Palladium-Catalyzed Picolinamide-Directed Coupling of C(sp^2)-H and C(sp^2)-H: a Straightforward Approach to Quinolinone and Pyridone Scaffolds

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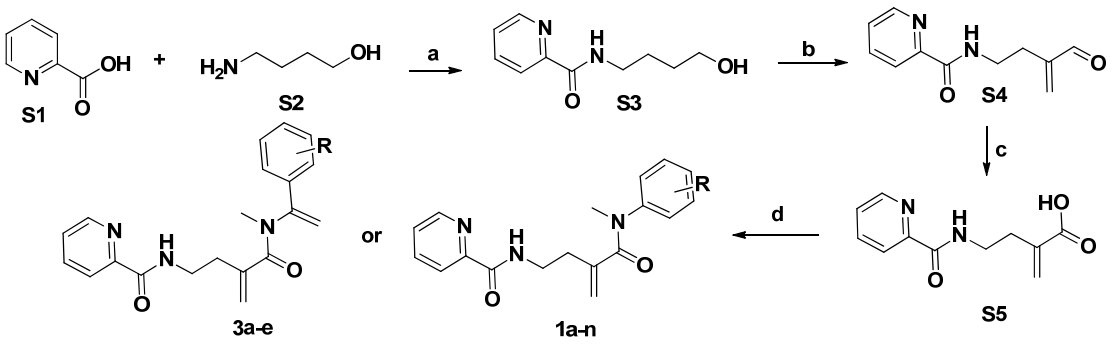
General information

Unless otherwise noted, the reagents (chemicals) were purchased from commercial sources, and used without further purification. Water was deionized before used. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15-0.2 mm thickness). Compound spots were visualized by UV light (254 nm). Column chromatography was performed on silica gel FCP 200-300. NMR spectra were run on 400 or 500 MHz instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were measured on spectrometer.

General procedure for preparation of substrates 1a-n and 3a-e

Scheme 1[a]**.**



[a] Reagents and conditions: (a) EDCI, HOBt, DIPEA, DCM; (b) $Py.SO_3$, Et_3N, DMSO; (c) NaH_2PO_4, $NaClO_2$, *t*BuOH/THF/H_2O (2/1/1); (d) $(CO)_2Cl_2$, DMF, DCM; K_2CO_3, DCM.

***N*-(4-Hydroxybutyl)picolinamide (S3)**

To a mixture of picolinic acid (10.00 g, 81.23 mmol) and HOBT (12.07 g, 89.35 mmol) in 100 mL of DCM was added DIPEA (31.73 mL, 178.70 mmol) at 0 ^oC, followed by the addition of EDCI (17.13 g, 89.35 mmol). The resulting mixture was stirred for 10 min and then 4-aminobutan-1-ol (7.24 g, 81.23 mmol) was added. The reaction was warmed to room temperature overnight. The mixture was diluted with DCM. The organic phase was washed with saturated sodium carbonate, water, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column (EA/PE = 1/1) to give the title compound (14.70 g, 93%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.3 Hz, 1H), 8.20-8.10 (m, 2H), 7.83 (t, J = 7.7 Hz, 1H), 7.41 (dd, J = 7.5, 4.8 Hz, 1H), 3.70 (t, J = 6.0 Hz, 2H), 3.51 (q, J = 6.5 Hz, 2H), 1.79-1.61 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.60, 149.97, 148.15, 137.52, 126.26, 122.33, 62.45, 39.25, 29.93, 26.33; ESI/MS: 195.1 $[M+H]^+$.

***N*-(3-Formylbut-3-en-1-yl)picolinamide (S4)**

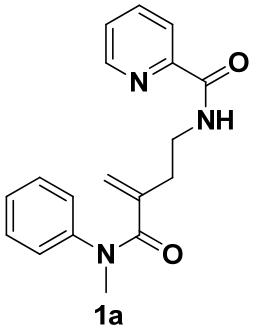
In a flask, *N*-(4-hydroxybutyl)picolinamide **S3** (0.93 g, 4.80 mmol) was dissolved in 5 mL of DMSO and 4 mL of triethyamine (28.82 mmol) under an atmosphere of argon. Sulfur trioxide pyridine complex (1.53 g, 9.61 mmol) was added as a solid over 20 min with the solution being stirred at the room temperature. After stirring for another 3 h, *N*, *N*′-dimethylmethyleneiminium iodide (0.98 g, 5.28 mmol)was added in one portion. After stirring overnight at room temperature, the reaction mixture was poured into a stirred biphasic mixture of cold saturated aqueous $NaHCO_3$ and ethyl acetate. Once the bubbling stopped, the organic layer was separated and then washed with water and brine. The product was purified by chromatography through silica gel column using 33% ethyl acetate in petroleum ether as eluent to afford the title compound (0.55 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.51 (d, *J* = 4.7 Hz, 1H), 8.14 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.39 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.37 (s, 1H), 6.08 (s, 1H), 3.59 (q, *J* = 6.8 Hz, 2H), 2.58 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.52, 164.47, 149.76, 148.18, 147.01, 137.43, 136.04, 126.27, 122.21, 37.74, 28.32; ESI/MS: 205.1 $[M+H]^+$.

2-Methylene-4-(picolinamido)butanoic acid (S5)

To an ice-cooled solution of *N*-(3-formylbut-3-en-1-yl)picolinamide **S4** (0.47 g, 2.30 mmol) and 1.36 mL of 2-methyl-2-butene in 6 mL of 2:1 *t*-BuOH:THF solution was added dropwise a solution of sodium chlorite (0.48 g, 5.29 mmol) and sodium dihydrogenphosphate (0.72 g, 4.26 mmol) in 2 mL of water. The resulting mixture was stirred at room temperature for 1 h. The mixture was extracted with 50 mL of 1:1 EA:THF. The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column using 50-100% ethyl acetate in petroleum ether as eluent to give the acid (0.46 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.80 (t, *J* = 6.2 Hz, 1H), 8.63 (d, *J* = 4.8 Hz, 1H), 8.06-7.93 (m, 2H), 7.60-7.57 (m, 1H), 6.05 (s, 1H), 5.61 (s, 1H), 3.45 (q, *J* = 6.7 Hz, 2H), 2.52-2.50 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 167.83, 163.74, 150.03, 148.39, 138.49, 137.77, 126.45, 125.78, 121.82, 37.76, 31.48; ESI/MS: 219.1 $[M+H]^+$.

N-(3-(Methyl(phenyl)carbamoyl)but-3-en-1-yl)picolinamide (1a).

General experimental procedure for 1a-f, 1l , 1n, 7 and 9.

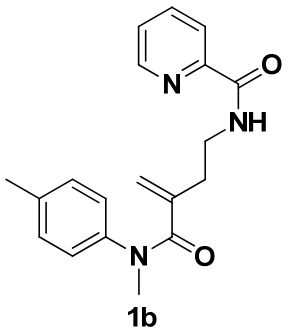


1a

To an ice-cooled solution of 2-methylene-4-(picolinamido)butan oic acid **S5** (0.26 g, 1.19 mmol) in 5 mL of DCM was added catalytic amount of DMF was added dropwise oxalyl chloride (0.11 mL, 1.31 mmol) at 0 ^{o}C. The resulting mixture was stirred at room temperature for 3 h and concentrated under vacuum to afford the crude acyl chloride, which was suspended in 10 mL of DCM. Potassium carbonate (0.41 g, 3.57 mmol) and *N*-methylaniline (0.14 mL, 1.31 mmol) were added to this

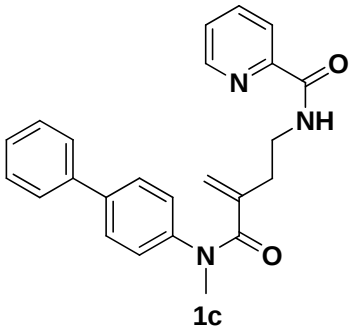
suspension. Stirring was continued for 24 h. The mixture was diluted with DCM. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column using 0-100% ethyl acetate in petroleum ether as eluent to give the title compound in 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.4 Hz, 1H), 8.31 (br, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.85 (t, *J* = 7.1 Hz, 1H), 7.46-7.40 (m, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 5.17 (s, 1H), 5.08 (s, 1H), 3.61 (q, *J* = 6.6 Hz, 2H), 3.35 (s, 3H), 2.44 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.27, 164.43, 150.03, 148.23, 144.51, 141.86, 137.43, 129.51, 127.20, 126.88, 126.20, 122.27, 120.87, 38.13, 38.05, 33.95; ESI/MS: 310.1 $[M+H]^+$.

***N*-(3-(Methyl(p-tolyl)carbamoyl)but-3-en-1-yl)picolinamide (1b).**



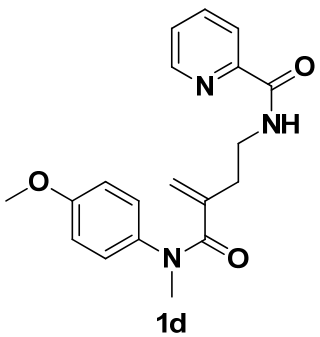
Compound **1b** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.7 Hz, 1H), 8.26 (br, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.42-7.37 (m, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 5.14 (s, 1H), 5.07 (s, 1H), 3.59 (q, *J* = 6.5 Hz, 2H), 3.30 (s, 3H), 2.41 (t, *J* = 6.6 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.06, 164.15, 149.72, 147.97, 141.71, 141.57, 137.23, 136.84, 129.85, 126.40, 125.99, 122.01, 120.37, 37.83, 33.70, 20.87; ESI/MS: 324.1 $[M+H]^+$.

***N*-(3-([1,1'-Biphenyl]-4-yl(methyl)carbamoyl)but-3-en-1-yl)picolinamide (1c)**



Compound **1c** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.7, 0.7 Hz, 1H), 8.29 (br, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.55-7.47 (m, 4H), 7.47-7.39 (m, 2H), 7.38 -7.32 (m, 2H), 7.22-7.16 (m, 2H), 5.22 (s, 1H), 5.15 (s, 1H), 3.64 (dd, *J* = 12.8, 6.6 Hz, 2H), 3.38 (s, 3H), 2.49 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.29, 164.28, 149.87, 148.06, 143.62, 141.84, 140.01, 137.56, 128.96, 128.08, 127.72, 127.11, 127.08, 126.19, 122.37, 120.99, 77.41, 77.16, 76.91, 38.06, 33.90; ESI/MS: 386.1 $[M+H]^+$.

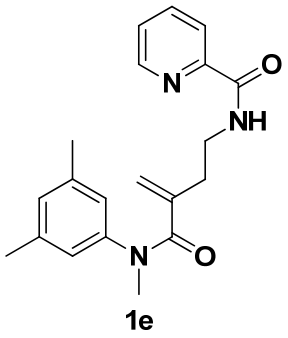
***N*-(3-((4-Methoxyphenyl)(methyl)carbamoyl)but-3-en-1-yl)picolinamide (1d)**



Compound **1d** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.1 Hz, 1H), 8.25 (br, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.15 (s, 1H), 5.07 (s, 1H), 3.75 (s, 3H), 3.59 (q, *J* = 6.5 Hz, 2H), 3.30 (s, 3H), 2.42 (t, *J* = 6.5 Hz, 2H); ^{13}C

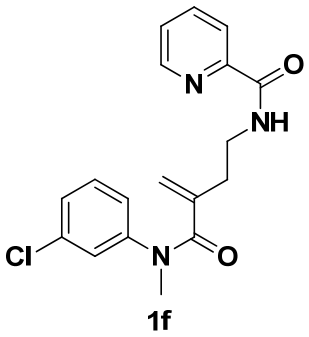
NMR (125 MHz, $CDCl_3$) δ 171.38, 164.19, 158.51, 149.87, 148.00, 142.05, 137.68, 137.25, 128.10, 126.23, 122.43, 120.47, 114.62, 55.52, 38.10, 34.01；ESI/MS: 340.1 $[M+H]^+$.

***N*-(3-((3,5-Dimethylphenyl)(methyl)carbamoyl)but-3-en-1-yl)picolinamide (1e)**



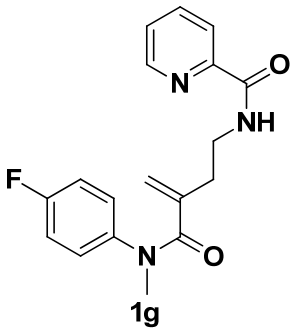
Compound **1e** was prepared in a similar manner as described for compound **1a**. ^1H NMR (400 MHz, $CDCl_3$) δ 8.55-8.50 (m, 1H), 8.28 (br, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.40 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.85 (s, 1H), 6.72 (s, 2H), 5.15 (s, 1H), 5.10 (s, 1H), 3.60 (q, *J* = 6.6 Hz, 2H), 3.30 (s, 3H), 2.43 (t, *J* = 6.6 Hz, 2H), 2.25 (s, 6H)；^{13}C NMR (125 MHz, $CDCl_3$) δ 171.23, 164.29, 149.94, 148.08, 144.29, 141.91, 139.21, 137.52, 128.88, 126.19, 124.51, 122.32, 120.53, 38.17, 38.07, 33.96, 21.25；ESI/MS: 338.1 $[M+H]^+$.

***N*-(3-((3-Chlorophenyl)(methyl)carbamoyl)but-3-en-1-yl)picolinamide (1f)**



Compound **1f** was prepared in a similar manner as described for compound **1a**. ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.0 Hz, 1H), 8.28 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.83 (t, *J* = 7.7 Hz, 1H), 7.43-7.38 (m, 1H), 7.24-7.13 (m, 3H), 7.01 (d, *J* = 7.2 Hz, 1H), 5.23 (s, 1H), 5.10 (s, 1H), 3.62 (q, *J* = 6.5 Hz, 2H), 3.33 (s, 3H), 2.47 (t, *J* = 6.7 Hz, 2H)；^{13}C NMR (100 MHz, $CDCl_3$) δ 171.08, 164.44, 149.95, 148.24, 145.60, 141.52, 137.39, 134.87, 130.40, 127.35, 126.97, 126.20, 125.07, 122.23, 121.19, 38.09, 38.02, 33.91；ESI/MS: 344.0 $[M+H]^+$.

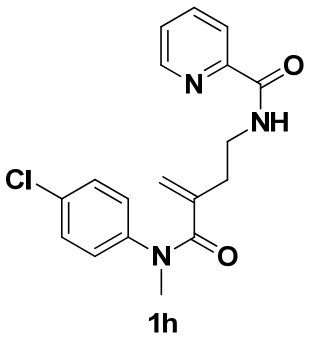
N-(3-((4-Fluorophenyl)(methyl)carbamoyl)but-3-en-1-yl)picolinamide (1g). General experimental procedure for 1g-k and 1m.



n-BuLi (0.38 mL, 2.4 M in hexanes) was added to a solution of 4-fluoro-*N*-methylaniline (0.13 g, 0.99 mmol) at -78 °C. The resulting solution was warmed to -20 °C for an additional 1 h and added to an ice-cooled solution of 2-methylene-4-(picolinamido)butanoic acyl chloride, which was prepared from the 2-methylene-4-(picolinamido)butanoic acid **S5** (200 mg, 0.91 mmol) according to a similar procedure as described for compound 1a. Stirring was continued for 24 h. The mixture was diluted with DCM. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by silica gel column using 0-100% ethyl acetate in petroleum ether as eluent to give the title compound in 34%

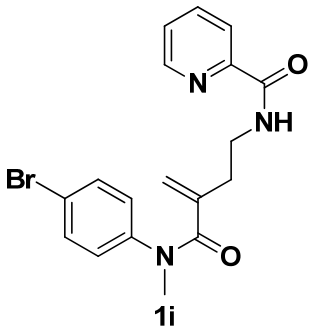
yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.1 Hz, 1H), 8.28-8.13 (m, 2H), 7.83 (t, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.12-7.08 (m, 2H), 6.99-6.95 (m, 2H), 5.19 (s, 1H), 5.06 (s, 1H), 3.60 (q, *J* = 6.5 Hz, 2H), 3.31 (s, 3H), 2.44 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.23, 164.46, 161.35 (d, *J* = 245 Hz, 1C) 149.95, 148.29, 141.75, 140.46, 137.40, 128.64, 128.57, 126.24, 122.22, 120.76, 116.51, 116.32, 38.17, 37.92, 33.98; ESI/MS:328.1 $[M+H]^+$.

***N*-(3-((4-Chlorophenyl)(methyl)carbamoyl)but-3-en-1-yl)picolinamide (1h)**



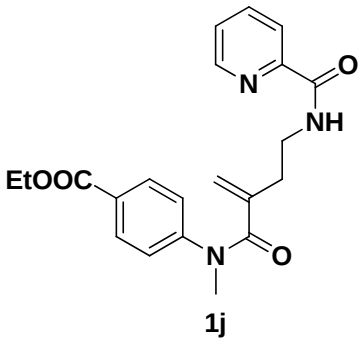
Compound **1h** was prepared in a similar manner as described for compound **1g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.7 Hz, 1H), 8.23 (br, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.45-7.40 (m, 1H), 7.29-7.23 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 5.21 (s, 1H), 5.07 (s, 1H), 3.62 (q, *J* = 6.2 Hz, 2H), 3.32 (s, 3H), 2.47 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.09, 164.47, 149.98, 148.32, 143.06, 141.65, 137.41, 132.86, 129.70, 128.11, 126.24, 122.24, 121.09, 38.04, 37.95, 33.96; ESI/MS: 344.0 $[M+H]^+$.

***N*-(3-((4-Bromophenyl)(methyl)carbamoyl)but-3-en-1-yl)picolinamide (1i)**



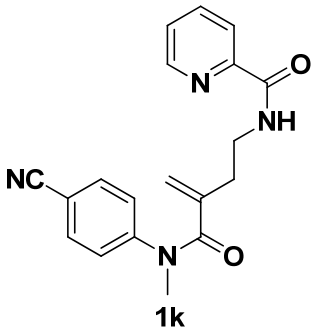
Compound **1i** was prepared in a similar manner as described for compound **1g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.2 Hz, 1H), 8.28-8.11 (m, 2H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.43-7.37 (m, 3H), 6.99 (d, *J* = 8.8 Hz, 2H), 5.21 (s, 1H), 5.06 (s, 1H), 3.60 (q, *J* = 6.5 Hz, 2H), 3.30 (s, 3H), 2.46 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.00, 164.43, 149.88, 148.30, 143.50, 141.51, 137.38, 132.64, 128.38, 126.23, 122.18, 121.18, 120.69, 37.95, 37.90, 33.87; ESI/MS:388.0 $[M+H]^+$.

Ethyl 4-(*N*-methyl-2-methylene-4-(picolinamido)butanamido)benzoate (1j)



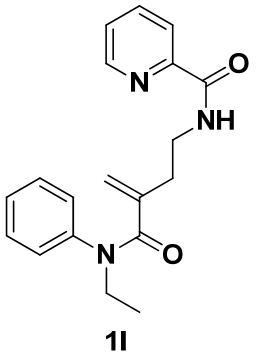
Compound **1i** was prepared in a similar manner as described for compound **1g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (ddd, *J* = 4.7, 1.6, 0.8 Hz, 1H), 8.23 (br, 1H), 8.14 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 2H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.39 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 5.20 (s, 1H), 5.06 (s, 1H), 3.87 (s, 3H), 3.61 (q, *J* = 6.6 Hz, 2H), 3.35 (s, 3H), 2.46 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.92, 166.12, 164.33, 149.80, 148.48, 148.18, 141.45, 137.26, 130.77, 128.39, 126.19, 126.10, 122.07, 121.35, 52.21, 37.84, 37.66, 33.65; ESI/MS: 368.0 $[M+H]^+$.

***N*-(3-((4-Cyanophenyl)(methyl)carbamoyl)but-3-en-1-yl)picolinamide (1k)**



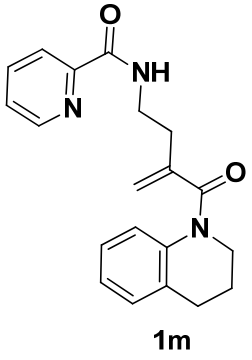
Compound **1k** was prepared in a similar manner as described for compound **1g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 2.9 Hz, 1H), 8.26-8.08 (m, 2H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.44-7.35 (m, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 5.25 (s, 1H), 5.06 (s, 1H), 3.60 (q, *J* = 6.3 Hz, 2H), 3.32 (s, 3H), 2.48 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.86, 163.35, 148.67, 147.33, 147.19, 140.25, 136.41, 132.26, 125.86, 125.30, 121.10, 120.63, 117.14, 109.21, 76.48, 76.16, 75.84, 36.76, 36.69, 32.58; ESI/MS: 335.1 $[M+H]^+$.

***N*-(3-(Ethyl(phenyl)carbamoyl)but-3-en-1-yl)picolinamide (1l)**



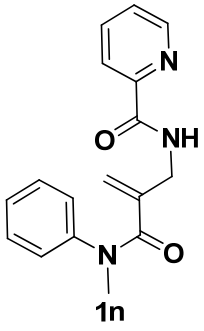
Compound **1k** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.7 Hz, 1H), 8.27 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.40 (dd, *J* = 6.8, 5.5 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 2H), 5.13 (s, 1H), 5.06 (s, 1H), 3.83 (q, *J* = 7.1 Hz, 2H), 3.60 (q, *J* = 6.5 Hz, 2H), 2.43 (t, *J* = 6.6 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.66, 164.41, 149.97, 148.20, 142.64, 142.07, 137.28, 129.36, 127.92, 127.28, 126.10, 122.12, 120.39, 44.84, 37.96, 33.94, 12.95; ESI/MS: 324.1 $[M+H]^+$.

***N*-(3-(1,2,3,4-Tetrahydroquinoline-1-carbonyl)but-3-en-1-yl)picolinamide (1m)**



Compound **1k** was prepared in a similar manner as described for compound **1g**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.31 (t, *J* = 5.3 Hz, 1H), 8.13 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 7.37 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.24-7.17 (m, 1H), 7.10-7.06 (m, 1H), 7.04-6.99 (m, 2H), 5.29 (s, 1H), 5.23 (s, 1H), 3.77 (t, *J* = 6.0 Hz, 2H), 3.63 (q, *J* = 6.7 Hz, 2H), 2.71 (t, *J* = 6.7 Hz, 2H), 2.50 (t, *J* = 6.7 Hz, 2H), 1.92 (p, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.79, 164.38, 149.83, 148.16, 142.62, 138.66, 137.27, 131.43, 128.54, 126.11, 125.91, 124.98, 124.47, 122.09, 120.15, 44.34, 38.06, 33.53, 26.72, 23.96; ESI/MS: 336.1 $[M+H]^+$.

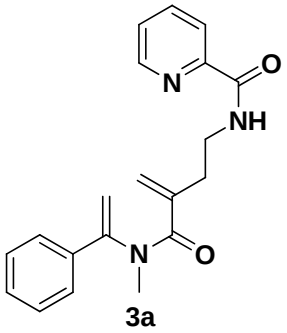
***N*-(2-(Methyl(phenyl)carbamoyl)allyl)picolinamide (1n)**



Compound **1n** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58-8.51 (m, 1H), 8.39 (br, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.85-7.78 (m, 1H), 7.41-7.38 (m, 1H), 7.31-7.28 (m, 2H), 7.24-7.19 (m, 1H), 7.15-7.10 (m, 2H), 5.30 (s, 1H), 5.04 (s, 1H), 4.17 (d, *J* = 6.2 Hz, 2H), 3.35 (d, *J* = 1.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.95, 164.26, 149.77, 148.28, 144.29, 140.55, 137.35, 129.46, 127.26, 126.73, 126.26,

122.25, 120.63, 42.14, 38.01； ESI/MS: 296.1 $[M+H]^+$.

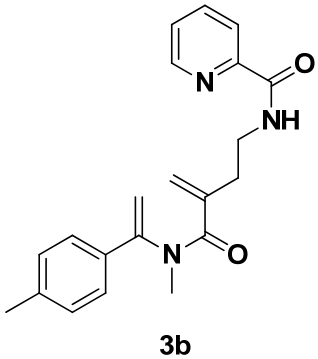
N-(3-(Methyl(1-phenylvinyl)carbamoyl)but-3-en-1-yl)picolinamide (3a). General experimental procedure for 3a-e.



3a

To an ice-cooled solution of 2-methylene-4-(picolinamido)bu--tanoic acid **S5** (1.0 g, 4.54 mmol) in 20 mL of DCM was added catalytic amount of DMF was added dropwise oxalyl chloride (0.47 mL, 5.45 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 2 h and concentrated under vacuum to afford the crude acyl chloride, which was suspended in 20 mL of DCM. Potassium carbonate (1.88 g, 13.62 mmol) was added to this suspension, followed by dropwise addition of *N*-(1-phenylethylidene)methanamine [S1] (0.73 g, 5.45 mmol). Stirring was continued for 1 h at 0 ^oC. The mixture was diluted with DCM. The organic phase was washed with water and brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by neutral Al_2O_3 column using 33% ethyl acetate in petroleum ether as eluent to give the title compound in 50% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.30 (br, 1H), 8.20 -8.15 (m, 1H), 7.84 (td, J = 7.7, 1.7 Hz, 1H), 7.44-7.31 (m, 6H), 5.49 (d, J = 0.6 Hz, 1H), 5.36 (s, 1H), 5.15 (s, 1H), 5.10 (s, 1H), 3.56 (q, J = 6.7 Hz, 2H), 3.20 (s, 3H), 2.42 (t, J = 6.7 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.09, 164.82, 151.12, 149.63, 149.59, 143.62, 139.01, 137.19, 130.05, 129.99, 127.70, 127.06, 123.01, 117.94, 112.80, 38.63, 34.27; ESI/MS: 336.1 $[M+H]^+$.

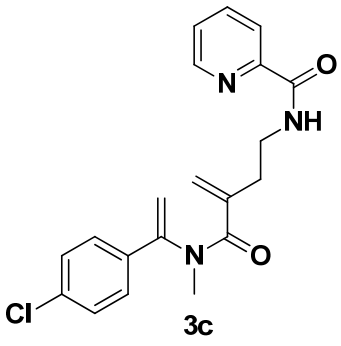
_N_-(3-(Methyl(1-(p-tolyl)vinyl)carbamoyl)but-3-en-1-yl)picolinamide (3b).



3b

Compound **3b** was prepared in a similar manner as described for compound **3a**. ^1H NMR (400 MHz, DMSO-d_6) δ 8.72-8.60 (m, 2H), 8.06-7.94 (m, 2H), 7.59 (ddd, J = 7.2, 4.8, 1.7 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 5.59 (s, 1H), 5.19 (s, 1H), 5.12 (s, 2H), 3.38 (q, J =7.0 Hz, 2H), 3.03 (s, 3H), 2.36 (t, J = 7.0 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.81, 163.55, 149.88, 148.38, 148.21, 142.39, 138.29, 137.76, 133.00, 129.38, 126.45, 125.74, 121.75, 116.47, 110.70, 37.37, 33.06, 20.70; ESI/MS: 350.1 $[M+H]^+$.

_N_-(3-((1-(4-Chlorophenyl)vinyl)(methyl)carbamoyl)but-3-en-1-yl)picolinamide (3c)

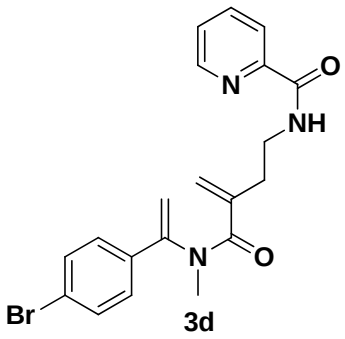


3c

Compound **3c** was prepared in a similar manner as described for compound **3a**. ^1H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, J = 6.0 Hz, 1H), 8.64-8.61 (m, 1H),

8.04-7.95 (m, 2H), 7.62-7.58 (m, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H), 5.69 (s, 1H), 5.25 (s, 1H), 5.19 (s, 1H), 5.15 (s, 1H), 3.42-3.35 (m, 2H), 3.06 (s, 3H), 2.36 (t, J = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.80, 163.61, 149.88, 148.43, 147.26, 142.34, 137.82, 134.92, 133.30, 128.83, 127.66, 126.52, 121.81, 116.83, 112.51, 37.36, 33.04; ESI/MS: 370.0 $[M+H]^+$.

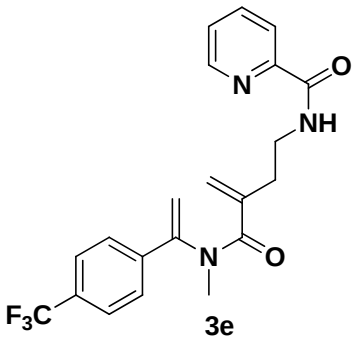
***N*-(3-((1-(4-Bromophenyl)vinyl)(methyl)carbamoyl)but-3-en-1-yl)picolinamide (3d)**



3d

Compound **3d** was prepared in a similar manner as described for compound **3a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, J = 5.5 Hz, 1H), 8.63 (ddd, J = 4.8, 1.6, 1.0 Hz, 1H), 8.05-7.94 (m, 2H), 7.62-7.54 (m, 3H), 7.41 (d, J = 8.8 Hz, 2H), 5.70 (s, 1H), 5.25 (s, 1H), 5.19 (s, 1H), 5.15 (s, 1H), 3.38 (q, J = 7.0 Hz, 2H), 3.05 (s, 3H), 2.36 (t, J = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.75, 163.58, 149.86, 148.38, 147.32, 142.30, 137.76, 135.25, 131.71, 127.88, 126.46, 121.91, 121.76, 116.82, 112.49, 37.35, 33.03; ESI/MS: 414.0 $[M+H]^+$.

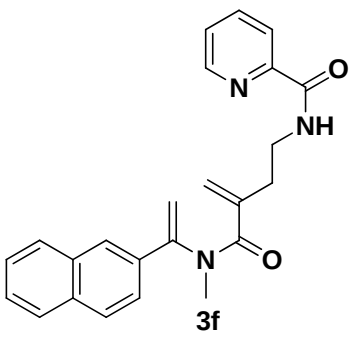
***N*-(3-(Methyl(1-(4-(trifluoromethyl)phenyl)vinyl)carbamoyl)but-3-en-1-yl)picolinamide (3e)**



3e

Compound **3e** was prepared in a similar manner as described for compound **3a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (t, J = 6.4 Hz, 1H), 8.63 (ddd, J = 4.8, 1.6, 1.0 Hz, 1H), 8.05-7.96 (m, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.59 (ddd, J = 7.1, 4.8, 1.8 Hz, 1H), 5.82 (s, 1H), 5.38 (s, 1H), 5.21 (s, 1H), 5.17 (s, 1H), 3.38 (q, J = 7.0 Hz, 2H), 3.09 (s, 3H), 2.36 (t, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.79, 163.61, 149.87, 148.42, 147.11, 142.29, 140.11, 137.82, 126.59, 126.52, 125.73, 125.20, 121.80, 117.06, 114.27, 37.33, 33.02; ESI/MS: 404.0 $[M+H]^+$.

***N*-(3-(Methyl(1-(naphthalen-2-yl)vinyl)carbamoyl)but-3-en-1-yl)picolinamide (3f)**



3f

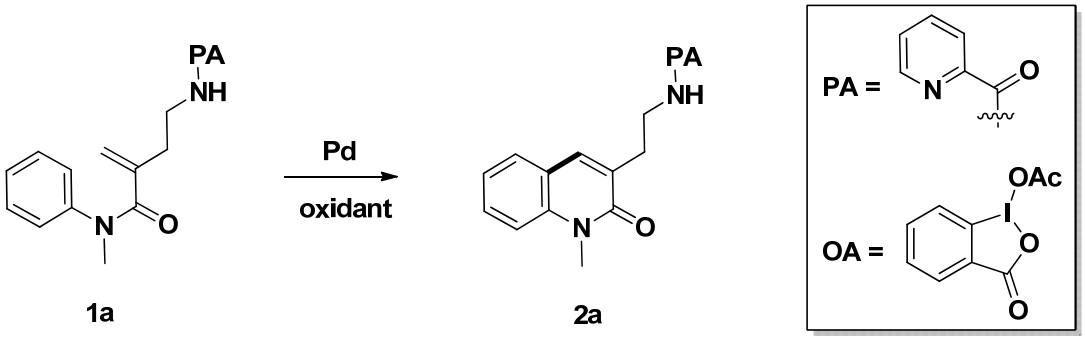
Compound **3f** was prepared in a similar manner as described for compound **3a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71-8.60 (m, 2H), 8.03-7.95 (m, 4H), 7.94-7.87 (m, 2H), 7.67 (dd, J = 8.7, 1.9 Hz, 1H), 7.58 (ddd, J = 7.1, 4.8, 1.7 Hz, 1H), 7.54-7.49 (m, 2H), 5.83 (s, 1H), 5.30 (s, 1H), 5.26 (s, 1H), 5.12 (s, 1H), 3.40 (q, J = 6.9 Hz, 2H), 3.13 (s, 3H), 2.39 (t, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.89, 163.55, 149.85, 148.36, 148.24, 142.38, 137.74, 133.11, 132.88,

128.44, 127.42, 126.66, 126.55, 126.43, 124.82, 123.71, 121.75, 116.60, 112.47, 37.43, 33.17；ESI/MS: 386.1 $[M+H]^+$.

General procedures for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H (2a-n)

A Schlenk tube equipped with a magnetic stir bar was charged with $PdBr_2$ (2.5-5% mmol), 3-oxo-3*H*-1λ³,2-benziodaoxol-1-yl acetate (153 mg, 0.50 mmol) and substrates **1a-n** (0.20 mmol) and then capped with septa. The vial was evacuated and backfilled with argon and the process was repeated three times. Under argon, 2 mL of xylene was charged to the vial via syringe, and then the resulting mixture was stirred in a pre-heated 110 °C oil bath for 48 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The collected organic phase was washed with aq. Na_2CO_3, water and brine, dried over anhydrous Na_2SO_4, concentrated under vaccum. The residue was purified by silica gel column chromatography.

Table S1. Optimization of palladium catalyzed C(sp^2)-H/C(sp^2)-H coupling of *N*-arylacrylamide.[a]

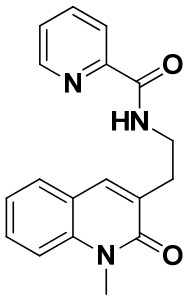


Entry	Pd (mol%)	Oxidant (equiv)	Solvent	Time (h)	T (^oC)	Yield %[b]
1	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	Toluene	24	80	32
2	$Pd(OAc)_2$ (10)	$PhI(TFA)_2$ (2)	Toluene	24	80	0
3	$Pd(OAc)_2$ (10)	$PhI(OPiv)_2$ (2)	Toluene	24	80	29
4	$Pd(OAc)_2$ (10)	$K_2S_2O_4$ (2)	Toluene	24	80	0
5	$Pd(OAc)_2$ (10)	O_2	Toluene	24	80	0
6	$Pd(OAc)_2$ (10)	OA (2)	Toluene	24	80	34
7	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	Toluene	36	100	34
8	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)/K_2CO_3 (2)	Toluene	36	100	7
9	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	CH_3CN	36	100	27
10	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	DCE	36	100	41
11	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$	DCE	36	100	0
12	$Pd(OAc)_2$ (10)	Ag_2CO_3	DCE	36	100	0
13	$Pd(OAc)_2$ (2.5)	OA (2.5)	Toluene	36	110	49
14	$Pd(OAc)_2$ (2.5)	OA (2.5)	$PhCF_3$	48	110	48

15	$Pd(OAc)_2$ (2.5)	OA (2.5)	Xylene	48	110	61
16	$PdCl_2$ (2.5)	OA (2.5)	Xylene	48	110	49%
17	$PdCl_2(MeCN)_2$ (2.5)	OA (2.5)	Xylene	48	110	43%
18	$Pd(acac)_2$ (2.5)	OA (2.5)	Xylene	48	110	63%
19	$PdBr_2$ (2.5)	OA (2.5)	Xylene	48	110	65%(60)[c]

[a] General reaction conditions: **1a** (0.2 mmol), Pd (mol%), oxidant (equiv), solvent (2.0 mL). [b] Determined by ^1H NMR analysis using CH_2Br_2 as an internal standard. [c] Yields of isolated products are given in parentheses.

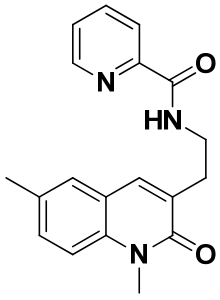
***N*-(2-(1-Methyl-2-oxo-1, 2-dihydroquinolin-3-yl)ethyl)picolinamide (2a)**



2a

Compound **2a** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 60%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52-8.46 (d, *J* = 4.8 Hz, 1H), 8.36 (br, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.79 (td, *J* = 7.7, 1.5 Hz, 1H), 7.60 (s, 1H), 7.51-7.46 (m, 2H), 7.38-7.34 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 3.78 (q, *J* = 6.7 Hz, 2H), 3.72 (s, 3H), 2.98 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.62, 162.61, 150.04, 148.20, 139.33, 137.33, 136.85, 130.63, 129.91, 128.38, 126.13, 122.24, 122.21, 120.62, 114.03, 38.61, 31.69, 29.87; ESI/MS: 308.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{18}H_{18}N_3O_2$ ($[M+H]^+$): 308.1399; found: 308.1394.

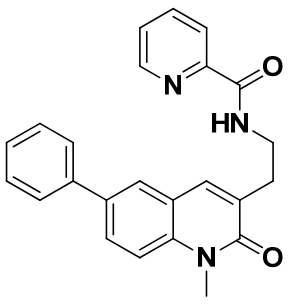
***N*-(2-(1,6-Dimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2b)**



2b

Compound **2b** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 45%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.5 Hz, 1H), 8.37 (br, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.56 (s, 1H), 7.41-7.36 (m, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.28 (s, 1H), 7.24 (t, *J* = 8.6 Hz, 1H), 3.80 (q, *J* = 6.6 Hz, 2H), 3.73 (s, 3H), 2.99 (t, *J* = 6.8 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.66, 162.57, 150.12, 148.25, 137.42, 137.36, 136.68, 131.81, 131.19, 130.60, 128.22, 126.15, 122.25, 120.64, 113.98, 38.70, 31.77, 29.90, 20.69; ESI/MS: 322.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{19}H_{20}N_3O_2$ ($[M+H]^+$): 322.1556; found: 322.1550.

***N*-(2-(1-Methyl-2-oxo-6-phenyl-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2c)**

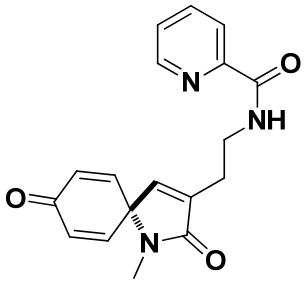


2c

Compound **2c** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 62%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.54-8.49 (m, 1H), 8.37 (br, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.76 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.73-7.67 (m, 2H), 7.61-7.59 (m, 2H), 7.49-7.33 (m, 5H), 3.82 (q, *J* = 6.8 Hz, 2H), 3.79 (s, 3H), 3.02

(t, J = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.67, 162.58, 150.09, 148.25, 139.89, 138.71, 137.38, 136.94, 135.32, 131.14, 129.08, 128.90, 127.54, 127.03, 126.48, 126.18, 122.26, 120.97, 114.59, 38.60, 31.82, 30.02; ESI/MS: 384.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{24}H_{22}N_3O_2$ ($[M+H]^+$): 384.1712; found: 384.1707.

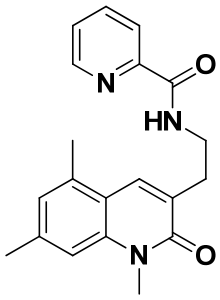
***N*-(2-(1-Methyl-2,8-dioxo-1-azaspiro[4.5]deca-3,6,9-trien-3-yl)ethyl)picolinamide (2d)**



2d

Compound **2d** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.6 Hz, 1H), 8.27 (br, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.84 (t, J = 7.7 Hz, 1H), 7.46-7.39 (m, 1H), 6.41 (d, J = 9.8 Hz, 2H), 6.35 (s, 1H), 6.33 (d, J = 9.6 Hz, 2H), 3.72 (q, J = 6.5 Hz, 2H), 2.83 (s, 3H), 2.71 (t, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.18, 170.71, 164.57, 149.73, 148.23, 145.57, 140.06, 137.81, 137.57, 132.47, 126.42, 122.27, 64.86, 37.27, 26.96, 26.03; ESI/MS: 324.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{18}H_{18}N_3O_3$ ($[M+H]^+$): 324.1348; found: 324.1343.

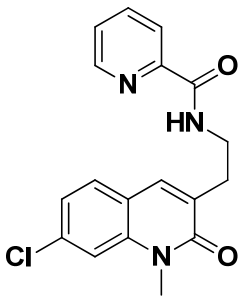
***N*-(2-(1,5,7-Trimethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2e)**



2e

Compound **2e** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 64%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br, 1H), 8.39 (br, 1H), 8.18 (br, 1H), 7.92-7.75 (m, 2H), 7.40 (br, 1H), 7.01 (s, 1H), 6.88 (s, 1H), 3.79 (dd, J = 12.7, 6.4 Hz, 2H), 3.74 (s, 3H), 3.00 (t, J = 6.5 Hz, 2H), 2.46 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 162.56, 148.17, 140.21, 139.93, 137.42, 135.60, 133.36, 128.59, 126.17, 125.34, 122.29, 117.12, 112.66, 38.76, 31.99, 30.12, 22.22, 19.07; ESI/MS: 336.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{20}H_{22}N_3O_2$ ($[M+H]^+$): 336.1712; found: 336.1707.

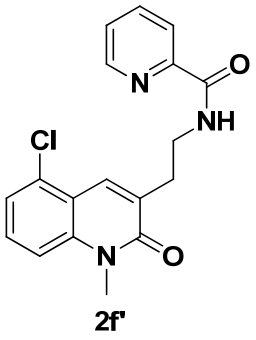
***N*-(2-(7-Chloro-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2f)**



2f

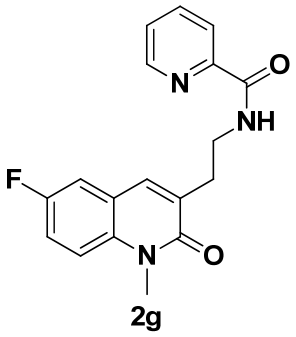
Compound **2f** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.33 (br, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.83 (t, J = 7.7 Hz, 1H), 7.58 (s, 1H), 7.45-7.36 (m, 2H), 7.33 (d, J = 1.6 Hz, 1H), 7.17 (dd, J = 8.3, 1.8 Hz, 1H), 3.79 (q, J = 6.5 Hz, 2H), 3.72 (s, 3H), 2.98 (t, J = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.56, 162.45, 149.96, 148.15, 140.19, 137.55, 136.21, 136.00, 130.91, 129.47, 126.27, 122.69, 122.36, 119.11, 114.18, 38.51, 31.74, 30.04; ESI/MS: 342.0 $[M+H]^+$, HRMS (ESI) calcd for $C_{18}H_{16}ClN_3O_2Na$ ($[M+H]^+$): 364.0829; found: 364.0839.

***N*-(2-(5-chloro-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2f′)**



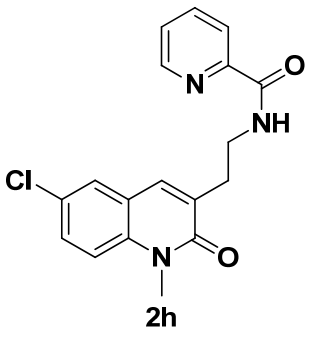
Compound **2f′** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.37 (br, 1H), 8.21-8.14 (m, 1H), 8.06 (s, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45-7.37 (m, 2H), 7.28-7.23 (m, 2H), 3.80 (q, *J* = 6.8 Hz, 2H), 3.75 (s, 3H), 3.03 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.63, 162.18, 150.03, 148.22, 140.62, 137.43, 132.86, 132.84, 131.91, 129.99, 126.21, 123.05, 122.29, 118.34, 113.06, 38.63, 32.07, 30.41; ESI/MS: 342.0 $[M+H]^+$, HRMS (ESI) calcd for $C_{18}H_{16}ClN_3O_2Na$ ($[M+H]^+$): 364.0829; found: 364.0839.

***N*-(2-(6-Fluoro-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2g)**

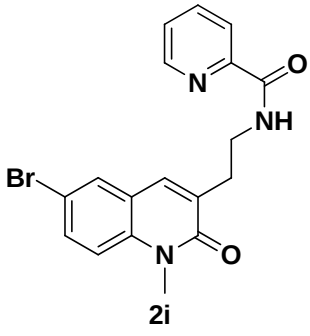


Compound **2g** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 44%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.1 Hz, 1H), 8.34 (br, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.56 (s, 1H), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.33-7.22 (m, 2H), 7.18 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.80 (q, *J* = 6.8 Hz, 2H), 3.75 (s, 3H), 3.00 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.62, 162.24, 157.95 (d, *J* = 241 Hz, 1C), 150.03, 148.21, 137.50, 136.00, 135.86, 132.33, 126.25, 122.33, 121.48 (d, *J* = 8 Hz, 1C), 117.64 (d, *J* = 24 Hz, 1C), 115.63 (d, *J* = 8 Hz, 1C), 113.32 (d, *J* = 22 Hz, 1C), 38.51, 31.85, 30.19; ESI/MS: 326.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{18}H_{17}FN_3O_2$ ($[M+H]^+$): 326.1305; found: 326.1299.

***N*-(2-(6-Chloro-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2h)**



Compound **2h** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 3.8 Hz, 1H), 8.33 (br, 1H), 8.19 (d, *J* = 7.5 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.54 (s, 1H), 7.49-7.39 (m, 3H), 7.28-7.26 (m, 1H), 3.80 (q, *J* = 6.4 Hz, 2H), 3.74 (s, 3H), 3.00 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.70, 162.24, 149.97, 148.20, 137.94, 137.50, 135.60, 132.24, 129.88, 127.66, 127.44, 126.26, 122.32, 121.66, 115.51, 38.43, 31.84, 30.07; ESI/MS: 342.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{18}H_{17}ClN_3O_2$ ($[M+H]^+$): 342.1009; found: 342.1004.

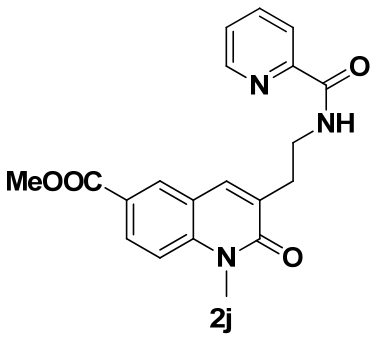


***N*-(2-(6-Bromo-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2i)**

Compound **2i** was prepared as described in general

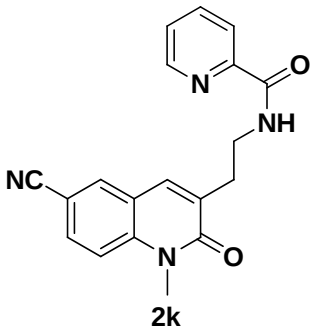
procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.8 Hz, 1H), 8.39 (s, 1H), 8.21 (d, *J* = 7.4 Hz, 1H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.64-7.57 (m, 2H), 7.54 (s, 1H), 7.48-7.41 (m, 1H), 7.21 (d, *J* = 8.9 Hz, 1H), 3.81 (q, *J* = 6.4 Hz, 2H), 3.73 (s, 3H), 3.00 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.61, 162.25, 150.01, 148.21, 138.34, 137.42, 135.53, 132.62, 132.21, 130.50, 126.23, 122.30, 122.14, 115.80, 115.03, 38.44, 31.84, 30.05; ESI/MS: 386.0 $[M+H]^+$, HRMS (ESI) calcd for $C_{18}H_{16}BrN_3O_2Na$ ($[M+Na]^+$): 408.0318; found: 408.0314; $C_{18}H_{16}{}^{81}BrN_3O_2Na$ ($[M+Na]^+$) 410.0298; found: 410.0284.

Methyl-methyl-2-oxo-3-(2-(picolinamido)ethyl)-1,2-dihydroquinoline-6-carboxyl ate (2j)



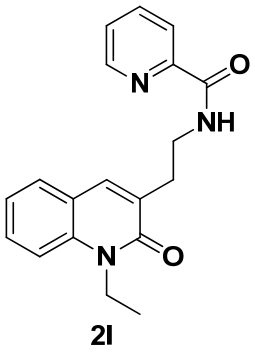
Compound **2j** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 59%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.31 (br, 1H), 8.22 -8.12 (m, 3H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.65 (s, 1H), 7.43-7.34 (m, 2H), 3.93 (s, 3H), 3.80 (q, *J* = 6.7 Hz, 2H), 3.77 (s, 3H), 3.00 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.43, 164.63, 162.67, 150.02, 148.23, 142.35, 137.43, 136.82, 131.69, 130.69, 130.44, 126.23, 124.02, 122.29, 120.09, 114.07, 52.37, 38.37, 31.80, 30.18; ESI/MS: 366.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{20}H_{20}N_3O_4$ ($[M+H]^+$): 366.1454; found: 366.1448.

***N*-(2-(6-Cyano-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2k)**



Compound **2k** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.7 Hz, 1H), 8.28 (br, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.6 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.73 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.61 (s, 1H), 7.43-7.39 (m, 2H), 3.80 (q, *J* = 6.7 Hz, 2H), 3.76 (s, 3H), 3.00 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.68, 162.33, 149.91, 148.24, 141.91, 137.51, 135.58, 133.12, 132.73, 132.44, 126.35, 122.32, 120.68, 118.53, 115.00, 105.74, 38.18, 31.84, 30.21; ESI/MS: 333.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{19}H_{17}N_4O_2$ ($[M+H]^+$): 333.1352; found: 333.1346.

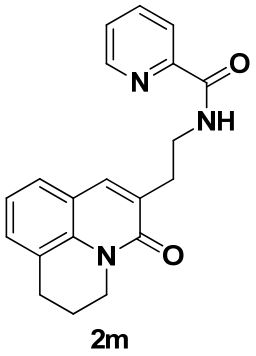
***N*-(2-(1-Ethyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)picolinamide (2l)**



Compound **2l** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.6 Hz, 1H), 8.39 (br, 1H), 8.17 (d,

J = 7.7 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.62 (s, 1H), 7.53-7.49 (dd, *J* = 7.3, 5.4 Hz, 2H), 7.44-7.32 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 3.80 (q, *J* = 6.6 Hz, 2H), 3.00 (t, *J* = 6.8 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.61, 162.16, 150.10, 148.18, 138.37, 137.39, 136.81, 130.77, 129.89, 128.68, 126.14, 122.26, 122.02, 120.98, 113.92, 38.85, 37.82, 31.40, 12.84; ESI/MS: 322.2 $[M+H]^+$, HRMS (ESI) calcd for $C_{19}H_{20}N_3O_2$ ($[M+H]^+$): 322.1556; found: 322.1550.

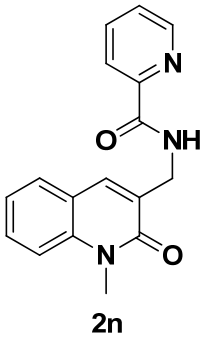
***N*-(2-(3-Oxo-3,5,6,7-tetrahydropyrido[3,2,1-ij]quinolin-2-yl)ethyl)picolinamide (2m)**



2m

Compound **2m** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 35%; H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.0 Hz, 1H), 8.37 (br, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.62 (s, 1H), 7.44-7.37 (m, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.28-7.23 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 4.26-4.18 (m, 2H), 3.81 (q, *J* = 6.6 Hz, 2H), 3.05-2.94 (m, 4H), 2.18-2.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.62, 162.13, 150.11, 148.24, 137.40, 136.78, 136.06, 130.29, 129.16, 126.24, 126.17, 124.80, 122.28, 121.88, 120.48, 42.66, 38.69, 31.58, 27.59, 20.90; ESI/MS: 334.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{20}H_{20}N_3O_2$ ($[M+H]^+$): 334.1556; found: 334.1550.

***N*-((1-Methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)picolinamide (2n)**



2n

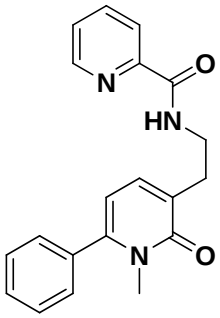
Compound **2n** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Aryl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br, 1H), 8.57 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.18 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.87-7.78 (m, 2H), 7.59-7.49 (m, 2H), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.22 (td, *J* = 7.6, 1.0 Hz, 1H), 4.66 (dd, *J* = 6.5, 0.8 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.64, 162.36, 149.98, 148.35, 139.52, 137.44, 136.58, 130.42, 129.28, 129.01, 126.30, 122.45, 122.41, 120.44, 114.11, 40.23, 29.76; ESI/MS: 294.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{17}H_{16}N_3O_2$ ($[M+H]^+$): 293.1243; found: 294.1237.

General procedures for palladium catalyzed picolinamide-directed coupling of Akenyl C(sp^2)-H and Alkenyl C(sp^2)-H (4a-f)

A Schlenk tube equipped with a magnetic stir bar was charged with $PdBr_2$ (2.5-5% mmol), 3-oxo-3*H*-1λ³,2-benziodaoxol-1-yl acetate (122 mg, 0.40 mmol) and substrates **3a-e** (0.20 mmol) and then capped with septa. The vial was evacuated and backfilled with argon and the process was repeated three times. Under argon, 2 mL of

xylene was charged to the vial via syringe, and then the resulting mixture was stirred in a pre-heated 80 °C oil bath for 24 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The collected organic phase was washed with aq. Na_2CO_3, water and brine, dried over anhydrous Na_2SO_4, concentrated under vaccum. The residue was purified by silica gel column chromatography.

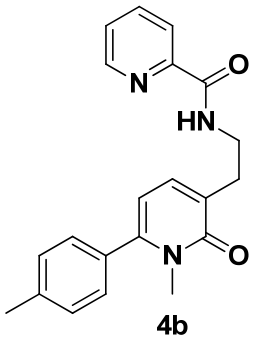
***N*-(2-(1-Methyl-2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)ethyl)picolinamide (4a)**



4a

Compound **4a** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Alkenyl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 45%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.7, 0.8 Hz, 1H), 8.44 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47-7.37 (m, 4H), 7.33-7.26 (m, 3H), 6.05 (d, *J* = 7.0 Hz, 1H), 3.76 (q, *J* = 6.7 Hz, 2H), 3.39 (s, 3H), 2.92 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.57, 163.80, 150.15, 148.40, 148.19, 137.38, 136.91, 135.70, 129.25, 128.78, 128.58, 128.37, 126.10, 122.26, 107.59, 38.76, 34.76, 31.41; ESI/MS: 334.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{20}H_{19}N_3O_2Na$ ($[M+Na]^+$): 356.1375; found: 356.1374.

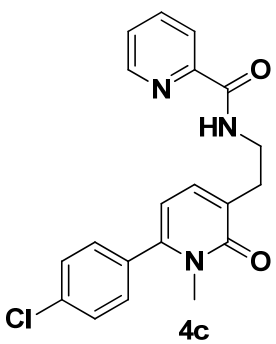
***N*-(2-(1-Methyl-2-oxo-6-(p-tolyl)-1,2-dihydropyridin-3-yl)ethyl)picolinamide (4b)**



4b

Compound **4b** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Alkenyl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.2 Hz, 1H), 8.44 (br, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.83 (td, *J* = 7.7, 1.6 Hz, 1H), 7.40 (dd, *J* = 6.5, 4.8 Hz, 1H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.26-7.19 (m, 4H), 6.05 (d, *J* = 7.0 Hz, 1H), 3.77 (q, *J* = 6.7 Hz, 2H), 3.40 (s, 3H), 2.92 (t, *J* = 6.8 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.62, 163.92, 150.25, 148.59, 148.25, 139.34, 137.39, 136.95, 132.93, 129.46, 128.52, 128.16, 126.11, 122.29, 107.58, 38.83, 34.77, 31.45, 21.42; ESI/MS: 348.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{21}H_{21}N_3O_2Na$ ($[M+Na]^+$): 370.1531; found: 370.1540.

***N*-(2-(6-(4-Chlorophenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)ethyl)picolina mide (4c)**

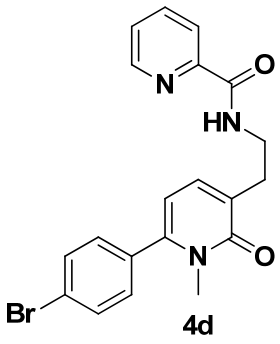


4c

Compound **4c** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Alkenyl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 42%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.1 Hz, 1H), 8.46 (br, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46-7.40 (m, 3H), 7.30-7.26 (m, 3H), 6.04 (d, *J* = 7.0 Hz, 1H), 3.77 (q, *J* = 6.7 Hz, 2H), 3.39 (s, 3H), 2.93 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.29, 163.77, 149.94, 147.89, 147.14, 137.85, 136.84, 135.55, 134.12, 130.02, 129.16,

128.95, 126.26, 122.58, 107.71, 38.82, 34.76, 31.42; ESI/MS: 368.0 $[M+H]^+$, HRMS (ESI) calcd for $C_{20}H_{18}ClN_3O_2Na$ ($[M+Na]^+$): 390.0985; found: 390.0996.

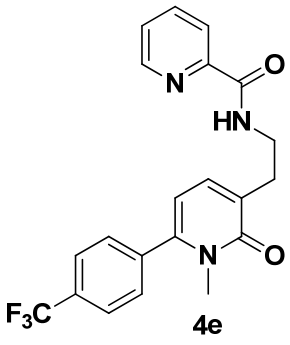
***N*-(2-(6-(4-Bromophenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)ethyl)picolinamide (4d)**



4d

Compound **4d** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Alkenyl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61-8.43 (m, 2H), 8.21 (d, *J* = 7.7 Hz, 1H), 7.87 (t, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.47-7.39 (m, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.04 (d, *J* = 7.0 Hz, 1H), 3.77 (q, *J* = 6.7 Hz, 2H), 3.39 (s, 3H), 2.93 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.78, 149.54, 147.44, 147.17, 138.47, 136.91, 134.58, 132.12, 130.27, 128.95, 126.43, 123.73, 122.93, 107.69, 38.95, 34.78, 31.38, 0.12; ESI/MS: 412.0 $[M+H]^+$, HRMS (ESI) calcd for $C_{20}H_{18}BrN_3O_2Na$ ($[M+Na]^+$): 434.0480; found: 434.0482.

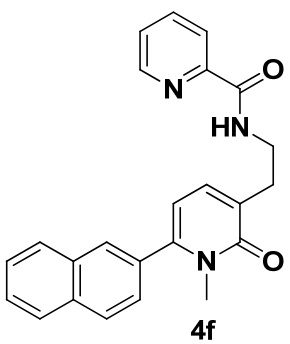
***N*-(2-(1-Methyl-2-oxo-6-(4-(trifluoromethyl)phenyl)-1,2-dihydropyridin-3-yl)ethyl)picolinamide (4e)**



4e

Compound **4d** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Alkenyl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 40%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64-8.38 (m, 2H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.88 (t, *J* = 7.4 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.52-7.41 (m, 3H), 7.32 (d, *J* = 7.0 Hz, 1H), 6.07 (d, *J* = 6.9 Hz, 1H), 3.79 (q, *J* = 6.5 Hz, 2H), 3.39 (s, 3H), 2.95 (t, *J* = 6.7 Hz, 2H)；^{13}C NMR (125 MHz, $CDCl_3$) δ 164.55, 163.68, 150.06, 148.16, 146.74, 139.11, 137.59, 136.79, 131.43 (q, *J* = 33 Hz, 1C), 129.48, 129.16, 126.24, 125.95, 125.92, 123.83 (q, *J* = 270 Hz, 1C), 122.40, 107.83, 38.71, 34.85, 31.47；ESI/MS: 402.0 $[M+H]^+$, HRMS (ESI) calcd for $C_{21}H_{18}F_3N_3O_2Na$ ($[M+Na]^+$): 424.1249; found: 424.1239.

***N*-(2-(1-Methyl-6-(naphthalen-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)ethyl)picolinamide (4f)**

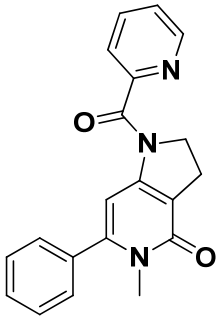


4f

Compound **4f** was prepared as described in general procedure for palladium catalyzed picolinamide-directed coupling of Alkenyl C(sp^2)-H and Alkenyl C(sp^2)-H. Yield: 32%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72-8.57 (m, 2H), 8.29 (d, *J* = 7.3 Hz, 1H), 7.96-7.83 (m, 5H), 7.60-7.49 (m, 3H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 6.8 Hz, 1H), 6.18 (d, *J* = 6.9 Hz, 1H), 3.82 (q, *J* = 6.1 Hz, 2H), 3.45 (s, 3H), 2.98 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.93, 163.15, 149.03, 148.52, 146.83, 139.40, 137.23, 133.30, 133.09, 128.54,

128.49, 128.40, 128.14, 127.95, 127.32, 127.12, 126.68, 125.90, 123.48, 108.08, 39.28, 35.07, 31.35; ESI/MS: 384.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{24}H_{21}ClN_3O_2Na$ ($[M+Na]^+$): 406.1531; found: 406.1536.

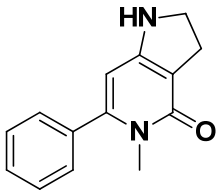
5-Methyl-6-phenyl-1-picolinoyl-2,3-dihydro-1*H*-pyrrolo[3,2-c]pyridin-4(5*H*)-one (5)



5

A Schlenk tube equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (10% mmol), 3-oxo-3*H*-1λ³,2-benziodaoxol-1-yl acetate (122 mg, 0.40 mmol) and **4a** (66 mg, 0.20 mmol) and then capped with septa. The vial was evacuated and backfilled with argon and the process was repeated three times. Under argon, 2 mL of HAc/ArmylOH (v/v, 4/1) was charged to the vial via syringe, and then the resulting mixture was stirred in a pre-heated 110 °C oil bath for 4 h. The reaction mixture was cooled to room temperature and extracted with DCM. The collected organic phase was washed with aq. $NaHCO_3$, water and brine, dried over anhydrous Na_2SO_4, concentrated under vaccum. The residue was purified by silica gel column chromatography (PE/EA = 1/1 ~ DCM/EA = 1/3 gradient dilution) to afford **5** as a white solid in 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 4.4 Hz, 1H), 7.84-778 (m, 2H), 7.57-7.27 (m, 7H), 4.42 (t, *J* = 8.4 Hz, 2H), 3.39 (s, 3H), 3.10 (t, *J* = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.10, 161.74, 153.53, 148.27, 137.37, 136.12, 129.37, 128.81, 128.62, 125.73, 124.51, 101.42, 51.34, 34.32, 29.82; ESI/MS: 332.0 $[M+H]^+$, HRMS (ESI) calcd for $C_{20}H_{18}N_3O_2$ ($[M+H]^+$): 332.1399; found: 332.1394.

5-Methyl-6-phenyl-2,3-dihydro-1*H*-pyrrolo[3,2-c]pyridin-4(5*H*)-one (6)



6

1N NaOH (0.11 mL, 0.11 mmol) was added to a solution of 5-methyl-6-phenyl-1-picolinoyl-2,3-dihydro-1*H*-pyrrolo[3,2-c]pyridin-4(5*H*)-one (24 mg, 0.07 mmol) in 1 mL of MeOH/THF/H_2O (v/v/v, 2/1/1). The resulting mixture was ~~refluxed~~ for 3.5 h. After cooled to room temperature, the solution was diluted with 10 mL of water and extracted with DCM three times. The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified silica gel column (DCM/EA = 1/3 ~EA gradient dilution) to give the title compound in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.38 (m, 3H), 7.28-7.26 (m, 2H), 5.72 (s, 1H), 3.66 (t, *J* = 9.2 Hz, 2H), 3.27 (s, 3H), 3.02 (t, *J* = 9.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.35, 158.84, 150.71, 136.60, 129.12, 128.73, 128.41, 106.66, 96.42, 47.29, 33.74, 26.82; ESI/MS: 227.1 $[M+H]^+$, HRMS (ESI) calcd for $C_{14}H_{15}N_2O$ ($[M+H]^+$): 227.1184; found: 227.1184.

***N*-(3-(methyl(phenyl)carbamoyl)but-3-en-1-yl)benzamide (7)**

Compound **7** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.57 (br, 1H), 7.49-7.39 (m, 3H), 7.36-7.29 (m, 2H), 7.29-7.23 (m, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 5.16 (s, 1H), 5.03 (s,

1H), 3.58 (dd, J = 11.9, 5.5 Hz, 2H), 3.36 (s, 3H), 2.40 (t, J = 5.9 Hz, 2H); ESI/MS: 309.1 $[M+H]^+$.

***N*-methyl-*N*-(3-(methyl(phenyl)carbamoyl)but-3-en-1-yl)picolinamide (8)**

To a solution of **1a** (50 mg, 0.16 mmol) in THF (5 mL) at 0 ^oC was added NaH (60%, 18.1 mg, 0.45 mmol). The reaction was warmed to rt and stirred for 1 h under Ar. MeI (90.5 mmL, 1.45 mmol) was then added and the reaction was stirred overnight. The reaction mixture was quenched with water and extracted with CH_2Cl_2. The organic layer were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (PE/EA = 4/1). Yield: 79%; ESI/MS: 324.1 $[M+H]^+$. NMR indicates **8** is a mixture.

***N*-methyl-*N*-phenylmethacrylamide (9)**

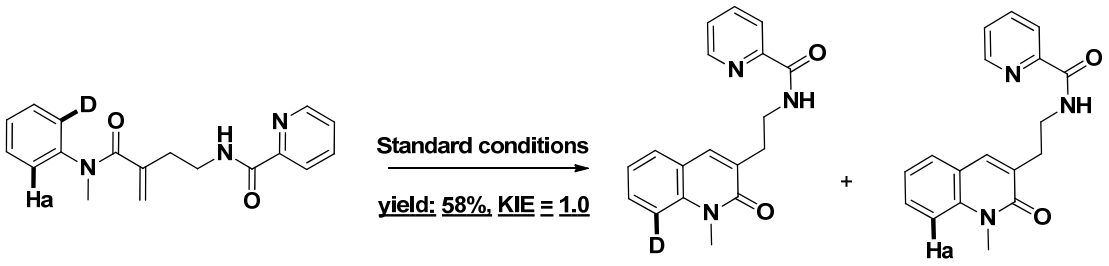
Compound **9** was prepared in a similar manner as described for compound **1a**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 2H), 7.28-7.23 (m, 1H), 7.16-7.11 (m, 2H), 5.05-5.01 (m, 1H), 5.00-4.97 (m, 1H), 3.35 (s, 3H), 1.78-1.74 (m, 3H); ESI/MS: 176.1 $[M+H]^+$.

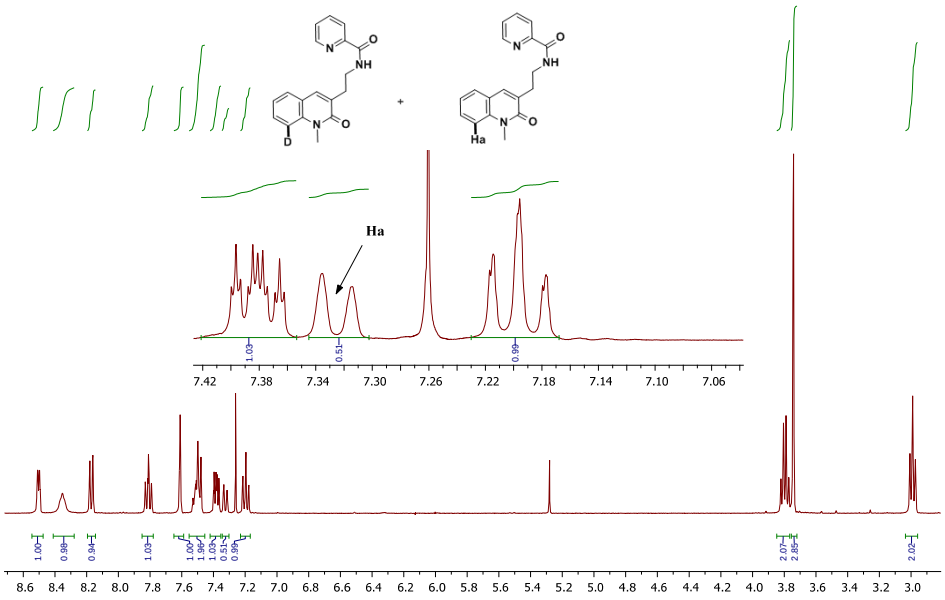
Mechanistic studies

1. Kinetic Isotopic Effect (KIE) Studies:

a) Intramolecular KIE experiment:

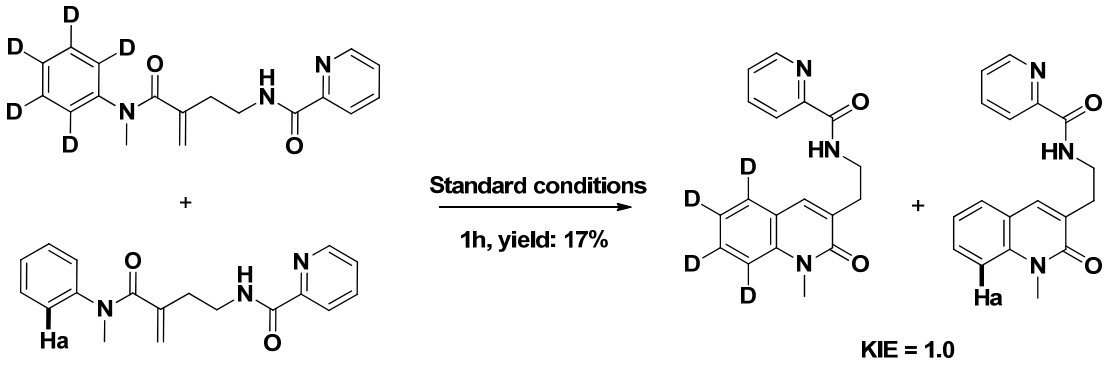
A vial equipped with a magnetic stir bar was charged with **1D** (109 mg, 0.35 mmol), $PbBr_2$ (4.67 mg, 17 μmol), and 3-oxo-3*H*-1λ³,2-benziodaoxol-1-yl acetate (269 mg, 0.88 mmol). The vial was evacuated and refilled with argon three times. Then 3.5 mL of xylene was added. The resulting mixture was stirred for 48 hrs 110 °C. The reaction was monitored by thin layer chromatography. After substrate consumed completely, the mixture was concentrated and subjected to column chromatography to give the product (yield: 58%). The products were under ^{1}H-NMR analysis.

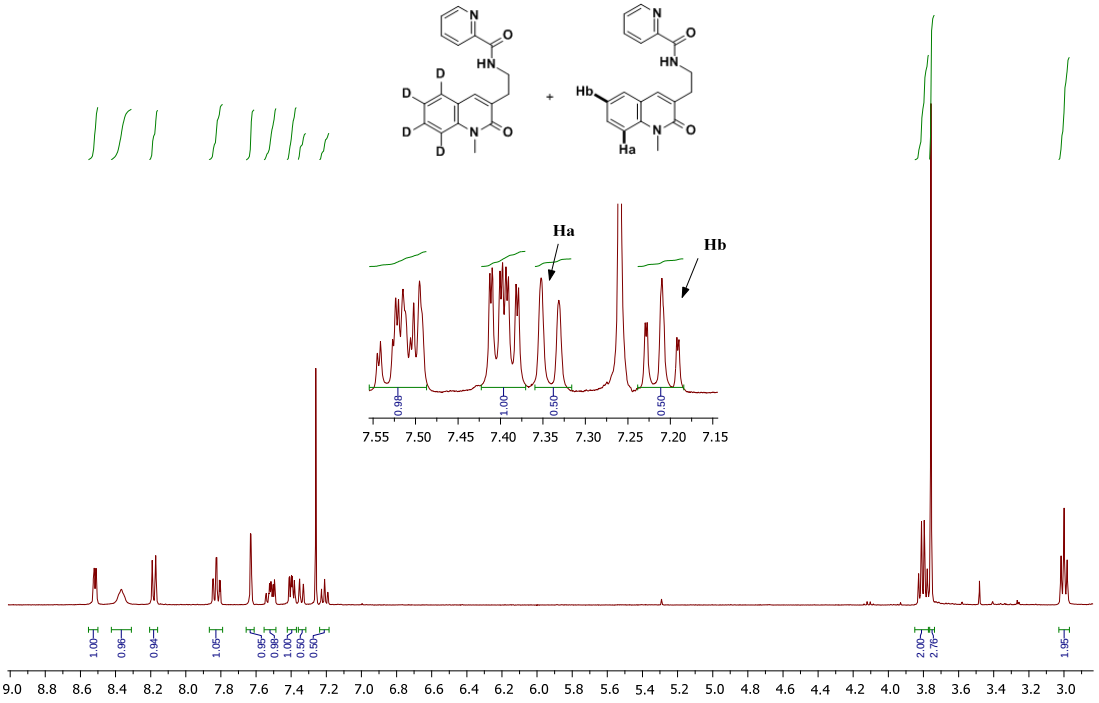




b) Intermolecular KIE experiment:

A vial equipped with a magnetic stir bar was charged with 5**D** (0.1 mmol), **noD** (0.1 mmol), $PbBr_2$ (1.33 mg, 5.01 umol), and 3-oxo-3*H*-1λ³,2-benziodaoxol-1-yl acetate (153 mg, 0.50 mmol). The vial was evacuated and refilled with argon three times. Then 2 mL of xylene was added. The resulting mixture was stirred for 1 hrs at 110 °C. The mixture was concentrated and subjected to column chromatography and the product was analyzed by ^{1}H-NMR.



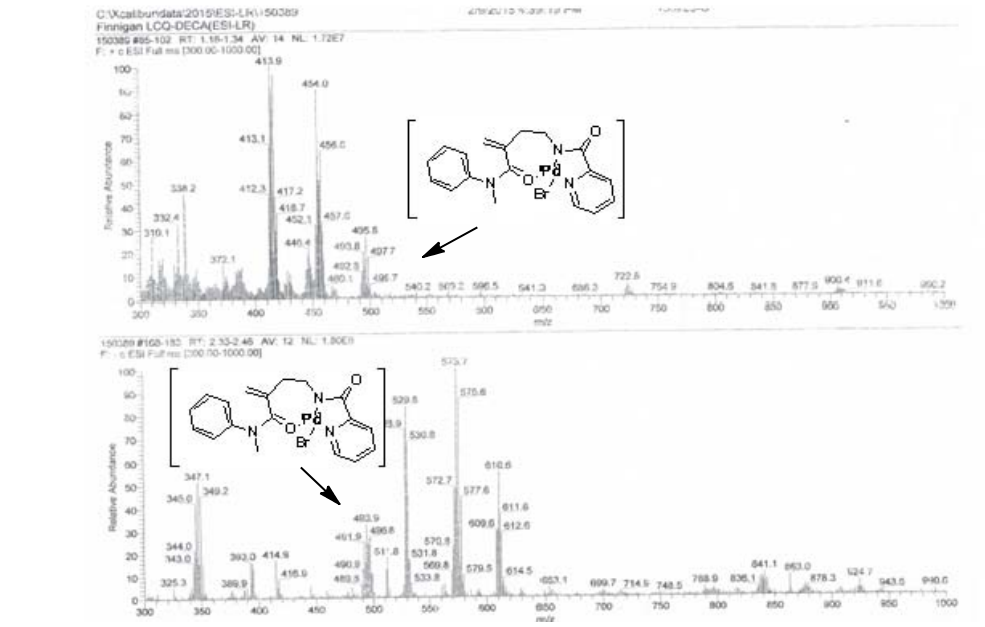


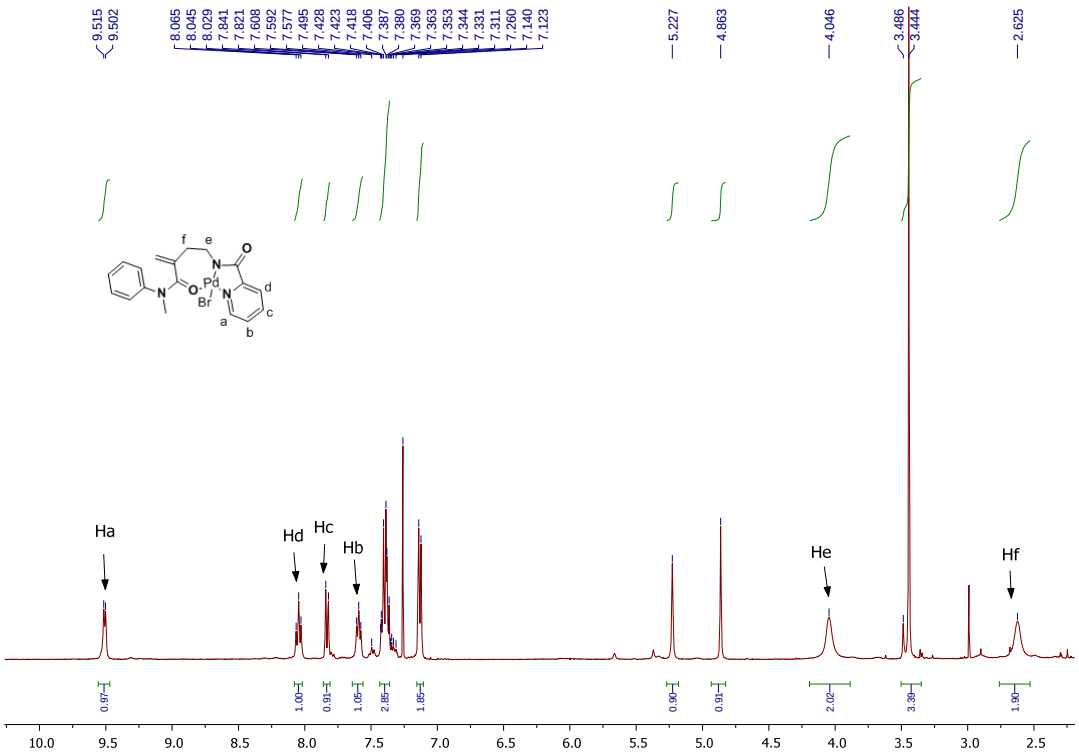
2. **Control experiments:**

A vial equipped with a magnetic stir bar was charged with 0.2 mmol of **7**, **8** or **9**, $PbBr_2$ (1.33 mg, 5.01 umol), and 3-oxo-3*H*-1λ³,2-benziodaoxol-1-yl acetate (153 mg, 0.50 mmol). The vial was evacuated and refilled with argon three times. Then 2 mL of xylene was added. The resulting mixture was stirred for 48 hrs at 110 °C. The mixture was filtered through a short pad of silica gel. The filtrate was concentrated and subjected to analysis by LCMS and NMR.

3. Preparation of palladium complex 11:

A Schlenk tube equipped with a magnetic stir bar was charged with $PdBr_2$ (26.7 mg, 0.1 mmol) and **1a** (31 mmol, 0.1mmol) and then capped with septa. The vial was evacuated and backfilled with argon and the process was repeated three times. Under argon, 1 mL of CH_3CN was charged to the vial via syringe, and then the resulting mixture was stirred in a pre-heated 70 °C oil bath for 2 h. The reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was subjected to analysis by ESI-MS and NMR. The probable structure of the complex is depicted in ESI-MS and NMR spectra.

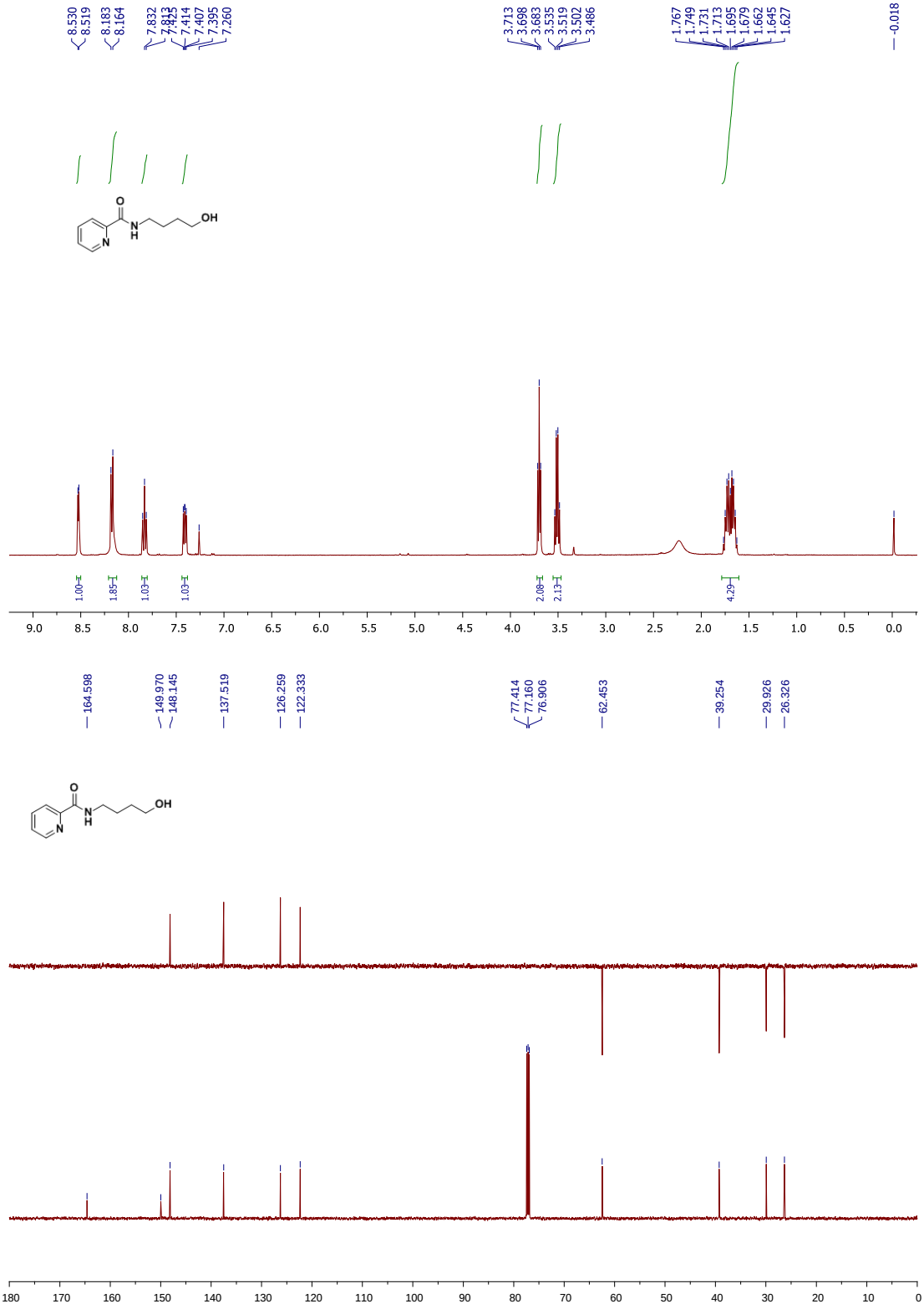


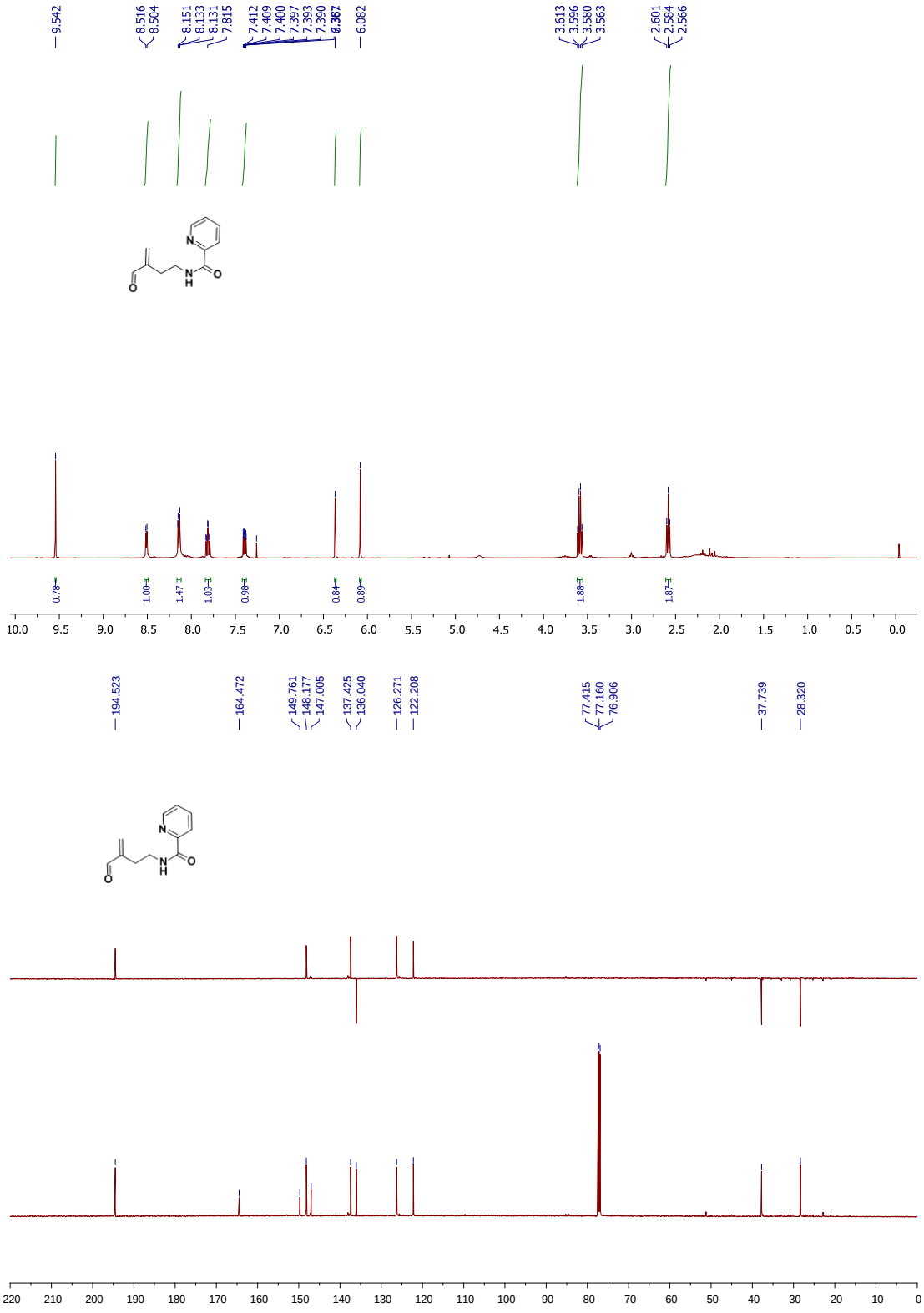


4. Oxidation of the complex 11 with the cyclic hypervalent iodine (III)

A Schlenk tube equipped with a magnetic stir bar was charged with the resulting complex (0.1 mmol) and oxidant (76.7 mg, 0.1 mmol) and then capped with septa. The vial was evacuated and backfilled with argon and the process was repeated three times. Under argon, 1 mL of xylene was charged to the vial via syringe, and then the resulting mixture was stirred in a pre-heated 110 °C oil bath for 24 h. Yield: 61%. The LC-MS and NMR data of the product match well with that of **2a**.

^{1}H-NMR and ^{13}C-NMR spectra

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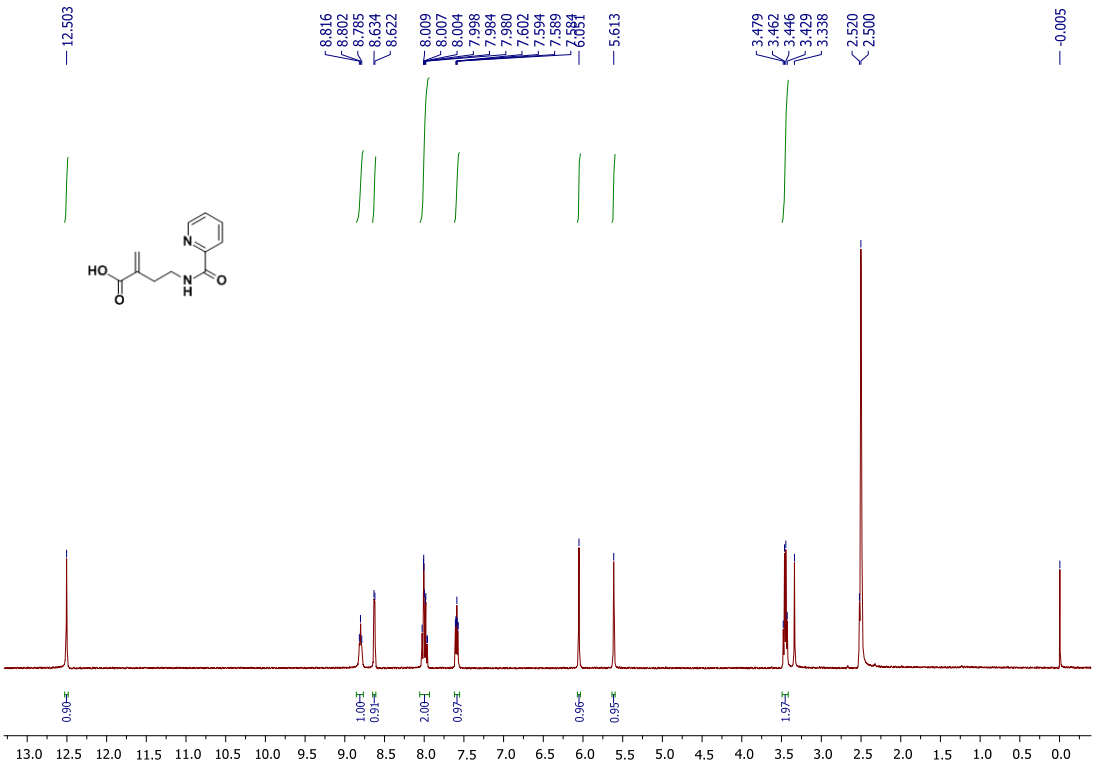
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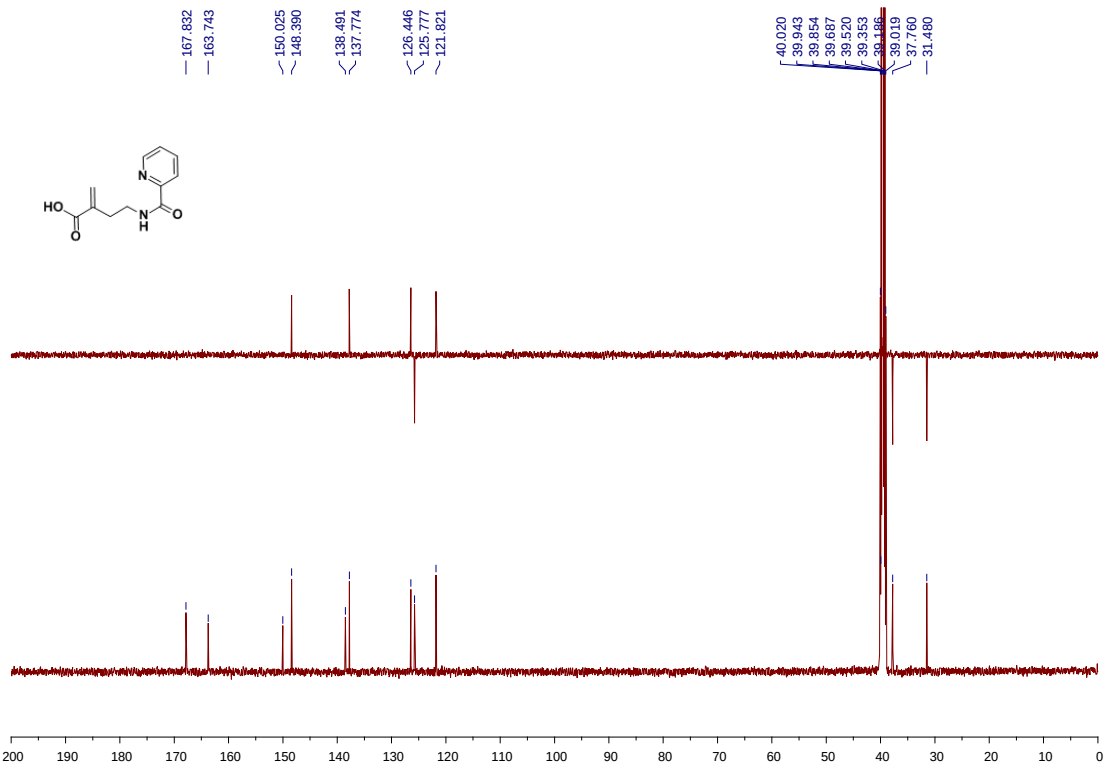
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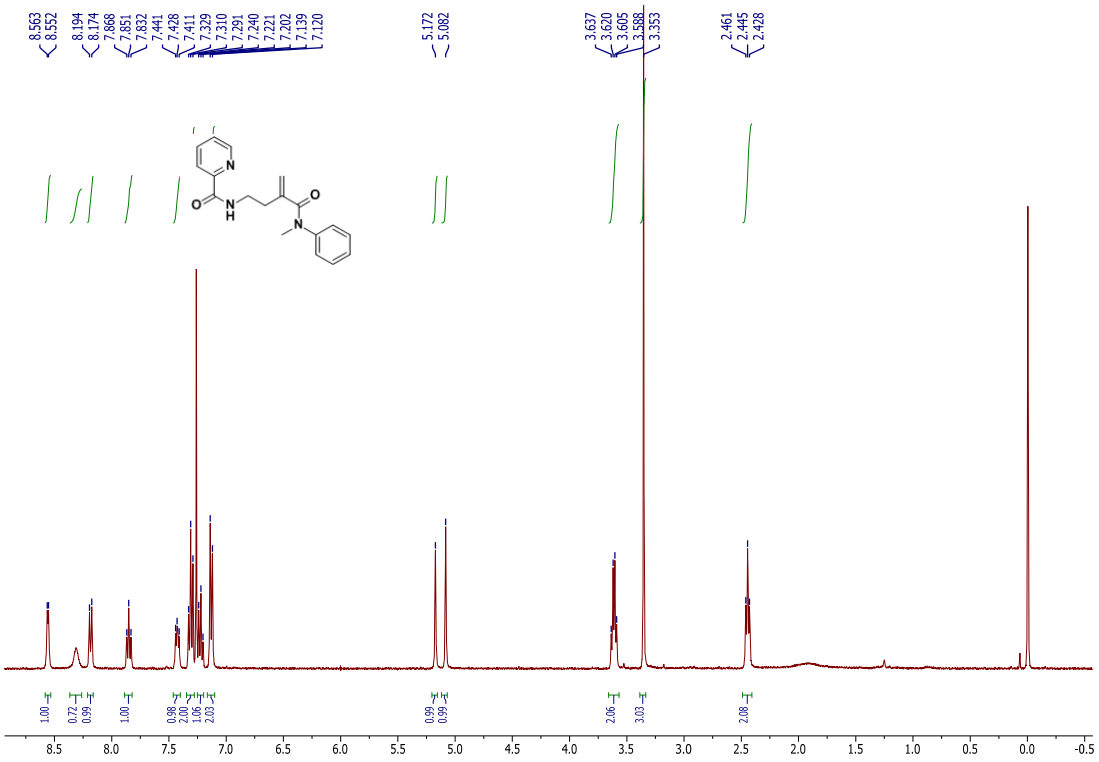
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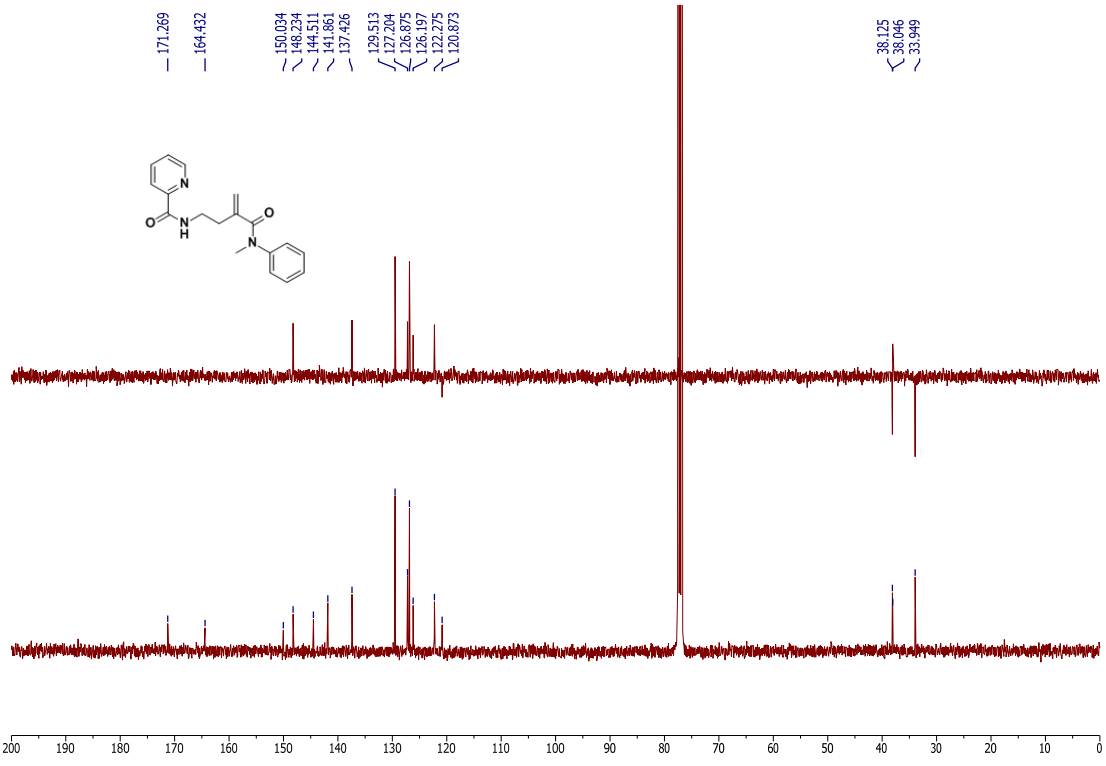
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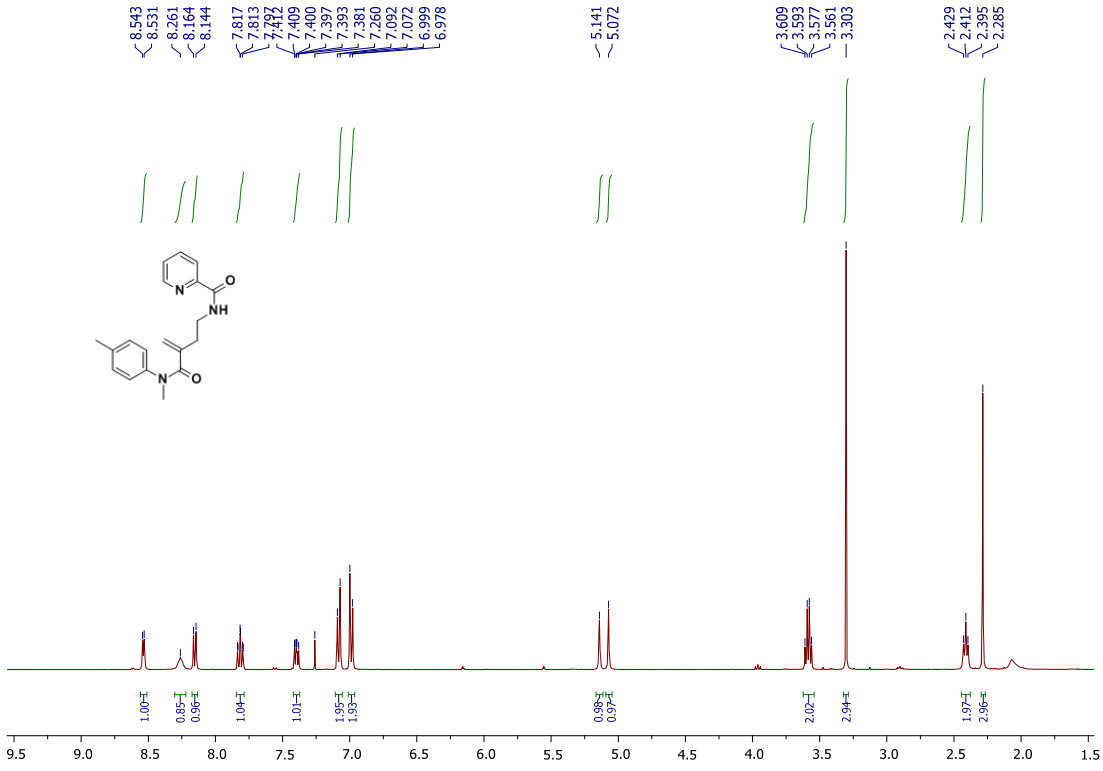
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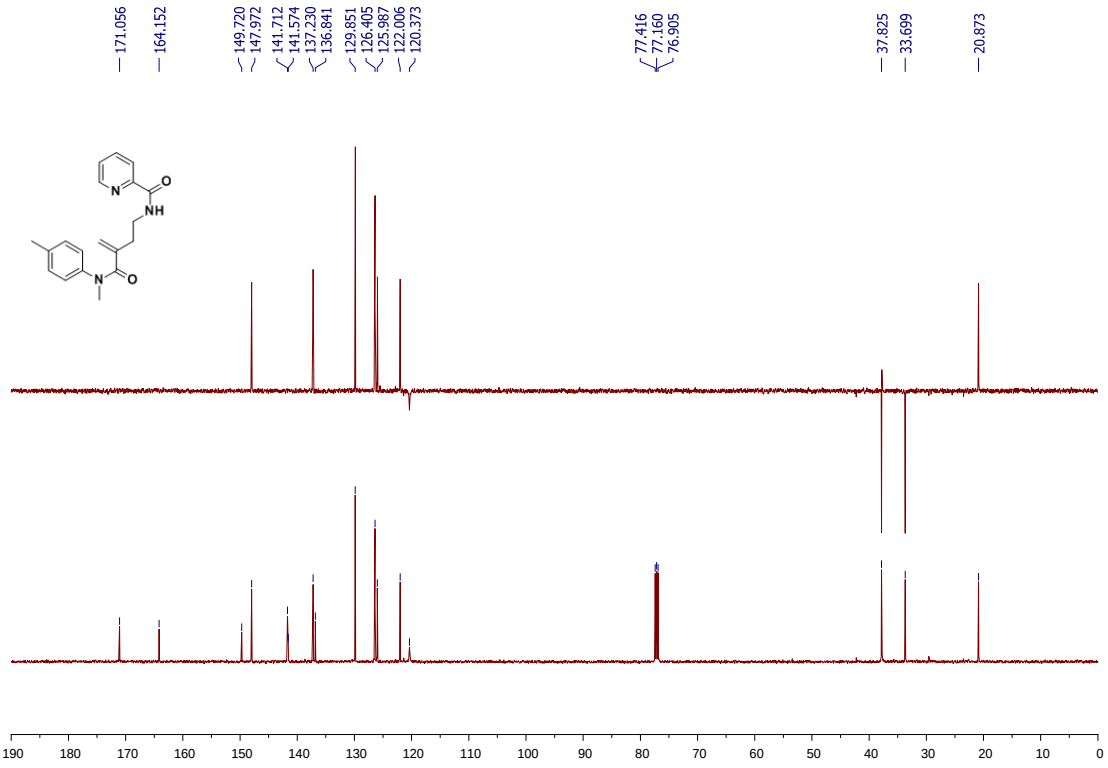
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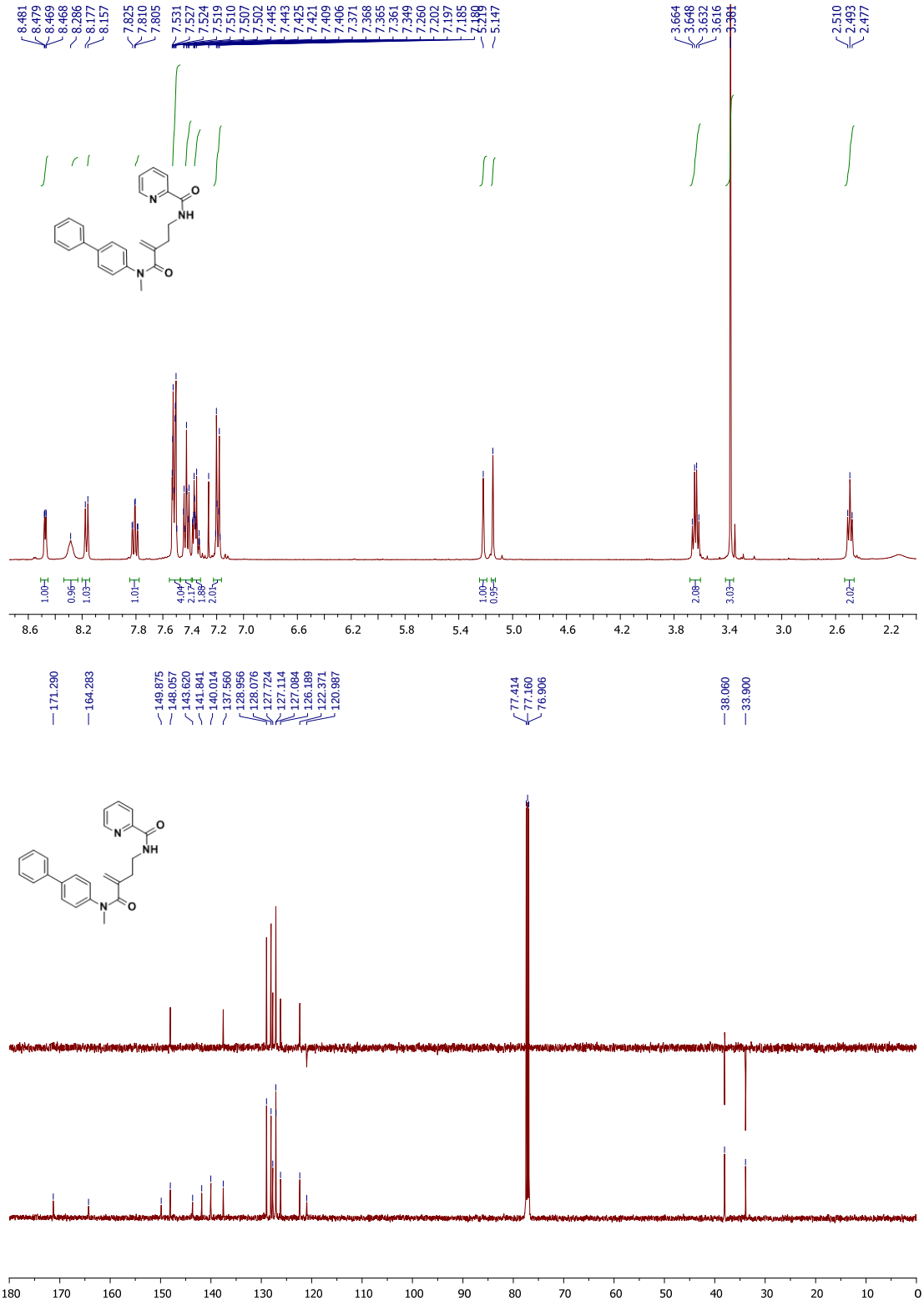
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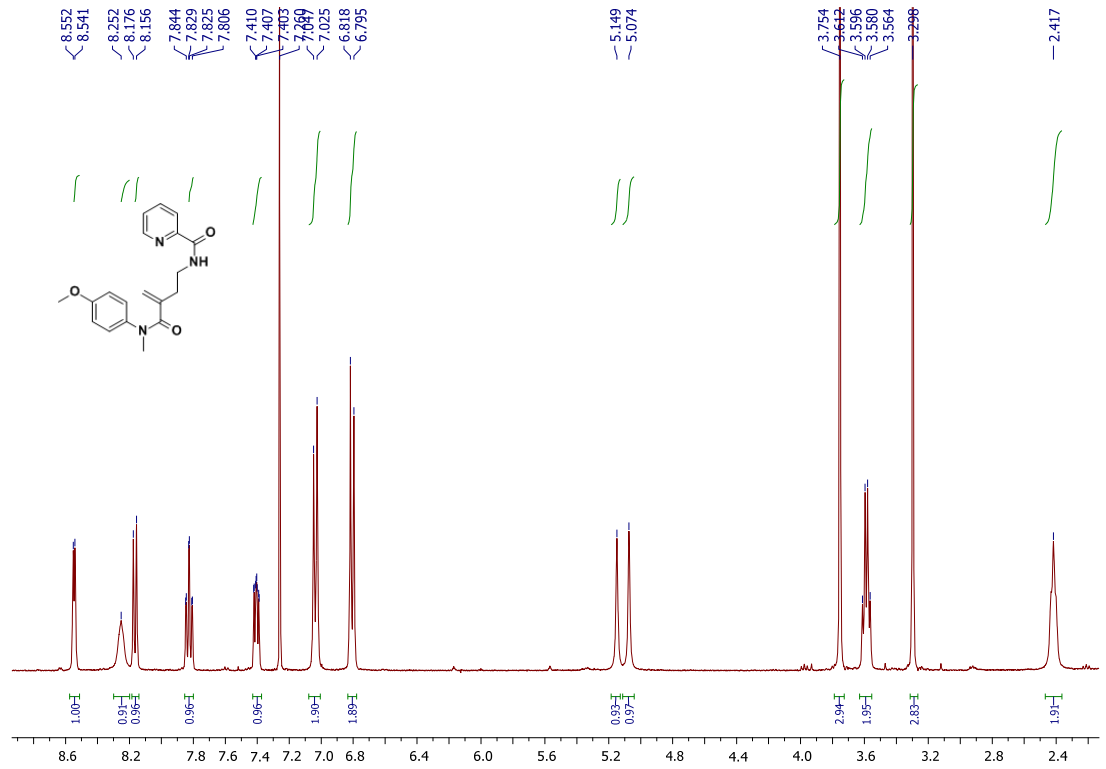
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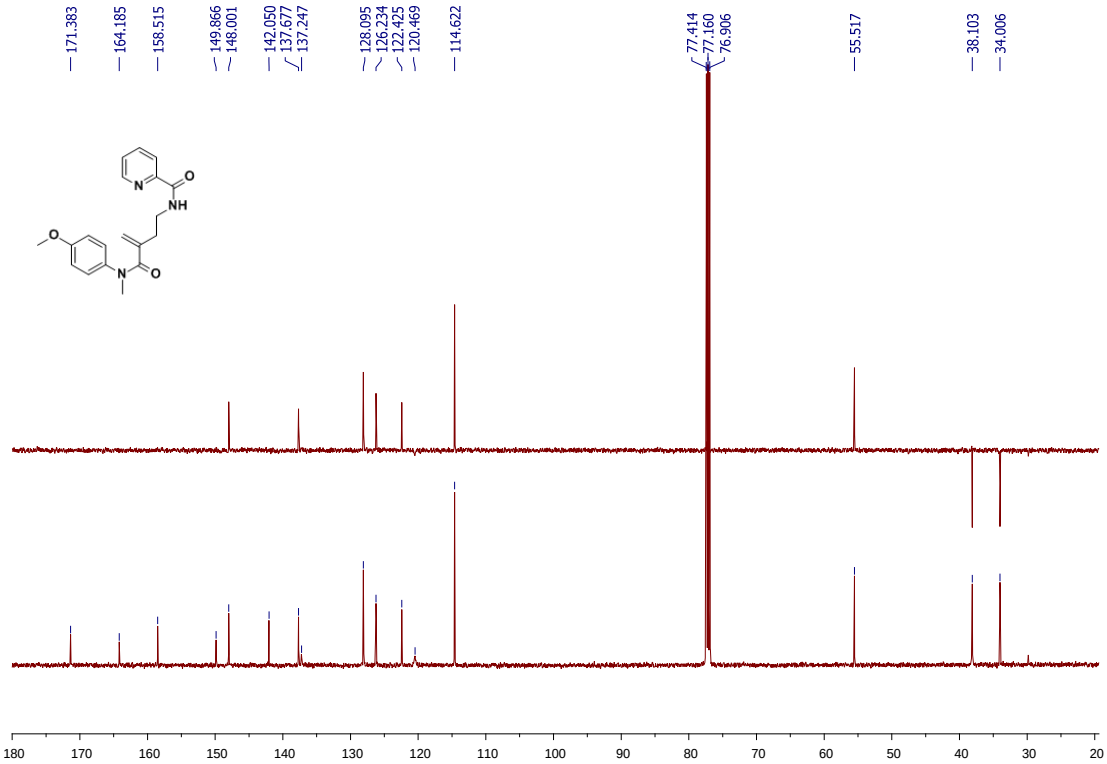
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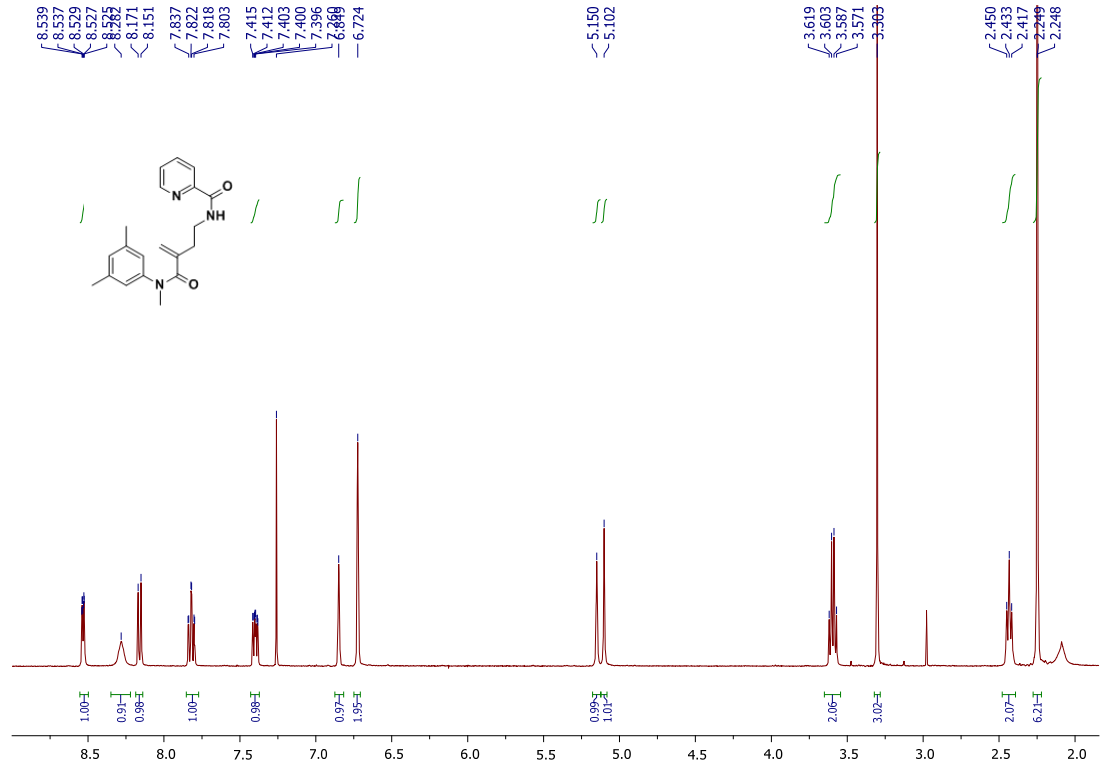
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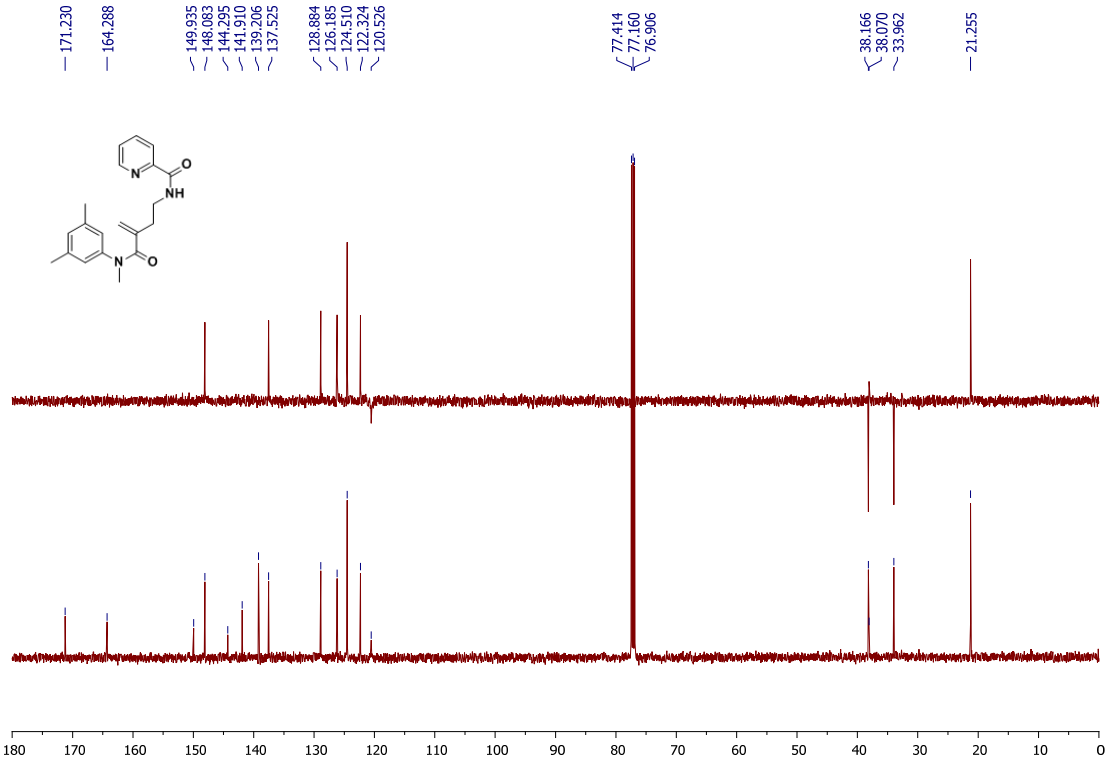
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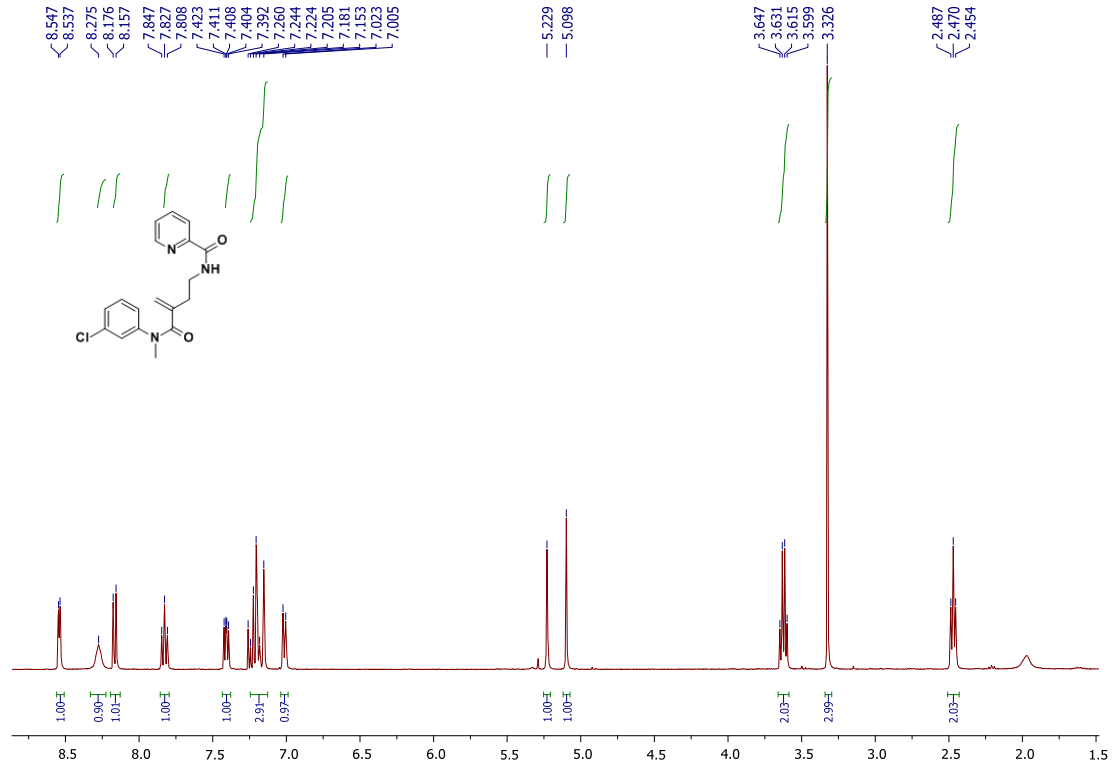
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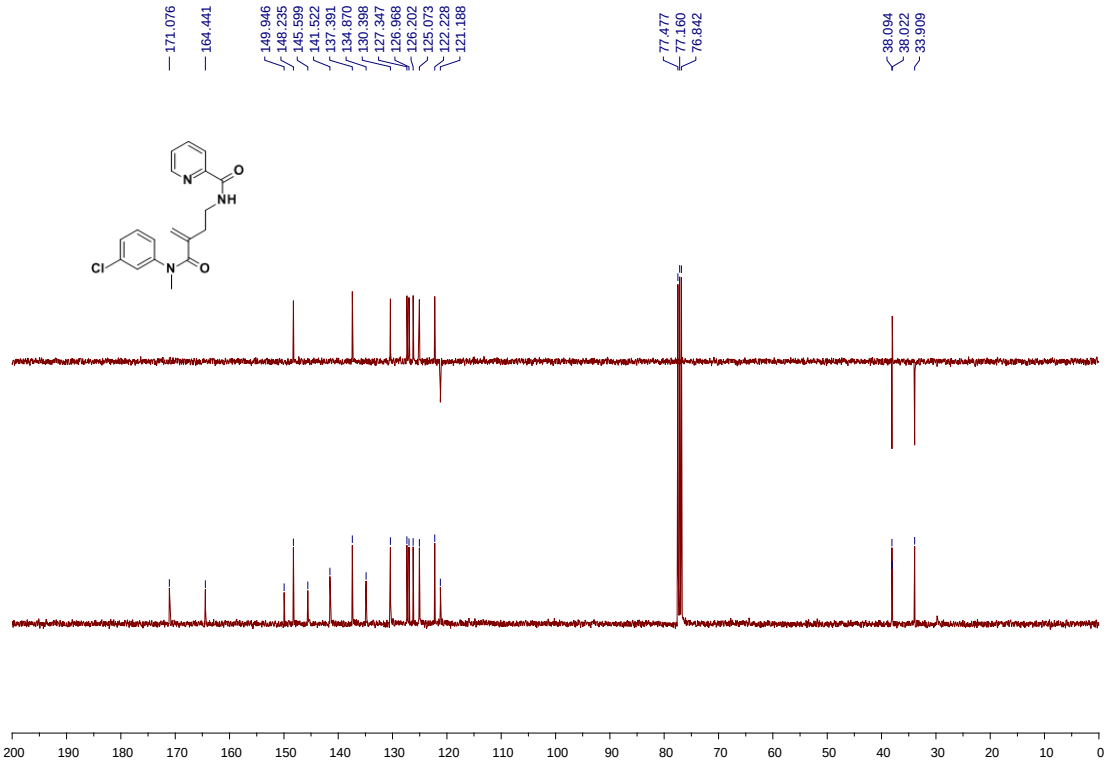
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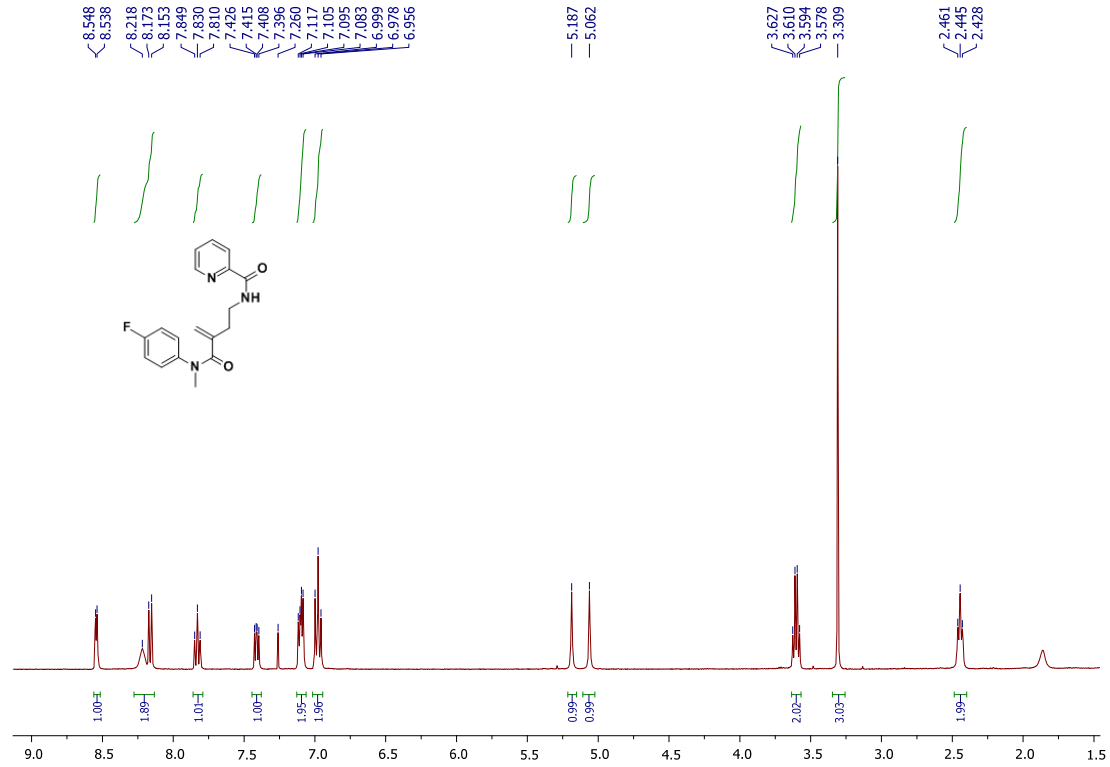
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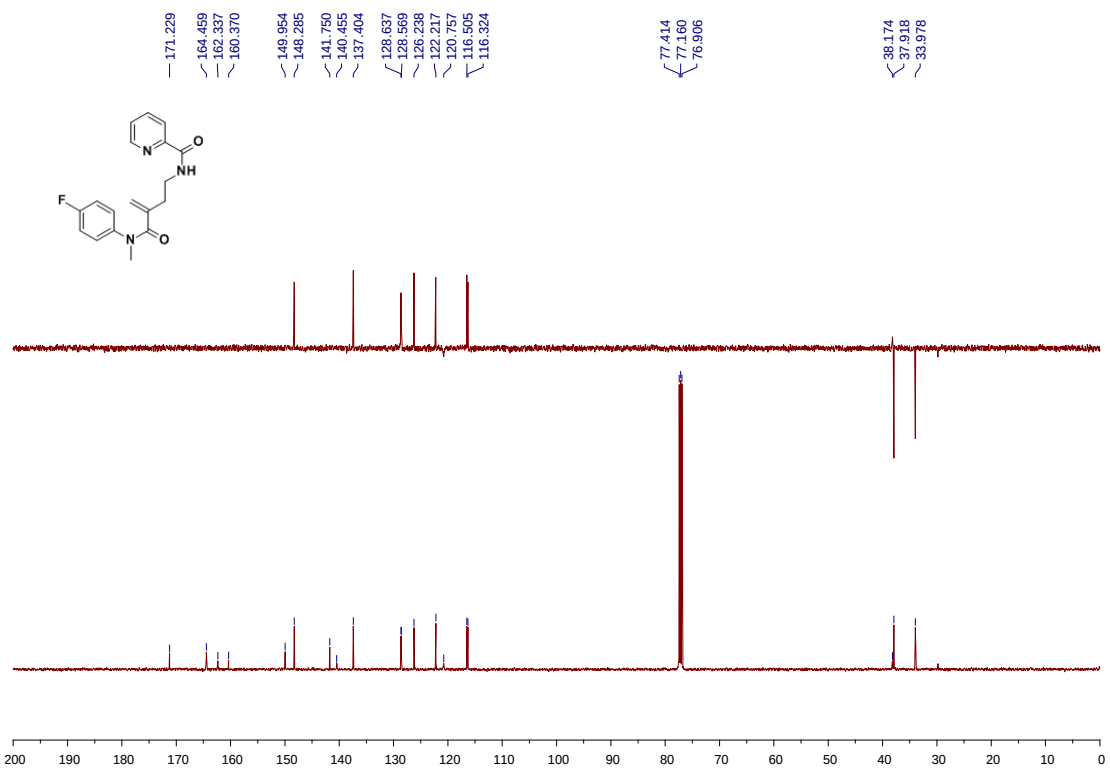
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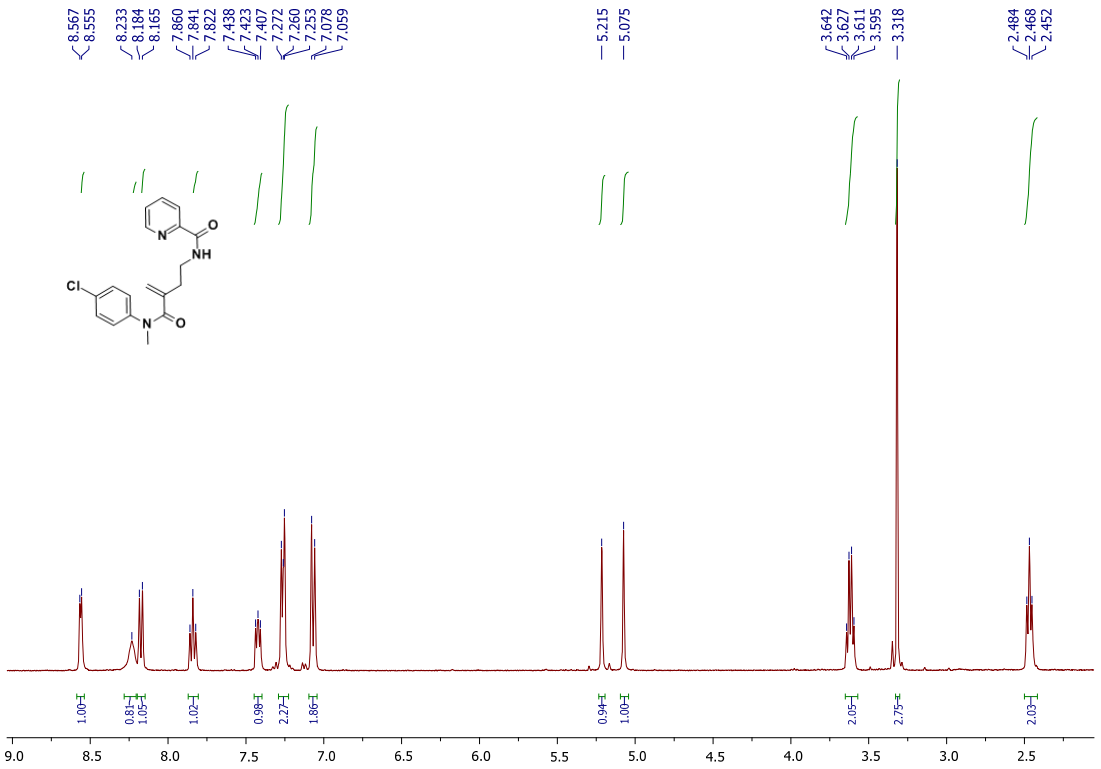
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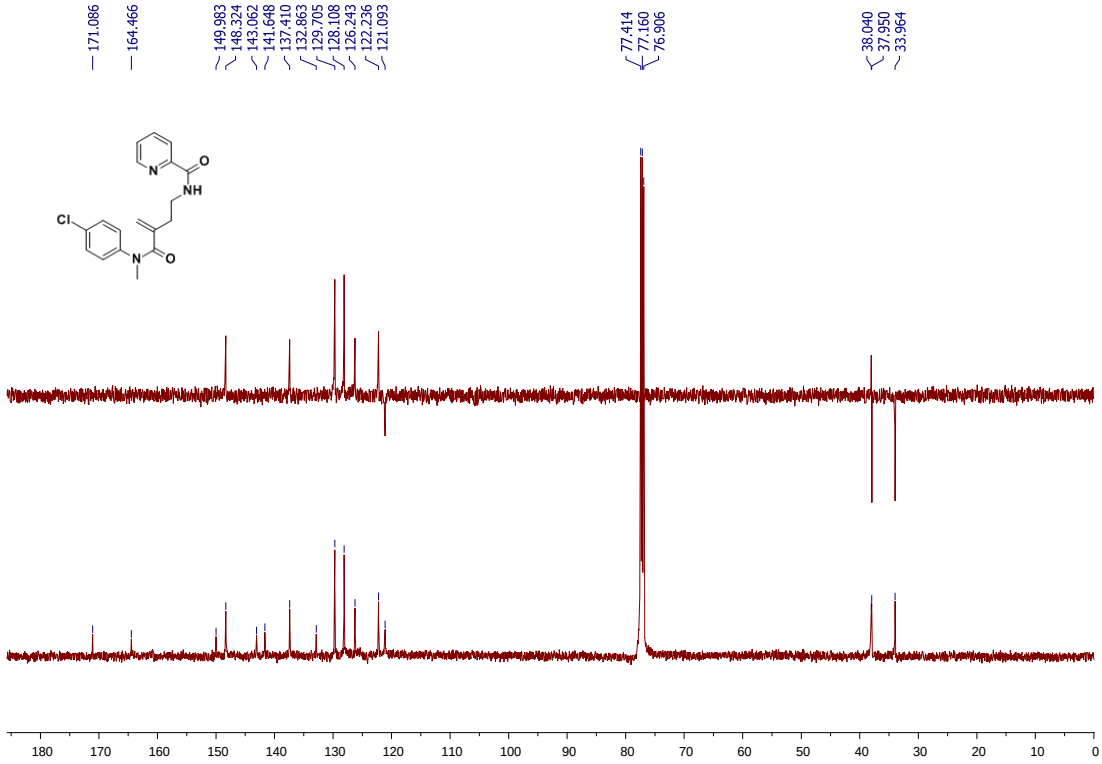
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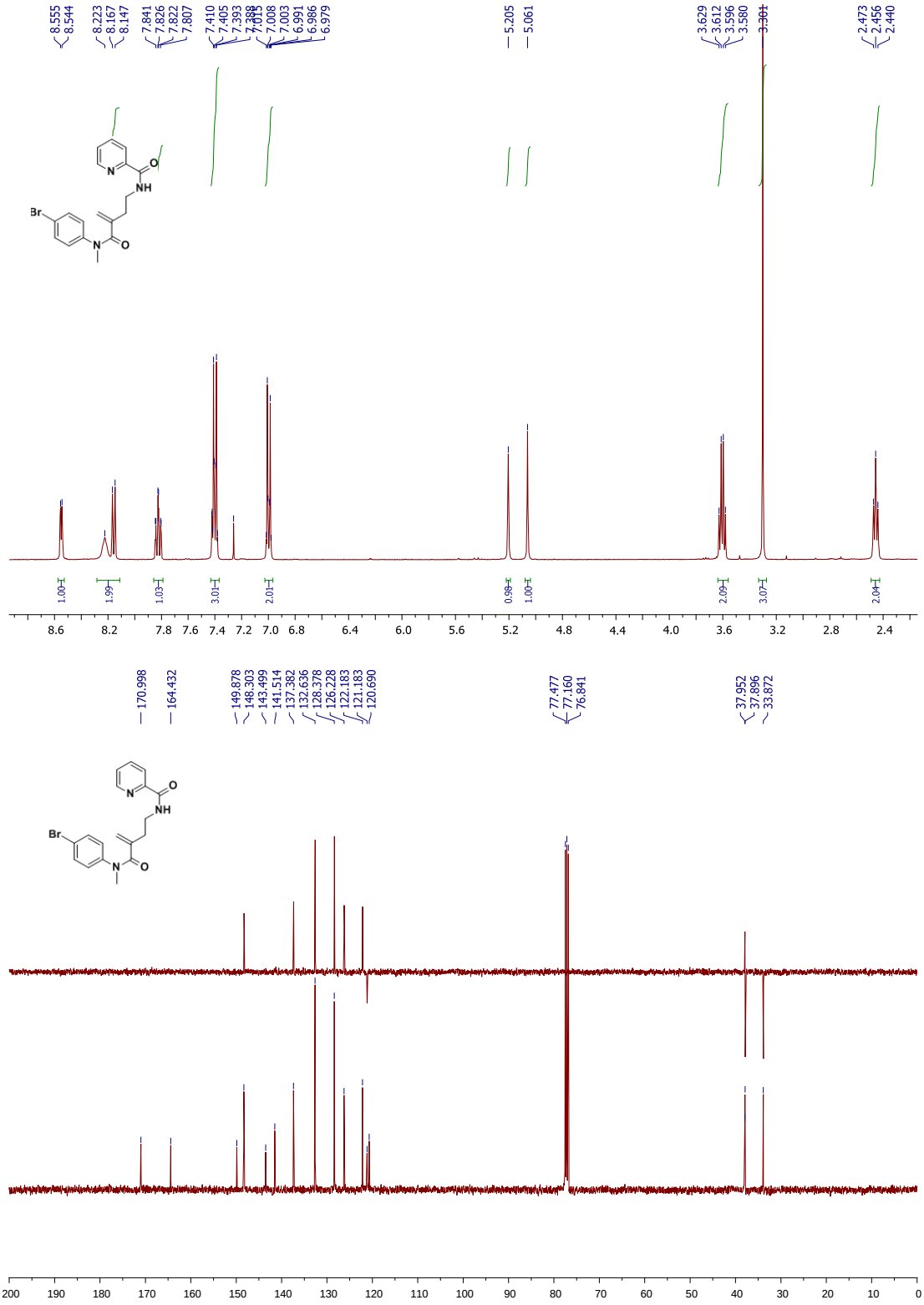
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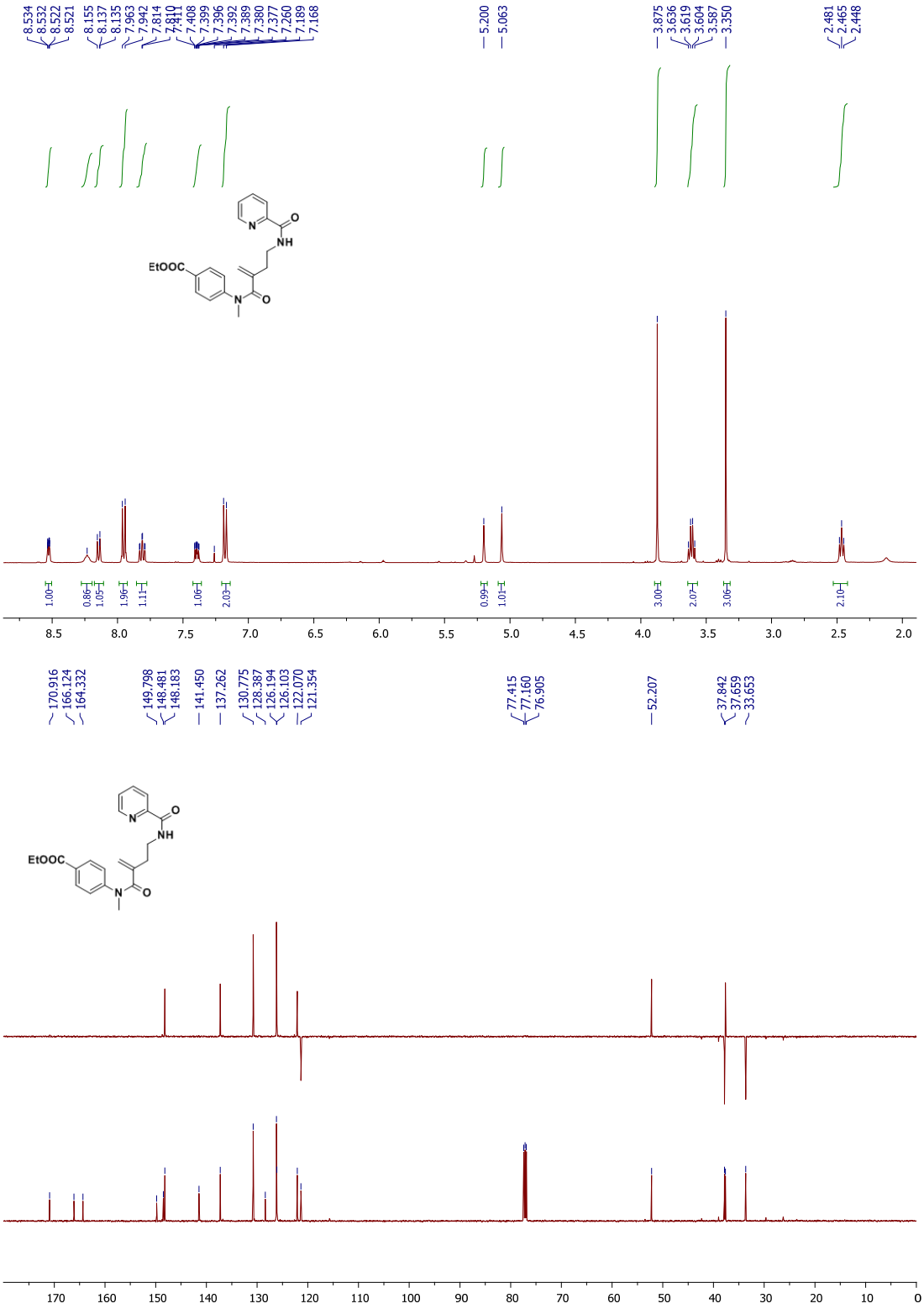
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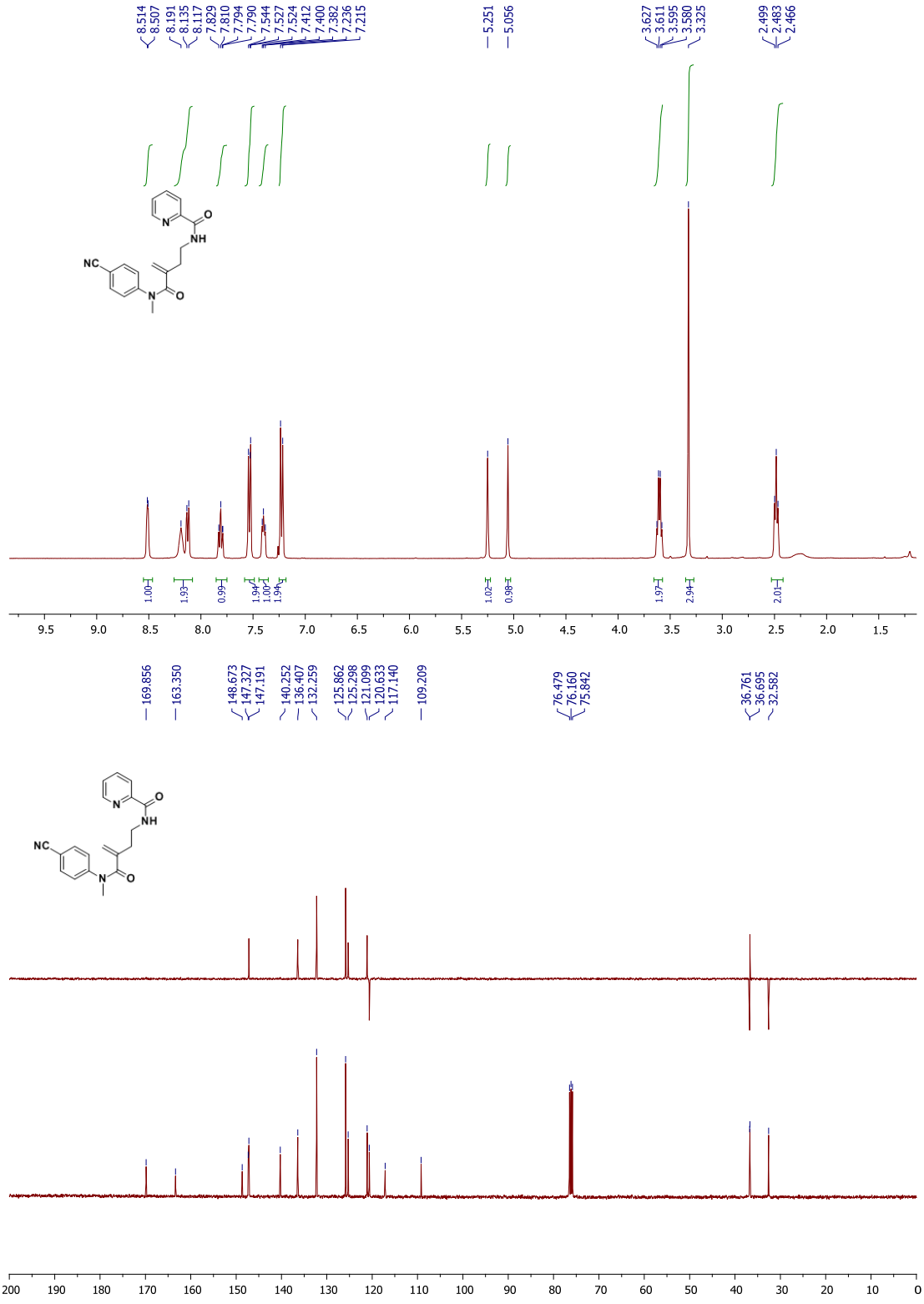
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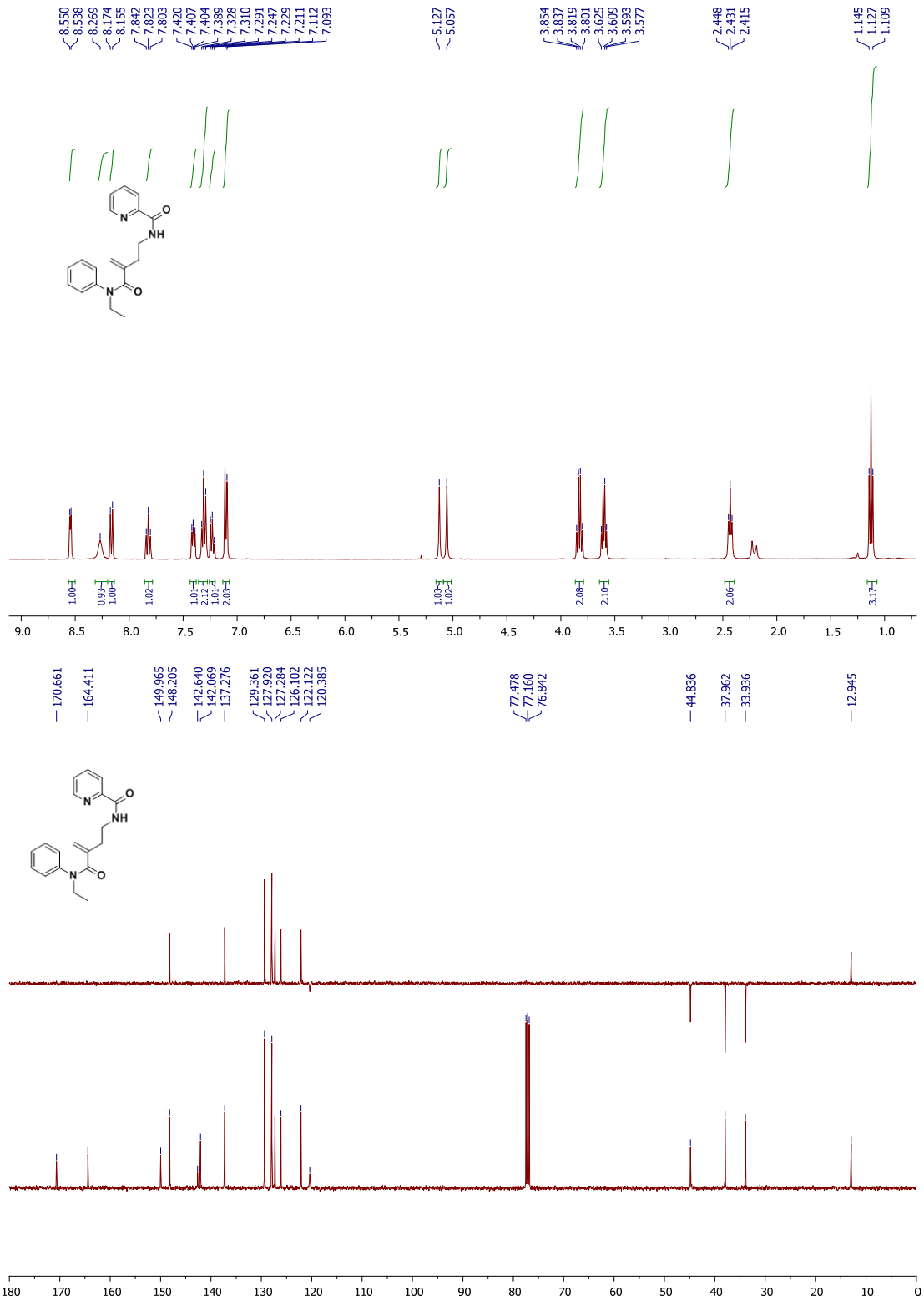
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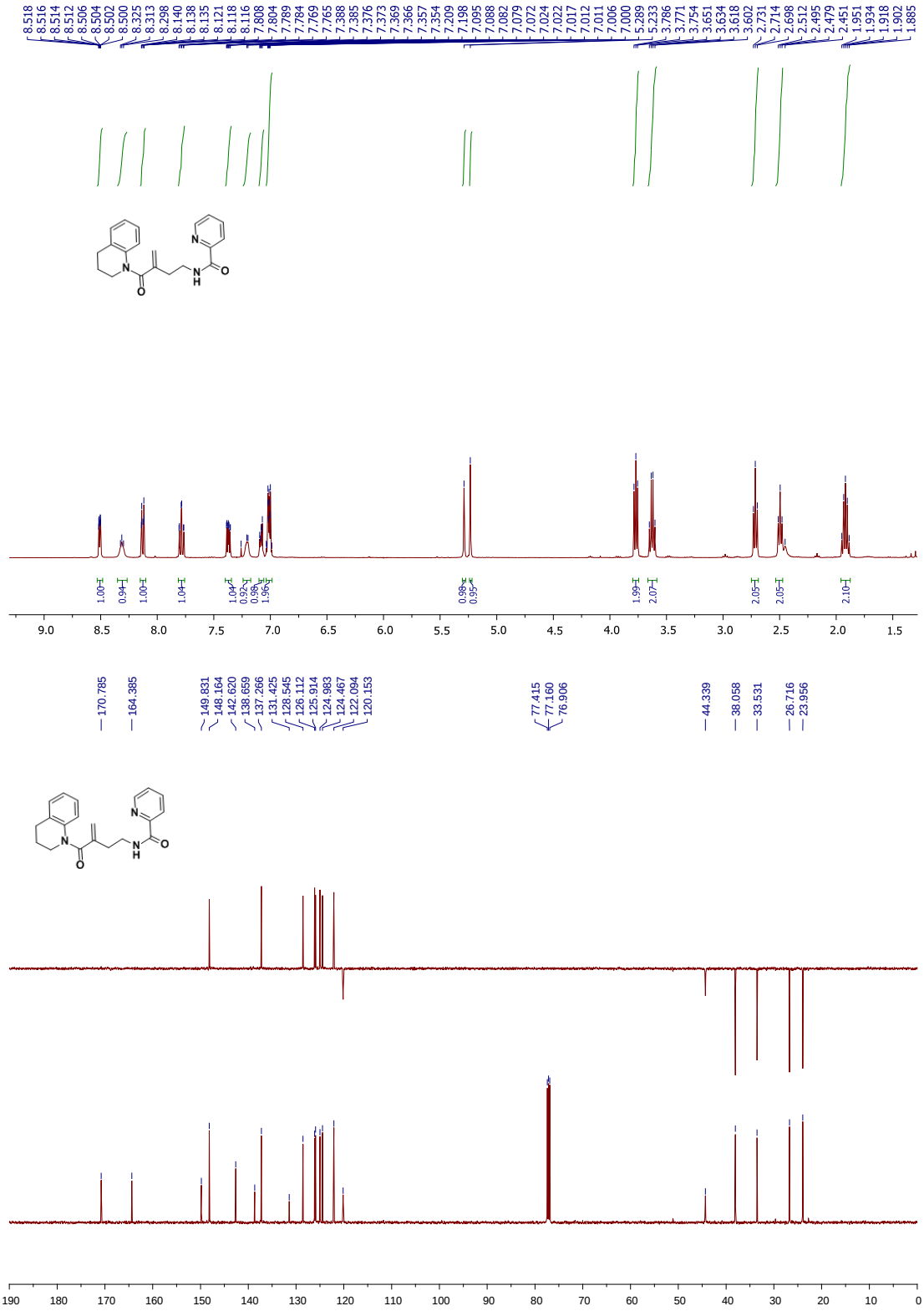
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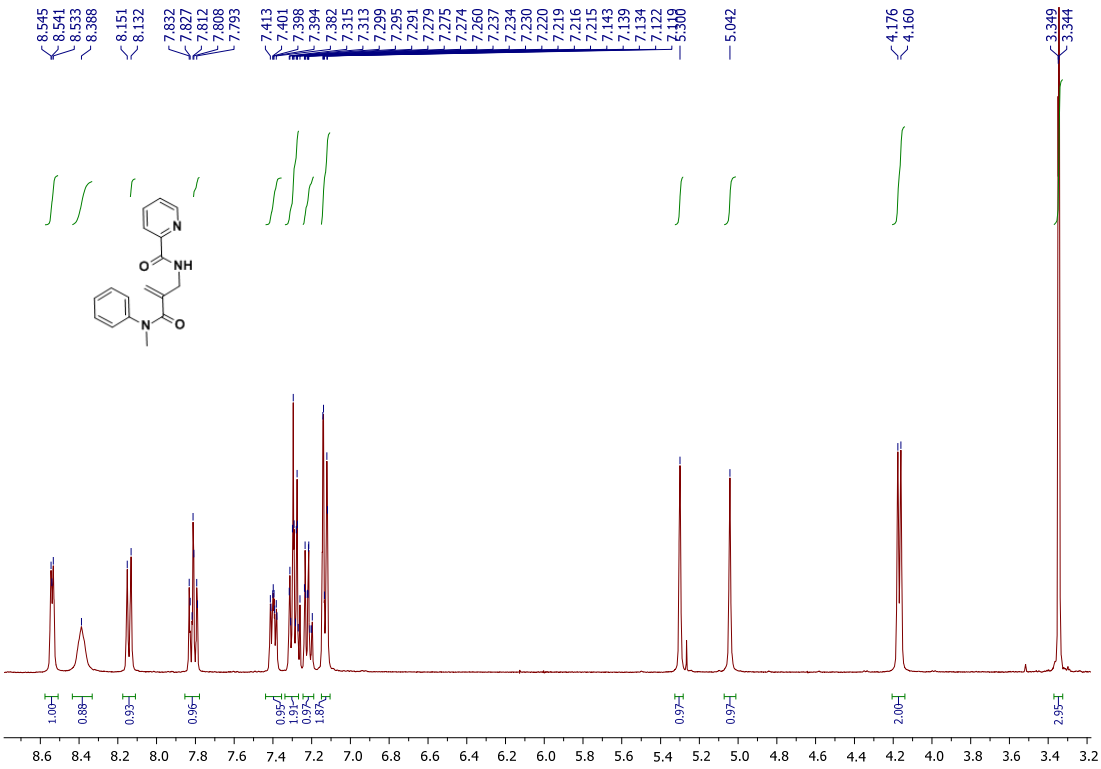
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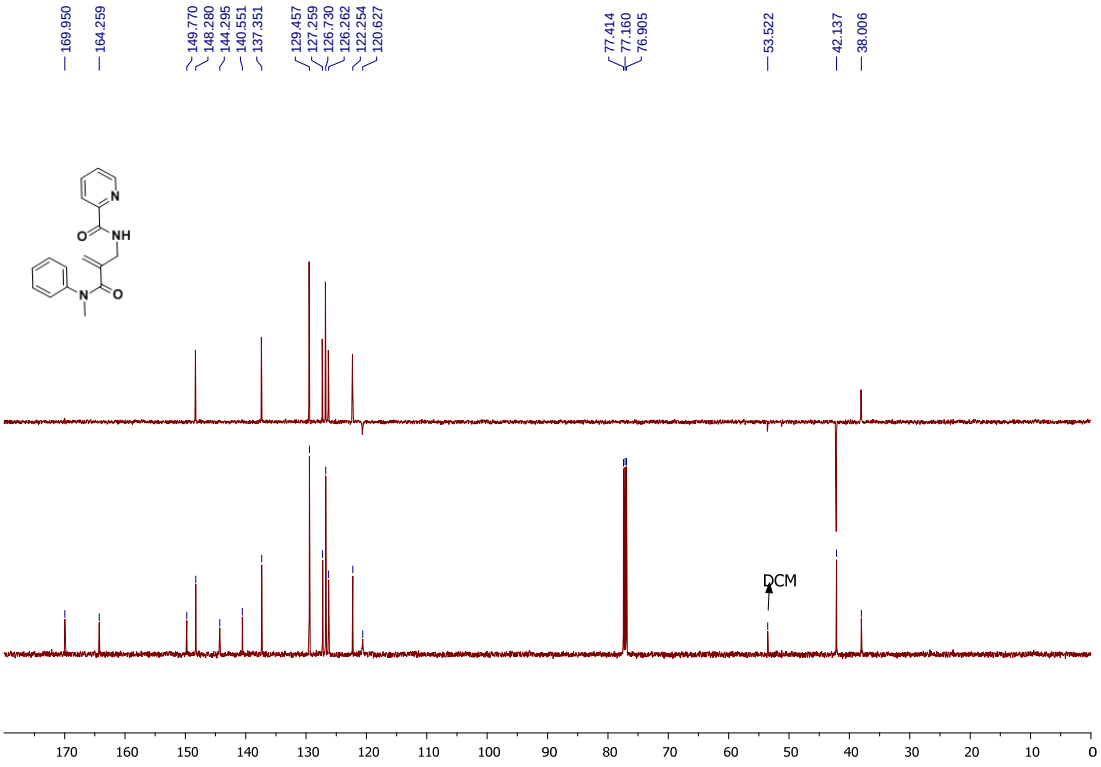
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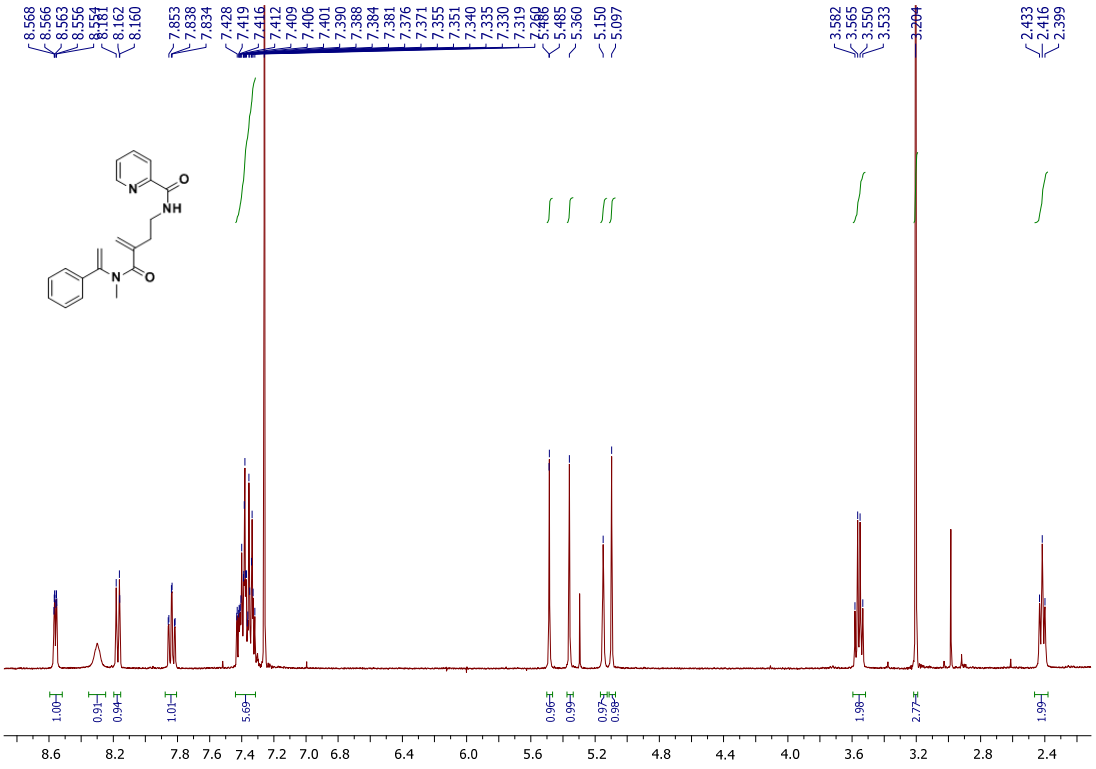
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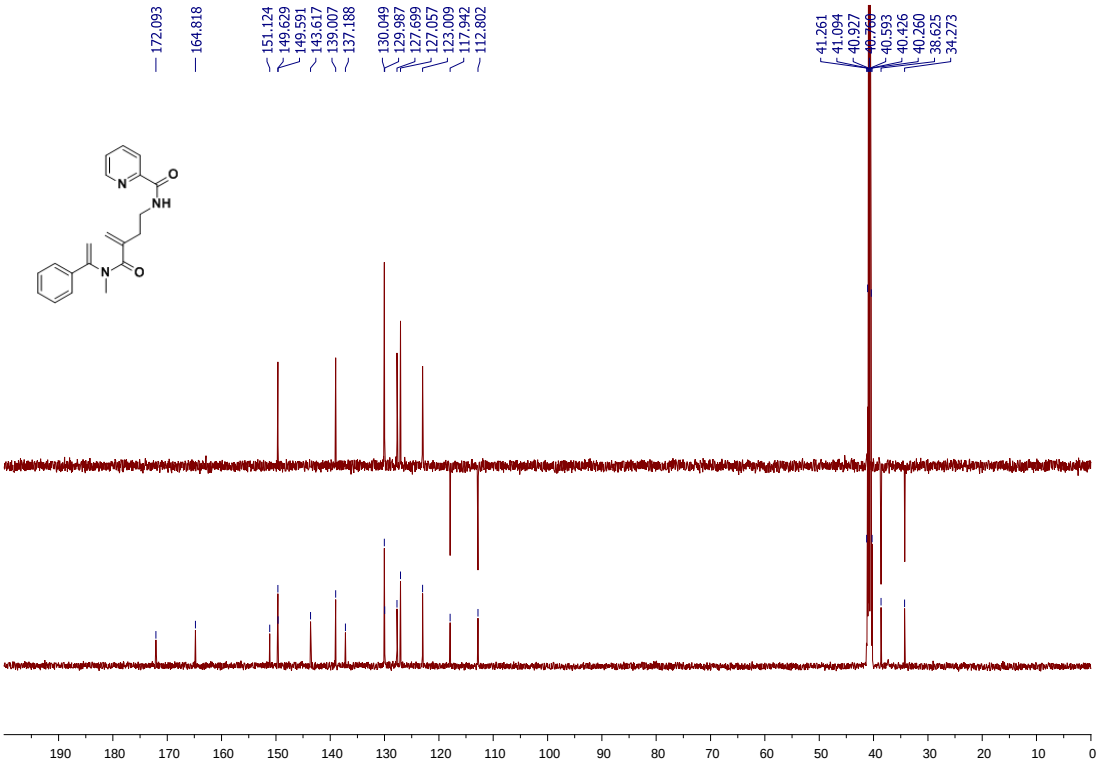
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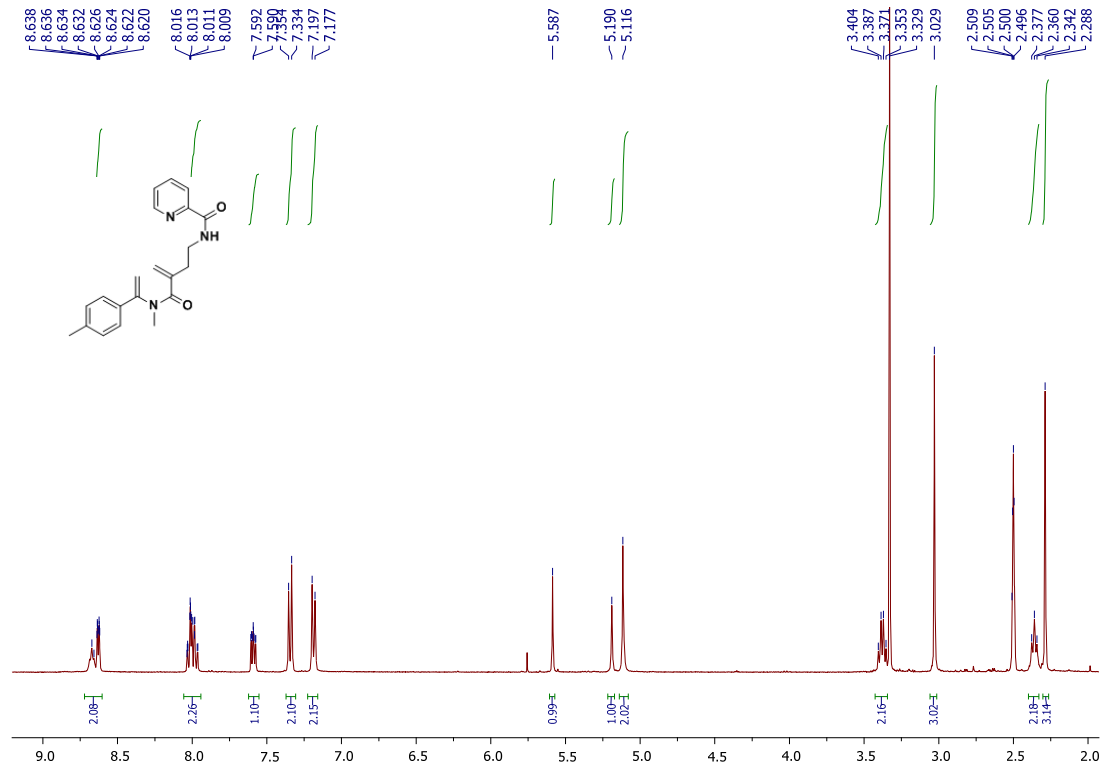
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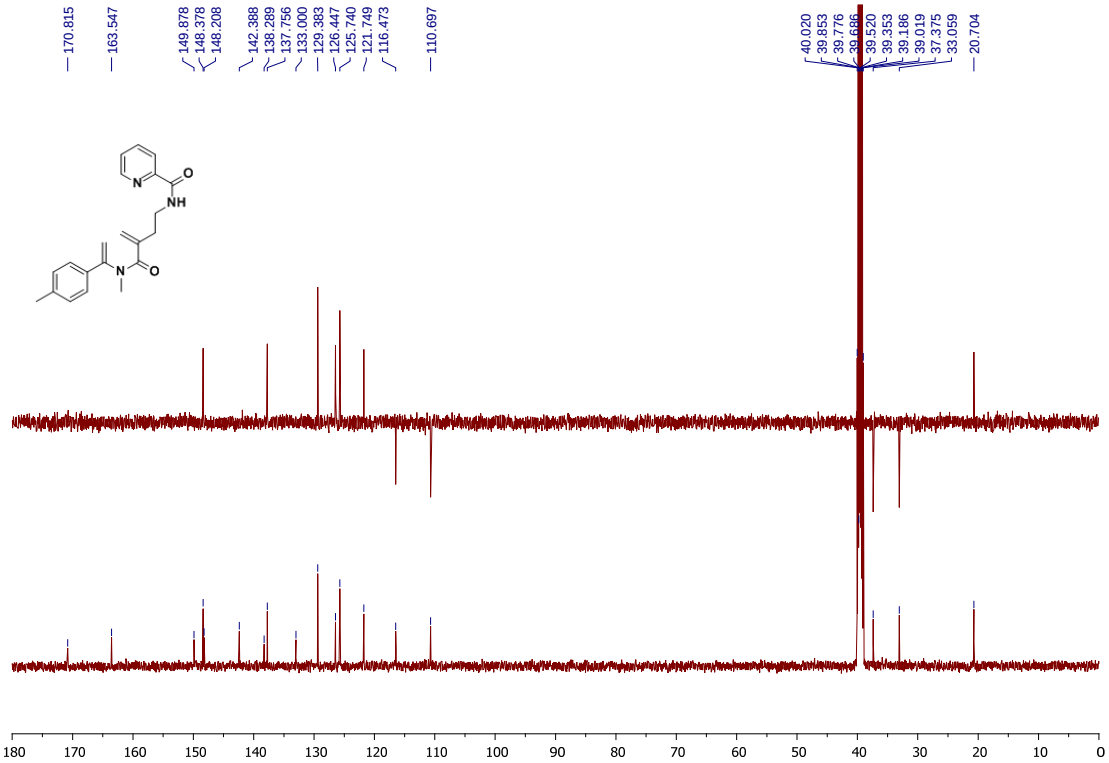
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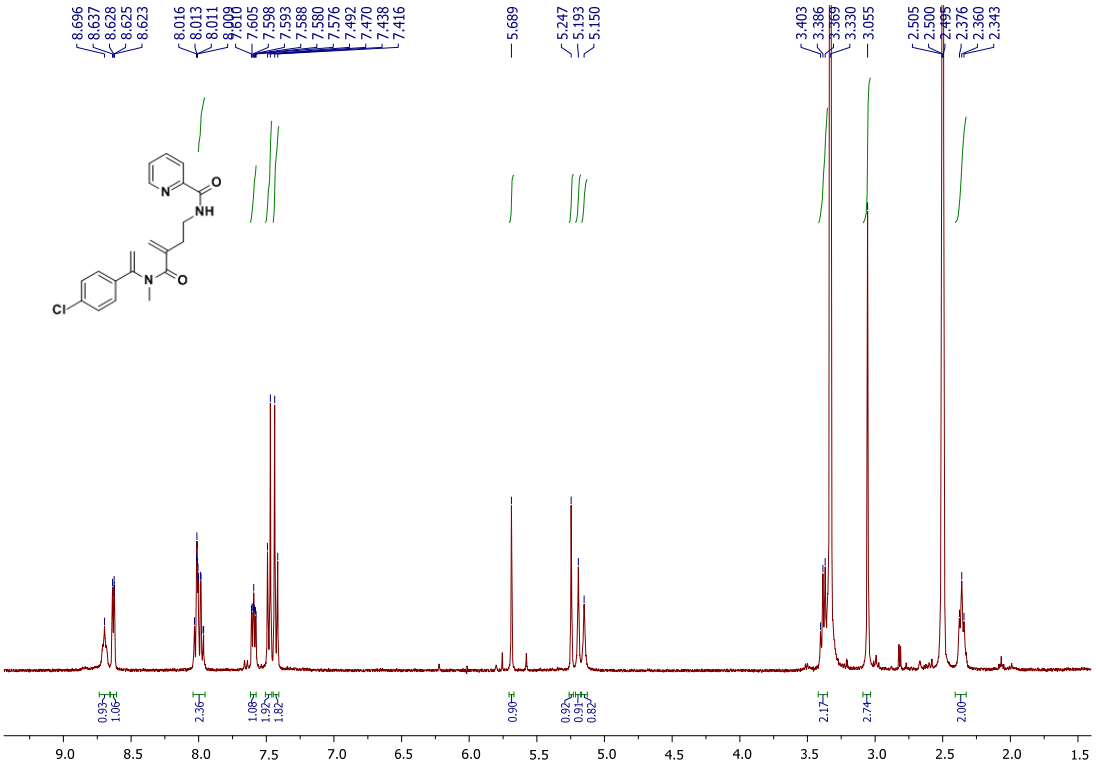
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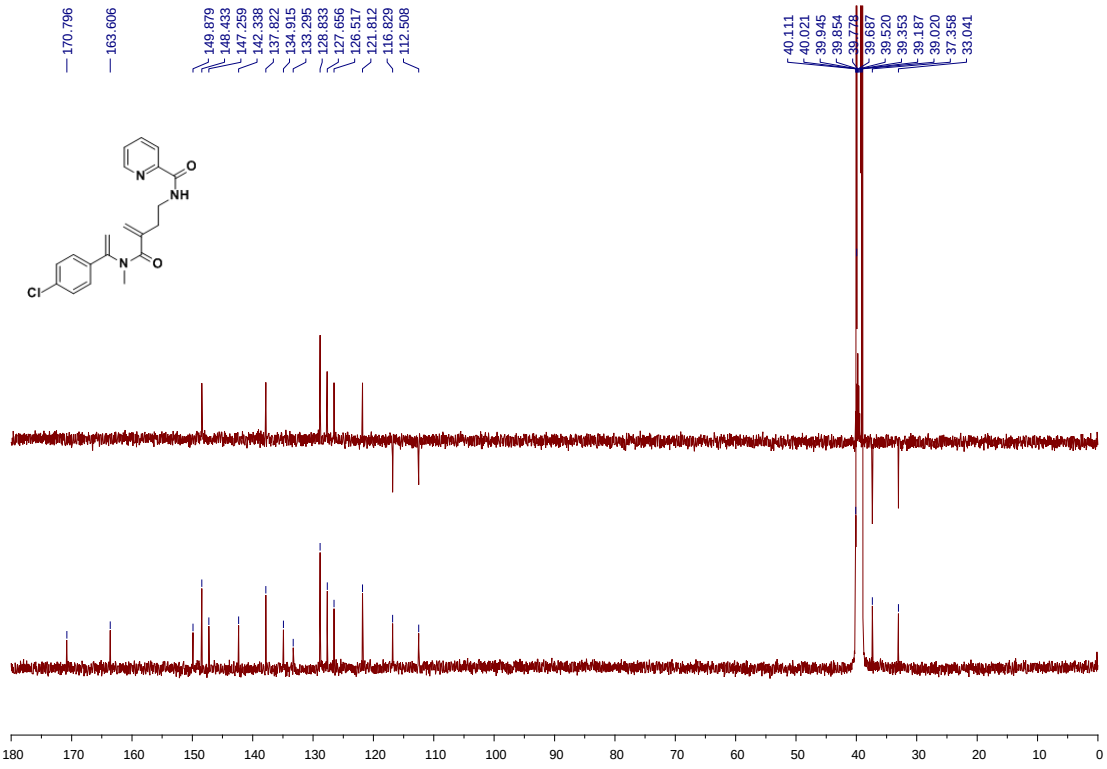
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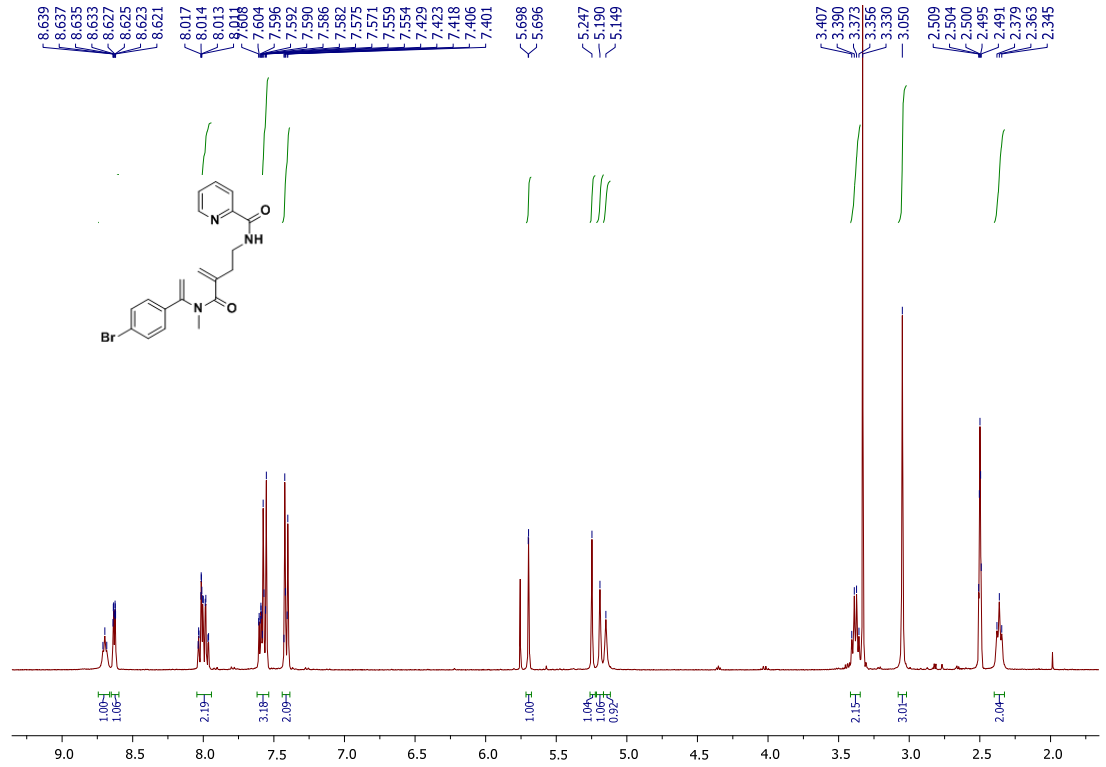
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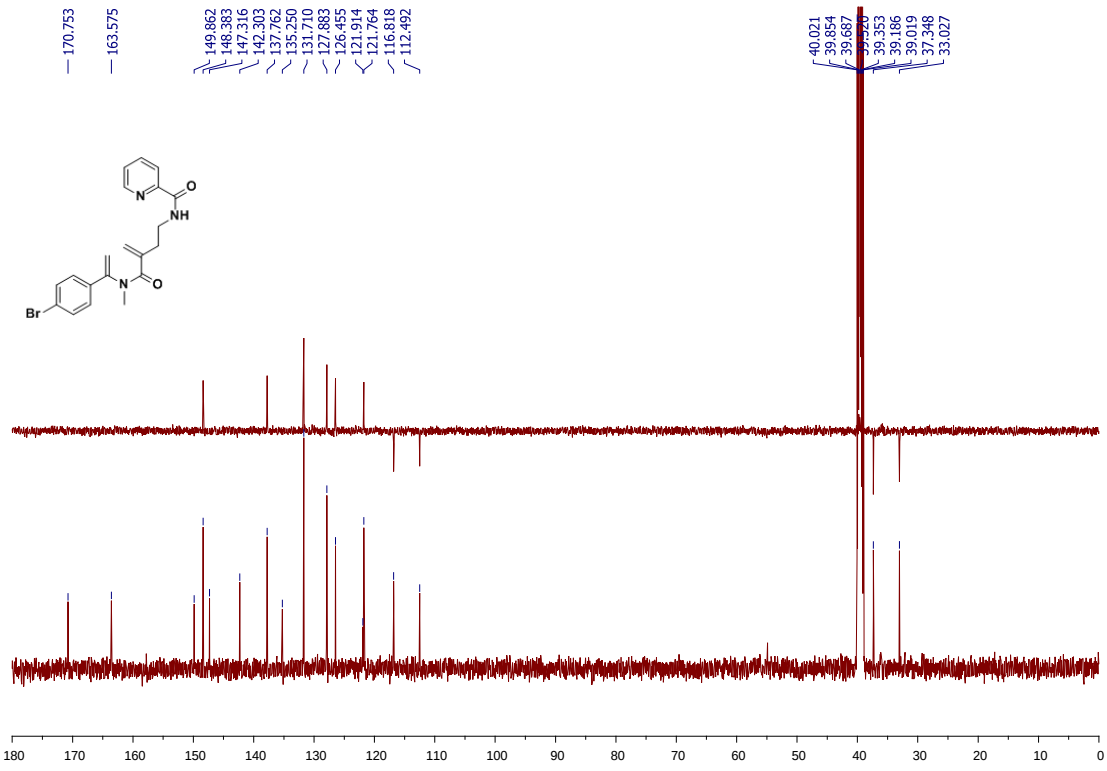
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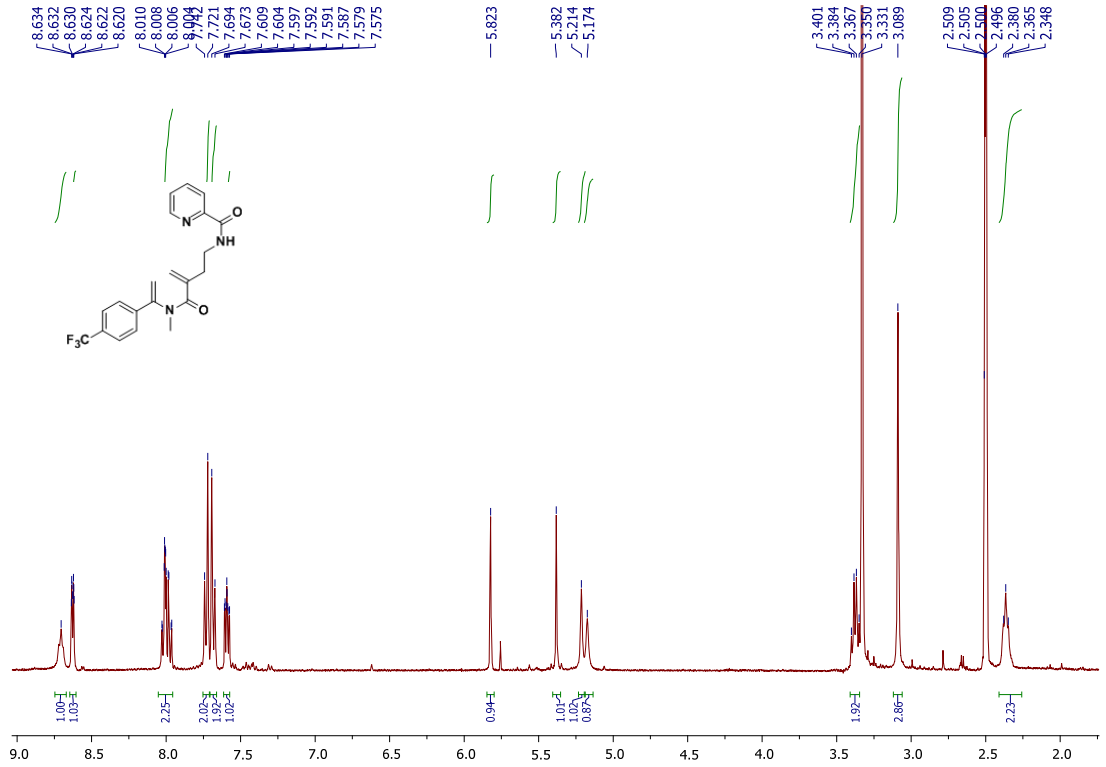
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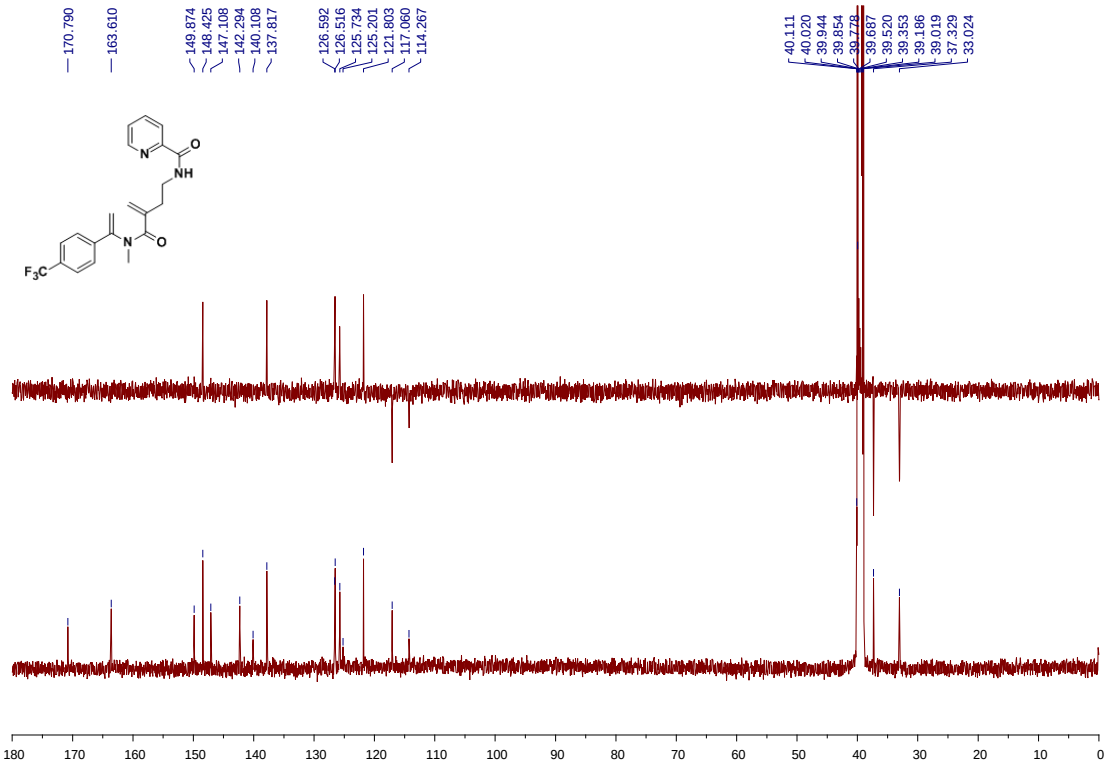
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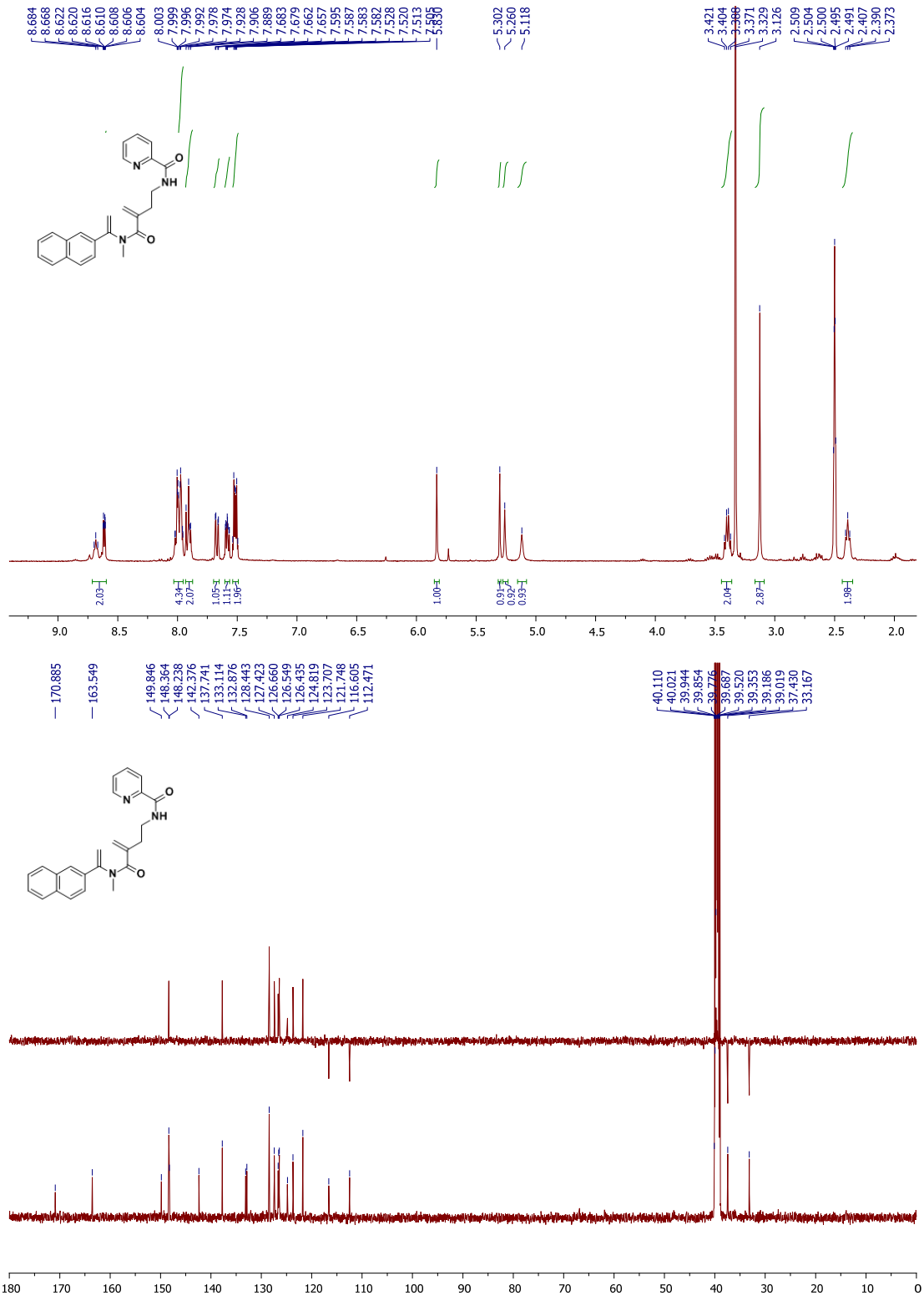
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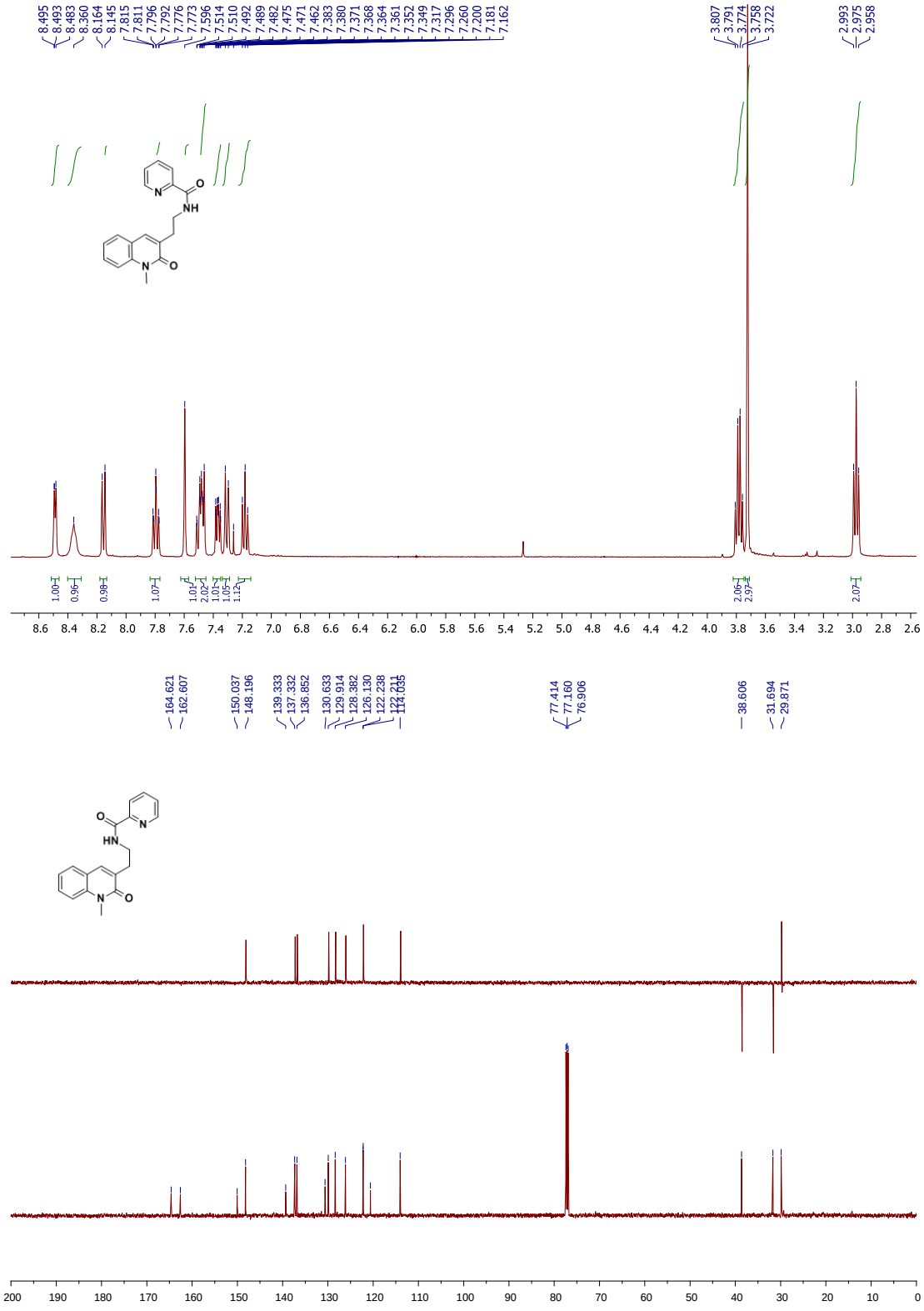
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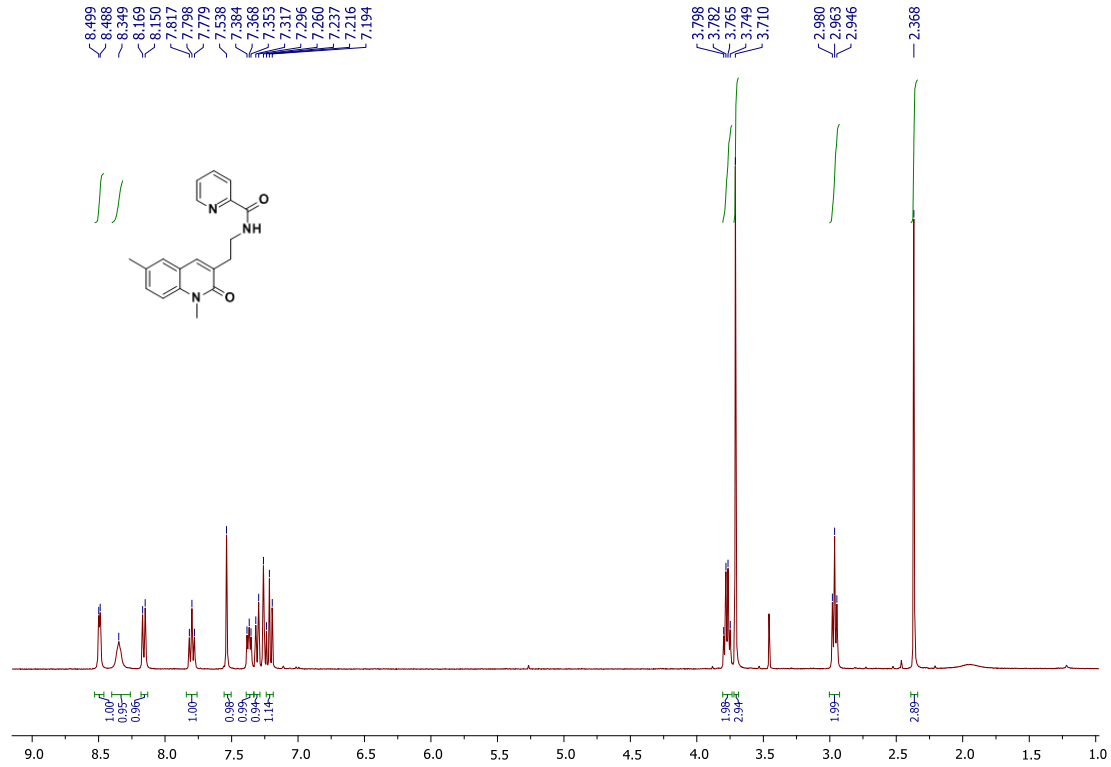
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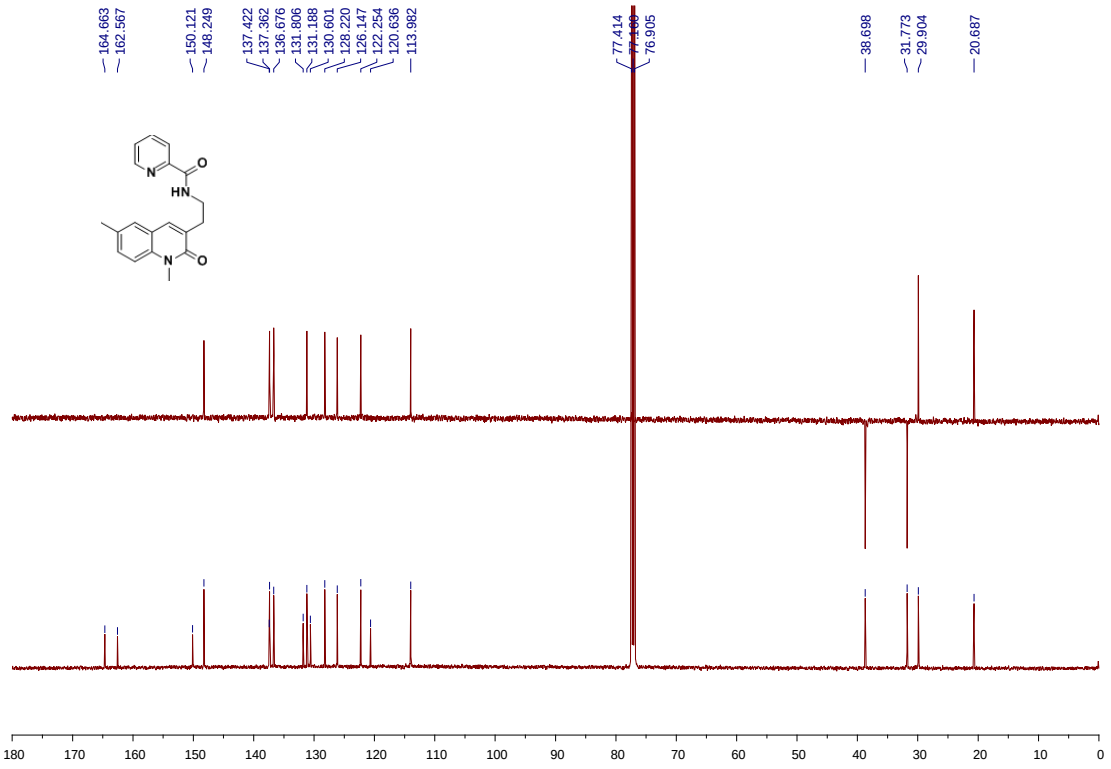
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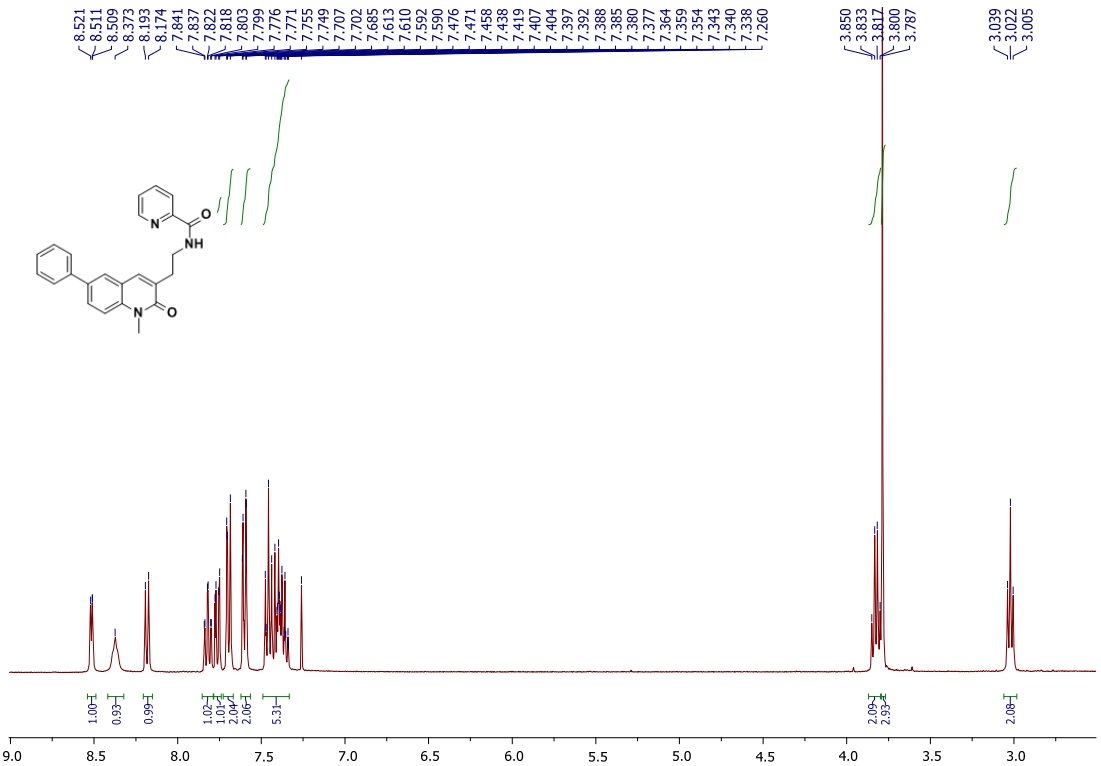
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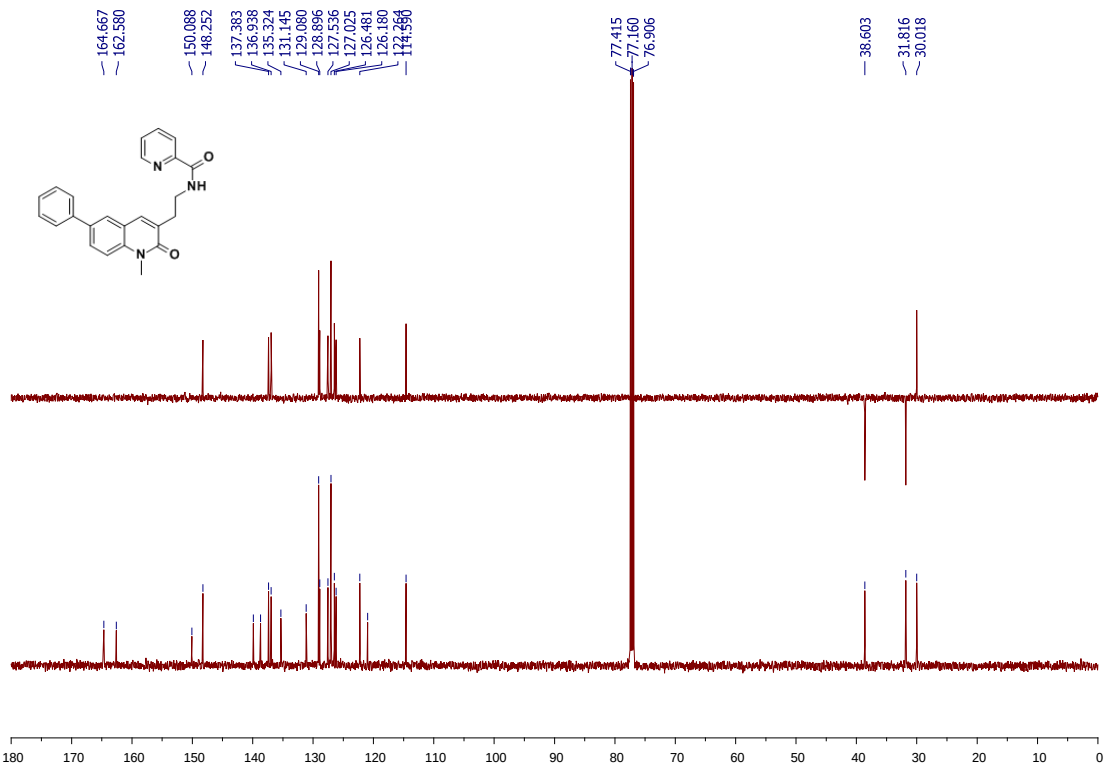
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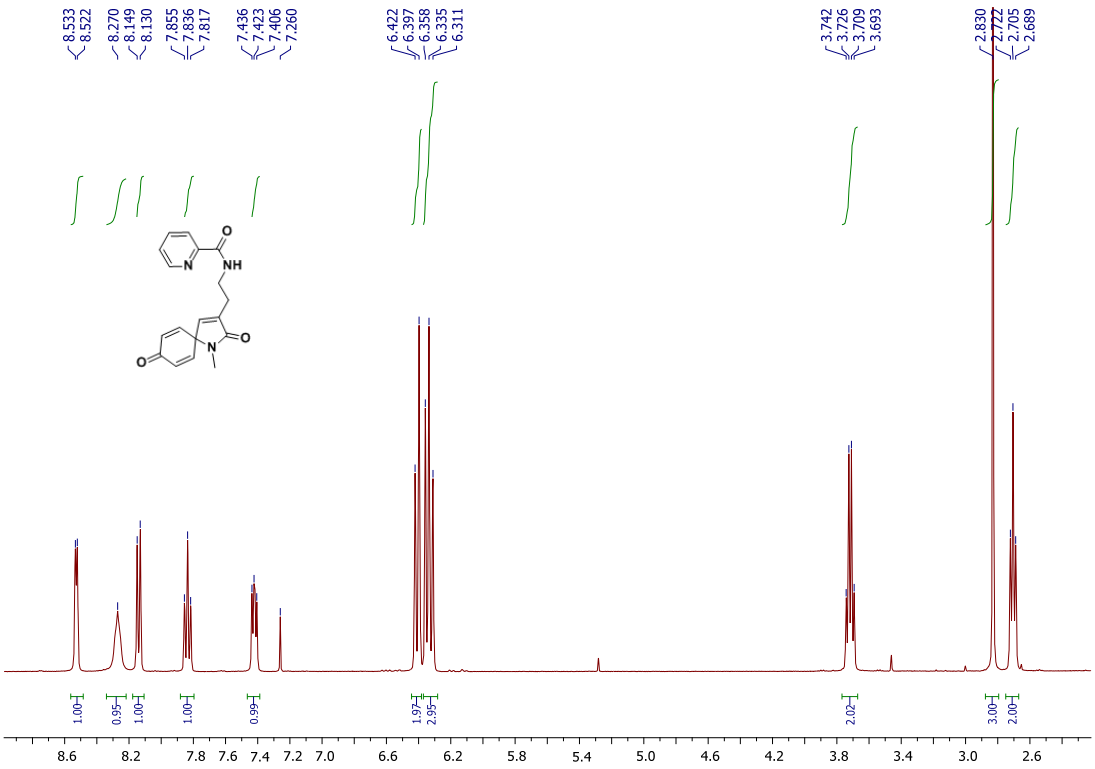
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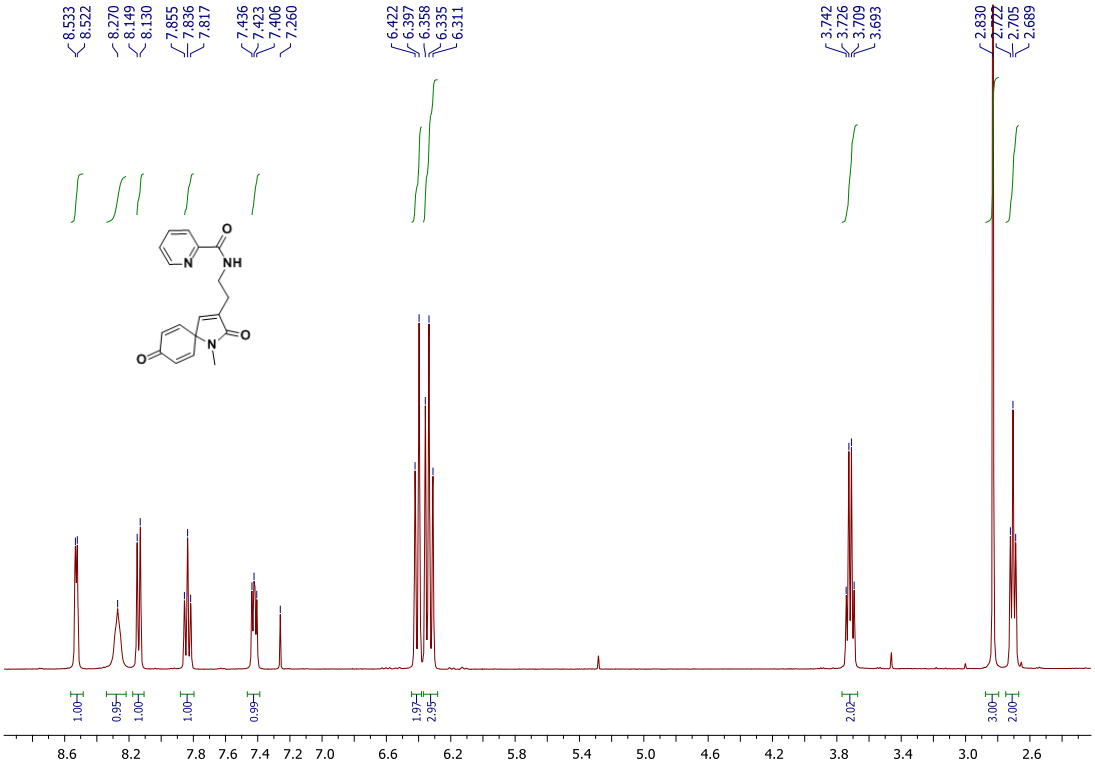
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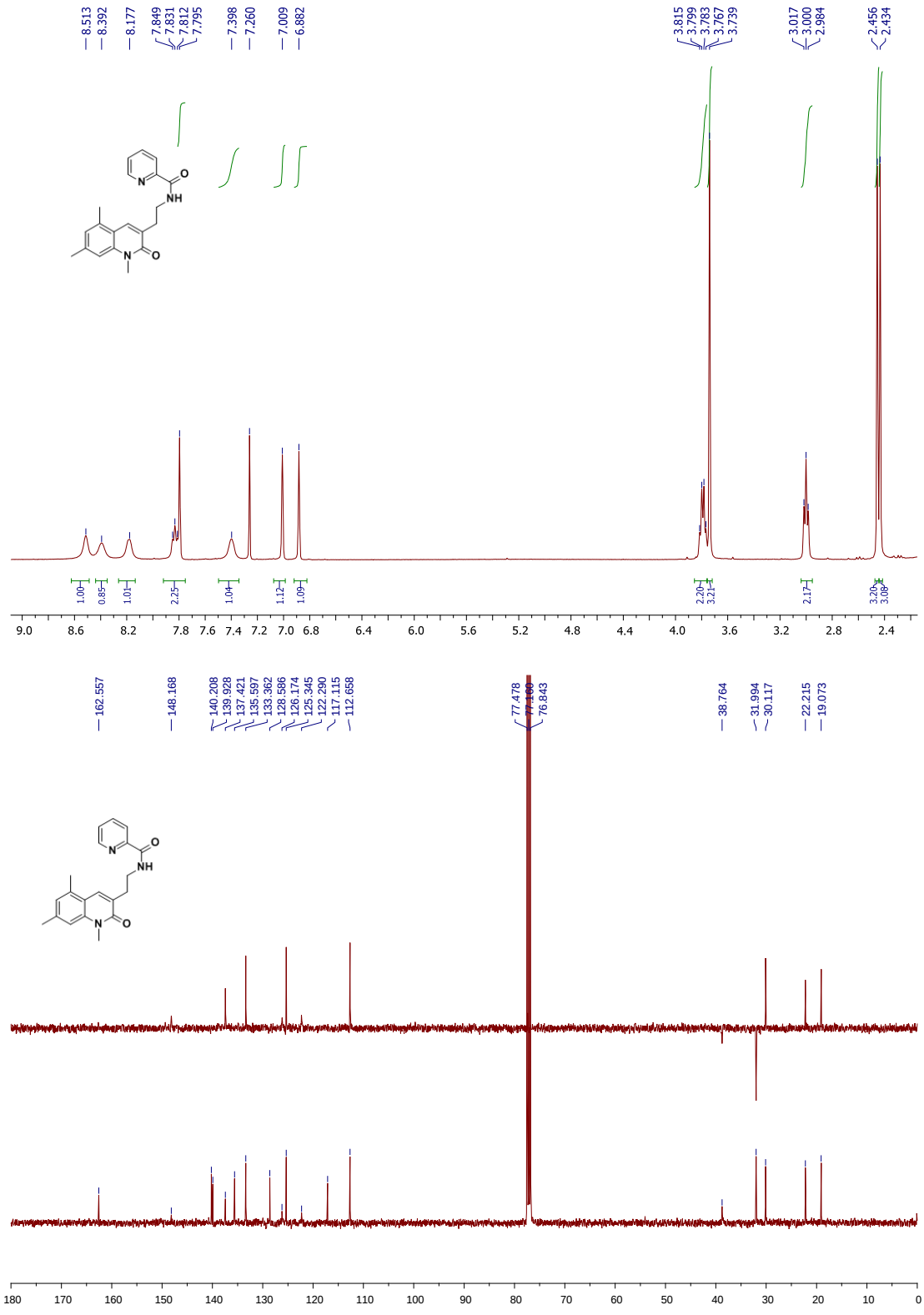
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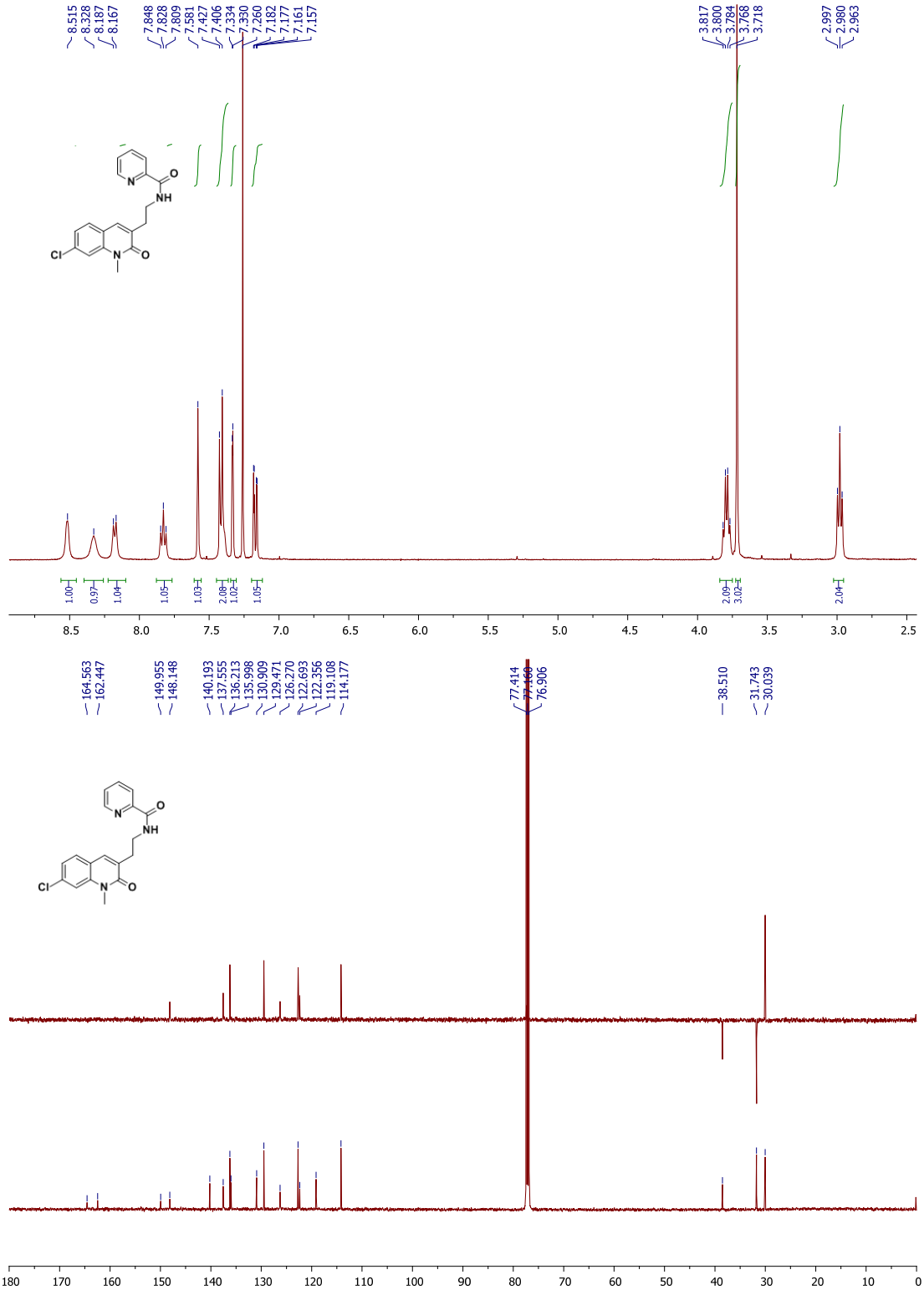
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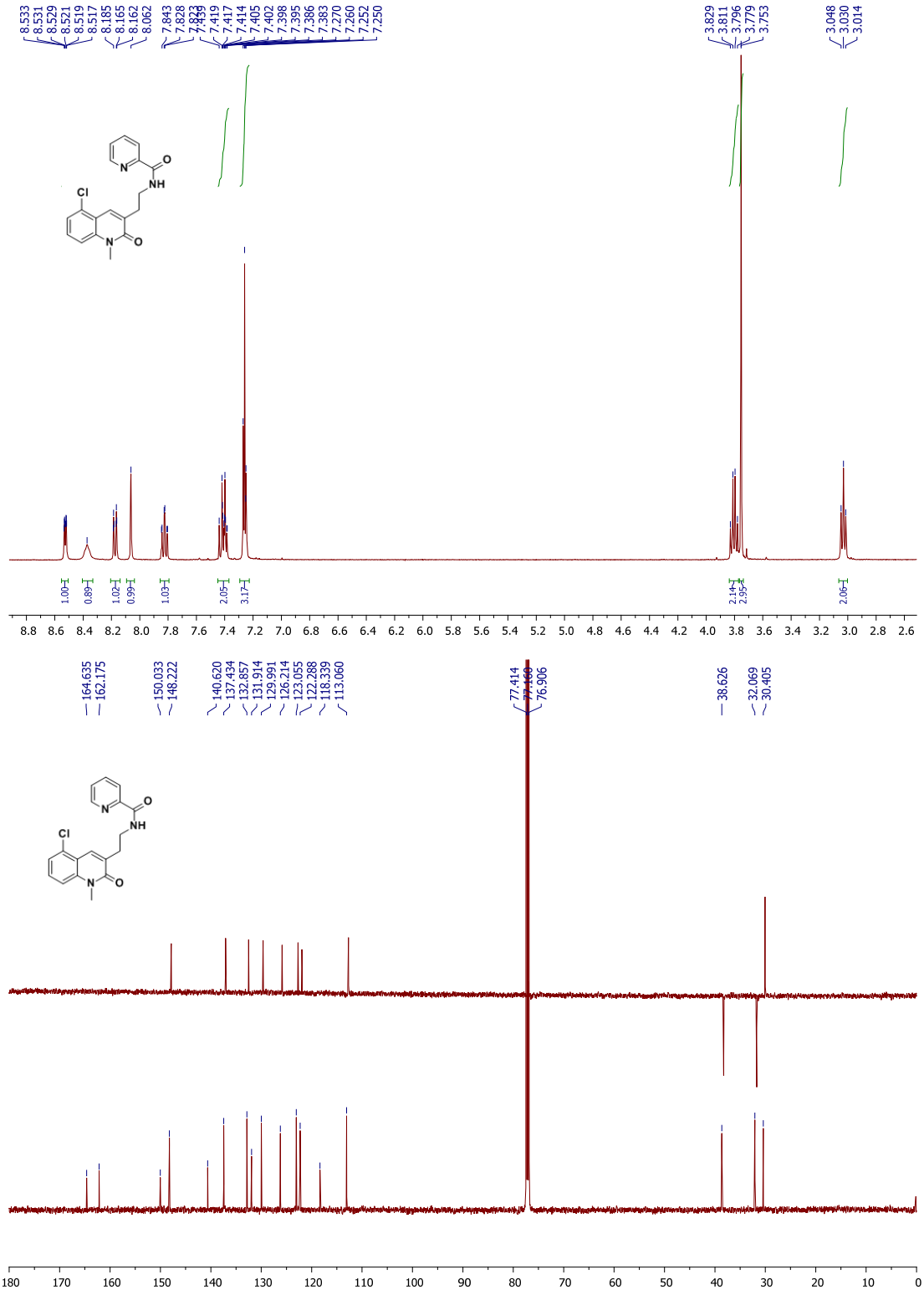
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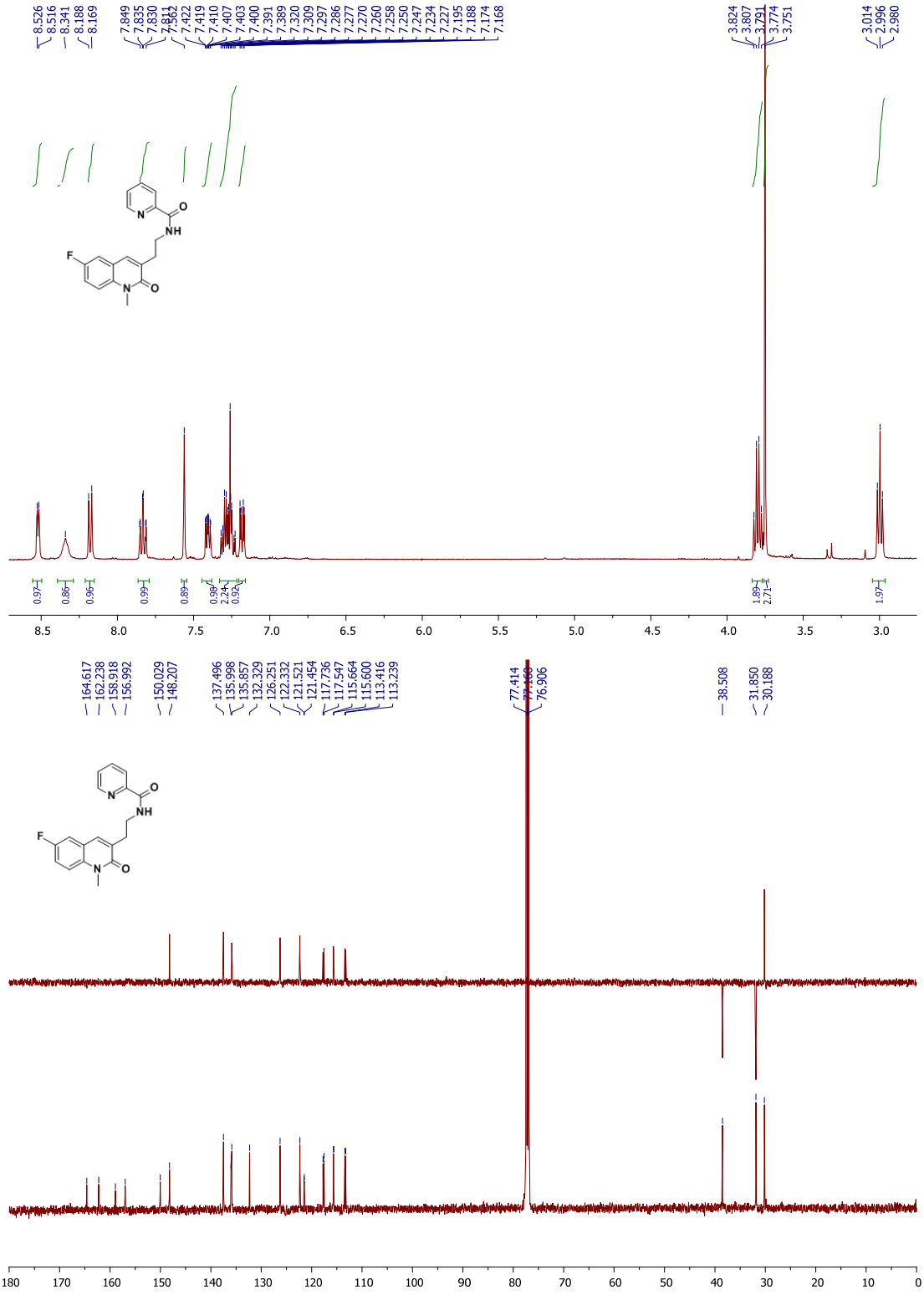
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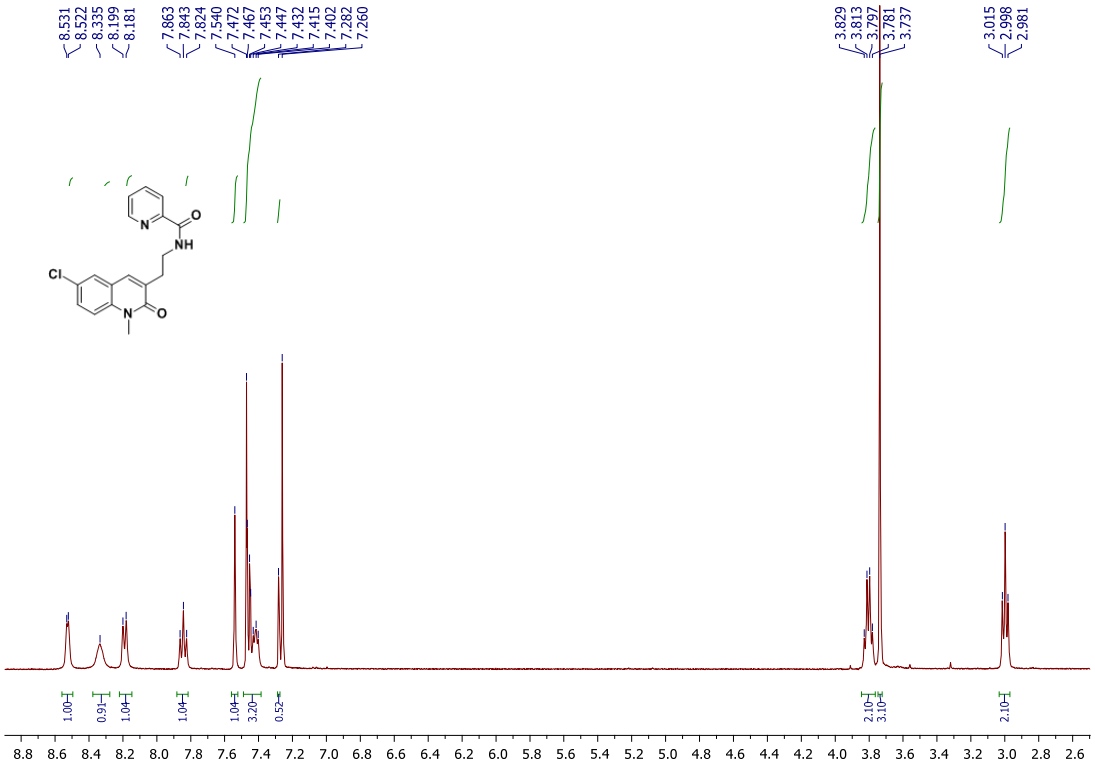
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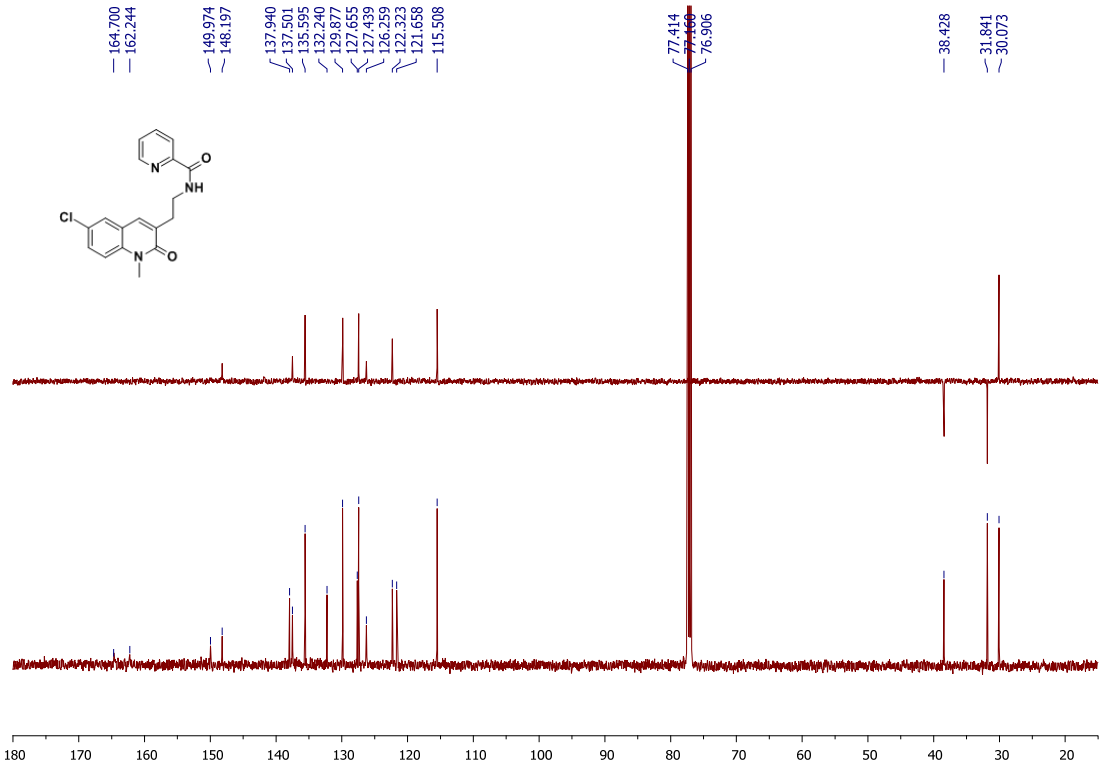
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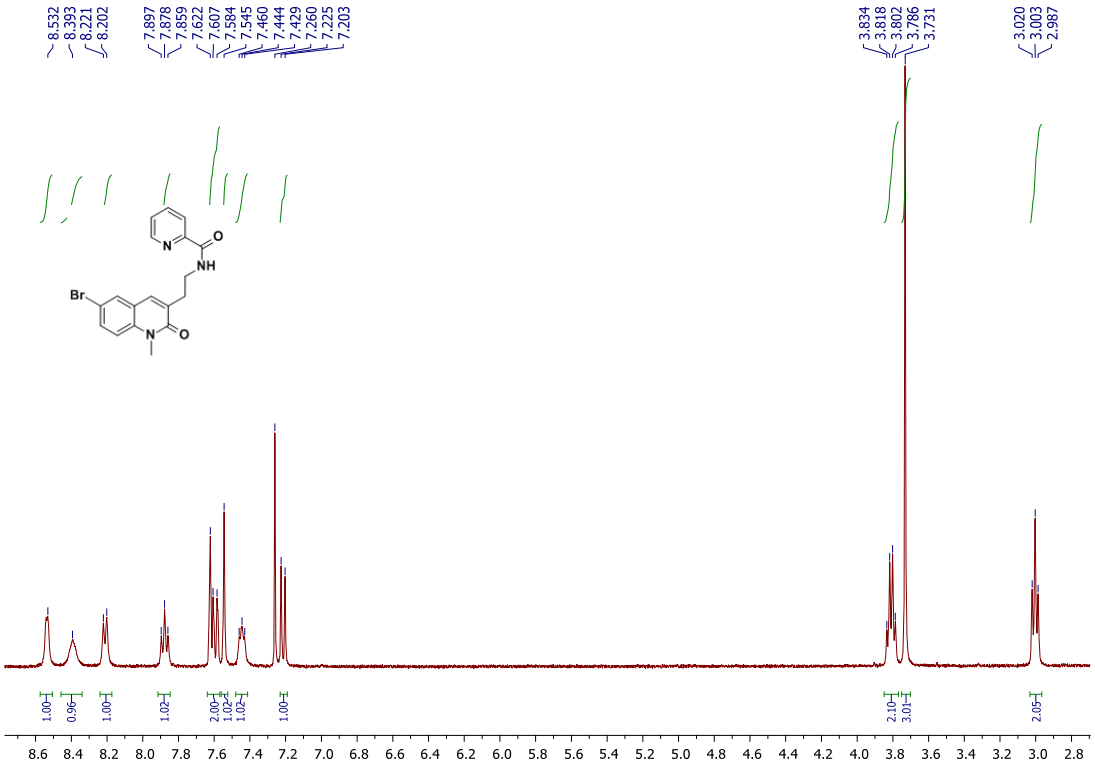
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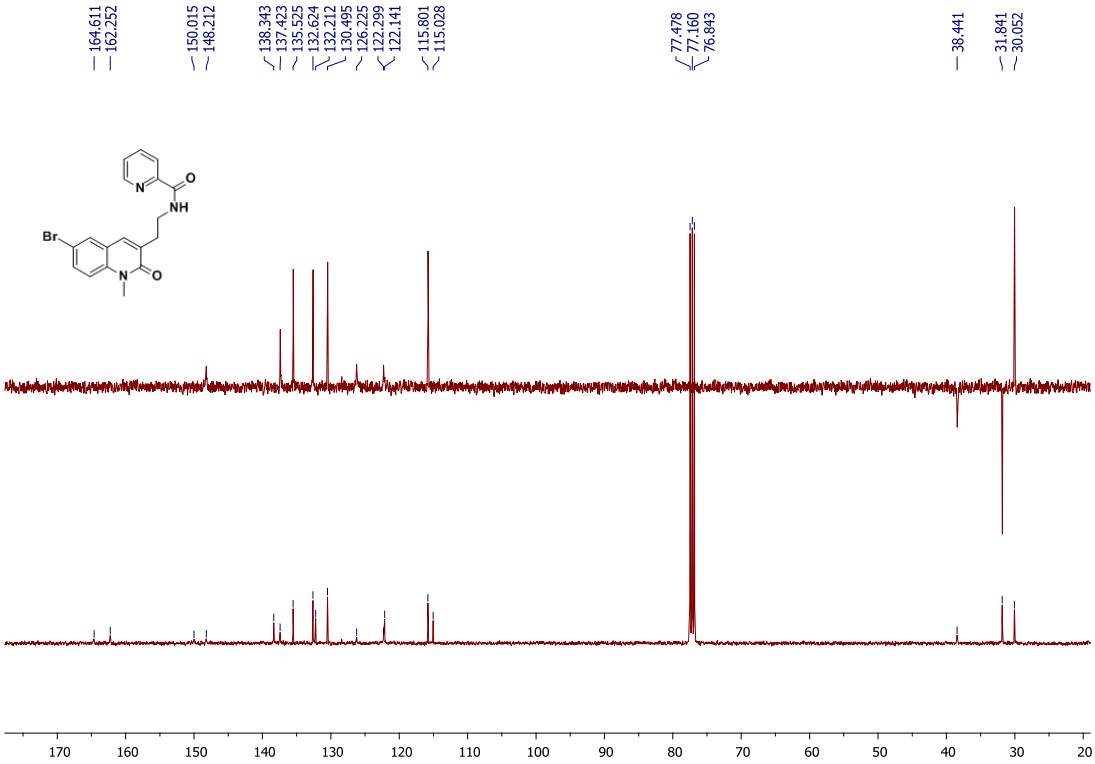
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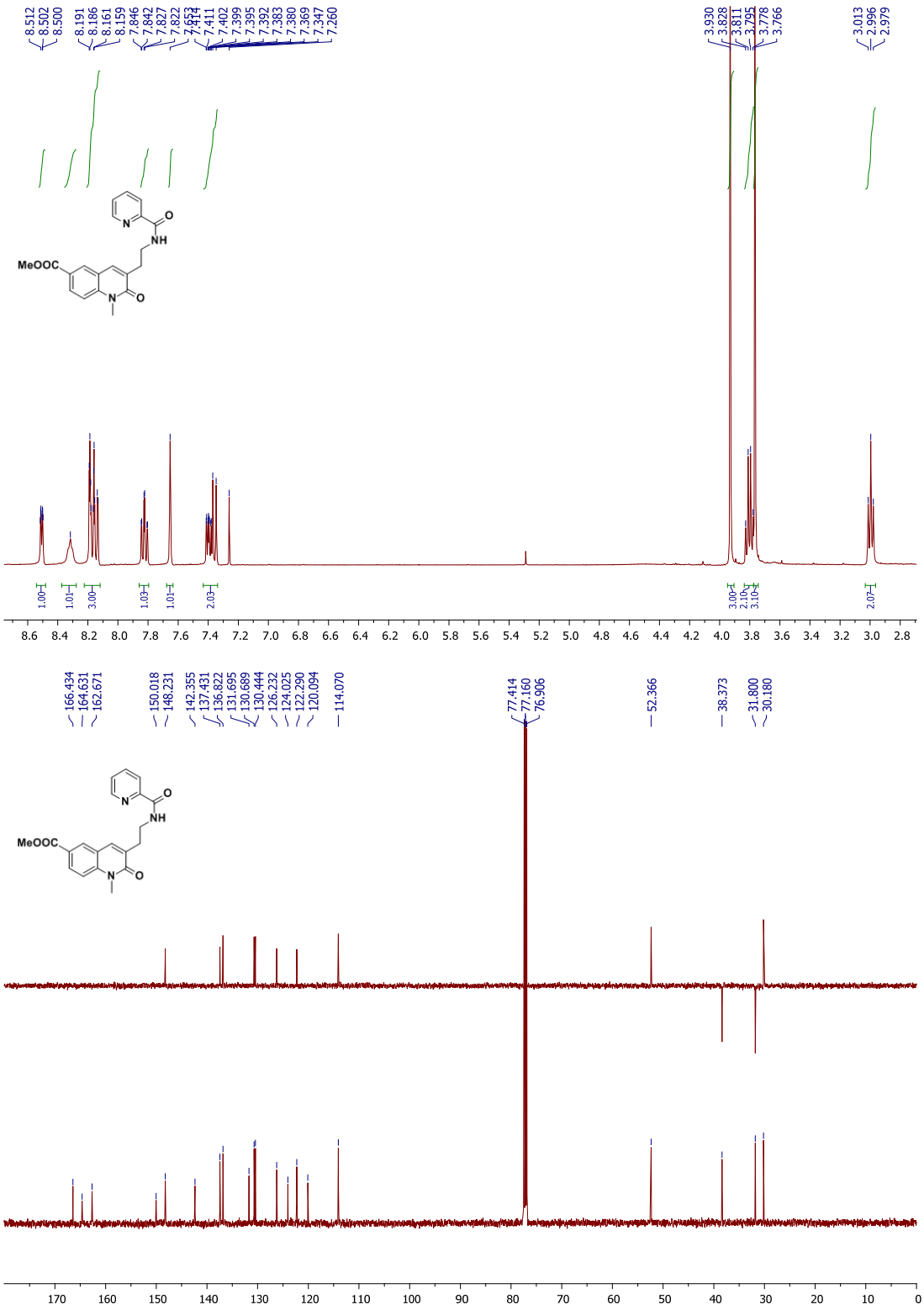
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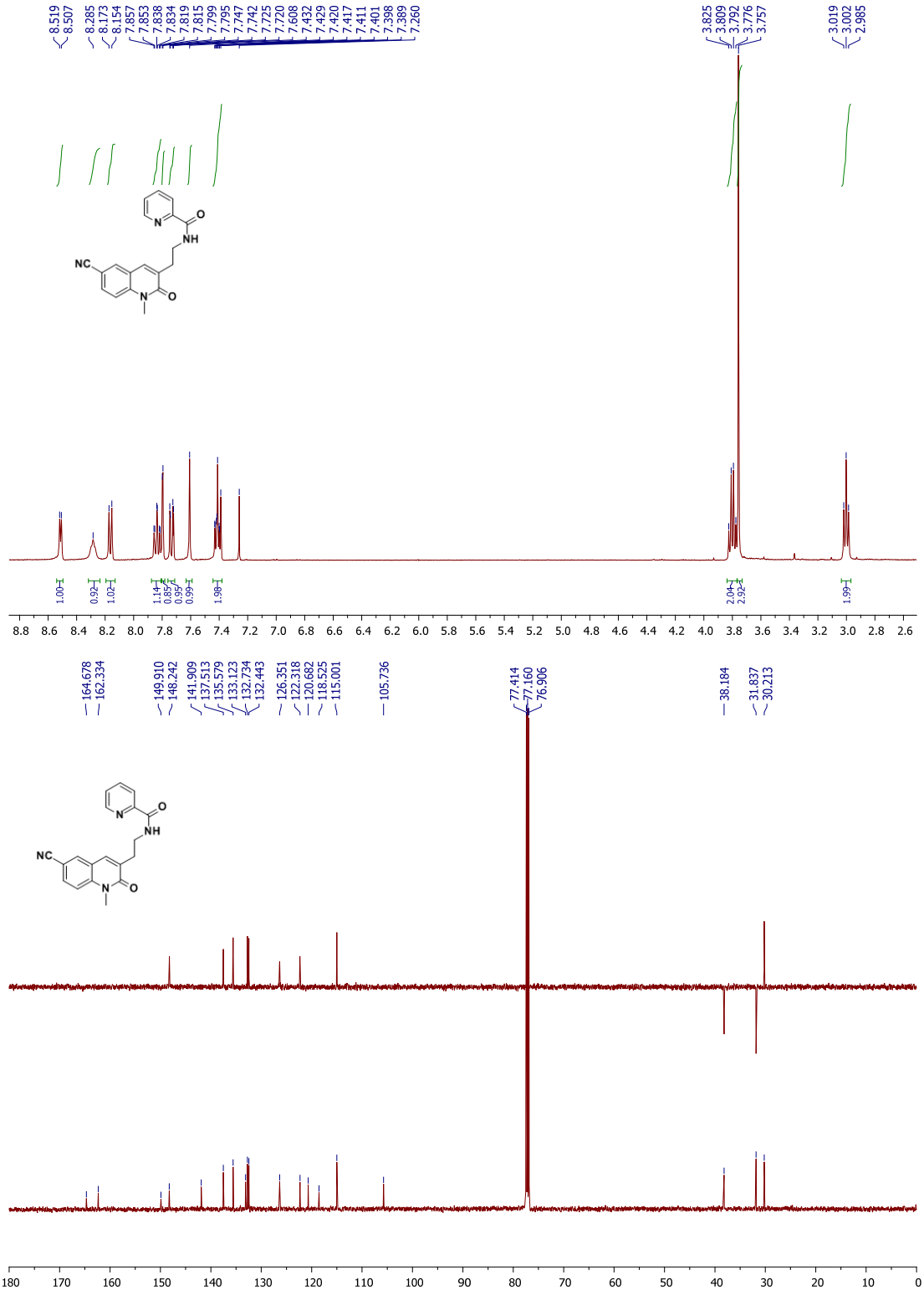
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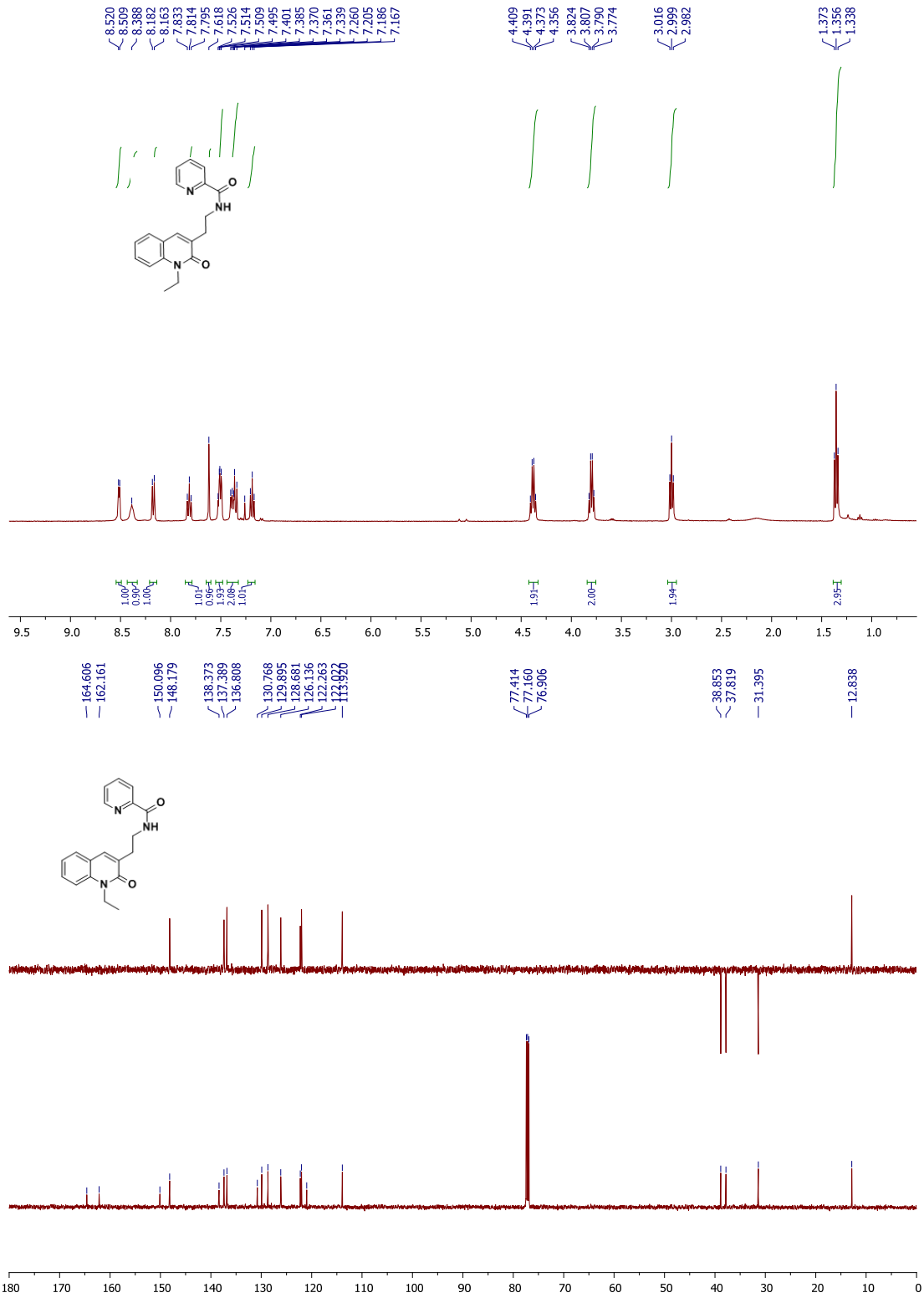
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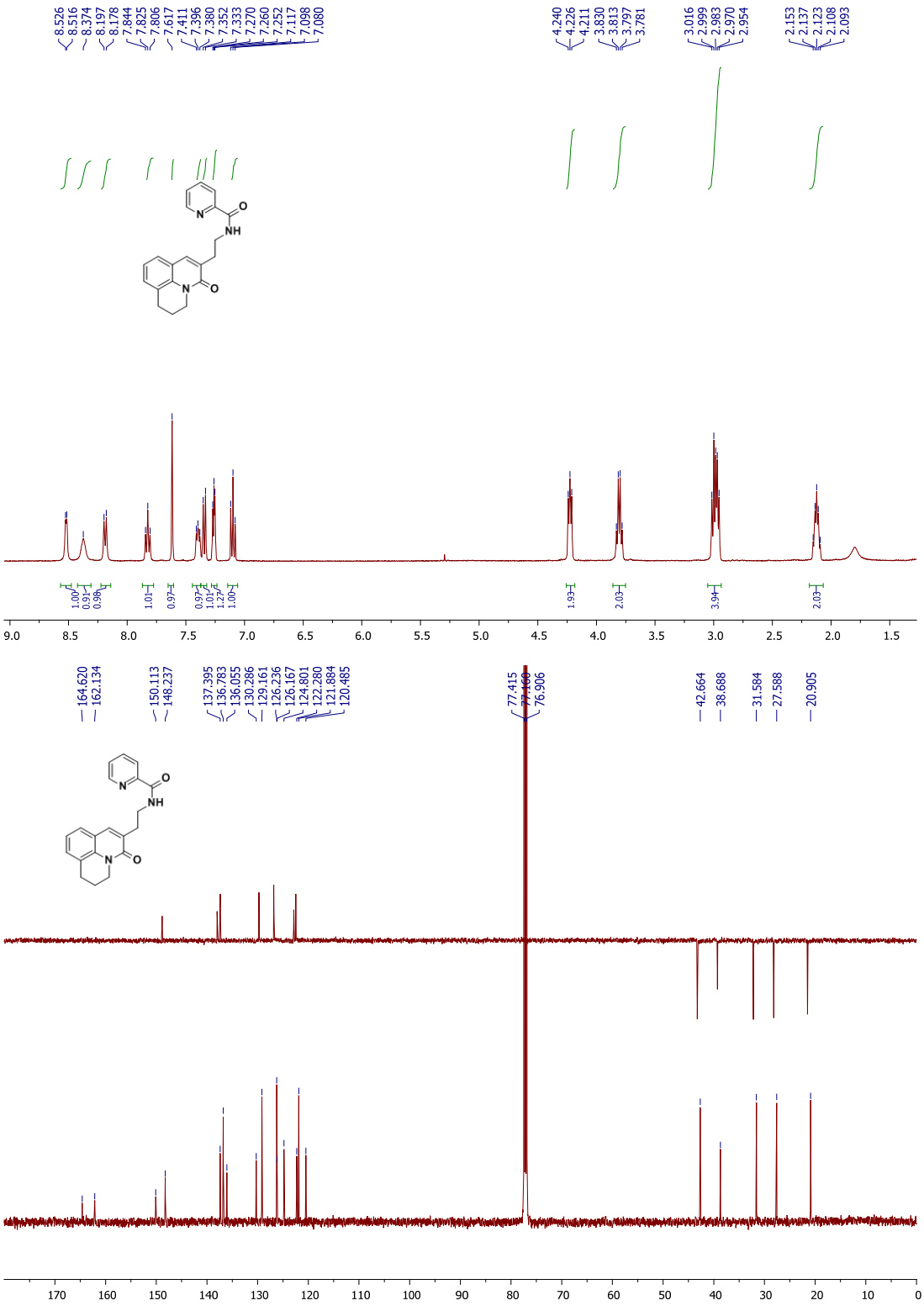
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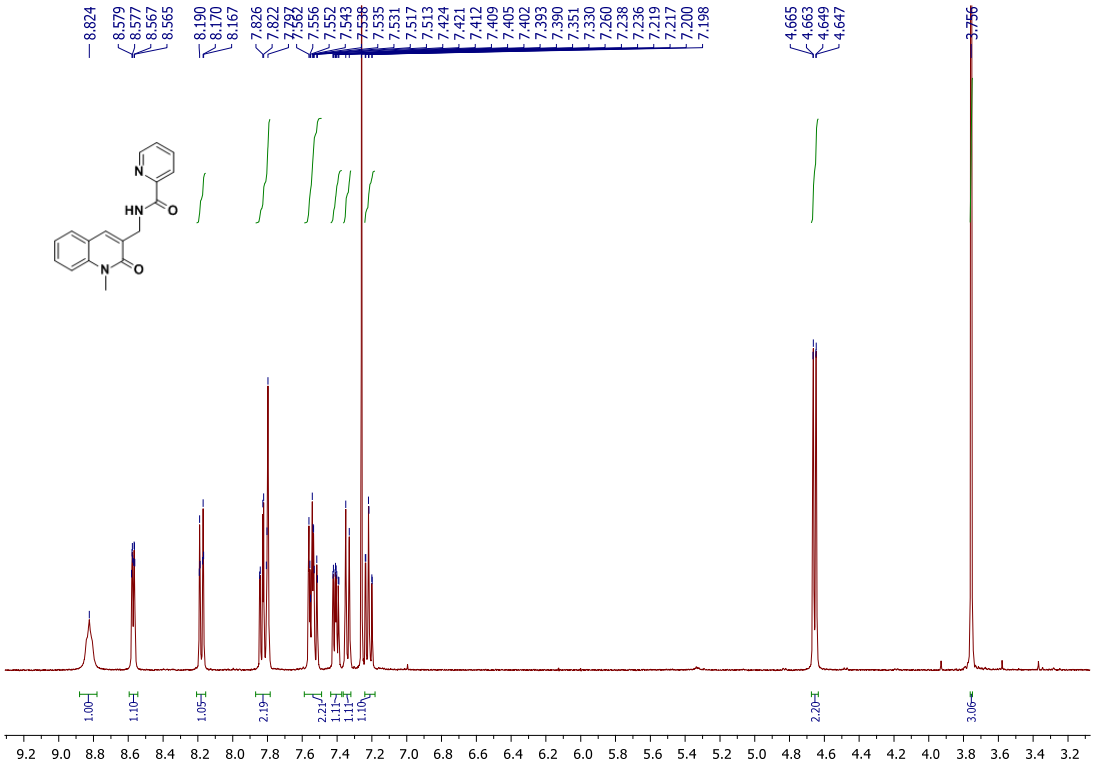
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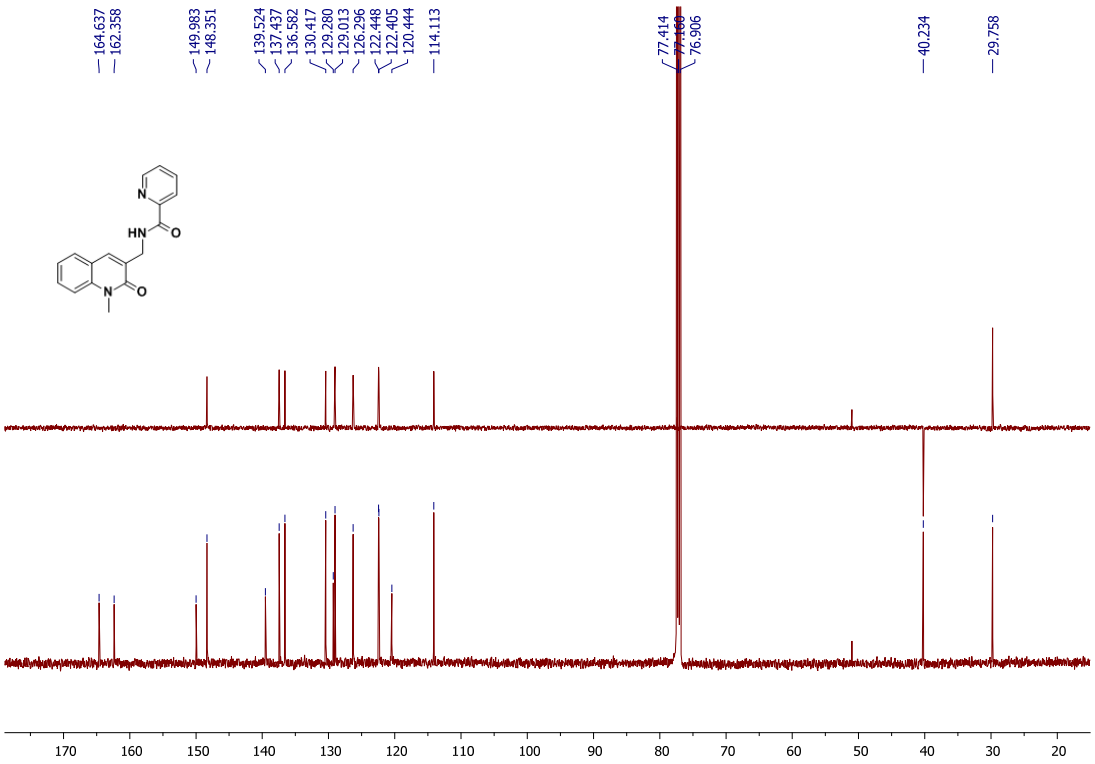
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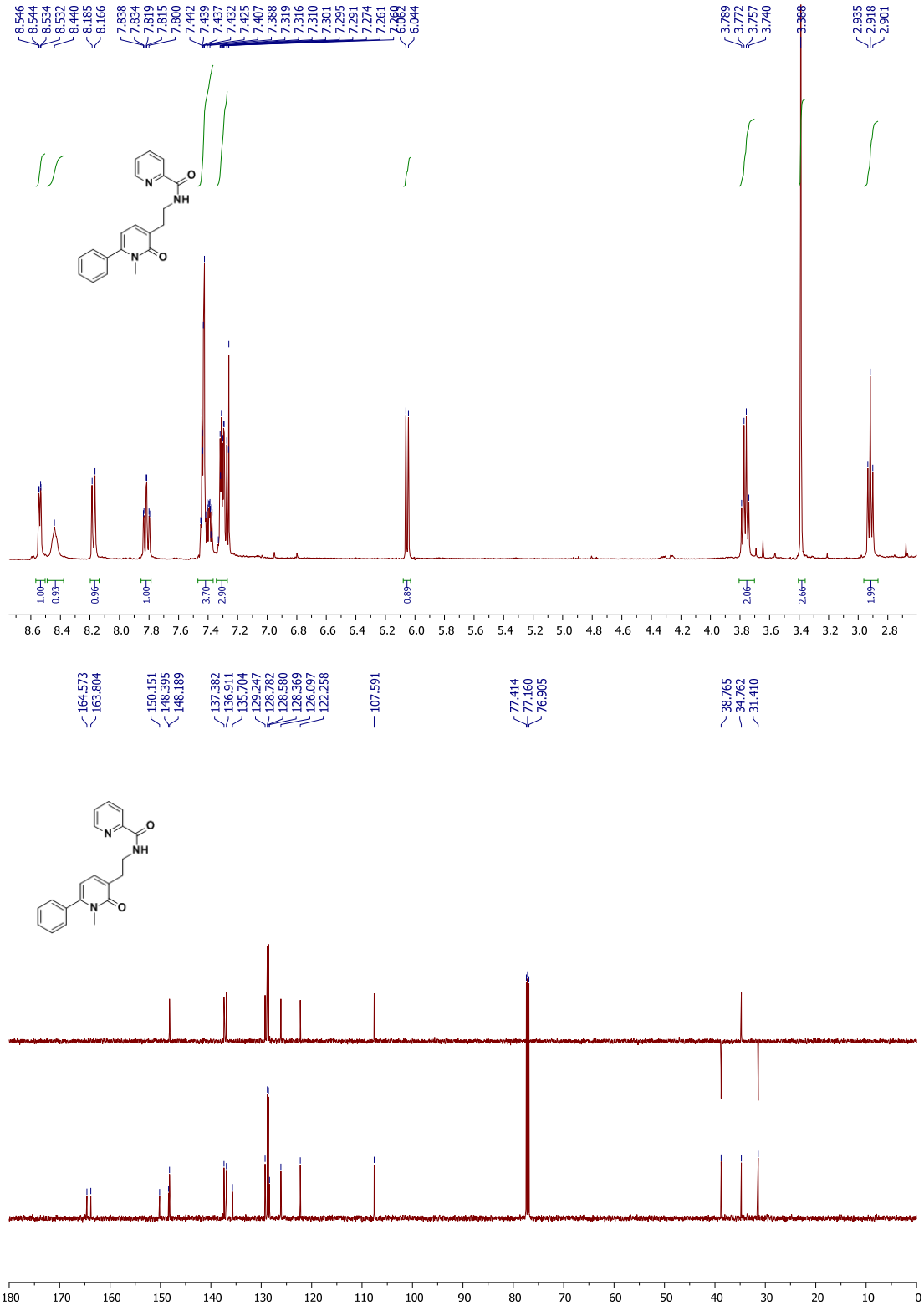
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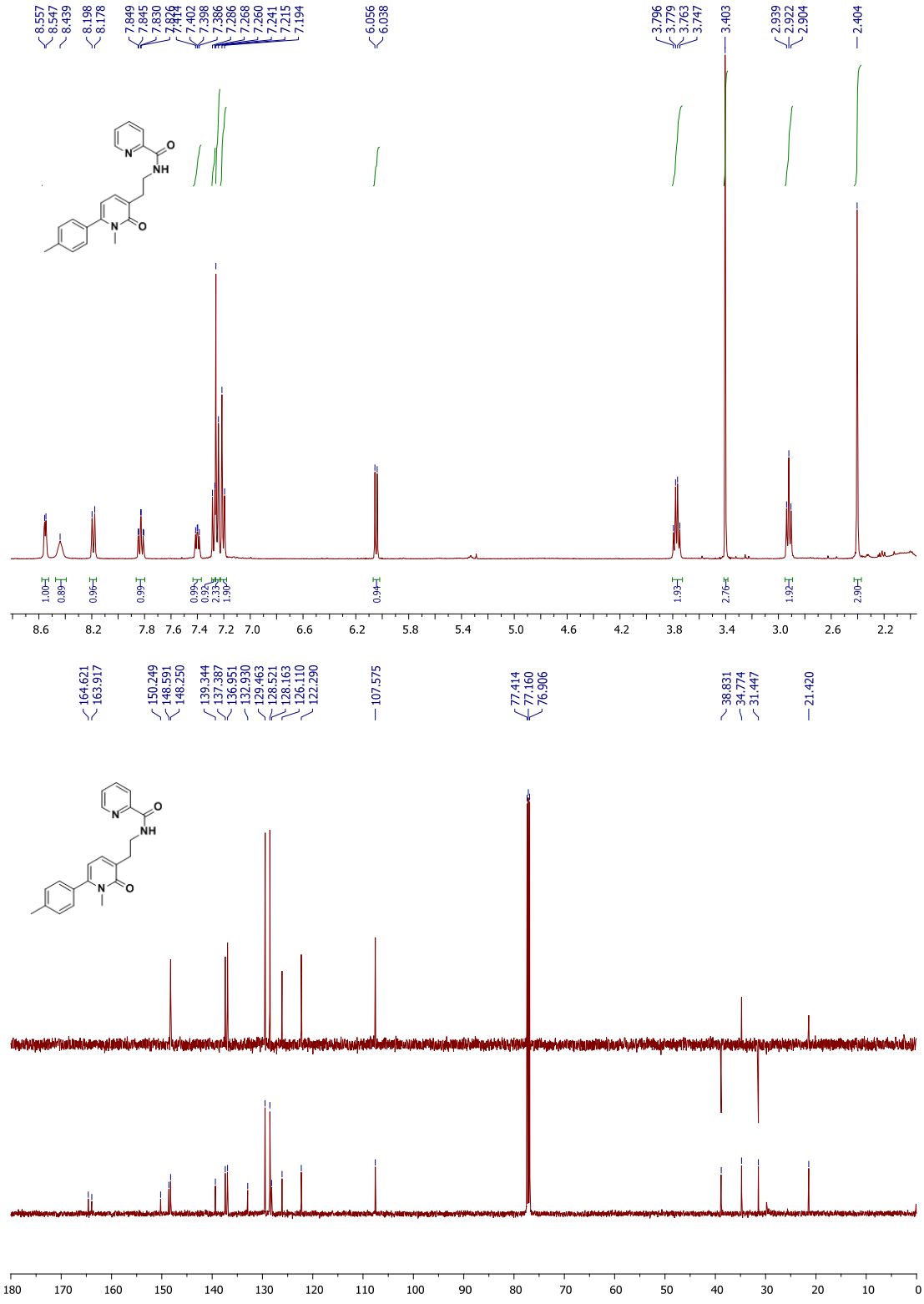
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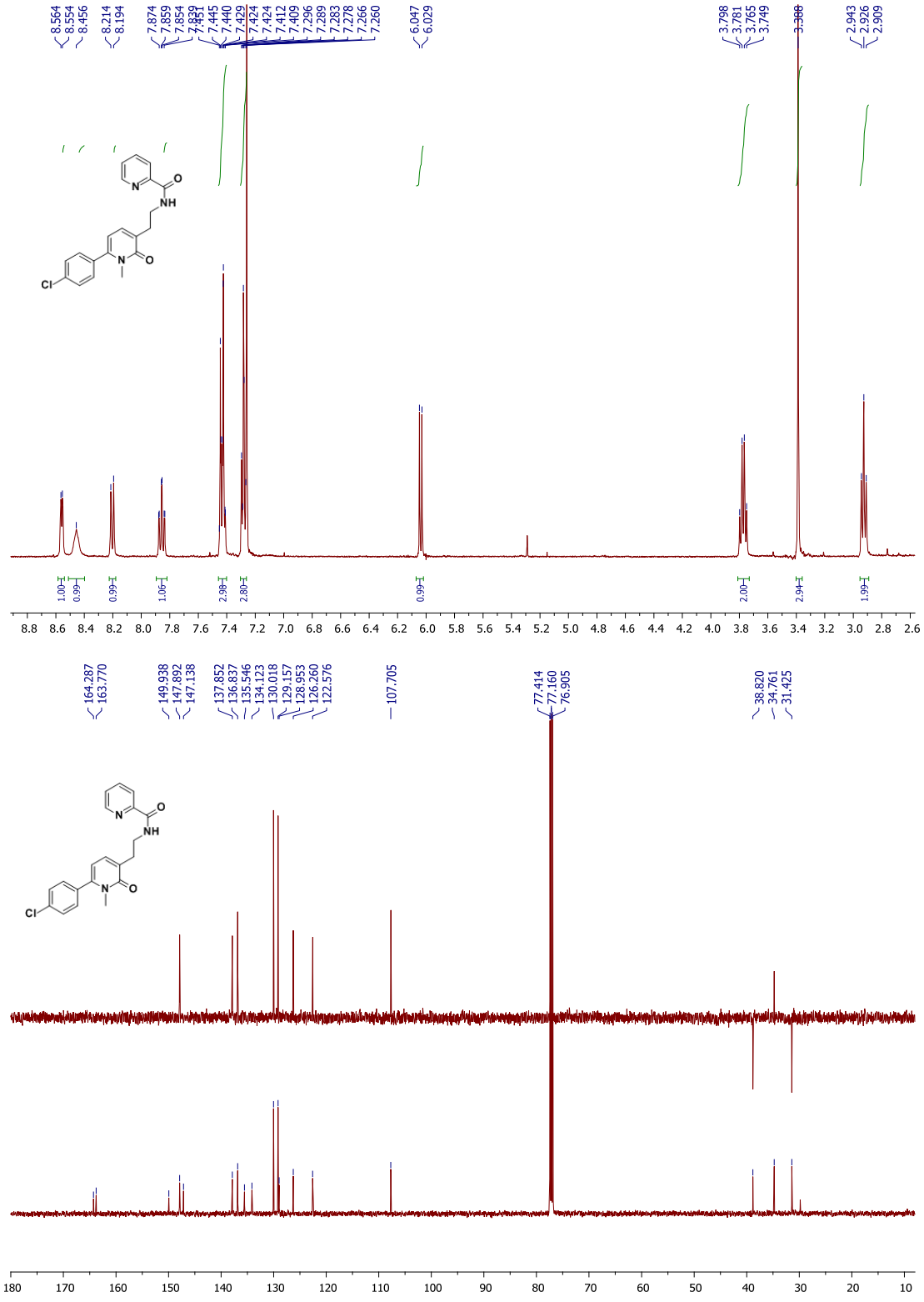
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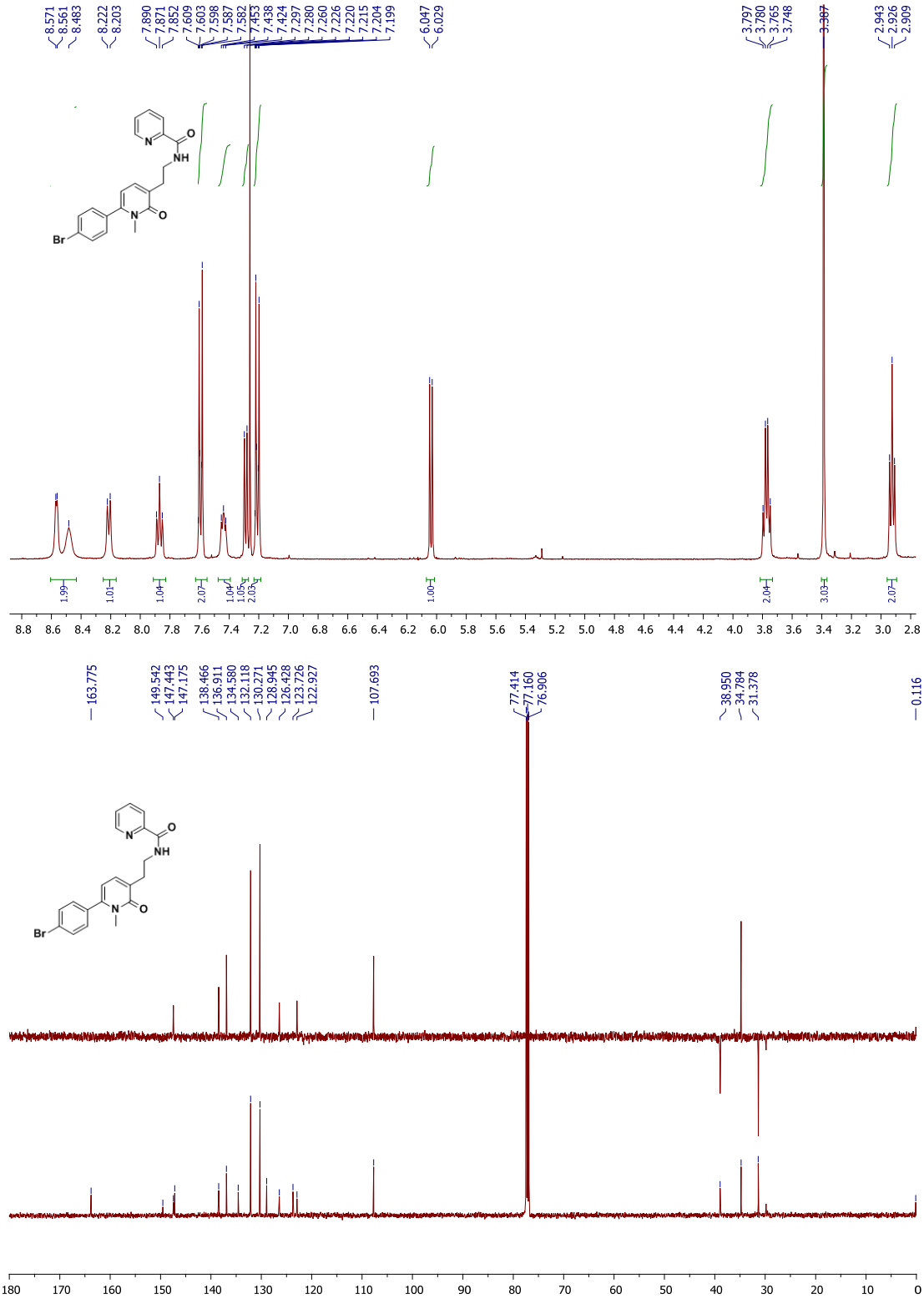
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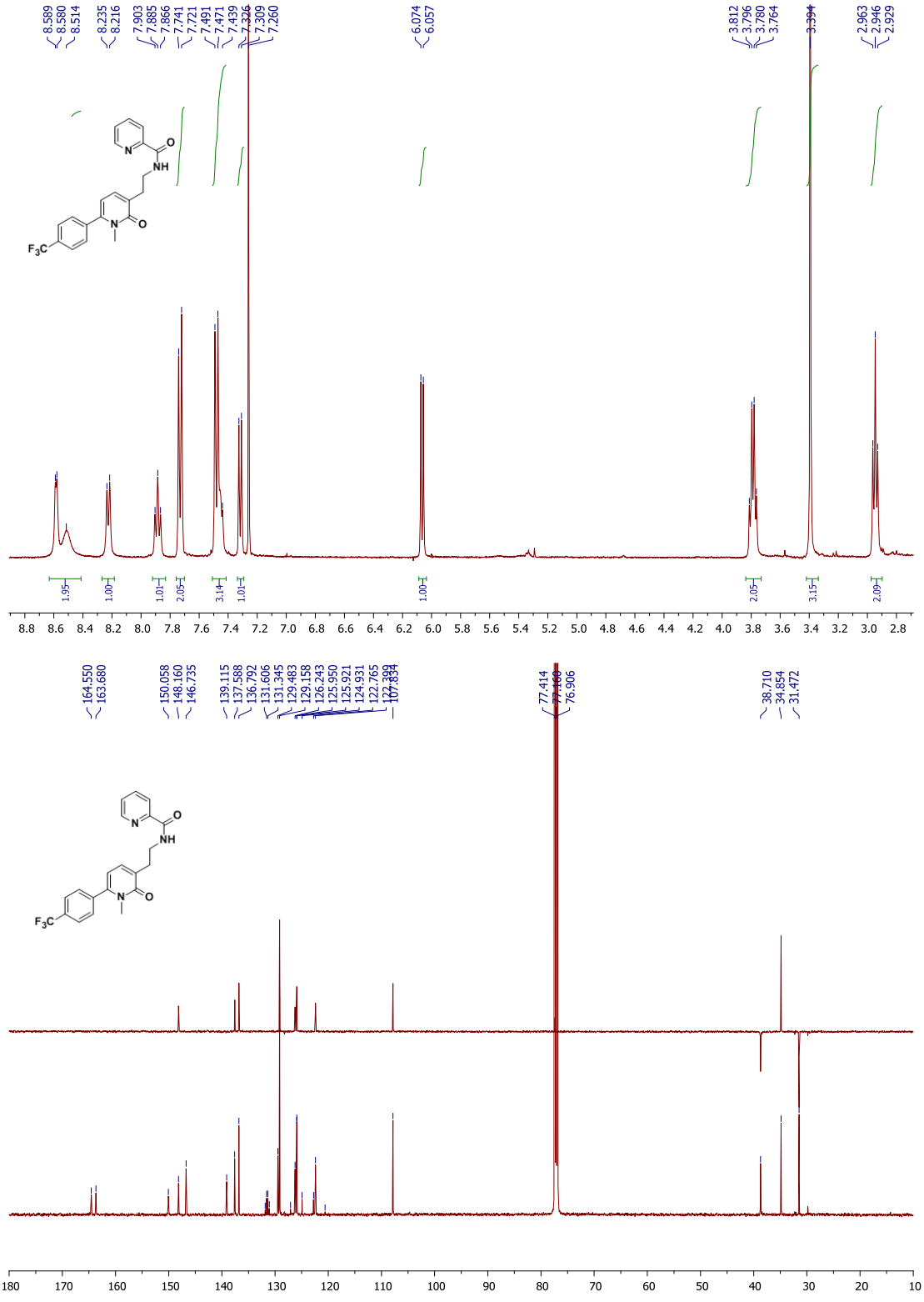
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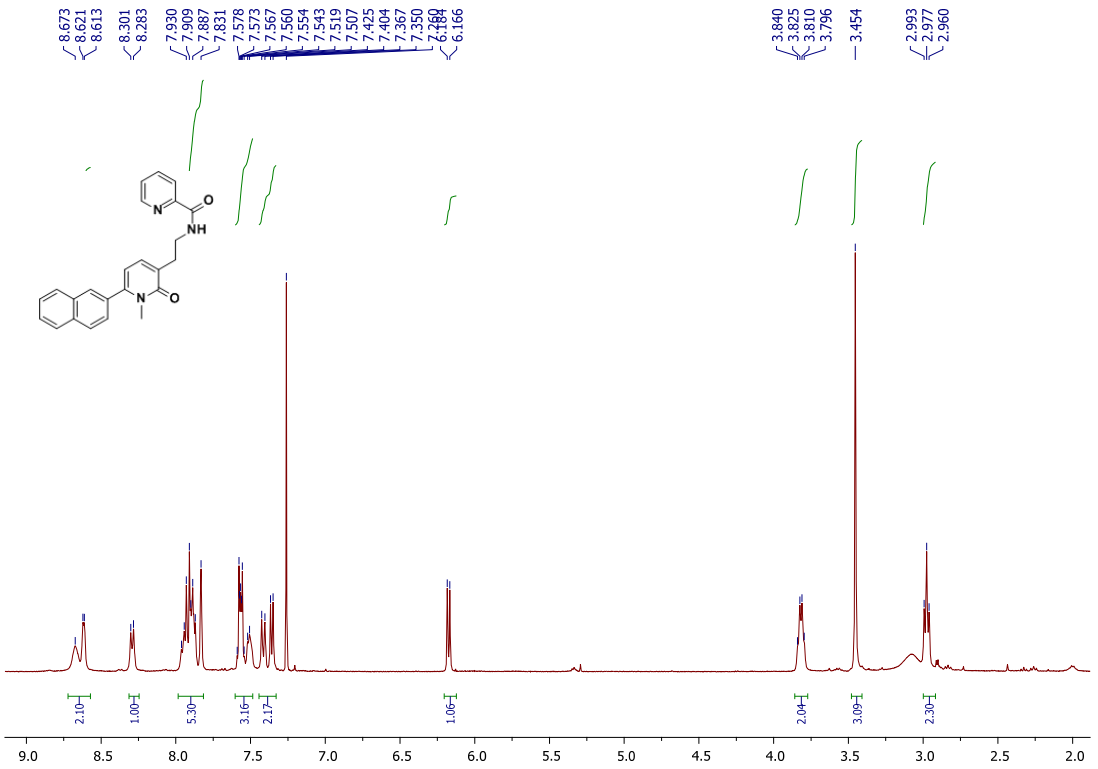
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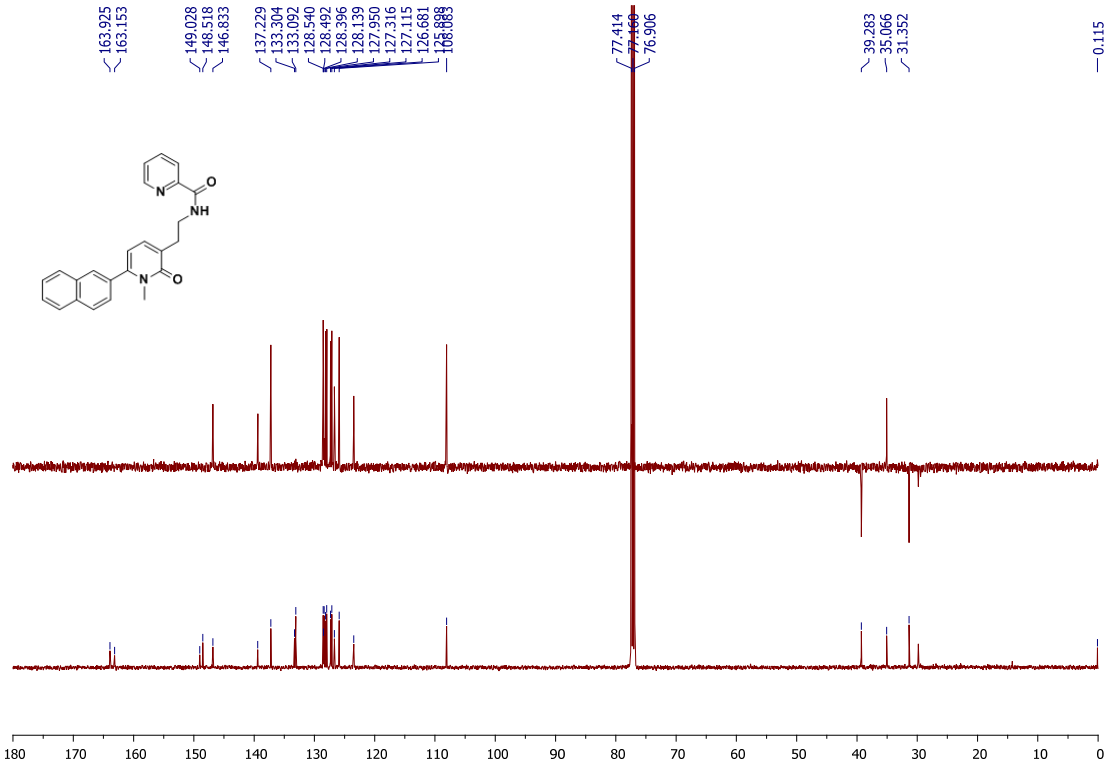
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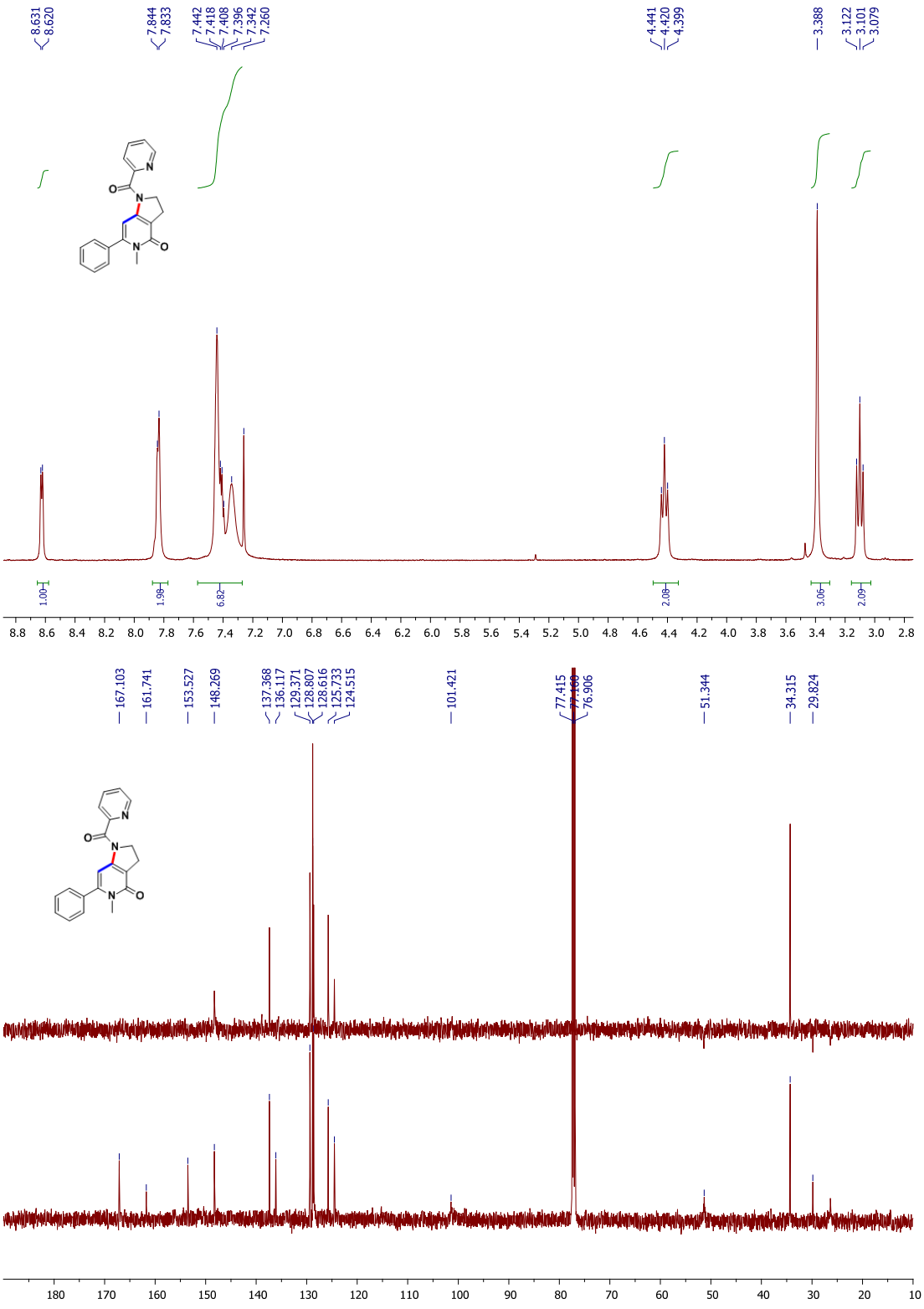
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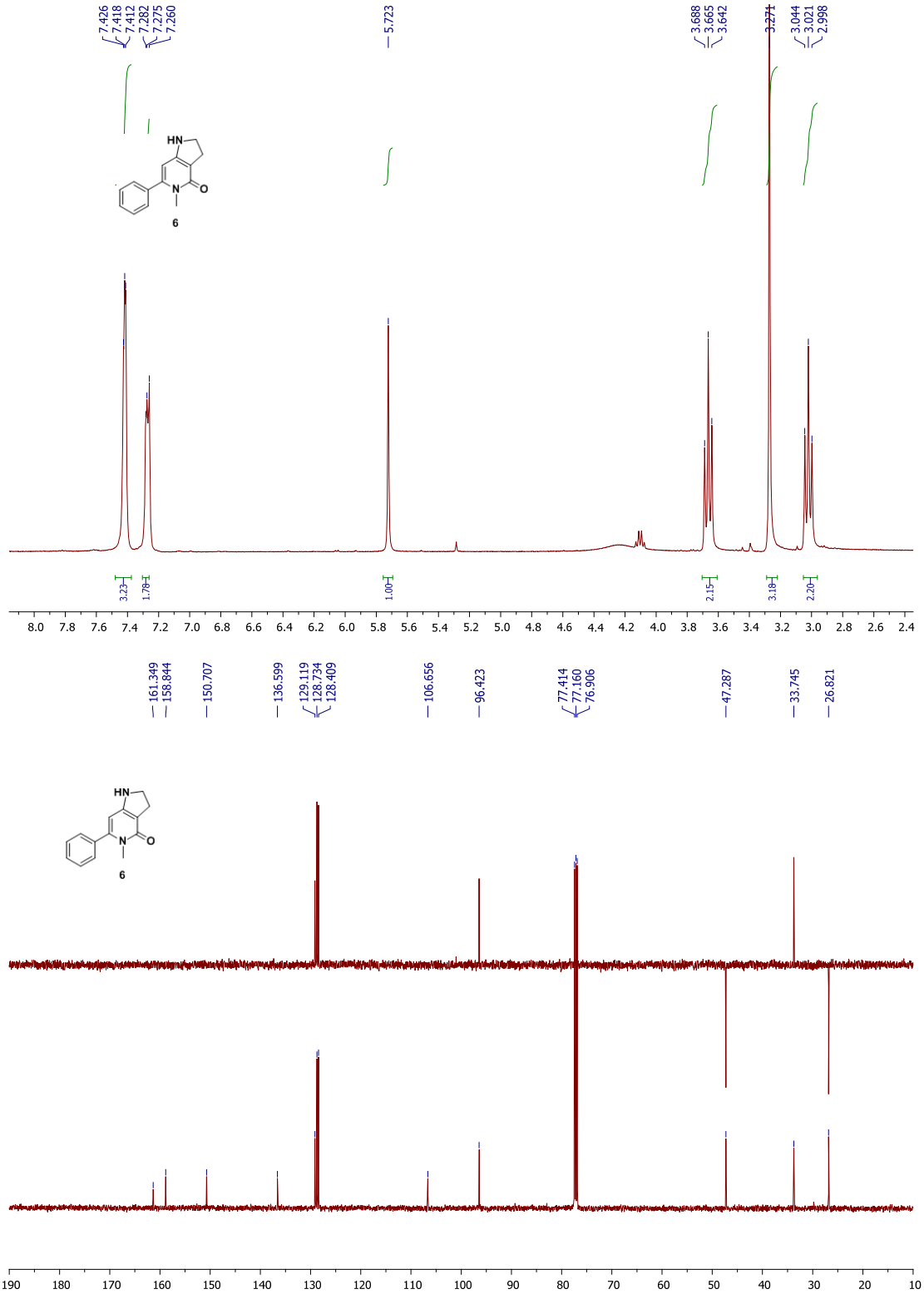
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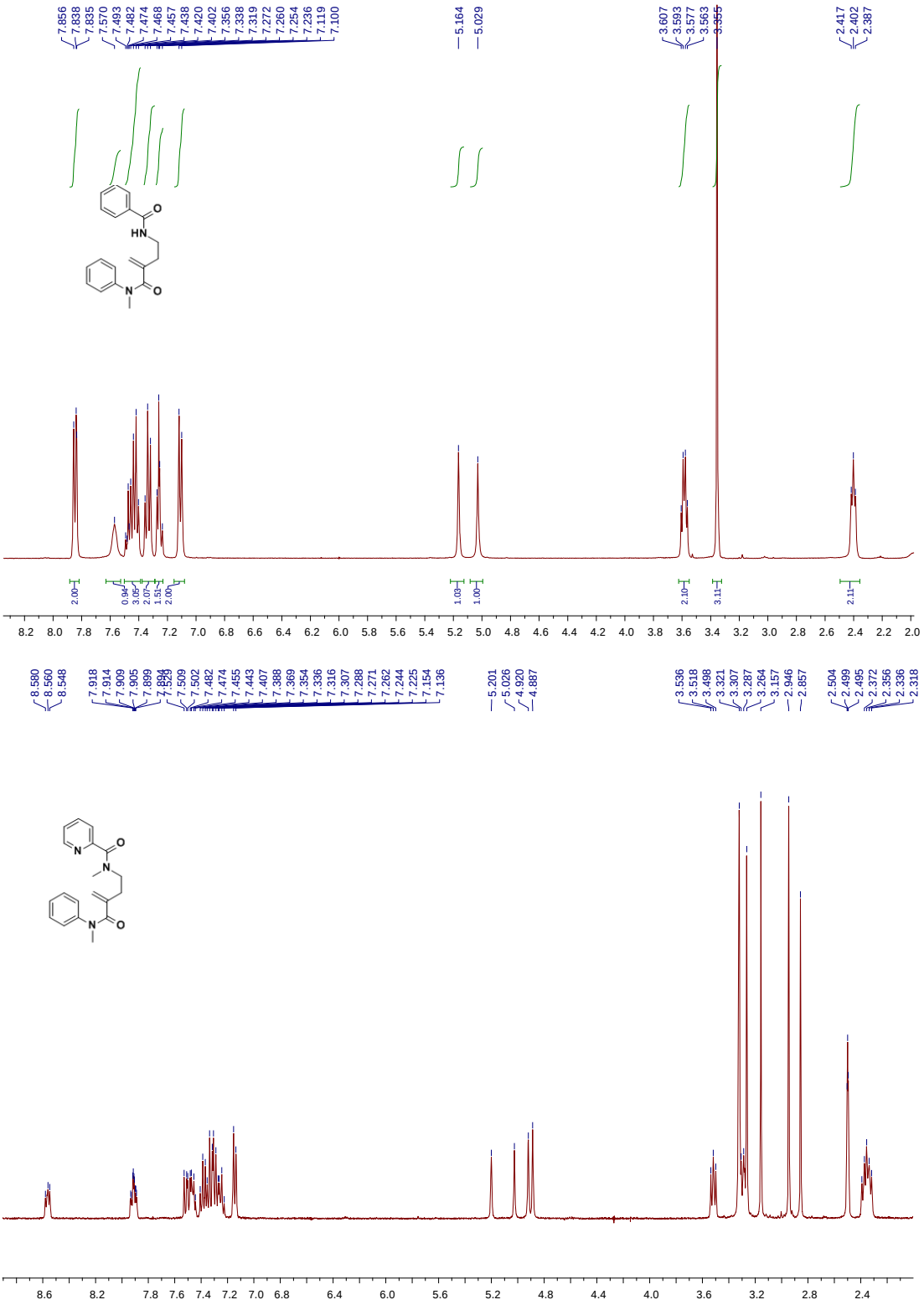
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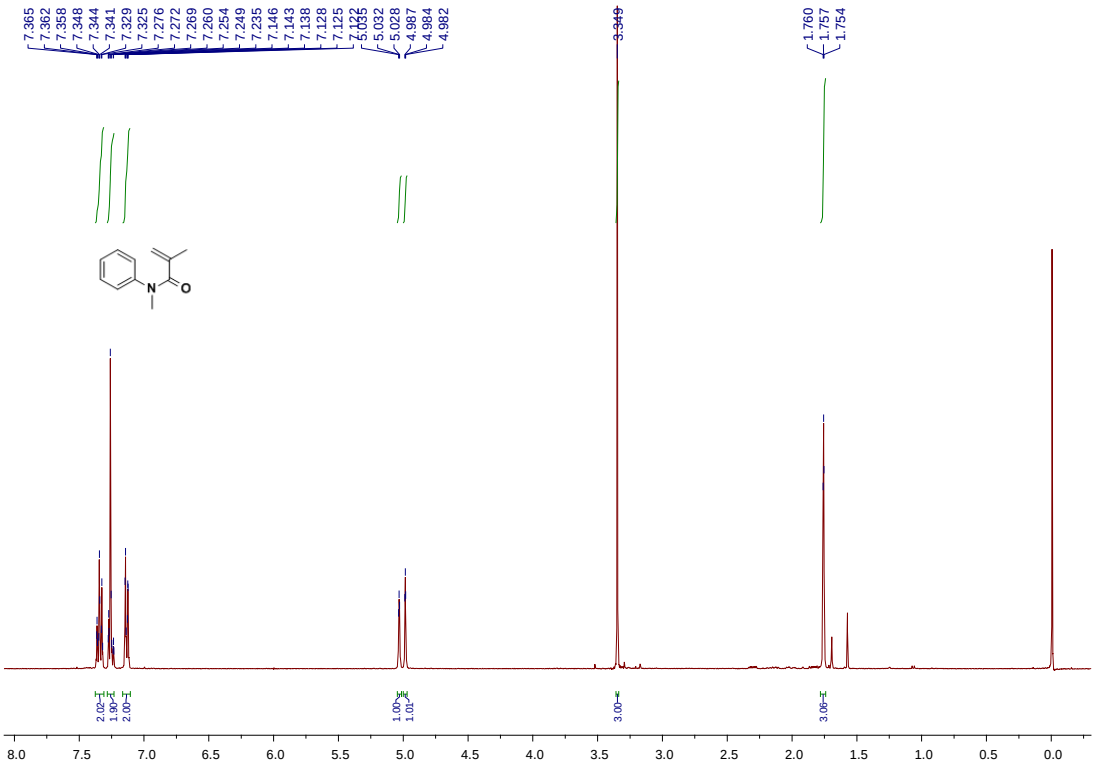

Reference

[S1] M. Tait, M. Donnard, A. Minassi, J. Lefranc, B. Bechi, G. Carbone, P. O'Brien, J. Clayden, *Org. Lett.* **2013**, *15*, 34-37.