Electronic Supplementary Material (ESI) for Catalysis Science & Technology.

Continuous flow Negishi cross-couplings employing silica supported *Pd-PEPPSI-IPr* Precatalyst

Gregory A. Price,[a] Andrew R. Bogdan,[b] Ana L. Aguirre,[b] Toshiyuki Iwai,[a] Stevan W. Djuric[b] and Michael G. Organ*[a]

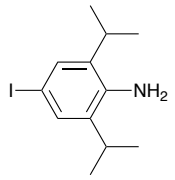
Electronic Supplementary Information

Table of Contents

General Considerations

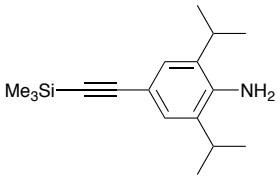
Chemicals and compounds whose syntheses are not mentioned were obtained from commercial sources and used as received. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. Toluene, acetonitrile (MeCN) and triethylamine (NEt_3) were distilled from CaH_2 prior to use. DMI was purchased from Sigma Aldrich and handled under argon. Zinc dust (325 mesh) was purchased from Strem Chemicals Inc. High purity silica gel (Davisil grade 646, 35-60 mesh, pore size 150 Å) was used for complex immobilisation. (3-Azidopropyl)triethoxysilane,[1] $PdCl_2(3\text{-}ClPy)_2$,[2] and 1-(2,6-diisopropylphenyl)-3-acetoxyoxazolinium perchlorate (**4**)[3] were prepared according to literature procedures. ^{1}H-NMR spectra were recorded on either a Bruker 400 AV spectrometer (400.1 MHz) or a Bruker 300 AV spectrometer (300 MHz), as indicated. ^{1}H NMR spectra were referenced to the residual protio impurity in the deuterated solvent used and $^{13}C\{^1H\}$ NMR spectra were referenced to the ^{13}C signal of the solvent used. All air and moisture sensitive procedures were carried out under an atmosphere of argon using standard Schlenk techniques. Analytical thin layer chromatography (TLC) was performed on Machery-Nagel SIL G F_{254} pre-coated glass plates and spots were visualized using UV light (254 nm) and $KMnO_4$ or phosphomolybdic acid as stain. Column chromatography was carried out utilizing a Biotage® Isolera™ Spektra System using SNAP Ultra flash column chromatography cartridges. A New Era NE-1000 pump (single channel) or a New Era NE-4000 (dual channel) pump was used in continuous flow experiments. All immobilisation and batch reactions were performed in a Fisher Scientific Isotemp oven 615F modified with a rotisserie, spinning at 10 rpm so as to avoid grinding of the silica. SEM/EDX analysis was performed on a Quantra 3D Dual-Beam FEG FIB-SEM equipped with an EDAX X-ray detector. ICP-OES analysis was performed by Galbraith Laboratories Inc. Knoxville, Tennessee. High Resolution Mass Spectrometry (HRMS) analysis was performed by the Mass Spectrometry and Proteomics Unit at Queen's University in Kingston, Ontario.

Synthetic Procedures



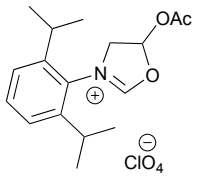
4-Iodo-2,6-diisopropyl-aniline (2)[4]

In air, a round bottom flask was charged with 2,6-diisopropylaniline (10.4 mL, 55.1 mmol) and 100 mL Et_2O. A saturated sodium bicarbonate solution (100 mL) was added followed by iodine (15.8 g, 62.5 mmol) and the mixture stirred vigorously for 3 h. After this time, the mixture was washed successively with sat. aq. sodium thiosulfate (200 mL) and water (100 mL). The organic phase was collected, dried over anhydrous $MgSO_4$ then filtered and the solvent removed *in vacuo* to give 4-iodo-2,6-diisopropyl-aniline as a brown oil (16 g, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 2H), 3.76 (br. s., 2H), 2.87 (spt, *J* = 6.7 Hz, 2H), 1.27 (d, *J* = 6.1 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.0, 134.9, 131.6, 81.0, 27.8, 22.2.



2,6-diisopropyl-4-[2-(trimethylsilyl)ethynyl]-aniline (3)[5]

4-Iodo-2,6-diisopropyl-aniline (7.7 g, 25.4 mmol) was added to a round bottom flask under argon, followed by $PdCl_2(PPh_3)_2$ (0.35 g, 0.5 mmol, 2 mol%) and CuI (0.1 g, 0.5 mmol, 2 mol%). Triethylamine (140 mL) and (trimethylsilyl)acetylene (4 mL, 28.1 mmol) were added and the mixture stirred at rt for 16 h. The solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel (10% EtOAc:hexanes) to yield a brown oil which crystallized on standing. (5.2 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (s, 2H), 3.90 (br. s., 2H), 2.85 (spt, *J* = 6.7 Hz, 2H), 1.27 (d, *J* = 6.8 Hz, 12H), 0.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 131.8, 126.9, 111.9, 107.2, 90.4, 27.7, 22.1, 0.2.



1-(2,6-Diisopropylphenyl)-3-acetoxyoxazolinium perchlorate (4)[3]

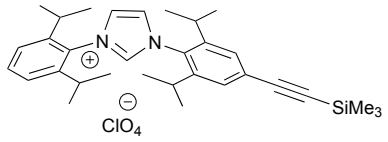
Under argon, ^{n}BuLi (2.5 M in hexanes, 35.0 mL, 87.5 mmol) was added to a solution of 2,6-diisopropylaniline (15 mL, 80.0 mmol) in THF (200 mL) at 0 ^{o}C and the reaction stirred for 30 min at rt. After this time bromoacetaldehyde diethylacetal (13.2 mL, 87.5 mmol) was added and the mixture stirred overnight. The solution was poured into a mixture of H_2O and sat. aq. $NaHCO_3$ (200 mL, 1:1) and extracted with Et_2O. The organic layer was collected, washed with H_2O (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and filtered. The solvent was removed from the filtrate under reduced pressure to give crude *N*-(2,2-diethoxyethyl)-2,6-diisopropylaniline as a brown oil which was used in the next step without further purification.

***N*-(2,6-Diisopropylphenyl)-N-(2-oxoethyl)formamide**

Formic acid (15 mL, 0.4 mol) and acetic anhydride (15 mL, 0.16 mol) were added to a round bottom flask under argon and stirred at rt. After 2 h the mixture was added to a solution of crude *N*-(2,2-diethoxyethyl)-2,6-diisopropylaniline (80.0 mmol) in THF (200 mL) at 0 ^{o}C and the reaction allowed to warm to rt overnight. The mixture was poured into a solution of NaOH (10%, 200 mL) and extracted with Et_2O (200 mL), the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The solvent was removed from the filtrate and then formic acid (150 mL, 4.0 mol) was added to the residue at 0 ^{o}C and the mixture stirred at rt for 4 h. After this time, all volatiles were removed from the reaction using a rotary evaporator, the remaining liquid dissolved in Et_2O (200 mL) and washed with sat. aq. $NaHCO_3$ (2 x 150 mL) and brine (150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to give a dark brown oil, which was used in the next step without further purification.

1-(2,6-Diisopropylphenyl)-3-acetoxyoxazolinium perchlorate

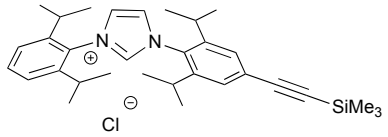
The crude *N*-(2,6-diisopropylphenyl)-N-(2-oxoethyl)formamide (80.0 mmol) obtained in the previous step was dissolved in acetic anhydride (1 mL/mmol) and $HClO_4$ (8 mL, 70 % *w/w* in water, 1.15 equiv) was added at rt. The mixture was stirred overnight before Et_2O (200 mL) was added to induce precipitation of the perchlorate salt. The solid was collected by filtration and washed with Et_2O (2 x 50 mL). Recrystallization from MeCN/Et_2O gave pure *N*-(2,6-diisopropylphenyl)-N-(2-oxoethyl)formamide as a white solid which was collected by filtration and dried in air (13.4 g, 43 %). The product was found decompose slowly at ambient temperature, however it could be stored at -10 ^oC for prolonged periods without significant decomposition. ^1H NMR (400 MHz,CD_3CN): δ 9.00 (s, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.1 Hz, 2H), 7.41 (dd, *J* = 7.1, 3.0 Hz, 1H), 4.74 (dd, *J* = 14.1, 7.1 Hz, 4H), 4.31 (dd, *J* = 14.1, 3.0 Hz, 1H), 2.79-2.99 (m, 2H), 2.25 (s, 3H),), 1.33 (d, *J* = 6.1 Hz, 3H), 1.24-1.31 (m, 12H). ^{13}C NMR (101 MHz, CD_3CN): δ 168.9, 167.9, 146.6, 146.4, 133.4, 127.3, 126.2, 126.2, 100.8, 58.6, 29.3, 29.1, 24.6, 24.5, 24.3, 24.0, 20.6.



1-(2,6-Diisopropylphenyl)-3-(2,6-diisopropylphenyl-4-((trimethylsilyl)ethynyl)phenyl)imidazolium perchlorate (5)

Representative procedure:

In air, a round bottom flask was charged with 2,6-diisopropyl-4-[2-(trimethylsilyl)ethynyl]-aniline (1.6 g, 6.0 mmol) and a mixture of CH_2Cl_2 and toluene (50 mL, 1:1). 1-(2,6-diisopropylphenyl)-3-acetoxyoxazolinium perchlorate (1.9 g, 4.9 mmol) was added in one shot and the solution stirred at rt overnight. The solvent was removed *in vacuo* and the resultant oil filtered through a plug of SiO_2 using CH_2Cl_2 as eluent. The filtrate was concentrated and then triturated with pentane to give a red/brown solid, which was collected by filtration. The solid was placed in a flame dried round bottom flask under argon, CH_2Cl_2 (15 mL) was added and the solution cooled to 0 ^oC. Pyridine (1.9 mL, 24.0 mmol, 5 equiv) was added before $SOCl_2$ (0.7 mL, 9.6 mmol, 2 equiv) was introduced dropwise and the mixture stirred at rt for 1 h. The volatiles were removed under reduced pressure and the residue taken up in CH_2Cl_2 and filtered through a plug of SiO_2 using a 1:1 mixture of EtOAc and CH_2Cl_2 as eluent. The solvent was evaporated from the filtrate and the brown oil sonicated with pentane to give perchlorate salt as an off-white solid, which was collected by filtration (1.9 g, 69 %). ^1H NMR (300 MHz,CD_3CN): δ 8.95 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.68 (t, *J* = 8.3 Hz, 1H), 7.49-7.55 (m, 3H), 7.48 (s, 1H), 2.41 (m, 4H), 1.28 (d, *J* = 6.8 Hz, 12H), 1.20 (d, *J* = 6.8 Hz, 12H), 0.29 (s, 9H). ^{13}C NMR (75 MHz, CD_3CN): δ 147.0, 146.2, 138.8, 133.1, 131.0, 130.7, 128.8, 127.7, 127.2, 126.9, 125.7, 104.2, 97.6, 29.8, 24.4, 24.2, 23.7, 23.5, -0.3. HRMS calculated for $C_{32}H_{45}N_2Si$ $[M\text{-}ClO_4]^+$: 485.3347, found: 485.3338.

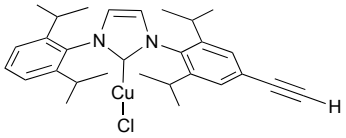


1-(2,6-Diisopropylphenyl)-3-(2,6-diisopropylphenyl-4-((trimethylsilyl)ethynyl)phenyl)imidazolium chloride (6)

Representative procedure:

A fritted funnel was packed with Dowex® 1X4 chloride form, 200-400 mesh ion exchange resin by suspending the resin in MeOH and packing by vacuum filtration. Water was removed by passing MeOH (50 mL) followed by acetone (50 mL) through the column. A mixture of 15 % toluene/ 5 % MeOH/ 80 % CH_2Cl_2 was passed through the resin (100 mL) before a solution of 1-(2,6-diisopropylphenyl)-3-(2,6-diisopropylphenyl-4-((trimethylsilyl)ethynyl)phenyl)imidazolium perchlorate (1.9 g, 3.2 mmol) in 15 % toluene/ 5 % MeOH/ 80 % CH_2Cl_2 (0.014 M, 250 mL) was filtered through the ion exchange column. The filtrate was evaporated to dryness, and triturated with pentane to give an off-white solid, which was collected by filtration (1.5 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20 (s, 1H), 8.06 (s, 1H), 8.01 (s, 1H), 7.54 (t, *J* = 8.1Hz 1H), 7.38 (s, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 2.31-2.43 (m, 4H), 1.23 (d, *J* = 5.1 Hz, 12H), 1.18 (dd, *J* = 6.1, 4.0 Hz, 12H), 0.28 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.1, 144.9, 138.9, 132.0, 129.8, 129.7, 128.2, 127.1, 126.6, 126.5, 124.6, 103.6, 96.9, 29.0, 29.0, 24.6, 24.4, 23.7, 23.5, -0.2. HRMS calculated for $C_{32}H_{45}N_2Si$ $[M\text{-}Cl]^+$: 485.3346, found: 485.3326.

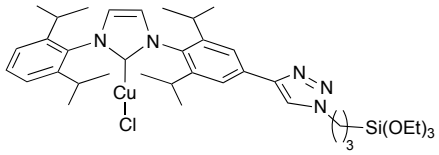
1-(2,6-Diisopropylphenyl)-3-(2,6-diisopropylphenyl-4-ethynylphenyl)imidazol-2-ylidene]copper(I) chloride (7)



Under argon, a two-necked round bottom flask equipped with a condenser was charged with Cu_2O (1.4 g, 10.1 mmol, 0.75 equiv) and 1-(2,6-diisopropylphenyl)-3-(2,6-diisopropylphenyl-4-((trimethylsilyl)ethynyl)phenyl)imidazolium chloride (**6**) (7 g, 13.4 mmol). Toluene (100 mL) was added and the suspension stirred at reflux for 48 h. After cooling to rt, the solvent was removed *in vacuo*, the remaining solid taken up in CH_2Cl_2 and filtered through a SiO_2 plug with CH_2Cl_2 as eluent. The filtrate was evaporated, and then THF (30 mL) added, followed by TBAF (1 M in THF, 13.0 mL, 13.0 mmol) and the mixture stirred at rt for 16 h. The solvent was removed under reduced pressure and the residue passed through a plug of SiO_2 using CH_2Cl_2 as eluent. The filtrate was concentrated to *ca.* 5 mL, hexanes (60 mL) added and the CH_2Cl_2 slowly removed under reduced pressure to induce precipitation of Cu-NHC complex as an off white solid, which was collected by filtration (4.3 g, 62 % (average over multiple reactions). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (t, *J* = 8.1Hz, 1H), 7.42 (s, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.14 (s, 1H), 7.11 (s, 1H), 3.18 (s, 1H), 2.54 (m, 4H), 1.29 (d, *J* = 7.1 Hz, 12H), 1.23 (s, 6H), 1.21 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.6, 145.9, 145.5, 134.7, 134.2, 130.7, 128.2, 124.5, 124.3, 123.4, 122.9, 83.0, 78.3, 28.7, 28.7, 24.8, 24.6, 23.8, 23.7. HRMS calculated for $C_{29}H_{36}ClCuN_2Na$ $[M+Na^+]^+$: 533.1755, found: 533.1736.

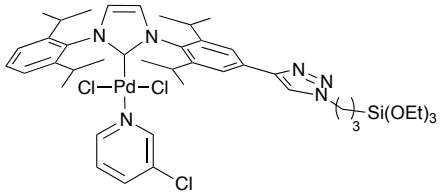
Direct route to **1-(2,6-Diisopropylphenyl)-3-(2,6-diisopropylphenyl-4-ethynylphenyl)imidazol-2-ylidene]copper(I) chloride (7)**

Under argon, a round bottom flask equipped with a condenser was charged with CuCl (0.17 g, 1.7 mmol, 2 equiv.), 1-(2,6-diisopropylphenyl)-3-(2,6-diisopropylphenyl-4-((trimethylsilyl)ethynyl)phenyl)imidazolium perchlorate (**5**) (0.5 g, 0.85 mmol) and K_2CO_3 (0.6 g, 4.3 mmol, 5 equiv.). 3-Chloropyridine (5 mL) was added and the suspension stirred at 100 °C for 16 h. After cooling to rt the slurry was taken up in CH_2Cl_2 and passed through a plug of SiO_2. The filtrate was concentrated to *ca.* 2 mL and hexane was added to induce precipitation of **7**, which was collected by filtration and washed with hexane (2 x 10 mL). (0.15 g, 35 %).



IPr-triazole-CuCl (8)

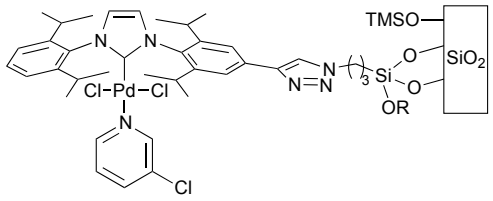
Under argon, a vial was charged with 1-(2,6-diisopropylphenyl)-3-(2,6-diisopropylphenyl-4-ethynylphenyl)imidazol-2-ylidene]copper(I) chloride (4.6 g, 9.0 mmol) and sealed with a septum. MeCN (100 mL) and (3-azidopropyl)triethoxysilane[1] (3.3 g, 13.3 mmol) were added and the mixture stirred for 16 h at 35 °C. After cooling to rt the solvent was removed *in vacuo* and the residue filtered through a plug of SiO_2 using CH_2Cl_2/EtOAc (1:1) as eluent. The filtrate was concentrated to ~5 mL and pentane was added to induce precipitation of **8** as an off-white solid which was collected by filtration (5.9 g, 86 %). ^{1}H NMR (400 MHz, ($CDCl_3$): δ 7.89 (s, 1H), 7.73 (s, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.15 (s, 2H), 4.46 (t, *J* = 7.1 Hz, 2H), 3.84 (q, *J* = 7.1 Hz, 6H), 2.52 - 2.65 (m, 4H), 2.12 (t, *J* = 8.1 Hz, 2H), 1.35 (d, *J* = 6.1 Hz, 6H), 1.31 (d, *J* = 7.1 Hz, 6H), 1.28 (d, *J* = 7.1 Hz, 6H), 1.21 - 1.26 (m, 15H), 0.68 (t, *J* = 8.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 179.9, 146.4, 145.8, 145.1, 134.0, 133.6, 132.5, 130.1, 123.7, 123.0, 123.0, 121.1, 120.3, 58.1, 52.1, 28.4, 28.3, 24.4, 24.3, 23.8, 23.4, 23.4, 17.9, 7.0. HRMS calculated for $C_{38}H_{58}ClCuN_5O_3Si$ $[M+H]^+$: 758.32880, found: 758.32951.



***Pd-PEPPSI-IPr*-triazole (9)**

Under argon, a two-necked round bottom flask equipped with a condenser was charged with IPr-triazole-CuCl (**8**, 1.3 g, 1.8 mmol) followed by $Cl_2Pd(3\text{-}ClPy)_2$[2] (0.85 g, 2.12 mmol, 1.2 equiv.) and toluene (100 mL) after which the suspension was stirred at 110 °C for 48 h. After cooling to rt, Et_2O (100 mL) was added and the suspension filtered through a pad of Celite® using Et_2O as eluent. The solvent was removed under reduced pressure and the residue extracted with boiling hexanes (100 mL). The solvent was removed to give a

yellow solid. In order to remove any remaining copper species the crude product was dissolved in CH_2Cl_2/EtOAc (95:5) and passed through a plug of SiO_2. Removal of the solvent *in vacuo* afforded *Pd-PEPPSI-IPr-triazole* (**9**) as a yellow solid (1.02 g, 61 %). (Alternatively the complex could by purified by column chromatography on SiO_2 (5 to 15% EtOAc/CH_2Cl_2). ^{1}H NMR (600 MHz, CDCl3): δ 8.59 (d, *J* = 2.7 Hz, 1H), 8.49-8.54 (m, 1H), 7.87 (s, 1H), 7.80 (s, 2H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.48-7.52 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 2.2 Hz, 2H), 7.06 (dd, *J* = 8.1, 5.4 Hz, 1H), 4.44 (t, *J* = 7.0 Hz, 2H), 3.83 (q, *J* = 7.0 Hz, 6H), 3.11-3.24 (m, 4H), 2.05-2.13 (m, 2H), 1.53 (d, *J* = 6.5 Hz, 6H), 1.48 (d, *J* = 6.5 Hz, 6H), 1.23 (t, *J* = 6.8 Hz, 9H), 1.16 (d, *J* = 7.0 Hz, 6H), 1.13 (d, *J* = 7.0 Hz, 6H), 0.60-0.71 (m, 2H). ^{13}C NMR (151MHz, $CDCl_3$): δ 153.7, 150.4, 149.4, 147.5, 147.3, 146.7, 137.4, 135.0, 134.8, 132.5, 132.0, 130.4, 125.2, 125.1, 124.3, 124.1, 121.6, 120.2, 58.6, 52.5, 28.9, 28.7, 26.3, 26.2, 24.3, 23.2, 23.2, 18.3, 7.5. HRMS calculated for $C_{43}H_{62}Cl_3N_6O_3PdSi$ $[M+H]^+$: 949.2747, found: 949.2742.



***Pd-PEPPSI-IPr*-triazole @SiO_2 (10)**

Silica gel (20 g) was first suspended in H_2O (100 mL) and HCl (conc., 20 mL) was added. The suspension was then heated to 90 ^{o}C for 5 h. After cooling to rt the silica gel was collected by filtration and washed thoroughly with H_2O (2 L) and acetone (2 L) before being dried *in vacuo* at 80 ^{o}C. [6]

In air, a vial was charged with SiO_2 (14.2 g), **9** (4.7 g, 4.9 mmol) mmol) and toluene the resultant suspension was rotated in a rotisserie oven for 24 h at 100 ^{o}C. After cooling to rt the silica was collected by filtration, washed with CH_2Cl_2 (100 mL) and subjected to Soxhlet extraction using EtOAc for 24 h. The silica was collected by filtration, washed with EtOAc (50 mL) and CH_2Cl_2 (100 mL) and then dried *in vacuo*. The supported complex was suspended in a mixture of toluene (20 mL) and hexamethyldisilazane (20 mL) and rotated for 24 h at rt. The supernatant liquid was decanted and the silica washed with CH_2Cl_2 (2 x 50 mL), EtOAc (2 x 50 mL) and EtOAc/MeOH (2:1) before being dried *in vacuo* (17.3 g of silica obtained after drying). Elemental analysis found: C 12.11; H 1.90; N 2.09; Pd 2.28; Cl 2.00; Si 37.4.

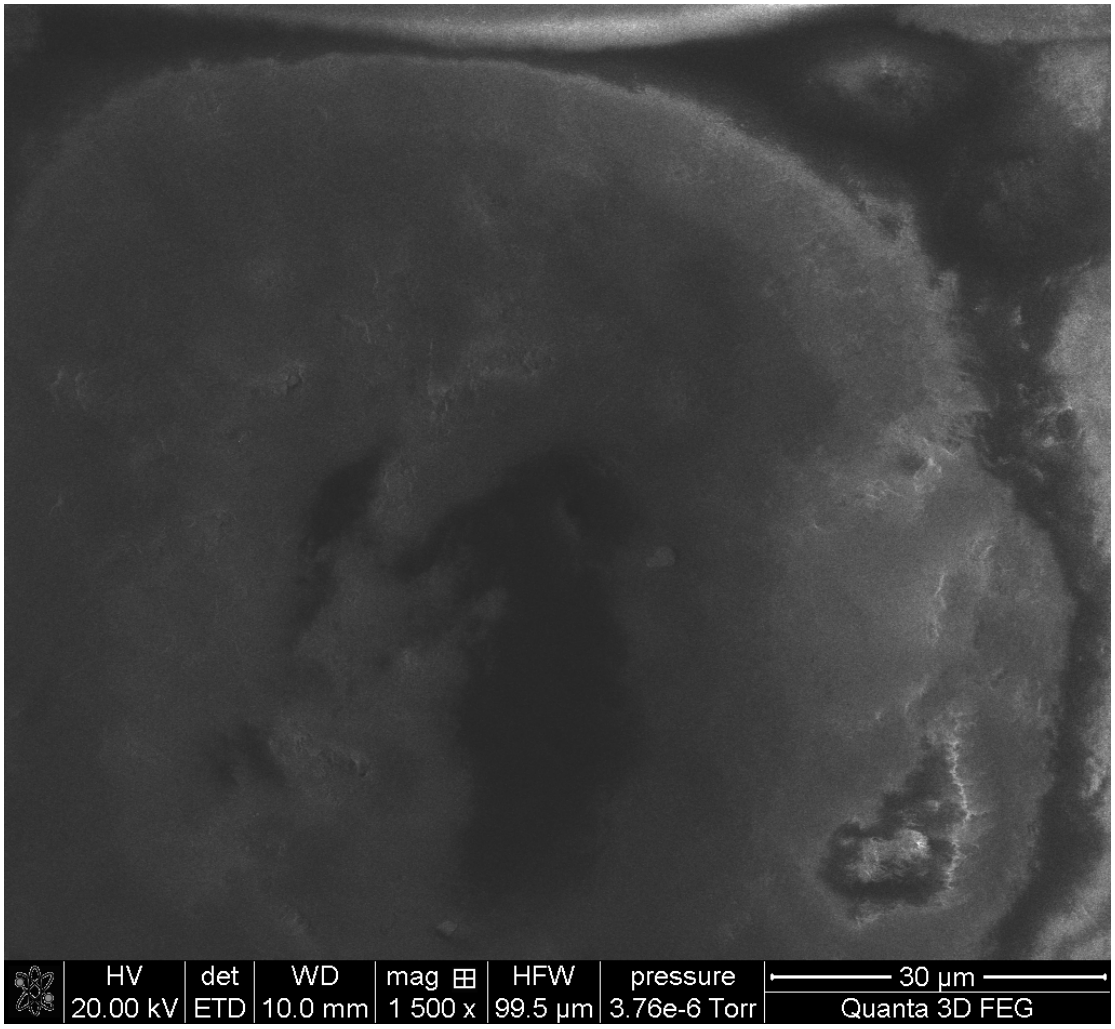


Figure S1: SEM image of 10, taken at 1500x magnification.

The silica particles remain intact after immobilisation and capping.

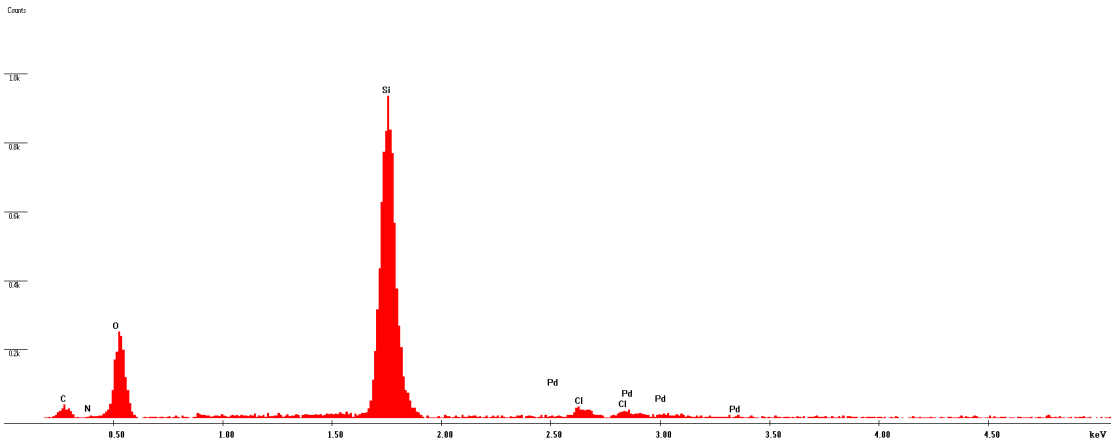


Figure S2: EDX spectrum of 10.

EDAX ZAF Quantification (Standardless)
Element Normalized
SEC Table : Default

Elem	Wt %	At %	K-Ratio	Z	A	F
C K	17.36	26.24	0.0241	1.0288	0.1349	1.0004
N K	2.15	2.78	0.0030	1.0211	0.1380	1.0012
O K	41.24	46.82	0.0841	1.0143	0.2008	1.0005
SiK	35.66	23.06	0.2502	0.9789	0.7159	1.0009
ClK	1.42	0.73	0.0084	0.9320	0.6334	1.0019
PdL	2.17	0.37	0.0156	0.7902	0.9119	1.0000
Total	100.00	100.00				

Element	Net Inte.	Backgrd	Inte. Error	P/B
C K	0.71	0.03	8.17	26.83
N K	0.09	0.05	31.23	1.91
O K	5.20	0.05	2.95	97.75
SiK	28.14	0.16	1.26	176.36
ClK	0.87	0.13	8.18	6.51
PdL	0.55	0.13	10.94	4.13

Table S1: EDX elemental analysis for 10.

General procedure for the preparation of alkylzinc reagents[7]

In a glovebox, a flame-dried round bottom flask was charged with zinc dust (3.9 g, 60 mmol, 1.5 equiv.). The flask was removed from the glovebox and I_2 (0.5 g, 2 mmol, 0.05 equiv.) was added before it was purged with argon (3x). DMI (40 mL) was added portion-wise and the resultant suspension stirred at rt until the colour of I_2 disappeared (ca. 5 min). The alkyl bromide (7.1 mL, 40 mmol) was added and the mixture heated to 80 ^{o}C for 16 h at which time it was cooled to rt. and allowed to stand without stirring for 10 h. The concentration of the organozinc solution was determined by iodometric titration of the resulting supernatant using Knochel's procedure.[8]

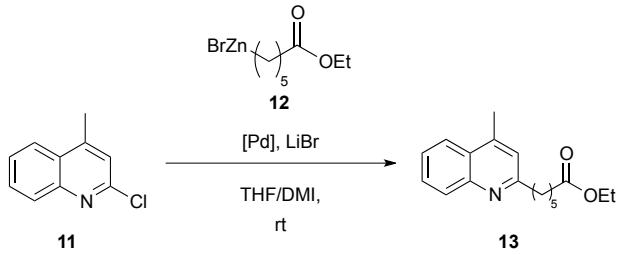
General procedure for batch Negishi coupling reactions

Under argon, a vial was charged with **10** (50 mg, 0.21 mmol/g loading, 2 mol%) and LiBr (139 mg, 1.6 mmol). THF (2.5 mL) was added followed by the organozinc reagent (1.25 mL, 0.65M in DMI, 0.8 mmol). After stirring for 2 min the aryl halide (0.5 mmol) was added and the reaction vial rotated in a rotisserie oven at 10 rpm under a static argon atmosphere for 16 h. Alternatively, if the aryl halide was a solid at rt, it was introduced into the reaction vial prior to the addition of THF. After this time, the reaction mixture was filtered in air and the heterogeneous catalyst washed with CH_2Cl_2 (2 x 20 mL) and Et_2O (2 x 20 mL), after which it was dried under vacuum. The reaction mixture was diluted with Et_2O (20 mL), and then washed successively with sat. aq. $NaHCO_3$ (25 mL), water (25 mL) and brine (25 mL). After drying over anhydrous $MgSO_4$ the solution was filtered and the solvent removed *in vacuo*. The residue was then purified by flash chromatography on silica gel.

Initial Batch screening reactions with 2-chloro-4-methylquinoline

Under argon, a vial was charged with the various Pd complexes (2-5 mol%) and LiBr (139 mg, 1.6 mmol). 2-Chloro-4-methylquinloine (88.5 mg, 0.5 mmol) was added followed by THF (2.5 mL) and the organozinc reagent (1.25 mL, 0.65M in DMI, 0.8 mmol). Alternatively, if an external ligand was used in combination with a Pd source then the ligand was pre-mixed with Pd complex in THF for 10 min prior to the addition of the coupling partners. The reaction vial was rotated in a rotisserie oven at

10 rpm under a static argon atmosphere for 16 h. After this time, the reaction mixture was diluted with Et_2O (20 mL), and then washed successively with sat. aq. $NaHCO_3$ (25 mL), water (25 mL) and brine (25 mL). After drying over anhydrous $MgSO_4$ the solution was filtered and the solvent removed *in vacuo*. A crude ^1H NMR spectrum was obtained in acetone in order to determine conversion to product. The residue was then purified by flash chromatography on silica gel.



Entry[a]	[Pd] (mol %)	Time (h)	Yield[d] (%)
1	**10** (2)	16	80
2	**9** (1)	2	90
3	Pd-PEPPSI-IPr (1)	2	81
4[b]	**10** (2)	2	85
5	$PdCl_2$ (5)	24	trace
6	$PdCl_2(MeCN)_2$ (5)	24	trace
7	$PdCl_2(MeCN)_2$ (5) + triazole[c] (5)	24	trace
8	Pd(OAc) (5) + $^nBu_4NBr$ (100)	24	trace
9	$PdCl_2(MeCN)_2$ (5) + triazole[c] (10)	24	trace
10	$Cl_2Pd(3\text{-}ClPy)_2$ (5)	24	trace

Table S2: Screening of various Pd complexes in batch Negishi couplings.

[a] Conditions: 2-chloro-4-methylquinoline (0.5 mmol, ~0.1 M), LiBr (3.2 equiv.), RZnBr (1.8 equiv., 0.6 M in DMI), THF [b] Conditions: 2-chloro-4-methylquinoline (0.5 mmol, ~0.5 M), LiBr (3.2 equiv.), RZnBr (1.8 equiv., 0.6 M in DMI), THF [c] triazole ligand = 1-benzyl-4-(p-tolyl)-1H-1,2,3-triazole. d isolated yield following purification on SiO_2

Recycling Tests

Under argon, a vial was charged with **10** (60 mg, 0.21 mmol/g loading, 0.013 mmol, 2.5 mol%), LiBr (139 mg, 1.6 mmol) and 2-chloro-4-methylquinoline (88.5 mg, 0.5 mmol). THF (2.5 mL) was added followed by the organozinc reagent (1.25 mL, 0.65M in DMI, 0.8 mmol) and the reaction vial rotated in a rotisserie oven at 10 rpm under a static argon atmosphere for 16 h. After this time, the reaction mixture was filtered in air and the heterogeneous catalyst washed with THF (2 x 20 mL), CH_2Cl_2 (2 x 20 mL) and Et_2O (2 x 20 mL) and then dried under vacuum. The reaction mixture was diluted with Et_2O (20 mL), and washed successively with sat. aq. $NaHCO_3$ (25 mL), water (25 mL) and brine (25 mL). After drying over anhydrous $MgSO_4$ the solution was filtered and the solvent removed *in vacuo*. A crude ^1H NMR spectrum was obtained in d^6-acetone in order to determine conversion to product.

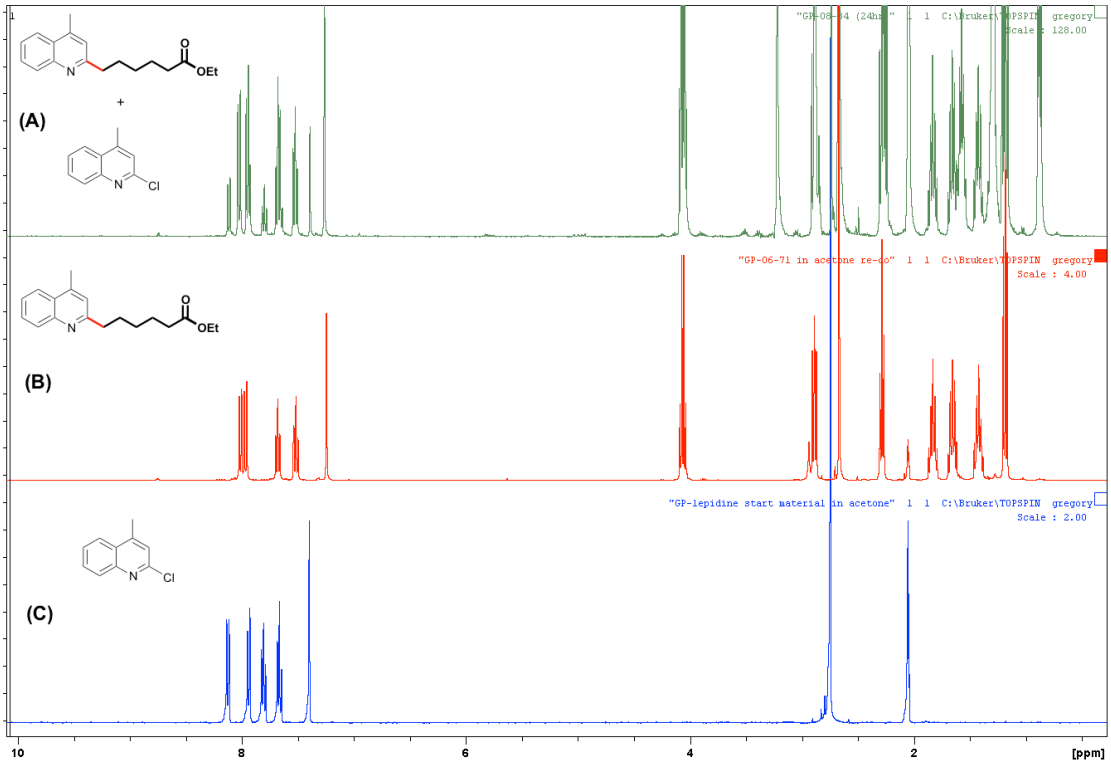
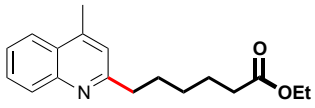


Figure S3: Samples of ^1H NMR spectra showing comparison between start material and product during in continuous flow reactions.

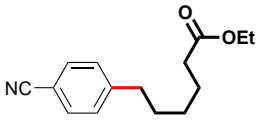
Spectrum (A): ^1H NMR spectrum of a mixture of 2-chloro-4-methylquinoline and coupled product obtained from a coupling reaction. Spectrum (B): ^1H NMR spectrum of pure coupled product. Spectrum (C): ^1H NMR spectrum of pure 2-chloro-4-methylquinoline.

General procedure for flow Negishi coupling reactions



Ethyl-6-(4-methylquinolin-2-yl)hexanoate (13), Scheme 4

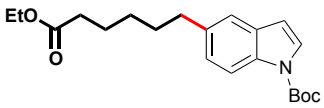
An FEP (fluorinated ethylene propylene) tube (0.159 cm ID x 8 cm) was packed with 70 mg of **10** and a small wad of cotton placed at the ends of the reactor to hold the supported catalyst in place. Connected to the reactor outlet was a length of FEP tubing (0.025 cm ID x 20 cm) that fed directly into a quench solution of saturated $NaHCO_3/H_2O$ (1:1). The total reactor volume was 171 µL. The tubing containing the catalyst was washed with THF (3 mL) pumped through the reactor at 20 µL/min. Under argon, a round bottom flask was charged with 2-chloro-4-methylquinoline (428 mg, 2.4 mmol) and LiBr (670 mg, 7.7 mmol, 3.2 equiv.). THF (13.6 mL) was added followed by (6-ethoxy-6-oxohexyl)zinc(II) bromide (6.8 mL, 0.66 M in DMI, 4.5 mmol, 1.8 equiv.) and the mixture stirred until the solids had dissolved. Contents of the flask were drawn into a 30 mL syringe and placed on a New-Era NE-1000 pump set to infuse at a rate of 20 µL/min. The reaction mixture was passed through the packed bed catalyst at rt and deposited in the stirred quench solution; after *ca*. 1 h had passed 19 mL was collected. The mixture was extracted with Et_2O (3 x 50 mL), the organic phase washed with brine (100 mL) and the organic layer dried over anhydrous $MgSO_4$. The suspension was filtered and the solvent removed *in vacuo*. The residue was then purified by flash chromatography on silica gel (0 to 20% EtOAc in hexanes) to give **13** as a clear oil (560 mg, 88%). R_f = 0.34 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.24 (s, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.67 (s, 3H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.83 (quint, *J* = 7.6 Hz, 2H), 1.66 (quint, *J* = 7.6 Hz, 2H), 1.42 (quint, *J* = 7.6 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ 173.7, 163.1, 149.0, 144.9, 130.5, 129.7, 127.8, 126.3, 124.8, 123.0, 60.5, 39.4, 34.7, 29.9, 29.7, 25.7, 18.7, 14.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6Hz, 1H), 7.11 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.9 (t, *J* = 8.1 Hz, 2H), 2.64 (s, 3H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.81 (quint, *J* = 7.8 Hz, 2H), 1.68 (quint, *J* = 7.6 Hz, 2H), 1.43 (quint, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 162.3, 147.6, 144.1, 129.2, 128.9, 126.7, 125.3, 123.5, 121.9, 60.1, 38.9, 34.2, 29.5, 28.9, 24.8, 18.6, 14.1. HRMS (ESI) calculated for $C_{18}H_{24}NO_2$ $[M+H]^+$: 286.1802, Found: 286.1793.



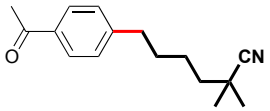
Ethyl-6-(4-cyanophenyl)hexanoate (14), Scheme 4

Following the general flow procedure a stock solution of 4-bromobenzonitrile (91 mg, 0.5 mmol), LiBr (139 mg, 1.6 mmol) and (6-ethoxy-6-oxohexyl)zinc(II) bromide (1.5 mL, 0.64 M in DMI, 0.95 mmol) in THF (1.5 mL) was passed through the packed bed catalyst and 2.9 mL was collected. Purification by flash chromatography on silica gel (0 to 15% EtOAc in hexanes) gave **14** as a clear oil (91 mg, 74%). R_f = 0.27 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.64 (t, *J* = 8.1 Hz, 2H), 2.26 (t, *J* = 7.6 Hz, 2H), 1.55 - 1.68 (m, 4H), 1.33 (quint, *J* = 7.6 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.5, 148.1, 132.0, 129.1, 119.0, 109.4, 60.1, 35.7, 34.0, 30.5,

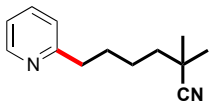
28.5, 24.5, 14.1. HRMS calculated for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.14886, Found: 246.14769.



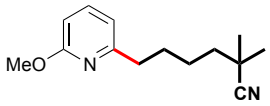
Tert-butyl-5-(6-ethoxy-6-oxohexyl)-1H-indole-1-carboxylate (15), Scheme 4[9]
Following the general flow procedure a stock solution of tert-butyl-5-bromo-1H-indole-1-carboxylate (530 mg, 1.8 mmol), LiBr (500 mg, 5.8 mmol) and (6-ethoxy-6-oxohexyl)zinc(II) bromide (5.4 mL, 0.6 M in DMI, 3.24 mmol) in THF (10.8 mL) was passed through the packed bed catalyst and 14 mL was collected. Purification by flash chromatography on silica gel (5% EtOAc in hexanes) gave **15** as a viscous oil (117 mg, 23%). R_f = 0.31 (5% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.1 Hz, 1H), 7.57 (d, *J* = 3.0 Hz, 1H), 7.35 (s, 1H), 7.14 (d, *J* = 9.1 Hz, 1H), 6.52 (d, *J* = 4.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.67 (s, 13H), 1.33 (quint, *J* = 8.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 149.7, 136.8, 133.5, 130.6, 125.8, 124.8, 120.2, 114.7, 107.0, 83.3, 60.1, 35.5, 34.2, 31.5, 28.6, 28.1, 24.8, 14.2.



6-(4-acetylphenyl)-2,2-dimethylhexanenitrile (16), Scheme 4[10]
Following the general flow procedure a stock solution of 4-bromoacetophenone (358 mg, 1.8 mmol), LiBr (500 mg, 5.8 mmol) and 6-(bromozinc)-2,2-dimethylhexanenitrile (4.2 mL, 0.65 M in DMI, 2.9 mmol) in THF (8.4 mL) was passed through the packed bed catalyst and 11 mL was collected. Purification by flash chromatography on silica gel (0 to 20% EtOAc in hexanes) gave **16** as a clear oil (235 mg, 63%). R_f = 0.37 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.55 (s, 3H), 1.57-1.70 (m, 2H), 1.48-1.54 (m, 4H), 1.29 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 147.8, 134.9, 128.4, 124.9, 40.7, 35.5, 32.2, 30.9, 26.5, 26.4, 24.8.

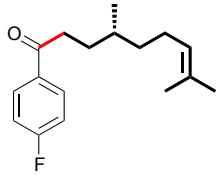


2,2-dimethyl-6-(pyridine-2-yl)hexanenitrile (17), Scheme 4
Following the general flow procedure a stock solution of 2-chloropyridine (170 µL, 1.8 mmol), LiBr (500 mg, 5.8 mmol) and 6-(bromozinc)-2,2-dimethylhexanenitrile (5.4 mL, 0.6 M in DMI, 3.2 mmol) in THF (10.8 mL) was passed through the packed bed catalyst and 11.4 mL was collected. Purification by flash chromatography on silica gel (0 to 30% EtOAc in hexanes) gave **17** as a clear oil (156 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 4.0 Hz, 1H), 7.48-7.55 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.02 (dd, *J* = 7.1, 5.1 Hz, 1H), 2.74 (t, *J* = 8,1, 2H), 1.61-1.75 (m, 2H), 1.40-1.53 (m, 4H), 1.24 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.5, 149.0, 136.2, 124.9, 122.5, 120.9, 40.6, 37.8, 32.1, 29.5, 26.4, 24.7. HRMS calculated for $C_{13}H_{19}N_2$ $[M+H]^+$: 203.1542, Found: 203.1534.



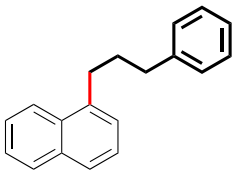
6-(6-methoxypyridin-2-yl)-2,2-dimethylhexanenitrile (18), Scheme 4

Following the general flow procedure a stock solution of 2-chloro-6-methoxy-pyridine (214 µL, 1.8 mmol), LiBr (500 mg, 5.8 mmol) and 6-(bromozinc)-2,2-dimethylhexanenitrile (5.4 mL, 0.6 M in DMI, 3.2 mmol) in THF (10.8 mL) was passed through the packed bed catalyst and 11.4 mL was collected. Purification by flash chromatography on silica gel (0 to 15% EtOAc in hexanes) gave **18** as a viscous oil (233 mg, 80%). R_f = 0.36 (15% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (t, *J* = 8.1 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 9.1 Hz, 1H), 3.86 (s, 3H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.73 (d, *J* = 5.1 Hz, 2H), 1.43-1.56 (m, 4H), 1.27 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.4, 159.4, 138.5, 124.9, 114.9, 107.2, 52.9, 40.7, 37.3, 32.1, 29.0, 26.4, 24.7. HRMS calculated for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1648, Found: 233.1638.



(4*R*)-1-(4-fluorophenyl)-4,8-dimethylnon-7-en-1-one (19), Scheme 4[9]

Following the general flow procedure a stock solution of 4-fluorobenzoyl chloride (220 µL, 1.8 mmol), LiBr (500 mg, 5.8 mmol) and bromo[(3*R*)-3,7-dimethyloct-6-en-1-yl]zinc (5.5 mL, 0.6 M in DMI, 3.2 mmol) in THF (11 mL) was passed through the packed bed catalyst and 12 mL was collected. Purification by flash chromatography on silica gel (3 % Et_2O in pentane) gave **19** as a viscous oil (147 mg, 43%). R_f = 0.40 (3 % Et_2O in pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-8.05 (m, 2H), 7.13 (t, *J* = 8.6 Hz, 2H), 5.09 (t, *J* = 7.1 Hz, 1H), 2.85-3.01 (m, 2H), 1.90-2.09 (m, 2H), 1.70-1.82 (m, 1H), 1.68 (s, 3H), 1.46-1.62 (m, 5H), 1.33-1.43 (m, 1H), 1.15-1.27 (m, 1H), 0.94 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.1,165.6 (J_{CF} = 254 Hz), 133 .5 (J_{CF} = 2.3 Hz), 131.3, 130.6 (J_{CF} = 9.8 Hz), 124.6, 115.6 (J_{CF} = 21.9 Hz), 36.9, 36.2, 32.2, 31.3, 25.7, 25.5, 19.4, 17.7.

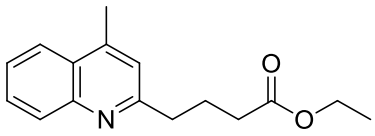


1-(3-phenylpropyl)naphthalene (20), Scheme 4[11]

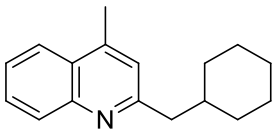
Following the general flow procedure a stock solution of 1-bromonaphthalene (252 µL, 1.8 mmol), LiBr (500 mg, 5.8 mmol) and bromo(3-phenylpropyl)zinc (5.4 mL, 0.6 M in DMI, 3.2 mmol) in THF (10.8 mL) was passed through the packed bed catalyst and 13 mL was collected. Purification by flash chromatography on silica gel (3 % Et_2O in pentane) gave **20** as a viscous oil (225 mg, 64%). R_f = 0.16 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.18 (m, 1H), 7.95-8.05 (m, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.59-7.69 (m, 2H), 7.55 (t, *J* = 7.6Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 3H), 7.32-7.42 (m, 3H), 3.28 (t, *J* = 8.1 Hz, 2H), 2.93 (t, *J* = 8.1 Hz, 2H), 2.28 (t, *J* = 8.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 142.1, 138.3, 133.9, 131.8, 128.7, 128.4, 128.3, 126.5, 125.9, 125.8, 125.6, 125.5, 125.3, 123.7, 35.8, 32.5, 32.2.

General procedure for larger-scale flow Negishi coupling reactions

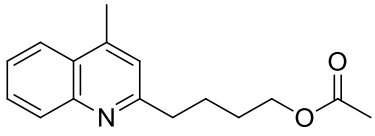
General considerations: All organozincs used were commercially available from Aldrich.
General Procedure: An 3mm x 10cm Omnifit column was packed with 350 mg of Pd-NHC on SiO_2. The void volume was measured to be 500 µL. Each end of the column was packed with a small piece of cotton as the frits on the Omnifit columns were prone to clogging. The column containing the catalyst was washed with 10 mL THF was flushed into the reactor at 5 µL/min. In a 4 mL vial, 2-chloro-4-methylquinoline (200 mg, 1.12 mmol, 1.0 eq) was dissolved in DMI (3.0 mL). (4-ethoxy-4-oxobutyl)zinc(II) bromide (0.5 M in THF, 4.5 mL, 2.25 mmol, 2.0 eq) was added to the vial. Contents of the vial were aspirated into a 5 mL Gas-Tite syringe and placed on a Harvard syringe pump set to 50 µL/min. The reaction mixture was passed through the catalytic packed bed at rt and collected in 4 mL vials (20 minutes per vial). Samples were directly injected onto a preparative HPLC column for purification using a 0.1% TFA in water/acetonitrile gradient. After completion of the reaction, the packed bed was washed using THF/DMI (3:2, 5 mL).



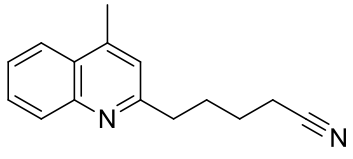
21, Scheme 5
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (dt, 1H), 7.89 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.67 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.25 (d, *J* = 1.1 Hz, 1H), 4.01 (q, *J* = 7.1 Hz, 2H), 2.85 (dd, *J* = 8.4, 7.0 Hz, 2H), 2.62 (d, *J* = 1.1 Hz, 3H), 2.34 (t, *J* = 7.4 Hz, 2H), 1.99 (p, *J* = 7.5 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 3H). MS (ESI^+) m/z 258.37 $(M+H)^+$



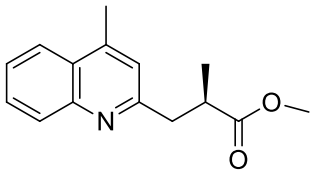
22, Scheme 5
^{1}H NMR (501 MHz, DMSO-d_6) δ 8.35 (d, *J* = 8.3 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.12 – 8.05 (m, 1H), 7.95 – 7.86 (m, 1H), 7.85 (s, 1H), 2.99 (d, *J* = 7.4 Hz, 2H), 2.89 (s, 3H), 1.91 – 1.78 (m, 1H), 1.68 – 1.51 (m, 5H), 1.24 – 0.98 (m, 5H). MS (ESI^+) m/z 240.2 $(M+H)^+$



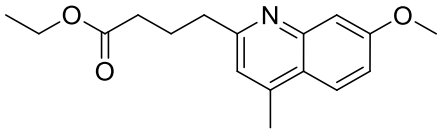
23, Scheme 5
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.87 (t, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.59 (s, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 2.98 (t, *J* = 7.7 Hz, 2H), 2.76 (s, 3H), 1.96 (s, 3H), 1.81 (tt, *J* = 8.8, 7.4 Hz, 3H), 1.64 (dt, *J* = 8.7, 6.5 Hz, 2H). MS (ESI^+) m/z 258.36 $(M+H)^+$



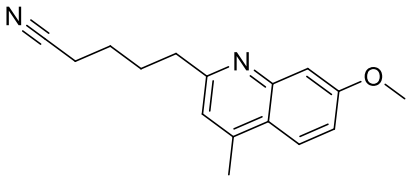
24, Scheme 5
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.93 – 7.84 (m, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.59 (s, 1H), 3.01 (t, *J* = 7.6 Hz, 2H), 2.77 (s, 3H), 2.55 (t, *J* = 7.1 Hz, 2H), 1.93 – 1.84 (m, 2H), 1.64 (p, *J* = 7.2 Hz, 2H). MS (ESI$^+$) m/z 225.38 (M+H)$^+$



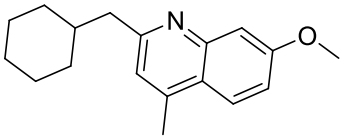
25, Scheme 5
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.69 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.25 (s, 1H), 3.56 (s, 3H), 3.19 (dd, *J* = 13.9, 7.4 Hz, 1H), 3.10 (q, *J* = 6.8 Hz, 1H), 2.94 (dd, *J* = 13.9, 6.5 Hz, 2H), 2.63 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H). MS (ESI$^+$) m/z 244.37 (M+H)$^+$



26, Scheme 5
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, *J* = 9.2 Hz, 1H), 7.62 (s, 1H), 7.50 – 7.44 (m, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 3H), 3.06 (t, *J* = 7.6 Hz, 2H), 2.81 (s, 3H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.04 (p, *J* = 7.5 Hz, 2H), 1.13 (t, *J* = 7.1 Hz, 3H). MS (ESI$^+$) m/z 288.35 (M+H)$^+$



27, Scheme 5
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, *J* = 9.3 Hz, 1H), 7.66 (s, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.48 (dd, *J* = 9.3, 2.5 Hz, 1H), 3.96 (s, 3H), 3.08 (t, *J* = 7.6 Hz, 2H), 2.82 (s, 3H), 2.53 (t, *J* = 7.1 Hz, 2H), 1.91 – 1.82 (m, 2H), 1.62 (p, *J* = 7.1 Hz, 2H). MS (ESI$^+$) m/z 255.38 (M+H)$^+$



28, Scheme 5
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, *J* = 9.3 Hz, 1H), 7.61 (s, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.45 (dd, *J* = 9.3, 2.5 Hz, 1H), 3.95 (s, 3H), 2.93 (d, *J* = 7.3 Hz, 2H), 2.82 – 2.77 (m, 3H), 1.83 (dqt, *J* = 10.3, 6.8, 3.3 Hz, 1H), 1.68 – 1.53 (m, 5H), 1.09 (dtd, *J* = 42.8, 12.5, 11.9, 3.1 Hz, 5H). MS (ESI$^+$) m/z 270.43 (M+H)$^+$

Long-term flow couplings

An FEP (fluorinated ethylene propylene) tube (0.159 cm ID x 8 cm) was packed with 70 mg of **10** and a small wad of cotton placed at the ends of the reactor to hold the supported catalyst in place. Connected to the reactor outlet was a length of FEP

tubing (0.025 cm ID x 20 cm) that fed directly into a quench solution of saturated $NaHCO_3/H_2O$ (1:1). The total reactor volume was 171 µL. The tubing containing the catalyst was washed with THF (3 mL) pumped through the reactor at 20 µL/min. Under argon, a round bottom flask was charged with 2-chloro-4-methylquinoline (428 mg, 2.4 mmol) and LiBr (670 mg, 7.7 mmol, 3.2 equiv.). THF (13.6 mL) was added followed by (6-ethoxy-6-oxohexyl)zinc(II) bromide (6.8 mL, 0.66 M in DMI, 4.5 mmol, 1.8 equiv.) and the mixture stirred until the solids had dissolved. Contents of the flask were drawn into a 30 mL syringe and placed on a New-Era NE-1000 pump set to infuse at a rate of 20 µL/min. The reaction mixture was passed through the packed bed catalyst at rt and deposited in the stirred quench solution; after *ca*. 1 h had passed. Samples were collected every 60-90 min using a LKB 2112 Redirac fraction collector. The samples were extracted with Et_2O (3 x 5 mL), and the organic layer dried over anhydrous $MgSO_4$. The solution was filtered and the solvent removed *in vacuo*. The residue was then analysed by ^{1}H NMR spectroscopy in d^6-acetone to determine product ratio.

Procedure for heterogeneity tests

Under argon, a vial was charged with **10** (60 mg, 0.21 mmol/g loading, 3 mol%), LiBr (139 mg, 1.6 mmol) and 2-chloro-4-methylquinoline (88.5 mg, 0.5 mmol). THF (2.8 mL) was added followed by organozinc reagent (1.4 mL, 0.65M in DMI, 0.8 mmol) and the mixture stirred for 10-20 min. The supported catalyst was removed by filtration under argon using a Schlenk filtration apparatus and a 0.2 mL aliquot of the reaction mixture withdrawn and analysed by ^{1}H NMR spectroscopy. After 24 h or 36 h, the reaction mixture was diluted with Et_2O (20 mL), and washed successively with sat. aq. $NaHCO_3$ (25 mL), water (25 mL) and brine (25 mL). After drying over anhydrous $MgSO_4$ the solution was filtered and the solvent removed *in vacuo*. The conversion was determined by ^{1}H NMR analysis.

Results with **10**:
Initial conversion after 10 min = 11%
Conversion in the filtrate after removal of catalyst = 34% (24 h)

Results with **10** after THF extraction:
Initial conversion after 15 min = 13%
Conversion in the filtrate after removal of catalyst = 23% (36 h)

Leaching experiments

An FEP (fluorinated ethylene propylene) tube (0.159 cm ID x 8 cm) was packed with 70 mg of **10** and a small wad of cotton placed at the ends of the reactor to hold the supported catalyst in place. Connected to the reactor outlet was a length of FEP tubing (0.025 cm ID x 20 cm). The total reactor volume was 171 µL. The tubing containing the catalyst was washed with THF (3 mL) pumped through the reactor at 20 µL/min. Under argon, a round bottom flask was charged with 2-chloro-4-methylquinoline (428 mg, 2.4 mmol) and LiBr (670 mg, 7.7 mmol, 3.2 equiv.). THF (13.6 mL) was added followed by (6-ethoxy-6-oxohexyl)zinc(II) bromide (6.8 mL, 0.66 M in DMI, 4.5 mmol, 1.8 equiv.) and the mixture stirred until the solids had dissolved. Contents of the flask were drawn into a 30 mL syringe and placed on a New-Era NE-1000 pump set to infuse at a rate of 20 µL/min. The reaction mixture was passed through the packed bed catalyst at rt and deposited in a 20 mL vial. The collected samples were analysed for Pd and Si content.

Time/h	Pd/ppm	Si/ppm	Pd/mg	Si/mg
4.5	82	7	0.4	0.04
7.5	23	5	0.08	0.02
10.5	17	5	0.06	0.02
13.5	11	7	0.04	0.02

Table S3: Palladium leaching results determined by ICP-OES analysis

References

1 S. Prasad, M. Bhadbhade and P. Thordarson, *J. Porphyr. Phthalocyanines*, 2011, **15**, 75–82.

2 A. Krogul, J. Skupińska and G. Litwinienko, *J. Mol. Catal. A Chem.*, 2011, **337**, 9–16.

3 A. Fürstner, M. Alcarazo, V. César and C. W. Lehmann, *Chem. Commun.*, 2006, 2176–8.

4 A. Hospital, C. Gibard, C. Gaulier, L. Nauton, V. Théry, M. El-Ghozzi, D. Avignant, F. Cisnetti and A. Gautier, *Dalton Trans.*, 2012, **41**, 6803–12.

5 K. Tomizaki, P. Thamyongkit, R. S. Loewe and J. S. Lindsey, *Tetrahedron*, 2003, **59**, 1191–1207.

6 A. Heckel and D. Seebach, *Chem. - A Eur. J.*, 2002, **8**, 559–72.

7 S. Huo, *Org. Lett.*, 2003, **5**, 423–5.

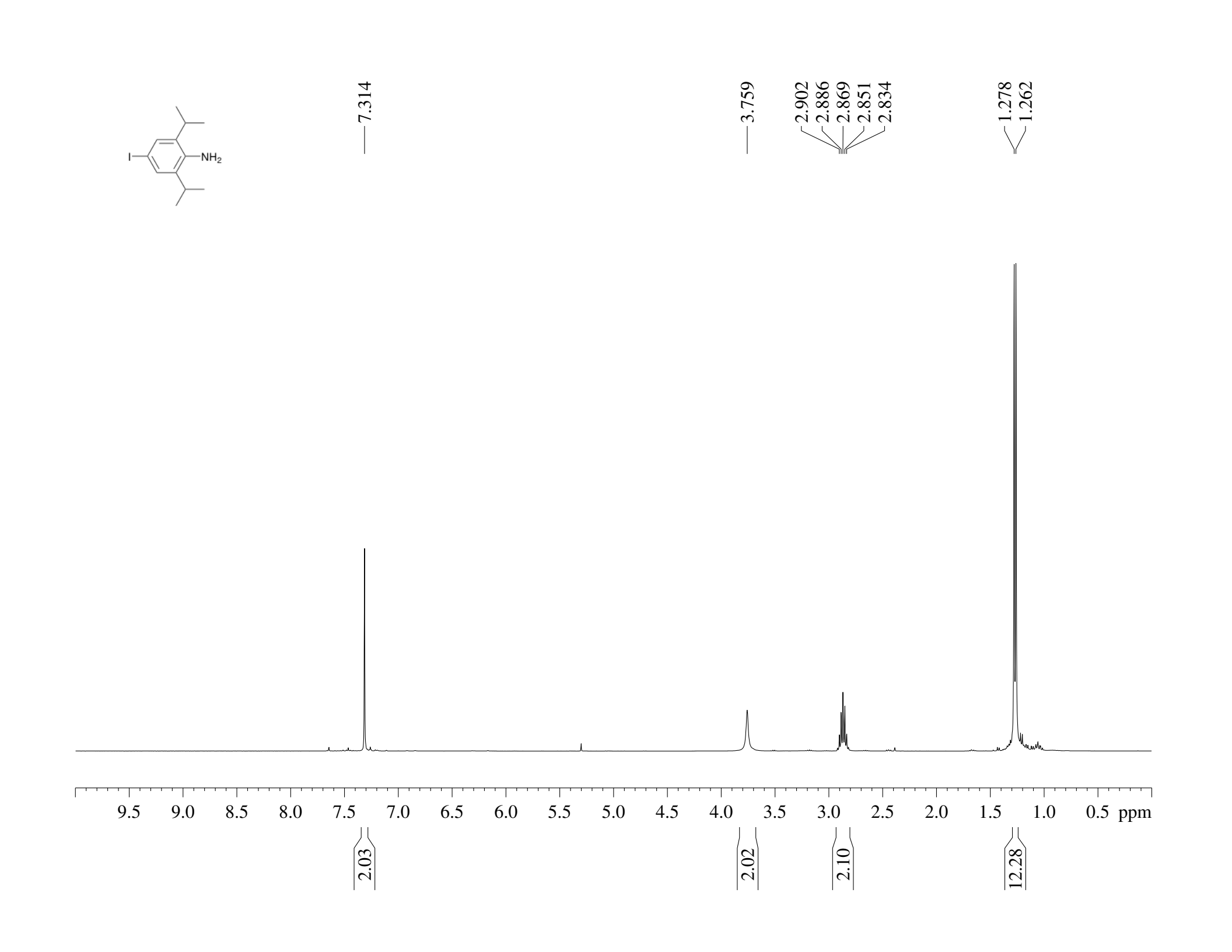
8 A. Krasovskiy and P. Knochel, *Synthesis*, 2006, 890–891.

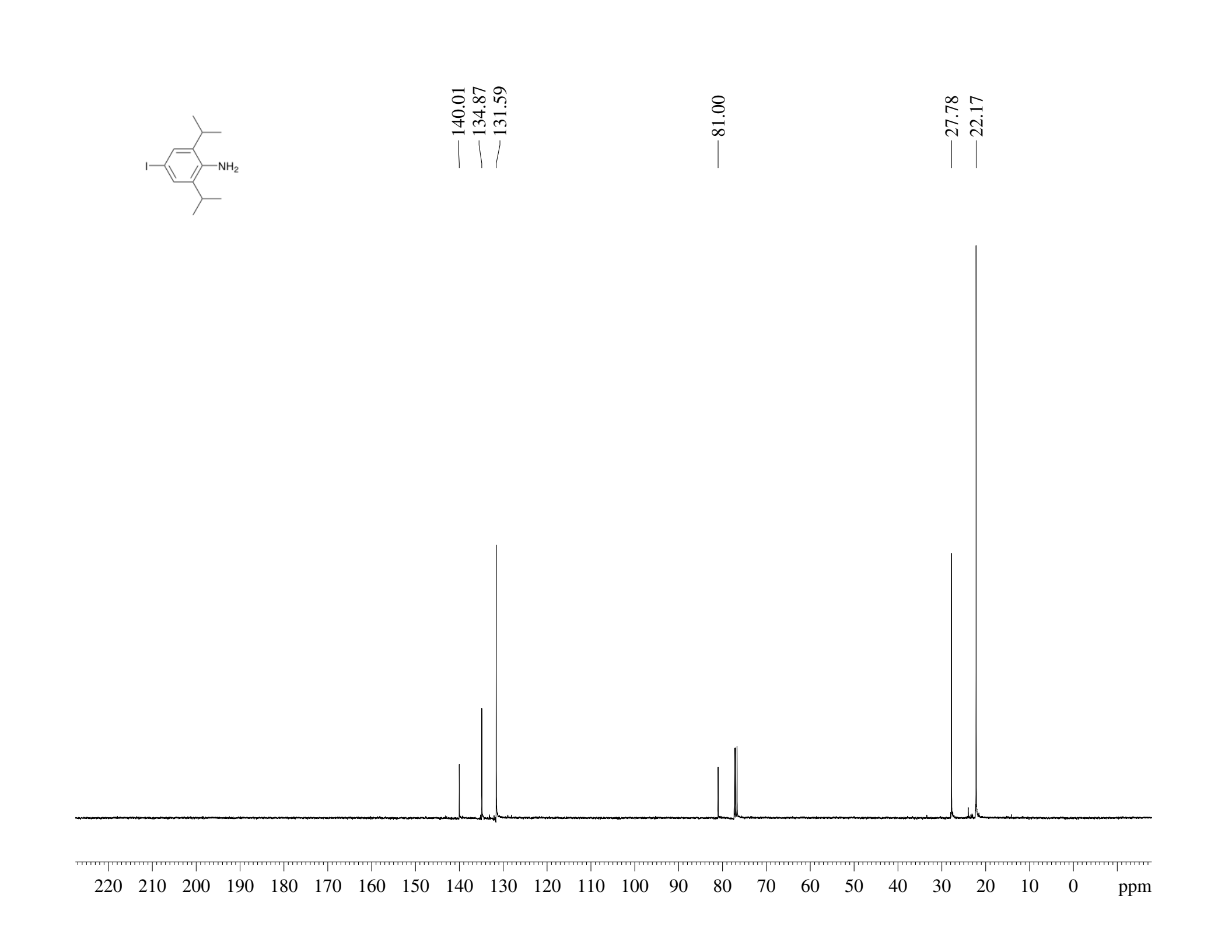
9 M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien and C. Valente, *Chem. Eur. J.*, 2006, **12**, 4749–55.

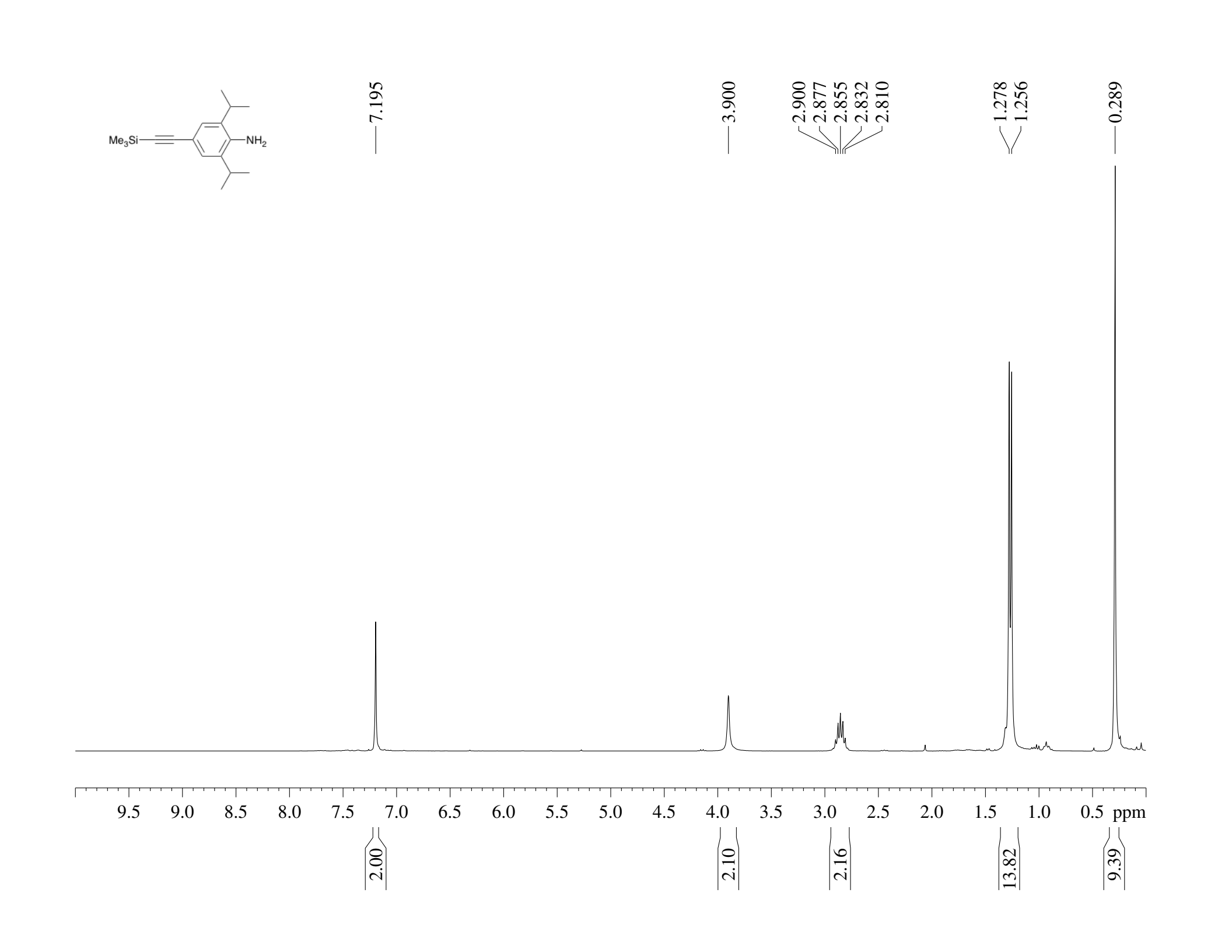
10 S. Bernhardt, Z. L. Shen and P. Knochel, *Chem. - A Eur. J.*, 2013, **19**, 828–833.

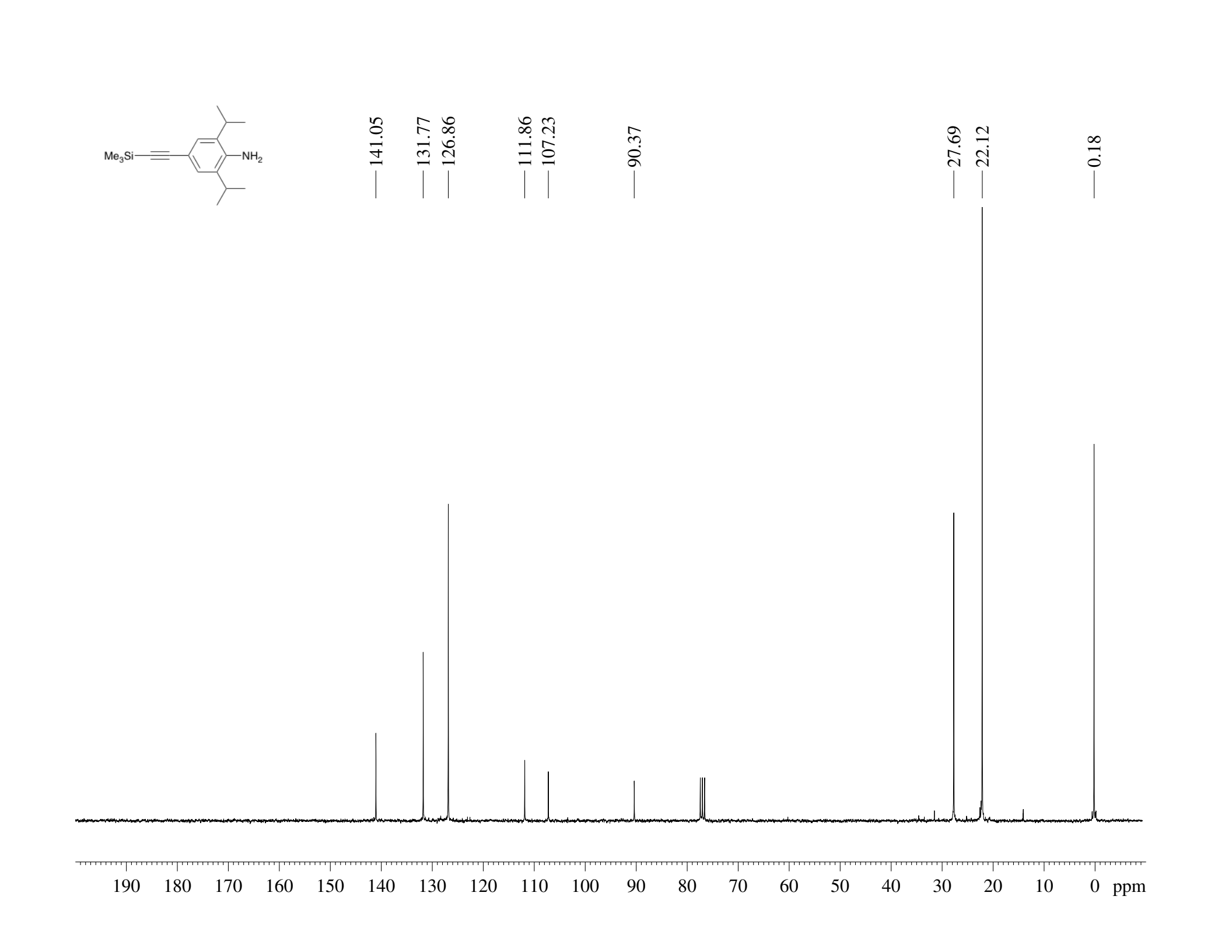
11 T. Takeda, Y. Takeda and T. Akira, *Chem. Lett.*, 2015, **44**, 809–811.

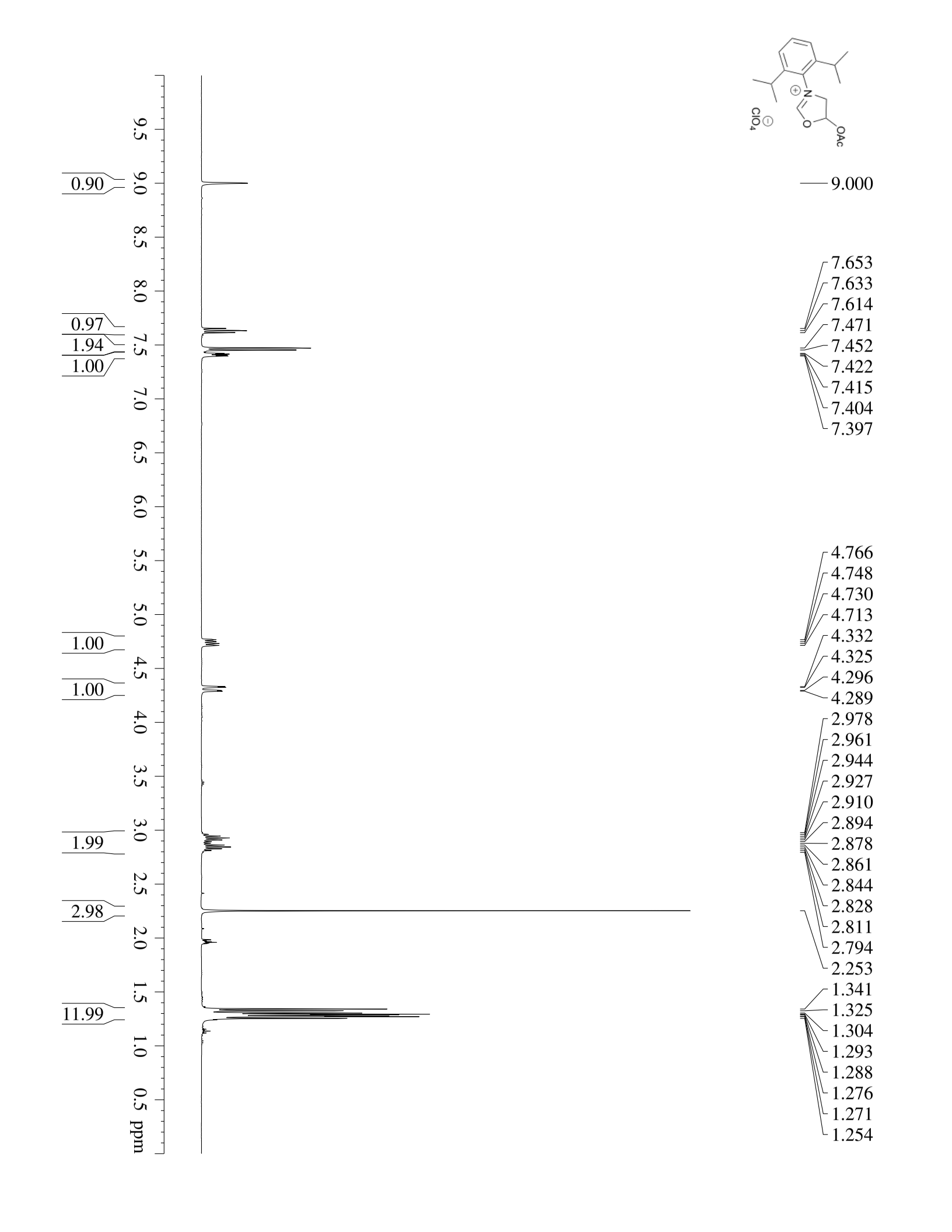
Copies of NMR Spectra

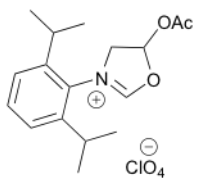

I
NH2
7.314
3.759
2.902
2.886
2.869
2.851
2.834
1.278
1.262
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.03
2.02
2.10
12.28


I
NH2
140.01
134.87
131.59
81.00
27.78
22.17
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

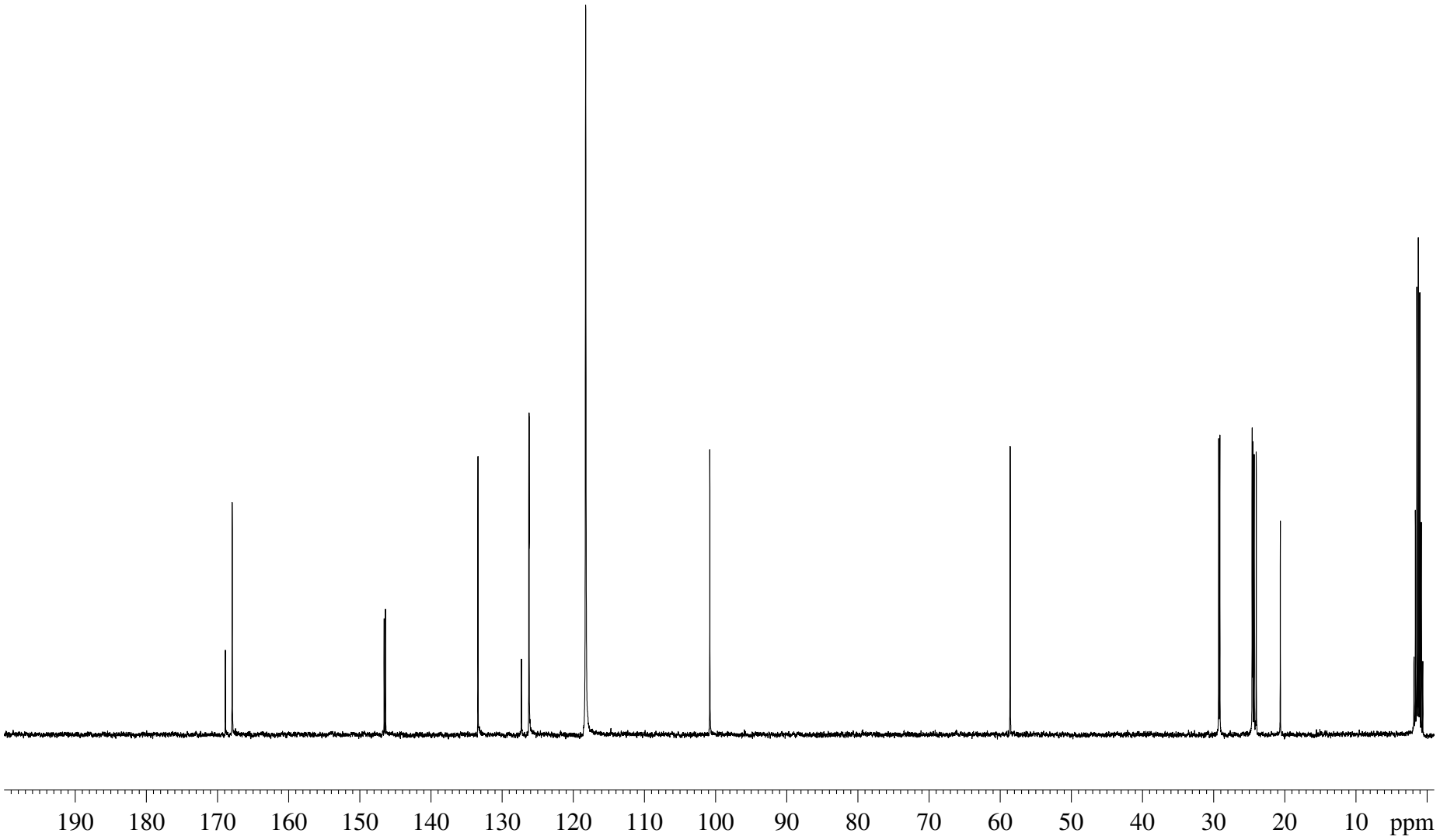

Me3Si
NH2
7.195
3.900
2.900
2.877
2.855
2.832
2.810
1.278
1.256
0.289
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
2.10
2.16
13.82
9.39


Me3Si
NH2
141.05
131.77
126.86
111.86
107.23
90.37
27.69
22.12
0.18
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

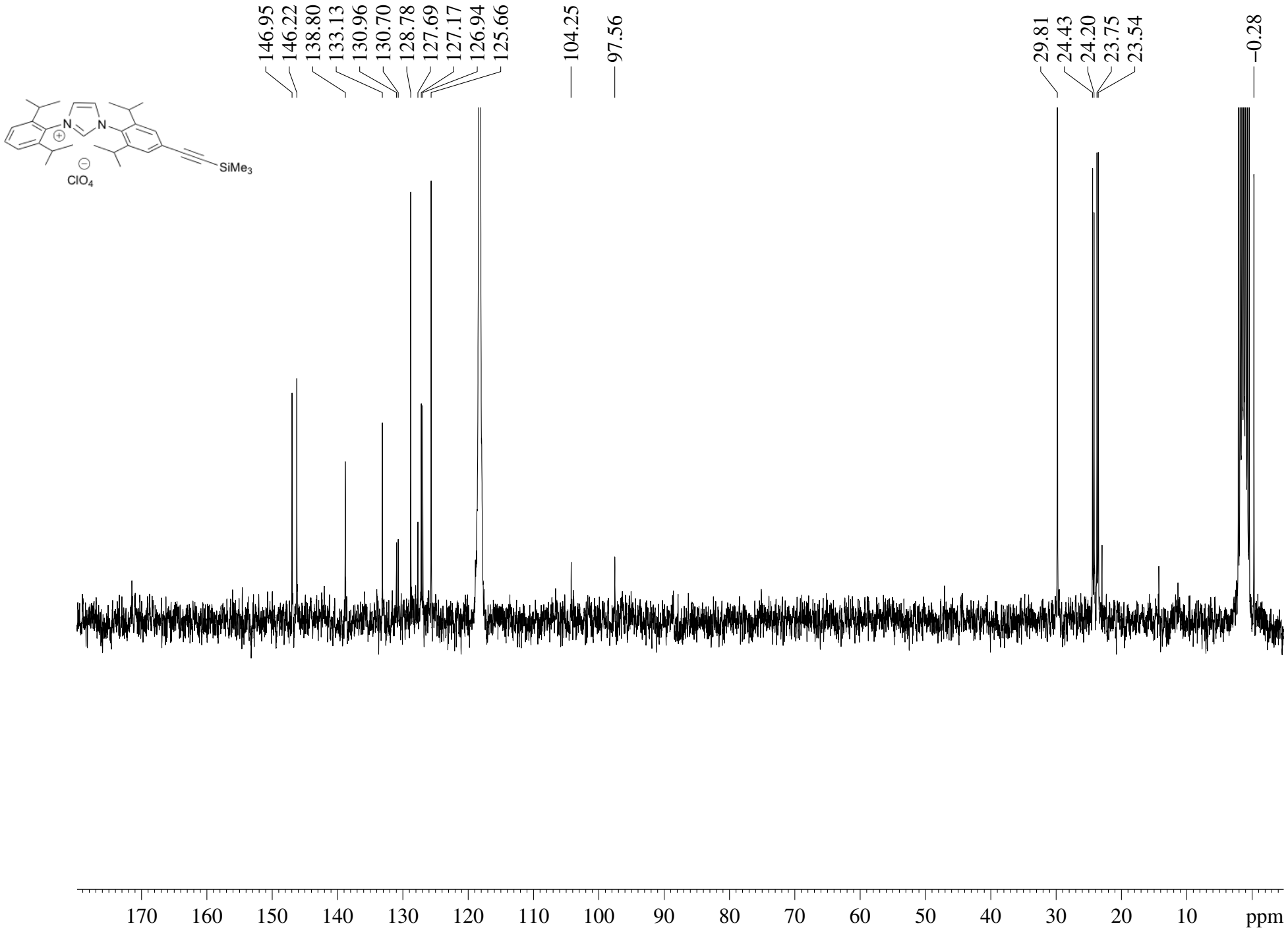

9.000
7.653
7.633
7.614
7.471
7.452
7.422
7.415
7.404
7.397
4.766
4.748
4.730
4.713
4.332
4.325
4.296
4.289
2.978
2.961
2.944
2.927
2.910
2.894
2.878
2.861
2.844
2.828
2.811
2.794
2.253
1.341
1.325
1.304
1.293
1.288
1.276
1.271
1.254
0.90
0.97
1.94
1.00
1.00
1.00
1.99
2.98
11.99
ppm

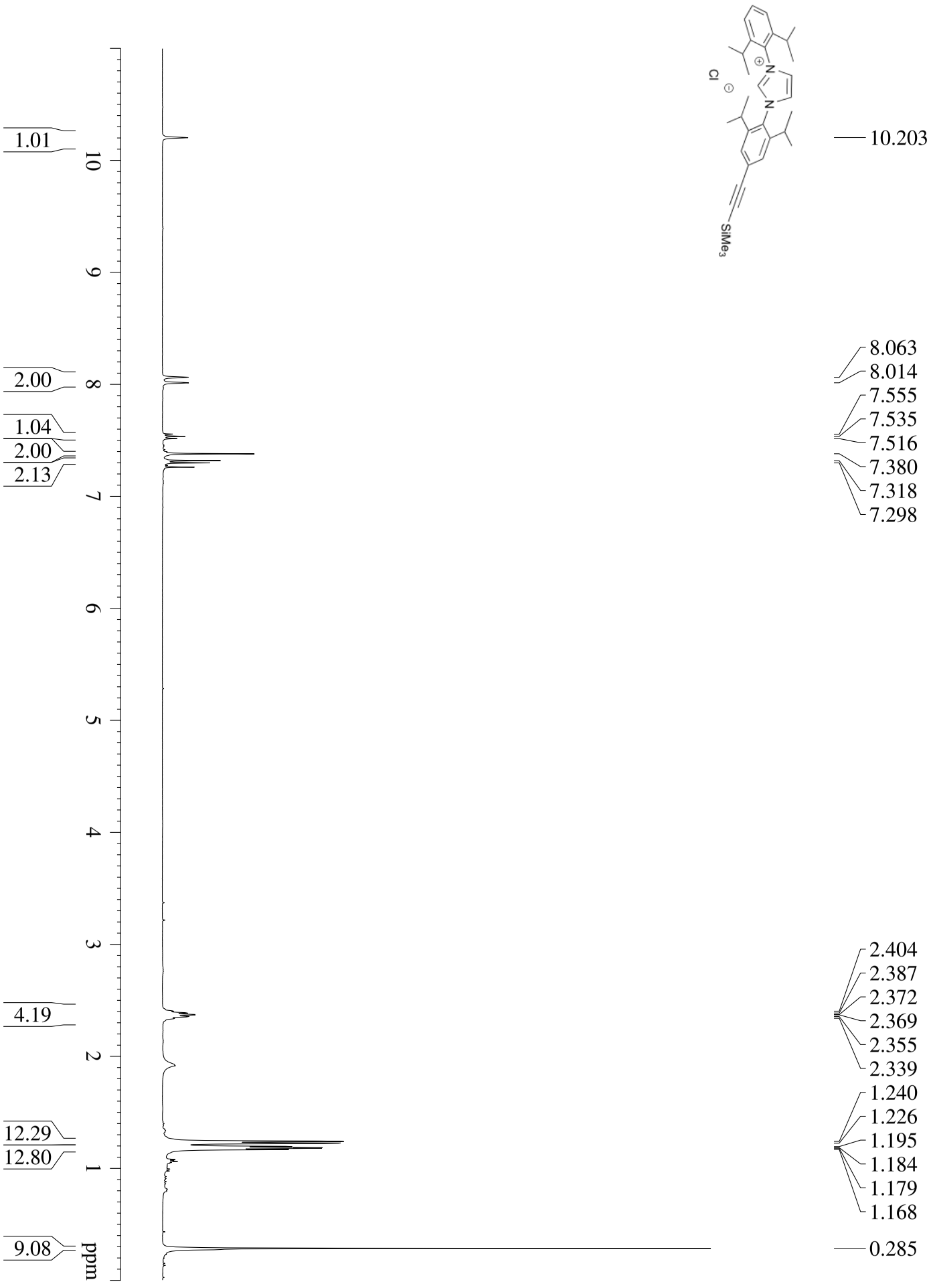


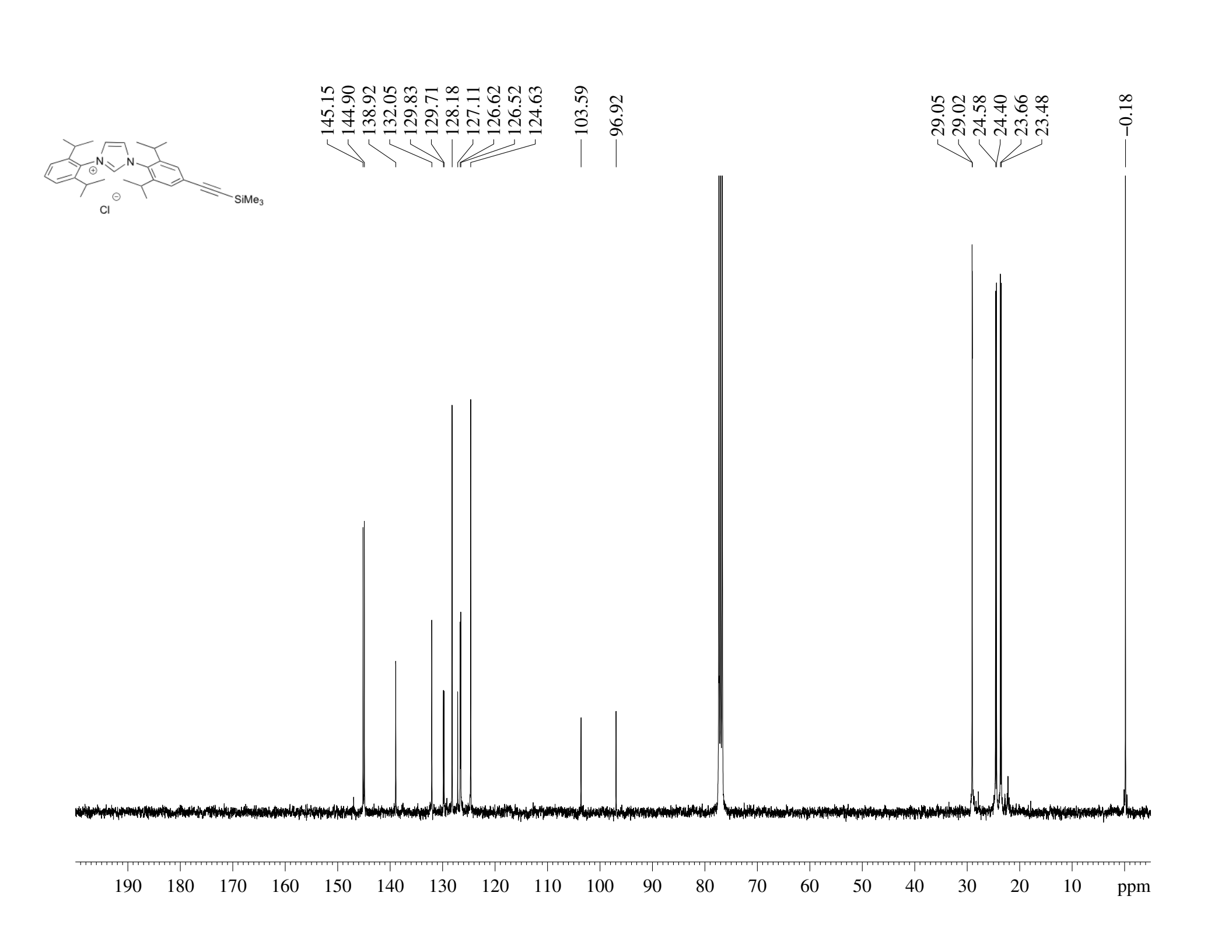
168.90
167.94
146.59
146.39
133.40
127.29
126.24
126.21
100.81
58.59
29.28
29.12
24.57
24.49
24.29
24.00
20.61

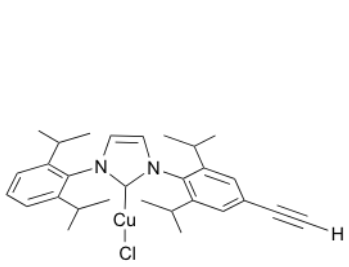


8.955
7.891
7.867
7.863
7.699
7.673
7.647
7.521
7.506
7.479
2.452
2.430
2.407
2.385
2.362
1.291
1.269
1.214
1.191
0.289
SiMe3
ClO4
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.03
1.05
4.17
4.14
12.86
13.60
8.98


146.95
146.22
138.80
133.13
130.96
130.70
128.78
127.69
127.17
126.94
125.66
104.25
97.56
29.81
24.43
24.20
23.75
23.54
−0.28
SiMe3
ClO4
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


1.01
2.00
1.04
2.00
2.13
4.19
12.29
12.80
9.08
10
9
8
7
6
5
4
3
2
1
ppm
Cl
N
N
SiMe3
10.203
8.063
8.014
7.555
7.535
7.516
7.380
7.318
7.298
2.404
2.387
2.372
2.369
2.355
2.339
1.240
1.226
1.195
1.184
1.179
1.168
0.285


145.15
144.90
138.92
132.05
129.83
129.71
128.18
127.11
126.62
126.52
124.63
103.59
96.92
29.05
29.02
24.58
24.40
23.66
23.48
−0.18
SiMe3
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



7.512
7.492
7.472
7.416
7.305
7.285
7.145
7.110

3.176
2.581
2.565
2.547
2.530
2.514
2.497

1.286
1.227
1.213
1.210

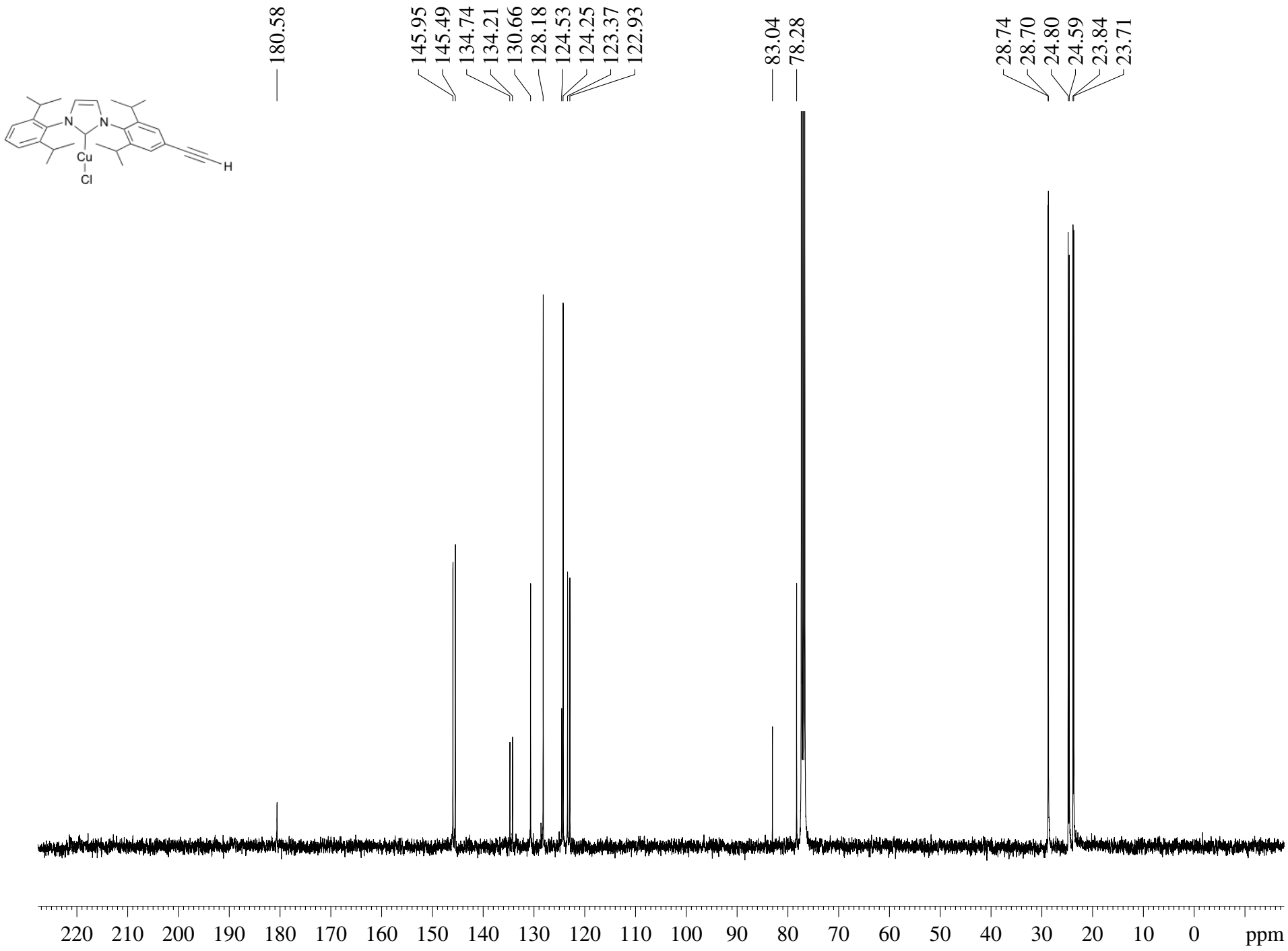
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

1.00
1.66
1.02
0.84
0.96
0.84

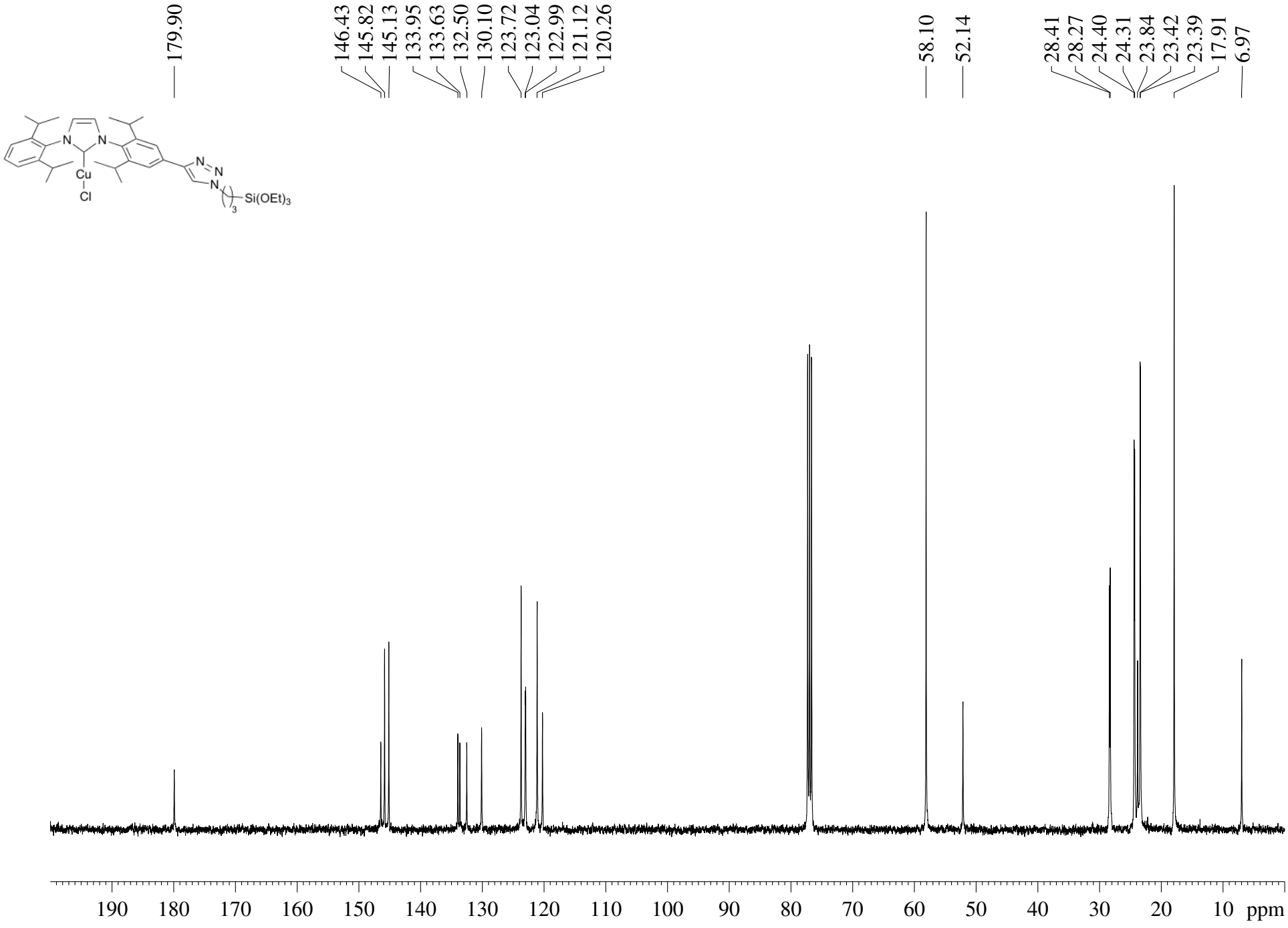
0.79

3.75

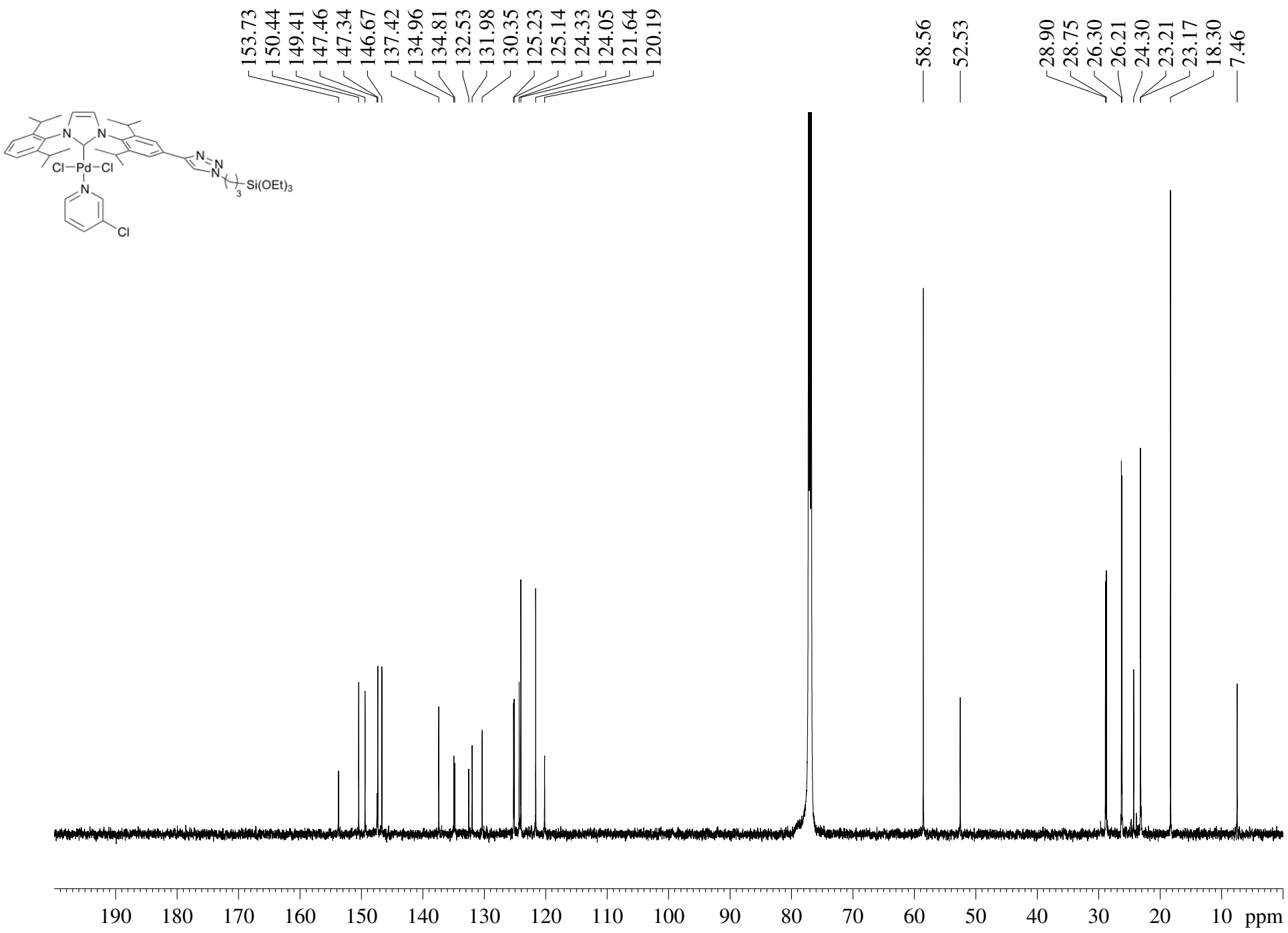
11.29
11.57

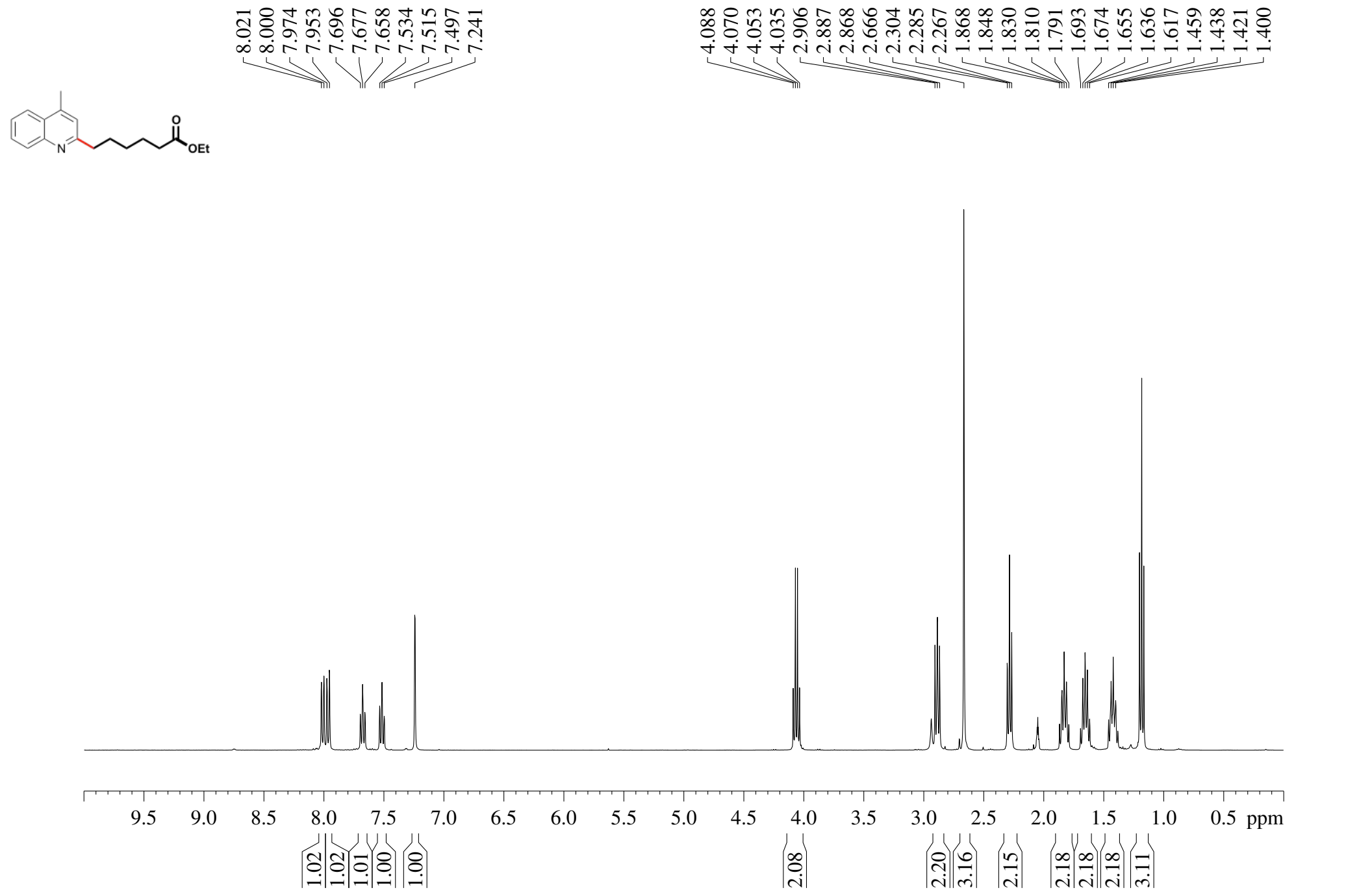

180.58
145.95
145.49
134.74
134.21
130.66
128.18
124.53
124.25
123.37
122.93
83.04
78.28
28.74
28.70
24.80
24.59
23.84
23.71
N
N
Cu
Cl
H
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

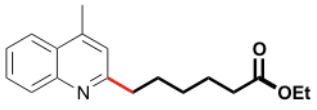
7.888
7.734
7.515
7.495
7.476
7.311
7.292
7.150
4.478
4.460
4.442
3.868
3.851
3.834
3.816
2.642
2.624
2.607
2.589
2.569
2.551
2.534
2.157
2.139
2.119
2.099
2.081
1.360
1.343
1.319
1.301
1.290
1.273
1.259
Cu
Cl
Si(OEt)3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.01
1.11
2.19
2.12
2.17
6.12
4.39
2.17
6.40
6.76
6.26
16.12
2.25


179.90
146.43
145.82
145.13
133.95
133.63
132.50
130.10
123.72
123.04
122.99
121.12
120.26
58.10
52.14
28.41
28.27
24.40
24.31
23.84
23.42
23.39
17.91
6.97
N
N
Cu
Cl
N
N
3
Si(OEt)3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

8.593
8.589
8.523
8.521
8.514
7.870
7.800
7.545
7.532
7.515
7.502
7.489
7.362
7.349
7.157
7.154
7.073
7.064
7.060
7.050
4.454
4.442
4.430
3.847
3.836
3.824
3.812
3.209
3.197
3.186
3.174
3.161
3.150
3.139
2.107
2.094
2.081
1.539
1.528
1.489
1.478
1.244
1.232
1.221
1.166
1.155
1.133
1.121
0.667
0.653
0.640
Cl—Pd—Cl
Si(OEt)3
Cl
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
ppm
0.91
0.96
0.97
1.84
1.04
1.05
2.01
1.99
0.98
2.02
6.40
4.00
2.09
6.34
6.19
9.73
5.82
6.26
1.91

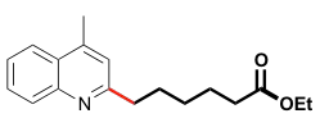

153.73
150.44
149.41
147.46
147.34
146.67
137.42
134.96
134.81
132.53
131.98
130.35
125.23
125.14
124.33
124.05
121.64
120.19
58.56
52.53
28.90
28.75
26.30
26.21
24.30
23.21
23.17
18.30
7.46
Cl—Pd—Cl
Si(OEt)3
Cl
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.021
8.000
7.974
7.953
7.696
7.677
7.658
7.534
7.515
7.497
7.241
4.088
4.070
4.053
4.035
2.906
2.887
2.868
2.666
2.304
2.285
2.267
1.868
1.848
1.830
1.810
1.791
1.693
1.674
1.655
1.636
1.617
1.459
1.438
1.421
1.400
O
OEt
N
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
ppm
1.02
1.02
1.01
1.00
1.00
2.08
2.20
3.16
2.15
2.18
2.18
2.18
3.11



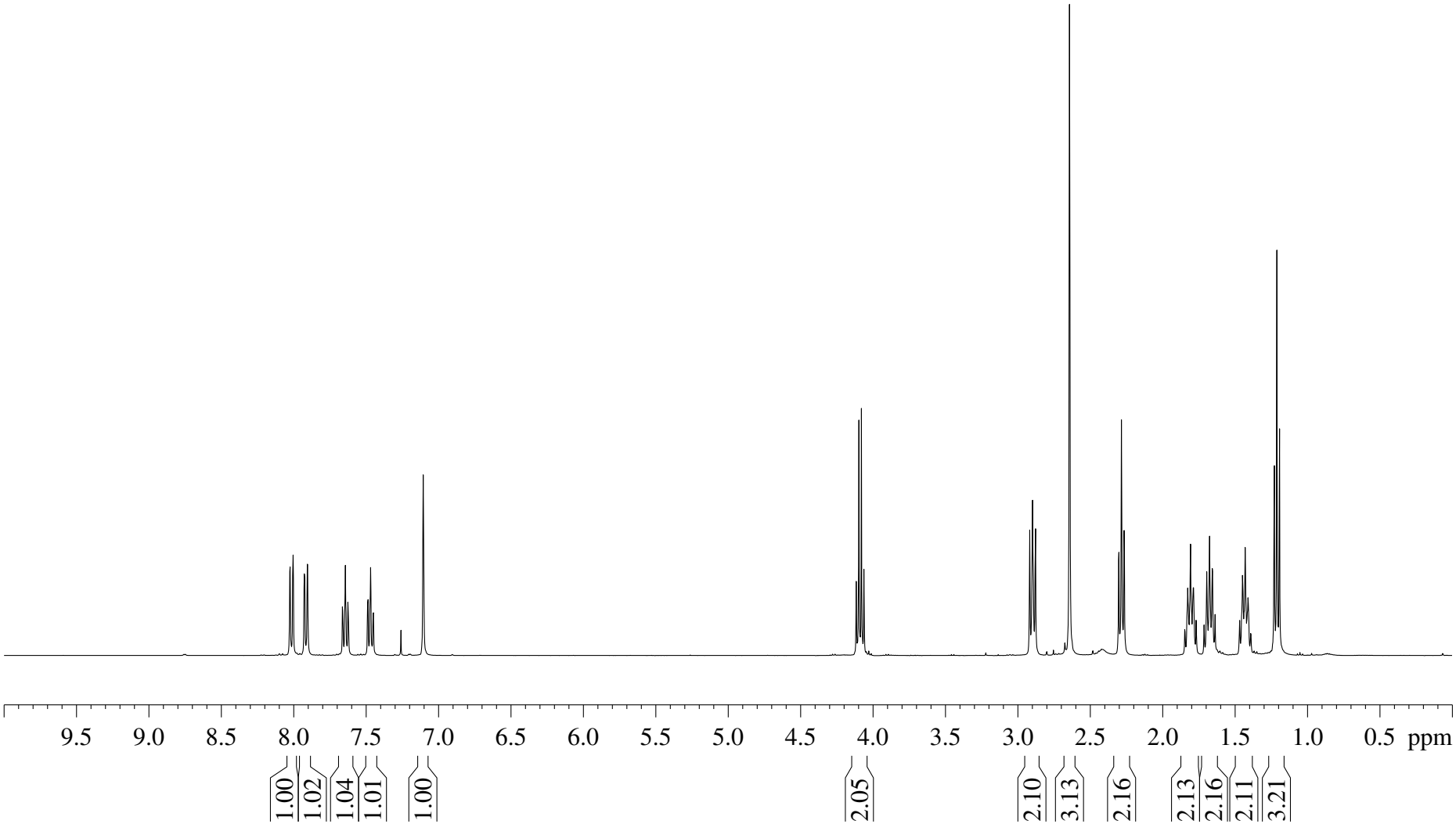
173.72
163.14
148.99
144.88
130.46
129.73
127.76
126.31
124.75
122.99
60.55
39.38
34.70
29.92
29.75
25.72
18.70
14.72

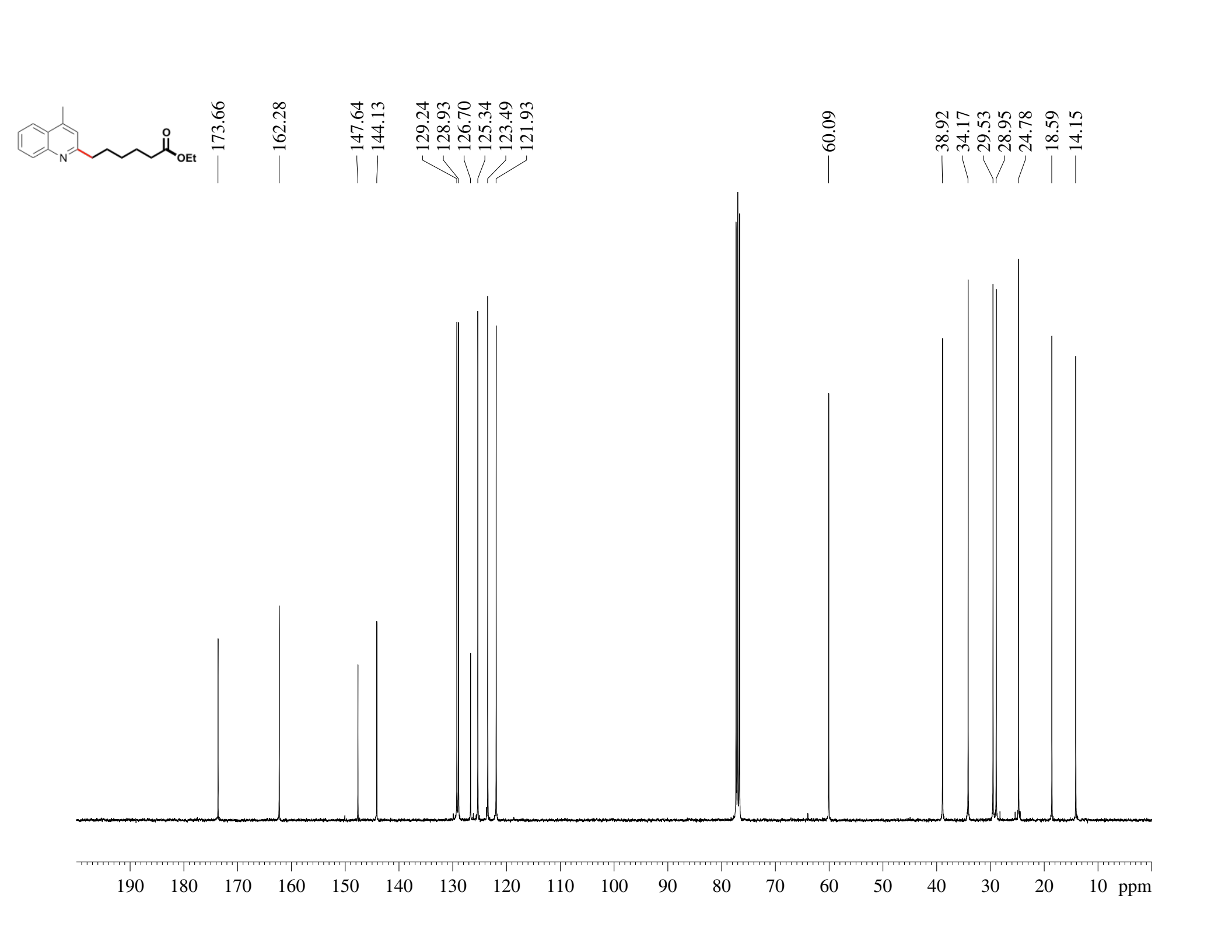
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

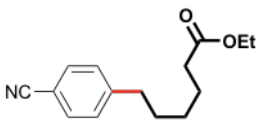


8.026
8.005
7.926
7.905
7.663
7.644
7.625
7.488
7.469
7.450
7.106

4.116
4.098
4.080
4.062
2.918
2.898
2.878
2.643
2.303
2.285
2.266
1.847
1.827
1.808
1.788
1.769
1.714
1.696
1.676
1.657
1.638
1.469
1.448
1.430

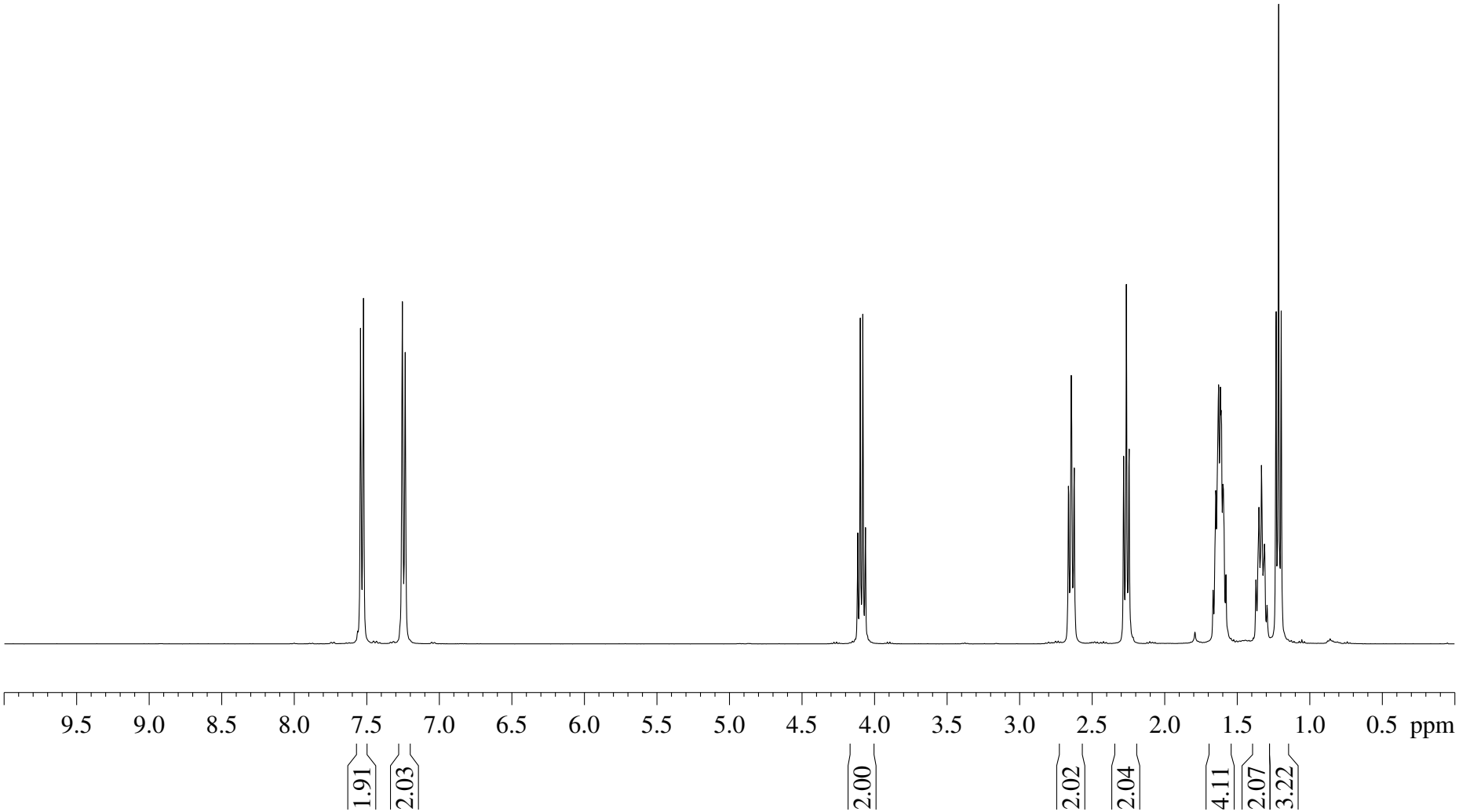


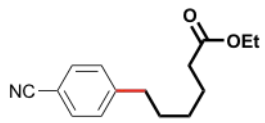

O
N
OEt
173.66
162.28
147.64
144.13
129.24
128.93
126.70
125.34
123.49
121.93
60.09
38.92
34.17
29.53
28.95
24.78
18.59
14.15
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm



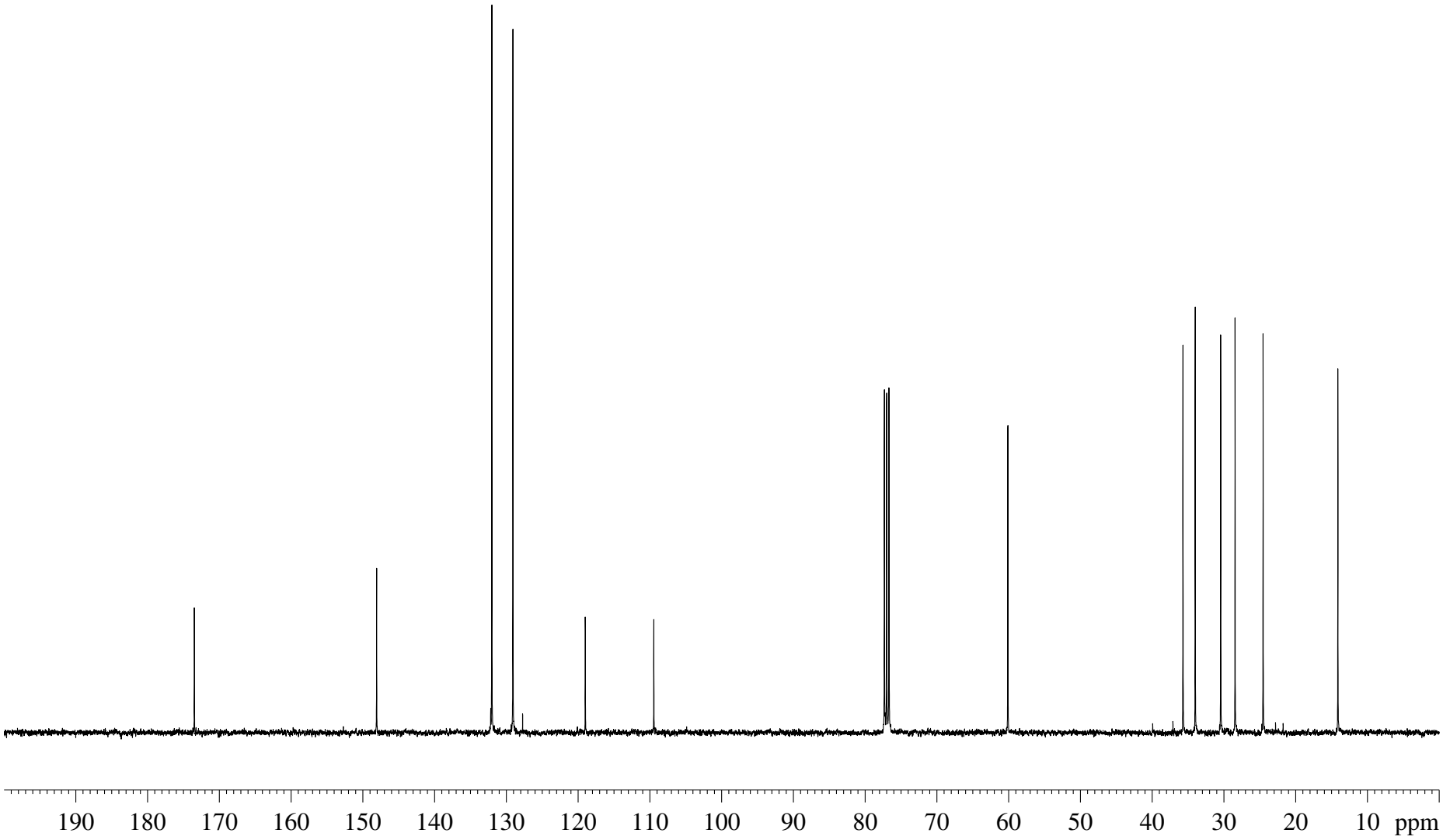
7.543
7.523
7.255
7.235

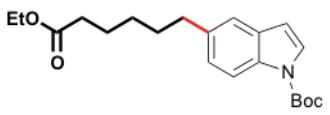
4.116
4.098
4.080
4.063
2.663
2.643
2.624
2.283
2.264
2.245
1.666
1.647
1.629
1.615
1.611
1.597
1.578
1.371
1.350
1.332
1.312
1.294
1.232



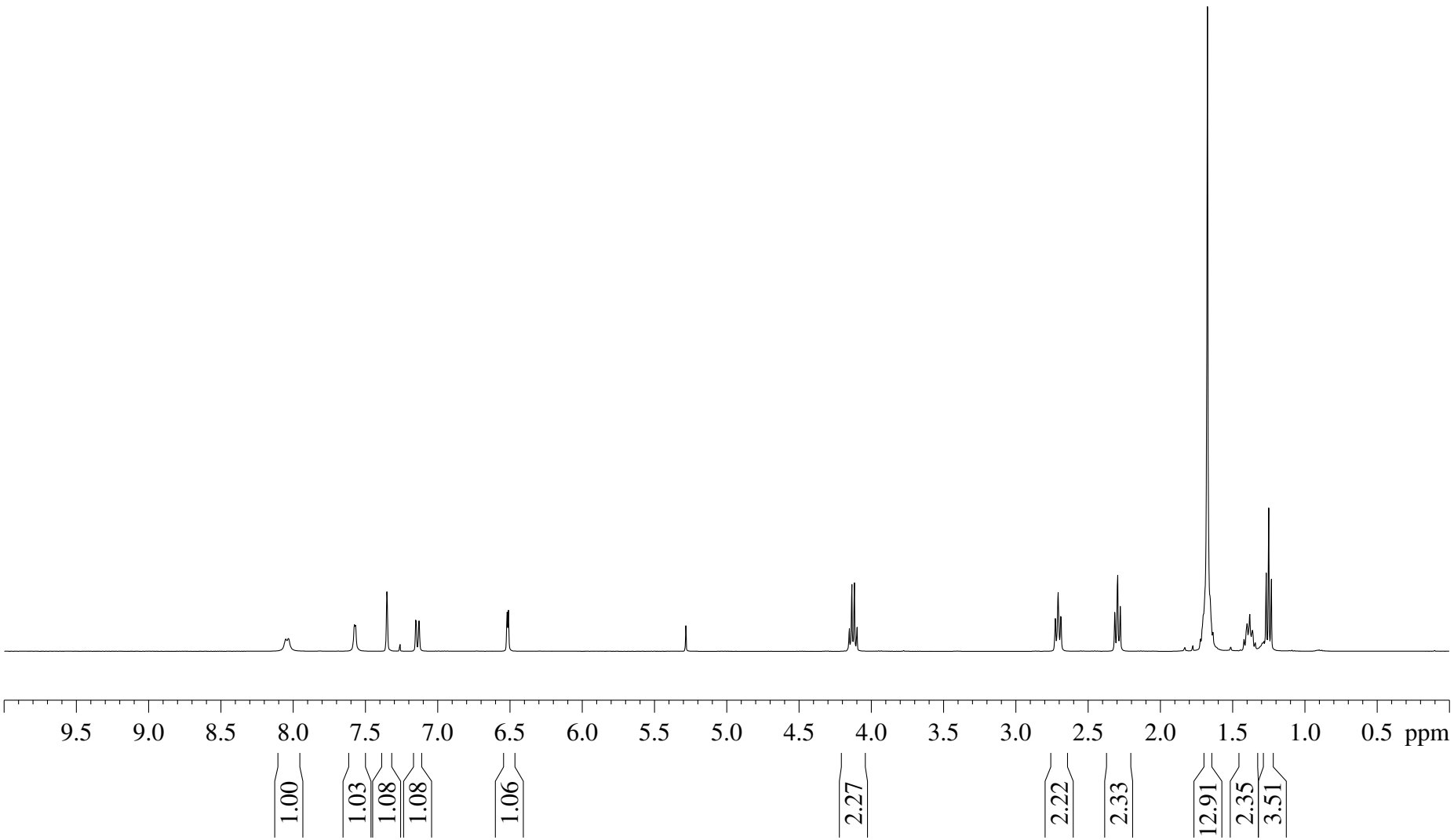


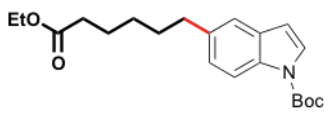
173.46
148.06
132.00
129.07
119.00
109.45
60.11
35.71
34.00
30.45
28.45
24.54
14.12



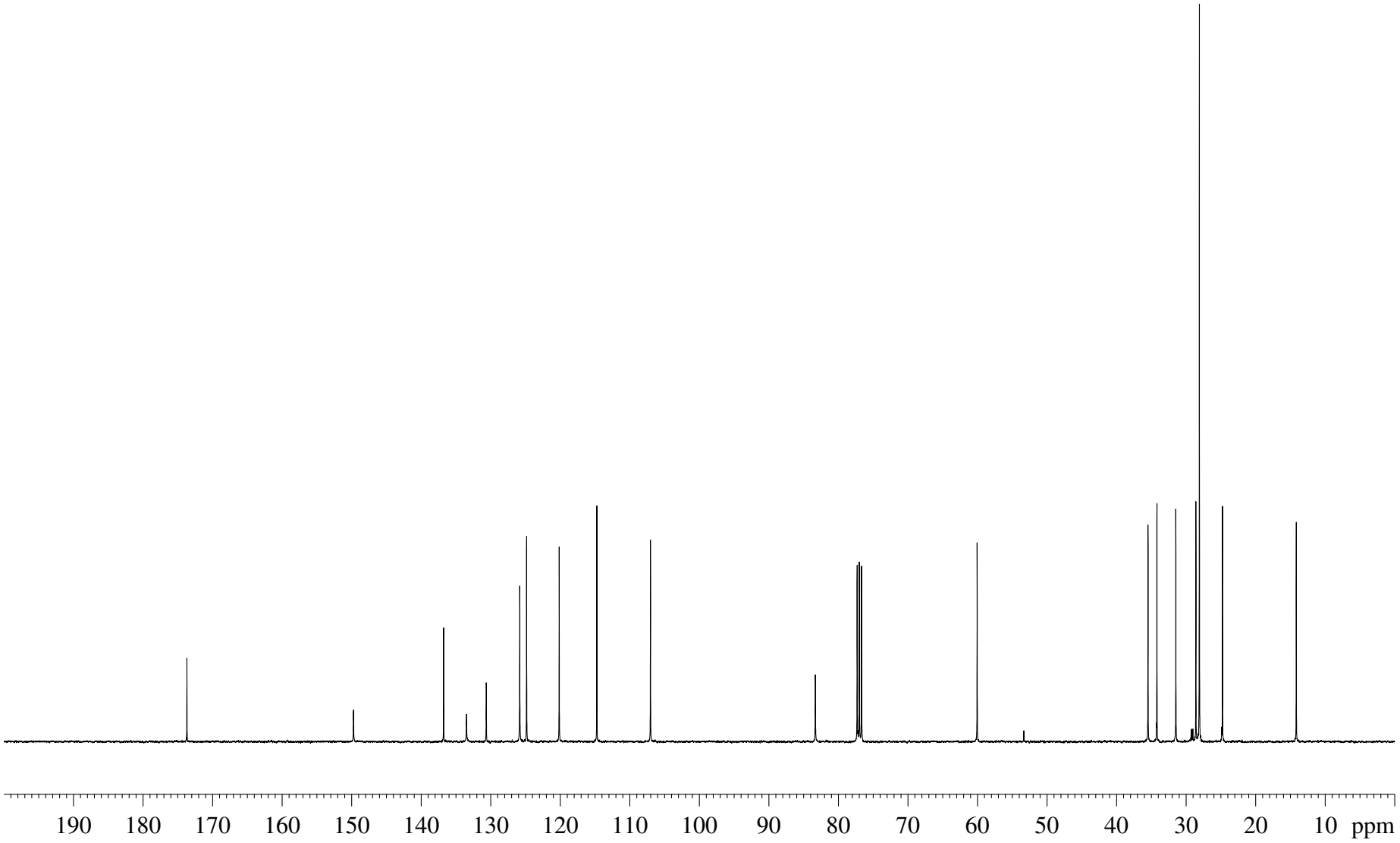


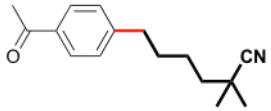
8.051
8.033
7.576
7.569
7.351
7.151
7.129
6.519
6.510
4.152
4.134
4.117
4.099
2.726
2.707
2.688
2.315
2.296
2.277
1.674
1.421
1.400
1.382
1.363
1.344
1.268
1.250
1.232





173.68
149.72
136.76
133.47
130.65
125.83
124.85
120.16
114.74
107.03
83.32
60.06
35.48
34.20
31.48
28.59
28.10
24.77
14.15

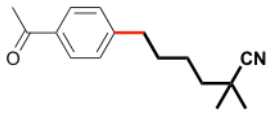




7.862
7.842
7.244
7.224
2.687
2.668
2.649
2.545
1.659
1.645
1.629
1.518
1.509
1.293

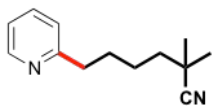
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

2.00
1.97
2.09
3.06
2.12
4.04
6.13



197.62
147.81
134.95
128.42
124.94
40.68
35.55
32.19
30.87
26.50
26.40
24.79

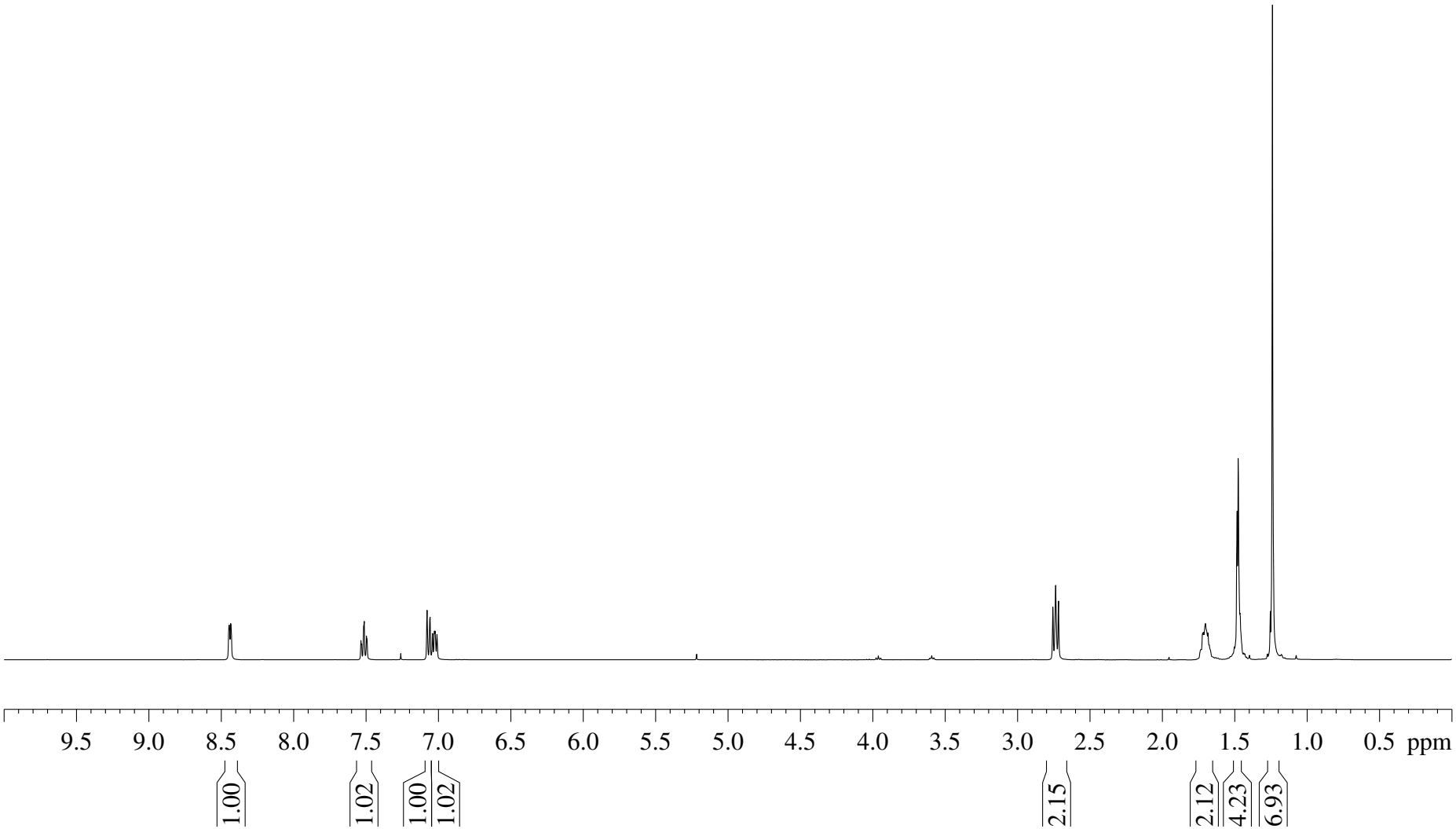
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

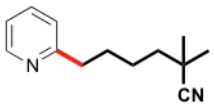


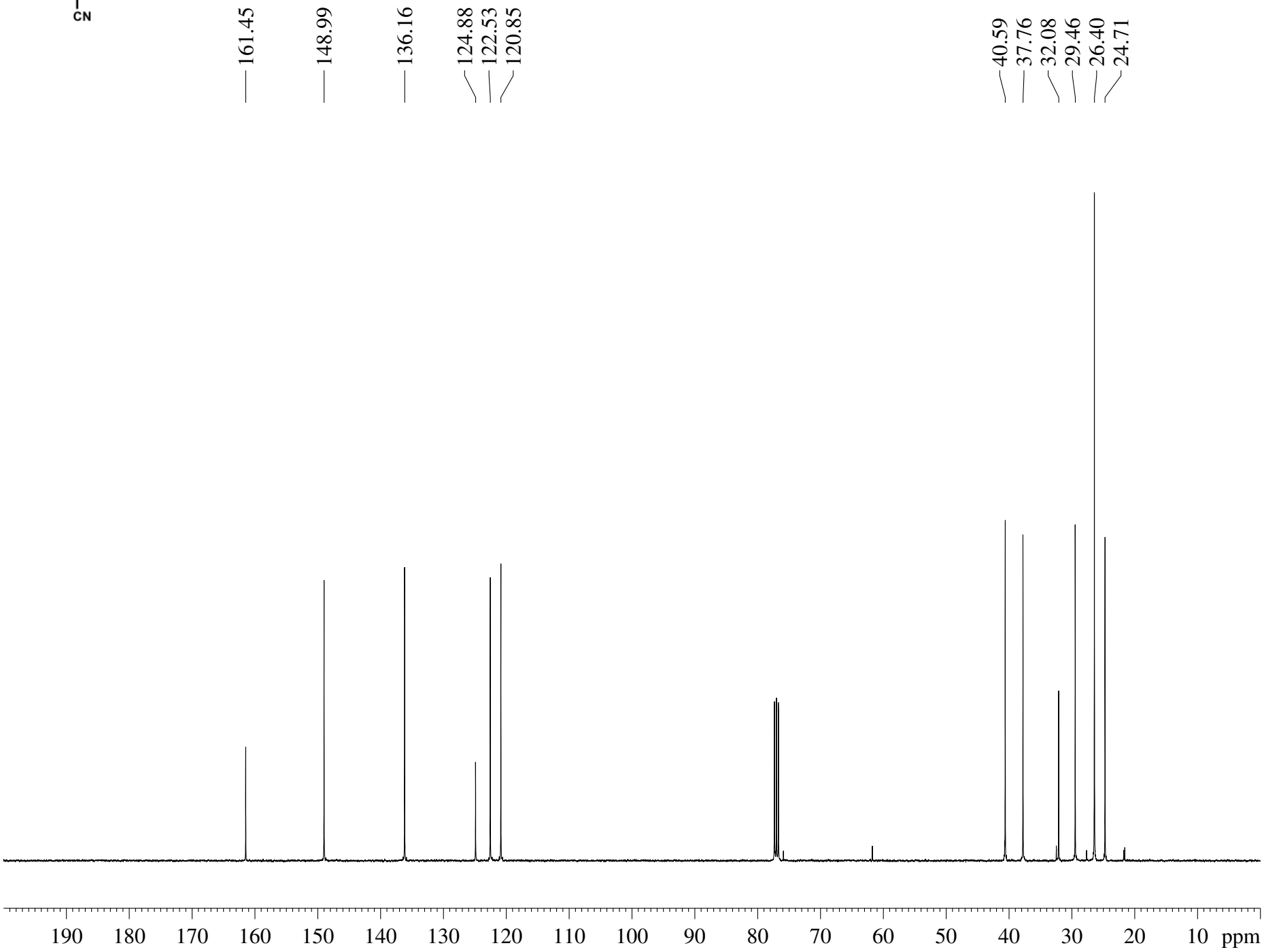
8.445
8.434
7.535
7.531
7.513
7.497
7.493
7.078
7.059
7.041
7.027
7.023
7.010

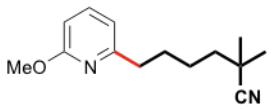
2.756
2.737
2.717

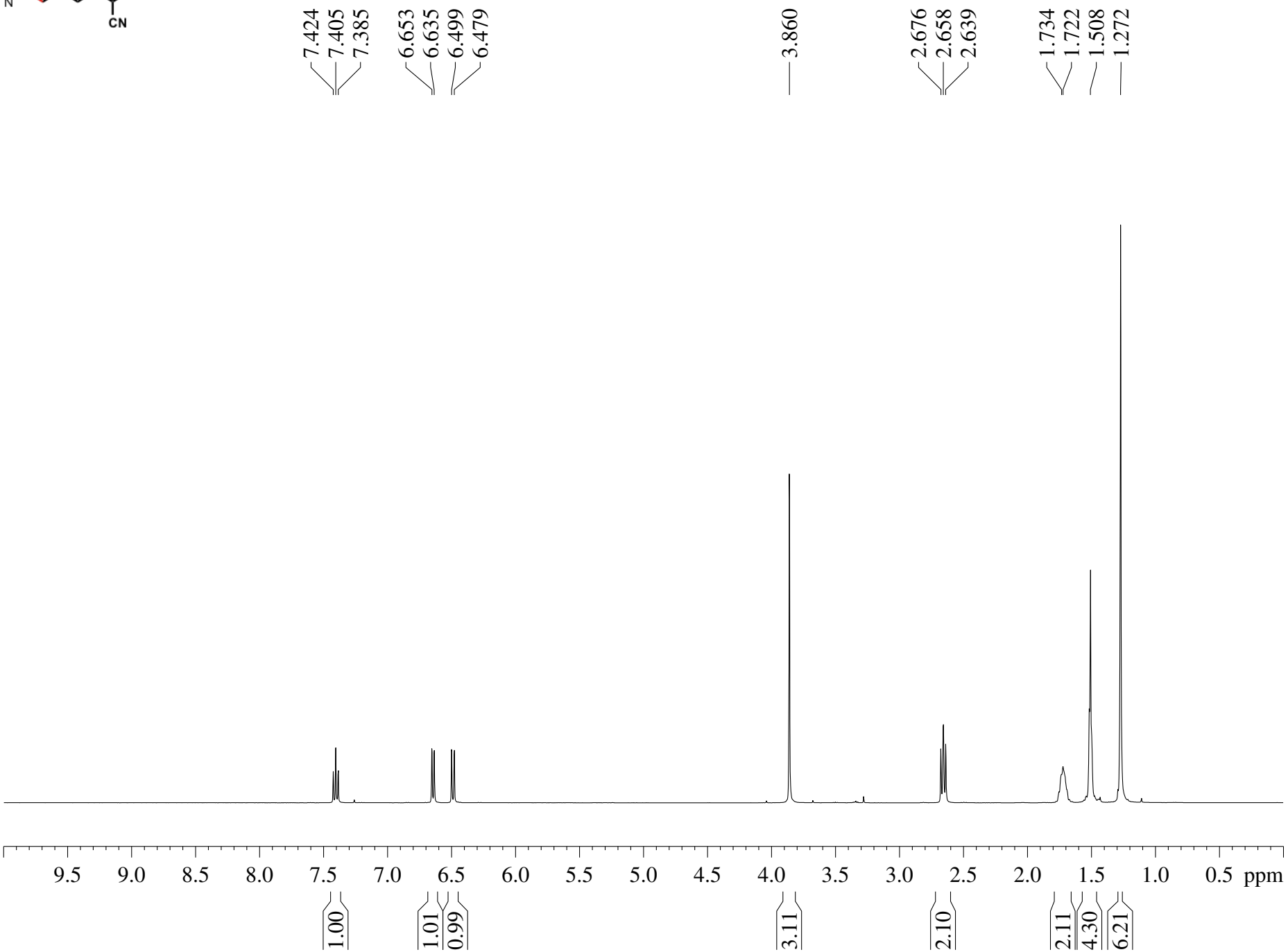
1.721
1.715
1.703
1.685
1.484
1.476
1.239

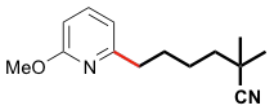


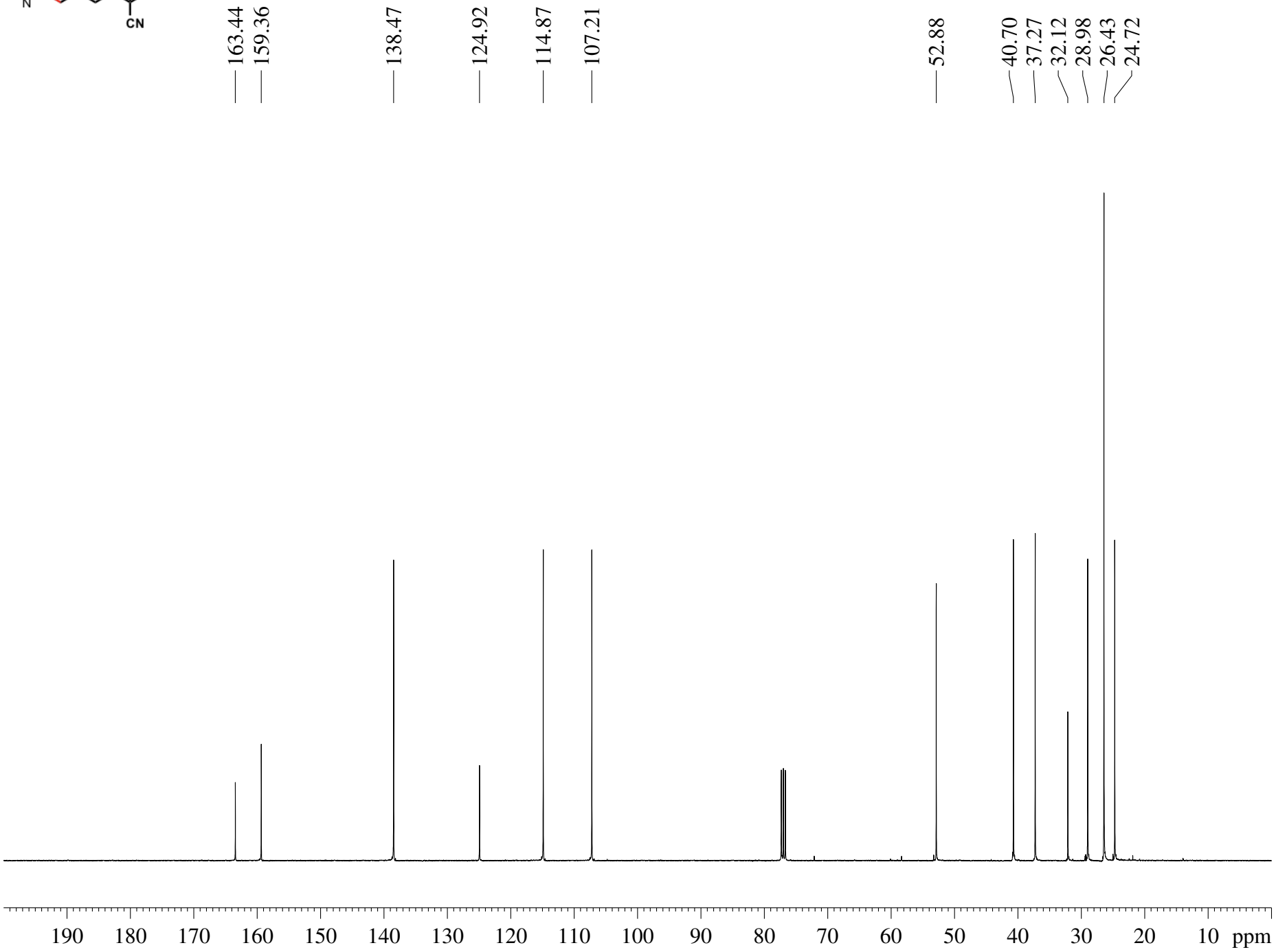

N
CN


161.45
148.99
136.16
124.88
122.53
120.85
40.59
37.76
32.08
29.46
26.40
24.71
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

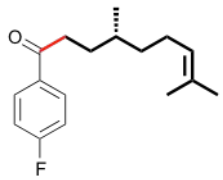

MeO
N
CN


7.424
7.405
7.385
6.653
6.635
6.499
6.479
3.860
2.676
2.658
2.639
1.734
1.722
1.508
1.272
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
ppm
1.00
1.01
0.99
3.11
2.10
2.11
4.30
6.21


MeO
N
CN

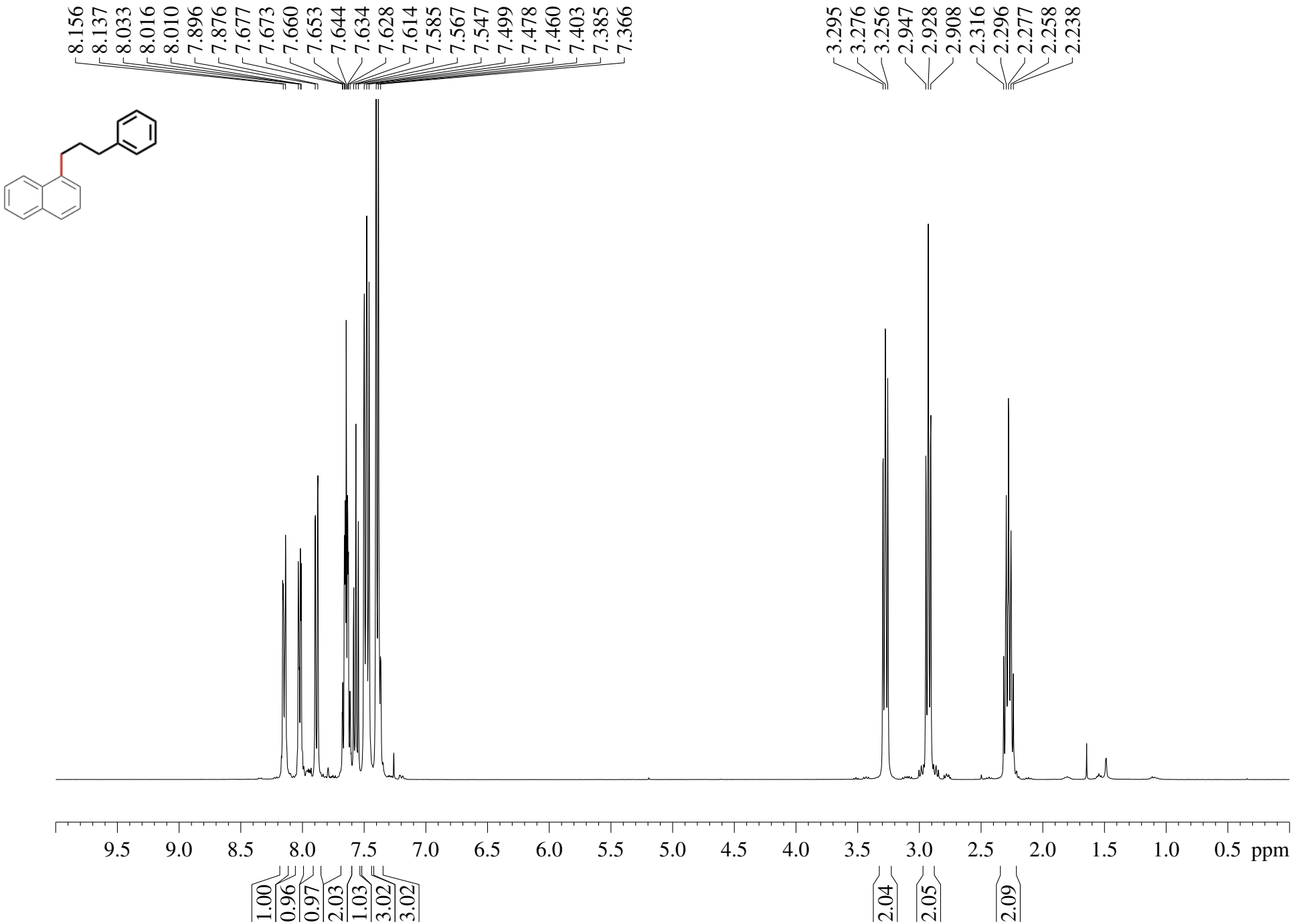

163.44
159.36
138.47
124.92
114.87
107.21
52.88
40.70
37.27
32.12
28.98
26.43
24.72
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

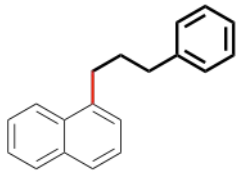
5.109
5.091
5.074
2.965
2.951
2.940
2.926
2.918
2.902
2.037
2.018
2.006
1.993
1.970
1.951
1.793
1.779
1.772
1.758
1.750
1.736
1.678
1.598
1.577
1.562
1.554
1.540
1.530
1.519
1.503
1.487
1.425
1.410
1.401
1.395
1.391
1.376
1.369
1.364
1.354
1.339
1.248
1.231
1.225
1.214
1.209
1.198
1.191
1.175
0.945
0.929
O
F
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
ppm
2.00
1.98
0.99
2.10
2.10
1.13
3.03
3.13
2.17
1.11
1.12
3.13

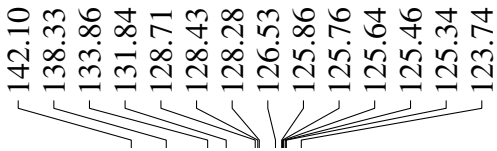


199.14
166.88
164.35
133.50
133.47
131.32
130.69
130.60
124.64
115.72
115.50
36.87
36.24
32.23
31.29
25.71
25.49
19.41
17.65

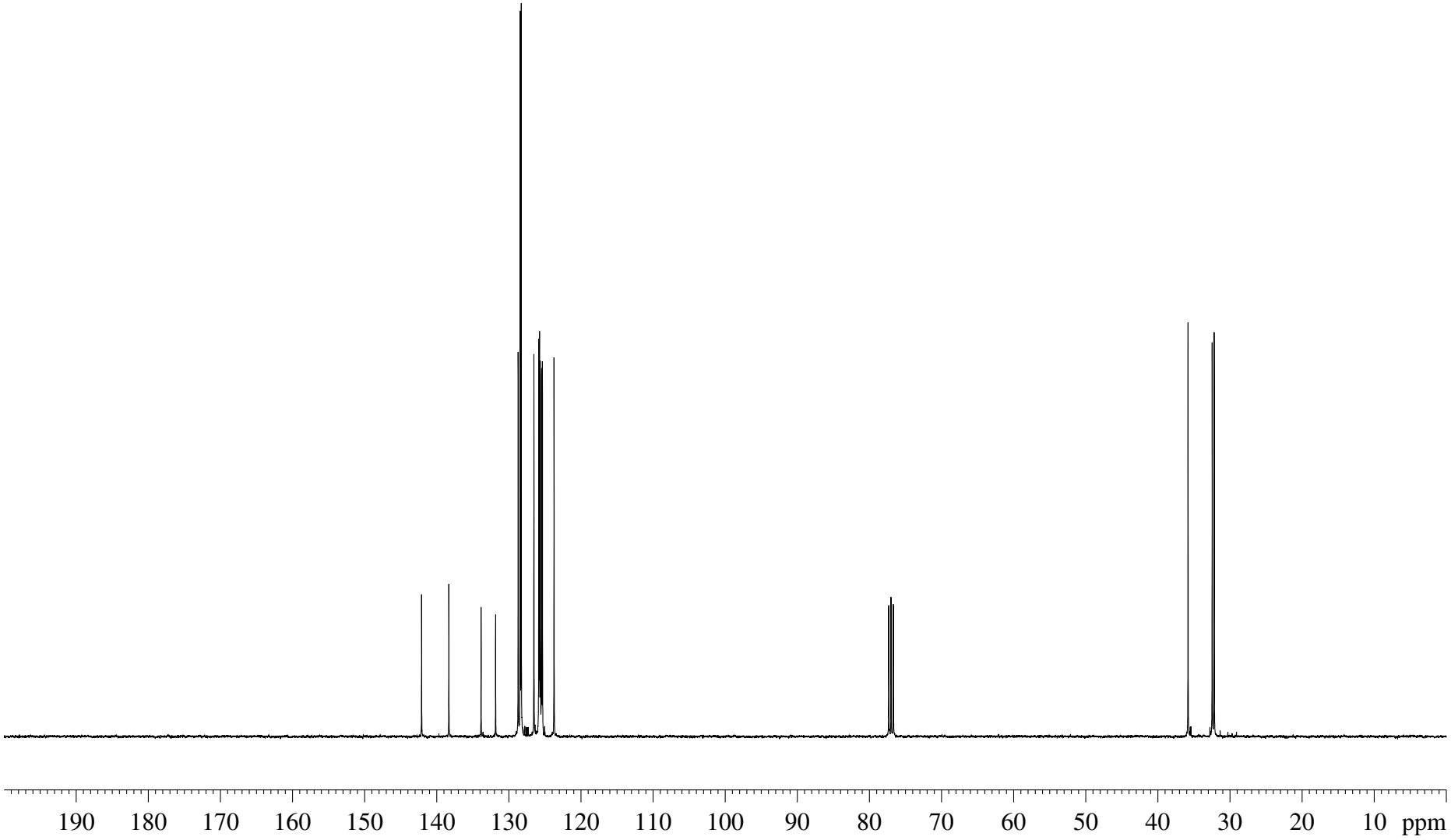
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

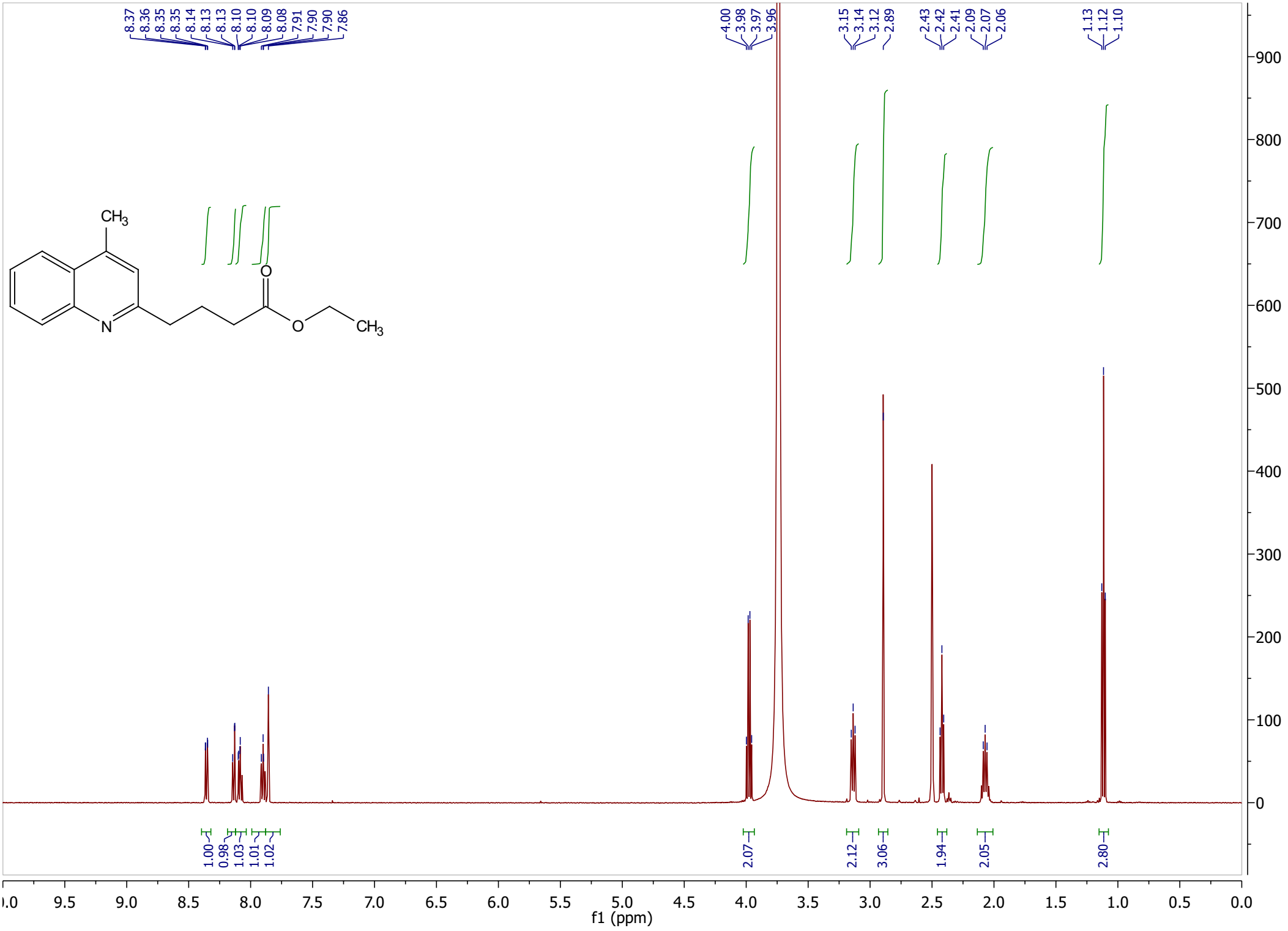

8.156
8.137
8.033
8.016
8.010
7.896
7.876
7.677
7.673
7.660
7.653
7.644
7.634
7.628
7.614
7.585
7.567
7.547
7.499
7.478
7.460
7.403
7.385
7.366
3.295
3.276
3.256
2.947
2.928
2.908
2.316
2.296
2.277
2.258
2.238
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.96
0.97
2.03
1.03
3.02
3.02
2.04
2.05
2.09

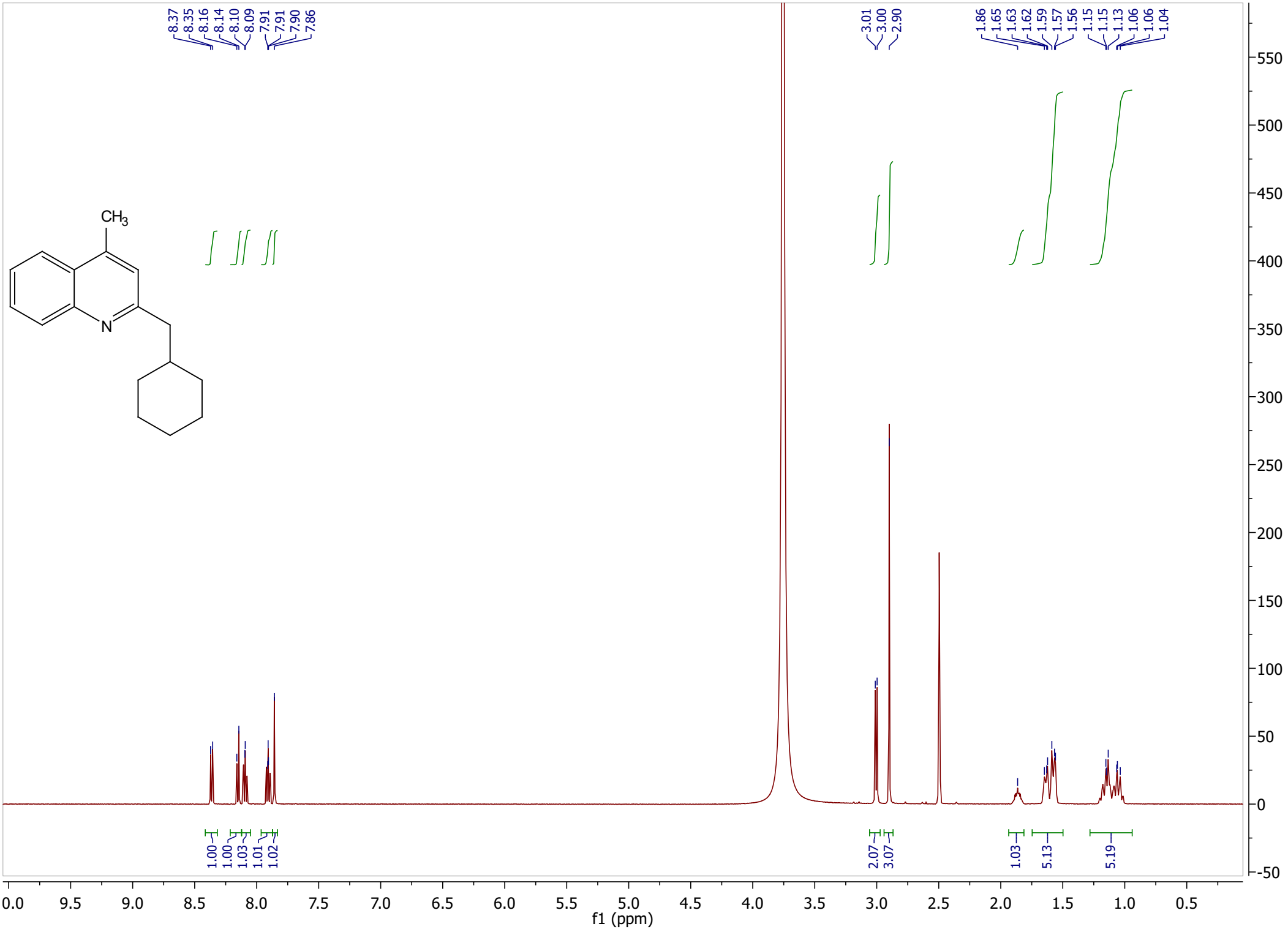


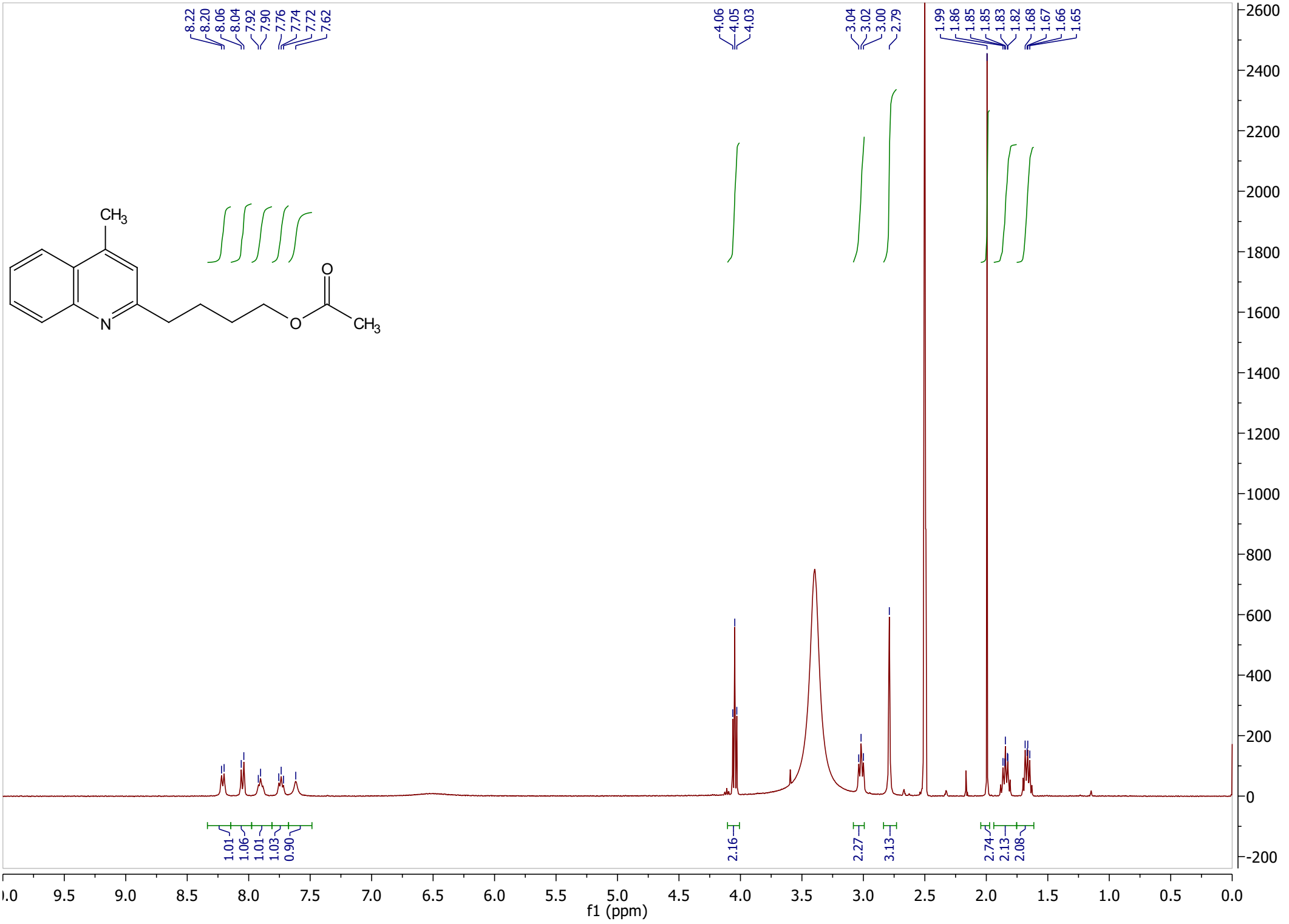

142.10
138.33
133.86
131.84
128.71
128.43
128.28
126.53
125.86
125.76
125.64
125.46
125.34
123.74

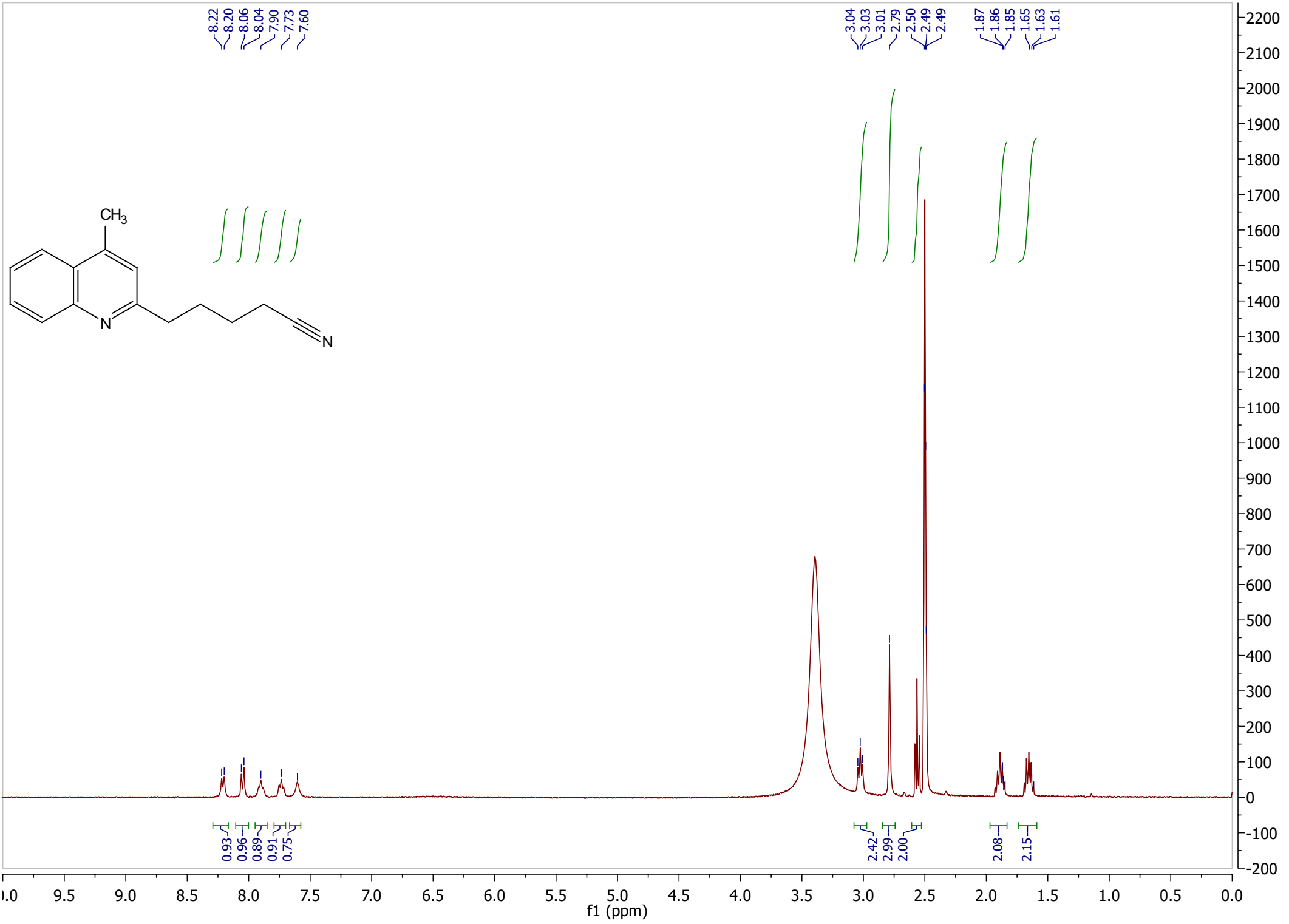

35.81
32.47
32.19

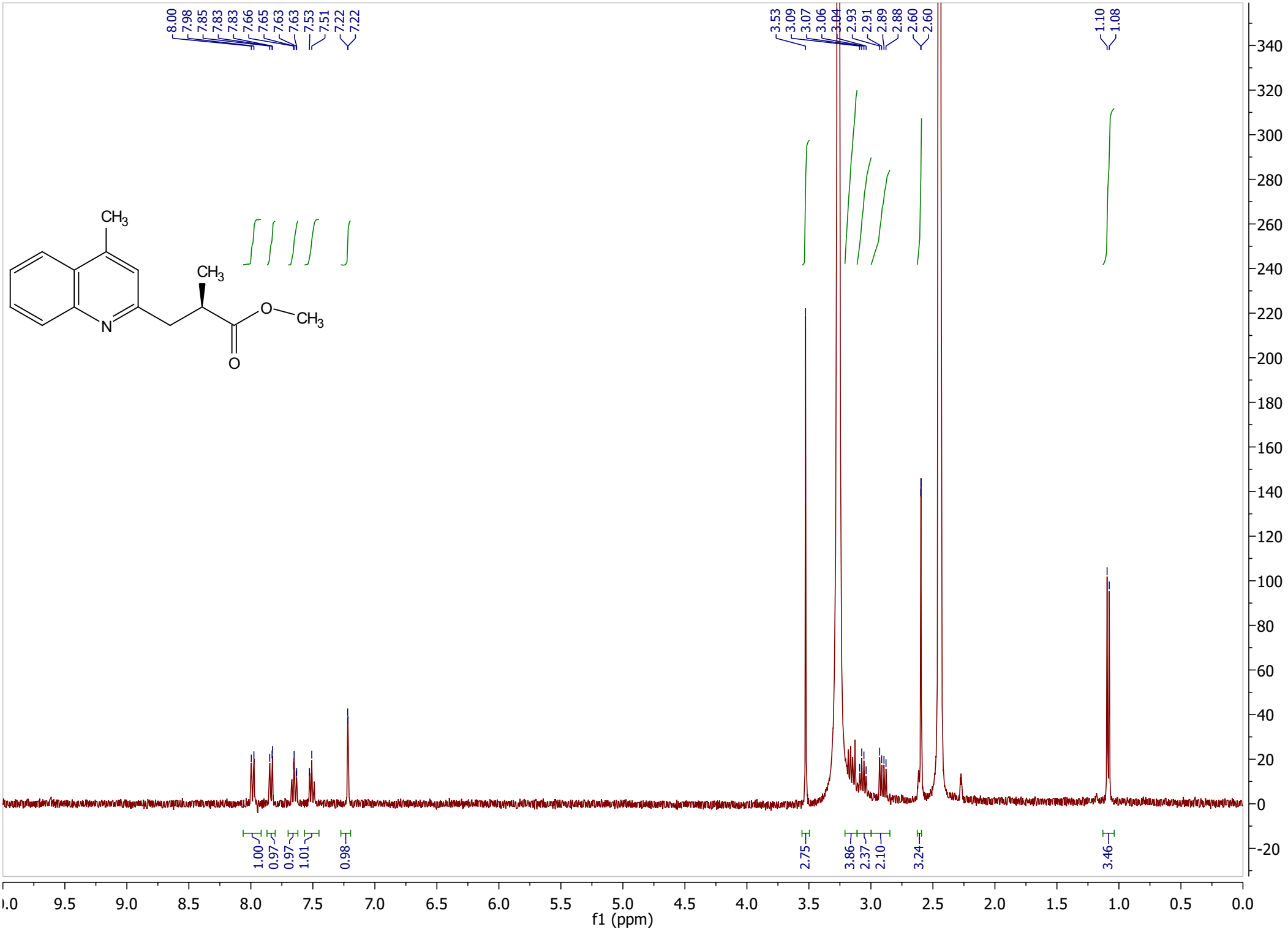

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

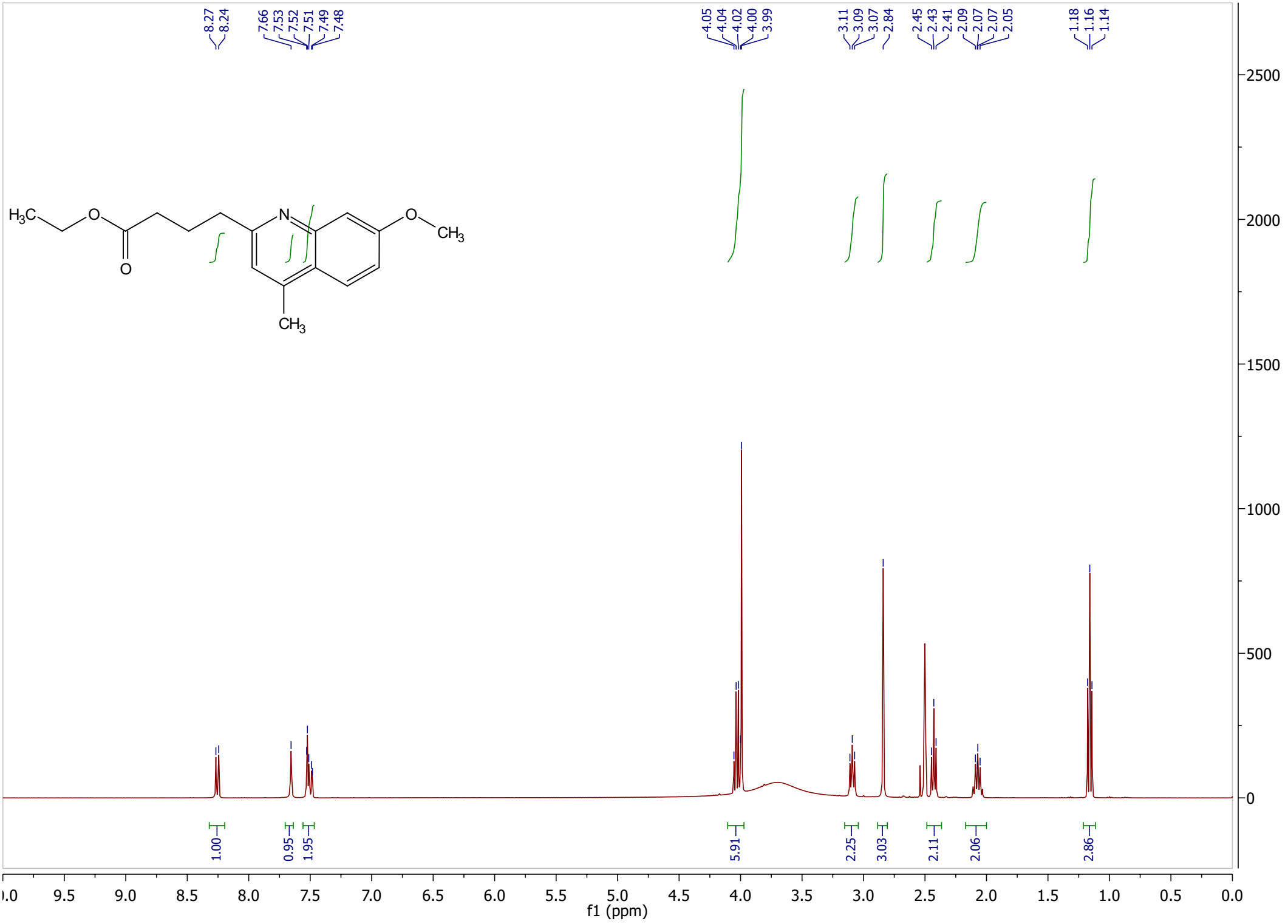

8.37
8.36
8.35
8.35
8.14
8.13
8.13
8.10
8.10
8.09
8.08
7.91
7.90
7.90
7.86
4.00
3.98
3.97
3.96
3.15
3.14
3.12
2.89
2.43
2.42
2.41
2.09
2.07
2.06
1.13
1.12
1.10
CH3
O
N
O
CH3
1.00
0.98
1.03
1.01
1.02
2.07
2.12
3.06
1.94
2.05
2.80
900
800
700
600
500
400
300
200
100
0
f1 (ppm)

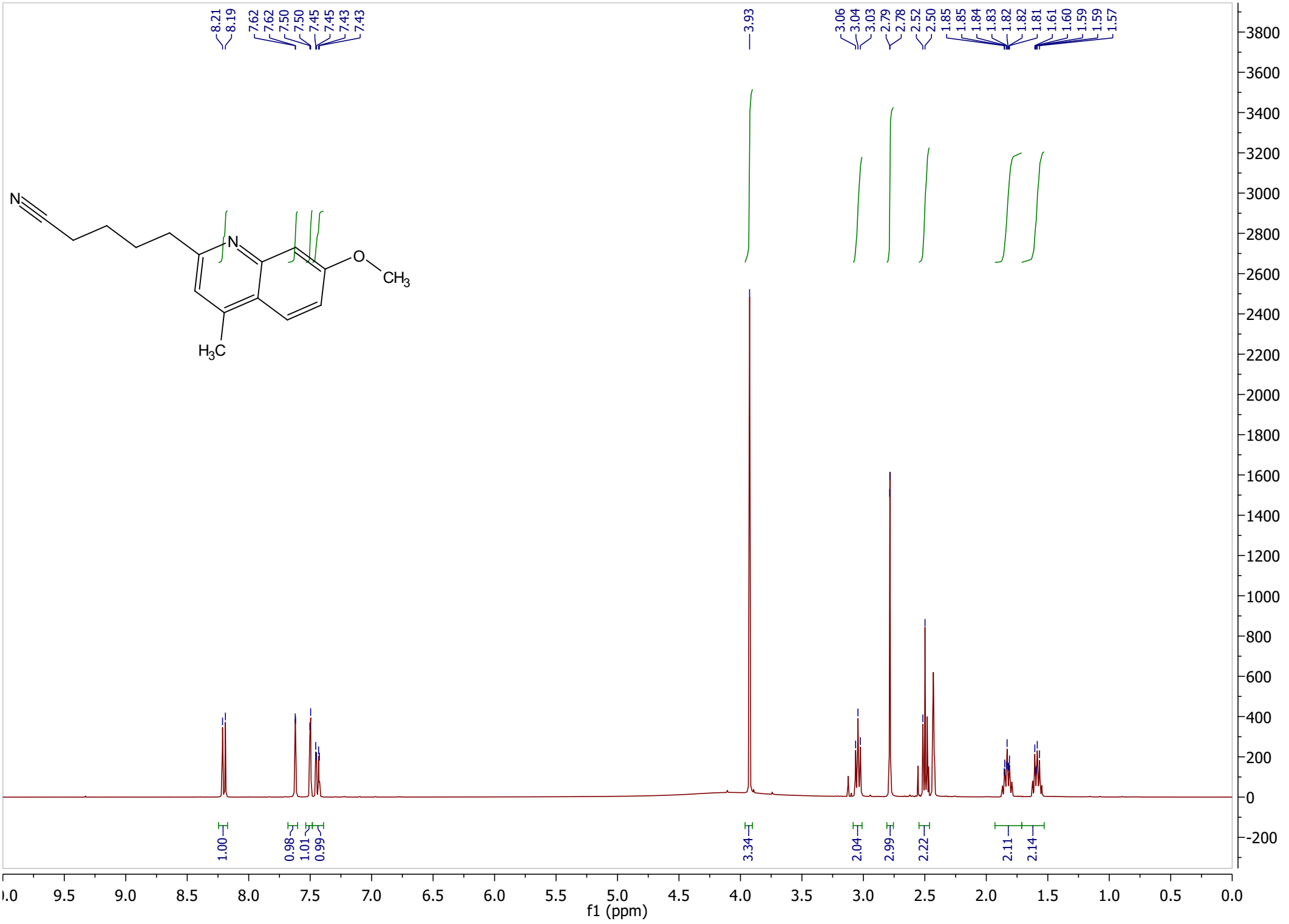

8.37
8.35
8.16
8.14
8.10
8.09
7.91
7.91
7.90
7.86
3.01
3.00
2.90
1.86
1.65
1.63
1.62
1.59
1.57
1.56
1.15
1.15
1.13
1.06
1.06
1.04
CH3
N
1.00
1.00
1.03
1.01
1.02
2.07
3.07
1.03
5.13
5.19
f1 (ppm)

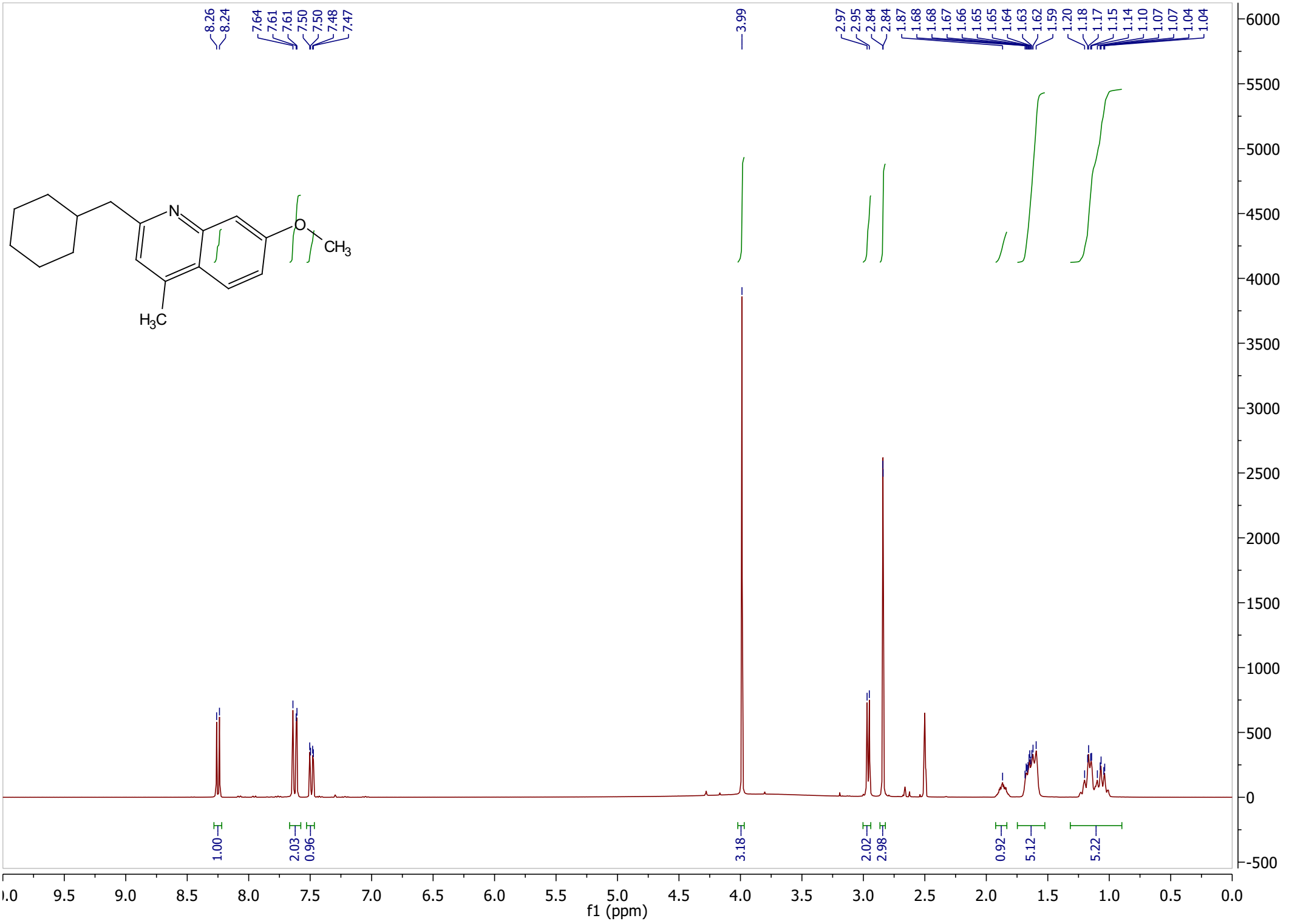

8.22
8.20
8.06
8.04
7.92
7.90
7.76
7.74
7.72
7.62
4.06
4.05
4.03
3.04
3.02
3.00
2.79
1.99
1.86
1.85
1.85
1.83
1.82
1.68
1.67
1.66
1.65
CH3
N
O
O
CH3
1.01
1.06
1.01
1.03
0.90
2.16
2.27
3.13
2.74
2.13
2.08
f1 (ppm)


8.22
8.20
8.06
8.04
7.90
7.73
7.60
3.04
3.03
3.01
2.79
2.50
2.49
2.49
1.87
1.86
1.85
1.65
1.63
1.61
CH3
N
N
0.93
0.96
0.89
0.91
0.75
2.42
2.99
2.00
2.08
2.15
f1 (ppm)


8.00
7.98
7.85
7.83
7.83
7.66
7.65
7.63
7.63
7.53
7.51
7.22
7.22
3.53
3.09
3.07
3.06
3.04
2.93
2.91
2.89
2.88
2.60
2.60
1.10
1.08
CH3
CH3
N
O
CH3
O
1.00
0.97
0.97
1.01
0.98
2.75
3.86
2.37
2.10
3.24
3.46
f1 (ppm)


8.27
8.24
7.66
7.53
7.52
7.51
7.49
7.48
4.05
4.04
4.02
4.00
3.99
3.11
3.09
3.07
2.84
2.45
2.43
2.41
2.09
2.07
2.07
2.05
1.18
1.16
1.14
H3C
O
O
N
O
CH3
CH3
1.00
0.95
1.95
5.91
2.25
3.03
2.11
2.06
2.86
2500
2000
1500
1000
500
0
f1 (ppm)


8.21
8.19
7.62
7.62
7.50
7.50
7.45
7.45
7.43
7.43
3.93
3.06
3.04
3.03
2.79
2.78
2.52
2.50
1.85
1.85
1.84
1.83
1.82
1.82
1.81
1.61
1.60
1.59
1.59
1.57
N
N
O
CH3
H3C
1.00
0.98
1.01
0.99
3.34
2.04
2.99
2.22
2.11
2.14
f1 (ppm)


8.26
8.24
7.64
7.61
7.61
7.50
7.50
7.48
7.47
3.99
2.97
2.95
2.84
2.84
1.87
1.68
1.68
1.67
1.66
1.65
1.65
1.64
1.63
1.62
1.59
1.20
1.18
1.17
1.15
1.14
1.10
1.07
1.07
1.04
1.04
N
O
CH3
H3C
1.00
2.03
0.96
3.18
2.02
2.98
0.92
5.12
5.22
f1 (ppm)