Supplementary Material (ESI) for Chemical Communications

Trimethylaluminum Mediated Amide Bond Formation in a Continuous Flow Microreactor as Key to the Synthesis of Rimonabant and Efaproxiral

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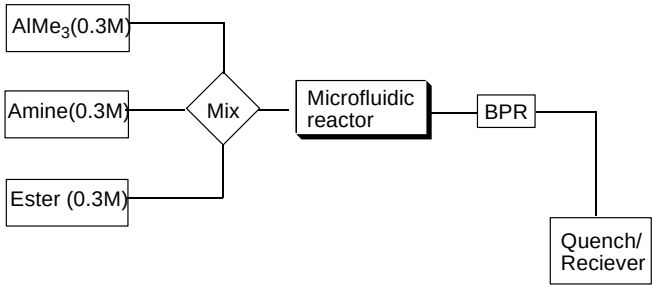
Schematic setup of microreactor system.



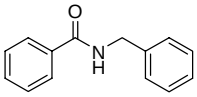
(P = pump, BPR = back pressure regulator)

A Syrris FRX-system was used, for mixing, a simple three way T-type mixer was used. The temperature was controlled using a Pt100 thermo-couple sensor in close proximity to the reaction channels. The rector consists of encased PTFE-tubing (1 mm id) heated on a conventional hotplate. For further information, visit http://www.syrris.com/

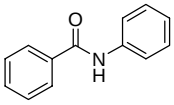
General methods. All chemicals were reagent grade and were used as supplied unless otherwise noted. All reactions under microwave conditions were performed in oven-dried glassware under an inert atmosphere (nitrogen or argon) unless noted otherwise. Tetrahydrofuran (THF) and toluene were purified by a J. C. Meyer Solvent Dispensing System (two packed columns of neutral alumina). Solvents for chromatography and work-up procedures were distilled from commercially available technical grade solvents. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates (0.25 mm). Compounds were visualized by UV and/or by dipping the plates in a cerium sulphate-ammonium molybdate solution followed by heating. Liquid column chromatography was performed using forced flow of the indicated solvent on Fluka silica gel 60 (40-63 μm). ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Mercury XL 300 spectrometer. The ^{1}H-NMR spectra (300 MHz) are expressed in ppm relative to $CHCl_3$ (7.26 ppm) as internal reference, the coupling constants are reported in Hz. The same is valid for ^{13}C-NMR spectra (75 MHz, internal reference $CDCl_3$: 77.0 ppm). Optical rotations $[\alpha]^D$ were recorded on a Jasco DIP-370 spectrometer using a sodium lamp (λ = 589 nm) at room temperature with a 10cm/1mL cell. The solvent and the concentration are specified, e.g. c = 1 = 10 mg/mL. IR spectra were recorded in chloroform on a Perkin-Elmer 1600 FT-IR spectrometer and are expressed in cm^{-1}. High-resolution mass spectroscopy (HRMS) was performed by the MS-service at the Laboratory for Organic Chemistry at ETH Zürich; 2,5-dihydroxybenzoic acid (DHB) was used as matrix.

General procedures for trimethylaluminum mediated amide bond formation.
Method A and B: Ester (0.3 mmol), amine (0.3 mmol) and $AlMe_3$ (0.3 mmol, 2 M solution in toluene) were dissolved in 3 mL of toluene (method A) or THF (method B) and heated in a microwave reactor to 100 °C (method A) or 130 °C (method B) for 2 min (70-80 s ramp time). The reaction solution was quenched with HCl (aq. 3%), diluted with EtOAc and washed with HCl (aq. 3%), the organic phase was dried over Na_2SO_4, concentrated and purified by silica gel flash column chromatography (hexane/EtOAc).

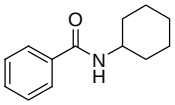
Method C: Ester (8 mmol, 0.3 M in THF), amine (8 mmol, 0.3 M in THF) and $AlMe_3$ (8 mmol, 0.3 M in THF/toluene) were mixed in a simple mixer and passed through a 16 mL tube reactor at a total flow rate of 8 mL/min (2 min retention time) at 125 °C. The reaction solution was collected in a mixture of EtOAc and HCl (aq. 3%), washed with HCl (aq. 3%), dried over Na_2SO_4, concentrated and purified on silica (hexane/EtOAc).



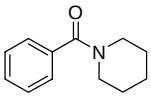
***N*-Benzylbenzamide (10)**: Prepared according to method A (92%) or method C (96%). Physical and spectral data in agreement with literature.



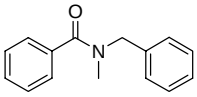
***N*-Phenylbenzamide (11)**: Prepared according to method A (98%), method B (95%) or method C on a 100 mmol scale, purified by crystallization from ethyl acetate/hexane (91%). Physical and spectral data in agreement with literature.



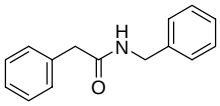
***N*-Cyclohexylbenzamide (12):** Prepared according to method C (85%). Physical and spectral data in agreement with literature.



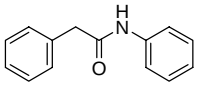
Phenyl(piperidin-1-yl)methanone (13): Prepared according to method C (37%). Physical and spectral data in agreement with literature.



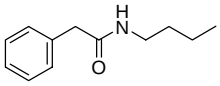
***N*-Benzyl-*N*-methylbenzamide (14)**: Prepared according to method B (56%) or method C (61%). Physical and spectral data in agreement with literature.



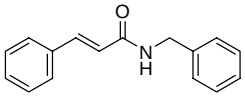
***N*-Benzyl-2-phenylacetamide (15)**: Prepared according to method C (98%) and method C using 200 mmol of each starting material, recrystallized from EtOAc/hexane (80%). Physical and spectral data in agreement with literature.



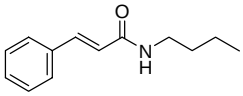
***N*,2-Diphenylacetamide (16)**: Prepared according to method C (92%). Physical and spectral data in agreement with literature.



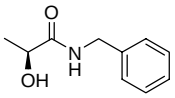
***N*-Butyl-2-phenylacetamide (17)**: Prepared according to method C (84%). Physical and spectral data in agreement with literature.



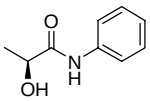
***N*-Benzylcinnamamide (18)**: Prepared according to method A (95%) or method C (94%). Physical and spectral data in agreement with literature.



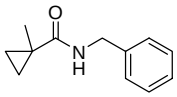
***N*-Butylcinnamamide (19)**: Prepared according to method C (88%). Physical and spectral data in agreement with literature.



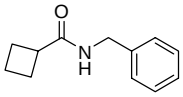
(*S*)-*N*-Benzyl-2-hydroxypropanamide (20): Prepared according to method B (70%) or method C (78%). Physical and spectral data in agreement with literature.



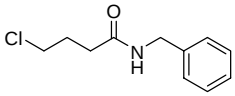
(*S*)-2-Hydroxy-*N*-phenylpropanamide (21): Prepared according to method C (78%). Physical and spectral data in agreement with literature.



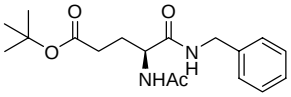
***N*-Benzyl-1-methylcyclopropanecarboxamide (22)**: Prepared according to method C (86%). ^{1}H NMR: 7.39-7.25 (m, 5H), 6.02 (br s, 1H), 4.45 (d, 2H, J = 5.5 Hz), 1.32 (s, 3H), 1.23 (q, 2H, J = 3.3 Hz), 0.59 (q, 2H, J = 3.3 Hz); ^{13}C NMR: 174.8, 138.5, 128.6, 127.7, 127.4, 43.9, 19.6, 18.9, 16.0; IR (thin film): 3289, 2938, 1646, 1621, 1533, 1224 cm^{-1}; HR-MS (ESI): calcd for $C_{12}H_{16}NO$ 189.1154 $[M+H]^+$, found 189.1149.



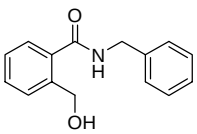
***N*-Benzylcyclobutanecarboxamide (23)**: Prepared according to method C (65%).^{1}H NMR: 7.37-7.22 (m, 5H), 5.86 (br s, 1H), 4.41 (d, 2H, J = 5.9 Hz), 3.02 (dquint, 1H, J = 5.9 Hz), 2.40-2.22 (m, 2H), 2.21-2.07 (m, 2H), 2.04-1.79 (m, 2H); ^{13}C NMR: 174.7, 138.4, 128.7, 127.8, 127.5, 43.5, 39.9, 25.4, 18.1; IR (thin film): 3291, 2932, 1630, 1520, 1453, 1229, 1205 cm^{-1}; HR-MS (ESI): calcd for $C_{12}H_{16}NO$ 189.1154 $[M+H]^+$, found 189.1150.



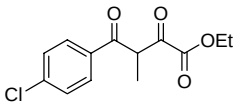
***N*-Benzyl-4-chlorobutanamide (24)**: Prepared according to method C (70%). Physical and spectral data in agreement with literature.



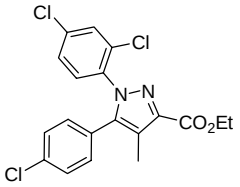
(*S*)-*tert*-Butyl 4-acetamido-5-(benzylamino)-5-oxopentanoate (25): Prepared according to method A (64%) or method C (80%). ^{1}H NMR: 7.37-7.22 (m, 5H), 5.86 (br s, 1H), 4.41 (d, 2H, J = 5.9 Hz), 3.02 (dquint, 1H, J = 5.9, 0.8 Hz), 2.40-2.22 (m, 2H), 2.21-2.07 (m, 2H), 2.04-1.79 (m, 2H); ^{13}C NMR: 174.7, 138.4, 128.7, 127.8, 127.5, 43.5, 39.9, 25.4, 18.1; IR (thin film): 3286, 2978, 1729, 1656, 1369, 1154 cm^{-1}; HR-MS (MALDI): calcd for $C_{18}H_{27}N_2O_4$ 335.1965 $[M+H]^+$, found 335.1965.



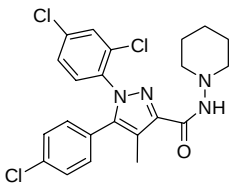
***N*-Benzyl-2-(hydroxymethyl)benzamide (26)**: Prepared according to method B with 1 equivalent of TMSCl added (89%). Physical and spectral data in agreement with literature.



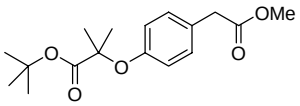
Ethyl 4-(4-chlorophenyl)-3-methyl-2,4-dioxobutanoate (29): 4-Chlorophenyl ethyl ketone **27** (0.12 M in THF, 0.5 mL/min) and lithium bis(trimethylsilyl)amide (0.12 M in THF, 0.5 mL/min) were mixed in a glass reactor (1 mL) at rt (retention time 1 min), the lithium enolate was then directly lead into a 16 mL tube reactor at 50 °C where it was mixed with diethyloxalate **28** (0.12 M in THF, 0.5 mL/min, retention time 10 min 40 sec). 360 mL of the reaction solution was collected (during 240 min) in a mixture of EtOAc and HCl (aq. 3%). The phases were separated and the organic phase was washed with HCl (aq. 3%) and brine, concentrated and the oily residue was purified on silica (hexane/EtOAc 5:1) to give 2.7 g (70%) of product **29** as a yellow amorphous solid (equilibrates to the corresponding enol-form upon standing in solution). ^{1}H NMR: 7.93 (d, 2H, J = 8.5 Hz), 7.49 (d, 2H, *J* = 8.5 Hz), 4.99 (q, 1H, *J* = 6.9 Hz), 4.27 (q, 2H, *J* = 8.0 Hz), 1.45 (d, 3H, *J* = 6.9 Hz), 1.30 (t, 3H, *J* = 8.0 Hz); ^{13}C NMR: 196.7, 190.1, 160.3, 140.3 (enol), 133.3 (enol), 130.0, 129.2, 62.9, 50.8, 13.8, 12.6; IR (thin film): 3071, 2990, 2941, 1748, 1668, 1586, 1252, 1087 cm^{-1}; HR-MS (MALDI): calcd for $C_{13}H_{14}ClO_4$ 269.0575 $[M+H]^+$, found 269.0580.



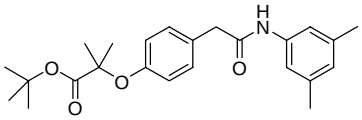
Ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylate (30): **29** (0.06 M in AcOH, 0.5 L/min) and 2,4-dichlorophenyl hydrazine hydrochloride salt (0.06 M in AcOH, 0.5 mL/min) were mixed in a 16 mL tube reactor at 125 °C (retention time 16 min). 300 mL were collected and concentrated then purified on silica (hexane/EtOAc 4/1) to give 2.96 g (80%) of product **30** as an light yellow amorphous solid. ^{1}H NMR: 7.39-7.25 (m, 5H), 7.07 (d, 2H, *J* = 8.6 Hz), 4.49 (q, 2H, *J* = 7.3 Hz), 2.33 (s, 3H), 1.42 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR: 162.7, 142.9, 135.9, 134.9, 132.9, 132.9, 130.8, 130.6, 130.0, 128.8, 127.7, 126.9, 119.0, 60.9, 14.4, 9.6; IR (thin film): 2980, 1712, 1495, 1248, 1089 cm^{-1};HR-MS (MALDI): calcd for $C_{19}H_{16}Cl_3N_2O_2$ 409.0272 $[M+H]^+$, found 409.0277.



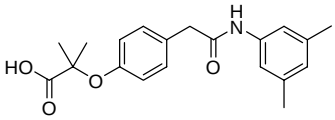
5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide (rimonabant, 31): Prepared according to method C on a 7 mmol scale. Instead of HCl (aq. 3%) in the quench and washing steps, Rochelle's salt (Na, K-tartrate, aq. 10%) was used (88%). ^{1}H NMR: 7.63 (s, 1H), 7.42-7.36 (m, 1H), 7.30-7.21 (m, 3H), 7.02 (d, 2H, *J* = 8.0 Hz), 5.26 (br s, 1H), 2.88-2.77 (m, 4H), 2.33 (s, 3H), 1.77-1.65 (m, 4H), 1.45-1.33 (m, 2H); ^{13}C NMR: 159.8, 144.2, 142.8, 135.8, 135.8, 134.8, 132.8, 130.7, 130.5, 130.2, 128.8, 127.8, 127.1, 118.1, 57.1, 53.5, 26.5, 23.5, 9.5; IR (thin film): 2936, 2854, 1677, 1528, 1484, 1091, 832 cm^{-1}; HR-MS (MALDI): calcd for $C_{22}H_{22}Cl_3N_4O$ 463.0854 $[M+H]^+$, found 463.0848.



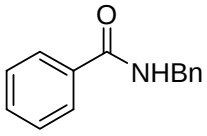
***tert*-Butyl 2-(4-(2-methoxy-2-oxoethyl)phenoxy)-2-methylpropanoate (34)**: Methyl 4-hydroxyphenylacetate (**32**, 1.2 g, 7.22 mmol), *tert*-butyl α-bromo isobutyrate (**33**, 4.83 g, 21.7 mmol), K_2CO_3 (3.0 g, 21.7 mmol) and $MgSO_4$ (920 mg, 7.22 mmol) were mixed in DMF (30 mL) and heated to 75 °C for 14 h. The mixture was diluted with Et_2O, filtered and washed with HCl (aq. 5%), the solid residue was thoroughly washed with $E_{t2}O$ and the combined organic phases were washed with HCl (aq. 5%) and dried over Na_2SO_4. The crude product was purified on silica (hexane:ethyl acetate 9:1 → 4:1) to give 1.67 g of product **34** (75%). ^{1}H NMR: 7.13 (d, 2H, *J* = 8.9 Hz), 6.80 (d, 2H, *J* = 8.9 Hz), 3.68 (s, 3H), 3.55 (s, 2H), 1.56 (s, 6H), 1.44 (s, 9H); ^{13}C NMR: 173.1, 172.1, 154.7, 129.7, 127.0, 118.8, 81.7, 79.4, 52.1, 40.4, 27.9, 25.5; IR (thin film): 2980, 2940, 1727, 1510, 1131 cm^{-1}; HR-MS (MALDI): calcd for $C_{17}H_{24}NaO_5$ 331.1516 [*M*+Na]$^+$, found 331.1500.



***tert*-Butyl 2-(4-(2-(3,5-dimethylphenylamino)-2-oxoethyl)phenoxy)-2-methylpropanoate (35)**: Prepared according to method C starting with 1.40 g (4.5 mmol) of **35** (77%). ^{1}H NMR: 7.26 (s, 1H), 7.18 (d, 2H, *J* = 8.9 Hz), 7.02 (s, 2H), 6.88 (d, 2H, *J* = 8.9 Hz), 6.71 (br s, 1H), 3.64 (s, 2H), 2.25 (s, 6H), 1.58 (s, 6H), 1.45 (s, 9H); ^{13}C NMR: 173.0, 169.2, 155.1, 138.5, 130.1 126.0, 119.3, 117.3, 81.7, 79.4, 43.9, 27.7, 25.3, 21.1; IR (thin film): 3298, 2979, 2922, 1725, 1658, 1615, 1548, 1130 cm^{-1}; HR-MS (MALDI): calcd for $C_{20}H_{24}NO_4$ 342.1700 [*M*+H]$^+$, found 342.1699.



2-(4-(2-(3,5-Dimethylphenylamino)-2-oxoethyl)phenoxy)-2-methylpropanoic acid (efaproxiral, 36): **35** (610 mg, 1.53 mmol) was dissolved in HCO_2H (30 mL, 0.05 M), passed through a tube reactor (16 mL) at 90 °C at a flow rate of 2 mL/min (8 min retention time), concentrated and filtered through silica to give 467 mg of product **36** (89%).^{1}H NMR: 9.99 (s, 1H), 7.57 (s, 1H), 7.15 (d, 2H, *J* = 8.5 Hz), 7.04 (s, 2H), 6.89 (d, 2H, *J* = 8.5 Hz), 6.71 (br s, 1H), 3.60 (s, 2H), 2.21 (s, 6H), 1.61 (s, 6H); ^{13}C NMR: 177.9, 169.7, 154.3, 138.6, 137.1, 130.3, 128.4, 126.3, 120.3, 117.6, 79.3, 43.7, 25.1, 21.2; IR (thin film): 3317, 2982, 2900, 2515, 1693, 1615, 1508, 1464, 1136 cm^{-1}; HR-MS (MALDI): calcd for $C_{17}H_{25}O_5$ 309.1697 [*M*+H]$^+$, found 309.1699.



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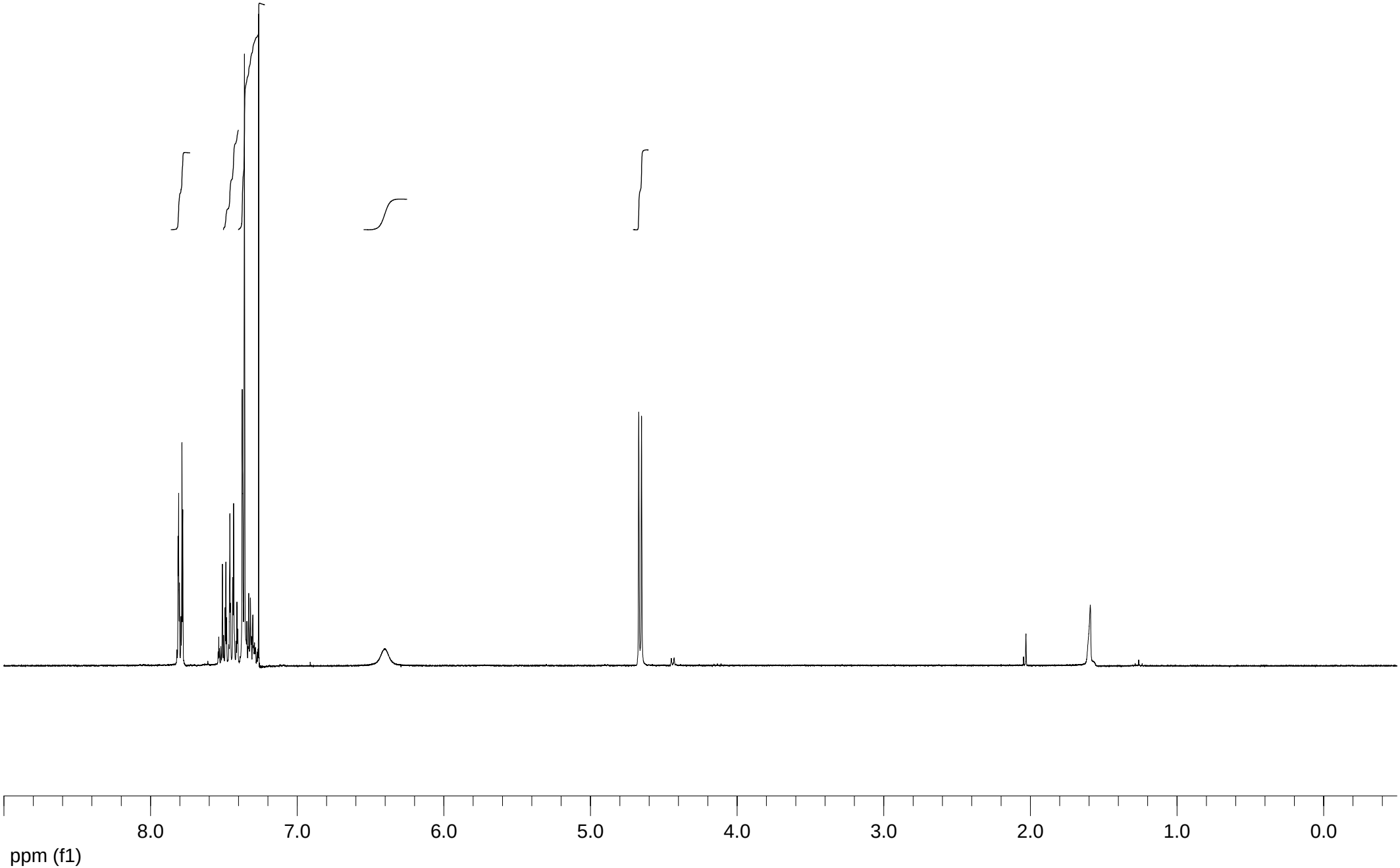

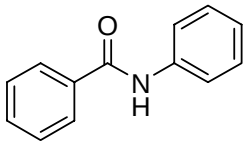

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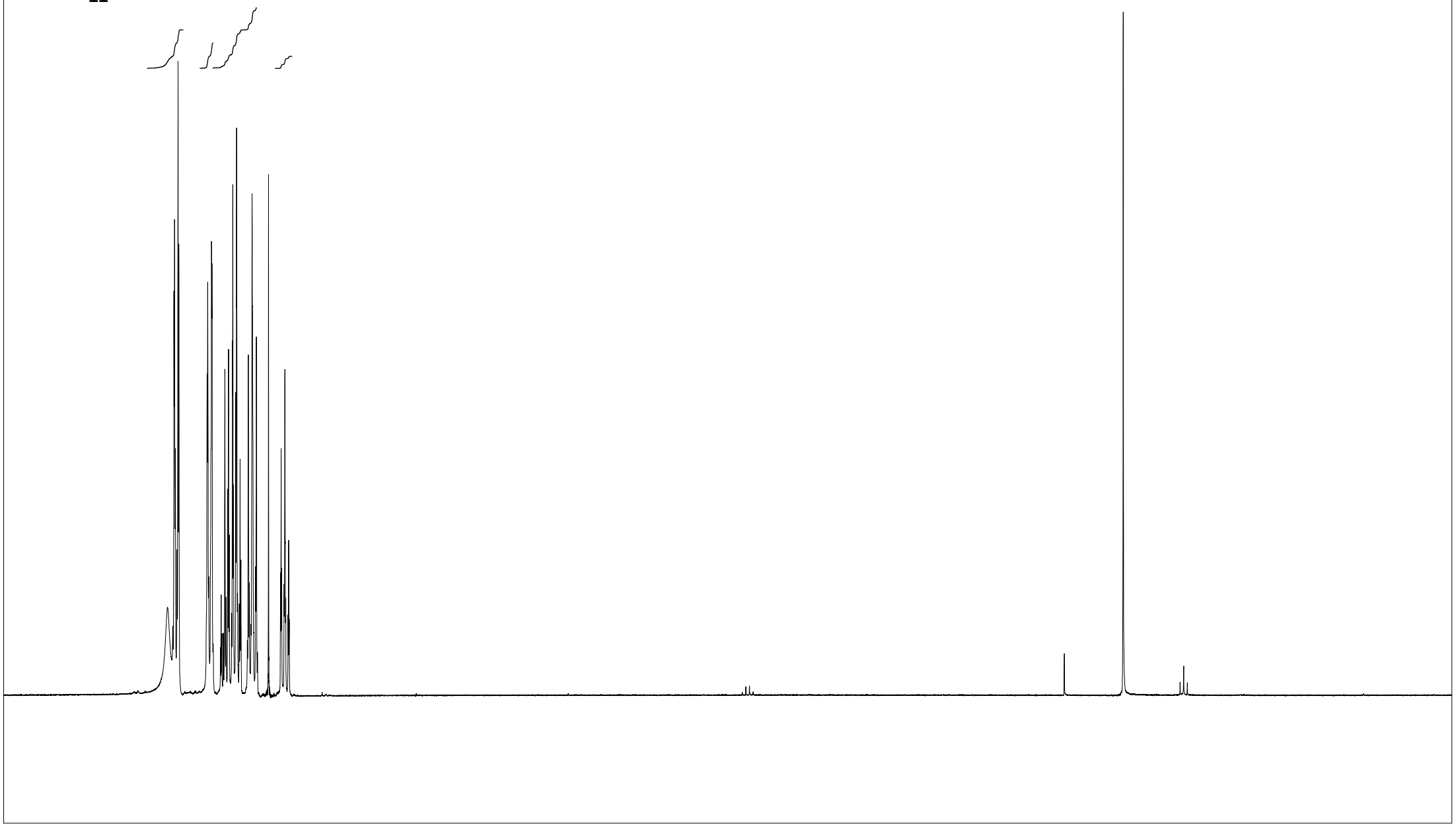

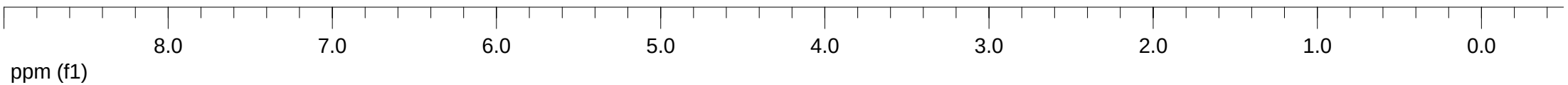

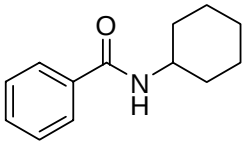

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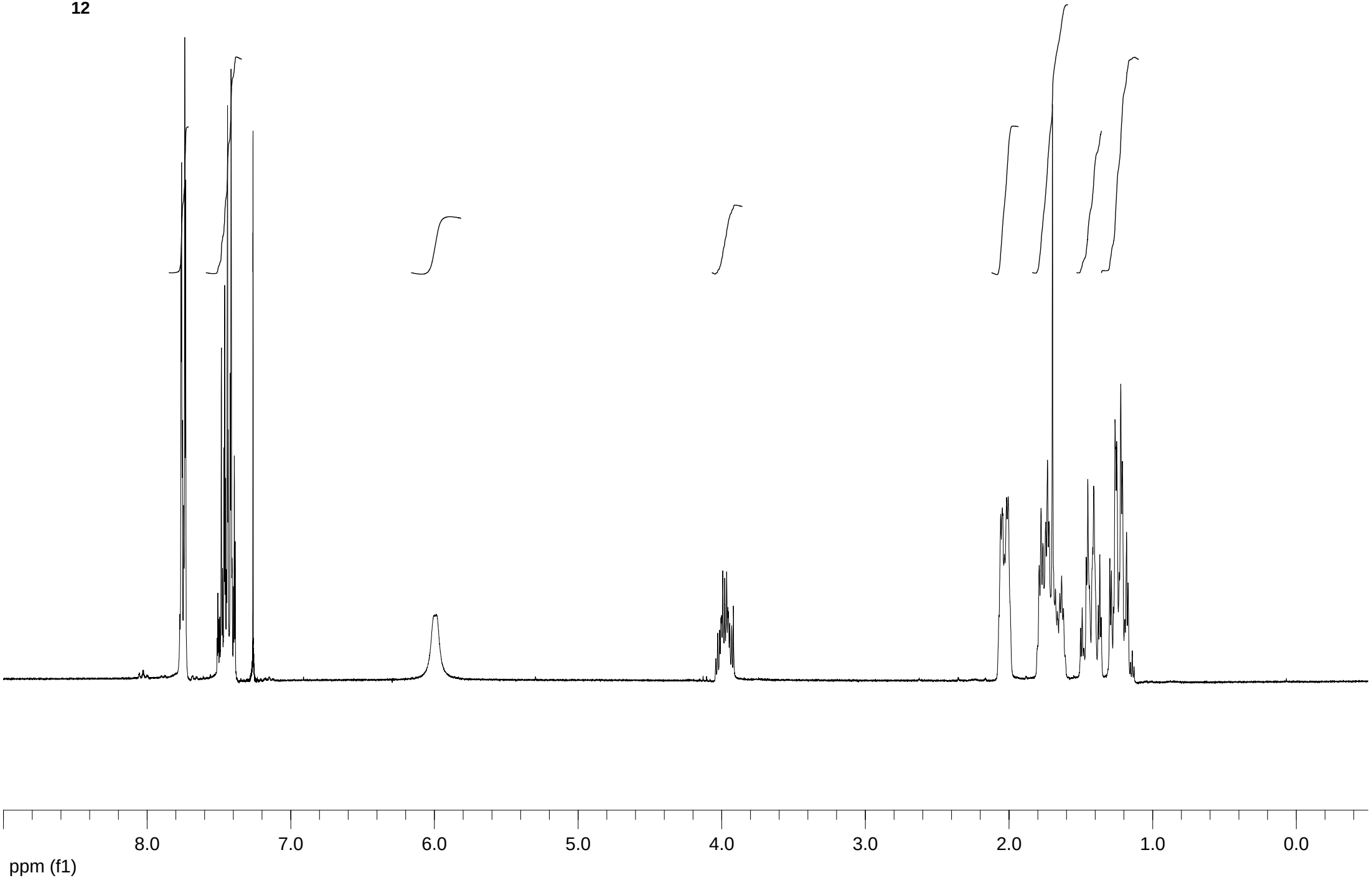

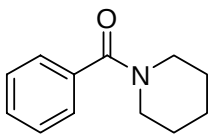

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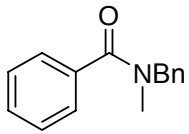

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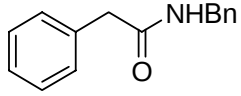

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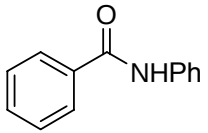

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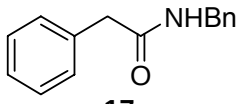

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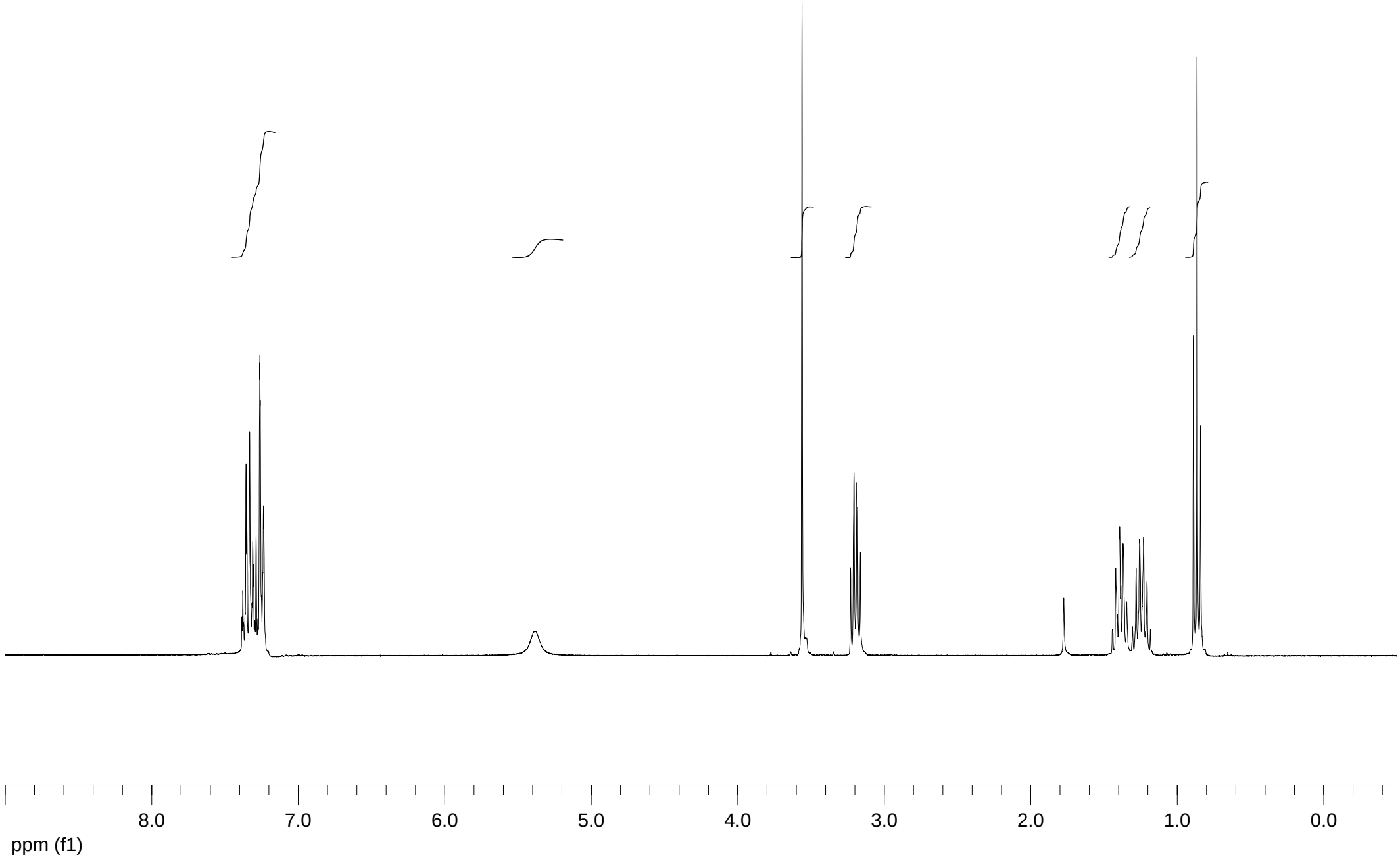

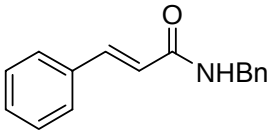

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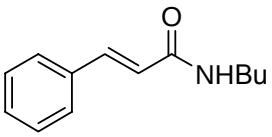

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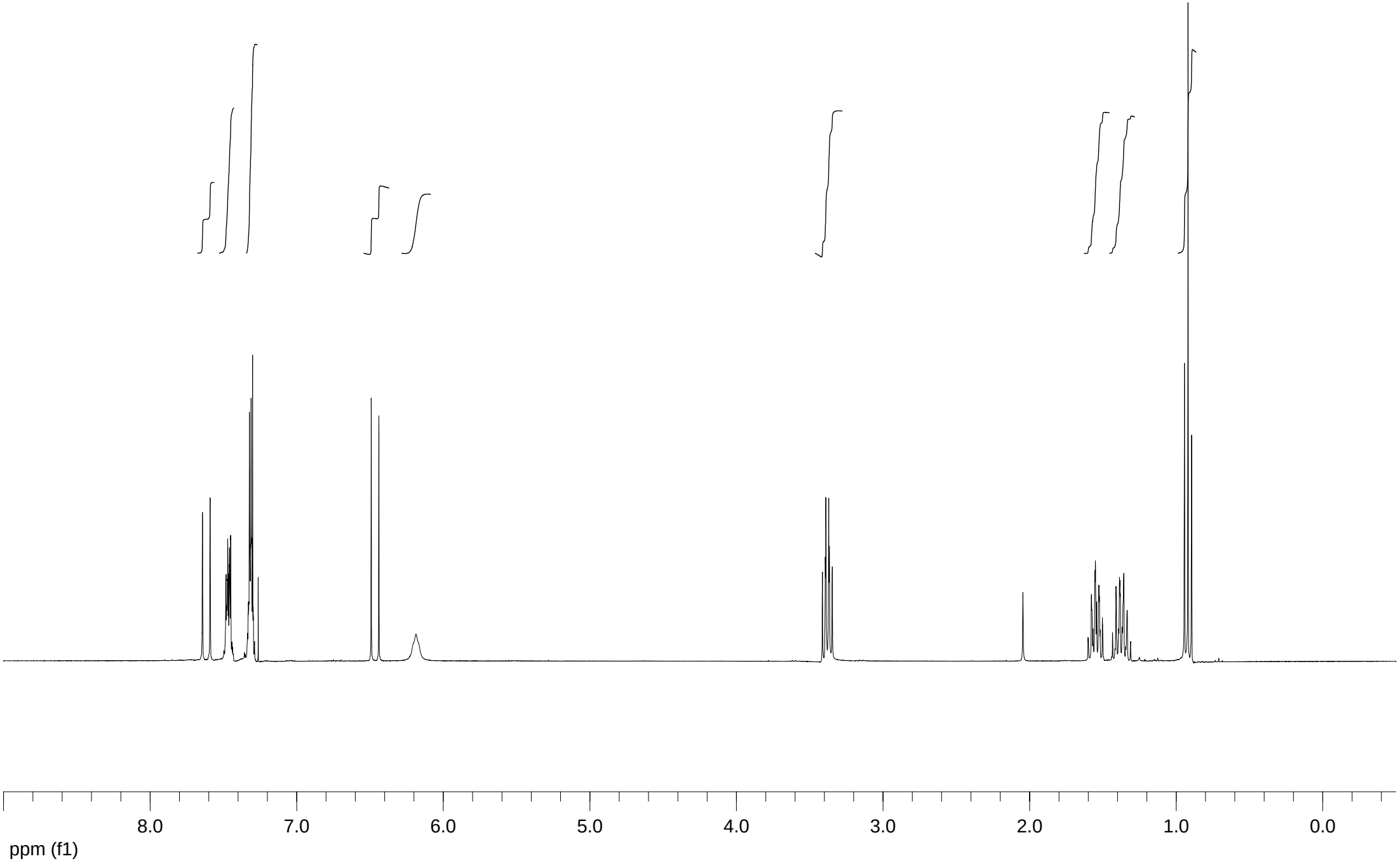

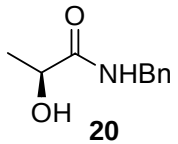

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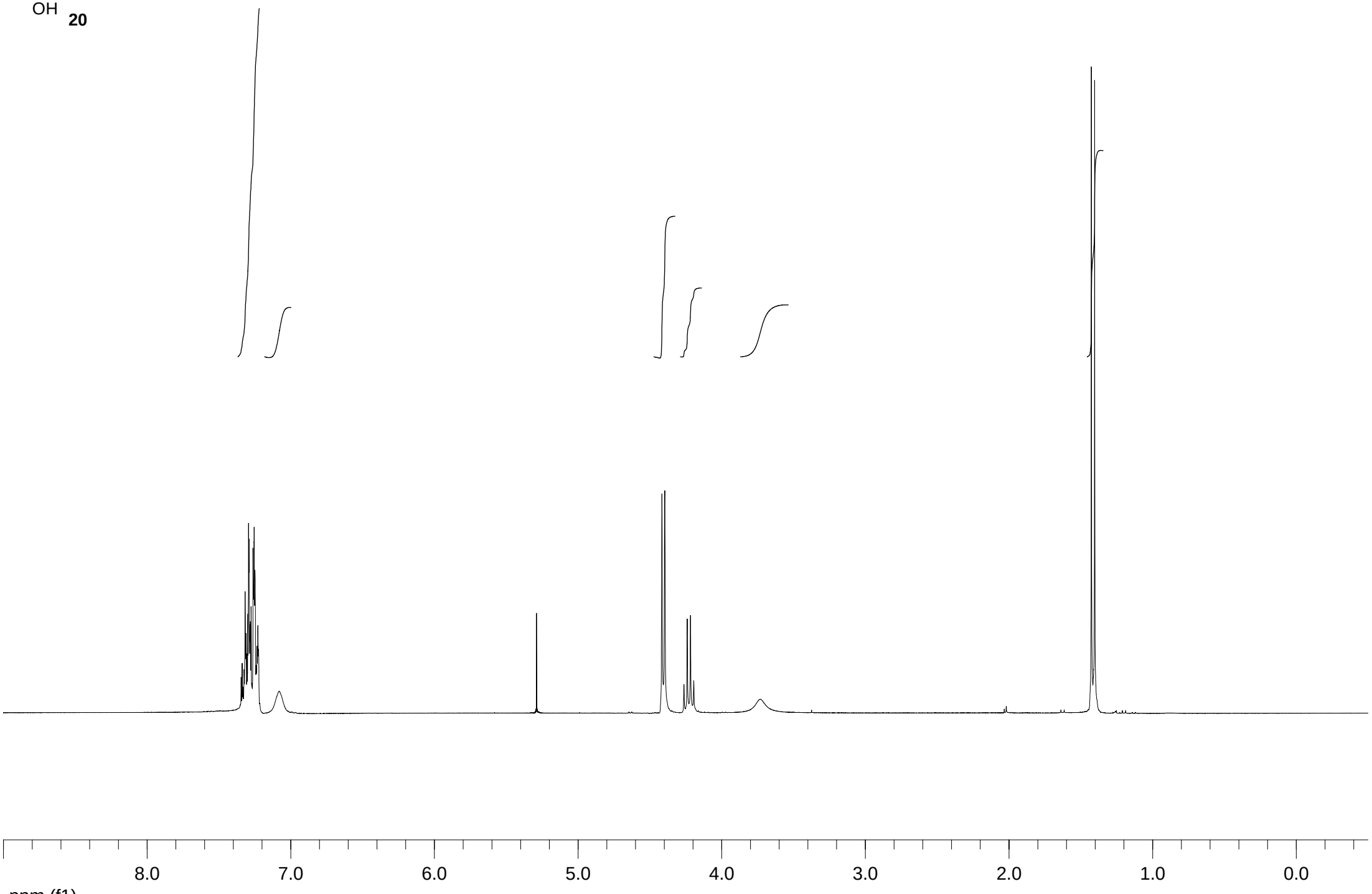

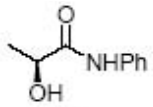
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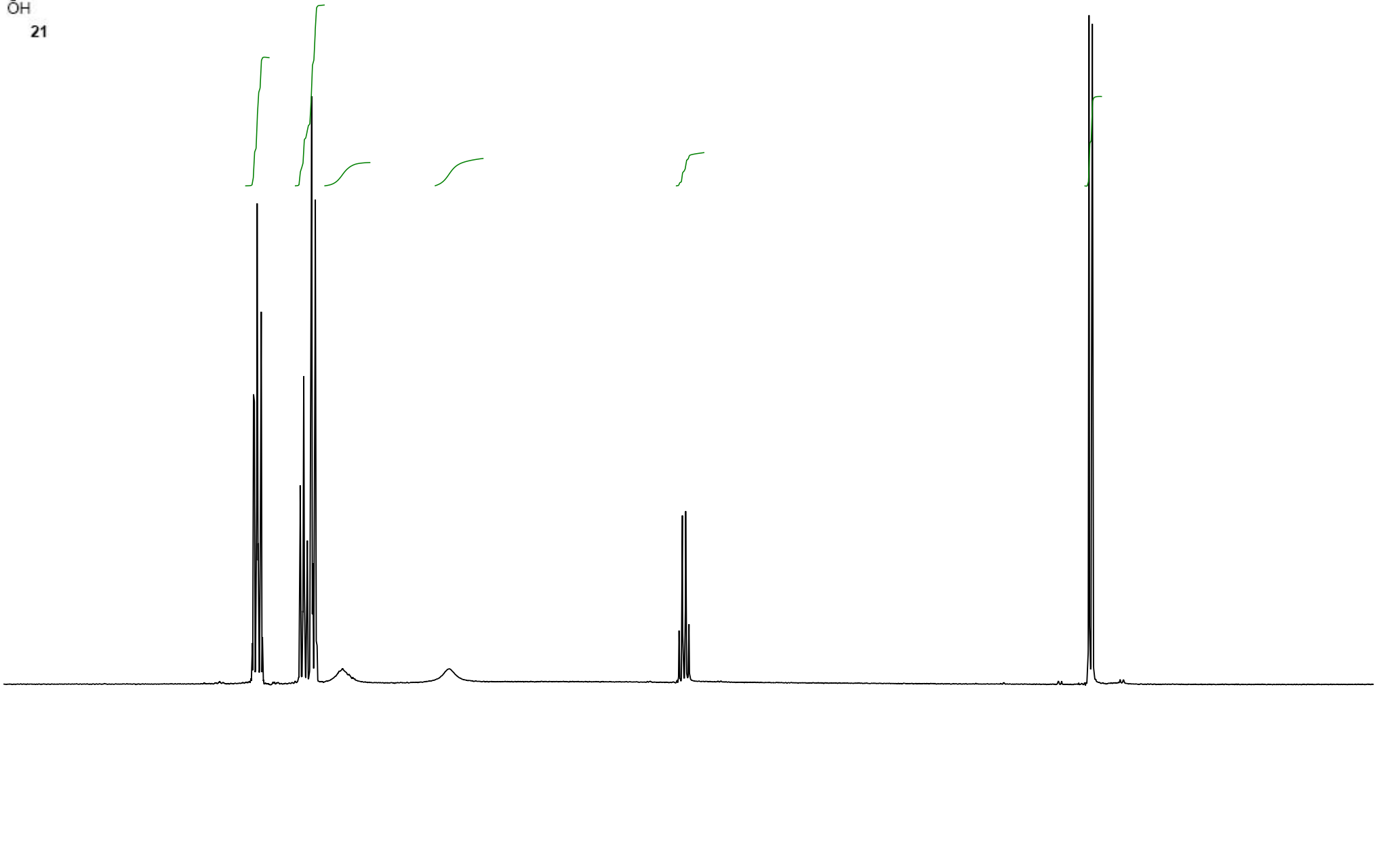
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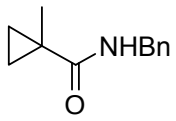
f1 (ppm)



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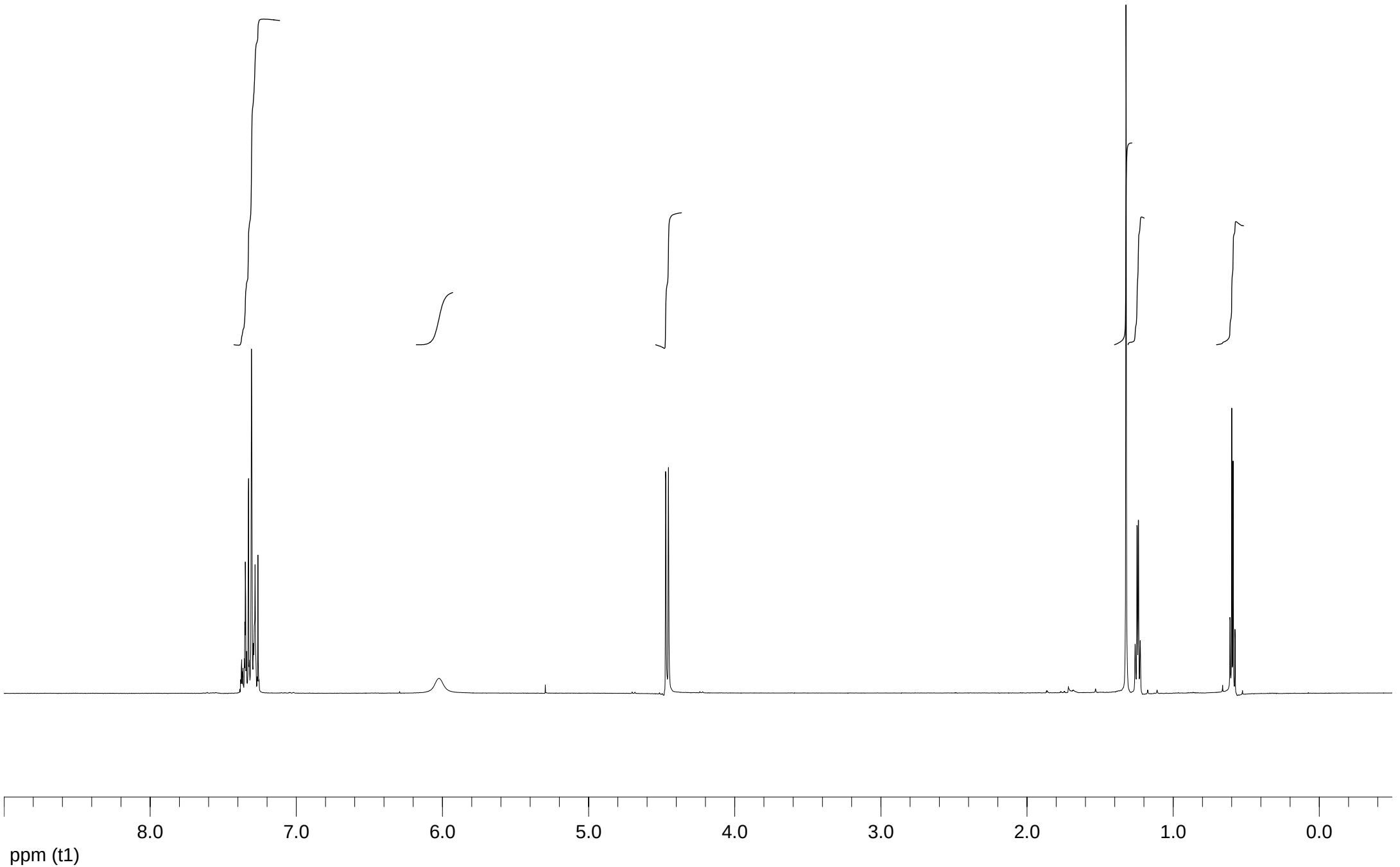

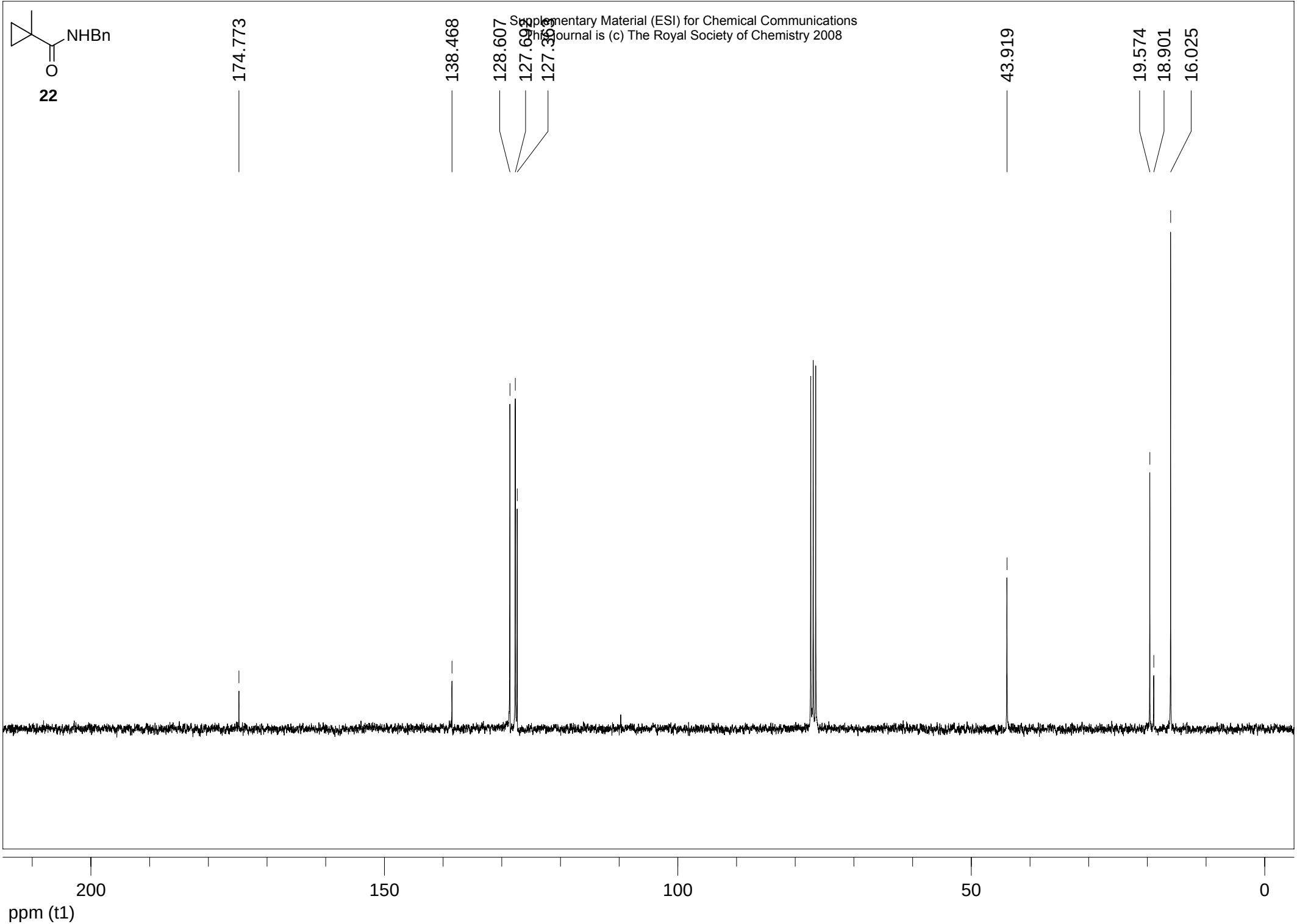

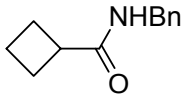

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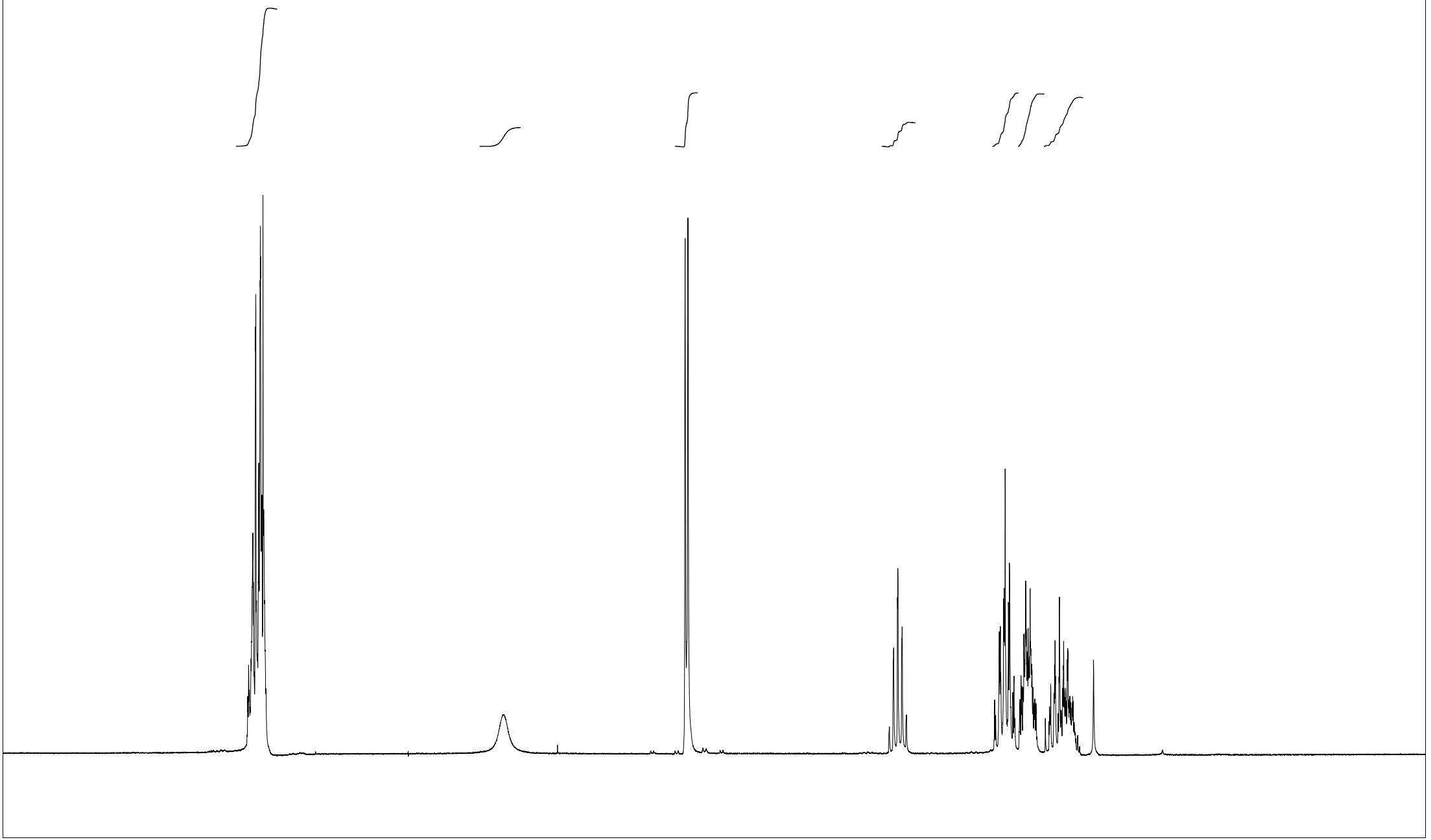

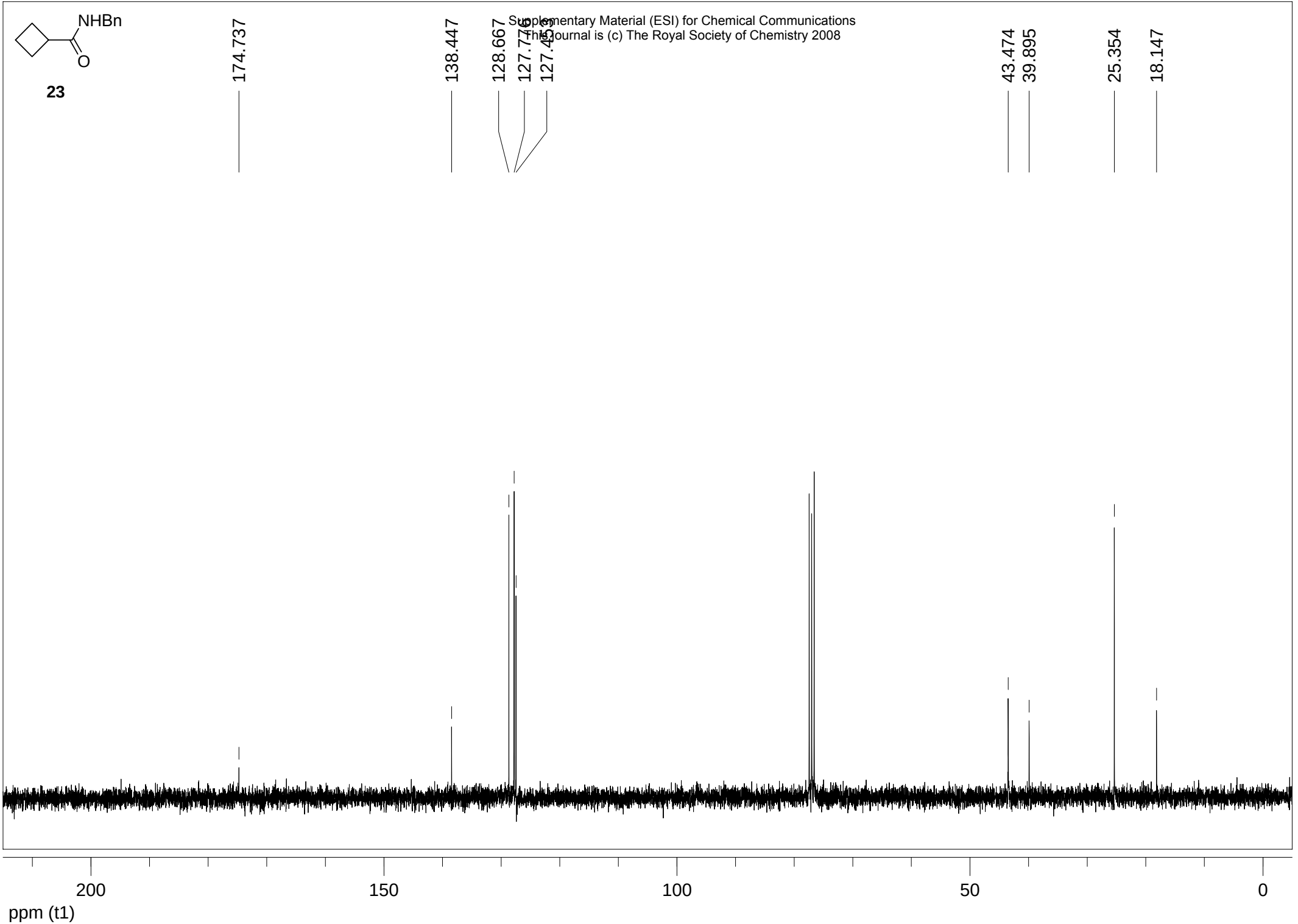

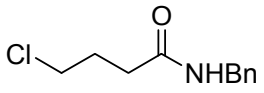

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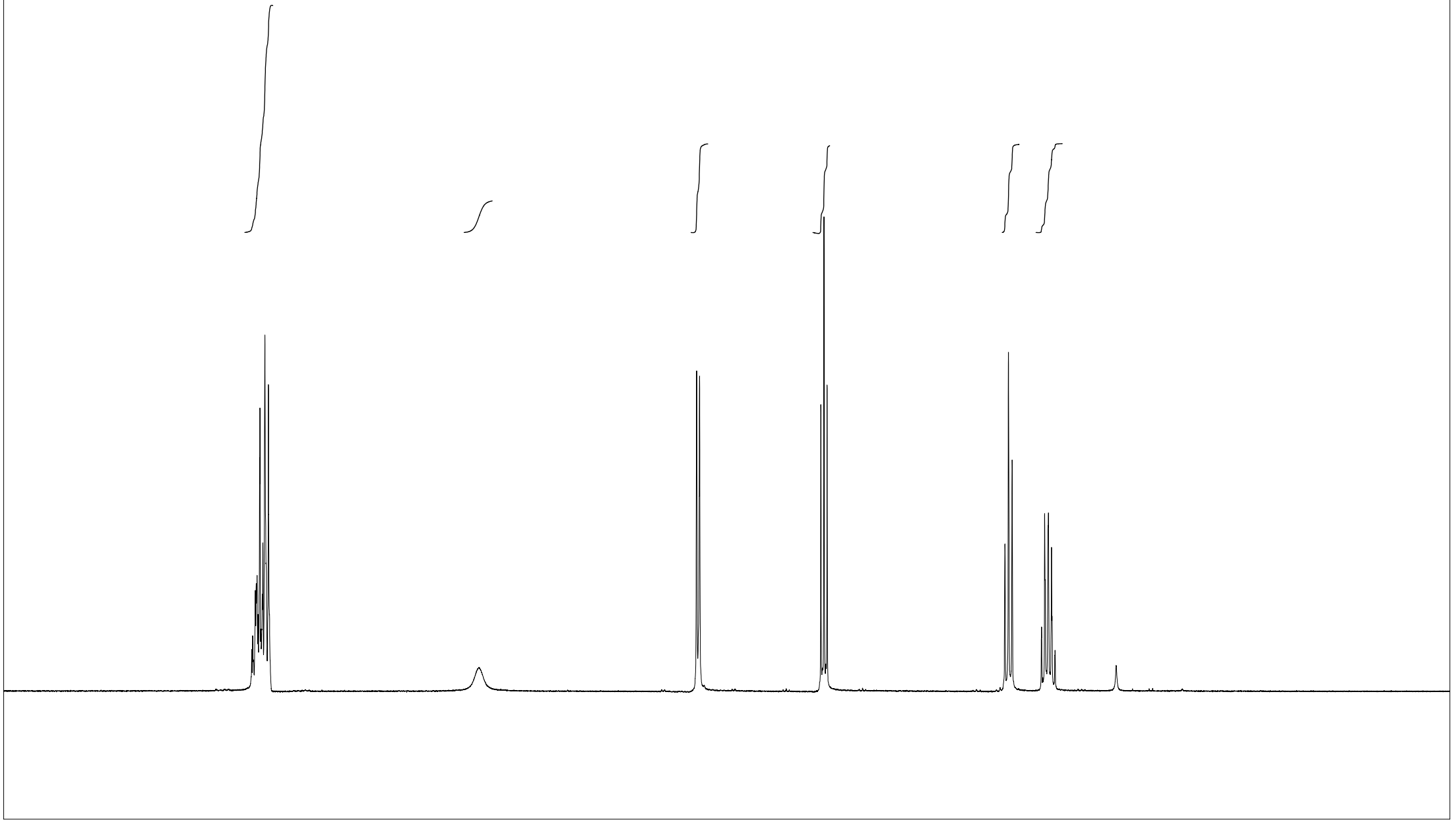

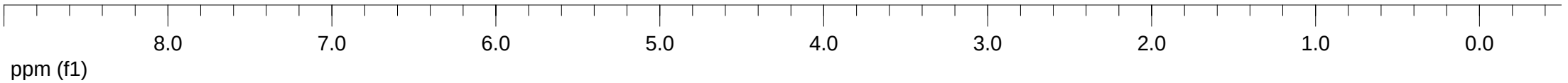

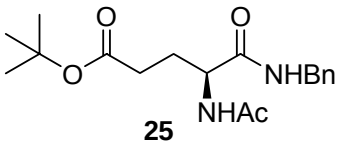

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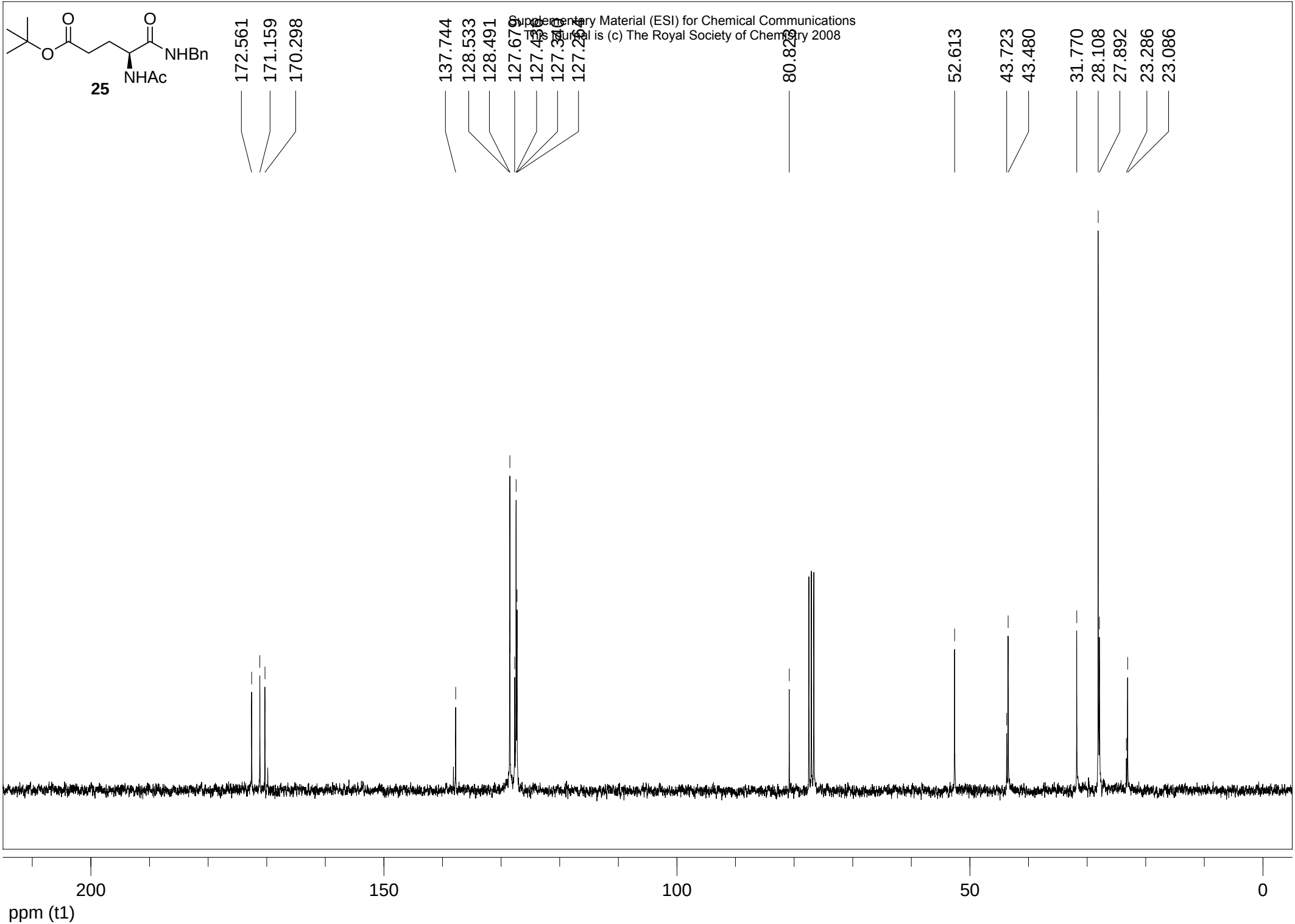

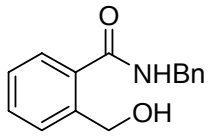

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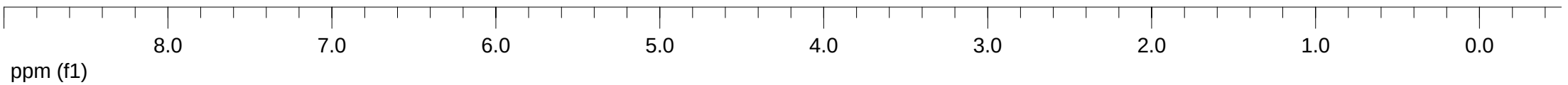

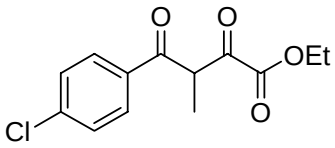

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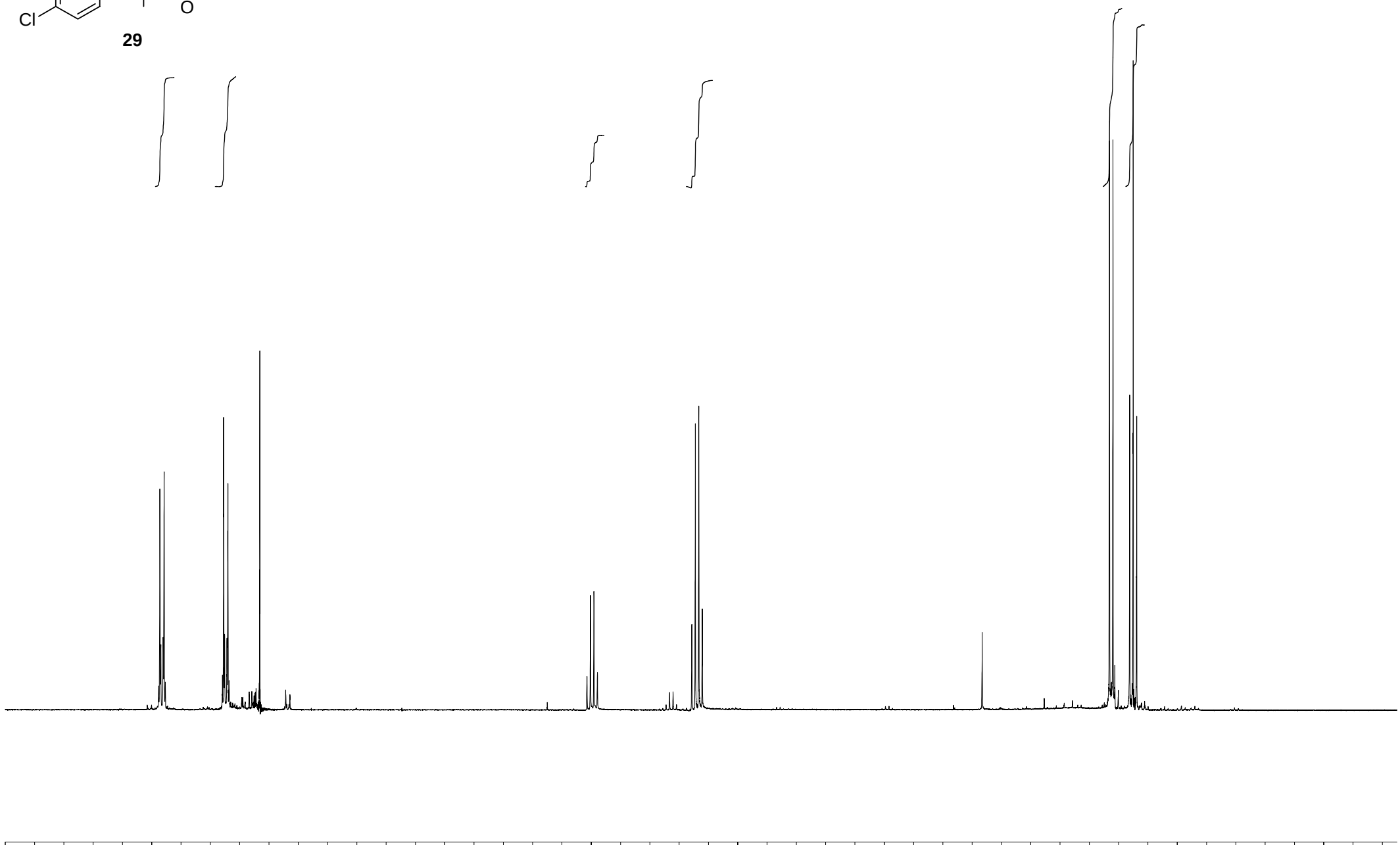

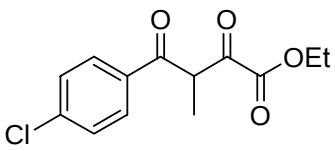

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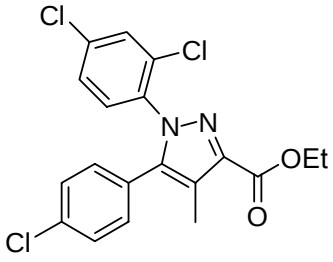

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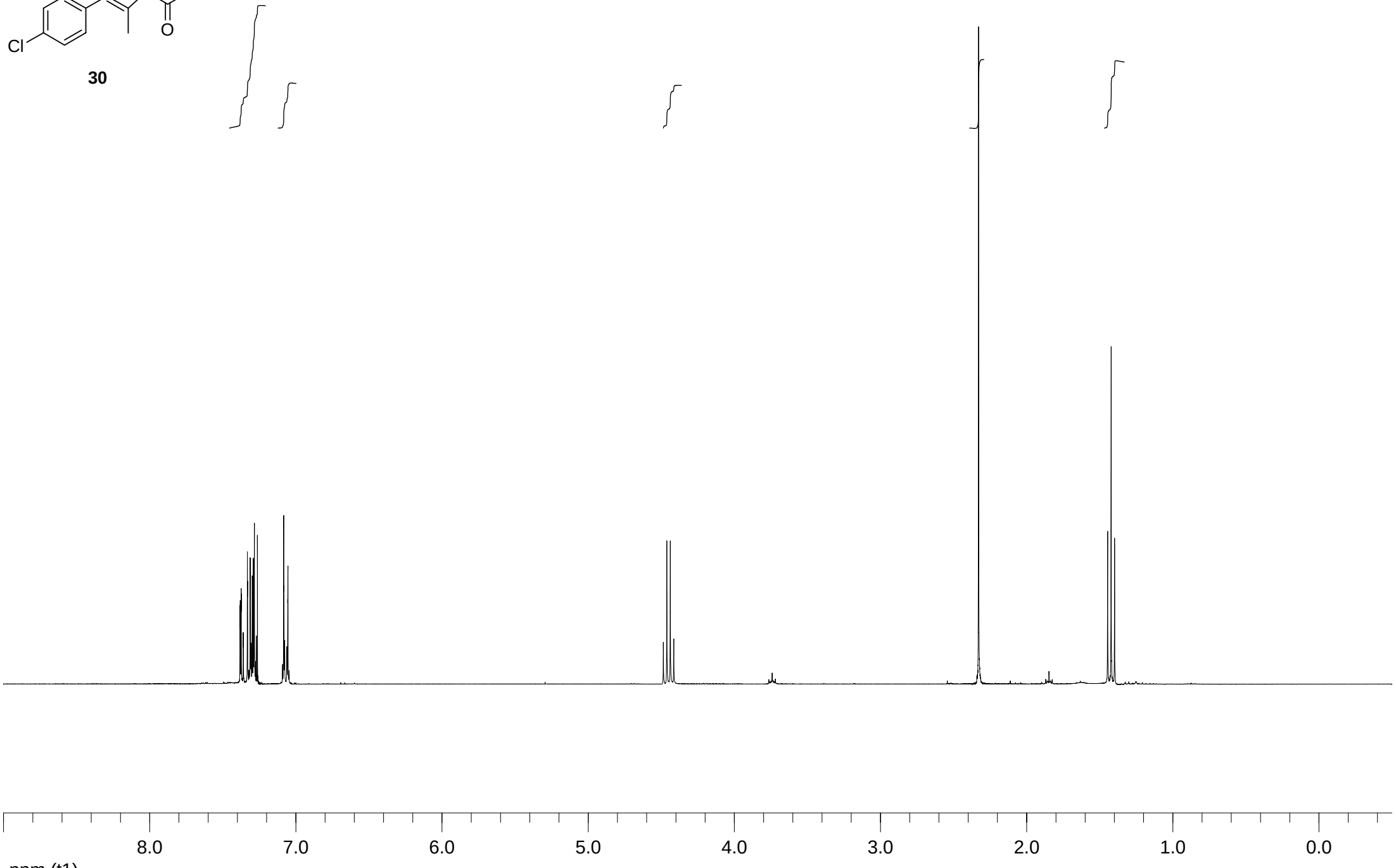

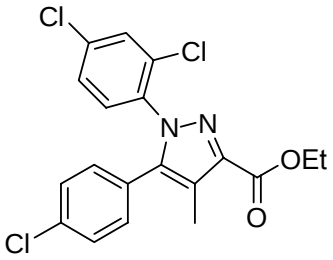

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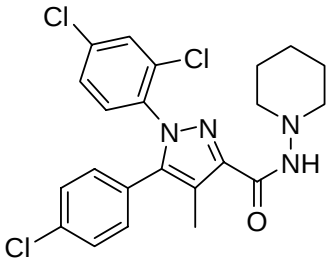

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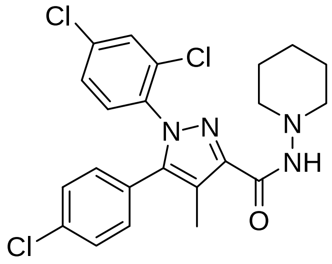

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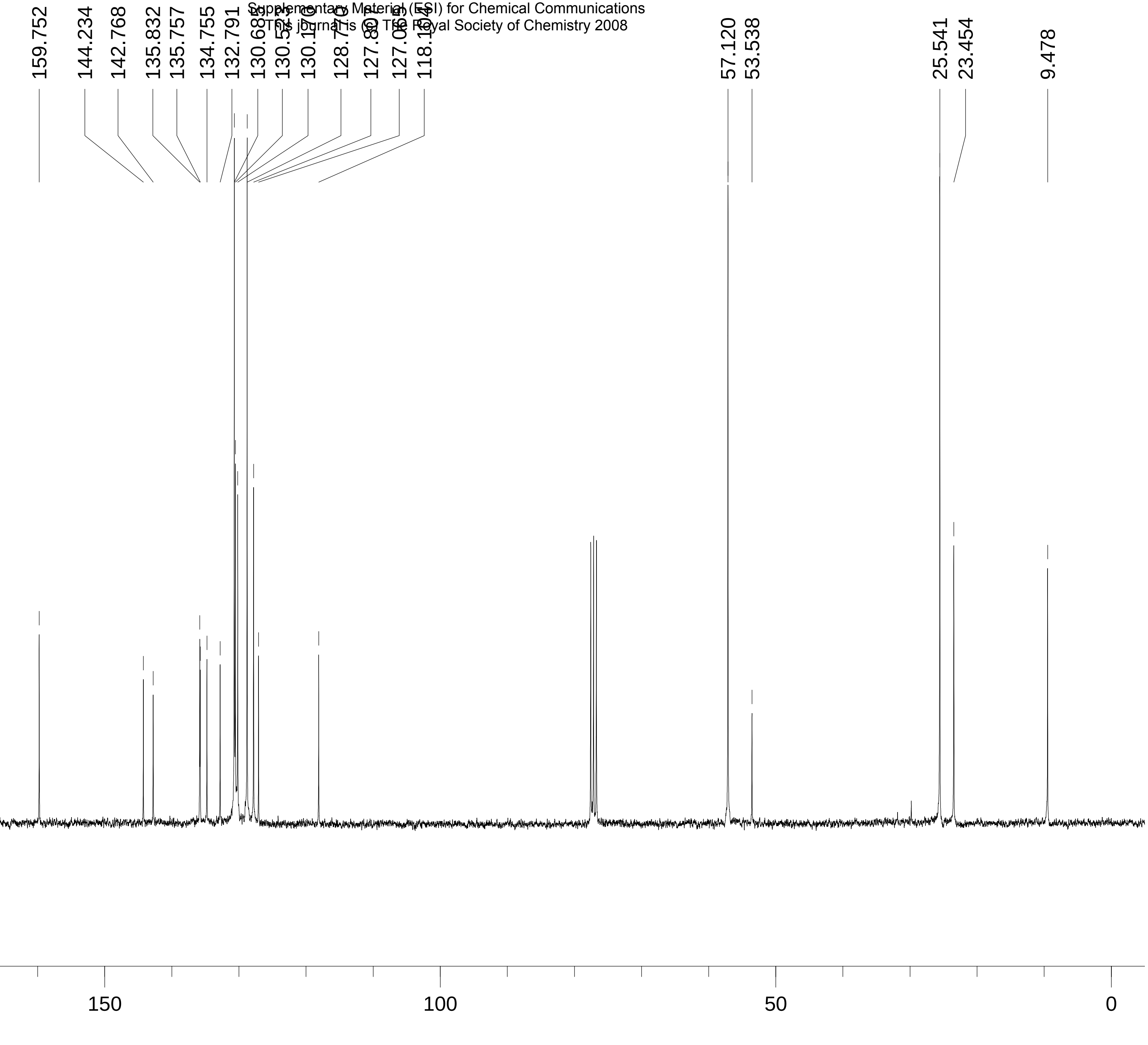

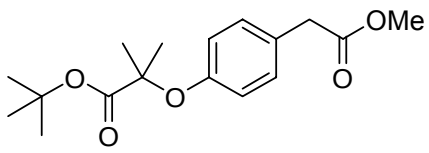

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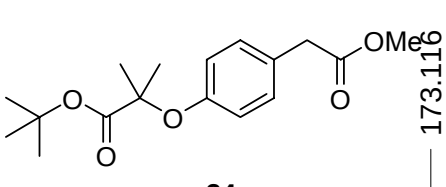
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34

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27.901
25.517
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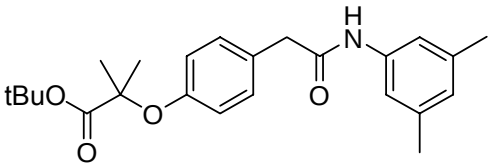
ppm (t1)



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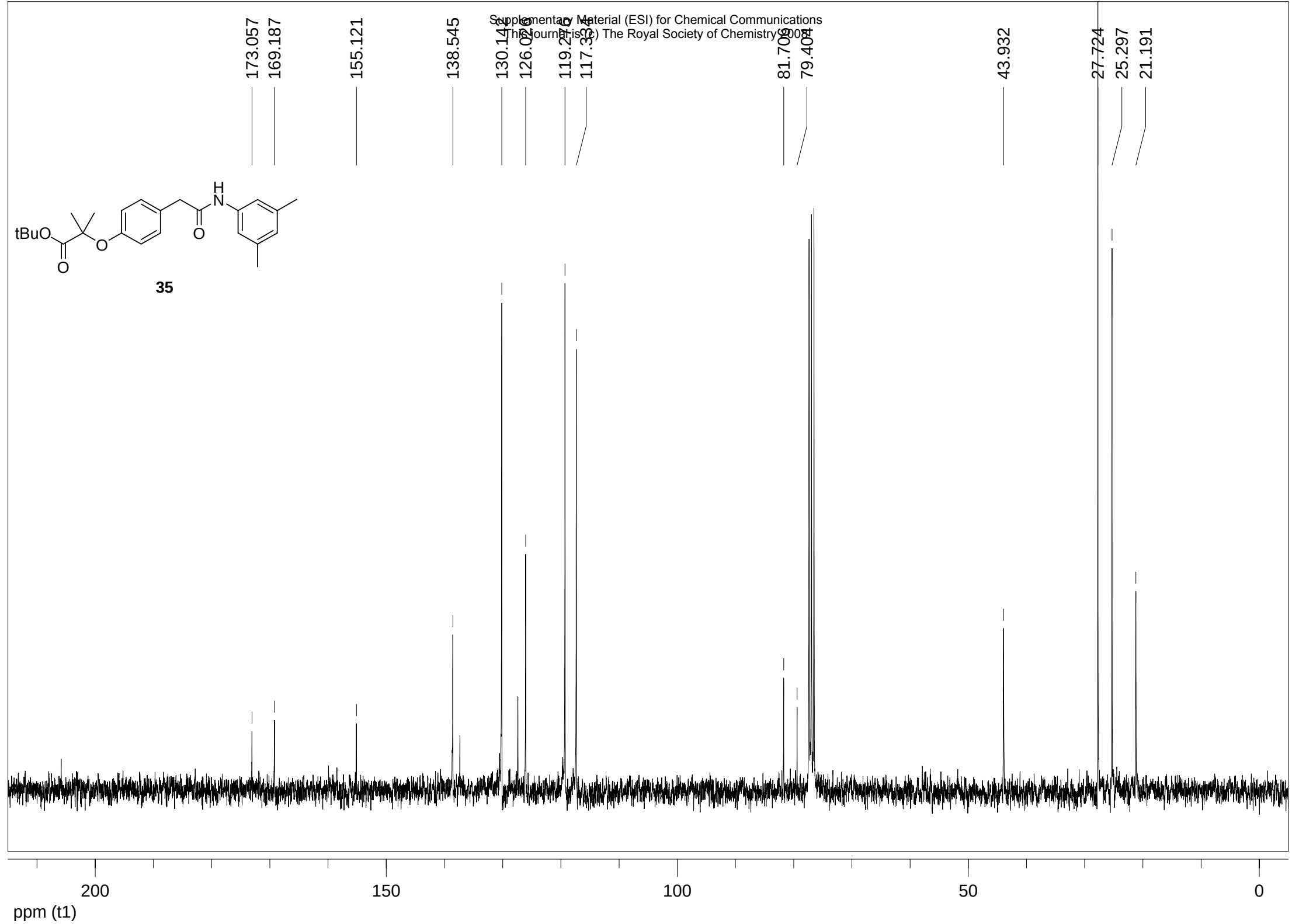

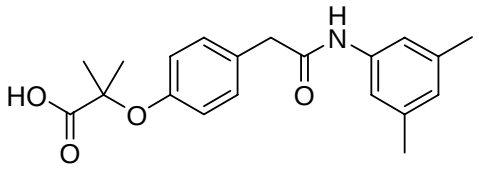

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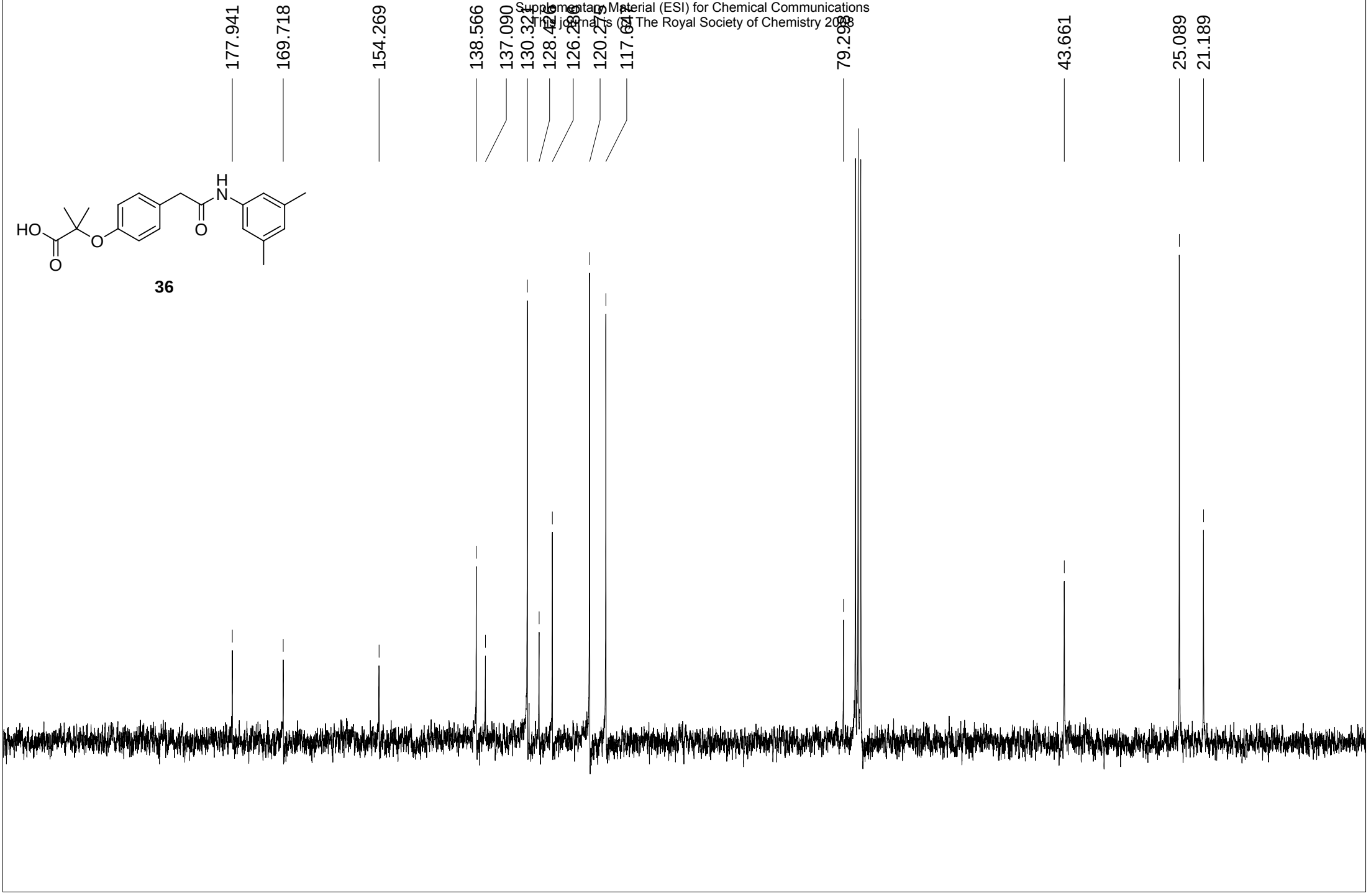

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