Strategic Approach to 8-Azacoumarins

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Supporting Information

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1.General Experimental

The preparation experiments were performed under air or an argon atmosphere in oven dried glassware. Solvents used as reaction media were distilled immediately before use: acetonitrile, THF and ether were distilled from Na/benzophenone ketyl, DCM was distilled from calcium hydride. All reagents were purchased at the highest commercial quality and used without further purification. Reactions were monitored by thin layer chromatography (TLC) using ultra violet light (UV) as the visualizing agent. Nuclear magnetic resonance spectra (NMR) were recorded on Bruker AV-400 instruments and were calibrated using residual undeuterated solvent as an internal reference (^{1}H NMR: $CHC1_3$ 7.26 ppm,^{13}C NMR: $CHC1_3$ 77.16 ppm). High resolution mass spectra (HRMS) were recorded on an Agilient LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. The following abbreviations were used to indicate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet).

The fluorescent properties were measured by HITACHI F-7000 fluorescence spectrophotometer. Absorbance was measured by a UV Spectrophotometer (SHIMADZU UV-1800). For analytical HPLC, using Agilent Technologies 1260 Infinity, a Venusil MP C18 (2) column (4.6 x 250 mm) was employed with a linear gradient of MeCN containing 0.1% (v/v) TFA at a flow rate of 1 ml/min, and eluting products were detected by UV at 340 nm.

2. General Procedure

Compounds **7** were prepared following a literature procedure (Heck reaction).[1]

General Procedure Ⅰ: Ester hydrolysis

To a solution of ester **7** in methanol (1.0 M) was added aqueous sodium hydroxide (3.0 M, 3.0 equiv). The resulting reaction mixture was refluxed and stirred for several hours until the reaction is complete as indicated by TLC. After cooled down to r.t., methanol was removed in vacuo. Water phase was acidified by 3.0 M HCl to pH 5~6,

and the resulting precipitate was filtered and washed with water and methanol. The title compound was obtained as a white solid after dried in a vacuum oven at 45 ℃. This was used directly in the next step without further purification.

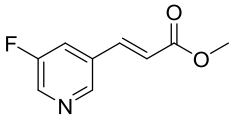
General Procedure Ⅱ: Oxidation of azines

To a 0 ℃ solution of azine in CH_2Cl_2 (0.5 M) was added *m*CPBA (1.2 equiv) and the reaction is allowed to stir at room temperature overnight. The resulting suspension was filtered and the filtrate cake was washed with ether for two to three times. Azine *N*-oxides (**3**) were obtained after dried in a vacuum oven at 45 ℃ and used without further purification.

General Procedure Ⅲ: Synthesis of 8-azacoumarin product

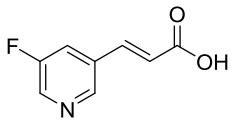
To a solution of azine *N*-oxides (**3**) in acetic anhydride (0.2 M) was added K_2CO_3 (3.0 equiv) and H_2O (7.0 equiv). The resulting mixture was heated to reflux and stirred overnight. After cooled down to r.t., acetic anhydride was removed in vacuo. Then the residue was diluted with water and DCM. After separation, the aqueous phase was extracted with DCM thoroughly. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography using DCM/MeOH (100:1~30:1) as eluent.

methyl (E)-3-(5-fluoropyridin-3-yl)acrylate (7b)



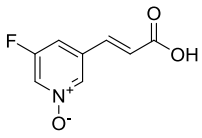
Compound **7b** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (1.2 g, 81% yield) as a white solid. The spectroscopic data are consistent with previously reported.[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.48 (d, *J* = 2.4 Hz, 1H), 7.67 (d, *J* = 16.0 Hz, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 159.6 (d, *J* = 257.5 Hz), 145.7 (d, *J* = 3.0 Hz), 139.8, 139.6 (d, *J* = 25.1 Hz), 131.8 (d, *J* = 4.0 Hz), 121.6, 120.5 (d, *J* = 18.1 Hz), 52.2.

(E)-3-(5-fluoropyridin-3-yl)acrylic acid (8b)



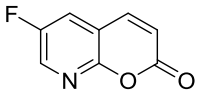
Using **7b** (1.5 g, 5.8 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (709 mg, 73% yield) as a white solid. The spectroscopic data are consistent with material from commercial sources. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.66 (s, 1H), 8.74 (s, 1H), 8.60 (d, *J* = 2.8 Hz, 1H), 8.20–8.17 (m, 1H), 7.65 (d, *J* = 16.0 Hz, 1H), 6.78 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.1, 159.3 (d, *J* = 254.5 Hz), 146.2 (d, *J* = 4.0 Hz), 139.2, 138.9 (d, *J* = 23.1 Hz), 132.1 (d, *J* = 4.0 Hz), 123.1, 121.0 (d, *J* = 19.1 Hz).

(E)-3-(2-carboxyvinyl)-5-fluoropyridine 1-oxide (3b)



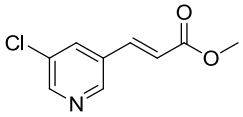
Using **8b** (700 mg, 4.2 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (587 mg, 76% yield) as a pale red solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.81 (s, 1H), 8.56 – 8.53 (m, 2H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 16.0 Hz, 1H), 6.81 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.9, 160.1 (d, *J* = 247.5 Hz), 137.3, 136.0 (d, *J* = 3.0 Hz), 134.2 (d, *J* = 10.1 Hz), 129.5 (d, *J* = 36.2 Hz), 125.3, 111.4 (d, *J* = 21.1 Hz). HRMS (ESI-TOF) calcd. for $C_8H_5NO_3F^-$ [$(M-H)^-$]: 182.0259, found 182.0264.

6-fluoro-2H-pyrano[2,3-b]pyridin-2-one (5b)



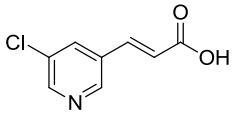
Using **3b** (150 mg, 0.8 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (88 mg, 65% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 3.2 Hz, 1H), 7.69 (d, *J* = 9.6 Hz, 1H), 7.62 (dd, *J* = 7.2, 3.2 Hz, 1H), 6.58 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.9, 155.0 (d, *J* = 61.4 Hz), 141.1, 138.6 (d, *J* = 27.2 Hz), 123.0 (d, *J* = 21.1 Hz), 119.6, 114.5. HRMS (ESI-TOF) calcd. for $C_8H_4NO_2FH^+$ [$(M+H)^+$]: 166.0299, found 166.0305.

(E)-methyl 3-(5-chloropyridin-3-yl)acrylate (7c)



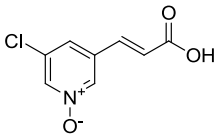
Compound **7c** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (2.71 g, 88% yield) as a white solid. The spectroscopic data are consistent with material from commercial sources. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.56 (d, *J* = 2.0 Hz, 1H), 7.81 (s, 1H), 7.63 (d, *J* = 16.4 Hz, 1H), 6.51 (d, *J* = 16 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 149.9, 147.4, 139.7, 133.8, 132.6, 131.5, 121.6, 52.2.

(E)-3-(5-chloropyridin-3-yl)acrylic acid (8c)



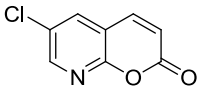
Using **7c** (2.06 g, 10.43 mmol), in accordance with General Procedure I, the title compound was obtained (1.80 g, 95% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.81 (s, 1H), 8.61 (d, *J* = 2.0 Hz, 1H), 8.34 (s, 1H), 7.58 (d, *J* = 16.4 Hz, 1H), 6.79 (d, *J* = 16 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.4, 149.0, 147.9, 138.6, 134.2, 132.0, 131.6, 123.9. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_5NO_2Cl^-$ [$(M-H)^-$]: 182.0014, found 182.0013.

(E)-3-(2-carboxyvinyl)-5-chloropyridine 1-oxide (3c)



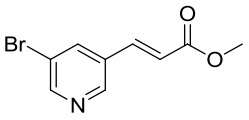
Using **8c** (1.80 g, 9.80 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (1.69 g, 78% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.63 (s, 1H), 8.50 (s, 1H), 7.94 (s, 1H), 7.47 (d, *J* = 16 Hz, 1H), 6.82 (d, *J* = 16 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.9, 138.2, 137.5, 137.1, 134.2, 132.4, 125.3, 123.9. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_4NO_3Cl$ H^+ [$(M+H)^+$]: 200.0109, found 200.0105.

6-chloro-2H-pyrano[2,3-b]pyridin-2-one (5c)



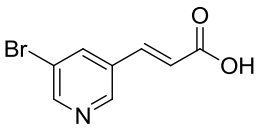
Using **3c** (200 mg, 1.0 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (145 mg, 80% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.4 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 9.6 Hz,

1H), 6.57 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 157.1, 149.2, 140.9, 136.1, 128.4, 119.6, 114.8. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_4NO_2ClH^+$ [$(M+H)^+$]: 182.0003, found 182.0009.



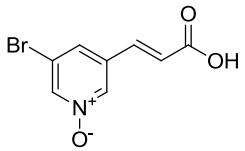
(E)-methyl 3-(5-bromopyridin-3-yl)acrylate (7d)

Compound **7d** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (780 mg, 38% yield) as a white solid. The spectroscopic data are consistent with material from commercial sources. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.6 Hz, 1H), 8.64 (s, 1H), 7.97 (s, 1H), 7.61 (d, *J* = 16.0 Hz, 1H), 6.51 (d, *J* = 16.4 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 152.0, 147.8, 139.6, 136.7, 131.9, 121.6, 121.3, 51.2.



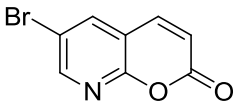
(E)-3-(5-bromopyridin-3-yl)acrylic acid (8d)

Using **7d** (690 mg, 2.85 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (565 mg, 87% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.85 (d, *J* = 1.6 Hz, 1H), 8.69 (d, *J* = 2.0 Hz, 1H), 8.47 (s, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 6.78 (d, *J* = 16.4 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.2, 151.2, 148.2, 139.1, 137.1, 132.3, 123.2, 120.8. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_5NO_2Br^-$ [$(M-H)^-$]: 225.9509, found 225.9498.

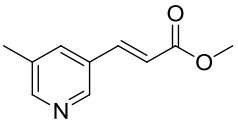


(E)-3-bromo-5-(2-carboxyvinyl)pyridine 1-oxide (3d)

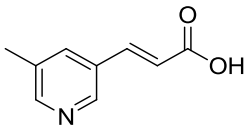
Using **8d** (539 mg, 2.36 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (562 mg, 97% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.65 (s, 1H), 8.56 (s, 1H), 8.04 (s, 1H), 7.46 (d, *J* = 16 Hz, 1H), 6.81 (d, *J* = 16 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.8, 140.1, 137.6, 137.3, 134.4, 126.6, 125.0, 120.2. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_6NO_3BrH^+$ [$(M+H)^+$]: 243.9604, found 243.9613.

6-bromo-2H-pyrano[2,3-b]pyridin-2-one (5d) 

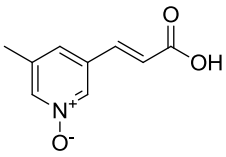
Using **3d** (200 mg, 0.82 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (140 mg, 76% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.4 Hz, 1H), 8.01 (d, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 9.6 Hz, 1H), 6.56 (d, *J* = 9.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 157.6, 151.4, 140.9, 139.0, 119.5, 116.1, 115.4. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_4NO_2BrH^+$ $[(M+H)^+]$: 225.9498, found 225.9495.

(E)-methyl 3-(5-methylpyridin-3-yl)acrylate (7e) 

Compound **7e** was prepared following a literature procedure (Heck reaction).[1] The literature procedure[1], the title compound was obtained (1.81 g, 88% yield) as a white solid. The spectroscopic data are consistent with material from commercial sources. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.35 (s, 1H), 7.55-7.60 (m, 2H), 6.42 (dd, J_1 = 3.2 Hz, J_2 = 16 Hz, 1H), 3.74 (d, *J* = 3.2 Hz, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 151.6, 147.0, 141.3, 134.5, 133.3, 129.6, 119.6, 51.8, 18.3.

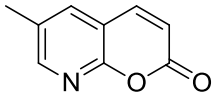
(E)-3-(5-methylpyridin-3-yl)acrylic acid (8e) 

Using **7e** (1.45 g, 8.18 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (697 mg, 52% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.63 (s, 1H), 8.43 (s, 1H), 7.98 (s, 1H), 7.59 (d, *J* = 16 Hz, 1H), 6.65 (d, *J* = 16 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.4, 151.4, 147.1, 140.8, 134.9, 133.4, 129.7, 121.2, 17.9. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_8NO_2^-$ $[(M-H)^-]$: 162.0561, found 162.0569.

(E)-3-(2-carboxyvinyl)-5-methylpyridine 1-oxide (3e) 

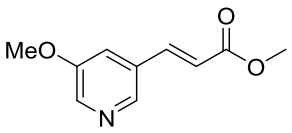
Using **8e** (680 mg, 3.84 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (637 mg, 85% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.46 (s, 1H), 8.14 (s, 1H), 7.59 (s, 1H), 7.47 (d, *J* = 16 Hz, 1H), 6.70 (d, *J* = 16 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.0, 139.2, 138.5, 136.8, 135.7, 133.1, 125.0, 123.5, 17.6. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_9NO_3H^+$ [$(M+H)^+$]: 180.0655, found 180.0656.

6-methyl-2H-pyrano[2,3-b]pyridin-2-one (5e)



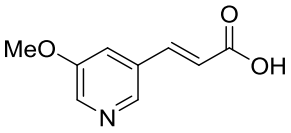
Using **3e** (300 mg, 1.12 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (205 mg, 76% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.66-7.69 (m, 2H), 6.50 (d, *J* = 9.6 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 157.2, 151.0, 142.0, 137.2, 130.9, 118.4, 113.6, 17.8. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_7NO_2H^+$ [$(M+H)^+$]: 162.0550, found 162.0552.

methyl (E)-3-(5-methoxypyridin-3-yl)acrylate (7f)

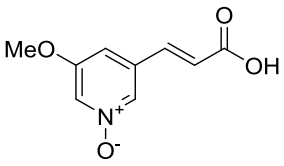


Compound **7f** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (1.85 g, 82% yield) as a yellow solid. The spectroscopic data are consistent with previously reported.[2]

(E)-3-(5-methoxypyridin-3-yl)acrylic acid (8f)

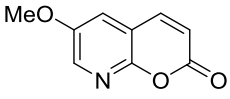


Using **7f** (1.4 g, 7.25 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (0.85 g, 66% yield) as a white solid. The spectroscopic data are consistent with previously reported.[3] ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.57 (s, 1H), 8.43 (s, 1H), 8.30 (d, *J* = 2.4 Hz, 1H), 7.77 (s, 1H), 7. 61 (d, *J* = 16.0 Hz, 1H), 6.75 (d, *J* = 16.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.3, 155.6, 142.2, 140.5, 139.5, 130.8, 121.8, 117.7, 55.7.



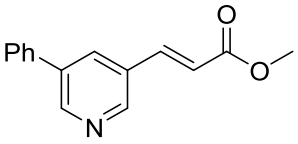
(E)-3-(2-carboxyvinyl)-5-methoxypyridine 1-oxide (3f)

Using **8f** (855 mg, 4.8 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (838 mg, 90% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.74 (s, 1H), 8.30 (s, 1H), 8.06 (s, 1H), 7.49 – 7.44 (m, 2H), 6.79 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.0, 157.7, 138.5, 133.4, 131.9, 127.9, 124.0, 110.4, 56.6. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_9NO_4$ [$(M+H)^+$]: 196.0604, found 196.0613.



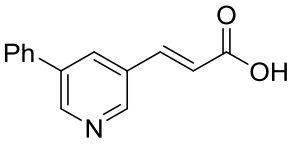
6-methoxy-2H-pyrano[2,3-b]pyridin-2-one (5f)

Using **3f** (150 mg, 0.77 mmol), in accordance with General Procedure Ⅲ, except for the reaction is stirred at 120℃ overnight. The title compound was obtained (81 mg, 59% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 2.4 Hz, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.34 (d, *J* = 2.8 Hz, 1H), 6.52 (d, *J* = 9.2 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 153.6, 153.1, 141.8, 138.6, 119.9, 118.9, 113.9, 56.5. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_7NO_3H^+$ [$(M+H)^+$]: 178.0499, found 178.0502.



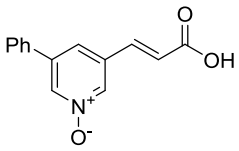
methyl (E)-3-(5-phenylpyridin-3-yl)acrylate (7g)

Compound **7g** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (3.2 g, 78% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.0 Hz, 1H), 8.72 (d, *J* = 2.0 Hz, 1H), 7.99 (s, 1H) , 7.76 (d, *J* = 16.0 Hz, 1H), 7.60 – 7.59 (m, 2H), 7.51 (t, *J* = 7.2 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 1H), 6.59 (d, *J* =16.0 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 149.8, 148.4, 141.3, 137.2, 137.0, 132.7, 130.2, 129.4, 128.7, 127.3, 120.4, 52.1. HRMS (ESI-TOF) *m/z* calcd. for $C_{15}H_{13}NO_2H^+$ [$(M+H)^+$]: 240.1019, found 240.1028.



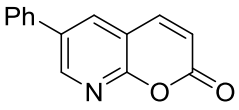
(E)-3-(5-phenylpyridin-3-yl)acrylic acid (8g)

Using **7g** (3.2 g, 13.4 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (3.01 g, 100% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.59 (s, 1H), 8.91 (s, 1H), 8.85 (s, 1H), 8.45 (s, 1H), 7. 82 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 16.4 Hz, 1H), 7.54 – 7.51 (m, 2H), 7.47 – 7.43 (m, 1H), 6.86 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.4, 148.8, 148.6, 140.5, 136.5, 135.6, 132.5, 130.2, 129.1, 128.4, 127.1, 121.9. HRMS (ESI-TOF) *m/z* calcd. for $C_{14}H_{10}NO_2^-$ [(M-H)$^-$]: 224.0717, found 224.0713.



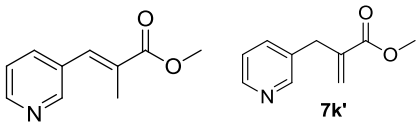
(E)-3-(2-carboxyvinyl)-5-phenylpyridine 1-oxide (3g)

Using **8g** (3.0 g, 13.3 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (2.5 g, 78% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.88 (s, 1H), 8.65 (s, 1H), 8.60 (s, 1H), 8.07 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 2H), 7.60 – 7.46 (m, 4H), 6.92 (d, *J* = 16.4 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.1, 138.9, 138.5, 136.9, 136.8, 134.4, 133.8, 129.3, 129.1, 127.2, 124.1, 122.2. HRMS (ESI-TOF) *m/z* calcd. for $C_{14}H_{10}NO_3^-$ [(M-H)$^-$] 240.0666, found 240.0672.

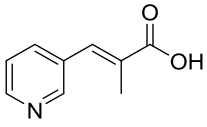


6-phenyl-2H-pyrano[2,3-b]pyridin-2-one (5g)

Using **3g** (150 mg, 0.62 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (122 mg, 88% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.05 (s, 1H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.60 – 7.58 (m, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 6.8 Hz, 1H), 6.56 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 158.2, 149.2, 142.1, 136.2, 135.2, 134.9, 129.5, 128.8, 127.3, 118.8, 113.9. HRMS (ESI-TOF) *m/z* calcd. for $C_{14}H_9NO_2H^+$ [(M+H)$^+$]: 224.0706, found 224.0709.

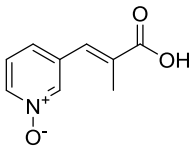
methyl (E)-2-methyl-3-(pyridin-3-yl)acrylate (7k) 

Compound **7k** was prepared following a literature procedure (Heck reaction).[1] The title compound, along with the isomeric product (**7k'**), were obtained as an inseparable mixture (ratio = 1:1, 4.0 g, total yield: 42%), yellow solid. The spectroscopic data are consistent with previously reported.[4]

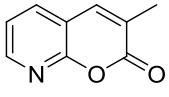
(E)-2-methyl-3-(pyridin-3-yl)acrylic acid (8k) 

Using the above mixture (4.0 g, 22.5 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (1.73 g, 47% yield) as a white solid. The spectroscopic data are consistent with previously reported.[5]

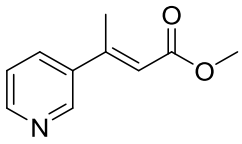
Note: It is found that most **7k'** was converted to the desired product in this reaction.

(E)-3-(2-carboxyprop-1-en-1-yl)pyridine 1-oxide (3k) 

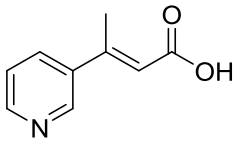
Using **8k** (1.8 g, 11.0 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (1.7 g, 85% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.35 (s, 1H), 8.19 (d, *J* = 5.6 Hz, 1H), 7.48 – 7.42 (m, 3H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.7, 138.8, 138.0, 134.9, 133.1, 131.9, 126.3, 125.9, 14.1. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_9NO_3H^+$ [$(M+H)^+$]: 180.0655, found 180.0651.

3-methyl-2H-pyrano[2,3-b]pyridin-2-one (5k) 

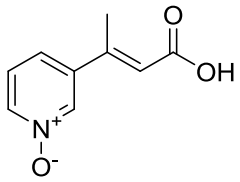
Using **3k** (120 mg, 0.67 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (57 mg, 53% yield) as a yellow solid. ^{1}H NMR (400 MHz, MeOD) δ 8.41 (d, *J* = 4.8 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.79 (s, 1H), 7.40 (dd, *J* = 7.6, 5.2 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, MeOD) δ 163.1, 159.4, 149.8, 139.5, 138.5, 128.7, 122.5, 116.7, 16.9. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_7NO_2$ H^+ [$(M+H)^+$]: 162.0550, found 162.0547.

methyl (E)-3-(pyridin-3-yl)but-2-enoate (7l) 

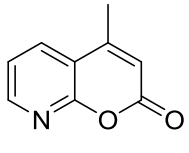
Compound **7l** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (5.0 g, 68% yield) as a yellow solid. The spectroscopic data are consistent with previously reported.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.51 (d, *J* = 4.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.08 (s, 1H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 152.1, 149.8, 147.2, 137.2, 133.3, 123.0, 117.8, 50.9, 17.4.

(E)-3-(pyridin-3-yl)but-2-enoic acid (8l) 

Using **7l** (2.67 g, 15.1 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (1.23 g, 50% yield) as a yellow solid. The spectroscopic data are consistent with previously reported.[7]

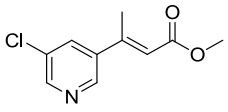
(E)-3-(1-carboxyprop-1-en-2-yl)pyridine 1-oxide (3l) 

Using **8l** (1.2 g, 7.3 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (0.98 g, 75% yield) as a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.56 (s, 1H), 8.41 (s, 1H), 8.22 (d, *J* =6.4 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.45–7.41 (m, 1H), 6.21 (s, 1H), 2.43 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.1, 148.0, 140.6, 138.5, 136.5, 126.3, 123.0, 120.5, 16.8. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_8NO_3^-$ [(M-H)$^-$]: 178.0510, found 178.0517.

(E)-3-(1-carboxyprop-1-en-2-yl)pyridine 1-oxide (5l) 

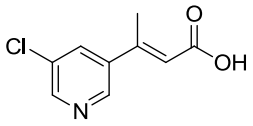
Using **3l** (150 mg, 0.84 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (114 mg, 85% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.8 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 7.6, 4.8 Hz,

1H), 6.34 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 158.5, 151.2, 150.8, 134.3, 121.0, 116.6, 115.5, 18.2. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_7NO_2H^+$ [$(M+H)^+$]: 162.0550, found 162.0558.



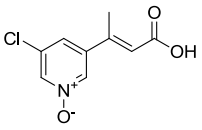
(E)-methyl 3-(5-chloropyridin-3-yl)but-2-enoate (7m)

Compound **7m** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (720 mg, 33% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 1.6 Hz, 1H), 8.55 (d, *J* = 2.0 Hz, 1H), 7.73 (s, 1H), 6.15 (s, 1H), 3.77 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 150.9, 148.9, 145.4, 138.9, 133.5, 132.2, 119.4, 51.6, 17.9. HRMS (ESI-TOF) *m/z* calcd. for $C_{10}H_{10}NO_2Cl$ H^+ [$(M+H)^+$]: 212.0473, found 212.0464.



(E)-3-(5-chloropyridin-3-yl)but-2-enoic acid (8m)

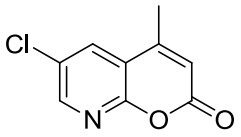
Using **7m** (600 mg, 2.84 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (550 mg, 98% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.51 (s, 1H), 8.73 (s, 1H), 8.65 (d, *J* = 1.6 Hz, 1H), 8.14 (s, 1H), 6.26 (s, 1H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.1, 148.9, 148.2, 145.6, 138.5, 133.6, 131.2, 120.3, 17.0. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_7NO_2Cl^-$ [$(M-H)^-$]: 196.0171, found 196.0172.



(E)-3-(1-carboxyprop-1-en-2-yl)-5-chloropyridine 1-oxide (3m)

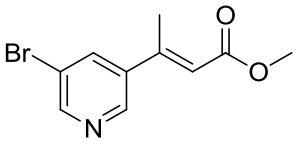
Using **8m** (500 mg, 2.53 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (300 mg, 57% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.52 (s, 1H), 8.40 (s, 1H), 7.71 (s, 1H), 6.25 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.0, 146.8, 140.8, 137.5, 135.8, 132.1, 123.4, 121.5, 16.8. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_7NO_3Cl^-$ [$(M-H)^-$]: 212.0120, found 212.0129.

6-chloro-4-methyl-2H-pyrano[2,3-b]pyridin-2-one (5m)



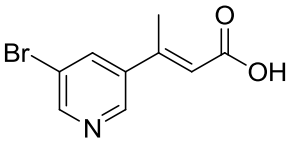
Using **3m** (200 mg, 0.94 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (166 mg, 91% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 1.6 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 6.42 (s, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 156.7, 150.2, 149.1, 133.5, 128.4, 117.5, 116.3, 18.2. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_6NO_2ClH^+$ [$(M+H)^+$]: 196.0160, found 196.0154.

(E)-methyl 3-(5-bromopyridin-3-yl)but-2-enoate (7n)



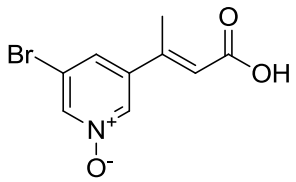
Compound **7n** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (1.01 mg, 31% yield) as a white solid. The spectroscopic data are consistent with material from commercial sources. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.62 (s, 1H), 7.88 (s, 1H), 6.14 (s, 1H), 3.77 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 151.1, 150.8, 145.7, 139.3, 136.4, 120.9, 119.4, 51.6, 17.9.

(E)-3-(5-bromopyridin-3-yl)but-2-enoic acid (8n)



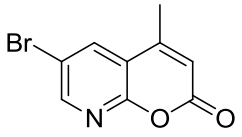
Using **7n** (950 mg, 3.71 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (860 mg, 96% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.49 (s, 1H), 8.74 (s, 1H), 8.70 (s, 1H), 8.23 (d, *J* = 1.6 Hz, 1H), 6.22 (s, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.2, 150.3, 149.0, 145.8, 138.9, 136.3, 120.4, 120.3, 17.0. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_7NO_2Br^-$ [$(M-H)^-$]: 239.9666, found 239.9648.

(E)-3-bromo-5-(1-carboxyprop-1-en-2-yl)pyridine 1-oxide (3n)



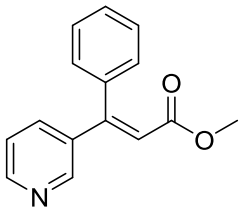
Using **8n** (770 mg, 3.18 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (486 mg, 59% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.60 (s, 1H), 8.58 (s, 1H), 8.42 (s, 1H), 7.80 (s, 1H), 6.24 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.0, 146.9, 141.0, 139.4, 136.0, 126.0, 121.5, 119.9, 16.8. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_7NO_3Br^-$ [$(M-H)^-$]: 255.9615, found 255.9616.

6-bromo-4-methyl-2H-pyrano[2,3-b]pyridin-2-one (5n)

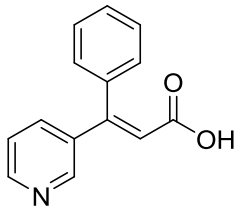


Using **3n** (200 mg, 0.74 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (145 mg, 82% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 2.4 Hz, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 6.40 (s, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 157.1, 151.3, 150.2, 136.3, 117.4, 116.9, 116.0, 18.2. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_6NO_2BrH^+$ [$(M+H)^+$]: 239.9655, found 239.9659.

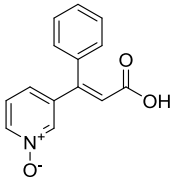
methyl (E)-3-phenyl-3-(pyridin-3-yl)acrylate (7o)



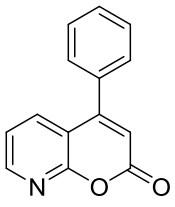
Compound **7o** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (2.4 g, 49% yield) as a yellow solid. The spectroscopic data are consistent with material from commercial sources. ^{1}H NMR (400 MHz, MeOD) δ 8.54 – 8.53 (m, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.45 –7.41 (m, 4H), 7.21–7.18 (m, 2H), 6.49 (s, 1H), 3.60 (s , 3H); ^{13}C NMR (100 MHz, MeOD) δ 167.6, 154.2, 150.6, 149.4, 139.2, 138.6, 137.6, 130.2, 129.8, 129.3, 125.1, 120.0, 51.9.

(E)-3-phenyl-3-(pyridin-3-yl)acrylic acid (8o) 

Using **7o** (1.0 g, 4.4 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (812 mg, 83% yield) as a yellow solid. The spectroscopic data are consistent with material from commercial sources. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.50 (s, 1H), 8.56 (d, *J* = 4.0 Hz, 1H), 8.46 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.38 (m, 4H), 7.18 – 7.17 (m, 2H), 6.48 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.6, 149.8, 149.8, 148.4, 138.1, 136.4, 135.3, 129.0, 128.1, 128.1, 123.5, 120.9.

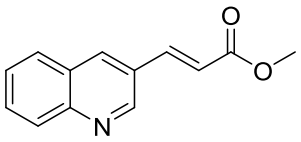
(E)-3-(2-carboxy-1-phenylvinyl)pyridine 1-oxide (3o) 

Using **8o** (1.0 g, 4.4 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (812 mg, 76% yield) as a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.50 (s, 1H), 8.21 (d, *J* = 6.0 Hz, 1H), 8.00 (s, 1H), 7.42 – 7.38 (m, 4H), 7.22 – 7.18 (m, 3H), 6.55 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.4, 147.3, 139.7, 138.7, 137.5, 137.1, 128.9, 128.5, 128.2, 126.2, 124.4, 122.3. HRMS (ESI-TOF) *m/z* calcd. for $C_{14}H_{11}NO_3H^+$ [$(M+H)^+$]: 242.0812, found 242.0804.

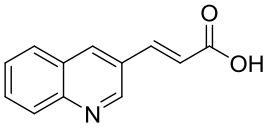
4-phenyl-2H-pyrano[2,3-b]pyridin-2-one (5o) 

Using **3o** (150 mg, 0.62 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (122 mg, 87% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 4.4, 1.2 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.56 – 7.55 (m, 3H), 7.45 – 7.43 (m, 2H), 7.28 (d, *J* = 4.8, 1H), 6.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.1, 154.5, 150.9, 136.6, 134.2, 130.3, 129.3, 128.5, 121.0, 116.5,

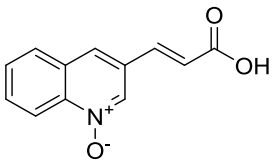
114.6. HRMS (ESI-TOF) *m/z* calcd. for $C_{14}H_9NO_2H^+$ [$(M+H)^+$]: 224.0706, found 224.0709.

methyl (E)-3-(quinolin-3-yl)acrylate (7r) 

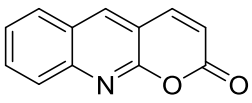
Compound **7r** (2.3 g, 11.05 mmol) was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (1.7 g, 73% yield) as a yellow solid. The spectroscopic data are consistent with previously reported.[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, *J* = 2.4 Hz, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.86 – 7.82 (m, 2H), 7.77 – 7.73 (m, 1H) , 7.60 – 7.56 (m, 1H), 6.66 (d, *J* = 16 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 149.4, 148.8, 141.6, 135.6, 130.8, 129.6, 128.5, 127.8, 127.6, 127.5, 119.9, 52.1.

(E)-3-(quinolin-3-yl)acrylic acid (8r) 

Using **7r** (2.35 g, 11.05 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (1.77 g, 80% yield) as a white solid. The spectroscopic data are consistent with previously reported.[9]

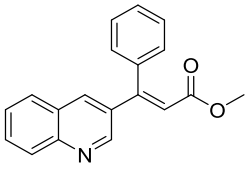
(E)-3-(2-carboxyvinyl)quinoline 1-oxide (3r) 

Using **8r** (2.12 g, 10.6 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (2.11 g, 92% yield) as a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.04 (s, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 8.28 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 16 Hz, 1H), 6.82 (d, *J* =16 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.2, 140.8, 139.0, 133.9, 131.2, 129.7, 129.5, 129.3, 129.1, 125.1, 123.0, 119.0. HRMS (ESI-TOF) *m/z* calcd. for $C_{12}H_8NO_3^-$ [$(M-H)^-$]: 214.0510, found 214.0514.

2H-pyrano[2,3-b]quinolin-2-one (5r) 

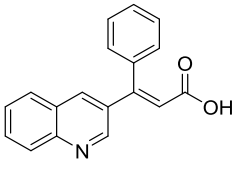
Using **3r** (150 mg, 0.69 mmol), in accordance with General Procedure Ⅲ, except for the reaction is stirred at 120℃ overnight. The title compound was obtained (124 mg, 90% yield) as a yellow solid. The spectroscopic data are consistent with previously reported.[10] ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.84 (s, 1H), 8.22 (d, *J* = 9.6 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.91 – 7.87 (m, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 160.2, 156.1, 146.2, 143.2, 139.1, 132.2, 128.8, 127.7, 126.4, 126.1, 117.7, 114.4.

methyl (E)-3-phenyl-3-(quinolin-3-yl)acrylate (7s)

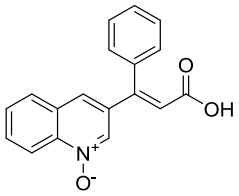


Compound **7s** was prepared following a literature procedure (Heck reaction).[1] The title compound was obtained (5 g, 60% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 2.0 Hz, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.76 – 7.72 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.45 – 7.44 (m, 3H), 7.27 (dd, *J* = 6.0, 2.0 Hz, 2H), 6.55 (s, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 153.9, 149.4, 148.2, 137.8, 136.0, 133.6, 130.5, 129.3, 129.2, 128.8, 128.7, 128.5, 128.3, 127.3, 118.3, 51.5. HRMS (ESI-TOF) *m/z* calcd. for $C_{19}H_{15}NO_2H^+$ $[(M+H)^+]$: 290.1176, found 290.1174.

(E)-3-phenyl-3-(quinolin-3-yl)acrylic acid (8s)

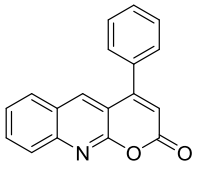


Using **7s** (550 mg, 1.9 mmol), in accordance with General Procedure, the title compound was obtained (391 mg, 75% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.37 (s, 1H), 8.86 (d, *J* = 1.6 Hz, 1H), 8.13 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.79 (t, *J* = 7.2 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.44 – 7.42 (m, 3H), 7.26 – 7.25 (m, 2H), 6.64 (s, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.6, 150.4, 149.4, 147.4, 138.1, 135.2, 135.6, 130.4, 129.1, 128.7, 128.6, 128.3, 128.2, 127.3, 126.9, 120.8. HRMS (ESI-TOF) *m/z* calcd. for $C_{18}H_{13}NO_2H^+$ $[(M+H)^+]$: 276.1019, found 276.1013.



(E)-3-(2-carboxy-1-phenylvinyl)quinoline 1-oxide (3s)

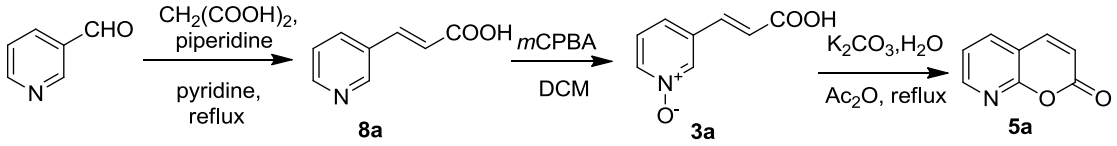
Using **8s** (391 mg, 1.42 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (220 mg, 73% yield) as a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.49 (s, 1H), 8.50 – 8.47 (m, 2H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.76 – 7.73 (m, 2H), 7.44 – 7.43 (m, 3H), 7.29 – 7.27 (m, 2H), 6.66 (s, 1H); ^{13}C NMR (100MHz, d_6-DMSO) δ 166.6, 148.2, 140.3, 137.3, 134.8, 134.1, 131.1, 129.4, 129.2, 128.8, 128.5, 128.3, 128.1, 124.5, 122.0, 118.8. HRMS (ESI-TOF) *m/z* calcd. for $C_{18}H_{13}NO_3H^+$ $[(M+H)^+]$: 292.0968, found 292.0962.

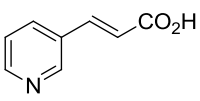


4-phenyl-2H-pyrano[2,3-b]quinolin-2-one (5s)

Using **3s** (150 mg, 0.5 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (85 mg, 61% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.84 – 7.81 (m, 2H), 7.62 – 7.51 (m, 6H), 6.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 156.2, 154.2, 147.1, 137.9, 134.3, 132.5, 130.3, 129.3, 128.5, 128.5, 128.3, 126.6, 126.1, 116.4, 114.5. HRMS (ESI-TOF) *m/z* calcd. for $C_{18}H_{11}NO_2H^+$ $[(M+H)^+]$: 274.0863, found 274.0863.

3. Synthetic Procedures for 5a, 5h-5j, 5p and 5q

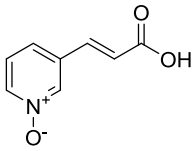




(E)-3-(pyridin-3-yl)acrylic acid (8a)

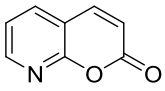
A mixture of nicotinaldehyde (2.85 g, 36.6 mmol), malonic acid (2.75 g, 36.6 mmol) in 2.1 ml of pyridine and 0.25 ml of piperidine was refluxed in an oil bath and stirred for 1 h. After cooling to room temperature, 5.0 ml of cold ethanol was added to the

mixture. The precipitate was collected by filtration, washed with H_2O and dried. The title compound was obtained (3.56 g, 89% yield) as a white solid. The spectroscopic data are consistent with previously reported.[11] ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.44 (s, 1H), 8.84 (d, *J* = 2.0 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.2 Hz, 1H) , 8.16 – 8.13 (m, 1H), 7.62 (d, *J* = 16.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.68 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.3, 150.8, 149.8, 140.6, 134.6, 130.1, 123.9, 121.4.



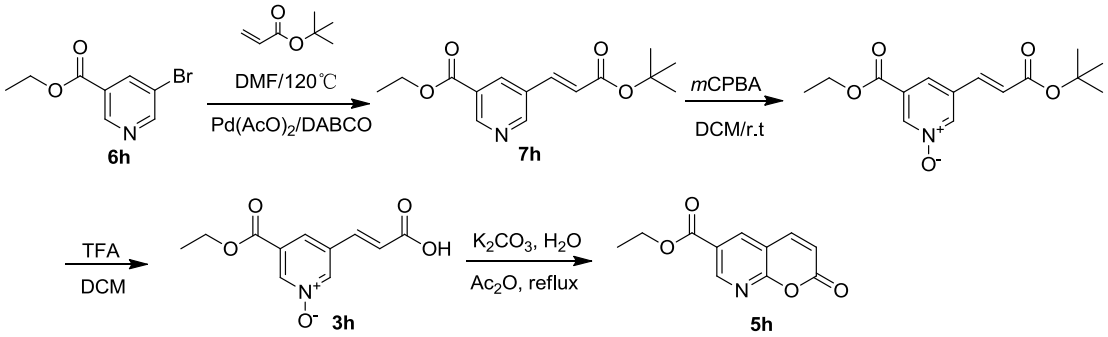
(E)-3-(2-carboxyvinyl)pyridine 1-oxide (3a)

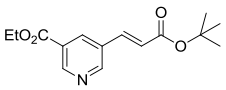
Using **8a** (1.0 g, 6.7 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (0.8 g, 73% yield) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.69 (s, 1H), 8.62 (s, 1H), 8.21 (d, *J* = 6.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.42 (m, 2H), 6.73 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.3, 139.3, 138,2, 137.8, 134.2, 126.7, 124.7, 124.2. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_7NO_3H^+$ [$(M+H)^+$]: 166.0499, found 166.0506.



2H-pyrano[2,3-b]pyridin-2-one (5a)

Using **3a** (130 mg, 0.787 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (89 mg, 70% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.8 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.72 (d, *J* = 9.6 Hz, 1H), 7.31 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.51 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 159.0, 150.8, 142.1, 137.3, 121.2, 118.5, 114.2. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_5NO_2H^+$ [$(M+H)^+$]: 148.0393, found 148.0398.

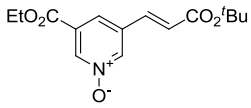




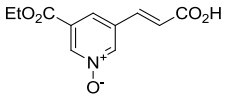
(E)-ethyl 5-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)nicotinate (7h)

Using ethyl 5-bromonicotinate (2.00 g, 8.69 mmol), following the literature procedure[1], the title compound was obtained (1.98 g, 82% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (d, *J* = 2.0 Hz, 1H), 8.86 (d, *J* = 2.4 Hz, 1H), 8.42-8.43 (m, 1H), 7.61 (d, *J* = 16.4 Hz, 1H), 6.53 (d, *J* = 16 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.55 (s, 9H), 1.43 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 164.9, 152.9, 151.6, 138.7, 135.0, 130.4, 126.6, 123.8, 81.3, 61.9, 28.3, 14.4. HRMS (ESI-TOF) *m/z* calcd. for $C_{15}H_{19}NO_4H^+$ [$(M+H)^+$]: 278.1387, found 278.1385.

(E)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-5-(ethoxycarbonyl)pyridine 1-oxide



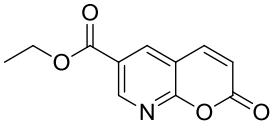
Using **7h** (1.98 g, 7.14 mmol), in accordance with General Procedure Ⅱ, except that extra *m*CPBA (total quantity: 1.5 eq.) was added. The title compound was obtained (1.63 g, 78% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.43 (s, 1H), 7.96 (s, 1H), 7.42 (d, *J* = 16 Hz, 1H), 6.51 (d, *J* = 16 Hz, 1H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.54 (s, 9H), 1.42 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.5, 141.1, 140.2, 136.2, 134.2, 130.3, 126.3, 124.7, 81.8, 62.7, 28.1, 14.2. HRMS (ESI-TOF) *m/z* calcd. for $C_{15}H_{19}NO_5H^+$ [$(M+H)^+$]: 294.1336, found 284.1321.



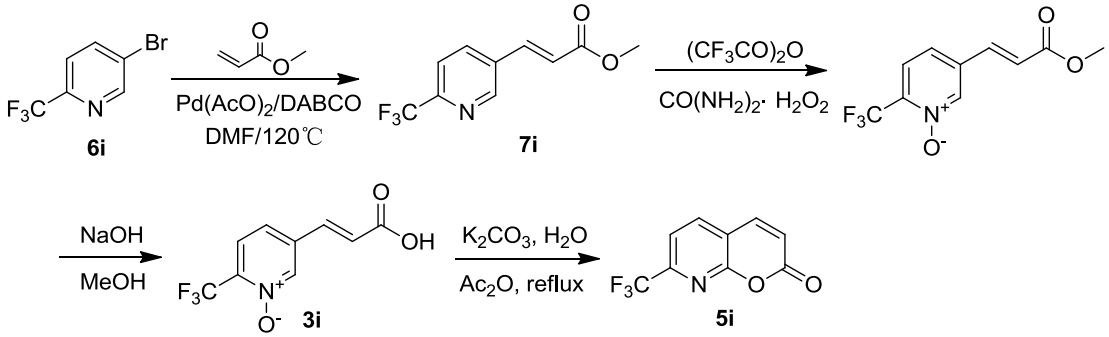
(E)-3-(2-carboxyvinyl)-5-(ethoxycarbonyl)pyridine 1-oxide (3h)

A solution of the (E)-3-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-5-(ethoxycarbonyl) pyridine 1-oxide (520 mg, 1.77 mmol) in 4 ml of TFA/DCM (1:1) was stirred at r.t for 1h. The reaction is complete as indicated by TLC. Evaporation of the solvent to dryness to give the desired product (410 mg, 98% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.98 (s, 1H), 8.86 (s, 1H), 8.41 (s, 1H), 7.72 (d, *J* = 16 Hz, 1H), 6.71 (d, *J* = 16 Hz, 1H), 4.50 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 161.4, 142.0, 141.1, 138.4, 134.6, 131.8, 131.1, 124.9, 63.6, 14.2. HRMS (ESI-TOF) *m/z* calcd. for $C_{11}H_{10}NO_5^-$ [$(M-H)^-$]: 236.0564, found 236.0577.

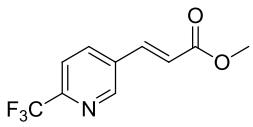
ethyl 2-oxo-2H-pyrano[2,3-b]pyridine-6-carboxylate (5h)



Using **3h** (140 mg, 059 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (68 mg, 55% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, *J* = 2.0 Hz, 1H), 8.51 (d, *J* = 2.4 Hz, 1H), 7.78 (d, *J* = 9.6 Hz, 1H), 6.59 (d, *J* = 9.6 Hz, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.1, 159.4, 152.2, 141.7, 138.6, 124.3, 119.2, 113.6, 62.1, 14.4. HRMS (ESI-TOF) *m/z* calcd. for $C_{11}H_9NO_4H^+$ [$(M+H)^+$]: 220.0604, found 220.0598.

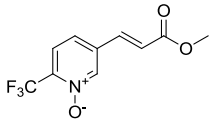


(E)-methyl 3-(6-(trifluoromethyl)pyridin-3-yl)acrylate (7i)



Using 5-bromo-2-(trifluoromethyl)pyridine (2.00 g, 8.85 mmol), following the literature procedure[1], the title compound was obtained (1.97 g, 96% yield) as a white solid. The spectroscopic data are consistent with material from commercial sources. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.68 (d, *J* = 6.4 Hz, 1H), 6.58 (d, *J* = 16 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.6, 139.4, 135.8, 133.0, 122.7, 122.6, 120.72 (q, *J* = 3.00 Hz), 120.0, 52.2.

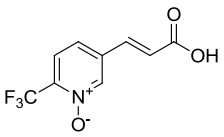
(E)-5-(3-methoxy-3-oxoprop-1-en-1-yl)-2-(trifluoromethyl)pyridine 1-oxide



To a stirred solution of **7i** (360 mg, 1.56 mmol) and urea hydrogen peroxide (608 mg,

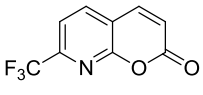
6.47 mmol) in DCM (7 ml) was added trifluoroacetic anhydride (0.81 ml, 5.83 mmol) at 0℃ under argon. The reaction mixture was warmed to r.t and stirred for 4 hs. The excess peroxide was destroyed by saturated aqueous $Na_2S_2O_3$ and water. The resulting mixture was extracted with DCM for three times. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the product (350 mg, 95% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 2.8 Hz, 1H), 7.53 (d, *J* = 4.0 Hz, 1H), 6.60 (d, *J* = 16 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 140.4, 137.1, 136.7, 125.3 (q, *J* = 4.0 Hz), 125.0, 123.8, 121.0, 118.3, 52.5. HRMS (ESI-TOF) *m/z* calcd. for $C_{10}H_8NO_3F_3H^+$ [$(M+H)^+$]: 248.0529, found 248.0539.

(E)-5-(2-carboxyvinyl)-2-(trifluoromethyl)pyridine 1-oxide (3i)



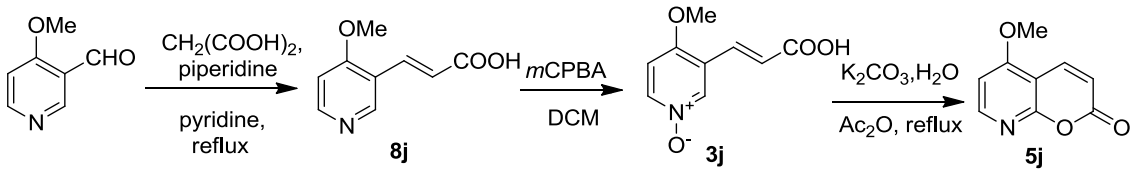
Using (E)-5-(3-methoxy-3-oxoprop-1-en-1-yl)-2-(trifluoromethyl)pyridine 1-oxide (200 mg, 0.77 mmol), in accordance with General Procedure Ⅰ, the title compound was obtained (104 mg, 55% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.88 (s, 1H), 8.89 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 16.4 Hz, 1H), 6.88 (d, *J* = 16.4 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 166.7, 140.4, 137.2, 137.1, 125.9, 125.6 (q, *J* = 4.0 Hz), 123.6, 121.4, 118.7. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_5NO_3F_3^-$[$(M-H)^-$]: 232.0227, found 232.0216.

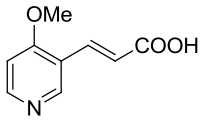
7-(trifluoromethyl)-2H-pyrano[2,3-b]pyridin-2-one (5i)



Using **3i** (150 mg, 0.61 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (103 mg, 76% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.8 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 158.4, 148.5, 148.1, 140.9, 138.9, 120.7 (q, *J* = 91.5 Hz), 117.7 (q, *J* = 3.0 Hz), 116.8. HRMS

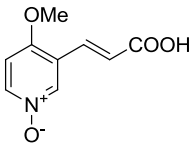
(ESI-TOF) *m/z* calcd. for $C_9H_4NO_2F_3H^+$ [$(M+H)^+$]: 216.0267, found 216.0257.





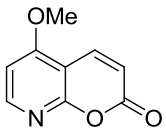
(E)-3-(4-methoxypyridin-3-yl)acrylic acid (8j)

A mixture of 4-methoxynicotinaldehyde (1.0 g, 7.3 mmol), malonic acid (0.76 g, 7.3 mmol) in 0.58 ml of pyridine and 0.08 ml of piperidine was refluxed in an oil bath and kept for 4 hs. After cooling to room temperature, 1.0 ml of cold ethanol was added to the mixture. The precipitate was collected by filtration, washed with H_2O and dried. The title compound was obtained (1.2 g, 92% yield) as a white solid. ^{1}HNMR (400 MHz, d_6-DMSO) δ 12.42 (s, 1H), 8.70 (s, 1H), 8.45 (d, *J* = 5.6 Hz, 1H), 7.66 (d, *J* = 16.4 Hz, 1H), 7.14(d, *J* = 6.0 Hz, 1H), 6.68 (d, *J* = 16.4 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.7, 163.4, 152.3, 150.4, 136.2, 121.8, 119.0, 107.4, 56.0. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_9NO_3H^+$ [$(M+H)^+$]: 180.0655, found 180.0662.

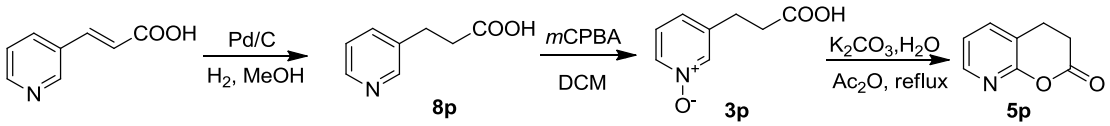


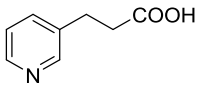
(E)-3-(2-carboxyvinyl)-4-methoxypyridine 1-oxide (3j)

Using **8j** (410 mg, 2.29 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (357 mg, 80% yield) as a white solid. ^{1}HNMR (400 MHz, d_6-DMSO) δ 12.65 (s, 1H), 8.59 (d, *J* = 2.0 Hz, 1H), 8.18 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.54 (d, *J* = 16.4 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 16.4 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.2, 154.8, 140.2, 138.1, 133.8, 123.8, 121.5, 110.1, 56.8. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_9NO_4H^+$ [$(M+H)^+$]: 196.0604, found 196.0613.

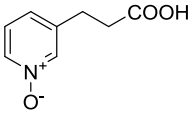
5-methoxy-2H-pyrano[2,3-b]pyridin-2-one (5j) 

Using **3j** (150 mg, 0.77 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (42 mg, 31% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 5.6 Hz, 1H), 8.01 (d, *J* = 9.6 Hz, 1H), 6.77 (d, *J* = 5.6 Hz, 1H), 6.40 (d, *J* = 9.6 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 160.5, 160.4, 152.0, 137.3, 116.0, 104.5, 103.6, 56.7. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_7NO_3H^+$ [$(M+H)^+$]: 178.0499, found 178.0493.

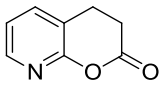


3-(pyridin-3-yl)propanoic acid (8p) 

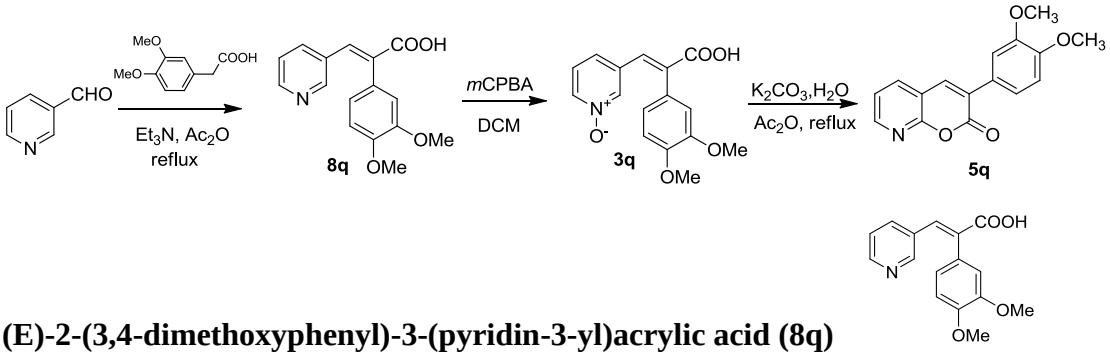
To a solution of (E)-3-(pyridin-3-yl)acrylic acid (2.5 g, 16.7 mmol) in methanol (5 ml) was added 10% Pd/C (200 mg), and the suspension was stirred under at room temperature for 5 hs under hydrogen atmosphere (balloon). After the reaction mixture was filtered through Celite, the filtrate was concentrated to dryness followed by column chromatography (DCM:MeOH = 50:1~30:1~10:1) to give the title compound (2.2 g, 88%) as yellow solid. The spectroscopic data are consistent with previously reported.[12]

3-(2-carboxyethyl)pyridine 1-oxide (3p) 

Using **8p** (2.2 g, 14.5 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (2.18 g, 90% yield) as a brown solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.26 (s, 1H), 8.15 (s, 1H), 8.06 (d, *J* = 6.4 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 173.4, 140.3, 138.4, 136.6, 126.1, 125.7, 34.0, 27.0. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_8NO_3^-$ [$(M-H)^-$]: 166.0510, found 166.0513.

3,4-dihydro-2H-pyrano[2,3-b]pyridin-2-one (5p) 

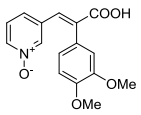
Using **3p** (200 mg, 1.2 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (105 mg, 59% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 4.4 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.11 (dd, *J* = 6.8, 5.2 Hz, 1H), 3.01 (t, *J* = 6.8 Hz, 2H), 2.82 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 158.6, 147.4, 137.7, 121.0, 117.9, 29.0, 22.9. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_5NO_2H^+$ [$(M-H_2+H)^+$]: 148.0393, found 148.0394.



(E)-2-(3,4-dimethoxyphenyl)-3-(pyridin-3-yl)acrylic acid (8q)

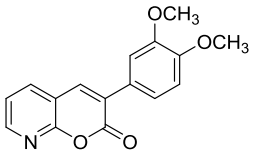
The desired product was obtained following a known procedure.[13] 2-(3,4-dimethoxyphenyl)acetic acid (4.2 g, 21 mmol), nicotinaldehyde (2.28 g, 21 mmol) and triethylamine (3.0 ml, 21 mmol) were dissolved in acetic anhydride (20 ml) and the mixture was refluxed under heating for 22 hours. The mixture was cooled to 110 ℃, and water (10 ml) was gradually added thereto while stirring. After 30 minutes, the reaction mixture was cooled to room temperature, and the solvent was removed under vacuum. The residue was diluted with water and DCM. The resulting mixture is separated and the aqueous phase is extracted with DCM thoroughly. The organic phases were combined and washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography using DCM/MeOH (100:1~30:1) as eluent. The title cpd. was obtained as a yellow solid (1.85 g, 30%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.78 (s, 1H), 8.39 (d, J = 4.4 Hz, 1H), 8.34 (s, 1H), 7.72 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.24 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.2, 151.0, 149.3, 148.8, 148.5, 136.4, 135.31, 135.29, 130.8, 127.9, 123.2, 121.7, 113.1,

111.9, 55.5, 55.4. HRMS (ESI-TOF) *m/z* calcd. for $C_{16}H_{14}NO_4^-$ [(M-H)$^-$]: 284.0928, found 284.0927.



(E)-3-(2-carboxy-2-(3,4-dimethoxyphenyl)vinyl)pyridine 1-oxide (3q)

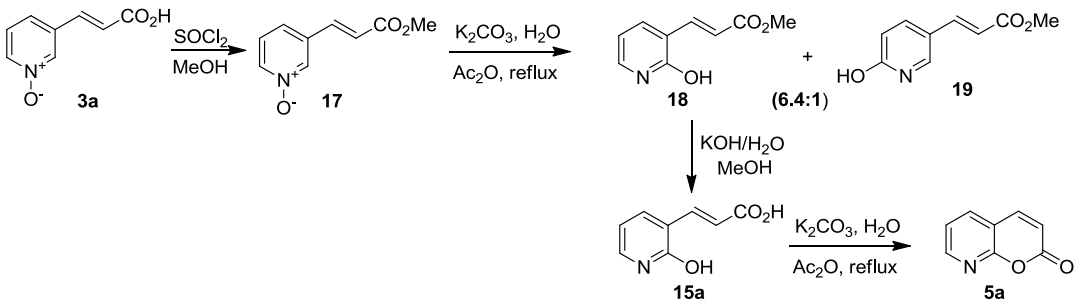
Using **8q** (1.8 g, 6.3 mmol), in accordance with General Procedure Ⅱ, the title compound was obtained (1.45 g, 76% yield) as a yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.95 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.60 (s, 1H), 7.26 (t, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 8.4 Hz, 2H), 6.78 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 167.9, 148.8, 148.7, 139.2, 138.2, 137.2, 134.4, 133.0, 127.2, 126.1, 126.0, 121.7, 112.9, 111.8, 55.6, 55.4. HRMS (ESI-TOF) *m/z* calcd. for $C_{16}H_{14}NO_5^-$ [(M-H)$^-$]: 300.0877, found 300.0865.

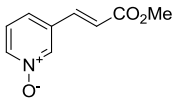


3-(3,4-dimethoxyphenyl)-2H-pyrano[2,3-b]pyridin-2-one (5q)

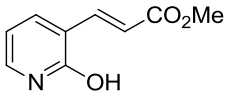
Using **3q** (150 mg, 0.50mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (130 mg, 92% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.8 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.77 (s, 1H), 7.33 – 7.28 (m, 3H), 6.93 (d, *J* = 8.4 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 158.2, 150.3, 149.9, 148.9, 137.0, 136.8, 129.7, 126.8, 121.5, 121.3, 115.2, 111.9, 111.2, 56.2, 56.1. HRMS (ESI-TOF) *m/z* calcd. for $C_{16}H_{13}NO_4H^+$ [(M+H)$^+$]: 284.0917, found 284.0922.

4. Mechanism Study Experiment



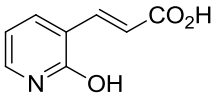
(E)-3-(3-methoxy-3-oxoprop-1-en-1-yl)pyridine 1-oxide (17) 

To a solution of **3a** (6.4 g, 38.7 mmol) in dry MeOH (77 mL) was added thionyl chloride (3.4 mL, 46.5 mmol) dropwise in an ice bath under nitrogen. The mixture was heated to reflux and stirred for 3 h. After cooled down, the reaction mixture was concentrated in vacuo. The title compound was obtained (6.8 g, 98%) as a white solid and was used directly in the next step without further purification. The spectroscopic data are consistent with previously reported.[14]

methyl (E)-3-(2-hydroxypyridin-3-yl)acrylate (18) 

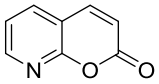
Using **17** (2.0 g, 11.1 mmol), in accordance with General Procedure Ⅲ, **19** was isolated as the minor product (125 mg, 6.2%), and the title compound **18** was obtained (800 mg, 40% yield) as a yellow solid. The spectroscopic data of **18** are consistent with previously reported.[15]

19: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.57 (d, *J* = 4.8 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 16.4 Hz, 1H), 7.30 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.48 (d, *J* = 16.4 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 151.0, 149.7, 141.1, 134.2, 130.1, 123.7, 119.9, 51.8. HRMS (ESI-TOF) *m/z* calcd. for $C_9H_9NO_3H^+$ [$(M+H)^+$]: 180.0655, found 180.0663.

(E)-3-(2-hydroxypyridin-3-yl)acrylic acid (15a) 

To a solution of **18** (200 mg, 1.12 mmol) in methanol (2.2 ml) was added aqueous potassium hydroxide (3 M, 3.0 equiv). The resulting reaction mixture was stirred for several hours at reflux until the reaction is complete as indicated by TLC. Methanol was removed in vacuo. Water phase was acidified by 3.0 M HCl to pH 5~6. The resulting precipitate was filtered and washed with water and methanol. After dried in a vacuum oven at 45 ℃, the title compound was obtained (160 mg, 87% yield) as a white solid and was used directly in the next step without further purification. ^{1}H NMR (400 MHz, d_6-DMSO) δ 12.17 (s, 1H), 12.04 (s, 1H), 7.83 (d, *J* = 5.6 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.00 (d, *J* = 15.6 Hz, 1H), 6.29 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR

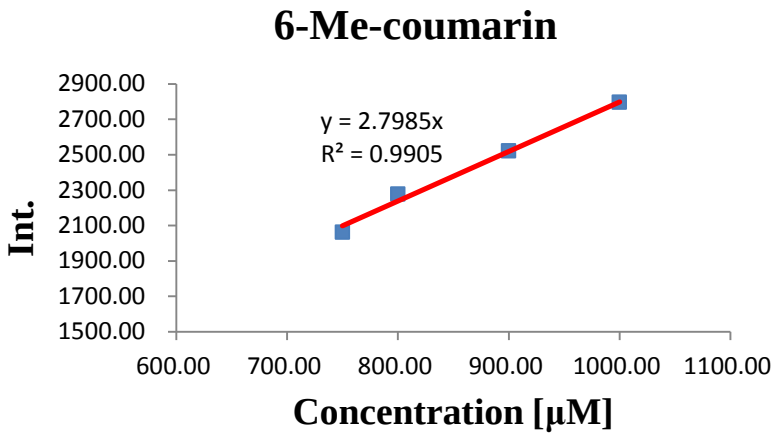
(100 MHz, d_6-DMSO) δ 168.3, 161.0, 142.9, 140.2, 137.1, 124.1, 119.8, 105.4. HRMS (ESI-TOF) *m/z* calcd. for $C_8H_7NO_3Na^+$ $[(M+Na)^+]$: 188.0318, found 188.0326.

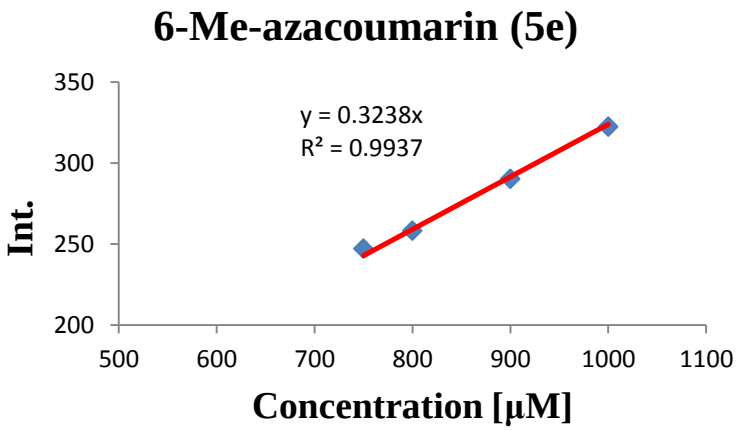
2H-pyrano[2,3-b]pyridin-2-one (5a) 

Using **15a** (150 mg, 0.91 mmol), in accordance with General Procedure Ⅲ, the title compound was obtained (96 mg, 72% yield) as a white solid.

5. Determination of Saturated Concentrations

Saturated concentrations of 6-methyl-coumarin and **5e** were calculated from the standard curves that related peak area (340 nm) against known concentration of compounds in PBS (0.1% DMSO).





compd	Peak areas	C_s / µ M
6-Me-coumarin	7312	2613
5e	2012	6214

6. Evaluation of Fluorescent Properties of 5d and 5e

The fluorescence quantum yield (ϕ) was determined relative to a reference compound of known ϕ. Quinine sulfate (ϕ = 0.577) as reference compound was used to this measurement, and two samples in PBS (100 μM) conducted fluorescence measurement using 350 nm excitation wavelength. Gain and slit bandwidths were applied for these samples then the ϕ was calculated as the following equation:

$$\emptyset = \emptyset_R \frac{I}{I_R} \frac{A_R}{A} \frac{n^2}{n_R^2}$$

Where ϕ_R was the quantum yields of quinine sulfate, I was the integrated fluorescence intensity, A was the absorbance at 350 nm excitation wavelength and n was the refractive index of the solvent. The concentration was sufficiently diluted to avoid concentration quenching, and absorbances at 350 nm is optimally kept in under A = 0.035 in order to avoid inner filter effects and ensure liner response on the intensity.

compd	λ_{ex} (nm)	λ_{em} (nm)	ϕ
Quinine	350	450	0.577
5d	367	441	0.122
5e	368	435	0.070

7. References

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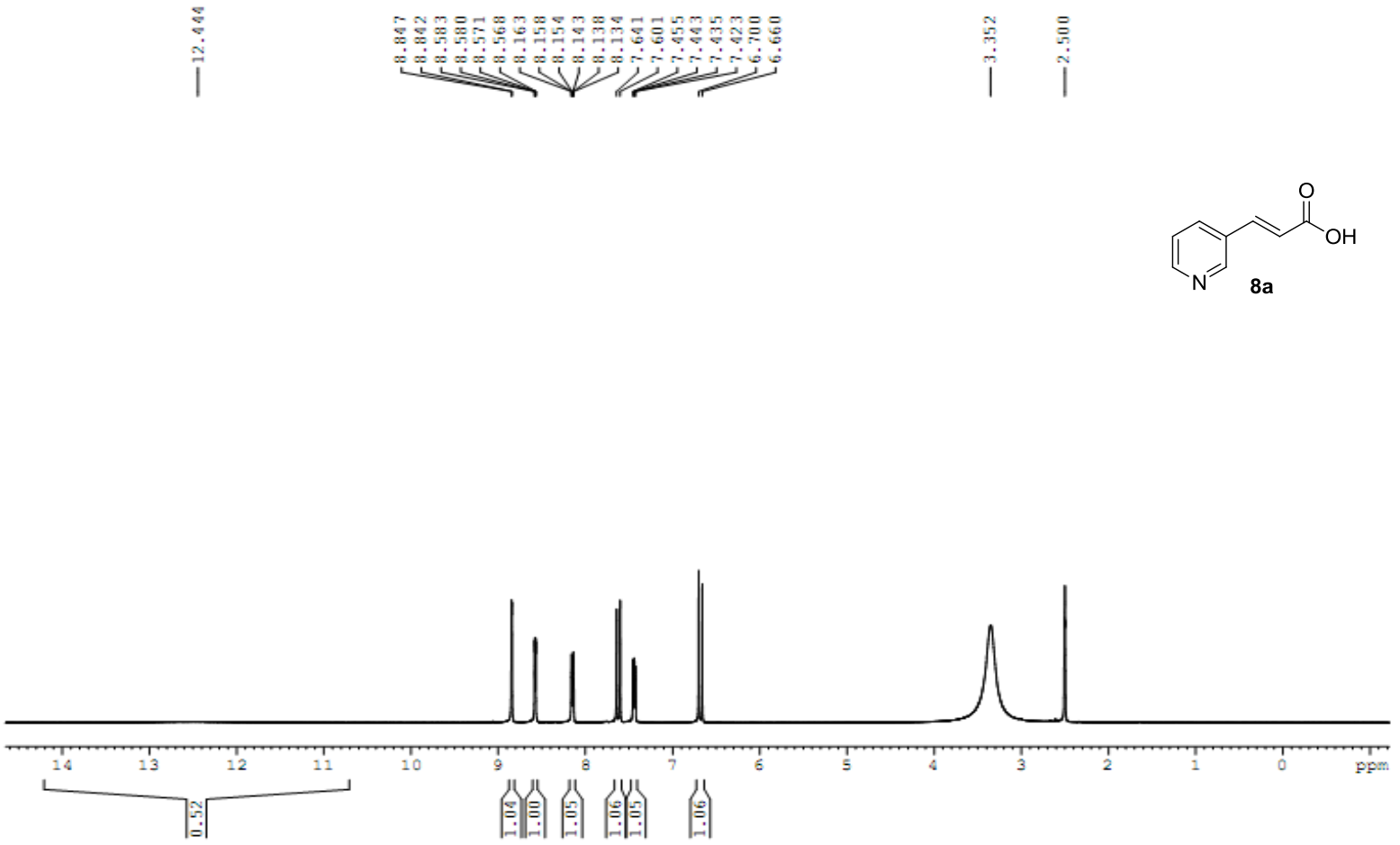
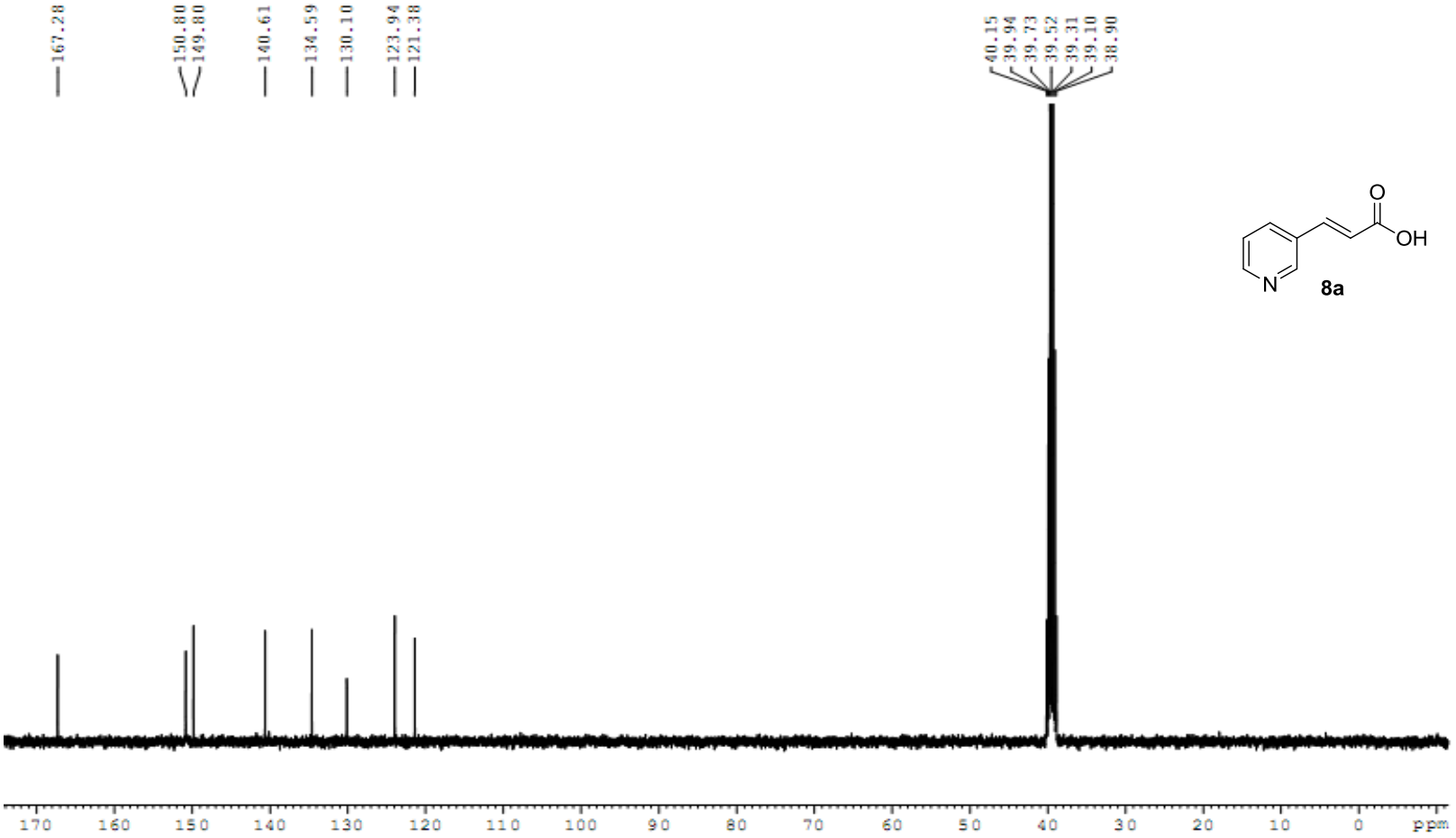
8. Spectra Data

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39.94
39.73
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39.10
38.90
O
OH
N
8a
170
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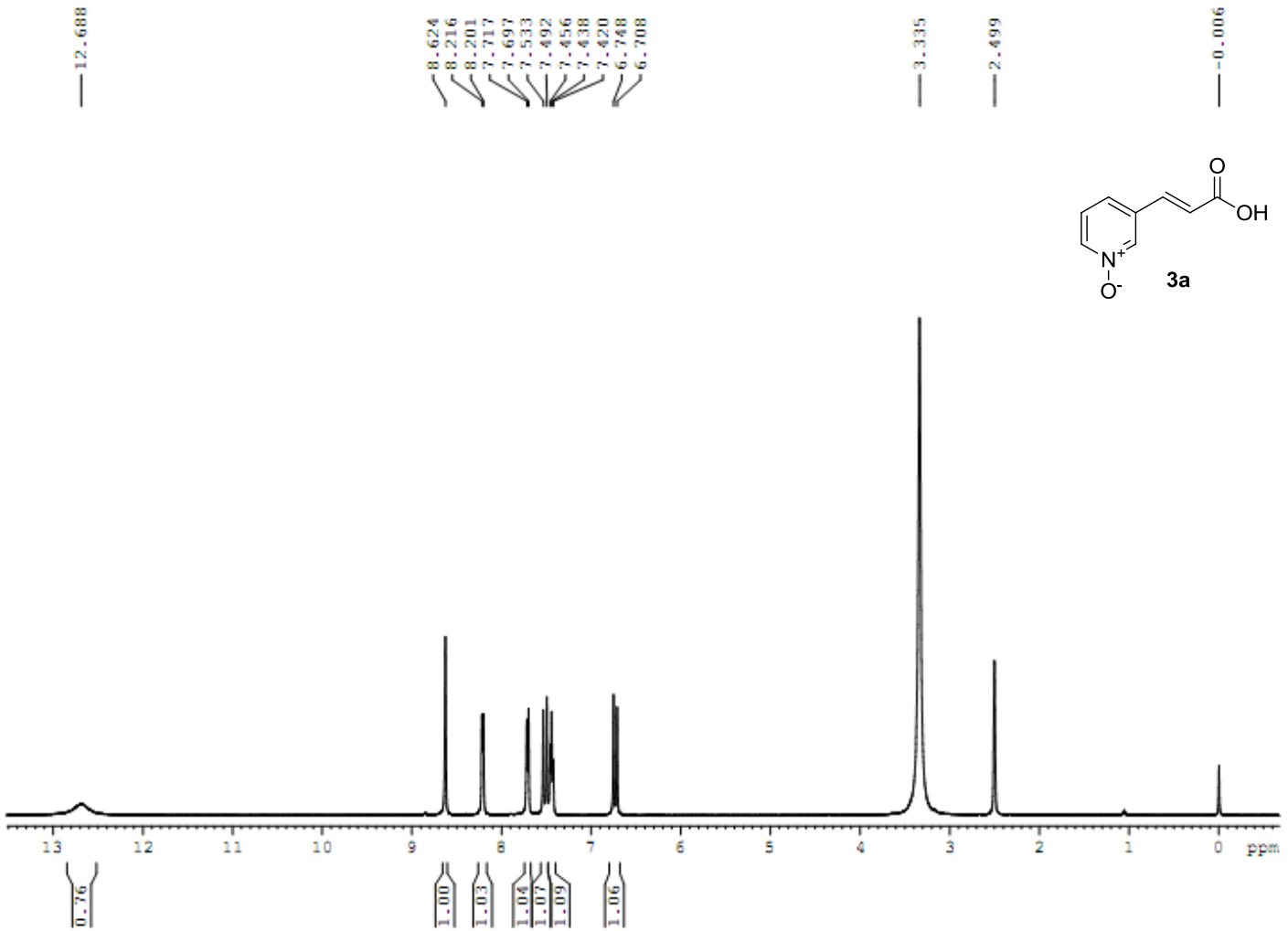
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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7.492
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6.708
3.335
2.499
-0.006
O
OH
N+
O-
3a
13
12
11
10
9
8
7
6
5
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3
2
1
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ppm
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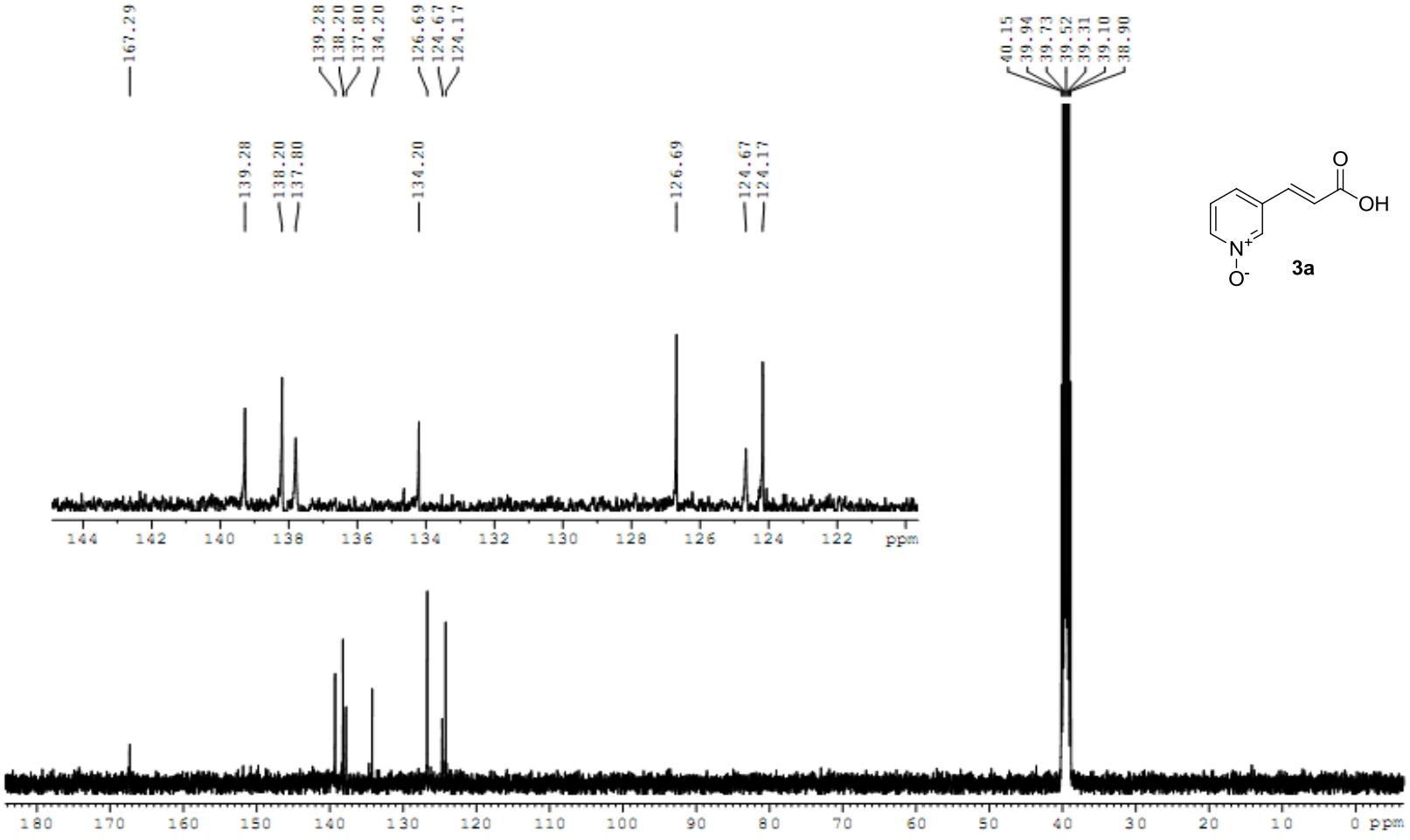
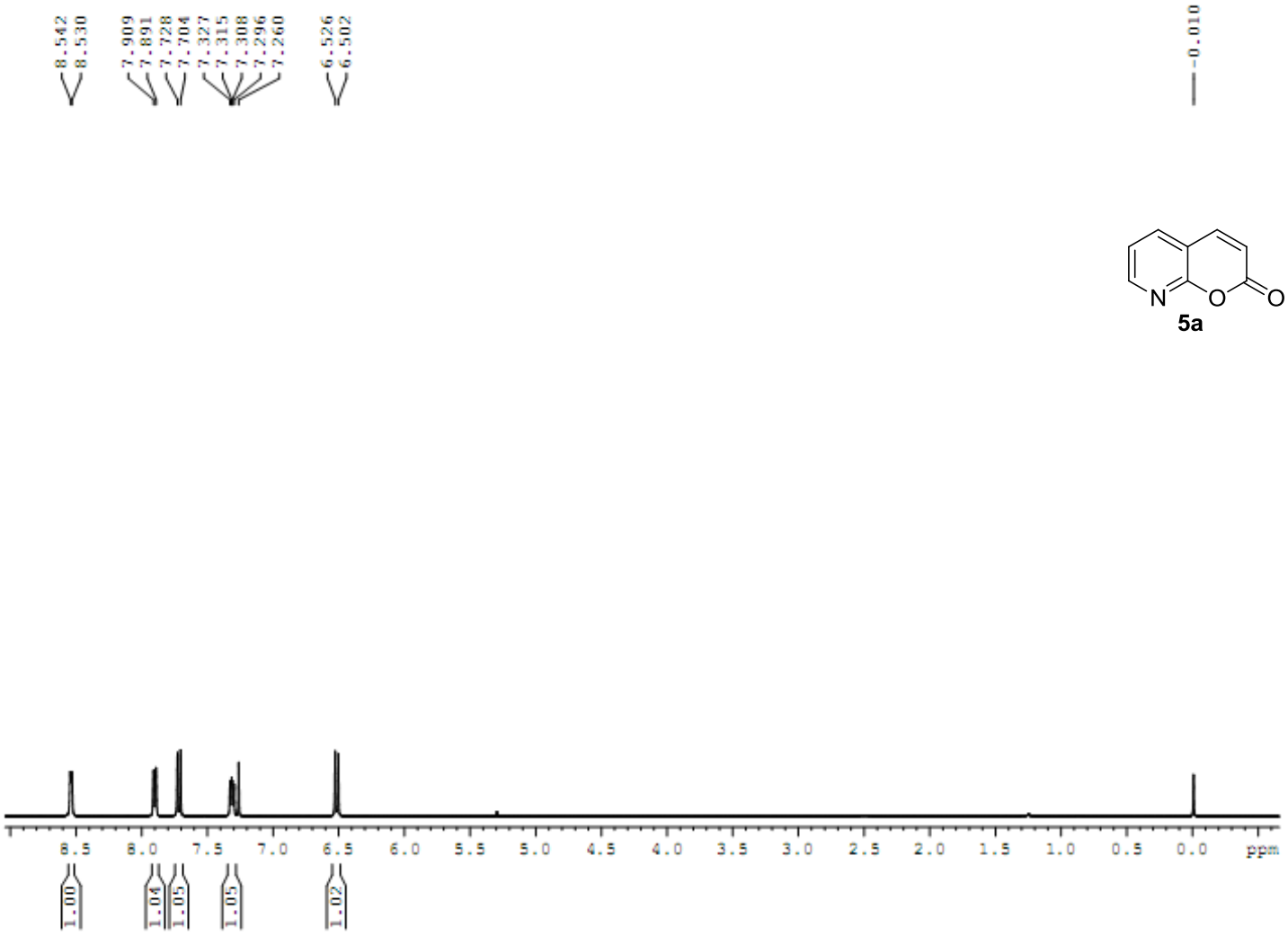
1.03
1.04
1.07
1.09
1.06



DOI: 10.1021/acs.orglett.6b03771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N
O
O
5a
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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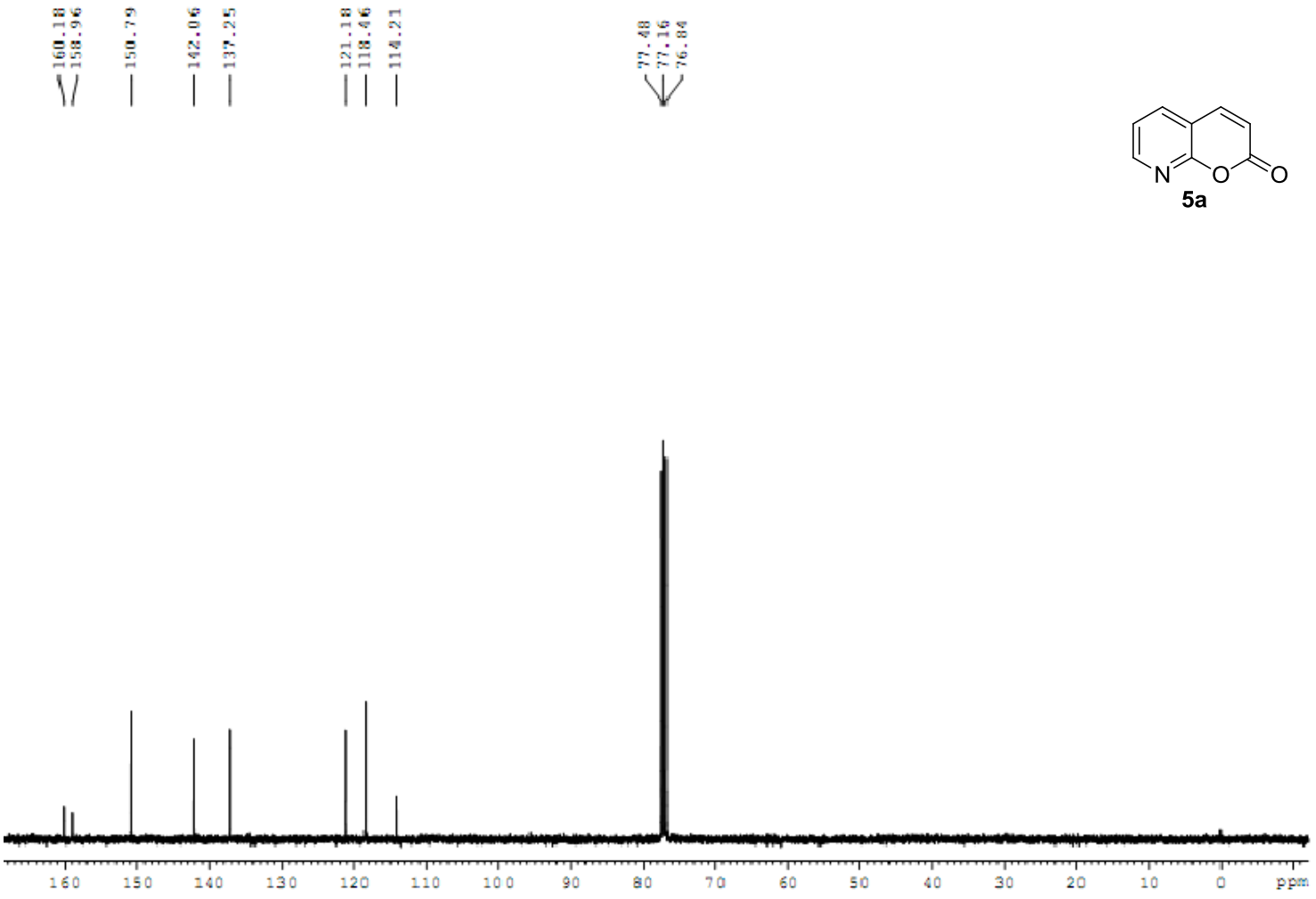
1.02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60
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20
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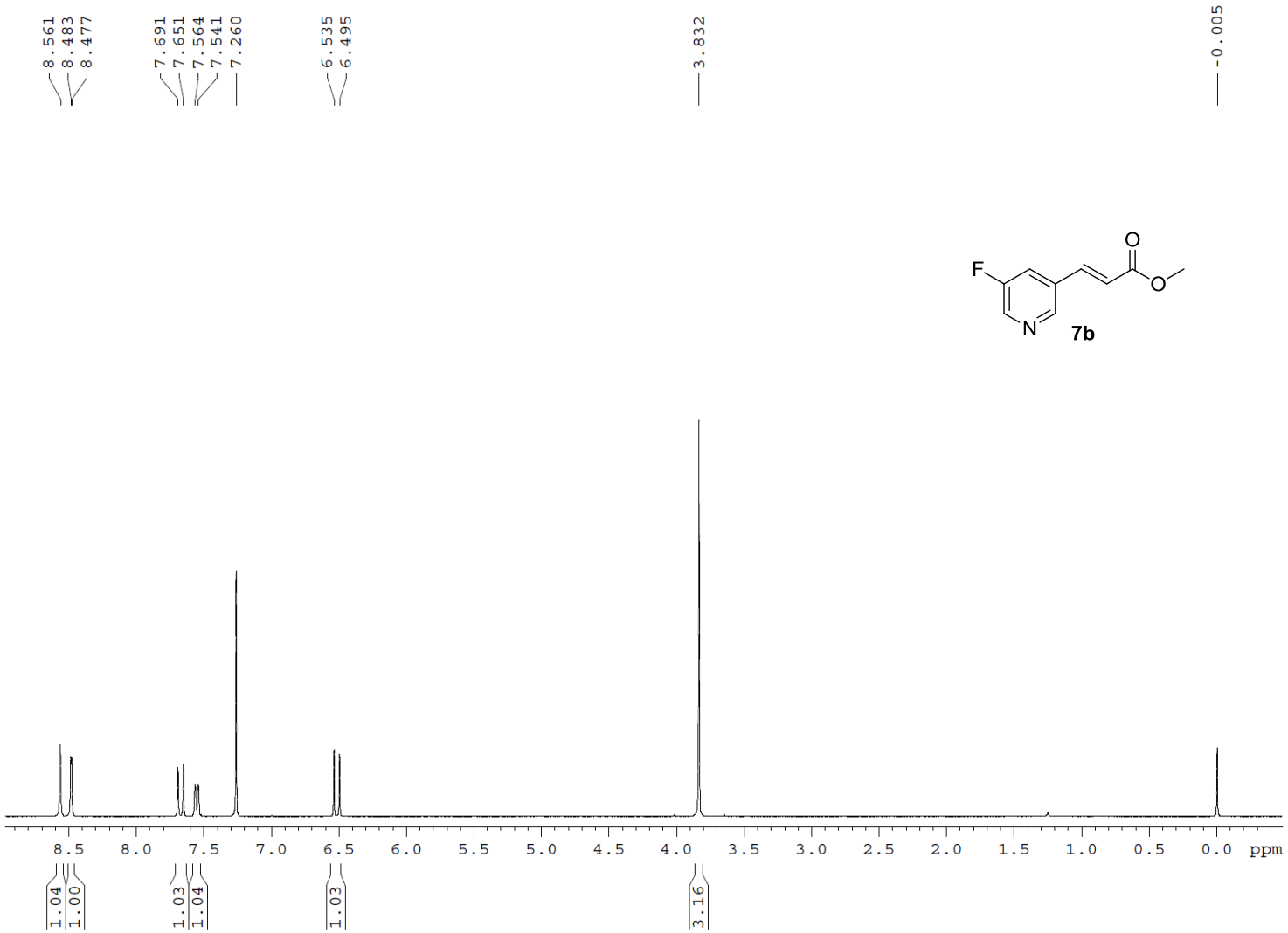
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7.0
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
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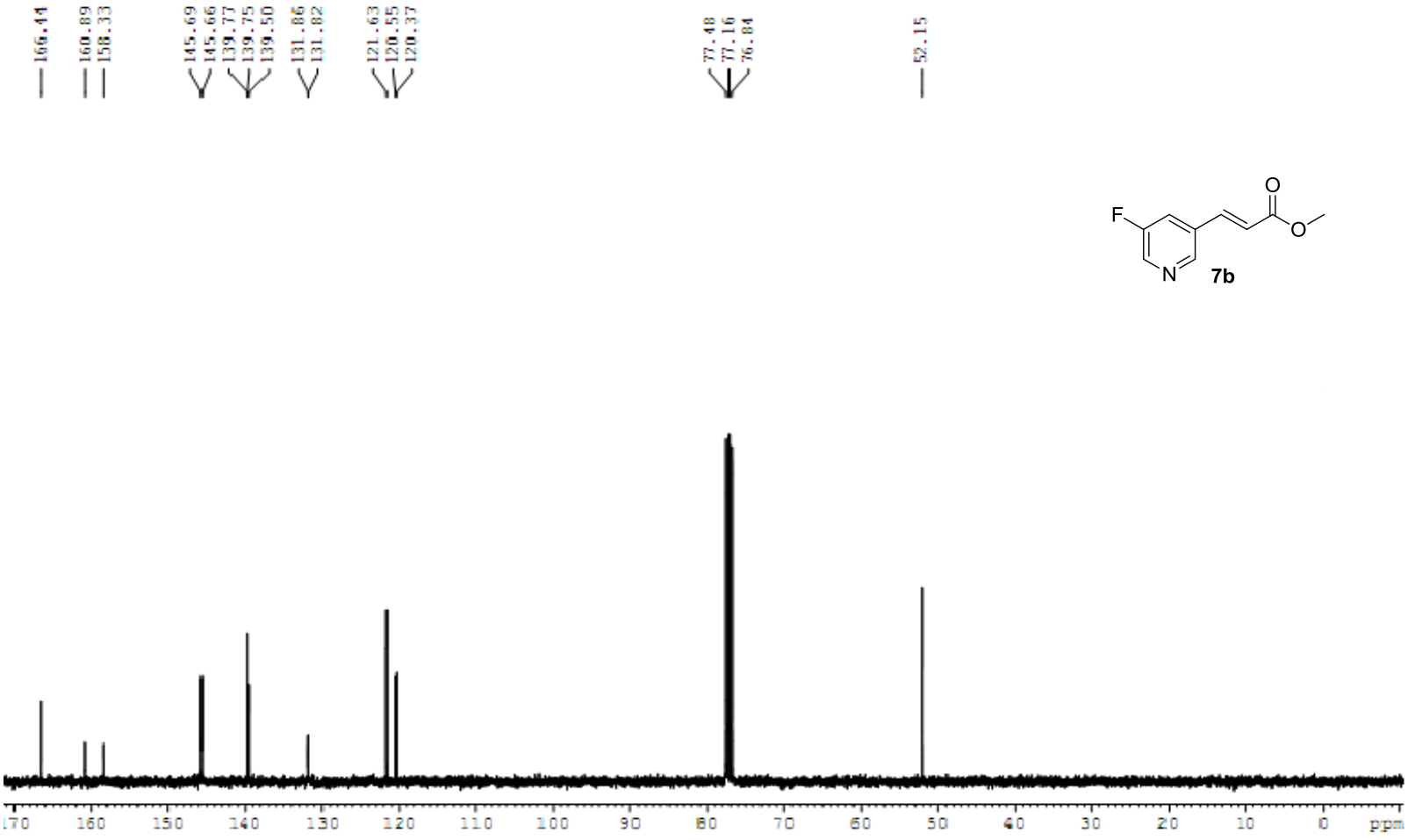
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120.37
77.48
77.16
76.84
52.15
F
O
O
N
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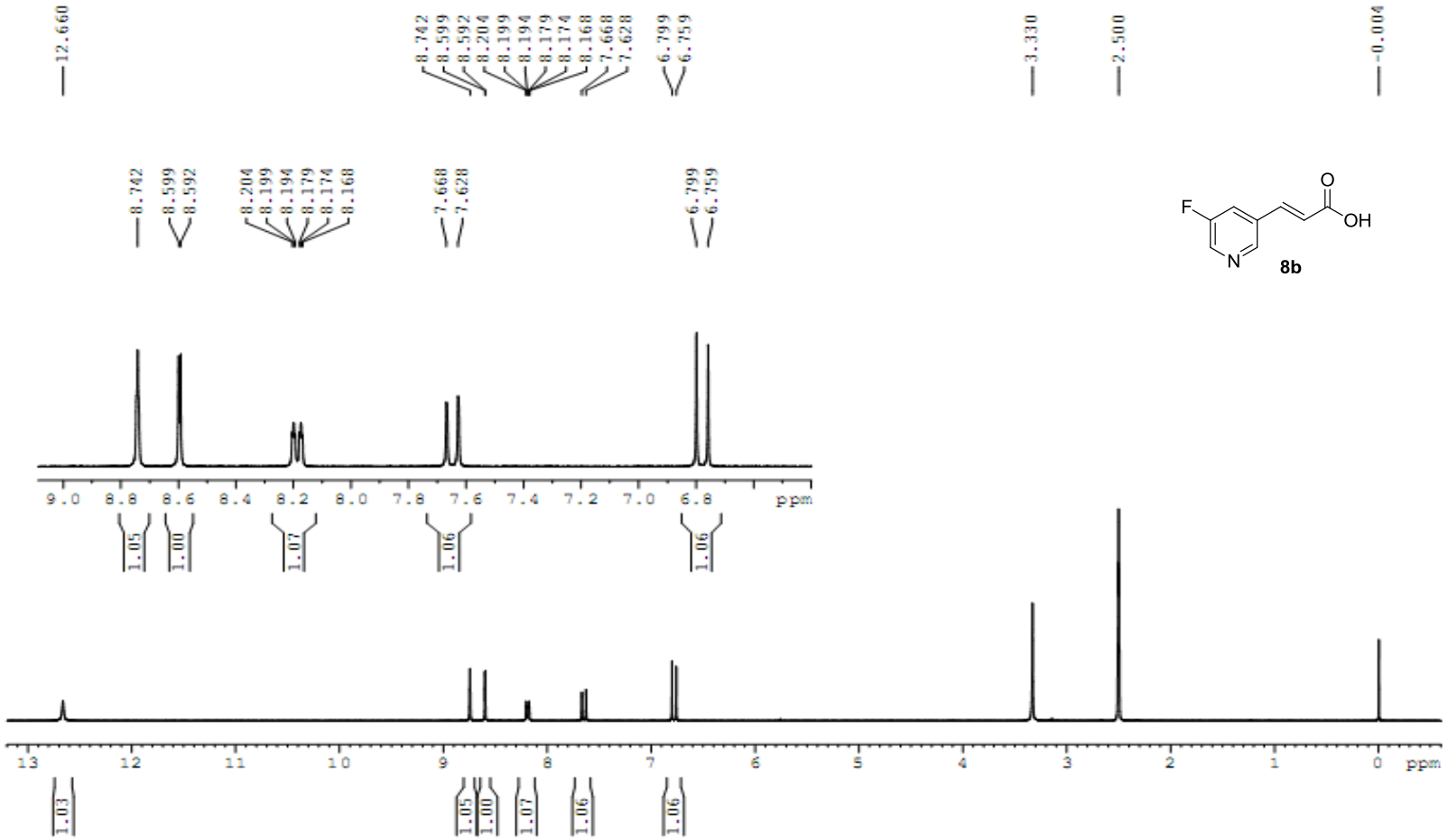
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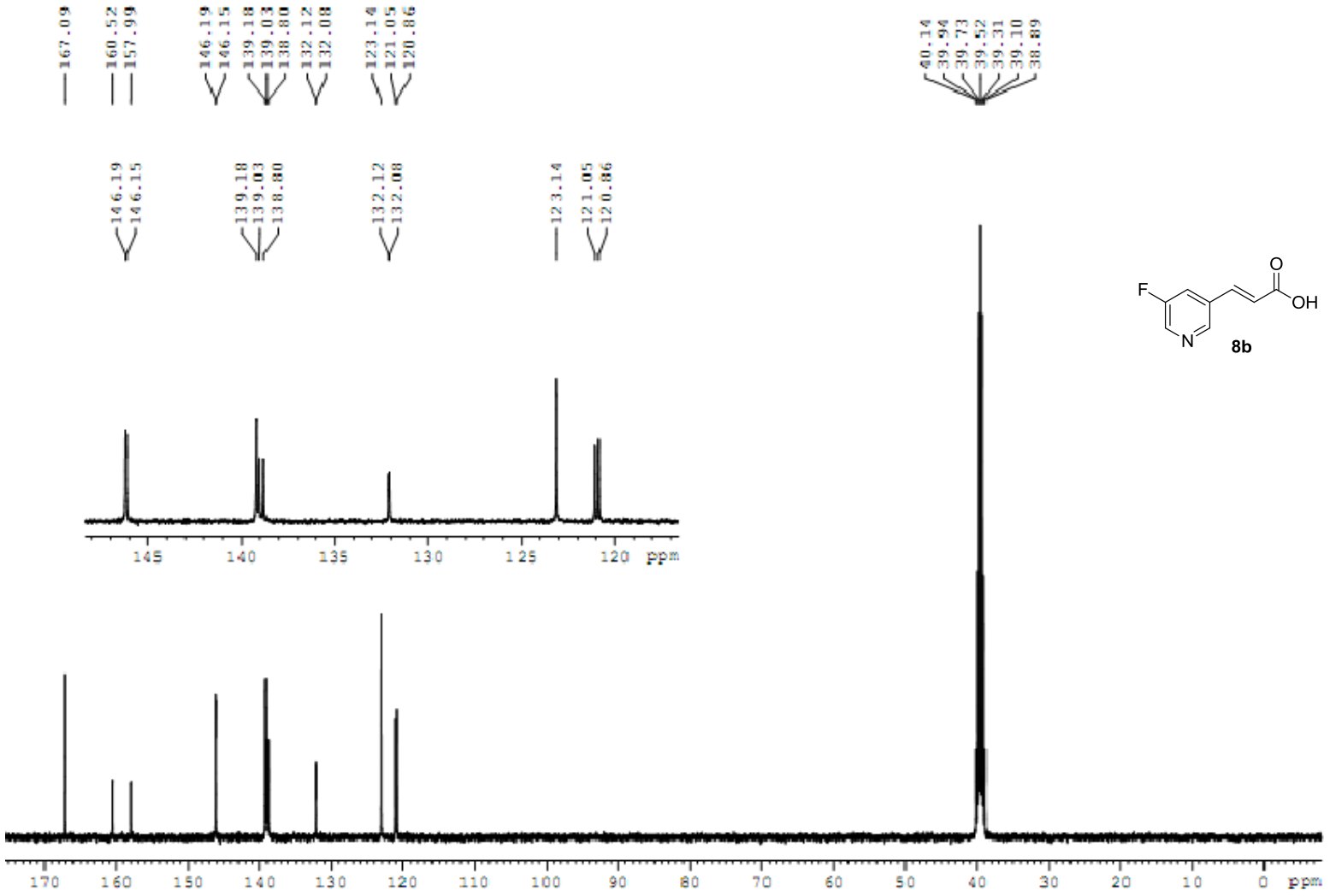
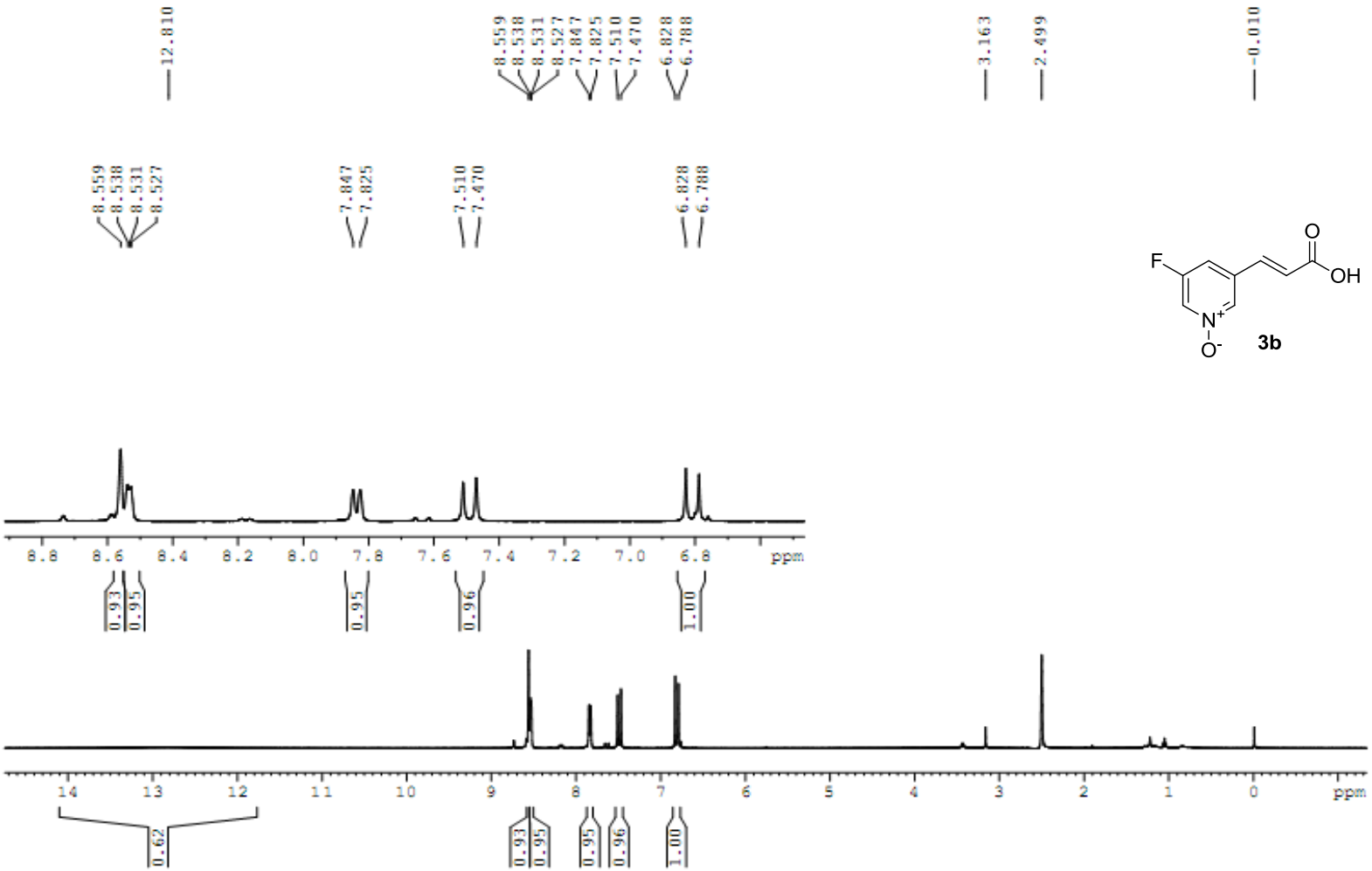


DOI: 10.1021/acs.orglett.6b03771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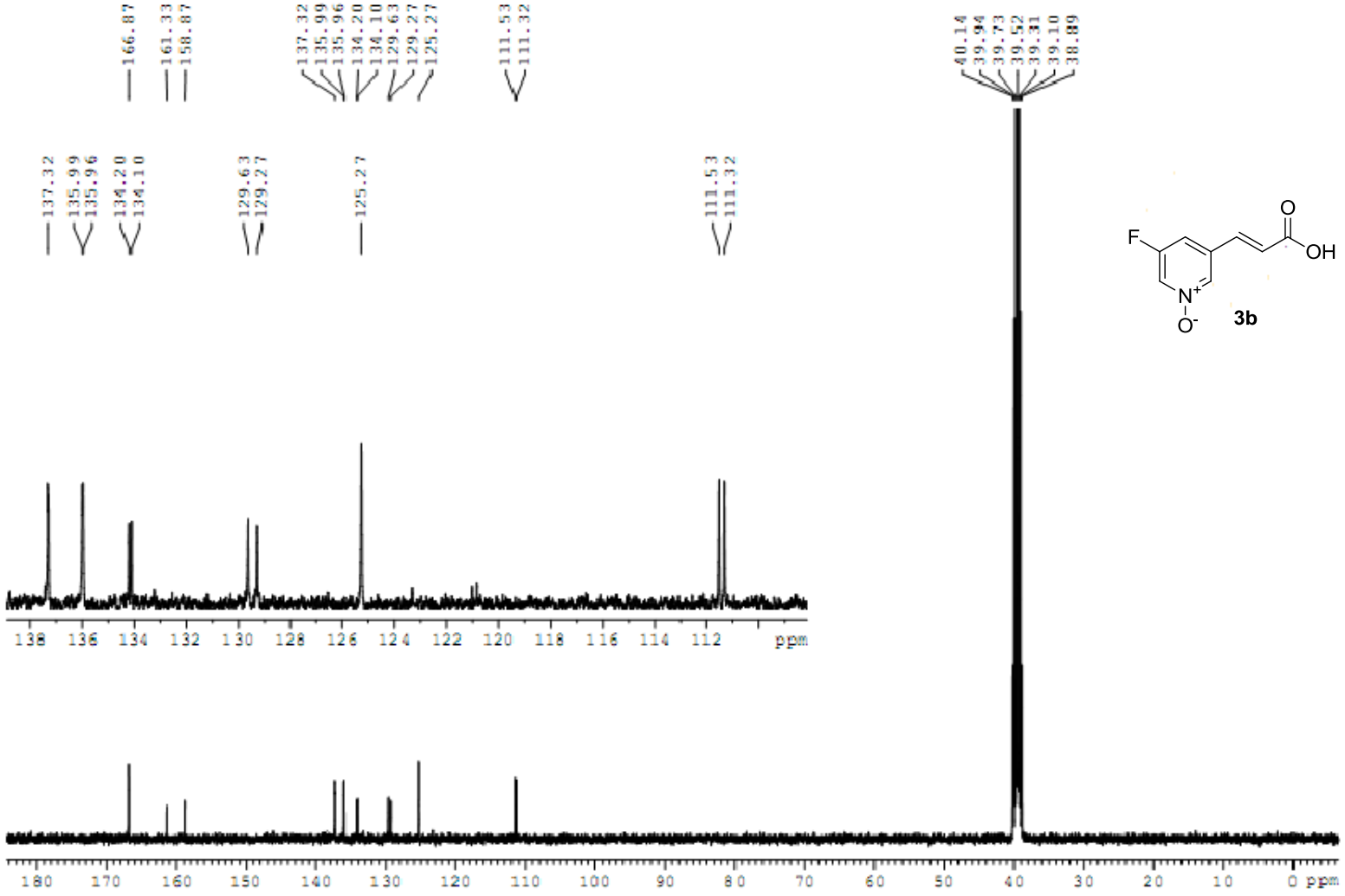
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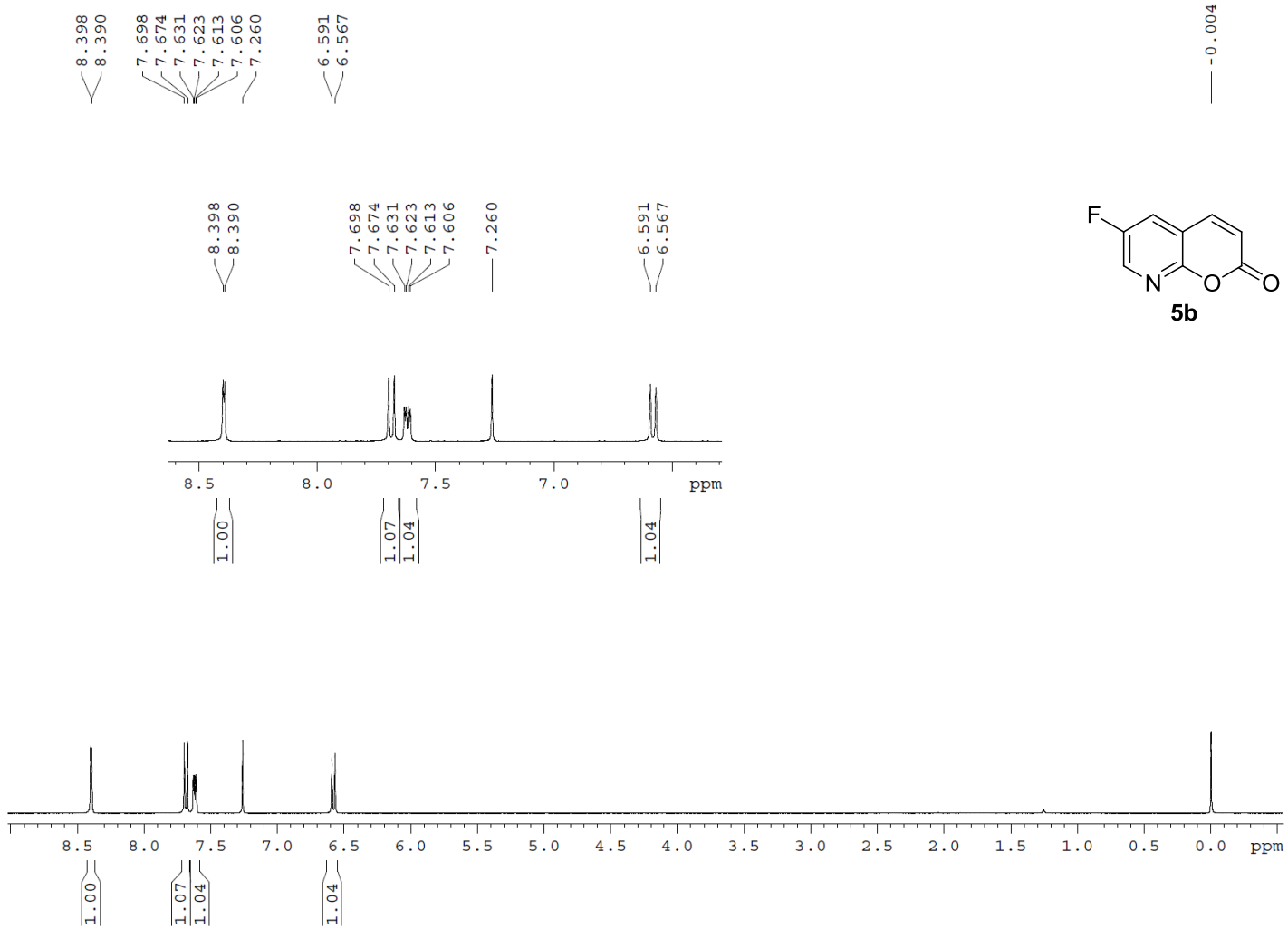
ppm
ppm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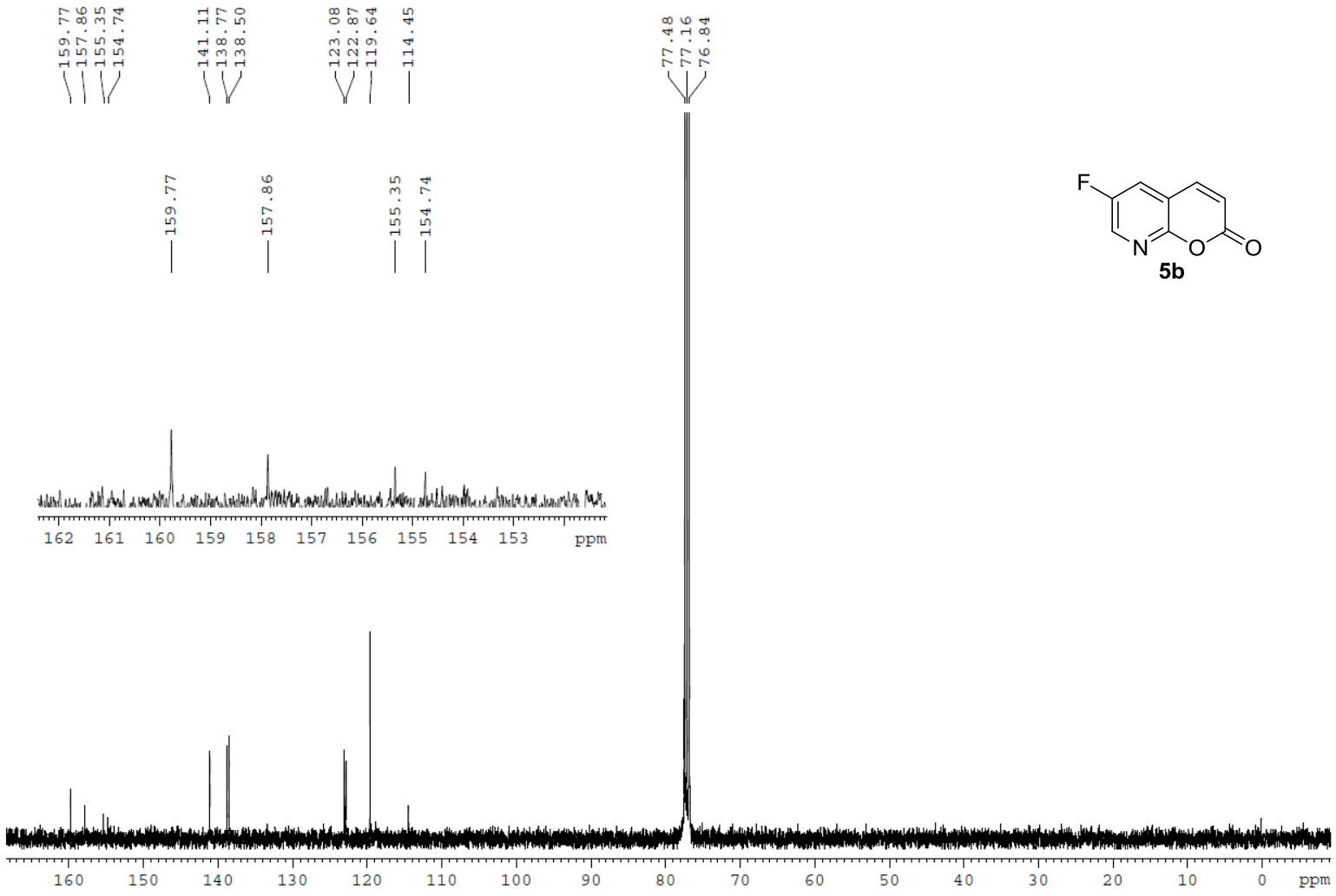
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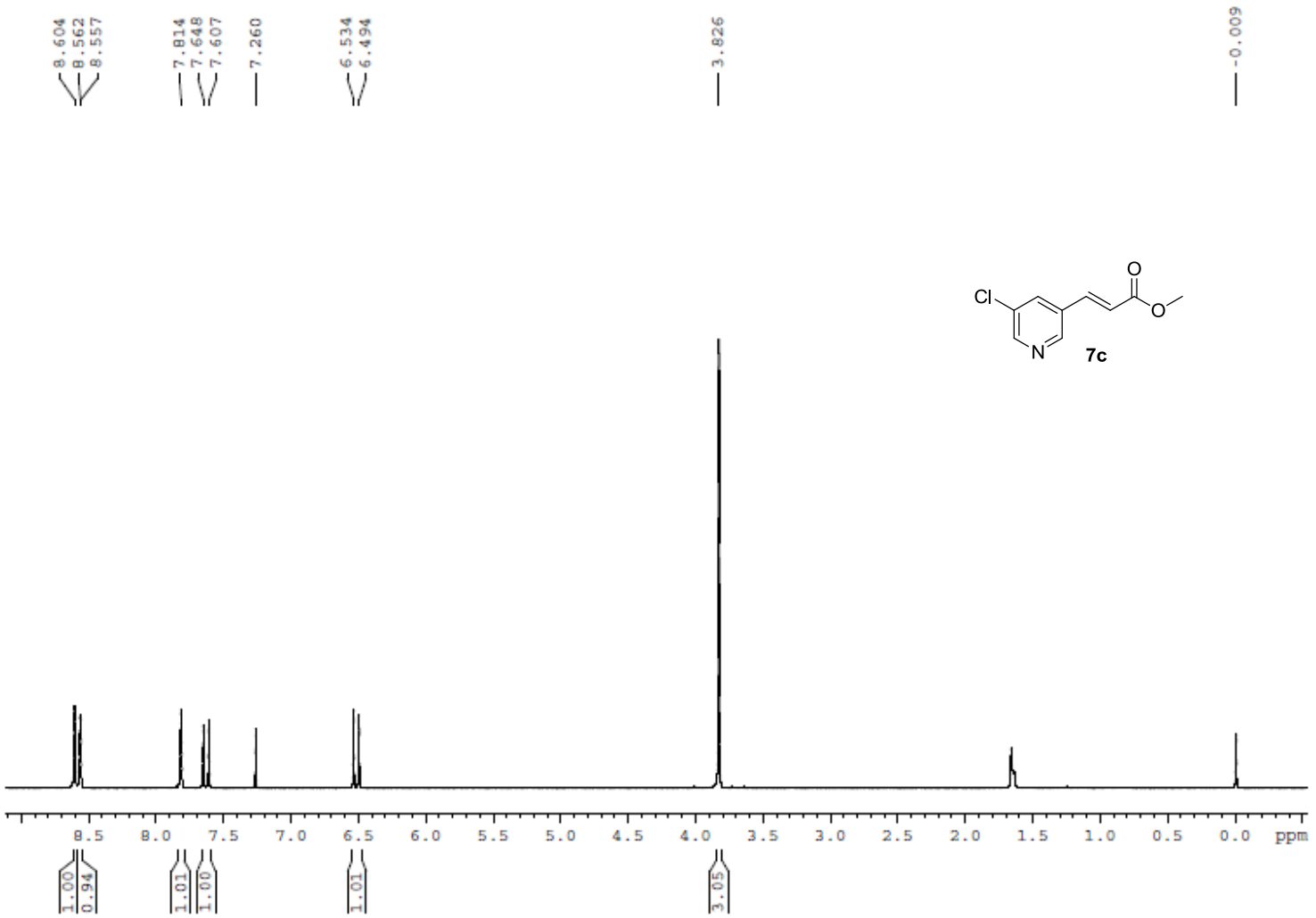
O
O
5b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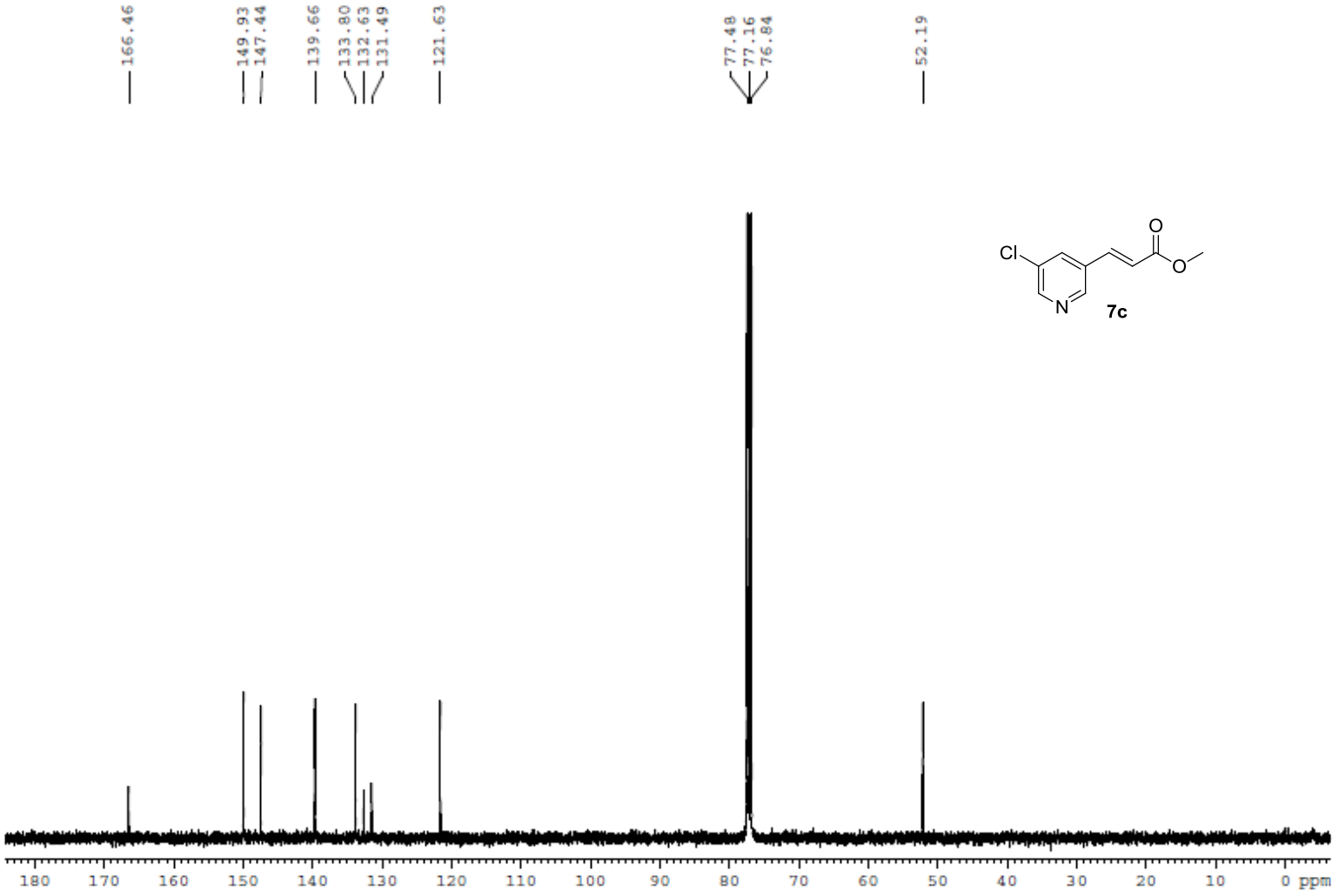
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O
O
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70
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30
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10
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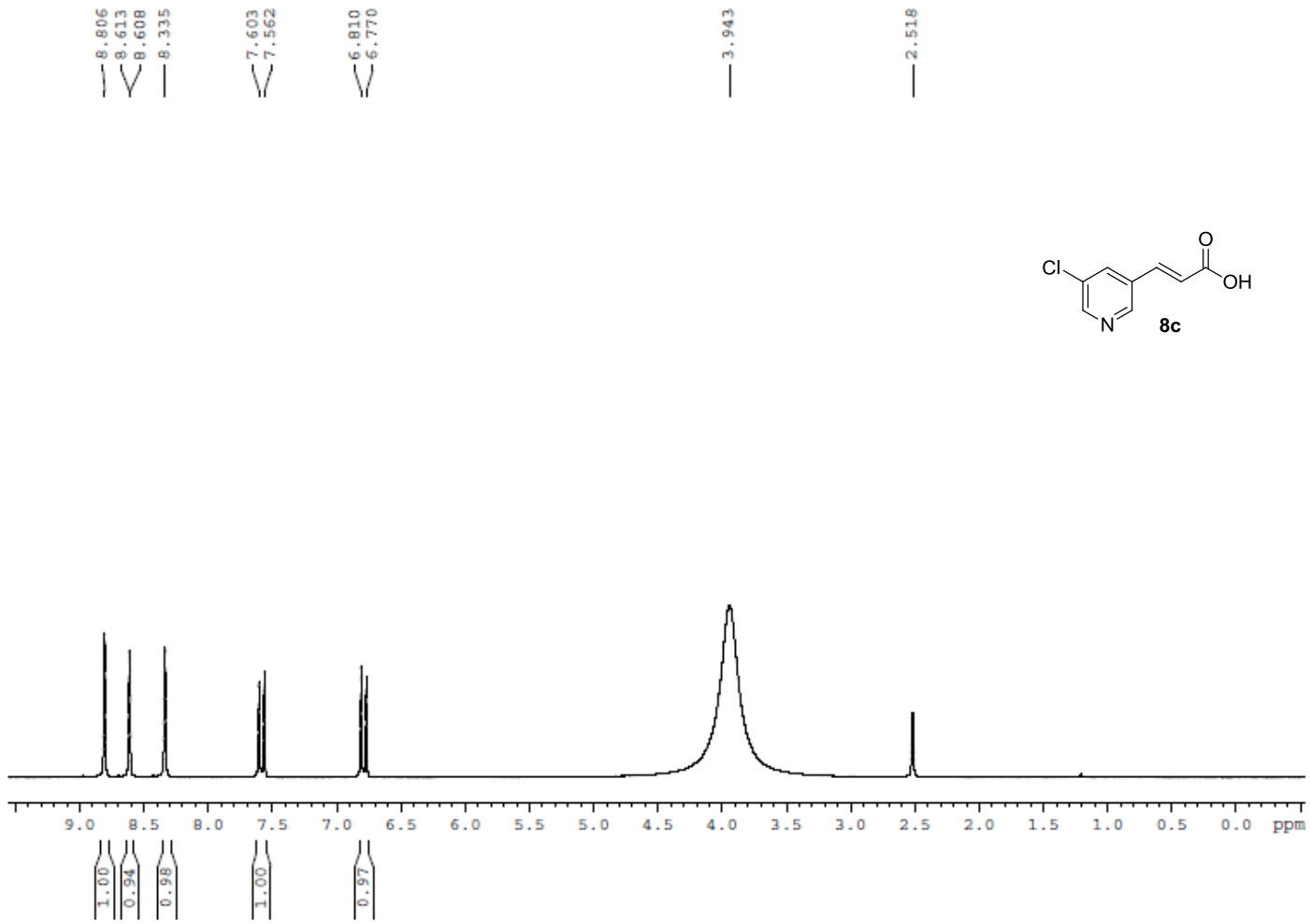
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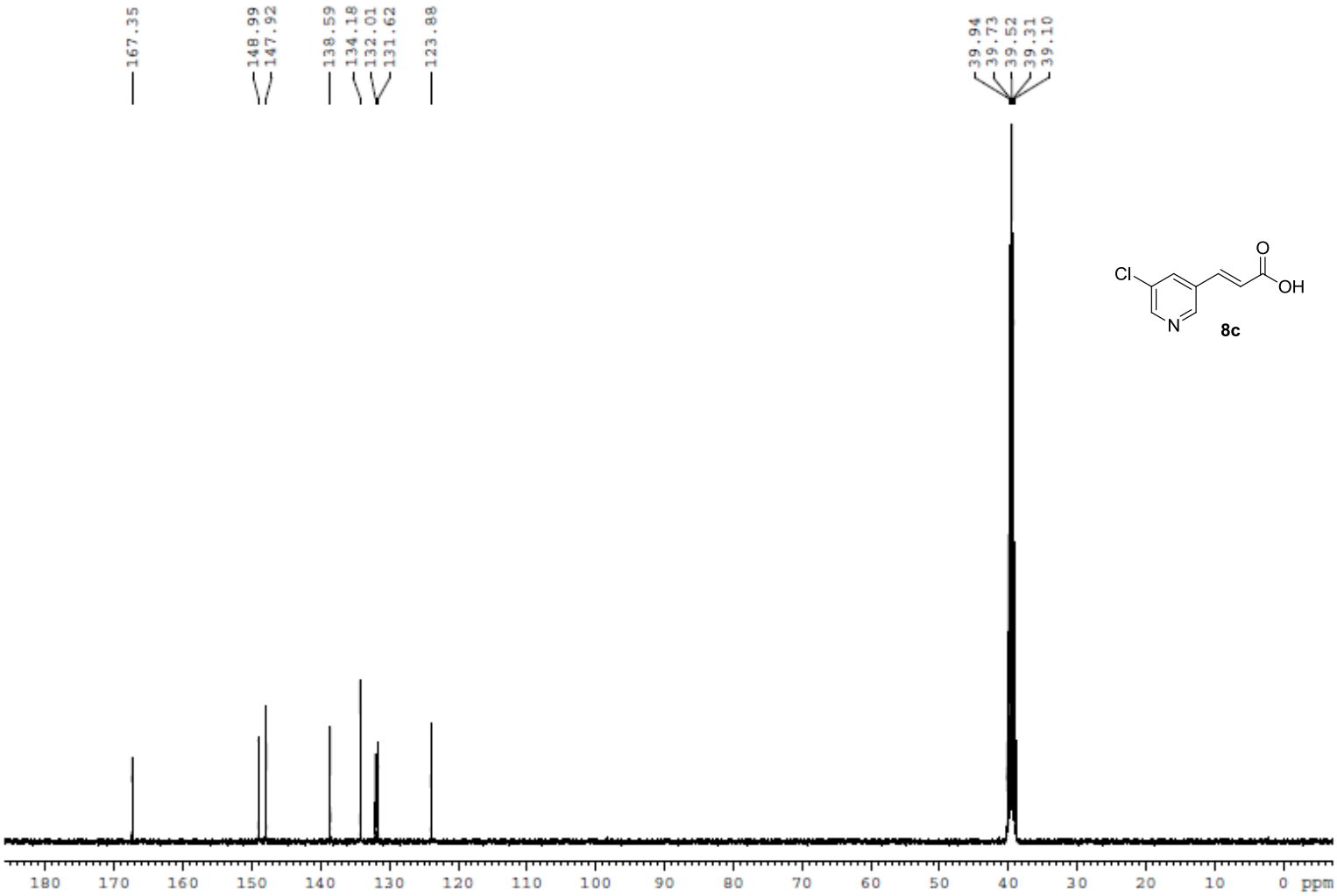
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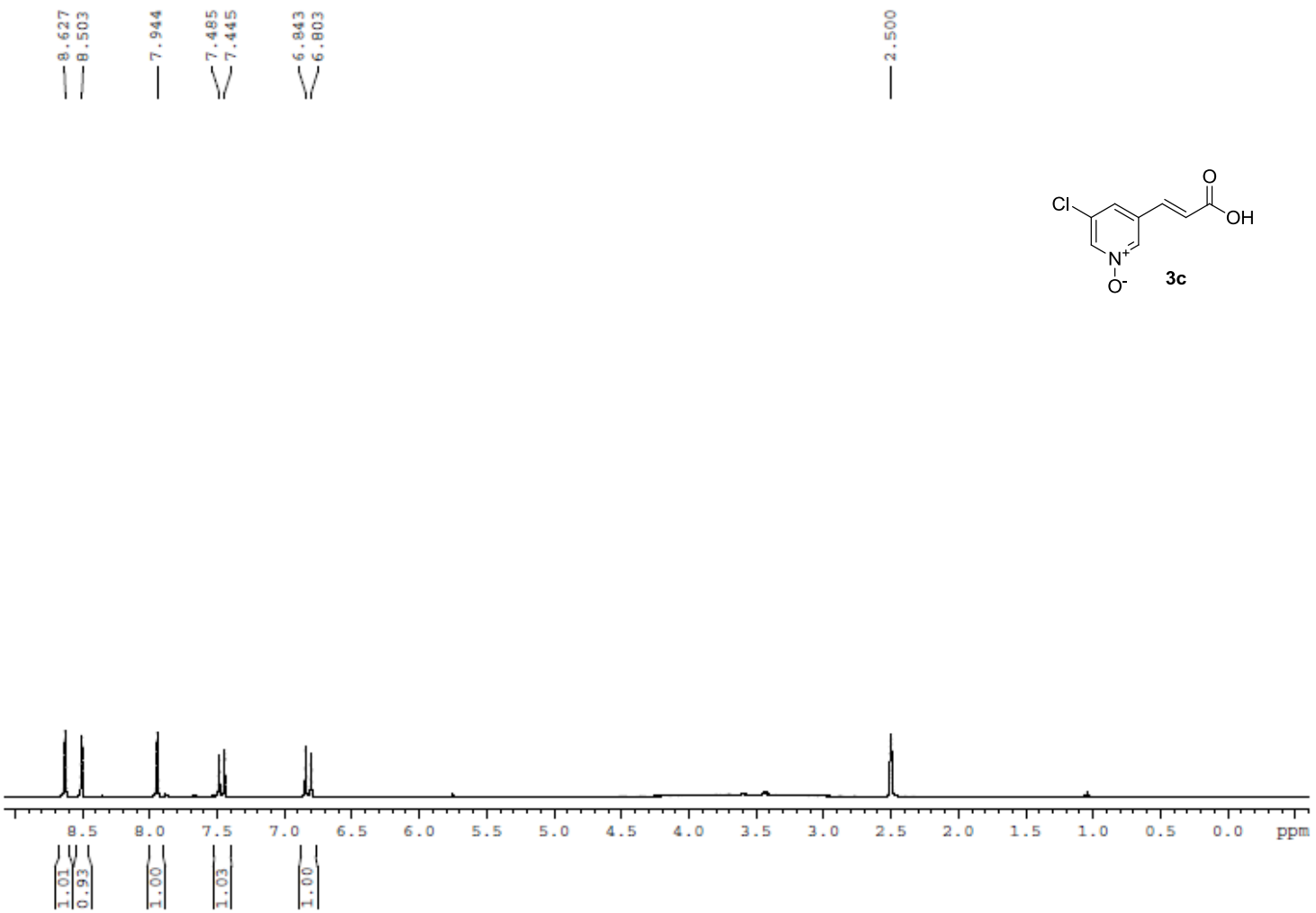
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6.5
6.0
5.5
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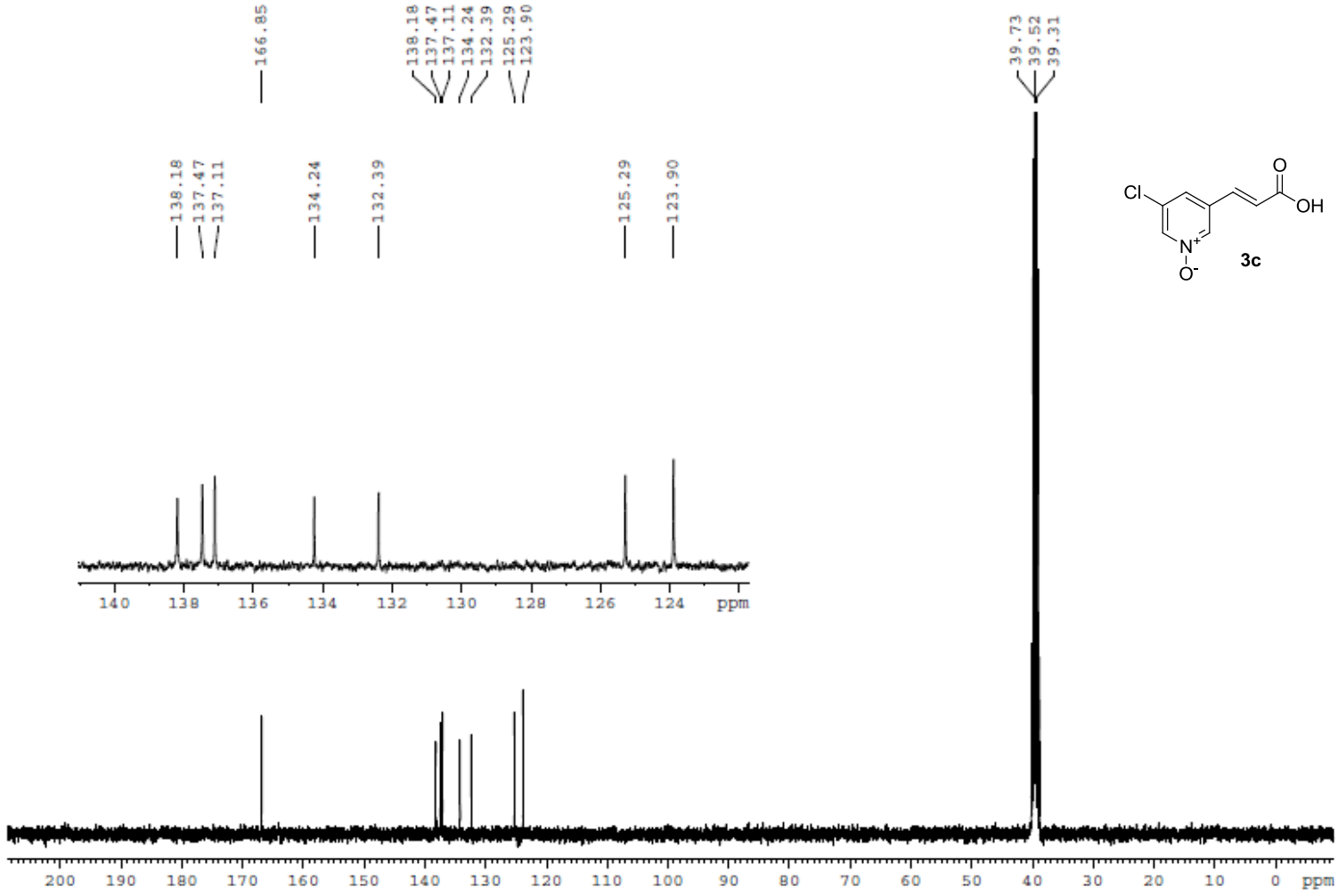
1.00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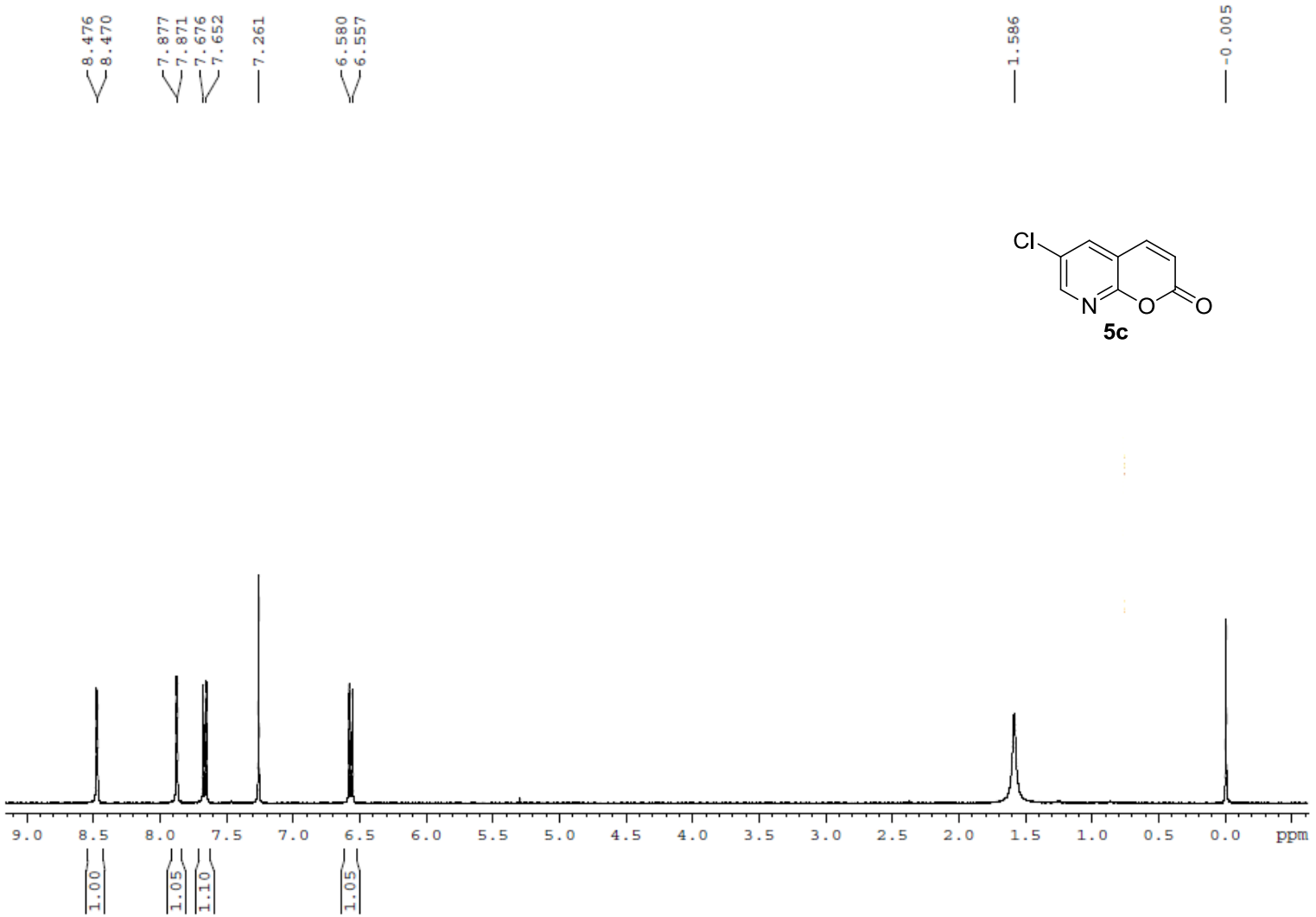
O-
3c
ppm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6.0
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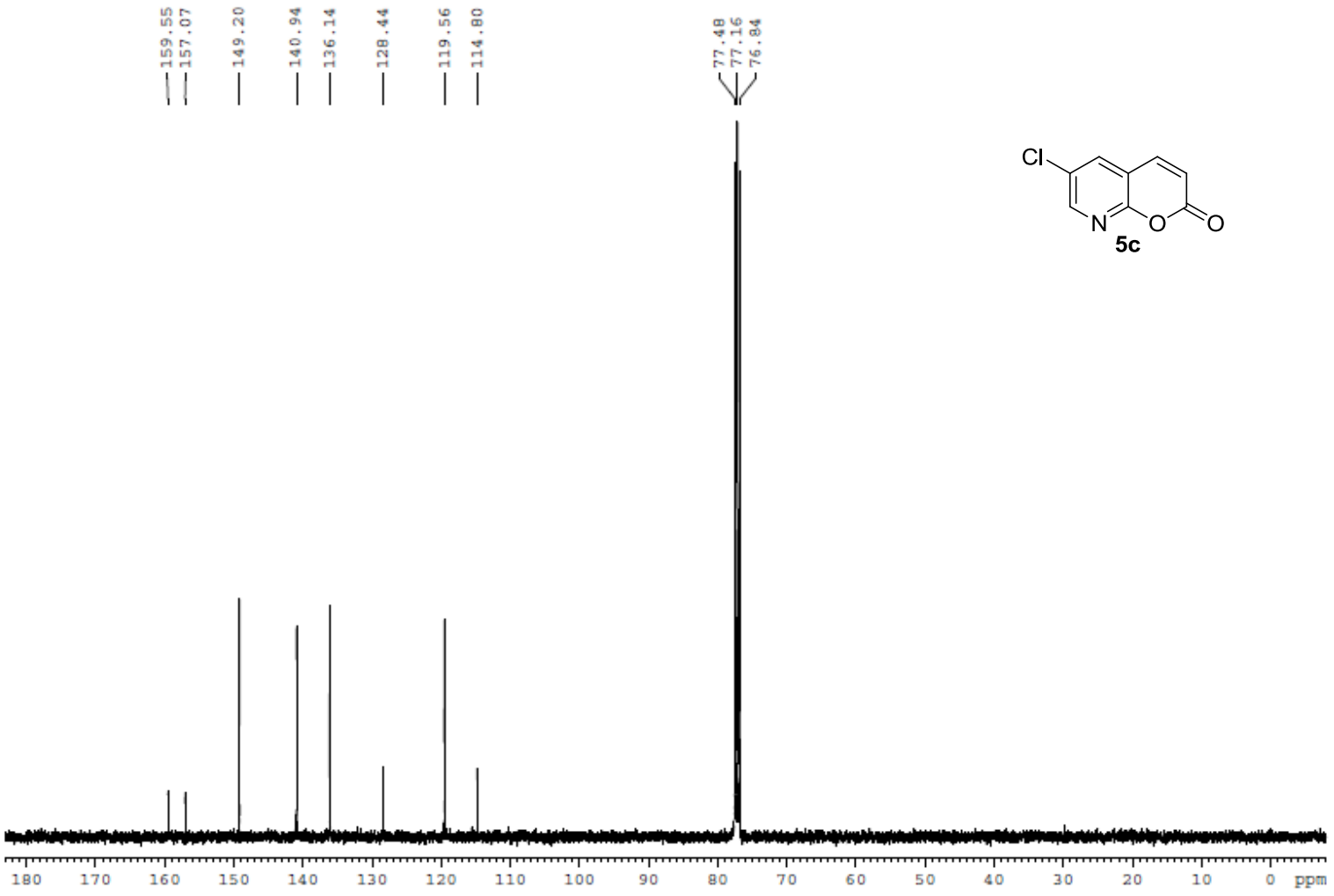
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140
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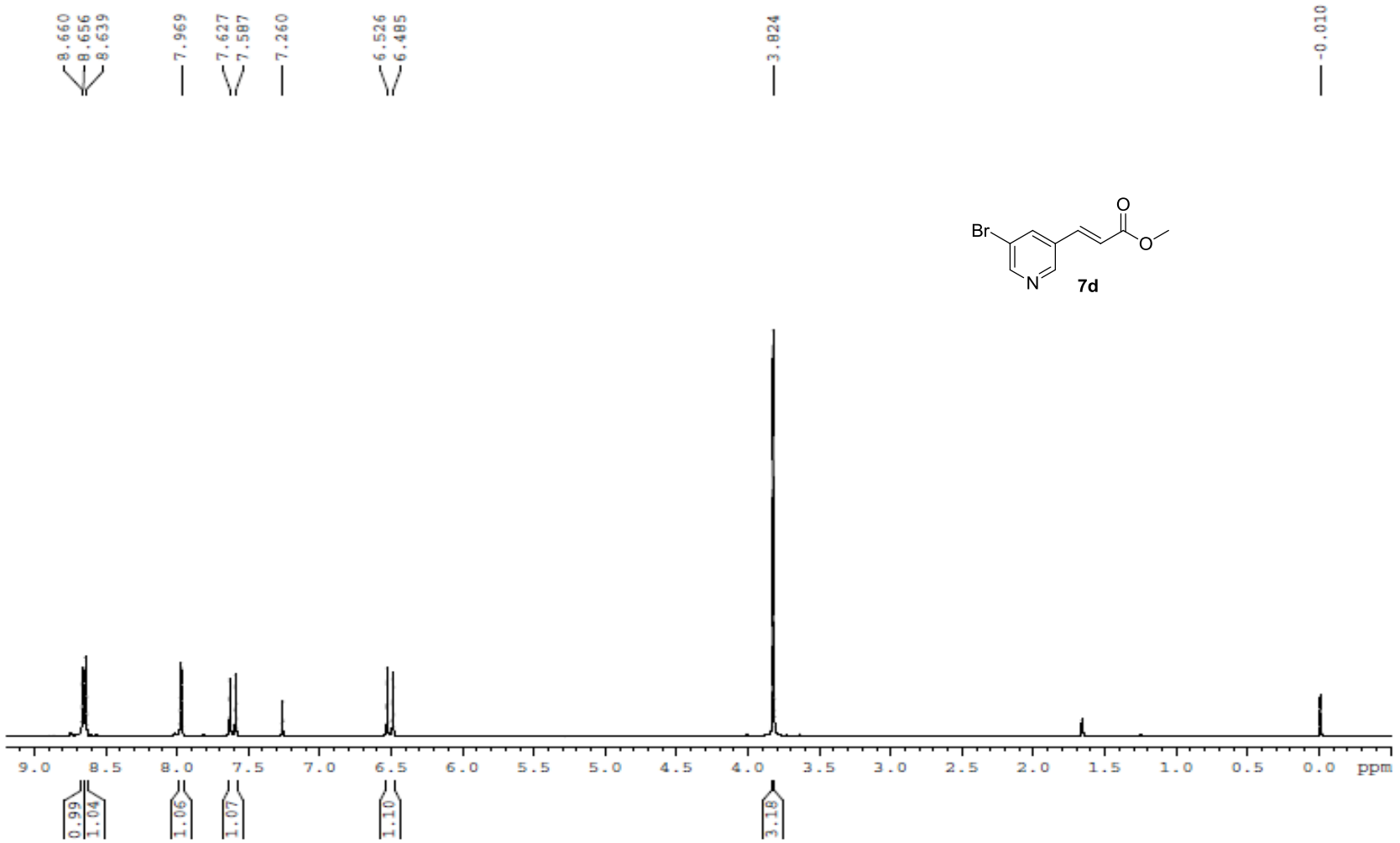
90
80
70
60
50
40
30
20
10
0
ppm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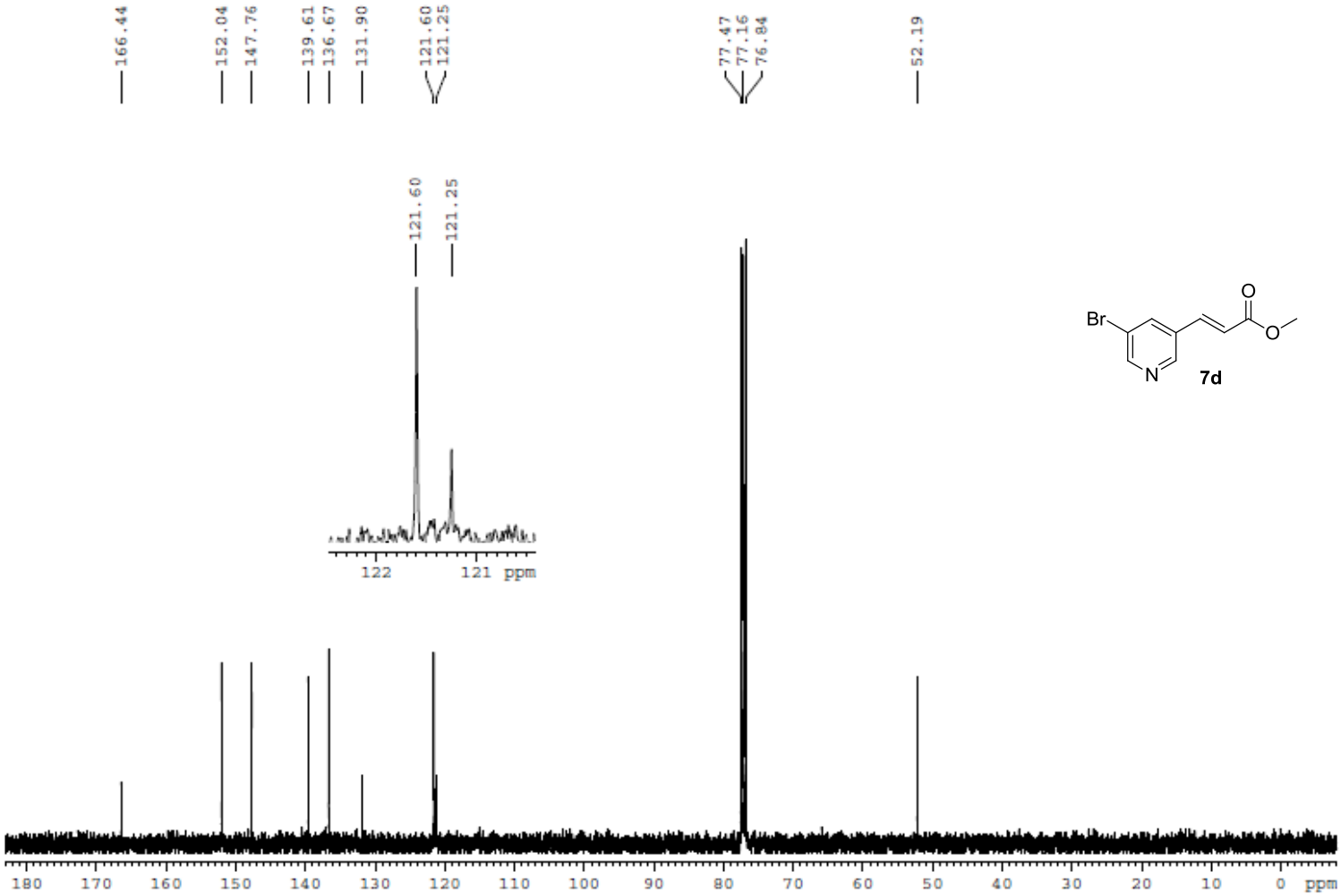
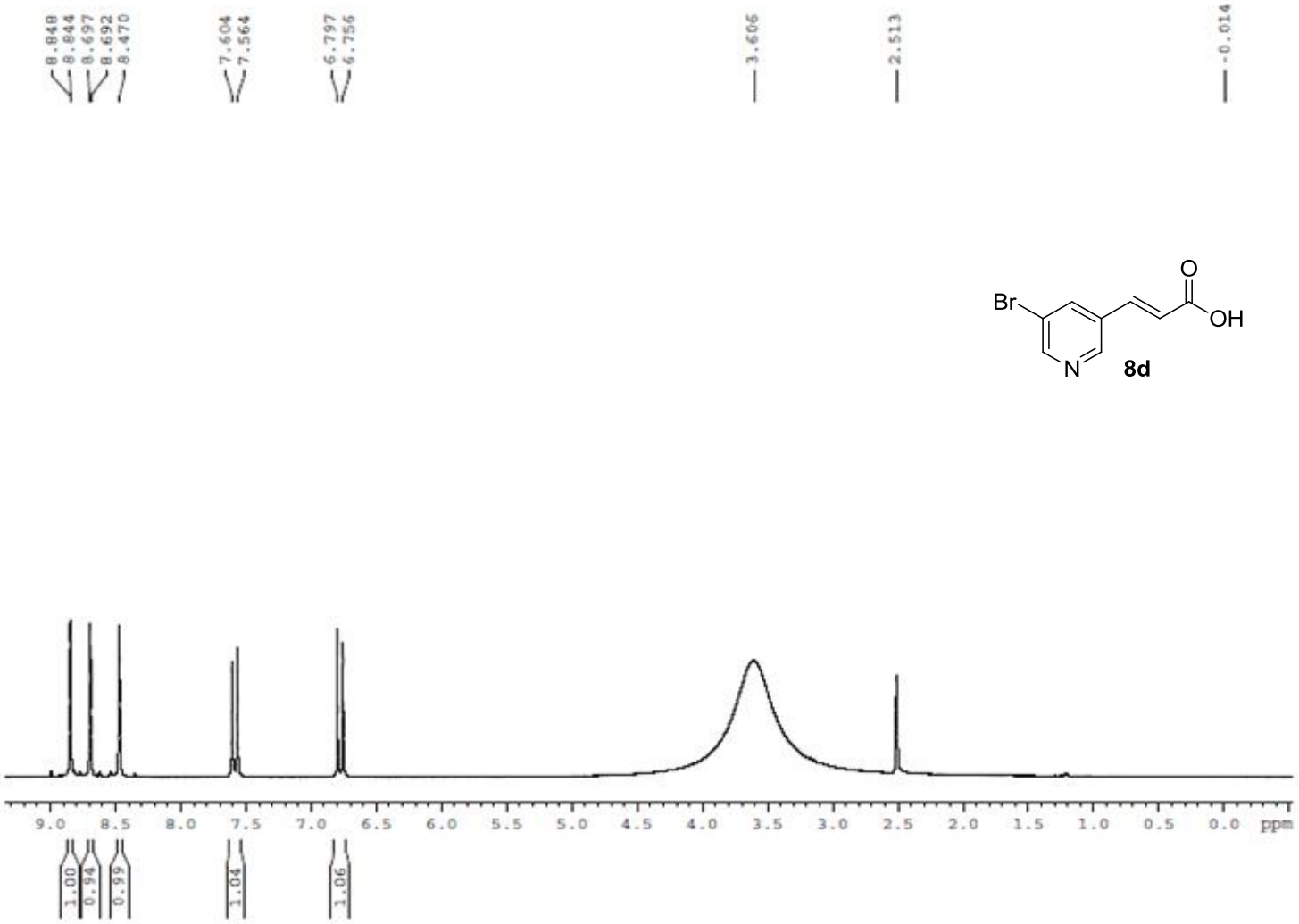
8.656
8.639
7.969
7.627
7.587
7.260
6.526
6.485
3.824
-0.010
Br
O
O
N
7d
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.99
1.04
1.06
1.07
1.10
3.18



DOI: 10.1021/acs.orglett.6b03771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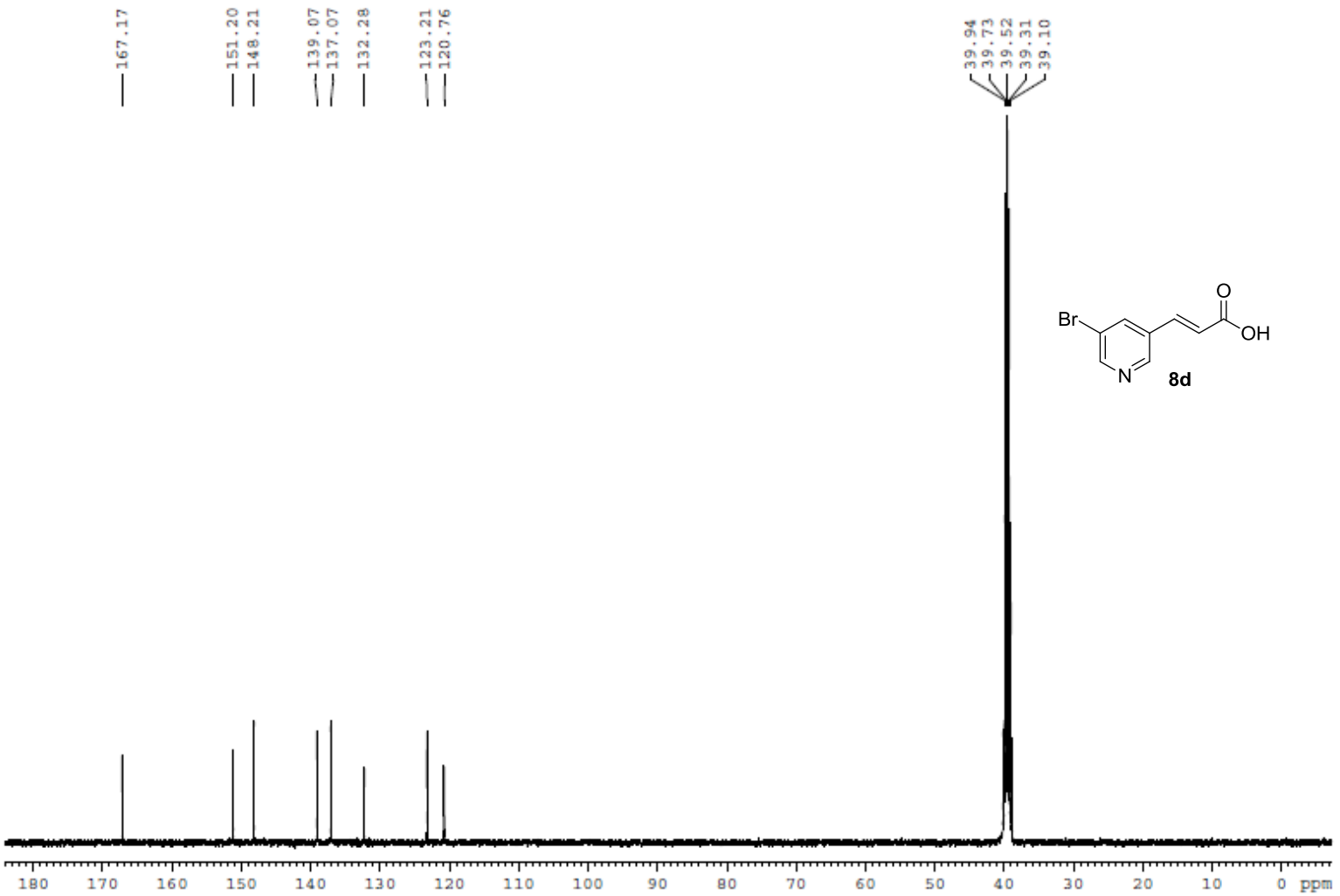
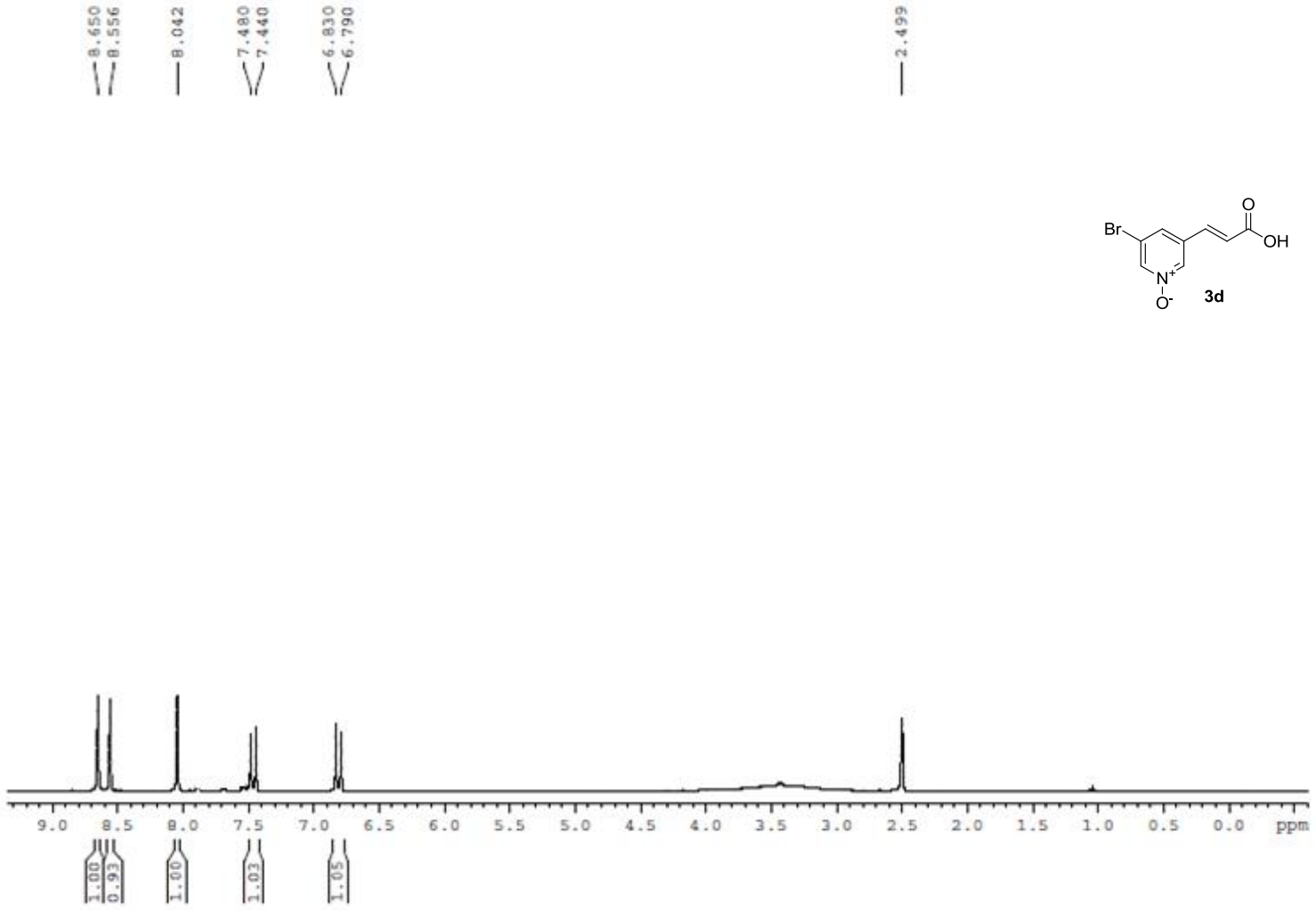
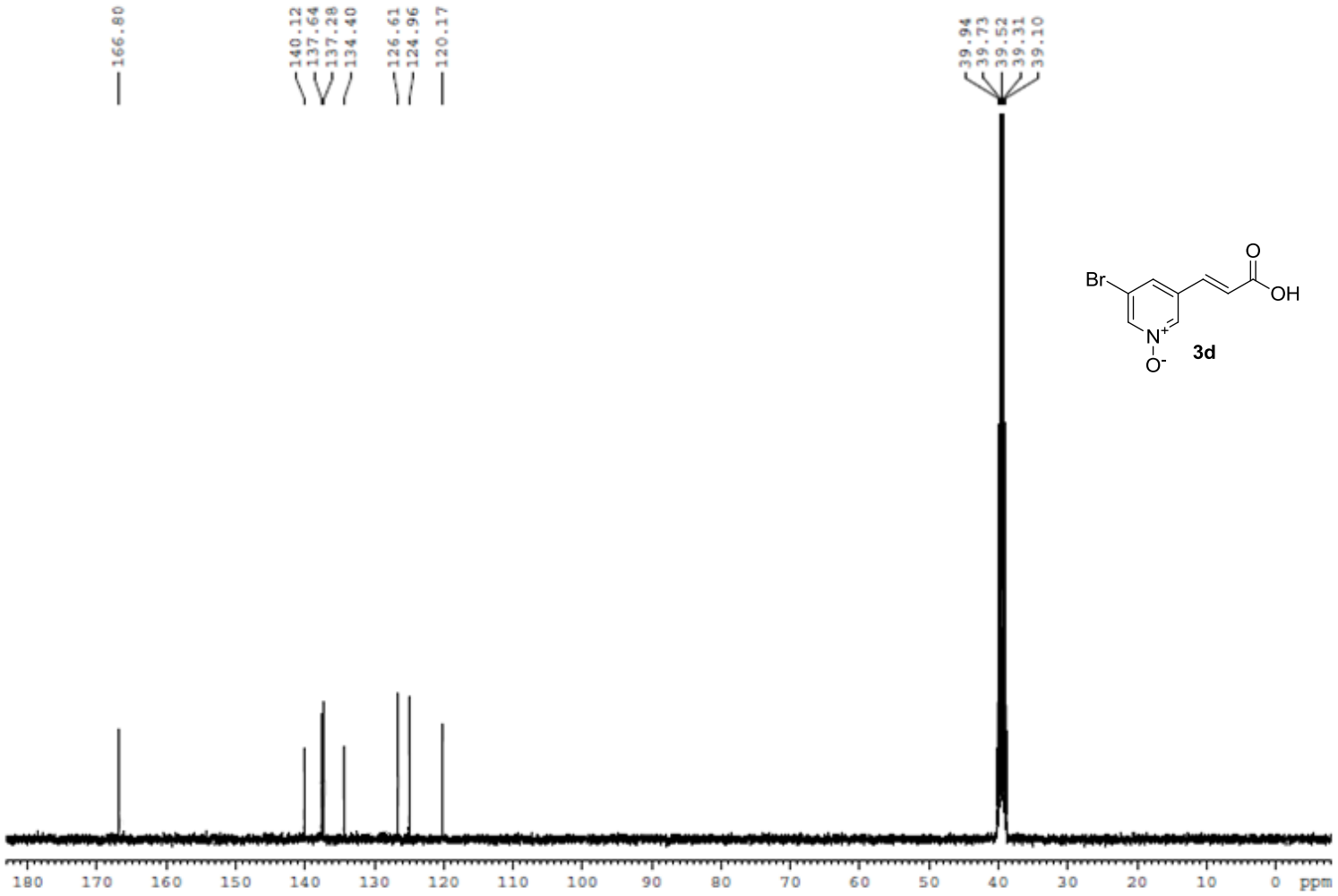
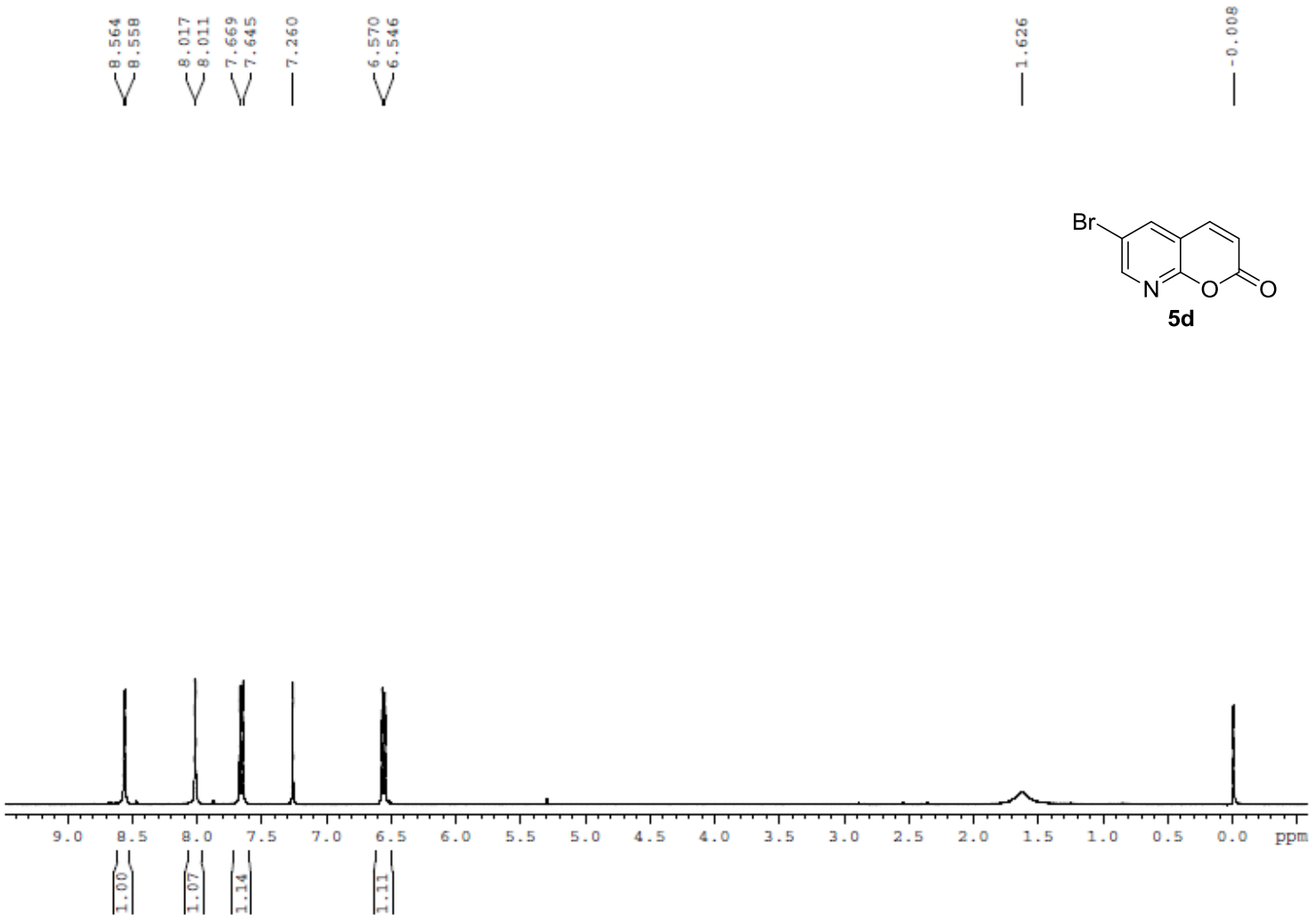
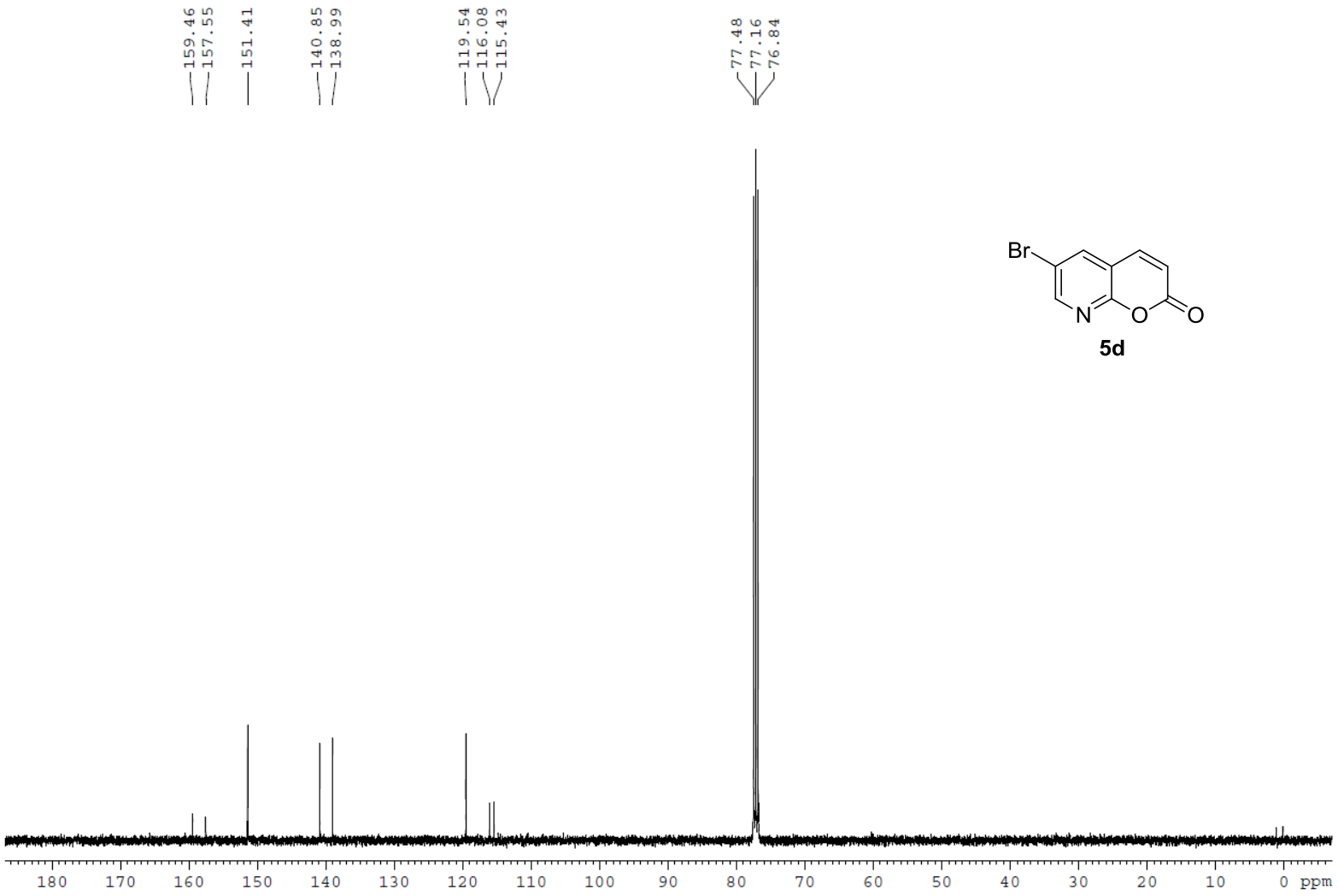
8.844
8.697
8.692
8.470
7.604
7.564
6.797
6.756
3.606
2.513
-0.014
Br
O
OH
N
8d
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
0.94
0.99
1.04
1.06


167.17
151.20
148.21
139.07
137.07
132.28
123.21
120.76
39.94
39.73
39.52
39.31
39.10
Br
N
O
OH
8d
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

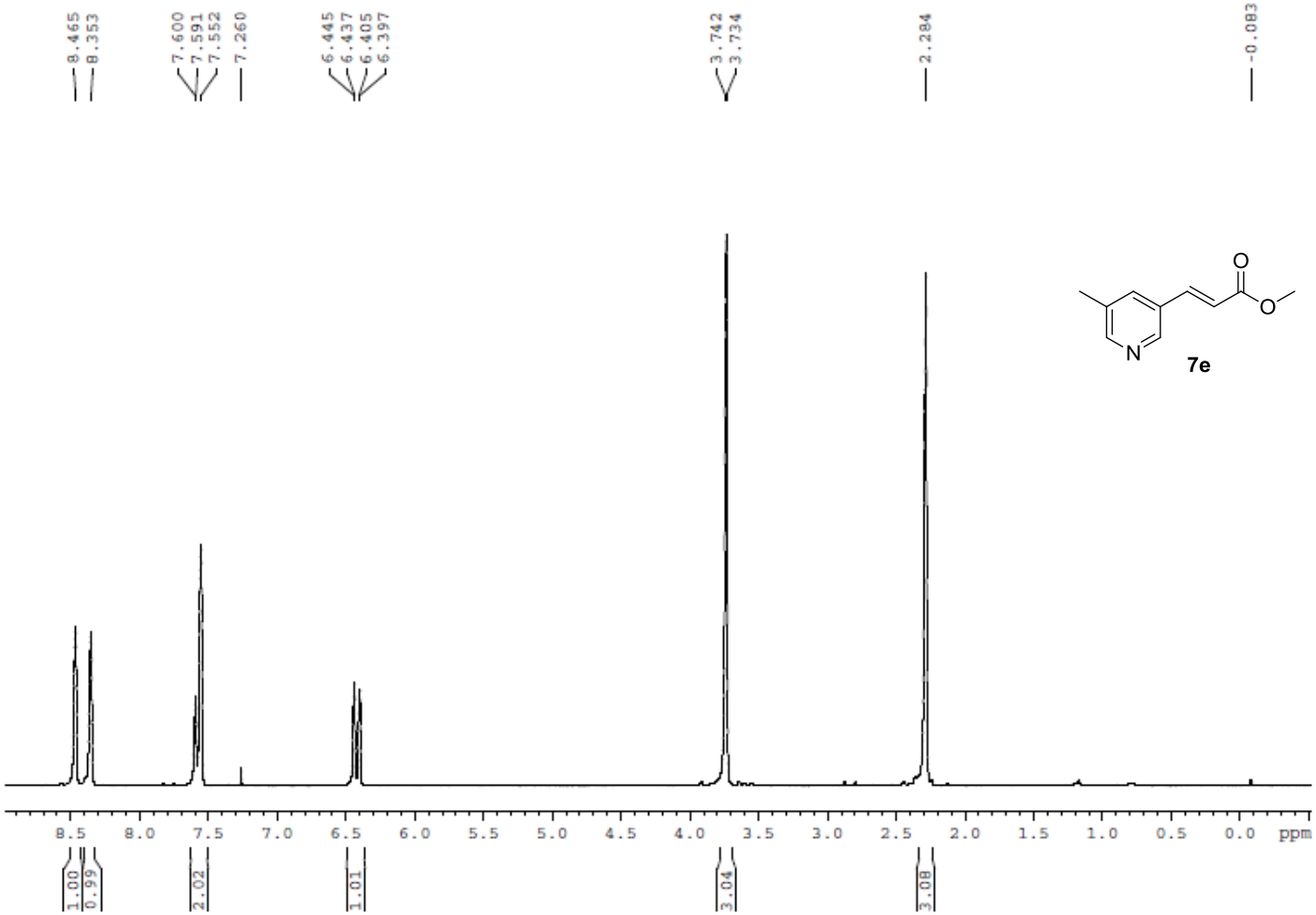

8.650
8.556
8.042
7.480
7.440
6.830
6.790
2.499
Br
O
OH
N+
O-
3d
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
0.93
1.00
1.03
1.05

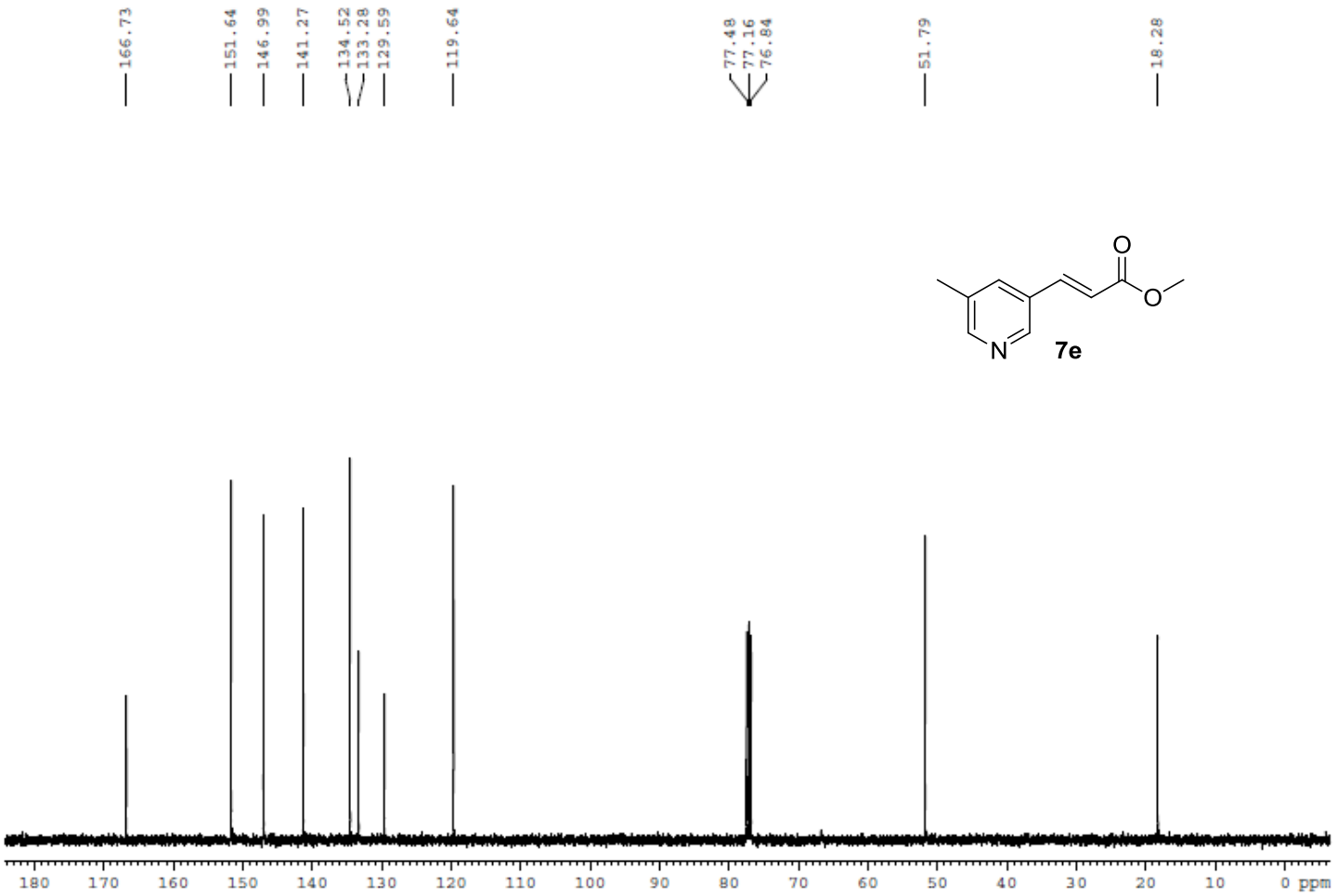

166.80
140.12
137.64
137.28
134.40
126.61
124.96
120.17
39.94
39.73
39.52
39.31
39.10
Br
O
OH
N+
O-
3d
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


8.564
8.558
8.017
8.011
7.669
7.645
7.260
6.570
6.546
1.626
-0.008
Br
N
O
O
5d
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.07
1.14
1.11

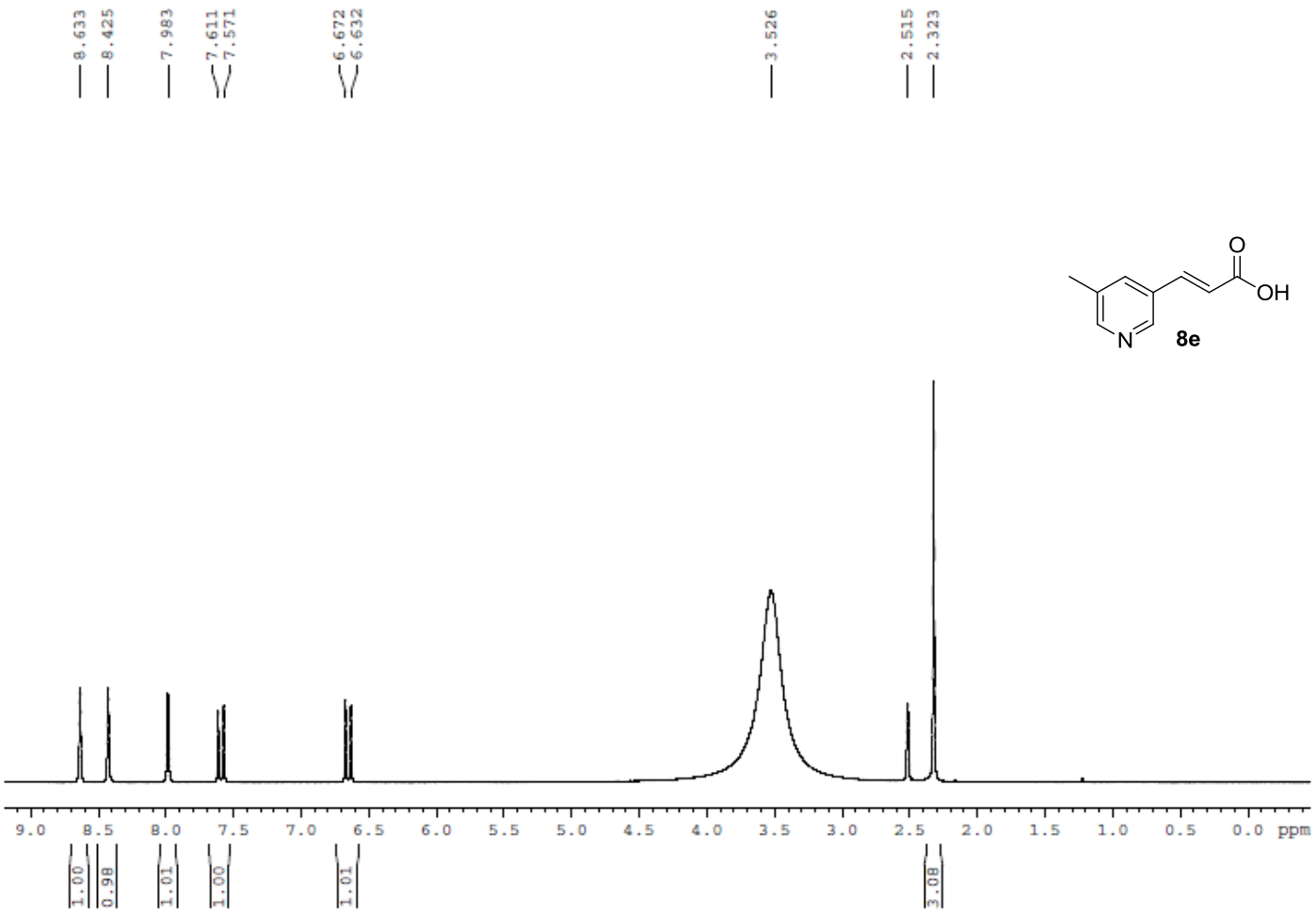

159.46
157.55
151.41
140.85
138.99
119.54
116.08
115.43
77.48
77.16
76.84
Br
N
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

5d

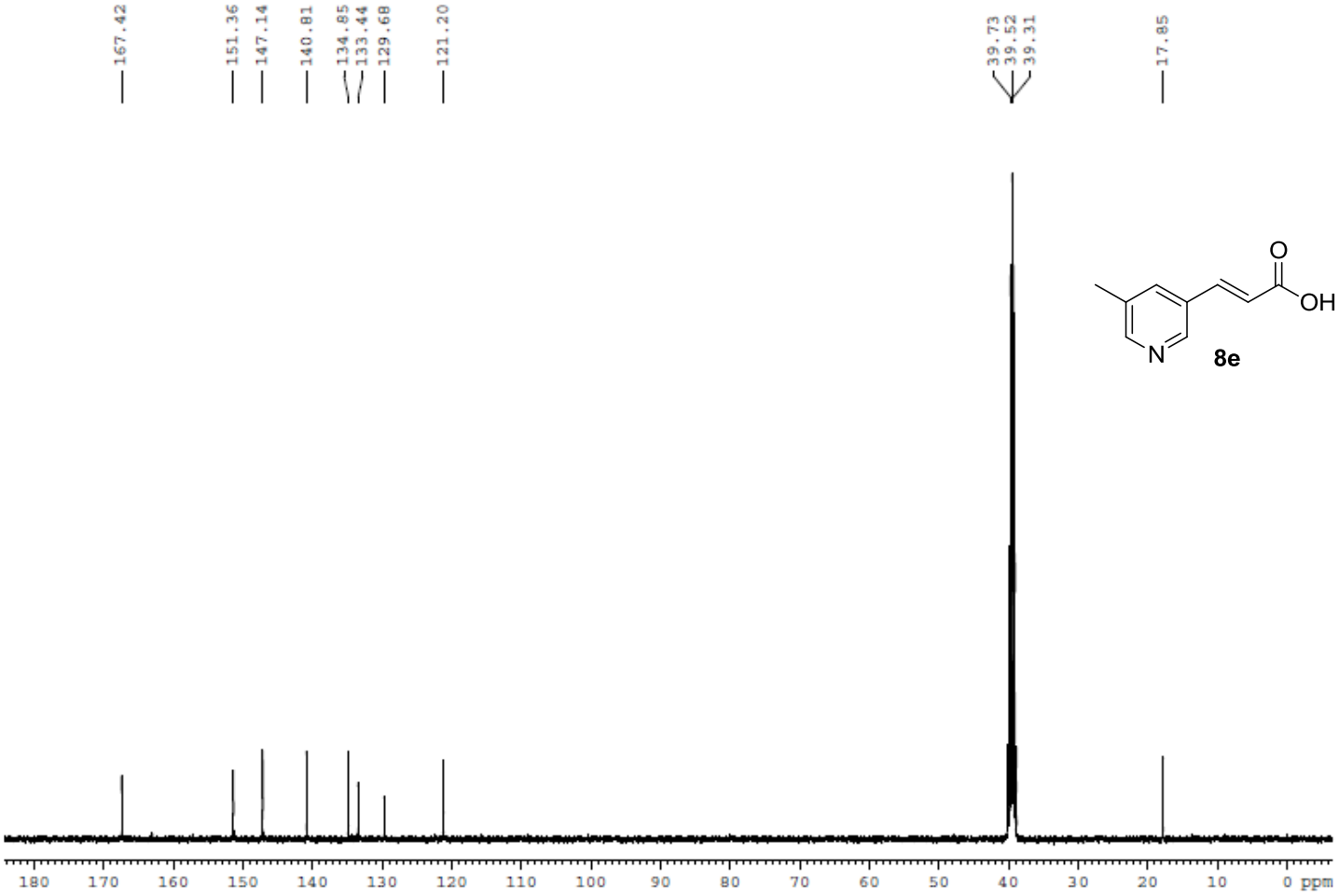

8.465
8.353
7.600
7.591
7.552
7.260
6.445
6.437
6.405
6.397
3.742
3.734
2.284
-0.083
O
O
N
7e
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
0.99
2.02
1.01
3.04
3.08

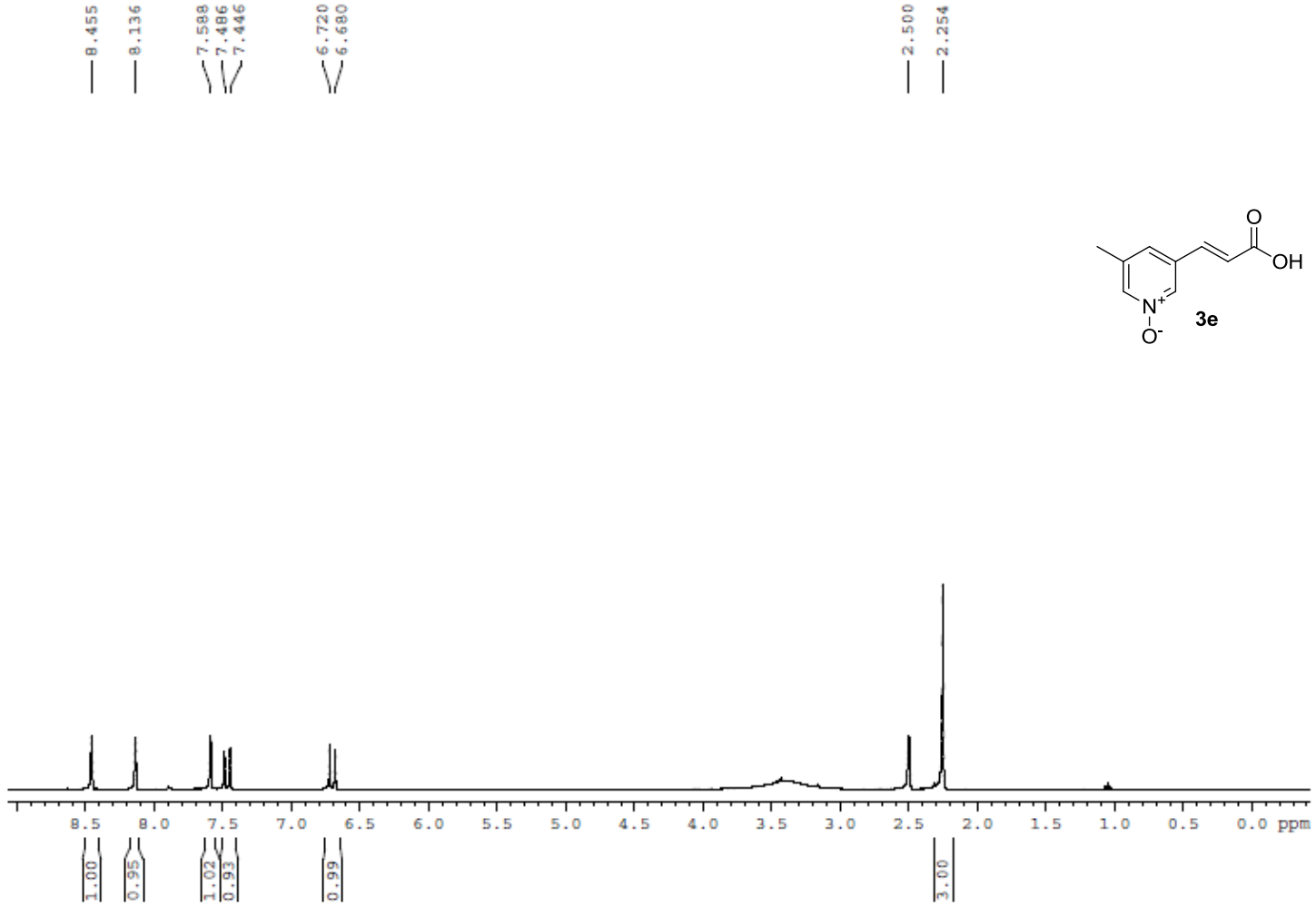


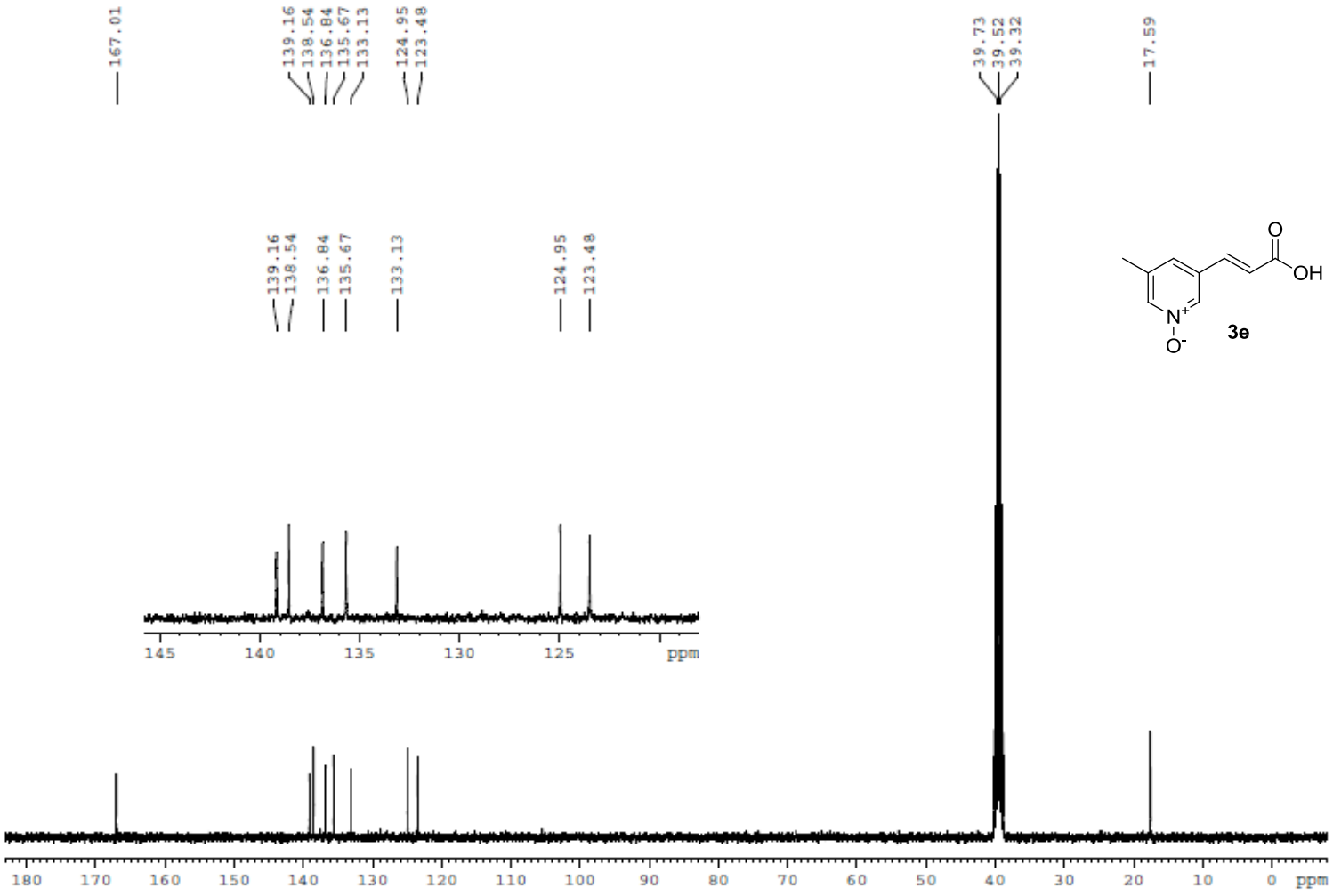
DOI: 10.1021/acs.orglett.6b03771



DOI: 10.1021/acs.orglett.6b03771


167.42
151.36
147.14
140.81
134.85
133.44
129.68
121.20
39.73
39.52
39.31
17.85
O
OH
N
8e
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


8.455
8.136
7.588
7.486
7.446
6.720
6.680
2.500
2.254
O
OH
N+
O-
3e
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
1.00
0.95
1.02
0.93
0.99
3.00



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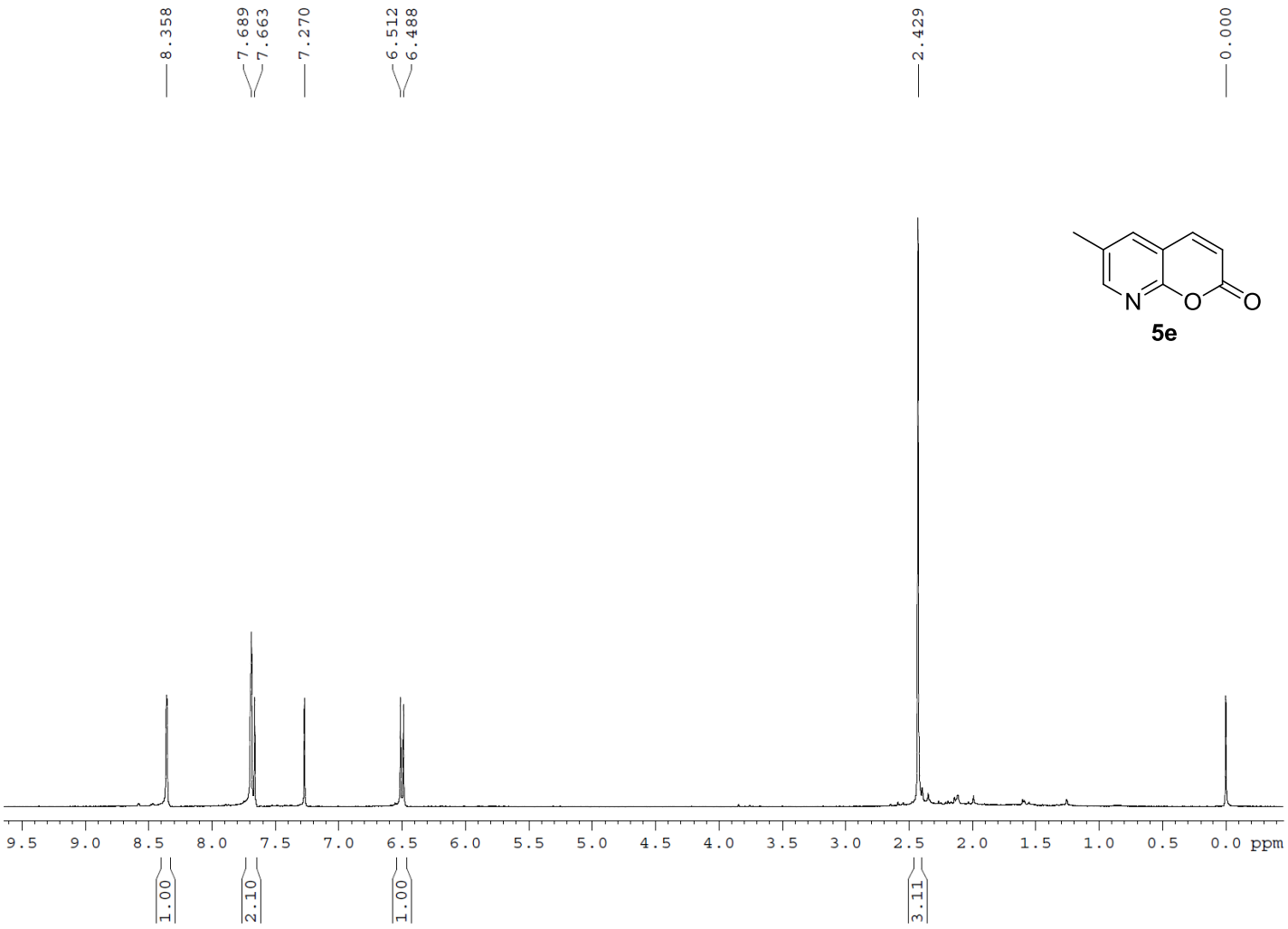

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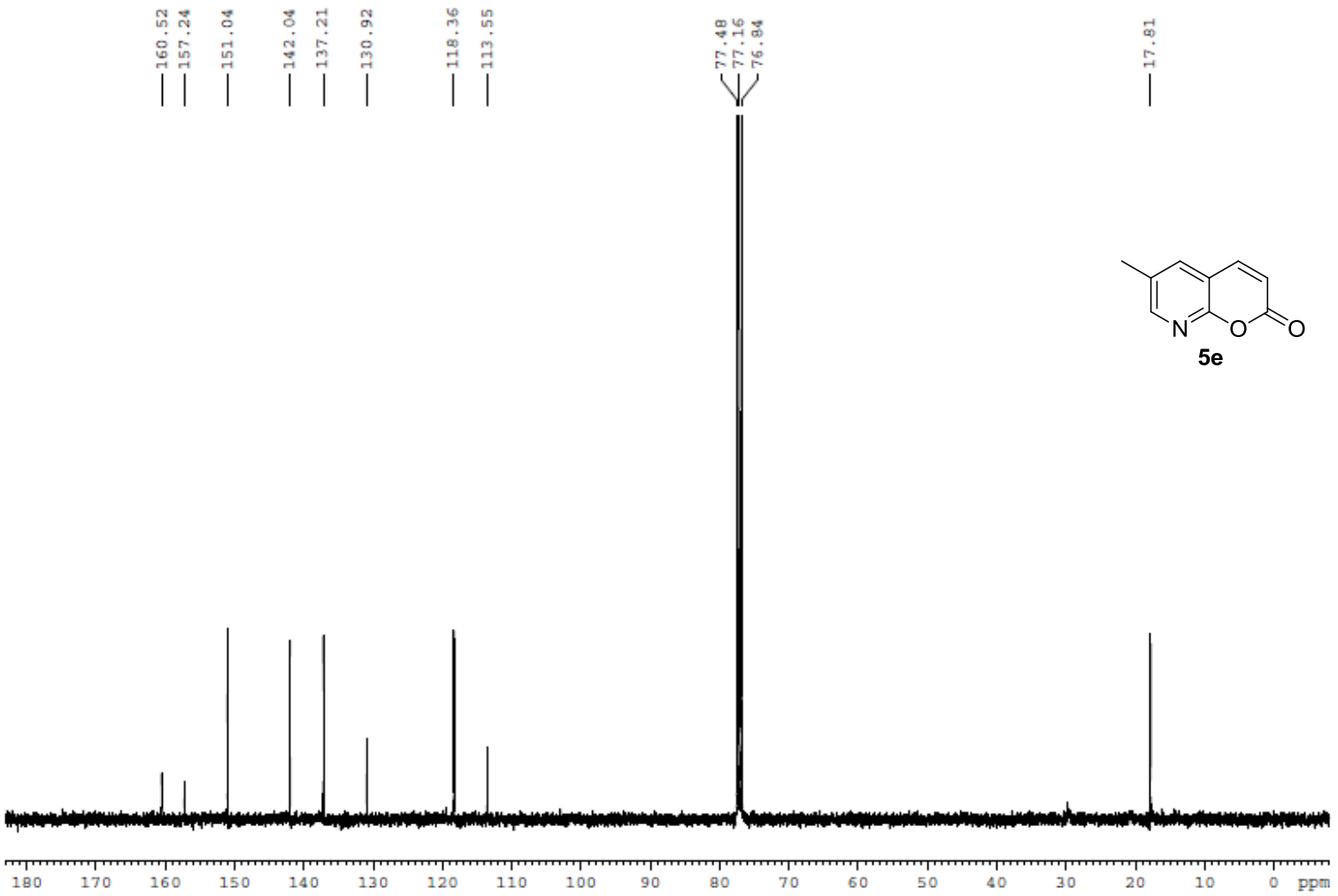
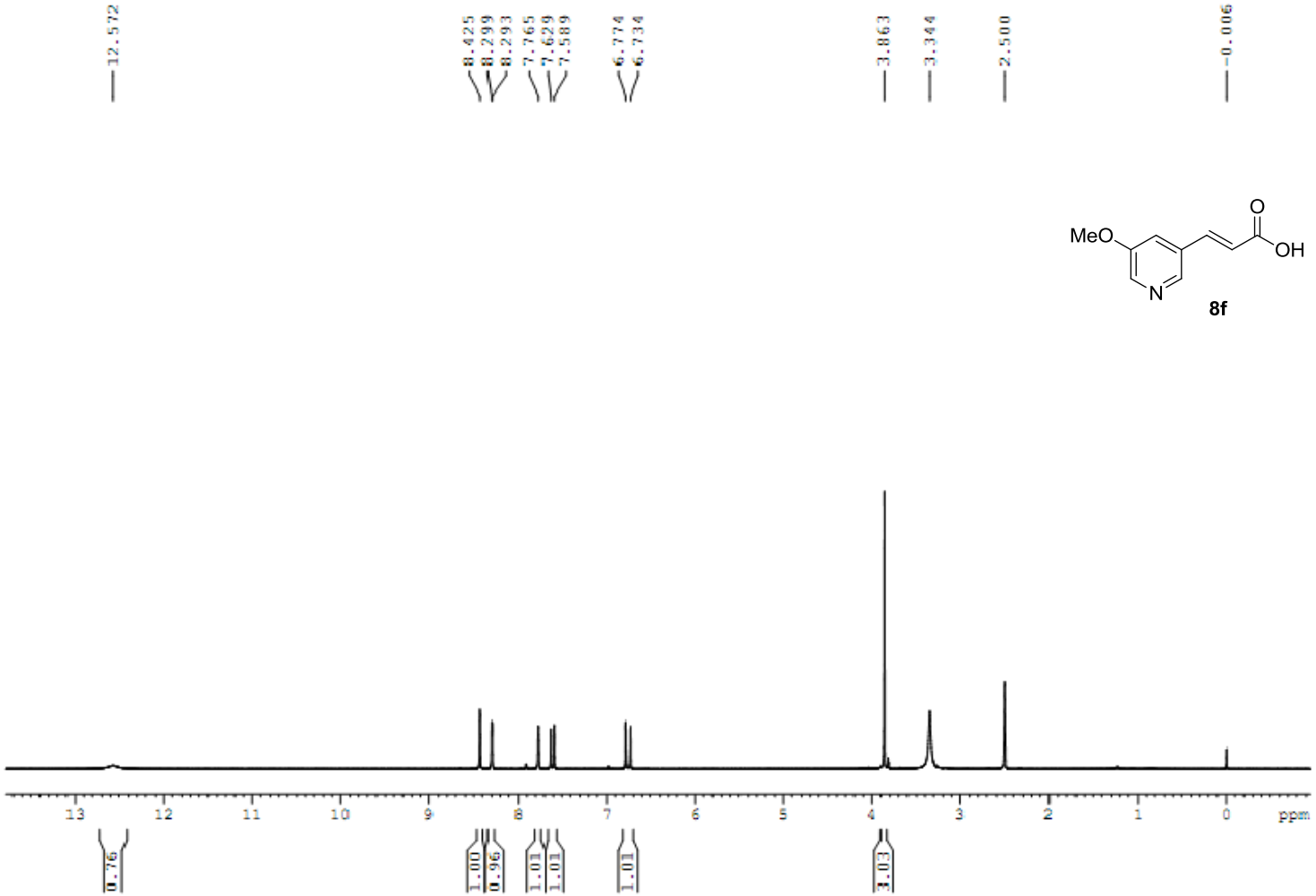
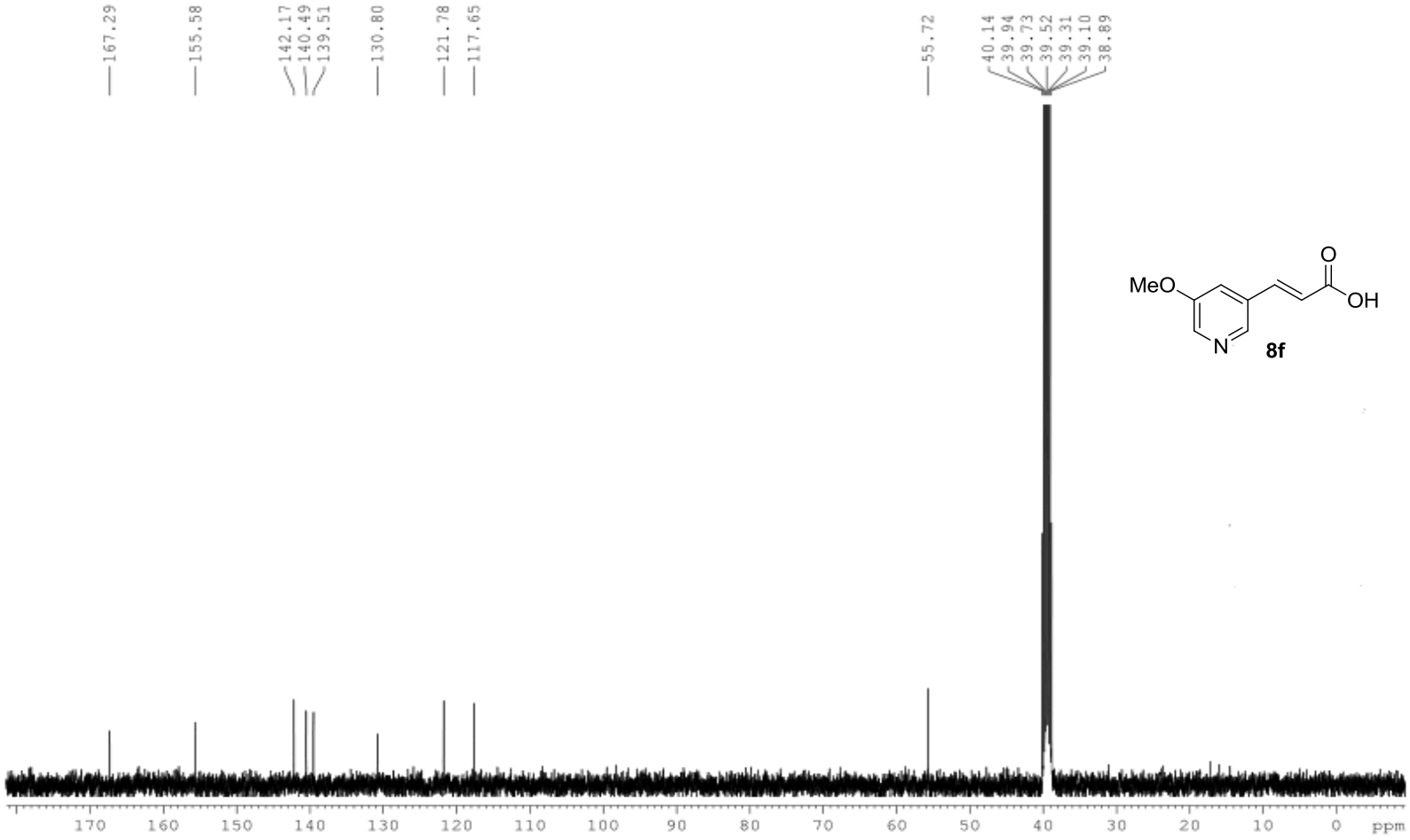
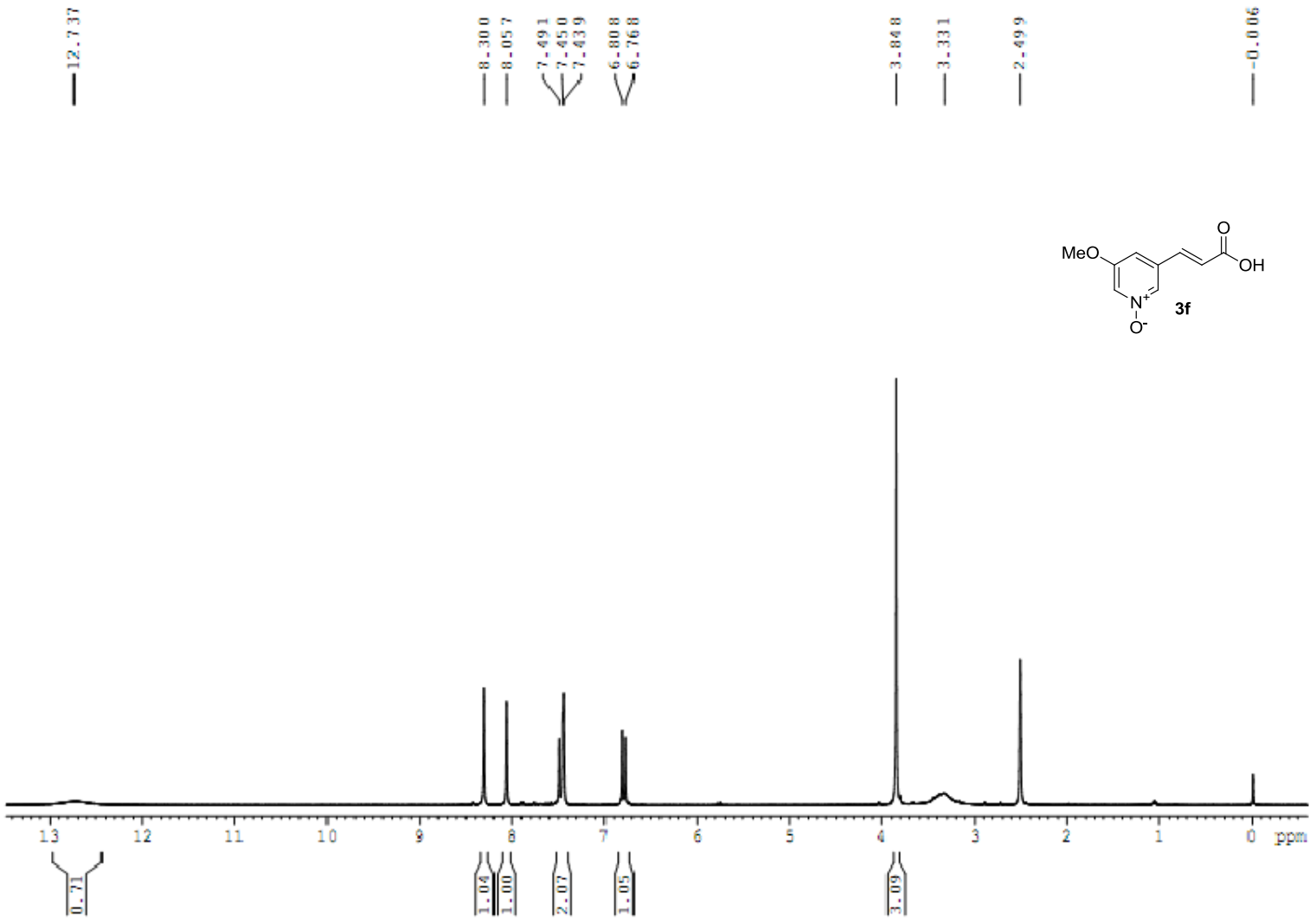

160.52
157.24
151.04
142.04
137.21
130.92
118.36
113.55
77.48
77.16
76.84
17.81
N
O
O
5e
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


12.572
8.425
8.299
8.293
7.765
7.629
7.589
6.774
6.734
3.863
3.344
2.500
0.006
MeO
O
OH
N
8f
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.76
1.00
0.96
1.03
1.03
1.01
3.03


167.29
155.58
142.17
140.49
139.51
130.80
121.78
117.65
55.72
40.14
39.94
39.73
39.52
39.31
39.10
38.89
MeO
O
OH
N
8f
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



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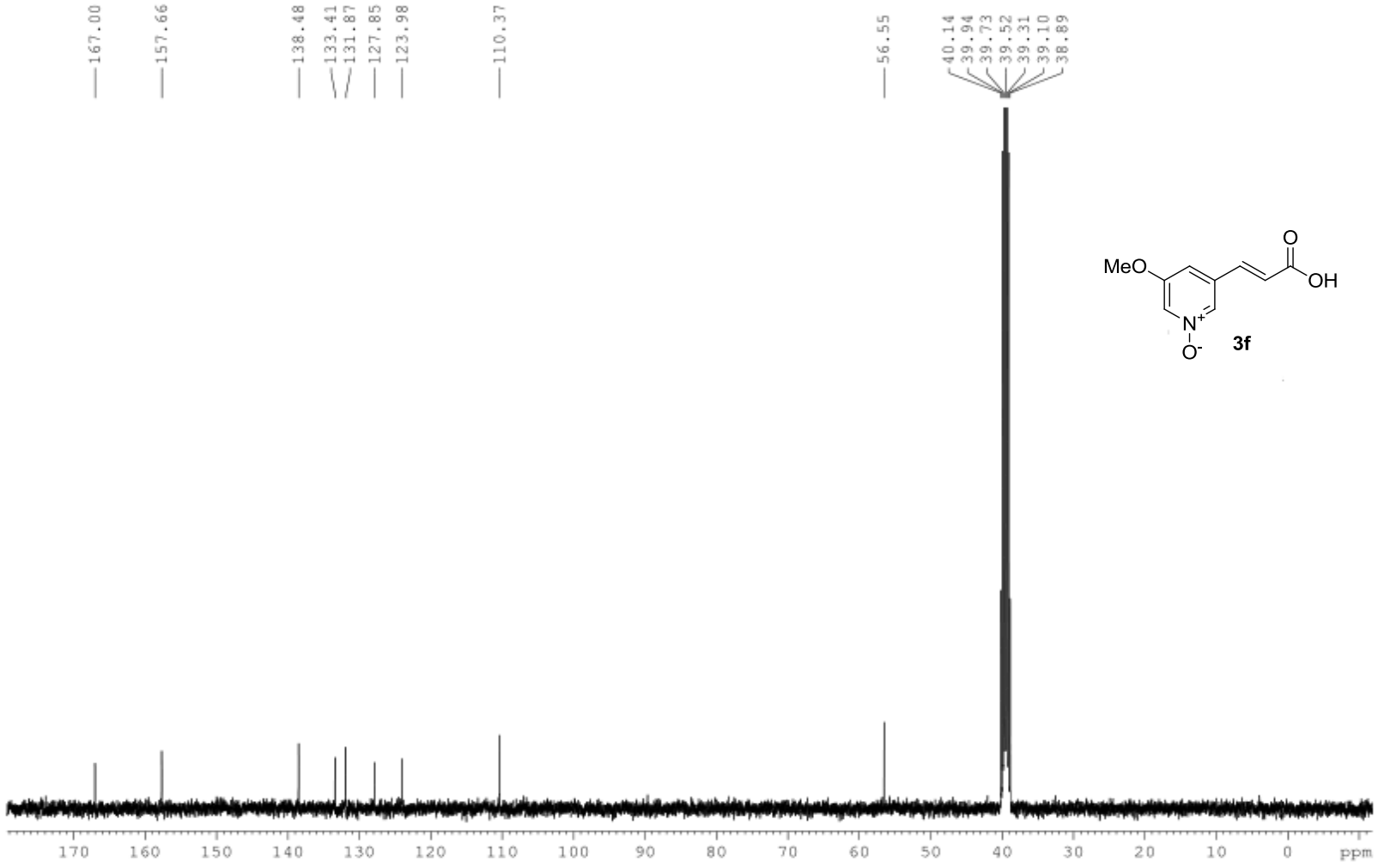
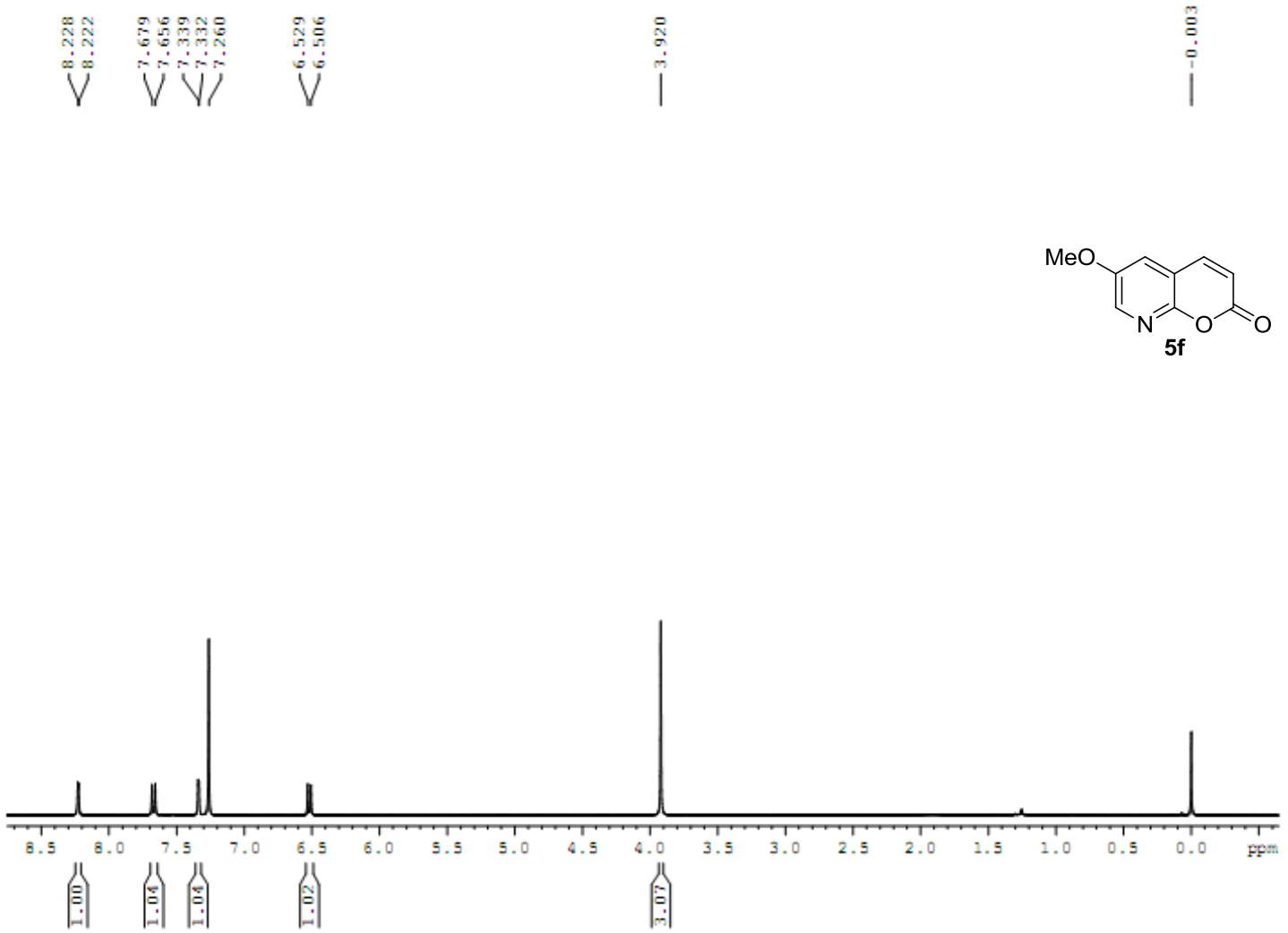
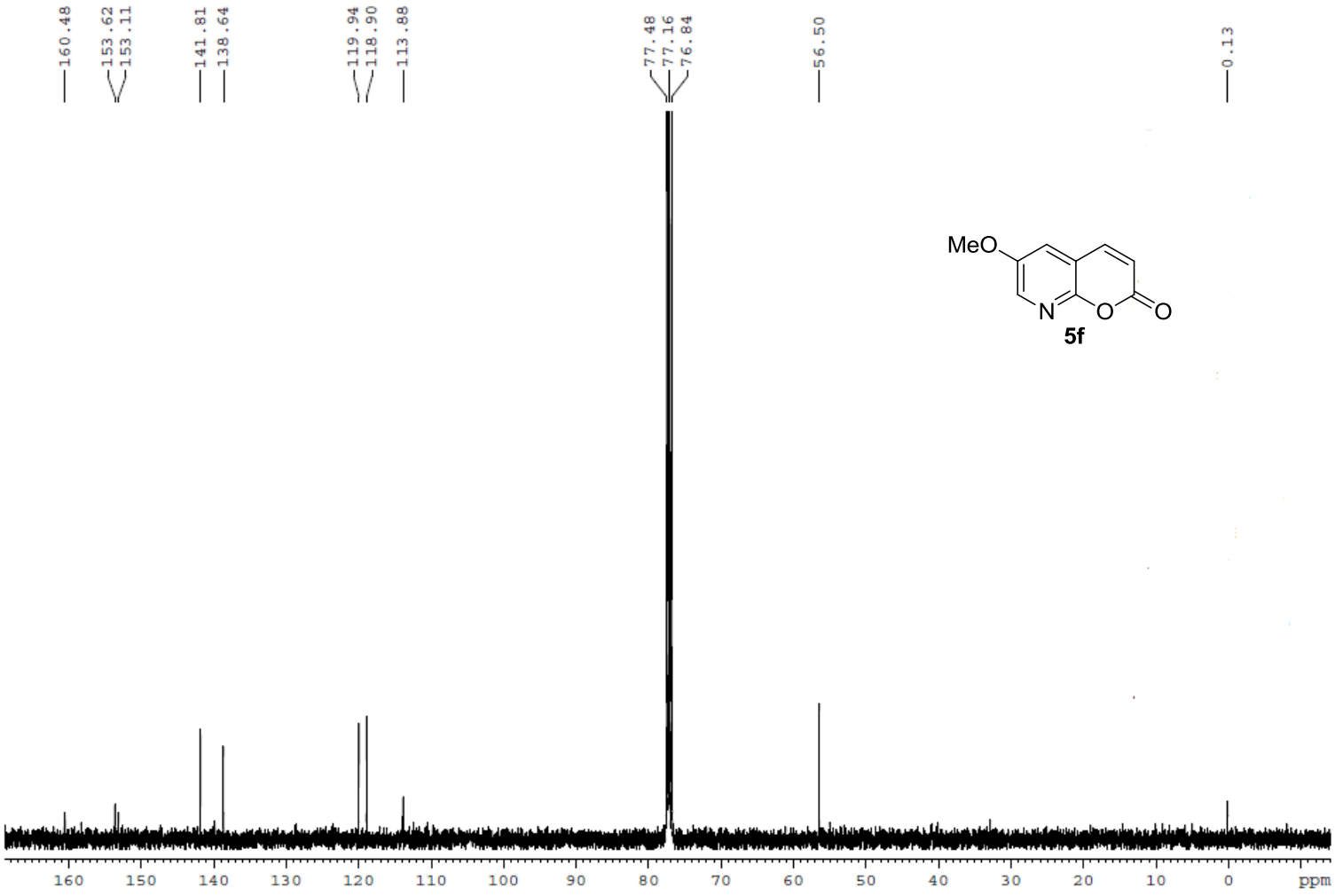
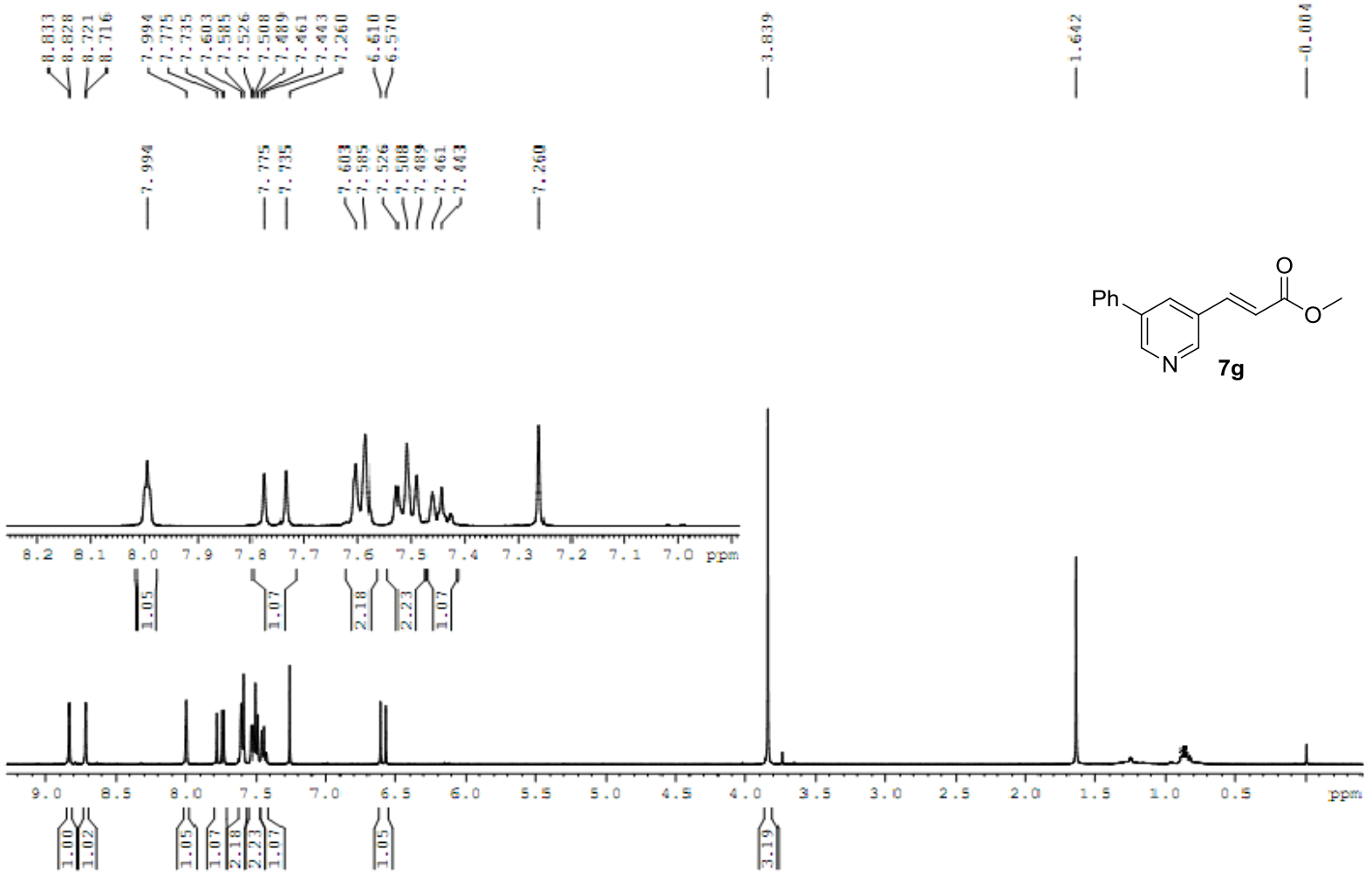

167.00
157.66
138.48
133.41
131.87
127.85
123.98
110.37
56.55
40.14
39.94
39.73
39.52
39.31
39.10
38.89
MeO
O
OH
N+
O-
3f
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


8.228
8.222
7.679
7.656
7.339
7.332
7.260
6.529
6.506
3.920
-0.003
MeO
N
O
O
5f
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.04
1.04
1.02
3.07


160.48
153.62
153.11
141.81
138.64
119.94
118.90
113.88
77.48
77.16
76.84
56.50
0.13
MeO
N
O
O
5f
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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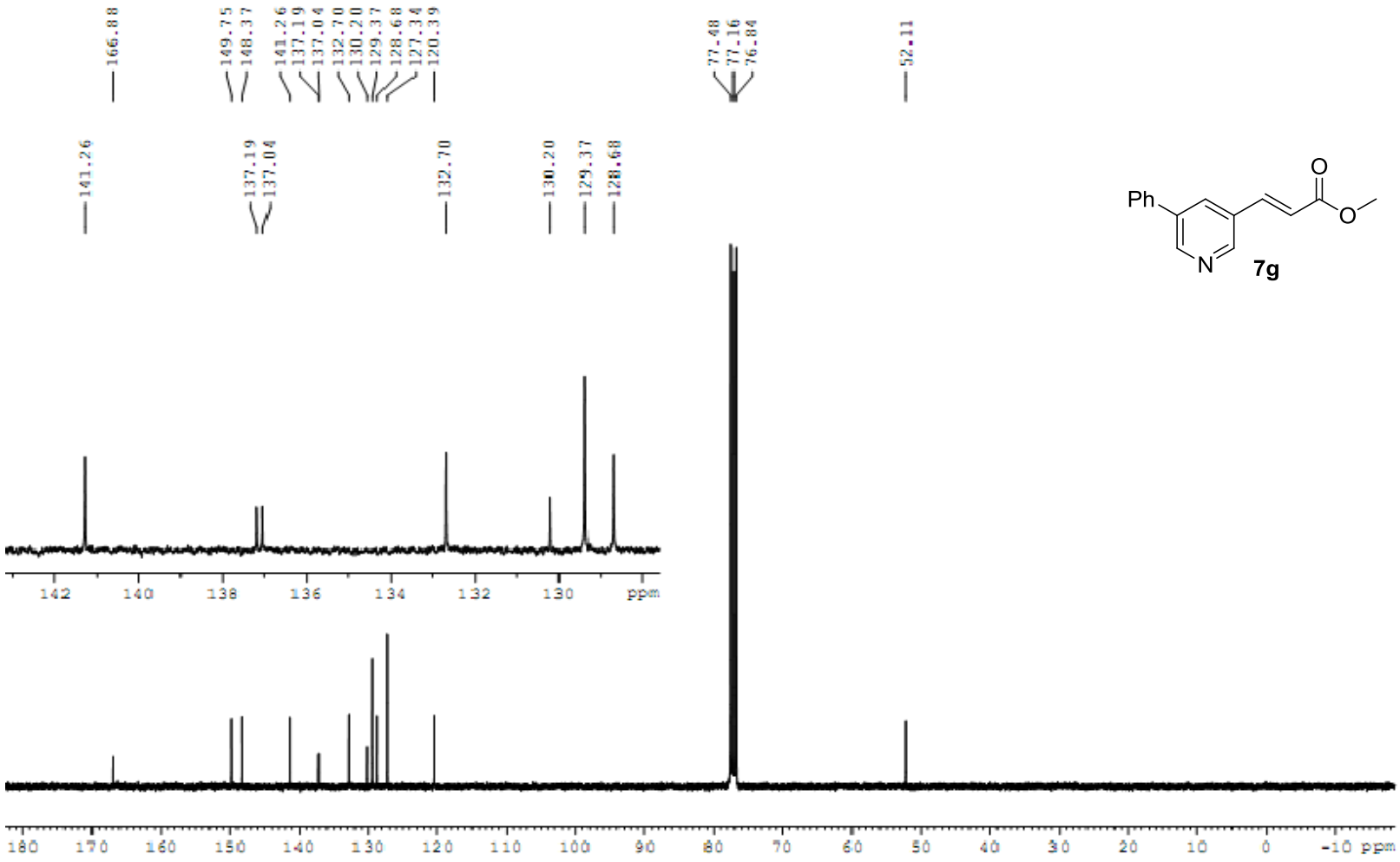
8.828
8.721
8.716
7.994
7.775
7.735
7.603
7.585
7.526
7.508
7.489
7.461
7.443
7.260
6.610
6.570
3.839
1.642
-0.004
Ph
O
O
N
7g
ppm
1.05
1.07
2.18
2.23
1.07
3.00
1.02
1.05
1.07
2.18
2.23
1.07
1.05
3.19



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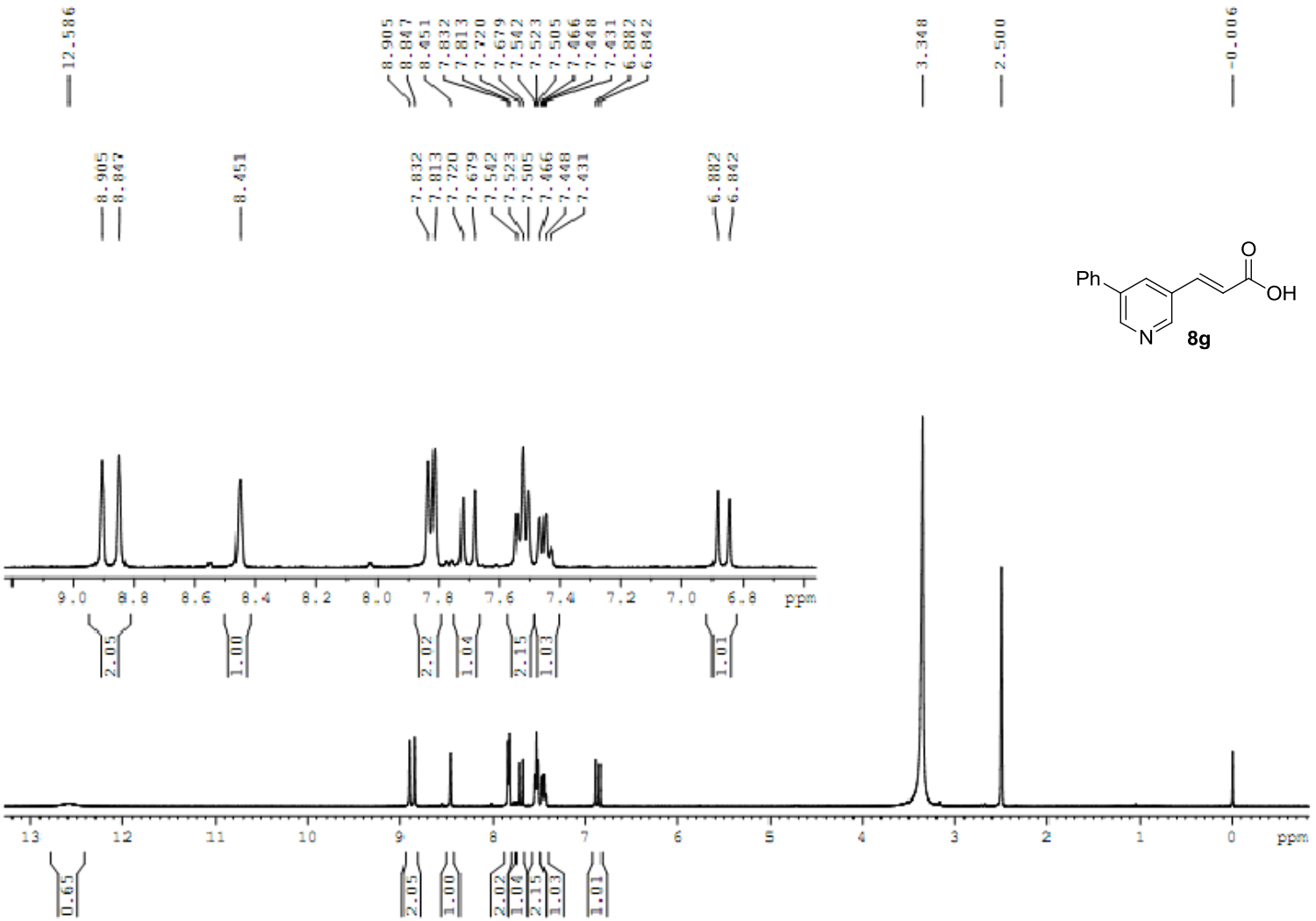
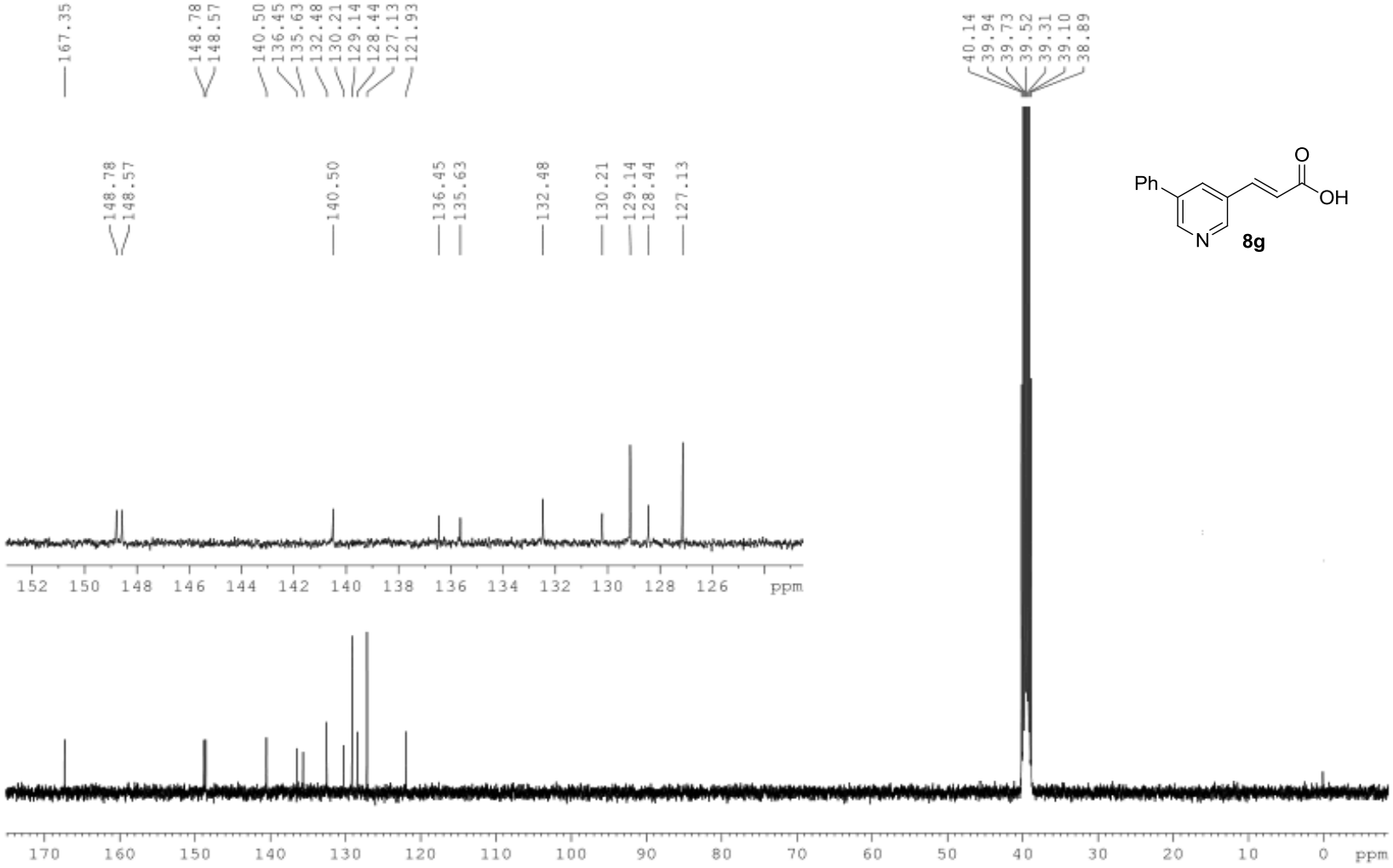
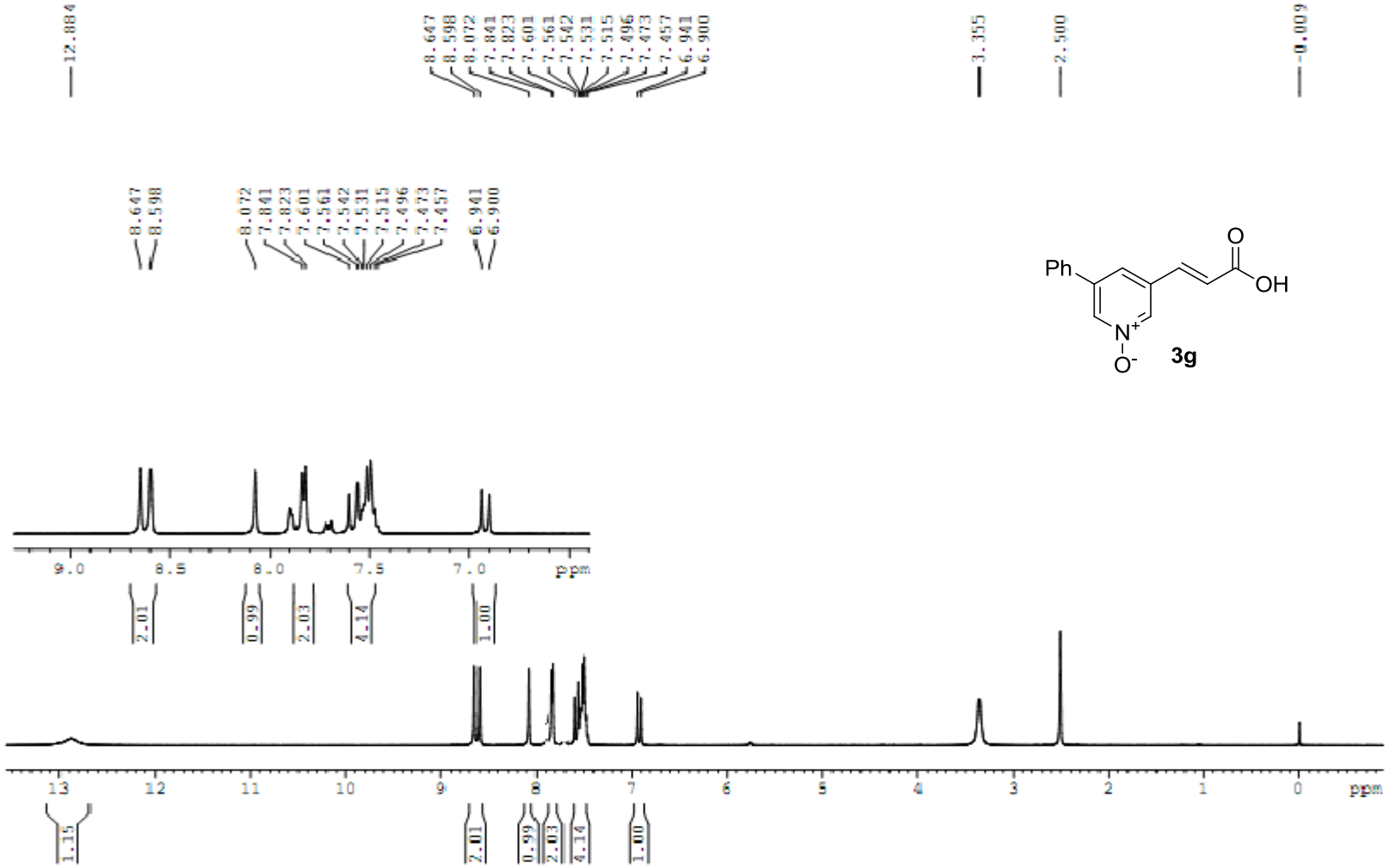
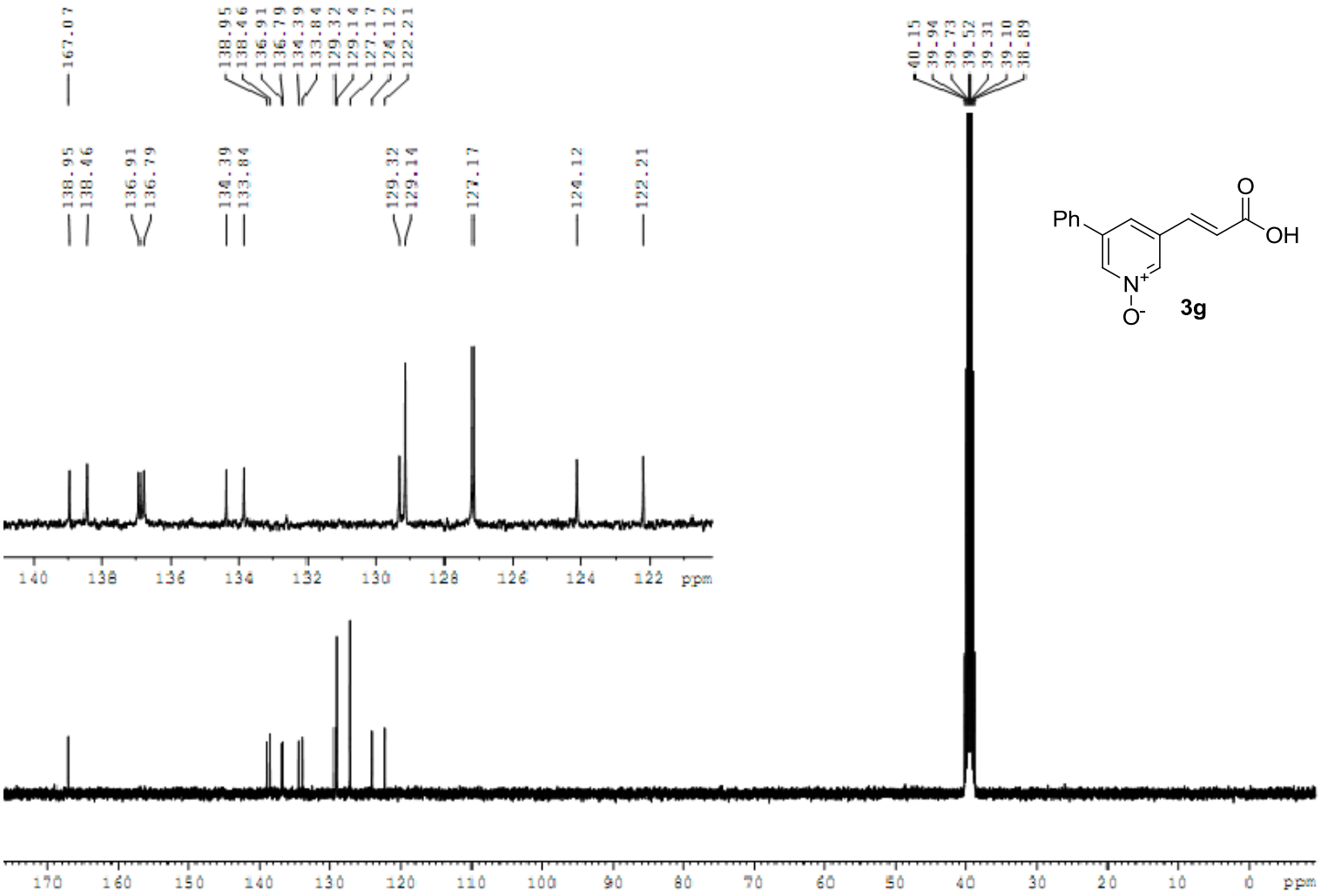

12.586
8.905
8.847
8.451
7.832
7.813
7.720
7.679
7.542
7.523
7.505
7.466
7.448
7.431
6.882
6.842
3.348
2.500
-0.006
Ph
O
OH
N
8g
ppm
2.05
1.00
2.02
1.04
2.15
1.03
1.01
0.65


167.35
148.78
148.57
140.50
136.45
135.63
132.48
130.21
129.14
128.44
127.13
121.93
40.14
39.94
39.73
39.52
39.31
39.10
38.89
Ph
N
O
OH
8g
ppm
ppm


12.884
8.647
8.598
8.072
7.841
7.823
7.601
7.561
7.542
7.531
7.515
7.496
7.473
7.457
6.941
6.900
3.355
2.500
0.009
Ph
O
OH
N+
O-
3g
ppm
2.01
0.99
2.03
4.14
1.00
1.15


167.07
138.95
138.46
136.91
136.79
134.39
133.84
129.32
129.14
127.17
124.12
122.21
40.15
39.94
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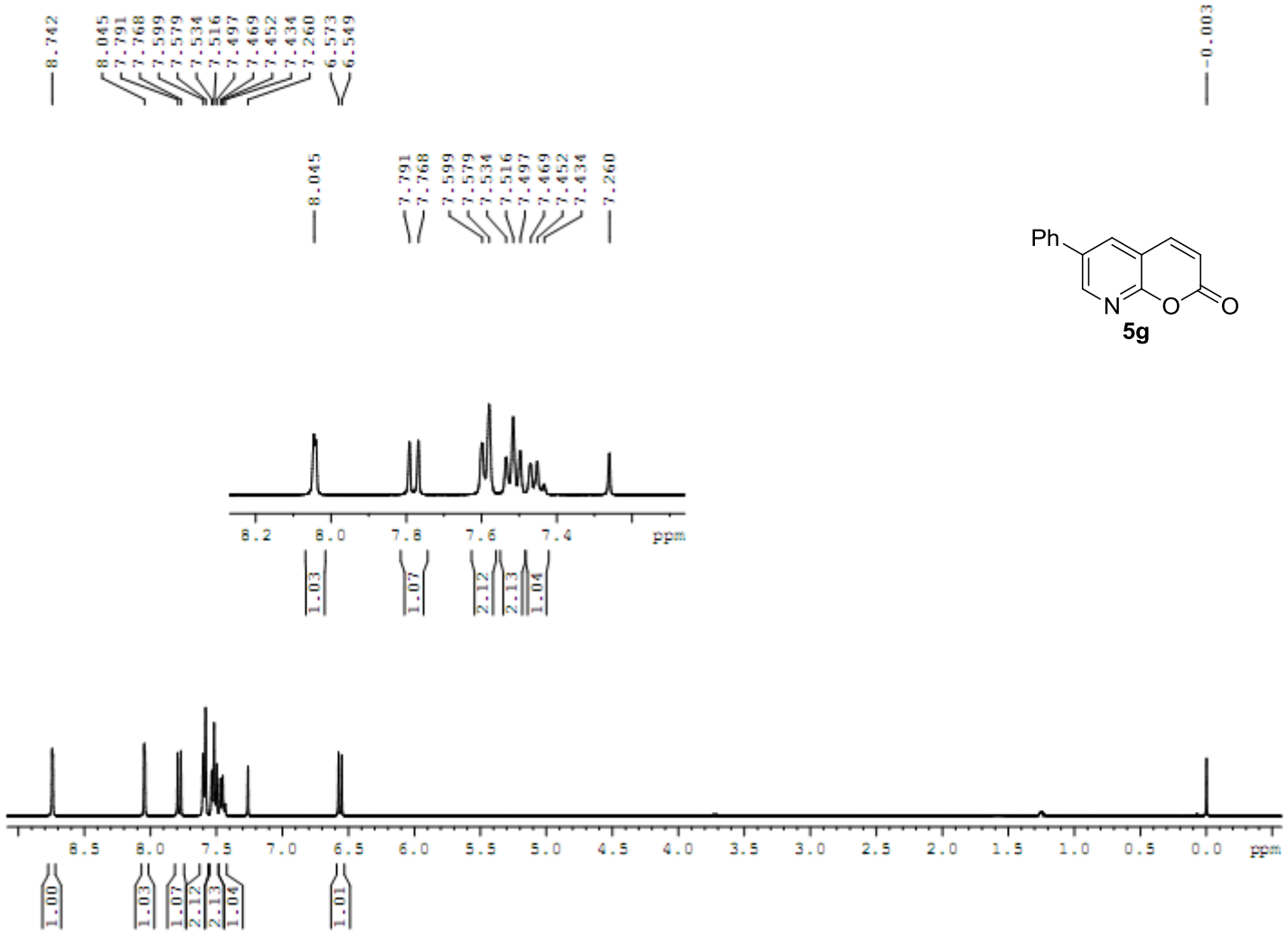
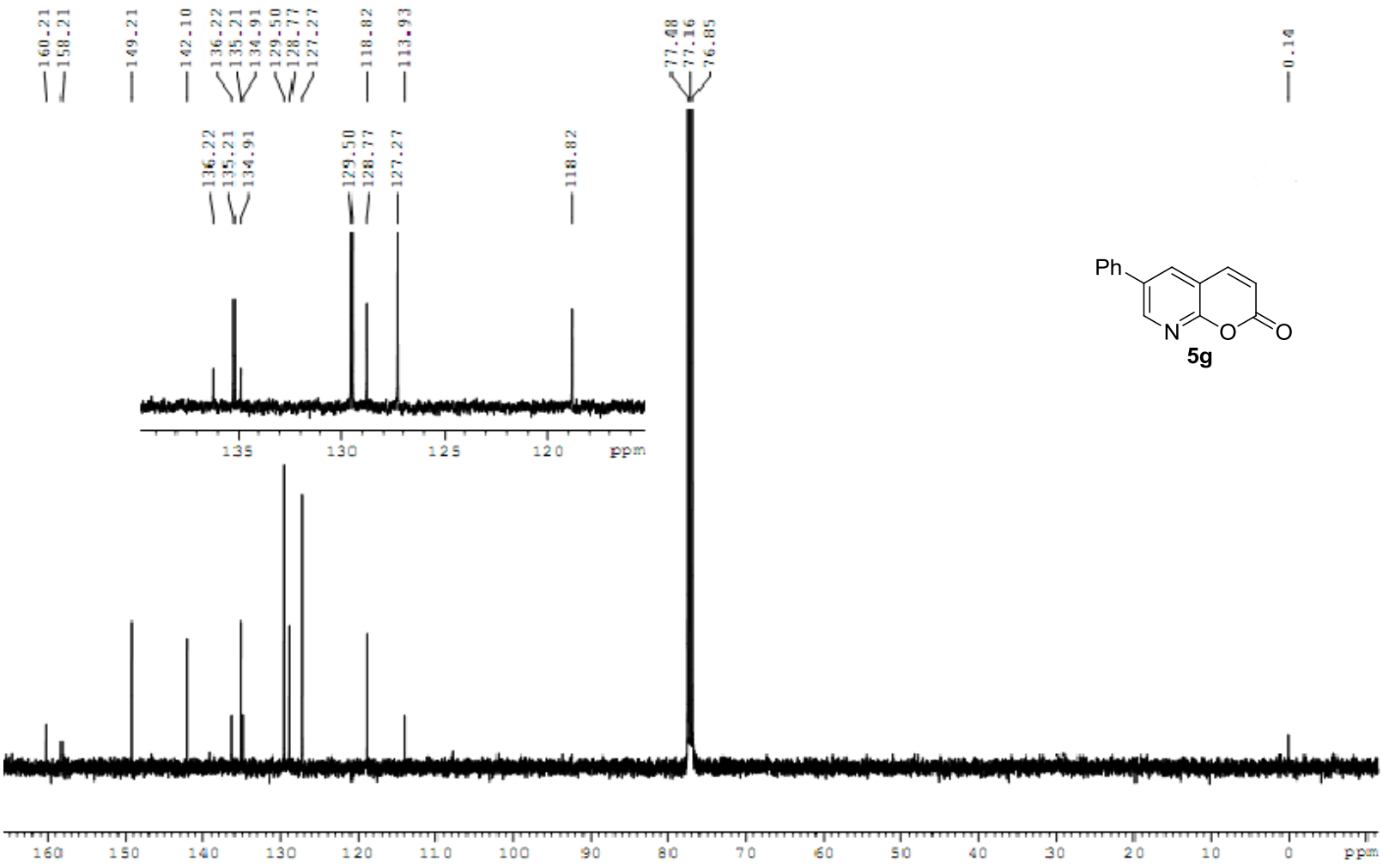
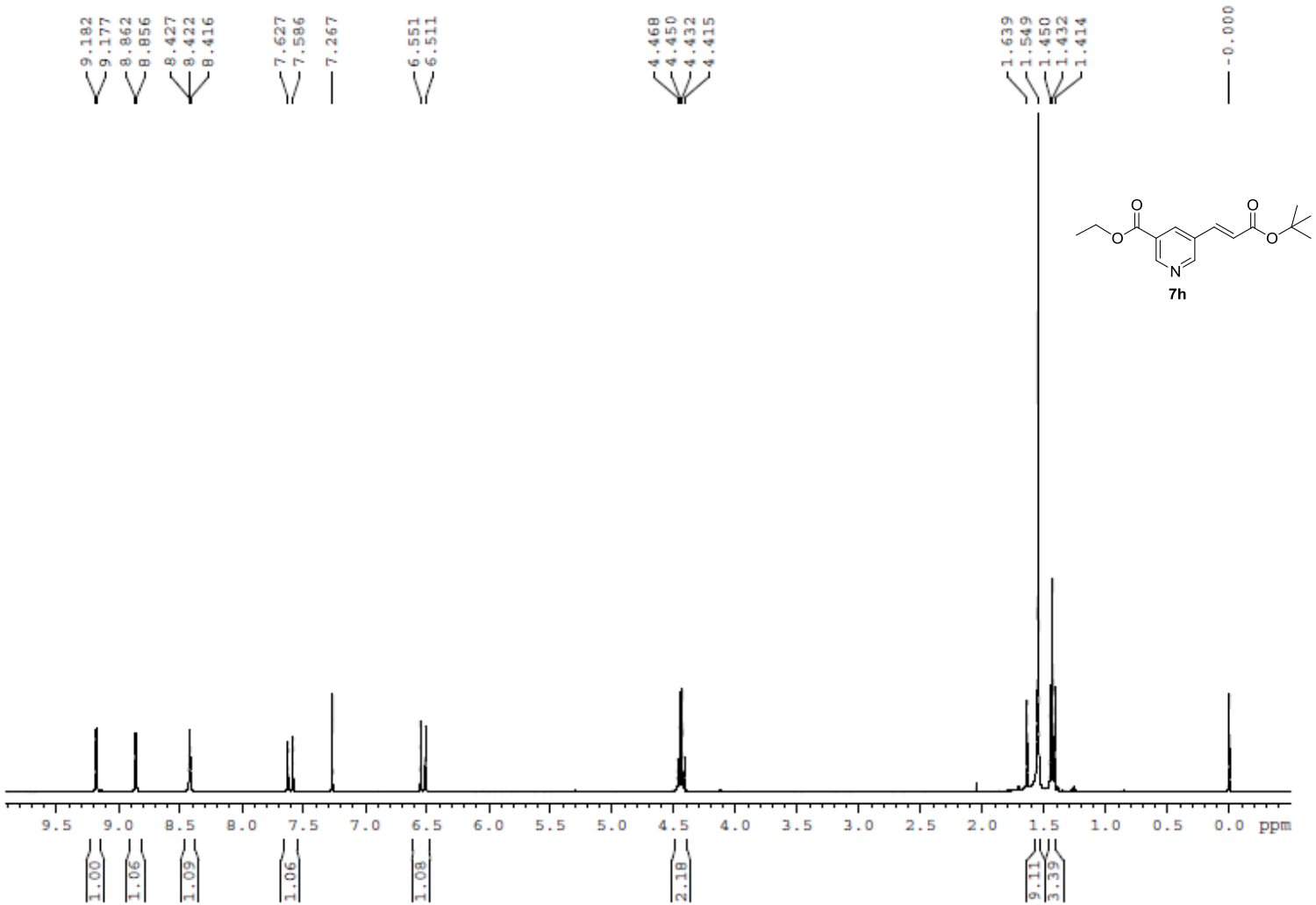
39.31
39.10
38.89
Ph
O
OH
N+
O-
3g
ppm


8.742
8.045
7.791
7.768
7.599
7.579
7.534
7.516
7.497
7.469
7.452
7.434
7.260
6.573
6.549
0.003
Ph
N
O
O
5g
ppm
1.03
1.07
2.12
2.13
1.04
1.00
1.01


160.21
158.21
149.21
142.10
136.22
135.21
134.91
129.50
128.77
127.27
118.82
113.93
77.48
77.16
76.85
0.14
Ph
N
O
O
5g
ppm



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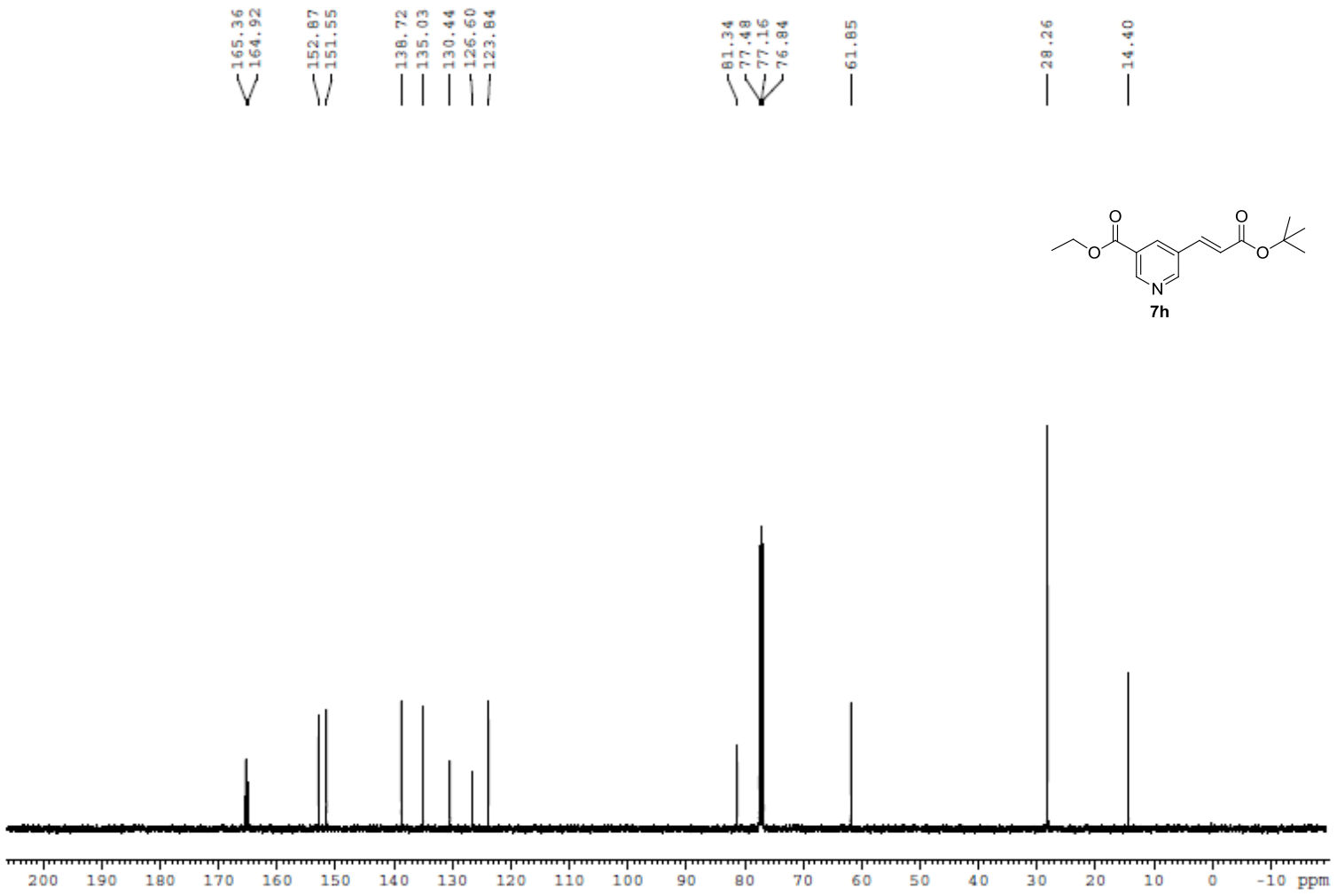
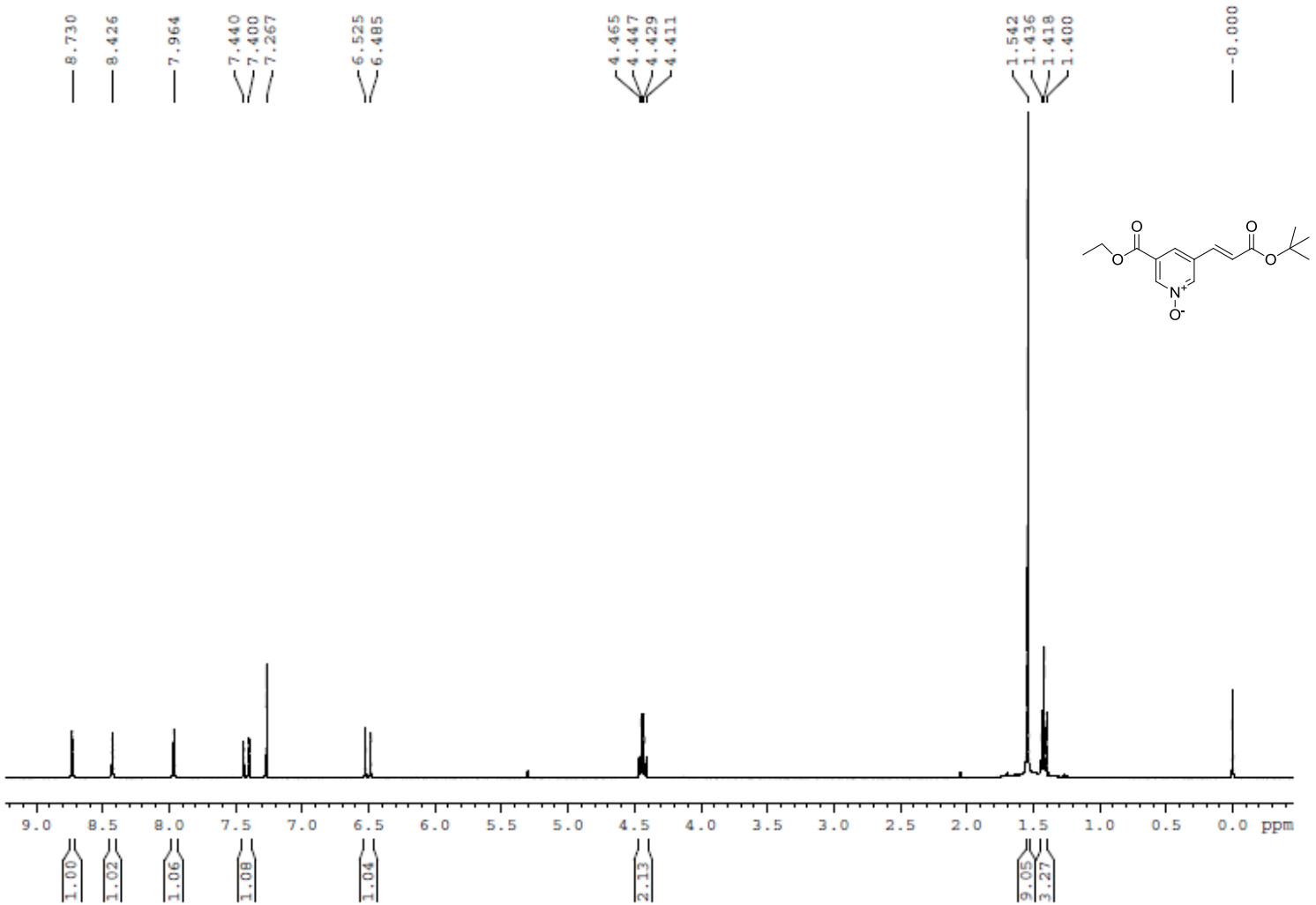
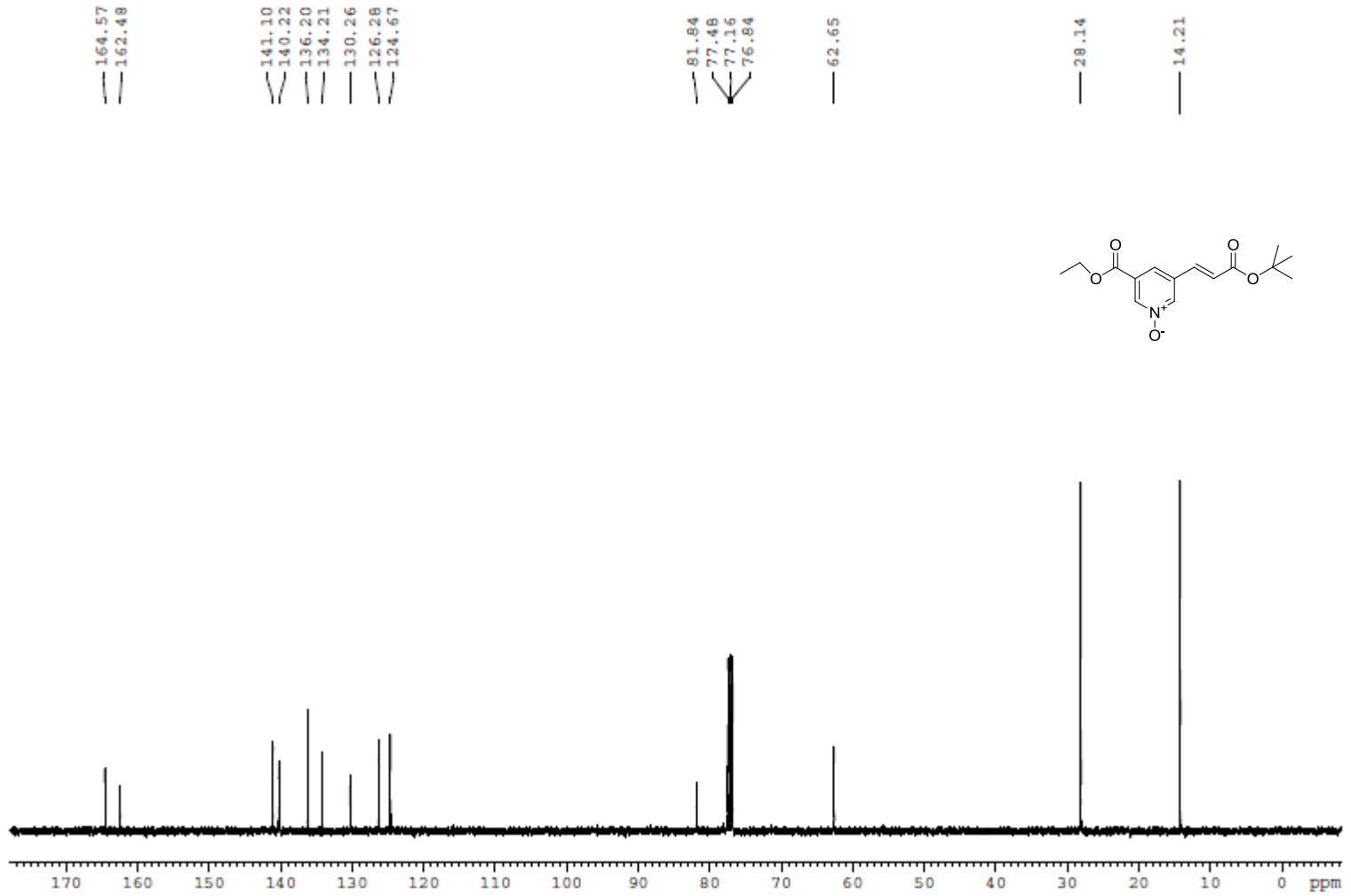

165.36
164.92
152.87
151.55
138.72
135.03
130.44
126.60
123.84
81.34
77.48
77.16
76.84
61.85
28.26
14.40
O
O
O
O
N
7h
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm



DOI: 10.1021/acs.orglett.6b03771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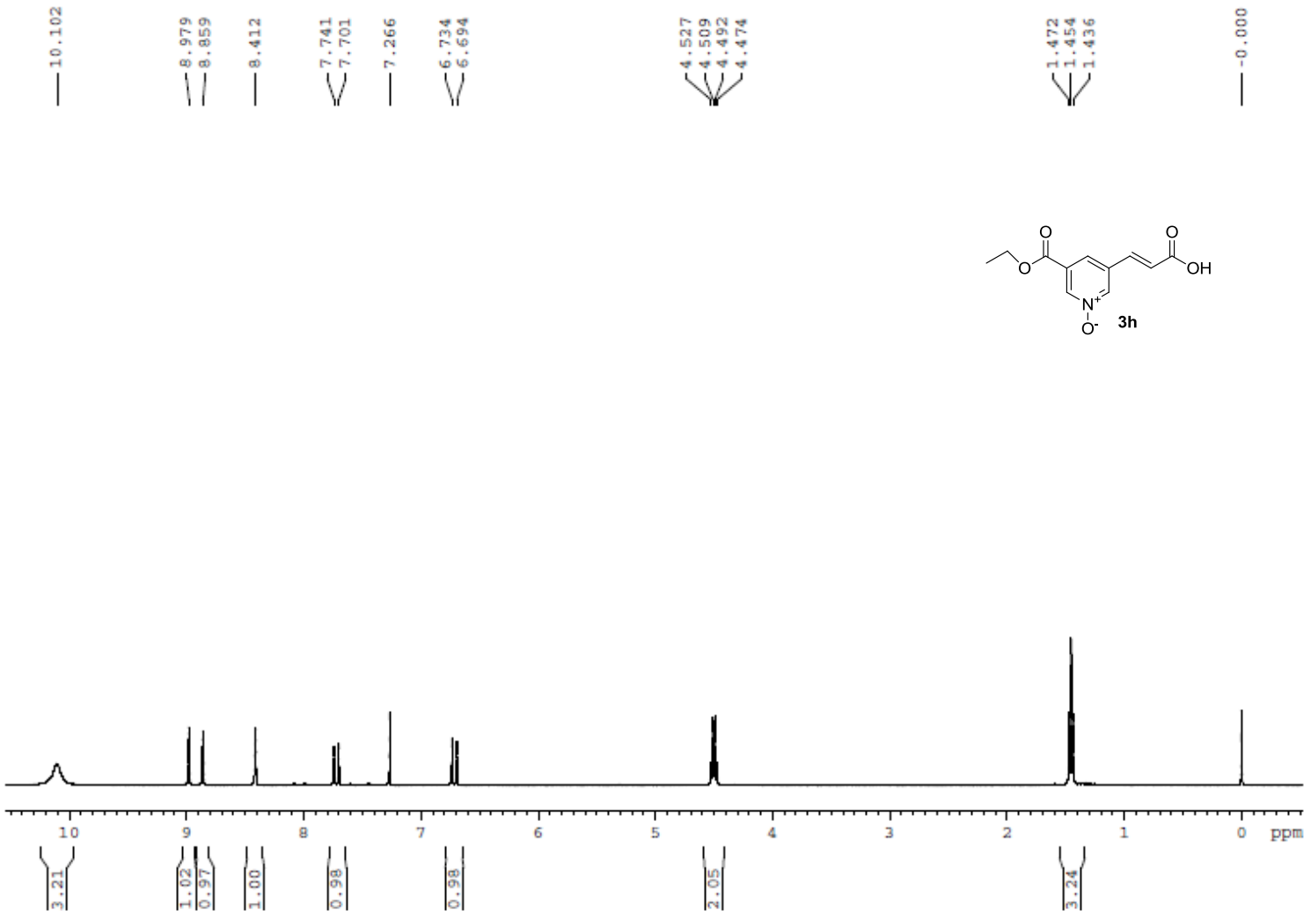
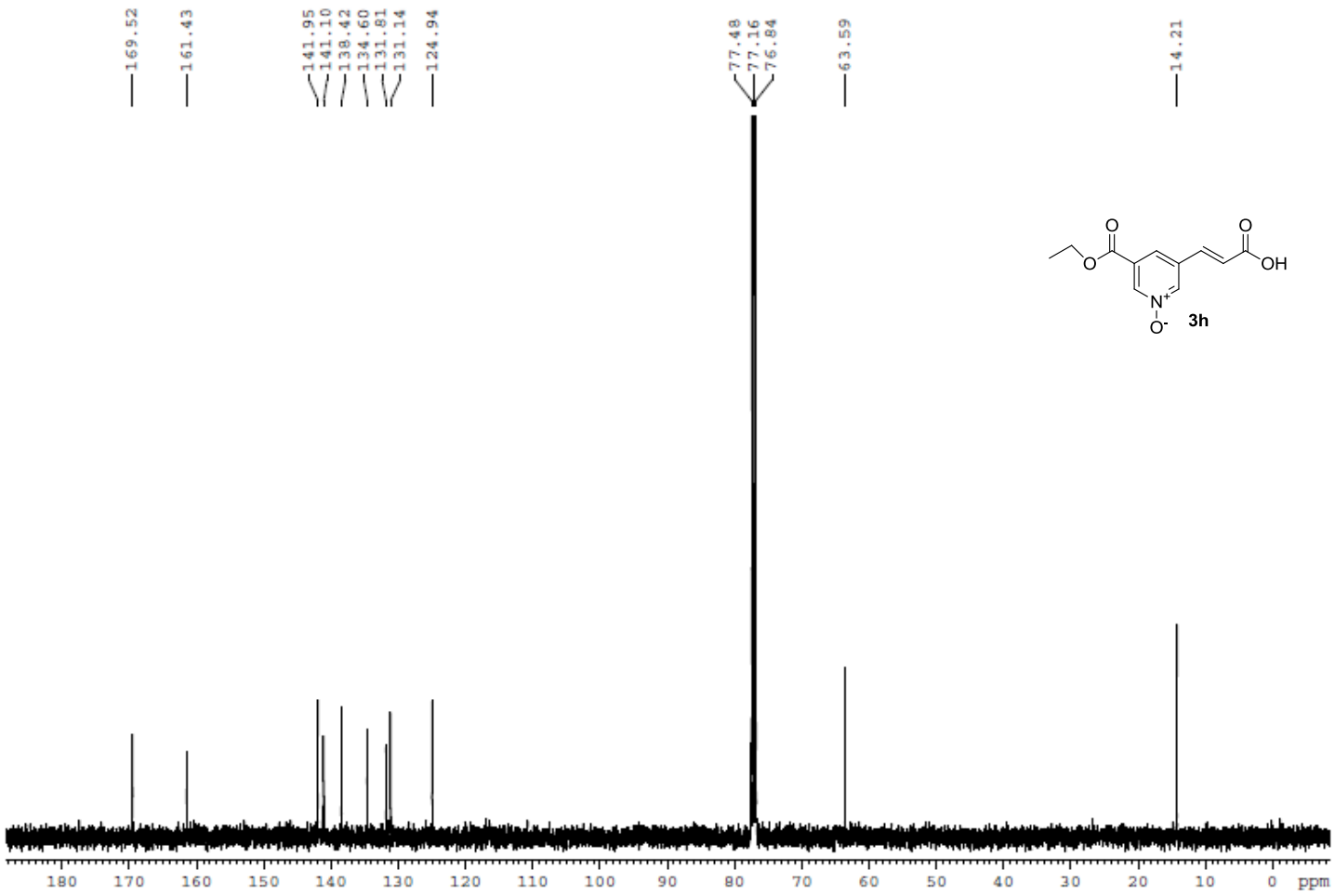
162.48
141.10
140.22
136.20
134.21
130.26
126.28
124.67
81.84
77.48
77.16
76.84
62.65
28.14
14.21
O
O
O
O
N+
O-
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


10.102
8.979
8.859
8.412
7.741
7.701
7.266
6.734
6.694
4.527
4.509
4.492
4.474
1.472
1.454
1.436
-0.000
O
O
O
OH
N+
O-
3h
10
9
8
7
6
5
4
3
2
1
0
ppm
3.21
1.02
0.97
1.00
0.98
0.98
2.05
3.24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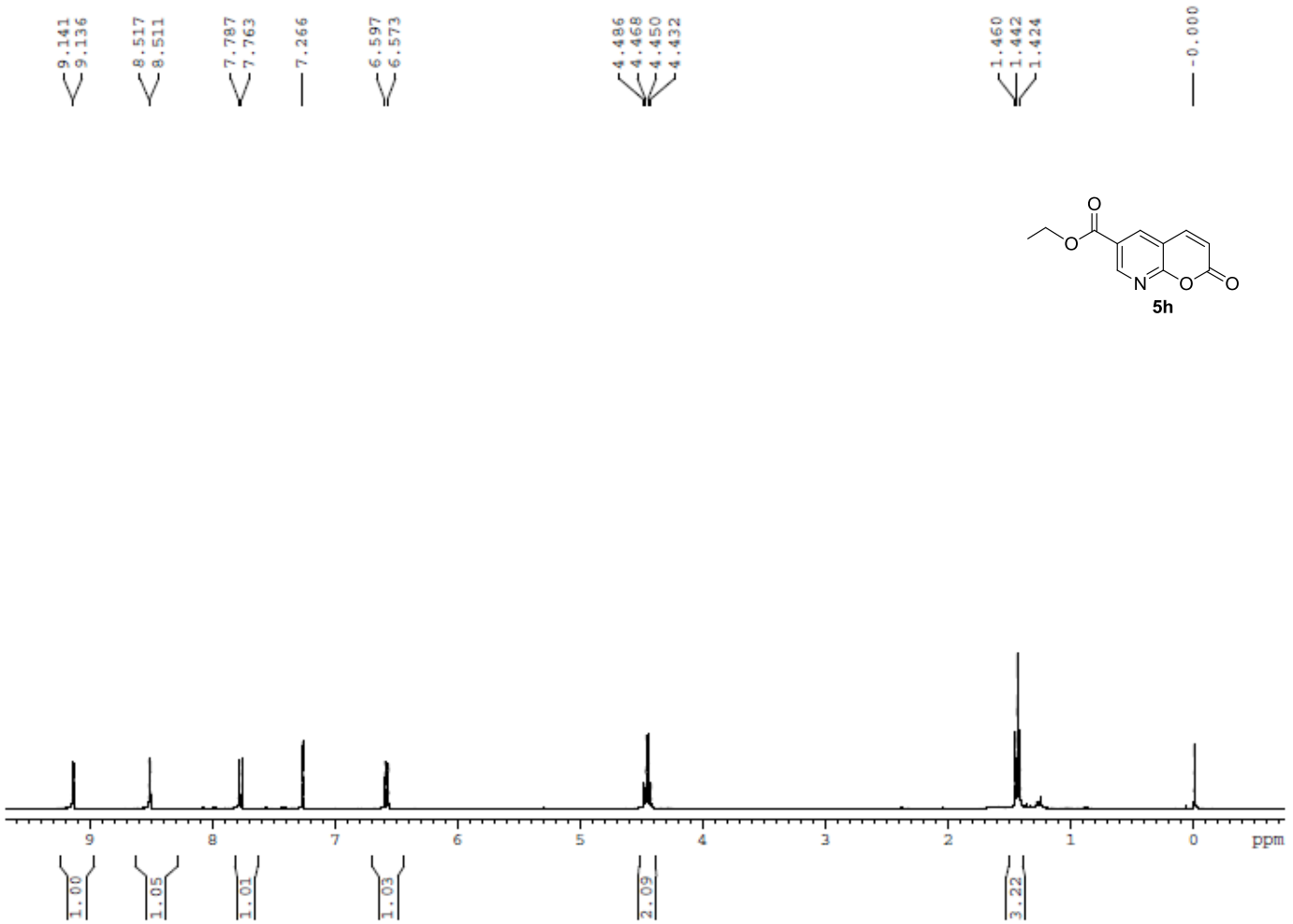
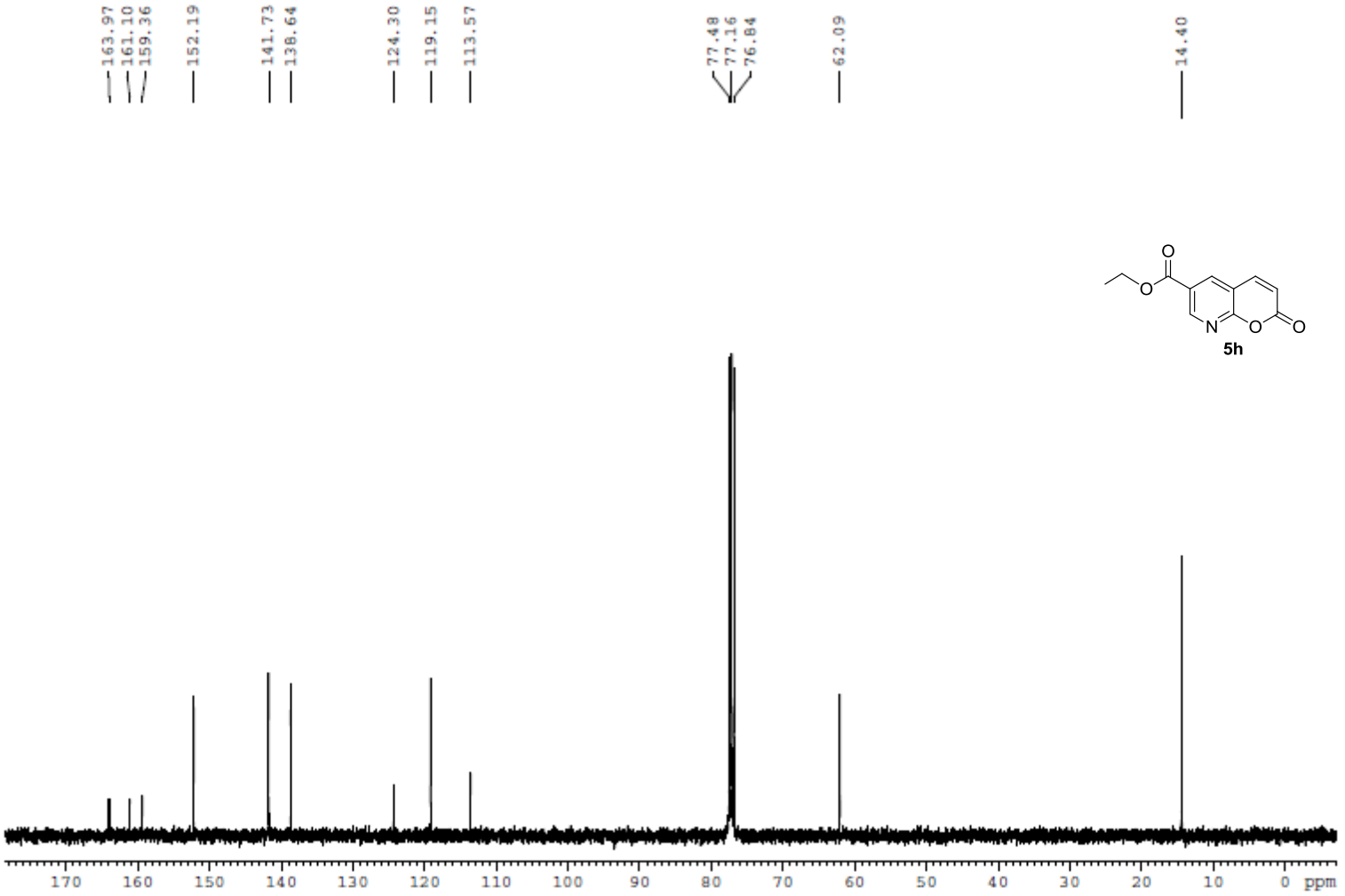
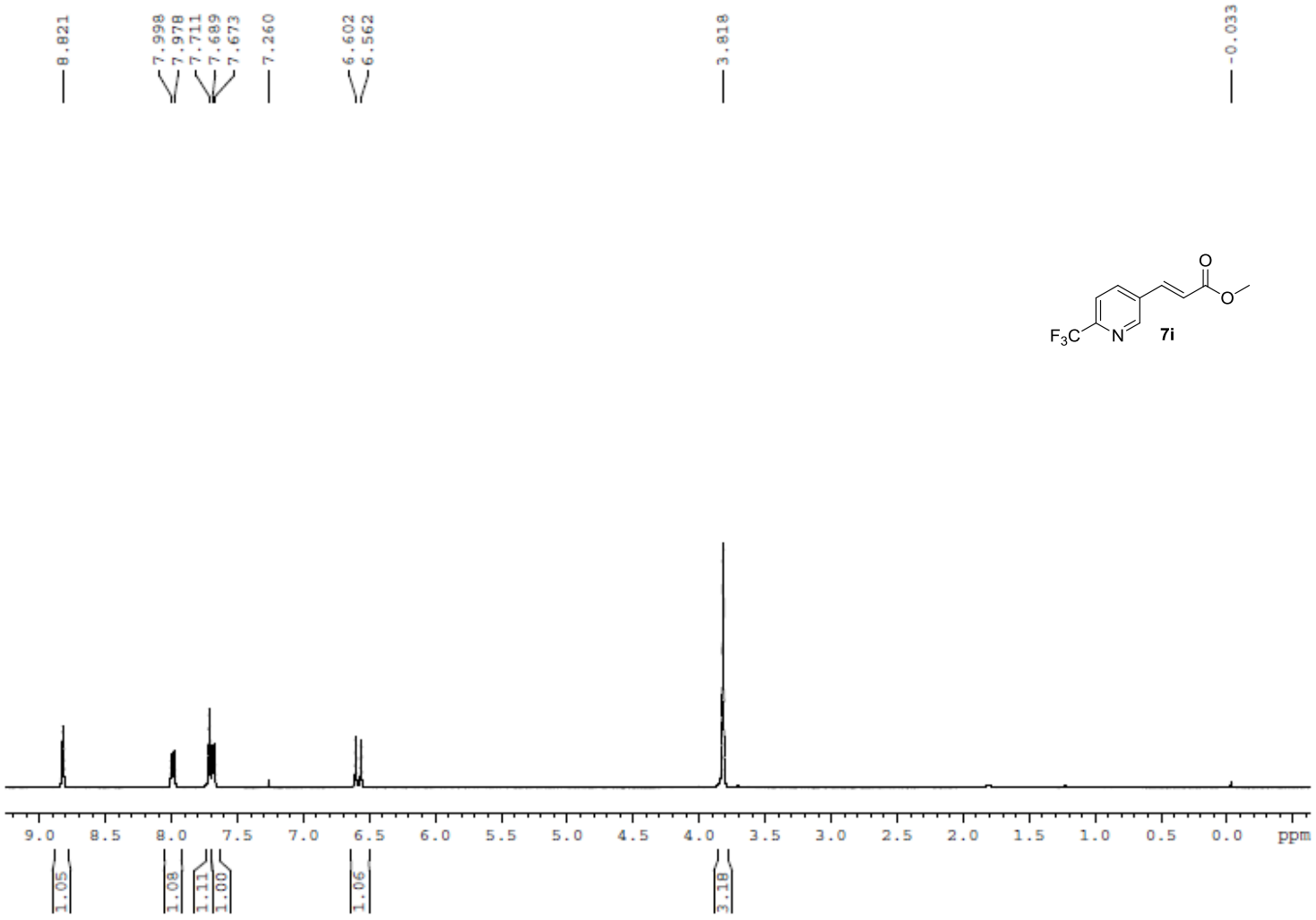
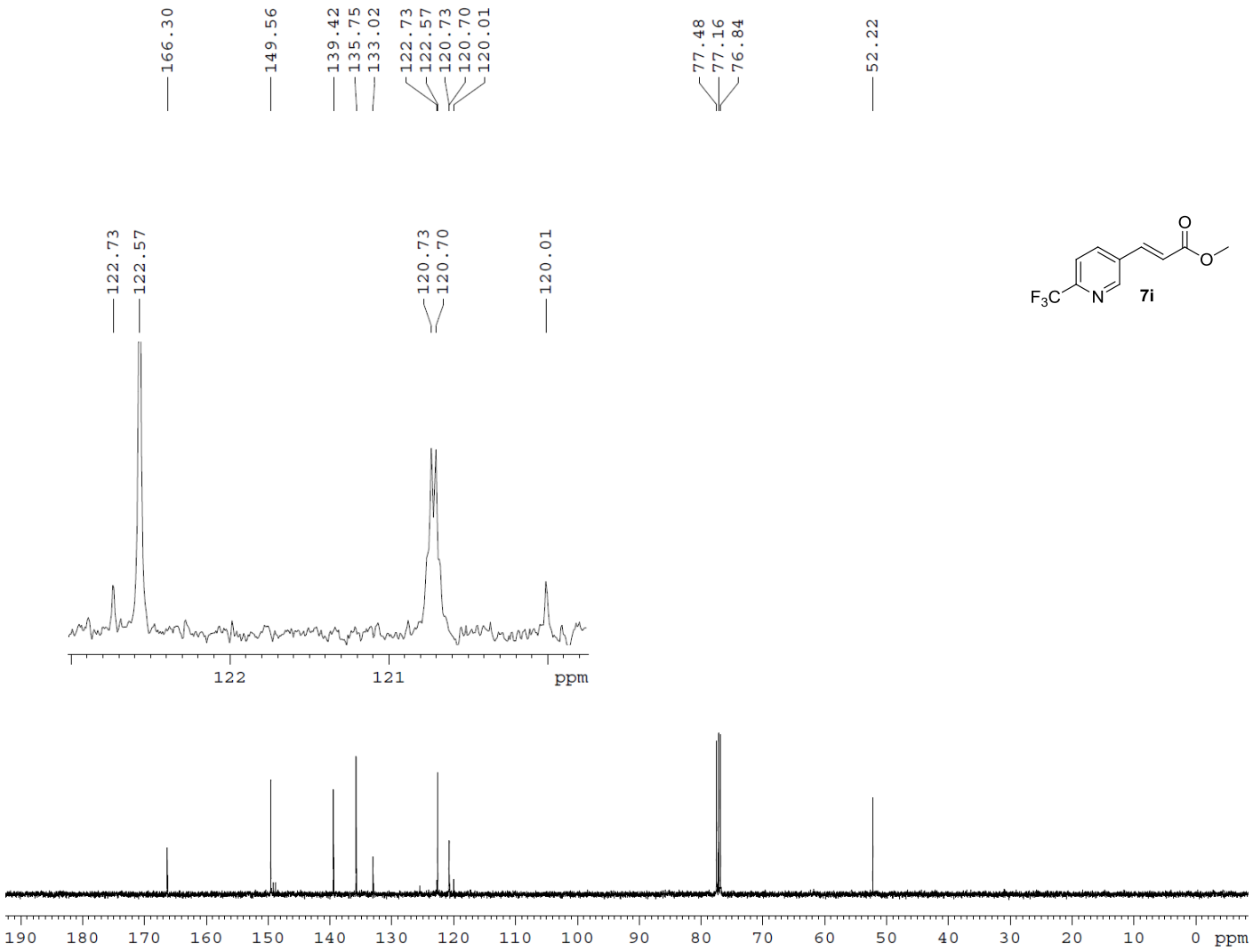
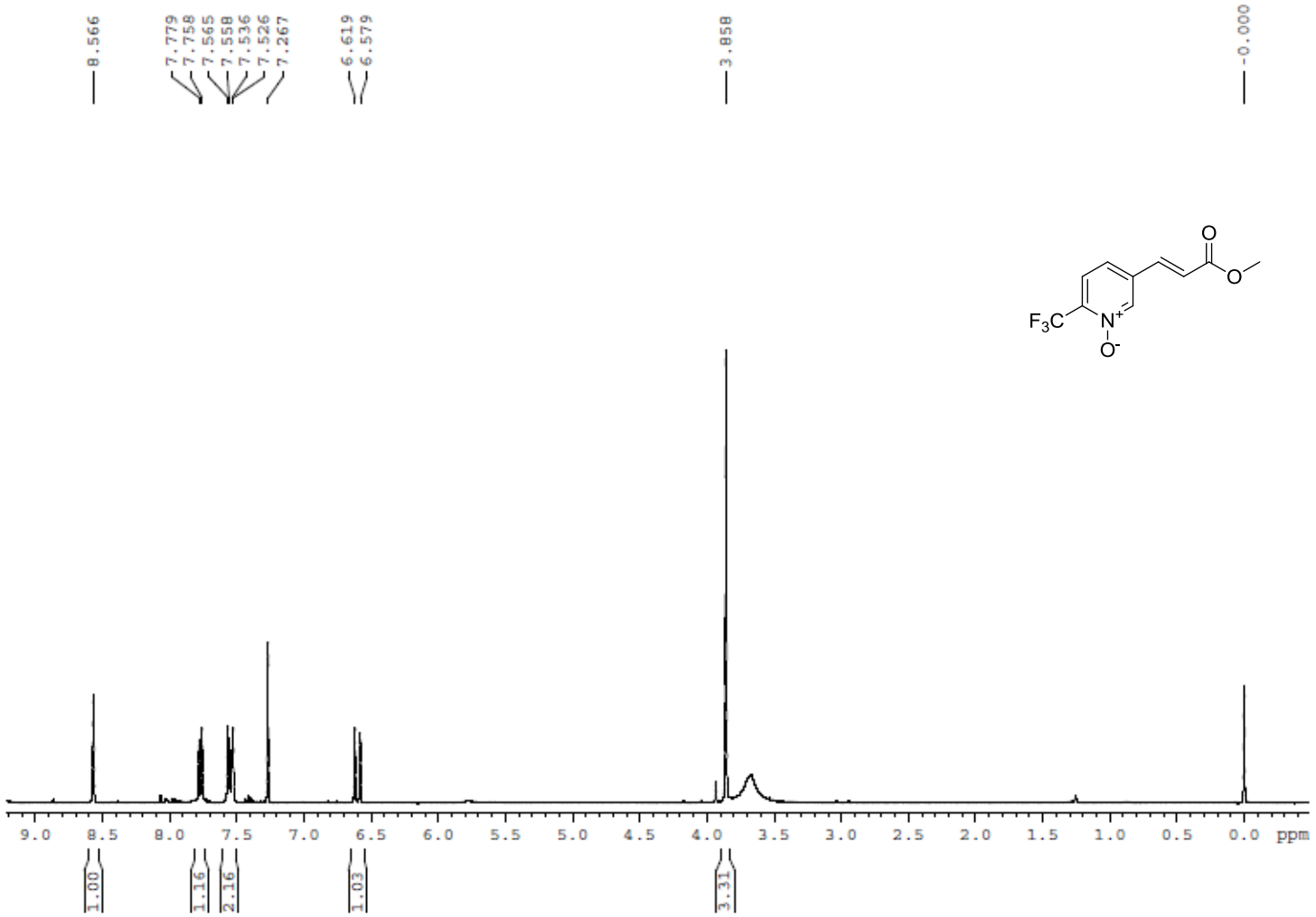
161.43
141.95
141.10
138.42
134.60
131.81
131.14
124.94
77.48
77.16
76.84
63.59
14.21
O
O
O
OH
N+
O-
3h
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


9.141
9.136
8.517
8.511
7.787
7.763
7.266
6.597
6.573
4.486
4.468
4.450
4.432
1.460
1.442
1.424
-0.000
O
O
N
O
O
5h
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.05
1.01
1.03
2.09
3.22


163.97
161.10
159.36
152.19
141.73
138.64
124.30
119.15
113.57
77.48
77.16
76.84
62.09
14.40
O
O
N
O
O
5h
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


8.821
7.998
7.978
7.711
7.689
7.673
7.260
6.602
6.562
3.818
-0.033
O
O
F3C
N
7i
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.05
1.08
1.11
1.00
1.06
3.18


166.30
149.56
139.42
135.75
133.02
122.73
122.57
120.73
120.70
120.01
77.48
77.16
76.84
52.22
122.73
122.57
120.73
120.70
120.01
O
O
F3C
N
7i
122
121
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



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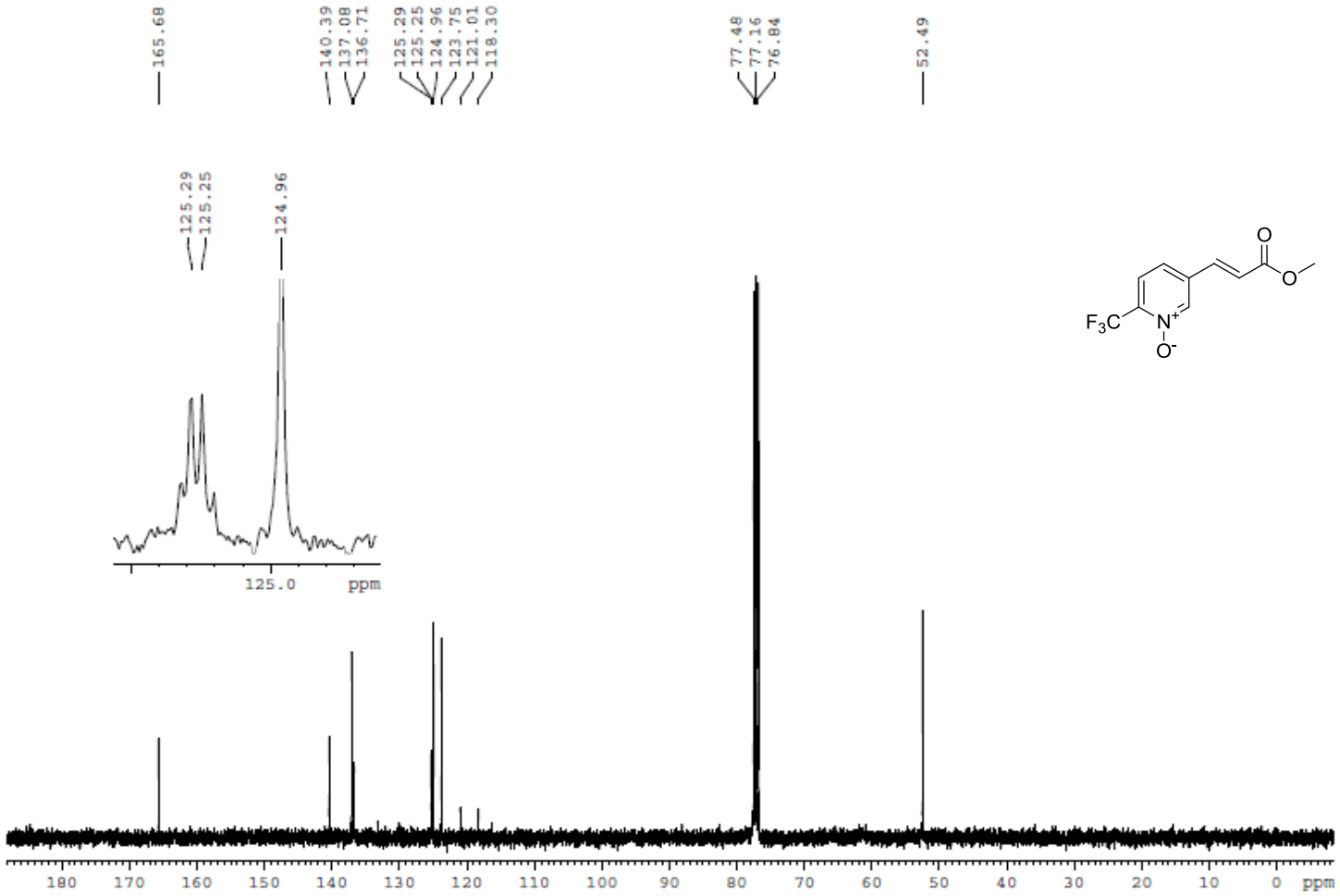
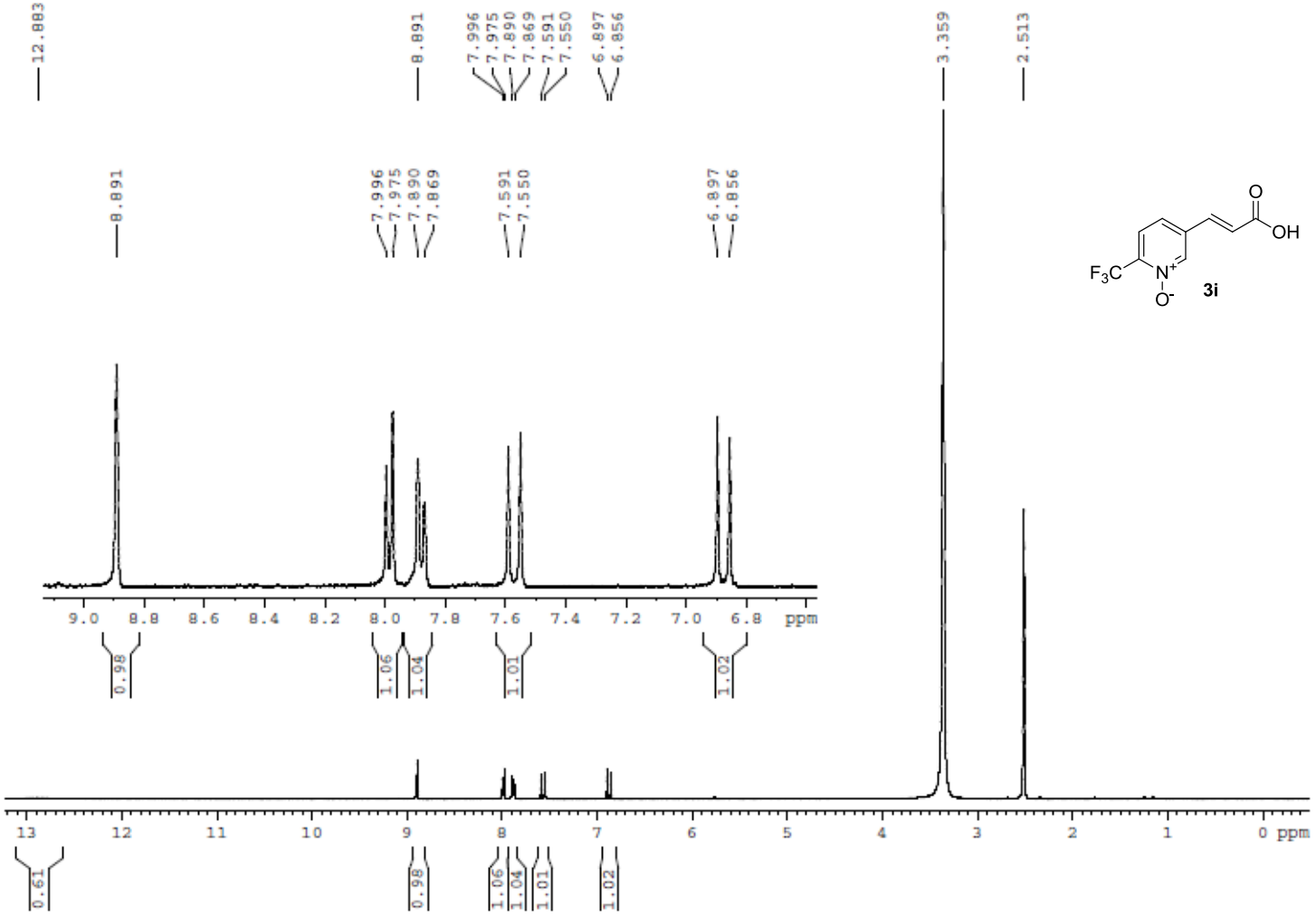
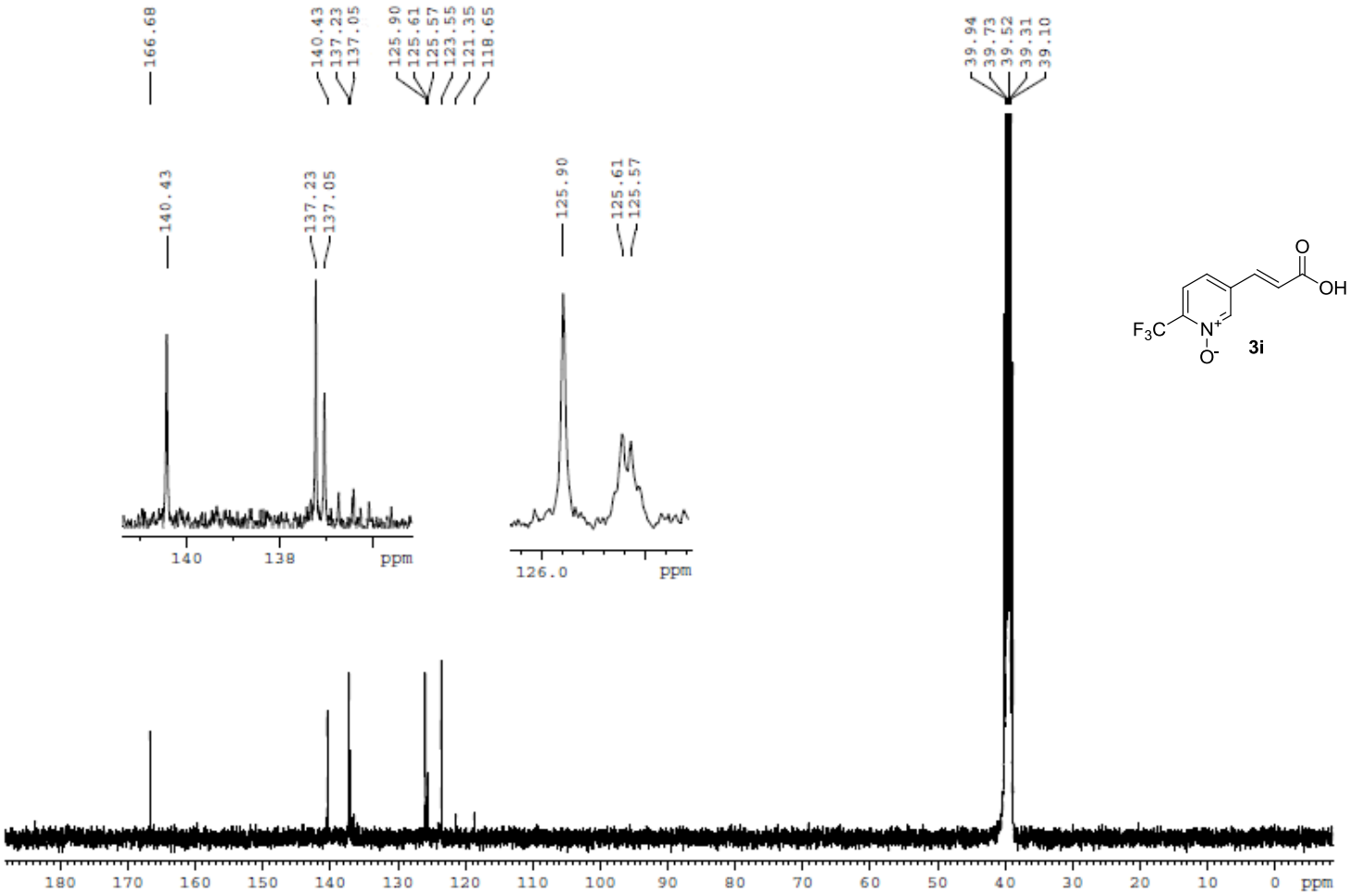
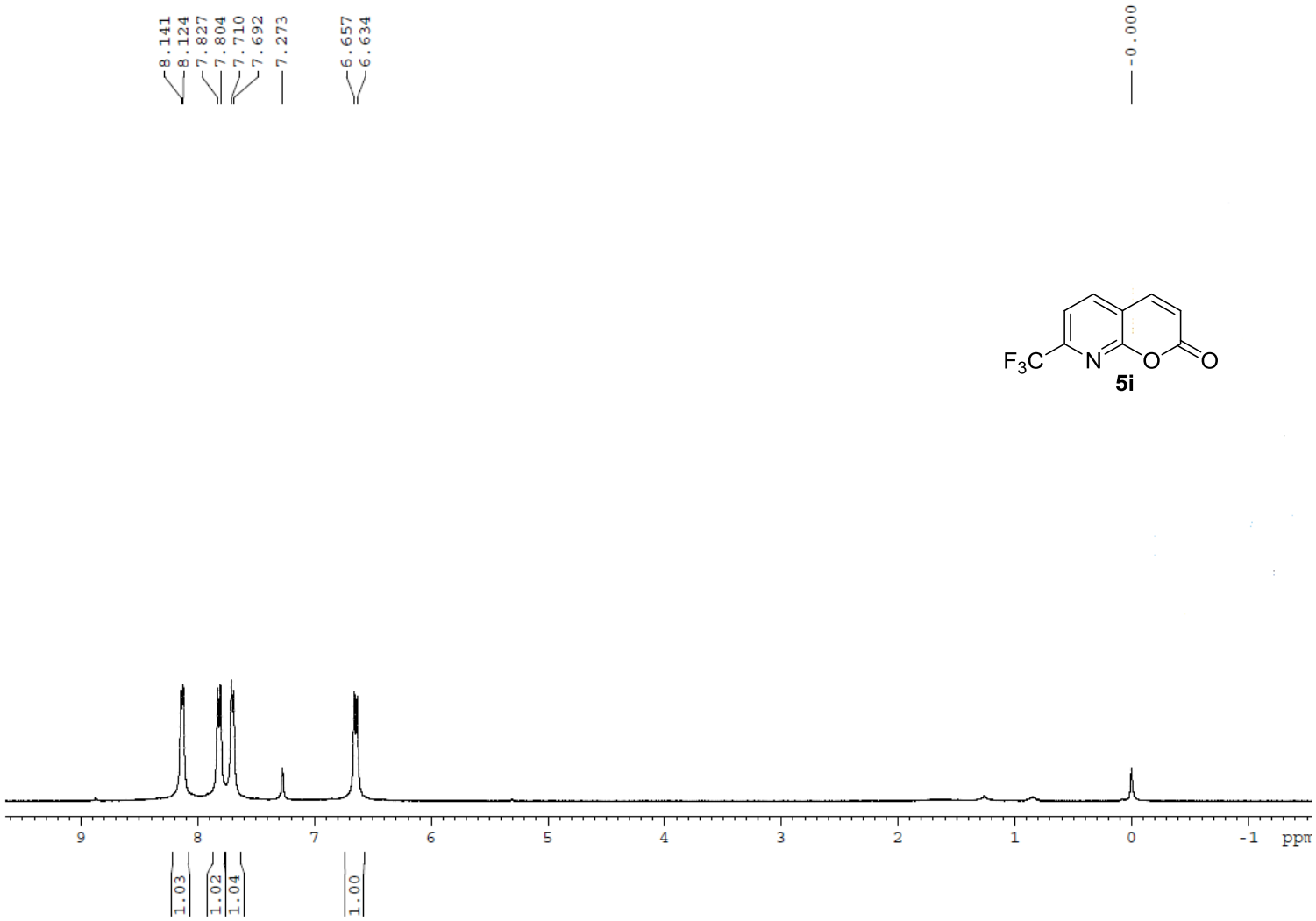
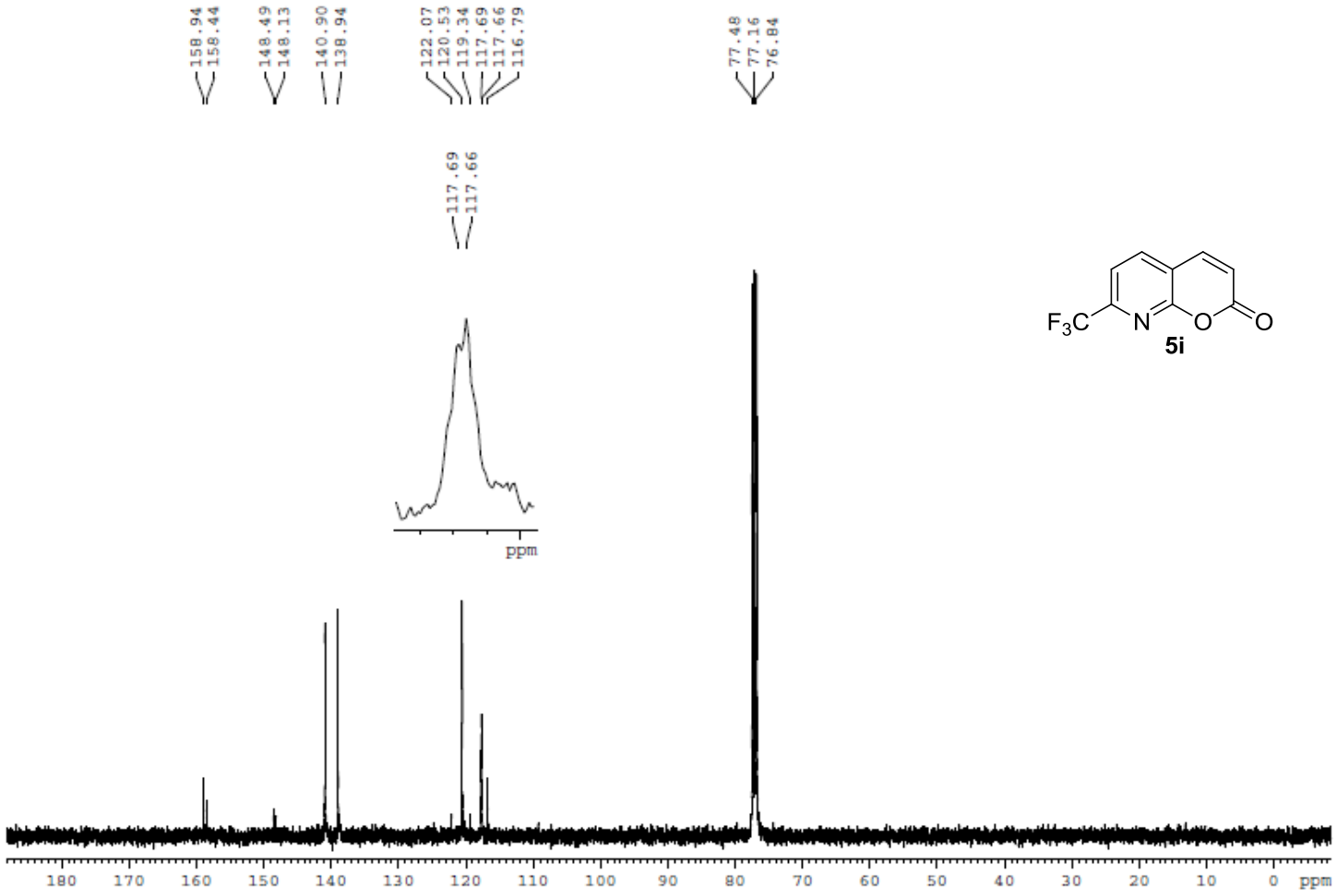


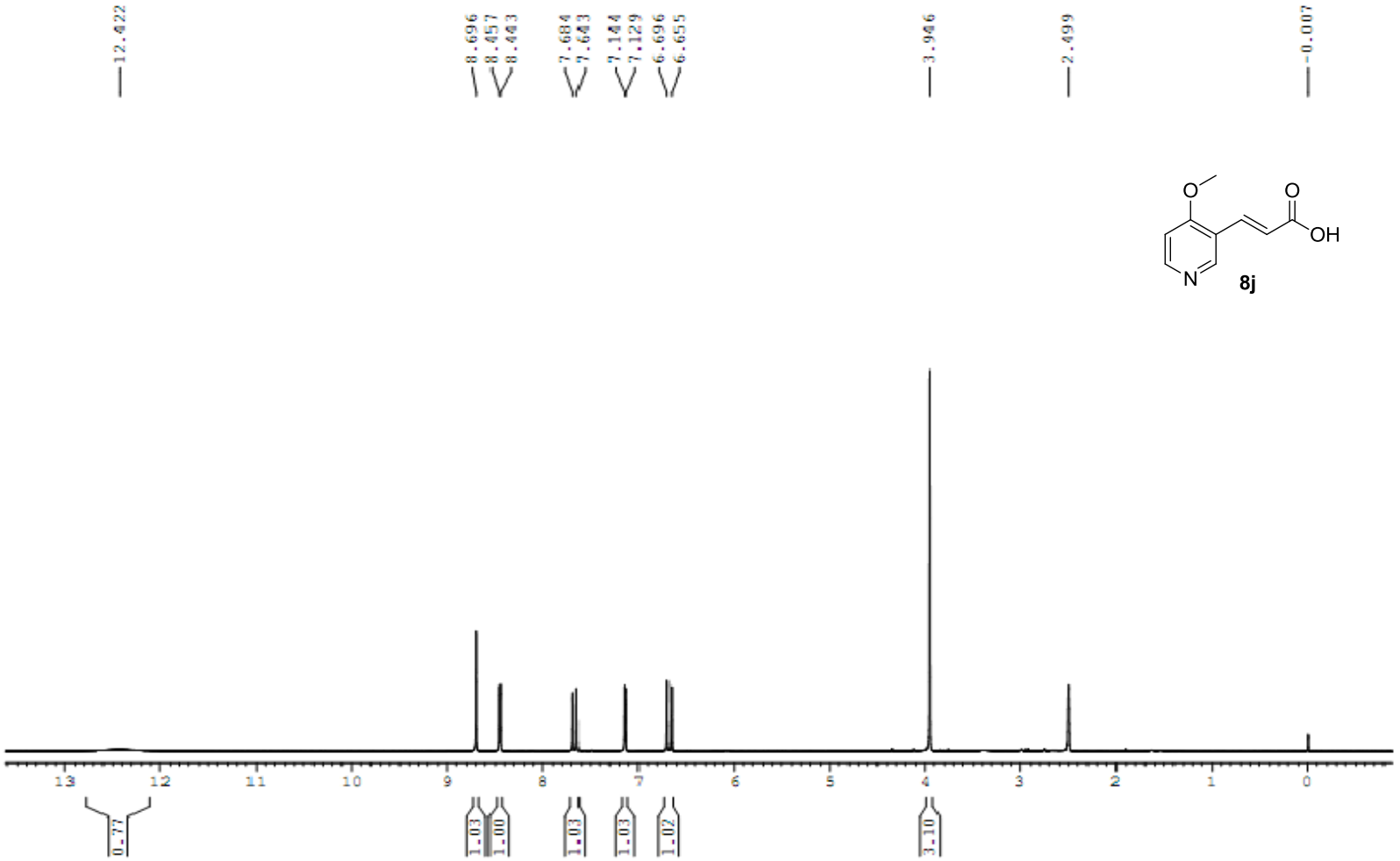
DOI: 10.1021/acs.orglett.6b03771


12.883
8.891
7.996
7.975
7.890
7.869
7.591
7.550
6.897
6.856
3.359
2.513
ppm
0.61
0.98
1.06
1.04
1.01
1.02
OH
O
F3C
N+
O-
3i


166.68
140.43
137.23
137.05
125.90
125.61
125.57
123.55
121.35
118.65
39.94
39.73
39.52
39.31
39.10
140.43
137.23
137.05
125.90
125.61
125.57
140
138
ppm
126.0
ppm
O
OH
F3C
N+
O-
3i
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


8.141
8.124
7.827
7.804
7.710
7.692
7.273
6.657
6.634
-0.000
F3C
N
O
O
5i
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.03
1.02
1.04
1.00


158.94
158.44
148.49
148.13
140.90
138.94
122.07
120.53
119.34
117.69
117.66
116.79
77.48
77.16
76.84
117.69
117.66
ppm
F3C
N
O
O
5i
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



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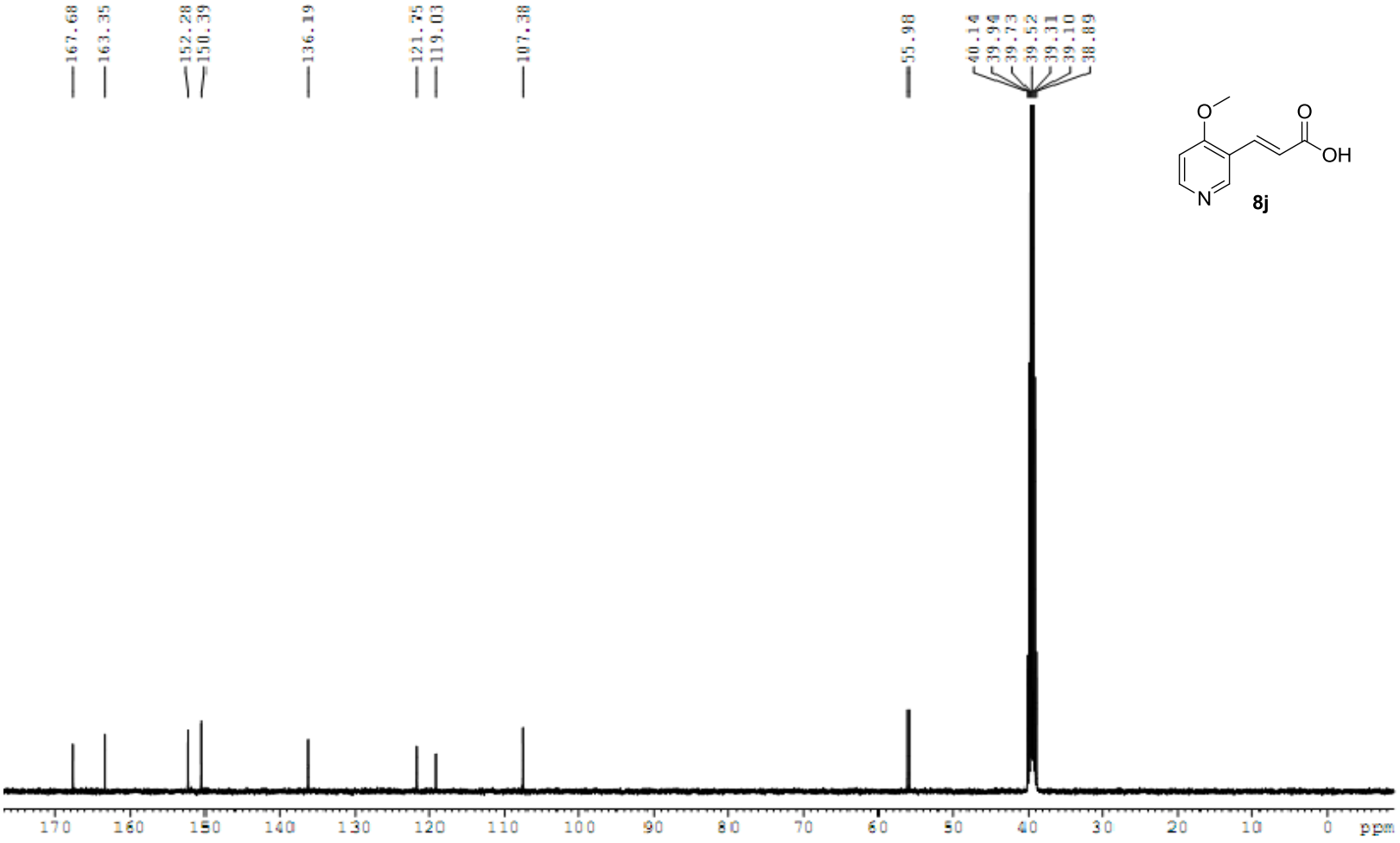
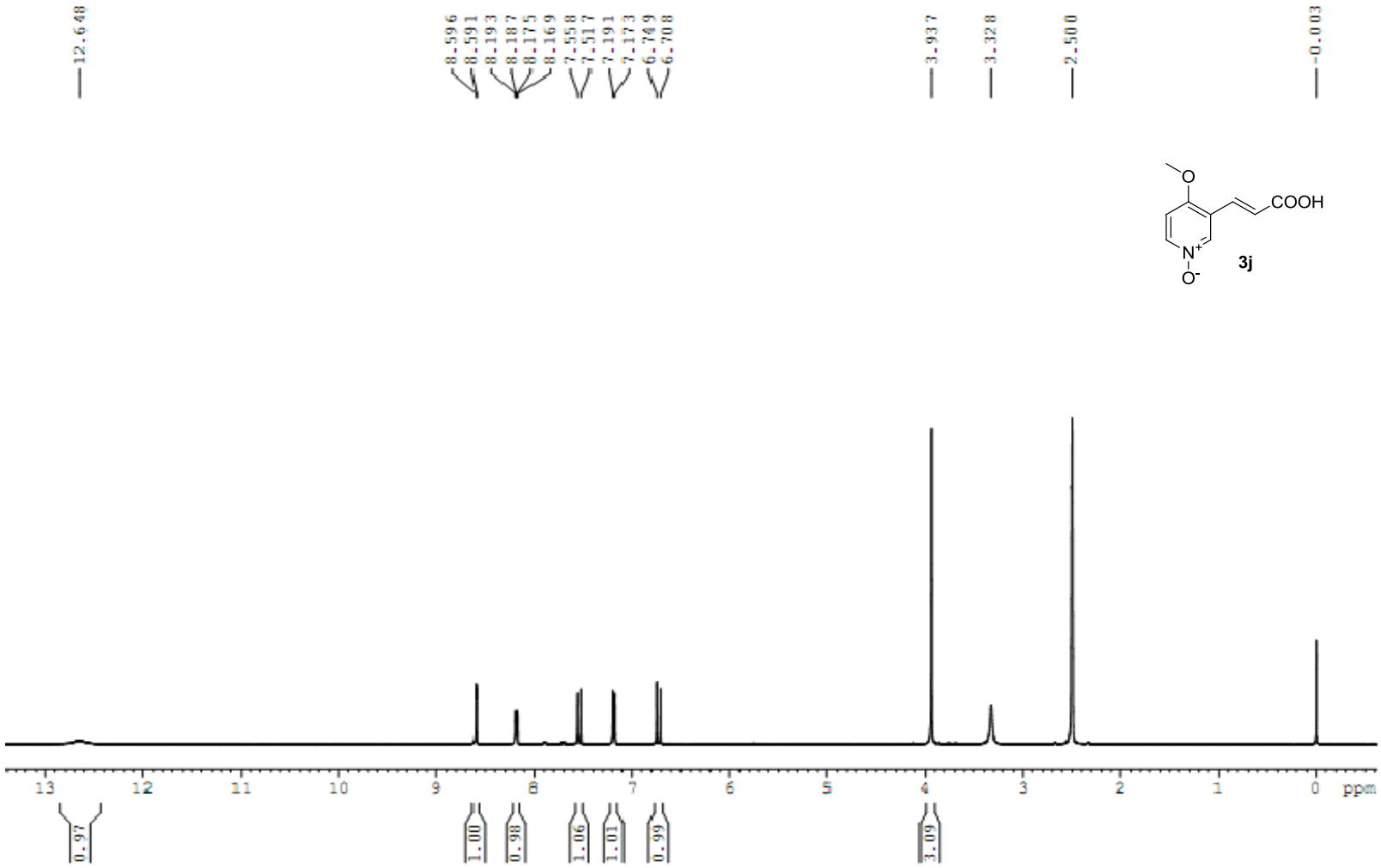
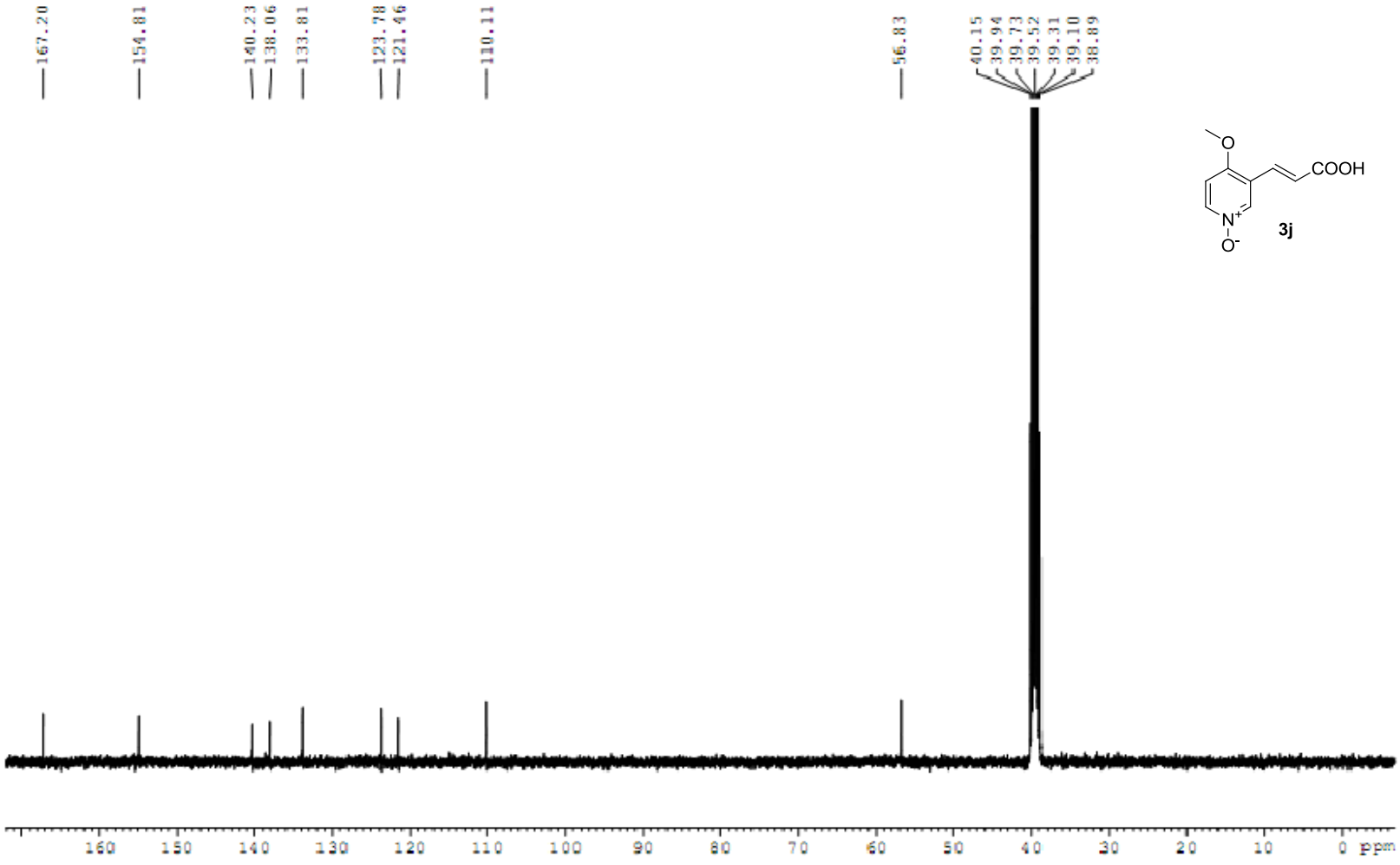
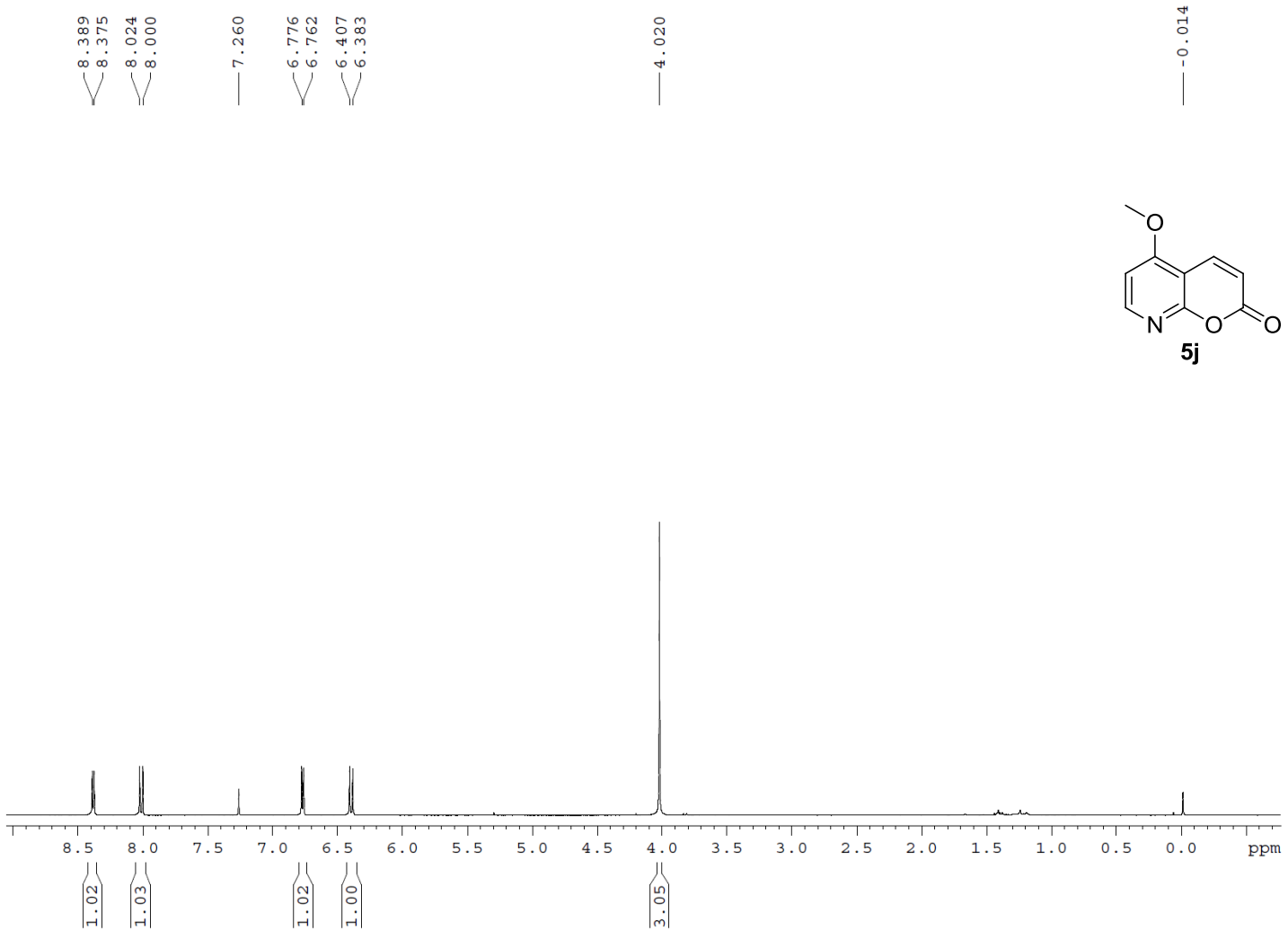
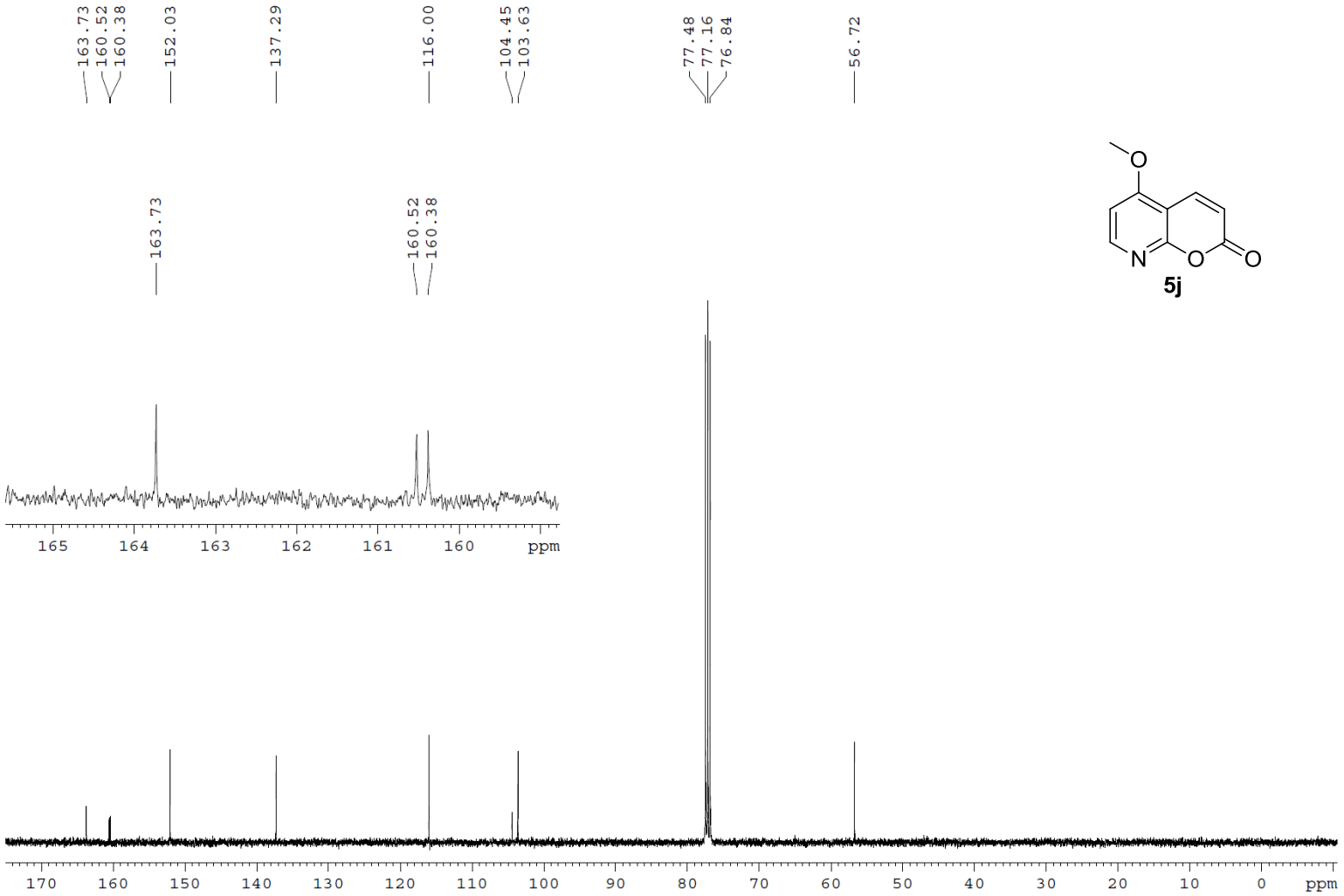
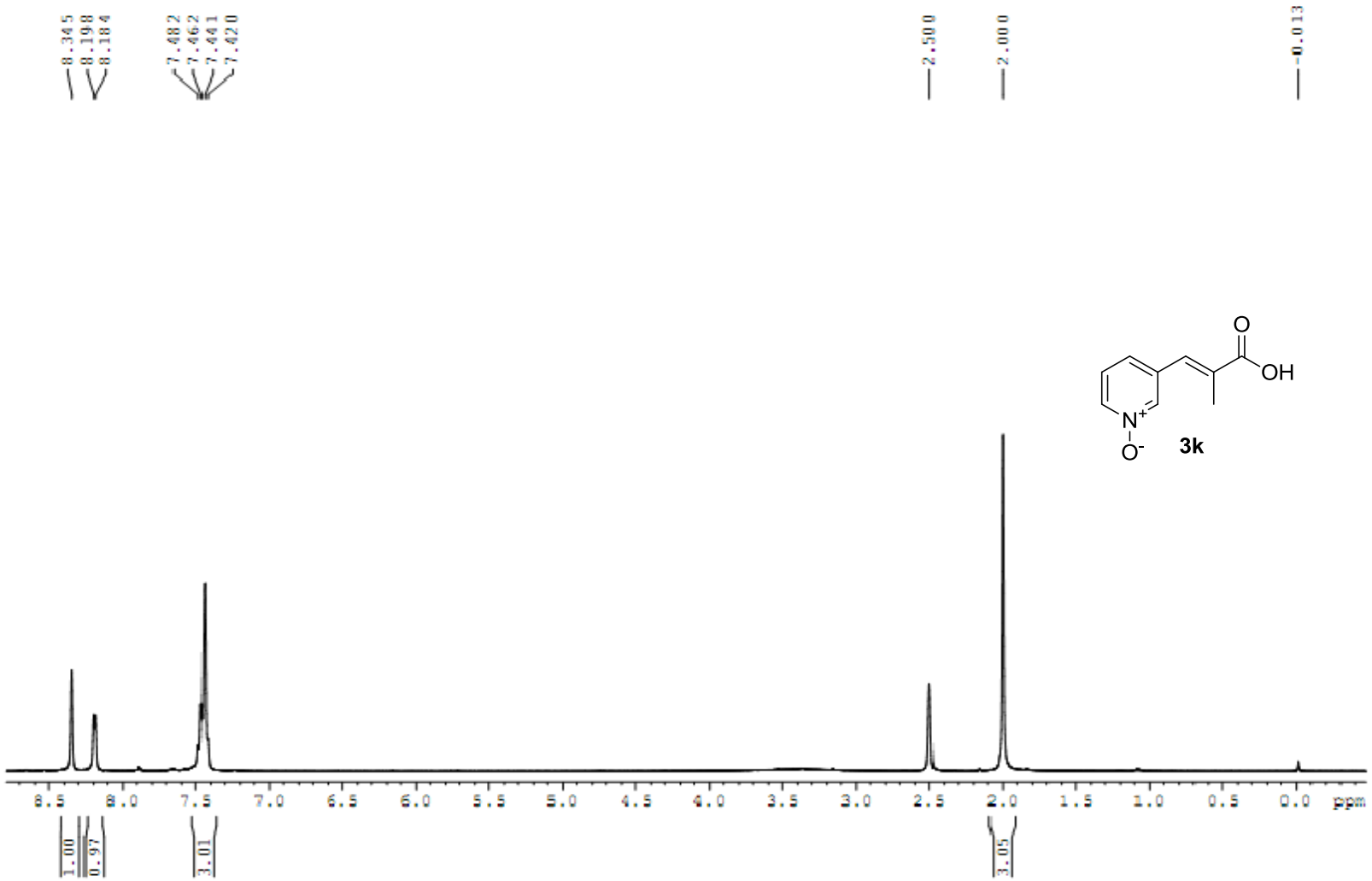

167.68
163.35
152.28
150.39
136.19
121.75
119.03
107.38
55.98
40.14
39.94
39.73
39.52
39.31
39.10
38.89
O
O
OH
N
8j
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

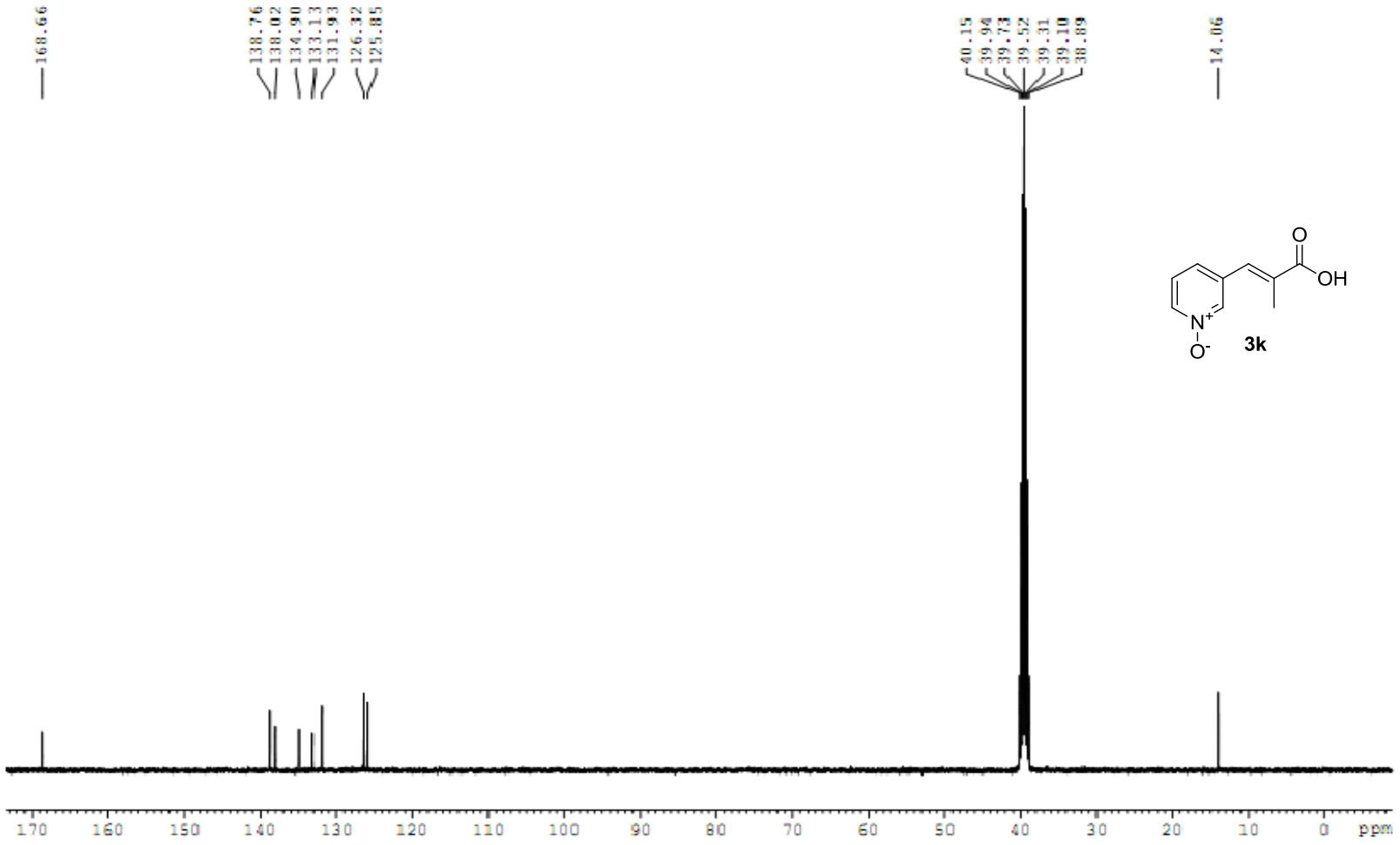

12.648
8.596
8.591
8.193
8.187
8.175
8.169
7.558
7.517
7.191
7.173
6.749
6.708
3.937
3.328
2.500
-0.003
O
COOH
N+
O-
3j
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.97
1.00
0.98
1.06
1.01
0.99
3.09

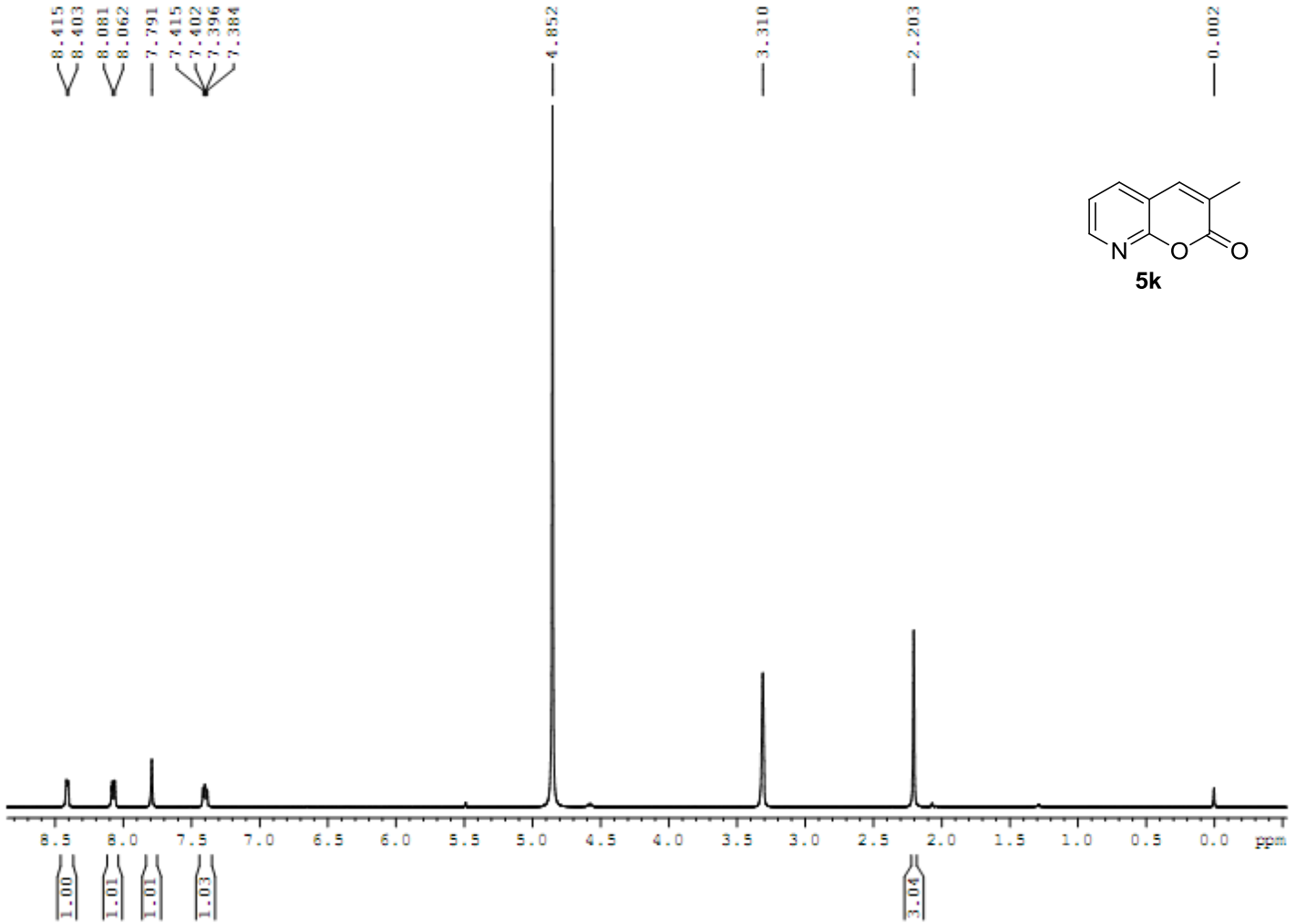

167.20
154.81
140.23
138.06
133.81
123.78
121.46
110.11
56.83
40.15
39.94
39.73
39.52
39.31
39.10
38.89
COOH
3j
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

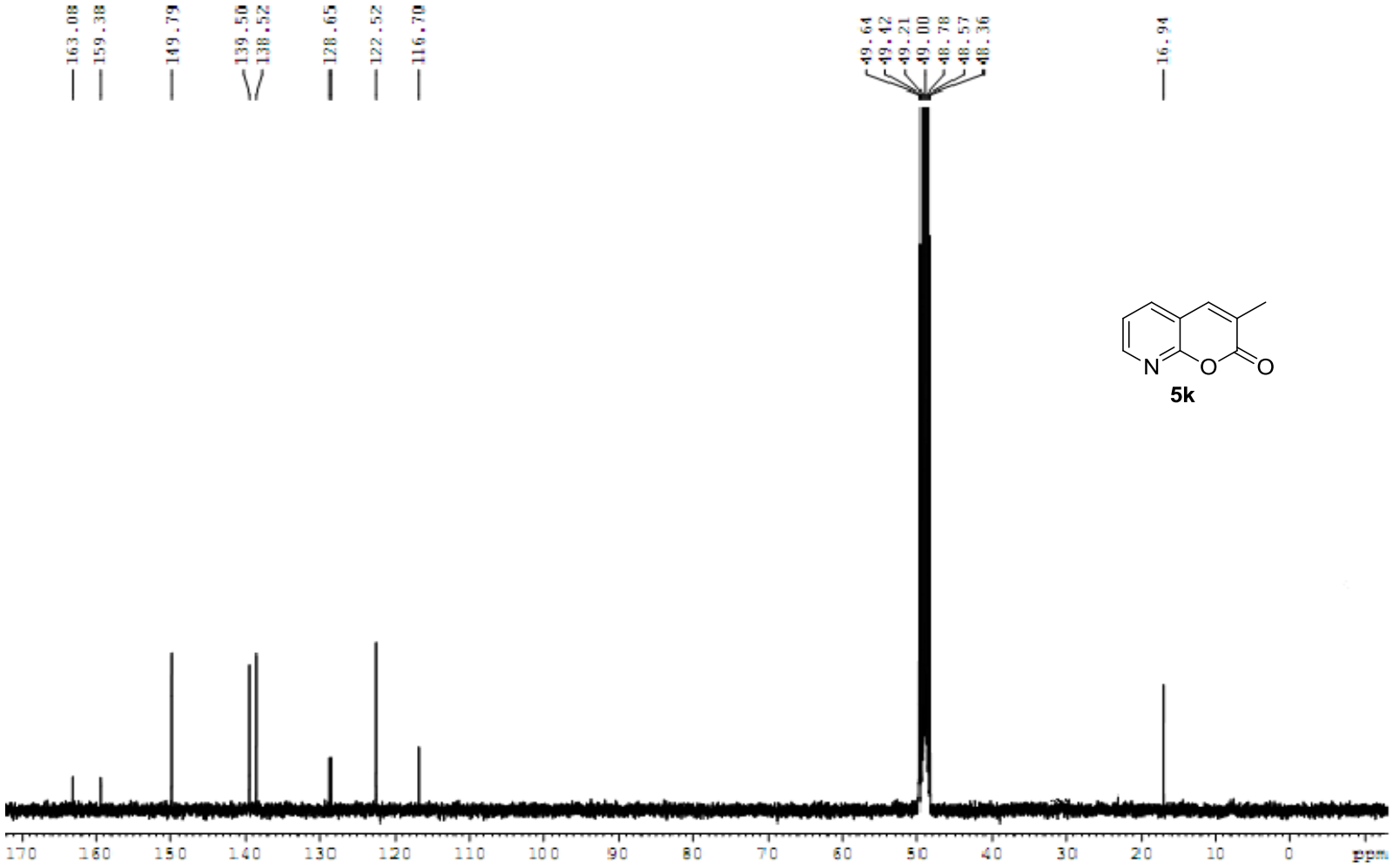

8.389
8.375
8.024
8.000
7.260
6.776
6.762
6.407
6.383
4.020
-0.014
O
N
O
O
5j
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.02
1.03
1.02
1.00
3.05

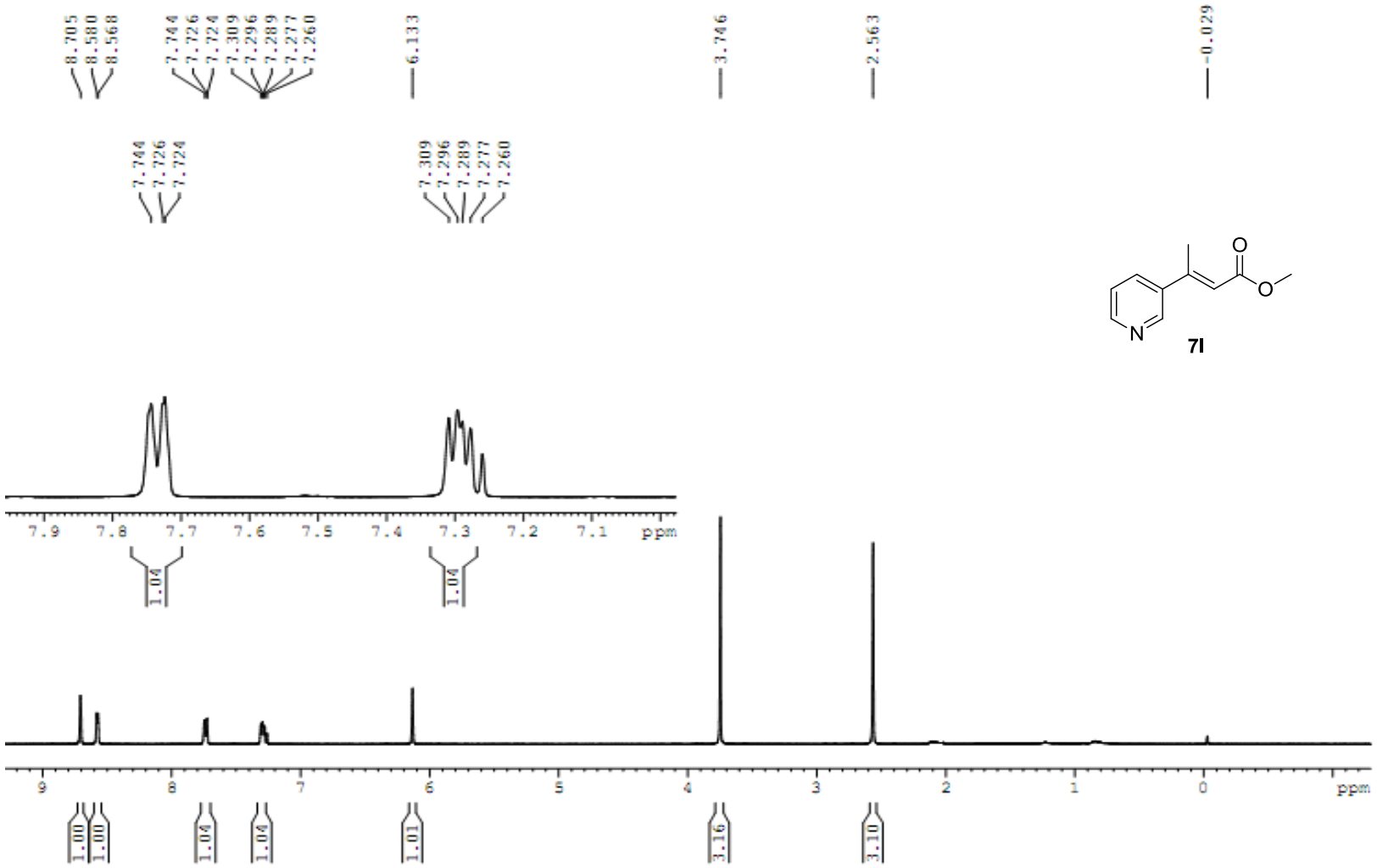

163.73
160.52
160.38
152.03
137.29
116.00
104.45
103.63
77.48
77.16
76.84
56.72
O
N
O
O
5j
165
164
163
162
161
160
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

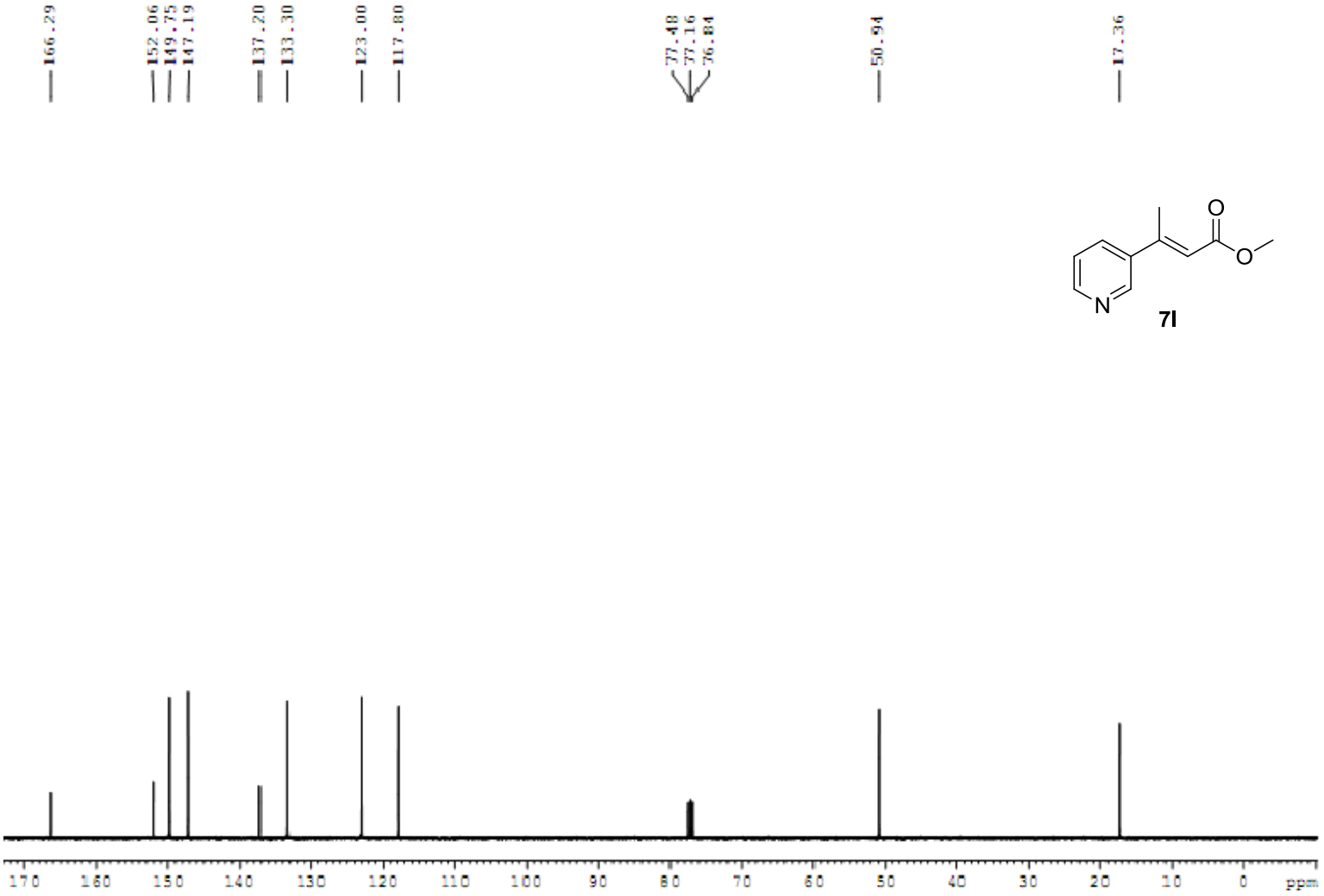

8.345
8.198
8.184
7.482
7.462
7.441
7.420
2.500
2.000
0.013
O
OH
N+
O-
3k
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
0.97
3.01
3.05

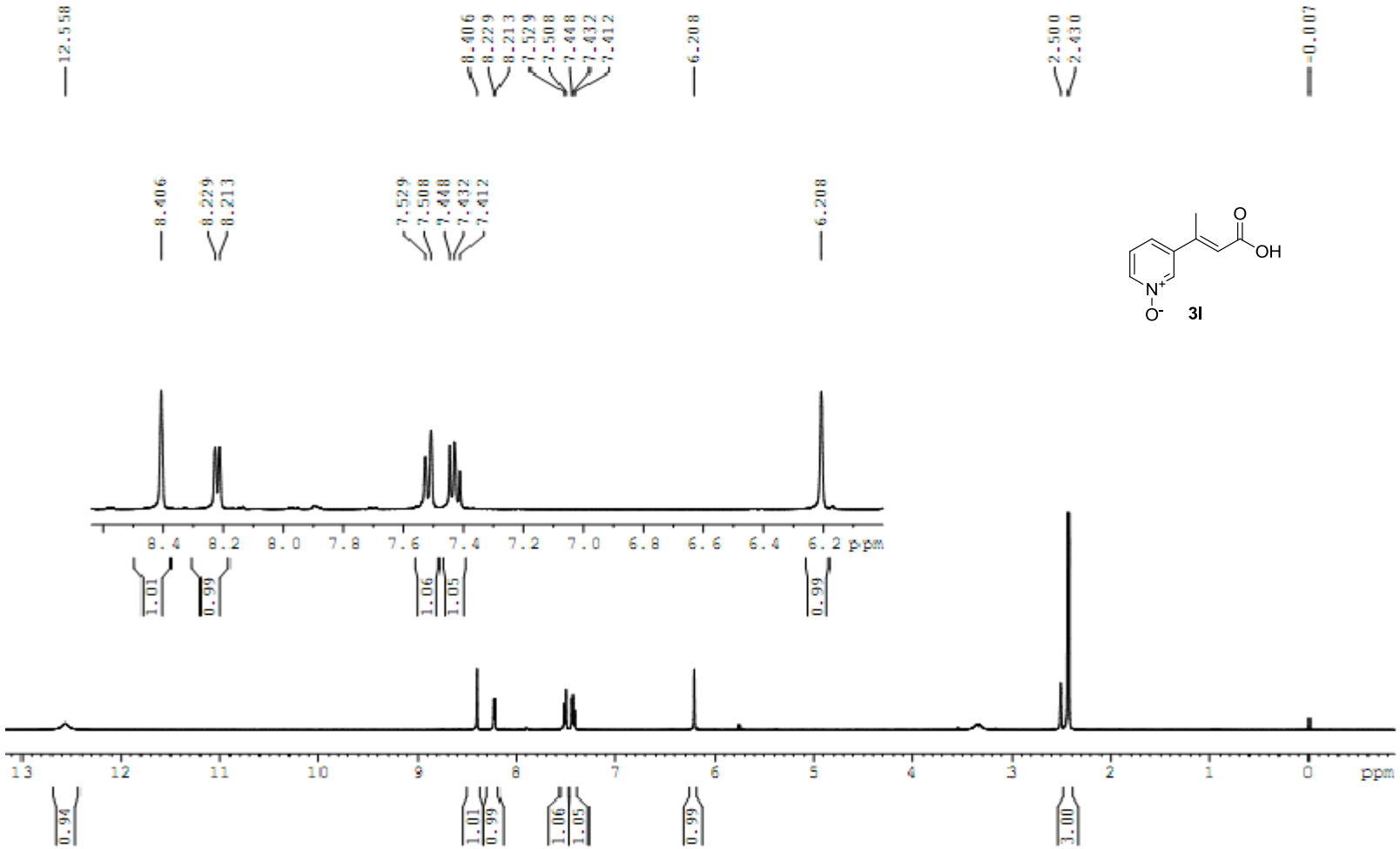

168.66
138.76
138.02
134.90
133.13
131.93
126.32
125.85
40.15
39.94
39.73
39.52
39.31
39.10
38.89
14.06
O
OH
N+
O-
3k
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

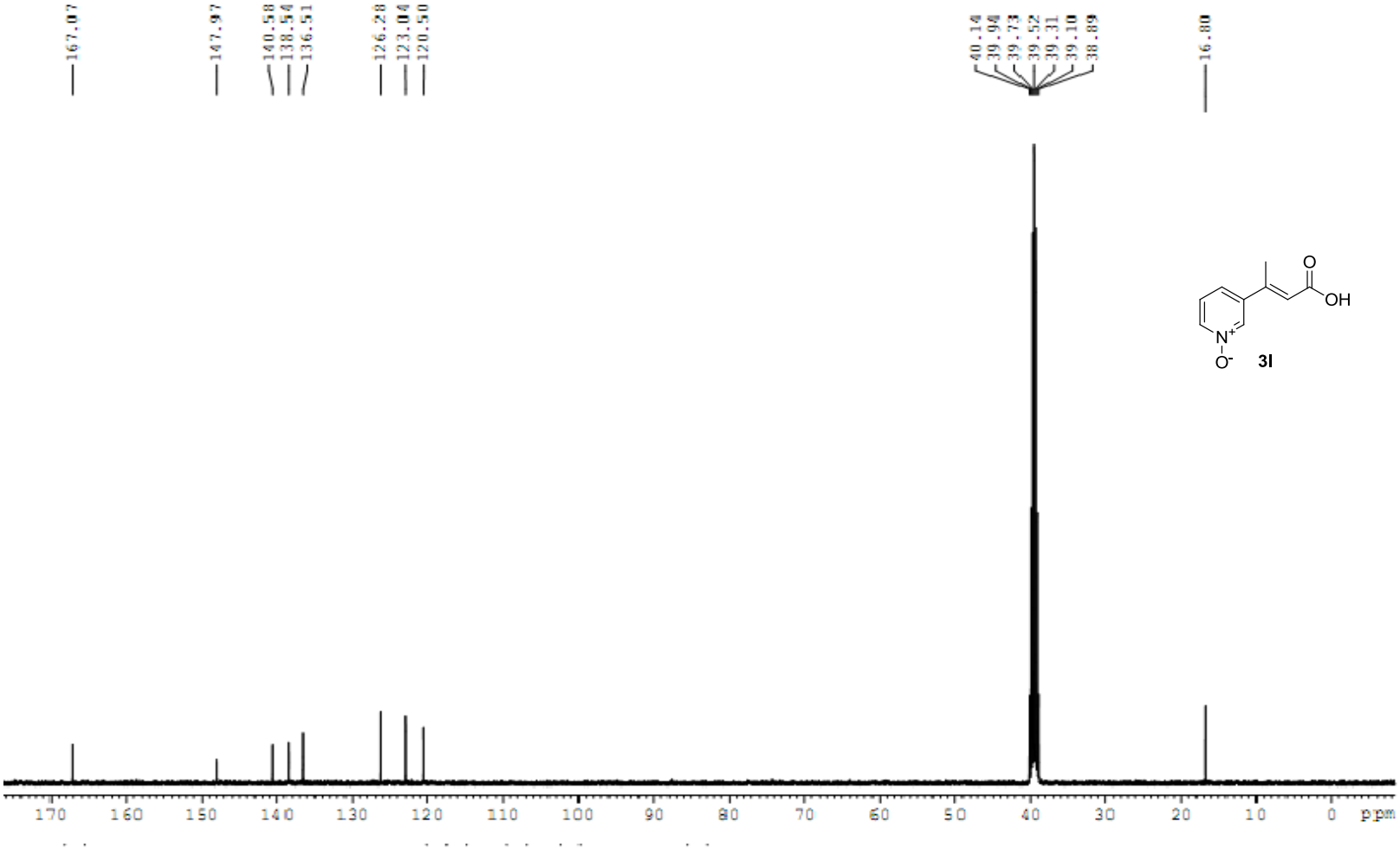

8.415
8.403
8.081
8.062
7.791
7.415
7.402
7.396
7.384
4.852
3.310
2.203
0.002
N
O
O
5k
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.01
1.01
1.03
3.04

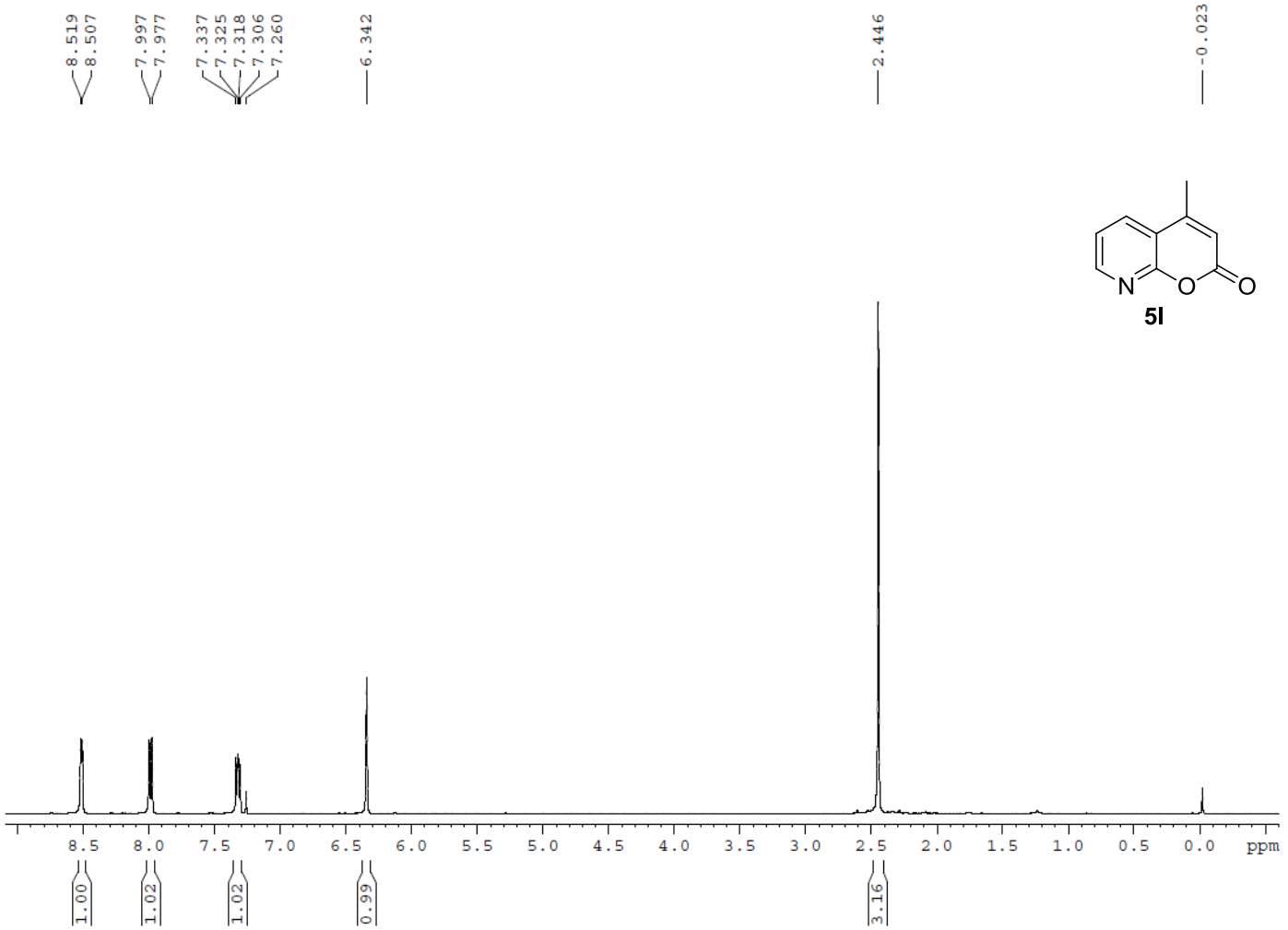

163.08
159.38
149.79
139.50
138.52
128.65
122.52
116.70
49.64
49.42
49.21
49.00
48.78
48.57
48.36
16.94
N
O
O
5k
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


8.705
8.580
8.568
7.744
7.726
7.724
7.309
7.296
7.289
7.277
7.260
6.133
3.746
2.563
-0.029
O
O
N
7l
ppm
1.00
1.00
1.04
1.04
1.01
3.16
3.10


166.29
152.06
149.75
147.19
137.20
133.30
123.00
117.80
77.48
77.16
76.84
50.94
17.36
O
O
N
7l
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


12.558
8.406
8.229
8.213
7.529
7.508
7.448
7.432
7.412
6.208
2.500
2.430
0.007
OH
O
N+
O-
3l
ppm
1.01
0.99
1.06
1.05
0.99
0.94
3.00


167.07
147.97
140.58
138.54
136.51
126.28
123.04
120.50
40.14
39.94
39.73
39.52
39.31
39.10
38.89
16.80
O
OH
N+
O-
3l
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



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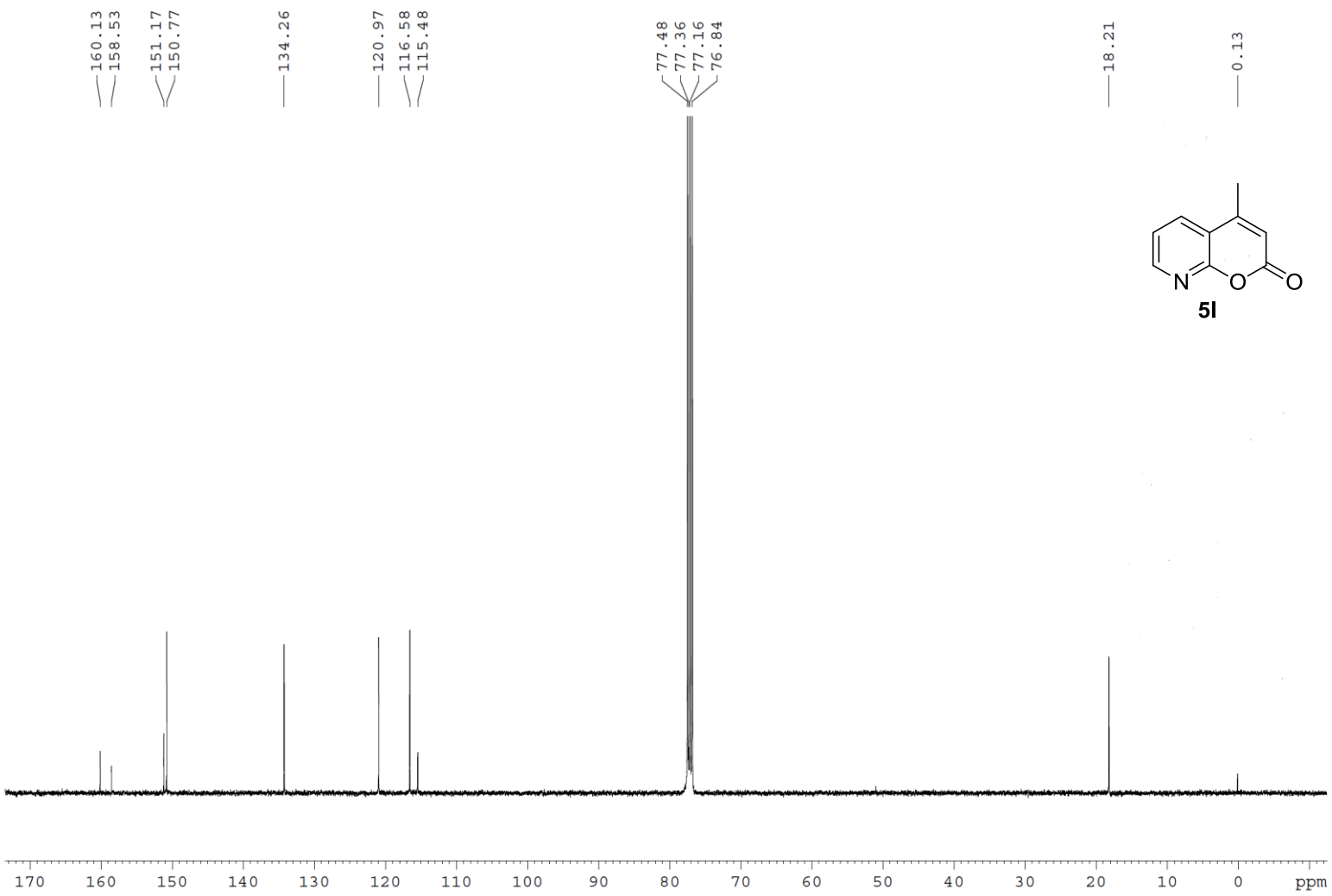
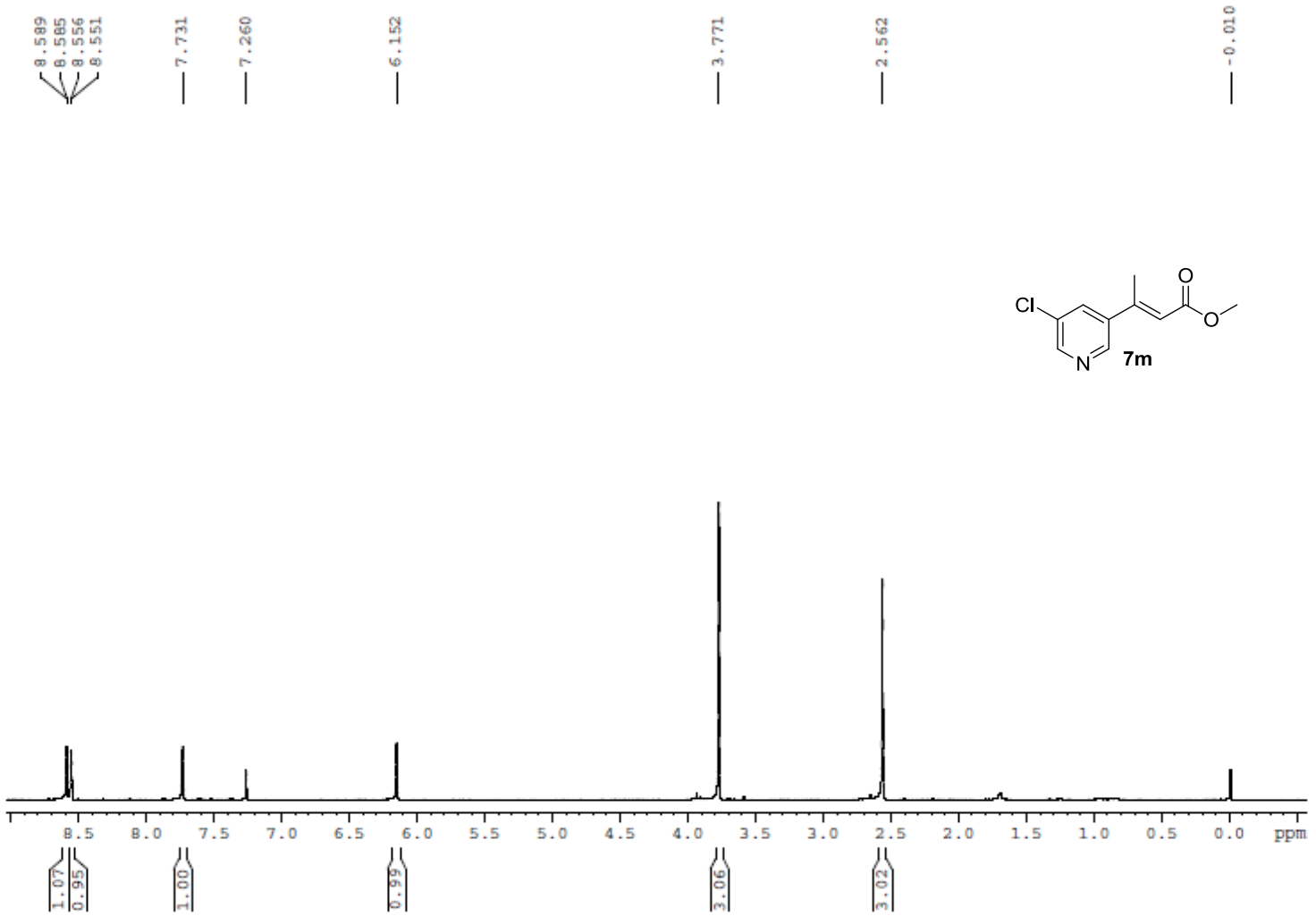
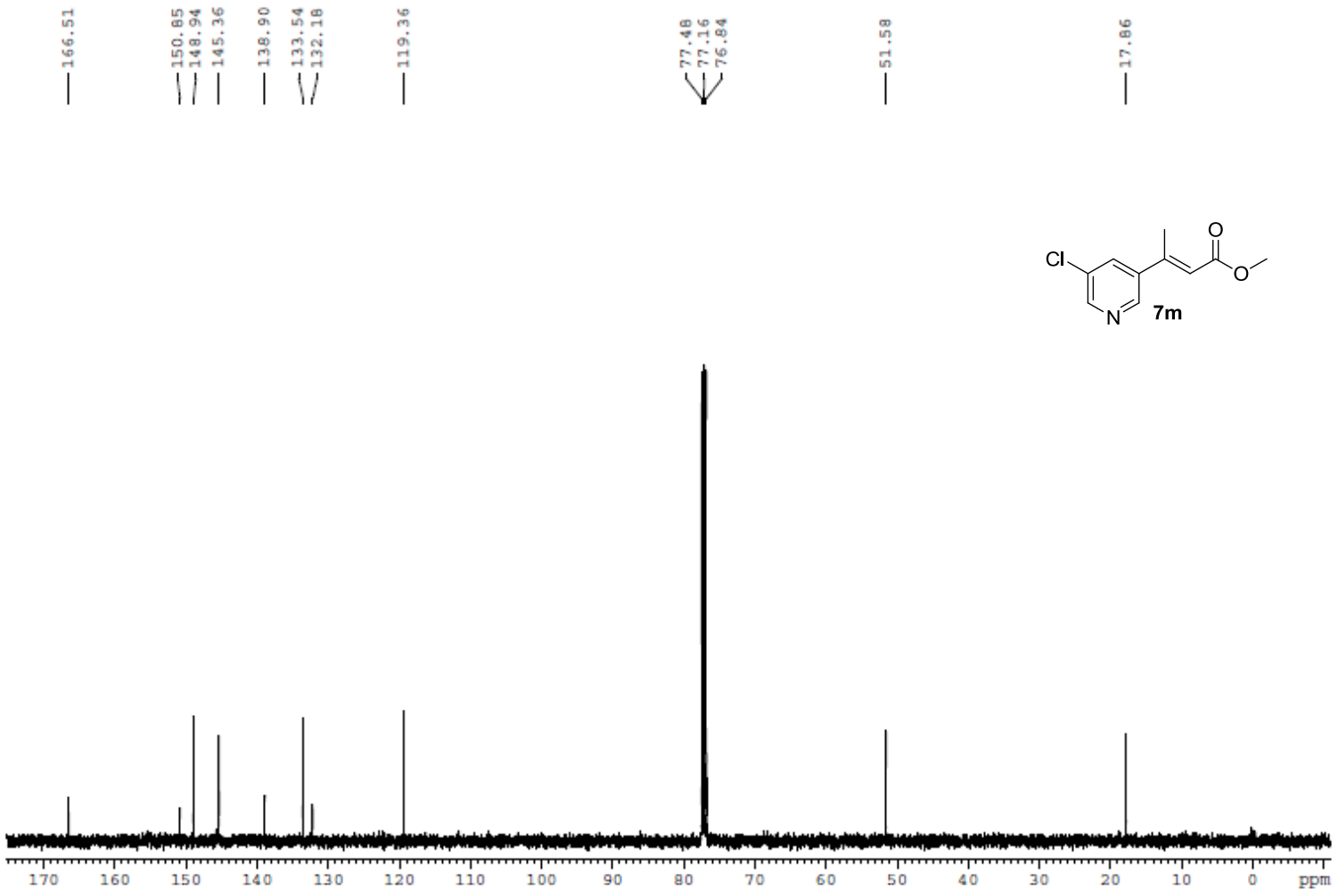
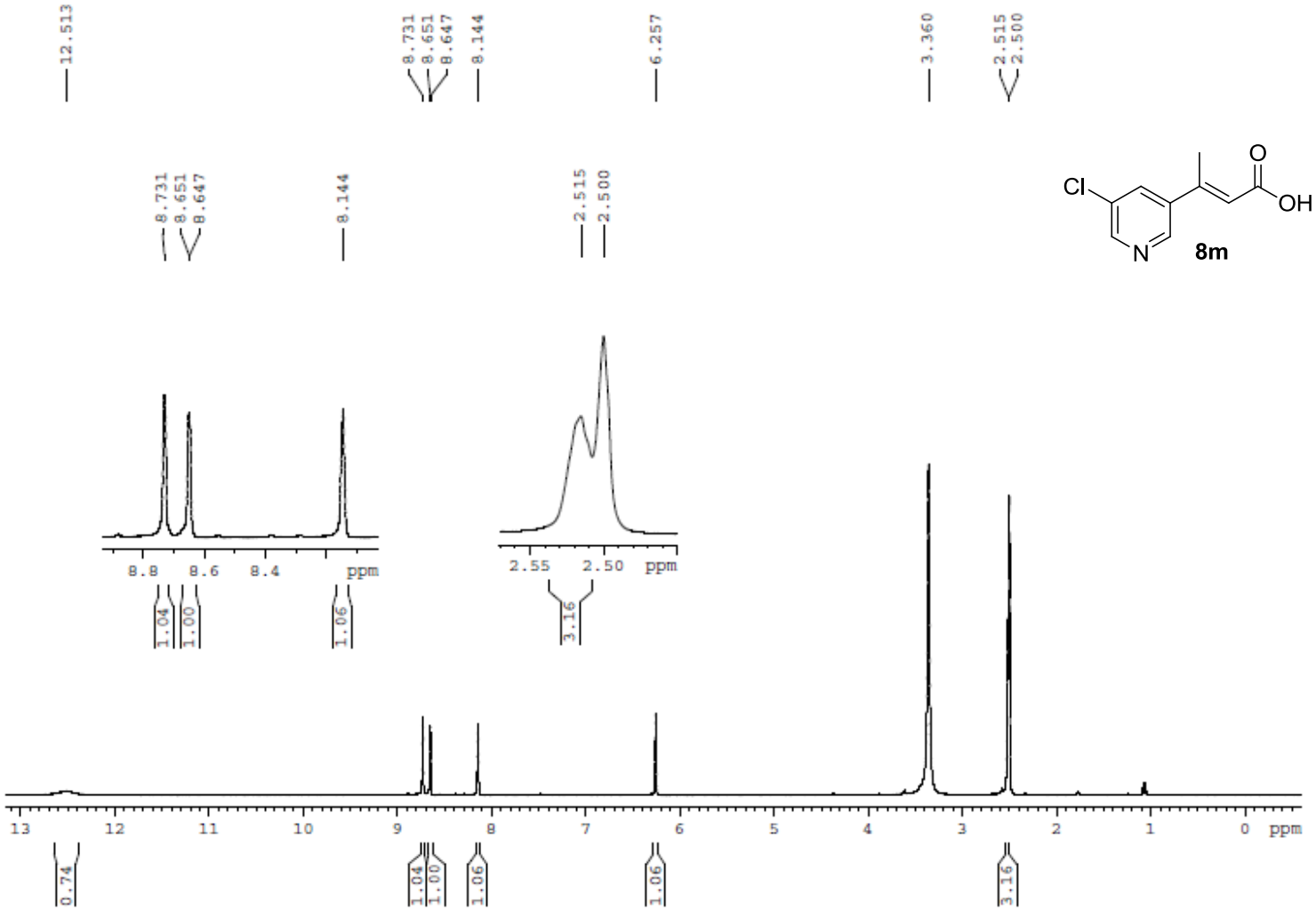


DOI: 10.1021/acs.orglett.6b03771


8.589
8.585
8.556
8.551
7.731
7.260
6.152
3.771
2.562
-0.010
Cl
O
O
N
7m
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.07
0.95
1.00
0.99
3.06
3.02


166.51
150.85
148.94
145.36
138.90
133.54
132.18
119.36
77.48
77.16
76.84
51.58
17.86
Cl
N
O
O
7m
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



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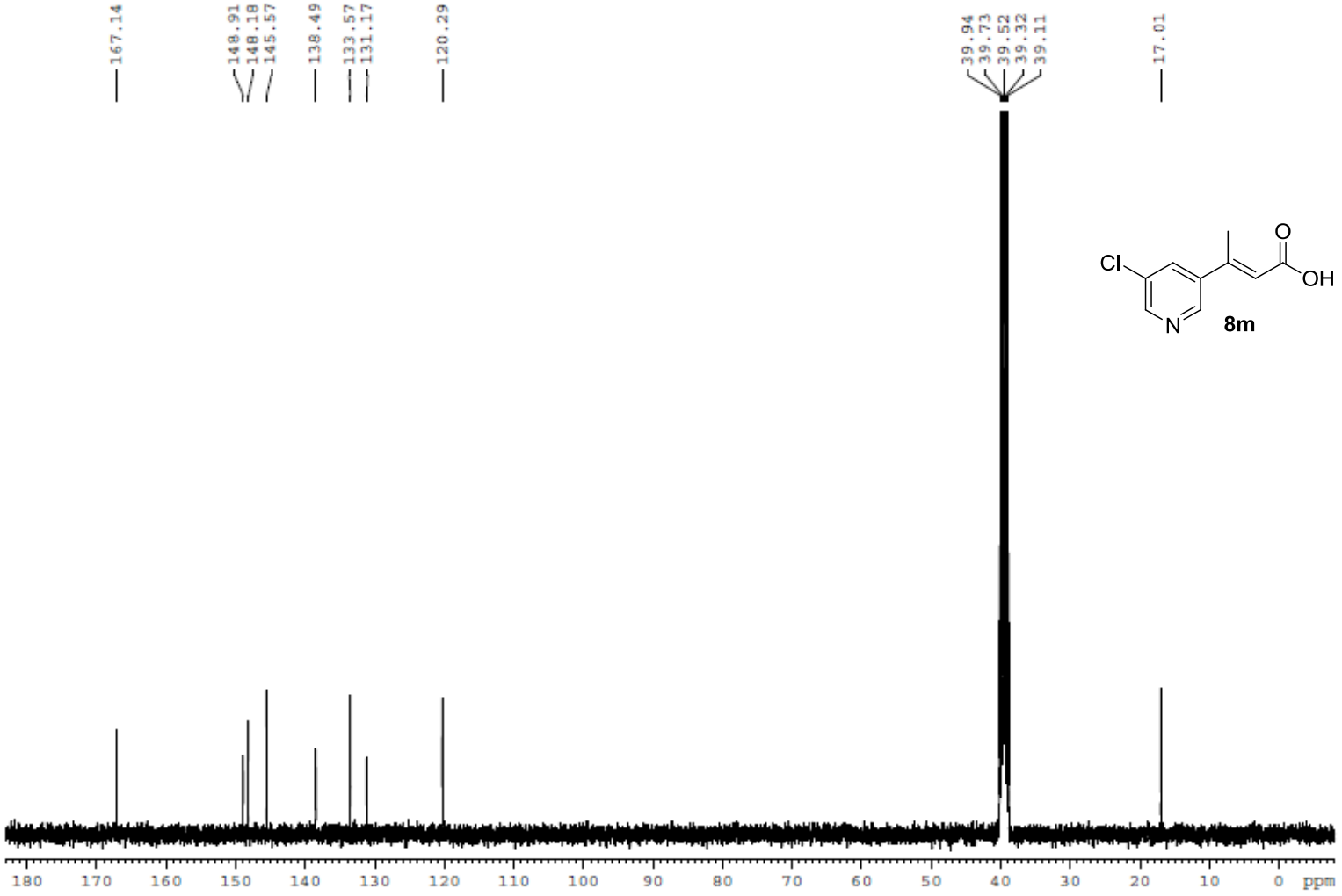
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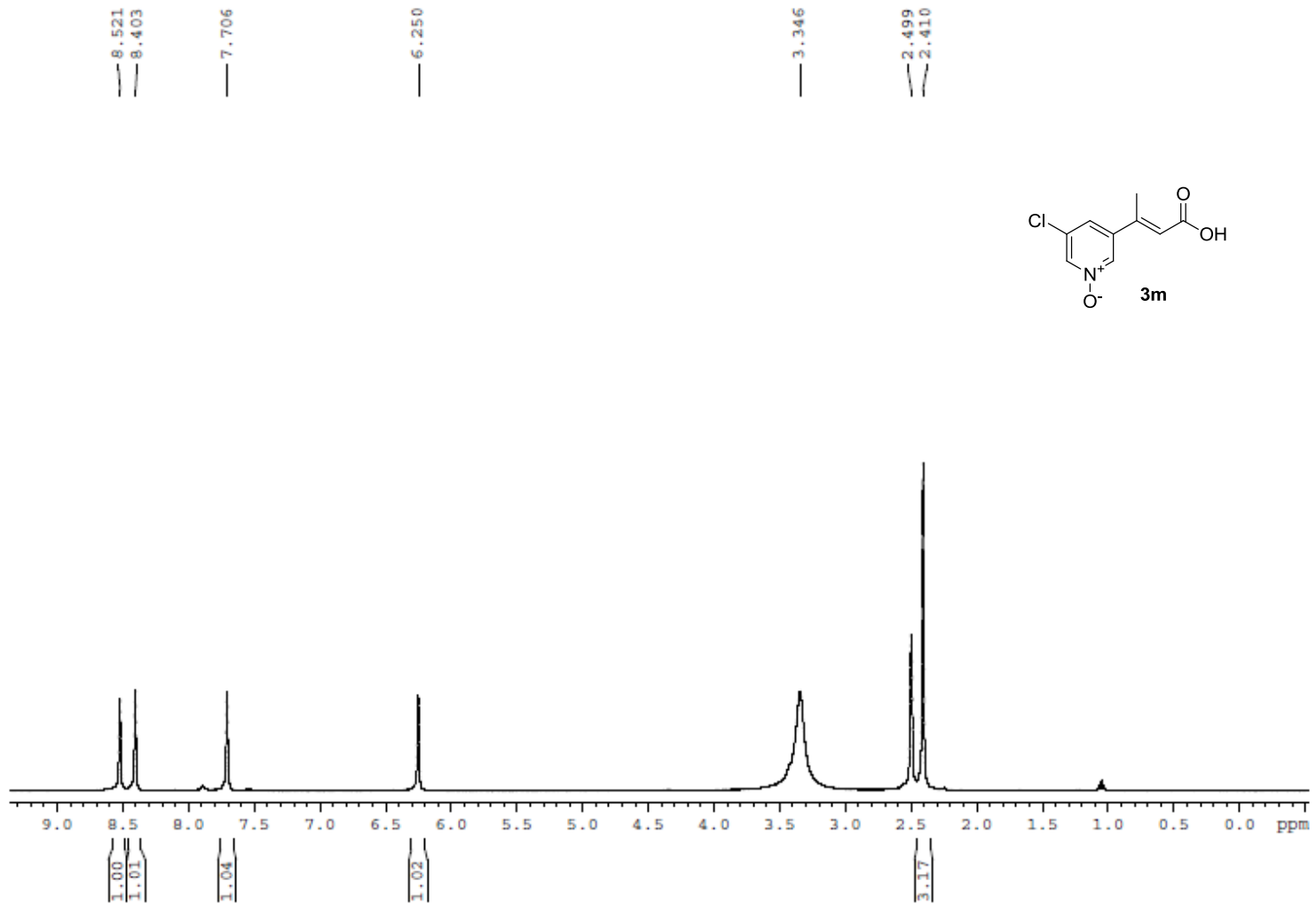
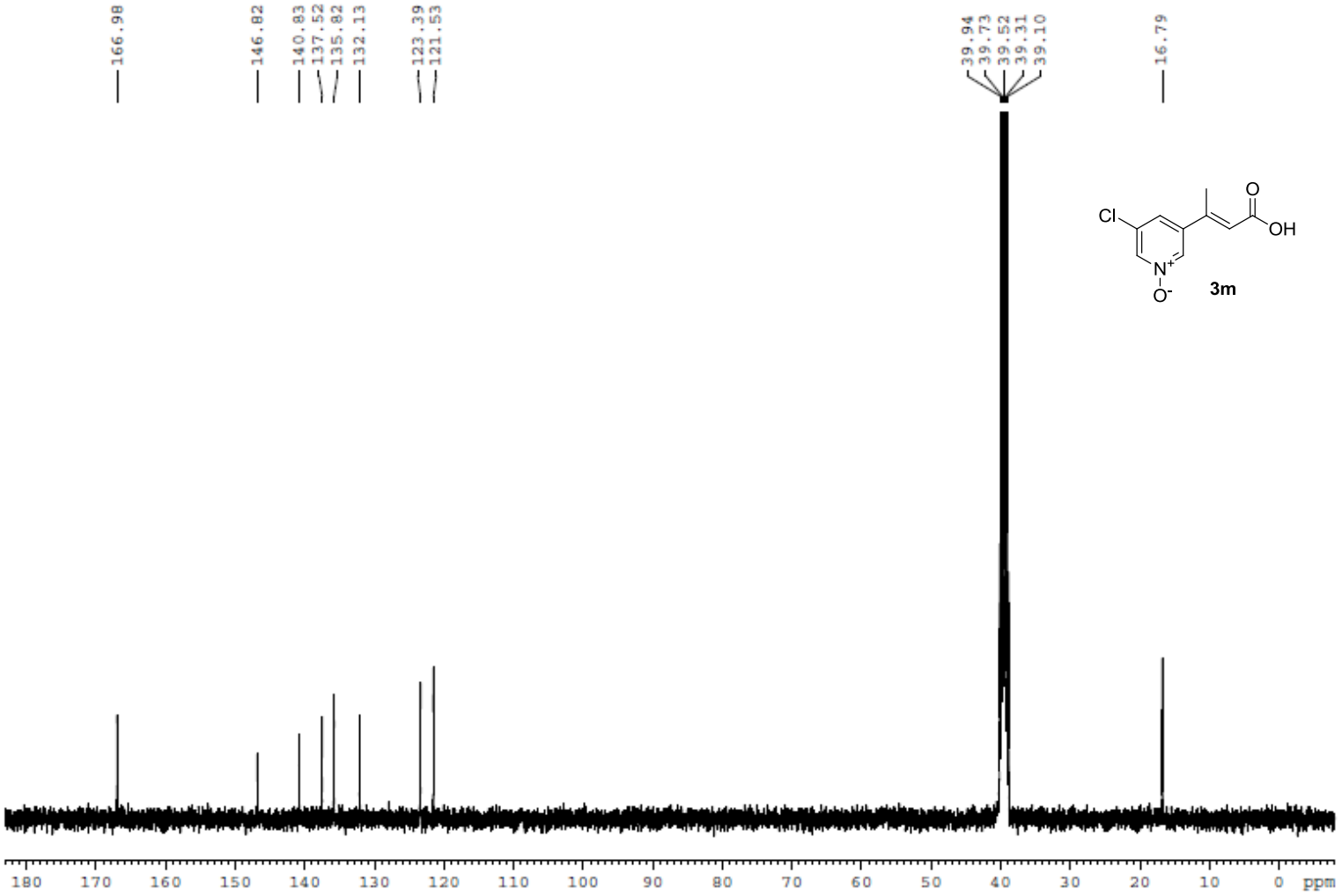
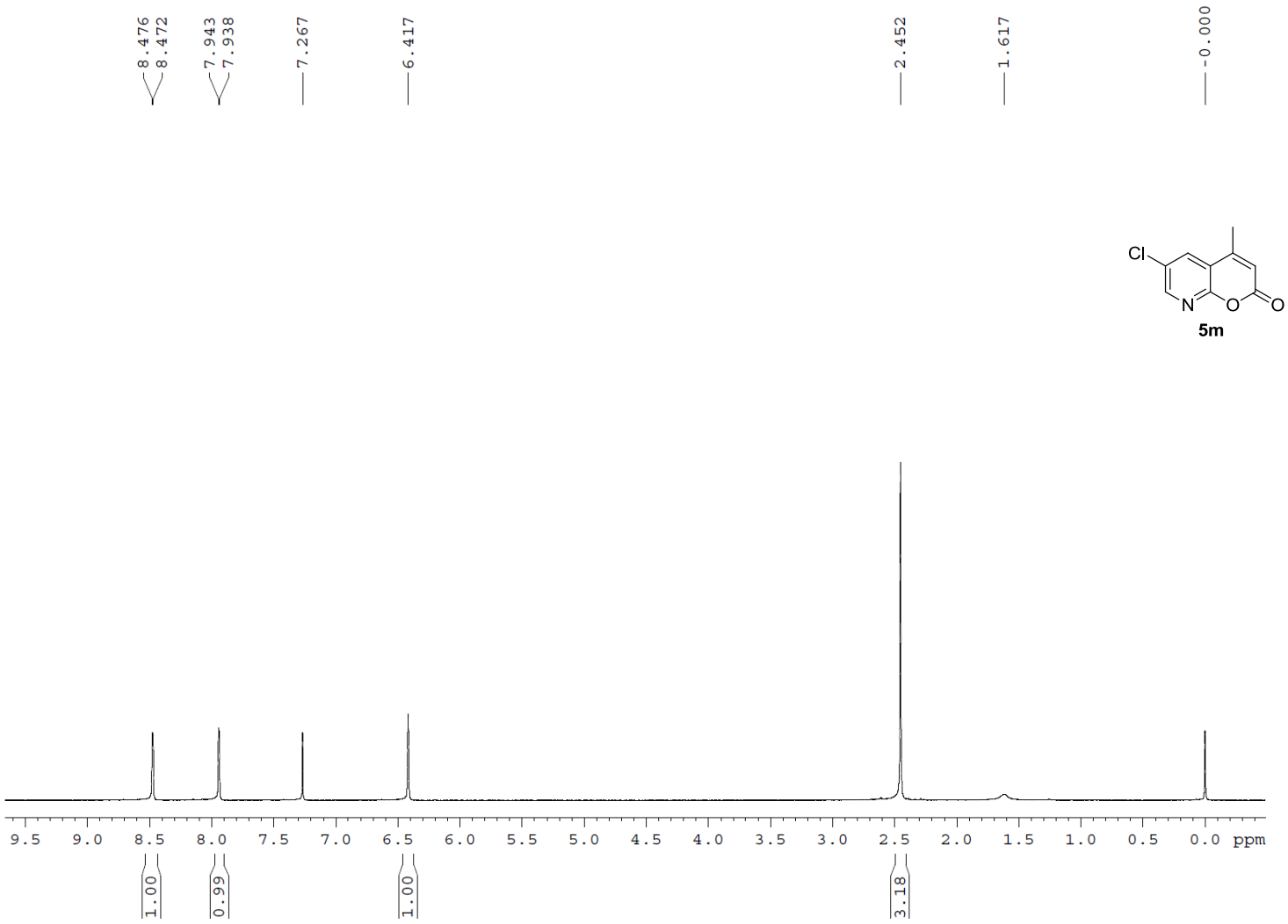
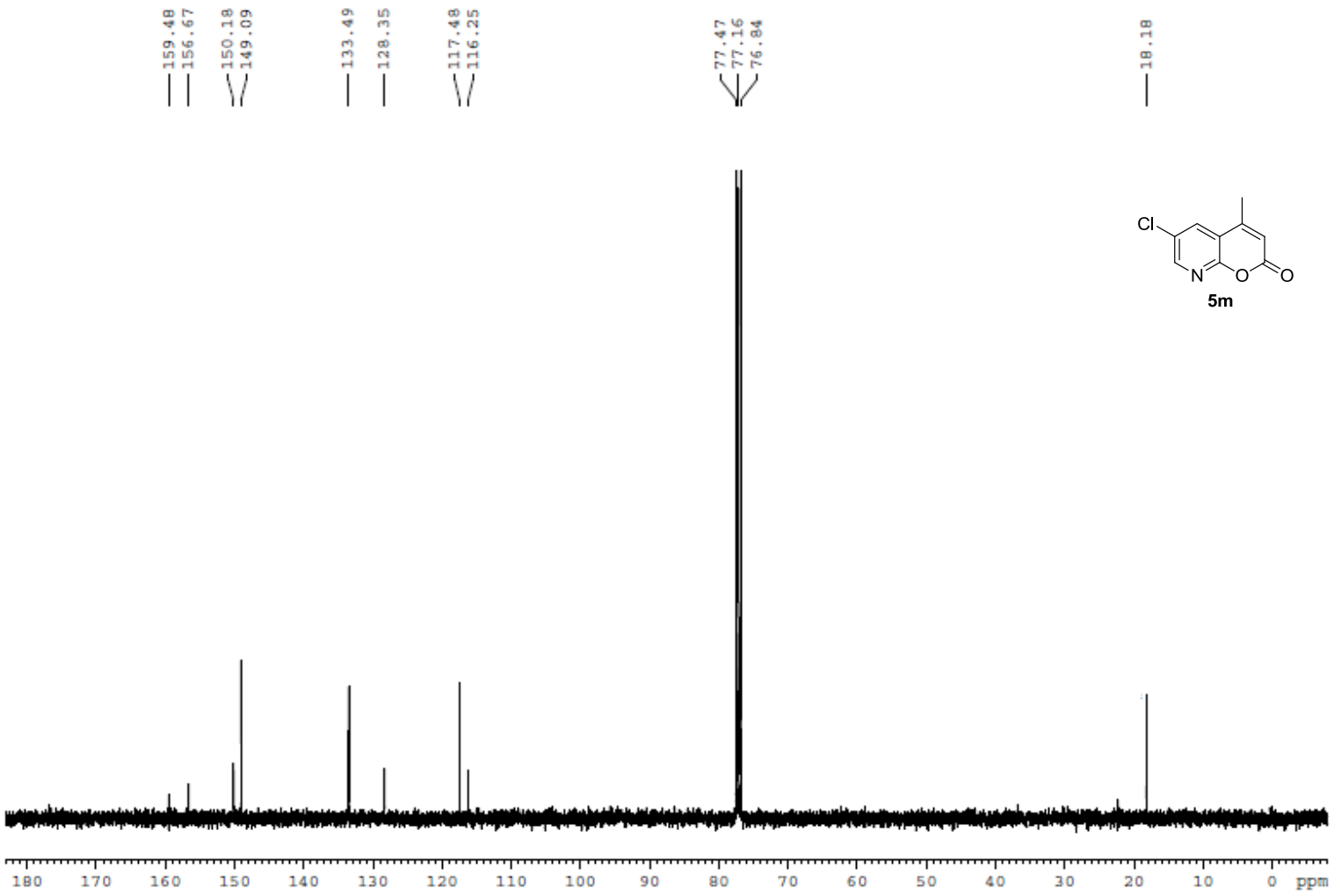
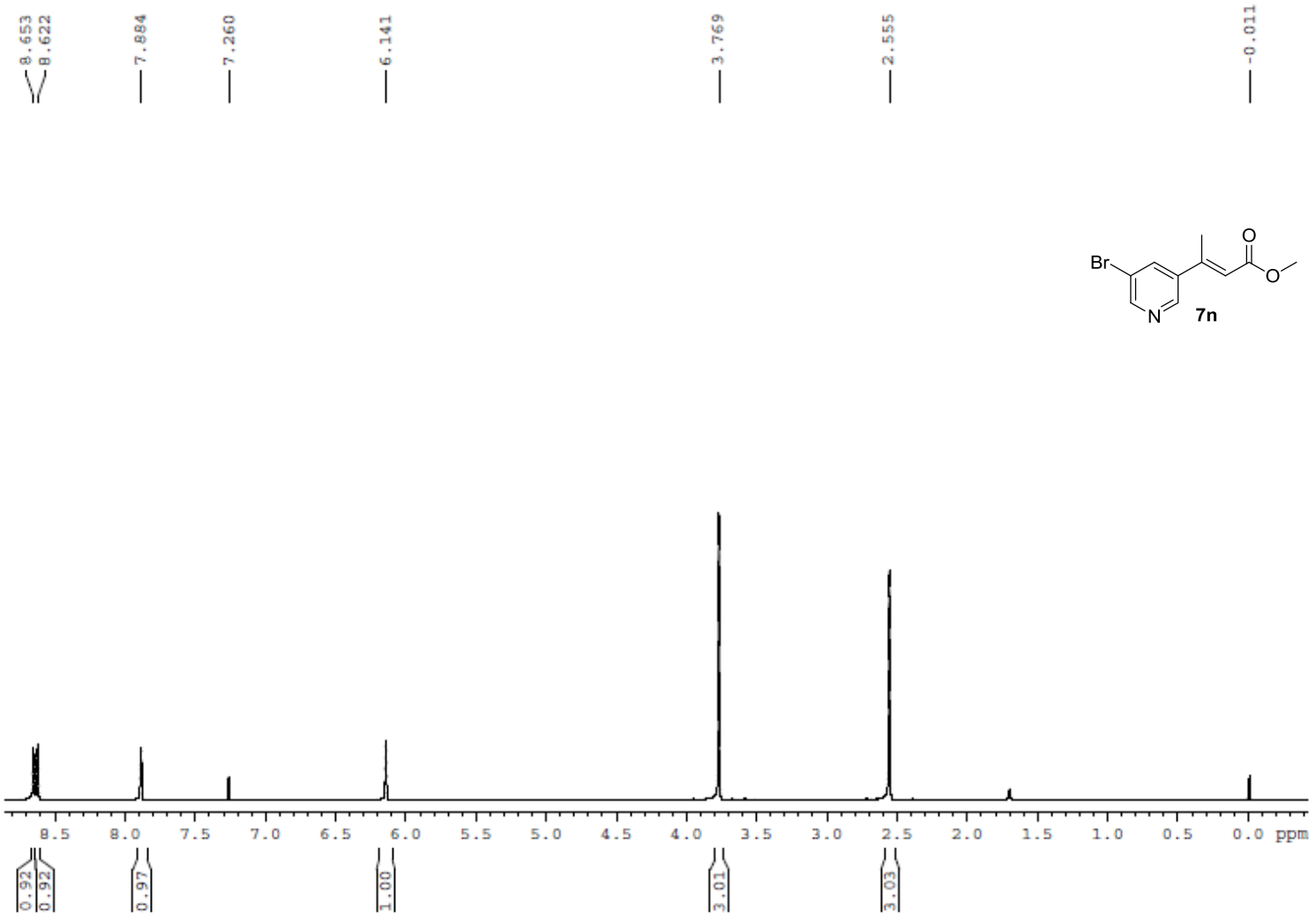
148.91
148.18
145.57
138.49
133.57
131.17
120.29
39.94
39.73
39.52
39.32
39.11
17.01
Cl
N
O
OH
8m
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

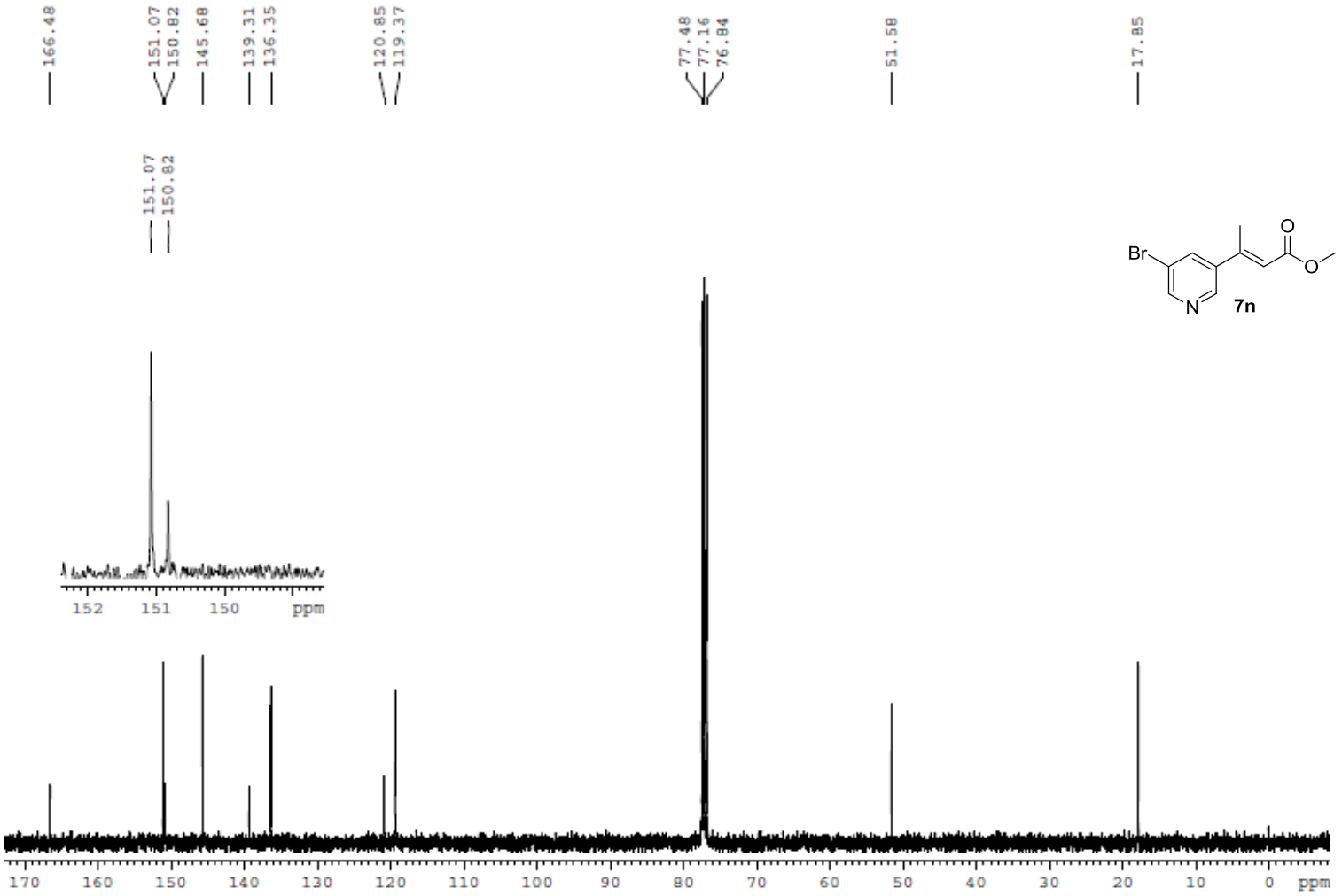

8.521
8.403
7.706
6.250
3.346
2.499
2.410
Cl
O
OH
N+
O-
3m
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.01
1.04
1.02
3.17

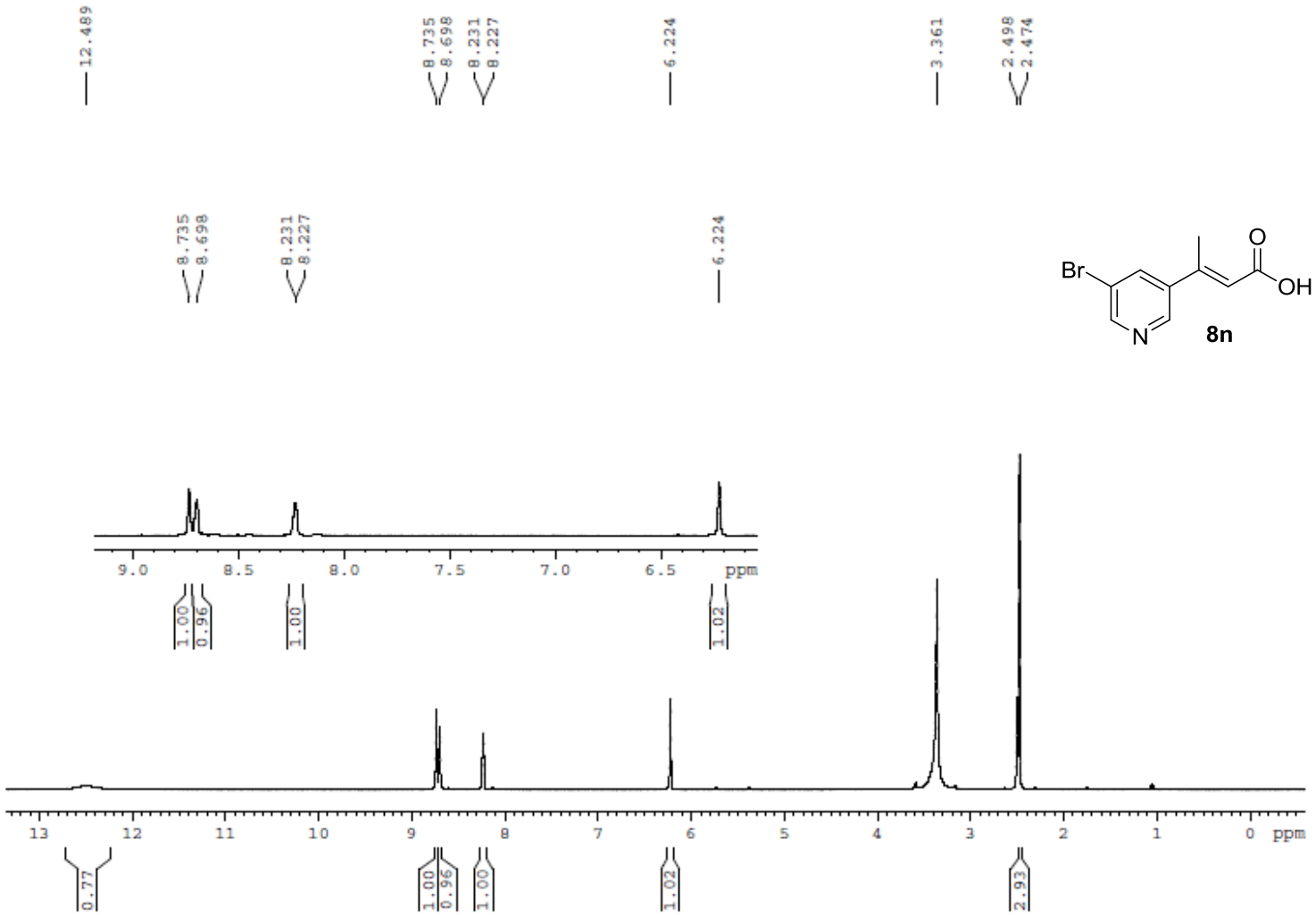

166.98
146.82
140.83
137.52
135.82
132.13
123.39
121.53
39.94
39.73
39.52
39.31
39.10
16.79
Cl
O
OH
N+
O-
3m
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

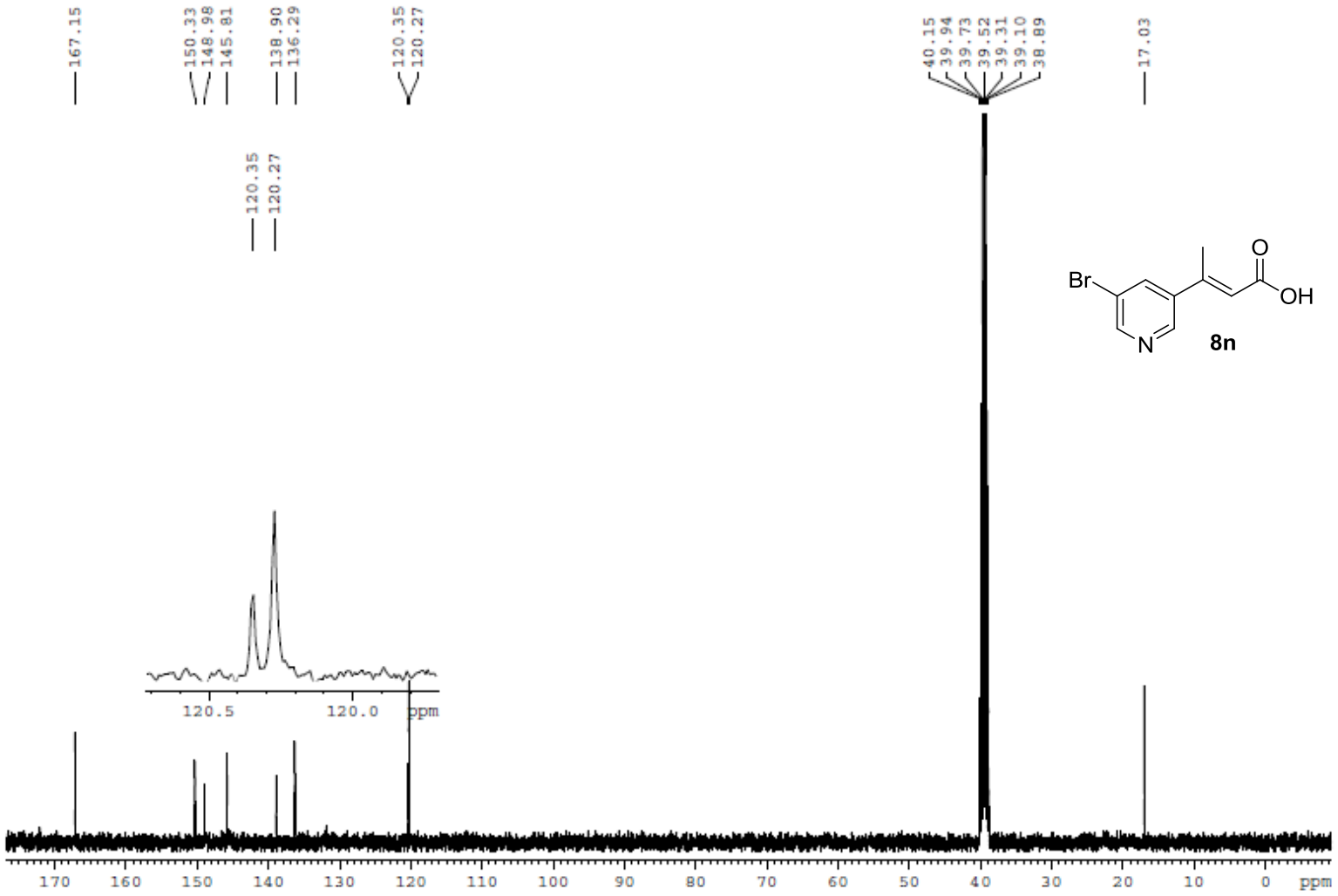

8.476
8.472
7.943
7.938
7.267
6.417
2.452
1.617
-0.000
Cl
N
O
O
5m
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
0.99
1.00
3.18

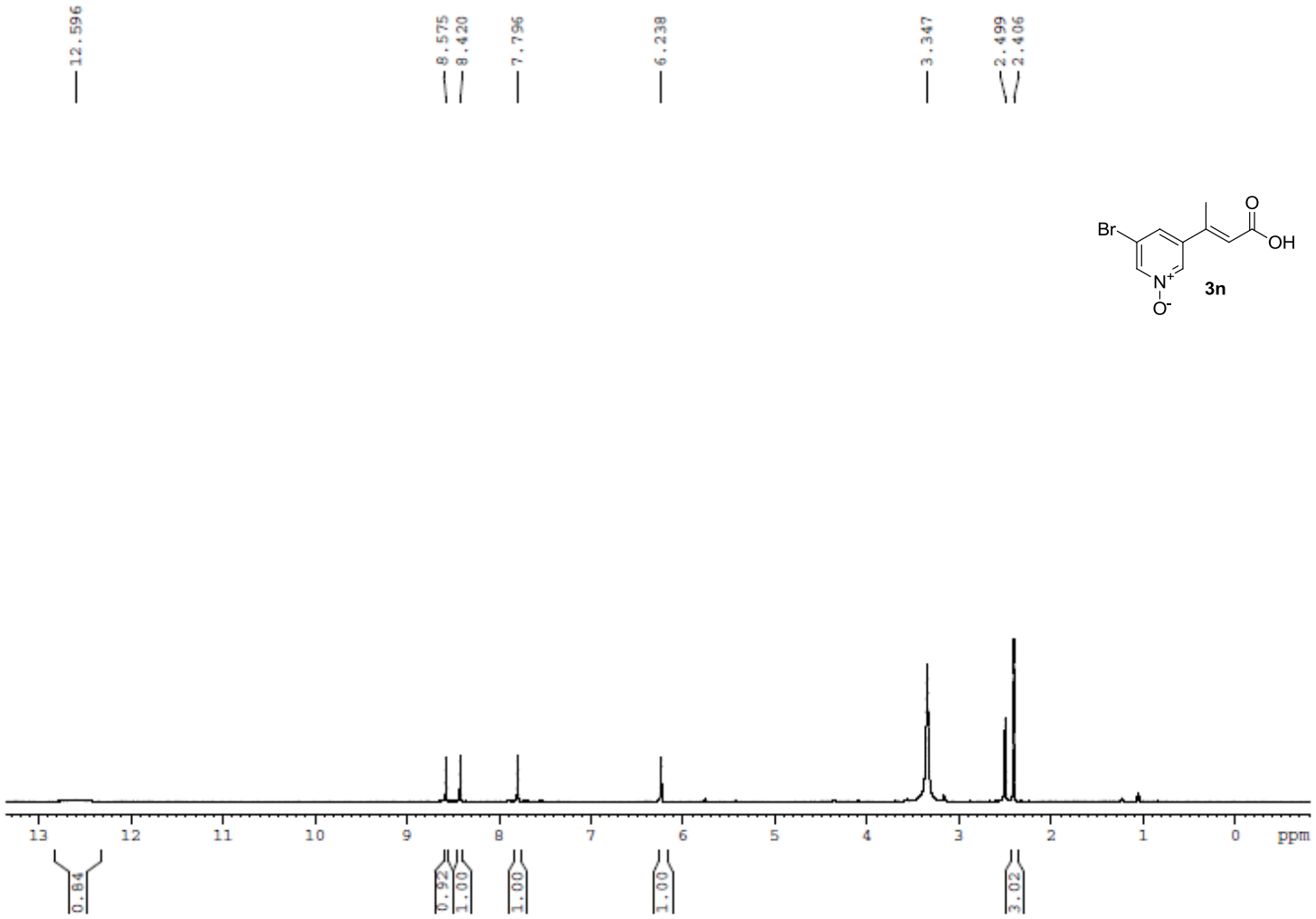

159.48
156.67
150.18
149.09
133.49
128.35
117.48
116.25
77.47
77.16
76.84
18.18
Cl
N
O
O
5m
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

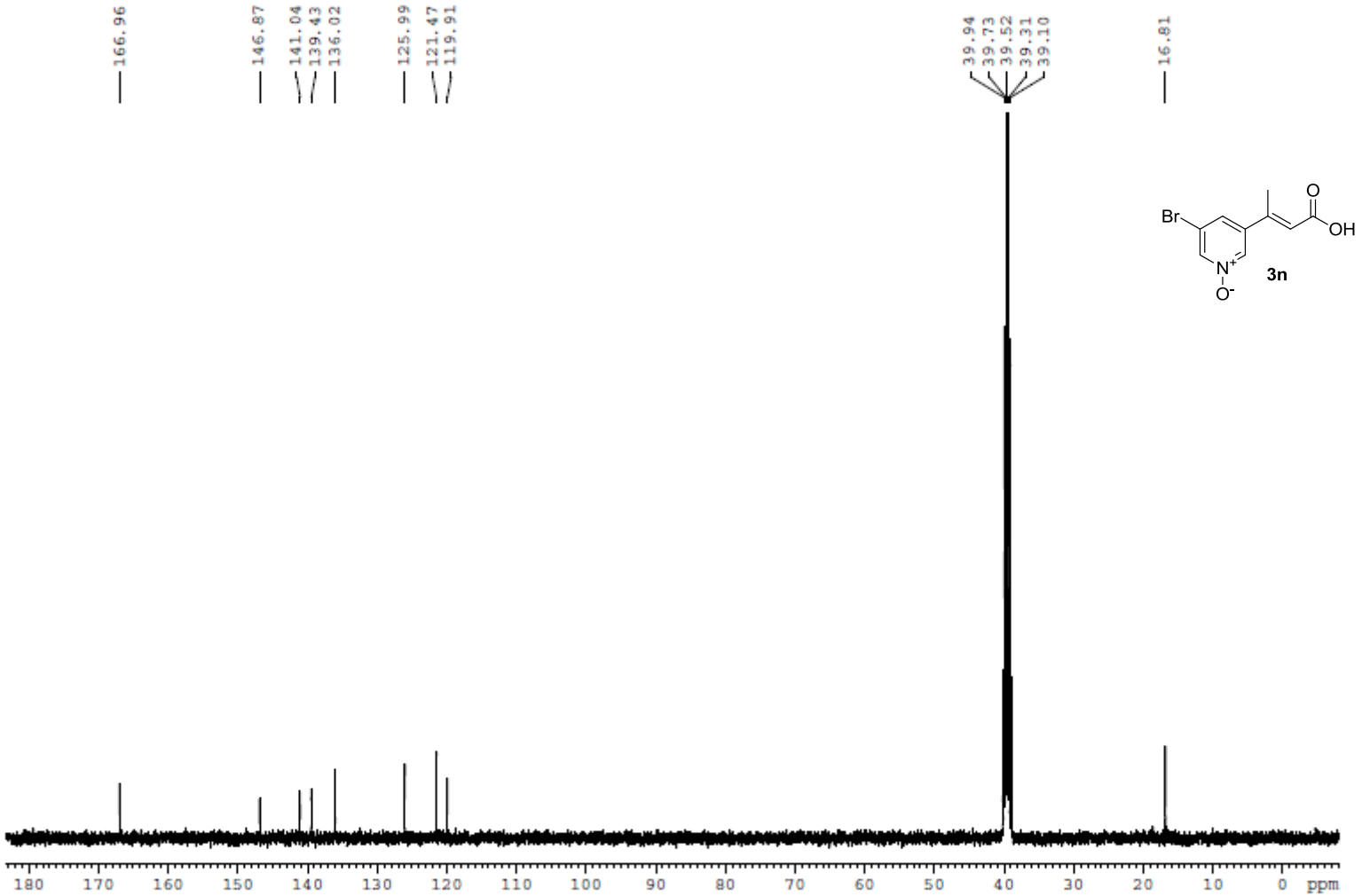

8.653
8.622
7.884
7.260
6.141
3.769
2.555
-0.011
Br
O
O
N
7n
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
0.92
0.92
0.97
1.00
3.01
3.03

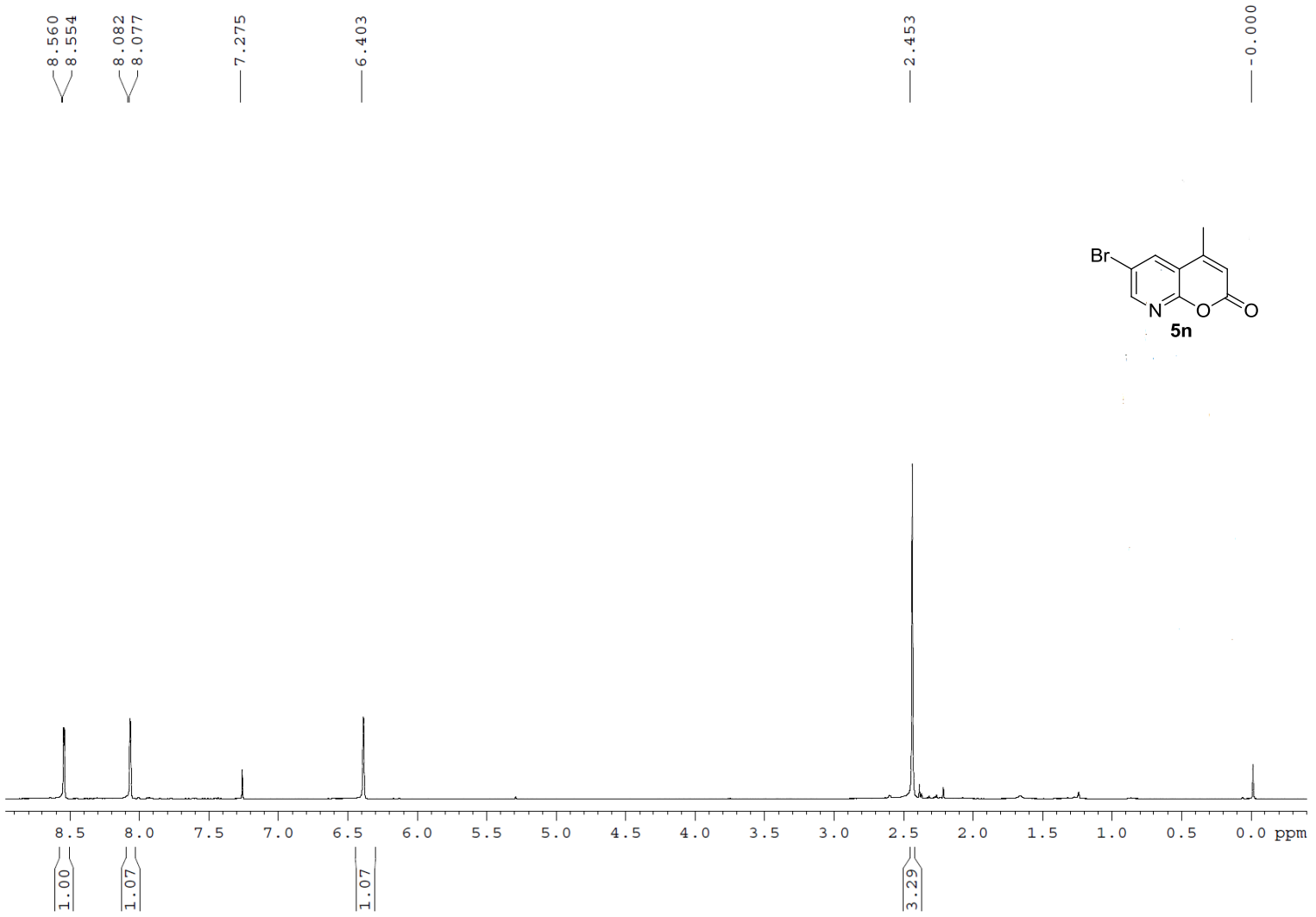

166.48
151.07
150.82
145.68
139.31
136.35
120.85
119.37
77.48
77.16
76.84
51.58
17.85
151.07
150.82
152
151
150
ppm
Br
N
O
O
7n
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


12.489
8.735
8.698
8.231
8.227
6.224
3.361
2.498
2.474
Br
N
O
OH
8n
ppm
1.00
0.96
1.00
1.02
0.77
2.93


167.15
150.33
148.98
145.81
138.90
136.29
120.35
120.27
120.35
120.27
40.15
39.94
39.73
39.52
39.31
39.10
38.89
17.03
120.5
120.0
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm
Br
N
O
OH
8n


12.596
8.575
8.420
7.796
6.238
3.347
2.499
2.406
Br
O
OH
N+
O-
3n
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.84
0.92
1.00
1.00
1.00
3.02


166.96
146.87
141.04
139.43
136.02
125.99
121.47
119.91
39.94
39.73
39.52
39.31
39.10
16.81
Br
O
OH
N+
O-
3n
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



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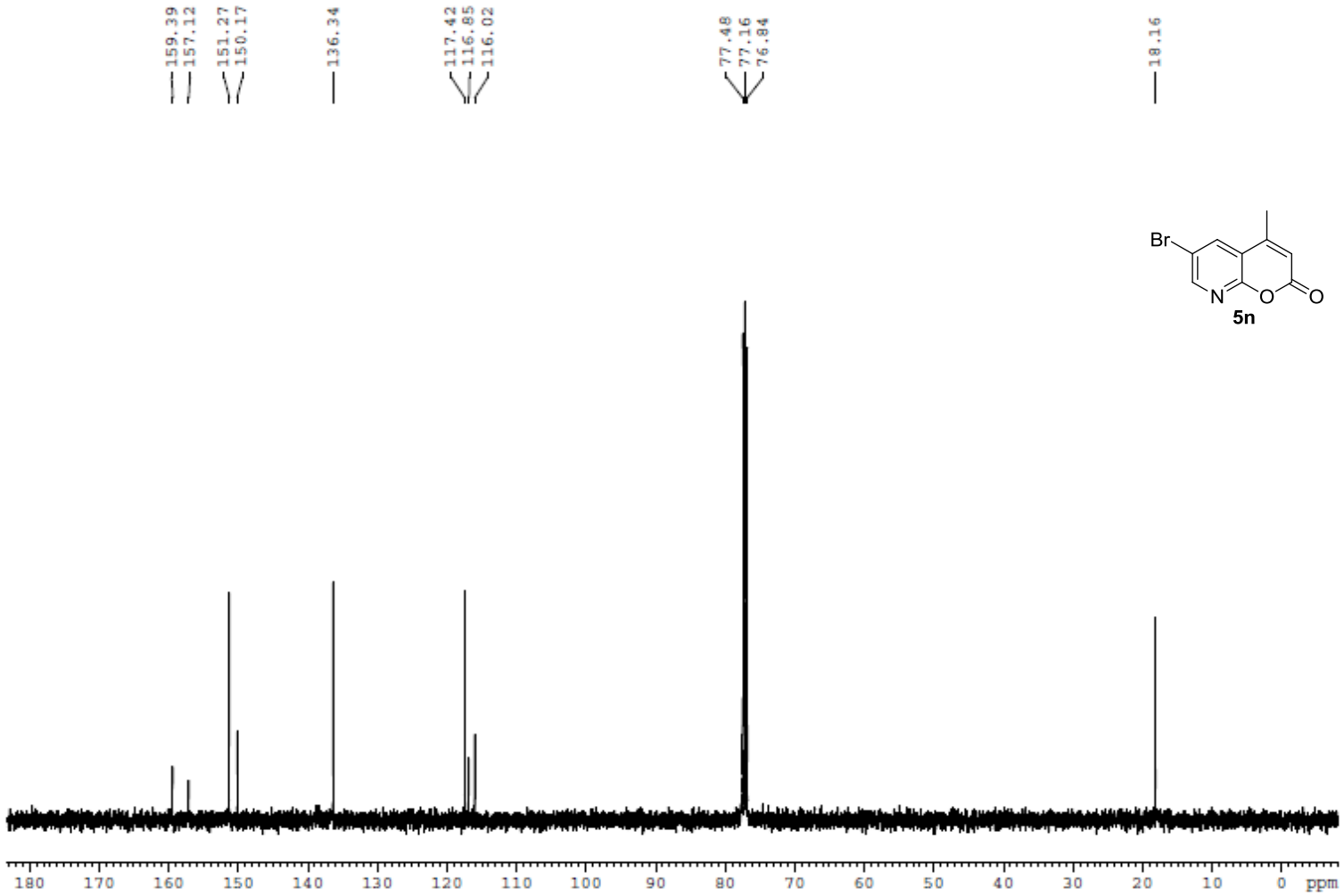
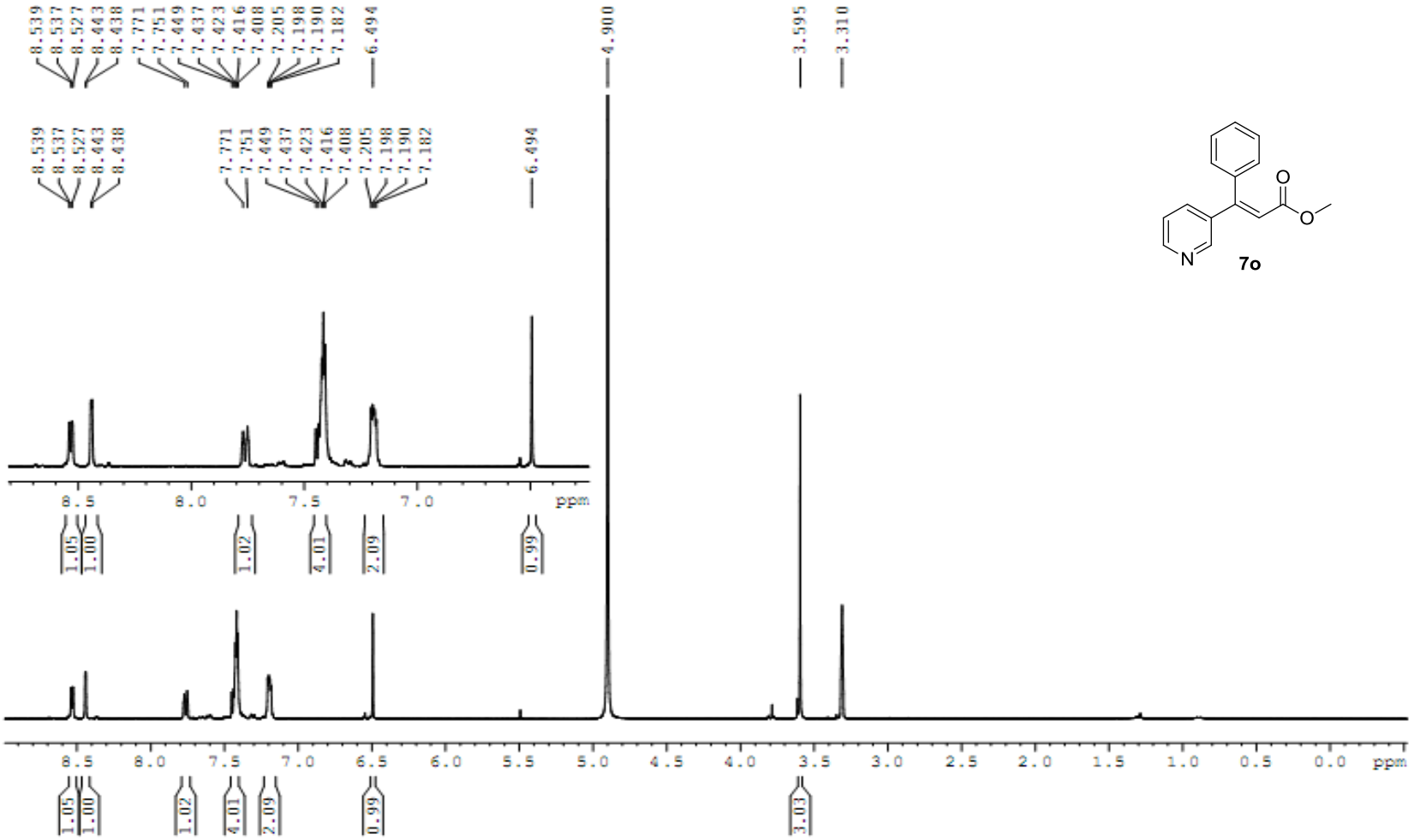
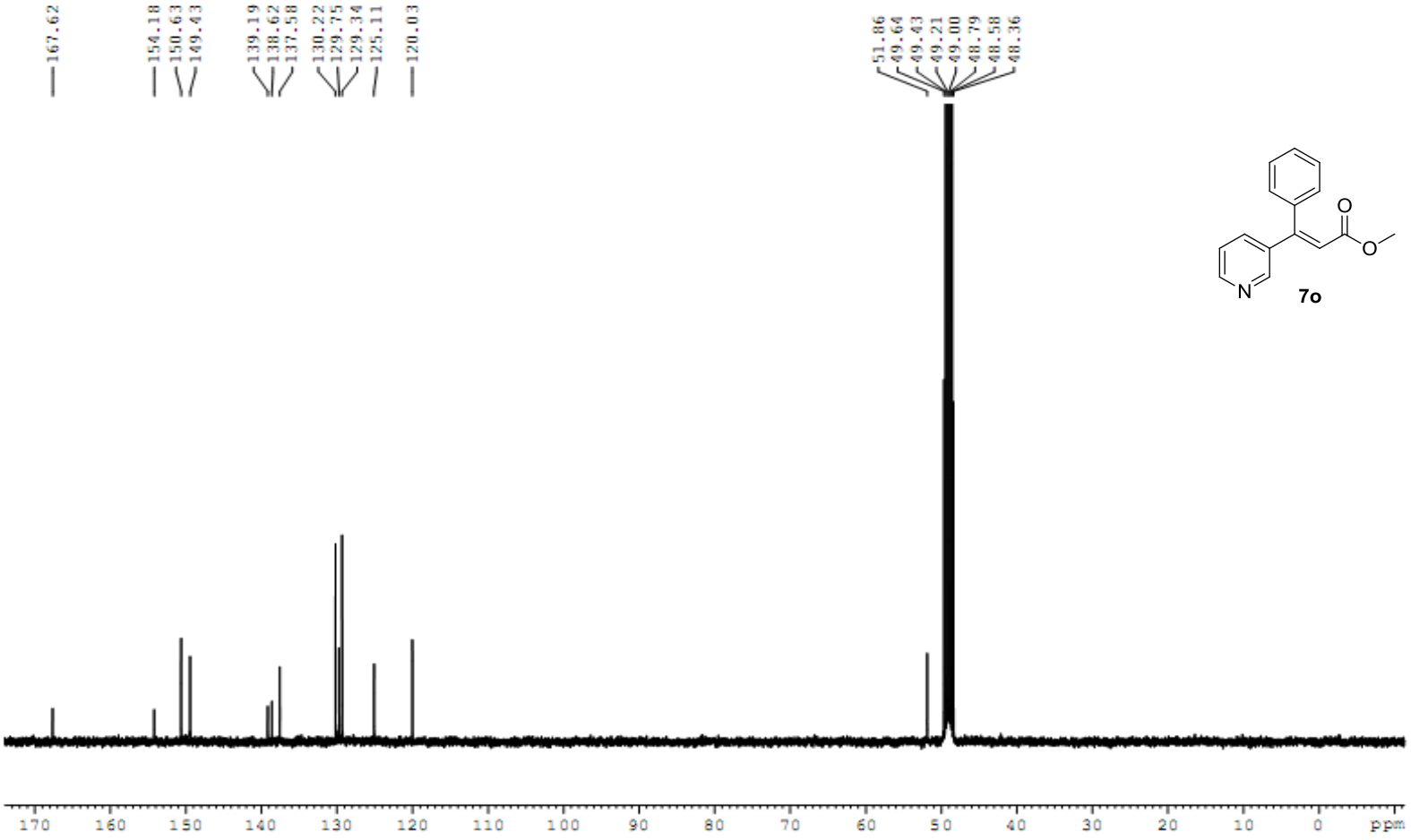
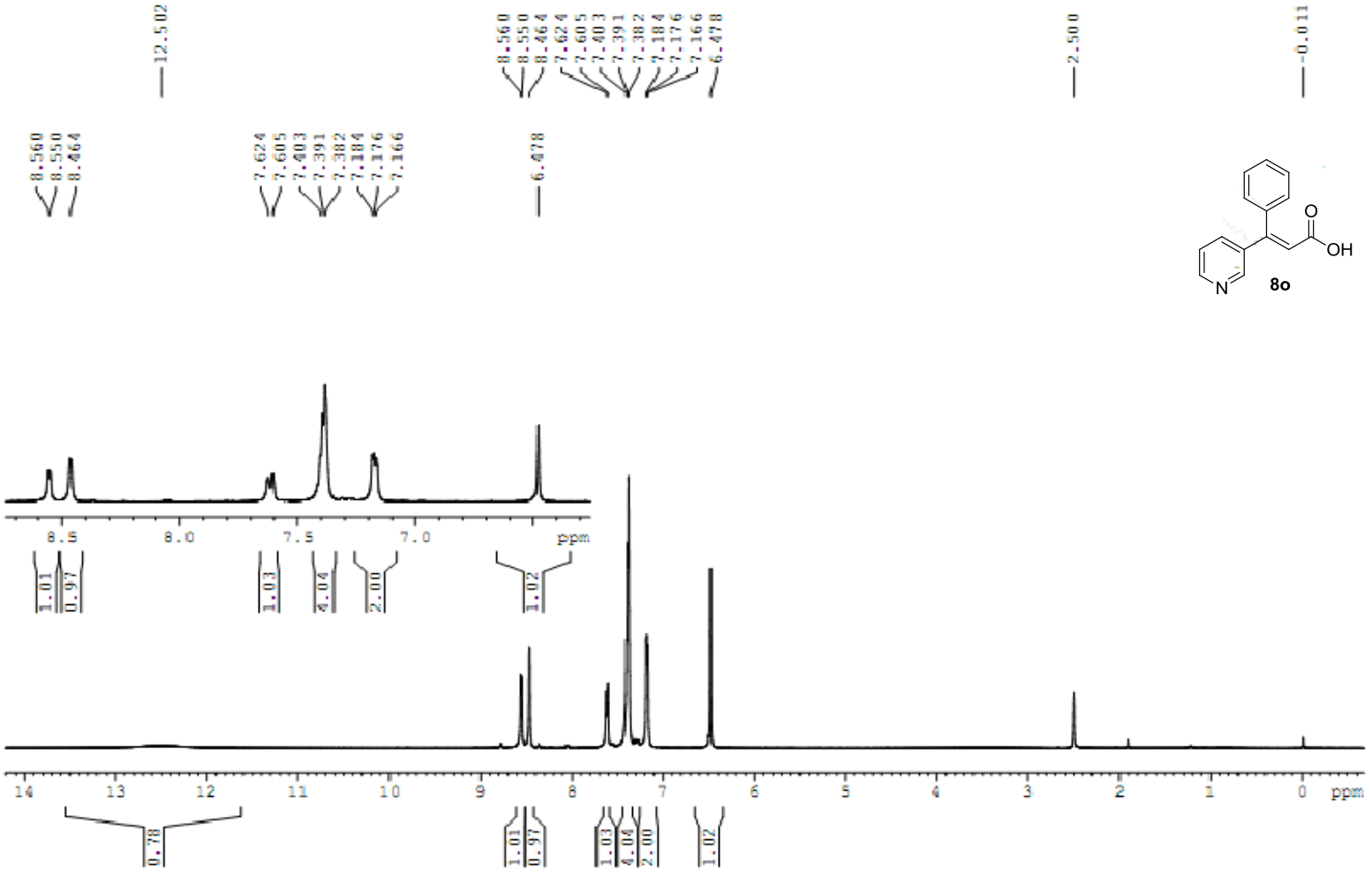
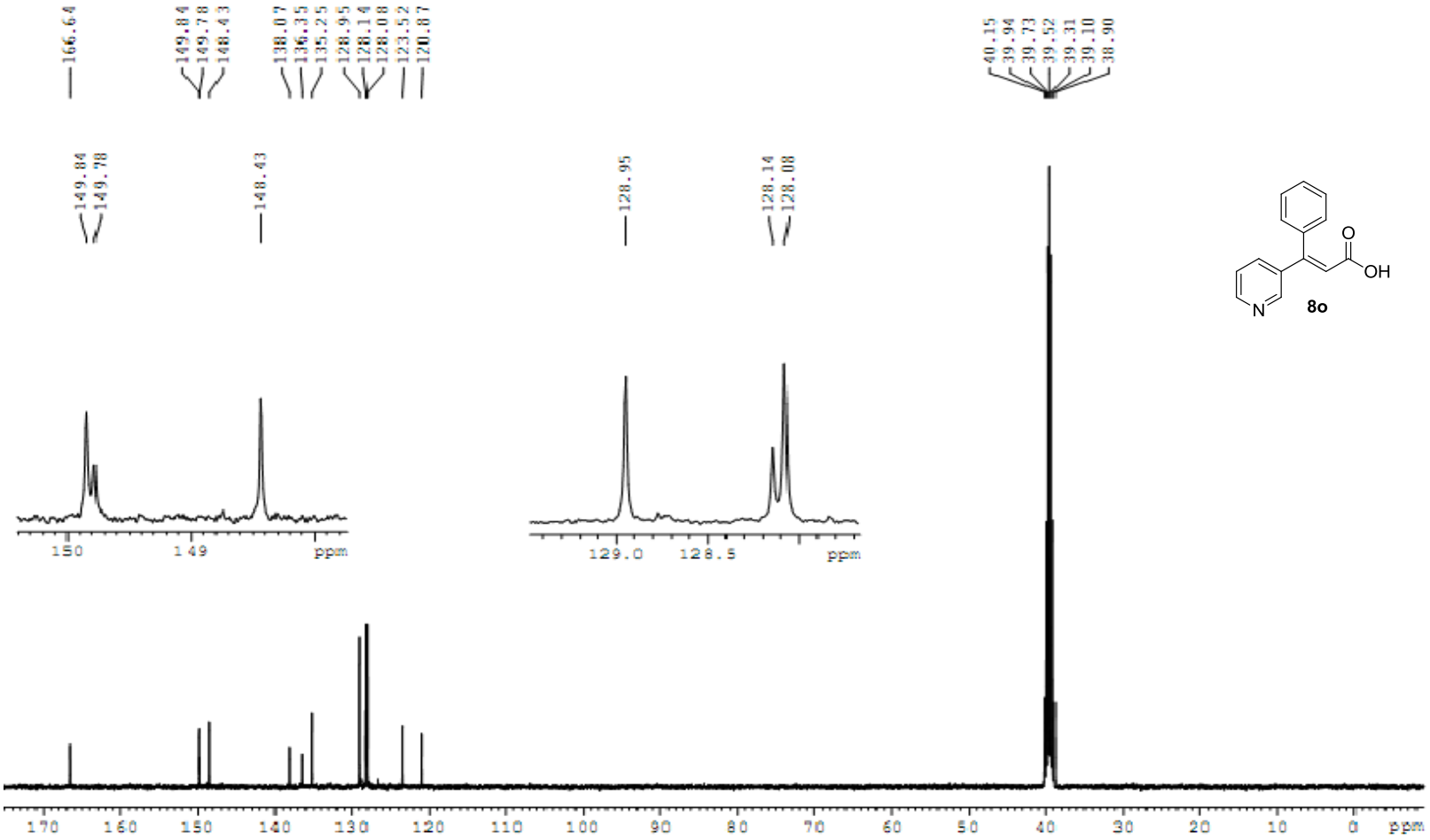

159.39
157.12
151.27
150.17
136.34
117.42
116.85
116.02
77.48
77.16
76.84
18.16
Br
N
O
O
5n
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


8.539
8.537
8.527
8.443
8.438
7.771
7.751
7.449
7.437
7.423
7.416
7.408
7.205
7.198
7.190
7.182
6.494
4.900
3.595
3.310
ppm
1.05
1.00
1.02
4.01
2.09
0.99
3.03
O
O
N
7o


167.62
154.18
150.63
149.43
139.19
138.62
137.58
130.22
129.75
129.34
125.11
120.03
51.86
49.64
49.43
49.21
49.00
48.79
48.58
48.36
O
O
N
7o
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


12.502
8.560
8.550
8.464
7.624
7.605
7.403
7.391
7.382
7.184
7.176
7.166
6.478
2.500
-0.011
O
OH
N
8o
ppm



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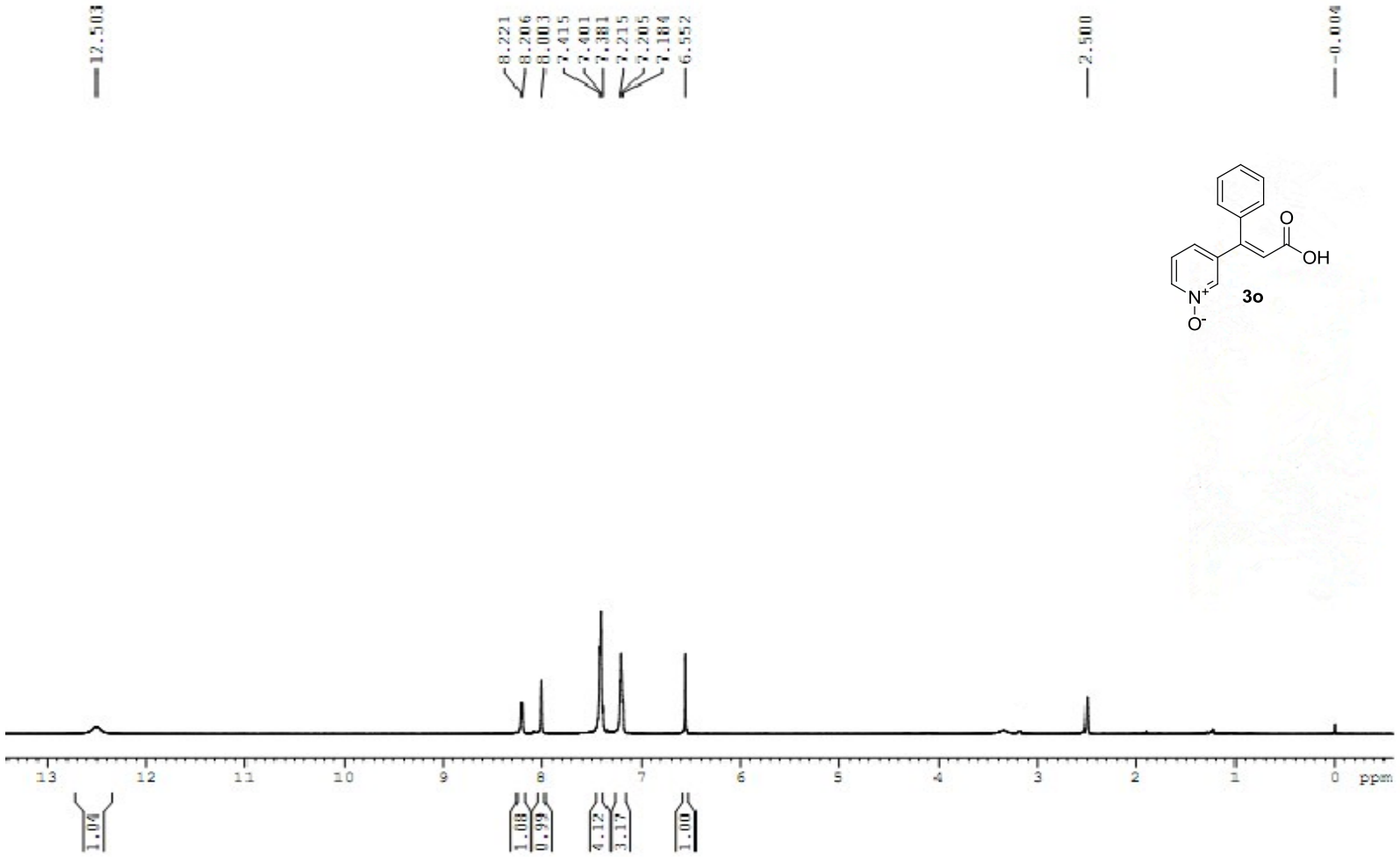
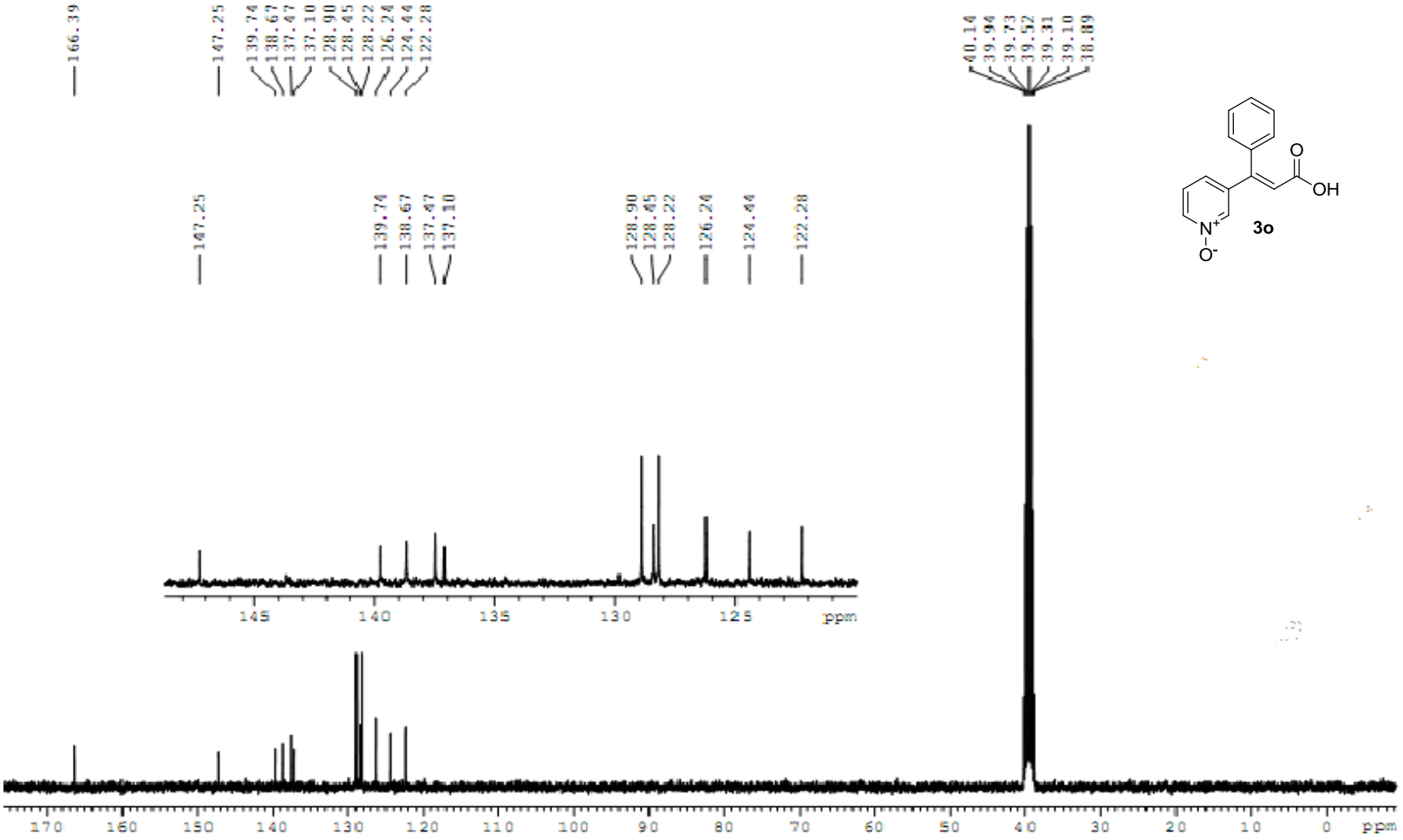
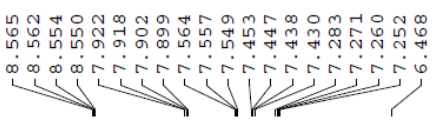
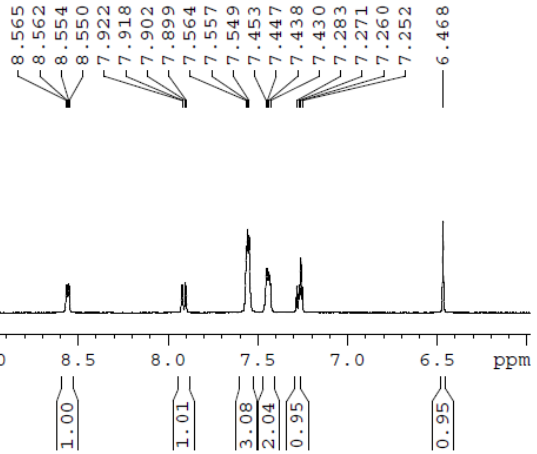
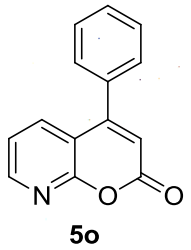

12.503
8.221
8.206
8.003
7.415
7.401
7.381
7.215
7.205
7.184
6.552
2.500
-0.004
O
OH
N+
O-
3o
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.04
1.08
0.99
4.12
3.17
1.00

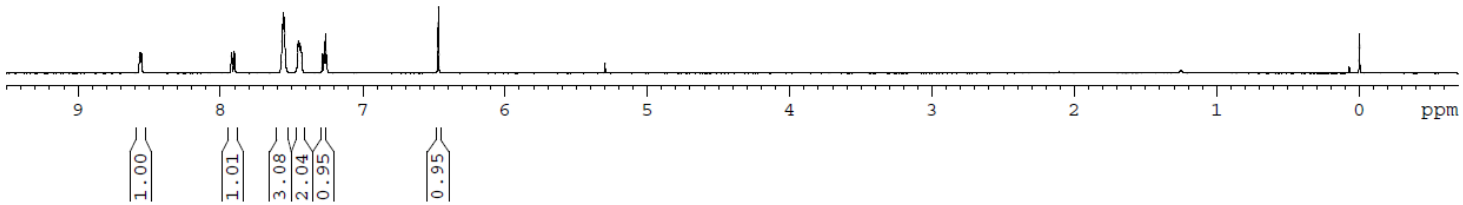

166.39
147.25
139.74
138.67
137.47
137.10
128.90
128.45
128.22
126.24
124.44
122.28
40.14
39.94
39.73
39.52
39.31
39.10
38.89
O
OH
N+
O-
3o
ppm







5o



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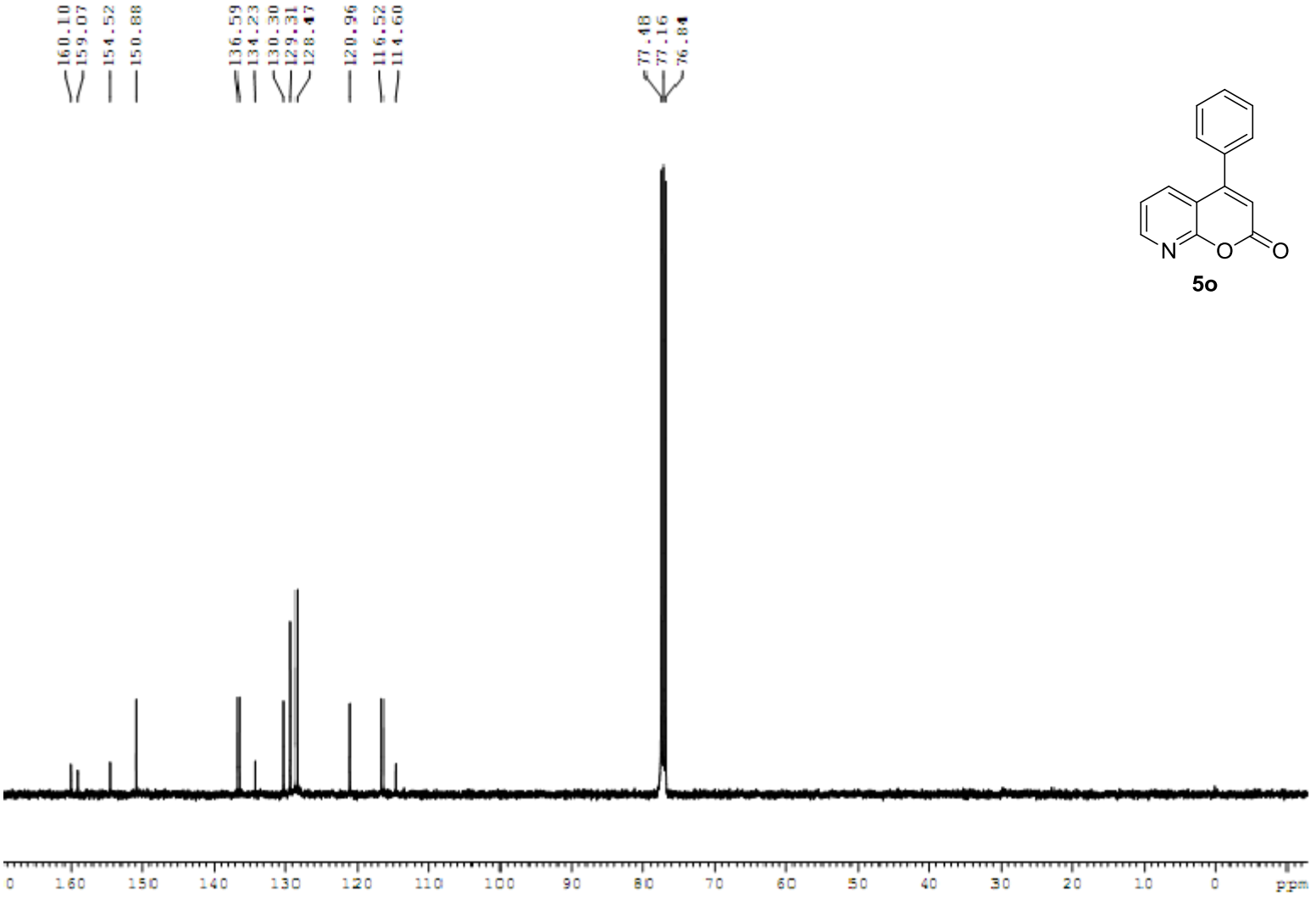
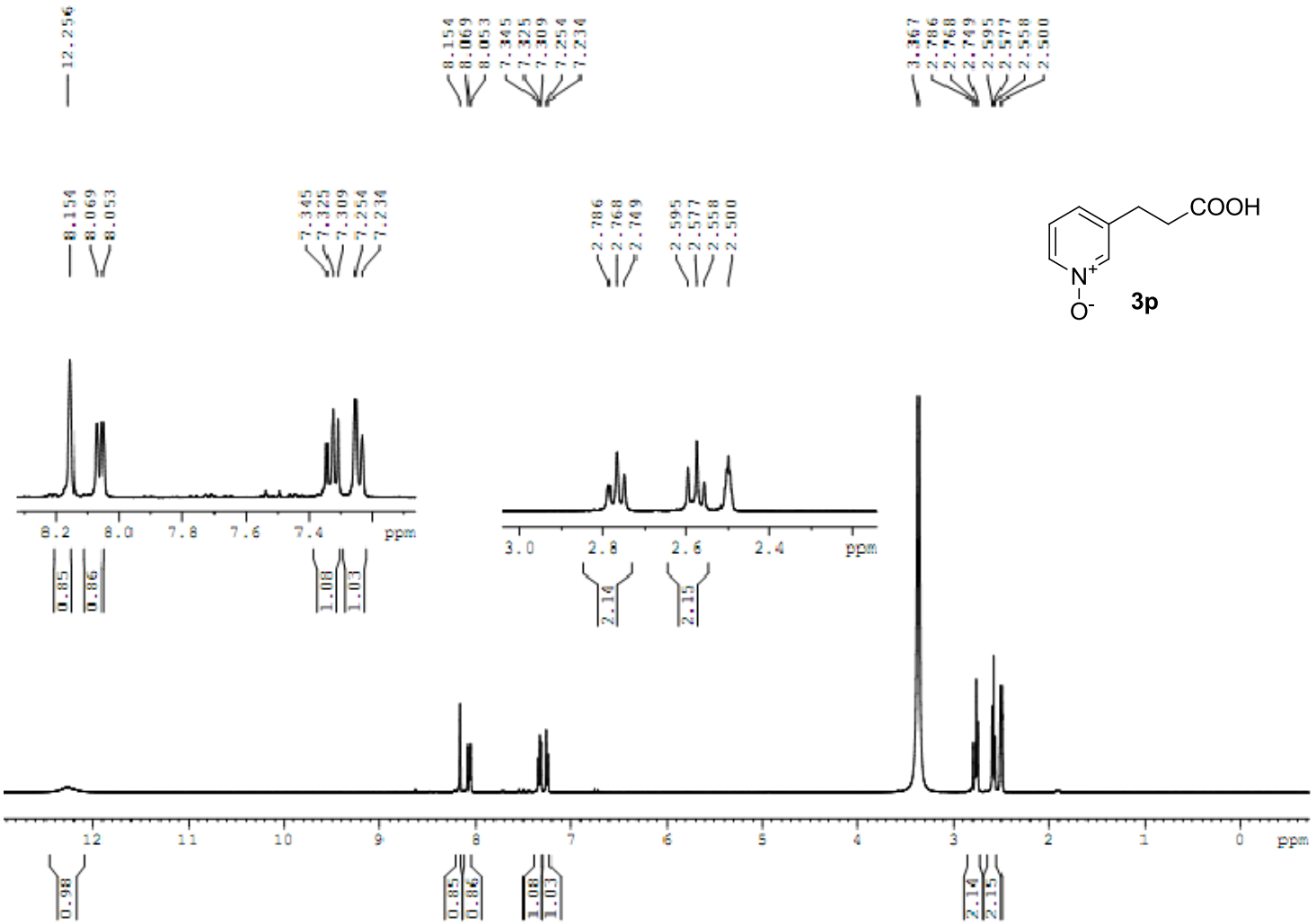
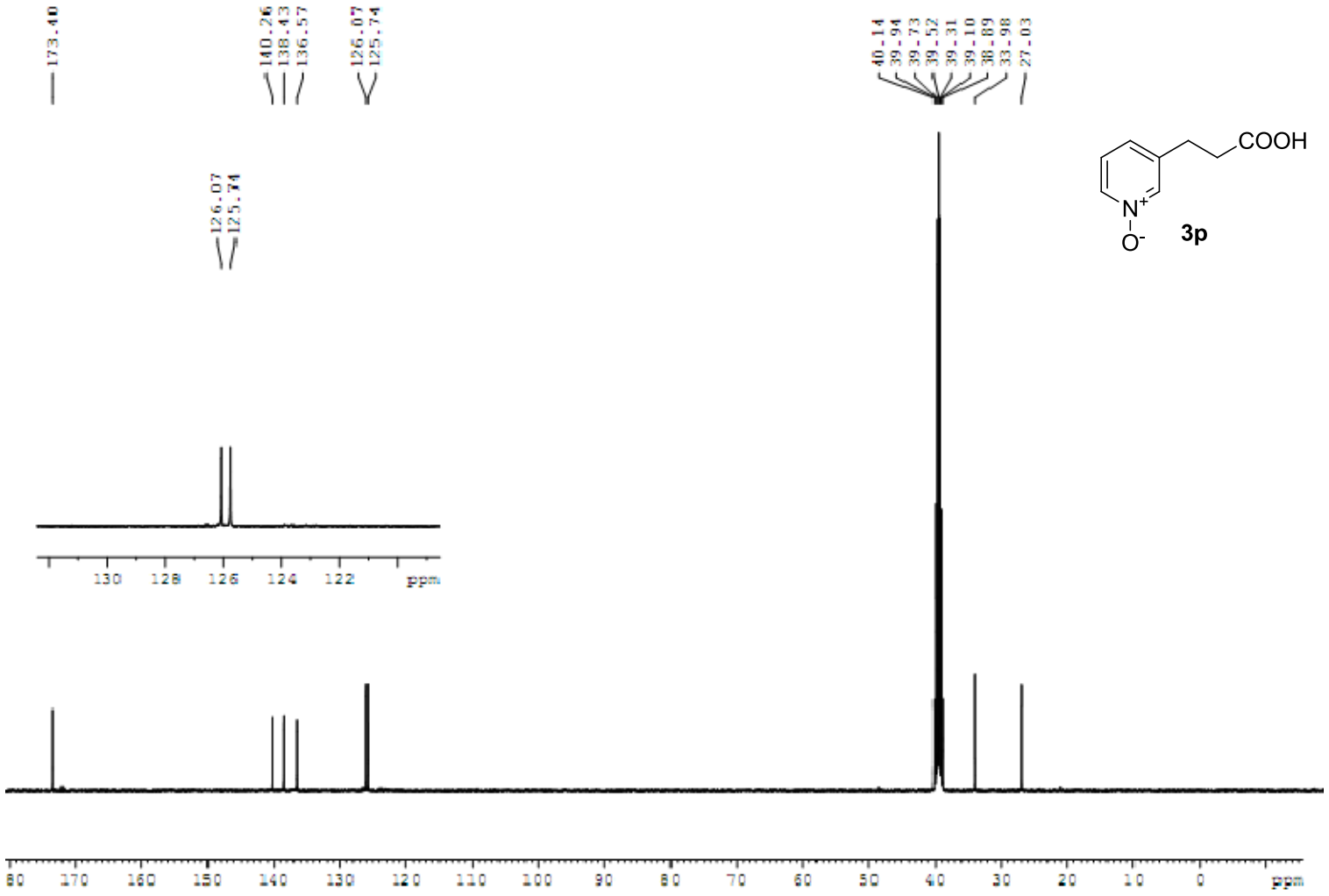
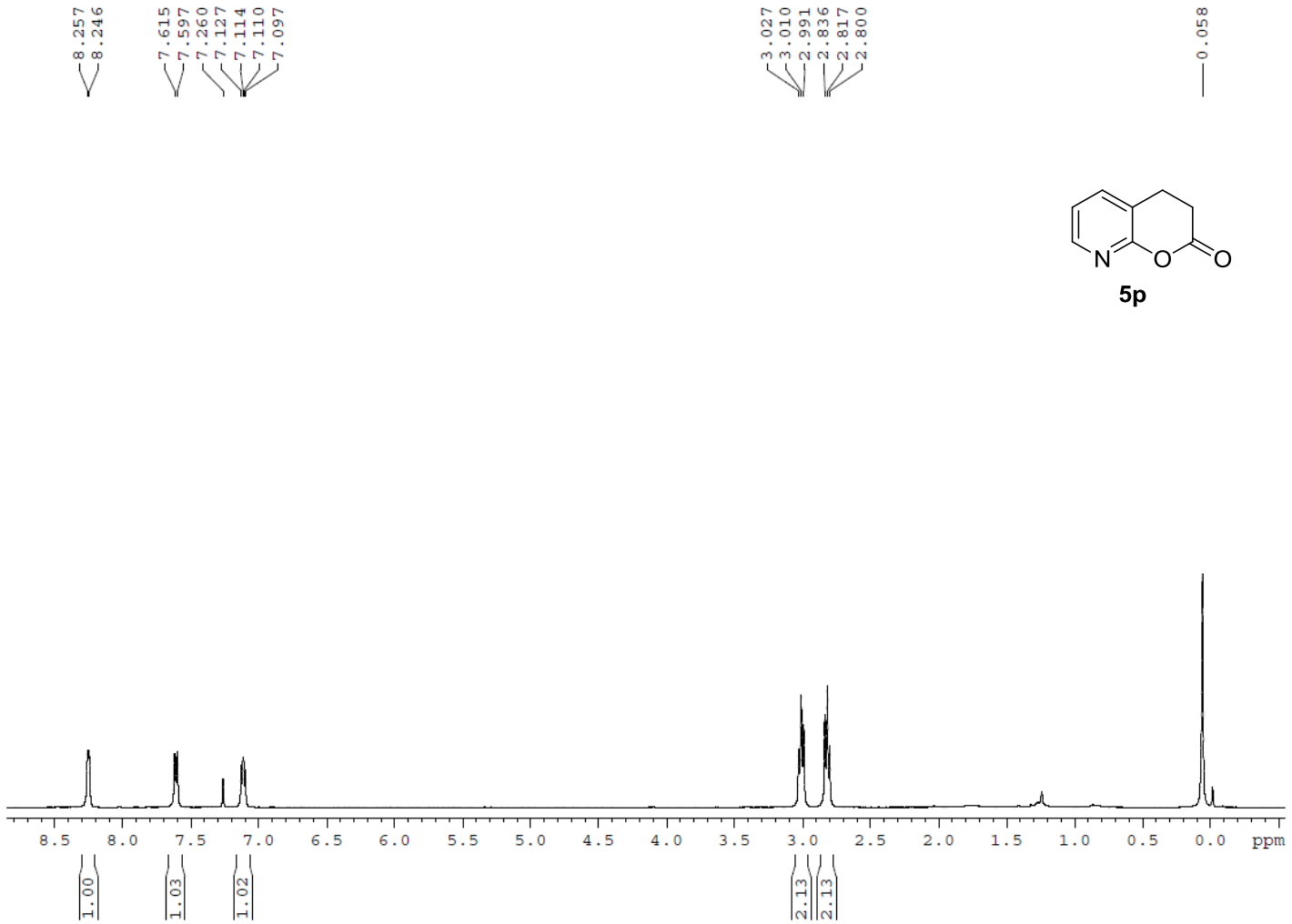
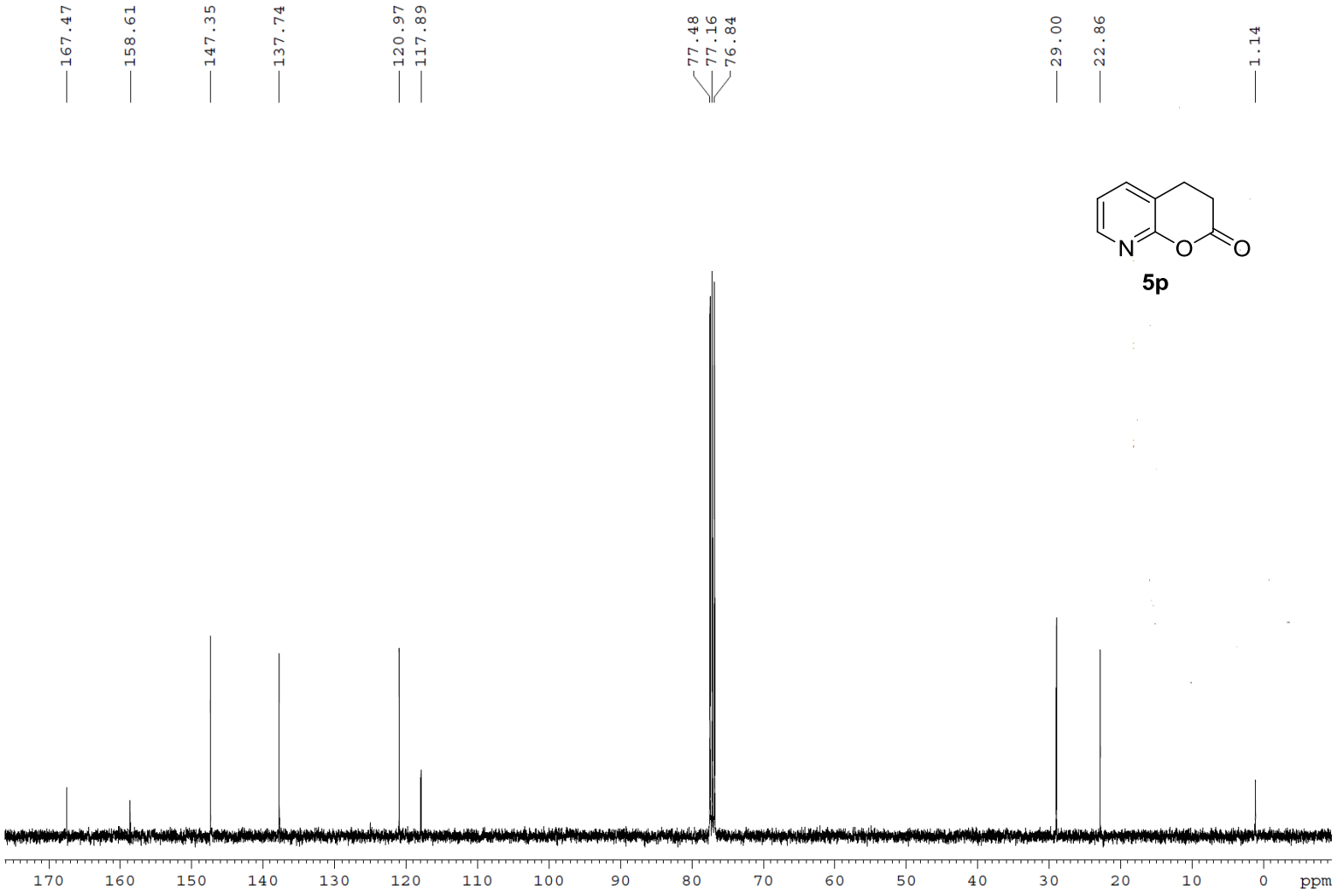

160.10
159.07
154.52
150.88
136.59
134.23
130.30
129.31
128.47
120.96
116.52
114.60
77.48
77.16
76.84
N
O
O
5o
0
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

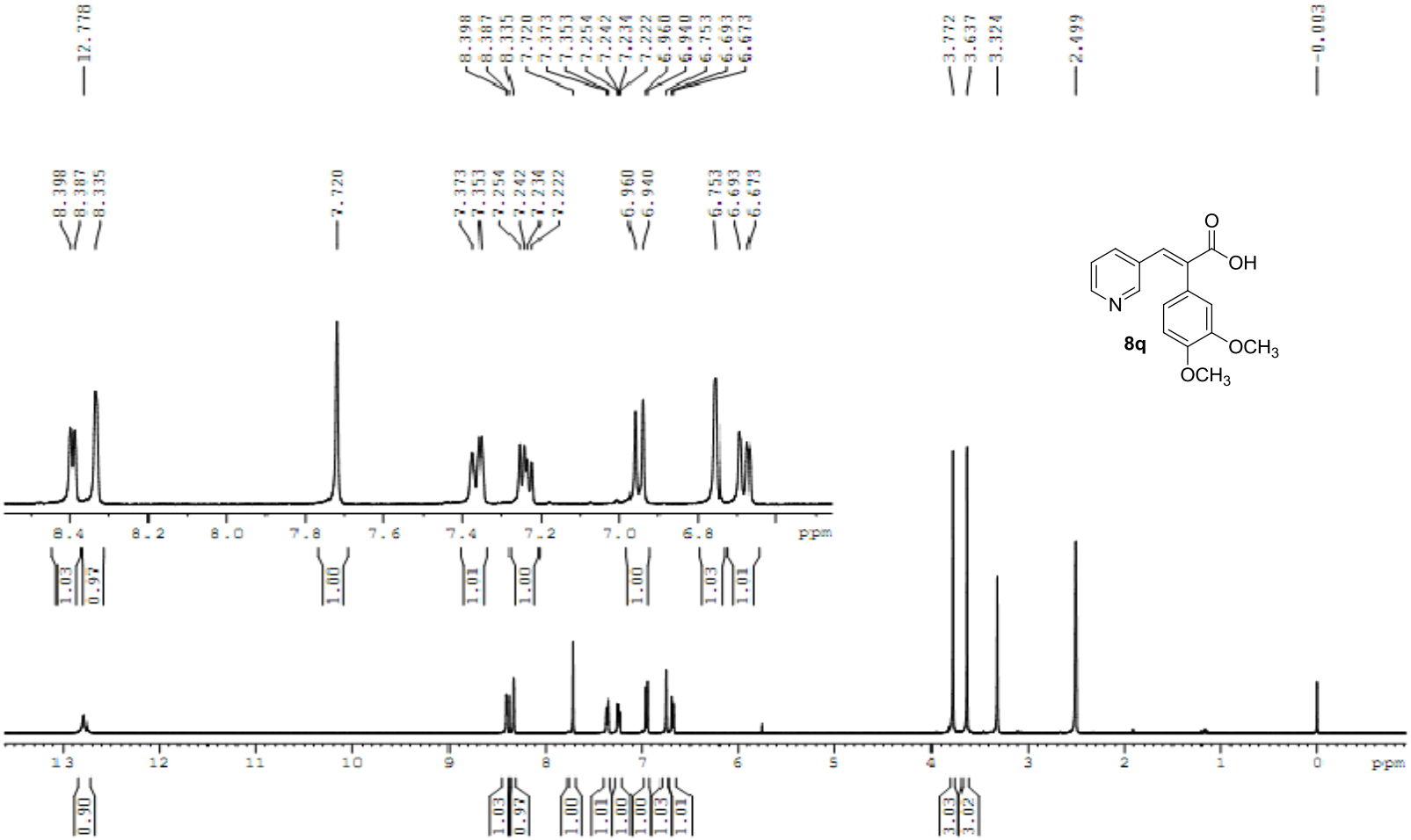

12.256
8.154
8.069
8.053
7.345
7.325
7.309
7.254
7.234
3.367
2.786
2.768
2.749
2.595
2.577
2.558
2.500
COOH
N+
O-
3p
ppm
0.98
0.85
0.86
1.08
1.03
2.14
2.15

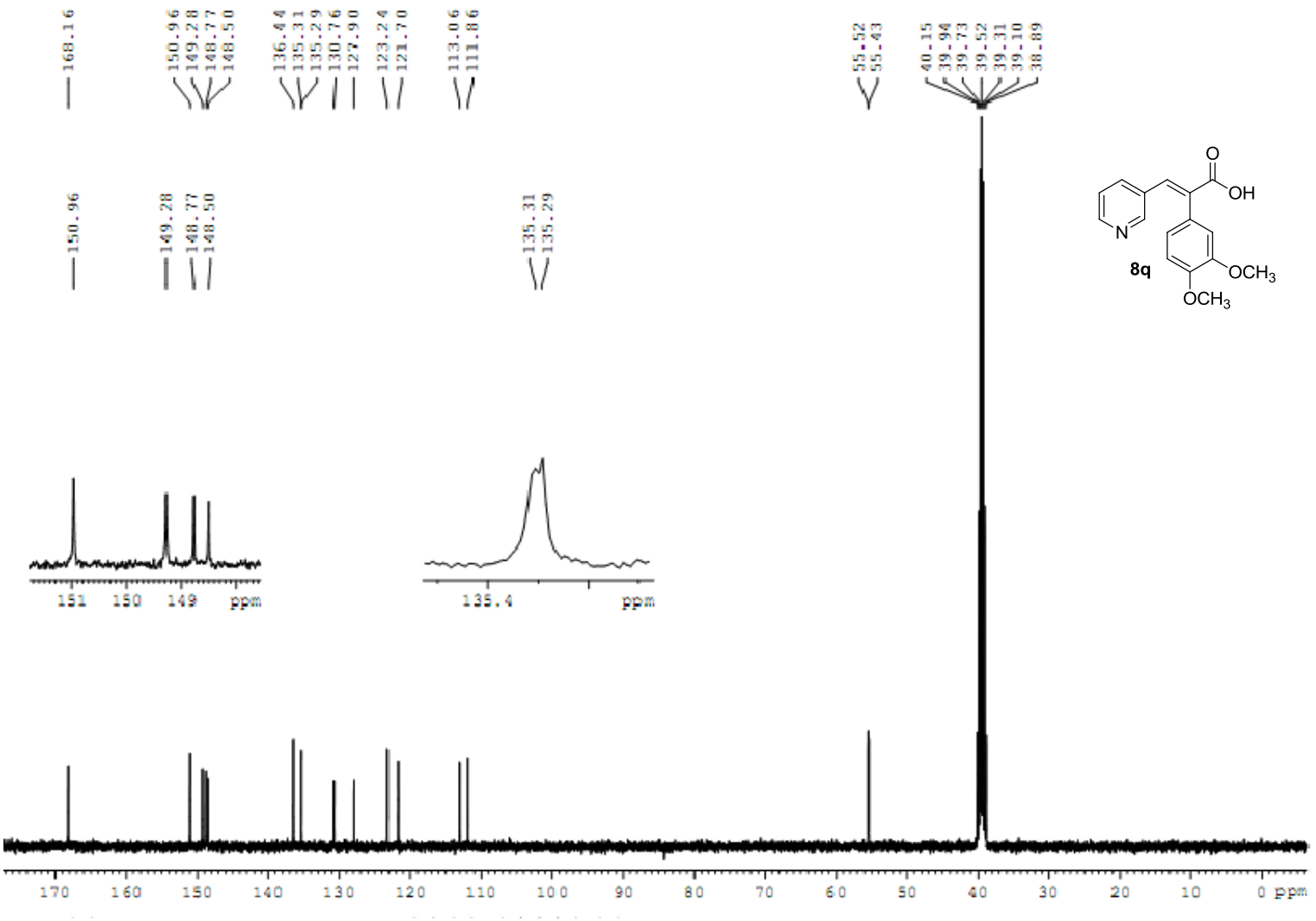

173.40
140.26
138.43
136.57
126.07
125.74
40.14
39.94
39.73
39.52
39.31
39.10
38.89
33.98
27.03
126.07
125.74
COOH
N+
O-
3p
130
128
126
124
122
ppm
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

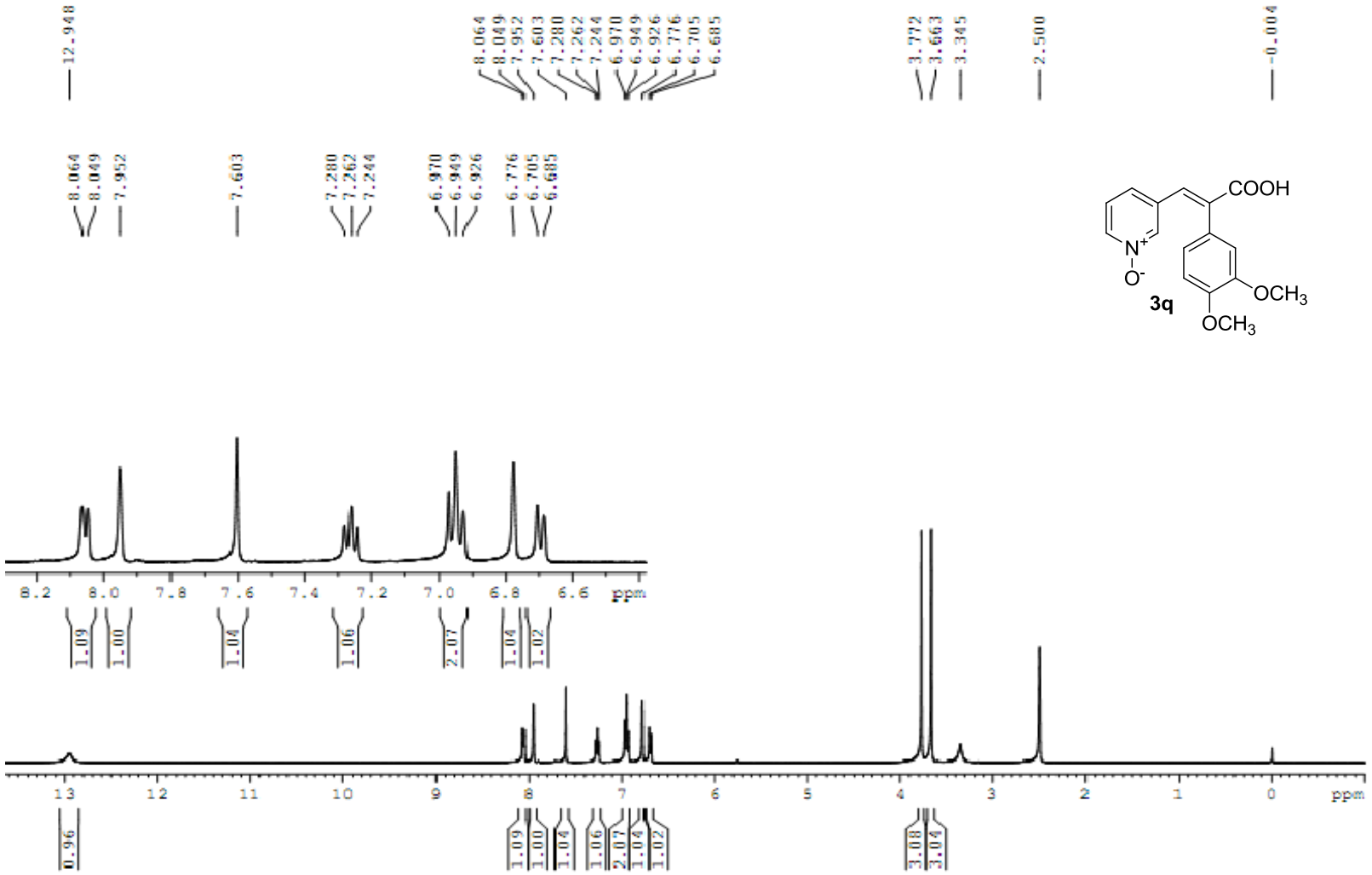

8.257
8.246
7.615
7.597
7.260
7.127
7.114
7.110
7.097
3.027
3.010
2.991
2.836
2.817
2.800
0.058
N
O
O
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.03
1.02
2.13
2.13

5p


167.47
158.61
147.35
137.74
120.97
117.89
77.48
77.16
76.84
29.00
22.86
1.14
N
O
O
5p
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


12.778
8.398
8.387
8.335
7.720
7.373
7.353
7.254
7.242
7.234
7.222
6.960
6.940
6.753
6.693
6.673
3.772
3.637
3.324
2.499
0.003
8q
OH
O
N
OCH3
OCH3
ppm


168.16
150.96
149.28
148.77
148.50
136.44
135.31
135.29
130.76
127.90
123.24
121.70
113.06
111.86
55.52
55.43
40.15
39.94
39.73
39.52
39.31
39.10
38.89
150.96
149.28
148.77
148.50
135.31
135.29
151
150
149
ppm
135.4
ppm
O
OH
N
8q
OCH3
OCH3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm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7.244
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6.949
6.926
6.776
6.705
6.685
3.772
3.663
3.345
2.500
-0.004
COOH
N+
O-
OCH3
OCH3
3q
ppm
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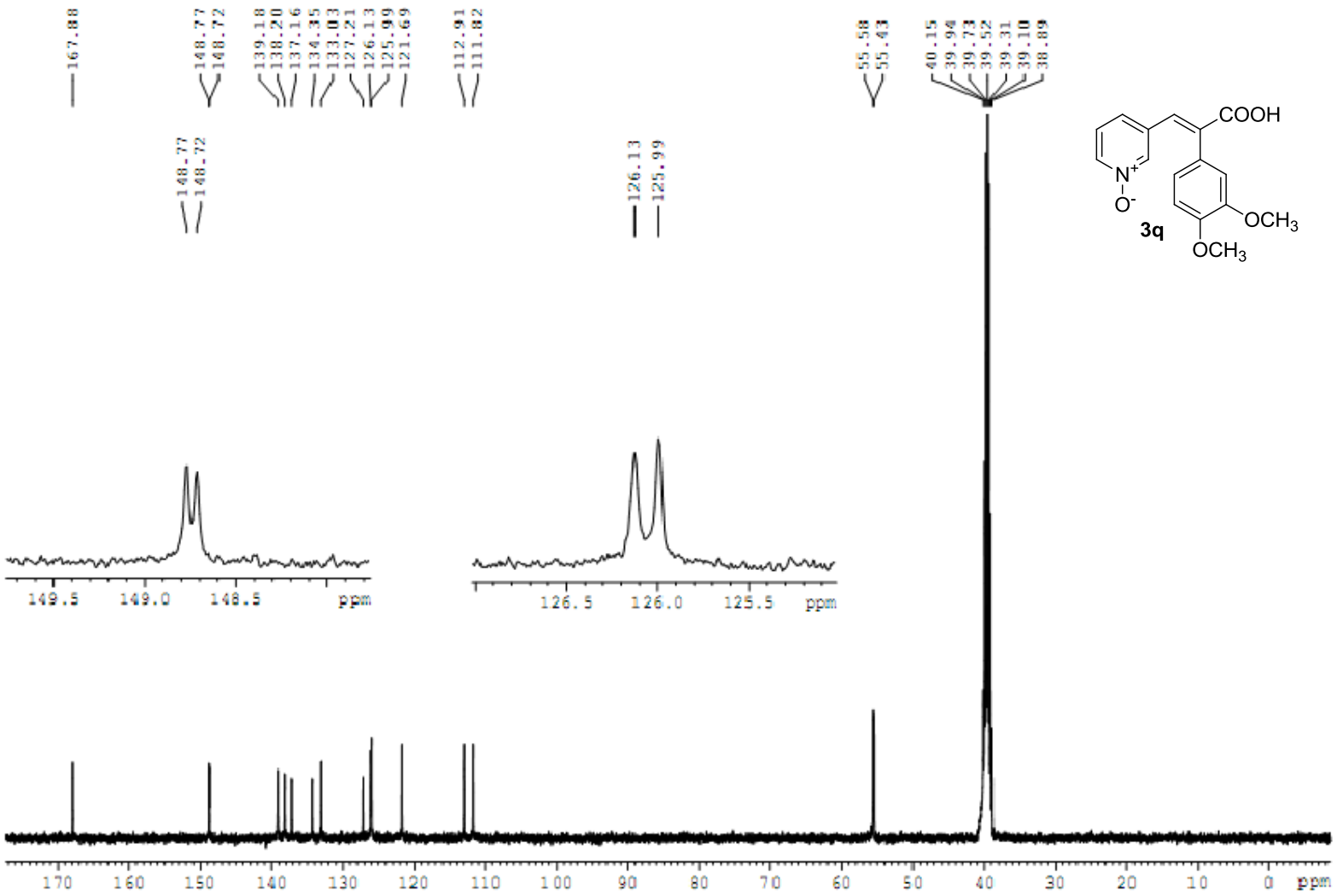
1.09
1.00
1.04
1.06
2.07
1.04
1.02
3.08
3.04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148.72
139.18
138.20
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134.35
133.03
127.21
126.13
125.99
121.69
112.91
111.82
55.58
55.43
40.15
39.94
39.73
39.52
39.31
39.10
38.89
148.77
148.72
126.13
125.99
COOH
N+
O-
OCH3
OCH3
3q
149.5
149.0
148.5
ppm
126.5
126.0
125.5
ppm
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140
130
120
110
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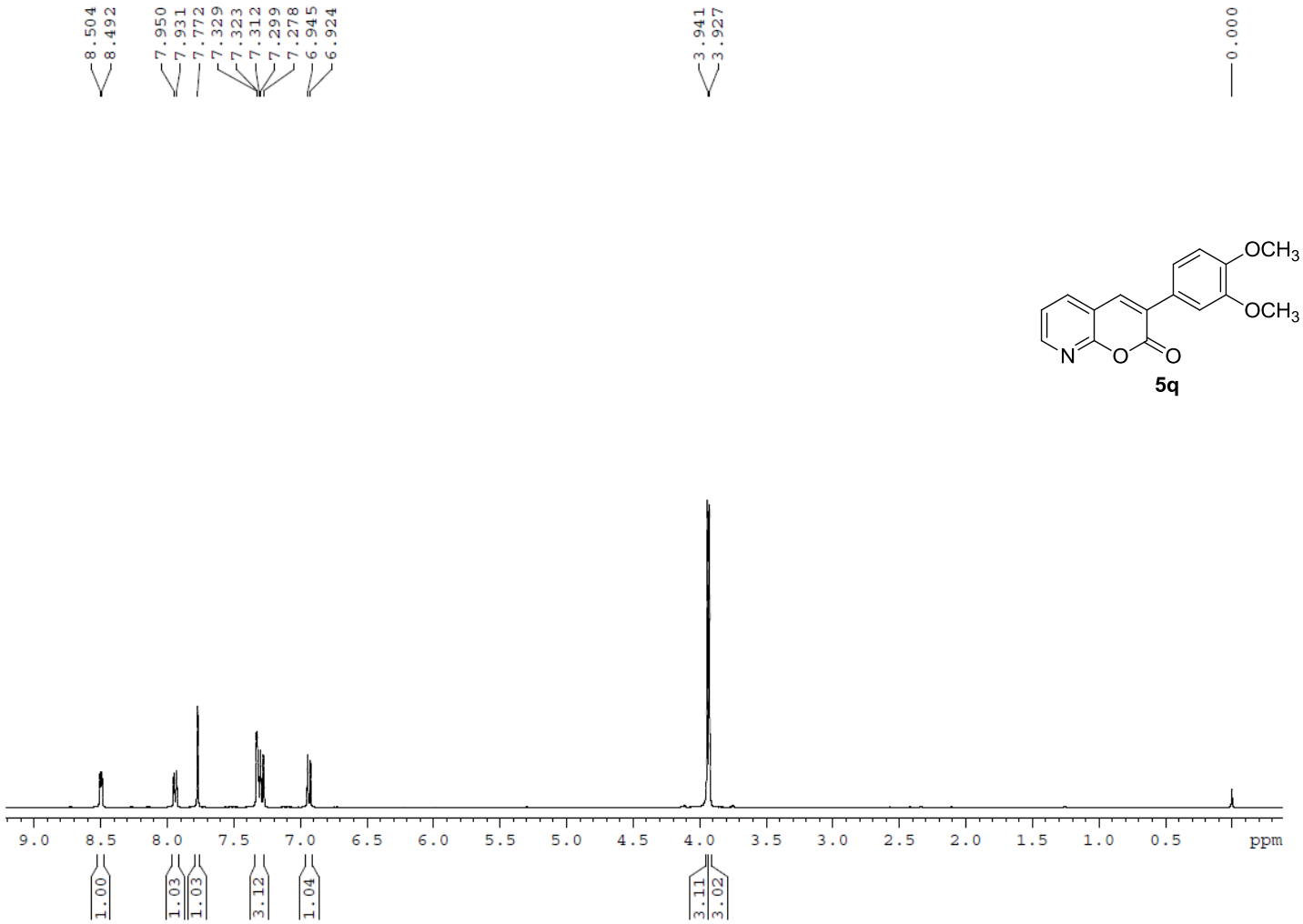
90
80
70
60
50
40
30
20
10
0
ppm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8.492
7.950
7.931
7.772
7.329
7.323
7.312
7.299
7.278
6.945
6.924
3.941
3.927
0.000
OCH3
OCH3
N
O
O
5q
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
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1.0
0.5
ppm
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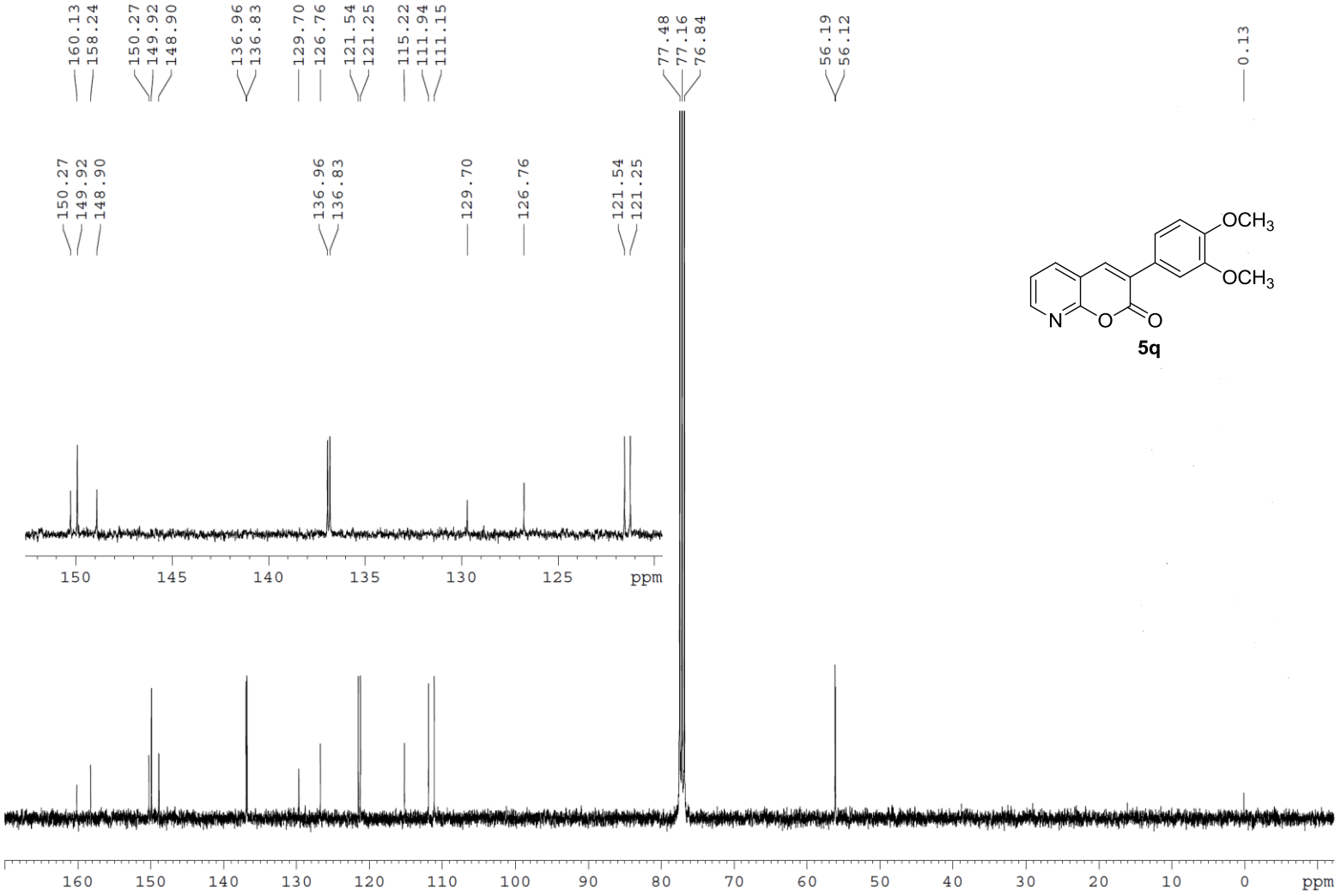
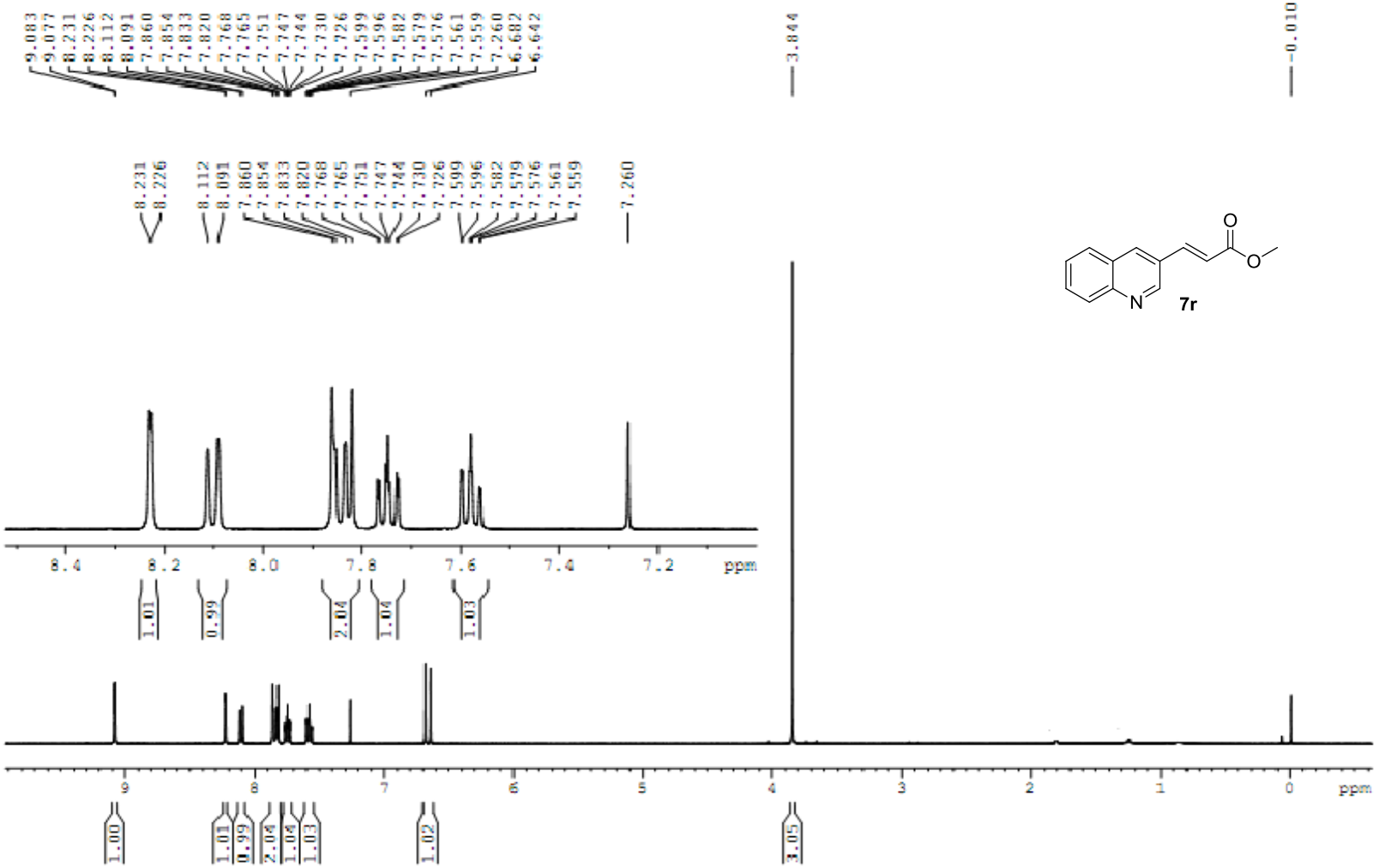
1.03
1.03
3.12
1.04
3.11
3.02



DOI: 10.1021/acs.orglett.6b03771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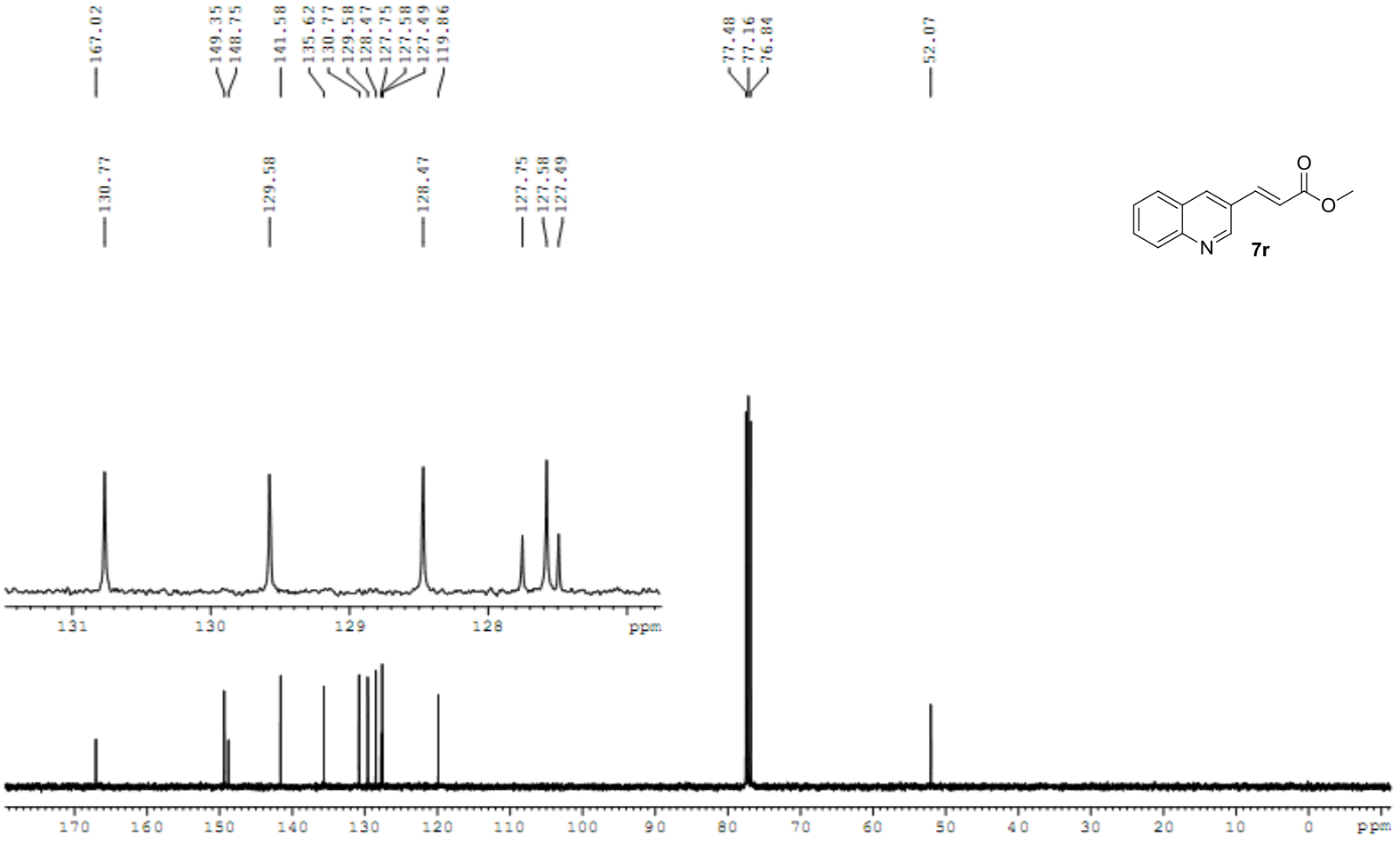
9.077
8.231
8.226
8.112
8.091
7.860
7.854
7.833
7.820
7.768
7.765
7.751
7.747
7.744
7.730
7.726
7.599
7.596
7.582
7.579
7.576
7.561
7.559
7.260
6.682
6.642
3.844
-0.010
O
O
N
7r
ppm
1.00
1.01
0.99
2.04
1.04
1.03
1.02
3.05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149.35
148.75
141.58
135.62
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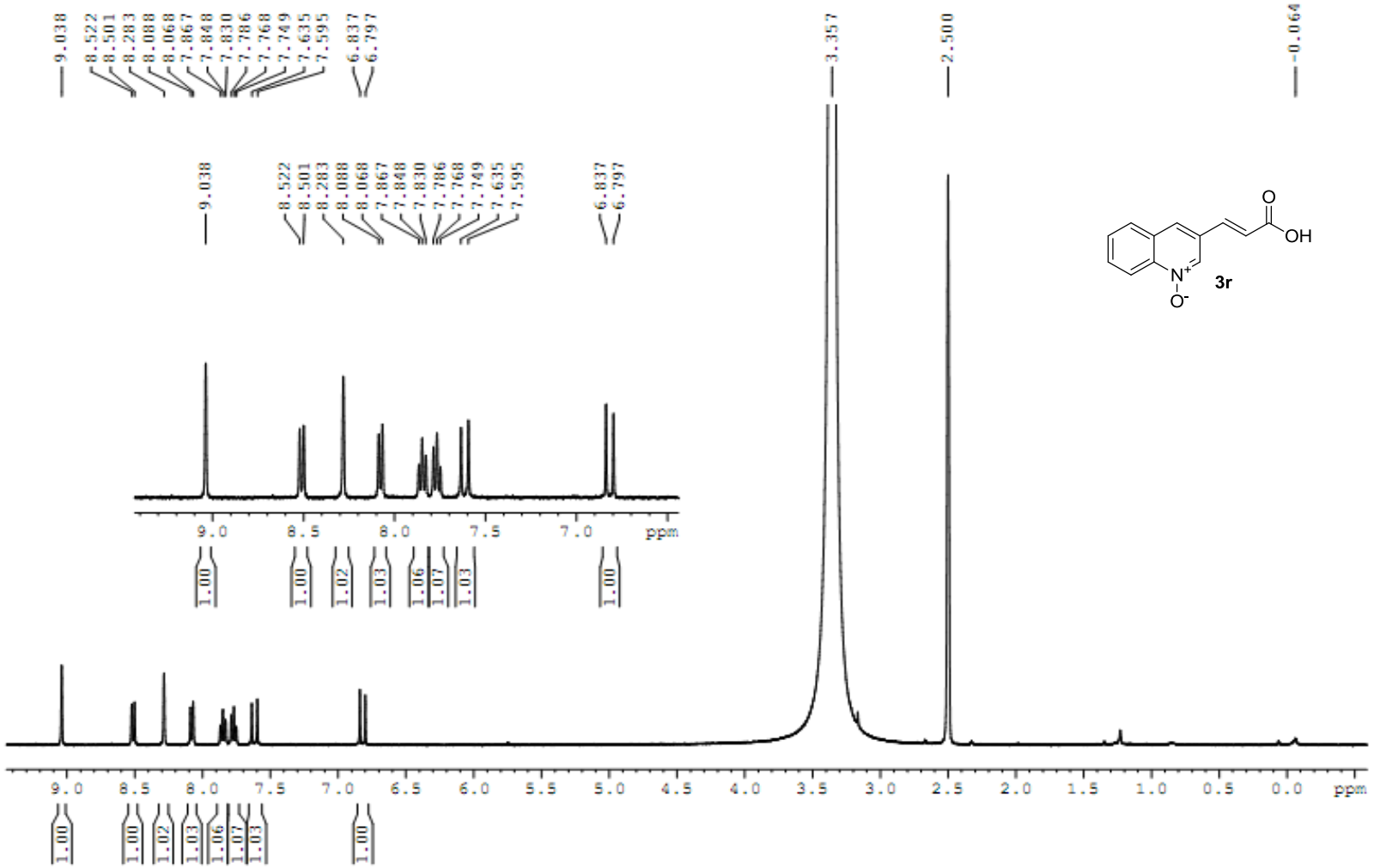
129.58
128.47
127.75
127.58
127.49
119.86
77.48
77.16
76.84
52.07
130.77
129.58
128.47
127.75
127.58
127.49
O
O
N
7r
131
130
129
128
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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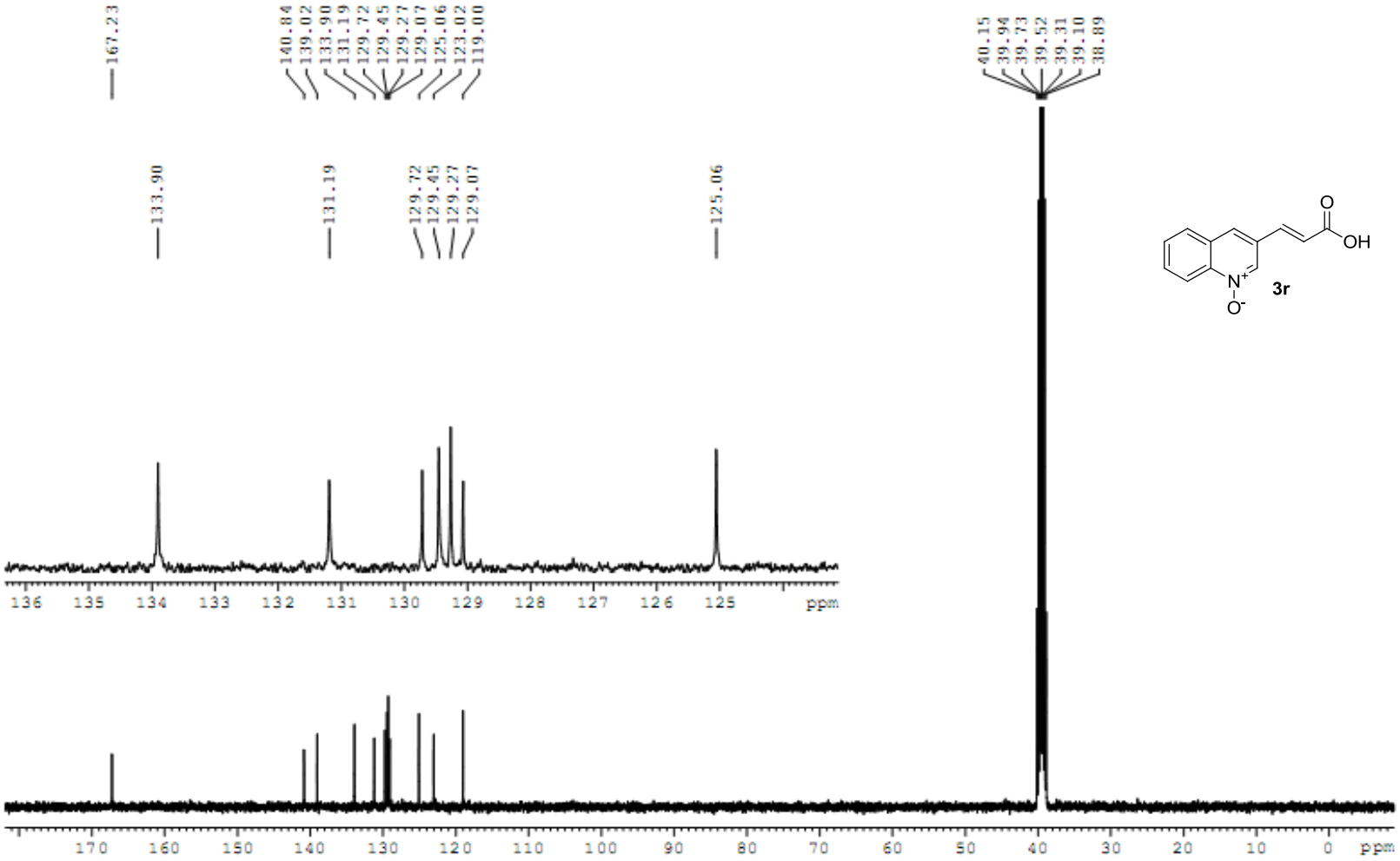
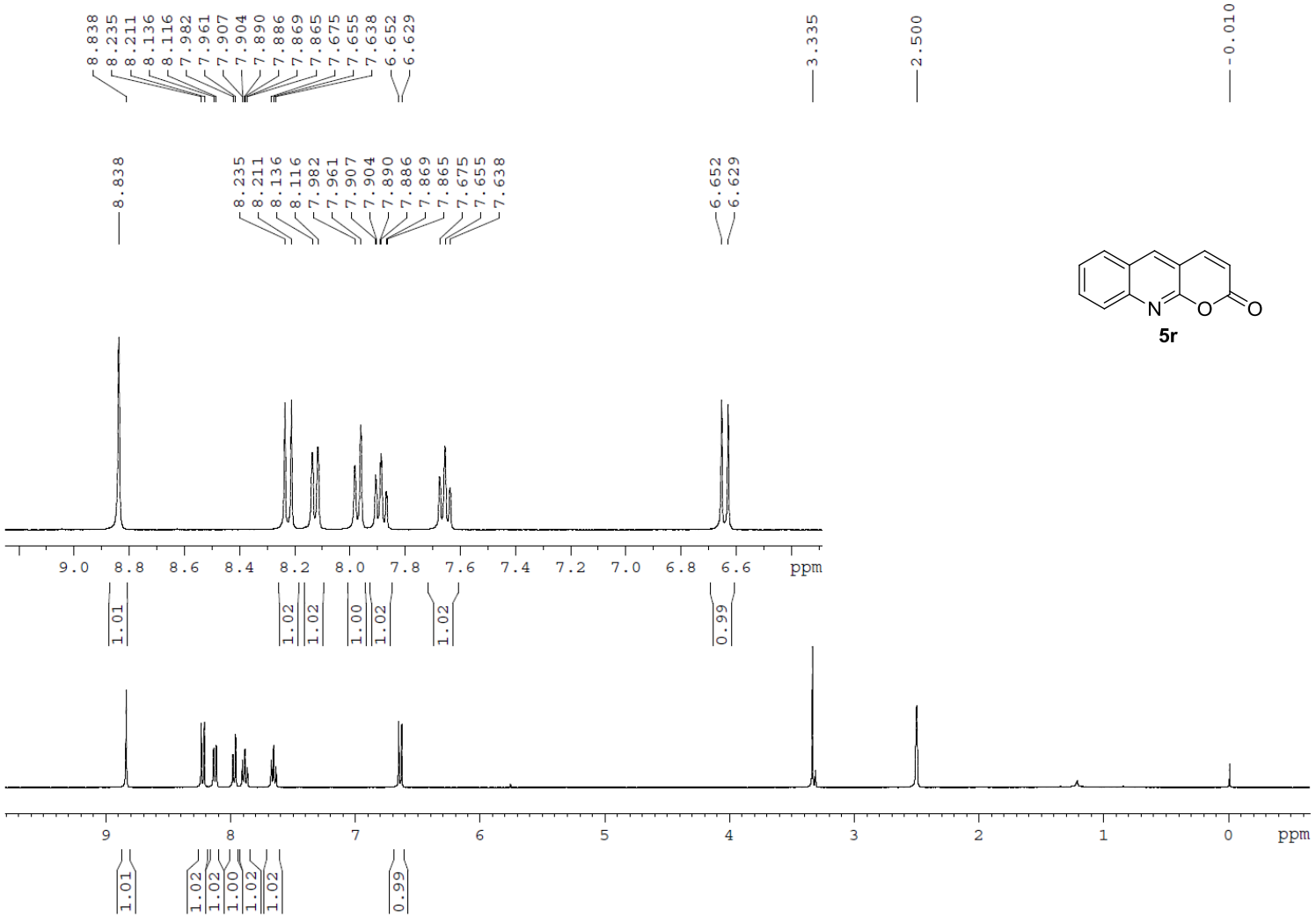
8.522
8.501
8.283
8.088
8.068
7.867
7.848
7.830
7.786
7.768
7.749
7.635
7.595
6.837
6.797
3.357
2.500
-0.064
OH
O
N+
O-
3r
ppm


167.23
140.84
139.02
133.90
131.19
129.72
129.45
129.27
129.07
125.06
123.02
119.00
40.15
39.94
39.73
39.52
39.31
39.10
38.89
133.90
131.19
129.72
129.45
129.27
129.07
125.06
O
OH
N+
O-
3r
136 135 134 133 132 131 130 129 128 127 126 125 ppm
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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8.235
8.211
8.136
8.116
7.982
7.961
7.907
7.904
7.890
7.886
7.869
7.865
7.675
7.655
7.638
6.652
6.629
3.335
2.500
-0.010
N
O
O
5r
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
ppm
1.01
1.02
1.02
1.00
1.02
1.02
0.99
9
8
7
6
5
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3
2
1
0
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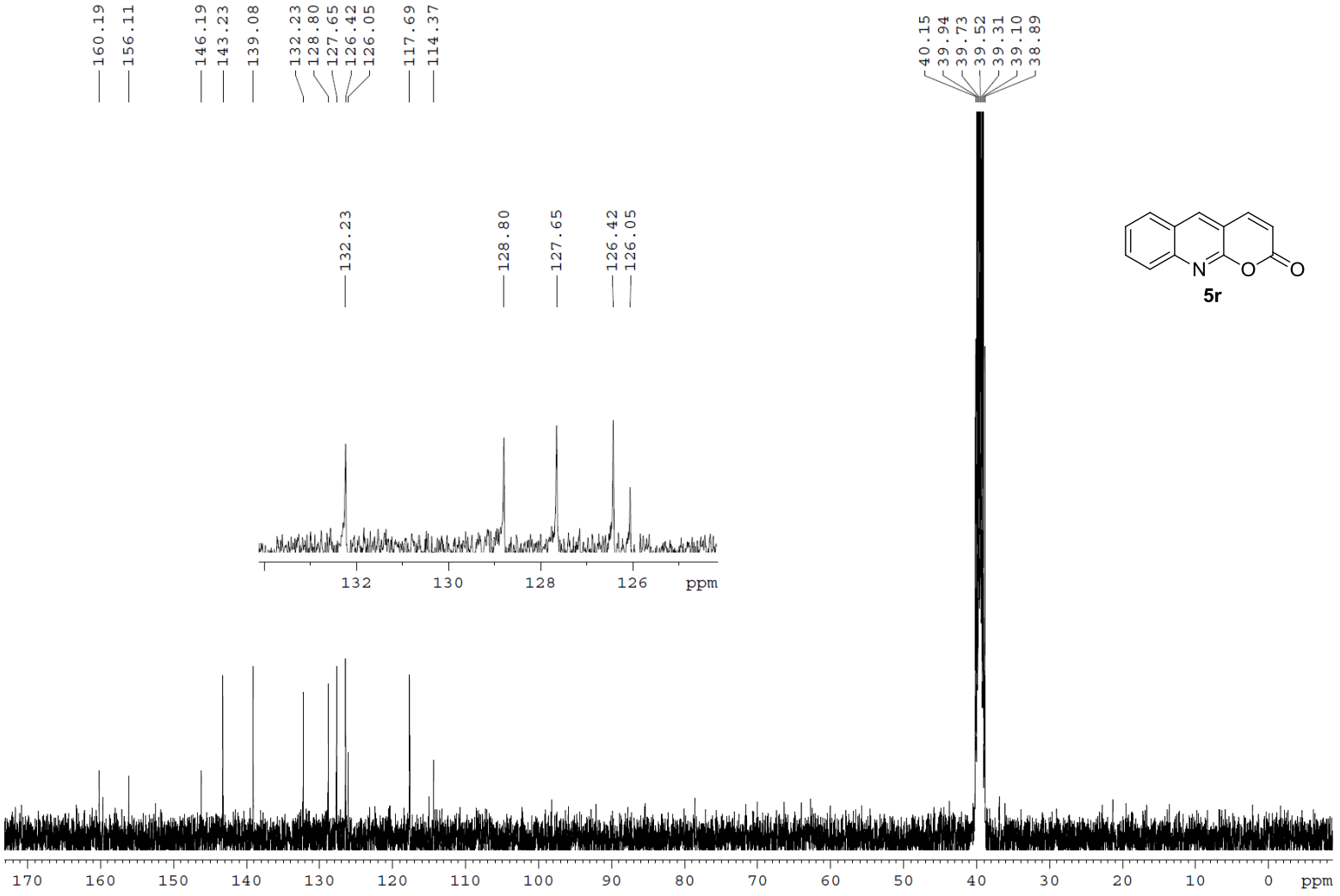
1.02
1.02
1.00
1.02
1.02
0.99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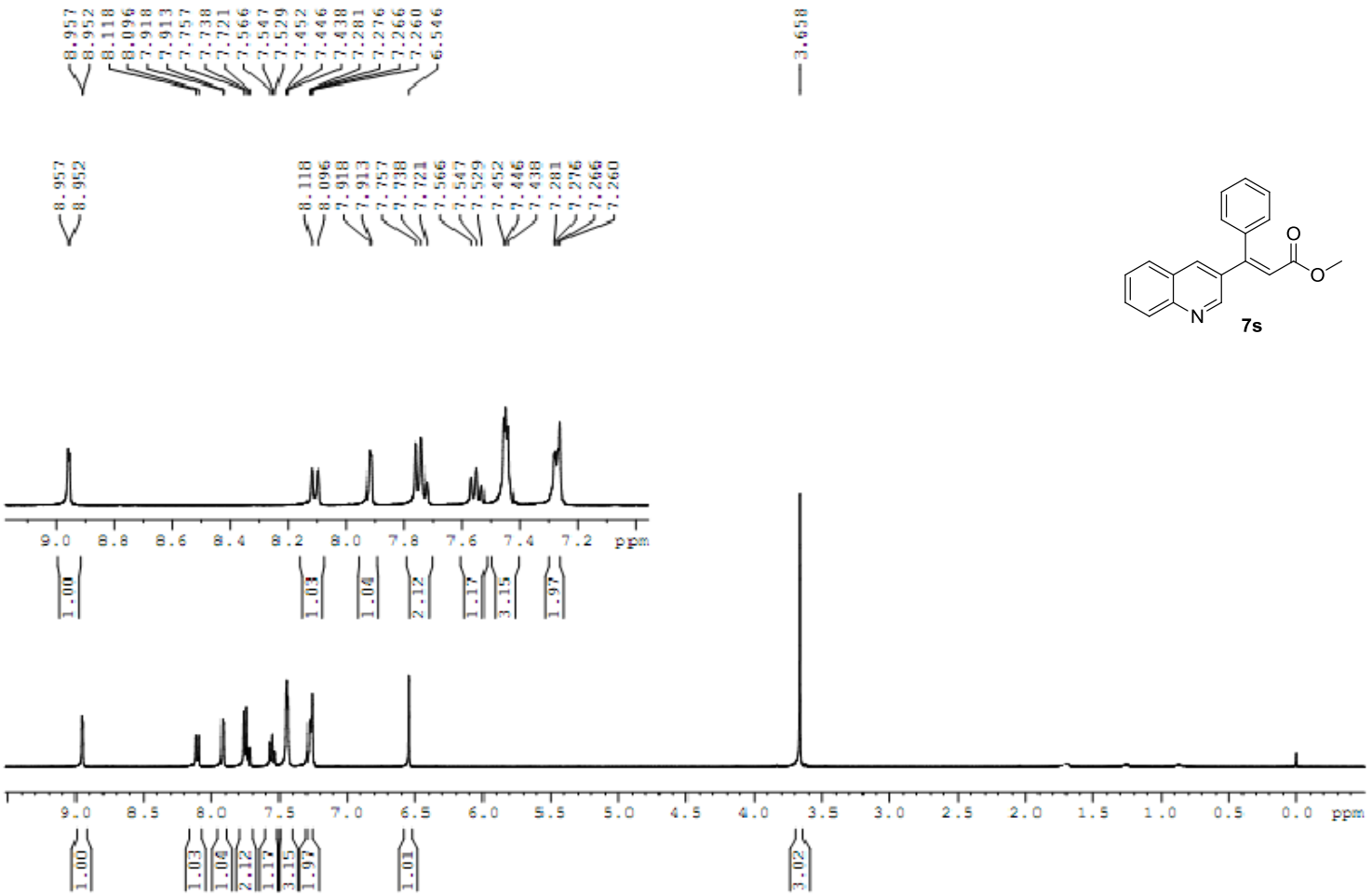
156.11
146.19
143.23
139.08
132.23
128.80
127.65
126.42
126.05
117.69
114.37
40.15
39.94
39.73
39.52
39.31
39.10
38.89
132.23
128.80
127.65
126.42
126.05
132
130
128
126
ppm
N
O
O
5r
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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8.118
8.096
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7.913
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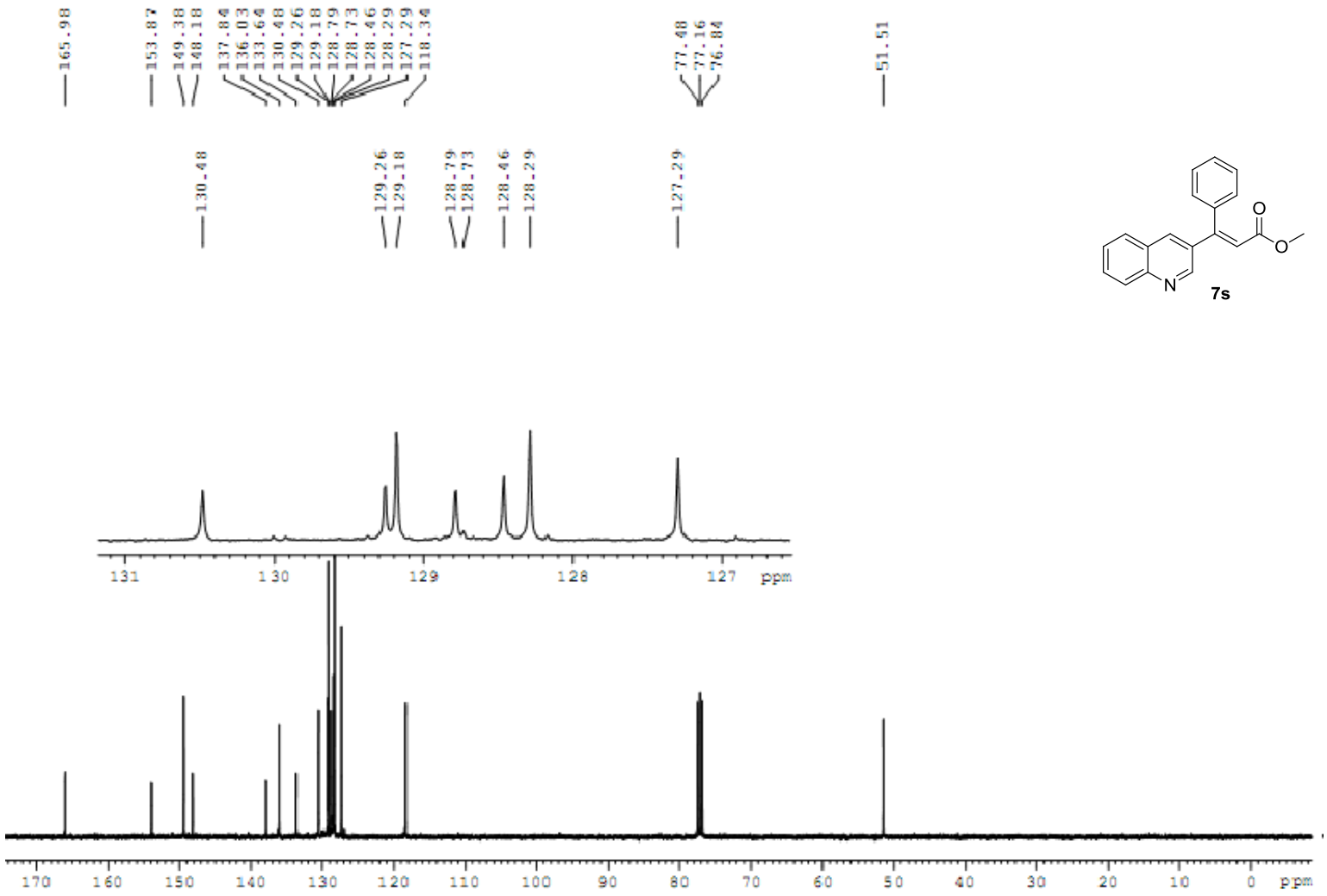
7.738
7.721
7.566
7.547
7.529
7.452
7.446
7.438
7.281
7.276
7.266
7.260
6.546
3.658
O
O
N
7s
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
ppm
1.00
1.03
1.04
2.12
1.17
3.15
1.97
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
1.03
1.04
2.12
1.17
3.15
1.97
1.01
3.02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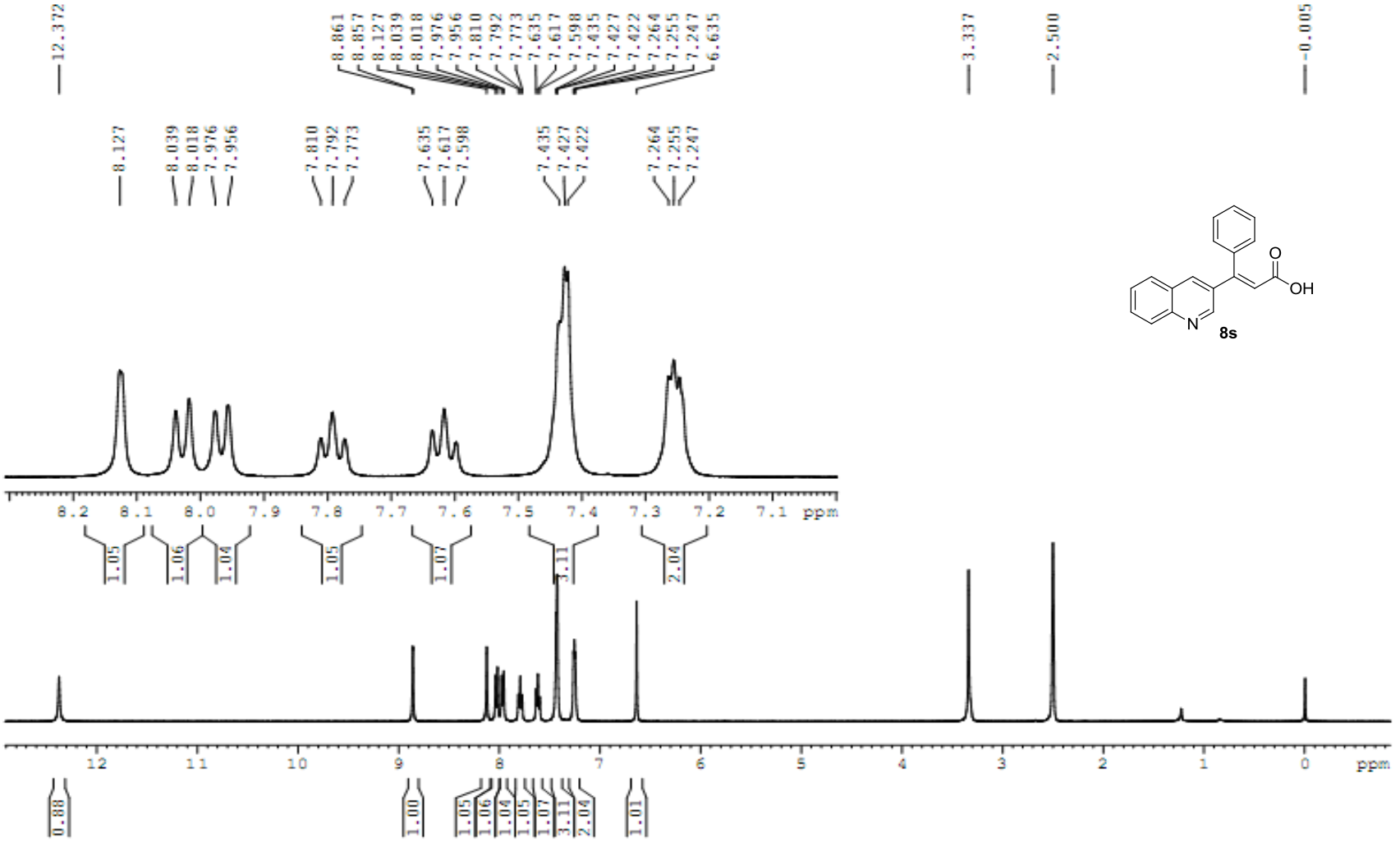
130.48
129.26
129.18
128.79
128.73
128.46
128.29
127.29
118.34
77.48
77.16
76.84
51.51
130.48
129.26
129.18
128.79
128.73
128.46
128.29
127.29
O
O
N
7s
131
130
129
128
127
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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8.018
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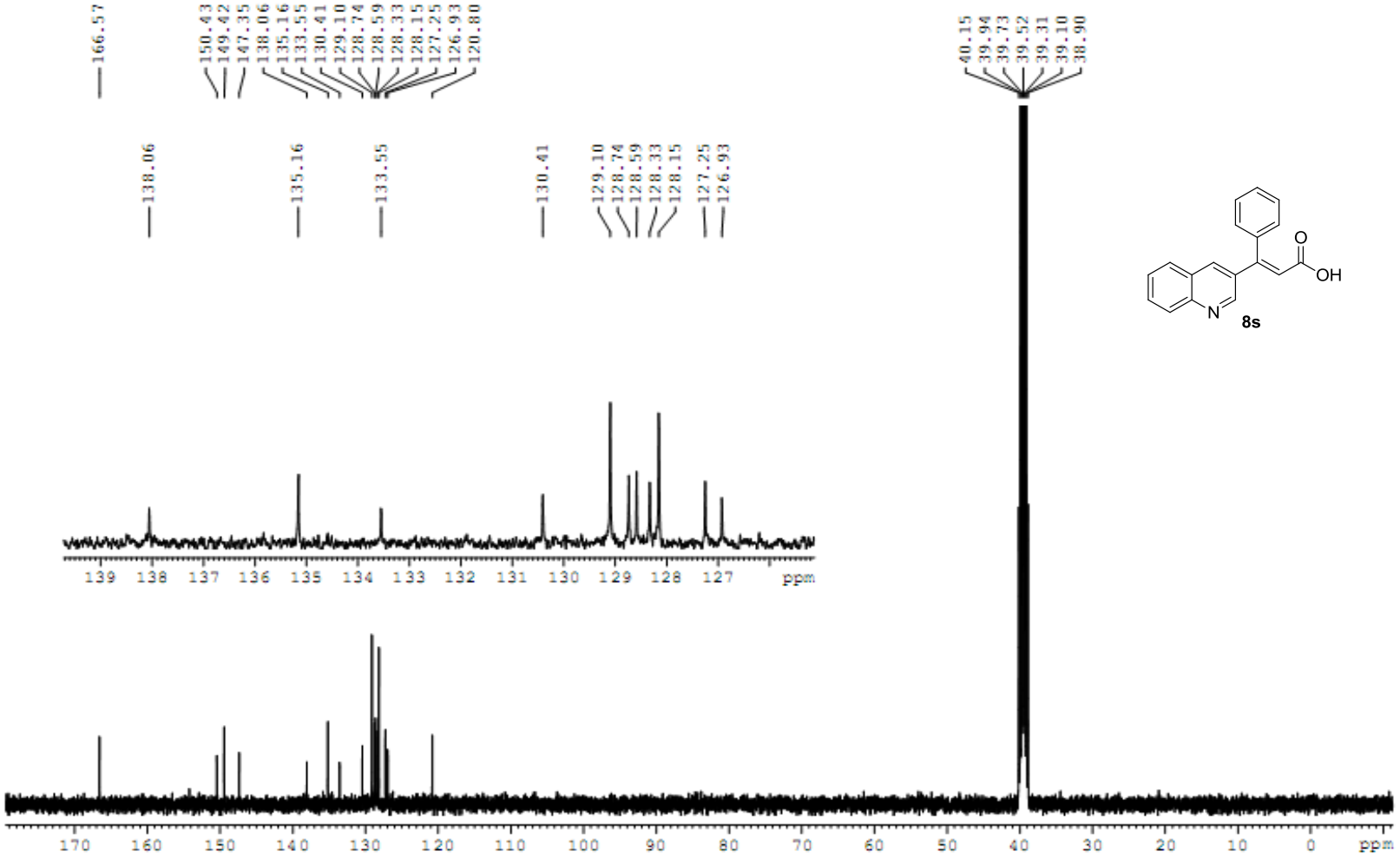
7.956
7.810
7.792
7.773
7.635
7.617
7.598
7.435
7.427
7.422
7.264
7.255
7.247
6.635
3.337
2.500
-0.005
O
OH
N
8s
ppm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149.42
147.35
138.06
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130.41
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128.59
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128.15
127.25
126.93
120.80
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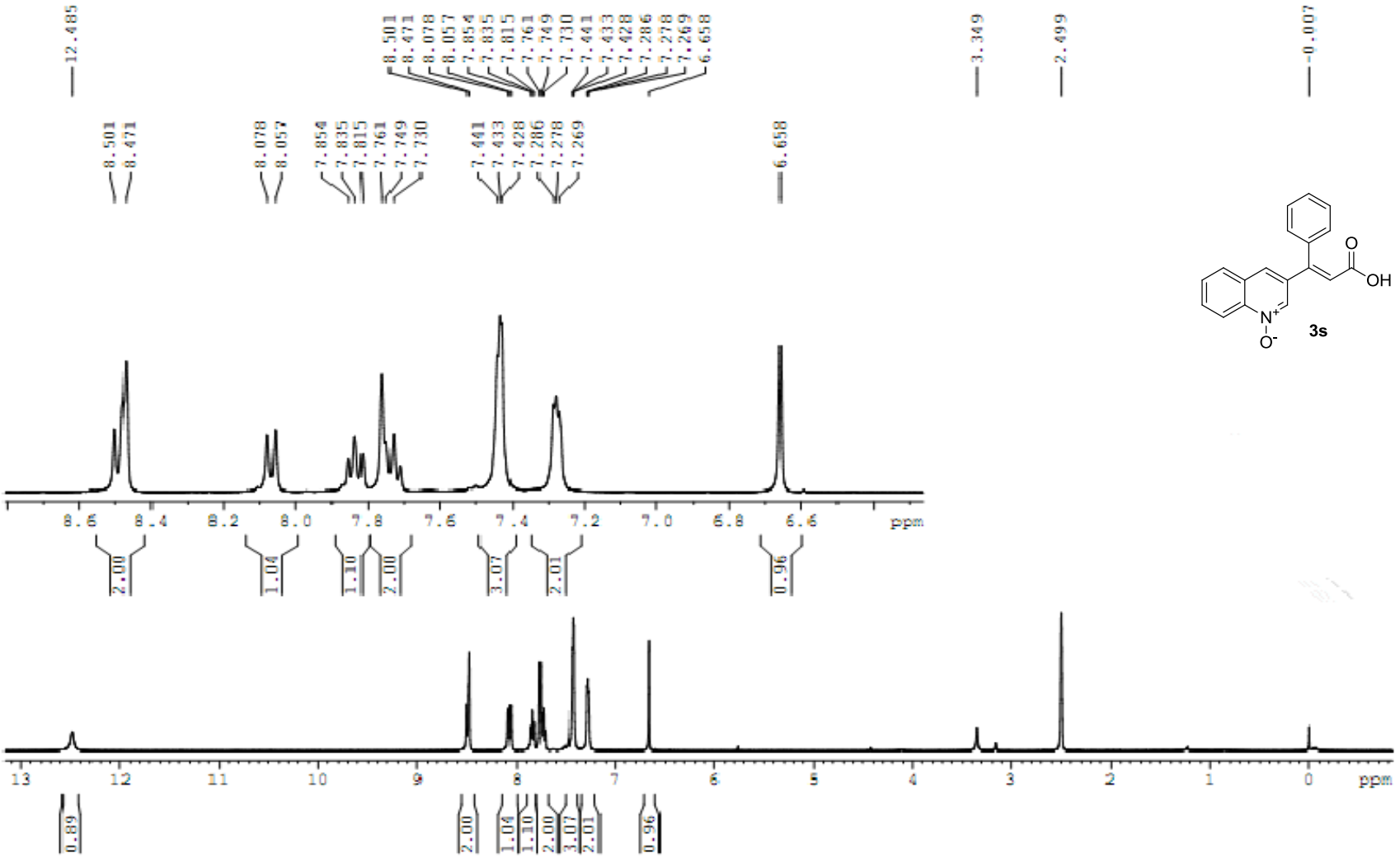
39.94
39.73
39.52
39.31
39.10
38.90
O
OH
N
8s
ppm
ppm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7.815
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7.749
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7.441
7.433
7.428
7.286
7.278
7.269
6.658
3.349
2.499
-0.007
O
OH
N+
O-
3s
ppm
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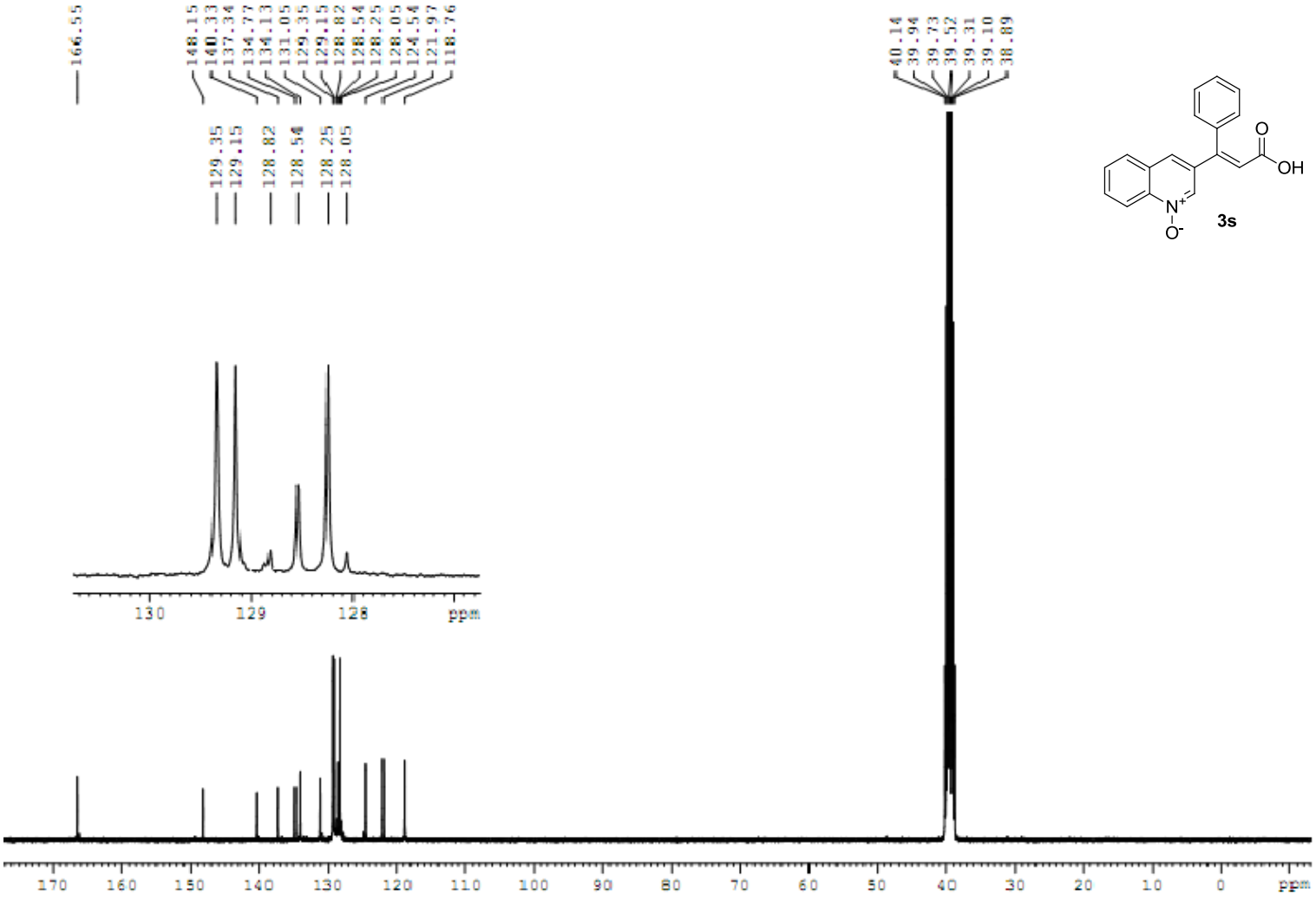
1.10
2.00
3.07
2.01
0.96
0.89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129.35
129.15
128.82
128.54
128.25
128.05
124.54
121.97
118.76
40.14
39.94
39.73
39.52
39.31
39.10
38.89
129.35
129.15
128.82
128.54
128.25
128.05
130
129
128
ppm
170
160
150
140
130
120
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100
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80
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40
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20
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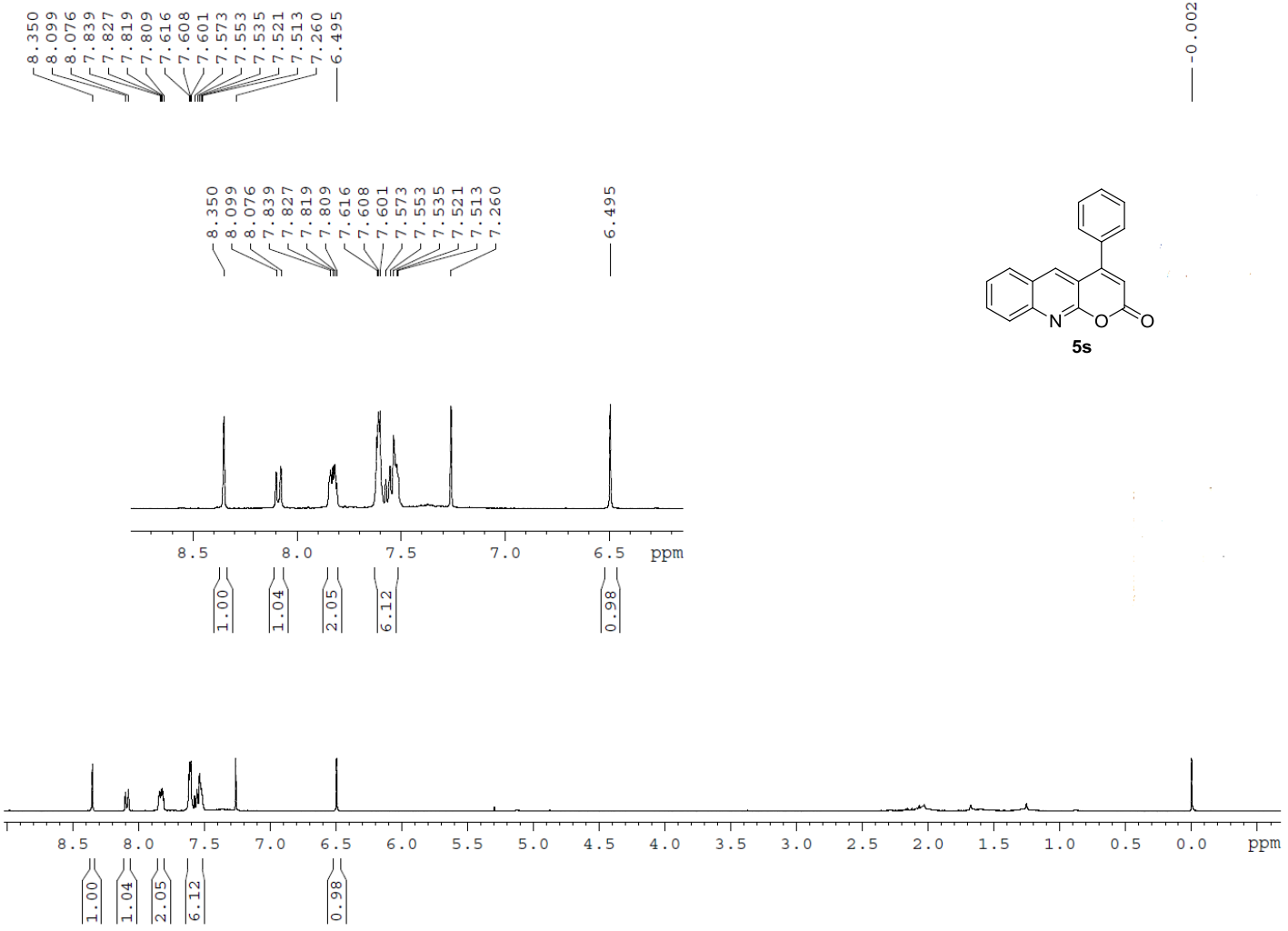
0
ppm
O
OH
N+
O-
3s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7.616
7.608
7.601
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7.553
7.535
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7.260
6.495
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1.04
2.05
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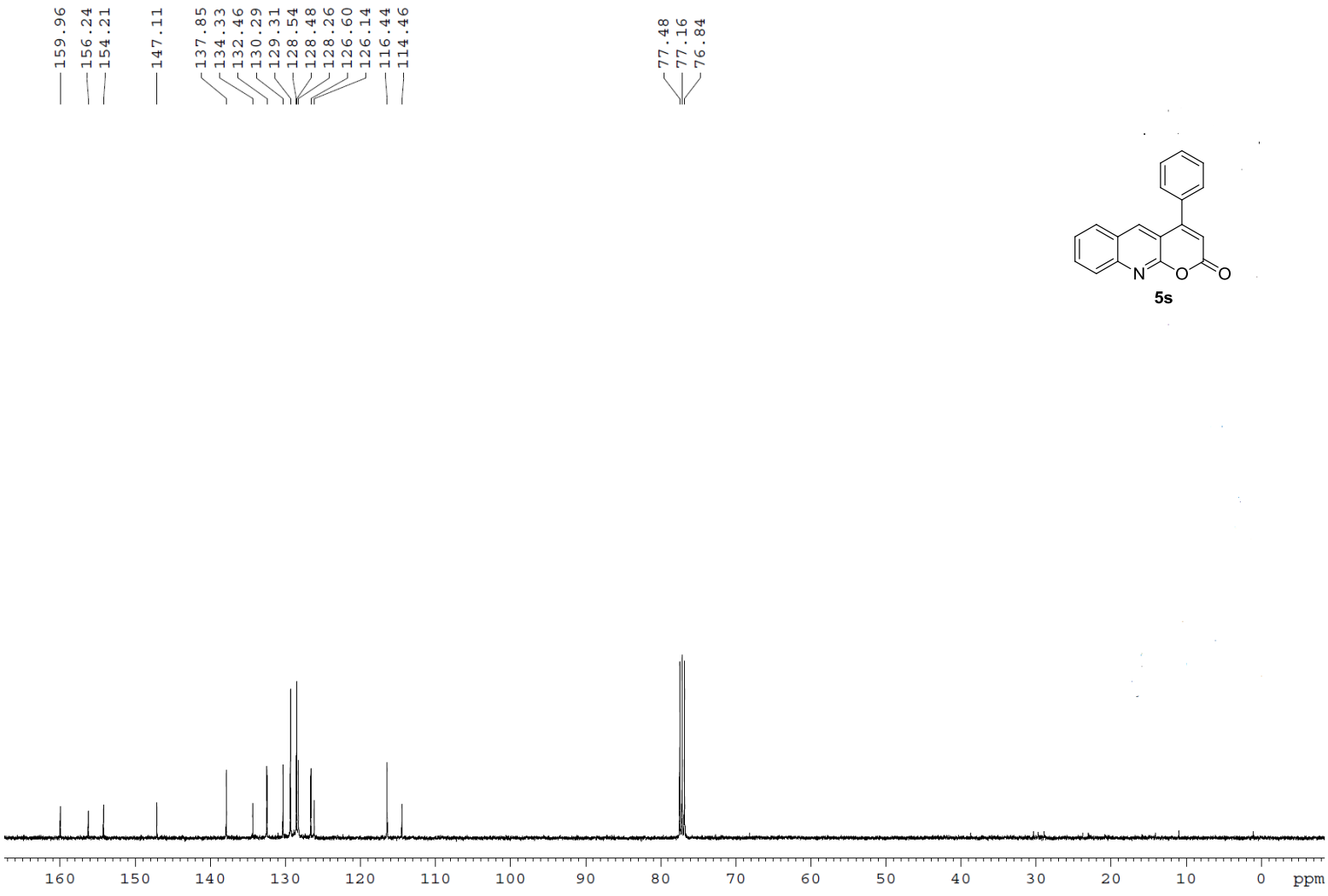
0.98


159.96
156.24
154.21
147.11
137.85
134.33
132.46
130.29
129.31
128.54
128.48
128.26
126.60
126.14
116.44
114.46
77.48
77.16
76.84
N
O
O
5s
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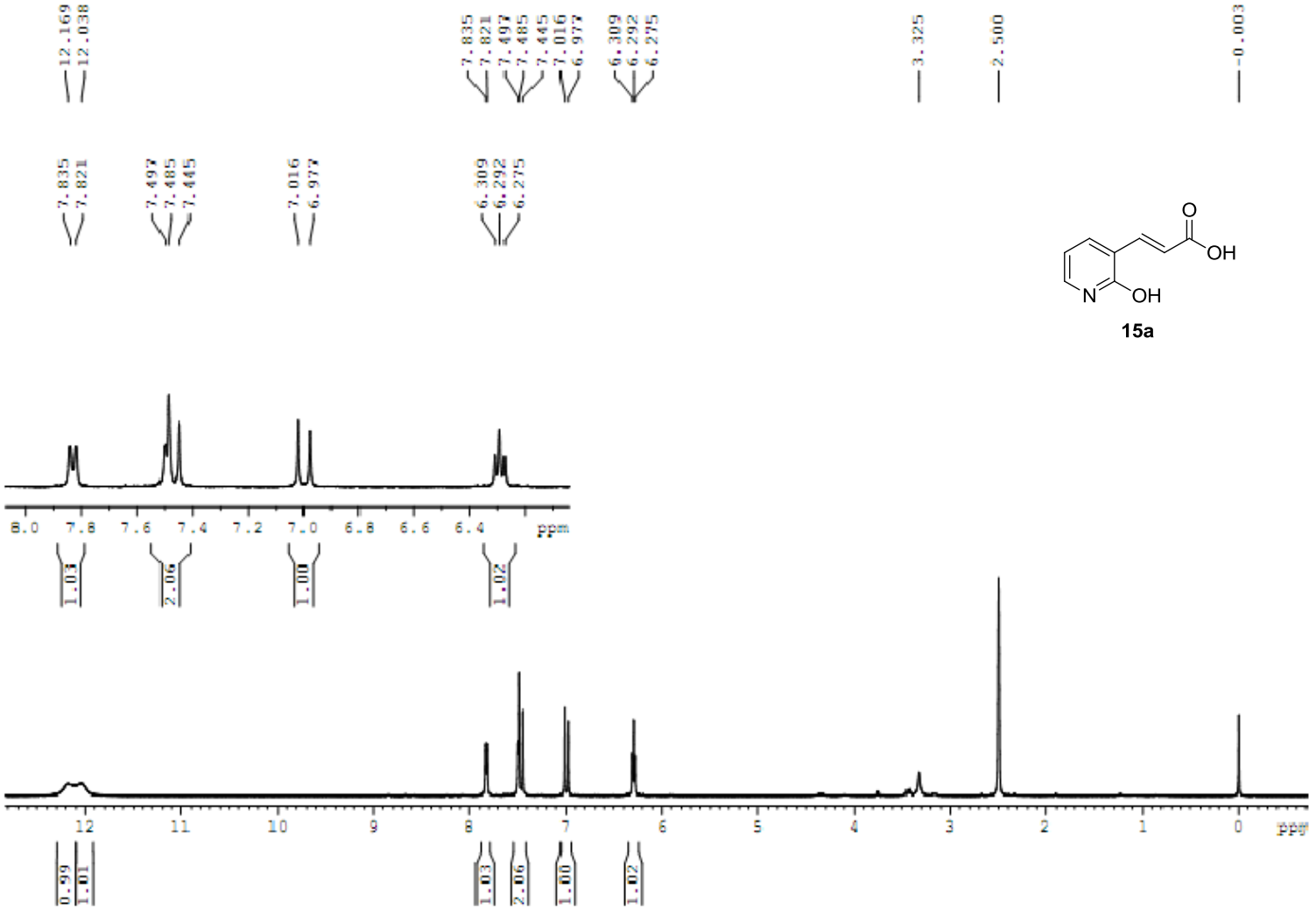
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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7.016
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6.309
6.292
6.275
3.325
2.500
-0.003
O
OH
N
OH
15a
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
ppm
1.03
2.06
1.00
1.02
12
11
10
9
8
7
6
5
4
3
2
1
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ppm
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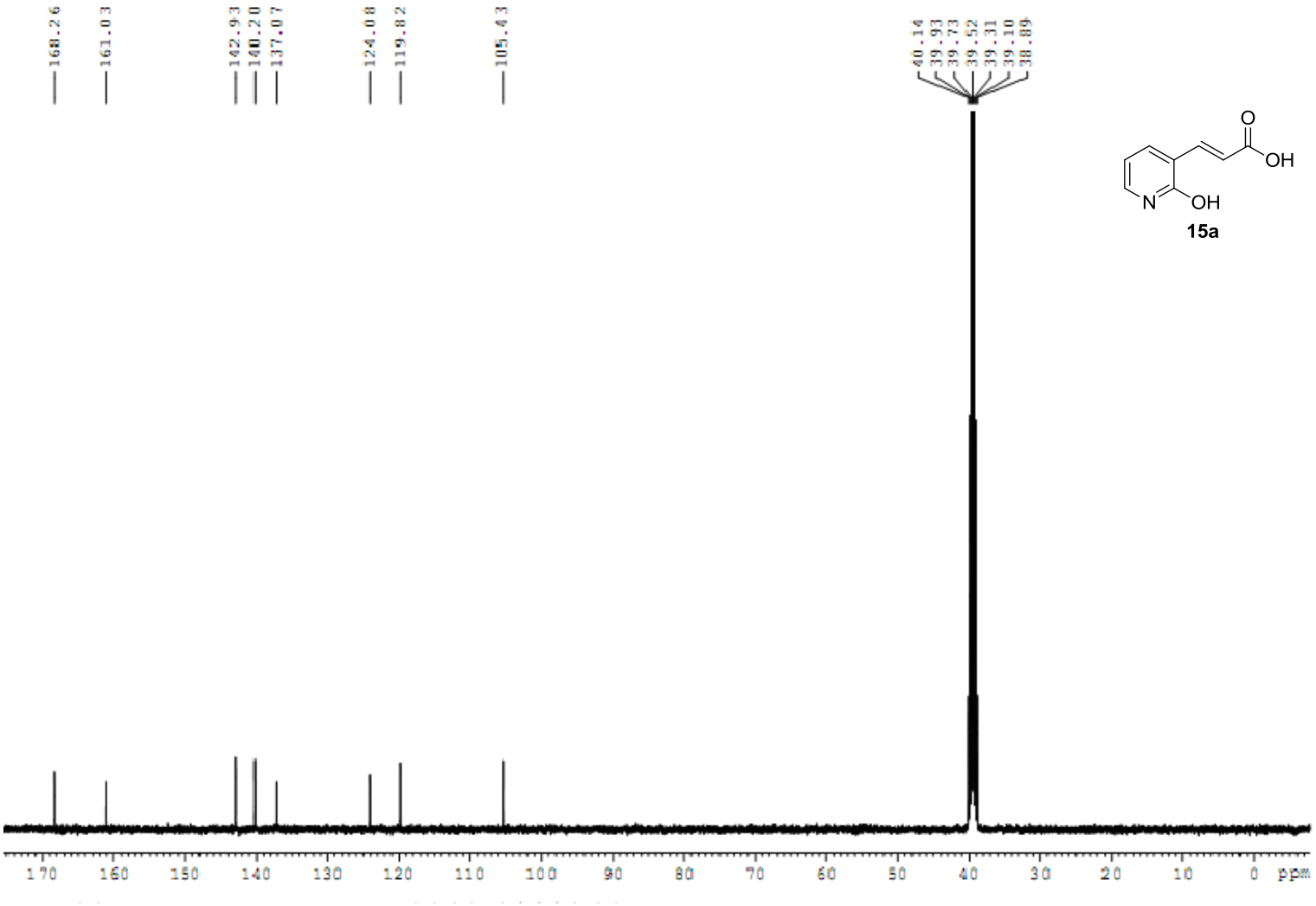
1.01
1.03
2.06
1.00
1.02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142.93
140.20
137.07
124.08
119.82
105.43
40.14
39.93
39.73
39.52
39.31
39.10
38.89
O
OH
N
OH
15a
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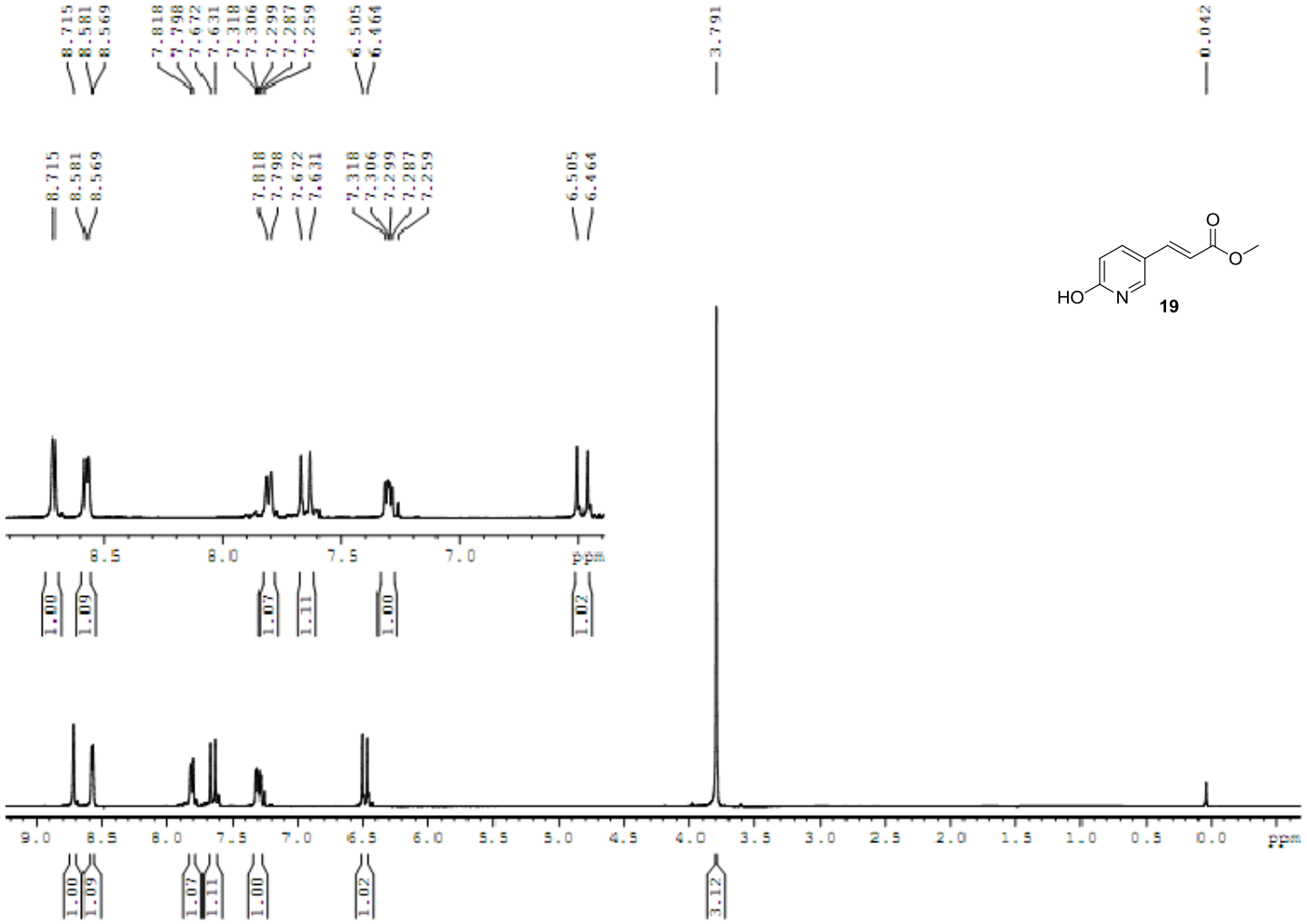
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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7.318
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7.299
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7.259
6.505
6.464
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O
19
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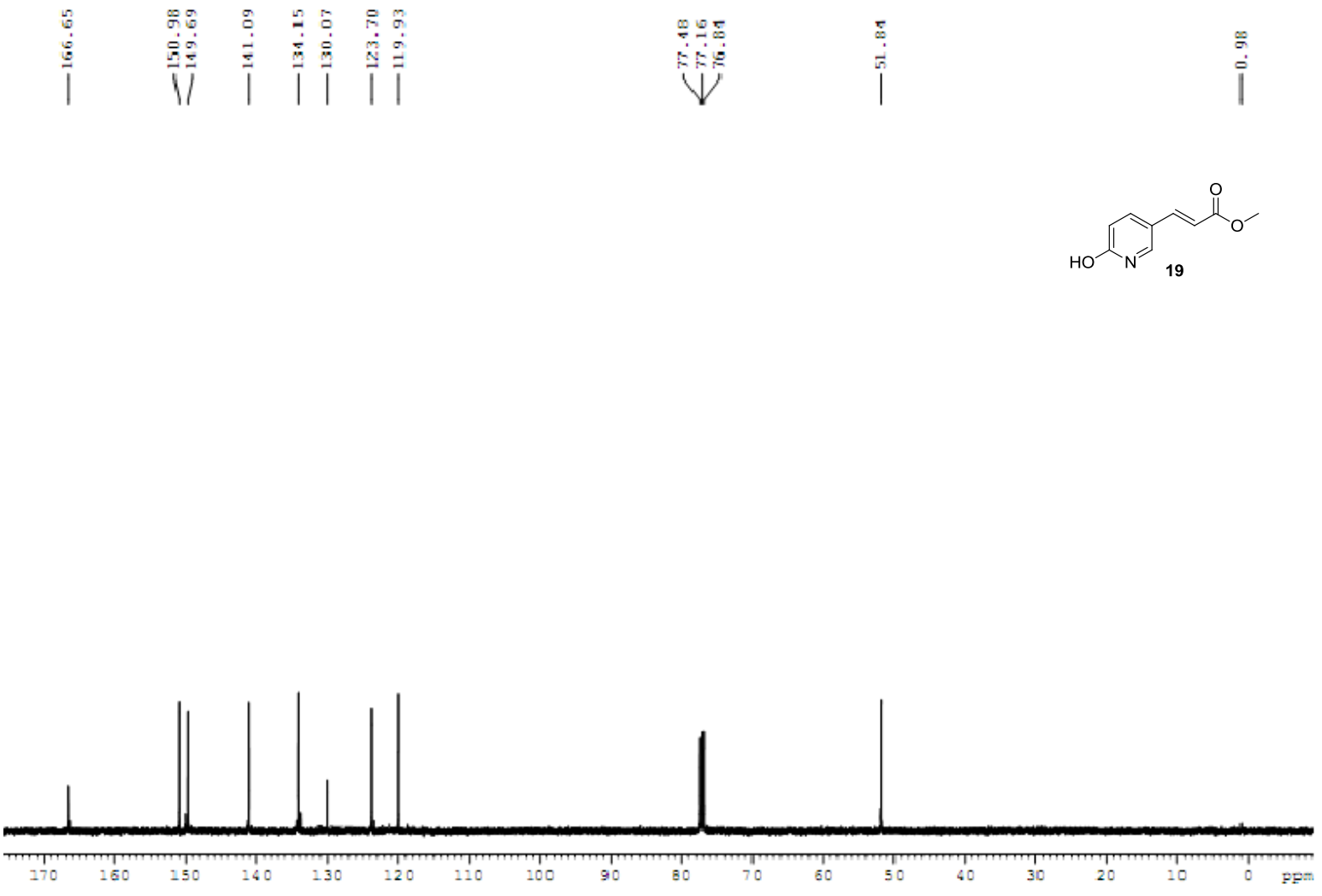
1.07
1.11
1.00
1.02
3.12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150.98
149.69
141.09
134.15
130.07
123.70
119.93
77.48
77.16
76.84
51.84
0.98
HO
N
O
O
19
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm