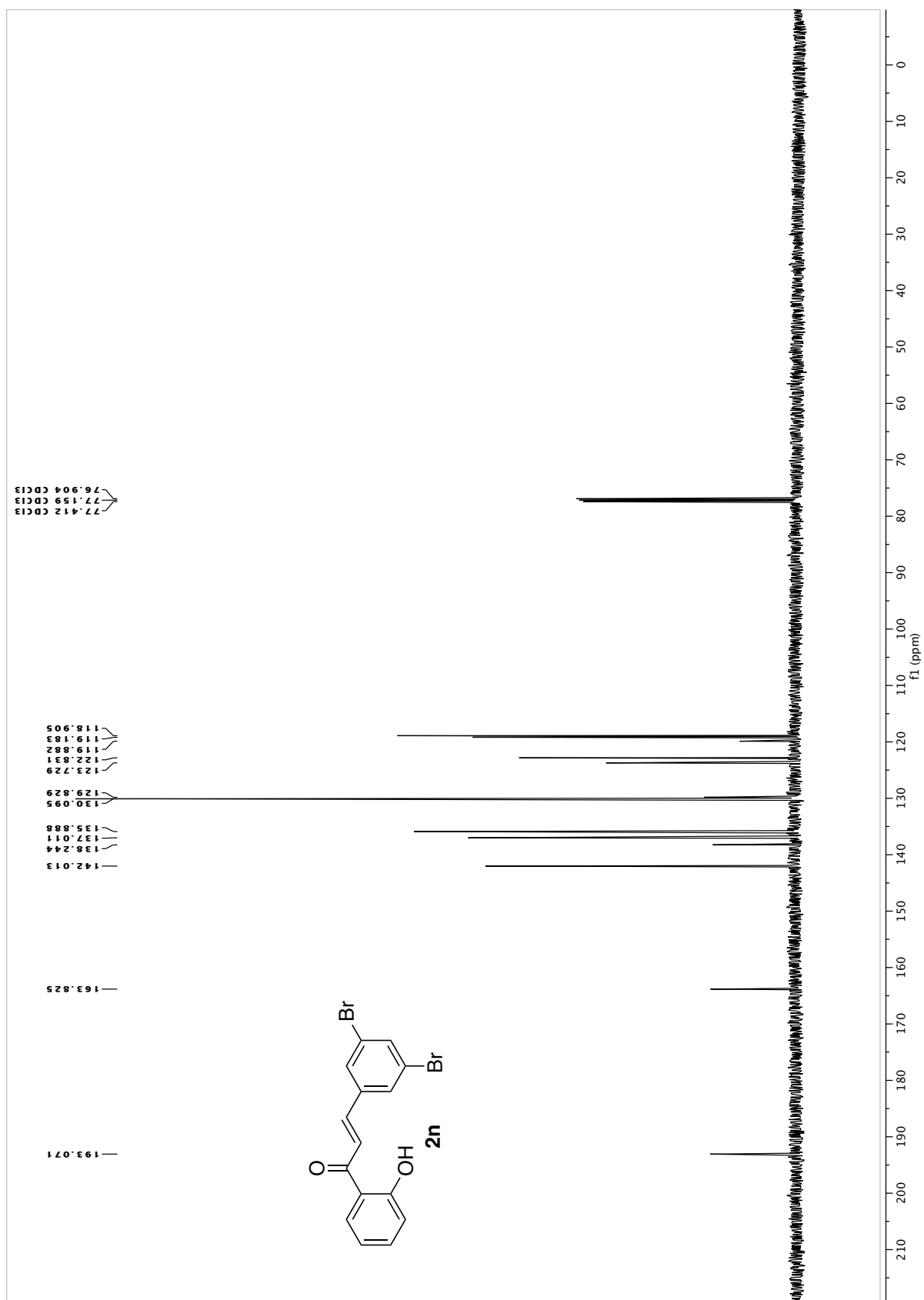


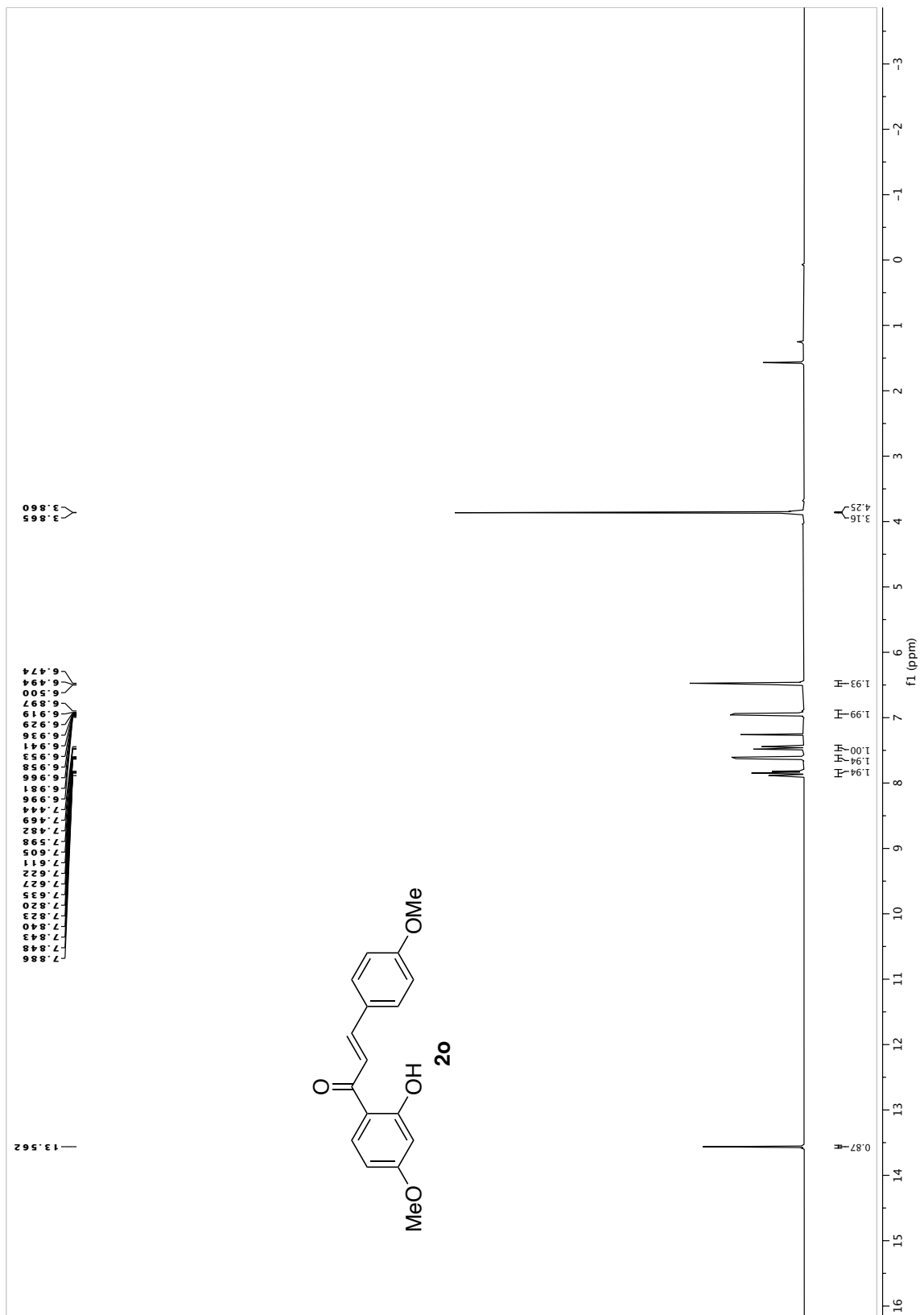


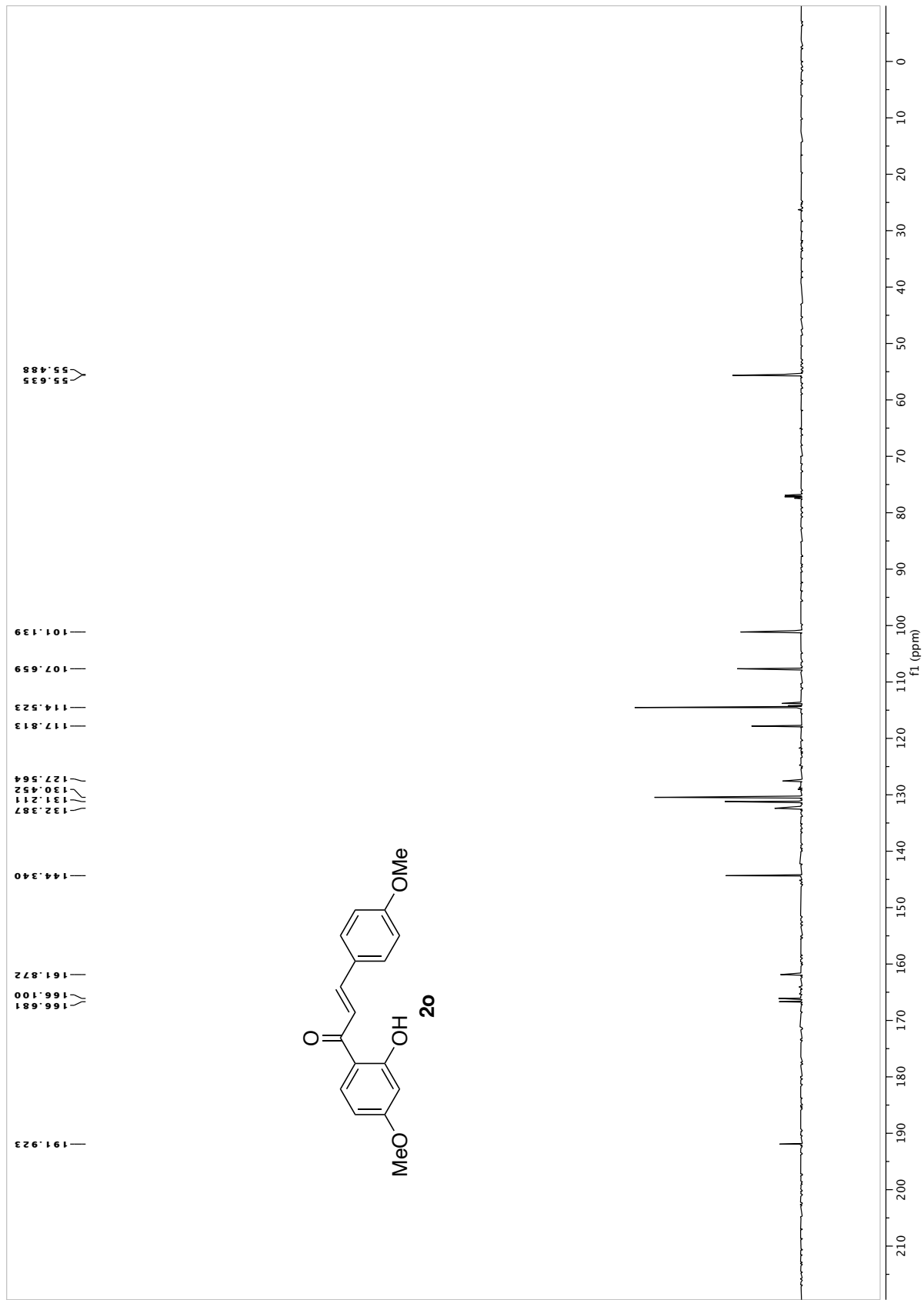


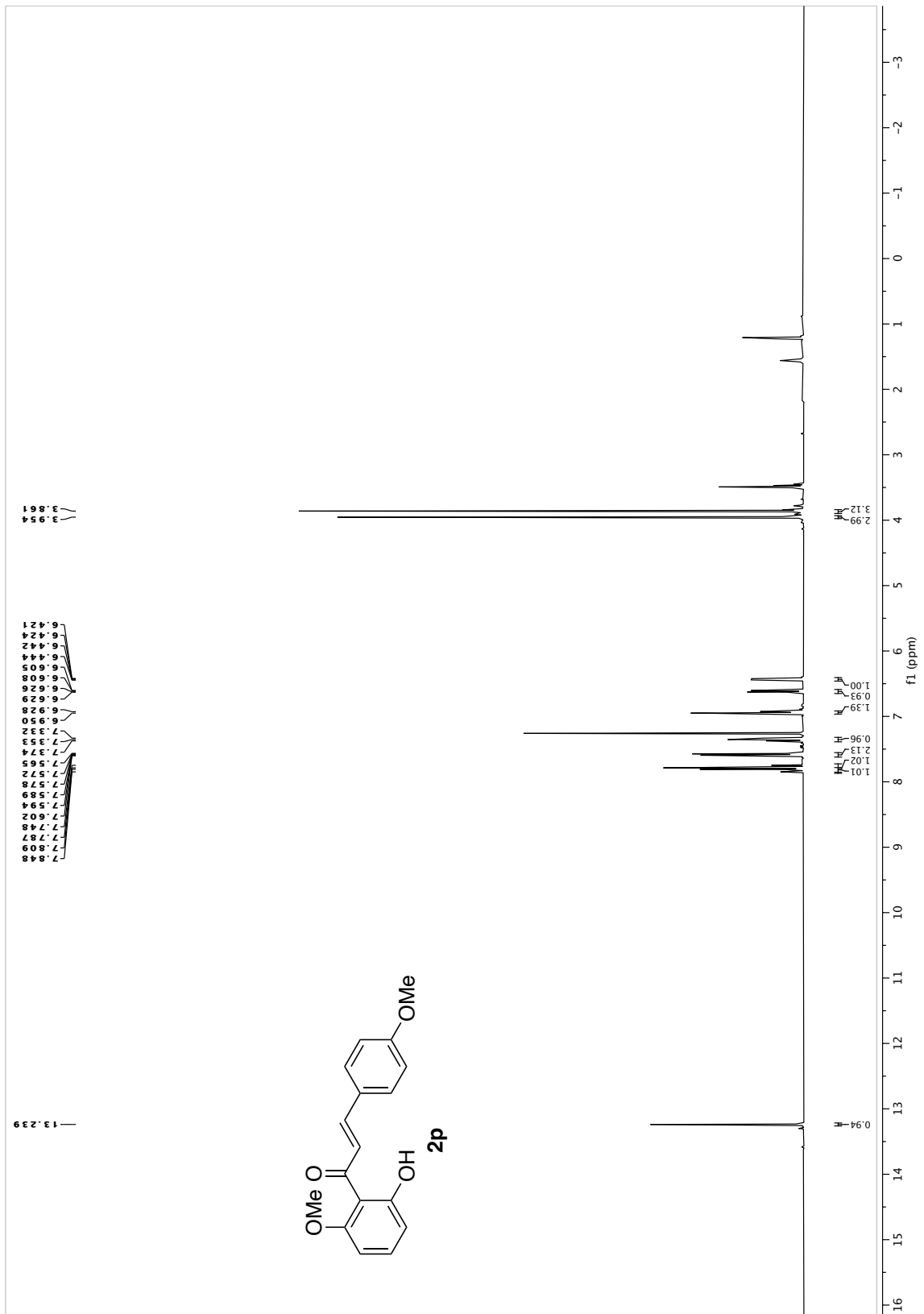


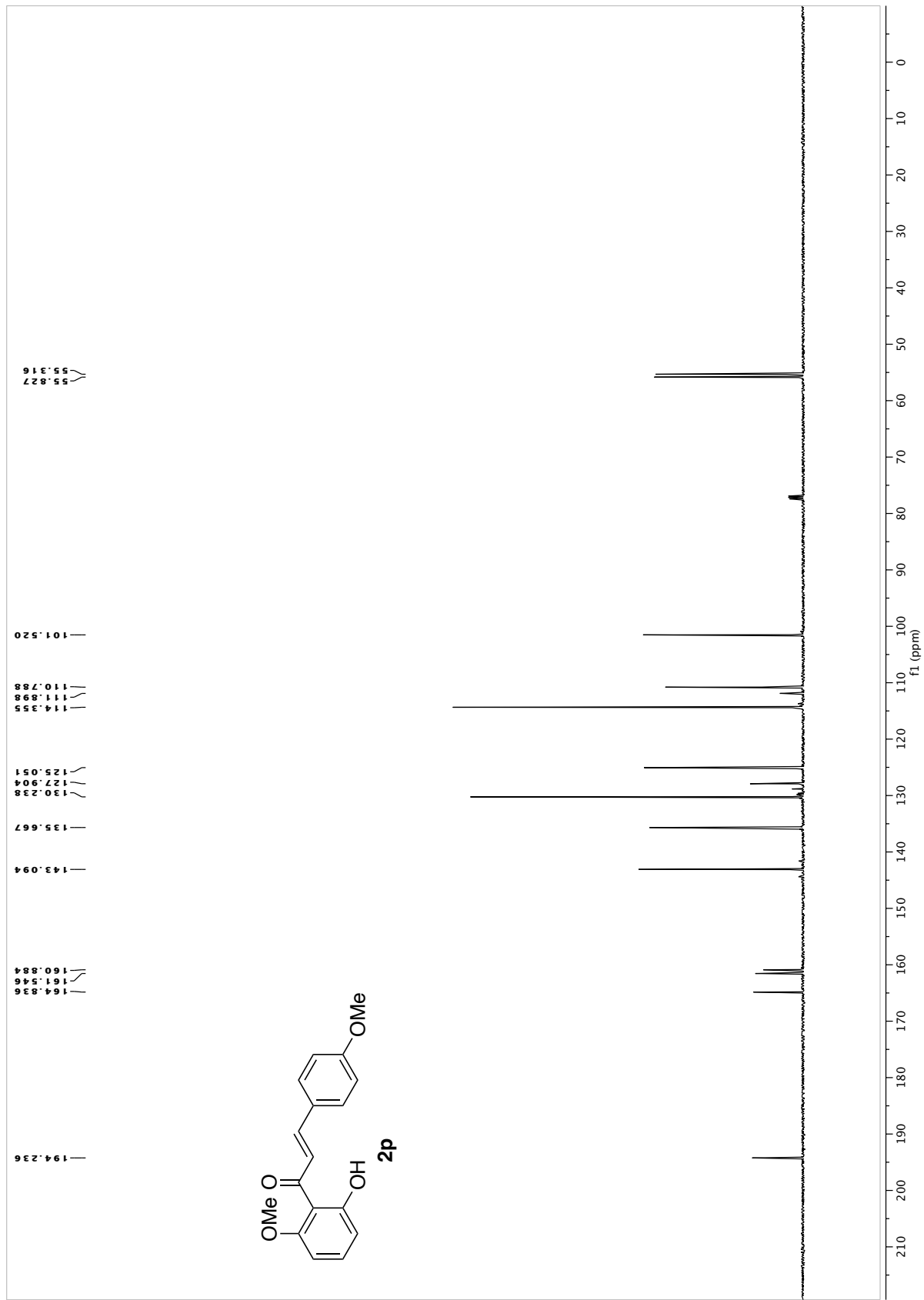


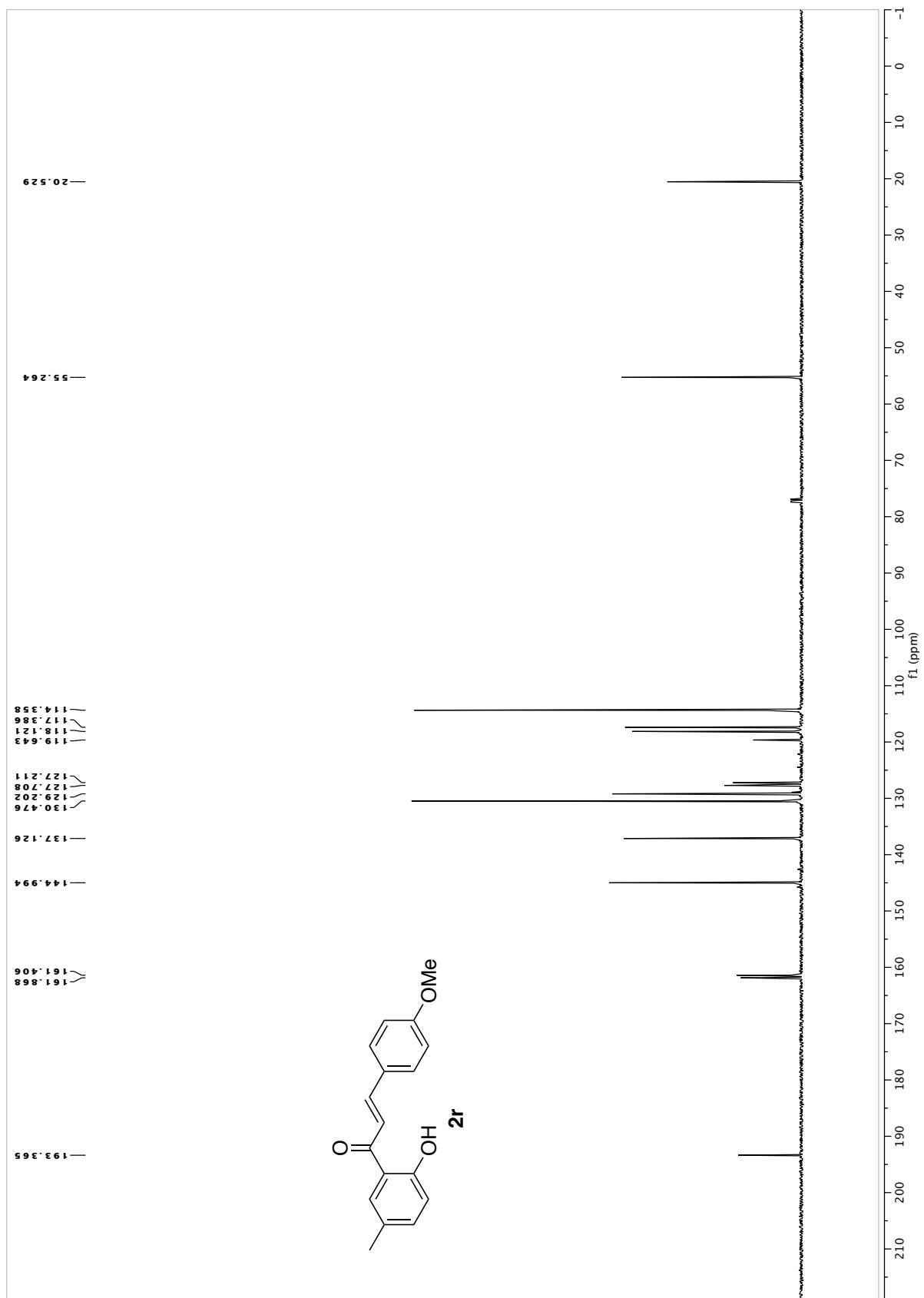


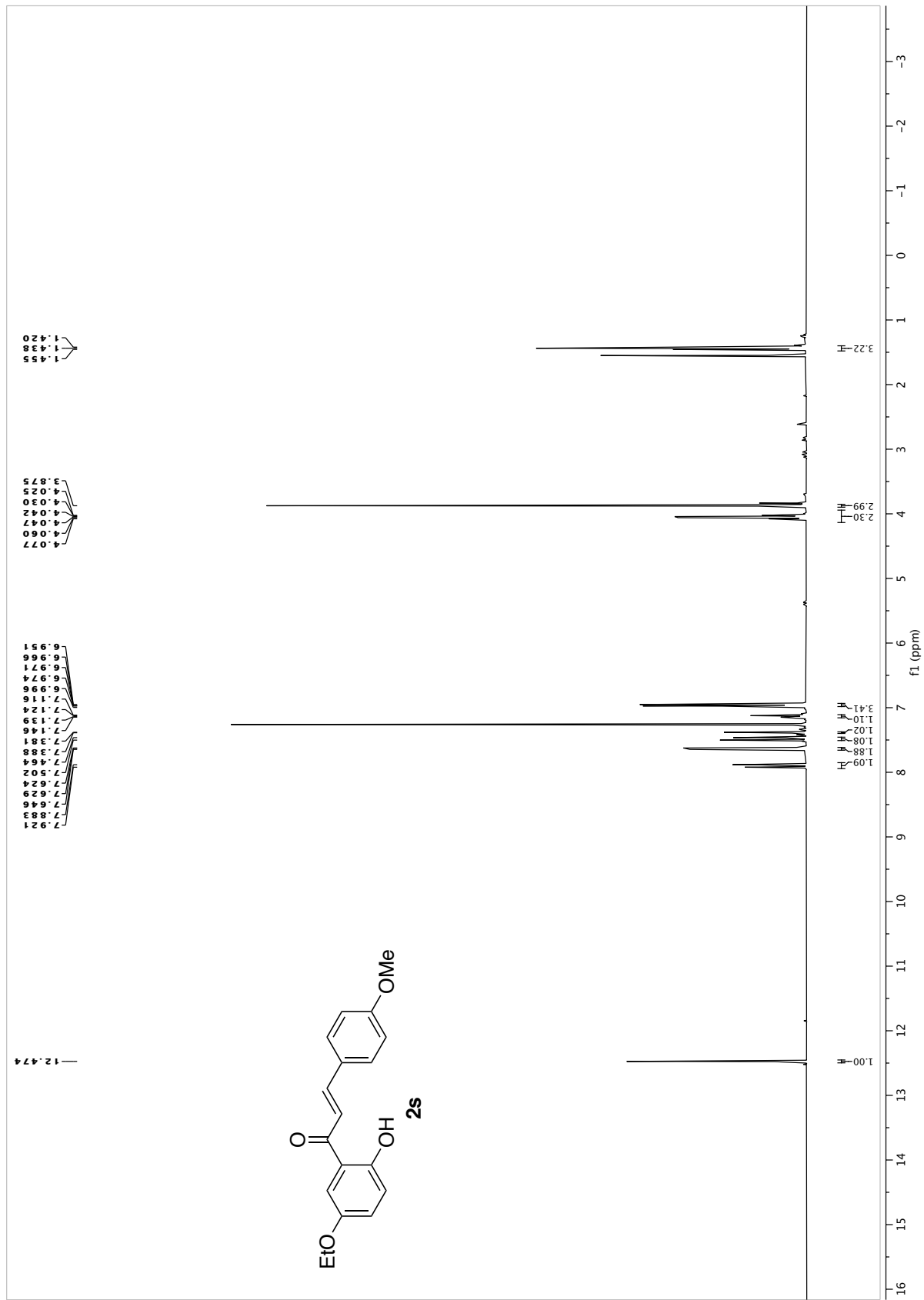


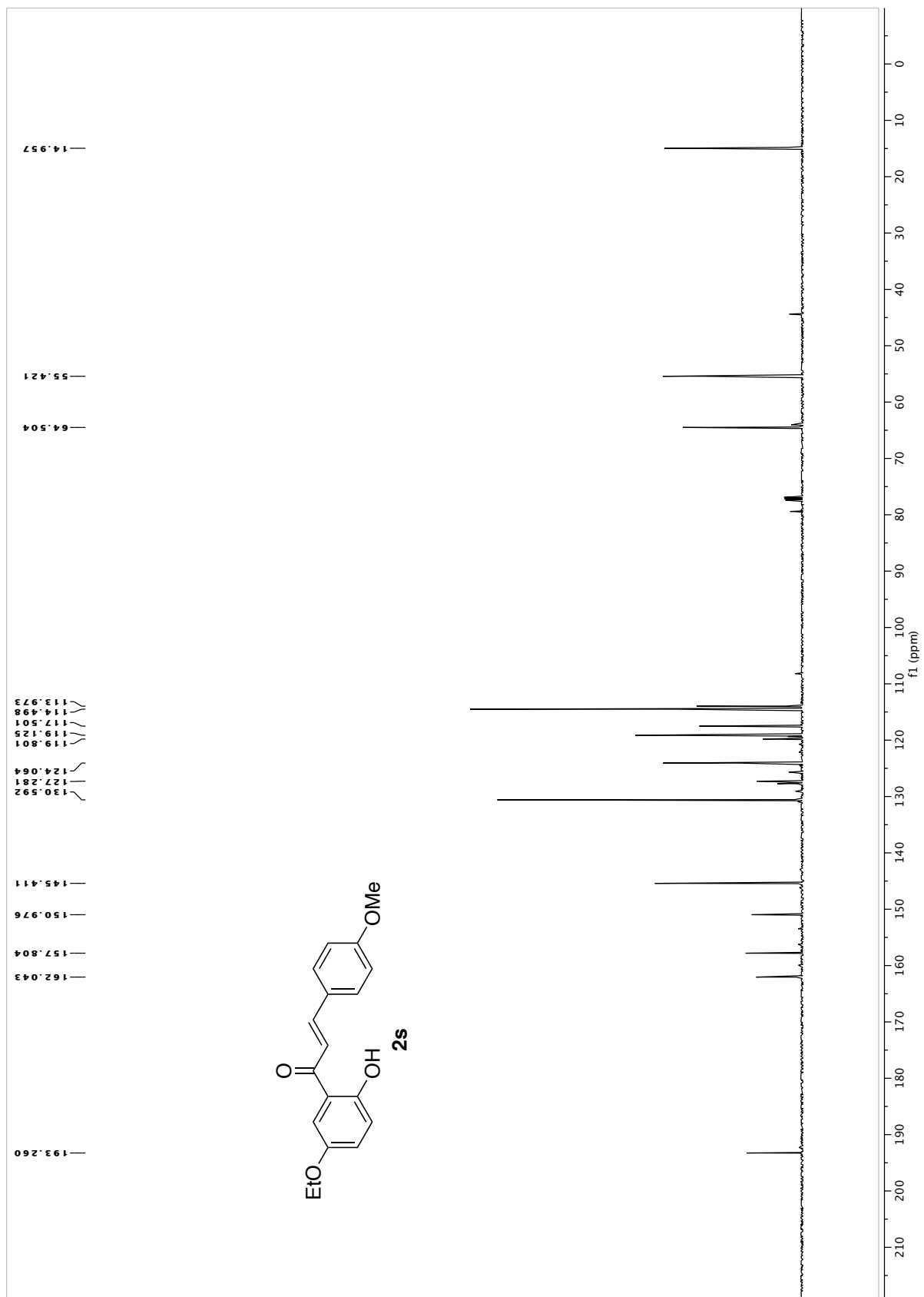


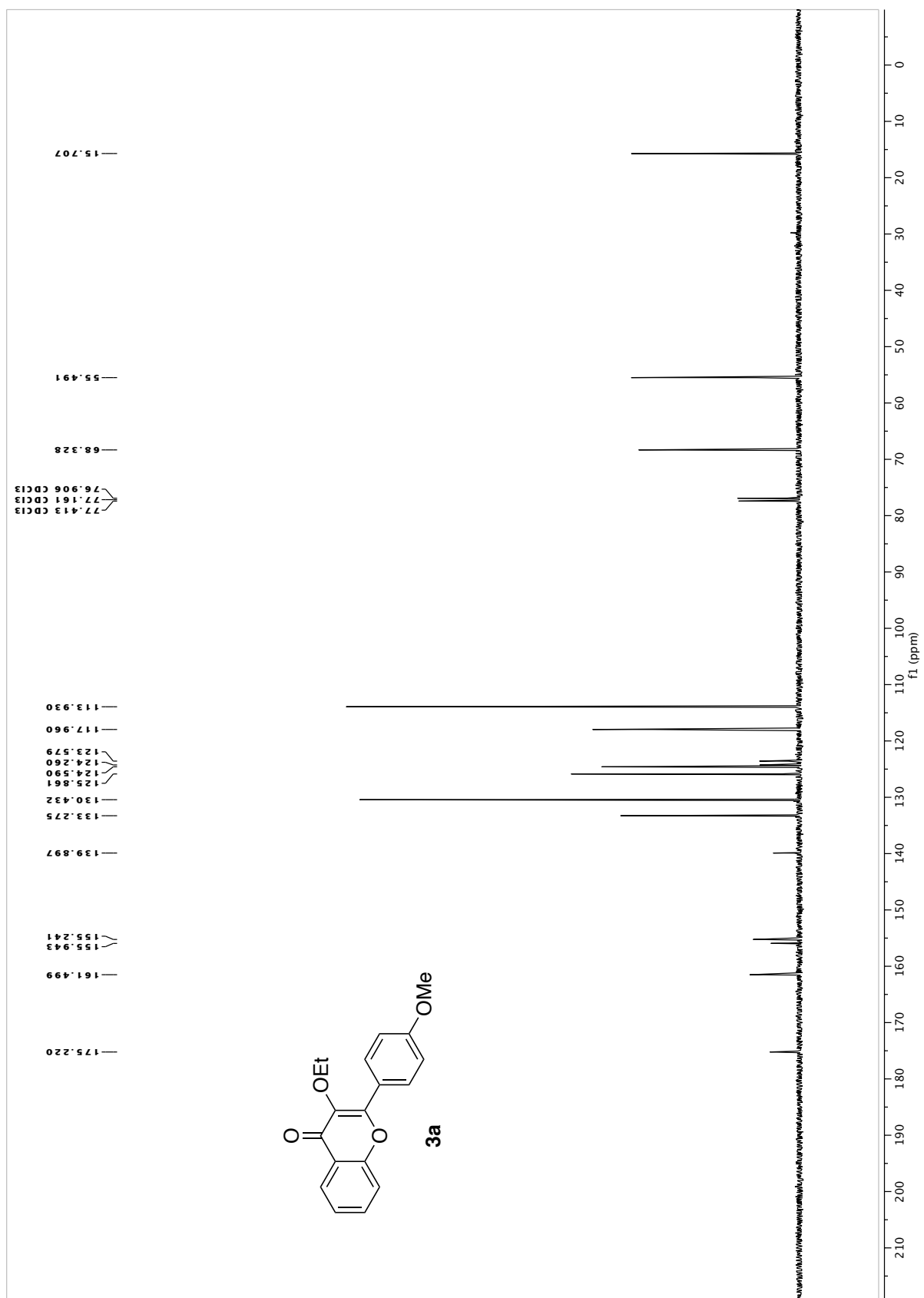


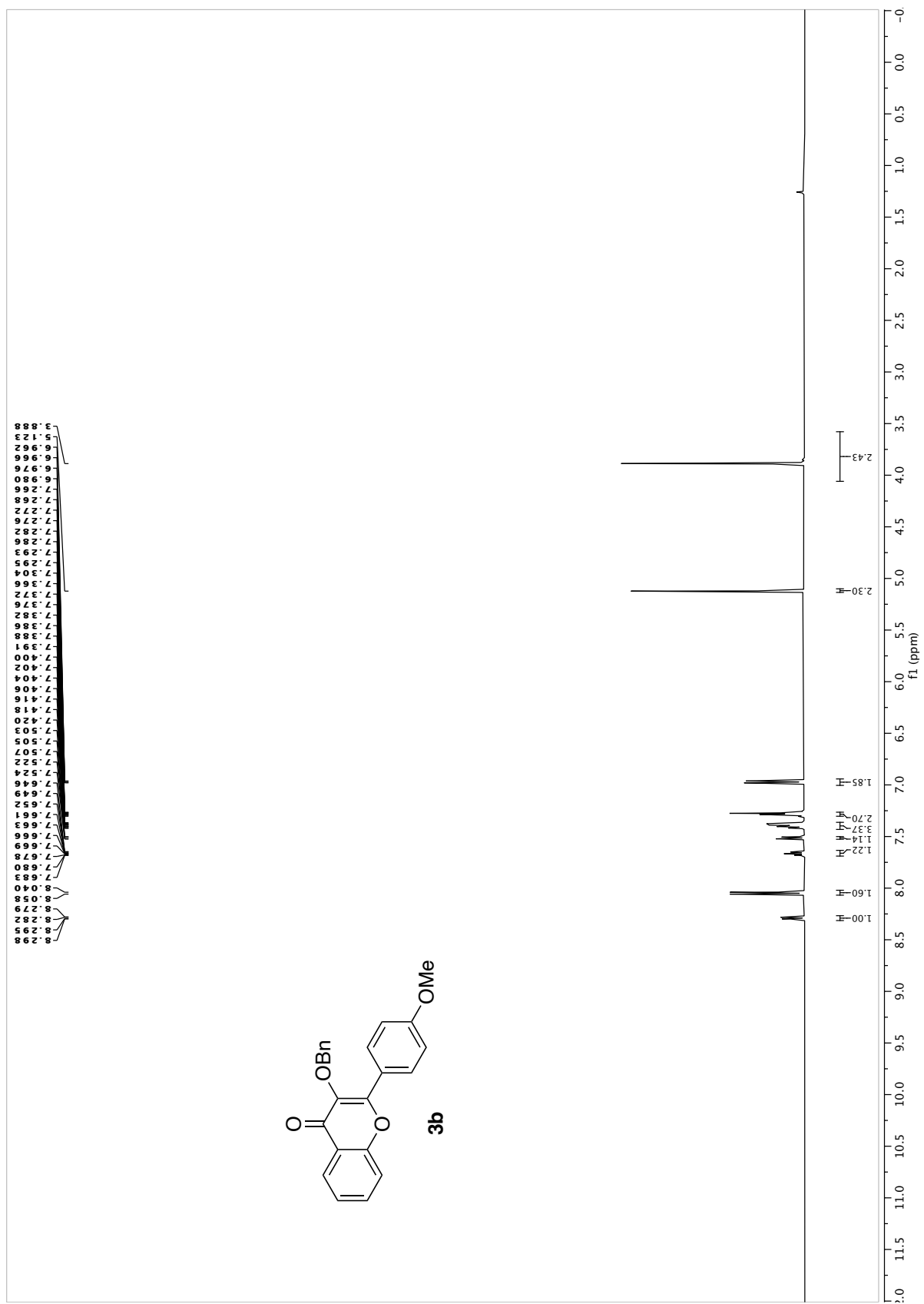


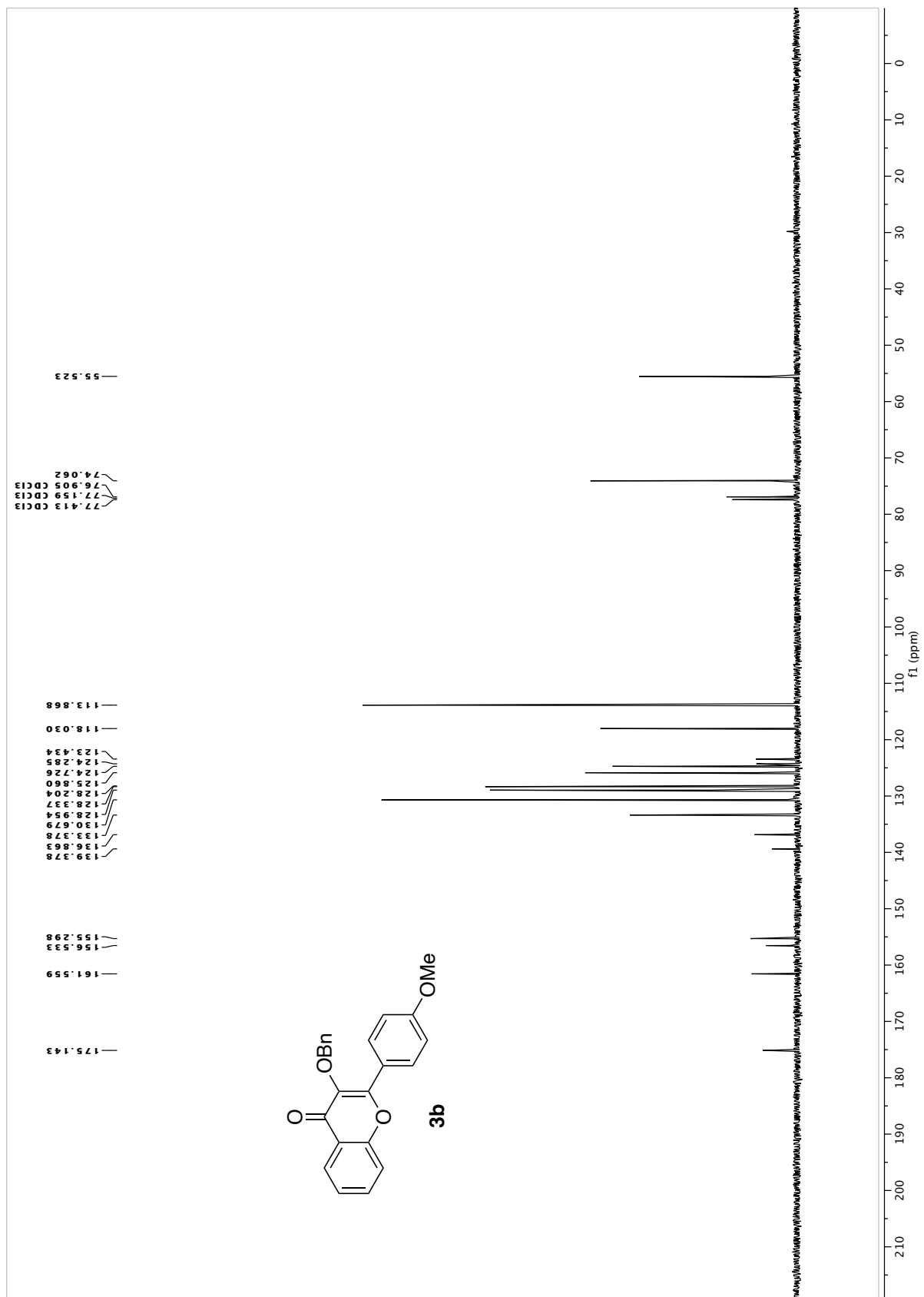


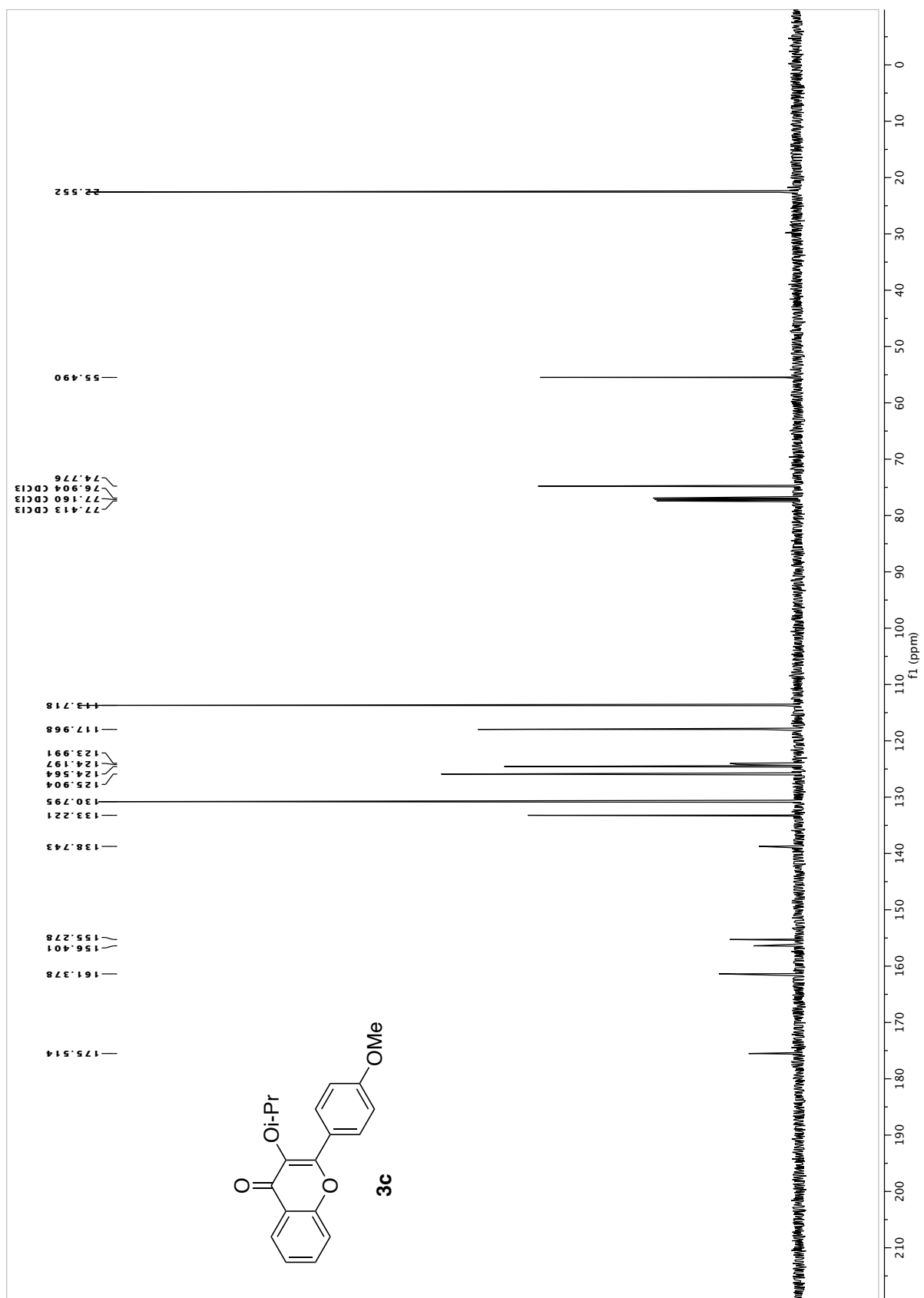


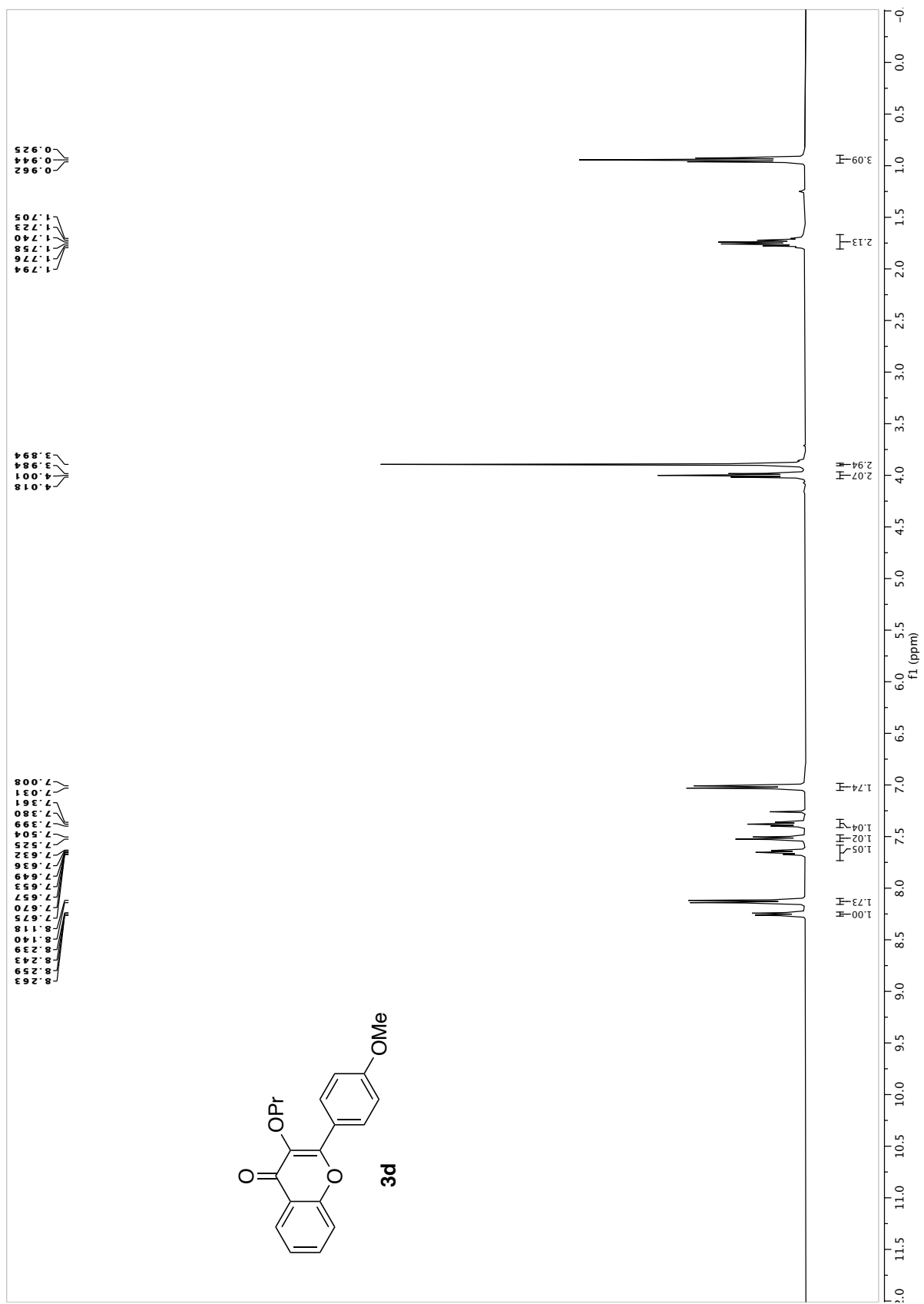


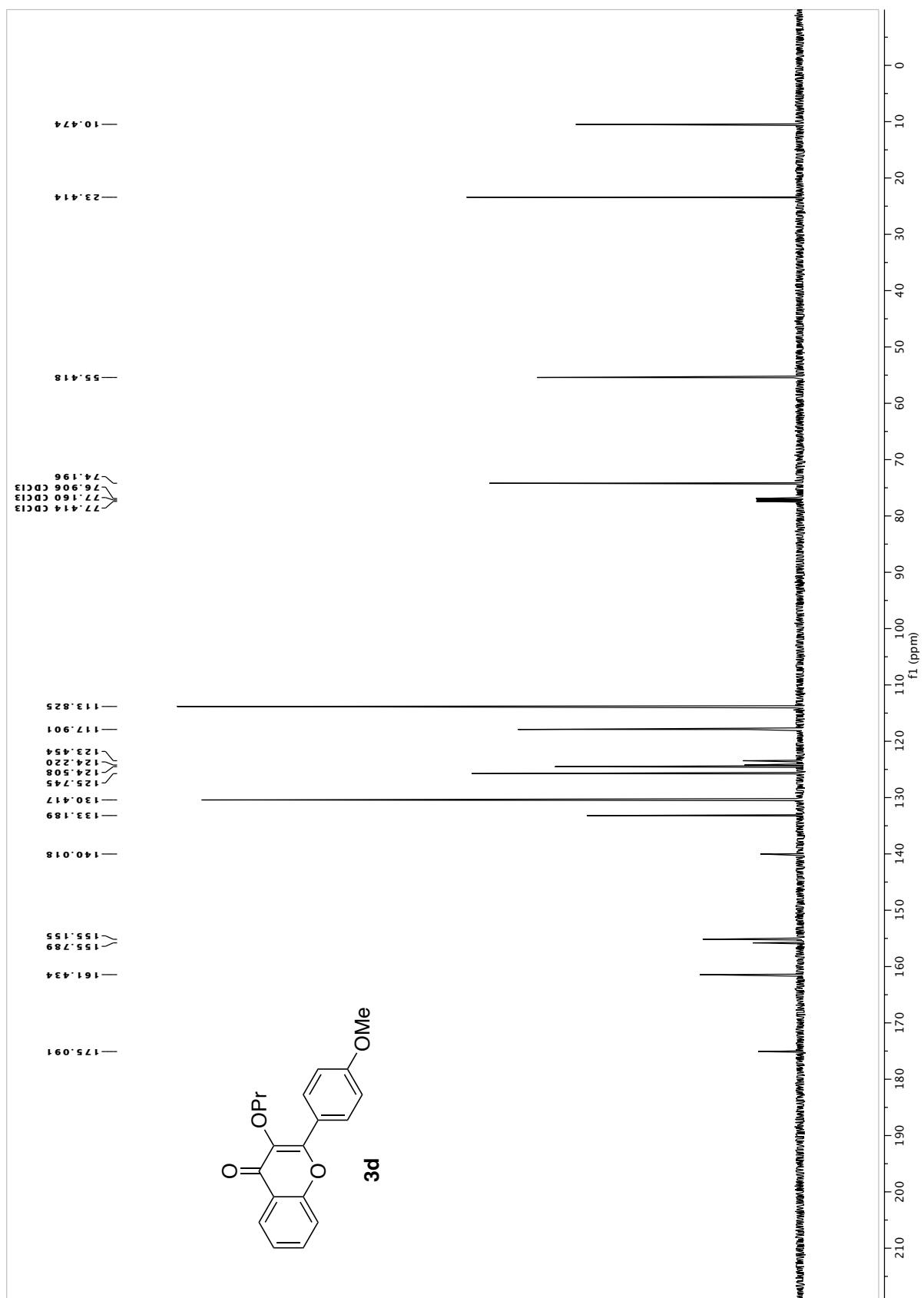


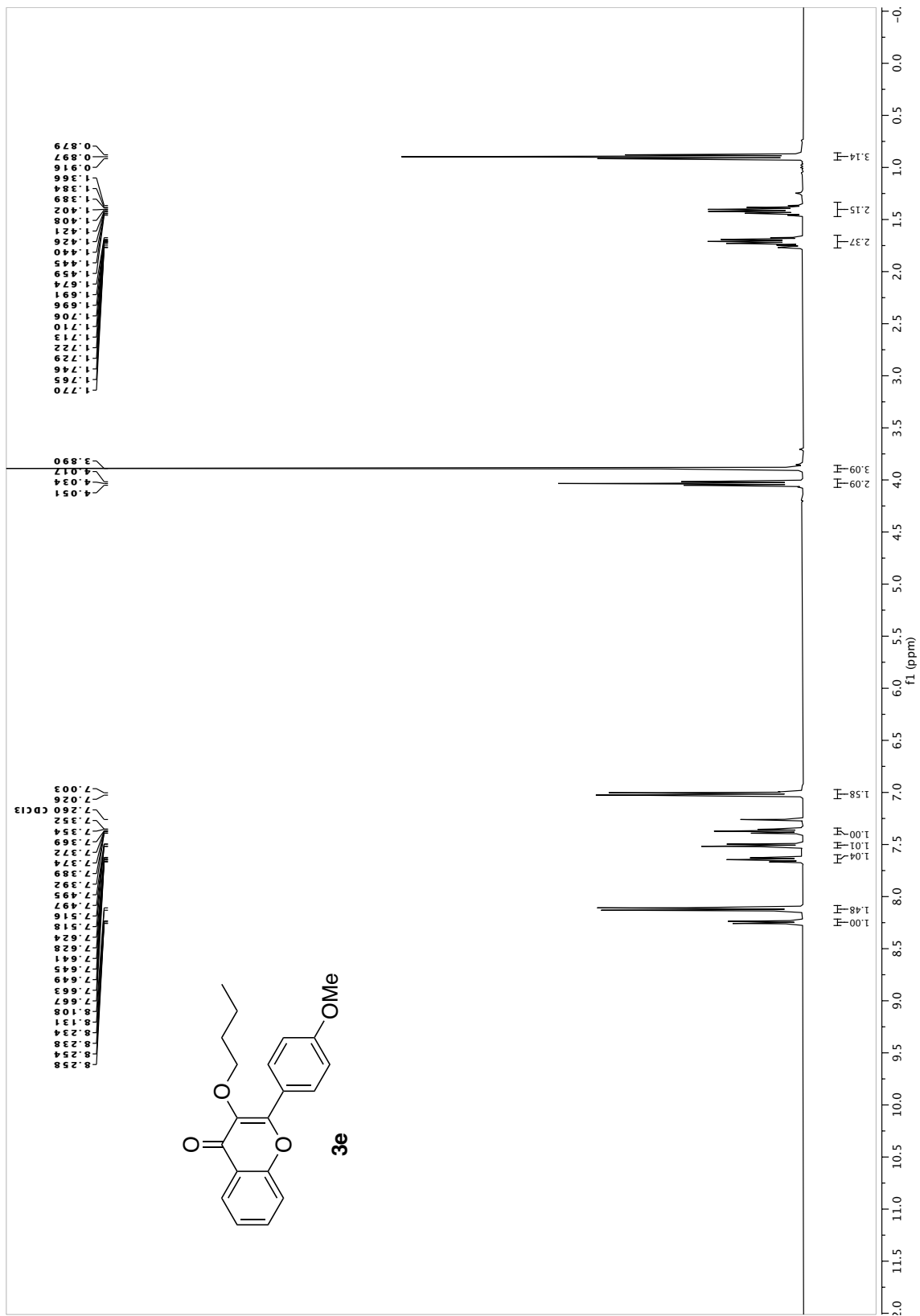


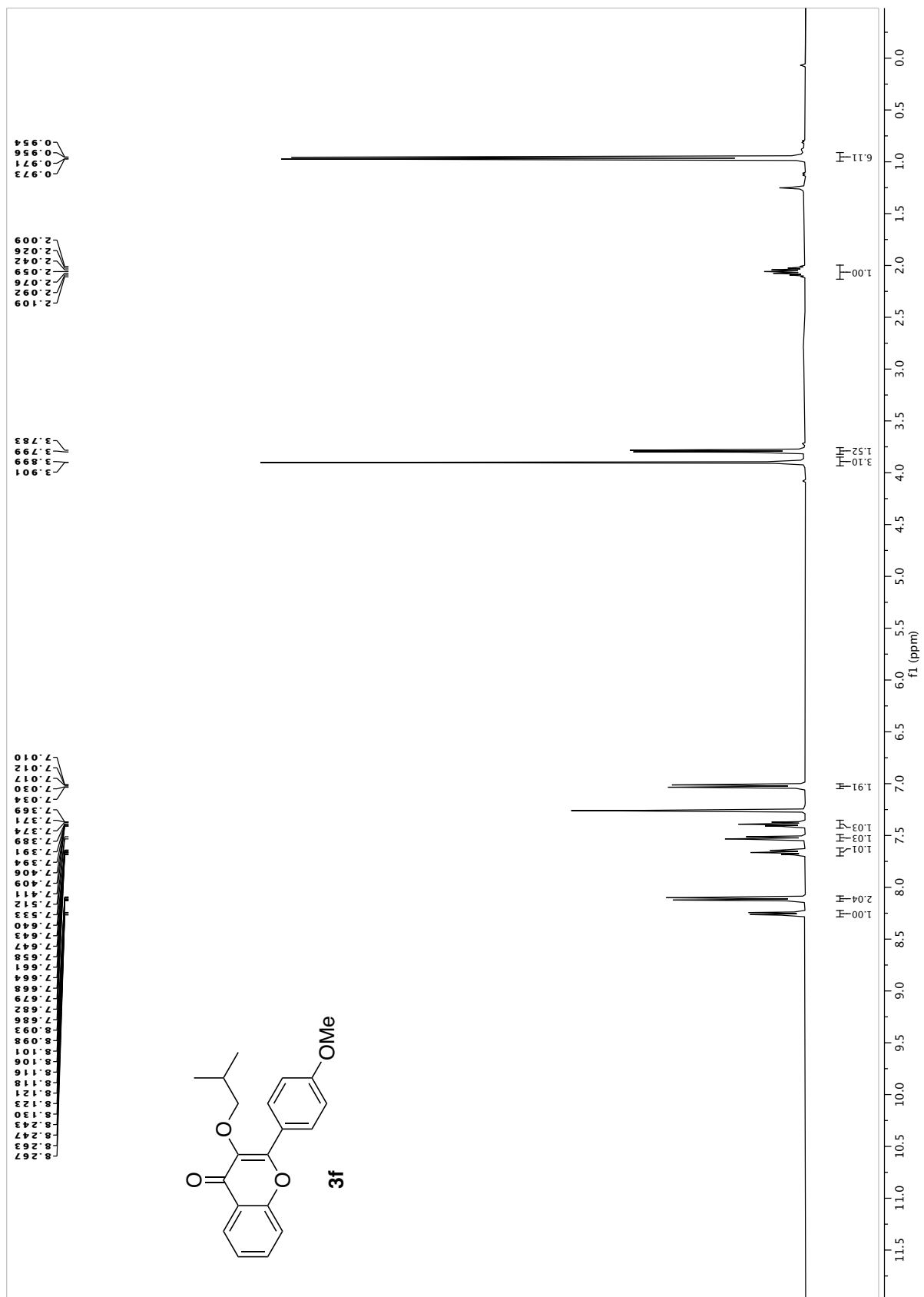


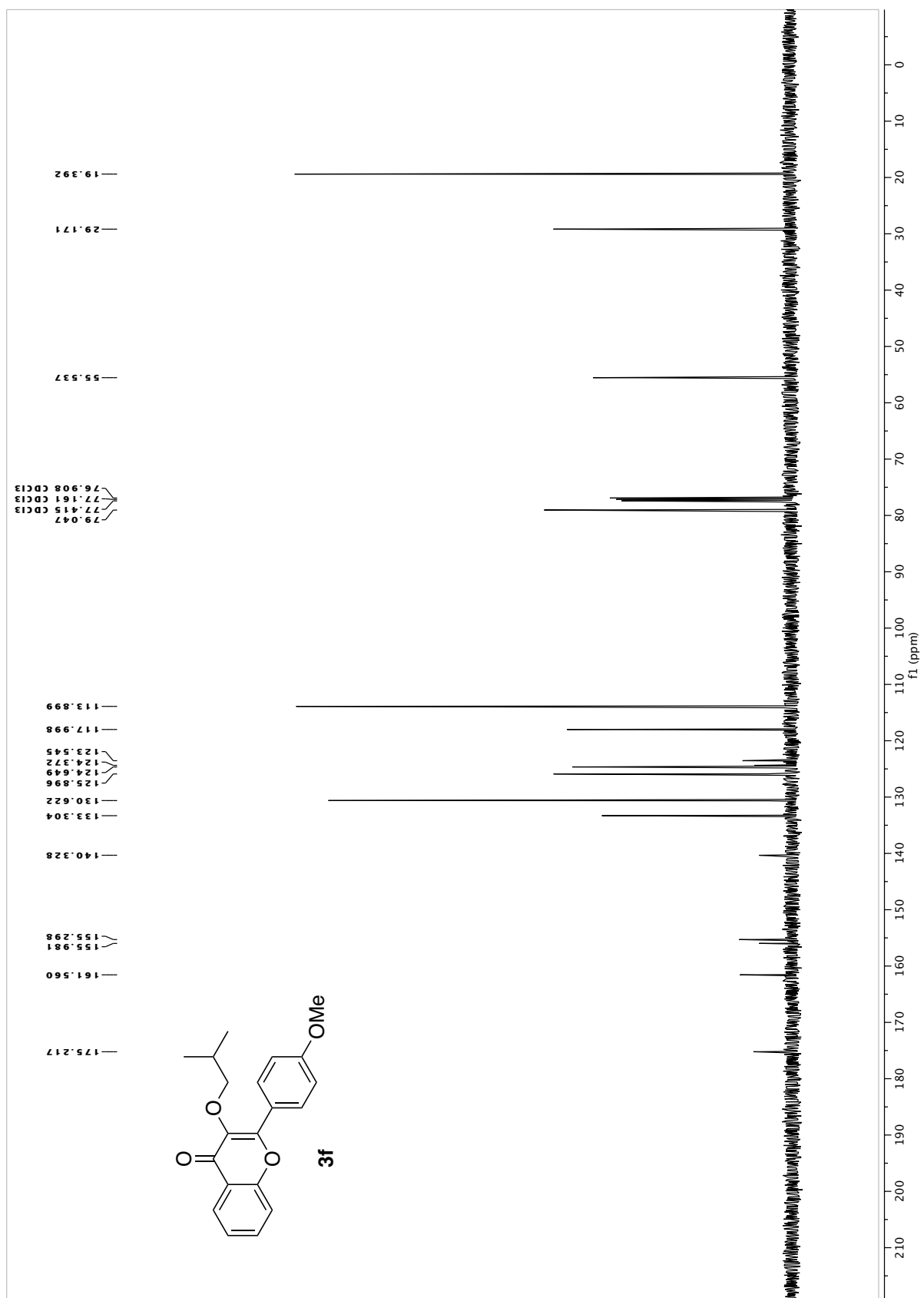


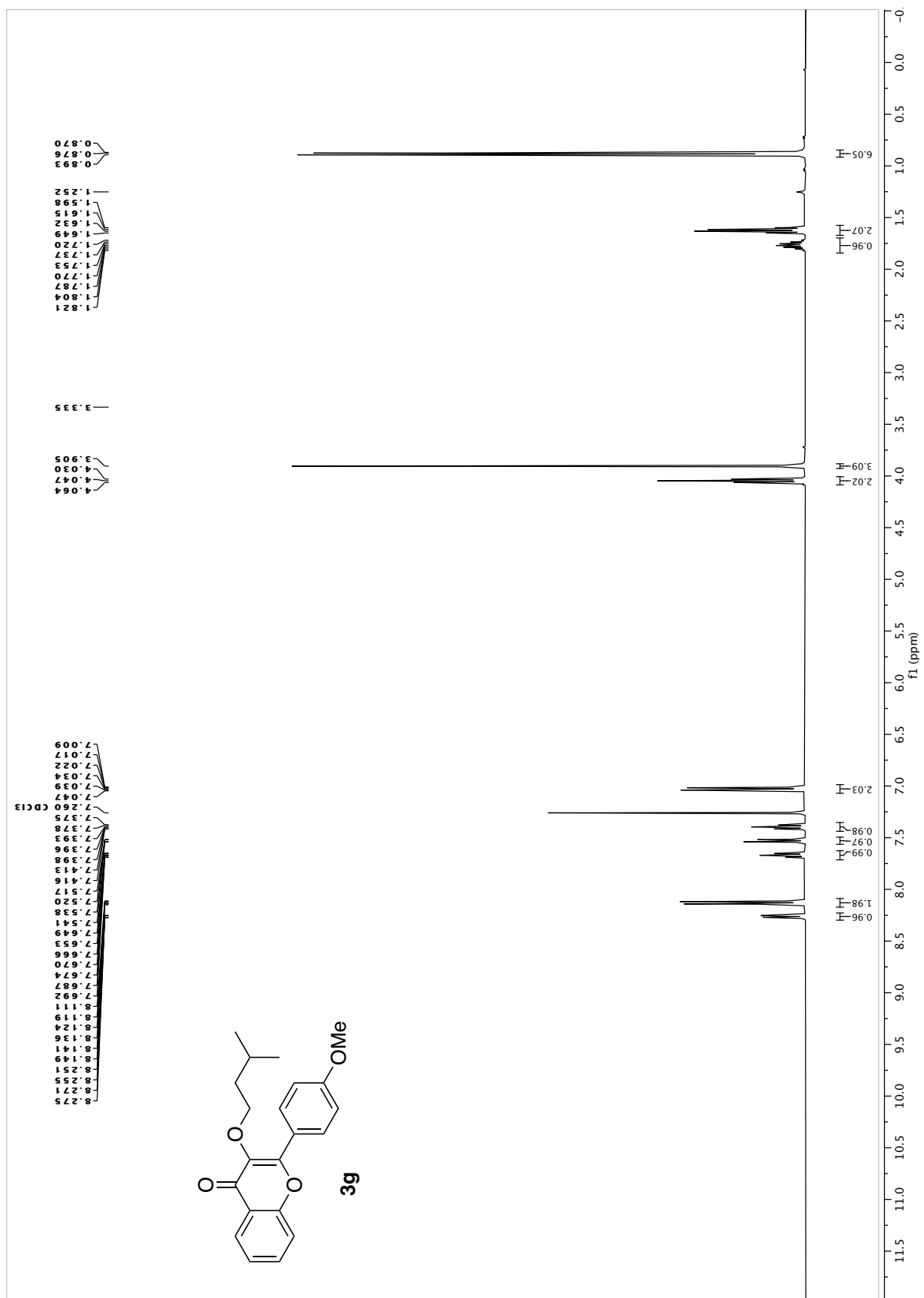


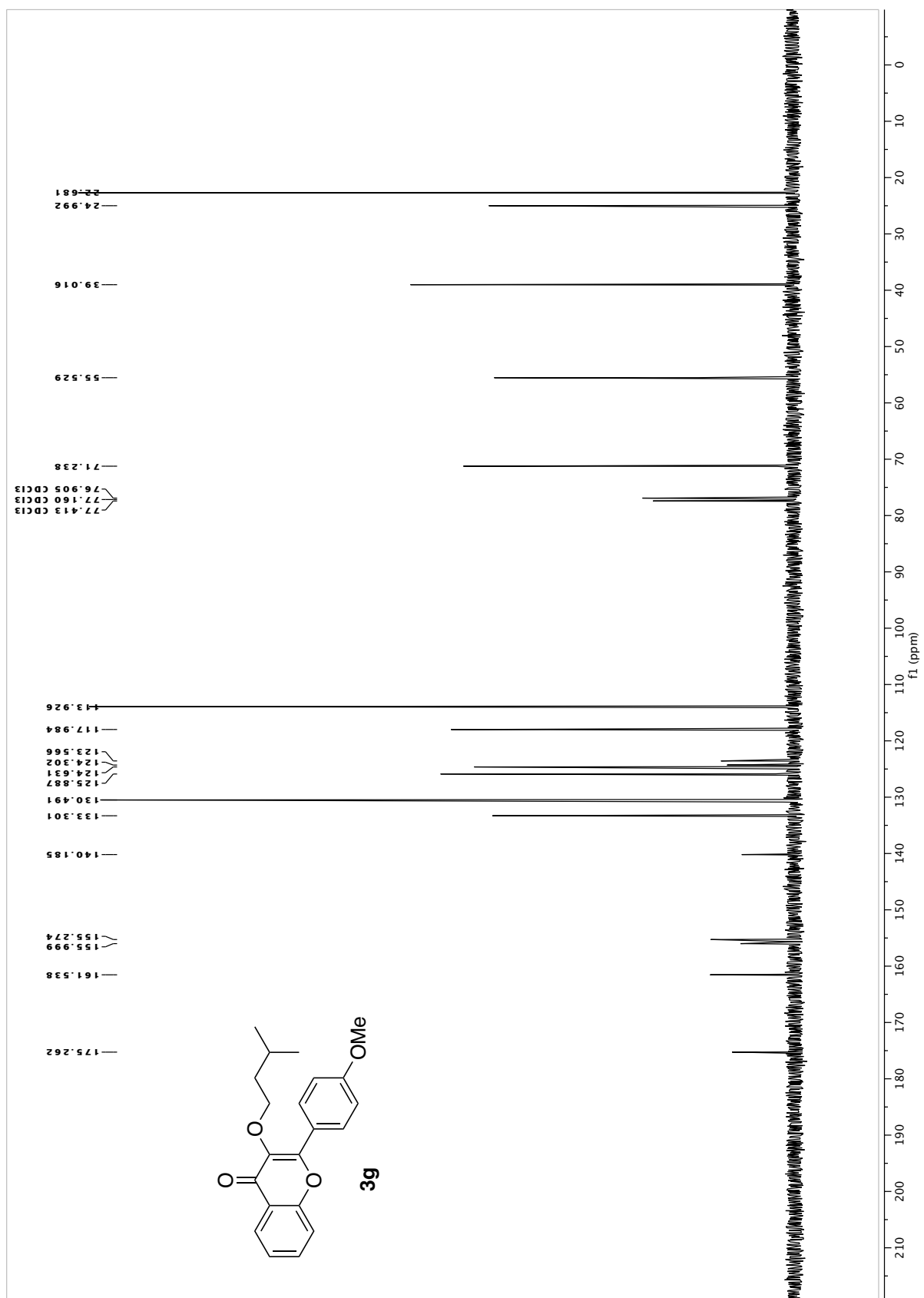


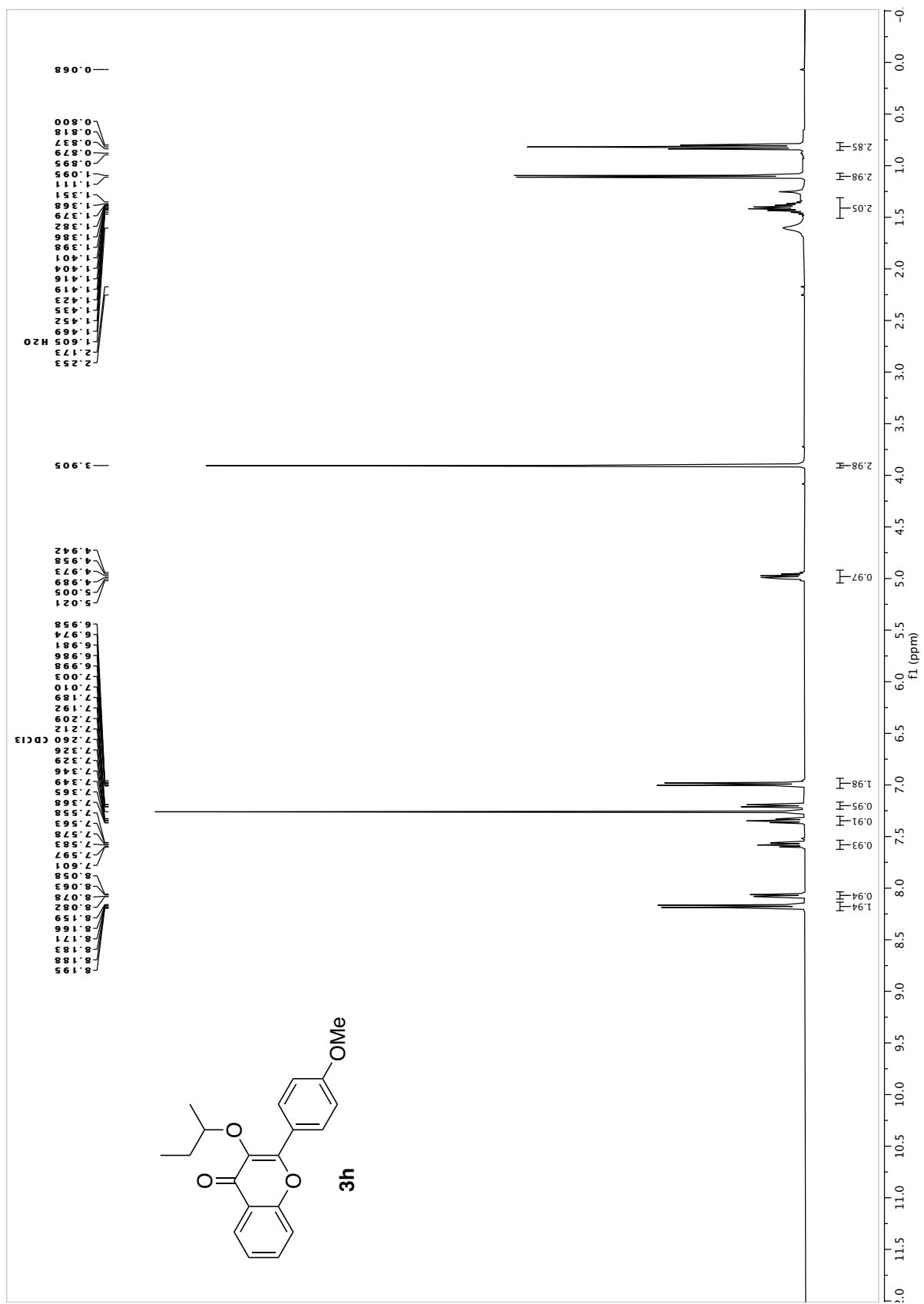


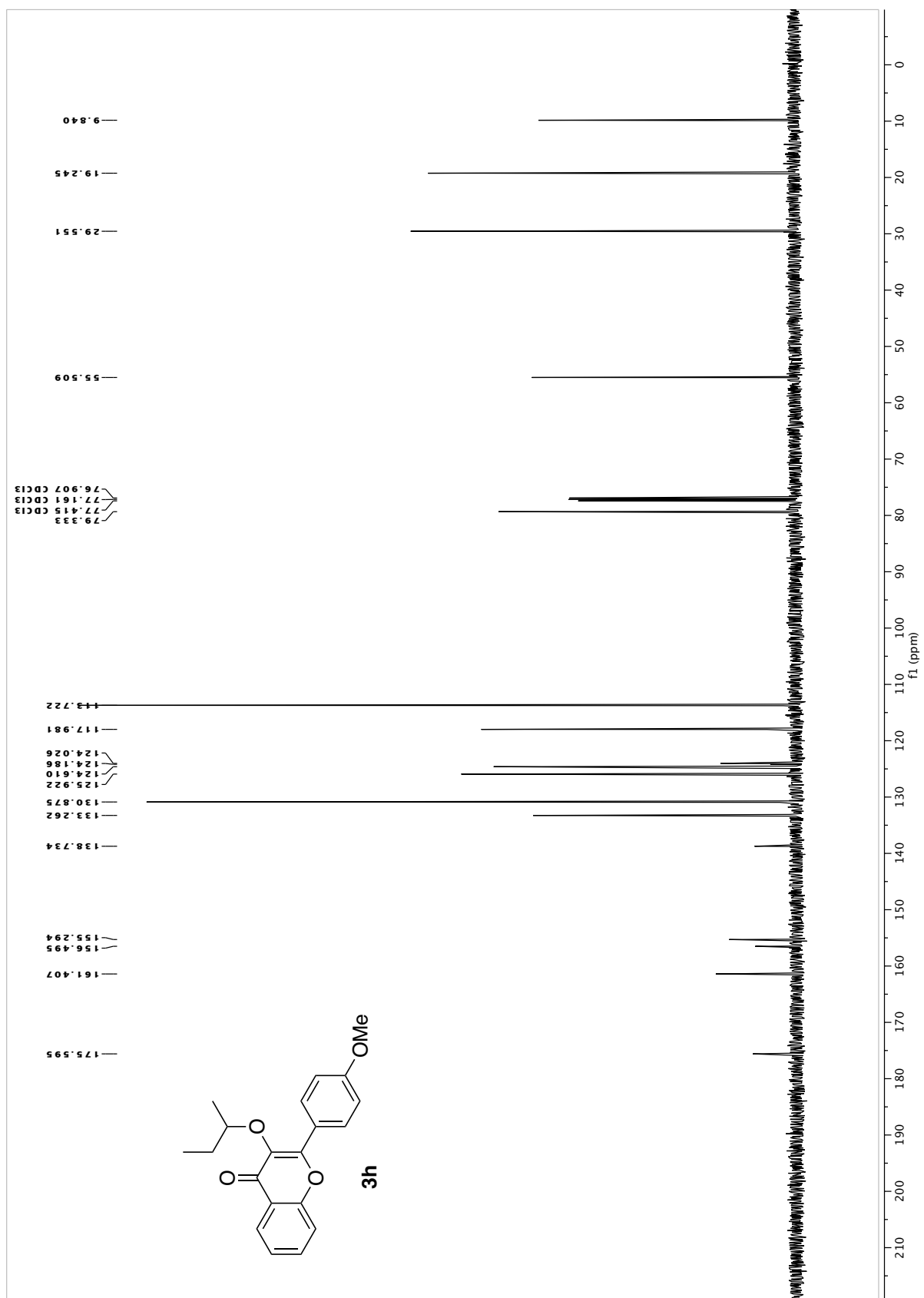


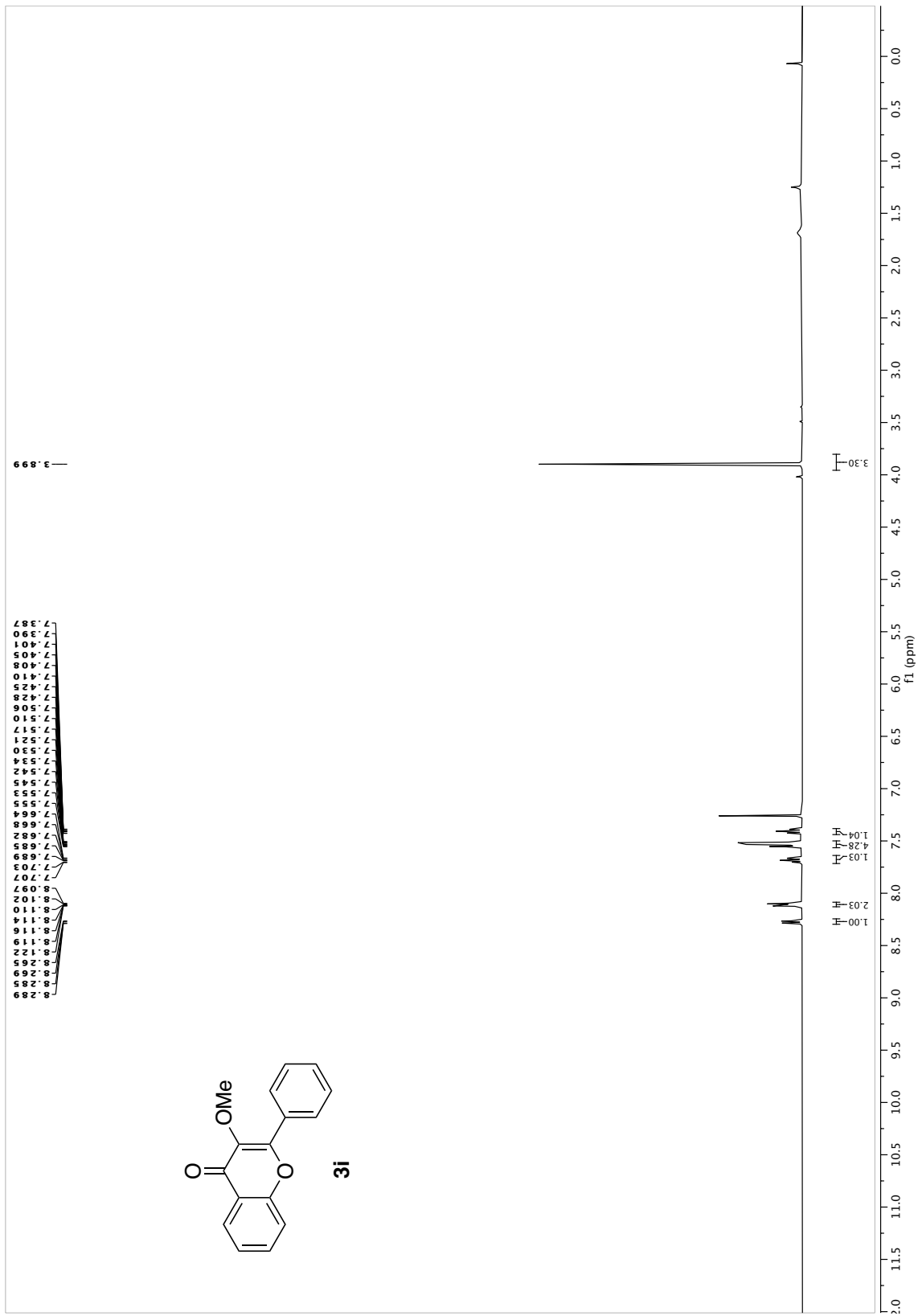


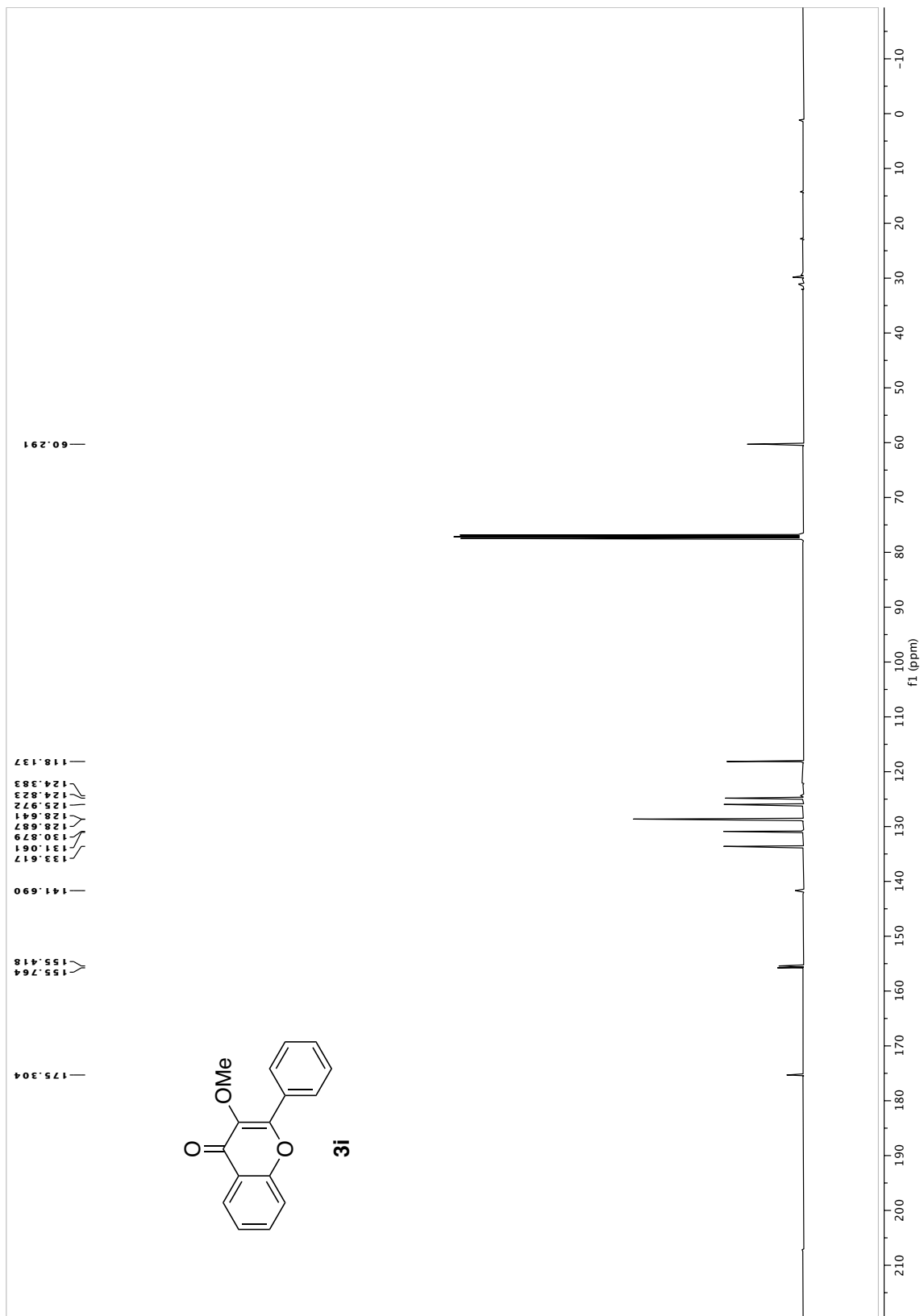


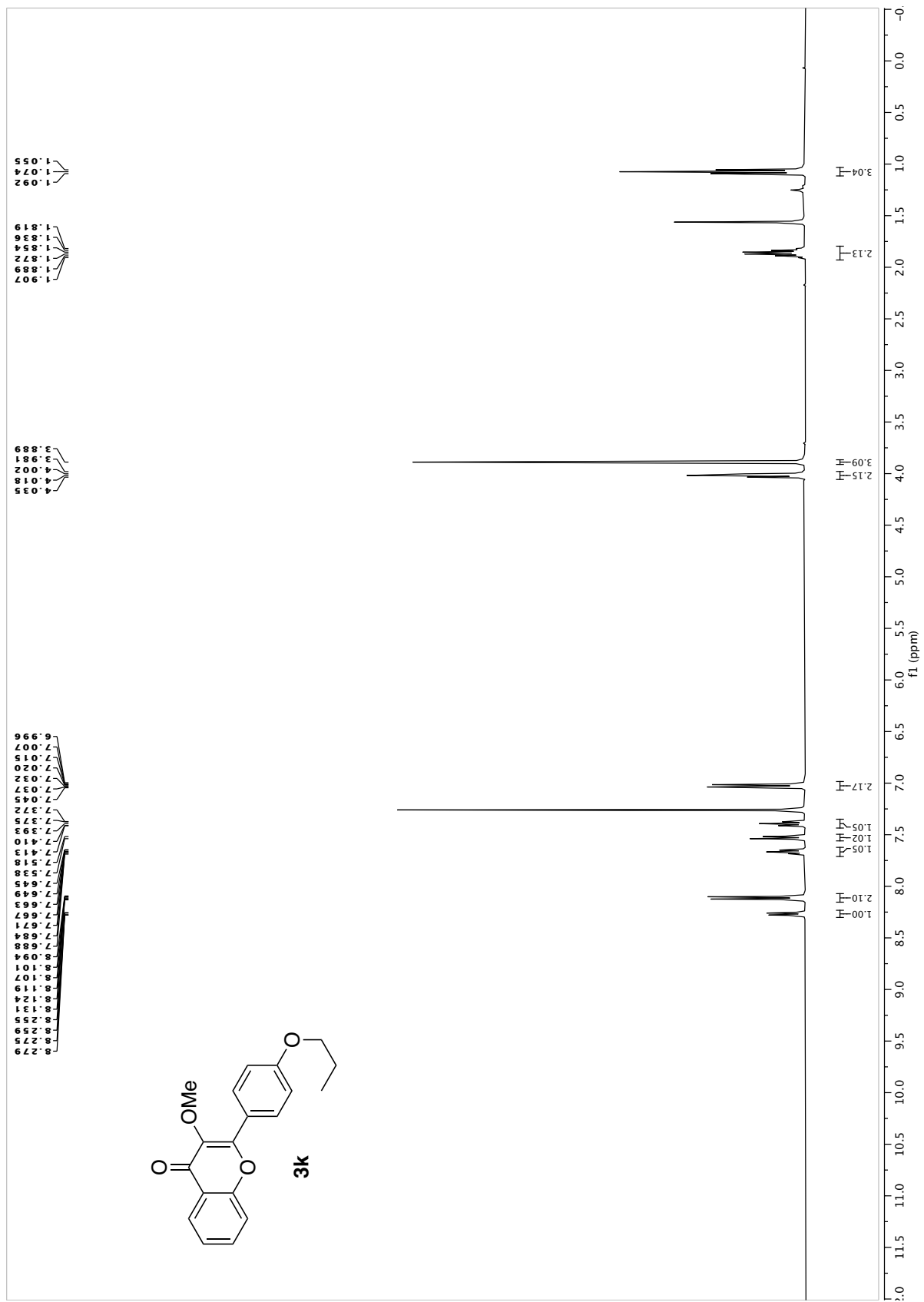


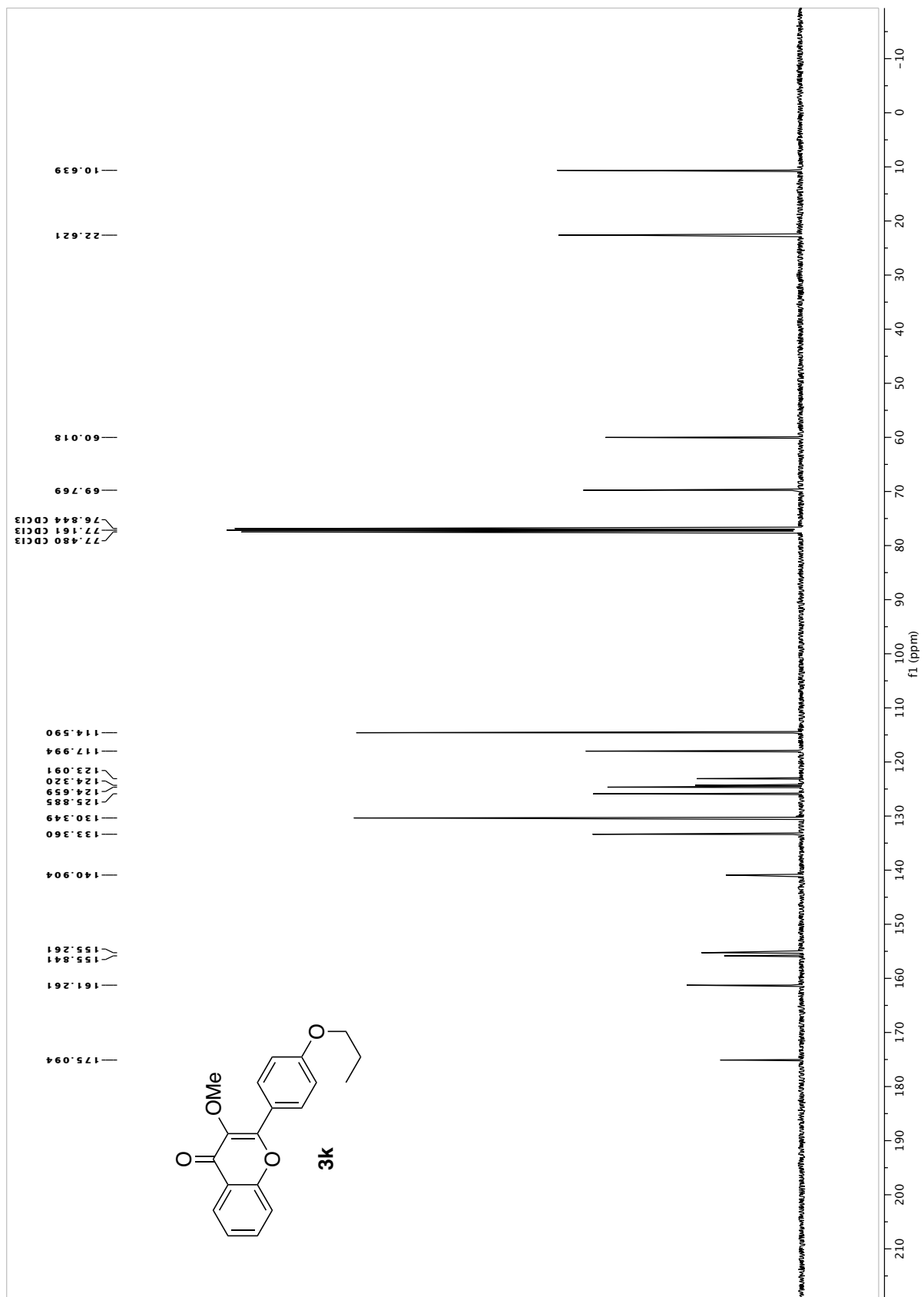


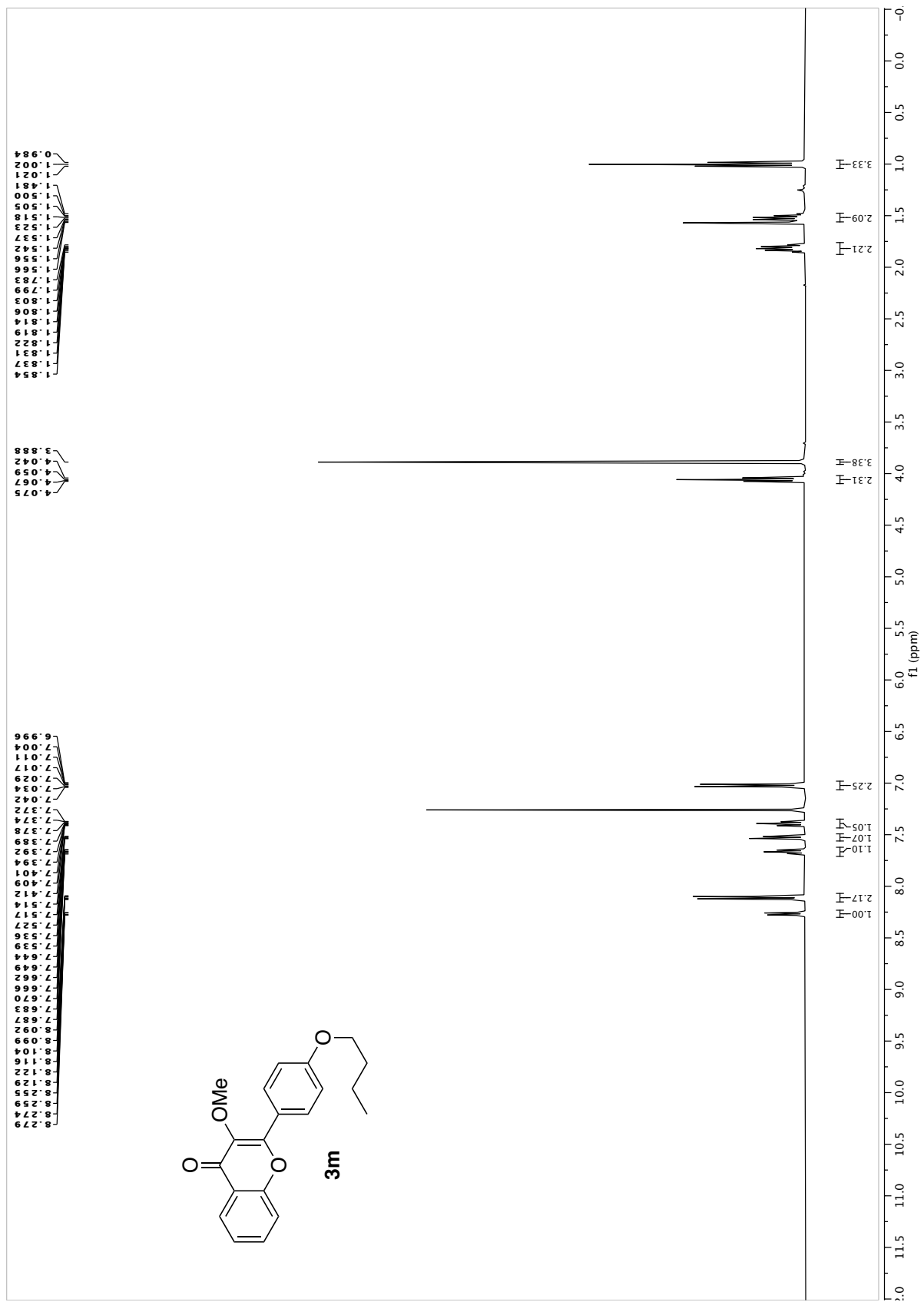


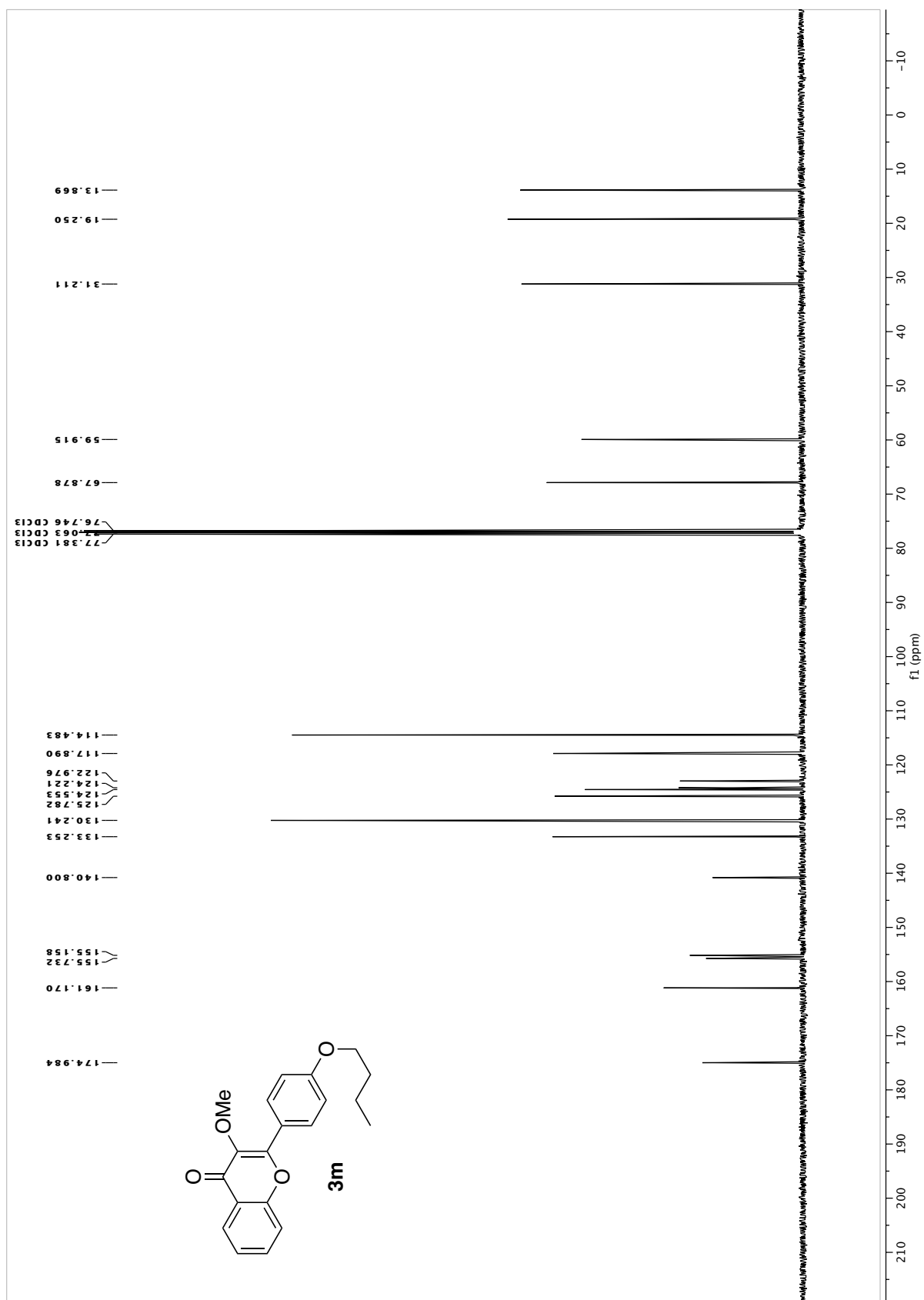


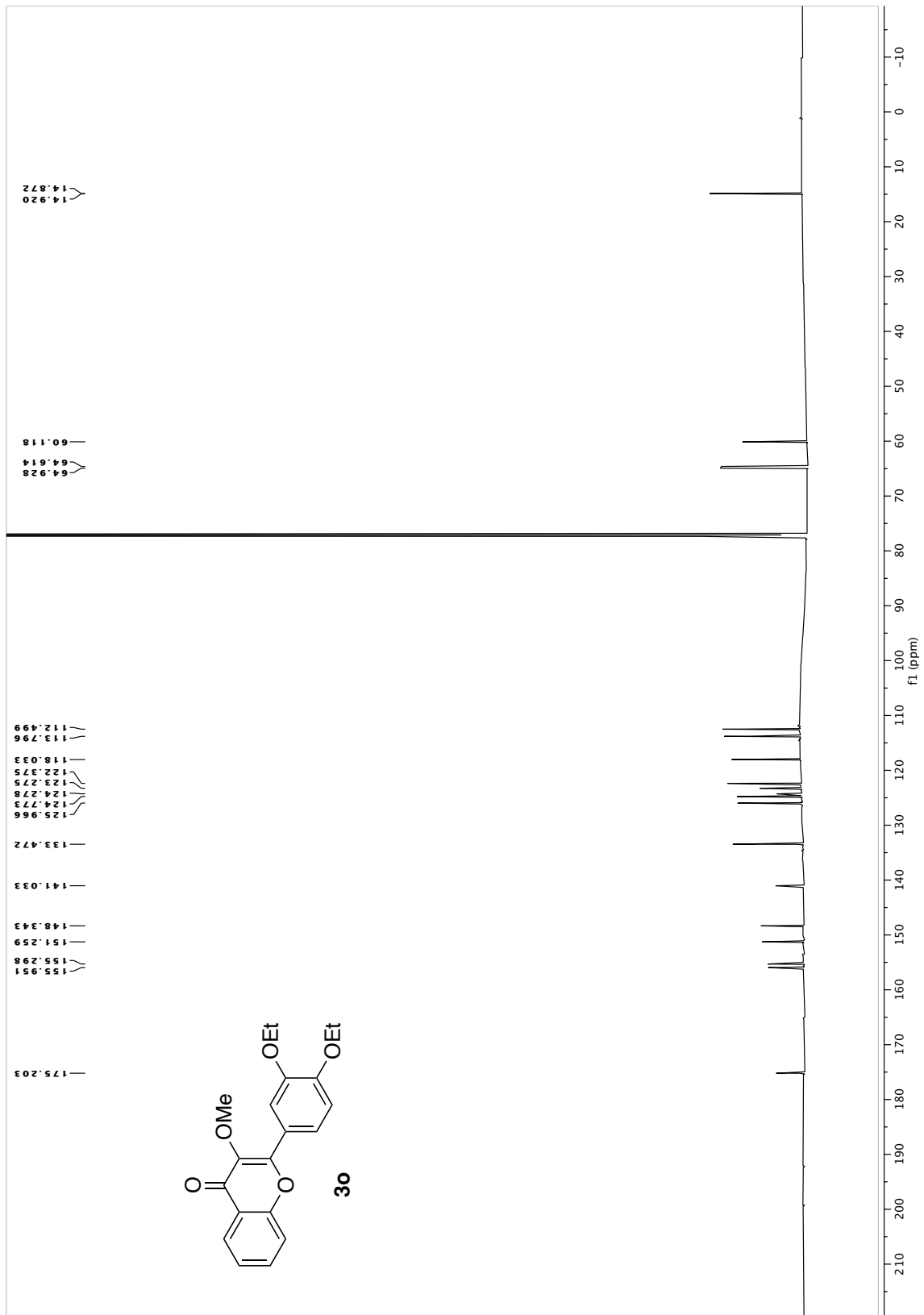


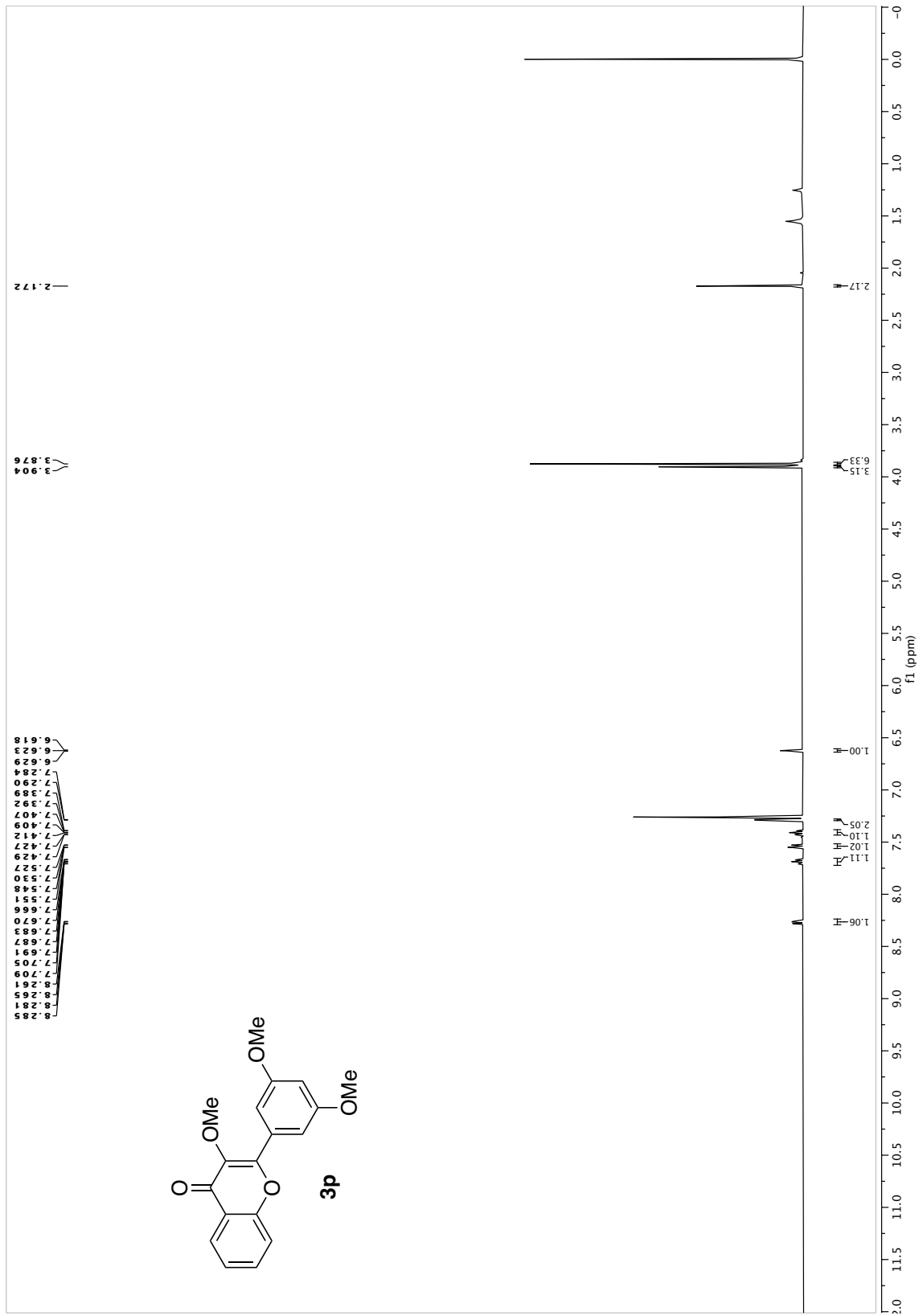


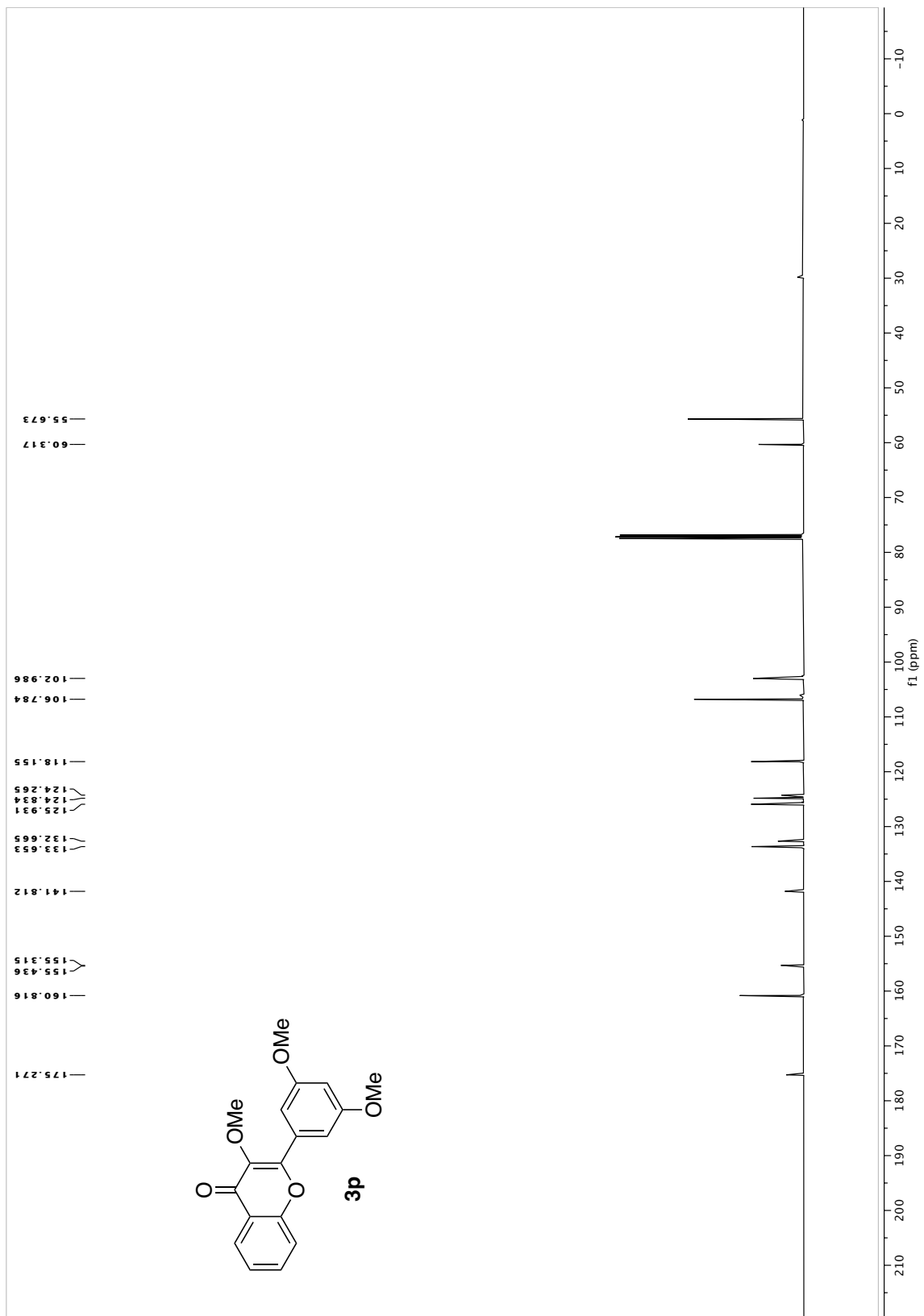


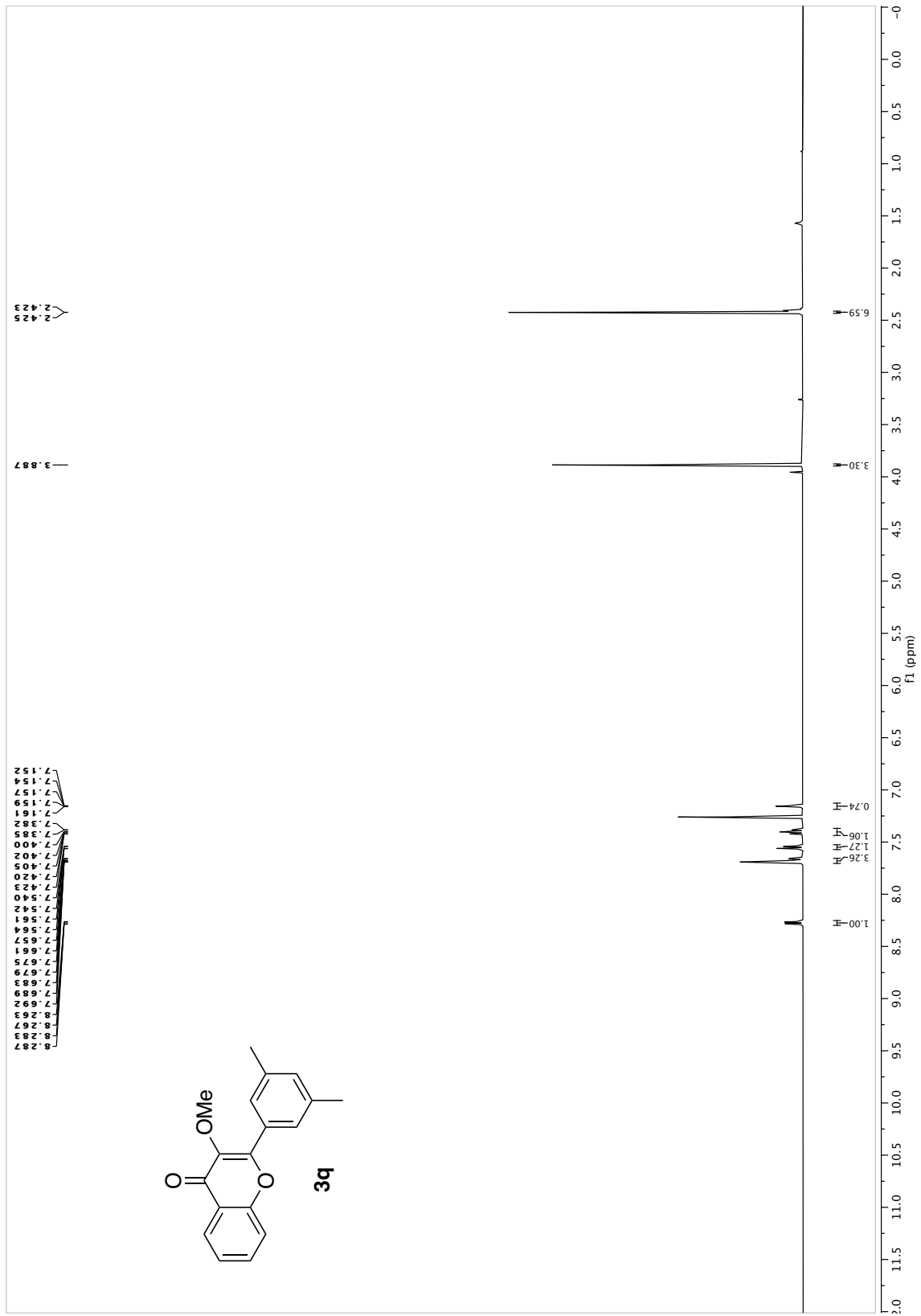


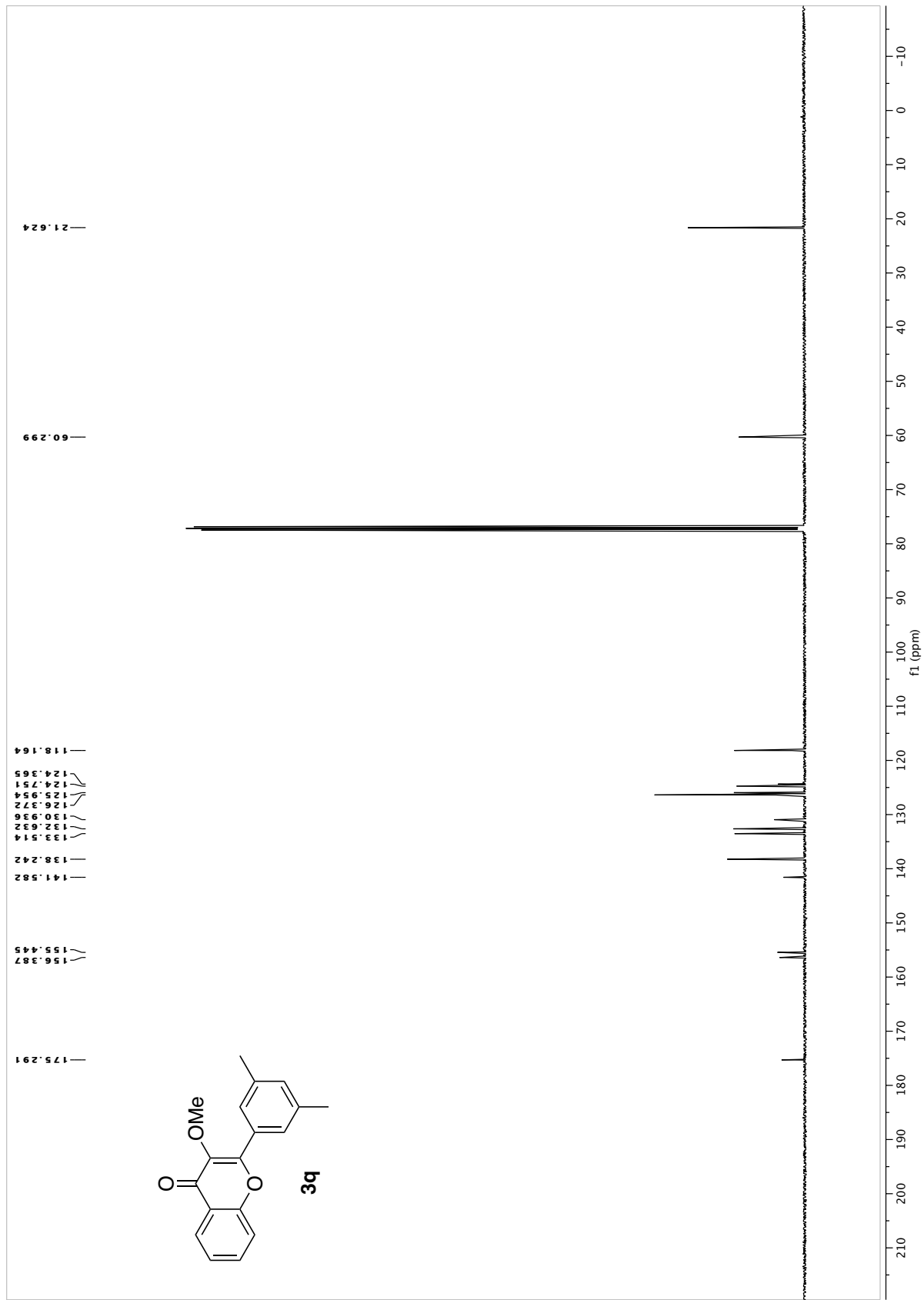


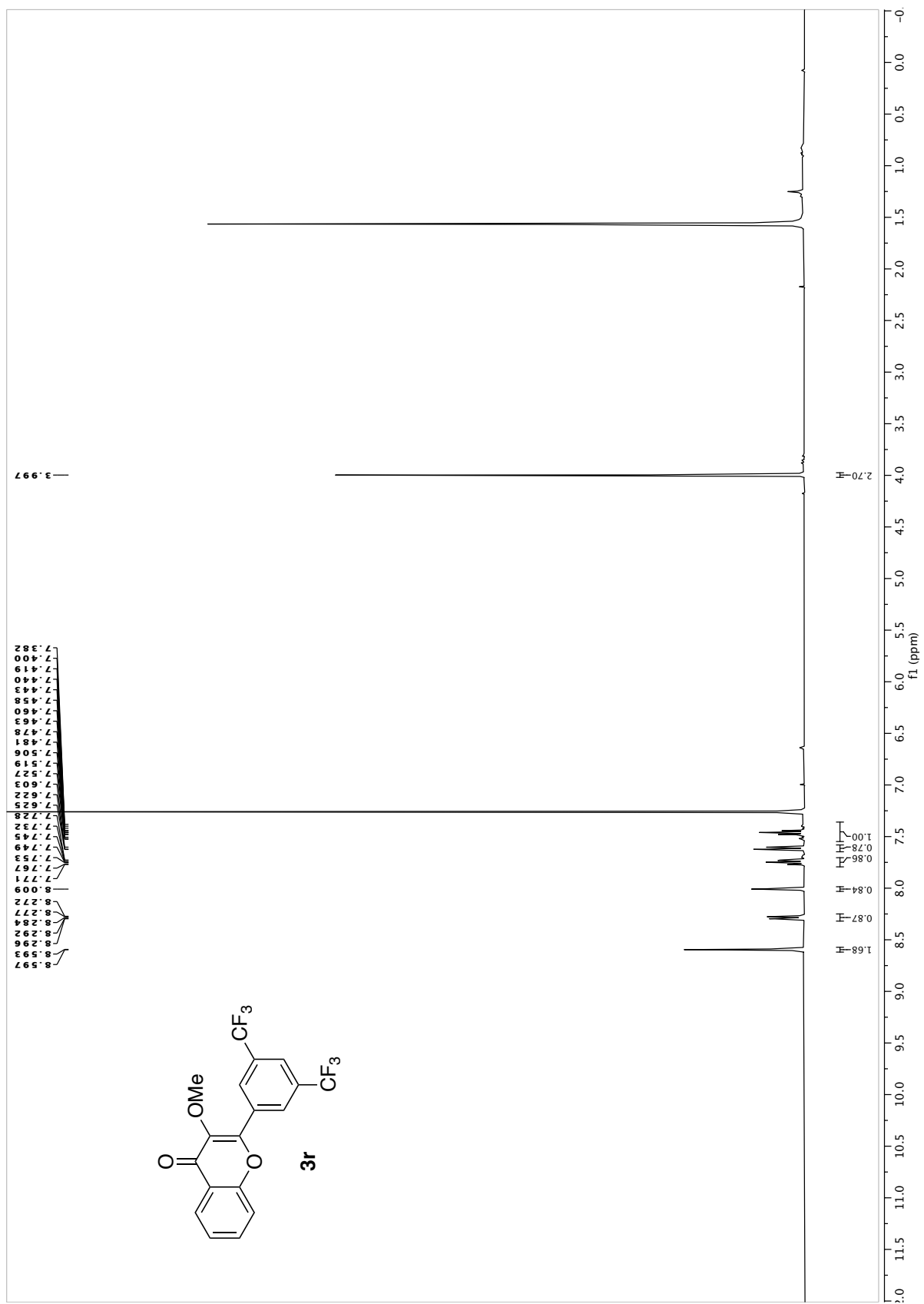


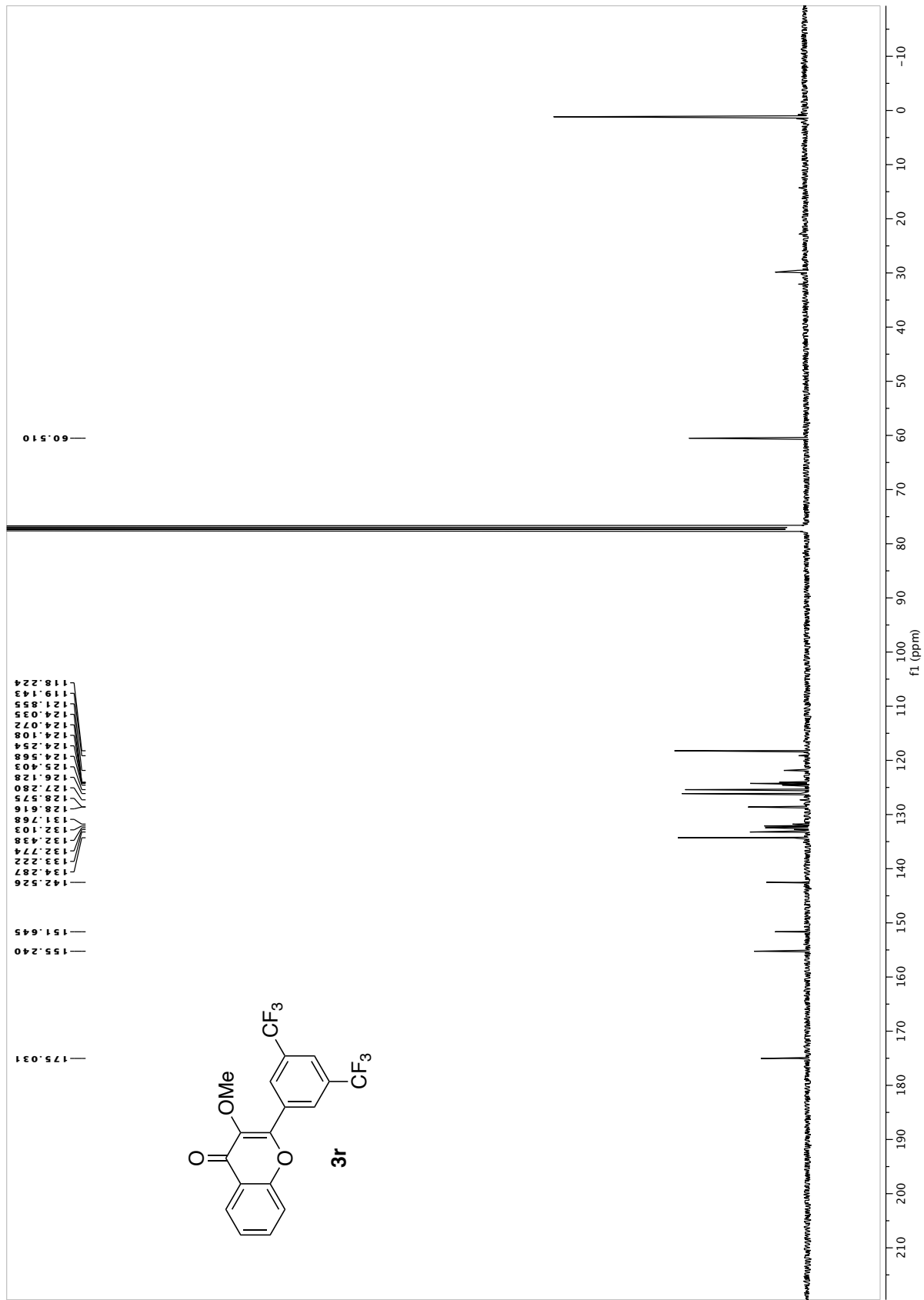


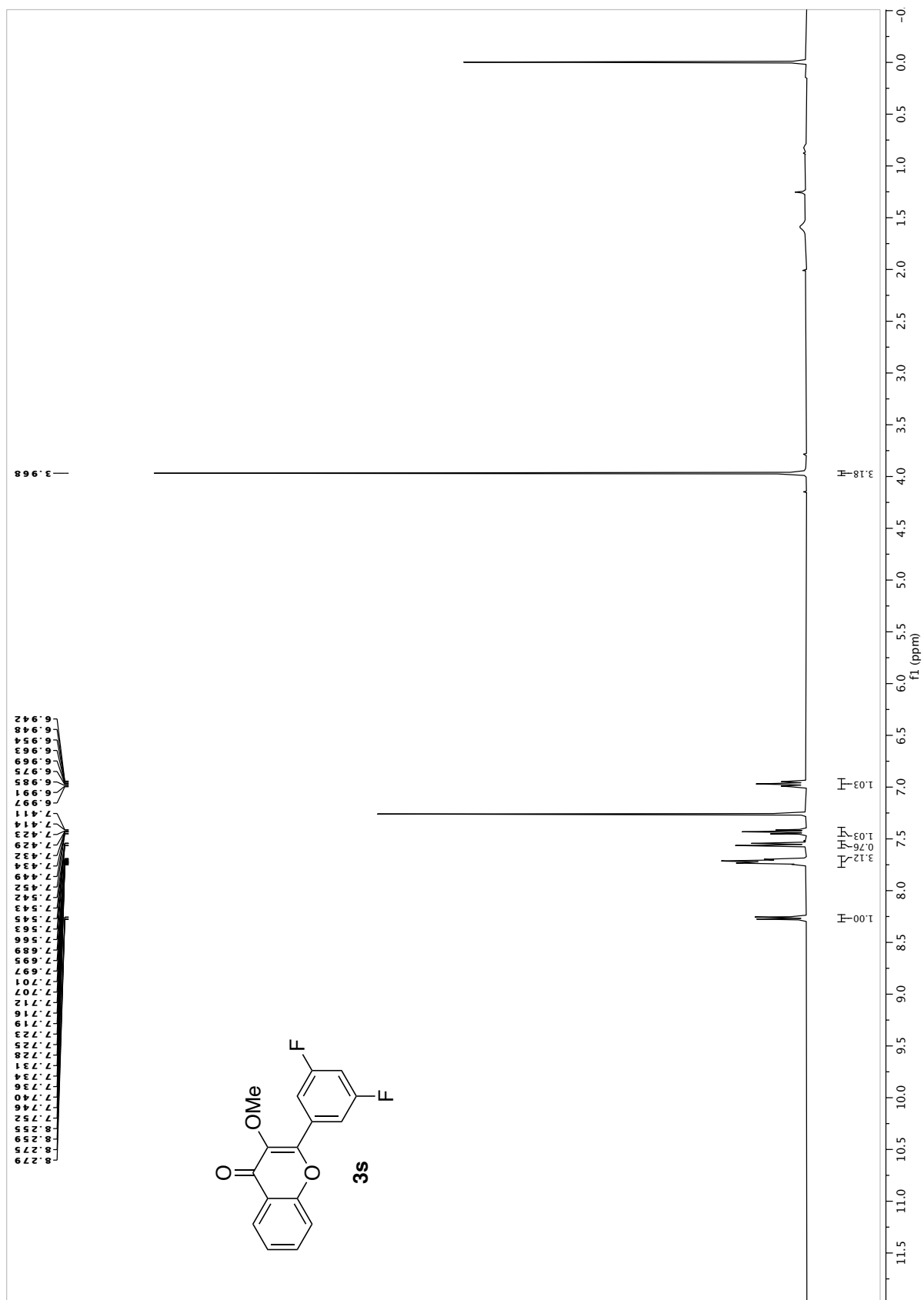


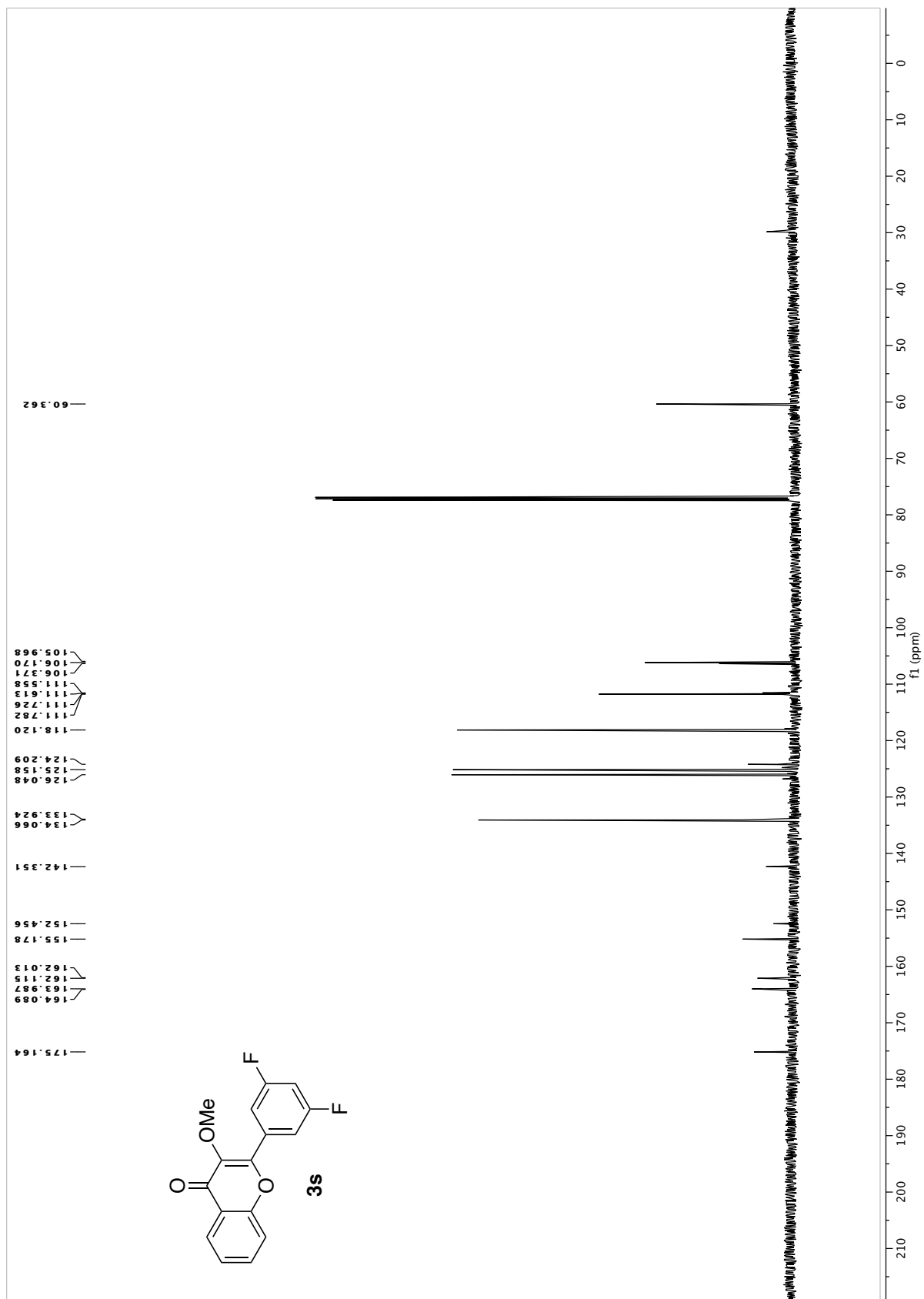


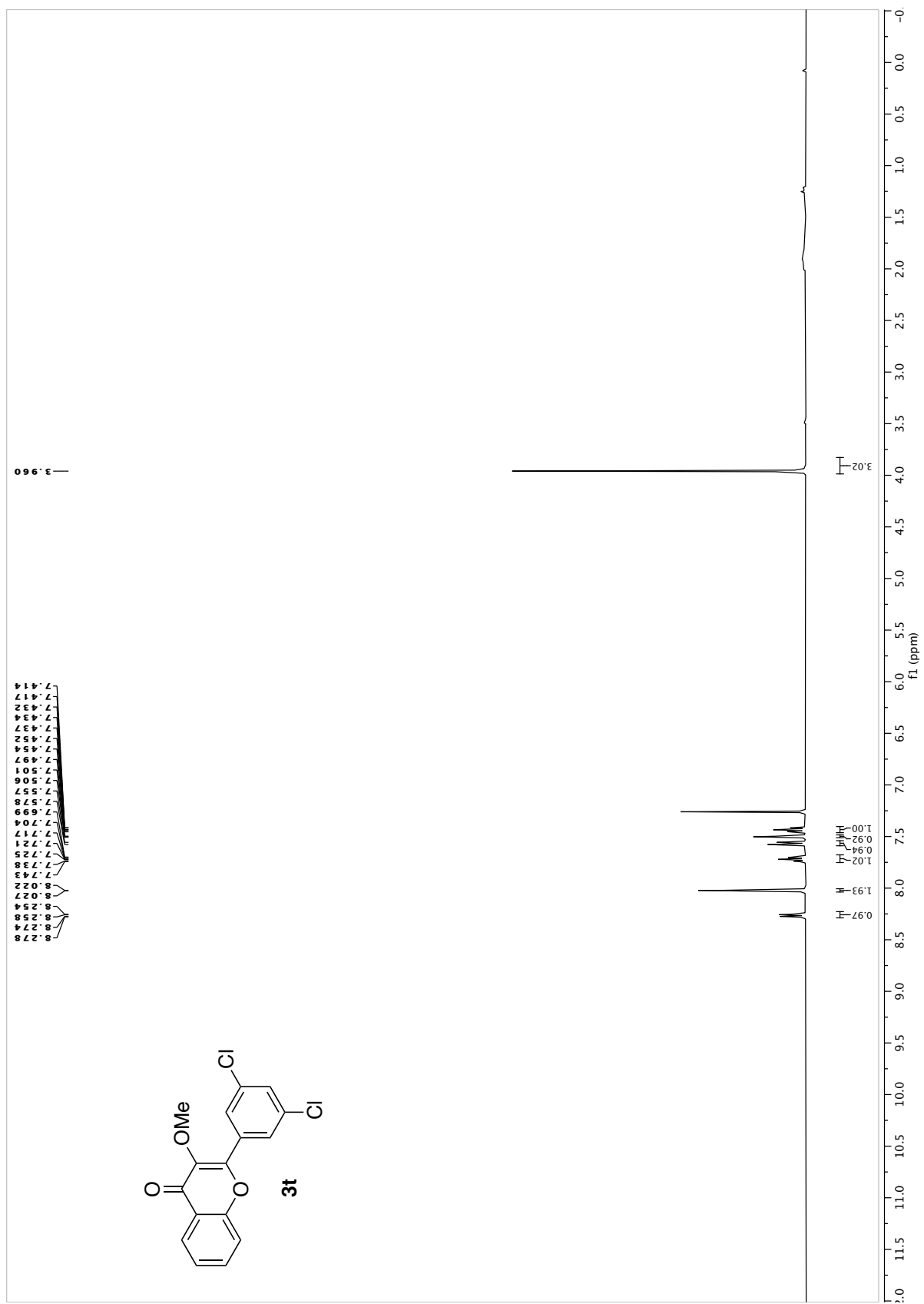


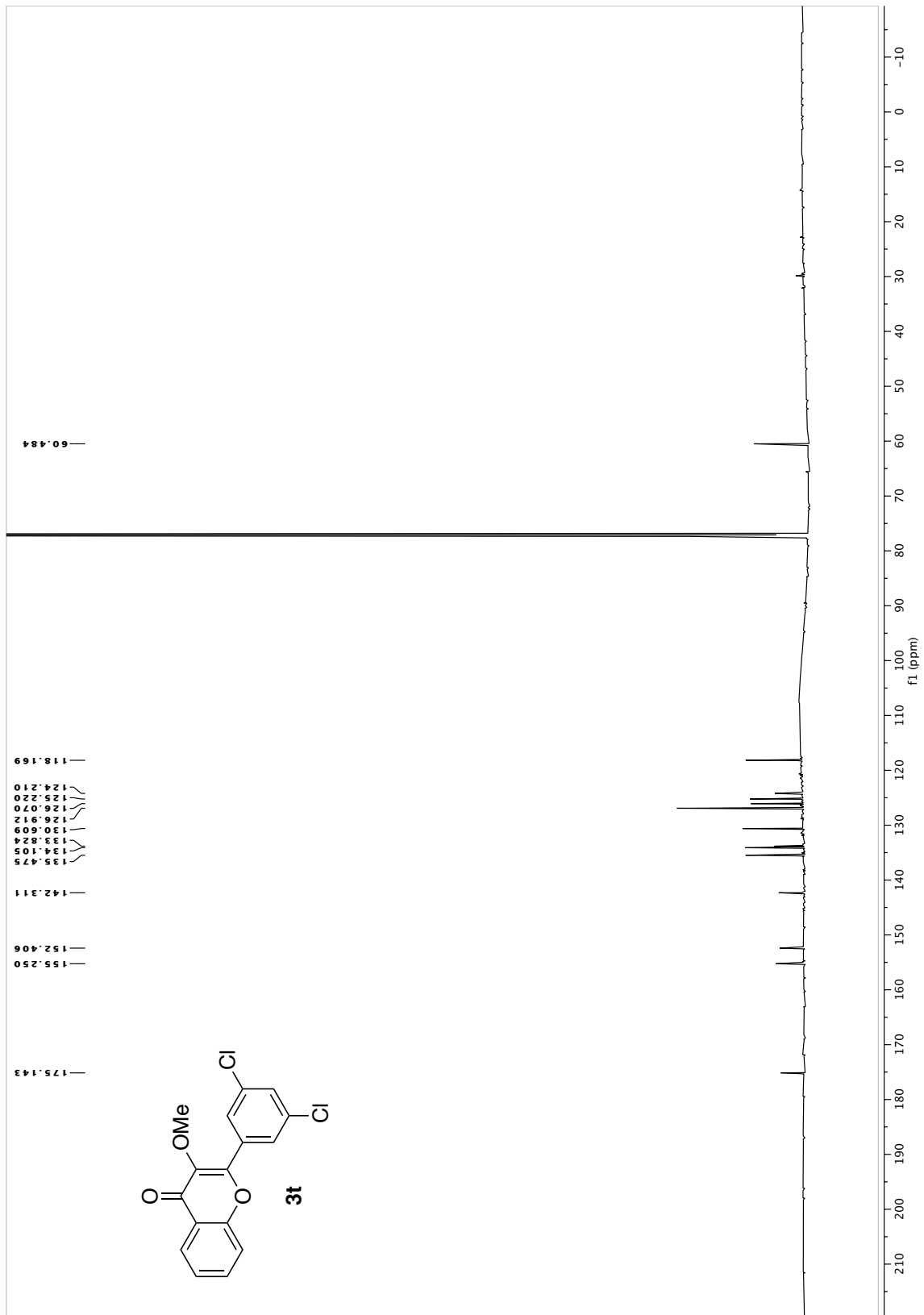


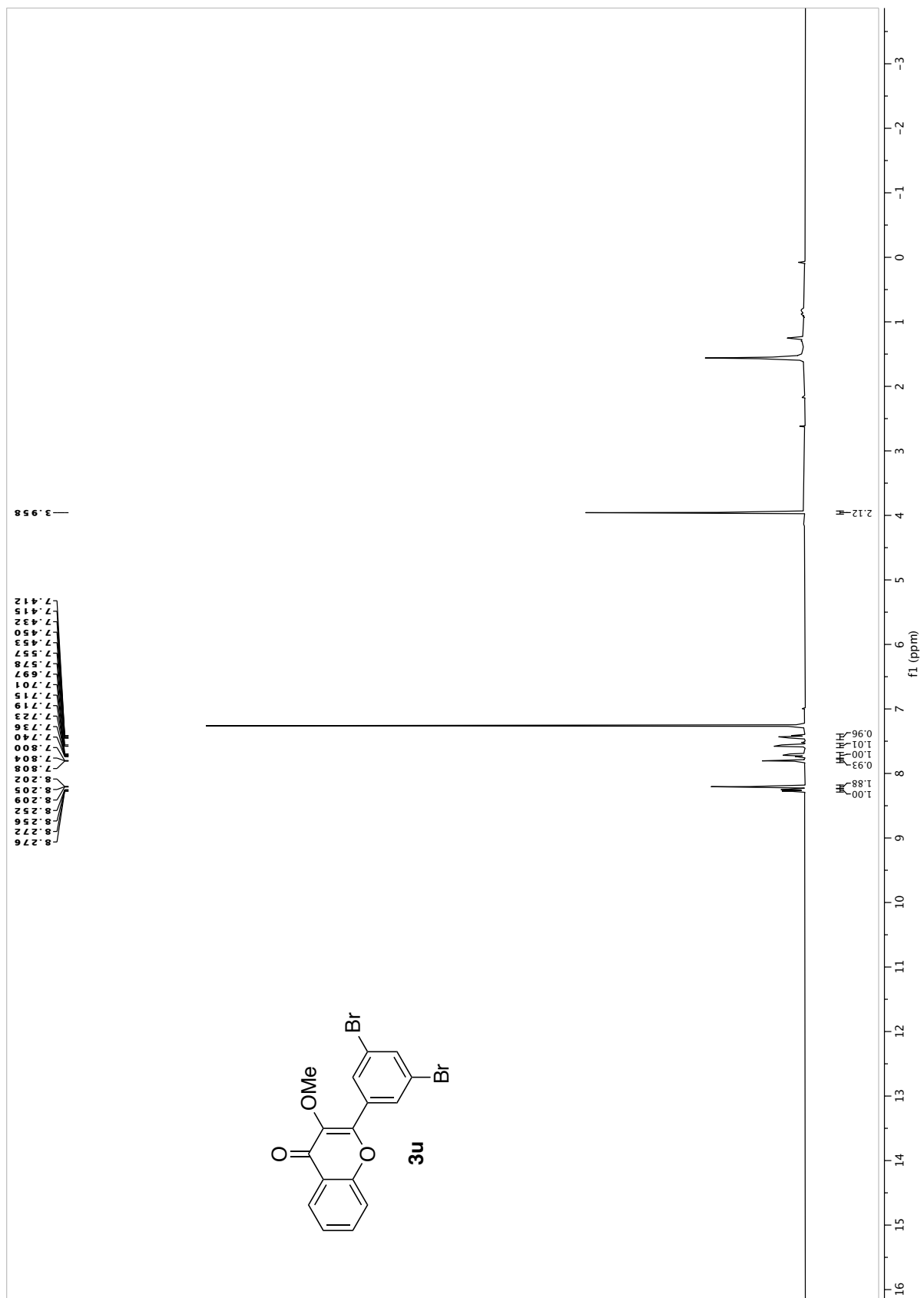


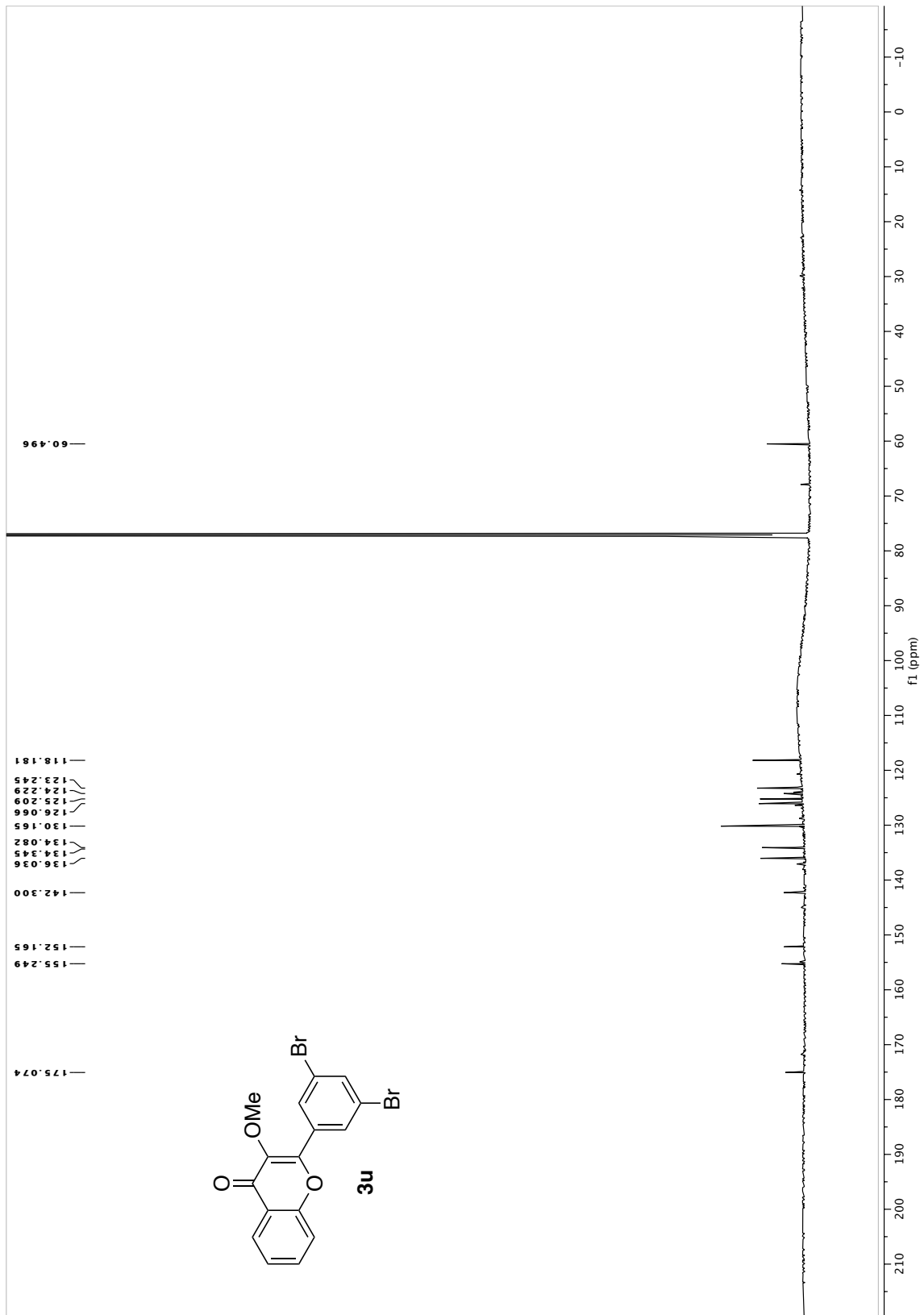


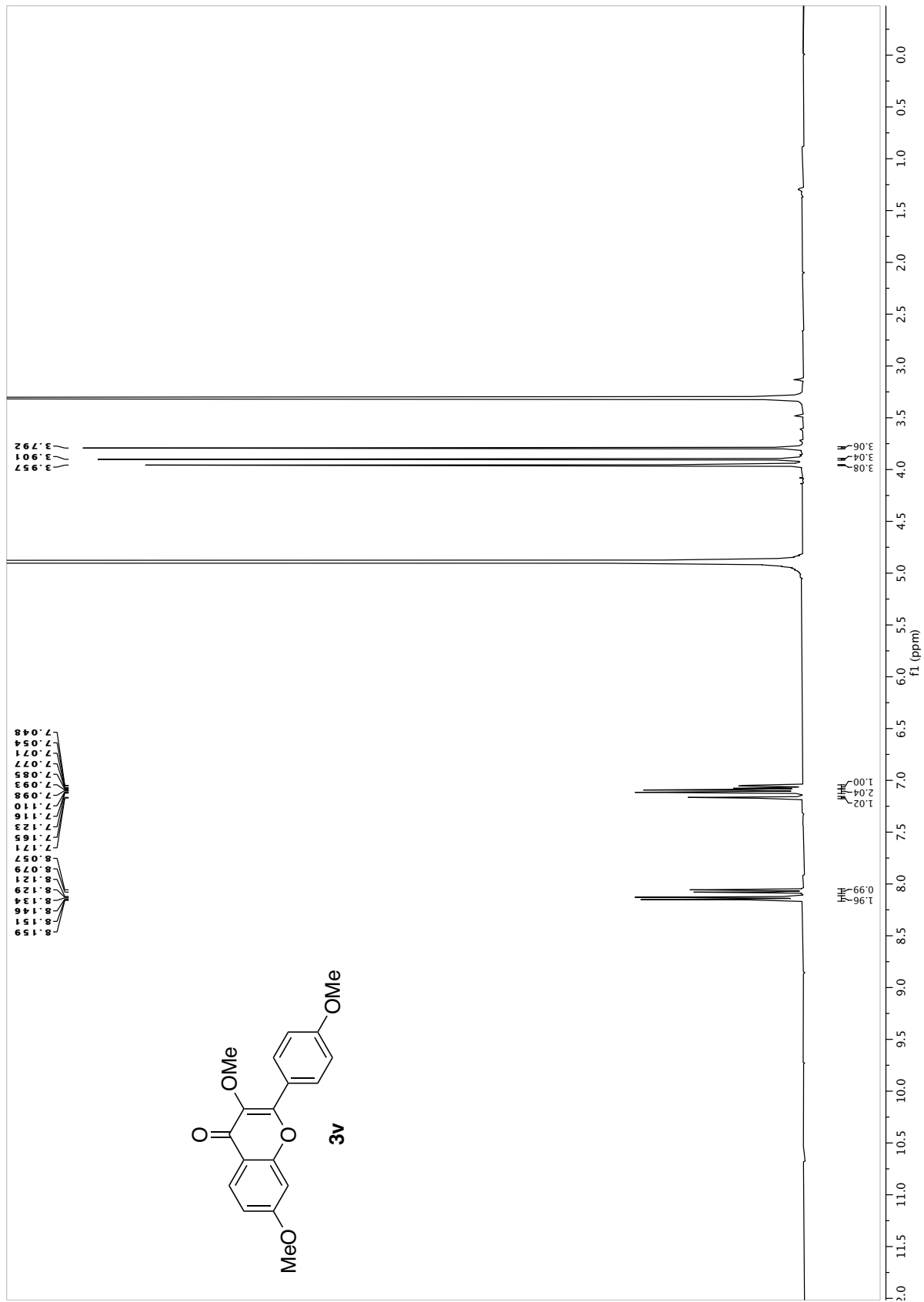


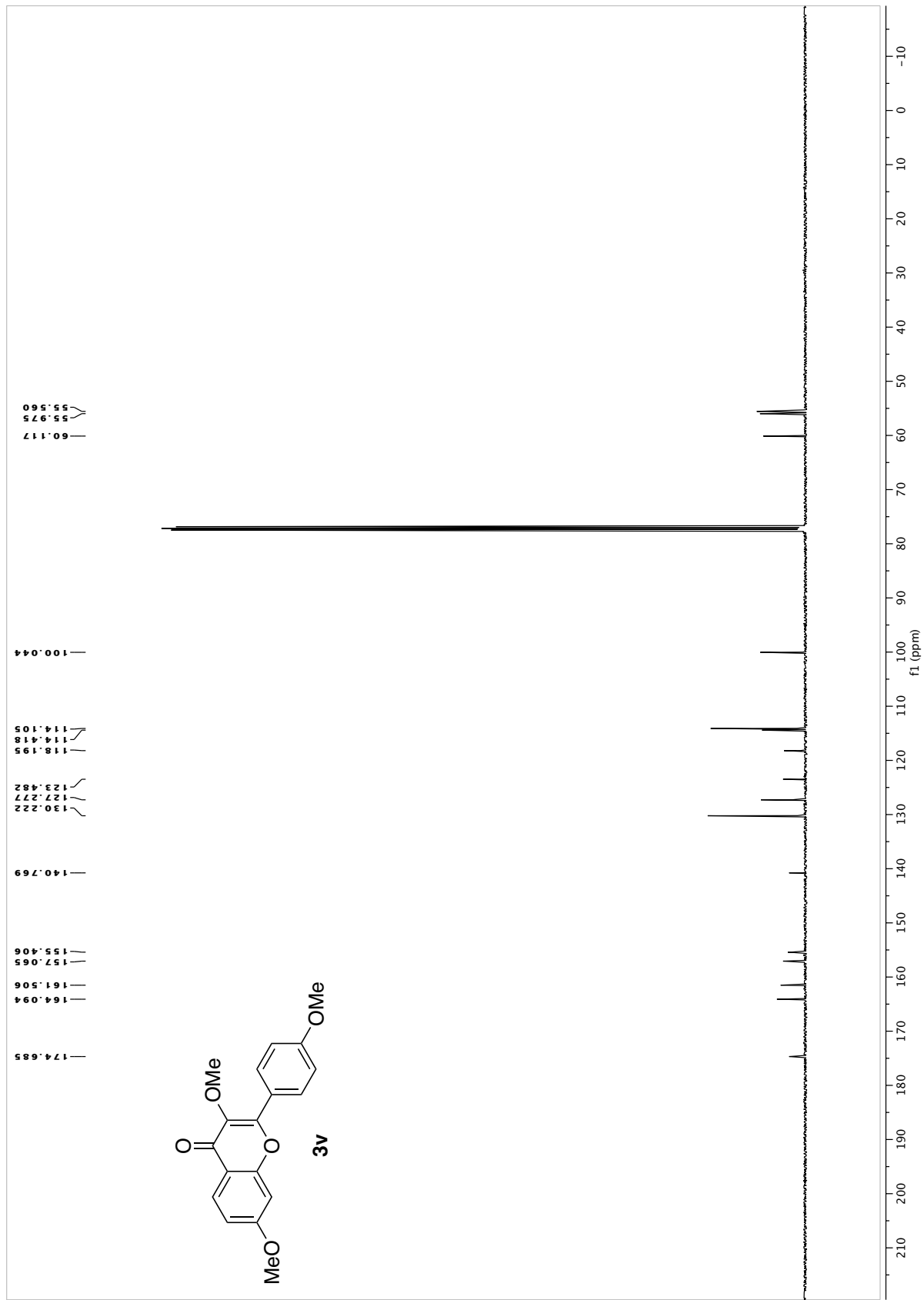


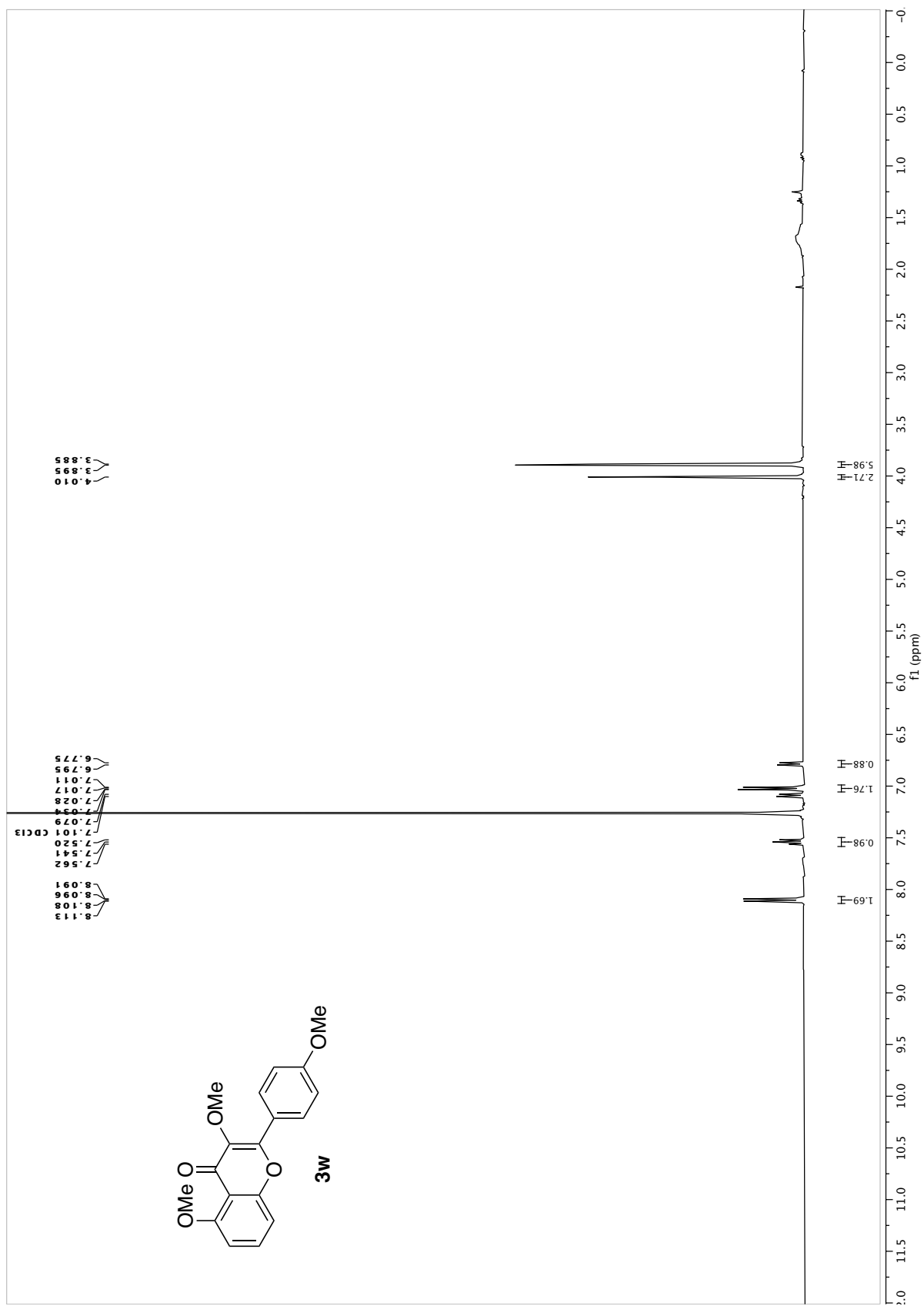


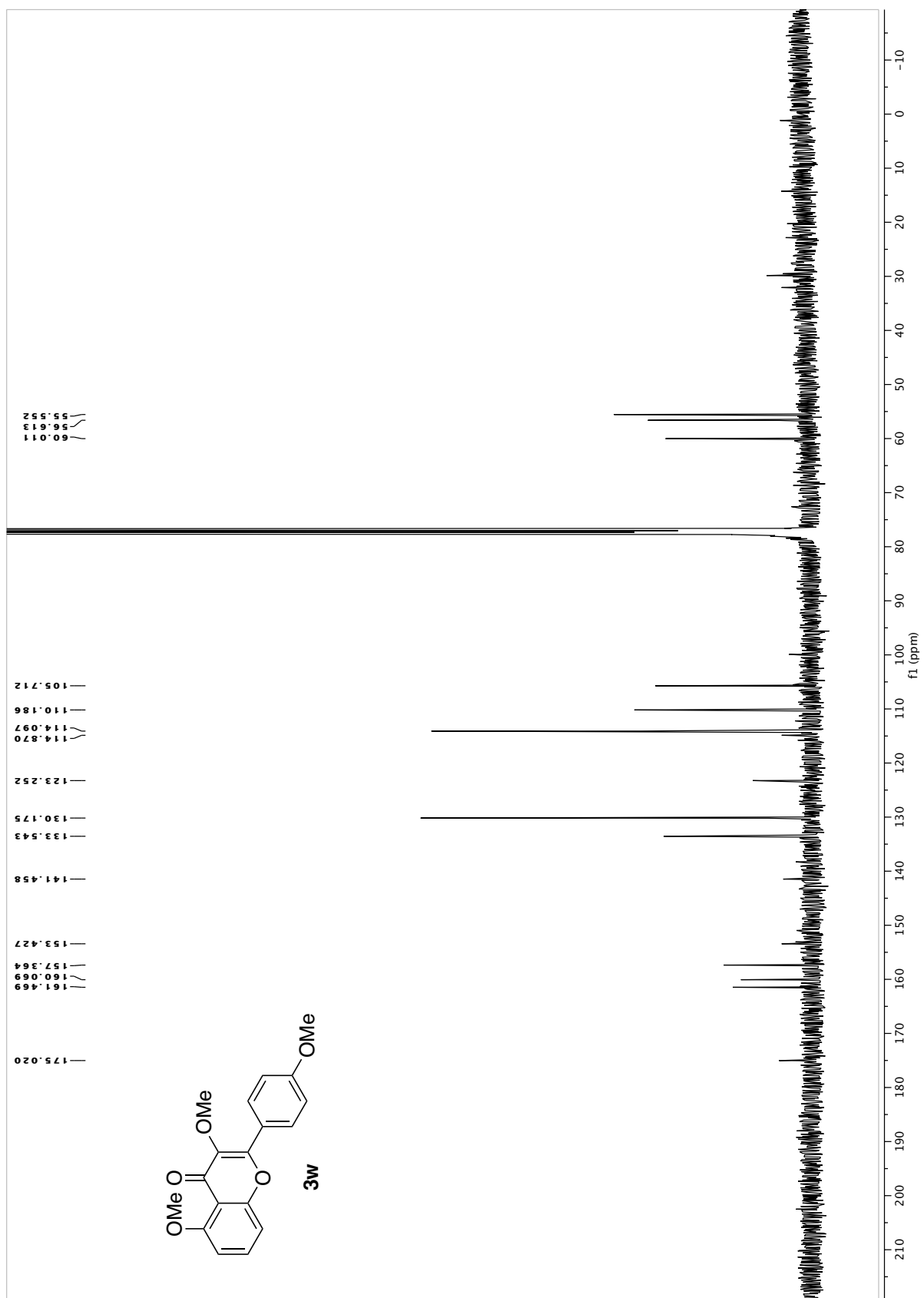


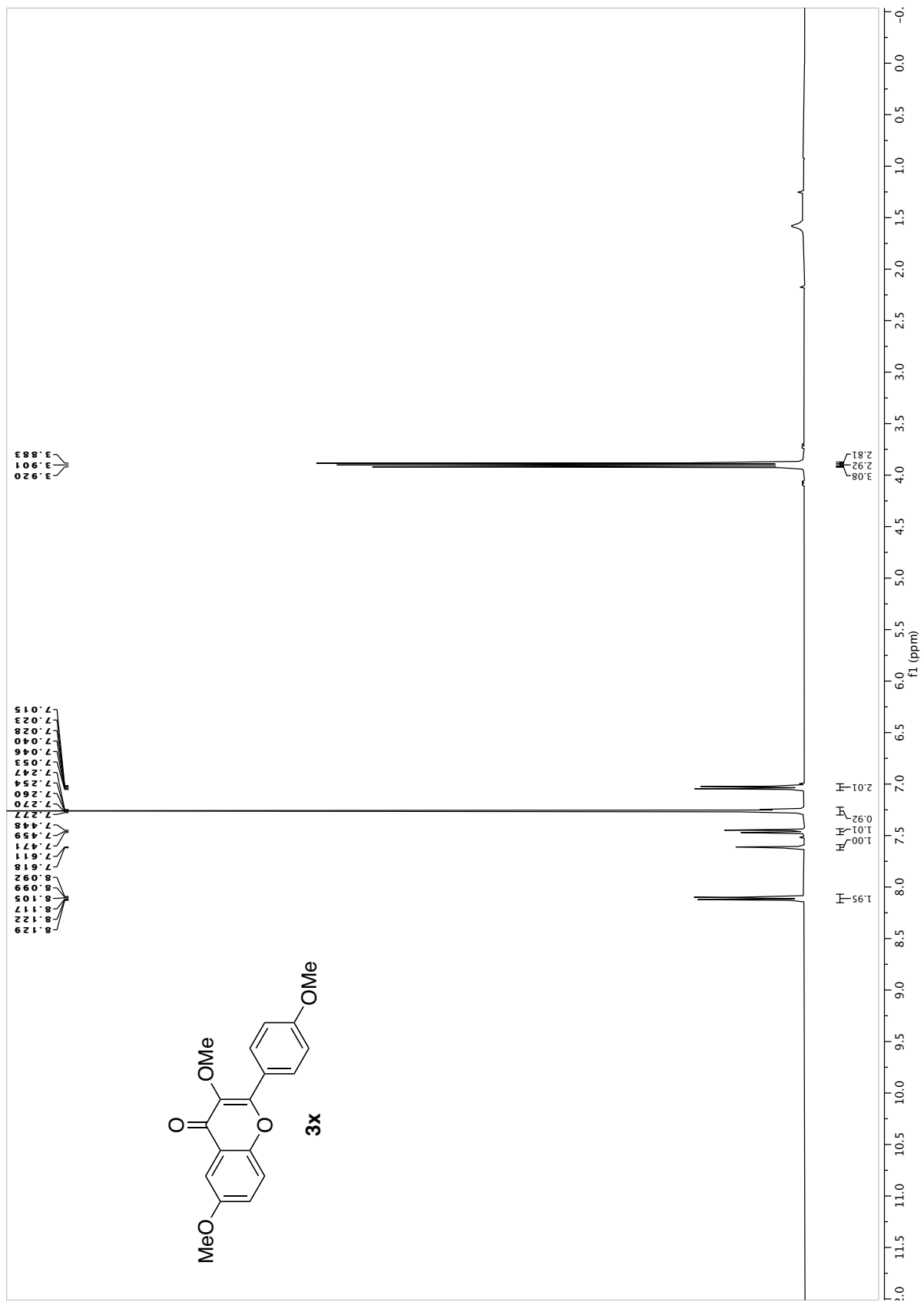


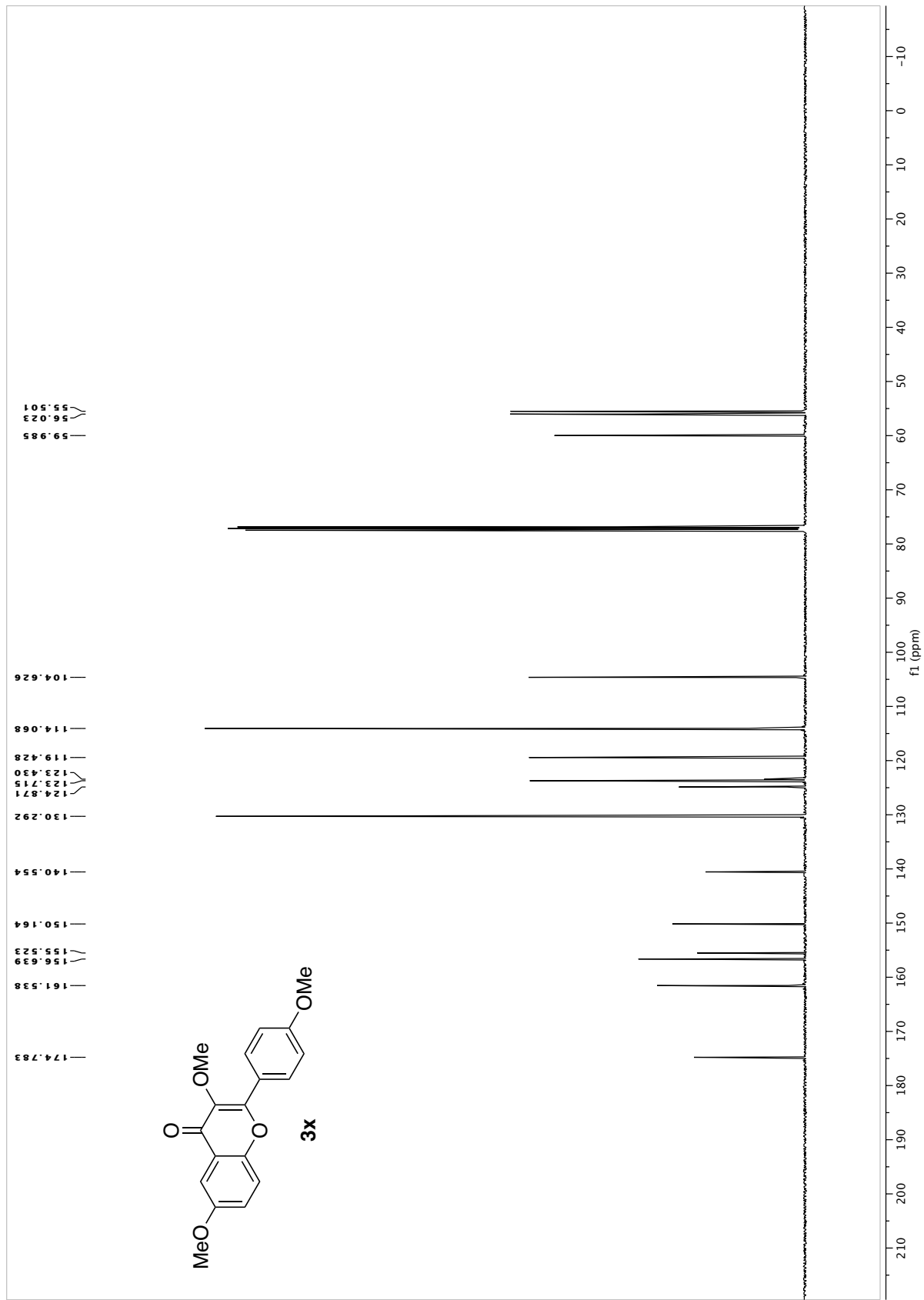


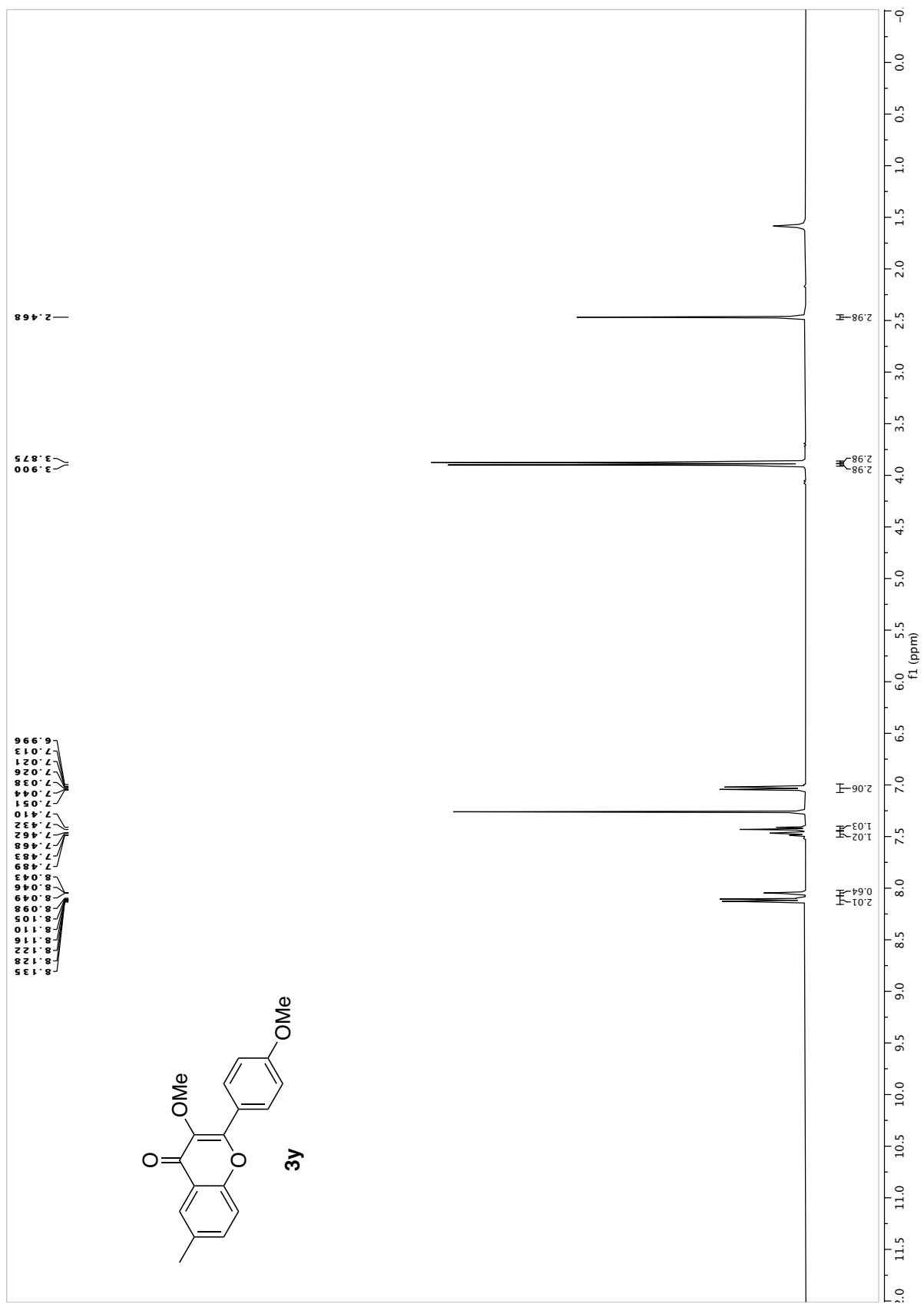


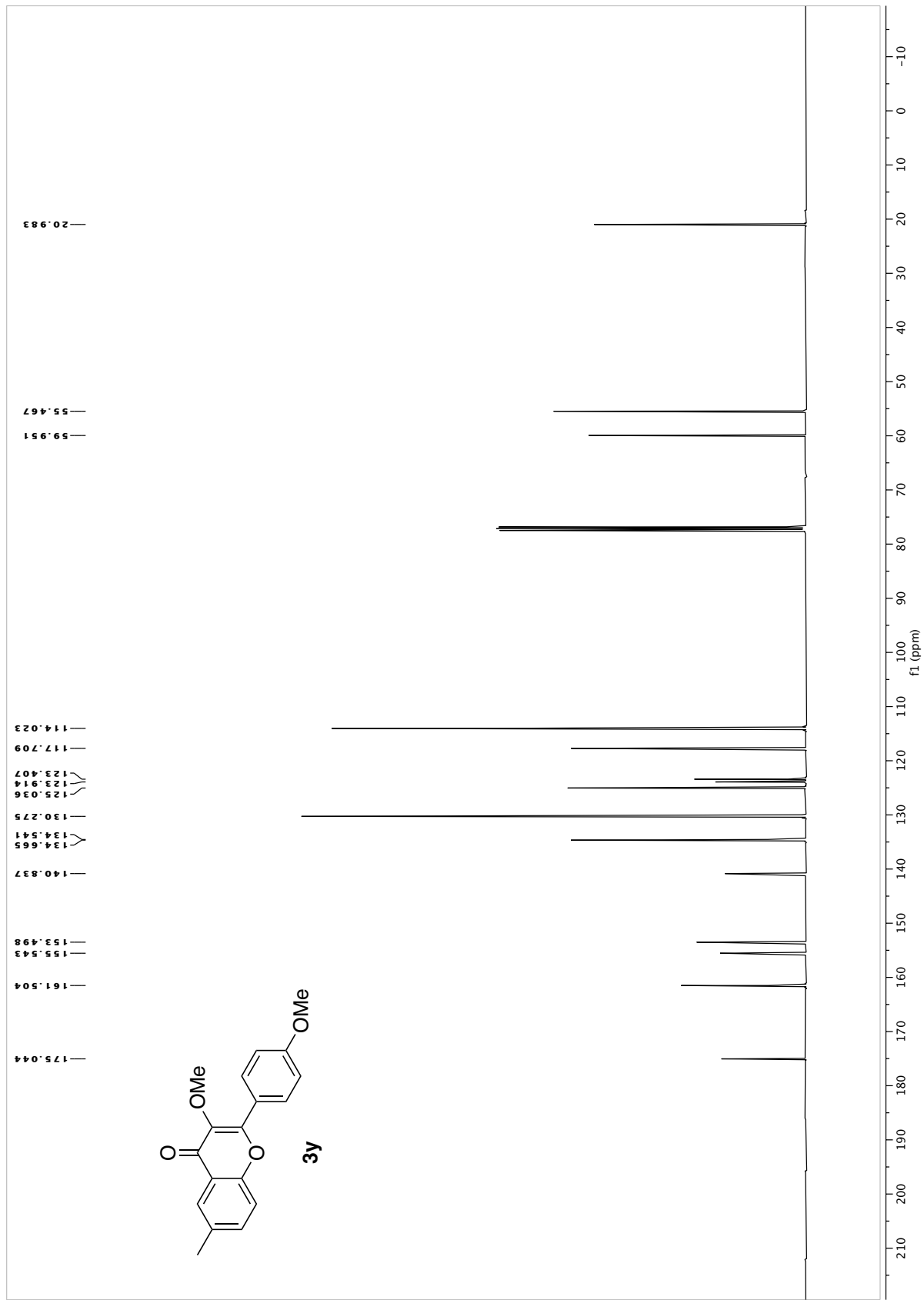


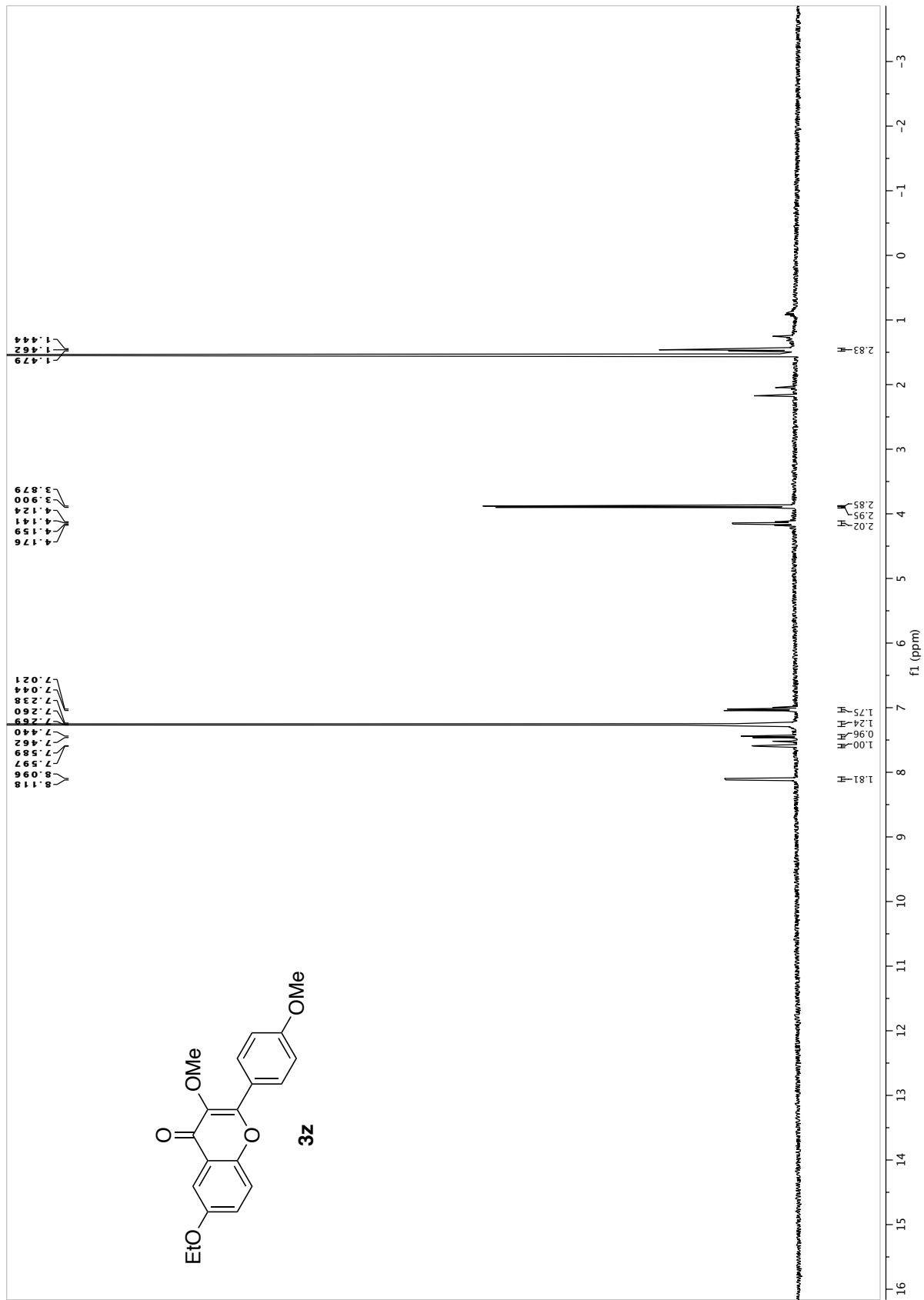


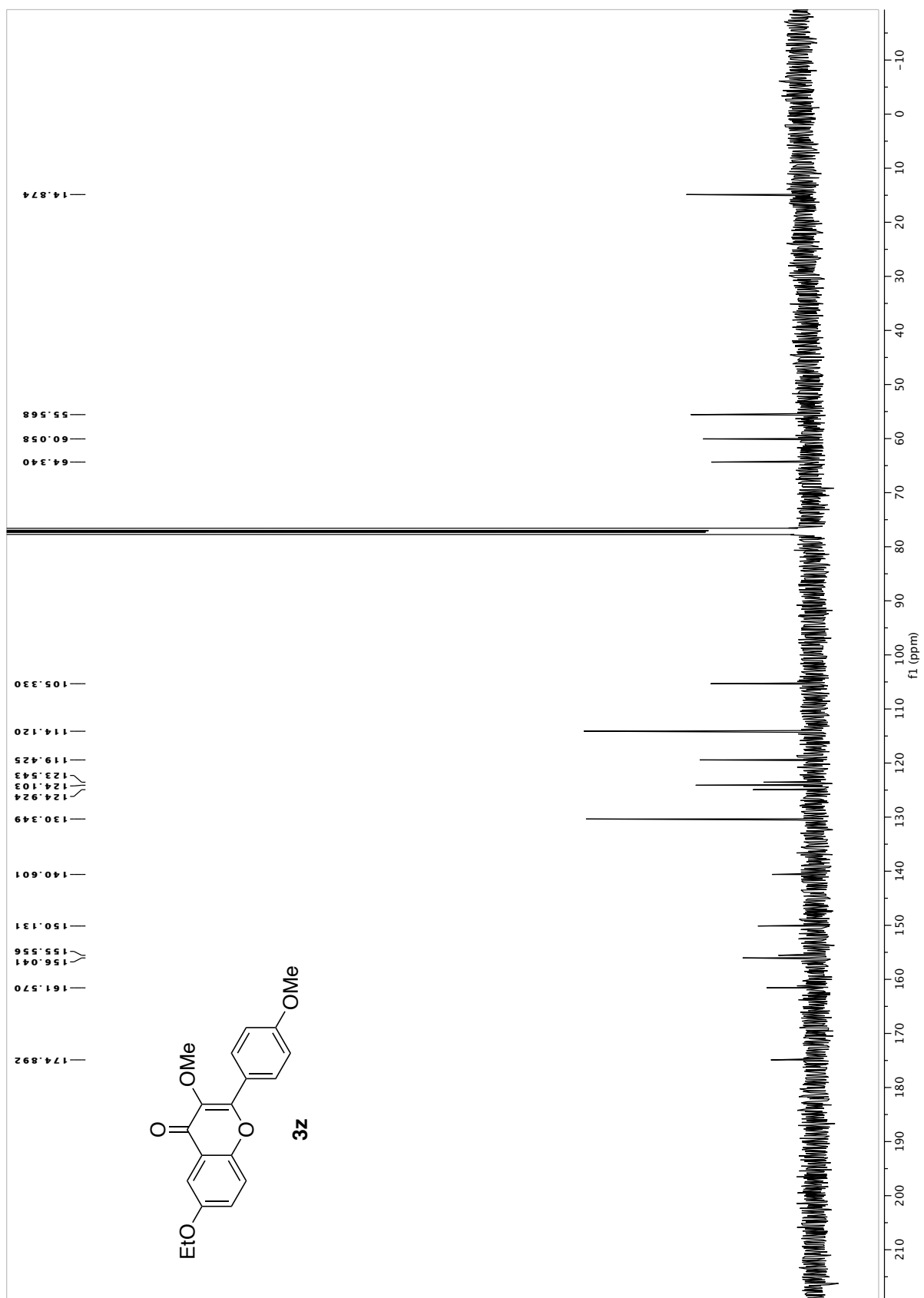


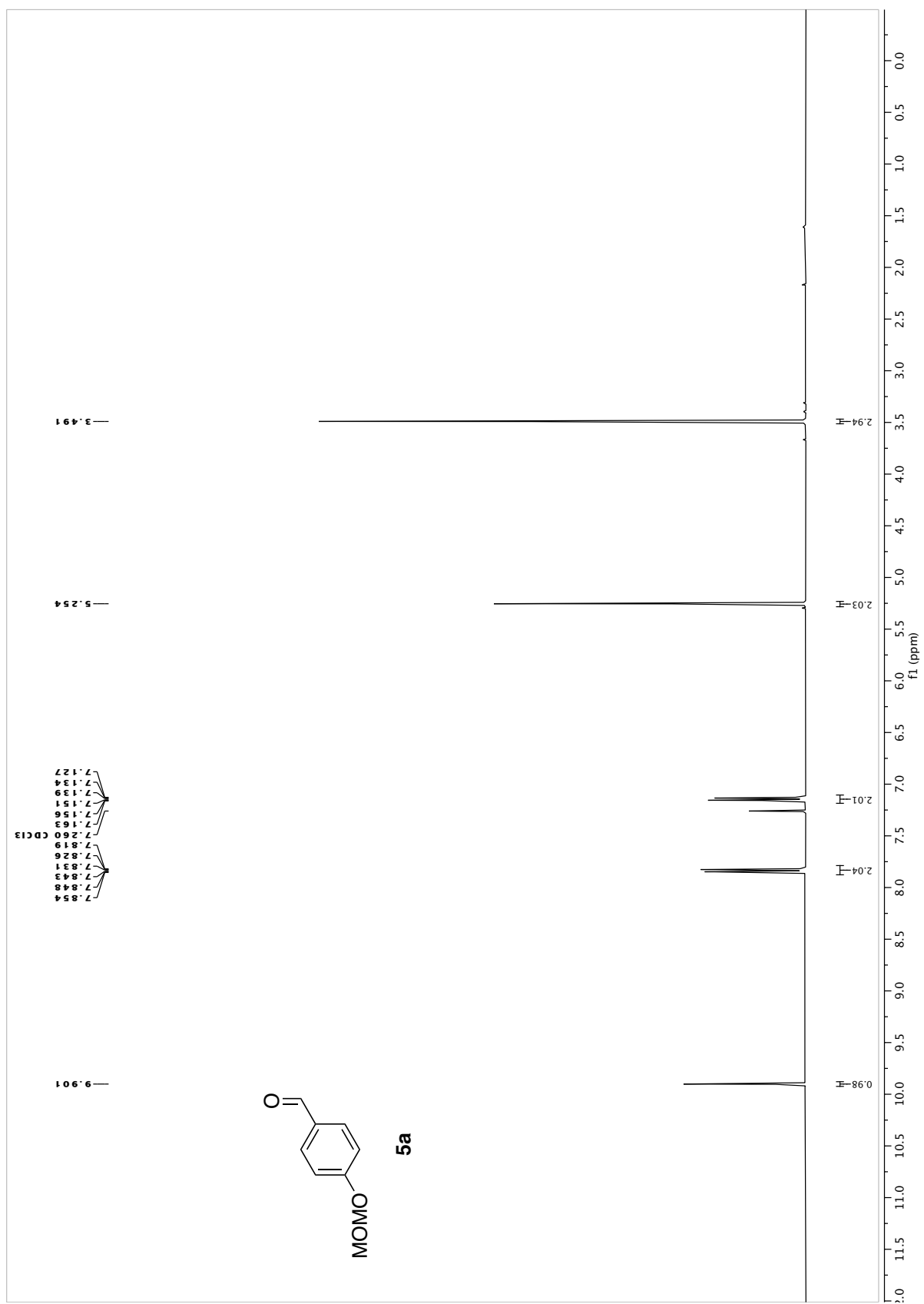


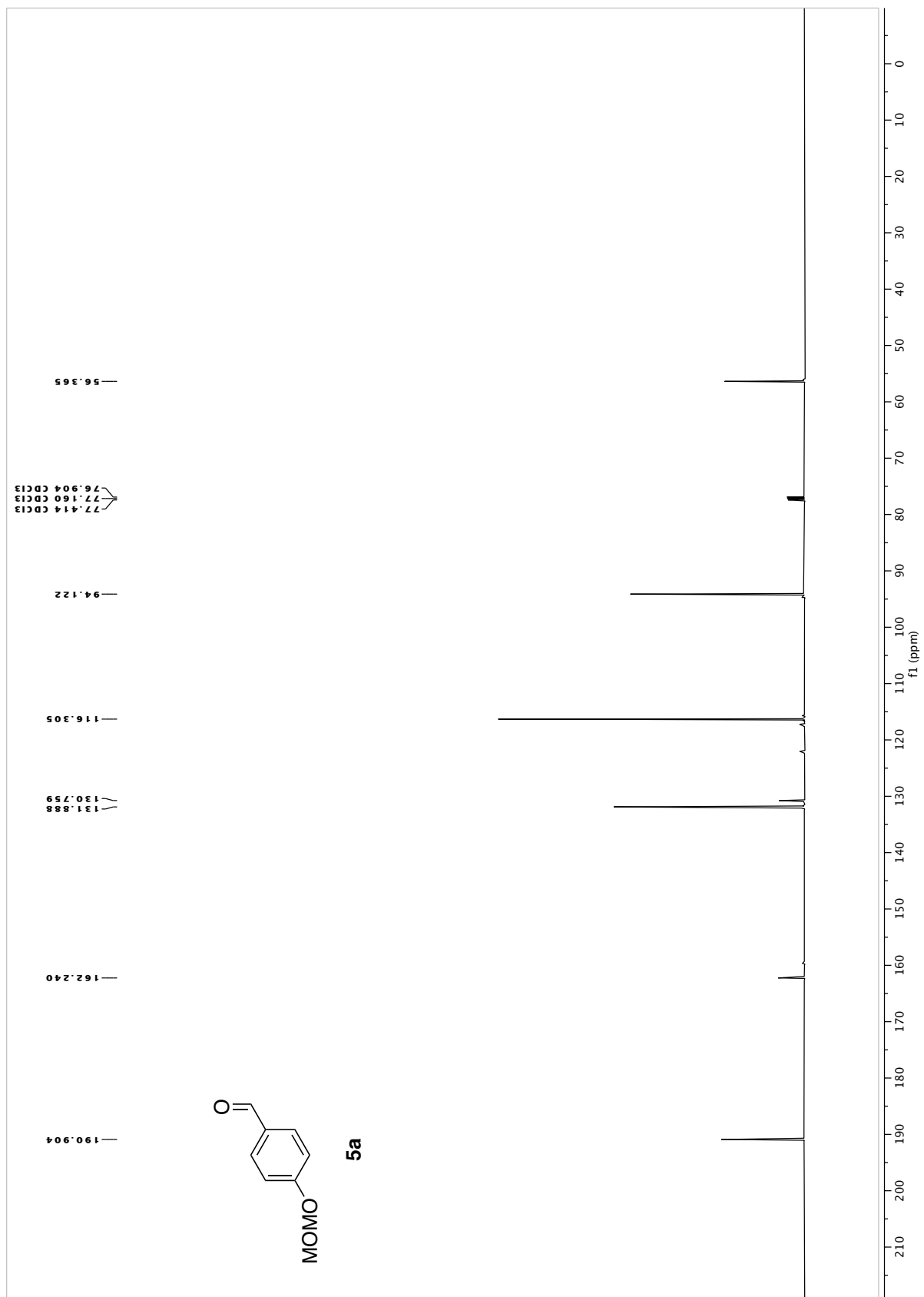


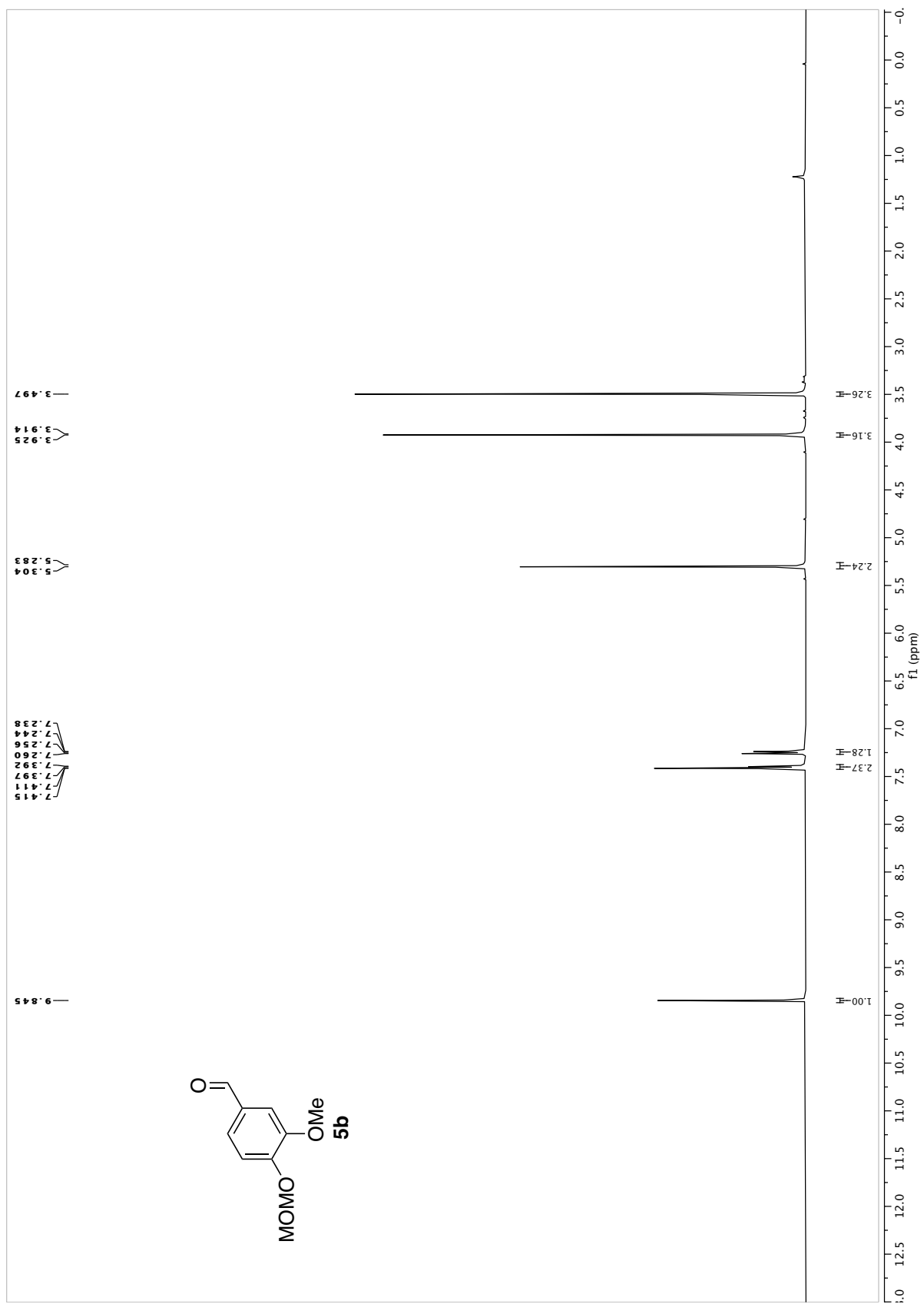


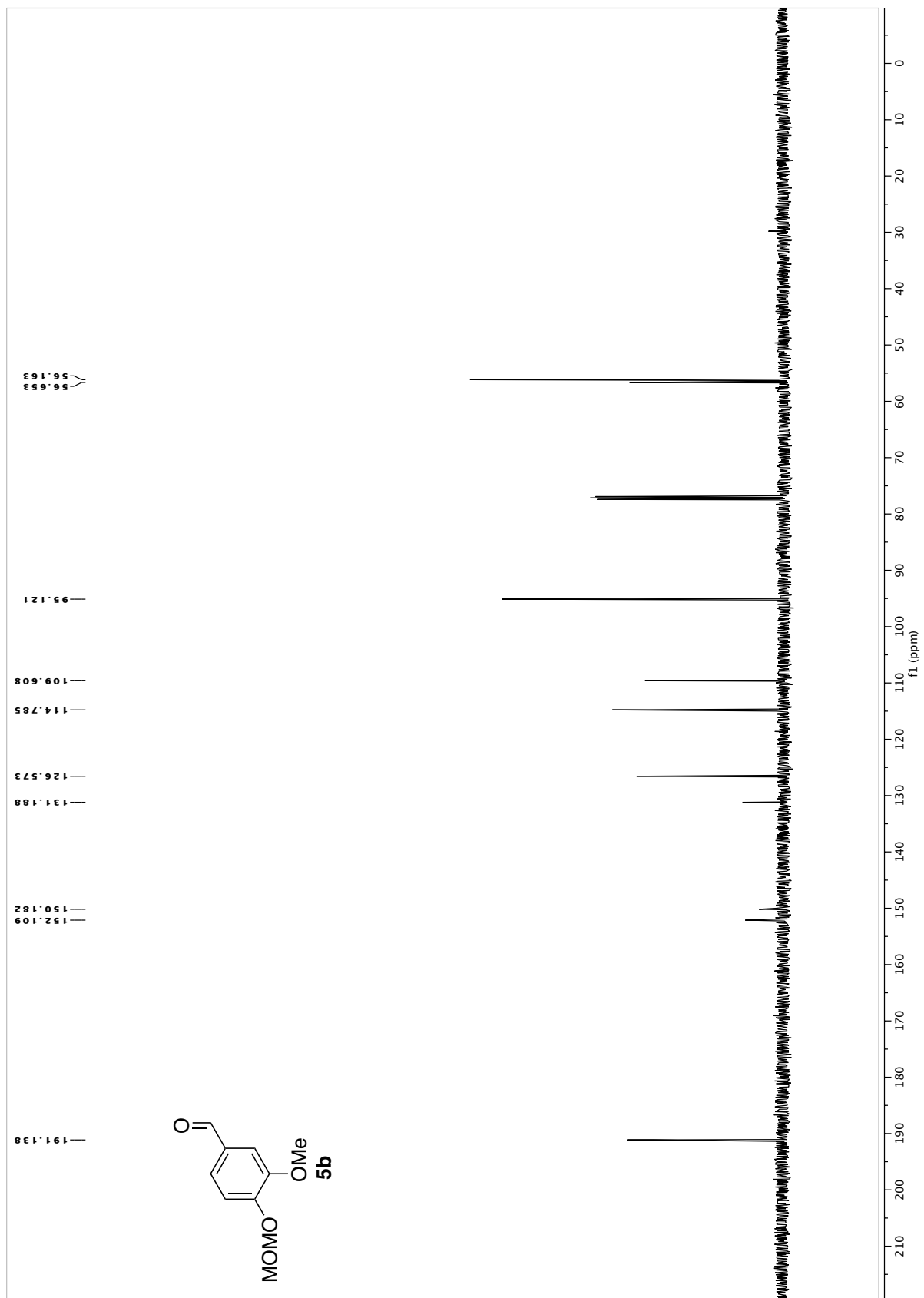


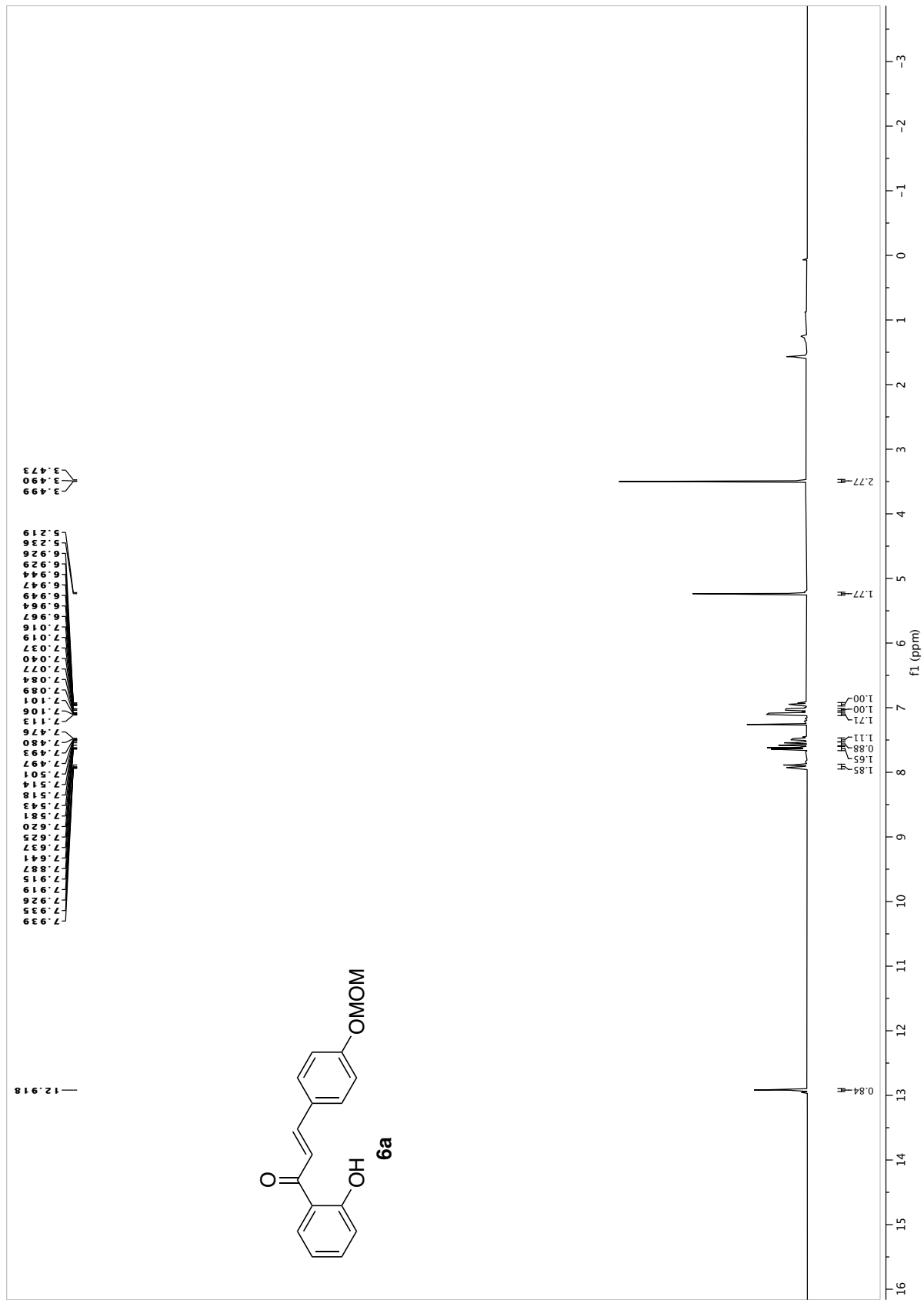


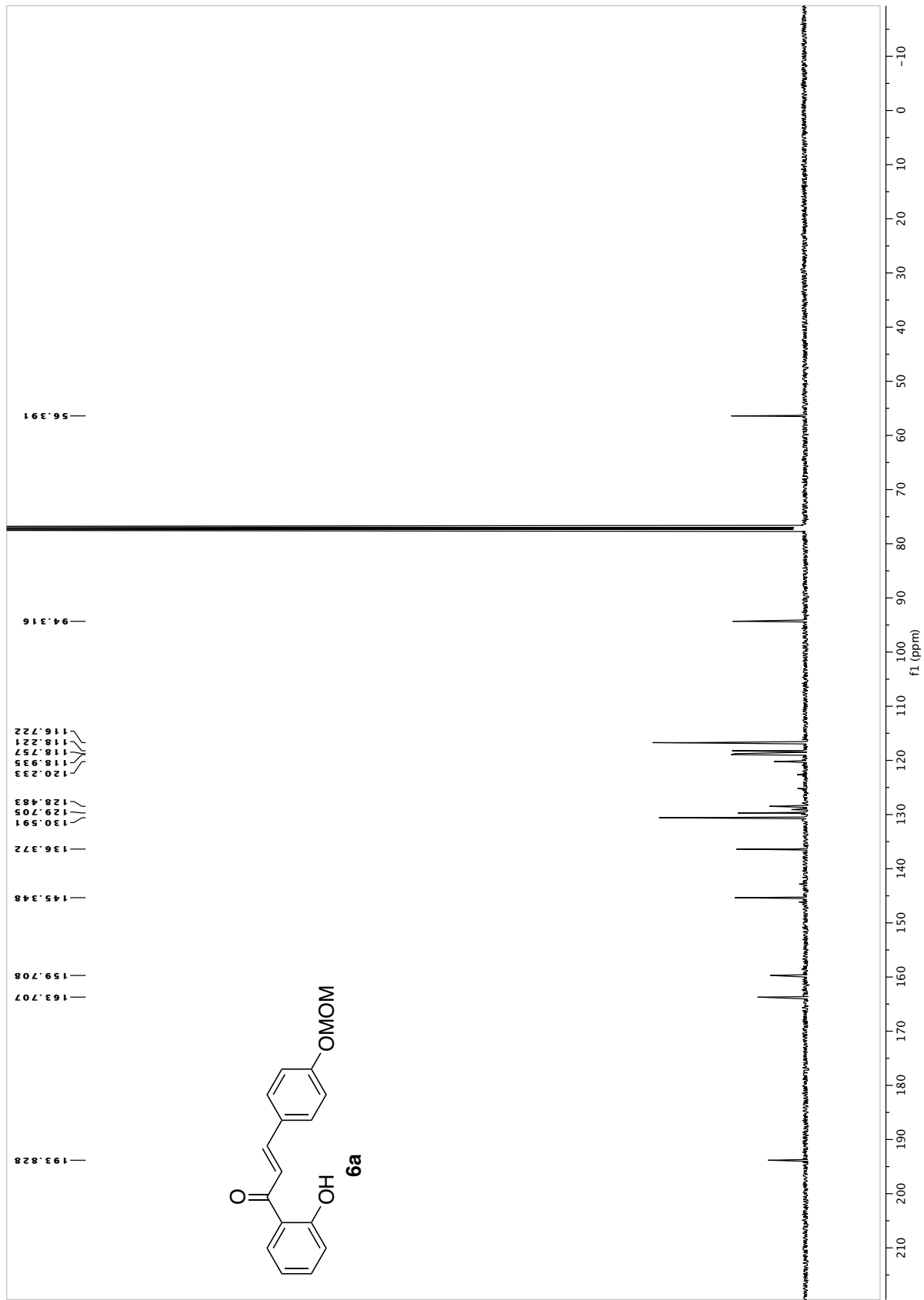


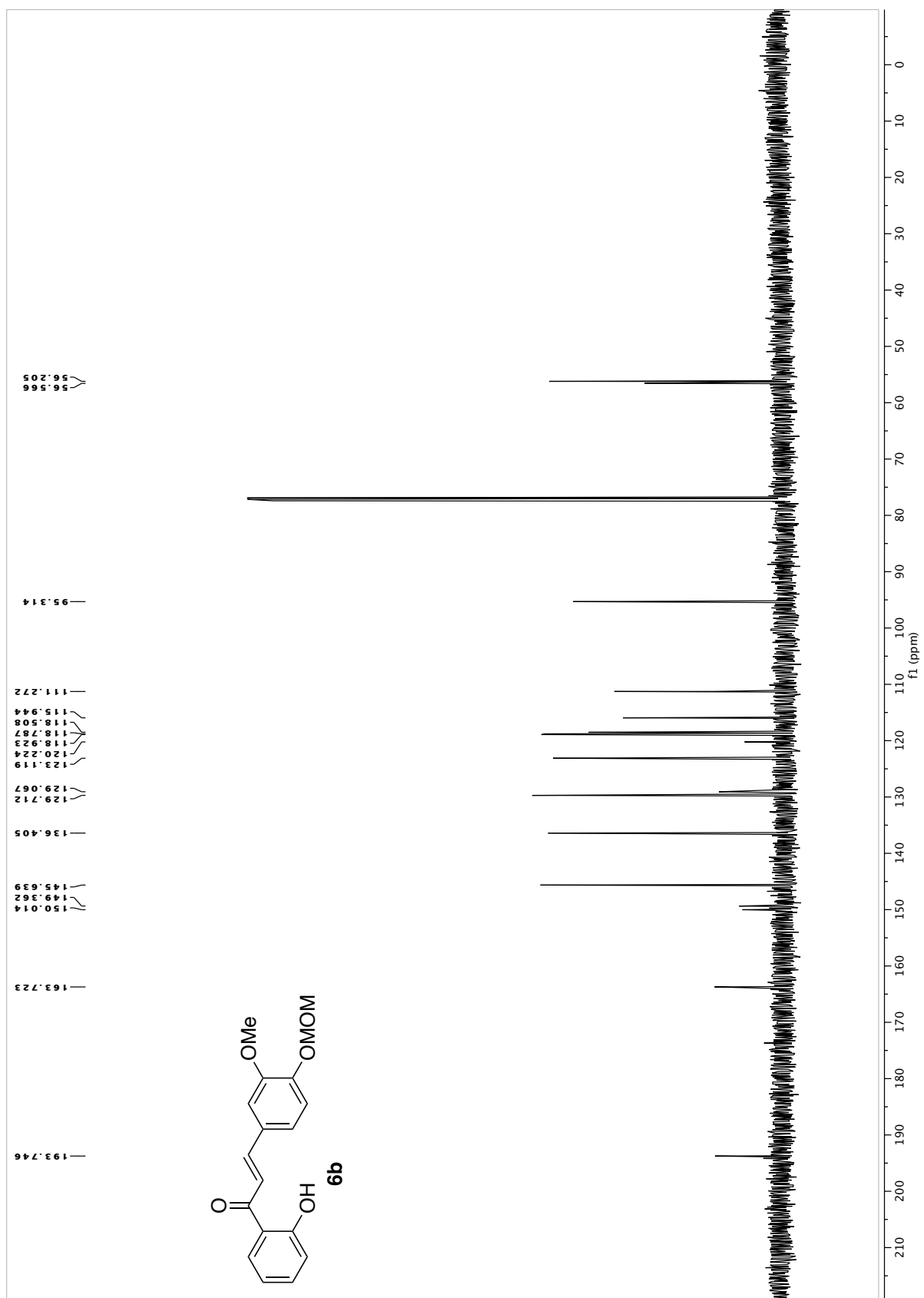


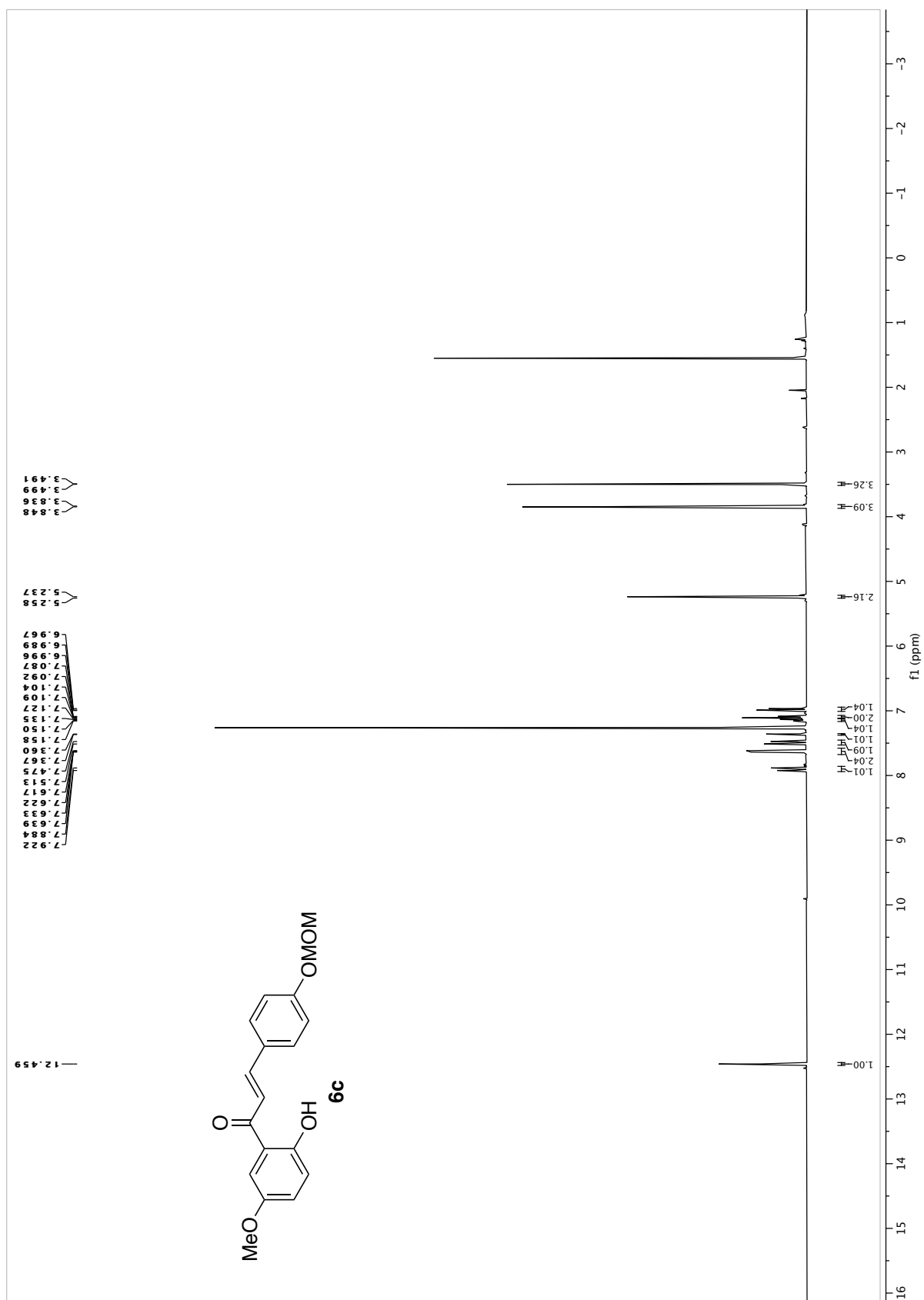


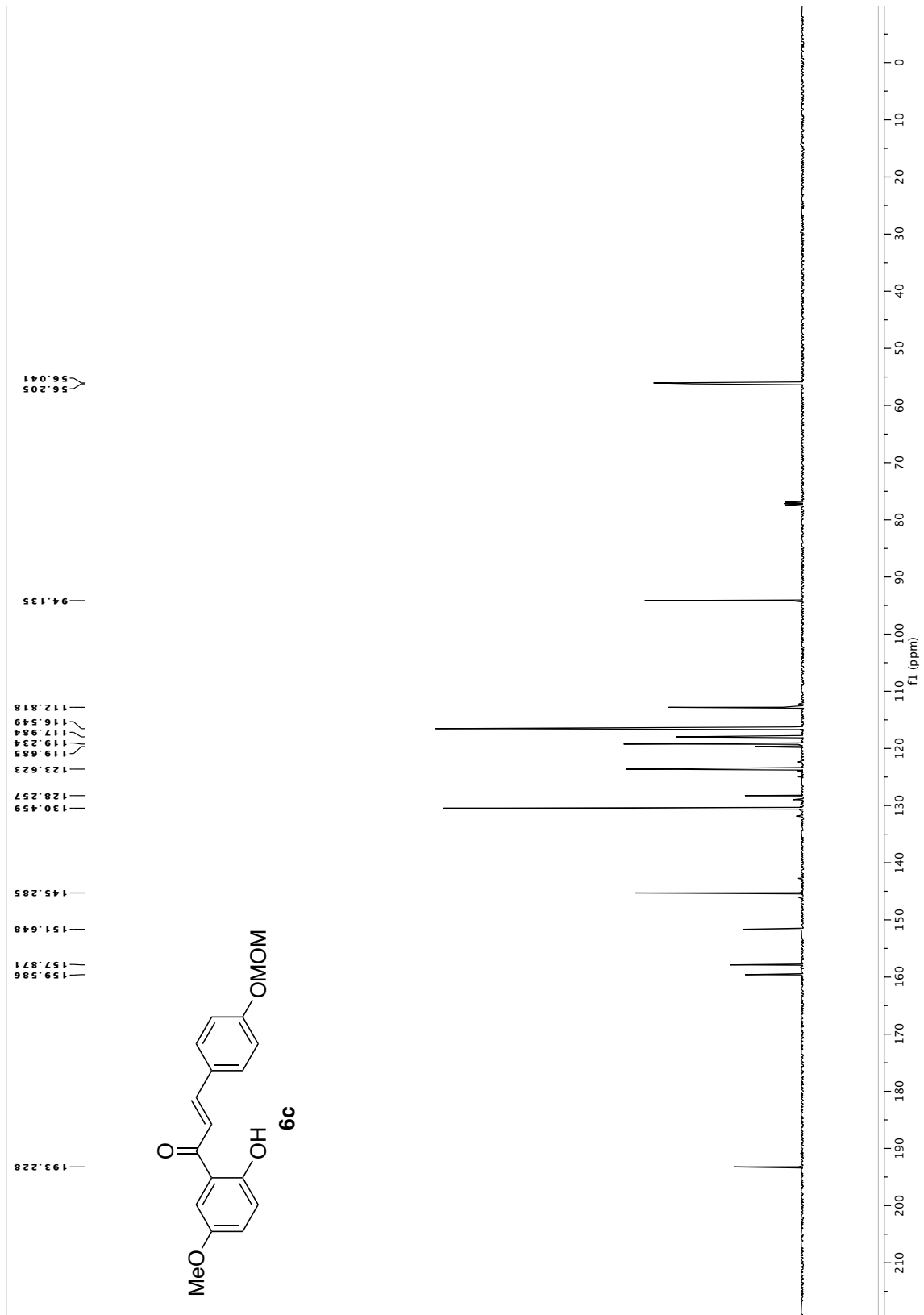


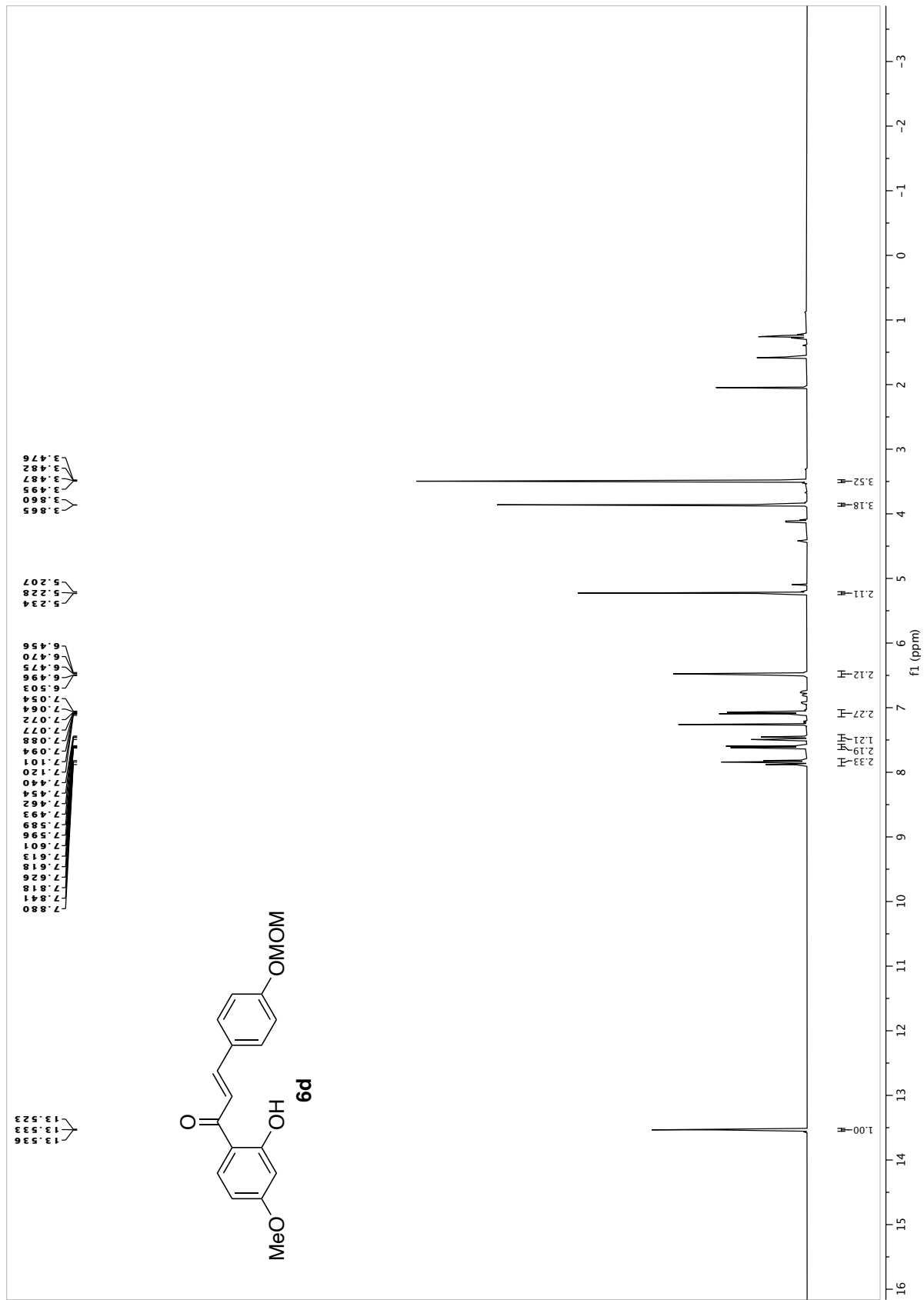


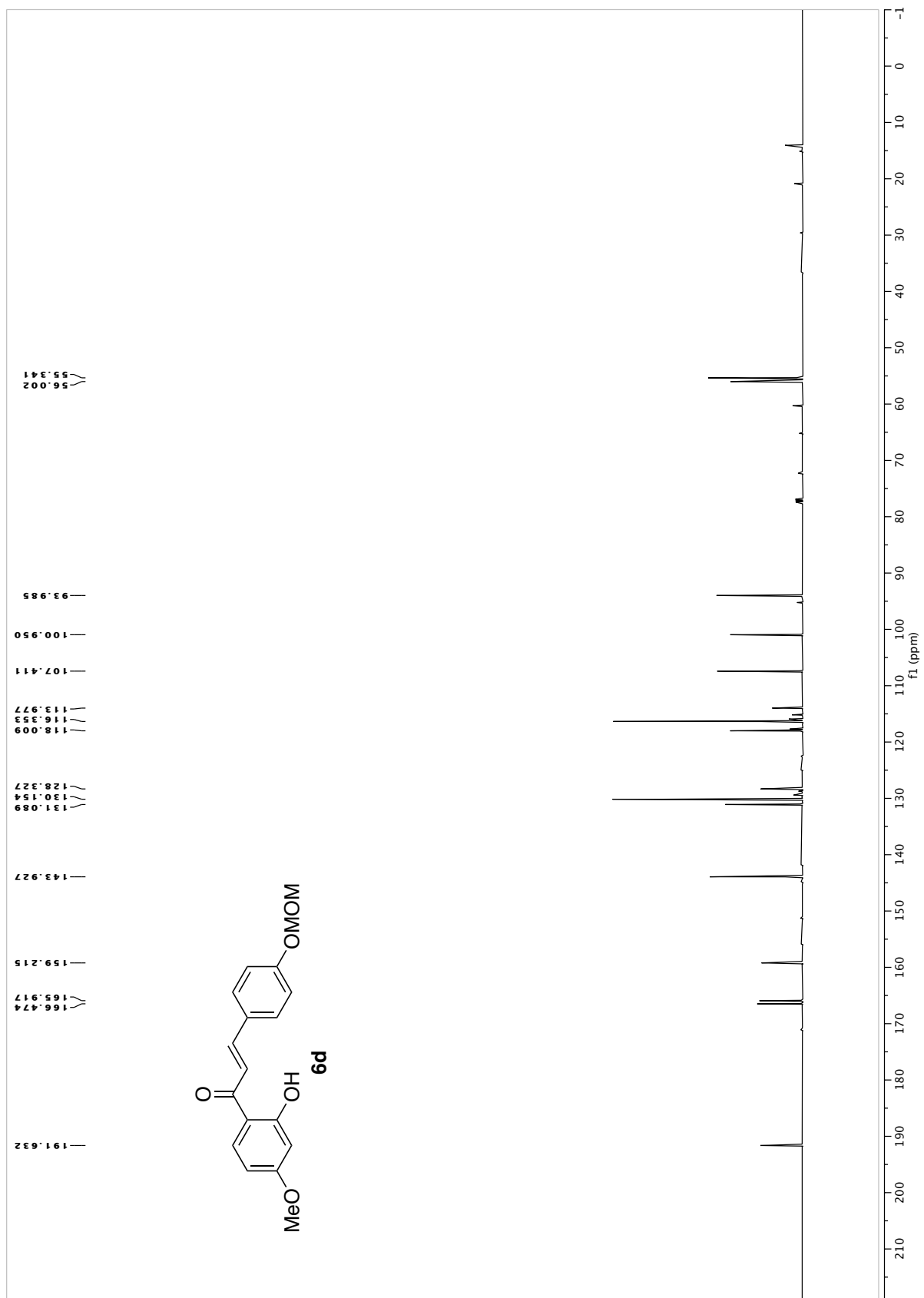


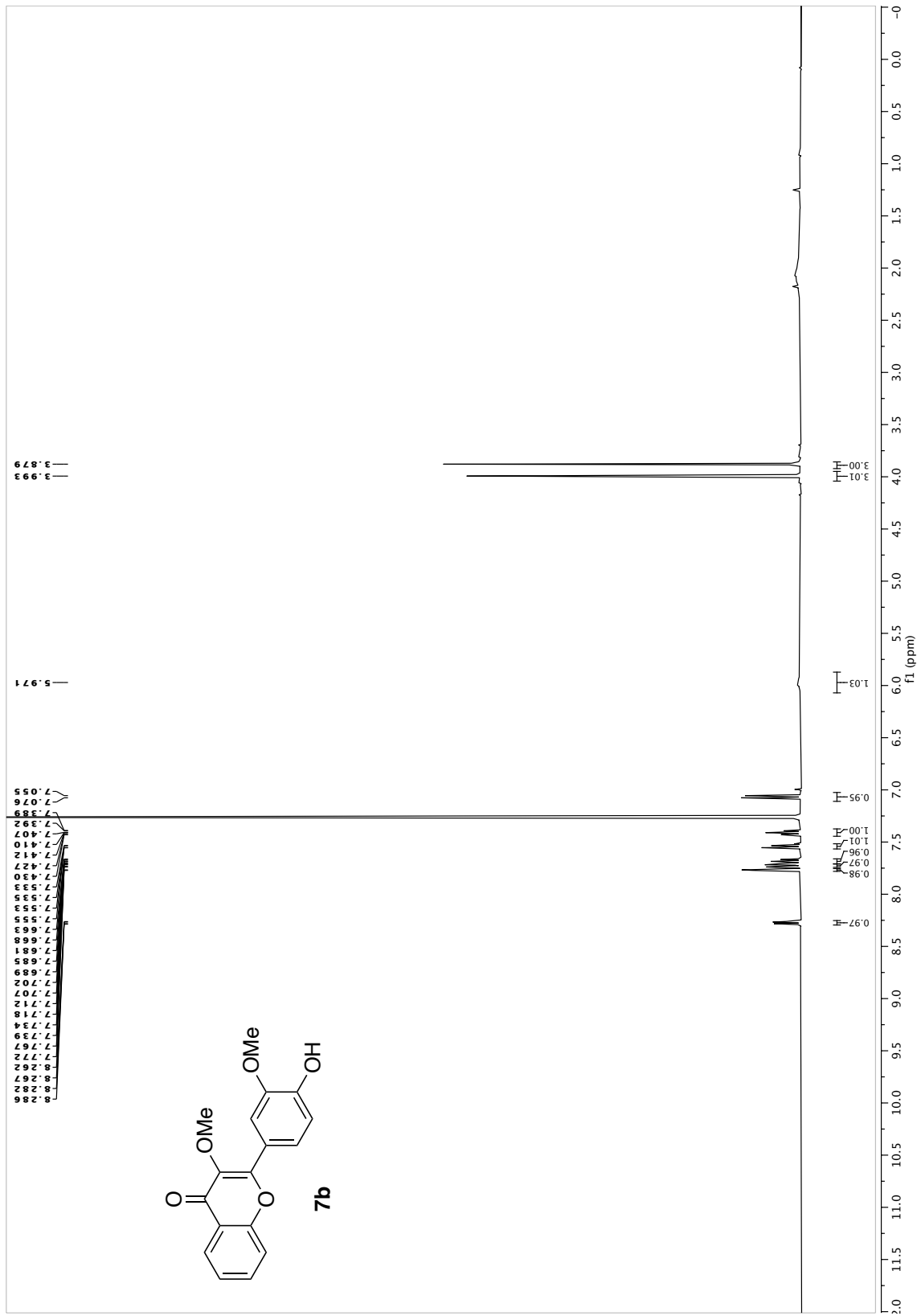


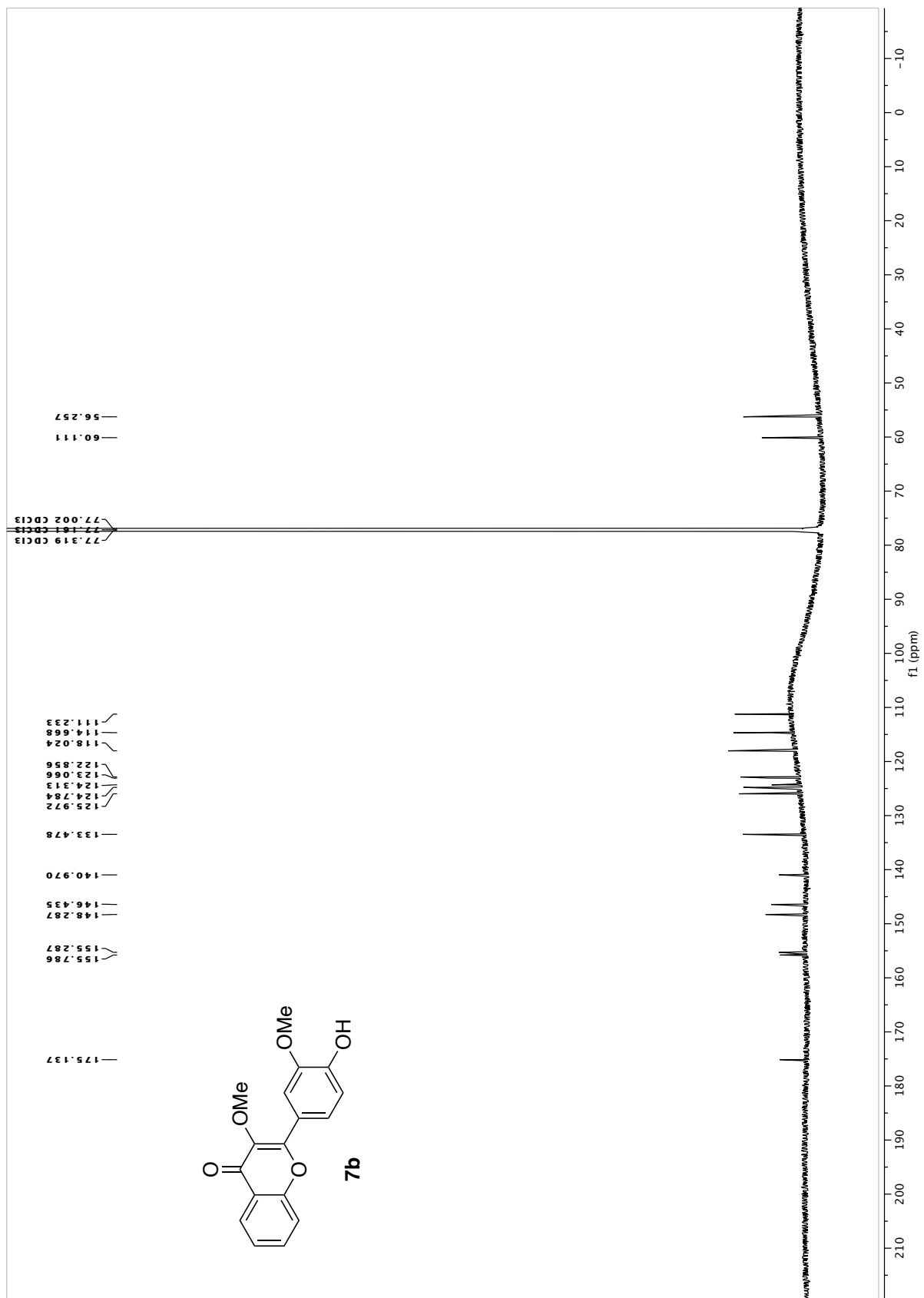


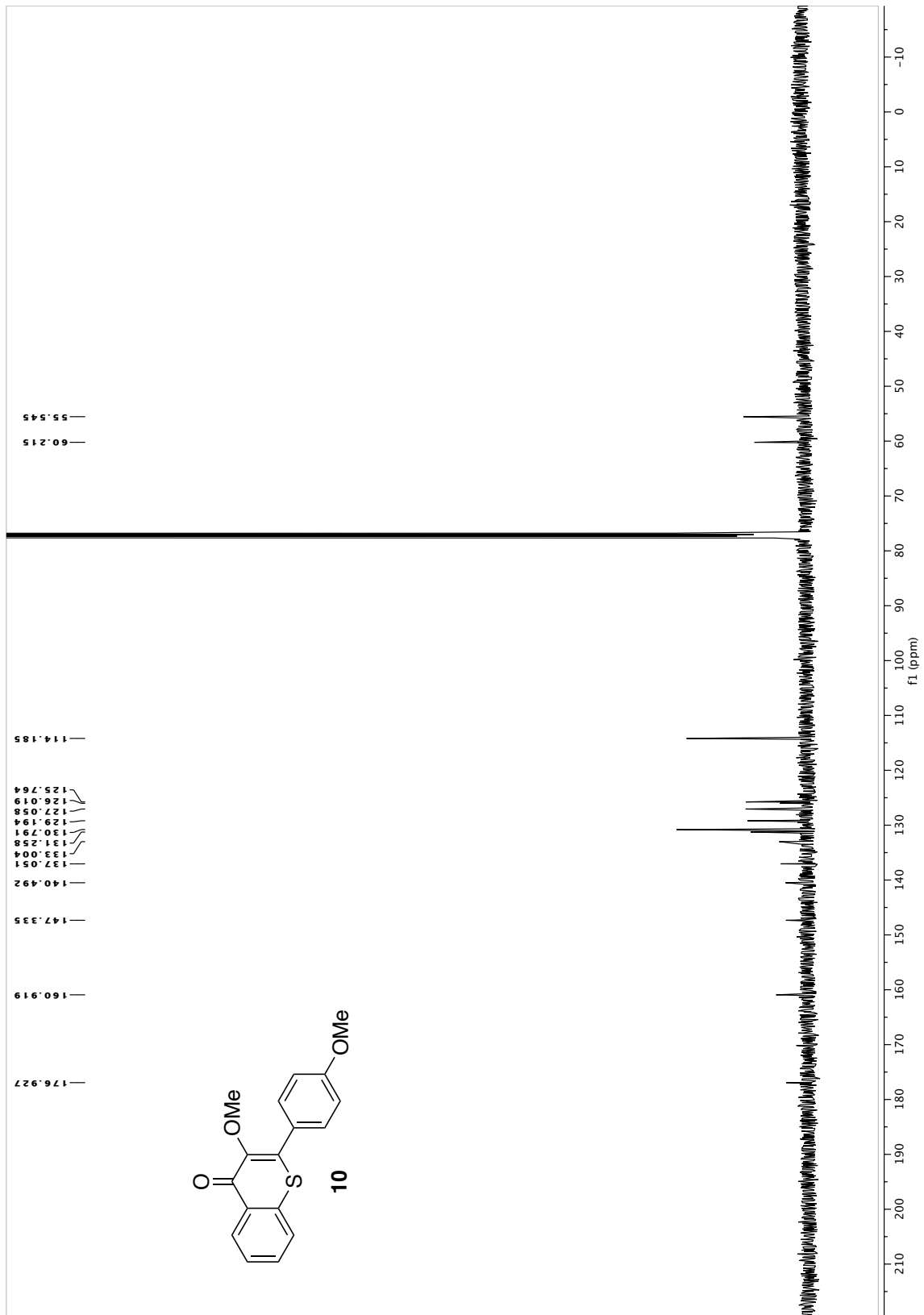


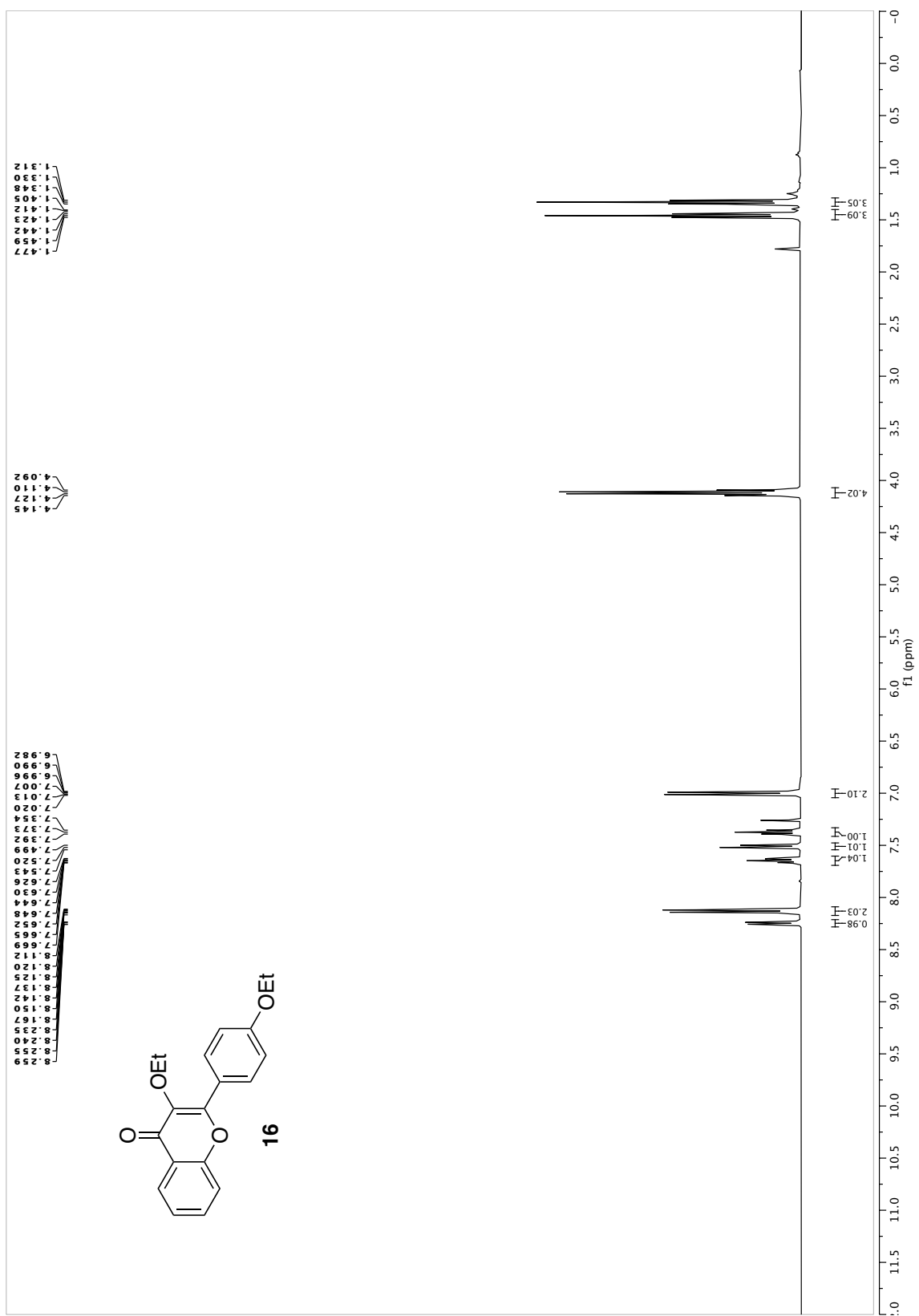


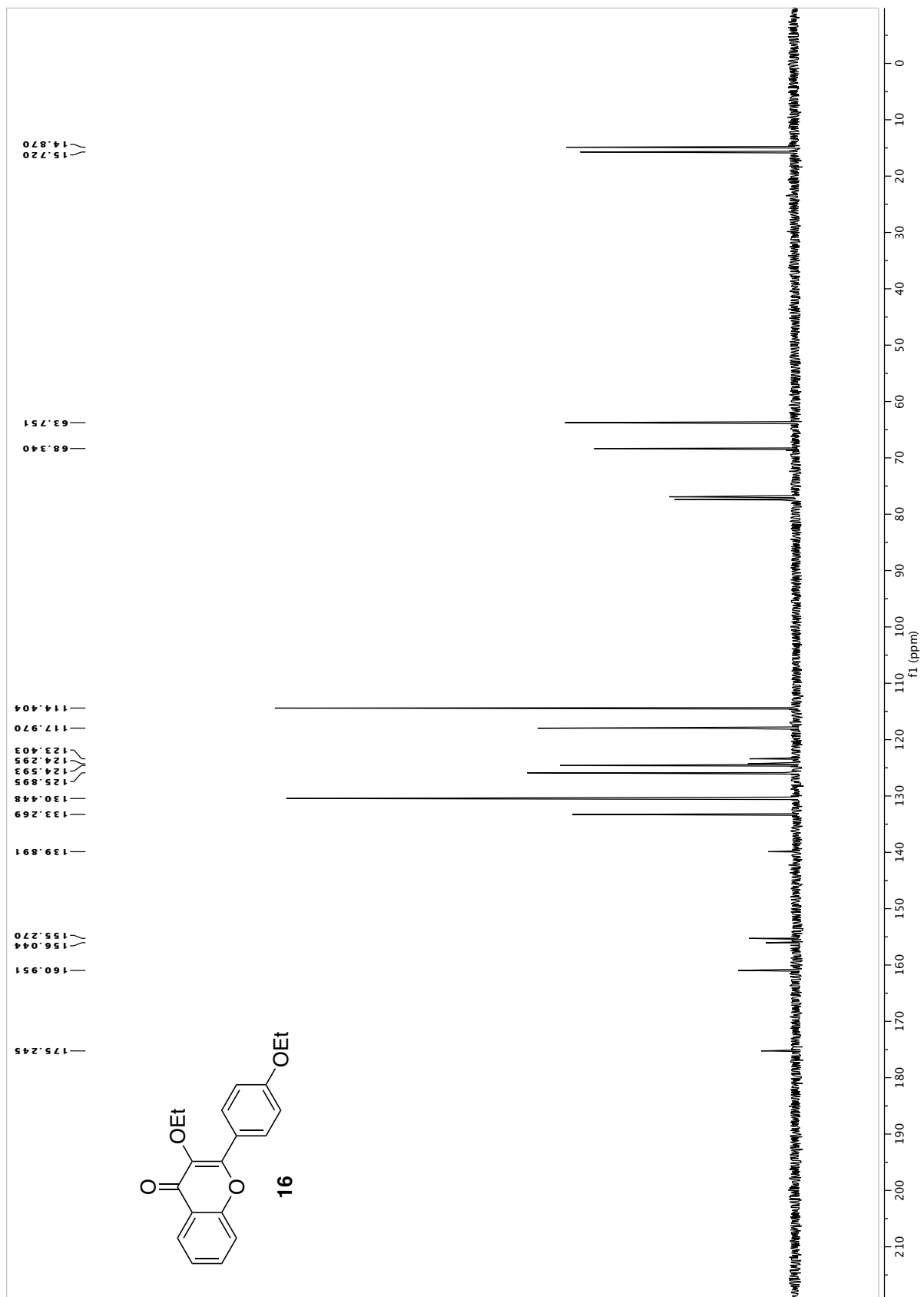


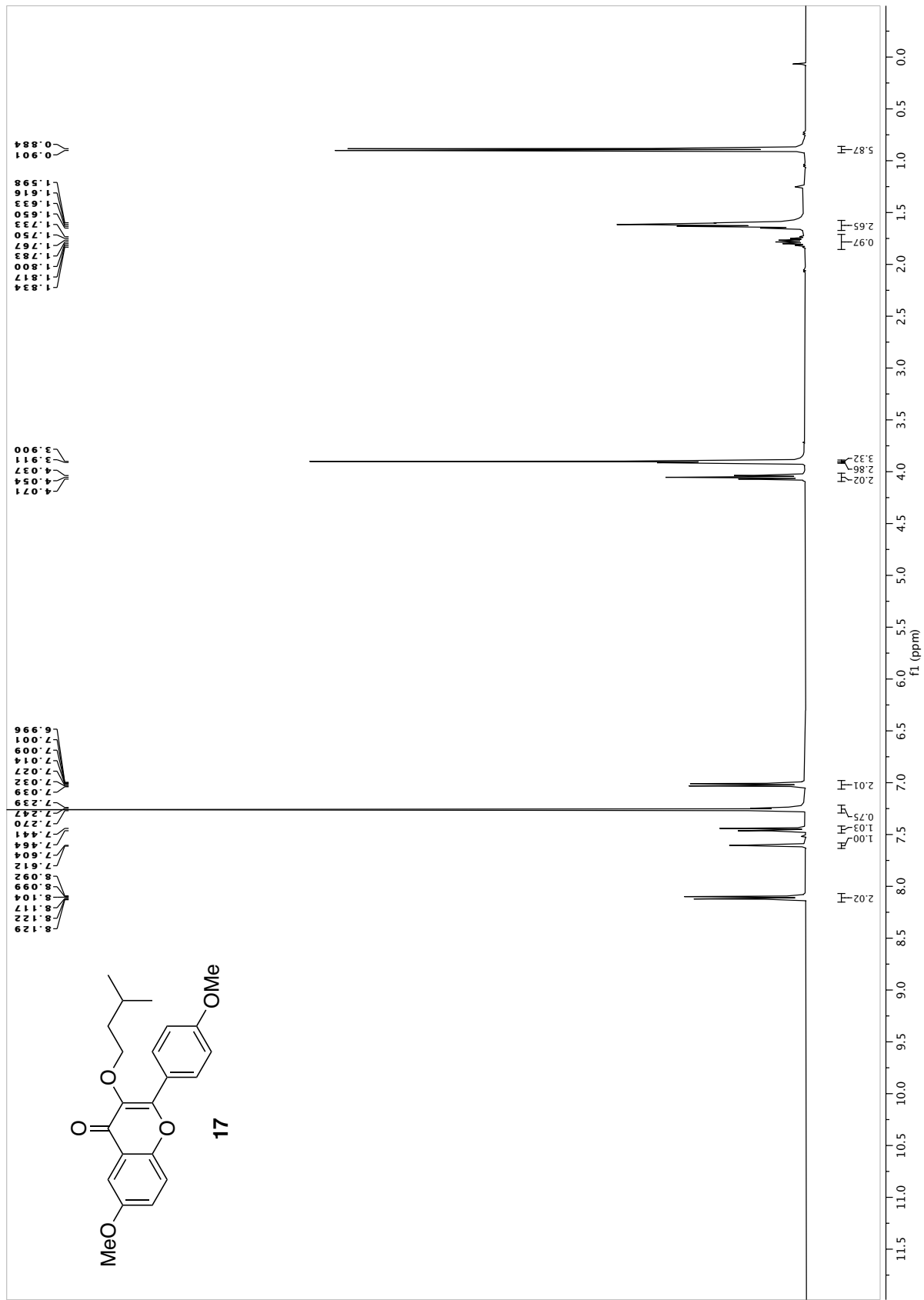


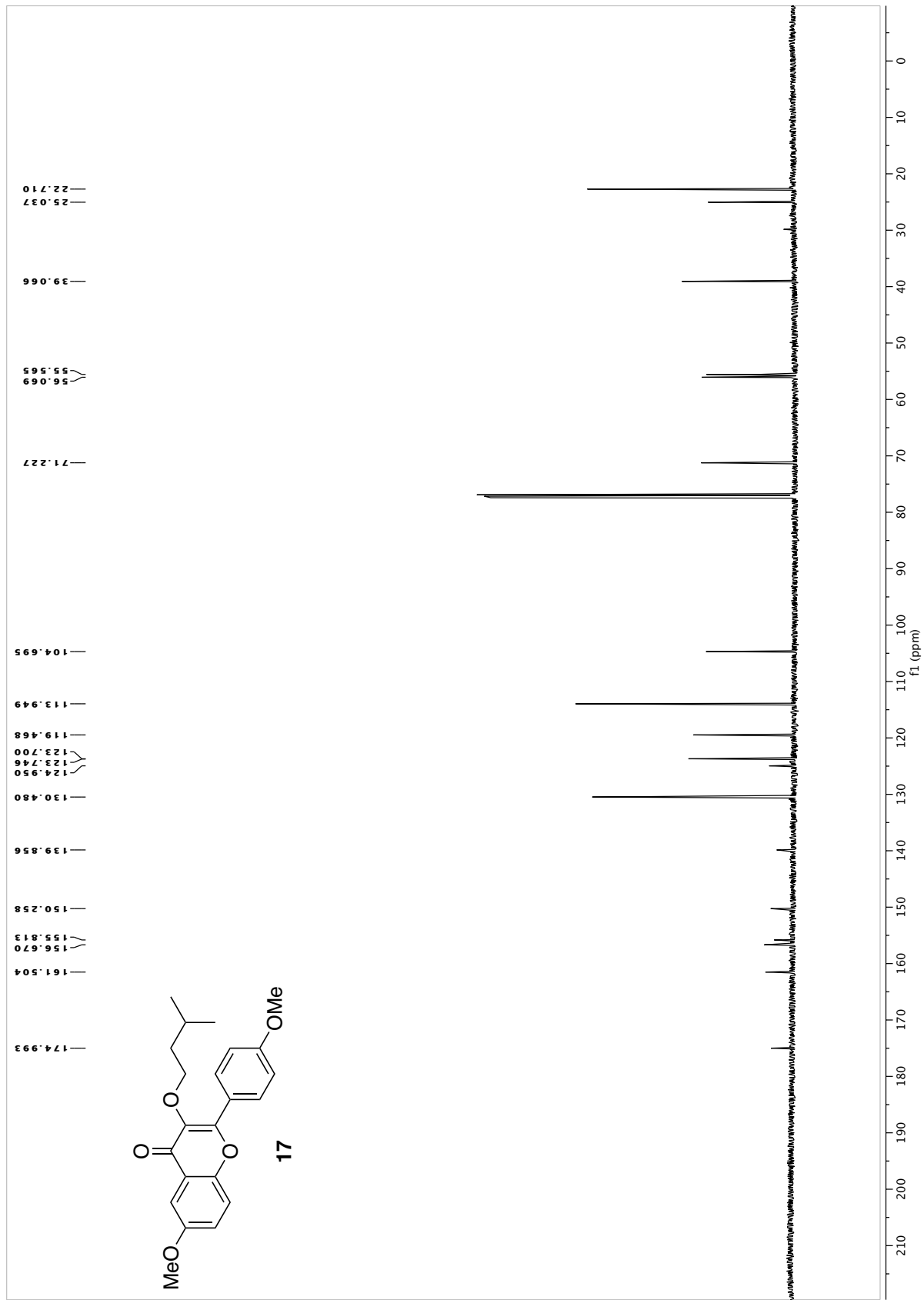


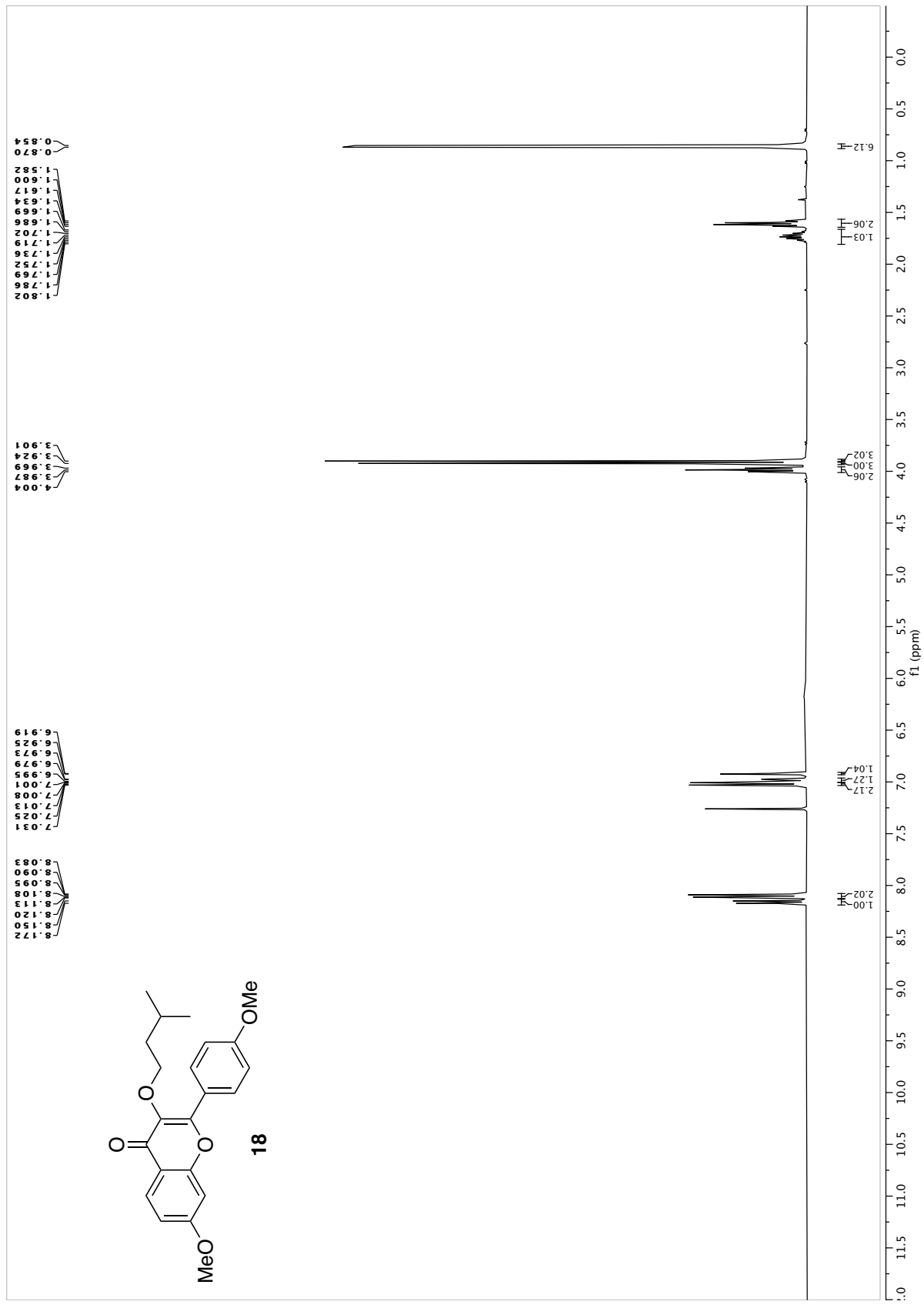


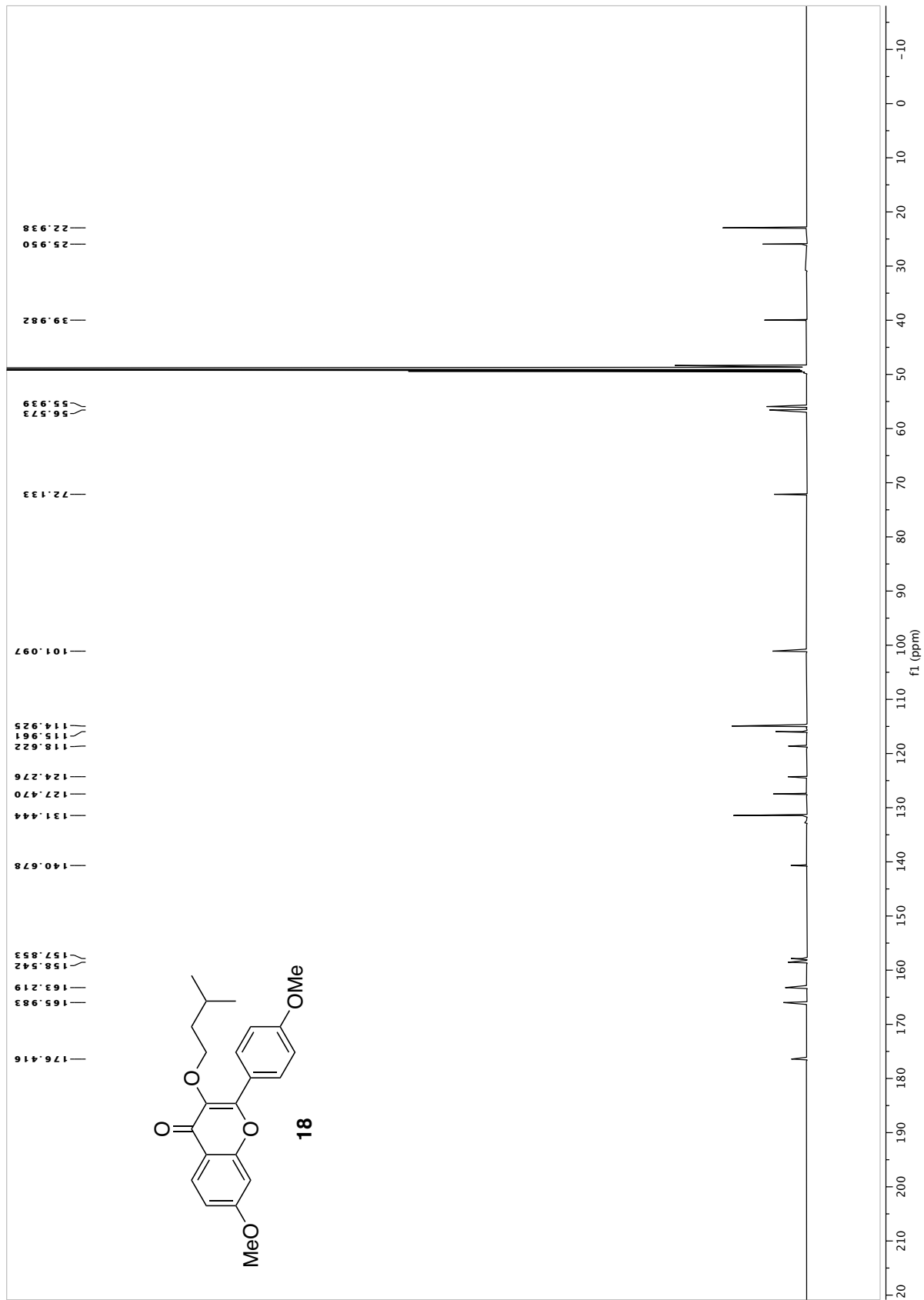


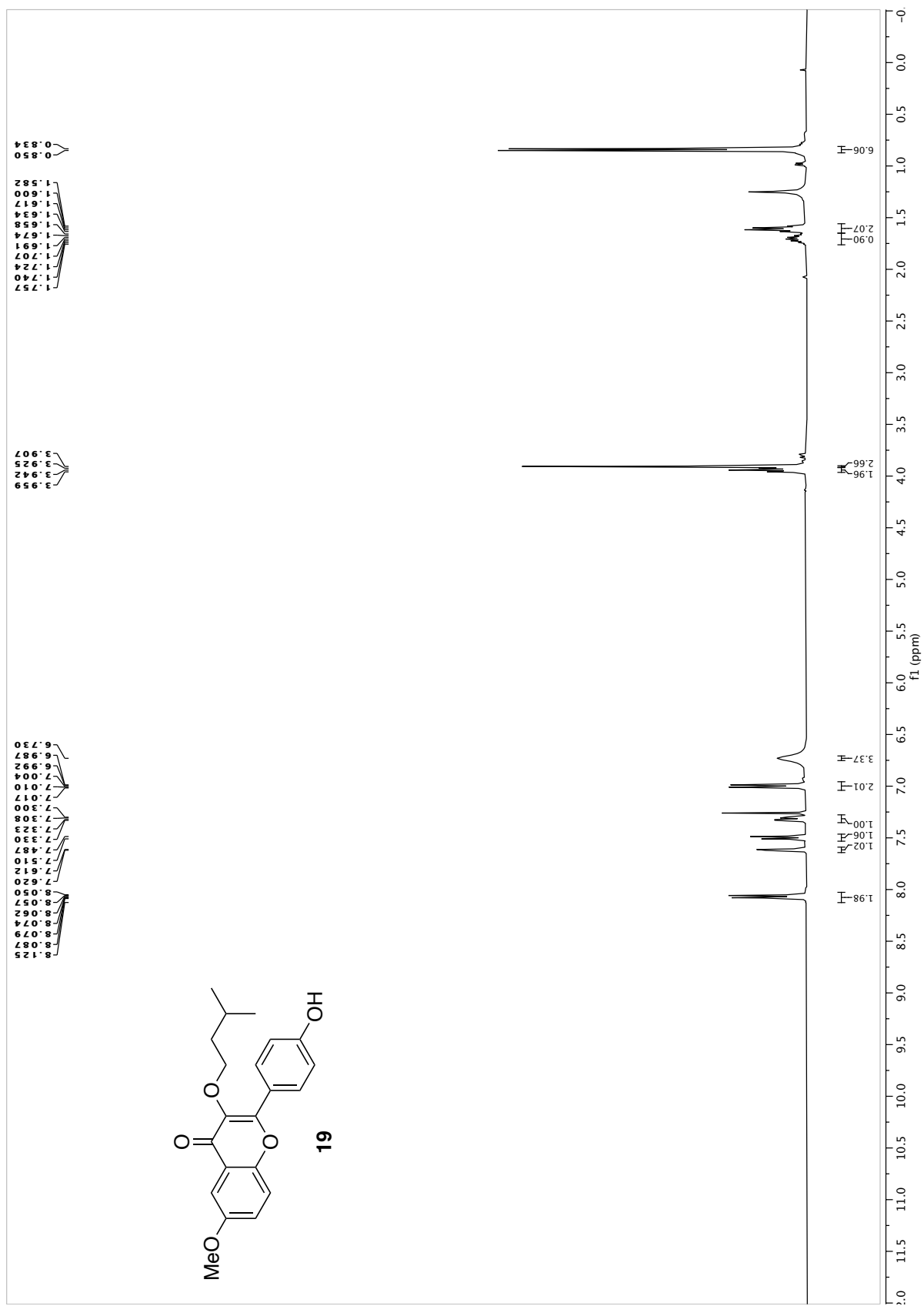


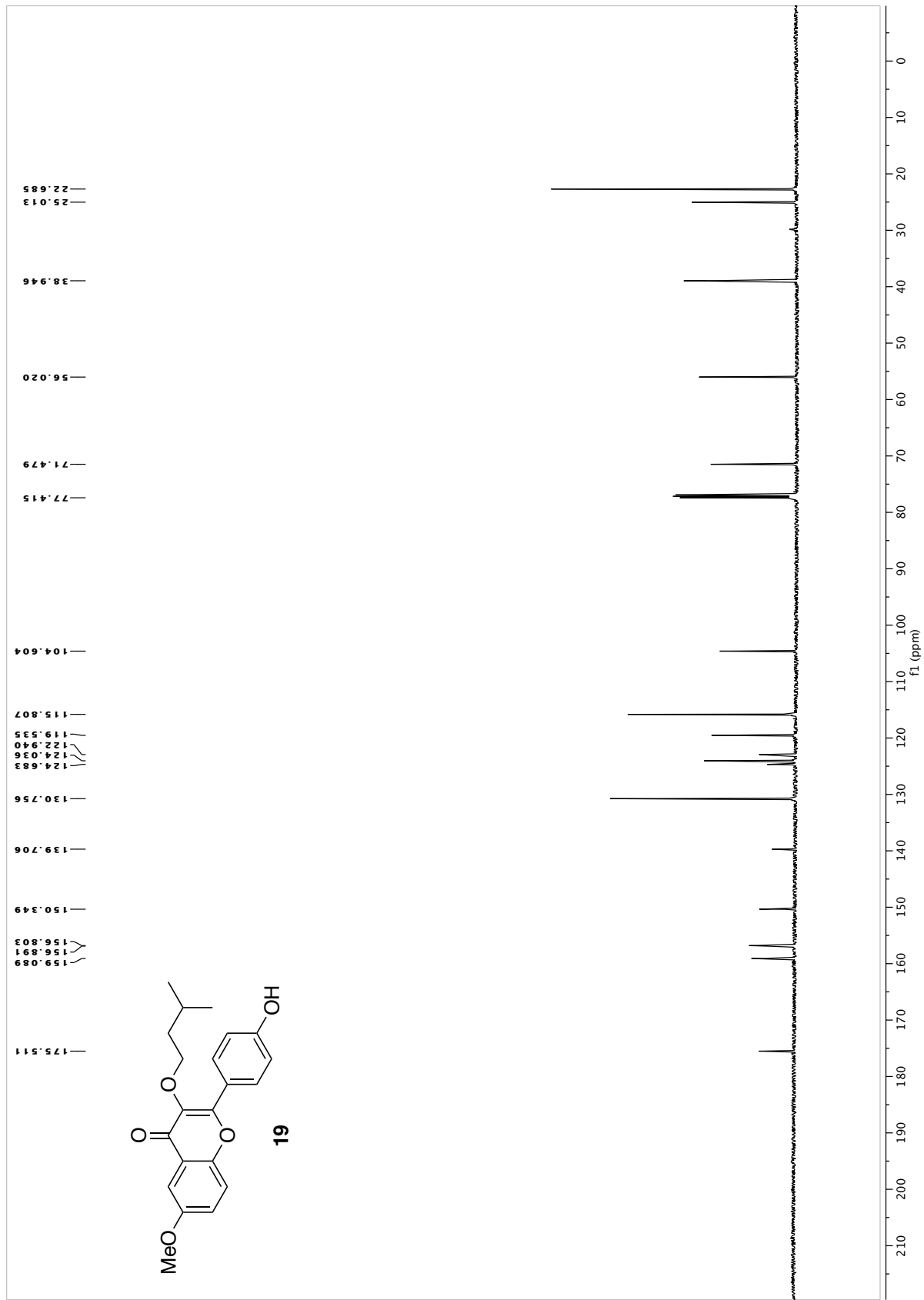


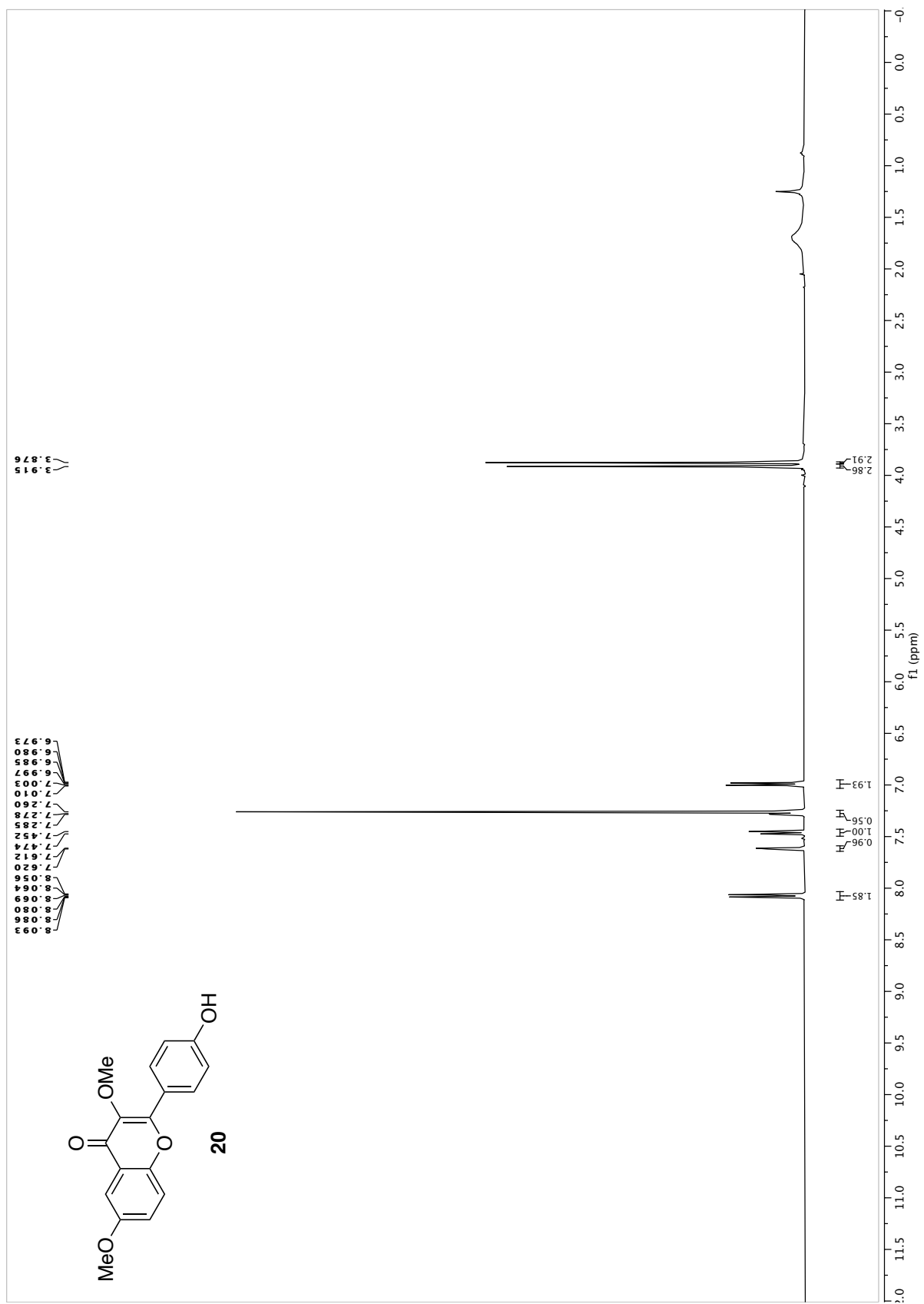


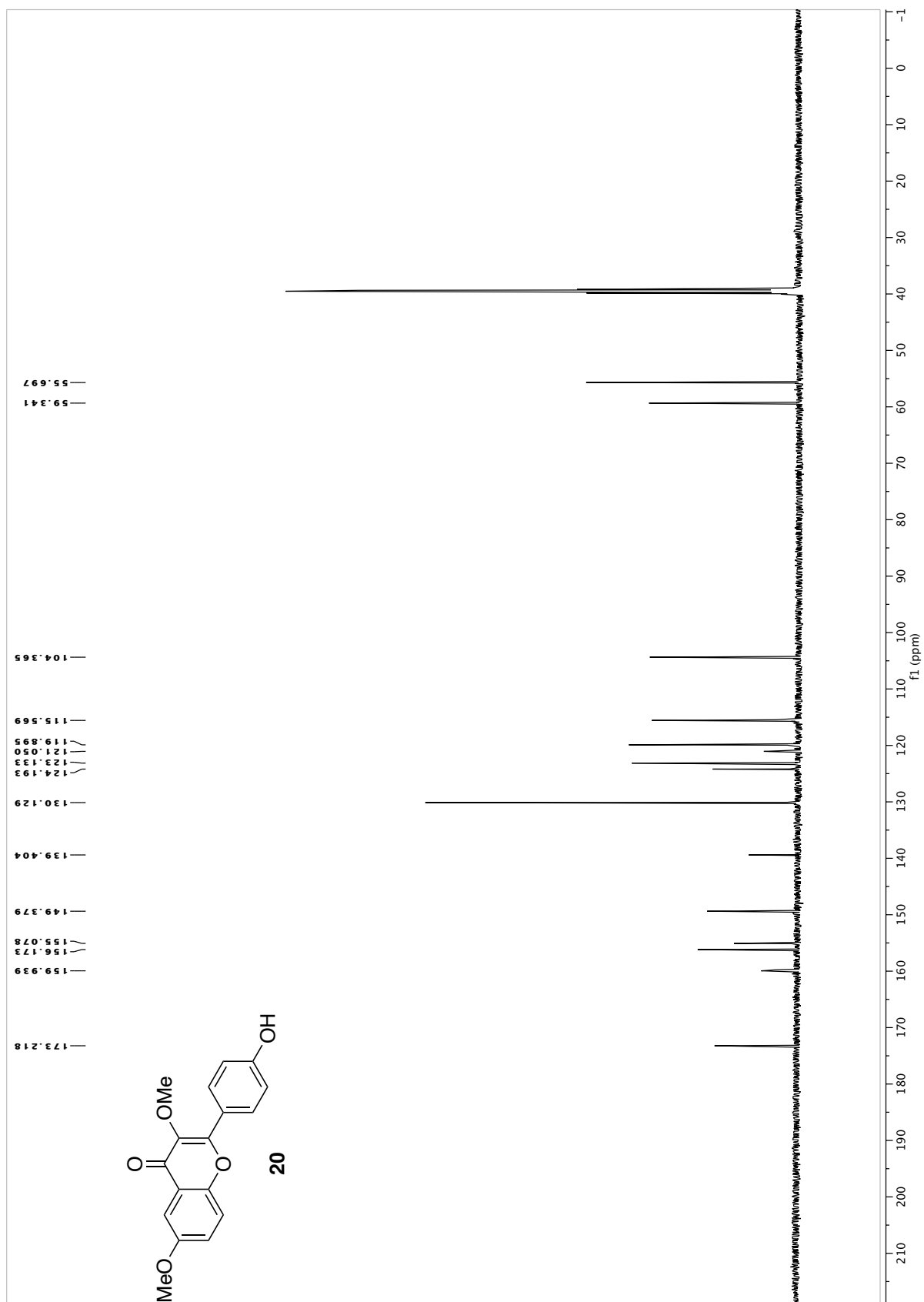


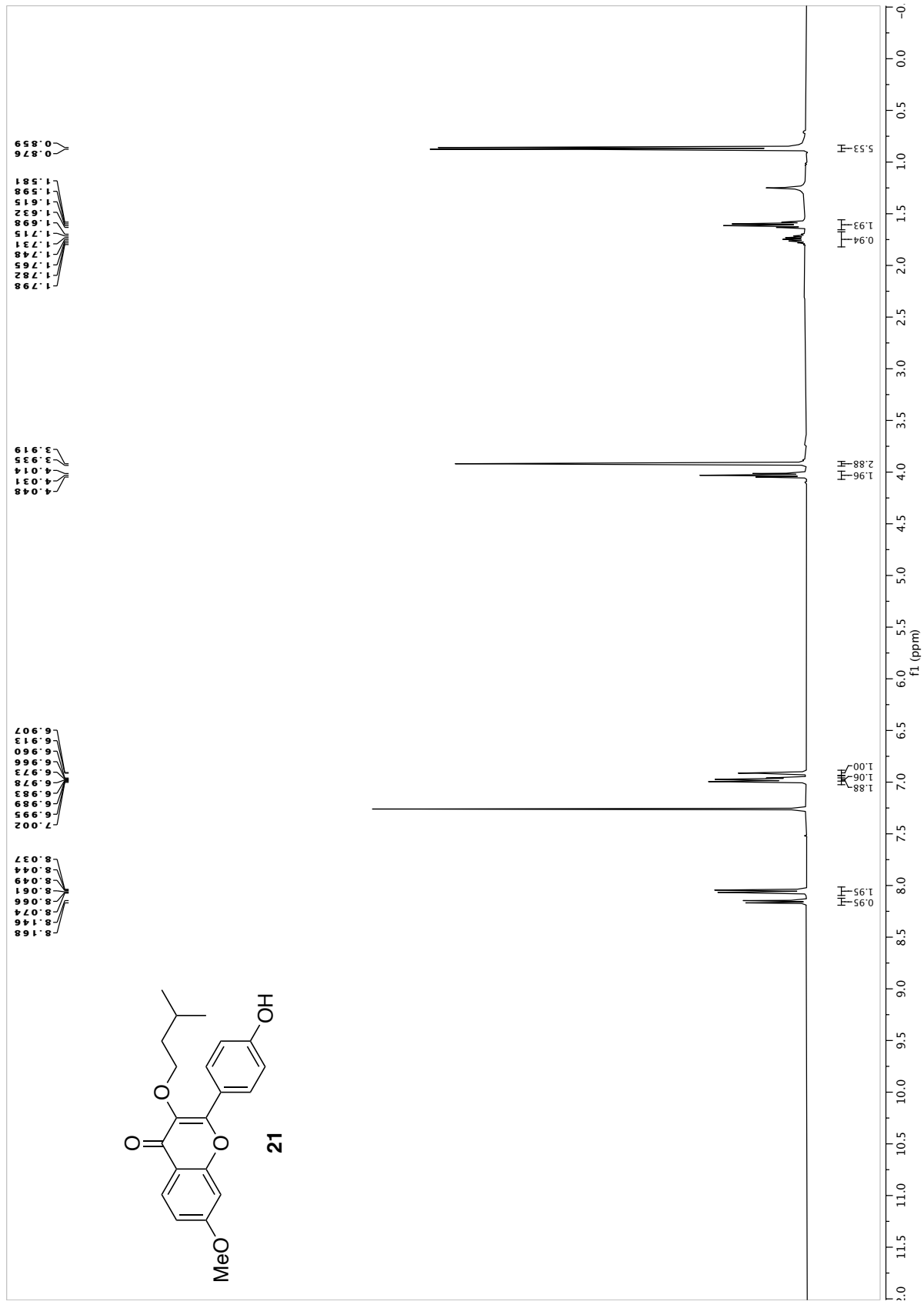


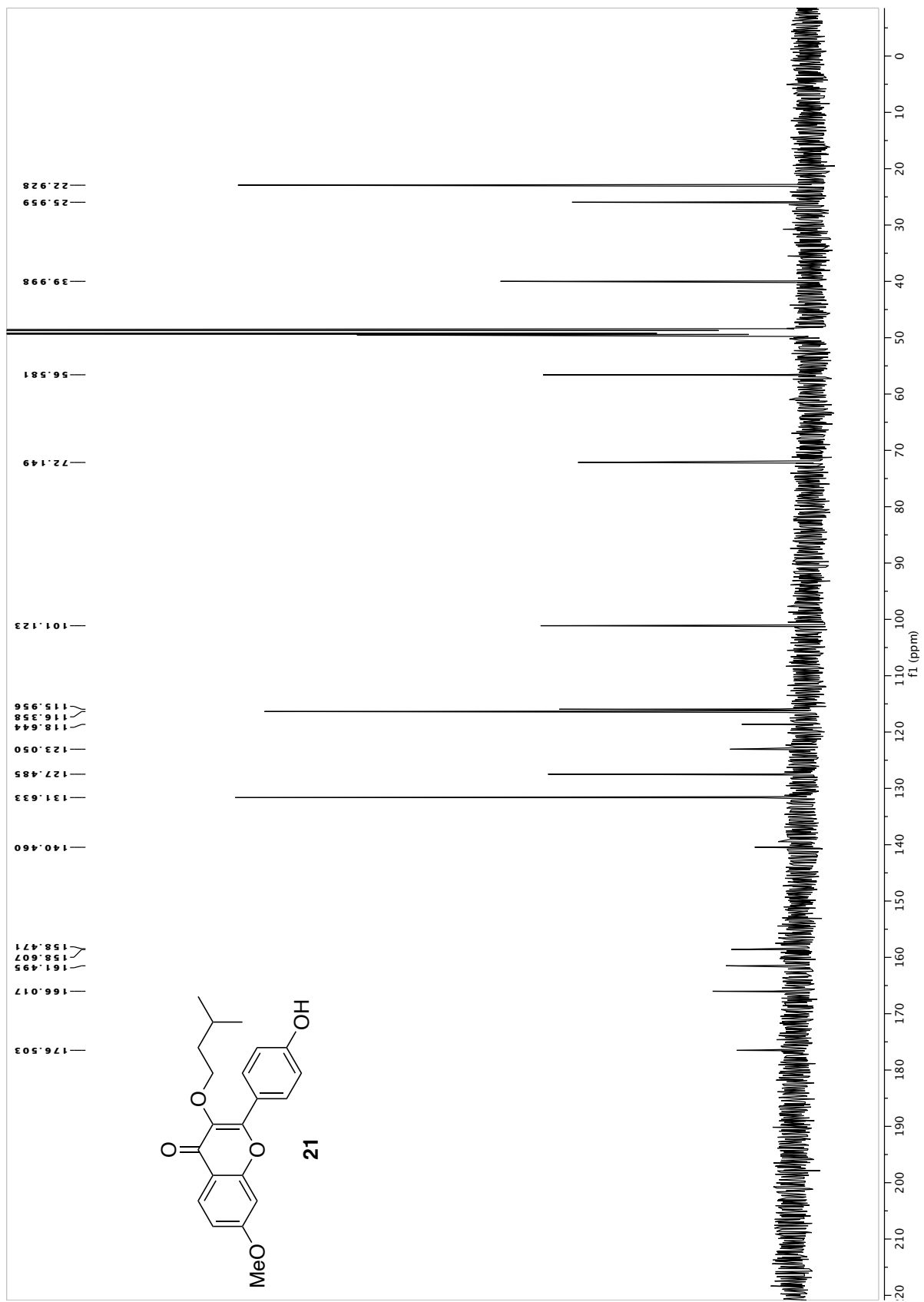












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