Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Palladium-Catalyzed Alkylation of Unactivated C(sp^3)−H Bonds with Primary Alkyl Iodides at Room Temperature: Facile Synthesis of β-Alkyl α-Amino Acids

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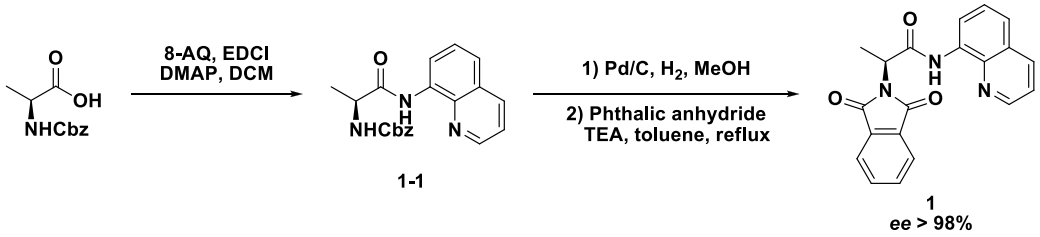
1. Reagents: All commercial materials were used as received unless otherwise noted. The toluene for reaction was obtained from a JC Meyer solvent dispensing system and used without further purification. Flash chromatography was performed using 230-400 mesh SiliaFlash 60® silica gel (Silicycle Inc.). $Pd(OAc)_2$ (98%, Aldrich), silver trifluoroacetate (98%, Alfa Aesar), silver acetate (98%, Alfa Aesar), 1,1,2,2-tetrachloroethane (98.5%, Acros), potassium bicarbonate (99.7%-100.5%, Alfa Aesar), trifluoroacetic acid (99.5+%, Alfa Aesar) and dioxane (99+%, Alfa Aesar) were used in the Pd-catalyzed reactions. 8-aminoquinoline (AQ) (98%, Aldrich) were purchased from Aldrich and used without further purification.

2. Instruments: NMR spectra were recorded on Bruker AV-360, DRX-400 or CDPX-300 instruments and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, q = quartet. High resolution ESI mass experiments were operated on a Waters LCT Premier instrument.

3. Preparation of alanine 1 and alkyl iodides for C-H alkylation

Alkyl bromide **16** and alkyl iodide **4**, **8**, **16**, **18**, **20**, **22**, **24**, **26** were commercially available. Alkyl iodide **12**, **28** and **30** were prepared according to the reported procedure [1] starting from commercially available methyl ketone. Alanine substrate **1** and alkyl iodide **6**, **10**, **14** were prepared as follows.

3.1 Preparation of alanine substrate 1

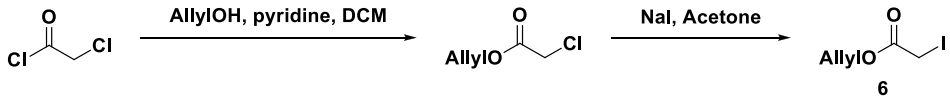


To a solution of *N*-Cbz alanine (2.23 g, 10 mmol, 1 equiv), 8-aminoquinoline (1.15 g, 8 mmol, 0.8 equiv) and DMAP (244 mg, 2 mmol, 0.2 equiv) in dichloromethane (60 mL) at 0 ^{o}C was added EDCI (2.33 g, 15 mmol, 1.5 equiv) portionwise. The reaction mixture was then stirred

at room temperature for 4 hours. After completion, the reaction was diluted with dichloromethane (100 mL), washed with 0.1 M aqueous solution of sodium hydroxide and brine. The organic layer was dried over anhydrous sodium sulfate. After concentration *in vacuo*, the residue was purified by flash silica gel chromatography (hexanes : ethyl acetate = 4 : 1), giving 2.70 g of intermediate **1-1** as a yellowish syrup in 96% yield (yield based on 8-aminoquinoline). **^{1}H NMR** ($CDCl_3$, 360 MHz, ppm): δ 1.60-1.62 (d, J = 6.8 Hz, 1H), 4.65 (s, 1H), 5.20 (s, 2H), 5.75 (s, 1H), 7.29-7.54 (m, 8H), 8.15-8.18 (m, 1H), 8.76-8.78 (m, 2H), 10.27 (s, 1H); **^{13}C NMR** ($CDCl_3$, 90 MHz, ppm) δ 19.21, 51.83, 67.05, 116.65, 121.72, 122.00, 127.27, 127.91, 128.09, 128.18, 128.56, 133.96, 136.31, 138.50, 148.41, 155.94, 170.84.

The mixture of intermediate **1-1** (2.0 g, 5.7 mmol, 1 equiv) and Pd/C (200 mg, 10% on carbon) in methanol (50 mL) was hydrogenated under 1 atmosphere of H_2 at rt for 4 hours. After filtration, the solution was concentrated *in vacuo*. The residue was re-suspended in toluene (100 mL) with phthalic anhydride (931 mg, 6.3 mmol, 1.1 equiv) and triethylamine (1.2 mL, 8.6 mmol, 1.5 equiv) and heated under reflux with Dean-Stark trap overnight. After concentration *in vacuo*, the residue was purified by flash silica gel chromatography (dichloromethane : ethyl acetate = 20:1), giving 1.40 g of alanine substrate **1** as a white crystal in a 71% yield over two steps.

3.2 Preparation of alkyl iodide 6

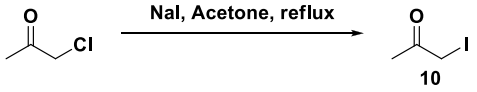


To a solution of allyl alcohol (1.74 g, 30 mmol, 1 equiv) and pyridine (474 mg, 60 mmol, 2 equiv) in dichloromethane (50 mL) was added 2-chloroacetyl chloride (3.39 g, 30 mmol, 1 equiv) dropwise at 0 ^{o}C. After 1 hour, the reaction mixture was quenched by water (50 mL). The organic layer was separated and washed with 1 M HCl, aqueous saturated sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate and filtered. After concentration *in vacuo*, the residue was used for the next step without further purification.

The mixture of the resulting residue and sodium iodide (11.2 g, 75 mmol, 2.5 equiv) in acetone (50 mL) was vigorously stirred at room temperature overnight. The reaction mixture was then diluted with diethyl ether (200 mL) and thoroughly washed with 1 M aqueous sodium

thiosulfate and water. The organic layer was dried over anhydrous sodium sulfate and filtered. After concentration *in vacuo*, the residue was directly used for the Pd-catalyzed alkylation reaction without further purification.

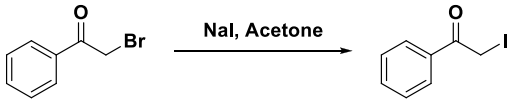
3.3 Preparation of alkyl iodide 10



10

The mixture of chloropropanone (2 g, 21.6 mmol, 1 equiv) and sodium iodide (8.1 g, 54 mmol, 2.5 equiv) in acetone (50 mL) was refluxed overnight. The reaction mixture was then diluted with diethyl ether (200 mL) and washed with 1 M aqueous sodium thiosulfate and water. The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduce pressure and the resulting residue was used for the Pd-catalyzed alkylation reaction without any purification.

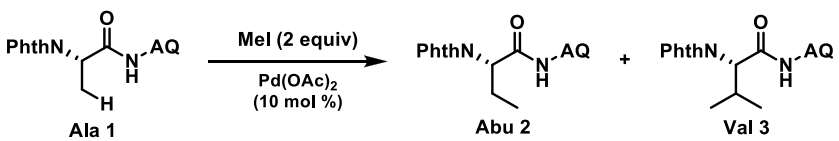
3.4 Preparation of alkyl iodide 14



14

A mixture of 2-bromoacetophenone (2.0 g, 10 mmol, 1 equiv) and sodium iodide (3.7 g, 25 mmol, 2.5 equiv) in acetone (20 mL) was vigorously stirred at room temperature overnight. The reaction mixture was then diluted with diethyl ether (150 mL) and washed with 1 M aqueous sodium thiosulfate and water. The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was removed under vacuum, and the resulting residue was used for the Pd-catalyzed alkylation reaction without any purification.

4. General screening procedure in Table 1



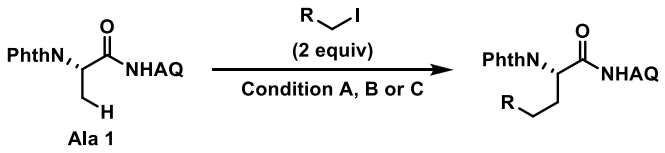
Ala 1 Abu 2 Val 3

Reactions in **Table 1** were performed at a 0.2 mmol scale, 0.1 M concentration in 10 mL vials under the conditions listed in **Table 1**. After completion, the reactions were diluted with dichloromethane (10 mL), and then filtrated through a pad of Celite. After concentration *in vacuo*, the crude residue was dissolved in 2000 μL of $CDCl_3$. 1,1,2,2-tetrachloroethane (33.57 mg, 0.2 mmol, 1 equiv, the integration of singlet around 6.0 ppm was set as 2.0) was added as internal standard. 600 μL of the solution was used for ^{1}H-NMR analysis. Yields of **Abu 2** and **Val 3** were determined as following:

$$\text{Yield (2)} = \text{integration of multiplet peak } (\delta\ 2.47\text{-}2.65) \times 50\%$$

$$\text{Yield (3)} = \text{integration of multiplet peak } (\delta\ 3.22\text{-}3.28) \times 100\%$$

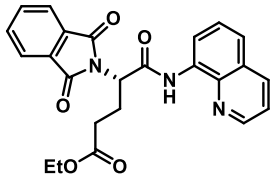
5. General procedure for Pd-catalyzed C-H alkylation of Ala 1



Conditions A: Alanine substrate **1** (69 mg, 0.2 mmol, 1 equiv), alkyl iodide (2 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), silver acetate (84 mg, 0.5 mmol, 2.5 equiv) and trifluoroacetic acid (15 μL, 0.2 mmol, 1 equiv) were suspended in dioxane (2 mL). The resulting mixture was stirred at room temperature. After completion, 1 M aq. NaOH solution (2 mL) and dichloromethane (20 mL) were added. The organic layer was separated, and the aqueous layer was re-extracted with dichloromethane (10 mL) twice. The combined organic layer was concentrated *in vacuo*, and the resulting residue was purified by flash silica gel chromatography.

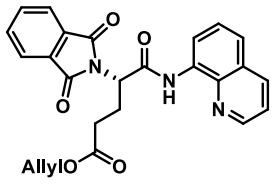
Conditions B: Alanine substrate **1** (69 mg, 0.2 mmol, 1 equiv), alkyl iodide (2 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), silver acetate (84 mg, 0.5 mmol, 2.5 equiv) and trifluoroacetic acid (15 μL, 0.2 mmol, 1 equiv) were suspended in dioxane (2 mL). The resulting mixture was stirred at 70 ^{o}C. Same workup as conditions A was then used.

Conditions C: A mixture of alanine substrate **1** (69 mg, 0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), Ag_2CO_3 (110 mg, 0.4 mmol, 2 equiv), $(BnO)_2PO_2H$ (11 mg, 0.04 mmol, 0.2 equiv), and alkyl iodide (2 equiv) in *t*-AmylOH (2 mL) in a 10 mL glass vial was heated at 110 ^{o}C for 24 hours. Same workup as conditions A was then used.



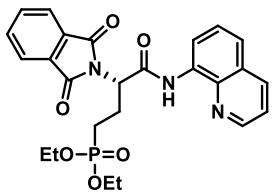
5

Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 3:1) gave 79 mg of product as a white foam in 92% yield under **Condition A**; 61 mg product in 71% yield under **Condition B;** 41 mg product in 48% yield under **Condition C**. ^{1}H NMR (400 MHz, CDCl3) δ 10.26 (s, 1H), 8.69 – 8.59 (m, 1H), 8.57 (d, *J* = 2.7 Hz, 1H), 8.08 – 7.99 (m, 1H), 7.83 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.68 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.41 (d, *J* = 3.9 Hz, 2H), 7.31 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.27 – 5.13 (m, 1H), 4.08 (dd, *J* = 13.7, 6.7 Hz, 2H), 2.97 – 2.72 (m, 2H), 2.50 – 2.46 (dd, *J* = 9.9, 5.1 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 172.20, 167.94, 166.32, 148.33, 138.34, 136.22, 134.35, 133.75, 131.71, 127.77, 127.13, 123.59, 122.02, 121.65, 116.61, 60.74, 54.17, 31.17, 24.13, 14.16; **HRMS**: calculated for $C_{24}H_{22}N_3O_5^+$ [M+H$^+$]: 432.1554; found: 432.1654.



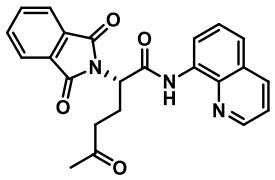
7

Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 3:1) gave 83 mg of product as a white foam in 94% yield under **Condition A**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.68 (t, *J* = 4.5 Hz, 1H), 8.64 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.89 – 7.86 (m, 2H), 7.76 – 7.73 (m, 2H), 7.48 – 7.47 (m, 2H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.88 (qd, *J* = 11.0, 5.8 Hz, 1H), 5.29 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.21 (dd, *J* = 13.2, 4.1 Hz, 2H), 4.56 (d, *J* = 5.8 Hz, 2H), 2.89 – 2.76 (m, 2H), 2.56 – 2.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.89, 167.96, 166.27, 148.31, 138.44, 136.38, 134.50, 133.80, 131.77, 127.83, 127.25, 123.84, 123.52, 122.03, 121.66, 118.52, 116.67, 65.47, 54.16, 31.10, 24.10; HRMS: calculated for $C_{25}H_{22}N_3O_5^+$ [M+H$^+$]: 444.1554; found: 444.1538.



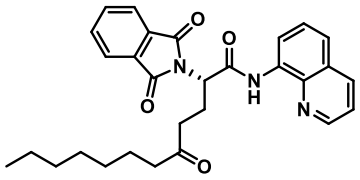
9

Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : acetone = 2:1) gave 69 mg of product as a white solid in 70% yield under **Condition B**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.64 (s, 2H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.89 (dd, *J* = 5.2, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.2, 3.0 Hz, 2H), 7.49 (d, *J* = 4.9 Hz, 2H), 7.39 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.18 (t, *J* = 7.9 Hz, 1H), 4.11 (dt, *J* = 10.3, 7.8 Hz, 4H), 2.76 (dq, *J* = 16.3, 8.1 Hz, 2H), 2.03 – 1.77 (m, 2H), 1.33 (dd, *J* = 11.5, 6.9 Hz, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.95, 166.24, 148.62, 138.59, 136.43, 134.45, 133.65, 131.71, 127.92, 127.25, 123.74, 122.35, 121.69, 117.40, 62.01 (d, *Jc-p* = 2.2 Hz), 61.93 (d, *Jc-p* = 2.2 Hz), 55.13 (d, *Jc-p* = 17.0 Hz), 23.80 (d, *Jc-p* = 2.2 Hz), 22.46 (d, *Jc-p* = 3.7 Hz), 16.49 (d, *Jc-p* = 1.8 Hz), 16.43 (d, *Jc-p* = 1.9 Hz); ^{31}P NMR (146 MHz, acetone-d6) δ 30.13. HRMS: calculated for $C_{25}H_{27}N_3O_6P^+$ [M+H$^+$]: 496.1632; found: 496.1590.



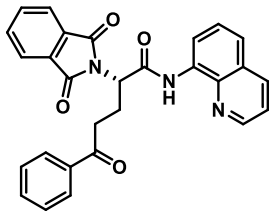
11

Reaction time: 24 hours. 3 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 2:1) gave 1.04 g of product as a yellowish foam in 86% yield under **Condition A**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.72 – 8.59 (m, 2H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.85 (dd, *J* = 5.0, 3.0 Hz, 2H), 7.71 (dd, *J* = 4.9, 2.9 Hz, 2H), 7.45 (d, *J* = 4.2 Hz, 2H), 7.36 (dd, *J* = 8.1, 4.1 Hz, 1H), 5.13 (dd, *J* = 9.0, 5.2 Hz, 1H), 2.85 – 2.56 (m, 4H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.02, 168.05, 166.45, 148.39, 138.42, 136.24, 134.35, 133.83, 131.75, 127.81, 127.17, 123.63, 122.01, 121.67, 116.66, 54.30, 40.15, 29.96, 23.02; HRMS: calculated for $C_{23}H_{20}N_3O_4^+$ [M+H$^+$]: 402.1448; found: 402.1604.



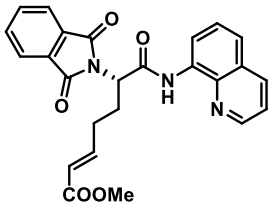
13

Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 2:1) gave 82 mg of product as a white foam in 85% yield under **Condition A**;[1]H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.69 – 8.66 (m, 2H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 5.1, 2.9 Hz, 2H), 7.74 (dd, *J* = 5.1, 2.9 Hz, 2H), 7.47 (d, *J* = 4.2 Hz, 2H), 7.38 (dd, *J* = 8.1, 4.1 Hz, 1H), 5.14 (dd, *J* = 9.5, 5.3 Hz, 1H), 2.95 – 2.65 (m, 2H), 2.64 – 2.49 (m, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 1.53 (s, 2H), 1.22 (brs, 8H), 0.85 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.45, 168.05, 166.50, 148.45, 148.33, 138.47, 136.36, 134.46, 133.88, 131.81, 127.83, 127.23, 123.80, 123.47, 121.99, 121.65, 116.75, 116.65, 54.41, 42.88,39.23, 31.63, 29.13, 29.04, 23.78, 23.01, 22.59, 14.03; HRMS: calculated for $C29H32N3O4^+$ [M+H^+]: 486.2387; found: 486.2479.



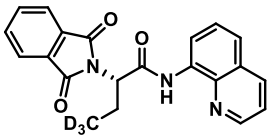
15

Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 2:1) gave 88 mg of product as a white foam in 95% yield under **Condition A**;[1]H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.73 – 8.70 (m, 2H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.90 (dd, *J* = 5.2, 3.1 Hz, 2H), 7.81 – 7.70 (m, 2H), 7.56 – 7.51 (m, 2H), 7.45 – 7.41 (m, 3H), 5.29 (dd, *J* = 9.3, 6.1 Hz, 1H), 3.28 – 3.16 (m, 2H), 3.04 – 2.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.51, 168.10, 166.59, 148.42, 138.52, 136.59, 136.28, 134.27, 133.93, 133.22, 131.86, 128.60, 128.12, 127.86, 127.25, 123.70, 121.99, 121.66, 116.78, 54.55, 35.37, 23.66; HRMS: calculated for $C_{28}H_{22}N_3O_4^+$ [M+H^+]: 464.1605; found: 464.1581.



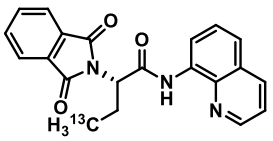
17

Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 2:1) gave 56 mg of product as a yellowish foam in 64% yield under **Condition A**; ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.80 – 8.57 (m, 2H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 3.0 Hz, 2H), 7.77 (dd, *J* = 4.4, 3.1 Hz, 2H), 7.50 (d, *J* = 4.2 Hz, 2H), 7.40 (dd, *J* = 8.1, 4.1 Hz, 1H), 7.05 – 6.85 (m, 1H), 5.87 (d, *J* = 15.7 Hz, 1H), 5.12 (dd, *J* = 10.6, 4.9 Hz, 1H), 3.66 (s, 3H), 2.87 – 2.67 (m, 1H), 2.64 – 2.55 (m, 1H), 2.49 – 2.25 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.01, 166.62, 166.32, 148.42, 146.84, 138.46, 136.32, 134.40, 133.75, 131.74, 127.86, 127.30, 123.78, 122.30, 122.08, 121.71, 116.73, 54.58, 51.50, 29.41, 27.15; HRMS: calculated for $C_{25}H_{22}N_3O_5^+$ [M+H$^+$]: 444.1554; found: 444.1516.



19

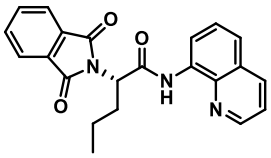
Reaction time: 5 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 2:1) gave 64 mg of product as a white foam in 89% yield under **Condition A;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.73 – 8.70 (m, 2H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.90 (dd, *J* = 5.2, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.2, 3.0 Hz, 2H), 7.51 – 7.50 (m, 2H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.06 (dd, *J* = 10.9, 5.4 Hz, 1H), 2.58 (t, *J* = 12.5 Hz, 1H), 2.46 (dd, *J* = 13.7, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.17, 166.96, 148.33, 138.51, 136.29, 134.23, 133.95, 131.84, 127.86, 127.30, 123.60, 121.90, 121.63, 116.71, 56.73, 21.95; HRMS: calculated for $C_{21}H_{15}D_3N_3O_3^+$ [M+H$^+$]: 363.1531; found: 363.1526.



21

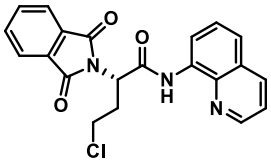
Reaction time: 5 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 2:1) gave 64 mg of product as a white foam in 89% yield under **Condition A**;^{1}H NMR (360 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.72 (d, *J* = 8.3 Hz, 2H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.91 (dd, *J* = 4.6, 3.4 Hz, 2H), 7.76 (dd, *J* = 4.9, 3.1 Hz, 2H), 7.51 (d, *J* = 4.2 Hz,

2H), 7.42 (dd, J = 8.2, 4.3 Hz, 1H), 7.26 (s, 1H), 5.14 – 4.98 (m, 1H), 2.88 – 2.21 (m, 2H), 1.25 (t, J = 7.3 Hz, 2H), 0.90 (t, J = 7.3 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.21, 166.96, 148.35, 138.51, 136.36, 134.26, 133.95, 131.86, 127.89, 127.36, 123.64, 121.94, 121.66, 116.77, 56.79,20.05 (d, *Jc-^{13}c* = 77.7 Hz), 11.23; HRMS: calculated for $C_{20}{}^{13}CH_{18}N_3O_3^+$ [M+H$^+$]: 361.1376; found:361.1356.



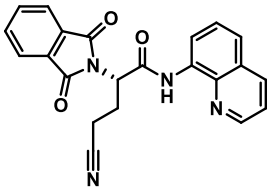
23

Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 4:1) gave 19 mg of product as a colorless gum in 19% yield under **Condition A;** ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.71 (dd, J = 9.0, 4.5 Hz, 2H), 8.20 – 8.07 (m, 1H), 7.89 (dd, J = 5.1, 3.1 Hz, 2H), 7.74 (dd, J = 5.1, 3.1 Hz, 2H), 7.49 (d, J = 4.0 Hz, 2H), 7.40 (dd, J = 8.2, 4.2 Hz, 1H), 5.15 (dd, J = 11.1, 5.1 Hz, 1H), 2.69 – 2.51 (m, 1H), 2.34 (td, J = 13.6, 7.8 Hz, 1H), 1.58 – 1.35 (m, 2H), 1.03 (t, J = 7.3 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.18, 167.13, 148.38, 138.51, 136.31, 134.26, 133.95, 131.85, 127.86, 127.31, 123.62, 121.93, 121.66, 116.69, 54.97, 30.69, 19.94, 13.56; HRMS: calculated for $C_{22}H_{20}N_3O_3^+$ [M+H$^+$]: 374.1499; found: 374.1503.



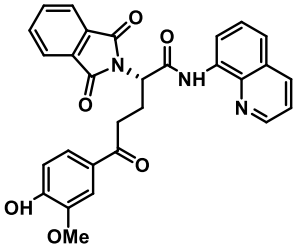
25

Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (toluene : ethyl acetate = 15:1) gave 25 mg of product as a colorless gum in 32% yield under **Condition A;** ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 3.6 Hz, 2H), 7.79 (d, J = 3.3 Hz, 2H), 7.51 (d, J = 4.1 Hz, 2H), 7.40 (dd, J = 8.1, 4.2 Hz, 1H), 5.45 (dd, J = 9.6, 5.5 Hz, 1H), 3.80 (dt, J = 11.0, 5.4 Hz, 1H), 3.69 – 3.54 (m, 1H), 3.10 – 2.85 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.97, 166.15, 148.42, 138.42, 136.31, 134.48, 133.68, 131.78, 127.84, 127.27, 123.82, 122.13, 121.72, 116.73, 52.33, 41.71, 31.41; HRMS: calculated for $C_{21}H_{17}ClN_3O_3^+$ [M+H$^+$]: 394.0953; found: 394.1102.



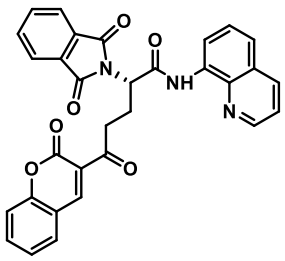
27

Reaction time: 36 hours. 3 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 2:1) gave 1.04 g of product as a yellowish foam in 90% yield under **Condition A**; ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.66 – 8.61 (m, 2H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.93 – 7.92 (m, 2H), 7.79 (dd, *J* = 5.1, 2.8 Hz, 2H), 7.57 (m, 2H), 7.45 (dd, *J* = 8.2, 4.3 Hz, 1H), 5.27 – 5.18 (m, 1H), 2.91 – 2.75 (m, 2H), 2.61 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.87, 165.73, 148.11, 137.83, 137.58, 134.66, 132.95, 131.63, 128.10, 127.63, 123.96, 122.82, 121.71, 118.74, 118.60, 53.38, 24.90, 14.99; HRMS: calculated for $C_{22}H_{17}N_4O_3^+$ [M+H$^+$]: 385.1295; found: 385.1280.



29

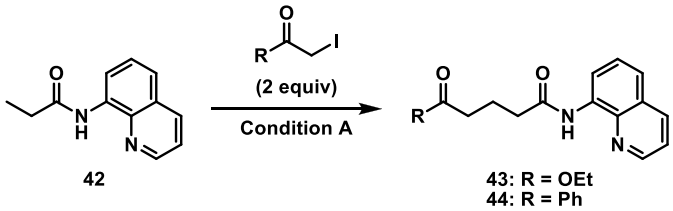
Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 2:1) gave 72 mg of product as a yellowish solid in 76% yield under **Condition A;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.72 – 8.68 (m, 2H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.87 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.50 – 7.47 (m, 4H), 7.40 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.26 (s, 1H), 5.28 (t, *J* = 7.7 Hz, 1H), 3.89 (s, 3H), 3.13 (t, *J* = 6.9 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.05, 168.10, 166.68, 150.53, 148.40,146.65, 138.49, 136.29, 134.25, 131.84, 129.52, 127.24, 123.63, 123.42, 122.01, 121.64, 116.83, 113.88, 109.89, 56.05, 54.62, 34.81, 24.03; HRMS: calculated for $C_{29}H_{24}N_3O_6^+$ [M+H$^+$]: 510.1660; found: 510.1647.



31

Reaction time: 24 hours. 0.2 mmol scale. Flash silica gel chromatography (hexanes : ethyl acetate = 2:1) gave 78 mg of product as a yellowish solid in 74% yield under **Condition A;** ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.78 – 8.62 (m, 2H), 8.51 (s, 1H), 8.12 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.87 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.65 – 7.62 (m, 2H), 7.50 – 7.49 (m, 2H), 7.40 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.35 – 7.31 (m, 2H), 5.26 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.35 (t, *J* = 6.5 Hz, 2H), 3.06 – 2.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.30, 168.09, 166.60, 159.04, 155.25, 148.35, 147.89, 138.49, 136.27, 134.47, 134.24, 133.94, 131.88, 130.30, 127.85, 127.29, 125.00, 124.08, 123.65, 121.91, 121.61, 118.25, 116.79, 116.65, 54.20, 39.07, 23.16; HRMS: calculated for $C_{31}H_{22}N_3O_6^+$ [M+H$^+$]: 532.1503; found: 532.1451.

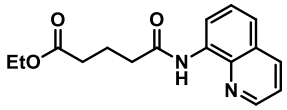
6. Synthesis of compounds 43 and 44



42

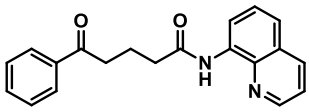
43: R = OEt
44: R = Ph

Propanamide **42** (40 mg, 0.2 mmol, 1 equiv), ethyl 2-iodoacetate (86 mg, 0.4 mmol, 2 equiv) or 2-iodo-1-phenylethanone (98 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), silver acetate (84 mg, 0.5 mmol, 2.5 equiv) and trifluoroacetic acid (15 μL, 0.2 mmol, 1 equiv) were suspended into dioxane (2 mL). The resulting solution was stirred at room temperature. After completion, 1 M aq. NaOH solution (2 mL) and dichloromethane (20 mL) were added. Organic layer was separated, and the aqueous layer was re-extracted with dichloromethane (10 mL) twice. Combined organic layer was concentrated *in vacuo*, and the resulting residue was purified by flash silica gel chromatography.



43

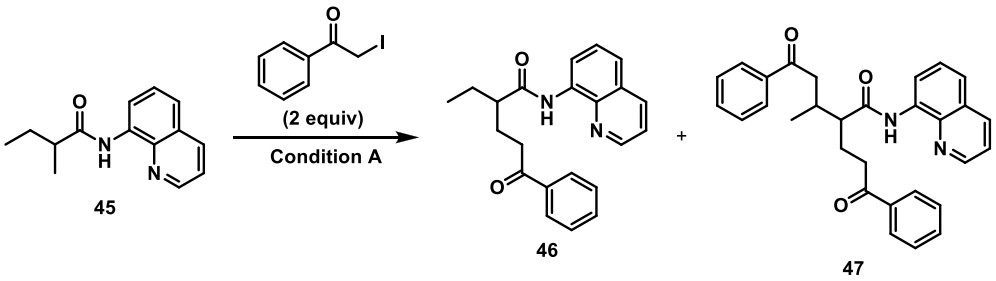
Reaction time: 24 hours. Flash silica gel chromatography (hexanes : ethyl acetate = 4:1) gave 31 mg of product as a white foam in 54% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.83 – 8.71 (m, 2H), 8.14 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.17 – 2.10 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.12, 170.81, 148.14, 138.30, 136.35, 134.45, 127.92, 127.39, 121.61, 121.46, 116.42, 60.40, 36.91, 33.44, 20.75, 14.24; HRMS: calculated for $C_{16}H_{19}N_2O_3^+$ [M+H$^+$]: 287.1390; found: 287.1400.



44

Reaction time: 24 hours. Flash silica gel chromatography (hexanes : ethyl acetate = 4:1) gave 44 mg of product as a yellowish foam in 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.77 (dd, *J* = 4.4, 1.5 Hz, 2H), 8.14 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.03 – 7.87 (m, 2H), 7.56 – 7.46 (m, 3H), 7.46 – 7.38 (m, 3H), 3.17 (t, *J* = 7.0 Hz, 2H), 2.71 (t, *J* = 7.1 Hz, 2H), 2.27 (p, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.70, 171.16, 148.20, 138.31, 136.86, 136.44, 136.25, 134.47, 133.08, 128.59, 128.21, 127.94, 127.41, 121.63, 116.47, 37.57, 36.94, 19.98; HRMS: calculated for $C_{20}H_{19}N_2O_2^+$ [M+H$^+$]: 319.1441; found: 319.1434.

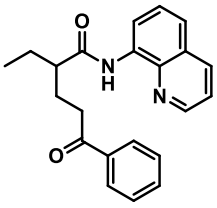
7. Synthesis of compounds 46 and 47



45 46 47

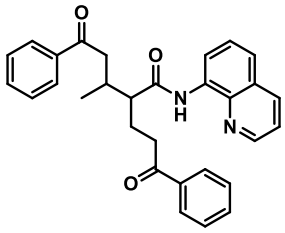
Compound **45** (46 mg, 0.2 mmol, 1 equiv), 2-iodo-1-phenylethanone (98 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), silver acetate (84 mg, 0.5 mmol, 2.5 equiv) and trifluoroacetic acid (15 μL, 0.2 mmol, 1 equiv) were suspended in dioxane (2 mL). The resulting solution was stirred at room temperature. After completion, 1 M aq. NaOH solution (2 mL) and dichloromethane (20 mL) were added. Organic layer was separated, and the aqueous

layer was re-extracted with dichloromethane (10 mL) twice. Combined organic layer was concentrated *in vacuo*, and the resulting residue was purified by flash silica gel chromatography.



46

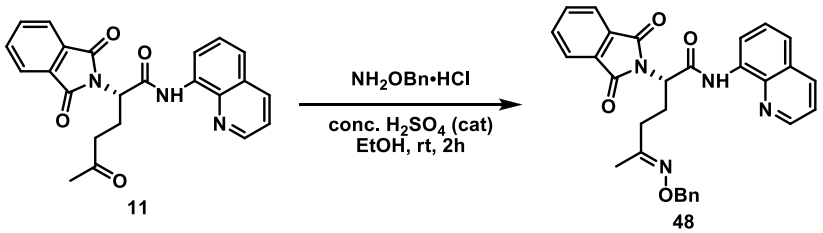
Reaction time: 24 hours. Flash silica gel chromatography (hexanes : ethyl acetate = 4:1) gave 46 mg of product as a yellowish foam in 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.82 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.98 – 7.83 (m, 2H), 7.51 (tt, *J* = 10.7, 7.8 Hz, 3H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 3.15 (ddd, *J* = 17.1, 8.4, 5.7 Hz, 1H), 3.05 (dt, *J* = 17.1, 7.1 Hz, 1H), 2.65 – 2.52 (m, 1H), 2.27 – 2.03 (m, 2H), 1.99 – 1.83 (m, 1H), 1.78 – 1.64 (m, 1H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.85, 174.16, 148.21, 148.14, 138.36, 136.83, 134.36, 132.97, 128.49, 128.21, 127.94, 127.43, 121.59, 121.54, 116.60, 49.82, 36.16, 26.95, 26.44, 11.98; HRMS: calculated for $C_{22}H_{23}N_2O_2^+$ [M+H$^+$]: 347.1754; found: 347.1826.



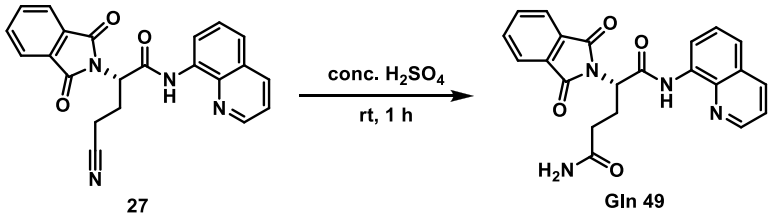
47

Reaction time: 24 hours. Flash silica gel chromatography (hexanes : ethyl acetate = 3:1) gave 4 mg of product as a yellowish gum in 4% yield; ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.81 (dd, *J* = 12.1, 4.7 Hz, 2H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.63 – 7.30 (m, 9H), 3.34 (dd, *J* = 16.5, 2.1 Hz, 1H), 3.27 – 3.12 (m, 1H), 2.99 (ddd, *J* = 23.5, 16.0, 7.7 Hz, 2H), 2.76 (m, 2H), 2.38 – 2.08 (m, 2H), 1.15 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.77, 199.65, 173.23, 148.39, 138.46, 137.12, 136.76, 136.30, 134.32, 133.03, 128.56, 128.51, 128.22, 128.09, 127.95, 127.29, 121.75, 121.68, 116.59, 52.73, 43.05, 36.37, 32.50, 23.61, 17.64; HRMS: calculated for $C_{30}H_{29}N_2O_3^+$[M+H$^+$]: 465.2173; found: 465.2180.

8. Further transformation in Scheme 3A



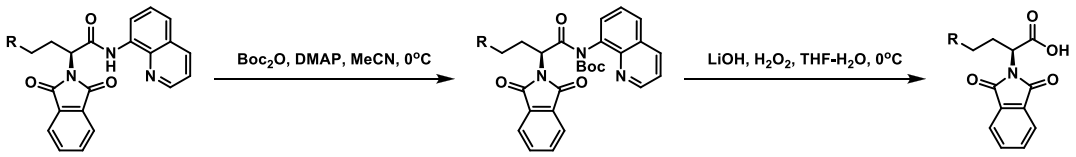
To a mixture of compound **11** (40 mg, 0.1 mmol, 1 equiv) and O-benzyl hydroxylamine hydrochloride (24 mg, 0.15mmol, 1.5 equiv) in ethanol (5 mL) were added one drop of concentrated sulfuric acid. The mixture was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ (10 mL) was added and the solvent was carefully evaporated *in vacuo*. The residue was extracted with CH_2Cl_2 (20 mL) three times and the combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under *vacuum*. The residue was purified on flash silica gel chromatography (hexane : ethyl acetate = 4 : 1), giving 45 mg product as colorless oil in 89% yield with E/Z > 20/1 determined by proton NMR. ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.74 – 8.69 (m, 1H), 8.67 (dd, J = 4.2, 1.5 Hz, 1H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.91 (dd, J = 5.4, 3.0 Hz, 2H), 7.76 (dd, J = 5.4, 3.1 Hz, 2H), 7.51 (d, J = 4.7 Hz, 2H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H), 7.34 – 7.23 (m, 5H), 5.22 (dd, J = 10.5, 5.0 Hz, 1H), 5.10 – 4.98 (m, 2H), 2.90 – 2.64 (m, 2H), 2.35 (t, J = 7.2 Hz, 2H), 1.90 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.13, 166.81, 156.05, 148.33, 138.50, 138.14, 136.33, 134.27, 133.95, 131.92, 128.31, 128.04, 127.88, 127.63, 127.33, 123.65, 121.96, 121.67, 116.79, 75.50, 54.60, 32.89, 25.07, 14.81; HRMS: calculated for $C_{30}H_{27}N_4O_4^+$ [M+H$^+$]: 507.2027; found: 507.2000.



Compound **27** (38 mg, 0.10mmol, 1 equiv) was dissolved in concentrated sulfuric acid (1 ml). The mixture was stirred at room temperature for 1 h, then carefully neutralized with saturated aqueous sodium bicarbonate. The residue was extracted with CH_2Cl_2 (20 mL) three times and the

combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent was evaporated *in vacuo*. The residue was purified on flash silica gel chromatography (dichloromethane : methanol = 10:1), giving 38 mg product as colorless oil in 95% yield. ^{1}H NMR (360 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.73 – 8.55 (m, 2H), 8.08 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.83 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.46 (d, *J* = 4.4 Hz, 2H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.01 (s, 1H), 5.91 (s, 1H), 5.18 (dd, *J* = 9.1, 6.3 Hz, 1H), 2.90 – 2.71 (m, 2H), 2.41 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.04, 168.17, 166.55, 148.46, 138.42, 136.28, 134.34, 133.79, 131.73, 127.83, 127.19, 123.66, 122.12, 121.71, 116.80, 54.53, 32.51, 24.78; HRMS: calculated for $C_{22}H_{19}N_4O_4^+$ [M+H$^+$]: 403.1401; found: 403.1394.

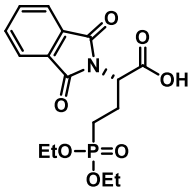
9. Removal of AQ auxiliary



General procedure:

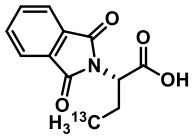
Step 1: To a solution of substrate (0.2 mmol, 1 equiv) in dry acetonitrile (5 mL) was added 4-(dimethylamino)pyridine (36 mg, 0.3 mmol, 1.5 equiv) and Boc anhydride (66 mg, 0.3 mmol, 1.5 equiv) at rt. The mixture was stirred at rt for 2 hours then concentrated under reduced pressure. Purification of the crude mixture by flash silica gel chromatography gave near quantitative Boc protected intermediate.

Step 2: A solution of Boc protected intermediate (1 equiv) in THF and water (3 mL : 1 mL) was cooled to 0 ^{o}C. 30% hydrogen peroxide (8.8 equiv) and lithium hydroxide monohydrate (1.1 equiv) were added and stirred at 0 ^{o}C for 2.5 hours. The reaction was quenched at 0 ^{o}C with 1.5 M aqueous sodium thiosulfate (1.2 mL); the mixture was concentrated under reduced pressure. The residue was washed with dichloromethane (10 mL) twice; the aqueous phase was then acidified to pH 2 with 10% aqueous hydrochloric acid and extracted with ethyl acetate (10 mL) twice. The organic extracts were dried with anhydrous sodium sulfate, concentrated under reduced pressure and purified on flash silica gel chromatography.



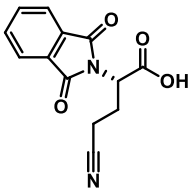
50

Flash silica gel chromatography (dichloromethane : methanol = 10:1) gave 22 mg of product as a colorless syrup in 47% yield over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (brs, 2H), 7.71 (brs, 2H), 4.82 (brs, 1H), 4.06 (brs, 4H), 2.56 (brs, 1H), 2.42 (brs, 1H), 1.82 (brs, 2H), 1.27 (brs, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.17, 167.67, 134.15, 131.87, 123.51, 62.34, 62.27, 23.64, 22.34, 16.37, 16.33; HRMS: calculated for $C_{16}H_{21}NO_7P^+$ [M+H$^+$]: 370.1050; found: 370.1044.



51

Flash silica gel chromatography (dichloromethane : methanol = 10:1) gave 36 mg of product as a colorless syrup in 76% yield over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (brs, 1H), 7.88 (dd, *J* = 5.2, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.2, 3.1 Hz, 2H), 4.91 – 4.74 (m, 1H), 2.38 – 2.19 (m, 2H), 1.11 (t, *J* = 7.4 Hz, 1.5H), 0.79 (t, *J* = 7.4 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.06, 167.71, 134.27, 131.67, 123.61, 53.45, 10.91, 9.64; HRMS: calculated for $C_{11}{}^{13}CH_{11}NNaO_4^+$ [M+Na$^+$]: 257.0614; found: 257.0627.

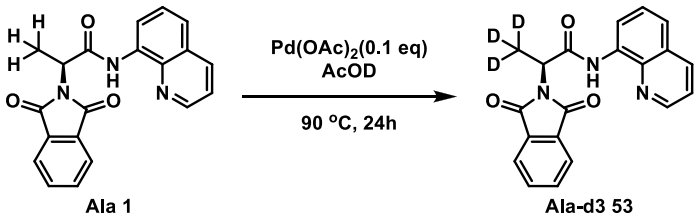


52

Flash silica gel chromatography (dichloromethane : methanol = 10:1) gave 40 mg of product as a colorless syrup in 60% yield over 2 steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (brs, 2H), 7.74 (brs, 2H), 4.87 (brs, 1H), 2.45 (brs, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 167.62, 134.63, 131.51, 123.89, 118.57, 50.96, 25.06, 14.75; HRMS: calculated for $C_{13}H_{10}N_2NaO_4^+$ [M+Na$^+$]: 281.0533; found: 281.0532.

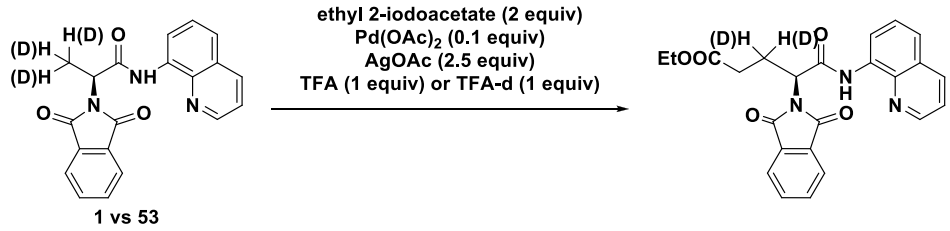
10. Kinetic isotope effect

10.1 Preparation of deuterated alanine 53



The solution of alanine substrate **1** (1.38 g, 4 mmol, 1 equiv) and $Pd(OAc)_2$ (90 mg, 0.4 mmol, 0.1 equiv) in deuterated acetic acid (40 mL) was heated at 90 ^oC for 24 hours. After completion the reaction was filtrated and concentrated. This procedure was repeated twice, and the product was purified on flash silica gel chromatography (ethyl acetate : dichloromethane = 1:99), giving 1.0 g of deuterated alanine substrate **53** in 72% yield. **^{1}H NMR** ($CDCl_3$, 360 MHz, ppm): δ 5.25 (s, 1H), 7.38-7.42 (m, 1H), 7.49-7.53 (m, 2H), 7.73-7.75 (m, 2H), 7.88-7.90 (m, 2H), 8.11-8.14 (d, *J* = 8.3Hz, 1H), 8.67-8.72 (m, 2H), 10.31 (s, 1H); **HRMS**: calculated for $C_{20}H_{13}D_3N_3O_3$ [M+H$^+$]: 349.1380; found: 349.1380.

10.2 KIE measurement

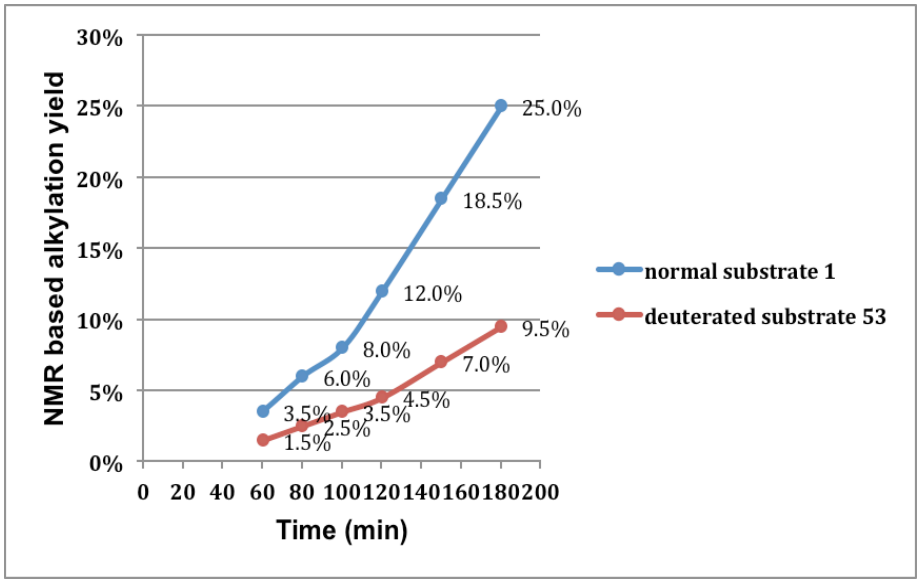


Normal substrate **1** (69 mg, 0.2 mmol, 1 equiv) or deuterated substrate **53** (70 mg, 0.2 mmol, 1 equiv), ethyl 2-iodoacetate (86 mg, 0.4 mmol, 2 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), silver acetate (84 mg, 0.5 mmol, 2.5 equiv), trifluoroacetic acid (15 μL, 0.2 mmol, 1 equiv) or TFA-*d*$_1$ (15 μL, 0.2 mmol, 1 equiv, for the deuterated substrate **53**) were suspended in dioxane (4 mL). The resulting reaction mixtures were stirred **vigorously** at room temperature. At the time point of 60, 80, 100, 120, 150 and 180 minutes, 300 μL of the reaction mixture was taken out from the reaction vials and re-suspended into ethyl acetate (3 mL) and quench by saturated aqueous sodium bicarbonate (3 mL). The organic layer was separated and concentrated

under reduced pressure. The resulting residue was dissolved in $CDCl_3$ (600 μL) for ^{1}H-NMR analysis. Average data of three runs were used. $k_{H/D}$ (~2.5) was estimated based on the ratio of alkylation yield. Alkylation yields were determined as follows:

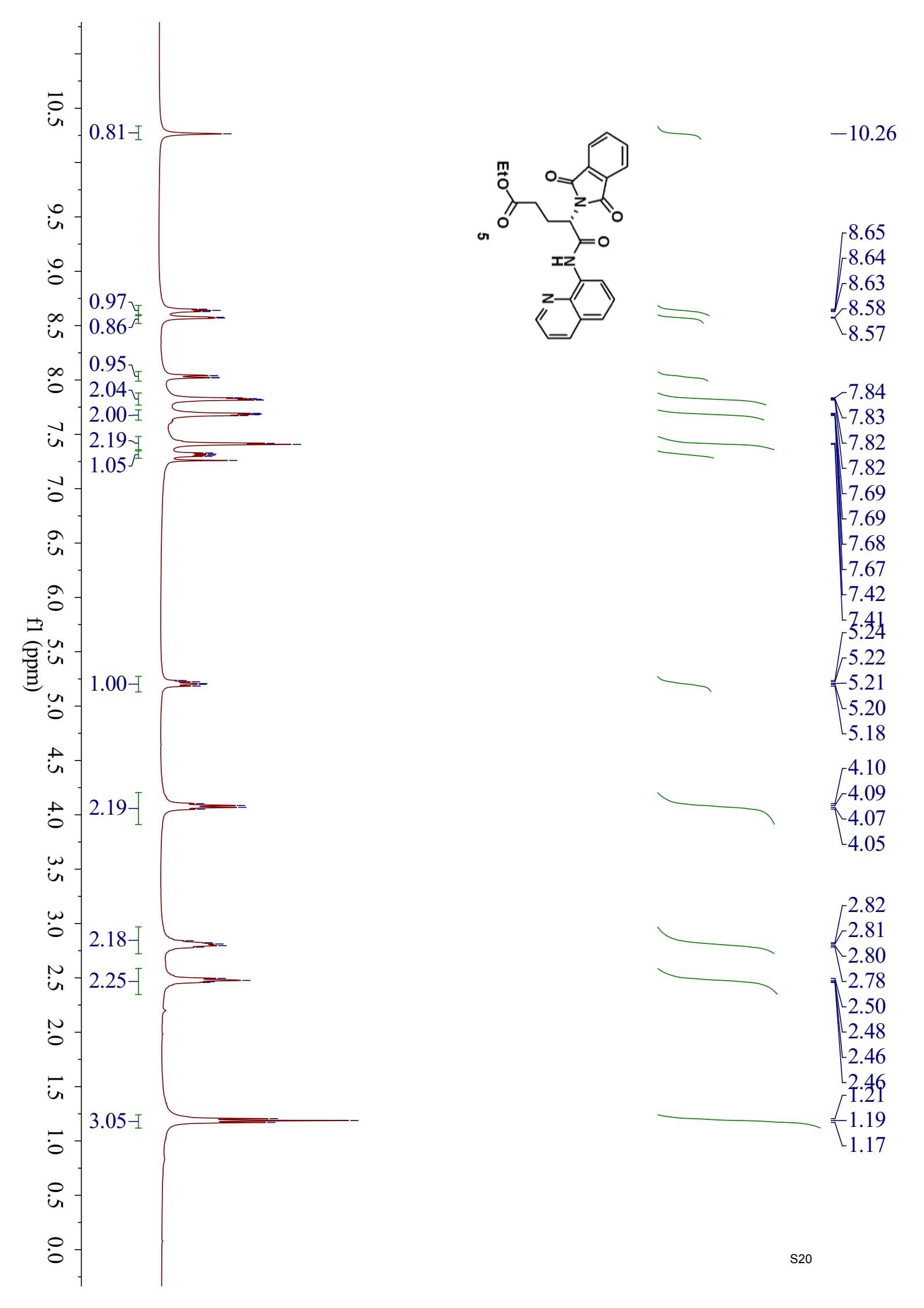
1) In the ^{1}H-NMR spectrum, the integration of the doublet around δ 8.15-8.17 was set as 1.0

2) Yield = (integration of multiplet around δ 2.51 ppm) × 50%



11. References

[1] R. Prebil, S. Stavber, *Tetrahedron Letters.* **2014**, *55*, 5643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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
0.81
0.97
0.86
0.95
2.04
2.00
2.19
1.05
1.00
2.19
2.18
2.25
3.05
EtO
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O
N
O
O
O
N
H
N
5
10.26
8.65
8.64
8.63
8.58
8.57
7.84
7.83
7.82
7.82
7.69
7.69
7.68
7.67
7.42
7.41
5.24
5.22
5.21
5.20
5.18
4.10
4.09
4.07
4.05
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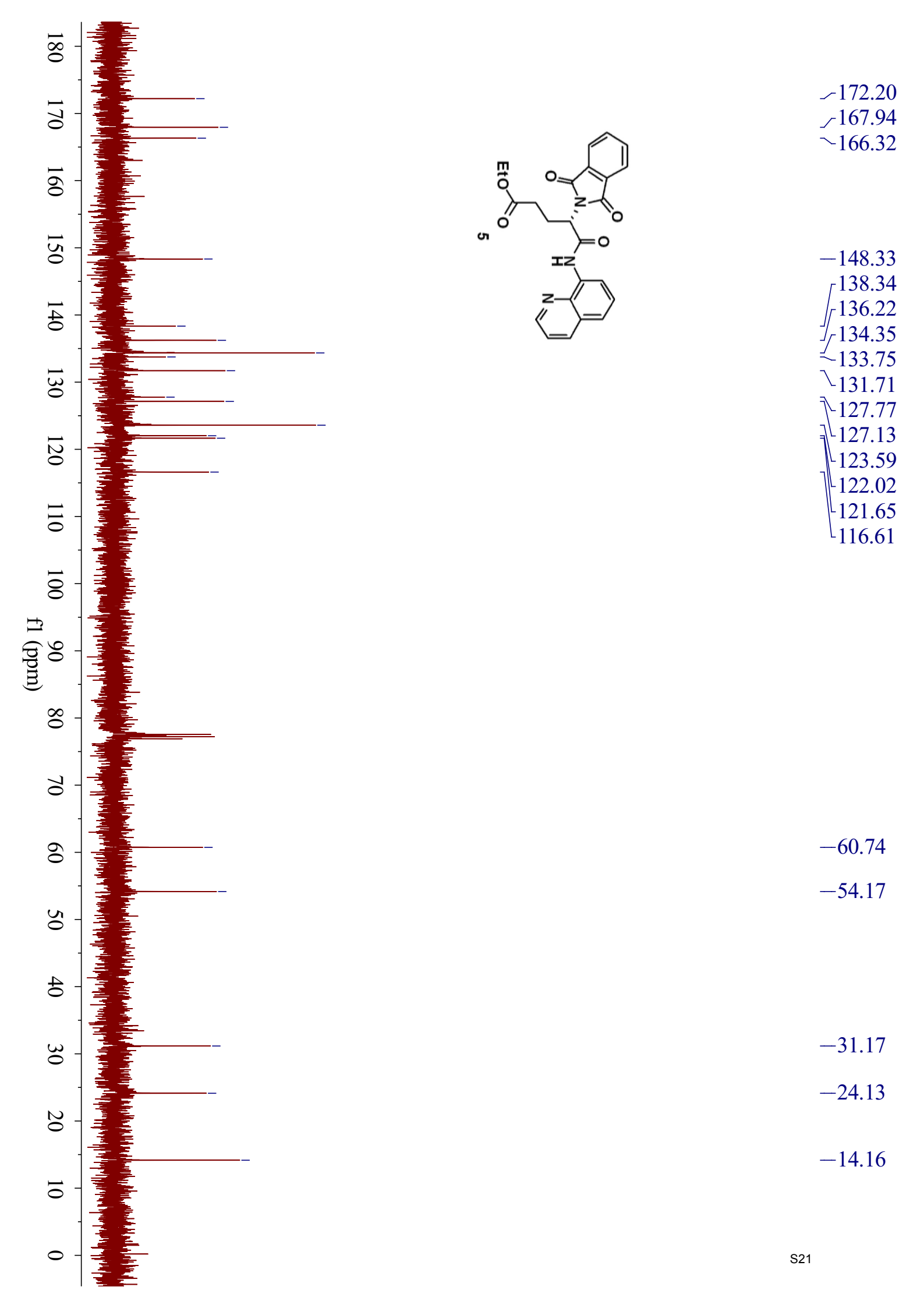
2.48
2.46
2.46
1.21
1.19
1.17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60
50
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167.94
166.32
148.33
138.34
136.22
134.35
133.75
131.71
127.77
127.13
123.59
122.02
121.65
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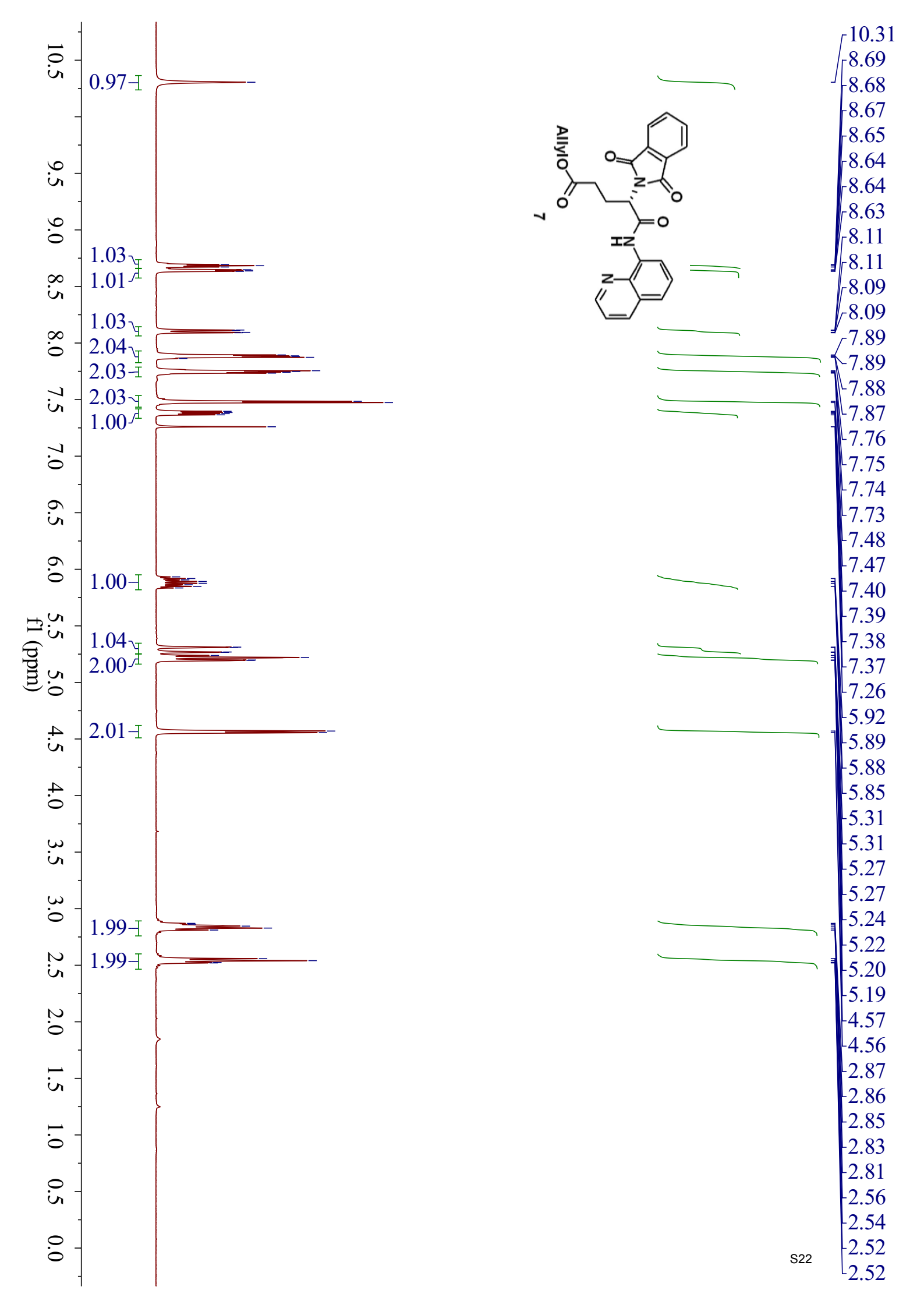
O
H
N
N
5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6.0
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4.0
3.5
3.0
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2.0
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1.0
0.5
0.0
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1.03
2.04
2.03
2.03
1.00
1.00
1.04
2.00
2.01
1.99
1.99
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O
N
O
O
N
H
N
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8.64
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8.63
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8.11
8.09
8.09
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7.76
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7.74
7.73
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7.37
7.26
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5.89
5.88
5.85
5.31
5.31
5.27
5.27
5.24
5.22
5.20
5.19
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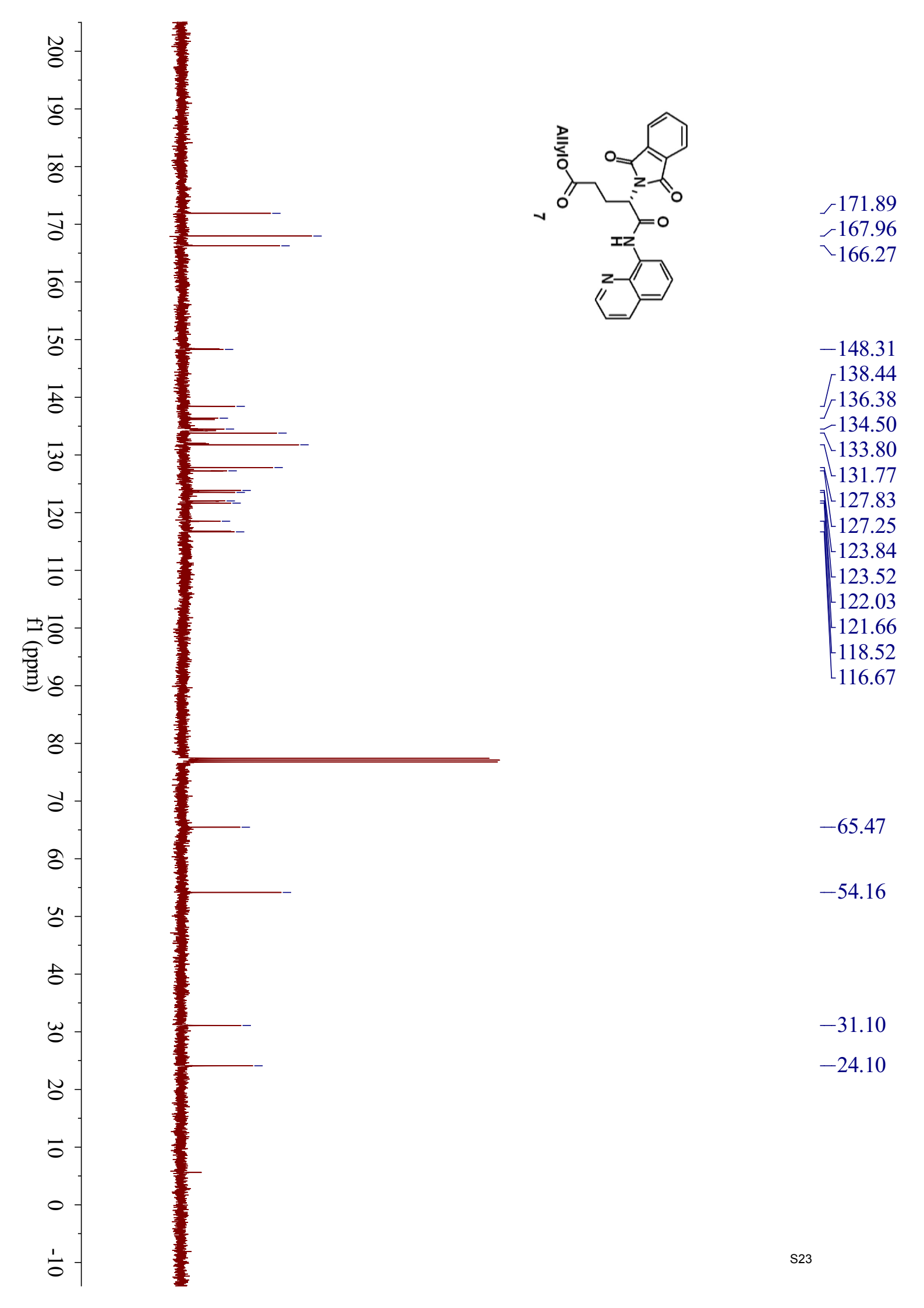
2.54
2.52
2.52
2.52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120
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80
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50
40
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10
0
-10
f1 (ppm)
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O
O
N
O
O
H
N
N
7
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167.96
166.27
148.31
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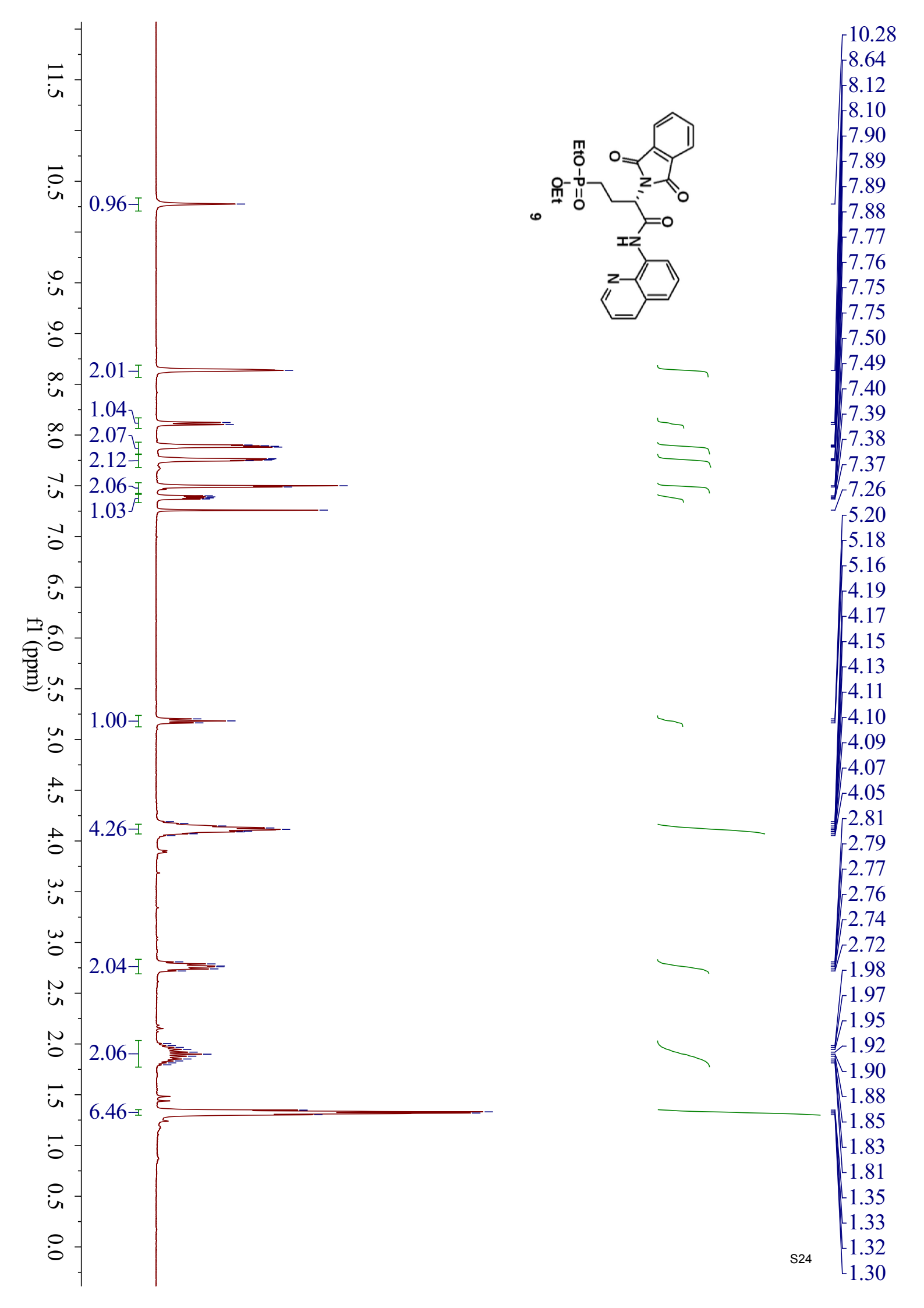
24.10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4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.96
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1.04
2.07
2.12
2.06
1.03
1.00
4.26
2.04
2.06
6.46
EtO–P=O
OEt
9
10.28
8.64
8.12
8.10
7.90
7.89
7.89
7.88
7.77
7.76
7.75
7.75
7.50
7.49
7.40
7.39
7.38
7.37
7.26
5.20
5.18
5.16
4.19
4.17
4.15
4.13
4.11
4.10
4.09
4.07
4.05
2.81
2.79
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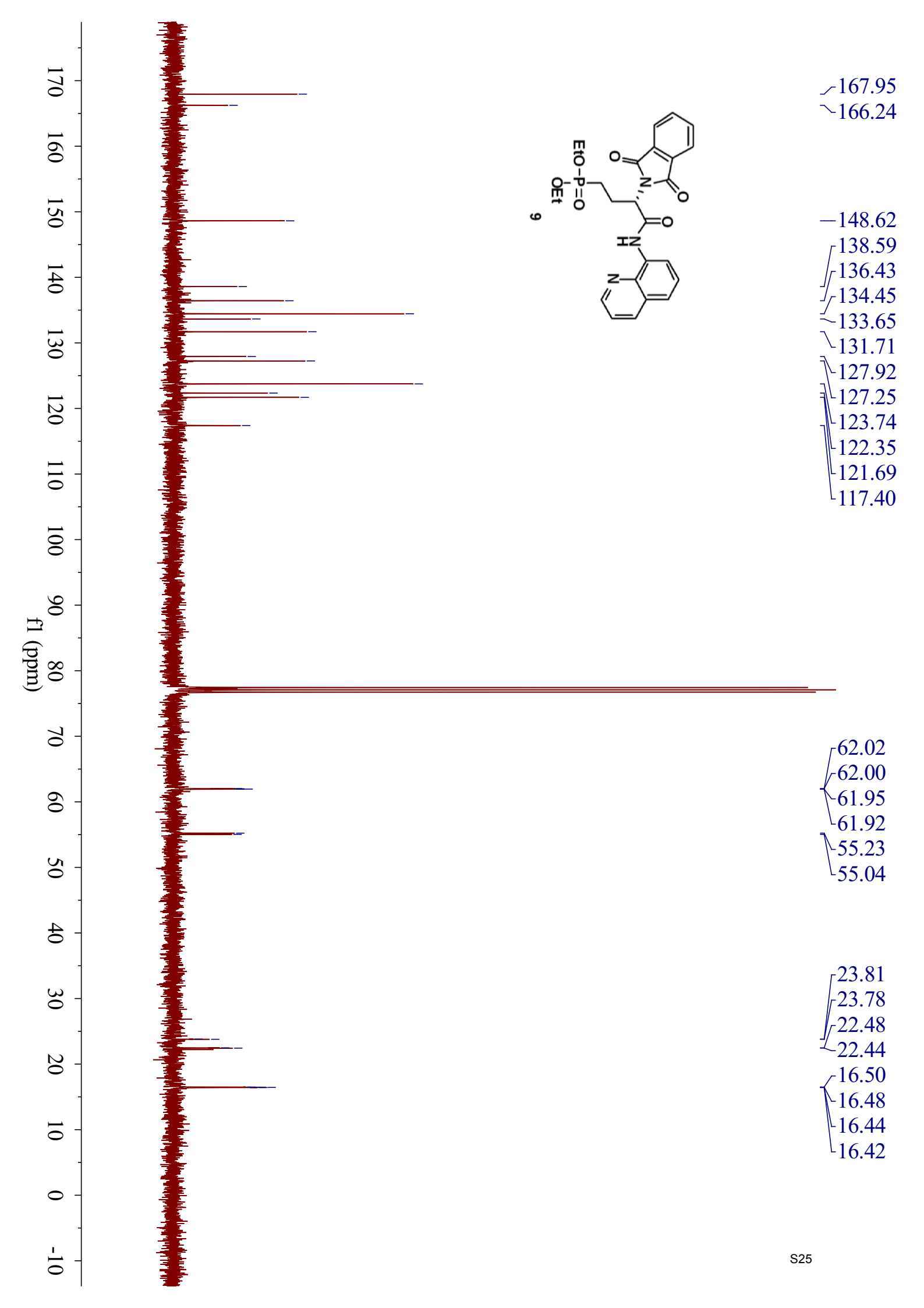
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121.69
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62.00
61.95
61.92
55.23
55.04
23.81
23.78
22.48
22.44
16.50
16.48
16.44
16.42
EtO-P=O
OEt
O
N
O
O
N
H
N
9
f1 (ppm)
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140
130
120
110
100
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50
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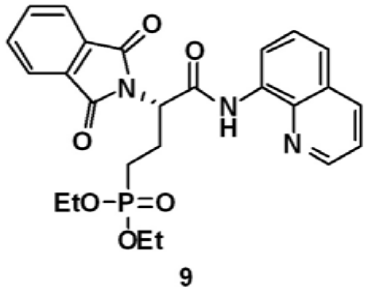
0
-10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N
O
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H
N
EtO–P=O
OEt

9

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110
100
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30
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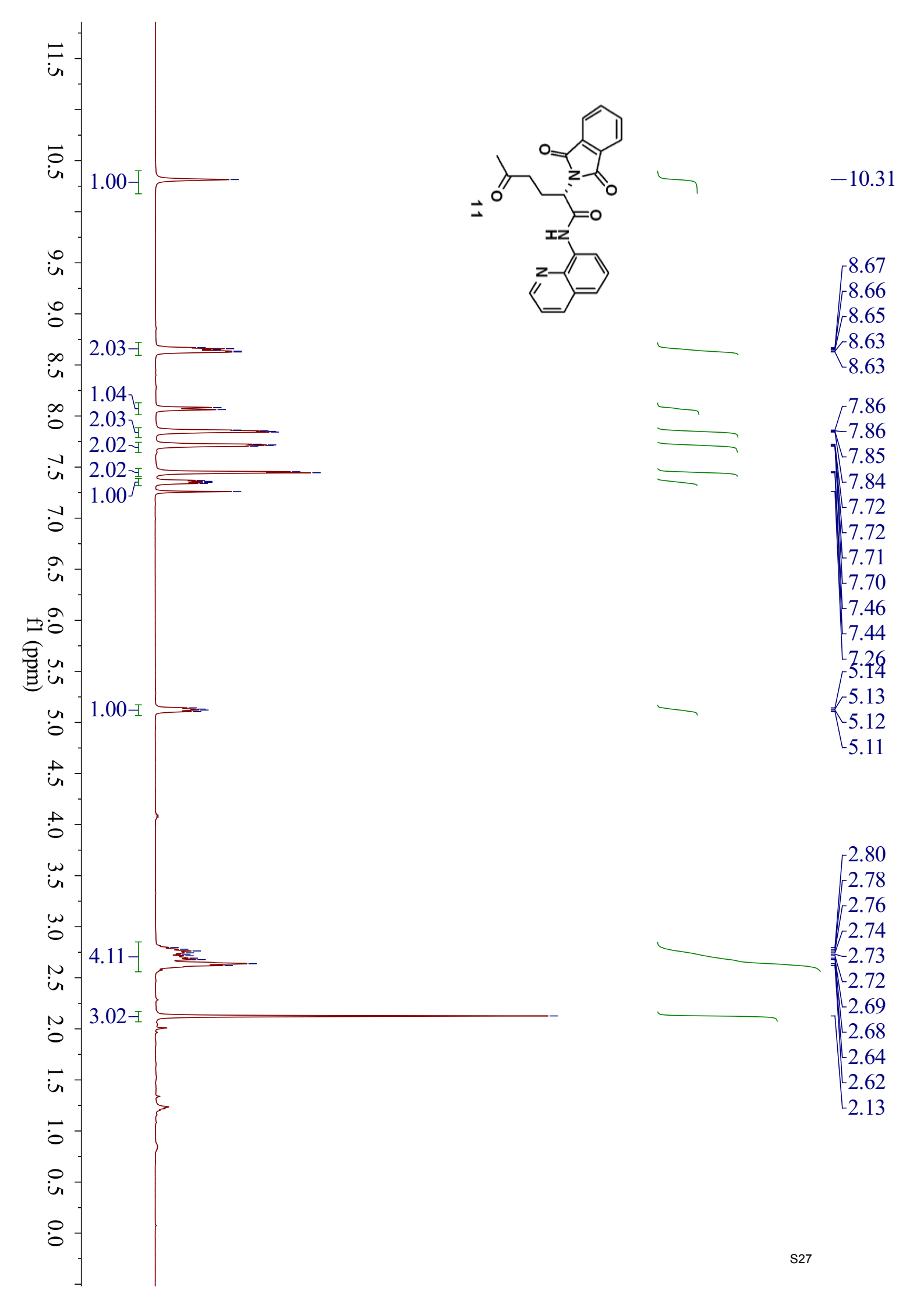
-50
-60
f1 (ppm)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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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2.03
2.02
2.02
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1.00
4.11
3.02
11
10.31
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7.86
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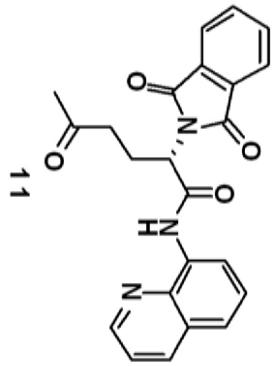

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121.67
116.66

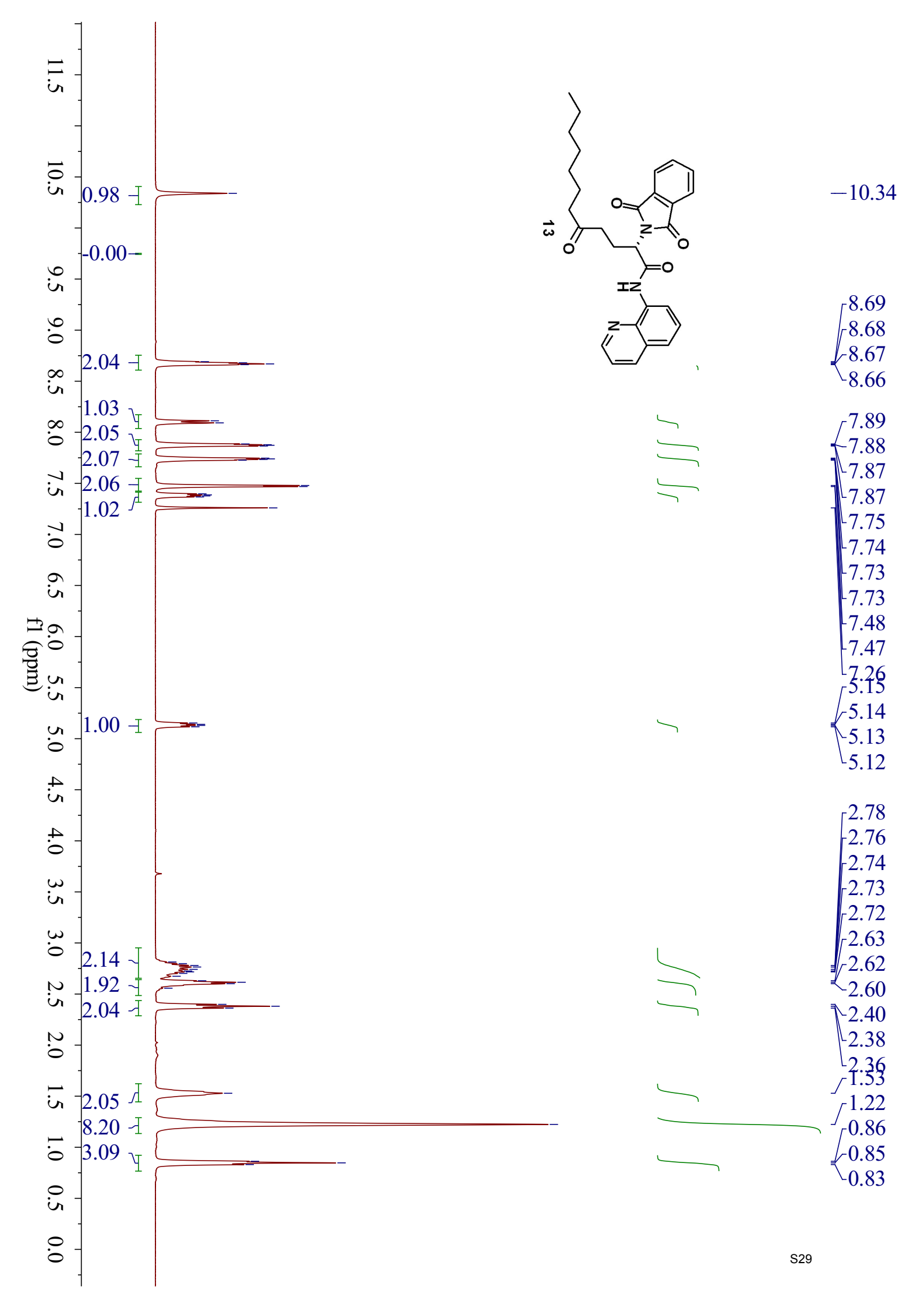
54.30

40.15

29.96

23.02

f1 (ppm)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3.5
3.0
2.5
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0.0
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2.05
2.07
2.06
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2.14
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2.05
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7.26
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5.14
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5.12
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2.73
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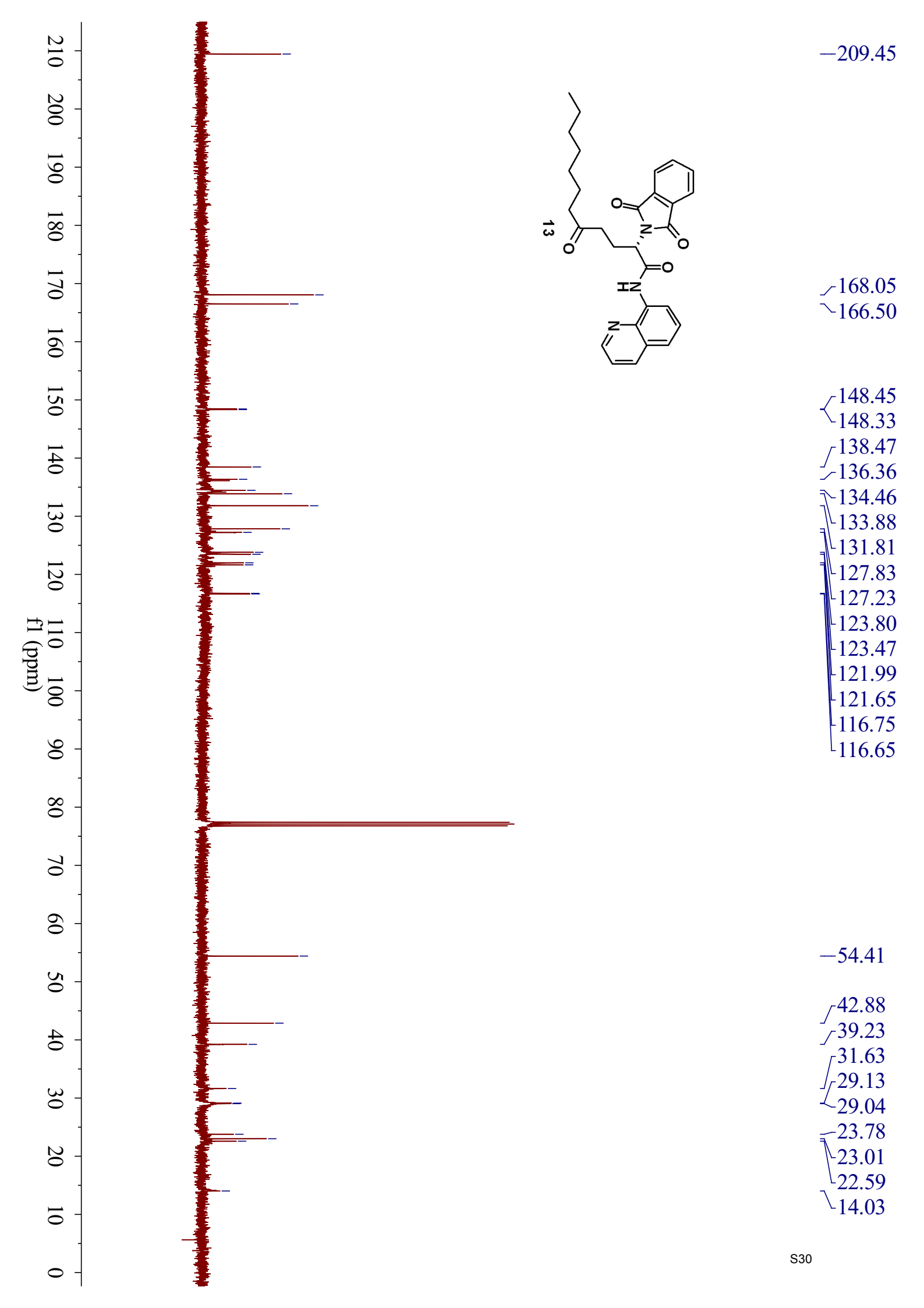
0.83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23.01
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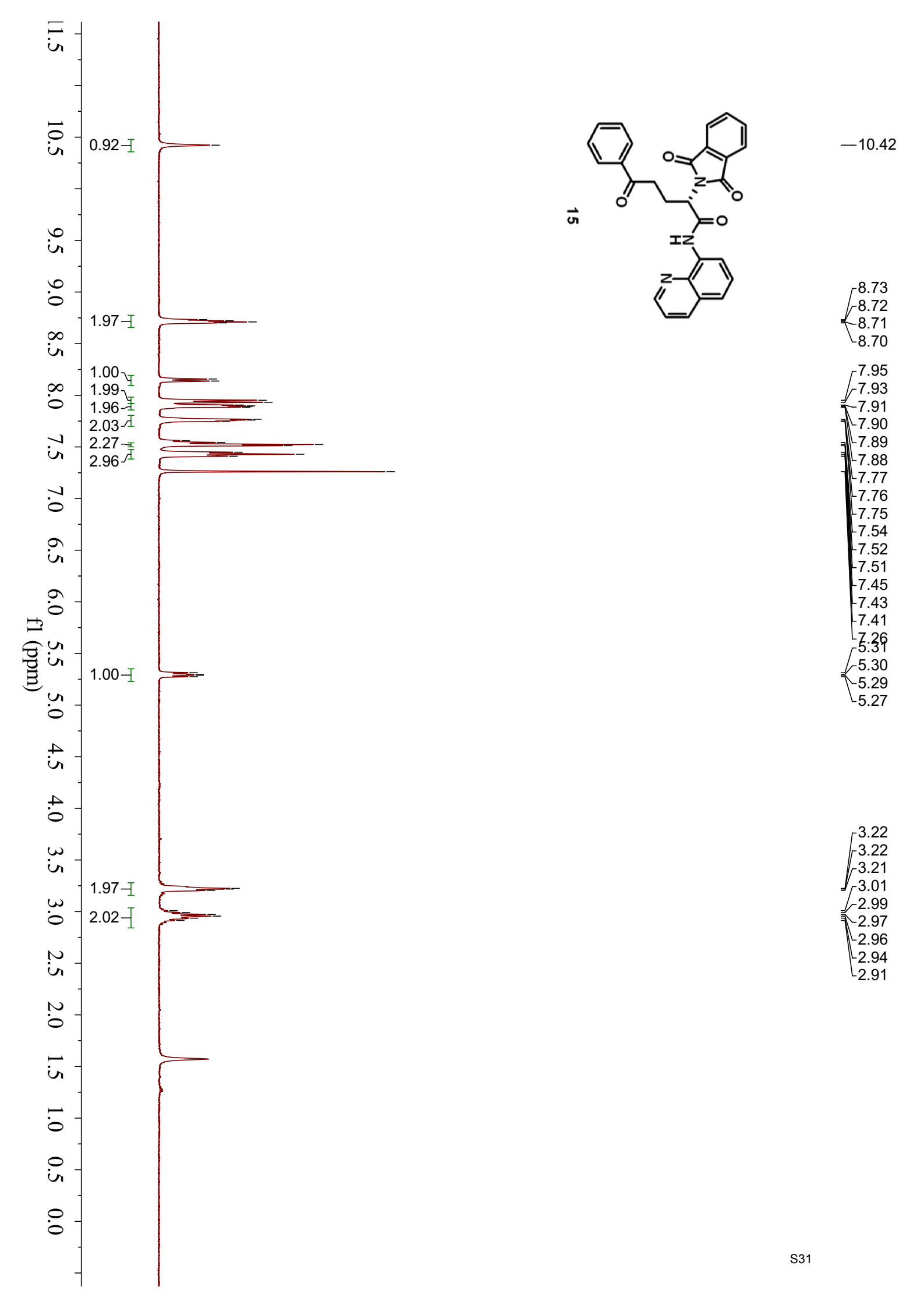
14.03
13
f1 (ppm)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4.0
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2.0
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0.0
f1 (ppm)
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1.97
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1.99
1.96
2.03
2.27
2.96
1.00
1.97
2.02
15
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7.76
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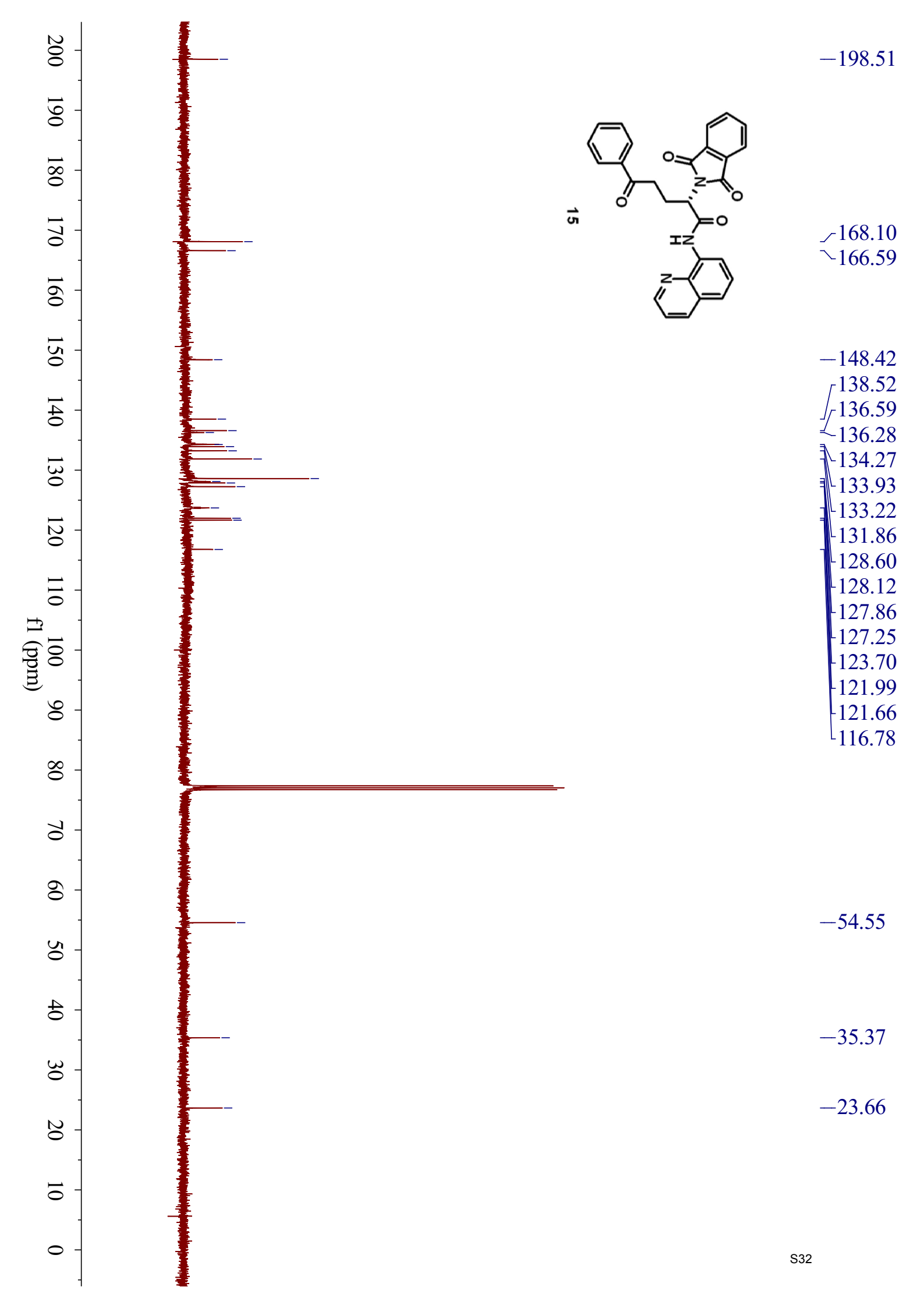
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54.55
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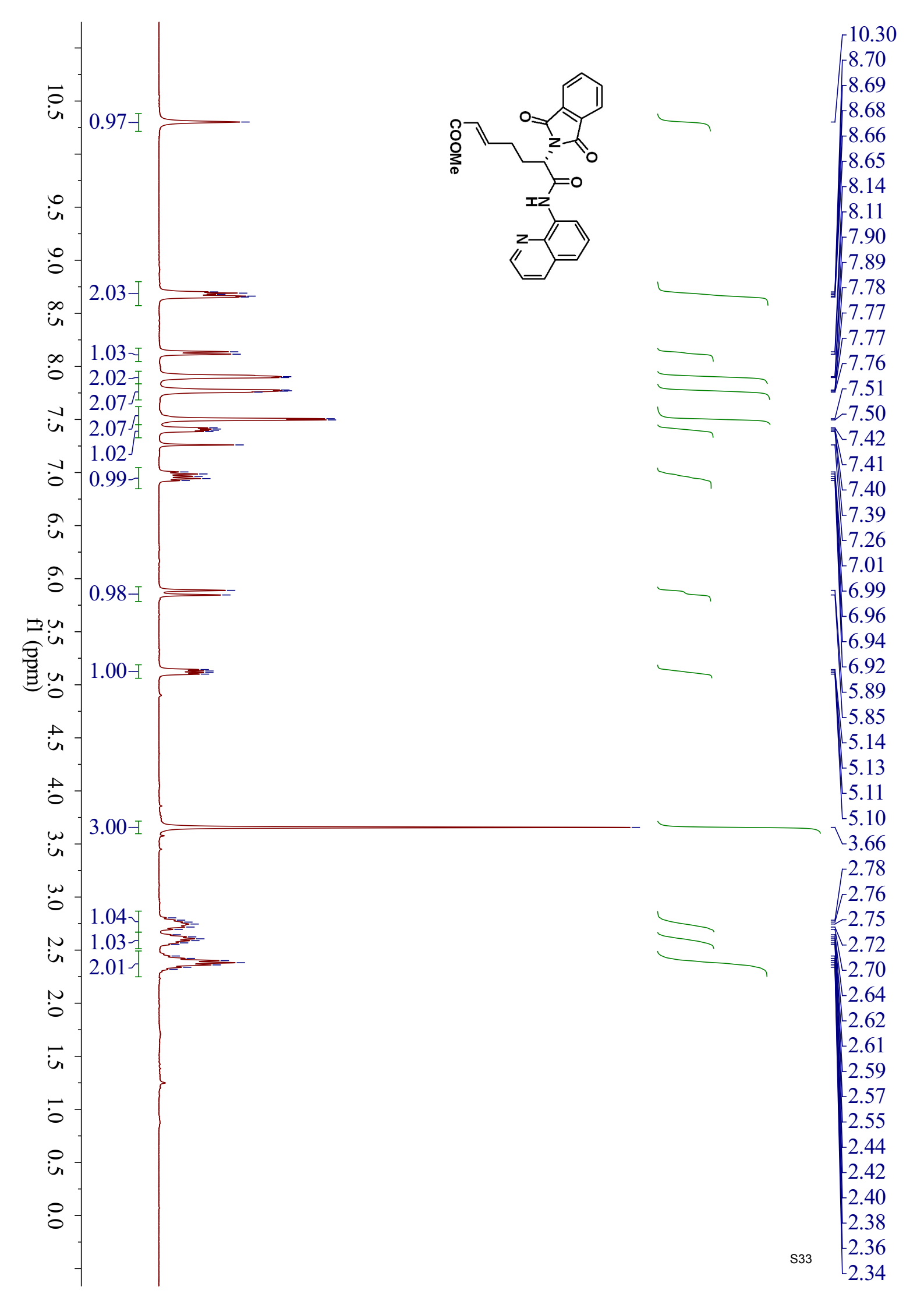
23.66
15
f1 (ppm)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2.55
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2.38
2.36
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2.03
1.03
2.02
2.07
2.07
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0.99
0.98
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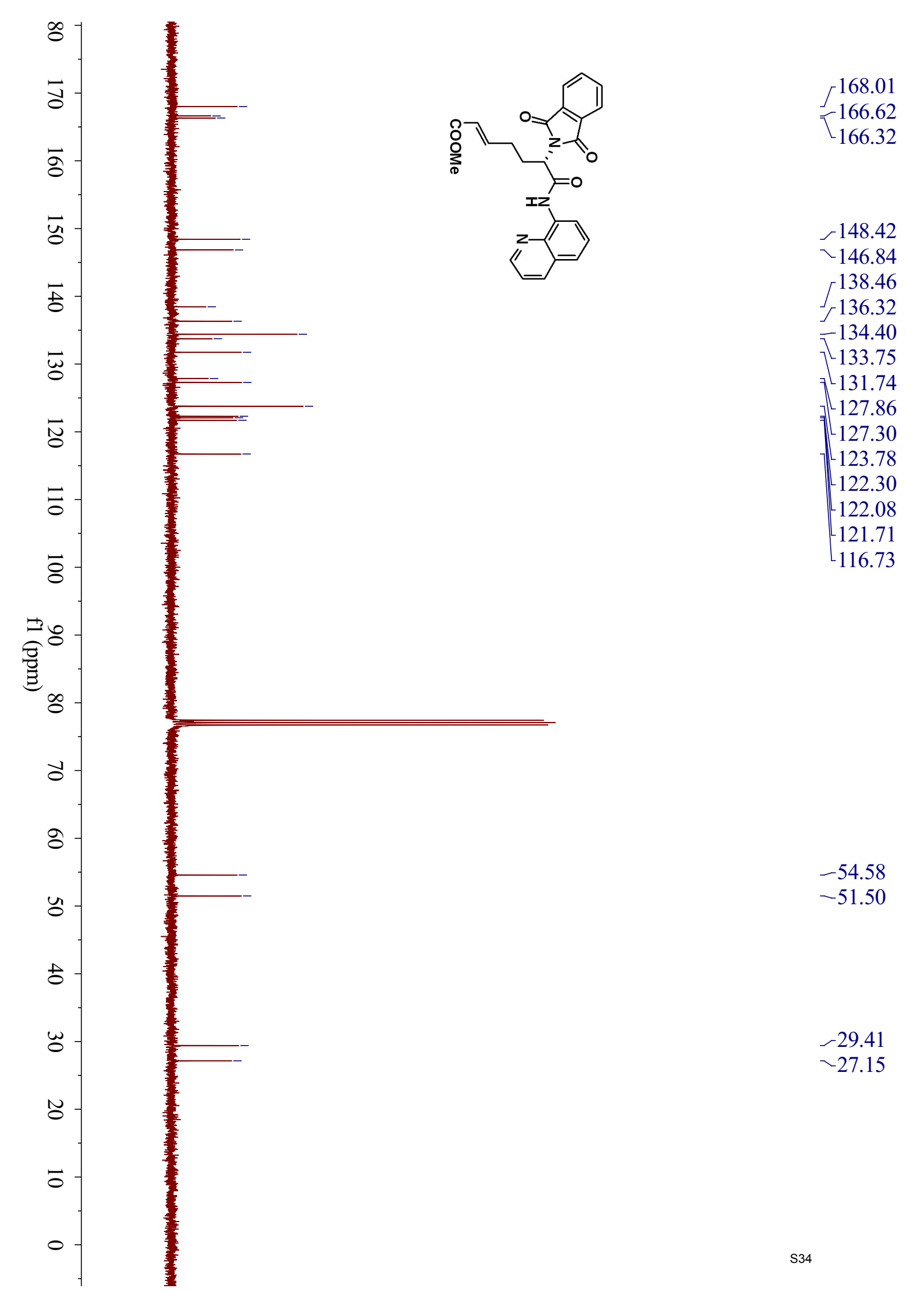
1.04
1.03
2.01
COOMe
f1 (ppm)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10
0
COOMe
O
N
O
O
N
H
N
168.01
166.62
166.32
148.42
146.84
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134.40
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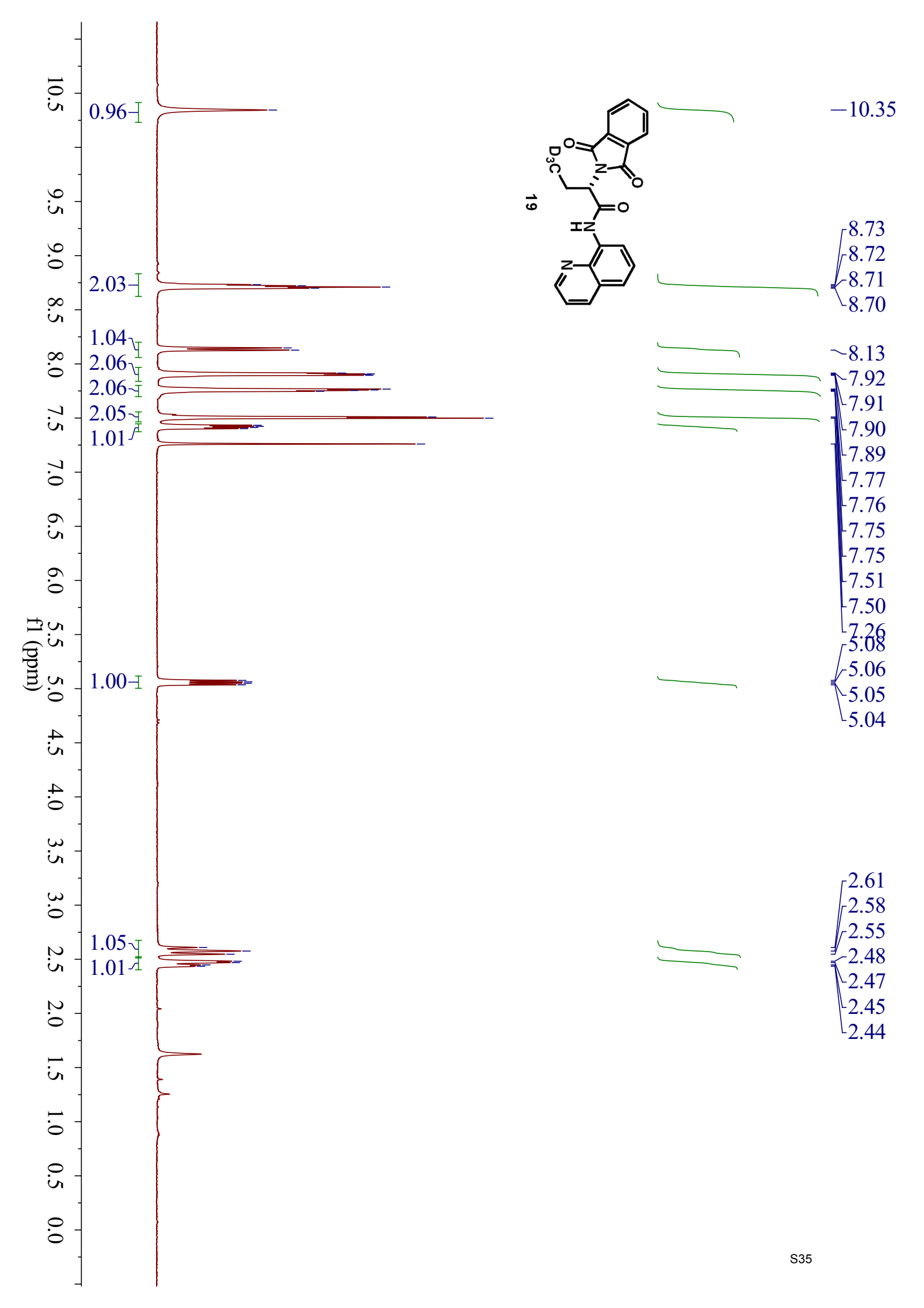
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7.26
5.08
5.06
5.05
5.04
2.61
2.58
2.55
2.48
2.47
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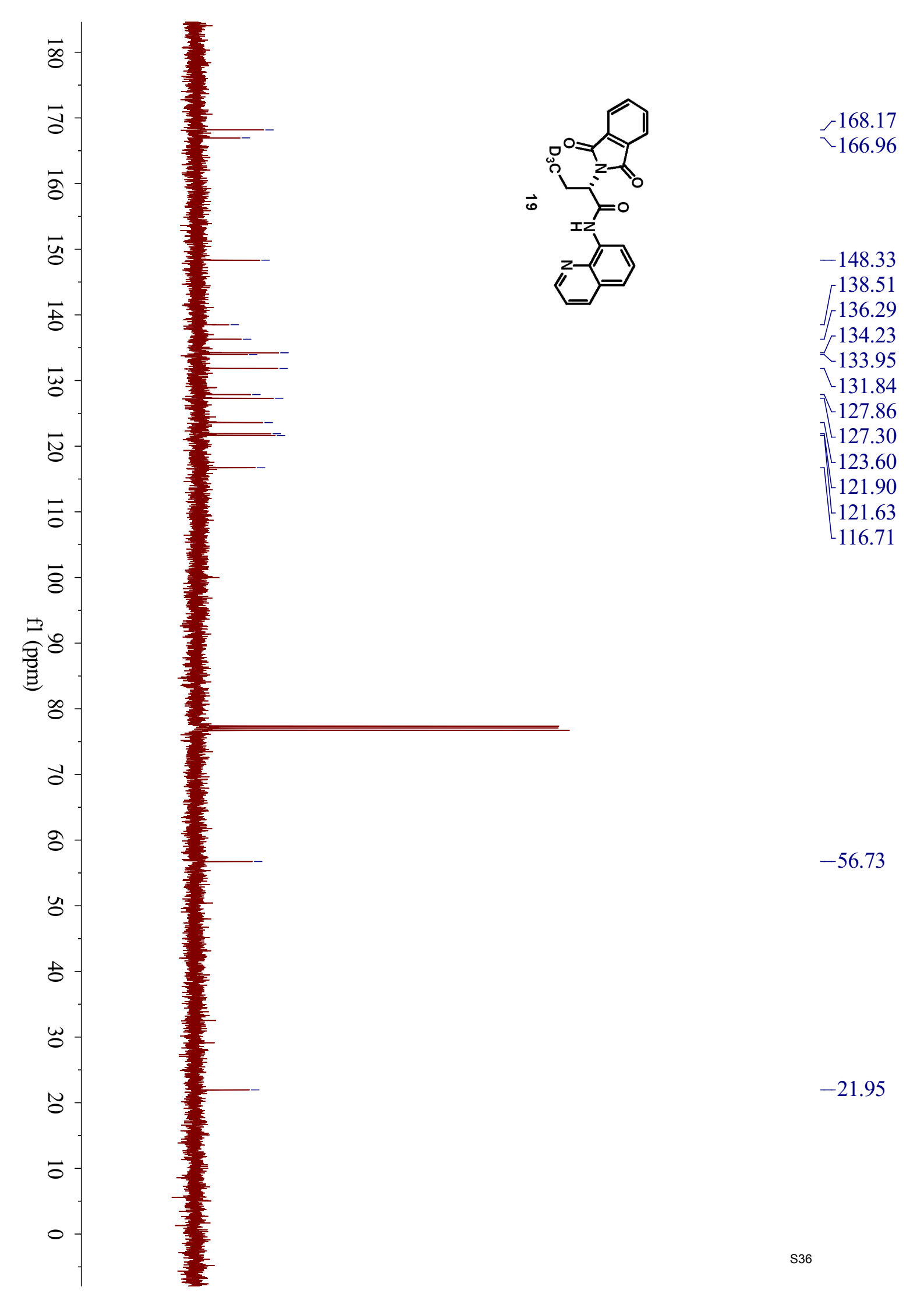
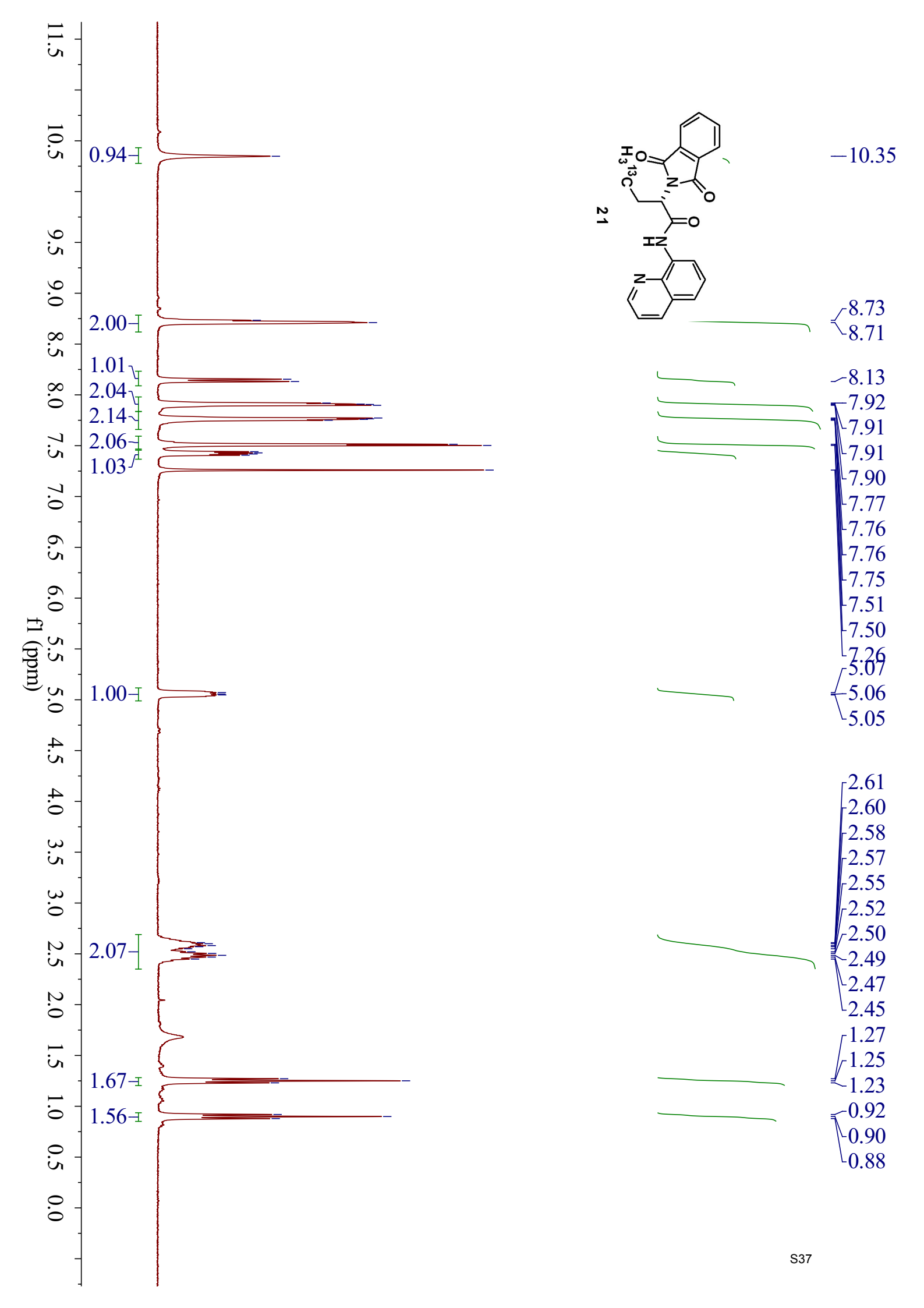
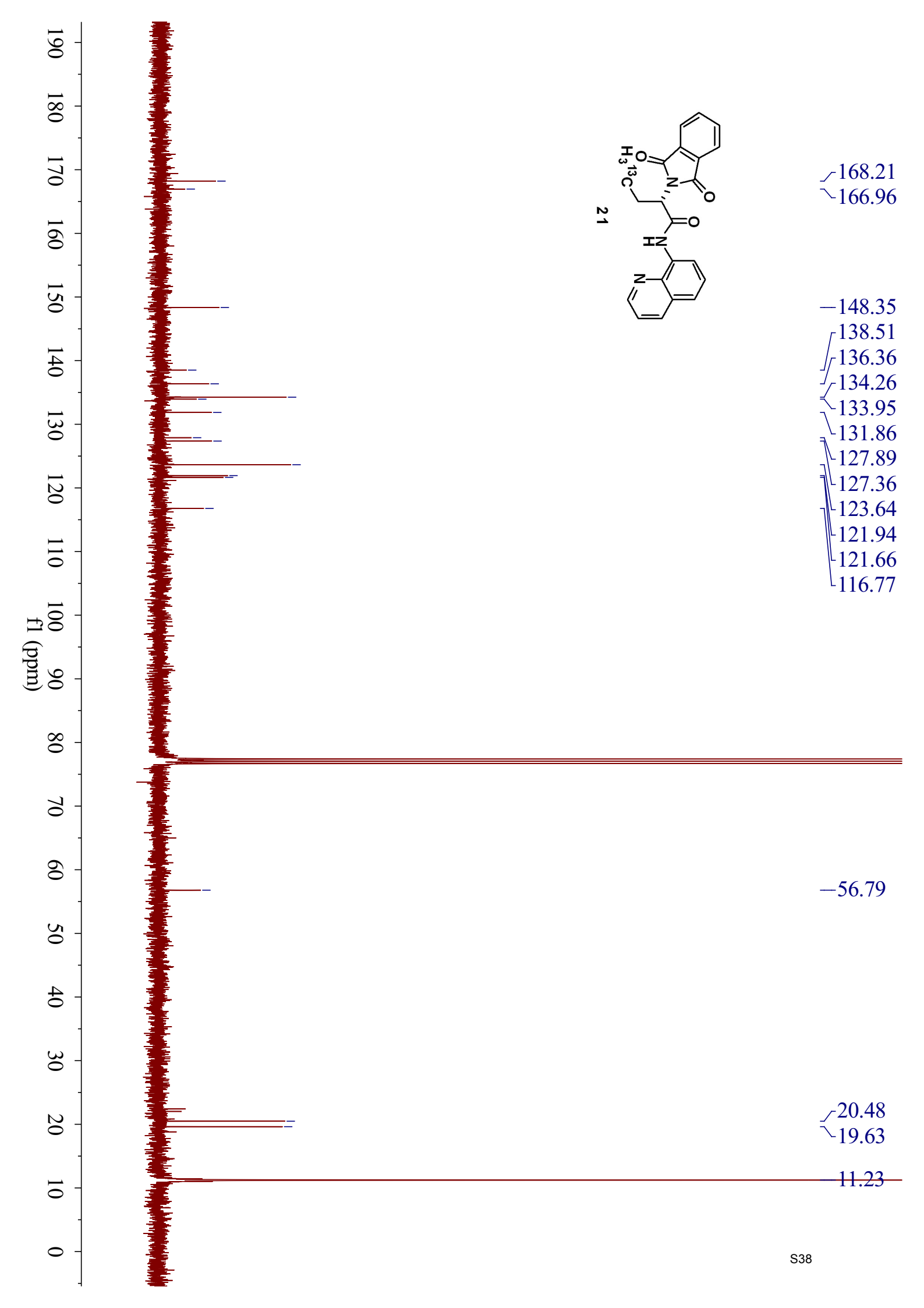
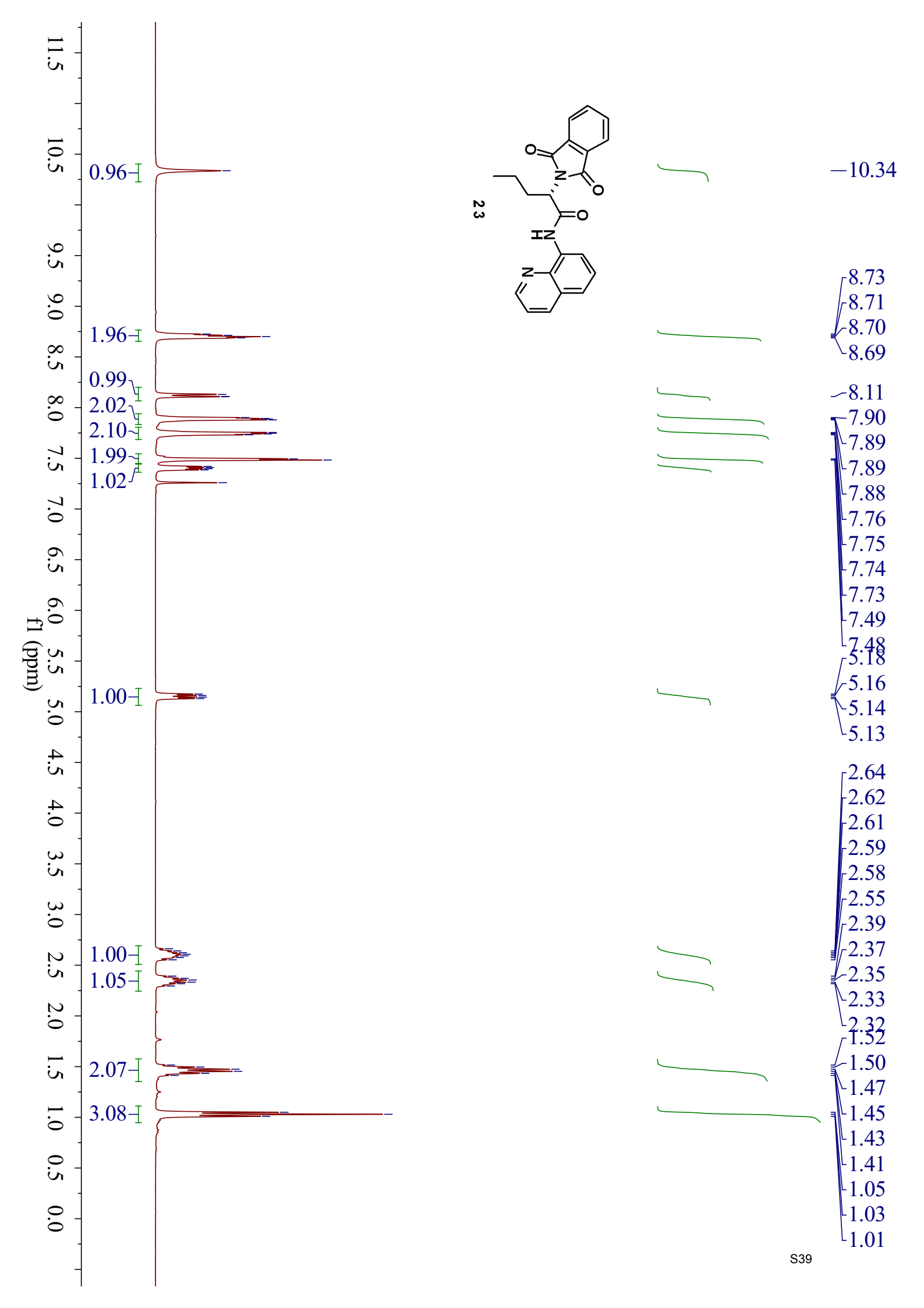
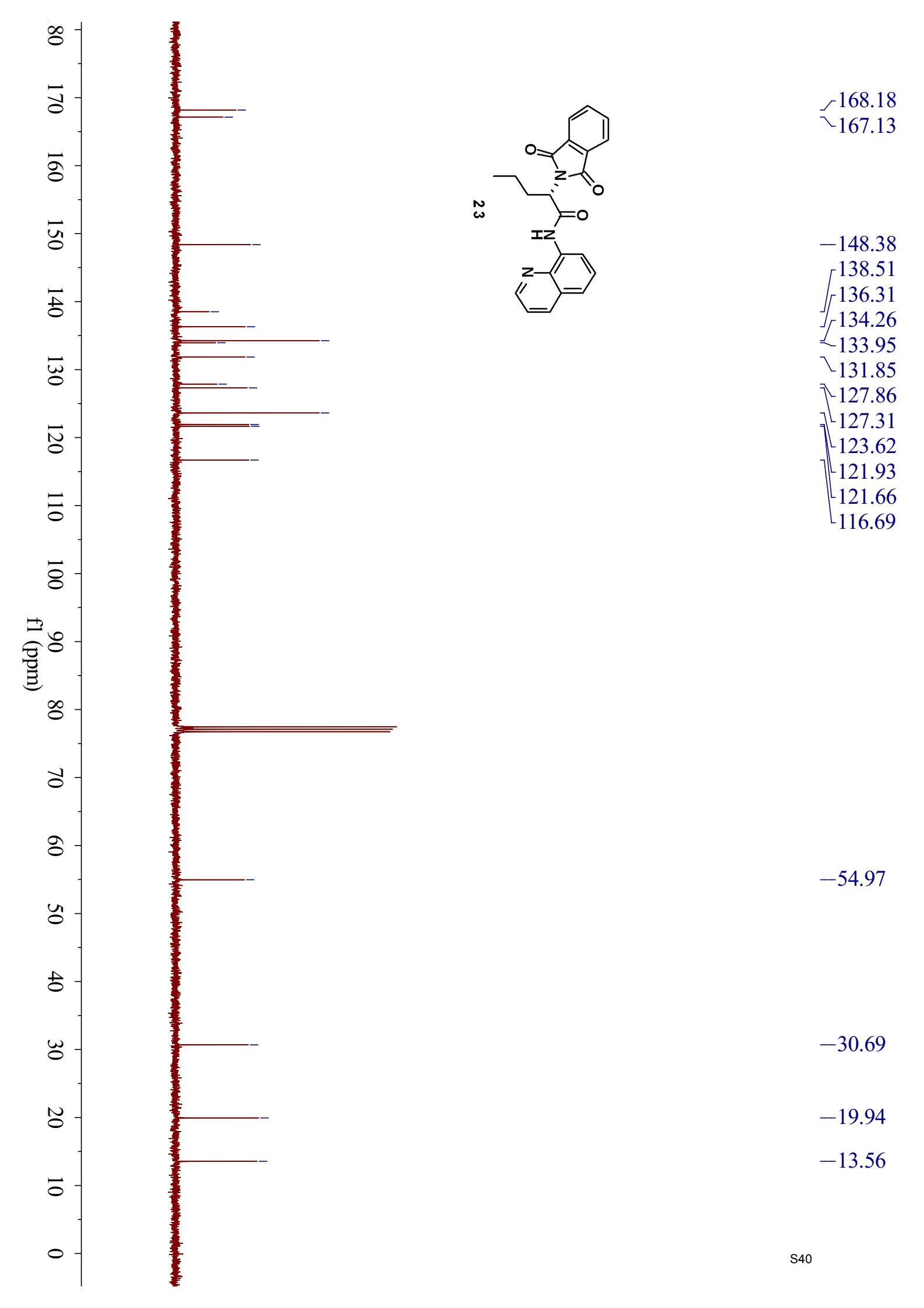
2.44
0.96
2.03
1.04
2.06
2.06
2.05
1.01
1.00
1.05
1.01
19
f1 (ppm)

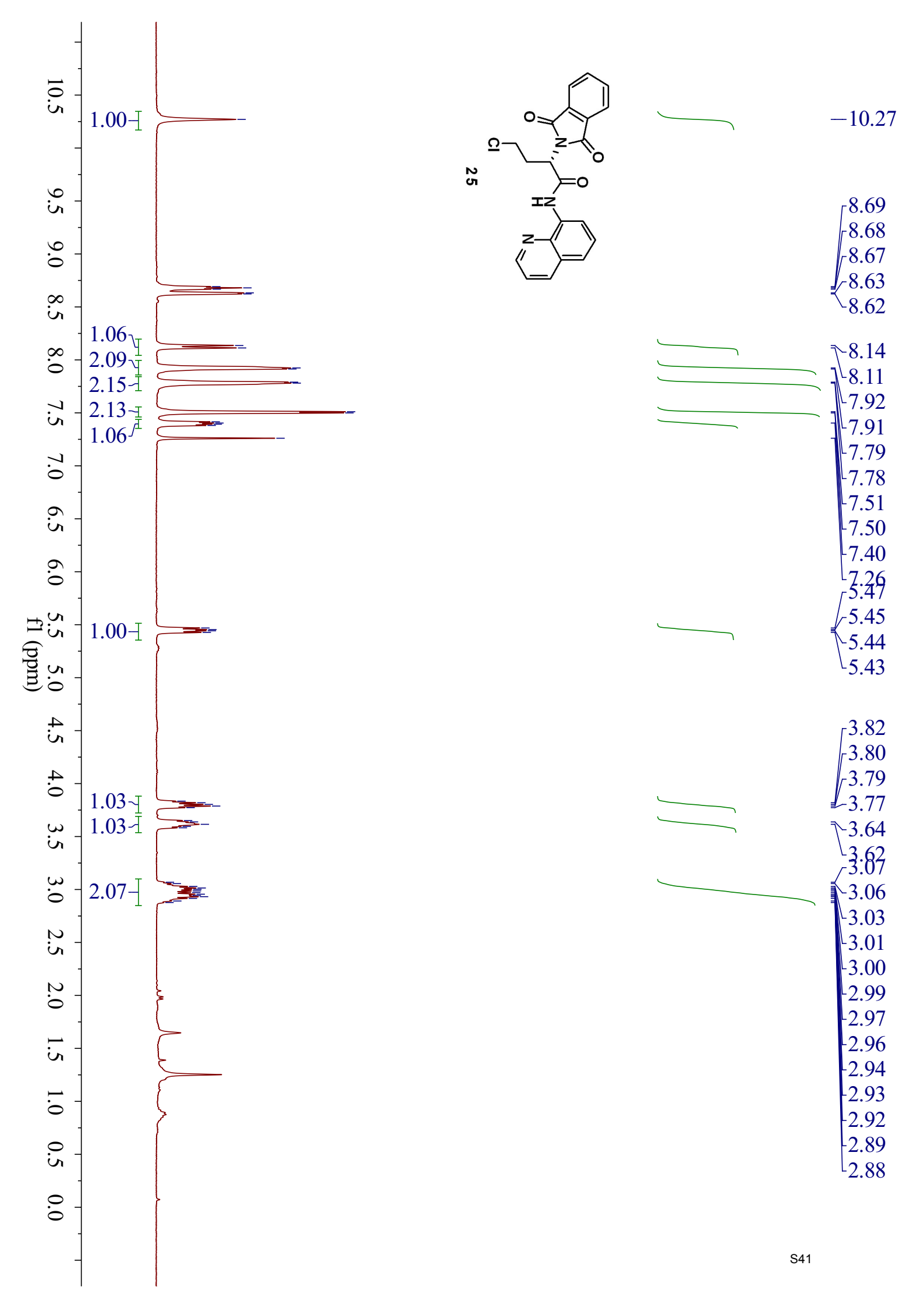

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
168.17
166.96
148.33
138.51
136.29
134.23
133.95
131.84
127.86
127.30
123.60
121.90
121.63
116.71
56.73
21.95
19

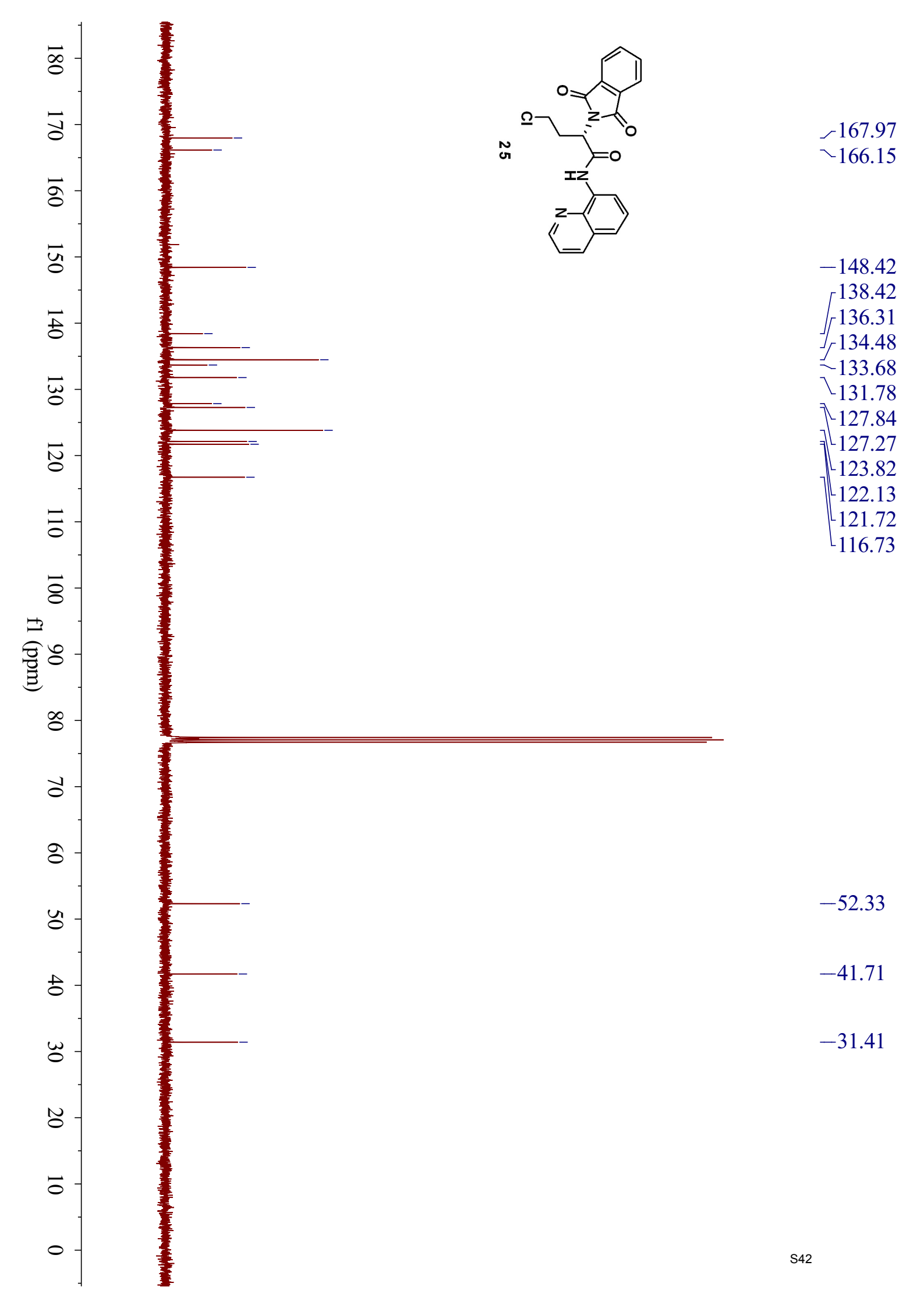

f1 (ppm)
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.94
2.00
1.01
2.04
2.14
2.06
1.03
1.00
2.07
1.67
1.56
21
10.35
8.73
8.71
8.13
7.92
7.91
7.91
7.90
7.77
7.76
7.76
7.75
7.51
7.50
7.26
5.07
5.06
5.05
2.61
2.60
2.58
2.57
2.55
2.52
2.50
2.49
2.47
2.45
1.27
1.25
1.23
0.92
0.90
0.88

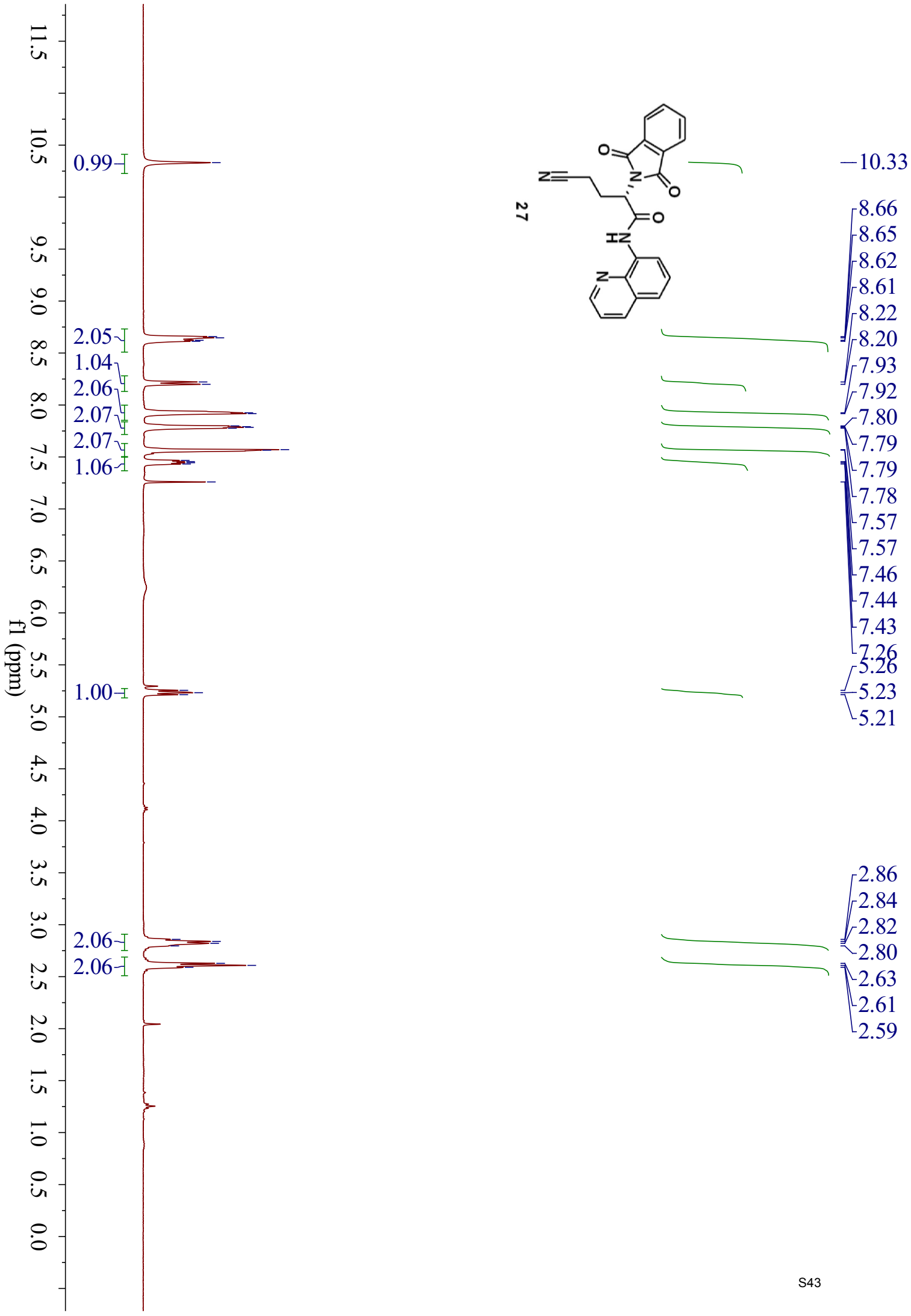

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
168.21
166.96
148.35
138.51
136.36
134.26
133.95
131.86
127.89
127.36
123.64
121.94
121.66
116.77
56.79
20.48
19.63
11.23
21

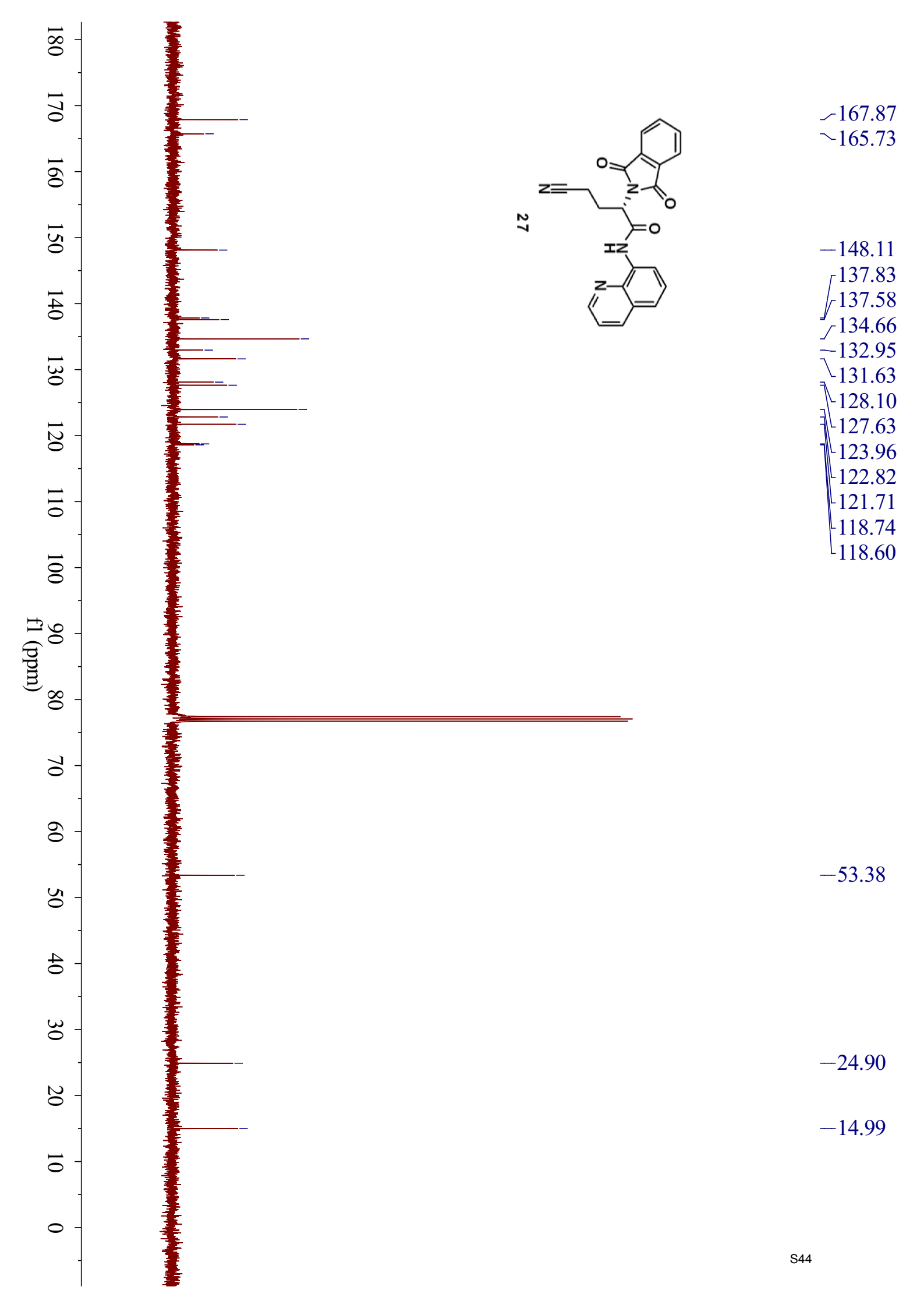

23
f1 (ppm)
0.96
1.96
0.99
2.02
2.10
1.99
1.02
1.00
1.00
1.05
2.07
3.08
10.34
8.73
8.71
8.70
8.69
8.11
7.90
7.89
7.89
7.88
7.76
7.75
7.74
7.73
7.49
7.48
5.18
5.16
5.14
5.13
2.64
2.62
2.61
2.59
2.58
2.55
2.39
2.37
2.35
2.33
2.32
1.52
1.50
1.47
1.45
1.43
1.41
1.05
1.03
1.01

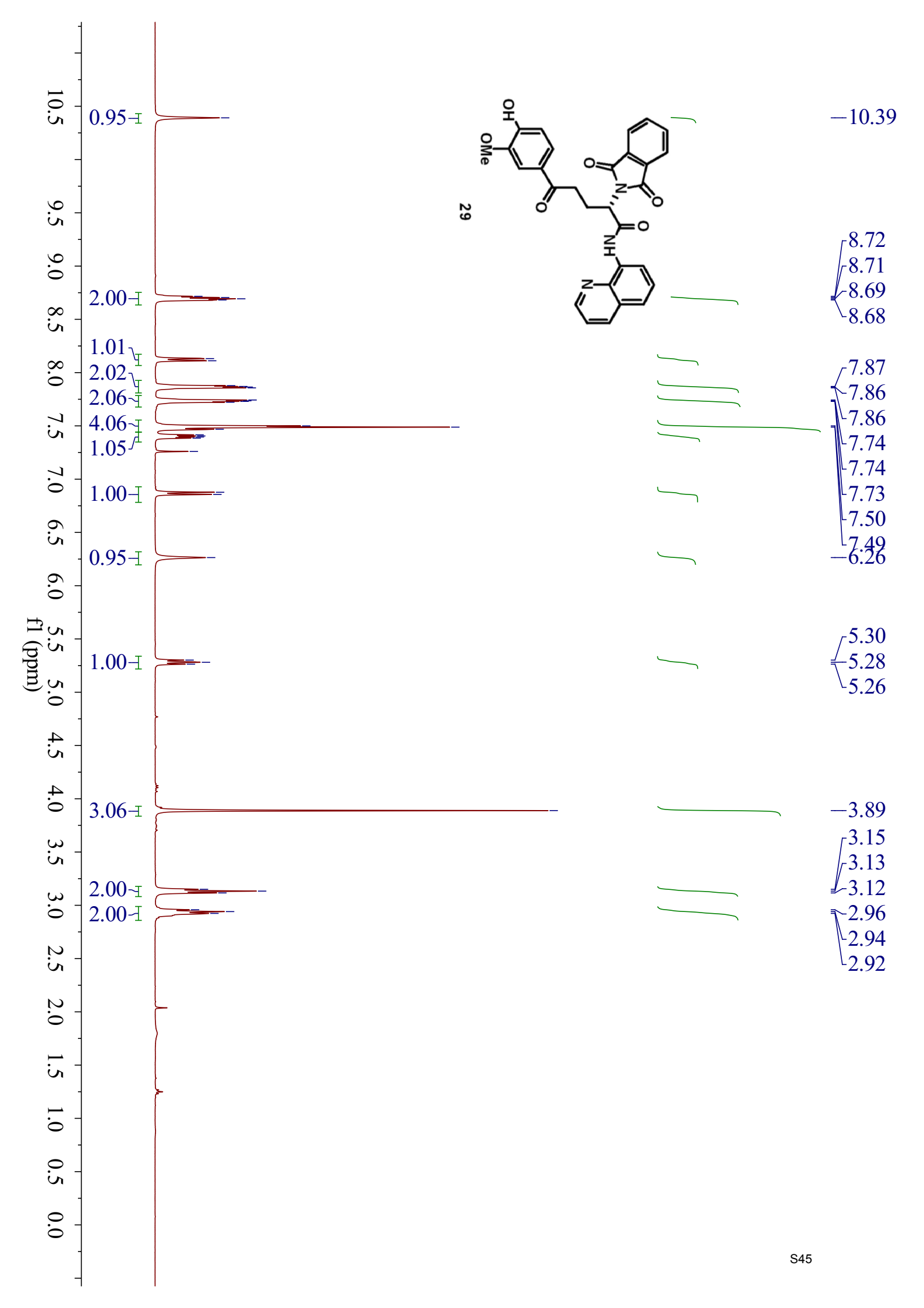

168.18
167.13
148.38
138.51
136.31
134.26
133.95
131.85
127.86
127.31
123.62
121.93
121.66
116.69
54.97
30.69
19.94
13.56
f1 (ppm)
23

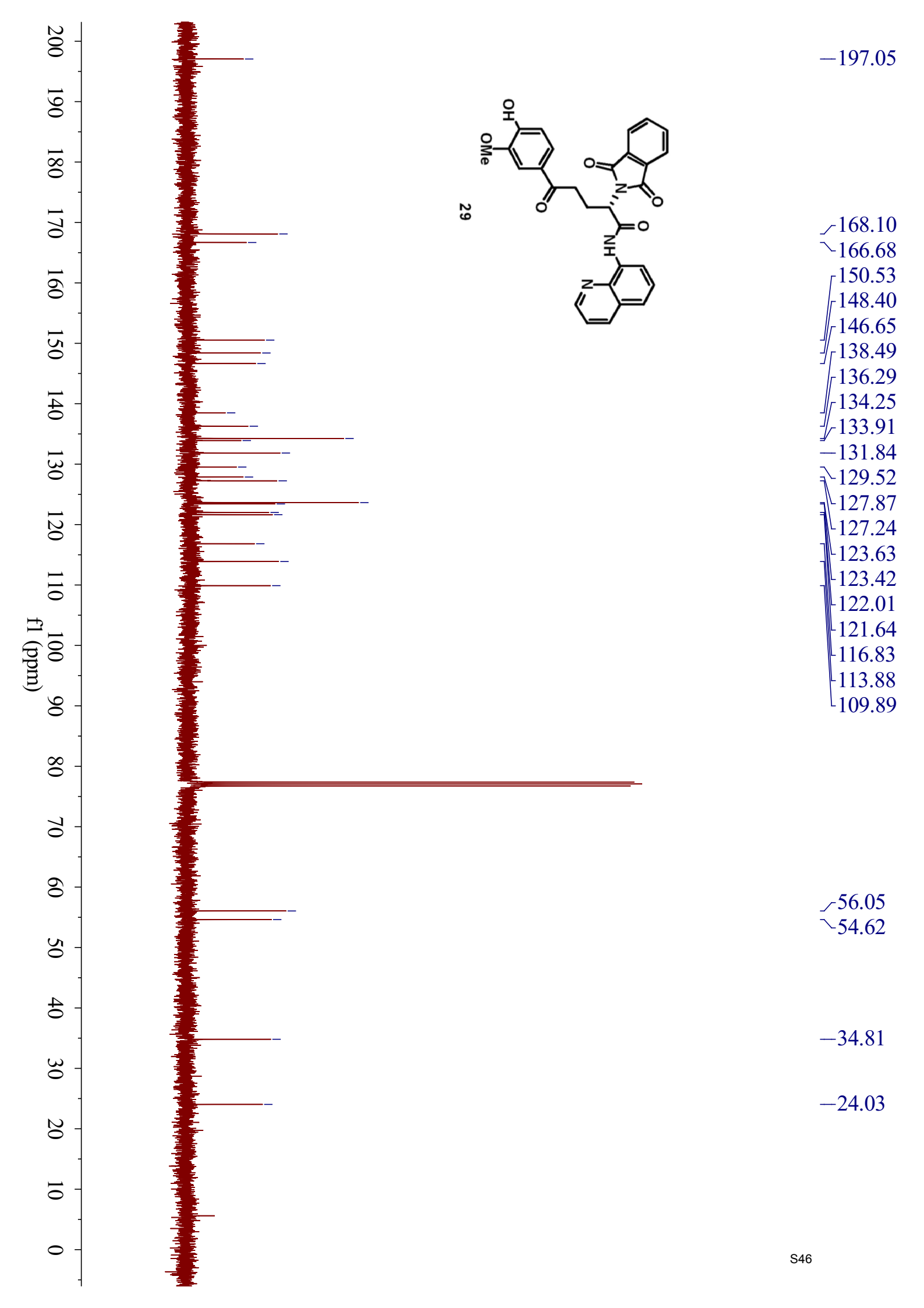

10.27
8.69
8.68
8.67
8.63
8.62
8.14
8.11
7.92
7.91
7.79
7.78
7.51
7.50
7.40
7.26
5.47
5.45
5.44
5.43
3.82
3.80
3.79
3.77
3.64
3.62
3.07
3.06
3.03
3.01
3.00
2.99
2.97
2.96
2.94
2.93
2.92
2.89
2.88
1.00
1.06
2.09
2.15
2.13
1.06
1.00
1.03
1.03
2.07
f1 (ppm)
25

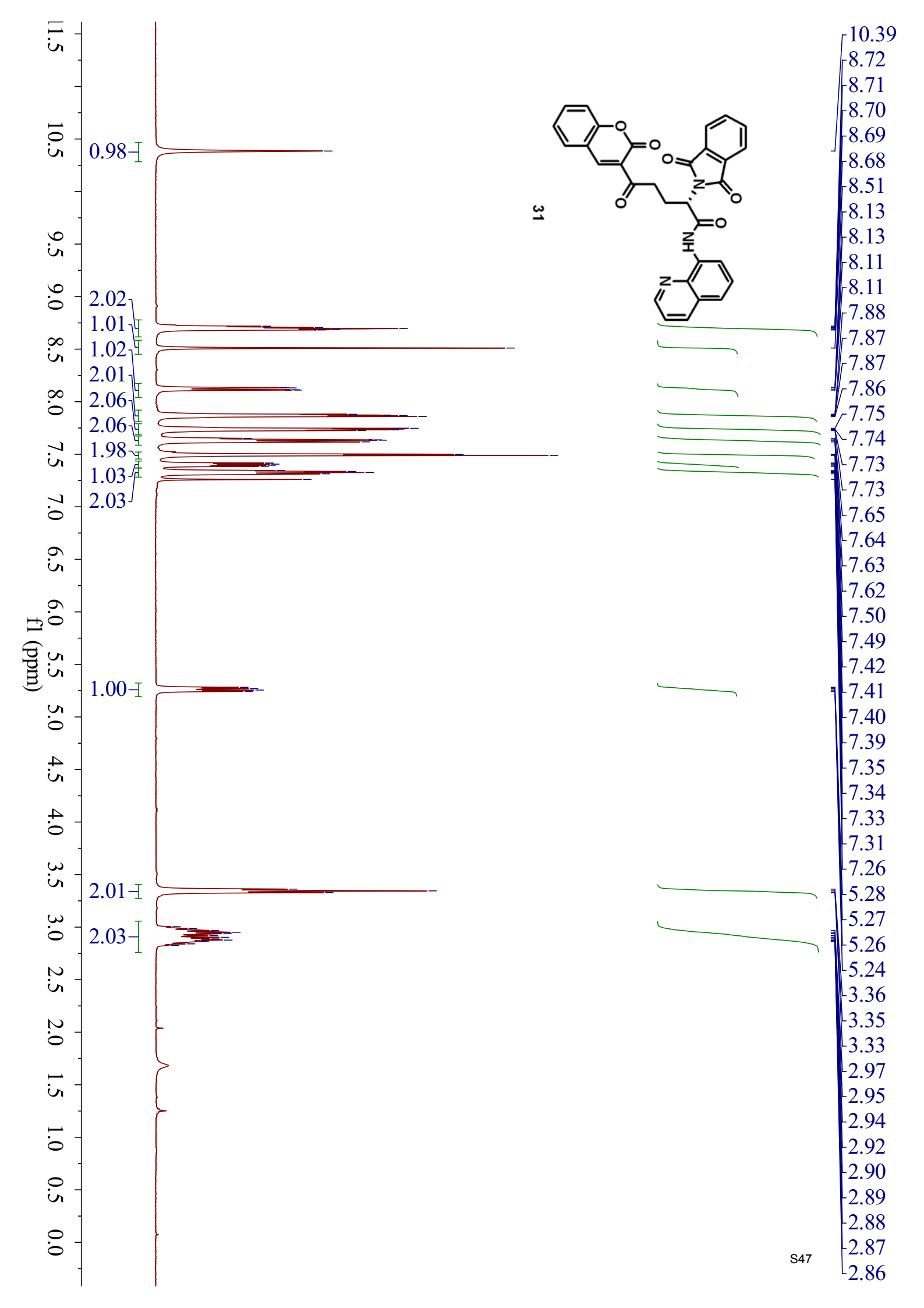

f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
25
O
N
O
Cl
O
H
N
N
167.97
166.15
148.42
138.42
136.31
134.48
133.68
131.78
127.84
127.27
123.82
122.13
121.72
116.73
52.33
41.71
31.41

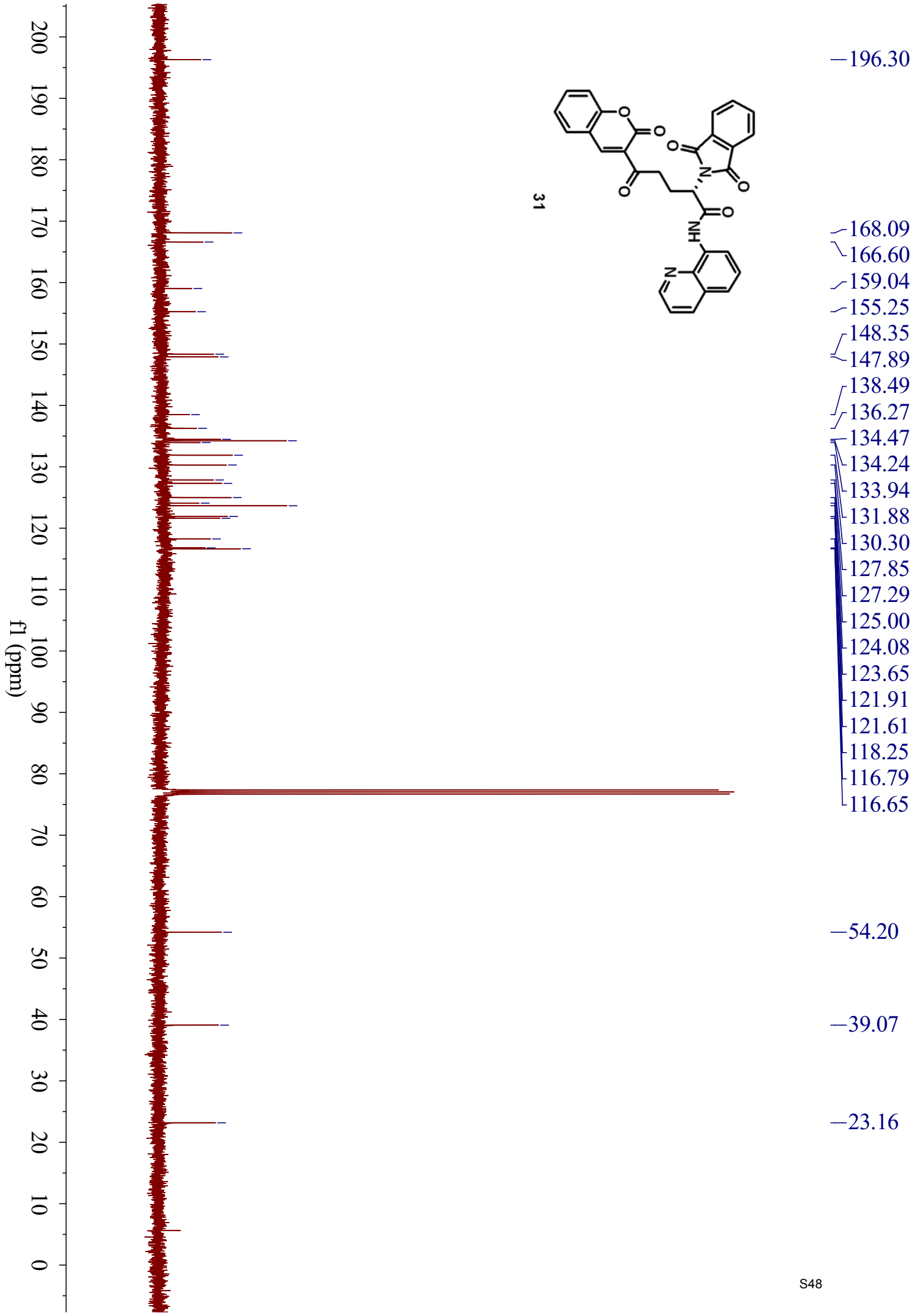

f1 (ppm)
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.99
2.05
1.04
2.06
2.07
2.07
1.06
1.00
2.06
2.06
27
10.33
8.66
8.65
8.62
8.61
8.22
8.20
7.93
7.92
7.80
7.79
7.79
7.78
7.57
7.57
7.46
7.44
7.43
7.26
5.26
5.23
5.21
2.86
2.84
2.82
2.80
2.63
2.61
2.59

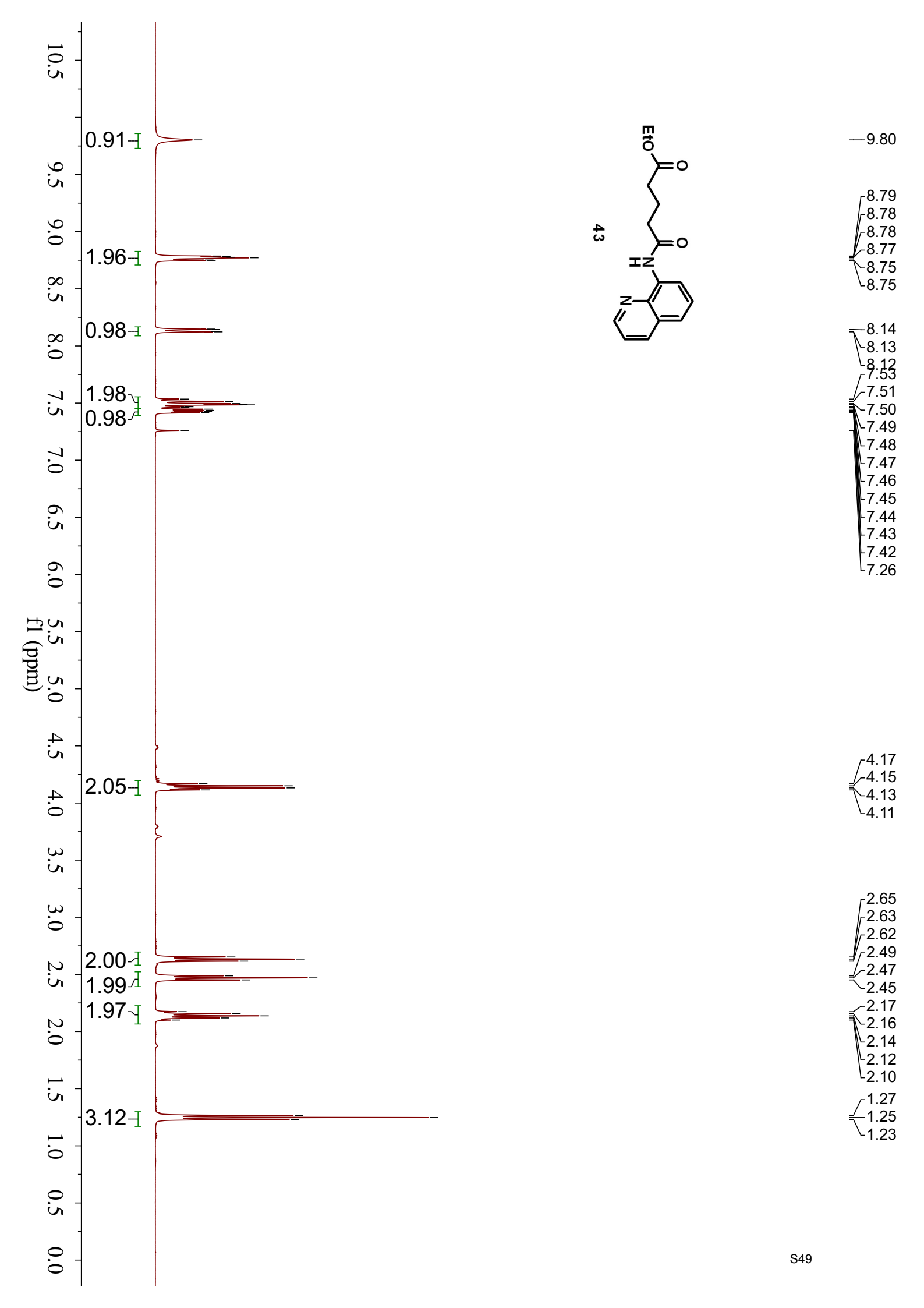

f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
27
167.87
165.73
148.11
137.83
137.58
134.66
132.95
131.63
128.10
127.63
123.96
122.82
121.71
118.74
118.60
53.38
24.90
14.99

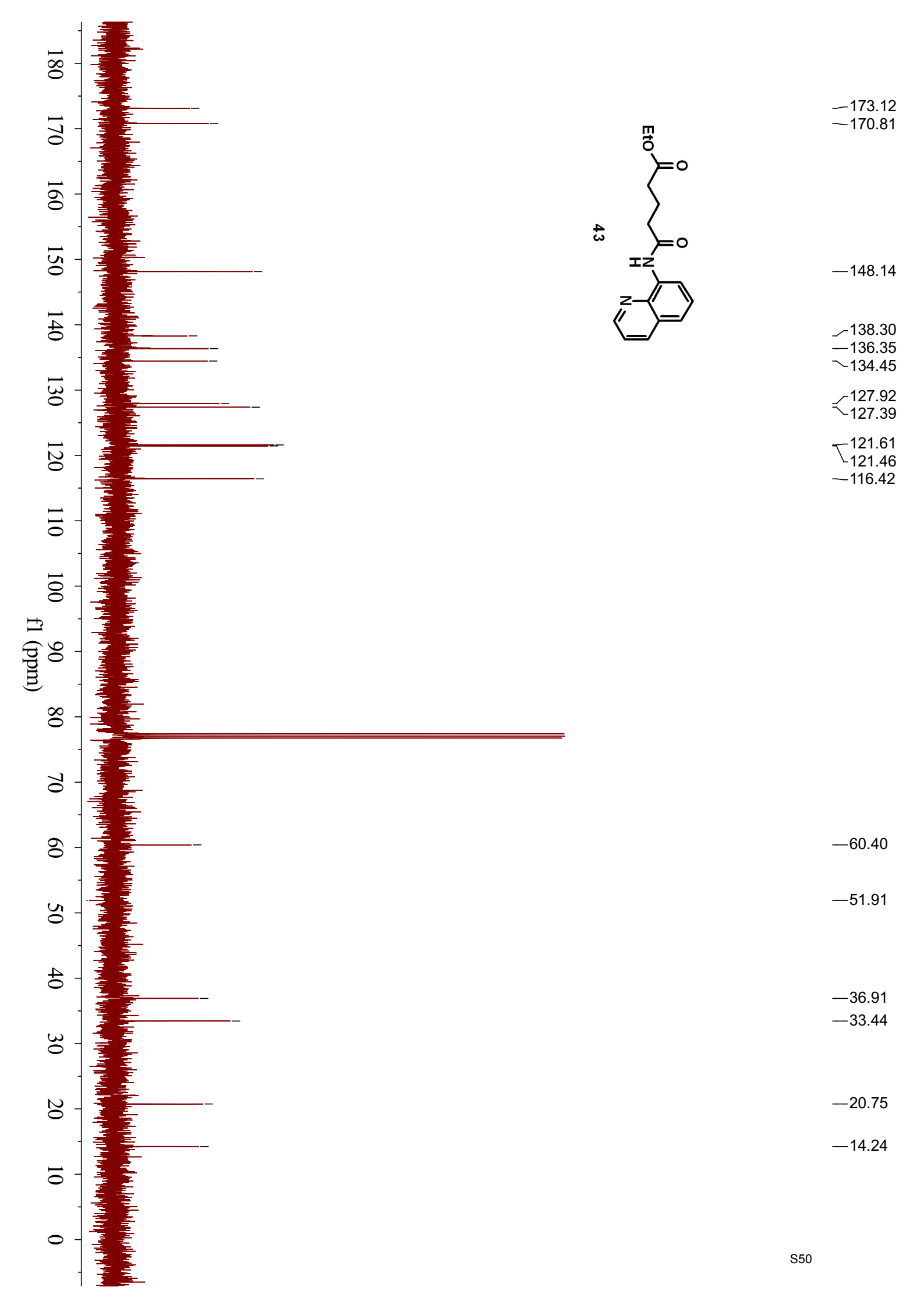

10.39
8.72
8.71
8.69
8.68
7.87
7.86
7.86
7.74
7.74
7.73
7.50
7.49
6.26
5.30
5.28
5.26
3.89
3.15
3.13
3.12
2.96
2.94
2.92
0.95
2.00
1.01
2.02
2.06
4.06
1.05
1.00
0.95
1.00
3.06
2.00
2.00
OH
OMe
O
N
O
O
O
NH
N
29
f1 (ppm)

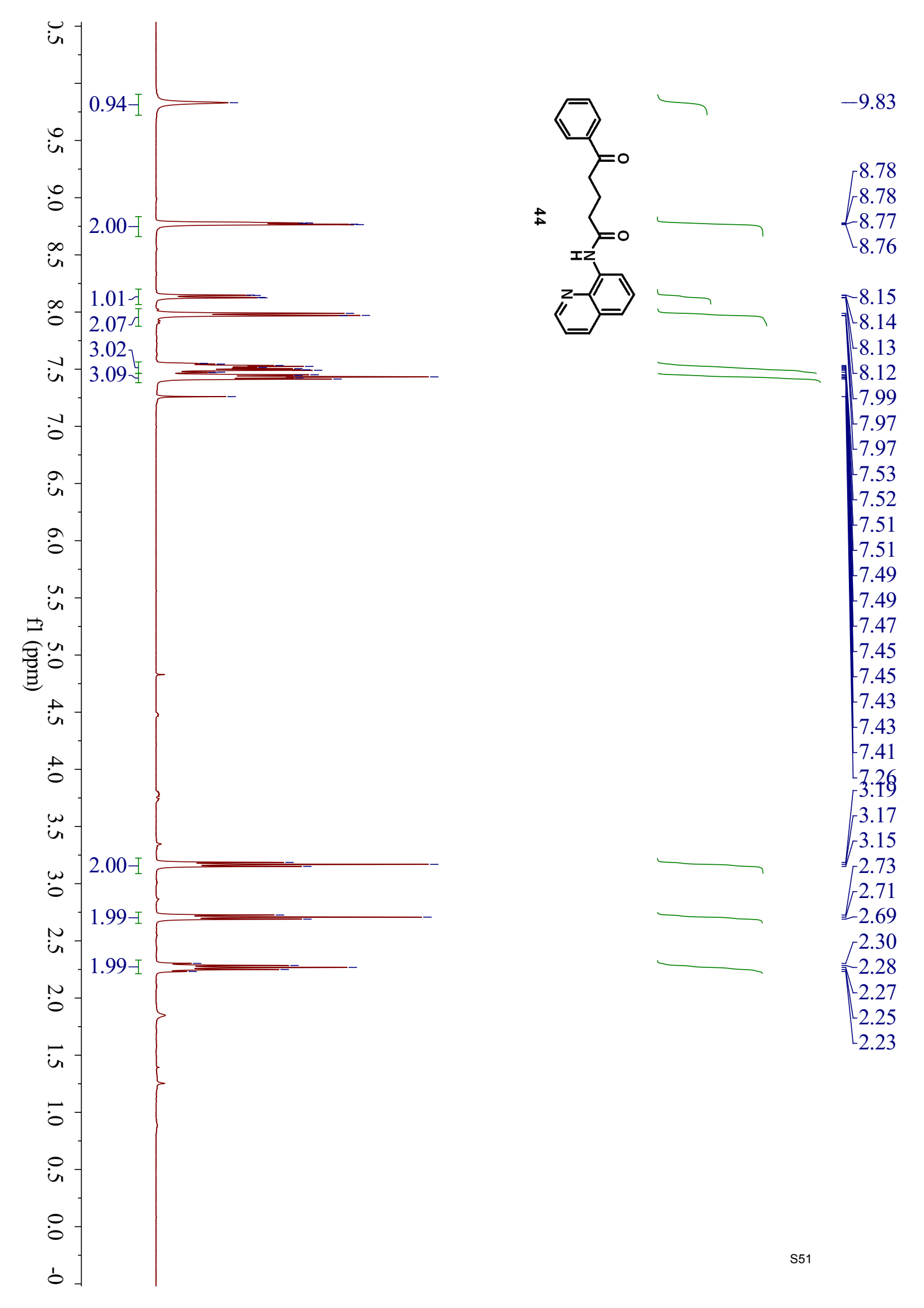

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
OH
OMe
O
N
O
O
O
NH
N
29
197.05
168.10
166.68
150.53
148.40
146.65
138.49
136.29
134.25
133.91
131.84
129.52
127.87
127.24
123.63
123.42
122.01
121.64
116.83
113.88
109.89
56.05
54.62
34.81
24.03

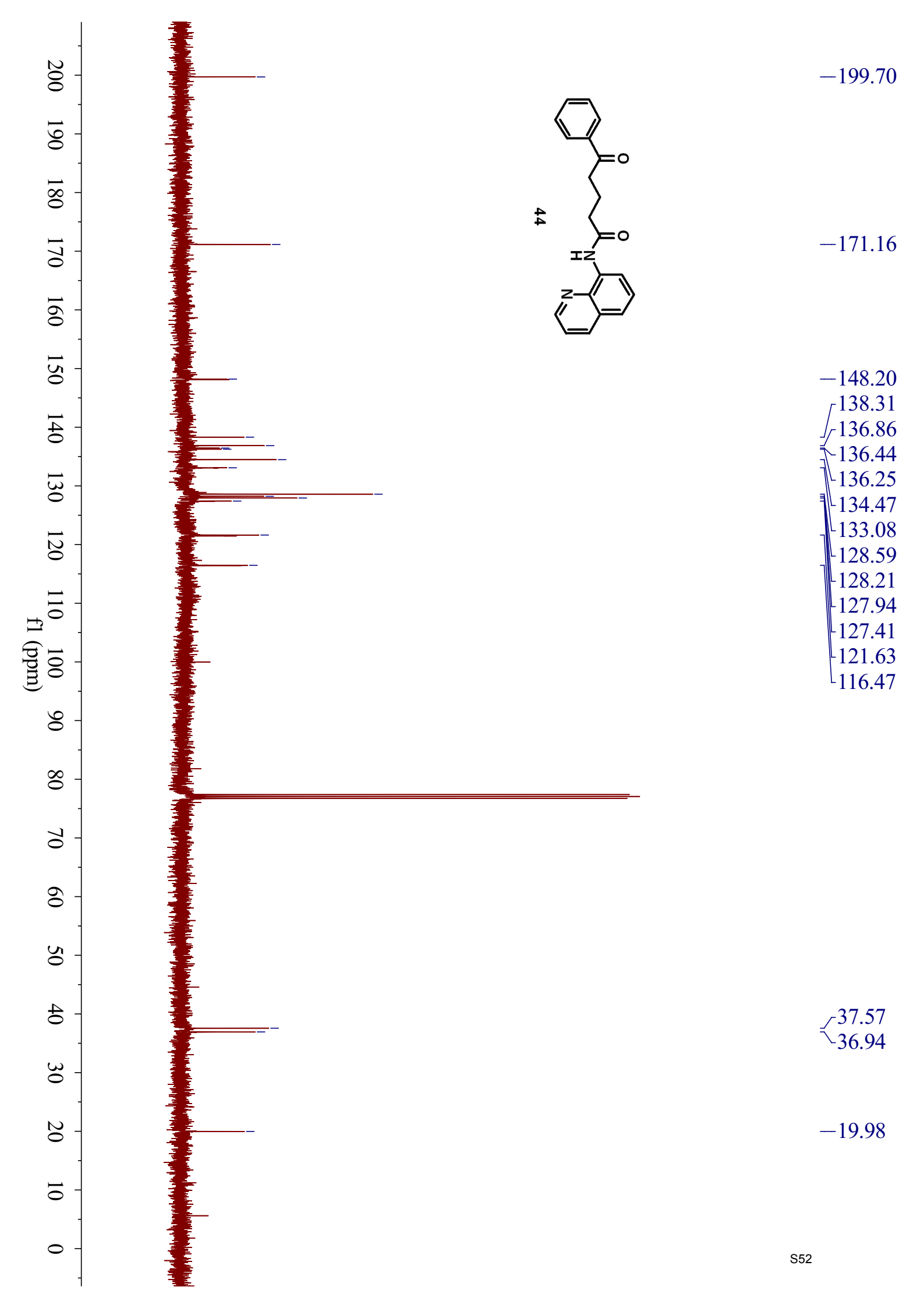

31
0.98
2.02
1.01
1.02
2.01
2.06
2.06
1.98
1.03
2.03
1.00
2.01
2.03
f1 (ppm)
10.39
8.72
8.71
8.70
8.69
8.68
8.51
8.13
8.13
8.11
8.11
7.88
7.87
7.87
7.86
7.75
7.74
7.73
7.73
7.65
7.64
7.63
7.62
7.50
7.49
7.42
7.41
7.40
7.39
7.35
7.34
7.33
7.31
7.26
5.28
5.27
5.26
5.24
3.36
3.35
3.33
2.97
2.95
2.94
2.92
2.90
2.89
2.88
2.87
2.86

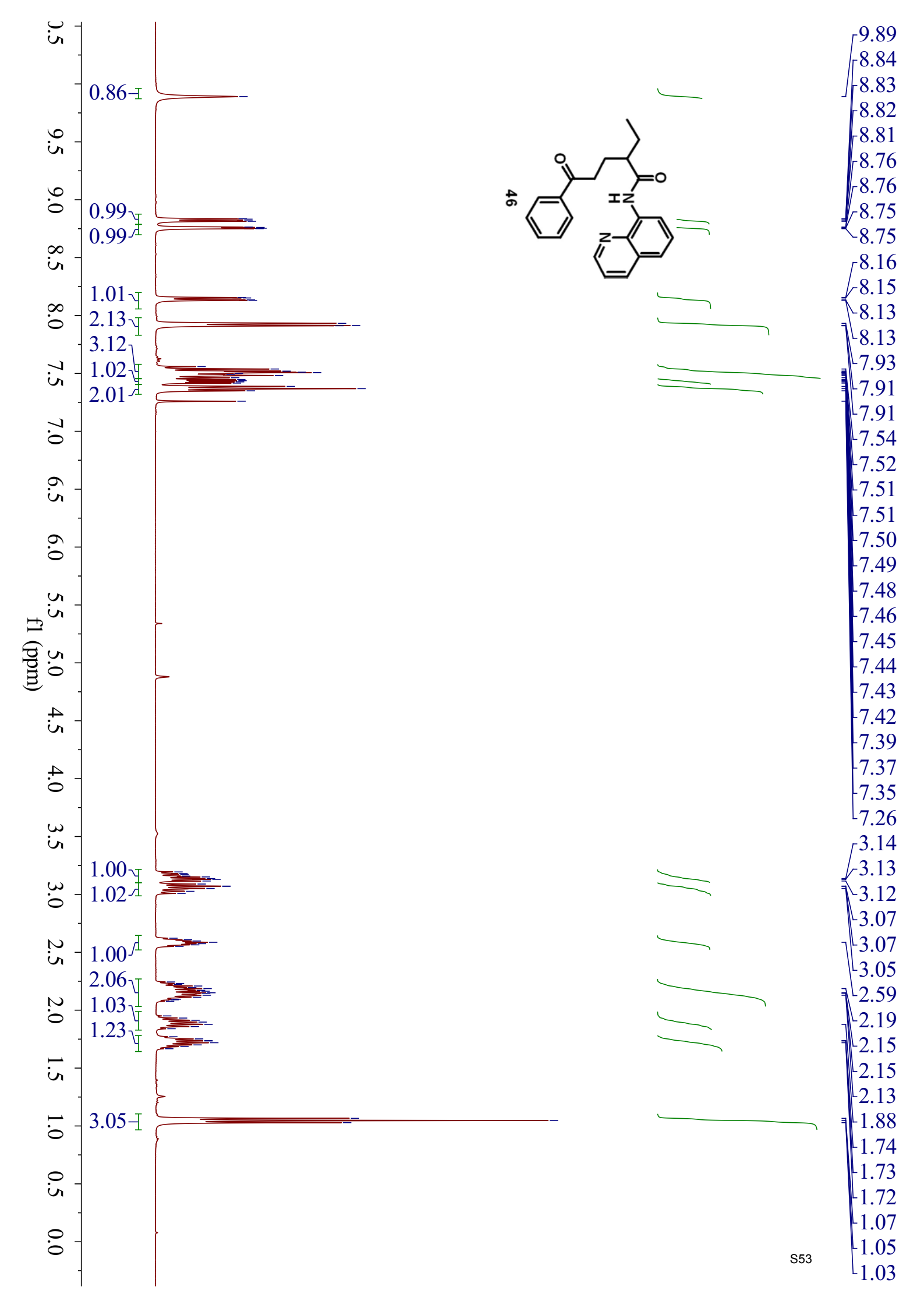

196.30
168.09
166.60
159.04
155.25
148.35
147.89
138.49
136.27
134.47
134.24
133.94
131.88
130.30
127.85
127.29
125.00
124.08
123.65
121.91
121.61
118.25
116.79
116.65
54.20
39.07
23.16
31
f1 (ppm)

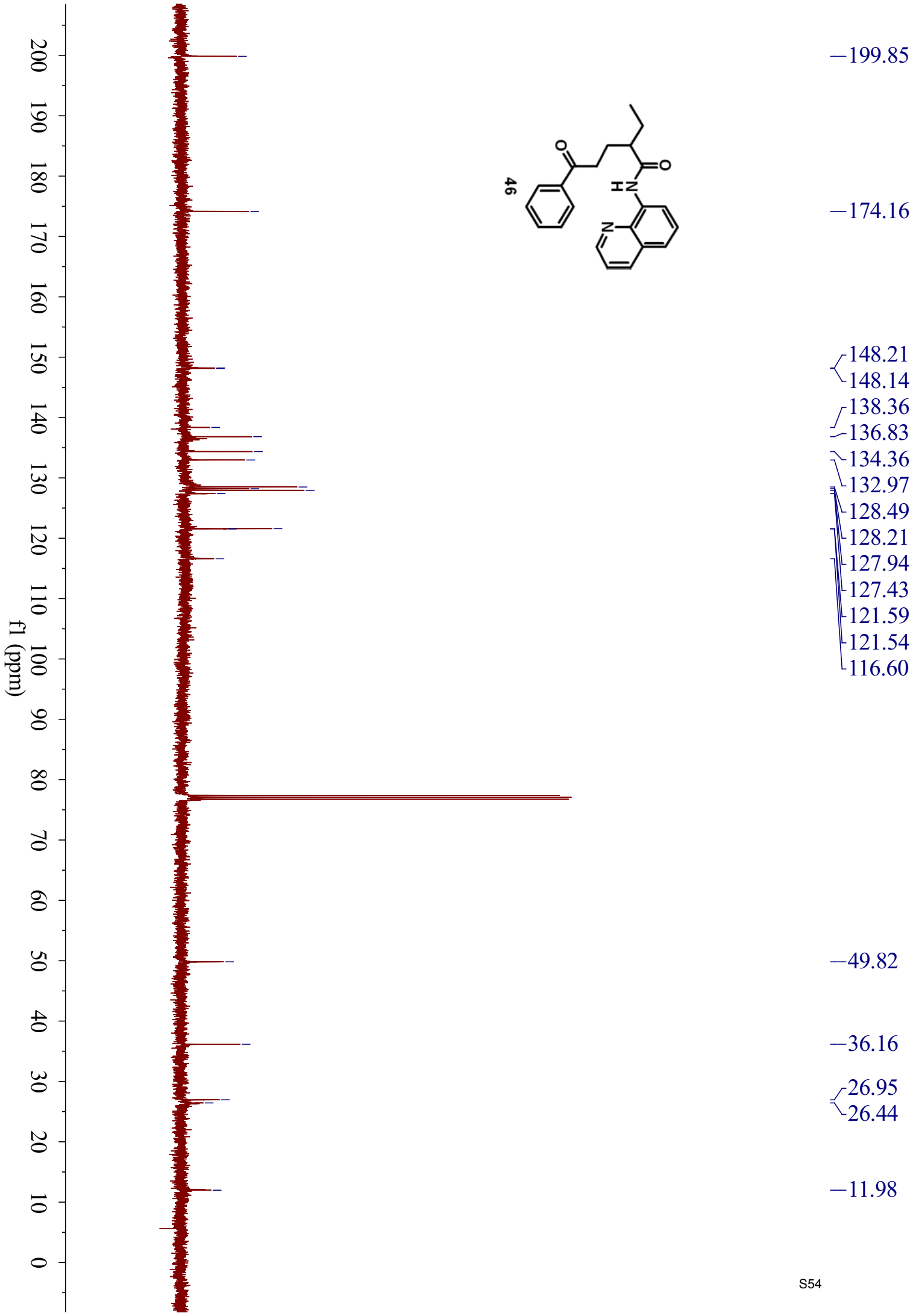

f1 (ppm)
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.91
1.96
0.98
1.98
0.98
2.05
2.00
1.99
1.97
3.12
EtO
O
O
N
H
N
43
9.80
8.79
8.78
8.78
8.77
8.75
8.75
8.14
8.13
8.12
7.53
7.51
7.50
7.49
7.48
7.47
7.46
7.45
7.44
7.43
7.42
7.26
4.17
4.15
4.13
4.11
2.65
2.63
2.62
2.49
2.47
2.45
2.17
2.16
2.14
2.12
2.10
1.27
1.25
1.23

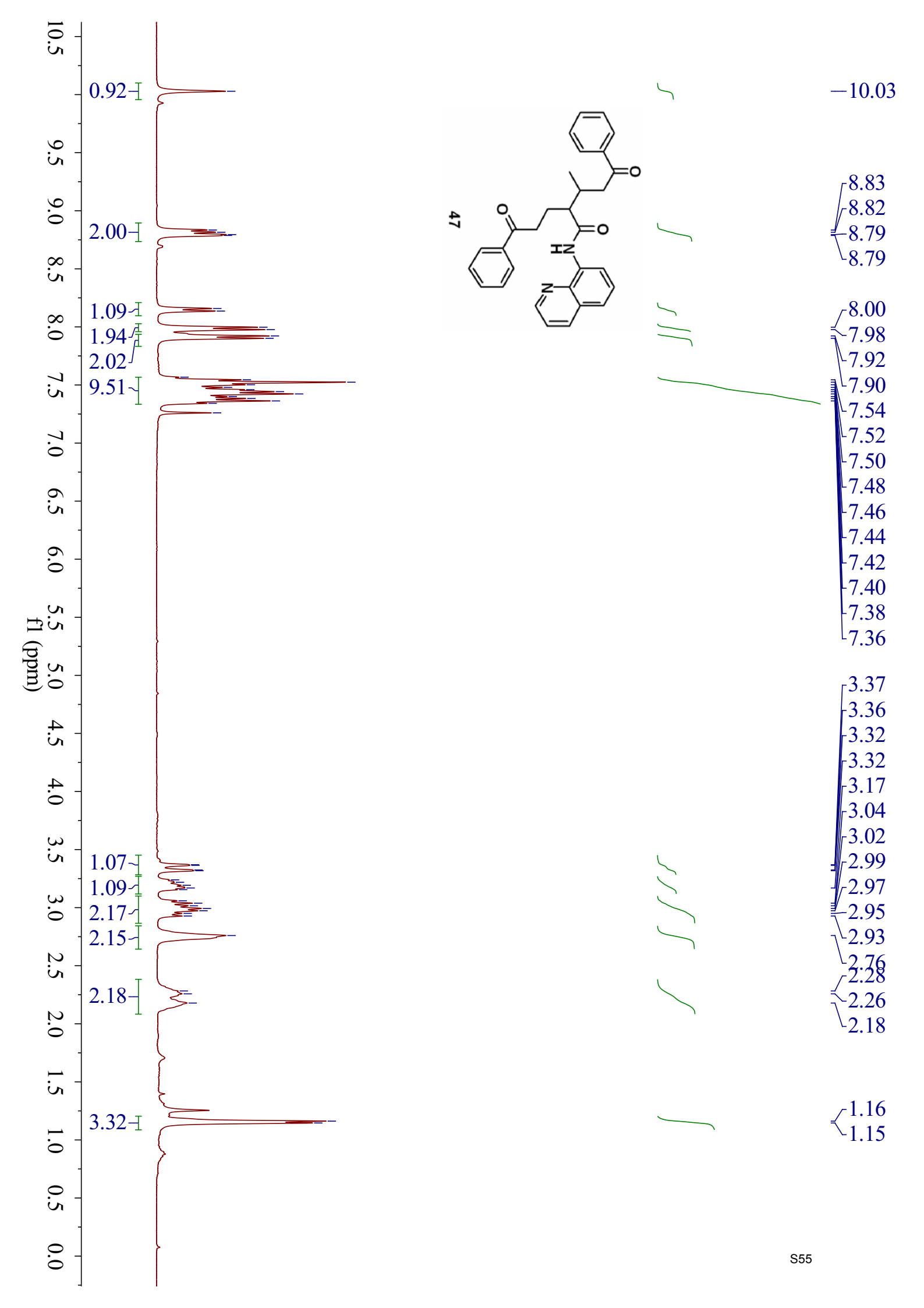

f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
EtO
O
O
N
H
N
43
173.12
170.81
148.14
138.30
136.35
134.45
127.92
127.39
121.61
121.46
116.42
60.40
51.91
36.91
33.44
20.75
14.24

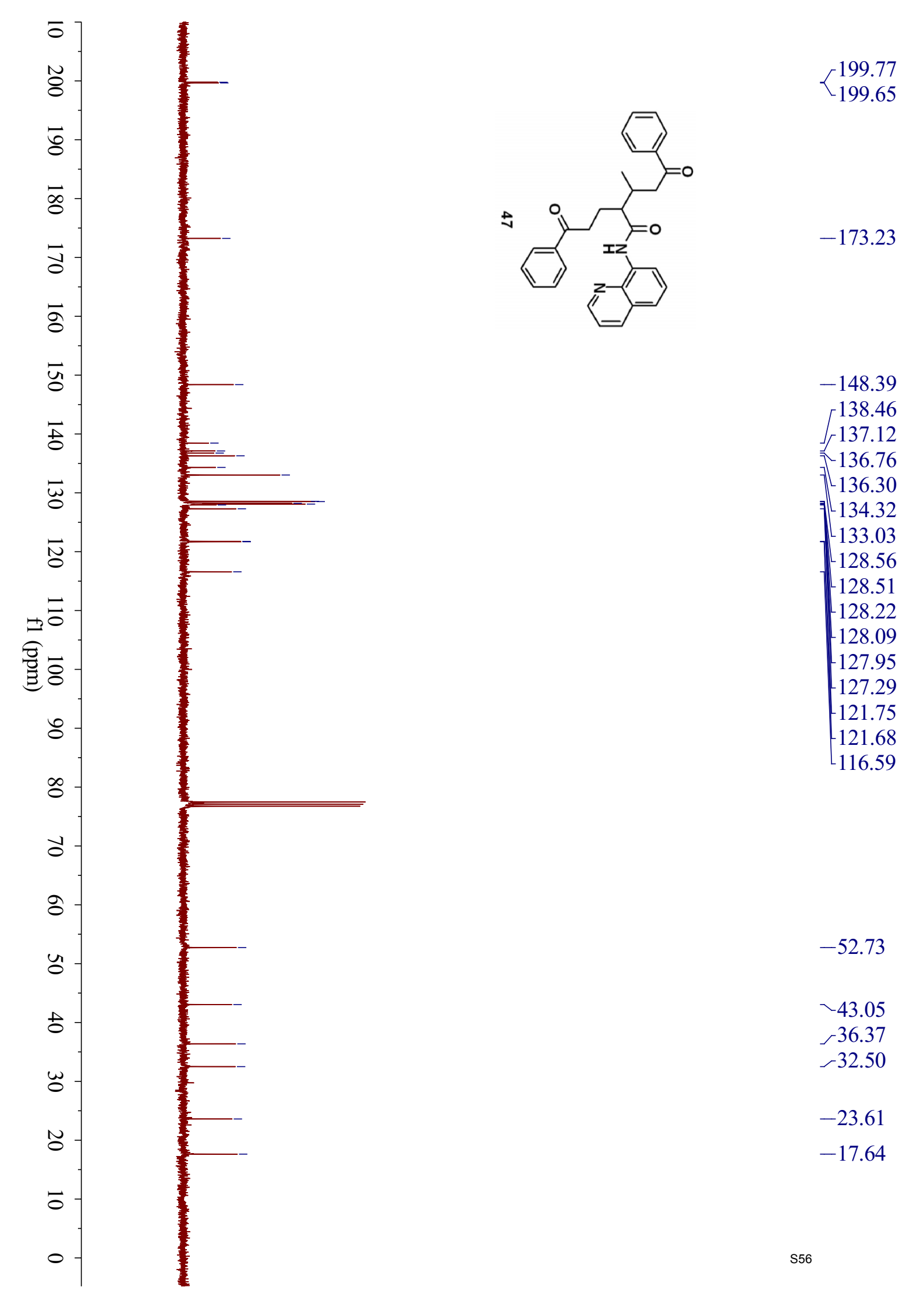

44
0.94
2.00
1.01
2.07
3.02
3.09
2.00
1.99
1.99
9.83
8.78
8.78
8.77
8.76
8.15
8.14
8.13
8.12
7.99
7.97
7.97
7.53
7.52
7.51
7.51
7.49
7.49
7.47
7.45
7.45
7.43
7.43
7.41
7.26
3.19
3.17
3.15
2.73
2.71
2.69
2.30
2.28
2.27
2.25
2.23
f1 (ppm)

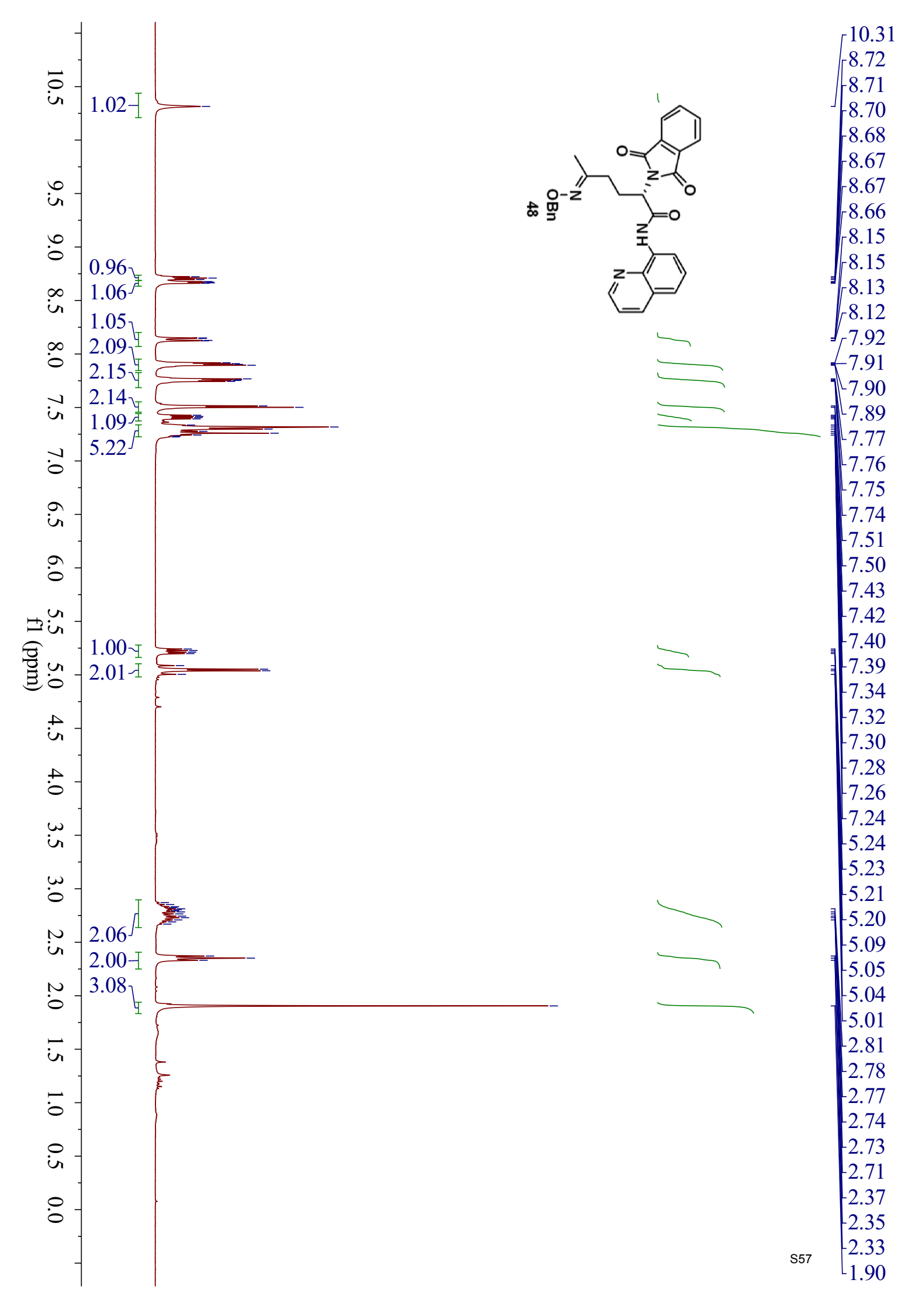

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
199.70
171.16
148.20
138.31
136.86
136.44
136.25
134.47
133.08
128.59
128.21
127.94
127.41
121.63
116.47
37.57
36.94
19.98
44
O
O
HN
N

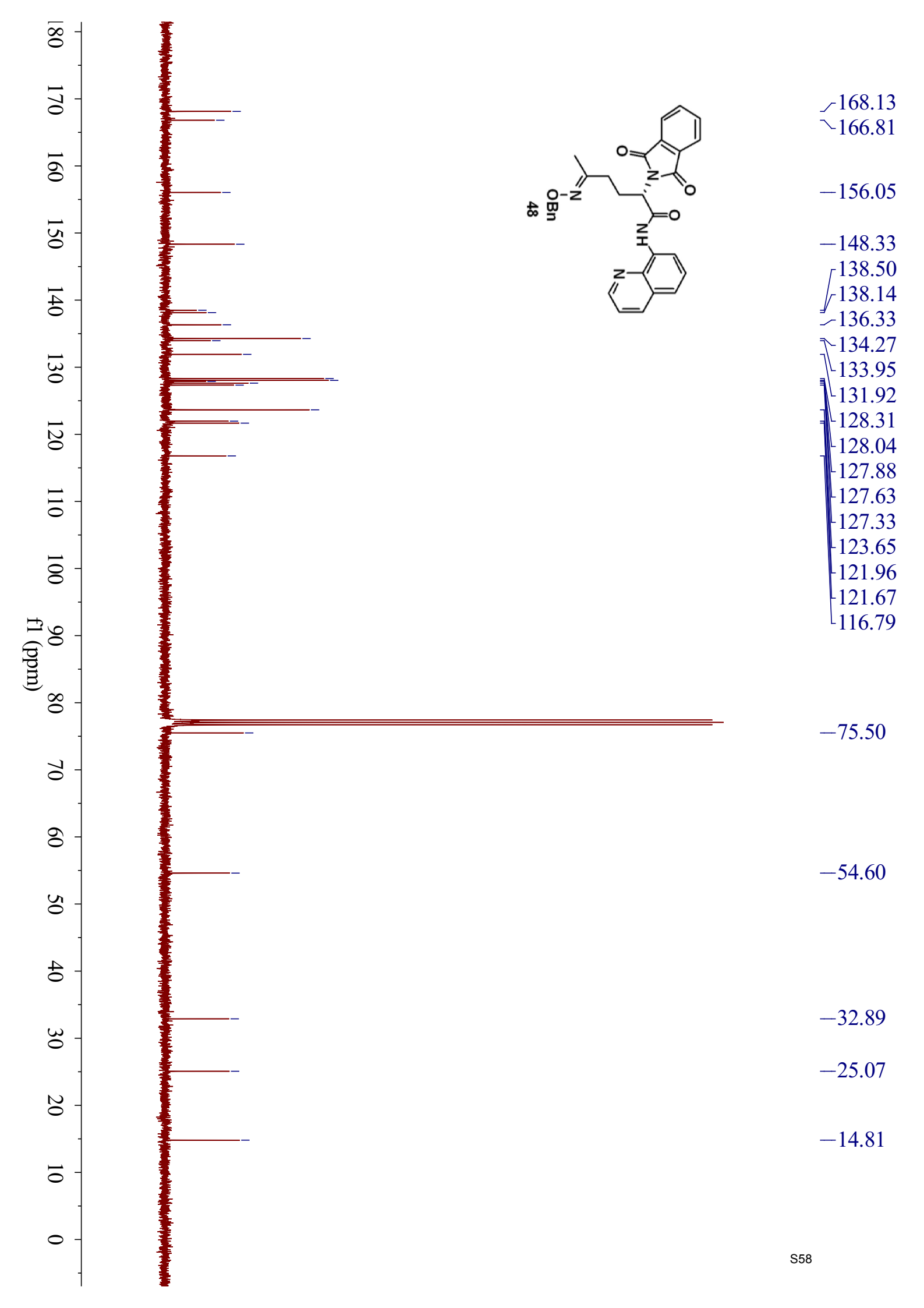

46
f1 (ppm)
0.86
0.99
0.99
1.01
2.13
3.12
1.02
2.01
1.00
1.02
1.00
2.06
1.03
1.23
3.05
9.89
8.84
8.83
8.82
8.81
8.76
8.76
8.75
8.75
8.16
8.15
8.13
8.13
7.93
7.91
7.91
7.54
7.52
7.51
7.51
7.50
7.49
7.48
7.46
7.45
7.44
7.43
7.42
7.39
7.37
7.35
7.26
3.14
3.13
3.12
3.07
3.07
3.05
2.59
2.19
2.15
2.15
2.13
1.88
1.74
1.73
1.72
1.07
1.05
1.03

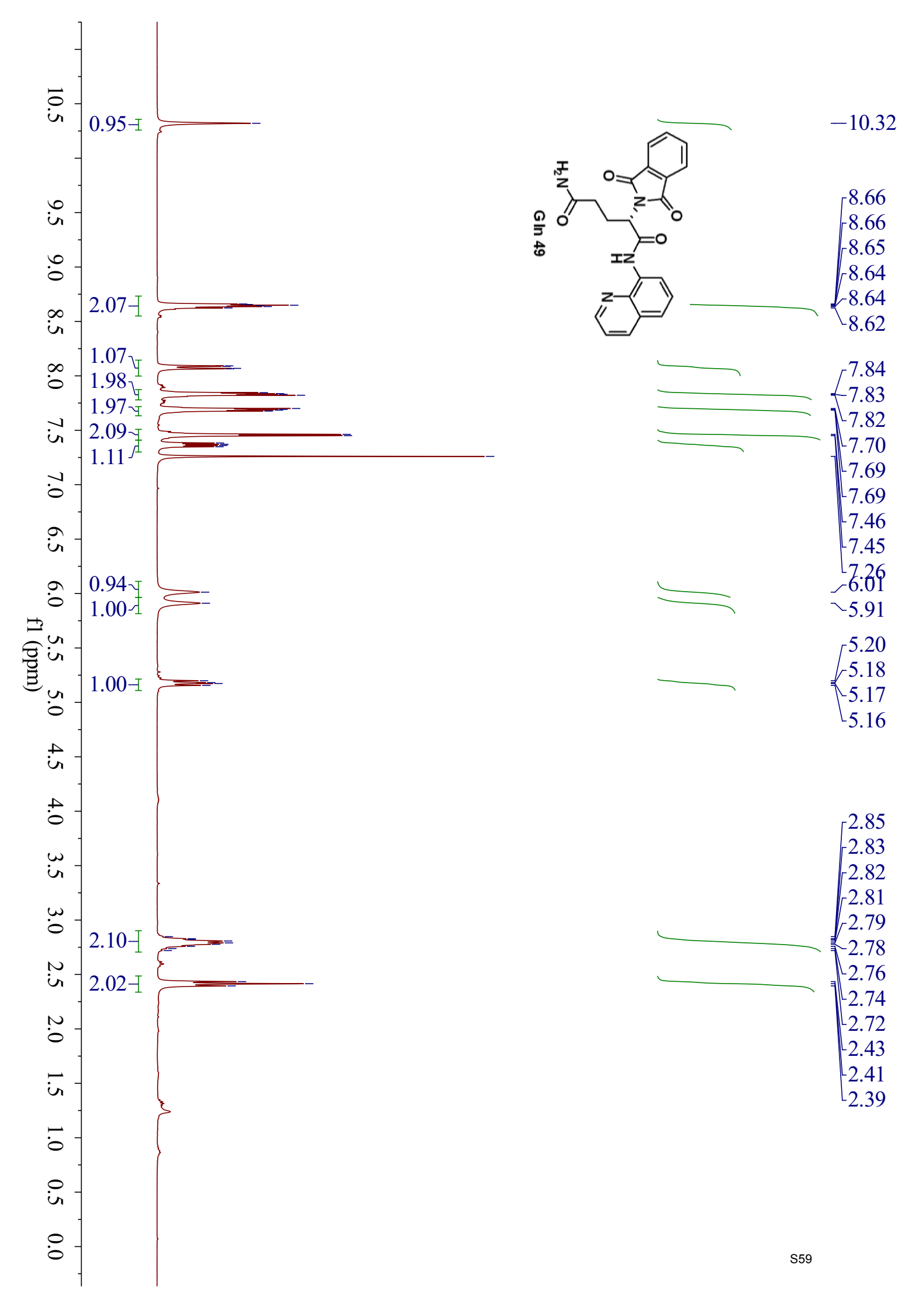

199.85
174.16
148.21
148.14
138.36
136.83
134.36
132.97
128.49
128.21
127.94
127.43
121.59
121.54
116.60
49.82
36.16
26.95
26.44
11.98
f1 (ppm)
46

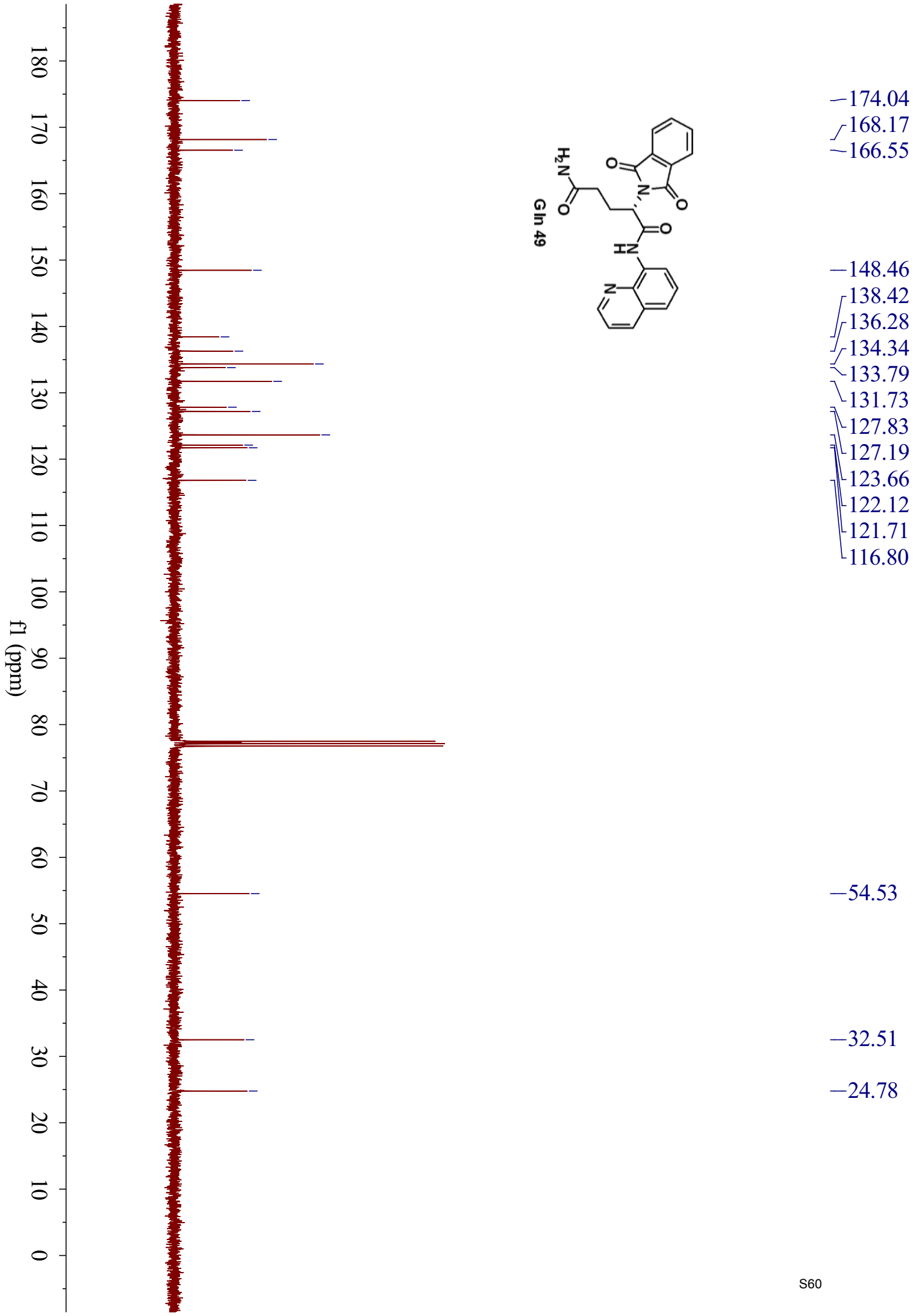

47
f1 (ppm)
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.92
2.00
1.09
1.94
2.02
9.51
1.07
1.09
2.17
2.15
2.18
3.32
10.03
8.83
8.82
8.79
8.79
8.00
7.98
7.92
7.90
7.54
7.52
7.50
7.48
7.46
7.44
7.42
7.40
7.38
7.36
3.37
3.36
3.32
3.32
3.17
3.04
3.02
2.99
2.97
2.95
2.93
2.76
2.28
2.26
2.18
1.16
1.15

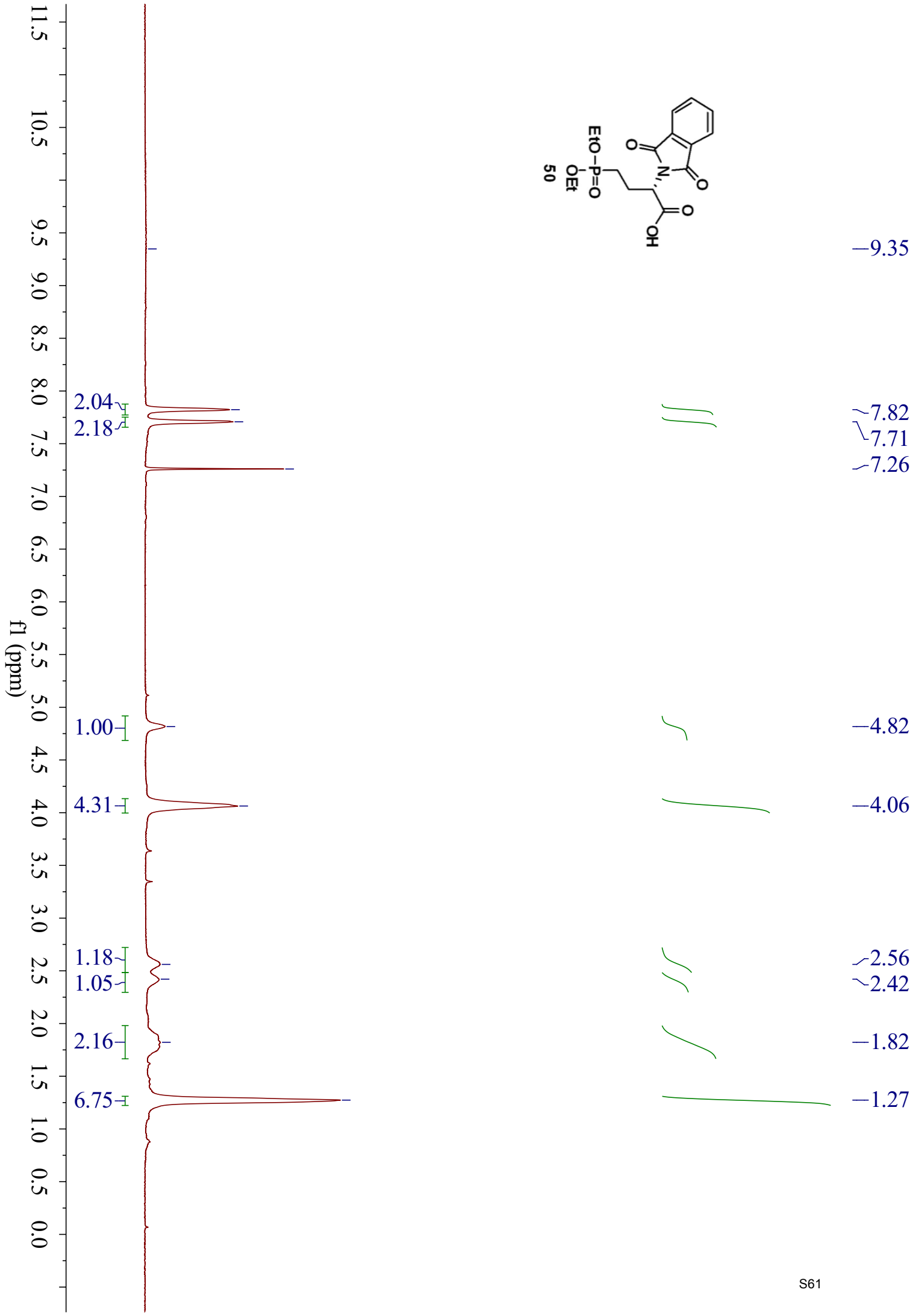

199.77
199.65
173.23
148.39
138.46
137.12
136.76
136.30
134.32
133.03
128.56
128.51
128.22
128.09
127.95
127.29
121.75
121.68
116.59
52.73
43.05
36.37
32.50
23.61
17.64
47
O
O
HN
N
f1 (ppm)
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

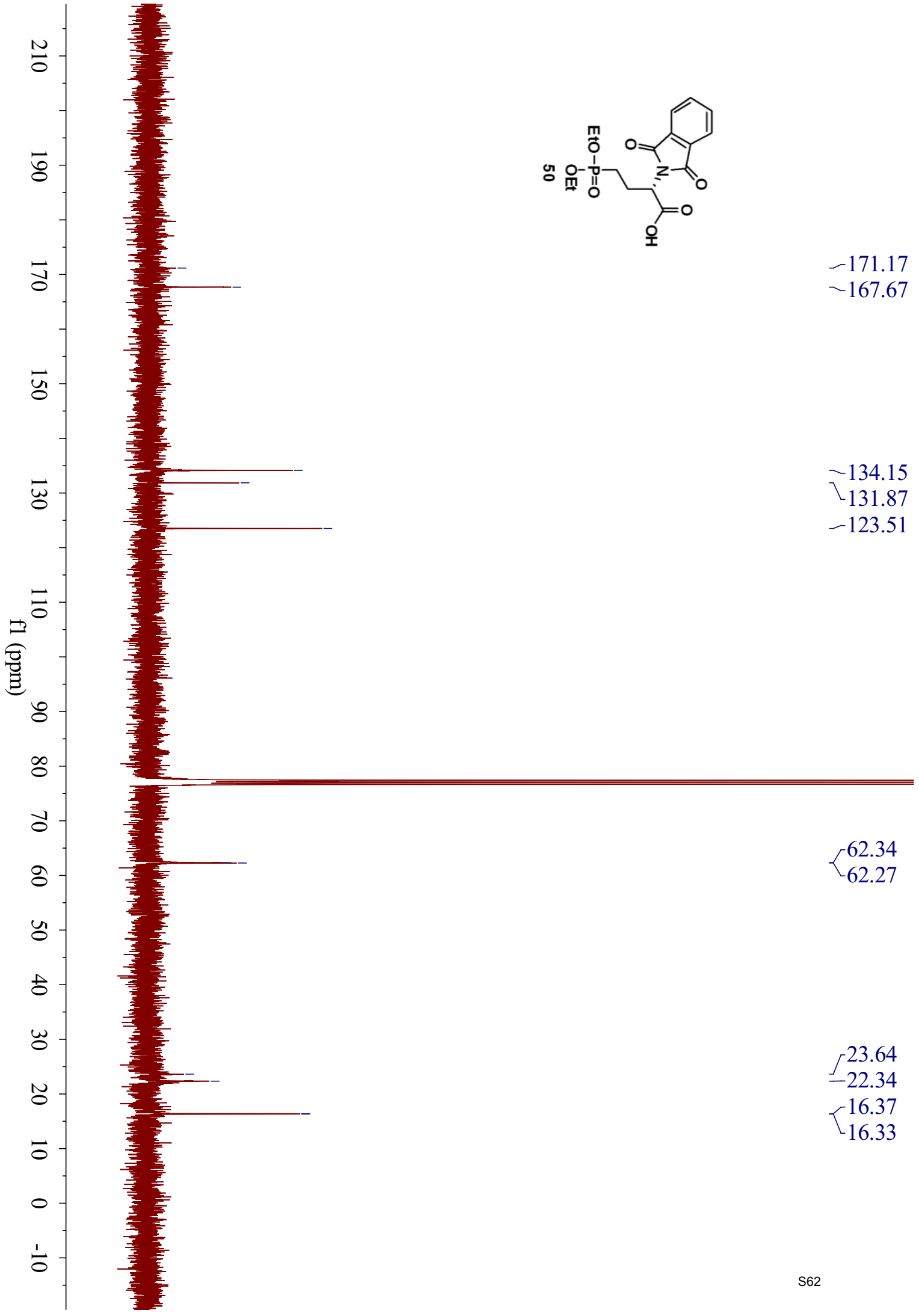

48
1.02
0.96
1.06
1.05
2.09
2.15
2.14
1.09
5.22
1.00
2.01
2.06
2.00
3.08
f1 (ppm)
10.31
8.72
8.71
8.70
8.68
8.67
8.67
8.66
8.15
8.15
8.13
8.12
7.92
7.91
7.90
7.89
7.77
7.76
7.75
7.74
7.51
7.50
7.43
7.42
7.40
7.39
7.34
7.32
7.30
7.28
7.26
7.24
5.24
5.23
5.21
5.20
5.09
5.05
5.04
5.01
2.81
2.78
2.77
2.74
2.73
2.71
2.37
2.35
2.33
1.90

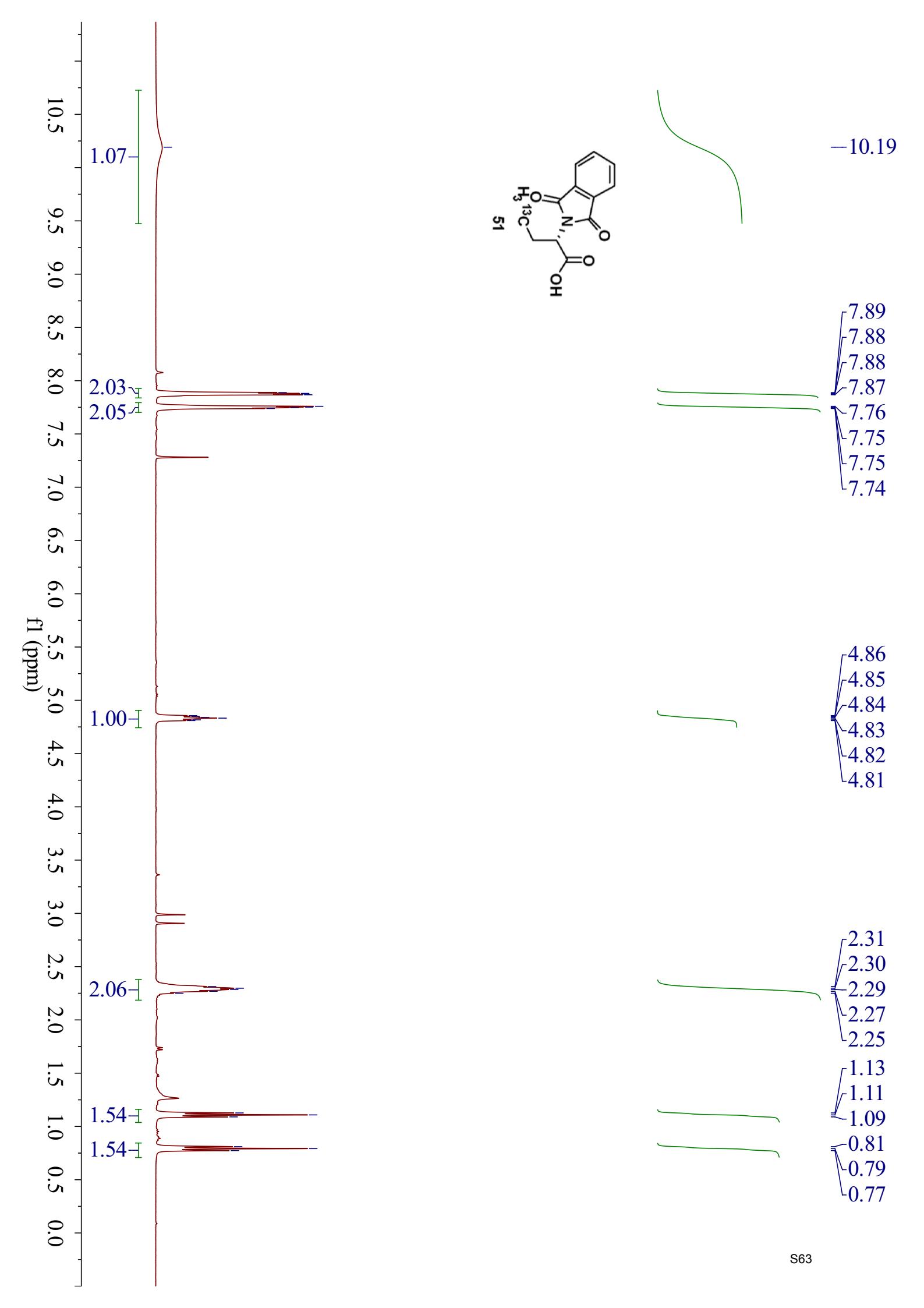

48
168.13
166.81
156.05
148.33
138.50
138.14
136.33
134.27
133.95
131.92
128.31
128.04
127.88
127.63
127.33
123.65
121.96
121.67
116.79
75.50
54.60
32.89
25.07
14.81
f1 (ppm)

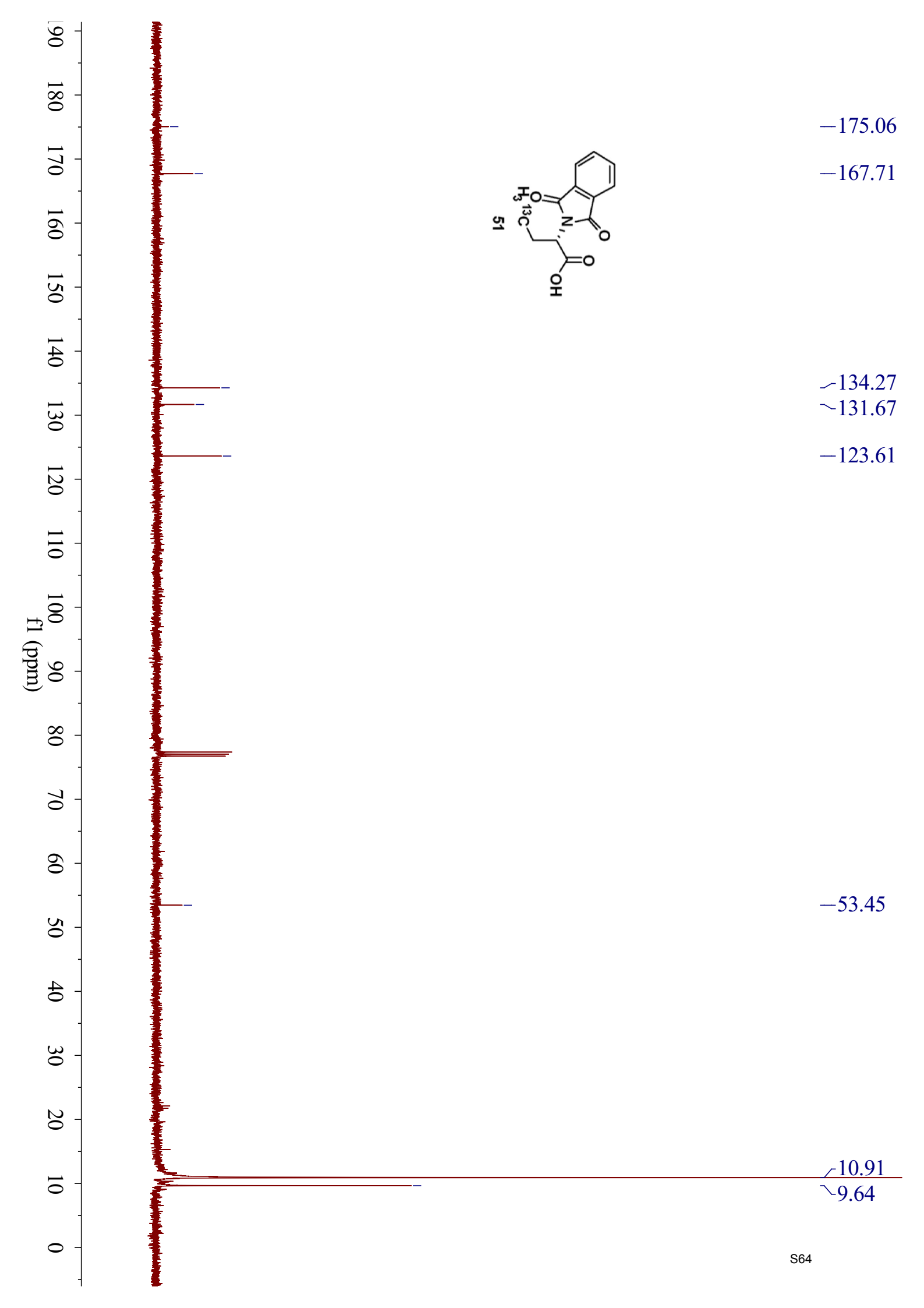

Gln 49
10.32
8.66
8.66
8.65
8.64
8.64
8.62
7.84
7.83
7.82
7.70
7.69
7.69
7.46
7.45
7.26
6.01
5.91
5.20
5.18
5.17
5.16
2.85
2.83
2.82
2.81
2.79
2.78
2.76
2.74
2.72
2.43
2.41
2.39
0.95
2.07
1.07
1.98
1.97
2.09
1.11
0.94
1.00
1.00
2.10
2.02
f1 (ppm)

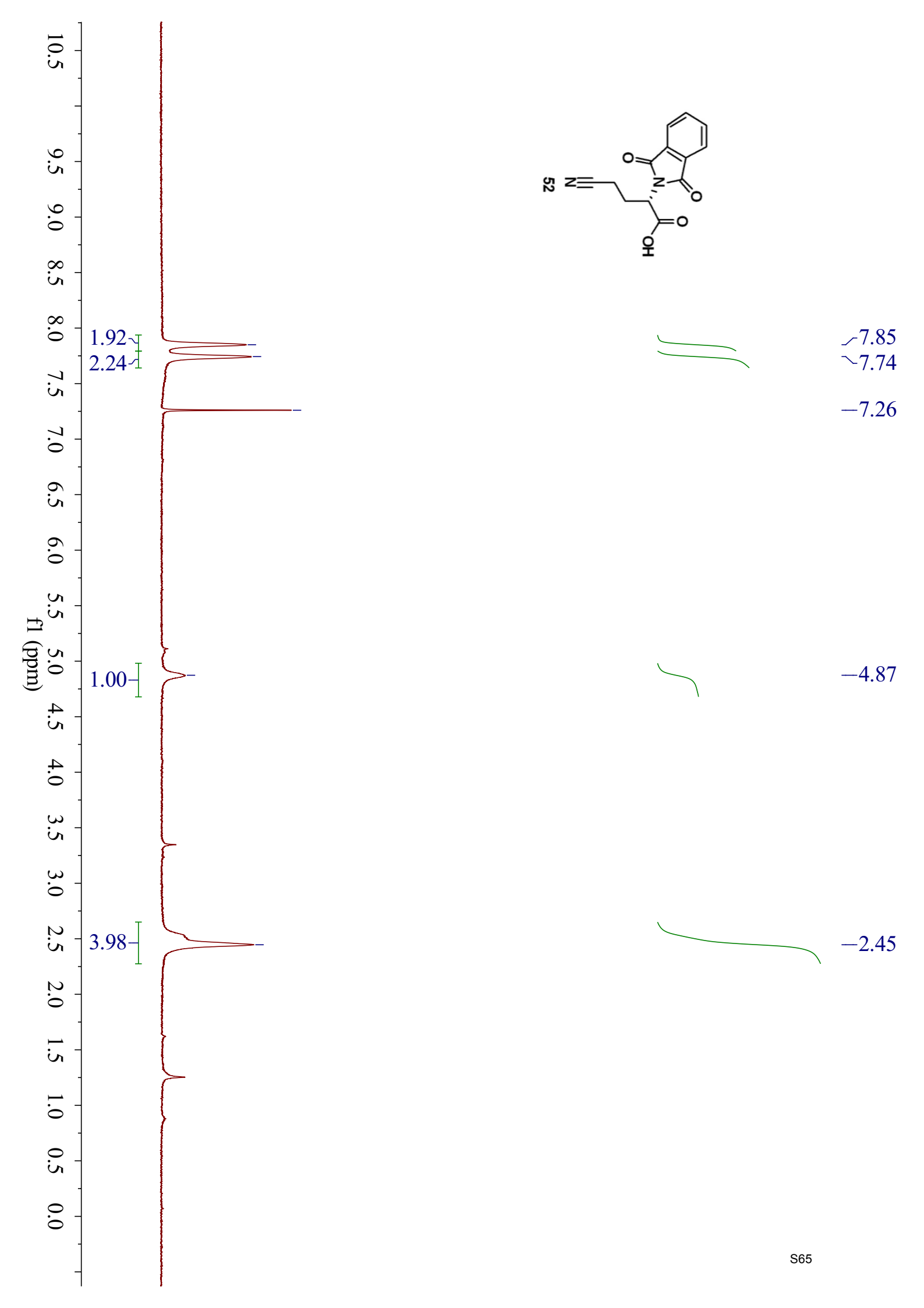

f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Gln 49
174.04
168.17
166.55
148.46
138.42
136.28
134.34
133.79
131.73
127.83
127.19
123.66
122.12
121.71
116.80
54.53
32.51
24.78

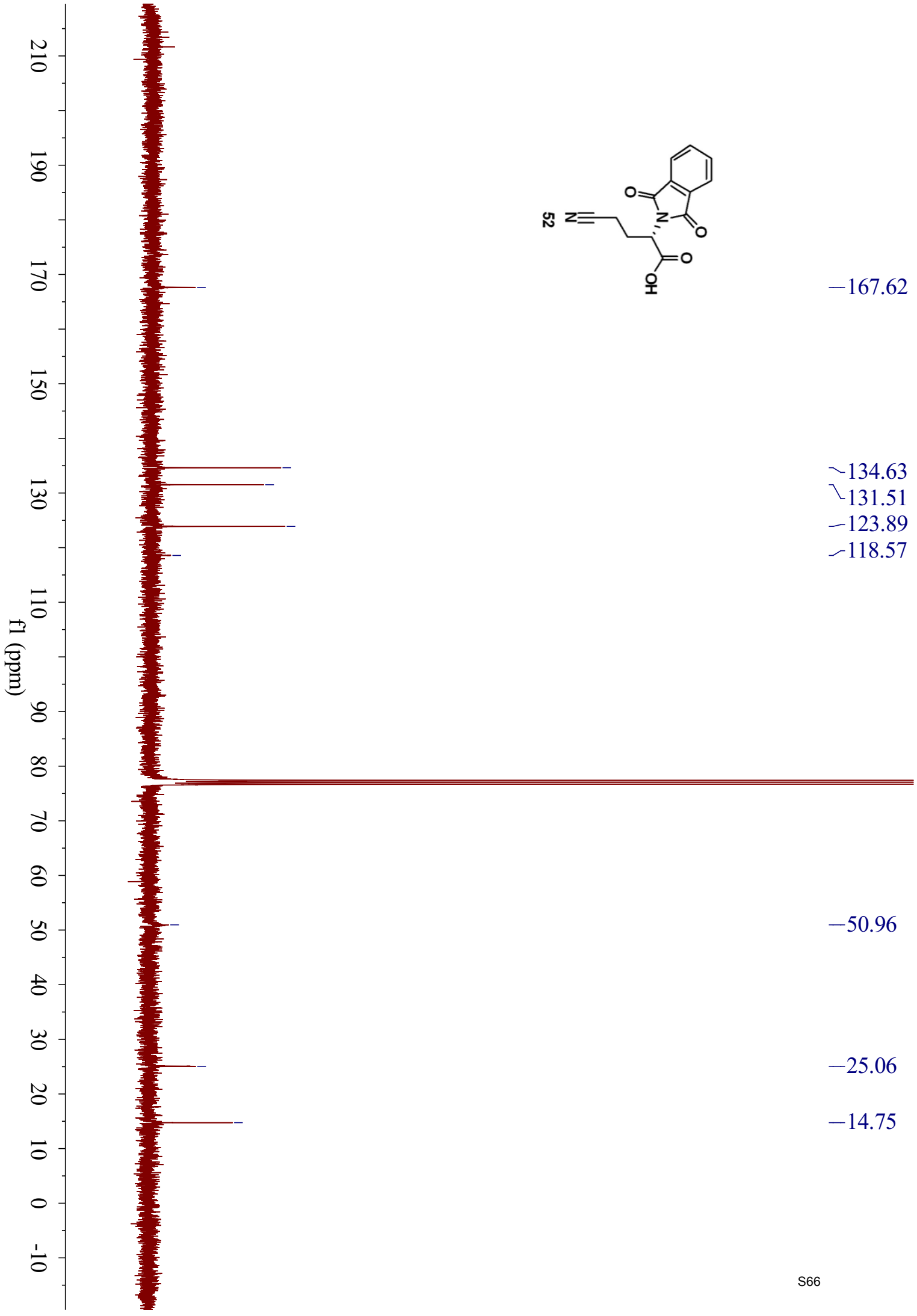

11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
2.04
2.18
1.00
4.31
1.18
1.05
2.16
6.75
9.35
7.82
7.71
7.26
4.82
4.06
2.56
2.42
1.82
1.27
EtO–P=O
OEt
50
O
N
O
O
OH


EtO–P=O
OEt
50
O
N
O
O
OH
171.17
167.67
134.15
131.87
123.51
62.34
62.27
23.64
22.34
16.37
16.33
f1 (ppm)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10


10.19
7.89
7.88
7.88
7.87
7.76
7.75
7.75
7.74
4.86
4.85
4.84
4.83
4.82
4.81
2.31
2.30
2.29
2.27
2.25
1.13
1.11
1.09
0.81
0.79
0.77
1.07
2.03
2.05
1.00
2.06
1.54
1.54
f1 (ppm)
51


175.06
167.71
134.27
131.67
123.61
53.45
10.91
9.64
f1 (ppm)
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
O
$H_3{}^{13}C$
N
O
O
OH
51


10.5
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
f1 (ppm)
1.92
2.24
1.00
3.98
7.85
7.74
7.26
4.87
2.45
52
N
O
O
O
O
OH


f1 (ppm)
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
52
N
O
O
O
OH
167.62
134.63
131.51
123.89
118.57
50.96
25.06
14.75